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The Synthesis and Biochemical Evaluation of Novel Isoquinoline Derivatives

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A thesis presented to the University of Dublin

for the degree of

Doctor of Philosophy in Pharmaceutical Chemistry

Based on research carried out under the supervision of

Mary Jane Meegan, B.Sc., M.A., Ph.D.(N.U.I.)

at the

School of Pharmacy,

Trinity College Dublin

April 2005

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Abstract

Isoquinolines are naturally occurring alkaloids, some of which have pharmacological activity. Previous work by the research group of Dr. Mary Jane Meegan, has shown diverse classes of isoquinoline derivatives to be active against monoamine oxidase and acetylcholinesterase. This provided pointers to structure-activity relationships, leading to the syntheses undertaken in this study.

Chapter One discusses current theories on the aetiology of depression, Parkinson's Disease and Alzheimer's Disease. Current clinical treatments are outlined, and the possible roles of monoamine oxidase and acetylcholinesterase inhibitors are placed in context. The current understanding of the structure of monoamine oxidase is summarised. The rationale for work to be undertaken is then presented.

Chapters Two through Six explore the synthetic routes employed, and the products isolated. Points of chemical interest, such as possible information on mechanisms and spectroscopic features, are discussed. Chapter Two is devoted to 7-carboxamido tetrahydroisoquinolines and their synthesis. Chapter Three outlines the synthesis of 3,4-dihydroisoquinolines by varied routes and the procedures used to obtain amides of the related 1,2,3,4-tetrahydroisoquinolines. Chapter Four reviews further modification of tetrahydroisoquinolines with piperazine functions at position 2. Chapter Five encompasses the synthesis of non-methoxylated 3,4-dihydroisoquinolines by conventional routes and by microwave-assisted chemistry, as well as the manufacture of phenoxyacetyltetrahydroisoquinolines. Chapter Six reviews the many routes evaluated in the synthesis of isoquinolines with a thioalkylether function.

Chapter Seven concerns the results obtained from biochemical assays of the compounds produced. Activity against monoamine oxidase B was examined for all compounds. A selection of these was tested for inhibition of monoamine oxidase A. The phenoxyacetyltetrahydroisoquinolines were further examined for inhibition of acetylcholinesterase. The results obtained are presented and analysed, and some explanation of structure-activity relationships is attempted. The biochemical protocols used are outlined in Chapter 8. The following section contains the experimental details for Chapters Two through Six and an associated appendix.

Acknowledgements

The road leading to this submission has been a long one, and many people have helped along the way. I wish to thank Dr. Mary Jane Meegan for her constant support, help, understanding and encouragement.

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List of Abbreviations

AChE	Acetylcholinesterase
^{13}C-NMR	^{13}Carbon nuclear magnetic resonance
CNS	Central nervous system
COMT	Catechol-O-methyl transferase
DCC	Dicyclohexylcarbodiimide
DEPT	Distortionless enhancement through polarisation transfer
DHIQ	Dihydroisoquinoline
DMAP	Dimethylaminopyridine
DPM	Disintegrations per minute
ECT	Electroconvulsive therapy
EGTA	Ethylene glycol-*bis*(aminoethylether)N,N,N',N'-tetraacetic acid
EI	Electron impact
FAD	Flavin adenine dinucleotide
GC-LRMS	Gas chromatography low resolution mass spectroscopy
5-HIAA	5-Hydroxyindole acetic acid
HMBC	Heteronuclear multiple bond connectivity
HMQC	Heteronuclear multiple quantum coherence
^{1}H-NMR	Proton nuclear magnetic resonance
5-HT	5-Hydroxytryptamine (serotonin)
HRMS	High resolution mass spectroscopy
IR	Infra-red
MAO	Monoamine oxidase
MAOI	Monoamine oxidase inhibitor
MPP+	1-Methyl-4-pyridinium
NOE	Nuclear Overhauser effect
PPA	Polyphosphoric acid
RIMA	Reversible inhibitor of monoamine oxidase
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant
THIQ	Tetrahydroisoquinoline
TOCSY	Total correlation spectroscopy
TRIS	*tris*(hydroxymethyl)aminomethane

1 Chapter 1: Tetrahydroisoquinolines: Physiological Role and Use in the Treatment of Depression, Parkinson's Disease and Alzheimer's Disease

1.1 Introduction

Mood and cognitive disorders are distinct illnesses, yet often occur together in the same individual. It is usually considered better medical practice to minimise the number of drugs any one patient takes at one time. For this reason, research into the treatment of neurological disorders follows three strands: firstly, elucidating the biochemical pathways and mechanisms which underlie the illnesses; secondly, identifying the chemical features which confer potency and selectivity on a drug so a single disorder may be targeted; and conversely, developing multipurpose drugs to treat several disorders simultaneously for patients which require such treatment.

1.2 Depression

1.2.1 Classification and Diagnosis

Depression is increasingly being recognised as one of the most common disorders afflicting individuals across boundaries of gender, race and age. The difficulty of providing a simple definition of the condition arises from an as yet incomplete understanding of the aetiology of the disorder. Diagnosis thus relies solely on clinical criteria. The approach of the American Psychiatric Association, as reflected in the Diagnostic and Statistical Manual of Mental Disorders (DSM IV), illustrates this: depression is defined as a mood disorder. Diagnosis is based on the presence, severity and duration of a number of symptoms and signs. These include emotions (for instance, feelings of inadequacy or suicidal tendencies), cognitive symptoms (such as forgetfulness and inability to concentrate) and physical signs (alterations in weight and sleep patterns being the most common examples).[1]

The estimated prevalence of depression of 5.2% in the general Irish population rises to 10% to 17% among those over sixty-five years.[2] The estimates are strikingly similar across many different societies. The Royal College of Psychiatrists quotes a point prevalence of 5% for depression in the United Kingdom, and British general practitioners treat about 3% of their patients for depression in any given year.[3]

1.2.2 Health and Economic Consequences of Depression

The seriousness of the condition is reflected by the link with suicide: effectively, depression can be a terminal illness. The majority of successful suicides are committed by those with depressive illness. The conclusion of the U.S. Surgeon General is that the most

effective prevention of suicide is by early diagnosis and treatment of depression and other psychiatric illnesses. [4]

The less drastic but serious impact of milder forms of depression is now being appreciated. The Disability Adjusted Life Year (DALY) is used to quantify both years lost by premature death due to a condition, and years lived in the shadow of disability brought on by the disease in question. Unipolar major depression is held to cost 6.7 million DALYs annually in developed countries. It is worth noting that depression is linked to two other major causes of death and disability: cardiovascular disease and alcoholism. These are estimated to exact 5.0 and 4.7 million DALYs yearly, respectively.[5]

This does not take into account other disorders, such as bipolar disorder – where episodes of mania and depression alternate – and dysthymia, in which many of the symptoms of major unipolar depression are displayed, with reduced severity but for a long period of time. The irrational behaviour displayed by sufferers from mania leads to difficulties with business and social affairs with economic consequences. Dysthymia reduces the productivity of an individual.[5] Furthermore, the strain imposed by all types of mood disorder not only on the sufferer but also on family and associates must be counted as a social ill.

1.2.3 Aetiology of Depression

1.2.3.1 Genetic Aspect

Depression is clearly a serious problem. So far, understanding of its origins and progress is limited. It has been linked to some biological markers, and theories on its evolution have been put forward, but none is completely convincing. Arguments for a genetic component are persuasive, but do not tell the entire story. Work among twins indicates that the monozygotic (identical) twin of a depressive is up to twice as likely to develop depression as the dizygotic (fraternal) twin of a sufferer.[6]

Much speculation has also been aroused by the greater prevalence of depression in women than in men in a variety of cultures. The interaction of hormones and other components has been suggested as a factor and, in some instances, there may be validity to this.[7] The influence of glucocorticoids on monoamine oxidase is discussed later in this chapter. However, caution must be exercised in drawing global conclusions. Bipolar disorder affects only 1% of the population, but the incidence in men and women is equal.[5]

To date, medical treatment has focussed on the biochemistry of the brain, and particularly the manipulation of neurotransmitter function at the synapse. Neurotransmitters act as chemical messengers, transmitting messages across synapses when depolarisation of the

neurone triggers their release from presynaptic termini. They then traverse the synapse and bind to post-synaptic receptors, propagating the depolarisation that captures a thought or feeling (see Figure 1-1 below, reproduced from the University of Plymouth Psychology Department website, http://salmon.psy.plym.ac.uk/year1/neurotr.htm#synapse).

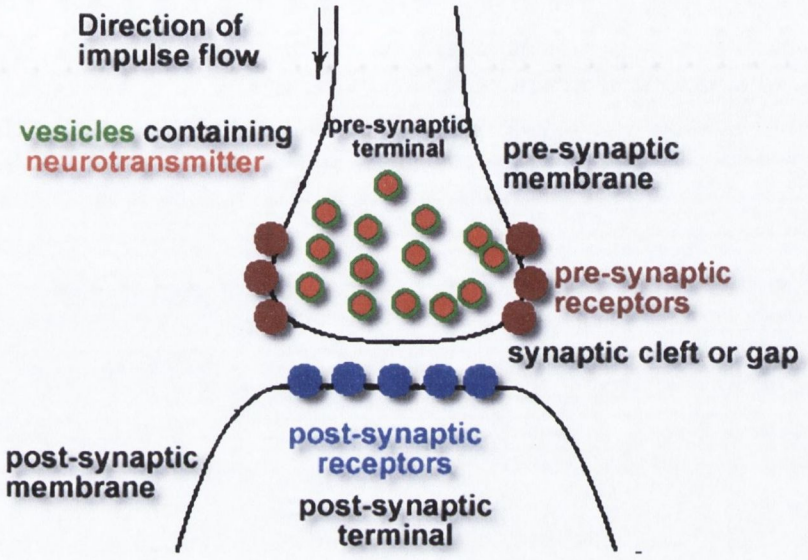
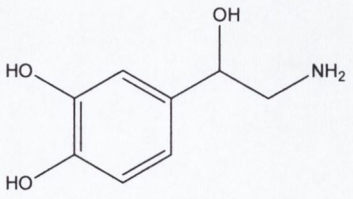


Figure 1-1: Neurotransmitters at the synapse

1.2.3.2 Noradrenergic Aspect

In most fields, research into the nature and causes of a disease leads to improved understanding, which in turn allows better treatments to be devised. To an extent, that process was reversed in the field of depressive disorders. The discovery, that use of reserpine as a treatment for either schizophrenia or hypertension, led to the development of depression in a minority of the patients, allowed the formulation of a biological theory of depression.[8] The effect was attributed to the depletion of the neurotransmitter noradrenaline **(1)** (shown in Figure 1-2). The conclusion was drawn that a relative deficiency of noradrenaline in the brain led to depression.



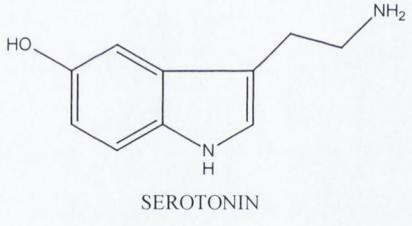
NORADRENALINE **(1)**

Figure 1-2: Noradrenaline (1)

For some years, the prevalent theory on the cause of depression, focussed on the levels of monoamine neurotransmitters in the brain. This appeared to be supported by the discovery that iproniazid, a monoamine oxidase inhibitor – and thus an agent that raised the level of central amines – relieved depression.[9] Iproniazid was a proposed anti-tubercular treatment, which did not treat the tuberculosis but improved the depressed mood of many of those receiving it. For some time, research into other possible anti-depressants concentrated on this aspect alone.

1.2.3.3 Serotonin

The initial concentration on the catecholamines was at first bolstered by investigation of the tricyclic anti-depressants (TCAs), which also increased noradrenaline levels. However, as additional actions of some TCAs were appreciated, this focus gave way to investigation of drugs that alter the levels of serotonin **(2)**, another monoamine neurotransmitter (shown in Figure 1-3). These agents, the Selective Serotonin Reuptake Inhibitors (SSRIs), were at least as efficacious as the older monoamine oxidase inhibitors and tricyclic antidepressants.[10]

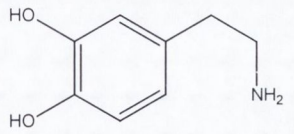


SEROTONIN

Figure 1-3: Serotonin (2)

A serotonergic hypothesis was therefore proposed. This did not totally discount the influence of noradrenergic mechanisms. It was held that reduced serotonin release from the raphe nuclei could cause depression by permitting noradrenaline levels to fall.[7] The idea was christened the "permissive hypothesis". Not only did SSRIs indicate that serotonin was involved in depression, further intriguing evidence accumulated that serotonin reuptake was compromised in the platelets of depressives. They were thus unable to clear serotonin quickly from their surroundings, and so were abnormally sensitive to serotonin. Serotonin increased sensitivity to even more powerful stimuli to clotting. An explanation was at last being offered for the well-documented phenomenon of the link between heart attack, stroke and depression.[7] In the brain the problem appeared to be *low* synaptic serotonin levels; in plasma, reduced reuptake seemed to lead to inappropriately *high* serotonin levels around platelets.

The catecholamine hypothesis was expanded to accommodate serotonin and dopamine **(3)**, yet another monoamine neurotransmitter (Figure 1-4), and the monoamine hypothesis held sway.



DOPAMINE

Figure 1-4: Dopamine (3)

1.2.3.4 Flaws of the Monoamine Hypothesis

However, it is now recognised that, despite the undoubted importance of monoamine levels as a marker of the disorder and a measure of the possible efficacy of new agents, this aspect does not fully explain the genesis of depression. Firstly, many other neurotransmitter systems are altered in depression: GABA (gamma-aminobutyric acid) and acetylcholine.[7] The amelioration of the clinical signs of depression by agents that raise levels of monoamines does not prove that problems with monoamine neurotransmission were the origin of the depressive episode. Furthermore, reduced synthesis of monoamines or increased degradation of same, are not always seen in cases of depression.[8] Another puzzle is the fact that the elevation of monoamine levels, which follows almost immediately on therapy with monoamine oxidase inhibitors, does not result in therapeutic effects until some weeks later.[10]

1.2.3.5 Current Model

Current thinking emphasises the complexity of the central nervous system. The alteration of neurotransmitter levels during the treatment of depression is seen as a global marker that may result from many different, often subtle, changes introduced by anti-depressants. The raised level of monoamines resulting from monoamine oxidase inhibition may cause a cascade of effects.

Neurotransmitter transporters have been shown to be regulated by anti-depressants via alterations of extracellular concentrations of monoamines.[11] Studies of the effects of amphetamines also indicate that substrates other than the endogenous neurotransmitters can alter the expression (i.e. number) and function (i.e. activity) of transporters in specific areas of the brain.[11]

An increase in noradrenaline levels will lead to downregulation of β-adrenergic receptors. Some anti-depressants affect these receptors directly, without interfering with

catecholamine levels, and this downregulation seems to be partly responsible for their efficacy.[12]

An apparent contradiction of the catecholamine hypothesis was the consistent finding that antidepressant treatments led to *reduced* concentrations of MHPG (3-methoxy-4-hydroxy-phenylglycol), a metabolite of noradrenaline, in the cerebrospinal fluid of patients. This was observed in a series of at least 17 papers between 1974 and 1987, across treatments ranging from the monoamine oxidase inhibitors clorgyline, pargyline and selegiline to tricyclic antidepressants amitriptyline **(9)**, chlorimipramine, imipramine **(8)**, desipramine and nortryptiline and selective serotonin inhibitors femoxetine and zimeldine as well as atypical agents bupropion and mianserin. The explanation advanced was that the higher level of noradrenaline in the brain must affect the firing of noradrenergic neurones, downregulating them. The *locus coeruleus* is the principal noradrenergic cell body group in the brain and work on this area supports this view. It is interesting to note that sufferers from Alzheimer's disease who develop clinical depression seem to do so as a result of degeneration of aminergic nuclei in the *locus coerulus*.[13] Tricyclics, SSRIs, MAOIs and electro convulsive therapy have all been shown to reduce electrophysiologic activity in the *locus coerulus* in rats.[12]

It is proposed that the presumed increased *locus coerulus* activity in depression leads to augmented release of the peptide galanin. Galanin will reduce release of dopamine in the forebrain, and this leads to signs and symptoms of depression such as anhedonia.[12] This theory illustrates another of the facets of current models of depression. In addition to neurotransmitters, which are directly involved in the propagation of signals across synaptic gaps, neuromodulators play a vital role in the CNS (central nervous system).

Neuromodulators influence the activity of neurotransmitters and indirectly affect brain activity. 2-Phenylethylamine is one of the substances that have been examined in this light. Reduced levels of phenylacetic acid in the CSF (cerebrospinal fluid) of depressed patients, and the efficacy of a combination of (-)deprenyl/selegiline **(33)** plus phenylethylamine in the relief of depression, point to involvement of the substance in the aetiology of the condition.[14] Once again, dopamine involvement is indicated. Phenylethylamine potentiates the action of dopamine at synapses. This is interesting as amphetamines affect monoamine oxidase and are renowned for the feeling of euphoria they induce; amphetamine reduces the accumulation of phenylethylamine, and coincidentally chronic use can result in psychosis. Antipsychotics, on the other hand, will potentiate the accumulation of phenylethylamine. [14] While this may seem irrelevant to depression, it throws light on the interrelated nature of neurotransmitter systems in the

brain. Interfering with a single agent may have far-reaching effects, which we as yet cannot predict.

It has been noted that undiagnosed thyroid deficiency prevented response to antidepressive therapies in patients. The hypothalamus, pituitary gland and adrenal glands are interconnected by the hormonal signals they secrete to give the hypothalamic-pituitary-adrenal axis (HPA). The main function of the HPA is to coordinate the response to stress, commonly called the "fight or flight" syndrome. It has consistently been demonstrated that depressives have unusually active HPA axes. This was marked by pathologies such as enlargement of the pituitary and adrenal glands, but most strikingly by elevated level of corticotropin releasing factor (CRF) in the cerebrospinal fluid of depressives. This factor is secreted by the hypothalamus and is the first step in activating the HPA axis. CRF drops again in the CSF of depressives undergoing therapy.[7]

It is worth noting that control of the HPA axis is often disrupted with aging, and depression is more common in the elderly. The majority of elderly depressives fail to respond to dexamethasone suppression tests. This is a test in which the administration of dexamethasone should reduce the endogenous production of glucocorticoids. Failure of suppression usually indicates the presence of Cushing's disease. This would seem to support hormonal involvement in depression. As usual, the picture defies simple explanations: young depressives do *not* show DST responses to the same degree.[15]

In short, theories on depression have been modified to take account of the possible influence of altered sensitivity of presynaptic and postsynaptic neurone receptors, roles for neurotrophic factors required for the growth of certain types of neurones and genetic and environmental elements which may interact with all these or operate through other pathways. Nevertheless, the close correlation between monoamine neurotransmitter levels and depression justify the continued use of this marker to establish the possible effectiveness of new agents. The established efficacy of monoamine oxidase inhibitors, in particular, has led to attempts to produce agents that operate in a similar fashion but are free from the dangerous side-effect profile which discourages the use of these drugs.

1.2.4 Treatment of Depression

Both electro convulsive therapy (ECT) and pharmacotherapy have been used to treat depression in the past six decades. In addition, psychotherapy and cognitive therapy, which encourage the analysis of experiences and thought processes, are used instead of, or in conjunction with, pharmacotherapy.

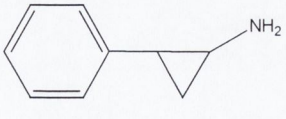
1.2.4.1 ECT

Electro convulsive therapy has similar rates of success to drug therapy, with between 60% and 70% recovery. [5] Basically, it involves passing an electric current through the patient's brain in order to precipitate a short general seizure. It is used only in cases of refractive depression, however, because of fears of stigma and effects on memory. While ECT does not usually cause chronic memory loss, it does affect memory of the experience itself, and sometimes of events up to six months prior to treatment.[5]

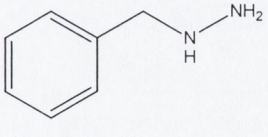
1.2.4.2 MAOIs

The original antidepressant agents, monoamine oxidase inhibitors, are still in clinical use but are no longer regarded as first line therapy.[10] This owes more to their side-effect profile than any doubts of efficacy. It is also true that switching from a tricyclic (TCA) to a MAOI antidepressant is more easily done than vice versa. It is recommended that MAOI therapy should cease two weeks prior to starting therapy with a TCA or SSRI. 7 to 14 days will generally suffice to clear tricyclics from a patient's system before starting to take a MAOI. The exceptions to this are clomipramine and imipramine **(8)**, the former of which is particularly dangerous in combination with tranylcypromine **(4)**, and for which a gap of 3 weeks between cessation of TCA and commencement of MAOI therapy is recommended.[10]

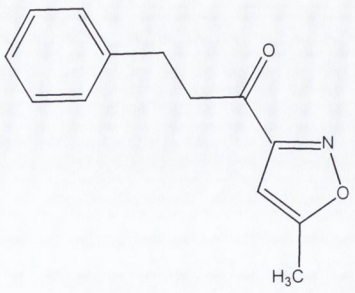
Monoamine oxidase exists as two isoenzymes, type A and type B, and only inhibition of type A relieves depression. Type B inhibitors have applications in the therapy of Parkinson's disease. The term "MAOI" is used only for the older irreversible inhibitors, used to treat depression. Tranylcypromine **(4)**, phenelzine **(5)** and isocarboxazid **(6)** are the MAOIs in clinical use in Britain. Only the first two, under the brand names Parnate and Nardil respectively, are available in Ireland. "Marplan" or isocarboxazid may be obtained in Britain but not in the U.S.A. or Ireland. They are used in the treatment of refractory cases, although phobic patients and depressives with atypical symptoms are held to be more responsive to MAOIs.[10]



Tranylcypromine **(4)**



Phenelzine **(5)**



Isocarboxazide **(6)**

Figure 1-5: Irreversible monoamine oxidase inhibitors in clinical use

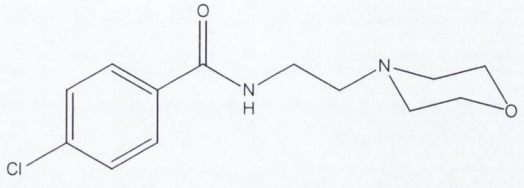
The adverse effect profile of MAOIs is due to their action on monoamine oxidase, for which they are irreversible inhibitors. The most common reactions (>10% incidence) are orthostatic hypotension, drowsiness, reduced sex drive, muscle weakness, trembling, and blurred vision.[16] Between 1% and 10% of patients experience tachycardia, peripheral oedema, nervousness, chills and gastrointestinal upset. Although less than 1% of patients on MAOIs suffer from Parkinsonism syndrome, [16] this is interesting, in view of the role of monoamine oxidase inhibitors of a different type in alleviating the symptoms of Parkinson's disease. This is considered in more detail in the sections dealing with Parkinson's disease and monoamine oxidase.

The drug and food interactions of MAOIs are in practice the most troublesome aspect of therapy. The cardiotoxicity of SSRIs and tricyclics is potentiated. By preventing the metabolism of amines, irreversible MAOIs allow amines such as tyramine in food to cause a hypertensive crisis, known colloquially as the "cheese reaction". Normally, tyramine in cheese, marmite, game, beer or a host of other common foodstuffs and drinks is metabolised by MAO in the gastrointestinal tract. Unfortunately, this is predominantly of type A, which must be inhibited for the anti-depressive effect, and the tyramine crosses the gut wall. It is taken up from the bloodstream into synaptic vesicles, forcing the displacement of the noradrenaline already present. The sudden, dramatic surge in blood pressure caused by massive noradrenergic stimulation may be fatal.[9] Irreversible MAOIs bind permanently to MAO and the body must generate fresh MAO to counter the effect. This may take up to 14 days.[9]

Drug interactions also pose a threat to the patient on MAOIs.[10] Indirectly acting sympathomimetics, which are commonly included in cold and 'flu remedies as decongestants, should be metabolised by MAO. When MAOIs prevent this, they cause a hypertensive crisis in a manner analogous to dietary tyramine.

In an attempt to reduce the likelihood of the cheese reaction reversible inhibitors of monoamine oxidase A (RIMAs) have been developed. Since these bind reversibly and

competitively to MAO large quantities of tyramine will simply displace the RIMA at the MAO site and the cheese reaction should not materialise. [9] Only one RIMA is as yet in clinical use. Moclobemide **(7)** (shown in Figure 1-6) is available as "Manerix". The aim is to allow patients a freer diet and lifestyle but sympathomimetic drugs must still be avoided. Food interactions are still possible if large doses (e.g.>600mg per day) are prescribed.[17] A clear advantage is the short duration of action so that no treatment free period is needed when changing a patient from moclobemide to another antidepressant, although the same precaution of a washout period must be observed *before* commencing therapy with moclobemide after tricyclics, SSRIs or the irreversible MAOIs. [10]



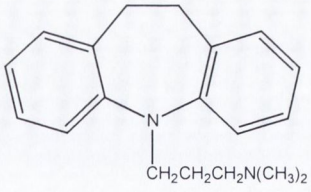
MOCLOBEMIDE (7)

Figure 1-6: Reversible monoamine oxidase inhibitor, moclobemide (7)

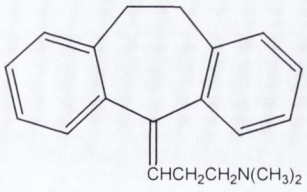
1.2.4.3 Tricyclic Antidepressants

80% to 90% of patients respond to tricyclic antidepressants, and they are, in conjuction with SSRIs, first line therapy. [10] The name indicates the three rings, which form the core of the structure in tricyclics (see Figure 1-7). The process by which tricyclics achieved their antidepressive effect was poorly understood at first, as some affect the noradrenergic system but others have no such action. It was shown that they affect serotonergic receptors, of which there are as many as 13 subtypes.[7] They thus have subtly different profiles.

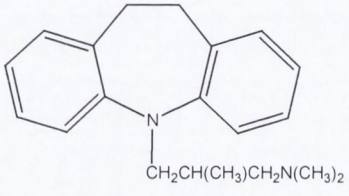
Amitriptyline **(9)** is the original TCA and is sedating. Its anti-cholinergic effects cause blurring of vision, dry mouth, constipation, and urinary retention and aggravate glaucoma. Nortriptyline is less sedating and has a milder anti-cholinergic action. Trimipramine **(10)** is, on the other hand, more sedating than amitriptyline but is safer in combination with MAOIs.[17] Rather than any particular agent being advocated as more effective, the practice is to tailor the therapy to the patient, giving due consideration to co-existing disease – such as heart disease – and concomitant therapy.



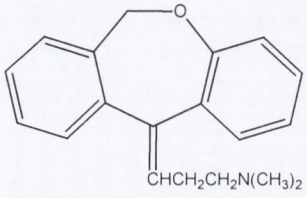
IMIPRAMINE **(8)**



AMITRIPTYLINE **(9)**



TRIMIPRAMINE **(10)**



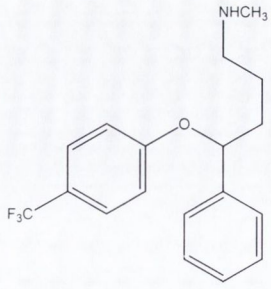
DOXEPIN **(11)**

Figure 1-7: Tricyclic anti-depressants

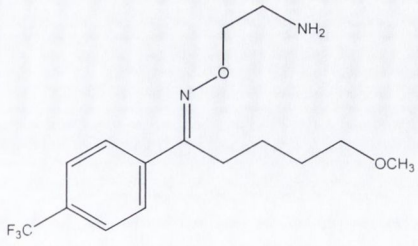
Being cardiotoxic in overdose TCAs are prescribed in limited quantities. There is a time lag of 2 weeks between commencement of therapy and onset of action.[10] They may be employed in cases of panic disorders also. TCAs have long half-lives so they offer the advantage of once daily dosage.

1.2.4.4 Selective Serotonin Reuptake Inhibitors (SSRIs)

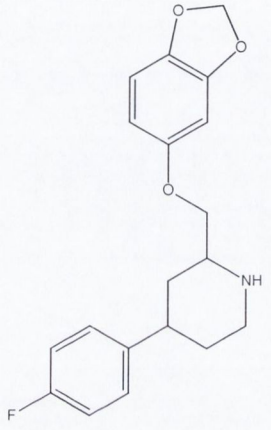
The SSRIs are less cardiotoxic than the TCAs and equally effective in most cases; they are therefore preferred in cases where suicide attempts are considered a serious risk.[10] They are also of benefit in some older patients with cardiac conditions. They are not free of side effects, the most notable being gastrointestinal upset. Tolerance to this normally develops in a matter of weeks. They are less sedating than the TCAs and cause fewer anti-cholinergic effects.[10] Interestingly, while the older agents, both TCAs and MAOIs, are associated with weight gain in 25% to 50% of patients, [17] SSRIs may cause anorexia and weight loss. [10] Examples of common SSRIs are illustrated in Figure 1- 8.



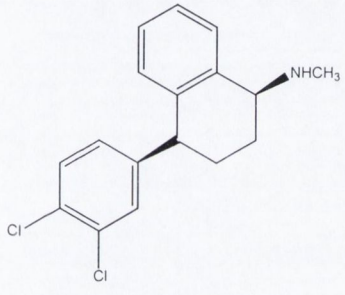
FLUOXETINE **(12)**



FLUVOXAMINE **(13)**



PAROXETINE **(14)**



SERTRALINE **(15)**

Figure 1-8: SSRIs in clinical use

1.3 Parkinson's Disease

1.3.1 Classification and Diagnosis

Parkinson's disease is also increasingly apparent in Western society, due to the aging population profile; Parkinson's disease affects 1% of the over sixty-fives.[18] The incidence in the overall population is 1 in 1000. It is not confined to older subjects, however, and approximately 5% of sufferers are under 40 at the time of diagnosis. There is some evidence that industrialisation, the use of some chemicals, rural residence and reliance on well water may be linked to occurrence of the disease.[18] It is equally common in both sexes. There is some speculation as to genetic components, which may predispose a person to the disease, but there is as yet no proof of such.

Like depression, Parkinson's disease is characterised by alterations in the levels of neurotransmitters in the brain. As yet, the aetiology of it is not fully understood.[19] However, specific changes in the brain have been unequivocally identified with Parkinson's disease, so that post-mortem examination of the brain of a victim can

positively identify them as a sufferer.[20] Diagnosis, in practice, is based on signs and symptoms in a clinical manner analogous to that for depression, but true Parkinson's disease, as distinct from parkinsonism, may be identified by its characteristic neuropathology.

1.3.2 Aetiology of Parkinson's Disease

1.3.2.1 Neuropathology

In 1817 James Parkinson described the disease which bears his name. It is characterised by rigidity of the limbs, tremor, loss of some reflexes and most of all by slow movement, termed "bradykinesia". The immediate cause of this is the loss of pigmented cells in the *substantia nigra* area of the basal ganglia in the brain. These cells produce dopamine, which they transport to the striatum, whence it is released as a neurotransmitter. Another feature of the disease is the development of Lewy bodies within the neurones. These eosinophilic, round inclusions were first described in 1912 by Lewy. Their role, if any, in the progress of the disease, has yet to be assigned.[21] In normal brains, acetylcholine and dopamine are in balance in the basal ganglia. The loss of dopamine allows the cholinergic influence to dominate, resulting in the movement disorder.

1.3.2.2 Parkinsonism

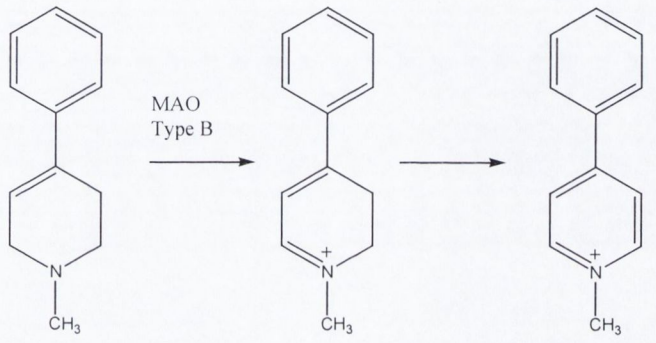
A distinction has already been drawn between parkinsonism and Parkinson's disease. Since the signs of Parkinson's disease are the result of the loss of dopaminergic activity in the striatum, any agent that replicates this will produce a similar syndrome. Reserpine depletes dopamine in the vesicles of the *nigrostriatum* and unsurprisingly a reversible parkinsonism is the result.[21] Alpha-methyltyrosine is another agent, which inhibits tyrosine hydroxylase, so preventing the synthesis of dopamine *and* replaces dopamine in the vesicles: again, parkinsonism is manifested. [21] Neither of these is used clinically, but dopamine antagonist anti-psychotics are used daily by millions. Parkinsonism is a well-documented side effect of these treatments, but is reversible and so seen as less of a problem than other adverse effects, such as tardive dyskinesia.[10]

Some neurotoxins produce syndromes similar to Parkinson's disease. Among these are manganese and carbon disulfide. The parkinsonism is the expression of cell destruction in the striatum rather than the *substantia nigra.* MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine **(16)**, a contaminant of a substance abused by heroin addicts in California in 1982, leads to rapid development of pronounced, irreversible parkinsonism, which displays neuropathology very similar to that of Parkinson's disease. The neurones of the *substantia nigra* are lesioned, producing bradykinesia and tremor, and also lesser

features of the disease, such as seborrhoea. For this reason MPTP has been used to induce a model of Parkinson's disease in primates, in order to study the disease and possible treatment models. It has also increased attempts to find the endogenous toxins which are suspected to caused Parkinson's disease, and which are supposed to resemble MPTP in structure, or mode of action, or both.[21]

1.3.2.3 Current Theories

MPTP itself does not attack the dopaminergic neurones. It is converted by monoamine oxidase B to $MPDP^+$, 1-methyl-4-phenyl-2, 3-dihydropyridine **(17)**. The final step converts $MPDP^+$ to MPP^+, 1-methyl-4-phenylpyridinium **(18)**, as shown in Scheme 1-1.



1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) **(16)**

1-Methyl-4-phenyl-2,3-dihydropyridinium ion ($MPDP^+$) **(17)**

1-Methyl-4-phenyl-pyridinium ion (MPP^+) **(18)**

Scheme 1-1: Conversion of MPTP to MPP+

This quaternary amine **(18)** is charged, a fact that appears to increase its affinity for the dopamine transporter.[21] It is therefore concentrated in the dopaminergic neurones, where it proceeds to selectively inhibit complex I and α-KGDH (alpha-ketogluterate dehydrogenase) activity. Output of ATP, which acts as the cell's fuel, is reduced while the superoxide radical ($O_2^{\bullet-}$) is generated. Together, these actions kill the cell.[22]

Postmortem studies have indicated that free radicals and suboptimal antioxidant defences may lead to damage in the nigrostriatal system of sufferers from Parkinson's disease.[23] Reduced complex I activity and reduced *substantia nigra* immunostaining for α-KGDH have both been demonstrated in Parkinson's disease. [19]

Given the toxicity of MPP^+ **(18)** it has been speculated that endogenous neurotoxins would also be N-methylated and oxidised, possibly by monoamine oxidase. Both tetrahydroisoquinolines and β-carbolines fulfil these criteria. They have been documented in the human brain.[24] The picture is as yet unclear, as some tetrahydroisoquinolines seemingly protect against parkinsonism, while others induce it in primate models.

Increased blood platelet MAO-B activity in Parkinson's and Alzheimer's disease has been found.[25] The evidence is not clear-cut, as Parkinson's disease may co-exist with Alzheimer's disease. Furthermore, MAO-B activity increases with age and both diseases predominantly affect older people.[26]

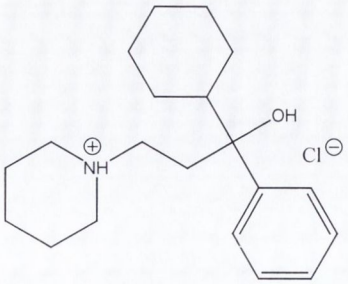
The assumption that an endogenous toxin acts in a manner similar to MPTP has not yet been conclusively proven. A genetic component is also proposed. Possibly inherited defects in cytochrome P450 isoenzymes and N-acetyltransferase 2 may allow a putative neurotoxin to damage the basal ganglia.[27] Treatment simply relieves the symptoms; there is, at present, no cure for Parkinson's disease.

1.3.3 Current Treatment

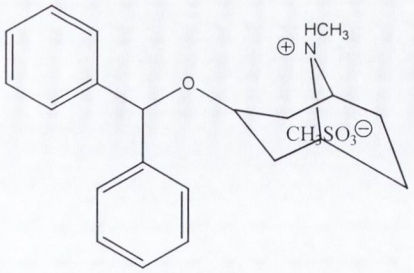
The symptomatic relief of Parkinson's disease is attempted by using a variety of classes of drugs, acting through several pathways.

1.3.3.1 Anticholinergics

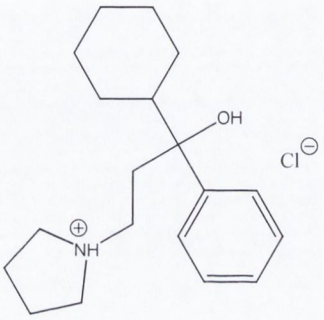
These control the socially unacceptable features of the illness, such as excessive salivation, as well as tremor and rigidity in the early stages. They do not affect bradykinesia and may cause confusion and memory loss. Since the elderly population in which they are used already experience a higher incidence of such cognitive difficulties, they are used with caution. They are unsuitable for patients with glaucoma, also associated with aging. The anticholinergics in use in Ireland are illustrated in Figure 1-9 and include benzhexol **(19)** ("Artane"), benztropine **(20)** ("Cogentin"), procyclidine **(21)** ("Kemadrin") and, less commonly, biperiden **(22)** ("Akineton").



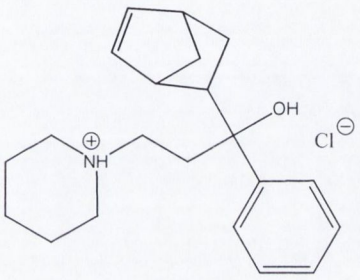
BENZHEXOL **(19)**



BENZTROPINE MESYLATE **(20)**



PROCYCLIDINE **(21)**



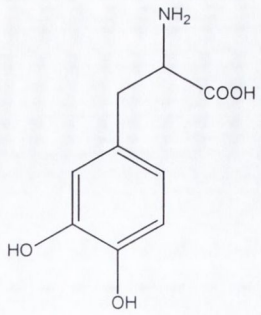
BIPERIDEN HYDROCHLORIDE **(22)**

Figure 1-9: Anti-cholinergic agents used to treat Parkinson's disease

1.3.3.2 Levo-Dopa

The laevorotatory precursor of dopamine, levo-dopa **(23)** (see Figure 1-10) is administered to boost dopamine levels. This is effective if extracerebral dopa-decarboxylase inhibitors are also taken to block peripheral metabolism of L-dopa to dopamine. The aim is to concentrate the dopamine in the basal ganglia. Smaller doses may therefore be employed, reducing side effects and prolonging the usefulness of L-dopa. The inhibitors "Madopar" (benserazide) and "Sinemet" (carbidopa) are used in Ireland. The inhibitors do not cross the blood brain barrier, so the L-dopa can be converted to dopamine in the brain.

L-dopa is the most effective therapy available for Parkinson's disease. It alleviates bradykinesia and rigidity rather than tremor. Sadly, over time it gives reduced relief. Dyskinesias, which are involuntary, abrupt movements, develop. The dose gives relief for progressively shorter periods. The patient also finds the therapy shows "on-off effects" throughout the day.



L-DOPA **(23)**

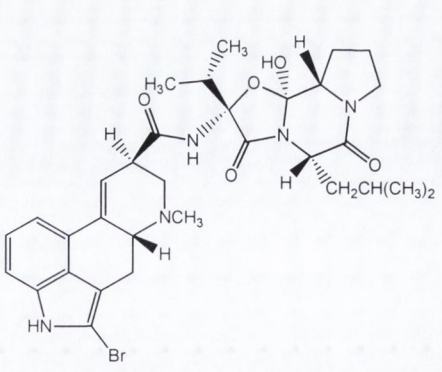
Figure 1-10: Levo-Dopa, used in the treatment of Parkinson's disease

1.3.3.3 Dopamine Agonists

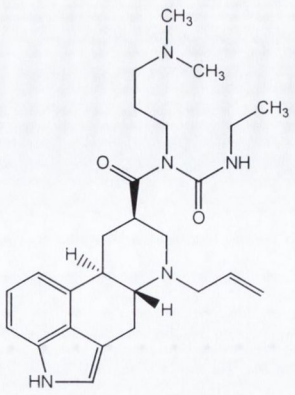
The dopamine agonists are illustrated in Figure 1-11. Bromocriptine **(24)** ("Parlodel") stimulates dopamine receptors directly. It is effective against all the symptoms of Parkinson's disease, but obviously works only where there are sufficient numbers of intact postsynaptic receptors. It is administered with L-dopa to reduce the dose of the latter. Cabergoline **(25)** ("Dostinex") is a D2 agonist, but is used for the treatment of hyperlactinemia. It is used along with L-dopa.

Apomorphine **(26)** is used only in advanced cases. It is an agonist at both D1 and D2 receptors, although D2 receptors are believed to be those of primary importance in the basal ganglia. It is useful for resolving the on-off effects but is available only as an injection. Therapy is initiated in hospital and it is not commonly available as either "APO-go" or "Britaject".

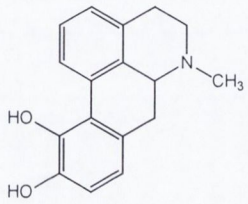
Ropinirole **(27)** ("Requip") is a specific D2 agonist. It may delay the inevitable start of L-dopa therapy. Pramipexole **(28)** is yet another D2 agonist with D3 binding. It is a new agent, and as "Mirapexin" is not yet available in Ireland. Pergolide **(29)** is available as "Celance".



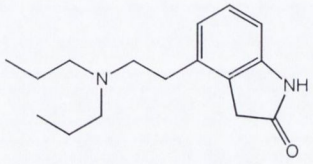
BROMOCRIPTINE **(24)**



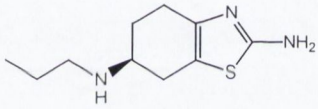
CABERGOLINE **(25)**



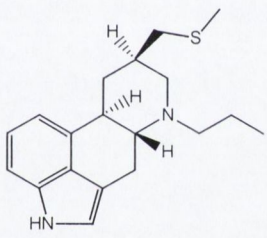
APOMORPHINE **(26)**



ROPINIROLE **(27)**



(S)-PRAMIPEXOLE **(28)**

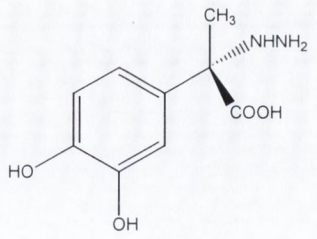


PERGOLIDE **(29)**

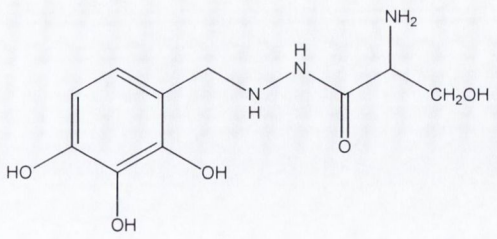
Figure 1-11: Dopamine agonists used in the treatment of Parkinson's disease

1.3.3.4 Catechol-O-Methyl Transferase Inhibitors

Catechol-O-Methyl transferase metabolises dopamine *in vivo*. COMT inhibitors should prolong the action of dopamine produced by L-dopa therapy, reducing the dose of L-dopa and any other agents being used. The COMT inhibitors carbidopa **(30)** and benserazide **(31)** are shown in Figure 1-12. As with the agonists, the aim is to keep the L-dopa doses low for as long as possible, to extend the time period over which it may be used.



CARBIDOPA **(30)**

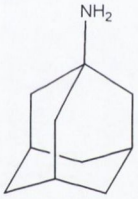


BENSERAZIDE **(31)**

Figure 1-12: COMT inhibitors used in the treatment of Parkinson's disease

1.3.3.5 Amantadine

"Symmetrel" or amantadine **(32)**, shown in Figure 1-13, is unusual because it works by stimulating dopamine release and preventing re-uptake, in a manner similar to the anti-depressants that work on serotonin and noradrenaline in depression. In cases of extensive damage to the nigrostriatal neurones it is ineffective. Since about 80% of neurones have usually degenerated by the time of diagnosis, it is of limited use. It is administered as adjuvant therapy with L-dopa in some cases. It was initially developed as an anti-viral treatment and is still used in this capacity.



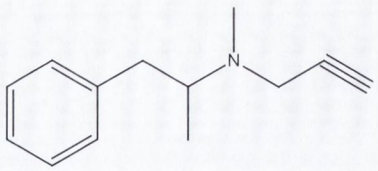
AMANTADINE **(32)**

Figure 1-13: Amantadine, an anti-viral agent that is also used in the treatment of Parkinson's disease

1.3.3.6 Monoamine Oxidase B Inhibitors

The logic behind the development of the MAO-B inhibitor, selegiline **(33)** ("Eldepryl") is that MAO is involved in the metabolism of dopamine and inhibition of the enzyme should prolong the action of L-dopa. Claims of a neuroprotective effect have not yet been fully substantiated. Selegiline is illustrated in Figure 1-14.

Selegiline is metabolised to methylamphetamine **(44)** and amphetamine **(40)** – this is discussed in Section 1.5.2.2; hence, vivid dreams and insomnia are possible side effects. Other adverse effects include mood changes, dizziness, nausea, vomiting, dry mouth, abdominal pain, dyskinesias, blood pressure fluctuations and increased involuntary muscle movements.[16] This less than ideal profile stimulated interest in the development of alternative MAO-B inhibitors. When used as monotherapy it has been estimated to delay the need for L-dopa therapy by 12 months.



SELEGILINE **(33)**

Figure 1-14: Selegiline, a MAO-B inhibitor used in the treatment of Parkinson's disease

Selegiline/(-)deprenyl was developed in the course of research into anti-depressants. Its application in Parkinson's disease has focussed attention on possible roles of MAO in its aetiology, as distinct from an enzyme that processes dopamine. It has been shown to reduce the loss of mesencephalic dopaminergic neurons caused by MPP^+. Its protective action appears to stem from an ability to alter new protein synthesis, which reduces apoptosis caused by a range of toxins and lesions.[28]

1.4 Alzheimer's Disease

1.4.1 Classification and Diagnosis of Alzheimer's Disease

Understanding of the processes that lead to Alzheimer's disease is improving with recent research. It appears to involve a cascade mechanism, whereby production of amyloid plaques leads to neurochemical and general cellular changes which encourage the formation of further plaques, and finally result in neuronal death.

Ultimately, Alzheimer's disease leads to widespread neuronal loss. In its initial stages, the damage is confined to multiple foci.[13] As a result, the symptoms of early Alzheimer's disease are varied. The multifocal deterioration can lead to differences in the type and degree of impairment shown by the sufferer, depending upon the exact location of degeneration. A patient may show significant memory loss of one nature, for example names of people and places, and yet retain information that is processed and stored in a different manner, such as the vocabulary of a second language.

The neuropathology of Alzheimer's disease is well documented. The presence of the characteristic lesions can only be confirmed by an autopsy, so diagnosis is based on clinical criteria and imaging scans. The latter show morphological changes in the brain. However, the extent of such changes varies between patients, and neuronal degeneration is seen in other conditions that produce dementia, so the diagnosis is confirmed only after death.

1.4.2 Aetiology of Alzheimer's Disease

1.4.2.1 Neuropathology

Alzheimer's disease is identified at post-mortem by the presence of mature senile plaques (SPs) and neurofibrillary tangles (NFTs) in the neocortex, hippocampus and subcortical

regions of the brain. Mature SPs are specific for Alzheimer's disease while NFTs may be formed in response to different stresses on the brain, including trauma.[13]

The formation of plaques proceeds from diffuse early plaques to the denser mature SPs, which have an amyloid core encased in dystrophic neurites and microglia. Diffuse plaques are found in the brains of healthy older people, indicating that their formation may be part of the normal aging process. They are also found in the hippocampus of Alzheimer's patients, where they do not progress to SPs. These two circumstances indicate that a pathological process may cause diffuse plaques to develop into SPs.[13]

The number of SPs found in the brain of a subject does not appear to correlate to severity of mental impairment. NFTs seem to proliferate as the condition worsens. NFTs increase in the hippocampus and inferior temporal cortex of non-sufferers. Again, a link with normal aging is suggested.[13]

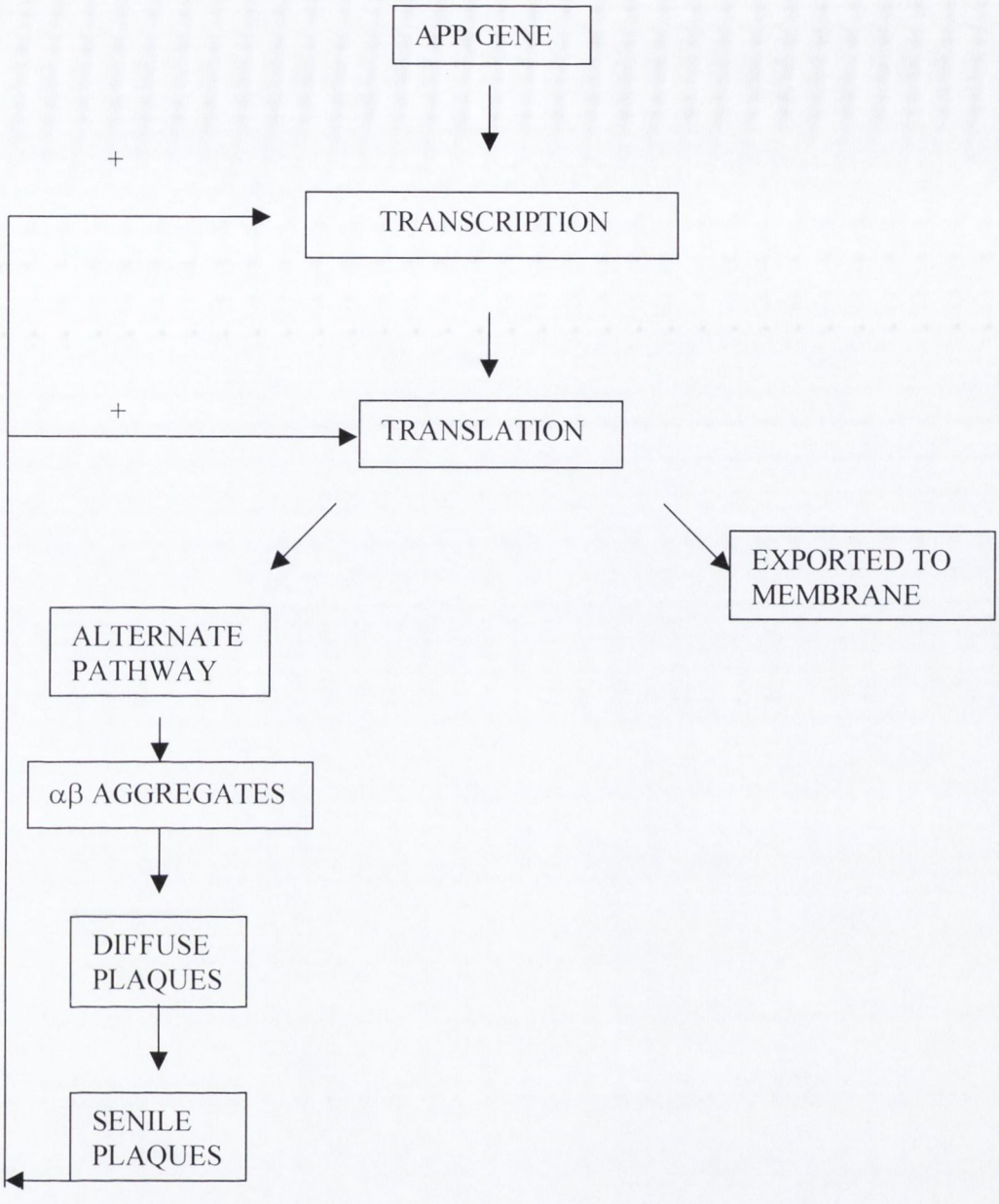
In some cases, amyloid deposits build up in the blood vessels of the brain of an Alzheimer's disease patient, in a manner similar to deposition of lipoproteins on the vascular walls in heart disease. The same dangers accrue to amyloid angiopathy: the flow of blood may be impeded by dislodged fragments, and haemorrhage may ensue.[13]

Another feature, seen only in some diseased patients, is the occurrence of amyloid granules in membrane-lined vacuoles in hippocampal pyramidal cells. This is associated with degeneration of the pyramidal cells, although the mechanism by which this happens is unknown.[13]

Atrophy of the brains of sufferers is seen in the cerebral cortex and overall brain mass is reduced. There is dilatation of the ventricles.[13] The exact location and extent of degeneration varies from patient to patient, so this cannot be used for definite diagnosis despite improvements in scanning techniques.

1.4.2.2 Current Model of Alzheimer's Disease

Early onset AD has been associated with mutation of the gene for APP (amyloid precursor protein, which fragments to provide the material for SPs). In such cases the signs are seen when the individual is 40 years or older. This indicates that the process does not consist simply of over expression of APP, or production of defective APP. A cascade of events is triggered, which gradually accelerates the damage being done (see Scheme 1-2). While it seems that it takes over 40 years for neuronal degeneration to produce clinical signs, the disease is generally fatal within 10 years of diagnosis.



Scheme 1-2: Simplified model of the progress of Alzheimer's Disease

First APP is produced in the normal course of living. The genetic information is transcribed from DNA to mRNA and then transported to the cytoplasm, where it is translated as the protein. It is either exported to the membrane, where it is part of normal physiological function, or is diverted to an alternate pathway. This pathological alternative produces the αβ pleated sheets, which form diffuse plaques. The factors which cause diffuse plaques to mature to SPs have not yet been elucidated. The SPs are surrounded by dendrites and astrocytes; the latter produce factors (such as interleukin I), which damage neurones in the vicinity. The generation of radicals, which can be by-products of this pathway, acts as positive feedback and accelerates the process.

1.4.3 Role of MAOIs in the Treatment of Alzheimer's Disease

It appears that the level of platelet MAO-B activity is elevated in both Parkinson's disease and Alzheimer's disease. However, it is unclear if this increase is due to Alzheimer's alone, as it often co-exists with Parkinson's disease.[25] In fact, Parkinson's disease and Alzheimer's disease occur together at a rate significantly higher than that expected from chance alone.[13]

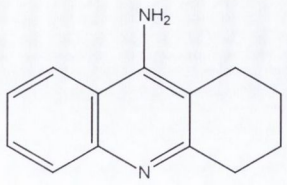
MAO-A activity is at adult levels at birth, but MAO-B becomes more active with the passage of time.[26] Monoamine oxidase may generate radicals that damage neurones. Other mechanisms may also be involved. While the mechanism is still unclear, it has been shown in clinical trials that selegiline (**33**) (the irreversible MAO-B inhibitor) can be useful in cases of Alzheimer's disease. 8 out of 11 controlled trials of the drug in AD sufferers concluded that selegiline was beneficial for cognition, and 2 out of 5 trials showed improved behaviour on the part of subjects.[25]

Milacemide (**47**) (a reversible MAO-B inhibitor) has not had a positive impact on Alzheimer's sufferers in a placebo-controlled trial.

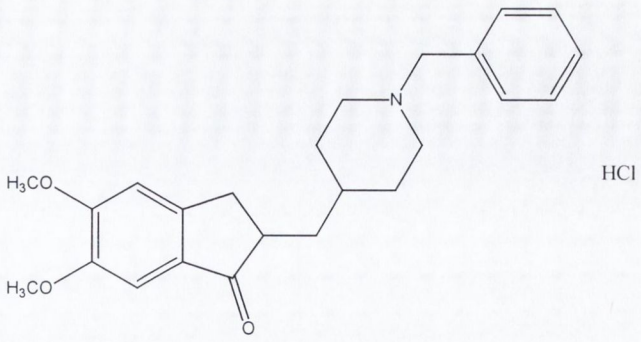
The complex nature of AD suggests that a single agent is unlikely to provide a complete answer. The promising results of trials of selegiline; the elevation of MAO-B in the condition, and the fact that oxidative stress can exacerbate the proposed development of the condition at several points, raise hopes that research on MAO inhibitors may yield improvements in the treatment of the disease.

1.4.4 Role of Acetylcholinesterase Inhibitors in the Treatment of Alzheimer's Disease

It has been noted that the autopsied brains of AD patients show a loss of cholinergic neurons. In addition, anti-cholinergic drugs have been observed to impair memory and thought processes. On this basis several drugs have been prepared which boost cholinergic activity in the brains of AD sufferers. Tacrine **(34)** (marketed as "Cognex") and donepezil **(35)** ("Aricept") have been approved for the symptomatic relief of mild to moderate AD (see Figure 1-15).



TACRINE **(34)**



DONEPEZIL **(35)**

Figure 1-15: Acetylcholinesterase inhibitors used in the treatment of Alzheimer's disease

These act as acetylcholinesterase (AChE) inhibitors. They do not alter the course of the disease but improve memory and cognitive function for some months. An important consideration is the development of AChE inhibitors that are selective for AChE rather than esterases generally, to minimise side-effects.[29]

1.5 Monoamine Oxidase

1.5.1 Structure

Monoamine oxidase is an enzyme found in the brain and peripheral tissues, which catalyses the oxidative deamination of both endogenous amines and those ingested which are then absorbed. It is found in the outer mitochondrial membrane. The reaction produces hydrogen peroxide as well as ammonia, or an amine and the relevant aldehyde.[25]

$$R^1CH_2NR^2R^3 + H_2O + O_2 \rightarrow R^1CHO + NHR^2R^3 + H_2O_2 \quad (I)$$

X-ray crystal structures of both MAO-A[30] and of MAO-B[31] have been prepared and analysed. The A and B forms have subunit molecular weights of 58,700 and 58,000. They are both found as dimers *in vivo*. [30,31] There is 70% coincidence of amino acid sequences.[26] The intron-exon organisation of the genes that code for the two types of MAO is identical, and has 15 exons in each case. The genes are found on the X chromosome. The active sites of the enzymes themselves show 93.9% amino acid sequence identity.[25] Furthermore, the sequence of each isoenzyme is strikingly conserved across a range of species: that of MAO-A in humans, cattle and rats has over 87% identity.[26] This usually indicates that the enzyme concerned is of vital importance, and thus has not been radically altered in the course of evolution.

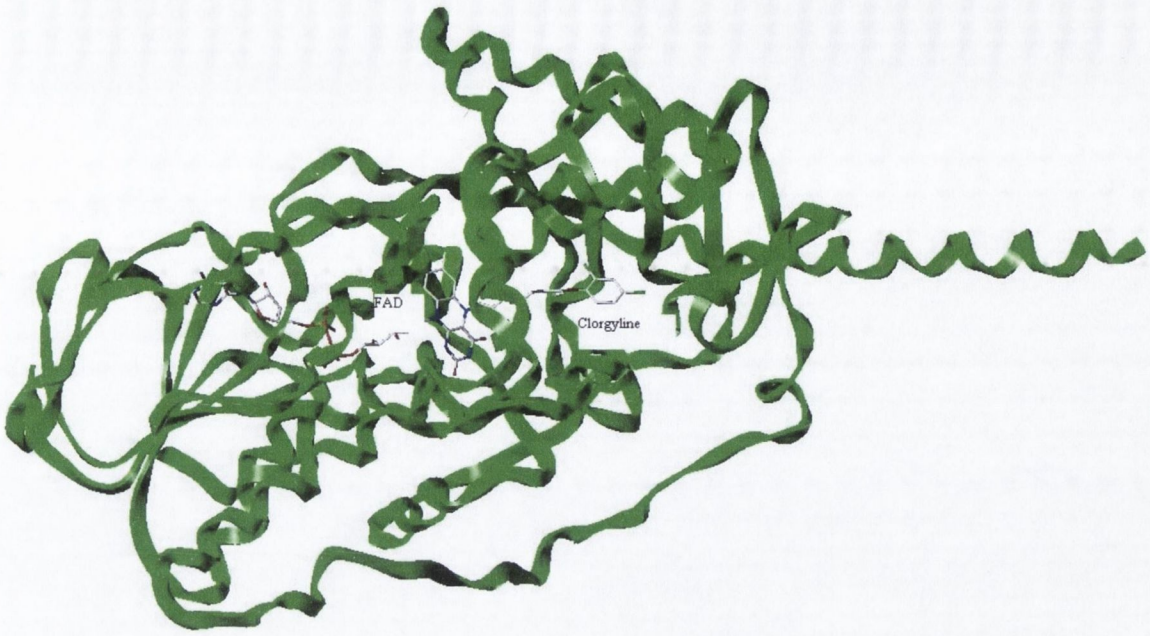
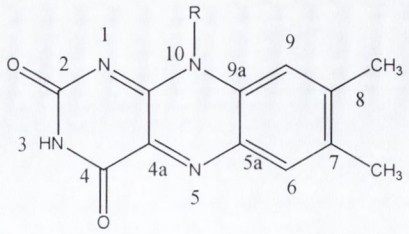


Figure 1-16: Substrate binding site of MAO-A, showing FAD ring and bound clorgyline



Figure 1-17: Substrate binding site of MAO-B, showing FAD ring and bound 1,4-diphenyl-2-butene

Research on MAO of both types focussed on conserved regions. The cofactor flavin adenine dinucleotide (FAD) **(36)** (Figure 1-18) is required for the activity of both isoenzymes. It is buried deep in the enzyme, as may be seen in the representations of the active sites in Figures 1-16 and 1-17.[32] It is linked to the same pentapeptide in both isoenzymes: Ser-Gly-Gly-Cys-Tyr. The carbonyl moieties of FAD induce an attractive zone and a repulsion is spread over the sides of the tricyclic ring; these aspects influence substrate binding.[33]



(36)

Figure 1-18: Flavin adenine dinucleotide, FAD

The binding site of MAO-B has been identified as the residues 62 to 103 and 146 to 220. The simple operation of exchanging the phenylalanine at position 208 in MAO-A for isoleucine converts the enzyme to MAO-B.[26] The binding sites of both isoenzymes are pockets lined by the isoalloxazine ring and aliphatic and aromatic residues. These give it a very hydrophobic character.[32] MAO-B has two pockets separated by a gateway, in which the configuration of Ile 199 is very important. This residue may block a substrate or allow it to lie across both pockets, facilitating inhibition by relatively large molecules.[32] The whole of loop 99-112 acts as a gateway to the active site and is thought to be partly embedded in the membrane.[34] This agrees with studies in the 1980s, which found that both *cis* and *trans* cinnamylamine derivatives had the same affinity for MAO-B, a fact that could only be explained by a large hydrophobic pocket at the active site, or by a site which allowed unusual flexibility.[35]

Both forms of the enzyme contain nine cysteine residues. It has been found that two of the cysteine residues in MAO-A (Cys-374 and Cys-406) are vital for catalytic activity. Three of the cysteines in MAO-B (Cys-156, Cys-365 and Cys-397) are similarly crucial. The Cys-406 and Cys-397 are involved in binding the FAD cofactor at position 8 of the FAD ring (shown in Figure 1-18).[32] This is supported by the finding, in studies using affinity labelling, that FAD modified the cysteinyl residue at 397.[26]

Modification of threonine 158 to alanine heavily reduces activity in MAO-B. This supports the claim for residues 146 through 220 as the binding site, and may also reflect the importance of Cys-156, which is part of the sequence.[26] However, crystal structure analysis indicates that Ile335 (MAO-A) and Tyr326 (MAO-B) are probably the key residues for the determinaion of substrate and inhibitor specificity.[30]

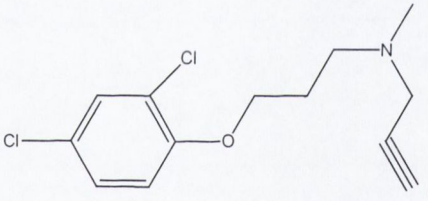
The greater hydrophobic character of the MAO-B active site compared to that of MAO-A has been commented on, and is supported by examinations of structure activity relationships which indicate that a charged substrate enjoys no advantage over its uncharged predecessor, isoquinolines and isoquinolinium ions being the substances in

question.[36] Lipophilicity has been found, unsurprisingly, to be the most important parameter when the influence of lipophilic, electronic and steric dispositions of inhibitors was assessed.[37] A histidine residue in MAO-A was examined in the analysis of the binding of inhibitors with trifluorohydroxyl groups. This residue nestles in a hydrophobic pocket and appears to form hydrogen bonds with inhibitors.[38] The same study emphasised the importance of charge transfer of the inhibitors to the isoalloxazine ring of FAD, which is an electron acceptor.

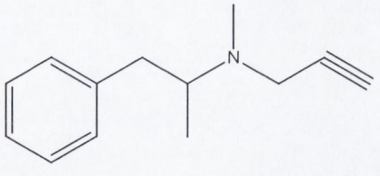
1.5.2 Function of MAO

Initially Hare, who first identified monoamine oxidase in 1928, classified it as "tyramine oxidase".[35] As work on the enzyme progressed it was realised that this was a simplistic descriptor of its function. A decade later Zeller renamed it monoamine oxidase, which better reflects its wide range of endogenous substrates and role in xenobiotic metabolism.[35] It deaminates and oxidises primary, secondary and tertiary amines according to equation I on page 24.[35]

In 1968, Johnston showed that MAO exists as two isoenzymes, one of which was more sensitive to inhibition by clorgyline **(37)** (type A), the other being preferentially inhibited by selegiline **(33)** (type B).[35] Both inhibitors are shown in Figure 1-19.



CLORGYLINE **(37)**



SELEGILINE **(33)**

Figure 1-19: Selective inhibitors of MAO-A (clorgyline (37)) and MAO-B (selegiline (33))

With time, the substrate preferences of the A and B forms were identified as noradrenaline and serotonin, and phenylethylamine and benzylamine respectively. This is a simplification, however, as the specificity of either isoenzyme depends on the concentration of the substrate and the concentration of the enzyme.[26] This allows one isoenzyme to compensate for loss of the other, and for this reason high levels of inhibition

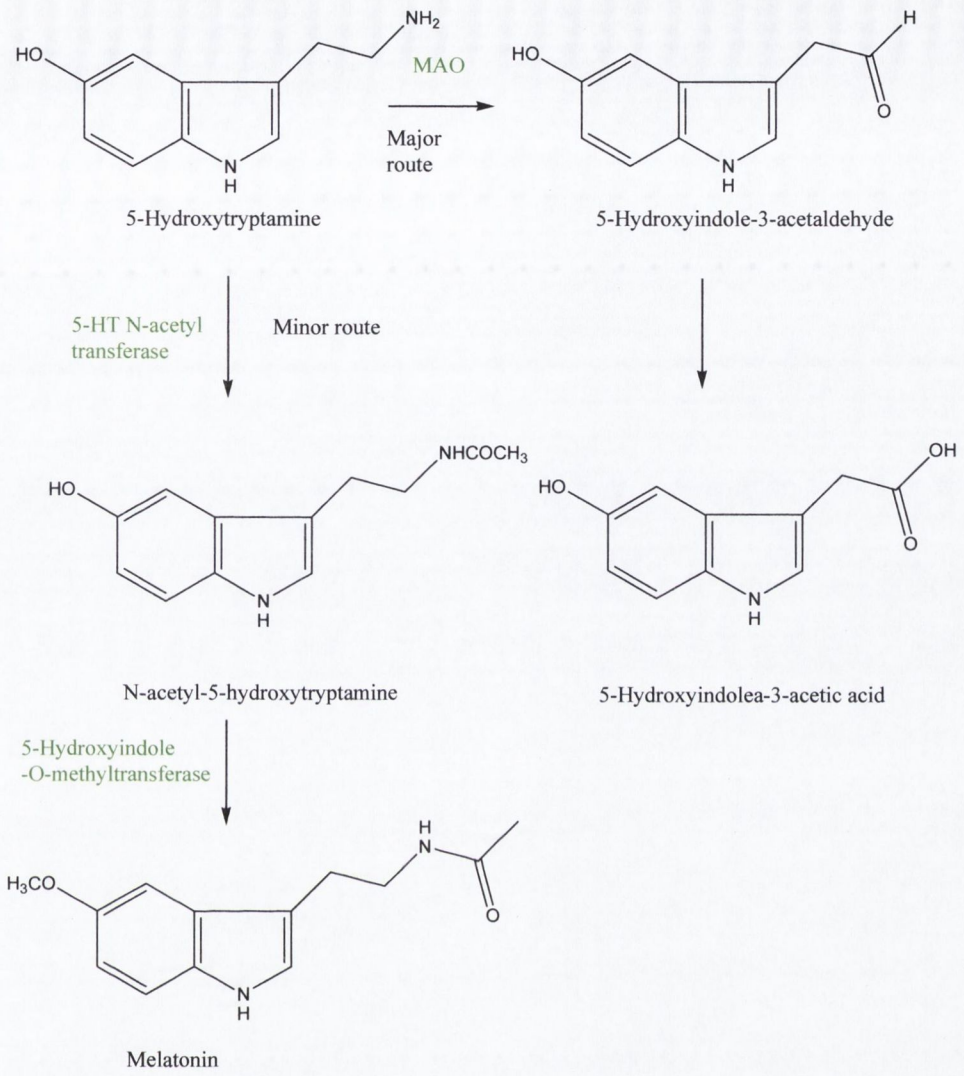
of total MAO activity may be needed in order to elevate levels of a substrate. For example, Green and Youdim estimated that both forms of the enzyme must be inhibited by 85% or greater in order to increase the activity of dopamine or serotonin.[39] Although both enzymes are capable of metabolising dopamine, this function appears to be the prerogative of MAO-A and only devolves to MAO-B when type A is inhibited.[39]

The distribution of the isoenzymes might be expected to shed further light on their functions. Again, a complex picture emerges. Platelet MAO in humans is predominantly type B.[25] It is found in the endocrine pancreas, liver and lungs.[40] MAO-B is also the dominant form in the human brain.[25] MAO-A in humans in found in the exocrine pancreas, liver, kidney, intestine and heart.[40] That in the intestine plays an important role in the mediation of the infamous "cheese reaction" of MAOIs. MAO-A in primate brains is manufactured in the adrenergic neurones of the *locus coeruleus* (LC), and is concentrated in the LC, *substantia nigra* and periventricular thalamus. MAO-B is synthesised in serotonergic neurones in the raphé nucleus and is then found there and in the ependyma and later hypothalamus.[40] The glial cells of the *substantia nigra* seem to contain both forms of the enzyme, as indicated by autoradiography. [40] This may be of importance in the story of Parkinson's disease.

There is a contradiction in the fact that MAO-A preferentially metabolises serotonin but is not found in serotonergic neurones while MAO-B is. One theory advanced is that the enzyme is present to oxidise amines with the potential to act as false transmitters.[26]

MAO-A does not alter in activity with time, while MAO-B increases dramatically. This may be due to the proliferation of glial cells with aging.[26] In humans, the increase in activity begins at 50 to 60 years of age.[25] The same phenomenon has been documented in rats.[15] Incidentally, reduced MAO-B activity in smokers parallels reduced risk for Parkinson's disease.[25] The mechanism of this is unknown, but the fact that cyanide and formaldehyde, both components of cigarette smoke, make adducts with amino groups in MAO, suggests that the formation of such adducts may alter the conformation of the enzyme and reduce its activity.[26]

At a simple level, MAO oxidatively deaminates serotonin (Scheme 1-3), noradrenaline (Scheme 1-4) and dopamine (Scheme 1-5).

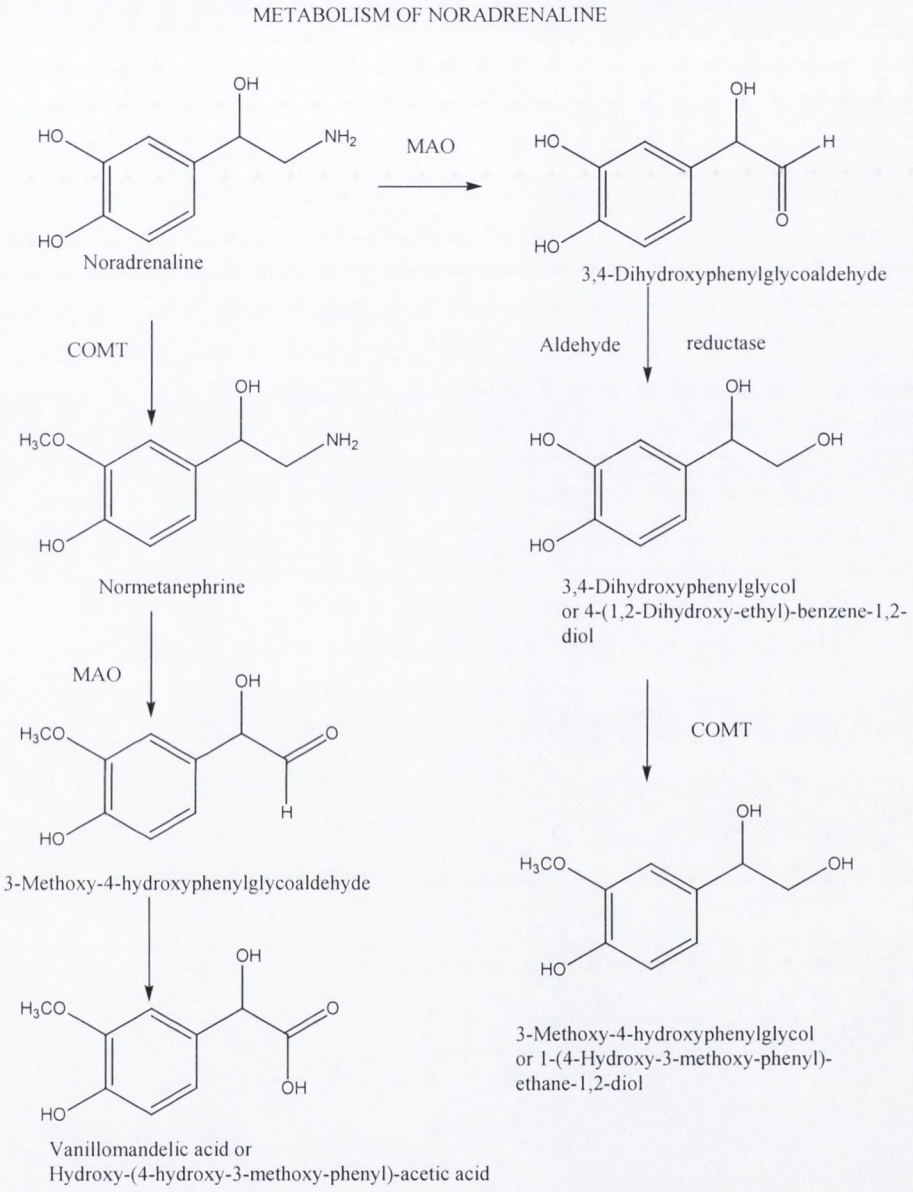


Scheme 1-3: Metabolism of serotonin

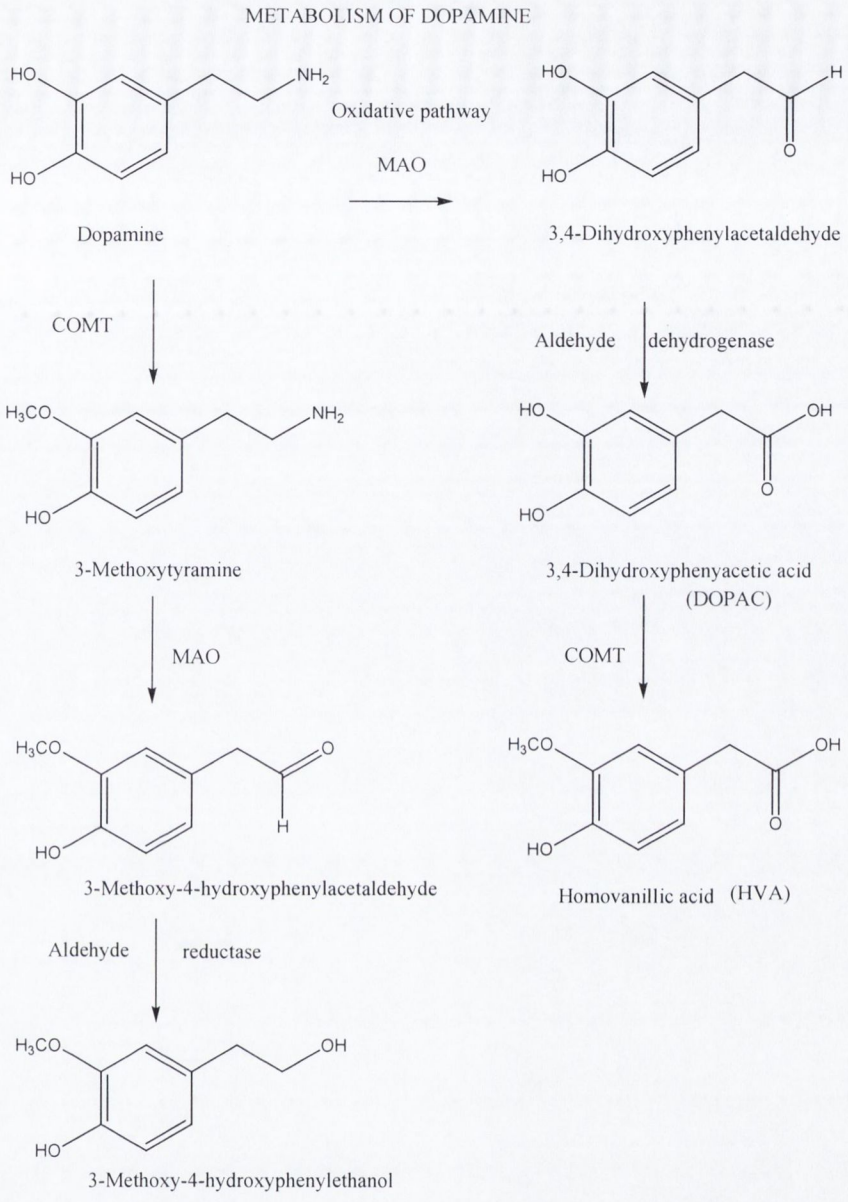
Exogenous amines are treated in the same way. MAO-A deaminates adrenaline and octopamine as well. MAO-B has a range of substrates, with benzylamine, phenylethylamine, methylhistamine, N-acetylputrescine, MPTP, N-phenylamine, octylamine and milacemide (**47**) all being metabolised by this enzyme. Tyramine, tryptamine, kynuramine and 3-methoxytyramine are metabolised by both forms.[25] However, the "cheese effect" is in practice seen only with MAO-A inhibitors, as gut and hepatic MAO are mainly of this type.

Monoamine oxidase only accomplishes the first step of the metabolism of amines. Aldehyde dehydrogenase is necessary to deal with the aldehydes it produces. This raises the possibility not only of eliminating some molecules from the body, but also of providing building blocks for other, more complex molecules such as tetrahydroisoquinolines. In addition, monoamine oxidase may be the principal metabolic enzyme in the brain, but other agents such as catecholamine-O-methyl-transferase, play a role both here and in the

periphery. In fact, the enzymes intervene at a series of points along the metabolic pathway, as illustrated by the Schemes 1-3, 1-4 and 1-5.



Scheme 1-4: Metabolism of noradrenaline



Scheme 1-5: Metabolism of dopamine

Monoamine oxidase is situated in the outer mitochondrial membrane in neurones. Its role is thus that of metabolising excess neurotransmitter *within* the presynaptic cleft. Most of the neurotransmitter released into the synaptic cleft is transported into the presynaptic area by the appropriate reuptake mechanism. The majority is restored to vesicles while MAO metabolises a small proportion. Some of the released neurotransmitter remains in the synaptic cleft, where COMT metabolises most of what is left, with the balance binding to extraneuronal tissue. From this overview, it is immediately apparent that the reuptake mechanism, rather than the metabolic enzymes, mainly dictates the level of neurotransmitter in the synaptic cleft.[41]

Inhibition of the enzyme causes a transient increase in the level of monoamines released. The effect is seen within the first few days of therapy. After three weeks of treatment with a MAOI, brain monoamine levels return to pre-treatment levels, even when a therapeutic effect is witnessed. In fact, relief of symptoms is customarily not seen for two to three weeks after commencement of therapy. That it is not a simple case of resetting the sensitivity of the receptors is illustrated by the propensity to relapse seen in patients whose anti-depressant therapy is discontinued too rapidly.[10]

1.5.3 Clinical Use of Monoamine Oxidase Inhibitors

The clinical use of MAOIs and RIMAs has already been discussed, along with the profile of those currently in use. The monoamine theory of depression was intimately connected with the discovery of these agents.

1.5.3.1 Irreversible Inhibitors of MAO-A

Isoniazid **(38)** is a hydrazide, having a terminal $NHNH_2$. Iproniazid **(39)** itself is a hydrazide derivative with an isopropyl group, as shown in Figure 1-20.

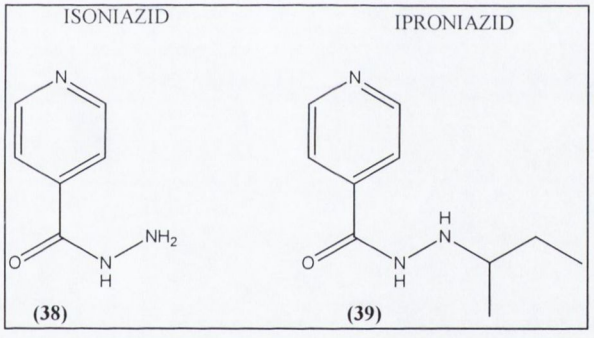


Figure 1-20: Original MAOIs

Phenelzine **(5)** is similar to isoniazid in structure, but does not have a carbonyl or a pyridine ring, substituting a CH_2 and benzene ring respectively. Isocarboxazid **(6)** is closer to iproniazid, but the carbonyl branches from a nitrogen substituted pentadienyl ring and an aromatic ring replaces the terminal isopropyl group, as may be seen in Figure 1-21. It has been shown that hydrazine itself does not inhibit MAO *in vivo*.[26]

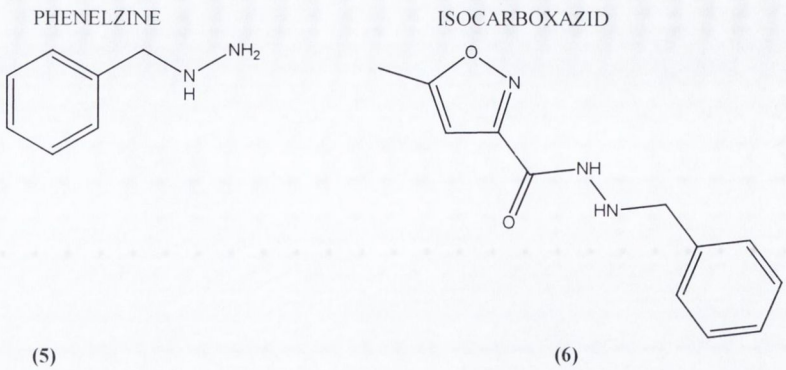


Figure 1-21: Hydrazide inhibitors of MAO

Tranylcypromine **(4)** does not fit into this chemical category. It is an amine of the amphetamine family (see Figure 1-22). It thus has stimulant properties, which are the basis of the BNF (British National Formulary) conclusion that phenelzine **(5)** and isocarboxazid **(6)** are safer.[10] Amphetamine **(40)** is one of its metabolites.[9] Besides the implications this carries for stimulant, hallucinogenic and dependence potential, the fact that amphetamine is itself a reversible inhibitor of MAO-A confuses the picture.

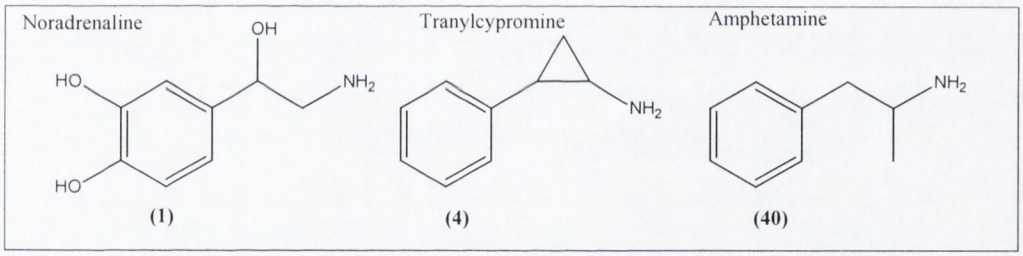
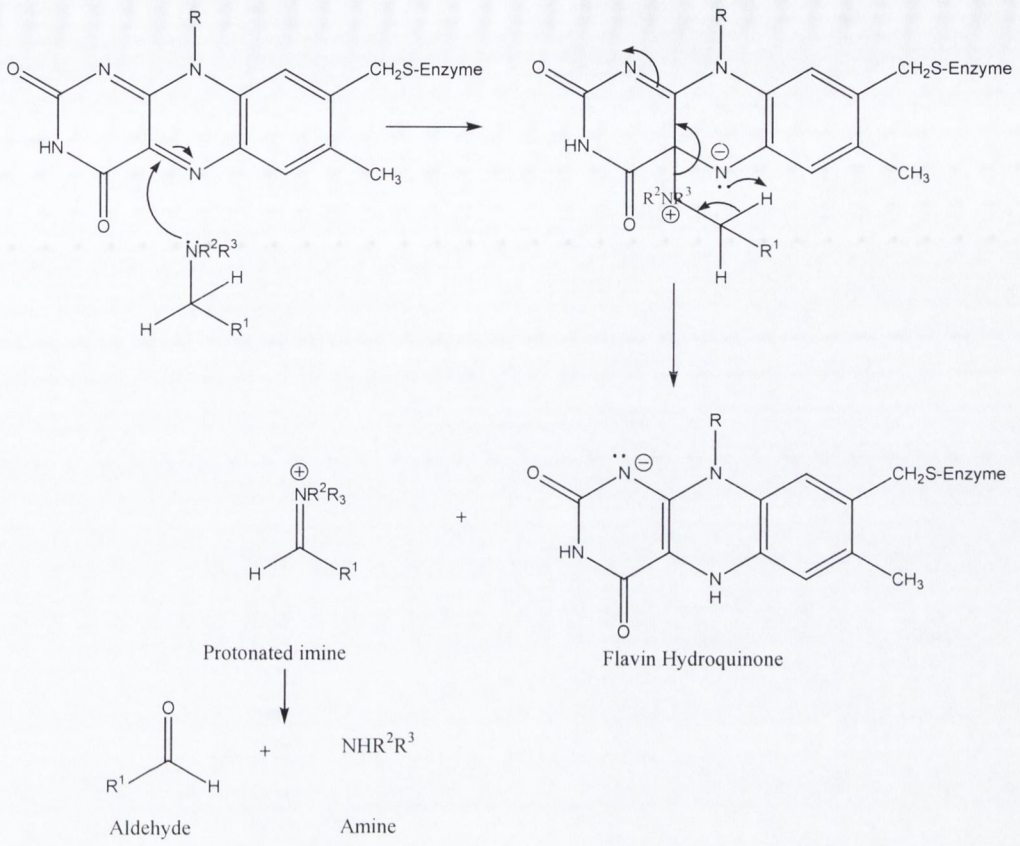


Figure 1-22: Amphetamine type substrate and inhibitors of MAO

Both classes of MAOI are inactivated by hepatic acetylation. Occasionally idiosyncratic hepatotoxicity is shown by the MAOIs.[10] This translates as unpredictable liver damage by the agents, unrelated to dose or known concurrent conditions or medication. It is suspected that such cases are due either to subtle differences in the metabolic enzymes of the patient, caused by genetic variation, or allergic reactions.

The mechanism underlying the oxidation reaction is not known with certainty, but is considered likely to be the following: [32]



Scheme 1-6: Proposed polar nucleophilic mechanism of MAO oxidation

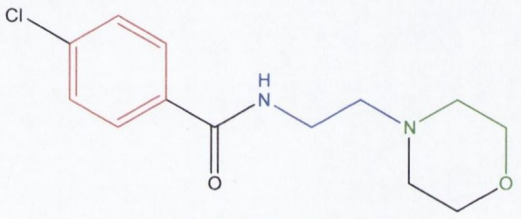
The mechanism of binding the irreversible inhibitors to MAO involves two steps. In the first step, a reversible complex is formed with the FAD cofactor. The second step creates an irreversible covalent bond through the FAD cofactor.[33] In support of this mechanism, it has been observed that inhibitors of MAO-A contain a plane of attractive potential, spread over an aryl ring.[33] The heteroatoms may also be involved.

Thus, the inhibitor proceeds by electron transfer, but forms an adduct with the cofactor rather than allowing the final hydrolysis. This charge transfer bonding renders the enzyme unavailable for interaction with substrates, and it is only by regeneration of the enzyme that the body may overcome the inhibition. Central effects therefore last for up to 14 days. This is the time taken to replenish MAO in brain tissue, although turnover varies in tissues.[9]

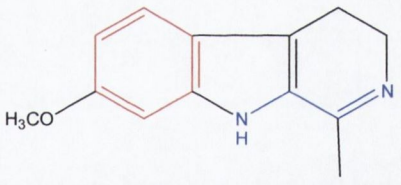
1.5.3.2 Reversible Inhibitors of MAO-A

Reversible inhibitors of MAO-A (RIMAs) may be divided into competitive, non-competitive and uncompetitive types. So far, only the competitive type is used as a drug. The substrates and drug compete for the available MAO. Both harmaline **(41)** and

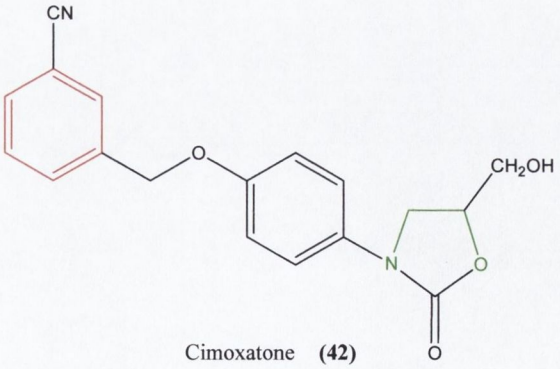
cimoxatone **(42)** were found to be reversible inhibitors, but dissociated slowly from the enzyme.[9] They were taken as a model and a more rapidly dissociating molecule was developed. This was moclobemide **(7)**, marketed as "Manerix." Moclobemide, already in clinical use, proceeds by a similar mechanism to the irreversible species, but does not form a covalent bond with FAD. It may be displaced by higher concentrations of substrates, such as tyramine. It thus is not involved in serious cheese reactions to the same extent as the irreversible MAOIs.[9] All three compounds are shown in Figure 1-23, with common structural features highlighted.



Moclobemide **(7)**



Harmaline **(41)**



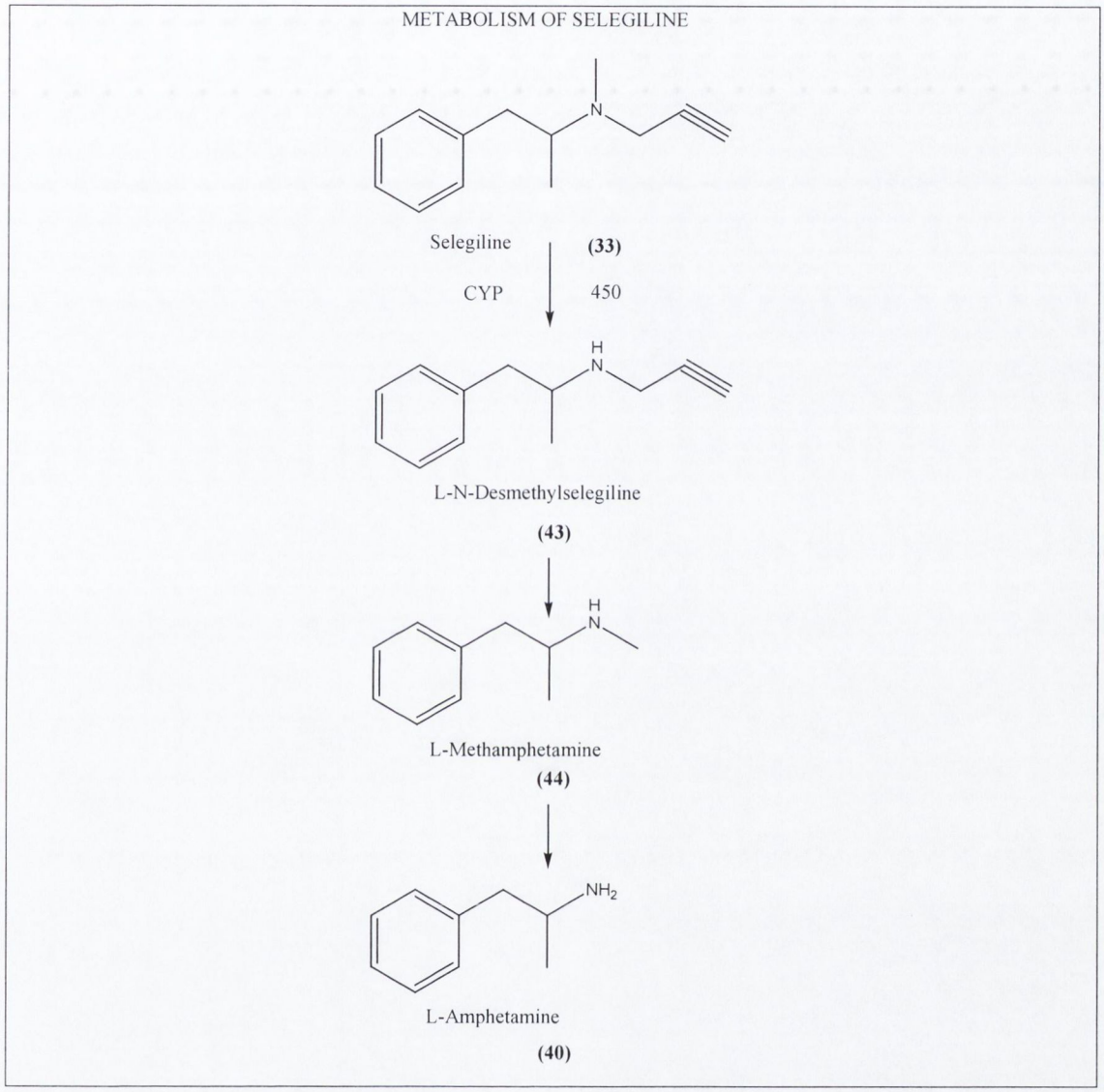
Cimoxatone **(42)**

Figure 1-23: Reversible inhibitors of MAO-A

1.5.3.3 Irreversible Inhibition of MAO-B

Selegiline **(33)** binds in a reversible reaction to both MAO-A and MAO-B (like rasagiline, as shown in Figure 1-24). The kinetics involved with MAO-B are, however, more favourable to the second step, which forms a covalent bond. Selegiline is therefore

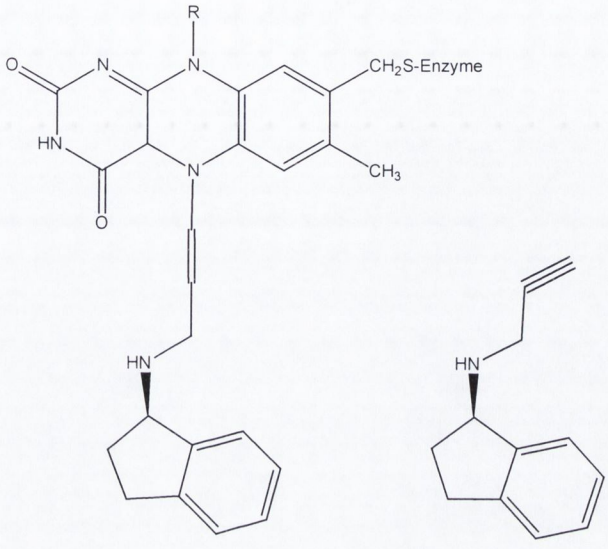
considered specific for MAO-B.[25] The propargyl type inhibitors bind to the FAD with the longer axis of the inhibitor perpendicular to the long axis of the isoalloxazine ring. [32] High doses will inhibit both forms of the isoenzymes and provoke a hypertensive crisis. Such doses are not used clinically.



Scheme 1-7: Metabolism of selegiline (33)

Selegiline is metabolised first to L-N-desmethylselegiline **(43)**, then to L-methamphetamine **(44)** and finally to L-amphetamine **(40)** (see Scheme 1-7). In the case of amphetamine the laevorotatary enantiomer is the R form. The dextrorotatary S form is much more potent. However, vivid dreams are reported as a side effect of selegiline treatment (see Section 1.3.3.6). The efficacy of desmethylselegiline as MAO-B inhibitor ensures prolongation of the action of selegiline. [25]

As already noted, the propargyl group is considered to favour recognition of the molecule by the active site of MAO-B.[9] Rasagiline **(45)** also has a propargyl moiety attached to the amine, and the bound form is shown in Figure 1-24.



Bound Rasagiline Rasagiline **(45)**

Figure 1-24: Binding of MAO inhibitors with propargyl moieties to FAD in the active site

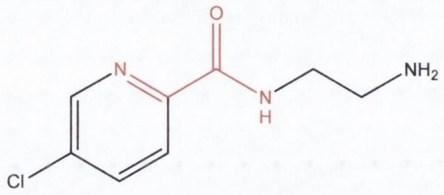
As an additional benefit of the inhibition of MAO-B, it has been suggested that phenylethylamine levels are raised. This endogenous amine is a preferential MAO-B substrate.[35] As previously mentioned, it is a neuromodulator which is linked to increased activity of dopamine, both endogenous and derived from L-dopa.[42]

Rasagiline **(45)** is still being tested, and has been found to be 5 times more potent than selegiline *in vivo*.[25] It too is irreversible. This does not pose problems with significant adverse reactions. Unlike selegiline, it is not metabolised to an amphetamine; its metabolite is aminoindan.[42]

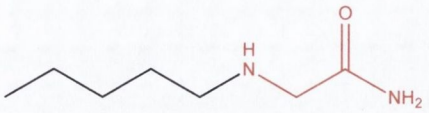
1.5.3.4 Reversible inhibitors of MAO-B

Inhibition of monoamine oxidase B may also be reversible. This class of inhibitor has been modelled on moclobemide, a RIMA, rather than MAO-B specific irreversible inhibitors. The leading compound is lazabemide **(46)**. It was developed from a metabolite of moclobemide. It is active only over a time span of 12 to 24 hours, but is highly specific for MAO-B. It displays almost no activity against MAO-A, even *in vitro*. It is finally

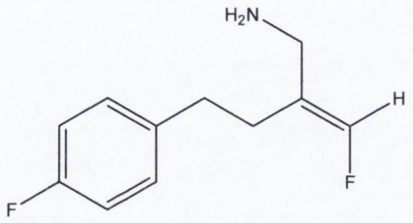
metabolised by MAO to N-(2-aminophenylacetic acid)-5-chloro-2-pyridine-carboxamide. [25]



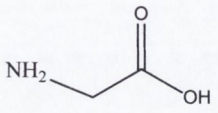
Lazabemide **(46)**



Milacemide **(47)**



Mofegiline **(48)**



Glycine **(49)**

Figure 1-25: Reversible inhibitors of MAO-B

Milacemide **(47)** echoes part of the lazabemide **(46)** structure. It also bears an affinity to glycine **(49)**. In fact, it is metabolised to glycinamide and pentanal. It combines partial reversible inhibition of MAO-B with a similar profile against MAO-A. Propargylamine derivatives of milacemide **(47)** have also been developed and inhibit MAO-B. [25] Mofegiline **(48)** does not possess these structural commonalities. All these reversible inhibitors are rapidly absorbed and penetrate the CNS. Rasagiline **(45)** reaches maximum plasma levels in less than 30 minutes.[25] A wide range of MAO inhibitors have been examined to elucidate the kinetics of the process. Very few have progressed to clinical use. Among the candidates unsuitable or undeveloped for clinical applications are the cinnamylamines and acetylenic inhibitors. In the guise of clorgyline and pargyline the latter class has been used to probe MAO activity *in vitro*.

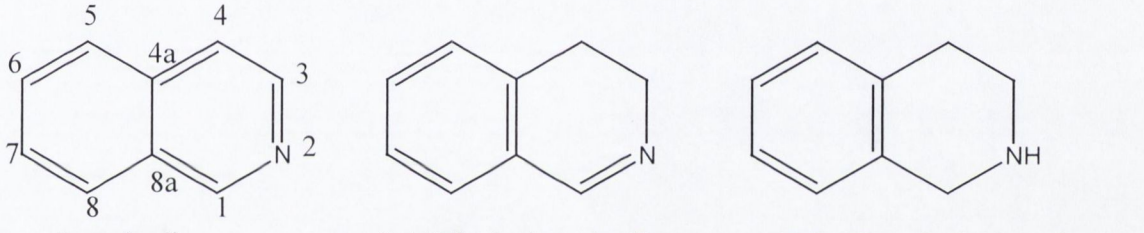
Coumarin derivatives have been studied and some have been shown to act as both MAO inhibitors and as acetylcholinesterase inhibitors.[43-46] This is interesting, in the light of ongoing research into AChE inhibitors for use in AD. Inhibitory activity and selectivity towards MAO-B have been reported for 7-benzyloxycoumarin derivatives.[46]

It also suggests that the structurally similar azanaphthalene family may be worth investigating for joint MAO and AChE inhibitory activity. Comprising quinolines, isoquinolines and quinazolines, this group has been speculated to be involved in the pathogenesis and the prevention of Parkinson's disease.

1.6 Azanaphthalene Derivatives

The research work in this thesis is an investigation of the effects of tetrahydroisoquinolines on MAO and AChE. Isoquinolines and tetrahydroisoquinolines have been investigated for explanations of alcoholism and Parkinson's disease. As yet, there is no consensus on a definite role for these agents. It has been established that they possess activity against both forms of MAO; that some agents induce parkinsonism in primates and appear to act via a mechanism like that of MPP^+; that others of these agents protect against parkinsonism, and that levels of salsolinol in the brains of alcoholics is lower than normal until they are intoxicated.

1.6.1 Structure of Isoquinolines and Related Compounds



Isoquinoline **(50)** 3,4-Dihydroisoquinoline **(51)** 1,2,3,4-Tetrahydroisoquinoline **(52)**

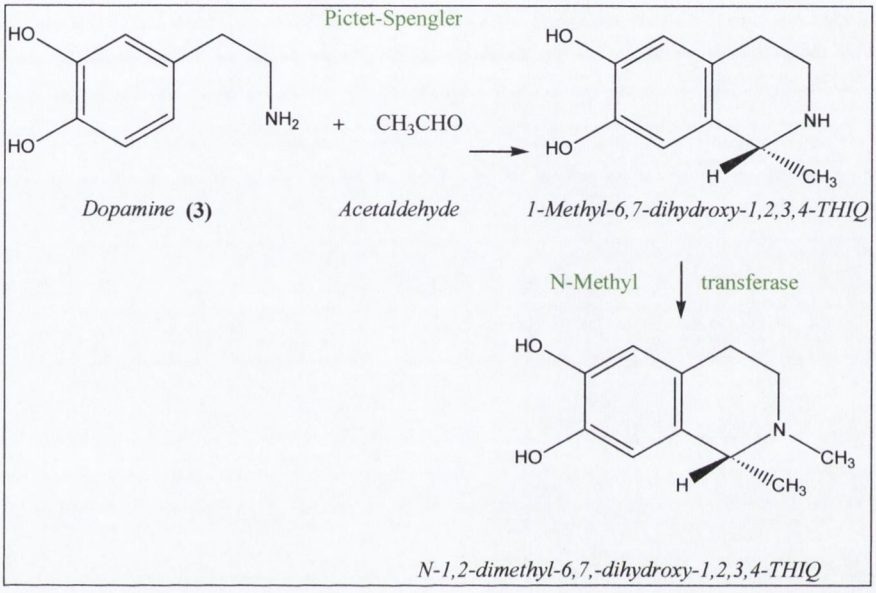
Figure 1-26: The main types of isoquinoline nucleus

The isoquinoline nucleus **(50)** consists of two aromatic rings, one with a nitrogen as part of the skeleton. The second ring must be planar, so that the delocalised electrons of the π orbitals may be shared. Dihydroisoquinolines **(51)** (DHIQs) share the same numbering system and tetrahydroisoquinolines **(52)** (THIQs) have an aliphatic second ring. The aliphatic ring in THIQ is more flexible than its aromatic counterpart, so the molecule may adopt either of two half chair conformations.

1.6.2 Biosynthesis of Isoquinolines

The condensation of an aldehyde (acetaldehyde) and an amine (dopamine **(3)**) can occur without enzymatic intervention under physiological conditions, and *in vivo* results in the formation of tetrahydroisoquinolines, as outlined in Scheme 1-8.[47] The Pictet-Spengler reaction, as this is called, may be used in the laboratory also. Tetrahydroisoquinolines can cross the blood brain barrier, and are found in a range of foods: flour, banana, cheese,

boiled sardine, boiled beef and eggs.[22] However, it seems likely that at least some are synthesised *in vivo*, as the ratio of R/S differs between the plant and animal kingdoms. 1-Methyl-1,2,3,4-tetrahydroisoquinoline, for example, occurs with a R/S ratio of 0.24 in wine but a ratio of 0.6 in mouse brain.[24] The tetrahydroisoquinolines are metabolised by methyltransferases and then monoamine oxidase, for which they act as substrates. The following scheme illustrates the process for THIQ formation from dopamine.



Scheme 1-8: Pictet-Spengler reaction *in vivo*

1.6.3 Pharmacological Role of Isoquinolines

Initial interest in the tetrahydroisoquinolines (THIQs) arose from their widespread occurrence in plants. Possible pharmacological uses for these compounds were eagerly sought. In 1969, 1-dimethoxybenzyl-6,7-dihydroxytetrahydroisoquinoline was shown to inhibit rat liver monoamine oxidase. The same group showed 1-dimethoxybenzyl-6,7-dihydroxytetrahydroisoquinoline also inhibited COMT.[48]

It was established that the main metabolic pathway for tetrahydroisoquinolines is that of O-methylation of the hydroxyl groups, usually by COMT. Thus, they act as inhibitors and substrates of the enzyme, and competitively inhibit the metabolism of dopamine.[48] N-methyltransferase has lately been implicated in the metabolism of THIQs, and may play a role in activating them as neurotoxins, as it does MPTP.[24]

Work initially focussed on 6,7-dihydroxytetrahydroisoquinolines, and established that the structural requirements for MAO inhibition were less flexible than for COMT. The latter enzyme tolerated substituents at positions 2 and 4.[48] O-methylation reduced the potency and selectivity of MAO inhibition. It has since been established by research in this laboratory that when the 6,7-tetrahydroisoquinolines are substituted at position 3 with a

methyl group the inhibition of COMT *in vitro* is increased, but MAO inhibition is less efficient.[47]

1.6.3.1 Role in Parkinson's Disease

It has been proposed that some THIQs may be the endogenous agents, which cause Parkinson's disease. This is based on their structural similarity to MPTP, and the fact that *in vitro* they display toxicity by the same mechanism. THIQs inhibit complex I in mitochondrial respiration. This should not be fatal for the mitochondria, as complex II provides an alternative. By blocking α-KGDH, which provides the succinate for complex II, THIQs inhibit this pathway also. The mitochondria are injured by this combination of actions.[22]

Isoquinolines of different types have been shown to have these properties. However, take-up by the mitochondria appears to be encouraged by a positive charge on the molecule. THIQs have a pK_a of about 9, and are positively charged at physiological pH. N-methylisoquinolinium and 1,2,3,4-tetrahydroisoquinoline have been shown to accumulate in intact mouse brain mitochondria.[22]

Most damning evidence is that provided by parkinsonism induced in primates using 1,2,3,4-THIQ itself and the closely related 1-benzyl-1,2,3,4-THIQ. Even so, the case is not complete. Even where 1,2,3,4-THIQ was shown to induce parkinsonism, no destruction of dopamine neurones was found after administration of THIQ for up to 104 days.[49] Although benzyl-THIQ accumulated in the monkey's brain, it showed no preference for the *substantia nigra*.[50]

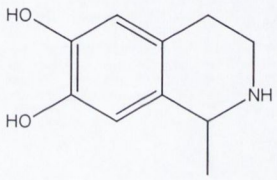
A *protective* role seems likely for another THIQ. 1-Methyl-1,2,3,4-tetrahydroisoquinoline is depleted in the brain of human sufferers of Parkinson's disease. When MPTP is used to engender parkinsonism in a mouse model, the level of 1-methyl-THIQ drops. The action attracted interest in possible differences in the activity of the R and S enantiomers. The study carried out once more showed that unsubstituted THIQ itself induced parkinsonism, but the racemic mixture and R-1-methyl-THIQ prevented this. The protection was monitored in terms of mouse movement, levels of dopamine and loss of tyrosine hydroxylase in the *substantia nigra pars compacta*. The R enantiomer successfully prevented reduction in levels of dopamine and its metabolites, as well as preserving TH. As a result, no bradykinesia developed in the treated mice.[51]

The protective role of 1-methyl-1,2,3,4-tetrahydroisoquinoline (1-MeTHIQ) was underlined by a study in which rotenone was used to induce a Parkinson's disease-like state in rats. From this it appears that 1-MeTHIQ may protect against radical mediated

oxidative damage of intra-cellular structures. Rotenone shifts dopamine catabolism towards the oxidative pathway which produces DOPAC, HVA and free oxygen radicals (see page 31). 1-MeTHIQ shifts catabolism back towards O-methylation, which does not produce high levels of the damaging radicals. It has been hypothesised that 1-MeTHIQ frustrates the catabolism of dopamine by the oxidative pathway by inhibiting MAO.[52]

1.6.3.2 Role in Alcoholism

The first flurry of investigation into THIQs was spurred by the discovery that the level of salsolinol **(53)** (shown in Figure 1-27) in the brain of sober alcoholics was lower than normal.[24] Intoxicated alcoholics, on the other hand, had normal levels of CNS salsolinol. The tantalising theory that alcoholics drink in order to elevate unnaturally low salsolinol levels thus emerged. Animal models did not all support this.[48] A link between THIQs and alcoholism is indicated, but its precise nature has not yet been defined.



Salsolinol **(53)**

Figure 1-27: Salsolinol

1.6.3.3 Effects on Endogenous Amines

The interactions of THIQs and amines have been examined. Dihyroxy-THIQ is transported by vesicles in the neurone. Its uptake, and that of other THIQs, is blocked by cocaine and desmethylimipramine; uptake is by a transporter, not a passive process. Some THIQs block uptake of norepinephrine and dopamine by synaptosomes.[48]

It was noted in 1977 that THIQs inhibited tyrosine hydroxylase.[48] Furthermore, it has been demonstrated that 1,2,3,4-THIQ reduces both the activity of tyrosine hydroxylase and the level of the enzyme. The latter effect may be due to depletion of the enzyme or loss of the neurones in the *substantia nigra* in which it is stored.[53]

This prevents the first step of catecholamine synthesis. Thus, THIQs reduce the level of biogenic amines synthesised.[24]

However, the proven inhibition of MAO by THIQs and other isoquinolines tends to raise levels of monoamines, at least temporarily. The profile of inhibition has been examined to determine structure activity relationships. Inhibition is competitive and reversible. Some THIQs serve as substrates for the enzyme after N-methylation, but this was not observed in the study.[36]

Generally, THIQ derivatives are more active inhibitors of MAO-A than their isoquinoline counterparts. This has been ascribed to their lower lipophilicity. Substitution at position 6 or 7 with methoxy or methylenedioxy groups increases activity; electron-donating groups are favoured at these positions. Charge delocalisation may also facilitate inhibition of MAO-A. Basicity seems to enhance selectivity for MAO-A.[36]

MAO-B has a more hydrophobic active site. As previously discussed, a positive charge does not appear to make a difference to inhibition of MAO-B. The presence of a methoxy or methylene dioxy group on the THIQ at position 6 is unfavourable to activity, while at position 7 it augments it, relative to the equivalent isquinoline.[36]

Clearly, although there is much information available about THIQs and the other isoquinolines, no conclusions can be drawn on their global impact *in vivo* in humans. Further investigation to shed light on the action of these compounds on enzymes would help to clarify their position. Study of a series of THIQs might allow the cause of Parkinson's disease to be identified. Their capacity to inhibit MAO-B suggests that a THIQ agent might have potential as a treatment for Parkinson's disease, and even Alzheimer's disease. Ironically, both cause and cure may be pursued simultaneously. The ability of THIQs to inhibit MAO-A may have applications in the treatment of depression.

1.6.4 4-Methylthioamphetamine

The amphetamines are α-methyl-substituted primary amines. Amphetamine **(40)** itself has obvious structural similarities with the main neurotransmitters (noradrenaline **(1)**, dopamine **(3)**, 5-hydroxytryptamine **(2)**) as well as the hormone adrenaline **(54)**. These common features are highlighted in Figure 1-28. The amphetamines can be cyclised to form dihydroisoquinolines, so the same structural elements can be seen in the dihydroisoquinolines and derived tetrahydroisoquinolines, such as salsolinol **(53)**, in Figure 1-27.

1.6.4.1 History of Amphetamines

Amphetamine **(40)** itself, 1-phenyl-2-propylamine, was synthesised in 1887 by Edeleano. Following investigations in the 1920s by Alles, it was used for its sympathomimetic activity.[54] More specifically, it was employed as an agent to aid weight loss. However, the hyperactivity and insomnia, which it invariably causes via central stimulation, caused it to fall out of favour. In addition, abuse of amphetamine and related substances caused concerns, which further curtailed its availability.

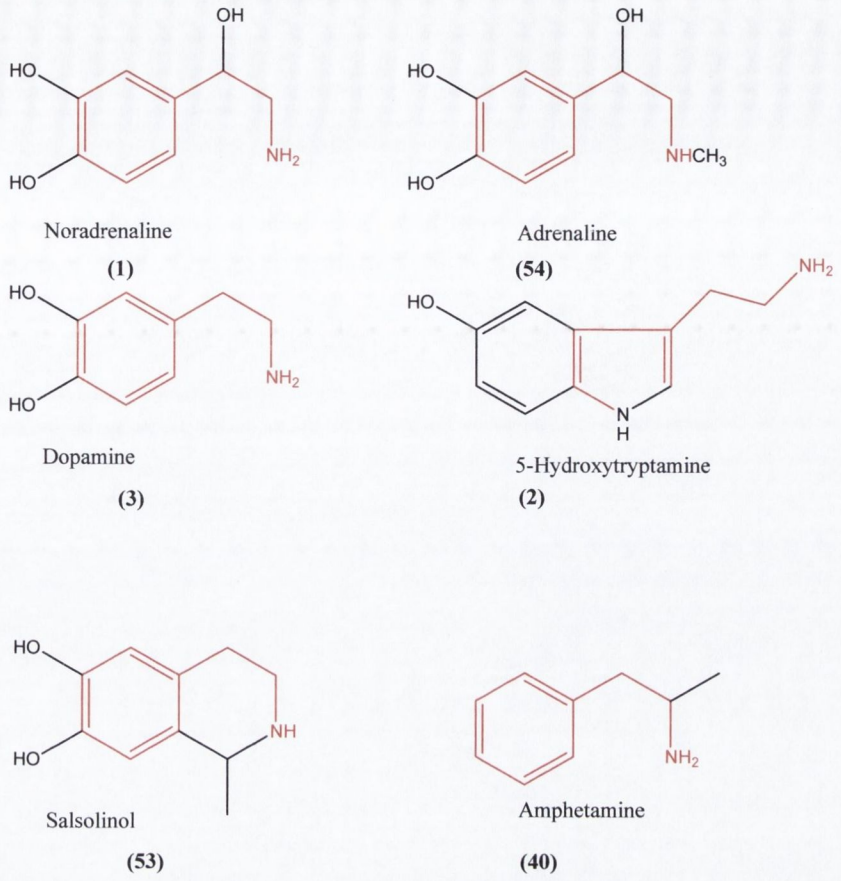


Figure 1-28: Structural similarities of amphetamines and isoquinolines

1.6.4.2 Action of Amphetamines on MAO

The amphetamine family of amines are reversible inhibitors of monoamine oxidase. Although not specific RIMAs, they are greatly more active against MAO-A than against the B form. This is intriguing, as structurally they are so similar to phenylethylamine, which is a preferential MAO-B inhibitor. Furthermore, selegiline **(33)** is essentially an amphetamine with a propargyl substituent, which modifies the amine. As mentioned in the discussion of MAO-B irreversible inhibitors, it is regarded as an irreversible inhibitor of MAO-B and does not cause a cheese reaction at clinical doses. However, it is the second step in the irreversible inhibition, which confers its specificity.

As well as inhibiting monoamine oxidase, the amphetamines cause release of both noradrenaline and dopamine from neuronal vesicles. They also prevent reuptake. A dramatic increase in the neurotransmitter levels in the synaptic cleft follows these multiple actions.

At a molecular level, the ability of an amphetamine to cause release of amines seems to be related to appropriate substituents at the *para* or 3,4 positions. Small, electronegative groups confer neurotoxicity.[55] The halogens chlorine and bromine generate this effect, but fluorine does not.[56] Substitution at position 4 only, seems to confer the greatest potency.

Sulfur's hydrophobicity and reduced electronegativity compared to chlorine gives it advantages, which are reflected by the low doses of 4-methylthioamphetamine (4-MTA) and 4-ethylthioamphetamine needed to inhibit MAO-A (IC_{50} 0.2μM and 0.1μM respectively).[57] Some capacity for electron donation must be required.[57]

While the potency may be varied by changing the substituents, especially that at position 4 of the aromatic ring, selectivity is not affected. All such amphetamines preferentially inhibit MAO-A.[57] Modification of the amine moiety, for example with a propargyl group, will cause preferential inhibition of MAO-B.

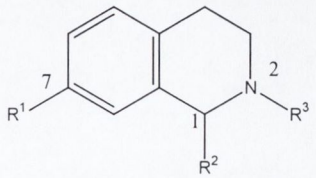
The aetiology of depression shows some hormonal influence. It is worth noting that some amphetamine derivatives, such as 4-methylthioamphetamine, can stimulate the secretion of ACTH, corticosterone, prolactin, oxytocin and renin in a dose-dependent fashion.[58] Investigation of further derivatives might help to explain the deep depression which may follow an amphetamine high, and such understanding could lead to improved anti-depressants.

The interesting profile of 4-MTA and its proven activity against MAO-A made the synthesis of isoquinoline analogues of this compound a worthwhile goal.

1.7 Summary and Objectives

Understanding of depression, Parkinson's disease and Alzheimer's disease is constantly evolving. It is already apparent that inhibiting monoamine oxidase may at least play a role in treatment. Further evidence of the importance of MAO-B in the production of alleged neurotoxins in the case of Parkinson's, and of radicals in the evolution of Alzheimer's disease, intimates that MAO control might even have a part to play in prevention.

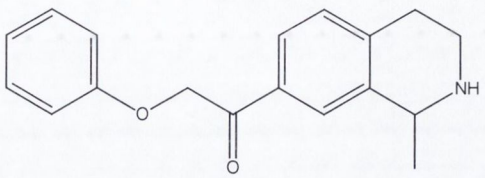
Figure 1-29 illustrates the numbering scheme of the isoquinoline nucleus. In this work, the first investigations involved introduction of a 7-carboxyamido group at position 7 of the tetrahydroisoquinoline nucleus, and examination of the effects of varied substitutents on the inhibition of MAO. The second target was a series of isoquinolines with varied substituents at positions 1 and 2 of the nucleus. These were also tested for MAO inhibition. The position 1 substituents embraced a range of alkyl and aromatic groups and the position 2 groups were aliphatic, aromatic and piperazinyl in nature.



Tetrahydroisoquinoline nucleus

Figure 1-29: Sites of modification of the tetrahydroisoquinoline nucleus

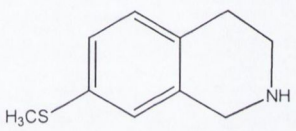
Previous work in this laboratory had discovered a potent dual inhibitor of MAO-B and AChE. This is shown as compound **(54)** in Figure 1-30. This phenoxyacetyltetrahydroisoquinoline was taken as a model for the development of further dual inhibitors of similar structure. These were naturally tested for inhibition of both forms of MAO and of AChE.



1-Methyl-7-(phenoxyacetyl)-1,2,3,4-tetrahydroisoquinoline **(54)**

Figure 1-30: Dual inhibitor of MAO-B and AChE

Finally, exploration of the MAO inhibitory potential of isoquinoline analogues of 4-MTA seemed indicated. A variety of routes to this final objective was explored and the final products were tested for MAO inhibition.



7-Methylsulfanyl-1,2,3,4-tetrahydro-isoquinoline

Figure 1-31: Tetrahydroisoquinoline analogue of 4-MTA

Tetrahydroisoquinolines lure the researcher both by offering a possible cause of Parkinson's disease, and by suggesting a preventive agent. The vastly different profiles of 1-benzyl-1,2,3,4-THIQ and 1-methyl-1,2,3,4-THIQ show that work on series of substituted THIQs and their activity is vital to give understanding of MAO-B and of applications for THIQs. Possible action on acetylcholinesterase opens up other avenues, which may lead to useful agents for the relief of dementia in AD.

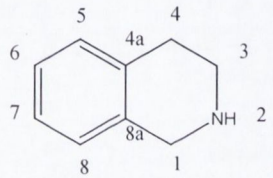
2 Chapter 2: Synthesis of *N*-(1,2,3,4-tetrahydroisoquinolin-7-yl)-amides

2.1 Introduction

The aim of this section was the production of a series of amides with varied substituents at position 7 of the tetrahydroisoquinoline nucleus. Previous work on 7-carboxamido-1-methyl- dihydroisoquinolines had shown them to be MAO inhibitors.[59] Examination of the activity of related tetrahydroisoquinolines was a logical extension of this. This would also allow comparison with similarly substituted phenoxyacetyltetrahydroisoquinolines, as well as 7-methylsulfanyl-1,2,3,4-tetrahydroisoquinoline.

2.2 Route of Synthesis

Synthesis of the isoquinoline nucleus is detailed elsewhere, more specifically chapter three. For this series of compounds, 1,2,3,4-tetrahydroisoquinoline **(1)*** was used as the starting material (see Figure 2-1).

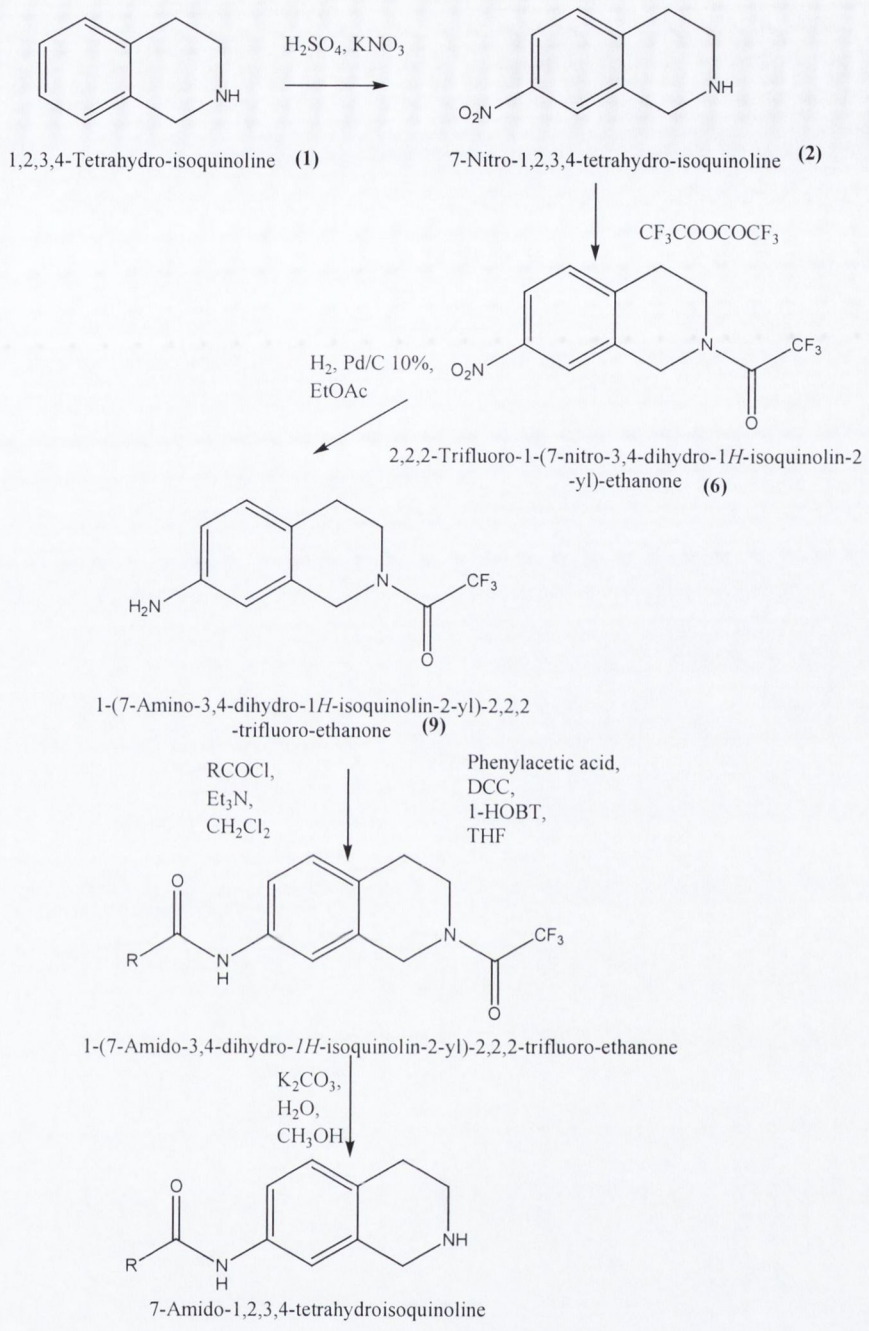


1,2,3,4-Tetrahydroisoquinoline

Figure 2-1: 1,2,3,4-Tetrahydroisoquinoline (1)

The first objective was to introduce an amino group at position 7, by means of a nitro function, which could be reduced to the amine. The amine function of the tetrahydroisoquinoline nucleus required protection, and this was afforded by trifluoroacetylation of the nitrogen at position 2. The nitro group at position 7 could then be hydrogenated with impunity and the resultant amine would be free to react with acid chlorides or phenylacetic acids, without interference from the functionalised nitrogen at position 2. Once the amide had been synthesised, the final step would be the removal of the trifluoroacetyl group to restore the basic character of the tetrahydroisoquinoline. The synthetic route is summarised in Scheme 2-1.

**Note: Numbering system for compounds in Chapter 1 is separate from all succeeding chapters. Thus, the numbers recommence at (1) for 1,2,3,4-tetrahydroisoquinoline. The numbers in the experimental section are in accordance with those in Chapters 2 through 8.*



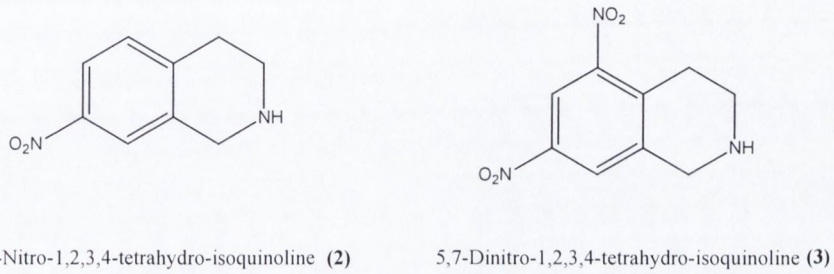
Scheme 2-1: Proposed Route of Synthesis of 7-Amido-1,2,3,4-Tetrahydroisoquinolines

Note on nomenclature: the names used throughout the thesis are those generated using the Autonom system within Beilstein Commander 2000. In some cases (e.g. ***(6)*** *above) this leads to an amide being named as a ketone. The nomenclature was retained, firstly to ensure consistency across the thesis and secondly because it reflected the isoquinoline nature of the nucleus despite modifications.*

2.3 Nitration of 1,2,3,4-Tetrahydroisoquinoline

2.3.1 Routes of Synthesis

Nitration of 1,2,3,4-tetrahydroisoquinoline **(1)** was first reported by McCoubrey and Mathieson in 1950, and it was shown that it led to substitution with the nitro group at position 7 of the tetrahydroisoquinoline nucleus **(2)**.[60] Two nitration procedures have been outlined in the literature for this compound.[61] The first involved fuming nitric acid and was tried as the more conventional route and that which should give higher yields. However, this vigorous treatment produced 5,7-dinitro-1,2,3,4-tetrahydroisoquinoline **(3)** instead of the desired monosubstituted 7-nitro-1,2,3,4-tetrahydroisoquinoline **(2)** (see Figure 2-2).



7-Nitro-1,2,3,4-tetrahydro-isoquinoline **(2)** 5,7-Dinitro-1,2,3,4-tetrahydro-isoquinoline **(3)**

Figure 2-2: Products of Nitration of 1,2,3,4-Tetrahydroisoquinoline

The second method outlined by Ajao and Bird was used instead.[61] This involved the dropwise addition of 1,2,3,4-tetrahydroisoquinoline to chilled, stirred concentrated sulfuric acid, followed by treatment with potassium nitrate (see Scheme 2-1). The temperature was kept at all times below 5°C. The product **(2)** was isolated as the hydrochloride salt, in 40% yield.

2.3.2 Improved Yield via Multifactorial Experiment

The yield quoted by Ajao and Bird for this nitration was 52%. Since large quantities of the nitrated tetrahydroisoquinoline would be required for the synthesis of the projected 14 amides, improvement of the yield was attempted by implementing a multifactorial experiment. This sought to identify the most important factors for maximising yield, and so allow the yield to be improved and the reaction streamlined by eliminating unimportant considerations.

2.3.2.1 Theory of Multifactorial Experimental Design

In experimental terms, a "factor" is any variable, which is thought to influence the outcome of the experiment. In a chemical scenario, typical factors would be the temperature, the duration of the reaction, or the pH at which it is conducted. In a classical experiment, each factor is examined at two or more levels, while all other factors are kept constant, and its influence on the outcome is assessed. The null hypothesis, which states that the factor

does *not* influence the outcome, is examined and a test statistic is calculated, which examines observed differences between outcomes at the varied levels of the factor. The test statistic gives a measure of the difference in outcomes, or *effect*, which takes note of the amount of data being examined. A difference of 3% may be observed in the actual yield at two temperature settings. Whether or not this is *statistically* significant will be assessed by the test statistic, which will take into account the *degrees of freedom* (here corresponding to the number of runs) of the data. If this difference is observed in only two runs it may well be due to random variation, or an uncontrolled factor. If it is seen over the course of 16 runs it is more likely to reflect an influence of temperature on yield. A test statistic therefore gives clear criteria for forming a judgement as to whether a factor does indeed influence the outcome of an experiment.

A multifactorial experiment varies several factors at once and uses statistical analysis to interpret the results. The advantages of such an approach are twofold: interactions between factors may be seen, which would not emerge using a conventional design, and fewer runs may be used. In a multifactorial experiment, A is held to interact with B if the effect of A at high B differs from the effect of A at low B. To minimise runs a plan called a design matrix is introduced to dictate the settings of the factors over the runs so as to examine the individual factors and interactions in the most efficient manner.

Runs must be carried out in random order, but it is more convenient at the planning stage to draw up runs in what is known as the "standard order". Table 2-1 shows the matrix for the nitration experiment in standard order. The critical steps of the nitration are shown in Scheme 2-2.

2.3.2.2 Results of Multifactorial Experiment

The factors examined in the course of 16 "runs" or syntheses were:

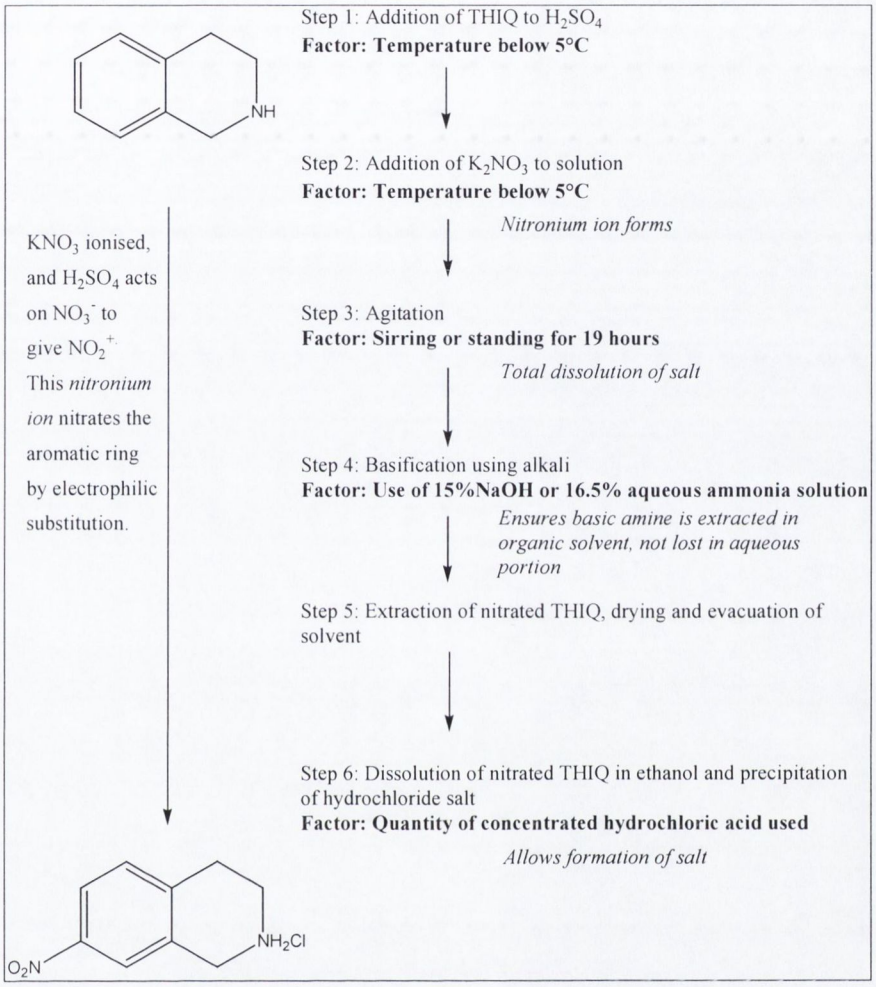
A cooling the sulfate solution below 5°C during the addition of tetrahydroisoquinoline;

B cooling the solution below 5°C during the addition of potassium nitrate;

C stirring the mixture, as opposed to allowing it to stand overnight;

D using 16.5% aqueous ammonia solution versus the use of 15% sodium hydroxide solution in the alkalisation step and

E the ratio of hydrochloric acid to ethanolic 7-nitro-1,2,3,4-tetrahydroisoquinoline.



Scheme 2-2: Critical steps in nitration examined by multifactorial experiment

Each factor was set to a "high" or "low" level for each run. In some cases, such as the temperatures, this meant a quantitative difference: for example, a "high" for factor A meant allowing the temperature of the sulfuric acid solution to rise above 5°C as the tetrahydroisoquinoline was added. In others, the terms are descriptive only: a "low" factor D was the use of aqueous ammonia solution and a "high" factor was the employment of sodium hydroxide solution. These are outlined in appendix one.

To fully investigate five factors 32 runs would be necessary. However, limiting the data to 16 runs would allow main effects to be distinguished from one another, and would only confound higher order interactions. Two factor interactions could be assessed, and higher order interactions were not expected to be of significance.

Standard Order	*A (Temp.)*	*B (Temp.)*	*C (Agitation)*	*D (Alkali)*	*E (Acid)*	*Yield %*
1	-1	-1	-1	-1	1	11.20
2	1	-1	-1	-1	-1	0.00
3	-1	1	-1	-1	-1	30.67
4	1	1	-1	-1	1	20.26
5	-1	-1	1	-1	-1	66.32
6	1	-1	1	-1	1	0.00
7	-1	1	1	-1	1	41.42
8	1	1	1	-1	-1	28.53
9	-1	-1	-1	1	-1	42.19
10	1	-1	-1	1	1	31.95
11	-1	1	-1	1	1	0.00
12	1	1	-1	1	-1	1.18
13	-1	-1	1	1	1	45.22
14	1	-1	1	1	-1	10.66
15	-1	1	1	1	-1	42.65
16	1	1	1	1	1	37.67

Table 2-1: Matrix of Multifactorial Experiment

Note: -1 refers to the low level of a factor, 1 to the high level of the factor. The matrix is drawn up in standard form, but the runs were randomised when conducting the experiment. Plots and calculations relating to the experiment may be found in Appendix 1.

The first conclusion reached was that control of the temperature during the initial addition of 1,2,3,4-tetrahydroisoquinoline to concentrated sulfuric acid was of the utmost importance. The difference in yield between the high and low settings was as much as 66% (of theoretical yield), e.g. the difference between the yields of runs 2 and 5. This was large, considering that the maximum yield achieved *was* 66% of the theoretical yield. This factor interacted with all others but in all cases, the lower temperature was optimal.

Control of the temperature during the addition of potassium nitrate interacted with other factors but the lower temperature was not in all instances that which gave the higher yield; for example, run 7 gave a yield of 41% despite a high level of factor B. Rapid addition of potassium nitrate was thus permissible.

In all cases, agitation much increased the yield of product and interacted with the temperatures used. The nature of the alkali used for basification did not have an effect of

itself, but did interact with the amount of acid used in the final step. It seems likely that any base carried over to the final ethanolic solution will neutralise some acid and thus counteract degradation when excess hydrochloric acid is used. The lower quantity of hydrochloric acid was found to give higher yields, and was of maximum benefit when combined with the use of ammonia solution in the alkalisation.

For all future syntheses 1,2,3,4-tetrahydroisoquinoline **(1)** was added to cooled concentrated sulfuric acid at -4°C. Potassium nitrate was added in one aliquot and the mixture was stirred overnight. The mixture was made alkaline using aqueous ammonia and the product was extracted with chloroform. After evacuation to brown oil the hydrochloride salt was precipitated from the ethanolic solution by addition of 1 mL HCl for every 8 mmol 7-nitro-1,2,3,4-tetrahydroisoquinoline **(2)**. This procedure increased the yield to 66.3%; not phenomenal, but an improvement on 52% in the literature reference[61] and the experimenter's initial result of 40%.

2.4 Protection of Amine Function of 1,2,3,4-tetrahydroisoquinoline

Ajao and Bird protected the nitrogen at position 2 using an acetyl group.[61] An acetyl group would be difficult to remove after the final amide had been formed, so this was abandoned as an option for the 7-amido series. Instead, the amine function of the tetrahydroisoquinoline was masked by addition of a trifluoroacetyl group so that this secondary amine could not interfere with subsequent steps in the synthetic route. The trifluoroacetyl group was chosen because it is not affected during hydrogenation using a palladium on carbon catalyst, but is removed with relative ease by alkaline hydrolysis, using potassium carbonate in aqueous methanol. An excess of trifluoroacetic anhydride was added dropwise to the tetrahydroisosquinoline **(2)** and the solution was stirred at room temperature for 2 hours, giving an 84% yield of trifluoroacetylated product **(6)**, as shown in Scheme 2-1[62]

2.5 Hydrogenation of 2-Acetyl-7-Nitro-1,2,3,4-tetrahydroisoquinoline and 1-(7-Nitro-3,4-dihydro-1H-isoquinolin-2-yl)-ethanone

2.5.1 Synthesis

Hydrogenation of the nitro group of compound **(6)** at room temperature using a hydrogen-filled balloon gave poor yields. Ajao and Bird had hydrogenated under pressure (60psi) at room temperature[61], but a simple set-up that sealed the hydrogen blanket under a copper sulfate solution was tried and found to be satisfactory. The catalyst was palladium adsorbed onto carbon (10%). The nitrated tetrahydroisoquinoline **(6)** was not very soluble in ethanol, the most common solvent used in hydrogenations, but dissolved readily in ethyl acetate, so this was used instead. The amine product **(9)** was obtained at a yield of 72% after approximately 4 to 5 hours stirring at room temperature.

2.5.2 Spectroscopy

Two sets of signals were clearly seen in the nuclear magnetic resonance (NMR) spectrum of **(9)**, 1-(7-amino-3,4-dihydro-*1H*-isoquinolin-2-yl)-2,2,2-trifluoro-acetyl-ethanone. Overlapping triplets at 2.75 to 2.79δ in the ^{1}H-NMR spectrum (shown in Figure 2-4) represent the methylene group at position 4 of the aliphatic ring. If these are integrated as a signal for two protons, the signals for the methylene group at 3.75δ and 3.79δ may be seen to appear as two unequal sets of triplets, the larger with a coupling constant of 6 Hz and the smaller with a J value of 5.5 Hz. The ratio observed is 1.3:0.7 and is repeated in the two singlets at 4.59δ and 4.61δ, which equate to the protons at position 1.

The two sets of signals result from the hindrance of rotation about the C-N bond at position 2. This bond has a partial double bond character and this gives rise to rotamers, as illustrated in Figure 2-3.

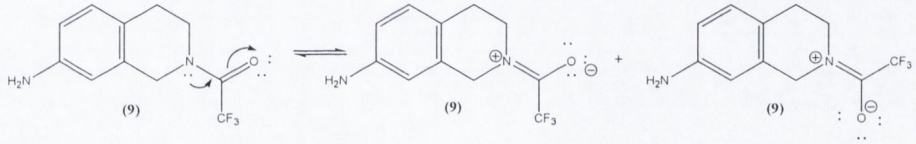


Figure 2-3: Psuedo *cis* and *trans* isomers, due to restricted rotation about CN bond in (9)

Although only one compound is present, the NMR signals for the pseudo *cis* and *trans* isomers may be distinguished at room temperature. Figure 2-4 presents the ^{1}H-NMR spectrum of **(9)**.

A singlet integrating for two protons at 3.87δ is that of the NH_2 protons. The aromatic protons of H-6 and H-8, at either side of the amine group, are seen at 6.50 – 6.54δ and 6.36 – 6.40δ respectively. That for H-8 is seen as two singlets, in the ratio of 0.7:0.3; *meta* coupling with the proton at H-6 is not observed. The signal for H-5 is found as a multiplet at 6.87 – 6.91 and integrates for one proton. Doublets should be observed for both H-5 and H-6, due to *ortho* coupling between the protons, but the rotamers multiply the peaks and lead to overlapping signals: the signals for the different rotamers cannot be distinguished.

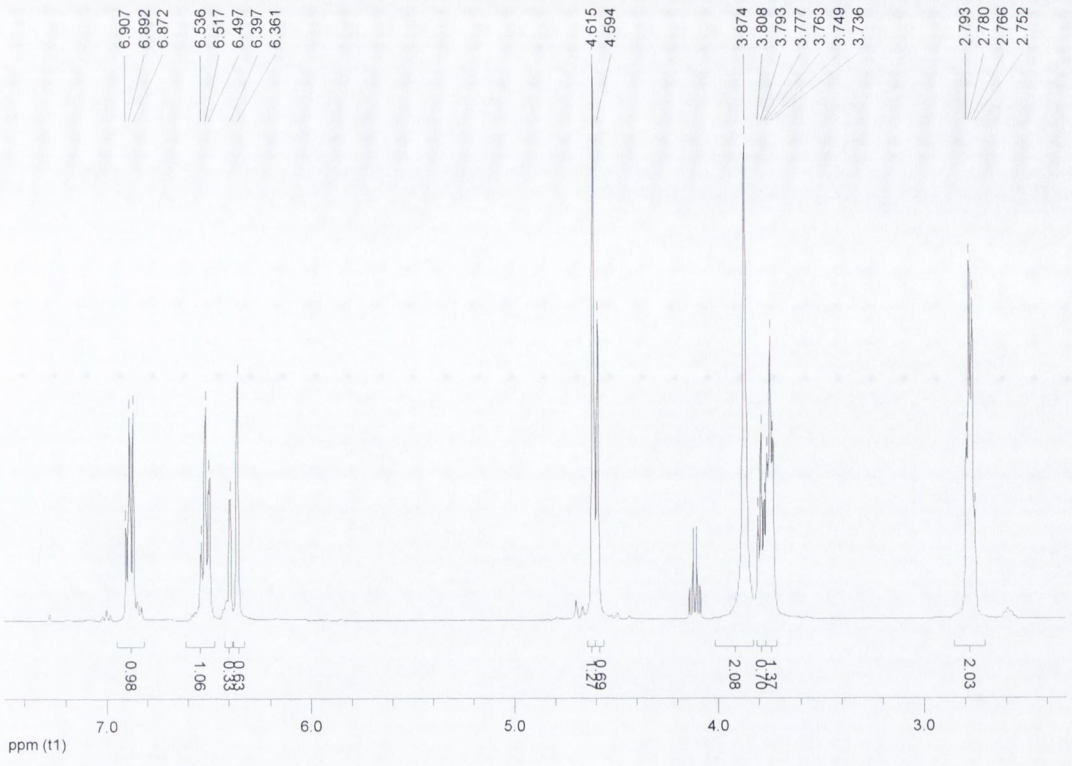


Figure 2-4: ^{1}H-NMR Spectrum of amine, (9)

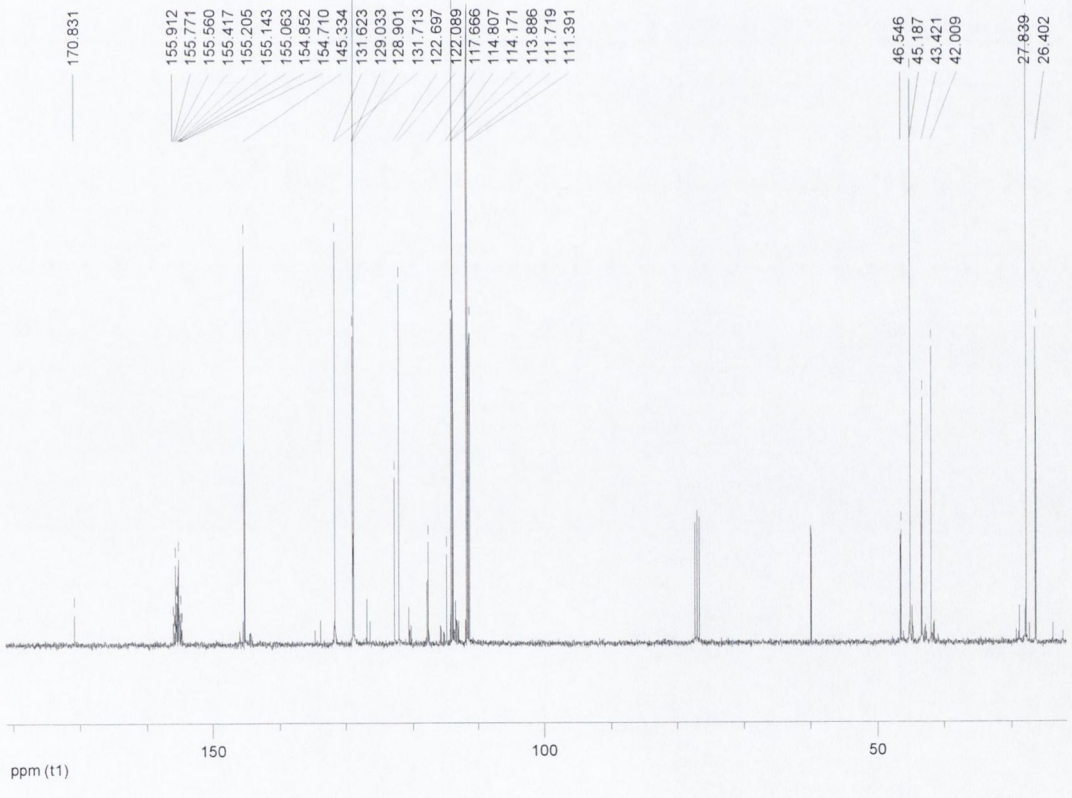


Figure 2-5: ^{13}C-NMR spectrum of amine, (9)

The ^{13}C-NMR spectrum (Figure 2-5) also shows doubling of signals, except in the case of the CO group. The signals for the methylene group at position 4 are seen as a small signal at 26.4 ppm and a large at 27.8 ppm. Similarly, pairs of signals are seen for $C3H_2$ – at 42.0 ppm (small) and 45.2 ppm (major) – and for $C1H_2$ – at 43.4 ppm (major) and 46.5 ppm (minor). Figure 2-6 shows the inverted peaks in the DEPT 135 spectrum, confirming that these are indeed methylene signals.

The signals for the aromatic protons at positions 6 and 8 are also paired, with minor signals being seen at 111.4 ppm and 114.2 ppm and stronger signals at 111.7 ppm and 113.9 ppm. The signals for C5H are also doubled, with a large signal being observed at 128.9 ppm and the partner appearing at 129.0 ppm. The appearance of all these signals in the DEPT 135 spectrum (Figure 2-6) in an upright position confirms that they represent aromatic protons.

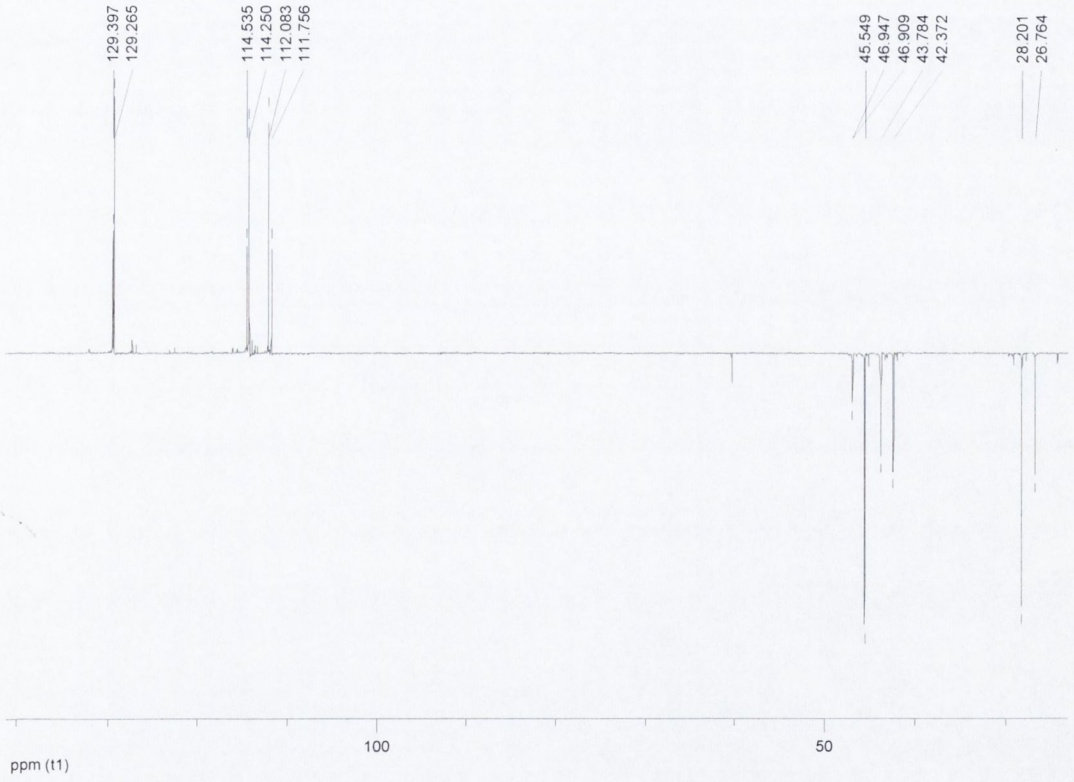


Figure 2-6: DEPT 135 Spectrum of amine, (9)

The signals for the quaternary carbons at positions C4a, C8a, C7 and the carbonyl group disappear in the DEPT spectrum (Figure 2-6). In the ^{13}C-NMR spectrum a major and minor rotamer effect may be seen with major signals for C4a and C8a at 122.1 ppm and 131.6 ppm respectively. Their minor signals appear at 122.7 ppm (C4a) and 131.7 ppm (C8a). The two signals for C7 almost coincide, at 145.2 ppm (small) and 145.3 ppm (large). Usually, one expects to see the carbon bearing the three fluorines as a quartet at

about 155 ppm. The quartet is doubled because of the rotamer effect, but some of the signals coincide, and the result is an unsightly multiplet. Finally, one signal only is seen for the carbonyl group.

A final piece of evidence is presented in the form of the ^{19}F-NMR spectrum in Figure 2-7. This clearly shows a major signal at –69.80 ppm and a smaller signal at –69.76 ppm. These NMR assignments will be used to confirm the identity of subsequent reaction products.

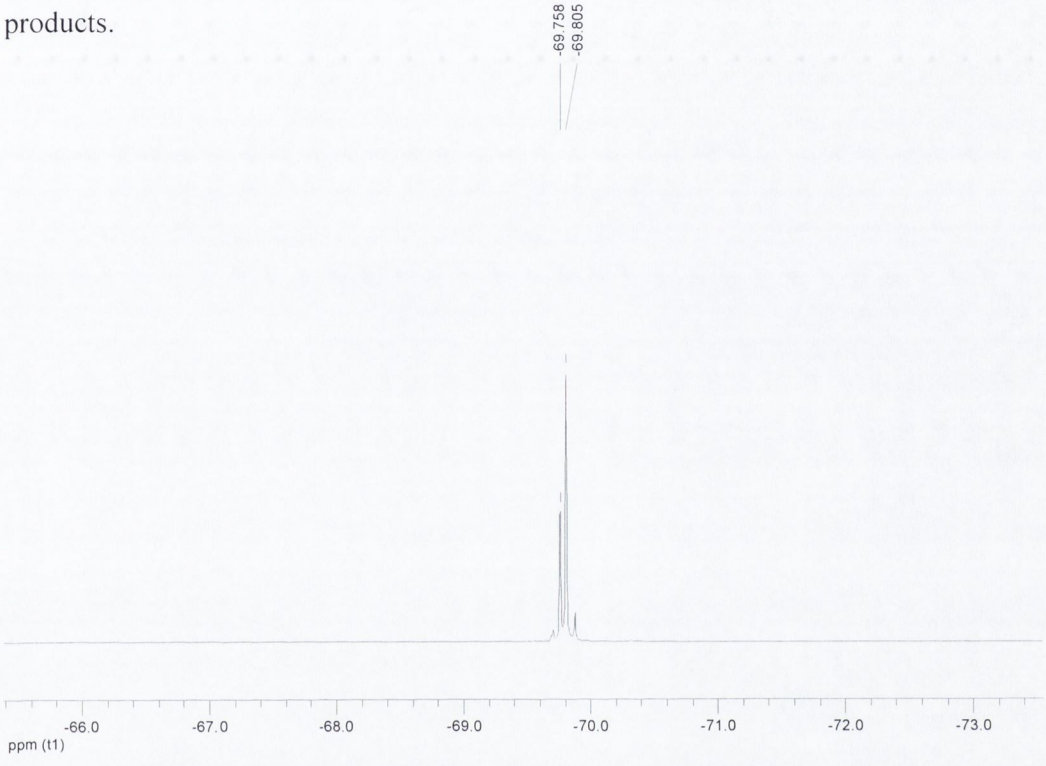


Figure 2-7: ^{19}F-NMR spectrum of amine, (9)

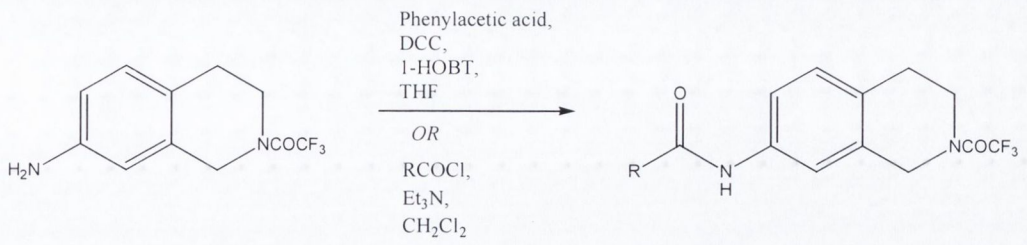
2.6 Acylation of 1-(7-Amino-3,4-dihydro-1H-isoquinolin-2-yl)-2,2,2-trifluoro-ethanone

2.6.1 Synthesis

The next step in the synthetic sequence (see Scheme 2-1) involved acylation of compound **(9)** to afford products **(10)** to **(23)** (see Table 2-2). This was accomplished in one of two ways. For simple aliphatic sidechains, the relevant acid chloride was employed. Similarly, a substituted aromatic ring was introduced using benzoyl chlorides. The acid chloride reacted readily with the primary amine at position 7 to give an amide. Triethylamine was used as the base in anhydrous dichloromethane.

An additional methylene between the amide function and aromatic ring necessitated the use of substituted phenylacetic acids. These were coupled with the amine using 1,3-dicyclohexylcarbodiimide (DCC). The first attempt, using 4-dimethylaminopyridine (DMAP) as the additive, was successful, but subsequent syntheses of amides at position 2 (discussed in chapter three) illustrated the shortcomings of this system and most of the

couplings were carried out in anhydrous tetrahydrofuran (THF), using 1-hydroxybenzotriazole (1-HOBT) as the auxiliary catalyst. The products synthesised **(10 – 23)**, and details of yields, are shown in Table 2-2.

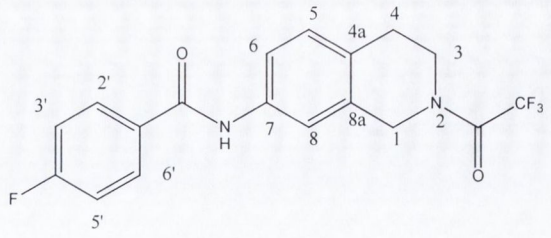


Compound Number	R	Yield %
10	C_2H_7	76
11	C_3H_9	88
12	C_6H_{11}	38
13	C_6H_5	63
14	C_6H_4F	51
15	C_6H_4Cl	20
16	C_6H_4Br	31
17	C_6H_4I	20
18	*o*-$C_6H_4OCH_3$	59
19	*m*-$C_6H_4OCH_3$	56
20	*p*-$C_6H_4OCH_3$	61
21	$C_6H_4NO_2$	45
22	$CH_2C_6H_5$	39
23	$CH_2C_6H_4OCH_3$	73

Table 2-2: *N*-[2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydroisoquinolin-7-yl]-amides

2.6.2 Spectroscopy

Similar patterns to those seen in the protected aminated tetrahydroisoquinoline were seen in the amides. A typical ^{1}H-NMR spectrum is shown in Figure 2-9, that of 4-fluoro-*N*-[2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-benzamide **(14)**, shown in Figure 2-8.



4-Fluoro-*N*-[2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-benzamide

Figure 2-8: 4-Fluoro-*N*-[2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-benzamide (14)

All the amides were of limited solubility in both chloroform and methanol, so deuterated acetone was used to prepare samples for NMR analysis. Rotamers, giving pseudo *cis* and *trans* isomers, create two sets of signals. A multiplet (2.93δ - 2.99δ) results from the peaks at C4$\underline{H}_2$, where the two sets of signals cannot be distinguished. Similarly, those for the pseudo *cis* and *trans* versions of the methylene at position 3, overlap at 3.88δ to 3.93δ. Two singlets for the methylene at position 1, at 4.78δ and 4.82δ, are seen to be unequal in intensity, integrating in a ratio of 1.86:1. This gives integrals of 1.3 H and 0.7 H respectively.

A similarly complex pattern may be observed in the aromatic region. The expected duo of doublets for H-5 at 7.18δ – 7.22δ partly coincide with the apparent triplet for H-3' and H-5' at 7.27δ with a coupling constant of 8.7 Hz. Coupling between the proton at H-6 and H-5 combined with the effect of rotamers gives the complex multiplet seen at 7.61δ - 7.67δ for H-6. The isolated proton at H-8 may be seen as two distinct singlets at 7.72δ and 7.80δ in an approximate ratio of 1.86:1. A multiplet at 8.07 δ to 8.10 δ represents the signals of H-2' and H-6' and the proton of the amide NH is seen at 9.60δ as an ill-defined singlet.

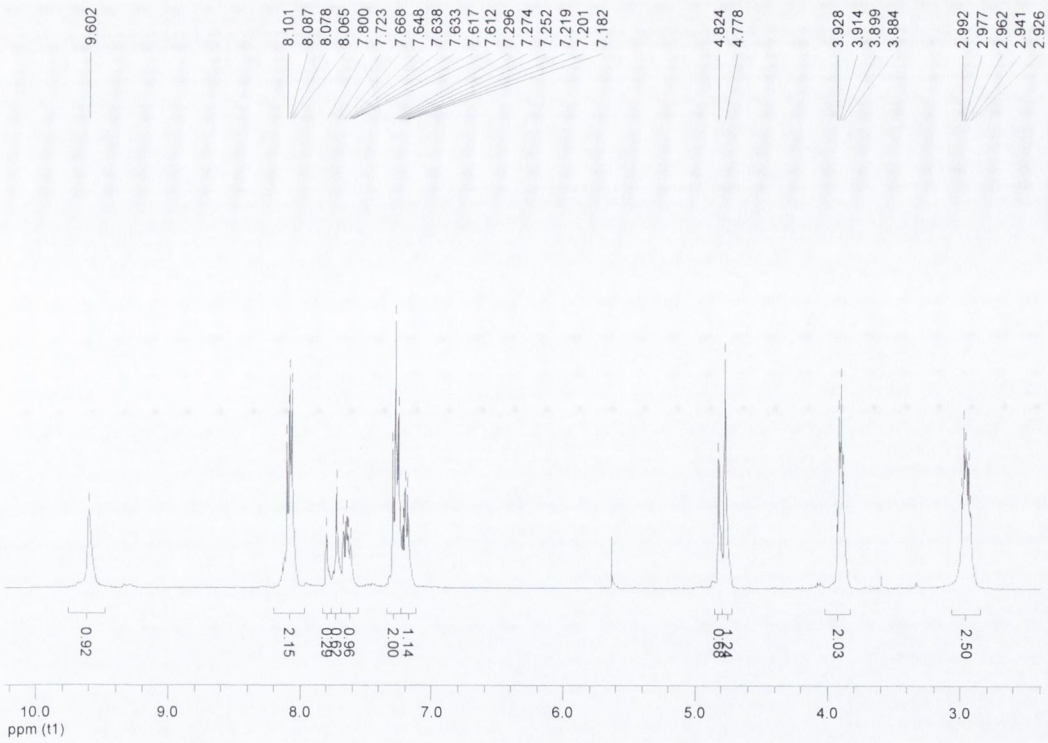


Figure 2-9: ^{1}H-NMR Spectrum of protected amide, (14)

As may be seen in Figure 2-10, the signal for the major isomer of the methylene carbon at position 4 is obscured by the acetone septet in the ^{13}C-NMR spectrum. However, it is clear from the DEPT 135 spectrum that the, now inverted, peaks occur at 28.05 ppm (minor) and at 29.5 ppm (major).

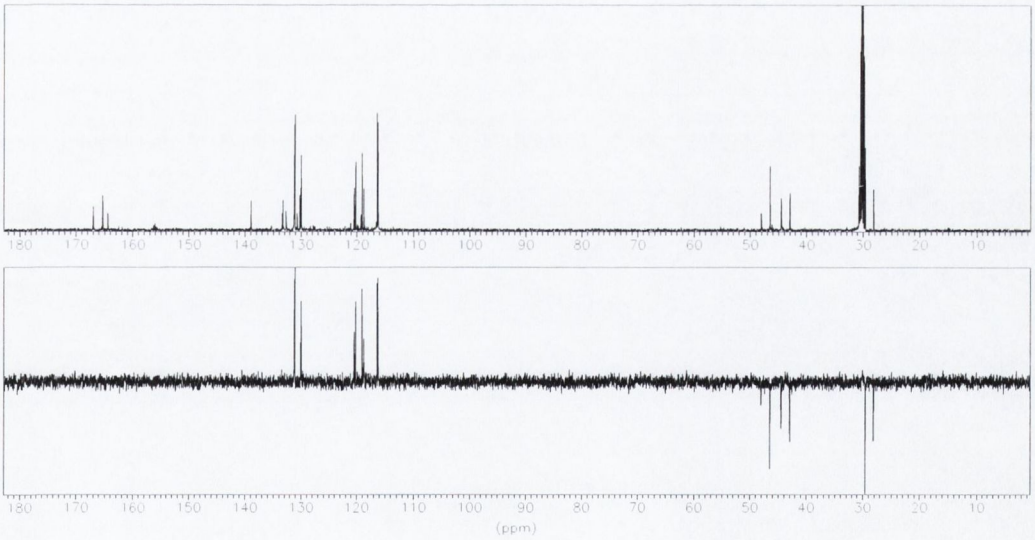


Figure 2-10: ^{13}C-NMR spectrum (upper) and DEPT 135 spectrum of protected amide, (14)

Figure 2-11 allows the shift values to be determined more accurately, being the ^{13}C-NMR spectrum alone. The signals for $C3H_2$ are found at 42.9 ppm (minor) and at 46.4 ppm (major). They are similar in intensity for those seen for $C4H_2$ although not equal. Signals

at 44.4 ppm (major) and 48.0 ppm (minor) for $C1H_2$ are markedly weaker than for the other protons in the aliphatic ring.

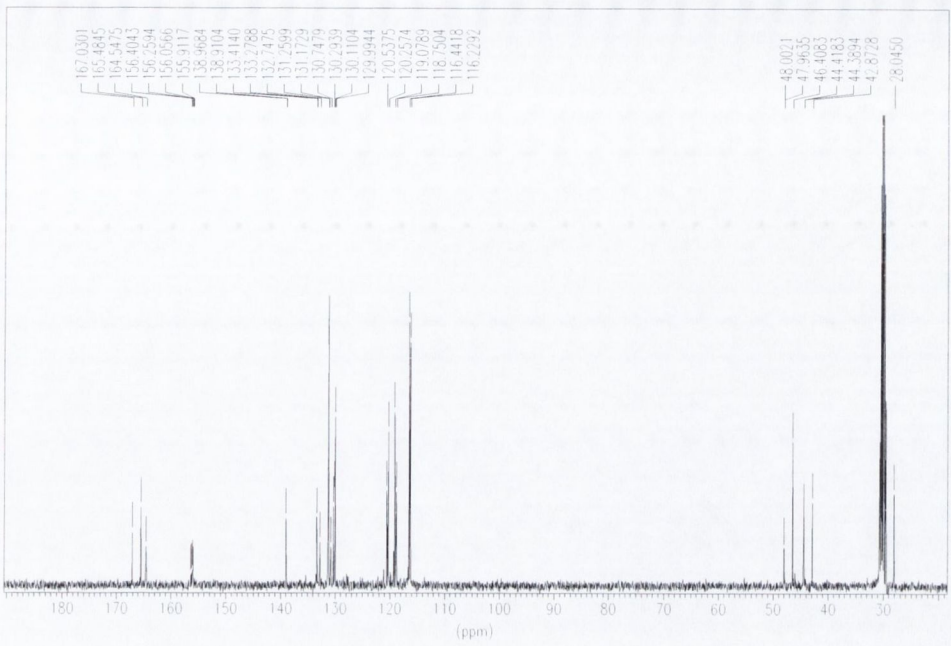


Figure 2-11: ^{13}C-NMR spectrum of protected amide, (14)

Doubling of signals continues in the aromatic region. The peaks for the major and minor isomers of the signals of C3'H and C5'H (116.4 ppm and 116.2 ppm respectively) of the fluorinated benzoyl function are of almost equal strength. The same is true for the signals for the major (131.2 ppm) and minor (131.3 ppm) isomers of C2'H and C6'H. As these are further in space from the CN bond at position 2, little spatial and electronic difference results from the pseudo *cis* and *trans* conformations. The differences are more marked in the cases of the H-6 at 118.8 ppm (minor) and 119.1 ppm (major), H-8 at 120.3 ppm (major) and 120.5 ppm (minor) and H-5 at 130.0 ppm (major) and 130.1 ppm (minor).
The quaternary signals for C4a are doubled, at 130.3 ppm (major) and 130.7 ppm (minor). C8a displays a similar pattern of weak signals at 133.3 ppm for the minor isomer and a stronger one at 133.4 ppm for the major. Only one signal can be distinguished for the quaternary carbon at C1', at 132.7 ppm. Those for the quaternary carbon at position 7 almost coincide, at 138.9 ppm (minor) and 139.0 ppm (major). A quartet at 156.1 ppm (coupling constant of 36 Hz) is visible for the quaternary carbon bearing the three fluorines of the trifluoroacetyl group. The carbonyl of the amide gives a quaternary signal at 164.5 ppm. No splitting is seen at the resolution of the spectrum for the quaternary carbon bearing the fluorine of the benzoyl substituent, at 165.5 ppm. The carbonyl portion of the trifluoroacetyl group is observed as a signal at 167.0 ppm.

The doubling of signals was echoed by duos in the ^{19}F-NMR spectrum (Figure 2-12), with a major peak at –79.54 ppm and a minor signal at –70.59 ppm for the trifluoroacetyl group fluorine, and signals at –110.73 ppm (major) and –110.70 ppm (minor) for the fluorine of the aromatic ring.

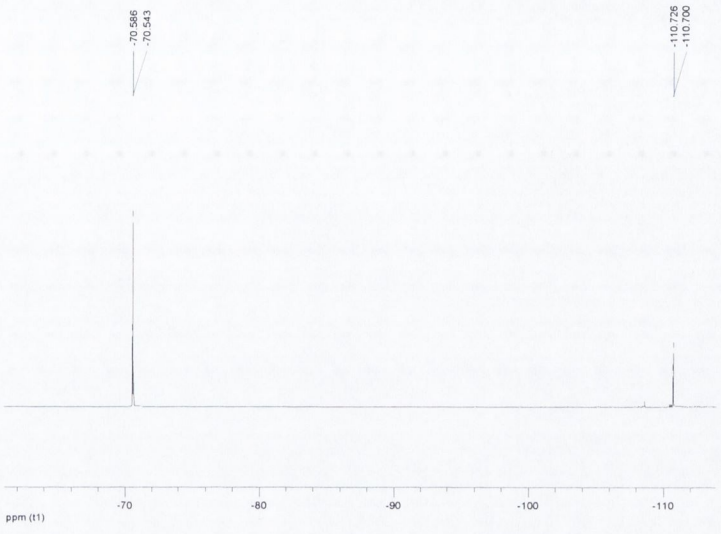
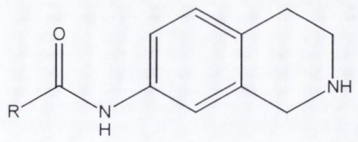


Figure 2-12: ^{19}F-NMR spectrum of protected amide, (14)

2.7 Deprotection of 1-(7-Amido-3,4-dihydro-1H-isoquinolin-2-yl)-2,2,2-trifluoro-ethanone compounds

2.7.1 Deprotection

Deprotection of the amides **(10 – 23)** afforded the products **(24 – 37)**. The trifluoroacetyl group was removed with relative ease once the amides were dissolved in methanol. This required heating to 50°C before the addition of water. The potassium carbonate was added in small aliquots to ensure dissolution and the progress of the reaction was monitored by TLC. The products and yields are shown in Table 2-3.

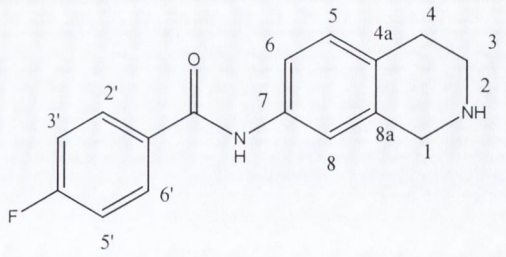


Compound Number	R	Yield %
24	C_2H_7	88
25	C_3H_9	36
26	C_6H_{11}	83
27	C_6H_5	63
28	C_6H_4F	27
29	C_6H_4Cl	62
30	C_6H_4Br	96
31	C_6H_4I	93
32	*o*-$C_6H_4OCH_3$	98
33	*m*-$C_6H_4OCH_3$	72
34	*p*-$C_6H_4OCH_3$	87
35	$C_6H_4NO_2$	64
36	$CH_2C_6H_5$	31
37	$CH_2C_6H_4OCH_3$	54

Table 2-3: *N*-(1,2,3,4-tetrahydroisoquinolin-7-yl)-amides

2.7.2 Spectroscopy

The removal of the trifluoroacetyl group simplified the ^{1}H-NMR spectrum, since the position 2 amide was no longer present. In contrast with its predecessor **(14)**, 4-fluoro-*N*-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-benzamide **(28)** (shown in Figure 2-13) was soluble in chloroform and presented a single set of signals (see Figure 2-14), as the amide resonance was no longer present. Steric factors preclude the amide function at position 7 having a similar effect.



4-Fluoro-*N*-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-benzamide

Figure 2-13: 4-Fluoro-*N*-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-benzamide, (28)

The methylene groups were now only visible as singlets, although quite well defined. The $C4H_2$ presented a signal at 2.76δ. The peaks for the proton of the NH at position 2 and for the methylene at position 3 overlapped, giving a single signal at 3.11δ, which integrated for 3 protons. The peak at 3.91δ stood for $C1H_2$ and was equivalent to 2 protons.

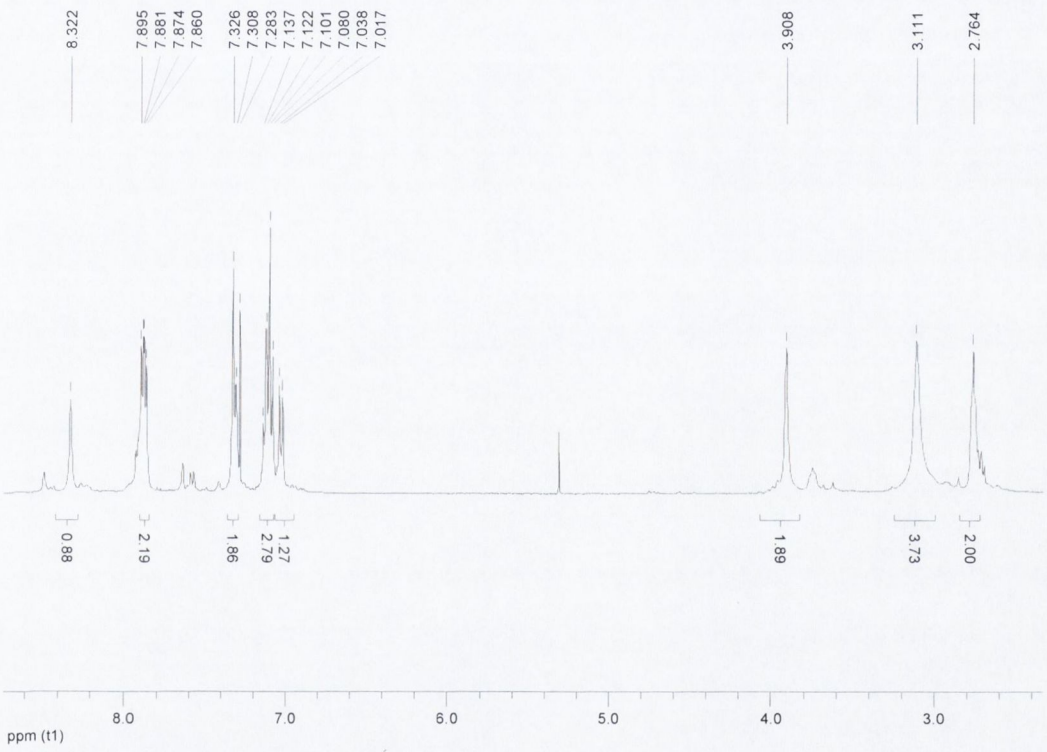


Figure 2-14: ^{1}H-NMR spectrum of deprotected amide, (28)

The aromatic region had also been simplified by the deprotection. The proton at position 5 gave a doublet at 7.02δ, with a coupling constant value of 8 Hz. It could now be separated from the multiplet at 7.08δ - 7.14δ, which corresponded to the protons at H-3' and H-5', coupling both with the fluorine at position 4' of the benzoyl ring and H-2' and H-6'. Peaks at 7.31δ - 7.33δ overlapped, giving a total of 2 protons, for H-6 and H-8. The second multiplet of the benzoyl ring at 7.86δ - 7.90δ represented H-2' and H-6'. A somewhat broad peak at 8.32δ signalled the presence of the proton of the amide bond.

In the case of 4-fluoro-*N*-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-benzamide, solubility in deuterated chloroform was satisfactory and both ^{13}C-NMR and DEPT spectra could be obtained in this solvent. The methylene peaks of the aliphatic ring are no longer obscured by the acetone septet, and only the ^{13}C-NMR spectrum is shown in Figure 2-15.

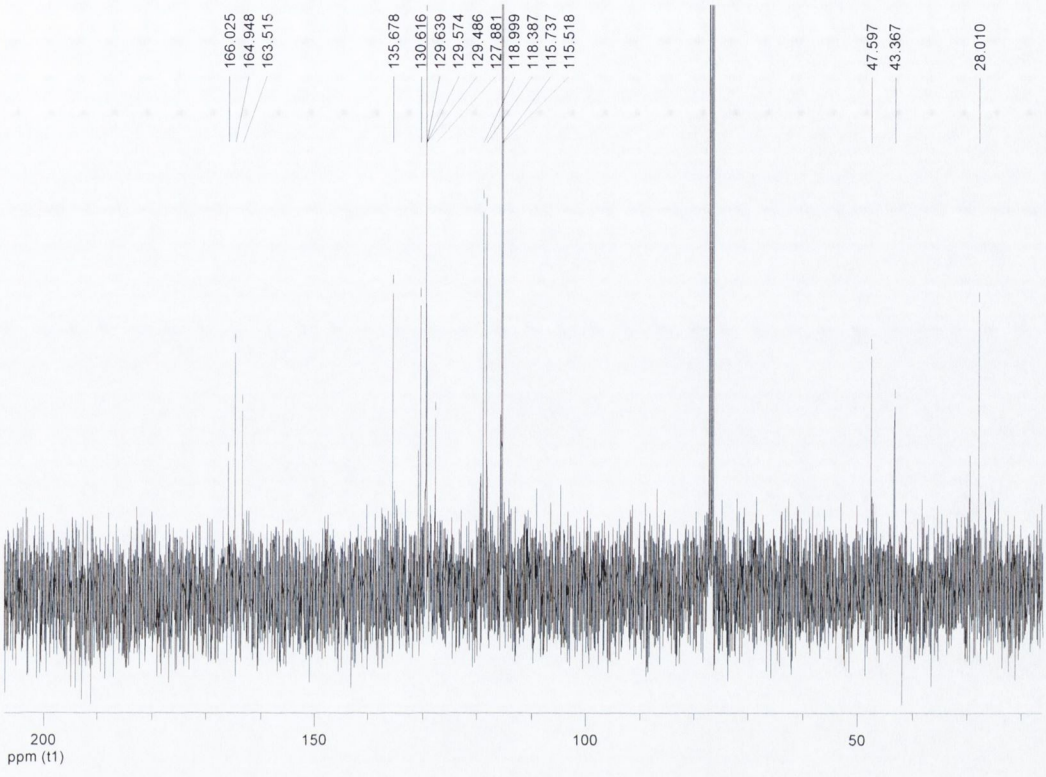


Figure 2-15: ^{13}C-NMR spectrum of deprotected amide, (28)

The simplification observed in the proton spectrum finds its counterpart in the ^{13}C-NMR spectrum. The methylenes at positions 4, 3 and 1 are now seen as signals at 28.0 ppm, 43.4 ppm and 47.6 ppm respectively. The aromatic region is also clearer, with signals for C6H and C8H to be seen at 118.4 ppm and 119.0 ppm. The signal for C5H is a lone peak at 129.5 ppm. The fluorinated benzoyl ring shows a doublet at 115.6 ppm for the carbons at positions C3'H and C5'H: the splitting due to fluorine coupling with the carbons is 22 Hz. The carbons at C2'H and C6'H do not couple with the fluorine *meta* to them and give a single signal at 129.6 ppm.

The quaternary carbon signal for C8a is found at 127.9 ppm and that for C4a at 130.6ppm. A lone signal at 135.7 ppm represents the quaternary carbon at position 7 of the tetrahydroisoquinoline aromatic ring. The signal for C4'F is at 164.8 ppm, but it is a doublet with a coupling constant of 251 Hz, thanks to the fluorine it bears. Only one carbonyl group is now present and its signal is observed at 164.9 ppm.

Finally, the ^{19}F-NMR spectrum (Figure 2-16) has collapsed to a lone signal at –108.04 ppm, proving that the trifluoroacetyl moiety has been cleaved from the isoquinoline.

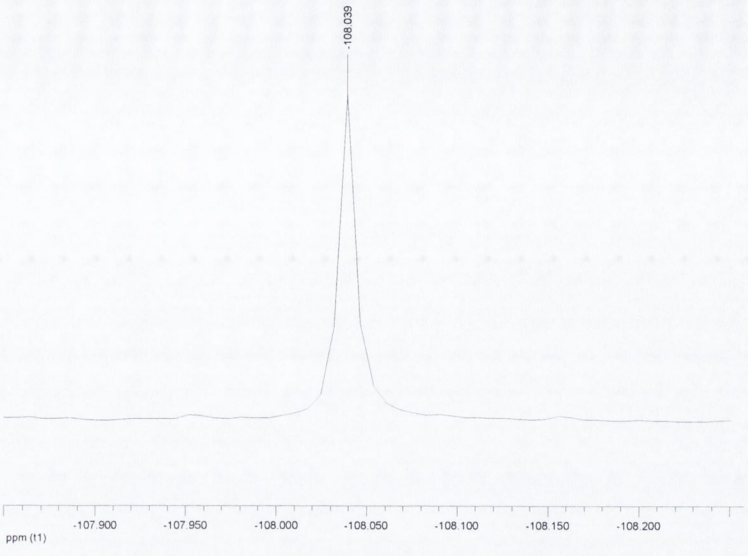


Figure 2-16: ^{19}F-NMR spectrum of deprotected amide, (28)

2.8 Summary

A series of structurally varied *N*-(1,2,3,4-tetrahydroisoquinolin-7-yl)-amides were prepared. The most efficient nitration procedure for 1,2,3,4-tetrahydroisoquinoline was identified and the secondary amine moiety of the tetrahydroisoquinoline was protected with a trifluoroacetyl group prior to hydrogenation. The purified amine was then coupled with an acid or reacted with an acid chloride via the tetrahedral mechanism. The amide series formed was deprotected, characterised and subsequently tested for monoamine oxidase inhibitory activity (see Chapter 7, Section 7.2.2).

3 Chapter 3: Tetrahydroisoquinolines with Amide Functions at Position 2

3.1 Introduction

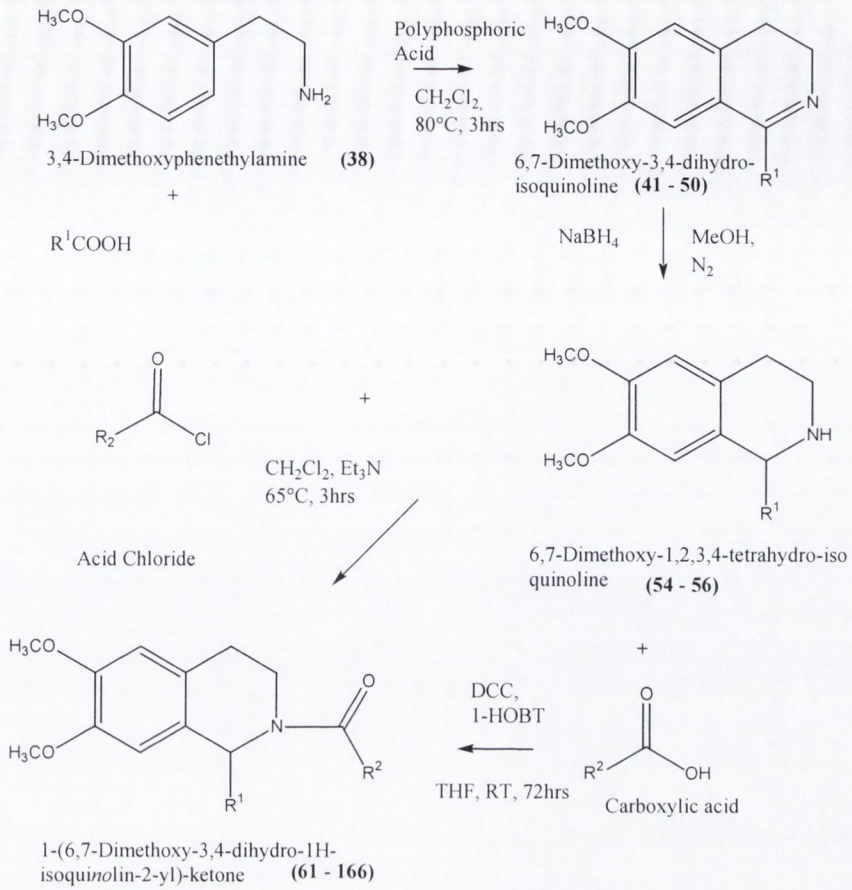
The investigation of the effect of an amide function on tetrahydroisoquinoline MAO inhibitory activity is most easily examined by acylating the nitrogen of the aliphatic ring, at position 2. 1,2,3,4-Tetrahydroisoquinoline **(1)** is commercially available, and further tetrahydroisoquinolines were synthesised and used as alternative starting materials. This furnished a means of examining the effects of modifying both positions 1 and 2.

3.2 Synthetic Route

Scheme 3-1 summarises the synthetic route adopted. It may be observed that in general the 3,4-dihydroisoquinolines were synthesised and reduced to tetrahydroisoquinolines before acylation, but 6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline was synthesised directly after experimentation with varied routes. The coupling of the tetrahydroisoquinoline with the relevant acid was intended as the sole route to the amides, but this was modified to include acylation with acid chlorides. This is discussed in greater detail in section 3.5.

3.3 1-Alkyl-3,4-dihydroisoquinolines

The production of tetrahydroisoquinolines may be accomplished in several different fashions. The chief synthetic routes are the Bischler-Napieralski synthesis[63] and the Pictet-Spengler synthesis.[64] Yields using the Bischler-Napieralski were low (see section 3.3.1). Scheme 3-1 illustrates the use of an alternative procedure pioneered by Venkov et al.[65], which was used in most cases as the first step of this project. The yields using this route were more satisfactory (see Table 3-1).



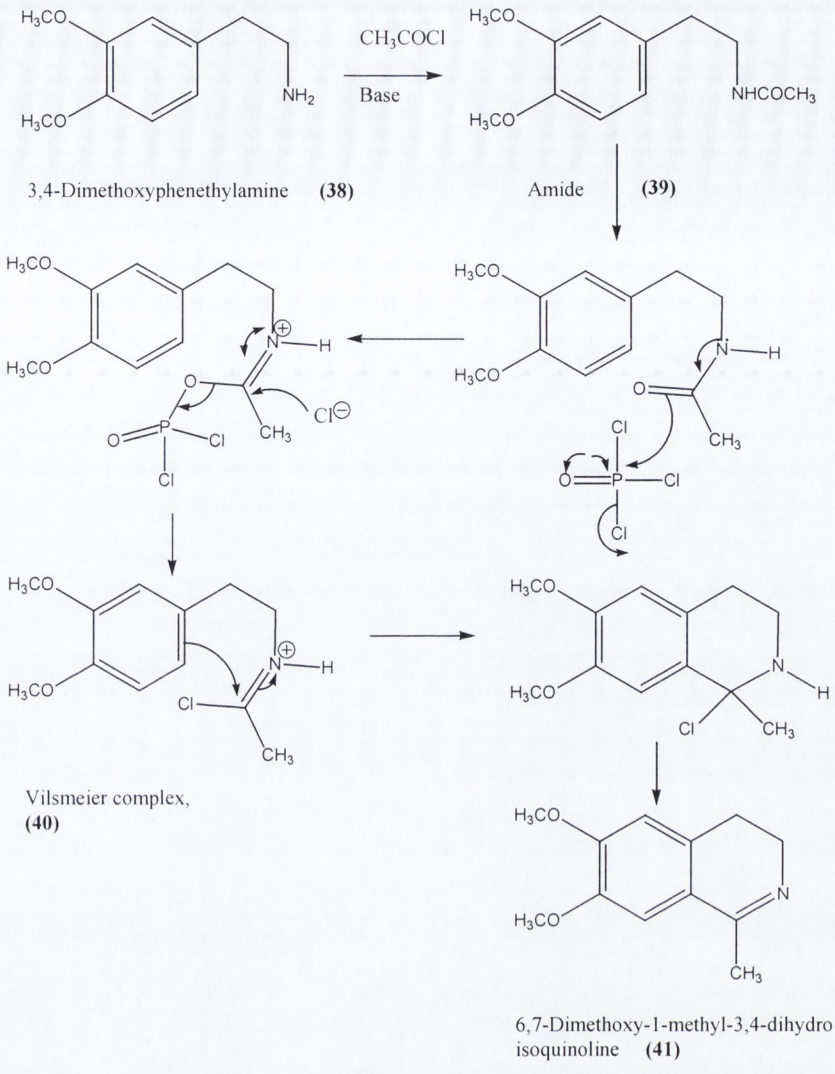
Scheme 3-1: Synthesis of 1-(3,4-dihydro-1H-isoquinolin-2-yl)-ketones from phenylethylamines

3.3.1 Bischler-Napieralski Synthesis

This is a somewhat laborious route, necessitating first acylation of the amine function of the parent β-phenylethylamine **(38)**, then cyclisation using phosphorous oxychloride (as illustrated in Scheme 3-2) and finally reduction of the dihydroisoquinoline by either hydrogenation with a palladium catalyst or reduction using sodium borohydride (see Scheme 3-7).

Phosphorous oxychloride converts the amide to a Vilsmeier complex **(40)**, and this protonated imidoyl chloride then reacts with the aromatic ring by electrophilic aromatic substitution to give the dihydroisoquinoline **(41)**[66] This route was unwieldy compared to the one pot synthesis outlined below, and was only used to synthesise **(41)**.

It is usual to substitute phosphorous pentoxide for phosphorous oxychloride where high temperatures are needed to force the cyclisation[47], and this was the dehydrating agent employed in obtaining 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline **(41)** in an overall yield of 20.7% over the two steps[67].

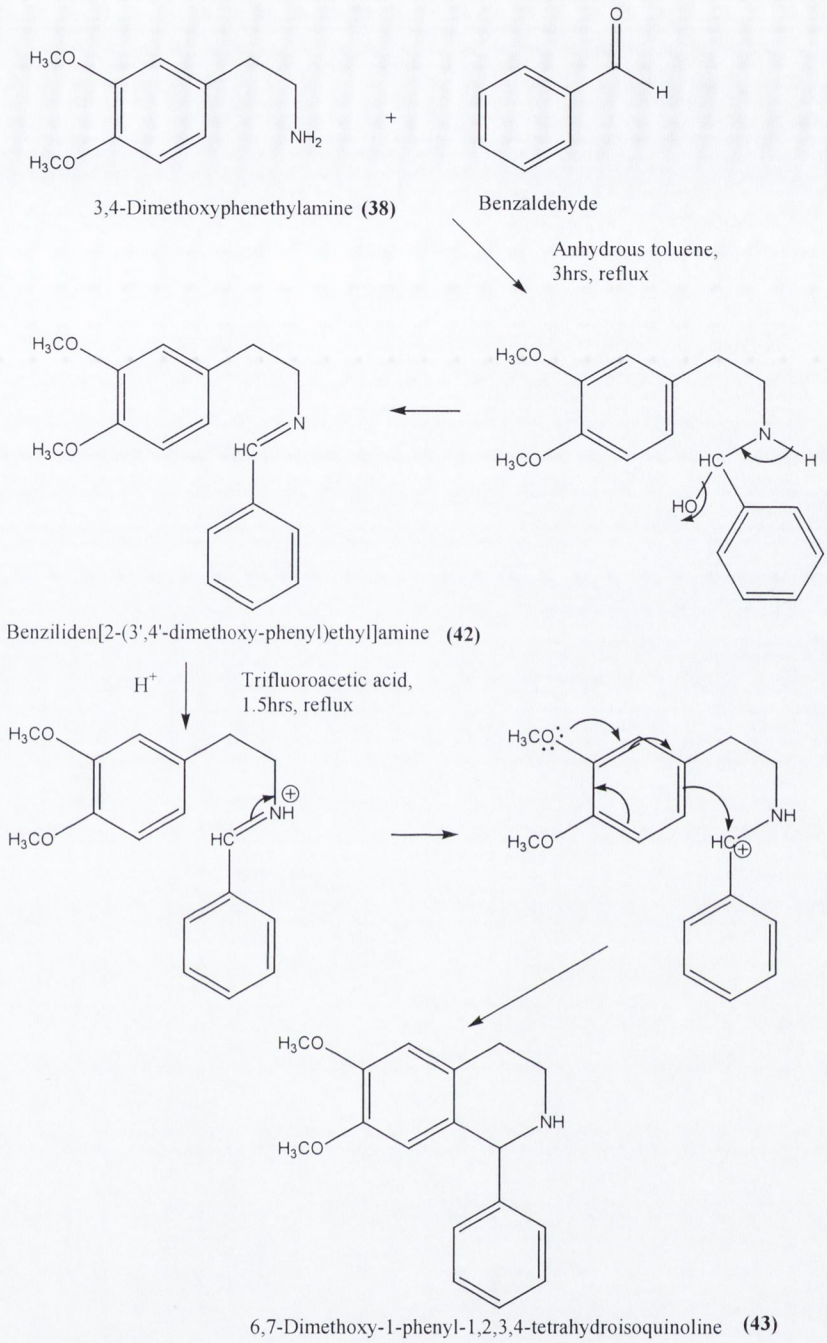


Scheme 3-2: Bischler-Napieralski synthesis of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinolines

3.3.2 Pictet-Spengler Synthesis

This process offers a more direct route to tetrahydroisoquinolines, eschewing the dihydroisoquinoline stage. An azobenzilidine **(42)** is formed by the β-phenylethylamine **(38)** and an aldehyde, and this is cyclised using an acid catalyst to give the tetrahydroisoquinoline **(43)** as illustrated in Scheme 3-3.

This procedure had been outlined by Gitto et al. and was found to give the 6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline in 99% yield![68] It was therefore adopted for the preparation of all amides with a phenyl group at position 1.

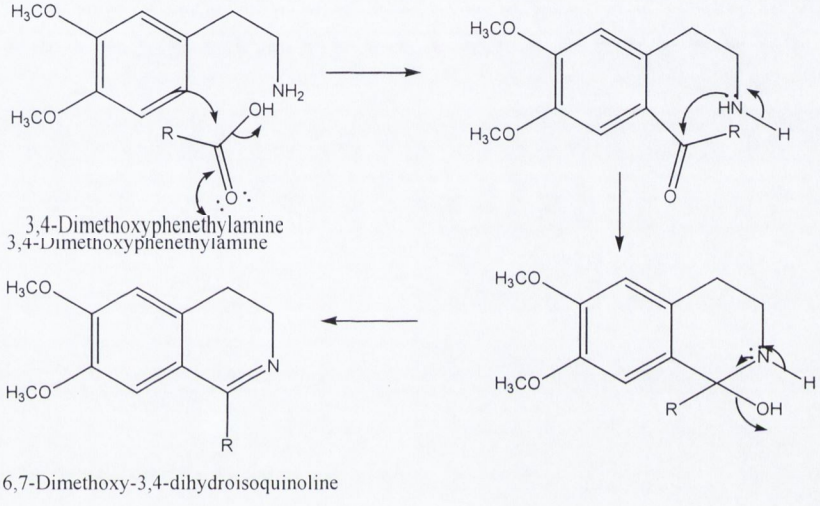


Scheme 3-3: Pictet-Spengler synthesis of 6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline

3.3.3 Acylation followed by Cyclisation

Both the Pictet-Spengler and Bischler-Napieralski syntheses give superior yields when electron-donating groups are present on the aromatic ring of the parent β-phenylethylamine, in a position *para* to the point of ring closure.[47] However, when methoxy groups are found at positions 3 and 4 the synthetic route can be simplified further. A one pot synthesis using 3,4-dimethoxyphenethylamine, the appropriate carboxylic acid and polyphosphoric acid has been profiled by Venkov and Ivanov.[65]

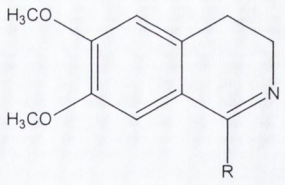
The mechanism of this synthesis is slightly different to those already encountered. Venkov et al. contended that the acid (or in some cases anhydride) acylated the phenylethylamine at the position *ortho* to the amine sidechain, and that this then cyclised with the amine during the alkaline work-up, as shown in Scheme 3-4. The theory was confirmed by the isolation of phenylacetyl-benzene-sulfonamide after 30 minutes heating of N-(3,4-dimethoxyphenylethyl)benzenesulphonamide with phenylacetic acid (in polyphosphoric acid) at 80°C. This intermediate was then treated with polyphosphoric acid for a further 3 hours at 80°C to give 6,7-dimethoxy-1-benzyl-3,4-dihydroisoquinoline **(50)**. N-(3,4-dimethoxyphenylethyl)benzenesulphonamide was once more heated at 80°C with polyphosphoric acid, but this time for 3 hours and gave the dihydroisoquinoline directly.[65]



Scheme 3-4: Venkov synthesis - mechanism

In the present work, this synthetic route was imitated and a series of dihydroisoquinolines **(41, 45 – 50)**, with varied alkyl and aromatic groups at position 1, were synthesised. The moderate yields (see Table 3-1) were more than twice that obtained with the Bischler-Napieralski route (e.g. 57.0% as against 20.7% for **(41)**). The ^{1}H-NMR spectra were simple, with a triplet for the C4$\underline{H}_2$ methylene protons upfield of that for the C3$\underline{H}_2$ protons. The carbon at position 1 was seen at about 165 ppm in the ^{13}C-NMR spectrum, confirming formation of the carbon-nitrogen double bond. This was echoed by a band at 1150 – 1140 cm^{-1} in the IR absorption spectra.

3,4-Dihydroisoquinolines of reasonable yield were chosen for subsequent reduction, with sodium borohydride, to the corresponding 1,2,3,4-tetrahydroisoquinoline (see Section 3.4).

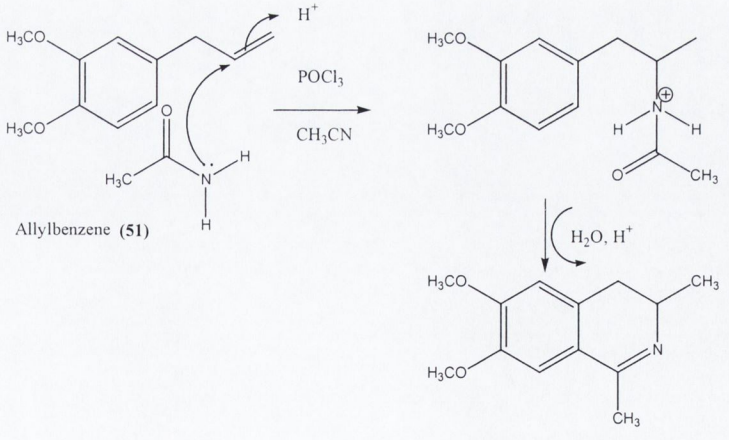


Compound Number	R =	Yield, %
41[69]	CH_3	57.0
45[70]	C_2H_5	39.8
46[71]	C_3H_7	42.0
47[65]	C_6H_5	42.6
48[72]	,*p*-$C_6H_4(OCH_3)$	42.4
49[65]	*m,p*-$C_6H_3(OCH_3)_2$	42.8
50[65]	$CH_2C_6H_5$	58.3

Table 3-1: Yields of 6,7-dimethoxy-dihydroisoquinolines synthesised using the Venkov one pot method

3.3.4 Ritter-Murphy Synthesis

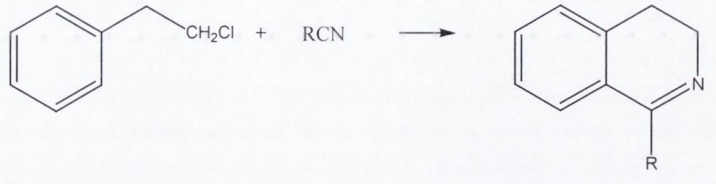
A type of Ritter-Murphy reaction was utilised for the preparation of compound **(52)**. The classic Ritter-Murphy involves acid catalysed attack by the nitrogen of a nitrile group on the double bond of an allylbenzene **(51)**; this generates a nitrilium salt which is hydrolysed to the amide, and then cyclised to the dihydroisoquinoline **(52)** at high temperatures.[73] An adaptation of this procedure, introduced by Kametani et al, uses acetamide in place of a nitrile and phosphorous oxychloride as the dehydrating agent[74], as seen in Scheme 3-5. The yield of **(52)** was a meagre 17.7%, so this synthesis was not routinely employed.



Scheme 3-5: Kametani modification of Ritter-Murphy synthesis of 6,7-dimethoxy-1,3-dimethyl-3,4-dihydroisoquinoline

3.3.5 Lora-Tamayo Synthesis

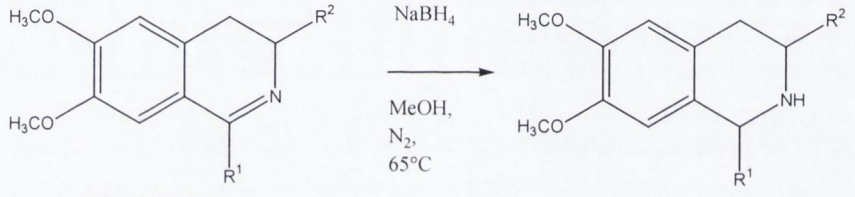
Closely related to the Ritter-Murphy synthesis is a procedure outlined by Lora-Tamayo et al[75], involving tin chloride as the catalyst for the attack of a nitrile on a chloroalkylbenzene **(53)**. This route gave low yields but proved convenient for the preparation of 3,4-dihydroisoquinolines with unsubstituted aromatic rings. The synthesis is discussed in detail in Chapter 5 (see section **5.3**), and is shown in Scheme 3-6.



2-Chloroethylbenzene **(53)** Nitrile 3,4-Dihydroisoquinoline

Scheme 3-6: Lora-Tamayo synthesis of 3,4-dihydroisoquinolines with unsubstituted aromatic rings

3.4 1-Alkyl-1,2,3,4-tetrahydroisoquinolines



(41, 47, 50, 52) **(43, 54, 56, 57)**

Scheme 3-7: Reduction of 6,7-dimethoxy-3,4-dihydroisoquinolines using sodium borohydride

Compound Number	R^1 =	R^2 =	Yield
54[76]	CH_3	H	84.9
43[77]	C_6H_5	H	71.0
56[78]	$CH_2C_6H_5$	H	15 (77)
57[79]	CH_3	CH_3	9.9

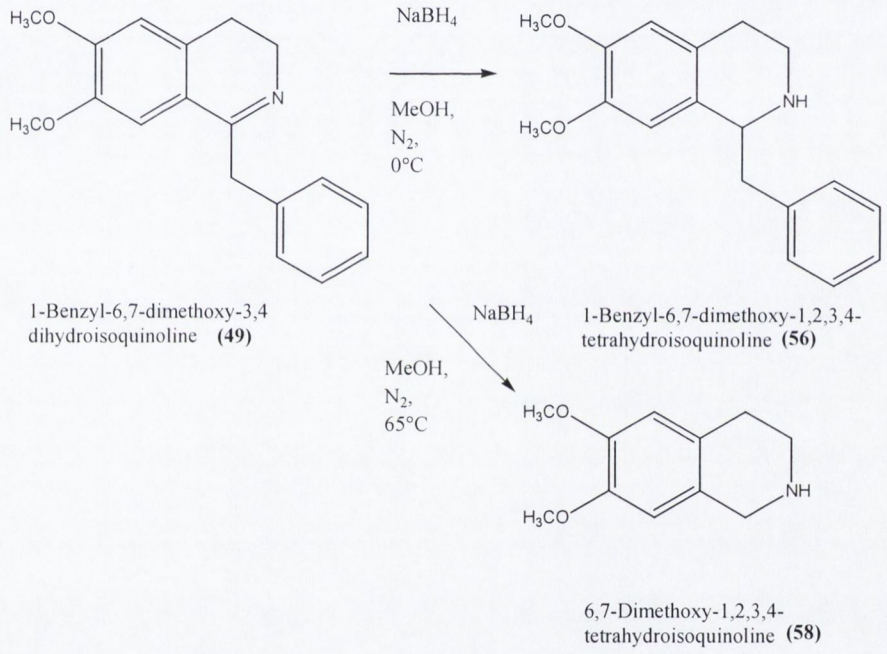
Table 3-2: Yield of 1,2,3,4-tetrahydroisoquinolines from sodium borohydride reduction

Hydrogenation of DHIQs **(41, 47, 50** and **52)** afforded the THIQs **(54, 43, 56** and **57)**. The use of sodium borohydride rather than a palladium/carbon catalyst and hydrogenation protected the aromatic ring. Although hydrogenation is a nucleophilic process, and should occur at the double bond of the saturated ring, more severe conditions could lead to hydrogenation of the aromatic ring also.[47]

The spectra of the tetrahydroisoquinolines **(43, 54, 56, 57)** were more complex than those of their precursors **(41, 47, 50, 52)**. The protons of the methylene groups at positions 3 and 4 now appeared separately. The combination of vicinal and geminal coupling, in signals close in shift value, gave a collection of multiplets. The shift values of C5H and C8H were closer together. The downfield signal of the C=N had disappeared from the ^{13}C-NMR spectrum and the related absorption in the IR spectrum was no longer to be seen.

3.4.1 Cleavage of 1-Benzyl group

Yields of 1-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **(56)** were very low (15.0%) after the 2 hours heating that sufficed for the other dihydroisoquinolines. A second, heavier product spot was noticed on the thin layer chromatograph. This was isolated and inspection using NMR spectroscopy showed it to be 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **(58)**, as shown in Scheme 3-8. Clearly sodium borohydride removes the benzyl group at position 1 of the isoquinoline nucleus of **(49)**. The reaction was therefore repeated at 0°C and monitored on TLC, to allow the solution to be treated with icy water and worked up as soon as the dihydroisoquinoline was seen to be completely reduced. The second yield listed (77%) is for the modified reduction procedure.



Scheme 3-8: Cleavage of benzyl group of 1-benzyl-6,7-dimethoxy-3,4-dihydroisoquinoline by sodium borohydride

3.5 2-Amido-1,2,3,4-tetrahydroisoquinolines

3.5.1 1-(3,4-Dihydro-*1H*-isoquinolin-2-yl)-ketones

3.5.1.1 Coupling using Dicyclohexylcarbodiimide

The production of a series of 2-amido-1,2,3,4-tetrahydroisoquinolines was next to be investigated. Initially, it was hoped to use dicyclohexylcarbodiimide (DCC) to generate most of the desired amides from the THIQ. DCC is a coupling reagent: that is, it is a condensing agent, which may be used to directly couple acids and amines. It is used extensively in peptide chemistry and also in ester formation. Although allergenic, it has

the advantage of promoting amide linkage formation at room temperature for a wide variety of acids and acid chlorides with amines.

DCC was first proposed as a coupling reagent for peptide synthesis by Sheehan and Hess in 1955. It is not an ideal reagent. One problem is that DCC can itself combine with amines to give guanidine derivatives; it is therefore preferable to carry out coupling reactions at room temperature or below, to discourage this alternative reaction.[80]

The by-product of coupling, *N,N'*-dicyclohexylurea (DCU), is soluble in alcohols, which cannot then be used as solvents for the reaction. Moreover, although only slightly soluble in organic solvents, such as dichloromethane, some DCU may remain after filtration and can be difficult to remove. THF and DMF have been reported to reduce reaction rates and to increase racemization in chiral carboxylic acids, but this was not of concern for the tetrahydroisoquinoline amides.[81]

Mechanism of DCC

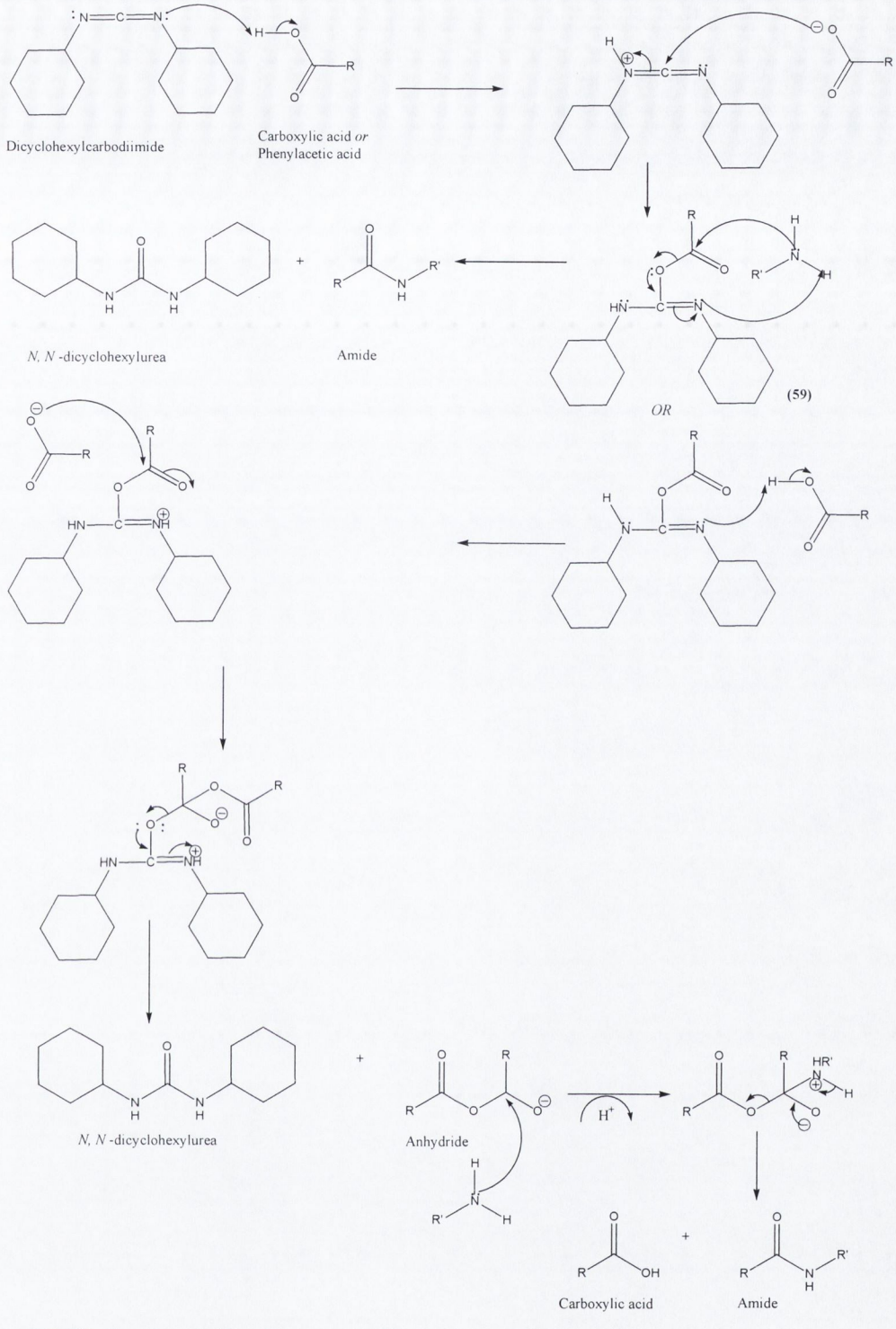
DCC may promote the formation of amide bonds in either of two ways, both of which are illustrated in Scheme 3-9. Abstraction by the nucleophilic nitrogen of DCC of the proton of the carboxylic acid OH allows the oxygen to link with the central carbon of DCC, giving the intermediate **(59)**. The amine may then attack the electrophilic carbon of the carbonyl group. Rearrangement of the DCC moiety generates DCU and the amide departs, fully formed.

The alternative involves attack by the second nitrogen of the O-acylisourea, **(59)**, on a second molecule of carboxylic acid. The proton of the OH is again removed and the remaining carboxylate anion attacks the electrophilic carbon of the ester linkage. DCU and a symmetrical anhydride are generated by this pathway. The anhydride is a potent acylating agent and reacts readily with the amine.[80]

In addition to DCC, 4-dimethylaminopyridine, hereafter referred to by its common abbreviation DMAP, was used as an acyl transfer agent. It enhances the rate of acylation of amines. [81] It is highly nucleophilic, and is used less extensively than heretofore for peptide synthesis, due to its tendency to cause racemization of chiral molecules.

3.5.1.1.1 Non-formation of product

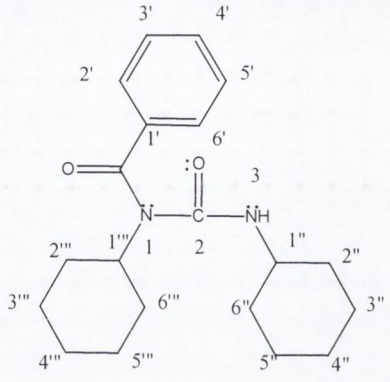
The procedure was successfully used to form amides at position 7 of the tetrahydroisoquinoline ring (see Chapter 2) and for certain amides at position 2. However, the first attempt to synthesise (3,4-dihydro-*1H*-isoquinolin-2-yl)-phenyl-methanone **(77)**), resulted only in the formation of a colourless solid, which was *not* the product and did not contain a tetrahydroisoquinoline nucleus.



Scheme 3-9: Mechanism of dicyclohexycarbodiimide in amide formation

3.5.1.1.2 Spectroscopy of ureide

Investigation by NMR spectroscopy suggested the presence of an ureide (Figure 3-1). A detailed analysis of the spectroscopic data of **(59a)** is now presented.



1-Benzoyl-1,3-dicyclohexyl-urea

Figure 3-1: Ureide (59a)

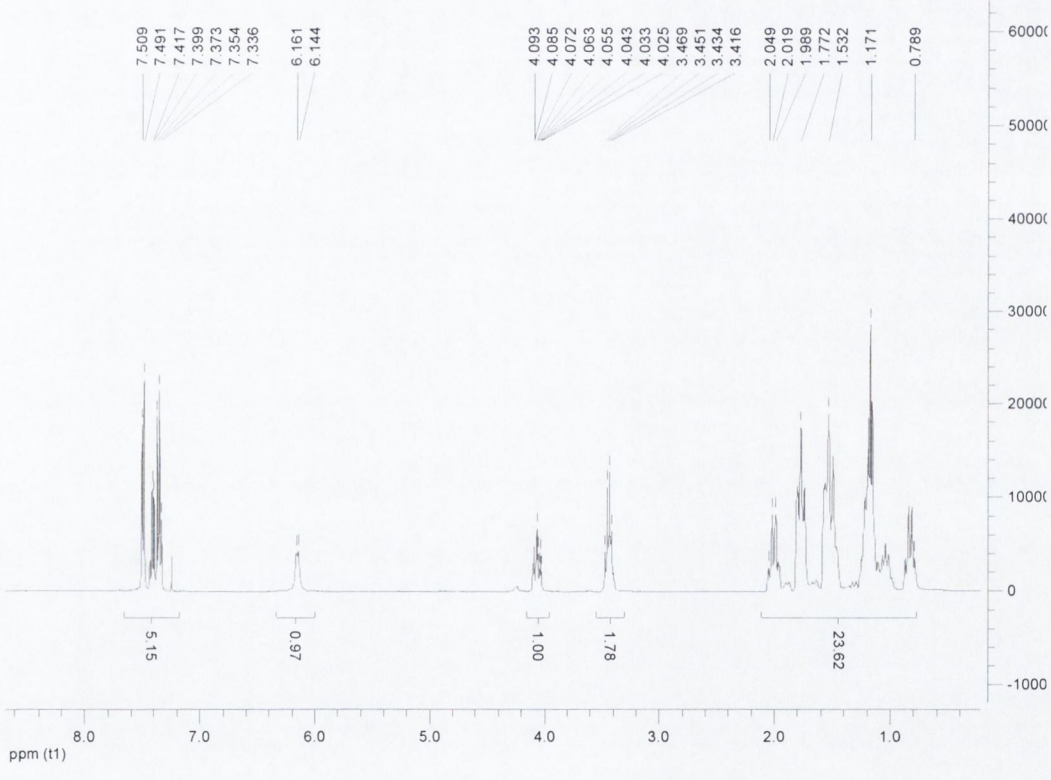


Figure 3-2: ^{1}H-NMR spectrum of (3,4-dihydro-1H-isoquinolin-2-yl)-phenyl-methanone

The ^{1}H-NMR spectrum (see Figure 3-2) shows a doublet at 6.15δ, and this downfield signal, not quite in the aromatic region, is consistent with an NH proton. A multiplet integrating for 5 protons is to be seen at 7.34δ to 7.51δ.

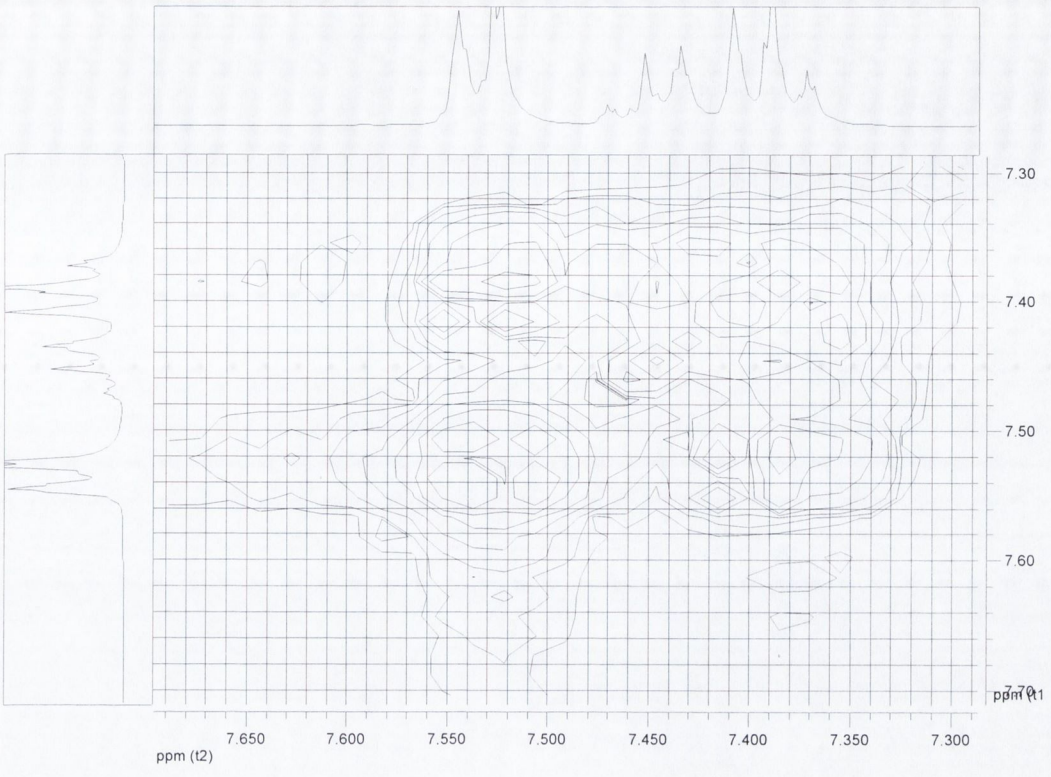


Figure 3-3: ^{1}H-^{1}H COSY

When this tangle of signals was examined more closely using a H-H COSY experiment (Figure 3-3), it was found that the multiplet at 7.34δ - 7.37δ, integrating for 2 protons, coupled with the doublet at 7.50δ (^{4}J), and with the multiplet at 7.40δ - 7.42δ (^{3}J). The latter integrates for one proton and must be the proton in the *para* position of the benzene ring. The coupling constant of 7Hz for the doublet at 7.50δ indicates the protons are neighbouring those at 7.34δ - 7.37δ: they must be the duos of protons, in the *ortho* and *meta* positions respectively, of the aromatic ring. The carbon signals are at 126.6ppm (C2'H, C6'H), 128.5ppm (C3'H, C5'H) and 130.6ppm (C4'H) (see Figure 3-9).

The inverted signals in the DEPT 135 spectrum (Figure 3-4) are of differing strengths. While the intensity of a signal in carbon spectra may not be used for integration and thus deduction of the number of groups present, there is a rough correlation between the size of a CH_2 signal and the number of methylene groups that contribute to it.

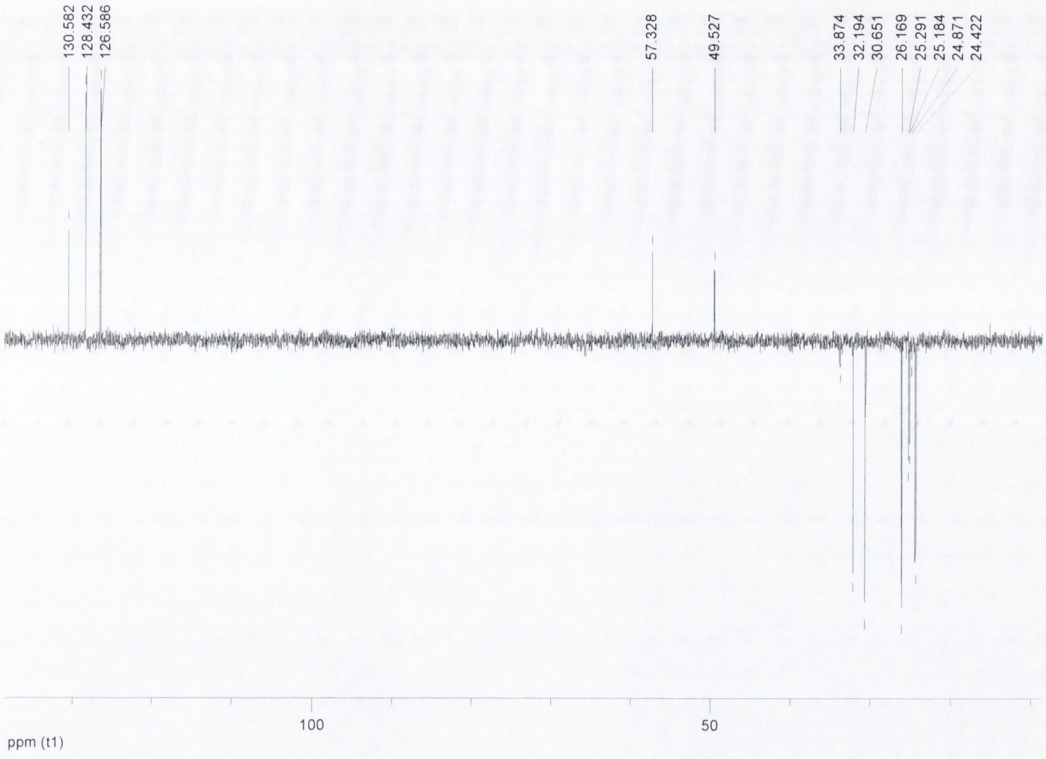


Figure 3-4: DEPT 135 spectrum of (3,4-dihydro-1H-isoquinolin-2-yl)-phenyl-methanone

The signals at 25.2ppm and 25.3ppm correspond to the methylene groups at positions 4" and 4"' of the cyclohexyl rings. They are attached to protons that give signals at approximately 1.1δ, 1.2δ, 1.5δ and 1.7δ (see HMQC in Figure 3-5).

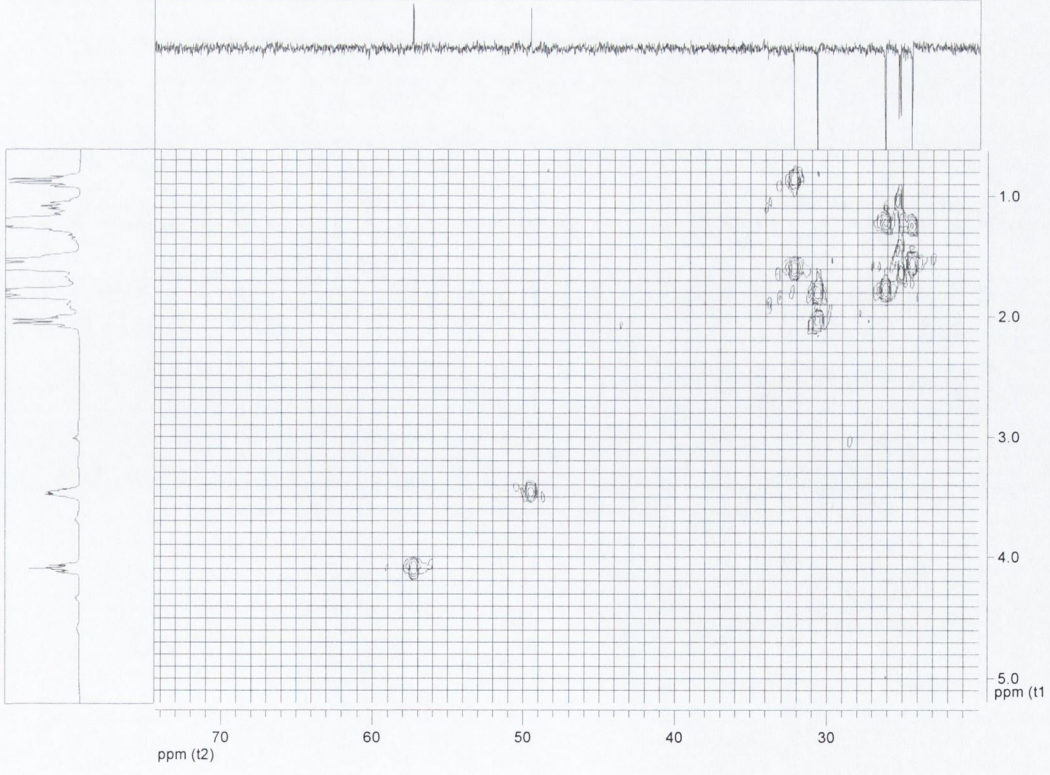


Figure 3-5: HMQC of ureide

The substantial effect of irradiation of the proton of the NH at 6.15δ, on the part of the cyclohexyl multiplet observed at about 0.8δ, evidences that this corresponds to the methylenes at C2"H_2 and C6"H_2 (see Figure 3-6).

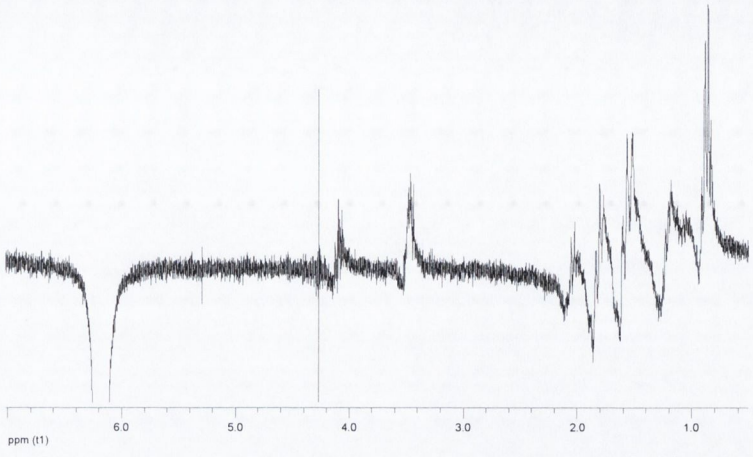


Figure 3-6: NOE difference spectrum with NH proton irradiated

More specifically, they must be the protons at those positions in the same plane as the NH proton. That these methylene protons are held by the carbon at 32.2ppm is indisputable from a glance at the HMQC of Figure 3-5. Their partners are found at 1.5δ - 1.7δ. The methylene groups at C2'"H_2 and C6'"H_2 would be expected to be in a similar electronic environment; the carbon signal at 30.7ppm is the obvious candidate. This is shown by the CH-COSY to bear the protons represented by signals at about 1.81δ and 2.00δ - 2.09δ. The protons at 1.78δ - 1.84δ are enhanced by an NOE experiment irradiating the proton at approximately 4.1δ (Figure 3-7).

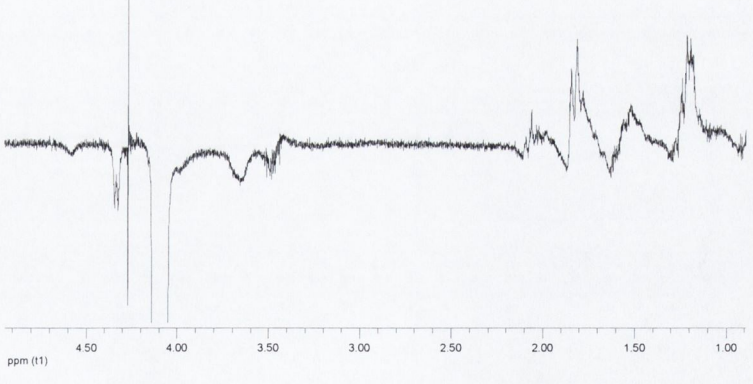


Figure 3-7: NOE difference spectrum, with irradiated proton at C1'"H

This is argued (below) to be the C1'"H and therefore the protons giving rise to the multiplet at around 1.8δ must be the C2'"H_2 and C6'"H_2 protons in the same plane.

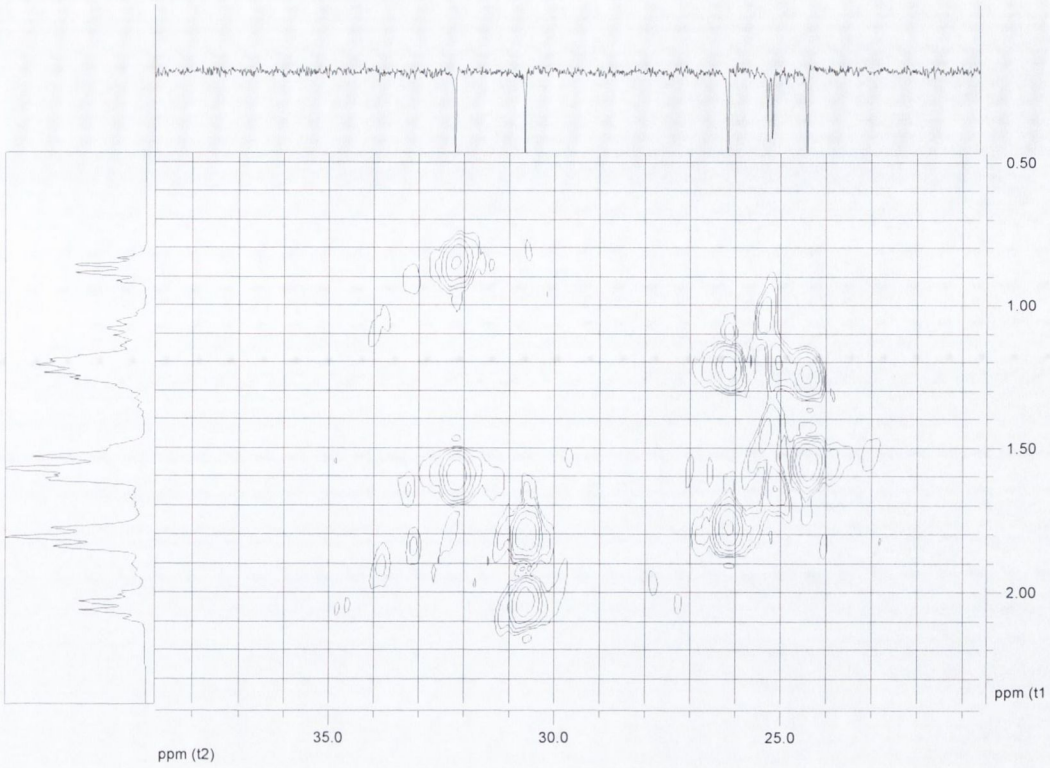


Figure 3-8: HMQC of cyclohexyl methylene groups in (3,4-dihydro-1H-isoquinolin-2-yl)-phenyl-methanone

C3"H_2 and C5"H_2 and their counterparts in the other ring have yet to be assigned. Upfield from the C4"H_2 and C4'"H_2 peaks are signals at 24.5ppm and again at 26.2ppm. The 2-D spectrum (HMQC, Figure 3-8) shows the methylene carbons to bear the protons signalling at about 1.2δ, 1.3δ, ca.1.5δ and approximately 1.8δ. These are C3"H_2, C5"H_2, C3'"H_2 and C5'"H_2.

The CH signals at 49.5ppm and 57.3ppm were clear from the DEPT 135 spectrum (Figure 3-4). The HMQC (Figure 3-5) shows that the more upfield proton (3.42δ - 3.47δ) is attached to the more upfield carbon (49.5ppm). NOE shows that irradiation of the proton of the NH at 6.15δ enhances this signal to a greater extent than that at 4.03δ - 4.09δ (see Figure 3-6). Thus, the multiplet at approximately 3.5δ must be the C1"H of the cyclohexyl ring, and the signal at 49.6ppm is its carbon peak. By a process of elimination, the multiplet at ca. 4.1δ must belong to the other CH in a cyclohexyl ring, at C1'"H, and its carbon signal is seen at 57.4ppm.

The quaternary signals remain to be assigned. The quaternary carbon signal at 137.1ppm can only belong to C1' of the aromatic ring. The carbonyl carbon between the nitrogens (C2O) should be somewhat upfield of the carbonyl signal of the benzoyl group. The signal at 154.3ppm is therefore attributed to C2O and that at 171.3.ppm to the benzoyl CO (see Figure 3-9).

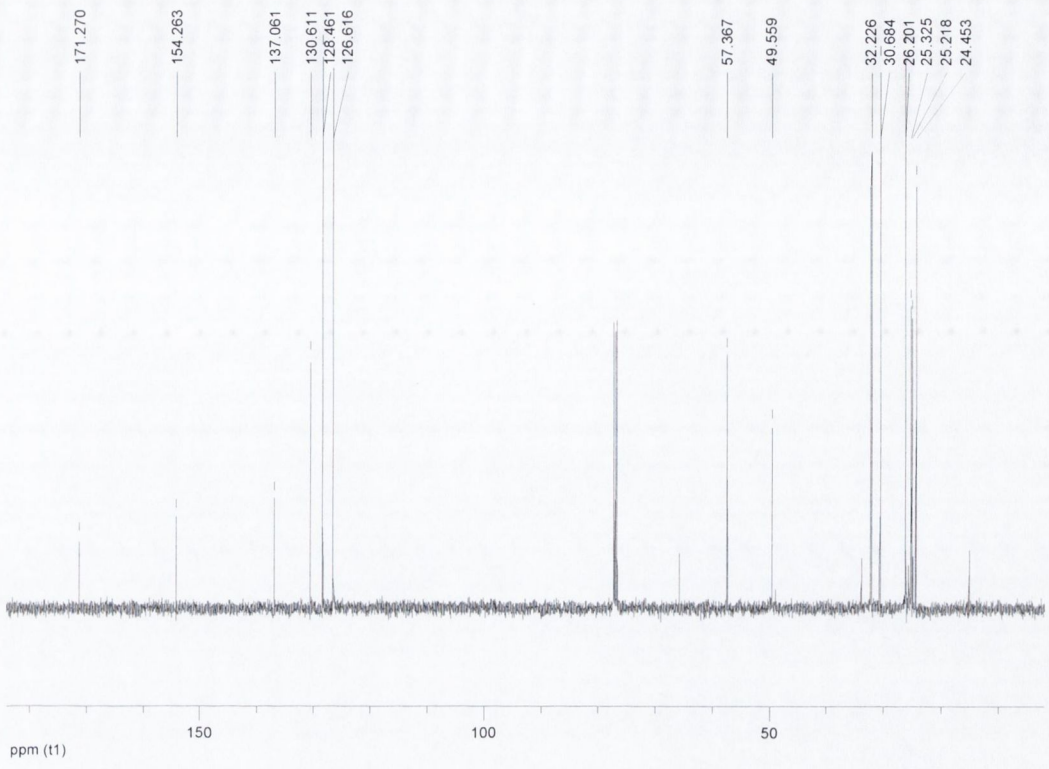
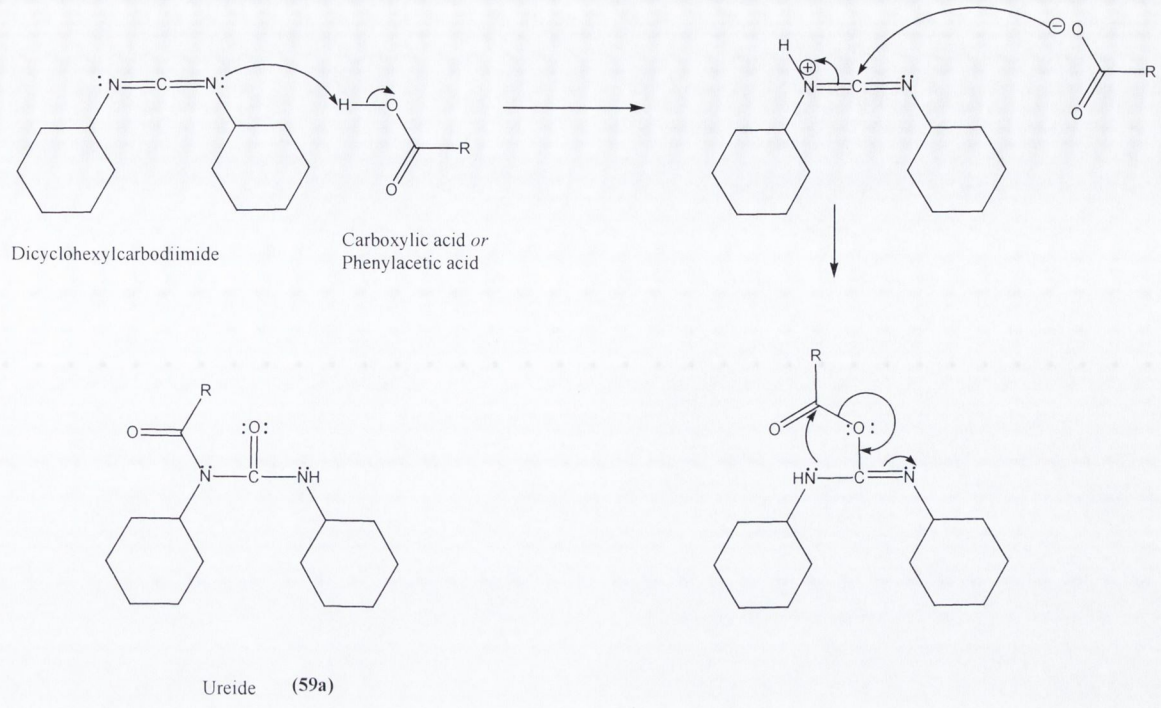


Figure 3-9: ^{13}C-NMR spectrum of ureide

An IR spectrum strengthened the evidence: it showed a strong amide carbonyl absorbance at 1650cm^{-1}. Moreover, there was no absorbance at 2260cm^{-1} 2240cm^{-1}, as would be expected with a nitrile intermediate.

3.5.1.1.3 Proposed mechanism of ureide formation

The formation of the *N*-acylurea derivative of the DCC-carboxylate intermediate **(59a)** is shown in Scheme 3-10. The nucleophilic attack of the nitrogen of the NH group of DCC causes an *O*→*N* shift and the intramolecular rearrangement gives the stable ureide.



Scheme 3-10: Formation of ureide

3.5.1.1.4 Function of 1-HOBT

One approach to counter the formation of ureides is to use two equivalents of carboxylic acid for each equivalent of DCC. This promotes the formation of symmetrical anhydrides and reduces the influence of *O*-acylisourea. Since there is less *O*-acylurea present, the *O*→*N* acyl migration plays a less significant role. This procedure wastes acid and will not entirely eliminate the difficulty.

Acylation with acid chlorides was therefore the preferred mode of synthesis. In some cases, the acid chloride was not available. Rather than prepare the acid chloride from the acid - introducing an additional step and reducing the overall yield – the coupling reaction was modified. Figure 3-10 shows 1-hydroxybenzotriazole (HOBT) **(60)**, which was substituted for DMAP.[82]

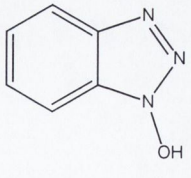
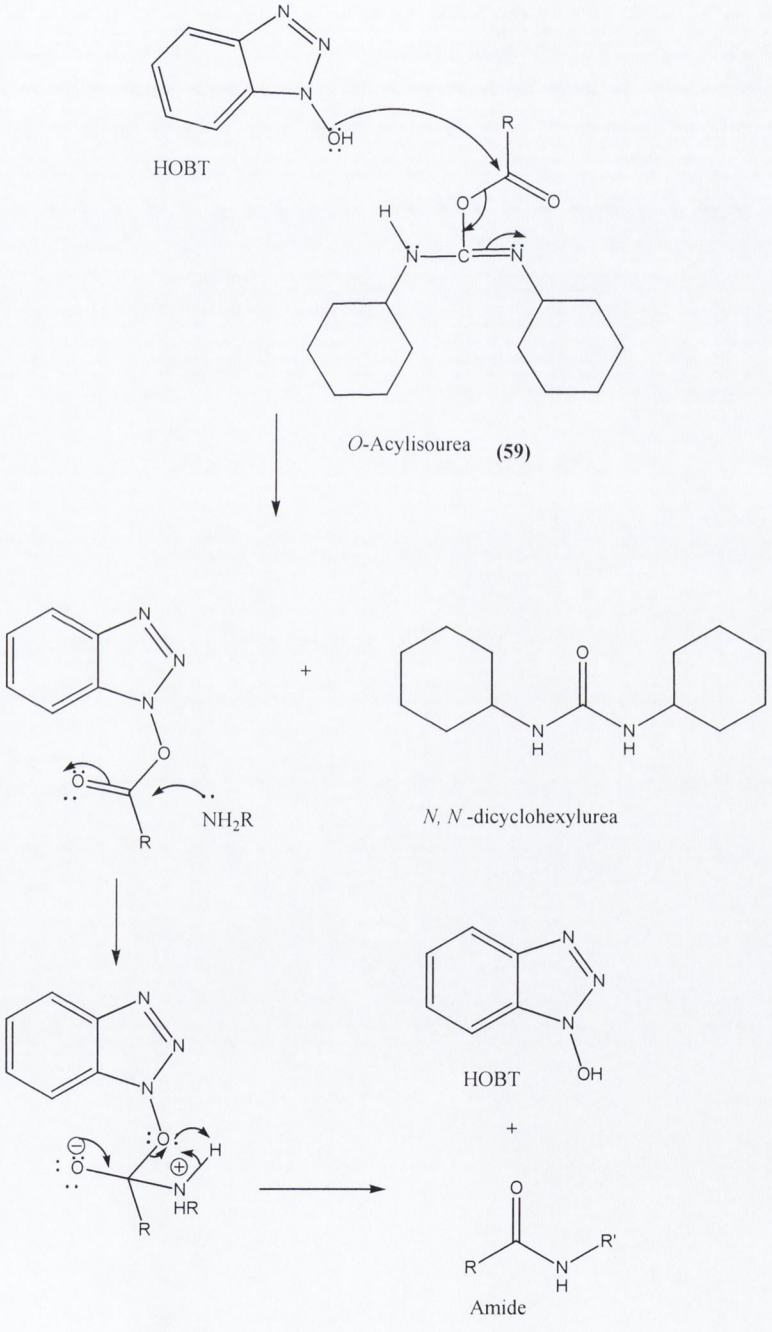


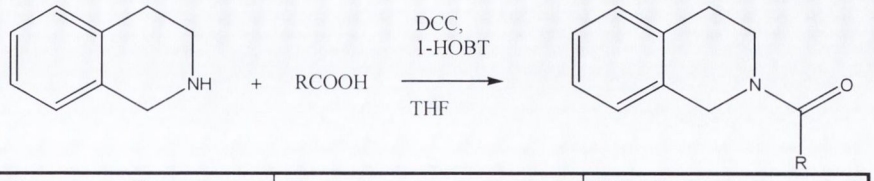
Figure 3-10: 1-Hydroxybenzotriazole, (60)

HOBT is used in eqimolecular amounts with the acid, amine and DCC. It thus provides a second mole of nucleophile for each mole of DCC. The reactive *O*-acylisourea now can react with the acid (to form the symmetrical anhydride), the amine (to form the desired amide) or HOBT. In the case of HOBT it transfers the carboxylate moiety to the triazole,

forming an ester that does not readily allow ureide formation. The ester is amenable to nucleophilic attack by the amine nitrogen, and the amide forms, regenerating HOBT (see Scheme 3-11). The lifetime of the *O*-acylisourea is reduced and it cannot perform the *O*→*N* shift. Furthermore, the concentration of HOBT remains constant and this affects the kinetics of the process and accelerates the reaction.[80] The products and yields from this route are shown in Tables 3-3, 3-5, 3-7 and 3-9.



Scheme 3-11: Mechanism of acylation involving DCC and HOBT as an additive



Compound Number	R =	Yield
61[83]	$CH_2C_6H_5$	64.5
62	$CH_2C_6H_4NO_2$	63.5
63	$CH_2C_6H_4SCH_3$	75.0
64	*m*-$CH_2C_6H_4OCH_3$	50.3
65[84]	*p*-$CH_2C_6H_4OCH_3$	33.2
66[85]	*m,p*-$CH_2C_6H_4(OCH_3)_2$	56.8
67	*p*-$C_6H_4NO_2$	98.0
68	*p*-$C_6H_4SCH_3$	51.0

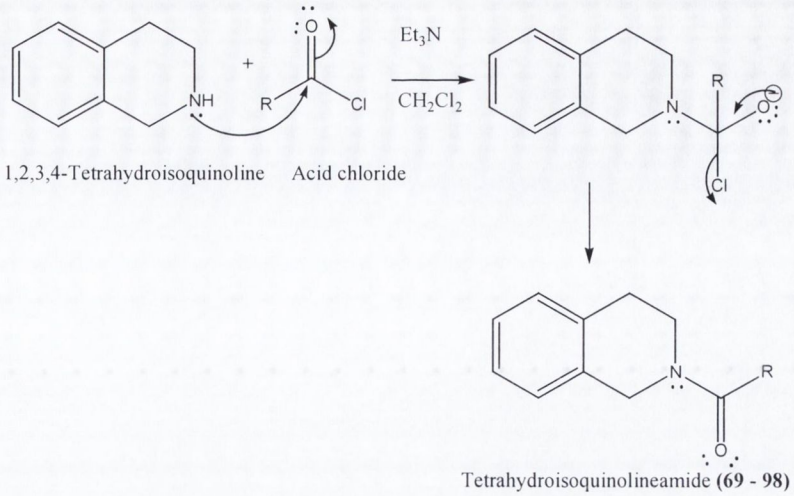
Table 3-3: (3,4-Dihydro-1H-isoquinolin-2-yl)-ketones synthesised using DCC

The IR spectra of compounds **(61 – 68)** displayed a prominent absorption at about 1630 cm^{-1}, typical of an amide CO. The ^{1}H and ^{13}C- NMR spectra exhibited *two* separate signals for each one expected, e.g. two singlets were observed for C1$\underline{H}_2$. This is not unusual with amides, and is discussed in section 3.5.1 below. A detailed discussion of a benzyl amide in section 3.5.4.1 illustrates the pattern of spectra seen with products **61 – 68.**

3.5.1.2 Amide formation using Acid Chlorides

Where acid chlorides were available, these were substituted for carboxylic acids. This allowed acylation to proceed by the tetrahedral mechanism. The Baumann-Schotten procedure[86], which involves vigorously shaking the amine and acid chloride together in aqueous alkali, was used in the case of both benzoyl chloride **(77)** and *p*-toluoylchloride **(80)**.

All the other amides presented in Tables 3-4 **(69 – 76, 78, 79, 81 – 98)**, 3-6 **(106 – 121)**, 3-8 **(130 – 144)** and 3-10 **(152 – 166)** were formed by reaction of the appropriate tetrahydroisoquinoline and acid chloride, as shown in Scheme 3-12.[87]



1,2,3,4-Tetrahydroisoquinoline Acid chloride

Tetrahydroisoquinolineamide **(69 - 98)**

Scheme 3-12: Formation of amide by tetrahedral mechanism, using acid chloride

Compound Number	R =	Yield, %
69	CH_3	71.1
70	C_2H_5	96.8
71	C_3H_7	86.8
72	C_4H_9	80.1
73	$CH_2CH(CH_3)_2$	99.9
74	Cyclopropyl	95.3
75	Cyclobutyl	61.7
76	Cyclohexyl	96.4
77	C_6H_5	51.6
78	*o*-$C_6H_4CH_3$	90.5
79	*m*-$C_6H_4CH_3$	82.6
80[86]	*p*-$C_6H_4CH_3$	80.5
81	*o*-$C_6H_4OCH_3$	78.5
82	*m*-$C_6H_4OCH_3$	70.5
83	*p*-$C_6H_4OCH_3$	67.0
84	*o*-C_6H_4F	84.0
85	*m*-C_6H_4F	87.1
86	*p*-C_6H_4F	80.3
87	*o*-C_6H_4Cl	76.9
88	*m*-C_6H_4Cl	81.8
89	*p*-C_6H_4Cl	96.1
90	C_6H_4Br	93.5
91	C_6H_4I	57.4
92	*o*-$C_6H_4NO_2$	61.9
93	*m*-$C_6H_4NO_2$	58.7
94	*o*-$C_6H_4CF_3$	68.0
95	*m*-$C_6H_4CF_3$	69.7
96	*p*-$C_6H_4CF_3$	72.2
97[86]	$C_6H_4C_2H_5$	61.9
98	2-Naphthalenyl	57.2

Table 3-4: (3,4-Dihydro-*1H*-isoquinolin-2-yl)-ketones from acid chlorides

The spectroscopy of amides **(61 – 166)** is complicated by the observation of rotamers, which may be seen as a result of the partial double bond nature of the C-N bond. This can give rise to pseudo *cis* and *trans* isomers (as shown in Figure 3-11). They interconvert, but usually slowly enough for two sets of signals to be observed in NMR spectra. An average is seen in IR spectra. Of course, there is no difference in the mass fragmentation pattern. Essentially, there is only one compound.

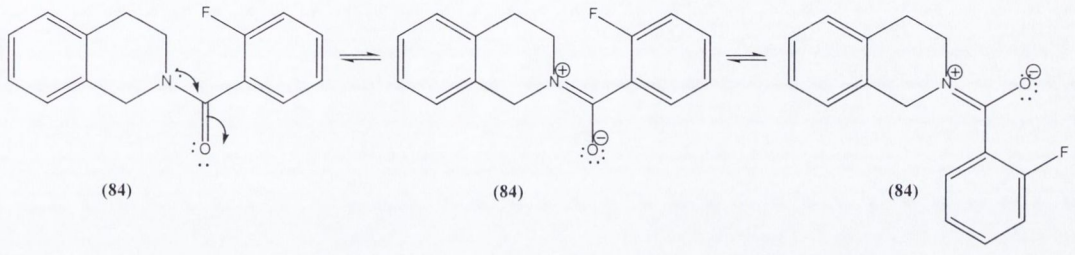


Figure 3-11: Psuedo *cis* and *trans* isomers from hindered rotation (rotamers) of (84)

The interconversion is of the order of 10^{-1} to $10^{3}s^{-1}$. If the difference between the shift values of the two signals is $\delta\nu$ Hz, then an exchange much slower than $2\prod\delta\nu$ (s^{-1}), will give two sets of signals, as in Figure 3-12 below, which is the spectrum of (3,4-dihydro-*1H*-isoquinolin-2-yl)-(2-fluoro-phenyl)-methanone **(84)**. [88]

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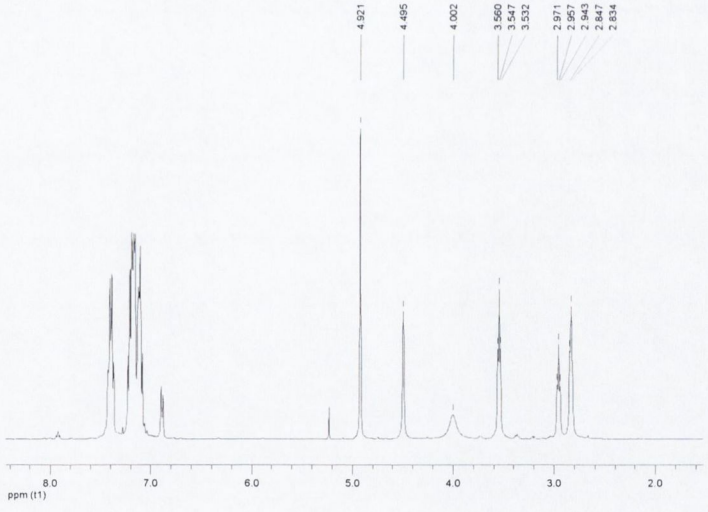


Figure 3-12: : ^{1}H-NMR spectrum of (3,4-dihydro-1H-isoquinolin-2-yl)-(2-fluoro-phenyl)-methanone (84), showing fine resolution of rotamers

If the *cis* and *trans* conformations interconvert much more rapidly than $2\prod\delta\nu(s^{-1})$, only a single signal is seen. At intermediate rates of conversion, the two peaks coalesce, and a broad peak is observed, as in the spectrum of (3,4-dihydro-*1H*-isoquinolin-2-yl)-(4-fluoro-phenyl)-methanone **(86)**, seen in Figure 3-13.

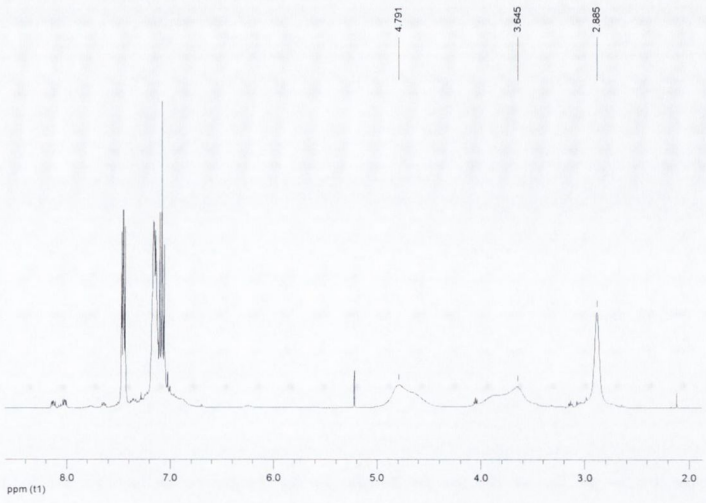


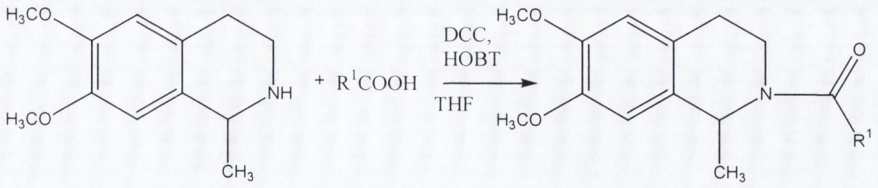
Figure 3-13: ^{1}H-NMR spectrum of (3,4-dihydro-1H-isoquinolin-2-yl)-(4-fluoro-phenyl)-methanone (86), showing broad peaks at the coalescence point of the rotamers

Clearly, an *ortho* substitutent on the benzoyl ring as in **(84)** hinders free rotation about the C-N bond to an appreciable extent, and the slow process results in two sets of finely resolved signals, duly detailed in the experimental section of the thesis. A *meta* substituent, as seen in **(85)**, provides less obstruction, and the more rapidly interconverting isomers give rise to separate signals, but fine detail is lost in the spectrum. A *para* substituent, as in **(86)**, particularly a bulky one, slows interconversion to the point where only one very broad signal is seen.

3.5.2 1-(6,7-Dimethoxy-1-methyl-3,4,-dihydro-*1H*-isoquinolin-2-yl)-ketones

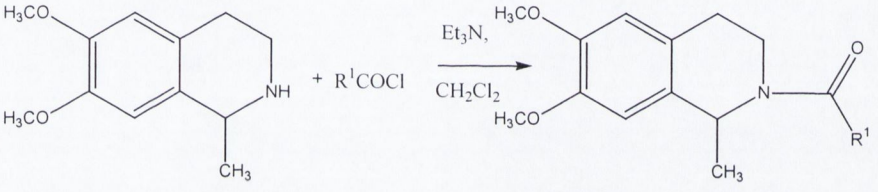
A quick comparison of Tables 3-3 and 3-5, and of Tables 3-4 and 3-6, will show that the presence of an alkyl substituent at position 1 depressed the yield of position 2 amides. This is hardly surprising, as some steric interference might be expected. The procedure using acid chlorides gave consistently higher yields than the route using phenylacetic acids. The highest yield of an amide derived from an acid coupling was that for the thiomethylbenzoyl **(105)**. This was not available commercially as an acid chloride. It is the smallest molecule of the acids used and gave a yield comparable to the best of the acid chloride route. This suggests that the bulk of the reacting acid in **(99)** to **(104)** might have a large influence on the lower yields seen with the coupling route.

The ^{1}H-NMR spectra of **(99 - 121)** now have two quartets for C1$\underline{H}$ at about 5.0 δ and 5.6 δ and the methyl itself is seen as two doublets at 1.5 δ approximately. The alkyl substituent at position 1 and the amide at position 2, hinder rotation on the part of the methylene protons. They are seen separately, and one C3$\underline{H}_2$ proton is very close to the upfield C1$\underline{H}$.



Compound Number	R^1 =	Yield
99[89]	$CH_2C_6H_5$	33.1
100	$CH_2C_6H_4NO_2$	46.5
101	$CH_2C_6H_4SCH_3$	35.3
102	*m*-$CH_2C_6H_4OCH_3$	62.2
103[90]	*p*-$CH_2C_6H_4OCH_3$	31.1
104[89]	*m,p*-$CH_2C_6H_4(OCH_3)_2$	68.3
105	$C_6H_4SCH_3$	82.7

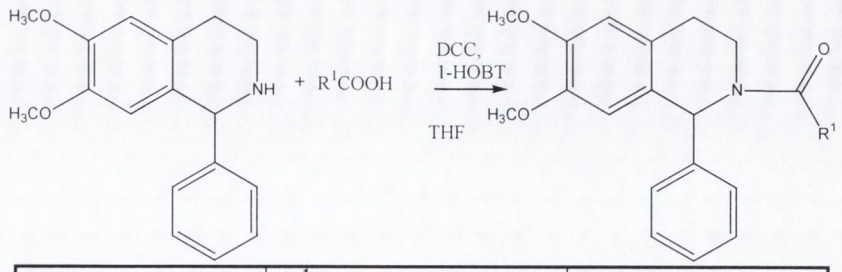
Table 3-5: (6,7-Dimethoxy-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-ketones synthesised using DCC



Compound Number	R^1 =	Yield, %
106[91]	CH_3	55.6
107	C_2H_5	63.1
108	C_3H_7	35.1
109	C_4H_9	49.2
110	Cyclopropyl	50.4
111	Cyclohexyl	63.1
112[76]	C_6H_5	66.4
113	$C_6H_4CH_3$	52.1
114	*o*-$C_6H_4OCH_3$	45.0
115	*m*-$C_6H_4OCH_3$	83.0
116	*p*-$C_6H_4OCH_3$	84.3
117	C_6H_4F	55.6
118[92]	C_6H_4Cl	71.1
119	C_6H_4Br	59.8
120	C_6H_4I	60.0
121	$C_6H_4NO_2$	51.0

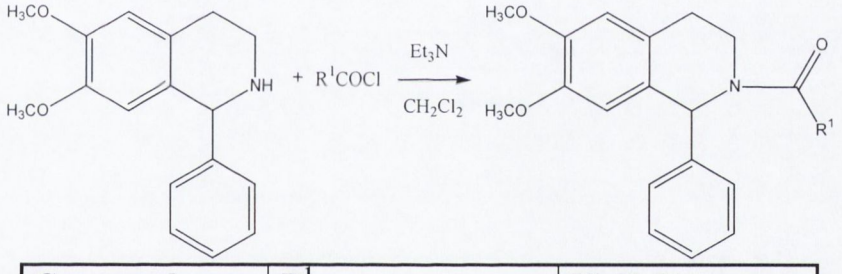
Table 3-6: (6,7-Dimethoxy-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-ketones synthesised using acid chlorides

3.5.3 1-(6,7-Dimethoxy-1-phenyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-ketones



Compound Number	R^1 =	Yield
122	$CH_2C_6H_5$	62.9
123	$CH_2C_6H_4NO_2$	34.4
124	$CH_2C_6H_4SCH_3$	38.8
125	*m*-$CH_2C_6H_4OCH_3$	68.5
126	*p*-$CH_2C_6H_4OCH_3$	49.0
127	*m,p*-$CH_2C_6H_4(OCH_3)_2$	57.7
128	$C_6H_4NO_2$	100
129	$C_6H_4SCH_3$	61.0

Table 3-7: (6,7-Dimethoxy-1-phenyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-ketones



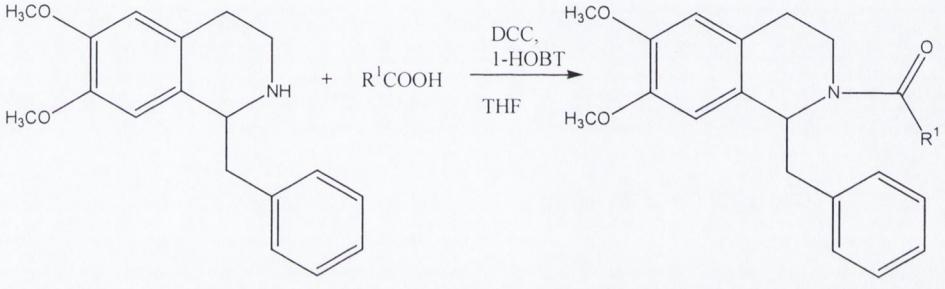
Compound Number	R^1 =	Yield, %
130	CH_3	76.1
131	C_2H_5	81.5
132	C_3H_7	36.6
133	C_4H_9	57.1
134	Cyclopropyl	52.6
135	Cyclohexyl	90.7
136[93]	C_6H_5	81.2
137	$C_6H_4CH_3$	16.7
138	*o*-$C_6H_4OCH_3$	55.7
139	*m*-$C_6H_4OCH_3$	72.8
140	*p*-$C_6H_4OCH_3$	40.1
141	C_6H_4F	58.5
142	C_6H_4Cl	57.1
143	C_6H_4Br	55.4
144	C_6H_4I	51.5

Table 3-8: (6,7-Dimethoxy-1-phenyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-ketones synthesised using acid chlorides

The yields of product when a phenyl substituent replaced the methyl at position 1 did not seem to be much affected. As before, the yields of acid-derived amides **(122 – 129)** (shown in Table 3-7) were usually lower than for those formed using acid chlorides **(130 – 144)** (illustrated in Table 3-8). The exception was quantitative formation of the *p*-nitro benzoyl amide **(128).** The acid chloride was not in good condition, so the acid was used instead. Its impressive yield in a direct coupling reaction supports the earlier suggestion that the main factor reducing the yields in the coupling reactions is the larger size of the acids used.

The most arresting spectroscopic feature of the phenyl amides **(122 – 144)** is the fact that the signal of C1H is now seen at 6.8 δ approximately, downfield of even the C5H and C8H. The additional aromatic signals of the $C1C_6H_5$ are also visible.

3.5.4 1-(1-Benzyl-6,7-dimethoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-ketones

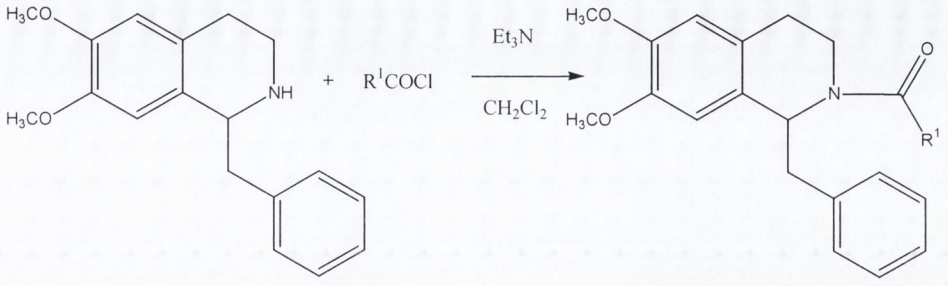


Compound Number	R^1 =	Yield, %
145	$CH_2C_6H_5$	30.9
146	$CH_2C_6H_4NO_2$	64.0
146a	$CH_2C_6H_4SCH_3$	73.6
147	*m*-$CH_2C_6H_4OCH_3$	66.7
148	*p*-$CH_2C_6H_4OCH_3$	99.6
149	*m,p*-$CH_2C_6H_4(OCH_3)_2$	28.7
150	$C_6H_4NO_2$	63.8
151	$C_6H_4SCH_3$	47.4

Table 3-9: (1-Benzyl-6,7-dimethoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-ketones synthesised using DCC

The yields of amides produced using acids **(145 – 151)** were comparable to those obtained with the previous series (see Tables 3-3, 3-5, 3-7 and 3-9). The yields of amides from the acid chloride route **(152 – 166)** were reduced slightly, as may be confirmed by comparing Tables 3-4, 3-6, 3-8 and 3-10. The spectra were the most complex of all the series, and one

is discussed in detail in section 3.5.4.1, to illustrate the features seen with all the amides, and with the benzyl amides in particular.



Compound Number	R^1 =	Yield, %
152[94]	CH_3	65.5
153	C_2H_5	65.6
154	C_3H_7	40.3
155	C_4H_9	60.4
156	Cyclopropyl	53.3
157	Cyclohexyl	40.6
158[94]	C_6H_5	29.3
159	$C_6H_4CH_3$	38.2
160	*o*-$C_6H_4OCH_3$	43.1
161	*m*-$C_6H_4OCH_3$	46.5
162	*p*-$C_6H_4OCH_3$	61.2
163	C_6H_4F	86.5
164	C_6H_4Cl	37.8
165	C_6H_4Br	59.7
166	C_6H_4I	98.4

Table 3-10: (1-Benzyl-6,7-dimethoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-ketones synthesised using acid chlorides

3.5.4.1 Spectroscopy

It has already been noted that amides at isoquinoline N2 may give rise to two sets of signals on an NMR timescale. This may be due to rotamers caused by hindered rotation about the C-N bond, which has a partial double bond character. Another theory, advanced by Dalton et al. [95] in 1965, proposes that the two sets of signals result from the siting of the position one aromatic ring above the amide nitrogen or below the THIQ nucleus aromatic ring. When the ring is below the THIQ aromatic ring C8H would be shielded and therefore moved upfield. This seems an inadequate explanation of the drastic difference in the C3H_2 signals seen in the two conformers. It also appears unlikely as the explanation of how a methyl or phenyl group at position 1 produces similar spectral effects. Furthermore, it fails to explain the presence of two sets of signals in spectra of the THIQ amides with no substituent at position 1. Interestingly, the same group performed further analysis and concluded that the observed signals in these cases were due to rotation of the acetyl group

about the CN bond.[91] For all these reasons, it is proposed that the spectrum observed and discussed below is probably the result of psuedoisomers of a *cis* and *trans* nature, rotating about the CN bond, as previously illustrated in Figure 3-11.

In a few of the amides synthesised, the nature of the substituent at position 2 meant that the signals were of equal intensity for the two rotamers. The cyclopropyl amide of the 1-methyl-1,2,3,4-tetrahydroisoquinoline (compound number **110**) provided the most striking example of this. In most cases, the two sets of signals are not of equal strength, and the signals are recorded as belonging to the major isomer (m) or the minor (denoted (s) for distinction). The assignment of signals in the spectrum of 1-(1-benzyl-6,7-dimethoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-pentan-1-one was pursued exhaustively, to provide a template for the assignment of all the other spectra in the series. The numbering system used in the discussion is illustrated in Figure 3-14.

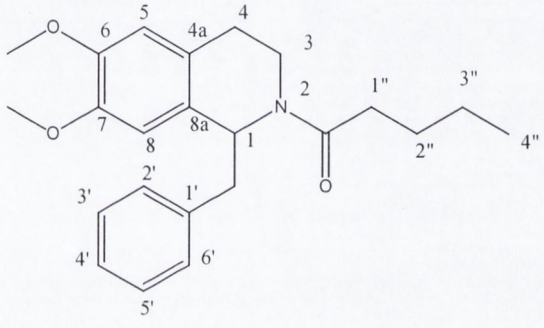


Figure 3-14: Numbering system for 1-(1-benzyl-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-pentan-1-one, 155

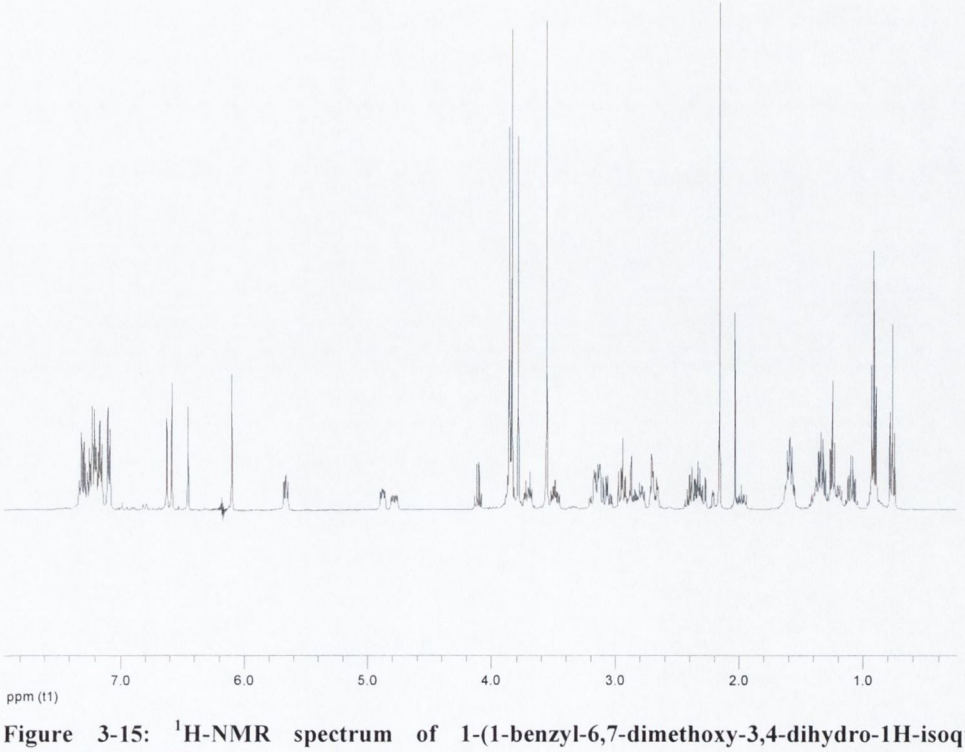


Figure 3-15: ^{1}H-NMR spectrum of 1-(1-benzyl-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-pentan-1-one, 155

Figure 3-15 shows the ^{1}H-NMR spectrum of **(155)**, and the two sets of signals may be clearly distinguished in the downfield region. The upfield portion of the spectrum is subject to much overlap of signals. The aliphatic side group provides the first challenge. The signals for the terminal methyl group of each rotamer (C4"$\underline{H}_3$) is readily identified as a triplet at 0.77δ and 0.92δ, the minor (s) and major (m) rotamers, integrating for 1.2 and 1.8 protons respectively. Overlapping multiplets confuse the region with signals for the adjacent methylene groups. These were distinguished by 1D-TOCSY experiments, which should allow inspection of the spin system of only the aliphatic sidechain. Figure 3-16 shows the result of irradiation of the minor triplet at 0.77δ, followed by a suitable mixing time. The terminal methyl group is beside a methylene (C3"$\underline{H}_2$) giving a signal at 1.05 – 1.15δ. This methylene is quite distant from the tetrahydroisoquinoline nucleus and free to rotate, so the protons give a signal for one multiplet. The methylene at C1"$\underline{H}_2$ is seen as two distinct multiplets at 1.55δ - 1.63δ and 1.95δ - 2.02δ. The multiplets are mirror images of one another. The signal of the adjacent C2"$\underline{H}_2$ has lost resolution and signal over the mixing time (being closer to the terminal methyl group and thus experiencing earlier coherence transfer) and this is shown by the smaller, less distinct multiplets observed at 1.22δ - 1.28δ and 1.35δ - 1.40δ for its two protons.

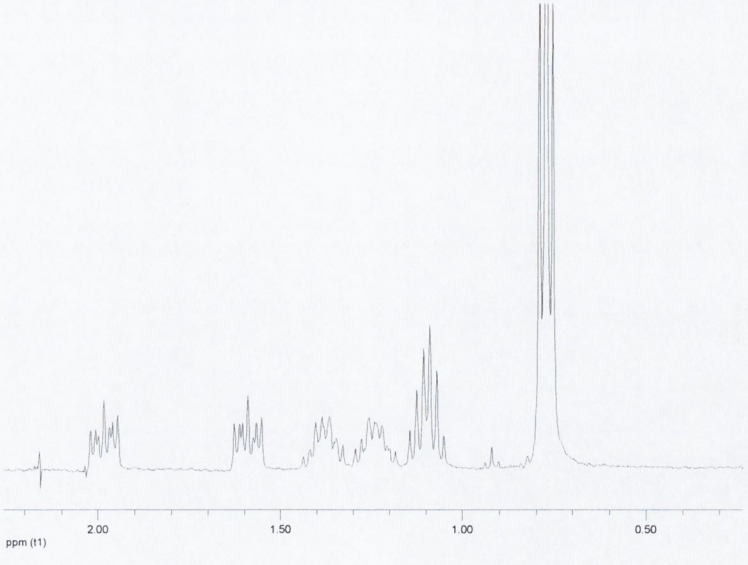


Figure 3-16: 1-D TOCSY experiment on minor isomer aliphatic side chain of 1-(1-benzyl-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-pentan-1-one, 155

A parallel procedure, irradiating the C4"$\underline{H}_3$ of the major isomer, showed a signal at 1.29 – 1.39δ (see Figure 3-17). It was smaller and less well resolved than the other multiplets in the TOCSY, and this was attributed to its being the signal of C3"H_2 and so the first to experience coherence transfer and to transfer it further. The pattern of the minor isomer suggests that the multiplet at 2.28δ - 2.44δ arises from the C1"$\underline{H}_2$ and that at 1.56δ - 1.64δ

from the methylene beside it. The protons of each methylene seem to be equivalent for this isomer. This suggests a greater flexibility of rotation for each proton about its bond with the carbon atom.

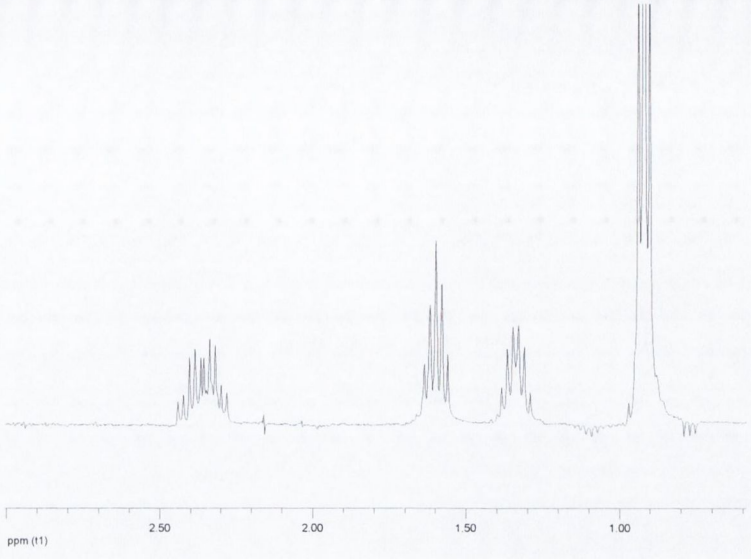


Figure 3-17: 1-D TOCSY of major isomer of 1-(1-benzyl-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-pentan-1-one aliphatic sidechain, 155

Tackling the tetrahydroisoquinoline nucleus necessitates a glance at the C-H COSY (HMQC) in Figure 3-25. This shows the non-aromatic C<u>H</u>, which can only be C1H, to couple to the double doublets at 4.88δ ($J_1 = J_2 = 5$Hz) and 5.67δ ($J_1 = 8$Hz, $J_2 = 5$Hz). The double doublet at 4.88δ integrates for 0.4H and must belong to the minor isomer, being split by the doublet of $C\underline{H}_2C_6H_5$ and the doublet at $C3\underline{H}_2$. Selective irradiation of the signal at 4.88δ (see Figure 3-18) showed a marked coherence transfer to the signal at 3.08δ. This must be the doublet of the benzyl CH_2, as the 2D spectrum (Figure 3-25) shows the double doublet at 4.79δ ($J_1 = 12$Hz, $J_2 = 5$Hz) to belong to $C3\underline{H}_2$.

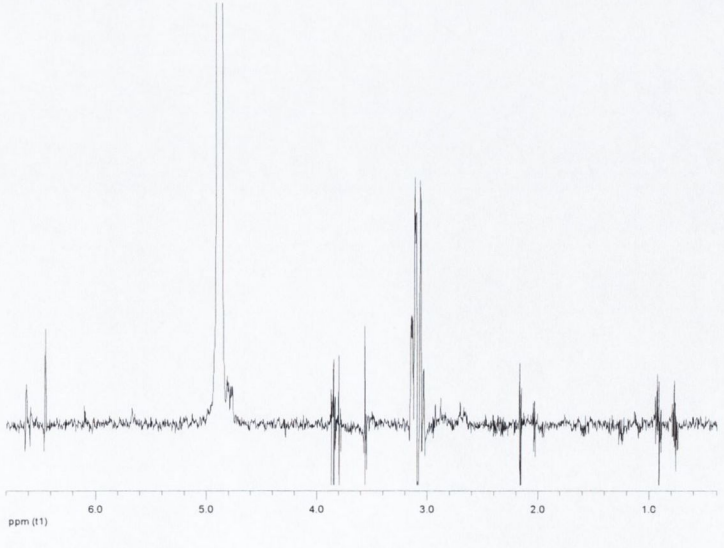


Figure 3-18: 1-D TOCSY with irradiation of C1H double doublet at 4.88δ (155)

When the double doublet of C1H (m) at 5.66δ is irradiated, it enhances the benzyl signal in its isomer at 3.00δ (Figure 3-19). These experiments also served to identify the aromatic proton of C8H, as it too benefited visibly from the coherence transfer. Its signals are to be found at 6.10δ (m) and 6.45δ (s).

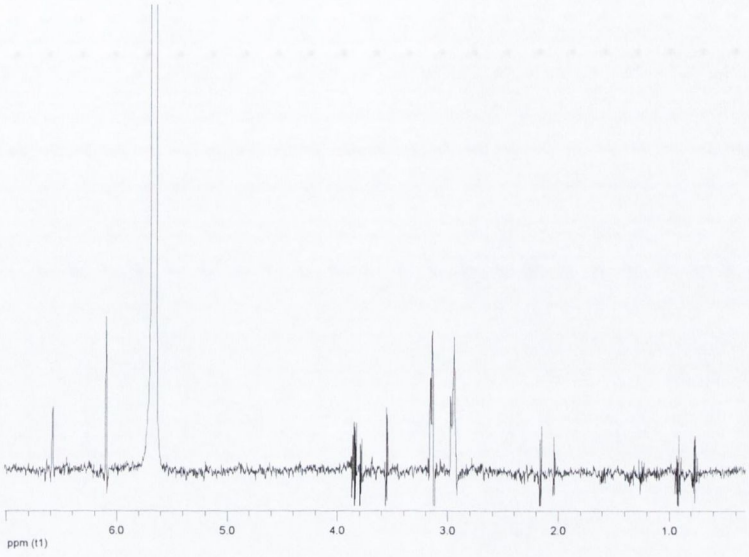


Figure 3-19: 1-D TOCSY irradiating C1H at 5.66δ (155)

It has already been observed that 2D work had been of use to identify the methylene nature of the double doublet at 4.78δ. When irradiated (Figure 3-20), it enhances the signal of the benzyl doublet at 3.1δ. It is surprisingly far downfield, but it may be conjectured that this is the result of the unwieldy groups at C2 and C1 forcing one of the methylene protons at $C3H_2$ into an area that is comparatively deshielded by the partial double bond of the C-N link. It is close in space to the protons of $C4H_2$, which show marked enhancement at 2.68δ. Their identity may be confirmed by recourse to the HMQC plot (Figure 3-25), which shows the multiplet at 2.68δ coupling with the carbon at 28.6ppm. Finally, irradiation of $C3H_2$ also produces a signal at 2.88δ, which is probably its geminal proton.

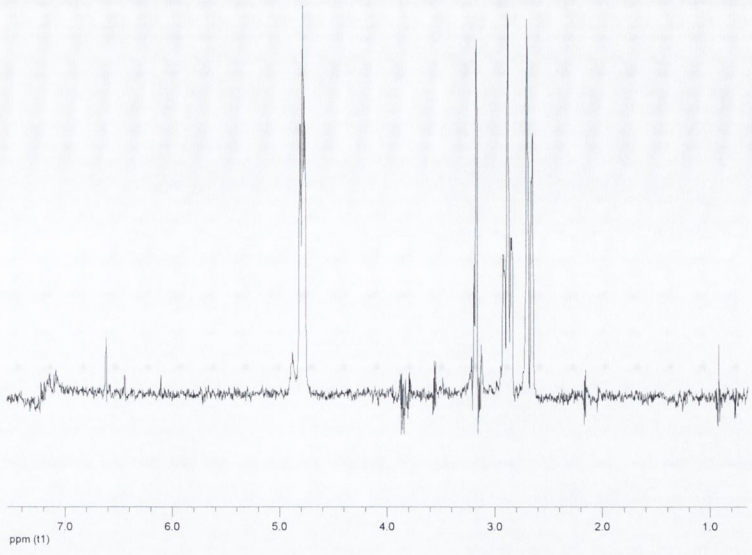


Figure 3-20: 1-D TOCSY irradiating C3H2 at 4.78δ

The methoxy signals are easily identified in the ^{1}H-NMR (Figure 3-15) and ^{13}C-NMR (Figure 3-23, upper) spectra by their shift values and size. The problem is to distinguish that at C6O$C\underline{H}_3$ from that at C7O$C\underline{H}_3$. It has already been established that the aromatic proton of C8$\underline{H}$ produces the signals seen at 6.10δ and 6.45δ. The signal at 6.10δ is enhanced by irradiation of the methoxy peak at 3.56δ (see Figure 3-21). This gives an integral of 1.8H. The signal at 6.45δ is similarly affected by the methoxy signal at 3.79δ (integrating for 1.2H). These must represent the methoxy groups at C7O$C\underline{H}_3$ in each rotamer.

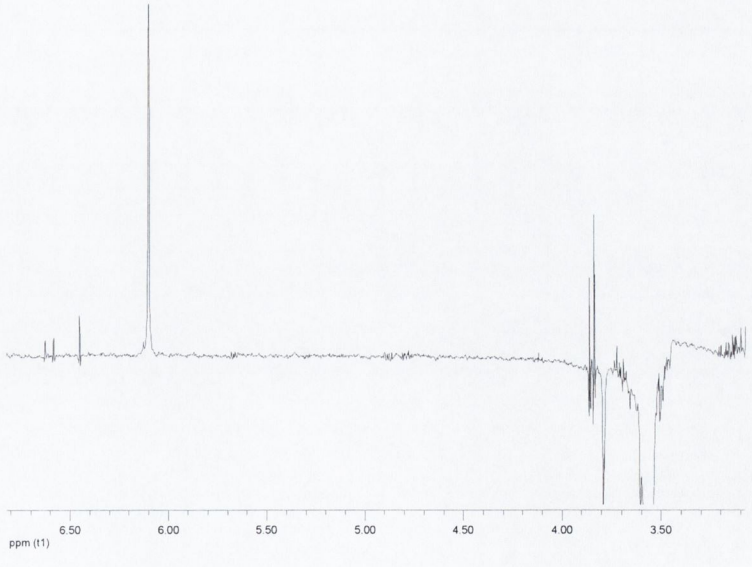


Figure 3-21: NOE experiment, irradiating C7OCH_3 of the major rotamer

This is fortunate, as the proximity of the methoxy groups at 3.84δ and 3.86δ hinders such an experiment. Both the signals are saturated and so enhancement is seen at both 6.59δ and 6.63δ, representing C5$\underline{H}$ (see Figure 3-22). The rotamers are distinguished on the

basis of integral value, and thus 3.84δ and 6.59δ belong to the dominant rotamer and 3.86δ and 6.63δ to the minority signals.

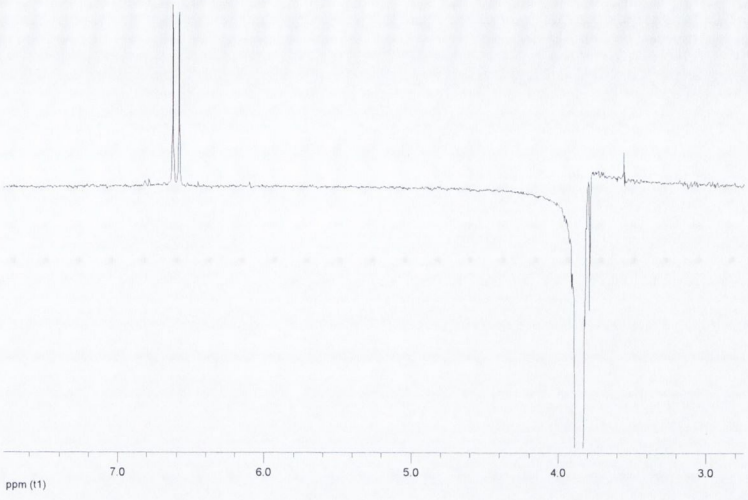


Figure 3-22: NOE experiment, irradiating both C6OCH$_3$ rotamers

The convergence of signals in the aromatic region, complicated by scalar coupling and by the rotamers, calls for examination of the ^{13}C-NMR spectrum (Figure 3-23 upper) and work in two dimensions. The ^{13}C-NMR spectrum displays a doubling of all signals.

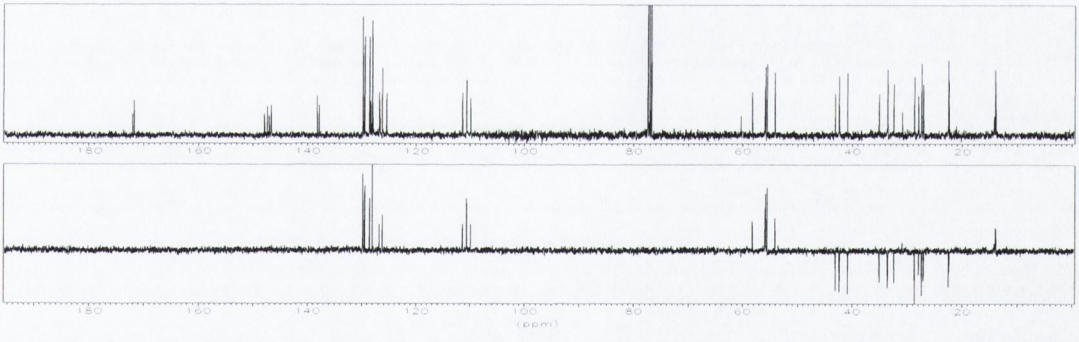


Figure 3-23: ^{13}C-NMR and DEPT 135 spectra for 1-(1-benzyl-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-pentan-1-one

Turning to the HMQC spectrum presented in Figure 3-24, among the aromatic signals a small signal for C4'H may be observed at 126.2ppm (m) and at 126.8ppm (s). The related protons cannot be distinguished within the multiplet at 7.15δ - 7.31δ. The doublet at 7.10δ (J = 7Hz) integrates for 1.2 protons and is seen from Figure 3-24 to have a corresponding carbon signal at 129.8ppm. The minor rotamer must generate the small, adjacent signal at 129.4ppm, which couples with protons at 7.16δ. These are all signals for the positions *meta* to the point of attachment.

The protons at the *ortho* positions would give rise to signals of the same magnitude. This must mean the signals at 128.0ppm (m) and 128.6ppm (s). The lesser rotamer is

represented by the proton signals at 7.28δ – 7.32δ approximately. The greater rotamer gives proton signals, which are clustered from ca. 7.18δ to 7.28δ.

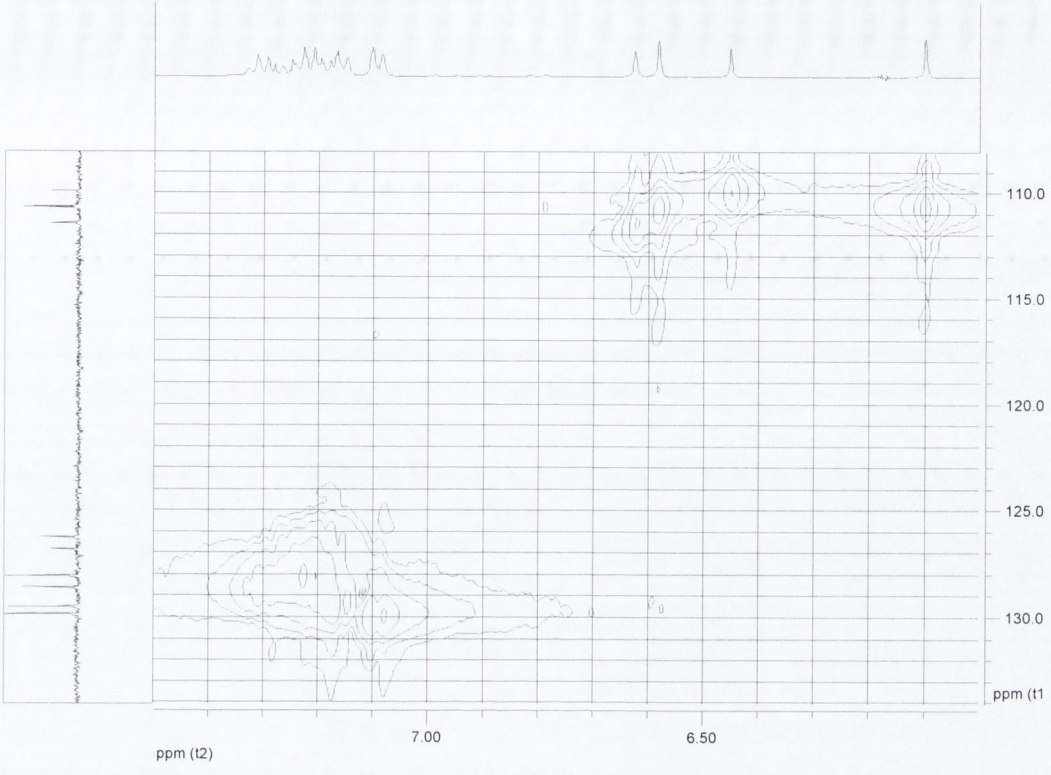


Figure 3-24: HMQC of aromatic regions and C1H signals

The signals assigned already to C8H (6.10δ and 6.45δ) couple with carbons signalling at 110.6ppm and 109.9ppm respectively. The lesser C5H rotamer has a carbon signal at 111.4ppm; the greater signal is seen at 110.65ppm.

Moving upfield (Figure 3-25), the double doublet for the dominant C1H is obviously coupled to the CH signal at 54.0ppm; the other rotamer has a signal seen at 58.1ppm. In between these is a mess of signals from methoxy group carbons, and close examination allows these to be assigned. The signal at 55.4ppm is that of the major C6OCH_3 and the smaller version is at 55.7ppm. The C7OCH_3 signals are those at 55.67ppm and 55.8ppm. The inverted signals at 43.0ppm and 42.3ppm are the minor and major signals for the benzyl CH_2. Huddled between the methoxy protons are the signals for the major isomers of the C3H_2 protons, naturally both coupling to the methylene carbon signal at 40.8ppm. The lesser partner (35.0ppm) is readily pinpointed by its coupling with the double doublet at 4.79δ. C1"H_2 (m) gives a signal at 33.4ppm and the smaller at 30.8ppm. The methylene carbon of C4H_2 generally gives a signal in the region of 30ppm: this time the major rotamer is seen at 28.6ppm and the minor at 27.8ppm. There is a methylene signal at 27.2ppm and this couples with the protons established by TOCSY experiments to be the major rotamer's C2"H_2. Its minor counterpart is at 26.9ppm. The last methylene of the

aliphatic sidechain, C3"H_2 has signals at 22.3ppm and 22.4ppm. The terminal methyl groups are clearly the upright signals at 13.7ppm (smaller) and 13.8ppm (larger).

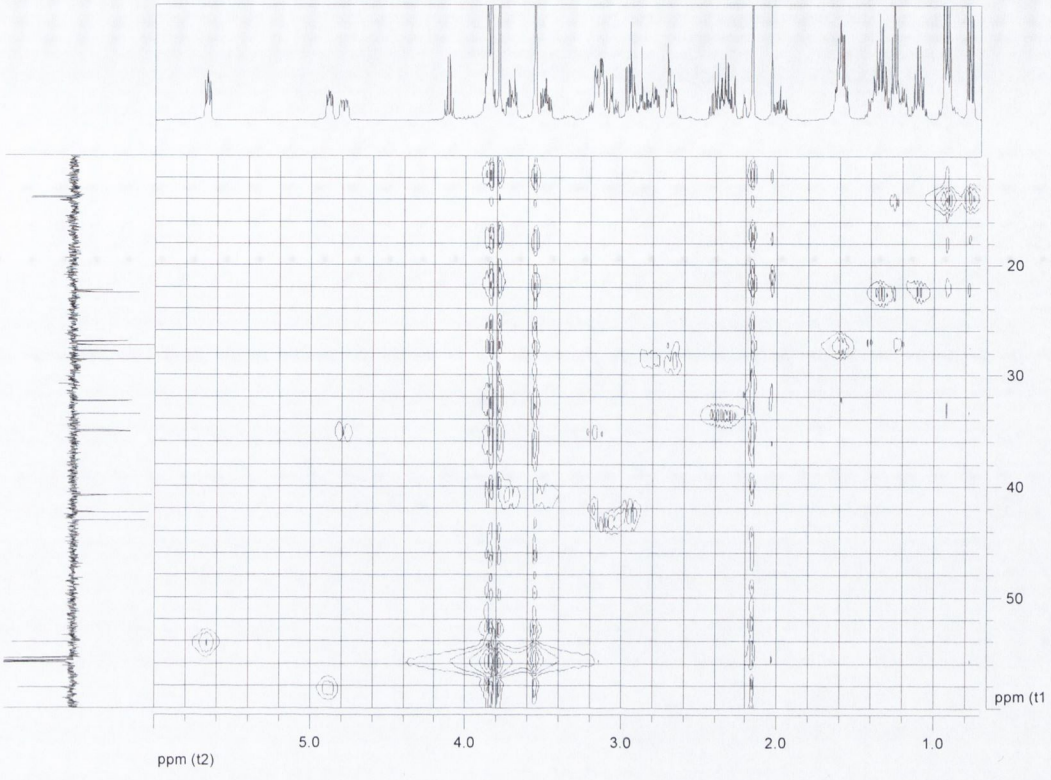


Figure 3-25: 2-D HMQC of saturated ring and sidechain region

Finally, referring back to ^{13}C-NMR spectrum in Figure 3-23, the quaternary carbon signals may be assigned. The signals at 125.4ppm, 126.6ppm, 127.9ppm and 128.3ppm should be for the carbons at C4a and C8a. The minor rotamer gives quaternary signals at 137.8ppm for C1', at 147.0ppm and 147.9ppm for C7 and C6 and at 172.1 ppm for the carbon of the amide carbonyl group. The larger signals at 138.2ppm (C1'), 146.7ppm (C7), 147.4ppm (C6) and 171.8ppm (CO) belong to the major rotamer.

The discussion about which rotamer may represent a *cis* and which a *trans* arrangement of the position 2 substituent has been deferred until now, as the flexibility of the butyl sidechain, and the closeness of the shift values of the groups within it, rendered it unsuitable for exploring this question. The acetyl amide of the 1-methyl series **(106)** offered a more convenient example. Irradiation of the major signal for the acetyl CH_3 (see Figure 3-26) showed a small nuclear Overhauser effect at the C1CH_3 signal but a slightly greater nOe at the double triplet of 3.51 δ (C3H_2) and a much greater effect at the quartet at 5.58 δ (C1H).

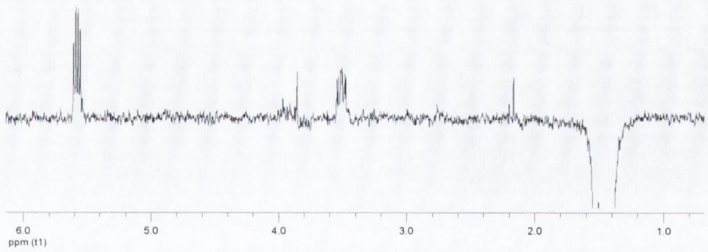


Figure 3-26: Small NOE observed at methyl signal in major conformer of 106

When the signal for the minor rotamer of the acetyl C<u>H</u>$_3$ was similarly treated, the nOe observed at the methyl signal was significantly stronger than that at the double triplet representing C3<u>H</u>$_2$ or the minor signal for C1<u>H</u> (see Figure 3-27). This indicates that in the minor rotamer the acetyl group is closer to the methyl at position 1 than it is in the major rotamer. Hence, the minor rotamer represents a *cis* conformation about the CN bond and the major rotamer is a *trans* conformer, as depicted in Figure 3-28.

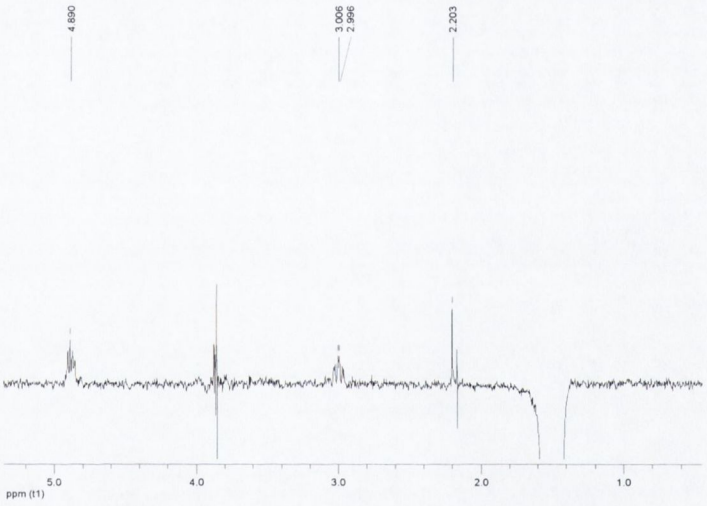


Figure 3-27: NOE observed at methyl signal in minor conformer of 106

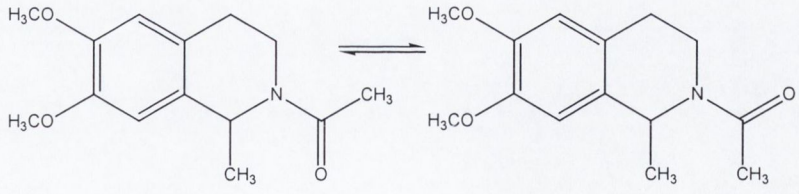


Figure 3-28: Proposed *trans* and *cis* conformations of methyl acetyl amide, (106)

A phenyl series amide with a *para*-nitrobenzoyl substituent at position 2 **(128)** was also scrutinised. When the larger signal for the protons *ortho* to the nitro group were irradiated, little effect was seen in the aromatic region, except at 7.56 δ, where the signal from the adjacent benzoyl protons appears (see Figure 3-29).

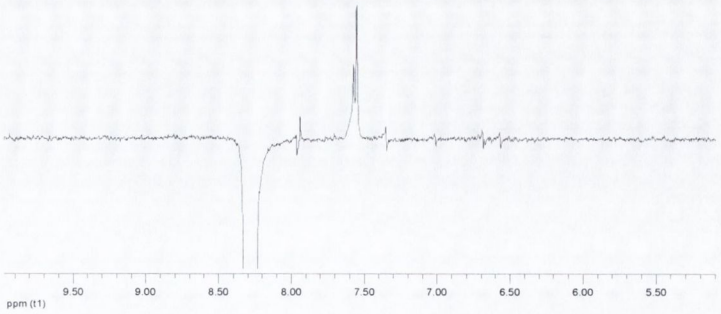


Figure 3-29: Little evidence of NOE in general aromatic region of major rotamer of (128)

Irradiation of the minor signal for the *ortho* protons (see Figure 3-30) had a more pronounced effect across the aromatic region. This indicates that the minor conformation is one in which the benzoyl group is closer in space to the phenyl group, or a *cis* conformation about the CN bond. The other rotamer would then be a *trans* isomer (see Figure 3-31). The *trans* rotamer is probably favoured on steric grounds. It seems likely that the same pattern obtains across the entire series, but each amide was not examined individually. The proposed rotamers are thus designated as "major" (m) or "smaller" (s) in the experimental reports of spectroscopic data.

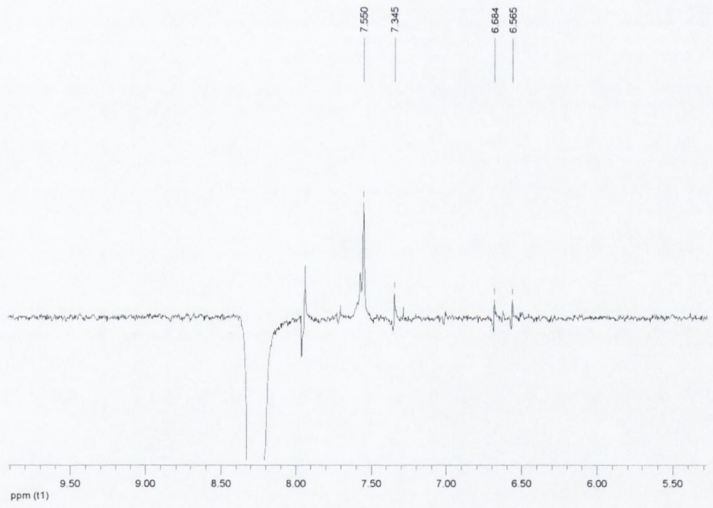
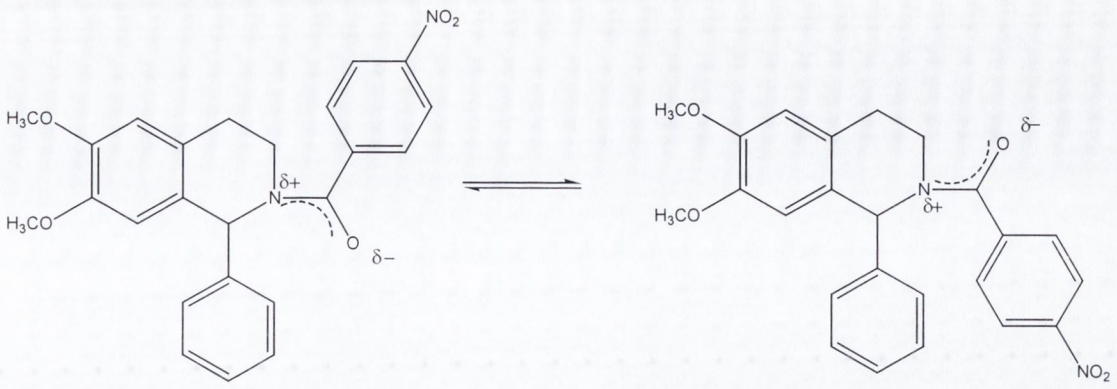


Figure 3-30: More pronounced NOE observed throughout aromatic region in minor conformer of (128)



Major Minor

Figure 3-31: Proposed *trans* and *cis* conformations of phenyl nitrobenzoyl compound (128)

3.6 Summary

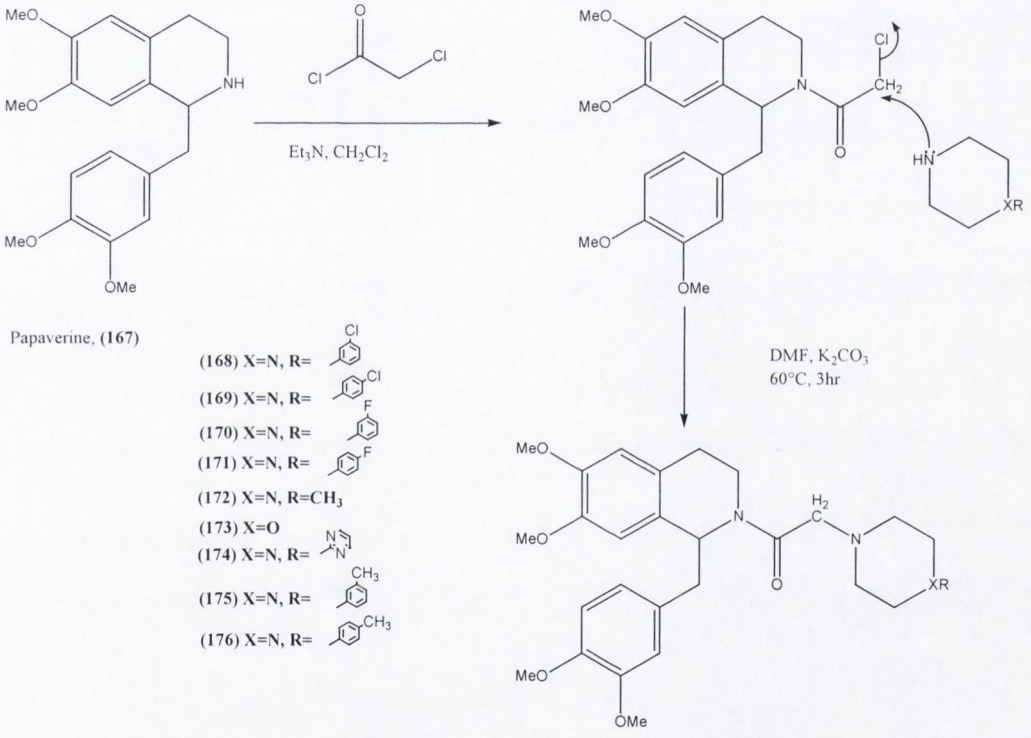
A series of dihydroisoquinolines and tetrahydroisoquinolines were synthesised using four different approaches, and the most efficient process was selected for the production of a comprehensive series of 6,7-dimethoxy-1-alkyl-tetrahydrisoquinolines. The unsubstituted tetrahydroisoquinoline nucleus was used to explore the feasibility of synthesising amides and a coupling reaction employing DCC was chosen for reactions involving phenylacetic acids. In cases where a ureide formed with use of the DCC, acid chlorides were preferred; 1-HOBT was used where no substitute acid chlorides were available. A comprehensive NMR analysis of the N-2 amides was undertaken, and a tentative assignment of rotameric structure was proposed.

4 Chapter 4: Synthesis of Piperazine Amides

4.1 Introduction

In order to examine further the possibilities of structurally modifying position two of the tetrahydroisoquinoline ring, the synthesis of amides linked to a piperazine ring was proposed. The ring could be used as a link between the isoquinoline moiety and another group, such as substituted aromatic rings. The effect on inhibition of monoamine oxidase could then be examined.

A related series of tetrahydroisoquinolines had been prepared by Kaur et al.[96], which were derived from papaverine **(167)**, a naturally occurring tetrahydroisoquinoline with powerful antispasmodic action. Those products **(168 - 176)** were therefore evaluated as antispasmodics. The route employed is shown in Scheme 4-1.

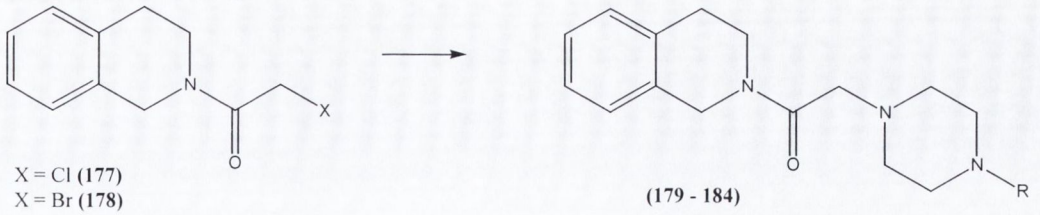


Scheme 4-1: Synthesis of piperazinyl amides of papaverine; synthetic method 1

In the present work, the proposed new series would examine the effect of a piperazine linked sidechain at position 2, on monoamine oxidase inhibition: firstly in the presence and absence of methoxy groups at positions 6 and 7 of the tetrahydroisoquinoline aromatic ring, and secondly in the presence of a variety of substituents at position 1 of the aliphatic ring of the tetrahydroisoquinoline.

4.2 Route of Synthesis

4.2.1 Unsubstituted Piperazine Amides

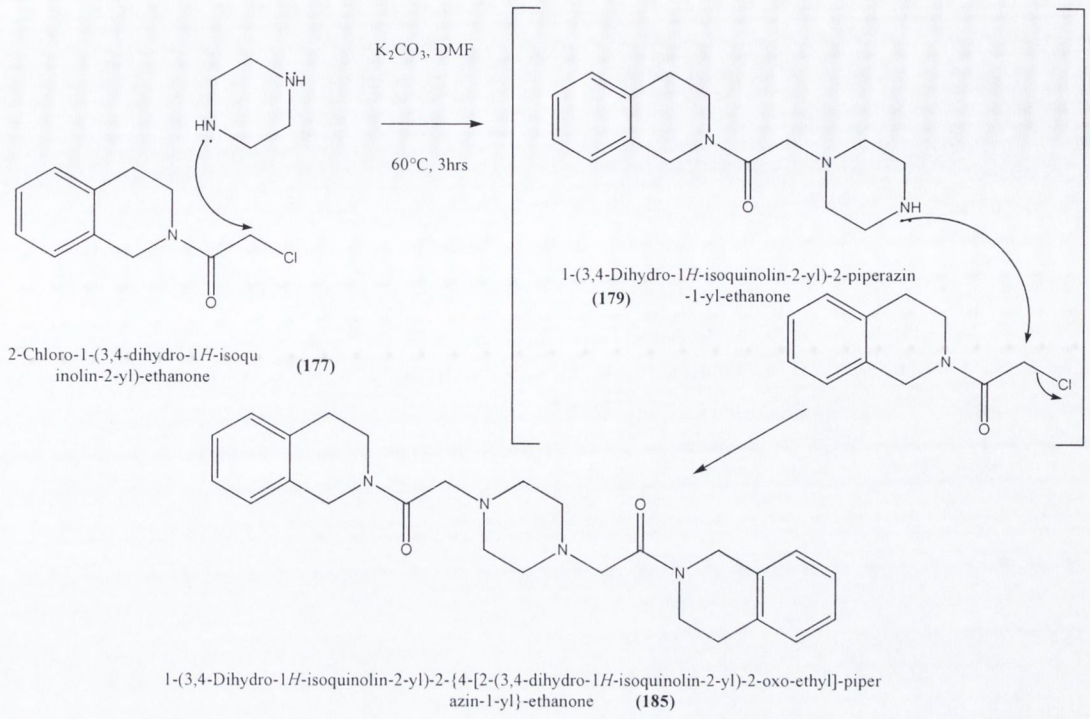


Compound Number	R =	Yield, %
179	H	0
180	CH_3	0
181	*m*-C_6H_4Cl	54
182	*p*-C_6H_4Cl	44
183	*p*-C_6H_4F	8
184	$CH_2C_6H_3(OCH_2O)$	33

Table 4-1: Unsubstituted Piperazine Amides

The preparation and biochemical testing of compounds **(179)** to **(184)** from **(177)**[94] and **(178)**[97] (see Table 4-1 and accompanying scheme) would provide insight into the effect of addition of a piperazine substituent at position 2, on inhibition of monoamine oxidase.

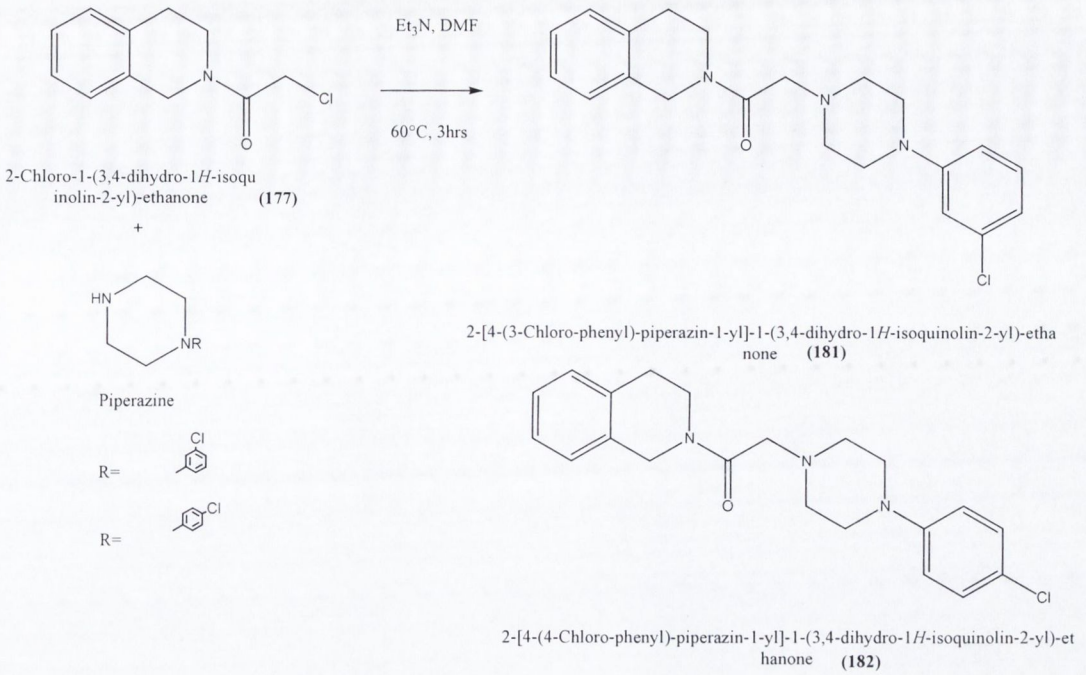
Initially, the synthetic route of Kaur et al was employed, hereafter referred to as **method 1**. This is shown in Scheme 4-2. The chloroamide **(177)** of 1,2,3,4-tetrahydroisoquinoline **(1)** was synthesised, then this was reacted with the relevant piperazine in dimethylformamide (DMF), with potassium carbonate as the base. The initial attempt to use this route to form the simplest amide, 1-(3,4-dihydro-*1H*-isoquinoline-2-yl)-2-piperazin-1-yl-ethanone, did not yield the expected product, **(179)**. Close examination of the NMR spectrum of the product showed it to be the dimer, 1-(3,4-dihydro-*1H*-isoquinolin-2-yl)-2-{4-[2-(3,4-dihydro-*1H*-isoquinolin-2-yl)-2-oxo-ethyl]-piperazin-1-yl}-ethanone **(185)**, as depicted in Scheme 4-2.



Scheme 4-2: Formation of dimer (Synthetic method 1)

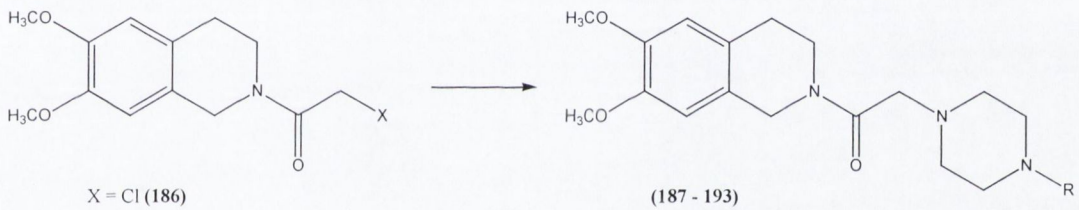
1-(3,4-Dihydro-*1H*-isoquinolin-2-yl)-2-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone **(183)** was isolated in very low yield (8%). All further attempts to use **method 1** in this series did not give products (see Table 4-6).

The first modification of the synthetic route involved substitution of triethylamine for potassium carbonate, being more soluble in DMF. This will be called **method 2**. This was successful for some substituted chlorophenyl piperazine amides **(181 - 182)**, as depicted in Scheme 4-3, and for "1-piperonylpiperazine", also called N-[3,4-(methylenedioxy)-benzyl]-piperazine **(184)**. (See Table 4-6 and Scheme 4-3).



Scheme 4-3: Synthetic method 2

4.2.2 Unsubstituted dimethoxy piperazine amides



Compound Number	R =	Yield, %
188	H	0
189	CH_3	0
190	*m*-C_6H_4Cl	85
191	*p*-C_6H_4Cl	59
192	*p*-C_6H_4F	45
193	$CH_2C_6H_3(OCH_2O)$	50

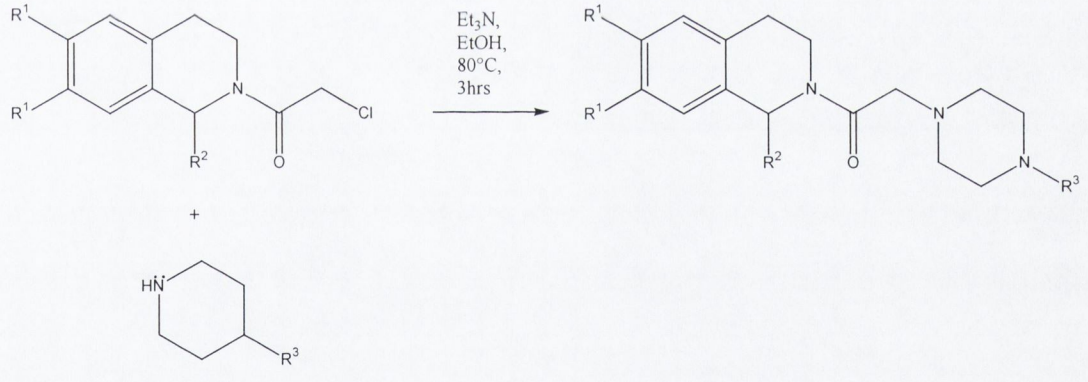
Table 4-2: Unsubstituted dimethoxy piperazine amides

The next series of compounds prepared, **(190** to **193)**, should give information about the effect of dimethoxy groups on monoamine oxidase inhibition, through comparison with **(181** to **184)**, from which they differ in each instance only by the methoxy groups at positions 6 and 7. Of course, they should also provide more data on the effect of piperazine groups at position 2 of the isoquinoline, on MAO activity.

6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline was available commercially, as the hydrochloride salt, and the chloroamide **(186)**[94] was prepared as in Scheme 4-1 (first step).

The presence of methoxy groups at positions 6 and 7 of the aromatic tetrahydroisoquinoline ring appeared to activate the chloroamide somewhat for reaction with the piperazines. **Method 1**, using potassium carbonate as the base in GPR DMF produced the halogenated phenyl-piperazinyl amides (**(191)** and **(192)**) and the piperonal-piperazine amide (**193**) (see Tables 4-2 and 4-6).

Use of the dipolar aprotic solvent DMF in the original paper indicated that the reaction was of the S_N2 type. Also, the potassium carbonate present would not only form salts with liberated chloride ions, it also would raise the pH of the environment, and S_N1 reactions usually take place under acidic conditions, while S_N2 reactions prefer a basic or neutral medium.[98] However, the terminal chlorine or bromine would be expected to occupy a position as far as possible from the bulk of the tetrahydroisoquinoline nucleus. This substantial group might be expected to hinder the approach of the nucleophile, the piperazine nitrogen, towards the carbon of the alkyl halide group. The transition state crowding about the terminal carbon of the alkyl halide would be severe, and would tend to slow formation of the transition state. In such circumstances, the reaction might proceed in the manner of S_N1 reactions. Another point is that S_N2 reactions are favoured by use of a good nucleophile, but piperazine's nitrogen is not especially nucleophilic.

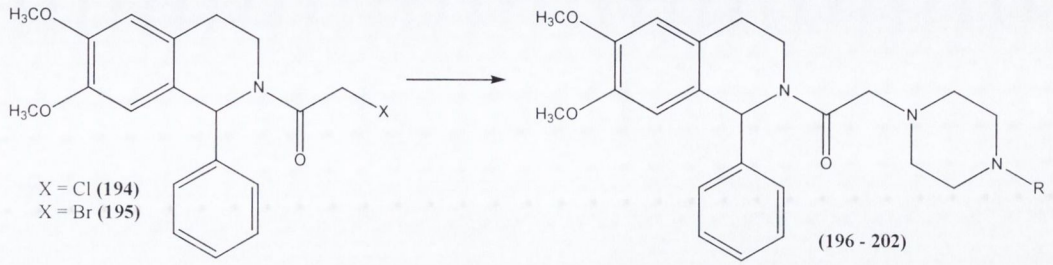


Scheme 4-4: Synthetic method 3

Taking these points into consideration, the polar protic solvent ethanol was given a trial. This procedure, illustrated in Scheme 4-4, will be called **method 3**. This should favour a substitution of the S_N1 variety, although it slows reactions of an S_N2 type. The increased solvation of ion pairs in a protic solvent aids the formation of the cation in an S_N1 reaction. The 3-chloro-piperazine amide **(190)** had not been forthcoming, so the solvent was changed to ethanol, and the product was synthesised after 3 hours of reflux, with a yield of 21%. The yield was further boosted by heating the reaction mixture for 7 hours (85%). As for the unsubstituted tetrahydroisoquinoline, the reaction did not proceed when 1-methylpiperazine was employed; it gave a dimer **(187)** (see Table 4-6 for yield and

structure), with the tetrahydroisoquinoline moieties linked by a piperazine bridge, when piperazine itself was used.

4.2.3 6,7-Dimethoxy-1-phenyl piperazine amides



Compound Number	R =	Yield, %
197	H	0
198	CH_3	0
199	*m*-C_6H_4Cl	64
200	*p*-C_6H_4Cl	67
201	*p*-C_6H_4F	38
202	$CH_2C_6H_3(OCH_2O)$	24

Table 4-3: 6,7-Dimethoxy-1-phenyl piperazine amides

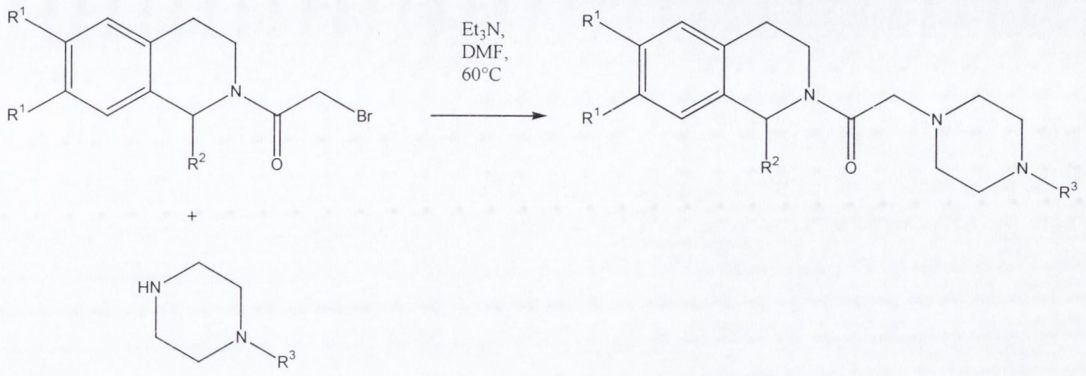
The next group of compounds investigated were 6,7-dimethoxy-1-phenyl compounds **(199 – 202)**. These compounds **(197** to **202)** would be considerably bulkier than the two series already synthesised, and would answer questions about the MAO inhibitory activity of compounds with two aromatic and two aliphatic rings in their structure.

The starting material (THIQ **(43)**) was obtained by cyclisation using the Pictet Spengler method, as outlined in Chapter 3 (see Section 3.3.2), followed by chloroamidation or bromoamidation of the nitrogen at position 2, using chloroacetylchloride or bromoacetylbromide, in accordance with Scheme 4-1. This gave the chloroamide **(194)**[93] or the bromoamide **(195)** (see scheme with Table 4-3).

An initial trial of chloroamide **(194)** and triethylamine in DMF for 2 hours at 60°C (i.e. **method 2**) gave the dimer **(196)**, which is shown in Table 4-9. The yields of piperazine amides obtained in the reaction of the chloroamide in DMF using triethylamine were improved thereafter by increasing the reaction time from 2 hours to 9 hours and even 24 hours. This boosted yields of the halogenated phenyl piperazine amides (**199 - 201**) but the piperonal amide **(202)** did not form.

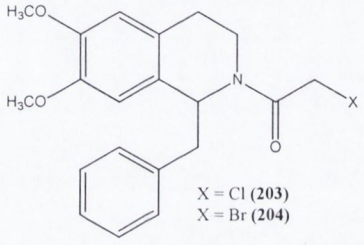
Bromine is a better leaving group than chlorine in substitution reactions of alkyl halides, of which this is an example. It was decided to change the leaving group and so the bromoamide (**195**) was synthesised according to the method of Ting et al [97] and was used

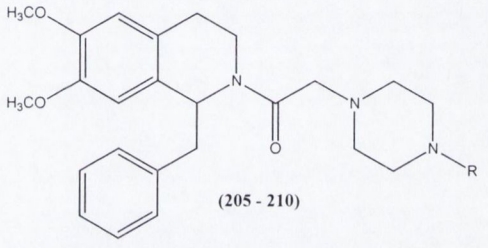
in place of the chloroamide. This gave **method 4**, illustrated in Scheme 4-5. By dint of extending the reaction time to 7 days the wished for amide (**202**) was finally obtained.



Scheme 4-5: Synthetic method 4

4.2.4 6,7-Dimethoxy-1-benzyl piperazine amides





Compound Number	R =	Yield, %
205	H	0
206	CH_3	0
207	*m*-C_6H_4Cl	20
208	*p*-C_6H_4Cl	22
209	*p*-C_6H_4F	35
210	$CH_2C_6H_3(OCH_2O)$	41

Table 4-4: 6,7-Dimethoxy-1-benzyl piperazine amides

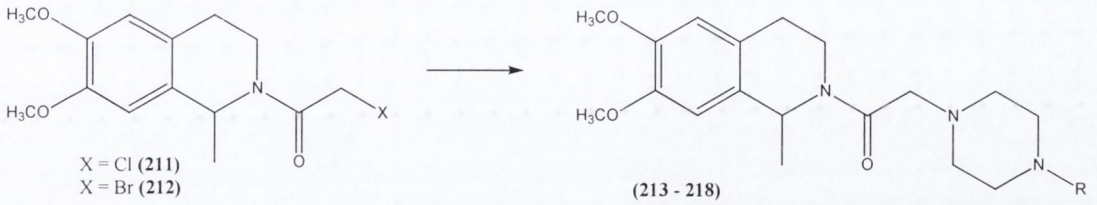
The benzyl substituted THIQs **(207 – 210)** were prepared as illustrated in Table 4-4. The benzyl substituent at position 1 would have more flexibility for reorientation than the phenyl group. Therefore, the MAO inhibitory activity of series **(205** to **210)** might differ considerably form that of (**197** to **202)**, and seemed worth investigation.

The dihydroisoquinoline **(50)** was prepared by a cyclisation using the Venkov method described in Chapter 3 (section 3.3.3), followed by reduction to the tetrahydroisoquinoline **(56)** and chloroamidation or bromoamidation at position 2 of the isoquinoline nucleus, to give **(203)** or **(204)** respectively.

This time even a dimer did not form when **method 1** was used. In view of this, **method 3** was tried, having already proved effective in synthesising the stubborn 3-chlorophenyl piperazine amide in the unsubstituted dimethoxy THIQ group **(190)**. The halogenated

phenyl amides **(207**, **208** and **209)** and piperonal amide **(210)** were produced by this route, as shown in Tables 4-4 and 4-8.

4.2.5 6,7-Dimethoxy-1-methyl piperazine amides



Compound Number	R =	Yield, %
213	H	23
214	CH_3	46
215	*m*-C_6H_4Cl	37
216	*p*-C_6H_4Cl	31
217	*p*-C_6H_4F	30
218	$CH_2C_6H_3(OCH_2O)$	45

Table 4-5: 6,7-Dimethoxy-1-methyl piperazine amides

In the products **(213 – 218)** the methyl group is intermediate in size between an aromatic ring and a proton, and series **(213)** to **(218)** should allow trends due to steric factors, in MAO inhibition, to be teased out more comprehensively. The products are listed in Table 4-5.

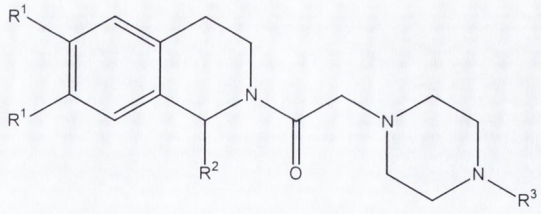
The starting material was afforded by a Venkov cyclisation to give **(41)**, a reduction (producing **(54)** and then acylation at position 2 of the nucleus, using chloroacetylchloride or bromoacetylbromide, to yield the chloroamide **(211)**[99] or bromoamide **(212)** (both shown in scheme accompanying Table 4-5).

An attempt was made to combine the information from the previous syntheses to draw conclusions about the mechanisms involved in the formation of the piperazine amides. There was a systematic effort to compare three modes of synthesis in the formation of the piperonal piperazine amide. **Method 1** with potassium carbonate in DMF at 60°C for 3 hours did not yield product. The bromoamide **(212)** with potassium carbonate in acetonitrile at reflux for 4 hours, as seen in the work by Fletcher et al [100] gave a negative result. This **method 5** was quickly abandoned. The bromoamide **(212)** with triethylamine in DMF at 60°C for 2 hours (**method 4)** did yield product (**218**). On this basis the method employed for the halogenated phenyl piperazine amides (**199**, **200** and **201**) (bromoamide, triethylamine, DMF, 60°C i.e. **method 4**) was used again successfully, to give **215**, **216** and **217**.

Eventually, a coordinated attempt to make a simple piperazine amide gave a result. The method that sufficed for all other piperazine amides in the series (i.e. **method 4**) did not force reaction of the bromoamide and 1-methylpiperazine, even after 5 days. Ethanol was again used as the solvent, in combination with triethylamine and the chloroamide (**method 3**) and after 14 hours of reflux 1-(6,7-dimethoxy-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-(4-methyl-piperazin-1-yl)-ethanone (**214**) was produced in a yield of 46%.

The same conditions were used when reacting unsubstituted piperazine with the chloroamide, except that piperazine was in threefold excess, to discourage formation of the dimer, and refluxing only continued for 4 hours. This gave 1-(6,7-dimethoxy-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-piperazin-1-yl-ethanone (**213**), the required product, albeit at a yield of only 23%.

The yields and routes are summarised in Tables 4-6 to 4-9.



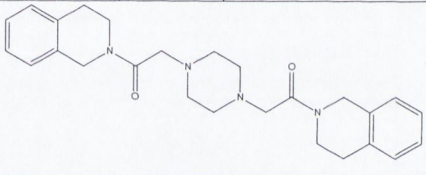
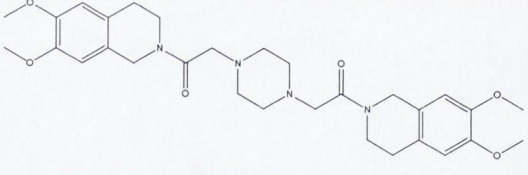
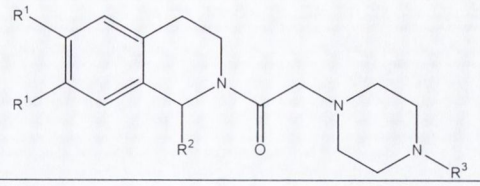
Method 1: K_2CO_3, DMF, 60°C						
Compound Number	**R^1=**	**R^2=**	**R^3=**	**Leaving Group**	**Time**	**Yield**
179	H	H	H	Cl	3hr	0
180	H	H	CH_3	Cl	3hr	0
181	H	H	*m*-C_6H_4Cl	Cl	3hr	11
181	H	H	*m*-C_6H_4Cl	Cl	2hr/40°C	0
182	H	H	*p*-C_6H_4Cl	Cl	3hr	0
182	H	H	*p*-C_6H_4Cl	Cl	2hr/40°C	0
183	H	H	*p*-C_6H_4F	Cl	3hr	8
184	H	H	$CH_2C_6H_3(OCH_2O)$	Cl	3hr	1
185				Cl	3hr	36%
191	OCH_3	H	*p*-C_6H_4Cl	Cl	3hr	59
192	OCH_3	H	*p*-C_6H_4F	Cl	3hr	45
193	OCH_3	H	$CH_2C_6H_3(OCH_2O)$	Cl	3hr	50
187				Cl	3hr	15%

Table 4-6: Summary of yields procured using Method 1



Method 2: Et_3N, DMF, 60°C						
180	H	H	CH_3	Cl	2.5hr	0
181	H	H	*m*-C_6H_4Cl	Cl	2hr	54
182	H	H	*p*-C_6H_4Cl	Cl	2hr	44
184	H	H	$CH_2C_6H_3(OCH_2O)$	Cl	2hr	33
198	OCH_3	C_6H_5	CH_3	Cl	24hr	0
199	OCH_3	C_6H_5	*m*-C_6H_4Cl	Cl	24hr	64
200	OCH_3	C_6H_5	*p*-C_6H_4Cl	Cl	9hr	67
201	OCH_3	C_6H_5	*p*-C_6H_4F	Cl	24hr	38
202	OCH_3	C_6H_5	$CH_2C_6H_3(OCH_2O)$	Cl	24hr	0

Table 4-7: Summary of yields from Method 2

Method 3: Et_3N, EtOH, 60°C						
Compound Number	**R^1=**	**R^2=**	**R^3=**	**Leaving Group**	**Time**	**Yield**
189	OCH_3	H	CH_3	Cl	8hr	0
189	OCH_3	H	CH_3	Cl	12hr,RT	0
190	OCH_3	H	*m*-C_6H_4Cl	Cl	3hr	21
190	OCH_3	H	*m*-C_6H_4Cl	Cl	7hr	85
213	OCH_3	CH_3	H	Cl	8hr	23
214	OCH_3	CH_3	CH_3	Cl	14hr	46
218	OCH_3	CH_3	$CH_2C_6H_3(OCH_2O)$	Cl	3hr	45
200	OCH_3	C_6H_5	*p*-C_6H_4Cl	Cl	2hr	70
206	OCH_3	$CH_2C_6H_5$	CH_3	Cl	4hr	0
207	OCH_3	$CH_2C_6H_5$	*m*-C_6H_4Cl	Cl	4hr, RT	0
207	OCH_3	$CH_2C_6H_5$	*m*-C_6H_4Cl	Cl	4hr	20
208	OCH_3	$CH_2C_6H_5$	*p*-C_6H_4Cl	Cl	4hr	22
209	OCH_3	$CH_2C_6H_5$	*p*-C_6H_4F	Cl	4hr	35
210	OCH_3	$CH_2C_6H_5$	$CH_2C_6H_3(OCH_2O)$	Cl	4hr	41

Table 4-8: Summary of yields from Method 3

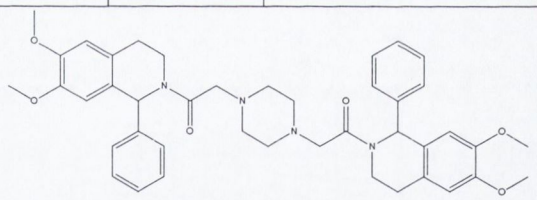
Method 4: Et_3N, DMF, 60°C						
Compound Number	**R^1 =**	**R^2 =**	**R^3 =**	**Leaving group**	**Time**	**Yield, %**
180	H	H	CH_3	Br	3hr	0
180	H	H	CH_3	Br	2 days	0
180	H	H	CH_3	Br	5 days	0
184	H	H	$CH_2C_6H_3(OCH_2O)$	Br	48hr	0
213	OCH_3	CH_3	H	Br	3hr	0
215	OCH_3	CH_3	*m*-C_6H_4Cl	Br	12hr	37
216	OCH_3	CH_3	*p*-C_6H_4Cl	Br	12hr	31
217	OCH_3	CH_3	*p*-C_6H_4F	Br	2hr	30
218	OCH_3	CH_3	$CH_2C_6H_3(OCH_2O)$	Br	2hr	26
197	OCH_3	C_6H_5	H	Br	7 days	0
202	OCH_3	C_6H_5	$CH_2C_6H_3(OCH_2O)$	Br	7 days	24
206	OCH_3	$CH_2C_6H_5$	CH_3	Br	3 hrs	0
208	OCH_3	$CH_2C_6H_5$	*p*-C_6H_4Cl	Br	3.5hr	0
196				Br	2hr	10

Table 4-9: Yields obtained using Method 4

4.3 Implications of Varied Routes and Yields

Inspection of the yields presented in Tables 4-6 to 4-9 resulted in the following observations on the reaction. The variation in yield of piperazine amides with alteration of base and solvent suggests some interesting points with regard to the amino-de-halogenation under discussion. Initially, it was expected to conform to classic S_N2 type. A carbocation with an α carbonyl group is destabilised by the partial positive charge on the neighbouring carbon. However, a resonance stabilisation is also possible, as pictured in Figure 4-1.[98]

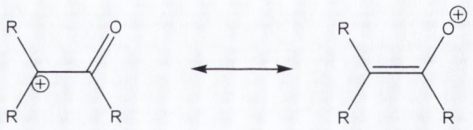


Figure 4-1: Resonance stabilisation of carbocation with adjacent carbonyl group

The nature of the piperazine nucleophile also indicated that the reaction was likely to proceed by an S_N2 mechanism. The nitrogen has a lone pair of electrons, but nitrogen is a small atom, so the hydrogen bonds between it and (a protic) solvent would be quite strong. In addition, it is not very easily polarised, so it has limited capacity to donate electron density to the substrate, the THIQ alkyl amide. It is not a soft (i.e. large, more polarizable) nucleophile, and soft nucleophiles have greater attraction to a substrate rather than to a proton in the solvent.[98]

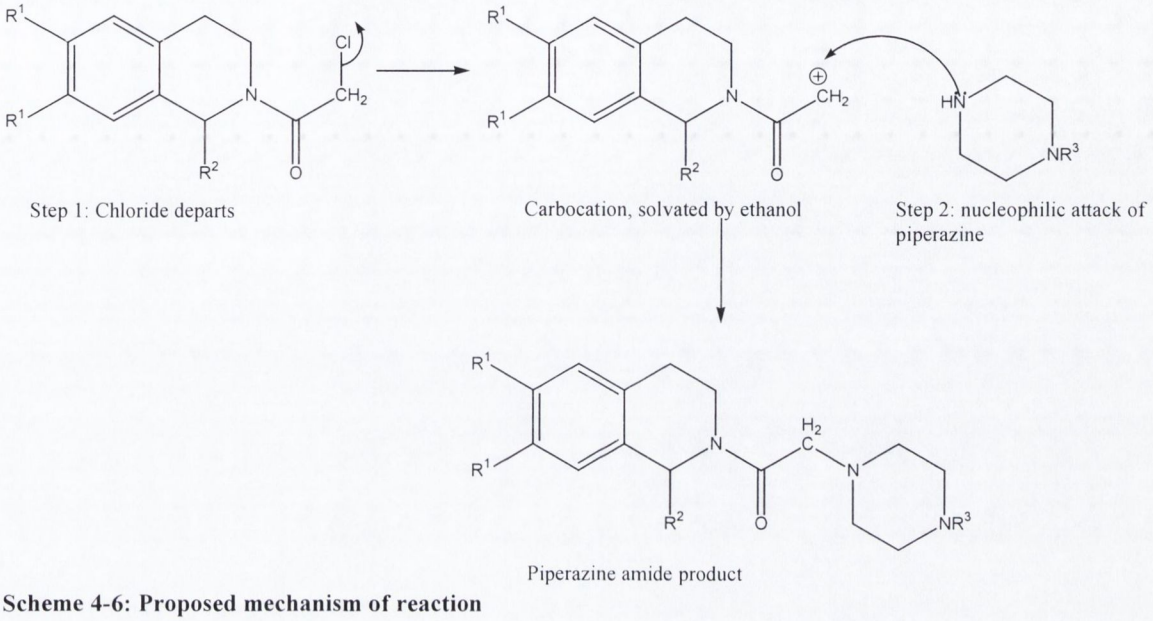
Despite this, the substitution of ethanol for DMF promoted the formation of the tetrahydroisoquinoline piperazinyl amine. Ethanol is a polar solvent. The substrate in this reaction (the halogenated tetrahydroisoquinoline amide) is not charged, so a polar solvent would quicken the reaction if a charged intermediate were formed. The effect on an S_N2 type intermediate would be negligible, as any charge is dispersed, but a carbocation would be solvated and stabilised.[101]

It is an interesting fact that the piperazine reacted more readily with the tetrahydroisoquinoline amide halide, in DMF with potassium carbonate, if the piperazine had an aromatic substituent. Piperazine itself only produced a dimer **(185)**, suggesting that the product of the first stage, **179**, was more reactive than piperazine itself. This is curious, as **179** is certainly a more bulky, awkward nucleophile. As an aprotic solvent, DMF is better able to solvate large molecules than ethanol, but this would allow the reaction to happen, rather than encourage it.

All the 1-benzyl-6,7-dimethoxy-tetrahydroisoquinoline piperazinyl amides were synthesised in ethanol. Since the benzyl group is the largest to be attached at position 1 of the current series, it seems likely that steric effects hindered an S_N2 approach by the piperazine.

The chloride ion *seemed* to act as a better leaving group in DMF, giving yields of over 40% where the reaction did proceed, compared to the bromide leaving group, which gave yields of under 40%. Reactivity varied so much with differences in substrate structure that comparisons are not valid, except in the case of 2-(4-benzo[1,3]dioxol-5-ylmethyl-piperazin-1-yl)-1-(6,7-dimethoxy-1-phenyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-ethanone, (**202**), which could only be formed using the bromide; and this contradicts the previous observation!

The main conclusion is that substitution of ethanol for DMF as the solvent favoured the reaction, and that this outweighed any advantage offered by altered leaving groups. On balance, it seems that the addition of substituents at position 1 may only allow the amino-de-halogenation to proceed through formation of a carbocation (as shown in Scheme 4-6).



Scheme 4-6: Proposed mechanism of reaction

4.4 Spectroscopy

4.4.1 Dimer

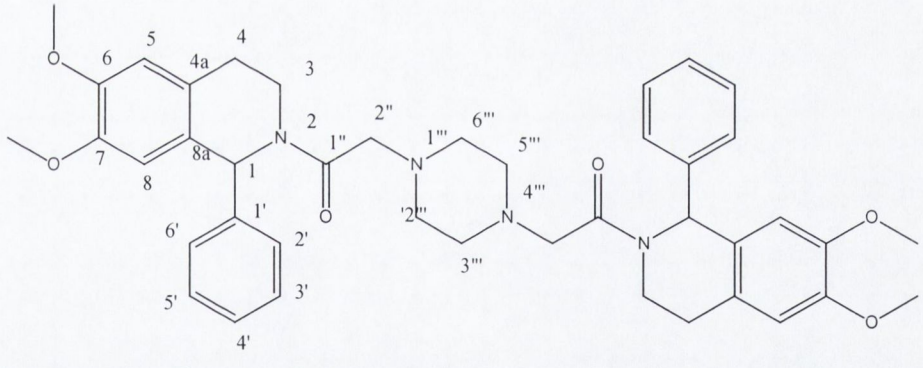


Figure 4-2: Numbering system applied to 1-(6,7-dimethoxy-1-phenyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-{4-[2-(6,7-dimethoxy-1-phenyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-oxo-ethyl]-piperazin-1-yl}-ethanone, 196

The spectroscopic characterisation of the dimer, 1-(6,7-dimethoxy-1-phenyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-{4-[2-(6,7-dimethoxy-1-phenyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-oxo-ethyl]-piperazin-1-yl}-ethanone **(196)**, was explored with a series of 2-D nuclear magnetic resonance experiments, and provides a good example of the spectroscopic features of the piperazinyl amides. The numbering is illustrated in Figure 4-2.

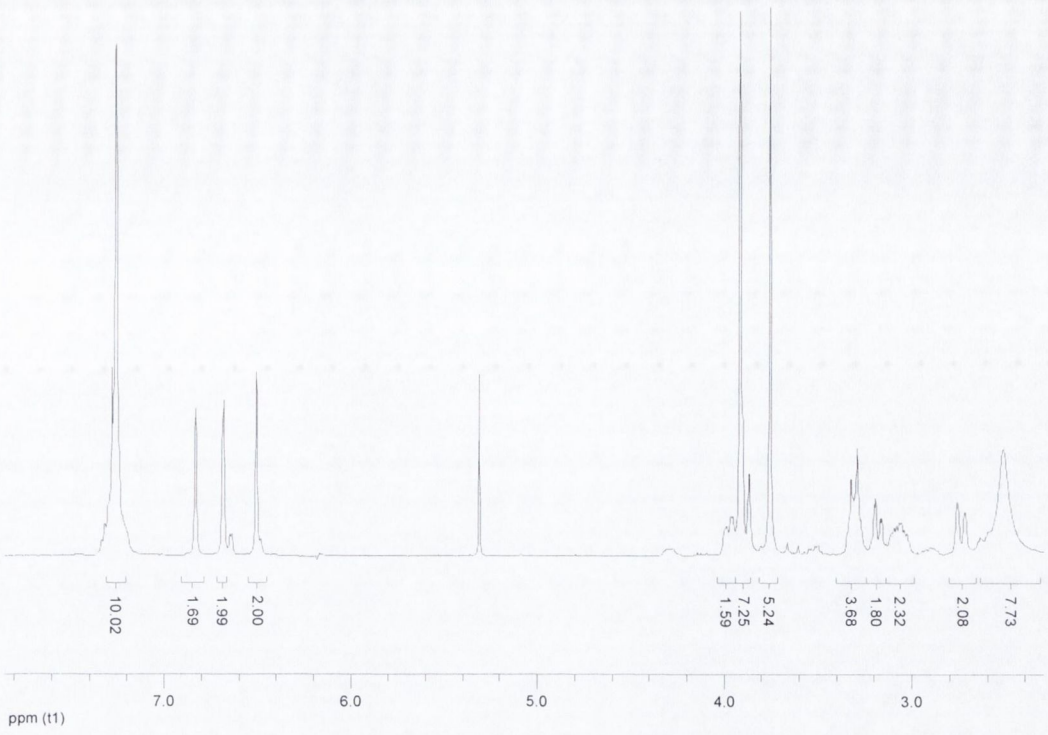


Figure 4-3: ^{1}H-NMR spectrum of 1-(6,7-dimethoxy-1-phenyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-{4-[2-(6,7-dimethoxy-1-phenyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-oxo-ethyl]-piperazin-1-yl}-ethanone (196)

The resonance effects usually seen with tetrahydroisoquinoline amides are almost absent, perhaps due to the size of the molecule. The minor rotamer produces signals so small as to be indistinct (see Figure 4-3) and in some cases not visible at all, so they are ignored in the discussion. The spectrum is simplified by this. The piperazine methylenes appear as one broad signal at 2.52δ. The protons of each methylene group in the saturated ring of the tetrahydroisoquinoline appear separately, as the rigidity of the large molecule means they appear on separate faces of the ring and do not have much flexibility of movement; but the dimeric nature of the compound means each signal integrates for 2 protons. C4$\underline{H}_2$ gives a doublet at 2.74δ (J = 16Hz) and a multiplet at 3.03 – 3.10δ. C3$\underline{H}_2$ may be observed as part of a multiplet at 3.26 – 3.30δ and as a doublet (J = 12Hz) at 3.96δ. The downfield proton couples with the methylene group beside the carbonyl group.

This is evident from the double doublet at 3.17δ, for C2"$\underline{H}_2$, which has a vicinal coupling constant of 13Hz, and a geminal coupling constant of 2Hz. C1$\underline{H}$ is surprisingly far downfield, at 6.83δ. Its identity, and that of the C8$\underline{H}$ and C5$\underline{H}$ protons at 6.51δ and 6.68δ respectively, is confirmed by reference to the HMQC spectrum (Figure 4-4).

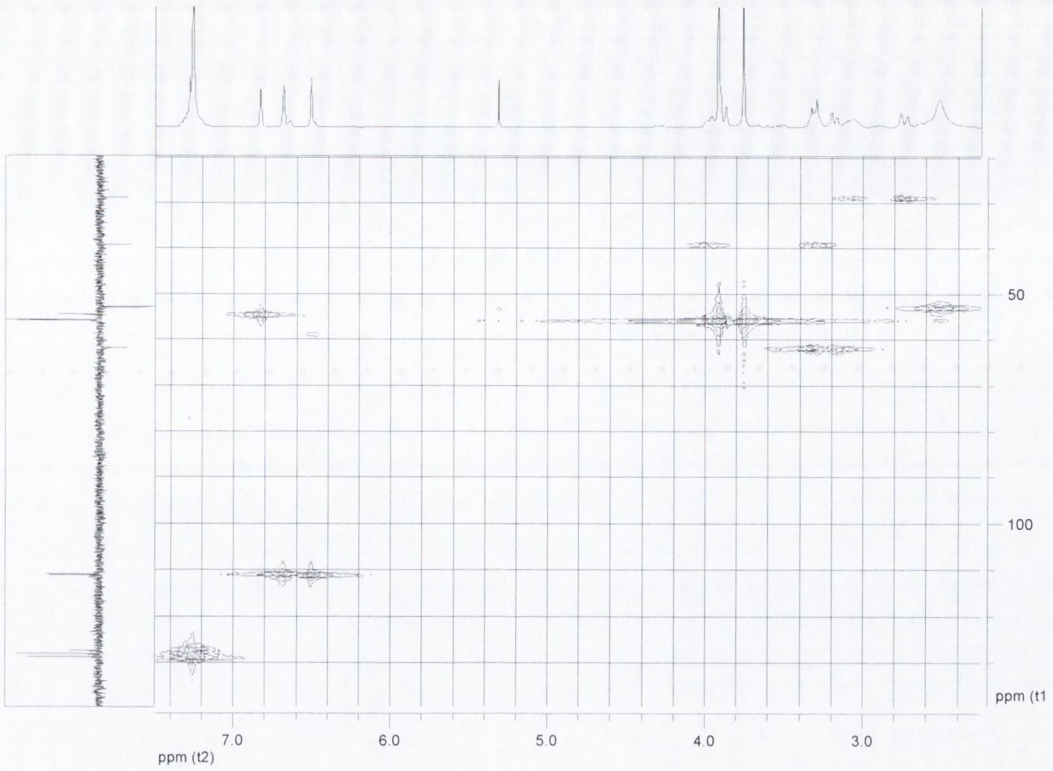


Figure 4-4: HMQC spectrum of dimer, (196)

Examination of the ^{13}C-NMR spectrum (Figure 4-5) shows a typical pattern for a phenyl substituent in the two strong signals, and one of about half their intensity, in the aromatic region. The quaternary carbons at 4a and 8a must coincide at 126.4ppm. The quaternary carbon at C1' is the most likely explanation for the signal at 142.5ppm, and this is confirmed by a HMBC spectrum (Figure 4-6), which shows coherence transfer from C1H to C1'. The quaternary carbons at C6 and C7 are at this point indistinguishable at 147.5ppm and 148.0ppm. The carbonyl group signals at 168.8ppm and 168.9ppm are all but amalgamated.

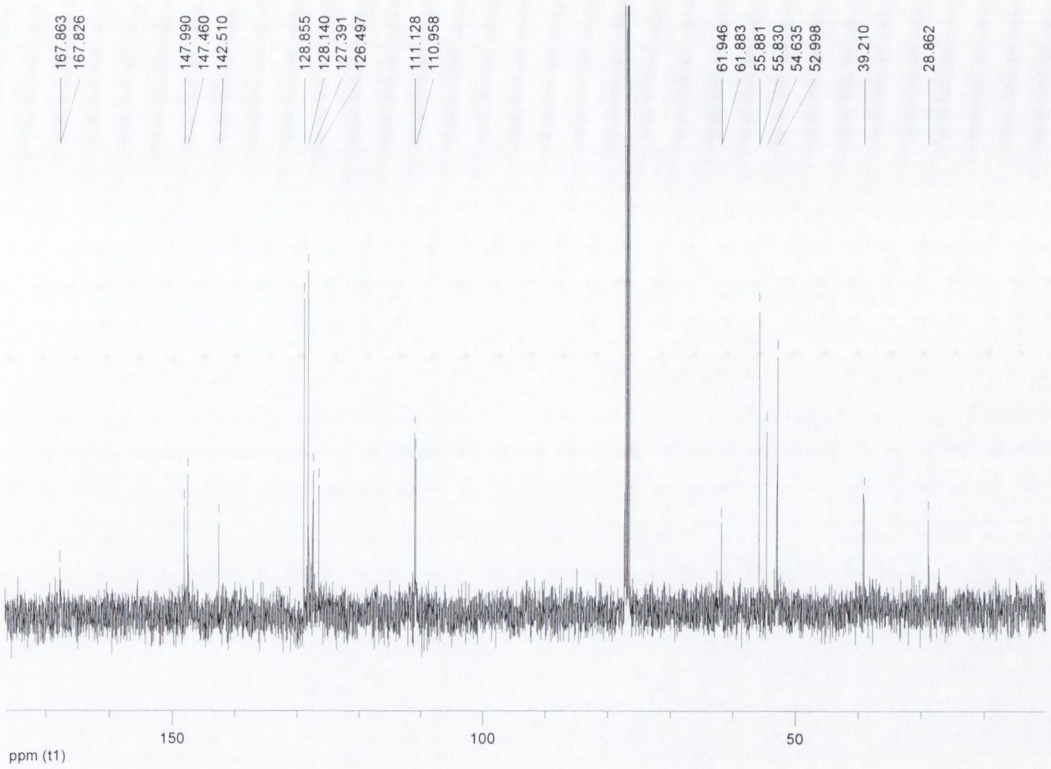


Figure 4-5: ^{13}C-NMR spectrum of dimer, (196)

The identities of the aromatic peaks may be established beyond a doubt by consulting the 2-D HMBC spectrum in Figure 4-6. This shows that the signal at 6.51δ is closer to the proton at C1H than that at 6.68δ, which has extra contours. The signal sequence of a HMBC experiment explores relationships between atoms via coherence transfer through bonds rather than through space. This spectrum indicates that that the signal at 6.68δ (C5H) represents a proton one bond further removed from the C1H proton than the proton at 6.51δ (C8H). It also singles out the carbon signal at 128.9ppm, which must belong to C2'H and C6'H.

Once C5H and C8H are known, it can be seen from the same experiment that the signal at 147.5ppm must be C6OCH_3, because of its relationship with C5H, and that C7OCH_3 must be at 148.0ppm, as it shows through bond coherence transfer from C8H.

Another region of the HMBC spectrum, shown in Figure 4-7, identifies the methoxy signal at 3.76δ as C6OCH_3 and that at 3.92δ as the C7OCH_3 peak.

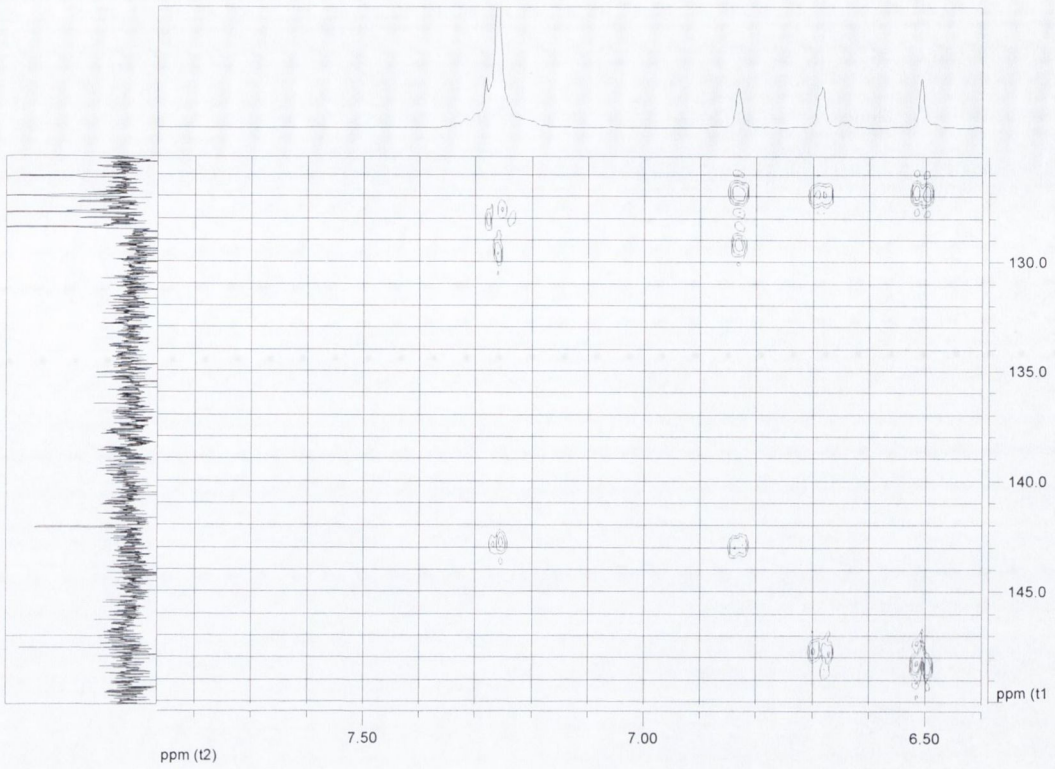


Figure 4-6: HMBC spectrum, illustrating relationships between C1H and both aromatic regions (196)

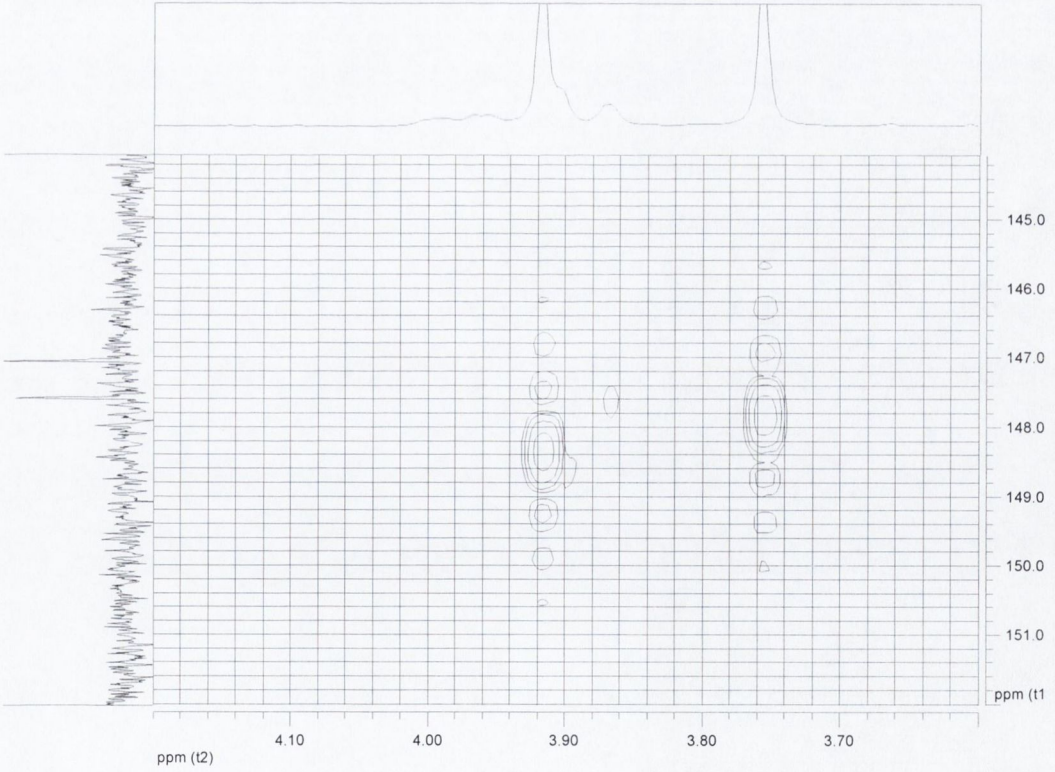


Figure 4-7: HMBC spectrum distinguishing the methoxy signals for C6OCH$_3$ and C7OCH$_3$ (196)

4.4.2 Halogenated Phenyl-Piperazinyl Amide

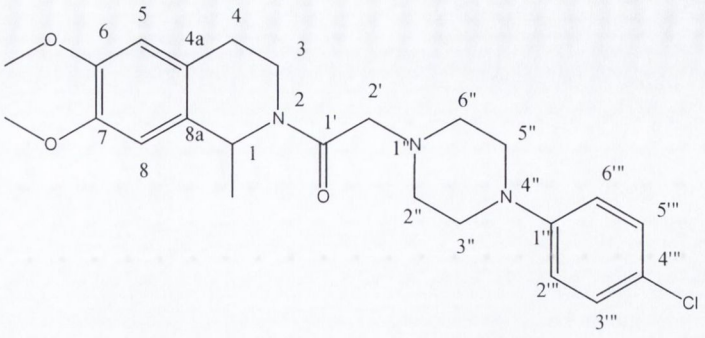


Figure 4-8: Numbering system applied to 2-[4-(4-chloro-phenyl)-piperazin-1-yl]-1-(6,7-dimethoxy-*1H*-isoquinolin-2-yl)-ethanone, (216)

As an example of the piperazine amides synthesised, **(216)** presented some interesting features when it was examined by nuclear magnetic resonance microscopy. The numbering scheme used in the description is as given in Figure 4-8. The usual doubling of signals, indicating the presence of rotamers at room temperature, was observed (see Figure 4-9). The pattern observed was consistent with that of the 1-methyl series of position 2 amides, as synthesised in Chapter 3.

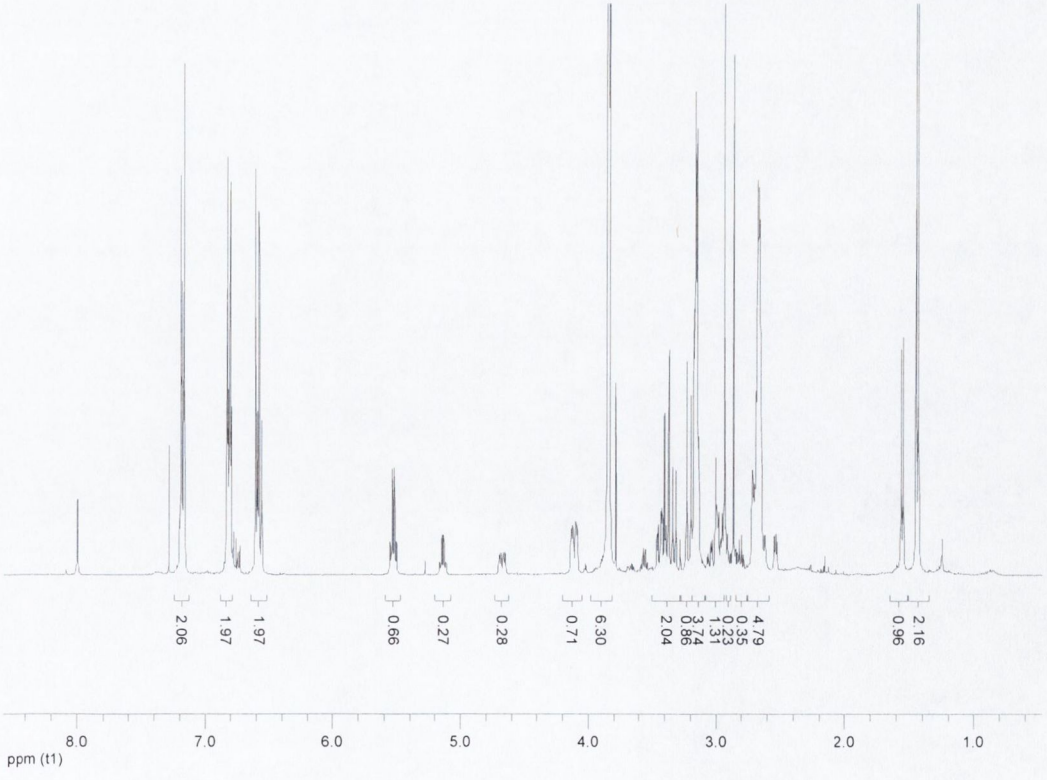


Figure 4-9: ^{1}H-NMR spectrum of 2-[4-(4-chloro-phenyl)-piperazin-1-yl]-1-(6,7-dimethoxy-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-ethanone, (216)

The appearance of a double double doublet for one proton of the position 3 methylene group, $C3H_2$, at 4.11δ (J_1 = 14Hz, J_2 = 5Hz and J_3 = 2Hz) and a double doublet at 4.67δ (J_1 = 13Hz J_2 = 5Hz) is diagnostic for tetrahydroisoquinoline amides with a methyl at position 1. In addition, the signal for C1H appears as two quartets, at 5.14δ and at 5.53δ (J = 6.8Hz), integrating for 0.3H and 0.7H respectively. The methyl group gives two well-defined doublets at 1.44δ and 1.56δ (J = 6.8Hz), integrating for 2.1H and 0.9H. The other features of a tetrahydroisoquinoline nucleus may be observed. Unfortunately, residual DMF complicates integration of the multiplet for the methylene protons of $C4H_2$. The second proton of $C3H_2$ gives a double triplet signal at 3.43δ. The methoxy protons give a multiplet, integrating for 6 protons, at 3.83δ - 3.84δ, due to the rotamers. The major and minor signals of C8H and C5H overlap at 6.56δ - 6.61δ.

The dimeric and regular piperazinyl amides differ in the disposition of the piperazine ring methylene proton signals. In the dimer it is seen as a single, broad signal. Here, and in all others of the series (with the exception of the piperonal piperazine amide), it may be seen as two distinct multiplets, at 2.66δ - 2.69δ and 3.14δ - 3.18δ. The methylene α to the amide function, $C2'H_2$, is constrained by the partial double bond nearby, hence its protons are observed individually. The minor set of doublets at ca. 3.18δ is obscured by the piperazine signal, but the major rotamer is seen at 3.21δ. Likewise, the other proton gives a doublet at 3.33δ for the minor component and at 3.39δ for the major. The aromatic protons *meta* to the chlorine atom are observed as a multiplet at 6.81δ - 6.84δ, and those at C3'"H and C5'"H are seen as a multiplet at 7.16δ - 7.20δ.

In the carbon spectrum of this compound (Figure 4-10), the signals have been doubled, although in weaker signals such as quaternaries it is not apparent at the level of resolution obtained.

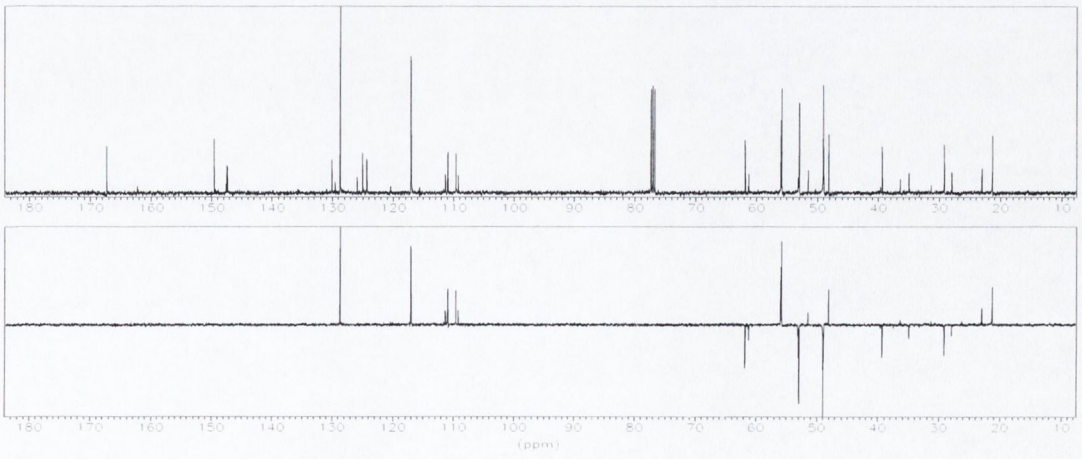


Figure 4-10: ^{13}C-NMR and DEPT spectra of (216)

The methyl signals are clearly those at 21.2ppm (major) and 22.9ppm (minor). C4H_2 is seen at 27.9ppm (minor) and 29.1ppm (major). Signals are observed at 34.9ppm and at 39.3ppm for the minor and major components of C3H_2 respectively. The methylated position one carbon is seen as a large signal at 48.0 ppm and a small one at 51.4ppm. The piperazinyl ring carbons give pronounced signals at 48.9ppm, 49.0ppm, 52.9ppm and 53.0ppm. The methoxy signals are presented at 55.7ppm and 55.9ppm. C2'H_2 is beside a carbonyl group and the signals are seen at 61.1ppm (minor) and 61.7 (major).

Using the 2-D work carried out on the dimer **196** as a template, it is assumed that the signals of **216** at 109.2ppm (minor) and 109.6ppm (major) belong to C8H and the adjacent signals at 111.0 (major) and 111.4 (minor) are those of C5H.

The carbons at positions *meta* to the chlorine atom have major and minor signals which almost coincide, at 117.03ppm and 117.06ppm respectively. C3'''H and C5'''H are seen at 128.74ppm (major) and 128.79 (minor). The quaternary signal at 124.3ppm bears the chlorine atom at C4'''. The quaternary carbons at C8a and C4a are found at 125.0ppm (major), 125.9ppm (minor), 129.6ppm (minor) and 130.1ppm (minor). The pattern established by examining the dimer suggests that 147.3ppm (minor) and 147.4ppm (major) belong to C6OCH_3, while 147.5ppm (major) and 147.7ppm (minor) appertain to C7OCH_3. C1' must therefore account for the signal at 149.6ppm and the signal at 167.4 can only be that of the carbonyl group.

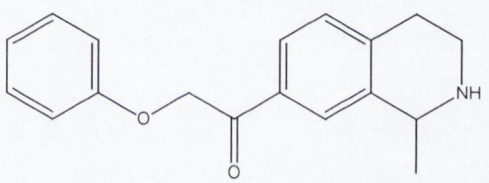
4.5 Summary

The synthesis of position 2 tetrahydroisoquinoline amides, elaborated by piperazine functions appended to the carbon α to the amide function, required substantial synthetic investigation in order to obtain the products desired. The modifications, which improved the yields of product, offered interesting insights into the mechanism of the synthesis, as well as affording compounds for biochemical testing. It appears that amino-de-halogenation at the carbon α to the carbonyl group could proceed by formation of a carbocation and an S_N1 mechanism. Detailed NMR spectroscopy was examined to confirm the structures of the products.

5 Chapter 5: Synthesis of 7-Phenoxy-acetyl-tetrahydroisoquinolines

5.1 Introduction

Previous work in this laboratory on 2-phenoxy-1- (1,2,3,4-tetrahydroisoquinolin-7-yl)-ethanone **(219)** indicated selectivity for MAO-B.[59] It also functioned as an inhibitor of MAO-A, albeit at a different concentration. In fact, the IC_{50} value for MAO-A was >100μM and for MAO-B the IC_{50} was 26+/-1μM. Investigation of the acetylcholinesterase inhibitory activity of the compound was encouraging. As observed in chapter one, both acetylcholinesterase inhibition and monoamine oxidase B inhibition are believed to be beneficial in the treatment of Alzheimer's disease, and an agent combining both activities would be of clinical use. It was decided to investigate a range of related 7-phenoxyacetyltetrahydroisoquinolines for further evaluation of the biochemical activity.



1-Methyl-7-(phenoxyacetyl)-1,2,3,4-tetrahydroisoquinoline

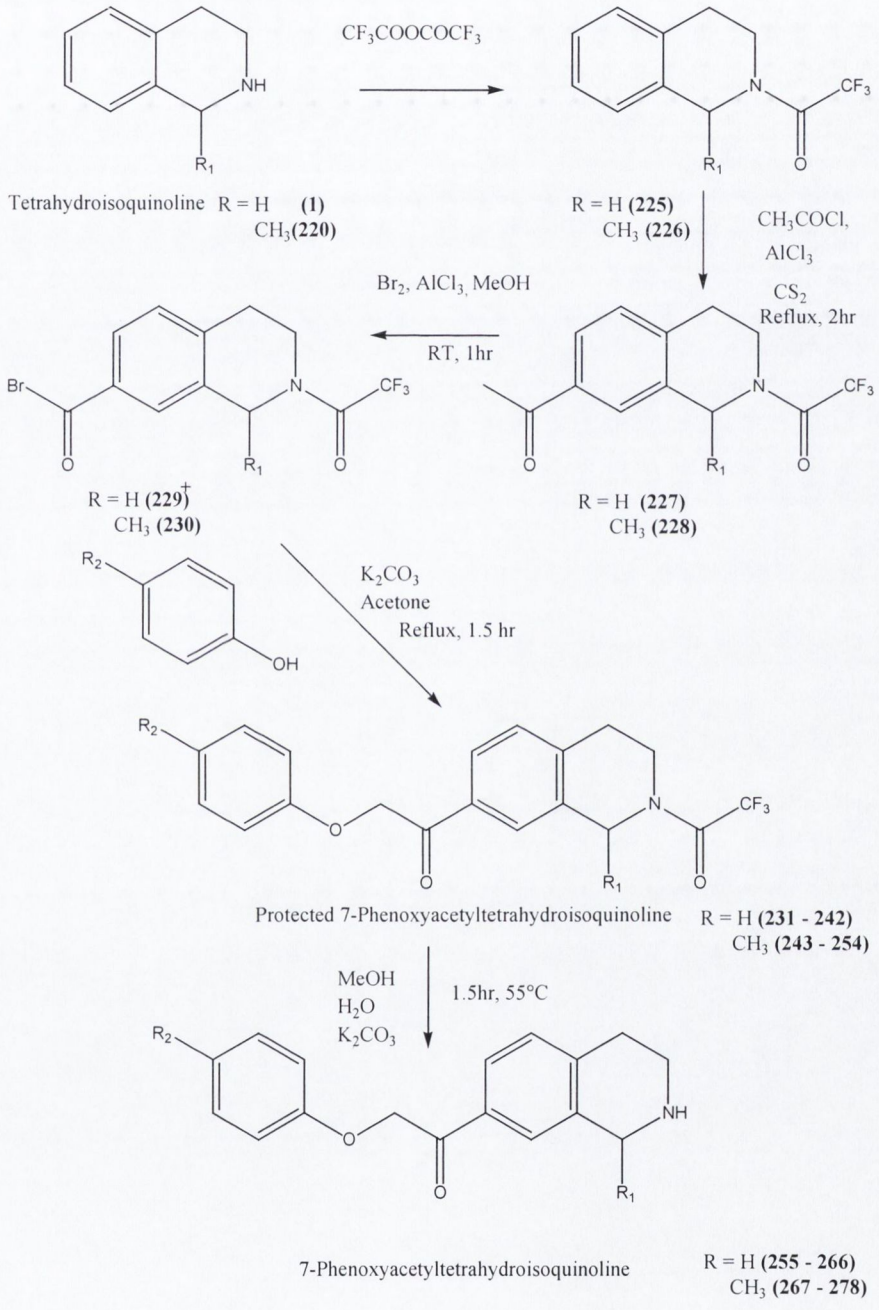
Figure 5-1: 2-Phenoxy-1-(1,2,3,4-tetrahydroisoquinolin-7-yl)-ethanone, (219)

5.2 General Scheme

Two series of compounds were scrutinised. The first series of phenoxyacetyltetrahydroisoquinolines contained no substituent at position 1 of the isoquinoline nucleus, and therefore could be prepared from purchased 1,2,3,4-tetrahydroisoquinline **(1)**. The introduction of a methyl group at position 1 necessitated a cyclisation of phenethylamine and reduction to afford the 1-methyl-tetrahydroisoquinoline **(224)**. The difficulties encountered in this process will be discussed in sections 5.3 and 5.4. Once the 1-methyl-tetrahydroisoquinoline had been obtained it was treated in a manner analogous to 1,2,3,4-tetrahydroisoquinoline to generate the phenoxyacetyltetrahydroisoquinolines **(255 - 278)**. The series of reactions is illustrated in Scheme 5-1.

Sections 5.5 to 5.9 address the synthetic process of the phenoxyacetyltetrahydroisoquinolines themselves. Trifluoroacetylation at the amine **(225,**

226) was followed by acetylation at position 7 **(227, 228)**. The acetyl function was then brominated (giving **229** and **230**) and this reacted with the appropriate phenol in alkaline acetone to synthesise the protected phenoxyacetyltetrahydroisoquinoline (**231 – 254**). The protecting group was cleaved in the final step to give the required phenoxyacetyltetrahydroisoquinoline (**255 – 278**) (see Scheme 5-1).



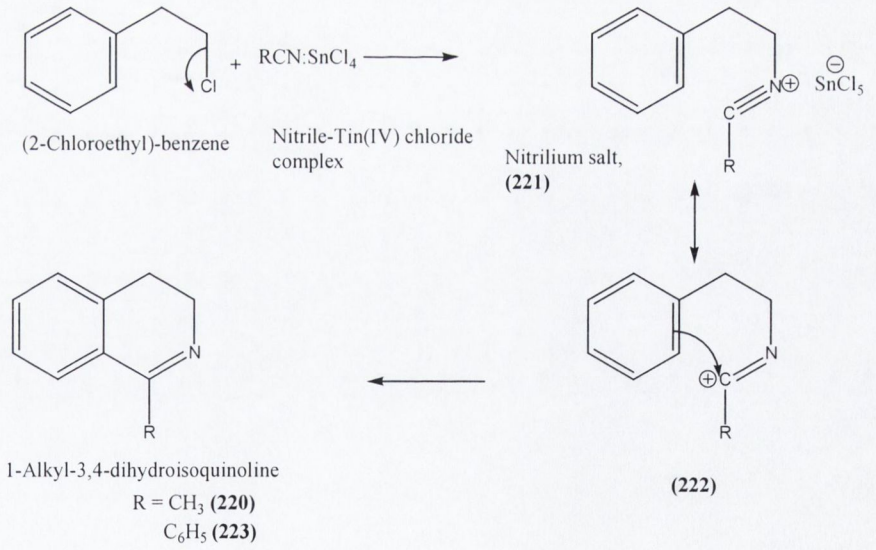
Scheme 5-1: Synthesis of 7-phenoxyacetyltetrahydroisoquinolines

5.3 Synthesis of 1-methyl-3,4-dihydroisoquinoline (220)

5.3.1 General method

The initial step in the synthesis of the 1-methyl series of phenoxyacetyltetrahydroisoquinolines required the efficient synthesis of 1-methyl-3,4-dihydroisoquinoline **(220)**. The Bischler-Napieralski process would seem indicated. This unfortunately involved a two-step synthesis, and was moreover difficult to purify. It is held to give improved yields when methoxy groups are present at positions 3 and 4 of the β-phenylethylamine, but this route afforded 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline **(41)** in only 20.7% yield (see Chapter 3, section 3.3.1). An initial poor yield of 15.2% for the 1-methyl-3,4-dihydroisoquinoline **(220)** was no surprise.

In view of this, an alternative procedure was evaluated.[75] This involved the formation of a tin IV chloride-nitrile complex, which then attacked the terminal carbon of (2-chloroethyl)-benzene. The nitrilium salt afforded had two mesomeric forms (see Scheme 5-2) and the electrophilic carbonyl carbon of **222** caused ring closure through electrophilic aromatic substitution at the position *ortho* to the sidechain, giving product **220** or **223**. This procedure is reported to be useful for the synthesis of a range of dihydroisoquinolines with alkyl and aromatic substituents at position 1, both in the presence and absence of methoxy groups at positions 3 and 4 of the benezene (i.e. positions 6 and 7 of the dihydroisoquinoline).



Scheme 5-2: Formation of 1-alkyl-3,4-dihydroisoquinoline from nitrile, (2-chloroethyl)-benzene and tin(IV)chloride

5.3.2 Optimisation

The reported experimental procedure was vague[75]; the appropriate nitrile, (2-chloroethyl)-benzene and tin (IV) chloride were added in differing orders for differing products, but the exact order used, the temperature of the reaction or the duration of the synthesis were not specified for any product. In some cases, an excess of one reagent had been used, but the instances were not detailed.

In order to optimise the yield of **220**, in the present work, acetonitrile and (2-chloroethyl)-benzene were stirred together under nitrogen and tin (IV) chloride was added drop wise with cooling in an ice-bath, since Lora-Tamayo mentions an exothermic reaction.[75] It was soon apparent that the ice-bath was unnecessary; indeed, an endothermic reaction forming a solid appeared to take place. The mixture was heated to 100°C for 3 hours and this resulted in the formation of a homogenous reaction mixture. After work-up of the reaction, thin layer chromatography and nuclear magnetic resonance spectroscopy showed that only starting material was present.

The reaction was of further interest for the formation of non-methoxylated dihydroisoquinolines with a phenyl group at position 1 **(223)**. The cyclisation involving benzonitrile was selected for investigation via a multifactorial experiment, similar to that used to improve the nitration step of Chapter 2. It was concluded that the nitrile, tin (IV) chloride and (2-chloroethyl)-benzene should be added in that order. Moreover, stirring at 130°C for 3 hours gave improved yields of 1-phenyl-3,4-dihydroisoquinoline **(223)**.

The lessons learned in the production of **223** were applied to the methyl dihydroisoquinoline, **220.** Yields were still very low: 26%. The reaction was divided into three lots, reacted simultaneously but worked up separately. Instead of adding NaOH solution in the initial stages of the work-up, the mixture was taken up in ethyl acetate. The organic phase was washed with 15% sodium hydroxide instead. After purification with column chromatography the yield was approximately 30%, which was acceptable. Further improvement was achieved through use of a microwave system, as outlined in Section 5.3.3.

5.3.3 Microwave innovation

5.3.3.1 Development of microwave chemistry

The genesis of microwave chemistry may be traced to research on RADAR (**RA**dio **D**etection **A**nd **R**anging) by Sir Robert Watson-Watts and his group in the late 1930s.[102] With the advent of World War II, development of a magnetron - to generate the fixed frequency microwaves required for RADAR use – became a British priority. Work with the magnetron afterwards led to the discovery of the heating effects of microwaves. One Percy LeBaron Spencer noticed a chocolate bar in his pocket melted while he experimented with radio waves, and this observation led to the development of the first domestic microwave ovens in the 1950s.[103]

Other applications for microwave technology were explored in succeeding decades, and the first papers on microwave-enhanced organic chemistry were published in 1986.[104,105] Initial experiments used domestic microwave ovens, the design of which was not optimal for chemical applications. In the course of the 1980s multi-mode ovens specifically for chemical synthesis were developed, but the next generation of microwave systems evolved into single-mode models.

5.3.3.2 Principles of microwave chemistry

Microwaves are found at the lower end of the electromagnetic spectrum, in the region of 300 MHz to 300,000 MHz (or a wavelength of approximately 1 mm to 1 m). Laboratory apparatus usually has a magnetron generating frequencies of about 2450MHz, as this provides suitable penetration for typical laboratory samples, and appropriate power sources are available for such equipment.[103]

Microwave energy consists of both an electric field and a magnetic field, although only electric field transfers of energy are implicated in most chemical syntheses. The electric field transfers energy directly to the molecules of a reaction through dipole rotation and, in some cases, ionic conduction. Dipole rotation arises when polar molecules attempt to align themselves with the electric field. This field is constantly changing, and the motion of the molecules as they orient themselves with respect to the field, transfers energy to the reaction. If ions are present, they will also attempt to align themselves with the electric field, and the ionic motion also results in energy transfers. In fact, ionic conduction can lead to instantaneous superheating of the reaction mixture.[103]

Traditional heating of a round bottomed flask in an oil bath relies on conduction through the walls of the flask, followed by convectional heating within the solution; there is thus a time lag between the application of heat and transfer of heat energy to the reactants. Microwaves transfer energy almost immediately upon initiation of the experiment. Each

cycle of electromagnetic energy takes about 10^{-9} seconds. Molecular relaxation is of the order of 10^{-5} seconds, so this is a much slower process. Energy thus accumulates as the electromagnetic cycles are repeated.[103]

The microwaves couple directly with the molecules of the reaction, and this is known as "molecular heating". Heat results from the transfer of energy, it is not the medium of energy transfer, and simultaneous cooling and microwave irradiation of a reaction will promote reactions at low temperatures. This is especially important for thermolabile reactants. The low energy of microwave photons (0.155kJ/mole) is lower than the energy usually required for bond breaking (335-500 kJ/mole), so the structure of reactants should not be affected.[103]

A domestic microwave has a multi-mode cavity, resulting in hot and cold spots; this is why food must be rotated in such ovens to ensure uniform heating. There was some controversy over this phenomenon in the early 1980s. While rotation of food and sufficient heating should guard against *salmonella* survival and similar gastronomic disasters, such variations in energy intensity within a multi-mode cavity would militate against the reproducibility of chemical syntheses. Field homogeneity is preferable, and single-mode systems offer this.[103]

An innovation, which compensates for variations in sample size and reactant coupling, is the circular waveguide. This provides multiple points of entry for the microwave energy and should avoid tuning problems.[103] "Enhanced Microwave Synthesis" (EMS) involves cooling the reaction cavity (usually with compressed air or nitrogen) during the reaction, so that microwave energy may be continuously supplied without causing deterioration of the reagents at very high temperatures.[106] Microwave systems incorporating such features are becoming common in organic synthetic laboratories.

5.3.3.3 Results of microwave mediated cyclisation

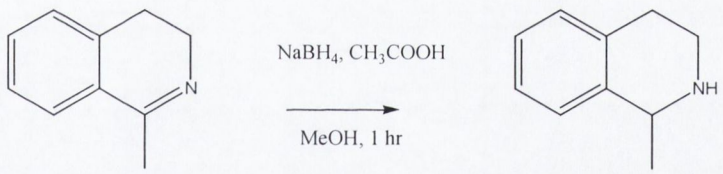
The cyclisation was attempted using a single-mode microwave system (CEM Discover system, using an indirect pressure gauge) and applying EMS. Low yields with conventional methods (see 5.2 above) made microwave experimentation attractive for the synthesis of 1-methyl-3,4-dihydroisoquinoline **(220)**. Acetonitrile is one of the reactants. Acetonitrile is categorised as a medium absorbing solvent in microwave terms. Solvents for microwave use are evaluated in terms of their dielectric constant, their loss tangent and their dielectric loss. The dielectric constant (ε') of a fluid is the ratio of the electrical capacity of a capacitor filled with the fluid to the electric capacity of the evacuated capacitor. Dielectric loss (ε'') is the amount of input microwave energy that is dissipated

as heat. The loss tangent is found from the equation Tan $\delta = \varepsilon''/\varepsilon$.[103] Unless a sink effect is desired from the solvent, solvents with high dielectric loss constants are preferred for microwave-mediated reactions.

In the case of the cyclisation to afford **(220)**, further solvent was considered unnecessary. The experimental details are given elsewhere (see Experimental Details). A power setting of 60 Watts was used, and the maximum temperature was set at 130°C. Cooling was achieved using compressed air. Total reactant volumes of about 1.5 mL were used (see experimental section), to leave sufficient headspace for hydrochloric acid evolved from the reaction and any break-down of acetonitrile under pressure. Each run lasted just 3 minutes, so appreciable quantities could be accumulated in a relatively short period of time, as microwave synthesis increased the yield to 71%. The other parameters were maximum pressure of 50psi and an initial 30 seconds ramping time.

5.4 Reduction of 1-methyl-3,4-dihydroisoquinoline

The dihydroisoquinoline **(220)** was reduced to its tetrahydroisoquinoline equivalent **(224)** using sodium borohydride in methanol, as illustrated in Scheme 5-3. This gave a yield of 68%. Thereafter the synthesis followed the same route as that adopted for the unsubstituted tetrahydroisoquinoline: protection, acylation, bromination and reaction with the appropriate phenol, summarised in Scheme 5-1.



1-Methyl-3,4-dihydro-isoquinoline
(220)

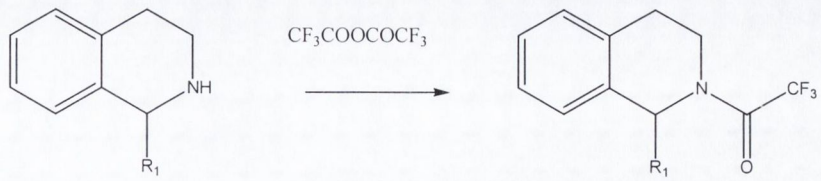
1-Methyl-1,2,3,4-tetrahydro-isoquinoline
(224)

Scheme 5-3: Reduction of 1-methyl-3,4-dihydroisoquinoline

5.5 Protection of amine function at position 2

A trifluoroacetyl group was chosen to protect the amine at position 2 from acylation. This group is stable under the conditions of a Friedel-Crafts acylation, bromination and formation of a phenoxy compound, but may be cleaved with relative ease by heating in methanol with potassium carbonate. An excess of trifluoroacetic anhydride was added dropwise to the tetrahydroisosquinolines **(225)** and **(226)** and the solution was stirred at

room temperature for 2 hours, giving yields of 81% and 73% of trifluoroacetylated product (**225, 226,** respectively).[59]



R = H, CH_3

Tetrahydroisoquinoline

N-Acetyl-tetrahydroisoquinoline

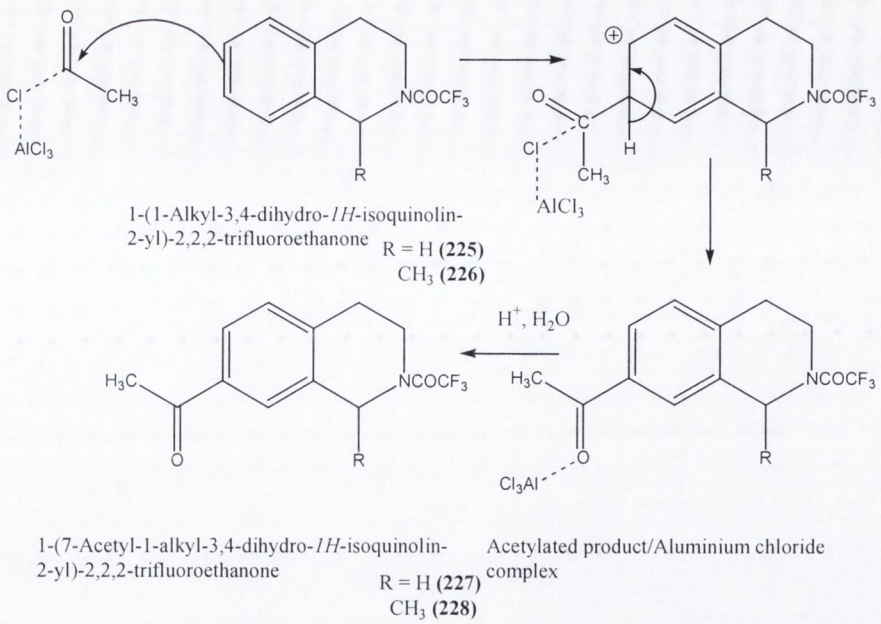
R = H **(225)**

CH_3 **(226)**

Scheme 5-4: Protection of amine function of tetrahydroisoquinolines

5.6 Acylation of 1,2,3,4-tetrahydroisoquinoline and 1-methyl-1,2,3,4-tetrahydroisoquinoline

Acylation of the THIQs was next effected via a Friedel-Crafts acylation.[107] The reaction was carried out in carbon disulfide, quite a non-polar solvent, with a dielectric constant of 2.6. It is therefore assumed that the acetyl chloride would not dissociate into an acyl cation and chloride ion; rather, the acetyl chloride would be expected to form a complex with aluminium chloride, the Lewis base.[101] About 2.5 equivalents of aluminium chloride were used, as the final product forms a complex with it and thus removes it from the reaction (see Scheme 5-5). Yields were 71% for the unsubstituted tetrahydroisoquinoline (227) and 94% for the 1-methyl-1,2,3,4-tetrahydroisoquinoline (228). Friedel-Crafts acylation is an electrophilic aromatic substitution reaction, similar to nitration, and the acetyl group would be expected to be substituted for the aromatic C7H, analogous to the nitro group. The substitution at position 7 was confirmed by both IR and NMR spectroscopic data. Only three protons could be observed in the aromatic region, with the proton at C5H being upfield from those adjacent to the acetyl group. The carbonyl function of the acetyl group was clearly visible in both the ^{13}C-NMR spectrum and the IR absorbtion spectrum.

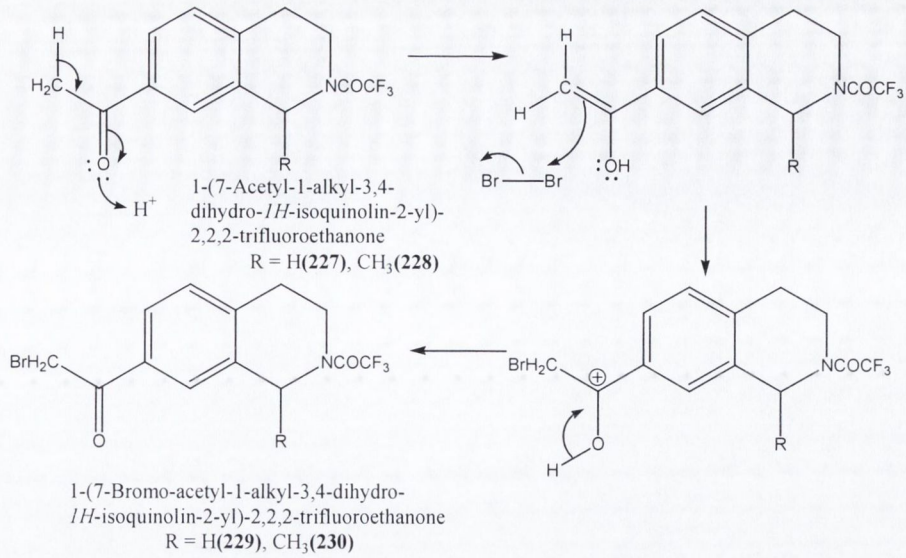


Scheme 5-5: Acylation of protected tetrahydroisoquinoline

5.7 Bromination of acetylated tetrahydroisoquinolines

Monobromination of the α carbon of the acetyl group in (227) and (228) was desired, so the bromination was carried out in acidic conditions, in methanol with a catalytic quantity of aluminium chloride, to afford (229) and (230) respectively. Basic conditions would promote replacement of all three hydrogens with bromine, as the reaction would then progress through the enolate anion. In the acid-catalysed procedure (see Scheme 5-6) aluminium chloride is present to increase polarisation of the bromine molecule, as the substitution of bromine in fact occurs in a manner similar to electrophilic addition at a double bond.

The disappearance of the singlet of the acetyl group, and its replacement in the ^{1}H-NMR spectrum by a signal at 4.43 δ integrating for 2 protons, supported IR absorption data indicating monobromination at the α carbon of the acetyl group.

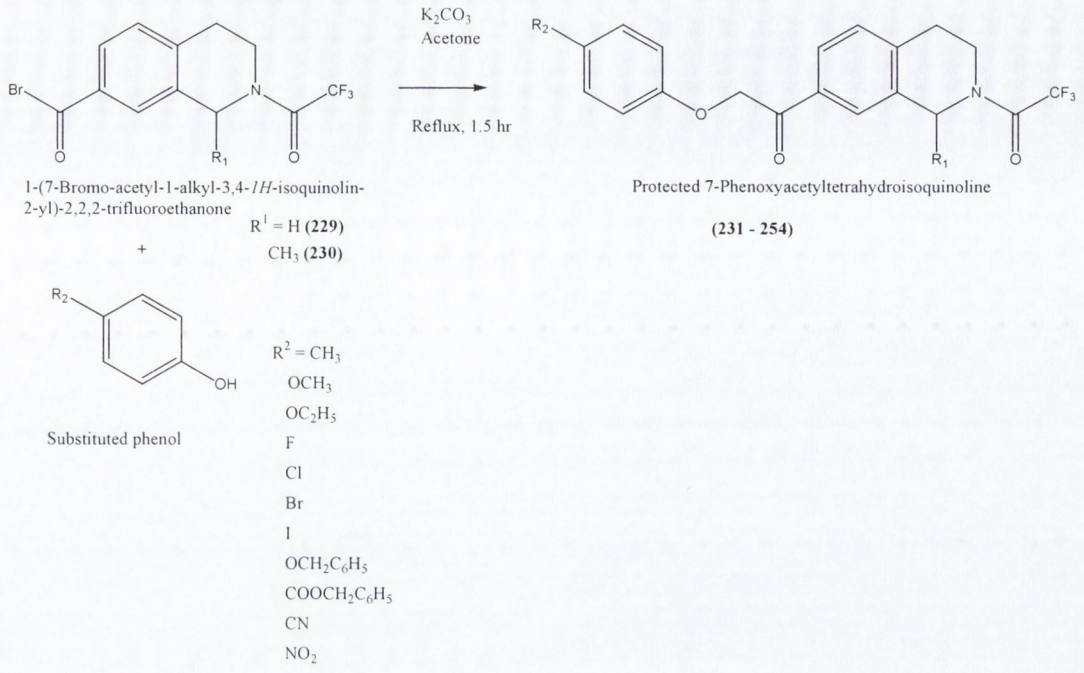


Scheme 5-6: Bromination of acetylated tetrahydroisoquinoline

5.8 1-(7-phenoxy-acetyl-3,4-dihydro-1H-isoquinolin-2-yl)-(2,2,2-trifluoro)-ethanones

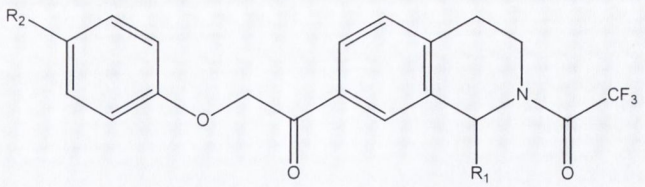
5.8.1 Synthesis

Introduction of a substituted phenol ether at the bromoacetyl substituent of **(229)** and **(230)** was next investigated. The reaction of substituted phenols and an alkyl bromide displaces the bromine, as in the Williamson synthesis of ethers. The procedure used to obtain 7-phenoxyacetyltetrahydroisoquinolines required less severe conditions, and the base chosen was potassium carbonate. The bromide (**229** or **230**) was refluxed with the phenol in acetone for 1.5 hours, to afford the phenoxyacetyl products **(231 – 254)**, as in Scheme 5-7. All the phenoxyacetyltetrahydroisoquinolines synthesised in this study were substituted at the *para* position. The assay of acetylcholinesterase inhibition could then be analysed to draw conclusions on the structure activity relationship. To this end the halogen family was investigated: 4-fluorophenoxy **(258, 270)**, 4-chlorophenoxy **(259, 271)**, 4-bromophenoxy **(260, 272)** and 4-iodophenoxy **(261, 273)**. This was expected to provide information on problems associated with bulk and steric hindrance and electronic properties. 4-Methylphenoxy **(255, 267)** and 4-methoxyphenoxy **(256, 268)** were planned to investigate electronic effects. 4-Ethoxyphenoxy **(257, 269)** also allowed bulk and extension in space at this position to be examined. A *para* nitro phenoxy **(263, 275)** offered an insight into the influence of electron withdrawing groups. Ester functions not only were of interest in themselves, they also afforded a route to the related acid, as in **(278)**. The full list of products obtained **(231 – 254)** are listed in Table 5-1.



Scheme 5-7: Synthesis of protected 7-phenoxyacetyltetrahydroisoquinolines

Lower yields were generally observed as the bulk of the phenol substituent increased. The phenol was in all cases substituted in the *para* position of the aromatic ring. The spectra displayed the usual feature of rotamers. An outline of the spectroscopic features of 1-{7-[2-(4-chlorophenoxy)-acetyl]-3,4-dihydro-*1H*-isoquinolin-2-yl}-2,2,2-trifluoro-ethanone **(235)** follows. All the spectra followed this basic pattern.



Protected 7-Phenoxyacetyltetrahydroisoquinoline

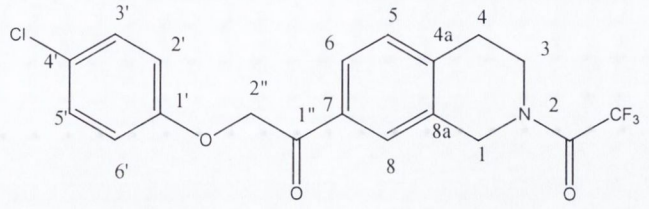
Compound Number	R^1	R^2	Yield
231	H	CH_3	89
232	H	OCH_3	45
233	H	OC_2H_5	40
234	H	F	73
235	H	Cl	63
236	H	Br	59
237	H	I	69
238	H	$NHCOCH_3$	67
239	H	NO_2	62
240	H	CN	61
241	H	$OCH_2C_6H_5$	21
242	H	$COOCH_2C_6H_5$	47
243	CH_3	CH_3	80
244	CH_3	OCH_3	45
245	CH_3	OC_2H_5	65
246	CH_3	F	60
247	CH_3	Cl	55
248	CH_3	Br	33
249	CH_3	I	35
250	CH_3	$NHCOCH_3$	45
251	CH_3	NO_2	60
252	CH_3	CN	87
253	CH_3	$OCH_2C_6H_5$	47
254	CH_3	$COOCH_2C_6H_5$	58

Table 5-1: Yields of N-acylated 7-phenoxyacetyltetrahydroisoquinolines

5.8.2 Spectroscopy of protected 7-phenoxyacetyltetrahydroisoquinolines

5.8.2.1 1-{7-[2-(4-chlorophenoxy)-acetyl]-3,4-dihydro-1H-isoquinolin-2-yl}-2,2,2-trifluoro-ethanone (235)

The numbering scheme used in the discussion is illustrated in Figure 5-2.



1-{7-[2-(4-Chloro-phenoxy)-acetyl]-3,4-dihydro-1*H*-isoquinolin-2-yl}-2,2,2-trif luoro-ethanone

Figure 5-2: Numbering scheme applied to 1-{7-[2-(4-chloro-phenoxy)-acetyl]-3,4-dihydro-*1H*-isoquinolin-2-yl}-2,2,2-trifluoro-ethanone, (235)

5.8.2.1.1 ^{1}H-NMR spectrum of 235

The spectrum of **235** may be examined in Figure 5-3. The methylene protons at positions 3 and 4 appear equivalent in these spectra. A multiplet is observed at 3.00 δ – 3.05 δ for C4$\underline{H}_2$ but the two triplets, which the rotamers generate, may be distinguished at 3.88 δ (*trans*, J = 5.5 Hz) and 3.92 δ (*cis*, J = 6.2 Hz) for C3$\underline{H}_2$. Two singlets at 4.82 δ (*cis*) and 4.85 δ (*trans*) represent C1$\underline{H}_2$. The methylene between the carbonyl group and oxygen atom is further downfield at 5.24 δ. The disubstituted benzene ring gives doublets at 6.85 δ (J = 11.7 Hz) and at 7.21 δ (J = 11.1 Hz), for C2'$\underline{H}$/C6'$\underline{H}$ and C3'$\underline{H}$/C5'$\underline{H}$ respectively. Finally, the C5$\underline{H}$ presents a multiplet at 7.21 δ - 7.34 δ; the C8$\underline{H}$ signal is a singlet at 7.80 δ and the multiplet at 7.82 δ - 7.87 δ results from the overlapping doublets of the C6$\underline{H}$ signals of the two rotamers.

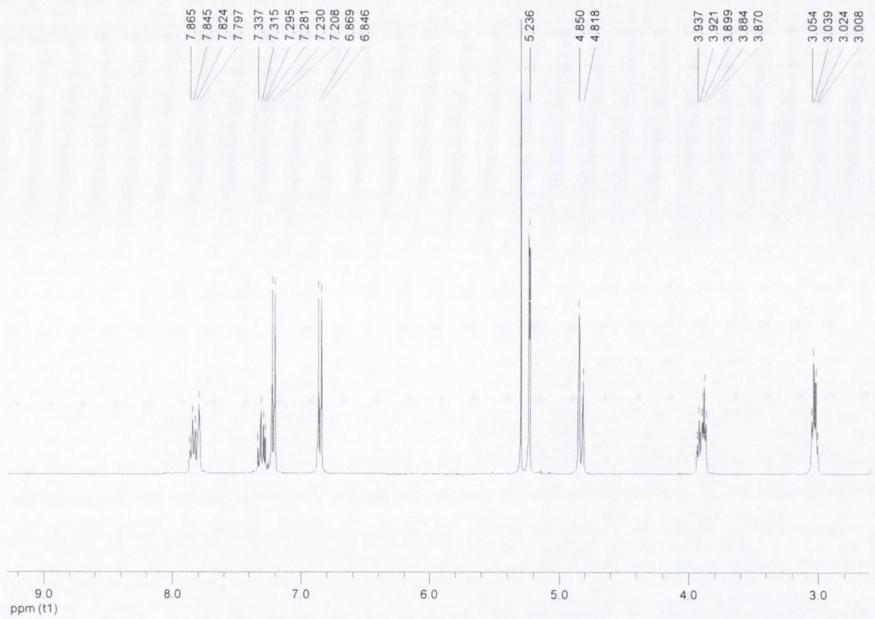


Figure 5-3: ^{1}H-NMR spectrum of specimen protected 7-phenoxyacetyltetrahydroisoquinoline, (235)

5.8.2.1.2 ^{13}C-NMR and DEPT 135 spectra of 235

These spectra are presented in Figure 5-4 (^{13}C-NMR uppermost and DEPT 135 beneath it). The inverted signals at 28.0 ppm (*cis*) and 29.4 ppm (*trans*) are produced by the methylene at position 4. The C3H$_2$ signals are observed at 41.2 ppm (*cis*) and 45.2 ppm (*trans*). The C1H$_2$ *trans* signal is interspersed among them at 42.8 ppm, while its other signal is seen at 45.5 ppm. Only one signal is observed for C2"H$_2$, at 70.8 ppm. Only one signal is seen at 116 ppm for the aromatic carbons of C2'H and C6'H. The signals at 125.9 ppm (*cis*), 126.4 ppm (*trans*), 126.6 ppm (*trans*) and 127.0 (*cis*) belong to the aromatic carbons of C8H and C6H, which are closer to the amide function and thus display the rotamer effect. The quaternary carbon sandwiched between them at 126.5 ppm is that of C4'Cl. The other aromatic carbons give a signal at 129.4 ppm, for C3'H and C5'H. C8a gives quaternary signals at 132.9 ppm (*cis*) and 133.0 ppm (*trans*), while those for C4a are seen at 139.7 ppm (*cis*) and 140.5 ppm (*trans*). Signals at 132.2 ppm (*cis*) and at 132.3 ppm (*trans*) are also for quaternary carbons, and C7 is expected to lie in this region. The deshielding effect of oxygen is seen in the downfield position of the C1' signal, at 156.4 ppm. The quaternary carbon of the trifluoroacetyl group would be expected to show the rotamer effect, while it should be almost invisible at the carbonyl at position 7: on that reasoning, the signal at 191.5 ppm is assigned to the latter, and those at 193.4 (*trans*) and 193.5 (*cis*) to the trifluoroacetyl carbonyl group.

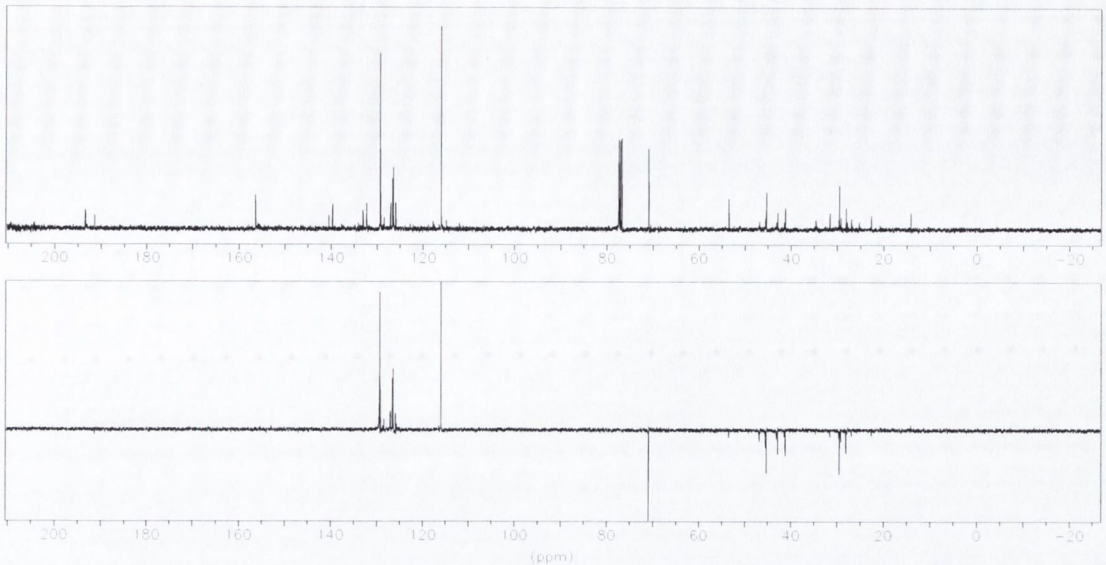
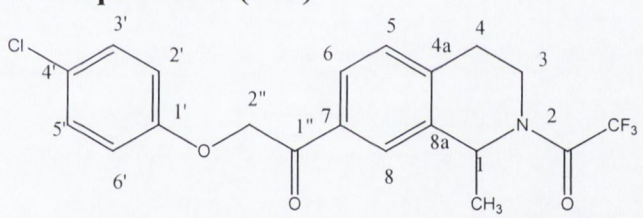


Figure 5-4: ^{13}C-NMR spectrum (top) and DEPT 135 spectrum (bottom) of typical protected 7-phenoxyacetyltetrahydroisoquinoline, 235

5.8.2.2 Spectroscopy of protected 7-phenoxyacetyl-1-methyl-tetrahydroisoquinoline (247)



1-{7-[2-(4-Chloro-phenoxy)-acetyl]-1-methyl-3,4-dihydro-1*H*-isoquinolin-2-yl}-2,2,2-trifluoro-ethanone

Figure 5-5: Numbering system applied to 1-{7-[2-(4-chloro-phenoxy)-acetyl]-1-methyl-*1H*-isoquinolin-2-yl}-2,2,2-trifluoro-ethanone, (247)

5.8.2.2.1 ^{1}H-NMR spectrum of 247

The ^{1}H-NMR spectrum of the corresponding 1-methyl phenoxyacetyltetrahydroisoquinoline (see Figure 5-5) is illustrated by Figure 5-6. It is more complex than that of the unsubstituted isoquinoline, but its distinguishing features (the separation of the signals of each proton in the C3$\underline{H}_2$ and C4$\underline{H}_2$ methylenes, the quartet for the C1$\underline{H}$ proton at 5.60 δ) are discussed in the examination of the chloro-phenyl-piperazinyl amide of 6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline (see section 4.4.2). The spectroscopic landmarks of the phenoxyacetyltetrahydroisoquinolines, the methylene proton signal at 5.20 δ and the disubstituted benzene pattern in the aromatic region, are the same as for the unsubstituted version, discussed above in 5.8.2.1.

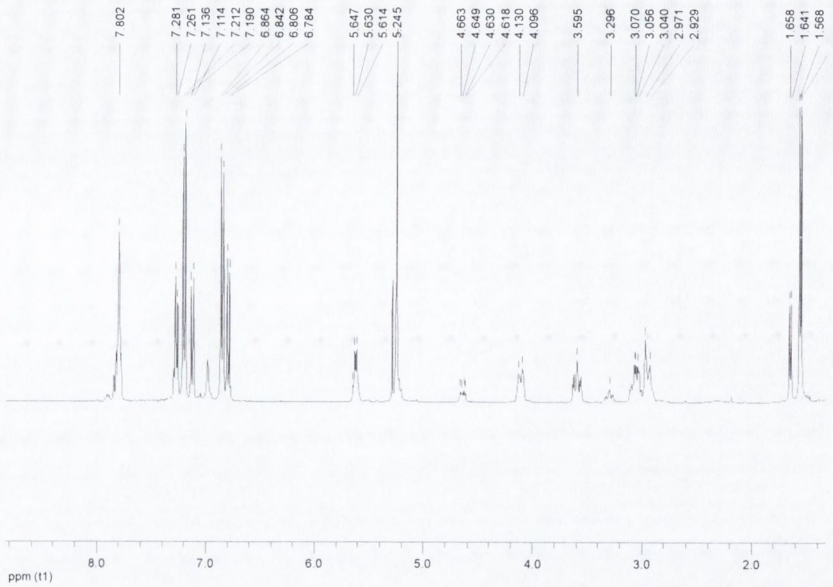


Figure 5-6: ^{1}H-NMR spectrum of a protected 7-phenoxyacetyl-1-methyl-tetrahydroisoquinoline, (247)

5.8.2.2.2 ^{13}C-NMR spectrum and DEPT 135 of 247

The main difference between these spectra (see Figure 5-7) and those of the unsubstituted type (see 5.8.2.1 above), is that the methyl group at position 1 hinders rotation about the C-N bond more seriously than the proton, and so the doubling of signals, due to rotamers, is seen even in the distant region of the phenoxy moiety aromatic ring.

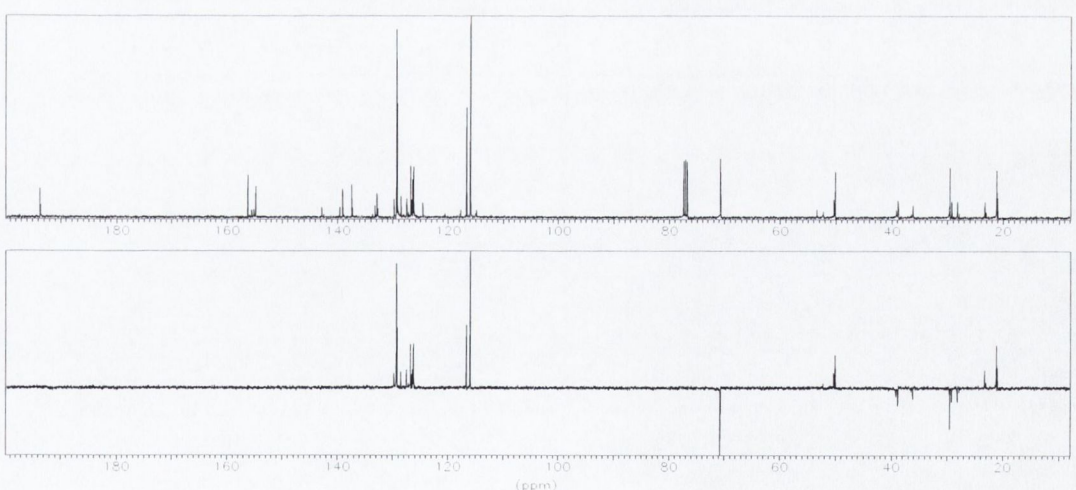
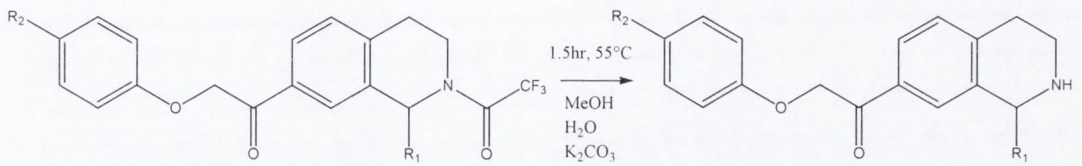


Figure 5-7: ^{13}C-NMR spectrum (upper) and DEPT 135 spectrum (lower) of protected 7-phenoxyacetyl-1-methyl-tetrahydroisoquinoline

5.9 Deprotection of trifluoroacetylated phenoxyacetyltetrahydroisoquinolines

5.9.1 Cleavage of protecting group

The removal of the trifluoroacetyl group was accomplished by dissolving the phenoxyacetyltetrahydroisoquinolines **(231 – 254)** in methanol with gentle heating, then adding the potassium carbonate in portions to ensure dissolution, and finally stirring at 55°C while very carefully monitoring the progress of the cleavage on TLC. More vigorous measures, such as refluxing in methanol for 3 hours, or adding the base in one lot, decomposed the molecule. The procedure is summarised by Scheme 5-8.



Protected 7-Phenoxyacetyltetrahydroisoquinoline

(231 - 254)

7-Phenoxyacetyltetrahydroisoquinoline

(255 - 278)

Scheme 5-8: Deprotection of N-2 of 7-phenoxyacetyltetrahydroisoquinolines

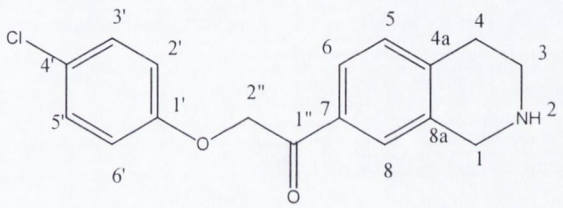
Compound Number	R^1	R^2	Yield
255	H	CH_3	86
256	H	OCH_3	64
257	H	OC_2H_5	60
258	H	F	87
259	H	Cl	52
260	H	Br	48
261	H	I	85
262	H	$NHCOCH_3$	70
263	H	NO_2	52
264	H	CN	52
265	H	$OCH_2C_6H_5$	71
266	H	$COOCH_2C_6H_5$	71
267	CH_3	CH_3	22
268	CH_3	OCH_3	44
269	CH_3	OC_2H_5	63
270	CH_3	F	57
271	CH_3	Cl	73
272	CH_3	Br	67
273	CH_3	I	71
274	CH_3	$NHCOCH_3$	40
275	CH_3	NO_2	25
276	CH_3	CN	72
277	CH_3	$OCH_2C_6H_5$	17
278	CH_3	COOH	81

Table 5-2: Yields of deprotected 7-phenoxytetrahydroisoquinolines

Mild conditions gave the tetrahydroisoquinolines **(255)** to **(278)** in good yield. A total of 24 were synthesised, and the criteria for selection of the substituents has already been given in 5.8.1. The deprotection of **(242)** afforded the acid directly, and this was the compound tested for MAO-B and AChE inhibition. An additional product **(280)** was synthesised using 2-(4-fluoro-phenoxy)-1-(1-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethanone **(258)** as starting material, and this is outlined in section 5.10 below.

5.9.2 Spectroscopy of deprotected 7-phenoxyacetyltetrahydroisoquinolines

5.9.2.1 2-(4-Chloro-phenoxy)-1-(1,2,3,4-tetrahydroisoquinolin-7-yl)-ethanone



2-(4-Chloro-phenoxy)-1-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethanone

Figure 5-8: Numbering system applied to 2-(4-Chlorophenoxy)-1-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethanone, (259)

5.9.2.1.1 ^{1}H-NMR spectrum of (259)

The numbering system used is shown in Figure 5-8. The spectrum may be examined in Figure 5-9.

The broad singlet at 2.2 δ is typical of that given by a proton attached to a highly electronegative atom (N<u>H</u>). The signals for methylenes at positions 4 and 3 have been simplified to triplets, at 2.85 δ and at 3.15 δ respectively (J = 5.5 Hz). A singlet is now observed as the C1<u>H</u>$_2$ signal, at 4.05 δ. The methylene signal C2"<u>H</u>$_2$ has hardly moved from 5.24 δ, being now at 5.21 δ. The doublet at 6.85 δ (J = 8.8Hz) is generated by C2'<u>H</u> and C6'<u>H</u>, and the other doublet at 7.21 (J = 8.8Hz) is produced by C3'<u>H</u> and C5'<u>H</u>. The latter doublet overlaps with another doublet, at 7.20 δ; this is the C5<u>H</u> signal. The coupling constant appears to be 6.8 Hz, but the overlap interferes with calculation of the J value. The neighbouring proton at C6<u>H</u> must be the doublet at 7.72 δ, which integrates for 1 proton and has a coupling constant of 8.2 Hz. The singlet at 7.63 δ belongs to C8<u>H</u>.

5.9.2.1.2 ^{13}C-NMR spectrum of (259)

Figure 5-10 illustrates the ^{13}C-NMR spectrum (upper) and DEPT 135 spectrum (lower) of **(259)**. A notable feature of the upfield region is the weakness of the methylene <u>C</u>4H$_2$ at

29.4 ppm. The inverted signals at 43.6 ppm (C3H_2) and at 48.1 ppm (C1H_2) are not as badly affected. There is a strong inverted signal at 70.7 ppm, given by C2"H_2. The protons at positions 2' and 6' are observed at 116.0 ppm. The other signal from the chlorinated ring is seen at 129.3 ppm, and this is clearly the signal belonging to C3'H and C5'H. The other aromatic carbon signals are observed at 125.5 ppm (C6H), 126.0 ppm (C8H) and 129.8 ppm (C5H).

The quaternary carbon at 126.4 ppm is that of C4'Cl. A signal at 129.0 ppm is also for a quaternary carbon, and should be that of C7. The quaternary signal at 131.9 ppm is that of C8a. C4a is observed at 141.9 ppm. The C1' signal is further downfield at 156.5 ppm. The remaining carbonyl carbon signal is at 193.7 ppm.

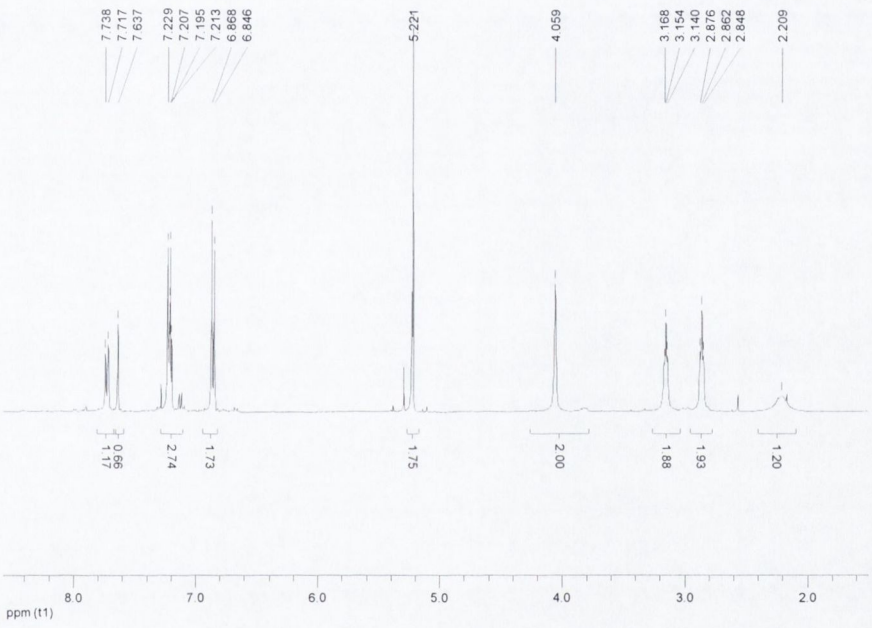


Figure 5-9: ^{1}H-NMR spectrum of 2-(4-chloro-phenoxy)-1-(1,2,3,4-tetrahydroisoquinolin-7-yl)-ethanone, (259)

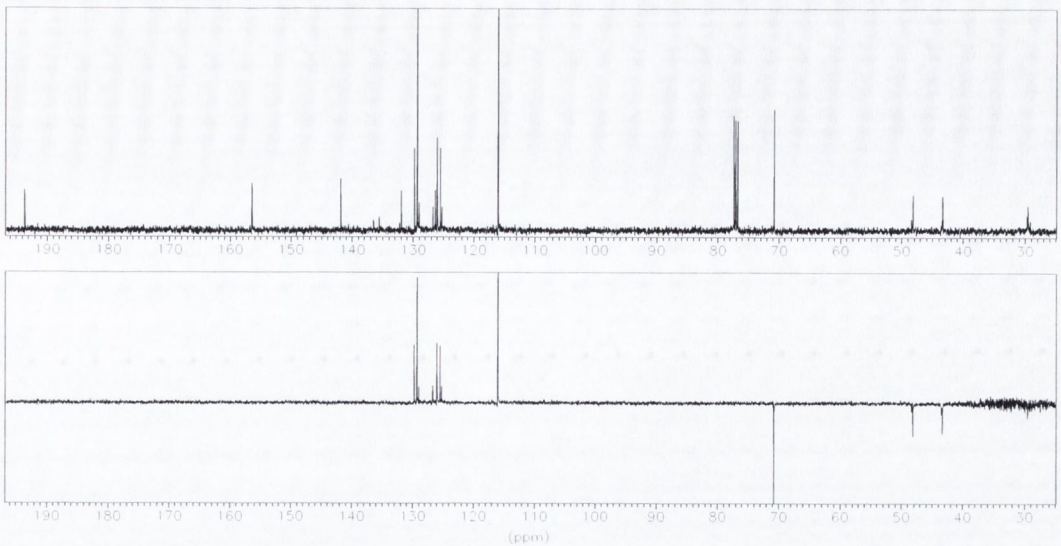
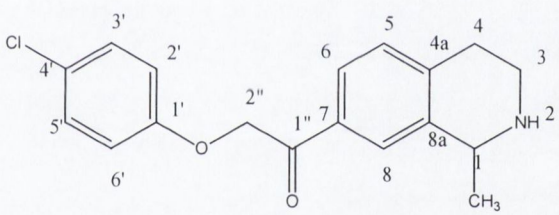


Figure 5-10: ^{13}C-NMR spectrum (upper) and DEPT 135 spectrum (lower) of 2-(4-chloro-phenoxy)-1-(1,2,3,4-tetrahydroisoquinolin-7-yl)-ethanone, (259)

5.9.2.2 2-(4-Chloro-phenoxy)-1-(1-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-ethanone (271)



2-(4-Chloro-phenoxy)-1-(1-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-ethanone

Figure 5-11: Numbering system applied to 2-(4-chloro-phenoxy)-1-(1-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-ethanone, (271)

5.9.2.2.1 ^{1}H-NMR spectrum of 271

The numbering system for compound **(271)**, an example of a 1-methyl product, is illustrated in Figure 5-11. The ^{1}H-NMR spectrum of 2-(4-chloro-phenoxy)-1-(1-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-ethanone **(271)** is shown in Figure 5-12 (complete with residual ethyl acetate!) to give an insight into the effect of 1-alkyl substitution on the molecule. The main differences observed from the protected isoquinoline is the disappearance of the rotamers, and the change in the shift value of the C1H proton from 5.64 δ to 4.18 δ indicates the amide function to have significantly deshielded the proton. The spectrum is still more complicated than that of an unsubstituted tetrahydroisoquinoline, with the individual protons of the methylene groups at C3H_2 and

C4$\underline{H_2}$ giving separate signals, complicated by coupling between themselves. The aromatic region and C2"$\underline{H_2}$ are almost identical to those of the unsubstituted tetrahydroisoquinoline, and do not merit separate discussion.

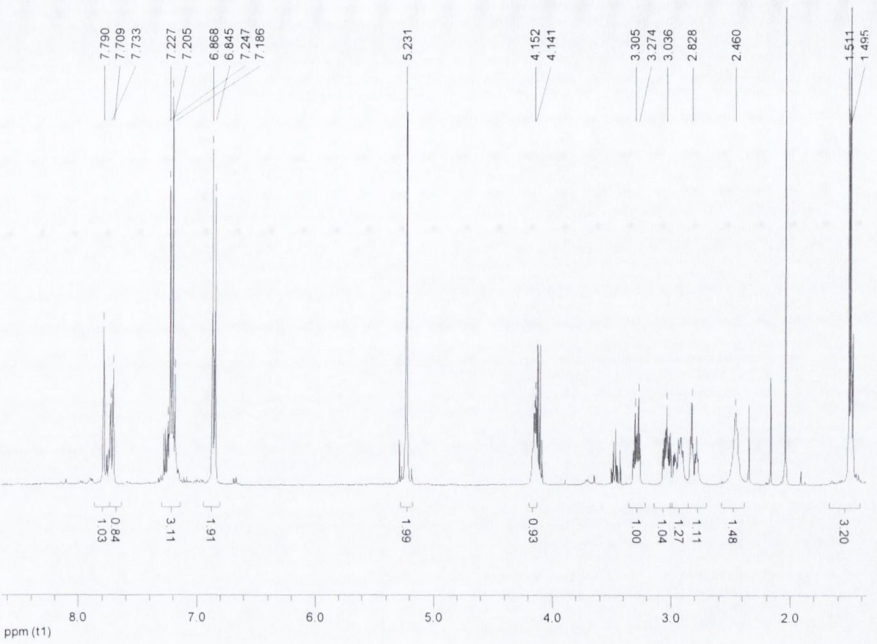


Figure 5-12: ^{1}H-NMR spectrum of 2-(4-chloro-phenoxy)-1-(1-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-ethanone, (271)

5.9.2.2.2 ^{13}C-NMR spectrum of 271

The main difference the ^{13}C-NMR spectrum of a 1-methyl-tetrahydroisoquinoline (Figure 5-13) shows from its unsubstituted relative is the $\underline{C}$1H signal at about 50 ppm (here 51.5 ppm) and the methyl signal at around 20 ppm (shown at 22.4 ppm).

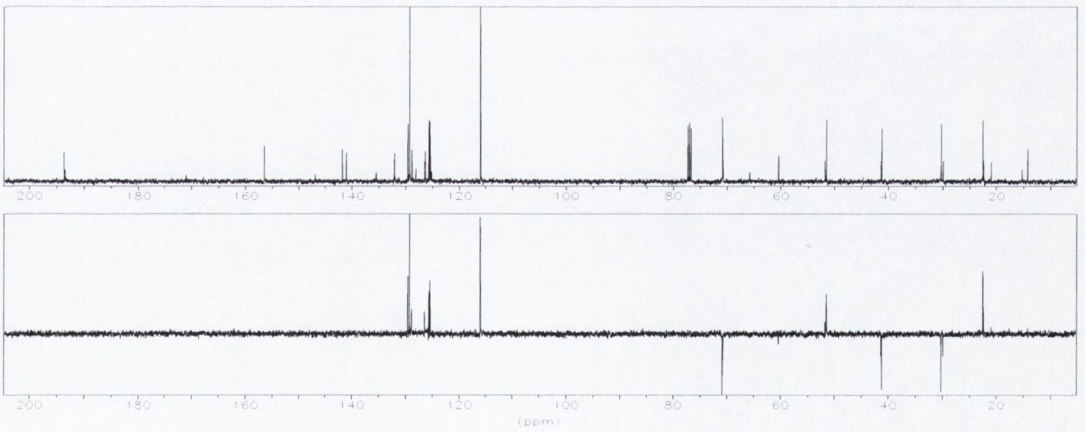
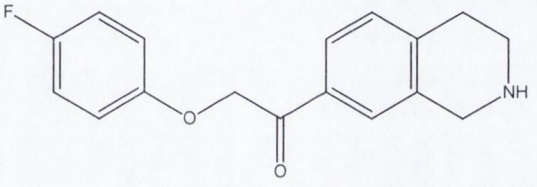


Figure 5-13: ^{13}C-NMR spectrum of 2(4-chloro-phenoxy)-1-(1-methyl-1,2,3,4-tetrahydroisoquinoline) (upper) and DEPT 135 spectrum (lower) of same

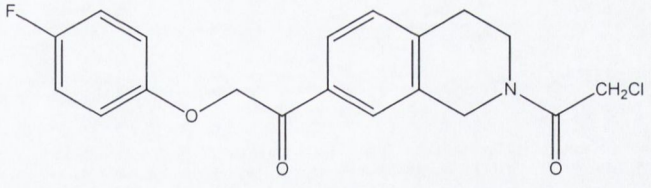
5.10 Modification of tetrahydroisoquinoline at both position 2 and position 7

It would be interesting to investigate what effects simultaneous modification of positions 2 and 7 would have on the activity of tetrahydroisoquinolines with regard to monoamine oxidase and acetylcholinesterase. The 4-fluorophenoxyacetyltetrahydroisoquinoline of the unsubstituted series **(258)** was chosen for addition of an amide function and piperazinyl sidechain. The 4-fluoro compound gave a mid-table value for acetylcholinesterase inhibition in the first assay conducted (see Chapter 7), and the high yields of its production meant plenty was available for chloroacetylation and the low-yielding nucleophilic substitution which followed (see Scheme 5-9 and Chapter 4). Compound **(280)** was obtained in 87% yield and characterised by NMR spectroscopy.



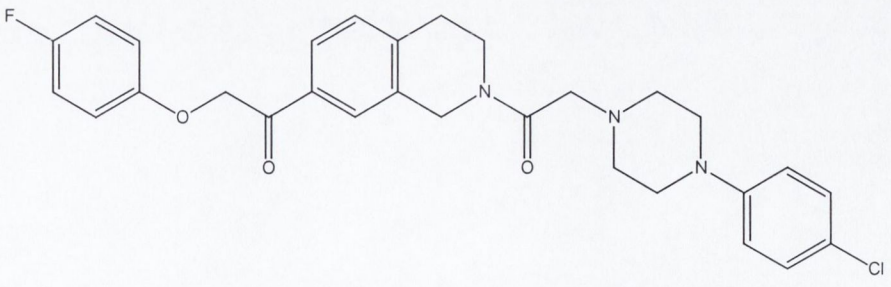
2-(4-Fluoro-phenoxy)-1-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethanone **(258)**

$CH_2ClCOCl$,
Et_3N,
CH_2Cl_2, 0°C



1-[2-(2-Chloro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-2-(4-fluoro-phenoxy)-ethanone **(279)**

(4-Chlorophenyl)-piperazin-1-yl dihydrochloride,
Et_3N,
EtOH, Reflux, 9 hrs



1-(2-{2-[4-(4-Chloro-phenyl)-piperazin-1-yl]-acetyl}-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-(4-fluoro-phenoxy)-ethanone **(280)**

Scheme 5-9: Synthesis of 1-(2-{2-[4-(4-chloro-phenyl)-piperazin-1-yl]-acetyl}-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-(4-fluoro-phenoxy)-ethanone, 280

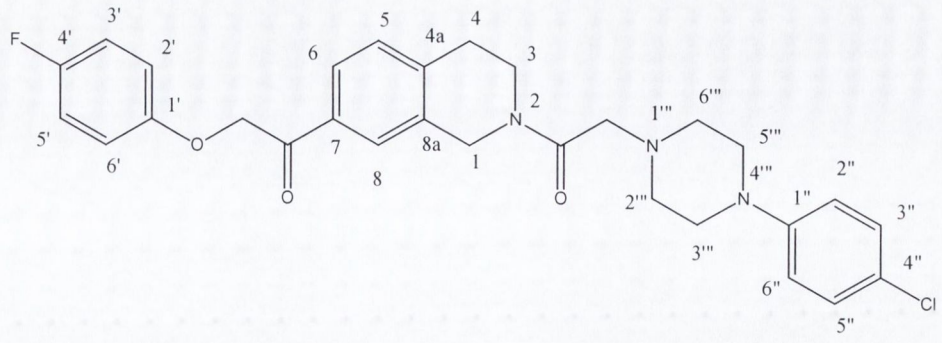


Figure 5-14: Numbering system applied to compound (280)

5.10.1.1 ^{1}H-NMR Spectrum

The numbering system applied to **(280)** is shown in Figure 5-14. The ^{1}H-NMR spectrum of **(280),** shown in Figure 5-15, shows spectroscopic features of both the phenoxyacetyltetrahydroisoquinolines and the piperazine amides, naturally. The methylene signal at 5.22 δ is an unmistakable trait of the phenoxy series. In the aromatic region, the division between C5H (at 7.28 – 7.31 δ) and the multiplet of C6H and C8H (at 7.80 δ - 7.83 δ) is clear-cut. The piperazine characteristics are evidenced by the broad multiplets for the cyclohexyl ring methylenes, at 2.69 δ and 3.10 – 3.19 δ. The rotamers are shown by the distinct triplets for C4H_2 at 2.95 δ (integrating for 0.7 protons) and 3.02 δ (integrating for 1.3 protons). They merge in a messy multiplet at 3.85 – 3.88 δ for C3H_2. The methylene at position 1 is seen as two singlets at 4.82 δ (1.3 H) and 4.87 δ (0.7H). The pseudoisomers further complicate the aromatic region, so that only a tangle of signals at 6.80 – 6.91 δ can be made out for the fluorinated ring. Two multiplets at 6.95 – 7.01 δ and 7.18 – 7.22 δ represent the protons of the 2"H/6"H and 3"H/5"H respectively.

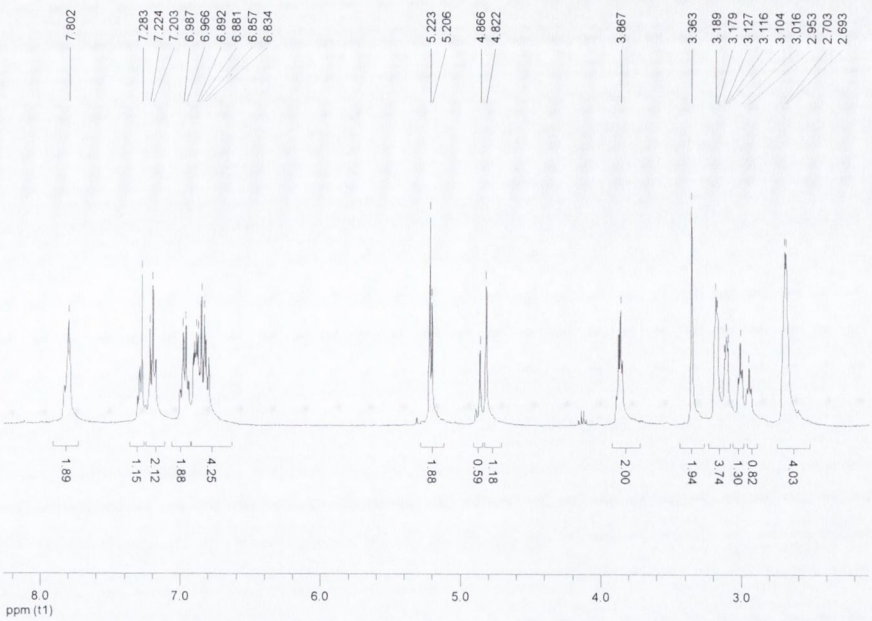


Figure 5-15: ^{1}H-NMR spectrum of (280)

5.10.1.2 ^{13}C-NMR Spectrum

The eyecatching signal of the phenoxyacetyltetrahydroisoquinoline **(280)** ^{13}C-NMR spectrum (as seen in Figure 5-16) is undoubtedly its pronounced methylene signal at 71.4 ppm. The piperazine ring methylene carbons also give strong signals, at 49.1 ppm and at 53.0 ppm. The usual signals for C4H$_2$, C3H$_2$ and C1H$_2$ are seen at 28.7ppm/29.9 ppm, 39.6 ppm/44.2 ppm and 42.9 ppm/44.5ppm. Splitting of the aromatic signal of the fluorinated ring provide a distinction between these signals and those of the nearby upfield carbons of the chlorinated ring. The smaller coupling constant also distinguishes the C2'H/C6'H from that of the C3'H/C5'H signal. The C5H, C6H, C8H, C8a, C4a, C7 and CO (phenoxy) signals all appear in the expected regions of the spectrum. They are joined by an additional carbonyl group signal at 168.1 ppm and a quaternary signal at 149.7 for C1" of the chlorinated ring.

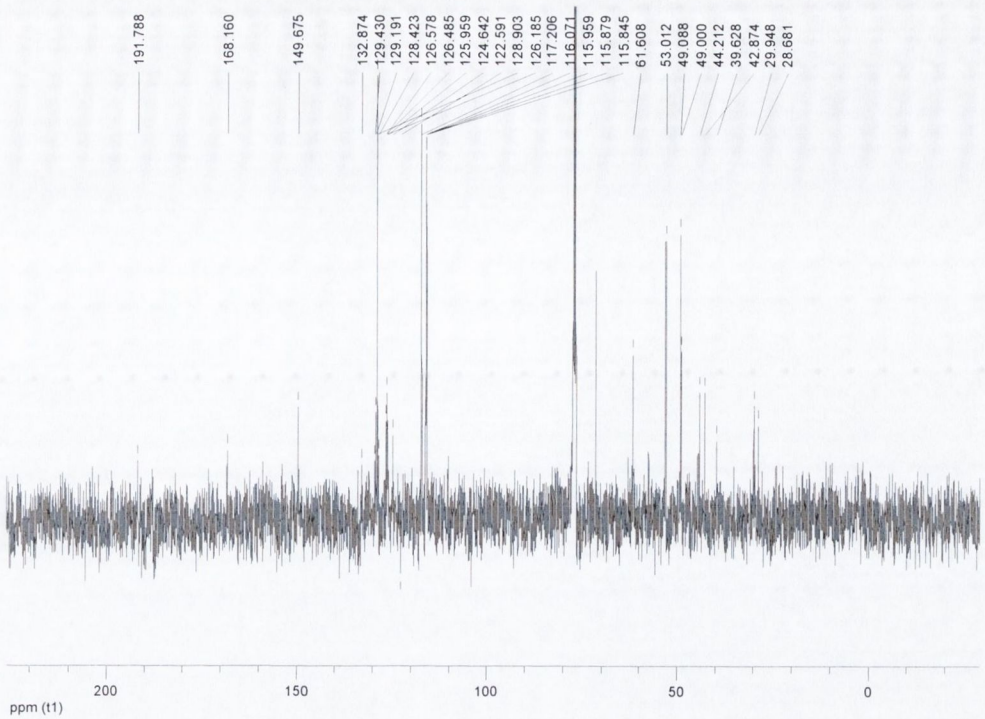


Figure5-16: ^{13}C-NMR spectrum of (280)

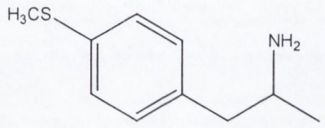
5.11 Summary

Generation of 7-phenoxyacetyltetrahydroisoquinolines required ready availability of 1-methyl-3,4-dihydroisoquinoline, so a synthetic route to this compound **(220)** via a Tin IV chloride-nitrile complex and (2-chloroethyl)-benzene was optimised using microwave synthesis. The series were then obtained as follows. The tetrahydroisoquinoline nucleus of each series was protected with a trifluoroacetyl group, acetylated, brominated and finally reacted with the appropriate phenol to give a phenoxy ether. The trifluoroacetyl group was then cleaved from the products, to afford the 7-phenoxyacetyltetrahydroisoquinolines. One such product, 2-(4-fluoro-phenoxy)-1-(1,2,3,4-tetrahydroisoquinolin-7-yl)-ethanone **(258)**, was then chloroacetylated and reacted with 1-(4-chloro-phenyl)-piperazine dihydrochloride. This gave **(280)**, which combined features of the phenoxyacetyltetrahydroisoquinolines and piperazine amides. All the compounds were assayed for inhibition of the acetylcholinesterase and monoamine oxidase B enzymes (see Chapter 7, section 7.3).

6 Chapter 6: Synthesis of Isoquinoline Analogues of 4-Methylthioamphetamine

6.1 Introduction

The objective for this section was to produce a series of dihydroisoquinolines substituted with a thioether group at position 7. This would allow investigation of the MAO inhibitory effects of isoquinolines structurally related to 4-methylthioamphetamine **(281)** (4-MTA), shown in Figure 6-1. This molecule is related in structure and use to methylenedioxymethylamphetamine, the notorious "ecstasy" which is synonymous with rave drug culture.



4-Methylthioamphetamine, 4-MTA **(281)**

Figure 6-1: 4-Methythioamphetamine

4-MTA causes its physiological and psychological effects through alteration of serotonin levels in the central nervous system, but has also been reported to inhibit monoamine oxidase.[57] Sulfur's hyrophobicity gives the amphetamine an advantage as a MAOI, which is reflected by the low IC_{50} values reported for the thioalkylamphetamines (IC_{50} 0.2μM for thiomethyl and 0.1μM for the thioethyl compound). The thioalkylated tetrahydroisoquinoline could be acylated at position 2 and its MAO inhibitory activity compared to the other tetrahydroisoquinolines with substituents at positions 2 or 7.

It was envisaged that the thioether could be introduced in the precursors used to form the isoquinoline, or by substitution of the isoquinoline itself. Thus, section 6.3 covers the investigation of the most efficient route to produce 4-methylthioamphetamine. Section 6.4 examines the attempted cyclisation of 4-MTA. This was unsuccessful, so alternative routes were explored, and these are detailed in sections 6.5 to 6.7. Finally, section 6.8 addresses the synthesis of a thioalkyltetrahydroisoquinoline amide, with a benzoyl function at position 2. This was introduced to allow comparison with other position 2 and position 7 analogues of tetrahydroisoquinoline in MAO inhibition studies (see Chapter 7).

6.2 Proposed Synthetic Route

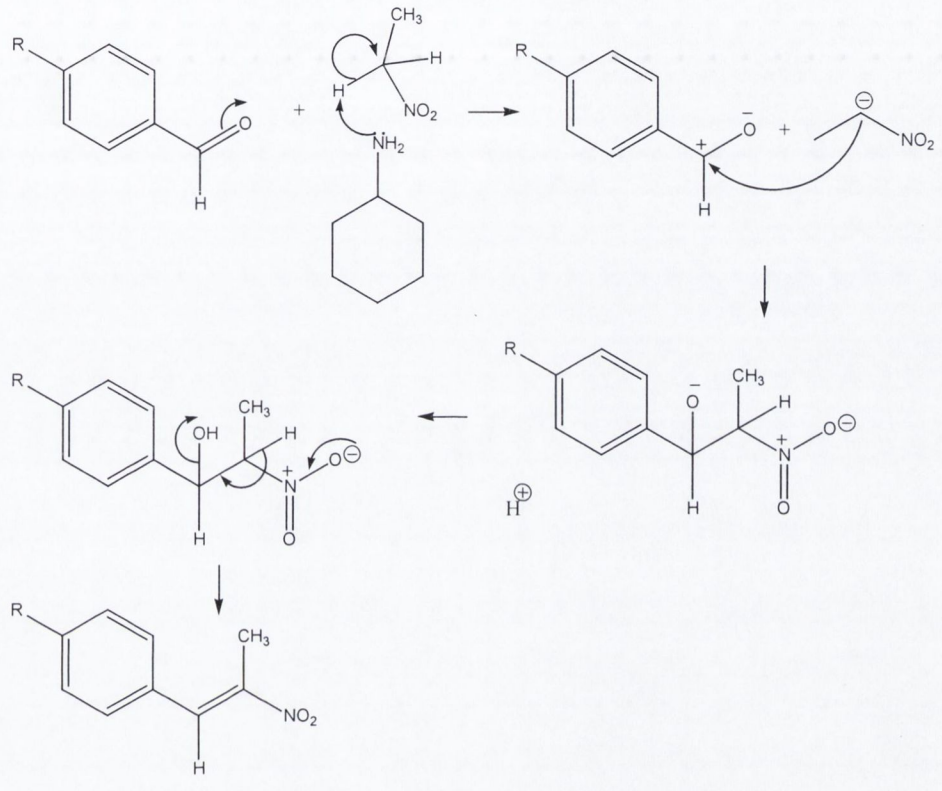
6.3 Synthesis of amphetamines

6.3.1 Synthesis of Nitrostyrenes

A series of amphetamine products were first investigated. Nitrostyrenes were prepared as the preliminary step in the production of para-substituted amphetamines.[108] The

preparation involved the Henry reaction, discussed below. The Henry reaction involves the substitution of the aldehyde functionality with a nitropropene side chain by nitroethane, activated by base (see Scheme 6-1).

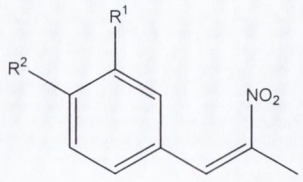
In this reaction, cyclohexylamine facilitates the removal of a proton from the α carbon of nitroethane. The nitroethane anion then reacts with the benzaldehyde and is dehydrated in an acidic environment to 1-(4-methylphenyl)-2-nitropropene.[98]



Scheme 6-1: Synthesis of nitrostyrenes via Henry reaction

This is known as the Henry reaction, and is a subtype of the Knoevenagel reaction. The first step, the nucleophilic attack, controls the rate of the reaction. If pyridine were used as the secondary amine catalyst it would be the Doebner modification of the Knoevenagel reaction. Acid catalysts may also be used.

Table 6-1 lists the nitrostyrenes obtained in this fashion **(282 – 292)**.

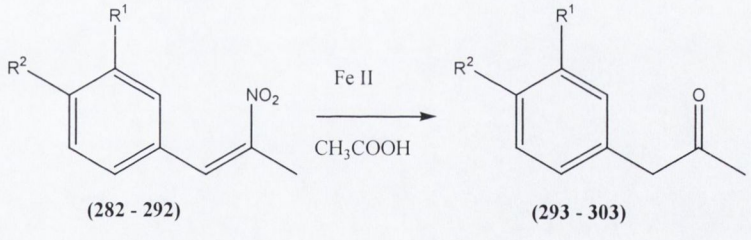


Number	R^1 =	R^2 =	Yield, %
282[54]	H	SCH_3	50.6
283[109]	H	CH_3	48.2
284[110]	H	OCH_3	37.4
285[111]	H	OH	30.6
286[112]	H	F	54.3
287[113]	H	Cl	43.3
288[111]	H	NO_2	96.0
289[67]	H	H	41.2
290[114]	OCH_3	OCH_3	53.7
291[108]	OCH_2	O	47.5
292[115]	H	Br	60.4

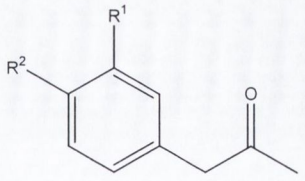
Table 6-1: Nitrostyrenes produced by Henry reaction

6.3.2 Reduction of Nitrostyrenes to Ketones using Iron

This simple reduction of the nitrostyrene allowed the preparation of a range of *para*-substituted ketones, intermediates in the synthesis of amphetamines substituted at the *para* position. The reaction is shown in Scheme 6-2. Iron II transfers one electron to the nitrostyrene in an acidic environment, being itself oxidised to iron III (Fe III) in the process.



Scheme 6-2: Reduction of nitrostyrene using iron



Number	R_1 =	R_2 =	Yield, %
293[116]	H	SCH_3	92.0
294[117]	Br	H	95.9
295[118]	H	Cl	86.1
296[118]	H	OCH_3	84.7
297[119]	H	NO_2	67.5
298[120]	OCH_2	O	98.4
299[121]	H	H	92.8
300[122]	OCH_3	OCH_3	60.5
301[118]	H	CH_3	30.2
302[116]	H	F	94.8
303[123]	H	Br	66.0

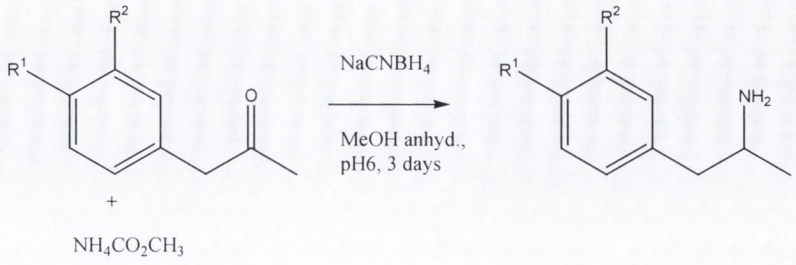
Table 6-2: Ketones produced by iron reduction of nitrostyrenes

The ketones **(293 – 303)** were subsequently reduced and aminated using a combination of sodium cyanoborohydride and ammonium acetate, as outlined in Scheme 6-3 of Section 6.3.3.

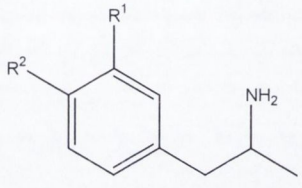
6.3.3 Reductive Amination of Ketones to give Amphetamines

The reductive amination of ketones **(293 – 295, 302 – 303)** to amphetamines **(281, 304 – 307)** is illustrated in Scheme 6-3. A nucleophilic attack by the ammonia generated by ammonium acetate is the first step in the reductive amination. Sodium cyanoborohydride contributes the hydride that allows reduction of the imine double bond. The pH of the reaction is monitored and retained at pH6.[124] The reaction is sensitive to changes in pH, as a balance must be struck between the protonation of the carbonyl oxygen, favoured at low pH, and protonation of the ammonia generated, which retards the reaction but is unfortunately also promoted by acidic pH.[125]

The reaction allowed *para*-substituted amphetamines to be produced via the equivalent ketone. Since the addition of derivatives of ammonia to carbonyl compounds proceeds with the elimination of water, dry conditions were necessary. The method was time consuming, taking 3 days for completion, but convenient. The products and yields are listed in Table 6-3.



Scheme 6-3: Reductive amination of ketones, giving amphetamines

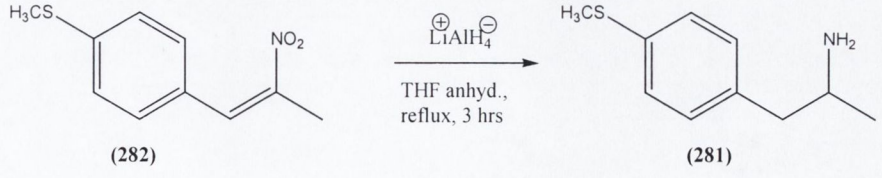


Number	R_1 =	R_2 =	Yield, %
281[54]	H	SCH_3	44
304[112]	H	F	66
305[126]	H	Cl	35
306[127]	H	Br	17.7
307[128]	Br	H	46.0

Table 6-3: Amphetamines produced by reductive amination of ketones

6.3.4 Direct Reduction of Nitrostyrenes to Amphetamines

This direct reduction of a nitrostyrene to the amphetamine member of the series offered a quick route of synthesis (shown in Scheme 6-4). While reducing the nitro group to an amine function, in the process releasing hydrogen gas, the lithium aluminium hydride simultaneously reduced the double bond. The initial transfer of a hydrogen atom to the nitrogen created an active hydrogen atom, which was then removed by reaction with the metal hydride. [129] This route was used for 1-(4-methylthiophenyl)-2-nitropropene, giving 4-MTA **(281)** with a 62% yield (see Scheme 6-4).

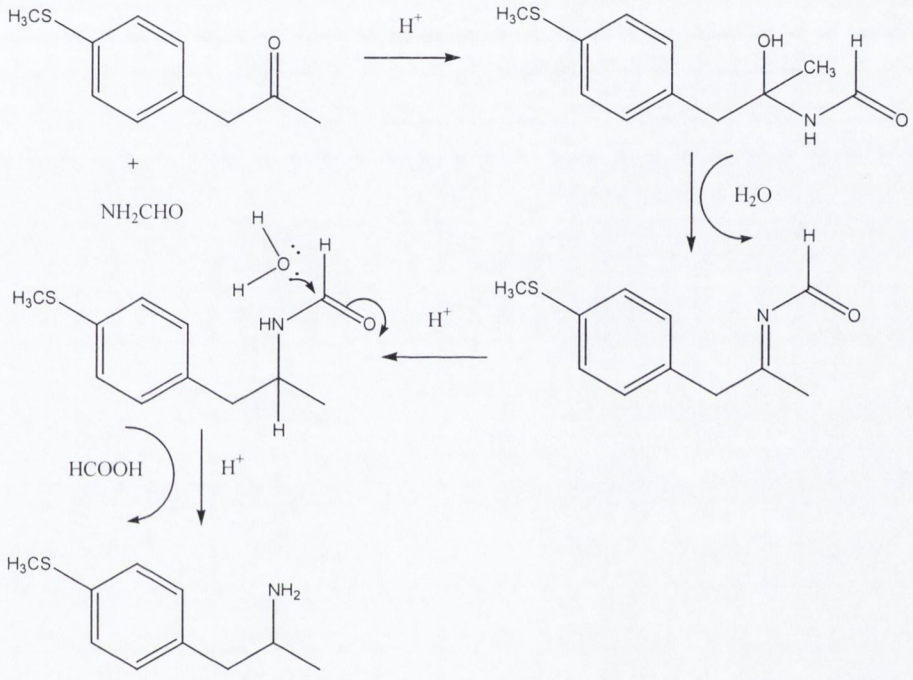


(282) **(281)**

Scheme 6-4: Reduction of nitrostyrene to amphetamine, using lithium aluminium hydride

6.3.5 Preparation of 4-Methylthioamphetamine via the Leuckart Reaction

An alternative route to the amphetamine series, the Leuckart reaction was tested with regard to 1-(4-methylthiophenyl)-2-aminopropane/4-methylthioamphetamine **(281)**, and rejected for routine use. It was unwieldy, requiring two steps instead of a single step for the reduction of nitrostyrenes using lithium aluminium hydride; it also produce a mixture of main product and impurities in the first step, necessitating the use of chromatography to isolate the product. This method is widely used in the clandestine manufature of MDMA and related amphetamines.[130,131]



Scheme 6-5: Synthesis of 4-MTA (281) from ketone (293) via Leuckart reaction

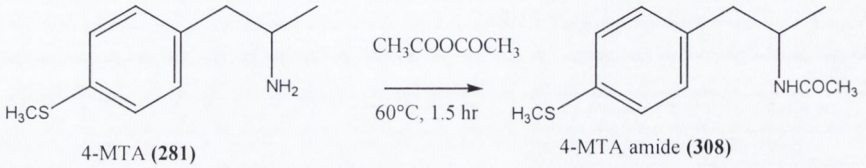
The Leuckart reaction is illustrated in Scheme 6-5. It may be summarised as formation of an amide followed by acid hydrolysis to amine. The formamide is used in large excess to avoid the formation of secondary and tertiary amines. The *Wallach reaction* is a reductive amination of a carbonyl compound using formic acid. If a formamide is used instead, as was the case, it is called the *Leuckart reaction.* The process is successful for aliphatic-aromatic, alicyclic and aliphatic-heterocyclic ketones, some aromatic ketones and aldehydes and some aliphatic ketones and aldehydes that boil at 100°C or above.

The process was evaluated using 1-(4-methylthiophenyl)-2-propanone, to produce 1-(4-methylthiophenyl)-2-aminopropane **(281)**. It was not used further, giving as it did a yield of only 17%.

6.4 Bischler-Napieralski Cyclisation of 4-Methylthioamphetamine

6.4.1 Acetylation of 4-Methylthioamphetamine

To progress the synthesis of the dihydroisoquinoline, the acetylation of the amine function of 4-methylthioamphetamine **(281)** (giving **(308)**) was accomplished with 97.1% yield, by treatment with acetic anhydride for 1.5 hours at 60°C (see Scheme 6-6).

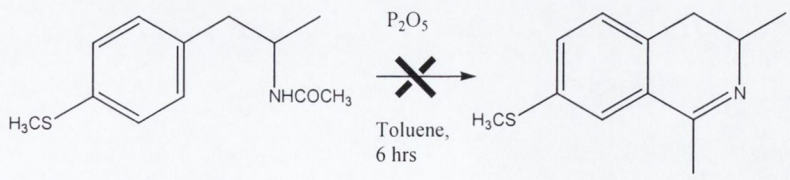


4-MTA **(281)** 4-MTA amide **(308)**

Scheme 6-6: Acetylation of 4-methylthioamphetamine (first step of Bischler-Napieralski cyclisation)

6.4.2 Cyclisation of N-Acetyl-1-(4-methylthiophenyl)-2-aminopropane

The first two attempts to cyclise the 4-methylthioamphetamine acetylate **(308)** used a simple Bischler-Napieralski approach (Scheme 6-7), with the phosphorous pentoxide being added in two portions 30 minutes apart. None of the required dihydroisoquinoline (see Scheme 6-7) formed. The procedure was next repeated using a Dean and Stark apparatus to remove water and ensure dryness. The fourth attempt was monitored using TLC and reflux was prolonged to a total of 6 hours. TLC showed some fluorescence, which indicates the presence of dihydroisoquinoline, but in negligible amounts: not even enough for characterisation. The Bischler-Napieralski approach for the synthesis of thioalkylisoquinolines was not pursued further. The failure of the route was not a complete surprise, as it is known to be favoured by electron donating groups on the amide in a position *para* to the point of ring closure.[47]



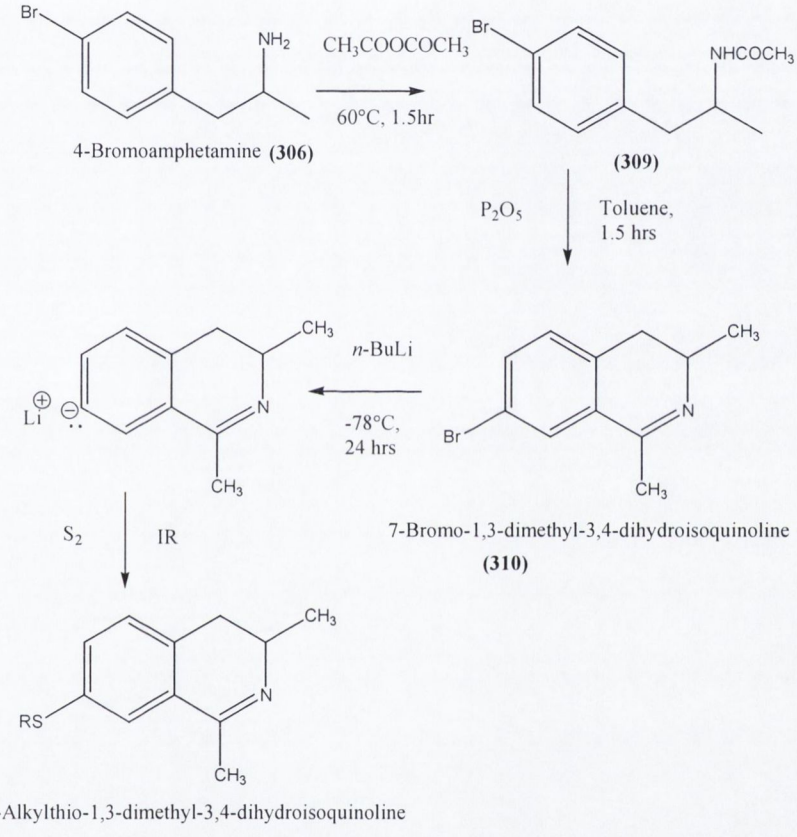
N-Acetyl-1-(4-methylthiophenyl)-2-amino-propane **(308)** 1,3-Dimethyl-7-methylsulfanyl-3,4-dihydro-isoquinoline

Scheme 6-7: Failed cyclisation of 4-methylthioamphetamine acetylate (second step of Bischler-Napieralski reaction)

6.5 Alternative Synthetic Route to a Dihydroisoquinoline with a Thiol function at Position 7

6.5.1 Planned Route

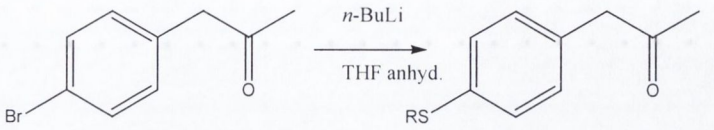
As an alternative to direct cyclisation of 4-MTA, cyclisation of a brominated amphetamine and subsequent thioalkylation was proposed. Aromatic bromides are easily dehalogenated by butyllithium, giving regiospecific aryllithium compounds, which may then be thioalkylated. This should afford a direct route from 7-bromo-1,3-dimethyl-3,4-dihydroisoquinoline to 7-methylthio-1,3-dimethyl-3,4-dihydroisoquinoline **(310)**, and thence to 7-methylsulfanyl-1.3-dimethyl-1,2,3,4-tetrahydroisoquinoline (see Scheme 6-8).



Scheme 6-8: Introduction of thioether function at position 7 of dihydroisoquinoline via halogen-metal exchange

6.5.2 Preliminary Investigation of Route: Ketone Approach

Since 4-bromoamphetamine **(306)** had been synthesised in low yield during the production of amphetamines, it was deemed prudent to experiment first with the ketone, 1-(4-bromophenyl)-2-propanone **(303)**. The efficacy of the route could be established without expenditure of time on the production of the amphetamine **(306)** and its low-yielding cyclisation to the 3,4-dihydroisoquinoline **(310)**.



1-(4-Bromo-phenyl)-propan-2-one **(303)**

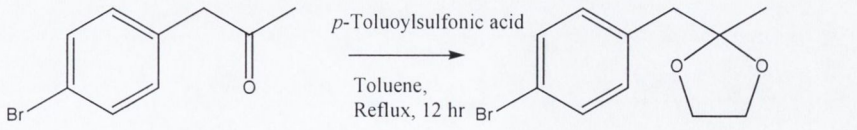
1-(4-Thioalkylphenyl)-propan-2-one

Scheme 6-9: Introduction of alkylthiofunction on aromatic ring of ketone through halogen-metal exchange

Efforts were made to introduce a thioether function in 1-(4-bromophenyl)-2-propanone **(303)** (see Scheme 6-9). In order to achieve this, 1-(4-bromophenyl)-2-propanone **(303)** was converted to the equivalent ketal **(311)** to protect the ketone function (as seen in Scheme 6-10). This was necessary to protect the ketone carbonyl group from attack by the butyllithium agent. Thioalkylation at the *para* position of the benzene ring was the next step attempted. If successful, this would give a thioalkylbenzeneketal, which might be hydrolysed to the ketone. The chemistry involved in the substitution of the bromine with a thioalkyl might be replicated in a procedure involving 7-bromo-1,3-dimethyl-3,4-dihydroisoquinoline.

6.5.2.1 Acetal Formation

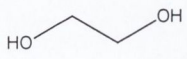
The formation of the acetal **(311)** is illustrated in Scheme 6-10. This is the most common route for the preparation of cyclic acetals.[132] *Para*-toluenesulfonic acid provides the proton for the initial protonation of the carbonyl oxygen. Ethylene glycol follows suit with a nucleophilic attack by one of its constituent oxygens on the electropositive carbon of the ketone. The acetal was formed in 97% yield.



1-(4-Bromo-phenyl)-propan-2-one **(303)**

2-(4-Bromobenzyl)-2-methyl-[1,3]-dioxolane **(311)**

+



Ethylene glycol

Scheme 6-10: Protection of ketone function by formation of acetal

6.5.2.2 Lithiation and Thioalkylation

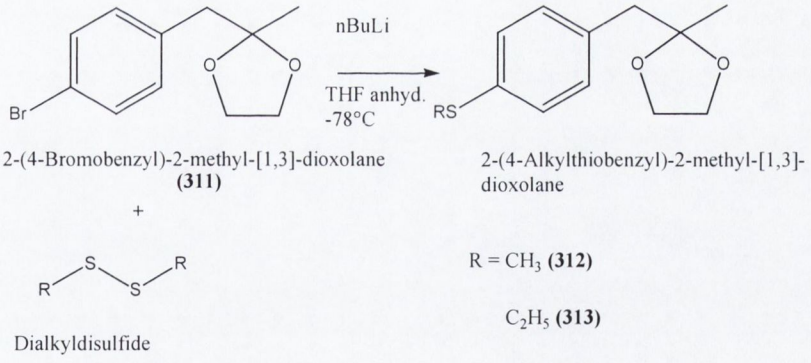
The halogen-metal interconversion reaction was discovered simultaneously by Gilman and co-workers, and by Wittig, Pockels and Dröge.[133] This affords a means of creating an aromatic carbanion. Iodine and bromine atoms exchange readily with lithium, but chlorine must be forced to react and fluorine does not exchange at all.[133] While ethyllithium and propyllithium are very reactive, they are prepared with difficulty,[133] so the more stable butyllithium is the organolithium of choice for most reactions involving their use.

Studies of x-ray crystal structure of butyllithium show it to be aggregated in solution, in a regular framework. Monomers and lower aggregates of butyllithium are more reactive than the higher aggregates and tetrahydrofuran may be used to coordinate with the reagent and encourage dimer and tetramer formation.[134] The reactions were carried out at -78°C, as at higher temperatures THF is itself attacked by butyllithium.[134]

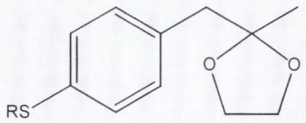
The lithium halogen exchange does not go to completion: rather an equilibrium is reached. In this case, the equilibrium would lie to the right, the aryl group being more electronegative than the butyl.[101,134]

6.5.2.2.1 Thioalkylation using Disulfides

Introduction of a thioalkyl substitutent at the *para* position was next considered. The initial step involved halogen-metal exchange, in which lithium was substituted for bromine. The aryllithium then reacted with the disulfide to give the thioalkylacetal and thiol. This allowed a thiomethyl group and a thioethyl group to be introduced on the aromatic ring (see Scheme 6-11) to afford **(312)** and **(313)**.



Scheme 6-11: Thioalkylation using disulfides



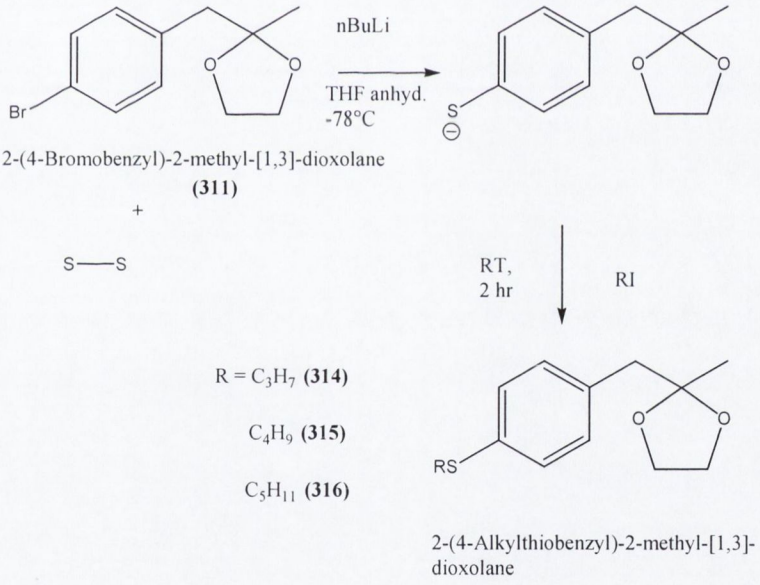
2-(4-Alkylthiobenzyl)-2-methyl-[1,3]-dioxolane

Number	R =	Yield, %
312	CH_3	7
313	C_2H_5	27

Table 6-4: Yields of thioalkylarylacetals via disulfides

6.5.2.2.2 Thioalkylaltion using sulfur and iodoalkanes

For the longer sidechains a combination of sulfur, iodoalkanes and *n*-butyllithium was investigated (see proposed route in Scheme 6-12). The conditions allowed only butylation of the dimer formed by the reaction of elemental sulfur and the ketal, as liberated lithium reacted with the iodoalkanes to form a lithium salt, leaving the butyl group free to undergo addition to the sulfur atom. The thiobutylarylacetal **(315)** only was isolated in 33.3% yield.

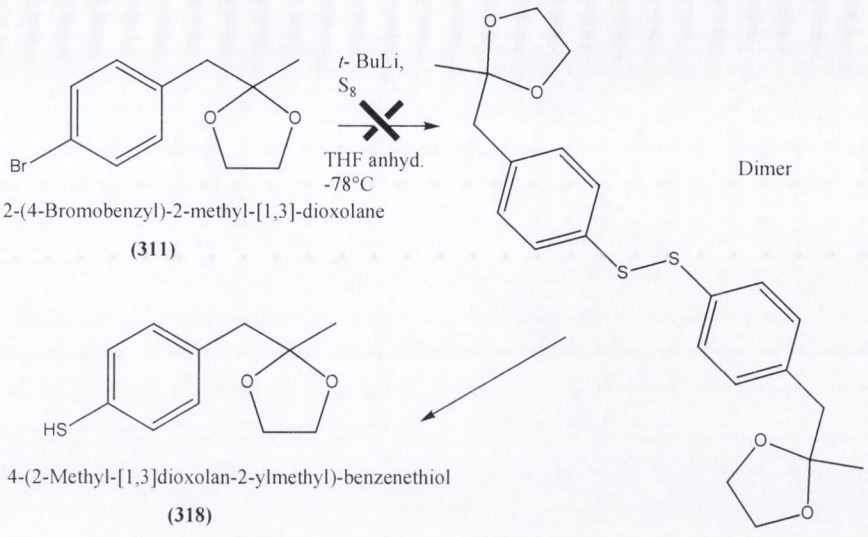


Scheme 6-12: Proposed thioalkylation of ketone using elemental sulfur and iodoalkanes

6.5.2.2.3 Attempt to form simple thiol using tertiary butyllithium and elemental sulfur.

In a further investigation, *tert*-butyl lithium was substituted for *n*-butyllithium.[135] This, in conjunction with elemental sulfur, was expected to give the dimer **(317)**, which could be hydrolysed to give the thiol **(318)**. A successful reaction could be replicated with 7-bromo-1,3-dimethyl-3,4-dihydroisoquinoline. The proposed route is shown in Scheme 6-

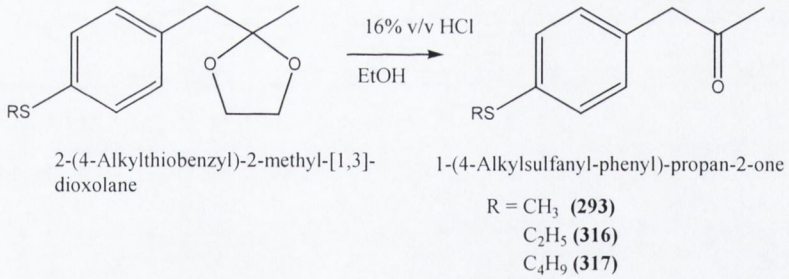
13. Unfortunately, this merely proved to be an expensive and difficult method to recover unsubstituted acetal.



Scheme 6-13: Proposed formation of thiol via dimer, using *t*-BuLi

6.5.2.3 Hydrolysis of Acetal

The thiomethyl (**312**), thioethyl (**313**) and thiobutyl (**315**) acetals were all successfully hydrolysed to their respective ketones (**293**, **316** and **317**) by reflux in ethanol with dilute hydrochloric acid (see Scheme 6-14 and Table 6-5).[132]



Scheme 6-14: Hydrolysis of acetals

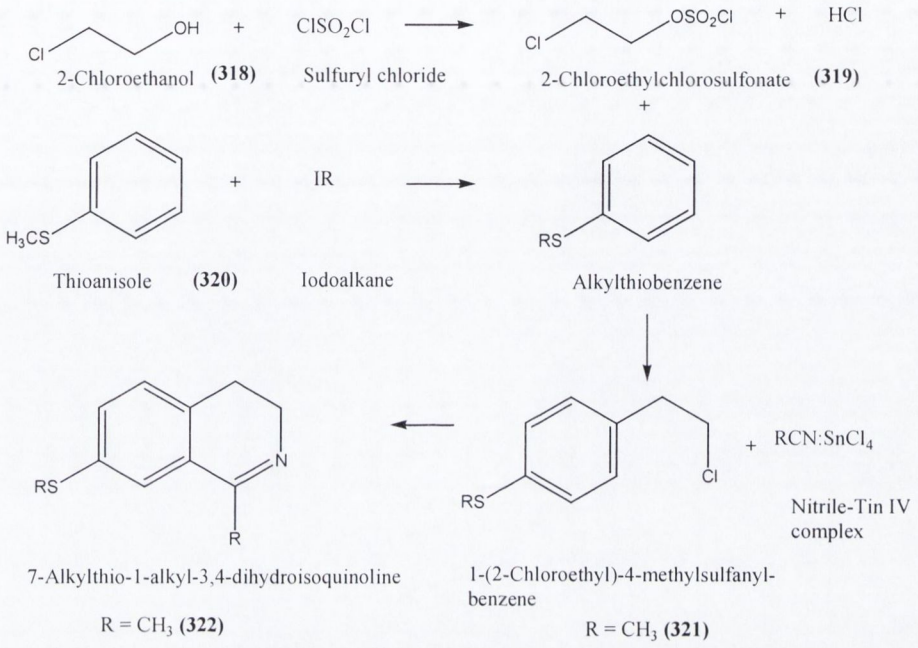
Although this approach gave thiomethyl **(293)**, thioethyl **(316)** and thiobutyl **(317)** groups in the *para* position of the ketone, it was too limited to provide the full set of thioalkyl groups which were needed to draw conclusions about structure activity relationships. It was not pursued further.

Number	R =	Yield, %
293[116]	CH_3	16.9%
316	C_2H_5	12%
317	C_4H_9	54%

Table 6-5: Thioalkyl ketones obtained by hydrolysis of acetals

6.6 Attempted Cyclisation via a Nitrilium Ion

The synthesis of an 1-alkyl-3,4-dihydroisoquinoline from a nitrile and (2-chloroethyl)-benzene was outlined in Chapter 5 (see **5.3**). This route (see Scheme 6-15) seemed to afford an alternative synthesis of a 7-thioether-3,4-dihydroisoquinoline and is discussed in detail in the following section.



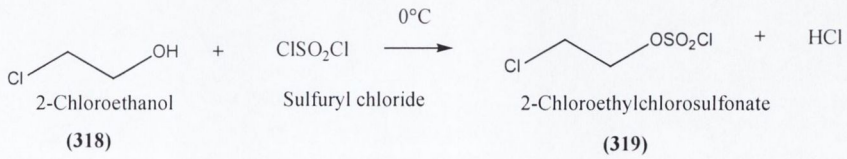
Scheme 6-15: Planned route of synthesis of 7-alkylthio-1-alkyl-3,4-dihydroisoquinolines

6.6.1 Introduction of β-Chlorethyl sidechain on Thioanisole

It may be seen in the general scheme above (Scheme 6-15) that extension of the alkyl chain of thioanisole was explored as a means of obtaining propyl and pentyl moieties on the sulfur atom of the dihydroisoquinoline. This lithiation and alkylation had been explored by Cabbidu et al for substituted benzenes.[136,137] It was considered prudent to first test the efficacy of the cyclisation using thioanisole.

6.6.1.1 Preparation of 2-Chloroethylchlorosulfonate (319)

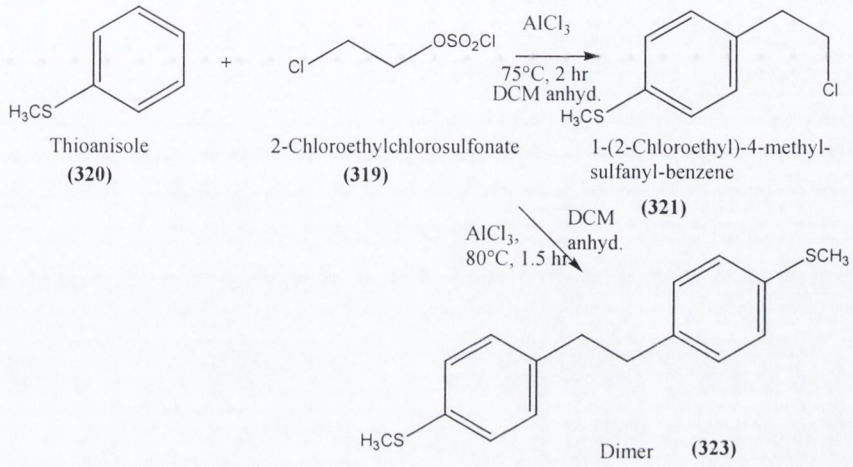
2-Chloroethanol **(318)** was treated with sulfuryl chloride according to a documented procedure. [138] The product was vacuum distilled and the distillate fraction at 75°C was collected in 73% yield. This is outlined in Scheme 6-16.



Scheme 6-16: Synthesis of 2-chloroethylchlorosulfonate, 319

6.6.1.2 Synthesis of 1-(2-Chloroethyl)-4-methylsulfanylbenzene (321)

Mansurov and Tsukervanik reported 75% yield of (2-chloroethyl)-benzene from a reaction of benzene and 2-chloroethylchlorosulfonate, under conditions of 0.2 – 0.3 equivalents of aluminium chloride and 50°C - 80°C for an unspecified duration.[139] However, when thioanisole was heated at 80°C for 1.5 hours with 2-chloroethylchlorosulfonate, and then stirred overnight, the product was a dimer (**323**) (see Scheme 6-17) in 53.8%.

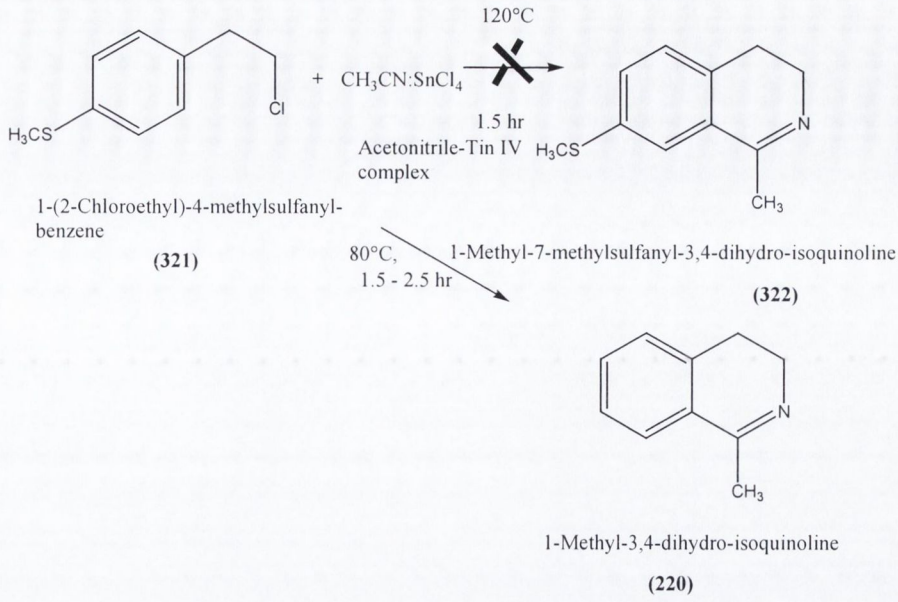


Scheme 6-17: Addition of chlorinated sidechain to thioanisole

The procedure was modified to discourage formation of the dimer. Initially, the procedure was repeated with 0.2 equivalents of aluminium chloride and heating for just one hour at 75°C, but this gave a low yield (20%), with much unreacted thioanisole mixed with the product, from which it was difficult to separate. Next, 2-chloroethylchlorosulfonate was dissolved in anhydrous dichloromethane as it was anticipated that a less concentrated reaction mixture should yield fewer dimers. The quantity of aluminium chloride was reduced to 0.2 equivalents. The mixture was heated at 75°C for 2 hours after the addition of thioanisole. This gave 1-(2-chloroethyl)-4-methylsulfanylbenzene[140] (321) in 41% yield.

6.6.1.3 Attempted Cyclisation of 1-(2-Chloroethyl)-4-methylsulfanylbenzene using Tin (IV) chloride

The procedure was broadly similar to that employed in Chapter 5 (see 5.3 and experimental details section). [75] Acetonitrile and tin (IV) chloride were added to the 1-(2-chloroethyl)-4-methyl-sulfurylbenzene **(321)** and the mixture was stirred at 120°C for 1.5 hours (see Scheme 6-18). It was worked up in the usual fashion, but an NMR spectrum showed no isoquinoline to be present. In fact, some of the starting material had broken down into its constituent thioanisole and 2-chloroethylchlorosulfonate.



Scheme 6-18: Attempted cyclisation of 1-(2-chloroethyl)-4-methylsulfanylbenzene to (322)

On the next occasion the acetonitrile and 1-(2-chloroethyl)-4-methyl-sulfanylbenzene **(321)** were mixed together under nitrogen and tin (IV) chloride was then added. The mixture was stirred at 80°C for 1.5 hours. TLC showed no characteristic dihydroisoquinoline fluorescence.

The same order of addition was used and the brown solution formed was stirred at 80°C for 2.5 hours. After work-up and purification the product was found to be 1-methyl-3,4-dihydroisoquinoline (**220**); reductive desulfuration had occurred.

Variation of the order of addition, and repeated efforts at 80°C for varying timeframes produced only 1-methyl-3,4-dihydroisoquinoline and the chloroethylester.

6.7 Dehalogenation and Thioalkylation at Position 7 via an Alternative Route

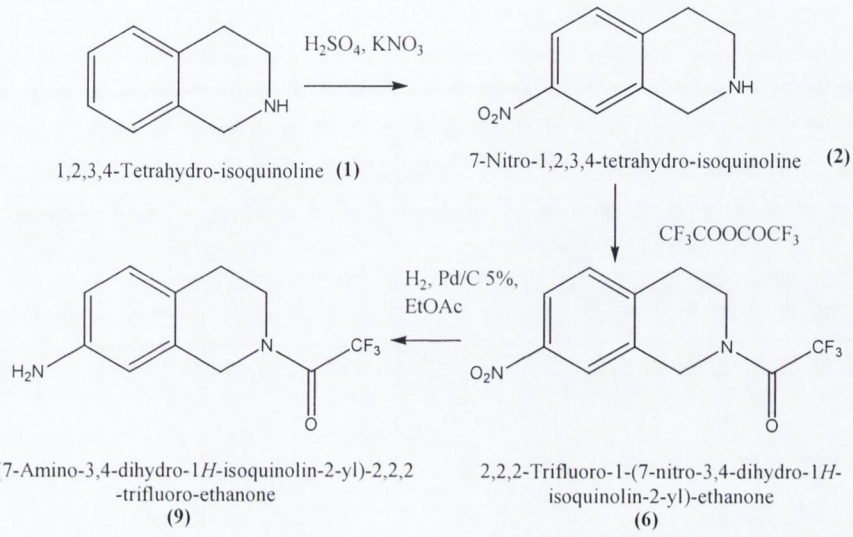
Given the lack of success heretofore, it was decided to investigate the method of Grunewald et al [141] for obtaining 7-methylsulfanyl-1,2,3,4-tetrahydroisoquinoline : bromination of 1,2,3,4-tetrahydroisoquinoline, then replacement of the bromine with a thiomethyl group, using lithiation. The alkyl chain could then be extended, using the procedure developed by Cabbidu et al.[136]

Bromination of position 7 in 1-methyl-3,4-dihydroisoquinoline **(220)** has been reported with a yield of 72%.[47] However, the difficulty and low yields (15.2%) of the Bischler-Napieralski synthesis made this an unattractive option. Microwave synthesis, as discussed in Chapter 5, offered a more efficient route to the dihydroisoquinoline, but bromination would still be followed by reduction to the tetrahydroisoquinoline, before introduction of the thiomethyl group using the Grunewald procedure. It was thus decided to aminate

1,2,3,4-tetrahydroisoquinoline in order to introduce the bromine at position 7 of the tetrahydroisoquinoline via the Sandmeyer reaction, and to follow this with thioalkylation.

6.7.1 Amination of 1,2,3,4-tetrahydroisoquinoline

This was accomplished by nitration of tetrahydroisoquinoline **(1)** at position 7 to afford **(2)**, protection of the amine function at position 2 to give **(6)** and then hydrogenation to yield an amine **(9)** at position 7 (see Scheme 6-19). The process is detailed in Chapter 2 (see **2.3** to **2.5**).

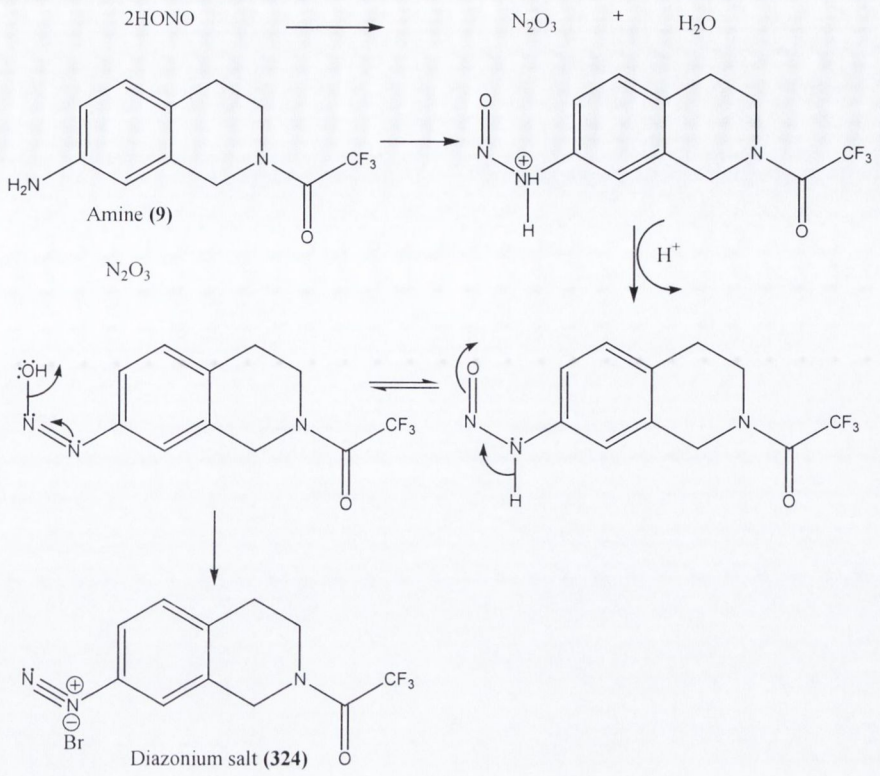


Scheme 6-19: Amidation of 1,2,3,4-tetrahydroisoquinoline

6.7.2 Sandmeyer Reaction

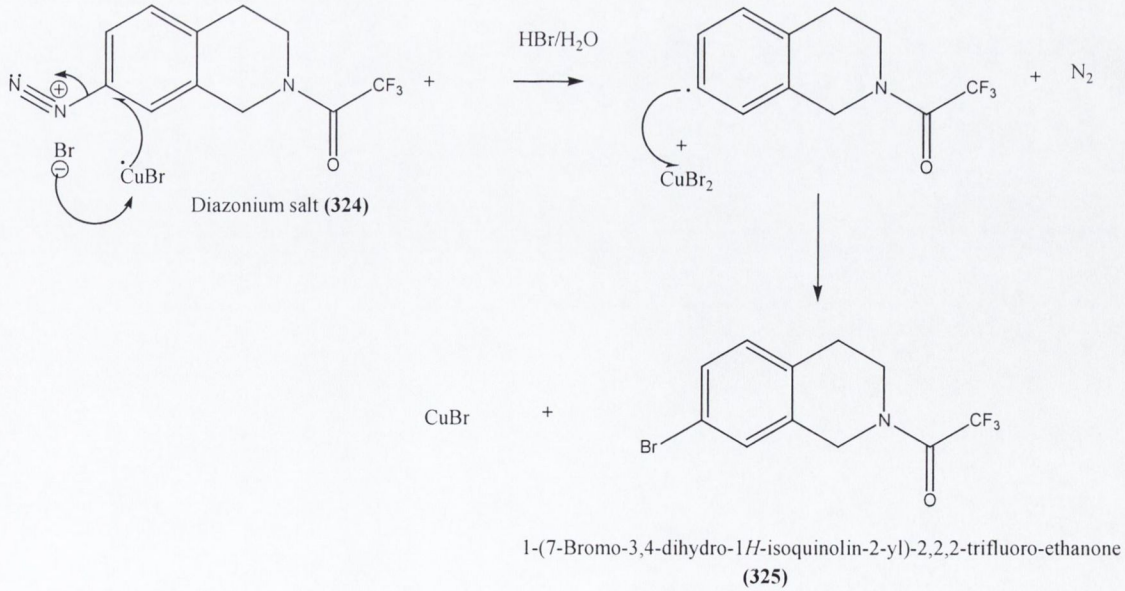
This substitution of an aromatic diazonium group by a halogen was first observed by Sandmeyer in 1884 when he found that benzene diazonium chloride gave chlorobenzene when treated with cuprous acetylide. He identified cuprous chloride as the catalyst. [142] The reaction offers a reliable route for the regiospecific introduction of a chlorine or bromine on an aromatic ring. This is attributable to the reluctance of a hydride to leave an aromatic ring, so that the azo group must leave and be *ipso* substituted by the nucleophile.[101]

The amine **(9)** was diazotised by addition of sodium nitrite to a solution of the amine in hydrobromic acid. This generated nitric acid, which attacked the amine group to afford the diazonium salt **(324)**. Despite the low pH the attack occurs on the small amount of free amine which remains (see Scheme 6-20).[98]



Scheme 6-20: Diazotization of amine

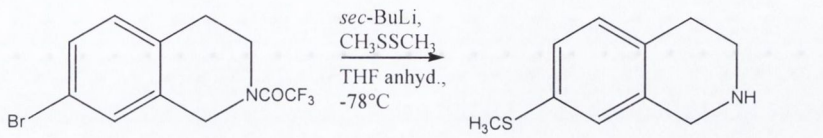
Cuprous bromide was added to the mixture. The mechanism of the Sandmeyer reaction is not known for certain, but is usually held to proceed by the formation of an aryl radical (see Scheme 6-21).[98] In this case it yielded the bromide **(325)**. The bromide was obtained in 51% yield.



Scheme 6-21: Sandmeyer reaction, introducing bromine at position 7

6.7.3 Thioalkylation

The first attempt to thioalkylate 1-(7-bromo-3,4-dihydro-*1H*-isoquinolin-2-yl)-2,2,2-trifluoro-ethanone **(325)** gave only 7-bromo-1,2,3,4-tetrahydro-isoquinoline **(326)**. A mere 10% excess of *n*-butyl lithium had been used, and this had been expended in a preliminary reaction in which the trifluoro-acetyl group had been removed. None was left to lithiate the isoquinoline at position 7.



1-(7-Bromo-3,4-dihydro-1*H*-isoquinolin-2-yl)-2,2,2-trifluoro-ethanone
(325)

7-Methylsulfanyl-1,2,3,4-tetrahydro-isoquinoline
(327)

Scheme 6-22: Thioalkylation of bromide, giving 7-methylsulfanyl-1,2,3,4-tetrahydroisoquinoline (327)

A larger excess was used in the second effort; 4 equivalents. This was a sufficient quantity to cleave the trifluoro-acetyl amide bond, remove the proton on the exposed secondary amine at position 2 (a possibility) and then replace the bromine at position 7 with a lithium ion (see Scheme 6-22). Moreover, the more active *sec*-butyllithium was employed. 7-Methylsulfanyl-1,2,3,4-tetrahydro-isoquinoline (**327**) was isolated in 18% yield and characterised.

The initial objective was finally achieved. A tetrahydroisoquinoline analogue of 4-methylthioamphetamine had been produced. Its ^{1}H-NMR spectrum showed the characteristic thiomethyl signal at 2.45 δ (see Figure 6-2). The methylene signals were not well resolved, appearing as broad singlets at 2.74 δ (C4$\underline{H}_2$), 3.12 δ (C3$\underline{H}_2$) and at 3.97 δ (C1$\underline{H}_2$). The proton of the amine function was just visible as a broad signal at 2.27 δ, integrating for one proton. The aromatic region presented a signal at 6.92 δ for C8$\underline{H}$. The doublets at 7.00 and 7.05 δ, both with coupling constants of 8 Hz, must be the signals for C5$\underline{H}$ and C6$\underline{H}$, coupling with one another.

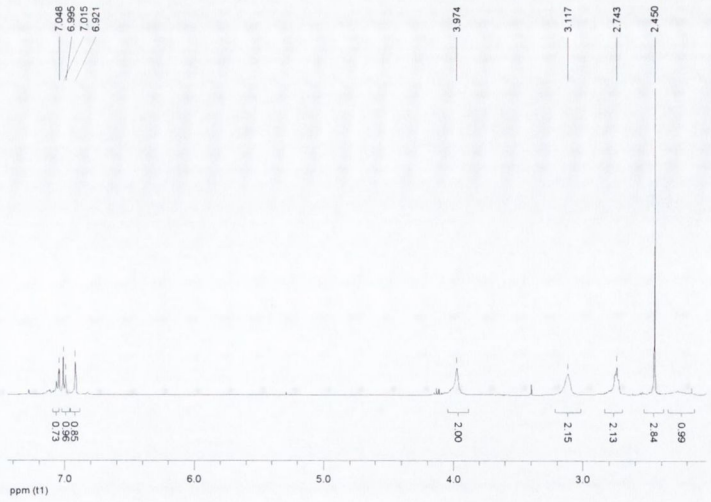


Figure 6-2: ^{1}H-NMR spectrum of 7-methylsulfanyl-1,2,3,4-tetrahydroisoquinoline, 327

The ^{13}C-NMR spectrum and DEPT spectrum are shown in Figure 6-3. The characteristic thiomethyl signal at 16.1 ppm is accompanied by methylene signals at 28.5 ($\underline{C}4H_2$), 43.6 ($\underline{C}3H_2$) and 48.0 ($\underline{C}1H_2$). The aromatic region shows three distinct signals for $\underline{C}6H$, $\underline{C}8H$ and $\underline{C}5H$, at 124.6 ppm, 124.9 ppm and 129.7 ppm. The quaternary carbon bearing the thiomethyl group is visible at 131.8 ppm and the quaternary carbons $\underline{C}4a$ and $\underline{C}8a$ seem to coincide at 135.1 ppm.

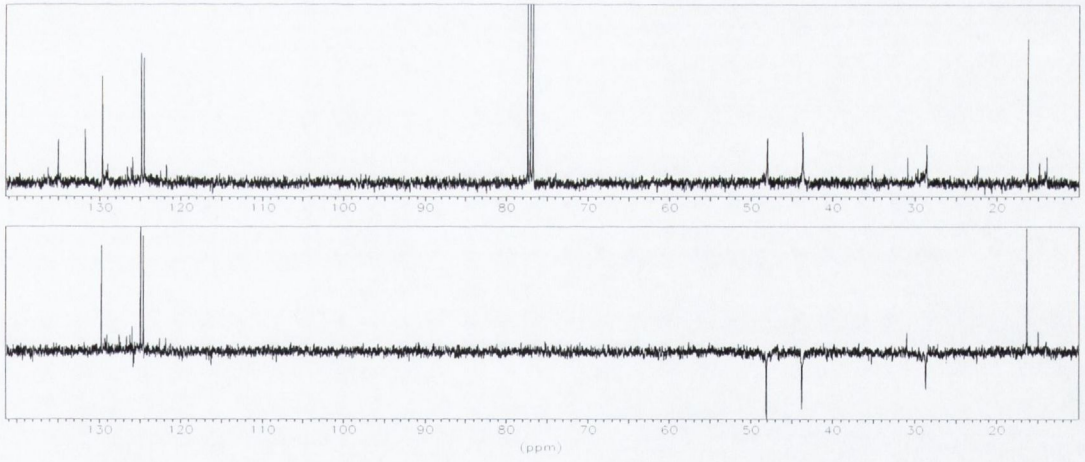


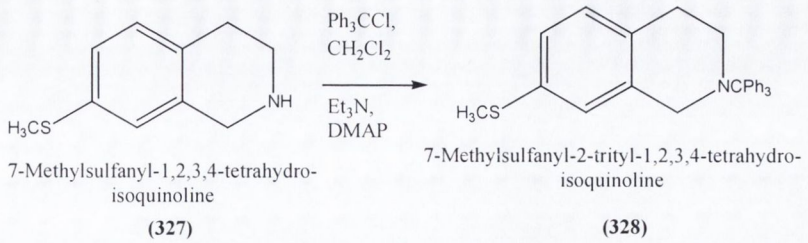
Figure 6-3: ^{13}C-NMR spectrum (upper) and DEPT spectrum (lower) for (327)

6.7.4 Attempted extension of Thioalkyl chain

6.7.4.1 Protection of amine function

The amine function was again protected, this time with a trityl group (see Scheme 6-23). This group would not be cleaved in *sec*-butyl lithium during extension of the alkyl group.[143] It was not used originally because it *is* easily removed by hydrogenation with a palladium catalyst, and would therefore not have survived the transformation of the nitro to

an amine. The procedure gave an 85% yield of 7-methylsulfanyl-2-trityl-1,2,3,4-tetrahydroisoquinoline (**328**).



7-Methylsulfanyl-1,2,3,4-tetrahydro-isoquinoline
(327)

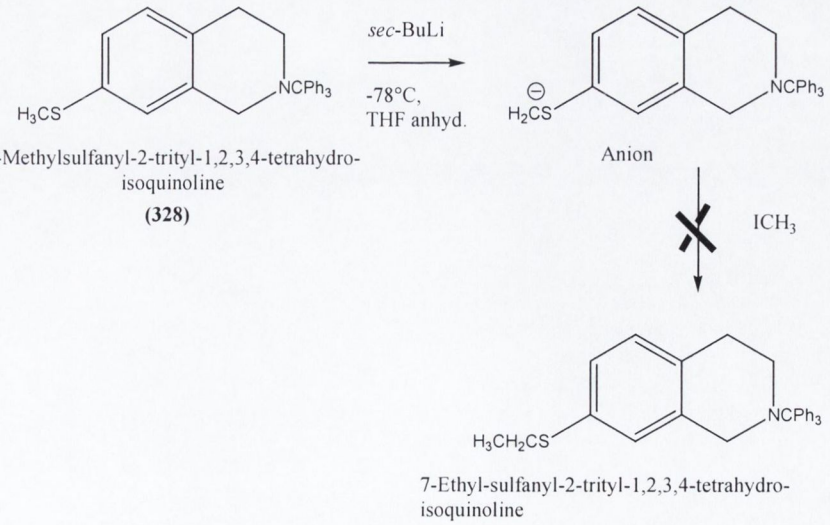
7-Methylsulfanyl-2-trityl-1,2,3,4-tetrahydro-isoquinoline
(328)

Scheme 6-23: Tritylation of position 2 amine function

6.7.4.2 Alkylation

The original intention had been to examine the properties of tetrahydroisoquinolines with a variety of thioalkyl groups at position 7. It was now proposed to extend the alkyl chain on the sulfur atom. The route followed was modelled on that employed by Cabbidu et al [136] with minor modifications (see Scheme 6-24). Tetrahydrofuran was substituted for anhydrous hexane, for ease of handling. The *sec*-butyl lithium (*sec*-BuLi) was added at -78°C. The temperature was allowed to rise to -10°C and the *sec*-BuLi was stirred with the protected tetrahydroisoquinoline for 1 hour before the solution was cooled to -78°C again. The iodomethane was then added, and the solution was stirred for 3 hours at room temperature, prior to work-up. Only starting material was obtained.

In a second attempt the tetrahydroisoquinoline and *sec*-BuLi were left stirring together at room temperature for 2 hours prior to addition of the iodomethane. The final mixture was left stirring at room temperature for 36 hours. Still no product was formed. This route was also abandoned as it was unclear why the reaction was not successful.



7-Methylsulfanyl-2-trityl-1,2,3,4-tetrahydro-isoquinoline
(328)

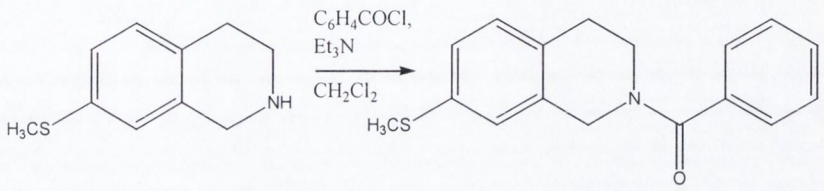
Anion

7-Ethyl-sulfanyl-2-trityl-1,2,3,4-tetrahydro-isoquinoline

Scheme 6-24: Attempted elaboration of alkyl function on sulfur

6.8 Acylation of Amine Function of 7-Methylsulfanyl-1,2,3,4-tetrahydroisoquinoline

The final modification of the thiomethyltetrahydroisoquinoline involved the formation of a position 2 amide analogous to those synthesised in Chapter 3. 7-Methylsulfanyl-1,2,3,4-tetrahydroisoquinoline was acylated at the position 2 nitrogen with benzoyl chloride. The acid chloride was used (see Scheme 6-25), but the simple procedure outlined in Chapter 3 (see section **3.5.1.2**) was employed instead of the Baumann-Schotten synthesis. The amide **(329)** was obtained in 19% yield.



7-Methylsulfanyl-1,2,3,4-tetrahydro-isoquinoline **(327)**

(7-Methylsulfanyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-phenyl-methanone **(329)**

Scheme 6-25: Acylation of 7-methylsulfanyl-1,2,3,4-tetrahydroisoquinoline

The ^{1}H-NMR spectrum of **(329)** in Figure 6-4 shows the familiar doubling of signals, and they are quite broad, as was often observed with unsubstituted tetrahydroisoquinoline amides in Chapter 3. The thiomethyl signal is seen at 2.48 δ, integrating for three protons. The broad multiplet at 2.84 δ - 2.96 δ is the C4$\underline{H}_2$. The pair of signals at 3.63 δ and 3.99 δ integrate for two protons and represent C3$\underline{H}_2$. There is another pair of signals at 4.57 δ and at 4.88 δ for C1$\underline{H}_2$. The three protons of the tetrahydroisoquinoline aromatic ring are not well resolved, and are seen together at 7.11 δ to 7.19 δ. The benzoyl aromatic signal is a singlet at 7.45 δ, integrating for 5 protons.

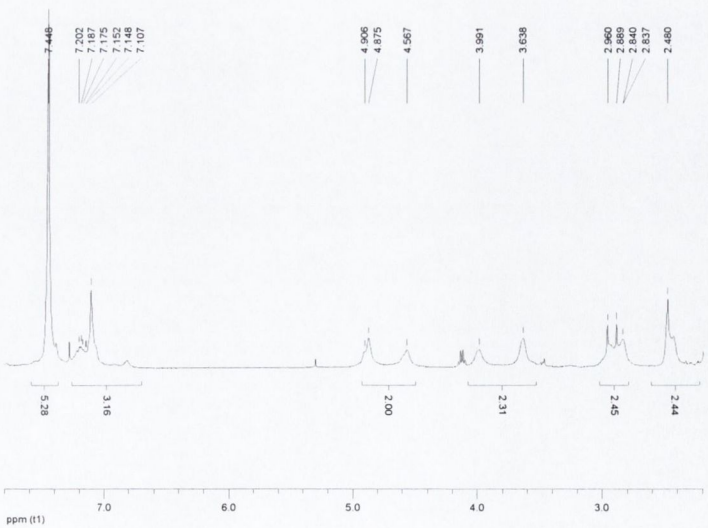


Figure 6-4: ^{1}H-NMR spectrum of thiomethylbenzoyl, 329

Apart from the methanol signal in the carbon spectrum in Figure 6-5, the strongest signal is in the aromatic region at 128.5 ppm. This dwarfs the three other aromatic signals at 125.3 ppm (C6H), 126.2 (C8H) and 129.8 (C5H). The thiomethyl carbon signal is observed at 16.0 ppm. The methylene signals are weak, relaxing fast. They are seen at 28.2 ppm ($C4H_2$), 44.7 ppm ($C1H_2$) and 45.2 ppm ($C3H_2$). The minor partners of these signals are difficult to identify with certainty, as they are weak signals, but seem to be at 29.1 ppm, 44.7 ppm and 45.2 ppm respectively. The quaternary signal for C7 is seen at 133.6 ppm and that for C4a and C8a at 135.9 ppm. The CO signal is too weak to be discerned, but comparison of the ^{1}H-NMR spectra of **327** and **329** indicate that an amide has been formed, due to the doubling and broadening of signals.

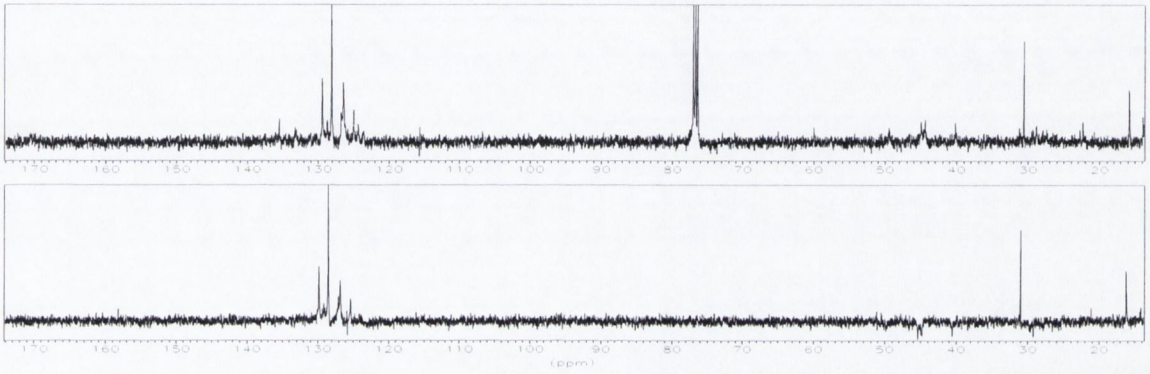


Figure 6-5: ^{13}**C-NMR spectrum (upper) and DEPT spectrum (lower) for (329)a**

6.9 Summary

The objective of the chapter was the preparation of thiomethyltetrahydroisoquinolines, as structural analogues of 4-MTA. The introduction of a thioether function at position 7 of the isoquinoline ring proved more laborious than envisaged. The first route was attempted cyclisation of 4-methylthioamphetamine via the Bischler-Napieralski synthesis. The amidation proceeded but the cyclisation did not.

While preparing 4-methylthioamphetamine a group of *para*-substituted amphetamines had also been synthesised. Among their ketone precursors was 1-(4-bromophenyl)-2-propan-1-one. This was used as a model, to see if 7-bromo-1,3-dimethyl-3,4-dihydroisoquinoline might be amenable to metallo-dehalogenation and thioalkylation. The ketone was protected as an acetal, and the acetal was successfully thioalkylated with disulfides. Elemental sulfur and iodoalkanes gave the thiobutyl compound (**315**) in all cases. The route was deemed insufficiently flexible for use with the amphetamine.

A variation of the lithiation using elemental sulfur was expected to give a dimer, but instead *tert*-butyl lithium resulted in reductive desulfuration.

The next effort concentrated on cyclisation of thioanisole by introducing a halogenated ethyl side-chain and reacting it with a nitrile-tin (IV) chloride complex. This route only afforded 1-methyl-3,4-dihydroisoquinoline.

Finally, the required thiomethyl tetrahydroisoquinoline was obtained by introduction of an amine function at position 7 of 1,2,3,4-tetrahydroisoquinoline, as in Chapter 3. Diazotization and subsequent Sandmeyer reaction allowed bromination at position 7. The bromine could be replaced with a methylthio group by lithiation (using *sec*-butyl lithium and dimethyl disulfide) to give 7-methylsulfanyl-1,2,3,4-tetrahydroisoquinoline (**327**). A benzoyl group was introduced at position 2 of 7-methylsulfanyl-1,2,3,4-tetrahydroisoquinoline, giving (7-methylsulfanyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-phenyl-methanone (**329**).

The two compounds **(327)** and **(329)** were tested for inhibition of monoamine oxidase A and monoamine oxidase B and the results are discussed in Chapter 7.

7 Chapter 7: Biological Activities

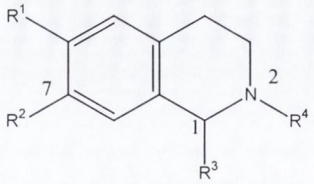
7.1 Introduction

Monoamine oxidase (MAO) inhibition by a variety of isoquinolines and their derivatives has been reported in scientific literature. [36,144] Further, previous work undertaken in this study group [47,59] examined the inhibition of MAO, catechol-O-methyl-transferase (COMT) and acetylcholinesterase (AChE) by a variety of dihydro and tetrahydroisoquinolines. Methoxy groups at positions 6 and 7 were found to increase MAO inhibition, while nitration of the isoquinoline nucleus reduced activity against MAO. 7-Aryl-1-methyl-3,4-dihydroisoquinolines were found to be especially effective MAO inhibitors, and their tetrahydroisoquinoline equivalents were only slightly less active. 7-Carboxamido derivatives of isoquinoline showed varied activity, with some dihydroisoquinolines being good inhibitors of MAO at 100μM. Most of the isoquinolines in the latter study [59] had a methyl substituent at position 1, and it was noted that removal of the methyl group increased activity against MAO-B while reducing inhibition of MAO-A. The selectivity of a phenoxyacetyltetrahydroisoquinoline **(219)** for MAO-B over MAO-A, combined with good inhibition of AChE, held out promise of a treatment for Alzheimer's Disease.

The present work investigates a series of 7-carboxamido tetrahydroisoquinolines without a methyl group at position 1 (Section 7.2.2). This was a natural development from the work on 7-carboxamido-1-methyl- dihydroisoquinolines.[59] The finding of AChE activity in a phenoxyacetyl-1-methyl-1,2,3,4-tetrahydroisoquinoline raised questions about the effect of further modifications, by removal of the methyl group at position 1 and by substitution of the phenoxy aromatic ring. Section 7.3 attempts to answer such questions.

A large number of tetrahydroisoquinolines with amide functions at position 2 were also examined. This area had not yet been subject to any study in relation to MAO inhibition, although a methyl substitutent at position 3 had been shown to leave MAO inhibition intact. [47] To extend the picture of structure-activity effects substituents at positions 1 and 2 were varied in separate series. The results of MAO inhibition studies of these series are presented in sections 7.2.3 through 7.2.5, with a preliminary discussion of structure activity relationships. Finally, a tetrahydroisoquinoline analogue of 4-methylthioamphetamine was examined for MAO inhibition, and it too was modified at position 2 to ascertain how this would affect activity (section 7.2.6). Figure 7-1 summarises the series.

R2 = NHCOR (Section 7.2.2)
R1 = R3 =R4=H



Tetrahydroisoquinoline nucleus

R^1=R^4=H
R^2 = $COCH_2OC_6H_4R$
R^3 = H (Section 7.3.2)
R^3 = CH_3 (Section 7.3.3)

R^1 = R^2= R^3 = H
R^4 = COR (Section 7.2.4.1)

R^1 = R^2 = OCH_3, R^4 = COR
R^3 = $CH_2C_6H_5$ (Section 7.2.4.2)
R^3 = C_6H_5 (Section 7.2.4.3)
R^3 = CH_3 (Section 7.2.4.4)

R^1 = R^2= R^3 = H
R^4 = $COCH_2N(CH_2CH_2)_2NR$ (Section 7.2.5.1)

R^1 = R^2 = OCH_3, R^4 = $COCH_2N(CH_2CH_2)_2NR$
R^3 = H (Section 7.2.5.2)
R^3 = CH_3 (Section 7.2.5.3)
R^3 = C_6H_5 (Section 7.2.5.4)
R^3 = $CH_2C_6H_5$ (Section 7.2.5.5)

Figure 7-1: Series examined in biochemical assays

7.2 Monoamine Oxidase Inhibition

7.2.1 Radiolabelled Assay

Monoamine oxidase occurs as two isoenzymes, of similar molecular weights (about 60kDa) and showing 70% identity.[32] These are called monoamine oxidase A (MAO-A) and monoamine oxidase B (MAO-B). Both isoenzymes oxidise primary aliphatic and aromatic amines and some secondary and tertiary amines also.[145] The isoforms have preferential substrates, but not absolute substrate specificity. 5-Hydroxytryptamine (5-HT) is preferentially oxidised by MAO-A, but with a sixfold higher K_m value for MAO-A than for MAO-B. This means that 5-HT will be oxidised by MAO-A, except at high concentrations. Similarly, phenethylamine (PEA) may be oxidised by MAO-A, but only at very high concentrations; it is oxidised by MAO-B alone under normal circumstances.[145] The two assays employed in the following sections are based on this substrate specificity at low concentrations, and are illustrated in Chapter 8, with experimental details. Thus, 5-HT was assumed to be oxidised by MAO-A alone under assay conditions and benzylamine to be oxidised by MAO-B. Benzylamine was used as the MAO-B substrate as it has a longer linear section in its time course, which allows for a longer assay time. This reduces the importance of any lagtime effect between addition of reagent to the first and last vials in any assay array.

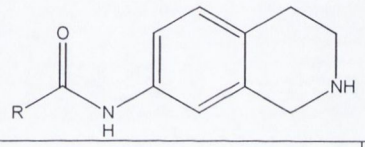
All compounds were tested at a concentration of 100μM. Activities were measured as a % inhibition, with substrate turnover in the absence of inhibitor being set at 100%. Thus, the

% inhibition in all tables is defined as 100 less the % enzyme turnover in the presence of the inhibitor. The substrates were radiolabelled at the α carbon of the phenethylamine chain. This allowed measurement of the quantity of aldehyde product in a scintillation counter, as detailed in the biochemical protocols presented in Chapter 8.

7.2.2 Inhibitory activities of *N*-(1,2,3,4-tetrahydroisoquinolin-7-yl)-amides

7.2.3 Monoamine oxidase B inhibition

There was no clearly defined trend among this class of compounds as inhibitors of the B isoenzymes (see Table 7-1). Generally, they acted as poor inhibitors at 100μM, with the halogenated phenyl compounds **(28**, **29**, **30** and **31)** giving the best results, although only the chlorinated phenyl compound **(29)** gave inhibition greater than 50% at this concentration. A methoxy group in the *para* position of a phenyl or a benzyl substituent at R abolished activity **(34** and **37)**.



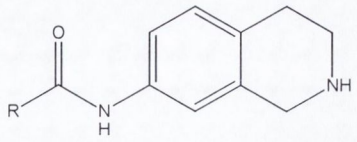
Compound Number	**R=**	**% Inhibition**
24	C_2H_5	2.3+/-4.6
25	C_3H_7	1.4+/-6.7
26	C_6H_{11}	39.1+/-17.6
27	C_6H_5	13.5+/-6.3
28	C_6H_4F	41.7+/-4.2
29	C_6H_4Cl	56.8+/-1.1
30	C_6H_4Br	37.7+/-6.1
31	C_6H_4I	39.2+/-9.6
32	*o*-$C_6H_4OCH_3$	13.6+/-13.2
33	*m*-$C_6H_4OCH_3$	24.6+/-11.9
34	*p*-$C_6H_4OCH_3$	No inhibition
35	$C_6H_4NO_2$	57.2+/-9.0
36	$CH_2C_6H_5$	30.7+/-4.7
37	$CH_2C_6H_4OCH_3$	No inhibition

Table 7-1: Monoamine oxidase B inhibition of (N-1,2,3,4-tetrahydroisoquinolin-7-yl)-amides at 100mM

7.2.3.1 Monoamine oxidase A inhibition

The series of compounds were far superior inhibitors of MAO-A (see Table 7-2), although the trends evident in MAO-B inhibition were repeated. A *para* methoxy group only abolished activity on the benzyl substituent this time **(37)**. The halogenated phenyl compounds were again the most active, with the brominated phenyl compound **(30)** showing slightly higher levels of activity (85% inhibition) than the chlorinated phenyl

compound **(29).** The most striking difference in activities is seen with the propyl compound, **(25)**, which hardly inhibited MAO-B at 1.4% but showed 45.5% inhibition of MAO-A. This may suggest that an elaborated aliphatic chain might give selectivity for MAO-A over MAO-B.



Compound Number	R=	% Inhibition
24	C_2H_5	33.2+/-7.9
25	C_3H_7	45.5+/-4.6
26	C_6H_{11}	65.0+/-4.9
27	C_6H_5	60.2+/-1.1
28	C_6H_4F	58.5+/-2.8
29	C_6H_4Cl	84.2+/-0.6
30	C_6H_4Br	85.1+/-3.0
31	C_6H_4I	73.7+/-3.8
32	*o*-$C_6H_4OCH_3$	6.1+/-5.0
33	*m*-$C_6H_4OCH_3$	35.1+/-2.3
34	*p*-$C_6H_4OCH_3$	53.6+/-5.1
35	$C_6H_4NO_2$	76.4+/-3.2
36	$CH_2C_6H_5$	28.7+/-5.1
37	$CH_2C_6H_4OCH_3$	No inhibition

Table 7-2: Monoamine oxidase A inhibition by (*N*-1,2,3,4-tetrahydroisoquinolin-7-yl)-amides at 100μM

7.2.4 Inhibitory activities of (3,4-dihydro-*1H*-isoquinolin-2-yl)-ketones and (1-alkyl-6,7-dimethoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-ketones

While the Autonom system denominates these compounds as "ketones", they are, of course, a series of amides, introduced at position 2 of the tetrahydroisoquinoline nucleus.

7.2.4.1 (3,4-Dihydro-*1H*-isoquinolin-2-yl)-ketones

7.2.4.1.1 Monoamine oxidase B inhibition

The large number of compounds in this series (see Table 7-3) renders the range of activities somewhat bewildering. It is clear that simple aliphatic amides, such as **(69 – 72)** are not good inhibitors of MAO-B. Branched chain **(73)** or cyclic saturated amides **(74 - 76)** are not much better. A phenyl substituent at position 2 is not of itself a good inhibitor **(77).** A substituent in the *ortho* position of the phenyl ring abolishes activity altogether in some cases (the *o*-Cl and *o*-NO_2 compounds **(87)** and **(92)**) and is low in the others, with the *o*-F benzoyl being the best inhibitor at just 35.4%.

Amides substituted in the *meta* position are generally even poorer inhibitors. The exception is **(95)**, the trifluoromethylbenzoyl compound, which causes 52.1% inhibition at

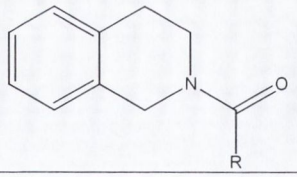
100μM. The *m*-F, *m*-Cl and *m*-NO_2 substituents (compounds **(85, 88, 93)**) all abolish inhibition completely. A toluoyl or anisoyl group in the *meta* position **(79, 82)** are hardly better, at 5.2% and 8.9% respectively.

By far the best inhibitor of MAO-B in this series was the thiomethylbenzoyl compound **(68)**. It gave 78.5% inhibition at 100μM. The interposition of a methylene group between the aromatic ring and the amide function in compound **(63)** reduced activity to 52.1%. This is the poorest inhibitor of the phenylacetic series **(61 – 66)**. However, with a range of activity as narrow as 52.1 % to 66.9% they may be considered to have broadly similar activity at this concentration.

The *para*-halogenated benzoyls showed moderately good activity, increasing from 44.1% for the fluorinated compound **(86)**, through 47.1% for the chlorinated product **(89)**, 58.0% for the brominated compound **(90)** and 49.0% for the iodinated benzoyl (**91**).

Time constraints did not allow for testing of all compounds for MAO-A activity. Only the better MAO-B inhibitors were chosen for further investigation. Clearly, this must mean the thioether compound **(68)**. The phenylacetic compound, **(63)**, which possesses a thiomethyl was taken for comparison with **(68)**; it also served as a representative of the phenylacetic subset of compounds.

The four halogenated benzoyls were chosen partly on the basis of moderate activity against MAO-B, partly due to good MAO-A inhibition shown by halogenated benzoyl amides at position 7 (see Table 7-2) and partly because they would provide a series of increasingly bulky groups at the *para* position with similar electronic characteristics.

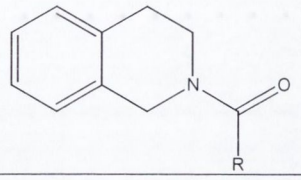


Compound Number	R =	% Inhibition
61	$CH_2C_6H_5$	63.4+/-2.8
62	$CH_2C_6H_4NO_2$	60.7+/-2.2
63	$CH_2C_6H_4SCH_3$	52.1+/-6.8
64	*m*-$CH_2C_6H_4(OCH_3)$	66.9+/-3.4
65	*p*-$CH_2C_6H_4(OCH_3)$	53.1+/-2.1
66	*m,p*-$CH_2C_6H_3(OCH_3)_2$	53.0+/-6.1
67	*p*-$C_6H_4NO_2$	33.6+/-9.0
68	$C_6H_4SCH_3$	78.5+/-16.2
69	CH_3	4.6+/-6.7
70	C_2H_5	21.1+/-8.2
71	C_3H_7	16.7+/-19.0
72	C_4H_9	13.2+/-9.8
73	$CH_2CH(CH_3)_2$	17.6+/-6.0
74	Cyclopropyl	35.3+/-1.6
75	Cyclobutyl	12.3+/-6.9
76	Cyclohexyl	9.4+/-9.9
77	C_6H_5	6.3+/-1.7
78	*o*-$C_6H_4CH_3$	18.9+/-0.8
79	*m*-$C_6H_4CH_3$	5.2+/-5.2
80	*p*-$C_6H_4CH_3$	5.7+/-4.7
81	*o*-$C_6H_4OCH_3$	1.0+/-1.9
82	*m*-$C_6H_4OCH_3$	8.9+/-4.4
83	*p*-$C_6H_4OCH_3$	57.4+/-2.6
84	*o*-C_6H_4F	35.4+/-10.6
85	*m*-C_6H_4F	No inhibition
86	*p*-C_6H_4F	44.1+/-4.6
87	*o*-C_6H_4Cl	No inhibition
88	*m*-C_6H_4Cl	No inhibition
89	*p*-C_6H_4Cl	47.1+/-5.7
90	C_6H_4Br	58.0+/-13.8
91	C_6H_4I	49.0+/-13.1
92	*o*-$C_6H_4NO_2$	No inhibition
93	*m*-$C_6H_4NO_2$	No inhibition
94	*o*-$C_6H_4CF_3$	23.6+/-1.0
95	*m*-$C_6H_4CF_3$	52.1+/-0.5
96	*p*-$C_6H_4CF_3$	47.4+/-4.7
97	$C_6H_4C_2H_5$	33.5+/-9.7
98	2-Naphthalenyl	37.5+/-4.3

Table 7-3: Monoamine oxidase B inhibition of (3,4-dihydro-*1H*-isoquinolin-2-yl)-ketones at 100 μM

7.2.4.1.2 Monoamine oxidase A inhibition

Those compounds tested for MAO-A inhibition proved very efficient inhibitors at this concentration (see Table 7-4). The thiomethylbenzoyl **(68)** was less effective than most of the halogenated compounds, but still gave a rate of inhibition of 88.4%. The halogenated compounds climbed in activity from 76.2% for the least active, the fluorine **(86)**, to 100% inhibition with the iodinated compound **(91)**. Insertion of a methylene group between the amide function and the aromatic ring reduced the activity of the thioether to 71.4% **(63).**



Compound Number	R =	% Inhibition
63	$CH_2C_6H_4SCH_3$	71.4+/-6.7
68	$C_6H_4SCH_3$	88.4+/-8.0
86	*p*-C_6H_4F	76.2+/-4.1
89	*p*-C_6H_4Cl	96.1+/-3.5
90	C_6H_4Br	93.0+/-6.4
91	C_6H_4I	100+/-0.2

Table 7-4: Monoamine oxidase A inhibition of (3,4-dihydro-*1H*-isoquinolin-2-yl)-ketones at 100 μM

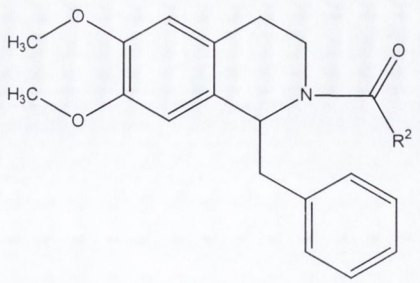
7.2.4.2 (1-Benzyl-6,7-dimethoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-ketones

7.2.4.2.1 Monoamine oxidase B inhibition

The poor activity of the simple aliphatic amides is again in evidence in compounds **(152 – 155)** in Table 7-5. The saturated ring amides are slightly better, at 30.1% for a cyclopropyl ring **(156)** and 25.5% for a cyclohexyl ring **(157).**

There are no trends evident from the anisoyl series or the benzoyl amides as a whole. The *ortho* methoxy group compound **(160)** showed the best inhibition of all the benzoyls, at 65.6%, but the *para* anisoyl compound **(162)** was more active than the *meta* version **(161)**. The halogenated benzoyls showed no clearcut progression, with activity dropping from 27.4% for the fluorinated benzoyl **(163)** to zero for the chlorinated compound and then 50.5% for the brominated benzoyl **(165)** and finally 24.7% for the iodo compound **(166)**.

A thiomethyl group on a benzyl sidechain **(146)** gave an impressive 93.4% inhibition, far superior to the phenyl version **(151)** with just 18.7% activity. Next best was the unsubstituted phenylacetic acid product **(145)** with 65.6% inhibition and then the *para* substituted methoxyphenylacetic acid amide **(148)** at 42.7%. The activities of other products were uniformly unimpressive.



Compound Number	R =	% Inhibition
145	$CH_2C_6H_5$	65.6+/-0.7
145a	$CH_2C_6H_4NO_2$	22.3+/-5.6
146	$CH_2C_6H_4SCH_3$	93.4+/-3.8
147	*m*-$CH_2C_6H_4(OCH_3)$	22.8+/-2.3
148	*p*-$CH_2C_6H_4(OCH_3)$	42.7+/-19.4
149	*m,p*-$CH_2C_6H_3(OCH_3)_2$	10.5+/-3.0
150	*p*-$C_6H_4NO_2$	28.6+/-5.2
151	$C_6H_4SCH_3$	18.7+/-3.8
152	CH_3	No inhibition
153	C_2H_5	2.7+/-3.3
154	C_3H_7	15.4+/-5.7
155	C_4H_9	5.5+/-2.9
156	Cyclopropyl	30.1+/-10.8
157	Cyclohexyl	25.5+/-14.2
158	C_6H_5	8.7+/-2.1
159	*p*-$C_6H_4CH_3$	37.6+/-2.5
160	*o*-$C_6H_4OCH_3$	65.6+/-2.7
161	*m*-$C_6H_4OCH_3$	22.8+/-1.8
162	*p*-$C_6H_4OCH_3$	42.7+/-5.9
163	*p*-C_6H_4F	27.4+/-8.1
164	*p*-C_6H_4Cl	No inhibition
165	C_6H_4Br	50.5+/-2.5
166	C_6H_4I	24.7+/-7.2

Table 7-5: Monoamine oxidase B inhibition of (1-Benzyl-6,7-dimethoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-ketones at 100 μM

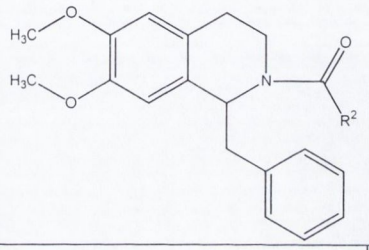
7.2.4.2.2 Monoamine oxidase A inhibition

The entire series was tested for activity in order to get an impression of MAO-A inhibitory trends among position 2 amides (see Table 7-6). The only clear conclusions which could be drawn were that a) the halogenated benzoyls were the most effective MAO-A inhibitors and b) the simple aliphatic amides were completely inactive against MAO-A at this concentration.

Anisoyl groups did not favour MAO-A inhibition, abolishing activity in any position on the benzoyl ring (see **(160 – 162)**) compared to the already weak inhibition of the unsubstituted aromatic group itself, **(158)** at 16.5%. They also slightly lowered inhibition

of the phenylacetic acid products from 40.6% for the unsubstituted ring of **(145)** to 34.7%, 35.5% and 38.8% with compounds **(147 – 149)**. All the phenylacetic acid products **(145 - 149)** were in the narrow range of 30.4% to 40.6%.

The inhibitory activity of the thiomethylphenylacetic product **(146)** may be paltry compared to its 93.4% inhibition of MAO-B at this concentration, but its benzoyl relative **(151)** is one of the best of its type, at 66.4% inhibition. This is slightly superior to 62.1% for the *p*-nitro benzoyl **(150)** and compares well with the halogenated benzoyls. These give inhibition of 59.6%, 69.0%, 67.3% and 77.7% as one moves down the periodic table from fluorine **(163)** through chlorine **(164)** and bromine **(165)** to iodine **(166)**. The surprise star of the series is the cyclohexyl amide **(157)** with 88.5% inhibition.



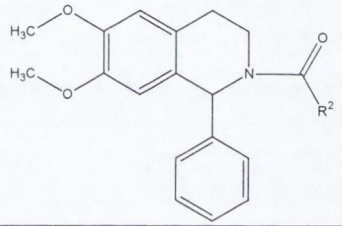
Compound Number	R =	% Inhibition
145	$CH_2C_6H_5$	40.6+/-3.5
145a	$CH_2C_6H_4NO_2$	30.4+/-3.5
146	$CH_2C_6H_4SCH_3$	40.3+/-4.3
147	*m*-$CH_2C_6H_4(OCH_3)$	34.7+/-5.9
148	*p*-$CH_2C_6H_4(OCH_3)$	35.5+/-3.7
149	*m,p*-$CH_2C_6H_3(OCH_3)_2$	38.8+/-3.9
150	*p*-$C_6H_4NO_2$	62.1+/-2.6
151	$C_6H_4SCH_3$	66.4+/-1.6
152	CH_3	No inhibition
153	C_2H_5	No inhibition
154	C_3H_7	No inhibition
155	C_4H_9	No inhibition
156	Cyclopropyl	No inhibition
157	Cyclohexyl	88.5+/-1.3
158	C_6H_5	16.5+/-2.7
159	*p*-$C_6H_4CH_3$	69.4+/-3.9
160	*o*-$C_6H_4OCH_3$	No inhibition
161	*m*-$C_6H_4OCH_3$	No inhibition
162	*p*-$C_6H_4OCH_3$	No inhibition
163	*p*-C_6H_4F	59.6+/-4.2
164	*p*-C_6H_4Cl	69.0+/-0.5
165	C_6H_4Br	67.3+/-3.3
166	C_6H_4I	77.7+/-6.5

Table 7-6: Monoamine oxidase A inhibition of (1-benzyl-6,7-dimethoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-ketones

7.2.4.3 (6,7-Dimethoxy-1-phenyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-ketones

7.2.4.3.1 Monoamine oxidase B inhibition

The introduction of a phenyl substituent at position 1 of the isoquinoline nucleus decimates MAO-B inhibitory activity, compared to the benzyl amides (see Table 7-5). Table 7-7 shows the inactivity of most of the phenyl amides and the low levels of inhibition seen with those that are active. Of these, the nitro and the fluoro compounds ((**128**) and (**141**) respectively) are the best inhibitors of MAO-B at 26.6% and 26.5% respectively. All other active compounds (**130**, **136**, **138**, **140**, **142**, **144**, **123** and **125**) exhibit inhibition rates of less than 15%.



Compound Number	R =	% Inhibition
122	$CH_2C_6H_5$	No inhibition
123	$CH_2C_6H_4NO_2$	No inhibition
124	$CH_2C_6H_4SCH_3$	No inhibition
125	*m*-$CH_2C_6H_4(OCH_3)$	13.6+/-5.0
126	*p*-$CH_2C_6H_4(OCH_3)$	No inhibition
127	*m,p*-$CH_2C_6H_3(OCH_3)_2$	No inhibition
128	*p*-$C_6H_4NO_2$	26.6+/-6.9
129	$C_6H_4SCH_3$	No inhibition
130	CH_3	0.1+/-8.5
131	C_2H_5	No inhibition
132	C_3H_7	No inhibition
133	C_4H_9	No inhibition
134	Cyclopropyl	No inhibition
135	Cyclohexyl	No inhibition
136	C_6H_5	7.0+/-5.8
137	*p*-$C_6H_4CH_3$	No inhibition
138	*o*-$C_6H_4OCH_3$	9.7+/-2.2
139	*m*-$C_6H_4OCH_3$	No inhibition
140	*p*-$C_6H_4OCH_3$	9.5+/-10.9
141	*p*-C_6H_4F	26.5+/-6.3
142	*p*-C_6H_4Cl	12.7+/-17.0
143	C_6H_4Br	No inhibition
144	C_6H_4I	3.1+/-11.5

Table 7-7: Monoamine oxidase B inhibition of (6,7-dimethoxy-1-phenyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-ketones at 100 μM

7.2.4.3.2 Monoamine oxidase A inhibition

Activity against MAO-A is moderately good in the few compounds tested (see Table 7-8), but not comparable to those obtained with the unsubstituted amides (see Table 7-4). Introducing a phenyl substituent on the isoquinoline nucleus reduces MAO-A inhibition by 40% to 70%. This may be seen with the halogenated benzoyl compounds **(141 – 144)** and also with the thioether **(129)**.

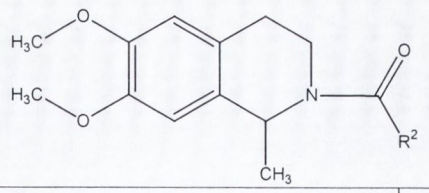
Compound Number	**R =**	**% Inhibition**
129	$C_6H_4SCH_3$	24.5+/-4.8
141	*p*-C_6H_4F	34.1+/-5.0
142	*p*-C_6H_4Cl	43.7+/-4.6
143	C_6H_4Br	24.3+/-2.0
144	C_6H_4I	34.3+/-5.9

Table 7-8: Monoamine oxidase A inhibition of (6,7-dimethoxy-1-phenyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-ketones at 100 μM

7.2.4.4 (6,7-Dimethoxy-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-ketones

7.2.4.4.1 Monoamine oxidase B inhibition

13 of the 23 compounds tested were inactive towards MAO-B, the same proportion as were inactive in the 1-phenyl series; but they were not in all cases the related compound! A handful of those, which are inhibitors among the 1-methyl series, show moderate inhibition of MAO-B (see Table 7-9). The two best are the thioethers **(105)** and **(101)**, at 49.7% and 33.6% respectively. The iodinated benzoyl **(120)** shows an inhibition rate of 33.3% and all the rest are below 15% inhibition of MAO-B.

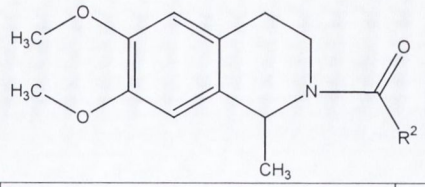


Compound Number	R =	% Inhibition
99	$CH_2C_6H_5$	10.7+/-6.6
100	$CH_2C_6H_4NO_2$	No inhibition
101	$CH_2C_6H_4SCH_3$	33.6+/-7.1
102	*m*-$CH_2C_6H_4(OCH_3)$	2.4+/-1.5
103	*p*-$CH_2C_6H_4(OCH_3)$	12.7+/-10.2
104	*m,p*-$CH_2C_6H_3(OCH_3)_2$	4.4+/-3.3
105	$C_6H_4SCH_3$	49.7+/-7.1
106	CH_3	No inhibition
107	C_2H_5	No inhibition
108	C_3H_7	No inhibition
109	C_4H_9	No inhibition
110	Cyclopropyl	No inhibition
111	Cyclohexyl	7.5+/-6.5
112	C_6H_5	No inhibition
113	*p*-$C_6H_4CH_3$	No inhibition
114	*o*-$C_6H_4OCH_3$	No inhibition
115	*m*-$C_6H_4OCH_3$	No inhibition
116	*p*-$C_6H_4OCH_3$	No inhibition
117	*p*-C_6H_4F	1.3+/-7.6
118	*p*-C_6H_4Cl	No inhibition
119	C_6H_4Br	13.6+/-11.7
120	C_6H_4I	33.3+/-3.8
121	*p*-$C_6H_4NO_2$	No inhibition

Table 7-9: Monoamine oxidase B inhibition of (6,7-dimethoxy-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-ketones at 100 μM

7.2.4.4.2 Monoamine oxidase A inhibition

This series (see Table 7-10) confirms that the introduction of a substituent at position 1 of the isoquinoline nucleus reduces inhibition of MAO-A activity, regardless of size. The inhibition of MAO-A is retarded to comparable extents by a methyl and a phenyl group at position 1 (see Table 7-8 for comparison).



Compound Number	R =	% Inhibition
101	$CH_2C_6H_4SCH_3$	55.5+/-4.5
105	$C_6H_4SCH_3$	14.1+/-4.8
117	*p*-C_6H_4F	4.4+/-7.8
118	*p*-C_6H_4Cl	43.1+/-0.5
119	C_6H_4Br	39.1+/-4.8
120	C_6H_4I	78.6+/-6.9

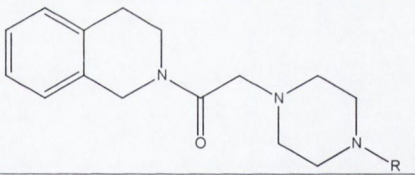
Table 7-10: Monoamine oxidase A inhibition of ((6,7-dimethoxy-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-ketones

7.2.5 Inhibitory activities of piperazine amides

7.2.5.1 Unsubstituted Piperazine Amides

The amides were disappointing inhibitors of monoamine oxidase B (see Table 7-11) and only the dimer **(185)**, which was synthesised unintentionally, gave moderate inhibition of 42.9%. The bulky piperonal piperazine amide **(184)** gave inhibition of 5.6%. The inactivity is thus not due to size considerations.

7.2.5.1.1 Monoamine oxidase B inhibition



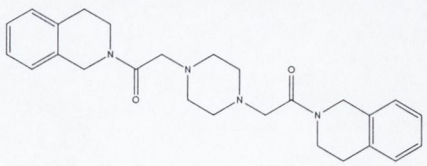
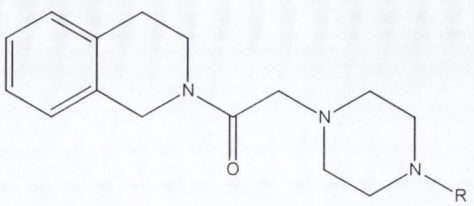
Compound Number	R=	% Inhibition
181	*m*-C_6H_4Cl	No inhibition
182	*p*-C_6H_4Cl	No inhibition
183	*p*-C_6H_4F	No inhibition
184	$CH_2C_6H_3(OCH_2O)$	5.6+/-4.3
185		42.9+/-5.3

Table 7-11: Monoamine oxidase B inhibition of unsubstituted piperazine amides

7.2.5.1.2 Monoamine oxidase A inhibition

The activity profile was reversed for MAO-A (see Table 7-12), with the halogenated phenyl piperazine amides **(181)** and **(182)** showing the best activity, with 46.0% and 51% inhibition respectively. Strangely, the fluoro compound **(183)** did not inhibit MAO-A.

The piperonal piperazine amide **(184)** was almost inactive at 3.6% inhibition and the dimer **(185)** did not affect MAO-A at all.



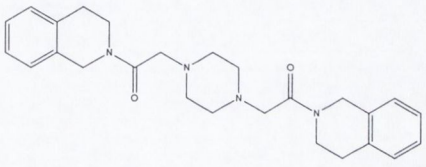
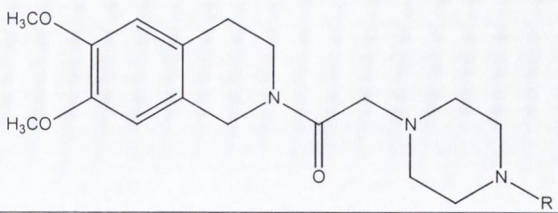
Compound Number	R=	% Inhibition
181	*m*-C_6H_4Cl	46.0+/-3.2
182	*p*-C_6H_4Cl	51.0+/-4.6
183	*p*-C_6H_4F	No inhibition
184	$CH_2C_6H_3(OCH_2O)$	3.6+/-1.2
185		No inhibition

Table 7-12: Monoamine oxidase A inhibition of unsubstituted piperazine amides

7.2.5.2 6,7-Dimethoxy-piperazine amides

7.2.5.2.1 Monoamine oxidase B inhibition

The overall activity of this series was low against MAO-B and even the dimer, **(187)**, did not show appreciable inhibition at just 4.3% inhibition (see Table 7-13).



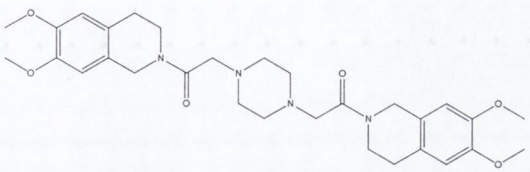
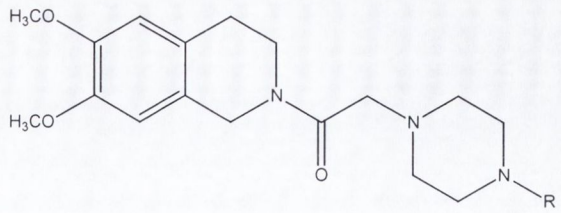
Compound Number	R=	% Inhibition
187		4.3+/-2.8
190	*m*-C_6H_4Cl	7.3+/-5.3
191	*p*-C_6H_4Cl	No inhibition
192	*p*-C_6H_4F	12.9+/-8.5
193	$CH_2C_6H_3(OCH_2O)$	10.0+/-5.0

Table 7-13: Inhibition of monoamine oxidase B by 6,7-dimethoxy-piperazine amides

7.2.5.2.2 Monoamine oxidase A inhibition

The trend manifested by the unsubstituted piperazine amides (see Table 7-12) was again seen in the 6,7-dimethoxy compounds (see Table 7-14). The halogenated phenyl piperazines were the better inhibitors of MAO-A, with the *m*-chloro compound **(190)** being better (65%) than the *para* equivalent **(191)** (36%), or the fluorinated compound **(192)** (5.9%). The piperonal piperazine amide **(193)** and dimer **(187)** were completely inactive against MAO-A.



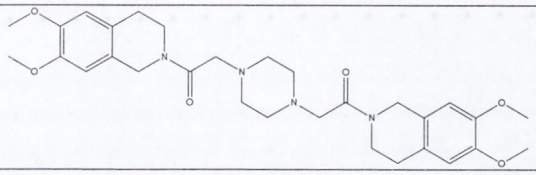
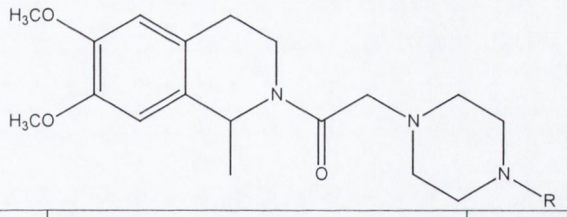
Compound Number	R=	% Inhibition
187		No inhibition
190	*m*-C_6H_4Cl	65.3+/-4.6
191	*p*-C_6H_4Cl	36.5+/-6.9
192	*p*-C_6H_4F	5.9+/-10.3
193	$CH_2C_6H_3(OCH_2O)$	No inhibition

Table 7-14: Monoamine oxidase A inhibition by 6,7-dimethoxy-piperazine amides

7.2.5.3 6,7-Dimethoxy-1-methyl-piperazine amides

7.2.5.3.1 Monoamine oxidase B inhibition

Some wry reflections were occasioned by the total lack of activity of the piperazine **(213)** and methyl piperazine **(214)** compounds against MAO-B in Table 7-15: they had cost some effort to make. It is scant consolation that the other methyl piperazine compounds are as inactive, with only the fluorophenyl product **(217)** showing inhibition of 21.7%.



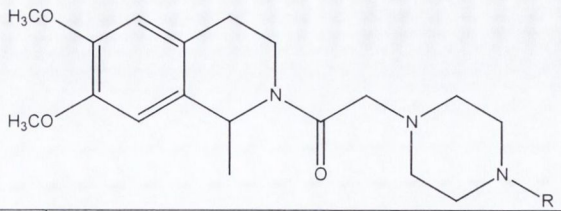
Compound Number	R=	% Inhibition
213	H	No inhibition
214	CH_3	No inhibition
215	*m*-C_6H_4Cl	No inhibition
216	*p*-C_6H_4Cl	No inhibition
217	*p*-C_6H_4F	21.7+/-5.2
218	$CH_2C_6H_3(OCH_2O)$	No inhibition

Table 7-15: Monoamine oxidase B inhibition of 6,7-dimethoxy1-methyl-piperazine amides

7.2.5.3.2 Monoamine oxidase A inhibition

The moderate activity of **(213)** and **(214)** against MAO-A (see Table 7-16) can hardly be counted compensation for the difficulties of their synthesis. The halogenated phenyl amides **(215)** and **(216)** showed good activity, with inhibition of 61.5% and 60.8% respectively. The fluoro piperazine **(217)** was less effective, just as it was in the other

piperazine series examined. The low activity of the piperonal piperazine amide **(218)** did not raise hopes that a dimer might have offered improved activity against MAO-A.



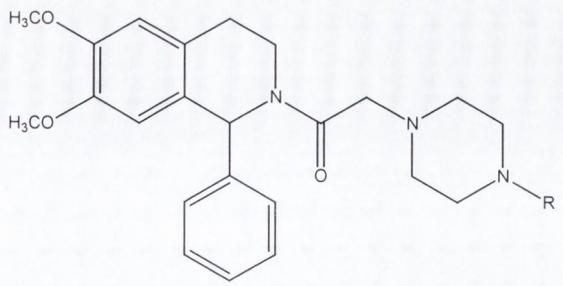
Compound Number	R=	% Inhibition
213	H	37.6+/-4.9
214	CH_3	38.4+/-8.4
215	*m*-C_6H_4Cl	61.5+/-3.7
216	*p*-C_6H_4Cl	60.8+/-4.3
217	*p*-C_6H_4F	27.6+/-4.5
218	$CH_2C_6H_3(OCH_2O)$	7.5+/-14.2

Table 7-16: Inhibition of monoamine oxidase A by 6,7-dimethoxy-1-methyl-piperazine amides

7.2.5.4 6,7-Dimethoxy-1-phenyl-piperazine amides

7.2.5.4.1 Monoamine oxidase B inhibition

Once again low rates of inhibition were seen with the halogenated pheny compounds (**199 - 201**) and the piperonal piperazine **(202)** (see Table 7-17). The inadvertent synthesis of the phenyl dimer **(196)** proved a lucky accident, as it caused 36.7% inhibition of monoamine oxidase B.



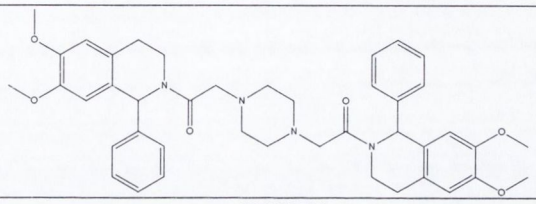
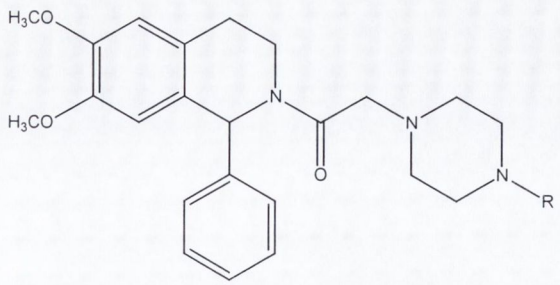
Compound Number	R=	% Inhibition
196		36.7+/-5.5
199	*m*-C_6H_4Cl	3.3+/-2.0
200	*p*-C_6H_4Cl	5.2+/-5.4
201	*p*-C_6H_4F	12.1+/-4.2
202	$CH_2C_6H_3(OCH_2O)$	1.5+/-4.2

Table 7-17: Monoamine oxidase B inhibition by 6,7-dimethoxy-1-phenyl-piperazine amides

7.2.5.4.2 Monoamine oxidase A inhibition

The dimer **(196)** did not display activity against MAO-A (see Table 7-18), but this is in keeping with the results seen with the other piperazine series. The aberrant negative result of the *meta*-chlorophenyl piperazine **(199)** is not in accord with all other series, and may be due to some problems with preparation of the sample. Unfortunately, time did not permit the assay to be revisited. Another surprise is the good activity of the piperonal piperazine compound **(202)**, at 50.5%. The other halogenated phenyl piperazines **(200)** and **(201)** display activity in the the expected range of 25 – 40%.



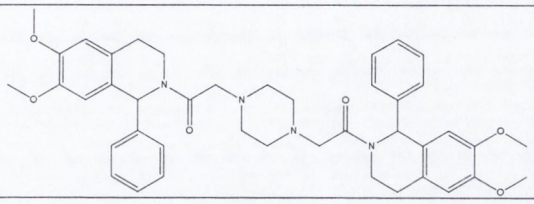
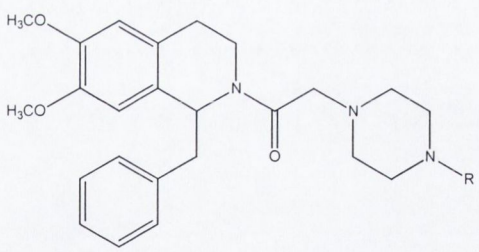
Compound Number	R=	% Inhibition
196		No inhibition
199	*m*-C_6H_4Cl	No inhibition
200	*p*-C_6H_4Cl	38.7+/-4.2
201	*p*-C_6H_4F	27.3+/-10.9
202	$CH_2C_6H_3(OCH_2O)$	50.5+/-7.4

Table 7-18: Monoamine oxidase A inhibition by 6,7-dimethoxy-1-phenyl-piperazine amides

7.2.5.5 1-Benzyl-6,7-dimethoxy-piperazine amides

7.2.5.5.1 Monoamine oxidase B inhibition

Table 7-19 shows the low activity of the benzyl series of piperazine amides against MAO-B. Only the fluoro **(209)** and piperonal **(210)** compounds show slight activity of 19.2% and 7.1% inhibition.

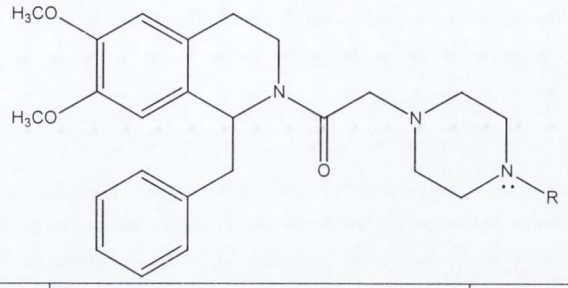


Compound Number	R=	% Inhibition
207	*m*-C_6H_4Cl	No inhibition
208	*p*-C_6H_4Cl	No inhibition
209	*p*-C_6H_4F	19.2+/-7.3
210	$CH_2C_6H_3(OCH_2O)$	7.1+/-3.1

Table 7-19: Inhibition of monoamine oxidase B by 1-benzyl-6,7-dimethoxy-piperazine amides

7.2.5.5.2 Monoamine oxidase A inhibition

All the compounds in the series are active against MAO-A (see Table 7-20). The fluorophenyl piperazine **(209)** is the most active of the halogenated compounds in this series, unlike the phenyl series (see Table 7-18). The piperonal piperazine **(210)** shows moderate inhibition of MAO-A.



Compound Number	R=	% Inhibition
207	*m*-C_6H_4Cl	41.9+/-6.6
208	*p*-C_6H_4Cl	16.8+/-6.1
209	*p*-C_6H_4F	56.1+/-2.1
210	$CH_2C_6H_3(OCH_2O)$	35.0+/-6.3

Table 7-20: Inhibition of monoamine oxidase A by 1-benzyl-6,7-dimethoxy-piperazine amides

7.2.6 Inhibitory activities of 7-methylsulfanyl-1,2,3,4-tetrahydroisoquinoline and (7-methylsulfanyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-phenyl-methanone

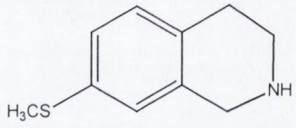
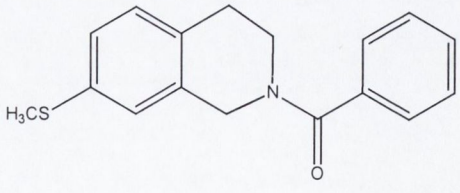
Compound Number	Compound	% Inhibition
327	 7-Methylsulfanyl-1,2,3,4-tetrahydro-isoquinoline	69.7+/-3.9
329	 (7-Methylsulfanyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-phenyl-methanone	2.9+/-16.1

Table 7-21: Monoamine oxidase B inhibition of thioalkyl compounds at 100 μM

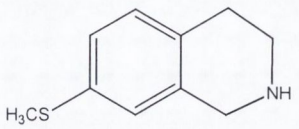
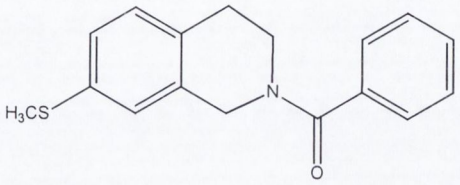
Compound Number	Compound	% Inhibition
327	 7-Methylsulfanyl-1,2,3,4-tetrahydro-isoquinoline	83.6+/-7.0
329	 (7-Methylsulfanyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-phenyl-methanone	77.5+/-12.2

Table 7-22: Inhibition of monoamine oxidase A of thioalkyl compounds at 100 μM

The results must be considered together (Tables 7-21 and 7-22). These show that a thioalkyl group at position 7 confers good activity against both monoamine oxidase A and monoamine oxidase B, but the subsequent addition of a benzoyl at position 2 drastically reduces the MAO-B inhibition.

7.2.7 Summary and conclusions of monoamine oxidase inhibitory activity displayed

In summary, substitution at position 7 with an amide function allowed for moderate MAO-B inhibition but superior MAO-A inhibition. The greatest activity against MAO-A in these series was achieved with the halogenated phenyl compounds **(28 – 31)** (see Table 7-2). This pattern was repeated amongst the position 2 amides. The *para* substituted halogenated benzoyl amides showed moderate activity against MAO-B (see Tables 7-3, 7-5, 7-7 and 7-9) and good to excellent inhibition of MAO-A (see Tables 7-6, 7-8, 7-10 and above all Table 7-4). Even the interposition of a piperazine ring did not abolish MAO-A inhibition, although it was in most cases lessened (see Tables 7-12, 7-14, 7-16, 7-18 and 7-20).

Thioether amides were the most active MAO-B inhibitors in several series (see Tables 7-3, 7-5 and 7-9). A phenyl substituent at position 1 abolished activity against MAO-B on the part of benzoylthioethers at position 2 (see Table 7-7), but the presence of a methyl or phenyl group at position 1 caused serious attenuation of MAO-B inhibition in all the

compounds investigated. A benzyl substituent at position 1 allowed activity to remain (see Table 7-5), although usually at lower levels than that seen with the unsubstituted amides. Substitution of the benzoyl ring in the *ortho* and *meta* positions, where the isoquinoline nucleus did **not** bear a substituent at position 1, did not favour activity against MAO-B; the generally inactive nature of the anisoyl compounds in all series (see Tables 7-5, 7-7 and 7-9) means general conclusions cannot be drawn for these.

The piperazine compounds demonstrated only moderate activity, but a promising feature was the selectivity of the dimers for MAO-B over MAO-A. None of the dimers showed any activity against MAO-A, but the unsubstituted dimer **(185)** and the phenyl dimer **(196)** showed inhibition rates of 42.9% and 36.7% respectively, of MAO-B.

After the long saga of its synthesis, it is fitting that the 7-methylsulfanyl amide **(329)** should show selectivity. Its predecessor, **(327)**, is a good inhibitor of both MAO-A and MAO-B (83.6% and 69.7% inhibition respectively) but the amide shows a decided preference for MAO-A. The inhibition of MAO-B by the amide is only 2.9%, while it shows a rate of 77.5% inhibition of MAO-A.

7.3 Phenoxyacetyltetrahydroisoquinolines

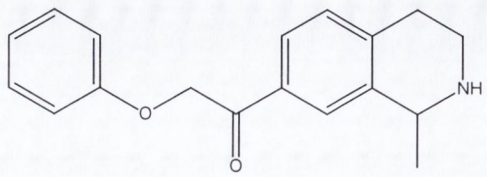
7.3.1 Background

It was noted in Chapter 1 that acetylcholinesterase inhibitors are currently used to relieve the symptoms of Alzheimer's disease. They improve cognitive function and boost memory function for several months. MAO-B inhibitors have also been suggested, as clinical agents, due to neuroprotective effects displayed in models of Parkinson-like syndromes and the presence of elevated levels of MAO-B in the platelets of sufferers from Alzheimer's disease. An agent combining inhibition of AChE and MAO-B would be of interest for alleviating the symptoms of the illness, and maybe somewhat delaying its progress.

Compound **(219)** was previously investigated in this research group in the course of work by Dr. Mary Breen.[59] It showed 77% inhibition of AChE, 89% inhibition of MAO-B and just 49% inhibition of MAO-A in assays at 100μM. Compound **(219)** was therefore taken as a model and a series of phenoxyacetytetrahydroisoquinolines modified at position 1 of the isoquinoline and the *para* position of the phenoxy ring were synthesised and tested for MAO-B, MAO-A and AChE inhibition. Discovery of an agent showing high AChE inhibition and selective, pronounced inhibition of MAO-B was the objective.

The MAO assays were as outlined in 7.2.1 above; experimental details are given in Chapter 8. The AChE assay was a microplate assay developed by Rhee et al.[146] from a

method originally described by Ellman et al.[147] Full details of the procedure employed may be found in Chapter 8 (Section 8.2).

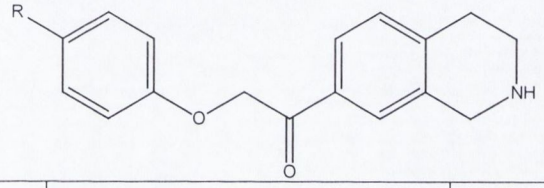


1-Methyl-7-(phenoxyacetyl)-1,2,3,4-tetrahydroisoquinoline

Figure 7-2: Acetylcholinesterase inhibitor with preference for MAO-B over MAO-A

7.3.2 Phenoxyacetyltetrahydroisoquinolines

7.3.2.1 Monoamine oxidase B inhibition



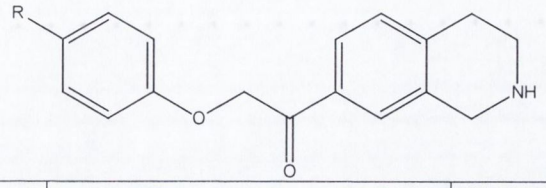
Compound Number	R=	% Inhibition
255	CH_3	81.4+/-2.3
256	OCH_3	58.1+/-6.7
257	OC_2H_5	60.2+/-3.5
258	F	94.2+/-1.5
259	Cl	82.3+/-1.7
260	Br	93.2+/-0.5
261	I	92.4+/-1.7
262	$NHCOCH_3$	67.2+/-2.5
263	NO_2	78.8+/-1.8
264	CN	71.3+/-0.4
265	$OCH_2C_6H_5$	81.5+/-1.5
266	$COOCH_2C_6H_5$	83.7+/-2.4
219	H	89.0+/-1

Table 7-23: Monoamine oxidase B inhibition by phenoxyacetyltetrahydroisoquinolines at 100 μM

These compounds demonstrated excellent activity against MAO-B (see Table 7-23). As expected, the halogenated compounds showed superior activity, ranging from 82.3% for the chlorinated compound **(259)** to 94.2% for the fluorinated product **(258)**. The 4-F, 4-Br and 4-I compounds **(258, 260, 261)** were more active than the parent compound **(219)** (see Section 7.3.1 above). The lowest rate of inhibition was a respectable 58.1% for the methoxy product **(256)**, while the benzyl ester **(266)**, the benzyl ether **(265)** and the methylated compound **(255)** were the best of the non-halogenated compounds.

7.3.2.2 Monoamine oxidase A inhibition

The activity against MAO-A was also higher than for the parent compound (see Table 7-24)! The exception to this was the cyano compound **(264)**, which only showed 32.5% inhibition for MAO-A, compared to 71.3% inhibition of MAO-B at the same concentration. Good inhibition of MAO-A on the part of the halogenated compounds was as expected from scrutiny of previous results.

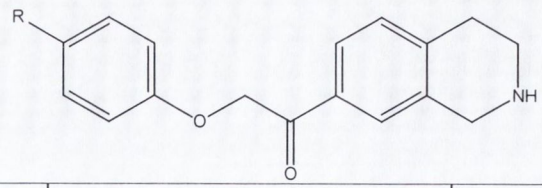


Compound Number	R=	% Inhibition
255	CH_3	55.9+/-2.0
256	OCH_3	57.6+/-4.1
257	OC_2H_5	61.5+/-1.6
258	F	72.6+/-5.9
259	Cl	62.5+/-6.3
260	Br	57.5+/-7.9
261	I	77.8+/-4.6
262	$NHCOCH_3$	75.3+/-2.2
263	NO_2	76.1+/-2.7
264	CN	32.5+/-7.3
265	$OCH_2C_6H_5$	75.1+/-3.2
266	$COOCH_2C_6H_5$	62.7+/-2.8
219	H	49.0+/-5

Table 7-24: Monoamine oxidase A inhibition by phenoxyacetyltetrahydroisoquinolines at 100 μM

7.3.2.3 Acetylcholinesterase inhibition

Unfortunately, the cyano compound **(264)** was the least active acetylcholinesterase inhibitor, at only 25.4% inhibition. The best compound in this regard was the benzyl ether **(265)**, with 66.0% inhibition (see Table 7-25). Even this is unimpressive beside the 77% inhibition obtained with the parent compound **(219)**.

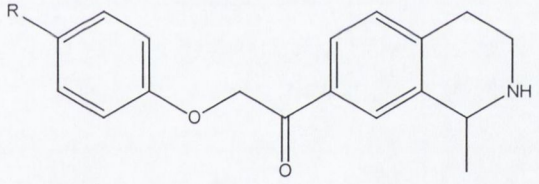


Compound Number	R	% Inhibition
255	CH_3	41.1+/-4.9
256	OCH_3	37.6+/-3.6
257	OC_2H_5	44.8+/-1.4
258	F	37.9+/-1.9
259	Cl	39.2+/-2.8
260	Br	55.0+/-1.6
261	I	47.4+/-2.2
263	NO_2	33.2+/-2.3
264	CN	25.4+/-2.7
265	$OCH_2C_6H_5$	66.0+/-6.6
266	$COOCH_2C_6H_5$	26.1+/-3.0
219	H	77+/-5

Table 7-25: Acetylcholinesterase inhibition by phenoxyacetyltetrahydroisoquinolines at 100 μM

7.3.3 1-Methylphenoxyacetyltetrahydroisoquinolines

7.3.3.1 Monoamine oxidase B inhibition



Compound Number	R=	% Inhibition
267	CH_3	54.3+/-7.1
268	OCH_3	17.9+/-0.8
269	OC_2H_5	23.1+/-7.9
270	F	82.7+/-2.2
271	Cl	80.7+/-3.2
272	Br	77.0+/-0.4
273	I	66.2+/-3.0
274	$NHCOCH_3$	48.0+/-9.3
275	NO_2	62.9+/-6.7
276	CN	48.9+/-1.0
277	$OCH_2C_6H_5$	28.6+/-9.4
278	COOH	53.6+/-3.0

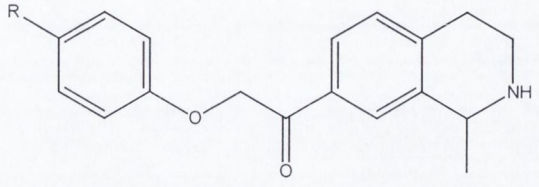
Table 7-26: Monoamine oxidase B inhibition by methylphenoxyacetyltetrahydroisoquinolines at 100 μM

The addition of a methyl substituent at position 1 lowered the MAO-B inhibition of all the compounds (see Table 7-26). This is in keeping with what was seen in the series of

position 2 amides. The benzyl ether compound **(277)** gave a very disappointing rate of just 28.6% inhibition. The best inhibitors were the halogenated compounds, but these were unlikely to be selective for MAO-B over MAO-A.

7.3.3.2 Monoamine oxidase A inhibition

The halogenated compounds (**270 - 273**) did indeed prove to be effective MAO-A inhibitors (illustrated by Table 7-27). The amide compound **(274)** reversed the trend, showing itself to be selective for MAO-A over MAO-B! The nitrated compound **(275)** was twice as active against MAO-B as against MAO-A and seemed the best of the series.

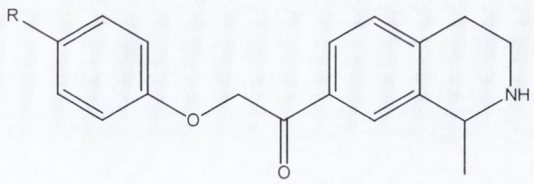


Compound Number	R=	% Inhibition
267	CH_3	48.1+/-9.5
268	OCH_3	52.5+/-2.1
269	OC_2H_5	46.9+/-9.9
270	F	64.3+/-8.9
271	Cl	76.4+/-5.2
272	Br	71.0+/-4.3
273	I	74.9+/-6.0
274	$NHCOCH_3$	83.9+/-1.3
275	NO_2	31.0+/-9.8
276	CN	48.8+/-2.2
277	$OCH_2C_6H_5$	50.2+/-4.5
278	COOH	56.2+/-7.5

Table 7-27: Monoamine oxidase A inhibition by methylphenoxyacetyltetrahydroisoquinolines at 100 μM

7.3.4 Acetylcholinesterase inhibition

The methyl series compounds were usually more active than the unsubstituted series against acetylcholinesterase (compare Tables 7-25 and 7-28). The hydrolysis of the benzyl ester group to give an acid abolished activity altogether (see compound **(278)**). The benzyl ether compound **(277)** was the most active inhibitor of acetylcholinesterase at 66.8%, but its poor activity against MAO-B is a clear disadvantage. The moderate activity of the nitro compound **(275)** of 42.7% is the best result, when viewed in conjunction with its preference for MAO-B rather than MAO-A.



Compound Number	R2	% Inhibition
267	CH_3	55.5+/-1.5
268	OCH_3	64.3+/-2.3
269	OC_2H_5	47.8+/-1.1
270	F	46.4+/-1.2
271	Cl	42.1+/-1.0
272	Br	44.5+/-1.8
273	I	45.4+/-3.9
274	$NHCOCH_3$	41.6+/-1.3
275	NO_2	42.7+/-3.3
276	CN	32.9+/-1.5
277	$OCH_2C_6H_5$	66.8+/-1.7
278	COOH	No inhibition

Table 7-28: Acetylcholinesterase inhibition by methylphenoxyacetyltetrahydroisoquinolines at 100 μM

7.3.5 Phenoxyacetyltetrahydroisoquinoline piperazine amide

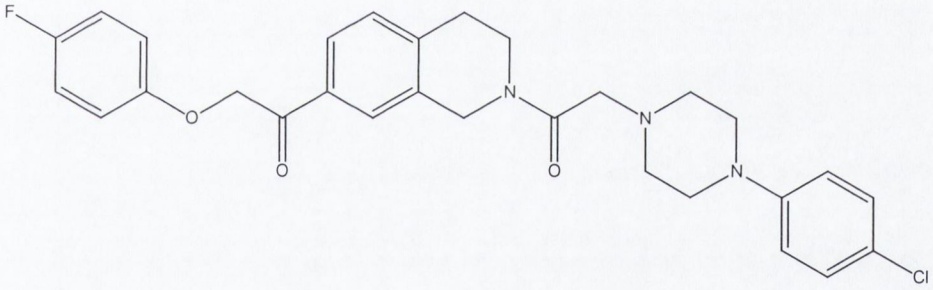


Figure 7-3: 7-Fluorophenoxy-4-chlorophenylpiperazine compound, 280

Assay	% Inhibition
MAO-B	59.3+/-4.3
MAO-A	69.4+/-4.5
Acetylcholinesterase	65.7+/-1.7

Table 7-29: Assay results for phenoxyacetyltetrahydroisoquinoline piperazine amide at 100 μM

The compound **(280)** was a good inhibitor of AChE, but showed a preference for MAO-A over MAO-B.

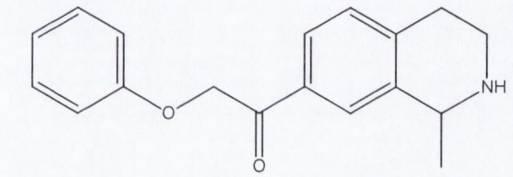
7.3.6 Summary and conclusions on activity profile of 7-phenoxyacetyltetrahydroisoquinolines

The objective of the investigation of phenoxyacetyltetrahydroisoquinolines was to find AChE/MAO-B inhibitors with reduced affinity for MAO-A. It appears that introducing a

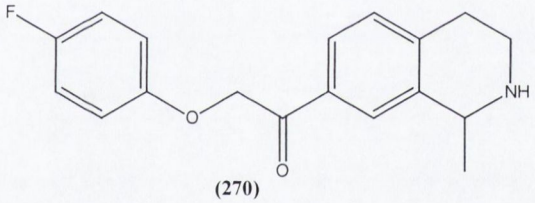
methyl group at position 1 retards MAO-B inhibition by about 20% while it boosts AChE inhibition circa 10%. An acid function abolished AChE inhibition altogether and must be avoided. The best candidate for further scrutiny is compound **275**, the nitro of the 1-methyl series, combining moderate AChE inhibition (42.7%), good MAO-B inhibition (62.9%) and poor activity against MAO-A (31.0%).

7.4 Structure Activity Relationships

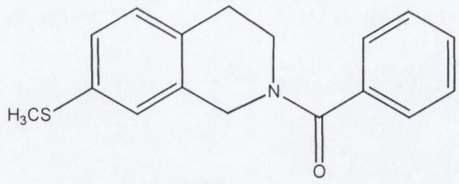
Several of the more interesting compounds tested were examined using molecular modelling tools. This work was carried out by Andrew Knox, a postgraduate student in this research group. This offered an explanation of the trends observed. The original phenoxyacetyltetrahydroisoquinoline **(219),** which had provided the target for combined MAO-B and AChE inhibitors, was used as a benchmark. Its binding with MAO-B and MAO-A were modelled. The three compounds examined **(219), (270)** and **(329)** are shown in Figure 7-4.



(219)



(270)



(329)

Figure 7-4: Ligands displayed in molecular modelling pictures Figure 7-5 to 7-9

It was noted in Chapter 1 that elucidation of the crystal structure of MAO-B by Binda et al. revealed it to have two pockets, which could fuse to accommodate a large substrate or inhibitor.[31] The first illustration (Figure 7-5) shows isoleucine 199 of MAO-B, and how it acts as a gate between the entrance cavity and the active site. Ile 199 is lowered when isatin binds, as the compact molecule can be accommodated within the active site. 1,4-Diphenyl-2-butene is a larger compound, and the residue rotates upward, thus allowing the inhibitor to extend into the entrance cavity. The second illustration (Figure 7-6) shows the

two pockets identified as separate spaces by the SiteID programme: one is outlined by red stars, the other by orange stars.

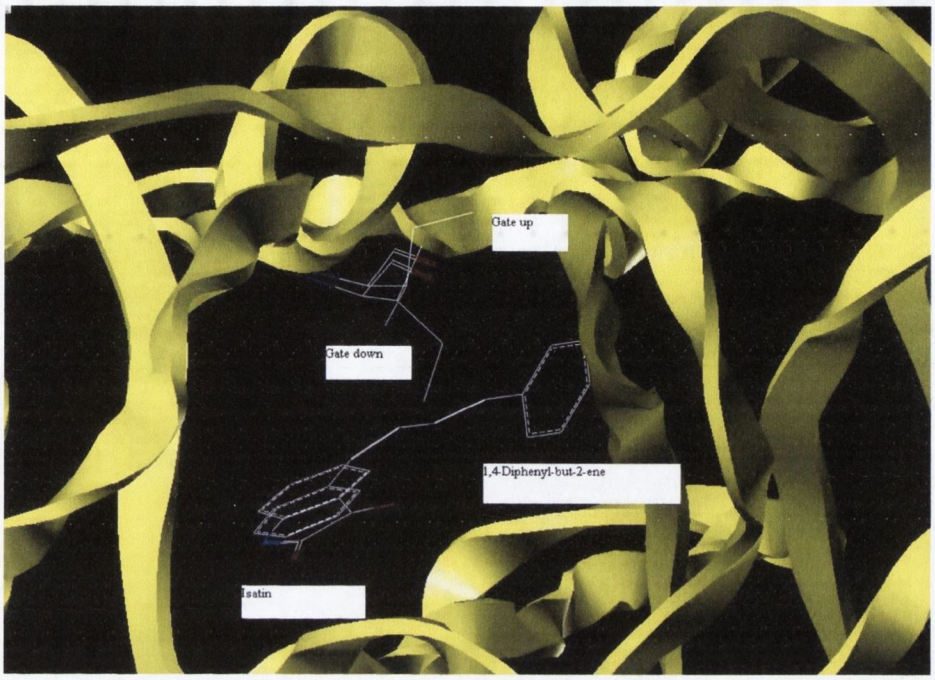


Figure 7-5: Isoleucine 199 acts as a gate between the substrate and entrance cavities in MAO-B.

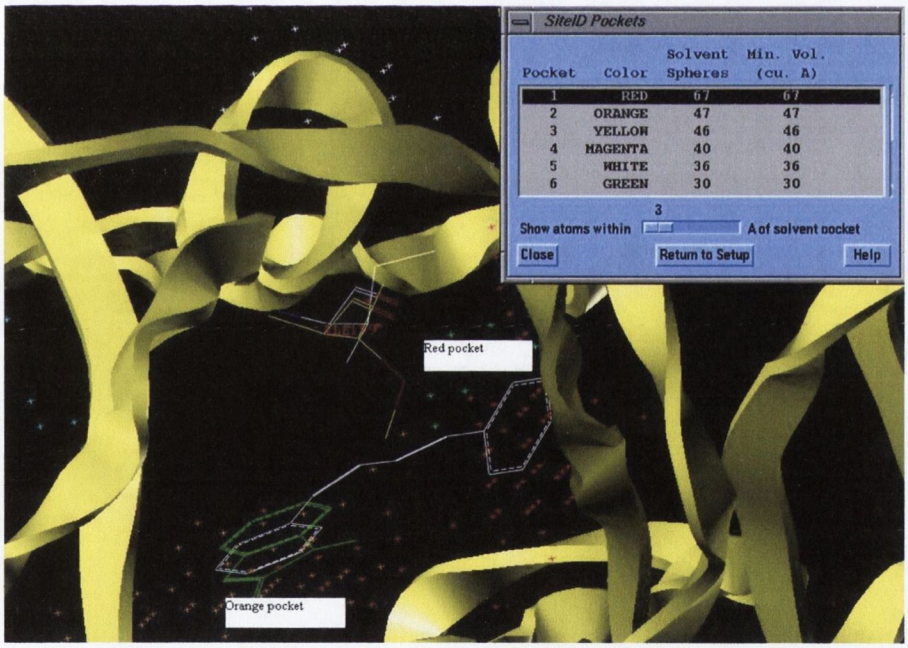


Figure 7-6: SiteID finds two pockets in MAO-B, shown by red stars and orange stars

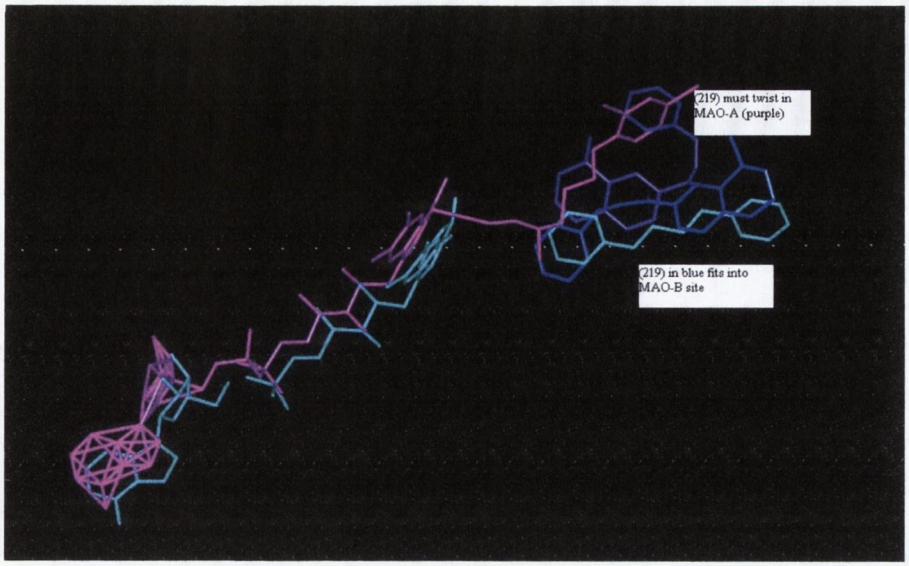


Figure 7-7: Compound (219) docks easily in MAO-B (shown in blue) but must twist to dock in MAO-A (shown in purple)

Compound **(219)** was docked in both the MAO-A and MAO-B active sites. It assumed a normal conformation in MAO-B, but was forced into a twisted conformation in MAO-A. This does not favour binding at MAO-A (see Figure 7-7).

The next picture (Figure 7-8) shows that docking **(270)** in MAO-A is obstructed by phenylalanine 208. The cyan conformation illustrates this point. The blue version of **(270)** shows it docked in MAO-B. The Ile 199 gate rotates upwards and provides little obstruction to the phenoxyacetyltetrahydroisoquinoline. In MAO-A the compound must assume a twisted conformation, and this high energy conformation militates against its binding. It faces a lesser obstacle in MAO-B.



Figure 7-8: Docking of (270) obstructed in MAO-A by phenylalanine residue, shown in cyan. Blue is the MAO-B docking conformation.

The selectivity of the thiomethylbenzoyl compound **(329)** is explained by the formation of a hydrogen bond between a substituent at position 2 and the aromatic residue Phe 208 (see

Figure 7-8), which would be expected to obstruct its binding. This hydrogen bond compensates for any energy cost in assuming a twisted conformation.

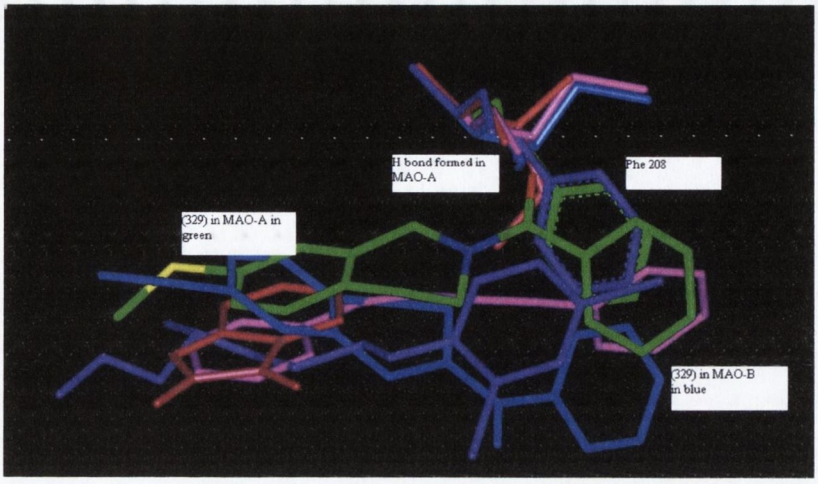


Figure 7-9: Formation of a hydrogen bond by benzoyl (329) compensates for twisted conformation

7.5 Future Work

Three strands emerge from the preceding discussions in 7.2.7 and 7.3.6. The first is that thioether groups seem to confer activity on tetrahydroisoquinline compounds, especially if added at position 7. The second is that the bulky sidegroups of the piperazine dimers abolished MAO-A activity. The final conclusion is that the modification of the phenoxyacetyltetrahydroisoquinolines, while possibly improving MAO-B inhibition, did not produce an agent clearly superior to the model compound **219** in term of selectivity for MAO-B rather than MAO-A, but yielded more information about MAO-A/MAO-B selectivity.

From the results obtained with **(329)**, further exploration of isquinolines containing thioether functions seems justified. It would be interesting to examine MAO inhibition by thioalkyl dihydroisoquinolines. The Enhanced Microwave Synthesis approach, which improved yields of the 1-methyl-3,4-dihydroisoquinoline so dramatically, might allow facile cyclisation of acetonitrile and the chloroalkyl-thioanisole compound: it allows for energy transfer at low temperatures, and the cyclisation might occur without desulfuration. The benzoyl amide **(329)** could be taken as a model of a MAO-A selective inhibitor and molecular modelling used to examine the effectiveness of other substituents at this position. The most promising candidates from the modelling studies could then be synthesised and evaluated.

The piperazine dimers **(185), (187)** and **(196)** may merit further investigation. Initially, the compounds could be assayed for AChE inhibition, as they are clearly selective for MAO-B. Modelling might be used to explore if introduction of a substituent at position 7 of the reactant nucleus would confer improved MAO-B inhibition on the final product. These

compounds are readily prepared. Once the isoquinoline has been synthesised the production of the dimer requires only one further synthetic step.

As for the combined AChE/MAO-B project, there is encouragement to be had from the phenoxyacetyltetrahydroisoquinoline piperazine amide **(280)**. Its bulk did not prevent it showing good activity against AChE (65.7%). The main drawback was high activity against MAO-A (69.4%). It is clear that halogen substituents favour MAO-A activity, so synthesis of an analogue with an alternative group at the *para* position, or no substituent there at all, would seem indicated. Introduction of a methyl substituent at position 1 of the tetrahydroisoquinoline nucleus in such a molecule might boost AChE inhibition further, while an amide sidechain with a piperazine ring at position 2 could abolish MAO-A inhibition altogether, leaving only AChE and MAO-B inhibition.

8 Biochemical Protocols

8.1 Monoamine Oxidase Inhibition

8.1.1 Mitochondrial Preparation

Rat liver mitochondria were the source of monoamine oxidase used in the radiochemical assay of the purported inhibitors produced. Male rats of approximately 250g were sacrificed by cervical dislocation. The liver was then removed and finely chopped in chilled sucrose-TRIS-EGTA buffer pH7.4. This buffer was composed of 250mM sucrose, 5mM TRIS (or *tris*(N-hydroxymethyl)aminomethane) and 1mM EGTA (ethylene glycol-*bis*(aminoethylether)N,N,N',N'-tetraacetic acid). The chopped liver was washed 5 to 6 times with fresh cold buffer to remove blood. It was then homogenised in a Thomas homogeniser, using five passes with a "loose" 0.026" clearance pestle and then five passes of a "tight" 0.012" clearance pestle. The homogenate was evenly divided by weight between two centrifuge tubes, and the weights were adjusted to +/-0.01g on an electronic balance. The homogenate was then centrifuged in a cool (4°C) Sorvall RC5C centrifuge using an SS34 rotor at 3,000 rpm for 3 minutes. The supernatant was decanted into fresh centrifuge tubes and again weighed to balance before centrifugation at 10,000 rpm for 10 minutes at 4°C. The supernatant was discarded and the pellet was suspended in sucrose-TRIS-EGTA buffer and again homogenised using the 0.012" clearance pestle. The homogenate was centrifuged at 10,000 rpm for 10 minutes. The homogenisation and centrifugation were repeated at least twice more. Finally, the mitochondria were suspended in 0.1M phosphate buffer pH7.4 and the protein concentration was determined by Biuret protein assay.

8.1.2 Biuret Protein Assay

Biuret reagent was prepared by dissolving cupric sulfate (1.5g) and sodium potassium tartrate (6.0g) in about 500mL distilled water. Sodium hydroxide solution (10%) was made up and 300mL of the cooled solution was added to the cupric solution. The blue solution was transferred to a 1L volumetric flask and made up to 1L using distilled water. A protein standard of 50mg/mL bovine serum albumin (BSA) in distilled water was prepared (see Table 8-1). Finally, 1.5% sodium deoxycholate in distilled water was prepared.

A standard curve was created by following the protocol indicated by the table and reading the absorbance at 540nm after 30 minutes in a spectrophotometer. Protein reacts with the Biuret reagent in the presence of sodium deoxycholate to give a blue colour, which increases in intensity in proportion to the concentration of protein present.

	Blank	0.25mg/5mL	0.5mg/5mL	0.75mg/mL	1.0mg/5mL	1.5mg/5mL	2.0mg/5mL
BSA 50mg/mL		5μL	10μL	15μL	20μL	30μL	40μL
Sodium deoxycholate	100μL	100μL	100μL	100μL	100μL	100μL	100μL
Distilled water	900μL	895μL	890μL	885μL	880μL	870μL	860μL
Biuret Reagent	4mL	4mL	4mL	4mL	4mL	4mL	4mL

Table 8-1: Protocol for preparation of bovine serum albumin standard curve

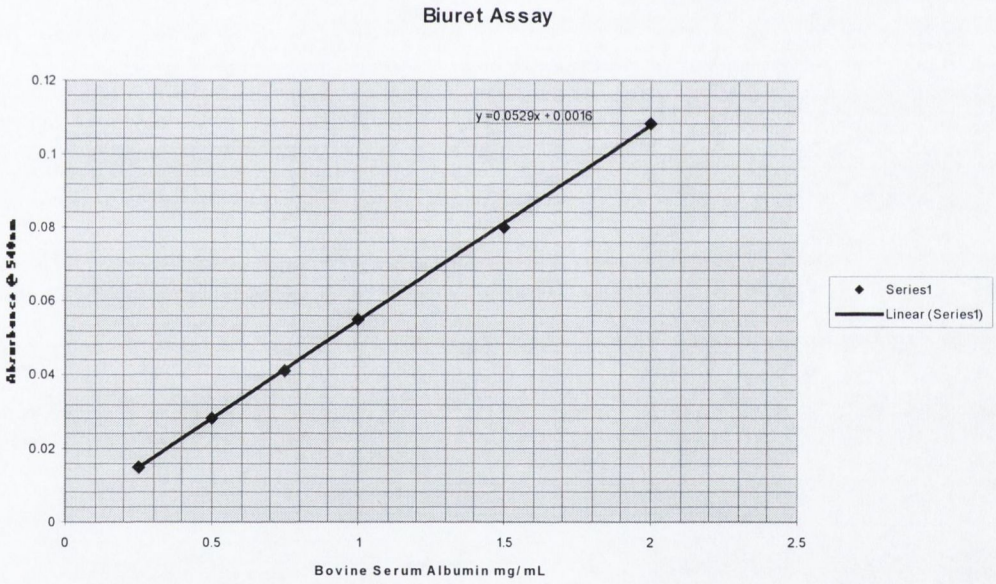


Figure 8-1: Protein concentration curve

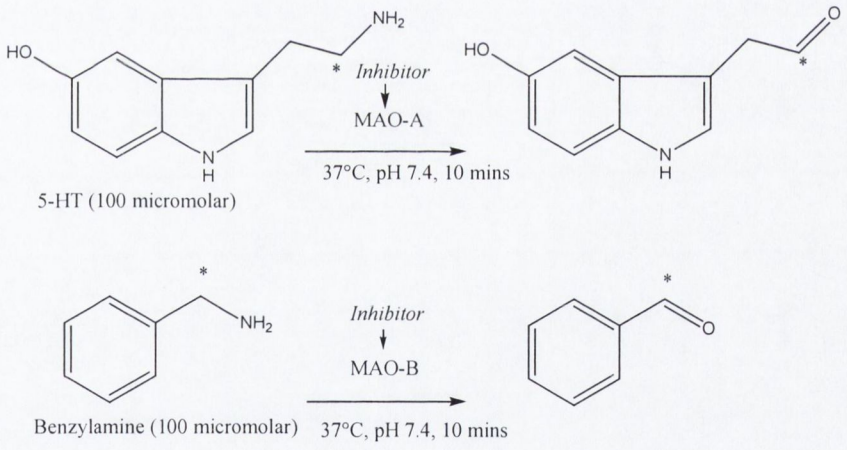
Every time mitochondria were prepared the protein content was found. A blank was prepared, as in the standard curve, with 100μL sodium deoxycholate solution, 900μL distilled water and 4mL Biuret reagent. Samples of 20μL mitochondria, 100μL sodium deoxycholate solution, 880μL distilled water and 4mL Biuret reagent were also prepared in triplicate and after 30 minutes at room temperature the absorbance

reading at 540nm was determined. The protein concentration of the mitochondria was found using the equation of the standard curve (Figure 8-1) and the mitochondria were diluted with sodium phosphate buffer pH7.4 to give 1.5mL aliquots of 10mg protein per mL.

8.1.3 Radiochemical Determination of Monoamine Oxidase Activity by Solvent Extraction

8.1.3.1 Time Course of Assay

The basis of the assay is the measurement of the concentration of radio labelled aldehyde produced by the action of monoamine oxidase on the substrate (see Scheme 8-1). The oxidation is linear in its initial stages, but then reaches a maximum and tails off, as the substrate concentration is reduced and the reaction approaches equilibrium. It is important that a biochemical assay be carried out in the initial linear phase of the reaction.



Scheme 8-1: Radiochemical assays of MAO-A and MAO-B

Time course reactions were therefore carried out with both 5-hydroxytryptamine and benzylamine, to determine the time spans over which the reaction remained linear. 21 vials containing 175μL potassium dihydrogen phosphate buffer pH7.4 and 25μL mitochondria were prepared. Citric acid 2M (100μL) was added to three vials prior to incubation in the shaking waterbath at 37°C and these served as blanks. The appropriate substrate was added to all vials (25μL) and 100μL citric acid 2M was added at 5-minute intervals to successive trios of vials. The vial contents were

extracted with scintillation fluid consisting of 1:1 ethyl acetate: toluene and 0.6% diphenyloxazole and then frozen at -80°C for 40 minutes. The organic portion was then decanted into fresh scintillation vials, capped, labelled and read in a Tricarb 2100 scintillation counter.

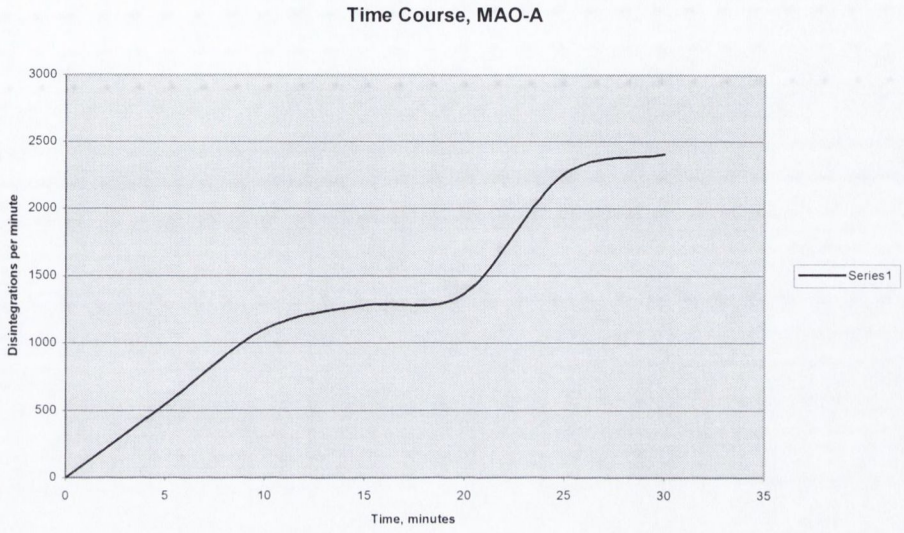


Figure 8-2: Time course for MAO-A (5-HT)

From the resulting time course curves (Figures 8-3 and 8-4), it could be seen that the oxidation of 5-hydroxytryptamine by monoamine oxidase was linear over the initial 15 minutes and that of benzylamine over a similar period. It was decided to stop the reaction during the assays, using citric acid, after 10 minutes. The citric acid lowers the pH, leaving any unoxidised amine with a positive charge so it remains in the aqueous portion. The uncharged aldehyde only is extracted into the organic scintillation fluid.

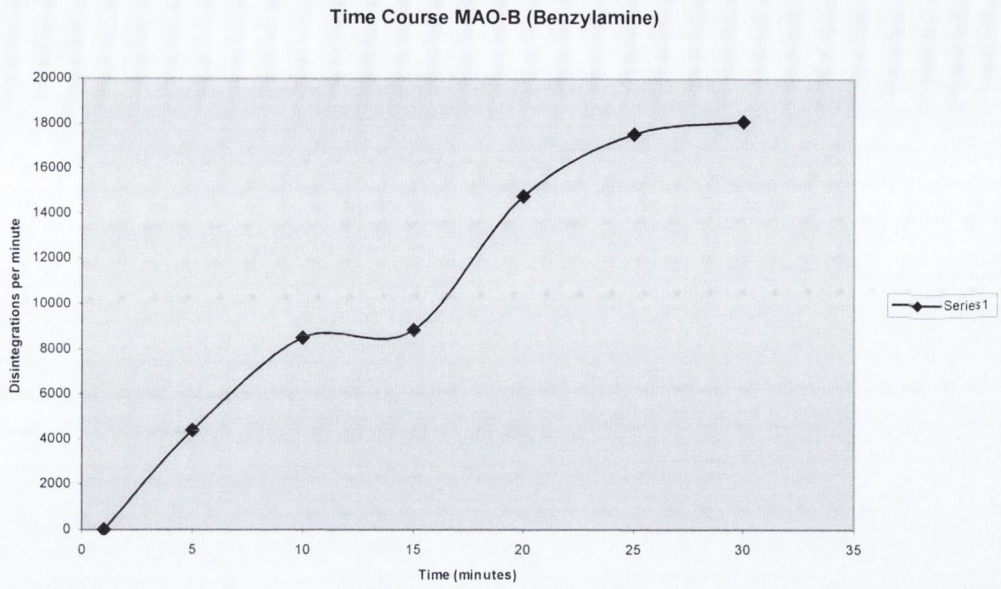


Figure 8-3: Time course of MAO-B (benzylamine)

8.1.3.2 Assay

Assays were carried out in 5mL plastic scintillation vials. This allowed the final aqueous assay volume of 325μL to accommodate 4mL of scintillation fluid, which was added to extract the deaminated aldehyde produced by monoamine oxidase action on substrates.

	Blank	Control	Assay
Phosphate buffer pH7.4	175μL	165μL	165μL
Substrate	25μL	25μL	25μL
Inhibitor 2.25mM			10μL
Mitochondria	25μL	25μL	25μL
Ethanol solution		10μL	
Citric Acid 2M	100μL	100μL	100μL

Table 8-2: Protocol for monoamine oxidase inhibition assay

All components, except the substrate, were added to the vials containing blank, as shown in Table 8-2; all save the citric acid and substrate were added to the remaining vials. The vials were equilibrated in the waterbath at 37°C for 5 minutes and then the substrate was added.

In order to test inhibition of MAO-A 5-hydroxy tryptamine creatinine sulfate with a radiolabelled ^{14}C sidechain was used. This was prepared in potassium dihydrogen

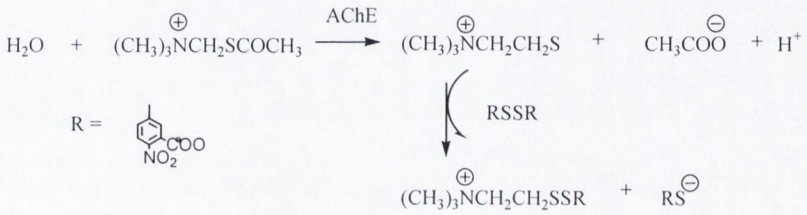
phosphate buffer pH7.4 as a 900μM solution, to give a specific activity of 0.6μCi/mol in the assay mixture.

Similarly, radio labelled benzylamine was used as a substrate for MAO-B. This was prepared to give a specific activity of 0.6μCi/mol in the assay mixture

After 10 minutes, citric acid was added to all vials besides the blanks, to stop the reaction and allow the aldehyde only to be extracted by the 4mL scintillation fluid. The vials were capped and left at -80°C for 40 minutes. This froze the aqueous portion, so only the organic phase was decanted into fresh vials, which were capped and read in the scintillation counter.

8.2 Acetylcholinesterase Inhibition

8.2.1 Acetylcholinesterase Assay



Scheme 8-2: Acetylcholinesterase assay

The basis of this assay is the measurement at 405nm of the absorbance of the yellow anion created by the reaction of thiocholine and dithio*bis*nitrobenzoate (DTNB). The substrate was 15mM acetylthiocholine iodide, which was cleaved by electric eel AChE to release thiocholine. This reacted with dithio*bis*nitrobenzoate to give a yellow anion, which was measured at 405nm. The rate of hydrolysis in the absence of inhibitor was taken as 100% and the % inhibition was calculated as 100 less the % activity observed in the presence of inhibitor.

	Blank	Control	Assay
Phosphate buffer pH8.0	150μL	140μL	140μL
Inhibitor 2.25mM			10μL
Solvent		10μL	
Distilled Water	25μL		
AChE solution, 0.22U/Ml		25μL	25μL
DTNB, 15Mm	25μL	25μL	25μL
Acetylthiocholine iodide, 15mM	25μL	25μL	25μL

Table 8-3: Protocol for acetylcholinesterase assay

A microplate array was used to test a larger number of compounds quickly. Table 8-3 indicates the contents of each column of wells. The phosphate buffer, inhibitor, solvent and water or enzyme solution were added initially and the enzyme was incubated for 5 minutes at room temperature with the inhibitor before the DTNB and acetylcholinesterase were added (see Table 8-3). The reaction was allowed to run for 5 minutes at room temperature and the absorbance was then read using an Anthos HT2 microplate reader.

The uv absorbance at 405nm was read using a kinetic measurement programme. This pools the data from 8 measurements of the absorbance over all 96 wells at 13 second intervals and calculates a slope, which is given as the output for the well. A reference filter was not used. The reader shook the plate for 1 second between readings. The optical density range was set to 200mOD and the reaction was known to be an increasing reaction. The results were processed using an Excel spreadsheet.

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Experimental note.

Uncorrected melting points were measured on a Gallenkamp apparatus. IR spectra were recorded on a Perkin Elmer FT-IR Paragon 100 spectrometer. Band positions are given in cm^{-1}. Solid samples were analysed by KBr disc, oils were analysed as neat films on NaCl plates. ^{1}H, ^{13}C, ^{19}F nuclear magnetic resonance (NMR) spectra were recorded at 20°C on a Brucker DPX 400 spectrometer (400.13MHz, ^{1}H; 100.61MHz, ^{13}C;,376.47MHz, ^{19}F) in either $CDCl_3$ (internal standard trimethyl silane) or CD_3OD. For $CDCl_3$, ^{1}H-NMR spectra were assigned relative to the TMS peak at 0.00 δ and ^{13}C-NMR spectra were assigned relative to the centre peak of the $CDCl_3$ triplet at 77.0 ppm. ^{19}F spectra were not calibrated. Coupling constants are reported in Hertz. For ^{1}H-NMR assignments, chemical shifts are reported: shift value (description of absorption, coupling constant(s) (where applicable), proton assignment). Compounds bearing an *N*-trifluoroacetyl moiety are represented in their respective ^{1}H, ^{13}C and ^{19}F-NMR spectra as two sets of signals (where observable) due to the presence of rotamers. The major rotamer is denoted (m), the minor as (s).

High resolution molecular ion determinations (HRMS) were aquired on a Micro mass spectrometer (EI mode) at the Department of Chemistry, Trinity College Dublin. All anhydrous solvents were prepared according to literature methods

For the generation of HCl salts the amine free base was dissolved in anhydrous diethyl ether, through which was bubbled HCl gas. The solid precipitating from solution was collected and recystallised from ethanol.

7-Nitro-1,2,3,4-tetrahydroisoquinolines

7-Nitro-1,2,3,4-tetrahydroisoquinoline (2)[1]

5mL/5.32g/40mmol 1,2,3,4-tetrahydroisoquinoline was dissolved in 30mL concentrated sulphuric acid, with cooling. 4.442g/44mmol potassium nitrate was added in portions. After standing overnight the mixture was poured onto ice, made alkaline and extracted with chloroform. The extract was dried, filtered and the solvent removed *in vacuo* to give brown oil, which was dissolved in ethanol and treated with concentrated hydrochloric acid to give the hydrochloride salt of 7-nitro-1,2,3,4-tetrahydroisoquinoline. The parameters were varied in accordance with the appended study, in an effort to both boost yield and to attain greater insight into the reaction (see Chapter 2, Section 2.3). The spectroscopic data refers to the base.

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.94 (1H, s, NH); 2.86 (2H, t, J = 5Hz, C4H_2); 3.14 (2H, T. J = 5Hz, C3H_2); 4.05 (2H, s, C1H_2); 7.19 – 7.22 (1H, d, J = 8.6Hz, C5H); 7.85 (1H, s, C8H); 7.91 – 7.93 (1H, m, C6H)

^{13}C-NMR (101MHz): PPM ($CDCl_3$); 29.3 (C4H_2); 43.0 (C3H_2); 48.0 (C1H_2); 120.8, 121.2 (C6H, C8H); 130.0 (C5H); 137.2 (C8a); 142.8 (C4a); 145.8 (C7NO_2)

Yield: 66%

IRν_{max}(KBr): 1348cm^{-1}(NO_2), 1519cm^{-1} (NO_2), 2254cm^{-1}(CH stretching), 2933cm^{-1} (CH stretching)

Melting point: 261°C (HCl)[1]

1-(7-Nitro-3,4-dihydro-*1H*-isoquinolin-2-yl)-ethanone (4)[2]

5.038g/23.5mmol of the hydrochloride salt was acetylated by heating for 3 hours on a water bath with 1.928g/23.5mmol of anhydrous sodium acetate and 18mL/19.44g/190mmol acetic anhydride. After cooling, the mixture was made alkaline with 15%w/v NaOH solution and extracted with dichloromethane. The extract was washed with water four times to remove anhydride, then dried and filtered. The remaining solvent was removed by the rotary evaporator, using toluene to form an azeotrope of remaining acetic anhydride. The solid which formed was recrystallised from ethyl acetate.

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.17 (3H, s, COCH_3); 2.92 (0.8H, s, C4H_2 (s)), 3.00 (1.2H, t, J = 5.7Hz, C4H_2 (m)); 3.72 (1.2H, t, J = 5.7Hz, C3H_2 (m)), 3.84 (0.8H, s, C3H_2 (s)); 4.71 (0.8H, s, C1H_2 (s)), 4.79 (1.2H, s, C1H_2 (m)); 7.28 – 7.32 (1H, m, C5H); 7.97 – 7.99 (2H, m, C6H, C8H)

^{13}C-NMR (101MHz): PPM ($CDCl_3$); 21.3 (CH_3 (m)); 21.7 (CH_3 (s)); 28.6 (C4H_2 (s)), 29.5 (C4H_2 (m)); 38.6 (C3H_2 (s)); 43.1 (C1H_2 (m)); 43.6 (C3H_2 (m)); 47.7 (C1H_2 (s)); 121.2, 121.3, 121.6 (C6H, C8H); 129.4 (C5H (m)), 129.9 (C5H (s)); 134.1 (C8a (s)), 135.1 (C8a (m)); 141.5 (C4a (m)), 142.7 (C4a (s)); 146.3 (C7NO_2 (m)), 146.5 (C7NO_2 (s)); 169.2 (CO (s)), 169.3 (CO (m))

Yield: 39.4%

IRν_{max}(KBr): 1346cm^{-1}(NO_2), 1517cm^{-1} (NO_2), 1656cm^{-1}(NCO stretching), 3059cm^{-1} (CH stretching)

Melting point: 86 - 88°C Literature: 84 - 86°C[2]

1-(5,7-Dinitro-3,4-dihydro-*1H*-isoquinolin-2-yl)-ethanone (5)[2]

10 mL/10.64 g/80 mmol 1,2,3,4-tetrahydroisoquinoline was dissolved in 35mL concentrated sulphuric acid, with cooling. Fuming nitric acid (8.00 mL/80 mmol) was added to the solution via dropping funnel over 20 minutes, with cooling continuing. After stirring overnight the mixture was poured onto ice, made alkaline

and extracted with chloroform. The extract was dried, filtered and the solvent removed *in vacuo* to give brown oil, which was dissolved in ethanol and treated with concentrated hydrochloric acid to give the hydrochloride salt of 5,7-nitro-1,2,3,4-tetrahydroisoquinoline. The hydrochloride salt was acetylated by heating for 3 hours on a water bath with 1.595 g/19.44 mmol of anhydrous sodium acetate and 18.4 mL/19.44 g/190 mmol acetic anhydride. After cooling, the mixture was extracted with dichloromethane. The extract was washed with water four times to remove anhydride, then dried and filtered. The remaining solvent was removed by the rotary evaporator, using toluene to form an azeotrope of remaining acetic anhydride. The solid which formed was recrystallised from ethyl acetate.

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.20 (3H, s, $COC\underline{H}_3$); 3.18 (0.8H, s, $C4\underline{H}_2$ (s)), 3.29 (1.2H, s, $C4\underline{H}_2$ (m)); 3.77 (1.2H, t, J = 5.6Hz, $C3\underline{H}_2$ (m)), 3.85 (0.8H, s, $C3\underline{H}_2$ (s)); 4.86 (0.8H, s, $C1\underline{H}_2$ (s)), 4.92 (1.2H, s, $C1\underline{H}_2$ (m)); 8.27 (1H, s, C86); 8.63 (1H, s, C6H)

^{13}C-NMR (101MHz): PPM ($CDCl_3$); 21.1 ($\underline{C}H_3$ (m)); 21.5 ($\underline{C}H_3$ (s)); 26.4 ($\underline{C}4H_2$ (s)), 27.3 ($\underline{C}4H_2$ (m)); 37.7 ($\underline{C}3H_2$ (s)); 42.3 ($\underline{C}1H_2$ (m)); 43.8 ($\underline{C}3H_2$ (m)); 47.9 ($\underline{C}1H_2$ (s)); 118.0 ($\underline{C}6H$ (m)), 118.3 ($\underline{C}6H$ (s)); 125.0 ($\underline{C}8H$ (s)), 125.6 ($\underline{C}8H$ (m)); 136.4 ($\underline{C}8a$ (m)), 137.6 ($\underline{C}8a$ (s)); 137.9 ($\underline{C}4a$ (s)), 139.0 ($\underline{C}4a$ (s)); 146.0 ($\underline{C}7NO_2$ (m)), 149.1 ($\underline{C}7NO_2$ (s)); 168.9 ($\underline{C}O$ (s)), 169.2 ($\underline{C}O$ (m))

Yield: 24.7%

IRν_{max}(KBr): 1350cm^{-1}(NO_2), 1540cm^{-1} (NO_2), 1648cm^{-1}(NCO stretching), 3448cm^{-1} (CH stretching)

Melting point: 136 - 138°C Literature: 136 - 138°C[2]

2,2,2-Trifluoro-1-(7-nitro-3,4-dihydro-*1H*-isoquinolin-2-yl)-ethanone (6)[3]

7-Nitro-1,2,3,4-tetrahydroisoquinoline **(2)** (5.953 g/ 33.4 mmol) was stirred with 5.1 mL/50 mmol trifluoroacetic anhydride for 2 hours. Trifluoroacetic acid was removed on the rotary evaporator, the residue was taken up in dichloromethane and washed with 15%w/v NaOH solution, then water. The extract was dried with sodium sulfate and evaporated to dryness on the rotary evaporator.

^{1}H-NMR (400MHz): δ($CDCl_3$): 3.06 – 3.11 (2H, m, $C4\underline{H}_2$); 3.92 (1.3H, t, J = 6Hz, $C3\underline{H}_2$ (m)), 3.97 (0.7H, t, J = 6Hz, $C3\underline{H}_2$ (s)); 4.87 (0.7H, s, $C1\underline{H}_2$ (s)), 4.91 (1.3H, s, $C1\underline{H}_2$ (m)); 7.36 – 7.40 (1H, m, C5H); 8.06 – 8.12 (2H, m, C6H, C8H)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 28.0 ($\underline{C}4H_2$ (s)), 29.4 ($\underline{C}4H_2$ (m)); 41.04 ($\underline{C}3H_2$ (s)); 42.6 ($\underline{C}1H_2$ (m)); 45.2 ($\underline{C}3H_2$ (m)); 46.7 ($\underline{C}1H_2$ (s)); 121.3,121.8, 122.0, 122.5 ($\underline{C}6H$, $\underline{C}8H$ (s), (m)); 129.8 ($\underline{C}5H$ (m)); 130.1 ($\underline{C}5H$ (s)); 132.9 ($\underline{C}8a$ (s)), 133.1 ($\underline{C}8a$ (m)); 140.7 ($\underline{C}4a$ (m)), 141.5 ($\underline{C}4a$ (s)); 146.8 ($\underline{C}7NO_2$)

^{19}F-NMR (376MHz): ppm($CDCl_3$): -69.86 (s), -69.94 (m)

Yield: 72%

IRν_{max}(KBr): 1347cm^{-1}(NO_2), 1521cm^{-1}(NO_2), 1694cm^{-1}(CO)

Melting point: 68 - 70°C Literature: 66 - 67°C[3]

7-Amino-1,2,3,4-tetrahydroisoquinolines

1-(7-Amino-3,4-dihydro-*1H*-isoquinolin-2-yl)-ethanone (7)[4]

100mg of 10% palladium on activated carbon was suspended in 50mL ethanol and hydrogenated at atmospheric pressure for 1.5 hours. 100mg of 1-(7-Nitro-3,4-dihydro-*1H*-isoquinolin-2-yl)-ethanone (4) was added and the suspension was left stirring under hydrogen overnight. The following morning the ethanolic suspension was filtered using glass wool and the ethanol was removed on the rotary evaporator.

The oil was taken up in dichloromethane, which was dried and then evaporated to dryness. The mixture was separated by column chromatography.

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.71 (2H, bs, $N\underline{H}_2$); 2.18 (3H, s, $COC\underline{H}_3$); 2.75 (0.8H, t, J = 6Hz, $C4\underline{H}_2$ (s)), 2.81 (1.2H, t, J = 6Hz, $C4\underline{H}_2$ (m)); 3.65 (1.2H, t, J = 6Hz,, $C3\underline{H}_2$ (m)), 3.80 (0.8H, t, J = 6Hz, $C3\underline{H}_2$ (s)); 4.53 (0.8H, s, $C1\underline{H}_2$ (s)), 4.65 (1.2H, s, $C1\underline{H}_2$ (m)); 6.45 (0.4H, s, C8H (s)); 6.49 (0.6H, s, C8H (m)); 6.50 – 6.54 (1H, dt, J_1 = 10Hz, J_2 = 2.5Hz, C6H); 6.93 – 6.95 (1H, m, C5H)
^{13}C-NMR (101MHz): ppm($CDCl_3$): 21.6 ($\underline{C}H_3$ (m)); 22.9 ($\underline{C}H_3$ (s)); 27.5 ($\underline{C}4H_2$ (s)), 28.5 ($\underline{C}4H_2$ (m)); 40.0 ($\underline{C}3H_2$ (s)), 44.3 ($\underline{C}1H_2$ (m)); 44.5 ($\underline{C}3H_2$ (m)); 48.3 ($\underline{C}1H_2$ (s)); 110.1 ($\underline{C}6H$ (s)), 110.6 ($\underline{C}6H$ (m)); 112.4 ($\underline{C}8H$ (m)), 112.8 ($\underline{C}8H$ (s)); 122.3 ($\underline{C}4a$); 128.9 (C5H (m)), 129.5 (C5H (s)); 134.2 ($\underline{C}8a$); 145.0 ($\underline{C}7NH_2$); 169.3 ($\underline{C}O$ (s)), 169.4 ($\underline{C}O$ (m))
Yield: 46.4%
IRν_{max}(KBr): 1610cm^{-1}(CO), 2872cm^{-1} (CH stretching), 3341cm^{-1}(CH), 3412cm^{-1} (NH_2)
Melting point: 150 - 152°C Literature: 148 - 149°C

1-(5,7-Diamino-3,4-dihydro-*1H*-isoquinolin-2-yl)-ethanone (8)[4]

As for **(7),** using **(5)** as the starting material.

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.16 (1.5H, s, $COC\underline{H}_3$); 2.18 (1.5H, s, $COC\underline{H}_3$); 2.49 (1H, t, J = 6Hz, $C4\underline{H}_2$), 2.56 (1H, t, J = 6Hz, $C4\underline{H}_2$); 3.53 (4H, bs, $N\underline{H}_2$*2); 3.71 (1H, t, J = 6Hz,, $C3\underline{H}_2$), 3.86 (1H, t, J = 6Hz, $C3\underline{H}_2$); 4.48 (1H, s, $C1\underline{H}_2$), 4.62 (1H, s, $C1\underline{H}_2$); 5.93, 5.98 – 5.99 (2H, m, C6H, C8H)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 21.3, 21.6 ($\underline{C}H_3$); 22.6, 23.6 ($\underline{C}4H_2$); 39.3, 44.4 ($\underline{C}3H_2$); 43.9, 48.4 ($\underline{C}1H_2$); 100.3, 100.4 ($\underline{C}6H$); 102.8, 103.8 ($\underline{C}8H$); 124.7 ($\underline{C}4a$); 133.9 ($\underline{C}8a$); 145.2, 152.3 ($\underline{C}5NH_2$, $\underline{C}7NH_2$); 166.7 ($\underline{C}O$)

Yield: 73%

IRν_{max}(KBr): 1610cm^{-1}(CO), 2872cm^{-1} (CH stretching), 3341cm^{-1}(CH), 3412cm^{-1} (NH_2)

1-(7-Amino-3,4-dihydro-*1H*-isoquinoline-2-yl)-2,2,2-trifluoro-ethanone (9)[3]

As for **(7)**, using **(6)** as the starting material.

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.75 – 2.79 ($C4\underline{H}_2$); 3.75 (1.3H, t, J = 6Hz, $C3\underline{H}_2$ (m)), 3.79 (0.7H, t, J = 5.5Hz, $C3\underline{H}_2$ (s)); 3.87 (2H, s, $N\underline{H}_2$); 4.59 (0.7H, s, $C1\underline{H}_2$ (s)), 4.62 (1.3H, s, $C1\underline{H}_2$ (m)); 6.36 (0.65H, s, C8H (m)), 6.40 (0.35H, s, C8H (s)); 6.50 – 6.54 (1H, m, C6H); 6.87 – 6.91 (1H, m, C5H)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 26.4 ($\underline{C}4H_2$ (s)), 27.8 ($\underline{C}4H_2$ (m)); 42.0 ($\underline{C}3H_2$ (s)), 43.4 ($\underline{C}1H_2$ (m)); 45.2 ($\underline{C}3H_2$ (m)); 46.5 ($\underline{C}1H_2$ (s)); 111.4, 111.7, 113.9, 114.2 ($\underline{C}6H$, $\underline{C}8H$); 122.1 ($\underline{C}4a$ (m)), 122.7 ($\underline{C}4a$ (s)); 128.9 (C5H (m)), 129.0 (C5H (s)); 131.6 ($\underline{C}8a$ (m)); 131.7 ($\underline{C}8a$ (s)); 145.2 ($\underline{C}7NO_2$ (s)), 145.3 ($C7NO_2$ (m)); 154.6 – 155.8 ($CO\underline{C}F_3$, overlapping quartets); 170.7 ($\underline{C}O$)

^{19}F-NMR (376MHz) ppm ($CDCl_3$): -69.75 (s), -69.80 (m)

Yield: 84%

IRν_{max}(KBr): 1628cm^{-1}(NH_2 scissoring), 1686cm^{-1}(CO), 3054cm^{-1}(CH), 3378cm^{-1} (CH aromatic)

Melting point: 62 - 64°C Literature: 61 - 62°C[3]

***N*-2-[(2,2,2-Trifluoro-acetyl)-1,2,3,4-tetrahydroisoquinolin-7-yl]-amides**

General synthesis of compounds **10** to **23**: the amine **(9)** (500 mg/2.05 mmol) was dissolved in 15 mL anhydrous DCM and triethylamine (0.7 mL/ 5 mmol) was added. The acid chloride (2.3 mmol) was added dropwise and the mixture was stirred at room temperature overnight. The organic solution was washed with water, dried with sodium sulfate and evaporated to dryness *in vacuo*. The product was purified by elution from a silica column using a mobile phase of 1:3 ethyl acetate: hexane.

N-[2-(2,2,2-Trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-propionamide (10)

^{1}H-NMR (400MHz): δ(CD_3COCD_3): 1.15 (3H, t, J = 7.5Hz, C$\underline{H}_3$); 2.38 (2H, q, J = 7.5Hz, C$\underline{H}_2$); 2.87 – 2.94 (2H, m, C4$\underline{H}_2$); 3.84 – 3.88 (2H, m, C3$\underline{H}_2$); 4.72 (1.4H, s, C1$\underline{H}$ (m)); 4.76 (0.6H, s, C1$\underline{H}_2$ (s)); 7.10 – 7.13 (1H, C5$\underline{H}$); 7.42 (0.3H, d, J = 8Hz, C6$\underline{H}$ (s)), 7.47 (0.7H, d, J = 8Hz, C6$\underline{H}$ (m)); 7.56 (0.7H, s, C8$\underline{H}$ (m)), 7.66 (0.3H, s, C8$\underline{H}$ (s)); 9.16 (N$\underline{H}$)

^{13}C-NMR (101MHz): ppm(CD_3COCD_3): 9.81 ($\underline{C}H_3$); 27.6 ($\underline{C}H_2$); 29.1 ($\underline{C}4H_2$ (m)), 30.5 ($\underline{C}4H_2$ (s)); 42.5 ($\underline{C}3H_2$ (s)); 44.0 ($\underline{C}1H_2$ (m)); 46.0 ($\underline{C}3H_2$ (m)); 47.6 ($\underline{C}1H_2$ (s)); 117.3 ($\underline{C}$6H, d, J = 9.6Hz (s)), 117.6 ($\underline{C}$6H, d, J = 9.6Hz (m)); 118.8 ($\underline{C}$8H, d, J = 9.6Hz (m)); 119.1 ($\underline{C}$8H, d, J = 9.6Hz (s)); 128.8 ($\underline{C}$8a (s)), 129.1 ($\underline{C}$8a (m)); 129.6 ($\underline{C}$5H (m)), 129.7 ($\underline{C}$5H (s)); 132.8 ($\underline{C}$4a (m)), 132.95 ($\underline{C}$4a (s)); 138.8 ($\underline{C}$7NH (s)), 138.9 ($\underline{C}$7NH (m)); 155.7 – 156.0 (CO$\underline{C}F_3$, m); 172.66 ($\underline{C}$ONH (s)), 172.7 ($\underline{C}$ONH (m)); 192.4 ($\underline{C}OCF_3$)

^{19}F-NMR (376MHz) ppm(CD_3COCD_3): -70.54 (s), -70.57 (m)

Yield: 76%

IRν_{max}(KBr): 740cm^{-1}(CF), 1690cm^{-1} (CO), 2927cm^{-1} (CH), 3330cm^{-1} (CH aromatic)

HRMS calcd. for C14H15N2O2F3Na (M^++23): 323.0983 Found: 323.0986

N-[2-(2,2,2-Trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-butyramide (11)

^{1}H-NMR (400MHz): δ($CDCl_3$): 0.96 (3H, t, J = 7Hz, C$\underline{H}_3$); 1.69 (2H, m, C$\underline{H}_2$CH$_3$); 2.34 (2H, t, J = 7Hz, C$\underline{H}_2$CH$_2$); 2.88 – 2.95 (2H, m, C4$\underline{H}_2$); 3.85 – 3.90 (2H, m, C3$\underline{H}_2$); 4.73 (1.4H, s, C1$\underline{H}$ (m)); 4.78 (0.6H, s, C1$\underline{H}_2$ (s)); 7.12 (0.7H, d, J = 8Hz, C5$\underline{H}$ (m)), 7.15 (0.3H, d, J = 8.5, C5$\underline{H}$ (s)); 7.42 (0.3H, d, J = 8.5Hz, C6$\underline{H}$ (s)), 7.47 (0.7H, d, J = 8Hz, C6$\underline{H}$ (m)); 7.58 (0.7H, s, C8$\underline{H}$ (m)), 7.67 (0.3H, s, C8$\underline{H}$ (s)); 9.17 (N$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 14.0 ($\underline{C}H_3$); 19.6 ($\underline{C}H_2CH_3$); 27.7 ($\underline{C}H_2CH_2$); 29.2 ($\underline{C}4H_2$ (m)), 39.5 ($\underline{C}4H_2$ (s)); 42.6 ($\underline{C}3H_2$ (s)); 44.2 ($\underline{C}1H_2$ (m)); 46.1 ($\underline{C}3H_2$ (m)); 47.7 ($\underline{C}1H_2$ (s)); 117.4 ($\underline{C}$6H (s)), 117.7 ($\underline{C}$6H (m)); 118.9 ($\underline{C}$8H (m)); 119.2 ($\underline{C}$8H (s)); 129.2 ($\underline{C}$8a (m)), 129.60 ($\underline{C}$8a (s)); 129.7 ($\underline{C}$5H (m)), 129.8 ($\underline{C}$5H (s)); 132.9 ($\underline{C}$4a (m)), 133.1 ($\underline{C}$4a (s)); 139.0 ($\underline{C}$7NH (s)), 139.0 ($\underline{C}$7NH (m)); 155.8 – 156.1 (CO$\underline{C}F_3$, m); 171.9 ($\underline{C}$ONH); 192.4 ($\underline{C}OCF_3$)

^{19}F-NMR (376MHz): -69.83 (m), -69.88 (s)

Yield: 88%

IRν_{max}(KBr): 1512cm^{-1}(NH bending), 1678cm^{-1}(CO), 2966cm^{-1}(CH), 3358cm^{-1} (CH aromatic)

HRMS calcd. for C15H17N2O2F3 Na (M^++23): 337.1140 Found: 337.1136

Cyclohexanecarboxylic acid [2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-amide (12)

^{1}H-NMR (400MHz) δ(CD_3COCD_3): 1.21 – 2.32 (11H, m, cyclohexyl ring); 2.87 – 2.90 (2H, m, C4$\underline{H}_2$); 3.81 – 3.87 (2H, m, C3$\underline{H}_2$); 4.69 – 4.70 (2H, s, C1$\underline{H}_2$); 7.02 – 7.09 (1H, m, C5$\underline{H}$); 7.19 – 7.28 (1H, m, C6$\underline{H}$), 7.38 – 7.59 (1H, m, C8$\underline{H}$); 8.05 (N$\underline{H}$)

^{13}C-NMR (101MHz) ppm(CD_3COCD_3): 25.5 ($\underline{C}H_2$ in cyclohexyl ring); 27.2 ($\underline{C}4H_2$)(s)), 28.6 ($\underline{C}4H_2$)(m)); 29.5 ($\underline{C}H_2$ in cyclohexyl ring); 41.9 ($\underline{C}3H_2$)(s)); 45.4 ($\underline{C}1H_2$)(m)); 46.2 ($\underline{C}3H_2$)(m)); 46.96 ($\underline{C}1H_2$)(s)); 117.3 ($\underline{C}$6H)(s)), 117.6 ($\underline{C}$6H)(m)); 118.8 ($\underline{C}$8H)(m)), 118.9 ($\underline{C}$8H)(s)); 128.6 ($\underline{C}$8a (m)); 129.O ($\underline{C}$5H (m)), 129.1 ($\underline{C}$5H (s)); 129.3 (C8a (s));131.7 ($\underline{C}$4a)(m)), 131.8 ($\underline{C}$4a)(s)); 136.8 ($\underline{C}$7NH)(s)), 137.0 ($\underline{C}$7NH)(m)); 174.9 (NH$\underline{C}$O, $\underline{C}OCF_3$)

^{19}F-NMR (376MHz) ppm(CD_3COCD_3): -69.84 (s), -69.85 (m)

Yield: 38%

IRν_{max}(KBr): 1524cm^{-1} (NH bending), 1693cm^{-1} (CO), 2987cm^{-1} (CH aliphatic), 3055cm^{-1} (CH aromatic)

Melting point: 166°C

HRMS calcd. for C18H21N2O2F3 Na (M^++23): 377.1453 Found: 377.1468

_N_-[2-(2,2,2-Trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-benzamide (13)

^{1}H-NMR (400MHz): δ(CD_3COCD_3): 2.92 – 2.98 (2H, m, C4H_2); 3.89 – 3.93 (2H, m, C3H_2); 4.79 (1.3H, s, C1H (m)); 4.83 (0.7H, s, C1H_2 (s)); 7.19 – 7.22 (1H, m, C5H); 7.52 (2H, d, J = 7Hz, C2'H, C6'H); 7.57 – 7.60 (1H, m, C4'H); 7.64 (0.35H, d, J = 8.3Hz, C6H (s)), 7.67 (0.65H, d, J = 8.3Hz, C6H (m)); 7.76 (0.65H, s, C8H (m)), 7.83 (0.35H, s, C8H (s)); 8.05 (2H, d, J = 7Hz, C3'H, C5'H); 9.60 (NH)

^{13}C-NMR (101MHz): ppm(CD_3COCD_3): 27.7 (C4H_2 (s)), 29.2 (C4H_2 (m)); 42.5 (C3H_2 (s)); 44.1 (C1H_2 (m)); 46.1 (C3H_2 (m)); 47.6 (C1H_2 (s)); 118.4 (C6H (s)), 118.6 (C6H (m)); 119.8 (C8H (m)); 119.9 (C8H (s)); 128.2 (C2'H, C6'H (m)), 129.2 (C3'H, C5'H (s)); 129.6 (C5H); 129.8 (C1' (m)), 129.9 (C1' (s)); 132.3 (C4'H); 132.9 (C8a (m)), 133.0 (C8a (s)); 136.02 (C4a (m)); 136.03 (C4a (s)); 138.7 (C7NH (s)), 138.8 (C7NH (m)); 155.6 – 156.1 (COCF_3, m); 166.2 (CONH); 192.1 (COCF_3)

^{19}F-NMR (376MHz) ppm(CD_3COCD_3) : -70.54 (s), -70.58 (m)

Yield: 63%

IRν_{max}(KBr): 1543cm^{-1}(NH bending), 1692cm^{-1}(CO), 3293cm^{-1} (CH aromatic)

Melting point: 186°C

HRMS calcd. for C18 H15N2O2F3Na (M^++23): 371.0983 Found: 371.0994

4-Fluoro-_N_-[2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-benzamide (14)

^{1}H-NMR (400MHz): δ(CD_3COCD_3): 2.93-2.99 (2H, m, C4H_2); 3.88-3.93 (2H, m, C3H_2); 4.78 (1.3H, s, C1H_2 (m)), 4.82 (0.7H, s, C1H_2 (s)); 7.18 – 7.30 (3H, m, overlapping doublets of both isomers, C5H, C3'H, C5'H); 7.62 – 7.67 (1H, m, overlapping doublets, C6H); 7.72 (0.65H, s, C8H (m)), 7.80 (0.35H, s, C8H (s)); 8.07 – 8.10 (2H, m, overlapping doublets of both isomers, C2'H, C6'H); 9.60 (1H, bs, NH)

^{13}C-NMR (101MHz): ppm(CD_3COCD_3); 28.1 (C4H_2)(s)), 29.5 (C4H_2)(m)); 42.9 (C3H_2)(s)); 44.4 (C1H_2)(m)); 46.4 (C3H_2)(m)); 48.0 (C1H_2)(s)); 116.2 (C3'H, C5'H)(s)), 116.4 (C3'H, C5'H)(m)); 118.8 (C6H)(s)), 119.1 (C6H)(m)); 120.3 (C8H)(m)), 120.5 (C8H)(s)); 130.0 (C5H)(m)), 130.1 (C5H)(s)); 130.3 (C4a)(m)), 130.7 (C4a)(s)); 131.2 (C2'H, C6'H)(m)), 131.3 (C2'H, C6'H)(s)); 132.7 (C1'); 133.3 (C8a)(m)), 133.4 (C8a)(s)); 138.7 (C7NH)(s)), 138.8 (C7NH)(m)); 164.5 (COCF_3, COCF_3); 165.8 (d, J = 146Hz, C4'F)

^{19}F-NMR (376MHz) ppm(CD_3COCD_3): -70.54, -70.59

Yield: 51%

IRν_{max}(KBr): 853cm^{-1} (CF), 1598cm^{-1}(NH bending), 1694cm^{-1}(CO), 3289cm^{-1} (CH aromatic)

HRMS calcd. for C18H14N2O2F4Na (M^++23): 389.0889 Found: 389.0908

4-Chloro-_N_-[2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-benzamide (15)

^{1}H-NMR (400MHz) δ(CD_3COCD_3): 2.97 – 3.02 (2H, m, C4H_2); 3.89-3.93 (2H, m, C3H_2); 4.79 (1.3H, s, C1H_2), 4.88 (0.7H, s, C1H_2); 7.19 – 7.31 (1H, m, overlapping doublets of both isomers, C5H); 7.55 (2H, d, J =8.5Hz, C3'H, C5'H); 7.61 – 7.80 (2H, m, overlapping doublets and singlets from both isomers, C6H, C8H); 8.02 (2H, d, J =8.5Hz, C2'H, C6'H); 9.66 (1H, bs, NH)

^{13}C-NMR (101MHz) ppm (CD_3COCD_3): 27.8 (C4H_2)(s)), 29.3 (C4H_2)(m)); 42.6 (C3H_2)(s)); 44.1 (C1H_2)(m)); 46.1 (C3H_2)(m)); 47.7 (C1H_2)(s)); 118.5 (C6H)(s)), 118.8 (C6H)(m)); 119.6(C8H)(m)), 120.0 (C8H)(s)); 128.9 (C2'H, C6'H)(m)), 129.2 (C2'H, C6'H)(s)); 129.8 (C3'H, C5'H)(m)), 130.2 (C3'H, C5'H)(s)); 133.0 (C4a)(m)), 133.1 (C4a)(s)); 134.7 (C8a)(m)), 135.0 (C8a)(s)); 135.6 (C1'); 137.9 (CCl); 138.6 (C7NH)(m)), 138.8(C7NH)(s)); 165.2 (NHCO); 190.1 (CO)

^{19}F-NMR (376MHz) ppm(CD_3COCD_3): -70.59, -70.61

Yield: 20%

IRν_{max}(KBr): 753cm^{-1} (CCl), 1598cm^{-1}(NH bending), 1699cm^{-1}(CO), 2926cm^{-1}, 3282cm^{-1} (CH aromatic)

HRMS calcd. for C18H14N2O2F3ClNa (M^++23): 405.0594 Found: 405.0584

4-Bromo-*N*-[2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-benzamide (16)

^{1}H-NMR (400MHz): δ(CD_3COCD_3): 2.94 – 3.01 (2H, m, C4H_2); 3.89-3.94 (2H, m, C3H_2); 4.79 (1.25H, s, C1H_2 (m)), 4.88 (0.75H, s, C1H_2 (s)); 7.20 – 7.32 (1H, m, overlapping doublets of both isomers, C5H); 7.62 – 7.80 (4H, overlapping doublets and singlets from both isomers) J = 8.5Hz, C6H, C8H, C3'H, C5'H); 7.95 (2H, d, J = 8.5Hz, C6H, C8H); 9.64 (1H, bs, NH)

^{13}C-NMR (101MHz) ppm(CD_3COCD_3): 27.9 (C4H_2)(s)), 28.6 (C4H_2)(m)); 42.7 (C3H_2)(s)); 44.2 (C1H_2)(m)); 46.3 (C3H_2)(m)); 47.9 (C1H_2)(s)); 118.6 (C6H)(s)), 118.9 (C6H)(m)) 120.1 (C8H)(m)), 120.4 (C8H)(s)); 126.5 (CBr); 129.9 (C5H)(m)) 130.0 (C5H)(s)); 130.4 (C2'H, C6'H); 130.6(C1'); 132.5 (C3'H, C5'H); 133.2 (C4a); 135.3 (C8a); 138.7 (C7NH)(s); 165.4 (NHCO, $COCF_3$)

^{19}F-NMR (376MHz) ppm(CD_3COCD_3): -70.57, -70.61

Yield: 31%

IRν_{max}(KBr): 1598cm^{-1}(NH bending), 1698cm^{-1}(CO), 2925cm^{-1}, 3281cm^{-1} (CH aromatic)

HRMS calcd. for C18H14N2O2F3Br Na (M^++23): 449.0088 Found: 449.0077

4-Iodo-*N*-[2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-benzamide (17)

^{1}H-NMR (400MHz): δ(CD_3COCD_3): 3.05 – 3.10 (2H, m, C4H_2); 3.84-3.97 (2H, m, C3H_2); 4.86 (0.7H, s, C1H_2 (s)), 4.89 (1.3H, s, C1H_2 (m)); 7.05 – 7.84 (7H, m, C5H, C6H, C8H, C2'H, C3'H, C5'H, C6'H)

^{13}C-NMR (101MHz) ppm(CD_3COCD_3): 26.5 (C4H_2)(s)), 30.3 (C4H_2)(m)); 42.7 (C3H_2)(s)); 44.2 (C1H_2)(m)); 46.1 (C3H_2)(m)); 47.6 (C1H_2)(s)); 99.2 (CI); 119.1 (C6H)(s)), 119.8 (C6H)(m)); 121.2 (C8H)(m)), 121.3 (C8H)(s)); 127.8 (C5H)(s)) 127.9 (C5H)(m)); 130.5 (C2'H, C6'H (m)); 130.6 (C2'H, C6'H (s)); 132.4 (C8a (s)), 133.0 (C8a (m)); 133.3 (C1' (s)), 134.1 (C1' (m)); 135.4 (C4a (s)), 136.0 (C4a (m)); 138.8 (C3'H, C5'H (m)), 138.84 (C3'H, C5'H (s)); 139.5 (C7NH)(s)), 139.7 (C7NH (m)); 165.8 (NHCO); 166.0 ($COCF_3$)

^{19}F-NMR (376MHz): ppm(CD_3COCD_3): -69.83 (s), -69.85 (m)

Yield: 20%

Melting Point: 192°C

IRν_{max}(KBr): 1587cm^{-1}(NH bending), 1691cm^{-1}(CO), 2987cm^{-1}, 3055cm^{-1} (CH aromatic)

HRMS calcd. for C18H14N2O2F3INa (M^++23): 496.9950 Found: 496.9970

2-Methoxy-*N*-[2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-benzamide (18)

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.94, 2.98 (2H, t, t, (overlapping), J(s) = 6.5Hz, J(m) = 6.0Hz, C4H_2); 3.89 – 3.93 (2H, m, C3H_2); 4.10, 4.11 (3H, s, s, (overlapping), OCH_3); 4.80 (1.3H, s, C1H_2(m)), 4.84 (0.7H, s,

C1$\underline{H}_2$(s)); 7.13 (1H, apparent triplet with J = 7Hz, C3'$\underline{H}$); 7.18 – 7.24 (2H, m, C5'$\underline{H}$(m), (s), C4'$\underline{H}$(m), (s)); 7.54, 7.56, 7.58 (1H, d, d, overlapping from both isomers, J_1 = 7Hz, J_2 = 2Hz, C5$\underline{H}$); 7.63, 7.65, 7.67, 7.69 (1.7H, dd, dd, dd, dd, s, overlapping from both isomers, J_1 = 9Hz, J_2 = 2Hz , C6$\underline{H}$(s), (m), C8$\underline{H}$(m)), 7.79 (0.3H, s, C8$\underline{H}$(s)); 8.10 (1H, dd, J_1 = 8Hz, J_2 = 2Hz, C6'$\underline{H}$(m), (s)); 9.95 (1H, bs, N$\underline{H}$)

^{13}C-NMR (101MHz): ppm ($CDCl_3$): 27.9 ($\underline{C}4H_2$)(s), 29.4 ($\underline{C}4H_2$)(m); 42.7 ($\underline{C}1H_2$)(m); 44.3 ($\underline{C}3H_2$)(s), 46.2 ($\underline{C}3H_2$)(m); 47.8 ($\underline{C}1H_2$)(s); 56.8 (O$\underline{C}H_3$); 112.9 ($\underline{C}$3'H); 118.3($\underline{C}$6H)(s), 118.6 ($\underline{C}$6H)(m); 119.8($\underline{C}$8H)(m), 120.1 ($\underline{C}$8H)(s); 121.9 ($\underline{C}$5'H); 123.4 ($\underline{C}$1'); 129.9 ($\underline{C}$5H)(m), 130.0 ($\underline{C}$5H)(s); 130.3 ($\underline{C}$8a); 132.5 ($\underline{C}$6'H); 133.2 ($\underline{C}$4a)(m), 133.3 ($\underline{C}$4a)(s); 134.1 ($\underline{C}$4'H); 138.7 ($\underline{C}$7NH); 158.4 ($\underline{C}$2'OCH$_3$); 164.0 ($\underline{C}$O)

^{19}F-NMR (376MHz): ppm ($CDCl_3$): -70.5 (s), -70.6 (m)

Yield: 59%

IRν_{max}(KBr): 1696cm^{-1}, 2932cm^{-1}, 3337cm^{-1}

HRMS calcd. for C19H17N2O3F3Na (M^++23): 401.1089 Found: 401.1083

3-Methoxy-*N*-[2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-benzamide (19)

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.91 – 3.00 (2H, m, overlapping triplets), C4$\underline{H}_2$(s), (m); 3.88 (3H, s, O$\underline{CH}_3$); 3.89 – 3.94 (2H, m, overlapping triplets, C3$\underline{H}_2$(s), (m); 4.79 (1.3H, s,C1$\underline{H}_2$ (m), 4.83 (0.7H, s, C1$\underline{H}_2$ (s); 7.14 (1H, dd, J_1 = 8Hz, J_2 = 2Hz, C5'$\underline{H}$); 7.19 – 7.23 (1H, m, C5$\underline{H}$); 7.42 (1H, t, J = 8Hz, C4'$\underline{H}$); 7.55, 7.57 (2H, s, t, overlapping, J = 8Hz, C2'$\underline{H}$, C6'$\underline{H}$); 7.64, 7.67 (1H, d, d, overlapping, J = 8.5Hz, J = 10.5Hz, C6$\underline{H}$ (s), (m); 7.74 (0.6H, s, C8$\underline{H}$ (m), 7.81 (0.4H, s, C8$\underline{H}$ (s); 9.53 (1H, bs, N$\underline{H}$)

^{13}C-NMR (101MHz) ppm($CDCl_3$): 27.9 ($\underline{C}4H_2$)(s), 29.3 ($\underline{C}4H_2$)(m); 42.7 ($\underline{C}1H_2$)(m); 44.2 ($\underline{C}3H_2$), 46.2 ($\underline{C}3H_2$)(m); 47.8 ($\underline{C}1H_2$); 55.8 (O$\underline{C}H_3$); 113.6 ($\underline{C}$2'H); 118.2 ($\underline{C}$4'H); 118.5 ($\underline{C}$8H)(s), 118.8 ($\underline{C}$6H)(m); 120.0 ($\underline{C}$8H)(m), 120.3 ($\underline{C}$8H)(m); 120.4 ($\underline{C}$6'H); 129.8 ($\underline{C}$5H)(m), 129.9 ($\underline{C}$5H)(s); 130.0 ($\underline{C}$7NH); 130.4 ($\underline{C}$5'H); 133.1 ($\underline{C}$1'); 137.6 ($\underline{C}$4a); 138.9 ($\underline{C}$8a); 160.8 ($\underline{C}$3'OCH$_3$); 166.1 ($\underline{C}$O)

^{19}F-NMR (376MHz) ppm ($CDCl_3$): -70.56(s); -70.60(m)

Yield: 56%

IRν_{max}(KBr): 1691cm^{-1}, 3295cm^{-1}

HRMS calcd. for C19H17N2O3F3Na (M^++23): 401.1089 Found: 401.1098

4-Methoxy-*N*-[2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-benzamide (20)

^{1}H-NMR (400MHz) δ($CDCl_3$): 2.93 – 2.99 (2H, m, C4$\underline{H}_2$); 3.87 (3H, s, O$\underline{CH}_3$); 3.90 – 3.93 (2H, m, C3$\underline{H}_2$); 4.78 (1.3H, s, C1$\underline{H}_2$)(m), 4.83 (0.7H, s, C1$\underline{H}_2$)(s); 7.04 (2H, d, J = 9Hz, C3'$\underline{H}$, C5'$\underline{H}$); 7.19 (1H, m, C5$\underline{H}$); 7.63 (0.4H, d, J = 8Hz, C6$\underline{H}$(s)), 7.67 (0.6H, d, J = 8.5Hz, C6$\underline{H}$ (m)); 7.74 (0.6H, s, C8$\underline{H}$(m)), 7.81 (0.4H, s, C8$\underline{H}$(s)); 8.00 (2H, d, J = 9Hz, C2'$\underline{H}$, C6'$\underline{H}$); 9.45 (1H, bs, N$\underline{H}$)

^{13}C-NMR (101MHz) ppm($CDCl_3$): 27.9 ($\underline{C}4H_2$)(s), 29.4 ($\underline{C}4H_2$)(m); 42.8 ($\underline{C}1H_2$)(m); 44.3 ($\underline{C}3H_2$)(s), 46.3 ($\underline{C}3H_2$)(m); 47.9 ($\underline{C}1H_2$)(s); 55.9 (O$\underline{C}H_3$); 114.5 ($\underline{C}$3'H, $\underline{C}$5'H); 118.5($\underline{C}$6H)(s), 118.8 ($\underline{C}$6H)(m); 120.0 ($\underline{C}$8H)(m), 120.3 ($\underline{C}$8H)(s); 128.3 ($\underline{C}$1'); 129.7 ($\underline{C}$5H)(m), 129.8 ($\underline{C}$5H)(s); 129.9 ($\underline{C}$7NH); 130.3 ($\underline{C}$2'H, $\underline{C}$6'H); 133.1 ($\underline{C}$4a); 139.2 ($\underline{C}$8a); 163.4 ($\underline{C}$4'OCH$_3$); 165.8 ($\underline{C}$O)

^{19}F-NMR (376MHz) ppm($CDCl_3$): -70.56(s), -70.6(m)

Yield: 61%

IRν_{max}(KBr): 1694cm^{-1}, 2937cm^{-1}, 3255cm^{-1}

HRMS calcd. for C19H17N2O3F3Na (M^++23): 401.1089 Found: 401.1100

4-Nitro-*N*-[2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-benzamide (21)

^{1}H-NMR (400MHz) δ(CD_3COCD_3): 2.95 – 3.01 (2H, m, C4$\underline{H}_2$); 3.90 - 3.94 (2H, m, C3$\underline{H}_2$); 4.80 (1.3H, s, C1$\underline{H}_2$ (m)), 4.85 (0.7H, s, C1$\underline{H}_2$ (s)); 7.21 – 7.25 (1H, m, C5$\underline{H}$); 7.62 – 7.68 (1H, d, d, overlapping, J = 9Hz, C6$\underline{H}$); 7.73 (0.7H, s, C8$\underline{H}$), 7.81 (0.3H, s, C8$\underline{H}$); 8.24 (2H, d, J = 9Hz, C2'$\underline{H}$, C6'$\underline{H}$); 8.36 (2H, d, J = 9Hz, C3'$\underline{H}$, C5'$\underline{H}$); 9.88 (1H, bs, N$\underline{H}$)

^{13}C-NMR (101MHz) ppm(CD_3COCD_3): 27.9 (C4$\underline{H}_2$)(s)), 29.4 (C4$\underline{H}_2$)(m)); 42.6 (C3$\underline{H}_2$)(s)); 44.2 (C1$\underline{H}_2$)(m)); 46.2 (C3$\underline{H}_2$)(m)); 47.8 (C1$\underline{H}_2$)(s)); 118.7 (C6H)(s)), 119.0 (C6H)(m)); 120.1 (C8H)(m)),120.4 (C8H)(s)); 124.4 (C3'H, C5'H); 129.8 (C2'H, C6'H); 129.9 (C5H)(m)), 130.0 (C5H)(s)); 130.6 (C4a)(m)), 131.1 (C4a)(s)); 133.2 (C8a)(m)), 133.4 (C8a)(s)); 138.3 (C7NH (s)), 138.4 (C7NH)(m)); 141.8 (C1'); 150.6 (C4'NO_2); 164.7 (NHCO); 171.2 ($COCF_3$)

^{19}F-NMR (376MHz) ppm(CD_3COCD_3): -70.41 (m), -70.43 (s)

IRν_{max}(KBr): 871cm^{-1} (CN), 1525cm^{-1}(NO), 1677cm^{-1}(CO), 2920cm^{-1}, 3371cm^{-1}(CH)

Yield: 45%

HRMS calcd. for C18H14N3O4F3Na (M^++23): 416.0834 Found: 416.0825

2-Phenyl-*N*-[2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-acetamide (22)

^{1}H-NMR (400MHz) δ(CD_3COCD_3): 2.90, 2.94 (2H, t, t, J = 6Hz, C4$\underline{H}_2$); 3.70 (2H, s, COC$\underline{H}_2$); 3.85 – 3.90 (2H, m, C3$\underline{H}_2$); 4.73 (1.3H, s, C1$\underline{H}$ (m)); 4.77 (0.7H, s, C1$\underline{H}_2$ (s)); 7.12 – 7.15 (1H, m, C5$\underline{H}$); 7.24 – 7.97 (C7H, C6$\underline{H}$, C8$\underline{H}$, C2'$\underline{H}$, C3'$\underline{H}$, C4'$\underline{H}$, C5'$\underline{H}$, C6'$\underline{H}$); 9.36 (1H, bs, N$\underline{H}$)

^{13}C-NMR (101MHz) ppm(CD_3COCD_3): 27.8 (C4$\underline{H}_2$ (s)), 29.3 (C4$\underline{H}_2$ (m)); 42.7 (C3$\underline{H}_2$ (s)); 44.3 (C1$\underline{H}_2$ (m)); 44.8 (CO$\underline{C}H_2$); 46.2 (C3$\underline{H}_2$ (m)); 47.8 (C1$\underline{H}_2$ (s)); 117.6 (C6H (s)), 117.9 (C6H (m)); 119.1 (C8H (m)); 119.4 (C8H (s)); 127.6 (C4'H); 129.3 (C2'H, C6'H (m)); 129.8 (C5H (m)), 129.96 (C5H (s)); 130.1 (C3'H, C5'H (s)); 133.2 (C1'); 133.3 (C8a); 136.9 (C4a (m)); 139.0 (C7NH (s)); 169.9 (CONH, $\underline{C}OCF_3$)

^{19}F-NMR (376MHz) ppm(CD_3COCD_3): -70.60 (s), -70.63 (m)

Yield: 39%

IRν_{max}(KBr): 1675cm^{-1}, 2927cm^{-1}, 3335cm^{-1}

HRMS calcd. for C19H17N2O2F3Na (M^++23): 385.1140 Found: 385.1135

2-(4-Methoxy-phenyl)-*N*-[2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-acetamide (23)

^{1}H-NMR (400MHz) δ(CD_3COCD_3): 2.80 – 2.95 (2H, m, C4$\underline{H}_2$); 3.61 (2H, s, COC$\underline{H}_2$); 3.77 (3H, s, $\underline{C}H_3$); 3.84 – 3.88 (2H, m, C3$\underline{H}_2$); 4.72 (1.2H, s, C1$\underline{H}$ (m)); 4.76 (0.8H, s, C1$\underline{H}_2$ (s)); 6.89 (2H, d, J = 8.5Hz, C3'$\underline{H}$, C5'$\underline{H}$); 7.10 – 7.14 (1H, m, C5$\underline{H}$); 7.29 (2H, d, J = 8.5Hz, C2'$\underline{H}$, C6'$\underline{H}$); 7.40 (0.35H, d, J = 10Hz, C6$\underline{H}$ (s)), 7.48 (0.65H, d, J = 9Hz, C6$\underline{H}$ (m)); 7.53 (0.65H, s, C8$\underline{H}$ (m)), 7.62 (0.35H, s, C8$\underline{H}$ (s)); 9.31 (1H, bs, N$\underline{H}$)

^{13}C-NMR (101MHz) ppm(CD_3COCD_3): 27.9 (C4$\underline{H}_2$ (s)), 29.3 (C4$\underline{H}_2$ (m)); 42.7 (C3$\underline{H}_2$ (s)); 43.9 (CO$\underline{C}H_2$); 44.3 (C1$\underline{H}_2$ (m)); 46.3 (C3$\underline{H}_2$ (m)); 47.8 (C1$\underline{H}_2$ (s)); 55.6 (O$\underline{C}H_3$); 114.7 (C3'H, C5'H); 117.6 (C6H (s)), 117.9 (C6H (m)); 119.1 (C8H (m)); 119.4 (C8H (s)); 129.8 (C5H (m)), 129.97 (C5H (s)); 131.1 (C2'H, C6'H); 133.1 (C1'); 133.3 (C8a); 134.2 (C4a (m)); 138.9 (C7NH (s)); 139.0 (C7NH (m)); 159.7 (CONH); 170.4 ($\underline{C}OCF_3$)

^{19}F-NMR (376MHz) ppm(CD_3COCD_3): -70.57 (s), -70.60 (m)

Yield: 73%

IRν_{max}(KBr): 1673cm^{-1}, 2928cm^{-1}, 3335cm^{-1}

HRMS calcd. for C20H19N2O3F3 Na (M^++23): 415.1245 Found: 415.1258

N-(1,2,3,4-tetrahydroisoquinolin-7-yl)-amides

General method of synthesis for **(24)** to **(37)**: the protected isoquinoline (0.78 mmol of **10** to **23**) was dissolved in 20 mL methanol at 65°C and 5 mL water was added dropwise. Potassium carbonate (540 mg/ 3.9 mmol) was added in portions, ensuring total dissolution. The mixture was stirred at 65° C for 30-180 minutes and the deprotection was monitored on TLC. On completion, the methanol was removed *in vacuo*; the residue was taken up in DCM, washed with water and dried with sodium sulfate. The DCM was removed *in vacuo* and the solid was purified by elution from a silica column using a mobile phase of 10:90 methanol: ethyl acetate.

N-(1,2,3,4-Tetrahydro-isoquinolin-7-yl)-propionamide (24)

^{1}H-NMR (400MHz) δ(CD_3COCD_3): 1.59 (3H, t, J = 7.6Hz, C$\underline{H}_3$); 2.79 (2H, q, J = 7.6Hz, C$\underline{H}_2$CH$_3$); 3.10 (3H, s, N2$\underline{H}$, C4$\underline{H}_2$); 3.46 (2H, s, C3$\underline{H}_2$); 4.32 (2H, s, C1$\underline{H}_2$); 7.41 (1H, d, J = 8Hz, C5$\underline{H}$); 7.78 – 7.81 (2H, m, C6$\underline{H}$, C8$\underline{H}$)

^{13}C-NMR (101MHz) ppm(CD_3COCD_3): 10.1 (C$\underline{H}_3$); 29.9 (C$\underline{H}_2$CH$_3$); 30.1 (C$\underline{4}$H$_2$); 44.7 (C$\underline{3}$H$_2$); 49.2 (C$\underline{1}$H$_2$); 117.6, 117.9 (C$\underline{6}$H, C$\underline{8}$H); 130.1 (C$\underline{5}$H); 130.9 (C$\underline{8}$a); 131.1 (C4a); 138.1 (C$\underline{7}$'NH); 164.7 (C$\underline{O}$)

Yield: 88%

IRν_{max}(KBr): 1583cm^{-1}(NH bending), 1688cm^{-1}(CO), 2987cm^{-1}, 3055cm^{-1} (CH aromatic)

HRMS calcd. for C12 H17N2O (M^++1): 205.1341 Found: 205.1335

N-(1,2,3,4-Tetrahydro-isoquinolin-7-yl)-butyramide (25)

^{1}H-NMR (400MHz) δ(CD_3COCD_3): 0.98 (3H, t, J = 7.6Hz, C$\underline{H}_3$); 1.69 – 1.78 (2H, m, C$\underline{H}_2$CH$_3$); 2.31 (2H, t, J = 7.5Hz, C$\underline{H}_2$CH$_2$); 2.67 (1H, s, N2$\underline{H}$); 2.73 (2H, t, J = 6Hz, C4$\underline{H}_2$); 3.10 (2H, t, J = 6Hz, C3$\underline{H}_2$); 4.13 (2H, s, C1$\underline{H}_2$); 6.98 (1H, d, J = 8Hz, C5$\underline{H}$); 7.20 – 7.29 (2H, m, C6$\underline{H}$, C8$\underline{H}$); 7.92 (1H, bs, CON$\underline{H}$)

^{13}C-NMR (101MHz) ppm(CD_3COCD_3): 13.7 (C$\underline{H}_3$); 10.0 (C$\underline{H}_2$CH$_3$); 28.3 (C$\underline{4}$H$_2$); 39.4 (CO$\underline{C}$H$_2$); 43.7 (C$\underline{3}$H$_2$); 48.0 (C$\underline{1}$H$_2$); 117.7, 118.2 (C$\underline{6}$H, C$\underline{8}$H); 129.5 (C$\underline{5}$H); 130.3 (C$\underline{8}$a, C4a); 135.8 (C$\underline{7}$'NH); 171.6 (C$\underline{O}$)

Yield: 36%

IRν_{max}(KBr): 1595cm^{-1}(NH bending), 1686cm^{-1}(CO), 2987cm^{-1}, 3055cm^{-1} (CH aromatic)

HRMS calcd. for C13 H19N2O (M^++1): 219.1497 Found: 219.1494

Cyclohexanecarboxylic acid-(1,2,3,4-Tetrahydro-isoquinolin-7-yl)-amide (26)

^{1}H-NMR (400MHz) δ(CD_3COCD_3): 1.24 – 2.30 (11H, m, cyclohexyl ring); 2.68 (3H, m, C4$\underline{H}_2$, N2$\underline{H}$); 3.02 (2H, m, C3$\underline{H}_2$); 3.87 (2H, s, C1$\underline{H}_2$); 6.95 – 6.97 (1H, m, C5$\underline{H}$); 7.36 – 7.40 (2H, m, C6$\underline{H}$, C8$\underline{H}$); 8.05 (N$\underline{H}$)

^{13}C-NMR (101MHz) ppm(CD_3COCD_3): 26.6 (C$\underline{H}_2$ in cyclohexyl ring); 28.6 (C$\underline{4}$H$_2$); 30.5 (C$\underline{H}_2$ in cyclohexyl ring); 40.9 (C$\underline{3}$H$_2$); 44.5 (C$\underline{1}$H$_2$); 117.8 (C$\underline{6}$H); 118.6 (C$\underline{8}$H); 128.7 (C$\underline{8}$a); 129.1 (C$\underline{5}$H); 129.7 (C$\underline{4}$a); 138.5 (C$\underline{7}$NH); 165.9 (NHC$\underline{O}$)

Yield: 83%

IRν_{max}(KBr): 1594cm^{-1}(NH bending), 1673cm^{-1}(CO), 2987cm^{-1}, 3054cm^{-1} (CH aromatic)

HRMS calcd. for C16H23N2O (M^++H): 259.1810 Found: 259.1815

_N_-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-benzamide (27)

^{1}H-NMR (400MHz) δ(CD_3COCD_3): 2.70 (2H, t, J = 6Hz, C4H_2); 3.01 (2H, s, C3H_2); 3.31 (1H, N2H); 3.88 (2H, s, C1H_2); 7.02 (1H, d, J = 8Hz, C5H); 7.47 – 7.58 (5H, m, C3'H, C5'H); 7.31 – 7.33 (2H, m, C6H, C8H); 7.86 – 7.93 (5H, m, C6H, C8H, C2'H, C3'H, C5'H, C6'H); 7.99 – 8.01 (2H, m, C4'H, CONH)

^{13}C-NMR (101MHz) ppm(CD_3COCD_3): 29.3 (C4H_2); 44.4 (C3H_2); 48.9 (C1H_2); 118.6, 118.9 (C6H, C8H); 128.2 (C2'H, C6'H); 129.1 (C3'H, C5'H); 129.9 (C5H); 131.5 (C8a, C4a); 132.1 (C4'H); 136.2 (C1'); 137.5 (C7'NH); 166.1 (CO)

Yield: 63%

IRν_{max}(KBr): 1594cm^{-1}(NH bending), 1673cm^{-1}(CO), 2987cm^{-1}, 3055cm^{-1} (CH aromatic)

HRMS calcd. for C16H17N2O (M^++1): 253.1341 Found: 253.1345

4-Fluoro-_N_-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-benzamide (28)

^{1}H-NMR (400MHz) δ($CDCl_3$): 2.76 (2H, s, C4H_2); 3.11 (3H, s, N2H, C3H_2); 3.91 (2H, s, C1H_2); 7.02 (1H, d, J = 8Hz, C5H); 7.08 – 7.14 (2H, m, C3'H, C5'H); 7.31 – 7.33 (2H, m, C6H, C8H); 7.86 – 7.90 (2H, m, C2'H, C6'H); 8.32 (1H, s, CONH)

^{13}C-NMR (101MHz) ppm($CDCl_3$): 28.0 (C4H_2); 43.4 (C3H_2); 47.6 (C1H_2); 115.6 (d, J = 22Hz, C3'H, C5'H); 118.4, 119.0 (C6H, C8H); 127.9 (C8a); 129.5 (C5H); 129.6 (C2'H, C6'H); 130.6 (C4a); 135.7 (C7'NH); 164.8 (d, J = 251Hz, C4'F); 164.9 (CO)

^{19}F-NMR (376MHz) ppm($CDCl_3$): -108.04

Yield: 27%

IRν_{max}(KBr): 1604cm^{-1}(NH bending), 1671cm^{-1}(CO), 2987cm^{-1}, 3055cm^{-1} (CH aromatic)

HRMS calcd. for C16H16N2OF (M^++1): 271.1247 Found: 271.1243

4-Chloro-_N_-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-benzamide (29)

^{1}H-NMR (400MHz) δ(CD_3COCD_3): 2.71 (2H, s, C4H_2); 2.88 (1H, s, N2H); 3.03 (2H, s, C3H_2); 3.91 (2H, s, C1H_2); 7.02 (1H, d, J = 8Hz, C5H); 7.53 – 7.55 (4H, m, C3'H, C5'H, C6H, C8H); 8.00 – 8.02 (2H, d, J = 8.5Hz, C2'H, C6'H); 8.05 (1H, s, CONH)

^{13}C-NMR (101MHz) ppm(CD_3COCD_3): 29.7 (C4H_2); 44.8 (C3H_2); 49.3 (C1H_2); 118.9, 119.1 (C6H, C8H); 130.3 (C3'H, C5'H); 130.5 (C8a); 130.4 (C2'H, C6'H); 131.3 (C1'); 132.0 (C5H); 132.0 (C4a); 137.7 (C7'NH); 138.0 (C4'Cl); 165.2 (CO)

Yield: 62%

IRν_{max}(KBr): 1596cm^{-1}(NH bending), 1667cm^{-1}(CO), 2987cm^{-1}, 3055cm^{-1} (CH aromatic)

HRMS calcd. for C16 H16N2OCl (M^++1): 287.0951 Found: 287.0951

4-Bromo-_N_-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-benzamide (30)

^{1}H-NMR (400MHz) δ(CD_3COCD_3): 2.73 (2H, s, C4H_2); 3.04 (3H, s, N2H, C3H_2); 3.92 (2H, s, C1H_2); 7.04 (1H, d, J = 8Hz, C5H); 7.52 – 7.56 (2H, m, C6H, C8H); 7.69 (2H, d, J = 8Hz, C3'H, C5'H); 7.95 (2H, d, J = 8.5Hz, C2'H, C6'H); 7.99 (1H, s, CONH)

^{13}C-NMR (101MHz) ppm(CD_3COCD_3): 29.5 (C4H_2); 44.6 (C3H_2); 49.1 (C1H_2); 118.8, 119.1 (C6H, C8H); 126.4 (CBr); 130.2 (C5H); 130.4 (C3'H, C5'H); 131.8 (C8a); 132.5 (C2'H, C6'H); 131.3 (C1'); 132.5 (C4a); 137.7 (C7'NH); 166.1 (CO)

Yield: 96%

IRν_{max}(KBr): 1594cm^{-1}(NH bending), 1674cm^{-1}(CO), 2987cm^{-1}, 3055cm^{-1} (CH aromatic)

HRMS calcd. for C16H16N2OBr (M^++1): 331.0446 Found: 331.0450

4-Iodo-*N*-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-benzamide (31)

^{1}H-NMR (400MHz) δ(CD_3COCD_3): 2.73 (2H, s, C4H_2); 3.05 (3H, s, N2H, C3H_2); 3.91 (2H, s, C1H_2); 6.92 – 7.16 (1H, m, C5H); 7.41 – 7.56 (2H, m, C6H, C8H); 7.79 (2H, d, J = 8Hz, C3'H, C5'H); 7.90 (2H, d, J = 8Hz, C2'H, C6'H); 7.94 (1H, s, CONH)

^{13}C-NMR (101MHz) ppm(CD_3COCD_3): 30.2 (C4H_2); 44.4 (C3H_2); 48.8 (C1H_2); 98.5 (CI); 118.5, 118.8 (C6H, C8H); 130.0 (C2'H, C6'H); 130.2 (C5H); 131.8 (C8a); 138.4 (C3'H, C5'H); 131.6 (C1'); 136.2 (C4a); 138.3 (C7'NH); 165.3 (CO)

Yield: 93%

IRν_{max}(KBr): 1588cm^{-1}(NH bending), 1673cm^{-1}(CO), 2987cm^{-1}, 3055cm^{-1} (CH aromatic)

HRMS calcd. for C16H16N2OI (M^++H): 379.0307 Found: 379.0317

2-Methoxy-*N*-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-benzamide (32)

^{1}H-NMR (400MHz) δ(CD_3COCD_3): 2.70 (2H, s, C4H_2); 3.01 (2H, s, C3H_2); 3.90 (2H, s, C1H_2); 4.05 (3H, s, OCH_3); 7.00 (1H, d, J = 8Hz, C5H); 7.08 (1H, dd, J_1 = 8Hz, J_2 = 2.4Hz, C5'H); 7.15 (1H, d, J = 8.3Hz, C3'H); 7.49 – 7.50 (4H, m, C6H, C8H, C4'H, C6'H); 8.08 (1H, dd, J_1 = 7.7Hz, J_2 = 1.7Hz, NH)

^{13}C-NMR (101MHz) ppm(CD_3COCD_3): 29.0 (C4H_2); 44.2 (C3H_2); 48.6 (C1H_2); 56.5 (OCH_3); 112.5 (C3'H); 118.1, 118.5 (C6H, C8H); 121.6 (C5'H); 123.2 (C8a); 129.2 (C5H); 129.9 (C4a); 132.1 (C6'H); 133.6 (C4'H); 137.1 (C7'NH); 158.0 (C4'OCH_3); 163.5 (CO)

Yield: 98%

IRν_{max}(KBr): 1265cm^{-1}, 1667cm^{-1}, 2987m^{-1}, 3055cm^{-1}

HRMS calcd. for C17H19N2O2 (M^++1): 283.1447 Found: 283.1438

3-Methoxy-*N*-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-benzamide (33)

^{1}H-NMR (400MHz) δ(CD_3COCD_3): 2.70 (2H, s, C4H_2); 3.02 (2H, s, C3H_2); 3.84 (3H, s, OCH_3); 3.88 (2H, s, C1H_2); 7.01 (1H, d, J = 8.2Hz, C5H); 7.08 (1H, dd, J_1 = 8Hz, J_2 = 2.4Hz, C4'H); 7.37 (1H, t, J = 7.9Hz, C5'H); 7.52 (1H, s, C8H); 7.55 – 7.59 (3H, m, C6H, C2'H, C6'H); 7.63 (1H, NH)

^{13}C-NMR (101MHz) ppm(CD_3COCD_3): 32.4 (C4H_2); 44.1 (C3H_2); 48.4 (C1H_2); 55.5 (OCH_3); 113.3 (C2'H); 117.8 (C4'H); 118.2, 118.5 (C6H, C8H); 118.8 (C6'H); 120.1 (C5'H); 129.0 (C4a); 129.8 (C5H); 130.0 (C6'H); 131.1 (C4a); 137.4 (C7'NH); 160.3 (C4'OCH_3); 165.8 (CO)

Yield: 72%

IRν_{max}(KBr): 1526cm^{-1}, 1670cm^{-1}, 2928cm^{-1}, 3055cm^{-1}

HRMS calcd. for C17H19N2O2 (M^++1): 283.1447 Found: 283.1440

4-Methoxy-*N*-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-benzamide (34)

^{1}H-NMR (400MHz) δ($CDCl_3$): 2.75 (2H, t, J = 5.5Hz, C4H_2); 3.04 (1H, s, N2H); 3.09 (2H, s, C3H_2); 3.84 (3H, s, OCH_3); 3.90 (2H, s, C1H_2); 6.90 (1H, d, J = 9Hz, C3' H, C5'H); 7.01 (1H, d, J = 8Hz, C5H); 7.31 – 7.34 (2H, m, C6H, C8H); 7.83 (2H, d, J = 9Hz, C2'H, C6'H); 8.28 (1H, bs, CONH)

^{13}C-NMR (101MHz) ppm($CDCl_3$): 28.2 (C4H_2); 43.5 (C3H_2); 47.8 (C1H_2); 55.4 (OCH_3); 113.7 (C3'H, C5'H); 118.2, 118.7 (C6H, C8H); 126.9 (C4a); 129.0 (C2'H, C6'H); 129.5 (C5H); 130.4 (C4a); 135.9 (C7'NH); 162.3 (C4'OCH_3); 165.4 (CO)

Yield: 87%

IRν_{max}(KBr): 1508cm^{-1}, 1660cm^{-1}, 2929cm^{-1}, 3054cm^{-1}

HRMS calcd. for C17H19N2O2 (M^++1): 283.1447 Found: 283.1439

4-Nitro-*N*-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-benzamide (35)

^{1}H-NMR (400MHz) δ(CD_3COCD_3): 2.80 (2H, bs, C4H_2); 3.03 – 3.11 (3H, bs, N2H, C3H_2); 4.00 (2H, s, C1H_2); 7.09 (1H, s, C5H); 7.59 (2H, s, C6H, C8H); 8.28 (2H, m, C2'H, C6'H); 8.36 (2H, bs, C3'H, C5'H)

^{13}C-NMR (101MHz) ppm(CD_3COCD_3): 28.7 (C4H_2); 40.8 (C3H_2); 41.7 (C1H_2); 119.0 (C6H)); 119.9 (C8H); 124.4 (C3'H, C5'H); 129.9 (C2'H, C6'H); 130.2 (C5H); 130.6 (C4a); 133.9 (C8a); 138.3 (C7NH (s)), 138.7 (C7NH)(m)); 141.8 (C1'); 150.7 (C4'NO_2); 164.7 (NHCO)

Yield: 64%

IRν_{max}(KBr): 1596cm^{-1}(NH bending), 1666cm^{-1}(CO), 2987cm^{-1}, 3055cm^{-1} (CH aromatic)

HRMS calcd. for C16H16N3O3 (M^++H): 298.1192 Found: 298.1185

2-Phenyl-*N*-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-acetamide (36)

^{1}H-NMR (400MHz) δ(CD_3COCD_3): 2.05 – 2.10 (2H, m, COCH_2); 2.65 (2H, s, C4H_2); 2.98 (3H, s, N2H, C3H_2); 3.83 (2H, s, C1H_2); 6.95 (1H, d, J = 9Hz, C5H); 7.22 – 7.42 (7H, m, C6H, C8H, C2'H, C3'H, C4'H, C5'H, C6'H)

^{13}C-NMR (101MHz) ppm(CD_3COCD_3): 29.5 (C4H_2); 44.7 (C3H_2, COCH_2); 49.1 (C1H_2); 117.8, 118.1 (C6H, C8H); 126.9 (C4a); 127.5 (C4'H); 129.2 (C2'H, C6'H); 130.1 (C3'H, C5'H); 30.15 (C5H); 131.3 (C8a, C4a); 137.75 (C1'); 137.8 (C7'NH); 169.7 (CO)

Yield: 31%

IRν_{max}(KBr): 1597cm^{-1}(NH bending), 1672cm^{-1}(CO), 2987cm^{-1}, 3055cm^{-1} (CH aromatic)

HRMS calcd. for C17H19N2O (M^++1): 267.1497 Found: 267.1505

2-(4-Methoxy-phenyl-*N*-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-acetamide (37)

^{1}H-NMR (400MHz) δ(CD_3COCD_3): 2.64 (2H, m, C4H_2); 2.74 (1H, bs, N2H); 2.98 (2H, s, C4H_2); 3.31 (2H, s, COCH_2); 3.77 (3H, s, CH_3); 3.83 (2H, s, C1H_2); 6.86 (2H, d, J = 8.5Hz, C3'H, C5'H); 6.93 (1H, d, J = 9 Hz, C5H); 7.27 (2H, d, J = 8.5Hz, C2'H, C6'H); 7.32 (2H, bs, C6H, C8H); 9.31 (1H, bs, NH)

^{13}C-NMR (101MHz) ppm(CD_3COCD_3):): 29.6 (C4H_2); 43.9 (COCH_2); 44.9 (C3H_2); 49.3 (C1H_2); 55.6 (OCH_3); 114.7 (C3'H, C5'H); 117.9 (C6H), 118.2 (C8H); 128.1(C4a, C8a); 129.3 (C5H); 130.3 (C2'H, C6'H); 130.4 (C1'); 137.1 (C7NH); 158.8 (C4'); 169.2 (CONH)

Yield: 54%

IRν_{max}(KBr): 1612cm^{-1}(NH bending), 1680cm^{-1}(CO), 2987cm^{-1}, 3054cm^{-1} (CH aromatic)

HRMS calcd. for C18H21N2O2 (M^++1): 297.1603 Found: 297.1591

SYNTHESIS OF DIHYDROISOQUINOLINES USING THE BISCHLER NAPIERALSKI METHOD

6,7-Dimethoxy-1-methyl-3,4-dihydroisoquinoline

i) Acetylation of β-phenethylamine

N-(3,4-DIMETHOXYPHENYL)ETHYLACETAMIDE (39)

2-(3,4-Dimethoxyphenyl)ethylamine **(38)** (0.5mL/537mg/2.96mmol) was pipetted into acetic anhydride (4.5mL/4.86g/47.6mmol) and the mixture was stirred at 60°C for 2 hours. The mixture was extracted with 20mL dichloromethane and washed to remove the anhydride. The extract was dried and the solvent removed under vacuum. Residual anhydride was dealt with by the addition of toluene to form an azeotrope which could be removed on the rotary evaporator. A colourless solid crystallised overnight.

Yield: 42%

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.93 (3H, COC<u>H</u>3); 2.75 (2H, t, J = 7.04Hz, C1<u>H</u>2NHCOCH3); 3.45 - 3.50 (2H, m, J1 = J2 = 6.52Hz, J3 = 7.04Hz, C2<u>H</u>2); 3.84 (6H, s, C3OC<u>H</u>3, C4OC<u>H</u>3); 5.72 (1H, s, N<u>H</u>COCH3); 6.71 (C5'<u>H</u> but overlaps with doublet of C2'<u>H</u> and C6'<u>H</u>); 6.72, 6.79, 6.81 (d, J = 6.52Hz, C2'<u>H</u>, C6'<u>H</u>); 3H in total in aromatic region.

^{13}C-NMR (101MHz): ppm($CDCl_3$): 22.77 (NHCO<u>C</u>H3); 34.73 (<u>C</u>2H2); 40.31 (<u>C</u>1H2NHCOCH3); 55.41 (C3O<u>C</u>H3, C4OC<u>H</u>3); 111.04, 111.56 (<u>C</u>2'H, <u>C</u>6'H); 120.17 (<u>C</u>5'H); 130.98 (<u>C</u>1'C2H2); 147.28, 148.64 (<u>C</u>3OCH3, <u>C</u>4OCH3); 169.59 (NH<u>C</u>OCH3)

IR ν_{max} (KBr): 3254cm^{-1}, 3085cm^{-1}, 2930cm^{-1}, 1634cm^{-1}, 1519cm^{-1}, 1263cm^{-1}, 1236cm^{-1}, 1140cm^{-1}, 1021cm^{-1}, 816cm^{-1}

Melting point: 92 - 94°C Literature: 95 - 97°C[5]

6,7-Dimethoxy-1-methyl-3,4-dihydroisoquinoline (41)

N-(3,4-Dimethoxyphenyl)ethylacetamide **(39)** (225mg/1.008mmol) was dissolved with stirring in 10mL toluene. Phosphorous pentoxide (286mg) was added and the reaction was refluxed at 120°C for 15 minutes. A further 143mg of phosphorous pentoxide was added and reflux was sustained for another 30 minutes. The toluene was removed on a rotary evaporator to give a brownish solid and white crystals. The mixture was purified by recrystallisation from hot methanol using diethyl ether.

Yield: 20.7% (from β-phenethylamine)

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.28 (3H, C1C<u>H</u>$_3$); 2.55 (2H, t, J = 7.52Hz, C4<u>H</u>$_2$); 3.56 (2H, t, J = 7.52Hz, C3<u>H</u>$_2$); 3.83 (6H, s, s, C6OC<u>H</u>$_3$, C7OC<u>H</u>$_3$); 6.61, 6.92 (1H, 1H; s, s; C5<u>H</u>, C8<u>H</u>)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 23.25 (C1<u>C</u>H$_3$); 25.03 (<u>C</u>4H$_2$); 46.88 (<u>C</u>3H$_2$); 56.21, 55.90 (C6O<u>C</u>H$_3$, C7O<u>C</u>H$_3$); 109.18,110.28 (<u>C</u>5H, <u>C</u>8H); 122.4 (<u>C</u>8a); 131.1 (<u>C</u>4a); 147.5, 151.0 (<u>C</u>6OCH$_3$, <u>C</u>7OCH$_3$); 163.6 (<u>C</u>1N)

IRν_{max} (KBr): 2942cm^{-1} (CH), 1515cm^{-1}, 1215cm^{-1}, 1160cm^{-1} (C=N), 1063cm^{-1}

Melting point: 106 - 108°C Literature: 105 - 106°C[6]

Pictet-Spengler Synthesis of 6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline (43)

3,4-Dimethoxyphenethylamine (5 mL/ 30 mmol) was dissolved in anhydrous toluene (100 mL approximately) and benzaldehyde (3.82 g/3.67 mL/35 mmol) was added by pipette. The solution was stirred

at reflux for 3 hours. The toluene was removed *in vacuo* and trifluoroacetic acid (30 mL) was added. The solution was refluxed for a further 1.5 hours. Icy water was then added to the solution, which was made alkaline with 15%w/v sodium hydroxide solution and extracted with DCM. The extract was dried with sodium sulfate and the solvent was removed *in vacuo* to give a yellow solid.

Yield: 99%

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.89 (2H, s, NH); 2.69 – 2.83 (2H, m, J1 = J2 = J5 = 5.52Hz, J3 = 10.56Hz, J4 = J8 = 6.0Hz, J6 = 6.04Hz, J 7 =10.04Hz, C4H2); 2.93 – 2.99 (2H, m, J1 = 3Hz, J2 = 6Hz, J3 = 5.04, J4 = 8.52Hz, C1HCH2); 3.20 – 3.24 (2H, m, J1 = 4.0Hz, J2 = 5.04Hz, J3 = 5.52Hz, C3H2); 3.49, 3.51 (6H; s,s;C6OCH3, C7OCH3); 4.17 – 4.21 (1H, m, J1 = 4.52Hz, J2 = 5.04, J3 = 4.0Hz, C1HCH2); 6.61, 6.63 (2H, C5H, C8H); 7.27 – 7.37 (5H, m, J1 = 5.04Hz, J2 = 2.52Hz, J3 = 7.0Hz, J4 = 7.52Hz, C2'H, C3'H, C4'H, C5'H, C6'H)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 29.44 (C4H2); 40.64 (C1HCH2); 42.80 (C3H2); 55.85, 55.96 (C6OCH3, C7OCH3); 56.86 (C1H); 109.61 (C5H); 111.92 (C8H); 126.44 (C4'H); 127.29 (C4a); 128.58, 129.40 (C2'H, C3'H, C5'H, C6'H); 130.46 (C8a); 139.11 (CH2C1'); 147.04 (C1HCH2C6H5)

IR ν_{max} (film): 3055cm^{-1}, 2987cm^{-1}, 1513cm^{-1}, 1266cm^{-1}

Melting point: 100 - 102°C Literature: 102 - 103°C[7]

VENKOV SYNTHESIS OF 6,7-DIMETHOXY-3,4-DIHYDROISOQUINOLINES

Compounds 41, 45 - 50

2-(3,4-Dimethoxyphenyl)ethylamine (0.5mL/0.537g/2.96mmol) was pipetted into the appropriate carboxylic acid (3.5mmol). Approximately 5mL of dichloromethane, dried with phosphorous pentoxide, was added and the flask contents were stirred to dissolution. Polyphosphoric acid was heated on a water bath and 10.271g was poured into the flask on the scales. The reaction was stirred and heated at 80°C for 3 hours, at the end of which the viscous contents were scraped onto ice and made alkaline with 15% NaOH w/v solution (about 30mL). The aqueous portion was extracted with two aliquots of 20mL dichloromethane. After drying with magnesium sulphate and filtration the solvent was removed *in vacuo* to give a solid, recrystallised from diethyl ether.

6,7-Dimethoxy-1-methyl-3,4-dihydroisoquinoline (41)

Yield: 57.0%

Spectroscopic details under Bischler-Napieralski synthesis above.

6,7-Dimethoxy-1-ethyl-3,4-dihydroisoquinoline (45)

Yield: 39.8%

^{1}H-NMR (400MHz): δ($CDCl_3$): 0.99 (3H, t, J = 7.04Hz, CH_3); 1.64 – 1.73 (2H, m, CH_2CH_3); 2.61 (2H, t, J = 8.04Hz, CH_2CH_2); 2.67 (2H, t, J = 7.52Hz, C4H_2); 3.62 (2H, t, J = 7.52Hz, C3H_2); 3.90, 3.91 (6H, s, s, C6OCH_3, C7OCH_3); 6.69, 7.00 (1H, 1H; s, s; C5H, C8H)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 13.95 (CH_3); 20.45 (CH_2CH_3); 25.82 (C4H_2); 37.84 (CH_2CH_2); 46.67 (C3H_2); 56.86, 55.17 (C6OCH_3, C7OCH_3); 108.81,110.26 (C5H, C8H); 121.79 (C8a); 131.58 (C4a); 147.33, 151.64 (C6OCH_3, C7OCH_3); 166.78 (C1N)

IRν_{max} (KBr): 2962cm^{-1} (CH), 1514cm^{-1}, 1266cm^{-1}, 1149cm^{-1} (C=N), 739cm^{-1}

Melting point: 44-46°C Literature: 45[8]

6,7-Dimethoxy-1-propyl-3,4-dihydroisoquinoline (46)

Yield: 42.0%

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.13 (3H, t, J = 7.56Hz, C$\underline{H}_3$); 2.53 (2H, t, J = 7.52Hz, C4$\underline{H}_2$); 2.65 (2H, q, J = 7.56Hz, C$\underline{H}_2$CH$_3$); 3.54 (2H, t, J = 7.52Hz, C3$\underline{H}_2$); 3.83, 3.84 (6H, s, s, C6OC$\underline{H}_3$, C7OC$\underline{H}_3$); 6.62, 6.94 (1H, 1H; s, s; C5$\underline{H}$, C8$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 11.06 (C$\underline{H}_3$); 25.56 (C$\underline{H}_2$CH$_3$); 28.57 (C$\underline{H}_2$CH$_3$); 46.51 (C$\underline{H}_2$); 55.62, 55.96 (C6OC$\underline{H}_3$, C7OC$\underline{H}_3$); 108.59,110.14 (C$\underline{H}$, C$\underline{H}$); 121.57 (C$\underline{H}$a); 131.28 (C$\underline{H}$a); 147.20, 150.48 (C$\underline{H}$OCH$_3$, C$\underline{H}$OCH$_3$); 166.26 (C$\underline{H}$N)

IRν_{max} (KBr): 2937cm^{-1} (CH), 1514cm^{-1}, 1273cm^{-1}, 1147cm^{-1} (C=N)

Boiling point: Literature: 170°C at 1mmHg[9]

6,7-Dimethoxy-1-phenyl-3,4-dihydroisoquinoline (47)

Yield: 42.6%

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.75 (2H, t, J = 7.52Hz, C4$\underline{H}_2$); 3.74 (3H, OC$\underline{H}_3$); 3.83 (2H, t, J = 7.52Hz, C3$\underline{H}_2$); 3.96 (3H, OC$\underline{H}_3$); 6.80, 6.81 (2H, C5$\underline{H}$, C8$\underline{H}$); 7.44, 7.45 (3H, overlapping singlet and doublet, J = 2Hz, C4'$\underline{H}$, C3'$\underline{H}$, C5'$\underline{H}$); 7.61 – 7.63 (2H, m, C2'$\underline{H}$, C6'$\underline{H}$)

^{13}C-NMR (101MHz): ppm ($CDCl_3$): 25.97 (C$\underline{H}_2$); 47.62 (C$\underline{H}_2$); 55.98, 56.13 (C6OC$\underline{H}_3$, C7OC$\underline{H}_3$); 110.30, 111.71 (C$\underline{H}$, C$\underline{H}$); 121.58 (C$\underline{H}$a); 128.08 (C$\underline{H}$'H, C$\underline{H}$'H); 128.71 (C$\underline{H}$'H, C$\underline{H}$'H); 129.21 (C$\underline{H}$'H); 132.57 (C$\underline{H}$a); 139.12 (C$\underline{H}$'); 147.13, 150.96 (C$\underline{H}$OCH$_3$, C$\underline{H}$OCH$_3$); 166.65 (C$\underline{H}$C$_6$H$_5$)

IR ν_{max} (KBr): 2938cm^{-1} (CH), 1562cm^{-1}, 1500cm^{-1}, 1278cm^{-1}, 1117cm^{-1} (C=N)

Melting point: 116 - 120°C Literature: 121 - 122°C[10]

6,7-Dimethoxy-1-(4-methoxy-phenyl)-3,4-dihydroisoquinoline (48)[11]

Yield: 42.4%

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.82 (2H, t, J = 8Hz, C4$\underline{H}_2$); 3.77 (2H, t, J = 9Hz, C3$\underline{H}_2$); 3.86 – 3.92 (9H, m, C6OC$\underline{H}_3$, C7OC$\underline{H}_3$, C4'OC$\underline{H}_3$); 6.92 – 6.96 (4H, C5$\underline{H}$, C8$\underline{H}$, C3'$\underline{H}$, C5'$\underline{H}$); 8.04 (2H, s, C2'$\underline{H}$, C6'$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 25.33 (C$\underline{H}_2$); 47.13 (C$\underline{H}_2$); 55.48, 55.94, 56.00 (C4'OC$\underline{H}_3$, C6OC$\underline{H}_3$, C7OC$\underline{H}_3$); 109.52, 110.40 (C$\underline{H}$, C$\underline{H}$); 114.20 (C$\underline{H}$'H, C$\underline{H}$'H); 128.4 (C$\underline{H}$'); 129.62 (C$\underline{H}$a); 131.03 (C$\underline{H}$a); 132.79 (C$\underline{H}$'H, C$\underline{H}$'H); 147.53, 151.54 (C$\underline{H}$OCH$_3$, C$\underline{H}$OCH$_3$, C$\underline{H}$'OCH$_3$); 164.18 (C$\underline{H}$C$_6$H$_5$)

IR ν_{max} (KBr): 2350cm^{-1}, 1514cm^{-1}, 1268cm^{-1}, 1143cm^{-1} (C=N)

Melting point: 112 - 118°C Literature: 118 - 119°C[11]

6,7-Dimethoxy-1-(3,4-dimethoxy-phenyl)-3,4-dihydroisoquinoline (49)

Yield: 42.8%

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.73 (2H, t, J = 7.52Hz, C4$\underline{H}_2$); 3.78 – 3.96 (14H, s, s, s, s, t, overlapping, C6OC$\underline{H}_3$, C7OC$\underline{H}_3$, C3'OC$\underline{H}_3$, C4'OC$\underline{H}_3$, C3$\underline{H}_2$); 6.80 (1H, s, C5$\underline{H}$); 6.89 (1H, s, C8$\underline{H}$); 6.93 (1H, d, J = 8.52Hz, C5'$\underline{H}$); 7.17 (1H, d, J = 8.52Hz, C6'$\underline{H}$); 7.25 (1H, s, C2'$\underline{H}$)

^{13}C-NMR (101MHz): ppm ($CDCl_3$): 26.05 (C$\underline{H}_2$); 47.46 (C$\underline{H}_2$); 55.91, 56.14 (C6OC$\underline{H}_3$, C7OC$\underline{H}_3$); 110.28, 110.41, 111.80, 111.87 (C$\underline{H}$, C$\underline{H}$); 121.57 (C$\underline{H}$a); 121.84 (C$\underline{H}$'H); 132.82 (C$\underline{H}$a); 139.12 (C$\underline{H}$'); 147.02, 148.77, 150.11, 150.90 (C$\underline{H}$'OCH$_3$, C$\underline{H}$'OCH$_3$, C$\underline{H}$OCH$_3$, C$\underline{H}$OCH$_3$); 166.6 (C$\underline{H}$C$_6$H$_5$)

IR ν_{max} (KBr): 2940cm^{-1} (CH), 1563cm^{-1}, 1516cm^{-1}, 1279cm^{-1}, 1161cm^{-1} (C=N)

Melting point: 168 - 170°C Literature: 167 - 168°C[10]

1-Benzyl-6,7-dimethoxy-3,4-dihydroisoquinoline (50)

Yield: 55.3%

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.64 – 2.68 (2H, m, C4$\underline{H_2}$); 3.73 (overlapping singlet and possible triplet, 5$\underline{H}$, C3$\underline{H_2}$, OC$\underline{H_3}$); 3.88 (3H, s, OC$\underline{H_3}$); 4.06 (2H, C$\underline{H_2}C_6H_5$); 6.67 (1H, C5$\underline{H}$); 6.96 (1H, C8$\underline{H}$); 7.19 (1H, t, J = 7.04Hz, C4'$\underline{H}$); 7.26 – 7.33 (4H, m, J1 = 7.56Hz, J2 = J4 = 7.52Hz, J3 = 5.0Hz, C2'$\underline{H}$, C3'$\underline{H}$, C5'$\underline{H}$, C6'$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 25.72 (C$\underline{4H_2}$); 43.47 (C$\underline{H_2}C_6H_5$); 47.19 (C$\underline{3H_2}$); 55.82, 55.92 (C6OC$\underline{H_3}$, C7OC$\underline{H_3}$); 109.72, 110.25 (C$\underline{5H}$, C$\underline{8H}$); 121.59 (C$\underline{4a}$); 126.33 (C$\underline{4'H}$); 127.60, 128.31 (C$\underline{2'H}$, C$\underline{3'H}$, C$\underline{5'H}$, C$\underline{6'H}$); 131.73 (C$\underline{8a}$); 138.16 (C$\underline{1}$); 147.19 (C$\underline{7}$OCH$_3$); 150.60 (C$\underline{6}$OCH$_3$); 165.21 (C$\underline{1}CH_2C_6H_5$)

IR ν_{max} (KBr): 1517cm^{-1}, 1269cm^{-1}, 1215cm^{-1}, 1147cm^{-1} (C=N)

Melting point: 76 - 78°C Literature: 82 - 84°C[10]

Ritter-Murphy Synthesis (52)

Acetamide (2.001 g/ 33.9 mmol) was stirred in acetonitrile (15 mL). Methyleugenol (5.8 mL/6.009 g/33.7 mmol) and phosphorous oxychloride (8.7 mL/14.312 g/93.33 mmol) were added and the mixture was heated at 125°C for 1 hour, under nitrogen. The flask contents were emptied onto ice, the solution was made alkaline using sodium carbonate solution and it was then extracted with dichloromethane. The extract was washed with water, dried with sodium sulfate and the solvent was then removed *in vacuo* to give yellow oil.

6,7-Dimethoxy-1,3-dimethyl-3,4-dihydroisoquinoline (52)

Yield: 17.7%

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.56 (3H, d, J = 6.52Hz, C3C$\underline{H_3}$); 2.79 – 2.83 (1H, m, C4$\underline{H_2}$); 2.85 (3H, s, C1C$\underline{H_3}$); 3.09 (1H, dd, J_1 = 16.7Hz, J_2 = 6.04Hz, C4$\underline{H_2}$); 3.95, 4.00 (6H, s, s, C6OC$\underline{H_3}$, C7OC$\underline{H_3}$); 4.12 (1H, bs, C3$\underline{H}$); 6.79, 7.16 (1H, 1H; s, s; C5$\underline{H}$, C8$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 18.03 (C3$\underline{C}H_3$); 19.36 (C1$\underline{C}H_3$); 32.56 (C$\underline{4}H_2$); 48.47 (C$\underline{3}$H); 56.34, 56.46 (C6OC$\underline{H_3}$, C7OC$\underline{H_3}$); 111.01, 111.04 (C$\underline{5}$H, C$\underline{8}$H); 117.41 (C$\underline{8a}$); 132.04 (C$\underline{4a}$); 148.61, 156.26 (C$\underline{6}$OCH$_3$, C$\underline{7}$OCH$_3$); 173.01 (C$\underline{1}$N)

IRν_{max} (KBr): 2942cm^{-1} (CH), 1515cm^{-1}, 1215cm^{-1}, 1160cm^{-1} (C=N), 1063cm^{-1}

Melting point: 76 - 78°C Literature: 77-78°C[12]

REDUCTION OF 6,7-DIMETHOXY-3,4-DIHYDROISOQUINOLINES TO 6,7-DIMETHOXY-1,2,3,4-TETRAHYDROISOQUINOLINES

Compounds 54 - 57

The 3,4-dihydroisoquinoline (0.36mmol) was dissolved in a stirred mixture of 5mL methanol and glacial acetic acid (30μL/0.48mmol). The flask was cooled to 0°C under nitrogen and sodium borohydride (68mg/1.775mmol) was added in aliquots through a funnel, which was rinsed with a further 1mL approximately of methanol. The yellow stirred solution was allowed to come to room temperature, then heated at 60°C for 4 hours. Water (1.5mL) was added to quench residual sodium borohydride and the flask contents were concentrated *in vacuo*. The residue was taken up in ca. 10mL dichloromethane, washed with 10mL water, dried with anhydrous sodium sulfate, filtered and evaporated to yellowish brown oil.

6,7-Dimethoxy-1-methyl -1,2,3,4-tetrahydroisoquinoline (54)

Yield: 84.9%

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.45 – 1.48 (3H, m, C1HC$\underline{H_3}$); 2.17 (s, NH); 2.67 (1H, d, J = 16.04, C4$\underline{H_2}$); 2.78 – 2.85 (1H, m, C3$\underline{H_2}$); 3.00 – 3.05 (1H, m, C1$\underline{H}$); 3.26 – 3.29 (1H, m C4$\underline{H_2}$); 3.87 (C6OC$\underline{H_3}$, C7OC$\underline{H_3}$); 4.08 (1H, d, J = 6.52Hz, C3$\underline{H_2}$); 6.59 (1H, C5$\underline{H}$); 6.64 (1H, C8$\underline{H}$)

IR ν_{max} (KBr): 3055cm^{-1}, 2987cm^{-1}, 1503cm^{-1}, 1265cm^{-1}

Melting point: 68 - 70°C Literature: 69 -70°C[13]

6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline (43)

As for **(43)** in description under Pictet-Spengler synthesis, above.

6,7-Dimethoxy-1-benzyl-1,2,3,4-tetrahydroisoquinoline (56)

As for **(43)**, but only 0.5 equivalents of sodium borohydride was used, and the solution was not heated after the addition of the borohydride. The reaction was monitored carefully on TLC to allow quenching of the borohydride as soon as cleavage of the benzyl group was observed.

Yield: 77%

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.89 (2H, s, NH); 2.69 – 2.83 (2H, m, C4H_2); 2.93 – 2.99 (2H, m, C1HCH_2); 3.20 – 3.24 (2H, m, C3H_2); 3.49, 3.51 (6H; s, s, C6OCH_3, C7OCH_3); 4.17 – 4.21 (1H, m, C1H); 6.61, 6.63 (2H, C5H, C8H); 7.27 – 7.37 (5H, m, C2'H, C3'H, C4'H, C5'H, C6'H)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 29.44 (C4H_2); 40.64 (C1HCH_2); 42.80 (C3H_2); 55.85, 55.96 (C6OCH_3, C7OCH_3); 56.86 (C1H); 109.61 (C5H); 111.92 (C8H); 126.44 (C4'H); 127.29 (C4a); 128.58, 129.40 (C2'H, C3'H, C5'H, C6'H); 130.46 (C8a); 139.11 (C1'); 147.04 (C1)

IR ν_{max} (KBr): 3055cm^{-1}, 2987cm^{-1}, 1519cm^{-1}, 1265cm^{-1}

Boiling point: (literature only): 135 - 140°C/0.01 Torr[14]

6,7-Dimethoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (57)

Yield: 9.9%

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.25 (3H, d, J = 6Hz, C3CH_3); 1.46 (3H, d, J = 6.04Hz, C1CH_3); 1.66 (1H, s, NH); 2.47 – 2.54 (1H, m, C4H2); 2.66 (2H, d, J = 15.6Hz, C4H_2); 3.03 (1H, bs, C1H); 3.86 (6H; s, C6OCH3, C7OCH3); 4.11 (1H, d, J1 = 6.0Hz, C3H); 6.57, 6.68 (2H, C5H, C8H)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 22.51, 22.57 (C3CH_3, C1CH_3); 37.87 (C4H_2); 49.18 (C1HCH_3); 52.25 (C3HCH_3); 55.85, 56.00 (C6OCH3, C7OCH3); 108.61, 111.64 (C5H, C8H); 127.25 (C4a); 131.97 (C8a); 147.28, 147.38 (C6OCH_3, C7OCH_3)

IRν_{max} (KBr): 3577cm^{-1} (NH), 3317cm^{-1} (CH aromatic), 2942cm^{-1} (CH aliphatic), 1522cm^{-1}, 1250cm^{-1}

Melting poing: 46 - 48°C Literature: 46°C[15]

Ureide (59a)

1,2,3,4-Tetrahydroisoquinoline **(1)** (2 mL/16 mmol) was dissolved in anhydrous DCM. Benzoic acid (2.146 g/17.6 mmol) was added. Dicyclocarbodiimide (4.391 g/21.3 mol) was added to the flask, along with a spatula tipful of dimethylaminopyridine. The mixture was stirred under nitrogen for 7 days. The precipitate was removed by filtration on a Buchner funnel. The organic solution was dried with sodium sulfate and the solvent was removed *in vacuo*. The product was recrystallised from hot methanol using diethyl ether, as a colourless solid.

^{1}H-NMR (400MHz): δ($CDCl_3$): 0.8 (2H, m, C2"H_2, C6"H_2); 1.2 – 1.88 (12H, m, C3"H_2, C5"H_2, C3'"H_2, C5'"H_2, C4"H_2, C4'"H_2); 1.5 – 1.7 (2H, m, C2"H_2, C6"H_2); 1.78 – 1.84 (2H, m, C2'"H_2, C6'"H_2); 1.81, 2.00 – 2.09 (2H, m,m, C2'"H_2, C6'"H_2); 3.42 – 3.47 (1H, m, C1"H); 4.03 – 4.09 (1H, m, C1'"H); 6.15 (1H, d, J = 14Hz, NH); 7.34 – 7.37 (2H, m, C3'H, C5'H); 7.40 – 7.42 (1H, C4'H); 7.50 (2H, d, J = 7 Hz, C2'H, C6'H)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 24.5, 26.2 (C3"H_2, C5"H_2, C3'"H_2, C5'"H_2); 25.2, 25.3 (C4"H, C4'"H); 30.7 (C2'"H_2, C6'"H_2); 32.2 (C2"H_2, C6"H_2); 49.5 (C1"H); 57.3 (C1'"H); 126.6 (C2'H, C6'H); 128.5 (C3'H, C5'H); 130.6 (C4'H); 137.1 (C1'); 154.3 (NCO); 171.3 (COC1')

Yield: 90%

IRν_{max}(KBr): 1450cm^{-1}(C=O stretching), 1698cm^{-1}(C=O stretching), 2055cm^{-1}, 2932cm^{-1}, 3302cm^{-1}(C-H stretching)

Melting point: 162 - 164°C Literature : 164 – 165.5°C[16]

Preparation of amides by direct coupling of carboxylic acid and amine

(61 – 68), (99 – 105), (122 – 129), (145 – 151)

The tetrahydroisoquinoline (2 mmol) was dissolved in anhydrous THF. The carboxylic acid (16 mmol) was added. 1-Hydroxybenzotriazole (16 mmol) was added and the suspension was stirred at room temperature for 15 minutes. It was cooled to 0°C in an ice-bath, and dicyclohexylcarbodiimide (16 mmol) was crushed and added to the flask. The mixture was stirred at 0°C for an hour, then allowed to return to room temperature. It was left stirring overnight. The precipitate was removed on a Buchner funnel and the solvent was removed *in vacuo*. The residue was taken up in DCM, was washed with water, dried with anhydrous sodium sulfate and again evaporated to dryness. If required, the product was purified by elution from a silica column, using a mobile phase of 5:95 ethyl acetate: hexane.

Preparation of amides by reaction of acid chloride and tetrahydroisoquinoline

(69 – 76, 78, 79, 81 - 98), (106 - 121), (130 - 144), (152 - 166)

The tetrahydroisoquinoline (2 mmol) was dissolved in anhydrous DCM and triethylamine (5 mol) was added. The set-up was flushed with nitrogen, and the acid chloride was added dropwise. The solution was refluxed for 1 hour, then stirred overnight at room temperature. The solution was washed with 10% HCl, then water. It was dried with anhydrous sodium sulfate and the solvent was removed *in vacuo*. If impure, the product was isolated by elution from a silica column, using a mobile phase of 5:95 ethyl acetate: hexane.

Preparation of amides using the Baumann-Schotten procedure

(77, 80)

The tetrahydroisoquinoline (40 mmol) was pipetted into 10%w/v sodium hydroxide solution (100mL). The acid chloride (60 mmol) was added to the emulsion and it was shaken vigorously for 20 minutes. The semi-solid which formed was isolated on a Buchner funnel. The remaining liquor was extracted with DCM, and the extract was washed and dried. The solvent was removed *in vacuo* and the combined product was purified by elution from a silica column, using a mobile phase of 5:95 ethyl acetate: hexane.

Position 2 amides

Unsubstituted amides

1-(3,4-Dihydro-*1H*-isoquinolin-2-yl)-2-phenyl-ethanone (61)

^{1}H-NMR (400MHz):

$\delta(CDCl_3)$:

2.70 (1.2H, t, J = 6Hz, C4$\underline{H}_2$); 2.89 (0.8H, t, J = 6Hz, C4$\underline{H}_2$); 3.68 (1.2H, t, J = 6Hz, C3$\underline{H}_2$); 3.85 – 3.90 (2.8H, t, s, overlapping, J = 6Hz, COC$\underline{H}_2$, C3$\underline{H}_2$); 4.63 (0.8H, s, C1$\underline{H}_2$); 4.80 (1.2H, s, C1$\underline{H}_2$); 7.02 – 7.25 (9H, m, C5$\underline{H}$, C6$\underline{H}$, C7$\underline{H}$, C8$\underline{H}$, C2'$\underline{H}$, C3'$\underline{H}$, C4'$\underline{H}$, C5'$\underline{H}$, C6'$\underline{H}$)

^{13}C-NMR (101MHz):

28.4 ($\underline{C}4H_2$ (s)), 29.2 ($\underline{C}4H_2$ (m)); 39.9 ($\underline{C}3H_2$ (s)); 41.3 ($\underline{C}1H_2$ (m)); 41.4 ($\underline{C}H_2$); 43.7 ($\underline{C}3H_2$ (m)); 47.7 ($\underline{C}1H_2$ (s)); 125.9 ($\underline{C}7H$ (s)); 126.3 ($\underline{C}6H$ (s)); 126.4, 126.5, 126.6 ($\underline{C}5H$, $\underline{C}6H$, $\underline{C}7H$ (m)); 126.7 ($\underline{C}5H$ (s));

126.8 (C4'H (m)), 126.83 (COC1'); 128.3 (C8H (m)); 128.6 (C3'H, C5'H); 128.7 (C2'H, C6'H); 128.8 (C8H (s)); 133.3 (C8a (s)), 133.9 (C8a (m)); 134.9 (C4a (m)), 135.0 (C4a (s)); 170.0 (CO)

Yield: 64.5%

IRν_{max}(KBr): 1456cm^{-1}(C-N stretching), 1634cm^{-1}(C=O stretching), 2863cm^{-1}, 2908cm^{-1}, 3024cm^{-1}(C-H stretching)

Melting point: 90 - 92°C Literature: 89 - 91°C[17]

1-(3,4-Dihydro-*1H*-isoquinolin-2-yl)-2-(4-nitro-phenyl)-ethanone (62)

^{1}H-NMR (400MHz):

$\delta(CDCl_3)$:

2.84 (1.2H, t, J = 6Hz, C4H$_2$); 2.90 (0.8H, t, J = 6Hz, C4H$_2$); 3.73 (1.2H, t, J = 6Hz, C3H$_2$); 3.88 (0.8H, t, J = 6Hz, C3H$_2$); 3.92 (2H, s, CH$_2$); 4.67 (0.8H, s, C1H$_2$); 4.78 (1.2H, s, C1H$_2$); 7.05 – 7.23 (4H, m, C5H, C6H, C7H, C8H); 7.44 (2H, t, J = 10Hz, C2'H, C6'H); 8.2 (2H, t, J = 10Hz, C3'H, C5'H)

^{13}C-NMR (101MHz):

28.3 (C4H$_2$ (s)), 29.3 (C4H$_2$ (m)); 40.2 (C3H$_2$ (s)); 40.6 (CH$_2$); 43.7 (C1H$_2$ (m)); 44.5 (C3H$_2$ (m)); 47.8 (C1H$_2$ (s)); 123.7 (C3'H, C5'H); 125.9 (C7H (s)); 126.4 (C6H (s)); 126.6 (C5H, C6H, C7H (m)); 127.1 (C5H (s)); 128.2 (C8H (m)), 128.9 (C8H (s)); 129.9 (C2'H, C6'H); 130.0 (COC1'); 133.1 (C8a); 133.7 (C4a (m)); 142.5 (C4'NO$_2$); 168.4 (CO)

Yield: 63.5%

IRν_{max}(KBr): 1444cm^{-1}(C-N stretching), 1637cm^{-1}(C=O stretching), 2899cm^{-1}, 3440cm^{-1}(C-H stretching)

HRMS calcd. for C17H17N2O3 (M^++1): 297.1239 Found: 297.1242

1-(3,4-Dihydro-*1H*-isoquinolin-2-yl)-2-(4-methylsulfanyl-phenyl)-ethanone (63)

^{1}H-NMR (400MHz):

$\delta(CDCl_3)$:

2.48 (3H, s, CH$_3$); 2.73 (1.2H, t, J = 6Hz, C4H$_2$); 2.87 (0.8H, t, J = 6Hz, C4H$_2$); 3.67 (1.2H, t, J = 6Hz, C3H$_2$); 3.79 (2H, s, CH$_2$); 3.86 (0.8H, t, J = 6Hz, C3H$_2$); 4.62 (0.8H, s, C1H$_2$); 4.78 (1.2H, s, C1H$_2$); 7.02 – 7.20 (8H, m, C5H, C6H, C7H, C8H, C2'H, C3'H, C5'H, C6'H)

^{13}C-NMR (101MHz):

15.8 (SCH$_3$ (m)), 15.9 (SCH$_3$ (s)); 28.4 (C4H$_2$ (s)), 29.2 (C4H$_2$ (m)); 39.9 (C3H$_2$ (s)); 40.60 (CH$_2$ (s)), 40.7 (CH$_2$ (m)); 43.6 (C1H$_2$ (m)); 44.3 (C3H$_2$ (m)); 47.7 (C1H$_2$ (s)); 125.9 (C7H (s)); 126.2 (C6H (s)); 126.4, 126.5, 126.55 (C5H, C6H, C7H (m)); 126.7 (C5H (s)); 126.9 (C3'H, C5'H (m)), 126.96 (C3'H, C5'H (s)); 128.2 (C8H (m)), 128.7 (C8H (s)); 129.0 (C2'H, C6'H (m)); 129.2 (C2'H, C6'H (s)); 132.3 (C8a (s)); 133.1 (COC1'); 133.8 (C8a, C4a (m)), 134.9 (C4a (s)); 136.7, 136.8 (C4'SCH$_3$); 169.8 (CO (s)), 169.9 (CO (m))

Yield: 75.0%

IRν_{max}(KBr): 1435cm^{-1}(C-N stretching), 1630cm^{-1}(C=O stretching), 2852cm^{-1}, 2902cm^{-1}, 3327cm^{-1}(C-H stretching)

HRMS calcd. for C18H19NONaS (M^++23): 320.1085 Found: 320.1090

1-(3,4-Dihydro-*1H*-isoquinolin-2-yl-(-2-(3-methoxy-phenyl)-ethanone (64)

^{1}H-NMR (400MHz):

$\delta(CDCl_3)$:

2.71 (1.2H, t, J = 6Hz, C4H$_2$); 2.87 (0.8H, t, J = 6Hz, C4H$_2$); 3.67 (1.2H, t, J = 6Hz, C3H$_2$); 3.74 (2H, s, CH$_2$); 3.81 (3H, d, J = 7.5Hz, OCH$_3$); 3.87 (0.8H, t, J = 6Hz, C3H$_2$); 4.62 (0.8H, s, C1H$_2$); 4.78 (1.2H, s, C1H$_2$); 6.78 – 6.89 (4H, m, C5H, C6H, C7H, C8H); 7.01 – 7.28 (4H, m, C2'H, C4'H, C5'H, C6'H)

^{13}C-NMR (101MHz):

28.2 (C$4H_2$ (s)), 29.0 (C$4H_2$ (m)); 39.8 (C$3H_2$ (s)); 41.15 (CH_2 (s)), 41.22 (CH_2 (m)); 43.5 (C$1H_2$ (m)); 44.2 (C$3H_2$ (m)); 47.6 (C$1H_2$ (s)); 54.9 (OCH_3 (s)), 54.97 (OCH_3 (m)); 112.1 (C4'H (m)), 112.2 (C4'H (s)); 113.9 (C2'H (s)), 114.0 (C2'H (m)); 120.7 (C6'H (s)), 120.8 (C6'H (m)); 125.8 (C7H (s)); 126.1 (C6H (s)); 126.3, 126.4 (C5H, C6H, C7H (m)); 126.7 (C5H (s)); 128.1 (C8H (m)), 128.6 (C8H (s)); 129.5 (C5'H (s)), 129.52 (C5'H (m)); 132.3 (C8a (s)), 133.0 (C8a (m)); 133.8 (C4a (m)), 134.7 (C4a (s)); 136.1 (C1'(s)), 136.2 (C1' (m)); 159.6 (C3'OCH_3); 169.6 (CO (s)), 169.8 (CO (m))

Yield: 50.3%

IRν_{max}(KBr): 1639cm^{-1}(C=O stretching), 2986cm^{-1}, 3054cm^{-1} (C-H stretching)

HRMS calcd. for C18H19NO2Na (M^++23): 304.1313 Found: 304.1319

1-(3,4-Dihydro-*1H*-isoquinolin-2-yl(-2-(4-methoxy-phenyl)-ethanone (65)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.66 (1.2H, t, J = 5.5Hz, C4H_2); 2.82 (0.8H, t, J = 5.5Hz, C4H_2); 3.62 (1.2H, t, J = 5.5Hz, C3H_2); 3.72 (2H, s, CH_2); 3.74 (3H, s, OCH_3); 3.83 (0.8H, t, J = 5.5Hz, C3H_2); 4.59 (0.8H, s, C1H_2); 4.75 (1.2H, s, C1H_2); 6.83 – 6.87 (2H, m, C3'H, C5'H) 7.02 – 7.22 (6H, m, C5H, C6H, C7H, C8H, C2'H, C6'H)

^{13}C-NMR (101MHz):

28.0 (C$4H_2$ (s)), 28.8 (C$4H_2$ (m)); 39.4 (C$3H_2$ (s)); 39.8 (CH_2 (s)), 39.9 (CH_2 (m)); 43.1 (C$1H_2$ (m)); 43.9 (C$3H_2$ (m)); 47.2 (C$1H_2$ (s)); 54.7 (OCH_3 (s)), 54.97 (OCH_3 (m)); 113.61, 113.65 (C3'H, C5'H); 125.6 (C7H (s)); 125.8 (C6H (s)); 126.0, 126.1 (C5H, C6H, C7H (m)); 126.4 (C5H (s)); 126.5 (COC1'); 127.9 (C8H (m)), 128.3 (C8H (s)); 129.2 (C2'H, C6'H (m)), 129.3 (C2'H, C6'H (s)); 132.1 (C8a (s)), 132.9 (C8a (m)); 133.6 (C4a (m)), 134.5 (C4a (s)); 157.91, 157.94 (C4'OCH_3); 169.7 (CO (s)), 169.8 (CO (m))

Yield: 33.2%

IRν_{max}(KBr): 1638cm^{-1}(C=O stretching), 2987cm^{-1}, 3054cm^{-1} (C-H stretching)

Melting point: 72 - 74°C Literature: 73 - 74°C[18]

HRMS calcd. for C18H19NO2Na (M^++23): 304.1313 Found: 304.1314

1-(3,4-Dihydro-*1H*-isoquinolin-2-yl(-2-(3,4-dimethoxy-phenyl)-ethanone (66)[19]

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.72 (1.2H, t, J = 6Hz, C4H_2); 2.87 (0.8H, t, J = 6Hz, C4H_2); 3.56 (0.8H, t, J = 5.5Hz, C3H_2); 3.69 (1.2H, t, J = 5.5Hz, C3H_2); 3.78 (2H, s, CH_2); 3.80 – 3.88 (6H, dd, J_1 = 7Hz, J_2 = 1.5Hz, 2*OCH_3); 4.64 (0.8H, s, C1H_2); 4.78 (1.2H, s, C1H_2); 6.75 – 6.85 (4H, m, C5H, C6H, C7H, C8H); 7.14 – 7.20 (3H, m, C2'H, C5'H, C6'H)

^{13}C-NMR (101MHz):

28.4 (C$4H_2$ (s)), 29.2 (C$4H_2$ (m)); 39.9 (C$3H_2$ (s)); 40.8 (CH_2 (s)), 41.2 (CH_2 (m)); 43.7 (C$1H_2$ (m)); 44.4 (C$3H_2$ (m)); 47.8 (C$1H_2$ (s)); 55.7 (OCH_3 (s)), 55.76, 55.8 (OCH_3 (m)); 111.1 (C5'H (m)), 111.6 (C5'H (s)); 112.3 (C2'H (s)), 112.4 (C2'H (m)); 120.6 (C6'H (s)), 121.6 (C6'H (m)); 125.9 (C7H (s)); 126.3(C6H (s)); 126.5, 126.6 (C5H, C6H, C7H (m)); 126.9 (C5H (s)); 127.9 (C8H (m)), 128.2 (C8H (s)); 131.1 (C8a (s)), 131.4 (C8a (m)); 132.2 (C4a (m)), 132.4 (C4a (s)); 134.7 (C1'(s)), 138.8 (C1' (m)); 147.8, 149 (C4'OCH_3, C3'OCH_3); 170.4 (CO (s)), 171.0 (CO (m))

Yield: 56.8%

IRν_{max}(KBr): 1456cm^{-1}(C-N stretching), 1634cm^{-1}(C=O stretching), 2863cm^{-1}, 2908cm^{-1}, 3024cm^{-1}(C-H stretching)

Boiling point: (Literature only): 190°C[19]

(3,4-Dihydro-*1H*-isoquinolin-2-yl)-(4-nitro-phenyl)-methanone (67)*

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.90 (1.2H, s, C4$\underline{H}_2$), 3.04 (0.8H, s, C4$\underline{H}_2$); 3.61 (1.2H, t, J = 5.5Hz, C3$\underline{H}_2$); 4.04 (0.8H, s, C3$\underline{H}_2$); 4.53 (0.8H, s, C1$\underline{H}_2$); 4.94 (1.2H, s, C1$\underline{H}_2$); 6.91 – 7.26 (4H, m, C5$\underline{H}$, C6$\underline{H}$, C7$\underline{H}$, C8$\underline{H}$); 7.64 (2H, d, J_1 = 7.5Hz, C2'$\underline{H}$, C6'$\underline{H}$); 8.22 – 8.32 (2H, d, J = 7.5Hz, C3'$\underline{H}$, C5'$\underline{H}$)

^{13}C-NMR (101MHz):

28.1 (C4$\underline{H}_2$ (s)), 29.4 (C4$\underline{H}_2$ (m)); 40.7 (C3$\underline{H}_2$ (s)); 44.8 (C1$\underline{H}_2$ (m); 45.2 (C3$\underline{H}_2$ (m)); 49.6 (C1$\underline{H}_2$ (s)); 121.3 (C3'H, C5'H (s)); 123.3 (C3'H, C5'H (m)); 125.1 (C7H (s)); 125.8 (C6H (s)); 126.5 (C5H, C6H, C7H (m)); 126.7 (C5H (s)); 127.8 (C2'H, C6'H (m)); 128.1 (C2'H, C6'H (s)); 128.6 (C8H (m)); 132.2 (C8a); 133.3 (C4a); 142.0 (COC1'); 148.4 (C4'NO_2); 168.7 (CO)

Yield: 98.0%

IRν_{max}(KBr): 1637cm^{-1}(C=O stretching), 2987cm^{-1}, 3055cm^{-1} (C-H stretching)

(3,4-Dihydro-*1H*-isoquinolin-2-yl)-(4-methylsulfanyl-phenyl)-methanone (68)*

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.53 (3H, SC$\underline{H}_3$); 2.93 (2H, bs, C4$\underline{H}_2$); 3.69 (1.2H, bs, C3$\underline{H}_2$); 3.99 (0.8H, bs, C3$\underline{H}_2$); 4.64 (0.8H, bs, C1$\underline{H}_2$); 4.89 (1.2H, bs, C1$\underline{H}_2$); 6.93 – 7.26 (4H, m, C5$\underline{H}$, C6$\underline{H}$, C7$\underline{H}$, C8$\underline{H}$); 7.29 (2H, d, J_1 = 8Hz, C3'$\underline{H}$, C5'$\underline{H}$); 7.42 (2H, d, J = 8Hz, C2'$\underline{H}$, C6'$\underline{H}$)

^{13}C-NMR (101MHz):

15.0 (C$\underline{H}_3$ (s)), 15.2 (C$\underline{H}_3$ (m)); 24.8 (C4$\underline{H}_2$ (m)), 25.5 (C4$\underline{H}_2$ (s)); 32.2 (C1$\underline{H}_2$ (s)); 33.7 (C3$\underline{H}_2$, C1$\underline{H}_2$ (m)); 43.8 (C3$\underline{H}_2$ (s)); 124.8 (C7H (s)); 125.3 (C6H (s)); 125.7 (C5H, C6H, C7H (m)); 126.6 (C5H (s)); 127.2 (C2'H, C6'H (m)); 127.8 (C2'H, C6'H (s)); 128.0 (C8H (m)), 128.1 (C8H (s)); 130.1 (C8a); 130.3 (C3'H, C5'H (m)); 130.7 (C3'H, C5'H (s)); 132.0 (C1'); 134.1 (C4a); 141.3 (C4'SCH_3); 157.4 (CO)

Yield: 51.0%

IRν_{max}(KBr): 1433cm^{-1}(C-N stretching), 1620cm^{-1}(C=O stretching), 2928cm^{-1}, 3155cm^{-1}(C-H stretching)

1-(3,4-Dihydro-*1H*-isoquinolin-2-yl)-ethanone (69)[20]

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.12 (3H, s, C$\underline{H}_3$); 2.77 (0.8H, t, J = 6Hz, C4$\underline{H}_2$), 2.83 (1.2H, t, J = 6Hz, C4$\underline{H}_2$); 3.59 (1.2H, t, J = 6Hz, C3$\underline{H}_2$); 3.75 (0.8H, t, J = 6Hz, C3$\underline{H}_2$); 4.55 (0.8H, s, C1$\underline{H}_2$); 4.66 (1.2H, s, C1$\underline{H}_2$); 7.05 – 7.12 (4H, m, C5$\underline{H}$, C6$\underline{H}$, C7$\underline{H}$, C8$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 21.3 (C$\underline{H}_3$ (m)), 21.5 (C$\underline{H}_3$ (s)); 28.1 (C4$\underline{H}_2$ (s)), 29.0 (C4$\underline{H}_2$ (m)); 39.0 (C3$\underline{H}_2$ (s)); 43.5 (C1$\underline{H}_2$ (m)); 43.6 (C3$\underline{H}_2$ (m)); 47.6 (C1$\underline{H}_2$ (s)); 125.6 (C7H (s)); 125.9 (C6H (s)); 126.1 (C7H (m)); 126.14, 126.18 (C5H, C6H (m)), 126.5 (C5H (s)); 127.9 (C8H (m)), 128.5 (C8H (s)); 132.2 (C8a (s)), 133.0 (C8a (m)); 133.7 (C4a (m)), 134.6 (C4a (s)); 169.0 (CO (s)), 169.1 (CO (m))

Yield: 71.1%

IRν_{max}(KBr): 1442cm^{-1}(C-N stretching), 1645cm^{-1}(C=O stretching), 3054cm^{-1}(C-H stretching)

1-(3,4-Dihydro-*1H*-isoquinolin-2-yl)-propan-1-one (70)[20]

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.15 (3H, t, J = 7Hz, C$\underline{H}_3$); 2.39 (2H, q, J =7Hz, C$\underline{H}_2$); 2.79 (0.8H, t, J = 6Hz, C4$\underline{H}_2$), 2.85 (1.2H, t, J = 6Hz, C4$\underline{H}_2$); 3.62 (1.2H, t, J = 6Hz, C3$\underline{H}_2$); 3.78 (0.8H, t, J = 6Hz, C3$\underline{H}_2$); 4.56 (0.8H, s, C1$\underline{H}_2$); 4.69 (1.2H, s, C1$\underline{H}_2$); 7.07 – 7.14 (4H, m, C5$\underline{H}$, C6$\underline{H}$, C7$\underline{H}$, C8$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 9.0 (C$\underline{H}_3$ (s)), 9.1 (C$\underline{H}_3$ (m)); 26.4 (C$\underline{H}_2$ (m), 26.6 (C$\underline{H}_2$) (s); 28.2 (C4$\underline{H}_2$ (s)), 29.2 (C4$\underline{H}_2$ (m)); 39.3 (C3$\underline{H}_2$ (s)); 42.7 (C1$\underline{H}_2$ (m)); 43.9 (C3$\underline{H}_2$ (m)); 46.9 (C1$\underline{H}_2$ (s)); 125.7 (C$\underline{7}$H (s)); 126.0 (C$\underline{6}$H (s)); 126.1 (C$\underline{7}$H (m)); 126.2, 126.3 (C$\underline{5}$H, C$\underline{6}$H (m)), 126.5 (C$\underline{5}$H (s)); 127.9 (C$\underline{8}$H (m)), 128.5 (C$\underline{8}$H (s)); 132.4 (C$\underline{8}$a (s)), 133.4 (C$\underline{8}$a (m)); 133.8 (C$\underline{4}$a (m)), 134.8 (C$\underline{4}$a (s)); 172.3 (C$\underline{O}$ (s)), 172.4 (C$\underline{O}$ (m))

Yield: 96.8%

IRν_{max}(KBr): 1436cm^{-1}(C-N stretching), 1644cm^{-1}(C=O stretching), 2940cm^{-1}, 3036cm^{-1}(C-H stretching)

1-(3,4-Dihydro-*1H*-isoquinolin-2-yl)-butan-1-one (71)[20]

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.01 (3H, t, J = 7Hz, C$\underline{H}_3$); 1.69 – 1.75 (2H, m, C$\underline{H}_2$CH$_3$); 2.40 (2H, t, J =7Hz, COC$\underline{H}_2$CH$_2$); 2.85 (0.9H, t, J = 6Hz, C4$\underline{H}_2$), 2.91(1.1 H, t, J = 6Hz, C4$\underline{H}_2$); 3.69 (1.1H, t, J = 6Hz, C3$\underline{H}_2$); 3.84 (0.9H, t, J = 6Hz, C3$\underline{H}_2$); 4.63 (0.9H, s, C1$\underline{H}_2$); 4.75 (1.1H, s, C1$\underline{H}_2$); 7.15 – 7.22 (4H, m, C5$\underline{H}$, C6$\underline{H}$, C7$\underline{H}$, C8$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 13.9 (C$\underline{H}_3$); 18.5 (C$\underline{H}_2$CH$_3$) (s)), 18.6 (C$\underline{H}_2$CH$_3$) (m)); 28.5 (C4$\underline{H}_2$ (s)), 29.5 (C4$\underline{H}_2$ (m)); 35.5 (COC$\underline{H}_2$) (m)), 35.7 (COC$\underline{H}_2$) (s)); 39.5 (C3$\underline{H}_2$ (s)); 43.2 (C1$\underline{H}_2$ (m)); 44.1 (C3$\underline{H}_2$ (m)); 47.3 (C1$\underline{H}_2$ (s)); 125.9 (C$\underline{7}$H (s)); 126.2 (C$\underline{6}$H (s)); 126.4 (C$\underline{7}$H (m)); 126.5, 126.6 (C$\underline{5}$H, C$\underline{6}$H (m)), 126.8 (C$\underline{5}$H (s)); 128.2 (C$\underline{8}$H (m)), 128.8 (C$\underline{8}$H (s)); 132.7 (C$\underline{8}$a (s)), 133.6 (C$\underline{8}$a (m)); 134.0 (C$\underline{4}$a (m)), 135.1 (C$\underline{4}$a (s)); 171.8 (C$\underline{O}$ (s)), 171.9 (C$\underline{O}$ (m))

Yield: 86.8%

IRν_{max}(KBr): 1432cm^{-1}(C-N stretching), 1640cm^{-1}(C=O stretching), 2947cm^{-1}, 3036cm^{-1}(C-H stretching)

1-(3,4-Dihydro-*1H*-isoquinolin-2-yl)-pentan-1-one (72)

^{1}H-NMR (400MHz): δ($CDCl_3$): 0.93 (3H, dt, J_1 = 7.3Hz, J_2 = 2.9Hz, C$\underline{H}_3$); 1.38 (2H, q, J = 7.3Hz, C$\underline{H}_2$CH$_3$); 1.60 – 1.69 (2H, m, C$\underline{H}_2$CH$_2$CH$_3$); 2.40 (2H, t, J =7Hz, COC$\underline{H}_2$CH$_2$); 2.82 (0.8H, t, J = 5.5Hz, C4$\underline{H}_2$), 2.88 (1.2 H, t, J = 5.5Hz, C4$\underline{H}_2$); 3.66 (1.2H, t, J = 5.8Hz, C3$\underline{H}_2$); 3.81 (0.8H, t, J = 5.8Hz, C3$\underline{H}_2$); 4.60 (0.8H, s, C1$\underline{H}_2$); 4.71 (1.2H, s, C1$\underline{H}_2$); 7.10 – 7.17 (4H, m, C5$\underline{H}$, C6$\underline{H}$, C7$\underline{H}$, C8$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 13.7 (C$\underline{H}_3$); 22.3 (C$\underline{H}_2$CH$_3$) (s)), 22.4 (C$\underline{H}_2$CH$_3$) (m)); 27.0 (C$\underline{H}_2$CH$_2$CH$_3$) (s)), 27.1 (CH$_2$C$\underline{H}_2$CH$_3$) (m)); 28.3 (C4$\underline{H}_2$ (s)), 29.3 (C4$\underline{H}_2$ (m)); 33.1 (COC$\underline{H}_2$) (m)), 33.3 (COC$\underline{H}_2$) (s)); 39.3 (C3$\underline{H}_2$ (s)); 43.0 (C1$\underline{H}_2$ (m)); 43.9 (C3$\underline{H}_2$ (m)); 47.1 (C1$\underline{H}_2$ (s)); 125.8 (C$\underline{7}$H (s)); 126.0 (C$\underline{6}$H (s)); 126.2 (C$\underline{7}$H (m)); 126.3, 126.4 (C$\underline{5}$H, C$\underline{6}$H (m)), 126.6 (C$\underline{5}$H (s)); 128.0 (C$\underline{8}$H (m)), 128.7 (C$\underline{8}$H (s)); 132.5 (C$\underline{8}$a (s)), 133.4 (C$\underline{8}$a (m)); 133.8 (C$\underline{4}$a (m)), 134.9 (C$\underline{4}$a (s)); 171.8 (C$\underline{O}$ (s)), 171.9 (C$\underline{O}$ (m))

Yield: 80.1%

IRν_{max}(film): 1423cm^{-1}(C-N stretching), 1638cm^{-1}(C=O stretching), 2961cm^{-1}, 3054cm^{-1}(C-H stretching)

HRMS calcd. for C14H20NO (M^++1): 218.1545 Found: 218.1538

1-(3,4-Dihydro-*1H*-isoquinolin-2-yl)-3-methyl-butan-1-one (73)

^{1}H-NMR (400MHz): δ($CDCl_3$): 0.98 (6H, t, J = 6.8Hz, (C$\underline{H}_3$)$_2$); 2.12 – 2.23 (1H, m C$\underline{H}$(CH$_3$)$_2$); 2.29 (2H, dd, J_1 = 6.8Hz, J_2 = 2.5Hz, C$\underline{H}_2$CH); 2.83 (0.85H, t, J = 6Hz, C4$\underline{H}_2$), 2.88 (1.15 H, t, J = 6Hz, C4$\underline{H}_2$); 3.67

(1.15H, t, J = 6Hz, C3$\underline{H}_2$); 3.82 (0.85H, t, J = 6Hz, C3$\underline{H}_2$); 4.62 (0.85H, s, C1$\underline{H}_2$); 4.73 (1.15H, s, C1$\underline{H}_2$); 7.10 – 7.20 (4H, m, C5$\underline{H}$, C6$\underline{H}$, C7$\underline{H}$, C8$\underline{H}$)

^{13}C-NMR (101MHz): ppm(CDCl $_3$): 22.6 (($\underline{C}H_3)_2$); 25.4 ($\underline{C}H(CH_3)_2$ (s)), 25.5 ($\underline{C}H(CH_3)_2$ (m)); 28.3 ($\underline{C}4H_2$ (s)), 29.4 ($\underline{C}4H_2$ (m)); 39.4 ($\underline{C}3H_2$ (s)); 42.2 ($\underline{C}H_2CH$) (m), 42.3 ($\underline{C}H_2CH$) (s)); 43.2 ($\underline{C}1H_2$ (m)); 43.9 ($\underline{C}3H_2$ (m)); 47.4 ($\underline{C}1H_2$ (s)); 125.8 ($\underline{C}7H$ (s)); 126.1 ($\underline{C}6H$ (s)); 126.2 ($\underline{C}7H$ (m)); 126.3, 126.4 ($\underline{C}5H$, $\underline{C}6H$ (m)), 126.6 ($\underline{C}5H$ (s)); 128.1 ($\underline{C}8H$ (m)), 128.7 ($\underline{C}8H$ (s)); 132.5 ($\underline{C}8a$ (s)), 133.4 ($\underline{C}8a$ (m)); 133.8 ($\underline{C}4a$ (m)), 134.9 ($\underline{C}4a$ (s)); 171.1 ($\underline{C}O$ (s)), 171.3 ($\underline{C}O$ (m))

Yield: 99.9%

IRν_{max}(KBr): 1436cm^{-1}(C-N stretching), 1640cm^{-1}(C=O stretching), 2960cm^{-1}, 3052cm^{-1}(C-H stretching)

HRMS calcd. for C14H20NO (M^++1): 218.1545 Found: 218.1534

Cyclopropyl-(3,4-dihydro-*1H*-isoquinolin-2-yl)-methanone (74)

^{1}H-NMR (400MHz): δ($CDCl_3$): 0.77 – 0.79 (1.8H, m, C$\underline{H}_2$); 0.98 – 1.02 (2.2H, m, C$\underline{H}_2$); 1.81 (1H, d, J = 4.5Hz, COC$\underline{H}$); 2.79 (0.9H, t, J = 5.5Hz, C4$\underline{H}_2$), 2.90 (1.1 H, t, J = 5.5Hz, C4$\underline{H}_2$); 3.79 (0.9H, t, J = 5.5Hz, C3$\underline{H}_2$); 3.85 (1.1H, t, J = 5.5Hz, C3$\underline{H}_2$); 4.9 (1.1H, s, C1$\underline{H}_2$); 4.82 (0.9H, s, C1$\underline{H}_2$); 7.10 – 7.16 (4H, m, C5$\underline{H}$, C6$\underline{H}$, C7$\underline{H}$, C8$\underline{H}$)

^{13}C-NMR (101MHz): ppm(CDCl $_3$): 7.0 ($\underline{C}H_2$) (m)); 7.2 ($\underline{C}H_2$) (s)); 10.9 ($\underline{C}H$) (m)), 11.1 ($\underline{C}H$) (s)); 28.2 ($\underline{C}4H_2$ (s)), 29.1 ($\underline{C}4H_2$ (m)); 39.6 ($\underline{C}3H_2$ (s)); 42.9 ($\underline{C}1H_2$ (m)); 44.3 ($\underline{C}3H_2$ (m)); 47.8 ($\underline{C}1H_2$ (s)); 125.7 ($\underline{C}7H$ (s)); 125.9 ($\underline{C}6H$ (s)); 126.07, 126.1 ($\underline{C}5H$, $\underline{C}6H$, $\underline{C}7H$ (m)), 126.3 ($\underline{C}5H$ (s)); 127.8 ($\underline{C}8H$ (m)), 128.4 ($\underline{C}8H$ (s)); 132.4 ($\underline{C}8a$ (s)), 133.4 ($\underline{C}8a$ (m)); 134.1 ($\underline{C}4a$ (m)), 134.8 ($\underline{C}4a$ (s)); 172.0 ($\underline{C}O$)

Yield: 95.3%

IRν_{max}(KBr): 1436cm^{-1}(C-N stretching), 1636cm^{-1}(C=O stretching), 2917cm^{-1}, 3036cm^{-1}(C-H stretching)

HRMS calcd. for C13H16NO (M^++1): 202.1232 Found: 202.1237

Cyclobutyl-(3,4-dihydro-*1H*-isoquinolin-2-yl)-methanone (75)*

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.84 – 1.89 (1H, m, C$\underline{H}_2$); 1.93 – 2.03 (1H, m, C$\underline{H}_2$); 2.14 – 2.22 (2H, m, C$\underline{H}_2$); 2.30 – 2.43 (2H, m, C$\underline{H}_2$); 2.81 – 2.83 (2H, m, C4$\underline{H}_2$); 3.28 – 3.36 (1H, m, C$\underline{H}$); 3.54 (1.2H, t, J = 5.8Hz, C3$\underline{H}_2$); 3.79 (0.8H, t, J = 5.8Hz, C3$\underline{H}_2$); 4.47 (0.8H, s, C1$\underline{H}_2$); 4.70 (1.2H, s, C1$\underline{H}_2$); 7.08 – 7.16 (4H, m, C5$\underline{H}$, C6$\underline{H}$, C7$\underline{H}$, C8$\underline{H}$)

^{13}C-NMR (101MHz): ppm(CDCl $_3$): 17.7 ($\underline{C}H_2$) (s)); 17.8 ($\underline{C}H_2$) (m)); 24.8 ($\underline{C}H_2$*2); 28.2 ($\underline{C}4H_2$ (s)), 29.3 ($\underline{C}4H_2$ (m)); 37.2 ($\underline{C}H$) (m)), 37.4 ($\underline{C}H$) (s)); 39.6 ($\underline{C}3H_2$ (s)); 42.3 ($\underline{C}1H_2$ (m)); 44.1 ($\underline{C}3H_2$ (m)); 46.5 ($\underline{C}1H_2$ (s)); 125.6 ($\underline{C}7H$ (s)); 126.0 ($\underline{C}6H$ (s)); 126.1 ($\underline{C}7H$ (m)); 126.2, 126.3 ($\underline{C}5H$, $\underline{C}6H$, (m)), 126.5 ($\underline{C}5H$ (s)); 128.1 ($\underline{C}8H$ (m)), 128.6 ($\underline{C}8H$ (s)); 132.6 ($\underline{C}8a$ (s)), 133.3 ($\underline{C}8a$ (m)); 133.8 ($\underline{C}4a$ (m)), 134.8 ($\underline{C}4a$ (s)); 173.15 ($\underline{C}O$ (s)), 173.19 ($\underline{C}O$ (m)

Yield: 61.7%

IRν_{max}(KBr): 1436cm^{-1}(C-N stretching), 1636cm^{-1}(C=O stretching), 2917cm^{-1}, 3036cm^{-1}(C-H stretching)

Cyclohexyl-(3,4-dihydro-*1H*-isoquinolin-2-yl)-methanone (76)*

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.22 – 1.33, 1.47 – 1.52, 1.63 – 1.73 (3H, 2H, 5H, m, m, m, C$\underline{H}_2$ of cyclohexyl ring); 2.49 – 2.54 (1H, m, COC$\underline{H}$); 2.75 (0.8H, t, J = 5.5Hz, C4$\underline{H}_2$), 2.83 (1.2 H, t, J = 5.5Hz, C4$\underline{H}_2$); 3.64 (1.2H, t, J = 5.5Hz, C3$\underline{H}_2$); 3.74 (0.8H, t, J = 5.5Hz, C3$\underline{H}_2$); 4.59 (0.8H, s, C1$\underline{H}_2$); 4.65 (1.2H, s, C1$\underline{H}_2$); 7.05 – 7.12 (4H, m, C5$\underline{H}$, C6$\underline{H}$, C7$\underline{H}$, C8$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 25.4, 28.0, 28.8 ($\underline{C}H_2$ of cyclohexyl ring); 28.9 ($\underline{C}4H_2$ (s)), 29.4 ($\underline{C}4H_2$ (m)); 39.3 ($\underline{C}3H_2$ (s)); 40.3 ($\underline{C}H$ (m)), 40.5 ($\underline{C}H$ (s)); 42.5 ($\underline{C}1H_2$ (m)); 43.8 ($\underline{C}3H_2$ (m)); 46.8 ($\underline{C}1H_2$ (s)); 125.5 ($\underline{C}7H$ (s)); 125.8 ($\underline{C}6H$ (s)); 125.9 ($\underline{C}7H$ (m)); 125.94, 126.1 ($\underline{C}5H$, $\underline{C}6H$, (m)), 126.3 ($\underline{C}5H$ (s)); 127.8 ($\underline{C}8H$ (m)), 128.4 ($\underline{C}8H$ (s)); 132.4 ($\underline{C}8a$ (s)), 133.2 ($\underline{C}8a$ (m)); 133.6 ($\underline{C}4a$ (m)), 134.6 ($\underline{C}4a$ (s)); 174.3 ($\underline{C}O$ (s)), 174.5 ($\underline{C}O$ (m))

Yield: 96.4%

IRν_{max}(KBr): 1447cm^{-1}(C-N stretching), 1636cm^{-1}(C=O stretching), 2954cm^{-1}, 3053cm^{-1}(C-H stretching)

(3,4-Dihydro-*1H*-isoquinolin-2-yl)-phenyl-methanone (77)

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.91 (2H, bs, C4$\underline{H}_2$); 3.66 (1.2H, bs, C3$\underline{H}_2$); 4.00 (0.8H, bs, C3$\underline{H}_2$); 4.61 (0.8H, bs, C1$\underline{H}_2$); 4.91 (1.2H, bs, C1$\underline{H}_2$); 6.93 – 7.21 (4H, m, C5$\underline{H}$, C6$\underline{H}$, C7$\underline{H}$, C8$\underline{H}$); 7.45 – 7.46 (5H, m, C2'$\underline{H}$, C3'$\underline{H}$, C4'$\underline{H}$, C5'$\underline{H}$, C6'$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 28.3 ($\underline{C}4H_2$ (s)), 29.4 ($\underline{C}4H_2$ (m)); 40.4 ($\underline{C}3H_2$ (s)); 44.7 ($\underline{C}1H_2$ (m)); 45.1 ($\underline{C}3H_2$ (m)); 49.7 ($\underline{C}1H_2$ (s)); 126.4, 126.5, 126.8 ($\underline{C}5H$, $\underline{C}6H$, $\underline{C}7H$, $\underline{C}8H$); 128.4 ($\underline{C}2'H$, $\underline{C}3'H$, $\underline{C}5'H$, $\underline{C}6'H$); 128.7 (CO$\underline{C}1'$); 129.6 ($\underline{C}4'H$); 132.8 ($\underline{C}8a$); 136.0 ($\underline{C}4a$); 170.5 ($\underline{C}O$)

Yield: 51.6%

IRν_{max}(KBr): 1431cm^{-1}(C-N stretching), 1638cm^{-1}(C=O stretching), 2840cm^{-1}, 2929cm^{-1}, 3024cm^{-1}(C-H stretching)

Melting point: 124 - 126°C Literature: 128°C[20]

(3,4-Dihydro-*1H*-isoquinolin-2-yl)-*o*-tolyl-methanone (78)

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.22 (1.2H, s, C$\underline{H}_3$) 2.32 (1.8H, s, C$\underline{H}_3$); 2.74 (1.2H, s, C4$\underline{H}_2$); 2.95 (0.8H, s, C4$\underline{H}_2$); 3.43 (1.2H, s, C3$\underline{H}_2$), 3.89 – 4.12 (0.8H, bs, C3$\underline{H}_2$); 4.34 (0.8H, s, C3$\underline{H}_2$); 4.96 (1.2H, bs, C1$\underline{H}_2$); 7.08 – 7.27 (8H, C5$\underline{H}$, C6$\underline{H}$, C7$\underline{H}$, C8$\underline{H}$, C3$\underline{H}$', C4'$\underline{H}$, C5'$\underline{H}$, C6'$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 18.4 ($\underline{C}H_3$ (s)), 18.6 ($\underline{C}H_3$ (m)); 28.0 ($\underline{C}4H_2$ (s)), 29.1 ($\underline{C}4H_2$ (m)); 39.4 ($\underline{C}3H_2$ (s)); 43.6 ($\underline{C}1H_2$ (m)); 43.8 ($\underline{C}3H_2$ (m)); 48.3 ($\underline{C}1H_2$ (s)); 125.0 ($\underline{C}7H$ (m)); 125.2 ($\underline{C}7H$ (s); ($\underline{C}6H$ (s)); 125.5 ($\underline{C}5H$, $\underline{C}6H$, $\underline{C}7H$ (m); 125.9 ($\underline{C}5H$ (s)); 126.1 ($\underline{C}5'H$ (m)); 126.2 ($\underline{C}6'H$ (m)); 126.23 126.4 128.2 ($\underline{C}3'H$ (m)); 128.5 ($\underline{C}8H$ (m)), 128.53 ($\underline{C}8H$ (s)); 130.0 ($\underline{C}4'H$); 132.4, 132.42 (C8a); 133.3, 133.7 ($\underline{C}4a$); 134.1 (CO$\underline{C}1'$); 141.8 ($\underline{C}2'CH_3$); 169.7 ($\underline{C}O$ (s)), 170.9 ($\underline{C}O$ (m))

Yield: 90.5%

IRν_{max}(KBr): 1423cm^{-1}(C-N stretching), 1631cm^{-1}(C=O stretching), 1695cm^{-1}, 2986cm^{-1}, 3054cm^{-1}(C-H stretching)

HRMS calcd. for C17H18NO (M^++1): 252.1388 Found: 252.1380

(3,4-Dihydro-*1H*-isoquinolin-2-yl)-*m*-tolyl-methanone (79)

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.38 (3H, s, C$\underline{H}_3$); 2.89 (2H, bs, C4$\underline{H}_2$); 3.64 (1.2H, bs, C3$\underline{H}_2$); 3.96 (0.8H, bs, C3$\underline{H}_2$); 4.60 (0.8H, bs, C1$\underline{H}_2$); 4.88 (1.2H, bs, C1$\underline{H}_2$); 7.15 – 7.32 (8H, m, C5$\underline{H}$, C6$\underline{H}$, C7$\underline{H}$, C8$\underline{H}$, C2'$\underline{H}$, C3'$\underline{H}$, C5'$\underline{H}$, C6'$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 21.0 ($\underline{C}H_3$); 28.1 ($\underline{C}4H_2$ (s)), 29.3 ($\underline{C}4H_2$ (m)); 40.1 ($\underline{C}3H_2$ (s)); 44.6 ($\underline{C}1H_2$ (m)); 44.9 ($\underline{C}3H_2$ (m)); 49.4 ($\underline{C}1H_2$ (s)); 123.5 ($\underline{C}2'H$); 126.1, 126.2 ($\underline{C}6H$, $\underline{C}7H$); 127.2, 128.0, 128.4, 130.1, 130.6 ($\underline{C}5H$, $\underline{C}8H$, $\underline{C}4'H$, $\underline{C}5'H$, $\underline{C}6'H$); 132.7 ($\underline{C}4a$, $\underline{C}8a$); 135.8 (CO$\underline{C}1'$);138.0 ($\underline{C}3'CH_3$); 170.6 ($\underline{C}O$)

Yield: 82.6%

IRν_{max}(KBr): 1434cm^{-1}(C-N stretching), 1634cm^{-1}(C=O stretching), 2859cm^{-1}, 2923cm^{-1}, 3023cm^{-1}(C-H stretching)

HRMS calcd. for C17H18NO (M^++1): 252.1388 Found: 252.1398

(3,4-Dihydro-*1H*-isoquinolin-2-yl)-*p*-tolyl-methanone (80)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.41 (3H, s, C$\underline{H}_3$); 2.90 – 2.97 (2H, bs, C4$\underline{H}_2$); 3.67 (1.2H, bs, C3$\underline{H}_2$); 4.00 (0.8H, bs, C3$\underline{H}_2$); 4.64 (0.8H, bs, C1$\underline{H}_2$); 4.90 (1.2H, bs, C1$\underline{H}_2$); 7.19 – 7.22 (4H, m, C5$\underline{H}$, C6$\underline{H}$, C7$\underline{H}$, C8$\underline{H}$); 7.25 (2H, d, J = 8Hz, C3'$\underline{H}$, C5'$\underline{H}$); 7.39 (2H, d, J = 8Hz, C2'$\underline{H}$, C6'$\underline{H}$)

^{13}C-NMR (101MHz):

21.2 (C$\underline{H}_3$); 28.1 (C4$\underline{H}_2$ (s)), 29.4 (C4$\underline{H}_2$ (m)); 40.4 (C3$\underline{H}_2$ (s)); 44.7 (C1$\underline{H}_2$ (m)); 45.2 (C3$\underline{H}_2$ (m)); 49.7 (C1$\underline{H}_2$ (s)); 126.4, 126.8 (C5H, C6H, C7H); 128.7 (CO$\underline{C}$1'); 128.9 ($\underline{C}$2'H, $\underline{C}$3'H, $\underline{C}$5'H, $\underline{C}$6'H); 132.9 ($\underline{C}$4a, $\underline{C}$8a); 139.8 ($\underline{C}$4'CH$_3$); 170.9 ($\underline{C}$O)

Yield: 80.5%

IRν_{max}(KBr): 1421cm^{-1}(C-N stretching), 1692cm^{-1}(C=O stretching), 2987cm^{-1}, 3054cm^{-1}(C-H stretching)

Melting point: 80 - 82°C Literature: 83°C[21]

(3,4-Dihydro-*1H*-isoquinolin-2-yl)-(2-methoxy-phenyl)-methanone (81)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.90 – 3.00 (1.2H, bs, C4$\underline{H}_2$); 3.15 (0.8H, t, J = 6Hz, C4$\underline{H}_2$); 3.64 (3H, s, OC$\underline{H}_3$); 4.00 (0.8H, bs, C3$\underline{H}_2$); 4.26 (1.2H, t, J = 6Hz, C3$\underline{H}_2$); 4.58 (0.8H, s, C1$\underline{H}_2$); 4.89 (1.2H, s, C1$\underline{H}_2$); 7.21 – 7.28 (6H, C5$\underline{H}$, C6$\underline{H}$, C7$\underline{H}$, C8$\underline{H}$, C3'$\underline{H}$, C5'$\underline{H}$); 7.79 – 7.81 (2H, m, C4'$\underline{H}$, C6'$\underline{H}$)

^{13}C-NMR (101MHz):

28.5 (C4$\underline{H}_2$); 43.0 (C1$\underline{H}_2$, C3$\underline{H}_2$); 55.5 (O$\underline{C}$H$_3$); 110.7 ($\underline{C}$3'H); 120.7 ($\underline{C}$5'H); 126.6 ($\underline{C}$6H); 127.2 ($\underline{C}$7H); 127.5 ($\underline{C}$5H); 128.6 ($\underline{C}$8H); 131.5 ($\underline{C}$4'H); 133.3 ($\underline{C}$6'H); 135.4 ($\underline{C}$4a, $\underline{C}$8a); 164.9 ($\underline{C}$2'OCH$_3$); 170.6 ($\underline{C}$O)

Yield: 78.5%

IRν_{max}(KBr): 1671cm^{-1}(C=O stretching), 2987cm^{-1}, 3055cm^{-1} (C-H stretching)

HRMS calcd. for C17H18NO2 (M^++1): 268.1338 Found: 268.1336

(3,4-Dihydro-*1H*-isoquinolin-2-yl)-(3-methoxy-phenyl)-methanone (82)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.83 (1.2H, bs, C4$\underline{H}_2$); 2.94 (0.8H, bs, C4$\underline{H}_2$); 3.60 (1.2H, bs, C3$\underline{H}_2$); 3.78 (3H, s, OC$\underline{H}_3$); 3.96 (0.8H, bs, C3$\underline{H}_2$); 4.56 (0.8H, s, C1$\underline{H}_2$); 4.86 (1.2H, s, C1$\underline{H}_2$); 6.93 – 7.00 (3H, m, C2'$\underline{H}$, C4'$\underline{H}$, C5'$\underline{H}$); 7.13 – 7.17 (4H, m, C5$\underline{H}$, C6$\underline{H}$, C7$\underline{H}$, C8$\underline{H}$); 7.30 (1H, m, C6'$\underline{H}$)

^{13}C-NMR (101MHz):

27.8 (C4$\underline{H}_2$ (s)), 29.2 (C4$\underline{H}_2$ (m)); 40.1 (C3$\underline{H}_2$ (s)); 44.4 (C1$\underline{H}_2$ (m)); 44.8 (C3$\underline{H}_2$ (m)); 49.3 (C1$\underline{H}_2$ (s)); 54.8 (O$\underline{C}$H$_3$); 111.8 ($\underline{C}$2'H); 115.2 ($\underline{C}$4'H); 118.4 ($\underline{C}$6'H); 126.2, 128.3 ($\underline{C}$5H, $\underline{C}$6H, $\underline{C}$7H); 129.2 ($\underline{C}$8H, $\underline{C}$5'H); 132.4 ($\underline{C}$4a, $\underline{C}$8a); 137.0 (CO$\underline{C}$1'); 159.2 ($\underline{C}$3'OCH$_3$); 170.2 ($\underline{C}$O)

Yield: 70.5%

IRν_{max}(KBr): 1693cm^{-1}(C=O stretching), 2987cm^{-1}, 3055cm^{-1} (C-H stretching)

HRMS calcd. for C17H18NO2 (M^++1): 268.1338 Found: 268.1340

(3,4-Dihydro-*1H*-isoquinolin-2-yl)-(4-methoxy-phenyl)-methanone (83)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.71 (1.2H, t, J = 6Hz, C4H_2); 2.88 (0.8H, t, J = 6Hz, C4H_2); 3.68 (1.2H, t, J = 6Hz, C3H_2); 3.80 (3H, s, OCH_3); 3.87 (0.8H, t, J = 6Hz, C3H_2); 4.63 (0.8H, s, C1H_2); 4.78 (1.2H, s, C1H_2); 6.85 – 6.89 (2H, m, C3'H, C5'H); 7.02 – 7.23 (6H, m, C5H, C6H, C7H, C8H, C2'H, C6'H)

^{13}C-NMR (101MHz):

28.4 (C4H_2 (s)), 29.6 (C4H_2 (m)); 40.4 (C3H_2 (s)); 44.5 (C1H_2 (m)); 45.4 (C3H_2 (m)); 49.7 (C1H_2 (s)); 55.3 (OCH_3); 113.6 (C3'H, C5'H); 126.3, 126.5, 128.7, 129.0 (C5H, C6H, C7H, C8H); 127.9 (COC1'); 129.8 (C4'OCH_3); 132.0 (C2'H, C6'H); 132.9 (C4a, C8a); 163.4 (C4'OCH_3); 169.5 (CO)

Yield: 67.0%

IRν_{max}(KBr): 1687cm^{-1}(C=O stretching), 2987cm^{-1}, 3055cm^{-1} (C-H stretching)

HRMS calcd. for C17H17NO2Na (M^++23): 290.1157 Found: 290.1151

(3,4-Dihydro-*1H*-isoquinolin-2-yl)-(2-fluoro-phenyl)-methanone (84)

δ($CDCl_3$):

2.84 (1.2H, s, C4H_2); 2.96 (0.8H, t, J = 5.5Hz, C4H_2); 3.55 (1.2H, t, J = 5.5Hz, C3H_2); 4.00 (0.8H, bs, C3H_2); 4.49 (0.8H, s, C1H_2); 4.92 (1.2H, s, C1H_2); 7.08 – 7.23 (6H, m, C5H, C6H, C7H, C8H, C3'H, C5'H); 7.37 – 7.42 (2H, m, C4'H, C6'H)

^{13}C-NMR (101MHz):

28.0 (C4H_2 (s)), 29.1 (C4H_2 (m)); 40.0 (C3H_2 (s)); 44.2 (C1H_2 (m)); 45.3 (C3H_2 (m)); 48.3 (C1H_2 (s)); 115.4 (C3'H (s)), 115.6 (C3'H (m)); 124.4 (C5'H (m)), 125.5 (C5'H (s)); 126.0, 126.3, 126.6, 128.3, 128.6, 128.9, 130.9 (C5H, C6H, C7H, C8H, C6'H); 131.07 (C4'H, q, J = 7.8Hz); 132.3 (C8a); 133.5 (C4a); 134.3 (COC1'); 156.8 (C2'F (s)), 159.2 (C2'F (m)); 165.2 (CO (s)), 165.6 (CO (m))

^{19}F-NMR (376MHz):

-115.3 (s), -115.6 (m)

Yield: 84.0%

IR (film): 1236cm^{-1} (CF), 1698cm^{-1}(C=O stretching), 2976cm^{-1}, 3055cm^{-1} (C-H stretching)

HRMS calcd. for C16H14NOFNa (M^++23): 278.0957 Found: 278.0948

(3,4-Dihydro-*1H*-isoquinolin-2-yl)-(3-fluoro-phenyl)-methanone (85)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.81, 2.90 (2H, bs, C4H_2); 3.56 (1.3H, bs, C3H_2); 3.92 (0.7H, bs, C3H_2); 4.53 (0.7H, bs, C1H_2); 4.84 (1.3H, bs, C1H_2); 7.06 – 7.20 (7H, m, C5H, C6H, C7H, C8H, C2'H, C4'H, C5'H); 7.32 – 7.36 (H, m, C6'H)

^{13}C-NMR (101MHz):

27.8 (C4H_2 (s)), 29.0 (C4H_2 (m)); 40.2 (C3H_2 (s)); 44.5 (C1H_2 (m)); 44.8 (C3H_2 (m)); 49.3 (C1H_2 (s)); 113.7, 113.9 (C2'H, C4'H (s)); 116.2, 116.4 (C2'H, C4'H (m)); 125.1 (C5H, C6H, C7H, C8H (s)), 126.1 (C5H, C6H, C7H, C8H (m)); 128.3 (C5'H, C6'H (s)), 129.4, 129.9 (C5'H, C6'H (m)); 132.2 (C8a, (C4a); 137.7 (COC1'); 160.8 (C3'F (s)), 163.3 (C3'F); 168.6 (CO (s)), 168.8 (CO (m))

^{19}F-NMR (376MHz):

-110.5

Yield: 87.1%

IRν_{max}(KBr): 1445cm^{-1}(C-N stretching), 1637cm^{-1}(C=O stretching), 2844cm^{-1}, 2932cm^{-1}, 3066cm^{-1}(C-H stretching)

HRMS calcd. for C16H14NOFNa (M^++23): 278.0957 Found: 278.0946

(3,4-Dihydro-*1H*-isoquinolin-2-yl)-(4-fluoro-phenyl)-methanone (86)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.89 (2H, bs, C4H_2); 3.64 (2H, bs, C3H_2); 4.79 (2H, bs, C1H_2); 7.02 – 7.16 (6H, m, C5H, C6H, C7H, C8H, C3'H, C5'H); 7.43 – 7.47 (2H, m, C2'H, C6'H)

^{13}C-NMR (101MHz):

28.0 (C4H_2 (s)), 29.4 (C4H_2 (m)); 40.6 (C3H_2 (s)); 44.9 (C1H_2 (m)); 45.5 (C3H_2 (m)); 49.6 (C1H_2 (s)); 115.1, 115.3 (C3'H, C5'H); 126.2, 126.4, 128.4 (C5H, C6H, C7H, C8H); 129.1 (C2'H, C6'H); 131.79, 132.82 (C8a, C4a); 132.0 (COC1'); 161.8 (COC4'F (s)), 164.3 (COC4'F (m)); 169.4(CO)

^{19}F-NMR (376MHz):

-110.5

Yield: 80.3%

IRν_{max}(KBr): 1432m^{-1}(C-N stretching), 1632cm^{-1}(C=O stretching), 2843cm^{-1}, 2914cm^{-1}, 3067cm^{-1}(C-H stretching)

HRMS calcd. for C16H15NOF (M^++1): 256.1138 Found: 256.1129

(2-Chloro-phenyl)-(3,4-dihydro-*1H*-isoquinolin-2-yl)-methanone (87)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.83 (1.2H, dt, J_1 = 21Hz, J_2 = 6Hz, C4H_2); 2.99 (0.8H, t, J = 6Hz, C4H_2); 3.45 – 3.52 (1.2H, m, C3H_2); 3.94 (0.4H, q, J = 6Hz, C3H_2); 4.11 (0.4H, q, J = 6Hz, C3H_2); 4.40 (0.8H, q, J = 16.1Hz, C1H_2); 4.95 (1.2H, q, J = 17.6Hz, C1H_2); 6.89 – 7.44 (8H, m, C5H, C6H, C7H, C8H, C3'H, C4'H, C5'H, C6'H)

^{13}C-NMR (101MHz):

28.2 (C4H_2 (s)), 29.2 (C4H_2 (m)); 39.7 (C3H_2 (s)); 43.9 (C1H_2 (m)); 44.0 (C3H_2 (m)); 48.1 (C1H_2 (s)); 125.6, 126.1 (C7H, C6H (s)); 126.35, 126.39, 126.42 (C7H, C6H, C5H (m)); 126.6 (C5H (s)); 127.0 (C3'H, C6'H (m)), 127.4, 127.6 (C3'H, C6'H (s)); 128.4 (C8H (m)), 128.7 (C8H (s)); 129.4 (C4'H, C5'H (m)), 130.0, 130.1 (C4'H, C5'H (s)); 132.2 (C8a); 133.5 (C4a); 134.3 (COC1'); 135.8 (C2'Cl); 166.9 (CO (s)), 169.7(CO (m))

Yield: 76.9%

IRν_{max}(KBr): 1637cm^{-1}(C=O stretching), 2986cm^{-1}, 3054cm^{-1} (C-H stretching)

HRMS calcd. for C16H14NONaCl (M^++23): 294.0662 Found: 294.0657

(3-Chloro-phenyl)-(3,4-dihydro-*1H*-isoquinolin-2-yl)-methanone (88)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.83 (1.2H, bs, C4H_2); 2.94 (0.8H, bs, C4H_2); 3.57 (1.2H, bs, C3H_2); 3.94 (0.8H, bs, C3H_2); 4.53 (0.8H, bs, C1H_2); 4.85 (1.2H, bs, C1H_2); 6.88 – 7.38 (8H, m, C5H, C6H, C7H, C8H, C2'H, C4'H, C5'H, C6'H)

^{13}C-NMR (101MHz):

27.8 (C4H_2 (s)), 29.3 (C4H_2 (m)); 40.3 (C3H_2 (s)); 44.5 (C1H_2 (m)); 44.9 (C3H_2 (m)); 49.4 (C1H_2 (s)); 124.6 (C7H (m)), 124.9 (C7H (s)); 125.5 (C6H (s)); 126.3 (C5H, C6H (m)); 127.0 (C5H (s)); 128.4 (C8H (m)),

128.7 (C8H (s)); 129.6 (C2'H, C4'H, C5'H C6'H); 132.3 (C8a, C4a (m)); 133.3 (C4a (s)); 134.2 (C3'Cl (m)), 137.5 (C3'Cl (s)); 169.4(CO (s)), 168.9 (CO (m))

Yield: 81.8%

IRν_{max}(KBr): 1694cm^{-1}(C=O stretching), 2986cm^{-1}, 3054cm^{-1} (C-H stretching)

HRMS calcd. for C16H14NONaCl (M^++23): 294.0662 Found: 294.0674

(4-Chloro-phenyl)-(3,4-dihydro-*1H*-isoquinolin-2-yl)-methanone (89)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.87, 2.97 (2H, bs, C4H$_2$); 3.62 (1.2H, bs, C3H$_2$); 3.97 (0.8H, bs, C3H$_2$); 4.57 (0.8H, bs, C1H$_2$); 4.87 (1.2H, bs, C1H$_2$); 7.16 – 7.20 (4H, m, C5H, C6H, C7H, C8H); 7.40 (4H, s, C2'H, C3'H, C5'H, C6'H)

^{13}C-NMR (101MHz):

28.1 (C4H$_2$ (s)), 29.5 (C4H$_2$ (m)); 40.6 (C3H$_2$ (s)); 44.9 (C1H$_2$ (m)); 45.3 (C3H$_2$ (m)); 49.7 (C1H$_2$ (s)); 126.3, 128.4 (C5H, C6H, C7H, C8H); 128.7 (C2'H, C3'H, C5'H C6'H); 132.6 (C8a); 134.3 (C4a); 135.8 (C4'Cl); 169.7(CO)

Yield: 96.1%

IRν_{max}(KBr): 1426m^{-1}(C-N stretching), 1636cm^{-1}(C=O stretching), 2925cm^{-1}, 3437cm^{-1}(C-H stretching)

HRMS calcd. for C16H14NONaCl (M^++23): 294.0662 Found: 294.0673

(4-Bromo-phenyl)-(3,4-dihydro-*1H*-isoquinolin-2-yl)-methanone (90)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.90, 2.99 (2H, bs, C4H$_2$); 3.65 (1.2H, bs, C3H$_2$); 4.00 (0.8H, bs, C3H$_2$); 4.59 (0.8H, bs, C1H$_2$); 4.90 (1.2H, bs, C1H$_2$); 6.94 – 7.22 (4H, m, C5H, C6H, C7H, C8H); 7.36 (2H, d, J = 8Hz, C3'H, C5'H); 7.59 (2H, d, J = 8Hz, C2'H, C6'H)

^{13}C-NMR (101MHz):

28.1 (C4H$_2$ (s)), 29.5 (C4H$_2$ (m)); 40.5 (C3H$_2$ (s)); 44.9 (C1H$_2$ (m)); 45.3 (C3H$_2$ (m)); 49.7 (C1H$_2$ (s)); 124.1 (C4'Br); 126.6, 128.6 (C5H, C6H, C7H, C8H); 131.7 (C2'H, C3'H, C5'H C6'H); 132.5, 132.6 (C8a, C4a); 134.8 (COC1'); 164.5(CO)

Yield: 93.5%

IRν_{max}(KBr): 1633cm^{-1}(C=O stretching), 2987cm^{-1}, 3054cm^{-1} (C-H stretching)

HRMS calcd. for C16H14NOBrNa (M^++23): 338.0156 Found: 338.0161

(3,4-Dihydro-*1H*-isoquinolin-2-yl)-(4-iodo-phenyl)-methanone (91)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.86, 2.96 (2H, bs, C4H$_2$); 3.61 (1.2H, bs, C3H$_2$); 3.96 (0.8H, bs, C3H$_2$); 4.57 (0.8H, bs, C1H$_2$); 4.87 (1.2H, bs, C1H$_2$); 6.91 – 7.20 (6H, m, d, J = 8Hz, overlapping, C5H, C6H, C7H, C8H, C2'H, C6'H); 7.76 (2H, d, J = 8Hz, C3'H, C5'H)

^{13}C-NMR (101MHz):

27.8 (C4H$_2$ (s)), 29.2 (C4H$_2$ (m)); 40.3 (C3H$_2$ (s)); 44.5 (C1H$_2$ (m)); 44.9 (C3H$_2$ (m)); 49.4 (C1H$_2$ (s)); 95.8 (C4'I); 126.3, 128.6 (C5H, C6H, C7H, C8H); 132.3 (C8a); 134.3 (C4a); 137.3 (C2'H, C3'H, C5'H, C6'H); 169.1(CO (s)), 169.5 (CO (m))

Yield: 57.4%

IRν_{max}(KBr): 1630cm^{-1}(C=O stretching), 2983cm^{-1}, 3051cm^{-1} (C-H stretching)

HRMS calcd. for C16H14NONaI (M^++23): 386.0018 Found: 386.0004

(3,4-Dihydro-*1H*-isoquinolin-2-yl)-(2-nitro-phenyl)-methanone (92)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.81 (1.2H, t, J = 5.5Hz, C4H_2); 3.02 (0.8H, bs, C4H_2); 3.45 (1.2H, t, J = 5.5Hz, C3H_2); 4.03 (0.8H, s, C3H_2); 4.37 (0.8H, s, C1H_2); 4.93 (1.2H, bs, C1H_2); 6.84 – 7.22 (4H, m, C5H, C6H, C7H, C8H); 7.42 (0.8H, t, J = 7.5Hz, C5'H (m)); 7.58 (0.8H, t, J = 7.5Hz, C4'H (m)); 7.70 – 7.80 (1.4H, m, C4'H (s), C5'H (s), C6'H); 7.98 – 8.04 (0.2H, m, C3'H); 8.17 (0.8H, t, J = 8Hz, C3'H)

^{13}C-NMR (101MHz):

27.8 (C4H_2 (s)), 28.8 (C4H_2 (m)); 39.7 (C3H_2 (s)); 44.2 (C1H_2 (m), C3H_2 (m)); 48.4 (C1H_2 (s)); 124.0 (C3'H (s)); 124.5 (C3'H (m)); 125.5 (C7H(s)); 126.1 (C6H(s)); 126.4 (C5H, C6H, C7H (m)); 126.7 (C5H (s)); 127.7 (C6'H); 128.3 (C8H (m)), 128.7 (C8H (s)); 129.7 (C4'H); 131.6 (C8a (s)), 131.9 (C8a (m)); 132.6 (C4a (s)), 132.7 (C4a (m)); 134.3 (COC1'); 134.5 (C5'H); 144.8 (C2'NO_2 (s)), 144.9 (C2'NO_2 (m)); 166.5 (CO (s)), 166.8 (CO (m))

Yield: 61.9%

IRν_{max}(KBr): 1643cm^{-1}(C=O stretching), 2987cm^{-1}, 3055cm^{-1} (C-H stretching)

HRMS calcd. for C16H15N2O3 (M^++1): 283.1083 Found: 283.1083

(3,4-Dihydro-*1H*-isoquinolin-2-yl)-(3-nitro-phenyl)-methanone (93)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.90, 3.00 (2H, s, s, overlapping, C4H_2); 3.64 (1.2H, t, J = 5.5Hz, C3H_2); 4.01 (0.8H, s, C3H_2); 4.59 (0.8H, s, C1H_2); 4.90 (1.2H, bs, C1H_2); 6.92 – 7.20 (4H, m, C5H, C6H, C7H, C8H); 7.65 (1H, t, J = 8Hz, C5'H); 7.82 (1H, d, J = 7.5Hz, C4'H); 8.27 (1H, d, J = 8.5Hz, C6'H); 8.32 (1H, s, C2'H)

^{13}C-NMR (101MHz):

27.7 (C4H_2 (s)), 29.1 (C4H_2 (m)); 40.6 (C3H_2 (s)); 44.7 (C1H_2 (m); 45.1 (C3H_2 (m)); 49.5 (C1H_2 (s)); 121.8 (C2'H (s)); 122.1 (C2'H (m)); 124.3 (C4'H (m)); 125.5 (C7H (s)); 126.2 (C6H (s)); 126.4 (C5H, C6H, C7H (m)); 126.9 (C5H (s)); 128.4 (C8H (m)), 128.7 (C8H (s)); 129.3 (C5'H (s)), 129.7 (C5'H (m)); 131.8 (C8a (s)), 131.9 (C8a (m)); 132.0 (C8a (s)); 132.7 (C6'H(s)); 133.2 (C4a (m)); 134.1 (C4a (s)); 135.2 (C6'H (m)); 137.1 (COC1'); 144.8 (C3'NO_2 (m)), 147.7 (C3'NO_2 (s)); 167.7 (CO (s)), 168.1 (CO (m))

Yield: 58.7%

IRν_{max}(KBr): 1637cm^{-1}(C=O stretching), 2987cm^{-1}, 3055cm^{-1} (C-H stretching)

HRMS calcd. for C16H14N2O3Na (M^++23): 305.0902 Found: 305.0891

(3,4-Dihydro-*1H*-isoquinolin-2-yl)-(2-trifluoromethyl-phenyl)-methanone (94)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.83 (1.2H, m, C4H_2); 2.92 (0.8H, C4H_2); 3.28 – 3.43 (1.2H, m, C3H_2); 3.89 (0.4H, q, J = 6Hz, C3H_2); 4.03 (0.4H, q, J = 6Hz, C3H_2); 4.28 (0.8H, dd, J_1 = 23Hz, J_2 = 16.6Hz, C1H_2); 4.69 (0.6H, d, J = 17.6Hz, C1H_2); 5.07 (0.6H, d, J = 17Hz, C1H_2); 6.77 – 7.68 (8H, m, C5H, C6H, C7H, C8H, C3'H, C4'H, C5'H, C6'H)

^{13}C-NMR (101MHz):

27.7 (C4H_2 (s)), 29.2 (C4H_2 (m)); 39.5 (C3H_2 (s)); 43.8 (C1H_2 (m)); 44.1 (C3H_2 (m)); 48.6 (C1H_2 (s)); 124.7 (C7H (s)), 125.3 (C6H (s)); 126.2 (C7H, C6H, C5H (m)); 126.5 (C5H), 126.6 (C3'H (m)); 126.8 (C3'H (s));

128.2 (C8H (m)), 128.5 (C8H (s)); 128.8 (C4'H); 132.6 (C5'H (s)), 132.8 (C5'H (m)); 133.2 (C4a, C8a); 134.0 (C2'CF_3); 134.6 (COC1'); 167.1 (CO (s)), 167.4 (CO (m))

^{19}F-NMR (376MHz):

-60.4 (m), -60.5 (s)

Yield: 68.0%

IRν_{max}(KBr): 1436cm^{-1}(C-N stretching), 1644cm^{-1}(C=O stretching), 2849cm^{-1}, 2931cm^{-1}, 3068cm^{-1} (C-H stretching)

HRMS calcd. for C17H15NOF3 (M^++1): 306.1106 Found: 306.118

(3,4-Dihydro-*1H*-isoquinolin-2-yl)-(3-trifluoromethyl-phenyl)-methanone (95)*

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.87 (1.2H, bs, C4H_2); 2.98 (0.8H, bs, C4H_2); 3.61 (1.2H, bs, C3H_2); 3.99 (0.8H, bs, C3H_2); 4.56 (0.8H, bs, C1H_2); 4.90 (1.2H, bs, C1H_2); 6.90 – 7.20 (4H, m, C5H, C6H, C7H, C8H); 7.54 – 7.75 (4H, m, C2'H, C4'H, C5'H, C6'H)

^{13}C-NMR (101MHz):

27.8 (C4H_2 (s)), 29.1 (C4H_2 (m)); 40.4 (C3H_2 (s)); 44.6 (C1H_2 (m)); 45.0 (C3H_2 (m)); 49.4 (C1H_2 (s)); 123.6 (C6H (s)), 125.5 (C7H (s)); 126.2 (C5H, C6H, C7H (m)); 126.4 (C2'H, C4'H);126.8 (C5H (s)); 128.4 (C8H (s)), 128.9 (C8H (m)); 129.9 (C5'H); 130.2 (C8a, C4a (m)); 133.4 (C6'H);134.2 (C1'); 136.6 (C3'CF_3);168.5 (CO (s)), 169.0 (CO (m))

^{19}F-NMR (376MHz):

-63.1 (m), -63.4 (m)

Yield: 69.7%

IRν_{max}(KBr): 1427cm^{-1}(C-N stretching), 1640cm^{-1}(C=O stretching), 2934cm^{-1}, 3067cm^{-1}(C-H stretching)

(3,4-Dihydro-*1H*-isoquinolin-2-yl)-(4-trifluoromethyl-phenyl)-methanone (96)*

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.89, 3.01 (2H, bs, C4H_2); 3.62 (1.2H, bs, C3H_2); 4.02 (0.8H, bs, C3H_2); 4.56 (0.8H, bs, C1H_2); 4.93 (1.2H, bs, C1H_2); 6.92 – 7.28 (4H, m, C5H, C6H, C7H, C8H); 7.59 (2H, d, J = 7Hz, C3'H, C5'H); 7.71 (2H, d, J = 7Hz, C2'H, C6'H)

^{13}C-NMR (101MHz):

27.9 (C4H_2 (s)), 29.2 (C4H_2 (m)); 40.4 (C3H_2 (s)); 44.6 (C1H_2 (m)); 45.0 (C3H_2 (m)); 49.4 (C1H_2 (s)); 122.2 (CF_3); 125.4 (C3'H, C5'H (m)); 125.6 (C3'H, C5'H (s)); 126.2, 126.9 (C6H, C7H (s)); 126.5 (C5H, C6H, C7H (m)); 127.3 (C2'H, C6'H (m)), 127.6 (C2'H, C6'H (s)); 128.5 (C8H (m)), 128.8 (C8H (s)); 132.7 (C8a); 134.3 (C4a); 139.4 (C1'); 168.8 (CO (s)), 169.3(CO (m))

^{19}F-NMR (376MHz):

-63.3 (m), -63.5 (m)

Yield: 72.2%

IRν_{max}(KBr): 1435cm^{-1}(C-N stretching), 1640cm^{-1}(C=O stretching), 2849cm^{-1}, 2933cm^{-1}, 3067cm^{-1}(C-H stretching)

(3,4-Dihydro-*1H*-isoquinolin-2-yl)-(4-ethyl-phenyl)-methanone (97)[21]

^{1}H-NMR (400MHz):

δ($CDCl_3$):

1.26 (3H, t, J = 7.5Hz, C$\underline{H}_3$); 2.68 (2H, q, J = 7.5Hz, C$\underline{H}_2$CH$_3$); 2.86 (2H, bs, C4$\underline{H}_2$); 3.65 (1.2H, bs, C3$\underline{H}_2$); 3.97 (0.8H, bs, C3$\underline{H}_2$); 4.62 (0.8H, bs, C1$\underline{H}_2$); 4.88 (1.2H, bs, C1$\underline{H}_2$); 6.89 – 7.19 (4H, m, C5$\underline{H}$, C6$\underline{H}$, C7$\underline{H}$, C8$\underline{H}$); 7.25 (2H, d, J = 8Hz, C3'$\underline{H}$, C5'$\underline{H}$); 7.40 (2H, d, J = 8Hz, C2'$\underline{H}$, C6'$\underline{H}$)

^{13}C-NMR (101MHz):

15.1 (C$\underline{H}_3$); 28.5 (C$\underline{H}_2$CH$_3$); 27.9 (C4$\underline{H}_2$ (s)), 29.2 (C4$\underline{H}_2$ (m)); 40.2 (C3$\underline{H}_2$ (s)); 44.5 (C1$\underline{H}_2$ (m)); 44.9 (C3$\underline{H}_2$ (m)); 49.5 (C1$\underline{H}_2$ (s)); 126.1, 126.7 (C5H, C6H, C7H); 127.5 (C2'H, C3'H, C5'H, C6'H); 128.4 (C8H); 132.6 (C8a, C4a); 132.9 (COC1'); 145.8 (C4'C_2H_5); 170.7 (CO)

Yield: 61.9%

IRν_{max}(KBr): 1634cm^{-1}(C=O stretching), 2987cm^{-1}, 3055cm^{-1} (C-H stretching)

(3,4-Dihydro-*1H*-isoquinolin-2-yl)-naphthalen-2-yl-methanone (98)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.92, 3.07 (2H, s, s, overlapping, C4$\underline{H}_2$); 3.72 (1.2H, t, J = 5.5Hz, C3$\underline{H}_2$); 4.11 (0.8H, s, C3$\underline{H}_2$); 4.70 (0.8H, s, C1$\underline{H}_2$); 5.02 (1.2H, s, C1$\underline{H}_2$); 6.89 – 7.28 (4H, m, C5$\underline{H}$, C6$\underline{H}$, C7$\underline{H}$, C8$\underline{H}$); 7.57 – 7.62 (3H, m, C3'$\underline{H}$, C4'$\underline{H}$, C5'$\underline{H}$); 7.90 – 8.03 (3H, m, C6'$\underline{H}$, C7'$\underline{H}$, C8'$\underline{H}$); 8.15 (1H, d, J = Hz, C2'$\underline{H}$)

^{13}C-NMR (101MHz):

28.2 (C4$\underline{H}_2$ (s)), 29.5 (C4$\underline{H}_2$ (m)); 40.6 (C3$\underline{H}_2$ (s)); 44.8 (C1$\underline{H}_2$ (m); 45.2 (C3$\underline{H}_2$ (m)); 49.9 (C1$\underline{H}_2$ (s)); 123.9 (C8'H); 125.3 (C7H (s)); 126.4 (C6H (s)); 126.6 (C5H, C6H, C7H (m)); 127.0 (C5'H (m)); 127.6 (C5H (s)); 127.7 (C4'H, C7'H (m)); 127.9 (C7'H (s)); 128.1 (C3'H(s)); 128.3 (C3'H(m)); 128.5 (C8H (m)); 128.9 (C8H (s)); 129.3 (C2'H (m)); 131.5 (C2'H (s)); 132.5, 132.7 (C8a, C4a); 133.1, 133.6 (C2'a, C6'a); 135.5 (COC1'); 171 (CO)

Yield: 57.2%

IRν_{max}(KBr): 1633cm^{-1}(C=O stretching), 2987cm^{-1}, 3054cm^{-1} (C-H stretching)

HRMS calcd. for C20H18NO (M^++23): 288.1388 Found: 288.1390

Methyl amides

1-(6,7-Dimethoxy-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-phenyl-ethanone (99)

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.37 (0.9H, d, J= 7Hz, C1C$\underline{H}_3$ (s)), 1.42 (2.1H, d, J = 6.5Hz, C1C$\underline{H}_3$ (m)); 2.51 – 2.55 (1.4 H, m, C4$\underline{H}_2$); 2.63 (0.3H, d, J = 15Hz, C4$\underline{H}_2$ (s)); 2.86 (0.3H, dt, J_1 = 13Hz, J_2 = 5.5Hz, C4$\underline{H}_2$ (s)), 3.01 (0.3H, dt, J_1 = 12Hz, J_2 = 4Hz, C3$\underline{H}_2$ (s)); 3.33 – 3.39 (0.7H, m, C3$\underline{H}_2$ (s)); 3.80, 3.81, 3.83, 3.83 (8.7H, overlapping singlets, multiplet, C6OC$\underline{H}_3$, C7OC$\underline{H}_3$, COC$\underline{H}_2$, C3$\underline{H}_2$ (m); 4.72 (0.3H, dd, J_1 = 12.5Hz, J_2 = 5Hz, C3$\underline{H}_2$ (s)); 4.96 (0.3H, dd, J_1 = 13.5Hz, J_2 = 6.5Hz, C1$\underline{H}$ (s)); 5.59 (0.6H, dd, J_1 = 13.5Hz, J_2 = 6.5Hz, C1$\underline{H}$ (m)); 6.47 (0.3H, s, C8$\underline{H}$ (s)), 6.50 (0.7H, s, C8$\underline{H}$ (m)); 6.58 (0.3H, s, C5$\underline{H}$ (s)), 6.60 (0.7H, s, C5$\underline{H}$ (m)); 7.23 – 7.33 (5H, m, C2'$\underline{H}$, C3'$\underline{H}$, C4'$\underline{H}$, C5'$\underline{H}$, C6'$\underline{H}$)

^{13}C-NMR (101MHz): 20.9 (C$\underline{H}_3$ (m)), 21.2 (C$\underline{H}_3$ (s)); 28.0 (C4$\underline{H}_2$ (s)), 28.6 (C4$\underline{H}_2$ (m)); 35.0 (C3$\underline{H}_2$ (s)); 39.9 (C3$\underline{H}_2$ (m)); 41.6 (COC$\underline{H}_2$); 48.1 (C1H (m)); 52.1 (C1H (s)); 55.7 (C6OC$\underline{H}_3$ (m) C7OC$\underline{H}_3$ (m)), 55.8 (C6OC$\underline{H}_3$ (s), C7OC$\underline{H}_3$ (s)); 109.2 (C8'H (s)), 109.7 (C8'H (m)); 110.9 (C5H (m)), 111.3 (C5H (s)); 124.9 (C8a); 126.6 (C4'H); 128.4 (C3'H, C5'H); 128.6 (C2'H, C6'H); 130.3 (C4a); 135.0 (COC1'); 147.4, 147.6 (C6OCH$_3$, C7OCH$_3$); 169.1 (CO)

Yield: 33.1%

IRν_{max}(KBr): 1422cm^{-1}(C-N stretching), 1634cm^{-1}(C=O stretching), 2987cm^{-1}, 3055cm^{-1}(C-H stretching)

Melting point: 80 - 82°C Literature: 80 - 81°C[22]

1-(6,7-Dimethoxy-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-(4-nitro-phenyl)-ethanone (100)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

1.44 (0.9H, d, J= 6.7Hz, C1C$\underline{H}_3$ (s)), 1.50 (2.1H, d, J = 6.7Hz, C1C$\underline{H}_3$ (m)); 2.66 – 2.69 (1.7 H, m, C4$\underline{H}_2$); 2.86 (0.3H, dt, J_1 = 12Hz, J_2 = 5.5Hz, C4$\underline{H}_2$ (s)); 3.06 (0.3H, dt, J_1 = 12Hz, J_2 = 4Hz, C3$\underline{H}_2$ (s)); 3.45 – 3.52 (0.7H, m, C3$\underline{H}_2$ (s)); 3.80, 3.81, 3.83, 3.84 (8.7H, overlapping singlets, multiplet, C6OC$\underline{H}_3$, C7OC$\underline{H}_3$, COC$\underline{H}_2$, C3$\underline{H}_2$ (m)); 4.71 (0.3H, dd, J_1 = 13Hz, J_2 = 4Hz, C3$\underline{H}_2$ (s)); 4.97 (0.3H, dd, J_1 = 13Hz, J_2 = 6Hz, C1$\underline{H}$ (s)); 5.58 (0.6H, dd, J_1 = 13Hz, J_2 = 6.7Hz, C1$\underline{H}$ (m)); 6.54 (0.3H, s, C8$\underline{H}$ (s)), 6.55 (0.7H, s, C8$\underline{H}$ (m)); 6.60 (1H, s, C5$\underline{H}$); 7.45 (2H, d, J = 7Hz, C2'$\underline{H}$, C6'$\underline{H}$); 8.17 (2H, d, J = 7Hz, C3'$\underline{H}$, C5'$\underline{H}$)

^{13}C-NMR (101MHz):

21.3 (C$\underline{H}_3$ (m)), 22.8 (C$\underline{H}_3$ (s)); 27.9 (C$\underline{4}H_2$ (s)), 28.7 (C$\underline{4}H_2$ (m)); 35.3 (C$\underline{3}H_2$ (s)); 40.0 (C$\underline{3}H_2$ (m)); 40.8 (CO$\underline{C}H_2$); 48.4 (C$\underline{1}$H (m)); 52.1 (C$\underline{1}$H (s)); 55.8 (C6O$\underline{C}H_3$ (m) C7O$\underline{C}H_3$ (m)), 55.9 (C6O$\underline{C}H_3$ (s), C7O$\underline{C}H_3$ (s)); 109.2 (C$\underline{8}$'H (s)), 109.6 (C$\underline{8}$'H (m)); 110.9 (C$\underline{5}$H (m)), 111.4 (C$\underline{5}$H (s)); 123.6 (C$\underline{3}$'H, C$\underline{5}$'H (s)), 123.7 (C$\underline{3}$'H, C$\underline{5}$'H (m)); 124.5 (C$\underline{8}$a (m)), 126.0 (C$\underline{8}$a (s)); 128.7 (C$\underline{4}$a (s)); 129.7 (C$\underline{2}$'H, C$\underline{6}$'H); 130.0 (C$\underline{4}$a (m); 130.1 (C$\underline{2}$'H, C$\underline{6}$'H (s)); 142.7 (CO$\underline{C}$1'); 146.8 (C$\underline{4}$'NO_2); 147.5, 147.7, 147.9 (C$\underline{6}$OCH_3, C$\underline{7}$OCH_3); 167.5 (C$\underline{O}$ (m)), 167.6 (C$\underline{O}$ (s))

Yield: 46.5%

IRν_{max}(KBr): 1442cm^{-1}(C-N stretching), 1640cm^{-1}(C=O stretching), 2987cm^{-1}, 3055cm^{-1}(C-H stretching)

HRMS calcd. for C20H22N2O5Na (M^++23): 393.1426 Found: 393.1409

1-(6,7-Dimethoxy-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-(4-methylsulfanyl-phenyl)-ethanone (101)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

1.44 (3H, d, J= 6.5Hz, C1C$\underline{H}_3$); 2.48 (3H, s, SC$\underline{H}_3$); 2.58 – 2.59 (1.4 H, m, C4$\underline{H}_2$); 2.65 (0.3H, d, J = 18Hz, C4$\underline{H}_2$ (s)), (0.3H, dt, J_1 = 14Hz, J_2 = 6Hz, C4$\underline{H}_2$ (s)); 3.03 (0.3H, dt, J_1 = 12Hz, J_2 = 4Hz, C3$\underline{H}_2$ (s)); 3.36 – 3.48 (0.7H, m, C3$\underline{H}_2$ (s)); 3.77, 3.84, 3.86 (8.7H, overlapping singlets, multiplet, C6OC$\underline{H}_3$, C7OC$\underline{H}_3$, COC$\underline{H}_2$, C3$\underline{H}_2$ (m)); 4.73 (0.3H, dd, J_1 = 13Hz, J_2 = 4Hz, C3$\underline{H}_2$ (s)); 4.97 (0.3H, dd, J_1 = 13Hz, J_2 = 6.5Hz, C1$\underline{H}$ (s)); 5.60 (0.6H, dd, J_1 = 13Hz, J_2 = 6.5Hz, C1$\underline{H}$ (m)); 6.50 (0.3H, s, C8$\underline{H}$ (s)), 6.53 (0.7H, s, C8$\underline{H}$ (m)); 6.60 (0.3H, s, C5$\underline{H}$ (s)), 6.61 (0.7H, C5$\underline{H}$ (m)); 7.19 – 7.21 (4H, m, C2'$\underline{H}$, C3'$\underline{H}$, C5'$\underline{H}$, C6'$\underline{H}$)

^{13}C-NMR (101MHz):

15.8 (S$\underline{C}H_3$ (m)), 15.9 (S$\underline{C}H_3$ (s)); 21.3 (C$\underline{H}_3$ (m)), 22.7 (C$\underline{H}_3$ (s)); 28.0 (C$\underline{4}H_2$ (s)), 28.7 (C$\underline{4}H_2$ (m)); 35.1 (C$\underline{3}H_2$ (s)); 39.9 (C$\underline{3}H_2$ (m)); 41.0 (CO$\underline{C}H_2$); 48.2 (C$\underline{1}$H (m)); 52.1 (C$\underline{1}$H (s)); 55.8 (C6O$\underline{C}H_3$ (m) C7O$\underline{C}H_3$ (m)), 55.9 (C6O$\underline{C}H_3$ (s), C7O$\underline{C}H_3$ (s)); 109.2 (C$\underline{8}$'H (s)), 109.7 (C$\underline{8}$'H (m)); 110.9 (C$\underline{5}$H (m)), 111.4 (C$\underline{5}$H (s)); 124.8 (C$\underline{8}$a (m)); 126.9 (C$\underline{3}$'H, C$\underline{5}$'H); 128.9 (C$\underline{2}$'H, C$\underline{6}$'H); 130.2 (C$\underline{4}$a (m); 131.9 (CO$\underline{C}$1'); 136.6 (C$\underline{4}$'SCH_3); 147.5, 147.7 (C$\underline{6}$OCH_3, C$\underline{7}$OCH_3); 169.0 (C$\underline{O}$)

Yield: 35.3%

IRν_{max}(KBr): 1441cm^{-1}(C-N stretching), 1635cm^{-1}(C=O stretching), 2937cm^{-1}, 3054cm^{-1}(C-H stretching)

HRMS calcd. for C21H25NO5Na (M^++23): 394.1630 Found: 394.1635

1-(6,7-Dimethoxy-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-(3-methoxy-phenyl)-ethanone (102)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

1.35 (1H, d, J= 6.5Hz, C1C$\underline{H}_3$ (s)), 1.39 (2H, d, J = 6.5Hz, C1C$\underline{H}_3$ (m)); 2.51 – 2.54 (1.34 H, m, C4$\underline{H}_2$); 2.59 (0.33H, d, J = 14.5Hz, C4$\underline{H}_2$); 2.82 (0.33H, dt, J_1 = 14.5Hz, J_2 = 5.5Hz, C4$\underline{H}_2$ (s)); 2.98 (0.3H, dt, J_1 = 12Hz, J_2 = 4Hz, C3$\underline{H}_2$ (s)); 3.29 – 3.36 (0.67H, m, C3$\underline{H}_2$ (s)); 3.65 – 3.83 (11.67H, overlapping singlets, multiplet, C6OC$\underline{H}_3$, C7OC$\underline{H}_3$, C3'OC$\underline{H}_3$, COC$\underline{H}_2$, C3$\underline{H}_2$ (m)); 4.69 (0.33H, dd, J_1 = 13Hz, J_2 = 4Hz, C3$\underline{H}_2$ (s)); 4.94 (0.33H, dd, J_1 = 13Hz, J_2 = 6.5Hz, C1$\underline{H}$ (s)); 5.56 (0.67H, dd, J_1 = 13Hz, J_2 = 6.5 Hz, C1$\underline{H}$ (m)); 6.45 (0.33H, s, C8$\underline{H}$ (s)), 6.48 (0.67H, s, C8$\underline{H}$ (m)); 6.55 (0.33H, s, C5$\underline{H}$ (s)), 6.56 (0.67H, s, (m)); 6.68 – 6.75 (1H, m, C2'$\underline{H}$); 6.78 – 6.81 (2H, m, C4'$\underline{H}$, C6'$\underline{H}$); 7.12 – 7.19 (1H, m, C5'$\underline{H}$)

^{13}C-NMR (101MHz):

21.0 ($\underline{C}H_3$ (m)), 22.4 ($\underline{C}H_3$ (s)); 27.7 ($\underline{C}4H_2$ (s)), 28.4 ($\underline{C}4H_2$ (m)); 34.8 ($\underline{C}3H_2$ (s)); 39.7 ($\underline{C}3H_2$ (m)); 41.3 (CO$\underline{C}H_2$); 47.9 ($\underline{C}$1H (m)); 51.9 ($\underline{C}$1H (s)); 54.7 (C3'O$\underline{C}H_3$ (s)), 54.73 (C3'O$\underline{C}H_3$ (m)); 55.6 (C6O$\underline{C}H_3$ (m) C7O$\underline{C}H_3$ (m)), 55.7 (C6O$\underline{C}H_3$ (s), C7O$\underline{C}H_3$ (s)); 109.0 ($\underline{C}$8'H (s)), 109.5 ($\underline{C}$8'H (m)); 110.8 ($\underline{C}$5H (m)), 111.1 ($\underline{C}$5H (s)); 112.1 ($\underline{C}$4'H (m)), 112.14 ($\underline{C}$4'H (s)); 113.6 ($\underline{C}$2'H (m)), 113.8 ($\underline{C}$2'H (s)); 120.7 ($\underline{C}$6'H (m)), 120.4 ($\underline{C}$6'H (s)); 124.7 ($\underline{C}$8a (m)), 125.8 ($\underline{C}$8a (s)); 129.0 ($\underline{C}$4a (s)), 129.1 ($\underline{C}$4a (m)); 129.2 ($\underline{C}$5'H (m)), 130.0 ($\underline{C}$5'H (s)); 136.3 (CO$\underline{C}$1'); 147.2, 147.4, 147.5 ($\underline{C}$6OCH$_3$, $\underline{C}$7OCH$_3$); 159.4 ($\underline{C}$3'OCH$_3$ (s)), 159.5 ($\underline{C}$3'OCH$_3$ (m)); 168.7 ($\underline{C}$O (m)); 168.9 ($\underline{C}$O (s))

Yield: 62.2%

IRν_{max}(KBr): 1423cm^{-1}(C-N stretching), 1635cm^{-1}(C=O stretching), 2938cm^{-1}, 3055cm^{-1}(C-H stretching)

HRMS calcd. for C21H26NO4 (M^++1): 356.1862 Found: 356.1865

1-(6,7-Dimethoxy-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-(4-methoxy-phenyl)-ethanone (103)[23]

^{1}H-NMR (400MHz):

δ($CDCl_3$):

1.39 (1H, d, J= 7Hz, C1C$\underline{H}_3$ (s)), 1.43 (2H, d, J = 7Hz, C1C$\underline{H}_3$ (m)); 2.53 – 2.57 (1.34 H, m, C4$\underline{H}_2$); 2.64 (0.33H, d, J = 16.5Hz, C4$\underline{H}_2$); 2.87 (0.33H, dt, J_1 = 13.5Hz, J_2 = 5.5Hz, C4$\underline{H}_2$ (s)); 3.02 (0.3H, dt, J_1 = 12.5Hz, J_2 = 4Hz, C3$\underline{H}_2$ (s)); 3.34 – 3.42 (0.67H, m, C3$\underline{H}_2$ (s)); 3.74 – 3.85 (11.67H, overlapping singlets, multiplet, C6OC$\underline{H}_3$, C7OC$\underline{H}_3$, C4'OC$\underline{H}_3$, COC$\underline{H}_2$, C3$\underline{H}_2$ (m)); 4.73 (0.33H, dd, J_1 = 13Hz, J_2 = 4Hz, C3$\underline{H}_2$ (s)); 4.98 (0.33H, dd, J_1 = 13.5Hz, J_2 = 7Hz, C1$\underline{H}$ (s)); 5.60 (0.67H, dd, J_1 = 13.5Hz, J_2 = 6.5 Hz, C1$\underline{H}$ (m)); 6.50 (0.33H, s, C8$\underline{H}$ (s)), 6.52 (0.67H, s, C8$\underline{H}$ (m)); 6.60 (0.33H, s, C5$\underline{H}$ (s)), 6.61 (0.67H, s, (m)); 6.86 (2H, d, J = 8.5Hz, C3'$\underline{H}$, C5'$\underline{H}$); 7.19 (2H, d, J = 8.5Hz, C2'$\underline{H}$, C6'$\underline{H}$)

^{13}C-NMR (101MHz):

21.3 ($\underline{C}H_3$ (m)), 22.6 ($\underline{C}H_3$ (s)); 28.0 ($\underline{C}4H_2$ (s)), 28.7 ($\underline{C}4H_2$ (m)); 35.0 ($\underline{C}3H_2$ (s)); 39.8 ($\underline{C}3H_2$ (m)); 39.9 (CO$\underline{C}H_2$ (s)), 40.7 (CO$\underline{C}H_2$); 48.0 ($\underline{C}$1H (m)); 52.0 ($\underline{C}$1H (s)); 55.1 (C4'O$\underline{C}H_3$ (m)); 55.7 (C6O$\underline{C}H_3$ (m) C7O$\underline{C}H_3$ (m)), 55.8 (C6O$\underline{C}H_3$ (s), C7O$\underline{C}H_3$ (s)); 55.9 (C4'O$\underline{C}H_3$ (s)); 109.2 ($\underline{C}$8'H (s)), 109.7 ($\underline{C}$8'H (m)); 110.9 ($\underline{C}$5H (m)), 111.3($\underline{C}$5H (s)); 113.9 ($\underline{C}$3'H, $\underline{C}$5'H (m)), 114.0 ($\underline{C}$3'H, $\underline{C}$5'H (s)); 124.9 ($\underline{C}$8a (m)), 126.1 ($\underline{C}$8a (s)); 127.0 (CO$\underline{C}$1' (m)), 127.03 (CO$\underline{C}$1' (s)); 129.3 ($\underline{C}$4a (s)); 129.4 ($\underline{C}$2'H, $\underline{C}$6'H (m)), 129.7 ($\underline{C}$2'H, $\underline{C}$6'H (s)); 130.3 ($\underline{C}$4a); 147.4, 147.6, 147.7 ($\underline{C}$6OCH$_3$, $\underline{C}$7OCH$_3$); 158.2 ($\underline{C}$4'OCH$_3$); 169.4 ($\underline{C}$O (m)); 169.5 ($\underline{C}$O (s))

Yield: 31.1%

IRν_{max}(KBr): 1442cm^{-1}(C-N stretching), 1633cm^{-1}(C=O stretching), 2938cm^{-1}, 3055cm^{-1}(C-H stretching)

Boiling point: (literature only): 214 - 215°C[23]

1-(6,7-Dimethoxy-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-(3,4-dimethoxy-phenyl)-ethanone (104)[22]

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.32 (3H, d, J= 6.5Hz, C1C$\underline{H}_3$); 2.45 – 2.48 (1.34 H, m, C4$\underline{H}_2$); 2.53 (0.33H, d, J = 14.5Hz, C4$\underline{H}_2$); 2.74 (0.33H, dt, J_1 = 14Hz, J_2 = 5.5Hz, C4$\underline{H}_2$ (s)); 2.91 (0.3H, dt, J_1 = 12Hz, J_2 = 4Hz, C3$\underline{H}_2$ (s)); 3.23 – 3.34 (0.67H, m, C3$\underline{H}_2$ (s)), 3.38 – 3.43 (0.67H, m, C3$\underline{H}_2$ (m)); 3.64 – 3.73 (12H, C6OC$\underline{H}_3$, C7OC$\underline{H}_3$, C3'OC$\underline{H}_3$, C4'OC$\underline{H}_3$, COC$\underline{H}_2$); 4.62 (0.33H, dd, J_1 = 13Hz, J_2 = 4Hz, C3$\underline{H}_2$ (s)); 4.91 (0.33H, dd, J_1 = 13.5Hz, J_2 = 6.5Hz, C1$\underline{H}$ (s)); 5.49 (0.67H, dd, J_1 = 13Hz, J_2 = 6.5 Hz, C1$\underline{H}$ (m)); 6.41 (0.33H, s, C8$\underline{H}$ (s)), 6.42 (0.67H, s, C8$\underline{H}$ (m)); 6.49 (0.33H, s, C5$\underline{H}$ (s)), 6.50 (0.67H, s, (m)); 6.67 (1H, s, C2'$\underline{H}$); 6.69 – 6.72 (2H, m, C5'$\underline{H}$, C6'$\underline{H}$)

^{13}C-NMR (101MHz): 20.8 ($\underline{C}H_3$ (m)), 22.3 ($\underline{C}H_3$ (s)); 27.6 ($\underline{C}4H_2$ (s)), 28.3 (C4H_2 (m)); 34.6 ($\underline{C}3H_2$ (s)); 39.5 ($\underline{C}3H_2$ (m)); 39.9 (CO$\underline{C}H_2$ (s)), 40.7 (CO$\underline{C}H_2$); 47.7 ($\underline{C}$1H (m)); 51.7 ($\underline{C}$1H (s)); 55.2 (C3'OC$\underline{H}_3$, C4'O$\underline{C}H_3$ (s)); 55.3 (C6O$\underline{C}H_3$ (m) C7O$\underline{C}H_3$ (m)), 55.5 (C6O$\underline{C}H_3$ (s), C7O$\underline{C}H_3$ (s)); 55.5 (C3'OCH$_3$, C4'O$\underline{C}H_3$ (s)); 108.9 ($\underline{C}$8'H (s)), 109.3 ($\underline{C}$8'H (m)); 110.7 ($\underline{C}$5'H(m)), 110.8 ($\underline{C}$5'H (s)); 110.9 ($\underline{C}$2'H (m)), 111.0 ($\underline{C}$2'H (s)); 111.1 ($\underline{C}$5H (m)), 111.3 ($\underline{C}$5H (s)); 120.1 ($\underline{C}$6'H (m)), 120.4 ($\underline{C}$6'H (s)); 124.6 ($\underline{C}$8a (m)), 125.7 ($\underline{C}$8a (s)); 127.16 (CO$\underline{C}$1' (m)), 127.19 (CO$\underline{C}$1' (s)); 129.0 ($\underline{C}$4a (s)); 129.9 ($\underline{C}$4a); 147.1,147.26, 147.3 ($\underline{C}$6OCH$_3$, $\underline{C}$7OCH$_3$); 147.34, 148.6 ($\underline{C}$3'OCH$_3$, $\underline{C}$4'OCH$_3$); 168.9 ($\underline{C}$O (m)); 170.5 ($\underline{C}$O (s))

Yield: 68.3%

IRν_{max}(KBr): 1465cm^{-1}(C-N stretching), 1634cm^{-1}(C=O stretching), 2937cm^{-1}, 3055cm^{-1}(C-H stretching)

Boiling point: (literature only): 244 - 245°C, 0.2 Torr[22]

(6,7-Dimethoxy-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-(4-methylsulfanyl-phenyl)-methanone (105)

^{1}H-NMR (400MHz): δ($CDCl_3$):

1.51 (1H, bs, C1C$\underline{H}_3$ (s)), 1.57 (2H, C1C$\underline{H}_3$ (m)); 2.52 (3H, s, SC$\underline{H}_3$); 2.62 – 2.73 (1H, m, C4$\underline{H}_2$); 2.93 (0.6H, bs, C4$\underline{H}_2$ (m)), 3.05 (0.4H, bs, C4$\underline{H}_2$ (s)); 3.22 (0.4H, bs, C3$\underline{H}_2$ (s)), 3.44 (0.6H, t, J = 12Hz, C3$\underline{H}_2$ (m)); 3.85, 3.87, 3.88, 3.89 (6.6H, overlapping singlets, multiplet, C6OC$\underline{H}_3$, C7OC$\underline{H}_3$, C3$\underline{H}_2$ (m); 4.80 (0.8H, bs, C3$\underline{H}_2$ (s), C1$\underline{H}$ (s)); 5.68 (0.6H, d, J = 5Hz, C1$\underline{H}$ (m)); 6.38 (0.4H, s, C8$\underline{H}$ (s)), 6.61 (1H, s, s overlapping C8$\underline{H}$ (m)), C5$\underline{H}$ (s)), 6.67 (0.6H, s, C5$\underline{H}$ (m)); 7.28 (2H, d, J = 8Hz, C3'$\underline{H}$, C5'$\underline{H}$); 7.37 (2H, d, J = 8Hz, C3'$\underline{H}$, C5'$\underline{H}$)

^{13}C-NMR (101MHz):14.1 (S$\underline{C}H_3$ (s)), 15.3 (S$\underline{C}H_3$); 21.3 ($\underline{C}H_3$ (m)), 23.2 ($\underline{C}H_3$ (s)); 27.8 ($\underline{C}4H_2$ (s)), 29.1 ($\underline{C}4H_2$ (m)); 35.3 ($\underline{C}3H_2$ (s)); 40.9 ($\underline{C}3H_2$ (m)); 48.4 ($\underline{C}$1H (m)); 53.4 ($\underline{C}$1H (s)); 55.8 (C6O$\underline{C}H_3$ (m) C7O$\underline{C}H_3$ (m)), 55.9 (C6O$\underline{C}H_3$ (s), C7O$\underline{C}H_3$ (s)); 109.7 ($\underline{C}$8'H); 111.1 ($\underline{C}$5H); 124.8 ($\underline{C}$8a); 125.8 ($\underline{C}$3'H, $\underline{C}$5'H); 127.2 ($\underline{C}$2'H, $\underline{C}$6'H); 130.2 ($\underline{C}$4a); 132.8 (CO$\underline{C}$1'); 140.7 ($\underline{C}$4'SCH$_3$); 147.6 ($\underline{C}$6OCH$_3$, $\underline{C}$7OCH$_3$); 148.0 ($\underline{C}$4'NO$_2$ (m)), 148.8 ($\underline{C}$4'NO$_2$ (s)); 169.7 ($\underline{C}$O)

Yield: 82.7%

IRν_{max}(KBr): 1465cm^{-1}(C-N stretching), 1623cm^{-1}(C=O stretching), 2937cm^{-1}, 3054cm^{-1}(C-H stretching)

HRMS calcd. for C20H24NO3S (M^++1): 358.1477 Found: 358.1465

1-(6,7-Dimethoxy-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-ethanone (106)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

1.41 (1.8H, d, J = 6.5Hz, C1C$\underline{H}_3$), 1.51 (1.2H, d, J = 6.5Hz, C1C$\underline{H}_3$); 2.15 (1.8H, s, COC$\underline{H}_3$), 2.18 (1.2H, s, COC$\underline{H}_3$); 2.63 (0.4H, dt, J_1 = 16Hz, J_2 = 3Hz, C4$\underline{H}_2$); 2.73 (0.6H, dt, J_1 = 16Hz, J_2 = 3Hz, C4$\underline{H}_2$); 2.79 – 2.91 (1H, m, C4$\underline{H}_2$); 2.98 (0.4H, dt, J_1 = 12Hz, J_2 = 4Hz, C3$\underline{H}_2$); 3.49 (0.6H, dt, J_1 = 11.5Hz, J_2 = 4Hz, C3$\underline{H}_2$); 3.80 (0.6H, ddd, J_1 = 15Hz, J_2 = 5Hz, J_3 = 3Hz, C3$\underline{H}_2$); 3.84, 3.85, 3.86 (6H, overlapping singlets, C6OC$\underline{H}_3$, C7OC$\underline{H}_3$); 4.68 (0.4H, ddd, J_1 = 13Hz, J_2 = 6Hz, J_3 = 2Hz, C3$\underline{H}_2$); 4.86 (0.4H, dd, J_1 = 13.5Hz, J_2 = 6.5Hz, C1$\underline{H}$); 5.56 (0.6H, dd, J_1 = 13Hz, J_2 = 6.5Hz, C1$\underline{H}$); 6.58 – 6.60 (2H, m, C5$\underline{H}$, C8$\underline{H}$)

^{13}C-NMR (101MHz):

21.3 (CO$\underline{C}H_3$ (m)), 21.4 (CO$\underline{C}H_3$ (s)); 21.8 (C1$\underline{C}H_3$ (m)), 22.4 (C1$\underline{C}H_3$ (s)); 27.9 ($\underline{C}4H_2$ (s)), 28.8 ($\underline{C}4H_2$ (m)); 34.6 ($\underline{C}3H_2$ (s)), 40.2 ($\underline{C}3H_2$ (m)); 47.8 ($\underline{C}$1H (m), 52.3 ($\underline{C}$1H (s)); 55.8 (O$\underline{C}H_3$ (m), 55.9 (O$\underline{C}H_3$ (s)); 109.3 ($\underline{C}$5H (s)), 109.6 ($\underline{C}$5H (m)); 111.0 ($\underline{C}$8H (m)), 111.3 ($\underline{C}$8H (s)); 124.9 ($\underline{C}$8a (m)), 126.2 ($\underline{C}$8a (s)); 129.2 ($\underline{C}$4a (m)), 130.5 ($\underline{C}$4a (s)); 147.39, 147.43, 147.62, 147.72 ($\underline{C}$6OCH$_3$ (s), (m), $\underline{C}$7OCH$_3$ (s), (m)); 168.6 ($\underline{C}$O (m)), 168.64 ($\underline{C}$O (s))

Yield: 55.6%

IRν_{max}(KBr): 1465cm^{-1}(C-N stretching), 1629cm^{-1}(C=O stretching), 2937cm^{-1}, 3156cm^{-1}(C-H stretching)

Melting point: 100 - 104°C Literature: 100 - 102°C[24]

1-(6,7-Dimethoxy-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-propanone (107)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

1.20 (3H, t, J = 7Hz, C$\underline{H}_3$); 1.37 (1.8H, d, J = 6.5Hz, C1C$\underline{H}_3$), 1.47 (1.2H, d, J = 7Hz, C1C$\underline{H}_3$); 2.27 – 2.46 (2H, m, COC$\underline{H}_2$); 2.63 (0.4H, ddd, J_1 = 16Hz, J_2 = 5Hz, J_3 = 2Hz, C4$\underline{H}_2$); 2.68 (0.6H, dt, J_1 = 16Hz, J_2 = 3Hz, C4$\underline{H}_2$); 2.73 – 2.86 (1H, m, C4$\underline{H}_2$); 2.95 (0.4H, dt, J_1 = 12Hz, J_2 = 4Hz, C3$\underline{H}_2$); 3.42 (0.6H, dt, J_1 = 12Hz, J_2 = 4Hz, C3$\underline{H}_2$); 3.79, 3.80, 3.81 (6.6H, overlapping singlets and doublets, C6OC$\underline{H}_3$, C7OC$\underline{H}_3$, C3$\underline{H}_2$); 4.66 (0.4H, ddd, J_1 = 13Hz, J_2 = 5.5Hz, J_3 = 1.5Hz, C3$\underline{H}_2$); 4.88 (0.4H, dd, J_1 = 13.5Hz, J_2 = 6.5Hz, C1$\underline{H}$); 5.53 (0.6H, dd, J_1 = 13.5Hz, J_2 = 7Hz, C1$\underline{H}$); 6.53 – 6.57 (2H, m, C5$\underline{H}$, C8$\underline{H}$)

^{13}C-NMR (101MHz):

9.3 ($CH_2\underline{C}H_3$ (m)), 9.4 ($CH_2\underline{C}H_3$ (s)); 21.2 (C1$\underline{C}H_3$ (m)), 22.5 (C1$\underline{C}H_3$ (s)); 26.3 ($\underline{C}H_2CH_3$ (s)), 26.7 ($\underline{C}H_2CH_3$ (m)); 27.8 ($\underline{C}4H_2$ (s)), 28.8 ($\underline{C}4H_2$ (m)); 34.6 ($\underline{C}3H_2$ (s)), 39.1 ($\underline{C}3H_2$ (m)); 47.8 ($\underline{C}$1H (m), 51.1 ($\underline{C}$1H (s)); 55.6 (O$\underline{C}H_3$ (m), 55.8 (O$\underline{C}H_3$ (s)); 109.2 ($\underline{C}$5H (s)), 109.6 ($\underline{C}$5H (m)); 111.0 ($\underline{C}$8H (m)), 111.2 ($\underline{C}$8H (s)); 124.9 ($\underline{C}$8a (m)), 126.2 ($\underline{C}$8a (s)); 129.3 ($\underline{C}$4a (m)), 130.5 ($\underline{C}$4a (s)); 147.26, 147.29, 147.49, 147.59 ($\underline{C}$6OCH$_3$ (s), (m), $\underline{C}$7OCH$_3$ (s), (m)); 171.7 ($\underline{C}$O (m)), 171.8 ($\underline{C}$O (s))

Yield: 63.1%

IRν_{max}(KBr): 1465cm^{-1}(C-N stretching), 1635cm^{-1}(C=O stretching), 2939cm^{-1}, 3055cm^{-1}(C-H stretching)

HRMS calcd. for C15H21NO3Na (M^++23): 286.1419 Found: 286.1407

1-(6,7-Dimethoxy-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-butanone (108)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

0.86 (3H, t, J = 7Hz, C$\underline{H}_3$); 1.36 (1.8H, d, J = 7Hz, C1C$\underline{H}_3$), 1.47 (1.2H, d, J = 7Hz, C1C$\underline{H}_3$); 1.53 – 1.59 (2H, m, C$\underline{H}_2$CH$_3$); 2.23 – 2.34 (2H, m, COC$\underline{H}_2$); 2.58 (0.4H, dt, J_1 = 16Hz, J_2 = 3Hz, C4$\underline{H}_2$); 2.76 – 2.86 (1H, m, C4$\underline{H}_2$); 2.95 (0.4H, dt, J_1 = 13Hz, J_2 = 5Hz, C3$\underline{H}_2$); 3.44 (0.6H, dd, J_1 = 13Hz, J_2 = 7Hz, C3$\underline{H}_2$); 3.80, 3.81, 3.813 (6.6H, overlapping singlets and double doublet, C6OC$\underline{H}_3$, C7OC$\underline{H}_3$); 4.66 (0.4H, ddd, J_1 = 13Hz, J_2 =

5.5Hz, J_3 = 1.5Hz, C3$\underline{H}_2$); 4.89 (0.4H, dd, J_1 = 13Hz, J_2 = 6.5Hz, C1$\underline{H}$); 5.54 – 6.56 (2H, m, C5$\underline{H}$, C8$\underline{H}$)

^{13}C-NMR (101MHz):

13.5 ($CH_2\underline{C}H_3$ (m)), 13.8 ($CH_2\underline{C}H_3$ (s)); 18.6 ($\underline{C}H_2CH_3$ (m)), 19.0 ($\underline{C}H_2CH_3$ (s)); 21.2 (C1$\underline{C}H_3$ (m)), 22.6 (C1$\underline{C}H_3$ (s)); 28.0 ($\underline{C}4H_2$ (s)), 28.9 ($\underline{C}4H_2$ (m)); 34.5 ($\underline{C}3H_2$ (s)), 35.1 (CO$\underline{C}H_2$ (m)), 35.5 (CO$\underline{C}H_2$ (s)); 39.3 ($\underline{C}3H_2$ (m)); 47.7 ($\underline{C}$1H (m), 51.3 ($\underline{C}$1H (s)); 55.6 (O$\underline{C}H_3$ (m), 55.8 (O$\underline{C}H_3$ (s)); 109.3 ($\underline{C}$5H (s)), 109.7 ($\underline{C}$5H (m)); 110.9 ($\underline{C}$8H (m)), 111.3 ($\underline{C}$8H (s)); 124.9 ($\underline{C}$8a (m)), 126.2 ($\underline{C}$8a (s)); 129.3 ($\underline{C}$4a (m)), 130.5 ($\underline{C}$4a (s)); 147.31, 147.38, 147.55, 147.63 ($\underline{C}$6OCH$_3$ (s), (m), $\underline{C}$7OCH$_3$ (s), (m)); 172.9 ($\underline{C}$O)

Yield: 35.1%

IRν_{max}(KBr): 1465cm^{-1}(C-N stretching), 1620cm^{-1}(C=O stretching), 2940cm^{-1}, 3437cm^{-1}(C-H stretching)

HRMS calcd. for C16H24NO3 (M^++1): 278.1756 Found: 278.1754

1-(6,7-Dimethoxy-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-pentan-1-one (109)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

0.91 – 0.96 (3H, m, C$\underline{H}_3$); 1.36 – 1.39 (2H, m, C$\underline{H}_2$CH$_3$); 1.41 (1.8H, d, J = 6.5Hz, C1C$\underline{H}_3$), 1.52 (1.2H, d, J = 7Hz, C1C$\underline{H}_3$); 1.61 – 1.68 (2H, m, C$\underline{H}_2$CH$_2$); 2.32 – 2.49 (2H, m, COC$\underline{H}_2$); 2.63 (0.4H, d, J = 16Hz, C4$\underline{H}_2$); 2.73 (0.6H, dt, J_1 = 16Hz, J_2 = 3Hz, C4$\underline{H}_2$); 3.44 (1H, ddd, J_1 = 26Hz, J_2 = 15Hz, J_3 = 5Hz, C4$\underline{H}_2$); 2.98 (0.4H, dt, J_1 = 12.5Hz, J_2 = 3.5Hz, C3$\underline{H}_2$); 3.46 (0.6H, dt, J_1 = 12Hz, J_2 = 4Hz, C3$\underline{H}_2$); 3.85, 3.87 (6.6H, overlapping singlets and double doublet, C6OC$\underline{H}_3$, C7OC$\underline{H}_3$, C3$\underline{H}_2$); 4.72 (0.4H, dd, J_1 = 13Hz, J_2 = 4Hz, C3$\underline{H}_2$); 4.93 (0.4H, dd, J_1 = 13Hz, J_2 = 6.5Hz, C1$\underline{H}$); 5.58 (0.6H, dd, J_1 = 13Hz, J_2 = 6.5Hz, C1$\underline{H}$); 6.58 – 6.61 (2H, m, C5$\underline{H}$, C8$\underline{H}$)

^{13}C-NMR (101MHz):

13.9 ($CH_2\underline{C}H_3$); 21.4 (C1$\underline{C}H_3$ (m)); 22.5 ($\underline{C}H_2CH_3$); 22.7 (C1$\underline{C}H_3$ (s)); 27.4 ($\underline{C}H_2CH_2$); 28.1 ($\underline{C}4H_2$ (s)), 29.0 ($\underline{C}4H_2$ (m)); 33.0 ($\underline{C}3H_2$ (s)), 33.5 (CO$\underline{C}H_2$ (m)), 34.6 (CO$\underline{C}H_2$ (s)); 39.4 ($\underline{C}3H_2$ (m)); 47.8 ($\underline{C}$1H (m), 51.4 ($\underline{C}$1H (s)); 55.8 (O$\underline{C}H_3$ (m), 55.9 (O$\underline{C}H_3$ (s)); 109.4 ($\underline{C}$5H (s)), 109.8 ($\underline{C}$5H (m)); 111.0 ($\underline{C}$8H (m)), 111.4 ($\underline{C}$8H (s)); 125.0 ($\underline{C}$8a (m)), 126.4 ($\underline{C}$8a (s)); 129.4 ($\underline{C}$4a (m)), 130.7 ($\underline{C}$4a (s)); 147.39, 147.44, 147.64, 147.73 ($\underline{C}$6OCH$_3$ (s), (m), $\underline{C}$7OCH$_3$ (s), (m)); 171.2 ($\underline{C}$O (m)), 171.3 ($\underline{C}$O (s))

Yield: 49.2%

IRν_{max}(KBr): 1465cm^{-1}(C-N stretching), 1620cm^{-1}(C=O stretching), 2072cm^{-1}, 2910cm^{-1}, 3437cm^{-1}(C-H stretching)

HRMS calcd. for C17H26NO3 (M^++1): 292.1913 Found: 292.1931

Cyclopropyl-(6,7-dimethoxy-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-methanone (110)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

0.78 (2H, t, J = 8Hz, C3'$\underline{H}_2$); 0.96 (1H, t, J = 4Hz, C2'$\underline{H}_2$), 1.08 (1H, dt, J_1 = 26Hz, J_2 = 4.5Hz, C2'$\underline{H}_2$); 1.43 (1.5H, d, J = 6.5Hz, C1C$\underline{H}_3$), 1.59 (1.5H, d, J = 6.5Hz, C1C$\underline{H}_3$); 1.80 – 1.85 (1H, m, C1'H); 2.65 (0.5H, d, J = 16Hz, C4$\underline{H}_2$); 2.78 (0.5H, d, J = 16Hz, C4$\underline{H}_2$); 2.83 – 2.98 (1H, m, C4$\underline{H}_2$); 3.05 (0.5H, dt, J_1 = 12Hz, J_2 = 4Hz, C3$\underline{H}_2$); 3.59 (0.5H, dt, J_1 = 12Hz, J_2 = 4Hz, C3$\underline{H}_2$); 3.85, 3.86, 3.88 (6H, overlapping singlets, C6OC$\underline{H}_3$, C7OC$\underline{H}_3$); 4.18 (0.5H, dt, J_1 = 14Hz, J_2 = 4Hz, C3$\underline{H}_2$); 4.65 (0.5H, dd, J_1 = 13Hz, J_2 = 4Hz, C3$\underline{H}_2$); 5.28 (0.5H, dd, J_1 = 14Hz, J_2 = 6.5Hz, C1$\underline{H}$); 5.56 (0.5H, dd, J_1 = 13Hz, J_2 = 6.5Hz, C1$\underline{H}$); 6.60 - 6.62 (2H, m, C5$\underline{H}$, C8$\underline{H}$)

^{13}C-NMR (101MHz):

6.9, 7.3, 7.5, 7.7 (C2'H_2, C3'H_2); 11.28, 11.39 (C1'H); 21.4, 22.8 (C1CH_3); 28.2, 29.0 (C4H_2); 35.6, 39.5 (C3H_2); 48.6, 51.3 (C1H); 55.8, 56.0 (OCH_3); 109.5, 109.8 (C5H); 111.0, 111.3 (C8H); 125.3, 126.6 (C8a);, 129.5, 130.8 (C4a); 147.40, 147.49, 147.62, 147.71 (C6OCH_3 (s), (m), C7OCH_3 (s), (m)); 171.4, 171.8 (CO)

Yield: 50.4%

IRν_{max}(KBr): 1464cm^{-1}(C-N stretching), 1632cm^{-1}(C=O stretching), 2937cm^{-1}, 3055cm^{-1}(C-H stretching)

HRMS calcd. for C16H22NO3 (M^++1): 276.1600 Found: 276.1601

Cyclohexyl-(6,7-dimethoxy-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-ethanone (111)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

1.21 – 1.78 (10H, m, CH_2 in cyclohexyl ring); 1.38 (1.8H, d, J = 6.5Hz, C1CH_3 (m)), 1.52 (1.2H, d, J = 7.0Hz, C1CH_3 (s)); 2.48 – 2.55 (1H, C1'H); 2.60 (0.4H, d, J = 16Hz, C4H_2 (s)), 2.72 (0.6H, d, J = 16Hz, C4H_2 (m)); 2.77 – 2.91 (1H, m, C4H_2); 2.96 (0.4H, dt, J_1 = 12Hz, J_2 = 3.5Hz, C3H_2); 3.43 (0.6H, dt, J_1 = 12Hz, J_2 = 3.5Hz, C3H_2); 3.83, 3.86 (6H, s, s, C6OCH_3, C7OCH_3); 3.91 (0.6H, d, J_1 = 16Hz, C3H_2); 4.70 (0.4H, dd, J_1 = 13Hz, J_2 = 5Hz, C3H_2); 4.96 (0.4H, dd, J_1 = 14Hz, J_2 = 6.5Hz, C1H); 5.56 (0.6H, dd, J_1 = 13Hz, J_2 = 7Hz, C1H); 6.57 - 6.60 (2H, m, C5H, C8H)

^{13}C-NMR (101MHz):

6.9, 7.3, 7.5, 7.7 (C2'H_2, C3'H_2, C4H_2, C5'H_2, C6'H_2); 11.28, 11.39 (C1'H); 21.4, 22.8 (C1CH_3); 28.1 (C4H_2) (s)), 29.3 (C4H_2 (m)); 34.7 (C3H_2 (s)), 38.9 (C3H_2); 47.7 (C1H (m)), 51.2 (C1H (s)); 55.7 (OCH_3 (m)), 55.9 (OCH_3 (s)); 109.3 (C5H (s), 109.7 (C5H (m)); 110.8 (C8H (m)), 111.3 (C8H (s)); 124.9 (C8a (m), 126.4 (C8a (s)); 129.4 (C4a (s)), 130.7 (C4a (m)); 147.29, 147.35, 147.55, 147.65 (C6OCH_3 (s), (m), C7OCH_3 (s), (m)); 174.1 (CO (m)), 174.5 (CO (s))

Yield: 63.1%

IRν_{max}(KBr): 1442cm^{-1}(C-N stretching), 1621cm^{-1}(C=O stretching), 2052cm^{-1}, 2939cm^{-1}, 3438cm^{-1}(C-H stretching)

HRMS calcd. for C19H28NO3 (M^++1): 318.2069 Found: 318.2054

(6,7-Dimethoxy-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-phenyl-methanone (112)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

1.48 (0.9H, bs, C1CH_3), 1.56 (2.1H, d, J = 6.5Hz, C1CH_3); 2.60 (0.7H, d, J = 15.5Hz, C4H_2 (m)), 2.70 (0.3H, d, J = 15.5Hz, C4H_2 (s)); 2.84 – 2.93 (0.7H, m, C4H_2 (m)), 3.04 (0.3H, bs, C4H_2 (s)); 3.20 (0.3H, t, J_1 = 11Hz, C3H_2 (s)); 3.40 (0.7H, t, J = 12Hz, C3H_2 (m)); 3.76, 3.83, 3.86 (6.7H, overlapping singlets and multiplet, C6OCH_3, C7OCH_3, C3H_2 (m)); 4.77 (0.6H, m, C3H_2 (s), C1H (s)); 5.69 (0.7H, d, J = 6.5Hz, C1H); 6.35 (0.3H, bs, C8H (s)); 6.58 (0.7H, s, C8H (m)), 6.61 (0.3H, s, C5H (s)); 6.66 (0.7H, s, C5H); 7.40 (5H, s, C2'H, C3'H, C4'H, C5'H, C6'H)

^{13}C-NMR (101MHz):

21.2 (CH_3 (m)), 22.9 (CH_3 (s)); 27.7 (C4H_2 (s)), 28.9 (C4H_2 (m)); 35.0 (C3H_2 (s)); 40.6 (C3H_2 (m)); 48.1 (C1H (m)); 53.1 (C1H (s)); 55.7 (OCH_3 (m)), 55.7 (OCH_3 (s)); 109.0 (C8H (s)), 109.6 (C8H (m)); 111.0 (C5H (m)), 111.3 (C5H (s)); 124.7 (C8a), 126.3 (C2'H, C6'H (m)); 128.3 (C3'H, C5'H (m)); 129.3 (C4'H); 130.0 (C4a); 136.3 (COC1'); 129.6 (C4'H); 147.4, 147.6 (C6OCH_3, C7OCH_3); 169.9 (CO)

Yield: 66.4%

IRν_{max}(KBr): 1438cm^{-1}(C-N stretching), 1619cm^{-1}(C=O stretching), 2848cm^{-1}, 2950cm^{-1}, 3438cm^{-1}(C-H stretching)

Melting point: 116 - 120°C Literature: 127 - 128°C[13]

(6,7-Dimethoxy-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-*p*-tolyl-methanone (113)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

1.49 (1.2H, bs, C1C$\underline{H}_3$), 1.56 (1.8H, d, J = 6Hz, C1C$\underline{H}_3$); 2.38 (3H, C4'C$\underline{H}_3$); 2.61 (0.6H, d, J = 15.6Hz, C4$\underline{H}_2$ (m)), 2.70 (0.4H, d, J = 15.6Hz, C4$\underline{H}_2$ (m)); 2.91 (0.6H, t, J = 11Hz, C4$\underline{H}_2$ (m)), 3.04 (0.4H, bs, C4$\underline{H}_2$ (s)); 3.19 (0.4H, t, J_1 = 12Hz, C3$\underline{H}_2$ (s)); 3.38 (0.6H, t, J_1 = 12Hz, C3$\underline{H}_2$ (m)); 3.80 - 3.87 (6.6H, overlapping singlets and multiplet, C6OC$\underline{H}_3$, C7OC$\underline{H}_3$, C3$\underline{H}_2$ (m)); 4.80 (0.8H, bs, C3$\underline{H}_2$ (s), C1$\underline{H}$ (s)); 5.68 (0.6H, d, J = 6Hz, C1$\underline{H}$); 6.36 (0.4H, bs, C8$\underline{H}$ (s)); 6.60 (0.6H, s, C8$\underline{H}$ (m)), 6.66 (0.6H, s, C5$\underline{H}$ (m)), 6.73 (0.4H, s, C5$\underline{H}$ (s)); 7.21 (2H, d, J = 8Hz, C3'$\underline{H}$, C5'$\underline{H}$); 7.31 (2H, d, J = 8Hz, C2'$\underline{H}$, C6'$\underline{H}$)

^{13}C-NMR (101MHz):

21.2, 21.4 (C$\underline{H}_3$ (m), C4'C$\underline{H}_3$), 23.0 (C$\underline{H}_3$ (s)); 27.8 (C4$\underline{H}_2$ (s)), 29.0 (C4$\underline{H}_2$ (m)); 35.1 (C3$\underline{H}_2$ (s)); 40.7 (C3$\underline{H}_2$ (m)); 48.2 (C1H (m)); 53.2 (C1H (s)); 55.6 (OC$\underline{H}_3$ (m)), 55.8 (OC$\underline{H}_3$ (s)); 109.1 (C8H (s)), 109.6 (C8H (m)); 111.1 (C5H (m)), 111.3 (C5H (s)); 124.7 (C8a), 125.8 (C2'H, C6'H); 129.0 (C3'H, C5'H); 130.1 (C4a); 133.4 (COC1'); 141.4 (C4'CH_3); 147.5, 147.6 (C6OCH_3, C7OCH_3); 170.1 (CO)

Yield: 52.1%

IRν_{max}(KBr): 1435cm^{-1}(C-N stretching), 1619cm^{-1}(C=O stretching), 2838cm^{-1}, 2934cm^{-1}, 3438cm^{-1}(C-H stretching)

HRMS calcd. for C20H24NO3 (M^++23): 326.1756 Found: 326.1761

(6,7-Dimethoxy-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-(2-methoxy-phenyl)-methanone (114)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

1.41 (1.H, dd, J_1 = 22Hz, J_2 = 6.5Hz, C1C$\underline{H}_3$), 1.57 (2H, apparent t, J = 6.5Hz, C1C$\underline{H}_3$); 2.56 (0.7H, t, J = 14Hz, C4$\underline{H}_2$ (m)), 2.73 – 2.81 (0.7H, m, C4$\underline{H}_2$ (m)); 2.86 – 3.07 (1H, m, C4$\underline{H}_2$ (m)), 3.12 – 3.25 (0.3H, m, C4$\underline{H}_2$ (s)); 3.34 (0.3H, dt, J_1 = 13Hz, J_2 = 3.5Hz, C3$\underline{H}_2$ (s)); 3.43 (0.3H, dt, J_1 = 13Hz, J_2 = 3.5Hz, C3$\underline{H}_2$ (s)); 3.52 – 3.59 (0.6H, m, C3$\underline{H}_2$ (m)); 3.78, 3.79 (3H, overlapping singlets, C2'OC$\underline{H}_3$); 3.85, 3.88 (9.7H, overlapping singlets, C6OC$\underline{H}_3$, C7OC$\underline{H}_3$, C2'OC$\underline{H}_3$); 4.55 (1.5H, dd, J_1 = 13Hz, J_2 = 6.5Hz, C3$\underline{H}_2$ (s)); 4.64 (0.15H, dd, J_1 = 13Hz, J_2 = 6.5Hz, C3$\underline{H}_2$ (s)); 4.89 (0.3H, dt, J_1 = 15.5Hz, J_2 = 6Hz, C1$\underline{H}$); 5.76 (0.6H, dd, J_1 = 13Hz, J_2 = 6.5Hz, C1$\underline{H}$); 6.36 (0.3H, d, J = 13Hz, C8$\underline{H}$ (s)), 6.57 (0.7H, d, J = 6Hz, C8$\underline{H}$ (m)); 6.63 (0.3H, d, J = 5Hz, C5$\underline{H}$ (s)), 6.68 (0.7H, d, J = 3.5Hz, C5$\underline{H}$ (m)); 6.81 – 7.39 (4H, m, C3'$\underline{H}$, C4'$\underline{H}$, C5'$\underline{H}$, C6'$\underline{H}$)

^{13}C-NMR (101MHz):

21.2 (C$\underline{H}_3$ (m)), 22.9 (C$\underline{H}_3$ (s)); 28.1 (C4$\underline{H}_2$ (s)), 28.9 (C4$\underline{H}_2$ (m)); 40.0 (C3$\underline{H}_2$ (s)); 40.8 (C3$\underline{H}_2$ (m)); 47.8 (C1H (m)); 52.7 (C1H (s)); 55.2 (C2'OC$\underline{H}_3$(s)), 55.6 (C2'OC$\underline{H}_3$ (m)); 55.8 (C6OC$\underline{H}_3$ (m) C7OC$\underline{H}_3$ (m)), 55.9 (C6OC$\underline{H}_3$ (s), C7OC$\underline{H}_3$ (m)); 109.0 (C3'H (s)), 110.7 (C3'H (m)); 110.7 (C8H (s)), 110.9 (C8H (m)); 111.0 (C5H (m)), 111.1 (C5H (s)); 120.8 (C5'H); 124.9, 125.7 (C8a), 125.3, 125.9 (C4a); 126.1 (COC1'); 127.2 (C6'H (m)), 128.0 (C6'H (s)); 130.1 (C4'H (m)); 132.1 (C4'H (s)); 147.4, 147.5, 147.6, 147.7 (C6OCH_3, C7OCH_3); 155.2 (COC$\underline{H}_3$ (s)), 155.4 (COC$\underline{H}_3$ (m)); 167.6 (CO (s)), 167.7 (CO (m))

Yield: 45.0%

IRν_{max}(KBr): 1466cm^{-1}(C-N stretching), 1627cm^{-1}(C=O stretching), 2938cm^{-1}, 3055cm^{-1}(C-H stretching)

HRMS calcd. for C20H24NO4 (M^++23): 342.1705 Found: 342.1721

(6,7-Dimethoxy-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-(3-methoxy-phenyl)-methanone (115)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

1.49 (1H, d, J_2 = 6.5Hz, C1C$\underline{H}_3$), 1.56 (2H, d, J = 6.5Hz, C1C$\underline{H}_3$); 2.66 (0.67H, d, J = 24Hz, C4$\underline{H}_2$ (m)), 2.70 (0.33H, d, J = 16Hz, C4$\underline{H}_2$ (s)); 2.90 (0.6H, dt, J_1 = 14Hz, J_2 = 5.5Hz, C4$\underline{H}_2$ (m)), 3.00 – 3.09 (0.33H, m, C4$\underline{H}_2$ (s)); 3.20 (0.33H, t, J = 13Hz, C3$\underline{H}_2$ (s)); 3.40 (0.67H, t, J = 13Hz, C3$\underline{H}_2$ (s)); 3.43, 3.80, 3.81, 3.84, 3.87 (9.67H, overlapping singlets and multiplet, C3'OC$\underline{H}_3$, C6OC$\underline{H}_3$, C7OC$\underline{H}_3$, C3$\underline{H}_2$); 4.76 (0.66H, bs, C3$\underline{H}_2$ (s), C1$\underline{H}$ (s)); 5.67 (0.7H, d, J = 6.5Hz, C1$\underline{H}$); 6.36 (0.3H, s, C8$\underline{H}$ (s)), 6.58, 6.62 (1.67H, s, s, overlapping, C8$\underline{H}$(m), C5$\underline{H}$(s), (m)); 6.66 (1H, s, C5$\underline{H}$ (m)); 6.94 – 6.97 (3H, m, C2'$\underline{H}$, C4'$\underline{H}$, C5'$\underline{H}$); 7.28 – 7.34 (1H, m, C6'$\underline{H}$)

^{13}C-NMR (101MHz):

21.2 (C$\underline{H}_3$ (m)), 23.0 (C$\underline{H}_3$ (s)); 27.7 (C$\underline{4}H_2$ (s)), 29.0 (C$\underline{4}H_2$ (m)); 35.1 (C$\underline{3}H_2$ (s)); 40.6 (C$\underline{3}H_2$ (m)); 48.1 (C$\underline{1}$H (m)); 53.2 (C$\underline{1}$H (s)); 55.1 (C3'OC$\underline{H}_3$); 55.7 (C6OC$\underline{H}_3$ (m) C7OC$\underline{H}_3$ (m)), 55.8 (C6OC$\underline{H}_3$ (s), C7OC$\underline{H}_3$ (m)); 109.1 (C$\underline{8}$'H (s)), 109.6 (C$\underline{8}$'H (m)); 111.0 (C$\underline{5}$H (m)), 111.3 (C$\underline{5}$H (s)); 111.6 (C$\underline{2}$'H); 115.2 (C$\underline{4}$'H); 118.3 (C$\underline{6}$'H); 124.7, 125.7 (C$\underline{8}$a); 129.5 (C$\underline{5}$'H); 129.4, 130.0 (C$\underline{4}$a); 137.6 (CO$\underline{C}$1'); 147.3, 147.5, 147.6, 147.64 (C$\underline{6}$OCH$_3$, C$\underline{7}$OCH$_3$); 159.5 (C$\underline{O}$CH$_3$); 169.6 (C$\underline{O}$ (m)), 170.1 (C$\underline{O}$ (s))

Yield: 83.0%

IRν_{max}(KBr): 1465cm^{-1}(C-N stretching), 1634cm^{-1}(C=O stretching), 2939cm^{-1}, 3055cm^{-1}(C-H stretching)

HRMS calcd. for C40H46N2O8Na ($2M^+$+23): 705.3152 Found: 705.3159

(Molecular ion formed by dimer and sodium).

(6,7-Dimethoxy-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-(4-methoxy-phenyl)-methanone(116)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

1.50 (3H, bs, C1C$\underline{H}_3$); 2.60 (1H, d, J = 14Hz, C4$\underline{H}_2$); 2.90 (1H, bs, C4$\underline{H}_2$); 3.16 (0.4H, bs, C3$\underline{H}_2$ (s)); 3.38 (0.6H, bs, C3$\underline{H}_2$ (m)); 3.78, 3.80 (9.6H, overlapping singlets and multiplet, C4'OC$\underline{H}_3$, C6OC$\underline{H}_3$, C7OC$\underline{H}_3$, C3$\underline{H}_2$ (m)); 4.69 (0.4H, bs, C3$\underline{H}_2$ (s)); 4.80 (0.4H, bs, C1$\underline{H}$ (s)); 5.60 (0.6H, bs, C1$\underline{H}$ (m)); 6.34 (0.4H, s, C8$\underline{H}$ (s)), 6.56 (1.2H, s, s, overlapping, C8$\underline{H}$(m), C5$\underline{H}$(m)), 6.62 (0.4H, s, C5$\underline{H}$ (s)); 6.88 (2H, d, J = 8.5Hz, C3'$\underline{H}$, C5'$\underline{H}$); 7.35 (2H, d, J = 8.5Hz, C2'$\underline{H}$, C6'$\underline{H}$)

^{13}C-NMR (101MHz):

21.0 (C$\underline{H}_3$ (m)), 22.8 (C$\underline{H}_3$ (s)); 27.6 (C$\underline{4}H_2$ (s)), 28.9 (C$\underline{4}H_2$ (m)); 35.2 (C$\underline{3}H_2$ (s)); 40.7 (C$\underline{3}H_2$ (m)); 48.3 (C$\underline{1}$H (m)); 53.3 (C$\underline{1}$H (s)); 55.0 (C3'OC$\underline{H}_3$); 55.5 (C6OC$\underline{H}_3$ (m) C7OC$\underline{H}_3$ (m)), 55.7 (C6OC$\underline{H}_3$ (s), C7OC$\underline{H}_3$ (m)); 109.0 (C$\underline{8}$'H); 111.0 (C$\underline{5}$H); 113.5 (C$\underline{3}$'H, C$\underline{5}$'H); 124.7 (C$\underline{8}$a); 125.6 (C$\underline{1}$'); 128.2 (C$\underline{2}$'H, C$\underline{6}$'H); 130.1 (C$\underline{4}$a); 147.4 (CO$\underline{C}$1'); 147.4 (C$\underline{6}$OCH$_3$, C$\underline{7}$OCH$_3$); 160.3 (C$\underline{O}$CH$_3$); 169.8 (C$\underline{O}$)

Yield: 84.3%

IRν_{max}(KBr): 1423cm^{-1}(C-N stretching), 1618cm^{-1}(C=O stretching), 2038cm^{-1}, 2935cm^{-1}, 3438cm^{-1}(C-H stretching)

HRMS calcd. for C20H24NO4 (M^++23): 342.1705 Found: 342.1695

(6,7-Dimethoxy-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-(4-fluoro-phenyl)-methanone (117)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

1.51 (1H, bs, C1C$\underline{H}_3$ (s)), 1.56 (2H, bs, C1C$\underline{H}_3$ (m)); 2.64 (0.67H, d, J = 15.5Hz, C4$\underline{H}_2$ (m)), 2.73 (0.33H, bs, C4$\underline{H}_2$ (s)); 2.86 – 2.94 (0.67H, m, C4$\underline{H}_2$ (m)), 3.05 (0.33H, bs, C4$\underline{H}_2$ (s)); 3.22 (0.33H, bs, C3$\underline{H}_2$ (s)), 3.44 (0.67H, t, J = 12Hz, C3$\underline{H}_2$ (m)); 3.79, 3.83, 3.85, 3.88 (6.67H, overlapping singlets and multiplet, C3$\underline{H}_2$ (m), C6OC$\underline{H}_3$, C7OC$\underline{H}_3$); 4.76 (0.66H, bs, C3$\underline{H}_2$ (s), C1$\underline{H}$ (s)); 5.67 (0.67H, d, J = 5.5Hz, C1$\underline{H}$ (m)); 6.35 (0.33H, s, C8$\underline{H}$ (s)), 6.61 (1.34H, overlapping singlets, C8$\underline{H}$ (m), C5$\underline{H}$ (m)); 6.67 (0.33H, s, C5$\underline{H}$ (s)); 7.11 (2H, apparent triplet, J = 8.5Hz, C3'$\underline{H}$, C5'$\underline{H}$); 7.41 – 7.45 (2H, m, C2'$\underline{H}$, C6'$\underline{H}$)

^{13}C-NMR (101MHz):

21.1 (C$\underline{H}_3$ (m)), 22.9 (C$\underline{H}_3$ (s)); 27.7 (C$\underline{4}H_2$ (s)), 29.0 (C$\underline{4}H_2$ (m)); 35.2 (C$\underline{3}H_2$ (s)); 40.7 (C$\underline{3}H_2$ (m)); 48.3 (C$\underline{1}$H (m)); 53.3 (C$\underline{1}$H (s)); 55.7 (C6OC$\underline{H}_3$ (m) C7OC$\underline{H}_3$ (m)), 55.8 (C6OC$\underline{H}_3$ (s), C7OC$\underline{H}_3$ (m)); 109.0 (C$\underline{8}$'H (s)), 109.6 (C$\underline{8}$'H (m)); 111.0 (C$\underline{5}$H (m)), 111.4 (C$\underline{5}$H (s)); 115.3, 115.5 (C$\underline{3}$'H, C$\underline{5}$'H); 124.5, 125.7 (C$\underline{8}$a); 128.6 (C$\underline{2}$'H, C$\underline{6}$'H); 129.0, 129.9 (C$\underline{4}$a); 132.4 (CO$\underline{C}$1'); 147.36, 147.41, 147.53, 147.7 (C$\underline{6}$OCH$_3$, C$\underline{7}$OCH$_3$); 165.5 (d, J = 189Hz, C$\underline{4}$'F); 169.0 (C$\underline{O}$ (m)), 169.6 (C$\underline{O}$ (s))

^{19}F-NMR (376MHz):

-109.2 (s), -111.1 (m)

Yield: 55.6%

IRν_{max}(KBr): 1228cm^{-1} (CF), 1466cm^{-1}(C-N stretching), 1627cm^{-1}(C=O stretching), 2938cm^{-1}, 3055cm^{-1}(C-H stretching)

Melting point: 136 - 138°C

HRMS calcd. for C19H21NO3F (M$^+$+23): 330.1505 Found: 330.1519

(4-Chloro-phenyl)-(6,7-dimethoxy-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-methanone (118)

^{1}H-NMR (400MHz):

δ(CDCl$_3$):

1.49 (1H, bs, C1C$\underline{H}_3$ (s)), 1.57 (2H, d, J = 6.5Hz, C1C$\underline{H}_3$ (m)); 2.63 (0.67H, d, J = 15.6Hz, C4$\underline{H}_2$ (m)), 2.72 (0.33H, d, J = 16.5Hz, C4$\underline{H}_2$ (s)); 2.84 – 2.90 (0.67H, m, C4$\underline{H}_2$ (m)), 3.04 (0.33H, bs, C4$\underline{H}_2$ (s)); 3.21 (0.33H, t, J = 12Hz, C3$\underline{H}_2$ (s)), 3.44 (0.67H, t, J = 12Hz, C3$\underline{H}_2$ (m)); 3.75 (0.67H, d, J = 14Hz, C3$\underline{H}_2$ (m)); 3.79, 3.84, 3.86, 3.88 (6H, overlapping singlets, C6OC$\underline{H}_3$, C7OC$\underline{H}_3$); 4.73 (0.66H, bs, C3$\underline{H}_2$ (s), C1$\underline{H}$ (s)); 5.67 (0.67H, d, J = 6.5Hz, C1$\underline{H}$ (m)); 6.37 (0.33H, s, C8$\underline{H}$ (s)), 6.59 (0.67H, s, C8$\underline{H}$ (m)); 6.62 (0.33H, s, C5$\underline{H}$ (s)); 6.66 (0.67H, s, C5$\underline{H}$ (m)); 7.11 (2H, apparent triplet, J = 8.5Hz, C3'$\underline{H}$, C5'$\underline{H}$); 7.28 – 7.36 (4H, m, C2'$\underline{H}$, C6'$\underline{H}$)

^{13}C-NMR (101MHz):

21.3 (C$\underline{H}_3$ (m)), 23.0 (C$\underline{H}_3$ (s)); 27.7 (C$\underline{4}H_2$ (s)), 29.0 (C$\underline{4}H_2$ (m)); 35.2 (C$\underline{3}H_2$ (s)); 40.8 (C$\underline{3}H_2$ (m)); 48.4 (C$\underline{1}$H (m)); 53.3 (C$\underline{1}$H (s)); 55.7 (C6OC$\underline{H}_3$ (m) C7OC$\underline{H}_3$ (m)), 55.9 (C6OC$\underline{H}_3$ (s), C7OC$\underline{H}_3$ (m)); 109.0 (C$\underline{8}$'H (s)), 109.6 (C$\underline{8}$'H (m)); 111.1 (C$\underline{5}$H (m)), 111.4 (C$\underline{5}$H (s)); 124.5 (C$\underline{8}$a); 128.0 (C$\underline{2}$'H, C$\underline{6}$'H); 128.7 (C$\underline{3}$'H, C$\underline{5}$'H); 129.9 (C$\underline{4}$a); 134.8 (CO$\underline{C}$1'); 135.4 (C$\underline{4}$'Cl); 147.6, 147.8 (C$\underline{6}$OCH$_3$, C$\underline{7}$OCH$_3$); 168.9 (C$\underline{O}$)

Yield: 71.1%

IRν_{max}(KBr): 1436cm^{-1}(C-N stretching), 1620cm^{-1}(C=O stretching), 2039cm^{-1}, 2934cm^{-1}(C-H stretching), 3437cm^{-1}

Melting point: 184 - 186°C Literature: 185°C[25]

(4-Bromo-phenyl)-(6,7-dimethoxy-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-methanone (119)

^{1}H-NMR (400MHz):

δ(CDCl$_3$):

1.60 (3H, m, C1C$\underline{H}_3$); 2.52 (0.67H, d, J = 15Hz, C4$\underline{H}_2$ (m)), 2.60 (0.33H, d, J = 15.5Hz, C4$\underline{H}_2$ (s)); 2.77 (0.67H, bs, C4$\underline{H}_2$ (m)), 2.94 (0.33H, bs, C4$\underline{H}_2$ (s)); 3.11 (0.33H, t, J = 12Hz, C3$\underline{H}_2$ (s)), 3.33 (0.67H, t, J =

12Hz, C3$\underline{H}_2$ (m)); 3.63 (0.67H, bs, C3$\underline{H}_2$ (m)); 3.68, 3.84, 3.72, 3.74, 3.77 (6H, overlapping singlets, C6OC$\underline{H}_3$, C7OC$\underline{H}_3$); 4.65 (0.66H, bs, C3$\underline{H}_2$ (s), C1$\underline{H}$ (s)); 5.56 (0.67H, s, C1$\underline{H}$ (m)); 6.29 (0.33H, s, C8$\underline{H}$ (s)), 6.50 (1H, overlapping singlets, C8$\underline{H}$ (m), C5$\underline{H}$ (s)); 6.58 (0.67H, s, C5$\underline{H}$ (m)); 7.21 (2H, d, J = 7.5Hz, C3'$\underline{H}$, C5'$\underline{H}$); 7.45 (2H, d, J = 7.5Hz, C2'$\underline{H}$, C6'$\underline{H}$)

^{13}C-NMR (101MHz):

20.3 (C$\underline{H}_3$); 27.4 (C$\underline{4}H_2$); 35.8 (C$\underline{3}H_2$); 48.2 (C$\underline{1}$H); 55.4 (C6OC$\underline{H}_3$ (m) C7OC$\underline{H}_3$ (m)), 55.5 (C6OC$\underline{H}_3$ (s), C7OC$\underline{H}_3$ (m)); 109.6 (C$\underline{8}$'H (m)); 111.0 (C$\underline{5}$H); 123.5 (C4'Br); 124.4 (C$\underline{8}$a); 128.1 (C$\underline{2}$'H, C$\underline{6}$'H); 129.8 (C$\underline{4}$a); 131.2 (C$\underline{3}$'H, C$\underline{5}$'H); 135.2 (CO$\underline{C}$1'); 147.6, 147.7 (C$\underline{6}$OCH$_3$, C$\underline{7}$OCH$_3$); 169.2 (C$\underline{O}$)

Yield: 59.8%

IRν_{max}(KBr): 1436cm^{-1}(C-N stretching), 1622cm^{-1}(C=O stretching), 2847cm^{-1}, 2932cm^{-1}, 3438cm^{-1} (C-H stretching)

Melting point: 140 - 142°C

HRMS calcd. for C38H40N2O6(79)Br2Na (2M$^+$+23): 801.1151 Found: 801.1125

(6,7-Dimethoxy-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-(4-iodo-phenyl)-methanone (120)

^{1}H-NMR (400MHz):

δ(CDCl$_3$):

1.47 (1.2H, d, J = 6Hz, C1C$\underline{H}_3$ (s)), 1.55 (1.8H, d, J = 6.5Hz, C1C$\underline{H}_3$ (m)); 2.62 (0.6H, d, J = 16Hz, C4$\underline{H}_2$ (m)), 2.71 (0.4H, d, J = 15Hz, C4$\underline{H}_2$ (s)); 2.82 – 2.91 (0.6H, m, C4$\underline{H}_2$ (m)), 3.03 (0.4H, bs, C4$\underline{H}_2$ (s)); 3.19 (0.4H, t, J = 11Hz, C3$\underline{H}_2$ (s)), 3.42 (0.6H, t, J = 11Hz, C3$\underline{H}_2$ (m)); 3.73 (0.6H, dd, J_1 = 14Hz, J_2 = 4.5Hz, C3$\underline{H}_2$ (m)); 3.75, 3.78, 3.83, 3.84, 3.87 (6H, overlapping singlets, C6OC$\underline{H}_3$, C7OC$\underline{H}_3$); 4.71 (0.8H, bs, C3$\underline{H}_2$ (s), C1$\underline{H}$ (s)); 5.65 (0.6H, d, J = 6.5Hz, C1$\underline{H}$ (m)); 6.36 (0.4H, s, C8$\underline{H}$ (s)), 6.58 (0.6H, s, C8$\underline{H}$ (m)); 6.61 (0.4H, s, C5$\underline{H}$ (s)), 6.65 (0.6H, s, C5$\underline{H}$ (m)); 7.16 (2H, d, J = 8Hz, C2'$\underline{H}$, C6'$\underline{H}$); 7.76 (2H, d, J = 8.0Hz, C3'$\underline{H}$, C5'$\underline{H}$)

^{13}C-NMR (101MHz):

21.2 (C$\underline{H}_3$ (m)), 23.0 (C$\underline{H}_3$ (s)); 27.7 (C$\underline{4}H_2$ (s)), 29.0 (C$\underline{4}H_2$ (m)); 35.2 (C$\underline{3}H_2$ (s)); 40.7 (C$\underline{3}H_2$ (m)); 48.3 (C$\underline{1}$H (m)); 53.2 (C$\underline{1}$H (s)); 55.6 (C6OC$\underline{H}_3$ (m) C7OC$\underline{H}_3$ (m)), 55.8 (C6OC$\underline{H}_3$ (s), C7OC$\underline{H}_3$ (m)); 95.5 (C$\underline{4}$'I); 109.0 (C$\underline{8}$'H (s)), 109.6 (C$\underline{8}$'H (m)); 111.0 (C$\underline{5}$H (m)), 111.1 (C$\underline{5}$H (s)); 124.5 (C$\underline{8}$a); 128.2 (C$\underline{2}$'H, C$\underline{6}$'H); 129.8 (C$\underline{4}$a); 135.8 (CO$\underline{C}$1'); 137.5 (C$\underline{3}$'H, C$\underline{5}$'H); 147.5, 147.7 (C$\underline{6}$OCH$_3$, C$\underline{7}$OCH$_3$); 169.0 (C$\underline{O}$)

Yield: 60.0%

IRν_{max}(KBr): 1429cm^{-1}(C-N stretching), 1634cm^{-1}(C=O stretching), 2832cm^{-1}, 2914cm^{-1}, 3062cm^{-1} (C-H stretching)

Melting point: 134 - 136°C

HRMS calcd. for C38H40N2O6NaI2 (M$^+$+23): 897.0874 Found: 897.0869

(6,7-Dimethoxy-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-(4-nitro-phenyl)-methanone (121)

^{1}H-NMR (400MHz):

δ(CDCl$_3$):

1.48 (1.2H, d, J = 6.5Hz, C1C$\underline{H}_3$ (s)), 1.57 (1.8H, d, J = 6.5Hz, C1C$\underline{H}_3$ (m)); 2.64 (0.6H, d, J = 16Hz, C4$\underline{H}_2$ (m)), 2.74 (0.4H, d, J = 16Hz, C4$\underline{H}_2$ (s)); 2.85 – 2.93 (0.6H, m, C4$\underline{H}_2$ (m)), 3.04 (0.4H, dt, J_1 = 14Hz, J_2 = 6Hz, C4$\underline{H}_2$ (s)); 3.24 (0.4H, t, J_1 = 12Hz, J_2 = 4Hz, C3$\underline{H}_2$ (s)), 3.46 (0.6H, t, J_1 = 12Hz, J_2 = 3.5Hz, C3$\underline{H}_2$ (m)); 3.61 (0.6H, dd, J_1 = 14Hz, J_2 = 4.5Hz, C3$\underline{H}_2$ (m)); 3.75, 3.84, 3.86 (6H, overlapping singlets, C6OC$\underline{H}_3$, C7OC$\underline{H}_3$); 4.59 (0.4H, dd, J_1 = 13Hz, J_2 = 6.5Hz, C3$\underline{H}_2$ (s)); 4.78 (0.4H, dd, J_1 = 13Hz, J_2 = 5.5Hz, C1$\underline{H}$ (s)); 5.66 (0.6H, dd, J_1 = 13Hz, J_2 = 6.5Hz, C1$\underline{H}$ (m)); 6.34 (0.4H, s, C8$\underline{H}$ (s)), 6.58 (0.6H, s, C8$\underline{H}$ (m)); 6.62

(0.4H, s, C5H (s)), 6.65 (0.6H, s, C5H (m)); 7.58 (2H, d, J = 9Hz, C2'H, C6'H); 8.27 (2H, d, J = 9Hz, C3'H, C5'H)

^{13}C-NMR (101MHz):

21.2 ($\underline{C}H_3$ (m)), 22.9 ($\underline{C}H_3$ (s)); 27.6 ($\underline{C}4H_2$ (s)), 28.8 ($\underline{C}4H_2$ (m)); 35.2 ($\underline{C}3H_2$ (s)); 40.7 ($\underline{C}3H_2$ (m)); 48.3 ($\underline{C}$1H (m)); 53.2 ($\underline{C}$1H (s)); 55.6 (C6O$\underline{C}H_3$ (m) C7O$\underline{C}H_3$ (m)), 55.8 (C6O$\underline{C}H_3$ (s), C7O$\underline{C}H_3$ (m)); 108.9 ($\underline{C}$8'H (s)), 109.5 ($\underline{C}$8'H (m)); 111.0 ($\underline{C}$5H (m)), 111.1 ($\underline{C}$5H (s)); 123.4 ($\underline{C}$3'H, $\underline{C}$5'H (s)), 123.7 ($\underline{C}$3'H, $\underline{C}$5'H (m)); 124.2 ($\underline{C}$8a (m)), 125.4 ($\underline{C}$8a (s)); 127.4 ($\underline{C}$2'H, $\underline{C}$6'H (m)), 127.9 ($\underline{C}$2'H, $\underline{C}$6'H (s)); 128.5 ($\underline{C}$4a (s)), 129.4 ($\underline{C}$4a); 142.5 (CO$\underline{C}$1'); 147.4, 147.5, 147.8,147.8 ($\underline{C}$6OCH$_3$, $\underline{C}$7OCH$_3$); 148.0 ($\underline{C}$4'NO$_2$ (m)), 148.8 ($\underline{C}$4'NO$_2$ (s)); 167.6 ($\underline{C}$O (m)), 168.0 ($\underline{C}$O (s))

Yield: 51.0%

IRν_{max}(KBr): 1466cm^{-1}(C-N stretching), 1670cm^{-1}(C=O stretching), 2986cm^{-1}, 3055cm^{-1}(C-H stretching)

HRMS calcd. for C19H21N2O5 (M^++1): 357.1433 Found: 357.1450

Phenyl amides

1-(6,7-Dimethoxy-1-phenyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-phenyl-ethanone (122)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.60 (1.8H, t, J = 4Hz, C4$\underline{H}_2$); 2.93 (0.2H, t, J = 16Hz, C4$\underline{H}_2$); 3.19 – 3.26 (0.2H, m, C3$\underline{H}_2$ (s)); 3.26 – 3.35 (0.8H, m, C3H_2 (m)); 3.77 – 3.83 (5.8H, m, C7OC$\underline{H}_3$, COC$\underline{H}_2$, C3$\underline{H}_2$ (m)); 3.89 (3H, s, C6OC$\underline{H}_3$); 4.32 – 4.37 (0.2H, bs, C3$\underline{H}_2$ (s)); 5.96 (0.2H, bs, C1H (s)), 6.38 (0.2H, bs, C8H (s)); 6.54 (0.8H, s, C8H); 6.60 (0.8H, s, C5H); 6.67 (0.2H, C5H (s)); 6.95 (0.8H, s, C1H (m)); 7.26 – 7.29 (10H, C2'H, C3'H, C4'H, C5'H, C6'H, C2"H, C3"H, C4"H, C5"H, C6"H)

^{13}C-NMR (101MHz):

28.3 ($\underline{C}4H_2$); 39.8 ($\underline{C}3H_2$); 41.4 (CO$\underline{C}H_2$); 54.7 ($\underline{C}$1H); 55.9 (C6O$\underline{C}H_3$, 7OC$\underline{H}_3$); 110.9 ($\underline{C}$8H); 111.2 ($\underline{C}$5H); 126.2 ($\underline{C}$8a); 126.6 ($\underline{C}$4a); 126.7 ($\underline{C}$4'H); 127.4 ($\underline{C}$4"H); 128.2 ($\underline{C}$2'H, $\underline{C}$6'H); 129.0 ($\underline{C}$3"H, $\underline{C}$5"H); 128.7 ($\underline{C}$2"H, $\underline{C}$6"H); 128.8 ($\underline{C}$3'H, $\underline{C}$5'H); 135.0 ($\underline{C}$1"); 142.5 (C1'); 147.5 ($\underline{C}$7OCH$_3$); 148.0 ($\underline{C}$6OCH$_3$); 169.3 ($\underline{C}$O)

Yield: 62.9%

IRν_{max}(KBr): 1450cm^{-1}(C-N stretching), 1634cm^{-1}(C=O stretching), 2932cm^{-1}, 3328cm^{-1}(C-H stretching)

Melting point: 188°C

HRMS calcd. for C25H25NO3Na (M^++23): 410.1732 Found: 410.1717

1-(6,7-Dimethoxy-1-phenyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-(4-nitro-phenyl)-ethanone (123)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.73 (2H, m, C4$\underline{H}_2$); 3.41 – 3.50 (2H, m, C3$\underline{H}_2$); 3.76, 3.89 (8H, s, s, C7OC$\underline{H}_3$, C6OC$\underline{H}_3$); 6.53 (1H, s, C8H); 6.65 (1H, s, C5H); 6.90 (1H, s, C1H); 7.25 – 7.28 (5H, C2'H, C3'H, C4'H, C5'H, C6'H); 7.41 (2H, d, J = 8Hz, C3"H. C5"H); 8.16 (2H, d, J = 8Hz, C2"H, C6"H);

^{13}C-NMR (101MHz):

28.5 ($\underline{C}4H_2$); 39.9 ($\underline{C}3H_2$); 40.6 (CO$\underline{C}H_2$); 55.1 ($\underline{C}$1H); 55.9 (C6O$\underline{C}H_3$, 7OC$\underline{H}_3$); 111.1 ($\underline{C}$8H); 111.3 ($\underline{C}$5H); 123.7 ($\underline{C}$3"H, $\underline{C}$5"H); 125.9 ($\underline{C}$8a); 126.5 ($\underline{C}$4a); 127.6 ($\underline{C}$4'H); 128.3 ($\underline{C}$2'H, $\underline{C}$6'H); 128.7 ($\underline{C}$3'H, $\underline{C}$5'H);

129.8 (C2"H, C6"H); 142.1 (C1'); 142.6 (C1"); 147.0 (C7OCH_3); 147.9 (C6OCH_3); 148.3 (CNO_2); 167.8 (CO)

Yield: 34.4%

IRν_{max}(KBr): 1445cm^{-1}(C-N stretching), 1627cm^{-1}(C=O stretching), 2929cm^{-1}, 3328cm^{-1}(C-H stretching)

Melting point: 156 - 158°C

HRMS calcd. for C25H24N2O5Na (M^++23): 455.1583 Found: 455.1561

1-(6,7-Dimethoxy-1-phenyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-(4-methylsulfanyl-phenyl)-ethanone (124)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.47 (3H, SCH_3); 2.63 (1.8H, m, C4H_2); 2.91 (0.2H, m, C4H_2); 3.22 (0.2H, bs, C3H_2); 3.28 – 3.36 (0.8H, m, C3H_3); 3.76 (5.8H, s, C7OCH_3, COCH_2, C3H_2); 3.89 (3H, s, C6OCH_3); 4.31 (0.2H, bs, C3H_2); 5.95 (0.2H, s, C1H); 6.41 (0.2H, s, C8H); 6.53 (0.8H, s, C8H); 6.62 (0.8H, s, C5H); 6.67 (0.2H, s, C5H); 6.93 (0.8H, s, C1H); 7.15 – 7.19 (4H, m, C2"H, C3"H, C5"H, C6"H); 7.27 – 7.28 (5H, m, C2'H, C3'H., C4'H, C5'H, C6"H)

^{13}C-NMR (101MHz):

15.9 (SCH_3); 28.4 (C4H_2); 39.7 (C3H_2); 40.7 (COCH_2); 54.7 (C1H); 55.9 (C6OCH_3, 7OCH_3); 110.9 (C8H); 111.1 (C5H); 126.2 (C8a); 126.6 (C4a); 126.9 (C3"H, C5"H); 127.4 (C4'H); 128.1 (C2'H, C6'H); 128.8 (C3'H, C5'H); 129.0 (C2"H, C6"H); 131.8 (C1"); 136.7 (C4"SCH_3); 142.4 (C1'); 147.5 (C7OCH_3); 147.9 (C6OCH_3); 169.2 (CO)

Yield: 38.8%

IRν_{max}(KBr): 1457cm^{-1}(C-N stretching), 1636cm^{-1}(C=O stretching), 2936cm^{-1}, 3450cm^{-1}(C-H stretching)

Melting point: 164°C

HRMS calcd. for C26H27NO3NaS (M^++23): 456.1609 Found: 456.1617

1-(6,7-Dimethoxy-1-phenyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-(3-methoxy-phenyl)-ethanone (125)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.63 (1.8H, m, C4H_2); 2.90 (0.2H, m, C4H_2); 3.28 – 3.35 (0.8H, m, C3H_3); 3.35 (0.2H, m, C3H_2); 3.71 – 3.80 (5.8H, s, C7OCH_3, COCH_2, C3H_2); 3.87 (3H, s, C6OCH_3); 4.40 (0.2H, bs, C3H_2); 5.90 (0.2H, s, C1H); 6.41 (0.2H, s, C8H); 6.54 (0.8H, s, C8H); 6.62 (0.8H, s, C5H); 6.67 (0.2H, s, C5H); 6.80 – 6.83 (3H, m, C2"H, C4"H, C5"H); 6.94 (0.8H, s, C1H); 7.20 – 7.27 (6H, m, C2'H, C3'H., C4'H, C5'H, C6'H, C6"H)

^{13}C-NMR (101MHz):

28.3 (C4H_2); 39.8 (C3H_2); 41.3 (COCH_2); 54.7 (C1H); 55.0 (C3"OCH_3); 55.9 (C6OCH_3, 7OCH_3); 111.1 (C8H); 111.4 (C5H); 112.6 (C2"H); 113.6 (C4"H); 120.8 (C6"H); 126.3 (C8a); 126.7 (C4a); 127.3 (C4'H); 128.1 (C2'H, C6'H); 128.7 (C3'H, C5'H); 129.5 (C5"H); 136.4 (C1"); 142.4 (C1'); 147.6 (C7OCH_3); 148.1 (C6OCH_3); 159.8 (C32OCH_3); 169.1 (CO)

Yield: 68.5%

IRν_{max}(KBr): 1458cm^{-1}(C-N stretching), 1635cm^{-1}(C=O stretching), 2933cm^{-1}, 2982cm^{-1}(C-H stretching)

Melting point: 172°C

HRMS calcd. for C26H27NO4Na (M^++23): 440.1838 Found: 440.1818

1-(6,7-Dimethoxy-1-phenyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-(4-methoxy-phenyl)-ethanone (126)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.61 (1.8H, m, C4H_2); 2.75 (0.2H, m, C4H_2); 3.32 – 3.51 (1..8H, m, C3H_3); 3.76 – 3.88 (8H, s, s, C7OCH_3, COCH_2, C6OCH_3); 4.40 (0.2H, bs, C3H_2); 5.90 (0.2H, s, C1H); 6.40 (0.2H, s, C8H); 6.54 (0.8H, s, C8H); 6.61 (1H, s, C5H); 6.84 (2H, d, J = 7Hz, C3"H, C5"H); 6.92 (0.8H, s, C1H); 7.15 (2H, d, J = 7.0Hz, C2"H. C6"H); 7.27 (5H, m, C2'H, C3'H., C4'H, C5'H, C6'H)

^{13}C-NMR (101MHz):

28.4 (C4H_2); 39.8 (C3H_2); 40.5 (COCH_2); 54.7 (C1H); 55.9 (C4"OCH_3); 56.0 (C6OCH_3, 7OCH_3); 111.1 (C8H); 111.4 (C5H); 114.1 (C3"H, C5"H); 126.4 (C8a); 126.8 (C4a); 127.0 (C1"); 127.3 (C4'H); 128.2 (C2'H, C6'H); 128.7 (C3'H, C5'H); 129.6 (C2"H, C6"H); 142.6 (C1'); 147.7 (C7OCH$_3$); 148.1 (C6OCH$_3$); 158.4 (C32OCH$_3$); 169.7 (CO)

Yield: 49.0%

IRν_{max}(KBr): 1451cm^{-1}(C-N stretching), 1634cm^{-1}(C=O stretching), 2933cm^{-1}, 3328cm^{-1}(C-H stretching)

Melting point: 166°C

HRMS calcd. for C26H27NO4Na (M^++23): 440.1838 Found: 440.1848

2-(3,4-Dimethoxy-phenyl)-1-(6,7-dimethoxy-1-phenyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-ethanone (127)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.59 – 2.66 (2H, m, C4H_2); 3.26 – 3.33 (1H, m, C3H_3); 3.74 – 3.88 (8.8H, s, s, C7OCH_3, COCH_2, C3H_2, C6OCH_3); 4.40 (0.2H, bs, C3H_2); 6.00 (0.2H, s, C1H); 6.41 (0.2H, s, C8H); 6.52 (0.8H, s, C8H); 6.60 (0.8H, s, C5H); 6.67 (0.2H, s, C5H); 6.73 – 6.80 (3H, C2"H, C5"H); 6.94 (0.8H, s, C1H); 7.15 (2H, d, J = 7.0Hz, C2"H. C6"H); 7.27 – 7.28 (6H, m, C2'H, C3'H., C4'H, C5'H, C6'H, C6"H)

^{13}C-NMR (101MHz):

28.4 (C4H_2); 39.7 (C3H_2); 40.9 (COCH_2); 54.6 (C1H); 55.6 (C3"OCH_3, C4"OCH_3); 55.8 (C6OCH_3, 7OCH_3); 110.8 (C8H); 111.0 (C5H); 111.13 (C2"H, C5"H); 120.5 (C6"H); 126.2 (C8a, C1"); 126.6 (C4a); 127.3 (C4'H); 128.1 (C2'H, C6'H); 128.8 (C3'H, C5'H); 129.6 (C2"H, C6"H); 142.4 (C1'); 147.4, 147.7, 147.9, 148.97 (C7OCH$_3$, C6OCH$_3$, C3"OCH$_3$, C4"OCH$_3$); 169.5 (CO)

Yield: 57.7%

IRν_{max}(KBr): 1426cm^{-1}(C-N stretching), 1628cm^{-1}(C=O stretching), 2934cm^{-1}, 3423cm^{-1}(C-H stretching)

Melting point: 142°C

HRMS calcd. for C27H29NO5Na (M^++23): 470.1943 Found: 470.1945

(6,7-Dimethoxy-1-phenyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-(4-nitro-phenyl)-methanone (128)*

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.69 (1H, d, J = 13Hz, C4H_2); 2.94 (1H, bs, C4H_2); 3.35 (1H, dt, J_1 = 14Hz, J_2 = 4Hz, C3H_2); 3.42 – 3.47 (0.8H, m, C3H_2 (m)); 3.74 (3H, s, C7OCH_3); 3.87 (3H, s, C6OCH_3); 4.56 (0.2H, bs, C3H_2 (s)); 5.74 (0.2H, bs, C1H (s)), 6.36 (0.2H, bs, C8H (s)); 6.54 (0.8H, s, C8H); 6.73 (1H, s, C5H); 6.98 (1H, s, C1H (m)); 7.00

(2H, d, J = 8.5Hz, C2"H, C6"H); 7.23 – 7.32 (5H, C2'H, C3'H, C4'H, C5'H, C6'H); 8.24 (2H, d, J = 8.5Hz, C3"H, C5"H)

^{13}C-NMR (101MHz):

28.5 (C4H_2); 40.5 (C3H_2); 54.8 (C1H); 55.7 (C6OCH_3, 7OCH_3); 110.9 (C8H, C5H); 123.7 (C3"H, C5"H); 125.5 (C8a); 125.6 (C4a); 127.0 (C2"H, C6"H); 127.3 (C4'H); 128.3 (C2'H, C6'H); 128.8 (C3'H, C5'H); 141.8 (C1"); 142.2 (C1'); 147.7 (C7OCH$_3$ (s)); 148.0 (C6OCH$_3$); 149.2 (C4"NO_2); 167.7 (CO)

Yield: 100.0%

IRν_{max}(KBr): 1436cm^{-1}(C-N stretching), 1522cm^{-1}(NO), 1628cm^{-1}(C=O stretching), 2933cm^{-1}, 3324cm^{-1}(C-H stretching)

Melting point: 166 - 170°C

(6,7-Dimethoxy-1-phenyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-(4-methylsulfanyl-phenyl)-methanone (129)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.52 (3H, s, SCH_3); 2.69 (1H, d, J = 16Hz, C4H_2); 2.97 (1H, bs, C4H_2); 3.32 (1H, dt, J_1 = 14Hz, J_2 = 4Hz, C3H_2); 3.69 (0.8H, m, C3H_2 (m)); 3.79 (3H, s, C7OCH_3); 3.92 (3H, s, C6OCH_3); 4.60 (0.2H, bs, C3H_2 (s)); 6.00 (0.2H, bs, C1H (s)), 6.42 (0.2H, bs, C8H (s)); 6.58 (0.8H, s, C8H); 6.69 (1H, s, C5H); 7.02 (1H, s, C1H (m)); 7.26 – 7.35 (9H, C2'H, C3'H, C4'H, C5'H, C6'H, C2"H, C3"H, C5"H, C6"H)

^{13}C-NMR (101MHz):

15.3 (SCH_3); 28.8 (C4H_2); 40.7 (C3H_2); 54.8 (C1H); 55.8 (C6OCH_3, 7OCH_3); 111.0 (C8H); 111.2 (C5H); 125.6 (C8a); 125.8 (C3"H, C5"H); 126.0 (C4a); 127.1 (C4'H); 127.5 (C2'H, C6'H); 128.3 (C2"H, C6"H); 129.0 (C3'H, C5'H); 132.6 (C1"); 139.2 (C4"SCH_3); 140.8 (C1'); 148.1 (C7OCH$_3$ (s)); 148.2 (C6OCH$_3$); 169.8 (CO)

Yield: 61.0%

IRν_{max}(KBr): 1431cm^{-1}(C-N stretching), 1625cm^{-1}(C=O stretching), 2929cm^{-1}, 3327cm^{-1}(C-H stretching)

Melting point: 116°C

HRMS calcd. for C25H26NO3S (M^++1): 420.1633 Found: 420.1650

1-(6,7-Dimethoxy-1-phenyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-ethanone (130)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.17 (2.4H, s, COCH_3 (m)), 2.34 (0.6H, s, COCH_3 (s)); 2.66 (0.2H, dt, J_1 = 16Hz, J_2 = 4.5Hz, C4H_2 (s)), 2.76 (0.8H,dt, J_1 = 15Hz, J_2 = 3Hz, C4H_2 (m)); 2.87 – 3.00 91H, m, C4H_2); 3.15 (0.2H, dt, J_1 = 11Hz, J_2 = 5Hz, C3H_2 (s)), (0.8H, dt, J_1 = 12Hz, J_2 = 5Hz, C3H_2 (m)); 3.71 (0.8H, dd, J_1 = 15Hz, J_2 = 5Hz, C3H_2 (m)); 3.76 (2.4H, s, C7OCH_3 (m)), 3.83 (0.7H, s, C7OCH_3 (s)), 3.90 (2.9H, s, C6OCH_3); 4.38 (0.2H, dt, J_1 = 9Hz, J_2 = 5Hz, C3H_2 (s)); 5.92 (0.2H, s, C1H (s)), 6.54 (0.8H, s, C8H (m)); 6.62 (0.2H, C8H (s)), 6.68 (0.8H, C5H (m)); 6.70 (0.2H, s, C5H (s)), 6.90 (0.8H, s, C1H (m)); 7.19 – 7.33 (5H, C2'H, C3'H, C4'H, C5'H, C6'H)

^{13}C-NMR (101MHz):

21.6 (CH_3); 27.3 (C4H_2 (s)), 28.4 (C4H_2); 36.8 (C3H_2 (s)), 40.1 (C3H_2 (m)); 54.3 (C1H (m)); 55.8 (C6OCH_3, C7OCH_3 (m)), 55.83 (C6OCH_3, C7OCH_3 (s)); 60.2 (C1H (s); 110.7 (C8H (s)), 110.9 (C8H (m)); 111.1 (C5H (m)), 111.4 (C5H (s)); 126.3 (C8a); 126.8 (C4a); 127.3 (C4'H (m)), 127.4 (C2'H, C6'H (s)); 128.1 (C2'H, C6'H (m)), 128.5 (C3'H, C5'H (s)); 128.7 (C3'H, C5'H (m)); 142.4 (C1'); 147.5 (C7OCH$_3$); 147.9 (C6OCH$_3$); 168.7 (CO)

Yield: 76.1%

IRν_{max}(KBr): 1441cm^{-1}(C-N stretching), 1638cm^{-1}(C=O stretching), 2987cm^{-1}, 3055cm^{-1}(C-H stretching)

Melting point: 120°C Literature: 190 - 191°C[26]

1-(6,7-Dimethoxy-1-phenyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-propan-1-one (131)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

1.21 (3H, t, J = 7.5Hz, C$\underline{H}_3$); 2.43 (2H, dd, J_1 = 7Hz, J_2 = 3Hz, COC$\underline{H}_2$); 2.75 (1H, d, J_1 = 16Hz, C4$\underline{H}_2$); 2.91 – 2.99 (1H, m, C4$\underline{H}_2$); 3.39 (1H, dt, J_1 = 16Hz, J_2 = 5Hz, C3$\underline{H}_2$); 3.74 (3H, s, C7OC$\underline{H}_3$ (m)); 3.90 (3H, s, C6OC$\underline{H}_3$); 6.57 (1H, s, C8$\underline{H}$ (m)); 6.68 (1H, C5$\underline{H}$ (m)); 6.91 (1H, s, C1$\underline{H}$); 7.26 – 7.28 (5H, C2'$\underline{H}$, C3'$\underline{H}$, C4'$\underline{H}$, C5'$\underline{H}$, C6'$\underline{H}$)

^{13}C-NMR (101MHz):

9.4 (C$\underline{H}_3$); 26.7 (CO$\underline{C}H_2$); 28.6 ($\underline{C}4H_2$); 39.3 ($\underline{C}3H_2$); 54.6 ($\underline{C}$1H); 55.9 (C6O$\underline{C}H_3$, C7O$\underline{C}H_3$); 110.2 ($\underline{C}$8H); 111.6 ($\underline{C}$5H); 126.4 ($\underline{C}$8a); 126.8 ($\underline{C}$4a); 127.3 ($\underline{C}$4'H); 128.2 ($\underline{C}$2'H, $\underline{C}$6'H); 128.7 ($\underline{C}$3'H, $\underline{C}$5'H); 142.7 ($\underline{C}$1'); 148.2 ($\underline{C}$7OCH$_3$, $\underline{C}$6OCH$_3$); 172.1 ($\underline{C}$O)

Yield: 81.5%

IRν_{max}(KBr): 1422cm^{-1}(C-N stretching), 1637cm^{-1}(C=O stretching), 2987cm^{-1}, 3055cm^{-1}(C-H stretching)

Melting point: 144 - 146°C

HRMS calcd. for C20H23NO3Na (M^++23): 348.1576 Found: 348.1585

1-(6,7-Dimethoxy-1-phenyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-butan-1-one (132)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

0.98 (3H, t, J = 7.5Hz, C$\underline{H}_3$); 1.72 (2H, m, COC$\underline{H}_2$); 2.31 – 2.45 (2H, m, C$\underline{H}_2$CH$_3$); 2.76 (1H, d, J = 16Hz, C4$\underline{H}_2$); 2.91 – 3.00 (1H, m, C4$\underline{H}_2$); 3.13 (0.2H, dt, J_1 = 12Hz, J_2 = 5Hz, C3$\underline{H}_3$); 3.37 (0.8H, dt, J_1 = 12Hz, J_2 = 4Hz, C3$\underline{H}_2$); 3.71 (0.8H, dd, J_1 = 15Hz, J_2 = 5Hz, C3$\underline{H}_2$); 3.77 (3.3H, s, C7OC$\underline{H}_3$); 3.90 (2.7H, s, C6OC$\underline{H}_3$); 4.39 (0.2H, m, C3$\underline{H}_2$ (s)); 5.98 (0.2H, s, C1$\underline{H}$ (s)), 6.55 (0.8H, s, C8$\underline{H}$ (m)); 6.63 (0.2H, C8$\underline{H}$ (s)), 6.68 (0.8H, C5$\underline{H}$ (m)); 6.70 (0.2H, s, C5$\underline{H}$ (s)), 6.93 (0.8H, s, C1$\underline{H}$ (m)); 7.20 – 7.33 (5H, C2'$\underline{H}$, C3'$\underline{H}$, C4'$\underline{H}$, C5'$\underline{H}$, C6'$\underline{H}$)

^{13}C-NMR (101MHz):

14.0 (C$\underline{H}_3$); 18.7 (C$\underline{H}_2$CH$_3$); 28.7 ($\underline{C}4H_2$); 35.4 (CO$\underline{C}H_2$); 39.3 ($\underline{C}3H_2$); 54.3 ($\underline{C}$1H); 55.8 (C6O$\underline{C}H_3$, C7O$\underline{C}H_3$); 110.9 ($\underline{C}$8H); 111.3 ($\underline{C}$5H); 126.3 ($\underline{C}$8a); 127.0 ($\underline{C}$4a); 127.2 ($\underline{C}$4'H); 128.1 ($\underline{C}$2'H, $\underline{C}$6'H); 128.7 ($\underline{C}$3'H, $\underline{C}$5'H); 142.7 ($\underline{C}$1'); 147.5 ($\underline{C}$7OCH$_3$); 147.9 ($\underline{C}$6OCH$_3$); 171.33 ($\underline{C}$O)

Yield: 36.6%

IRν_{max}(KBr): 1422cm^{-1}(C-N stretching), 1636cm^{-1}(C=O stretching), 2987cm^{-1}, 3055cm^{-1}(C-H stretching)

Melting point: 156 - 160°C

HRMS calcd. for C21H25NO3SNa (M^++23): 362.1732 Found: 362.1721

1-(6,7-Dimethoxy-1-phenyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-pentan-1-one (133)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

^{13}C-NMR (101MHz): 0.92 (3H, t, J = 7Hz, C$\underline{H}_3$); 1.25 – 1.39 (2H, m, C$\underline{H}_2$CH$_3$); 1.61 – 1.69 (2H, m, C$\underline{H}_2$CH$_2$); 2.31 – 2.44 (2H, m, COC$\underline{H}_2$); 2.74 (1H, d, J = 16Hz, C4$\underline{H}_2$); 2.89 – 2.94 (1H, m, C4$\underline{H}_2$); 3.12 (0.2H, dt, J_1 = 12Hz, J_2 = 5Hz, C3$\underline{H}_3$); 3.35 (0.8H, dt, J_1 = 12Hz, J_2 = 5Hz, C3$\underline{H}_2$); 3.71 (0.8H, dd, J_1 = 15Hz, J_2 = 5Hz, C3$\underline{H}_2$); 3.74 (3.3H, s, C7OC$\underline{H}_3$); 3.87 (2.7H, s, C6OC$\underline{H}_3$); 4.36 (0.2H, m, C3$\underline{H}_2$ (s)); 5.97 (0.2H, s, C1$\underline{H}$ (s)), 6.53 (0.8H, s, C8$\underline{H}$ (m)); 6.63 (0.2H, C8$\underline{H}$ (s)), 6.66 (0.8H, C5$\underline{H}$ (m)); 6.70 (0.2H, s, C5$\underline{H}$ (s)), 6.91 (0.8H, s, C8$\underline{H}$ (m)); 7.19 – 7.28 (5H, C2'$\underline{H}$, C3'$\underline{H}$, C4'$\underline{H}$, C5'$\underline{H}$, C6'$\underline{H}$)

^{13}C-NMR (101MHz):

13.7 (C$\underline{H}_3$); 22.4 (C$\underline{H}_2$CH$_3$); 27.2 (C$\underline{H}_2$CH$_2$); 28.5 (C4$\underline{H}_2$); 33.1 (CO$\underline{C}\underline{H}_2$); 39.1 (C3$\underline{H}_2$); 54.2 (C1H); 55.7 (C6O$\underline{C}\underline{H}_3$, C7O$\underline{C}\underline{H}_3$); 110.8 (C8H); 111.1 (C5H); 126.2 (C8a); 126.8 (C4a); 127.1 (C4'H); 128.0 (C2'H, C6'H); 128.6 (C3'H, C5'H); 142.5 (C1'); 147.4 (C7OCH$_3$); 147.8 (C6OCH$_3$); 171.3 (CO)

Yield: 57.1%

IRν_{max}(KBr): 1466cm^{-1}(C-N stretching), 1636cm^{-1}(C=O stretching), 2987cm^{-1}, 3055cm^{-1}(C-H stretching)

Melting point: 144°C

HRMS calcd. for C22H27NO3Na (M^++23): 376.1889 Found: 376.1906

Cyclopropyl-(6,7-dimethoxy-1-phenyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-methanone (134)

^{1}H-NMR (400MHz):

δ(CDCl$_3$):

0.80 (1.4H, dd, J_1 = 8Hz, J_2 = 2Hz, (m) C$\underline{H}_2$ in ring), 0.84 (0.6H, d, J = 4Hz, (s) C$\underline{H}_2$ in ring); 1.04 – 1.14 (2H, m, C$\underline{H}_2$ in ring); 1.78 – 1.84 (0.7H, m, C$\underline{H}$ (m)), 2.07 (0.3H, s, C$\underline{H}$ (s)); 2.67 (0.3H, d, J = 16Hz, C4$\underline{H}_2$ (s)), 2.78 (0.7H, d, J = 16Hz, C4$\underline{H}_2$); 2.91 (0.3H, m, C4$\underline{H}_2$ (s)); 2.98 – 3.06 (0.7H, m, C4$\underline{H}_2$ (m)); 3.48 (0.7H, dt, J_1 = 12Hz, J_2 = 4Hz, C3$\underline{H}_2$ (m)); 3.77 (2.1H, s, C7OC$\underline{H}_3$); 3.84 (0.9H, s, C7OC$\underline{H}_3$ (s)); 3.90 (3H, s, C6OC$\underline{H}_3$); 4.09 (0.7H, d, J = 11Hz, C3$\underline{H}_2$ (m)), 4.37 (0.3H, d, J = 14Hz, C3$\underline{H}_2$ (s)); 6.35 (0.3H, s, C1$\underline{H}$ (s)), 6.57 (0.7H, s, C8$\underline{H}$ (m)); 6.66 (0.3H, C8$\underline{H}$ (s)), 6.69 (1H, C5$\underline{H}$ (m), C5$\underline{H}$ (s)); 6.89 (0.7H, s, C1H (m)); 7.26 – 7.28 (5H, C2'$\underline{H}$, C3'$\underline{H}$, C4'$\underline{H}$, C5'$\underline{H}$, C6'$\underline{H}$)

^{13}C-NMR (101MHz):

7.2 (C$\underline{H}_2$ (m) in ring); 7.4 (C$\underline{H}_2$ (m) in ring); 7.9 (C$\underline{H}_2$ (s) in ring), 8.1 (C$\underline{H}_2$ (s) in ring); 11.2 (C$\underline{H}$ (m) in ring); 11.8 (C$\underline{H}$ (s) in ring); 27.5 (C4$\underline{H}_2$ (s)), 28.7 (C4$\underline{H}_2$ (m)); 37.3 (C3$\underline{H}_2$ (s)), 39.4 (C3$\underline{H}_2$ (m)); 55.1 (C1H (m)); 55.8 (C6O$\underline{C}\underline{H}_3$, C7O$\underline{C}\underline{H}_3$ (m)), 55.9 (C6O$\underline{C}\underline{H}_3$, C7O$\underline{C}\underline{H}_3$ (s)); 59.1 (C1H (s)); 110.9 (C8H (s)), 111.0 (C8H (s)); 111.2 (C5H (m)), 111.4 (C5H (s)); 126.5 (C8a (m)), 126.7 (C8a (s)); 127.1 (C4a (m)); 127.2 (C4'H (m)); 127.5 (C4'H (s)); 127.6 (C2'H, C6'H (s)); 127.8 (C4a (s)); 128.1 (C2'H, C6'H (m)); 128.4 (C3'H, C5'H (s)); 128.6 (C3'H, C5'H (m)); 141.9 (C1' (s)), 142.5 (C1' (m)); 147.3 (C7OCH$_3$ (s)), 147.4 (C7OCH$_3$ (m)); 147.9 (C6OCH$_3$ (m)), 148.3 (C6OCH$_3$ (s); 171.8 (CO (m)), 172.2 (CO (s))

Yield: 52.6%

IRν_{max}(KBr): 1441cm^{-1}(C-N stretching), 1631cm^{-1}(C=O stretching), 2987cm^{-1}, 3055cm^{-1}(C-H stretching)

Melting point: 156°C

HRMS calcd. for C21H23NO3Na (M^++23): 360.1576 Found: 360.1587

Cyclohexyl-(6,7-dimethoxy-1-phenyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-methanone (135)

^{1}H-NMR (400MHz):

δ(CDCl$_3$):

1.24 – 1.27 (4H, m, (m) $C\underline{H}_2$ in ring), 1.68 – 1.79 (6H, m, $C\underline{H}_2$ in ring); 2.24 (0.2H, d, J = 9Hz, C$\underline{H}$ (s)), 2.50 (0.8H, apparent triplet, J = 11Hz, C$\underline{H}$ (m)); 2.59 (0.2H, d, J = 16Hz, C4$\underline{H}_2$ (s)), 2.75 (0.8H, d, J = 16Hz, C4$\underline{H}_2$ (m)); 2.90 – 2.99 (0.8H, m, C4$\underline{H}_2$ (m)), 3.06 (0.2H, t, J = 10Hz, C4$\underline{H}_2$ (s)); 3.33 (0.8H, dt, J_1 = 13Hz, J_2 = 4Hz, C3$\underline{H}_2$ (m)); 3.73 (2.2H, s, C7OC$\underline{H}_3$); 3.79 (0.8H, d, J = 5Hz, C3$\underline{H}_2$ (m)); 3.82 (0.8H, s, C7OC$\underline{H}_3$ (s)); 3.86 (3H, s, C6OC$\underline{H}_3$); 4.36 (0.2H, m, C3$\underline{H}_2$ (s)); 6.02 (0.2H, s, C1$\underline{H}$ (s)), 6.54 (0.8H, s, C8$\underline{H}$ (m)); 6.64 (0.2H, C8H (s)), 6.66 (0.8H, C5$\underline{H}$ (m)); 6.68 (0.2H, s, C5$\underline{H}$ (s)); 6.92 (0.8H, s, C1H (m)); 7.15 – 7.31 (5H, C2'$\underline{H}$, C3'$\underline{H}$, C4'$\underline{H}$, C5'$\underline{H}$, C6'$\underline{H}$)

^{13}C-NMR (101MHz):

25.6, 25.66 ($\underline{C}H_2$ in ring); 28.9 ($\underline{C}4H_2$); 29.1, 29.4 ($\underline{C}H_2$ in ring); 38.8 ($\underline{C}3H_2$ (s)), 40.5 ($\underline{C}$H in ring)); 54.0 ($\underline{C}$1H (m)); 55.7 (C6O$\underline{C}H_3$, C7O$\underline{C}H_3$); 110.8 ($\underline{C}$8H (m)); 111.2 ($\underline{C}$5H (m)); 126.1 ($\underline{C}$8a (m); 126.8 ($\underline{C}$4a); 127.0 ($\underline{C}$4'H); 127.9 ($\underline{C}$2'H, $\underline{C}$6'H (m)); 128.4 ($\underline{C}$3'H, $\underline{C}$5'H (m)); 142.6 ($\underline{C}$1'); 147.3 ($\underline{C}$7OCH$_3$); 147.8 ($\underline{C}$6OCH$_3$); 174.3 ($\underline{C}$O)

Yield: 90.7%

IRν_{max}(KBr): 1451cm^{-1}(C-N stretching), 1630cm^{-1}(C=O stretching), 2936cm^{-1}, 3055cm^{-1}(C-H stretching)

Melting point: 156°C

HRMS calcd. for C24H29NO3Na (M^++23): 402.2045 Found: 402.2050

(6,7-Dimethoxy-1-phenyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-phenyl-methanone (136)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.67 (0.8H, d, J = 16Hz, C4$\underline{H}_2$ (m)), 2.78 (0.2H, bs, C4$\underline{H}_2$ (s)); 2.97 (0.8H, dt, J_1 = 14Hz, J_2 = 6Hz, C4$\underline{H}_2$ (m)), 3.11 – 3.20 (0.2H, m, C4$\underline{H}_2$ (s)); 3.31 (0.8H, t, J = 12Hz, C3$\underline{H}_2$ (m)); 3.64 (0.8H, dd, J_1 = 13Hz, J_2 = 6Hz, C3$\underline{H}_2$ (m)); 3.78 (3H, s, C7OC$\underline{H}_3$); 3.91 (3H, s, C6OC$\underline{H}_3$); 4.62 (0.2H, bs, C3$\underline{H}_2$ (s)); 5.97 (0.2H, s, C1$\underline{H}$ (s)), 6.59 (0.8H, s, C8$\underline{H}$ (m)); 6.69 (0.2H, C8$\underline{H}$ (s)), 6.76 (0.8H, C5$\underline{H}$ (m)); 7.01 (0.2H, s, C5$\underline{H}$ (s)); 7.06 (0.8H, s, $\underline{C}$1H (m)); 7.28 – 7.45 (10H, C2'$\underline{H}$, C3'$\underline{H}$, C4'$\underline{H}$, C5'$\underline{H}$, C6'$\underline{H}$, C2"$\underline{H}$, C3"$\underline{H}$, C4"$\underline{H}$, C5"$\underline{H}$, C6"$\underline{H}$)

^{13}C-NMR (101MHz):

28.7 ($\underline{C}4H_2$); 40.5 ($\underline{C}3H_2$); 54.6 ($\underline{C}$1H (m)); 55.8 (C6O$\underline{C}H_3$, 7O$\underline{C}H_3$); 111.0 ($\underline{C}$8H); 111.1 ($\underline{C}$5H); 126.0 ($\underline{C}$8a); 126.3 ($\underline{C}$4a); 126.4 ($\underline{C}$4'H); 127.4 ($\underline{C}$2"H, $\underline{C}$6"H); 128.1 ($\underline{C}$2'H, $\underline{C}$6'H); 128.4 ($\underline{C}$3'H, $\underline{C}$5'H); 128.9 ($\underline{C}$3"H, $\underline{C}$5"H); 129.8 ($\underline{C}$4"H); 142.4 ($\underline{C}$1'); 147.6 ($\underline{C}$7OCH$_3$); 148.1 ($\underline{C}$6OCH$_3$); 170.1 ($\underline{C}$O)

Yield: 81.2%

IRν_{max}(KBr): 1465cm^{-1}(C-N stretching), 1627cm^{-1}(C=O stretching), 2987cm^{-1}, 3055cm^{-1}(C-H stretching)

Melting point: 142 - 144°C Literature: 143 - 144°C[27]

(6,7-Dimethoxy-1-phenyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-*p*-tolyl-methanone (137)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.44 (3H, s, C$\underline{H}_3$); 2.74 (1H, m, C4$\underline{H}_2$); 3.02 – 3.06 (1H, m, C4$\underline{H}_2$); 3.35 – 3.55 (1H, m, C3$\underline{H}_2$); 3.70 (1H, s, C3$\underline{H}_2$); 3.83 (3H, s, C7OC$\underline{H}_3$); 3.96 (3H, s, C6OC$\underline{H}_3$); 6.29 (0.2H, s, C1$\underline{H}$ (s)), 6.64 (0.8H, s, C8$\underline{H}$ (m)); 6.71 (0.2H, C5H (s)), 6.74 (0.8H, C5$\underline{H}$ (m)); 7.08 (0.8H, s, C1$\underline{H}$); 7.26 (2H, d, J = 7.5Hz, C3"$\underline{H}$, C5"$\underline{H}$); 7.33 – 7.43 (7H, C2'$\underline{H}$, C3'$\underline{H}$, C4'$\underline{H}$, C5'$\underline{H}$, C6'$\underline{H}$, C2"$\underline{H}$, C6"$\underline{H}$)

^{13}C-NMR (101MHz):

15.2 (CH_3 (s)), 21.3 (CH_3 (m)); 26.0 ($\underline{C}4H_2$ (s)) 28.8 ($\underline{C}4H_2$ (m)); 40.7 ($\underline{C}3H_2$); 54.8 ($\underline{C}1H$ (m)); 55.9 ($C6O\underline{C}H_3$, $7OC\underline{H}_3$ (m)), 55.95 ($C6O\underline{C}H_3$, $C7O\underline{C}H_3$ (s)); 59.5 ($\underline{C}1H$ (s)); 111.2 ($\underline{C}8H$); 111.3 ($\underline{C}5H$); 125.1 ($\underline{C}8a$); 126.3 ($\underline{C}4a$); 126.6 ($\underline{C}4'H$); 127.4 ($\underline{C}2"H$, $\underline{C}6"H$); 128.2 ($\underline{C}2'H$, $\underline{C}6'H$); 129.0 ($\underline{C}3'H$, $\underline{C}5'H$); 130.1 ($\underline{C}3"H$, $\underline{C}5"H$); 133.5 ($\underline{C}4"$); 139.5 ($\underline{C}1'$); 147.7 ($\underline{C}7OCH_3$); 148.3 ($\underline{C}6OCH_3$); 170.4 ($\underline{C}O$)

Yield: 16.7%

IRν_{max}(KBr): 1422cm^{-1}(C-N stretching), 1625cm^{-1}(C=O stretching), 2987cm^{-1}, 3055cm^{-1}(C-H stretching)

Melting point: 142°C

HRMS calcd. for C25H25NO3Na (M^++23): 410.1732 Found: 410.1747

(6,7-Dimethoxy-1-phenyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-(2-methoxy-phenyl)-methanone (138)

^{1}H-NMR (400MHz):

$\delta(CDCl_3)$:

2.60 (0.8H, t, J = 14Hz, $C4\underline{H}_2$ (m)), 2.73 (0.2H, d, J = 17Hz, $C4\underline{H}_2$ (s)); 2.78 – 3.14 (1H, m, $C4\underline{H}_2$ (m)), 3.21 – 3.28 (1H, m, $C3\underline{H}_2$ (m)); 3.45 (0.8H, dt, J_1 = 14Hz, J_2 = 6Hz, $C3\underline{H}_2$ (s)); 3.70, 3.73 (3H, $C2"OC\underline{H}_3$); 3.78, 3.81 (3H, s, $C7OC\underline{H}_3$); 3.90, 3.93 (3H, s, $C6OC\underline{H}_3$); 4.66 – 4.71 (0.2H, m, $C3\underline{H}_2$ (s)); 5.66, 5.75 (0.2H, s, s, $C1\underline{H}$ (s)); 6.32, 6.34 (0.2H, s, s, $C8\underline{H}$ (s)), 6.58 (0.8H, s, $C8\underline{H}$ (m)); 6.66 (0.8H, $C5\underline{H}$ (m)), 6.75 (0.2H, $C5\underline{H}$ (s)); 6.88 – 7.10 (4H, m, $C3"\underline{H}$, $C4"\underline{H}$, $C5"\underline{H}$, $C1\underline{H}$ (m)); 7.23 – 7.38 (6H, m, $C2'\underline{H}$, $C3'\underline{H}$, $C4'\underline{H}$, $C5'\underline{H}$, $C6'\underline{H}$, $C6"\underline{H}$)

^{13}C-NMR (101MHz):

28.5 ($\underline{C}4H_2$ (m)) 28.8 ($\underline{C}4H_2$ (s)); 40.1 ($\underline{C}3H_2$ (m)), 40.5 ($\underline{C}3H_2$ (s)); 54.2 ($\underline{C}1H$ (m)); 55.2 ($C2"O\underline{C}H_3$ (s)), 55.5 ($C2"O\underline{C}H_3$ (m)); 55.8 ($C6O\underline{C}H_3$, $7OC\underline{H}_3$ (m)), 55.9 ($C6O\underline{C}H_3$, $C7O\underline{C}H_3$ (s)); 60.2 ($\underline{C}1H$ (s)); 110.3 ($\underline{C}8H$ (s)), 110.4 ($\underline{C}8H$ (m)); 110.8 ($\underline{C}3"H$ (s)), 110.9 ($\underline{C}3"H$ (m)); 111.3 ($\underline{C}5H$ (m)); 111.5 ($\underline{C}5H$ (s)); 120.7 ($\underline{C}5"H$ (s)), 120.8 ($\underline{C}5"H$ (m)); 125.96 ($\underline{C}8a$ (m)), 126.0 ($\underline{C}8a$ (s)); 126.31 ($\underline{C}1"$ (s)), 126.34 ($\underline{C}1"$ (m)); 126.6 ($\underline{C}4a$ (m)), 127.1 ($\underline{C}4a$ (s)); 127.2 ($\underline{C}4'H$ (m)); 127.23 ($\underline{C}6"H$ (m)); 127.3 ($\underline{C}4'H$ (s)); 127.7 ($\underline{C}6"H$ (s)); 127.9 ($\underline{C}2'H$, $\underline{C}6'H$ (m)); 128.2 ($\underline{C}2'H$, $\underline{C}6'H$ (s)); 128.7 ($\underline{C}3'H$, $\underline{C}5'H$ (m)), 128.9 ($\underline{C}3'H$, $\underline{C}5'H$ (s)); 130.0 ($\underline{C}4"H$ (s)), 130.3 ($\underline{C}4"H$ (m)); 142.1 (C1' (m)), 142.9 ($\underline{C}1'H$ (s)); 139.5 ($\underline{C}1'$); 147.0 ($\underline{C}7OCH_3$ (s)); 147.7 ($\underline{C}6OCH_3$ (s)), 147.9 ($\underline{C}7OCH_3$ (m)), 148.0 ($\underline{C}6OCH_3$ (m)); 155.29 ($\underline{C}2"OCH_3$ (s)), 155.34 ($\underline{C}2"OCH_3$ (m)); 167.8 ($\underline{C}O$ (s)), 167.9 ($\underline{C}O$ (m))

Yield: 55.7%

IRν_{max}(KBr): 1422cm^{-1}(C-N stretching), 1628cm^{-1}(C=O stretching), 2987cm^{-1}, 3055cm^{-1}(C-H stretching)

Melting point: 140°C

HRMS calcd. for C25H26NO4N (M^++1): 404.1862 Found: 404.1863

(6,7-Dimethoxy-1-phenyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-(3-methoxy-phenyl)-methanone (139)

^{1}H-NMR (400MHz):

$\delta(CDCl_3)$:

2.68 (0.8H, d, J = 16Hz, $C4\underline{H}_2$ (m)), 2.76 (0.2H, d, J = 16Hz, $C4\underline{H}_2$ (s)); 2.97 (0.8H, dt, J_1 = 14Hz, J_2 = 6Hz, $C4\underline{H}_2$ (m)), 3.09 (0.2H, bs, $C4\underline{H}_2$ (s)); 3.30 (1H, dt, J_1 = 13Hz, J_2 = 4Hz, $C3\underline{H}_2$); 3.65 (0.8H, dd, J_1 = 14Hz, J_2 = 6Hz, $C3\underline{H}_2$ (m)); 3.79, 3.82, 3.91 (9H, s,s, s, $C7OC\underline{H}_3$, $C6OC\underline{H}_3$, $C3"OC\underline{H}_3$); 4.56 (0.2H, bs, $C3\underline{H}_2$ (s)); 5.97 (0.2H, bs, $C1\underline{H}$ (s)); 6.41 (0.2 H, bs, $C8\underline{H}$ (s)); 6.58 (0.8H, s, $C8\underline{H}$ (m)); 6.69 (0.8H, s, $C5\underline{H}$ (m)); 6.75 (0.2H, bs, $C5\underline{H}$ (s)); 6.93 – 6.96 (3H, m, $C2"\underline{H}$, $C4"\underline{H}$, $C5"\underline{H}$); 7.03 (0.8H, s, $C1\underline{H}$); 7.28 – 7.36 (5H, $C2'\underline{H}$, $C3'\underline{H}$, $C4'\underline{H}$, $C5'\underline{H}$, $C6'\underline{H}$, $C6"\underline{H}$)

^{13}C-NMR (101MHz):

28.8 (C4H$_2$); 40.5 (C3H$_2$); 54.6 (C1H); 55.3 (C3"OCH$_3$); 55.8 (C6OCH$_3$, 7OCH$_3$); 111.0 (C8H); 111.2 (C5H); 111.7 (C2"H); 115.3 (C4"H); 118.4 (C6"H); 126.1 (C8a); 126.3 (C4a); 127.5 (C4'H); 128.3 (C2'H, C6'H); 129.0 (C3'H, C5'H); 129.6 (C5"H); 137.6 (C1"); 142.4 (C1'); 147.6 (C7OCH$_3$ (s)); 148.1 (C6OCH$_3$); 159.6 (C3"OCH$_3$); 169.8 (CO)

Yield: 72.8%

IRν_{max}(KBr): 1465cm^{-1}(C-N stretching), 1627cm^{-1}(C=O stretching), 2987cm^{-1}, 3055cm^{-1}(C-H stretching)

Melting point: 128°C

HRMS calcd. for C25H25NO4Na (M^++23): 426.1681 Found: 426.1697

(6,7-Dimethoxy-1-phenyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-(4-methoxy-phenyl)-methanone (140)

^{1}H-NMR (400MHz):

δ(CDCl$_3$):

2.60 (1H, d, J = 15Hz, C4H$_2$); 2.90(1H, bs, C4H$_2$); 3.60 (1H, bs, C3H$_2$); 3.64 – 3.66 (0.8H, m, C3H$_2$ (m)); 3.70 (3H, s, C4"OCH$_3$); 3.76 (3H, s, C7OCH$_3$); 3.83 (3H, s, C6OCH$_3$); 4.46 (0.2H, bs, C3H$_2$ (s)); 5.95 (0.1H, bs, C1H (s)), 6.18 (0.1H, s, C8H (s)); 6.49 (0.9H, s, C8H); 6.57 (0.1H, s, C5H (s)), 6.61 (0.9H, s, C5H); 6.84 (2H, d, J = 8Hz, C3"H, C5"H); 6.93 (0.9H, s, C1H (m)); 7.19 – 7.31 (7H, C2'H, C3'H, C4'H, C5'H, C6'H, C2"H, C6"H)

^{13}C-NMR (101MHz):

28.8 (C4H$_2$); 40.7 (C3H$_2$); 54.8 (C1H); 55.3 (C4"OCH$_3$); 55.8 (C6OCH$_3$, 7OCH$_3$); 111.1 (C8H, C5H); 113.7 (C3"H, C5"H); 126.1 (C8a); 126.5 (C4a, C1"); 127.5 (C4'H); 128.2 (C2'H, C6'H); 128.5 (C2"H, C6"H); 129.0 (C3'H, C5'H); 129.6 (C5"H); 142.5 (C1'); 147.6 (C7OCH$_3$ (s)); 148.1 (C6OCH$_3$); 160.5 (C4"OCH$_3$); 170.1 (CO)

Yield: 40.1%

IRν_{max}(KBr): 1431cm^{-1}(C-N stretching), 1611cm^{-1}(C=O stretching), 2987cm^{-1}, 3055cm^{-1}(C-H stretching)

Melting point: 140°C

HRMS calcd. for C25H26NO4 (M^++1): 404.1862 Found: 404.1862

(6,7-Dimethoxy-1-phenyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-(4-fluoro-phenyl)-methanone (141)

^{1}H-NMR (400MHz):

δ(CDCl$_3$):

2.71 (1H, m, C4H$_2$); 2.97 (1H, bs, C4H$_2$); 3.33 (1H, bs, C3H$_2$); 3.62 (0.8H, m, C3H$_2$ (m)); 3.77 (3H, s, C7OCH$_3$); 3.91 (3H, s, C6OCH$_3$); 4.57 (0.2H, bs, C3H$_2$ (s)); 5.90 (0.2H, bs, C1H (s)), 6.41 (0.2H, bs, C8H (s)); 6.57 (0.8H, s, C8H); 6.69 (1H, s, C5H); 7.00 (0.8H, s, C1H (m)); 7.08 – 7.14 (2H, m, C3"H, C5"H); 7.28 – 7.34 (5H, C2'H, C3'H, C4'H, C5'H, C6'H); 7.41 (1H, m, C2"H, C6"H); 7.75 (1H, d, J = 8Hz, C2"H, C6"H)

^{13}C-NMR (101MHz):

28.7 (C4H$_2$); 40.5 (C3H$_2$); 54.7 (C1H); 55.8 (C6OCH$_3$, 7OCH$_3$); 110.97 (C8H); 111.04 (C5H); 115.4, 115.7 (C3"H, C5"H); 125.8 (C8a); 126.1 (C4a); 127.5 (C4'H); 128.3 (C2'H, C6'H, C2"H, C6"H); 128.9 (C3'H, C5'H); 132.2 (C1"); 142.2 (C1'); 147.6 (C7OCH$_3$ (s)); 148.1 (C6OCH$_3$); 163.1 (d, J = 250Hz, C4"F); 169.1 (CO)

^{19}F-NMR (376MHz): -110.7 (s), -111.0 (m)

Yield: 58.5%

IRν_{max}(KBr): 1465cm^{-1}(C-N stretching), 1628cm^{-1}(C=O stretching), 2986cm^{-1}, 3055cm^{-1}(C-H stretching)

Melting point: 156 - 160°C

HRMS calcd. for C24H22NO3NaF (M^++23): 414.1481 Found: 414.1484

(4-Chloro-phenyl)-(6,7-dimethoxy-1-phenyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-methanone (142)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.68 (1H, d, J = 16Hz, C4H$_2$); 2.95 (1H, bs, C4H$_2$); 3.32 (1H, bs, C3H$_2$); 3.58 (0.8H, m, C3H$_2$ (m)); 3.76 (3H, s, C7OCH$_3$); 3.89 (3H, s, C6OCH$_3$); 4.56 (0.2H, bs, C3H$_2$ (s)); 5.89 (0.2H, bs, C1H (s)), 6.41 (0.2H, bs, C8H (s)); 6.57 (0.8H, s, C8H); 6.69 (1H, s, C5H); 7.01 (0.8H, s, C1H (m)); 7.30 – 7.37 (9H, C2'H, C3'H, C4'H, C5'H, C6'H, C2"H, C3"H, C5"H, C6"H)

^{13}C-NMR (101MHz):

28.6 (C4H$_2$); 40.5 (C3H$_2$); 54.7 (C1H); 55.8 (C6OCH$_3$, 7OCH$_3$); 110.9 (C8H, C5H); 125.7 (C8a); 126.1 (C4a); 127.5 (C4'H); 127.9 (C2"H, C6"H); 128.2 (C2'H, C6'H); 128.6 (C3"H, C5"H); 128.8 (C3'H, C5'H); 134.5 (C1"), 135.4 (C4"Cl); 142.1 (C1'); 147.6 (C7OCH$_3$ (s)); 148.1 (C6OCH$_3$); 168.9 (CO)

Yield: 57.1%

IRν_{max}(KBr): 1434cm^{-1}(C-N stretching), 1629cm^{-1}(C=O stretching), 2987cm^{-1}, 3055cm^{-1}(C-H stretching)

Melting point: 186 - 188°C

HRMS calcd. for C24H22NO3NaCl (M^++23): 430.1186 Found: 430.1198

(4-Bromo-phenyl)-(6,7-dimethoxy-1-phenyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-methanone (143)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.69 (1H, d, J = 15Hz, C4H$_2$); 2.95 (1H, bs, C4H$_2$); 3.33 (1H, t, J = 12Hz, C3H$_2$); 3.59 (0.8H, m, C3H$_2$ (m)); 3.78 (3H, s, C7OCH$_3$); 3.91 (3H, s, C6OCH$_3$); 4.56 (0.2H, bs, C3H$_2$ (s)); 5.89 (0.2H, bs, C1H (s)), 6.40 (0.2H, bs, C8H (s)); 6.57 (0.8H, s, C8H); 6.69 (1H, s, C5H); 7.01 (0.8H, s, C1H (m)); 7.27 – 7.34 (7H, C2'H, C3'H, C4'H, C5'H, C6'H, C3"H, C5"H); 7.55 (2H, d, J = 7.5Hz, C2"H, C6"H)

^{13}C-NMR (101MHz):

28.7 (C4H$_2$); 40.6 (C3H$_2$); 54.8 (C1H); 55.9 (C6OCH$_3$, 7OCH$_3$); 110.98 (C8H); 111.09 (C5H); 123.7 (C4"Br); 125.8 (C8a); 126.1 (C4a, C1"); 127.6 (C4'H); 128.2 (C2'H, C6'H); 128.3 (C2"H, C6"H); 128.9 (C3'H, C5'H); 135.1 (C3"H, C5"H); 132.2 (C1"); 142.2 (C1'); 147.7 (C7OCH$_3$ (s)); 148.2 (C6OCH$_3$); 169.0 (CO)

Yield: 55.4%

IRν_{max}(KBr): 1422cm^{-1}(C-N stretching), 1629cm^{-1}(C=O stretching), 2987cm^{-1}, 3055cm^{-1}(C-H stretching)

Melting point: 186°C

HRMS calcd. for C24H22NO3NaBr (M^++23): 474.0681 Found: 474.0676

(6,7-Dimethoxy-1-phenyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-(4-iodo-phenyl)-methanone (144)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

3.24 (1H, d, J = 13Hz, C4$\underline{H}_2$); 3.48 (1H, bs, C4$\underline{H}_2$); 3.79 (1H, m, C3$\underline{H}_2$); 4.03 (0.8H, m, C3H_2 (m)); 4.16 (3H, s, C7OC$\underline{H}_3$); 4.28 (3H, s, C6OC$\underline{H}_3$); 4.85 (0.2H, bs, C3$\underline{H}_2$ (s)); 5.99 (0.2H, bs, C1$\underline{H}$ (s)), 6.44 (0.2H, bs, C8$\underline{H}$ (s)); 6.57 (0.8H, s, C8$\underline{H}$); 6.68 (1H, s, C5$\underline{H}$); 6.94 – 7.06 (3H, m, C2"$\underline{H}$, C6"$\underline{H}$, C1$\underline{H}$ (m)); 7.19 – 7.23 (5H, C2'$\underline{H}$, C3'$\underline{H}$, C4'$\underline{H}$, C5'$\underline{H}$, C6'$\underline{H}$); 7.29 (1H, s, C3"$\underline{H}$, C5"$\underline{H}$), 7.58 (1H, d, J = 6.5Hz, C3"$\underline{H}$, C5"$\underline{H}$)

^{13}C-NMR (101MHz):

28.6 (C$\underline{H}_2$); 40.4 (C$\underline{H}_2$); 54.6 (C$\underline{H}$); 55.7 (C6OC$\underline{H}_3$, 7OC$\underline{H}_3$); 95.5 (C"I); 110.9 (C8H, C5H); 115.3 125.7 (C8a); 126.0 (C4a); 127.4 (C4'H); 128.2 (C2'H, C6'H, C2"H, C6"H); 128.8 (C3'H, C5'H); 135.5 (C1"); 137.4 (C3"H, C5"H); 142.1 (C1'); 147.5 (C7OCH_3 (s)); 148.0 (C6OCH_3); 169.0 (CO)

Yield: 51.5%

IRν_{max}(KBr): 1423cm^{-1}(C-N stretching), 1628cm^{-1}(C=O stretching), 2987cm^{-1}, 3055cm^{-1}(C-H stretching)

Melting point: 156 - 158°C

HRMS calcd. for C24H22NO3NaI (M^++23): 522.0542 Found: 522.0529

Benzyl Amides

(1-Benzyl-6,7-dimethoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-phenyl-ethanone (145)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.72 (0.4H, d, J = 15Hz, C4$\underline{H}_2$); 2.90 – 3.03 (1H, m, C4$\underline{H}_2$); 3.05 – 3.13 (1H, m, C1C$\underline{H}_2$); 3.18 (1H, dd, J_1 = 13Hz, J_2 = 6Hz, C1C$\underline{H}_2$); 3.27 (1H, d, J = 16Hz, C3$\underline{H}_2$); 3.40 – 3.46 (1H, m,); 3.59 (2H, s, COC$\underline{H}_2$); 3.77 (1.8H, s, C7OC$\underline{H}_3$); 3.78 (1.2H, s, OC$\underline{H}_3$ (m)); 3.63 – 3.66 (0.6H, m, C3$\underline{H}_2$ (m)); 3.84 (1.8H, s, C6OC$\underline{H}_3$ (m)), 3.88 (1.2H, s, C6OC$\underline{H}_3$ (s)); 4.82 (0.4H, dd, J_1 = 13Hz, J_2 = 4Hz, C3$\underline{H}_2$ (s)); 4.93 (0.4H, dd, J_1 = 9Hz, J_2 = 6Hz, C1$\underline{H}$ (s)); 5.74 (0.6H, apparent triplet, J = 7Hz, C1$\underline{H}$); 6.15 (0.6H, s, C8$\underline{H}$ (s)), 6.33 (0.6H, s, C8$\underline{H}$ (m)); 6.55 (0.6H, s, C5$\underline{H}$ (m)), 6.64 (0.4H, s, C5$\underline{H}$ (s)); 6.92 (1H, d, J = 7Hz,); 7.10 (1H, d, J = 8Hz,); 7.17 – 7.25 (5H, m,); 7.27 – 7.37 (3H, C2"$\underline{H}$, C6"$\underline{H}$)

^{13}C-NMR (101MHz):

27.7 (C$\underline{H}_2$ (s)), 28.3 (C$\underline{H}_2$ (m)); 33.8 (CO$\underline{C}H_2$ (s)); 35.3 (C$\underline{H}_2$ (s)); 41.1 (C$\underline{H}_2$ (m)); 41.5 (CO$\underline{C}H_2$ (m); 42.2 (C1$\underline{C}H_2$ (m)); 42.9 (C1$\underline{C}H_2$ (s)); 54.0 (C$\underline{H}$ (m)); 55.4, 55.7 (C7OC$\underline{H}_3$, C6OC$\underline{H}_3$ (m)); 55.73, 55.8 (C6OC$\underline{H}_3$, C7OC$\underline{H}_3$ (s)); 58.5 (C$\underline{H}$ (s)); 109.7 (C8H (s)); 110.5 (C8H (m); 110.7 (C5H (m)); 111.3 (C5H (s)); 125.3 (C8a (m)); 126.26 (C4'H (m)); 126.38 (CC4"H (s)), 126.6 (C4"H (m)); 126.9 (C4'H (m)); 127.7 (C4a (s)); 128.0 (C3"H, C5"H (m)), 128.1 (C3"H, C52H (s)); 128.5 (C2"H, C6"H (m)); 128.6 (C2'H, C6'H (m); 128.7 (C2"H, C6"H (s));128.8 (C2'H, C6'H (s)); 129.6 (C3'H, C5'H (s)), 129.8 (C3'H, C5'H (m)); 134.87 (C1" (s)), 134.9 (C1" (m)); 137.8 (C1' (s)); 137.9 (C1' (m)); 146.7 (C7OCH_3 (m)), 146.9 (C7OCH_3 (s)); 147.4 (C6OCH_3 (m)), 147.9 (C6OCH_3 (s)); 169.6 (CO (m)); 169.9 (CO (s))

Yield: 30.9%

IRν_{max}(KBr): 1454cm^{-1}(C-N stretching), 1639cm^{-1}(C=O stretching), 2936cm^{-1}, 3437cm^{-1}(C-H stretching)

HRMS calcd. for C26H27NO3Na (M^++23): 424.1889 Found: 424.1887

(1-Benzyl-6,7-dimethoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-(4-nitro-phenyl)-ethanone (146)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.74 (1H, d, J = 13Hz, C4$\underline{H}_2$); 2.85 (0.4H, d, J = 16Hz, C4$\underline{H}_2$); 2.90 – 2.97 (0.4H, m, C4$\underline{H}_2$); 2.98 – 3.04 (0.6H, m, C4$\underline{H}_2$); 3.12 – 3.18 (1H, m, C1C$\underline{H}_2$); 3.22 – 3.35 (1H, m, C1C$\underline{H}_2$); 3.51 – 3.58 (0.6H, m, ?); 3.61

(2H, s, COC$\underline{H}_2$); 3.69 – 3.74 (0.6H, m, ?); 3.82, 3.85, 3.87, 3.88 (4H, s, C7OC$\underline{H}_3$, C6OC$\underline{H}_3$); 4.83 (0.4H, dd, J_1 = 13Hz, J_2 = 5.5Hz, C3$\underline{H}_2$ (s)); 4.94 (0.4H, dd, J_1 = 9Hz, J_2 = 5Hz, C1$\underline{H}$ (s)); 5.74 (0.6H, apparent triplet, J = 7Hz, C1$\underline{H}$); 6.18 (0.4H, s, C8$\underline{H}$ (s)), 6.59 (1.2H, s, C8$\underline{H}$, C5$\underline{H}$); 6.65 (0.4H, s, C5$\underline{H}$ (m)); 6.92 (1H, d, J = 8.5Hz,); 7.10 – 7.12 (1H, m,); 7.23 – 7.29 (4H, m,); 7.37 – 7.42 (1H, m); 8.02 (1H, d, J = 8.5Hz,); 8.13 (1H, d, J = 8.5Hz,)

^{13}C-NMR (101MHz):

27.7 (C$\underline{H}_2$ (s)), 28.3 (C$\underline{H}_2$ (m)); 33.8 (CO$\underline{C}H_2$ (s)); 35.2 (C$\underline{H}_2$ (s)); 40.7 (C$\underline{H}_2$ (m)); 41.0 (CO$\underline{C}H_2$ (m); 42.2 (C1$\underline{C}H_2$ (m)); 42.8 (C1$\underline{C}H_2$ (s)); 54.1 (C1H (m)); 55.5, 55.7 (C7O$\underline{C}H_3$, C6O$\underline{C}H_3$ (m)); 55.8, 55.9 (C6O$\underline{C}H_3$, C7O$\underline{C}H_3$ (s)); 58.6 (C1H (s)); 109.6 (C8H (s)); 110.4 (C8H

(m); 110.7 (C5H (m)); 111.4 (C5H (s)); 123.1 (C3"H, C5"H (s)), 123.6 (C3"H, C5"H (m)); 124.9 (C8a (m)); 126.3 (C8a (s)); 126.4 (C4'H (m)); 127.1 (CC4'H (s)); 127.4 (C4a (s)); 127.9 (C4a (m)); 128.1 (C2'H, C6'H (m); 128.9 (C2'H, C6'H (s)); 129.6 (C3'H, C5'H (s)), 129.66 (C3'H, C5'H (m)); 129.7 (C2"H (m)), 130.3 (C6"H (s)); 137.7 (C1' (m)); 137.8 (C1' (s)); 142.6 (C1" (m)), 142.7 (C1" (s)); 146.5 ($\underline{C}NO_2$ (s)), 146.7 ($\underline{C}NO_2$ (m)); 146.9 (C7OCH$_3$ (s)), 147.4 (C7OCH$_3$ (m)); 147.6 (C6OCH$_3$ (s)), 148.2 (C6OCH$_3$ (m)); 168.1 (CO (m)); 168.4 (CO (s))

Yield: 64.0%

IRν_{max}(KBr): 1452cm^{-1}(C-N stretching), 1638cm^{-1}(C=O stretching), 2933cm^{-1}, 3328cm^{-1}(C-H stretching)

HRMS calcd. for C26H27N2O5 (M^++1): 447.1920 Found: 447.1925

(1-Benzyl-6,7-dimethoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-(4-methylsulfanyl-phenyl)-ethanone (146a)

^{1}H-NMR (400MHz):

δ(CDCl$_3$):

2.40 (1.2H, s, SC$\underline{H}_3$), 2.47 (1.8H, s, SC$\underline{H}_3$); 2.60 – 2.62 (0.6H, m, C4$\underline{H}_2$); 2.72 (0.4H, d, J = 16Hz, C4$\underline{H}_2$); 2.92 – 3.00 (1 H, m, C4$\underline{H}_2$); 3.09 – 3.17 (1H, m, C1C$\underline{H}_2$); 3.20 – 3.28 (1H, m, C1C$\underline{H}_2$); 3.40 – 3.50 (0.6H, m, C3$\underline{H}_2$); 3.58 (2H, s,COC$\underline{H}_2$); 3.70 (0.6H, m, C3$\underline{H}_2$); 3.72, 3.78, 3.84, 3.87 (6H, overlapping singlets, C7OC$\underline{H}_3$, C6OC$\underline{H}_3$); 4.81 (0.4H, dd, J_1 = 13Hz, J_2 = 5Hz, C3$\underline{H}_2$ (s)); 4.92 (0.4H, dd, J_1 = 9Hz, J_2 = 5Hz, C1$\underline{H}$ (s)); 5.73 (0.6H, apparent triplet, J = 7Hz, C1$\underline{H}$); 6.14 (0.6H, s, C8$\underline{H}$ (s)), 6.38 (0.4H, s, C8$\underline{H}$); 6.56 (0.6H, s, C5$\underline{H}$), 6.64 (0.4H, s, C5$\underline{H}$ (m)); 6.81 (1H, d, J = 8Hz,); 7.09 – 7.11 (3H, m,); 7.19 - 7.23 (4H, m,); 7.36 (1H, d, J = 7Hz,)

^{13}C-NMR (101MHz):

15.8 (S$\underline{C}H_3$ (s)), 15.9 (S$\underline{C}H_3$ (m)); 27.7 (C$\underline{H}_2$ (s)), 28.3 (C$\underline{H}_2$ (m)); 33.8 (CO$\underline{C}H_2$ (s)); 35.3 (C$\underline{H}_2$ (s)); 40.8 (C$\underline{H}_2$ (m)); 41.0 (CO$\underline{C}H_2$ (m); 42.1 (C1$\underline{C}H_2$ (m)); 42.9 (C1$\underline{C}H_2$ (s)); 54.0 (C1H (m)); 55.4, 55.7 (C7O$\underline{C}H_3$, C6O$\underline{C}H_3$ (m)); 55.72, 55.8 (C6O$\underline{C}H_3$, C7O$\underline{C}H_3$ (s)); 58.5 (C1H (s)); 109.7 (C8H (s)); 110.4 (C8H (m); 110.7 (C5H (m)); 111.3 (C5H (s)); 125.2 (C8a (m)); 126.2 (C4'H (m)); 126.4 (C8a (s)); 126.7 (C4'H (m)); 126.9 (C3"H, C5"H (m)); 127.6 (C4a (s)); 128.0 (C4a (m)); 128.04 (C2"H, C6"H (m)); 128.7 (C2"H, C6"H (s)); 129.0 (C2'H, C6'H (m); 129.3 (C2'H, C6'H (s)); 129.5 (C3'H, C5'H (s)), 129.8 (C3'H, C5'H (m)); 131.7 (C1" (s)), 131.9 (C1" (m)); 136.2 (CSCH$_3$ (s)), 136.5 (CSCH$_3$ (m)); 137.8 (C1' (s)); 137.9 (C1' (m)); 146.7 (C7OCH$_3$ (m)), 147.0 (C7OCH$_3$ (s)); 147.4 (C6OCH$_3$ (m)), 147.9 (C6OCH$_3$ (s)); 169.4 (CO (m)); 169.8 (CO (s))

Yield: 73.6%

IRν_{max}(KBr): 1455cm^{-1}(C-N stretching), 1639cm^{-1}(C=O stretching), 2929cm^{-1}, 3328cm^{-1}(C-H stretching)

HRMS calcd. for C27H29NO3NaS (M^++23): 470.1766 Found: 470.1777

(1-Benzyl-6,7-dimethoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-(3-methoxy-phenyl)-ethanone (147)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.60 (1H, s, C4H$_2$); 2.73 (0.4H, d, J = 16Hz, C4H$_2$); 2.95 – 3.00 (0.6H, m, C4H$_2$); 3.03 - 3.12 (1H, m, C1CH$_2$); 3.24 (1H, d, J = 16Hz, C1CH$_2$); 3.41 – 3.47 (0.6H, m, ?); 3.58 (2H, s, COCH$_2$); 3.66, 3.76, 3.79, 3.84, 3.88 (9H, overlapping singlets, C3"OCH$_3$, C7OCH$_3$, C6OCH$_3$); 4.83 (0.4H, dd, J_1 = 13Hz, J_2 = 5Hz, C3H$_2$ (s)); 4.92 (0.4H, dd, J_1 = 8Hz, J_2 = 5Hz, C1H (s)); 5.72 (0.6H, apparent triplet, J = 6.5Hz, C1H); 6.12 (0.6H, s, C8H (s)), 6.33 (0.4H, s, C8H); 6.55 (0.6H, s, C5H); 6.63 (0.4H, s, C5H (m)); 6.78 – 6.82 (2H, m,); 7.09 – 7.12 (2H, m,); 7.17 – 7.28 (4H, m,); 7.36 - 7.37 (1H, m)

^{13}C-NMR (101MHz):

27.7 (C4H$_2$ (s)), 28.3 (C4H$_2$ (m)); 33.8 (COCH$_2$ (s)); 35.3 (C3H$_2$ (s)); 40.2 (C3H$_2$ (m)); 41.2 (COCH$_2$ (m); 42.2 (C1CH$_2$ (m)); 42.9 (C1CH$_2$ (s)); 54.2 (C1H (m)); 54.9, 55.7, 55.8 (C3"OCH$_3$, C7OCH$_3$, C6OCH$_3$ (s)), 55.1, 55.4, 55.7 (C3"OCH$_3$, C6OCH$_3$, C7OCH$_3$ (m)); 58.6 (C1H (s)); 109.7 (C8H (s)); 110.5 (C8H (m); 110.6 (C5H (m)); 111.3 (C5H (s)); 112.2 (C2"H (m)), 112.3 (C2"H (s)); 113.9 (C4"H (s)), 114.1 (C4"H (m)); 120.8 (C6"H (m)), 121.1 (C6"H (s)); 125.3 (C8a (m)); 126.26 (C4'H (m)); 126.3 (C8a (s)); 126.9 (C4'H (m)); 127.7 (C4a (s)); 128.0 (C4a (m)); 128.1 (C2'H, C6'H (m), 128.7 (C2'H, C6'H (s)); 129.2 (C5"H (s)), 129.5 (C5"H (m)); 129.6 (C3'H, C5'H (s)), 129.8 (C3'H, C5'H (m)); 136.3 (C1" (m)), 136.4 (C1" (s)); 137.9 (C1' (s)), 138.0 (C1' (m)); 146.7 (C7OCH$_3$ (m)), 147.0 (C7OCH$_3$ (s)); 147.4 (C6OCH$_3$ (m)), 147.9 (C6OCH$_3$ (s)); 159.5 (C3"OCH$_3$ (s)), 159.7 (C3"OCH$_3$ (m)); 169.5 (CO (m)); 169.8 (CO (s))

Yield: 66.7%

IRν_{max}(film): 1466cm^{-1}(C-N stretching), 1639cm^{-1}(C=O stretching), 2939cm^{-1}, 3055cm^{-1}(C-H stretching)

HRMS calcd. for C27H29NO4Na (M^++23): 454.1994 Found: 454.1980

(1-Benzyl-6,7-dimethoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-(4-methoxy-phenyl)-ethanone (148)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.57 - 2.60 (1H, s, C4H$_2$); 2.71 (0.4H, d, J = 18Hz, C4H$_2$); 2.93 – 3.00 (0.6H, m, C4H$_2$); 3.03 - 3.12 (1H, m, C1CH$_2$); 3.22 (1H, d, J = 16Hz, C1CH$_2$); 3.39 – 3.46 (0.6H, m, ?); 3.57 (2H, s, COCH$_2$); 3.76, 3.79, 3.83, 3.87 (9H, overlapping singlets, C4"OCH$_3$, C7OCH$_3$, C6OCH$_3$); 4.80 (0.4H, dd, J_1 = 13Hz, J_2 = 5Hz, C3H$_2$ (s)); 4.94 (0.4H, dd, J_1 = 9Hz, J_2 = 5Hz, C1H (s)); 5.72 (0.6H, apparent triplet, J = 7Hz, C1H); 6.13 (0.6H, s, C8H (s)), 6.35 (0.4H, s, C8H); 6.54 (0.6H, s, C5H); 6.63 (0.4H, s, C5H (m)); 6.73 (1H, d, J = 8.5Hz,); 6.82 – 6.85 (2H, m,); 7.09 – 7.11 (2H, m,); 7.17 – 7.28 (3H, m,); 7.33 – 7.36 (1H, m)

^{13}C-NMR (101MHz):

27.7 (C4H$_2$ (s)), 28.3 (C4H$_2$ (m)); 33.7 (COCH$_2$ (s)); 35.3 (C3H$_2$ (s)); 40.5 (C3H$_2$ (m)); 41.0 (COCH$_2$ (m); 42.1 (C1CH$_2$ (m)); 42.9 (C1CH$_2$ (s)); 54.0 (C1H (m)); 55.0, 55.7, 55.8 (C4"OCH$_3$, C7OCH$_3$, C6OCH$_3$ (s)), 55.1, 55.4, 55.6 (C4"OCH$_3$, C6OCH$_3$, C7OCH$_3$ (m)); 58.4 (C1H (s)); 109.8 (C8H (s)); 110.5 (C8H (m); 110.7 (C5H (m)); 111.3 (C5H (s)); 113.6 (C3"H, C5"H (s)), 114.0 (C3"H, C5"H (m)); 125.3 (C8a (m)); 126.2 (C4'H (m)); 126.4 (C8a (s)); 126.8 (C4'H (m)); 126.9 (C4a (m)); 127.7 (C4a (m)); 128.0 (C2'H, C6'H (m), 128.7 (C2'H, C6'H (s)); 129.5 (C2"H, C6"H (m)), 129.7 (C2"H, C6"H (s)); 129.74 (C3'H, C5'H (m)),

129.78 (C3'H, C5'H (s)); 130.2 (C1"); 137.8 (C1' (s)), 137.9 (C1' (m)); 146.7 (C7OCH_3 (m)), 147.0 (C7OCH_3 (s)); 147.4 (C6OCH_3 (m)), 147.9 (C6OCH_3 (s)); 158.0 (C4"OCH_3 (s)), 158.2 (C4"OCH_3 (m)); 170.0 (CO (m)); 170.3 (CO (s))

Yield: 99.6%%

IRν_{max}(KBr): 1454cm^{-1}(C-N stretching), 1636cm^{-1}(C=O stretching), 2937cm^{-1}, 3055cm^{-1}(C-H stretching)

HRMS calcd. for C27H29NO4Na (M^++23): 454.1994 Found: 454.1983

1-(1-Benzyl-6,7-dimethoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-(3,4-dimethoxy-phenyl)-ethanone (149)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.60 (1H, s, C4H_2); 2.74 (0.4H, d, J = 15Hz, C4H_2); 2.93 – 2.99 (0.6H, m, C4H_2); 3.06 - 3.18 (1H, m, C1CH_2); 3.20 – 3.28 (1H, m, C1CH_2); 3.43 – 3.49 (0.6H, m, ?); 3.57 (2H, s, COCH_2); 3.69, 3.73, 3.78, 3.81, 3.84, 3.88 (9H, overlapping singlets, C4"OCH_3, C7OCH_3, C6OCH_3); 4.84 (0.4H, dd, J_1 = 13Hz, J_2 = 5.5Hz, C3H_2 (s)); 4.96 (0.4H, dd, J_1 = 9Hz, J_2 = 5Hz, C1H (s)); 5.72 (0.6H, apparent triplet, J = 7Hz, C1H); 6.11 (0.6H, s, C8H (s)), 6.38 (0.4H, s, C8H); 6.41 – 6.46 (1H, m,); 6.55 (0.6H, s, C5H); 6.64 (0.4H, s, C5H (m)); 6.70 – 6.74 (1H, m,); 6.79 – 6.82 (1H, m,); 7.09 – 7.10 (2H, m,); 7.20 – 7.23 (2H, m,); 7.32 – 7.39 (1H, m)

^{13}C-NMR (101MHz):

27.9 (C4H_2 (s)), 28.4 (C4H_2 (m)); 35.3 (C3H_2 (s)); 39.6 (COCH_2 (s)); 41.1 (COCH_2, C3H_2 (m)); 42.2 (C1CH_2 (m)); 43.0 (C1CH_2 (s)); 54.2 (C1H (m)); 55.5, 55.7, 55.9 (C3"OCH_3, C4"OCH_3, C7OCH_3, C6OCH_3 (s)), 55.8, 55.9 (C3"OCH_3, C4"OCH_3, C6OCH_3, C7OCH_3 (m)); 58.6 (C1H (s)); 109.8 (C8H (s)); 110.6 (C8H (m); 110.7 (C5H (m)); 111.0 (C5H (s)); 111.2 (C2"H (m)), 111.4 (C2"H (s)); 111.7 (C5"H (m)), 111.8 (C5"H (s)); 120.7 (C6"H (m)), 120.9 (C6"H (s)); 125.3 (C8a (m)); 126.3 (C4'H (m)); 126.5 (C8a (s)); 126.9 (C4'H (s)); 127.4 (C4a (m)); 127.5 (C4a (m)); 127.8 (C1" (s)), 128.1 (C1" (m)); 128.14 (C2'H, C6'H (m), 128.8 (C2'H, C6'H (s)); 129.6 (C3'H, C5'H (s)), 129.9 (C3'H, C5'H (m)); 138.0 (C1' (s)), 138.1 (C1' (m)); 146.8, 147.5, 147.8, 149.0 (C3"OCH_3, C4"OCH_3, C7OCH_3, C6OCH_3 (m)), 147.2, 147.6, 148.1, 148.7 (C3"OCH_3, C4"OCH_3, C7OCH_3, C6OCH_3 (s)); 169.8 (CO (m)); 170.2 (CO (s))

Yield: 28.7%

IRν_{max}(KBr): 1454cm^{-1}(C-N stretching), 1636cm^{-1}(C=O stretching), 2938cm^{-1}, 3055cm^{-1}(C-H stretching)

HRMS calcd. for C28H31NO5Na (M^++23): 484.2100 Found: 484.2096

(1-Benzyl-6,7-dimethoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-(4-nitro-phenyl)-methanone (150)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.62 (0.5H, d, J = 15.5Hz, C4H_2); 2.77 – 2.85 (1H, m, C4H_2); 2.92 (0.5H, dd, J_1 = 14Hz, J_2 = 4Hz, C4H_2); 3.14 – 3.19 (1H, m, C3H_2); 3.25 (1H, t, J = 7Hz, C1CH_2); 3.39 – 3.54 (1.5H, m, C1CH_2, C3H_2); 3.73 (1.5 H, s, C7OCH_3); 3.78 (1.5H, s, C7OCH_3); 3.87 (1.5H, s, C6OCH_2), 3.90 (1.5H, s, OCH_3); 4.62 (0.5H, d, J = 9.5Hz, C3H_2); 4.95 (0.5H, dd, J_1 = 13Hz, J_2 = 6Hz, C1H); 5.94 (0.5H, apparent triplet, J = 7Hz, C1H); 6.31 (0.5H, s, C8H), 6.40 (0.5H, s, C8H); 6.60 (0.5H, s C5H); 6.70 (0.5H, s, C5H); 6.73 (1H, d, J = 8Hz, C2"H, C6"H); 6.99 (1H, d, J = 7Hz, C2"H, C6"H); 7.25 – 7.37 (5H, m, C2'H, C3'H, C4'H, C5'H, C6'H); 8.02 (1H, d, J = 8Hz, C3"H, C5"H); 8.26 (1H, d, J = 8.5Hz, C3"H, C5"H)

^{13}C-NMR (101MHz):

27.8 (C4H_2 (s)), 28.8 (C4H_2 (m)); 35.4 (C3H_2 (s)); 41.6 (C3H_2 (m)); 42.2 (C1CH_2 (m)); 42.9 (C1CH_2 (s)); 53.2 (C1H (m)); 55.7 (C6OCH_3, C7OCH_3 (s)); 55.8 (C7OCH_3, C6OCH_3 (m)); 60.0 (C1H (s)); 109.4 (C8H (s)); 110.2 (C8H (m); 111.1 (C5H (m)); 111.6 (C5H (s)); 123.4 (C3"H, C5"H (m)), 123.9 (C3"H, C5"H (s)); 124.5 (C8a (s)); 125.8 (C8a (m)); 126.8 (C4'H (s)), 127.2 (C4'H (m)); 127.26 (C4a (s)), 127.30 (C4a (m)); 127.37 (C2"H, C6"H (s)), 127.45 (C2"H, C6"H (m)); 128.0 (C2"H, C6"H (s)), 128.1 (C2"H, C6"H (m)); 128.4 (C2'H, C6'H (m), 128.9 (C2'H, C6'H (m)); 129.7 (C3'H, C5'H (s)), 129.8 (C3'H, C5'H (m)); 137.3 (C1' (s)); 137.5 (C1' (m)); 142.0 (C1" (s)), 142.6 (C1" (m)); 145.2 (C4"NO_2 (m)), 146.1 (C4"NO_2 (s)); 147.5 (C7OCH_3, C6OCH_3 (m)), 148.1 (C7OCH_3, C6OCH_3 (s)); 168.0 (CO (s)); 168.7 (CO (m))

Yield: 63.8%

IRν_{max}(KBr): 1430cm^{-1}(C-N stretching), 1630cm^{-1}(C=O stretching), 2935cm^{-1}

HRMS calcd. for C25H24N2O5Na (M^++23): 455.1583 Found: 455.1587

(1-Benzyl-6,7-dimethoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-(4-methylsulfanyl-phenyl)-methanone (151)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.50 (3H, s, SCH_3); 2.58 (0.6H, d, J = 16Hz, C4H_2); 2.80 – 2.82 (1H, m, C4H_2); 2.93 (0.4 H, dd, J_1 = 13.5Hz, J_2 = 5.5Hz, C4H_2); 3.09 – 3.17 (1H, m, C1CH_2); 3.23 – 3.25 (1H, m, C1CH_2); 3.39 (1H, d, J = 13.5Hz, C3H_2); 3.67 (1.8 H, s, C7OCH_3); 3.69 (1.2H, s, C7OCH_3); 3.74 (0.6H, dd, J_1 = 13.5Hz, J_2 = 4.5Hz, C3H_2); 3.86 (1.8H, s, C6OCH_2), 3.88 (1.2H, s, OCH_3); 4.83 – 4.90 (0.8H, m, C3H_2, C1H_2); 5.89 (0.6H, apparent triplet, J = 7Hz, C1H); 6.16 (0.4H, s, C8H), 6.31 (0.6H, s, C8H); 6.58 (0.6H, s C5H); 6.67 (0.4H, s, C5H); 6.72 - 7.25 (6H, m, C2'H, C3'H, C4'H, C5'H, C6'H, C2"H, C3"H, C5"H, C6"H);

^{13}C-NMR (101MHz):

15.3 (SCH_3); 27.7 (C4H_2 (s)), 28.9 (C4H_2 (m)); 35.5 (C3H_2 (s)); 41.7 (C3H_2 (m)); 42.1 (C1CH_2 (m)); 43.1 (C1CH_2 (s)); 53.3 (C1H (m)); 55.6 (C6OCH_3, C7OCH_3 (s)); 55.7 (C7OCH_3, C6OCH_3 (m)); 59.7 (C1H (s)); 109.6 (C8H (s)); 110.3 (C8H (m); 111.0 (C5H (m)); 111.5 (C5H (s)); 125.0 (C8a (m)); 125.4 (C3"H, C5"H (s)), 125.8 (C3"H, C5"H (m)); 126.0 (C8a (s); 126.5 (C4'H (m)), 126.7 (C4'H (s)); 127.0 (C2"H, C6"H (s)), 127.1 (C2"H, C6"H (m)); 127.8 (C4a (s)), 128.0 (C4a (m)); 128.2 (C2'H, C6'H (m)), 128.6 (C2'H, C6'H (m)); 129.7 (C3'H, C5'H (s), 129.8 (C3'H, C5'H (m)); 132.5 (C1" (s)); 132.7 (C1" (m)); 137.4 (C1' (s)), 137.9 (C1' (m)); 140.1 (C4"SCH_3 (s)), 140.6 (C4"SCH_3 (m)); 146.9, 147.0 (C7OCH_3, C6OCH_3 (m)), 147.6 (C7OCH_3 (s)), 148.0 (C6OCH_3 (s)); 169.9 (CO (m)); 170.7 (CO (s))

Yield: 47.4%

IRν_{max}(KBr): 1426cm^{-1}(C-N stretching), 1629cm^{-1}(C=O stretching), 2930cm^{-1}, 3328cm^{-1}(C-H stretching)

HRMS calcd. for C26H27NO3NaS (M^++23): 456.1609 Found: 456.1602

1-(1-Benzyl-6,7-dimethoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-ethanone (152)[28]

^{1}H-NMR (400MHz):

δ($CDCl_3$):

1.55 (1.5H, s, COCH_3), 2.10 (1.5H, s, COCH_3); 2.67 (1H, dd, J_1 = 21.5Hz, J_2 = 5Hz, C4H_2); 2.87 (1H, t, J = 16Hz, C4H_2); 2.94 (0.5H, t, J = 13.5Hz, C3H_2); 3.09 (2H, dd, J_1 = 17Hz, J_2 = 7Hz, C1CH_2); 3.14 (0.5H, d, J = 7Hz, C3H_2); 3.43 – 3.50 (0.5H, m, C3H_2); 3.54 (1.5H, s, C7OCH_3); 3.61 – 3.67 (0.5H, m, C3H_2); 3.77, 3.81, 3.83 (4.5H, m, C6OCH_3, C7OCH_3); 4.73 (0.5H, dd. J_1 = 13Hz, J_2 = 4.5Hz, C3H_2); 4.80 (0.5H, dd, J_2 = 8.5Hz, J_2 = 5.5Hz, C1H); 5.63 (0.5H, t, J = 7Hz, C1H); 6.10 (0.5H, s, C8H), 6.45 (0.5H, s, C8H); 6.57 (0.5H, s, C5H), 6.61 (0.5H, s, C5H); 7.06 (1H, d, J= 7Hz, C2'H, C6'H); 7.14 (1H, d, J = 8Hz, C2'H, C6'H); 7.16 –

7.17 (0.5H, m, C4'H); 7.19 (1H, d, J = 7.5Hz, C3'H, C5'H); 7.22 – 7.24 (0.5H, m, C4'H); 7.27 (1H, d, J = 7.5Hz, C3'H, C5'H)

^{13}C-NMR (101MHz):

20.7 ($\underline{C}H_3$ (s)), 21.7 ($\underline{C}H_3$ (m)); 27.6 ($\underline{C}4H_2$ (s)), 28.2 ($\underline{C}H_2$ (m)); 34.7 ($\underline{C}3H_2$ (s)); 41.4 ($\underline{C}3H_2$ (m)); 42.1 (C1$\underline{C}H_2$ (m)); 42.9 (C1$\underline{C}H_2$ (s)); 53.9 ($\underline{C}$1H (m)); 55.4, 55.65, 55.7, 55.8 (C6O$\underline{C}H_3$, C7O$\underline{C}H_3$); 59.1 ($\underline{C}$1H (s)); 109.7 ($\underline{C}$8H (s)); 110.4 ($\underline{C}$8H (m)); 110.5 ($\underline{C}$5H (m)); 111.2 ($\underline{C}$5H (s)); 125.3 ($\underline{C}$8a (m)); 125.6 ($\underline{C}$8a (s)); 126.1 ($\underline{C}$4'H (m)); 126.3 ($\underline{C}$4a (m)); 126.6 ($\underline{C}$4'H (s)); 127.6 ($\underline{C}$4a (s)); 127.8 ($\underline{C}$2'H, $\underline{C}$6'H (m)), 128.4 ($\underline{C}$2'H, $\underline{C}$6'H (s)); 128.3 ($\underline{C}$3'H, $\underline{C}$5'H (s)); 129.6 ($\underline{C}$3'H, $\underline{C}$5'H (m)); 137.5 ($\underline{C}$1" (m)), 137.9 ($\underline{C}$1" (s)); 146.5 ($\underline{C}$7OCH$_3$ (m)), 146.9 ($\underline{C}$7OCH$_3$ (s)); 147.2 ($\underline{C}$6OCH$_3$ (m)), 147.7 ($\underline{C}$6OCH$_3$ (s)); 168.9 ($\underline{C}$O (s)); 169.3 ($\underline{C}$O (m))

Yield: 65.5%

IRν_{max}(KBr): 1454cm^{-1}(C-N stretching), 1636cm^{-1}(C=O stretching), 2937cm^{-1}, 3037cm^{-1}(C-H stretching)

Melting point: 110 - 112°C Literature: 115 - 116°C[28]

1-(1-Benzyl-6,7-dimethoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-propan-1-one (153)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

0.88 (1.2H, t, J = 7.5Hz, CH$_2$C$\underline{H}_3$ (s)), 1.15 (1.8H, t, J = 7.5Hz, CH$_2$C$\underline{H}_3$ (m)); 1.63 – 1.72 (0.4H, m, C$\underline{H}_2$CH$_3$ (s)), 2.01 – 2.08 (0.4H, m, C$\underline{H}_2$CH$_3$ (s)), 2.34 – 2.49 (1.2H, m, C$\underline{H}_2$CH$_3$ (m)); 2.67 (0.4H, t, J = 4Hz, C4$\underline{H}_2$ (s)), 2.71 (0.6, t, J = 4Hz, C4$\underline{H}_2$ (m)); 2.77 - 2.80 (0.4H, m, C4$\underline{H}_2$ (m)); 2.82 – 2.91 (0.4H, m, C3$\underline{H}_2$ (s)); 2.92 – 2.98 (0.6H, m, C4$\underline{H}_2$ (m)); 3.03 – 3.23 (2H, m, C1C$\underline{H}_2$); 3.46 – 3.53 (0.6H, m, C3$\underline{H}_2$ (m)); 3.56 (1.8H, s, C7OC$\underline{H}_3$ (m)); 3.65 – 3.71 (0.6H, m, C3$\underline{H}_2$ (m)); 3.77 (1.2H, s, C7OC$\underline{H}_3$ (s)); 3.84 (1.8H, s, C6OC$\underline{H}_3$ (m)), 3.86 (1.2H, s, C6OC$\underline{H}_3$ (s)); 4.78 (0.4H, ddd. J_1 = 17Hz, J_2 = 6Hz, J_3 = 2Hz, C3$\underline{H}_2$ (s)); 4.88 (0.4H, dd, J_1 = 8.5Hz, J_2 = 5.5Hz, C1$\underline{H}$ (s)); 5.66 (0.6H, dd, J_1 = 8.5Hz, J_2 = 5.5Hz, C1$\underline{H}$ (m)); 6.10 (0.6H, s, C8$\underline{H}$ (m)), 6.42 (0.4H, s, C8$\underline{H}$ (m)); 6.59 (0.6H, s, C5$\underline{H}$ (m)), 6.63 (0.4H, s, C5$\underline{H}$ (s)); 7.09 (1.2H, d, J= 7Hz, C2'$\underline{H}$, C6'$\underline{H}$ (m)); 7.15 (0.8H, d, J = 7Hz, C2'$\underline{H}$, C6'$\underline{H}$ (s)); 7.18 – 7.20 (0.4H, m, C4'$\underline{H}$ (s)); 7.22 (1.2H, d, J = 7.5Hz, C3'$\underline{H}$, C5'$\underline{H}$ (m)); 7.25 – 7.28 0.6H, m, C4'$\underline{H}$ (m)); 7.31 (0.8H, d, J = 7.5Hz, C3'$\underline{H}$, C5'$\underline{H}$ (s))

^{13}C-NMR (101MHz):

9.1 ($\underline{C}H_3$ (s)), 9.3 ($\underline{C}H_3$ (m)); 25.8 (CO$\underline{C}H_2$ (s)), 26.9 (CO$\underline{C}H_2$ (m)); 27.8 ($\underline{C}4H_2$ (s)), 28.5 ($\underline{C}4H_2$ (m)); 35.2 ($\underline{C}3H_2$ (s)); 40.7 ($\underline{C}3H_2$ (m)); 42.4 (C1$\underline{C}H_2$ (m)); 43.1 (C1$\underline{C}H_2$ (s)); 54.2 ($\underline{C}$1H (m)); 55.5, 55.78, 55.81, 55.9 (C6O$\underline{C}H_3$, C7O$\underline{C}H_3$); 58.1 ($\underline{C}$1H (s)); 110.2 ($\underline{C}$8H (s)); 110.9 ($\underline{C}$8H (m), ($\underline{C}$5H (m)); 111.6 ($\underline{C}$5H (s)); 125.6 ($\underline{C}$8a (s)); 126.2 ($\underline{C}$4'H (m)); 126.3 ($\underline{C}$4a (m)); 126.7 ($\underline{C}$8a (m)); 126.8 ($\underline{C}$4'H (s)); 128.0 ($\underline{C}$2'H, $\underline{C}$6'H (m)), 128.4 ($\underline{C}$4a); 128.6 ($\underline{C}$2'H, $\underline{C}$6'H (s)); 129.5 ($\underline{C}$3'H, $\underline{C}$5'H (s)); 129.8 ($\underline{C}$3'H, $\underline{C}$5'H (m)); 137.8 ($\underline{C}$1" (s)), 138.3 ($\underline{C}$1" (m)); 146.9 ($\underline{C}$7OCH$_3$ (m)), 147.2 ($\underline{C}$7OCH$_3$ (s)); 147.6 ($\underline{C}$6OCH$_3$ (m)), 148.1 ($\underline{C}$6OCH$_3$ (s)); 172.4 ($\underline{C}$O (m)); 172.7 ($\underline{C}$O (s))

Yield: 65.6%

IRν_{max}(KBr): 1447cm^{-1}(C-N stretching), 1638cm^{-1}(C=O stretching), 2940cm^{-1}, 3055cm^{-1}(C-H stretching)

HRMS calcd. for C21H25NO3Na (M^++23): 362.1732 Found: 362.1735

1-(1-Benzyl-6,7-dimethoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-butanone (154)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

0.71 (1.2H, t, J = 7.5Hz, $CH_2C\underline{H}_3$ (s)), 0.93 (1.8H, t, J = 7.5Hz, $CH_2C\underline{H}_3$ (m)); 1.19 – 1.53 (2H, m, $C\underline{H}_2CH_3$); 1.95 – 2.44 (2H, m, $COC\underline{H}_2$); 2.67 – 2.68 (0.4H, m, $C4\underline{H}_2$ (s)), 2.70 - 2.71 (0.6H, m, $C4\underline{H}_2$ (m)); 2.77 - 2.89 (1H, m, $C4\underline{H}_2$ (s), (m)); 2.88 – 2.98 (0.4H, m, $C3\underline{H}_2$ (s)); 3.02 – 3.21 (2H, m, $C1C\underline{H}_2$ (s), (m)); 3.45 – 3.52 (0.6H, m, $C3\underline{H}_2$ (m)); 3.56 (1.8H, s, $C7OC\underline{H}_3$ (m)); 3.68 – 3.74 (0.6H, m, $C3\underline{H}_2$ (m)); 3.79 (1.2H, s, $C7OC\underline{H}_3$ (s)); 3.84 (1.8H, s, $C6OC\underline{H}_3$ (m)), 3.86 (1.2H, s, $C6OC\underline{H}_3$ (s)); 4.79 (0.4H, dd, J_1 = 13Hz, J_2 = 5Hz, $C3\underline{H}_2$ (s)); 4.88 (0.4H, dd, J_1 = 8Hz, J_2 = 5Hz, $C1\underline{H}$ (s)); 5.67 (0.6H, dd, J_1 = 8Hz, J_2 = 5.5Hz, $C1\underline{H}$ (m)); 6.10 (0.6H, s, $C8\underline{H}$ (m)), 6.45 (0.4H, s, $C8\underline{H}$ (s)); 6.58 (0.6H, s, $C5\underline{H}$ (m)), 6.63 (0.4H, s, $C5\underline{H}$ (s)); 7.09 (1.2H, d, J= 7Hz, $C2'\underline{H}$, $C6'\underline{H}$ (m)) 7.16 (0.8H, d, J = 7Hz, $C2'\underline{H}$, $C6'\underline{H}$ (s)); 7.18 – 7.20 (0.4H, m, $C4'\underline{H}$ (s)); 7.22 (1.2H, d, J = 7.5Hz, $C3'\underline{H}$, $C5'\underline{H}$ (m)); 7.27 (0.6H, dd, J_1 = 10Hz, J_2 = 3Hz, $C4'\underline{H}$ (m)); 7.31 (0.8H, d, J = 7.5Hz, $C3'\underline{H}$, $C5'\underline{H}$ (s))

^{13}C-NMR (101MHz):

13.7 ($\underline{C}H_3$ (s)), 13.9 ($\underline{C}H_3$ (m)); 18.2 ($\underline{C}H_2CH_3$ (s)), 18.5 ($\underline{C}H_2CH_3$ (m)); 27.8 ($\underline{C}4H_2$ (s)), 28.5 ($\underline{C}4H_2$ (m)); 34.5 ($CO\underline{C}H_2$ (s)); 35.0 ($\underline{C}3H_2$ (s)); 35.6 ($CO\underline{C}H_2$ (m)); 40.7 ($\underline{C}3H_2$ (m)); 42.3 ($C1\underline{C}H_2$ (m)); 43.0 ($C1\underline{C}H_2$ (s)); 54.0 ($\underline{C}1H$ (m)); 55.4, 55.7, 55.74, 55.8 ($C6O\underline{C}H_3$, $C7O\underline{C}H_3$); 58.1 ($\underline{C}1H$ (s)); 109.9 ($\underline{C}8H$ (s)); 110.6 ($\underline{C}8H$ (m); 110.7 ($\underline{C}5H$ (m)); 111.4 ($\underline{C}5H$ (s)); 125.4 ($\underline{C}8a$ (s)); 126.2 ($\underline{C}4'H$ (m)); 126.6 ($\underline{C}8a$ (m)); 126.8 ($\underline{C}4'H$ (s)); 127.9 ($\underline{C}4a$ (s)); 128.0 ($\underline{C}2'H$, $\underline{C}6'H$ (m)); 128.3 ($\underline{C}4a$ (m)); 128.6 ($\underline{C}2'H$, $\underline{C}6'H$ (s)); 129.5 ($\underline{C}3'H$, $\underline{C}5'H$ (s)); 129.8 ($\underline{C}3'H$, $\underline{C}5'H$ (m)); 137.8 ($\underline{C}1''$ (s)), 138.2 ($\underline{C}1''$ (m)); 146.7 ($\underline{C}7OCH_3$ (m)), 147.0 ($\underline{C}7OCH_3$ (s)); 147.4 ($\underline{C}6OCH_3$ (m)), 147.9 ($\underline{C}6OCH_3$ (s)); 171.6 ($\underline{C}O$ (m)); 172.0 ($\underline{C}O$ (s))

Yield: 40.3%

IRν_{max}(KBr): 1454cm^{-1}(C-N stretching), 1638cm^{-1}(C=O stretching), 2937cm^{-1}, 3055cm^{-1}(C-H stretching)

HRMS calcd. for C22H27NO3Na (M^++23): 376.1889 Found: 376.1900

1-(1-Benzyl-6,7-dimethoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-pentanone (155)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

0.77 (1.2H, t, J = 7Hz, $CH_2C\underline{H}_3$ (s)), 0.92 (1.8H, t, J = 7.5Hz, $CH_2C\underline{H}_3$ (m)); 1.05 – 1.15 (0.8H, $C\underline{H}_2CH_2$ (s)); 1.22 – 1.28 (0.4H, m, $C\underline{H}_2CH_3$ (s)); 1.29 – 1.39 (1.2H, m, $C\underline{H}_2CH_2$ (m)); 1.35 – 1.40 (0.4H, m, $C\underline{H}_2CH_3$ (s)); 1.55 – 1.63 (0.4H, m, $COC\underline{H}_2$ (s)); 1.56 – 1.64 (1.2H, m, $C\underline{H}_2CH_3$ (m)); 1.95 – 2.02 (0.4H, m, $COC\underline{H}_2$ (s)); 2.28 – 2.44 (1.2H, m, $COC\underline{H}_2$ (m)); 2.66 – 2.68 (0.4H, m, $C4\underline{H}_2$ (s)), 2.70 - 2.72 (0.6H, m, $C4\underline{H}_2$ (m)); 2.76 - 2.86 (1H, m, $C4\underline{H}_2$ (s), (m)); 2.87 – 2.98 (0.4H, m, $C3\underline{H}_2$ (s)); 3.03 – 3.21 (2H, m, $C1C\underline{H}_2$ (s), (m)); 3.46 – 3.52 (0.6H, m, $C3\underline{H}_2$ (m)); 3.56 (1.8H, s, $C7OC\underline{H}_3$ (m)); 3.68 – 3.74 (0.6H, m, $C3\underline{H}_2$ (m)); 3.79 (1.2H, s, $C7OC\underline{H}_3$ (s)); 3.84 (1.8H, s, $C6OC\underline{H}_3$ (m)), 3.86 (1.2H, s, $C6OC\underline{H}_3$ (s)); 4.79 (0.4H, dd, J_1 = 12Hz, J_2 = 5Hz, $C3\underline{H}_2$ (s)); 4.88 (0.4H, dd, J_2 = 5Hz, J_2 = 5Hz, $C1\underline{H}$ (s)); 5.67 (0.6H, dd, J_1 = 8Hz, J_2 = 5Hz, $C1\underline{H}$ (m)); 6.10 (0.6H, s, $C8\underline{H}$ (m)), 6.45 (0.4H, s, $C8\underline{H}$ (s)); 6.59 (0.6H, s, $C5\underline{H}$ (m)), 6.63 (0.4H, s, $C5\underline{H}$ (s)); 7.10 (1.2H, d, J= 7Hz, $C2'\underline{H}$, $C6'\underline{H}$ (m)); 7.16 (0.8H, d, J = 7Hz, $C2'\underline{H}$, $C6'\underline{H}$ (s)); 7.18 – 7.20 (0.4H, m, $C4'\underline{H}$ (s)); 7.22 (1.2H, d, J = 7.5Hz, $C3'\underline{H}$, $C5'\underline{H}$ (m)); 7.24 – 7.27 (0.6H, m, $C4'\underline{H}$ (m)); 7.30 (0.8, d, J = 7.5Hz, $C3'\underline{H}$. $C5'\underline{H}$ (s))

^{13}C-NMR (101MHz):

13.7 ($\underline{C}H_3$ (s)), 13.8 ($\underline{C}H_3$ (m)); 22.3 ($\underline{C}H_2CH_3$ (s)), 22.4 ($\underline{C}H_2CH_3$ (m)); 26.9 ($\underline{C}H_2CH_2$ (s)), 27.2 ($\underline{C}H_2CH_2$ (m)); 27.8 ($\underline{C}4H_2$ (s)), 28.5 ($\underline{C}4H_2$ (m)); 30.8 ($CO\underline{C}H_2$ (s)); 33.4 ($CO\underline{C}H_2$ (m)); 35.0 ($\underline{C}3H_2$ (s)); 40.8 ($\underline{C}3H_2$ (m)); 42.3 ($C1\underline{C}H_2$ (m)); 43.0 ($C1\underline{C}H_2$ (s)); 54.0 ($\underline{C}1H$ (m)); 55.4, 55.67, 55.72, 55.8 ($C6O\underline{C}H_3$, $C7O\underline{C}H_3$); 58.1 ($\underline{C}1H$ (s)); 109.9 ($\underline{C}8H$ (s)); 110.6 ($\underline{C}8H$ (m); 110.65 ($\underline{C}5H$ (m)); 111.4 ($\underline{C}5H$ (s)); 125.4 ($\underline{C}8a$ (m));

126.2 (C4'H (m)); 126.6 (C8a (s)); 126.8 (C4'H (s)); 127.9 (C4a (s)); 128.0 (C2'H, C6'H (m)); 128.3 (C4a (m)); 128.5 (C2'H, C6'H (s)); 129.4 (C3'H, C5'H (s)); 129.8 (C3'H, C5'H (m)); 137.8 (C1" (s)), 138.2 (C1" (m)); 146.7 ($C7OCH_3$ (m)), 147.0 ($C7OCH_3$ (s)); 147.4 ($C6OCH_3$ (m)), 147.9 ($C6OCH_3$ (s)); 171.8 (CO (m)); 172.1 (CO (s))

Yield: 60.4%

IRν_{max}(KBr): 1454cm^{-1}(C-N stretching), 1634cm^{-1}(C=O stretching), 2930cm^{-1}, 3436cm^{-1}(C-H stretching)

HRMS calcd. for C23H30NO3 (M^++1): 368.2226 Found: 368.2224

(1-Benzyl-6, 7-dimethoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-cyclopropyl-methanone (156)

^{1}H-NMR (400MHz):

2.65 (0.5H, dt, J_1 = 15Hz, J_2 = 4Hz, C4H_2), 2.74 (0.5H, dt, J_1 = 16Hz, J_2 = 5Hz, C4H_2); 2.81 – 2.86 (1H, m, C4H_2); 2.88 – 2.92 (0.5H, m, C3H_2); 3.09 (0.5H, dd, J_1 = 13.5Hz, J_2 = 5.5Hz, C1CH_2); 3.15 (0.5H, d, J = 5.5Hz, C1CH_2); 3.17 – 3.22 (1H, m, C1CH_2); 3.50 (1.5H, s, C7OCH_3); 3.64 – 3.73 (0.5H, m. C3H_2); 3.76 (1.5H, s, C7OCH_3); 3.82 (1.5H, s, C6OCH_3); 3.84 (1.5H, s, C6OCH_3); 3.94 – 4.00 (0.5H, m, C3H_2); 4.67 (0.5H, ddd, J_1 = 13Hz, J_2 = 4.5Hz, J_3 = 2.5Hz, C3H_2); 5.24 (0.5H, dd, J_2 = 9Hz, J_2 = 5.5Hz, C1H); 5.57 (0.5H, dd, J_1 = 9Hz, J_2 = 5.5Hz, C1H); 6.01 (0.5H, s, C8H), 6.45 (0.5H, s, C8H); 6.59 (0.5H, s, C5H), 6.62 (0.5H, s, C5H); 7.06 (1H, d, J= 7Hz, C2'H, C6'H); 7.13 (1H, d, J = 7Hz, C2'H, C6'H); 7.15 – 7.17 (0.5H, m, C4'H); 7.19 (1H, d, J = 7Hz, C3'H, C5'H); 7.22 – 7.23 (0.5H, m, C4'H); 7.27 (1H, d, J = 7Hz, C3'H, C5'H)

^{13}C-NMR (101MHz):

6.8, 7.2, 7.3, 7.4 (CH_2 in cyclopropyl ring); 11.0 (COCH (m)), 11.4 COCH (s)); 27.8 ($C4H_2$ (s)), 28.5 ($C4H_2$ (m)); 35.8 ($C3H_2$ (s)); 40.9 ($C3H_2$ (m)); 42.3 ($C1CH_2$ (m)); 43.1 ($C1CH_2$ (s)); 54.9 (C1H (m)); 55.3, 55.6, 55.67, 55.72 ($C6OCH_3$, $C7OCH_3$); 57.8 (C1H (s)); 110.0 (C8H (s)); 110.6 (C8H (m); 110.64 (C5H (m)); 111.3 (C5H (s)); 125.6 (C8a (m)); 126.1 (C4'H (m)); 126.6 (C4'H (s)); 126.7 (C8a (s)); 127.9 (C4a (s)); 127.93 (C2'H, C6'H (m)); 128.3 (C4a (m)); 128.4 (C2'H, C6'H (s)); 129.5 (C3'H, C5'H (s)); 129.8 (C3'H, C5'H (m)); 137.7 (C1" (s)), 138.3 (C1" (m)); 146.6 ($C7OCH_3$ (m)), 147.0 ($C7OCH_3$ (s)); 147.4 ($C6OCH_3$ (m)), 147.8 ($C6OCH_3$ (s)); 171.9 (CO (m)); 172.4 (CO (s))

Yield:

IRν_{max}(KBr): 1454cm^{-1}(C-N stretching), 1631cm^{-1}(C=O stretching)

HRMS calcd. for C22H25NO3Na (M^++23): 374.1732 Found: 374.1725

(1-Benzyl-6, 7-dimethoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-cyclohexyl-methanone (157)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

0.83 – 1.93 (10H, m, CH_2 of cyclohexyl ring); 2.45 – 2.52 (1H, m, COCH); 2.64 – 2.70 (1H, m, C4H_2 (s)); 2.77 - 2.90 (1H, m, C4H_2); 2.94 – 2.99 (0.5H, m, C3H_2 (s)); 3.08 – 3.16 (2H, m, C1CH_2); 3.45 (0.5H, dt, J_1 = 11Hz, J_2 = 4.5Hz, C3H_2 (m)); 3.56 (1.5H, s, C7OCH); 3.77 – 3.83 (3H, s, s, C6OCH_3, C7OCH_3), 3.85 (1.5H, s, C6OCH_3); 4.78 (0.5H, dd, J_1 = 13Hz, J_2 = 4Hz, C3H_2); 4.91 (0.5H, apparent triplet, J_1 = 7Hz, C1H); 5.67 (0.5H, dd, J_1 = 8Hz, J_2 = 5.5Hz, C1H); 6.12 (0.5H, s, C8H), 6.53 (0.5H, s, C8H); 6.57 (0.5H, s, C5H), 6.62 (0.5H, s, C5H); 7.09 (1H, d, J= 7Hz, C2'H, C6'H); 7.16 – 7.18 (1.5H, m, C2'H, C6'H, C4'H); 7.21 (1H, d, J = 7.5Hz, C3'H, C5'H); 7.24 – 7.25 (0.5H, m, C4'H); 7.31 (1H, d, J = 7.5Hz, C3'H, C5'H)

^{13}C-NMR (101MHz):

25.4, 25.6, 25.62, 25.7, 25.8, 25.9 (CH_2 in cyclohexyl ring); 27.9 ($C4H_2$ (s)), 28.3, 28.9 (CH_2 in ring); 29.0 ($C4H_2$ (m)); 29.4, 29.6 (CH_2 in ring); 34.9 ($C3H_2$ (s)); 40.2 ($C3H_2$ (m)); 40.6 (CCCH (s)); 40.8 (COCH (m));

42.2 (C1$\underline{C}H_2$ (m)); 43.1 (C1$\underline{C}H_2$ (s)); 53.6 ($\underline{C}$1H (m)); 55.4, 55.65, 55.69, 55.9 (C6O$\underline{C}H_3$, C7O$\underline{C}H_3$); 57.7 ($\underline{C}$1H (s)); 109.9 ($\underline{C}$8H (s)); 110.5 ($\underline{C}$8H (m); 110.6 ($\underline{C}$5H (m)); 111.4 ($\underline{C}$5H (s)); 125.3 ($\underline{C}$8a (m)); 126.1 ($\underline{C}$4'H (m)); 126.3 ($\underline{C}$8a (s)); 126.7 ($\underline{C}$4'H (s)); 127.7 ($\underline{C}$4a (s)); 127.9 ($\underline{C}$2'H, $\underline{C}$6'H (m)); 128.4 ($\underline{C}$4a (m)); 128.5 ($\underline{C}$2'H, $\underline{C}$6'H (s)); 129.4 ($\underline{C}$3'H, $\underline{C}$5'H (s)); 129.8 ($\underline{C}$3'H, $\underline{C}$5'H (m)); 137.8 ($\underline{C}$1" (s)), 138.1 ($\underline{C}$1" (m)); 146.7 ($\underline{C}$7OCH$_3$ (m)), 147.1 ($\underline{C}$7OCH$_3$ (s)); 147.4 ($\underline{C}$6OCH$_3$ (m)), 147.9 ($\underline{C}$6OCH$_3$ (s)); 174.6 ($\underline{C}$O (m)); 175.2 ($\underline{C}$O (s))

Yield: 40.6%

IRν_{max}(KBr): 1452cm^{-1}(C-N stretching), 1633cm^{-1}(C=O stretching), 2342cm^{-1}, 2360cm^{-1}(C-H stretching)

HRMS calcd. for C25H32NO3 (M^++1): 394.2382 Found: 394.2388

(1-Benzyl-6,7-dimethoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-phenyl-methanone (158)[28]

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.52 (0.6H, d, J = 15.5Hz, C4$\underline{H}_2$); 2.73 – 2.80 (1H, m, C4$\underline{H}_2$); 2.88 (0.4H, dd, J_1 = 13Hz, J_2 = 6Hz, C4$\underline{H}_2$ (s)); 3.02 – 3.10 (1H, m, C1C$\underline{H}_2$); 3.19 (1H, t, J = 7Hz, C1C$\underline{H}_2$); 3.26 – 3.40 (1H, m, C3$\underline{H}_2$); 3.58 (1.2H, s, C7OC$\underline{H}_3$); 3.62 (1.8H, s, OC$\underline{H}_3$ (m)); 3.63 – 3.66 (0.6H, m, C3$\underline{H}_2$ (m)); 3.79 (1.8H, s, C6OC$\underline{H}_3$ (m)), 3.82 (1.2H, s, C6OC$\underline{H}_3$ (s)); 4.78 (0.4H, apparent triplet, J = 7Hz, C3$\underline{H}_2$ (s)); 4.84 (0.4H, dd, J_1 = 13Hz, J_2 = 5.5Hz, C1$\underline{H}$ (s)); 5.88 (0.6H, apparent triplet, J = 7Hz, C1$\underline{H}$); 6.06 (0.4H, s, C8$\underline{H}$ (s)), 6.29 (0.6 H, s, C8$\underline{H}$ (m)); 6.54 (0.6H, s, C5$\underline{H}$ (m)), 6.63 (0.4H, s, C5$\underline{H}$ (s)); 6.78 (0.6H, d, J = 7Hz, C4"$\underline{H}$ (m)); 6.86 (0.6H, d, J = 3.5Hz, C4'$\underline{H}$ (m)); 7.17 – 7.27 (6.8H, m, C2'$\underline{H}$, C3'$\underline{H}$, 5'$\underline{H}$, C6'$\underline{H}$, C3"$\underline{H}$, C4"$\underline{H}$, C5"$\underline{H}$); 7.33 – 7.34 (2H, C2"$\underline{H}$, C6"$\underline{H}$)

^{13}C-NMR (101MHz):

27.6 ($\underline{C}$4H$_2$ (s)), 28.6 ($\underline{C}$4H$_2$ (m)); 35.3 ($\underline{C}$3H$_2$ (s)); 41.4 ($\underline{C}$3H$_2$ (m)); 41.9 (C1$\underline{C}$H$_2$ (m)); 42.9 (C1$\underline{C}$H$_2$ (s)); 53.0 ($\underline{C}$1H (m)); 55.3, 55.4, 55.5 (C6O$\underline{C}$H$_3$, C7O$\underline{C}$H$_3$); 59.4 ($\underline{C}$1H (s)); 109.5 ($\underline{C}$8H (s)); 110.1 ($\underline{C}$8H (m); 110.9 ($\underline{C}$5H (m)); 111.3 ($\underline{C}$5H (s)); 124.9 ($\underline{C}$8a (m)); 125.8 ($\underline{C}$8a (s)); 126.1 ($\underline{C}$2"H, $\underline{C}$6"H (s)), 126.2 ($\underline{C}$2"H, $\underline{C}$6"H (m)); 126.3 ($\underline{C}$4'H (m)), 126.5 (C4'H (s)); 127.5 ($\underline{C}$4a (s)); 127.8 ($\underline{C}$4a (m)); 127.9 ($\underline{C}$3"H, $\underline{C}$5"H (s)), 128.0 ($\underline{C}$3"H, $\underline{C}$5"H (m)); 128.2 ($\underline{C}$2'H, $\underline{C}$6'H (m)), 128.3 ($\underline{C}$2'H, $\underline{C}$6'H (s)); 128.8 ($\underline{C}$4"H (s)), 129.1 ($\underline{C}$4"H (m)); 129.4 ($\underline{C}$3'H, $\underline{C}$5'H (s)), 129.6 ($\underline{C}$3'H, $\underline{C}$5'H (m)); 135.9 ($\underline{C}$1" (s)), 136.3 ($\underline{C}$1" (m)); 137.3 ($\underline{C}$1' (s)), 137.7 ($\underline{C}$1' (m)); 146.7 ($\underline{C}$7OCH$_3$ (s)), 146.8 ($\underline{C}$7OCH$_3$ (m)); 147.4 ($\underline{C}$6OCH$_3$ (m)), 147.8 ($\underline{C}$6OCH$_3$ (s)); 170.0 ($\underline{C}$O (s)); 170.7 ($\underline{C}$O (m))

Yield: 29.3%

IRν_{max}(KBr): 1422cm^{-1}(C-N stretching), 1635cm^{-1}(C=O stretching), 2987cm^{-1}, 3055cm^{-1}(C-H stretching)

Melting point: 122 - 124°C Literature: 127 - 128°C[28]

(1-Benzyl-6,7-dimethoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-*p*-tolyl-methanone (159)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.37 (1H, s, C$\underline{H}_3$ (s)), 2.38 (2H, s, C$\underline{H}_3$ (m)); 2.57 (0.6H, d, J = 16Hz, C4$\underline{H}_2$); 2.79 – 2.87 (1H, m, C4$\underline{H}_2$); 2.94 (0.4H, dd, J_1 = 13Hz, J_2 = 6Hz, C4$\underline{H}_2$ (s)); 3.08 – 3.30 (2H, m, C1C$\underline{H}_2$); 3.33 – 3.43 (1H, m, C3$\underline{H}_2$); 3.64 (1.2H, s, C7OC$\underline{H}_3$); 3.66 (1.8H, s, OC$\underline{H}_3$ (m)); 3.44 (0.6H, dd, J_1 = 13.5Hz, J_2 = 3.5Hz, C3$\underline{H}_2$ (m)); 3.86 (1.8H, s, C6OC$\underline{H}_3$ (m)), 3.88 (1.2H, s, C6OC$\underline{H}_3$ (s)); 4.87- 4.91 (0.8H, m, C3$\underline{H}_3$ (s), C1$\underline{H}$ (s)); 5.91 (0.6H, apparent triplet, J = 7Hz, C1$\underline{H}$); 6.09 (0.4H, s, C8$\underline{H}$ (s)), 6.31 (0.6 H, s, C8$\underline{H}$ (m)); 6.59 (0.6H, s, C5$\underline{H}$ (m)),

6.67 (0.4H, s, C5H (s)); 6.77 (0.6H, d, J = 7.5Hz, C3"H, C5"H (m)); 6.94 (0.6H, s, C4'H (m))); 7.06 (0.6H, d, J = 7.5Hz, C3"H, C5"H (m)); 7.19 – 7.33 (6H, m, C2'H, C3'H, C5'H, C6'H, C2"H, C6"H, C4'H, C3"H, C5"H (s))

^{13}C-NMR (101MHz):

21.3 ($\underline{C}H_3$); 27.8 ($\underline{C}4H_2$ (s)), 28.9 ($\underline{C}4H_2$ (m)); 35.5 ($\underline{C}3H_2$ (s)); 41.7 ($\underline{C}3H_2$ (m)); 42.1 (C1$\underline{C}H_2$ (m)); 43.1 (C1$\underline{C}H_2$ (s)); 53.2 ($\underline{C}$1H (m)); 55.5, 55.6, 55.8 (C6O$\underline{C}H_3$, C7O$\underline{C}H_3$); 59.6 ($\underline{C}$1H (s)); 110.7 ($\underline{C}$8H (s)); 110.3 ($\underline{C}$8H (m); 111.0 ($\underline{C}$5H (m)); 111.4 ($\underline{C}$5H (s)); 125.1 ($\underline{C}$8a (m)); 126.0 ($\underline{C}$8a (s)); 126.38 ($\underline{C}$3"H, $\underline{C}$5"H (s)); 126.44 ($\underline{C}$4'H (m)); 126.5 ($\underline{C}$3"H, $\underline{C}$5"H (m)); 126.6 ($\underline{C}$4'H (s)); 127.8 ($\underline{C}$4a (s)); 128.1 ($\underline{C}$4a (m)); 128.2 ($\underline{C}$2'H, $\underline{C}$6'H (m), 128.5 ($\underline{C}$2'H, C6'H (s)); 128.7 ($\underline{C}$2"H, $\underline{C}$6"H (s)), 129.0 $\underline{C}$2"H, $\underline{C}$6"H (m)); 129.7 ($\underline{C}$3'H, $\underline{C}$5'H (s)), 129.8 ($\underline{C}$3'H, $\underline{C}$5'H (m)); 133.2 ($\underline{C}$4"CH_3 (s)), 133.5 ($\underline{C}$4"CH_3 (m)); 137.5 ($\underline{C}$1" (s)), 137.9 ($\underline{C}$1" (m)); 139.0 ($\underline{C}$1' (s)), 139.4 ($\underline{C}$1' (m)); 146.8 ($\underline{C}$7OCH_3 (s)), 146.9 ($\underline{C}$7OCH_3 (m)); 147.6 ($\underline{C}$6OCH_3 (m)), 147.9 ($\underline{C}$6OCH_3 (s)); 170.4 ($\underline{C}$O (m)); 171.2 ($\underline{C}$O (s))

Yield: 38.2%

IRν_{max}(KBr): 1430cm^{-1}(C-N stretching), 1628cm^{-1}(C=O stretching), 2938cm^{-1}, 3037cm^{-1}(C-H stretching)

HRMS calcd. for C23H30NO3 (M^++1): 402.2069 Found: 402.2065

(1-Benzyl-6,7-dimethoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-(2-methoxy-phenyl)-methanone (160)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.47 (0.6H, apparent triplet, J = 16Hz, C4$\underline{H}_2$ (m)); 2.63 – 2.71 (1H, m, C4$\underline{H}_2$ (s)); 2.76 (0.4H, d, J = 16Hz, C4$\underline{H}_2$ (s)); 2.82 - 2.93 (0.6H, m, C4$\underline{H}_2$ (m)); 2.96 – 3.12 (1H, m, C3$\underline{H}_2$); 3.16 – 3.36 (2H, m, C1$\underline{C}H_2$); 3.44 – 3.48 (0.6H, m, C3$\underline{H}_2$ (m)); 3.59 (1.2H, s, C2"O$\underline{C}H_3$ (s)), 3.67, 3.69 (1.5H, s, C7O$\underline{C}H_3$); 3.74 (1.8H, s, C2"O$\underline{C}H_3$ (m)), 3.82, 3.83, 3.87 (4.5H, s, C7O$\underline{C}H_3$, C6O$\underline{C}H_3$); 4.50 (0.4H, dd, J_1 = 8.5Hz, J_2 = 5.5Hz, C3$\underline{H}_3$ (s)); 4.88 (0.4H, dd, J_1 = 13Hz, J_2 = 5.5Hz, C1$\underline{H}$ (s)); 5.88 – 5.95 (0.6H, m, C1$\underline{H}$ (m)); 6.20 (0.6H, s, C8$\underline{H}$ (s)), 6.36 (0.4 H, s, C8$\underline{H}$ (m)); 6.54 (0.6H, s, C5$\underline{H}$ (m)), 6.67 (0.4H, s, C5$\underline{H}$ (s)); 6.72 – 7.37 (9H, m, C2'$\underline{H}$, C3'$\underline{H}$, C4'$\underline{H}$, C5'$\underline{H}$, C6'$\underline{H}$, C2"$\underline{H}$, C3"$\underline{H}$, C5"$\underline{H}$, C6"$\underline{H}$)

^{13}C-NMR (101MHz):

27.6 ($\underline{C}4H_2$ (s)), 28.7 ($\underline{C}4H_2$ (m)); 35.5 ($\underline{C}3H_2$ (s)); 41.9 ($\underline{C}3H_2$ (m)); 42.1 (C1$\underline{C}H_2$ (m)); 42.8 (C1$\underline{C}H_2$ (s)); 53.4 ($\underline{C}$1H (m)); 55.3, 55.5, 55.6, 55.7 (C6O$\underline{C}H_3$, C7O$\underline{C}H_3$); 59.3 ($\underline{C}$1H (s)); 110.2 ($\underline{C}$8H (s)); 110.6 ($\underline{C}$8H (m); 110.7 ($\underline{C}$3"H (s)), 110.8 ($\underline{C}$3"H (m)); 111.1 ($\underline{C}$5H (m)); 111.2 ($\underline{C}$5H (s)); 120.5 ($\underline{C}$5"H (s)), 120.7 ($\underline{C}$5" (m)); 125.3 ($\underline{C}$8a (m)); 125.6 ($\underline{C}$8a (s)); 126.13 ($\underline{C}$4'H (m)); 126.2 ($\underline{C}$4a (s)); 126.3 ($\underline{C}$4'H (s)); 127.56 ($\underline{C}$4a (m)); 127.6 ($\underline{C}$6"H (s)); 127.85 ($\underline{C}$4"H (s)); 127.9 ($\underline{C}$6"H (m)); 128.0 ($\underline{C}$4"H (m)); 128.2 ($\underline{C}$2'H, $\underline{C}$6'H (m), 128.5 ($\underline{C}$2'H, C6'$\underline{H}$ (s)); 129.7 ($\underline{C}$3'H, $\underline{C}$5'H (s)), 129.8 ($\underline{C}$3'H, $\underline{C}$5'H (m)); 137.6 ($\underline{C}$1" (m)), 137.8 ($\underline{C}$1' (m)); 137.9 ($\underline{C}$1" (s)), 138.0 ($\underline{C}$1' (s)); 146.6 ($\underline{C}$7OCH_3, $\underline{C}$6OCH_3 (s)), 147.8 ($\underline{C}$7OCH_3, $\underline{C}$6OCH_3 (m)); 154.6 ($\underline{C}$2"OCH_3 (s)), 155.1 ($\underline{C}$2"OCH_3 (m)); 167.9 ($\underline{C}$O (m)); 168.3 ($\underline{C}$O (s))

Yield: 43.1%

IRν_{max}(KBr): 1461cm^{-1}(C-N stretching), 1629cm^{-1}(C=O stretching), 2938cm^{-1}, 3438cm^{-1}(C-H stretching)

HRMS calcd. for C26H28NO4 (M^++1): 418.2018 Found: 418.2003

(1-Benzyl-6,7-dimethoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-(3-methoxy-phenyl)-methanone (161)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.57 (0.6H, d, J = 16Hz, C4$\underline{H}_2$ (m)); 2.77 – 2.84 (1H, m, C4$\underline{H}_2$); 2.93 (0.4H,dd, J_1 = 14Hz, J_2 = 6.5Hz, C4$\underline{H}_2$ (s)); 3.06 – 3.19 (1H, m, C1C$\underline{H}_2$); 3.22 (1H, d, J = 7Hz, C1C$\underline{H}_2$); 3.30 – 3.42 (1H, m, C3$\underline{H}_2$ (m)); 3.44 – 3.51 (0.6H, m, C3$\underline{H}_2$); 3.63 (1.2H, s, C2"OC$\underline{H}_3$ (s)), 3.79 (1.8H, s, C2"OC$\underline{H}_3$ (m)); 3.71 (1.2H, s, C7OC$\underline{H}_3$ (s)), 3.79 (1.8H, s, C7OC$\underline{H}_3$ (m)), 3.84 (1.8H, s, C6OC$\underline{H}_3$); 3.87 (1.2H, s, OC$\underline{H}_3$ (s)); 4.12 (0.4H, dd, J_1 = 14Hz, J_2 = 7Hz, C3$\underline{H}_3$ (s)); 4.86 – 4.89 (0.4H, m, C1$\underline{H}$ (s)); 5.92 (0.6H, apparent triplet, J = 7Hz, C1$\underline{H}$ (m)); 6.09 (0.4H, s, C8$\underline{H}$ (s)), 6.34 (0.6 H, s, C8$\underline{H}$ (m)); 6.42 – 6.47(); 6.58 (0.6H, s, C5$\underline{H}$ (m)), 6.67 (0.4H, s, C5$\underline{H}$ (s)); 6.75 -7.35 (4H, m, C2'$\underline{H}$, C3'$\underline{H}$, C4'$\underline{H}$, C5'$\underline{H}$, C6'$\underline{H}$, C2"$\underline{H}$, C4"$\underline{H}$, C5"$\underline{H}$, C6"$\underline{H}$

^{13}C-NMR (101MHz):

27.7 (C$\underline{H}_2$ (s)), 28.7 (C$\underline{H}_2$ (m)); 35.4 (C$\underline{H}_2$ (s)); 41.4 (C$\underline{H}_2$ (m)); 42.0 (C1C$\underline{H}_2$ (m)); 43.0 (C1C$\underline{H}_2$ (s)); 53.0 (C$\underline{H}$ (m)); 53.3, 55.1, 55.55 (C3"OC$\underline{H}_3$, C7OC$\underline{H}_3$, C6OC$\underline{H}_3$ (s)), 55.13, 55.5, 55.6 (C6OC$\underline{H}_3$, C7OC$\underline{H}_3$, C3"OC$\underline{H}_3$ (m)); 59.4 (C$\underline{H}$ (s)); 109.6 (C$\underline{H}$ (s)); 110.2 (C$\underline{H}$ (m); 111.0 (C$\underline{H}$ (m)); 111.4 (C$\underline{H}$"H (s)), 111.5 (C$\underline{H}$"H (m)), 115.2 (C$\underline{H}$"H (s)), 115.3 (C$\underline{H}$"H (m)); 118.26 (C$\underline{H}$"H (s)), 118.30 (C$\underline{H}$"H (m)); 124.9 (C8a (m)); 125.8 (C8a (s)); 126.4 (C$\underline{H}$'H (m)); 126.6 (C$\underline{H}$'H (s)); 127.6 (C4a (s)); 127.9 (C4a (m)); 128.1 (C$\underline{H}$'H, C$\underline{H}$'H (m); 128.4 (C$\underline{H}$'H, C6'$\underline{H}$ (s)); 129.1 (C$\underline{H}$"H (s)), 129.5 (C$\underline{H}$"H (m)); 129.4 (C$\underline{H}$'H, C$\underline{H}$'H (s)), 129.7 (C$\underline{H}$'H, C$\underline{H}$'H (m)); 137.2 (C1" (s)), 137.4 (C1' (s)); 137.6 (C1" (m)), 137.7 (C1' (m)); 146.8 (C7OCH$_3$ (m)), 146.9 (C7OCH$_3$ (s)); 147.6 (C6OCH$_3$ (m)), 147.9 (C6OCH$_3$ (s)); 159.2 (C3"OCH$_3$ (s)), 159.4 (C3"OCH$_3$ (m)); 170.0 (CO (m)); 170.6 (CO (s))

Yield: 46.5%

IRν_{max}(KBr): 1431cm^{-1}(C-N stretching), 1622cm^{-1}(C=O stretching), 29324cm^{-1}

HRMS calcd. for C23H30NO3 (M^++1): 418.2018 Found: 418.2032

(1-Benzyl-6,7-dimethoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-(4-methoxy-phenyl)-methanone (162)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.58 (0.6H, d, J = 16Hz, C4$\underline{H}_2$ (m)); 2.78 – 2.85 (1H, m, C4$\underline{H}_2$); 2.93 (0.4H, dd, J_1 = 13Hz, J_2 = 5.5Hz, C4$\underline{H}_2$ (s)); 3.06 – 3.11 (0.4H, m, C3$\underline{H}_2$); 3.24 – 3.20 (1H, m, C1C$\underline{H}_2$); 3.24 – 3.29 (1H, m, C1C$\underline{H}_2$); 3.32 – 3.42 (1H, m, C3$\underline{H}_2$ (m)); 3.64 (3H, s, C4"OC$\underline{H}_3$ (s)); 3.81, 3.84, 3.86 (6H, s, C7OC$\underline{H}_3$, C6OC$\underline{H}_3$); 4.85 – 4.88 (0.8H, m, C3$\underline{H}_2$ (s), C1$\underline{H}$ (s)); 5.88 (0.6H, apparent triplet, J = 7Hz, C1$\underline{H}$ (m)); 6.11 (0.4H, s, C8$\underline{H}$ (s)), 6.29 (0.6 H, s, C8$\underline{H}$ (m)); 6.58 (0.6H, s, C5$\underline{H}$ (m)), 6.66 (0.4H, s, C5$\underline{H}$ (s)); 6.78 (2H, dd. J_1 = 23Hz, J_2 = 8Hz, C3"$\underline{H}$, C5"$\underline{H}$); 6.89 (1H, d, J = 8Hz, C2"$\underline{H}$), 6.95 (1H, C6"$\underline{H}$); 7.25 (5H, m, C2'$\underline{H}$, C3'$\underline{H}$, C4'$\underline{H}$, C5'$\underline{H}$, C6'$\underline{H}$)

^{13}C-NMR (101MHz):

27.7 (C$\underline{H}_2$ (s)), 28.8 (C$\underline{H}_2$ (m)); 35.5 (C$\underline{H}_2$ (s)); 41.7 (C$\underline{H}_2$ (m)); 42.0 (C1C$\underline{H}_2$ (m)); 43.0 (C1C$\underline{H}_2$ (s)); 53.3 (C$\underline{H}$ (m)); 55.4, 55.6 (C4"OC$\underline{H}_3$, C6OC$\underline{H}_3$, C7OC$\underline{H}_3$ (s)); 55.1, 55.7 (C4"OC$\underline{H}_3$, C7OC$\underline{H}_3$, C6OC$\underline{H}_3$ (m)); 59.7 (C$\underline{H}$ (s)); 109.6 (C$\underline{H}$ (s)); 110.2 (C$\underline{H}$ (m); 110.9 (C$\underline{H}$ (m)); 111.4 (C$\underline{H}$ (s)); 113.3 (C$\underline{H}$"H, C$\underline{H}$"H (s)), 113.5 (C$\underline{H}$"H, C$\underline{H}$"H (s)); 125.0 (C8a (m)); 126.0 (C8a (s)); 126.4 (C$\underline{H}$'H (m)), 126.6 (C$\underline{H}$'H (s)); 127.8 (C4a (s)); 127.9 (C4a (m)); 128.11 (C$\underline{H}$"H, C$\underline{H}$"H (m)), 128.15 (C$\underline{H}$"H, C$\underline{H}$"H (s)); 128.3 (C$\underline{H}$'H, C$\underline{H}$'H (m), 128.4 (C$\underline{H}$'H, C6'$\underline{H}$ (s)); 129.6 (C$\underline{H}$'H, C$\underline{H}$'H (s)), 129.8 (C$\underline{H}$'H, C$\underline{H}$'H (m)); 137.5 (C1", C1' (s)), 137.9 (C1", C1' (m)); 146.75 (C7OCH$_3$ (m)), 146.8 (C7OCH$_3$ (s)); 147.5 (C6OCH$_3$ (m)), 147.9 (C6OCH$_3$ (s)); 160.0 (C4"OCH$_3$ (s)), 160.3 (C4"OCH$_3$ (m)); 170.1 (CO (m)); 171.0 (CO (s))

Yield: 61.2%

IRν_{max}(KBr): 1454cm^{-1}(C-N stretching), 1639cm^{-1}(C=O stretching), 2931cm^{-1}, 3328cm^{-1}(C-H stretching)

HRMS calcd. for C23H30NO3 (M^++1): 418.2018 Found: 418.2036

(1-Benzyl-6,7-dimethoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-(4-fluoro-phenyl)-methanone (163)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.58 (0.6H, d, J = 16Hz, C4H_2 (m)); 2.76 – 2.85 (1H, m, C4H_2); 2.91 (0.4H, dd, J_1 = 14Hz, J_2 = 5.5Hz, C4H_2 (s)); 3.06 – 3.16 (1H, m, C3H_2); 3.20 – 3.23 (1H, m, C1CH_2); 3.34 – 3.45 (1H, m, C1CH_2); 3.66 (1.8H, s, C7OCH_3 (m)); 3.70 (1.2H, s, C7OCH_3 (s)); 3.83 (0.6H, m, C3H_2 (m)); 3.84 (1.8H, s, C6OCH_2 (m)), 3.87 (1.2H, s, OCH_3 (s)); 4.78 (0.4H, dd, J_1 = 9Hz, J_2 = 5.5Hz, C3H_2 (s)); 4.88 (0.4H, dd, J_1 = 13Hz, J_2 = 6Hz, C1H (s)); 5.89 (0.6H, apparent triplet, J = 7Hz, C1H (m)); 6.20 (0.4H, s, C8H (s)), 6.32 (0.6 H, s, C8H (m)); 6.58 (0.6H, s, C5H (m)), 6.67 (0.4H, s, C5H (s)); 6.70 –7.31 (9H, m, C2'H, C3'H, C4'H, C5'H, C6'H, C2"H, C3"H, C5"H, C6"H)

^{13}C-NMR (101MHz):

27.7 (C4H_2 (s)), 28.7 (C4H_2 (m)); 35.4 (C3H_2 (s)); 41.6 (C3H_2 (m)); 42.0 (C1CH_2 (m)); 42.9 (C1CH_2 (s)); 53.2 (C1H (m)); 55.5 (C6OCH_3, C7OCH_3 (s)); 55.7 (C7OCH_3, C6OCH_3 (m)); 59.8 (C1H (s)); 109.5 (C8H (s)); 110.2 (C8H (m); 111.0 (C5H (m)); 111.14 (C5H (s)); 115.4 (d, J = 21.25Hz, C3"H, C5"H (s)), 115.0 (d, J = 23.18Hz, C3"H, C5"H (s)); 124.8 (C8a (m)); 125.9 (C8a (s)); 126.5 (C4'H (m)), 126.7 (C4'H (s)); 127.6 (C4a (s)); 127.9 (C4a (m)); 128.2 (C2"H, C6"H (m)), 128.4 (C2"H, C6"H (s)); 128.5 (C2'H, C6'H (m), 128.6 (C2'H, C6'H (s)); 129.6 (C3'H, C5'H (s)), 129.7 (C3'H, C5'H (m)); 132.0 (C1" (s)), 132.4 (C1" (m)); 137.4 (C1' (s)), 137.7 (C1' (m)); 147.0 (C7OCH_3, C6OCH_3 (m)), 147.6 (C7OCH_3 (s)); 148.0 (C6OCH_3 (s)); 161.8 (C4"F (s)), 164.2 (C4"F (m)); 179.3 (CO (m)); 170.1 (CO (s))

^{19}F-NMR (376MHz):

-111.5 (m), -111.6 (s)

Yield: 86.5%

IRν_{max}(KBr): 1423cm^{-1}(C-N stretching), 1630cm^{-1}(C=O stretching), 2935cm^{-1}, 3009cm^{-1}(C-H stretching)

HRMS calcd. for C25H24NO3FNa (M^++23): 418.1638 Found: 418.1627

(1-Benzyl-6,7-dimethoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-(4-chloro-phenyl)-methanone (164)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.58 (0.6H, d, J = 15.5Hz, C4H_2 (m)); 2.76 – 2.84 (1H, m, C4H_2); 2.91 (0.4H, dd, J_1 = 14Hz, J_2 = 5Hz, C4H_2 (s)); 3.02 – 3.16 (1H, m, C3H_2); 3.22 (1H, d, J = 7.5Hz, C1CH_2); 3.32 – 3.46 (1H, m, C1CH_2); 3.63 (0.6H, m, C3H_2 (m)); 3.67 (1.8H, s, C7OCH_3 (m)); 3.71 (1.2H, s, C7OCH_3 (s)); 3.84 (1.8H, s, C6OCH_2 (m)), 3.87 (1.2H, s, OCH_3 (s)); 4.75 (0.4H, dd, J_1 = 9Hz, J_2 = 5Hz, C3H_2 (s)); 4.89 (0.4H, dd, J_1 = 13Hz, J_2 = 6Hz, C1H (s)); 5.90 (0.6H, apparent triplet, J = 7Hz, C1H (m)); 6.22 (0.4H, s, C8H (s)), 6.33 (0.6 H, s, C8H (m)); 6.58 (0.6H, s, C5H (m)); 6.63 (1H, d, J = 8Hz, C3"H, C5"H): 6.67 (0.4H, s, C5H (s)); 6.95 – 6.97 (1H, m, C4'H); 7.18 (2H, d, J = 8Hz, C3"H, C5"H); 7.22 – 7.30 (4H, m, C2'H, C3'H, C5'H, C6'H); 7.35 (2H, d, J = 8Hz, C2"H, C6"H)

^{13}C-NMR (101MHz):

27.6 (C4H_2 (s)), 28.7 (C4H_2 (m)); 35.3 (C3H_2 (s)); 41.5 (C3H_2 (m)); 42.0 (C1CH_2 (m)); 42.9 (C1CH_2 (s)); 53.2 (C1H (m)); 55.5 (C6OCH_3, C7OCH_3 (s)); 55.7 (C7OCH_3, C6OCH_3 (m)); 59.7 (C1H (s)); 109.4 (C8H (s)); 110.2 (C8H (m); 110.9 (C5H (m)); 111.4 (C5H (s)); 124.7 (C8a (m)); 125.8 (C8a (s)); 126.5 (C4'H (m)), 126.7 (C4'H (s)); 127.5 (C4a (s)); 127.8 (C2"H, C6"H (s)), 127.9 (C2"H, C6"H (m)); 128.13 (C3"H,

C5"H (m)), 128.2 (C3"H, C5"H (m)); 128.4 (C4a (m)); 128.45 (C2'H, C6'H (m), 128.54 (C2'H, C6'H (s)); 129.5 (C3'H, C5'H (s)), 129.7 (C3'H, C5'H (m)); 134.3 (C4"Cl (s)), 134.7 (C4"Cl (m)); 134.8 (C1" (s)), 135.2 (C1" (m)); 137.2 (C1' (s)), 137.6 (C1' (m)); 147.0 ($C7OCH_3$, $C6OCH_3$ (m)), 147.6 ($C7OCH_3$ (s)); 148.0 ($C6OCH_3$ (s)); 169.1 (CO (m)); 169.9 (CO (s))

Yield: 37.8%

IRν_{max}(KBr): 1426cm^{-1}(C-N stretching), 1630cm^{-1}(C=O stretching), 2932cm^{-1}, 3437cm^{-1}(C-H stretching)

HRMS calcd. for C25H24NO3ClNa (M^++23): 444.1342 Found: 444.1364

(1-Benzyl-6,7-dimethoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-(4-bromo-phenyl)-methanone (165)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.59 (0.6H, d, J = 15.5Hz, C4H_2 (m)); 2.76 – 2.85 (1H, m, C4H_2); 2.92 (0.4H, dd, J_1 = 13.5Hz, J_2 = 5Hz, C4H_2 (s)); 3.07 – 3.17 (1H, m, C3H_2); 3.23 (1H, d, J = 6Hz, C1CH_2); 3.33 – 3.46 (1H, m, C1CH_2); 3.63 (0.6H, m, C3H_2 (m)); 3.68 (1.8H, s, C7OCH_3 (m)); 3.73 (1.2H, s, C7OCH_3 (s)); 3.86 (1.8H, s, C6OCH_2 (m)), 3.89 (1.2H, s, OCH_3 (s)); 4.75 (0.4H, dd, J_1 = 9Hz, J_2 = 5Hz, C3H_2 (s)); 4.90 (0.4H, dd, J_1 = 13Hz, J_2 = 6Hz, C1H (s)); 5.90 (0.6H, apparent triplet, J = 7Hz, C1H (m)); 6.23 (0.4H, s, C8H (s)), 6.34 (0.6 H, s, C8H (m)); 6.58 (0.6H, s, C5H (m)); 6.68 (0.4H, s, C5H (s)); 6.97 – 6.98 (1H, m, C4'H); 7.12 (2H, d, J = 8Hz, C3"H, C5"H); 7.23 – 7.35 (4H, m, C2'H, C3'H, C5'H, C6'H); 7.53 (2H, d, J = 8Hz, C2"H, C6"H)

^{13}C-NMR (101MHz):

27.7 (C4H_2 (s)), 28.8 (C4H_2 (m)); 35.4 (C3H_2 (s)); 41.6 (C3H_2 (m)); 42.1 (C1CH_2 (m)); 43.0 (C1CH_2 (s)); 53.2 (C1H (m)); 55.6 ($C6OCH_3$, C7OCH_3 (s)); 55.7 ($C7OCH_3$, $C6OCH_3$ (m)); 59.8 (C1H (s)); 109.5 (C8H (s)); 110.2 (C8H (m); 111.0 (C5H (m)); 111.5 (C5H (s)); 123.2 (C8a (m)); 123.6 (C8a (s)); 124.8 (C4"Br (m)), 125.9 (C4"Br (s)); 126.6 (C4'H (m)), 126.8 (C4'H (s)); 127.6 (C4a (s)); 128.05 (C2"H, C6"H (s)), 128.14 (C2"H, C6"H (m)); 128.2 (C2'H, C6'H (m), 128.7 (C2'H, C6'H (s)); 129.7 (C3'H, C5'H (s)), 129.8 (C3'H, C5'H (m)); 131.2 (C3"H, C5"H (s)); 131.6 (C3"H, C5"H (m)); 134.8 (C1" (s)), 135.2 (C1" (m)); 137.3 (C1' (s)), 137.7 (C1' (m)); 147.1 ($C7OCH_3$, $C6OCH_3$ (m)), 147.7 ($C7OCH_3$ (s)); 148.1 ($C6OCH_3$ (s)); 169.2 (CO (m)); 170.0 (CO (s))

Yield: 59.7%

IRν_{max}(KBr): 1426cm^{-1}(C-N stretching), 1631cm^{-1}(C=O stretching), 2361cm^{-1}

HRMS calcd. for C25H24NO3BrNa (M^++23): 488.0837 Found: 488.0820

(1-Benzyl-6,7-dimethoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-(4-iodo-phenyl)-methanone (166)

^{1}H-NMR (400MHz):

δ($CDCl_3$):

2.57 (0.6H, d, J = 15.5Hz, C4H_2 (m)); 2.74 – 2.83 (1H, m, C4H_2); 2.91 (0.4H, dd, J_1 = 14Hz, J_2 = 5Hz, C4H_2 (s)); 3.05 – 3.15 (1H, m, C3H_2); 3.20 (1H, d, J = 7Hz, C1CH_2); 3.32 – 3.44 (1H, m, C1CH_2); 3.62 (0.6H, d, J = 6Hz, C3H_2 (m)); 3.66 (1.8H, s, C7OCH_3 (m)); 3.71 (1.2H, s, C7OCH_3 (s)); 3.84 (1.8H, s, C6OCH_2 (m)), 3.86 (1.2H, s, OCH_3 (s)); 4.74 (0.4H, dd, J_1 = 9Hz, J_2 = 5Hz, C3H_2 (s)); 4.86 (0.4H, dd, J_1 = 13Hz, J_2 = 6Hz, C1H (s)); 5.87 (0.6H, apparent triplet, J = 7Hz, C1H (m)); 6.23 (0.4H, s, C8H (s)), 6.32 (0.6 H, s, C8H (m)); 6.41 (1H, d, J = 8Hz,); 6.57 (0.6H, s, C5H (m)); 6.66 (0.4H, s, C5H (s)); 6.96 (2H, d, J = 8Hz, C2"H, C6"H); 7.21 – 7.30 (5H, m, C2'H, C3'H, C4'H, C5'H, C6'H); 7.71 (2H, d, J = 8Hz, C3"H, C5"H)

^{13}C-NMR (101MHz):

27.6 (C4H_2 (s)), 28.7 (C4H_2 (m)); 35.3 (C3H_2 (s)); 41.5 (C3H_2 (m)); 42.0 (C1CH_2 (m)); 42.9 (C1CH_2 (s)); 53.1 (C1H (m)); 55.5 (C6OCH_3, C7OCH_3 (s)); 55.7 (C7OCH_3, C6OCH_3 (m)); 59.6 (C1H (s)); 95.0 (CI (s)), 95.3 (CI (m)); 109.4 (C8H (s)); 110.1 (C8H (m); 110.9 (C5H (m)); 111.1 (C5H (s)); 124.7 (C8a (m)); 125.8 (C8a (s)); 126.5 (C4'H (m)), 126.7 (C4'H (s)); 127.5 (C4a (s)); 127.7 (C4a (m)); 128.0 (C2"H, C6"H (s)), 128.1 (C2"H, C6"H (m)); 128.1 (C2'H, C6'H (m), 128.5 (C2'H, C6'H (s)); 129.6 (C3'H, C5'H (s)), 129.7 (C3'H, C5'H (m)); 135.3 (C1" (s)), 135.7 (C1" (m)); 137.0 (C3"H, C5"H (s)); 137.2 (C1' (s)); 137.4 (C3"H, C5"H (m)); 137.6 (C1' (m)); 147.0 (C7OCH_3 (m)), 147.6 (C6OCH_3 (m)), 148.0 (C7OCH_3 (s)); 148.8 (C6OCH_3 (s)); 169.2 (CO (m)); 169.9 (CO (s))

Yield: 98.4%

IRν_{max}(KBr): 1422cm^{-1}(C-N stretching), 1624cm^{-1}(C=O stretching)

HRMS calcd. for C25H24NO3BrNa (M^++23): 514.0879 Found: 514.0859

*Note: In some cases (marked *) the molecular ion did not form for HRMS. This may be due to loss of a leaving group (e.g. CF_3) or a systematic inability of the micromass spectrometer to find the molecular ion of some nitrated products. Product 68 was lost in the interim between biochemical testing and the renewed availability of HRMS analysis.*

Piperazine amides

Four methods of synthesis of the piperazine amides were established by trial and error. One called for use of the appropriate bromoamide, while the other three were variations of a synthetic route using a chloroamide as the starting material. The same general method was used to form the chloroamide or the bromoamide, using the appropriate tetrahydroisoquinoline.

Chloroamide formation 177, 186, 194, 203, 211

The relevant tetrahydroisoquinoline (20mmol) was dissolved in anhydrous dichloromethane and the set up was flushed with nitrogen. Triethylamine (30mmol) was added and the mixture was stirred. Chloroacetylchloride (23mmol) was added, drop wise, and the solution was stirred, with cooling in an ice-bath, for 15 minutes. The organic solution was washed with 10%v/v hydrochloric acid, then with water. It was dried, filtered and evacuated to a colourless solid. This was purified by column chromatography, using a mobile phase of 1:9 ethyl acetate: hexane increasing to 100% ethyl acetate, to elute the amide from a column of silica.

Bromoamide formation 178, 195, 204, 212

As for the chloroamide, bromoacetyl bromide being substituted for the chloroacetylchloride.

Piperazine amide formation: method 1.

The chloroamide in question (2mmol) was dissolved in dimethylformamide (10mL) with potassium carbonate (6mmol) by stirring at 60°C. Piperazine (2.1mmol) was dissolved in DMF and added slowly to the chloroamide. The brown solution was then stirred at 60°C for 3 hours. The DMF was removed on a rotary evaporator at high vacuum and the residue was taken up in dichloromethane and washed with water. It was then dried over anhydrous sodium sulfate and filtered. The solvent was removed *in vacuo* to give brown oil, which was purified by elution from a silica column using 5:95 ethyl acetate: hexane, increasing to 100% ethyl acetate.

Piperazine amide formation: method 2

The piperazine salt (1.1mmol) was dissolved in dimethylformamide (10mL) with stirring at 60°C and the addition of triethylamine (4mmol). The chloroamide (1mmol) was dissolved separately in dimethylformamide, and the solution was then added to the alkaline piperazinyl solution. The mixture was stirred at 60°C for 2 to 24 hours. It was diluted with water, and then extracted with ethyl acetate. The extract was washed with water, dried over anhydrous sodium sulfate, filtered and evacuated on a rotary evaporator to give yellow oil. This was purified by elution from a silica chromatographic column using a mobile phase of 5:95 ethyl acetate: hexane, increasing to 100% ethyl acetate.

Piperazine amide formation: method 3

The chloroamide (1.11mmol) was dissolved in ethanol at 60°C with the addition of triethylamine (2.5mmol). The piperazine salt (1mmol) was also dissolved in ethanol by the addition of triethylamine (3mmol) and the

piperazinyl solution was added to the chloroamide solution. The combined ethanolic solutions were a) stirred at room temperature, b) stirred at 60°C or c) refluxed for 3 to 4 hours. The ethanol was removed on a rotary evaporator and the residue was taken up in dichloromethane. It was washed with water, dried with anhydrous sodium sulfate and filtered. The extract was evacuated to a yellow oil, which was purified by column chromatography - with a mobile phase of 5:95 ethyl acetate: hexane increasing to 100% ethyl acetate - to give a yellow oil.

Piperazine amide formation: method 4

The appropriate bromoamide (2mmol) was dissolved in dimethylformamide by stirring at 60°C with triethylamine (2mmol). The piperazine salt (2.1mmol) was dissolved in DMF with triethylamine (4mmol) and this was added to the bromoamide solution. The combined solution was stirred at 60°C for 2 hours to 7 days. The DMF was diluted with water and the aqueous solution was extracted with ethyl acetate. The extract was washed with water, dried with anhydrous sodium sulfate and filtered. The solvents were removed *in vacuo* and the oil was purified on a silica column by elution using a mobile phase increasing in polarity from 5: 95 ethyl acetate: hexane to 100% ethyl acetate.

3.2.1 Unsubstituted amides

2-Chloro-1-(3,4-dihydro-*1H*-isoquinolin-2-yl)-ethanone(177)

^{1}H-NMR (400MHz): δ($CDCl_3$); 2.90 (0.8H, t, J = 6Hz, C4$\underline{H}_2$ (s)), 2.99 (1.2H, t, J = 6Hz, C4$\underline{H}_2$ (m)); 3.76 (1.2H, t, J = 6Hz, C3$\underline{H}_2$ (m)), 3.85 (0.8H, t, J = 6Hz C3$\underline{H}_2$ (s)); 4.18 (1.2H, s, COC$\underline{H}_2$ (m)), 4.19 (0.8H, s, COC$\underline{H}_2$ (s)); 4.70 (0.8H, s, C1$\underline{H}_2$ (s)), 4.76 (1.2H, s, C1$\underline{H}_2$ (m)); 7.16 – 7.25 (4H, m, C5$\underline{H}$, C6$\underline{H}$, C7$\underline{H}$, C8$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 28.1 (C4$\underline{H}_2$ (s)), 29.3 (C4$\underline{H}_2$ (m)); 40.4 (C3$\underline{H}_2$ (s)), 41.2 (C3$\underline{H}_2$ (m)), 41.4 (C1$\underline{H}_2$ (s)), 43.8 (C1$\underline{H}_2$ (m)), 44.7 (COC$\underline{H}_2$ (m)), 47.7 (COC$\underline{H}_2$ (s)); 126.0,126.5, 126.54, 126.6, 126.7, 127.1 (C5H, C6H, C7H); 128.3 (C8H (m)); 128.8 (C8H(s)); 131.9 (C8a (s)), 132.5 (C8a (m)); 133.6 (C4a (m)), 134.6 (C4a (s)); 165.3 (CO (s)), 165.5 (CO (m))

Yield: 69%

IRν_{max}(KBr): 834cm^{-1}, 1445cm^{-1}, 1656cm^{-1}, 2932cm^{-1}

Melting point: 56 - 60°C Literature: 63 - 64°C[28]

2-Bromo-1-(3,4-Dihydro-*1H*-isoquinolin-2-yl)-ethanone (178)[29]

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.90 (0.8H, t, J = 6Hz, C4$\underline{H}_2$ (s)), 3.00 (1.2H, t, J = 6Hz, C4$\underline{H}_2$ (m)); 3.76 (1.2H, t, J = 6Hz, C3$\underline{H}_2$ (m)), 3.86 (0.8H, t, J = 6Hz C3$\underline{H}_2$ (s)); 3.97 (1.2H, s, COC$\underline{H}_2$ (m)), 3.98 (0.8H, s, COC$\underline{H}_2$ (s)); 4.71 (0.8H, s, C1$\underline{H}_2$ (s)), 4.75 (1.2H, s, C1$\underline{H}_2$ (m)); 7.16 – 7.23 (4H, m, C5$\underline{H}$, C6$\underline{H}$, C7$\underline{H}$, C8$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 26.1 (C$\underline{H}_2$Br (m)), 26.3 (C$\underline{H}_2$Br (s)); 28.2 (C4$\underline{H}_2$ (s)), 29.3 (C4$\underline{H}_2$ (m)); 40.4 (C3$\underline{H}_2$ (s)), 44.2 (C3$\underline{H}_2$ (m)), 44.7 (C1$\underline{H}_2$ (s)), 48.2 (C1$\underline{H}_2$ (m)); 126.0,126.47, 126.54, 126.6, 126.7, 127.1 (C5H, C6H, C7H); 128.3 (C8H (m)); 128.8 (C8H(s)); 131.9 (C8a (s)), 132.5 (C8a (m)); 133.6 (C4a (m)), 134.6 (C4a (s)); 165.5 (CO (s)), 165.6 (CO (m))

Yield: 68%

IRν_{max}(film): 651cm^{-1} (C-Br), 1439cm^{-1}, 1634cm^{-1}(CO), 2928cm^{-1}(saturated ring CH), 3156cm^{-1}(aromatic CH)

2-[4-(3-Chloro-phenyl)-piperazin-1-yl]-1-(3,4-dihydro-*1H*-isoquinolin-2-yl)-ethanone (181)

Synthesised by method 2, stirring at 60°C for 2 hours.

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.67 – 2.71 (4H, m, CH_2 of ring); 2.87 – 2.90 (0.8H, m, C4H_2 (s)), 2.93 – 2.96 (1.2, m, C4H_2 (m)); 3.17 (2H, t, J = 5Hz, CH_2 of ring); 3.22 (2H, t, J = 5Hz, CH_2 of ring); 3.35 (2H, s, COCH_2); 3.81 – 3.87 (2H, m, C3H_2); 4.77 (1.2H, s, C1H_2 (m)), 4.79 (0.8H, s, C1H_2 (s)); 6.75 – 6.83 (2H, m, C2'H, C4'H); 6.85 – 6.89 (1H, m, C6'H); 7.10 – 7.24 (5H, m, C5H, C6H, C7H, C8H, C5'H)

^{13}C-NMR (101MHz):

28.2 (C4H_2 (s)), 29.5 (C4H_2 (m)); 40.0 (C3H_2 (s)), 43.2 (C3H_2 (m)), 44.3 (C1H_2 (m)), 47.1 (C1H_2 (s)); 48.4, 48.5 (CH_2 in ring); 52.9 (CH_2 in ring); 61.2 (COCH_2 (s)), 61.5 (COCH_2 (m)); 113.75, 113.79 (C2'H); 115.6 (C6'H); 119.10, 119.19 (C4'H); 125.9 (C3'Cl); 126.2, 126.4, 126.5, 126.8 (C5H, C6H, C7H); 128.4 (C8H (m)), 128.8 (C8H (s)); 129.9 (C5'H); 132.9 (C8a (s)), 133.0 (C8a (m)); 133.9 (C4a (s)), 134.7 (C4a (m)); 152.1 (C1'); 167.9 (CO (s)), 168.2 (CO (m))

Yield: 54%

IRν_{max}(film): 1422cm^{-1}, 1643cm^{-1}(CO), 2987cm^{-1}(saturated ring CH), 3055cm^{-1}(aromatic CH)

HRMS calcd. for C21H25N3OCl (M^++1): 370.1686 Found: 370.1681

2-[4-(4-Chloro-phenyl)-piperazin-1-yl]-1-(3,4-dihydro-*1H*-isoquinolin-2-yl)-ethanone (182)

Synthesised by method 2, stirring at 60°C for 2 hours.

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.68 – 2.70 (4H, m, CH_2 of ring); 2.80 (2H, m, C4H_2); 3.12 (2H, t, J = 5Hz, CH_2 of ring); 3.17 (2H, t, J = 5Hz, CH_2 of ring); 3.33 (2H, s, COCH_2); 3.80 – 3.85 (2H, m, C3H_2); 4.75 (1.2H, s, C1H_2 (m)), 4.78 (0.8H, s, C1H_2 (s)); 6.79 – 6.84 (2H, m, C2'H, C6'H); 7.14 – 7.19 (6H, m, C5H, C6H, C7H, C8H, C3'H, C5'H)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 28.2 (C4H_2 (s)), 29.5 (C4H_2 (m)); 40.0 (C3H_2 (s)), 43.2 (C3H_2 (m)), 44.2 (C1H_2 (m)), 47.0 (C1H_2 (s)); 48.8, 48.9 (CH_2 in ring); 52.9 (CH_2 in ring); 61.2 (COCH_2 (s)), 61.5 (COCH_2 (m)); 117.0 (C2'H, C6'H); 124.2 (C4'Cl (s)), 124.3 (C4'Cl (m)); 125.9, 126.2, 126.3, 126.5, 126.7, 128.3 (C5H, C6H, C7H, C8H); 128.7 (C3'H, C5'H); 132.9 (C8a (s)), 133.0 (C8a (m)); 133.9 (C4a (m)), 134.7 (C4a (s)); 149.6 (C1'); 167.9 (CO (s)), 168.2 (CO (m))

Yield: 44%

IRν_{max}(film): 1497cm^{-1}, 1644cm^{-1}(CO), 2827cm^{-1}(saturated ring CH), 3401cm^{-1}(aromatic CH)

HRMS calcd. for C21H25N3OCl (M^++1): 370.1686 Found: 370.1691

1-(3,4-Dihydro-*1H*-2-yl)-2-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone (183)

Synthesised by method 1 in very low yield.

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.73 (4H, m, CH_2 of ring); 2.89 (0.8H, t, J = 6Hz, C4H_2 (s)), 2.95 (1.2H, t, J = 6Hz, C4H_2 (m)); 3.12 (2H, t, J = 5Hz, CH_2 of ring); 3.17 (2H, t, J = 5Hz, CH_2 of ring); 3.37 (2H, s, COCH_2); 3.82 – 3.86 (2H, m, C3H_2); 4.77 (1.2H, s, C1H_2 (m)), 4.81 (0.8H, s, C1H_2 (s)); 6.85 – 6.91 (2H, m, C2'H, C6'H); 6.95 – 7.00 (2H, m, C3'H, C5'H); 7.11 – 7.17 (4H, m, C5H, C6H, C7H, C8H)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 28.4 (C4H_2 (s)), 29.6 (C4H_2 (m)); 40.1 (C3H_2 (s)), 43.3 (C3H_2 (m)), 44.4 (C1H_2 (m)), 47.2 (C1H_2 (s)); 50.0, 50.1 (CH_2 in ring); 53.2 (CH_2 in ring); 61.5 (COCH_2 (s)), 61.6 (COCH_2 (m)); 115.4, 115.6 (C2'H, C6'H); 117.8 (C3'H, C5'H); 126.0, 126.3, 126.5, 126.7, 126.9 (C5H, C6H, C7H); 128.5 (C8H (m)), 128.9 (C8H (s)); 133.2 (C8a); 134.0 (C4A); 147.79, 147.82 (C1', C4'F); 168.4 (CO)

^{19}F-NMR (376MHz): ppm($CDCl_3$): -124.95 (m), -125.01 (m)

Yield: 8%

IRν_{max}(film): 1265cm^{-1}(CF), 1668cm^{-1}(CO), 2987cm^{-1}(saturated ring CH), 3055cm^{-1}(aromatic CH)

HRMS calcd. for C21H25N3OF (M^++1): 354.1982 Found: 354.1979

2-(4-Benzo[1,3]dioxol-5-ylmethyl-piperazin-1-yl)-1-(3,4-dihydro-*1H*-isoquinolin-2-yl)-ethanone (184)

Finally produced using method 2, stirring at 60°C for 48 hours.

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.46 – 2.54 (8H, m, C$\underline{H}_2$ of ring); 2.83 (0.8H, t, J = 6Hz, C4$\underline{H}_2$ (s)), 2.91 (1.2, t, J = 6Hz, C4$\underline{H}_2$ (m)); 3.26 (2H, s, NC$\underline{H}_2$); 3.38 (0.8H, s, COC$\underline{H}_2$), 3.40 (1.2H, s, COC$\underline{H}_2$); 3.76 – 3.81 (2H, m, C3$\underline{H}_2$); 4.71 (1.2H, s, C1$\underline{H}_2$ (m)), 4.75 (0.8H, s, C1$\underline{H}_2$ (s)); 5.90 (2H, s, OC$\underline{H}_2$O); 6.72 (C2'$\underline{H}$, C5'$\underline{H}$); 6.83 (1H, C6'$\underline{H}$); 7.09 – 7.12 (4H, m, C5$\underline{H}$, C6$\underline{H}$, C7$\underline{H}$, C8$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 28.2 (C$\underline{H}_2$ (s)), 29.4 (C$\underline{H}_2$ (m)); 39.9 (C$\underline{H}_2$ (s)), 43.0 (C$\underline{H}_2$ (m)), 44.1 (C$\underline{H}_2$ (m)), 46.9 (C$\underline{H}_2$ (s)); 52.5, 52.6 (C$\underline{H}_2$ in ring); 52.9 (C$\underline{H}_2$ in ring); 61.2 (CO$\underline{C}H_2$ (s)), 61.5 (CO$\underline{C}H_2$ (m)); 62.38 (N$\underline{C}H_2$(s)), 62.4 (N$\underline{C}H_2$ (m)); 100.6 (O$\underline{C}H_2$O); 107.6 (C5'H); 109.2 (C2'H); 122.0 (C6'H); 125.8, 126.0, 126.2, 126.4, 126.5 (C5H, C6H, C7H); 128.3 (C8H (m)), 128.6 (C8H (s)); 131.60 (C1' (s)), 131.66 (C1' (m)); 132.9 (C8a (m)), 133.0 (C8a (s)); 133.9 (C4a (m)), 134.6 (C4a (s)); 146.3, 147.4 (C3'OCH$_2$OC4'); 168.2 (CO (s)), 168.4 (CO (m))

Yield: 33%

IRν_{max}(film): 1490cm^{-1}, 1640cm^{-1}(CO), 2986cm^{-1}(saturated ring CH), 3055cm^{-1}(aromatic CH)

HRMS calcd. for C23H28N3O3 (M^++1): 394.2131 Found: 394.2144

1-(3,4-Dihydro-*1H*-isoquinolin-2-yl)-2-{4-[2-(3,4-dihydro-1H-isoquinolin-2-yl)-2-oxo-ethyl]-piperazin-1-yl}-ethanone (185)

Synthesised using method 1.

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.39 – 2.51 (8H, m, C$\underline{H}_2$ of ring, N$\underline{H}$); 2.80 (4H, m, C4$\underline{H}_2$); 3.13 – 3.17 (4H, m, COC$\underline{H}_2$); 3.69 (4H, t, J = 5.5Hz, C3$\underline{H}_2$); 4.60 (2.4H, s, C1$\underline{H}_2$ (m)), 4.66 (1.6H, s, C1$\underline{H}_2$ (s)); 7.04 – 7.09 (8H, m, C5$\underline{H}$, C6$\underline{H}$, C7$\underline{H}$, C8$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 28.0 (C$\underline{H}_2$, C4'$\underline{H}_2$(s)), 29.3 (C$\underline{H}_2$, C4'$\underline{H}_2$ (m)); 39.8 (C$\underline{H}_2$, C3'$\underline{H}_2$ (s)), 43.0 (C$\underline{H}_2$, C3'$\underline{H}_2$ (m)), 44.0 (C$\underline{H}_2$, C1'$\underline{H}_2$ (m)), 46.9 (C$\underline{H}_2$, C1'$\underline{H}_2$ (s)); 52.6 (C$\underline{H}_2$ in piperazine ring (s)), 52.7 (C$\underline{H}_2$ in piperazine ring (m)); 61.1 (CO$\underline{C}H_2$, C'$\underline{H}_2$CO (s)), 61.4 (CO$\underline{C}H_2$, C'$\underline{H}_2$CO (m)); 125.8, 126.0, 126.1, 126.1, 126.3, 126.5 (C5H, C6H, C7H, C5'H, C6'H, C7'H); 128.2 (C8H, C8'H (m)); 128.5 (C8H, C8'H (s)); 132.8 (C8a, C8'a); 133.8 (C4a, C4'a); 168.0 (CO, C'O (s)), 168.3 (CO, C'O (m))

Yield: 36%

IRν_{max}(film): 1490cm^{-1}, 1640cm^{-1}(CO), 2986cm^{-1}(saturated ring CH), 3055cm^{-1}(aromatic CH)

Melting point: 160°C

HRMS calcd. for C26H33N4O2 (M^++1): 433.2604 Found: 433.2604

3.2.2 Dimethoxy amides

2-Chloro-1-(6,7-dimethoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-ethanone (186)

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.79 (0.8H, t, J = 6Hz, C4$\underline{H}_2$ (s)), 2.88 (1.2H, t, J = 6Hz, C4$\underline{H}_2$ (m)); 3.72 (1.2H, t, J = 6Hz, C3$\underline{H}_2$ (m)), 3.81 (0.8H, t, J = 6Hz, C3$\underline{H}_2$ (s)); 3.84 (2H, s, C7OC$\underline{H}_3$, C6OC$\underline{H}_3$ (s)), 3.847

(2H, s, C7OC$\underline{H}_3$ (m)), 3.85 (2H, s, C6OC$\underline{H}_3$ (m)); 4.15 (1.2H, s, COC$\underline{H}_2$ (m)), 4.17 (0.8H, s, COC$\underline{H}_2$ (s)); 4.61 (0.8H, s, C1$\underline{H}_2$ (s)), 4.65 (1.2H, s, C1$\underline{H}_2$ (m)); 6.60 – 6.63 (2H, m, C5$\underline{H}$, C8$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 27.6 (C$\underline{H}_2$ (s)), 28.7 (C$\underline{H}_2$ (m)); 40.37 (C$\underline{H}_2$ (s)), 41.1 (C$\underline{H}_2$ (m)); 41.3 (C$\underline{H}_2$ (s)), 43.8 (C$\underline{H}_2$ (m)); 44.3 (C$\underline{O}$ (m)), 47.4 (C$\underline{O}$ (s)); 55.8 (C7OC$\underline{H}_3$, C6OC$\underline{H}_3$ (m)), 55.9 (C7OC$\underline{H}_3$, C6OC$\underline{H}_3$ (s)); 108.6 (C$\underline{8}$H (s)), 109.1 (C$\underline{8}$H (m)); 111.0 (C$\underline{5}$H (m)), 111.4 (C$\underline{5}$H (s)); 123.4 (C$\underline{8}$a(s)), 124.2 (C$\underline{8}$a (m)); 125.3 (C$\underline{4}$a (m)), 126.4 (C$\underline{4}$a(s)); 147.6, 147.8, 147.9 (C$\underline{7}$OCH$_3$, C$\underline{6}$OCH$_3$ (m), (s)); 165.2 (C$\underline{O}$ (s)), 165.4 (C$\underline{O}$ (m))

Yield: 56%

IRν_{max}(KBr): 760cm^{-1}(CCl), 1215cm^{-1}, 1650cm^{-1} (CO stretching), 3020cm^{-1}(Aromatic CH)

Melting point: 116 - 120°C Literature: 124°C[30]

1-(6,7-Dimethoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-{4-[2-(6,7-dimethoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-oxo-ethyl]-piperazin-1-yl}-ethanone (187)

Synthesised by method 1

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.35 – 2.53 (8H, m, C$\underline{H}_2$ *4 piperazine ring); 2.74 (1.6H, bs, C4$\underline{H}_2$ (s)); 2.81 (2.4H, bs, C4$\underline{H}_2$ (m)); 3.22 (1.6H, s, COC$\underline{H}_2$ (s)), 3.25 (2.4H, s, COC$\underline{H}_2$ (m)); 3.74 – 3.77 (4H, m, C3$\underline{H}_2$); 3.82 – 3.85 (12H, m, C6OC$\underline{H}_3$, C7OC$\underline{H}_3$); 4.61 (2.4H, s, C1$\underline{H}_2$ (m)), 4.66 (1.6H, s, C1$\underline{H}_2$ (s)); 6.58 – 6.60 (4H, m, C5$\underline{H}$, C8$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 27.8 (C$\underline{H}_2$ (s)), 29.0 (C$\underline{H}_2$ (m)); 40.0 (C$\underline{H}_2$ (s)), 43.3 (C$\underline{H}_2$ (m)), 43.9 (C$\underline{H}_2$ (m)), 46.8 (C$\underline{H}_2$ (s)); 52.9 (C$\underline{H}_2$ in piperazine ring); 55.8 (C7OC$\underline{H}_3$, C6OC$\underline{H}_3$ (m)), 55.9 (C7OC$\underline{H}_3$, C6OC$\underline{H}_3$ (s)); 61.3 (COC$\underline{H}_2$ (s)), 61.7 (COC$\underline{H}_2$ (m)); 108.7 (C$\underline{8}$H (s)), 109.1 (C$\underline{8}$H (m)); 111.1 (C$\underline{5}$H (m)), 111.4 (C$\underline{5}$H (s)); 124.6 (C$\underline{8}$a (s)), 124.8 (C$\underline{8}$a (m)); 125.7 (C$\underline{4}$a (m)), 126.5 (C$\underline{4}$a (s)); 147.5 (C$\underline{7}$OCH$_3$ (m), C$\underline{6}$OCH$_3$ (m)); 147.6 (C$\underline{7}$OCH$_3$ (s), C$\underline{6}$OCH$_3$ (s)); 168.1 (C$\underline{O}$ (s)), 168.4 (C$\underline{O}$ (m))

Yield: 15%

IRν_{max}(film): 1422cm^{-1}, 1638cm^{-1}(CO), 2987cm^{-1}(saturated ring CH), 3055cm^{-1}(aromatic CH)

Melting point: 190°C

HRMS calcd. for C30H41N4O6(M^++1): 553.3026 Found: 553.3028

2-[4-(3-Chloro-phenyl)-piperazin-1-yl]-1-(6,7-dimethoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-ethanone (190)

Synthesised via method 3, refluxing for 7 hours.

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.62 – 2.64 (4H, m, C$\underline{H}_2$ *4 piperazine ring); 2.74 (0.8H, t, J = 6Hz, C4$\underline{H}_2$ (s)); 2.81 (1.2H, t, J = 6Hz, C4$\underline{H}_2$ (m)); 3.12 – 3.17 (4H, m, C$\underline{H}_2$ in piperazine ring); 3.29 (2H, s, COC$\underline{H}_2$); 3.74 – 3.78 (2H, m, C3$\underline{H}_2$); 3.80 (6H, S, C6OC$\underline{H}_3$, C7OC$\underline{H}_3$); 4.62 (1.2H, s, C1$\underline{H}_2$ (m)), 4.66 (0.8H, s, C1$\underline{H}_2$ (s)); 6.55 – 6.60 (2H, m, C5$\underline{H}$, C8$\underline{H}$); 6.70 – 6.75 (2H, m, C2'$\underline{H}$, C4'$\underline{H}$); 6.80 – 6.82 (C6'$\underline{H}$); 7.07 – 7.12 (C6'$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 27.7 (C$\underline{H}_2$ (s)), 29.0 (C$\underline{H}_2$ (m)); 39.9 (C$\underline{H}_2$ (s)), 43.3 (C$\underline{H}_2$ (m)), 43.8 (C$\underline{H}_2$ (m)), 46.7 (C$\underline{H}_2$ (s)); 48.4, 48.45, 52.8 (C$\underline{H}_2$ in piperazine ring); 55.7 (C7OC$\underline{H}_3$, C6OC$\underline{H}_3$ (m)), 55.77 (C7OC$\underline{H}_3$, C6OC$\underline{H}_3$ (s)); 61.1 (COC$\underline{H}_2$ (s)), 61.5 (COC$\underline{H}_2$ (m)); 108.7 (C$\underline{8}$H (s)), 109.1 (C$\underline{8}$H (m)); 111.1 (C$\underline{5}$H (m)), 111.4 (C$\underline{5}$H (s)); 113.67 (C$\underline{2}$'H (s)), 113.73 (C$\underline{2}$'H (m)); 115.5 (C$\underline{6}$'H); 119.0 (C$\underline{4}$'H (s)); 119.1 (C$\underline{4}$'H (m)); 124.4 (C$\underline{8}$a (s)), 124.8 (C$\underline{8}$a (m)); 125.6 (C$\underline{4}$a (m)), 126.5 (C$\underline{4}$a (s)); 129.8 (C$\underline{5}$'H); 134.7

(C3'Cl); 147.5 (C7OCH_3 (m), C6OCH_3 (m)); 147.6 (C7OCH_3 (s), C6OCH_3 (s)); 152.0 (C1'); 167.8 (CO (s)), 168.0 (CO (m))

Yield: 85%

IRν_{max}(film): 1422cm^{-1}, 1656cm^{-1}(CO), 2987cm^{-1}(saturated ring CH), 3055cm^{-1}(aromatic CH)

HRMS calcd. for C23H29N3O3Cl (M^++1): 430.1897 Found: 430.1909

2-[4-(4-Chloro-phenyl)-piperazin-1-yl]-1-(6,7-dimethoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-ethanone (191)

Manufactured using method 1.

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.62 (4H, bs, CH_2 *4 piperazine ring); 2.73 (0.8H, t, J = 6Hz, C4H_2 (s)); 2.80 (1.2H, t, J = 6Hz, C4H_2 (m)); 3.08 – 3.11 (4H, m, CH_2 in piperazine ring); 3.27 (2H, s, COCH_2); 3.72 – 3.75 (2H, m, C3H_2); 3.78 – 3.79 (6H, m, C6OCH_3, C7OCH_3); 4.61 (1.2H, s, C1H_2 (m)), 4.64 (0.8H, s, C1H_2 (s)); 6.54 – 6.58 (2H, m, C5H, C8H); 6.72 – 6.77 (2H, m, C2'H, C6'H); 7.09 – 7.14 (2H, m, C3'H, C5'H)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 27.6 (C4H_2 (s)), 28.8 (C4H_2 (m)); 39.7 (C3H_2 (s)), 43.1 (C3H_2 (m)), 43.6 (C1H_2 (m)), 46.5 (C1H_2 (s)); 48.6, 48.7, 52.7 (CH_2 in piperazine ring); 55.55 (C7OCH_3, C6OCH_3 (m)), 55.6 (C7OCH_3, C6OCH_3 (s)); 60.9 (COCH_2 (s)), 61.2 (COCH_2 (m)); 108.6 (C8H (s)), 108.9 (C8H (m)); 110.9 (C5H (m)), 111.2 (C5H (s)); 116.8 (C2'H, C6'H (m)), 117.5 (C2'H, C6'H (s)); 124.0 (C8a (s)); 124.2 (C4'Cl); 124.6 (C8a (m)); 125.4 (C4a (m)), 126.3 (C4a (s)); 128.5 (C3'H, C5'H (m)), 128.6 (C3'H, C5'H (s)); 147.3 (C7OCH_3 (m), C6OCH_3 (m)); 147.4 (C7OCH_3 (s), C6OCH_3 (s)); 149.4 (C1'); 167.7 (CO (s)), 167.9 (CO (m))

Yield: 59%

IRν_{max}(film): 1497cm^{-1}, 1672cm^{-1}(CO), 2987cm^{-1}(saturated ring CH), 3055cm^{-1}(aromatic CH)

HRMS calcd. for C23H29N3O3Cl (M^++1): 430.1897 Found: 430.1892

1-(6,7-Dimethoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone (192)

Synthesised using method 1.

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.68 (4H, bs, CH_2 *4 piperazine ring); 2.77 (0.8H, t, J = 5Hz, C4H_2 (s)); 2.84 (1.2H, t, J = 5Hz, C4H_2 (m)); 3.08 – 3.13 (4H, m, CH_2 in piperazine ring); 3.32 (2H, s, COCH_2); 3.77 – 3.80 (2H, m, C3H_2); 3.83 – 3.84 (6H, m, C6OCH_3, C7OCH_3); 4.65 (1.2H, s, C1H_2 (m)), 4.69 (0.8H, s, C1H_2 (s)); 6.58 – 6.62 (2H, m, C5H, C8H); 6.81 – 6.87 (2H, m, C2'H, C6'H); 6.90 – 6.95 (2H, m, C3'H, C5'H)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 27.8 (C4H_2 (s)), 29.0 (C4H_2 (m)); 39.9 (C3H_2 (s)), 43.3 (C3H_2 (m)), 43.9 (C1H_2 (m)), 46.7 (C1H_2 (s)); 49.8, 49.9, 52.97, 53.0 (CH_2 in piperazine ring); 55.55 (C7OCH_3, C6OCH_3 (m)), 55.6 (C7OCH_3, C6OCH_3 (s)); 61.1 (COCH_2 (s)), 61.5 (COCH_2 (m)); 108.7 (C8H (s)), 109.1 (C8H (m)); 111.1 (C5H (m)), 111.4 (C5H (s)); 115.2 (C2'H, C6'H (m)), 115.4 (C2'H, C6'H (s)); 117.6 (C3'H, C5'H (m)), 117.7 (C3'H, C5'H (s)); 124.4 (C8a (s)); 124.8 (C8a (m)); 125.6 (C4a (m)), 126.5 (C4a (s)); 128.5 (C3'H, C5'H (m)), 128.6 (C3'H, C5'H (s)); 147.4 (C7OCH_3 (m)), 147.6 (C7OCH_3 (s)); 147.63 (C6OCH_3 (s)), 147.7 (C6OCH_3 (m)); 155.7 (C1'); 158.1 (C4'F); 167.8 (CO (s)), 168.1 (CO (m))

Yield: 45%

IRν_{max}(film): 1422cm^{-1}, 1640cm^{-1}(CO), 2987cm^{-1}(saturated ring CH), 3055cm^{-1}(aromatic CH)

HRMS calcd. for C23H29N3O3F (M^++1): 414.2195 Found: 414.2193

2-(4-Benzo[1,3]dioxol-5-ylmethylo-piperazin-1-yl)-1-(6,7-dimethoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-ethanone (193)

Produced using method 1.

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.42 - 2.54 (8H, m, C$\underline{H}_2$ *4 piperazine ring); 2.76 (0.8H, t, J = 5.5Hz, C4$\underline{H}_2$); 2.84 (1.2H, t, J = 5.5Hz, C4$\underline{H}_2$); 3.26 (2H, s, COC$\underline{H}_2$); 3.39 (0.8H, s, NC$\underline{H}_2$ (s)); 3.41 (1.2H, s, NC$\underline{H}_2$ (m)); 3.76 – 3.79 (2H, m, C3$\underline{H}_2$); 3.86, 3.87 (6H, s, s, C6OC$\underline{H}_3$, C7OC$\underline{H}_3$); 4.64 (1.2H, s, C1$\underline{H}_2$ (m)), 4.68 (0.8H, s, C1$\underline{H}_2$ (s)); 5.93 (2H, s, OC$\underline{H}_2$O); 6.58 – 6.63 (2H, s,s, C5$\underline{H}$, C8$\underline{H}$); 6.73 (2H, s, C2'$\underline{H}$, C6'$\underline{H}$); 6.83 (1H, s, C5'$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 27.8 (C$\underline{H}_2$ (s)), 29.0 (C$\underline{H}_2$ (m)); 40.0 (C$\underline{H}_2$ (s)), 43.3 (C$\underline{H}_2$ (m)); 43.9 (C$\underline{H}_2$ (m)), 46.8 (C$\underline{H}_2$ (s)); 52.7, 52.8, 53.0 (C$\underline{H}_2$ *4 piperazine ring); 55.8 (C6OC$\underline{H}_3$, C7OC$\underline{H}_3$ (m)), 55.9 (C6OC$\underline{H}_3$, C7OC$\underline{H}_3$ (s)); 60.3 (COC$\underline{H}_2$ (s)); 61.3 (NC$\underline{H}_2$ (s)); 61.6 (COC$\underline{H}_2$ (m)); 62.6 (NC$\underline{H}_2$ (m)); 100.8 (OC$\underline{H}_2$O); 107.7 (C5'H); 108.8 (C8H (s)), 109.2 (C8H (m)); 109.4 (C2'H); 111.1 (C5H (m)), 111.4 (C5H (s)); 122.1 (C6'H); 124.7 (C8a (s)), 124.9 (C8a (m)); 125.7 (C4a (m)), 126.6 (C4a (s)); 131.75 (C1' (s)), 131.8 (C1' (m)); 146.5, 147.7 (C3'OCH$_2$OC4'); 147.5 (C6OCH$_3$, C7OCH$_3$); 168.2 (CO (s)), 168.5 (CO (m))

Yield: 50%

IRν_{max}(film): 1490cm^{-1}, 1640cm^{-1}(CO), 2986cm^{-1}(saturated ring CH), 3055cm^{-1}(aromatic CH)

HRMS calcd. for C25H32N3O5 (M^++1): 454.2342 Found: 454.2350

Phenyl amides

2-Chloro-1-(6,7-dimethoxy-1-phenyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-ethanone (194)

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.80 (1H, d, J = 16Hz, C4$\underline{H}_2$); 3.07 – 3.15 (1H, m, C4C$\underline{H}_2$); 3.47 (1H, dt, J_1 = 12Hz, J_2 = 4.1Hz, C3$\underline{H}_2$); 3.76 (4H, overlapping singlet and probably a multiplet, C7OC$\underline{H}_3$, C3$\underline{H}_2$); 3.91 (3H, s, C6OC$\underline{H}_3$); 4.15 (2H, q, J = 12.3Hz, C$\underline{H}_2$Cl); 6.52 (1H, s, C8$\underline{H}$); 6.69 (1H, s, C5$\underline{H}$); 6.82 (1H, s, C1$\underline{H}$); 7.24 – 7.32 (5H, m, C2'$\underline{H}$, C3'$\underline{H}$, C4'$\underline{H}$, C5'$\underline{H}$, C6'$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 28.5 (C$\underline{H}_2$); 39.9 (C$\underline{H}_2$); 41.4 (C$\underline{H}_2$Cl); 55.2 (C1C$\underline{H}$); 55.8, 55.9 (C6OC$\underline{H}_3$, C7OC$\underline{H}_3$); 110.9 (C8H); 111.0 (C5H); 125.9, 126.1 (C8a, C4a); 127.6 (C4'H); 128.3 (C2'H, C6'H); 128.8 (C3'H, C5'H); 141.8 (C1'); 147.6 (C7OCH$_3$); 148.1 (C6OCH$_3$); 165.0 (CO)

Yield: 67%

IRν_{max}(KBr): 1020cm^{-1}, 1246cm^{-1} (asymmetric COC stretching), 1645cm^{-1} (CO stretching), 2935cm^{-1} (aliphatic CH stretching), 3448cm^{-1} (aromatic CH stretching)

Melting point: 216 - 220°C Literature: 220 - 221°C[27]

2-Bromo-1-(6,7-dimethoxy-1-phenyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-ethanone (195)

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.78 (1H, d, J = 16Hz, C4$\underline{H}_2$); 3.09 – 3.18 (1H, m, C4C$\underline{H}_2$); 3.46 (1H, dt, J_1 = 12.5Hz, J_2 = 4.1Hz, C3$\underline{H}_2$); 3.76 (4H, overlapping singlet and probably a multiplet, C7OC$\underline{H}_3$, C3$\underline{H}_2$); 3.89, 3.91 – 3.97 (5H, overlapping quartet and singlet, C$\underline{H}_2$Br, C6OC$\underline{H}_3$); 6.52 (1H, s, C8$\underline{H}$); 6.69 (1H, s, C5$\underline{H}$); 6.81 (1H, s, C1$\underline{H}$); 7.22 – 7.30 (5H, m, C2'$\underline{H}$, C3'$\underline{H}$, C4'$\underline{H}$, C5'$\underline{H}$, C6'$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 26.3 (C$\underline{H}_2$Br); 28.4 (C$\underline{H}_2$); 40.4 (C$\underline{H}_2$); 55.1 (C1C$\underline{H}$); 55.85, 55.91 (C6OC$\underline{H}_3$, C7OC$\underline{H}_3$); 110.9 (C5H); 111.1 (C8H); 126.0, 126.1 (C4a, C8a); 127.6 (C4'H); 128.3 (C2'H, C6'H); 128.7 (C3'H, C5'H); 141.8 (C1'); 147.6 (C7OCH$_3$); 148.2 (C6OCH$_3$); 165.2 (CO)

Yield: 92%

IRν_{max}(KBr): 702cm^{-1}(CBr), 1642cm^{-1}(CO), 2934cm^{-1}(saturated ring CH), 3448cm^{-1}(aromatic ring CH)

HRMS calcd. for C19H20NO3NaBr (M^++23): 412.0524 Found: 412.0540

1-(6,7-Dimethoxy-1-phenyl-3, 4-dihydro-*1H*-isoquinolin-2-yl)-2-{4-[2-(6,7-dimethoxy-1-phenyl-3, 4-dihydro-*1H*-isoquinolin-2-yl)-2-oxo-ethyl]-piperazin-1-yl}-ethanone (196)

Produced using method 4, with stirring at 60°C for 6 days. It was purified by column chromatography (1:9 ethyl acetate: hexane increasing to 100% ethyl acetate, then 2:3 methanol: ethyl acetate).

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.52 (8H, m, C$\underline{H}_2$ *4 piperazine ring); 2.74 (2H, d, J = 16Hz, C4$\underline{H}_2$, C4"$\underline{H}_2$); 3.02 – 3.10 (2H, m, C4$\underline{H}_2$, C4"$\underline{H}_2$); 3.17 (2H, dd, J_1 = 13Hz, J_2 = 2 Hz, COC$\underline{H}_2$, COC"$\underline{H}_2$ (m)); 3.26 – 3.30 (4H, m, COC$\underline{H}_2$, NC"$\underline{H}_2$CO; C3$\underline{H}_2$); 3.76, 3.85, 3.92 (12H, s, s, s, C7OC$\underline{H}_3$, C6OC$\underline{H}_3$, C7"OC$\underline{H}_3$, C6"OC$\underline{H}_3$); 3.96 (2H, d, J = 12Hz, C3$\underline{H}_2$, C3"$\underline{H}_2$ (m)); 6.51 (2H, s, C8$\underline{H}$, C8"$\underline{H}$); 6.68 (2H, s, C5$\underline{H}$, C5"$\underline{H}$); 6.83 (2H, s, C1$\underline{H}$, C1"$\underline{H}$); 7.24 (10H, m, C2'$\underline{H}$, C3'$\underline{H}$, C4'$\underline{H}$, C5'$\underline{H}$, C6'$\underline{H}$, C2"'$\underline{H}$, C3"'$\underline{H}$, C4"'$\underline{H}$, C5"'$\underline{H}$, C6"'$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 28.9 (C$\underline{4}H_2$, C$\underline{4}$"H_2); 39.2(C$\underline{3}H_2$, C$\underline{3}$"H_2); 53.0 (C$\underline{H}_2$ *4 piperazine ring); 54.6 (C$\underline{1}$H, C$\underline{1}$"H); 55.8 (C7OC$\underline{H}_3$, C7"OC$\underline{H}_3$); 55.9 (C6OC$\underline{H}_3$, C6"OC$\underline{H}_3$); 61.9 (COC$\underline{H}_2$N, NC"H_2C"O); 110.9 (C$\underline{8}$H, C$\underline{8}$"H); 111.1 (C$\underline{5}$H, C$\underline{5}$"H); 126.4 (C$\underline{8}$a, C$\underline{8}$"a, C$\underline{4}$a, C$\underline{4}$"a); 127.3 (C$\underline{4}$'H, C$\underline{4}$"'H); 128.1 (C$\underline{3}$'H, C$\underline{5}$'H, C$\underline{3}$"'H, C$\underline{5}$"'H); 128.9 (C$\underline{2}$'H, C$\underline{6}$'H, C$\underline{2}$"'H, C$\underline{6}$"'H); 142.5 (C$\underline{1}$', C$\underline{1}$"'); 147.5 (C$\underline{6}$OCH$_3$, C$\underline{6}$"OCH$_3$); 148.0 (C$\underline{7}$OCH$_3$, C$\underline{7}$"OCH$_3$); 168.8, 168.9 (C$\underline{O}$)

Yield: 9.5%

IRν_{max}(film): 1442cm^{-1}, 1636cm^{-1}(CO), 2986cm^{-1}(saturated ring CH), 3055cm^{-1}(aromatic CH)

Melting point: 126°C

HRMS calcd. for C42H49N4O6 (M^++1): 705.3652 Found: 705.3652

2-[4-(3-Chloro-phenyl)-piperazin-1-yl]-1-(6,7-dimethoxy-1-phenyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-ethanone (199)

Synthesised using method 2, with stirring at 60°C for 24 hours.

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.67 (4H, m, C$\underline{H}_2$ *4 piperazine ring); 2.76 (1H, dd, J_1 = 16Hz, J_2 = 2Hz, C4$\underline{H}_2$); 3.04 – 3.11 (1H, m, C4C$\underline{H}_2$); 3.19 – 3.21 (4H, m, C$\underline{H}_2$ piperazine ring); 3.25, 3.28 (0.8H, s, s, COC$\underline{H}_2$); 3.35 - 3.39 (2H, m, COC$\underline{H}_2$, C3$\underline{H}_2$); 3.76 (3H, s, C7OC$\underline{H}_3$); 3.90 (3H, s, C6OC$\underline{H}_3$); 3.96 (0.8H, dd, J_1 = 15Hz, J_2 = 5Hz, C3$\underline{H}_2$); 4.30 – 4.34 (0.2H, m, C3$\underline{H}_2$ (s)); 6.47 (0.2H, s, C1$\underline{H}$ (s)); 6.53 (0.8H, s, C8$\underline{H}$ (m)); 6.65 (0.2H, s, C8$\underline{H}$ (s)); 6.68 (0.8H, s, C5$\underline{H}$ (m)); 6.70 (0.2H, s, C5$\underline{H}$ (s)); 6.79 (1H, dd, J_1 = 19Hz, J_2 = 2Hz, C6"$\underline{H}$); 6.80 (0.8H, s, C1$\underline{H}$ (m)); 6.87 – 6.88 (2H, m, C2"$\underline{H}$, C4"$\underline{H}$); 7.16 (1H, t, J = 8Hz, C5"$\underline{H}$); 7.23 – 7.33 (5H, m, C2'$\underline{H}$, C3'$\underline{H}$, C4'$\underline{H}$, C5'$\underline{H}$, C6'$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 27.1 (C$\underline{4}H_2$ (s)), 28.8 (C$\underline{4}H_2$ (m)); 37.3 (C$\underline{3}H_2$ (s)), 39.2 (C$\underline{3}H_2$ (m)); 48.5, 52.9 (C$\underline{H}_2$ in piperazine ring); 54.6 (C$\underline{1}$H); 55.77, 55.83 (C6OC$\underline{H}_3$, C7OC$\underline{H}_3$); 61.6 (COC$\underline{H}_2$N (m)), 65.8 (COC$\underline{H}_2$N (s)); 110.9, 110.9 (C$\underline{5}$H); 111.1, 111.5 (C$\underline{8}$H); 113.8 (C$\underline{6}$''H); 115.6 (C$\underline{2}$''H); 119.2 (C$\underline{4}$''H); 126.3, 126.5 (C$\underline{4}$a, C$\underline{8}$a); 127.4 (C$\underline{4}$'H); 128.1 (C$\underline{2}$'H, C$\underline{6}$'H); 128.8 (C$\underline{3}$'H, C$\underline{5}$'H); 129.9 (C$\underline{5}$''H); 134.8 (C$\underline{3}$''Cl); 142.4 (C$\underline{1}$'); 147.5, 148.0 (C$\underline{7}$OCH$_3$, C$\underline{6}$OCH$_3$); 152.1 (C1''); 167.6 (C$\underline{O}$)

Yield: 64%

IRν_{max}(KBr): 1120cm^{-1}(aromatic C-Cl), 1638cm^{-1}(CO), 2826cm^{-1}(saturated ring CH), 3448cm^{-1} (aromatic CH)

HRMS calcd. for C29H33N3O3Cl (M^++1): 506.2210 Found: 506.2196

2-[4-(4-Chloro-phenyl)-piperazin-1-yl]-1-(6,7-dimethoxy-1-phenyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-ethanone (200)

Synthesised using method 2, with stirring at 60°C for 9 hours.

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.66 (4H, m, CH_2 in piperazine ring); 2.75 (1H, d, J = 16.4Hz, C4H_2); 3.04 – 3.10 (1H, m, C4CH_2); 3.15 (4H, m, CH_2 in piperazine ring); 3.24 – 3.27 (0.8H, s, s, COCH_2); 3.31 – 3.40 (2H, s, COCH_2, C3H_2); 3.56 – 3.61 (0.2H, m, C3H_2 (s)); 3.74 (3H, s, C7OCH_3); 3.88 (3H, s, C6OCH_3); 3.96 (0.8H, dd, J_1 = 13Hz, J_2 = 5Hz, C3H_2 (m)); 4.32 (0.2H, m, C3H_2 (s)); 6.48 (0.2H, C1H (s)); 6.52 (0.8H, s, C8H (m)); 6.65 (0.2H, s, C8H (s)); 6.68 (0.8H, s, C5H (m)); 6.70 (0.2H, s, C5H (s)); 6.82 (2H, d, J = 9Hz, C2''H, C6''H); 6.88 (0.8H, s, C1H (m)); 7.19 (2H, d, J = 9Hz, C3''H , C5''H); 7.25 – 7.28 (5H, m, C2'H, C3'H, C4'H, C5'H, C6'H)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 27.1 (C4H_2 (s)), 28.8 (C4H_2 (m)); 37.3 (C3H_2 (s)), 39.2 (C3H_2 (m)); 48.5, 52.9 (CH_2 in piperazine ring); 54.6 (C1CH); 55.78, 55.85 (C6OCH_3, C7OCH_3); 61.6 (COCH_2N (m)), 65.8 ((COCH_2N (s)); 110.9, 111.0 (C5H, C8H); 117.0 (C2''H, C6''H); 124.3 (C4''Cl); 126.3, 126.4 (C4a, C8a); 127.3 (C4'H); 128.0 (C2'H, C6'H); 128.7 (C3'H, C5'H, C3''H, C5''H); 142.3 (C1'); 147.3, 147.9 (C7OCH_3, C6OCH_3); 149.6 (C1''); 167.5 (CO)

Yield: 67%

IRν_{max}(KBr): 1119cm^{-1}(Aromatic C-Cl), 1640cm^{-1}(CO), 2937cm^{-1} (aliphatic CH), 3055cm^{-1}(aromatic CH)

HRMS calcd. for C29H33N3O3Cl (M^++1): 506.2210 Found: 506.2190

1-(6,7-Dimethoxy-1-phenyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone (201)

Synthesised using method 2, with stirring at 60°C for 24 hours.

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.66 (4H, m, CH_2 in piperazine ring); 2.74 (1H, d, J = 16Hz, C4H_2); 3.05 (1H, dd, J_1 = 12Hz, J_2 = 5Hz, C4CH_2); 3.11 (4H, m, CH_2 in piperazine ring); 3.26 (0.8H, s, s, COCH_2); 3.30 – 3.37 (2H, s, COCH_2, C3H_2); 3.55 – 3.60 (0.2H, m, C3H_2 (s)); 3.74 (3H, s, C7OCH_3); 3.88 (3H, s, C6OCH_3); 3.98 (0.8H, dd, J_1 = 14Hz, J_2 = 5Hz, C3H_2 (m)); 4.29 – 4.32 (0.2H, m, C3H_2 (s)); 6.49 (0.2H, s, C1H (s)); 6.51 (0.8H, s, C8H (m)); 6.64 (0.2H, s, C8H (s)); 6.67 (0.8H, s, C5H (m)); 6.68 (0.2H, s, C5H (s)); 6.85 - 6.87 (3H, m, C1H (m), C2''H, C6''H); 6.93 – 6.98 (2H, m, C3''H , C5''H); 7.24 – 7.28 (5H, m, C2'H, C3'H, C4'H, C5'H, C6'H)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 28.7 (C4H_2); 39.1 (C3H_2); 49.9, 53.1 (CH_2 *4 piperazine ring); 54.5 (C1CH); 55.7, 55.8 (C6OCH_3, C7OCH_3); 61.5 (COCH_2N); 110.8, 111.1 (C5H, C8H); 115.2, 115.4 (C2''H, C6''H); 117.5, 117.7 (C3''H, C5''H); 126.3, 126.4 (C4a, C8a); 127.1 (C4'H); 128.0 (C2'H, C6'H); 128.7 (C3'H, C5'H); 142.3 (C1'); 147.4, 147.6, 147.9 (C7OCH_3, C6OCH_3); 155.7 (C1''); 158.1(C4''F); 167.6 (CO)

^{19}F-NMR (376MHz): ppm($CDCl_3$): -124.82 (s), -124.96 (m)

Yield: 38%

IRν_{max}(KBr): 1251cm^{-1}(aryl C-F), 1642cm^{-1}(CO), 2824cm^{-1}(aliphatic CH), 3448cm^{-1} (aromatic CH)

HRMS calcd. for C29H33N3O3F (M^++1): 490.2506 Found: 490.2529

2-(4-Benzo[1,3]dioxol-5-ylmethyl-piperazin-1-yl)-1-(6,7-dimethoxy-1-phenyl-3,4-dihydro-*1H*--isoquinolin-2-yl)-ethanone (202)

Created using method 4, with stirring at 60°C over 7 days.

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.46 – 2.52 (8H, m, C$\underline{H}_2$ *4 piperazine ring); 2.74 (1H, d, J = 15Hz, C4$\underline{H}_2$); 3.06 – 3.10 (1H, m, C4$\underline{H}_2$); 3.17, 3.20 (1H, s, s, COC$\underline{H}_2$); 3.30 – 3.33 (2H, COC$\underline{H}_2$, C3$\underline{H}_2$); 3.40 (2H, s, NC$\underline{H}_2$C); 3.75 (3H, s, C7OC$\underline{H}_3$); 3.90 (3H, s, C6OC$\underline{H}_3$); 3.86-3.97 (0.8H, m, C3$\underline{H}_2$); 4.27 – 4.31 (0.2H, m, C3$\underline{H}_2$ (s)); 5.92 (OC$\underline{H}_2$O); 6.51 (1H, s, C8$\underline{H}$); 6.68 (1H, s, C5$\underline{H}$); 6.73 (2H, s, C2''$\underline{H}$, C6''$\underline{H}$); 6.84 (2H, s, C1$\underline{H}$, C5''$\underline{H}$); 7.25 (5H, m, C2'$\underline{H}$, C3'$\underline{H}$, C4'$\underline{H}$, C5'$\underline{H}$, C6'$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 28.7 (C$\underline{4}H_2$); 39.1 (C$\underline{3}H_2$); 52.7, 53.1, 53.3 (C$\underline{H}_2$ *4 piperazine ring); 54.5 (C$\underline{1}$H); 55.7, 55.8 (C6OC$\underline{H}_3$, C7OC$\underline{H}_3$); 61.7 (CO$\underline{C}H_2$), 62.5 (N$\underline{C}H_2$); 100.7 (CO$\underline{C}H_2$OC); 107.7 (C$\underline{5}$''H); 109.3 (C$\underline{2}$''H); 110.9 (C$\underline{5}$H); 111.1 (C$\underline{8}$H); 126.48, 126.53 (C$\underline{4}$a, C$\underline{8}$a); 127.2 (C4'H); 128.0 (C$\underline{2}$'H, C$\underline{6}$'H); 128.8 (C$\underline{3}$'H, C$\underline{5}$'H); 131.9 (C$\underline{1}$''); 142.5 (C$\underline{1}$'); 146.4, 147.4 (C$\underline{7}$OCH$_3$); 147.5 (C$\underline{6}$OCH$_3$); 167.9 (C$\underline{O}$)

Yield: 24%

IRν_{max}(KBr): 732cm^{-1}, 1661cm^{-1}(CO), 2816cm^{-1}(aliphatic CH), 2939cm^{-1}(aromatic CH)

HRMS calcd. for C31H36N3O5 (M^++1): 530.2655 Found: 530.2667

Benzyl amides

1-Benzyl-6,7-dimethoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-chloro-ethanone (203)

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.66 – 2.78 (1H, m, C4$\underline{H}_2$); 2.87 – 2.97 (1H, m, C4$\underline{H}_2$); 3.02 (0.6H, dd, J_1 = 13Hz, J_2 = 8.2Hz, C3$\underline{H}_2$ (m)); 3.19 (1H, dd, J_1 = 13Hz, J_2 = 6Hz, C1$\underline{H}_2$); 3.28 (0.4H, dt, J_1 = 12Hz, J_2 = 4.5Hz, C3$\underline{H}_2$ (s)); 3.38 (0.4H, d, J_1 = 12Hz, C1C$\underline{H}_2$); 3.49 (0.6H, d, J = 12Hz, C1C$\underline{H}_2$ (m)); 3.59 (1.8H, s, C7OC$\underline{H}_3$ (m)); 3.61 – 3.74 (0.6H, m, C3$\underline{H}_2$); 3.82 (1.2H, s, C7OC$\underline{H}_3$ (s)); 3.86 (1.8H, s, C6OC$\underline{H}_3$ (m)); 3.88 (1.2H, s, C6OC$\underline{H}_3$ (s)); 4.14 (2H, s, COC$\underline{H}_2$Cl); 4.76 (0.4H, dd, J_1 = 13Hz, J_2 = 4.5Hz, C3$\underline{H}_2$ (s)); 4.85 (0.4H, dd, J_1 = 9Hz, J_2 = 5Hz, C1$\underline{H}$ (s)), 5.61 (0.6H, dd, J_1 = 8Hz, J_2 = 5.5Hz, C1$\underline{H}$ (m)); 6.14 (0.6H, s, C8$\underline{H}$ (m)), 6.48 (0.4H, s, C8$\underline{H}$ (s)); 6.60 (0.6H, s, C5$\underline{H}$ (m)), 6.65 (0.4H, s, C5$\underline{H}$ (s)); 7.10 (1H, d, J = 6Hz, C4'$\underline{H}$); 7.19 – 7.36 (4H, C2'$\underline{H}$, C3'$\underline{H}$, C5'$\underline{H}$, C6'$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 27.6 (C$\underline{4}H_2$ (s)), 28.4 (C$\underline{4}H_2$ (m)); 35.9 (C$\underline{3}H_2$ (s)); 40.6 (C1C$\underline{H}_2$ (s)); 41.4 (C$\underline{3}H_2$ (m)); 41.44 (C1C$\underline{H}_2$ (m)); 42.0 (CO$\underline{C}H_2$Cl (m)), 43.0 (CO$\underline{C}H_2$Cl (s)); 54.7 (C$\underline{1}$H (m)); 55.5, 55.8 (C6O$\underline{C}H_3$, C7O$\underline{C}H_3$ (m)), 55.8, 55.9 (C7OC$\underline{H}_3$, C6OC$\underline{H}_3$ (s)); 59.2 (C$\underline{1}$H (s)); 109.8 (C$\underline{8}$H (s)); 110.4 (C$\underline{8}$H (m)); 110.7 (C$\underline{5}$H (m)); 111.4 (C$\underline{5}$H (s)); 125.1 (C$\underline{8}$a (m)); 126.1 (C$\underline{8}$a (s)); 126.5 (C$\underline{4}$'H (m)); 127.1 (C$\underline{4}$a (m)); 127.2 (C$\underline{4}$'H (s)); 127.4 (C$\underline{4}$a (s)); 128.2 (C$\underline{2}$'H, C$\underline{6}$'H (m)), 128.9 (C$\underline{2}$'H, C$\underline{6}$'H (s)); 129.4 (C$\underline{3}$'H, C$\underline{5}$'H (s)); 129.9 (C$\underline{3}$'H, C$\underline{5}$'H (m)); 137.5 (C$\underline{1}$" (s)), 137.6 (C$\underline{1}$" (m)); 146.9 (C$\underline{7}$OCH$_3$ (m)), 147.3 (C$\underline{7}$OCH$_3$ (s)); 147.7 (C$\underline{6}$OCH$_3$ (m)), 148.2 (C$\underline{6}$OCH$_3$ (s)); 165.3 (C$\underline{O}$ (s)); 169.7 (C$\underline{O}$ (m))

Yield: 25%

IRν_{max}(KBr): 739cm^{-1} (C-Cl), 1266cm^{-1} (CH wagging), 1455cm^{-1} (CN), 1645cm^{-1} (CO), 2972cm^{-1} (aliphatic CH stretching), 3055cm^{-1} (aromatic CH stretching)

HRMS calcd. for C20H23NO3Cl (M^++1): 360.1366 Found: 360.1343

1-Benzyl-6,7-dimethoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-bromo-ethanone (204)

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.65 – 2.76 (1H, m, C4H_2); 2.89 – 2.96 (1H, m, C4H_2); 3.02 (0.6H, dd, J_1 = 13Hz, J_2 = 8.2Hz, C3H_2 (m)); 3.18 (1H, d, J = 11Hz, C1CH_2); 3.25 (1H, d, J = 11Hz, C1CH_2); 3.5 (2H, d, J = 7Hz, COCH_2); 3.52 – 3.56 (0.4H, m, C3H_2); 3.60 (1.8H, s, C6OCH_3 (m)); 3.74 – 3.80 (0.6H, m, C3H_2); 3.82 – 3.92 (4.2H, m, C7OCH_3, C6OCH_3 (s)); 3.88 (1.2H, s, C6OCH_3 (s)); 4.74 (0.4H, dd, J_1 = 13Hz, J_2 = 4Hz, C3H_2 (s)); 4.87 (0.4H, dd, J_1 = 10Hz, J_2 = 4Hz, C1H (s)), 5.60 (0.6H, dd, J_1 = 8Hz, J_2 = 5.5Hz, C1H (m)); 6.15 (0.6H, s, C8H (m)), 6.51 (0.4H, s, C8H (s)); 6.60 (0.6H, s, C5H (m)), 6.65 (0.4H, s, C5H (s)); 7.10 (1H, d, J = 6.8Hz, C4'H); 7.20 – 7.38 (4H, C2'H, C3'H, C5'H, C6'H)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 25.9 (C1CH_2 (s)), 26.5 (C1CH_2 (m)); 27.5 (C4H_2 (s)), 28.4 (C4H_2 (m)); 35.9 (C3H_2 (s)); 41.8 (C3H_2 (m)); 41.9 (COCH_2 (m)); 43.0 (COCH_2 (s)); 54.6 (C1H (m)); 55.5, 55.8 (C6OCH_3, C7OCH_3 (m)), 55.8, 55.9 (C7OCH_3, C6OCH_3 (s)); 59.7 (C1H (s)); 109.8 (C8H (s)); 110.4 (C8H (m)); 110.7 (C5H (m)); 111.4 (C5H (s)); 125.2 (C8a (m)); 126.1 (C8a (s)); 126.5 (C4'H (m)); 127.1 (C4a (m)); 127.2 (C4'H (s)); 127.4 (C4a (s)); 128.2 (C2'H, C6'H (m)), 128.9 (C2'H, C6'H (s)); 129.4 (C3'H, C5'H (s)); 129.9 (C3'H, C5'H (m)); 137.6 (C1"); 146.9 (C6OCH_3 (m)); 147.7 (C7OCH_3 (m)); 165.4 (CO (s)); 165.8 (CO (m))

Yield: 25%

IRν_{max}(KBr): 739cm^{-1} (C-Cl), 1266cm^{-1} (CH wagging), 1455cm^{-1} (CN), 1645cm^{-1} (CO), 2972cm^{-1} (aliphatic CH stretching), 3055cm^{-1} (aromatic CH stretching)

HRMS calcd. for C20H22NO3NaBr (M^++23): 426.0681 Found: 426.0685

1-(1-Benzyl-6,7-dimethoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-[4-(3-chloro-phenyl)-piperazin-1-yl]-ethanone (207)

Synthesised using method 3, with stirring at 60°C for 4 hours.

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.42 – 2.45 (1.4H, m, CH_2 in piperazine ring (s)), 2.53 – 2.58 (2.6H, m, CH_2 in ring (m)); 2.67 – 2.75 (1H, m, C4H_2); 2.83 (0.4H, d, J = 14Hz, C4H_2 (s)); 2.86 – 2.96 (1H, m, C4H_2 (m), C3H_2 (m)); 3.02 – 3.30 (6H, m, COCH_2, CH_2 in ring); 3.21 – 3.30 (2H, m, C1CH_2); 3.46 – 3.53 (0.6H, m, C3H_2 (m)); 3.63 (1.8H, s, C7OCH_3 (m)), 3.76 (1.2H, s, C7OCH_3 (s)); 3.86 (1.8H, s, C6OCH_3 (m)), 3.88 (1.2H, s, C6OCH_3 (s)); 4.02 – 4.07 (0.6H, m, C3H_2 (m)), 4.80 (0.4H, dd, J_1 = 13Hz, J_2 = 5Hz, C3H_2 (s)); 5.23 (0.4H, dd, J_1 = 9Hz, J_2 = 5Hz, C1H (s)), 5.74 (0.6H, t, J_1 = 7Hz, C1H (m)); 6.22 (0.6H, s, C8H (m)), 6.41 (0.4H, s, C8H (s)); 6.60 (0.6H, s, C5H (m)), 6.64 (0.4H, s, C5H (s)); 7.10 – 6.83 (2H, m, C2"H, C6"H); 6.87 (0.6H, t, J = 2Hz, C4"H (m)); 7.11 – 7.36 (6H, C2'H, C3'H, C4'H, C5'H, C6'H, C4"H (s), C5"H)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 27.8 (C4H_2 (s)), 28.7 (C4H_2 (m)); 35.2 (C3H_2 (s)); 40.1 (C3H_2 (m)); 42.2 (C1CH_2 (m)); 42.9 (C1CH_2 (s)); 52.7, 52.8 (CH_2 in piperazine ring); 53.6 (C1H (m)); 55.5, 55.77 (C6OCH_3, C7OCH_3 (m)), 55.7, 55.8 (C7OCH_3, C6OCH_3 (s)); 57.8 (C1H (s)); 60.2 (COCH_2 (s)), 61.6 (COCH_2 (m)); 109.8 (C8H (s)); 110.4 (C8H (m)); 110.9 (C5H (m)); 111.4 (C5H (s)); 113.8 (C6"H); 115.6 (C2"H); 119.2 (C4"H); 125.3 (C8a); 126.3 (C4'H (m)); 126.9 (C4'H (s)); 127.9 (C4a); 128.1 (C2'H, C6'H (m)), 128.7 (C2'H, C6'H (s)); 129.5 (C3'H, C5'H (s)); 129.8 (C3'H, C5'H (m)); 129.9 (C5"H); 134.8 (C3"Cl); 138.0 (C1' (m)), 138.2 (C1' (s)); 146.9 (C7OCH_3 (m)), 147.1 (C7OCH_3 (s)); 147.6 (C6OCH_3 (m)), 148.0 (C6OCH_3 (s)); 152.07 (C1" (s)), 152.2 (C1" (m)); 167.8 (CO (s)); 168.0 (CO (m))

Yield: 20%

IRν_{max}(film): 1454cm^{-1}, 1638cm^{-1}(CO), 2987cm^{-1}(saturated ring CH), 3055cm^{-1}(aromatic CH)

HRMS calcd. for C30H35N3O3Cl (M^++1): 520.2367 Found: 520.2387

1-(1-Benzyl-6,7-dimethoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-[4-(4-chloro-phenyl)-piperazin-1-yl]-ethanone (208)

Manufactured using method 3, with stirring at 60°C for 4 hours.

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.41 – 2.44 (1.4H, m, C$\underline{H}_2$ in piperazine ring (s)), 2.48 – 2.59 (2.6H, m, C$\underline{H}_2$ in ring (m)); 2.66 – 2.74 (1H, m, C4$\underline{H}_2$); 2.82 (0.4H, d, J = 14Hz, C4$\underline{H}_2$ (s)); 2.85 – 2.95 (1H, m, C4$\underline{H}_2$ (m), C3$\underline{H}_2$ (m)); 3.01 – 3.13 (6H, m, COC$\underline{H}_2$, C$\underline{H}_2$ in ring); 3.16 – 3.19 (0.8H, m, C1C$\underline{H}_2$ (s)); 3.22 – 3.29 (1.2H, m, C1C$\underline{H}_2$ (m)); 3.45 – 3.51 (0.6H, m, C3$\underline{H}_2$ (m)); 3.61 (1.8H, s, C7OC$\underline{H}_3$ (m)), 3.74 (1.2H, s, C7OC$\underline{H}_3$ (s)); 3.84 (1.8H, s, C6OC$\underline{H}_3$ (m)), 3.86 (1.2H, s, C6OC$\underline{H}_3$ (s)); 4.01 – 4.07 (0.6H, m, C3$\underline{H}_2$ (m)), 4.78 (0.4H, dd, J_1 = 13Hz, J_2 = 4.8Hz, C3$\underline{H}_2$ (s)); 5.23 (0.4H, dd, J_1 = 9Hz, J_2 = 5.5Hz, C1$\underline{H}$ (s)), 5.73 (0.6H, t, J_1 = 7Hz, C1$\underline{H}$ (m)); 6.21 (0.6H, s, C8$\underline{H}$ (m)), 6.40 (0.4H, s, C8$\underline{H}$ (s)); 6.59 (0.6H, s, C5$\underline{H}$ (m)), 6.63 (0.4H, s, C5$\underline{H}$ (s)); 6.75 (0.8H, d, J = 8.88Hz, C2"$\underline{H}$, C6"$\underline{H}$ (s)); 6.81 (1.2H, d, J= 8.88Hz, C2"$\underline{H}$, C6"$\underline{H}$ (m)); 7.14 – 7.35 (6H, C2'$\underline{H}$, C3'$\underline{H}$, C4'$\underline{H}$, C5'$\underline{H}$, C6'$\underline{H}$, C3"$\underline{H}$, C5"$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 27.7 (C$\underline{H}_2$ (s)), 28.6 (C$\underline{H}_2$ (m)); 35.1 (C$\underline{H}_2$ (s)); 40.0 (C$\underline{H}_2$ (m)); 42.1 (C1C$\underline{H}_2$ (m)); 42.8 (C1C$\underline{H}_2$ (s)); 48.7, 48.9, 52.6, 52.7 (C$\underline{H}_2$ in piperazine ring); 53.5 (C1H (m)); 55.4, 55.6, (C6OC$\underline{H}_3$, C7OC$\underline{H}_3$ (m)), 55.6, 55.7 (C7OC$\underline{H}_3$, C6OC$\underline{H}_3$ (s)); 57.7 (C1H (s)); 60.2 (COC$\underline{H}_2$ (s)), 61.5 (COC$\underline{H}_2$ (m)); 109.7 (C8H (s)); 110.3 (C8H (m)); 110.8 (C5H (m)); 111.3 (C5H (s)); 117.0 (C2"H, C6"H); 124.2 (C4"Cl); (s)), 125.2 (C8a (m)); 126.1 (C8a (s)); 126.2 (C4'H (m)); 126.8 (C4'H (s)); 127.8 (C4a (s)); 128.0 (C2'H, C6'H (m)); 128.1 (C4a (m)); 128.6 (C2'H, C6'H (s)); 128.66 (C3"H, C5"H (s)), 126.7 (C3"H, C5"H (m)); 129.4 (C3'H, C5'H (s)); 129.7 (C3'H, C5'H (m)); 137.9 (C1' (m)), 138.1 (C1' (s)); 146.7 (C7OCH$_3$ (m)), 146.9 (C7OCH$_3$ (s)); 147.5 (C6OCH$_3$ (m)), 147.8 (C6OCH$_3$ (s)); 149.6 (C1" (s)), 149.63 (C1" (m)); 167.7 (CO (m)); 167.9 (CO (s))

Yield: 22%

IRν_{max}(KBr): 815cm^{-1}, 1240cm^{-1}, 1500cm^{-1}, 1639cm^{-1}, 2936cm^{-1}, 3438cm^{-1}

HRMS calcd. for C30H35N3O3Cl (M^++1): 520.2367 Found: 520.2354

1-(1-Benzyl-6,7-dimethoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone (209)

Synthesised using method 3, with stirring at 60°C for 4 hours.

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.45 (1.4H, m, C$\underline{H}_2$ in piperazine ring (s)), 2.55 – 2.58 (2.6H, m, C$\underline{H}_2$ in ring (m)); 2.71 (0.6H, t, J = 14Hz, C4$\underline{H}_2$); 2.82 (0.4H, d, J = 14Hz, C4$\underline{H}_2$ (s)); 2.90 (1H, m, C4$\underline{H}_2$ (m)); 3.02 – 3.14 (6H, m, COC$\underline{H}_2$, C$\underline{H}_2$ in ring); 3.18 – 3.30 (2H, m, C1C$\underline{H}_2$); 3.48 (0.6H, m, C3$\underline{H}_2$ (m)); 3.62 (1.8H, s, C7OC$\underline{H}_3$ (m)), 3.74 (1.2H, s, C7OC$\underline{H}_3$ (s)); 3.85 (1.8H, s, C6OC$\underline{H}_3$ (m)), 3.86 (1.2H, s, C6OC$\underline{H}_3$ (s)); 4.06 (0.6H, d, J = 12Hz, C3$\underline{H}_2$ (m)), 4.79 (0.4H, d, J = 8.8Hz, C3$\underline{H}_2$ (s)); 5.26 (0.4H, s, C1$\underline{H}$ (s)), 5.73 (0.6H, s, C1$\underline{H}$ (m)); 6.21 (0.6H, s, C8$\underline{H}$ (m)), 6.40 (0.4H, s, C8$\underline{H}$ (s)); 6.59 (0.6H, s, C5$\underline{H}$ (m)), 6.63 (0.4H, s, C5$\underline{H}$ (s)); 6.82 – 6.98 (4H, m, C2"$\underline{H}$, C3"$\underline{H}$, C5"$\underline{H}$, C6"$\underline{H}$); 7.16 – 7.34 (5H, C2'$\underline{H}$, C3'$\underline{H}$, C4'$\underline{H}$, C5'$\underline{H}$, C6'$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 27.8 (C$\underline{H}_2$ (s)), 28.7 (C$\underline{H}_2$ (m)); 35.2 (C$\underline{H}_2$ (s)); 40.1 (C$\underline{H}_2$ (m)); 42.2 (C1C$\underline{H}_2$ (m)); 42.9 (C1C$\underline{H}_2$ (s)); 49.8, 50.0, 52.9, 53.0 (C$\underline{H}_2$ in piperazine ring); 53.6 (C1H (m)); 55.5, 55.7 (C6OC$\underline{H}_3$, C7OC$\underline{H}_3$ (m)), 55.74, 55.8 (C7OC$\underline{H}_3$, C6OC$\underline{H}_3$ (s)); 57.8 (C1H (s)); 60.3 (COC$\underline{H}_2$ (s)), 61.7 (COC$\underline{H}_2$ (m)); 109.8 (C8H (s)); 110.4 (C8H (m)); 110.8 (C5H (m)); 111.4 (C5H (s)); 115.3, 115.5 (C2"H, C6"H); 117.6, 117.7 (C3"H, C5"H); 125.3 (C8a); 126.3 (C4'H (m)); 126.9 (C4'H (s)); 128.0 (C4a); 128.1 (C2'H, C6'H (m)); 128.7 (C2'H, C6'H (s)); 129.5 (C3'H, C5'H (s)); 129.8 (C3'H, C5'H (m)); 137.98 (C1');

138.2 (C1"); 146.8 (C7OCH_3 (m)), 147.5 (C6OCH_3 (m)); 147.8 (C7OCH_3 (m)), 147.9 (C6OCH_3 (s)); 163.1 (C4"F); 167.9 (CO (m)); 168.0 (CO (s))

Yield: 35%

IRν_{max}(film): 1422cm^{-1}, 1675cm^{-1}(CO), 2987cm^{-1}(saturated ring CH), 3055cm^{-1}(aromatic CH)

2-(4-Benzo[1,3]dioxol-5-ylmethyl-piperazin-1-yl)-1-(1-benzyl-6,7-dimethoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-ethanone (210)

Synthesised using method 3, stirring at room temperature for 4 hours.

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.28 – 2.39 (8H, m, CH_2 *4 piperazine ring); 2.53 (0.6H, d, J = 14Hz, C4H_2 (m)); 2.62 (1H, dt, J_1 = 16Hz, J_2 = 4Hz, C4H_2); 2.70 (0.4H, d, J = 14Hz, C4H_2 (s)); 2.79 – 2.87 (1H, m, C1CH_2); 2.96 – 3.01 (1H, m, C1CH_2); 3.06 - 3.11 (0.8H, m, COCH_2 (s)), 3.14 (1.2H, d, J = 5.4Hz, COCH_2 (m)); 3.30 (0.8H, s, NCH_2 (s)), 3.37 (1.2H, d, J = 2Hz, NCH_2 (m)); 3.40 – 3.44 (0.6H, m, C3H_2 (m)); 3.55 (1.8H, s, C7OCH_3 (m)); 3.71 (1.2H, s, C7OCH_3 (s)); 3.80 (1.8H, s, C6OCH_3 (m)); 3.81 (1.2H, s, C6OCH_3 (s)); 3.94 – 3.96 (0.6H, m, C3H_2 (m)); 4.69 (0.4H, dd, J_1 = 13Hz, J_2 = 4.5Hz, C3H_2 (s)); 5.26 (0.4H, dd, J_1 = 9Hz, J_2 = 5.4Hz, C1H (s)); 5.65 (0.6H, t, J = 6.8Hz, C1H (m)); 5.85 (0.8H, s, OCH_2O (s)), 5.87 (1.2H, s, OCH_2O (m)); 6.14 (0.6H, s, C8H (m)), 6.32 (0.4H, s, C8H (s)); 6.55 (0.6H, s, C5H (m)), 6.57 (0.4H, s, C5H (s)); 6.64 – 6.65 (0.8H, m, C2"H, C5"H (s)), 6.69 (1.2H, s, C2"H, C5"H (m)); 6.75 (0.4H, s, C6"H (s)), 6.80 (0.6H, s, C6"H (m)); 7.08 – 7.29 (5H, m, C2'H, C3'H, C4'H, C5'H, C6'H)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 27.7 (s), 28.7 (m) (C4H_2); 35.2 (s), 40.1 (m) (C3H_2); 42.1 (m), 42.8 (s) (NCH_2C1''); 52.4, 52.7, 52.9 (CH_2 *4 piperazine ring); 53.6 (C1H (m)); 55.4, 55.7 (C6OCH_3, C7OCH_3 (s)), 55.6 (C7OCH_3, C6OCH_3 (m)); 57.7 (C1H (s)); 60.4 (COCH_2 (s)), 61.6 (COCH_2 (m)); 62.4 (C1CH_2 (s)), 62.5 (C1CH_2 (m)); 100.7 (COCH_2OC); 107.7 (C5''H); 109.4 (C2''H); 109.9 (C5H (s)), 110.4 (C5H (m)); 110.8 (C8H (m)), 111.3 (C8H (s)); 122.1 (C6"H); 125.4 (C8a); 127.1 (C4'H (m)), 126.7 (C4'H (s)); 128.0 (C2'H, C6'H (m)), 128.6 (C2'H, C6'H (s)); 129.5 (C3'H, C5'H (s)), 129.7 (C3'H, C5'H (m)); 131.4 (C1'' (s)), 131.6 (C1" (m)); 137.9 (C1' (m)), 138.2 (C1' (s)); 146.4 (C7OCH_3 (m)), 146.7 (C6OCH_3 (m)), 146.8 (C7OCH_3 (s)), 147.4 (C7OCH_3); 147.43 (C3"OCH_2OC4" (m)), 147.8 (C3"OCH_2OC4" (s)); 168.0 (CO (m)), 168.2 (CO (s))

Yield: 41%

IRν_{max}(film): 1442cm^{-1}, 1637cm^{-1}(CO), 2986cm^{-1}(saturated ring CH), 3055cm^{-1}(aromatic CH)

HRMS calcd. for C32H38N3O5 (M^++1): 544.2811 Found: 544.2819

Methyl amides

2-Chloro-1-(6,7-dimethoxy-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-ethanone (211)

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.38 (2.1H, d, J = 7Hz, C1CH_3 (m)), 1.53 (0.9H, d, J = 6.5Hz, C1CH_3 (s)); 2.60 (0.3H, d, J = 14.6Hz, C4H_2 (s)), 2.69 (0.7H, d, J = 15.6Hz, C4H_2 (m)); 2.80 (0.3H, dt, J_1 = 15.6Hz, J_2 = 6Hz, C4H_2 (s)), 2.88 – 2.96 (0.7H, m, C4H_2 (m)); 3.03 (0.3H, dt, J_1 = 12.5Hz, J_2 = 4Hz, C3H_2 (s)), 3.47 (0.7H, dt, J_1 = 12.5Hz, J_2 = 4Hz, C3H_2 (m)); 3.78 – 3.79 (6.7H, overlapping singlet and multiplet, C7OCH_3, C6OCH_3, C3H_2); 4.08 – 4.13 (2H, m, COCH_2Cl); 4.56 (0.3H, dd, J_1 = 13Hz, J_2 = 4.5Hz, C3H_2 (s)); 4.87 (0.3H, q, J = 6.5Hz, C1H (s)), 5.42 (0.7H, q, J = 6.5Hz, C1H (m)); 6.54 (2H, m, C5H, C8H)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 20.9 (CH_3 (m)), 22.8 (CH_3 (s)); 27.4 (C4H_2 (s)), 28.5 (C4H_2 (m)); 35.3 (C3H_2 (s)), 39.8 (C3H_2 (m)); 41.0 (CH_2Cl (s)), 41.2 (CH_2Cl (m)); 48.4 (C1H (m)), 52.0 (C1H (s)); 55.5

(C7O$\underline{C}H_3$, C6O$\underline{C}H_3$ (m)), 55.6 (C7O$\underline{C}H_3$, C6O$\underline{C}H_3$ (s)); 109.0 ($\underline{C}$8H (s)), 109.3 ($\underline{C}$8H (m)); 110.8 ($\underline{C}$5H (m)), 111.1 ($\underline{C}$5H (s)); 124.5 ($\underline{C}$8a (m)), 125.4 ($\underline{C}$8a (s)); 128.6 ($\underline{C}$4a (s)); 129.4 ($\underline{C}$4a (m)); 147.3 ($\underline{C}$7OCH_3 (s)), 147.33 ($\underline{C}$7OCH_3 (m)); 147.5 ($\underline{C}$6OCH_3 (m)), 147.6 ($\underline{C}$6OCH_3 (s)); 164.5 ($\underline{C}$O (m)), 164.54 ($\underline{C}$O (s))

Yield: 36%

IRν_{max}(film): 1422cm^{-1}, 1674cm^{-1}(CO), 2987cm^{-1}(saturated ring CH), 3055cm^{-1}(aromatic CH)

Melting point: 80 - 82°C Literature: 82 - 83°C[31]

2-Bromo-1-(6,7-dimethoxy-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-ethanone (212)

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.42 (2.1H, dt, J_1 = 5Hz, J_2 = 3Hz, C1C$\underline{H}_3$ (m)), 1.58 (0.9H, d, J = 7Hz, C1C$\underline{H}_3$ (s)); 2.64 (0.3H, d, J = 16Hz, C4$\underline{H}_2$ (s)), 2.73 (0.7H, d, J = 16Hz, C4$\underline{H}_2$ (m)); 2.82 – 2.90 (0.3H, m, C4$\underline{H}_2$ (s)), 2.93 – 3.01 (0.7H, m, C4$\underline{H}_2$ (m)); 3.07 (0.3H, dt, J_1 = 13Hz, J_2 = 4Hz, C3$\underline{H}_2$ (s)), 3.48 – 3.56 (0.7H, m, C3$\underline{H}_2$ (m)); 3.82 (6.7H, overlapping singlet and multiplet, C7OC$\underline{H}_3$, C6OC$\underline{H}_3$, C3$\underline{H}_2$); 3.86 – 4.00 (2H, m, COC$\underline{H}_2$Br); 4.61 (0.3H, d, J_1 = 13Hz, C3$\underline{H}_2$ (s)); 4.91 (0.3H, q, J = 7.0Hz, C1$\underline{H}$ (s)), 5.47 (0.7H, q, J = 7Hz, C1$\underline{H}$ (m)); 6.56 – 6.58 (2H, m, C5$\underline{H}$, C8$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 20.8 ($\underline{C}H_3$ (m)), 22.9 ($\underline{C}H_3$ (s)); 27.5 ($\underline{C}$4H_2 (s)), 28.7 ($\underline{C}$4H_2 (m)); 35.5 ($\underline{C}$3H_2 (s)), 40.0 ($\underline{C}$3H_2 (m)); 40.5 ($\underline{C}H_2$Br (s)), 41.2 ($\underline{C}H_2$Br (m)); 48.6 ($\underline{C}$1H (m)), 52.7 ($\underline{C}$1H (s)); 55.7 (C7O$\underline{C}H_3$, C6O$\underline{C}H_3$ (m)), 55.8 (C7O$\underline{C}H_3$, C6O$\underline{C}H_3$ (s)); 109.1 ($\underline{C}$8H (s)), 109.5 ($\underline{C}$8H (m)); 110.8 ($\underline{C}$5H (m)), 111.1 ($\underline{C}$5H (s)); 124.6 ($\underline{C}$8a (m)), 125.6 ($\underline{C}$8a (s)); 128.7 ($\underline{C}$4a (s)); 129.5 ($\underline{C}$4a (m)); 147.5 ($\underline{C}$7OCH_3); 147.6 ($\underline{C}$6OCH_3); 164.6 ($\underline{C}$O (s)), 164.8 ($\underline{C}$O (m))

Yield: 31%

IRν_{max}(KBr): 732cm^{-1} (C-Br), 1644cm^{-1}(CO), 2038cm^{-1}, 3009cm^{-1}

1-(6,7-Dimethoxy-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-piperazin-1-yl-ethanone (213)

Synthesised by using method 3, with some adjustments. The piperazine was in threefold excess, to discourage formation of the tetraisoquinoline dimer linked by a piperazine bridge. Reflux continued for 8 hours.

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.27 (2.1H, d, J = 6.5Hz, C1C$\underline{H}_3$ (m)), 1.40 (0.9H, d, J = 7Hz, C1C$\underline{H}_3$ (s)); 2.27 – 2.31 (5H, C$\underline{H}_2$ in piperazine ring, N$\underline{H}$); 2.47 (0.3H, d, J = 16Hz, C4$\underline{H}_2$ (s)), 2.55 (0.7H, d, J = 16Hz, C4$\underline{H}_2$ (m)); 2.72 – 2.74 (4H, m, C$\underline{H}_2$ in ring); 2.76 – 2.84 (0.7H, m, C4$\underline{H}_2$ (s)), 2.86 – 2.90 (0.3H, m, C4$\underline{H}_2$ (m)); 2.97, 3.00 (0.6H, s, s, COC$\underline{H}_2$ (s)); 3.04 – 3.16 (1.4H, m, COC$\underline{H}_2$ (m)); 3.25 (1H, dt, J_1 = 12Hz, J_2 = 4Hz, C3$\underline{H}_2$ (m)); 3.67 (6H, overlapping singlet and multiplet, C7OC$\underline{H}_3$, C6OC$\underline{H}_3$); 3.96 (0.7H, dd, J_1 = 13Hz, J_2 = 3Hz, C3$\underline{H}_2$ (m)), 4.48 (0.3H, dd, J_1 = 12Hz, J_2 = 5Hz, C3$\underline{H}_2$ (s)); 4.99 (0.3H, q, J = 7.0Hz, C1$\underline{H}$ (s)), 5.34 (0.7H, q, J = 7Hz, C1$\underline{H}$ (m)); 6.40 – 6.45 (2H, m, C5$\underline{H}$, C8$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 21.1 ($\underline{C}H_3$ (m)), 22.7 ($\underline{C}H_3$ (s)); 27.7 ($\underline{C}$4H_2 (s)), 28.9 ($\underline{C}$4H_2 (m)); 34.7 ($\underline{C}$3H_2 (s)), 39.1 ($\underline{C}$3H_2 (m)); 45.5, 45.6 ($\underline{C}H_2$ in piperazine ring); 47.8 ($\underline{C}$1H (m)), 51.3 ($\underline{C}$1H (s)); 54.0, 54.3 ($\underline{C}H_2$ in ring); 55.6 (C7O$\underline{C}H_3$, C6O$\underline{C}H_3$ (m)), 55.8 (C7O$\underline{C}H_3$, C6O$\underline{C}H_3$ (s)); 61.7 (CO$\underline{C}H_2$ (s)), 61.3 (CO$\underline{C}H_2$ (m)); 109.1 ($\underline{C}$8H (s)), 109.5 ($\underline{C}$8H (m)); 110.9 ($\underline{C}$5H (m)), 111.2 ($\underline{C}$5H (s)); 125.0 ($\underline{C}$8a (m)), 125.8 ($\underline{C}$8a (s)); 129.6 ($\underline{C}$4a (s)); 130.0 ($\underline{C}$4a (m)); 147.2 ($\underline{C}$7OCH_3 (s)), 147.22 ($\underline{C}$7OCH_3 (m)); 147.4 ($\underline{C}$6OCH_3 (m)), 147.44 ($\underline{C}$7OCH_3 (s)); 167.5 ($\underline{C}$O (s)), 167.6 ($\underline{C}$O (m))

Yield: 23%

IRν_{max}(film): 1422cm^{-1}, 1636cm^{-1}(CO), 2987cm^{-1}(saturated ring CH), 3054cm^{-1}(aromatic CH)

HRMS calcd. for C18H28N3O3 (M^++1): 334.2131 Found: 334.2128

1-(6,7-Dimethoxy-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-(4-methyl-piperazin-1-yl)-ethanone (214)

Synthesised by method 3, with stirring at reflux prolonged for 14 hours.

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.25 (2.1H, d, J = 6.5Hz, C1C$\underline{H}_3$ (m)), 1.38 (0.9H, d, J = 6.5Hz, C1C$\underline{H}_3$ (s)); 2.0 (0.9H, s, NC$\underline{H}_3$ (s)), 2.10 (2.1H, s, NC$\underline{H}_3$ (m)); 2.28 – 2.40 (5.6H, m, C$\underline{H}_2$ in piperazine ring); 2.53 (1.4H, d, J = 16Hz, C4$\underline{H}_2$ (m)); 2.65 (0.6H, dt, J_1 = 16Hz, J_2 = 5.5Hz, C4$\underline{H}_2$ (s)); 2.73 – 2.89 (1H, m, C3$\underline{H}_2$); 2.97, 3.00 (0.6H, s, s, COC$\underline{H}_2$ (s)); 3.05 – 3.17 (1.4H, m, COC$\underline{H}_2$ (m)); 3.23 (2.4H, s, C$\underline{H}_2$ in piperazine ring); 3.66 (6H, s, C7OC$\underline{H}_3$, C6OC$\underline{H}_3$); 3.91 – 3.94 (0.7H, m, C3$\underline{H}_2$ (m)), 4.45 (0.3H, dd, J_1 = 13Hz, J_2 = 5Hz, C3$\underline{H}_2$ (s)); 4.98 (0.3H, q, J = 6.5Hz, C1$\underline{H}$ (s)), 5.32 (0.7H, q, J = 7Hz, C1$\underline{H}$ (m)); 6.41 – 6.43 (2H, m, C5$\underline{H}$, C8$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 20.8 (C$\underline{1}H_3$ (m)), 22.5 (C$\underline{1}H_3$ (s)); 27.4 (C$\underline{4}H_2$ (s)), 28.6 (C$\underline{4}H_2$ (m)); 34.5 (C$\underline{3}H_2$ (s)), 38.8 (C$\underline{3}H_2$ (m)); 45.3 (NC$\underline{H}_3$ (m)); 47.6 (C$\underline{1}$H (m)); 49.4 (NC$\underline{H}_3$ (s)); 51.0 (C$\underline{1}$H); 52.4, 54.3, 54.4 (C$\underline{H}_2$ in piperazine ring); 55.4 (C7OC$\underline{H}_3$, C6OC$\underline{H}_3$ (m)), 55.5 (C7OC$\underline{H}_3$, C6OC$\underline{H}_3$ (s)); 60.7 (CO$\underline{C}H_2$ (s)), 61.2 (CO$\underline{C}H_2$ (m)); 108.9 (C$\underline{8}$H (s)), 109.3 (C$\underline{8}$H (m)); 110.7 (C$\underline{5}$H (m)), 111.0 (C$\underline{5}$H (s)); 124.8 (C$\underline{8}$a (m)), 125.4 (C$\underline{8}$a (s)); 129.3 (C$\underline{4}$a (s)); 129.7 (C$\underline{4}$a (m)); 146.9 (C$\underline{7}$OCH$_3$ (s)), 147.0 (C$\underline{7}$OCH$_3$ (m)); 147.1 (C$\underline{6}$OCH$_3$ (m)), 147.2 (C$\underline{7}$OCH$_3$ (s)); 167.3 (C$\underline{O}$)

Yield: 46%

IRν_{max}(film): 1463cm^{-1}, 1635cm^{-1}(CO), 2939cm^{-1}(saturated ring CH), 3054cm^{-1}(aromatic CH)

HRMS calcd. for C19H30N3O3 (M^++1): 348.2287 Found: 348.2286

2[4-(3-Chloro-phenyl)-piperazin-1-yl]-1-(6,7-dimethoxy-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-ethanone (215)

Produced using method 4, with stirring of the piperazine solution at 60°C for 12 hours.

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.45 (2.1H, d, J = 6.5Hz, C1$\underline{H}_3$ (m)), 1.57 (0.9H, d, J = 6.5Hz, C1$\underline{H}_3$ (s)); 2.69 (4H, C$\underline{H}_2$ in piperazine ring); 3.21 – 3.23 (4H, C$\underline{H}_2$ in ring); 3.24, 3.27 (0.6H, s, s, COC$\underline{H}_2$ (s)); 3.36 – 3.48 (1.7H, m, COC$\underline{H}_2$ (m), C3$\underline{H}_2$ (s)); 3.85 (6H, s, C7OC$\underline{H}_3$, C6OC$\underline{H}_3$); 4.10 (0.7H, dd, J_1 = 13.5Hz, J_2 = 3Hz, C3$\underline{H}_2$ (m)), 4.67 (0.3H, dd, J_1 = 13Hz, J_2 = 4Hz, C3$\underline{H}_2$ (s)); 5.13 (0.3H, q, J = 6.5Hz, C1$\underline{H}$ (s)), 5.53 (0.7H, q, J = 6.5Hz, C1$\underline{H}$ (m)); 6.57 – 6.61 (2H, C8$\underline{H}$, C5$\underline{H}$); 6.77 – 6.81 (2H, C2'$\underline{H}$, C4'$\underline{H}$); 6.86 – 6.87 (1H, C6'$\underline{H}$); 7.13 – 7.17 (1H, C5'$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 20.9 (C$\underline{1}H_3$ (m)), 22.6 (C$\underline{1}H_3$ (s)); 27.6 (C$\underline{4}H_2$ (s)), 28.8 (C$\underline{4}H_2$ (m)); 34.7 (C$\underline{3}H_2$ (s)), 39.0 (C$\underline{3}H_2$ (m)); 47.8 (C$\underline{1}$H (m)); 48.1, 52.5 (C$\underline{H}_2$ in piperazine ring); 51.1 (C$\underline{1}$H); 55.4 (C7OC$\underline{H}_3$, C6OC$\underline{H}_3$ (m)), 55.6 (C7OC$\underline{H}_3$, C6OC$\underline{H}_3$ (s)); 60.6 (CO$\underline{C}H_2$ (s)), 61.2 (CO$\underline{C}H_2$ (m)); 108.9 (C$\underline{8}$H (s)), 109.3 (C$\underline{8}$H (m)); 110.7 (C$\underline{5}$H (m)), 111.1 (C$\underline{5}$H (s)); 113.5 (C$\underline{6}$'H); 115.3 (C$\underline{2}$'H); 118.9 (C$\underline{4}$'H); 124.7 (C$\underline{8}$a (m)), 125.6 (C$\underline{8}$a (s)); 129.2 (C$\underline{4}$a (s)); 129.6 (C$\underline{5}$'H); 129.8 (C$\underline{4}$a (m)); 134.4 (C$\underline{3}$'Cl); 147.1 (C$\underline{7}$OCH$_3$ (s)), 147.13 (C$\underline{7}$OCH$_3$ (m)); 147.3 (C$\underline{6}$OCH$_3$ (m)), 147.4 (C$\underline{6}$OCH$_3$ (s)); 151.7 (C$\underline{1}$'); 166.89 (C$\underline{O}$ (s)), 166.9 (C$\underline{O}$ (m))

Yield: 37%

IRν_{max}(film): 1422cm^{-1}, 1637cm^{-1}(CO), 2986cm^{-1}(saturated ring CH), 3055cm^{-1}(aromatic CH)

HRMS calcd. for C24H31N3O3Cl (M^++1): 444.2054 Found: 444.2054

2-[4-(4-Chloro-phenyl)-piperazin-1-yl]-1-(6,7-dimethoxy-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-ethanone (216)

Synthesised by method 4, with stirring at 60°C for 12 hours.

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.44 (2.1H, d, J = 6.8Hz, C$\underline{H}_3$ (m)), 1.56 (0.9H, d, J = 6.8Hz, C$\underline{H}_3$ (s)); 2.66 – 2.68 (4H, C$\underline{H}_2$ in piperazine ring); 2.69 – 3.10 (2H, m, C4$\underline{H}_2$); 3.14 – 3.18 (4H, C$\underline{H}_2$ in ring); 3.20, 3.24 (1H, d, d, COC$\underline{H}_2$ (s),(m)); 3.33, 3.39 (2H, d, d, dt, overlapping, COC$\underline{H}_2$ (J_S = 10Hz, J_M = 13Hz, (s), (m)), C3$\underline{H}_2$, J_1 = 12Hz, J_2 = 4Hz, (m), (s)); 3.84 (6H, s, C7OC$\underline{H}_3$, C6OC$\underline{H}_3$); 4.11 (0.7H, ddd, J_1 = 14Hz, J_2 = 5Hz, J_3 = 2Hz, C3$\underline{H}_2$ (m)), 4.67 (0.3H, dd, J_1 = 13Hz, J_2 = 5Hz, C3$\underline{H}_2$ (s)); 5.14 (0.3H, q, J = 6.8Hz, C1$\underline{H}$ (s)), 5.53 (0.7H, q, J = 6.8Hz, C1$\underline{H}$ (m)); 6.56 – 6.61 (2H, C8$\underline{H}$, C5$\underline{H}$); 6.81 – 6.84 (2H, C2'$\underline{H}$, C6'$\underline{H}$); 7.16 – 7.20 (2H, C3'$\underline{H}$, C5'$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 21.2 (C$\underline{1}H_3$ (m)), 22.9 (C$\underline{1}H_3$ (s)); 27.9 (C$\underline{4}H_2$ (s)), 29.1 (C$\underline{4}H_2$ (m)); 34.9 (C$\underline{3}H_2$ (s)), 39.3 (C$\underline{3}H_2$ (m)); 48.0 (C$\underline{1}$H (m)); 48.9, 52.9 (C$\underline{H}_2$ in piperazine ring); 51.4 (C$\underline{1}$H (s)); 55.7 (C7O$\underline{C}H_3$, C6O$\underline{C}H_3$ (m)), 55.8 (C7O$\underline{C}H_3$, C6O$\underline{C}H_3$ (s)); 61.1 (CO$\underline{C}H_2$ (s)), 61.7 (CO$\underline{C}H_2$ (m)); 109.2 (C$\underline{8}$H (s)), 109.6 (C$\underline{8}$H (m)); 111.0 (C$\underline{5}$H (m)), 111.4 (C$\underline{5}$H (s)); 117.0 (C$\underline{2}$'H, C$\underline{6}$'H (m)), 117.1 (C$\underline{2}$'H, C$\underline{6}$'H (s)); 124.3 (C$\underline{4}$'Cl); 125.0 (C$\underline{8}$a (m)); 125.9 (C$\underline{8}$a (s)); 128.7 (C$\underline{3}$'H, C$\underline{5}$'H (m)); 128.8 (C$\underline{3}$'H, C$\underline{5}$'H (s)); 129.6 (C$\underline{4}$a (s)); 130.1 (C$\underline{4}$a (m)); 147.37 (C$\underline{6}OCH_3$ (s)), 147.41 (C$\underline{6}OCH_3$ (m)); 147.55 (C$\underline{7}OCH_3$ (m)), 147.65 (C$\underline{7}OCH_3$ (s)); 149.6 (C$\underline{1}$'); 167.4 (C$\underline{O}$)

Yield: 31%

IRν_{max}(film): 1497cm^{-1}, 1636cm^{-1}(CO), 2986cm^{-1}(saturated ring CH), 3055cm^{-1}(aromatic CH)

HRMS calcd. for C24H31N3O3Cl (M^++1): 444.2054 Found: 444.2075

1-(6,7-Dimethoxy-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethanone (217)

Method 4 was used, with stirring at 60°C for 2 hours.

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.46 (2.1H, d, J = 6.8Hz, C$\underline{H}_3$ (m)), 1.58 (0.9H, d, J = 6.8Hz, C$\underline{H}_3$ (s)); 2.70 – 2.71 (4H, C$\underline{H}_2$ in piperazine ring); 2.80 – 3.06 (2H, m, C4$\underline{H}_2$); 3.13 – 3.16 (4H, C$\underline{H}_2$ in ring); 3.22, 3.26 (0.6H, s, s, COC$\underline{H}_2$ (s)); 3.31 – 3.48 (2.7H, m, COC$\underline{H}_2$ (m), C3$\underline{H}_2$); 3.88 (6H, s, C7OC$\underline{H}_3$, C6OC$\underline{H}_3$); 4.14 (0.7H, ddd, J_1 = 13Hz, J_2 = 5Hz, J_3 = 2Hz, C3$\underline{H}_2$ (m)), 4.70 (0.3H, dd, J_1 = 13Hz, J_2 = 5Hz, C3$\underline{H}_2$ (s)); 5.16 (0.3H, q, J = 6.8Hz C1$\underline{H}$ (s)), 5.55 (0.7H, q, J = 6.8Hz, C1$\underline{H}$ (m)); 6.57 – 6.63 (2H, C8$\underline{H}$, C5$\underline{H}$); 6.85 – 6.90 (2H, C2'$\underline{H}$, C6'$\underline{H}$); 6.94 – 6.99 (2H, C3'$\underline{H}$, C5'$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 21.4 (C$\underline{1}H_3$ (m)), 23.0 (C$\underline{1}H_3$ (s)); 28.0 (C$\underline{4}H_2$ (s)), 29.2 (C$\underline{4}H_2$ (m)); 35.1 (C$\underline{3}H_2$ (s)), 39.4 (C$\underline{3}H_2$ (m)); 48.2 (C$\underline{1}$H (m)); 49.8, 49.9, 53.0 (C$\underline{H}_2$ in piperazine ring); 51.5 (C$\underline{1}$H (s)); 55.85 (C7O$\underline{C}H_3$, C6O$\underline{C}H_3$ (m)), 55.96 (C7O$\underline{C}H_3$, C6O$\underline{C}H_3$ (s)); 61.3 (CO$\underline{C}H_2$); 109.4 (C$\underline{8}$H (s)), 109.7 (C$\underline{8}$H (m)); 111.1 (C$\underline{5}$H (m)), 111.4 (C$\underline{5}$H (s)); 115.4, 115.6 (C$\underline{2}$'H, C$\underline{6}$'H (m)), 117.8, 117.9 (C$\underline{2}$'H, C$\underline{6}$'H (s)); 125.1 (C$\underline{8}$a); 130.2 (C$\underline{4}$a); 130.1 (C$\underline{4}$a (m)); 147.6 (C$\underline{7}OCH_3$); 147.7 (C$\underline{6}OCH_3$); 154.2 (C$\underline{1}$'); 163.8 (C$\underline{4}$'F); 167.0 (C$\underline{O}$)

^{19}F-NMR (376MHz): ppm($CDCl_3$): -124.62 (s), -124.7 (m)

Yield: 30%

IRν_{max}(film): 1465cm^{-1}, 1635cm^{-1}(CO), 2938cm^{-1}(saturated ring CH), 3055cm^{-1}(aromatic CH)

HRMS calcd. for C24H31N3O3F (M^++1): 428.2349 Found: 428.2354

2-(4-Benzo[1,3]dioxol-5-ylmethyl-piperazin-1-yl)-1-(6,7-dimethoxy-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-ethanone (218)

Synthesised using method 4, for 2 hours.

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.31 (2.1H, d, J = 6.5Hz, C1$\underline{H}_3$ (m)), 1.44 (0.9H, d, J = 6.5Hz, C1$\underline{H}_3$ (s)); 2.34 – 2.40 (8H, C$\underline{H}_2$ in piperazine ring); 2.58 (0.7H, d, J = 16Hz, C4$\underline{H}_2$); 2.71 (0.3H, dt, J_1 = 5Hz, J_2 = 16Hz, C4$\underline{H}_2$); 2.80 – 2.93 (1H, m, C4$\underline{H}_2$); 3.02, 3.05 (0.6H, s, s, COC$\underline{H}_2$); 3.13, 3.16 (0.6H, s, s, NC$\underline{H}_2$ (s)); 3.18 – 3.30 (3.1H, m, NC$\underline{H}_2$ (m), COC$\underline{H}_2$ (m), C3$\underline{H}_2$ (s)); 3.38 – 3.43 (0.7H, m, C3$\underline{H}_2$); 3.72 (6H, s, s, C6OC$\underline{H}_3$, C7OC$\underline{H}_3$); 4.02 (0.7H, m, C3$\underline{H}_2$); 4.53 (0.3H, dd, J_1 = 13Hz, J_2 = 5Hz, C3$\underline{H}_2$ (s)); 5.06 (0.3H, q, J = 6.5Hz, C1$\underline{H}$ (s)); 5.39 (0.7H, q, J = 6.5Hz, C1$\underline{H}$ (m)); 5.78 (2H, s, OC$\underline{H}_2$O); 6.47 – 6.49 (2H, m, C5$\underline{H}$, C8$\underline{H}$); 6.59 (2H, s, C2'$\underline{H}$, C6'$\underline{H}$); 6.71 (1H, s, C5'$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 20.8 (C$\underline{H}_3$ (m)), 22.6 (C$\underline{H}_3$ (s)); 27.5 (C$\underline{4}H_2$ (s)), 28.8 (C$\underline{4}H_2$ (m)); 34.5 (C$\underline{3}H_2$ (s)), 38.9 (C$\underline{3}H_2$ (m)); 47.6 (C$\underline{1}$H (m)); 51.1 (C$\underline{1}$H (s)); 52.4, 52.6, 59.8 (C$\underline{H}_2$ in piperazine ring); 55.4 (C7OC$\underline{H}_3$, C6OC$\underline{H}_3$ (m)), 55.5 (C7OC$\underline{H}_3$, C6OC$\underline{H}_3$ (s)); 61.6 (COC$\underline{H}_2$ (m)); 62.2 (NC$\underline{H}_2$ (m)); 66.0 (COC$\underline{H}_2$ (s)); 71.3 (NC$\underline{H}_2$ (s)); 100.3 (OC$\underline{H}_2$O); 107.3 (C$\underline{5}$'H); 108.9(C$\underline{8}$H (s)), 109.0 (C$\underline{8}$H (m)); 109.4 (C$\underline{2}$'H); 111.1 (C$\underline{5}$H); 121.6 (C$\underline{6}$'H); 124.9 (C$\underline{8}$a (m)), 125.6 (C$\underline{8}$a (s)); 129.6 (C$\underline{4}$a (s)), 129.9 (C$\underline{4}$a (m)); 131.5 (C$\underline{1}$'); 146.1, 147.1 (C$\underline{3}$'OCH$_2$OC$\underline{4}$'); 147.0, 147.2 (C$\underline{6}$OCH$_3$, C$\underline{7}$OCH$_3$); 170.5 (C$\underline{O}$)

Yield: 26%

IRν_{max}(film): 1422cm^{-1}, 1674cm^{-1}(CO), 2987cm^{-1}(saturated ring CH), 3055cm^{-1}(aromatic CH)

HRMS calcd. for C26H34N3O5 (M^++1): 468.2498 Found: 468.2507

Chapter 5

Phenoxyacetyltetrahydroisoquinoline precursors

1-Methyl-3,4-dihydroisoquinoline (220)[32]

Method 1 **i) Acetylation of β-phenethylamine *(220a)***

2-Phenylethylamine (5 mL/39.8 mmol) was pipetted into acetic anhydride (60 mL) and the mixture was stirred at 60°C for 2 hours. The mixture was extracted with 20mL dichloromethane and washed to remove the anhydride. The extract was dried and the solvent removed under vacuum. Residual anhydride was dealt with by the addition of toluene to form an azeotrope, which could be removed on the rotary evaporator. The colourless solid was recrystallised from hot methanol.

N-(2-Phenylethyl)acetamide

Yield: calculated over two steps (see ii below)

IR ν_{max} (KBr): 2925cm^{-1}, 1703cm^{-1}, 1371cm^{-1}, 1260cm^{-1}, 1178cm^{-1}, 700cm^{-1}

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.94 (3H, NHCOC<u>H</u>3); 2.83 (2H, t, J = 7.04Hz, C2<u>H</u>2); 3.48 – 3.53 (2H, m, J1 = J2 = 6.52Hz, J3 = 7.04Hz, C1<u>H</u>2NHCOCH3); 6.02 (1H, N<u>H</u>); 7.10 – 7.33 (6H (appears to include chloroform peak), J1 = 7.04Hz, J2 = 7.52Hz, J3 = 3.0Hz, J4 = 4.52Hz, J5 = 8.04Hz, J6 = 8.0Hz, <u>H</u>2', <u>H</u>3', <u>H</u>4', <u>H</u>5', <u>H</u>6')

^{13}C-NMR (101MHz):ppm($CDCl_3$): 22.70(NHCO<u>C</u>H3); 35.17 (<u>C</u>2H2); 40.29 (<u>C</u>1H2NHCOCH3); 124.85 (<u>C</u> 1'C2H2); 126.01 (<u>C</u>4'H); 128.15, 128.25 (<u>C</u>2'H, <u>C</u>3'H, <u>C</u>5'H, <u>C</u>6'H); 138.50 (<u>C</u>1'C2H2); 169.85 (<u>C</u>OCH3)

Melting point: 44 - 46°C Literature: 45°C[33]

ii) Cyclisation of β-phenethylamide

N-(2-Phenylethyl)acetamide (4.176 g/ 25.6 mmol) was dissolved with stirring in 10mL toluene. Phosphorous pentoxide (5.448 g/38.4 mmol) was added and the reaction was refluxed at 120°C for 15 minutes. A further portion (5.448 g/38.4 mmol) of phosphorous pentoxide was added and reflux was sustained for another 30 minutes. The toluene was removed on a rotary evaporator to give a tar, which was extracted with dichloromethane. The extract was washed and dried and the DCM was removed *in vacuo*. The product was purified by column chromatography. A mobile phase of 100% ethyl acetate was used to elute the product.

Yield: 15.2% over two steps.

Method 2. Acetonitrile (0.63 mL/12 mmol) was added to the vessel. This was followed by addition of tin IV chloride (1.4 mL/12 mmol) and the solid was dissolved by (2-chloroethyl)benzene (2.0 mL/ 14 mmol). The mixture was stirred at 130°C for 3 hours. At the end of the period, the vessel was allowed to cool to room temperature. The vessel contents were extracted with DCM. The DCM extract was washed with 15%w/v NaOH solution and dried and the solvent was removed *in vacuo*. The product was cleaned by elution using 10:90 methanol:ethyl acetate.

Yield: 30%

Method 3. The microwave procedure required prior drying of the vessel and stirrer. Acetonitrile (0.1 mL/1.9 mmol) was added to the vessel. This was followed by addition of tin IV chloride (0.23 mL/1.9 mmol) and the solid was dissolved by (2-chloroethyl)benzene (0.28 mL/ 2.1 mmol). The conditions were set on the CEM Discover unit as "acetonitrile", 130°C, power at 60 Watt, maximum pressure 50psi, 30 second ramp period and 3 minutes reaction time. At the end of the period, the vessel was allowed to cool to room

temperature. The contents were made alkaline with 15%w/v NaOH solution. The salts were washed on a Buchner funnel with DCM. The DCM extract was washed and dried and the solvent was removed *in vacuo*. The product was cleaned by elution using 10:90 methanol:ethyl acetate.

Yield: 71%

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.32 (3H, s, C$\underline{H}_3$); 2.61 (2H, t, J = 7.5Hz, C4$\underline{H}_3$); 3.58 (2H, t, J = 7.5Hz, C3$\underline{H}_2$); 7.08 (1H, d, J = 7.5Hz, C5'$\underline{H}$); 7.19 – 7.28 (2H, m, C6$\underline{H}$, C7$\underline{H}$); 7.38 (1H, d, J = 7.5Hz, C8$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 22.8 (C$\underline{H}_3$); 25.5 (C$\underline{4}H_2$); 46.4 (C$\underline{3}H_2$); 124.8, 126.4, 126.9, 130.1 (C$\underline{5}$H, C$\underline{6}$H, C$\underline{7}$H, C$\underline{8}$H); 129.0 (C$\underline{8}$a); 136.8 (C$\underline{4}$a); 163.7 (C$\underline{N}$)

IRν_{max}(KBr): 980cm^{-1}, 1100cm^{-1}, 1518cm^{-1}, 1739cm^{-1}, 2854cm^{-1}, 2934cm^{-1}

Melting point: Literature (picrate only): 187 - 188°C[32]

1-Phenyl-3,4-dihydroisoquinoline (223)

As for (220), method 2.

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.89 (2H, t, J = 7.0Hz, C4$\underline{H}_3$); 3.62 – 3.67 (2H, m, C3$\underline{H}_2$); 7.17 – 7.40 (9H, m, C5$\underline{H}$, C6$\underline{H}$, C7$\underline{H}$, C8$\underline{H}$, C2'$\underline{H}$, C3'$\underline{H}$, C4'$\underline{H}$, C5'$\underline{H}$, C6'$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 35.5 (C$\underline{4}H_2$); 41.1 (C$\underline{3}H_2$); 126.2, 126.7, 128.2, 128.3, 128.4, 128.9, 132.6 (C$\underline{5}$H, C$\underline{6}$H, C$\underline{7}$H, C$\underline{8}$H, C$\underline{2}$'H, C$\underline{3}$'H, C$\underline{4}$'H, C$\underline{5}$'H, C$\underline{6}$'H); 134.5 (C$\underline{8}$a); 138.9 (C$\underline{4}$a); 167.3 (C$\underline{N}$)

Yield: 10%

IRν_{max}(KBr): 1122cm^{-1}, 1514cm^{-1}, 1744cm^{-1}, 2934cm^{-1}, 3077cm^{-1}

Melting point: Literature (picrate only): 173 - 175°C[32]

1-Methyl-1,2,3,4-tetrahydroisoquinoline (224)

1-Methyl-3,4-dihydroisoquinoline **(220)** (1.464 g/10.1 mmol) was suspended in methanol. Glacial acetic acid (0.6 mL/10.1 mmol) was added. The flask was flushed with nitrogen and sodium borohydride (946 mg/25 mmol) was added in portions. The mixture was stirred at room temperature for 3 hours. Icy water was added and the methanol was removed *in vacuo*. The residue was extracted with DCM, dried with sodium sulfate and evacuated to oil. If required, this was purifed by elution from a silica column using a mobile phase of 10:90 methanol:ethyl acetate.

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.48 (3H, d, J = 6.8Hz, C1C$\underline{H}_3$); 1.90 (1H, s, N$\underline{H}$); 2.73 (1H, dt, J_1 = 15.7Hz, J_2 = 4.8Hz, C4$\underline{H}_3$); 2.84 – 2.94 (1H, m, C4$\underline{H}_2$); 2.98 – 3.04 (1H, m, C3$\underline{H}_2$); 3.26 (2H, dt, J_1 = 12.3Hz, J_2 = 4.8Hz, C3$\underline{H}_2$); 4.10 (1H, q, J = 6.8Hz, C1$\underline{H}$); 6.96 – 7.23 (4H, m, C5$\underline{H}$, C6$\underline{H}$, C7$\underline{H}$, C8$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 22.2 (C$\underline{H}_3$); 29.5 (C$\underline{4}H_2$); 41.3 (C$\underline{3}H_2$); 51.0 (C$\underline{1}$H); 125.3, 128.7 (C$\underline{5}$H, C$\underline{6}$H, C$\underline{7}$H, C$\underline{8}$H); 134.2 (C$\underline{8}$a); 140.0 (C$\underline{4}$a)

Yield: 68%

IRν_{max}(KBr): 820cm^{-1}, 1199cm^{-1}, 1511cm^{-1}, 1708cm^{-1}, 2897cm^{-1}, 3422cm^{-1}

Boiling point: Literature only 125°C/14Torr[34]

1-(3,4-Dihydro-*1H*-isoquinolin-2-yl)-2,2,2-trifluoro-ethanone (225)

1,2,3,4-Tetrahydroisoquinoline **(1)** (5 mL/40 mmol) was stirred in an icebath as trifluoroacetic anhydride was added dropwise. The mixture was left stirring for 1.5 hours. Trifluroacetic acid was removed *in vacuo*, the residue was extracted into DCM and washed and dried. The solvent was removed *in vacuo* and the product was purified by elution from a silica column using a mobile phase of 100% DCM.

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.95 – 2.99 (2H, m, C4$\underline{H}_3$); 3.86, 3.90 (2H, t, t, overlapping J_1 = 6.2Hz, J_2 = 5.5Hz, C3$\underline{H}_2$); 4.77 (0.6H, s, C1$\underline{H}_2$) (s), 4.81 (1.4H, s, C1$\underline{H}_2$) (m); 7.16 – 7.27 (4H, m, C5$\underline{H}$, C6$\underline{H}$, C7$\underline{H}$, C8$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 27.6 (C4$\underline{H}_2$) (s), 29.0 (C4$\underline{H}_2$) (m); 41.7 (C3$\underline{H}_2$) (s), 43.2 (C1$\underline{H}_2$) (m); 45.4 (C3$\underline{H}_2$) (m), 46.8 (C1$\underline{H}_2$) (s); 116.4 ($\underline{C}F_3$, q, J = 277Hz); 125.8, 126.4, 126.6, 126.7, 127.4, 128.4, 128.7 ($\underline{C}$5H, $\underline{C}$6H, $\underline{C}$7H, $\underline{C}$8H); 131.3 ($\underline{C}$8a) (m); 132.4 ($\underline{C}$8a) (s); 133.1 ($\underline{C}$4a) (m), 133.8 ($\underline{C}$4a) (s); 155.7 ($\underline{C}OCF_3$)

^{19}F-NMR (376MHz): -69.45 (s), -69.8 (m)

Yield: 81%

IRν_{max}(KBr): 675cm^{-1}, 1111cm^{-1}, 1692cm^{-1}, 2849cm^{-1}, 3030cm^{-1}

2,2,2-Trifluoro-1-(1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-ethanone (226)

As for **(225).**

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.52 (2.1H, d, J = 6.8Hz, C1C$\underline{H}_3$) (m), 1.60 (0.9H, d, J = 6.8Hz, C1C$\underline{H}_3$) (s); 2.79 – 2.88 (1H, m, C4$\underline{H}_3$); 2.96 – 3.06 (1H, m, C4$\underline{H}_2$); 3.28 (0.3H, dt, J_1 = 12Hz, J_2 = 4.1Hz, C3$\underline{H}_2$) (s); 3.58 (0.7H, dt, J_1 = 12Hz, J_2 = 4.8Hz, C3$\underline{H}_2$) (m); 4.05 (0.7H, d, J = 12Hz, C3$\underline{H}_2$) (m), 4.60 (0.3H, dd, J_1 = 13Hz, J_2 = 4.8Hz, C3$\underline{H}_2$) (s); 5.14 (0.3H, q, J = 6.2Hz, C1$\underline{H}$) (s), 5.56 (0.7H, q, J = 6.8Hz, C1$\underline{H}$) (m); 7.10 – 7.24 (4H, m, C5$\underline{H}$, C6$\underline{H}$, C7$\underline{H}$, C8$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 20.8 ($\underline{C}H_3$) (m), 23.0 ($\underline{C}H_3$) (s); 27.5 (C4$\underline{H}_2$) (s), 28.8 (C4$\underline{H}_2$) (m); 36.3 (C3$\underline{H}_2$) (s), 39.0 (C3$\underline{H}_2$) (m); 49.8 (C1H) (m), 52.0 (C1H) (s); 126.2, 126.24, 126.4, 126.5, 126.54, 126.8, 128.3, 128.8 ($\underline{C}$5H, $\underline{C}$6H, $\underline{C}$7H, $\underline{C}$8H); 132.0 ($\underline{C}$8a) (m); 132.4 ($\underline{C}$8a) (s); 136.2 ($\underline{C}$4a) (s), 136.3 ($\underline{C}$4a)

^{19}F-NMR (376MHz): -69.45 (s), -69.8 (m)

Yield: 73%

IRν_{max}(KBr): 1150cm^{-1}, 1699cm^{-1}, 2894cm^{-1}, 3002cm^{-1}

1-(7-Acetyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-2,2,2-trifluoro-ethanone

ethanone (227)[35]

1-(3,4-Dihydro-*1H*-isoquinolin-2-yl)-2,2,2-trifluoroethanone **(225)** (2.18 g/9.5 mmol) was stirred in carbon disulphide. Aluminium chloride (3.167 g/24 mmol) was added. Acetyl chloride (2.1 mL/28.5 mmol) was added dropwise to the suspension. The mixture was refluxed for 1.5 hours. Icy 10%v/v HCl solution was added and the carbon disulphide was removed *in vacuo*. The residue was extracted with DCM, washed, dried and the solvent removed *in vacuo*. If required, it was purified by elution from a silica column with1:1 ethyl acetate: hexane.

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.60 (3H, s, COC$\underline{H}_3$); 3.00 – 3.04 (2H, m, C4$\underline{H}_3$); 3.88, 3.92 (2H, t, t, overlapping J_1 = 6.1Hz, J_2 = 5.4Hz, C3$\underline{H}_2$); 4.81 (0.6H, s, C1$\underline{H}_2$) (s), 4.86 (1.4H, s, C1$\underline{H}_2$) (m); 7.26 – 7.30 (1H, m, C5$\underline{H}$); 7.75 – 7.84 (2H, m, C6$\underline{H}$, C8$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 26.5 (CO$\underline{C}H_3$); 27.8 (C4$\underline{H}_2$) (s), 29.4 (C4$\underline{H}_2$); 43.0 (C3$\underline{H}_2$) (s), 45.4 (C1$\underline{H}_2$) (m), 45.5 (C3$\underline{H}_2$) (m), 47.0 (C1$\underline{H}_2$) (s); 126.0, 126.7, 126.9, 126.93 ($\underline{C}$6H, $\underline{C}$8H) (s), (m), (m), (s); 129.0 ($\underline{C}$5H) (m), 129.2 ($\underline{C}$5H) (s); 133.6 ($\underline{C}$8a); 136.7 ($\underline{C}$4a) some quaternary signals not visible.

^{19}F-NMR (376MHz): -69.85 (s), -69.90 (m)

Yield: 71%

IRν_{max}(KBr): 705cm^{-1}, 1147cm^{-1}, 1422cm^{-1}, 1689cm^{-1}, 2987cm^{-1}, 3055cm^{-1}

Melting point: 66 - 68°C Literature: 66 - 68°C[36]

Boiling point: (literature only): 158 - 167°C[37]

1-(7-Acetyl-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-2,2,2-trifluoro-ethanone (228)

As for **(227)**.

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.54 (2.1H, d, J = 6.8Hz, C1C$\underline{H}_3$) (m), 1.64 (0.9H, d, J = 6.8Hz, C1C$\underline{H}_3$) (s); 2.59 (3H, s, COC$\underline{H}_3$); 2.92 – 3.10 (2H, m, C4$\underline{H}_3$); 3.28 (0.3H, dt, J_1 = 12Hz, J_2 = 4.1Hz, C3$\underline{H}_2$) (s); 3.59 (0.7H, dt, J_1 = 13Hz, J_2 = 3.4Hz, C3$\underline{H}_2$) (m); 4.10 (0.7H, d, J = 14Hz, C3$\underline{H}_2$) (m), 4.63 (0.3H, dd, J_1 = 13Hz, J_2 = 5.5Hz, C3$\underline{H}_2$) (s); 5.20- 5.22 (0.3H, m, C1$\underline{H}$) (s), 5.62 (0.7H, q, J = 6.8Hz, C1$\underline{H}$) (m); 7.21 – 7.28 (1H, m, C5$\underline{H}$); 7.74 – 7.82 (2H, m, C6$\underline{H}$, C8$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 27.6 (CO$\underline{C}H_3$) (s), 29.0 (CO$\underline{C}H_3$) (s); 28.0 ($\underline{C}4H_2$) (s), 29.4 ($\underline{C}4H_2$) (m); 36.1 ($\underline{C}3H_2$) (s), 39.1 ($\underline{C}3H_2$) (m); 50.0 ($\underline{C}1H$) (m), 53.4 ($\underline{C}1H$) (s); 116.3 ($\underline{C}F_3$, q, J = 286Hz); 126.4, 126.6, 126.7, 127.1 ($\underline{C}6H$, $\underline{C}8H$) (s), (m), (m), (s); 129.1 ($\underline{C}5H$) (m), 129.5 ($\underline{C}5H$) (s); 132.9 ($\underline{C}7CO$); 135.6 ($\underline{C}8a$) (s); 135.8 ($\underline{C}8a$) (m); 138.0 ($\underline{C}4a$) (s), 141.9 ($\underline{C}4a$) (m); 155.1 ($\underline{C}OCF_3$) (m), 155.5 ($\underline{C}OCF_3$) (s); 197.3 ($\underline{C}OCH_3$) (m), 197.4 ($\underline{C}OCH_3$) (s)

^{19}F-NMR (376MHz): -69.45 (s), -69.8 (m)

Yield: 94%

IRν_{max}(KBr): 705cm^{-1}, 1265cm^{-1}, 1422cm^{-1}, 1684cm^{-1}, 2986cm^{-1}, 3055cm^{-1}

Melting point: 68 - 70°C Literature: 68 - 70°C[36]

1-[7-(2-Bromo-acetyl)-3,4-dihydro-*1H*-isoquinolin-2-yl]-2,2,2-trifluoro-ethanone (229)[35]

1-(7-Acetyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-2,2,2-trifluoroethanone **(227)** (1.8 g/6.6 mmol) was dissolved in dry methanol. A spatula tipful of aluminium chloride was added. Bromine (0.36 mL/7.0 mmol) was added under nitrogen and the solution was stirred at room temperature for 1 hour. The methanol was removed *in vacuo*. The residue was dissolved in water, extracted with DCM and dried with anhydrous sodium sulfate. It was evacuated to dryness, and purified by elution with 100% DCM, giving colourless oil.

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.99 – 3.04 (2H, m, C4$\underline{H}_3$); 3.85 – 3.91 (2H, t, t, overlapping, J = 5.5Hz, J = 6.0Hz, C3$\underline{H}_2$) (m); 4.43 (2H, s, C$\underline{H}_2$Br); 4.81 (0.6H, s, C1$\underline{H}_2$) (s), 4.83 (1.4H, s, C1$\underline{H}_2$) (s); 7.28 – 7.32 (1H, m, C5$\underline{H}$); 7.77 – 7.87 (2H, m, C6$\underline{H}$, C8$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 27.9 ($\underline{C}4H_2$) (s), 29.0 ($\underline{C}4H_2$) (m); 30.8 ($\underline{C}H_2$Br); 41.1 ($\underline{C}3H_2$) (s), 42.7 ($\underline{C}1H_2$) (m), 45.4 ($\underline{C}3H_2$) (m), 46.7 ($\underline{C}1H_2$); 116.2 ($\underline{C}F_3$, q, J = 286Hz); 126.5, 126.9, 127.3, 128.0 ($\underline{C}6H$, $\underline{C}8H$) (s), (m), (m), (s); 129.1 ($\underline{C}5H$) (m), 129.4 ($\underline{C}5H$) (s); 132.1 ($\underline{C}7CO$) (s), 132.2 ($\underline{C}7CO$) (m); 132.36 ($\underline{C}8a$) (s); 132.4 ($\underline{C}8a$) (m); 139.6 ($\underline{C}4a$) (m), 140.4 ($\underline{C}4a$) (m); 156.0 ($\underline{C}OCF_3$) (m); 190.6 ($\underline{C}OCH_3$) (m), 190.65 ($\underline{C}OCH_3$) (s)

^{19}F-NMR (376MHz): -69.83 (s), -69.90 (m)

Yield: 49%

IRν_{max}(KBr): 1163cm^{-1}, 1427cm^{-1}, 1685cm^{-1}, 2997cm^{-1}, 3322cm^{-1}

1-[7-(2-Bromo-acetyl)-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl]-2,2,2-trifluoro-ethanone (230)[36]

As for **(229).**

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.58 (2.1H, d, J = 6.8Hz, C1C$\underline{H}_3$) (m), 1.66 (0.9H, d, J = 6.8Hz, C1C$\underline{H}_3$) (s); 2.92 – 3.13 (2H, m, C4$\underline{H}_3$); 3.30 (0.3H, dt, J_1 = 12.6Hz, J_2 = 4.8Hz, C3$\underline{H}_2$) (s); 3.60 (0.7H, dt, J_1 = 13Hz, J_2 =

4.1Hz, C3$\underline{H}_2$) (m); 4.13 (0.7H, d, J = 14Hz, C3$\underline{H}_2$) (m); 4.43 (2H, s, C$\underline{H}_2$Br); 4.65 (0.3H, dd, J_1 = 12Hz, J_2 = 4.8Hz, C3$\underline{H}_2$) (s); 5.23 (0.3H, q, J = 6.8Hz, C1$\underline{H}$) (s), 5.63 (0.7H, q, J = 6.8Hz, C1$\underline{H}$) (m); 7.27 – 7.31 (1H, m, C5$\underline{H}$); 7.80 – 7.81 (2H, m, C6$\underline{H}$, C8$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 21.1 ($\underline{C}H_3$) (m), 23.3 ($\underline{C}H_3$) (s); 28.2 ($\underline{C}4H_2$) (s), 29.5 ($\underline{C}4H_2$) (m); 30.5 ($\underline{C}H_2$Br); 36.0 ($\underline{C}3H_2$) (s), 38.7 ($\underline{C}3H_2$) (m); 50.0 ($\underline{C}$1H) (m), 52.1 ($\underline{C}$1H) (s); 116.3 ($\underline{C}F_3$, q, J = 286Hz); 126.8, 127.2, 127.6, 127.7 ($\underline{C}$6H, $\underline{C}$8H) (s), (m), (m), (s); 129.4 ($\underline{C}$5H) (m), 129.8 ($\underline{C}$5H) (s); 132.4 ($\underline{C}$7CO) (s), 132.5 ($\underline{C}$7CO) (m); 137.4 ($\underline{C}$8a) (s); 137.6 ($\underline{C}$8a) (m); 139.0 ($\underline{C}$4a) (m), 139.6 ($\underline{C}$4a) (m); 155.2 ($\underline{C}OCF_3$) (m); 190.6 ($\underline{C}OCH_3$) (m), 190.7 ($\underline{C}OCH_3$) (s)

^{19}F-NMR (376MHz): -69.49 (s), -69.87 (m)

Yield: 52%

IRν_{max}(KBr): 1114cm^{-1}, 1422cm^{-1}, 1686cm^{-1}, 2872cm^{-1}, 3082cm^{-1}

Phenoxyacetyltetrahydroisoquinolines (Protected) (231-254)

The bromide **(229/230)** (1.2 mmol) was dissolved in acetone (10 mL) and potassium carbonate (182 mg/1.32 mmol) was added. The mixture was stirred at room temperature for 10 minutes. The appropriate phenol (1.32 mmol) was added and the solution was refluxed for 1.5 hours. The acetone was removed *in vacuo*, the residue was taken up in DCM and the extract was washed. It was dried and the solvent was removed *in vacuo* to give the protected phenoxyacetyltetrahydroisoquinoline, almost always as a yellow oil.

*Note: In some cases (marked *) the HRMS molecular ion of the* ***protected*** *product did not form, but that of the related* ***final*** *product was obtained.*

2,2,2-Trifluoro-1-[7-(2-*p*-tolyloxy-acetyl)-3,4-dihydro-1H-isoquinolin-2-yl]-ethanone (231)

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.27, 2.29 (3H, s, s, C$\underline{H}_3$), 2.96 – 3.04 (2H, m, C4$\underline{H}_2$); 3.84 – 3.93 (2H, m, C3$\underline{H}_2$); 4.76, 4.80 (2H, s, s C1$\underline{H}$); 5.21 (1.6H, s, COC$\underline{H}_2$), 5.22 (0.4H, s, COC$\underline{H}_2$); 6.78 (0.4H, dd, J_1 = 6Hz, J_2 = 2Hz, C2'$\underline{H}$, C6'$\underline{H}$); 6.86 (1.6H, dd, J_1 = 6Hz, J_2 = 2Hz, C2'$\underline{H}$, C6'$\underline{H}$); 7.02 (0.4H, d, J = 8Hz, C3'$\underline{H}$, C5'$\underline{H}$), 7.09 (1.6H, d, 8Hz, C3'$\underline{H}$, C5'$\underline{H}$); 7.23– 7.33 (1H, m, C5$\underline{H}$); 7.81 – 7.89 (2H ,m, C6H, C8H)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 20.3 ($\underline{C}H_3$); 27.9 ($\underline{C}4H_2$)(s), 29.3 ($\underline{C}4H_2$)(m); 41.2 ($\underline{C}1H_2$) (m); 42.8 ($\underline{C}3H_2$)(s); 45.2 ($\underline{C}3H_2$)(m); 46.7 ($\underline{C}1H_2$)(s); 70.7 (CO$\underline{C}H_2$); 114.4 ($\underline{C}$2'H, $\underline{C}$6'H)(m), 115.0 ($\underline{C}$2'H, $\underline{C}$6'H)(s); 125.8 ($\underline{C}$6H)(s), 126.6 ($\underline{C}$6H)(m); 126.7 ($\underline{C}$8H)(m), 127.0 ($\underline{C}$8H)(s); 127.3 ($\underline{C}F_3$, q, J = 115Hz); 129.1 ($\underline{C}$5H)(m), 129.3 ($\underline{C}$5H)(s); 130.4 ($\underline{C}$3'H, $\underline{C}$5'H)(s), 130.8 ($\underline{C}$3'H, $\underline{C}$5'H)(m); 132.1 ($\underline{C}4'CH_3$); 133.1 ($\underline{C}$7CO); 137.4 ($\underline{C}$8a); 139.5 ($\underline{C}$4a); 153.7 ($\underline{C}OCF_3$); 155.6 ($\underline{C}$1'); 194.3 ($\underline{C}OCH_2$)

^{19}F-NMR (376MHz): -69.82 (s), -69.89 (m)

Yield: 89%

IRν_{max}(KBr): 1162cm^{-1}, 1694cm^{-1}(CO), 2353cm^{-1}, 2393cm^{-1}(CH)

HRMS calcd. for C20H18NO3F3Na (M^++23): 400.1136 Found: 400.1121

2,2,2-Trifluoro-1-{7-[2-(4-methoxy-phenoxy)-acetyl]-3,4-dihydro-*1H*-isoquinolin-2-yl}-ethanone (232)

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.99 – 3.04 (2H, m, C4$\underline{H}_3$); 3.74 (3H, s, OC$\underline{H}_3$); 3.86, 3.90 (2H, t,t, (overlapping triplets), J = 6.1Hz, C3$\underline{H}_2$); 4.80, 4.83 (2H, s, s, C1$\underline{H}_2$); 5.17, 5.18 (2H, s, s, COC$\underline{H}_2$); 6.80 (2H, d, J = 8.9Hz, C2'$\underline{H}$, C6'$\underline{H}$); 6.87 (2H, d, J = 8.9Hz, C3'$\underline{H}$. C5'$\underline{H}$); 7.26 – 7.31 (1H, m, C5$\underline{H}$); 7.79 – 7.86 (2H, m, C6$\underline{H}$, C8$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 28.0 ($\underline{C}4H_2$)(s), 29.3 ($\underline{C}4H_2$)(m); 41.2 ($\underline{C}1H_2$)(m); 42.7 ($\underline{C}3H_2$)(s), 45.2 ($\underline{C}3H_2$)(m); 46.7 ($\underline{C}1H_2$)(s); 55.5 ($O\underline{C}H_3$); 71.6 ($CO\underline{C}H_2$); 114.5 (C2'H, C6'H); 115.7 (C3'H, C5'H); 125.9 (C6H)(s), 126.4 (C6H)(m); 126.6 (C8H)(m), 127.0 (C8H)(s); 127.7 (q, J = 145Hz, $\underline{C}F_3$); 129.1 (C5H)(m), 129.3 (C5H)(s); 132.2 (C7CO); 133.2 (C8a); 139.4 (C4a); 140.2 ($\underline{C}4'OCH_3$); 151.9 (C1'); 154.3 ($\underline{C}OCF_3$); 194.2 (CO)

^{19}F-NMR (376MHz): -69.82 (s), -69.90 (m)

Yield: 45%

IRν_{max}(KBr): 820cm^{-1}, 1199cm^{-1}, 1511cm^{-1}, 1708cm^{-1}, 2897cm^{-1}, 3422cm^{-1}

HRMS calcd. for C20H19NO4F3 (M^++1): 394.1266 Found: 394.1251

1-{7-[2-(4-Ethoxy-phenoxy)-acetyl]-3,4-dihydro-*1H*-isoquinolin-2-yl}-2,2,2-trifluoro-ethanone (233)

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.37 (3H, t, J = 6.8Hz, $OCH_2C\underline{H}_3$); 2.99 – 3.03 (2H, m (overlapping triplets), C4$\underline{H}_2$); 3.85 – 3.90 (2H, m (overlapping triplets), C3$\underline{H}_2$); 3.95 (2H, q, J = 1.7Hz, $OC\underline{H}_2CH_3$); 4.80 (0.7H, s, C1$\underline{H}_2$); 4.83 (1.3H, s, C1$\underline{H}_2$); 5.17 (2H, s, $COC\underline{H}_2$); 6.80 (2H, dd, J_1 = 6.8Hz, J_2 = 2.8Hz, C2'H, C6'H); 6.86 (2H, dd, J_1 = 6.8Hz, J_2 = 2.8Hz, C3'H, C5'H); 7.26 – 7.31 (1H, m, C5H); 7.79 – 7.86 (2H, m, C6H, C8H)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 14.7 ($\underline{C}H_3$); 27.9 ($\underline{C}4H_2$)(s), 29.3 ($\underline{C}4H_2$)(m); 41.2 ($\underline{C}1H_2$)(m); 42.7 ($\underline{C}3H_2$)(s), 45.2 ($\underline{C}3H_2$)(m); 46.7 ($\underline{C}1H_2$)(s); 63.8 ($O\underline{C}H_2$); 71.6 ($CO\underline{C}H_2$); 115.2 (C2'H, C6'H); 115.6 (C3'H, C5'H); 125.9 (C6H)(s), 126.4 (C6H)(m); 127.5 (q, J = 120Hz, $\underline{C}F_3$); 126.6 (C8H)(m), 127.0 (C8H)(s); 129.1 (C5H)(m), 129.3 (C5H)(s); 132.1 (C7CO); 133.2 (C8a); 139.4 (C4a); 140.2 ($\underline{C}4'OCH_2$); 151.8 (C1'); 153.7 ($\underline{C}OCF_3$) 194.2(CO)

Yield: 40%

IRν_{max}(KBr): 817cm^{-1}, 1210cm^{-1}, 1511cm^{-1}, 1707cm^{-1}(CO), 2895cm^{-1}, 3405cm^{-1}(CH)

HRMS calcd. for C21H21NO4F3 (M^++1): 408.1423 Found: 408.1434

2,2,2-Trifluoro-1-{7-[2-(4-fluoro-phenoxy)-acetyl]-3,4-dihydro-*1H*-isoquinolin-2-yl}-ethanone (234)

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.99 – 3.04 (2H, m (overlapping triplets), C4$\underline{H}_2$); 3.86 – 3.92 (2H, m (overlapping triplets), C3$\underline{H}_2$); 4.81, 4.83 (2H, s, s, C1$\underline{H}_2$); 5.21, 5.22 (2H, s, s, $COC\underline{H}_2O$); 6.84 – 6.88 (2H, m, C2'H, C6'H); 6.90 – 6.96 (2H, m, C3'H, C5'H); 7.26 – 7.33 (1H, m, C5H); 7.78 – 7.86 (2H, m, C6H, C8H)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 27.7 ($\underline{C}4H_2$)(s), 29.3 ($\underline{C}4H_2$)(m); 41.2 ($\underline{C}3H_2$)(s); 42.8 ($\underline{C}1H_2$) (m); 45.2 ($\underline{C}3H_2$)(m); 46.7 ($\underline{C}1H_2$)(s); 71.3 ($CO\underline{C}H_2$)(m), 74.1 ($CO\underline{C}H_2$)(s); 115.7 (d, J = 7.7 Hz, C2'H, C6'H); 115.9 (d, J = 7.7 Hz, C3'H, 5'H); 126.4 (C6H); 126.5 (C8H); 127.7($\underline{C}F_3$, q, J = 120Hz); 129.2 (C5H)(s); 132.2 (C7CO); 132.9 (C8a); 139.7 (C4a); 153.9 (C4'F); 156.4 (C1'); 158.8 ($\underline{C}OCF_3$); 193.8 ($\underline{C}OCH_2$)

^{19}F-NMR (376MHz): -69.83 (s), -69.91 (m)

Yield: 73%

IRν_{max}(KBr): 1160cm^{-1} (CF aromatic), 1206cm^{-1} (CF), 1672cm^{-1} (CO), 1702cm^{-1} ($COCF_3$), 2906 cm^{-1}, 3448cm^{-1}(CH)

HRMS calcd. for C19H16NO3F4 (M^++1): 382.1066 Found: 382.1069

1-{7-[2-(4-Chloro-phenoxy)-acetyl]-3,4-dihydro-*1H*-isoquinolin-2-yl}-2,2,2-trifluoro-ethanone (235)*

^{1}H-NMR (400MHz): δ($CDCl_3$): 3.00 – 3.05 (2H, m, C4$\underline{H}_2$); 3.88, 3.92 (2H, t, t, overlapping, J_1 = 5.5Hz, J_2 = 6.2Hz, C3$\underline{H}_2$, C3$\underline{H}_2$); 4.82 (0.7 Hz, s, C1$\underline{H}_2$ (m)), 4.85 (1.3H, s, C1$\underline{H}_2$ (m)); 5.24 (2H, s, $COC\underline{H}_2$); 6.85 (2H,

d, J = 11.7 Hz, C2'H, C6'H); 7.21 (2H, d, J = 11.1 Hz, C3'H, C5'H); 7.21 – 7.34 (1H, m, C5H); 7.80 (1H, C8H); 7.82 – 7.87 (1H, m, C6H)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 28.0 ($C4H_2$)(s), 29.4 ($C4H_2$)(m); 41.2 ($C3H_2$)(s); 42.8 ($C1H_2$ (m)); 45.2 ($C3H_2$)(m); 45.5 ($C1H_2$); 70.8 ($COCH_2$); 116.0 (C2'H, C6'H); 125.9, 126.4; 126.6, 127.0 (C6H, C8H (s) (m) (m) (s)); 126.5 (C4'Cl); 128.0 (CF_3, q, J = 115Hz); 129.4 (C3'H, 5'H); 132.2 (C7CO)(s)), 132.3 (C7CO (m)); 132.9 (C8a (s)), 133.0 (C8a (m)); 139.7 (C4a)(m)), 140.5 (C4a (s)); 154.9 ($COCF_3$)(m); 155.2 ($COCF_3$)(s); 156.4 (C1'); 191.5 ($COCH_2$)

^{19}F-NMR (376MHz): -69.83 (s), -69.91 (m)

Yield: 63%

IRν_{max}(film): 1095cm^{-1} (CCl aromatic), 1694cm^{-1} (CO), 2987 cm^{-1}, 3055cm^{-1}(CH)

1-{7-[2-(4-Bromo-phenoxy)-acetyl]-3,4-dihydro-*1H*-isoquinolin-2-yl}-2,2,2-trifluoro-ethanone (236)*

^{1}H-NMR (400MHz): δ($CDCl_3$): 3.00 – 3.05 (2H, m, C4H_2); 3.86 - 3.91 (2H, m, C3H_2); 4.82 (0.7 Hz, s, C1H_2 (m)), 4.84 (1.3H, s, C1H_2 (m)); 5.23 (2H, s, COCH_2); 6.80 (2H, d, J = 8.6 Hz, C2'H, C6'H); 7.32 (2H, d, J = 8.5 Hz, C3'H, C5'H); 7.23 – 7.39 (1H, m, C5H); 7.76 – 7.86 (1H, m, C8H, C6H)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 28.0 ($C4H_2$)(s), 29.4 ($C4H_2$)(m); 41.2 ($C3H_2$)(s); 41.5 ($C1H_2$ (m)); 45.2 ($C3H_2$)(m); 46.7 ($C1H_2$); 70.7 ($COCH_2$); 113.8 (C'Br); 116.4 (C2'H, C6'H); 125.8, 126.4; 126.5, 127.0 (C6H, C8H (s) (m) (m) (s)); 128.3 (CF_3, q, J = 115Hz); 129.2 (C3'H, 5'H); 132.3 (C7CO); 132.9 (C8a); 139.7 (C4a)(m)), 140.5 (C4a (s)); 154.7 ($COCF_3$); 156.9 (C1'); 191.3 ($COCH_2$ (s)), 193.4 ($COCH_2$ (m))

^{19}F-NMR (376MHz): -69.81 (s), -69.89 (m)

Yield: 59%

IRν_{max}(KBr): 1695cm^{-1} (CO), 1702cm^{-1}, 2987 cm^{-1}, 3055cm^{-1}(CH)

2,2,2-Trifluoro-1-{7-[2-(4-iodo-phenoxy)-acetyl]-3,4-dihydro-*1H*-isoquinolin-2-yl}-ethanone (237)

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.99 – 3.05 (2H, m (overlapping triplets), C4H_2); 3.86 – 3.93 (2H, m m (overlapping triplets), C3H_2); 4.80, 4.83 (2H, s, s, C1H_2); 5.22, 5.23 (2H, s, s, COCH_2), 6.69 (2H, d, J = 8.6Hz, C2'H, C6'H,); 7.25 – 7.32 (1H, m, C5H); 7.52 (2H, d, J = 8.6Hz, C3'H, C5'H); 7.78 – 7.85 (2H, m, C6H, C8H)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 28.0 ($C4H_2$)(s), 29.3 ($C4H_2$)(m); 41.2 ($C3H_2$)(s); 42.7 ($C1H_2$)(m); 45.2 ($C3H_2$)(m), 45.4 ($C1H_2$)(s); 70.5 ($COCH_2$)(s), 70.44 ($COCH_2$)(m); 83.9 (CI); 117.0 (C2'H, C6'H)(m), 117.8 (C2'H, C6'H)(s); 125.8, 126.3, 126.5, 127.0 (C6H, C8H, (s), (m), (m), (s)); 129.2 (C5H (m)), 129.4 (C5H (s)); 132.1 (C7CO (s)), 132.2 (C7CO (m)); 132.8 (C8a (m)), 132.9 (C8a (m)); 138.1 (C3'H, C5'H)(s), 138.2 (C3'H, C5'H); 140.5 (C4a); 155.6 ($COCF_3$); 157.6 (C1'); 193.3 (CO)

^{19}F-NMR (376MHz): -69.75 (s), -69.83 (m)

Yield: 69%

IRν_{max}(KBr): 1694cm^{-1} (CO), 2986 cm^{-1}, 3055cm^{-1}(CH)

HRMS calcd. for C19H15NO3F3NaI (M^++23): 511.9946 Found: 511.9934

N*-(4-{2-[2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-2-oxo-ethoxy}-phenyl)-acetamide (238)

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.77 (1H, bs, NH); 2.18 (3H, s, $COCH_3$); 3.03 – 3.06 (2H, m, $C4H_2$); 3.89 – 3.96 (2H, m, $C3H_3$); 4.84 (0.7 Hz, s, $C1H_2$ (m)), 4.88 (1.3H, s, $C1H_2$ (m)); 5.22 (2H, s, $COCH_2$); 6.90 (2H, d, J = 9 Hz, C2'H, C6'H); 7.12 (1H, m, C5H); 7.41 (2H, d, J = 9 Hz, C3'H, C5'H); 7.81 – 7.88 (2H, C8H, C6H)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 24.1 (CH_3 (m)); 28.0 ($C4H_2$)(s), 29.1 (CH_3 (s)); 29.4 ($C4H_2$)(m); 41.2 ($C3H_2$)(s); 42.8 ($C1H_2$ (m)); 45.3 ($C3H_2$)(m); 45.5 ($C1H_2$); 70.6 ($COCH_2$); 114.9 (C2'H, C6'H); 121.9 (C3'H, 5'H); 125.9, 126.4; 126.6, 127.1 (C6H, C8H (s) (m) (m) (s)); 129.2 (C5H (m)), 129.4 (C5H (s)); 132.1 (C7CO)), 132.2 (C8a); 133.8 (C4'NH); 139.7 (C4a); 154.4 (C1'); 156 ($COCF_3$); 168.7 ($COCH_3$); 194.2 ($COCH_2$)

^{19}F-NMR (376MHz): -69.83 (s), -69.91 (m)

Yield: 67%

IRν_{max}(KBr): 1607 cm^{-1} (CO), 2428 cm^{-1}, 2908 cm^{-1} (CH)

2,2,2-Trifluoro-1-{7-[2-(4-nitro-phenoxy)-acetyl]-3,4-dihydro-1H-isoquinolin-2-yl}-ethanone (239)*

^{1}H-NMR (400MHz): δ($CDCl_3$): 3.03 – 3.07 (2H, m, $C4H_2$); 3.89 – 3.96 (2H, m, $C3H_3$); 4.83 (0.7 Hz, s, $C1H_2$ (m)), 4.88 (1.3H, s, $C1H_2$ (m)); 5.22 (2H, s, $COCH_2$); 6.90 (2H, d, J = 8.5 Hz, C2'H, C6'H); 7.17 (1H, m, C5H); 7.41 (2H, d, J = 8.5 Hz, C3'H, C5'H);

7.80 – 7.87 (2H, C8H, C6H)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 28.1 ($C4H_2$)(s), 29.5 ($C4H_2$)(m); 41.2 ($C3H_2$)(s); 42.8 ($C1H_2$ (m)); 45.3 ($C3H_2$)(m); 45.5 ($C1H_2$); 70.6 ($COCH_2$); 114.7 (C2'H, C6'H); 125.9 (C3'H, 5'H); 126.4; 126.6, 127.0 (C6H, C8H (m) (m) (s)); 129.5 (C5H (m)), 129.7 (C5H (s)); 132.6 (C7CO)), 132.7 (C8a); 140.1 (C4a), 142.1 ($C4'NO_2$); 162.7 (C1'); 192.2 ($COCH_2$)

^{19}F-NMR (376MHz): -69.83 (s), -69.91 (m)

Yield: 62%

IRν_{max}(KBr): 1501 cm^{-1} (NO), 1607 cm^{-1} (CO), 2428 cm^{-1}, 2908 cm^{-1} (CH)

4-{2-[2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-2-oxo-ethoxy}-benzonitrile (240)*

^{1}H-NMR (400MHz): δ($CDCl_3$): 3.04 – 3.09 (2H, m, $C4H_2$); 3.90 – 3.97 (2H, m, $C3H_2$); 4.84 (0.7 Hz, s, $C1H_2$ (m)), 4.89 (1.3H, s, $C1H_2$ (m)); 5.32 (2H, s, $COCH_2$); 7.00 (2H, d, J = 9 Hz, C2'H, C6'H); 7.33 – 7.38 (1H, m, C5H); 7.61 (2H, d, J = 9 Hz, C3'H, C5'H); 7.79 – 7.82 (2H, m, C8H, C6H)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 28.0 ($C4H_2$)(s), 29.4 ($C4H_2$)(m); 41.2 ($C3H_2$)(s); 42.8 ($C1H_2$ (m)); 45.2 ($C3H_2$)(m); 45.5 ($C1H_2$); 70.3 ($COCH_2$); 104.8 (C4'CN); 115.4 (C2'H, C6'H); 118.8 (CN);125.8, 126.4; 126.5, 127.0 (C6H, C8H (s) (m) (m) (s)); 128.0 (CF_3, q, J = 115Hz); 132.2 (C7CO)(s)), 132.3 (C7CO (m)); 132.9 (C8a (s)), 133.0 (C8a (m)); 134.0 (C3'H, 5'H); 139.7 (C4a)(m)), 140.5 (C4a (s)); 154.9 ($COCF_3$)(m); 155.2 ($COCF_3$)(s); 156.4 (C1'); 191.5 ($COCH_2$)

^{19}F-NMR (376MHz): -69.82 (s), -69.91 (m)

Yield: 61%

IRν_{max}(KBr): 1703cm^{-1} (CO), 2987 cm^{-1}, 3055cm^{-1}(CH)

1-{7-[2-(4-Benzyloxy-phenoxy)-acetyl]-3,4-dihydro-*1H*-isoquinolin-2-yl}-2,2,2-trifluoro-ethanone (241)

^{1}H-NMR (400MH): δ($CDCl_3$): 3.01 – 3.05 (2H, m, C4H_2); 3.89, 3.93 (2H, t, t, (overlapping), J = 6.1Hz, C3H_2); 4.82, 4.86 (2H, s, s, C1H_2); 5.01 (OC$H_2C_6H_5$); 5.19 (COCH_2); 6.83 – 6.93 (4H, m, C2'H, C3'H, C5'H, C6'H); 7.26 – 7.44 (6H, C5H, C2"H, C3"H, C4"H, C5"H, C6"H); 7.78 – 7.89 (2H, m, C6H, C8H)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 28.0 (C$4H_2$)(s), 29.4 (C$4H_2$)(m); 41.2 (C$1H_2$)(m); 42.8 (C$3H_2$)(s), 45.3 (C$3H_2$)(m); 46.8 (C$1H_2$)(s); 70.5 (OC$H_2C_6H_5$); 71.6 (COCH_2); 115.8 (C2'H, C3'H, C5'H, C6'H); 126.0 (C6H)(s), 126.5 (C6H)(m); 126.7 (C8H)(m); 127.0 (CF_3); 127.1(C8H)(s); 127.4 (C2"H, C6"H); 127.8 (C4"H); 128.5 (C3"H, C5"H); 129.2 (C5H)(m), 129.4 (C5H)(s); 132.1 (C7CO); 133.2 (C8a); 137.0 (C4a); 139.5 (C1"); 140.3 (C1'); 152.2 (C4'); 153.6(COCF_3); 194.2 (CO)

Yield: 21%

IRν_{max}(KBr): 732cm^{-1}, 1141cm^{-1}, 1202cm^{-1}, 1506cm^{-1}, 1694cm^{-1} (CO), 2914cm^{-1}, 3046cm^{-1}(CH)

Melting point: 112°C

HRMS calcd. for C26H22NO4F3Na (M^++23): 492.1399 Found: 492.1408

4-{2-[2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-2-oxo-ethoxy}-benzoic acid benzyl ester (242)

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.99- 3.00 (2H, m, C4H_2); 3.85, 3.89 (2H, t, t, (overlapping), J = 6Hz, C3H_2); 4.80, 4.82 (2H, s, s, C1H_2); 5.33 (4H, COCH_2, COOCH_2); 6.95, 6.91 (2H, d, d, J = 8.9Hz, C2'H, C6'H); 7.24 – 7.44 (6H, m, C5H, C2"H, C3"H, C4"H, C5"H, C6"H); 7.79 – 7.86 (2H, m, C6H, C8H); 7.96, 8.01 (2H, d, d, J = 8.9Hz, C3'H, C5'H)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 27.8 (C$4H_2$)(s), 29.2 (C$4H_2$)(m); 41.1 (C$3H_2$)(s); 42.6 (C$1H_2$)(m), 45.1 (C$3H_2$)(m); 46.6 (C$1H_2$)(s); 66.3 (COOCH_2); 70.1 (COCH_2); 114.2, 115.1(C2'H, C6'H (m), (s)); 121.5 (CF_3); 123.1 (C4'CO); 125.7 (C6H)(s), 126.2 (C6H)(m); 126.4 (C8H)(m), 126.9 (C8H)(s); 127.8, 127.9, 127.92, 128.0, 128.35, 128.37 (C2"H, C3"H, C4"H, C5"H, C6"H (m), (s), (s), (m), (s), (m)); 129.2 (C5H)(m), 129.3 (C5H)(s); 131.6 131.7 (C3'H, C5'H); 132.2, 132.7 (C7CO (m), (s)); 134.0, 135.9 (C8a (m), (s)); 137.7, 139.7 (C4a (m), (s)); 140.5 (C1") 155.6 (COCF_3); 161.0, 161.5 (C1' (s), (m)); 165.9 (C$OOCH_2$); 193.0 (CO)

Yield: 47%

IRν_{max}(KBr): 1696cm^{-1} (CO), 2987 cm^{-1}, 3055cm^{-1}(CH)

HRMS calcd. for C27H22NO5F3Na (M^++23): 520.1348 Found: 520.1368

1-Methyl

2,2,2-Trifluoro-1-[1-methyl-7-(2-*p*-tolyloxy-acetyl)-3,4-dihydro-1H-isoquinolin-2-yl]-ethanone (243)*

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.57 (2.3H, d, J = 7 Hz, CH_3), 1.66 (0.7Hz, d, J = 6.8Hz, CH_3); 2.27 (3H, s, CH_3); 2.90 – 3.14 (2H, m, C4H_2); 3.29 (0.3H, dt, J_1 = 12Hz, J_2 = 4Hz, C3H_2), 3.59 (0.7H, dt, J_1 = 12Hz, J_2 = 3Hz, C3H_2), 4.11 (0.7H, d, J = 14Hz, C3H_2); 4.67 (0.3H, dt, J_1 = 10Hz, J_2 = 4Hz, C3H_2); 5.16 - 5.22 (2.3 H, s, q overlapping COCH_2); 5.64 (0.7H, q, J = 6.8Hz, C1H), 6.84 (2H, d, J = 8.2Hz, C2'H, C6'H); 7.08 (2H, d, 8.2Hz, C3'H, C5'H); 7.26 – 7.29 (1H, m, C5H); 7.82 – 7.87 (2H,m, C6H, C8H)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 20.0 (C4'CH_3)(m); 20.5 (C4'CH_3)(s), 20.7 (C1CH_3)(m); 22.9 (C1CH_3)(s); 28.8 (C4H_2)(s), 29.1 (C4H_2)(m); 35.7 (C3H_2)(s); 38.6 (C3H_2)(m); 49.6 (C1H)(m), 49.8 (C1H)(s); 70.57 (COCH_2)(s), 70.65 (COCH_2)(m); 114.2 (C2'H, C6'H)(m), 114.6 (C2'H, C6'H)(s); 126.06

(C6H)(m), 126.1 (C6H)(s); 126.25 (C8H)(s), 126.5 (C8H)(m); 127.6 (CF_3, q, J = 115Hz); 128.9(C5H)(m), 129.3 (C5H)(s); 129.5 (C3'H, C5'H)(s), 129.6 (C3'H, C5'H)(m); 130.6 (C4'CH_3); 132.8 (C7CO)(s), 132.9(C7CO)(m); 136.9 (C8a)(s), 137.1 (C8a)(m); 138.4 (C4a)(m), 138.9 (C4a)(s); 155.2 ($COCF_3$)(s), 155.4 ($COCF_3$)(m); 193.8 ($COCH_2$)(s), 193.95 ($COCH_2$)(m)

^{19}F-NMR (376MHz): -69.48 (s), -69.85 (m)

Yield: 80%

IRν_{max}(KBr): 1509 cm^{-1}(CO ether), 1686 cm^{-1}(CO), 2985 cm^{-1}, 3055 cm^{-1}(CH)

2,2,2-Trifluoro-1-{7-[2-(4-methoxy-phenoxy)-acetyl]-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl]-ethanone (244)

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.56 (2.3H, d, J = 6.8Hz, CH_3), 1.64 (0.7Hz, d, J = 6.8Hz, CH_3); 2.90 – 3.11 (2H, m, C4H_2); 3.29 (0.3H, dt, J_1 = 12.6Hz, J_2 = 4Hz, C3H_2), 3.59 (0.7H, dt, J_1 = 12Hz, J_2 = 3Hz, C3H_2), 3.75 (3H, s, OCH_3); 4.11 (0.7H, d, J = 14Hz, C3H_2); 4.66 (0.3H, dt, J_1 = 13Hz, J_2 = 4Hz, C3H_2); 5.19 (2H, s, COCH_2); 5.64 (0.7H, q, J = 6.8Hz, C1H), 6.12 (0.3H, s, C1H), 6.82 (2H, d, J = 8.8 Hz, C2'H, C6'H); 6.89 (2H, d, 8.8 Hz, C3'H, C5'H); 7.25 – 7.28 (1H, m, C5H); 7.79 – 7.86 (2H,m, C6H, C8H)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 20.8 (CH_3)(m), 23.2 (CH_3)(s); 28.1(C4H_2)(s), 29.5 (C4H_2)(m); 36.1 (C3H_2)(s); 38.8 (C3H_2)(m); 50.0 (C1H)(m), 50.2(C1H)(s); 55.5 (OCH_3) (m), 55.6 (OCH_3) (s); 71.6 (COCH_2); 114.6 (C2'H, C6'H); 115.8 (C3'H, C5'H); 126.35 (C6H)(m), 126.4 (C6H)(s); 126.5 (C8H)(s), 126.8 (C8H)(m); 127.0 (CF_3, q, J = 115Hz); 129.3 (C5H)(m), 129.7 (C5H)(s); 132.8 (C7CO)(s), 132.9(C7CO)(m); 137.2 (C8a)(s), 137.4 (C8a)(m); 138.8 (C4a (m)), 139.3 (C4a (s)); 149.9 (C4'OCH_3); 151.9 (C1'); 153.2 (C1'); 155.5 ($COCF_3$); 194.4 ($COCH_2$)(s), 194.5 ($COCH_2$)(m)

^{19}F-NMR (376MHz): -69.45 (s), -69.83 (m)

Yield: 80%

IRν_{max}(KBr): 1509 cm^{-1} (CO ether), 1690 cm^{-1}(CO), 2934 cm^{-1}, 3055 cm^{-1} (CH)

HRMS calcd. for C21H20NO4F3Na (M^++23): 430.1242 Found: 430.1246

1-{7-[2-(4-Ethoxy-phenoxy)-acetyl]-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl]-2,2,2-trifluoro-ethanone (245)*

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.26 – 1.37 (3H, m, CH_2CH_3), 1.53 (2.3Hz, d, J = 6.8Hz, CH_3), 1.62 (0.7H, d, J =6.8Hz, CH_3) ; 2.86 – 3.07 (2H, m, C4H_2); 3.26 (0.3H, dt, J_1 = 13Hz, J_2 = 5.5Hz, C3H_2), 3.59 (0.7H, dt, J_1 = 13Hz, J_2 = 3Hz, C3H_2), 3.90 (2H, m, OCH_2); 4.11 (0.7H, d, J = 14Hz, C3H_2); 4.60 (0.3H, dt, J_1 = 13Hz, J_2 = 4.8Hz, C3H_2); 5.18 – 5.25 (2.3H, s, COCH_2, C1H); 5.60 (0.7H, q, J = 6.8Hz, C1H), 6.72 – 6.88 (4H, m, C2'H, C3'H, C5'H, C6'H); 7.22 – 7.24 (1H, m, C5H); 7.76 – 7.91 (2H, m, C6H, C8H)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 14.7 (CH_2CH_3)(m); 20.9 (C1CH_3)(m); 23.0 (C1CH_3)(s); 27.9 (C4H_2)(s), 29.3 (C4H_2)(m); 36.0 (C3H_2)(s); 39.0 (C3H_2)(m); 49.9 (C1H)(m), 52.1 (C1H)(s); 63.7 (OCH_2) (m), 63.8 (OCH_2) (s); 71.3 (COCH_2); 114.8 (C2'H, C6'H) (m), 115.2 (C2'H, C6'H (s); 115.8 (C3'H, C5'H)) (m), 115.9 (C3'H, C5'H (s)); 126.2 (C6H)(m), 126.3 (C6H)(s); 126.6 (C8H)(s), 126.7 (C8H)(m); 127.0 (CF_3, q, J = 116Hz); 129.2 (C5H)(m), 129.6 (C5H)(s); 132.85 (C7CO)(s), 132.9 (C7CO)(m); 137.1 (C8a)(s), 137.2 (C8a)(m); 138.7 (C4a (m)), 139.3 (C4a (s)); 150.0 (C4'OCH_2); 151.7 (C1'); 153.5 (C1'); 155.1 ($COCF_3$); 194.4 ($COCH_2$)(s), 194.5 ($COCH_2$)(m)

^{19}F-NMR (376MHz): ppm($CDCl_3$): -69.45 (s), -69.82 (m)

Yield: 80%

IRν_{max}(KBr): 1509 cm^{-1} (CO ether), 1690 cm^{-1}(CO), 2934 cm^{-1}, 3422 cm^{-1} (CH)

2,2,2-Trifluoro-1-{7-[2-(4-fluoro-phenoxy)-acetyl]-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl}-ethanone (246)

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.57 (2.3H, d, J = 6.5Hz, C$\underline{H}_3$); 1.65 (0.7H, d, J = 6.5Hz, C$\underline{H}_3$); 2.91 – 3.12 (2H, m, C4$\underline{H}_2$); 3.3 (0.3H, dt, J_1 = 12Hz, J_2 = 3Hz, C3$\underline{H}_2$) ; 3.6 (0.7H, dt, J_1 = 12Hz, J_2 = 3Hz, C3$\underline{H}_2$); 4.10 – 4.13 (0.7H, m, C3$\underline{H}_2$); 4.66 (0.3H, dd, J_1 = 12Hz, J_2 = 6Hz, C3$\underline{H}_2$); 5.23 (2H, s, COC$\underline{H}_2$O); 5.61 – 5.66 (0.7H, m, C1$\underline{H}$); 6.78 – 6.82 (0.3H, m, C1$\underline{H}$); 6.86 – 6.9 (2H, m, C2'$\underline{H}$, C6'$\underline{H}$); 6.93 – 6.98 (2H, m, C3'$\underline{H}$, C5'$\underline{H}$); 7.26 – 7.30 (1H, m, C5$\underline{H}$); 7.79 – 7.86 (2H, m, C6$\underline{H}$, C8$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 21.1 (C$\underline{H}_3$)(m), 23.2 (C$\underline{H}_3$)(s); 28.1 (C$\underline{4}H_2$)(s), 29.5 (C$\underline{4}H_2$)(m); 36.1 (C$\underline{3}H_2$)(s), 38.7 (C$\underline{3}H_2$)(m); 50.0 (C$\underline{1}$H)(m), 52.1 (C$\underline{1}$H)(s); 71.3 (CO$\underline{C}H_2$)(s), 71.4 (CO$\underline{C}H_2$)(m); 115.5 (C$\underline{2}$'H, C$\underline{6}$'H), d, J = 5Hz); 115.9 (C$\underline{3}$'H, 5'H), d, J = 11Hz); 126.2 (C$\underline{6}$H)(m), 126.3 (C$\underline{6}$H)(s); 126.7 (C$\underline{8}$H)(s), 126.9 (C$\underline{8}$H)(m); 128.1 (C$\underline{F}_3$, q, J = 115Hz); 129.4 (C$\underline{5}$H)(m), 129.8 (C$\underline{5}$H)(s); 133.1 (C$\underline{7}$CO)(m), 133.3 (C$\underline{7}$CO)(s); 137.3 (C$\underline{8}$a)(s), 137.5 (C$\underline{8}$a)(m); 139.0 (C$\underline{4}$a)(m), 139.5 (C$\underline{4}$a)(s); 153.9 (C$\underline{1}$'); 157.6 (C$\underline{4}$'F, d, J = 238Hz); 155.6 (C$\underline{O}CF_3$)(s); 193.8 (C$\underline{O}CH_2$)(s), 193.9 (C$\underline{O}CH_2$)(m)

^{19}F-NMR (376MHz): ppm($CDCl_3$): -69.48 (s), -69.86 (m)

Yield: 60%

IRν_{max}(KBr): 750cm^{-1}, 1265cm^{-1}, 1506cm^{-1}(CO ether), 1690cm^{-1}(CO), 2306cm^{-1}, 2987cm^{-1}, 3055cm^{-1}(CH)

HRMS calcd. for C20H18NO3F4 (M^++1): 396.1223 Found: 396.1238

1-{7-[2-(4-Chloro-phenoxy)-acetyl]-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl}-2,2,2-trifluoro-ethanone (247)

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.56 (2.3H, d, J = 6.8Hz, C$\underline{H}_3$), 1.65 (0.7H, d, J = 6.8Hz, C$\underline{H}_3$); 2.93 – 3.11 (2H, m, C4$\underline{H}_2$); 3.30 (0.3H, dt, J_1 = 12Hz, J_2 = 3.5Hz, C3$\underline{H}_2$), 3.60 (0.7H, dt, J_1 = 12Hz, J_2 = 4Hz, C3$\underline{H}_2$); 4.11 (0.7Hz, d, J = 13Hz, C3$\underline{H}_2$), 4.64 (0.3H, dd, J_1 = 13Hz, J_2 = 6Hz, C3$\underline{H}_2$); 5.25, 5.29 (2.3H, overlapping sinlets, quartet, COC$\underline{H}_2$, C1$\underline{H}$); 5.62 (0.7H, q, J = 6.8Hz, C1$\underline{H}$); 6.80 (0.6H, d, J = 8.8Hz, C2'$\underline{H}$, C6'$\underline{H}$); 6.85 (1.4H, d, J = 8.8Hz, C2'$\underline{H}$, C6'$\underline{H}$); 7.13 (0.6Hz, d, J = 8Hz, C3'$\underline{H}$, C5'$\underline{H}$); 7.20 (1.4H, d, J = 8.8Hz, C3'$\underline{H}$, C5'$\underline{H}$); 7.27 (1H, d, J = 7.5Hz, C5$\underline{H}$); 7.78 – 7.85 (2H, C6$\underline{H}$, C8$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 21.0 (C$\underline{H}_3$)(m), 23.1 (C$\underline{H}_3$)(s); 28.1 (C$\underline{4}H_2$)(s), 29.4 (C$\underline{4}H_2$)(m); 36.1 (C$\underline{3}H_2$)(s), 38.7 (C$\underline{3}H_2$)(m); 50.0 (C$\underline{1}$H)(m), 52.2 (C$\underline{1}$H)(s); 70.65 (CO$\underline{C}H_2$)(s), 70.7 (CO$\underline{C}H_2$)(m); 115.9 (C$\underline{2}$'H, C$\underline{6}$'H)(m), 116.6 (C$\underline{2}$'H, C$\underline{6}$'H)(s); 124.6 (C$\underline{4}$'Cl); 126.3 (C$\underline{6}$H)(m), 126.4 (C$\underline{6}$H)(m); 126.7 (C$\underline{8}$H)(s), 126.8 (C$\underline{8}$H)(m); 128.0 (C$\underline{F}_3$, q, J = 115Hz); 129.1 (C$\underline{3}$'H, 5'H)(s), 129.29 (C$\underline{3}$'H, C$\underline{5}$'H)(m); 129.3 (C$\underline{5}$H)(m), 129.4 (C$\underline{5}$H)(s); 132.9 (C$\underline{7}$CO)(m), 133.3 (C$\underline{7}$CO) (s); 137.3 (C$\underline{8}$a)(s), 137.4 (C$\underline{8}$a)(m); 139.1 (C$\underline{4}$a)(m), 139.6 (C$\underline{4}$a)(s); 154.9 (C$\underline{O}CF_3$)(m); 155.2 (C$\underline{O}CF_3$)(s): 156.3 (C$\underline{1}$'); 193.7 (C$\underline{O}CH_2$)(s), 193.8 (C$\underline{O}CH_2$)(m)

^{19}F-NMR (376MHz): -69.42 (s), -69.80 (m)

Yield: 55%

IRν_{max}(KBr): 732 cm^{-1}(CCl), 1172cm^{-1}, 1265cm^{-1}, 1493cm^{-1}, 1690cm^{-1}(CO), 2306cm^{-1}, 2930cm^{-1} 2907cm^{-1}, 3055cm^{-1}, 3387cm^{-1}(CH)

HRMS calcd. for C20H17NO3F3NaCl (M^++23): 434.0747 Found: 434.0764

1-{7-[2-(4-Bromo-phenoxy)-acetyl]-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl}-2,2,2-trifluoro-ethanone (248)

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.56 (2.3H, d, J = 6.8Hz, C$\underline{H}_3$), 1.64 (0.7H, d, J = 6.8Hz, C$\underline{H}_3$); 2.90 – 3.11, m, C4$\underline{H}_2$); 3.29 (0.3H, dt, J_1 = 12Hz, J_2 = 4Hz, C3$\underline{H}_2$), 3.59 (0.7H, dt, J_1 = 14Hz, J_2 = 3.4Hz, C3$\underline{H}_2$); 4.11 (0.7H, d, J = 14Hz, C3$\underline{H}_2$), 4.64 (0.3H, dd, J_1 = 13Hz, J_2 = 5.5Hz, C3H2); 5.19 – 5.29 (2.3H, s, s, m, CO$\underline{CH}_2$, C1$\underline{H}$); 3.58 (0.7H, q, J = 6.8Hz, C1$\underline{H}$); 6.8 (2H, d, J = 8.8Hz, C2'$\underline{H}$, C6'$\underline{H}$); 7.26 – 7.29 (1H, m, C5$\underline{H}$); 7.34 (2H, d, J = 8.8Hz, C3'$\underline{H}$, C5'$\underline{H}$); 7.78 – 7.84 (2H, m, C6$\underline{H}$, C8$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 21.0 ($\underline{C}H_3$)(m), 23.2 ($\underline{C}H_3$)(s); 28.1 ($\underline{C}4H_2$)(s), 29.4 ($\underline{C}4H_2$)(m); 36.0 ($\underline{C}3H_2$)(s), 38.7 ($\underline{C}3H_2$)(m); 49.9 ($\underline{C}$1H)(m), 52.0 ($\underline{C}$1H)(s); 70.64 (CO$\underline{C}H_2$)(s), 70.7 (CO$\underline{C}H_2$)(m); 113.7 ($\underline{C}$Br); 115.9 ($\underline{C}$2'H, $\underline{C}$6'H)(m), 116.6 ($\underline{C}$2'H, $\underline{C}$6'H)(s); 126.25 ($\underline{C}$6H)(m), 126.28 ($\underline{C}$6H)(s); 126.7 ($\underline{C}$5H)(s), 126.8 ($\underline{C}$5H)(m); 128.0 ($\underline{C}F_3$, q, J = 115Hz); 129.0 ($\underline{C}$8H)(s), 129.3 ($\underline{C}$8H)(m); 132.18 ($\underline{C}$3'H, $\underline{C}$5'H)(s), 132.23 ($\underline{C}$3'H, $\underline{C}$5'H)(m); 132.8 ($\underline{C}$7CO)(m), 133.3 ($\underline{C}$7CO)(s); 137.4 ($\underline{C}$8a)(s), 137.5 ($\underline{C}$8a)(m); 139.0 ($\underline{C}$4a)(m), 139.5 ($\underline{C}$4a)(s); 155.1, 155.4 (C1');156.9 ($\underline{C}OCF_3$); 193.7 ($\underline{C}OCH_2$)(s), 193.8 ($\underline{C}OCH_2$)(m)

^{19}F-NMR (376MHz): -69.49 (s), -69.87 (m)

Yield: 33%

IRν_{max}(KBr): 739cm^{-1}, 1147cm^{-1}, 1266cm^{-1}, 1400cm^{-1}, 1690cm^{-1}, 2306cm^{-1}, 2306cm^{-1}, 2907cm^{-1}, 3055cm^{-1}

HRMS calcd. for C20H17NO3F3NaBr (M^++23): 478.0242 Found: 478.0222

2,2,2-Trifluoro-1-{7-[2-(4-iodo-phenoxy)-acetyl]-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl}-ethanone (249)

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.52 (2.3H, d, J = 6.8Hz, C$\underline{H}_3$), 1.61 (0.7H, d, J = 6.8Hz, C$\underline{H}_3$); 2.86 – 3.07 (2H, m, C4$\underline{H}_2$); 3.26 (0.3H, dt, J_1 = 14Hz, J_2 = 4Hz, C3$\underline{H}_2$), 3.56 (0.7H, dt, J_1 = 14Hz, J_2 = 4Hz, C3$\underline{H}_2$), 4.06 (0.7H, d, J = 14Hz, C3$\underline{H}_2$); 4.59 (0.3H, dd, J_1 = 14Hz, J_2 = 4Hz, C3$\underline{H}_2$); 5.19, 5.21 (2.3H, CO$\underline{CH}_2$, C1$\underline{H}$); 5.576 – 5.58 (0.7H, m, C1$\underline{H}$), 6.61 – 6.67 (2H, m, C2'$\underline{H}$, C6'$\underline{H}$); 7.22 – 7.28 (1H, m, C5$\underline{H}$); 7.46 (2H, d, J = 8.8Hz, C3'$\underline{H}$, C5'$\underline{H}$); 7.75 – 7.80 (2H, m, C6$\underline{H}$, C8$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 21.0 ($\underline{C}H_3$)(m), 23.1 ($\underline{C}H_3$)(s); 28.0 ($\underline{C}4H_2$)(s), 29.4 ($\underline{C}4H_2$)(m); 36.0 ($\underline{C}3H_2$)(s), 38.6 ($\underline{C}3H_2$)(m); 49.9 ($\underline{C}$1H)(m), 52.0 ($\underline{C}$1H)(s); 70.4 (CO$\underline{C}H_2$)(s), 70.44 (CO$\underline{C}H_2$)(m); 83.8 ($\underline{C}$I); 116.9 ($\underline{C}$2'H, $\underline{C}$6'H)(m), 117.8 ($\underline{C}$2'H, $\underline{C}$6'H)(s); 126.1 ($\underline{C}$6H)(m), 126.2 ($\underline{C}$6H)(s); 126.6 ($\underline{C}$8H)(s), 126.7 ($\underline{C}$8H)(m); 128.0 ($\underline{C}F_3$, q, J = 115Hz); 129.3 ($\underline{C}$5H)(m), 129.7 ($\underline{C}$5H)(s); 132.7 ($\underline{C}$7CO)(s); 132.8 ($\underline{C}$7CO)(m), 137.96 ($\underline{C}$3'H, $\underline{C}$5'H)(s), 138.1 ($\underline{C}$3'H, $\underline{C}$5'H)(m); 137.3 ($\underline{C}$8a)(s), 137.4 ($\underline{C}$8a)(m); 142.4 ($\underline{C}$4a) (s), 142.8 ($\underline{C}$4a)(m); 155.1, 155.3 (C1');157.6 ($\underline{C}OCF_3$); 193.3 ($\underline{C}OCH_2$)(s), 193.4 ($\underline{C}OCH_2$)(m)

^{19}F-NMR (376MHz): -69.40 (s), -69.78 (m)

Yield: 54%

IRν_{max}(KBr): 739cm^{-1}, 1266cm^{-1}, 1486cm^{-1}(CO ether), 1694cm^{-1}(CO), 2987cm^{-1}, 3055cm^{-1}(CH)

HRMS calcd. for C20H17NO3F3NaI (M^++23): 526.0103 Found: 526.0099

_N_-(4-{2-[1-Methyl-2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-2-oxo-ethoxy}-phenyl)-acetamide (250)*

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.53 (2.2H, d, J_1 = 6.8Hz, C$\underline{H}_3$), 1.62 (0.8H, d, J = 6.8Hz, C$\underline{H}_3$); 2.08 (3H, s, CO$\underline{CH}_3$); 2.89 – 3.09 (2H, m, C4$\underline{H}_2$); 3.27 (0.3H, t, J = 15Hz, C3$\underline{H}_2$), 3.58 (0.7H, dt, J_1 = 14Hz, J_2 = 3.4Hz, C3$\underline{H}_2$), 4.09 (0.7H, d, J = 14Hz, C3$\underline{H}_2$); 4.62 (0.2H, dd, J_1 = 13Hz, J_2 = 4Hz, C3$\underline{H}_2$); 5.17 - 5.21 (2H, s, CO$\underline{CH}_2$); 5.58 (0.7H, q, J = 6.8Hz, C1$\underline{H}$), 6.80 (2H, d, J = 8.9Hz, C2'$\underline{H}$, C6'$\underline{H}$); 7.24 – 7.28 (1H, m, C5$\underline{H}$); 7.37 (2H, d, J = 8.9 Hz, C3'$\underline{H}$, C5'$\underline{H}$); 7.77 – 7.81 (2H, m, C6$\underline{H}$, C8$\underline{H}$);8.28 (1H, bs, N$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 21.0 (C$\underline{H}_3$)(m), 20.9 (C$\underline{H}_3$)(s); 23.9 (CO$\underline{C}H_3$): 29.1 (C$\underline{4}H_2$)(s), 29.4 (C$\underline{4}H_2$)(m); 38.0 (C$\underline{3}H_2$)(m), 38.7 (C$\underline{3}H_2$)(s); 49.9 (C$\underline{1}$H)(m), 50.1 (C$\underline{1}$H)(s); 70.8 (CO$\underline{C}H_2$)(s), 70.9 (CO$\underline{C}H_2$)(m); 114.8 (C$\underline{2}$'H, C$\underline{6}$'H); 121.7 (C$\underline{3}$'H, C$\underline{5}$'H); 126.25 (C$\underline{6}$H)(m), 126.3 (C$\underline{6}$H)(s); 126.39 (C$\underline{8}$H)(s), 126.7 (C$\underline{8}$H); 127.4 (C$\underline{F}_3$, q, J = 115Hz); 129.3 (C$\underline{5}$H)(m), 129.7 (C$\underline{5}$H)(s); 132.2 (C$\underline{7}$CO)(m); 133.0 (C$\underline{4}$'NH); 133.2 (C7CO)(m); 137.2 (C$\underline{8}$a)(s), 137.4 (C$\underline{8}$a)(m); 139.4 (C$\underline{4}$a)(m), 142.7 (C$\underline{4}$a)(m); 154.2 (C$\underline{1}$'); 155.1 ($COCF_3$), 168.8 (C$\underline{O}CH_3$); 194.16 (C$\underline{O}CH_2$)(s), 194.2 (C$\underline{O}CH_2$)(m)

^{19}F-NMR (376MHz): ppm($CDCl_3$): -69.45 (s), -69.84 (m)

Yield: 60%

IRν_{max}(KBr): 1508cm^{-1}(CO ether), 1686cm^{-1}(CO), 2934cm^{-1}, 3323cm^{-1}(CH)

2,2,2-Trifluoro-1-{1-methyl-7-[2-(4-nitro-phenoxy)-acetyl]-3,4-dihydro-1H-isoquinolin-2-yl}-ethanone (251)

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.55 – 1.58 (2.2H, m, C$\underline{H}_3$), 1.64 – 1.67 (0.7H, m, C$\underline{H}_3$); 2.93 – 3.13 (2H, m, C4$\underline{H}_2$); 3.29 (0.3H, m, C3$\underline{H}_2$), 3.60 (0.7H, dt, J_1 = 12Hz, J_2 = 3.4Hz, C3$\underline{H}_2$), 4.12 (0.7H, d, J = 14Hz, C3$\underline{H}_2$); 4.65 (0.3H, dd, J_1 = 14Hz, J_2 = 6Hz, C3$\underline{H}_2$); 5.21 – 5.24 (0.3H, m, C1$\underline{H}$); 5.43 (2H, s, CO$\underline{CH}_2$); 5.61 – 5.66 (0.7H, m, C1$\underline{H}$), 6.94 – 6.70 (1.4H, d, J = 8.9Hz, C2'$\underline{H}$, C6'$\underline{H}$); 7.16 – 7.18 (0.6H, d, J = 8.7Hz, C2'$\underline{H}$, C6'$\underline{H}$); 7.29 – 7.32 (1H, m, C5H); 7.75 (2H, m, C8$\underline{H}$, C6$\underline{H}$); 8.14 (1.4H, d, J = 9.6Hz, C3'$\underline{H}$, C5'$\underline{H}$), 8.19 (0.6H, D, J = 8.9Hz, C3'$\underline{H}$, C5'$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 20.7 (C$\underline{H}_3$)(m), 22.9 (C$\underline{H}_3$)(s); 28.8 (C$\underline{4}H_2$)(s), 29.2 (C$\underline{4}H_2$)(m); 35.7 (C$\underline{3}H_2$)(m), 38.4 (C$\underline{3}H_2$)(s); 49.6 (C$\underline{1}$H)(m), 49.8 (C$\underline{1}$H)(s); 70.1 (CO$\underline{C}H_2$)(s), 70.2 (CO$\underline{C}H_2$)(m); 114.3 (C$\underline{2}$'H, C$\underline{6}$'H)(m), 116.7 (C$\underline{2}$'H, C$\underline{6}$'H)(s); 125.8 (C$\underline{3}$'H, C$\underline{5}$'H) (m), 125.126.5 (C$\underline{8}$H); 127.3 (C$\underline{F}_3$, q, J = 115Hz); 9 (C$\underline{3}$'H, C$\underline{5}$'H) (s); 126.2 (C$\underline{6}$H) (m), 126.3 (C$\underline{6}$H) (s), 126.6 (C$\underline{8}$H) (s), 126.7 (C$\underline{8}$H) (m); 128.6 (C$\underline{5}$H) (s), 129.5 (C$\underline{5}$H)(m); 133.2 (C$\underline{7}$CO) (s), 133.6 (C7CO)(m); 137.3 (C$\underline{8}$a)(s), 137.4 (C$\underline{8}$a)(m); 139.8 (C$\underline{4}$a)(s), 141.6 (C$\underline{4}$a)(m); 142.9 (C$\underline{4}$'NO_2) (s), 143.0 (C$\underline{4}$'NO_2) (m); 156.0 ($COCF_3$), 162.4 (C$\underline{1}$'); 191.8 (C$\underline{O}CH_2$)(s), 191.9 (C$\underline{O}CH_2$)(m)

^{19}F-NMR (376MHz): ppm($CDCl_3$): -69.48 (s), -69.85 (m)

Yield: 60%

IRν_{max}(KBr): 738cm^{-1}, 1173cm^{-1}, 1593cm^{-1}(CO ether), 1694cm^{-1}(CO), 2964cm^{-1}, 3057cm^{-1}(CH)

HRMS calcd. for C20H17NO5F3Na (M^++23): 445.0987 Found: 445.0972

4-{2-[1-Methyl-2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-2-oxo-ethoxy}-benzonitrile (252)

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.54 (2.2H, dd, J_1 = 6.8Hz, J_2 = 2.7Hz, C$\underline{H}_3$), 1.63 (0.8H, d, J = 6.8Hz, C$\underline{H}_3$); 2.91 – 3.10 (2H, m, C4$\underline{H}_2$); 3.29 (0.2H, dt, J_1 = 12Hz, J_2 = 4Hz, C3$\underline{H}_2$), 3.56 (0.8H, dt, J_1 = 12Hz, J_2 = 3.4Hz, C3$\underline{H}_2$), 4.09 (0.8H, d, J = 14Hz, C3$\underline{H}_2$); 4.62 (0.2H, dd, J_1 = 14Hz, J_2 = 4.8Hz, C3$\underline{H}_2$); 5.21 (0.2H, t, J

= 7Hz, C1H); 5.37 (2H, s, $COCH_2$); 5.54 – 5.63 (0.8H, m, C1H), 6.95 (2H, d, J = 8.8Hz, C2'H, C6'H); 7.28 (1H, d, 8.2Hz, C5H); 7.53 (2H, d, J = 8.8Hz, C3'H, C5'H); 7.78 (2H, m, C6H, C8H)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 20.7 (CH_3)(m), 20.9 (CH_3)(s); 29.4 ($C4H_2$)(s), 29.5 ($C4H_2$)(m); 38.6 ($C3H_2$)(m), 38.9 ($C3H_2$)(s); 49.9 (C1H)(m), 50.1 (C1H)(s); 70.1 ($COCH_2$)(s), 70.2 ($COCH_2$)(m); 102.6 (C4'CN)(s),104.6 (C4'CN)(m); 115.3 (C2'H, C6'H)(m), 116.2 (C2'H, C6'H)(s); 117.6 (CN)(s), 118.8 (CN)(m); 126.1 (C6H)(m), 126.14 (C6H)(s); 126.3 (C8H)(s), 126.5 (C8H); 127.3 (CF_3, q, J = 115Hz); 129.4 (C5H)(m), 129.8 (C5H)(s); 132.4 (C8a)(s); 132.6 (C3'H, C5'H)(s); 133.4(C7CO)(m); 133.8 (C3'H, C5'H)(m); 137.4 (C8a)(s), 137.6 (C8a)(m); 139.3 (C4a)(m), 139.8 (C4a)(s); 156.0 ($COCF_3$), 161.0 (C1'); 192.4 ($COCH_2$)(s), 192.5 ($COCH_2$)(m)

^{19}F-NMR (376MHz): ppm($CDCl_3$): -69.48 (s), -69.87 (m)

Yield: 60%

IRν_{max}(KBr): 730cm^{-1}, 1172cm^{-1}, 1265cm^{-1}, 1508cm^{-1}(CO ether), 1607cm^{-1}, 1690cm^{-1}(CO), 2228cm^{-1}, 2987cm^{-1}, 3055cm^{-1}(CH)

HRMS calcd. for C21H17N2O3F3Na (M^++23): 425.1089 Found: 425.1104

1-{7-[2-(4-Benzyloxy-phenoxy)-acetyl]-1-methyl-3,4-dihydro-*1H*-isoquinolin-2-yl}-2,2,2-trifluoro-ethanone (253)*

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.59 (2.3H, m, CH_3), 1.67 (0.7H, m, CH_3); 2.93 – 3.10 (2H, m, C4H_2); 3.27 (0.3H, m, C3H_2), 3.60 (0.7H, dt, J_1 = 13Hz, J_2 = 4Hz, C3H_2), 4.12 (0.7H, overlaps EtOAc, C3H_2); 4.43 (2H, s, OCH_2); 4.70 (0.3H, m, C3H_2); 5.01 (2H, $COCH_2$); 5.23 – 5.30 (0.3H, m, C1H); 5.63 – 5.68 (0.7H, m, C1H); 6.77 – 6.81 (2H, m, C2'H, C6'H); 6.85 – 6.91 (2H, m, C3'H, C5'H); 7.19 – 7.45 (6H, m, C2"H, C3"H, C4"H, C5"H, C6"H, C5H); 7.78 – 7.96 (2H, m, C6H, C8H)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 21.1 (CH_3)(m), 23.2 (CH_3)(s); 28.1 ($C4H_2$)(s), 29.5 ($C4H_2$)(m); 36.1 ($C3H_2$)(s), 38.8 ($C3H_2$)(m); 50.0 (C1H)(m), 52.1 (C1H)(s); 60.5 (OCH_2); 70.6 ($COCH_2$); 115.9 (C2'H, C3'H, C5'H, C6'H); 127.2 (C6H); 127.4 (C2"H, C6"H); 127.7 (C8H); 127.8 (C4"H); 128.4 (C3"H, C5"H); 129.4 (C5H); 132.5 (C7CO); 137.2 (C8a); 137.5 (C4a); 150.1 (C4') 152.5 (C1'); 155.3 ($COCF_3$); 190.8 ($COCH_2$)

^{19}F-NMR (376MHz): -69.44 (s), -69.81 (m)

Yield: 47%

IRν_{max}(KBr): 1500cm^{-1} (CO, ether), 1686cm^{-1} (CO), 2986cm^{-1}, 3053cm^{-1}(CH)

4-{2-[1-Methyl-2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-2-oxo-ethoxy}-benzoic acid benzyl ester (254)

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.58 (2.3H, m, CH_3), 1.67 (0.7H, m, CH_3); 2.93 – 3.12 (2H, m, C4H_2); 3.27 (0.3H, t, J = 13Hz, C3H_2), 3.60 (0.7H, t, J = 12Hz, C3H_2), 4.12 (0.7H, d, J = 14Hz, C3H_2); 4.62 – 4.69 (0.3H, m, C3H_2); 5.33 (2H, $COCH_2$); 5.22 – 5.26 (0.3H, m, C1H); 5.63 – 5.66 (0.7H, m, C1H); 6.90 – 6.98 (2H, m, C2'H, C6'H); 7.27 – 7.46 (6H, m, C2"H, C3"H, C4"H, C5"H, C6"H, C5H); 7.81 – 7.85 (2H, m, C6H, C8H); 7.98 – 8.08 (2H, m, C3'H, C5'H)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 21.1 (CH_3)(m), 23.2 (CH_3)(s); 28.1 ($C4H_2$)(s), 29.5 ($C4H_2$)(m); 36.1 ($C3H_2$)(s), 38.8 ($C3H_2$)(m); 50.0 (C1H)(m), 50.2 (C1H)(s); 66.3 (OCH_2) (s), 66.4 (OCH_2) (m); 70.3 ($COCH_2$) (s), 70.4 (CO CH_2) (m); 114.2 (C2'H, C6'H) (m), 115.2 (C2'H, C6'H) (s); 121.7 (C4') (s), 123.3 (C4'); 126.3 (C6H) (m), 126.5 (C6H) (s); 126.7 (C8H) (s), 126.9 (C8H); 127.9 (C2"H, C6"H) (s), 127.97 (C2"H, C6"H) (m); 128.0 (C4"H) (m), 128.1 (C4"H) (s); 128.4 (C3"H, C5"H (s), 128.5 (C3"H, C5"H) (m); 129.4

(C5H) (m), 129.9 (C5H) (s); 131.7 (C3'H, C5'H) (m); 131.8 (C3'H, C5'H) (s); 132.9 (C7CO); 136.0 (C8a) (s), 136.1 (C8a) (m); 137.5 (C4a); 139.1 (C1"); 155.0 ($COCF_3$); 165.6 (C1') (s), 166.0 (C1') (m); 166.3 (COO); 193.1 ($COCH_2$) (s), 193.2 ($COCH_2$) (m)

^{19}F-NMR (376MHz): -69.45 (s), -69.83 (m)

Yield: 58%

IRν_{max}(KBr): 1607cm^{-1} (CO, ether), 1689cm^{-1} (CO), 1710cm^{-1} (CO ester), 2987cm^{-1}, 3054cm^{-1}(CH)

HRMS calcd. for C28H24NO5F3Na (M^++23): 534.1504 Found: 534.1500

Phenoxyacetyltetrahydroisoquinolines (Deprotected) (255 – 278)

The protected phenoxyacetyltetrahydroisoquinoline (0.71 mmol) was dissolved in methanol, with heating to 55°C. Water was added dropwise (about 2 mL). Potassium carbonate (490 mg/3.55 mmol) was added in portions, allowing for full dissolution. Stirring continued at 55°C for 1.5 hours. The methanol was removed *in vacuo*. The aqueous residue was extracted with DCM. It was washed with water, dried and the solvent removed *in vacuo* to give the product, usually as an oil. The oils were purified by elution from a silica column using a mobile phase of 10:90 methanol:ethyl acetate.

1-(1,2,3,4-Tetrahydro-isoquinolin-7-yl)-2-p-tolyloxy-ethanone (255)

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.30 (3H, s, CH_3); 2.89 (2H, t, J = 5.4 Hz, C4H_2); 3.19 (2H, t, J = 5.4 Hz, C3H_2); 4.09 (2H, s, C1H_2); 4.21 (1H, bs, N2H); 5.21 (2H, s, $COCH_2O$); 6.85 (2H, d, J = 8.8 Hz, C2'H, C6'H); 7.09 (2H, d, J = 8 Hz, C3'H, C5'H); 7.21 (1H, d, J = 8.2Hz, C5H); 7.67 (1H, s, C8H); 7.77 (1H, d, J = 8 Hz, C6'H)

^{13}C-NMR (101MHz): ppm(CD_3COCD_3): 29.1 (C4H_2); 43.0 (C3H_2); 47.7 (C1H_2); 70.8 (COCH_2); 114.5 (C2'H, C6'H); 125.8, 126.1 (C6H, C8H); 128.6 (C4'CH_3); 129.1 (C7CO); 129.8 (C3'H, C5'H); 130.8 (C5H); 132.3 (C8a); 141.3 (C4a); 155.8 (C1'); 194.4 ($COCH_2$)

Yield: 86%

IRν_{max}(KBr): 1610cm^{-1} (CO), 2986 cm^{-1}, 3054cm^{-1}(CH)

HRMS calcd. for C18H20NO2 (M^++1): 282.1494 Found: 282.1502

2-(4-Methoxy-phenoxy)-1-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethanone (256)

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.66 (1H, bs, NH); 2.87 (1H, t, J = 5.5Hz, C4H_2); 3.16 (2H, s, C3H_2); 3.76 (3H, s, OCH_3); 4.07 (2H, s, C1H_2); 5.19 (2H, $COCH_2$); 6.81 (2H, d, J = 6Hz, C2'H, C6'H); 6.83 (2H, d, J = 6Hz, C3'H; C5'H); 7.20 (1H, d, J = 7.5Hz, C5H); 7.66 (1H, C8'H); 7.75 (1H, d, J = 7.5Hz, C6'H)

^{13}C-NMR (101MHz): ppm(CD_3COCD_3): 29.4 (C4H_2); 43.3 (C3H_2); 48.0 (C1H_2); 55.6 (OCH_3); 71.6 (COCH_2); 114.6 (C2'H, C6'H); 115.9 (C3'H, C5'H); 125.6, 126.1 (C6H, C8H); 129.1 (C7CO); 129.7 (C5H); 132.2 (C8a); 141.5 (C4a); 152.1 (C4'OCH_3); 154.3(C1'); 194.5 ($COCH_2$)

Yield: 64%

IRν_{max}(KBr): 1699cm^{-1} (CO), 2933 cm^{-1}, 3054cm^{-1}(CH)

HRMS calcd. for C18H20NO3 (M^++1): 298.1443 Found: 298.1433

2-(4-Ethoxy-phenoxy)-1-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethanone (257)

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.39 (3H, t, J = 6.8 Hz, CH_3); 2.40 (1H, bs, NH); 2.87 (1H, t, J = 6 Hz, C4H_2); 3.16 (2H, t, J = 6Hz, C3H_2); 3.97 (2H, q, J = 6.8 Hz, OCH_2); 4.07 (2H, s, C1H_2); 5.19 (2H, s, COCH_2O); 6.81 (2H, d, J = 9.5 Hz, C2'H, C6'H); 6.88 (2H, d, J = 9.5 Hz, C3'H; C5'H); 7.20 (1H, d, J = 8.2 Hz, C5H); 7.67 (1H, C8'H); 7.75 (1H, d, J = 8.8 Hz, C6'H)

^{13}C-NMR (101MHz): ppm(CD_3COCD_3): 14.8 (CH_3); 29.3 (C4H_2); 43.2 (C3H_2); 48.0 (C1H_2); 63.8 (OCH_2); 71.6 (COCH_2); 115.3 (C2'H, C6'H); 115.9 (C3'H, C5'H); 125.7, 126.1 (C6H, C8H); 129.1 (C7CO); 129.7 (C5H); 132.3 (C8a); 141.5 (C4a); 152.1 (C4'OCH_2); 153.7 (C1'); 194.5 (COCH_2)

Yield: 60%

IRν_{max}(KBr): 1675cm^{-1} (CO), 2986 cm^{-1}, 3055cm^{-1}(CH)

HRMS calcd. for C19H22NO3 (M^++1): 312.1600 Found: 312.1604

2-(4-Fluoro-phenoxy)-1-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethanone (258)

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.6 (1H, bs, NH); 2.93 (2H, s, C4H_2); 3.18 (2H, s, C3H_2); 4.08 (2H, s, C1H_2); 5.22 (COCH_2); 6.90 (2H. m, C2'H, C6'H); 6.95 (2H, m, C3'H, C5'H); 7.22 (1H, d, J = 8Hz, C5H); 7.65 (1H, s, C8H); 7.75 (1H, d, J = 8Hz, C6H)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 29.4 (C4H_2); 43.2 (C3H_2); 47.9 (C1H_2); 71.3 (COCH_2); 115.9 (C2'H, C6'H, d, J = 19 Hz); 115.93 (C3'H, C5'H, d, J = 12 Hz); 125.6, 126.1 (C6H, C8H); 129.1 (C7CO); 129.8 (C5H); 132.1 (C8a); 141.7 (C4a); 154.1 (C1'); 157.6 (C4'F, d, J = 239 Hz); 194.0 (COCH_2)

^{19}F-NMR (376MHz): -123.32

Yield: 87%

IRν_{max}(KBr): 1674cm^{-1} (CO), 2987 cm^{-1}, 3055cm^{-1}(CH)

HRMS calcd. for C17H17NO2F (M^++1): 286.1243 Found: 286.1257

2-(4-Chloro-phenoxy)-1-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethanone (259)

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.2 (1H, bs, NH); 2.85 (2H, t, J = 5.5Hz, C4H_2); 3.15 (2H, t, J = 5.5Hz, C3H_2); 4.05 (2H, s, C1H_2); 5.21 (2H, s, COCH_2); 6.85 (2H, d, J = 8.8Hz, C2'H, C6'H); 7.21 (3H, overlapping doublets, C3'H, C5'H, C5H); 7.63 (1H, s, C8H); 7.72 (1H, d, J = 8.2Hz, C6H)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 29.4 (C4H_2); 43.6 (C3H_2); 48.1 (C1H_2); 70.7 (COCH_2); 116.0 (C2'H, C6'H); 125.5, 126.0 (C6H, C8H); 126.4 (C4'Cl); 129.0 (C7CO) 129.3 (C3'H, 5'H); 129.8 (C5H); 131.9 (C8a); 141.9 (C4a); 156.5 (C1'); 193.7 (COCH_2)

Yield: 52%

IRν_{max}(KBr): 1701cm^{-1} (CO), 2987 cm^{-1}, 3055cm^{-1}(CH)

HRMS calcd. for C17H17NO2Cl (M^++1): 302.0948 Found: 302.0944

2-(4-Bromo-phenoxy)-1-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethanone (260)

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.17 (bs, NH); 2.87 (2H, t, J = 5.5Hz, C4H_2); 3.16 (2H, t, J = 5.5Hz, C3H_2); 4.07 (2H, s, C1H_2); 5.22 (2H, s, COCH_2); 6.81 (2H, d, J = 8.6Hz, C2'H, C6'H); 7.21 (1H, d, J = 8Hz, C5H); 7.36 (2H, d, J = 8.6Hz, C3'H, C5'H); 7.64 (1H, s, C8H); 7.73 (1H, d, J = 8Hz, C6H)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 29.5 (C4H_2); 43.3 (C3H_2); 48.1 (C1H_2); 70.7 (COCH_2); 113.8 (C4'Br); 116.5 (C2'H, C6'H); 125.6, 126.1 (C6H, C8H); 126.8 (C7CO) 129.8 (C5H); 132.0 (C8a); 132.4 (C3'H, 5'H); 141.9 (C4a); 157.1 (C1'); 193.7 (COCH_2)

Yield: 48%

IRν_{max}(KBr): 1702cm^{-1} (CO), 2987 cm^{-1}, 3055cm^{-1}(CH)

HRMS calcd. for C17H17NO2Br (M^++1): 346.0443 Found: 346.0432

2-(4-Iodo-phenoxy)-1-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethanone (261)

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.89 (2H, bs, C4$\underline{H}_2$); 3.00 (1H, bs, N$\underline{H}$); 3.19 (2H, bs, C3$\underline{H}_2$); 4.08 (2H, s, C1$\underline{H}_2$); 5.22 (2H, s, COC$\underline{H}_2$); 6.71 (2H, d, J = 8.9Hz, C2'$\underline{H}$, C6'$\underline{H}$); 7.21 (1H, d, J = 8.2Hz, C5$\underline{H}$); 7.55 (2H, d, J = 8.9Hz, C3'$\underline{H}$, C5'$\underline{H}$); 7.65 (1H, C8$\underline{H}$); 7.73 (1H, d, J = 8.2Hz, C6$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 30 (C$\underline{H}_2$); 43.3 (C$\underline{H}_2$); 48.0 (C$\underline{H}_2$); 70.5 (CO$\underline{C}H_2$); 83.8 (C4'I); 117.1 (C2'H, C6'H); 125.4, 126.1 (C6H, C8H); 129.1 (C7CO) 129.8 (C5H); 132.0 (C8a); 138.2 (C3'H, 5'H); 141.8 (C4a); 157.8 (C1'); 193.6 ($\underline{C}OCH_2$)

Yield: 85%

IRν_{max}(KBr): 1700cm^{-1} (CO), 2986 cm^{-1}, 3054cm^{-1}(CH)

HRMS calcd. for C17H17NO2I (M^++1): 394.0304 Found: 394.0314

***N*-{4-[2-(1,2,3,4-tetrahydroisoquinolin-7-yl)-2-oxo-ethoxy]-phenyl}-acetamide (262)**

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.11 (3H, s, COC$\underline{H}_3$); 2.81 (2H, s, C4$\underline{H}_2$); 3.86 (2H, s, C3$\underline{H}_2$); 4.42 (1H, s, C1$\underline{H}_2$); 5.30 (2H, COC$\underline{H}_2$); 6.86 (2H, d, J = 9Hz, C2'$\underline{H}$, C6'$\underline{H}$); 7.35 – 7.48 (5H, m, C5'$\underline{H}$, C3'$\underline{H}$, C5'$\underline{H}$, C6$\underline{H}$, C8$\underline{H}$); 8.9 (1H, s, N$\underline{H}$CO)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 24.1 (CO$\underline{C}H_3$); 29.4 (C$\underline{H}_2$); 41.2 (C$\underline{H}_2$); 45.2 (C$\underline{H}_2$); 70.9 (CO$\underline{C}H_2$); 114.9 (C3'H, C5'H); 121.9 (C2'H, C6'H); 126.4, 126.6 (C6H, C8H); 129.2 (C5H); 129.4 (C7CO); 132.1 (C8a); 139.7 (C4a); 154.4 (C1'); 168.7 (NH$\underline{C}OCH_3$); 194.2 ($\underline{C}OCH_2$)

Yield: 70%

IRν_{max}(KBr): 739cm^{-1}, 1607cm^{-1} (NHCO); 1688cm^{-1}(CO), 2987cm^{-1}, 3055cm^{-1}(CH)

HRMS calcd. for C19H21N2O3 (M^++1): 325.1552 Found: 325.1563

2-(4-Nitro-phenoxy)-1-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethanone (263)

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.86 (2H, s, C4$\underline{H}_2$); 3.16 (2H, s, C3$\underline{H}_2$); 4.06 (2H, s, C1$\underline{H}_2$); 5.21 (2H, s, COC$\underline{H}_2$O); 6.86 (2H, d, J = 7.5 Hz, C2'$\underline{H}$, C6'$\underline{H}$); 7.11 - 7.21 (1H, m, C5$\underline{H}$); 7.36 (2H, d, J = 9 Hz, C3'$\underline{H}$, C5'$\underline{H}$); 7.61 – 7.74 (2H, m, C6'$\underline{H}$, C8'$\underline{H}$)

^{13}C-NMR (101MHz): ppm(CD_3COCD_3): 31.5 (C$\underline{H}_2$); 42.9 (C$\underline{H}_2$); 45.3 (C$\underline{H}_2$); 71.7 (CO$\underline{C}H_2$); 114.8 (C2'H, C6'H); 126.6 (C3'H, C5'H);

Yield: 52%

IRν_{max}(KBr): 1694cm^{-1} (CO), 2987 cm^{-1}, 3055cm^{-1}(CH)

4-[2-Oxo-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethoxy]-benzonitrile (264)

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.35 (1H, bs, N$\underline{H}$); 2.86 (2H, s, C4$\underline{H}_2$); 3.14 (2H, s, C3$\underline{H}_2$); 4.05 (2H, s, C1$\underline{H}_2$); 5.33 (2H, s, COC$\underline{H}_2$O); 6.95 (2H, d, J = 8.9 Hz, C2'$\underline{H}$, C6'$\underline{H}$); 7.21 (1H, d, J = 8.2Hz, C5$\underline{H}$); 7.36 (2H, d, J = 8.9 Hz, C3'$\underline{H}$, C5'$\underline{H}$); 7.71 (2H, d, J = 8.2Hz, C6'$\underline{H}$, C8'$\underline{H}$)

^{13}C-NMR (101MHz): ppm(CD_3COCD_3): 30.6 (C$\underline{H}_2$); 44.3 (C$\underline{H}_2$); 49.1 (C$\underline{H}_2$); 71.3 (CO$\underline{C}H_2$); 116.8 (C2'H, C6'H); 126.3, 127.1 (C6H, C8H); 129.1 (C7CO) 130.8 (C5H); 132.0 (C8a); 135.0 (C3'H, 5'H); 143.4 (C4a); 163.1 (C1'); 193.8 ($\underline{C}OCH_2$)

Yield: 52%

IRν_{max}(KBr): 1701cm^{-1} (CO), 2987 cm^{-1}, 3055cm^{-1}(CH)

HRMS calcd. for C18H17N2O2 (M^++1): 293.1290 Found: 293.1302

2-(4-Benzyloxy-)-1-(1,2,3,4-tetrahydroisoquinolin-7-yl)-ethanone (265)

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.85 (1H, t, J = 6 Hz, C4$\underline{H}_2$); 3.15 (2H, t, J = 6Hz, C3$\underline{H}_2$); 4.05 (2H, s, C1$\underline{H}_2$); 4.98 (OC$\underline{H}_2$); 5.17 (2H, s, COC$\underline{H}_2$O); 6.88 (4H, C2'$\underline{H}$, C3'$\underline{H}$, C5$\underline{H}$, C6'$\underline{H}$); 7.12 – 7.40 (6H, m, C2"$\underline{H}$, C3"$\underline{H}$, C4"$\underline{H}$, C5"$\underline{H}$, C6"$\underline{H}$, C5$\underline{H}$); 7.65 (1H, s, C8'$\underline{H}$); 7.73 (1H, d, J = 8.8 Hz, C6'$\underline{H}$)

^{13}C-NMR (101MHz): ppm(CD_3COCD_3): 29.4 ($\underline{C}4H_2$); 43.3 ($\underline{C}3H_2$); 48.0 ($\underline{C}1H_2$); 70.5 (O$\underline{C}H_2$); 71.6 (CO$\underline{C}H_2$); 115.8, 115.9 ($\underline{C}$2'H, $\underline{C}$6'H, $\underline{C}$3'H, $\underline{C}$5'H); 125.7, 126.1 ($\underline{C}$6H, $\underline{C}$8H); 127.4 ($\underline{C}$2"H, $\underline{C}$6"H); 127.9 ($\underline{C}$4"H); 128.5 ($\underline{C}$3"H, $\underline{C}$5"H); 129.1 ($\underline{C}$7CO); 129.7 ($\underline{C}$5H); 132.3 ($\underline{C}$8a); 137.3 ($\underline{C}$1"); 141.6 ($\underline{C}$4a); 152.4 ($\underline{C}$4'OCH$_2$); 153.6 ($\underline{C}$1'); 194.5 ($\underline{C}OCH_2$)

Yield: 71%

IRν_{max}(KBr): 1701cm^{-1} (CO), 2987 cm^{-1}, 3054cm^{-1}(CH)

HRMS calcd. for C24H24NO3 (M^++1): 374.1756 Found: 374.1743

4-[2-Oxo-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethoxy]-benzoic acid benzyl ester (266)

^{1}H-NMR (400MHz): δ(CD_3COCD_3): 2.81 (1H, t, J = 6 Hz, C4$\underline{H}_2$); 3.05 (2H, t, J = 6Hz, C3$\underline{H}_2$); 4.00 (2H, s, C1$\underline{H}_2$); 5.28 (OC$\underline{H}_2$); 5.60 (2H, OC$\underline{H}_2$); 6.89 – 6.92 (2H, m, C2'$\underline{H}$, C6'$\underline{H}$); 7.20 – 7.37 (6H, m, C2"$\underline{H}$, C3"$\underline{H}$, C4"$\underline{H}$, C5"$\underline{H}$, C6"$\underline{H}$, C5$\underline{H}$); 7.65 (4H, m, C8'$\underline{H}$, C6'$\underline{H}$, C3'$\underline{H}$, C5'$\underline{H}$)

^{13}C-NMR (101MHz): ppm(CD_3COCD_3): 30.3 ($\underline{C}4H_2$); 44.0 ($\underline{C}3H_2$); 48.8 ($\underline{C}1H_2$); 66.7 (O$\underline{C}H_2$); 71.2 (CO$\underline{C}H_2$); 116.4 ($\underline{C}$2'H, $\underline{C}$6'H); 122.1 ($\underline{C}$4'CO); 126.3, 127.1 ($\underline{C}$6H, $\underline{C}$8H); 129.0 ($\underline{C}$7CO); 129.05 ($\underline{C}$2"H, $\underline{C}$6"H); 129.1 ($\underline{C}$4"H); 129.5 ($\underline{C}$3"H, $\underline{C}$5"H); 130.7 ($\underline{C}$5H); 132.7 ($\underline{C}$3'H, $\underline{C}$5'H); 133.4 ($\underline{C}$8a); 138.0 ($\underline{C}$1"); 143.0 ($\underline{C}$4a); 166.7 ($\underline{C}$1'); 167.0 ($\underline{C}$OO); 194.0 ($\underline{C}OCH_2$)

Yield: 71%

IRν_{max}(KBr): 1712cm^{-1} (CO), 2987 cm^{-1}, 3055cm^{-1}(CH)

HRMS calcd. for C25H24NO4 (M^++1): 402.1705 Found: 402.1703

1-(1-Methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-*p*-tolyloxy-ethanone (267)

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.54 (3H, d, J = 6Hz, C1C$\underline{H}_3$); 2.29 (3H, s, C4'C$\underline{H}_3$); 2.83 – 2.89 (1H, m, C4$\underline{H}_2$); 2.94 – 3.01 (1H, m, C4$\underline{H}_2$); 3.05 – 3.11 (1H, m, C3$\underline{H}_2$); 3.31 – 3.34 (1H, m, C3$\underline{H}_2$); 3.96 (1H, bs, N$\underline{H}$); 4.20 (1H, d, J = 6Hz, C1$\underline{H}$); 5.21 (2H, COC$\underline{H}_2$); 6.85 (2H, d, J = 8.5Hz, C2'$\underline{H}$, C6'$\underline{H}$); 7.08 (1H, d, J = 8.0Hz, C3'$\underline{H}$, C5'$\underline{H}$); 7.20 (1H, d, J = 8Hz, C5$\underline{H}$); 7.76 (1H, d, J = 8Hz, C6$\underline{H}$); 7.83 (1H, s, C8$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 20.4 ($\underline{C}H_3$); 22.1 (C1$\underline{C}H_3$); 29.7 ($\underline{C}4H_2$); 40.8 ($\underline{C}3H_2$); 51.3 ($\underline{C}$1H); 70.9 (CO$\underline{C}H_2$); 114.6 ($\underline{C}$2'H, $\underline{C}$6'H); 125.8 ($\underline{C}$6H); 125.9 ($\underline{C}$8H); 129.6 ($\underline{C}$5H); 129.9 (C3'H, C5'H); 130.8 ($\underline{C}$4'CH$_3$); 132.6 ($\underline{C}$7CO); 140.3 ($\underline{C}$8a); 141.1 ($\underline{C}$4a); 155.9 ($\underline{C}$1'); 194.3 ($\underline{C}$O)

Yield: 22%

IRν_{max}(KBr): 738cm^{-1}, 1702cm^{-1}(CO), 2985cm^{-1}, 3054cm^{-1}(CH)

HRMS calcd. for C19H22NO2 (M^++1): 296.1651 Found: 296.1646

2-(4-Methoxy-phenoxy)-1-(1-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethanone (268)

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.51 (3H, d, J = 6Hz, C1C$\underline{H}_3$); 2.46 (1H, bs, N$\underline{H}$); 2.82 (1H, dt, J_1 = 17Hz, J_2 = 4.1Hz, C4$\underline{H}_2$); 2.91 – 2.99 (1H, m, C4$\underline{H}_2$); 3.02 – 3.08 (1H, m, C3$\underline{H}_2$); 3.29 – 3.32 (1H, m, C3$\underline{H}_2$); 3.77 (3H, s, OC$\underline{H}_3$); 4.13 (1H, m, C1$\underline{H}$); 5.21 (2H, COC$\underline{H}_2$); 6.74 (2H, d, J = 8.9Hz, C2'$\underline{H}$, C6'$\underline{H}$); 6.90 (1H, d, J = 9.6Hz, C3'$\underline{H}$, C5'$\underline{H}$); 7.20 (1H, d, J = 7.5Hz, C5$\underline{H}$); 7.75 (1H, d, J = 9.6Hz, C6$\underline{H}$); 7.85 (1H, s, C8$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 22.5 (C1$\underline{C}H_3$); 30.3 ($\underline{C}4H_2$); 41.2 ($\underline{C}3H_2$); 51.3 ($\underline{C}$1H); 55.6 (OC$\underline{H}_3$); 71.6 (CO$\underline{C}H_2$); 114.6 ($\underline{C}$2'H, $\underline{C}$6'H); 115.9 ($\underline{C}$3'H, $\underline{C}$5'H); 125.5 ($\underline{C}$6H); 125.6 ($\underline{C}$8H); 129.6 ($\underline{C}$5H); 132.4 ($\underline{C}$7CO); 135.5 ($\underline{C}$8a); 141.6 ($\underline{C}$4a); 152.2 ($\underline{C}$4'OCH$_3$); 154.3 ($\underline{C}$1'); 194.7 ($\underline{C}$O)

Yield: 44%

IRν_{max}(KBr): 738cm^{-1}, 1702cm^{-1}(CO), 2987cm^{-1}, 3055cm^{-1}(CH)

HRMS calcd. for C19H22NO3 (M^++1): 312.1600 Found: 312.1592

2-(4-Ethoxy-phenoxy)-1-(1-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethanone (269)

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.39 (3H, t, J = 6.8Hz, C$\underline{H}_3$); 1.51 (3H, d, J = 6.8Hz, C1C$\underline{H}_3$); 2.32 (1H, bs, N$\underline{H}$); 2.82 (1H, dt, J_1 = 16Hz, J_2 = 4.1Hz, C4$\underline{H}_2$); 2.91 – 2.99 (1H, m, C4$\underline{H}_2$); 3.02 – 3.08 (1H, m, C3$\underline{H}_2$); 3.27 – 3.33 (1H, m, C3$\underline{H}_2$); 3.97 (2H, s, OC$\underline{H}_2$); 4.16 (1H, d, J = 6.2Hz, C1$\underline{H}$); 5.19 (2H, COC$\underline{H}_2$); 6.81 (2H, d, J = 8.9Hz, C2'$\underline{H}$, C6'$\underline{H}$); 6.88 (1H, d, J = 8.9Hz, C3'$\underline{H}$, C5'$\underline{H}$); 7.19 (1H, d, J = 8.2Hz, C5$\underline{H}$); 7.74 (1H, d, J = 8.9Hz, C6$\underline{H}$); 7.85 (1H, s, C8$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$):14.8 ($\underline{C}H_3$); 22.5 (C1$\underline{C}H_3$); 30.2 ($\underline{C}4H_2$); 41.2 ($\underline{C}3H_2$); 51.5 ($\underline{C}$1H); 63.9 (OC$\underline{H}_2$); 71.7 (CO$\underline{C}H_2$); 125.5 ($\underline{C}$2'H, $\underline{C}$6'H); 125.6 ($\underline{C}$3'H, $\underline{C}$5'H); 126.4 ($\underline{C}$6H); 129.0 ($\underline{C}$8H); 129.6 ($\underline{C}$5H); 132.4 ($\underline{C}$7CO); 141.0 ($\underline{C}$8a); 141.6 ($\underline{C}$4a); 152.1 ($\underline{C}$4'OCH$_2$); 153.7 ($\underline{C}$1'); 194.7 ($\underline{C}$O)

Yield: 63%

IRν_{max}(KBr): 739cm^{-1}, 1701cm^{-1}(CO), 2986cm^{-1}, 3055cm^{-1}(CH)

HRMS calcd. for C20H24NO3 (M^++1): 326.1756 Found: 326.1750

2-(4-Fluoro-phenoxy)-1-(1-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethanone (270)

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.52 (3H, d, J = 6.8Hz, C$\underline{H}_3$); 1.74 (1H, bs, N$\underline{H}$); 2.78 – 2.86 (1H, dt, J_1 = 17Hz, J_2 = 4Hz, C4$\underline{H}_2$); 2.90 – 3.00 (1H, m, C4$\underline{H}_2$); 3.03 – 3.09 (1H, m, C3$\underline{H}_2$); 3.29 – 3.34 (1H, m, C3$\underline{H}_2$); 4.16 (1H, d, J = 6.8Hz, C1$\underline{H}$); 5.20 (2H, COC$\underline{H}_2$); 6.89 – 6.93 (2H, m, C2'$\underline{H}$, C6'$\underline{H}$); 6.97 – 7.01 (2H, m, C3'$\underline{H}$, C5'$\underline{H}$); 7.22 (1H, d, J = 8.2Hz, C5$\underline{H}$); 7.73 (1H, d, J = 8.2Hz, C8$\underline{H}$); 7.82 (1H, C8$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 22.3 ($\underline{C}H_3$); 30.0 ($\underline{C}4H_2$); 41.2 ($\underline{C}3H_2$); 51.4 ($\underline{C}$1H); 71.3 (CO$\underline{C}H_2$); 115.8 ($\underline{C}$2'H, $\underline{C}$6'H, d, J = 12Hz); 115.9 ($\underline{C}$3'H, $\underline{C}$5'H, d, J = 19Hz); 125.4 ($\underline{C}$6H); 125.7 ($\underline{C}$8H); 129.6 ($\underline{C}$5H); 132.2 ($\underline{C}$7CO); 140.9 ($\underline{C}$8a); 141.6 ($\underline{C}$4a); 154.1 ($\underline{C}$4'F); 158.7 ($\underline{C}$1'); 193.9 ($\underline{C}$O)

^{19}F-NMR (376MHz): ppm($CDCl_3$): -123.34

Yield: 57%

IRν_{max}(KBr): 739cm^{-1}(CF), 1265cm^{-1}(CO ether), 1506cm^{-1}, 1700cm^{-1}(CO), 2987cm^{-1}, 3055cm^{-1}(CH)

HRMS calcd. for C18H19NO2F (M^++1): 300.1400 Found: 300.1410

2-(4-Chloro-phenoxy)-1-(1-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethanone (271)

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.50 (3H, d, J = 6Hz, C1C$\underline{H}_3$); 2.46 (1H, bs, N$\underline{H}$); 2.78 – 2.86 (1H, m, C4$\underline{H}_2$); 2.92 – 3.00 (1H, m, C4$\underline{H}_2$); 3.03 – 3.09 (1H, m, C3$\underline{H}_2$); 3.30 – 3.33 (1H, m, C3$\underline{H}_2$); 4.18 (1H, d, J =

6Hz, C1H); 5.24 (2H, $COCH_2$); 6.87 (2H, d, J = 8.9Hz, C2'H, C6'H); 7.20 – 7.28 (3H, d, d, overlapping, C3'H, C5'H, C5H); 7.73 (1H, d, J = 4.1Hz, C6H); 7.80 (1H, s, C8H)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 22.4 (CH_3); 30.2 ($C4H_2$); 41.1 ($C3H_2$); 51.5 (C1H); 70.7 ($COCH_2$); 116.0 (C2'H, C6'H); 125.5 (C6H); 125.7 (C8H); 126.4 (C4'Cl); 129.3 (C3'H, C5'H); 129.6 (C5H); 132.1 (C7CO); 141.1 (C8a); 141.8 (C4a); 156.6 (C1'); 193.6 (CO)

Yield: 73%

IRν_{max}(KBr): 738cm^{-1}, 1700cm^{-1}(CO), 2984cm^{-1}, 3054cm^{-1}(CH)

HRMS calcd. for C18H19NO2Cl (M^++1): 316.1104 Found: 316.1101

2-(4-Bromo-phenoxy)-1-(1-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethanone (272)

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.51 (3H, d, J = 6.8Hz, CH_3); 1.81 (1H, bs, NH); 2.83 (1H, dt, J_1 = 16Hz, J_2 = 4Hz, $C4H_2$); 2.92 – 3.00 (1H, m, $C4H_2$); 3.02 – 3.09 (1H, m, $C3H_2$); 3.28 – 3.34 (1H, m, $C3H_2$); 4.13 (1H, q, J = 6.8Hz, C1H); 5.20 (2H, $COCH_2$); 6.83 (2H, d, J = 8.9Hz, C2'H, C6'H); 7.21 (1H, d, J = 8.2Hz, C5H); 7.38 (2H, d, J = 8.9Hz, C3'H, C5'H); 7.73 (1H, d, J = 8.9Hz, C8H); 7.81 (1H, C8H)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 22.4 (CH_3); 30.2 ($C4H_2$); 41.3 ($C3H_2$); 51.5 (C1H); 71.7 ($COCH_2$); 113.7 (C4'Br); 116.5 (C2'H, C6'H, d, J = 12Hz); 125.5 (C6H); 125.7 (C8H); 129.7 (C5H); 132.1 (C7CO); 132.3 (C3'H, C5'H); 141.1 (C8a); 141.9 (C4a); 157.1 (C1'); 193.9 (CO)

Yield: 67%

IRν_{max}(KBr): 744cm^{-1}(CF), 1266cm^{-1}(CO ether), 1733cm^{-1}(CO), 2933cm^{-1}, 3055cm^{-1}(CH)

HRMS calcd. for C18H19NO2Br(M^++1): 360.0599 Found: 360.0606

2-(4-Iodo-phenoxy)-1-(1-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethanone (273)

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.51 (3H, d, J = 6Hz, CH_3); 1.86 (1H, bs, NH); 2.82 (1H,dt, J_1 = 17Hz, J_2 = 4Hz, $C4H_2$); 2.90 – 2.99 (1H, m, $C4H_2$); 3.02 – 3.09 (1H, m, $C3H_2$); 3.28 – 3.34 (1H, m, $C3H_2$); 4.16 (1H, d, J = 6.2Hz, C1H); 5.24 (2H, $COCH_2$); 6.72 (2H, d, J = 8.9Hz, C2'H, C6'H); 7.21 (1H, d, J = 8.2Hz, C5H); 7.56 (2H, d, J = 8.9Hz, C3'H, C5'H); 7.73 (1H, d, J = 9.6Hz, C6H); 7.80 (1H, s, C8H)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 22.4 (CH_3); 30.2 ($C4H_2$); 41.1 ($C3H_2$); 51.4 (C1H); 70.4 ($COCH_2$); 83.7 (C4'I); 117.0 (C2'H, C6'H); 125.3 (C6H); 125.7 (C8H); 129.6 (C5H); 132.1 (C7CO); 138.2 (C3'H, C5'H); 141.1 (C8a); 141.9 (C4a); 157.8 (C1'); 193.7 (CO)

Yield: 71%

IRν_{max}(KBr): 1265cm^{-1}, 1702cm^{-1}(CO), 2987cm^{-1}, 3055cm^{-1}(CH)

HRMS calcd. for C18H19NO2Cl (M^++1): 408.0461 Found: 408.0449

***N*-{4-[2-(1-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-oxo-ethoxy]-phenyl}-acetamide (274)**

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.48 (3H, d, J = 6.1Hz, $C1CH_3$); 2.06 (3H, s, $COCH_3$); 2.61 (1H, bs, NH); 2.76 – 2.81 (1H, m, $C4H_2$); 2.88 – 2.91 (1H, m, $C4H_2$); 2.94 – 3.04 (1H, m, $C3H_2$); 3.23 – 3.28 (1H, m, $C3H_2$); 4.09 – 4.12 (1H, m, C1H); 5.20 (2H, $COCH_2$); 6.80 (2H, d, J = 9.6Hz, C2'H, C6'H); 7.17 (1H, d, J = 8.2Hz, C5H); 7.36 (2H, d, J = 8.9Hz, C3'H, C5'H); 7.70 (1H, m, C6H); 7.77 (1H, s, C8H); 8.29 (1H, s, NHCO)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 22.2 (CH_3); 24.0 ($COCH_3$); 30.1 ($C4H_2$); 40.0 ($C3H_2$); 51.4 (C1H); 70.8 ($COCH_2$); 114.9 (C2'H, C6'H); 121.8 (C3'H, C5'H); 125.5 (C6H); 125.7 (C8H); 128.9 (C4'NH); 129.6 (C5H); 132.1 (C7CO); 135.4 (C8a); 141.7 (C4a); 154.4 (C1'); 168.7 ($COCH_3$); 194.3 (CO)

Yield: 40%

IRν_{max}(KBr): 739cm^{-1}, 1607cm^{-1} (NHCO); 1688cm^{-1}(CO), 2987cm^{-1}, 3055cm^{-1}(CH)

HRMS calcd. for C18H19NO2Cl (M^++1): 339.1709 Found: 339.1707

Melting point: 110°C

1-(1-Methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-(4-nitro-phenoxy)-ethanone (275)

^{1}H-NMR (400MHz): δ(CD_3OD): 1.60 (3H, d, J = 6.1Hz, C1C$\underline{H}_3$); 3.04 – 3.08 (2H, m, C4$\underline{H}_2$); 3.32 (1H, d, J = 7Hz, C3$\underline{H}_2$); 3.45 – 3.48 (1H, m, C3$\underline{H}_2$); 4.58 (1H, bs, C1$\underline{H}$); 5.50 (2H, COC$\underline{H}_2$); 7.00 (2H, dd, J_1 = 9Hz, J_2 = 2.5Hz, C2'$\underline{H}$, C6'$\underline{H}$); 7.29 (1H, d, J = 8.2Hz, C5$\underline{H}$); 7.71 (1H, m, C6$\underline{H}$); 7.85 (1H, s, C8$\underline{H}$); 7.56 (2H, dd, J = 9Hz, J_2 = 2Hz, C3'$\underline{H}$, C5'$\underline{H}$)

^{13}C-NMR (101MHz): ppm(CD_3OD): 19.6 (C$\underline{H}_3$); 26.7 (C$\underline{4}H_2$); 40.0 (C$\underline{3}H_2$); 52.4 (C$\underline{1}$H); 71.9 (CO$\underline{C}H_2$); 116.1 (C$\underline{2}$'H, C$\underline{6}$'H); 126.7 (C$\underline{3}$'H, C$\underline{5}$'H); 127.3 (C$\underline{6}$H); 128.4 (C$\underline{8}$H); 130.9 (C$\underline{5}$H); 134.6 (C$\underline{7}$CO); 135.8 (C$\underline{8}$a); 139.4 (C$\underline{4}$a); 143.2 (C$\underline{4}$'NO_2); 164.7 (C$\underline{1}$'); 194.6 (C$\underline{O}$)

Yield: 25%

IRν_{max}(KBr): 1689cm^{-1} (CO), 2987 cm^{-1}, 3056cm^{-1}(CH)

HRMS calcd. for C18H19N2O4 (M^++1): 327.1345 Found: 327.1331

2-(4-Isocyano-phenoxy)-1-(1-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethanone (276)

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.50 (3H, d, J = 6.1Hz, C1C$\underline{H}_3$); 2.11 (1H, bs, N$\underline{H}$); 2.79 – 2.85 (1H, m, C4$\underline{H}_2$); 2.91 – 2.99 (1H, m, C4$\underline{H}_2$); 3.00 – 3.07 (1H, m, C3$\underline{H}_2$); 3.27 – 3.32 (1H, m, C3$\underline{H}_2$); 4.14 (1H, q, J = 6.1Hz, C1$\underline{H}$); 5.35 (2H, COC$\underline{H}_2$); 6.96 (2H, d, J = 8.9Hz, C2'$\underline{H}$, C6'$\underline{H}$); 7.21 (1H, d, J = 8.2Hz, C5$\underline{H}$); 7.56 (2H, d, J = 8.9Hz, C3'$\underline{H}$, C5'$\underline{H}$); 7.71 (1H, d, J = 8.2Hz, C6$\underline{H}$); 7.78 (1H, s, C8$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 22.5 (C$\underline{H}_3$); 30.3 (C$\underline{4}H_2$); 41.2 (C$\underline{3}H_2$); 51.5 (C$\underline{1}$H); 70.2 (CO$\underline{C}H_2$); 104.7 (C$\underline{4}$'CN); 115.3 (C$\underline{2}$'H, C$\underline{6}$'H); 118.9 (C$\underline{N}$); 125.3 (C$\underline{6}$H); 125.6 (C$\underline{8}$H); 126.5 (); 128.9 (); 129.8 (C$\underline{5}$H); 131.8 (C$\underline{7}$CO); 133.9 (C$\underline{3}$'H, C$\underline{5}$'H); 141.4 (C$\underline{8}$a); 142.3 (C$\underline{4}$a); 161.2 (C$\underline{1}$'); 192.6 (C$\underline{O}$)

Yield: 72%

IRν_{max}(KBr): 750cm^{-1}, 1699cm^{-1}(CO), 2985cm^{-1}, 3054cm^{-1}(CH)

HRMS calcd. for C19H19N2O2 (M^++1): 307.1447 Found: 307.1447

2-(4-Benzyloxy-phenoxy)-1-(1-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethanone (277)

^{1}H-NMR (400MHz): δ(CD_3OD): 1.58 (3H, d, J = 6Hz, C1C$\underline{H}_3$); 2.94 (1H, d, 17.6 Hz, C4$\underline{H}_2$); 3.03 (1H, t, J = 6Hz, C4$\underline{H}_2$); 3.08 – 3.16 (2H, m, C3$\underline{H}_2$); 4.28 (1H, d, J = 6Hz, C1$\underline{H}$); (O$\underline{C}H_2$ hidden by methanol singlet); 5.02 (2H, COC$\underline{H}_2$); 6.93 (4H, s, C2'$\underline{H}$, C3'$\underline{H}$, C5'$\underline{H}$, C6'$\underline{H}$); 7.28 – 7.43 (6H, m, C2"$\underline{H}$, C3"$\underline{H}$, C4"$\underline{H}$, C5"$\underline{H}$, C6"$\underline{H}$, C5$\underline{H}$); 7.85 (1H, d, J = 8Hz, C6$\underline{H}$); 7.91 (1H, s, C8$\underline{H}$)

^{13}C-NMR (101MHz): ppm(CD_3OD): 21.4 (C$\underline{H}_3$); 29.3 (C$\underline{4}H_2$); 41.2 (C$\underline{3}H_2$); 52.5 (C$\underline{1}$H); 71.5 (CO$\underline{C}H_2$, O$\underline{C}H_2$); 116.8 (C$\underline{2}$'H, C$\underline{3}$'H, C$\underline{5}$'H C$\underline{6}$'H); 127.0 (C$\underline{6}$H); 127.4 (C$\underline{8}$H); 128.4 (C$\underline{2}$"H, C$\underline{6}$"H); 128.9 (C$\underline{4}$"H); 129.5 (C$\underline{3}$"H, C$\underline{5}$"H); 130.8 (C$\underline{5}$H); 134.2 (C$\underline{7}$CO); 138.9 (C$\underline{8}$a); 140.0 (C$\underline{4}$a); 141.7 (C$\underline{1}$"); 153.8 (C$\underline{4}$'); 154.9 (C$\underline{1}$'); 197.0 (C$\underline{O}$)

Yield: 17%

IRν_{max}(KBr): 738cm^{-1}, 1700cm^{-1}(CO), 2984cm^{-1}, 3054cm^{-1}(CH)

HRMS calcd. for C25H26NO3 (M^++1): 388.1913 Found: 388.1924

4-[2-(1-Methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethoxy]-benzoic acid (278)

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.56 (3H, d, J = 6Hz, C1C$\underline{H}_3$); 2.65 (1H, bs, N$\underline{H}$); 2.84 (1H, d, 17.6 Hz, C4$\underline{H}_2$); 2.95 - 3.00 (1H, m, C4$\underline{H}_2$); 3.05 – 3.08 (1H, m, C3$\underline{H}_2$); 3.29 – 3.35 (1H, m, C3$\underline{H}_2$); 4.21 (1H, bs, C1$\underline{H}$); 5.33 (2H, s, COC$\underline{H}_2$); 6.96 (2H, d, J = Hz, C2'$\underline{H}$, C6'$\underline{H}$); 7.23 (1H, d, J = Hz, C5$\underline{H}$); 7.76 (1H, d, J = 8Hz, C6$\underline{H}$); 7.82 (1H, s, C8$\underline{H}$); 8.00 (2H, d, J = Hz, C3'$\underline{H}$, C5'$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 21.3 (C$\underline{H}_3$); 28.7 (C$\underline{4}H_2$); 39.9 (C$\underline{3}H_2$); 51.9 (C$\underline{1}$H); 70.4 (CO$\underline{C}H_2$, OCH_2); 114.3 (C$\underline{2}$'H, C$\underline{6}$'H); 123.4 (C$\underline{4}$'); 125.9 (C$\underline{6}$H); 126.1 (C$\underline{8}$H); 129.7 (C$\underline{5}$H); 131.6 (C$\underline{3}$'H, C$\underline{5}$'H); 132.5 (C$\underline{7}$CO); 140.4 (C$\underline{4}$a, C$\underline{8}$a); 161.5 (C$\underline{1}$'); 166.6 (C$\underline{O}$OH); 193.2 (C$\underline{O}$)

Yield: 81%

IRν_{max}(KBr): 732cm^{-1}, 1718cm^{-1}(CO), 2963cm^{-1}, 3006cm^{-1}(CH)

1-[2-(2-Chloro-acetyl)-1,2,3,4-tetrahydroisoquinolin-7-yl]-2-(4-fluoro-phenoxy-ethanone) (279)

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.93 (0.9H, t, J = 5.5Hz, C4$\underline{H}_2$), 3.03 (1.1H, t, J = 6.0Hz, C4$\underline{H}_2$); 3.77 (1.1H, t, J = 5.5Hz, C3$\underline{H}_2$), 3.85 (0.9H, t, J = 6.0Hz, C3$\underline{H}_2$); 4.17, 4.18 (2H, s, s, overlapping, C1$\underline{H}_2$); 4.75 (0.9H, s, C$\underline{H}_2$Cl) (s), 4.78 (1.1H, s, C$\underline{H}_2$Cl) (m); 5.21 (COC$\underline{H}_2$); 6.85 – 6.90 (2H. m, C2'$\underline{H}$, C6'$\underline{H}$); 6.92 – 6.97 (2H, m, C3'$\underline{H}$, C5'$\underline{H}$); 7.25 – 7.30 (1H, m, C5$\underline{H}$); 7.77 – 7.82 (2H, m, C8$\underline{H}$, C6$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 28.4 (C$\underline{4}H_2$) (s), 29.5 (C$\underline{4}H_2$) (m); 39.9 (C$\underline{3}H_2$) (s); 41.0 (C$\underline{H}_2$Cl) (m), 41.2 (C$\underline{H}_2$Cl) (s); 43.2 (C$\underline{1}H_2$) (m); 44.4 (C$\underline{3}H_2$) (m); 47.5 (C$\underline{H}_2$) (s); 71.3 (CO$\underline{C}H_2$); 115.86 (C$\underline{2}$'H, C$\underline{6}$'H, d, J = 9 Hz); 115.9 (C$\underline{3}$'H, C$\underline{5}$'H, d, J = 22 Hz); 125.9, 126.3, 126.4, 126.7 (C$\underline{6}$H, C$\underline{8}$H) (s), (m), (m), (s); 127.0 (C$\underline{7}$CO); 129.0 (C$\underline{5}$H) (m), 129.4 (C$\underline{5}$H) (s); 132.9 (C$\underline{8}$a) (m), 133.4 (C$\underline{8}$a) (s); 140.1 (C$\underline{4}$a) (m), 141.2 (C$\underline{4}$a) (s); 154.0 (C$\underline{1}$'); 157.6 (C$\underline{4}$'F, d, J = 28 Hz); 165.5 (C$\underline{O}CH_2$Cl); 193.7 (C$\underline{O}CH_2$)

^{19}F-NMR (376MHz): -123.04 (s), -123.14 (m)

Yield: 87%

IRν_{max}(KBr): 1655cm^{-1}, 1703 cm^{-1} (CO), 2987 cm^{-1}, 3055cm^{-1}(CH)

HRMS calcd. for C19H17NO3NaFCl (M^++23): 384.0779 Found: 384.0797

1-(2-{2-[4-Chloro-phenyl)-piperazin-1-yl]-acetyl}-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-(4-fluoro-phenoxy)-ethanone (280)

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.69 – 2.70 (4H, m, cyclohexyl ring); 2.95 (0.7H, t, J = 6.0Hz, C4$\underline{H}_2$), 3.02 (1.3H, t, J = 6.0Hz, C4$\underline{H}_2$); 3.10 – 3.19 (4H, m, cyclohexyl ring); 3.36 (2H, s, COC$\underline{H}_2$N); 3.87 (2H, t, J = 5.5Hz, C3$\underline{H}_2$); 4.82 (1.3H, s, C1$\underline{H}_2$) (m), 4.89 (0.7H, s, C1$\underline{H}_2$) (s); 5.20, 5.22 (2H, s, s, overlapping, COC$\underline{H}_2$); 6.80 – 6.91 (4H. m, C2'$\underline{H}$, C3'$\underline{H}$, C5'$\underline{H}$, C6'$\underline{H}$); 6.95 – 7.01 (2H, m, C2"$\underline{H}$, C6"$\underline{H}$); 7.18 – 7.22 (1H, m, C5$\underline{H}$); 7.28 – 7.31 (2H, m, C3"$\underline{H}$, C5"$\underline{H}$); 7.90 – 7.83 (2H, m, C8$\underline{H}$, C6$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 28.7 (C$\underline{4}H_2$) (s), 29.9 (C$\underline{4}H_2$) (m); 39.6 (C$\underline{3}H_2$) (s); 42.9 (C$\underline{1}H_2$) (m); 44.2 (C$\underline{3}H_2$) (m); 44.5 (C$\underline{1}H_2$) (s); 49.1, 53.0 (C$\underline{H}_2$ of cyclohexyl ring) (s); 61.6 (CO$\underline{C}H_2$N); 71.4 (CO$\underline{C}H_2$); 115.9 (C$\underline{2}$'H, C$\underline{6}$'H, d, J = 8 Hz); 116.0 (C$\underline{3}$'H, C$\underline{5}$'H, d, J = 22 Hz); 117.2 (C$\underline{2}$"H, C6"H); 124.6 (C$\underline{4}$"Cl); 126.2, 126.6 (C$\underline{6}$H, C$\underline{8}$H); 128.9 (C$\underline{3}$"H, C$\underline{5}$"H); 129.0 (C$\underline{5}$H);129.2 (C$\underline{7}$CO); 132.9 (C$\underline{8}$a); 134.1 (C$\underline{4}$a); 149.7 (C$\underline{1}$"); 154.0 (C$\underline{1}$'); 158.8 (C$\underline{4}$'F); 168.2 (C$\underline{O}CH_2$N); 191.8 (C$\underline{O}CH_2$)

^{19}F-NMR (376MHz): -123.00 (s), -123.16 (m)

Yield: 87%

IRν_{max}(KBr): 1157cm^{-1}(CN piperazine), 1422cm^{-1}, 1644cm^{-1}, 1702cm^{-1} (CO), 2987 cm^{-1}, 3055cm^{-1}(CH)

HRMS calcd. for C29H30N3O3FCl (M^++1): 522.1960 Found: 522.1982

METHOD A

1-(4-Methylthiophenyl)-2-nitropropene (282)

12.8mL/15.0g/98.7mmol 4-methylthiobenzaldehyde was pipetted into 80mL of glacial acetic acid. 15mL/15.75g/210mmol nitroethane and 11.5mL/9.971g/100.5mmol cyclohexylamine were added and the mixture was heated on a waterbath for 6 hours. 10mL/10g/555mmol water was added to the hot solution and it was left to cool overnight. The resultant yellow crystals of 1-(4-methylthiophenyl)-2-nitropropene were isolated, washed with water and dried on a Buchner funnel.

Percentage yield: 50.6%

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.47 (3H, C2C$\underline{H}_3$); 2.54 (3H, SC$\underline{H}_3$); 7.30 (2H, d, J = 8.52Hz, H-3', H-5'); 7.38 (2H, d, J = 8.56Hz, H-2', H-6'); 8.06 (1H, C1H)

^{13}C-NMR (101MHz): δ($CDCl_3$): 14.10 (C2$\underline{C}H_3$); 15.00 (S$\underline{C}H_3$); 125.89($\underline{C}$3'H, $\underline{C}$5'H); 128.58($\underline{C}$2(NO_2)CH_3); 130.44 ($\underline{C}$2'H, $\underline{C}$6'H); 133.11 ($\underline{C}$1H); 142.14 ($\underline{C}$4'SCH_3); 146.87 ($\underline{C}$1'C1H)

IRν_{max} (KBr): 1590cm^{-1} (s), 1514 cm^{-1} (s), 1315 cm^{-1} (s), 1097cm^{-1} (s), 816cm^{-1} (s)

Melting point: literature 76-77°C[38]

experimental, from glacial acetic acid/water 68°C

1-(4-Methylphenyl)-2-nitropropene (283)

Prepared by method A.

Percentage yield: 48.2%

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.45 (3H, C4'C$\underline{H}_2$); 2.49 (3H, C2(NO_2)C$\underline{H}_3$); 7.31 (2H, d, J = 8.04, H2', H6'); 7.39 (2H, d, J = 8.04, H3', H5'); 8.09 (1H, C1$\underline{H}$)

^{13}C-NMR (101MHz): δ($CDCl_3$): 13.78 (C2(NO_2)$\underline{C}H_3$)); 21.17 (C4'$\underline{C}H_3$); 129.30 ($\underline{C}$2(NO_2)CH_3); 129.44 ($\underline{C}$2'H, $\underline{C}$6'H); 129.92 ($\underline{C}$3'H, $\underline{C}$5'H); 133.37 ($\underline{C}$1H); 140.31 ($\underline{C}$4'CH_3); 146.73 ($\underline{C}$1'C1H)

IRν_{max} (KBr): 1650 cm^{-1}, 1611 cm^{-1}, 1522 cm^{-1}, 1386 cm^{-1}, 1325 cm^{-1}, 904 cm^{-1}, 815 cm^{-1}

Melting point: literature, from petroleum ether 55°C[39]

experimental, from glacial acetic acid/water 40-42°C

1-(4-Methoxyphenyl)-2-nitropropene (284)

METHOD B

5.0mL/5.595g/40.92mmol 4-methoxybenzaldehyde (or para-anisaldehyde) was dissolved in 40mL glacial acetic acid. 8.8mL/9.216g/122.76mmol nitroethane and 4.7mL/4.69g/40.92mmol cyclohexylamine were pipetted into the solution and the flask contents were heated on a water bath for 8 hours. 10mL/10g/556mmol water was added but this failed to cause precipitation of the nitrostyrene. The acidic solution was diluted with ca.650mL water and the acid was neutralised with approximately 300mL saturated sodium bicarbonate solution. The fine suspension produced was extracted with two aliquots of 200mL dichloromethane. The extract was dried with anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. The nitrostyrene was separated from the aldehyde and a further impurity by column chromatography, using Merck silica 60 (0.04-0.063mm) and a mobile phase of 1:9 diethyl ether/hexane. The yellow solid isolated was recrystallised from hexane to give bright yellow raphide crystals.

Yield: 37.4%

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.44 (3H, C2(NO_2)C3$\underline{H}_3$); 3.85 (3H, O$\underline{CH}_3$); 6.97 (2H, d, J = 12.52, $\underline{H}$3', $\underline{H}$5'); 7.40 (2H, d, J = 8.52, $\underline{H}$2', $\underline{H}$6'); 8.02 (1H, C1$\underline{H}$)

^{13}C-NMR (101MHz): δ($CDCl_3$): 14 (C(NO_2)$\underline{C}H_3$); 55 (O$\underline{C}H_3$); 114 ($\underline{C}$1H); 125 (C2(NO_2)); 132 ($\underline{C}$3'H, $\underline{C}$5'H); 134 ($\underline{C}$2'H, $\underline{C}$6'H); 146 ($\underline{C}$1'C1H); 161 ($\underline{C}$4'OCH_3)

IRν_{max} (KBr): 1647cm^{-1}, 1606cm^{-1}, 1518cm^{-1}, 1457cm^{-1}, 1460cm^{-1}, 1304cm^{-1}, 1260cm^{-1}, 1180cm^{-1}, 1029cm^{-1}, 986cm^{-1}, 838cm^{-1}

Melting point: literature 44°C[40]

experimental 32-38°C

1-(4-Hydroxyphenyl)-2-nitropropene (285)

Prepared by method B. A rusty brown solid resulted. This was slightly water soluble, and while yellow in dichloromethane, turned red in water.

Yield: 30.6%

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.49 (C3$\underline{H}$); 6.95 (2H, d, J = 8.52Hz, $\underline{H}$3', $\underline{H}$5'); 7.40 (2H, d, J = 8.52 Hz, $\underline{H}$2', $\underline{H}$6); 8.08 (C1$\underline{H}$)

^{13}C-NMR (101MHz): δ($CDCl_3$): 14 ($\underline{C}H_3$); 116 ($\underline{C}$1H); 125 ($\underline{C}$2(NO_2)CH_3); 132 ($\underline{C}$3'H, $\underline{C}$5'H); 134 ($\underline{C}$2'H, $\underline{C}$6'H) 146 ($\underline{C}$1'C1H); 157 ($\underline{C}$4'OH)

IRν_{max} (KBr): 3386 cm^{-1} (s); 1605 cm^{-1} (s); 1524 cm^{-1} (s); 1500 cm^{-1} (s); 1436cm^{-1} (s); 1301 cm^{-1} (s); 1203 cm^{-1} (s)

Melting point: literature 124°C[41]

experimental 110-112°C

Product was still clearly wet.

1-(4-Fluorophenyl)-2-nitropropene (286)

Prepared using method A.

Yield: 54.3%

^{1}H-NMR (400MHz): (δ$CDCl_3$): 2.45 (C3$\underline{H}_3$); 7.17 (2H, t, J = 8.56Hz, $\underline{H}$2', $\underline{H}$6'); 7.45 (2H, q, J = 5.52Hz, $\underline{H}$3', $\underline{H}$5'); 8.05 (1H, C1$\underline{H}$)

^{13}C-NMR (101MHz): δ($CDCl_3$): 13.86 ($\underline{C}H_3$); 116.01 ($\underline{C}$1H); 128.50 (d, J = 3.86Hz, $\underline{C}$3'H, $\underline{C}$5'H); 132.00 (d, J = 8.7Hz, $\underline{C}$2'H, $\underline{C}$6'H); 132.31 ($\underline{C}$2(NO_2)CH_3); 147.53 ($\underline{C}$1'C1H); 163.37(d, J = 251Hz, $\underline{C}$4'F)

19F-NMR (378.5MHz): δ($CDCl_3$): -109.94 (F)

Melting point: literature 64-66°C[42]

experimental 60 -64°C

IRvmax: 1510 cm^{-1} (s); 1500 cm^{-1} (s); 1319 cm^{-1} (s); 1227 cm^{-1} (s)

1-(4-Chlorophenyl)-2-nitropropene (287)

Synthesised using method B.

Yield: 43.3%

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.45 (3H, C2(NO_2)C3$\underline{H}_3$); 7.39(2H, d, J = 8.56Hz , $\underline{H}$2', $\underline{H}$6'); 7.45 (2H, d, J = 8.52Hz, $\underline{H}$3', $\underline{H}$5'); 8.04(1H, C1$\underline{H}$)

^{13}C-NMR (101MHz): δ($CDCl_3$): 13.94($C(NO_2)\underline{C}H_3$; 129.19($\underline{C}$3'H, $\underline{C}$5'H); 130.87(C2(NO_2)); 130.83 ($\underline{C}$2'H, $\underline{C}$6'H); 132.12($\underline{C}$1H); 136.03($\underline{C}$4'); 148.08($\underline{C}$1'C1H)

Melting point: literature 85°C[43]

Experimental 80 - 82°C

IRν_{max} (KBr): 3438 cm^{-1} (broad); 1514 cm^{-1}, 1410 cm^{-1}, 1312 cm^{-1}, 1090 cm^{-1}, 984 cm^{-1}, 844 cm^{-}

1-(4-nitrophenyl)-2-nitropropene (288)

Method A employed.

IRν_{max} (KBr): 1522 cm^{-1}(s),1337cm^{-1}(s), 3450 cm^{-}1(w), 1603 cm^{-1}(w)

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.47 (3H, C2(NO_2)C3$\underline{H}_3$); 7.61(2H, d, J = 8.56Hz, $\underline{H}$2', $\underline{H}$6'); 8.32 (2H, d, J = 9.04Hz, $\underline{H}$3', $\underline{H}$5'); 8.09 (1H, C1$\underline{H}$)

^{13}C-NMR (101MHz): δ($CDCl_3$): 13.97($C(NO_2)\underline{C}H_3$); 130.66($\underline{C}$1H); 123.98 ($\underline{C}$3'H, $\underline{C}$5'H); 130.46 ($\underline{C}$2'H, $\underline{C}$6'H);138.82 (C2(NO_2)); 148.10 ($\underline{C}$1'C1H); 150.22 ($\underline{C}$4')

Yield: 95.7%

Melting point: literature 114 - 115°C[41]

experimental : 104°C - 108°C

2-Nitropropenylbenzene (289)

Method B used.

Yield: 41.4%

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.4673(3H, C2'(NO_2)C3'$\underline{H}_3$); 7.4537(5H, $\underline{H}$2, $\underline{H}$3, $\underline{H}$4, $\underline{H}$5,$\underline{H}$6); 8.0959(1H, C1'$\underline{H}$)

^{13}C-NMR (101MHz): δ($CDCl_3$): 13.93 ($C(NO_2)\underline{C}H_3$); 128.83 ($\underline{C}$2'H, $\underline{C}$6'H); 129.88 ($\underline{C}$1H); 129.84 ($\underline{C}$3', $\underline{C}$5'H); 132.40 (C2(NO2)); 133.39 ($\underline{C}$4'H); 147.74 ($\underline{C}$1'C1H);

Melting point: literature 65 - 66°C[5]

experimental 52°C-56°C

IRν_{max} (KBr): 1652cm^{-1}, 1508cm^{-1}, 1328 cm^{-}1, 901 cm^{-1},764cm^{-1}

1-(3,4-Dimethoxyphenyl)-2-nitropropene (290)

METHOD C

5.000g/30.09mmol 3,4-dimethoxybenzaldehyde, also called veratraldehyde, was stirred in 6.5mL/6.776g/90.27mmol nitroethane for 10 minutes, then 0.4mL/298mg/3.01mmol cyclohexylamine was added by pipette. The flask was fitted with a drying tube and left in a cool, dark cupboard for 17 days. The orange semi-solid produced was recrystallised from hot ethanol to give bright orange crystals.

Yield: 53.7%

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.42 (3H, C2(NO_2)C3$\underline{H}_3$); 3.85 (6H, $_2$OC$\underline{H}_3$); 6.93, 7.04 (3H, $\underline{H}$2', $\underline{H}$5', $\underline{H}$6'); 8.00(1H, C1$\underline{H}$)

^{13}C-NMR (101MHz): δ($CDCl_3$): 13.26 ($C(NO_2)\underline{C}H_3$); 55.07 ($O\underline{C}H_3$); 56.51 ($O\underline{C}H_3$), 110.35 ($\underline{C}$5'H); 112.21 ($\underline{C}$2'H); 122.99 ($\underline{C}$6'H); 132.71 ($\underline{C}$1H); 134.28($\underline{C}$2(NO_2));145.65 (C1'C1H);150.57, 148.92($\underline{C}$3'OCH_3, $\underline{C}$4'OCH_3)

IR ν_{max} (KBr): 2932cm^{-1}, 1515cm^{-1}, 1317cm^{-1}, 1259cm^{-1}, 1143cm^{-1}, 1022cm^{-1}

Melting point: literature 72.5 - 74°C [44]

Experimental 64 - 66°C

1-(3,4-Methylenedioxyphenyl)-2-nitropropene (291)

Method A produced rusty brown crystals.

Yield: 47.5%

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.48 (3H, C2(NO_2)C3$\underline{H}_3$); 6.06 (2H, O$\underline{CH}_2$O); 6.92 (1H, t, J = 7.04Hz, $\underline{H}$2'); 6.99 (2H, t, J = 6.52, $\underline{H}$5', $\underline{H}$6'); 7.28 (1H, C1$\underline{H}$)

^{13}C-NMR (101MHz): δ($CDCl_3$): 14.13 (C(NO_2)$\underline{C}H_3$); 101.75 (O$\underline{C}H_2$O); 133.55 ($\underline{C}$1H); (C2(NO_2)); 108.85, 109.52 ($\underline{C}$5'H, $\underline{C}$6'H); 125.86 ($\underline{C}$2'H,);149.68, 150.00 (C3',C4')

No other discernable signal from a quaternary carbon.

Melting point: literature 93 - 94°C from glacial acetic acid/water[45]

Experimental 90 - 92°C

1-(4-Bromophenyl)-2-nitropropene (292)

Method A gave rise to bright yellow crystals upon standing.

Yield: 60.4%

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.44 (3H, C2(NO_2)C3$\underline{H}_3$); 7.31 (2H, d, J = 8.52Hz, $\underline{H}$2', $\underline{H}$6'); 7.60 (2H, d, J = 8.56Hz, $\underline{H}$2', $\underline{H}$6'); 8.01(1H, C1$\underline{H}$)

^{13}C-NMR (101MHz): δ($CDCl_3$): 13.94 (C(NO_2)$\underline{C}H_3$); 131.28 ($\underline{C}$3'H, $\underline{C}$5'H); 132.14 ($\underline{C}$2'H, $\underline{C}$6'H); 124.31($\underline{C}$1'C1H); 148.13 ($\underline{C}$4')

Melting point: literature 85 - 86°C[46]

experimental 86°C - 89°C

IRν_{max} (KBr): 3879cm^{-1}, 2345 cm^{-1}(w), 1654cm^{-1}(m), 1508cm^{-1}(s), 1315cm^{-1}(s), 1076cm^{-1}(m)

KETONES PRODUCED BY IRON REDUCTION OF NITROSTYRENES

1-(4-Methylthiophenyl)-2-propanone (293)[47]

1.000g/4.779mmol of 1-(4-Methylphenyl)-2-nitropropene was dissolved in 7.6mL glacial acetic acid with heating on a water bath. 3.04g/57.4mmol of iron powder was weighed out and suspended in 14mL hot glacial acetic acid. The nitrostyrene solution was pipetted into the iron suspension and the mixture was heated on the waterbath and stirred periodically for 1.5hours. The mixture was emptied into 120mL iced water. The aqueous suspension was extracted with 200mL dichloromethane and the extract was washed with first three aliquots of 50mL 15%w/v sodium hydroxide solution, then 75mL water. The extract was dried over anhydrous sodium sulfate and filtered. The solvent was removed *in vacuo* to give a yellow oil. Thin layer chromatography showed this to be impure, so the oil was distilled under vacuum at 144°C.

Percentage yield: 92%

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.16 (C3$\underline{H}_3$); 2.49 (3HSC$\underline{H}_3$); 3.67 (2H, C1$\underline{H}_2$); 7.14, (2H, q, J = 8.04); 7.25 (2H, d, J = 8.52Hz, H-3',H5')

^{13}C-NMR (101MHz): δ($CDCl_3$): 15.93 ($\underline{C}$3H_3); 29.19 (S$\underline{C}H_3$); 50.36 ($\underline{C}$1H_2); 127.10 ($\underline{C}$3'H, $\underline{C}$5'H); 129.82 ($\underline{C}$ 2'H, $\underline{C}$6'H); 131.06 ($\underline{C}$1'C1H2); 137.23 (S$\underline{C}H_3$); 206.05 (C2O)

IR (film): 2987cm^{-1}, 2922cm^{-1}, 1715cm^{-1}, 1494cm^{-1}, 1358cm^{-1}, 1160cm^{-1}

1-(3-Bromophenyl)-2-propanone (294)[48]

Synthesis analogous to that for 1-(4-Methylthiophenyl)-2-propanone.

Yield: 95.92%

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.95 (3H, C2OC3$\underline{H}_3$); 3.48 (2H, C1$\underline{H}_2$); 6.93, 6.95, 6.98, 6.98, 7.00, 7.02 (2H, m, $\underline{H}$5', $\underline{H}$6') 7.13, 7.21, 7.22 (2H, m, $\underline{H}$3', $\underline{H}$4)

IRν_{max} (film): 2925cm^{-1}, 1714cm^{-1} (s), 1409cm^{-1}(s), 1357cm^{-1}(s), 1160cm^{-1}(m), 1072cm^{-1}(s), 1013cm^{-1}(s)

Boiling point: 86°C

1-(4-Chlorophenyl)-2-propanone (295)

Preparation as for other ketones in the series.

Yield: 86.05%

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.16 (3H, C3$\underline{H}_3$), 3.68 (2H, C1$\underline{H}_2$), 7.13 (2H, d, J = 8.56, $\underline{H}$2', $\underline{H}$6'); 7.30 (2H, d, J = 8.56, $\underline{H}$3', $\underline{H}$5')

^{13}C-NMR (101MHz): δ($CDCl_3$): 29.25 ($\underline{C}$3H_3), 49.91 ($\underline{C}$1H_2); 128.60, 128.74 ($\underline{C}$3'H, $\underline{C}$5'H), 130.23, 130.69 ($\underline{C}$2'H, $\underline{C}$6'H); 134.45 (C1'C1H_2); 132.91 (C4'Cl); 205.42 ($\underline{C}$2O)

Boiling point: 75 - 79°C, 0.3 Torr[49]

IRν_{max} (film): 3004cm^{-1}(w, broad), 1715(s)cm^{-1}, 1491(s)cm^{-1}, 1358(s)cm^{-1}, 1161(s)cm^{-1}, 1089(s)cm^{-1}, 1017(s)cm^{-1}

1-(4-Methoxyphenyl)-2-propanone (296)

The method of synthesis employed was that used in the manufacture of 1-(4-methylthiophenyl)-2-propanone.

Yield: 84.72%

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.14 (3H, C3$\underline{H}_3$); 3.63 (2H, C1$\underline{H}_2$); 3.80 (3H, OC$\underline{H}_3$); 6.88 (2H, d, J = 8.52Hz, $\underline{H}$3', $\underline{H}$5'); 7.13 (2H, d, J = 8.56Hz, $\underline{H}$2', $\underline{H}$6')

^{13}C-NMR (101MHz): δ($CDCl_3$): 28.92 ($\underline{C}$3H_3); 49.97 ($\underline{C}$1H_2); 55.11 (O$\underline{C}$$H_3$); 114.10 ($\underline{C}$3'H, $\underline{C}$5'H); 126.25 ($\underline{C}$1'C1H_2); 130.27 ($\underline{C}$2'H, $\underline{C}$6'H); 158.62 ($\underline{C}$4'OCH_3); 206.63 ($\underline{C}$2O)

Boiling point: 82 - 85°C/0.1 Torr[49]

IRν_{max} (film): 3404(w)cm^{-1},3004(s)cm^{-1}, 2936(s), 2038cm^{-1}, 1715 cm^{-1}(s), 1614 cm^{-1}(s), 1515 cm^{-1}(s), 1248 cm^{-1}(s), 1179 cm^{-1}(s), 1035 cm^{-1}(s)

1-(4-Nitrophenyl)-2-propanone (297)

Prepared by iron reduction analogous to the synthesis of 1-(4-Methylthiophenyl)-2-propanone.

Yield: 67.52%

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.39 (3H, C3$\underline{H}_3$); 3.67 (2H,C2$\underline{H}_2$); 7.13 (2H, d, J = 8.52Hz, $\underline{H}$2', $\underline{H}$6'); 7.47 (2H, d, J = 7.52Hz, $\underline{H}$3', $\underline{H}$5')

^{13}C-NMR (101MHz): δ($CDCl_3$): 29.60 ($\underline{C}$3H_3); 50.20 ($\underline{C}$1H_2); 120.28 ($\underline{C}$3'H, $\underline{C}$5'H); 128.04 (C1'C1H_2); 129.82 ($\underline{C}$2'H, $\underline{C}$6'H); 168.69 ($\underline{C}$4'NO_2); 206.65 ($\underline{C}$2O)

IR (film): 2924cm^{-1}, 1716cm^{-1}, 1510cm^{-1}, 1223cm^{-1}, 1158cm^{-1}, 841cm^{-1}

Boiling point: 212 – 215°C[50]

1-(3,4-Methylenedioxyphenyl)-2-propanone (298)

Produced by reduction as described for 1-(4-Methylthiophenyl)-2-propanone.

Yield: 98.43%

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.15 (3H,C3$\underline{H}_3$); 3.60 (2H, C1$\underline{H}_2$); 5.94 (2H, OC$\underline{H}_2$O); 6.65 (2H, d, J = 7.52Hz, $\underline{H}$2', $\underline{H}$5'); 6.77 (1H, d, J = 8.0, $\underline{H}$6')

^{13}C-NMR (101MHz): δ($CDCl_3$): 28.99 (C$\underline{H}_3$); 50.46 (C$\underline{H}_2$); 100.98 (O$\underline{C}H_2$O); 108.39 ($\underline{C}$5'H); 109.68 ($\underline{C}$2'H); 122.43 ($\underline{C}$6'H); 127.80 ($\underline{C}$1'CH$_2$); 146.65, 152.97 ($\underline{C}$3' OCH$_2$O$\underline{C}$4'); 206.28 ($\underline{C}$2O)

Melting point: literature: 71 - 73°C[51]

Experimental: 70 - 72°C

IR (film): 2901cm^{-1}, 1715cm^{-1}, 1499cm^{-1}, 1446cm^{-1}, 1250cm^{-1}, 1039cm^{-1},

Phenylpropanone (299)

Prepared by iron reduction of the nitrostyrene; see details of the synthesis of 1-(4-methylthiophenyl)-2-propanone.

Yield: 92.83%

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.18 (3H, C3$\underline{H}_3$); 3.72 (2H, C1$\underline{H}_2$), 7.23, 7.25, 7.37, 7.38 (4H, d, d, J1 = 7.04Hz, J2 = 7.56Hz, $\underline{H}$2', $\underline{H}$3', $\underline{H}$5', $\underline{H}$6'); 7.30, 7.32 (1H, d, J = 7.04Hz, $\underline{H}$4')

^{13}C-NMR (101MHz): δ($CDCl_3$): 29.10 (C$\underline{H}_3$); 50.89 (C$\underline{H}_2$); 126.94 ($\underline{C}$4'H); 128.64 ($\underline{C}$3'H, $\underline{C}$5'H); 129.29 ($\underline{C}$2'H, $\underline{C}$6'H); 134.20 ($\underline{C}$1'CH$_2$); 206.15 ($\underline{C}$2O)

Boiling point: 89 - 90°C[52]

IR (film): 3406cm^{-1}, 1714cm^{-1},1497cm^{-1}, 1455cm^{-1}, 1358cm^{-1}, 1159cm^{-1}

1-(3,4-Dimethoxyphenyl)-2-propanone (300)

Yield: 60.5%

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.0396 (3H, C3$\underline{H}_3$); 3.5248 (2H, C1$\underline{H}_2$); 3.7556 (6H, OC$\underline{H}_3$*2); 6.6477 (2H, d, J = 11.52, $\underline{H}$2', $\underline{H}$5'); 6.7374 (1H, d, J = 8.0, $\underline{H}$6')

^{13}C-NMR (101MHz): δ($CDCl_3$): 28.60 (C$\underline{H}_3$); 50.02 (C$\underline{H}_2$); 55.45 (O$\underline{C}H_3$*2); 111.21, 112.23 ($\underline{C}$2'H, $\underline{C}$5'H); 121.23 ($\underline{C}$6'H); 126.48 ($\underline{C}$1'CH$_2$); 147.81, 147.76 ($\underline{C}$3'OCH$_3$, $\underline{C}$4'OCH$_3$); 206.13 ($\underline{C}$2O)

Boiling point: 129 - 133°C[53]

IR (film): 2900cm^{-1}, 1705cm^{-1}, 1514cm^{-1}, 1442cm^{-1}, 1039cm^{-1}

1-(4-Methylphenyl)-2-propanone (301)

Synthesised in the manner of 1-(4-Methylthiophenyl)-2-propanone.

Yield: 30.23%

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.16 (3H, C3$\underline{H}_3$); 2.36 (3H, C4'C$\underline{H}_3$); 3.67 (2H, C1$\underline{H}_2$); 7.11, 7.13, 7.16, 7.18 (4H, m, $\underline{H}$2',$\underline{H}$3; $\underline{H}$5', $\underline{H}$6')

^{13}C-NMR (101MHz): δ($CDCl_3$): 20.90 (C$\underline{H}_3$); 28.95 (C4'C$\underline{H}_3$); 50.49 (C$\underline{H}_2$); 129.12 ($\underline{C}$2'H, $\underline{C}$6'H); 129.32 ($\underline{C}$3'H, $\underline{C}$5'H); 131.12 ($\underline{C}$1'CH$_2$); 136.51 ($\underline{C}$4'CH$_3$); 206.43 ($\underline{C}$2O)

Boiling point: 62 - 67°C[49]

IRν_{max} : 2924 cm^{-1}(m), 2361 cm^{-1}(s), 1715 cm^{-1}(m), 1356 cm^{-1}(w)

1-(4-Fluorophenyl)-2-propanone (302)

This was produced by the reduction of the equivalent nitrostyrene, using iron in the fashion described for 1-(4-methylthiophenyl)-2-propanone.

Yield: 94.78%

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.16 (3H, C3$\underline{H}_3$); 3.68 (2H, C1$\underline{H}_2$); 7.01 (2H, t, J = 8.52Hz, $\underline{H}$3', $\underline{H}$5');
7.16 (2H, $\underline{H}$2', $\underline{H}$6')

^{13}C-NMR (101MHz): δ($CDCl_3$): 29.14 ($\underline{C}3H_3$); 49.76 ($\underline{C}1H_2$); 115.34, 115.55 (d, J = 21.46Hz, $\underline{C}$3'H, $\underline{C}$5'H); 129.87 ($\underline{C}$1'C1H_2)); 130.82 ($\underline{C}$2'H, $\underline{C}$6'H); 163.12, 160.68 (C4'F, d, J = 243.52Hz); 205.87 ($\underline{C}$2O)

19F-NMR (378.5MHz) δ($CDCl_3$): -116.31 (C4'$\underline{F}$)

Boiling point: 60 - 65°C[47]

IR (film): 3006cm^{-1}, 1715cm^{-1}, 1511cm^{-1}, 1359cm^{-1}, 1223cm^{-1}, 1158cm^{-1}, 841cm^{-1}

1-(4-Bromophenyl)-2-propanone (303)

Prepared in the same manner as 1-(4-methylthiophenyl)-2-propanone.

Yield: 66%

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.17 (3H, C3$\underline{H}_3$); 3.66 (2H, C1$\underline{H}_2$); 7.08 (2H, d, J = 8.04Hz, $\underline{H}$2', $\underline{H}$6'); 7.46 (2H, d, J = 8.0Hz, $\underline{H}$3', $\underline{H}$5')

^{13}C-NMR (101MHz): ($CDCl_3$): 30($\underline{C}3H_3$); 50($\underline{C}1H_2$); 121($\underline{C}$4'Br); 131($\underline{C}$2', $\underline{C}$6'); 132($\underline{C}$3', $\underline{C}$5'); 133($\underline{C}$1'C1H_2); 204(C2O)

Boiling point: 80 – 84°C[54]

IRν_{max} (film): 3396cm^{-1}, 2921cm^{-1}(s), 1714cm^{-1}(s),
1488cm^{-1}(s), 1357cm^{-1}(s), 1159cm^{-1}(s), 1159cm^{-1}(s),
1013cm^{-1}(s)

REDUCTIVE AMINATION OF KETONE TO AMINE

1-(4-Methylthiophenyl)-2-aminopropane (281)

14.314g/185.7mmol ammonium acetate, 0.914g/14.54mmol sodium cyanoborohydride and 1.002g/5.5585mmol 1-(4-Methylthiophenyl)-2-propanone were dissolved in 53.5mL dry methanol (added by syringe) and stirred for 3.5 days. The pH was monitored and maintained at pH6 by the addition of concentrated hydrochloric acid as necessary. The solution was poured into 500mL dilute (3% v/v) hydrochloric acid and after evolution of hydrogen cyanide ceased the solution was washed with dichloromethane. The solution was made alkaline with 15% w/v sodium hydroxide solution and extracted with 100mL dichloromethane. The extract was washed with water, dried with anhydrous sodium sulfate and filtered before the solvent was removed *in vacuo*. The unstable amine was thus isolated as oil which was dissolved in dry diethyl ether prior to precipitation as the hydrochloride salt upon treatment with dry hydrogen chloride gas.

Yield: 44%

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.03 (3H, d, J = 6.04Hz, C3$\underline{H}_3$); 1.20 (2H, N$\underline{H}_2$); 2.40 (3H, SCH_3); 2.42 (1H, d, J = 7.52Hz, C1$\underline{H}_2$); 3.03 (1H, d, J = 5.52Hz, C1H_2); 3.05 (1H, m, C2H(NH_2)); 7.03 (2H, d, J = 8.52Hz, $\underline{H}$3', $\underline{H}$5'); 7.13 (2H, d, J = 8.0Hz, $\underline{H}$2', $\underline{H}$6')

^{13}C-NMR (101MHz): δ($CDCl_3$): 16.19 ($\underline{C}3H_3$); 23.51 (S$\underline{C}H_3$); 46.07 ($\underline{C}1H_2$); 48.43 ($\underline{C}$2H); 127.07 ($\underline{C}$3'H, $\underline{C}$5'H); 129.75 ($\underline{C}$2'H, $\underline{C}$6'H); 135.84 ($\underline{C}$4'SCH_3); 136.73 ($\underline{C}$1'C1H_2)

IRν_{max} (KBr): 3357cm^{-1}, 2961cm^{-1}, 1598cm^{-1}, 1405cm^{-1}, 1439cm^{-1}, 1094cm^{-1}, 794cm^{-1}, 595cm^{-1}

1-(4-Fluorophenyl)-2-aminopropane (304)

Yield: 66%

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.08 (3H, d, J = 6.04Hz, C3$\underline{H}$3); 1.75 (2H, N$\underline{H}$2); 2.48 (1H, m, C1$\underline{H}_2$); 2.64 (1H, d, C1$\underline{H}_2$); 3.10 (1H, m, C2$\underline{H}$(NH_2)); 6.96 (2H, d, J = 8.52Hz, $\underline{H}$2', $\underline{H}$6'); 7.11 (2H, m, $\underline{H}$3', $\underline{H}$5')

^{13}C-NMR (101MHz): δ($CDCl_3$): 23.2 (CH_3); 45.5 (CH_2); 48.3 (C1H1(NH_2)); 114.85, 115.1 (C3'H, C5'H); 130.4, 130.45 (d, J = 7.8Hz, C2'H, C6'H); 135.1 (C1'CH_2);160.4 (d, J = 244.88Hz, C4'F)

IR: 3359cm^{-1}, 2963 cm^{-1}, 1601 cm^{-1}, 1511 cm^{-1}, 1222 cm^{-1}, 850 cm^{-1}, 810 cm^{-1}

Melting point: literature 78°C[42]

Experimental 76 - 78°C

1-(4-Chlorophenyl)-2-aminopropane (305)

Yield: 35%

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.02 (3H, d, J = 6.52Hz, C3H$_3$); 1.36 (2H, NH_2); 2.43 (1H, m, C1H$_2$); 2.58 (1H, m, C1H$_2$); 3.05 (1H, q, J = 6.52Hz, C1H(NH_2)); 7.04 (2H, d, J = 8.0Hz, H2', H6'); 7.19 (2H, d, J = 8.04Hz, H3', H5')

^{13}C-NMR (101MHz): δ($CDCl_3$): 23.01 (CH_3); 45.5 (CH_2); 48.0 (C2H(NH_2)); 128.1 (C3'H, C5'H); 130.3 (C2'H, C6'H); 131.6 (C1'CH_2); 137.9 (C4'Cl)

Boiling point: 127 - 128°C [55]

IR: 3272cm^{-1}, 3020cm^{-1}, 2911cm^{-1}, 1668cm^{-1}, 1574cm^{-1}, 1500cm^{-1}, 1455cm^{-1}, 1236cm^{-1}, 1091cm^{-1}, 1016cm^{-1}, 797cm^{-1}

1-(4-Bromophenyl)-2-aminopropane (306)

Yield: 17.73%

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.24 (3H, d, J = 6.52Hz, C3H$_3$); 2.77 (1H, m, C1H$_2$); 3.02 (1H, m, C1H$_2$); 3.52 (1H, m, C2H(NH_2)); 7.2 (2H, d, J = 8.0Hz, H2', H6'); 7.47 (2H, d, J = 8.04Hz, H3', H5')

^{13}C-NMR (101MHz): δ($CDCl_3$): 23.5 (CH_3); 44.2 (CH_2); 47.9 (C2H(NH_2)); 123.5 (C4'Br); 130.3 (C2'H, C6'H); 132.0 (C3'H, C5'H); 141.8 (C1'CH_2)

Boiling point: 123 - 124°C/ 10 Torr[56]

IR: 3272 cm^{-1}, 2962cm^{-1}, 1591cm^{-1}, 1488cm^{-1}, 1404cm^{-1}, 1107cm^{-1}, 1072cm^{-1}, 1012cm^{-1}, 828cm^{-1}, 791cm^{-1}

1-(3-Bromophenyl)-2-aminopropane (307)[57]

Yield: 46%

^{1}H-NMR (400MHz): δ($CDCl_3$): 0.85 (3H, d, J = 6.52Hz, C3H$_3$); 1.03 (2H, NH$_2$); 2.22 (1H, m, C1H$_2$); 2.39 (1H, m, C1H$_2$); 8.88 (1H, m, C2H(NH_2)); 6.89 (2H, m, H5', H6'); 7.11 (2H, d, J = 9.03Hz, H2', H4')

^{13}C-NMR (101MHz): δ($CDCl_3$): 24 (CH_3); 46 (CH_2); 48 (C2H(NH_2)); 122 (C3'Br); 127 (C6'H); 129(C4'H); 130(C5'H); 132(C2'H); 142 (C1'CH_2)

IR: 3397cm^{-1}, 3015cm^{-1}, 2924cm^{-1}, 2348cm^{-1}, 1596cm^{-1}, 1506cm^{-1}, 1475cm^{-1}, 1073cm^{-1}, 776cm^{-1}, 670cm^{-1}

REDUCTION OF NITROSTYRENE DIRECTLY TO AMINE

1-(4-Methylthiophenyl)-2-amino-propane (281)

8.014g/211.1mmol Lithium aluminium hydride powder was suspended in 175mL of stirred dry tetrahydrofuran (THF). 10.005g/47.81mmol 1-(4-Methylthiophenyl)-2-nitropropene was dissolved in 125mL dry THF and added dropwise to the stirred suspension. The mixture was refluxed for 3 hours then left stirring and cooling overnight. Residual LAH was destroyed by the careful addition of 10mL isopropyl

alcohol. 10mL 15% w/v sodium hydroxide solution raised the pH and caused the precipitation of alumium hydroxide salts. 30mL water reacted with any remaining LAH and the metal salts were removed on a Buchner funnel. The filtrate was concentrated *in vacuo*. The emulsion which resulted was extracted with diethyl ether and the extract was dried with sodium sulfate. After filtration and the removal of the solvent on a rotary evaporator the oil was dissolved in dry diethyl ether and the hydrochloride salt of 1-(4-methylthiophenyl)-2-aminopropane was precipitated by bubbling dry HCl gas through the solution. The salt was dissolved in ethanol and recrystallised by addition of diethyl ether.

Yield: 62%

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.02 (3H, d, J = 6.04Hz, C3H_3); 1.20 (2H, NH_2); 2.40 (3H, SCH_3); 2.42 (1H, d, J = 7.52Hz, C1H_a); 3.03 (1H, d, J = 5.52Hz, C1H_b); 3.05 (1H, m, C2H(NH_2)); 7.03 (2H, d, J = 8.52Hz, H3', H5'); 7.13 (2H, d, J = 8.0Hz, H2', H6')

^{13}C-NMR (101MHz): δ($CDCl_3$): 16.19 (CH_3); 23.51 (SCH_3); 46.07 (C1H_2); 48.42 (C2H); 127.07 (C3'H, C5'H); 129.75 (C2'H, C6'H); 135.84 (C4'SCH_3); 136.73 (C1'C1H_2)

Melting point: literature 190 - 191°C [38]

Experimental 188 - 190°C

IRv_{max} (KBr): 3357cm^{-1}, 2961cm^{-1}, 1598cm^{-1}, 1405cm^{-1}, 1439cm^{-1}, 1094cm^{-1}, 794cm^{-1}, 595cm^{-1}

LEUCKART REACTION

1-(4-Methylthiophenyl)-2-aminopropane (281)

2.000g/11.1mmol of 1-(4-Methylthiophenyl)-2-propanone was measured into a flask and 5.0mL/5.67g/125.9mmol formamide was added. The mixture was refluxed at 190°C for 4hours 50 minutes, then cooled, diluted with water an extracted with two portions of 15mL diethyl ether. After further extraction with 30mL dichloromethane the extracts were combined, dried and the solvents removed *in vacuo*, leaving brown oil. This was refluxed with 35mL 10% HCl and 5ml methanol (previously dried over magnesium methoxide) for 7 hours. Upon cooling, the mixture was washed with 20mL dichloromethane, then made alkaline with 15% w/v sodium hydroxide solution. Extraction with 30mL dichloromethane gave oil after removal of the solvent using a rotary evaporator. HCl gas was bubbled through an ethereal solution to give the hydrochloride salt.

Yield: 17%

Spectroscopic details under reductive amination.

SYNTHESIS OF DIHYDROISOQUINOLINES USING THE BISCHLER NAPIERALSKI METHOD

Amidation (308)

4-Methylthioamphetamine (1.400 g/77.3 mmol) was dissolved in acetic anhydride (11.7 mL) and the mixture was stirred at 60°C for 1.5 hours. The mixture was extracted with 20mL dichloromethane and washed to remove the anhydride. The extract was dried and the solvent removed under vacuum. Toluene was added and the last of the anhydride was thus removed on the rotary evaporator. The colourless solid was recrystallised from hot methanol.

Yield: 97.1%

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.94 (3H, $NHCOCH_3$); 2.45 (3H, s, SCH_3); 2.66 –2.78 (2H, m, $C2H_2$); 4.20 (1H, t, J = 6.52Hz, C1HNH); 5.54 (1H, bs, NH); 7.08 (2H, d, J = 8.04 Hz, H2', H6'), 7.18 (2H, d, J = 8.04 Hz, H3', H5')

^{13}C-NMR (101MHz): δ($CDCl_3$): 19.7 (SCH_3); 22.0 ($COCH3$); 41.7 ($C2H_2$); 46.0 (C1NH); 125.8 (C3'H, C5'H); 129.4 (C2'H, C6'H); 134.9 (C1'); 169.3 (CO)

IR ν_{max} (KBr): 2925cm^{-1}, 1703cm^{-1}, 1371cm^{-1}, 1260cm^{-1}, 1178cm^{-1}, 700cm^{-1}

HRMS calcd. for C12H17NOSNa (M^++23): 246.0929 Found: 246.0919

Cyclisation

N-Acetyl-4-methylthioamphetamine (1.47 g/ 6.58 mmol) was dissolved with stirring in 10mL toluene. Phosphorous pentoxide (934 mg/6.58 mmol) was added and the reaction was refluxed at 120°C for 15 minutes. A further portion (5.448 g/6.58 mmol) of phosphorous pentoxide was added and reflux was sustained for another 2.5 hours. TLC showed only starting material to be present. A further equivalent of phosphorous pentoxide was added and reflux continued for another 3.5 hours. The aqueous layer was isolated and made alkaline using 15%w/v NaOH solution. The alkaline solution was then extracted with DCM. The extract was washed, dried and evacuated to dryness. No product had formed.

ATTEMPT TO SYNTHESISE 7-THIOETHER ISOQUINOLINES

iii) Protection of carbonyl group with acetal

1-(4-Bromobenzyl)-2-methyl-[1,3]-dioxolane (311)

1-(4-Bromobenzyl)-2-propanone (1.700g/7.98mmol) was dissolved in ethylene glycol (7.8mL/8.67g/140mmol) and toluene (150m). *para*-Toluenesulfonic acid (38mg/0.2mmol) was added. The biphasic mixture was refluxed with a Dean and Stark apparatus for 14 hours and after cooling the ethylene glycol portion was extracted with toluene and the combined toluyl extracts were washed with saturated sodium hydrogen carbonate solution. They were dried over sodium sulfate, filtered and the toluene removed *in vacuo*, with the help of dichloromethane to form an azeotrope to remove the last traces.

Yield: 85%

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.33 (3H, C2(OCH_2CH_2O)CH_3); 2.90 (2H, $C1H_2$); 3.73, 3.91 (2H, OCH_2CH_2O); 7.17 (2H, d, J = 8.04Hz, H2', H6'); 7.42 (2H, d, J = 8.04Hz, H3', H5')

^{13}C-NMR (101MHz): δ($CDCl_3$): 23.97 (C2(OCH_2CH_2O)CH3); 44.32 (C1H2), 64.40 (OCH_2CH_2O), 108.93 (C2); 120.00 (C4'Br), 130.54 (C2'H, C6'H); 131.80 (C3'H, C5'H); 135.47 (C1'$C1H_2$)

IR (film): 2970cm^{-1}, 2883cm^{-1}, 1490cm^{-1},1376cm^{-1},1215cm^{-1},1048cm^{-1},832cm^{-1}

iv) Halogen metal exchange, followed by thioalkylation using disulfide

The aceta (**311**) (5.259 g/20.45 mmol) was dissolved in anhydrous THF, and cooled to -78°C. *n*-Butyllithium (8.18 mL/20.45 mmol) was added under nitrogen and stirring continued at -78°C for 1.5 hours. The dialkyl disulfide (20.45 mmol) was added under nitrogen and the solution was allowed to return to room temperature. It was stirred at room temperature for 24 hours. Residual butyllithium was quenched using saturated ammonium chloride solution. The THF was removed on the rotary evaporator, and the aqueous

residue was extracted with diethyl ether. The extract was washed, dried and evacuated to dryness, and the resultant oil was purified by column chromatography. The mobile phase used was 20:80 diethyl ether:hexane.

1-(Thiomethylbenzyl)-2-methyl-[1,3]-dioxolane (312)

Yield: 6.65%

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.33 (3H, C2(OCH_2CH_2O)CH_3); 2.49 (2H, SCH_3); 2.87, 2.95 (C1H_2); 3.77 – 3.92 (4H,m, OCH_2CH_2O); 7.22, 7.29, 7.30 (4H, H2', H3', H5', H6')

^{13}C-NMR (101MHz): δ($CDCl_3$): 15.64 (SCH_3), 23.87 (C2OCH_2CH_2O)C3H_3), 44.36 (C1H_2), 64.36 (OCH_2CH_2O), 64.38 (OCH_2CH_2O), 109.23 (C2(OCH_2CH_2O)CH_3), 125.90 (C3'H, C5'H), 130.01 (C2'H, C6'H), 133.49 (SCH_3), 135.66 (C1'C1H_2)

IR (film): 2968cm^{-1}, 2923cm^{-1}, 2882cm^{-1}, 1495cm^{-1}, 1377cm^{-1}, 1216cm^{-1}, 1128cm^{-1}, 1088cm^{-1}, 1047cm^{-1}, 832cm^{-1}

1-(4-Thioethylbenzyl)-2-methyl-[1,3]-dioxolane (313)

Yield: 27%

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.33 (3H, s, CH_3); 2.91- 3.80 (2H, m, SCH_2); 3.89 - 3.91 (4H, m, OCH_2CH_2O); 7.17 (1H, d, J = 8.04Hz, H2', H6); 7.23 (3H, J = 2.04Hz, H3', H'5)

^{13}C-NMR (101MHz): δ($CDCl_3$): 14.24 (SCH_2CH_3), 24.11 (C2(OCH_2CH_2O)CH_3), 27.69 (SCH_2CH_3), 44.76 (C1H_2), 62.95 (OCH_2CH_2O), 109.43 (C2(OCH_2CH_2O)CH_3), 127.79 (C3'H, C5'H), 128.80 (C2'H, C6'H), 133.91 (C4'SCH_2CH_3), 134.14 (C1'C1H_2)

IR (film): 2970cm^{-1}, 2923cm^{-1}, 1497cm^{-1}, 1214cm^{-1}, 1088cm^{-1}, 1048cm^{-1}, 829cm^{-1}

v) Halogen metal exchange followed by thio-de-dimetallo-aggre-substitution and alkylation

The acetal (2.925 g/11.38 mmol) was dissolved in anhydrous THF, and cooled to -90°C. *n*-Butyllithium (4.55 mL/11.38 mmol) was added under nitrogen and stirring continued at -90°C for 1 hour. The flask was allowed to return to room temperature and was stirred at room temperature for 30 minutes. It was then returned to -90°C and sulfur powder (402 mg/12.52 mmol) was added under nitrogen. The solution was again allowed to return to room temperature and was stirred for 2 hours. It was cooled once more to -90°C and the iodoalkane (12.52 mmol) was added under nitrogen. The flask was finally allowed to warm to room temperature and was left stirring overnight. Residual butyllithium was quenched using saturated ammonium chloride solution. The THF was removed on the rotary evaporator, and the aqueous residue was extracted with diethyl ether. The extract was washed, dried and evacuated to dryness, and the resultant oil was purified by column chromatography. The mobile phase used was 20:80 diethyl ether:hexane.

1-(4-Thiobutylbenzyl)-2-methyl-[1,3]-dioxolane (315)

Yield: 33%

^{1}H-NMR (400MHz): δ($CDCl_3$): 0.96 (3H, t, J = 7.52Hz, $SCH_2CH_2CH_2CH_3$); 1.34 (C2(OCH_2CH_2O)CH_3); 1.39 (2H, q, J = 7.52Hz, $SCH_2CH_2CH_2CH_3$); 1.63 (2H, m, J = 8.04Hz, $SCH_2CH_2CH_2CH_3$); 2.62 (2H, t, J = 7.52Hz, $SCH_2CH_2CH_2CH_3$); 2.92 (2H, C1H2); 3.79, 3.81, 3.82, 3.83, 3.85 (2H, m, OCH_2CH_2O); 3.90, 3.93, 3.93, 3.94, 3.96 (2H, m, OCH_2CH_2O); 7.13 (2H, d, J = 8.04Hz, H3', H5'); 7.21 (2H, d, J = 8.04Hz, H2', H6')

^{13}C-NMR (101MHz): δ($CDCl_3$): 13.49 ($SCH_2CH_2CH_2CH_3$); 21.91 ($SCH_2CH_2CH_2CH_3$); 23.75 (C2(OCH_2CH_2O)CH_3); 33.20 ($SCH_2CH_2CH_2CH_3$), 34.83 ($SCH_2CH_2CH_2CH_3$); 44.50 (C1H_2); 64.35

($O\underline{C}H_2\underline{C}H_2O$); 109.40 ($\underline{C}2(OCH_2CH_2O)CH_3$); 127.56 ($\underline{C}3'H$, $\underline{C}5'H$); 129.82 ($\underline{C}2'H$, $\underline{C}6'H$); 133.62 ($\underline{C}1'C1H_2$); 140.43 ($\underline{C}4'S$)

IR (film): $2946cm^{-1}$, $2874cm^{-1}$, $1515cm^{-1}$, $1377cm^{-1}$, $1217cm^{-1}$, $1049cm^{-1}$, $833cm^{-1}$

i) Hydrolysis of acetal

1-(4-Methylthiophenyl)-2-propanone (293)

Preparation as for **(316).** See under ketones **(293)** for spectroscopic data.

1-(4-Ethylthiophenyl)-2-propanone (316)

4.018g of the (impure) 2-(4-Ethylthiobenzyl)-2-methyl-[1,3]-dioxolane was mixed in 100mL ethanol and 100mL dilute hydrochloric acid and was heated on a waterbath for 1 hour. It was allowed to cool, then extracted with 2 aliquots of diethyl ether of 50mL each, and one of dichloromethane. The organic extracts were combined, dried, and the solvents removed under vacuum. A column was run to isolate the ketone. The stationary phase employed was Merck Silica 60 gel (0.04 – 0.063mm) and the mobile phase was initially 5:95 diethyl ether/hexane, being increased in polarity to 10:90 ether/hexane to obtain the ketone.

Yield: 386mg/12%.

^{1}H-NMR (400MHz): δ($CDCl_3$): 1.29 (3H, d, J = 7.52, C4'$SCH_2C\underline{H}_3$); 2.13 (3H, C3$\underline{H}_3$); 2.91 (2H, q, J = 7.52Hz, C4'$SC\underline{H}_2CH_3$); 3.64 (2H, C1$\underline{H}_2$); 7.11 (2H, d, J = 8.52Hz, $\underline{H}2'$, $\underline{H}6'$); 7.28 (2H, d, J = 8.0Hz, $\underline{H}3'$, $\underline{H}5'$)

^{13}C-NMR (101MHz): δ($CDCl_3$): 14.16 ($\underline{C}3H_3$); 27.46 ($S\underline{C}H_2$); 29.46 ($SCH_2\underline{C}H_3$); 50.11 ($\underline{C}2H_2$); 129.12 ($\underline{C}2'H$, $\underline{C}6'H$); 129.68 ($\underline{C}3'H$, $\underline{C}5'H$); 131.65 ($\underline{C}4'SCH_2CH_3$); 135.23 ($\underline{C}1'C1H_2$); 205.73 ($\underline{C}2O$)

IR (film): $2969cm^{-1}$, $2928\ cm^{-1}$, $1714\ cm^{-1}$, $1494cm^{-1}$, $1357cm^{-1}$, $1160cm^{-1}$, $1092cm^{-1}$, $782\ cm^{-1}$, $572cm^{-1}$

HRMS calcd. for C11H14NOSK (M^++39): 233.0402 Found: 233.0405

1-(4-Butylthiophenyl)-propanone (317)

Yield: 54%

^{1}H-NMR (100MHz): δ($CDCl_3$): 0.97 (3H, m, J1 = 7.52Hz, J2 = 7.04, $SCH_2CH_2CH_2C\underline{H}_3$); 1.40 (2H, m, J1 = 7.52Hz, J2 = 7.04Hz, $SCH_2CH_2C\underline{H}_2CH_3$); 1.63 (2H, m, $SCH_2C\underline{H}_2CH_2CH_3$); 2.16 (3H, C3$\underline{H}_3$); 2.63 (2H, t, J1 = 8.04Hz, J2 = 7.52Hz, $SC\underline{H}_2CH_2CH_2CH_3$); 3.68 (2H, C1$\underline{H}_2$); 7.16 (4H, q, J = 8.04Hz, $\underline{H}2'$, $\underline{H}3'$, $\underline{H}5'$, $\underline{H}6'$)

^{13}C-NMR (101MHz): δ($CDCl_3$): 13.80 ($\underline{C}3H_3$); 22.21 ($S\underline{C}H_2$); 28.99 ($SCH_2CH_2CH_2\underline{C}H_3$); 33.44; 35.13 ($2\underline{C}H_2$); 50.52 ($\underline{C}1H_2$); 128.66 ($\underline{C}3'H$, $\underline{C}5'H$); 129.11 ($\underline{C}2'H$, $\underline{C}6'$); 131.32 ($\underline{C}1'C1H$); 141.55 ($\underline{C}4'S$); 206.38 ($\underline{C}2O$)

IR (film): $2946\ cm^{-1}$, $2930cm^{-1}$, $2859cm^{-1}$, $2993cm^{-1}$, $1905cm^{-1}$, $1714cm^{-1}$ $1514cm^{-1}$, $1465cm^{-1}$, $1421cm^{-1}$, $1356cm^{-1}$, $1229\ cm^{-1}$, $1157cm^{-1}$

1-(2-Chloroethyl)-4-methyl-sulfanyl-benzene (321)

2-Chloroethylchlorosulfonate **(319)** (1.00 g/6 mmol) was dissolved in anhydrous dichloromethane with aluminium chloride (160 mg/1.2 mmol). Thioanisole **(320)** (0.7 mL/6 mmol) was added under nitrogen. The mixture was stirred at 75°C for 2 hours after the addition of thioanisole. It was then taken up in DCM and

hexane, washed and dried. The solvents were removed *in vacuo*. This gave 1-(2-chloroethyl)-4-methylsulfanylbenzene (**321**) as an oil in 41% yield.

Yield: 41%

^{1}H-NMR (100MHz): δ($CDCl_3$): 2.54 (3H, s, SCH_3); 3.27 (2H, t, J1 = 8Hz, C1C$\underline{H}_2$); 3.67 (2H, t, J = 8.5Hz, C$\underline{H}_2$Cl); 7.30 – 7.39 (4H, m, C2$\underline{H}$, C3$\underline{H}$, C5$\underline{H}$, C6$\underline{H}$)

^{13}C-NMR (101MHz): δ($CDCl_3$): 15.6 (S$\underline{C}H_3$); 35.9 ($\underline{C}H_2CH_2$); 42.2 ($\underline{C}H_2$Cl); 124.8 ($\underline{C}$3H, $\underline{C}$5H); 128.7 ($\underline{C}$2H, $\underline{C}$6H); 140.0 ($\underline{C}SCH_3$)

IRν_{max} (KBr): 1588cm^{-1} (s), 1514 cm^{-1} (s), 1213 cm^{-1} (s), 1097cm^{-1} (s)

Boiling point: (literature only): 131°C[58]

Dimer (323)

Thioanisole (0.7 mL/6 mmol) was heated at 80°C for 1.5 hours with 2-chloroethylchlorosulfonate (1.00 g/6 mmol) and aluminium chloride (200 mg/1.5 mmol) and then stirred overnight. The product was taken up in hexane and washed with water. It was dried and evacuated to dryness.

Yield: 54%

^{1}H-NMR (100MHz): δ($CDCl_3$): 2.53 (6H, s, SCH_3*2); 3.75 (4H, s, CH_2*2); 7.33 – 7.35 (8H, m,(C2$\underline{H}$, C3$\underline{H}$, C5$\underline{H}$, C6$\underline{H}$)*2)

^{13}C-NMR (101MHz): δ($CDCl_3$): 15.5 (S$\underline{C}H_3$); 43.4 ($\underline{C}H_2$); 124.8, 126.3, 128.6 ($\underline{C}$2H, $\underline{C}$3H, $\underline{C}$5H, $\underline{C}$6H); 138.2 ($\underline{C}SCH_3$)

Was not characterised further.

1-(7-Bromo-3,4-dihydro-*1H*-isoquinolin-2-yl)-2,2,2-trifluoro-ethanone (325)

48%w/v Hydrobromic acid (11.3mL) was stirred with 37.9mL ice-cold water to give a solution to which 1-(7-amino-3,4-dihydro-*1H*-isoquinolin-2-yl)-2,2,2-trifluoroethanone (5.8g/23.7mmol) was added dropwise. Sodium nitrite (1.799g/26.1mmol) was dissolved in 21mL water and added to the solution of amine. This gave an azo product. The mixture gave a negative starch-iodide test. Copper bromide (10.2g/71.1mmol) was suspended in a combination of 48% hydrobromic acid (24mL) and water (59.3mL) and the mixture was heated to 35°C. The azo mixture was pipetted into the copper suspension, which was then stirred at 80°C for 1.5 hours. The mixture was made alkaline with 50%w/v potassium hydroxide solution and the brown scum generated was filtered off on a Buchner funnel. The salts were washed down with dichloromethane, which was collected. The aqueous filtrate was extracted with dichloromethane. The organic fractions were combined, washed with water and dried with sodium sulfate. The filtered solution was evacuated to a reddish brown oil, which was purified to a colourless oil using 5:95 ethyl acetate/hexane on Merck Silica 60.

Yield: 31%

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.89 – 2.92 (2H, m, C4$\underline{H}_2$); 3.83, 3.87 (2H, t, t (overlapping), J = 6.0HZ, C3$\underline{H}_2$ (m), (s)); 4.71, 4.74 (2H, s, s, C1$\underline{H}_2$, (s), (m)); 7.02 – 7.05 (1H, m (overlapping doublets from 2 isomers, C5$\underline{H}$); 7.28 – 7.32 (2H, m (overlapping doublet and singlet from each isomer, C6$\underline{H}$, C8$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 27.6 ($\underline{C}4H_2$ (s)), 28.8 ($\underline{C}4H_2$ (m)); 41.2 ($\underline{C}3H_2$ (s)); 42.9 ($\underline{C}1H_2$ (m)); 43.2 ($\underline{C}3H_2$ (m)); 46.3 ($\underline{C}1H_2$ (s)); 128.4 ($\underline{C}$5H (s)), 128.7 ($\underline{C}$5H (m)); 129.8 ($\underline{C}$6H (m)), 130.0 ($\underline{C}$8H (m)), 130.3 ($\underline{C}$8H (s)); 131.3 ($\underline{C}$8a (s)), 131.5 ($\underline{C}$8a (m)); 133.3 ($\underline{C}$4a (s)), 133.4 ($\underline{C}$4a (m)); 155.2 – 155.9 ($\underline{C}OCF_3$)

^{19}F-NMR (376MHz): ppm($CDCl_3$): -69.88 (s); -69.94 (m)

IRν_{max}(KBr): 1694 cm^{-1}, 2306 cm^{-1}, 2987 $^{-1}$, 3055 cm^{-1}

7-Bromo-1,2,3,4-tetrahydroisoquinoline (326)[3]

1-(7-Bromo-3,4-dihydro-*1H*-isoquinolin-2-yl)-ethanone (2.59g/8.4mmol) was dried thoroughly and dissolved in anhydrous THF. The solution was stirred in an oven-dried three-neck flask under nitrogen and cooled to -55°C. *n*-Butyl lithium (3.7mL/9.2mmol) was added dropwise via a glass syringe and the solution turned yellow. It was allowed to heat to -10°C over one hour, then was cooled to -60°C. Dimethyl disulfide (0.84mL/ 9.2mmol) was added slowly; the solution was left to heat to room temperature and was left stirring overnight. Saturated ammonium chloride solution was added to quench residual butyl lithium. The organic layer was collected. The aqueous layer was extracted with dichloromethane. The aqueous layer was made alkaline with 15%w/v sodium hydroxide solution and again extracted with dichloromethane. The organic extracts were combined, washed with water and dried with sodium sulfate. The organic solvents were removed *in vacuo* to give brown oil which was purified by elution through silica using a mobile phase increasing in polarity from 100% ethyl acetate to 25:75 methanol:ethyl acetate.

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.73 (2H, s, C4$\underline{H}_2$); 3.11 (2H, s, C3$\underline{H}_2$, N$\underline{H}$); 3.96 (2H, C1$\underline{H}_2$); 6.92 (1H, d, J = 8Hz, C5$\underline{H}$); 7.14 (1H, s, C8$\underline{H}$); 7.22 – 7.24 (1H, m C6$\underline{H}$)

^{13}C-NMR (101MHz): 28.2 (C4$\underline{H}_2$); 43.1 (C3$\underline{H}_2$); 47.2 (C1$\underline{H}_2$); 119.2 (C7Br) 128.8, 129.1 (C6H, (C8H); 130.8 (C5H); 133.2 (C4a, C8a)

Yield: 20%

IRν_{max}(film): 1421 cm^{-1}, 1638 cm^{-1}, 2985 cm^{-1}, 3053 cm^{-1}

7-Methylsulfanyl-1,2,3,4-tetrahydro-isoquinoline (327)[3]

1-(7-Bromo-3,4-dihydro-*1H*-isoquinolin-2-yl)-ethanone (2.59g/8.4mmol) was dried thoroughly and dissolved in anhydrous THF. The solution was stirred in an oven-dried three-neck flask under nitrogen and cooled to -55°C. *n*-Butyl lithium (13.44mL/33.6mmol) was added dropwise via a glass syringe and the solution turned yellow. It was allowed to heat to -10°C over one hour, then was cooled to -60°C. Dimethyl disulfide (2mL/ 22mmol) was added slowly; the solution was left to heat to room temperature and was left stirring overnight. Saturated ammonium chloride solution was added to quench residual butyl lithium. The organic layer was collected. The aqueous layer was extracted with dichloromethane. The aqueous layer was made alkaline with 15%w/v sodium hydroxide solution and again extracted with dichloromethane. The organic extracts were combined, washed with water and dried with sodium sulfate. The organic solvents were removed *in vacuo* to give brown oil which was purified by elution through silica using a mobile phase increasing in polarity from 100% ethyl acetate to 25:75 methanol:ethyl acetate.

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.27 (1H, bs, N$\underline{H}$); 2.45 (3H, s, SC$\underline{H}_3$); 2.75 (2H, s, C4$\underline{H}_2$); 3.12 (2H, s, C3$\underline{H}_2$); 3.97 (2H, C1$\underline{H}_2$); 6.92 (1H, s, C8$\underline{H}$); 7.00 (1H, d, J = 8Hz, C6$\underline{H}$); 7.05 (1H, dd, J_1 = 8Hz, J_2 = 2Hz, C6$\underline{H}$)

^{13}C-NMR (101MHz): ppm($CDCl_3$): 16.1 (S$\underline{C}H_3$); 28.5 (C4$\underline{H}_2$); 43.6 (C3$\underline{H}_2$); 48.0 (C1$\underline{H}_2$); 124.6 (C6H); 124.9 (C8H); 129.7 (C5H); 131.8 (C7SCH_3); 135.1 (C4a, C8a)

Yield: 18%

IRν_{max}(film): 1422 cm^{-1}, 2306 cm^{-1}, 2987 cm^{-1}, 3055 cm^{-1}

7-Methylsulfanyl-2-trityo-1,2,3,4-tetrahydro-isoquinoline (328)

7-Methylsulfanyl-1,2,3,4-tetrahydro-isoquinoline (170mg/ 0.95mmol) was dissolved in 10ml anhydrous dichloromethane and triethylamine (146μL/ 1.05mmol) was added. The solution was cooled in an ice-bath.

Trityl chloride (417mg/ 1.5mmol) and a catalytic amount of 4-(dimethylamino)-pyridine were added in one portion. The solution was left stirring at room temperature for 36 hours. Approximately 5mL 1N sodium hydroxide solution was added. The organic layer was separated, washed and dried. The solvent was removed *in vacuo* and the membranous solid was purified on a silica column through elution with 5:95 ethyl acetate: hexane. This gave a colourless solid.

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.46, 2.47 (3H, s, $SC\underline{H}_3$); 2.57 (2H, s, $C4\underline{H}_2$); 3.02 (2H, s, $C3\underline{H}_2$); 3.49 (2H, $C1\underline{H}_2$); 6.90, 7.10 (2H, s, s,); 7.20 – 7.24 (3H, d, J = 7.5Hz); 7.31 – 7.35 (7H, t, J = 7Hz); 7.61 (6H, d, J = 6.5Hz,)

^{13}C-NMR (101MHz): 16.1 ($S\underline{C}H_3$); 28.5 ($\underline{C}4H_2$); 43.6 ($\underline{C}3H_2$); 48.0 ($\underline{C}1H_2$); 124.6 ($\underline{C}6H$); 124.9 ($\underline{C}8H$); 129.7 ($\underline{C}5H$); 131.8 ($\underline{C}7SCH_3$); 135.1 ($\underline{C}4a$, $\underline{C}8a$)

Yield: 85%

IRν_{max}(KBr): 1422 cm^{-1}, 1600 cm^{-1}, 2306 cm^{-1}, 2987 cm^{-1}, 3055cm^{-1}

(7-Methylsulfanyl-3,4-dihydro-1H-isoquinolin2-yl)-phenyl-methanone (329)

7-Methylsulfanyl-1,2,3,4-tetrahydro-isoquinoline (170mg/ 0.95mmol) was dissolved in 10ml anhydrous dichloromethane and triethylamine (146μL/ 1.05mmol) was added. The solution was cooled in an ice-bath. Benzoyl chloride 70 μL was added dropwise. The solution stirred at reflux for 4 hours. The solution was washed with dilute acid, then with water. It was dried with sodium sulfate and evaporated to dryness *in* vacuo. The product was purified on a silica column by elution with 1:3 ethyl acetate: hexane. This gave yellow oil.

^{1}H-NMR (400MHz): δ($CDCl_3$): 2.43 - 2.48 (3H, s, $SC\underline{H}_3$); 2.89 – 2.96 (2H, m, $C4\underline{H}_2$); 3.64, 3.99 (2H, bs, bs, $C3\underline{H}_2$); 4.57, 4.88 (2H, bs, bs, $C1\underline{H}_2$); 7.11 – 7.19 (3H, m, C5H, C6H, C8H); 7.45 (5H, s, C2'H, C3'H, C4'H, C5'H, C6'H)

^{13}C-NMR (101MHz): 16.0 ($S\underline{C}H_3$); 28.2, 29.1 ($\underline{C}4H_2$); 40.4 ($\underline{C}3H_2$); 44.7 ($\underline{C}1H_2$); 45.2 ($\underline{C}3H_2$); 49.8 ($\underline{C}1H_2$); 124.7, 125.3, 126.2 (C6H, C8H); 128.5 (C2'H, C3'H, C4'H, C5'H, C6'H); 129.8 ($\underline{C}5H$); 133.6 ($\underline{C}7SCH_3$); 135.9 ($\underline{C}4a$, $\underline{C}8a$); 191.1 ($\underline{C}O$)

Yield: 19%

IRν_{max}(KBr): 1422 cm^{-1}, 1630 cm^{-1}, 2306 cm^{-1}, 2987 cm^{-1}, 3055cm^{-1}

HRMS calcd. for C17H18NOS (M^{+}+23): 284.1109 Found: 284.1115

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Appendix 1: Supplemental Data on Multifactorial Experiment

(see Chapter Two)

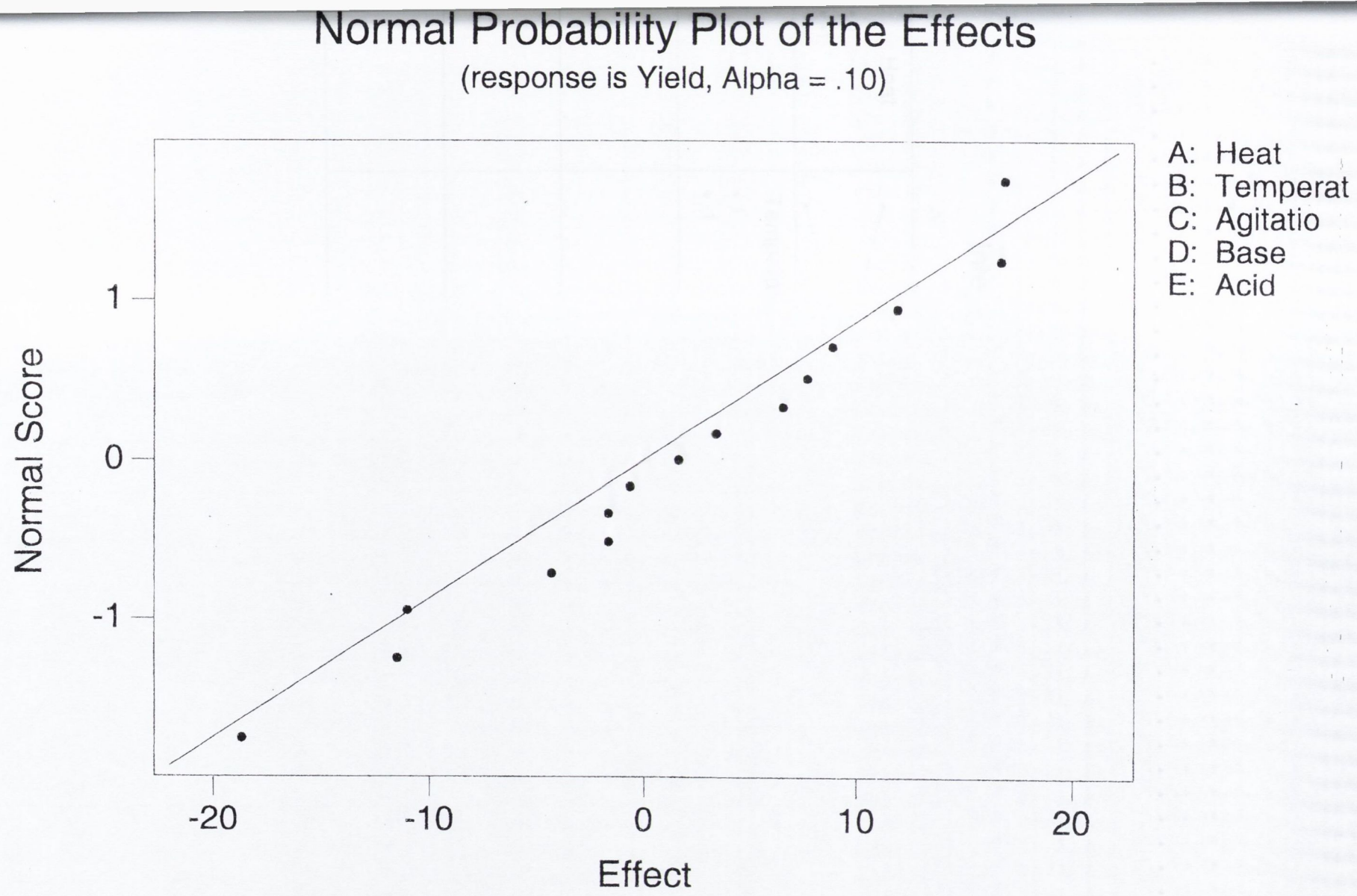
Fractional Factorial Fit: Yield versus Heat, Temperature, ...

Estimated Effects and Coefficients for Yield (coded units)

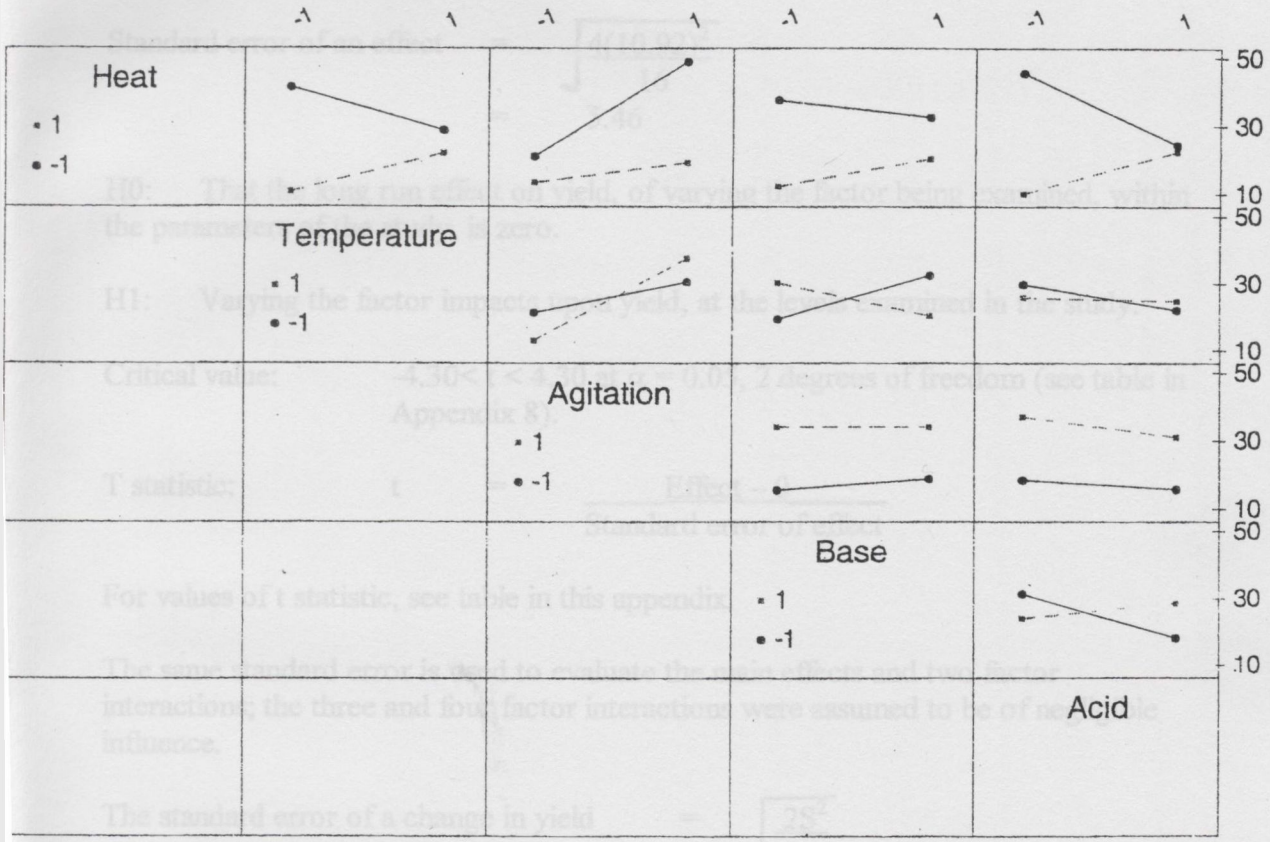
Term	Effect	Coef
Constant		25.620
Heat	-18.677	-9.339
Temperat	-0.645	-0.323
Agitatio	16.877	8.439
Base	1.640	0.820
Acid	-4.310	-2.155
Heat*Temperat	11.903	5.951
Heat*Agitatio	-11.010	-5.505
Heat*Base	6.527	3.264
Heat*Acid	16.688	8.344
Temperat*Agitatio	7.662	3.831
Temperat*Base	-11.485	-5.743
Temperat*Acid	3.390	1.695
Agitatio*Base	-1.657	-0.829
Agitatio*Acid	-1.652	-0.826
Base*Acid	8.850	4.425

Analysis of Variance for Yield (coded units)

Source	DF	Seq SS	Adj SS	Adj MS	F	P
Main Effects	5	2622	2622	524.3	*	*
2-Way Interactions	10	3480	3480	348.0	*	*
Residual Error	0	0	0	0.0		
Total	15	6101				


Normal Probability Plot of the Effects
(response is Yield, Alpha = .10)
Normal Score
1
0
-1
-20
-10
0
10
20
Effect
A: Heat
B: Temperat
C: Agitatio
D: Base
E: Acid

Interaction Plot (data means) for Yield



Calculations

Yields at low A, low B, high C, low D, low E: 66.32%
52.36%
44.79%

Mean yield under these conditions: 54.49%

Standard deviation for three replicates: 10.92%

Based on three measurements, so two degrees of freedom involved.

Standard error of an effect = $\sqrt{\frac{4S^2}{N}}$ where S = 10.92%
N = 16
α = 0.05

Standard error of an effect = $\sqrt{\frac{4(10.92)^2}{16}}$

= 5.46

H0: That the long run effect on yield, of varying the factor being examined, within the parameters of the study, is zero.

H1: Varying the factor impacts upon yield, at the levels examined in the study.

Critical value: $-4.30 < t < 4.30$ at $\alpha = 0.05$, 2 degrees of freedom (see table in Appendix 8).

T statistic: $t = \frac{\text{Effect} - 0}{\text{Standard error of effect}}$

For values of t statistic, see table in this appendix.

The same standard error is used to evaluate the main effects and two factor interactions; the three and four factor interactions were assumed to be of negligible influence.

The standard error of a change in yield = $\sqrt{\frac{2S^2}{N}}$ where S = 10.92%
N = 4
α = 0.05
t = 4.30

Standard error of change in yield = 7.72

H0: The long run change in yield due to variation of one factor at a given level of a second factor is zero

H1: Varying one factor at a given level of another leads to a non-random change in yield.

Critical value: $-4.30 < t < 4.30$ at $\alpha = 0.05$, 2 degrees of freedom.

T statistic: $t = \dfrac{\text{Change in yield}}{\text{Standard error of yield change}}$

See table for values of t statistic

Long term yield at optimal levels of parameters

95% confidence interval for long term yield $= Y +/- t_{0.025} \dfrac{S^2}{3}$ where $t = 4.30$, 2 degrees of freedom

$= 54.49 +/- (4.30) \dfrac{(10.92)^2}{3}$

$= 27.38\%, 81.60\%$

Table B

Selected critical values of the t-distribution

α	.25	.10	.05	.02	.01	.002	.001
ν = 1	2.41	6.31	12.71	31.82	63.66	318.32	636.61
2	1.60	2.92	4.30	6.96	9.92	22.33	31.60
3	1.42	2.35	3.18	4.54	5.84	10.22	12.92
4	1.34	2.13	2.78	3.75	4.60	7.17	8.61
5	1.30	2.02	2.57	3.36	4.03	5.89	6.87
6	1.27	1.94	2.45	3.14	3.71	5.21	5.96
7	1.25	1.89	2.36	3.00	3.50	4.79	5.41
8	1.24	1.86	2.31	2.90	3.36	4.50	5.04
9	1.23	1.83	2.26	2.82	3.25	4.30	4.78
10	1.22	1.81	2.23	2.76	3.17	4.14	4.59
12	1.21	1.78	2.18	2.68	3.05	3.93	4.32
15	1.20	1.75	2.13	2.60	2.95	3.73	4.07
20	1.18	1.72	2.09	2.53	2.85	3.55	3.85
24	1.18	1.71	2.06	2.49	2.80	3.47	3.75
30	1.17	1.70	2.04	2.46	2.75	3.39	3.65
40	1.17	1.68	2.02	2.42	2.70	3.31	3.55
60	1.16	1.67	2.00	2.39	2.66	3.23	3.46
120	1.16	1.66	1.98	2.36	2.62	3.16	3.37
∞	1.15	1.64	1.96	2.33	2.58	3.09	3.29

Note that this table gives the percentage split between the two tails. For example, 95% of the area under a t-distribution with 1 degree of freedom lies between -12.71 and 12.71

Table copied from Table B of lecture notes, E. Mullins, QI course, Trinity College Dublin, 2000 - 2001