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Studies in the Design and Synthesis of Novel Selective Serotonin Reuptake Inhibitors

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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
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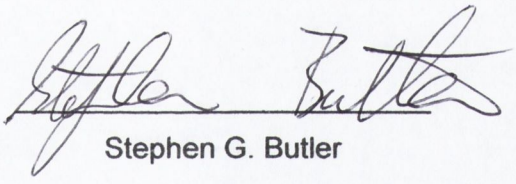

Stephen G. Butler

Abstract

The serotonin transporter (SERT) has been the target of several modern day antidepressants with the focus on achieving selectivity over other monoamine transporters, thereby minimising the side effects observed in the older generation of tricyclic antidepressants. Selective serotonin reuptake inhibitors (SSRIs) have shown to be among the most effective treatment of depression currently available. However they are known to have several considerable disadvantages over other classes of antidepressant drugs, such as a slow onset of action (often taking several weeks), headaches, nausea and sleep disruption. With this in mind researchers are constantly trying to improve the profile of compounds used to treat depression. The main aim of this thesis is to design, synthesise and biochemically test a series of novel compounds in the search for a selective SERT inhibitor, from which further work in derivatising the most active skeletal structure may proceed.

In chapter one the biochemical nature of depression and neurotransmission, including the role played by the serotonin transporter, with the main focus being the monoamine theory of depression is discussed. A comprehensive range of compounds active at SERT is reviewed based on the biochemical activities imparted by the various structural properties of the ligands. Attention is also drawn to the studies carried out on the proposed active binding sites within SERT and the computational models produced as a result.

Chapter two investigates the synthesis of a series of 1-phenylpropyl amines with particular exploration at position-6 of the aromatic ring as well as around the amino functionality. This series of structures was proposed based on the known biochemical and SERT inhibitory activity of the amphetamine family of compounds.

Chapter three details the stereoselective synthesis of *N*-methyl-1-(3,4-methylenedioxy)phenylpropylamine and 1-(3,4-methylenedioxy)phenylpropylamine. A novel approach in the stereoselective synthesis of methylenedioxyamphetamine (MDA) is also investigated.

4-methylthioamphetamine (4-MTA, flatliner) is a known drug of abuse. Its activity is based on its ability to increase extra-cellular CNS serotonin by monoamine oxidase inhibition and by SERT inhibition. Research has emerged stating that large hydrophobic groups corresponding to the methylthio moiety of the structure may

lead to an increased selectivity and activity at SERT. In chapter four, a series of thioamphetamines are synthesised with the intention of biochemical testing. 1-phenylproylamine analogues are also prepared.

In the fifth chapter of this thesis, the synthesis of a novel series of selective serotonin reuptake inhibitors is carried out, based on the tetrahydroisoquinoline scaffold. Particular attention in drawn to the importance of chirality in the ligand design process in the compounds derivatised at position-3 of the 1,2,3,4-tetrahydroisoquinoline ring system. The cell-based biochemical testing of these compounds is proceeding presently.

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I wish to express sincere thanks to Dr. Mary Meegan, whose pleasant nature and encouraging manner coupled with an expert knowledge, has guided me at all stages through the research presented in this thesis.

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Abbreviations

$[\alpha]_D^{20}$	specific rotation	GC	gas chromatography
Ac	acetate	HMBC	heteronuclear multiple bond coherence
aq	aqueous	HMQC	heteronuclear multiple quantum coherence
Ar	aryl	^{1}H NMR	proton nuclear magnetic resonance
Boc	*tert*-butoxycarbonyl	HRMS	high resolution mass spectrum
BuLi	butyl lithium	$NaCNBH_4$	sodium cyanoborohydride
^{13}C	carbon-13 nuclear magnetic resonance	5-HT	serotonin
CNS	central nervous system	IC_{50}	concentration required to produce 50% inhibition
DAT	dopamine transporter	LRMS	low resolution mass spectrum
DA	dopamine	MAO	monoamine oxidase
DCC	dicyclohexylcarbodiimide	4-MTA	4-methylthioamphetamine
DCM	dichloromethane	MDA	methylenedioxy amphetamine
Dept	distortionless enhancement by polarisation transfer	MDMA	methylenedioxymethamphetamine
DMF	dimethylformamide	NAT	noradrenaline transporter
DMSO	dimethylsulfoxide	*N*-TFA	*N*-trifluoroacetyl
DA	dopamine	Pd/C	palladium on charcoal
EtOH	ethanol	PCC	pyridinium chlorochromate
J	absolute value of coupling in Hertz	IR	infa-red
lit.	literature	ppm	parts per million
LPC	ligand-protein contacts	rt	room temperature
Me	methyl	R_f	In TLC-ratio of distance travelled by compound to that of solvent front
MeOH	methanol	SAR	Structure activity relationship
EI	Electron ionisation	SERT	serotonin transporter
m.p.	melting point	SSRI	Selective serotonin reuptake inhibitor
m/z	mass of an ion divided by its charge	TOCSY	total correlation spectroscopy
NOE	nuclear overhauser effect	TLC	thin layer chromatography
^{19}F NMR	fluorine-19 nuclear magnetic resonance	TMS	Trimethyl silane

1. Chapter One: Compounds Acting at Serotonergic Transporters and Receptors - Structure and Function.

1.1 Introduction

Major depression is an extremely prevalent disease affecting over 8% of the world's population and accounting for over $40 billion every year in health costs and lost productivity in the US alone.[1,2] Worldwide it is estimated to affect 121 million people and is among the leading causes of disability.[3,4] It is estimated that the prevalence of unipolar depressive episodes to be 1.9% for men and 3.2% for women, and that 5.8% of men and 9.5% of women will experience a depressive episode in a 12-month period, however these figures vary across populations.[5]

According to IMS HEALTH's world review, [6] antidepressants were the world's third-largest therapy class in the year 2000. Global sales amounted to over $13 billion. When taking into account, the number of years living with the disease, depression ranks as the most important disorder in developed countries (Figure 1-1) and when considering years lost to premature death (Disease Associated Lost Years (DALY), (Figure 1-2), unipolar major depression ranks as the second most important disease.[3] Depression undoubtedly represents a sizeable burden on modern society and consequently, novel drugs and treatment are constantly being developed. Biochemists, with an ever increasing knowledge of the neurochemical, endocrine and immunological changes associated with depression have proposed several potential therapeutic targets for the disease, among these are:

- the mono-amine receptor agonists and antagonists (to date the most widely studied),
- corticotrophin releasing hormone (CRH) antagonists,
- glucocorticoid synthesis inhibitors and receptor antagonists,
- neuropeptide targets have included neuropeptide Y (NPY) and neurokinin (NK) receptors.[7, 8]

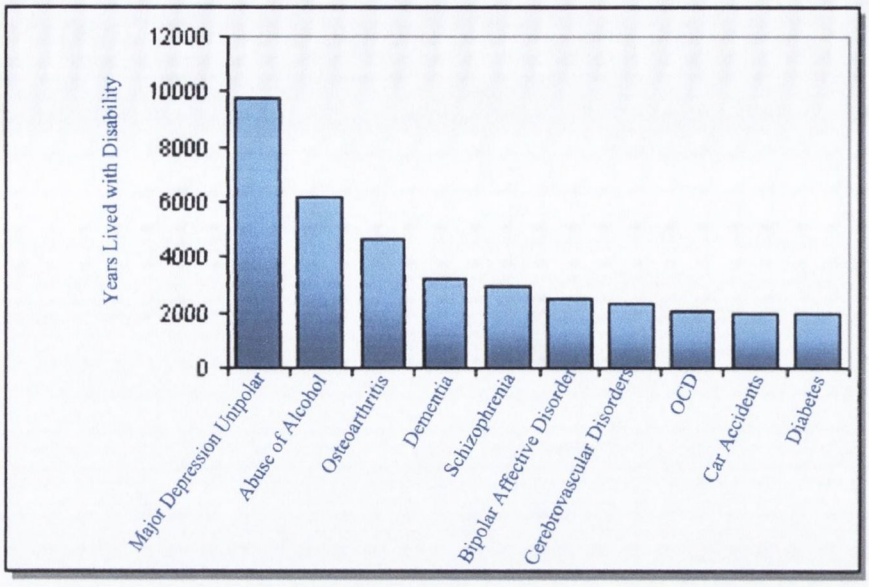


Figure 1-1: Total years lived with disability[3]

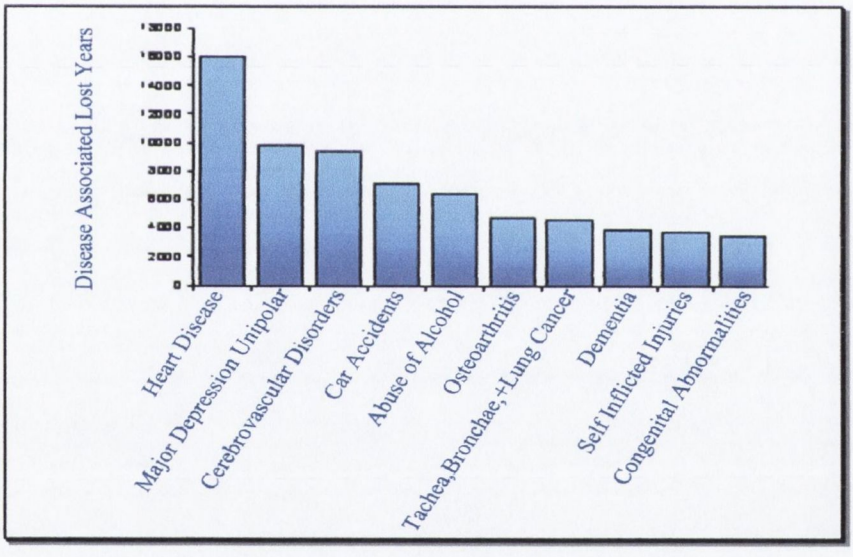


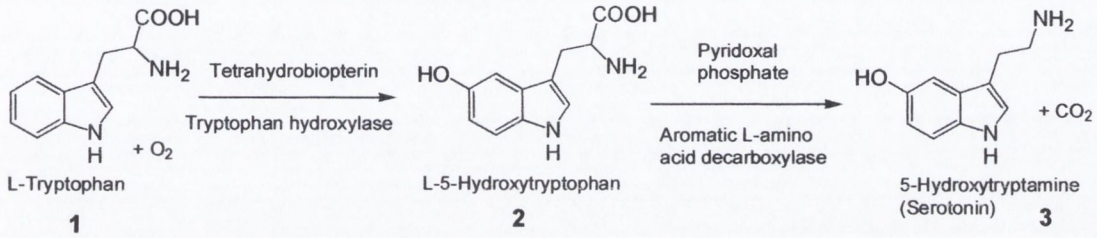
Figure 1-2: Years lost due to premature death[3]

The main focus in this chapter will be the monoamine theory and in particular, the affect and activity of drugs acting on CNS serotonin levels in depression.

1.2 Serotonergic Biochemistry

1.2.1 Biosynthesis

Seventy five years before its discovery, the effects of the neurotransmitter 5-Hydroxytryptamine **3** (5-HT, Serotonin, Scheme 1-1) present in blood serum, as having vascoconstrictor properties, were observed.[9]



Scheme 1-1: Serotonin biosynthesis

Depicted in Scheme 1-1 is the biosynthesis of serotonin **3** from L-tryptophan **1** *via* L5-hydroxytryptophan **2** in which the hydroxylation of the natural amino acid L-tryptophan **1** is the rate-limiting step.[10] Serotonin is one of the main CNS neurotransmitters while others of significant importance include noradrenalin and dopamine. The roles of the main CNS neurotransmitters are summarised in the Venn diagram (Figure. 1-3).

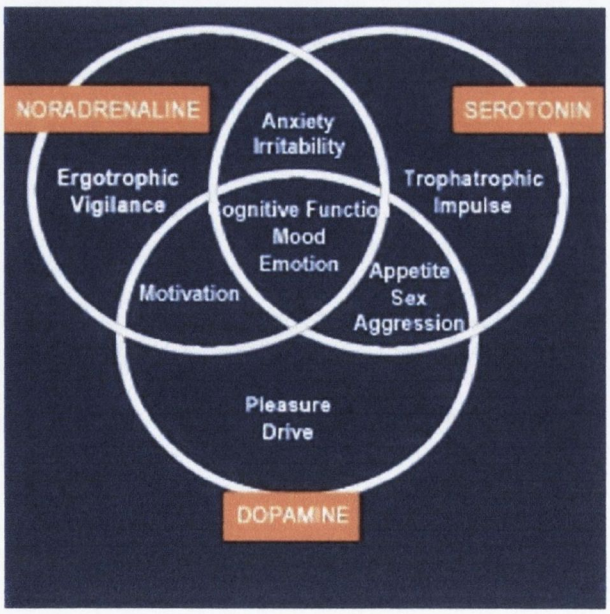


Figure 1-3: Summary of the main CNS neurotransmitters[11]

Generally, it is regarded that dopamine (targeted by cocaine) is involved in a person's drive, while serotonin **3** is involved primarily with mood. In reality, it seems there are complex interactions between the various neurotransmitters that are not yet fully understood. Studies involving the neuroimaging of people suffering from major depression, some suicidal, have implicated the involvement of serotonergic abnormalities in the disease.[12] The serotonergic system has been a target for antidepressants since the 1950s when Imipramine (a tricyclic antidepressant) was found to have antidepressant affects, while undergoing trials as an anti-histamine.[8]

1.2.2 Neurotransmission

Figure 1-4 depicts the mechanisms of neurotransmission at a cellular level. A basic knowledge of these events is crucial in understanding the mode of action of so many antidepressants on the market which are targeted at monoamine neurotransmitters.[10] The key to Figure 1-4 is as follows:

1. Serotonin is synthesised biochemically and stored in the sac-like structures called vesicles in the presynaptic neuron.
2. Upon depolarisation (a change in the electrochemical gradient of the cell body), an influx of Ca^{2+} ions mediates the migration of the vesicles to the cell membrane at the presynaptic cleft.
3. Serotonin **3** is released into the synaptic cleft, which is approximately 50nm across, by two mechanisms. (A) The serotonin transporter protein in the presynaptic membrane (labelled 7) can actively pump out any neurotransmitter available in the cytoplasm. (B) The vesicles merge with the cell membrane and dump their serotonergic stores into the synaptic cleft.
4. Extracellular serotonin **3** exerts its effects on the post-synaptic serotonin receptors of which there are five main types. Depicted as 4 is the 5-HT_{1A} receptor sub-types. Postsynaptically, when activated by serotonin 3, these auto-receptors lead to depolarisation of the post-synaptic cell body, leading to an influx of Ca^{2+} ions, thereby enhancing serotonergic transmission. Pre-synaptically (shown on the presynaptic neuron to the top left) they act to down-regulate the vesicular serotonin 3 being transferred to the cleft. [10]
5. Illustrates the postsynaptic membrane, which contains the different auto receptors. The serotonin transporter protein is not found on this membrane.
6. The process of depolarisation starts in the postsynaptic neuron and the entire process starts again in that cell body.

6. The process of depolarisation starts in the postsynaptic neuron and the entire process starts again in that cell body.
7. Excess extracellular serotonin **3** may be broken down by the enzyme monoamine oxidase (MAO).
8. Remaining extracellular serotonin **3** may be removed from the cleft by active transport through the serotonin transporter.
9. Once transported back into the presynaptic cell, any excess neurotransmitter is metabolised by mitochondrial-bound MOA and/or taken back into the vesicle by a transporter which uses a H^+ gradient, rather than dependency on Na^+ ions (which is the case with the membrane transporter.[13]

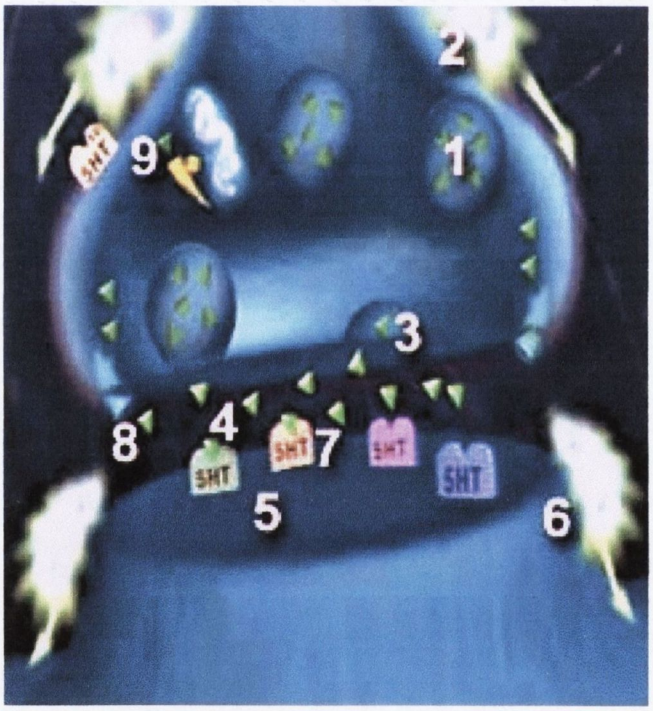


Figure 1-4: Neurotransmission at the Synapse[11]

1.2.3 The Serotonin Transporter (SERT, 5-HTT)

As described in Section 1.2.2, the serotonin transporter plays a key role in the regulation of serotonin **3** neurotransmission. Excess extraceullar serotonin **3** is pumped back across the presynaptic cell membrane, thereby reducing the concentration in the synaptic cleft, which in turn diminishes the serotonergic transmission. Considerable evidence has accrued in the past twenty years to postulate the theory that alterations in serotonergic neural function in the CNS occur in patients with major depression. These findings include the following:[14]

- Reduced cerebrospinal fluid concentrations of major serotonergic metabolites, namely 5-hydroxyindolacetic acid (5-HIAA).
- Reduced concentrations of serotonin and 5-HIAA in post-mortem brain tissue of depressed and suicidal patients.
- A decreased level of L-tryptophan **1** in the blood plasma of depressed patients when compared to controls.
- Increases in the density of 5-HT_{2A} binding sites in the post-mortem brain tissue of depressed patients.
- A reduction in 5-HT transporter binding sites in the post-mortem brain of suicide victims and depressed patients, which is not due to prior antidepressant treatment.

For these reasons, the SERT protein has been the target of several antidepressant therapies, since inhibiting its function would increase the concentration of synaptic serotonin, thus increasing serotonergic neurotransmission, thereby possibly helping to alleviate the symptoms of depression. The group of compounds acting directly and selectively on SERT are known as SSRIs (Selective Serotonin Reuptake Inhibitors).

The SERT protein belongs to a large family of transporters that are dependent on Na^+ ions. This family has been labelled the sodium neurotransmitter symporter family, of which over 40 such transporters have been cloned.[15] Structural features common to these proteins are summarised as follows (Figure. 1-8): twelve helical putative membrane spanning domains, consisting of approximately 25 hydrophobic amino acids each, a large extra-cellular loop spanning helix 3 and 4 which has potential N-glycosylation sites, large N- and C- terminus domains on the intra-

cellular side of the domain that contain potential phosphorylation sites. [16] The dimensions of the secondary structure have been elucidated from its arrangement at the air/water interface.[17] When in solution the protein can change shape, however as conditions approach those experienced at the physiological environment the protein may refold to its original conformation. These studies have shown the protein to approximately 84 Å in depth.[17]

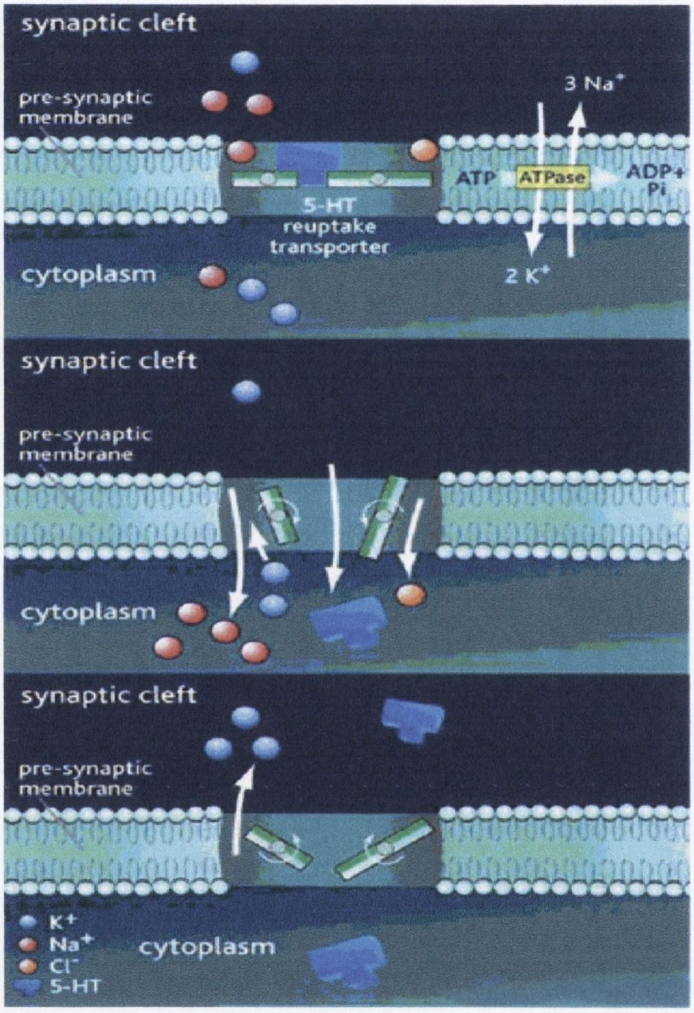


Figure 1-5: Serotonin transporter mechanism[1]

The binding of serotonin to the SERT protein has been described.[18, 19] Extracellular uptake of serotonin 3 from the synaptic cleft is mediated by the transporter (Figure. 1-5). Serotonin, Na^+ and Cl^- form a quaternary complex with the transporter before being co-transported across the plasma membrane (from the extracellular side to the cytoplasmic side), followed by counter transport of K^+. As serotonin 3 is

protonated at physiological pH (7.4), the net change in charge across the membrane is zero.

The first putative 3-D arrangement of the twelve helices published for computational purposes, was by Ravna and Edvardsen.[20] The proteins gene sequence may be mapped to chromosome 17q11.1 to 17q12 and consists of 630 amino acids in total.[15] From species scanning mutagenesis studies[21, 22] and site directed mutagenesis studies,[15, 23-27] two binding sites (A and B) within the transporter have been postulated (Figure 1-6).

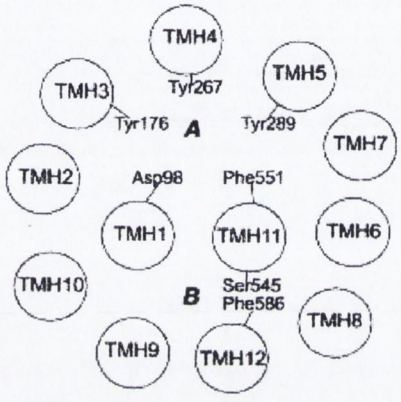


Figure 1-6: Putative SERT arrangement showing two binding sites. [20]

The schematic view of the relative positions of the 12 transmembrane helices (TMH) of the SERT model is illustrated in Figure 1-6. Residues from the published site directed mutagenesis studies imply a cocaine binding region A: (Asp98, Tyr176, Tyr267, Tyr289 and Phe551)[28] and imipramine binding region B: (Ser545 and Phe586).[29] In constructing this model the extracellular loops were ignored because they could not be predicted or modelled with confidence[20] and the mutagenesis studies indicate the binding sites are located in the transmembrane domain.[30] Using the amino acid sequence, the helices were constructed and placed in order; inter-helical hydrogen bonding and hydrophobic interaction were used in the energy minimisation to furnish the structure shown in Figure 1-7.

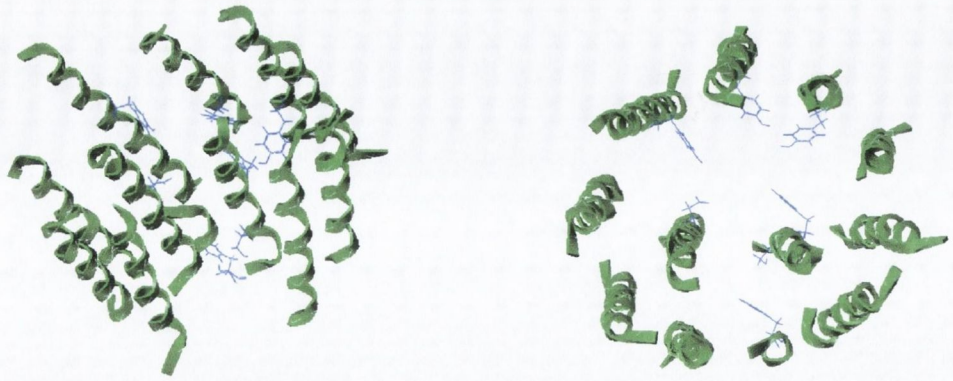


Figure 1-7: Putative SERT model with key residues involved in binding in blue

At the time of publishing this model, a high-resolution X-ray crystal structure data of a transmembrane transporter was not available because of the inherent difficulty in crystallising such a protein. The main difficulties in forming such crystals were due to:

a) the amphipathic nature of their surface, with hydrophobic areas in contact with the membrane phosphlipids and polar hydrophilic surface areas in contact with aqueous phases on both sides of the membrane,
b) transporter proteins are only present in membranes at tiny concentrations
c) the flexibility of the structure.[31] With advances in cloning, the over-expression of bacterial transporters has been made possible. Thus far, the X-ray crystal structures of six such transporters have been elucidated.[31]

Based on the structure of the bacterial (*E-coli)* transporter NhaA (Na^+/H^+ anti-porter), elucidated by electron cryo-microscopy, Ravna *et al*[4] constructed a more accurate model of the serotonin transporter, for use in potential ligand design (Figure 1-8). Localisation of the TMH agreed well with subsequently published X-Ray crystal structures of the LacY (lactose permease) transporter; only TMH 12 was significantly displaced.[31] This model represents a significant improvement on the one developed in Figure 1-7. By using an electron density projection map of the *E. coli* Na^+/H^+ anti-porter (a transporter that shares a common functional mechanism), and site-directed mutagenesis on SERT, a 3-D molecular model of SERT was constructed.[4] This model could be used to simulate the molecular interactions between various ligands, such as drugs currently used to treat depression.

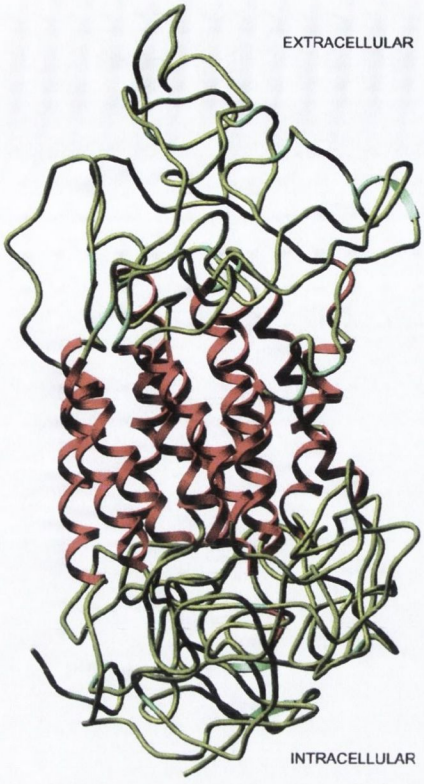


Figure 1-8: Latest computational SERT model[4]

The arrangement of the latest SERT model is a far more appropriate representation of the proteins tertiary structure. It is based on the sequence elicited by the imaging of a transporter in a biological setting, as opposed to constructing the model around a proposed binding site and computationally manipulating the structure, resulting from the theoretical energy minimisation.

Docking of cocaine into the putative binding area of the SERT model indicated that the ligand participates in hydrogen bonding with Tyr176 (TMH3), Tyr267 (TMH4), and Tyr289 (TMH5). Similarly, a hydrogen bond interaction between the benzoate carboxyl of cocaine interacted with Tyr267 in docking position 3 and Tyr289 in

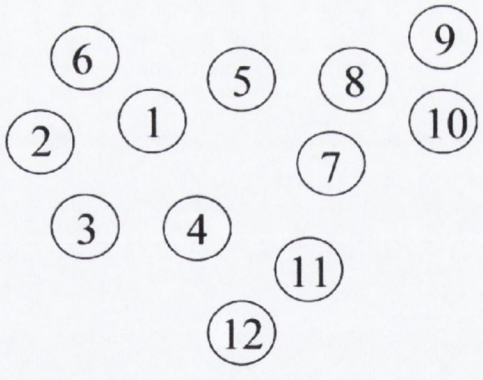


Figure 1-9: Layout of helices in latest SERT model

docking position 4. The positively charged nitrogen atom (on the cocaine tropane ring) interacted with Asp98 creating a salt bridge.[31] Although these results agree well with the site directed mutagenesis studies, possible conformational changes that may occur within the transporter during translocation would be ignored, as the docking procedure was carried out by the authors was on a rigid SERT molecule.[31]

1.2.4 Serotonergic Autoreceptors

The serotonin family of receptors are responsible for a plethora of physiological functions, among them: vascular and non-vascular smooth muscle contraction, platelet aggregation, modulation of mood, perception, anxiety and feeding behaviour.[32] There are 15 different 5-HT receptor sub-types with 5 main types namely 5-HT_1, 5-HT_2, 5-HT_3, 5-HT_4, 5-HT_5. [33] Depicted in Figure 1-10, is a serotonergic auto-receptor.[1] A common feature of these proteins is the seven membrane spanning hydrophobic segments, representing the α-helices shown, some believe the recognition sites for natural agonists and synthetic ligands are located within this bundle of helices, albeit toward the extracellular region of the transmembrane domain.[32, 34, 35] These proteins belong to a family of G-protein coupled receptors. A cascade of events occurs upon the signalling of a G-protein coupled receptor, starting with the binding of a suitable ligand (in this case serotonin **3**) to the extracellular receptor site. A conformational change within the auto-receptor results in the dissociation of the α-subunit *via* a series of steps. [36] These events lead to an enhancement or reduction of the activity of a transducing enzyme such as adenylate cyclase or phospholipase C, which are responsible for the synthesis/release of a secondary messenger such as: cAMP, inositol triphosphate, Ca^{2+}.[37]

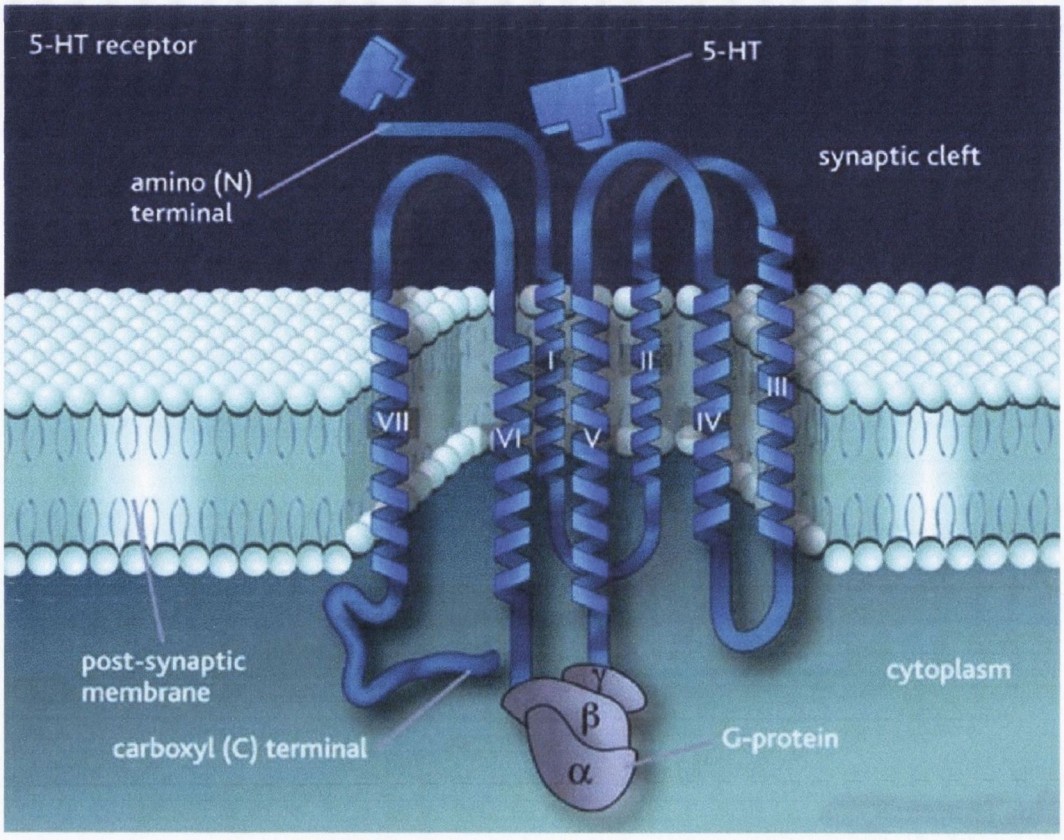


Figure 1-10: Serotonergic Autoreceptor[1]

The downstream effect is either inhibitory or stimulatory, depending on the type of G-protein linked to the receptor. 5-HT_1 type receptors are linked to inhibitory G-proteins, whereas 5-$HT_{2,4,6,7}$ types are linked to stimulatory G-proteins.[36]

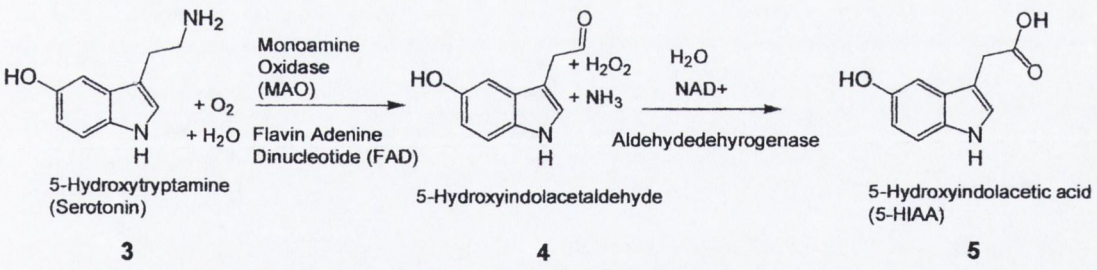
With 5-HT_2 type receptors exhibiting an excitatory response, several of the side-effects associated with SSRI anti-depressant therapy are linked to activation of this auto-receptor (particularly 5-HT_{2A}) on the post-synaptic membrane.[38, 39] Some of the adverse medical effects resulting from the administration of SSRIs have been reviewed. These include: nausea, insomnia, tremor, sedation, headache, dizziness, anxiety, dry-mouth, fatigue, diarrhoea, constipation and sexual dysfunction.[37, 38, 40] The less common but more adverse side-effects are: inappropriate antidiuretic hormone secretion, extrapyrimidal effects, bleeding complications, cardiac arrhythmias and the serotonin syndrome.[41] The somatodendritic 5-HT_{1A} receptors, on the other hand, act to down-regulate (negative feed-back decreases the cells firing rate) the transmission of serotonin by preventing the vesicles migrating to the post-synaptic membrane.[8] Any compounds acting at this site will negate the affect of transport inhibition. Until the receptors are desensitised (taken into the cell body

and destroyed), no anti-depressive effects are observed, a process that can take two to six weeks. This is one of the major drawbacks of conventional SSRI therapy.[42] Several groups are now targeting these receptors, as well as the SERT protein, in an attempt to find a faster acting anti-depressant with fewer side affects.

1.3 Selective Serotonin Reuptake Inhibitors (SSRI)

1.3.1 History of SSRIs

SSRIs are among the most widely prescribed drugs in the developed world and are considered the second generation of antidepressants. Having revolutionised anti-depressive therapy,[43] their therapeutic usefulness is still expanding to other disease such as anxiety, obsessive-compulsive disorder, post-traumatic stress disorder and pre-menstrual dysphoric disorder.[39] The first generation antidepressants were the MAOs (mono-amine oxidase inhibitors) and TCAs (tricyclic antidepressants), first used in the late 1950's. MAO is the mitochondrial bound enzyme described in Figure 1-4. It is responsible for the degradation of excess serotonin **3** to 5-hydroxyindole acetaldehyde **4** and 5-hydroxyindolacetic acid (5HIAA) **5** *via* the pathway shown in Scheme 1-2.



Scheme 1-2: Metabolism of Serotonin

MAO metabolises amines other than serotonin **3**, therefore it's inhibition gives rise to numerous side-effects. For this reason, it is usually only prescribed to those not responding to SSRI therapy. The TCAs, even though they are efficacious, are non-selective in their binding. They are active at the serotonin and noradrenaline transporters, however they also bind to muscarinic, cholinergic, H_1 histamine receptors and α_1-adrenergic receptors. [44] This non-selectivity results in difficult dosing routines and several unwanted side effects.[37]

SSRIs such as Citalopram, Paroxetine, Fluoxetine *etc.* have been clinically available since the 1980's and the key to their success has come from their relatively favourable side-effect profile and their very high selectivity.[40] Even though they are far more selective than the TCAs, they are not more efficacious proven by the prescribing of TCAs to patients not responding to SSRI therapy.[43]

1.3.2 SERT Pharmacophore

A pharmocophoric model for serotonin reuptake inhibitors was developed by Rupp *et al,*[45] using pharmacophore elements geometry and molecular electrostatic potential. An active analogue approach, whereby 25 molecules considered to be active and 7 inactive compounds were taken, and by using the method of receptor site mapping which involves: critical consideration of the active molecule (the compounds must be active at the same binding site), definition of the pharmacophore by comparison of active analogues, 3-D calculations and presentation of active compounds in the active conformation, investigation of inactive compounds by small molecular variations), a 3-D pharmacophore was developed as shown in Figure 1-11.

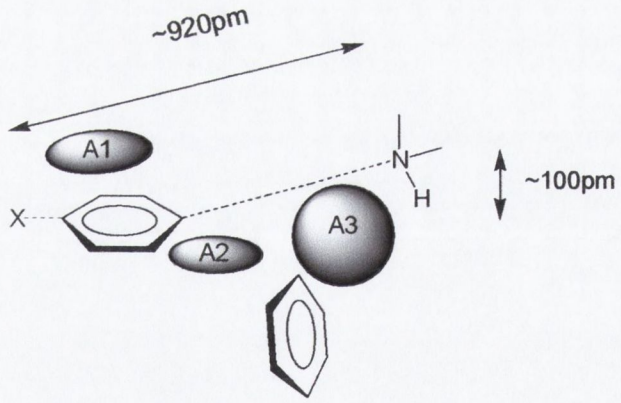


Figure 1-11: Rupp's pharmocophoric model[45]

The following structural properties are conveyed in the pharmacophoric model:[45]

- The positioning of a positively charged amino group, a distance of 910 pm from a negatively charged functional group X.
- The nitrogen atom must be a distance of approximately 100 pm above the plane of the substituted aromatic ring.

- Region A1 is a void volume (any substitution at A1 results in a loss of tubular structure), functional groups in this region tend to give rise to hallucinogenic activity.
- Region A2 is a volume containing *n*- and or π-electrons.
- A3 is an aliphatic side chain.
- To increase potency and selectivity for SERT a steric group must protrude into a different plane *i.e.* out of the page.

Rupp's model was later verified using a similar set of compounds. The updated pharmacophore was based on 3-D QSAR (3-dimensional structure-activity relationship).[46]

Comparative Molecular Field Analysis (CoMFA) and Comparative Molecular Similarity Indices Analysis (CoMSIA) are used in drug discovery to find the common features that are important in binding to the biologically relevant target.[47] Both techniques are based on the assumption that changes in binding affinities of ligands are related to changes in different fields surrounding the molecules. These fields can be of steric and electrostatic, of hydrophobic, or of hydrogen bond accepting and hydrogen-bond donating nature.[47] Muszynski *et al* later developed a model for inhibition of three monoamine transporters (SERT, NAT, DAT) using quantitative structure-activity relationships by CoMFA (Comparative Molecular Field Analysis) and classical 2D methods. [48] The 54 compounds the study was based on were phenyltropane derivatives whose activities at each of the monoamine transporters are known, shown in Figure 1.12 (the phenyltropane moiety being a major constituent of the cocaine molecule).

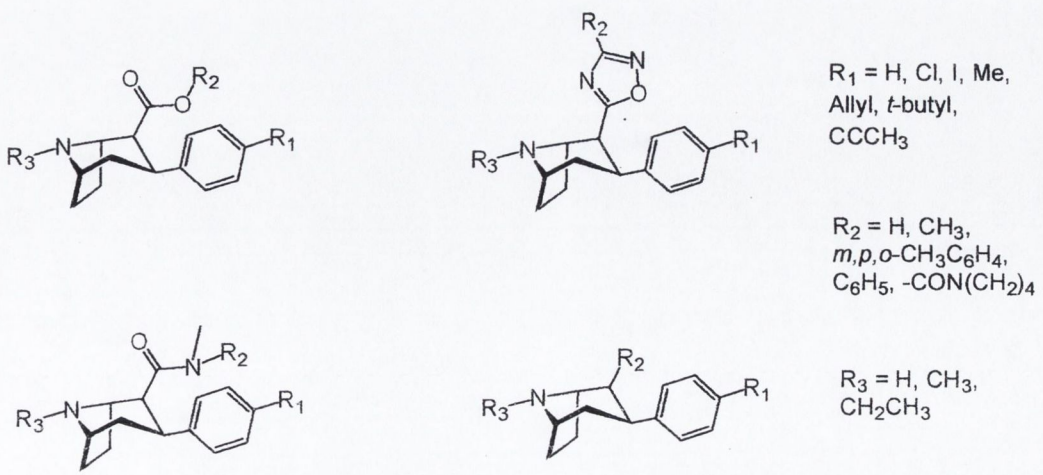


Figure 1-12: Phenyltropane skeleton structure used by Muszynski[48]

Large substituent groups in position C2 of the tropane ring such as the oxadiazole group, or a secondary *N*-methyl amide, decreased binding affinity to SERT and NAT. Steric bulk was found to be favourable at R_1 and between C2 and the nitrogen atom. A negative charge was also found to be favourable at R_1, a little closer to the ring than the fore mentioned steric group. Side chains protruding 4-5 bond lengths out from C2 with negative charges were found to be unfavourable in that region.[48] The effectiveness of the model was tested by comparing known biological activity to predictions made by the model. Were the nitrogen of the tropane ring placed over that of the nitrogen in Rupp's model, the two pharmacophores agree quite well.

A later CoMFA and CoMSIA (Comparative Molecular Similarities Indices Analysis) study of serotonin transporter ligands,[49] where (S)-citalopram **7** (the most selective SSRI on the market, Figure 1-13) was used as the basis of the investigation, found that the steric group (shown as an unsubstituted ring in Rupp's model) must be aromatic and substituted with an electronegative functional group. Furthermore, the electronegative region on the "main" ring should be electronegative without being hydrogen bond donating, in this case a cyano group.[49]

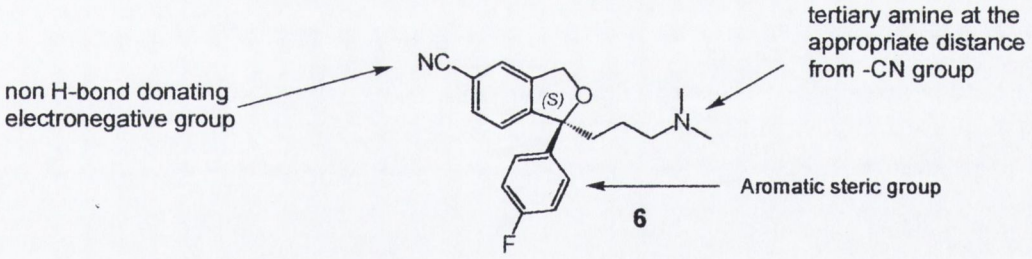
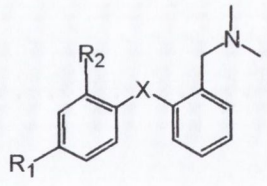


Figure 1-13: (*S*)-Citalopram

In a search to design new radiolabeled ligands for SERT, which could have potential for use as PET (positron emission topography) radiotracers, Wellsow and Kovar carried out CoMFA and CoMSIA studies on compounds of the type shown in Figure 1-14.[50] They used this backbone because diphenyl sulfide derivatives of this type had been proven to be promising PET ligands for SERT.[51, 52]



X = S, O

R_1 = Fluoroethyloxycarbonyl, cyano, I

R_2 = CHO, oxime, imine, amine, CH_2OH

Figure 1-14: Structural scaffold for radiotracer design[50]

A series of novel potential SERT ligands were proposed, the most promising of which comprised of the following: a fluoroethyloxycarbonyl group at position 4′ and an electron withdrawing group in position 2′ *e.g.* an aldehyde, oxime or imine. Illustrated in Figure 1-15, is the pharmacophore resulting from the QSAR of known substances.

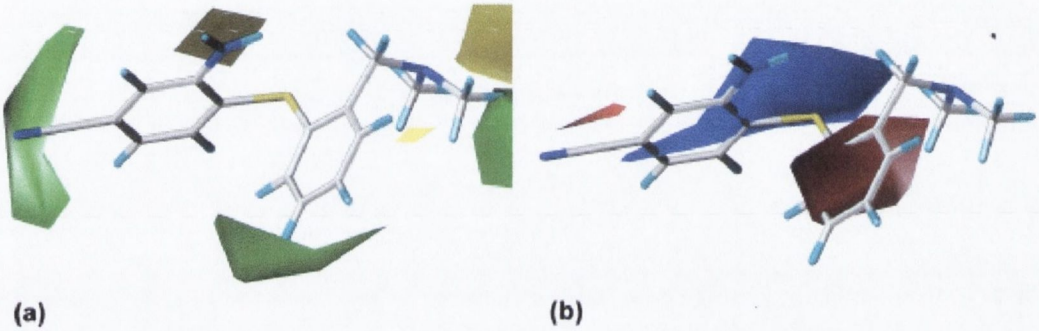


Figure 1-15: a) Steric, b) Electrostatic factors of the proposed model[50]

Figure 1-15 agrees with the other proposed pharmacophores of Rupp and Wellsow. The molecule at the centre of the CoMFA model is DASB, which is analogue of Figure 1-14 with the bridging heteroatom being sulfur, substituent R_2 is an amino group and R_1 is a cyano group. Green areas indicate regions where steric bulk favourably effects binding affinity and the yellow volumes are regions in which sterically demanding groups have a detrimental effect on binding affinity to the serotonin transporter. Blue shading enclose areas where partial positive charges increase binding affinity whereas in the regions enclosed by red contours partial negative charges are favoured. [50]

The green regions representing the steric groups, correspond well with the rings shown in the pharmacophore illustrated in Figure 1-11. The less substituted ring being in front of that farthest from the nitrogen. The red area of partial negative charge, coincide with the area donated A2 and X (Figure 1-11). The yellow region of Figure 1-15, although its position is slightly closer to the amino group, it is still on the

same side of the ring and in the general area of the void volume in Rupp's model labelled as A1. Zhuang *et al* synthesised a group of similar compounds, with the most active having an oxygen as the bridging atom X, a methyl alcohol at postion R_2 and an iodine atom substituted at R_1.[53]

All of the modern class of SSRIs agree well with the models proposed. (*S*)-citalopram **6** for example, has an electronegative cyano group which would be represented by X in Rupp's model,[45] and the later CoMFA model suggested that this functional group be electronegative but not hydrogen bond donating.[49] In the of (*S*)-citalopram (Figure 1-13), the nitrogen is at the required distance from the fore mentioned electro negative cyano group (donated X in Rupps model Figure 1-11) and has two aromatic rings perpendicular to each other thereby satisfying another of the factors required in the proposed models. The oxygen of the benzofuran ring fulfills the requirement of having π-electrons[45] or a partial negative charge[49, 50] in the area between the steric regions. Each of the SSRIs on the market share some if not all of these properties *i.e.* having an electronegative substituted aromatic ring with an amino functional group at a set distance from it. A Steric group lying in a different plane to the ring and π-electrons, usually from a heteroatom, positioned between the steric groups.

Interestingly one study has confirmed that derivatives of cocaine (analogous to the structures given in Figure 1-12), where the nitrogen is replaced with an oxygen, are highly potent at both SERT and DAT,[54] this contradicts the belief that the amine in cocaine, directly interacts with the Asp98 on TMH1 of the serotonin transporter.[4, 43] It also suggests the potential for a pharmocophoric study using compounds similar to clinical SSRIs with the terminal nitrogen replaced with an oxygen atom.

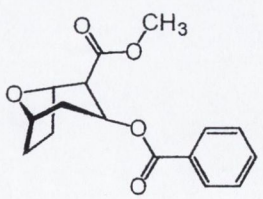


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Figure 1-16: Oxygenated cocaine derivative[54]

1.3.3 Structure-Activity Relationships for (SAR) for Compounds Active at SERT

1.3.3.1 Selective Serotonin Reuptake Inhibitors (SSRI)

The products shown in Figure 1-17, are the most commonly prescribed SSRIs currently in clinical use.

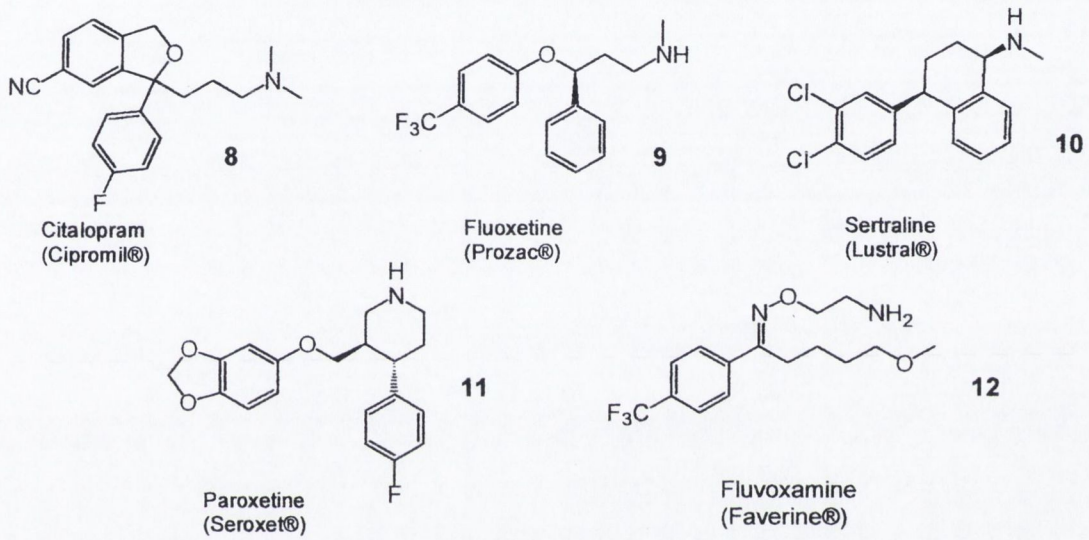


Figure 1-17: Widely prescribed SSRIs

The SSRIs have been available since the 1980's for treating depression.[43] The key to the success of this family of compounds is their high selectivity at the SERT protein, leaving other receptors largely untouched. As well as conforming to the pharmacophores already proposed, the SSRIs are sufficiently lipophilic to pass the blood brain barrier (BBB) and are therefore available for rapid brain uptake.[55] The mode of action of antidepressants acting at SERT and the various 5-HT auto receptors has been reviewed.[8, 16, 33, 37, 39-41, 56]

Although initially marketed as the racemic mixture, it is the (*S*)-enantiomer of Citalopram **8** that is most active. Upon expiry of the patent, Lundbeck marketed separately the (S)-enantiomer as ecitalopram **6**. Citalopram **8** is the most selective marketed SSRI and is prescribed for depression and panic disorder.[57] Shown in Table 1-1, is the IC_{50} for the racemate at three monoamine transporters (the IC_{50}

value being the concentration in nM, at which half of the serotonin is inhibited from reuptake). It is over 3000 times more selective for the SERT protein over the NAT.[58]

Table 1-1: Activity of Racemic Citalopram[58]

	SERT	NAT
Citalopram **8** IC_{50} (nM)	1.8	6100

Fluoxetine **9** by Eli Lilly, is a very effective SSRI prescribed for the following conditions: depression, bulimia nervosa and OCD (obsessive compulsive disorder).[57] Initially it was marketed as a racemate, even though there is very little difference in the *in vivo* activity of the two enantiomers. However because the (*R*)-enantiomer is eliminated more quickly, it was the (*S*)-isomer that was repatented.[2] Table 1-2, gives the IC_{50} of the racemate at the different transporters involved in the treatment of depression.[58]Fluoxetine **9** is 55 times more selective for the SERT protein relative to NAT making it the least selective of the widely used SSRIs.

Table 1-2: Activity of Fluoxetine[58]

	SERT	NAT
Fluoxetine **9** IC_{50} (nM)	6.8	370

Sertraline **10** from Pfizer, is a useful SSRI prescribed for the following conditions: depressive illness, obsessive-compulsive disorder (under specialist supervision in children), and post-traumatic stress disorder in women.[57] Fluoxetine **9**, Paroxetine **11** and Citalopram **8** are not suitable for treating children or adolescents.[57] Table 1-3 gives the IC_{50} value in nM for Sertraline **10**. Although slightly active at the NAT, Sertraline **10** is a potent SERT inhibitor with a selectivity factor of 850.

Table 1-3: Activity of Sertraline[58]

	SERT	NAT
Sertraline **10** IC_{50} (nM)	0.19	160

Paroxetine **11** was launched in 1991 by SmithKline-Beecham, for the treatment of depressive illness, obsessive-compulsive disorder, panic disorder, social phobia, post-traumatic stress disorder, generalised anxiety disorder.[39, 57] Paroxetine **11** has a high first pass metabolism[39] and has been taken off the market for treating

adolescents. Table 1-4 contains the IC_{50} for Paroxetine **11** at each of the three receptors associated with depression. As in the case of Sertraline **10**, Paroxetine **11** is active at the NAT protein but is a highly potent SERT inhibitor leading to a selectivity factor of 280.

Table 1-4: Activity of Paroxetine[58]

	SERT	NAT
Paroxetine **11** IC_{50} (nM)	0.29	81

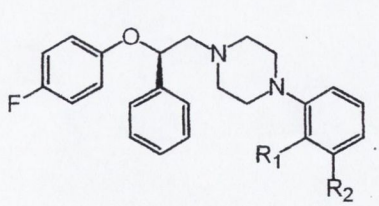
Fluvoxamine **12** by Solvay, is used to treat depressive illness and obsessive-compulsive disorder.[57] It has also been found to be useful in treating panic disorder[39]. The IC_{50} values are presented in Table 1-5. Fluvoxamine **12** shows good selectivity for SERT, having very low affinity for the NA transporter.

Table 1-5: Fluvoxamine activity[58]

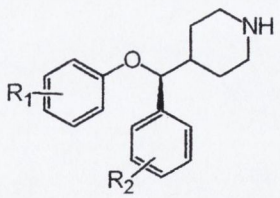
	SERT	NAT
Fluvoxamine **12** IC_{50} (nM)	0.29	81

Dorsey *et al*[59] have prepared three new Fluoxetine analogues Figure 1-18, 2-(4-Fluorophenoxy)-2-phenyl-ethylpiperazines, which demonstrate single-site binding at the site of the serotonin reuptake transporter (SERT). Each of the three compounds (**13-15**) are much less potent than typical SSRIs, having micro-molar affinity for the SERT with IC_{50} in the range 1.4 μm to 9.56 μm respectively.

13 R_1= Cl; R_2= H
14 R_1= H; R_2= OCH_3
15 R_1= CF_3; R_2= H



Dorsey *et al*



Orjales *et al*

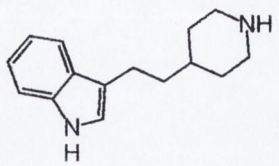
Figure 1-18: Fluoxetine analogues

However, in a study by Orjales *et al* [60] on another set of fluoxetine analogues (17-32) (Figure 1-18), several compounds compared very well to the marketed SSRIs. The main focus of the study, was on various substituents on the aromatic rings. Presented in Table 1-6, are the more active compounds from the study[60].

Table 1-6: Latest SAR on Fluoxetine Analogues[60]

Compd.	R_1	R_2	SERT (K_i nM)
16	H	H	2.3
17	2-F	H	6.3
18	2-Cl	H	8.2
19	3-I	H	3.7
20	3-F	H	1.0
21	3-CN	H	1.0
22	3-Cl	H	2.6
23	4-NO_2	H	2.4
24	4-I	H	20.6
25	4-F	H	1.1
26	4-F	4-F	0.9
27	4-OCH_3	4-F	0.9
28	3-Cl, 4-CN	H	3.9
39	3-F, 5-OCH_3	H	1.9
30	3-F, 5-CN	H	2.6
31	3,5-diF	H	3.4

Structures based on indalpine **32** (Figure. 1-19), *i.e.* 3-(alkylpiperidin-4-yl)indoles have been described as SSRIs[61]. The most active molecule being **33**, with IC_{50} at SERT, NAT and DAT of 0.01μM, 1.6μM and 18μM respectively. These sets of ligands are based primarily on the backbone of serotonin itself **3**.



32

Figure 1-19: Indalpine

A precurser of the current set of SSRI's was Zimelidine **33** (Figure. 1-20). Eventhough it was a therapeutically successful SSRI introduced in the mid 1980's,[62] it was withdrawn in the late 1980's because of severe side effects.

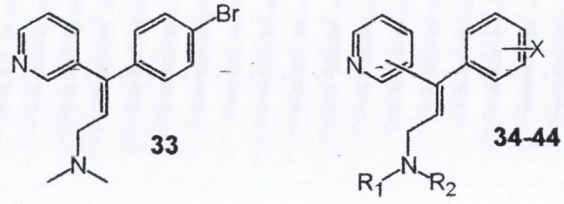
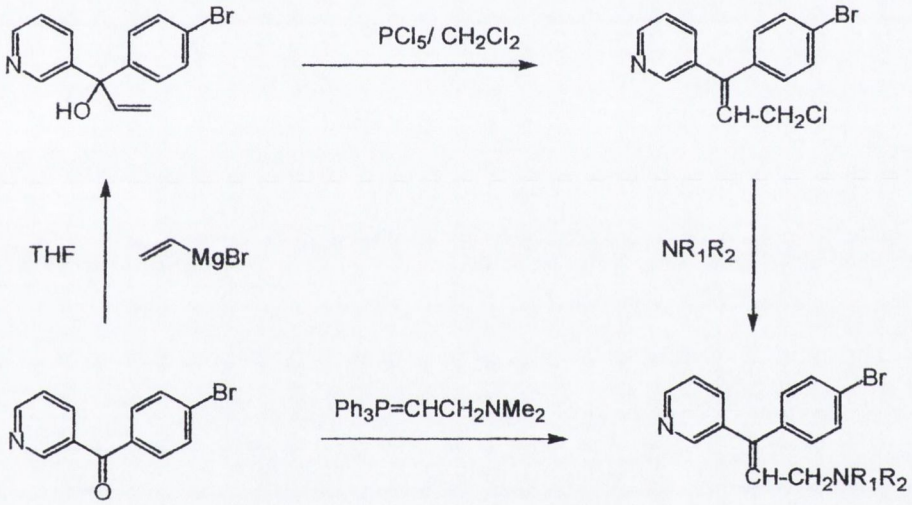


Figure 1-20: Zimilidine 34 and analogues synthesised[62]

Hogberg *et al* synthesised (using the chemistry shown in Scheme 1-3) and tested a range of 30 analogues, based on the Zimelidine **33** scaffold structure, for SSRI activity (Figure. 1-20). The IC_{50} values, for examples **34-44**, are displayed below in Table 1.7, based on the inhibition of (-)[^{3}H]Noradrenaline and [^{14}C]serotonin accumulation in mouse brain slices.[62]



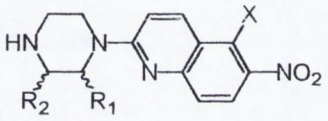
Scheme 1-3: Synthesis of Zimelidine analogues[62]

Table 1-7: Zimelidine SAR[62]

Compd	X	R_1	R_2	Pyridine	NA	5-HT
					In vitro IC_{50}, μM	
33	4-Br	Me	Me	3	24	1.7
34	4-Cl	Me	Me	3	10	2.1
35	4-Br	H	Et	3	26	2.0
36	4-I	Me	Me	3	>22	1.0
37	4-Ome	Me	Me	3	>28	0.8
38	4-Sme	Me	Me	3	>27	0.5
39	3-Br	Me	Me	3	4.2	0.9
40	3-Br	H	Me	3	0.9	1.4
41	2,4-Cl_2	Me	Me	3	11	1.5
42	2,4-Cl_2	H	Me	3	2.3	0.5
43	4-NMe_2	Me	Me	2	11	1.6

Compound **36** (Table 1-7) is a more potent inhibitor than zimelidine **33** (Table 1-7). Secondary amines with larger N-alkyl groups were less active while secondary amines were more active than the tertiary analogue. The bromo-substitutions on the phenyl rings revealed a decrease in serotonergic activity and an increase in NA activity in the order of 4-Br, 3-Br, 2-Br.[62]

Gerdes *et al* have carried out studies based on the 6-nitroquazine backbone.[63] The compounds **43-46**, shown in Figure 1-21, have a high inhibitory affinity for SERT, comparable to some of the more commonly used SSRIs (K_i being the concentration in nM at which 50% of the receptors are bound with the ligand).



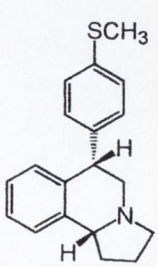
43-46

Figure 1-21: 6-Nitroquipazine analogues

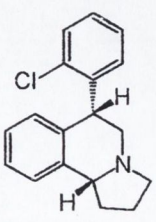
Table 1-8: 6-Nitroquipazine analogues and their activities[63]

Compd.	R_1	R_2	X	SERT K_i (nM)
43	H	H	H	0.16
44	H	H	I	0.19
45	CH_3	H	H	0.08
46	H	CH_3	H	4.56

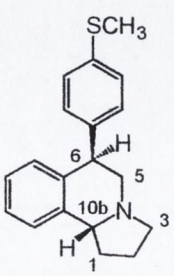
Another type of SERT inhibitor, derived from isoquinoline, are the McN-analogues **47-49**. (Figure 1-22).[64] McN-5652 is an example of this series, that potently inhibits serotonin reuptake, however, this series of compounds are not as selective as the main SSRIs on the market.



47 (+) McN-5652-X



48 (+) McN-5707-X



49 (+)-McN-5652-Z

Figure 1-22: McN Analogues

First noted as inhibitors of both noradrenaline and serotonin uptake, and antagonising 5-HT_2 receptors,[64, 65] further work proved the active isomers to be those shown in Figure 1-22.[64, 66, 67] Compound McN 5652-Z **49** (the (+)-6-(*S*), 10b-(*R*) isomer) has exceptionally high affinity for rat SERT pK_i=0.4[68]. McN 5652-Z **49** is the *trans* (+) enantiomer. It is moderately selective with a selectivity factor for NAT and DAT of 4.6 and 60.3 respectively. Early studies on the binding affinity of various antidepressants and their metabolites, were carried out at 20°C.[69] When comparing affinity of various SSRIs for SERT at 37°C *vs.* 21°C, [^{3}H]-(+)-McN5652, had a much slower dissociation from SERT, compared to [^{3}H]-(*S*)-citalopram.[70]

1.3.3.2 Tricyclic Antidepressants (TCAs)

Although not as selective as the SSRIs, some of the compounds from the TCA class have a high affinity for SERT.[16]. Unfortunately they bind to a wide range of receptors and therefore their use is not as widespread due to the many side effects associated with them. Figure 1-23, depicts the most commonly used TCAs (**50-58**).

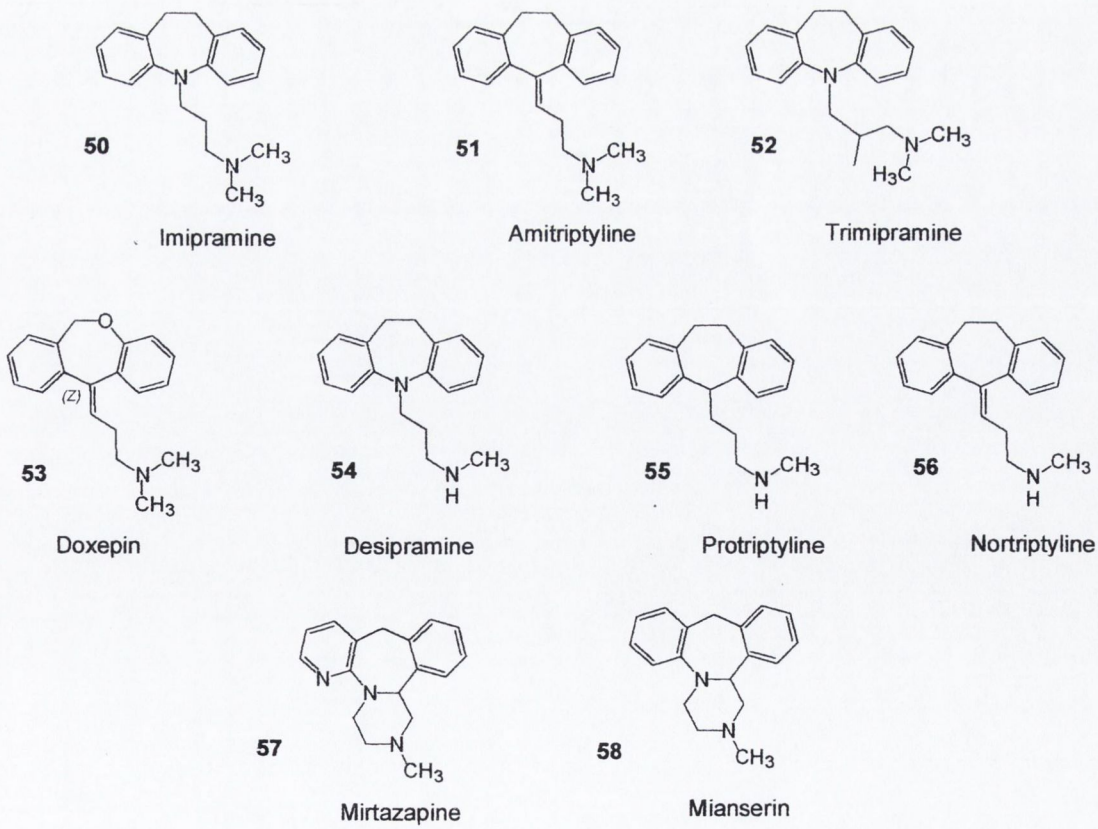


Figure 1-23: Structures of TCAs

Since the TCAs do not have a high degree of selectivity with regard to the SERT protein, it has been difficult to ascertain how much of their antidepressant effect is based on serotonin uptake inhibition.[40] Their interaction with various physiological functions has lead to several theories regarding the causes of depression.[8, 56, 71] It is perhaps this non-selective binding that leads to the TCAs having a faster on-set of action than the SSRIs. Mirtazapine **57** and Mianserin **58** are structurally members of the TCA family, yet their mode of action differs remarkably to other monoamine uptake inhibitors, in that they target to α_1-adrenoreceptors and 5-HT_2 and 5-HT_3 type receptors. Table 1-9 gives the IC_{50} values for the TCAs active at the serotonin and noradrenaline transporters. [40]

Table 1-9: TCA Activity at the Monoamine Transporters NAT and SERT

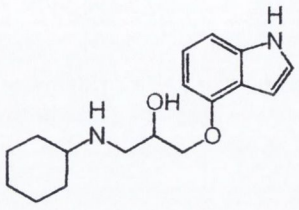
Compd.	Drug	IC_{50} Values (nM)	
		NAT	SERT
51	Amitriptyline	25	100
54	Desipramine	2	300
53	Doxepin	150	2000
50	Imipramine	25	50
56	Nortriptyline	6	200
55	Protriptyline	10	250
52	Trimipramine	5000	10000

1.3.4 SSRIs with Dual Activity

The focus in developing novel antidepressants has shifted in recent years from being directed towards one specific site (SERT), to compounds with dual activity. As previously described, the SSRIs have a good safety profile and are reasonably efficacious, with the one major disadvantage being their slow onset of action, arising from non-specific binding to the $5HT_1$ type presynaptic receptors. They are not completely devoid of side effects, most of which arise from agonistic binding to the 5-HT_2 and 5-HT_3 type receptors. To improve the side effect profile and action of SSRIs one would need to retain their selectivity and affinity for SERT, while antagonistically binding to 5-HT_2 receptors, agonistically binding postsynaptic 5-HT_1 receptors and antagonistically binding the 5-HT_1 presynaptic and somatodendritic receptors.

1.3.4.1 SSRI + 5-HT Receptor Affinity

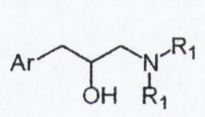
Pindolol **59** is a 5-HT_{1A} antagonist (Figure 1-24) that accelerates and in certain cases enhances the action of anti-depressant drugs.[72, 73] As a result, research interests have shifted somewhat towards finding a compound with activity at the desired receptors as well as having SERT inhibitory activity.



59

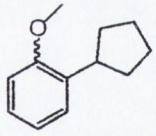
Figure 1-24: Pindolol

In a search for a faster acting antidepressant with a similar or improved safety profile to widely prescribed SSRIs, Perez *et al*[74] directly coupled compounds with known activity at the SERT protein, to known structures with affinity for the 5-HT_{1A} receptor (**60-71**) illustrated in Figure 1-25. The known SERT inhibitors chosen were fluoxetine **9**, paroxetine **11** and milnacipran (TCA). The 5-HT_{1A} antagonists used in the study were pindolol **59**, propranolol and penbutolol.

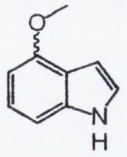


R_1 =
a) Fluoxetine
b) Milnacipran
c) Paroxetine

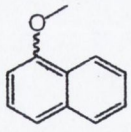
Ar=



60-63



64-67



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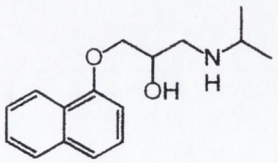
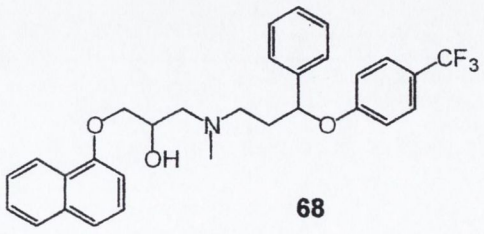


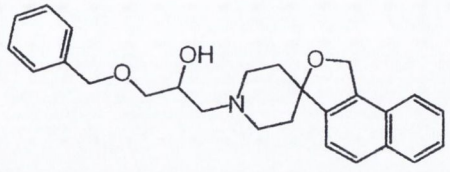
Propranolol **72**



68

Figure 1-25: Coupling compounds of known SERT activity to those of known 5-HT_{1A} affinity[74]

For illustrative purposes **68** (Figure 1-25) is drawn out showing the product from coupling propranolol **72** with Fluoxetine **9**. None of the compounds exhibited **60-71** dual activity. 5-HT_{1A} antagonism was in the range of K_i 6-200 (nM) and none were active as reuptake inhibitors.

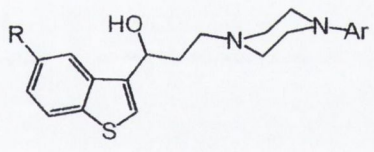


73

Figure 1-26: Dual SERT Inhibitors/5-HT_{1A} Antagonist[75]

Figure 1-26 is representative of the range of compounds, synthesised as potential dual SERT inhibitors/5-HT_{1A} antagonists, by Merck. [75] The most active dual compound was one in which Ar = Benzyl **73**, having K_i of 37 and 10 nM at the 5-HT_{1A} receptor and SERT inhibition, respectively.

An additional range of compounds have been designed and synthesised with activity at both the 5-HT_{1A} receptor and SERT, based on the structure depicted in Figure 1-27.[76-78] The design was based on the coupling of structural moieties related to SSRI activity, with arylpiperazines (5-HT_{1A} receptor ligands).



74, R = H; Ar = quinolyl
75, R = H; Ar = indolyl
76, R = F; Ar = quinolyl
77, R = F; Ar = indolyl
78, R = H; Ar = methoxyphenol

Figure 1-27:Dual activity potential antidepressants[77]

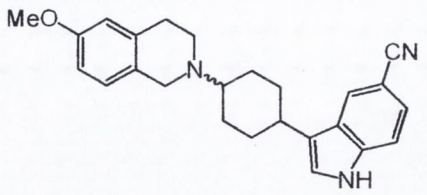
Table 1-10: SERT and 5-HT_{1A} activity data for compounds 74-77

Compd.	Activity (K_i nM)	
	SERT	5-HT_{1A}
74	24.0	6.3
75	4.1	5.5
76	7.5	2.7
77	7.3	5.9

The biological activity data for the compounds **74-77** is listed in Table 1-10. The most active analogues synthesised in this study were found to be: **74** a partial 5-HT_{1A} agonist[#], **75** a 5-HT antagonist, **76** a full 5-HT agonist and **77** a partial 5-HT agonist.[77] **78** was synthesised by the same group,[78] and was tested *in vivo* by Tordera *et al.*[79] Rat body temperature studies, suggested weak presynaptic 5-HT_{1A} activity. Doses in the range (0.01-0.5 mg/kg), partially antagonised the hypothermia induced by 8-OH-DPAT. In the learned helplessness test in rats (animal model for depression), 1-5 mg/kg significantly reduced the number of escape failures.[79]

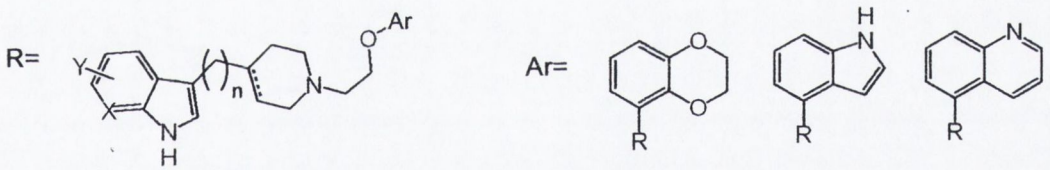
[#] Characterisation at 5-HT_{1A} receptors was carried out by [^{35}S] GTPγS binding assay. The agonist activity of increasing concentration of the compounds was determined by stimulation of [^{35}S] GTPγS binding, whereas the antagonist activity was evaluated by the inhibition of 8-hydroxy-2-(di-*n*-propylamino)tetraline 8-OH-DPAT (a 5-HT_{1A} agonist)-stimulated [^{35}S] GTPγS binding[77].

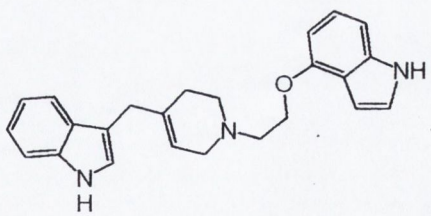
Wyeth-Ayerst has reported several compounds designed as potential dual SERT inhibitors/5-HT_{1A} receptor antagonists Figure 1-28 being a representative example.[80]



79

The most potent dual compound being **79** (K_i (nM) SERT= 8.0, 5-HT_{1A}= 300nM).[80] However, the range of compounds had moderate activity at the α_1 receptor (activities in the range K_i (nM) = 66-300).[80] A later publication yielded the structures of the type illustrated in Figure 1-28.[81] This set of products did not show any activity as 5-HT_{1A} agonists. 5-F substitution at position Y, had a detrimental effect on serotonin reuptake inhibition. Reduction of the double bond led to a reduction in the SERT activity and an increase in 5-HT_{1A} affinity. The most significant structure **80** has following biological activity: 5-HT_{1A} antagonist K_i= 41.2 (nM) and SERT inhibition K_i= 21.6 (nM). Yet again these compounds displayed a significant undesirable activity at the α_1 receptor.[81]





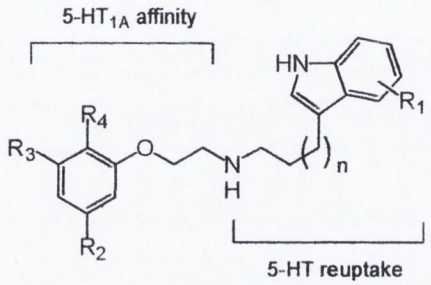
80

Figure 1-28: Wyeth-Ayerst dual compounds[81]

Incorporating a more flexible amine moiety led to a structurally similar set of compounds (Figure. 1-29), with a higher affinity for the 5-HT_{1A} receptor.[82] Even though these compounds had an increased 5-HT_{1A} affinity, a loss in 5-HT_{1A}

antagonism was observed. A key pharmacophoric element of this 5-HT_{1A} antagonistic affinity was found to be in the substitution of a halogen on the ring of the 5-HT_{1A} component of the molecule. In optimising dual activity, it was beneficial to have the following:[81]

- At least one heteroatom in the aryloxy group (*ortho* to the oxyethylamine linkage).
- n = 1 (Figure 1-29)
- A 5-fluoro-3-indolylpropyl group increased 5-HT transporter affinity.
- A halogen meta to the oxyethylamine lowered 5-HT_{1A} intrinsic activity.

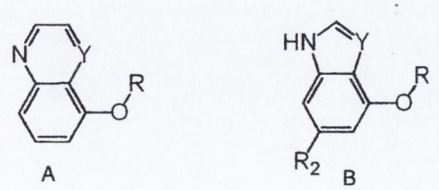


81 R_1=F, R_2=H, R_3=H, R_4=OCH_3, n=1

82 R_1=F, R_2=F, R_3=H, R_4=OCH_3, n=1

Figure 1-29: Dual SERT 5-HT_{1A} affinity[82]

The two compounds depicted in Figure 1-29 were non-selective with α_1-receptor activity in the range K_i= 2.5-300 nM. The most promising of the compounds tested were **81**; having biological activities of: 5-HT_{1A} affinity K_i= 0.48 nM, SERT inhibition K_i= 1.3 nM and **82**, having biological activities of: 5-HT_{1A} affinity K_i= 1.36 nM, SERT inhibition K_i= 35.0 nM. Other related compounds proving to have moderate to high affinity for SERT and 5-HT_{1A}, are those where the aryl group associated with 5-HT_{1A} component of the pharmacophore, was substituted as shown in Figure 1-30. The biological data from the most active dual analogues in this series is presented in Tables 1-11 and 1-12.



83-87

Figure 1-30: Aryl substitutions[82]

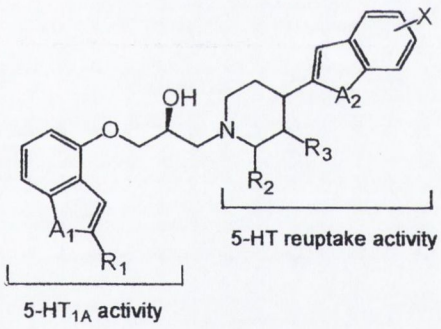
Table 1-11: Most active compounds of substitution pattern A (Figure 1-30)

Aromatic A (Figure 1-30)					
Compd	X	Y	R_1	5-HT_{1A} K_i (nM)	SERT K_i (nM)
83	N	C	F	1.10	35.5
84	N	N	F	1.20	9.8

Table 1-12: Most active compounds of substitution pattern B

Aromatic B (Figure 1-30)						
Compd	Y	R_1	n	R_2	5-HT_{1A} K_i (nM)	SERT K_i (nM)
85	N	H	1	H	0.87	15.5
86	N	H	1	F	0.69	0.39
87	N	Cl	1	F	10.7	0.39

Eli Lilly have been developing a similar series of analogues, based on the skeleton structure of Figure 1-31, with affinity for both the SERT protein, combined with a moderate to high affinity as an antagonist for the 5-HT_{1A} receptor.[83-86]



88 A_1=N, A_2=S, R_1,R_2,R_3=H,X=4-OMe

89 A_1=N, A_2=S, R_1,R_3=H,R_2=(*S*)Me,X=4-OMe

90 A_1=N, A_2=S, R_1,R_3=H,R_2=(*S*)Me,X=$_6$F

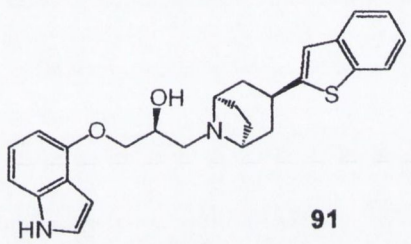
Figure 1-31: Dual SSRI/5-HT_{1A} activity[87]

In the first report from the group, substitution at the 4-position of the benzothiophene ring (when A_2= S) was preferred. Larger substituents, such as isopropoxy and hydroxy substitution, led to a loss in biological activity, especially of SERT reuptake inhibition. Dual substitution was also detrimental to biological affinity when compared to the first high affinity analogue **88** (K_i=1.89nM at the 5-HT_{1A} receptor and 12.63nM at 5-HT reuptake sites).[85]

The most balanced dual action compound based on the general structure reported in the study of piperidine substitution was **89** Figure 1-31, having with 5-HT_{1A} K_i=3.09nM and SERT K_i=0.51nM. Another highly promising compound was **90** with

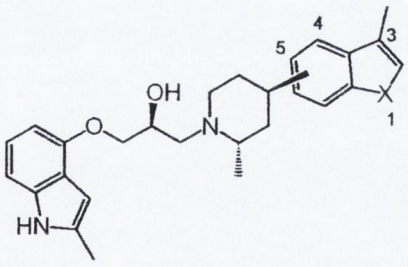
the following activities; 5-HT_{1A} K_i=5.52nM and SERT K_i=0.31nM.[84] It was also found that substitution at the indole ring (when A_1=O) and the piperidine ring (which were potential metabolic sites) lead to an increase in binding affinity at both 5-HT_{1A} and SERT binding sites.[83] Overall dual activity was enhanced with A_1=N rather than A_1=O.

Takeuchi *et al* published a report,[84] where substitution at the piperidine ring was studied. It was remarked, the importance of conformational bias at the receptor site. The X-substituent (Figure 1-31) was most active as a hydrogen or fluorine group at position 6. Substitutions on the piperidine ring lead to the discovery of compound **91**, which was an extremely potent SERT inhibitor and a modest 5-HT_{1A} antagonist. (5-HT_{1A} K_i=30.54nM and SERT K_i=0.07nM).



91

When studying the effect of connectivity at the benzothiophen ring, it was reported that substitution at position 4 and 5, resulted in excellent dual activities (Figure 1-32).[86]



92, X = S, connectivity at 4

93, X = S, connectivity at 5

94, X = O, connectivity at 4

Figure 1-32: Study of connectivity in the series[86]

Compounds **92-94** (Figure 1-32), when substituted at position 4 or 5 had the following activity values: 5-HT_{1A} K_i=1.82 nM and SERT K_i=4.35 nM (for position-4 **92** substitution) and 5-HT_{1A} K_i=1.43 nM and SERT K_i=0.30 nM (for position-5 **93** substitution). Replacement of the benzothiophen ring with an indole ring and having the substitution at postion-5 gave **94**, which had binding affinities of 5-HT_{1A} K_i=1.39 nM and SERT K_i=1.69 nM.[86]

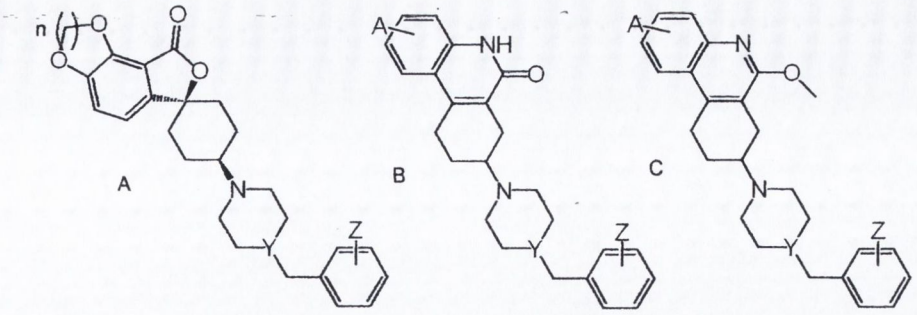


Figure 1-33: Ligand conformation affects Dual SERT/5-HT_{1A} activity[88]

Table 1-13: Activities of compounds 95-101 Figure 1-34[88]

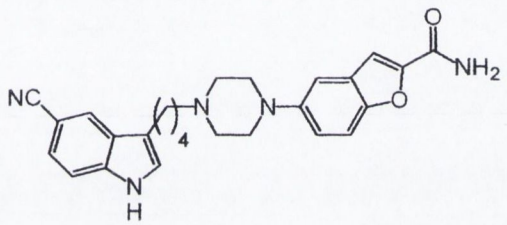
Comp	Structure	n	X	Z	SERT IC_{50}(nM)	5-HT_{1A} IC_{50}(nM)
95	A	1	N	2-I	48	18
96	A	2	N	2-I	54	9.6
97	A	1	CH	2-Br	45	9.6
98	A	2	CH	2-Br	73	9.8
99	A	2	CH	3-OCH_3	59	4.3
100	B	1	CH	2,5-di-F	5.0	440
101	C	1	CH	2,5-di-F	14	450

To gain insight into the structured requirements for dual SERT 5-HT activity, a conformational study of various potent ligands synthesised by BristolMyers-Squibb (Figure 1-33) was carried out.[88] It was hypothesised that the angle formed between the dialkoxyphenyl group and the cyclohexane ring, was a key determininant of dual affinity for SERT and 5-HT_{1A}. To test this idea, compounds of the type illustrated in Figure 1-34, which form differing angles between the groups mentioned were synthesised. In series A the angle is close to 90° (between the aryl ring and the spirolactone) and in series B the aryl and cyclohexene ring are nearly planar. Compounds of the type C tested the importance of the lactam functional group for dual activity.[88] The range of activities exhibited by these compounds is summarised in Table 1-13.

By manipulating the global conformation of these serotonin modulators, two series of compounds were produced. Structures A, for example **95,** gave a balance of nanomolar 5-HT_{1A} (antagonist) and SERT (antagonist) activities, achieved by fixing the aryl ring in a perpendicular orientation *via* a spirolactone. The SSRI activity was

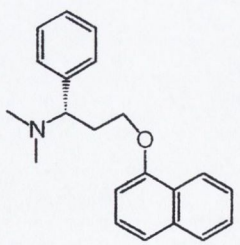
improved at the expense of 5-HT_{1A} activity upon rotation of the aryl ring to an orthogonal planar conformation. By manipulating the topology of the ligand *via* conformational constraint, potent, dual antagonists at the 5-HT_{1A} and SERT receptors were obtained.[88]

Vilazodone **102** was discovered by Merck and developed with Glaxo-SmithKline. Its mode of action was found to be as a SERT inhibitor with dual activity as a 5-HT_{1A} agonist. It was shown to augment extracellular 5-HT levels in rat forebrain regions to a greater extent than fluoxetine **10**.[89] However, promising as early results were, the compound never reached phase II clinical trials.[90] One of the major metabolites of vilazodone **102** is the hydroxylation at position 3 of the indole ring (*ortho* to the cyano group), which lead to a significant decrease in the dual activity of the parent compound.[91]



102

Dapoxetine **103**, was originally developed by Eli Lilly, as an antidepressant with dual activity as both an SSRI and 5-HT_{1A} antagonist. No specific data on the 5-HT antagonism have been released. However, PPT have recently bought the patent from Eli Lilly and are currently in phase III of clinical trials with the hope of marketing the compound, as a treatment for premature ejaculation.[92]



103

Matzen *et al* used a similar approach of combining moieties, in an attempt to find a lead compound with affinity for both SERT and 5-$HT_{1B/1D}$ receptors.[87] The reuptake section of the compound was taken from the compound indalpine **32** and the 5-$HT_{1B/1D}$ fragment was derived from known agonists of those receptors to yield potentially dual acting ligands of the type presented in Figure 1-34.

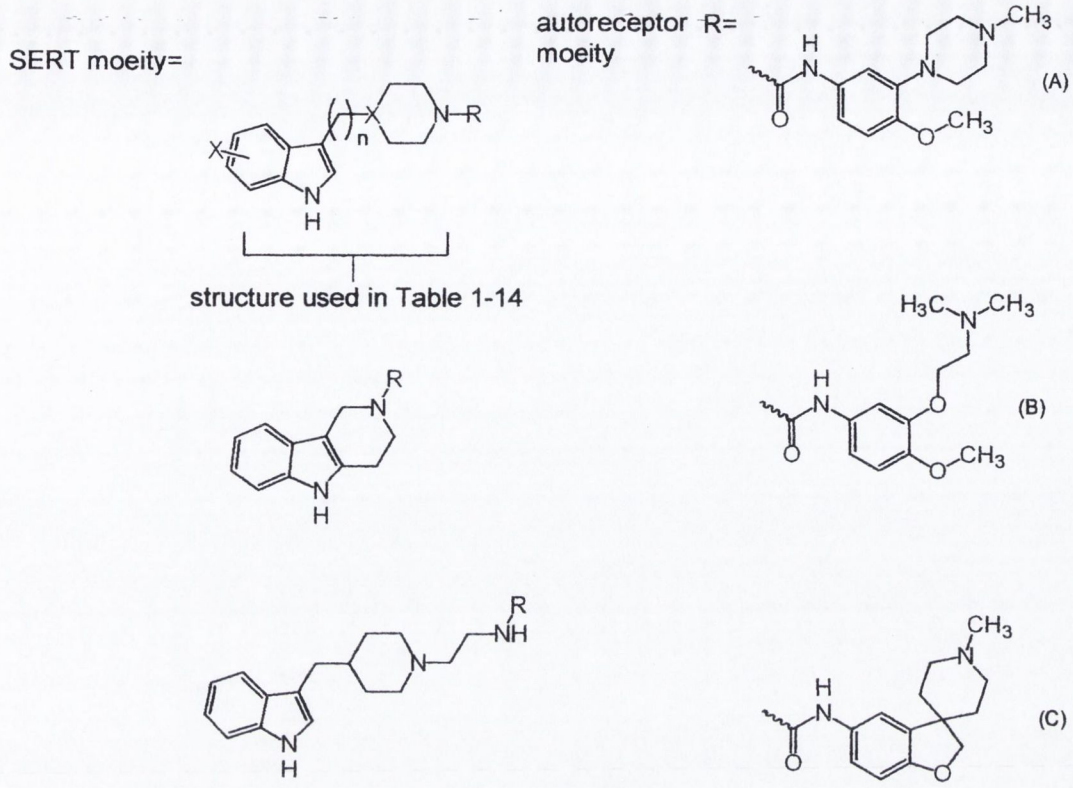


Figure 1-34: Dual SERT/5-$HT_{1B/1D}$ receptor study[87]

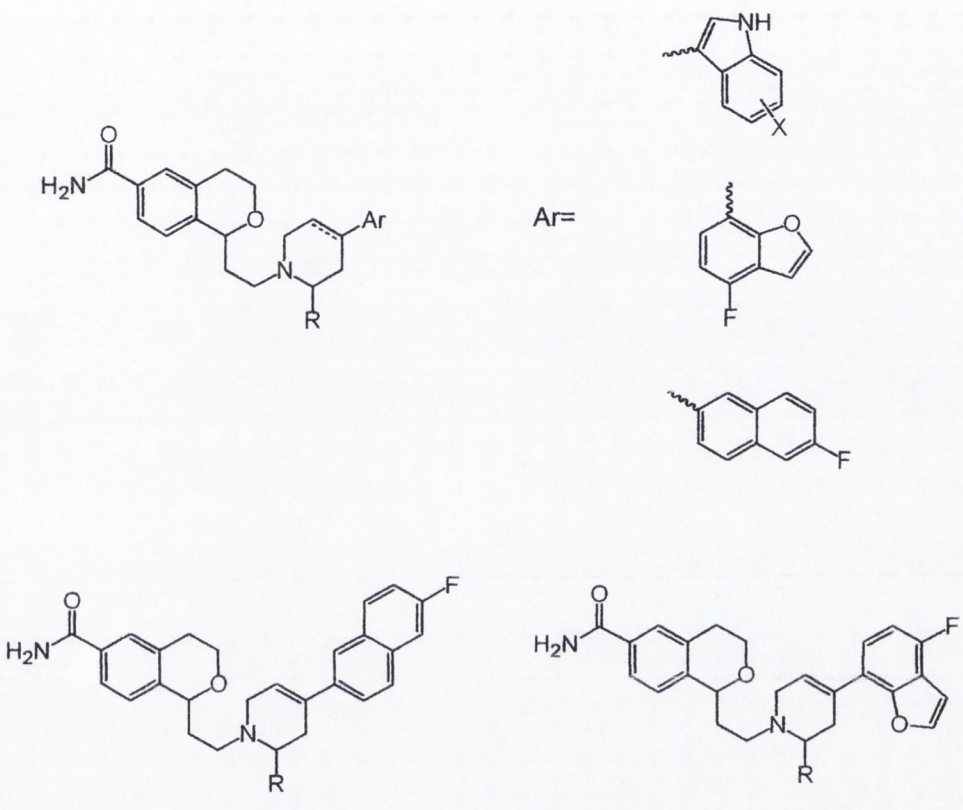
Table 1-14: Biological activity at SERT, 5-HT_{1A} and 5-HT_{1B} receptors

Comp	Structure			Activity IC_{50} nM		
	n	X	R	SERT	5-HT_{1B}	5-HT_{1A}
104#	1	5-F	A	-	50	65
105	4	4-F	A	0.7	77	50
106	0	4-F	B	-	23	0.2

Figure 1-34 is a representative example of the compounds synthesised. From the biological data it was concluded that coupling of certain indole moieties to the anilines, resulted in some cases to an increase and in others a decrease in reuptake inhibition, meaning the 5-HT reuptake inhibitory activity is not only due to the indole part of the molecule but is also modulated by the aniline moiety.[87] None of the compounds had outstanding dual receptor/reuptake inhibitory activity. The most promising being **104**, **105** and **106** the biological activities for which are reported in Table 1-14.[87]

The piperidine ring is replaced with a piperazine ring for **104**

Eli Lilly have recently published work on lead structures with dual activity at both SERT and 5-HT_{1D} receptors.[93] The study involved combining the structure of a known 5-HT_{1D} antagonist with an SSRI. Compounds of the type given in Figure 1-35, were synthesised and tested as dual action potential antidepressants.



107 **108**

Figure 1-35: Dual SSRI/5-HT_{1D} Antagonists[93]

With the aryl group set as the indole derivative, the series exhibited potent SERT antagonists with K_i 0.76-3.50 (nM) and were antagonists of the 5-HT_{1D} receptor in the range K_i 5.4-130 (nM). Unfortunately selectivity was poor with K_i for both D_2 and α_1 receptors with K_i in the range 2.1-224 (nM). To circumvent this lack of selectivity the authors used the naphtyl and benzofuryl aryl groups and replaced the piperidine ring with a piperizine moiety. Presented in Table 1-15 are the activities of the most active analogues from the study.[93]

Table 1-15: Dual SSRI/5-HT_{1D} Antagonists[#][93]

Compd	Aryl	5-HT_{1D}	5-HT_{1B}	SSRI	α_1	D_2
107	5-F-Naphtyl	71	>1000	2.2	36	491
108	4-F-Benzofuran	27	19%@50nM	1.9	31	52

Several of the side effects associated with SSRIs, have been attributed to non-selective binding at post-synaptic 5-HT_{2A} receptors.[38, 41] With this in mind, some compounds have been proposed as potential antidepressants, with dual activity at SERT and antagonistically at the 5-HT_{2A} receptor. Compound LY367265 **109** developed by Eli Lilly displayed an affinity for SERT and 5-HT_{2A} (K_i = 2.3 (nM) for SERT and 0.81 (nM) for 5-HT_{2A}).[94] Nefazodone **110** by BristolMyers-Squibb, has been reported as having a similar mode of action with an improved side effect profile.[90] Yamanouchi have developed YM-35992 **111** (Figure 1-36) as an antidepressant with SERT/5-HT_{2A} affinity K_i = 21 (nM) SERT and K_i = 86 (nM) 5-HT_{2A}. YM-35992 **111** is also highly selective.[95]

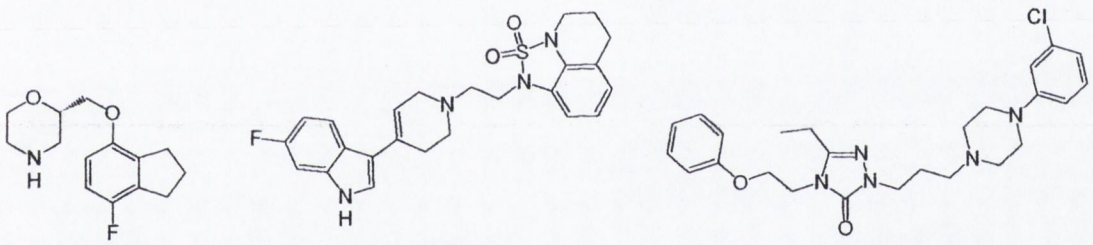
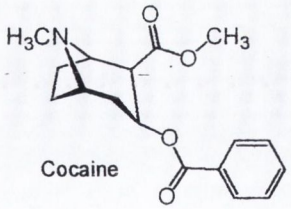


Figure 1-36: SERT and 5-HT_{2A} affinity

1.3.4.2 Structures with dual SERT + DAT affinity

Cocaine **111** Figure 1-37 is a well known CNS stimulant and drug of abuse. While it's mode of action is primarily as a monoamine transport inhibitor, it is also active at cholinergic, muscarinic and σ receptors and sodium channels.[96] It's affinity for the dopamine transporter is significantly greater than the SERT protein. Several groups have made structural alterations to the cocaine backbone, producing predominantly dual DAT/SERT inhibitors. The most potent SERT inhibiting compounds are summarised in **111-123** Table 1-16.

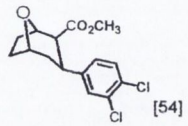
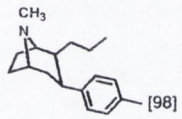
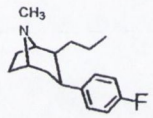
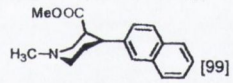
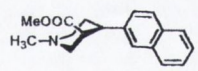
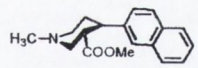
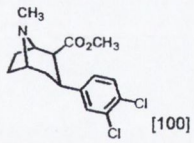
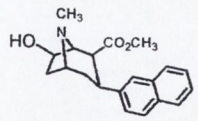
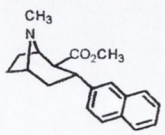
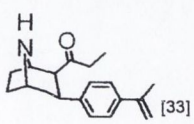
[#] Activities reported as K_i in (nM)

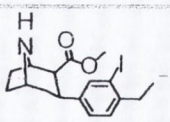
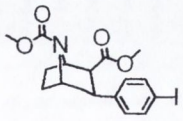


Cocaine **111**

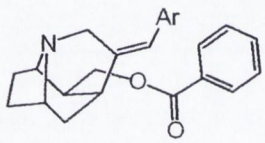
Figure 1-37: Cocaine

Table 1-16: Summary of the most potent cocaine analogues at SERT (activity of 134-136 are reported as K_i (nM)

	Structure	IC_{50} (nM)		
		DAT	SERT	NAT
111	Cocaine[97]	266	737	3530
112	 [54]	71	39.1	-
113	 [98]	1.19	11.3	-
114		2.16	23.7	-
115	 [99]	23	8.2	-
116		94	209	-
117		293	13	-
118	 [100]	1.09	2.47	-
119		1.26	5.57	-
120		0.57	5.95	-
121	 [33]	16	0.11	94

122		329	0.69	148
123		11.9	0.81	29.1

This class of compound have been proposed as potential treatments for addiction therapy.[96] From these studies has come a structurally unique cocaine analogue. The compounds (shown in Figure 1-38) are some of the most potent and selective SERT inhibitors ever reported. Their development was as an adjunct, to compounds targeting the serotonergic system in the treatment of cocaine addiction.[101]



124-126

Figure 1-38: Highly selective and potent SERT inhibitor[101]

Table 1-17: Activity data for highly selective and potent strained cocaine analogues

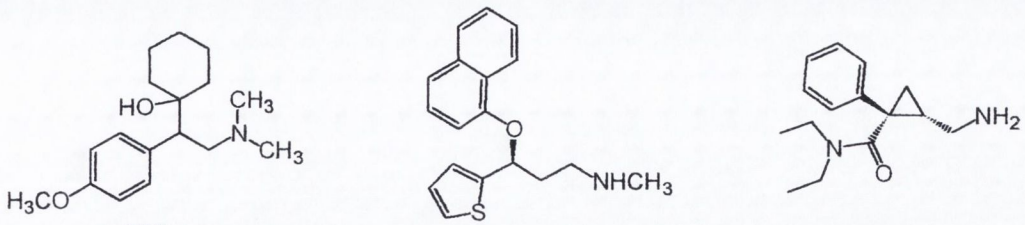
Compd.	Ar	K_i (nM)		
		DAT	SERT	NAT
124	2-Naphthyl	5530	0.1	3220
125	4-Iodophenyl	>10,000	0.1	8190
126	3-Cl-4-I-Phenyl	>10,000	0.06	>10,000

This range of compound is highly rigidified cocaine analogues. Yet, the structures listed in Table 1-15 have absolutely no affinity for the dopamine transporter, unlike the parent molecule[101]. Compound **125** in particular shows extraordinary selectivity and potency for the SERT protein.

1.3.4.3 Dual SERT + NAT inhibitors (SNRI)

Entities acting as dual noradrenaline and serotonin reuptake inhibitors have some noted advantages over normal SSRIs in that they have a faster onset of action with the same relatively favourable side-effect profile.[102] The antidepressant venlafaxine **126** (Figure 1-39) has been used in the treatment of depression for over ten years.[43] Its beneficial effects are observed after one week of treatment, compared

with two to six weeks for normal SSRIs. Like milnacipran **128** and duloxetine **127**, venlafaxine **126** is a serotonin and noradrenaline reuptake inhibitor.



126 Venlafaxine

127 Duloxetine

128 Milnacipran

Figure 1-39: SNRI antidepressants

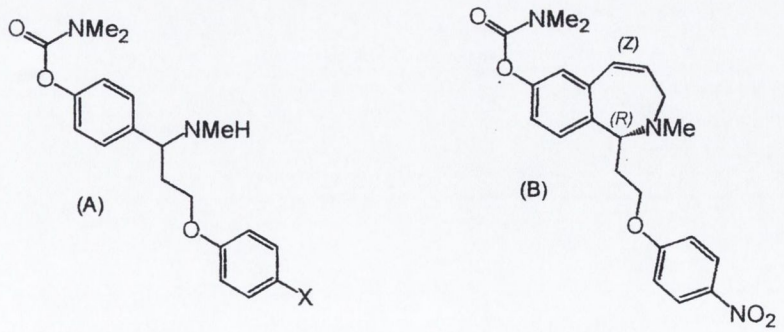
Table 1-18 lists the biological activities of the SNRIs depicted in Figure 1-39.[39]

Table 1-18: SNRI Activities

	Compd	SERT IC_{50} (nM)	NAT IC_{50} (nM)
126	Venlafaxine	210	640
127	Duloxetine	0.53	2.1
128	Milnacipran	203	100

1.3.4.4 Dual SERT/Acetylcholinesterase Inhibitors (**129-134**)

In an attempt to find a drug suitable for easing depression in those suffering from Alzheimer's disease, Sankyo have synthesised a range of compounds (Figure 1-40) active both as an acetylcholinesterase (AChE) inhibitor (to combat Alzheimer's) and a SERT inhibitor (to alleviate depression).[103, 104]



129-134 **135**

Figure 1-40: Dual Acetycholinesterase/SERT inhibitors 143-148

Table 1-19: Dual Acetylcholinesterase/SERT inhibitors[103]

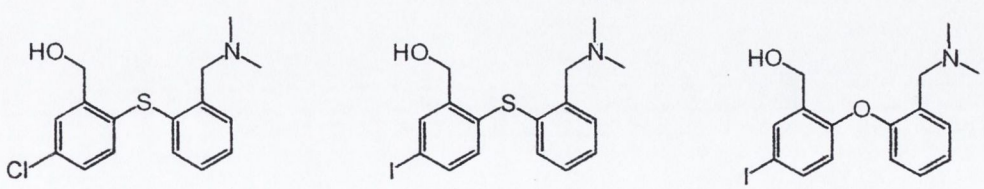
Compd.		X	IC_{50} (nM)	
			AChE	SERT
129	-(rac)	4-NO_2	125	44
130	-(S)	4-NO_2	101	42
131	-(R)	4-NO_2	143	135
132[#]	(*R*)	4-NO_2	221	52
133	-(R)	4-Cl	343	270
134	-(S)	4-Cl	377	83

The fragment relating to SERT activity was taken with reference to the SSRI Fluoxetine **9**; the moiety, hypothetically responsible for AChE activity was taken with reference to the marketed AchE inhibitor donepezil. Table 1-19 summarises the most potent dual inhibitors of the open ring compounds.[103]

The more strained analogues (Figure 1-40 type B) were made in an attempt to increase the potency as an AChE inhibitor. The most active dual compound **135** had the following arrangement: n=2, double bond in place, R= H, dimethyl carbamate substituted at position-6, X= 4-NO_2 with IC_{50} (nM)= 14 (AChE) and 6 (SERT).[104]

1.3.5 SERT Imaging Ligands

To gain an insight into the distribution of the serotonin transporter within the brain a large amount of work has been carried out using several of the structures already mentioned, with weakly radioactive labels such as: ^{11}C, ^{18}F, ^{3}H incorporated. The class of compounds shown in Figure 1-41 are structurally unique entities used in PET (positron emission topography) and SPECT (single photon emission tomography).



403U76 **136** IDAM **137** ODAM **138**

Figure 1-41: SERT radio-ligands

[#] Dimethylcarbamate is substituted from position-3 on the relevant aromatic ring

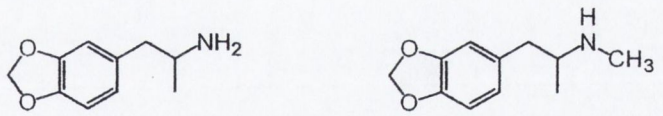
403U76 **136** is an inhibitor of noradrenaline and serotonin uptake with activities of K_i (NAT) 55 nM and K_i (SERT) 2.1 nM[105], [^{123}I]IDAM **137** has high selectivity for SERT with K_i= 0.097 nM [52], [^{125}I]ODAM **138** has inhibitory activity for SERT with K_i=0.12 nM, DAT K_i=3.9 μM and NAT K_i=20.0 nM.[53]

1.4 *Amphetamines*

To avoid prosecution clandestine chemists have tended to make small structural changes to amphetamines with known activity, thereby producing a stimulant that has not been characterised. This keeps them a step ahead of the law and has resulted in an abundance of amphetamine type compounds in the literature. Presented here are some of the more commonly encountered drugs to which, structural enhancement may yield a substance of therapeutic benefit.

1.4.1 Methylenedioxyamphetamine (MDA "Love Drug") and Methylenedioxymethamphetamine (MDMA "Ecstacy")

Methylenedioxyamphetamine **139** (MDA) was first synthesised in 1910 by Mannich and Jacobson. Both MDA **139** and the *N*-methyl analogue methylenedioxymethamphetamine **140** (MDMA) were prepared and patented in 1912 by E. Merck Pharmaceuticals.[106] Originally developed as an appetite suppressant, they never became commercially successful and subsequent to military testing as possible "truth" drugs, further applications of both MDA and MDMA were not investigated until the mid-fifties, when psychiatrists used this class of compounds as a method of lowering the inhibitions of patients.[107]

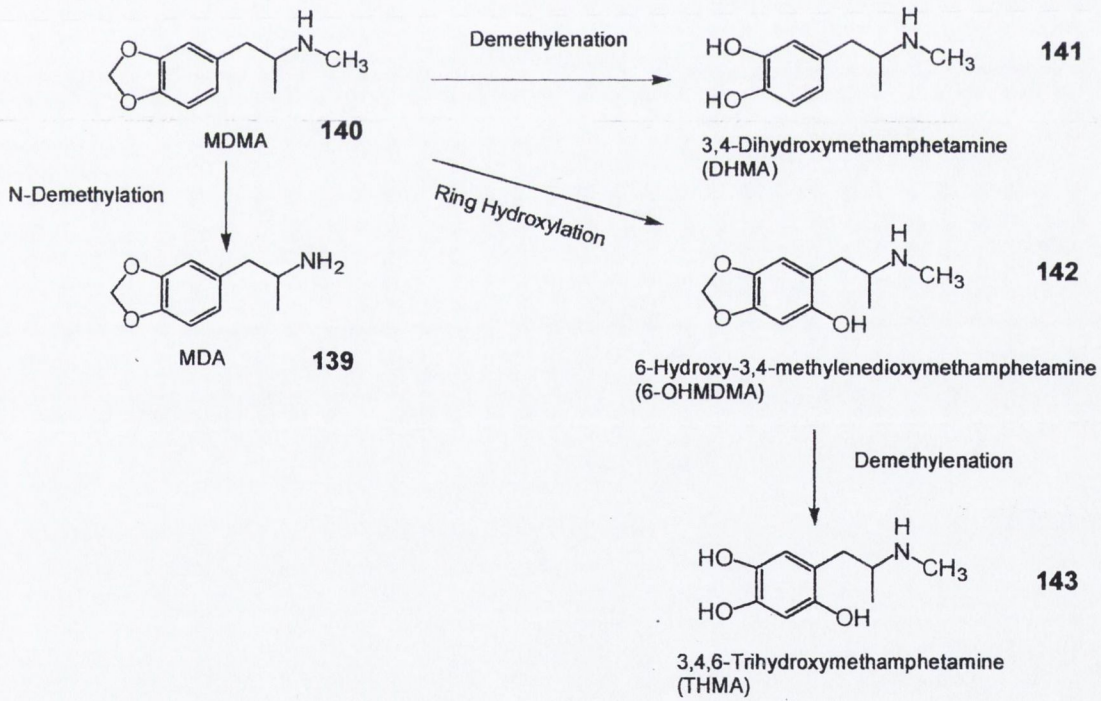


MDA **139** MDMA **140**

Figure 1-42: Methylenedioxyamphetamine and Methylenedioxymethamphetamine (Ecstacy)

In the seventies, from these medically controlled surroundings, MDA **139** rapidly became a popular recreational drug known as "The Love Drug". In the early Eighties MDMA **140** (Ecstasy) became the more commonly abused compound, particularly in Europe. It was made illegal in several countries as concern mounted over its growing misuse and possible neurotoxicity.[108] Adverse reactions to MDMA **140** are constantly being documented. It is known that it can lead to serotonin syndrome,[109] cardiac arrhythmia, severe hyperthermia, renal failure and in certain cases disseminated intravascular coagulation.[110, 111]

For several years the neurotoxicity in primates[112] of MDA **139** and MDMA **140**, especially on 5-HT neural pathways of primates, has been examined.[113, 114] Ricaurte *et al* published the first study reporting the neurotoxic affects of MDMA **140** dosage (similar to that taken by recreational users) on dopaminergic as well as serotonergic neurons,[115] with the dopaminergic toxicity being substantially more acute than that of the serotonergic system. Previous work only showed selective serotonergic toxicity,[111] however the doses administered by Ricaurte *et al,*[115] were more frequent, smaller doses, to mirror that of the club scene where dancers often take three 100 mg doses over four to six hours.[116] One possible reason this dopaminergic neuro-degradation had not previously been observed, may have been due to the temperature dependence of ecstasy-induced neurotoxicity,[117] with smaller more evenly spaced dosages raising core body temperature for a longer period than a once off larger dose. The neurotoxicity of these amphetamines has been attributed to its metabolites, which are shown in Scheme 1-4.[118]



Scheme 1-4: Metabolism of MDMA[118]

THMA **143** is a non-selective neurotoxin to both serotonin and dopamine neurons while DHMA **141** and 6-OHMDMA **142** have little chronic effect.[118]There is however, still debate over its exact neurotoxic activity arising from the complex interactions of amphetamines, with several transporters and receptors.

Chemically MDA **139** and MDMA **140** differ only by the methylation of the amino group, yet this small structural change has a pronounced effect on their pharmacology, as it greatly reduces or abolishes hallucinogenic activity.[119] Shulgin and Shulgin have demonstrated that however similar these compounds may be, it is apparent they exhibit varying modes of action at different receptor sites.[120] MDA **139** and MDMA **140** have three main modes of action, predominantly on the 5-HT neural pathways. They are as follows:[121]

1) Although MDA and MDMA are not powerful MAOIs they have been shown to act predominantly on MAO type A. The IC_{50} for MDMA on MAO-A has been calculated as 44 μM while for MAO-B it is 370 μM.[122] The IC_{50} values for MDA on MAO A and B are 9.3 μM and >100 μM respectively.[123]

2) MDMA **140** has been shown to bind antagonistically to the serotonin transporter thereby increasing the concentration of 5-HT in the synaptic cleft creating a stimulus response. *In-vitro* using radiolabeled imipramine (standardised SERT agonist), Rudnick and Wall[18] studied the agonistic binding of (*R*) and (*S*) MDMA to the SERT protein, concluding an initial rate of serotonin uptake is inhibited by >60% at 1 μM (S)-MDMA. The (*R*)-isomer is less potent in this case with <10% inhibition at 1 μM. The IC_{50} values for the inhibition of ^{3}H-serotonin reuptake for MDMA and MDA have been proven to be 425 nM and 478 nM respectively.[123]

3) CNS nerve terminals contain 'reservoirs' of neurotransmitter stores in vesicles. Its release from these stores depends on the influx of Ca^{2+} ions, which increase in concentration, in response to a depolarisation of the nerve terminal. This allows the migration of the vesicles to the pre-synaptic membrane and release of the vesicular 5-HT into the synaptic cleft. Schmidt *et al*have shown MDMA to induce monoamine release, 5-HT in particular *via* the Ca^{2+} independent process.[124] Studies by McKenna *et al*have compared the effect of MDA and its analogues on release of ^{3}H-5-HT from rat brain synapsomes.[125] (*R*)-MDA releasing 190% of basal ^{3}H-monoamine at a concentration of 1 μM. The values for (S)-MDA, (R)-MDMA and (S)-MDMA are 180%, 185% and 170% respectively.

The hallucinogenic nature of these amphetamines can be traced to the (*R*)-stereoisomer interacting agonistically with post-synaptic 5-HT receptors, where as the anti-depressant response results from the described pre-synaptic activity of the (S)-form. MDA can also act on dopaminergic pathways with the (*S*)-isomer being the more effective inhibitor of synapsomomal [^{3}H] dopamine, where as the (*R*)-isomers were virtually devoid of activity,[107] MDMA has greater selectivity in this regard, although is not devoid of activity at dopaminergic receptors. Generally ring substitution at postions 2 and 5 result in hallucinogenic compounds. Examples (4-Methyl-2,5-dimethoxyamphetamine **144** "DOM" and 2,5-dimethoxyamphetamine **145** "DMA") given in Figure 1-43.[106, 120]

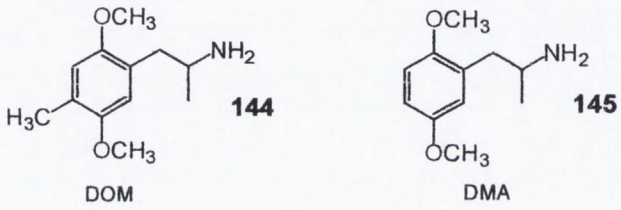


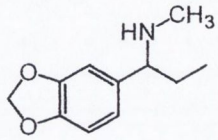
Figure 1-43: Hallucinogenic amphetamines

With an explosive surge in amphetamine abuse predicted in the far-eastern region, primarily resulting from the extensive availability of the botanical starting material ephidrine,[126]a thorough knowledge of the potential pharmacophore is required to predict the various "designer drugs" of the future and prepare comprehensive legislation in advance of the clandestine chemists, whose subtle structural changes can ensure they stay free from prosecution.

1.4.2 1-Phenylpropylamines (1-PEA)

Since 1993 several seizures of 1-phenylpropylamine type stimulants (1-PEA) **146** (Figure 1-44) have been made in Europe. It was originally believed these substances were produced in error as they were often present as mixtures with MDMA **140** and caffeine, however this is no longer thought to be the case. Analytical methods have been developed for 1-PEA analysis.[127-130] Very little is known regarding the toxicity of 1-PEA type compounds relative to that of amphetamine. The few drugs based on the 1-PEA skeleton fall into various therapeutic categories, none of which are widespread or have obvious potential for abuse.[131]

The 1-phenylpropylamine compound shown in Figure 4 is reported to have MDMA like effects in humans at doses up to 140 mg with a duration of action of three hours for the free amine and six hours for the *N*-Methyl analogue.[120] Very little is known about the pharmacology of these drugs. Were they to be potent CNS stimulants, devoid of any hallucinogenic side effects then a range of compounds, based on the backbone (Figure 1-44), could be of significant therapeutic value.

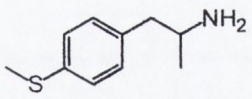


146

Figure 1-44: (N-Methyl)-1-phenylpropylamine

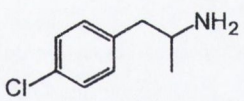
1.4.3 4-Methylthioamphetamine (4-MTA "Flatliner")

4-Methylthioamphetamine **147**, first synthesised in 1963 and studied as a possible appetite suppressant,[132] is an interesting amphetamine in that it acts as a selective serotonin-releasing agent.[133] In comparable tests with 4-chloroamphetamine **148**, it was two times more potent at inhibiting [^{3}H]-serotonin reuptake (IC_{50} (nM) 74) and seven and ten times less potent at inhibiting the uptake of [^{3}H]-dopamine (IC_{50} (nM) 3073) and [^{3}H]-noradrenaline (IC_{50} (nM) 2375), respectively (Figure 1-45).[133]



4-Methylthioamphetamine

147



4-Chloroamphetamine

148

Figure 1-45: 4-MTA and PCA

4-MTA **147** is an inhibitor of serotonin reuptake as distinguished to a serotonin releasing agent.[134] It is not neurotoxic,[106, 133, 134] although several deaths have been reported from its abuse in the dance culture in Britain and Europe.[135] It is thought that because it may often be sold as ecstasy and as 4-MTA **147** has a slower onset of action than MDMA **140**, many related deaths result-abusers believing the tablet to be inactive, take several doses before the affects of the first tablet are realised.[136] The fact that 4-MTA **147** is not neurotoxic and is relatively selective as a SERT inhibitor, makes it a potential starting point for the development of potential SSRIs.[137]

1.5 Conclusions

From dual acting compounds and TCAs to the SSRIs and amphetamines, the structural diversity of compounds with notable affinity for the serotonin transporter protein, is truly remarkable. The site directed mutagenisis and species scanning mutagenisis studies indicate the presence of two binding sites within SERT, yet much of the pharmacophores constructed, were on the assumption that SSRIs and TCAs bind in the one active site. Many of the early antidepressants were discovered by chance. However, with the emergance of more realistic SERT models and the crystal structures of certain transporters being published, the design of future antidepressants will become much less serendipitous. With the prevalence of so many side effects and the slow onset of action of several prescribed antidepressants, it is clear that the so called "magic bullet" for depression has yet to be realised. With this in mind, there remains scope for the continual improvement of current therapies.

1.6 Aims of this thesis

The aims of this thesis were as follows:

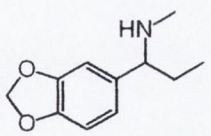
- Develop a range of 1-PEA **146** analogues, optimising synthetic routes to the relevant intermediates, with subsequent substitution at the less explored 6-position of the aromatic ring.
- Stereoselectively synthesise the enantiomers of **146** and the primary amine analogue.
- Explore a novel synthetic route for the stereoselective synthesis of MDA **139** and MDMA **140**.
- Synthesise a range of compounds based on 4-MTA **147**, with various thio substitutions.
- Design and synthesise (investigating stereoselectivity) a range of novel potential SSRIs, based on the 1,2,3,4-tetrahydroisoquinoline scaffold.
- Biochemical screening of all final products produced using cell based expressed SERT.

2. Chapter Two: Studies in the Synthesis of (1)-Phenylpropylamines

2.1 *Introduction*

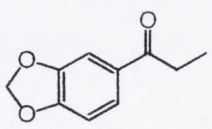
1-Benzo[1,3]dioxol-5-yl-propylamine, the primary amino analogue of (1-benzo[1,3]dioxol-5-yl-propy)-methyl-amine **149** (Figure 2-1), was first reported in 1914 by Merck,[138] however no pharmacological data exists on this type of compound. The publication by King *et al* of the emergence of these compounds in an illicit setting has been the only report from a biological perspective of compounds of the type **149**. With this in mind, it was considered of interest to investigate the chemistry of these compounds and their possible pharmacological properties. For internal consistency in this thesis, the structural names for the remainder of this chapter have been generated using the Beilstein autonom naming system. The objectives in this section of the current study were as follows:

- To develop a high yielding synthetic route to 1-benzo[1,3]dioxol-5-yl-propylamine **149** *via* the major ketone intermediate **150**.
- To produce a set of structured analogues based on substitution at the nitrogen.
- To explore the synthesis of various derivatives gained by substitution at postion-6 of the aromatic ring of **149.**



149

(1-Benzo[1,3]dioxol-5-yl-propyl)-methyl-amine



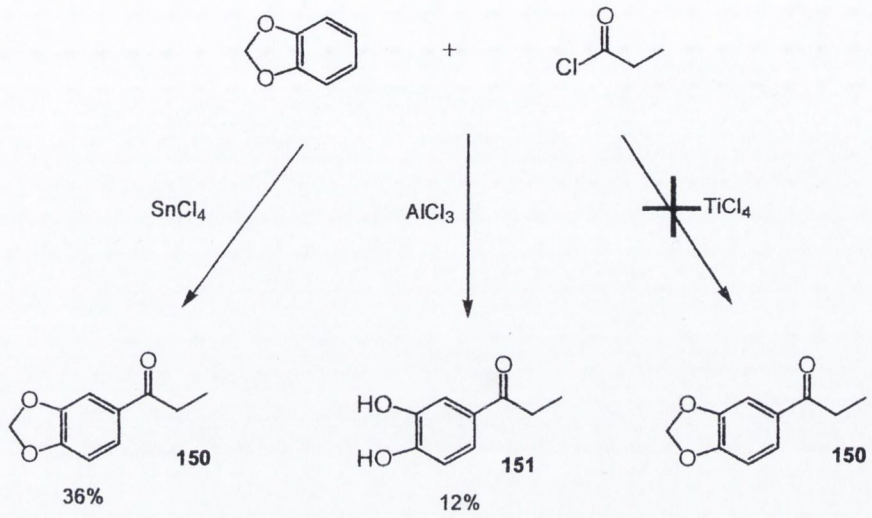
150

1-Benzo[1,3]dioxol-5-yl-propan-1-one

Figure 2-1: Target compound 149 and its key intermediate 150

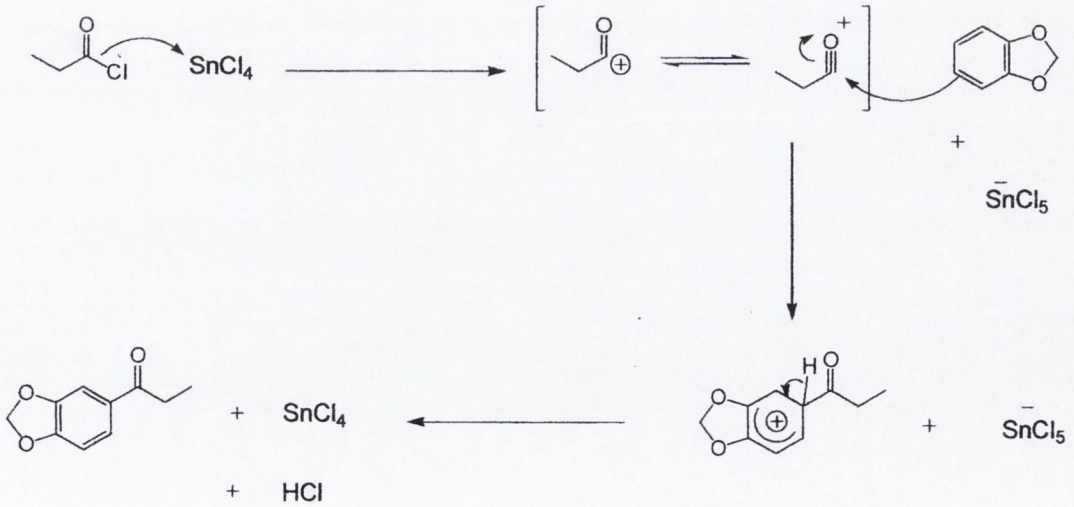
2.2 *Synthesis of Target 1-Phenylpropylamines* via *the intermediate ketone*

The first route investigated, in attempting to synthesise the carbonyl intermediate **150**, was by the direct Friedel-Crafts acylation of 1,3-benzodioxole, **151** Scheme 2-1.



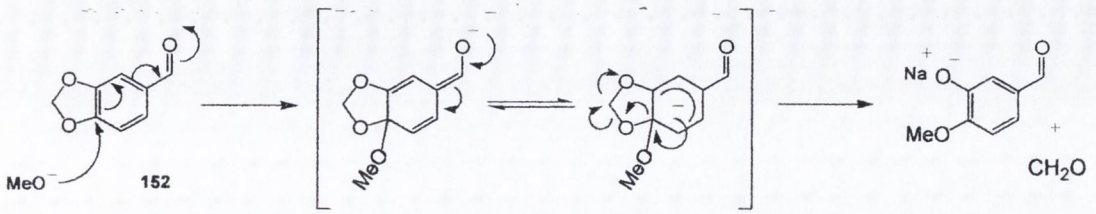
Scheme 2-1: Friedel-Crafts acylation of 151

Although $AlCl_3$ and $TiCl_4$ are stronger Lewis acids than $SnCl_4$, when used in the Friedel-Crafts acylation (the mechanism of which is given in Scheme 2-2), they were found to cleave the dioxole ring. Dioxole rings are known to be cleaved in the presence of strong bases such as sodium alkoxides in DMSO.[139, 140]



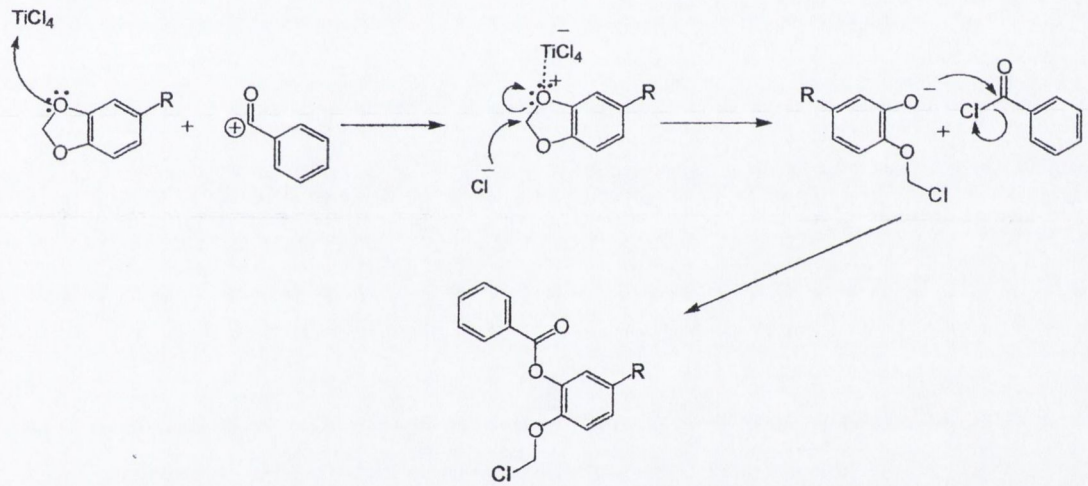
Scheme 2-2: Friedel-Crafts acylation[141]

The base induced cleavage of the dioxole ring in piperonal **152** is described in Scheme 2-3.[140]



Scheme 2-3: Base cleavage of the dioxole ring in piperonal 152[140]

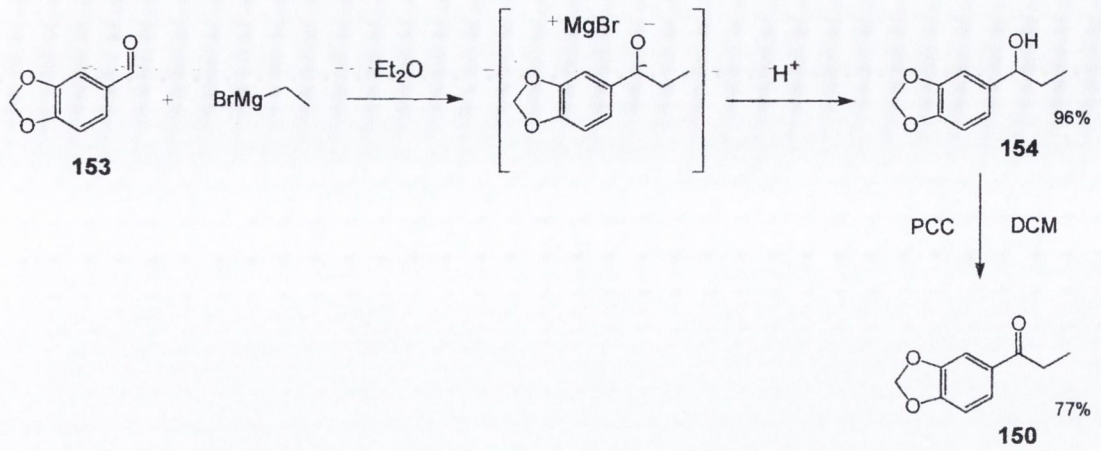
The cleavage of cyclic ethers using Lewis acids has been documented.[142-145] This results from the strong complexation of Lewis acids, such as titanium tetrachloride, with aryl ethers. One of the expected products from any dioxole ring cleavage of in the acylation described in Scheme 2-2 could be predicted as occurring *via* the mechanism illustrated in Scheme 2-4.[144]



Scheme 2-4: Predicted ether cleavage

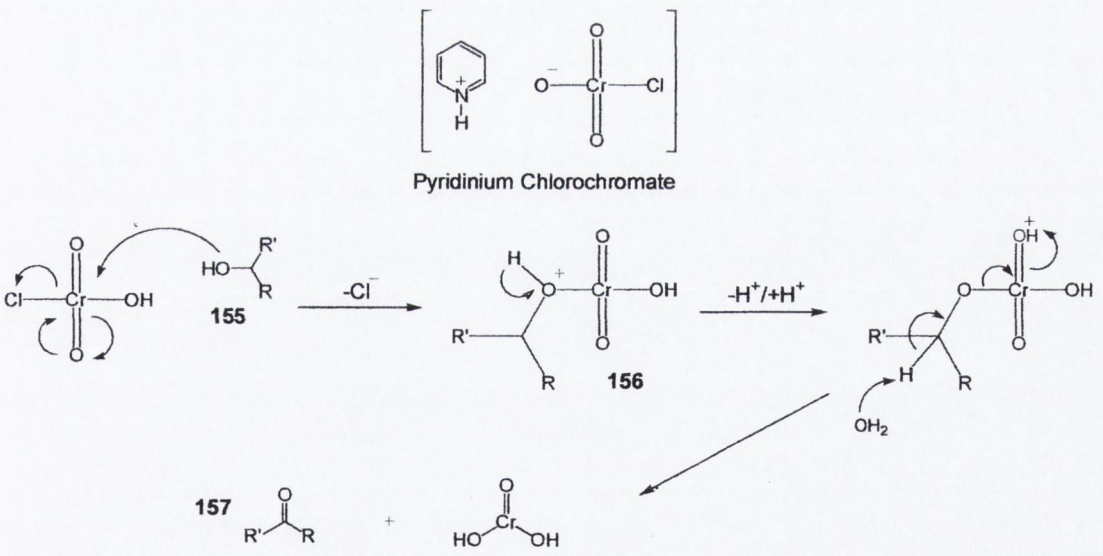
Vicario *et al* have reported the cleavage of a dioxole ring in Friedel-Crafts acylation, stipulating the need for $SnCl_4$ in place of the more commonly used Lewis acids such as $AlCl_3$.[145] As expected, the dioxole ring in **152** was cleaved when $AlCl_3$ was used as the Lewis acid. No product was gained from the $TiCl_4$ reaction. By using $SnCl_4$, the carbonyl product **150** was isolated in 46% yield (Scheme 2-1).

The second route to be examined was the Grignard alkylation of piperonal **153** to the alcohol **154**, followed by PCC oxidation (Scheme 2-5) to yield the target carbonyl intermediate **150**. Although this was a two step synthesis, the over all yield (72%) deemed it to be more practical than the direct acylation.



Scheme 2-5: Most efficient route to ketone 150

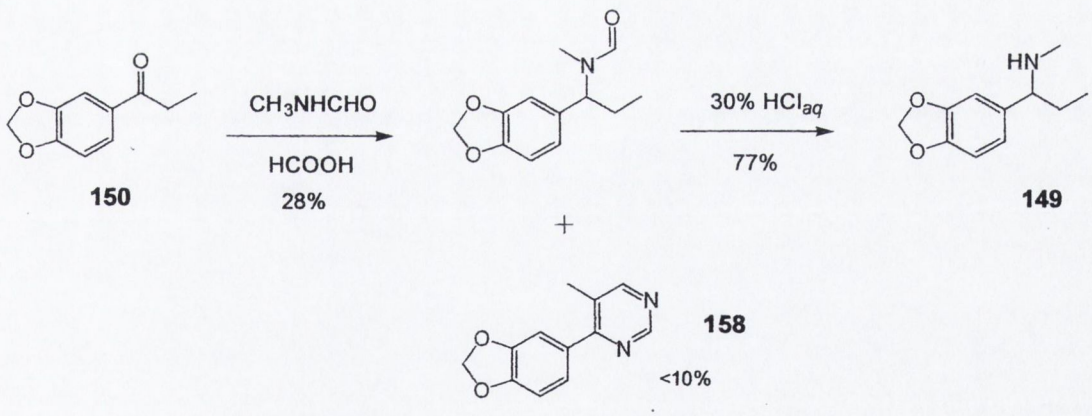
The mechanism for the PCC oxidation of 2° alcohols to ketones is described in Scheme 2-6. Attack from the alcohol **154** yields the chromate ester **155**. Following proton transfer from the alcohol, the α-proton is removed, allowing for formation of the ketone **150**. The chromium metal atom is reduced from Cr (VI) to Cr (IV), with the net result being the oxidation of the alcohol **154** to the desired ketone **150**. The Cr IV) degrades further to Cr (III). [146]



Scheme 2-6: PCC oxidation of 2°alcohols

The key carbonyl intermediate **150,** in the synthesis of 1-Benzo[1,3]dioxol-5-yl-propylamine, was characterised by NMR, IR and melting point. There was a strong band in the IR spectrum at 1673 and 1252 cm^{-1}, which correspond to a C=O and a C-O respectively. The ^1H NMR displayed a triplet (J = 7.5 Hz) integrating for three protons at 1.23 ppm, this along with the quartet (J = 7.5 Hz) integrating for two

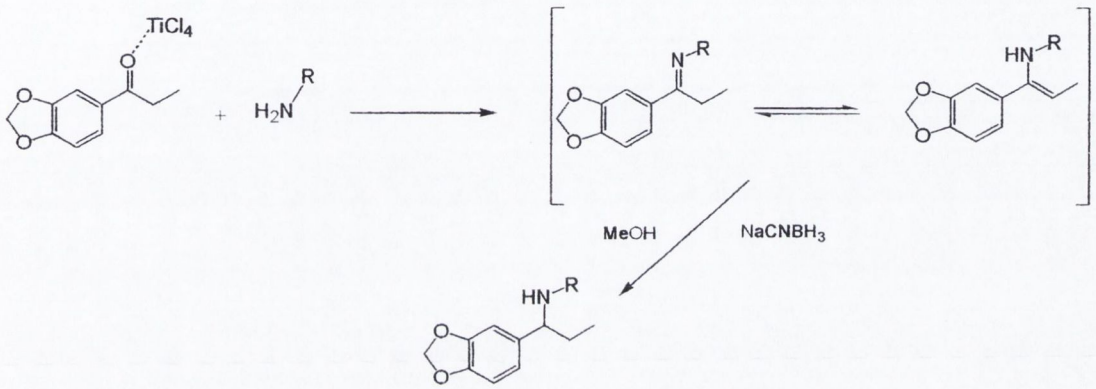
protons at 2.93 ppm, indicate the presence of slightly deshielded ethyl group. A singlet at 6.05 ppm representing two protons, is a characteristic signal of the dioxole group. The aromatic region of the ^{1}H NMR spectrum has patterns integrating for three protons. The splitting of these signals is indicative of an *amx* substitution pattern. At 6.85 ppm is a doublet with a coupling of 8.0 Hz (*ortho* coupling), at 7.46 ppm resides a doublet coupled at 1.2 Hz (*meta* coupling) and at 7.58 there exists a double doublet, with J_o = 8.0 Hz and J_m = 1.2 Hz. Most notable in the ^{13}C NMR spectra was the quaternary peak at 198.88 ppm, corresponding to the C=O. The Dept 135 experiment, revealed the compound to have two CH_2 peaks at 31.52 and 101.74 ppm representing the ethyl CH_2 and that of the dioxole group respectively. One CH_3 signal appears at 8.46 ppm and the three aromatic CH carbons resonate at 107.82, 107.89 and 124.05 ppm. Three aromatic quaternary carbon signals occur at 131.88, 148.14 and 151.54 ppm. The melting point of 37-38°C is comparable to the literature value of 36 - 39°C. The next step in the synthesis of the target amine **149**, was the introduction of an amino group at carbon one of the propylene chain. Previous studies within the group found that direct reductive amination of the ketone **150** was unsuccessful, perhaps on account of the steric hindrance from the aromatic ring.[147] A successful synthesis of **149** was achieved *via* the Leuckart-Wallach formylation, followed by acid hydrolysis of the N-formyl shown in Scheme 2-7.[147]



Scheme 2-7: Leuckart synthesis of amine 149

The Leuckart amination was not very efficient yielding a high number of impurities, one isolated being the pyrimidine **158**, a typical side product that forms in the Leuckart synthesis of amphetamines[147] was partially characterised by NMR. A one step reaction with better yields was required. In a paper published by Barney *et al*, stericly hindered amines were synthesised in one step from the corresponding ketones by using a reductive amination type reaction catalysed by Ti(IV)Cl (Scheme

2-8).[148] The Lewis acid can act catalytically to polarise the carbonyl bond, which allows for attack from the nucleophilic amine to furnish the imine/enamine, with the oxygen being transferred to the titanium species.[149] In a similar study no enamine or imine was observed in the formation of the amine **149**, suggesting that it is a transient intermediate in the reaction.[150] This is a one pot synthesis with the intermediate imine reduced by methanolic $NaCNBH_3$ (Scheme 2-8) to give the desired product.[148, 151] The reaction was used to produce a number of desired amines listed in Table 2-1.

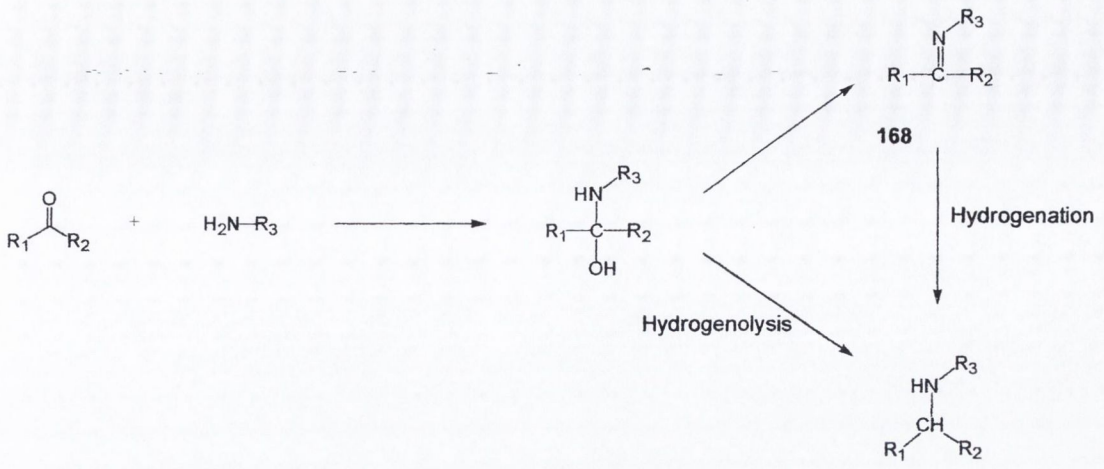


Scheme 2-8: Ti catalysed reductive amination of ketone 150

Table 2-1: Yields melting points and IR Bands of target amines 149-167

Comp.	Amine	IR Bands cm^{-1}	HCl mp°C	%Yield
149	Methyl amine	2897, 1497, 1257, 1043	216-218	48
159	Dimethyl amine	1040, 745, 647	oil	76
160	Ethyl amine	2971, 2504, 1039, 930	220-224	35
161	HMDS (NH_2)	2905, 1449, 1256	196-198	51
162	Morpholine	1502, 1265, 1039, 884	241-242	55
163	Piperidine	2945, 1491, 1253, 1038, 929	oil	63
164	Pyrrolidine	2559, 1491, 1255, 1037, 815	oil	60
165	Aniline	2868, 2488, 1034, 817	164	80
166	3,4-MD aniline	2889,2495,1501,1037,933	172-174	87
167	Allylamine	2963, 1503, 1040, 808	210	74.

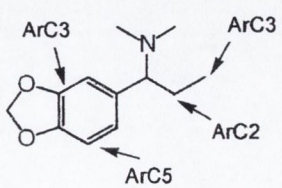
The mechanism in Scheme 2-9 describes the most likely pathway (hydrogenation of the imine **168**) taken when a primary amine is the nucleophile. However in the case of compounds, where a secondary amine is used, the products are formed *via* a different pathway (Scheme 2-9). [152]



Scheme 2-9 : Reductive amination pathways

The primary amine **161**, was afforded from the reaction of HMDS (hexamethyldisilizane). To ensure that the dioxole ring remained intact, it was initially attempted to produce the *N*-methyl molecule **149** with $SnCl_4$ as the Lewis acid. However, under these conditions no product was isolated from the reaction mixture. An attempt was then made with 1-phenyl-1-propanone (no dioxole ring), using $TiCl_4$ as the Lewis acid and methylamine-HCl. The method proved successful and so the amination of 1-benzo[1,3]dioxol-5-yl-propan-1-one **150** with methylamine-HCl catalysed by $TiCl_4$, was attempted. Surprisingly the dioxole ring remained intact in every amination attempted. The Ti species complexes preferentially with the more rigid carbonyl oxygen over that of a cyclic aryl ether.[149]

Each of the amines produced **149, 159-167**, was characterised using NMR, IR and HRMS spectroscopy. An illustrative example being (1-benzo[1,3]dioxol-5-yl-propyl)-dimethyl-amine **159**. There were no bands observed in the IR corresponding to an *N*-H signal, indicating it to be a tertiary amine. Bands at 2771, 1040, and 745 cm^{-1} representing carbon-carbon stretching, carbon-oxygen single bond and aromatic absorptions respectively were observed.



(1-Benzo[1,3]dioxol-5-yl-propyl)-dimethyl-amine **159**

Figure 2-2: Numbering system for spectroscopic peak assignments of (1-Benzo[1,3]dioxol-5-yl-propyl)-amino derivatives

The numbering system used for assigning spectroscopic data is shown in Figure 2-2. For simplicity, the three carbon backbone protons are assigned H3, H2 and H1 in the ^{1}H NMR. The aromatic protons are labelled as ArH2, ArH5, and ArH6 with positions 1, 3 and 4 of the aromatic ring being substituted. The same numbering system is used in the ^{13}C spectra replacing H with C (Figure 2-2).

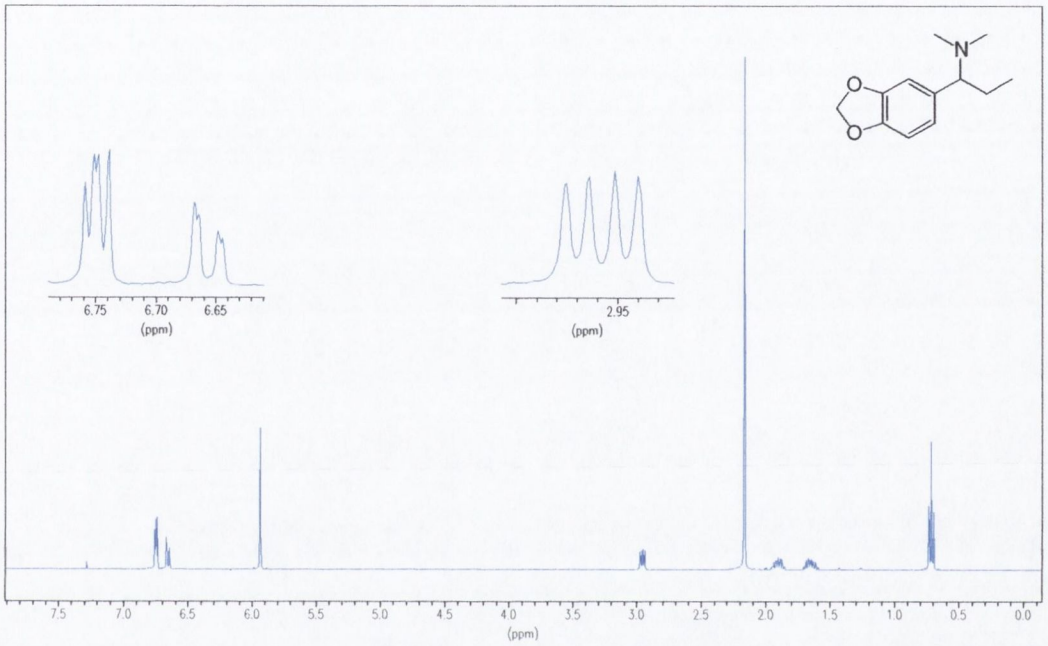


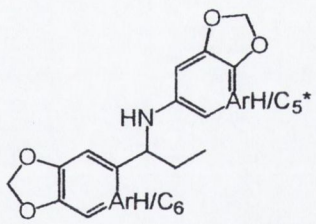
Figure 2-3: ^{1}H NMR of compound 159

In the ^{1}H NMR spectrum of compound **159** Figure 2-3, a triplet integrating for three protons with a coupling constant of 7.5 Hz, represents C1. The complex double multiplet representing two protons, (the pattern suggesting restricted rotation around the C1-C2 bond and also that the methylene group is adjacent to a chiral centre (Figure 2-2)), is indicative of the ethyl group present in the molecule. At 2.16 ppm exists a large singlet integrating for six protons, which is very characteristic for an N-dimethyl functionality. The restricted rotation alluded to, is more evident in the splitting pattern observed for the proton of C1. A double doublet at 2.95 ppm with J_1 = 4.5 Hz and J_2 = 9.0 Hz, integrating for one proton, suggests by the difference in the coupling constants, that the protons of the methylene group (C2) are not magnetically equivalent. The singlet of two protons at the relatively deshielded shift value of 5.94 ppm, is characteristic of the dioxole group. In the aromatic region of the spectrum at 6.65 ppm integrating for one proton, is a double doublet where J_o =

8.0 Hz and J_m = 1.5 Hz, at 6.75 ppm are two doublets one with coupling constant for *meta* at 1.5 Hz, the other *ortho* coupling of 8.0 Hz is observed, the two doublets integrate for two protons. This aromatic pattern is typical for that of an *AMX* trisubstituted system.

In the ^{13}C NMR, signals representing methyl groups resonate at 10.89 and 42.87 ppm representing the methyl of the ethyl group and the *N*-dimethyl respectively. Two methylene signals (inverted in the Dept 135 experiment) appear at 26.18 and 100.76 ppm; the more downfield corresponds to the dioxole carbon and the shielded peak represents the other CH_2 in the molecule. A CH peak at 72.40 ppm signifies the presence of the C1 carbon. Three aromatic CH peaks at 107.57, 108.37 and 121.96 ppm are indicative of the aromatic protons H5, H2 and H6 respectively. Three quaternary signals in the aromatic region of the spectrum at 134.53, 146.38 and 147.72 ppm represent $ArC1_q$, $ArC4_q$ and $ArC3_q$ respectively. The mass of the compound **159** was calculated for $C_{12}H_{17}NO_2$ at 208.1337 m/z, from HRMS the value found for M^+ was 208.1338 m/z.

Many of the predictions made in assigning the spectroscopic signals in this chapter, were made with reference to **159** Figure 2-4, on which extensive NMR studies were carried out, including ^1H, ^{13}C, Dept 135, Dept 90, HMQC, HMBC, Tocsy and NOE.



Benzo[1,3]dioxol-5-yl-(1-benzo[1,3]dioxol-5-yl-propyl)-amine

Figure 2-4: Detailed NMR study on 166

From the ^1H NMR of the above compound the ethyl group is clearly visible as a triplet at 0.92 and a multiplet at 1.72 ppm integrating for a total of five protons. What is interesting in comparing the spectra of **166** (Figure 2-4) with that of **159** (Figure 2-2), is that each of the two protons in the C2 methylene are not as clearly resolved in this case, indicating they are more magnetically equivalent than in the *N*-dimethyl analogue. Further evidence for this lies in the fact that the proton for C1 appears as a triplet at 3.29 ppm, rather than as a double doublet. With two very similar aromatic

rings in the molecule, 2D NMR experiments were required for a complete assignment to be made.

The six quaternary carbons were all distinguished from the HMBC experiment. In Figure 2-5 the long range through bond C-H coupling, from C1 (triplet at 3.29 ppm in ^{1}H) to both quaternaries ArC1 and ArC1* is apparent. These can be distinguished from one another on the grounds that one would expect a stronger coupling from ArC1 (138.05 ppm) to C1 than from ArC1* (143.19 ppm), also there is a coupling from C2 to ArC1 which is absent from C2 to ArC1*, providing more evidence in this regard. Both quaternary peaks at 139.34 and 148.10 ppm have long range coupling to all CH peaks on ring B (Ar*) and the dioxole signal at 5.8 ppm. The signal at the more shielded value was assigned ArC4* on account of the ring donating effects (through the π aromatic system) of the nitrogen at the *para* position. The aromatic carbon directly attached to the nitrogen ArC3* resonates further downfield at 148.10 ppm, as a result of electron withdrawing effects of the nitrogen through the σ bond. This leaves two quaternaries ArC3/4 at 147.88 and 146.39 ppm. Each signal has a long-range interaction with the dioxole proton signal at 5.94 ppm. They were assigned based on the magnitude of their long range C-H coupling evident in the HMBC from each quaternary in question to the proton signal of ArC2 at 6.85 ppm in the ^{1}H spectra. There is a stronger interaction from the quaternary carbon signal at 147.88 ppm. For this reason the signal at 146.39 was deemed to be from ArC4, while the peak at 148.10 was assigned to be ArC3.

A study by Braun *et al* demonstrated that various *N*-substituted analogues (N – alkyl, alkenyl, hydroxy, alkoxy, and alkoxyalkyl) of MDA had activity in the central nervous system. It was noted however that biological activity decreased with an increase in the bulk of the N-substituent.[153]

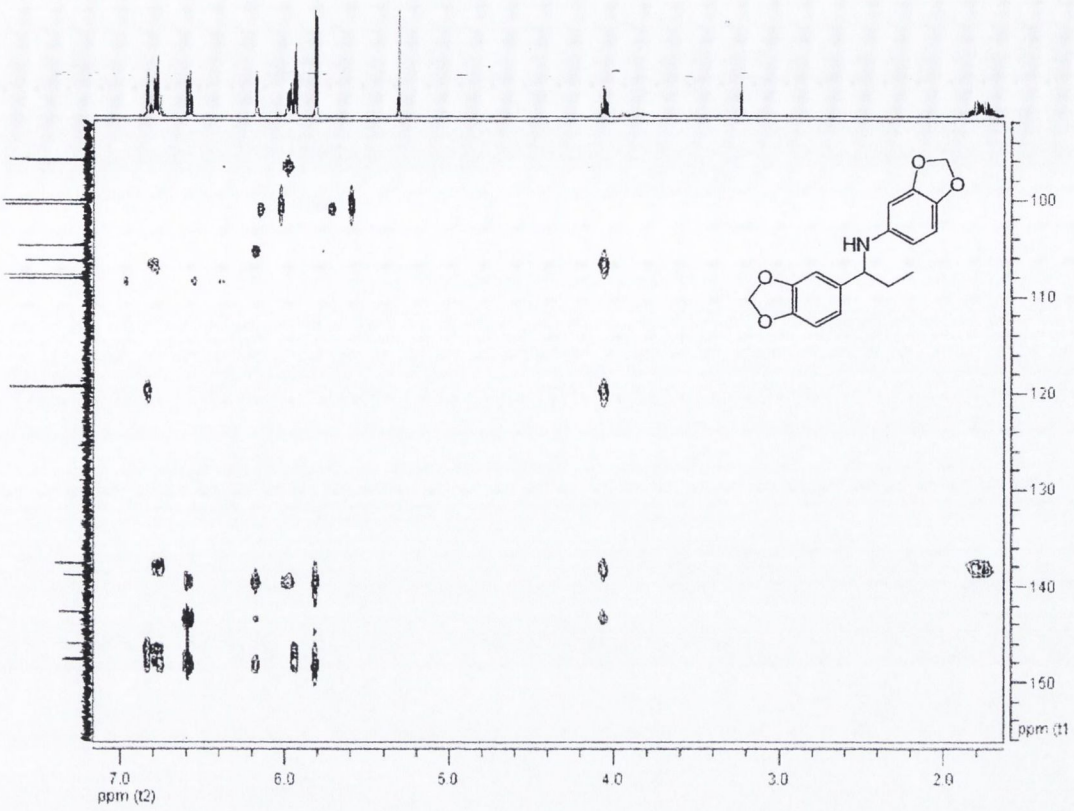


Figure 2-5: HMBC of the aromatic region of 166

The 2D H-H Tocsy experiment (Figure 2-6) shows the H-H coupling from which it was possible to discern two distinct sets of aromatic peaks. The ^{1}H NMR signals at 5.98, 6.18 and 6.60 ppm belong to one ring system, while those at 6.77, 6.81 and 6.85 ppm are part of another. The *amx* pattern is evident with one doublet J_o = 8.0 Hz (6.60 ppm), the doublet with J_m = 2.0 Hz (6.18 ppm) and a double doublet at 5.98 ppm (J_o = 8.0, J_m = 2.0 Hz). The first set of peaks listed were assigned as being part of ring B (Ar*). The doublet at 6.60 ppm would be the predicted pattern for ArH5* or ArH5. The positive NOE resulting from H2 to the signal at 6.18 ppm (the coupling constant suggests the signal has to be either ArH2 or ArH2*) and from H1 to ArH6*/2* and to ArH2 (Figure 2-6), defines the set of signals to which the peak at 6.18 ppm belongs, as being part of ring B.

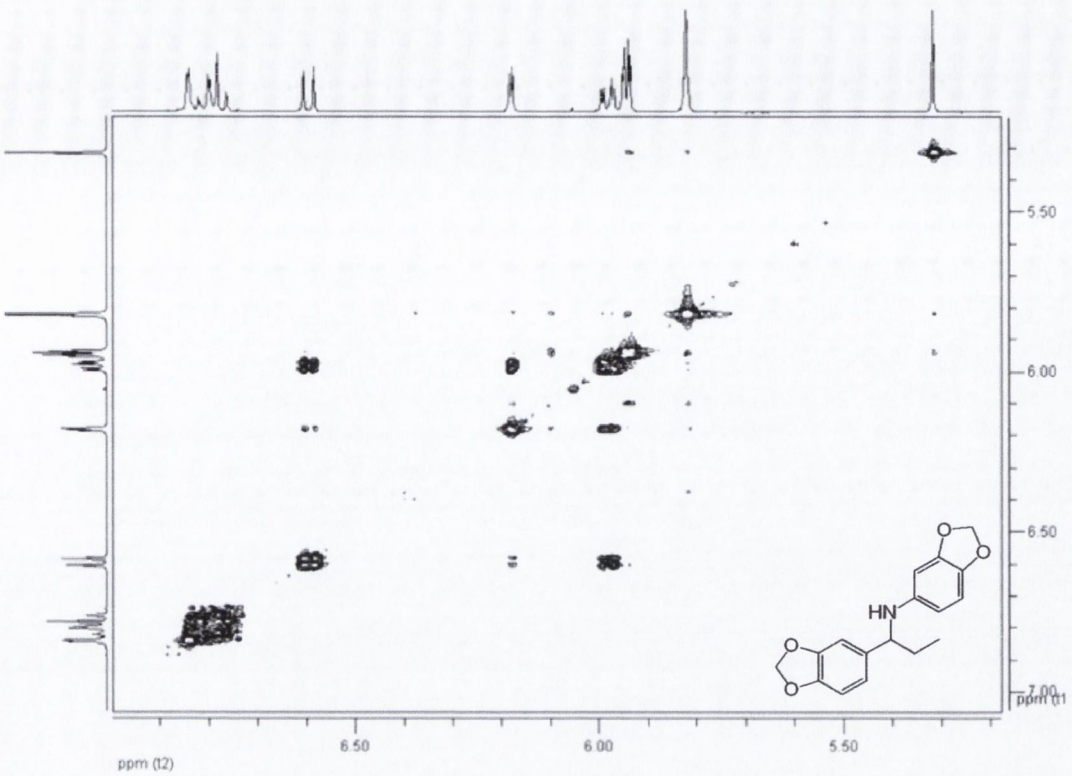


Figure 2-6: 2D Tocsy of 166

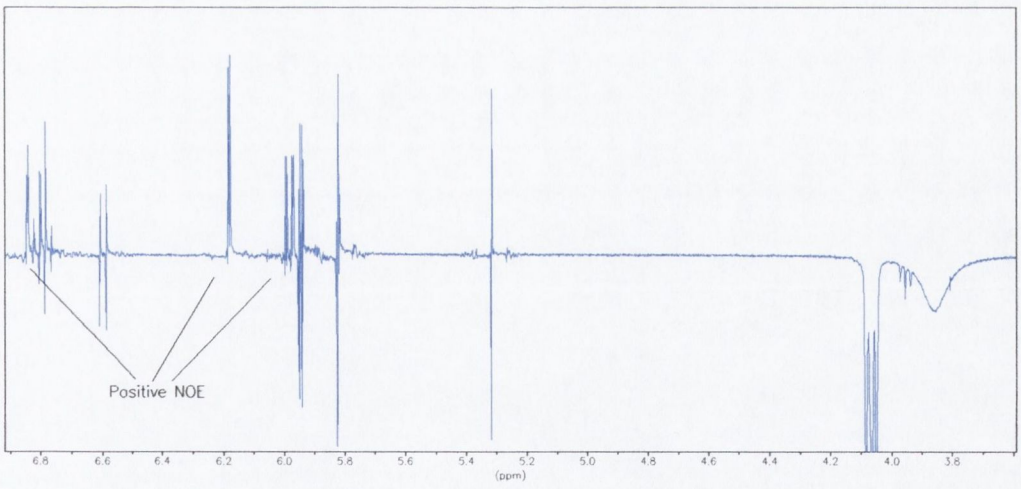


Figure 2-7: Positive NOE from H1 to ArH6*/2* and ArH1 for 166

Any remaining carbon assignments (*e.g.* determining which dioxole peak belongs to ring A or B *etc*) were made with the help of HMQC. Figure 2-8 summarizes some of the NMR experimental results.

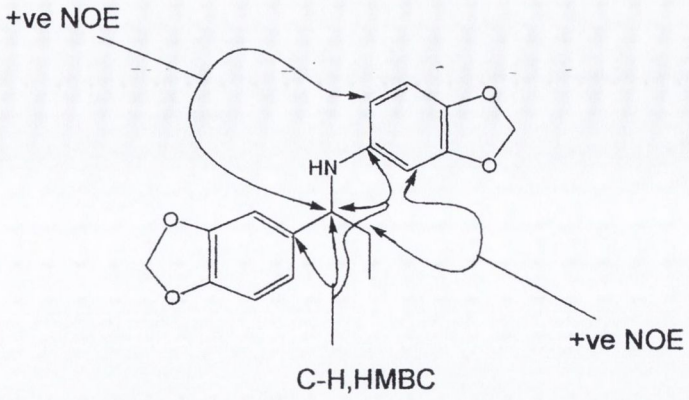
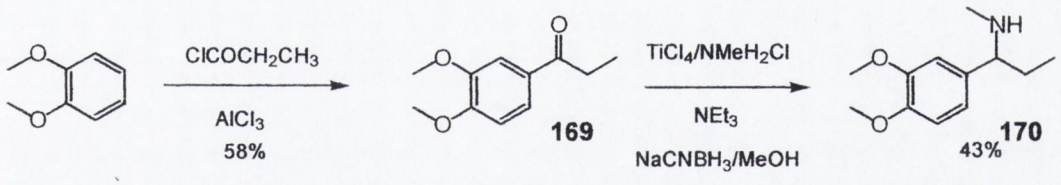


Figure 2-8: NOE and HMBC interactions for 166

In an effort to examine the effects of the dioxole ring on activity, it was decided to study the effects of a less rigid ring substitution namely a 3,4-dimethoxy pattern. Reports in the literature on the biological activity of 3,4-dimethoxyamphetamines have determined them to be active at serotonin receptors.[106, 154, 155] Since the methoxy groups are less sensitive to strong Lewis acids, direct Friedel-Crafts acylation was achieved from veratrole using $AlCl_3$ and propionyl chloride followed by the titanium catalysed reductive amination (Scheme 2-10). **170** was produced from **169** in 43% yield.

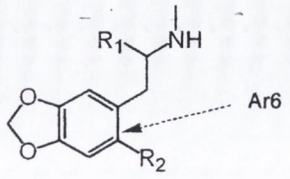


Scheme 2-10: Synthesis of [1-(3,4-Dimethoxy-phenyl)-propyl]-methyl-amine

2.3 Position-6 ring chemistry

A literature search by Keating, on aromatic amphetamine substitutions at the 6-position of the ring yielding no results, prompted the synthesis of several analogues at the 6-position shown in Figure 2-9.[147] When MDMA **140** is drawn in the conformation in Figure 2-9, the similarities with the pharmacophores described in Section 1.3.2 are obvious. The amine is at its furthest point from the electronegative region (the dioxole ring) and the void volume at ArH2 is conserved.

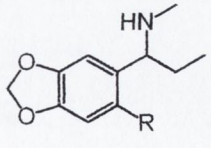
Figure 2-9: Substitution study by Keating[147]



R = H = MDMA **140**

R_1	R_2
CH_3 or CH_2CH_3	NO_2, NH_2
	NHCOR (R = CH_3, CH_2CH_3, $CH_2CH(CH_3)_2$,
	cyclopropyl, phenyl, Benzyl
	F, Cl, Br, I
	CF_3
	COOH
	Phenyl
	OR, SR, (R = H, CH_3, CH_2CH_3)
	Vinyl
	-C≡C-R (R = H, CH_2OH, CH_2NH_2)
	COR (R = CH_3, CH_2CH_3)

Aside from there being very little work carried out in substituting position-6 in amphetamines, from a pharmacophoric point of view, it is of interest. With the conformation drawn in Figure 2-9, position-6 of MDMA **140** matches the volume described in Rupp's model for SSRIs (Figure 1-11), as requiring π - electrons and also a steric group (preferentially aromatic,[49]) suggesting this to be a very important region of the pharmacophore. It was for this reason that the substitution of postion-6 in the 1-phenylpropylamines was undertaken with the objective of investigating the following structural types Figure 2-10:



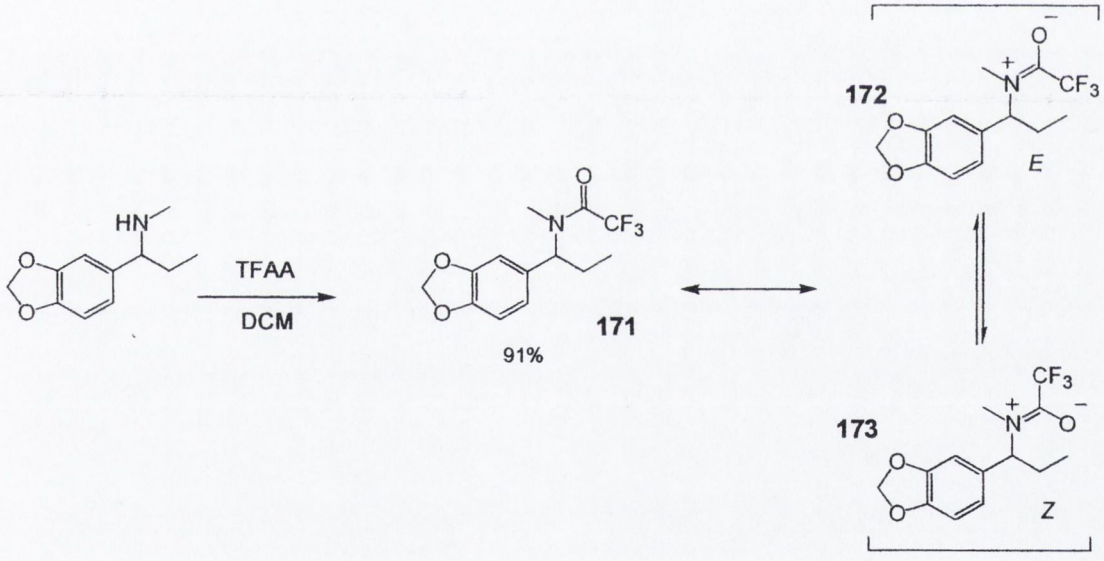
R = Br, I, NO_2, C≡CCH_2OH,
C≡CC_6H_5, CN, C_6H_5,
$CH{=}CHC_6H_5$, vinyl, CF_3,
$CH{=}CHCOOR_2$(Heck products)

Figure 2-10: proposed position-6 study of phenylpropylamines

Functionalisation at position-6 of 1-phenylpropylamines requires protection of the amino function. The protecting of an amine by means of a trifluoroacetyl group (TFA) has been used extensively.[156] The amino group of amphetamines and

tetrahydroisoquinolines have been protected using this method.[157-160] It is removed by acid or base hydrolysis at room temperature.[156] The use of the TFA protecting group greatly increases the R_f of the compound in a typical hexane:diethyl ether eluent providing a more readily achievable chromatographic purification. For characterisation purposes many of the amine final products in this chapter do not give a molecular ion in the HRMS, however the TFA derivatised amine does making the use of this protecting group all the more desirable. The preparation of the TFA protected amine **171** is illustrated in Scheme 2.11.

The amide created in using the TFA group often results in a distinctive peak splitting in the various NMR spectra. This is more evident in signals belonging to protons in close proximity to the protected amine. The cause of this apparent pattern, is due to the restricted rotation about the transient double bond formed from the delocalisation of the lone pair of electrons on the nitrogen of the amide. This is illustrated in Scheme 2-11.



Scheme 2-11: TFA protection of 149. Inset-delocalisation of nitrogen electrons forming rotamers

The (*E/Z*) rotamers **173** and **172** are evident in the ^{1}H spectrum Figure 2-10. The two double doublets at 4.90 ppm and 5.65 ppm, integrate for 0.24 and 0.75 protons respectively. The major isomer in the TFA protected amines in this chapter is assigned R1 and the minor R2. A splitting of the other peaks in the same ratio is also apparent. One example being the *N*-methyl group, with the singlet at 2.73 ppm [R2] integrating for 0.74 protons and the adjacent singlet at 2.80 ppm [R1]

integrating for 2.26 protons. Present in a ratio of 3.1:1. For a nucleus to be magnetic it must possess spin angular momentum. Nuclei with an odd mass number, *A*, and even charge, *Z*, have quantum spin numbers *I*, = ½. These nuclei behave as spherical spinning magnetically charged bodies.[161] The naturally occurring isotope of fluorine is ^{19}F, which has a spin number = ½, can magnetically couple with ^{13}C signals#. Another trait of the TFA group is the long range C-F coupling to the N-CH_3 peak observed in the ^{13}C NMR, splitting it into a quartet with J = 4 Hz. The ^{19}F NMR spectra shows the fluorine signal for R1 at –70.13 ppm and the minor rotamer R2 occurs at`-66.93 ppm. In the instances where rotamers are not reported, distinction could not be made between the two.

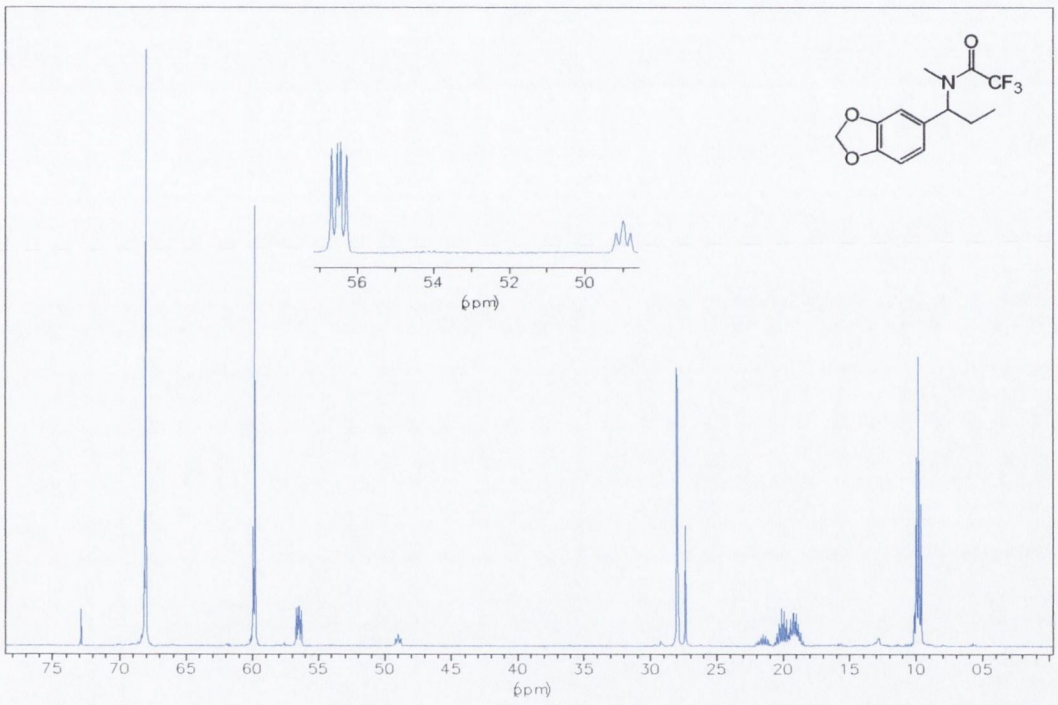


Figure 2-11: ^{1}H NMR of 171

In a study by Dawson *et al*, the *(E/Z)* nature of the amide bond in *N*-formylmethamphetamine was investigated using a lanthanide shift reagent. [162] It was found that the major isomer was the one in which the carbonyl oxygen was *(Z)* to the *N*-methyl. A chemical shift study in this instance was not carried out, however from the clear difference in the coupling constants observed for H1 in the double doublets at 4.90 and 5.65 ppm for the two rotamers R1 and R2, certain estimations

^{1}H also has spin *I* = ½, however, unless otherwise stated, all ^{13}C spectra in this thesis are proton decoupled.

can be made. The minor rotamer signal at 4.90 ppm (J_1 = 7.5 Hz and J_2 = 7.6 Hz) implies the protons to which they are coupled (methylene H2) are almost equivalent. In the case of the major isomer, there is not only a sizeable difference in the J values but also a dramatic change in the chemical shift of the peak at 5.65 ppm (J_1 = 9.5Hz, J_2 = 6.0 Hz). In the *(Z)* and *(E)* isomers **173** and **172** (Scheme 2-11), the methylene protons at C2 would be the most inequivalent when in the -CF_3 group was closest, which may give rise to the coupling experienced in the major rotamer R1. This would suggest that the major rotamer is *(Z)*, however further study would be required on this system in proving this to be the case.

2.3.1 Bromination at position-6

From the electron donating effects of both oxygens in the dioxole ring of compound **171** (Figure 2-11) and taking steric factors into consideration, position six is the most likely place for electrophilic aromatic substitution to take place. In a paper by Daukšaas *et al*, the dioxole ring has been described as being 'quasiaromatic', an effect which decreases as derivatisation of the methylene group leads to a loss of coplanarity between the two rings, thus disrupting its aromatic nature.[163] One method to distinguish between the electron donating effects of the oxygens in the heterocyclic ring, is by studying the rate of bromination using elemental bromine in glacial acetic acid.

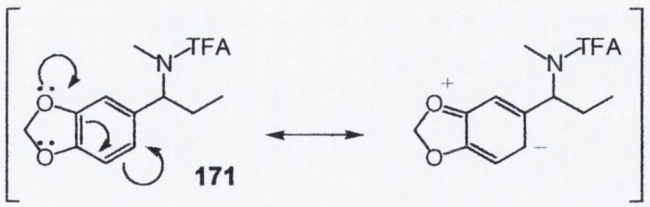


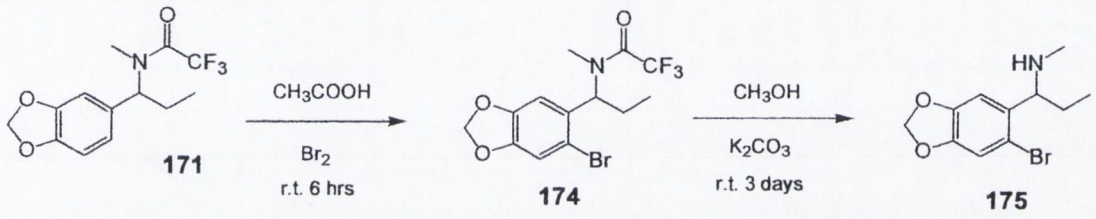
Figure 2-12: Electron donating effects of dioxole ring[163]

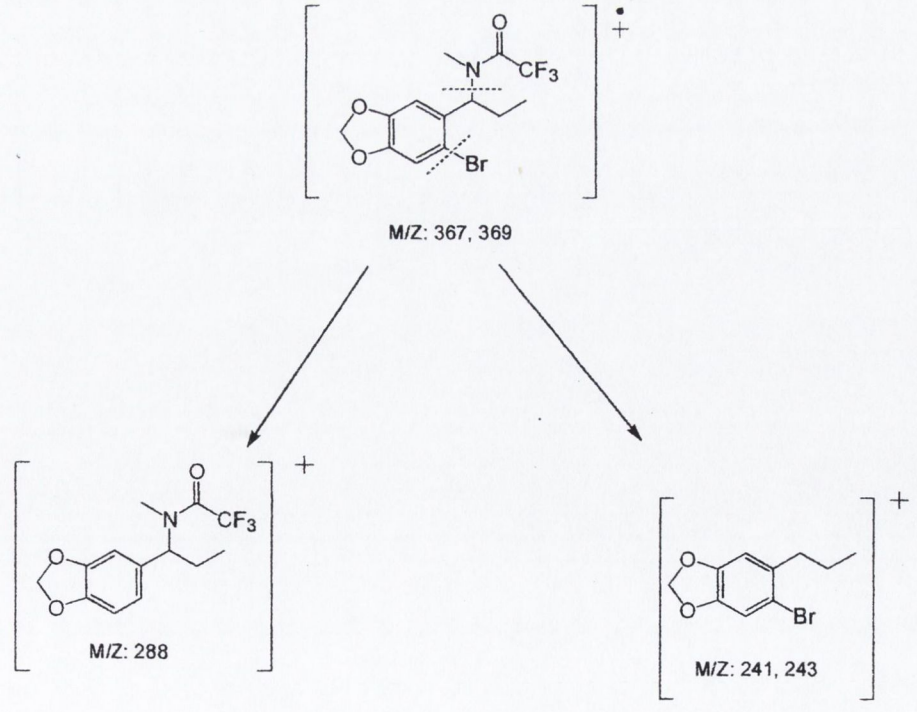
Amphetamines derivatives brominated at the *para* postion have been prepared directly using elemental bromine in acetic acid.[120, 147, 154, 158, 163, 164] This method was employed to brominate the TFA protected amine **171** Scheme 2-12. The protecting group was removed in a solution of K_2CO_3 in aqueous methanol. In the HRMS the molecular ion ($M^+ + Na^+$) was found at 389.9930, m/z calculating ($M^+ + Na^+$) for $C_{13}H_{13}BrF_3NO_3$. A peak at $M^+ + 2$ which was in equal intensity to M^+ occurred, accounting for the 50% natural abundance of the isotope ^{81}Br. The GC-LRMS (Figure 2-13) of the ring brominated intermediate shows peaks at m/z: 338, 288 and

241, signifying the presence of the fragment ions depicted in Scheme 2-11. The peaks at 241, 243 and m/z indicate the presence of the bromine atom in the molecule, Figure 2-12. In the ^{1}H NMR spectrum of **174** two singlets in the aromatic region integrating for a total of two protons was indicative of position six substitution. In the ^{13}C NMR of **174** the quaternary signal at the rather shielded value of 116.86 ppm pointed towards the presence of the bromine atom. Table 2-2 contains the IR, melting point (HCl salt) and yield of the final product **175**.

Table 2-2: Yields, IR and melting points of 174-175

Compd.	IR	m.p.°C (HCl)	Yield %
174	1692, 1504, 1242, 1034, 926	69-70	85
175	2927, 1482, 1246, 1035, 924	oil	57





Scheme 2-12: Ring bromination 175

Chromatogram Plot

File: c:\documents and settings\butlersg\desktop\gc-ms\6-br.sms
Sample: Default Sample 7/17/2002 4:49 PM
Sample Notes:
Operator: pg Scan Range: 1 - 1281 Time Range: 0.00 - 21.10 min.

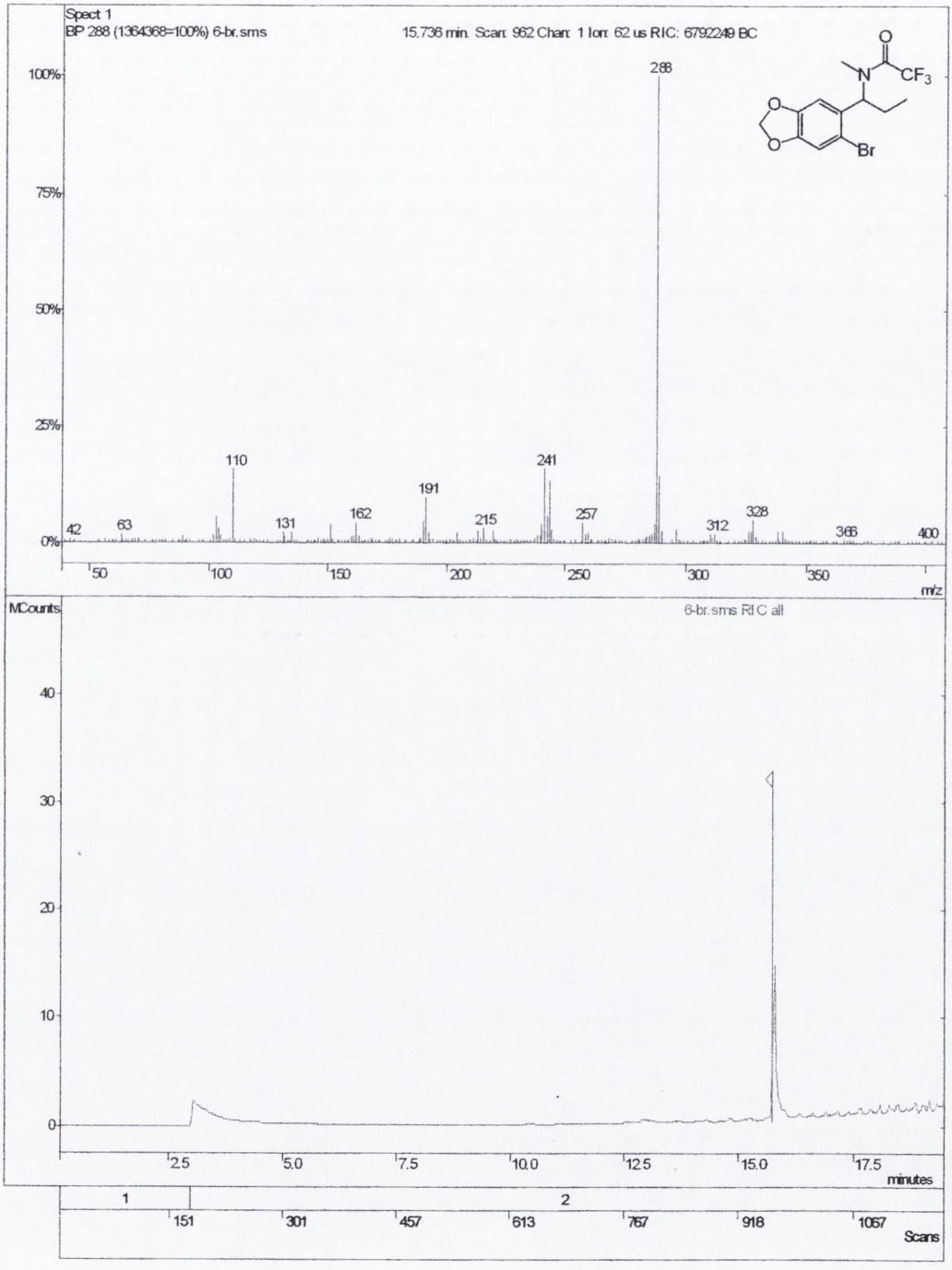
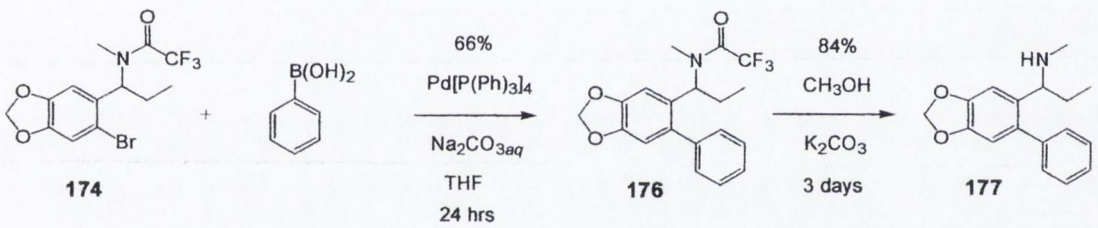


Figure 2-13:GC-MS for bromide 175

2.3.2 Suzuki Arylation

Access to the protected bromide **174** provided the opportunity for further substitution at postion-6. When considering pharmacophoric elements, the insertion of π-electrons and steric bulk was deemed desirable. With this in mind the Suzuki arylation **174** was carried out to afford the biaryl intermediate **176**, the deprotection of which gives **177** (Scheme 2-13). The Suzuki reaction is a palladium catalysed coupling reaction, between a conjugated electro-negative group and an organoboron compound forming a new carbon-carbon bond (described in Scheme 2-14).[165][166, 167] It was successfully utilised in the synthesis of many biaryl compounds.[147, 168] Palladium catalysed cross coupling reactions offer tremendous scope for the formation of a variety of carbon-carbon bonds, developments have resulted in these reactions being carried out in aqueous media.[169]



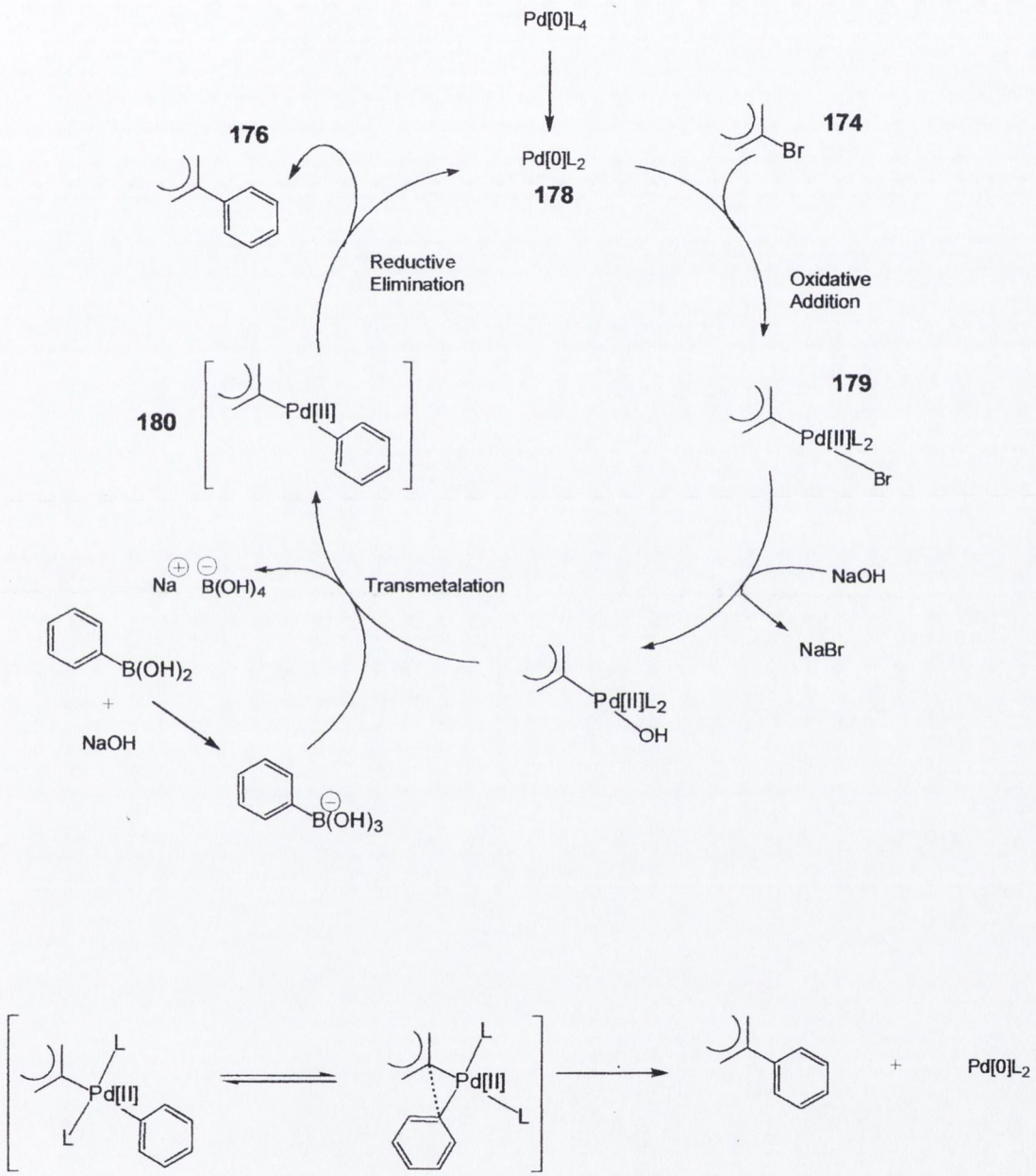
Scheme 2-13: Suzuki arylation at position-6

The aryl-aryl coupling proceeds *via* the mechanism described in Scheme 2-14:[165, 170]

1. Two of the ligands disassociate from the Pd[0] complex, forming **178** (delagation).
2. The oxidative addition of **178** to the arylhalide **174** can then take place. In this step the Pd[0] species is oxidised to Pd[II] by aquiring one electron from the halide and an other from the aryl group (this is not equivalent to general oxidation, but could be compared to the formation of a Grignard reagent *e.g.* Mg(0) + CH_3-I giving CH_3-Mg(II)-I).
3. The halide in the complex **179** is then replaced by a hydroxyl group (metathetical displacement). The hydroxyl group coming from one equivalent of NaOH, yielded from the reaction of Na_2CO_3 with water.
4. The boronic acid is activated by another equivalent of base and the charged anion then undergoes transmetalation producing the boronic salt and the

biaryl-palladium complex **180**. This intermediate when in the *cis* arrangement can undergo the final step.

5. The final phase of the cycle (reductive elimination is the reverse of oxidative addition), regenerates the Pd[0] species which can undergo another coupling cycle along with the desired product **176**.



Scheme 2-14: Proposed mechanism for the Suzuki reaction

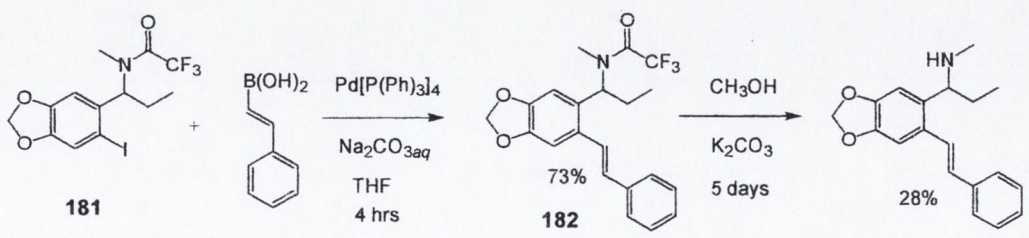
From the ^{1}H NMR spectrum of **176**, it could be determined the reaction was successful. The most notable difference between the diaryl product **176** and it's starting material **174** was in the aromatic region. The protons on the dioxole

substituted ring occur characteristically as sharp singlets, integrating for one proton each, at 6.74 and 6.98 ppm. The five mono-substituted phenyl protons resonate from 7.14 to 7.40 ppm. The doublet at 7.15 ppm, integrating for two protons, with J = 7.5 Hz was assigned ArH2* and ArH6*. The multiplet representing three protons at 7.38 ppm was assigned ArH3/5* and ArH4*. These sets of peaks show coupling to one another in the H-H COSY. Carbon protons were assigned with the assistance of a 2-D C-H COSY experiment. The peak at 107.82 ppm was assigned as ArC2 and the one at 111.02 ppm was assigned as ArC5, both signals were apparent in the Dept 90 experiment. Rotamers were indistinguishable in all spectra. GC-MS gave M^+ at m/z 365. Predominant peaks at m/z: 288 and 239 indicating $M^+ - C_6H_5$, $M^+ - CH_3NCOCF_3$ respectively. The product was a clear oil for which the calculated mass was 388.1136 ($M^+ + Na^+$) m/z, HRMS found $M^+ + Na^+$ to be m/z 388.1131. Base hydrolysis of the amide **176**, yielded the secondary amine **177** in 84%.

Table 2-3: IR, yield and MS data for 176 - 177

Compd.	IR	HRMS m/z	Yield %
176	1693, 1483, 1244, 1039	388.1131(Calc 388.1136)	66
177	3414, 1484, 1141, 1037, 932	-	84

A further application of the Suzuki reaction lies in the coupling of aryl halides with vinyl boronic acids and in order to extend the linkage between the aromatic rings, this modified Suzuki was employed as shown in Scheme 2-15. The reaction was initially attempted from the bromide **174** and no product was formed. The reaction was attempted again, the second time the starting material was the aryl iodide **181**, (the synthesis of which is described in Section 2.3.6.). After four hours, monitoring with TLC, the reaction yielded the intermediate **182** in 73% yield, which was clearly visible as a bright blue fluorescent spot on TLC (R_f = 0.69 using a 60:40 hexane:diethylether eluent.



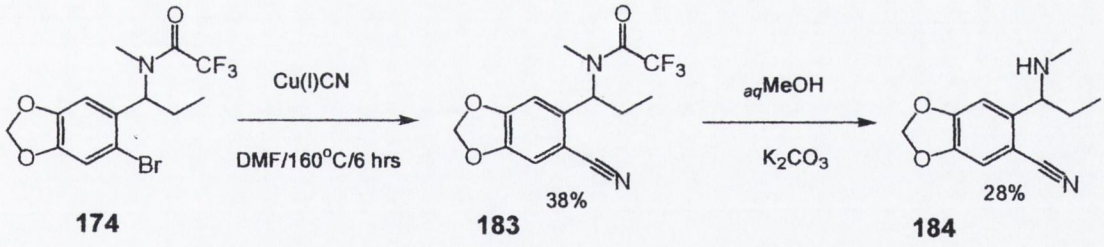
Scheme 2-15: Suzuki reaction with a vinylboronic acid

2.3.3 6-Cyanation

Seggel *et al* synthesised a set of 2,5-dimethoxyamphetamines with derivatisation at position-4.[171] One example being the 4-cyano derivative synthesised directly from the corresponding bromide using the method of Chen and Castagnoli.[171, 172] In the synthesis of non-fibrinogen receptor antagonists Stilz *et al* were able to replace an aromatic halide with a cyano group in one step.[173] Patrick *et al* achieved the transformation in a tricyclic type compound using Cu(I)CN and 1-methyl-2-pyrrolidinone.[174] The mechanism of this reaction is similar in some respects to nucleophilic substitution and has been reviewed by Ellis and Romney-Alexander.[175]

The purpose of the copper species is to polarise the halide substrate, thereby facilitating attack from the nucleophilic cyano group and also to receive and remove the halide from the reaction.[176] An sp^2 hybridised electron-pair donor atom is an essential component of the substrate.[176] One proposed mechanism for this displacement when the reaction is carried out at normal pressure in DMF or pyridine at ~160°C goes as follows (Scheme 2-16).[175]

$$2ArX + 2Cu(I)CN \longrightarrow [ArCN]_2CuX + CuX \longrightarrow 2ArCN + CuX$$



Scheme 2-16: Cyanation of bromide 174

The introduction of the CN function at C-6 was carried out as illustrated in Scheme 2-16. The 6-cyano derivatised compound N-[1-(6-cyano-benzo[1,3]dioxol-5-yl)-propyl]-2,2,2-trifluoro-N-methyl-acetamide **183,** was characterised by IR, ^1H and ^{13}C NMR. The reaction was deemed a success from the IR spectrum, which showed a strong signal at 2224 cm^{-1}, the region in which triple bonds appear. The aromatic signals in the ^1H NMR spectrum appeared as sharp singlets at 7.04 and 7.07 ppm.. The most notable signal in the ^{13}C spectrum was a quaternary carbon at 117.35 ppm, which was assigned as the –CN. The rotamers were again indistinguishable

with the $-CF_3$ group appearing in the ^{19}F as a lone singlet at –70.37 ppm. The yields, IR and HRMS for **183** are presented in Table 2-4. The secondary amine **184** was obtained as described in Scheme 2-16.

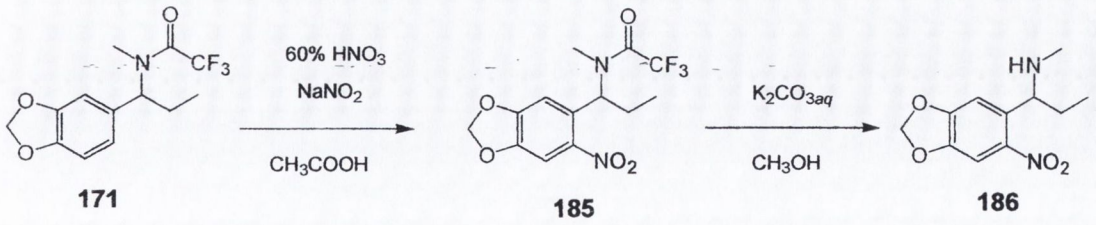
Table 2-4: IR, HRMS and yield for 183-184

Compd.	IR υ cm^{-1}	HRMS	Yield%
183	2224, 1680, 1038	337.0776(Calc 388.0775)	38
184	2927, 2351, 1246, 1034	-	28

Cyano groups are generally unstable under basic conditions.[152] However base hydrolysis with carbonate under aqueous conditions did yield the secondary amine final product in 28% yield. The most notable difference in the ^1H NMR of the product **184**, when compared to that of the protected intermediate **183**. (which is characteristic to compounds in this series) is the difference in the chemical shift observed for the peak assigned as H1. In the TFA protected intermediate **184**, the H1 proton precesses at 5.44 ppm as a triplet (J = 7.5 Hz) and the equivalent proton in the secondary amine final product **184** appears as a multiplet at 3.35 ppm. This significant difference in chemical shift can be attributed to the influence of the strong electron withdrawing (delocalisation of the nitrogen π-electrons leaving a partial positive charge) effect of the TFA group on the proton H1, i.e. the equivalent peak in the final product **184** is less deshielded.

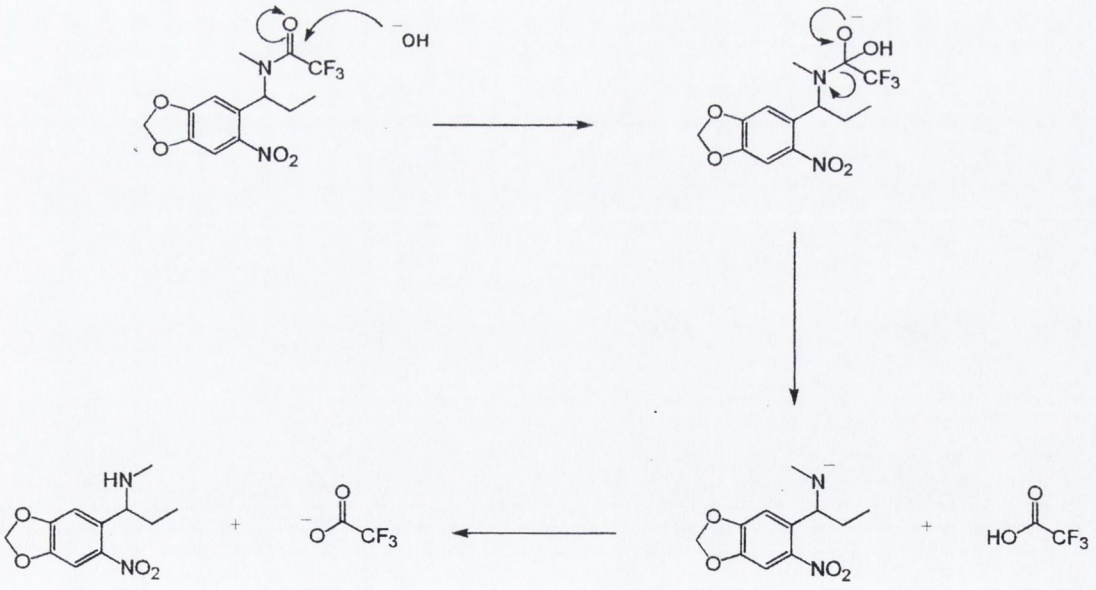
2.3.4 Nitration at position-6

In order to produce a substituted 1-phenylpropylamine with a strong electron withdrawing effect at position-6, it was decided to use direct nitration of the ring. Nitro analogues of hallucinogenic amphetamines have been prepared, [177] [178] as well as nitro analogues of MDMA and MBDB. [147] Dopamine has also been nitrated under physiological conditions. [179] Using concentrated nitric acid with a catalytic amount of sodium nitrite, the nitration of **171** was achieved in a good yield (Scheme 2-17).



Scheme 2-17: Nitration at position-6

The IR spectra of both **185** and the deprotected secondary amine **186**, both had prominent absorption bands pointing toward the presence of a nitro group (Table 2-5). In the ^{1}H NMR spectrum the rotamers are again evident in a ratio of 8.1:1. The substitution at position-6 is clear from the pattern observed in the aromatic region with the major rotamer signals appearing as singlets at 6.99 and 7.37 ppm, both integrating for 0.86 protons. The downfield peak at 7.37 ppm being more deshielded, was assigned ArH5 on account of the electron withdrawing effects of the nitro group. The minor rotamer accounted for the two singlets, integrating for 0.11 protons at 6.75 and 7.52 ppm. Four aromatic quaternaries confirmed the ring substitution, with the peak at 144.67 ppm assigned as ArC6. The deprotected final product **186** was afforded smoothly *via* base hydrolysis in aqueous methanol the potential mechanism is given in Scheme 2-15.



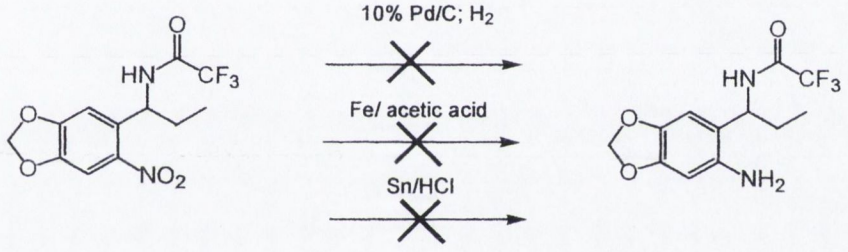
Scheme 2-18: Base hydrolysis of TFA protecting group

The nucleophilic substitution of an aromatic nitro group has been reported by Effenberger *et al* and by Lauhoff *et al.*[180, 181] In an effort to replace the nitro group with an ethylthio moiety, sodium ethane thiolate was added to **185** in dry DMF. The

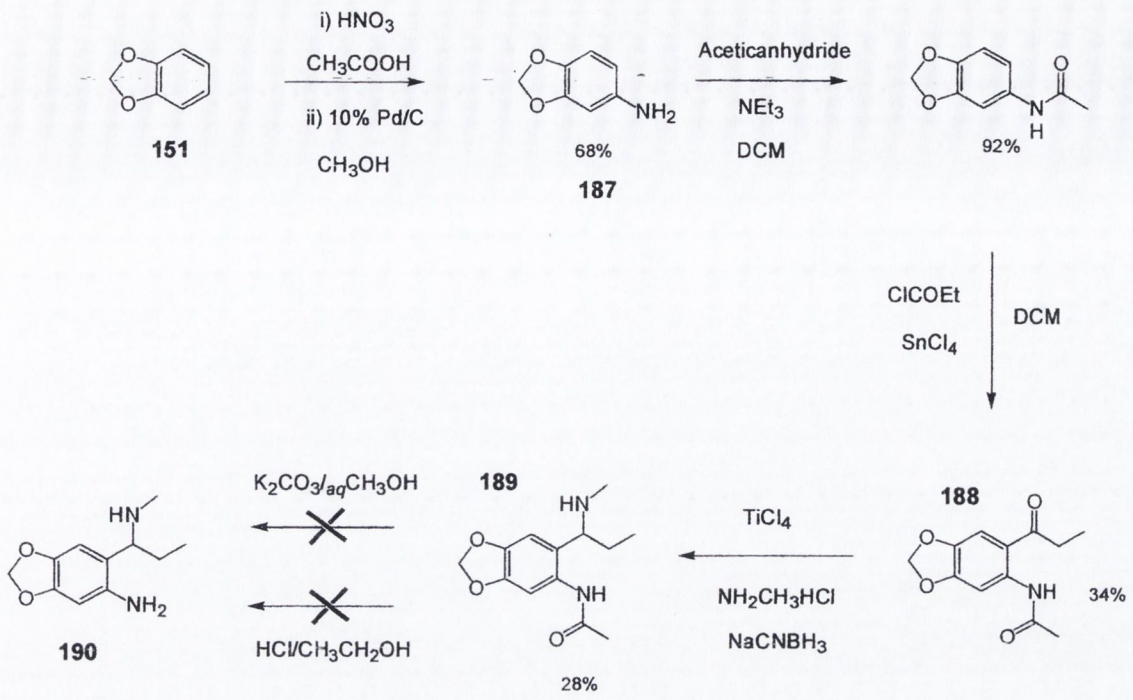
reaction was heated to 100°C for three hours under nitrogen. In the resulting product, the dioxole ring had cleaved and the product was not fully characterised. This can be explained because of the known ability of sodium ethane thiolate to promote demethylation reactions.[152]

2.3.5 6-Amino substitution of 1-phenylpropylamines.

Several methods were investigated in the direct reduction of the group in nitro **185**, none of which were successful. Initially (hydrogenation and 10% Pd/C in ethanol) was attempted. (Scheme 2-19) Reaction monitoring by TLC, demonstrated the rapid conversion of the starting material to product. Unfortunately, the product degraded very quickly upon during purification. When **185** was treated with iron powder in glacial acetic acid or tin/HCl, a similar outcome resulted, indicating that the initially formed aromatic amine was unstable under the reaction conditions.



At this point it was decided to use an alternative route for introduction of the required amine function. The route taken (Scheme 2-19) started with the nitration and subsequent reduction of 1,3-benxodioxole **151** to give 3,4-methylenedioxyaniline **187**. The aniline was first protected with an acetyl group using acetic anhydride. The next step involved the Friedel-Crafts acylation of the protected aniline **187**, to yield the carbonyl product **188** in 34% yield. The direct amination of **188** with $TiCl_4$ was successful using the method of Barney *et al.*[148] The removal of the acetyl group proved problematic. The usual base hydrolysis was not effective. In attempting acid hydrolysis, the initial attempts proved futile (reaction monitored by TLC), when the pH was decreased further, a complete degradation of amide **185** resulted.

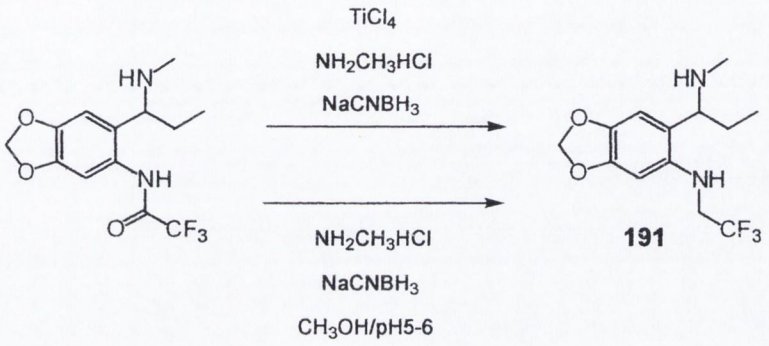


Scheme 2-19: Alternate route attempted to 6-nitro compounds

The secondary amine N-[6-(1-methylamino-propyl)-benzo[1,3]dioxol-5-yl]-acetamide **189**, was characterised using IR, in which the NH stretching was observed at υ cm^{-1} 3424, while the amide C=O bond absorbed at 1690 cm^{-1}. In the ^1H NMR spectrum the three methylene groups were apparent. The methyl constituent of the ethyl group resonates as a triplet (J = 7.2 Hz), at 0.80 ppm. The acetamide protons appears as a singlet (three protons) at 2.16 ppm, while the N-methyl occurring as a singlet integrating for three protons at 3.05 ppm. The aromatic protons were present in the spectrum as two singlets at 6.35 and 6.62 ppm following pattern for substitution of this type. The CH_2 of the ethyl group again emerges as a complex set of two multiplets. Restricted rotation may exist around the bond from C1-C2, which seems evident from the large difference in coupling constants experienced by H1, to give the double doublet at 4.29 ppm (J_1 = 6.1 Hz; J_2 = 3.4 Hz). The protons of H2, being beside a chiral centre are diastereotopic and so appear as separate multiplets. The dioxole CH_2 resonates characteristically as a singlet at 5.90 ppm, integrating for two protons. The restricted rotation observed in the TFA protected amines was not apparent. The most notable signal in the ^{13}C NMR spectrum, was the quaternary peak at 155.79 ppm which was assigned N<u>C</u>=O.

The synthesis in Scheme 2-19 was repeated from **187**, however in the second instance, a trifluroacetyl group was used in place of the acetyl protecting group in

the hope that it would be more easily removed by base hydrolysis. In this case when undergoing the Ti-catalysed reductive amination, the protecting group reacted to give the product **190**. It was felt the Lewis acid may be responsible for the removal of the oxygen in the TFA group, therefore the regular reductive amination was attempted. The same product **191** was isolated from the reductive amination. The synthesis was not pursued any further as the secondary amine function had been successfully introduced at C-6.



Scheme 2-20: Amination of carbonyl 188 yielded 191

The various spectra of the diamine amine product **191** are quite interesting. The most notable feature of the ^{1}H NMR spectrum, was the two doublets observed for the trifluoroethylamino group, resonating at 3.67 ppm, with J_1 = 9.0 Hz. The carbonyl group had been replaced by the N-methyl group with its three protons assigned to the singlet at 2.31 ppm integrating for three protons. The proton H1 appears as a customary double doublet J_1 = 8.5 Hz, J_2 = 6.0 Hz at 2.31 ppm. The aromatic peaks retained the pattern of two singlets at 6.31 and 6.51 ppm. These were assigned ArH5 and ArH2.

The ^{13}C NMR spectrum revealed more information about **191**. The trifluoroethylamino group is immediately obvious as a quartet at 45.90 ppm with J = 33.0 Hz. This quartet is inverted in the Dept 135 experiment (see vertical trace in HMQC Figure 2-13), suggesting the presence of a methylene carbon α to a trifluoromethyl group. At 125.32 ppm exists a broadly coupled quartet with J = 280.9 Hz. This large J value indicated the carbon in question was directly attached to three fluorine nuclei. This signal was not observed in the Dept 135 experiment, therefore it was assigned as the trifluromethyl moiety. The carbon nucleus at ArC5 being *ortho* to two electron donating groups, precesses at the more shielded value of 93.84 ppm.

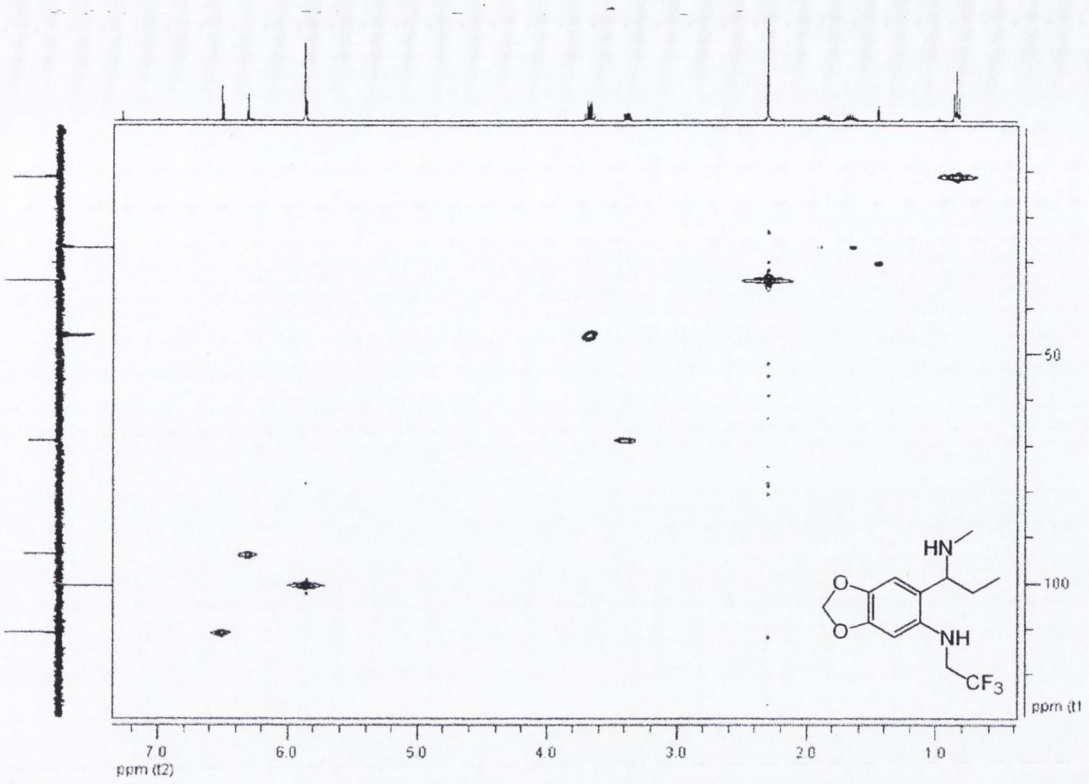


Figure 2-14: HMQC of compound 191

Figure 2-14 is the result of the decoupling experiment, in which the spin of the methyl group is locked. What is interesting in this experiment is the complex set of multiplets characteristically observed for the methylene group, collapse into a pair of double doublets, the third extremely small coupling arising presumably from the quadrupole of the nitrogen. This shows the magnetic inequivalence of the two methylene protons at H2* and the fact that they couple each other, also supports the restricted rotation alluded to earlier. The more downfield multiplet (appears as double doublet when decoupled from H3*), having J_g = 13.7 Hz and J_v = 8.5 Hz belongs to the proton of H2* *cis* to H1*, while the multiplet at 1.68 ppm belongs to the proton *trans* to H1* with J_g = 13.7 Hz and J_v = 5.7 Hz.

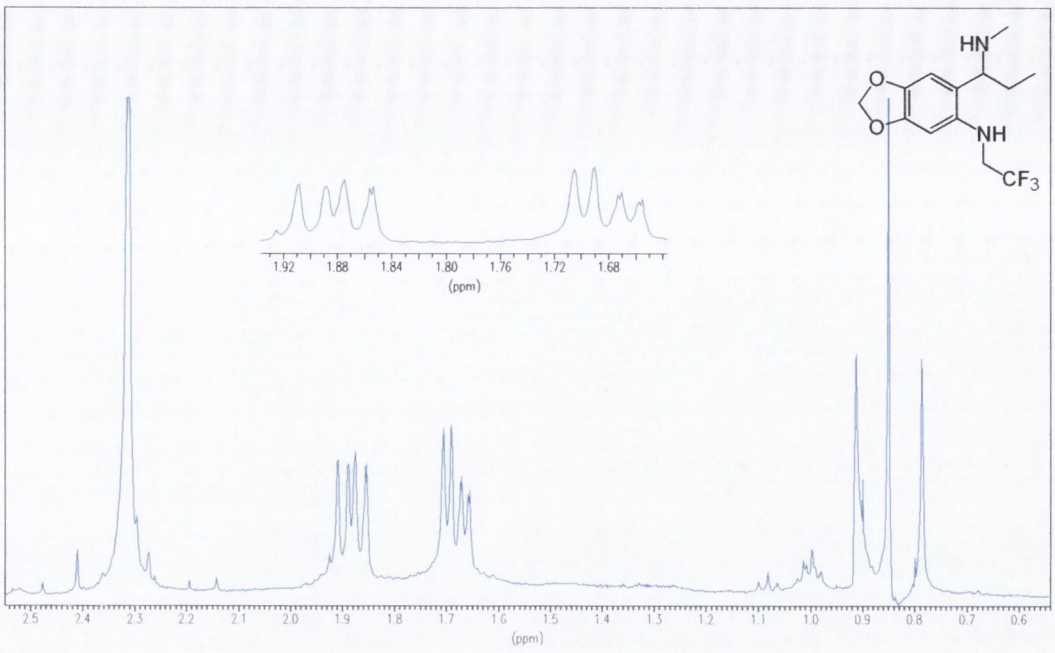


Figure 2-15: Spin decoupling experiment on 191

Table 2-5: Yields and IR for compound 191

Compd.	IR	Yield %
189	3434, 1638, 1479, 1035	28
191	3429, 1481, 1267, 1040, 935	35

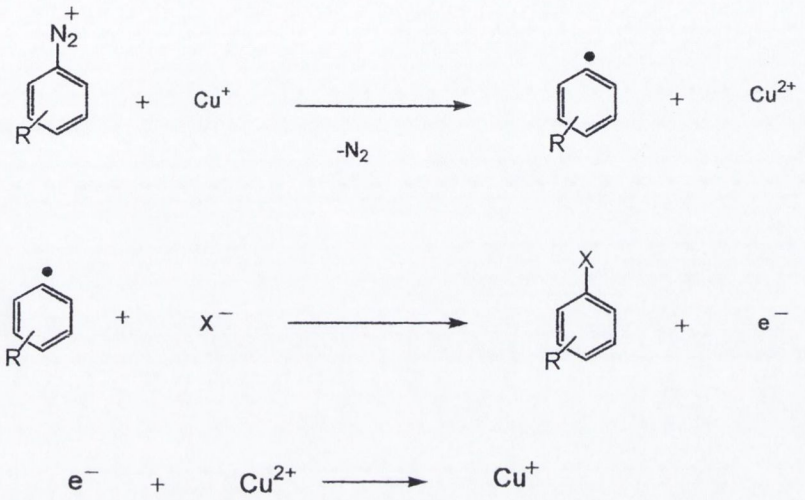
2.3.6 Aromatic Iodination of 1-phenylethylamine

Iodination at position six of the 1-phenylethylamine was viewed as an important substitution for the following reasons:

1) It provides an interesting product to compare with the bromide **174** in studying the effects of various halogens in this region of the pharmacophore.
2) It also provides an opportunity for further coupling reactions to produce various new C-C bonds.

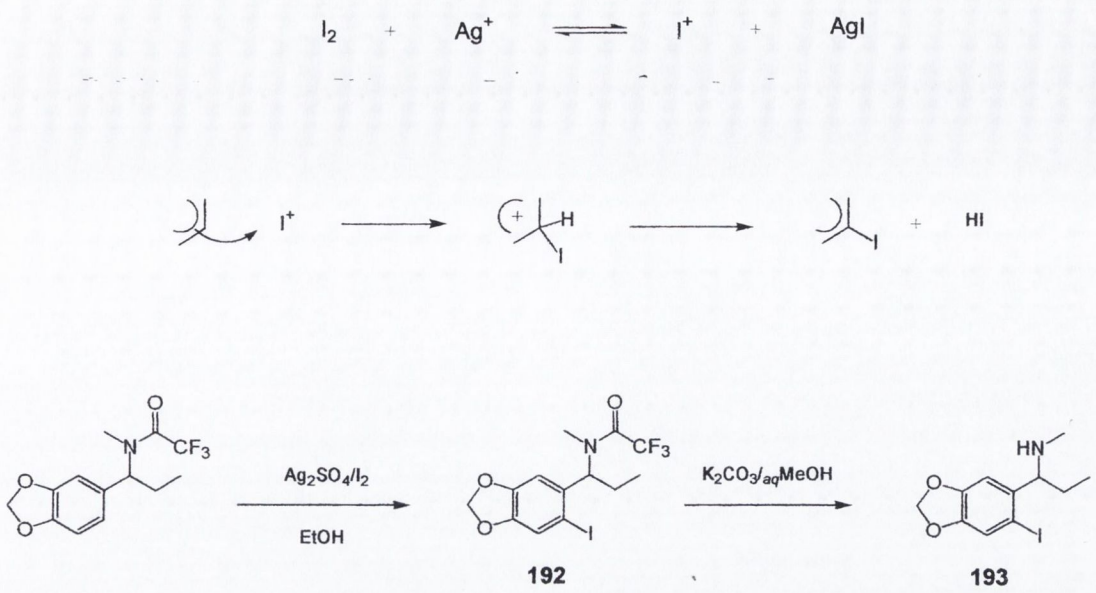
In a review by Merkushev the potential for derivatisation of aromatic halides and the different methods of their synthesis is reviewed.[182] Thioalkylation, trifluoromethylation, alkylation and palladium catalysed cross coupling reactions are just a sample of the potential derivations that are accessible from aromatic iodides.[182] When aryl bromides are utilised in palladium catalysed cross coupling reactions, the rate limiting step of the catalytic cycle is that of oxidative addition.[183] By using an aryl iodide, the use of phosphine substituted ligands is not required. [183]

There are various routes from which an aryl iodide can be synthesised. One of the most useful methods is the substitution of a diazonium salt known as the Sandmeyer reaction Scheme 2-21.[141] There is evidence that I^- is not the attacking nucleophile. The radical mechanism given is in Scheme 2-21.[152]



Scheme 2-21: Sandmeyer iodination

Iodination by molecular iodine does not occur easily since it is such a weak electrophile (unlike bromination with elemental bromine).[184] However, Young *et al* were able to iodinate an aldehyde protected piperonal in *n*-BuLi/DME at -78°C with iodine.[185] Direct iodination by using acetic acid as solvent and adding solid iodine followed by a nitric/sulphuric acid mixture is known as the Tronov-Novikov method, where sulphuric and nitric acid acts as the oxidants.[182] Another strategy used in aromatic iodination, is the use of Ag(I) species as oxidants/Lewis acids, with iodine.[186, 187] This method has been utilised in the iodination of various amphetamines as well as tetrahydrobenzoxepins.[147, 186, 188] A mechanistic study by Galli showed several different silver (I) salts were as efficient as Ag_2SO_4 , all of which were incapable of oxidising the aromatic ring to the radical cation and also that proton-deiodination does not occur.[189] This method was chosen as a suitable method for the iodination of the TFA protected amine **171** Scheme 2-22.



Scheme 2-22: Aromatic Iodination

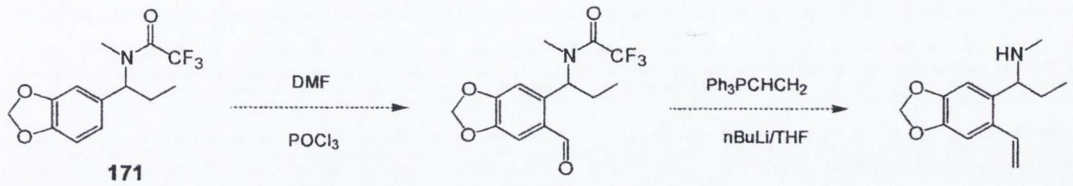
Iodination of **171** proceeded smoothly to give the iodinated intermediate **192** in 65% yield as a colourless solid. TFA base hydrolysis in aqueous methanol afforded the final product **193** in 72% yield as a colourless oil. The iodinated intermediate **192** was immediately evident from the substitution pattern in the aromatic region of the ^{1}H NMR, with two sharp singlets both integrating for one hydrogen, each occurring at 6.90 and 7.36 ppm. They were assigned as H5 and H2 respectively. The usual patterns for the series were evident elsewhere in the ^{1}H NMR spectrum with the ethyl group triplet integrating for three protons resonating at 0.97 ppm, J = 7.5 Hz and the multiplet from 1.93 to 2.01 ppm integrating for two protons. The N-methyl singlet was evident at 2.79 ppm integrating for three protons. In the ^{13}C NMR spectrum the evidence of iodination was observed in the quaternary carbon peak at the unusually shielded shift value of 90.21 ppm, characteristic of an iodo-substituted aromatic carbon. The peak representing the N-methyl carbon was split into a quartet with J = 4 Hz resulting from the long range C-F coupling experienced from the TFA protecting group. Table 2-6 gives the yields ^{13}C NMR and IR data of compounds **192-193**.

Table 2-6: IR, yields and ^{13}C NMR data of 171, 192, 193

Compd.	IR bands cm^{-1}	ArC-6 ^{13}C NMR (ppm)	Yield %
171	1144, 1040, 767	121.17	80
192	1698, 1488, 1038, 881	90.21	65
193	3418, 1472, 1039, 884	88.42	72

2.3.7 Allylic substitution *via* Stille coupling

The isolation of iodide **192** provided the potential access to a variety of new compounds. One possibility was the synthesis of a C-6-ethyl derivative, providing π-electrons without much steric bulk. Routes initially considered were Vilsmeier formylation of **171**, followed by Wittig olefination (Scheme 2-21). The availability of the iodide **192** afforded an alternative route for synthesis.



171

Scheme 2-23: Proposed synthesis of 6-vinyl derivative

However, in what is known as the Stille reaction, organic electrophiles (including aryl halides) can be cross coupled with organo-tin reagents to afford a new carbon-carbon bond.[190] The palladium catalysed Stille reaction in Scheme 2-24, is similar to the Suzuki reaction. The three main steps are oxidative addition, transmetalation and reductive elimination. The rate limiting step in this reaction is believed to be transmetalation which proceeds *via* ligand dissociation and formation of a Pd(II)-stannane π-complex, illustrated in Figure 2-16.[191]

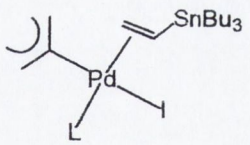
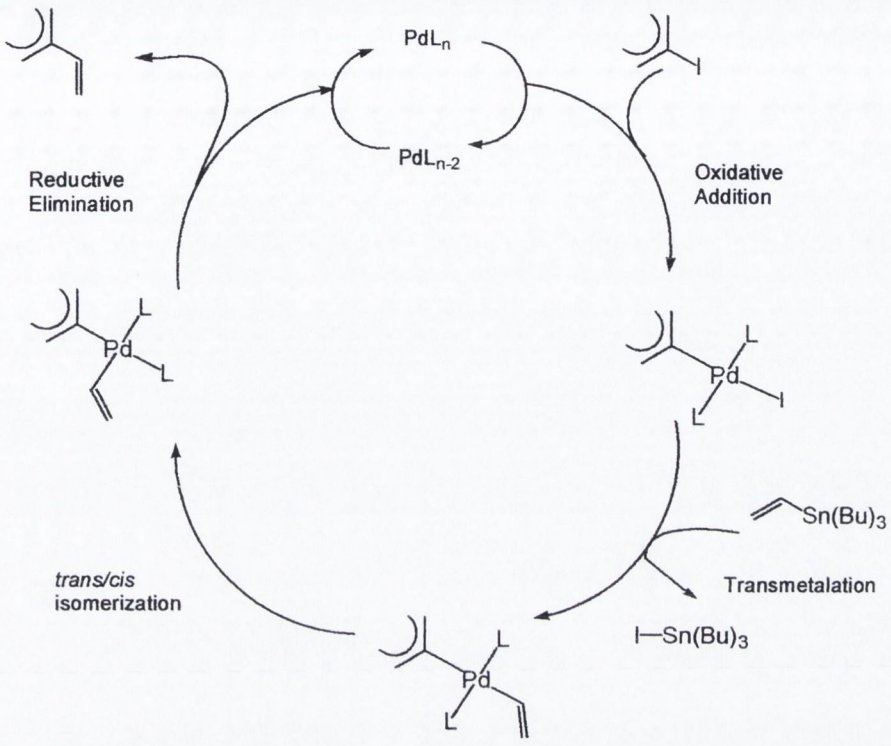


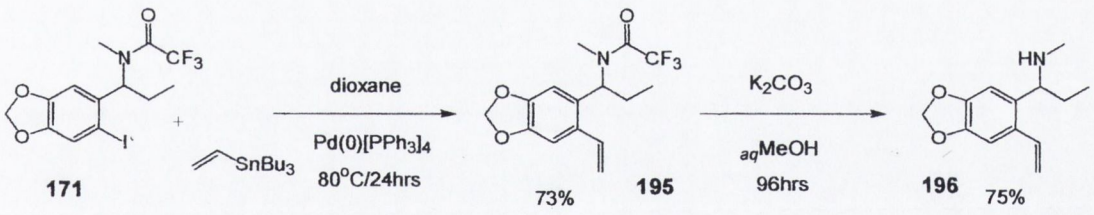
Figure 2-16: Possible π-intermediate in Stille transmetalation[191]

The Stille reaction has been modified with the use of Cu(I) cocatalysts, which are believed to scavenge any free ligand in solution (free ligands in solution are believed to inhibit the Stille reaction) resulting in a one hundred fold rate increase over the more traditional methods.[192] The Stille reaction, compared to the route given in Scheme 2-21, reduced the number of steps and with the conditions being somewhat milder it was chosen as the most suitable method. The reaction was carried out in dioxane under anhydrous conditions. The R_f of the product **195** was expected to be similar to the starting material **192**, fortunately this did not turn out to be the case and the reaction provided the vinyl coupled intermediate **195** cleanly in 72% yield

with base hydrolysis of **195** in carbonate yielding the final product **196** as the free base (Scheme 2-25).



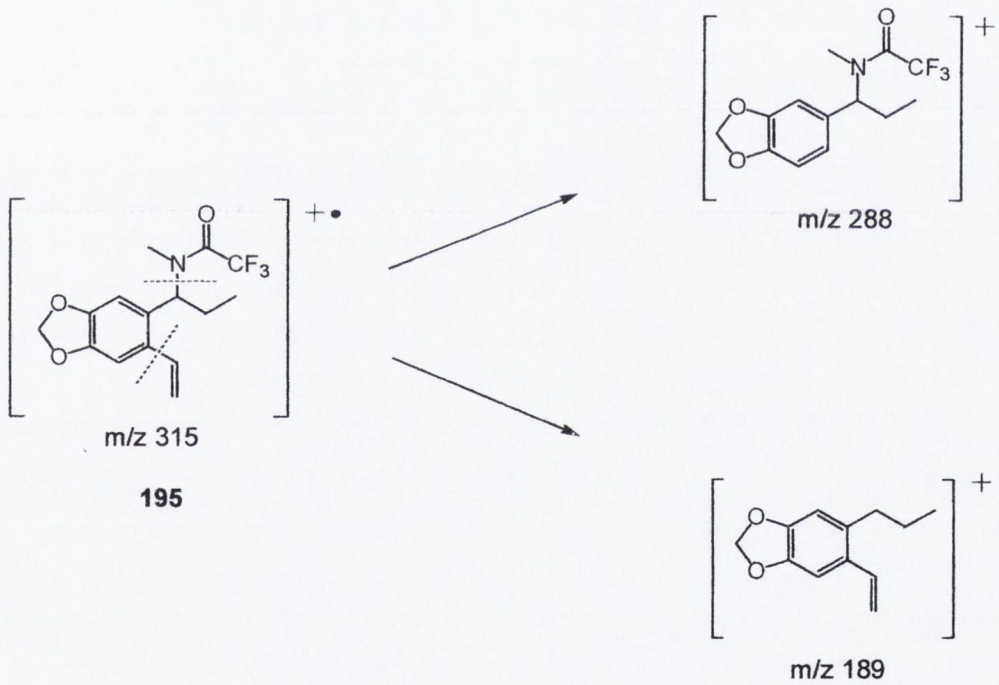
Scheme 2-24: Mechanism for Stille cross coupling[190]



Scheme 2-25: Stille cross coupling

The intermediate **195** was isolated as a fawn solid with elemental analysis confirming the molecular formula to be $C_{15}H_{16}F_3NO_3$. In the ^{1}H NMR of **195** the vinyl group was immediately apparent as three sets of double doublets, rotamer splitting was not observed. The terminal protons of the vinylic group precess at 5.23 and 5.48 ppm with the latter corresponding to the one *trans* in respect of the vinyl CH. The double doublet at 5.48 ppm integrating for one proton, was assigned as *trans* resulting from the coupling constants where J_1 = 1.6 Hz and J_2 = 17.0 Hz. $J_2 = J_{trans}$ i.e. the coupling is sufficiently large to indicate *trans* coupling. The *geminal* coupling J_1 being so small, suggests the terminal protons in the vinylic group are almost magnetically equivalent. The dd at 5.23 ppm integrating for one proton, has J_{cis} =

10.8 Hz and J_{gem} = 1.6 Hz. The remaining *dd* of the vinylic system resonates at the more down field shift value of 6.79 ppm, resulting from the anisotropic effect of the aromatic ring. This *dd* integrating again for one proton, has two large J-values equating to both *cis* and *trans* coupling with J_{trans} = 17.0 Hz and J_{cis} = 10.8 Hz. The aromatic protons again emerge as two distinct singlets pointing toward ArC6 as the derivatised carbon. In the ^{13}C NMR spectrum the vinylic CH appears at 106.69 ppm, while the CH_2 occurs at 115.17 ppm and is inverted in the Dept 135 experiment. The N-methyl group appears as a quartet with J = 4 Hz (long range C-F coupling). The TFA group is evident from the pair of quaternary quartets. The $\underline{C}F_3$ carbon forms a quartet at 155.55 ppm with J = 247 Hz, with the $\underline{C}OCF_3$ carbonyl carbon at 156.72 ppm with J = 36 Hz. In the LRMS the molecular ion appears as 70% of the base peak at 315 m/z. The predominant ions being m/z 288 (28), 246 (38) and 189 (100). The fragments are suggested in Scheme 2-26.



Scheme 2-26: Selected LRMS fragments of 195

Base hydrolysis afforded the secondary amine final product **196** in 74% yield. The ^1H NMR is shown in Figure 2-17. The allyl pattern is clearly visible as described for the protected compound **195**. The most striking difference being the change in chemical shift for the proton H1, *i.e.* 5.77 ppm for **195** and 3.81 ppm in the product **196**. In the ^{13}C spectra the N-methyl peak collapses to a singlet at 34.36 ppm. The quaternary signals observed for the TFA carbons are absent.

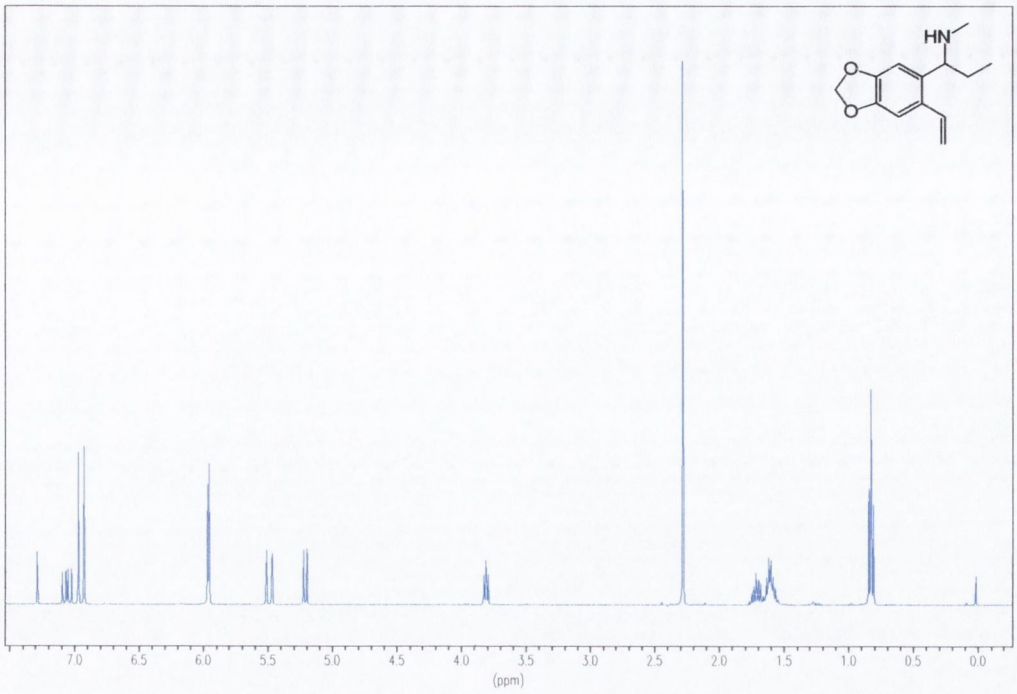


Figure 2-17: ^{1}H NMR spectrum of free base final product 196

2.3.8 Vinylic substitution at position-6 *via* the Heck reaction

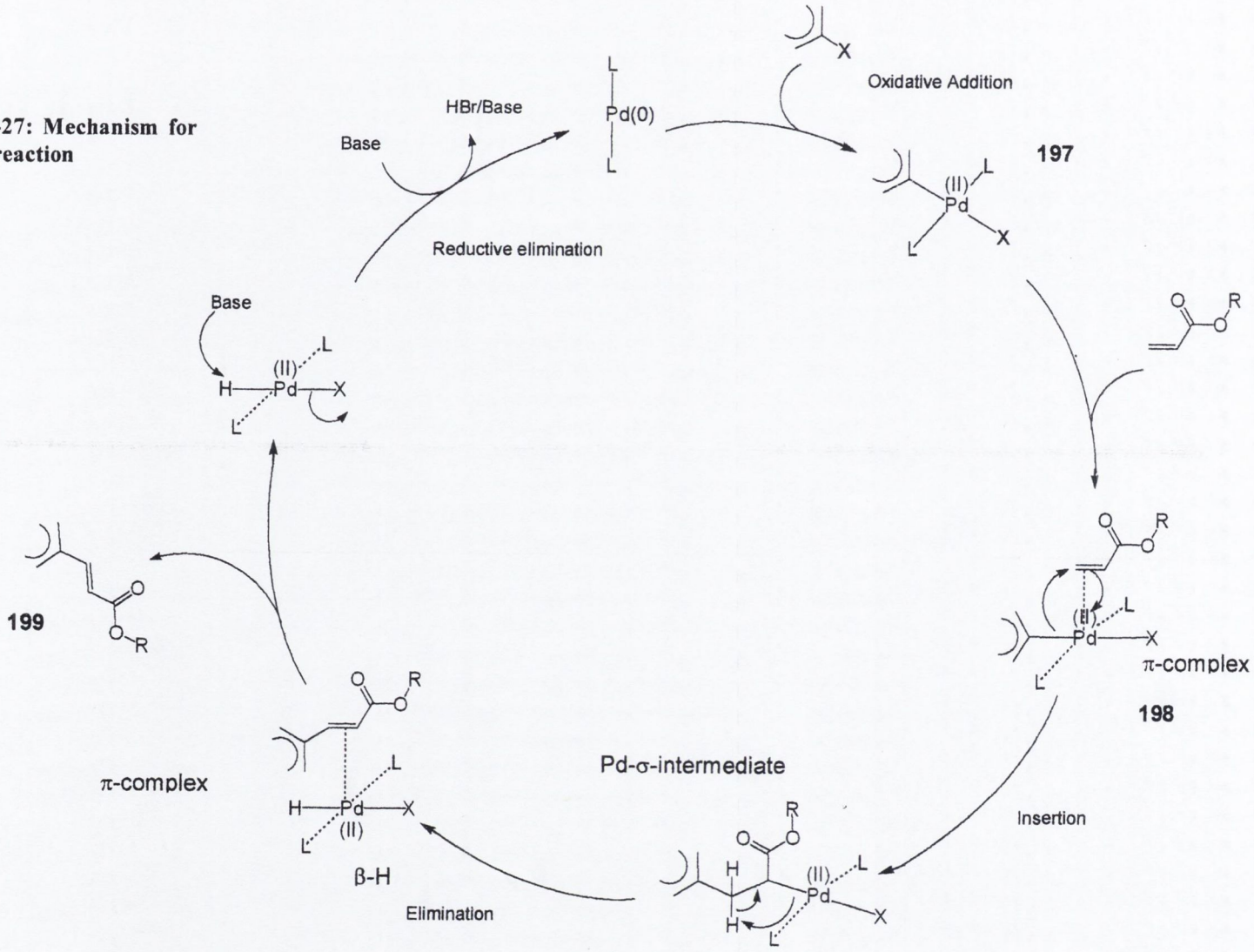
The introduction of a series of vinyl substituents at C-6 of the halogenated 1-phenylethylamine structure was achieved using Heck type chemistry. The Heck reaction is a palladium catalysed reaction capable of coupling aryl or alkenyl halides with alkenes.[193] Although palladium is used as a catalyst, the mechanism is a little more complex than those mentioned thus far. The mechanism is given in Scheme 2-27.[194]

- Oxidative addition sees the palladium oxidation state increase from Pd(0) to Pd(II), since two non-bonding electrons of palladium are involved in bonding forming a σ-arylpalladium(II)complex **197**. The rate of oxidative addition follows the series $ArN_2X > I^- >> OTf^- > Br^- >> Cl^-$.[195] Iodides are reactive at room temperature even without the need for phosphine ligands and can be selectively reacted in the presence of aryl bromides.[183, 196]
- Various unsaturated bonds can insert themselves into the Pd-C bond **198**, which can take place in one of two ways: α,β- or α,α-.[193] The regioselectivity of this reaction is determined by the formation of the π-complex **198**, followed by the insertion step. [197, 198]

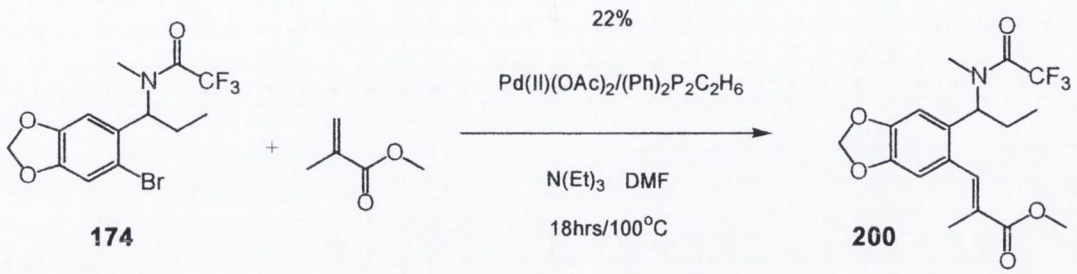
- Insertion dictates whether the aryl carbon will be added to the α- or β- vinyl carbon (Scheme 2-25). Steric factors often usually result in terminally arylated.[199]
- β-hydride elimination can take place, with the hydride *syn* (if there are two β-hydrogens) being transferred to the palladium, giving a *trans* alkene **199** in the event.
- Reductive elimination is driven by the presence of base which also acts to neutralise the acid produced in this step.[199]

Fukuda *et al*, introduced an ethylacrylate side chain, using a Heck reaction, to both aryl-triflates and arylbromides.[200] In both cases 1,3-(diphenylphosphino)propane, a *bidentate* ligand, was employed.[200] Some interesting Heck couplings have also been reported between alkenyl tosylates and various olefins.[201] Terao *et al* have demonstrated the α-arylation of aldehydes with aryl bromides.[202]One interesting side chain which could potentially undergo further derivatisation is the acrylate moiety depicted as the olefin in Scheme 2-27. Choi *et al* was able to couple a 5-iodouracil with methyl acrylate.[203] In examining the effects of various ligands in the Heck reaction, Qadair *et al* coupled methyl acrylate with various aryl bromides and aryl iodides and also determined that *bidentate* ligands had greater catalyst stability and a higher turnover rate.[183] It was also noted that the reaction with aryl iodides is not ligand accelerated.[183]

Scheme 2-27: Mechanism for the Heck reaction



The initial olefinic coupling reaction attempted was between the TFA protected bromide **174** and methyl methacrylate. Initially palladium(0)-*tetrakis*triphenylphosphine was used as catalyst without any success. *Triortho*-tolyl triphenylphosphine also proved fruitless. The reaction temperature was limited to below 100°C as a result of catalyst instability at higher temperature. However, the *bidentate* palladium ligand 1,3-(diphenylphosphino)propane when utilised, provided the coupled product **200** in 22% yield (Scheme 2-28).

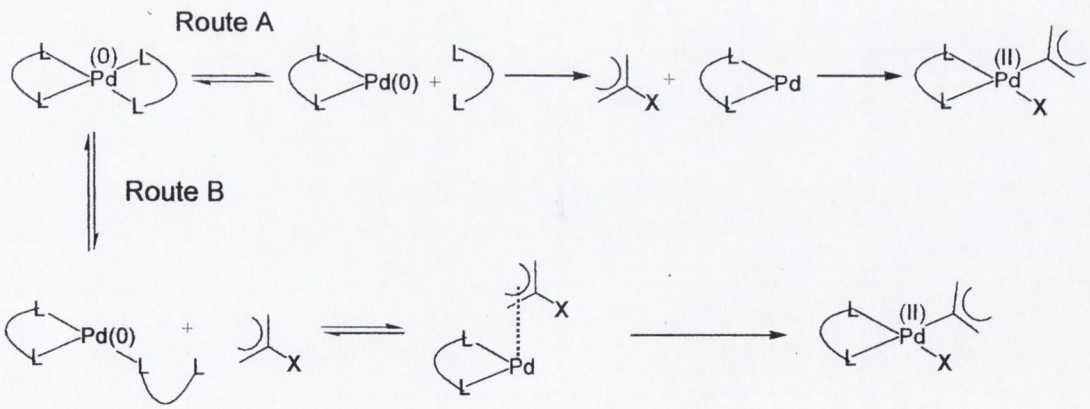


Scheme 2-28: Heck olefination

The *bidentate* ligand can undergo oxidative addition by one of two possible means (Scheme 2-29):

A) loss of one of the chelated species to immediately leave two sites free in the palladium species for complexation or

B) the dissociation of one of the chelating sites resulting from the formation of ArX through a number of steps.[204]



Scheme 2-29: Oxidative addition of palladium species with *bidentate* ligands

Monitoring of the reaction illustrated in Scheme 2-28 by TLC indicated the presence of product has a bright blue fluorescent spot, with R_f = 0.29 in a 70:30 hexane:diethyl ether eluent. After 18 hrs, the black metal precipitate provided evidence that the

palladium species was no longer in solution, therefore the catalysis had finished and the reaction could be worked up. The product was identified primarily by ^{1}H and ^{13}C NMR. The rotamer splitting was present in a ratio of 9:1. The proton NMR indicated two new methyl groups in the molecule with two singlets integrating for three protons each resonating at 1.91 and 3.81 ppm (R1). These were assigned as the methylene group attached to the vinyl carbon and the methyl ester respectively. The minor rotamer (R2) for the methyl ester resonated at 3.75 ppm integrating for 0.31 protons while the major isomer integrated for 2.72 protons. The methyl group attached to the vinylic moiety overlaps with the complex multiplet assigned for H2. The minor rotamer was not distinguishable from the multiplet. The signal for the vinylic proton resonates at the deshielded shift of 7.52 ppm, resulting from the anisotropic effect of the aromatic ring with the rotamers equivalent, therefore it was used for calibrating the integration. The aromatic singlets were evident as the usual pair of sharp singlets at 6.74 and 6.93 ppm both integrating for 0.90 protons (R1) with the minor rotamers (R2) precessing at 6.69 and 6.89 ppm both integrating for 0.12 protons. The aromatic singlets indicate the substitution pattern shown in Scheme 2-28. The proton peak for H1 exists as a double doublet at 5.55 ppm, with J_1 = 8.6 Hz and J_2 = 6.7 Hz and integrating for 0.9 protons with the minor rotamer at 5.74 ppm, appearing as a triplet (J = 7.7 Hz) integrating for 0.12 protons. Evidence for the existance of the TFA group could be found in the ^{19}F NMR spectra, with a major peak at a shift value of 70.58 ppm with another small peak at 70.07 ppm.

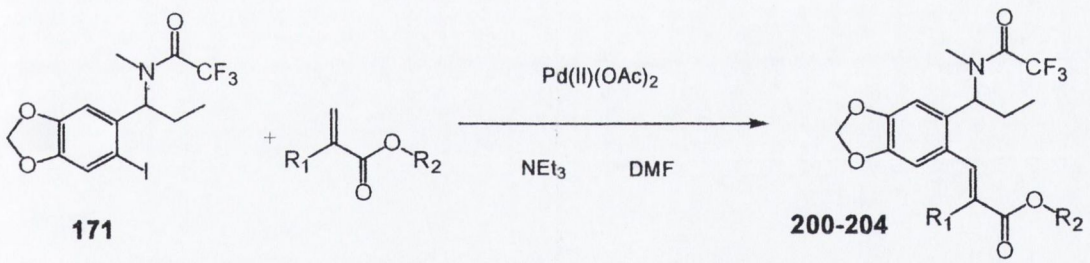
The ^{13}C NMR spectrum displayed the four methyl groups which were not evident in the Dept 90 experiment, with the N-methyl displaying a quartet at 28.60 ppm with J = 4 Hz. Four CH peaks were observed with one being in the aliphatic region. A total of eight quaternary carbons were noted from their absence in the Dept experiments. The triflouroacetyl carbons were evident, with the carbonyl quartet (J = 35 Hz) at 156.76 ppm and the trifluoromethyl group at 116.90 ppm split into a quartet with a coupling constant of J = 289 Hz , the minor rotamer peaks of quaternary carbon signals were not observed. The peak at 168.19 ppm was assigned as the carbonyl carbon of the methyl ester. The quaternary peaks at 146.95 and 147.64 ppm were assigned ArC4 and ArC3 respectively. The signal corresponding to the vinylic quaternary carbon was recognized as the peak at 130.08 ppm. The remaining quaternary signals at 129.65 and 130.46 ppm were assigned as ArC1 and ArC6. The dioxole carbon was inverted in the Dept 135 experiment and had a chemical shift of 101.60 ppm with the minor isomer present at 101.31 ppm. The exact mass for the molecular ion plus sodium was calculated as m/z (M^{+}+Na) 410.1191, the observed

value being m/z 410.1182 corresponds to a molecular formula of $C_{18}H_{20}F_3NO_5$. The yields and the prominent IR absorbtion bands for **200** are presented in Table 2-7.

Table 2-7: IR data and yields for Heck product 200

Compd.	IR υ cm^{-1}	Yield %
200	1638, 1488, 1244, 1144	22

In an attempt to improve the yield of the vinyl substitution, an aryl iodide was considered as substrate in place of the aryl bromide used in Scheme 2-28. It has been reported that ring activated aryl bromides are difficult to couple with olefins in the Heck reaction.[196] It is also known that the activity of aryl iodides is higher than the aryl bromides in these kinds of reactions, with many aryl iodides coupling with olefins in the absence of palladium ligands.[183, 193, 194, 196, 205] The effect of increased pressure and the use of aryl iodides increases the yields of coupled products.[205] With this in mind the reaction was attempted with the iodide **171**, methyl methacrylate, triethylamine as base and palladium(II)acetate was the catalyst used without any phosphonium ligands to give **200-204** Scheme 2-30. The reaction could be carried out at 140°C without the risk of decomposing any palladium-phosphino complexes and a thick walled pressure tube was employed as the reaction vessel, sealed with a teflon cap.



Scheme 2-30: Improved Heck coupling

Table 2-8: IR, yields and melting points of products from the optimised Heck reaction

Compd.	R_1	R_2	IR υ cm^{-1}	m.p.°C	Yield%
201	H	CH_3	1702, 1687, 1038, 854	160-164	58
202	H	C_2H_5	1712, 1683, 1489, 1268, 1027	122-124	62
203	H	Bn	1688, 1407, 1259, 1146, 1038,	oil	47
204	CH_3	Ph	1644, 1486, 1243, 1038	oil	28
200	CH_3	CH_3	1639, 1478, 1311, 1036, 933	oil	44

The reaction proceeded cleanly in four and a half hours to give the product **200** Scheme 2-28, in 58% yield. The coupling of aryl iodides with acrylates under pressure can form dimers in substantial yields, resulting from the coupling of a second aryl iodide to the first vinylic product.[205] Under the conditions used in Scheme 2-30, no such dimers were isolated. Unfortunately none of the compounds **200-204** listed in Scheme 2-30 yielded the free base final product by acid or base hydrolysis (anhydrous or aqueous). A complex array of compounds resulted, none of which were the desired structure. The reaction was again attempted with a Boc group used in place of the TFA protecting group, using the boc protected iodide **194**. Mild acid hydrolysis again failed to yield any products from the Boc protected coupled product **194a**. When the coupling was attempted on the unprotected secondary amine, the reaction again failed to yield any coupled products of significant yield. It has been reported that amino species can coordinate with palladium species, in some instances to help improve regio-selectivity.[206] However in this instance it was conceivable that the amino group was either interfering with the formation of the key π-complex **198**, or immediately degrading once the acrylate side chain was in place.

In an attempt to synthesis a compound containing both the acrylate side chain and a basic nitrogen at position one of the three carbon chain, the decision was taken to go through the synthesis with a tertiary N,N-dimethyl amino moiety at position one. This was to circumvent any degradation that may result from the possible attack of the π-electrons from the secondary nitrogen in any of the compounds **200-204** Table 2-8, to the β-vinylic carbon of the acrylate side chain. Initially the unlikely problem of iodinating the N-dimethylamine **159** occurred. The product was inseparable from the starting material and appeared to be in poor yield. The next step was to methylate the already iodinated secondary amine **171** (Scheme 2-31), this was achieved *via* a methylation using formic acid and formaldehyde, known as the Eschweiler-Clarke reaction.[152] Once the tertiary amine **205** was produced with the iodide at position-6 the Heck reaction was carried out with ethyl acrylate under the conditions previously described. The final product **206** was isolated as a clear oil in 8% yield. The yield may have been higher had the separation on silica gel not proved so difficult. The product **206** was characterised by the usual means. The ^{1}H NMR spectrum is provided in Figure 2-18. The double bond is easily assigned as *trans*geometry with J_{trans} = 16.4 Hz for the vinylic protons at 6.66 and 7.62 ppm.

Table 2-9: IR absorption bands and yield for 206

Compd	IR υ cm^{-1}	Yield %
206	3428, 1713, 1635, 1478, 1036	8

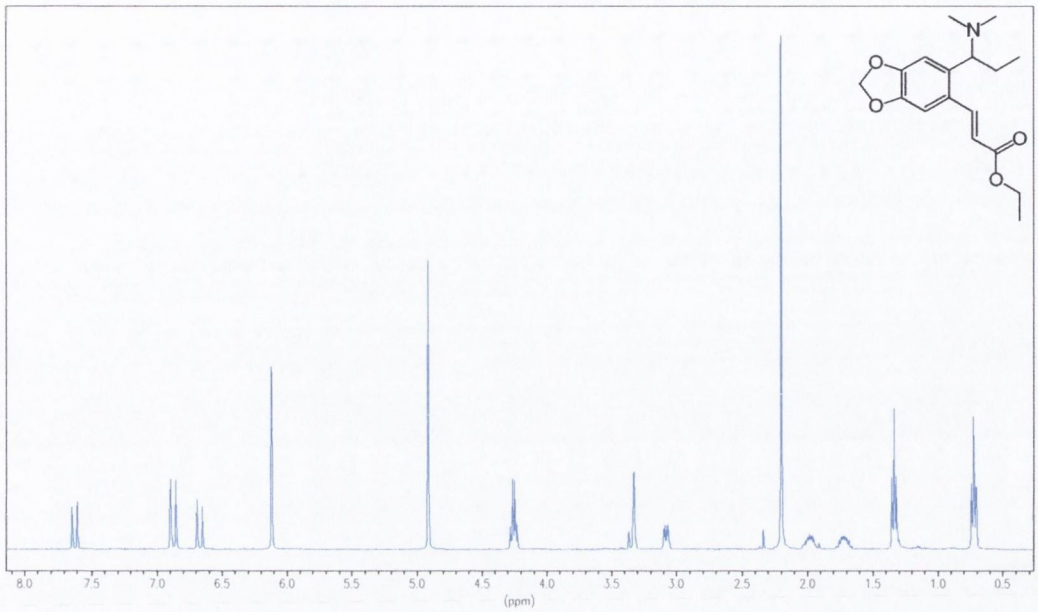
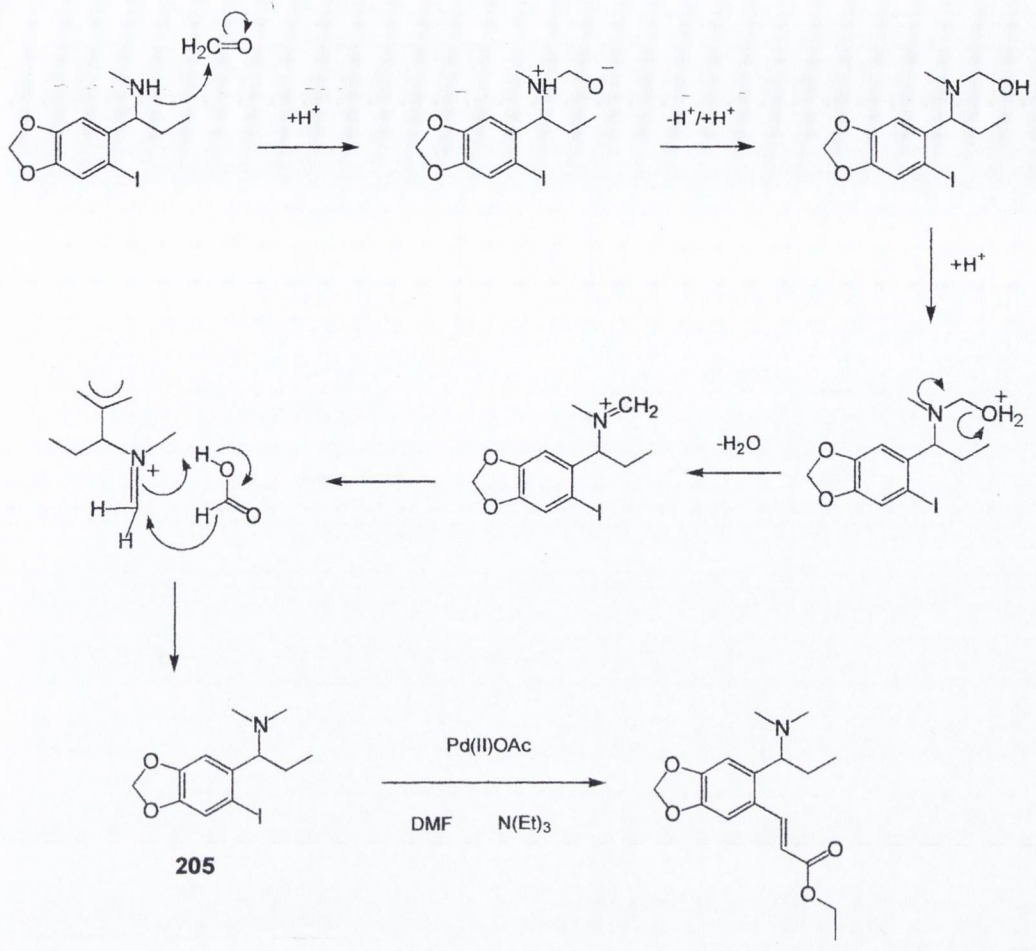


Figure 2-18: ^{1}H NMR of 206

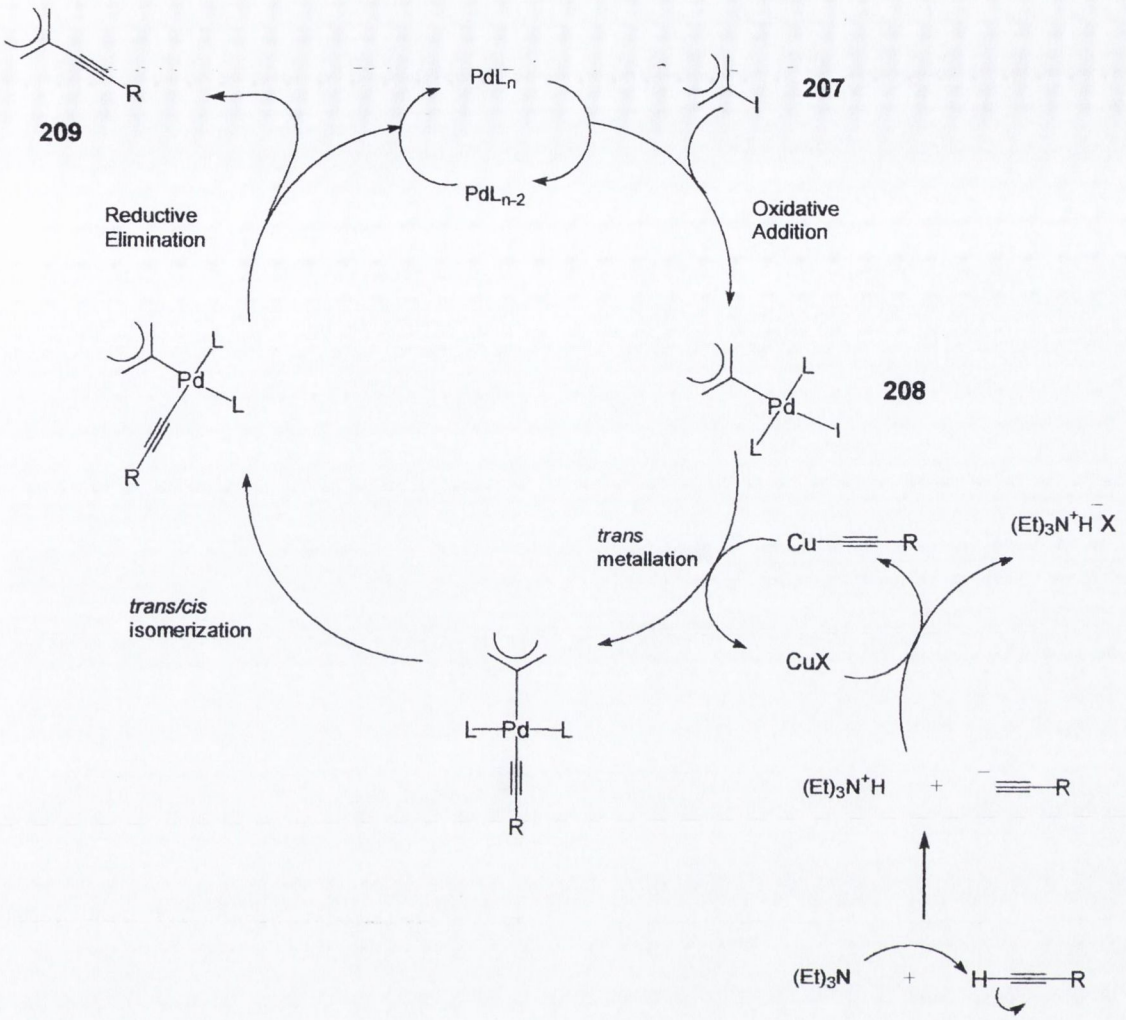


Scheme 2-31: Wallach alkylation followed by Heck olefination

2.1.1

2.3.9 Sonogashira alkynyl-coupling

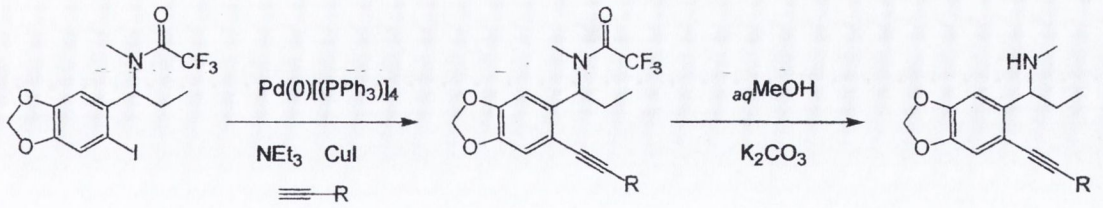
To further explore the postion six chemistry of these amphetamine derivatives, another palladium catalysed coupling reaction, namely the Sonogashira reaction, was employed to introduce *sp*-hybridised groups.[207] Keating synthesised MDMA analogues with alkynyl moieties (propargyl amine and propargyl alcohol) at position-6.[147] Mu *et al* were able to couple 4-phenyl-1-butyne with ring activated aromatic iodides in quantitative yields.[208] The alkynyl aromatic substitution of ring deactivated quinolones was carried out using propargyl alcohol and the corresponding iodide in good yield using the Sonogashira coupling.[209] The mechanism for the catalytic cycle of the Sonogashira reaction is given in Scheme 2-32.[207]



Scheme 2-32: Mechanism for Sonogashira coupling[207]

$Pd(0)(PPh_3)_2$ is the active catalyst which undergoes oxidative addition to the aryl halide **207** to form the complex **208** and this step is common to palladium catalysed coupling reactions. Copper (I) has been shown to scavenge free ligand, which can retard the catalytic process.[192] In this instance however it was used as a cocatalyst to alkynylate the aryl halide **207**. Internal rotation followed by reductive elimination yields the alkyne **209** as the final product with the palladium (0) species which can undergo another catalytic cycle.[207]

The Sonogashira alkynylation of iodide **171** was carried out using triethylamine as both solvent and reagent to give the intermediates **210-211** in good yields (Scheme 2-33). Deprotection of the TFA protecting group furnished the secondary amine final products in **212-213** moderate yields.



Scheme 2-33: Postion-6 alkynylation

In the ^{1}H NMR spectrum of **210**, the methylene group α to the OH produced a signal at the relatively deshielded value of 4.36 ppm, occurring as a multiplet and integrating for two protons. At 3.17 ppm a signal split into a triplet, integrating for one proton was assigned as the hydroxyl proton. The two alkynyl quaternary carbon signals were immediately apparent at 82.68 and 92.84 ppm in the ^{13}C NMR spectrum. Elemental analysis of **210** was calculated as C – 55.98%, H – 4.70%, N – 4.08%, with the experimental values found as C – 55.78%, H – 4.41%, N – 3.93%. The IR spectral data, yields and melting points are reported in Table 2-9.

Table 2-10: Yields, melting points and IR data for compounds 210-213

Compd	R	IR υ cm^{-1}	m.p.	Yield %
210	CH_2OH	3412, 2350, 1669, 1489, 1041	98-100	40
211	C_6H_5	1696, 2236, 1696, 1495, 1132, 1040	-	87
212	CH_2OH	3436, 2344, 1428, 1037	-	96
213	C_6H_5	3428, 2321, 1645, 1053	-	23

The palladium catalysed cross coupling reactions have become invaluable tools in the synthesis of more complex structures particularly natural products such as TMC-95A, Figure 2-19.

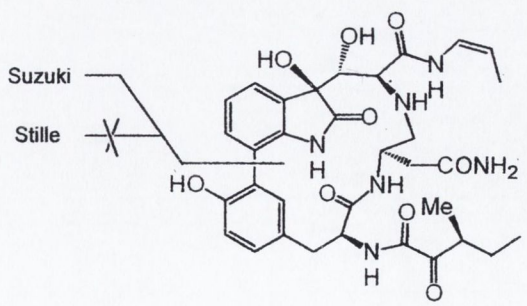
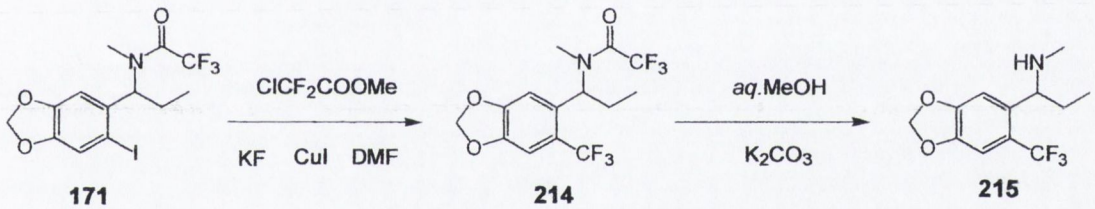


Figure 2-19: Palladium catalysed coupling reactions in synthesis of natural products[210]

Albrecht and Williams achieved the total synthesis of TMC-95A/B (Figure 2-19) in twenty two steps, with eighteen steps in the longest linear sequence. During the synthesis two key fragments were coupled by Suzuki arylation from the appropriate iodide and boronic ester. The initial attempt involved a Stille reaction using the corresponding aryl stannyl moiety and the aryl iodide but the yields were not sufficient for further synthesis and several side products accompanied the desired intermediate.[210]

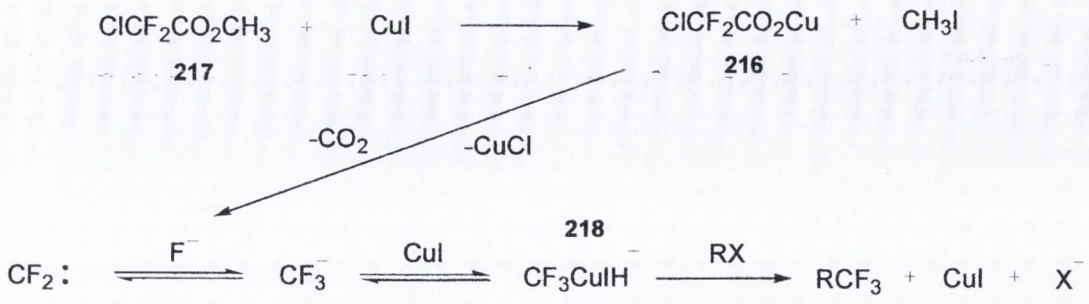
2.3.10 Postion-6 trifluoromethylation

A trifluoromethyl group is always a useful moiety when carrying out an SAR. It is very electronegative, small in radius, a hydogen bond accepting and it also imparts an increase in lipophilicity on the molecule to which it is being attached.[211] With this in mind the method of Su *et al* was employed to introduce a trifluoromethyl group in place of the iodide in **171** (Scheme 2-34).[212]



Scheme 2-34: Position-6 trifluoromethylation

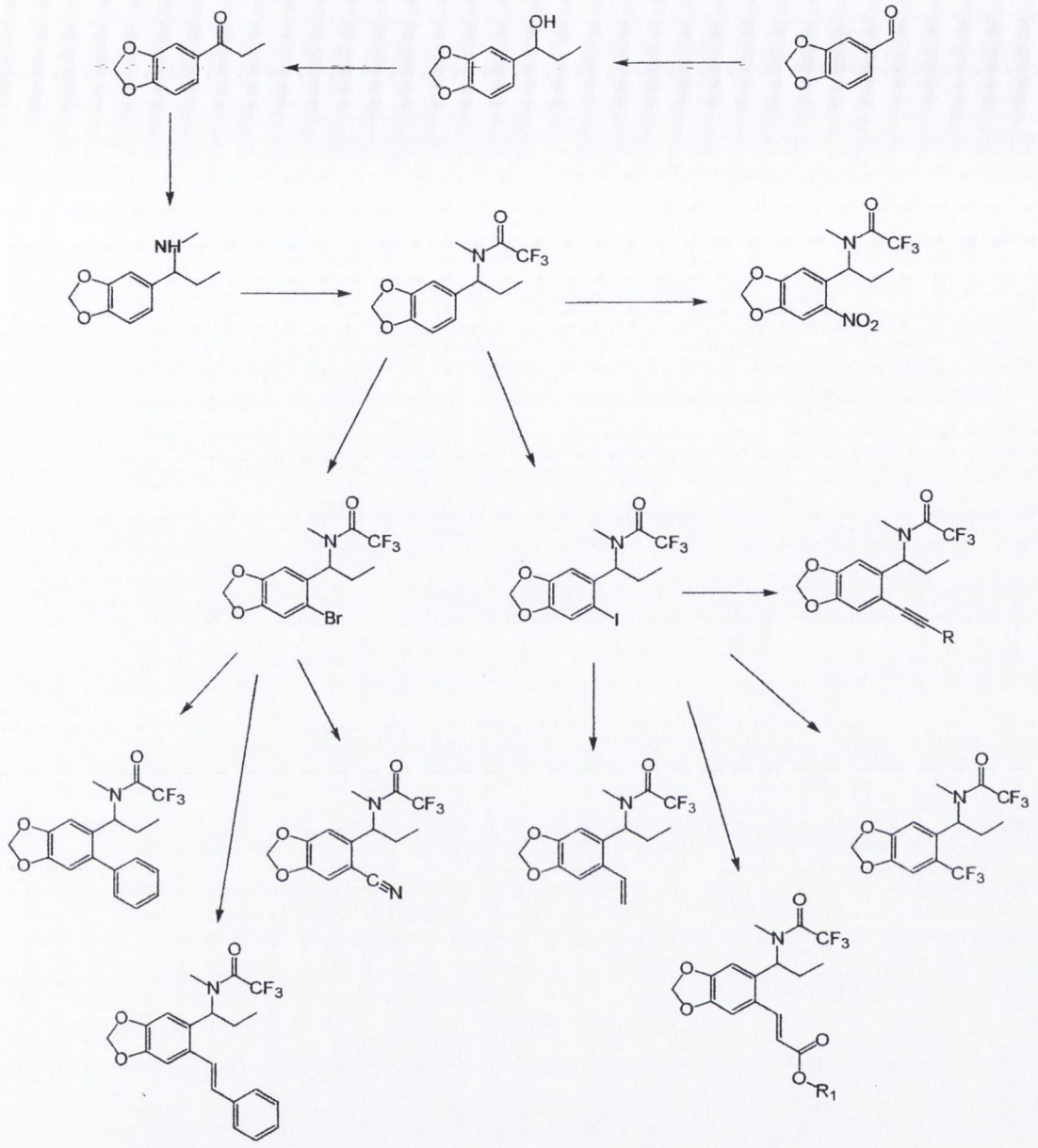
The mechanism for this reaction is described by Su, (Scheme 2-35).[212] A copper salt **216** is formed between the trifluoromethylating agent **217** and CuI. Decarboxylation of the salt **216** forms $:CF_2$ which forms CF_3^- when F^- ions are present. CuI (which is essential for the reaction) shifts the equilibrium to the right forming the trifluoromethylating entity **218** which can react with the aryl iodide to give the desired product.



Scheme 2-35: Mechanism for trifluoromethylation[212]

In the present work, the intermediate **214** was isolated in 59% yield as a pale yellow oil that solidified on standing. In the ^{1}H NMR spectrum, the singlet resonating at 2.82 ppm integrating for three protons was assigned as the N-methyl. The dioxole protons were evident as the characteristic sharp singlet at 6.10 ppm. The aromatic protons were evident as two singlets corresponding to the substitution at position-6. The singlet at 7.12 ppm was assigned as ArH5 with the peak at 7.18 ppm representing ArH2, both singlets integrated for one proton each. The ^{13}C NMR spectra provided information on the reaction being successful with evidence of the trifluoromethyl group apparent from the quaternary signal split into a quartet (J = 270 Hz) at 123.74 ppm. A similar signal (J = 282 Hz) resonating at 116.53 ppm was assigned to the trifluoromethylene group from the TFA protecting group. Long range coupling from the trifluoroacetyl fluorine atoms splits the peak assigned as the N-methyl into a quartet (J = 4 Hz). Further proof of the aryl trifluoromethylene group can be obtained from the aromatic CH carbon signal, which is split into a quartet at 107.35 ppm (J = 7 Hz), the unusually small coupling constant can be attributed to long range C-F coupling and so this peak was assigned ArC5 as it remained unchanged in the Dept 90 experiment. The carbonyl signal in the TFA group occurs as a quartet (J = 35 Hz) at 156.76 ppm. The Dept 135 experiment showed two methylene carbons and the Dept 90 exhibited three CH carbons with two being aromatic. The secondary amine final product **215** was isolated as a clear oil.

The various substitutions, which were introduced onto the 1-phenylpropylamine structure **149** are summarized in Scheme 2-36. Each of the TFA protected initially synthesised compounds were deprotected by base hydrolysis in *aqueous* methanol. These provide a useful series of 1-phenylpropylamines for further pharmocological and SAR evaluation.



Scheme 2-36: A summary of position-6 substitutions of the series

Scheme 2-36 summarizes the various synthetic routes utilised in the exploration of the position-6 chemistry in this chapter.

3 Chapter Three: Studies in the stereoselective synthesis of (1)-phenylpropylamines and methylenedioxyamphetamine

3.1 Introduction

In the 1950's the pharmaceutical industry learned tragically the importance of chirality in drug design and manufacture. The thalidomide disaster arose as a result of the drug being administered as a racemic mixture of enantiomers. The (*S*) - enantiomer had the desired sedative therapeutic properties and was used to treat morning sickness in pregnant women, but the (*R*) – stereoisomer, its mirror image, was teratogenic and induced gross foetal abnormalities leading to the withdrawal of the drug.[213] This was an oversight from which suffering is still being felt to this day.

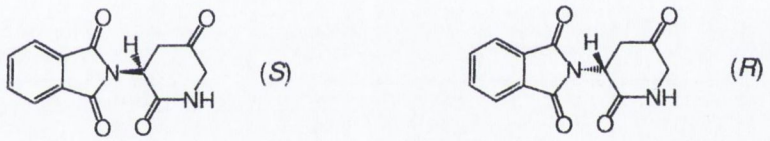


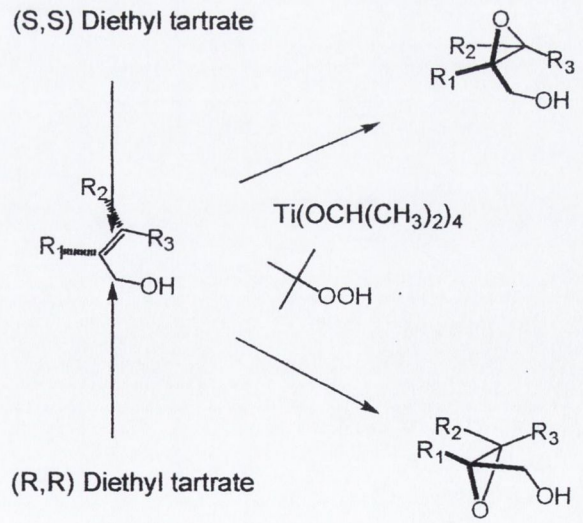
Figure 3-1: Stereoisomers of Thalidomide

The interactions of different enantiomers of a single chiral substance within a biological system can vary widely. As alluded to in Section 1.4.1, the hallucinogenic response of MDA **139** has been attributed to the (*R*) - stereoisomer, while the antidepressant response has been proposed as resulting from the effects of the (*S*) - enantiomer.[107] From plasma concentration studies on humans, the enantiomers of MDMA **140** have been shown to have varying metabolic profiles, with the (*R*) - enantiomer having a longer half life than its (*S*) – form.[214] A study on the introduction of a chiral centre substituent at position-4 of an hallucinogenic amphetamine found that a slight but non significant difference in binding resulted, however the side chain used at position-4 was an *iso*-butyl group. The activity at the receptors in question decreases on alkyl groups exceeding a propyl group or being branched.[215] With the biochemical mode of action often determined by stereochemistry, it was deemed necessary to gain the stereoisomers of the (1)-

phenylpropylamine amphetamine structural isomers either through synthesis or appropriate resolution.

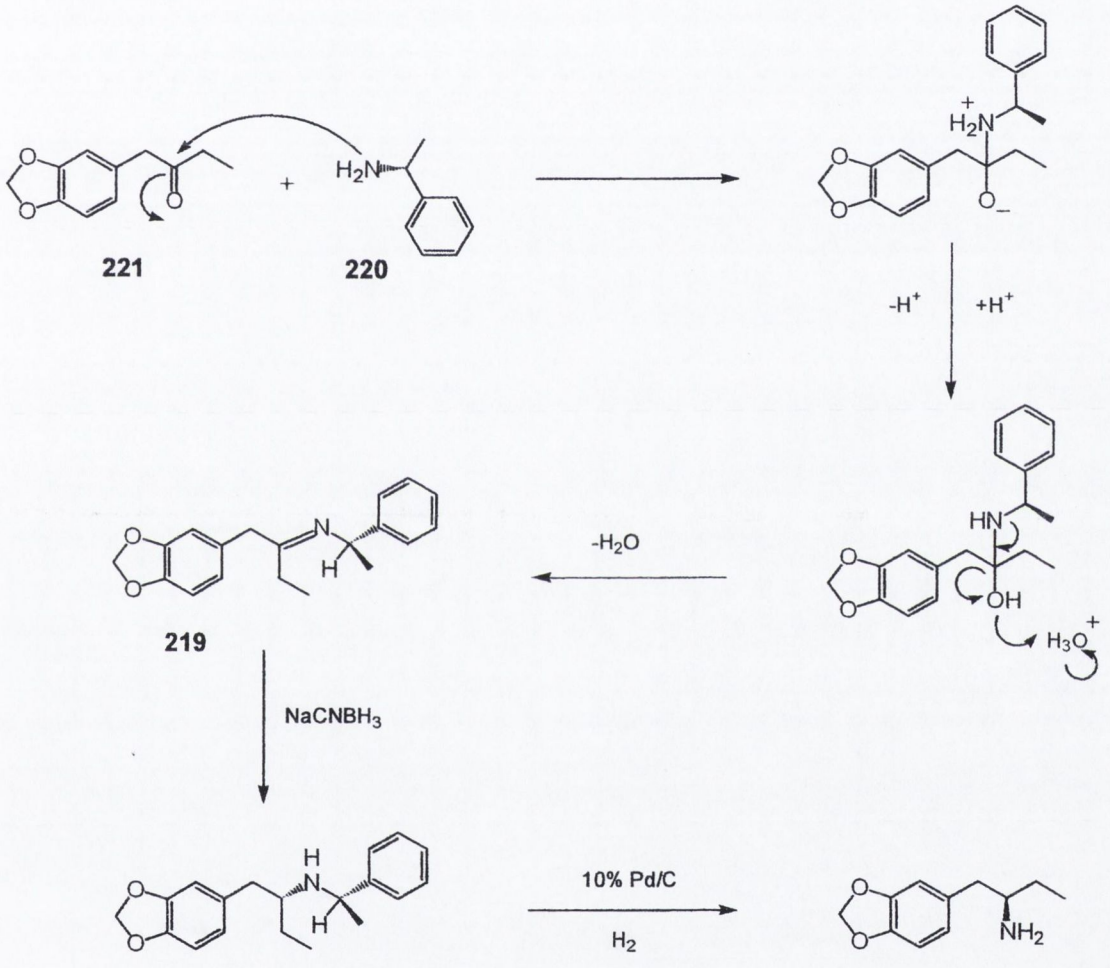
3.2 *The stereoselective synthesis of (R) and (S) phenylpropylamines*

There are a number of methods available to the chemist to resolve two enantiomers from a racemic mixture. One of the more common techniques being, a chromatographic procedure in which the stationary phase consists of a chiral moiety to which one enantiomer will have a higher affinity than the other, thus affecting a separation. Biochemical methods are used whereby one enantiomer of a racemic mixture can be metabolised by the organism leaving the required compound enantiomerically pure. Also the conversion of the racemic mixture into two sets of diastereomers allows a chromatographic separation without the use of chiral columns. The derivatising agent can then be removed leaving the resolved enantiomers. More recently attention has turned to stereoselective synthesis in an attempt to specifically synthesis the enantiomerically pure form of the chiral product, removing the need for tedious and timely separation. A typical example of this reaction is the enantioselective derivatisation of prochiral allylic alcohols. Selectivity is achieved by adding diethyl tartrate. This reaction is known as Sharpless epoxidation (Scheme 3-1).[216]



Scheme 3-1: Sharpeless epoxidation of allylic alcohols[216]

There are several examples in the literature of the synthesis of enantiomerically pure amphetamines and amphetamine type derivatives (Scheme 3-2) by stereoselectively reducing the imine bond formed in the intermediate **219**.[217-221] The imine is formed by reacting a primary chiral amine **220** with the corresponding ketone **221**, eliminating water in the process (Scheme 3-3). The enantioselectivity is achieved by the stereoselective reduction of the imine double bond in **221**, which is directed by the chirality of the benzyl amine moiety **220**.

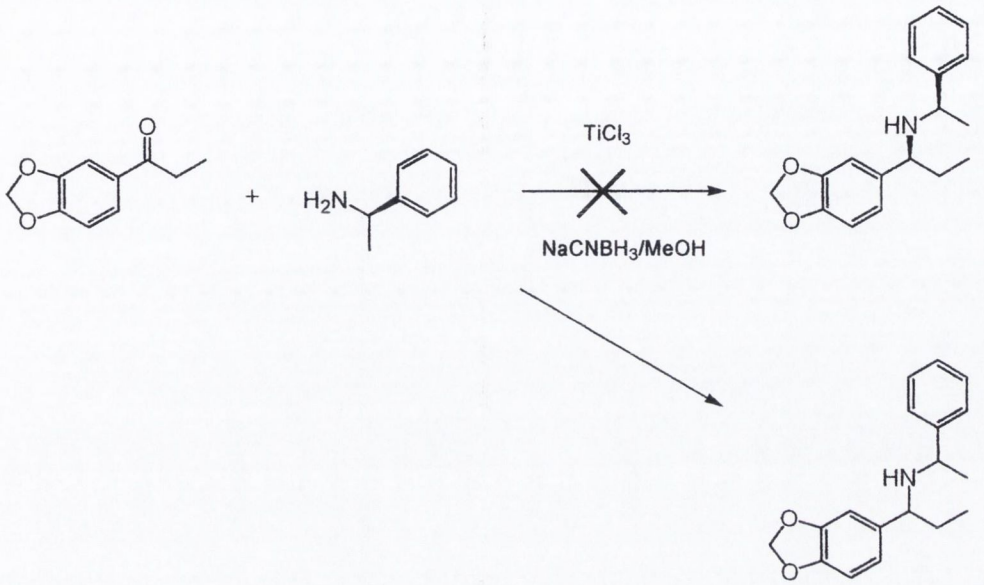


Scheme 3-2: Stereoselective synthesis by Nichols[217]

3.2.1 Stereoselective imine reduction

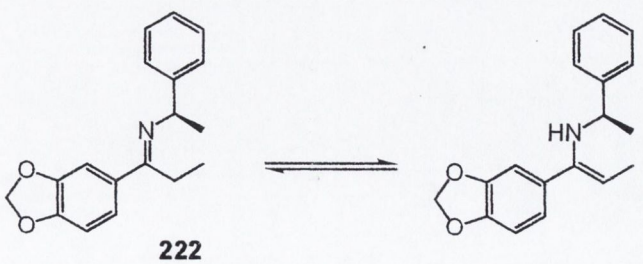
Vicario *et al* in the synthesis of alkaloids, carried out a similar reaction to the one shown in (Scheme 3-2), with the addition of a titanium catalyst to help form the desired imine intermediate.[145] The $TiCl_4$ catalysed reaction was attempted in the current work on account of the optimised reaction employed in Scheme 2-8.

Unfortunately the reduction of the imine was not stereoselective resulting in equal yields of the diastereomers (ratio determined from the ^1H nmr, which showed two sets of peaks in identical proportion) (Scheme 3-3).



Scheme 3-3: Attempted $TiCl_4$ catalysed imine formation followed by stereoselective reduction

The approach of dehydration and stereoselective imine reduction was attempted. Such reductions in a manner analogous to that described in Scheme 3-2, have been adapted to amines substituted α to the aryl group.[222-227] There were several factors which were considered when carrying out the imine reduction. Firstly the imine-enamine tautomerisation process (Scheme 3-4) would induce racemization at the chiral centre of interest, resulting in a mixture of diastereomers in the reduced intermediate.[145] However temperatures below -20°C prevents this process from taking place.[145]

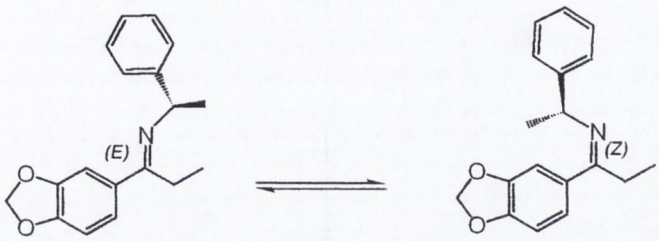


222

Scheme 3-4: Imine - enamine tautomers

Another system which could have a large bearing on the enantiomeric excess of the reaction is the potential *(E/Z)* isomerization of the imine **223-224** (Scheme 3-5). The

selectivity of the reducing agent is dependent on the borohydride species approaching the imine double bond from the least hindered side (Figure 3-2). With the phenyl ring α to the newly inserted stereocentre providing the bulk to direct the reduction stereospecifically, the least hindered side of the double bond is different in the *(Z)* form of the imine to that of the *(E)* (Scheme 3-5). The *(E/Z)* isomerization can occur from rotation of the single bond C1–N formed in the enamine tautomer.



223 **224**

Scheme 3-5: *E/Z* isomerization

A study of the asymmetric reduction of the type of imine bond shown in Scheme 3-4 concluded the palladium/charcoal catalysed hydrogenation of the (Z) isomer takes place at a faster rate than that of the *(E)* isomer.[226] By keeping the amount of catalyst small, the more reactive *(Z)* isomer was adsorbed faster than the *(E)* form, providing a higher stereoselectivity.[226] The relative rates of formation of the *(E/Z)* : imine-enamine isomers is structurally dependent and is determined largely by steric factors.[228, 229]

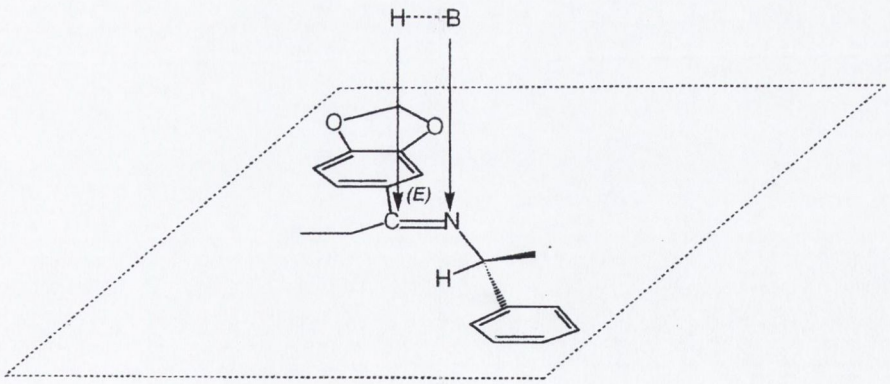
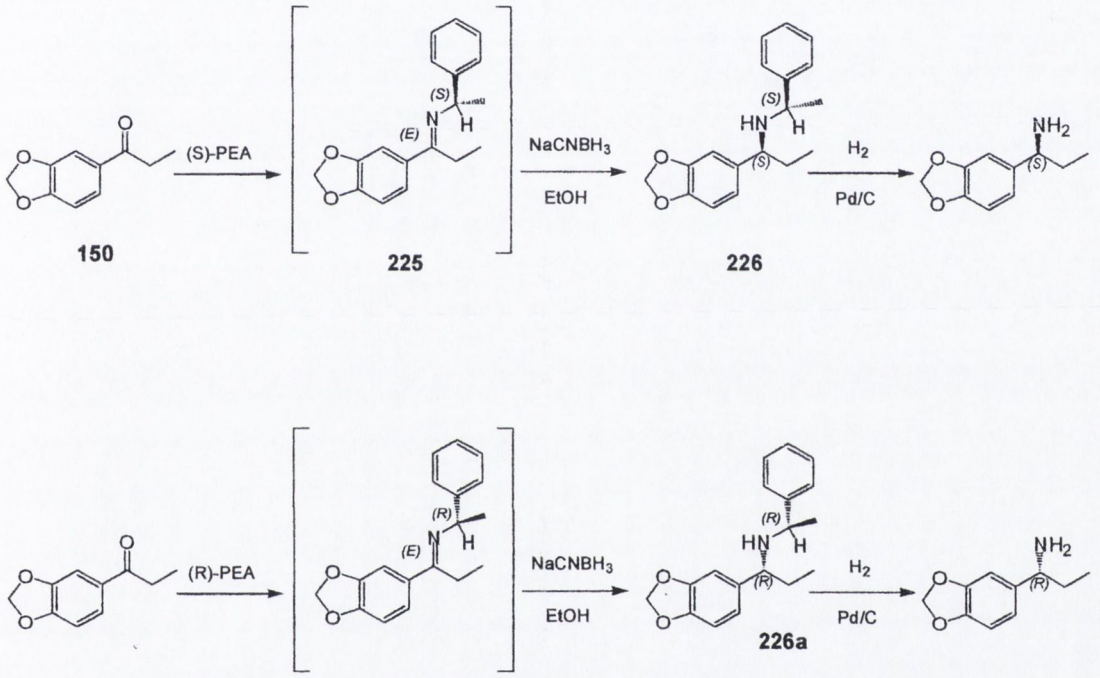


Figure 3-2: Asymmetric reduction

Figure 3-2 represents pictorially, the approach of the borohydride from the least hindered face of the imine bond. The hydride is added to the carbon C1 yielding the (*R*)–stereoisomer. Using the method of Gutmann *et al*, the required imine **225** was

formed from the ketone **150** (Scheme 3-5). Imine **225** formation is a reversible reaction and it can be hydrolysed back to the ketone starting material **150** and the enantiomerically pure α-benzylamine **220**, (the corresponding alcohol reduced from the ketone **150** by $NaCNBH_3$ was isolated from the reaction). With this in mind, the reaction is carried out under anhydrous conditions, refluxing in toluene with a Dean-Stark trap, thereby continuously removing water from the system. The imine was not characterised, and the reaction mixture was cooled to -30°C before being added to an ethanolic solution of $NaCNBH_3$ (also at -30°C) to give the amine **226** in 77% diastereomeric excess (determined by GCMS Figure 3-3).



Scheme 3-6: Stereoselective synthesis of 1-phenylpropylamine 227, 228

Chromatogram Plot

File: c:\gc-msspectra\sb5-s,s.sms
Sample: Manual Sample 2/4/2002 12:16 PM
Sample Notes:
Operator: pg Scan Range: 1 - 1269 Time Range: 0.00 - 20.49 min.

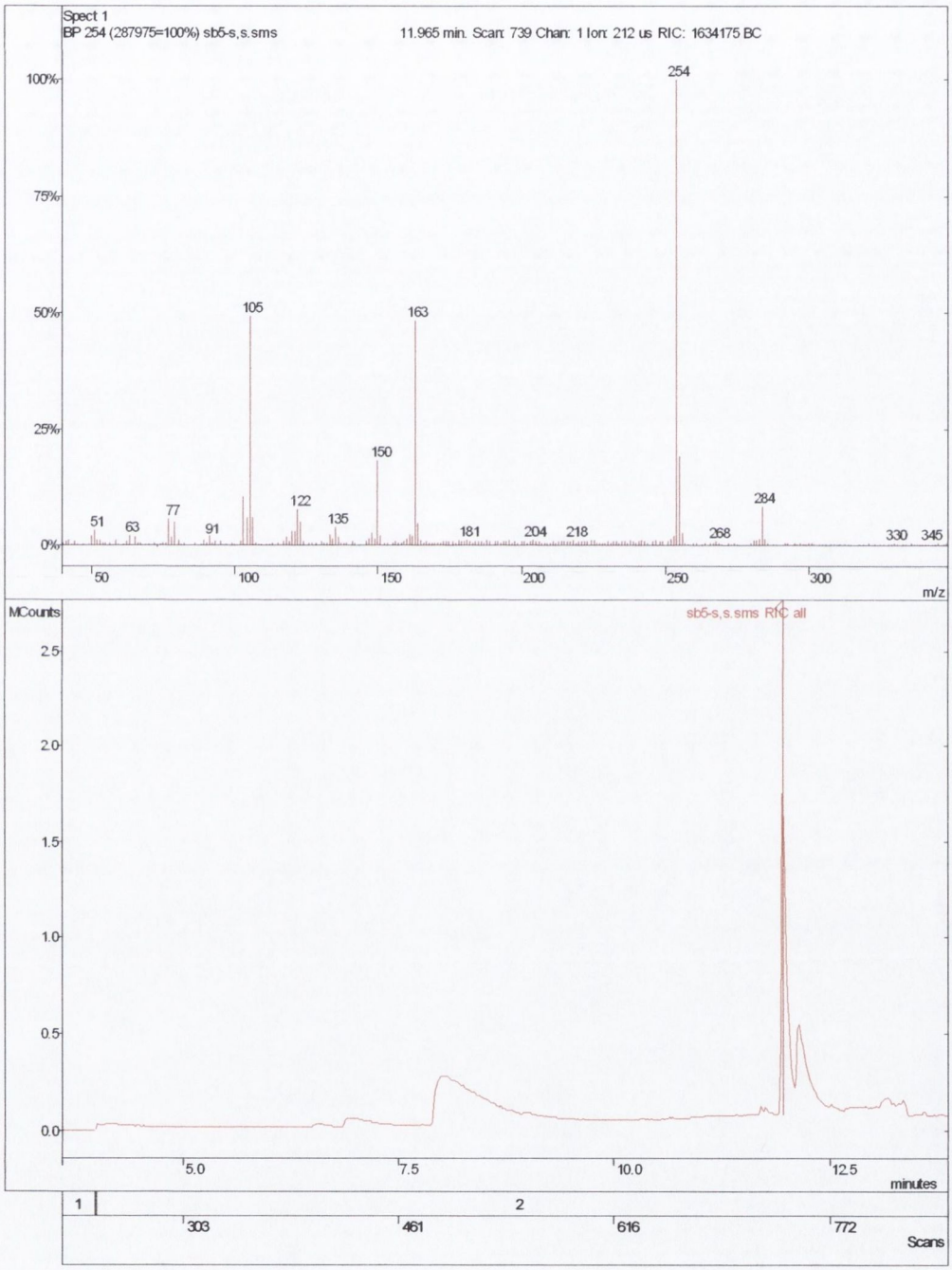


Figure 3-3: GCMS trace of diastereomer (*S,S*) 226 crude reaction mixture

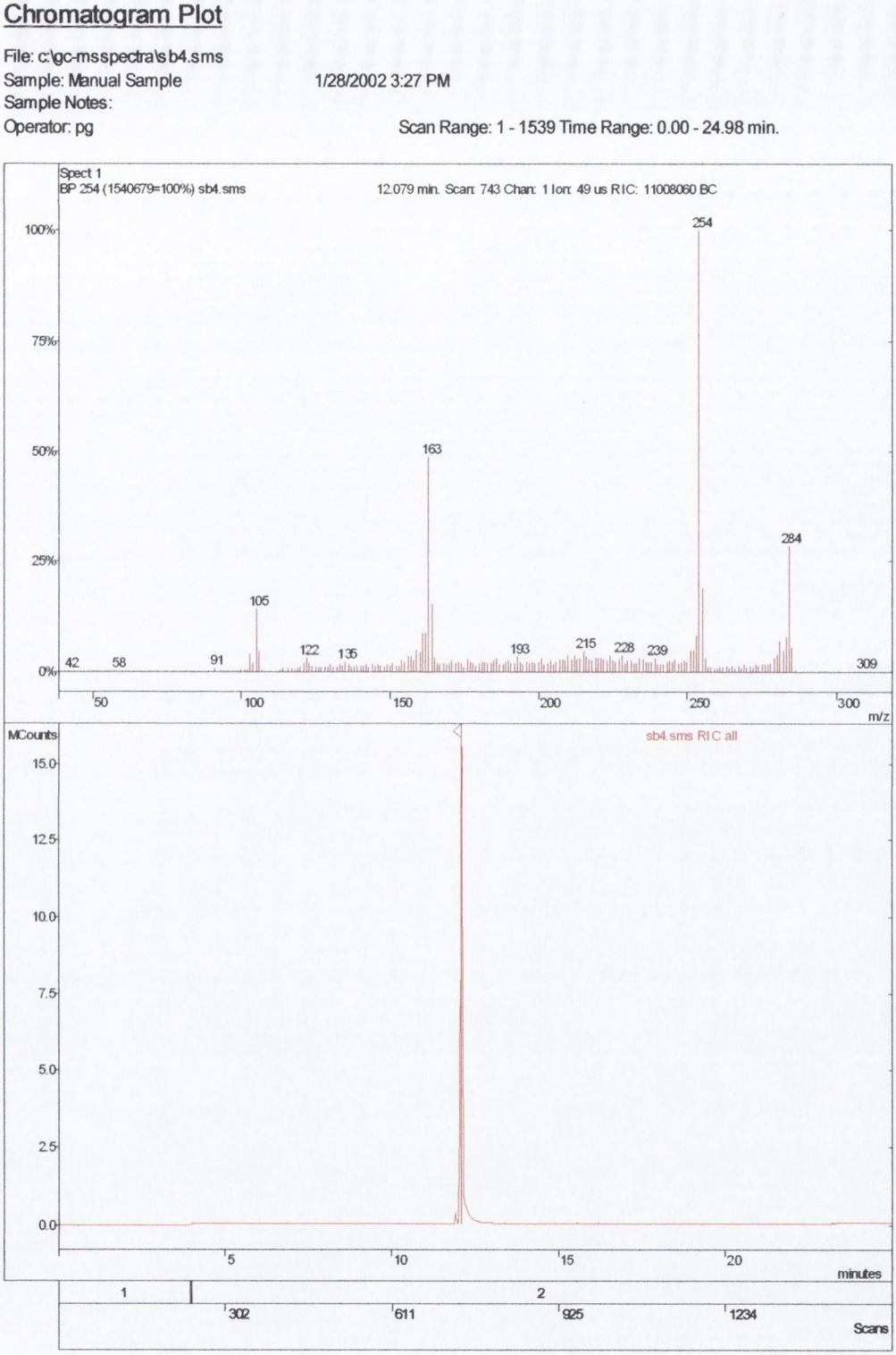
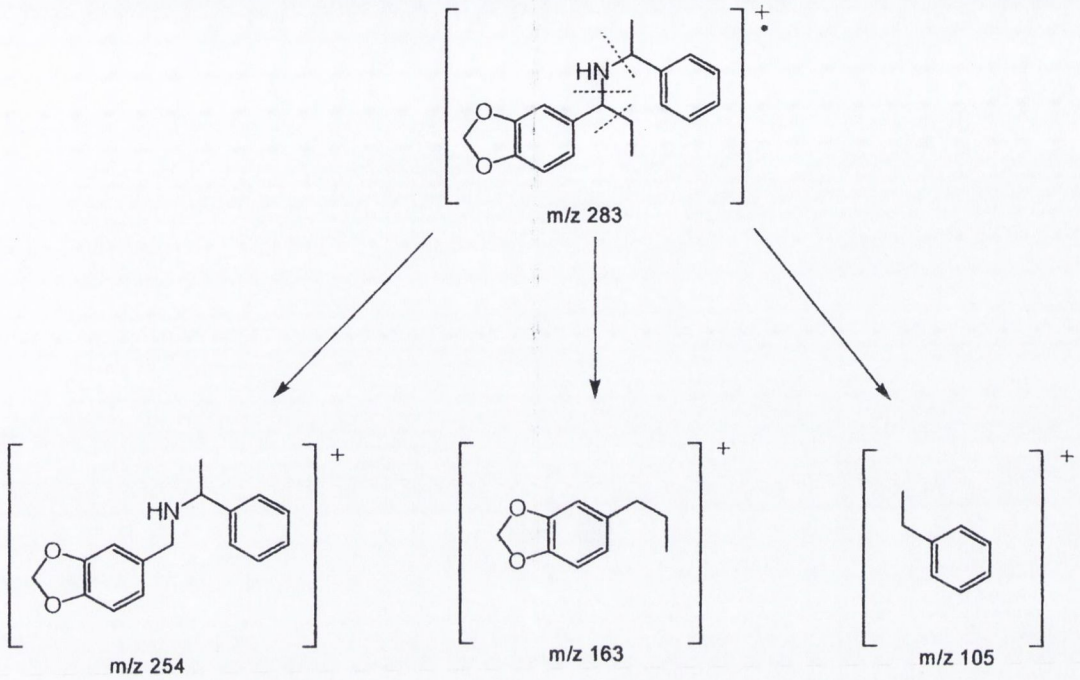


Figure 3-4: GCMS trace of pure diastereomer *(S,S) 226*

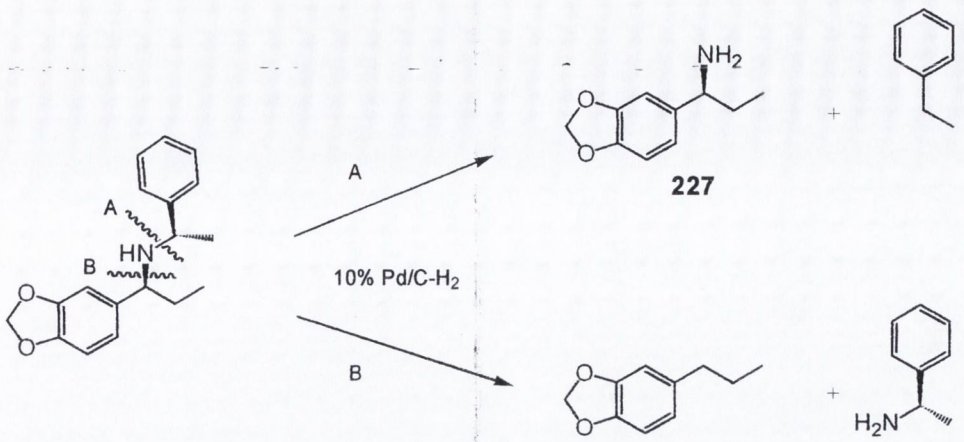
The mass spectra for the both sets of diastereomers of **226** contain the same fragment ions (the minor diastereomer evident as the shoulder peak in the GC trace

(Figure 3-3). A plausible fragmentation pattern resulting in the mass spectra observed is given in Scheme 3-6.



Scheme 3-7: Possible fragmentation pattern for diastereomer 226

The synthesis was repeated using (*R*)-phenylethylamine to yield the opposite (*R, R*) diastereomer Scheme 3-6. The final step in the synthesis involved the removal of the benzyl group *via* hydrogenation using 10% palladium on charcoal under a H_2 atmosphere. One problem envisaged was the fact that the bond from the carbon C1 to the nitrogen is benzylic and may be prone to hydrogenation *via* route B, with the desired bond cleavage proceeding through path A (Scheme 3-8). This posed the potential of non regioselective bond cleavage resulting in a loss of the final amine product **227** (Scheme 3-8). A detailed study by Bringmann *et al* has reported that in cases where two benzylic bonds are available for cleavage and are attached to the same nitrogen, the amine functionality is retained by the group having the more substituted phenyl ring.[224, 225] The only exception being an N-methyl in the *ortho* position of the ring, in which case the hydrogenation occurs on the more substituted side.[225]

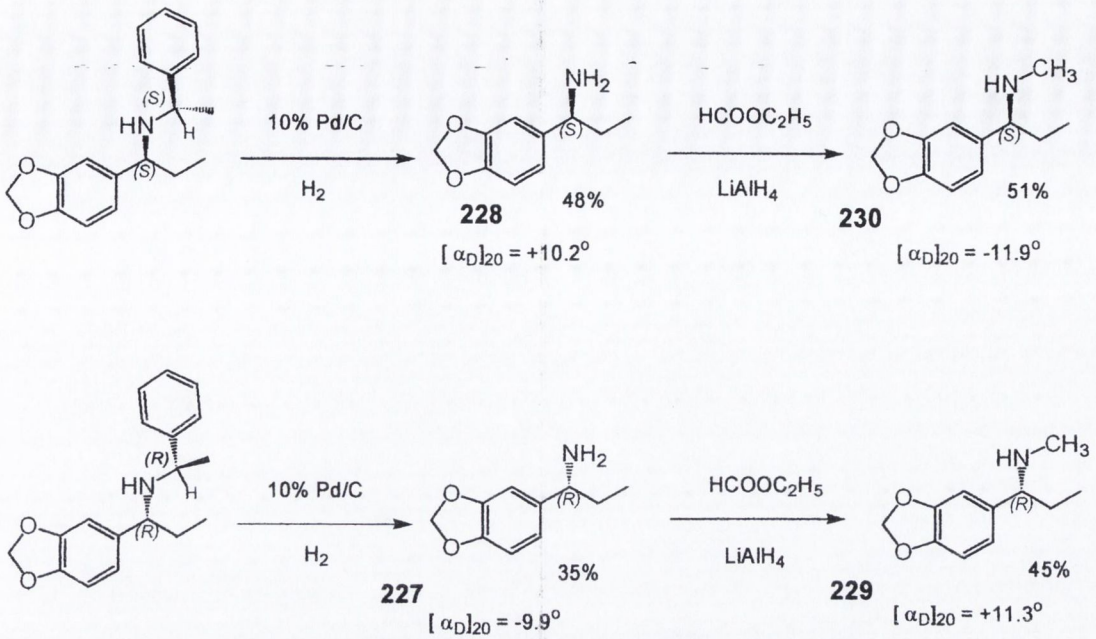


Scheme 3-8: Hydrogenation of 226

In the case of the hydrogenation in Scheme 3-8, the ring of interest has a dioxole ring where as the ring of the chiral reagent is unsubstituted and therefore the amine is retained by the more substituted group yielding the enantiomerically pure amine **227** (Scheme 3-8). The hydrogenation of the appropriate diastereomers gave the enantiomerically pure amines in 35% and 48% yield for (*R*) and (*S*) 1-benzo[1,3]dioxol-5-yl-propylamine respectively. The products were converted to the HCl salts, recrystallised from ethanol:diethylether and the optical rotation was measured, with (*R*) - 1-benzo[1,3]dioxol-5-yl-propylamine.HCl $[\alpha_D]_{20}$ = -9.9° (c = 0.014, H_2O) and (*S*) - 1-benzo[1,3]dioxol-5-yl-propylamine.HCl $[\alpha_D]_{20}$ = +10.2° (c = 0.012, H_2O). To gain access to the N-methyl analogues the route of Nichols *et al* was adopted where by refluxing the free base of the chiral primary amine **227** and **228** (Scheme 3-9) with ethylformate followed by $LiAlH_4$ reduction affords the desired (*R*) and (*S*) - (1-benzo[1,3]dioxol-5-yl-propyl)-methyl-amine product **229** and **230**.[119, 120] The reaction was achieved in 45% for the (*R*)-isomer and in 51% for the (*S*). The specific optical rotation (*R*) - (1-benzo[1,3]dioxol-5-yl-propyl)-methyl-amine product **229** $[\alpha_D]_{20}$ = +11.3° (c = 0.014, ethanol) and (*S*) - (1-Benzo[1,3]dioxol-5-yl-propyl)-methyl-amine product **230** $[\alpha_D]_{20}$ = -11.9° (c = 0.019, ethanol). This is a novel method used to produce (*R*) and (*S*) 1-phenylpropylamines.

Table 3-1: Physical data for stereoselective amine synthesis

Compd.	IR cm^{-1}	$[\alpha_D]_{20}$°	m.p.(HCl)	Yield %
227	2991, 1250, 1044, 921	-9.9	204-206	35
228	2983, 1257, 1043, 932	+10.2	208-210	48
229	3414, 1455, 1250, 873	+11.3	-	45
230	3414, 1454, 1257, 874	-11.9	-	51



Scheme 3-9: Stereoselective synthesis of amines 227-230

3.3 Studies in the stereoselective synthesis of MDA

To enantiospecifically synthesise a range of conformationally restricted 5-$HT_{2A/2C}$ agonists, Chambers *et al* introduced a chiral stereocentre from the commercially available enantiomerically pure, amino acid alanine.[158] The chiral centre was β to an aromatic ring and substituted with an amino group. This arrangement exists in the amphetamine backbone and so this method was considered a viable alternative to the one used in Scheme 3-9. The main advantage with this route was in abolishing the requirement to purify diastereomeric mixtures. The proposed synthetic route is given in Scheme 3-10.

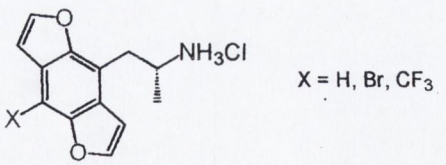
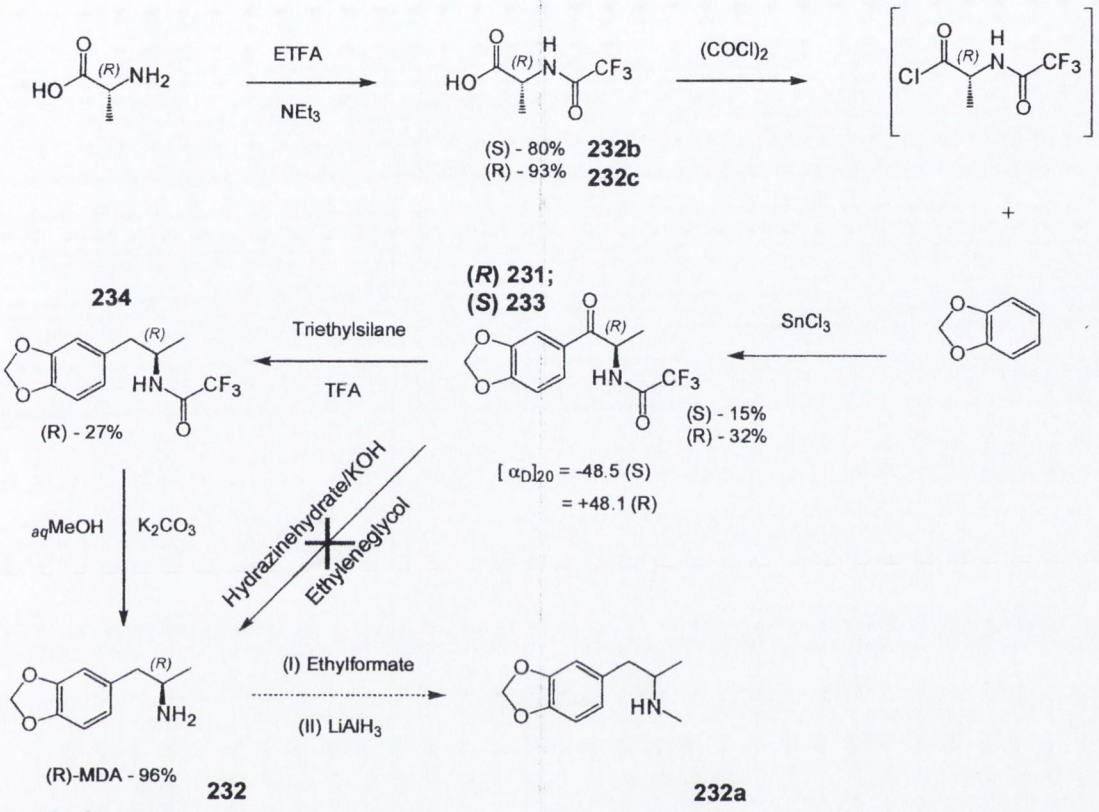


Figure 3-5: Stereoselective synthesis of 5-HT2A/2C receptor agonists[158]

Ethyltrifluoroacetate has been found useful as a TFA protecting agent capable of differentially protecting a primary amine while leaving secondary amines unreacted.[230] Through the method of Curphey, the commercially available (*R*)-and (*S*)-alanine was protected as the TFA derivative.[231] Using oxalyl chloride, the acid group was converted to the acid chloride from which Friedel-Crafts acylation could

be carried out to afford the key amino-carbonyl intermediate **231** (Scheme 3-9). One concern was the formation of a ketene (O=C=C-) that would result in racemisation and therefore a loss of stereoselectivity at the crucial C2 position, however in the absence of an organic base this does not occur.[152]



Scheme 3-10: Stereselective synthesis of (R) – MDA

The key chiral intermediate **231** was characterised using spectroscopic techniques and elemental analysis. The infra-red spectrum displayed a significant absorption at 3299 (NH), 1700 ($C=OCF_3$), 1676 (C=O), 1259 (ArOC) and 1034 (C-O) cm^{-1} The methyl group appears in the ^1H nmr as a doublet (J = 7.0 Hz) integrating for three protons at 1.53 ppm. The proton at H2 appears as a multiplet integrating for one proton, resonating at 5.46 ppm. The dioxole protons resonated characteristically as a singlet at the deshielded value of 6.11 ppm. The aromatic region of the ^1H nmr indicates an *AMX* coupling system with two doublets and one double doublet each signal integrated for one proton. The doublet at 6.92 ppm has coupling constants of J_o = 8.2 Hz and was assigned as ArH5. The doublet at 7.45 ppm displays *meta* coupling of 1.8 Hz and so was assigned as ArH2. The double doublet precessing at 7.60 ppm had J_o = 8.0 Hz and J_m = 1.8 Hz and so corresponded to ArH6. The N-H proton was assigned as the broad singlet resonating at 7.65 ppm. In the ^{13}C nmr,

the methyl group (C3) was evident as the signal at 19.58 ppm staying positive in the Dept 135 experiment and not observable in the Dept 90 experiment. The signal corresponding to C1 was present in the Dept 90 experiment at 50.50 ppm. The dioxole carbon could be assigned as the signal inverted in the Dept 135 experiment at a chemical shift of 102.24 ppm. The aromatic proton signals were evident at 108.32 ppm (ArC2/6) and 125.43 ppm (ArC5). In total there were six quaternary carbons in the molecule. The most obvious being the carbonyl group at C1, which was observed at the deshielded chemical shift value of 194.99 ppm. The carbonyl carbon of the TFA group was split into a quartet with J = 37.9 Hz at 156.41 ppm with the remaining carbon (CF_3) of the protecting group emerging at 115.73 ppm with J = 287.7 Hz. The three aromatic quaternary signal were apparent at 127.59 ppm (ArC1), 148.70 ppm (ArC4) and 153.07 ppm (ArC3). The LRMS gave a molecular ion equivalent to ($M^+ + H^+$) in 9% abundance, with the base at m/z 149 equal in mass to the acylium ion (Figure 3-5).

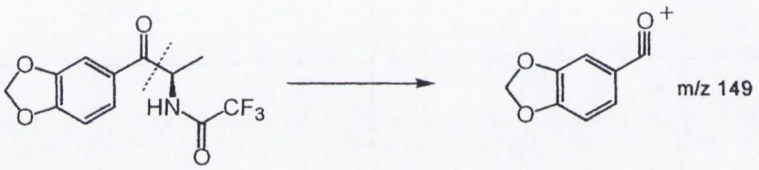
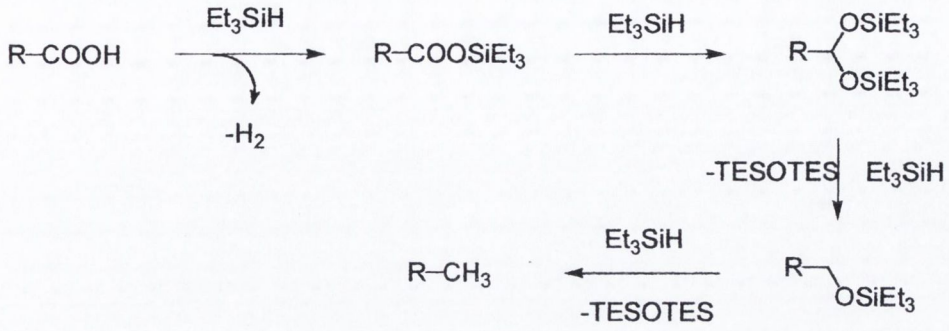


Figure 3-6: Base peak in the LRMS corresponds to acylium ion 149

The remaining steps in the synthesis involved the reduction of the carbonyl group at C1 to a methylene group followed by removal of the protecting group to yield the enantiomerically pure MDA **232**. It was considered advantageous to utilise the Wolff-Kishner reduction, which it was thought would reduce the C=O to a methylene group while simultaneously removing the TFA protecting group under basic conditions. Unfortunately, eventhough the reaction yielded the reduced product as the free base from (*R*) **231** and (*S*) **233** in good yields, the stereoselectivity had been lost due to the acidic proton H2 being eliminated under basic conditions leading to a racemization at the chiral centre resulting in the products as a racemate. When the carbonyl intermediate **231** (Scheme 3-9) was reduced according to the method employed by Chambers *et al*[158] the protected amine **234** was isolated and was subsequently reduced to (*R*)-MDA **232** the HCl salt of which gave an optical rotation $[\alpha_D]^{50}$ = -24.3° (c = 0.016, H_2O). This equates to an enantiomeric excess of 94.9% when compared to the literature value of –25.6.[217] The relatively poor yield of 27% in the triethylsilane reduction step can be explained mainly through the difficulty in separating the reducing agent from the product. The reduction of the intermediate

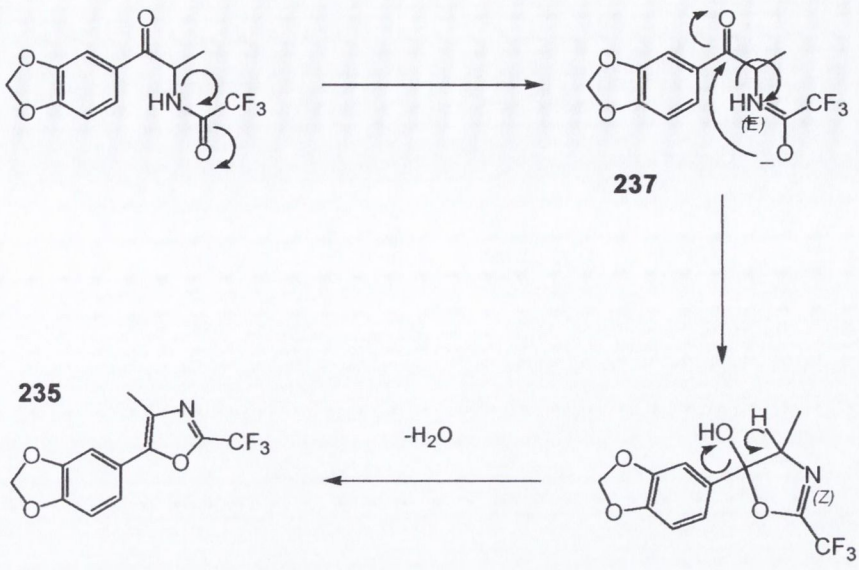
231 requires at least three molar equivalents of the silane (in some cases up to six) when the mechanism given in Scheme 3-11 for the silyl reduction of carboxylate derivatives is taken into account.[232]



Scheme 3-11: Silyl reduction of carboxylates[232]

3.4 5-Benzo[1,3]dioxol-5-yl-4-methyl-2-trifluoromethyl-4,5-dihydro-oxazole

In the synthesis described in Scheme 3-10, the Friedel-Crafts acylation to yield the carbonyl intermediate **231** afforded an interesting side product in moderate yields. Initially observed as a bright blue fluorescent spot with R_f = 0.57 in a 70/30 hexane:diethyl ether mobile phase, it was isolated as yellow-orange crystals. LRMS gave a prominent peak at m/z 271 as the base peak, indicating stability if this were the molecular ion. Most notably the peak at *m/z* 271 was equal to the exact mass of the molecular ion of the desired product **231** minus water, signifying a possible dehydration reaction. Further characterisation *via* spectroscopic techniques proved the structure to be that of the cyclised oxazole product **235** (Scheme 3-12).



Scheme 3-12: Oxazole formation

The ^{1}H NMR spectrum of **235** as seen in Figure 3-7, gave information on the presence of the benzodioxole moiety and an aliphatic methyl group. ^{19}F NMR spectra confirmed the presence of a trifluoromethyl group. The ^{13}C NMR spectrum provided the key information in assigning the structure as **235**. The quaternary carbons NMR signals (expanded in Figure 3-6) suggest there was no longer a -$COCF_3$ in the molecule. The methylene carbon of the -CF_3 was not adjacent to a carbonyl as the quartet shown in Figure 3-7 occurs from 147.06 to 148.37 ppm if it were in a -$COCF_3$ group it would be downfield closer to 160 ppm. The singlet occurring at 148.13 ppm is unusually broad indicative of interaction with a nitrogen. This peak was assigned as C2 of the 3-carbon chain and showed interaction with H3 in the HMBC.

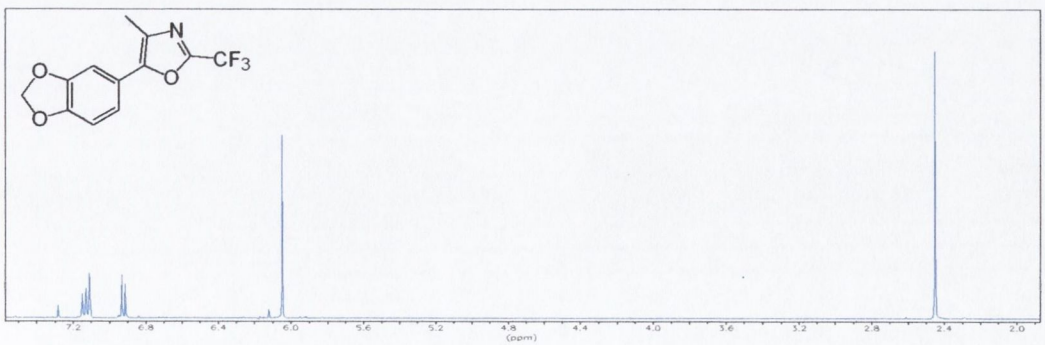


Figure 3-7: ^{1}H nmr of oxazole 235

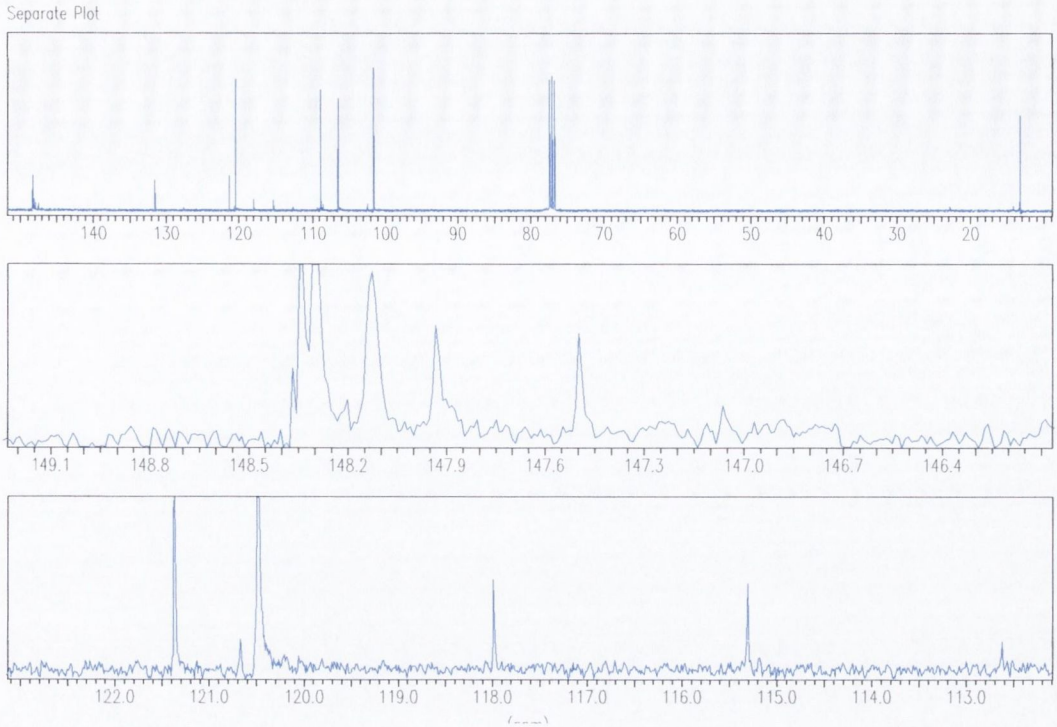


Figure 3-8: ^{13}C NMR spectrum of oxazole 235 (top) with expanded peaks of importance (middle and bottom)

The IR spectrum showed there to be no carbonyl bonds present in the molecule and N-H bonds were also absent. In the HMBC experiment, coupling was evident from the peaks assigned as ArH5 (doublet J_o = 8.0 Hz) to the quaternary peak at 148.30 ppm which was assigned as ArC4. The signal split into a doublet J_m = 2.0 Hz displayed long range C-H interaction to the quaternary peak at 148.34 ppm which was assigned as ArC3. The singlet corresponding to the dioxole protons showed coupling to both quaternary carbons ArC3 and ArC4. At 121.37 ppm resonates a quaternary peak that experiences an interaction with ArH2 and ArH5 proton signals in the HMBC experiment. This signal was assigned as ArC1. The remaining quaternary signal appearing as a singlet, was proposed as C1 at 131.56 ppm and also showed long rang C-H coupling with C3. The remaining carbon signal were assigned with the aid of a C-H Cosy experiment. The interactions commented on in the HMBC are shown in Figure 3-8.

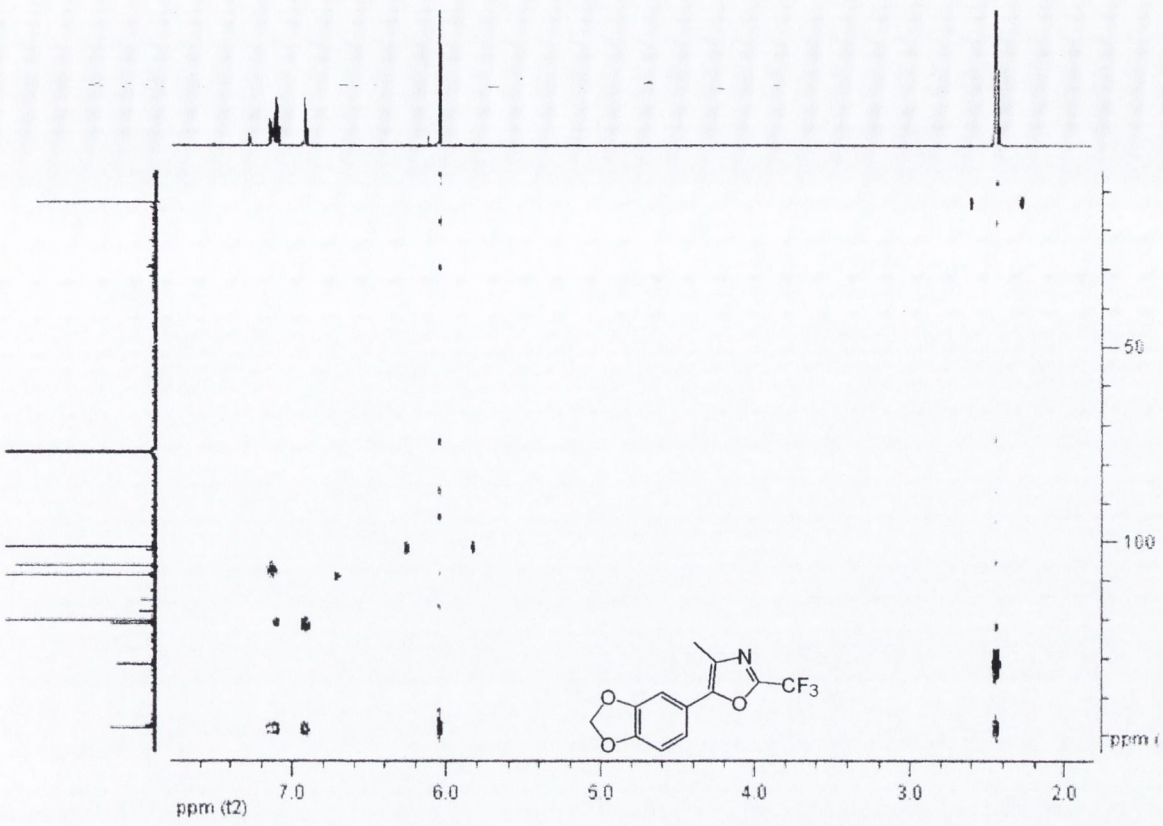
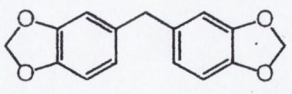


Figure 3-9: HMBC NMR experiment of oxazole 235

The exact mass of the **235** was calculated as 272.0535 with the observed mass from HRMS found as *m/z* 272.0532. Elemental analysis also confirmed the structure to be that of 5-benzo[1,3]dioxol-5-yl-4-methyl-2-trifluoromethyl-oxazole **235**. The oxazole **235** was obtained in 37% yield. There was also an impurity isolated in 8% yield. It was the diphenyl compound **236** (Figure 3-10), probably formed as a result of the solvent DCM under going a Friedel-Crafts type reaction with two equivalents of 1,3-benzodioxole. The structural assignments were made using NMR, melting points and elemental analysis.



236

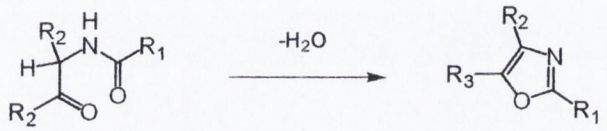
6-Benzo[1,3]dioxol-5-ylmethyl-6-benzo[1,3]dioxole

Figure 3-10: Impurity isolated from stereoselective MDA synthesis

The oxazole nucleus has been reported in a number compounds isolated from natural sources. Such examples being Rhizoxin, a macrocyclic lactone antibiotic with biological activity against human and murine tumor cells.[233] Unusual bisoxazole compounds have been isolated from a marine sponge.[234] Bisoxazoles

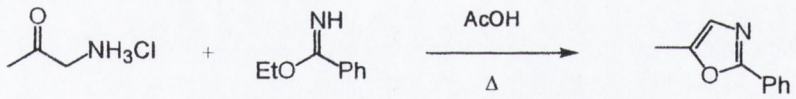
have been reported to also have anti-tumour activity.[235] Synthetic substituted oxazoles are being investigated for a number of biological activities. Momse *et al* have reported oxazole derivatives as insulin sensitizers with antidiabetic activities.[236] Wang *et al* have incorporated the oxazole ring into compounds with anti-tumour activity.[237] Oxazoles are also being explored for *COX* inhibitory activity as a potential non-steroidal anti-inflamatories, with fewer side effects than the more traditional aspirin and indomethacin.[238]

Oxazoles traditionally have been synthesised using the Robinson-Gabriel method which is often carried out in the presence of sulphuric acid, phosphorous pentachloride or other such dehydrating agents (Scheme 3-13).



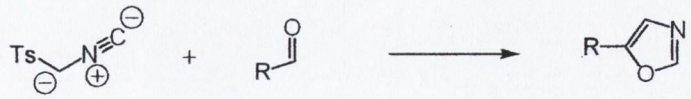
Scheme 3-13: Robinson-Gabriel synthesis

In accessing general 1,3-oxazoles the Hantzsch synthesis can be modified to yield the appropriate oxazole (Scheme 3-14).



Scheme 3-14: Modified Hantzsch oxazole synthesis

In Scheme 3-15 is another reported method of oxazole synthesis based on the reactivity of the anion produced from TOMIC. This synthesis is applicable to the synthesis of 1,3-oxazoles. [239, 240]

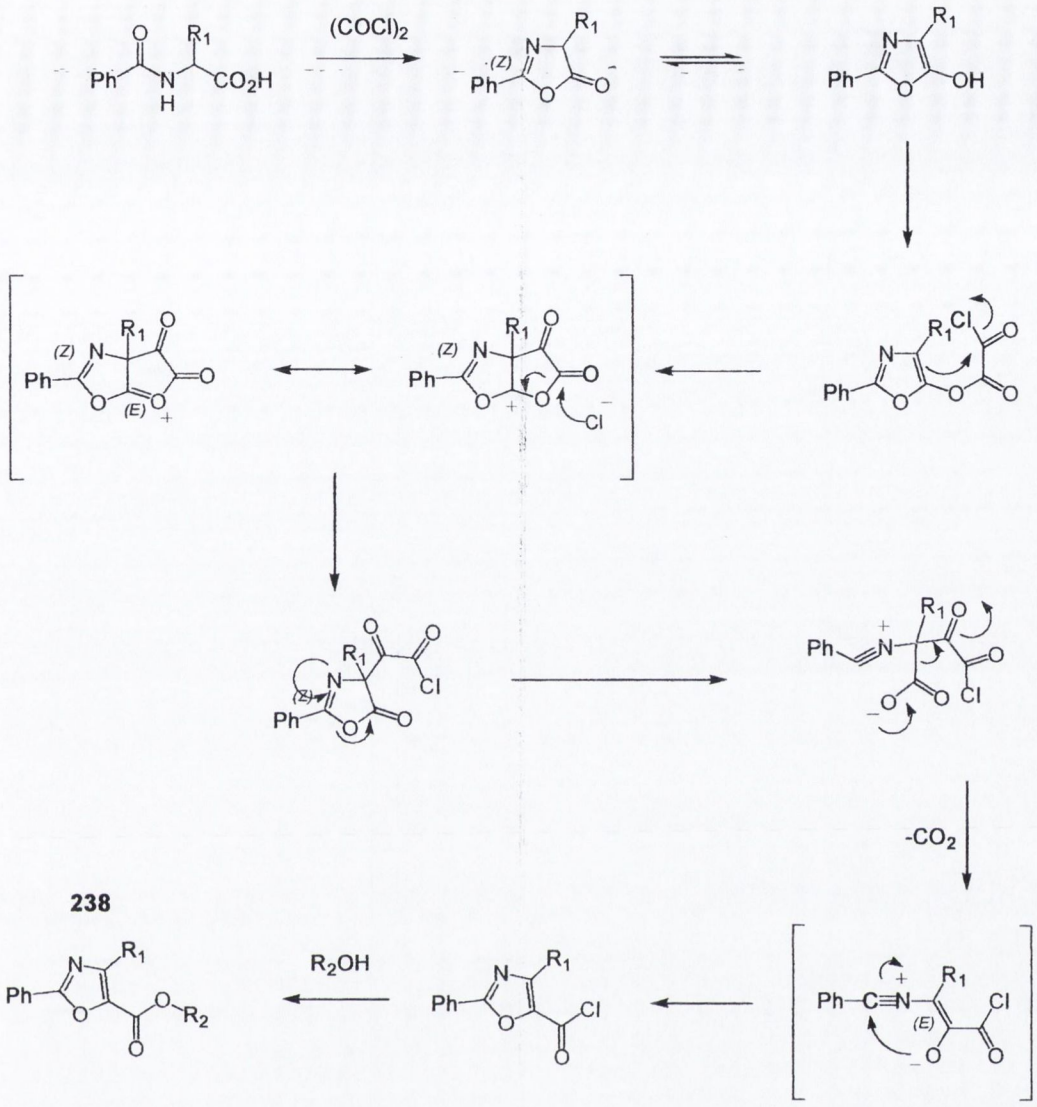


Scheme 3-15: More recent oxazole synthesis

The synthesis of oxazoles and oxazolones from the corresponding amino acids is well documented.[241-244] Kawase *et al* developed a method for the preparation of 5-trifluoromethylated oxazoles from α-amino acids. The most relevant synthesis of

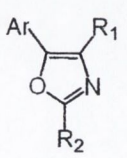
1,3-oxazoles in terms of similarity to the results observed in Scheme 3-11, has been by Cynkowski *et al.*[243] In his work a range of N-benzoyl amino acids reacted with excess oxalyl chloride at room temperature, to which the addition of alcohols afforded the analogous 4-substituted 2-phenyloxazole-5-carboxylates. The difference in the method used of the current study (Scheme 3-12) being that the oxalyl chloride was removed after forming the necessary acid chloride from the amino acid to facilitate Friedel-Crafts acylation. In the work reported by Cynkowski, the carbon at position 2 of the oxazole ring is derived from the second equivalent of oxalyl chloride, with the acid chloride forming the oxazole ester **238** when reacted with the desired alcohol. Scheme 3-15 details the mechanism proposed for the synthesis, which was supported by the use of ^{13}C labelling within the molecule.[243]

In the current work, no form of oxazolone ester (of the type **238** Scheme 3-16) was isolated. The enol tautomer could not have been formed in the manner reported by Cynkowski, otherwise racemization would have resulted in loss of chirality at the vital carbon centre C2. The Lewis acid and ring activated 1,3-benzodioxole will undergo Friedel-Crafts acylation with the acid chloride to form the carbonyl amine intermediate **237** (Scheme 3-12). In the absence of base this does not undergo enolisation to lose the chiral centre at C2. Chambers *et al* reported the stereoselective synthesis of compounds shown in Figure 3-10, without reporting any oxazole formation or loss of stereoselectivity.[158]



Scheme 3-16: Proposed mechanism for the synthesis of oxazoles from amino acids and oxalyl chloride[243]

The mechanistic differences are clear between the two methods. However, [to the best of my knowledge] there have been no one pot methods of preparation of 5-aryl substituted oxazoles reported. The reaction shown in Scheme 3-12, yielded the oxazole **235**, in moderate yields at room temperature. Various experiments were attempted in the hope of establishing a convenient one-pot synthesis of 2,4,5-trisubstituted oxazoles of the type shown in Figure 3-11.



Ar = any aryl group
R1= any amino acid side chain
R2=From amino protecting group

Figure 3-11: Attempted oxazole preparation

It was found that carbamate protecting groups were unstable in the presence of the Lewis acid, resulting in a solid that precipitated from solution. Formylation or acylation of racemic alanine followed by attempted oxazole ring formation did not yield any desired products. The use of various amino acids was employed in an effort to produce oxazoles with various groups at position-4. When either phenylglycine or phenylalanine were used as starting materials with the amine protected with TFA groups, an inextractable tar resulted with an inseparable series of products. Finally, when veratrole was taken as the aromatic group (labelled Ar in Figure 3-11) $TiCl_4$ was utilised as the Lewis acid in the hope of complexing the carbonyl carbon at C1 and prompting the dehydration cyclisation ($TiCl_4$ is a good scavenger of water in solution). For each of the attempted oxazole syntheses described, the general reaction conditions for the formation of the isolated oxazole **235** were used. At this stage the oxazole study was reluctantly discontinued. However, further work would be of interest in optimising this promising oxazole synthesis.

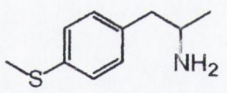
Table 3-2: IR, yield and melting point for oxazole 235

Compd	IR cm^{-1}	Yield%
235	1497, 1254, 1156, 1042, 804	37

4 Chapter Four: Derivatisation of the methylthio group of 4-methylthioamphetamine

4.1 Introduction

4-methylthioamphetamine (4-MTA) is a potent SERT plus MAO-A inhibitor.[133, 137, 245] Although not generally regarded as neurotoxic in comparison to MDMA and MDA, its powerful ability to release intracellular and maintain extra cellular serotonin can give rise to serotonin syndrome, a sometimes fatal side effect of SSRIs.[38, 41] MDMA and MDA cause degeneration of serotonergic nerve terminals *via* the primary metabolites.[246] This effect is not observed for 4-MTA or other amphetamine derivatives such as 3-methoxy-4-methylamphetamine (MMA) or 5-methoxy-6-methyl-2-aminoindan (MMAI).[19] Although 4-MTA was first synthesised in 1963 as an anorexigenic agent along with 4-benzyl, 4-ethyl thioamphetamine and their regioisomers, there are no examples in the literature of derivatives of the potent serotonin releasing agent 4-MTA **147**.[132]

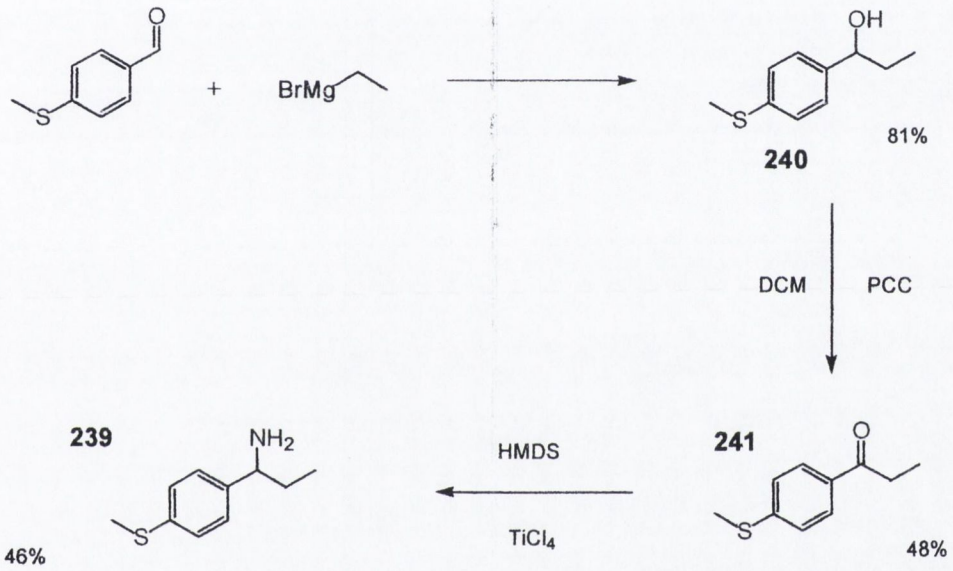


147

In an amphetamine based CoMFA study carried out by Roman *et al*, it was found that position-4 of the aromatic ring in amphetamines provides optimal SERT activity when substituted with hydrophobic steric groups.[247] In the paper detailing the original synthesis of 4-MTA, the S-benzyl group is also reported.[132] In testing the anorectic properties in both rat and dog, 4-MTA was reported as moderately active in both species with the S-benzyl derivative being inactive in rat at 30 mg/Kg and mildly active in dog at 10-30 mg/Kg dosages.[132] As 4-MTA is a known SERT inhibitor, coupled with the fact that minimal derivatisation has been carried out at the 4-methylthio group, it was decided to investigate the synthesis of a series of compounds based on 4-MTA with various substituted groups linked to the sulphur atom at position-4. From the chemistry of the 1-phenylpropylamines, the corresponding analogue of 4-MTA with the nitrogen on carbon-1 of the propyl chain namely 1-(4-methylsulfanyl-phenyl)-propylamine **239** was also of interest.

4.2 *Initial synthesis*

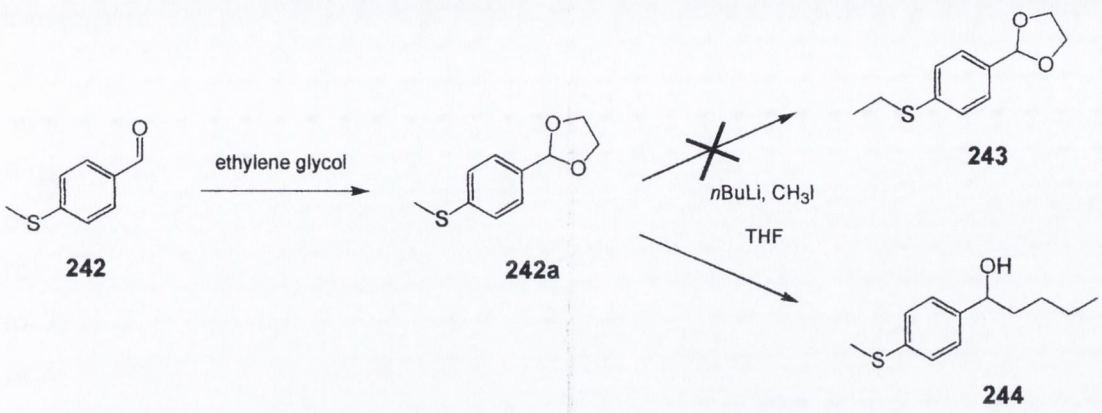
The synthesis of 1-(4-methylsulfanyl-phenyl)-propylamine **239** Scheme 4-1 proved straight forward using the chemistry developed in chapter two The Grignard alkylation of 4-methylthio benzaldehyde provided the alcohol **240**. From **240** the necessary ketone **241** was accessible using a PCC oxidation, the yield of which was not as high as in the dioxole derivatives, possible reasons being the difficult work up or the oxidation of the thio group.



Scheme 4-1: Synthesis of 1-(4-Methylsulfanyl-phenyl)-propylamine 239

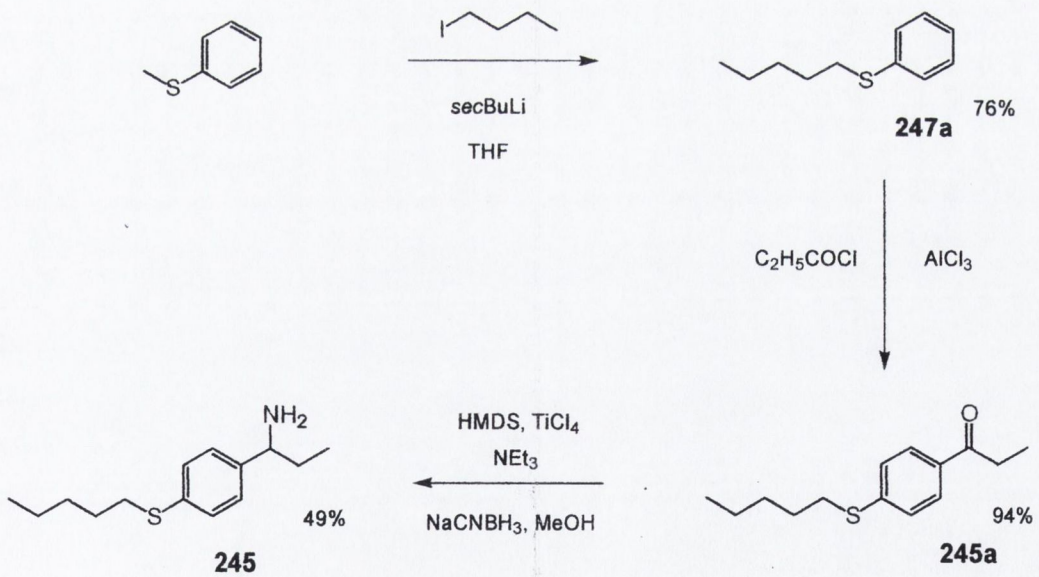
The production of allternative thioethers was next investigated. Cabiddu *et al* carried out an extensive study of metallation reactions of aromatic thioethers.[248, 249] The protons of the methylthio group are acidic enough to be removed by a powerful base, in this case *sec*-BuLi, the carbanion remaining can then attack an alkyl iodide to furnish the desired aromatic alkyl thioether. In the first attempted derivitization of the methyl thio ether, the aldehyde **242** (Scheme 4-2) was protected as the acetal **242a**. However the subsequent reaction did not afford the required alkyl thioether **243**, as the butyl group from the base added to carbon-1 of the backbone chain Scheme 4-2 giving **244**, using secBuLi gave a similar addition. The reaction was repeated from the acetal protected ketone using conditions described by Cabiddu.[248] Yet again the butyl group from the base underwent addition to carbon-1. In order to simplify matters

the reaction was carried out from thioanisole and the alkylation proceeded in 76% yield to give **247a**, albeit after a tedious chromatographic separation on silica gel.



Scheme 4-2: Attempted derivatisation of thiomethyl group

Once the phenylthio ether group was in place, the Friedel-Crafts acylation proceeded very well using $AlCl_3$ (a stronger Lewis acid than $SnCl_4$, which was required in chapter-1 to prevent cleavage of the dioxole ring) to give **245a**. The usual amination provided 1-(4-pentylsulfanylphenyl)-propylamine **245** in 49% yield (Scheme 4-3).

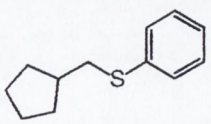


Scheme 4-3: Synthesis of 1-(4-Pentylsulfanyl-phenyl)-propylamine 245 from Pentylsulfanyl-benzene 247a

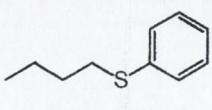
The characterisation of 1-(4-pentylsulfanylphenyl)-propylamine **245** was carried out with the aid of the various spectroscopic techniques and elemental analysis. The product, isolated as a waxy solid, displayed two pairs of triplets each integrating for three protons. The triplet from 0.77 to 0.83 ppm (J = 7.4 Hz) was proven to be part of

the same spin system *via* a 2D TOCSY experiment and so was assigned as the methyl group belonging to the pentylthio moiety. The triplet from 0.88 to 0.91 ppm (J = 7.14 Hz) was assigned as H3. The complex multiplet from 1.26 to 1.43 ppm integrated for four protons and was assigned as H2 of the three carbon chain, overlapping with the terminal methylene protons of the pentylthio group. The pair of methylene groups that were at positions-2 and 3 of the thiopentyl group resonated as a multiplet from 1.61 to 1.72 ppm representing four protons. The amino protons were evident as a broad multiplet at 2.80 ppm integrating for two protons next to the remaining methylene protons adjacent to the sulphur, producing the triplet from 2.88 to 2.92 ppm. The proton H1 resontated as a triplet (J = 6.8 Hz) integrating for one proton from 3.73 to 3.76 ppm. The aromatic signals were evident as two sets of doublets. ArH1/H6 were assigned as the doublet (J = 8.2 Hz) with the remaining doublet assigned as ArH3/H5.

In the ^{13}C NMR spectrum the terminal methyl group from the pentylthio fragment was apparent at 10.73 ppm beside C3 at 13.87 ppm. There were five methylene peaks all inverted in the Dept 135 experiment. Positions 4, 3 and 2 of the pentylthio group were evident at 22.14, 28.75 and 30.89 ppm respectively. The peak at 31.76 ppm was assigned as C2 with the remaining methylene peak at 33.59 ppm assigned as the CH_2 adjacent the sulphur. C1 was assigned as the signal that remained in the Dept 90 experiment at 57.12 ppm. The aromatic signals evident in the Dept 90 experiment resonated at 126.94 and 128.87 ppm. These were assigned as ArC2/C6 and ArC3/C5 respectively. The quaternary carbons produced the signals precessing at 135.27 and 142.29 ppm. These were attributed to ArC4 and ArC1 respectively. In the IR spectrum prominent absorption bands were found at ν = 3377, 2861, 1595 and 794 cm^{-1}. The synthetic route described in Scheme 4-3 did produce cyclopropyl, *iso*propyl and propyl thio derivatives **246-248** Figure 4-1. Although vacuum distillation proved to sufficiently purify the products from the first step, they did not form in appropriate yields to be carried through to the relevant final products.



246



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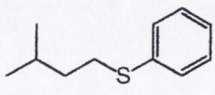
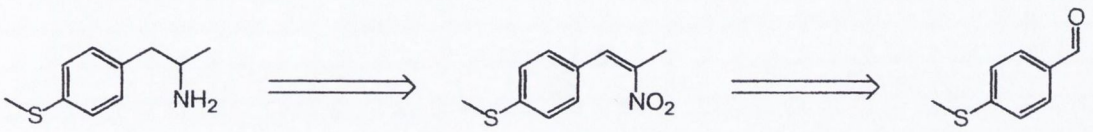


248

Figure 4-1: Derivatives of thioanisole produce

4.3 *Improved thio derivatisation*

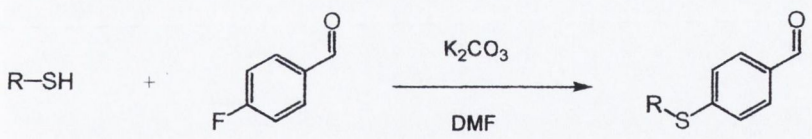
With the main focus of this work being on producing 4-MTA derivatives, an alternative route was taken from a *retro* synthetic analysis of the desired amines (Scheme 4.4). Amphetamines can be synthesised from the LAI reduction of the appropriate nitrostyrene **249**.[250-252] The base catalysed condenstaion of an aromatic aldehyde with nitroethane readily affords the corresponding nitrostyrene.[152]



249

Scheme 4-4: 4-MTA retrosynthesis

Aromatic aldehyde groups provide a sufficient electon withdrawing effect to facilitate nucleophilic aromatic substitution at an *ortho* or *para* fluorinated carbon of the ring.[152] This method was employed for the synthesis of the amines **250-253** and had been successful used by Tanaka *et al* in the preparation of 4-Phenylsulfanyl-benzaldehyde **251**.[253] The reaction was carried out at 120°C which presented a problem in using nucleophilic thiols with lower boiling points *e.g.* 2-Methyl-propane-2-thiol. These reactions had to be carried out in thick-walled pressure tubes with securely fitted Teflon® caps (the headspace flushed with nitrogen before sealing) Scheme 4.5.



R = (**250**) *t*-Butyl,
(**251**) Phenyl,
(**252**) Benzyl,
(**253**) $C_2H_4N(CH_3)_2$

Scheme 4-5: Nucleophilic aromatic substitutions to furnish aldehydes 250-253

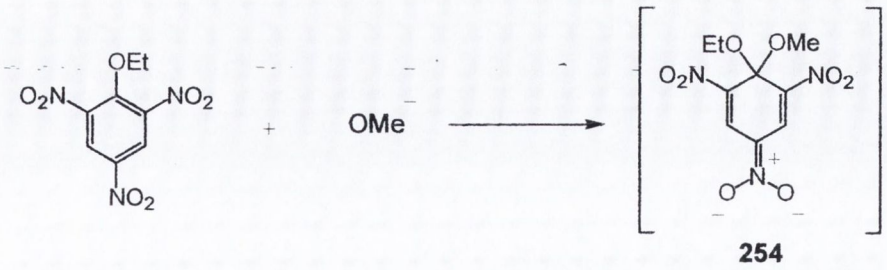
The reaction proved highly efficient in instances where the pressure tubes were used. In the case of the *t*-butyl analogue **250**, the success of the reaction was apparent mainly from the NMR as reaction monitoring by TLC did not show any difference in R_f on silica using 6:1 hexane:diethylether between 4-fluorobenzaldehyde and 4-tert-butylsulfanylbenzaldehyde **250**, although vanillin TLC staining did indicate a difference from the starting material. The successful formation of the aldehyde **250** was immediately evident from the presence of a large singlet at

1.34 ppm integrating for nine protons, a characteristic signal for a *tert*-butyl group. Looking elsewhere in the ^{1}H NMR, the aldehyde proton resonated at 10.03 ppm. The pattern of the aromatic signals was typical for that of a 1,4 disubstitution with two pairs of doublets (J = 8.0 Hz) both integrating for two protons at 7.67-7.69 and 7.82-7.84 ppm. The more downfield of the two was assigned as ArH2/H6. In the ^{13}C NMR spectrum the *tert*-butyl group produced a prominent signal at 31.04 ppm with an aliphatic quaternary peak at 47.07 ppm. ArC3/C5 were found to precess at the chemical shift value of 129.35 ppm. The quaternary carbon ArC_4 was assigned as the signal at 135.76 ppm with the signal at 136.94 ppm (present in the Dept 90) attributed to ArC2/C6. The remaining quaternary carbon signal resonates at the chemical shift value of 141.19 ppm with the deshielded formyl proton producing the signal that also remained in the Dept 90 experiment, downfield at 191.60 ppm. The IR bands, yields and melting points for the series are reported in Table 4-1.

Table 4-1: IR, melting points and yields for NAS reactions

Compd.	IR ν cm^{-1}	m.p. °C		Yield %
		Expt.	Lit.	
250	1704, 1591, 1457, 1166	oil	oil	100
253	1698, 1590, 1457, 1090	oil	-	89
251	1697, 1592, 1168, 837	54-56	52-54	100
252	1699, 1591, 1172, 822	68-70	70	51

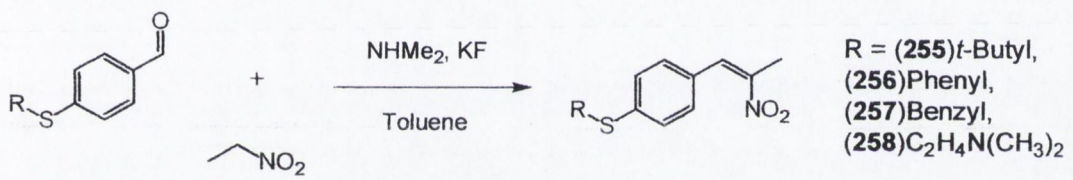
The mechanism of this reaction is believed to proceed through an S_NAr mechanism. Salts of such complexes as **254** Scheme 4-6, have been isolated as early as 1902 and are known as Meisenheimer salts.[152] The reaction is similar to an S_N2 reaction mechanism in that the rate determining step is the attack of the nucleophile to form the intermediate complex. However the difference is highlighted by the fact that even though flouride ion is not as good a leaving group as bromide ion, it can undergo NAS more quickly resulting from the electron deficiency created at the aromatic carbon to which they are bound (site of attack).



254

Scheme 4-6: Formation of Meisenheimer salt

With a variety of 4-thio benzaldehyde derivatives available, the remaining two steps could be carried out to afford the desired amphetamines. The first method tested was that used in the original 4-MTA synthesis where 4-benzylsulfanyl-benzaldehyde was refluxed with nitroethane in ethanol, to which butylamine was added.[132] The yield was poor when compared to the reaction where the aldehyde, nitroethane, dimethylamine and potassium floride were refluxed in dry toluene with water removed by the use of a Dean-Stark trap shown in Scheme 4-7.



Scheme 4-7: Synthesis of the nitrostyrenes 255-258

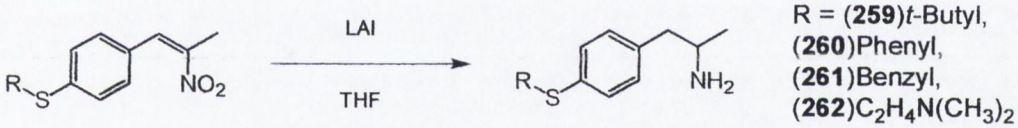
In the case of 1-tert-butylsulfanyl-4-(2-nitro-propenyl)-benzene **255**, NMR, IR and elemental analysis were used to fully characterise the compound. In the ^{1}H NMR spectrum again the *tert*-butyl group produced the characteristic singlet integrating for nine protons at 1.30 ppm. The methyl group of H3 resonates as a singlet at 2.45 ppm representing three protons. In the aromatic region of the spectrum, the typical pattern for 1,4 substitution is evident with two doublets each integrating for two protons with *ortho* coupling constants of 8.0 Hz. The doublet from 7.37-7.39 ppm was assigned as ArH3/H5 with the remaining doublet from 7.58-7.60 attributed to ArH2/H6. The remaining peak at the deshielded value of 8.05 ppm was assigned as the proton from the nitrostyrene group at H1. In the ^{13}C NMR spectrum C3 was evident as a methyl signal upright in the Dept 135 experiment at 13.78 ppm. The *tert*-butyl group produced a prominent signal resonating at 30.85 ppm, with the corresponding quaternary signal present at 46.52 ppm. The Dept 90 contained prominent signals at 129.73, 132.56 and 137.24 ppm, assigned at ArC3/C5 (two signals overlap), C1 and ArC2/C6 respectively. The quaternary peak at 132.35 ppm was assigned as ArC4,

with the remaining quaternary signals at 135.34 and 147.86 ppm attributed to ArC1 and C2 respectively. The main absorption bands in the IR spectra were ν cm^{-1}: 2862 (C-H), 1511, 1318 (NO_2), 1167 (C-C). Elemental analysis of the nitrostyrene **255** found C, H, N % – 62.05, 6.78, 5.51, theory – 62.12, 6.82, 5.51 % confirming the molecular formula to be $C_{13}H_{17}NO_2S$. The yields, IR and melting point data for the series of nitrostyrenes in Scheme 4-7 are presented in Table 4-2.

Table 4-2: IR, melting points and yields for nitrostyrenes 255-258

Compd	IR ν cm^{-1}	m.p. °C	Yield %
255	2973, 1650, 1511, 1318, 1167	60-62	75
258	1638, 1509, 1310, 1091	oil	73
256	1651, 1584, 1300, 1080, 825	92	46
257	1699, 1591, 1518, 1316, 1090	84 (lit. 74-75)	72

The final step in the synthesis involved the direct LAI reduction of the nitrostyrenes **255-258** to the subsequent amphetamines **259-262**, Scheme 4-8.



Scheme 4-8: LAI reduction of nitrostyrene intermediates to amphetamines 259-262

The reduction proceeded well for each of the amphetamines described in Scheme 4-8. For illustrative purposes the spectroscopic characterisation of the *tert*-butyl analogue is described here (see Figure 4.2). In the ^1H NMR spectrum[#] the characteristic singlet appears at 1.23 ppm integrating for nine protons. The methyl group at H3 resonates as a doublet at 1.06-1.08 ppm, the coupling constant equating to 6.0 Hz with the integral value corresponding to three protons. The amino protons appear as a singlet at 1.39 ppm. The methylene protons at H1 appear as two double doublets from 2.47-2.68 ppm integrating for two protons. The *geminal* coupling (H1-H1*) is 13.0 Hz, the *vicinal cis* coupling (H1-H2) is equal to 8.0 Hz, with the *trans vicinal* coupling constant (H1*-H2) equal to 5.5 Hz. The proton at H2 emerges as a complex multtilet from 3.09-3.17 ppm, integrating for one proton. The usual pattern for a 1,4 disubstituted ring pattern is evident with two doublets, each integrating for

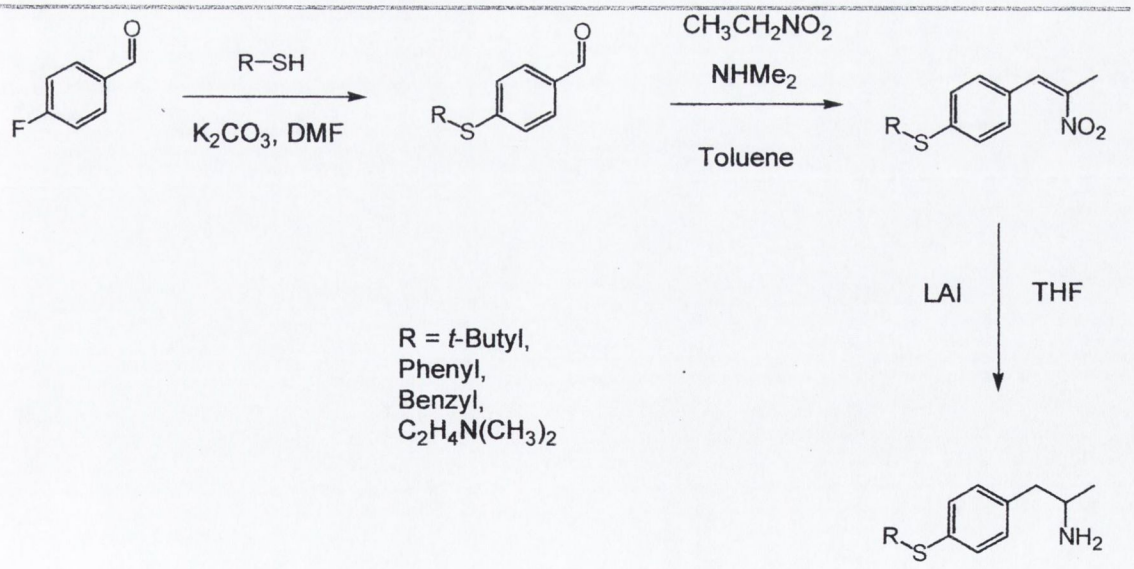
[#] In the cases two protons are attached to the same carbon atom, the * symbol denotes one from the other and if a CH proton exists adjacent to a CH_2, * represents the methylene proton *cis* to the CH.

two protons with coupling constants of 8.0 Hz. The doublet from 7.10-7.12 ppm was assigned as ArH3/H5 with the one from 7.41-7.43 ppm attributed to ArH2/H6.

In the ^{13}C NMR spectra the methyl group at C3 precesses at 23.34 ppm, remains upright in the Dept 135 experiment and is not present in the Dept 90. The *tert*-butyl moiety resonates at 30.71 ppm with the corresponding quaternary signal evident at 45.47 ppm. The signal for C1, present in the Dept 90, was found at the chemical shift value of 46.07 ppm. The peak assigned as C2, inverted in the Dept 135 experiment, resonates at 48.17 ppm. The aromatic protons produced responses at 129.17 and 137.30 ppm, each present in the Dept 90 experiment assigned as ArC3/C5 and ArC2/C6 respectively. The two quaternary peaks from ArC4 and ArC1 were evident at 129.97 and 140.22 ppm respectively. The IR, melting points (HCl salts) and yields of the amphetamine derivatives **259-262,** the synthesis described in Scheme 4-8 are given in Table 4-3.

Table 4-3: Yields, IR and melting point (HCl salt) data for amphetamines 259-262

Compd.	IR υ cm^{-1}	m.p. °C (HCl)	Yield %
259	2936, 1505, 1131, 797	232-234	58
262	2998, 1494, 1018, 782	oil	52
260	2991, 1496, 1016, 740	160	47
261	2936, 1494, 1088, 793	169-172 (lit.173-174)	71



Scheme 4-9: Summary of the synthesis of alkylthio amphetamine derivatives

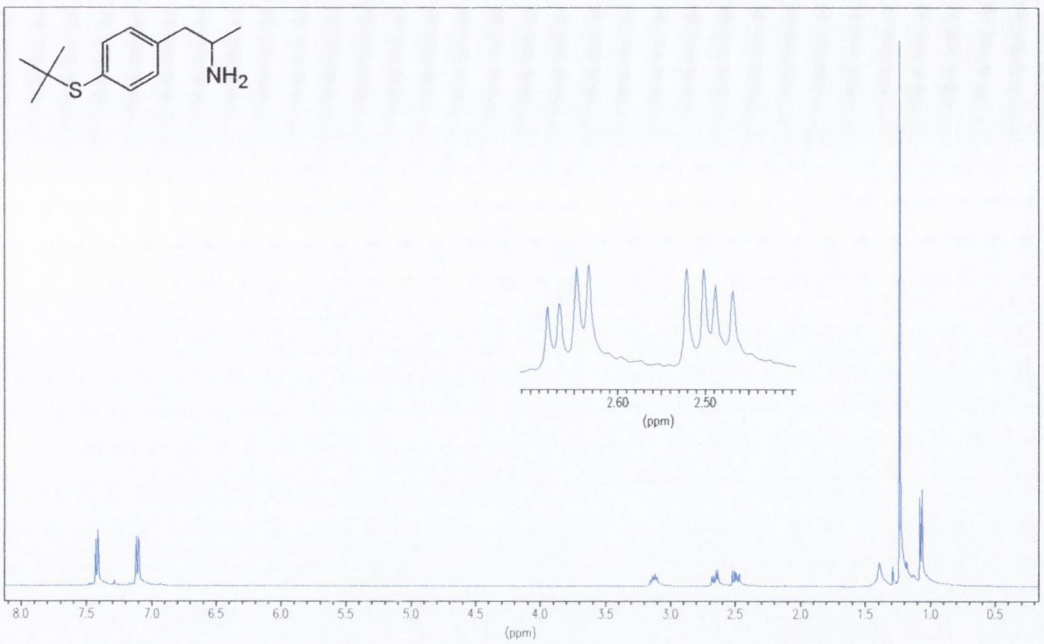


Figure 4-2: ^{1}H NMR of the amphetamine 2-(4-tert-Butylsulfanyl-phenyl)-1-methyl-ethylamine-259

4.4 Conclusions and future work

A synthetic route to a variety of thio derivatised amphetamines has been established. The initial metallation reaction (Scheme 4-3) although providing the different alkyl substituted thioanisole derivatives, was not efficient enough to be utilised on a large scale with poor to moderate yields and difficult purifications required. The nucleophilic aromatic substitution reactions from 4-fluorobenzaldehyde to the various thiobenzaldehydes (Scheme 4-5) proved suitable for the main objective of the current study that being the derivatisation of the alkyl thio group of 4-MTA. With this chemistry in place interesting future work could include a wider variety of thio substitutions at position four while also varying the position of the amino group on the propylene chain, thus providing products of potential interest for study of SERT inhibitory properties.

5 Chapter Five: Strategies in the design and synthesis of potential SSRIs

5.1 Introduction

5.1.1 Design

Based on a review of the various pharmacophores developed for SSRIs, it was decided to attempt the design and synthesis of a novel SSRI. From this pharmacophoric model a backbone structure was to be proposed to satisfy each of the seven components described. The distance from the electronegative region (in this case the dimethoxy group, which facilitates the ring closing reaction in tetrahydroisoquinoline synthesis and is present in amphetamine type stimulants) to the positively charged nitrogen corresponds to between five and six carbon-carbon bonds from the aromatic ring (n = 1, 2; Figure 5-1). This trait is apparent through many of the currently prescribed SSRIs on the market. The proposed structure Figure 5-1 satisfies each of the criteria from the pharmacophore described by Rupp Figure 5-2.

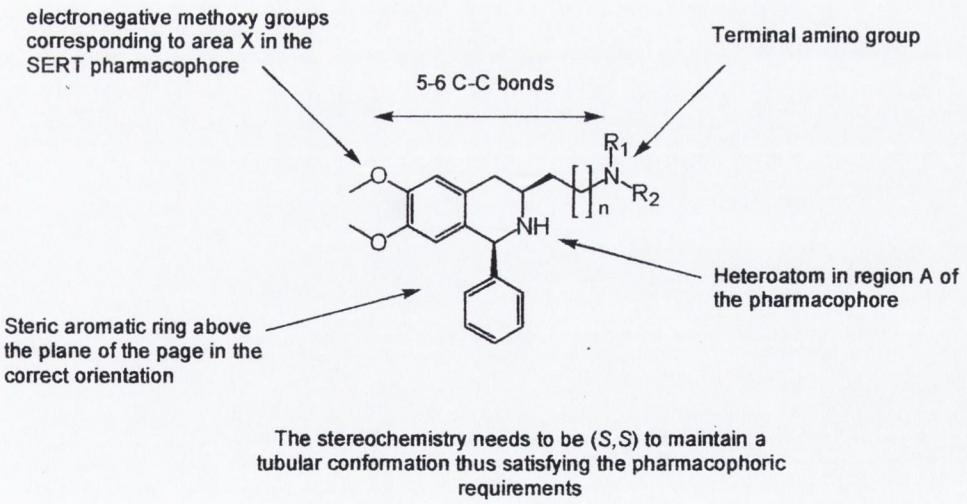


Figure 5-1: Proposed SSRI basic structure

A key requirement for optimal SERT inhibitory activity is to have a steric group protruding out of the plane in which the substituted aromatic ring lies. The isoquinoline side ring is puckered as the relevant carbons are sp^2 hybridised, therefore any substitution on C-1 would sit in a different plane to that of the phenyl

ring. With this in mind a phenyl was group placed on C-1. A crucial feature of the proposed structure (Figure 5-1.), is that it must have (*S,S*) stereochemistry at both chiral centres to satisfy the tubular arrangement described in the pharmacophore (Figure 1-11 and Figure 1-15). The nitrogen atom of the isoquinoline ring fulfills the requirement of having π-electrons in the region A2 (as is the case with the oxygen of citalopram **8**).

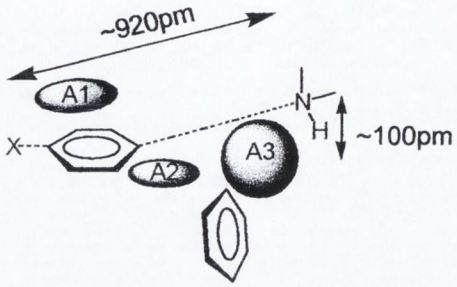
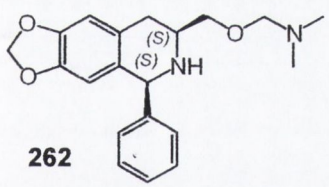


Figure 5-2: Previously described SERT pharmacophore

For comparative purposes, the 1,2,3,4-terahydroisoquinoline **262** (Figure 5-3) was used in the initial structural studies. In Figure 5-4 **262** (in blue) is superimposed over the structure of Citalopram **8** (shown in green) and Sertraline **10**(shown in red) using Sybyl 6.8.



262

Figure 5-3: Structure used for initial modelling

The conclusions drawn from Figure 5-4 were that the two aromatic rings of **262** relative to each other were in the correct region of the pharmacophore, the clinically available SSRIs were noticeably different from one another and that the position of the terminal amino group was not in the same orientation as that of Citalopram **8** and Sertraline **10**. At this stage in the work, the only published computational arrangement of SERT had been generated by Ravna *et al.*[20] **262** was manually docked in the proposed binding site of the putative SERT model using Sybyl 6.8. The proposed structure was found to fit manually in the binding site of the putative SERT model (Figure 1-7) in a comparable orientation to that of citalopram (Figure 5-5). In Figure 5-5 is the docking of citalopram in the aforementioned model (Figure 1-7) performed by Ravna *et al.* [20] The amino acid residues involved in binding are coloured for clarity with Tyr95 (TMH1, red), Asp98 (TMH1, magenta), Ile172 (TMH3, green), Trp271 (TMH4, green), Ile552 (TMH11, green). In Figure 5-5 citalopram is covered with dots representing its van der Waals surfaces, with the nitrogen shown in cyan, fluorine is coloured magenta and the

oxygen is in red. For clarity the author made the lines closer to the viewer more solid than those further away, allowing some perspective in viewing the model.

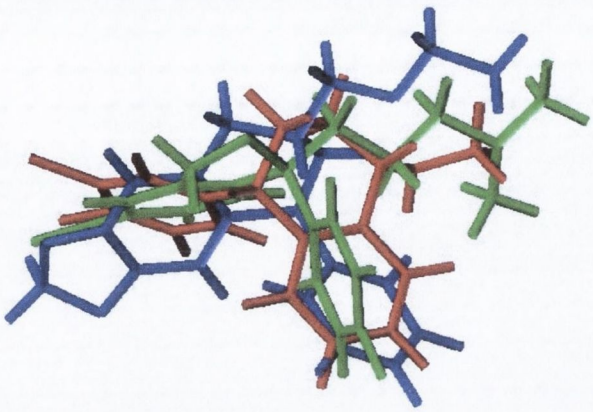


Figure 5-4: THIQ 262 superimposed with Citalopram and Sertraline

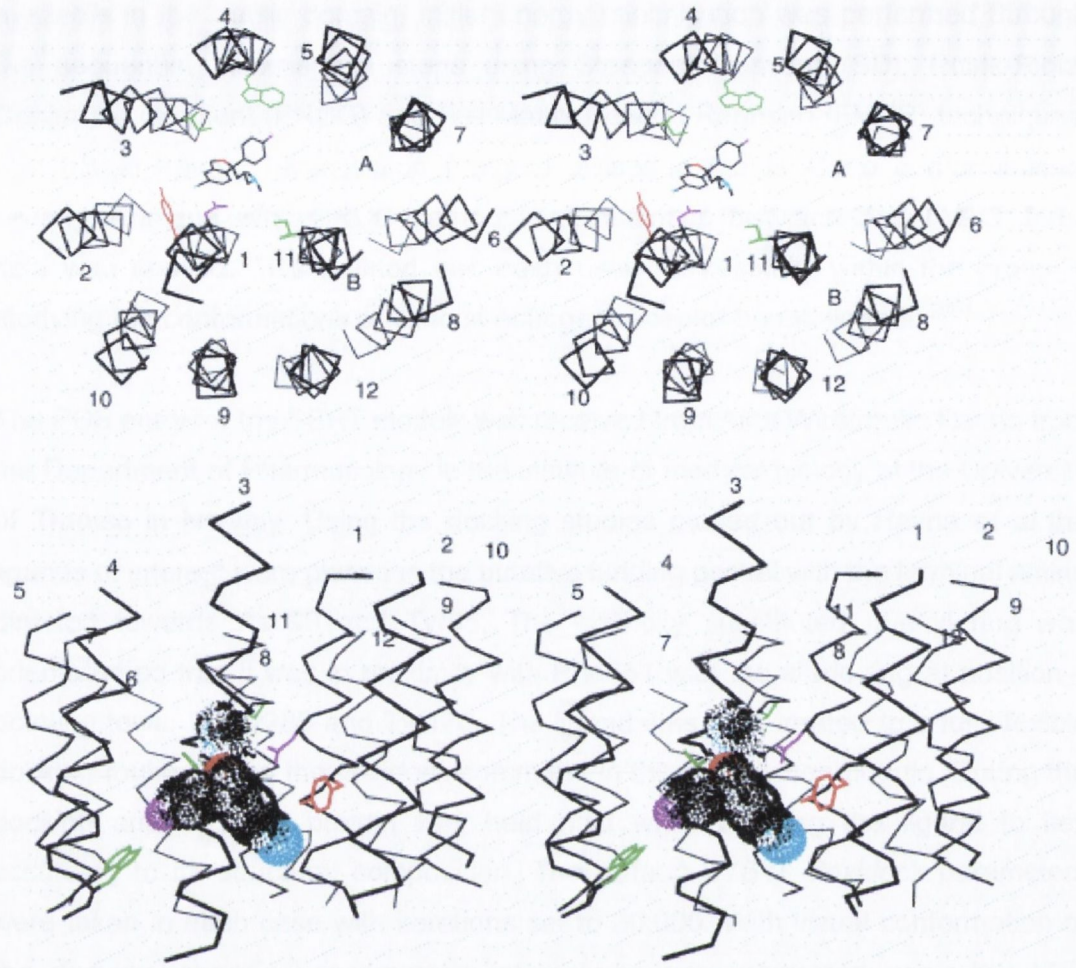


Figure 5-5: Docking of citalopram in the active site of putative SERT model[20]

The citalopram ligand was manually docked using MIDASPlus software with the nitrogen of the ligand directed towards Asp98 and then energy minimised.[20] It sits in the proposed active site with the amino functional group pointing down into the protein. The ligand also appears to sit in the lower half of the helical structure. Amino acids involved in ligand binding were identified on the basis of their having van der Waals contact with the ligand as well as those having van der Waals contact after increasing all van der Waals radaii by 20%.[20]

5.1.2 Molecular modelling procedures

5.1.2.1 Computational hardware, software and methods

All manipulations and calculations were carried out on Silicon Graphics O2 workstations with 300MHz MIPS R1200 (IP32) processor and 256MB RAM, running IRIX 6.5.. Ligand modelling and energy minimisations was achieved in MacroModel

6.5. using the MM3* force field which is a modified version of the MM3 force field available in the public domain. Initial energy minimisation was performed through the sequential minimisation steps using Steepest Descent (SD), Polak-Ribier Conjugate Gradient (PRCG) and Full Matrix Newton Raphson (FMNR) techniques. The global energy minimisation protocol utilised a Monte Carlo conformational search technique with a PRCG method. In all instances the MacroModel MM3* force field was applied. This method has been used successfully within the group in studying the conformations of various estrogen receptor bound ligands.[254]

The PDB entry for the SERT models was received from Aina Westrheim Ravna from the Department of Pharmacology in the institute of medical biology at the University of Tromso in Norway. Using the docking studies carried out by Ravna *et al* the ligands of interest were placed in the putative binding pocket with the terminal amine directed towards Asp98 and Tyr95. The methoxy substituted phenyl ring was orientated so that it was in proximity with Phe551 with the steric ring at position-1 pointing towards Tyr289 and Tyr176. The ligand was then treated to a fully fexible docking routine using the *flexidock* command in the *biopolymer* module. During the docking analyses the protein was held rigid while allowing the ligand to flex according to its structural composition. The default SYBYL *flexidock* parameters were taken in each case with iterations set to 30,000. With visual conformation of the docking, specific ligand-protein interactions were gererated using the LPC programme. All text editing was performed using the SGI "nedit" program, version 4.0.3i.

The ligands strongest binding orientation depicted in Figure 5-5, had the terminal amine pointing down into the cleft. It was not close to Asp98 or Tyr95 as was the case for citalopram. Several favourable interactions exist between the aromatic steric group on position-1 of the aromatic ring and the phenylalanine rich binding region. The dioxole oxygen atoms were calculated to participate in hydrogen bonding with the amino acid Ile172. However very few amino acid residues donated as the cocaine binding pocket interacted with the ligand. This was a result calculated by the *flexidock* facility in SYBYL 6.91 as being the best fit. The authors in producing the images shown in Figure 5-5 did not run any such automated docking procedures. The citalopram **8** ligand was manually placed in the proposed active site without using a docking protocol.

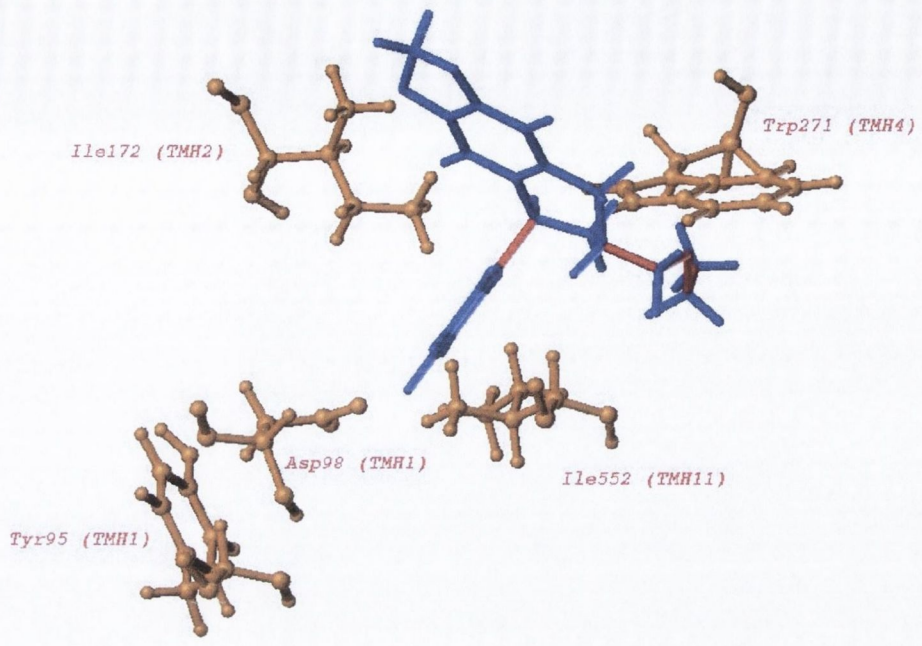


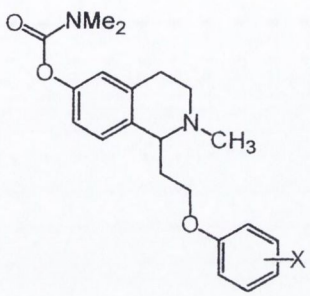
Figure 5-6: Docking result of proposed ligand 262 in the active site

With this SERT model constructed very much on computational methods and approximations, with no biological tertiary structural information incorporated, it was felt the poor docking results were not convincing enough to validate an abandonment of the study. The updated SERT model was used in a subsequent binding study, the results of which will be discussed later in the chapter. The binding site in SERT is rich in phenylalanine residues and so is somewhat hydrophobic in nature, the ClogP values of the proposed compounds were comparable to several of the SSRIs currently on the market being quite lipophilic with values of 2.7-3.3 for structures of the type **262**. The higher the ClogP is of a compound value the more lipophilic it will be. The calculation is based on the distribution of the compound in question between the two phases formed by water and 8-octanol. A representative list of ClogP calculations using ClogP for windows will be produced in Appendix 1.

5.1.3 Tetrahydroisoquinolines in the treatment of depression

A literature search for compounds of the type given in Figure 5-2, with an inhibitory activity at the serotonin transporter yielded few results. The only tetrahydroisoquinoline structures studied for such activity, were developed in an attempt to achieve dual activity as acetylcholinesterase and serotonin transporter

inhibitors in the hope of producing a drug for the simultaneous treatment of both Alzheimer's disease and depression.[103, 104] The compounds used in the study incorporating the tetrahydroisoquinoline ring (Figure 5-7) were found to be moderately active at SERT, the results are given in Table 5-1.



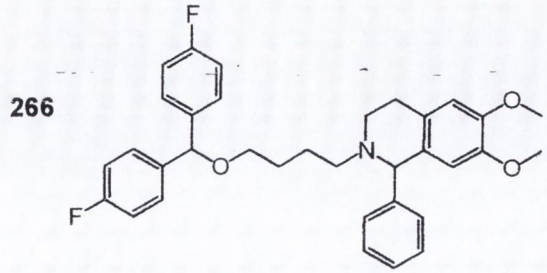
X = 3-Me-4-NO_2
$3NO_2$
4-Cl

Figure 5-7: Dual acetylcholinesterase/SERT inhibitors[104]

Table 5-1: SERT inhibitory activity of compounds shown in Figure 5-6

Compd	X	SERT IC_{50} (nM)
263	3-Me-4-NO_2	170
264	3-NO_2	125
265	4-Cl	660

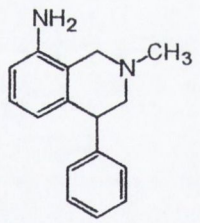
In the structures **263-265** shown in Figure 5-7, the isoquinoline amine could be considered as being in the region of the terminal amine in the proposed structure Figure 5-1, with the electronegative region denoted X equating to the methoxy groups in the present study, or the cyano group in cilatopram. For this reason it would be appropriate to suggest these isoquinolines would sit in the active site in a different orientation to the ones being developed in the present work. Choi *et al* produced a similar compound in searching for molecules with activity at dopamine receptor sites.[255] The isoquinolines synthesised had the nitrogen at a set distance from the phenyl rings that were substituted with electronegative groups. An example being **266** Figure 5-8, which was found not to be active as an inhibitor of SERT.[255] One potential reason for the inactivity at SERT of the compounds **263-266** is that when examined in terms of the pharmacophoric data available, the terminal amine in SSRI type structures could be superimposed with the nitrogen of the isoquinoline ring in Figure 5-7 with X representing the necessary electronegative region. This would imply a large bulky group (a THIQ ring in the case of **266**) may be detrimental to SERT inhibitory potential.



266

Figure 5-8: Isoquinoline inactive at SERT[255]

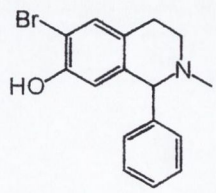
The cyclic McN-5652 series are isoquinoline derivatives and are very potent SERT inhibitors. This group of compounds have been well studied and are dealt with in chapter 1.3.3.1 (Figure 1-22).[64-68, 256] The main difference with the compounds proposed are the inclusion of the terminal side chain and the increase in structural flexibility as well as the use of dimethoxy groups to provide the desired electronegativity. Nomifensine **267** (Figure 5-9) is a tetrahydroisoquinoline that has been prescribed in the treatment of depression. It has not been dealt with in Chapter one because its main mode of action is as an inhibitor of NAT (K_i = 4.7 x 10^{-9} M) and DAT (K_i = 2.6 x 10^{-8} M).[257] It is also however, a weak SERT inhibitor (K_i = 4 x 10^{-6}).[257]



267

Figure 5-9: Nomifensine, an inhibitor of NAT and SERT with low SERT activity

Minor *et al* have demonstrated the importance of ring substitution at position-7 of the THIQ **268** Figure 5-10. It was found that the pattern of having a bromine at position-7 and an hydroxy group at position-8 lead to activity at the dopamine D-1 receptor, while the 7,8-dihydroxy analogues had no significant activity.[258]

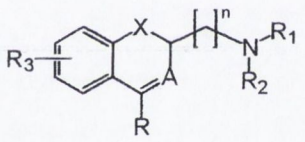


268

Figure 5-10: Dopamine D1 antagonist[258]

Cabedo *et al* have recently published work on a set of compounds analogous to that of **268** Figure 5-10, where 7,8-methylenedioxy and 7,8-dimethoxy substitution with a benzyl moiety in place of a phenyl group was studied.[259] The interesting point noted is that for optimal dopaminergic activity the chiral centre at position-1 of the isoquinoline must be (*S*), which coincides with the proposed structure Figure 5-1 and agrees with the stereochemistry used in the SERT pharmacophores.

A very interesting work was reported in a Belgian patent from 1982, in which a comprehensive range of benzoxepines and dihydroisoquinolines (Figure 5-11) with substitution patterns similar to those of the proposed compound Figure 5-1, were prepared with the aim of development as general anti-depressants and/or analgesics[260] In no instance did the inventors reduce the dihydroisoquinoline to the tetrahydroisoquinoline nor was the issue of stereoselectivity raised. No specific biological mode of action of the compounds was discussed. The patent described the preparation of the compounds.[260]



269 **270** **271**

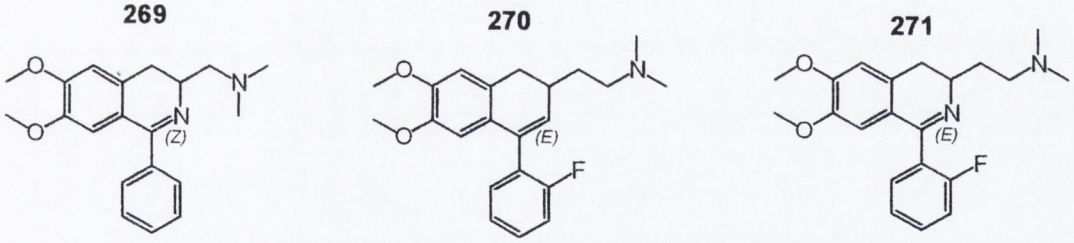


Figure 5-11: Patent study for analgesic and antidepressant activity[260]

The three compounds **269-271** (Figure 5-11) were reported as the most active, expressed only in mg/kg/i.p. using an animal model according to a method cited.[260] In producing compounds with various side chains at position-3, it was recognised that having an acid functionality at position-3 of the 1-phenyl-6,7-dimethoxytetrahydroisoquinoline would provide access to a range of side chain derivatives.

To date few isoquinolines have been developed as SERT inhibitors. The structures **269-271** were incorporated as part of a dual acting compound and so were not developed solely from the pharmacophoric data available but on the hope that joining compounds that are active at different biological receptors or enzymes will give rise to structures with a dual activity.[104, 255] The proposed entity **262** is presented as a potential starting point for an interesting set of THIQ structures to be developed solely as SERT inhibitors. In Figure 5-12 are a group of compounds investigated following the rational described.

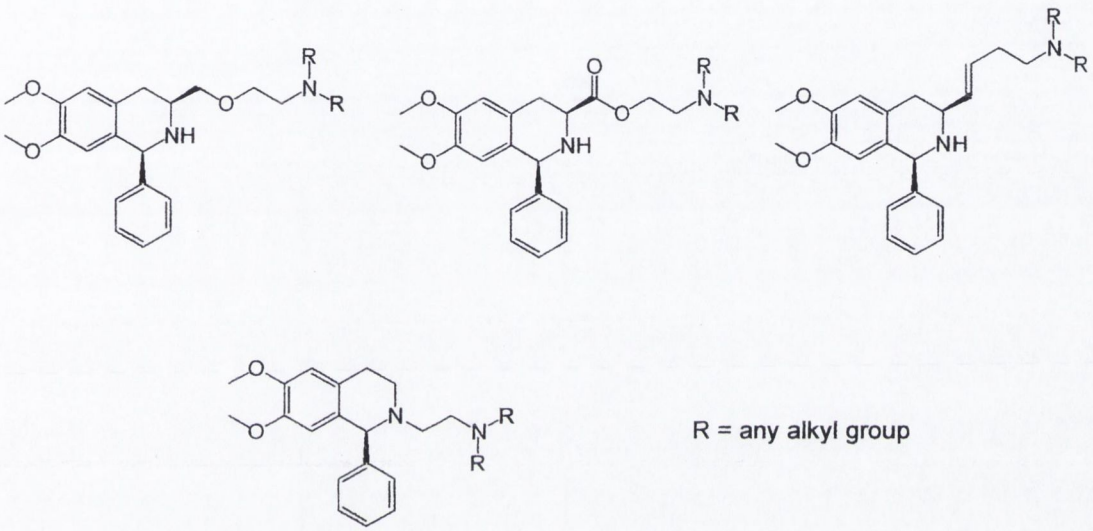
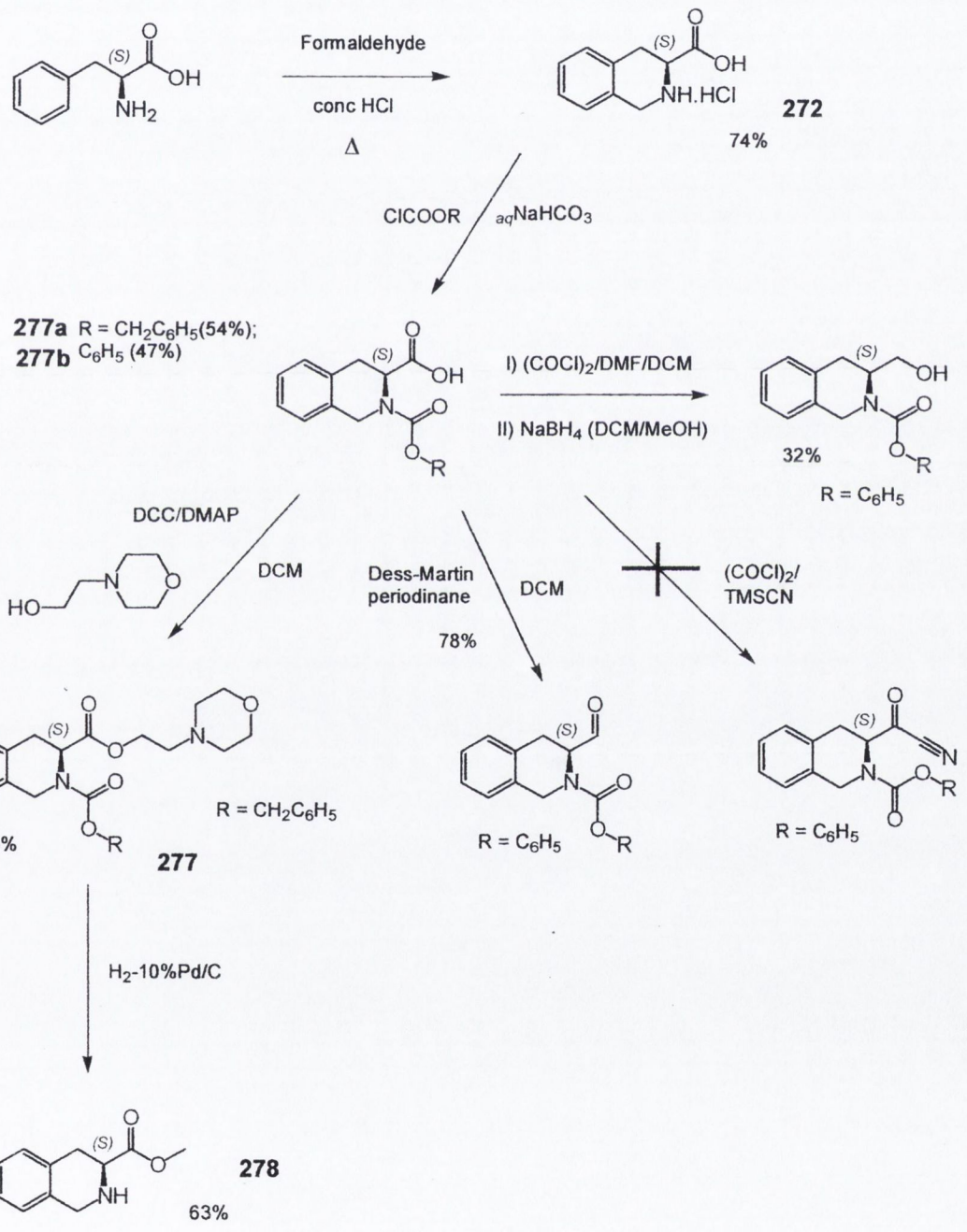


Figure 5-12: Set of tetrahydroisoquinolines proposed for study

5.2 Synthesis

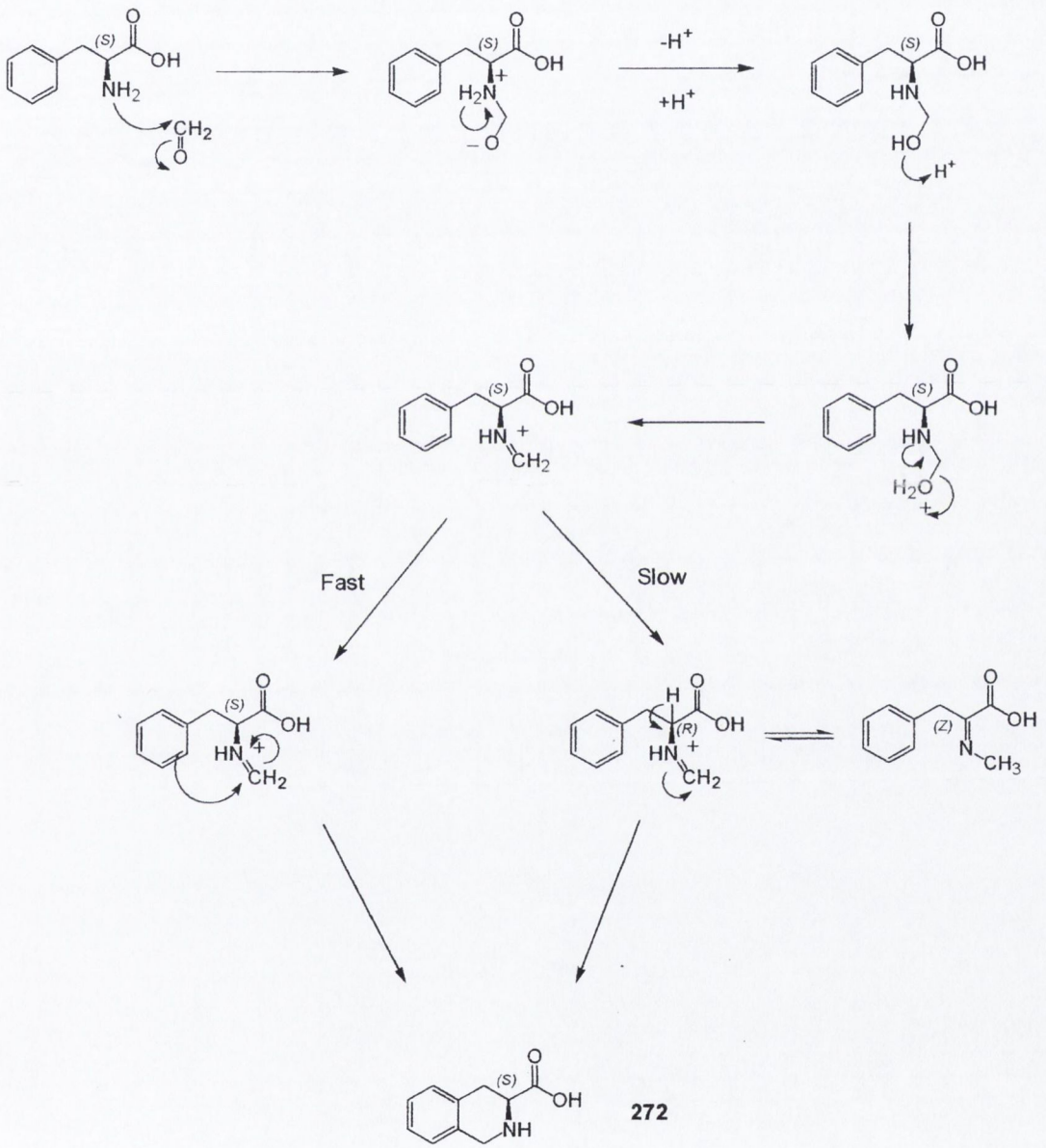
A model compound investigation (Scheme 5-1) was undertaken in order to derivatise position-3 of the tetrahydroisoquinoline ring. It was decided that the relevant 3-carboxylic acid methyl ester **272** would be a useful intermediate. To optimise the chemistry of the amino acids (at position-3 of the THIQ ring), the following synthesis was completed on a trial bases.



Scheme 5-1: Derivatisation of position-3 model synthesis

5.2.1 Stereoselective ring closure to form the requisite 1,2,3,4-tetrahydroisoquinoline.

The mechanism to the THIQ **272** is illustrated in Scheme 5.2. The harsh reaction conditions of the tetrahydroisoquinoline ring formation lead to partial racemization (10-15%) of the stereocentre resulting from protonation of the unprotected amine Scheme 5-2.[261-263]

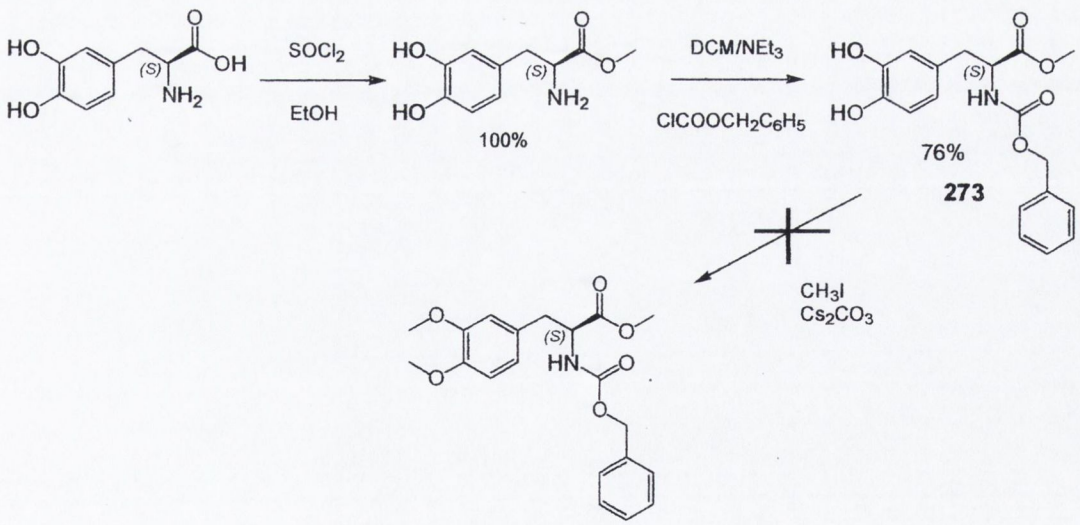


Scheme 5-2: Partial racemization under harsh conditions

5.2.2 Synthesis of 6,7-dimethoxy-1-phenyltetrahyroisoquinolines-3-methylestercarboxylic acid

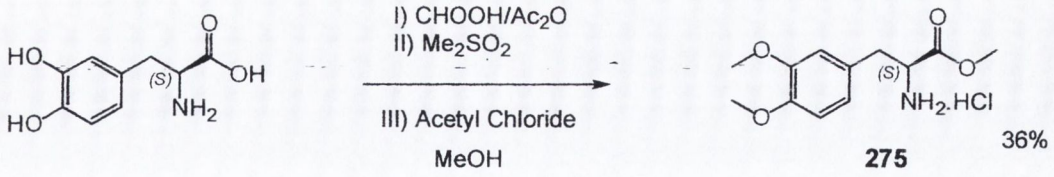
5.2.2.1 Protection of 2-Amino-3-(3,4-dihydroxy-phenyl)-propionic acid

Using the Pectet-Spengler synthesis for 6,7-dimethoxy substituted ring derivatives of **272** Scheme 5-2, the aromatic ring is sufficiently activated to attack the positive carbon of the imine cation before the racemization can take place resulting in an optically pure final product.[264] With the most suitable routes chosen to the alcohol and aldehyde, the next step in the synthesis of the proposed SSRI (Figure 5-1) was to produce the required amino acid intermediate on which to carry out the Pectet-Spengler ring closure to furnish the key chiral 6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid methyl ester **274**. The initial attempt in the synthesis of the appropriate methylated amino acid is given in Scheme 5-3. It was required to sequentially protect the three functional groups of the starting material (acid,amine and catechal), as the purchase of the protected compound **275** was not viable on a large scale. The acid was converted to the methyl ester, followed by the CBz protection of the amino group. The attempted methylation of the catechol **273** using methyl iodide yielded an inseparable mixture of compounds. For this reason a different route was taken (Scheme 5-4).



Scheme 5-3: Attempted protection of catechol

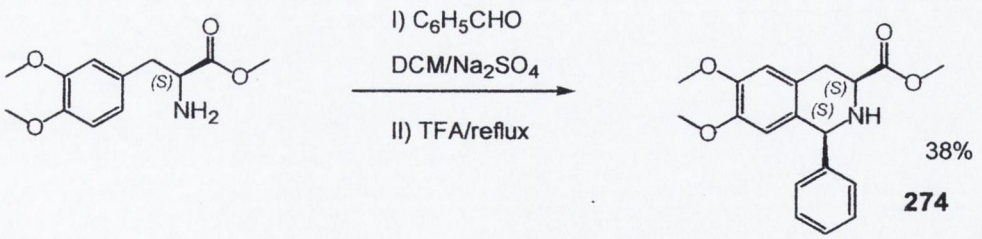
Using a one pot synthesis developed by Schrecker and Hartwell the fully protected amino acid was isolated in 36% overall yield.[265]



Scheme 5-4: One pot amino acid protection

5.2.2.2 Pictet-Spengler formation of the chiral tetrahydroisoquinoline

From molecular modelling studies of the proposed skeletal structure **262** Figure 5-3, it was evident that the stereocentre at position-1 had to be maintained as (*S*) to keep the phenyl ring in a separate plane "above" that of the dimethoxy substituted aryl ring. The second chiral centre (at position-3) also had to be in the (*S*) conformation in order to hold the terminal amine at the optimal distance from the electronegative region. The third consideration taken into account was the conformational state of the tetrahydroisoquinoline ring itself. The nitrogen of tetrahydroisoquinolines can potentially "flip" above and below the plane of the ring to yield two potential conformers. Minor *et al* reported that the 'flip' can occur slowly at room temperature and that 1-phenyl-1,2,3,4-tetrahydroisoquinoline has a low energy conformation (discovered computationally) in which the heterocyclic ring exists as a half chair with an equatorial *N*-substituent.[258] If a side chain were extended from position three of the tetrahydroisoquinoline ring, it would need to do so equatorially in order to hold the terminal amino group in the optimum position according to the SERT pharmacophore.



Scheme 5-5: Pictet-Spengler THIQ synthesis

To determine which enantiomer had formed, an X-ray crystal structure of the compound was needed. In a similar synthesis (where the phenyl ring of the aldehyde was substituted at position-1 with an iodide) Griggs *et al* reported a 3:2 *cis/trans* mixture of products. However in this instance only the required *cis* (*S,S*) diastereomer had formed. The X-ray crystal study highlights also the fact that the

correct conformer as predicted from the molecular modelling studies had also formed with the secondary nitrogen sitting above the plane of the aromatic ring as displayed in Figure 5-13-b-c. Carbon side chain additions at position three would maintain the tubular arrangement specified by the pharmacophore. Also evident from Figure 5-13, is the position of the steric aromatic group as being out of the plane of the methoxy substituted aryl ring.

274 was characterised by X-ray crystallography, melting point and by various spectroscopic techniques. The results of the X-ray study are evident in Figure 5-13. The main bands in the IR spectra and melting point are given in Table 5-2. In the ^{1}H NMR spectra the broad singlet at 2.44 ppm integrating for one proton was assigned as the NH proton. From 3.05 to 3.16 ppm were two sets of double doublets, the complex integrating for two protons. The *geminal* coupling from H4 to H4* was calculated as 15.2 Hz and the *vicinal* coupling from H4* *trans* to H3 was 5.0 Hz. The third existing coupling constant was the *vicinal* coupling of 10.0 Hz between H4 *cis* and H3. The double doublets were assigned as H4 and H4*. At 3.60 and 3.78 ppm are two singlets, each equivalent to three protons, representing the two methoxy groups. The methyl ester precesses similarly at 3.87 ppm. Beneath the singlet at 3.87 ppm exists a part of the double doublet the only J value that can be obtained is equal to 5 Hz (*vicinal* coupling from H4* *trans* to H3 was 5.0 Hz) when taken from the singlet which it over laps it integrate for one proton and so was assigned as H3. The sharp singlet at 5.11 ppm was characteristic for tetrahydroisoquinolines of this type unsubstituted at position-2. H5 and H8 resonate also as distinct singlets at 6.19 and 6.66 ppm respectively. From 7.31 to 7.36 ppm a complex multiplet integrating for five protons was indicative of the phenyl ring substituted at position-1.

The ^{13}C NMR[#] displayed a signal at 32.08 ppm (inverted in the Dept 135 experiment) assigned at C4 with the peak at 52.08 ppm (remaining in the Dept 90 experiment) equivalent to C3. The two methoxy carbons were evident from the methylene peaks (upright in the Dept 135 and not present in the Dept 90 experiment) at 55.68 and 55.74 ppm. The methyl ester was assigned as the remaining methyl carbon peak at 56.40 ppm. C1 was determined from the Dept 90 experiment, as the peak at 62.73 ppm, while the signals at 110.33 and 111.11 were assigned as C8 and C5 respectively. A total of six quaternary carbons exist in the

[#] The asterix denotes atoms of the phenyl ring substituted at carbon-1 of the tetrahydroisoquinoline. When present in describing nuclei of the THIQ moiety when two protons are attached to the same carbon atom, the * symbol denotes one from the other *e.g.* CH proton exists adjacent to a CH_2, * represents the methylene proton *cis* to the CH.

structure and for each one a quaternary signal was assigned;the most obvious being the ester carbonyl group, apparent at 172.84 ppm. The signals for C6 and C7 appear characteristically at 147.22 and 147.52 ppm respectively. The quaternary carbon C1* of the phenyl ring was observed at 143.75 ppm. The signal at 130.07 ppm was assigned as the quaternary carbon between C8 and C1, while the last remaining signal was at 125.91 ppm, which was equivalent to the carbon between C5 and C4. The ester was evident also in the IR spectra with prominent bands at 1738 cm^{-1} (C=O), 3343 cm^{-1} (N-H), 1202 and 1065 cm^{-1} (C-O).

Table 5-2: Yields, IR and melting point data for 274 and 275

Compd	IR υ cm^{-1}	m.p.°C	Lit.°C	Yield%
275	2991, 1743, 1519, 1026	158-160	158-159	36
274	3343, 1738, 1202, 1065, 829	118-120	118	38

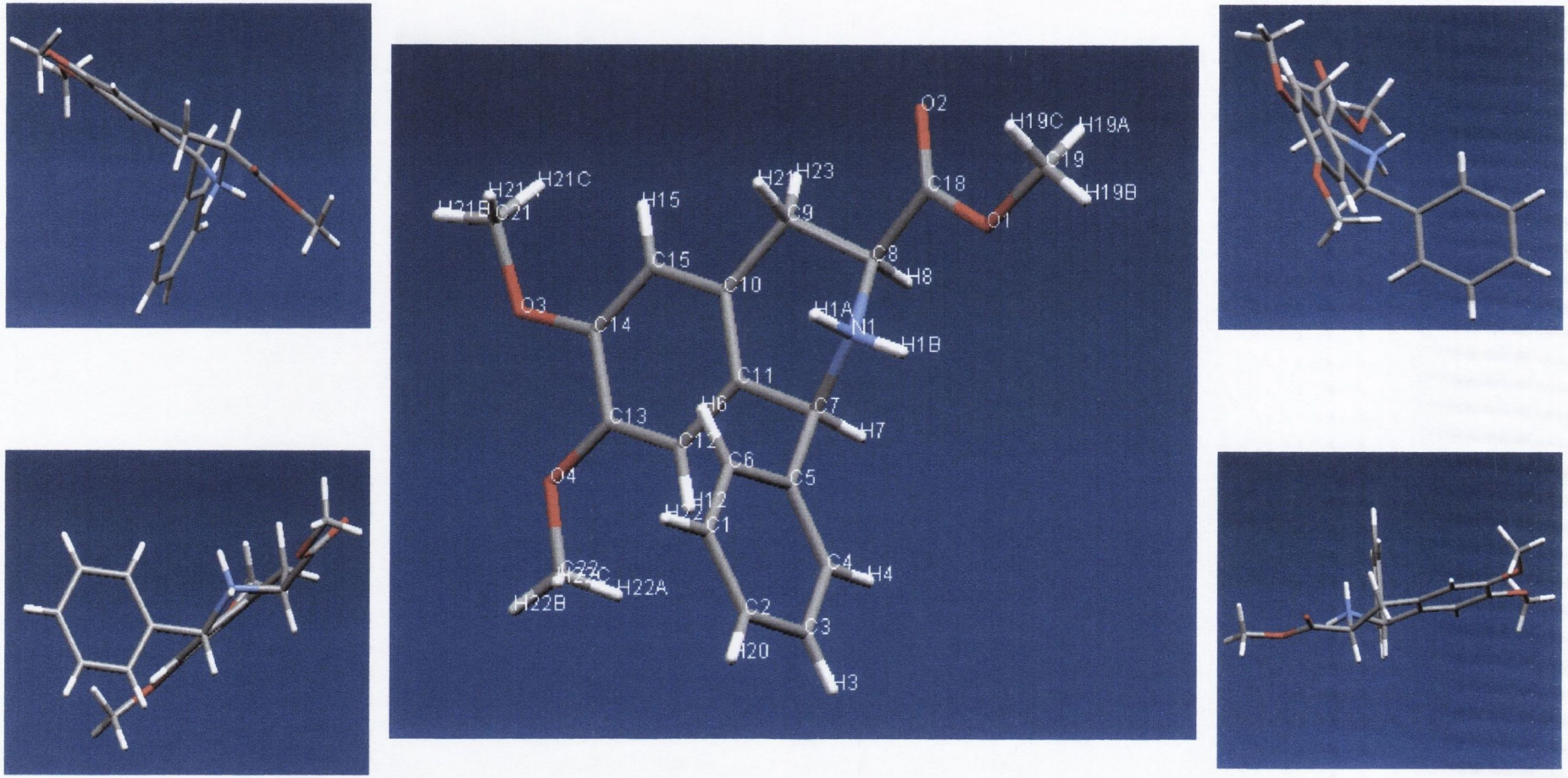
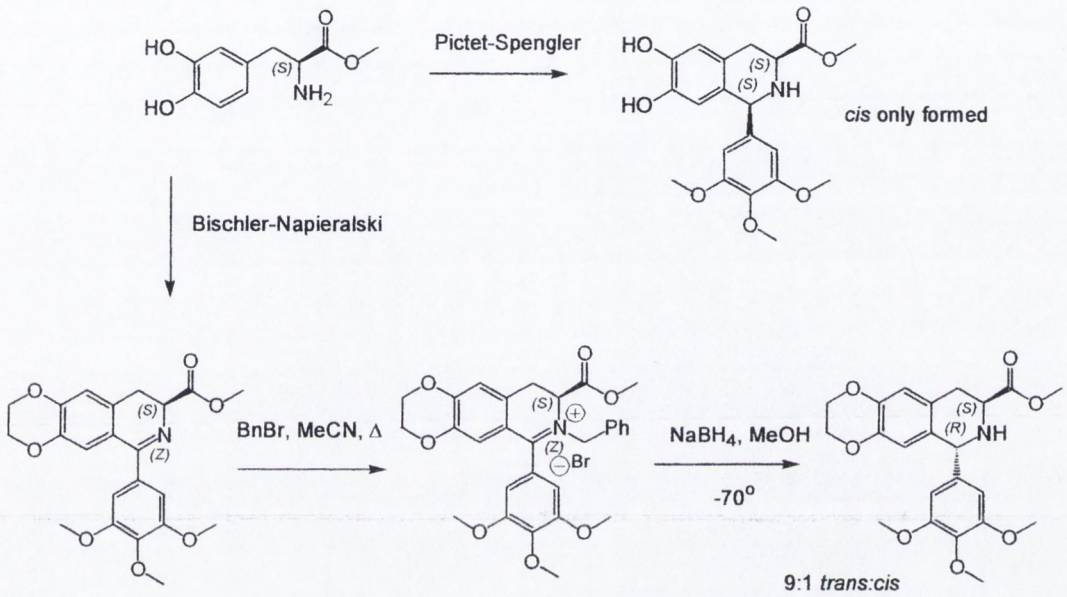


Figure 5-13: X-ray crystal structure of 274

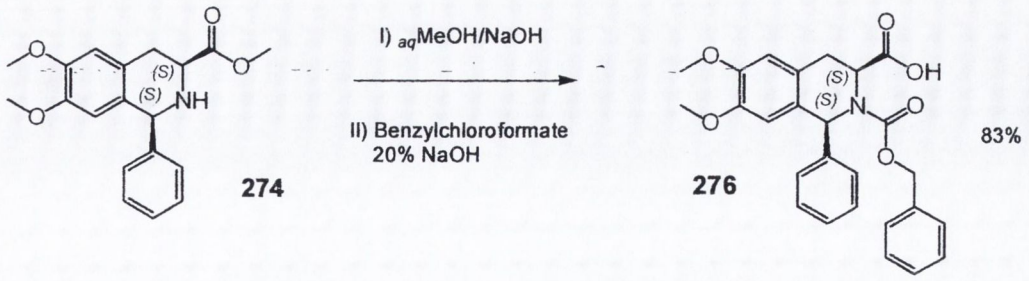
Van der Eycken *et al,* in the synthesis of THIQ-analogues of podophyllotoxins *via* Pictet-Spengler cyclisation produced only the *cis* products (Scheme 5-6.[266] To gain access to the *trans* product the group used an alternative method incorporating the Bischler-Napieralski ring closure to form the quaternarised dihydroisoquinoline from which the stereoselective reduction of the C=N double bond yielded the *trans* product in 9:1 excess (Scheme 5-6).[266]



Scheme 5-6: Stereoselective synthesis of *cis* and *trans* 1-phenylTHIQ[266]

Saxena *et al* using an *aqueous* acidic method, synthesised the 1-(*R*) analogue of 6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methyl ester **274** by the Bischler-Napieralski method, the starting material was the racemic mixture and so the product was reported as a mixture of diastereomers.[267]

With the correct stereochemistry established as being in place at both of the required chiral centres, the next stage in the study (the derivatisation of the ester group as had been carried out in the model compound Scheme 5-1) could now be persued. As the secondary amine of **274** had to be protected and the ester hydrolysed, the benzylcarbamate was chosen as the amine protecting group as it could be put in place under basic, aqueous conditions which would simultaneously leave the acid unprotected (Scheme 5-7). The hydolysis of the intermediate methyl ester **274** to the acid had been tested in $_{aq}$MeOH and NaOH.



Scheme 5-7: Base hydrolysis of methyl ester followed by CBz protection of the amine

The introduction of the carbamate group has a profound affect on the appearance of the ^{1}H NMR spectrum **276** (Scheme 5-7). The flipping of the THIQ ring in these types of compounds has been predicted computationally at room temperature, however the peaks for each signal in the ^{1}H NMR spectra of the methyl ester **274** appear as sharp bands (with the exception of the NH) indicating the presence of a single structural form. On examining the ^{1}H NMR spectra of the CBz protected acid **276** the most prominent difference in chemical shift from that of its precursor exists for the proton H1. In the secondary amino methyl ester **274,** H1 resonates as a sharp singlet at 5.11 ppm. In the CBz protected derivative the signal is shifted further downfield and split into two separate singlets integrating for 0.43 protons at 6.26 ppm and 0.58 protons at a chemical shift of δ 6.46 ppm. The methoxy groups resonate as broader singlets at δ 3.90 and 3.93 ppm. The coupling constants at the peaks representing the pair of protons at position-4 (H4/H4*) cannot be distinguished as each component in the pattern has been broadened resulting in a multiplet from δ 2.74 to 3.04 ppm. H3 also exists as two separate multiplets with one from δ 4.43 to 4.47 ppm integrating for 0.56 protons and the rest of the signal is from δ 4.52 to 4.56 ppm integrating for 0.44 protons. The methylene group attributed to the CBz exists as a distinctive and complex multiplet at the relatively deshielded value of δ 5.18 – 5.29 ppm integrating for two protons. The aromatic signals of H5 and H8 also have a strikingly different appearance to the corresponding peaks in the precursor. The proton at H5 produces a singlet at δ 6.77 ppm that overlaps with part of the signal for H8 producing a singlet integrating for 1.43 protons. The remains of the signal of H8 precess at δ 6.87 ppm integrating for 0.57 protons. The remaining aromatic signals of ten protons are indistinguishable as a large multiplet from δ 7.17 to 7.33 ppm. The acid proton produced the broad singlet at 9.46 ppm that integrated for one proton. This splitting of peaks can be explained in terms of the delocalisation of the nitrogen π-electrons producing a restricted rotation around the nitrogen – carbonyl bond similar to the system described in section 2.3 (Scheme 2-11). In the

peak assignments, the more prominent rotamer is ascribed R1 with the minor being R2, in cases were the peak is defined as normal rotamer splitting was not observed.

^{13}C NMR spectrum of **276**, peak splitting is also evident in certain cases and peak assignments were made with the aid of a 2D HMQC experiment (Figure 5-14). The methylene signals (both inverted in the Dept 135 experiment) of the carbon nucleus C4 was found at 30.01 [R1] and 30.26 [R2] ppm. The aromatic methoxy groups did not undergo rotamer splitting in either the ^{1}H or ^{13}C spectra, appearing as methyl carbons, upright in the Dept 135 experiment, at 55.96 and 56.03 ppm. The minor rotamer of C3 [R2] precesses at 56.51 ppm while the partnering signal C3 [R1] was found at a chemical shift of 56.61 ppm. The rotamer peaks of C1 occurred at 58.47 ppm [R1] and 58.74 ppm [R2]. The methylene group from the carbamate moiety resonates as a single peak inverted in the Dept 135, at 67.99 ppm. There are eight quaternary carbon signals within the molecule which were assigned as follows: at the deshielded chemical shift value of 176.40 ppm resonates the carbonyl group of the acid. The carbonyl group belonging to the carbamate undergoes rotamer splitting with [R1] evident at 156.55 ppm and [R2] at 156.37 ppm. The signal of C6 and C7 are noticeable at 148.41 and 147.80 ppm respectively. The aromatic quaternary peak at 140.59 ppm was assigned as that corresponding to the benzyl carbamate group. The phenyl ring at position one produces quaternary peaks in the spectra at 135.85 [R1] and 135.93 [R2] ppm. With only two such signals remaining, the quaternary carbon nucleus adjacent to C8 was deemed to generate the signal at 129.23 ppm and the slightly less deshielded carbon nucleus beside C5 was assigned as that producing the signal at 125.36ppm. All quaternary signals do not appear in any of the Dept experiments. With the IR spectra giving the appropriate absorption bands reported in Table 5-3 and the HRMS producing a clear and prominent peak for the molecular ion plus sodium calculated as m/z 470.1580 with the experimental value found as 470.1581 equivalent to $C_{26}H_{25}NO_6Na$.

Table 5-3: IR, yield and HRMS data for 276

Compd	IR υ cm^{-1}	HRMS m/z	Yield %
276	3441, 1752, 1699, 1515, 1227	470.1581	83

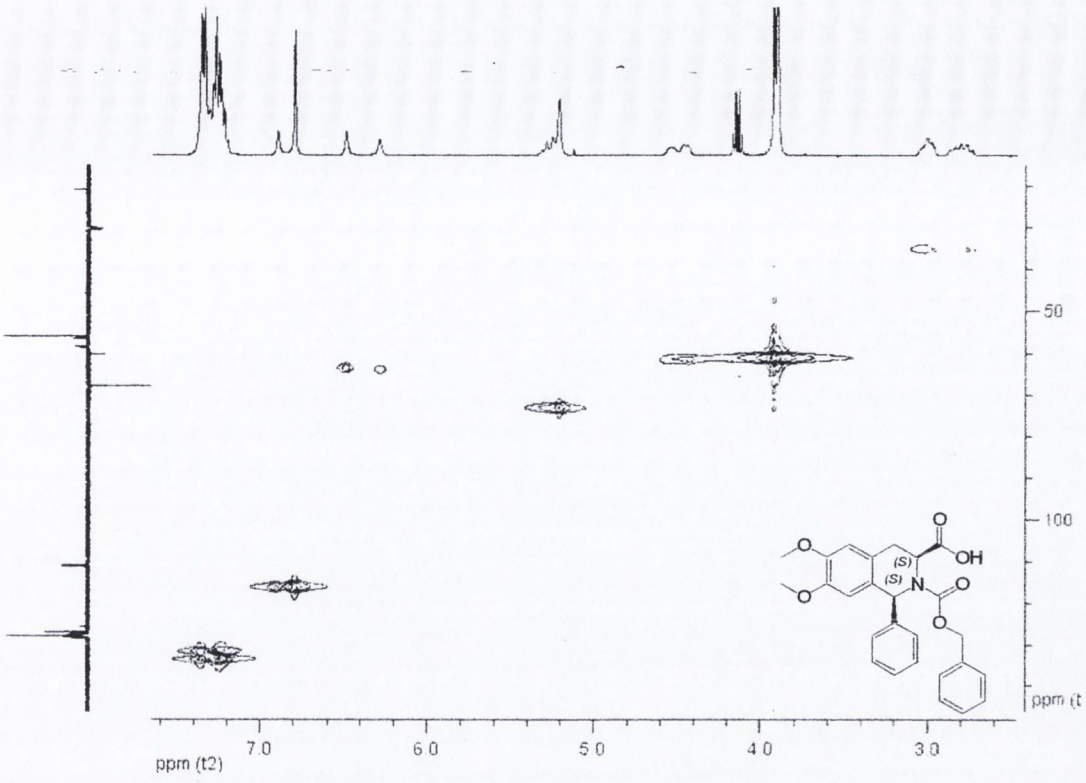
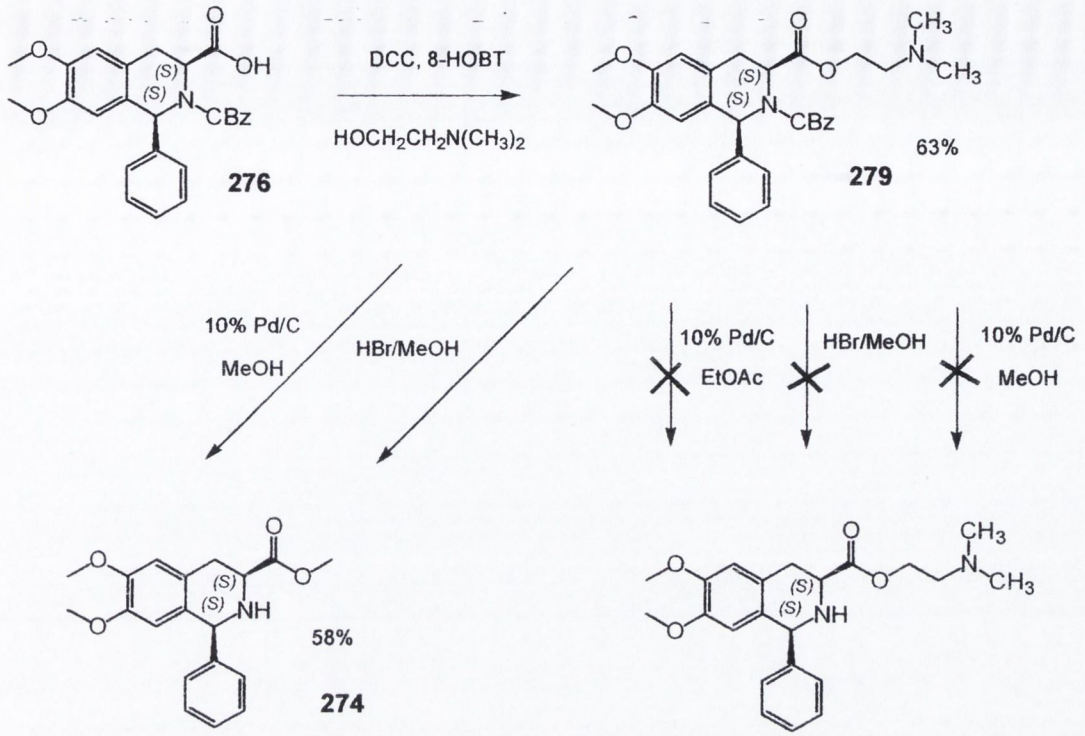


Figure 5-14: C-H Cosy of CBz protected compound 276

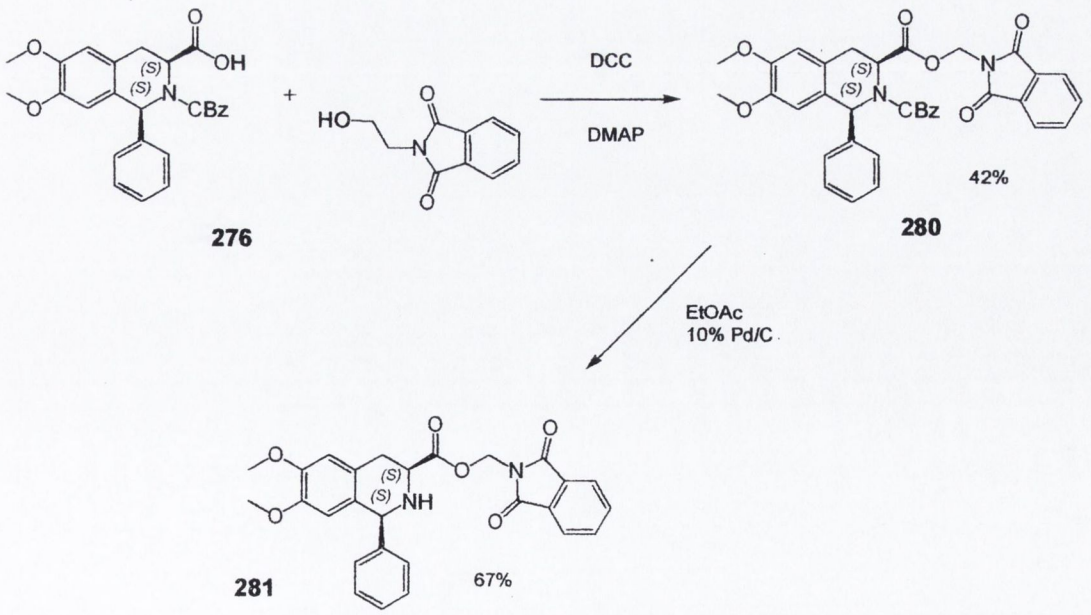
5.2.3 Introduction of ester side chains at position-3

With the acid now in place at position-3 of the THIQ and the amine protected, the first side chain was added as the ethyl(dimethyl)amino ester **279** (Scheme 5-8) using DCC as the dehydrating agent, an appropriate base and the relevant alcohol in *anhydrous* DCM. The removal of the CBz protecting group by hydrogenation in the model 3-carboxylic acid-2-morpholin-4-yl-ethyl ester **277** Scheme 5-1 proved unsuccessful yielding the methyl ester **278**. Unfortunately a similar degradation transpired giving the 6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid methyl ester **274** Scheme 5-8. A complete degradation resulted when the hydrogenation was attempted in ethyl acetate after a reaction time of three days, prior to which any distinct transformation of the starting material could not be observed. For this reason it was felt a more stable side chain may be of use, therefore esterification of the acid **276** with the alcohol 2-(2-Hydroxy-ethyl)-isoindole-1,3-dione **280** was considered.



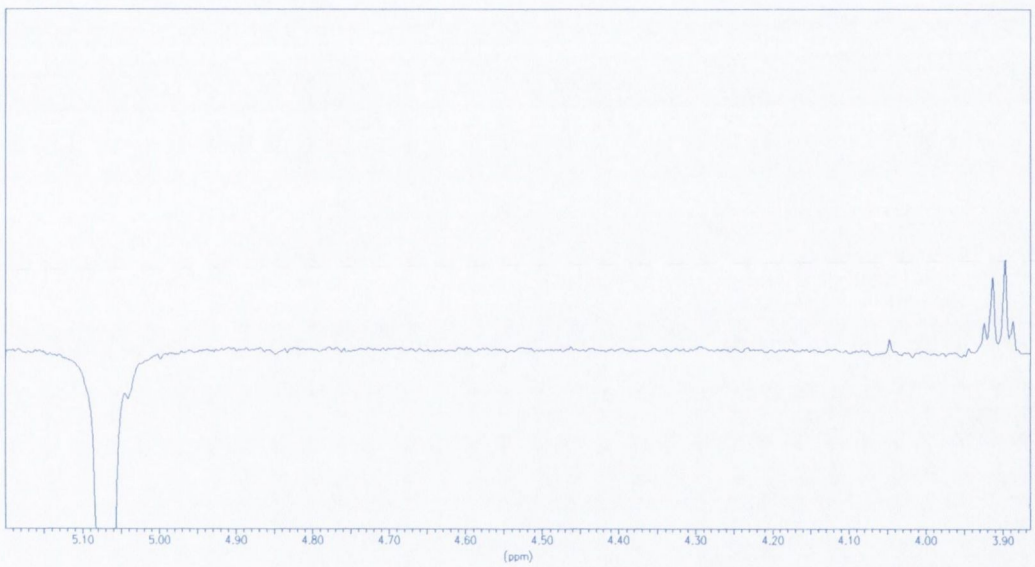
Scheme 5-8: Attempted CBz deprotection of 279

The synthesis of the amide derivative **280** was carried out in similar fashion to furnish the relevant ester. The CBz hydrogenation in ethyl acetate was successful, the final product **281** having the same R_f as the starting material in a 100% diethyl ether mobile phase, however the pure ester intermediate **280** was isolated after a reaction time of twelve hours in 67% yield (Scheme 5-9).



Scheme 5-9: Successful CBz deprotection to yield 281

In order to ensure the correct stereochemistry had been conserved NOE NMR experiment were conducted to determine if there was an NOE enhancement from H1 to H3, an effect only possible if the protons in question are on the same side of the isoquinoline ring. Figure 5-15 is the result of the NOE experiment showing a positive enhancement from H1 to H3, which points to *cis* protons at H1 and H2 and since the chiral centre at H3 is set as being (*S*) from the starting material the compound was proposed as having (*S,S*) stereochemistry.



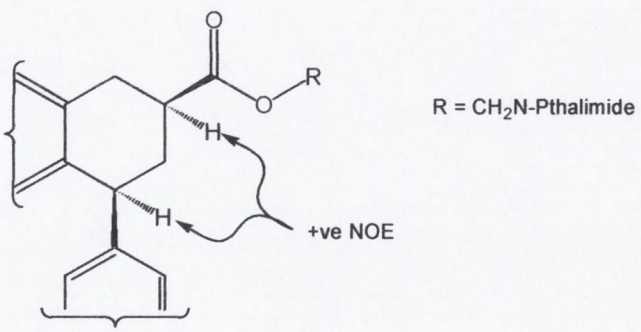
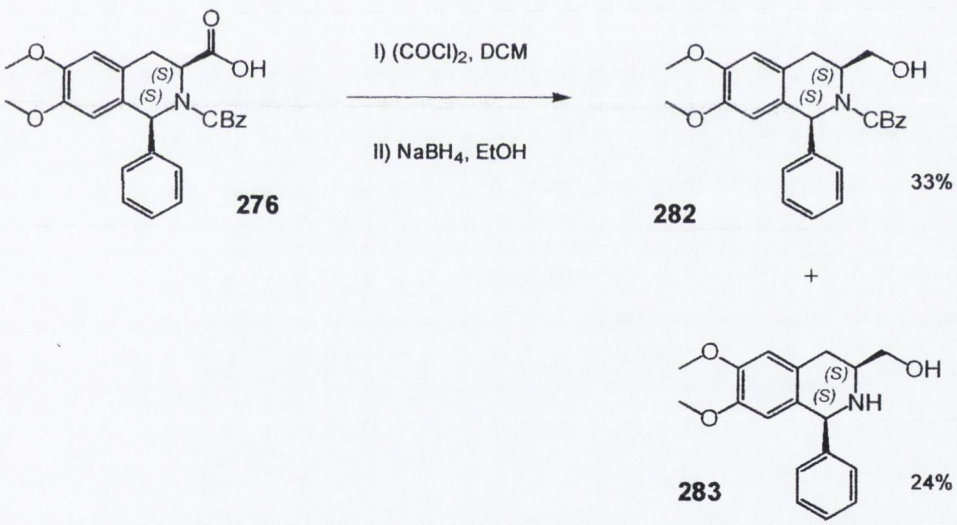


Figure 5-15: NOE interactions supporting (*S,S*) stereochemistry

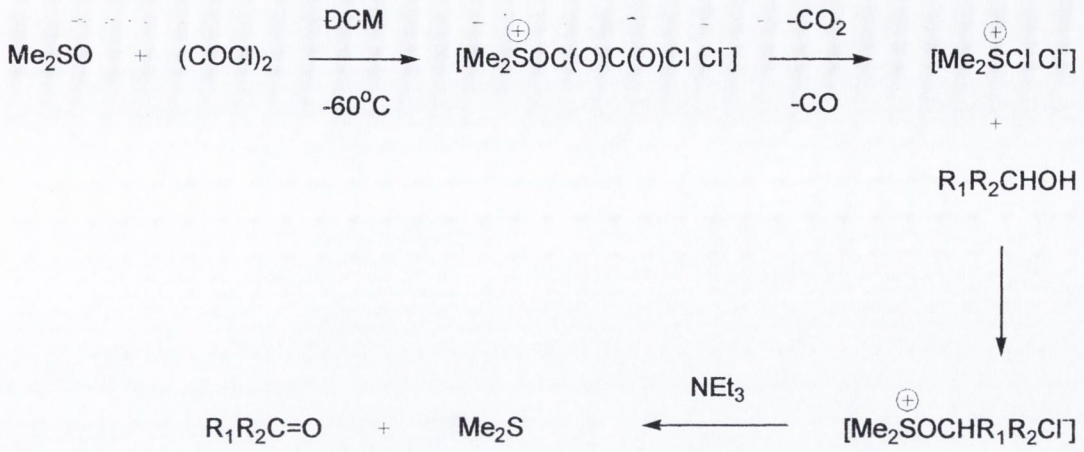
5.2.4 Reduction of the acid **276** to the relevant alcohol **282** with subsequent oxidation to the aldehyde derivative **284**

With the chemistry in place to form ester linkages at position-3, the next viable transformation persued was etherification. There were various options available, with a considered route being the transformation of the acid **276** to the alcohol **282** followed by bromination. A bromide would be an intermediate on which several different nucleophilic substitution reactions could be carried out. However the aforementioned alcohol could also be used as a nucleophile to attack a brominated alkyl substrate side chain, thereby reducing the number of sequential steps in the synthesis. Therefore regardless of which path was chosen, the alcohol was a required intermediate. The initial route was *via* the acid chloride of **276** followed by a relatively mild $NaBH_4$ reduction. Although the reaction furnished the desired alcohol **282**, the yield was lowered as a result of the CBz protecting group removal, to give the amino alcohol **246** in a similar yield Scheme 5-10.



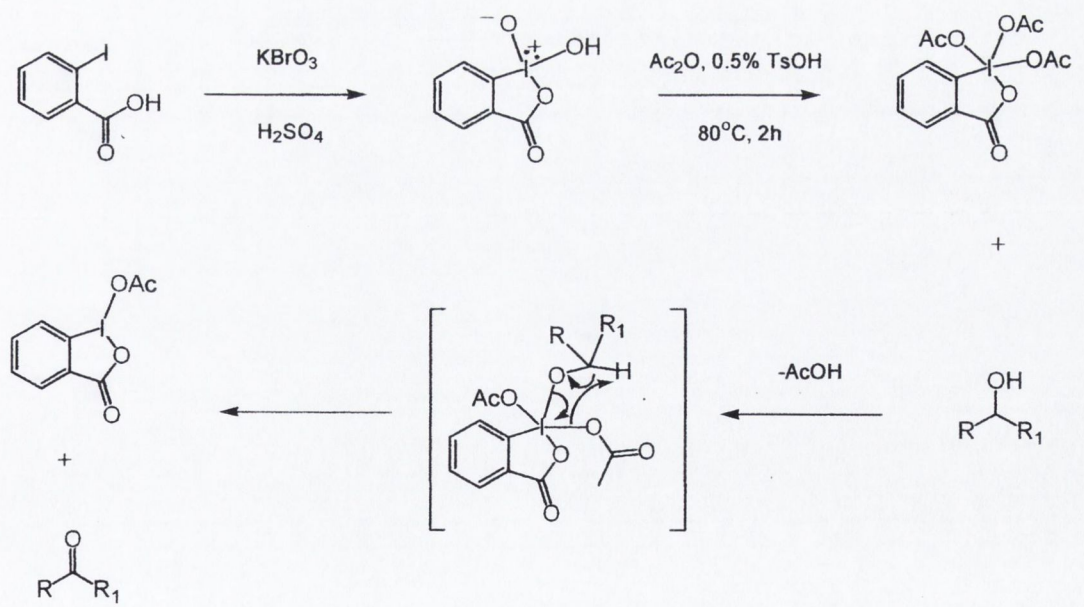
Scheme 5-10: Reduction of the acid 276 to alcohol 282

To introduce olefinic side chains at C-3 position, it was deemed desirable to achieve the 3-formyl analogue of the alcohol **282**. Direct reductions from the acid to the aldehyde may not prove straightforward with appreciable amounts of alcohol isolated as a likely side product. The synthesis had been carried out on the model compounds Scheme 5-1. One method considered was the Swern oxidation, where a variety of alcohols can be mildly oxidised to the carbonyl compounds using DMSO activated by oxalyl chloride, the mechanism for which is given in Scheme 5-11.[268, 269]



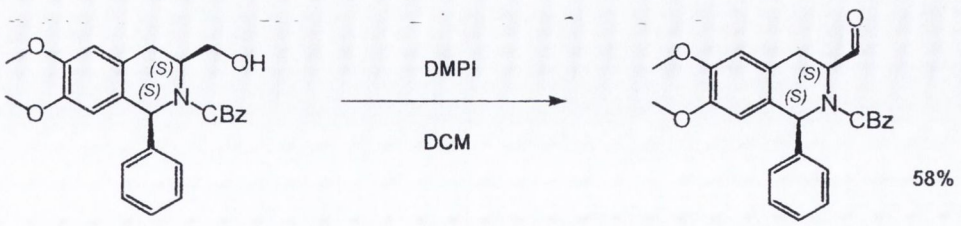
Scheme 5-11: Swern oxidation[268]

The Dess-Martin Periodinane, a hyper-valent iodine compound, offers selective and very mild oxidation of alcohols to aldehydes or ketones and as a result, has been used in the synthesis of many complex natural products as a result.[270] In order not to affect the stereochemistry in the compounds being studied it was initially deemed as the most promising route to a potentially useful aldehyde intermediate from the corresponding alcohol. The preparation and the mode of action of the Dess-Martin reagent is described in Scheme 5-12.[271, 272]



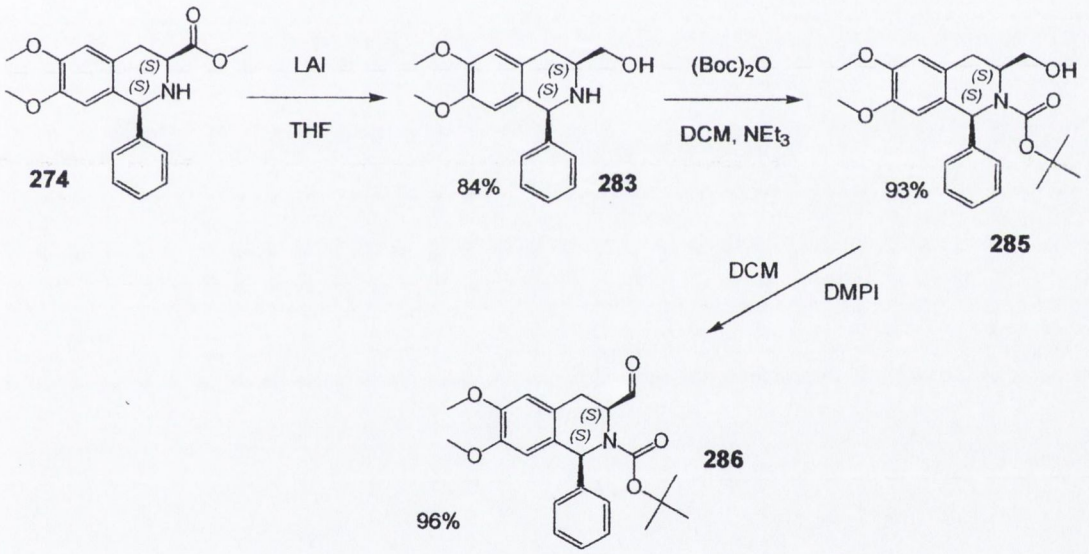
Scheme 5-12: Preparation of Dess-Martin periodinane and its oxidation of alcohol substrates

The CBz protected alcohol **282** was successfully converted to the aldehyde **284** in 58% yield *via* the Dess-Martin oxidation Scheme 5-13.



Scheme 5-13: Dess-Martin oxidation of alcohol 282 to the aldehyde 284

In order to increase the yield of the relavent alcohol intermediate, a separate reduction was attempted. The reduction of methyl esters directly to the subsequent alcohol by LAl is well known, particularly in amino acid and highly substituted THIQ type entities.[266, 273] Following the poor yield of the key alcohol intermediate **276** from the synthesis described in Scheme 5-10, a direct LAl reduction of the methyl ester **274** in which the amine is unprotected was carried out.



Scheme 5-14: Improved alcohol synthesis

The secondary amine of the THIQ ring in **283** was protected as a *tert*-butylcarbamate (Boc) from which the Dess-Martin oxidation of the alcohol **285** to the aldehyde **286** was achieved in excellent yield Scheme 5-14. Protecting the secondary amine of the THIQ has a profound effect on the chemical shift and the pattern of several signals in the molecule. In Figure 5-16 the ^{1}H NMR for the alcohol **283** and the protected derivative **285** are given. The existence of the restricted rotation around the partial double bond formed upon the delocalisation of the *N* - π electrons creates the potential for *cis/trans* isomerization, this can give rise to two

sets of signals evident in Figure 5-16. Also a factor in examining these spectra is the extremely quick t_1 relaxation times in certain *t*- Boc protected THIQ type compounds.

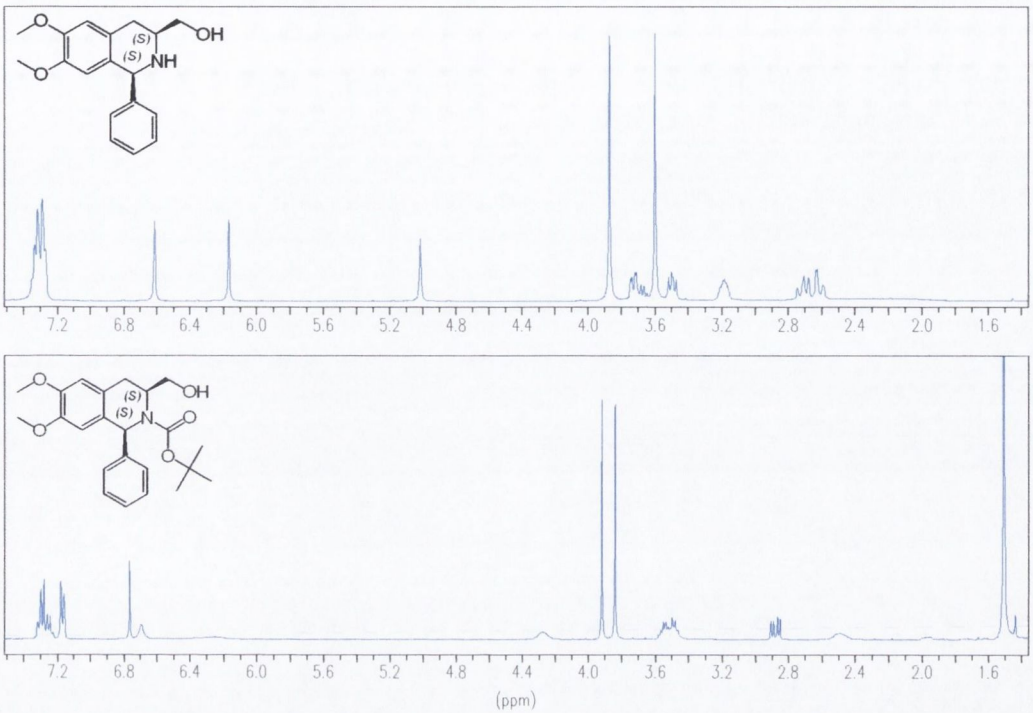


Figure 5-16: Effect of carbamate protecting group on the appearance of the ^{1}H NMR spectrum

In Figure 5-16 it is clear the signal produced by H1 in the amino alcohol **283** is drastically altered by the formation of the carbamate at position-2 giving the intermediate **285**. In the top spectrum it appears as a sharp singlet resonating at 5.01 ppm, while in the *t*-Boc protected derivative it is shifted well downfield to a value of 6.26 ppm. The signal H1 in the protected **285** is also extremely broadened. Also in the protected structure, the proton H3 is moved from 3.18 ppm in the amino alcohol **283** to 4.34 ppm in **285**. The two sets of double doublets observed for the methylene group at H4 are transformed in the protected compound to a broadened multiplet (shifted downfield by one chemical shift unit) in which none of the coupling constants are distinguishable. This is typical of the pattern observed for compounds of this type.

The various NMR spectra of the aldehyde **286** provided some interesting features. In the ^{1}H spectrum the peak splitting was again observed in approximately a 2:1 ratio with the peaks again markedly broadened. The unresolved pair of singlets at 1.50 and 1.55 ppm integrated as a total for nine protons and as a result were

attributed to the *tert*-butyl part of the protecting group. From 2.55 to 2.93 ppm existed a broadened and complex multiplet which integrated for two protons. The signal was assigned as both rotamers belonging to the H4 methylene group. The two methoxy groups resonated as singlets at the characteristic chemical shift value of 3.86 and 3.90 ppm, the remarkable feature being, the more upfield of the two was broadened to the extent where it was only one quarter of the peak height of the other yet both integrated identically for three protons. This suggests that the different methoxy groups are resolved but the corresponding rotamer signals are not. The first distinct rotamer signals are apparent for the proton H3 with R1 occuring as a broad singlet at 4.20 ppm integrating for 0.64 protons and the partnering signal was found resonating at 4.54 ppm again as a broad singlet integrating for 0.34 protons. A similar pattern emerges for the proton at H1 with the main segment at the more deshielded value of 6.44 ppm, with the singlet at 6.23 ppm assigned as the minor rotamer together they integrate for one proton. The aromatic signals for H5 and H8 are evident as a multiplet from 6.68 to 6.84 ppm integrating for two protons. The protons ArH2*/H5* of the phenyl ring at postion-1 exhibited a doublet (J_o = 7.4 Hz) splitting pattern integrating for two protons with the remaining protons of the mono-substituted phenyl ring appearing as a multiplet from 7.22 to 7.28 ppm integrating for three protons. The most significant peak in the spectrum was undoubtedly that of the aldehyde protons, showing the oxidation had been successful, precessing at the notably deshielded chemical shift value of 9.30 [R2] and 9.29 [R1] ppm. The signal was split similarly to that of the Boc protons; however the integration returned a value of 0.90 protons. The pattern was assigned as the aldehyde proton signals.

The rotamer effects were again largely evident in the ^{13}C spectrum. At 26.69 and 27.56 ppm were two peaks which had t_1 relaxation times that were so short they were barely visible (expanded region in the Dept 135 experiment is given in Figure 5-16), however they were both inverted in the Dept 135 experiment and displayed a positive interaction in the C-H COSY with the protons signals of H2. For this reason the two signals were assigned as R2 and R1 for C4 respectively. The large methyl carbon signal produced by the *t*-Boc protecting group was evident at 28.16 ppm [R1] and 28.28 ppm [R2] (Figure 5-17). As was the case in the ^1H NMR, the two methoxy groups did not produce the rotamer splitting experienced by the signals corresponding to the methylene carbon of C4 and were present as upright signals in the Dept 135 experiment at 55.88 and 55.91 ppm. The two CH carbon nuclei displayed a similarly quick t_1 relation to that of C4 and each displayed two signals as a result of rotamer splitting. The carbon of C3 was evident as two signals with R1 at

56.62 ppm and R2 at 57.50 ppm. Likewise the signals for C1 were apparent at 60.25 [R2] and 61.95 [R1] ppm. The most shielded quaternary carbon in the molecule was that of the *t*-butly moiety from the protecting group and was present in the ^{13}C spectrum at 81.61 ppm.

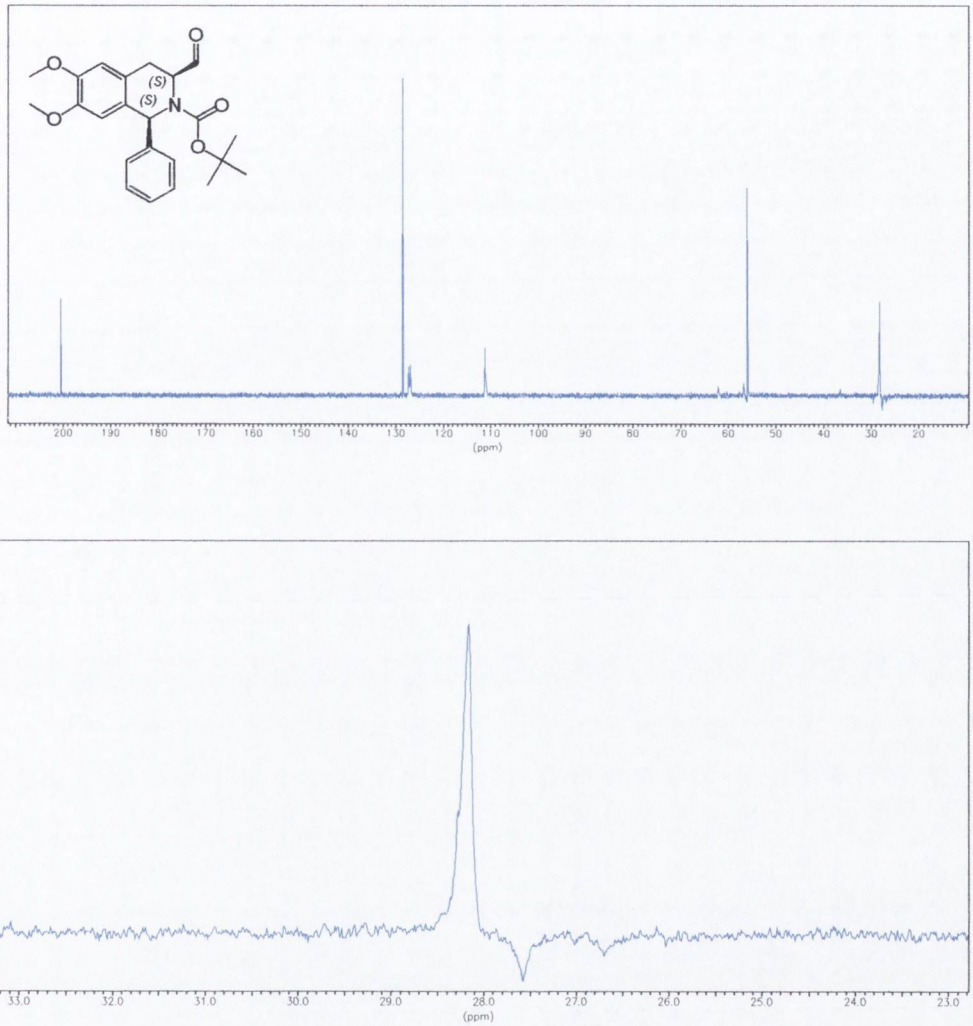


Figure 5-17: Expanded region of the Dept 135 experiment for aldehyde 286

The signal corresponding to the aromatic carbon C8 appears broadened in the spectrum, the chemical shift for the signal being 110.99 ppm; it overlaps with a similar signal at 111.19 ppm. Both signals were designated as being C8 and C5 with the aid of the 2D C-H COSY experiment. ArC3* and ArC5* were evident as one prominent signal at 126.79 ppm. ArC2*/C6* also produced an overlapping response at 127.21 ppm with the remaining ArC4* of the phenyl group resonating at 128.40 ppm. The aldehyde proton, present in the Dept 90 experiment, precesses at the deshielded chemical shift value of 200.33 ppm. The quaternary carbon of the

carbamate resonates at the deshielded chemical shift of 155.47 ppm. The quaternaries of C6 and C7 are observed in the characteristic positions of 148.30 and 147.70 ppm respectively. Elemental analysis of the aldehyde **286** found C, H, N % – 69.47, 6.88, 3.43, theory – 69.50, 6.85, 3.52 % confirming the molecular formula to be $C_{23}H_{27}NO_5$.

5.2.5 Introduction of a 1-(2-Methoxy-ethyl)-piperidinyl side chain at position-3 by etherification

Access to the alcohol **285** provided the opportunity to gain not only the corresponding aldehyde, but also to probe the region of the terminal amine. The formation of an ether at position three from molecular modelling studies, retains the necessary tubular profile and also provides a further hydrogen bond donor in the ligand. Overall this structure displays several of the criteria determined by the pharmacophores dealt with in Chapter 1.

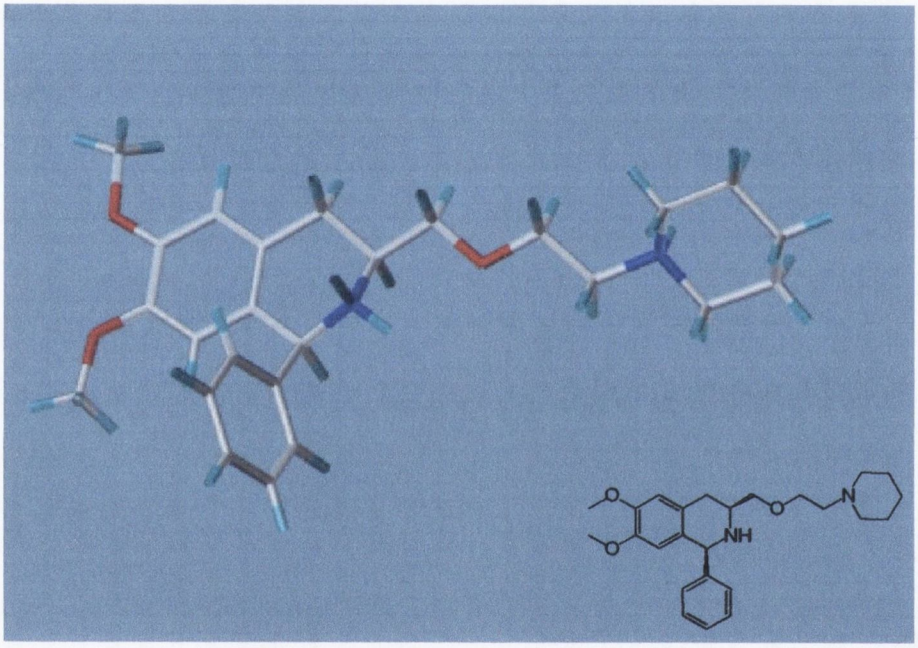
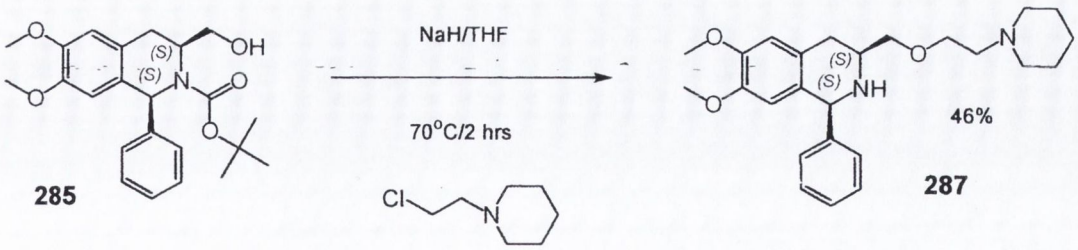


Figure 5-18: Energy minimised structure of 287

For the ether formation to take place, the *t*-Boc protected amine was used to prevent addition at position-2. Side chains of the type added in forming 6,7-dimethoxy-1-phenyl-3-(2-piperidin-1-yl-ethoxymethyl)-1,2,3,4-tetrahydroisoquinoline **287** have been formed using the relevant alcohol and bromide.[274] Amino alcohols (where the amine is protected) can give benzyl ethers in the same manner.[275] *t*-Boc protecting groups are generally stable under basic conditions, however in the reaction employed (two equivalents of sodium hydride and refluxing in THF) it was removed to furnish in one step the required ether final product **287** Scheme 5-15.



Scheme 5-15: Etherification at position-3

The ^{1}H NMR spectrum of the final product **287** provided immediate evidence of the loss of the *t*-Boc protecting group from the absence of the prominent singlet in the aliphatic region produced by the *tert* butyl group. The two sets of multiplets from 1.38 - 1.45 ppm and from 1.52–1.57 ppm were assigned as three of the five piperidine methylene groups, integrating for a total of six protons. The broadened singlet at 2.44 ppm was assigned as the remaining pair of methylene group protons of the piperidine ring. The proton of the secondary amine produced a broad singlet at 2.46 ppm which overlaps with the aforementioned piperidine signals. At 2.55 ppm resonates an unusual double triplet with J_1 = 6.3 Hz and J_2 = 3.9 Hz integrating for two protons. This pattern was assigned as the methylene group alpha to the piperidine ring. The customary pair of double doublets integrating for two protons at a chemical shift from 2.60 to 2.75 ppm, was attributed to the methylene H4 group at position-4. One interesting point was noted in a 1D TOCSY experiment which was carried out. H1 was found to interact with the pair of double doublets assigned as H4 producing a sharper and clearer pair of double doublets (Figure 5-20) than in the normal ^{1}H NMR spectrum. This suggests a through bond long range coupling that can cause peak broadening of the H4 signals.

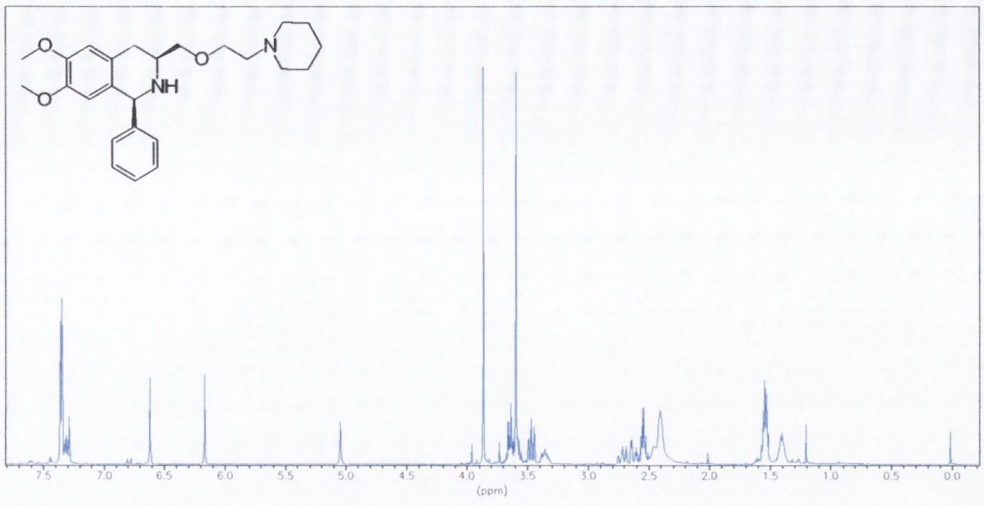


Figure 5-19: ^{1}H NMR of ether 287

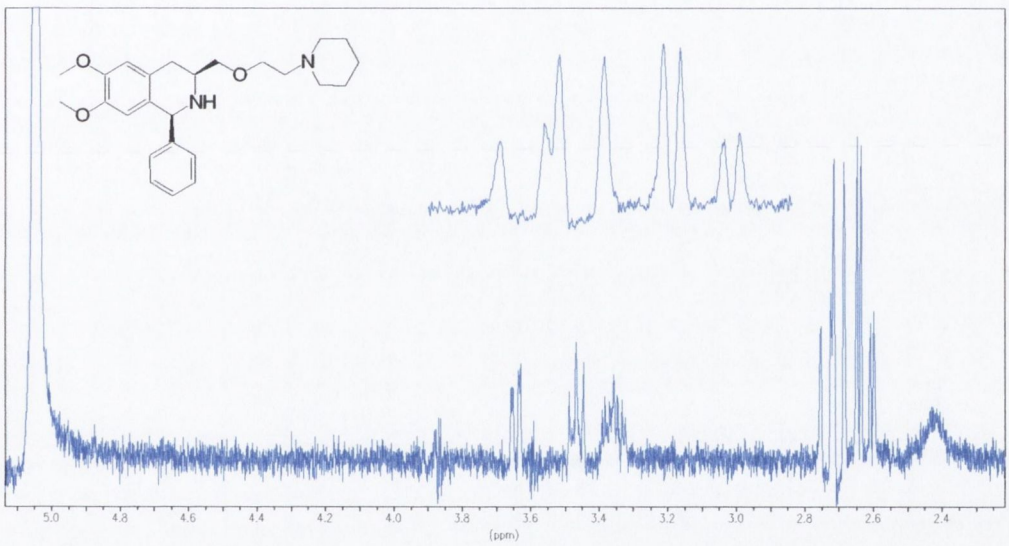


Figure 5-20: 1D TOCSY experiment irradiating H1 of ether 287

The multiplet appears from 3.33 to 3.39 ppm was assigned as H3. The double doublet from 3.45 to 3.49 ppm integrating for one proton (J_{vic} = 8.0 Hz and J_{gem} = 10.0 Hz) was produced by the methylene proton *cis* to H3 and adjacent to the etheral oxyygen. The double doublet from 3.63 to 3.66 ppm was assigned as the methylene proton *trans* to H3 and adjacent the etheral oxygen (J_{vic} = 3.0 Hz and J_{gem} = 10.0 Hz). The assignments of this pair of double doublets was made using the results gained from both HMQC and a H-H COSY experiment. The pair of protons of the ethyl group *alpha* to the ethereal oxygen did not produce a similar double triplet pattern as the partnering signals *alpha* to the nitrogen. The signal appeared as a

multiplet (mainly because of a partial overlap with the peaks of H3) integrating for two protons from 3.57 to 3.64 ppm. The two methoxy moieties produced the characteristic singlets integrating for three protons at 3.59 and 3.87 ppm. This pair of singlets are distinguishable from NOE and HMBC NMR experiments. The removal of the *t*-Boc protecting group at position-2 has a remarkable effect on the chemical shift, pattern and shape of the peak produced by the proton H1 at position-1. In the final product **287**, the proton H1 is attributed to the sharp singlet at 5.05 ppm and the other two similar shaped peaks at 6.17 and 6.62 ppm, each integrating for one proton, were assigned as H5 and H8. The compact multiplet from 7.28 to 7.35 ppm integrated for five protons and was assigned as the phenyl group at position-1.

Assignments from the ^{13}C NMR spectrum of **287** were made using the HMBC experiment Figure 5-21. The vertical trace showing seven distinct methylene groups with correlation to the relevant proton signals in the horizontal trace.

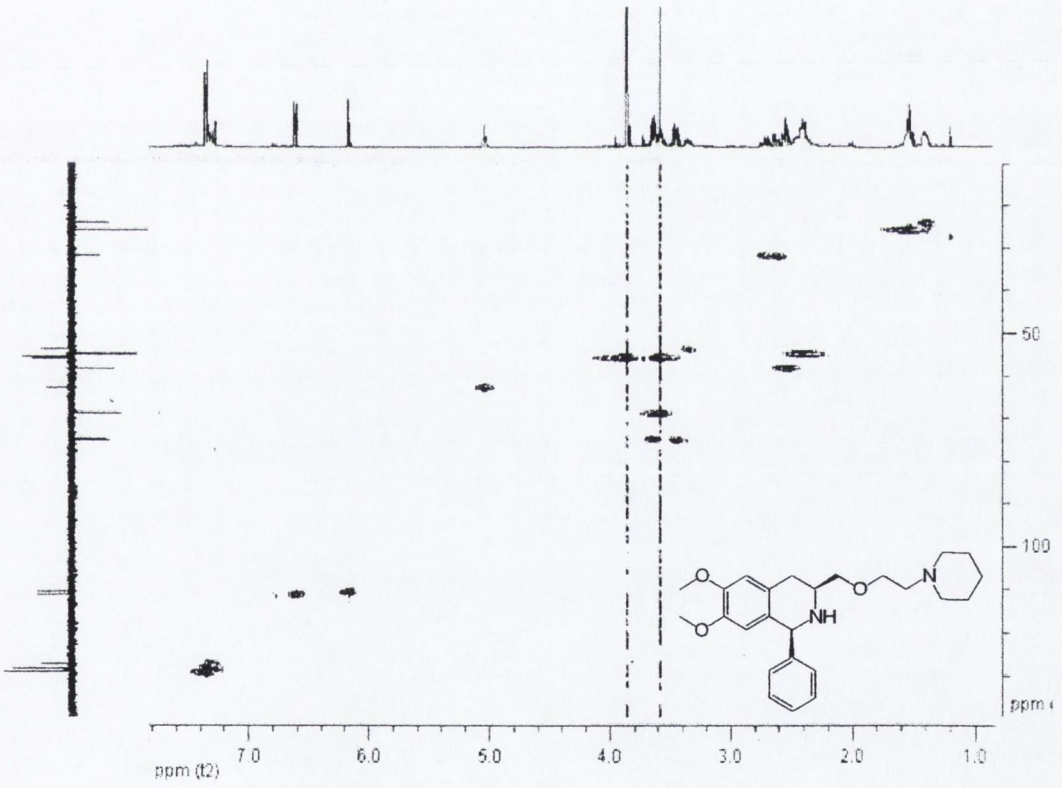


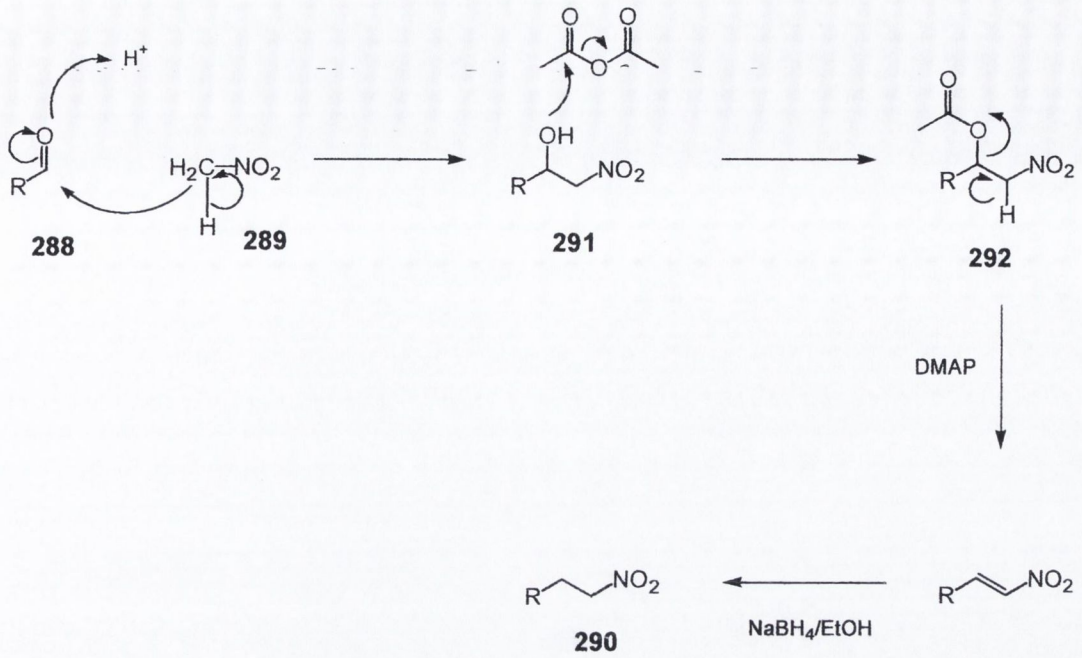
Figure 5-21: HMQC NMR experiment of ether 287

With the NMR data described, plus the HRMS providing the appropriate molecular ion and the IR data, (Table 5-4) the structural assignment was made as being that of **287** Scheme 5-14.

5.2.6 Attempted addition of a terminal amino group at position-3 using an alkyl side chain

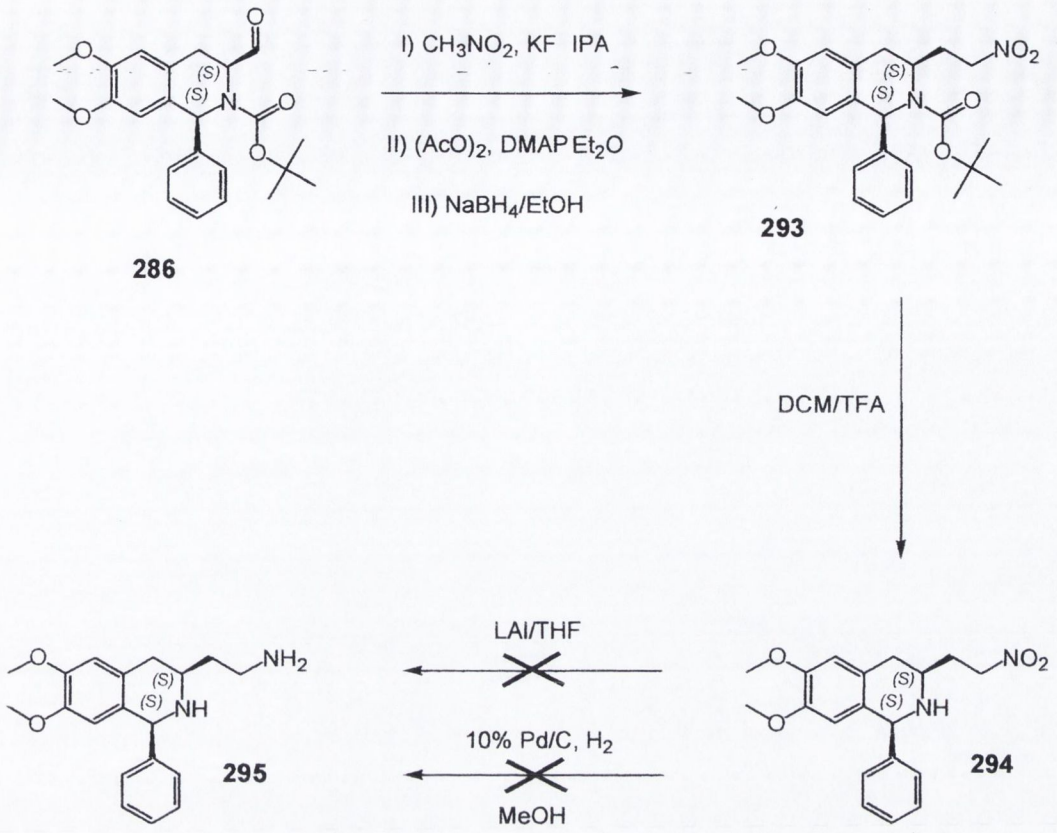
From the pharmacophores described in Chapter 1, one of the key properties in the majority of SERT inhibitors is the four to five carbon alkyl chain used to hold a terminal amino group in position. The tubular structure must also be maintained so for these reasons it was deemed of interest to use an alkyl side chain from position-3 of the tetrahydroisoquinoline ring system extending to the amine. Aliphatic acid chlorides have been successfully converted to the equivalent acyl cyanides using trimethylsilyl cyanide.[276-279] This method was attempted with the intension of subsequent LAI reduction to the alky amine. However the synthesis on the model compound in Scheme 5-1 yielded only the starting material and its unprotected analogue. Two alternative routes were considered, the first being the synthesis of the tosylate derivative of the alcohol **283** or **285** followed by its displacement with a nucleophilic cyano group from potassium cyanide or TMS-cyanide and the second one was through the aldehyde **286**. The **286** gained from the Dess-Martin oxidation of the alcohol **285**, provided the opportunity for access to the aliphatic nitro compound from which it was hoped appropriate reduction would furnish the desired terminal amine located at position-3 of the THIQ connected by an alkyl chain.

The latter option for synthesis was selected, which is achieved by a reductive elimination analagous to the Henry reaction. The probable mechanism is provided in Figure 5-18 and can be described as a base catalysed condensation of an aldehyde **288** and a nitroalkane **289** followed by acylation and reductive elimination to provide the nitroalkane **290**.[280] A catalytic amount of KF (H-bonding agent) in IPA is used to facilitate the condensation of nitromethane with the *N*-Boc protected aldehyde **286** to give the β-hydroxynitroalkane which was not characterised. Reaction monitoring by TLC showed the complete consumption of starting material and the formation of a new product of lower R_f than the starting material, which was turned green when the TLC was stained with vanillin (characteristic colour for alcohols). Acetylation of the alcohol **291**, using DMAP as a catalytic base gives the acetate intermediate **292**. In the current synthesis the corresponding intermediate **293** was not characterised the solvent was removed on the rotary evaporator to leave a residue that was reduced using an ethanolic solution of sodium borohydride to yield the nitroalkane **294** as the final product in 54% overall yield Scheme 5-17.



Scheme 5-16: Reductive elimination yielding nitroalkane 290[280]

There was little information available in the ^{1}H NMR spectrum of the *N*- *t*-Boc protected nitroalkane **293** because of extremely broadened peaks that were relaxing quickly. For this reason the protected intermediate **293** was not fully characterised and instead was brought through the next step of deprotection to give the unprotected intermediate **294**. Spectroscopic studies determined the structure to be that of **294** Scheme 5-17. The product **295** could not be isolated from the attempted reduction of **294** to the corresponding alkyl amine, using either LAI or Pd/C catalysed hydrogenation. The reduction of alkyl nitro compounds to the relevant amines by hydrogenation has been reported in the literature.[159, 281] At this stage in the synthesis the reaction scale was less than 1 mmol. Time constraints did not allow for the optimisation of this route which would have included the isolation of a (Scheme 5-16) nitroalkene from the reductive elimination, from which a more achievable reduction to the alkyl amine may have resulted. Conversion of nitro alcohols to the nitroalkene has been reported.[282, 283] One other option may have been to reduce any alkenyl products formed from a Wittig reaction from the aldehyde **286**.

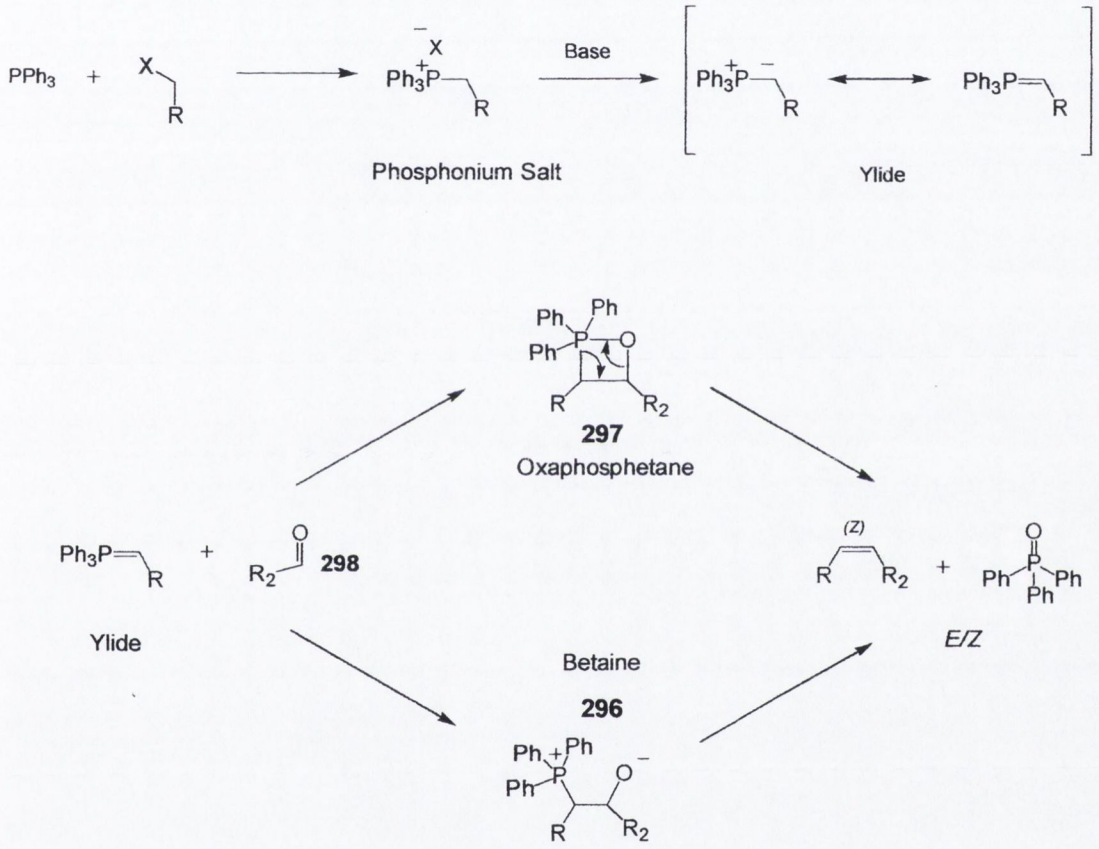


Scheme 5-17: Attempted synthesis of alkyl amine side chain

5.2.7 Wittig olefination at position-3

Further derivatisation at the C-3 position of the THIQ ring was explored by utilising the Wittig olefination reaction, one of the most fundamental organic transformations available.[152] From molecular modelling studies, it was deemed desirable to have an olefinic side chain at position-3 in the *trans* orientation. The reaction proceeds through the formation of an ylide, generated from the relevant phosphonium salt using a strong base such as sodium hydride, sodium alkoxide and butyl lithium. The presence of lithium ions in the base can stabilise the intermediate resulting in side products formed by the addition of a second equivalent of the carbonyl.[152] There are several factors governing to the stereoselectivity of the reaction. The presence of stabilising groups adjacent to the negative charge in the ylide have been deemed responsible for the formation of (*E*)-olefins, resulting from the formation of a certain conformation of betaine.[284] The Wittig reaction generally yields a mixture of *E/Z* alkenes.[152] The exact mechanism through which the reaction proceeds has been hotly contested with two theories persisting.[152] Scheme 5-18 illustrates the potential pathways for the reaction with the main question being whether the transient intermediate formed is the betaine **296** or the oxaphosphetane **297**. There have

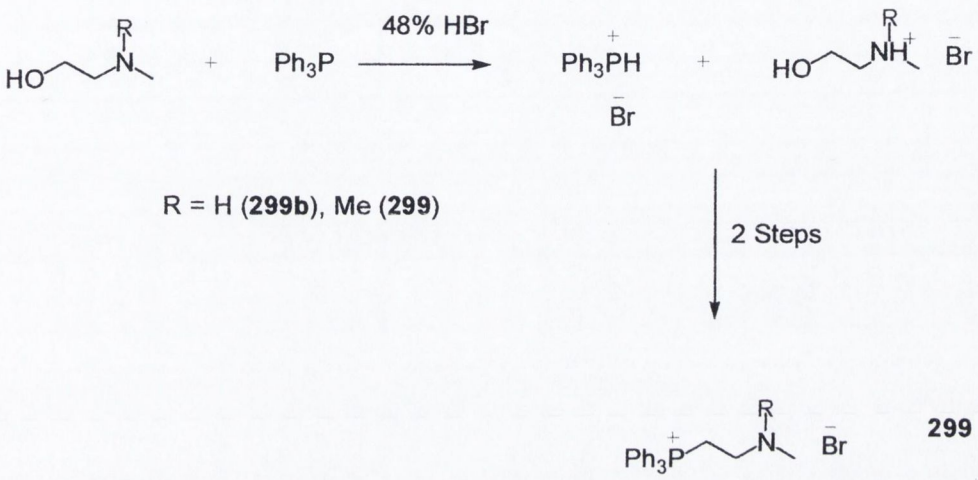
been betaine type precipitates found from Wittig type conditions but it is possible they result from the degradation of the oxaphosphetane.[284] ^{32}P NMR reaction monitoring have shown the presence of a pentavalent phosphorous intermediate supporting the argument for pathway B Scheme 5-18.[285] Although these intermediates degrade extremely quickly to the aldehyde **298** and phosphane products, stabilised oxaphosphetanes and their X-ray structures have been reported.[286, 287] The high stability of the phosphine oxide drives the reaction forward once the betaine/oxaphosphetane has been formed.



Scheme 5-18: Potential Wittig pathways

Few examples exist in the literature using the ylide of interest (derived from the phosphin salt **299** Scheme 5-19)[62, 288, 289]. The lack of conjugative stabilising groups α to the negative charge meant it was not possible to predict the *trans* stereochemistry as had been hoped. In the synthesis of Zimilidine analogues (Figure 1-19) Högberg and Ulff used Wittig chemistry to olefinate a ketone resulting in *cis/trans* ratios of about 3:2.[62] The stereochemical outcome would hinge also on steric constraints in the betaine/oxaphosphetane intermediate. The method of Marxer and Leutert was employed in the preparation of the necessary ylide. Initial

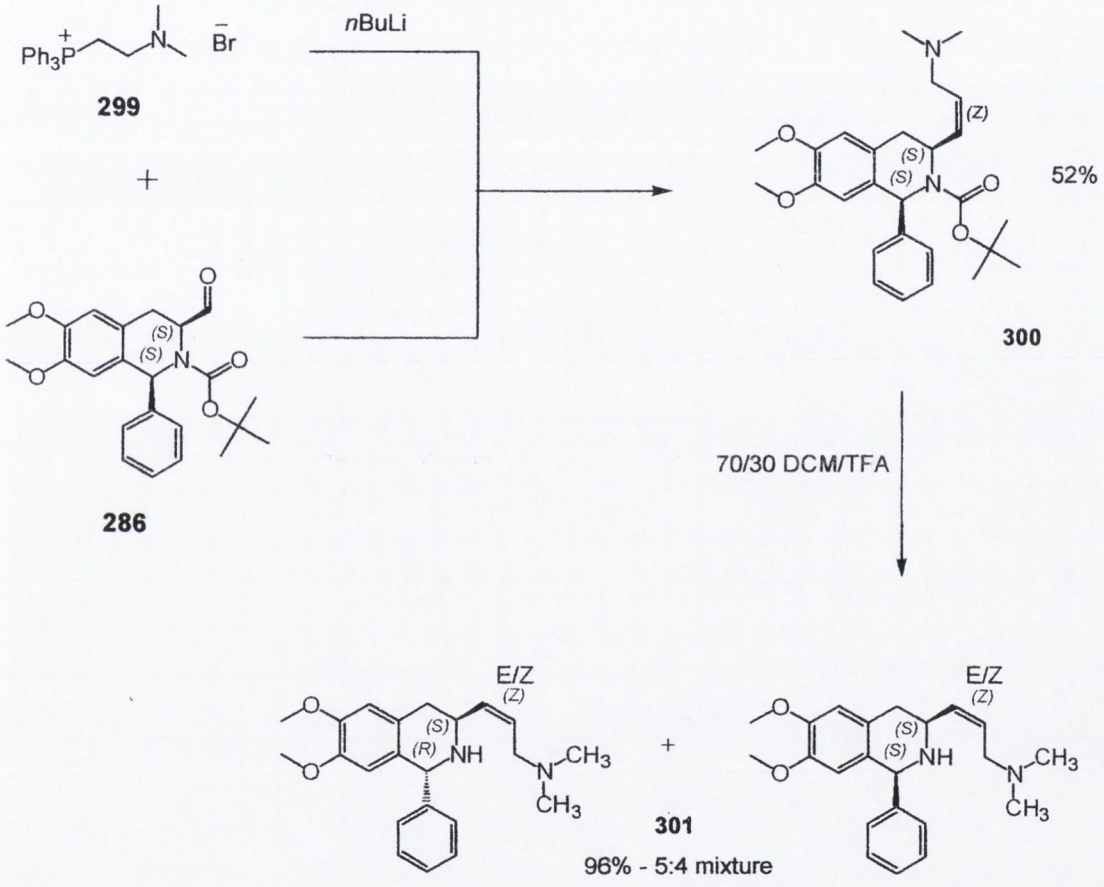
attempts using at forming the phosphonium salts involved the bromination of 2-diethylaminoethanol using 48% HBr gave (2-bromoethyl)diethyl amine **299a** in 73% yield. Conversion to the subsequent phosphonium salt proved problematic as the hydrobromide of (2-bromoethyl)diethyl amine is inert against triphenylphosphine.[288] Without solvent however, the required amino alcohol can form a melt with triphenylphosphine from which basic work up yields the β- amino triphenylphosphine **299** Scheme 5-19.



Scheme 5-19: Production of the phosphonium salt 299

In the ^{1}H NMR spectrum of **299**, it was noted that the expected singlet integrating for six protons was only giving an integration of three protons. When the experiment was repeated for the mono methylamine analogue, the same response was noted, this time the peak of interest only integrated for 1.5 protons. This was not reported in the literature.[288, 289] however, the ^{32}P and ^{13}C NMR on the dimethyl amine phosphonium salt **299**, demonstrated bonding between the α-carbon and the phosphorous atom. The melting point of 188-190°C for **299** concurred with the literature value of 191°C.[288] For this reason the phosphonium salt **299** was used to form the ylide for the Wittig olefination with aldehyde **286**. Marxer and Leutert reported an excess of 14/85 *cis/trans* when the ylide of **299** was reacted with 4-chlorobenzaldehyde.[288] The reaction conditions adopted by Hogberg and Ulff, were used in Scheme 5-20 with the expectancy of a *cis/trans* mixture of products. The alkene formed in the reaction could not be determined as being either *cis* or *trans* on account of the peak broadening experienced from the *t*-Boc protecting group. Both vinylic protons were overlapping and seriously broadened but the *N*-dimethyl singlet integrating for six protons was evident at 2.22 ppm. The ^{13}C NMR spectrum was

useful in confirming that the olefinic side chain was in place with the Dept 135 experiment showing two methylene groups within the molecule. The extremely fast T_1 relaxation times were evident again in the ^{13}C spectrum with C1 and both vinylic carbon nuclei only determined by the HMQC experiment. The vinylic carbon β to the terminal amine was found at 134.49 ppm while the other vinylic carbon was underneath the signals attributed to the phenyl group at position-1 at a chemical shift of 127.23 ppm, again determined only by the appropriate 2-D NMR experiments.



Scheme 5-20: Wittig olefination of aldehyde 286

From the ^1H NMR spectrum, the signals produced by the pair of methoxy peaks, it is clear the alkene **300** is present as a single diastereomer. The tertiary amino group led to **300** having a low R_f on silica gel (R_f = 0.28 (streak) in a 4:1 diethyl ether:methanol mobile phase). The vinylic coupling constants measured from the HMQC NMR experiment, were less than 10.0 Hz, indicating *cis* isomerization. With both vinylic protons producing overlapping signals, it was not possible to determine whether there was ABX_2 coupling from the proton α to C3 to the methylene protons

adjacent to the tertiary amine, which may be observed if the double bond was in the *trans* configuration. In the HRMS ($M^+ + H^+$) was found at m/z: 453.2730, with $C_{27}H_{37}N_2O_4$ calculated as m/z = 453.2754.

The acid hydrolysis of the *t*-Boc protecting group in **300** gave rise to some unexpected results. Two inseparable compounds appear in the NMR spectra as a result of diastereomerization. This was proven by NOE studies in which each of the H1 proton peaks was irradiated, with only one positive enhancement to the partnering signal at H3 was observed. The disappointing feature in the spectrum of the alkenyl final product **301**, is that again the vinylic signals overlap and in this instance even though the signals are sharper than the *t*-Boc protected analogue **300**, there are now four different vinylic protons on account of their being two sets of compounds (diastereomers). The two compounds are present in a 5:4 ratio. The ^1H NMR and the NOE enhancements described, are provided in Figure 5-22. The two sets of diastereomers can be defined by their ratios in the ^1H NMR spectra, from which HMQC and HMBC 2D NMR experiments were used to determine the relevant carbon peaks in the ^{13}C NMR spectra.

The minor of the two isomers was that in which the protons of H1 and H3 were in the *syn* conformation, proven by the positive NOE (evident from the bottom trace Figure 5-22). There is no NOE enhancement from H1 to H3 in the major *anti* isomer, which is obvious from the middle trace Figure 5-22. Also observed was a positive NOE enhancement from H1 in both compounds to the broad singlet assigned of the secondary amino proton. From distances measured in the energy minimised structure (carried out using Sybyl 6.91), when the double bond is in the *cis* arrangement the distance from H1 to the terminal methylene group is 2.3 Å and with the *trans* isomer it is 4.6 Å. A strong NOE enhancement from H3 to the terminal methylene group was observed in both diastereomers. It is evident *cis/trans* isomerism has not taken place as there are two sets of methoxy peaks and not four, which would have been the case had there been two sets of diastereomers, each with a *cis* and a *trans* isomer. The stereoselectivity of the double bond could not be confirmed with any degree of certainty although it appears it may have formed as the *cis* isomer. The loss of chirality may have been at position-1 since the positive charge created by losing a proton at postion-1 would be stabilised more than at position-3. The difference in chemical shifts for H3 in both diastereomers are less than 0.25 ppm while that for the aromatic proton of each at H8 differs by more than 0.45 ppm. The similar NOE enhancements from H3 in each diastereomer to the

terminal methylene group points towards the loss of chirality to have occurred at position-1 producing the two sets of peaks observed in the various NMR spectra.

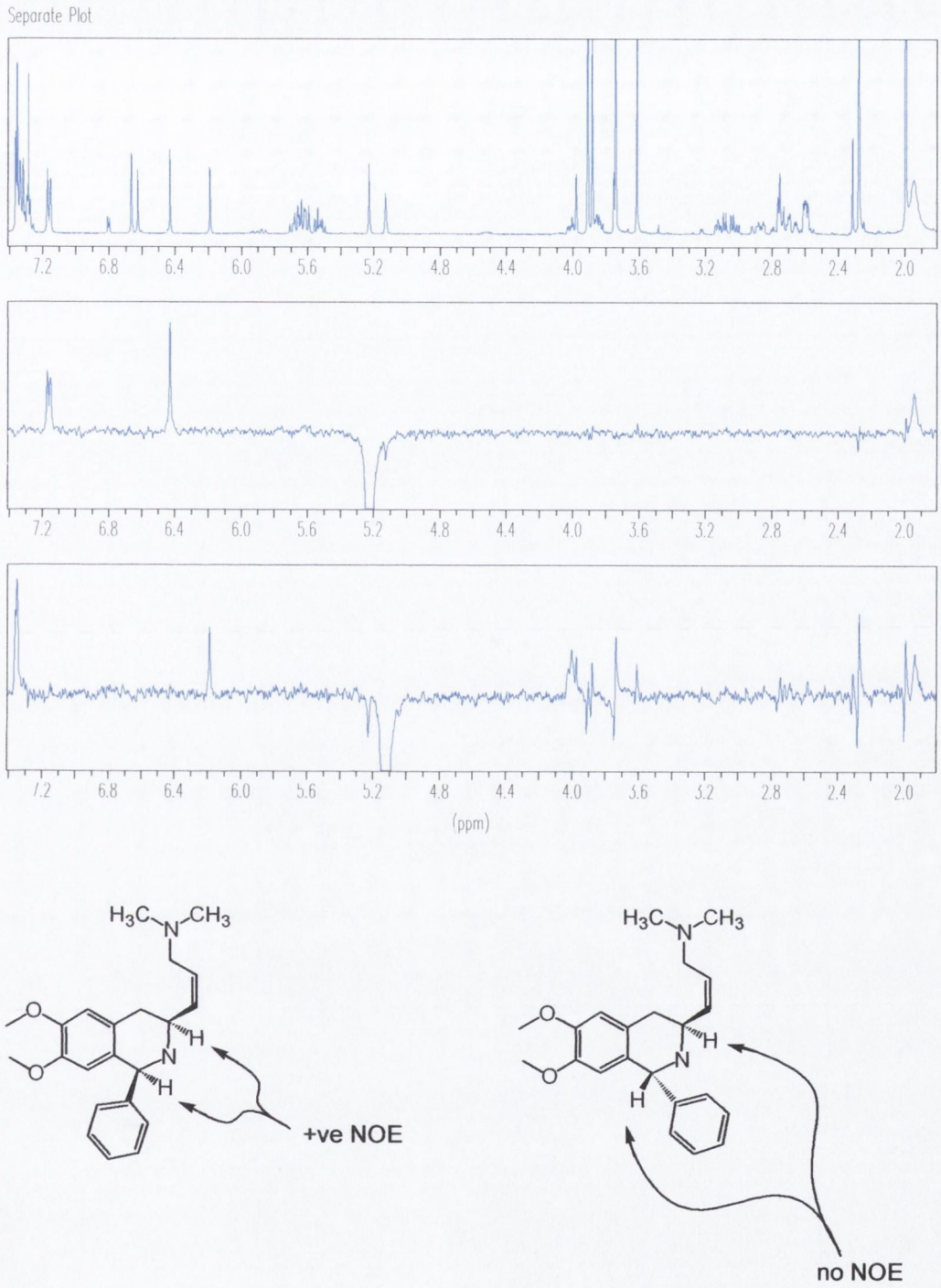


Figure 5-22: NOE experiments showing sets of diastereomers of 301

In Table 5-10 the IR, melting points and yields for the main compounds in this section are presented.

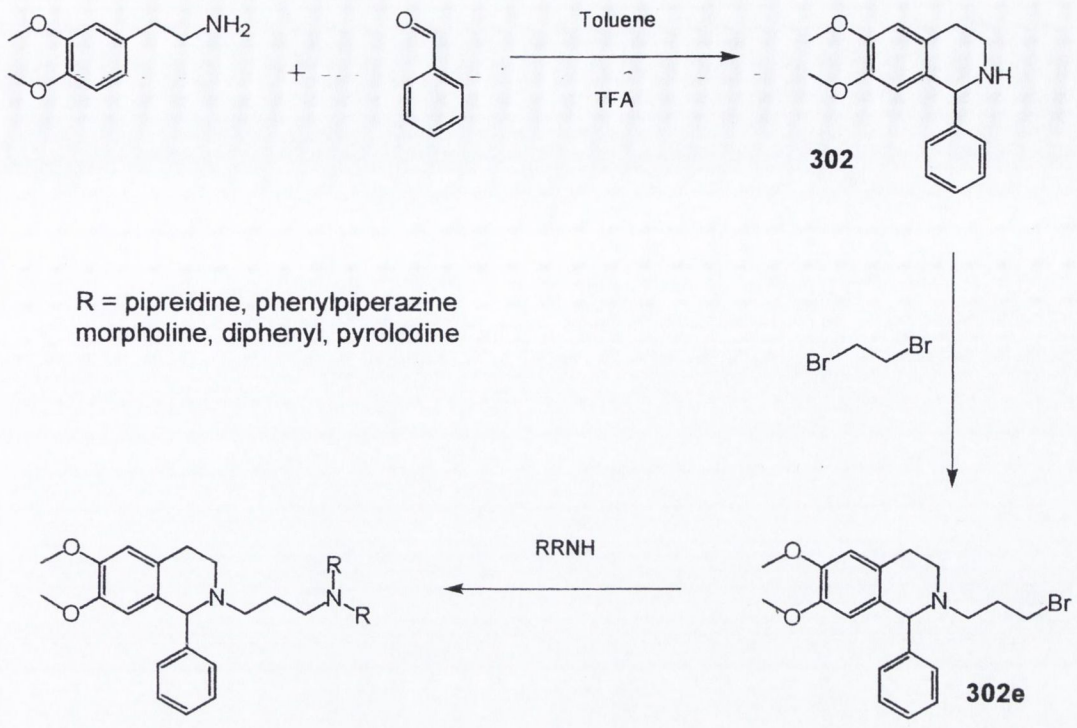
Table 5-4: IR, m.p. and yields for compounds synthesised in the study of position-3 analogues

Compd	IR υ cm^{-1}	m.p.°C		Yield%
		Expt.	Lit.[#]	
273	3351, 1734, 1691, 1520, 1280	118-120	116-118	76
275	2914, 1743, 1519, 1269	158-160	158-159	36
274	2953, 1737, 1518, 829	120	118	31
283	3591, 2919, 1514, 1217	180-184	-	84
276	1750, 1629, 1266, 759	oil	-	83
285	3424, 1715, 1699, 1203	oil	-	92
282	3414, 1639, 1454, 1276, 749	oil	-	33
280	1784, 1731, 1699, 1402, 997	oil	-	42
279	3413, 1751, 1699, 1407, 699	oil	-	63
281	3160, 1738, 1688, 1286	184	-	67
286	1732, 1693, 1675, 1164	128-130	-	96
294	3072, 1673, 1554, 1514, 1202	oil	-	54
287	3326, 2933, 1513, 1114	oil	-	46
300	1684, 1514, 1382, 1166	oil	-	52
301	3434, 1513, 1464	oil	-	95

5.2.8 Side chain substitution at position-2 of the THIQ ring.

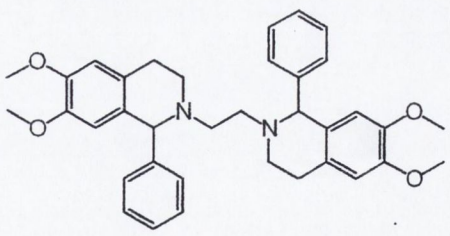
A facile method for exploring the pharmacophore was thought to be the derivatisation of the isoquinoline at position-2, thereby providing a terminal amine extending at a very different angle when compared to the various substitutions made at position-3. The necessary properties of the two phenyl rings would be retained with both sitting in two different planes. The most promising prospect being access to potentially active SERT inhibitors in far fewer synthetic steps that afford the option of probing the active site with an array of analogues with slightly varying properties. A set of compounds very similar to those proposed were synthesis as possible anti tubercular agents against *Mycobacterium smegmatis* about 50-100 with some totally inhibiting colony growth.[290]

[#] Reference to corresponding compound reported in the experimental chapter-6



Scheme 5-21: Anti tubercular agents[290]

For the purposes of this work the optimum spacer between the two nitrogens was determined to be an ethyl chain. The synthesis used in Scheme 5-21 was attempted using 1,2-dibromoethane but the bromide analogous to that of **302e** was not isolated on account of the dimer **303** forming in substantial yields. **303** may have formed from two equivalents of the tetrahydroisoquinoline reacting with the 1,2-dibromoethane.

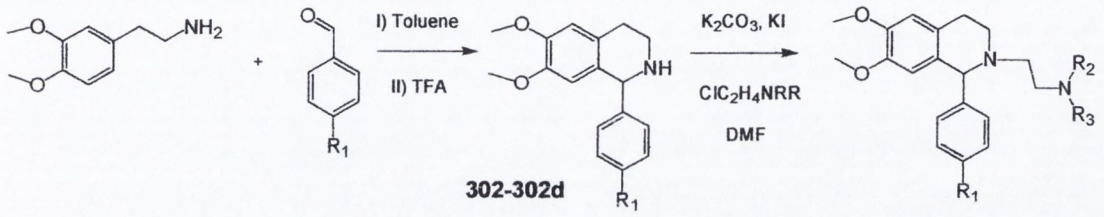


303

Formation of the dimer **303** prompted the investigation of an alternative route to the desired isoquinolines **302**, **302a-d**. A method used by Choi *et al* in the synthesis of (bisarylmethoxy)butylpiperidine analogues DAT inhibitors with dual activity at dopamine receptors, was adapted to yield in two steps a range of over twenty based on the analogues described in Table 5-5.

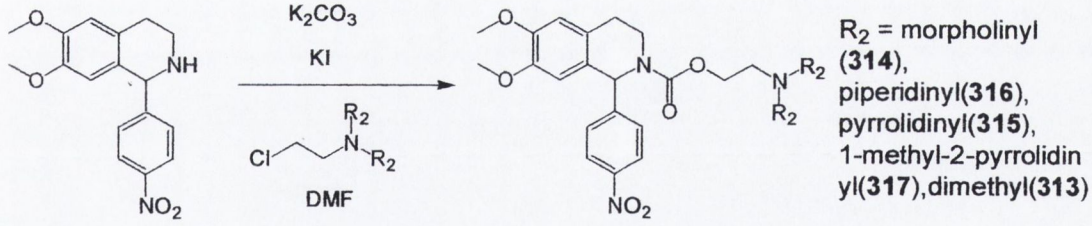
Table 5-5: Yields % for substitutions at position-2

Compd	R	$N(Me)_2$	morpholine	pyrrolidine	piperidine	1-methyl-2-pyrrolidine[#]
304-307	H	8	58	16	25	-
308-312	F	12	17	20	-	15
313-317	NO_2[#]	26	21	36	32	18
318-321	Br	11	19	-	21	18
322-326	SCH_3	10	17	15	18	15



Scheme 5-22: Two step synthesis to THIQ analogues

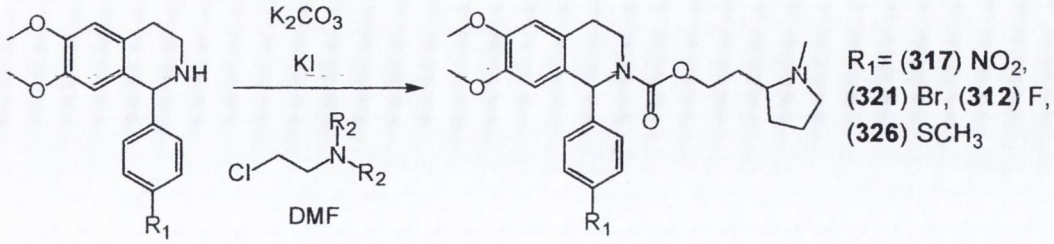
The generally poor yields can be attributed to the difficult purification of such polar compounds. In the range of compounds **313-317** and **307**, **312**, **317**, **321**, **326** (Table 5-5) where $R_1 = NO_2$ and/or R_2 = 1-methyl-2-pyrrolidinyl, the alkylated THIQs were not isolated. What was observed was the formation of the corresponding carbamates **313-317**. Scheme 5-23, 5-24.



Scheme 5-23: isolated carbamates 313-317

The most likely reason for the isolation of these carbamates in certain cases, may have been down to the difficulty in purifying the desired alkylated products. The R_f of the carbamates is quite similar to the alkylated THIQ compounds and so in cases where the yield was poor it is plausible the carbamates may have been isolated inadvertently.

[#] Compounds in which $R_1 = NO_2$ and/or R_2 = 1-methyl-2-pyrrolidine were isolated as the corresponding carbamates Scheme 5-23, 5-24.



Scheme 5-24: Carbamate formation

The exact mechanism defining the formation of the range of carbamte compounds is not very clear however one possible pathway may be a nucleophillic attack from the nitrogen at position-2 to the carbon of the carbonate anion, followed by subsequent attack of carbamate anion to the alkyl halide. The characterisation was made using HRMS with the relevent molecular ion peak at + m/z 45 from the molecular ion of the expected product. The elemental composition of **314** was found to contain + CO_2H with the carbamate species picking up a proton. The ^1H NMR had methylene groups resonating at δ 4.0 – 4.2 ppm, indicative of protons adjacent to an oxygen atom. The fast relaxation times and H1 peak splitting so characteristic of carbamates was also observed. The quaternary carbamate signal in the ^{13}C NMR at δ 154 – 156 ppm only appears after a significant number of scans because of the fast T_1 relaxation times. The carbamates all gave a molecular ion + H^+ in the HRMS confirming their structural ellucidation to be as presented in Scheme 5-24 and 5-23.

The diamine final products were easily distinguished from the various THIQ secondary amines by the extra peaks in the aliphatic region of the ^1H NMR. For demonstrative purposes the example taken for characterisation is the compound in which R_1 = Br and the terminal amine is a tertiary substituted with a dimethyl moiety isolated as a brown oil. In the ^1H NMR the singlet integrating for six protons at 2.15 ppm was assigned as the *N*-dimethyl group. From 2.35 to 3.18 ppm resonate five separate signals. Each of these belong to a methylene group so to determine which assignments to make the pattern of each multiplet was studied. The characteristic pattern in this region was the one from 2.73 to 2.80 ppm. It was the only one from which clear coupling constants could be determined. It appears almost like a pair of triplets, however the protons at positions-3 and 4 would be expected to have a double double doublet splitting pattern on account of the strained system providing three coupling opportunities to each proton. In this example the reason the system emerges looking like a double triplet (although similar to triplets the peak intensities are not in line with those of a true triplet) is because the *vicinal* coupling constants

are practically identical. With the *ddd* integrating for one proton and bearing in mind the chemical shift, the pattern was assigned as H4, with 2D TOCSY experiments on the series proving its partnering proton H4* exists as part of the multiplet from 2.59 to 2.68 ppm. The pair of multiplets one from 2.94 to 3.01 ppm and the other from 3.12 to 3.21 ppm both appear as potential ddd but the distinct coupling constants were not measured and with each pattern integrating for one proton they were assigned as H3* and H3 respectively. The methoxy peaks were observed as a pair of singlets each corresponding to three protons at 3.63 and 3.85 ppm. H1 was evident as the sharp singlet precessing at 4.51 ppm with the protons of H5 and H8 resonating also as sharp singlets at 6.14 and 6.60 ppm respectively. The aromatic signals of the phenyl ring at position-1 exist as a pair of doublets J_o = 8.0 Hz, both integrating for two protons.

In studies of the ^{13}C NMR spectrum, four methylene carbons were immediately apparent in the Dept 135 experiment. HMQC experiments aided in assigning the signals. C4 was attributed to the signal at 27.94 ppm with the *N*-dimethyl carbon nuclei each resonating at 45.75 ppm. C3 was evident as the peak at 47.31 ppm, inverted in the Dept 135 experiment. The methylene group adjacent to position-2 was assigned as the peak at 52.33 ppm with the other peak from the ethyl spacer chain appearing at 57.29 ppm. Between these peaks were found the signals upright in the Dept 135 and absent in the Dept 90 experiment, which were produced by the two methoxy groups. The remaining CH peaks were all present in the Dept 90 experiment and were assigned as follows: C1 appeared at 67.46 ppm, C8 and C5 resonate at 110.74 and 111.32 ppm respectively. Both sets of peaks for ArC3*/C5* and ArC2*/C6* were overlapping as a prominent peak at 131.13 ppm. Six quaternary signals exist in the compound. C7 and C6 were found characteristically at 146.98 and 147.41 ppm. The quaternary signals of the 4-bromophenyl ring at position-1 were assigned as ArC1* precessing at 143.20 ppm and ArC4* at 120.87 ppm. The peaks at 126.76 and 129.15 ppm were assigned as the quaternary carbons adjacent C5 and C8 respectively. In the HRMS ($M^+ + H^+$) was found at m/z: 419.1334 for $C_{21}H_{28}{}^{79}Br\ N_2O_2$, calculated as m/z = 453.2754.

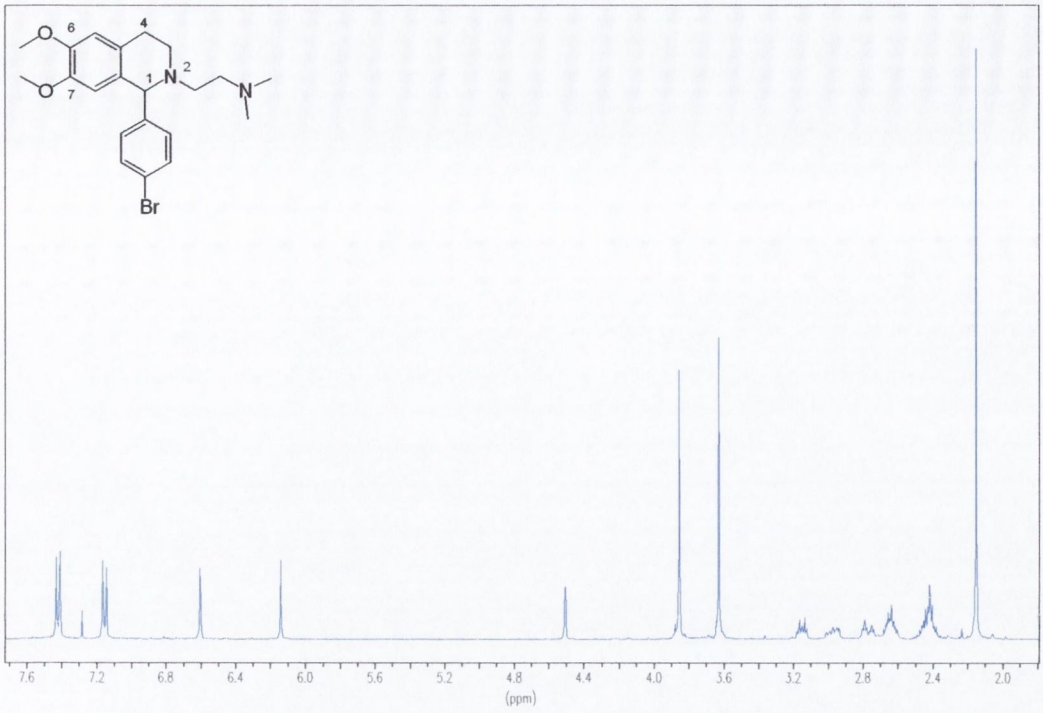


Figure 5-23: ^{1}H NMR spectrum of compound 318

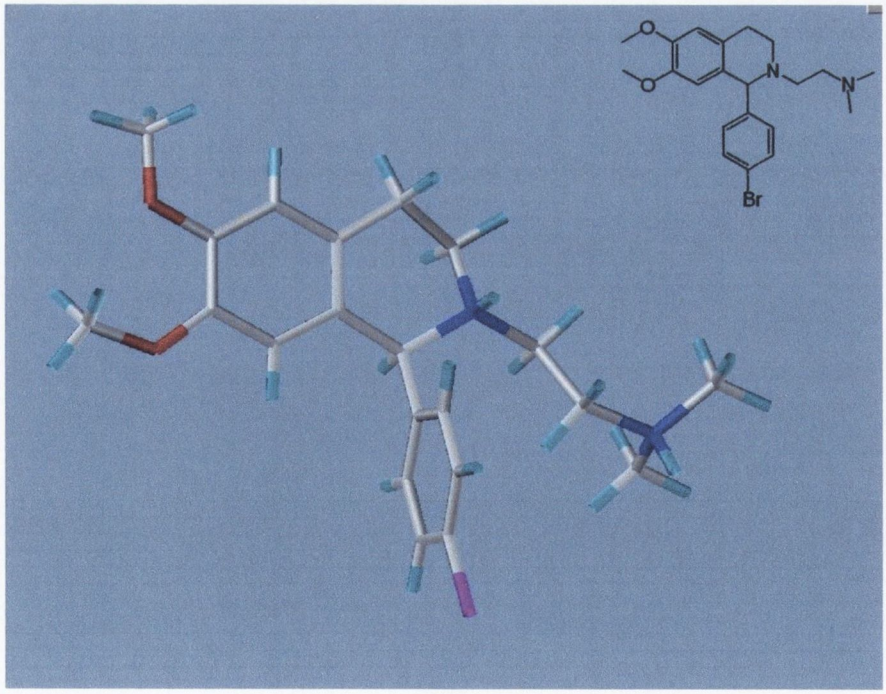
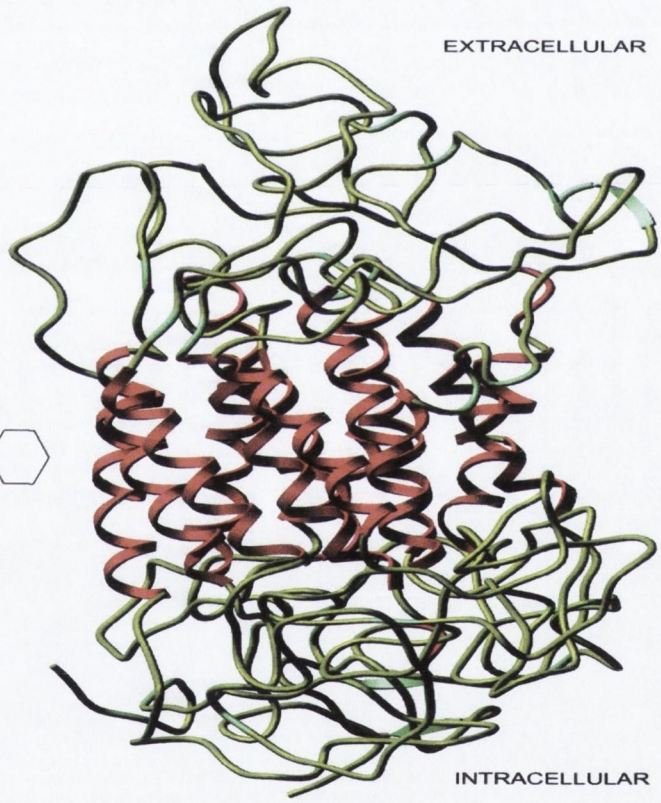


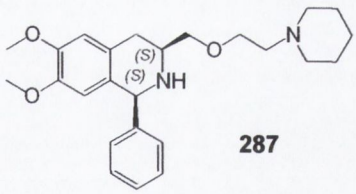
Figure 5-24: The energy minimised structure of the bromide 318. The phenyl ring at position-1 still lies in a different plane to ring A. The terminal amine lies in a different region to that of the ether 287.

5.3 *Docking studies with the optimised SERT protein model*

Earlier in this chapter 5.1.1, the proposed SERT modulator **262** was docked in the first computational SERT model (Figure 1-7). The only conclusions drawn from the study was that when manually placed in the proposed active site, **262** spanned the membranes in a manner similar to citalopram **8**. The tertiary structure of the new SERT protein model, developed by Dahl *et al*, was based on an electron density projection map of *E. coli* NhaA antiporter image.[4] The relevant loops of the models were constructed from the known sequence and orientated with the image of the *E. coli* NhaA transporter.[4, 31] In this instance the protein was constructed based on the tertiary structure of a biological transporter. From the site directed mutgenesis data, the binding pocket within the new model could be mapped. The compound used in the current docking study was the ether **287**.

Updated SERT model as described in Figure 1-8





287

The LPC calculation are summerised in Table 5-6. All the amino acid residues cited by Ravna *et al* as being crucial to ligand binding have positive interactions with the ether **287** in the binding site.[4, 20] Figure 5-25 dipicts the interaction of the ligand **287** with the residues of interest. Coloured in yellow is the Asp98, to which the ligand experiences hydrogen bonding. The remaining residues of interest are coloured in blue. Tyr289 experiences aromatic interactions with the methoxy subtstituted phenyl

ring, Phe263 interacts with the ligand very well forming hydrogen bonds and hydrophobic interactions.

Figure 5.25 shows the conformations of the complex formed between the SERT protein and (*S*)-citalopram (left) and cocaine in a separate docking on the right.[4] The residues reported in the site directed mutagenesis work are rendered as ball and stick models. The one notable feature is that the ether **287** spans the proposed binding pocket in a similar manner to the cocaine molecule interacting with the same residues of interest Table 5-6.

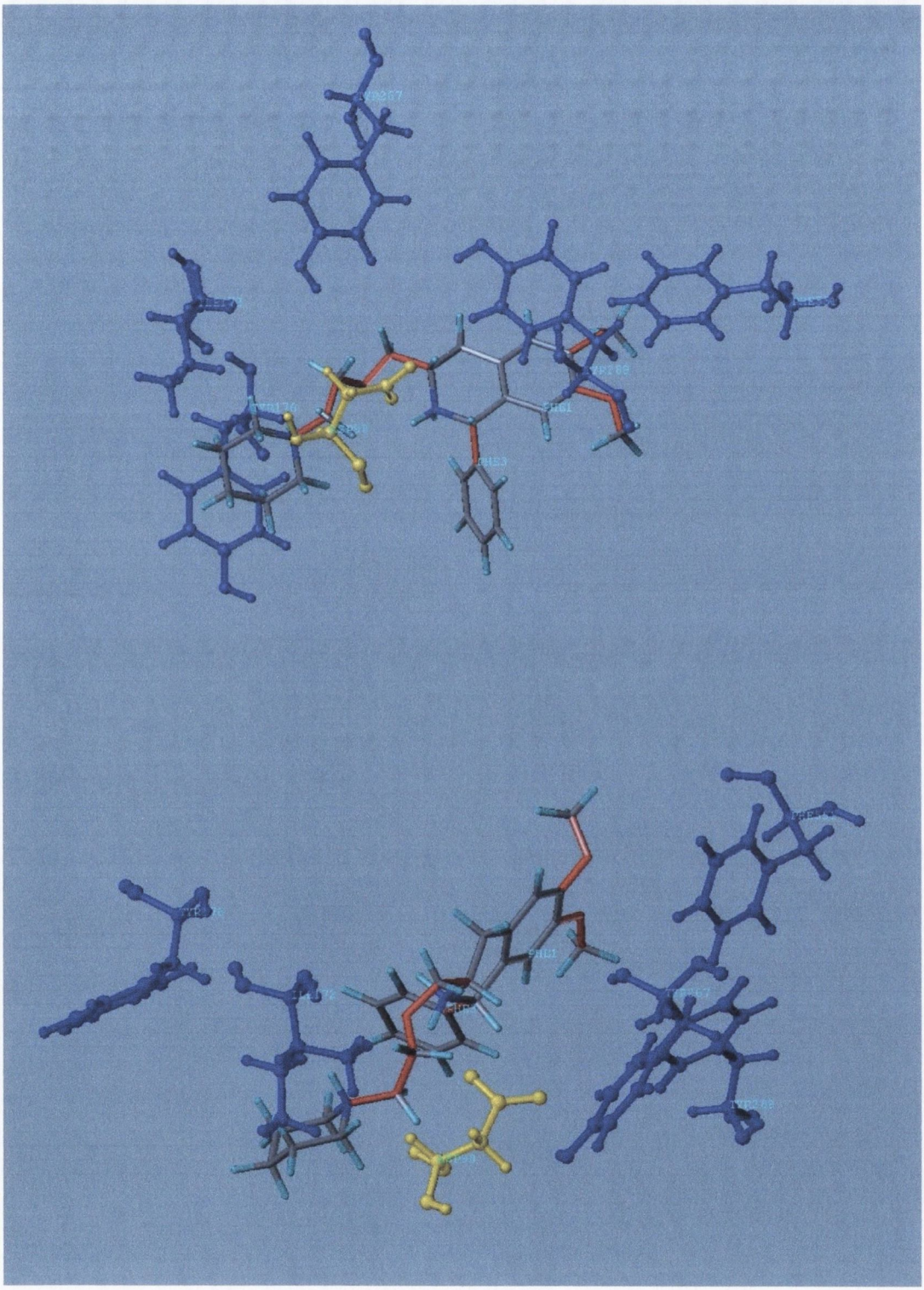


Figure 5-25: Different perspectives of the *Flexidock* result for the binding of ether 287 (centre) within the active site of the new SERT model. Asp98 (yellow) Tyr289, Tyr267, Phe551, Tyr176 and Ile172 (all in blue)

Table 5-6: Direct ligand protein interaction results from *flexidock*

Residue		Dist.	Surf.	Specific Contacts			
				HB	Arom	Phob	DC
95	TYR	2.3	56.3	-	+	-	-
98	ASP	1.2	113.8	+	-	-	+
99	LEU	2.3	50.3	-	-	+	-
102	VAL	1.7	48.9	-	-	+	+
106	PRO	6.3	0.4	-	-	-	-
171	TYR	1.9	56.8	-	-	+	+
172	ILE	3.6	11.0	-	-	-	-
175	TYR	2.8	40.8	-	-	+	-
176	TYR	5.6	1.1	-	-	-	-
179	ILE	5.6	0.2	-	-	-	-
256	ALA	2.4	39.1	-	-	-	+
257	LEU	4.2	6.5	-	-	-	-
259	ILE	1.6	67.3	-	-	+	+
260	MET	0.9	272.7	-	-	+	+
262	ILE	1.5	154.5	-	-	+	+
263	PHE	2.0	91.2	+	-	+	+
265	VAL	4.4	7.2	-	-	+	
266	ILE	2.4	42.0	-	-	+	+
267	TYR	4.1	0.2	-	+	-	-
288	PRO	3.3	11.0	-	-	+	-
289	TYR	2.0	81.7	-	+	-	+
292	LEU	3.6	25.4	-	-	-	-
293	SER	5.7	0.7	-	-	-	-
551	PHE	4.7	0.4	-	-	-	-

Legend:

Dist - nearest distance (A) between atoms of the ligand and the residue

Surf - contact surface area (A**2) between the ligand and the residue

HB - hydrophilic-hydrophilic contact (hydrogen bond)

Arom - aromatic-aromatic contact

Phob - hydrophobic-hydrophobic contact

DC - hydrophobic-hydrophilic contact (destabilizing contact)

+/- - indicates presence/absence of a specific contacts

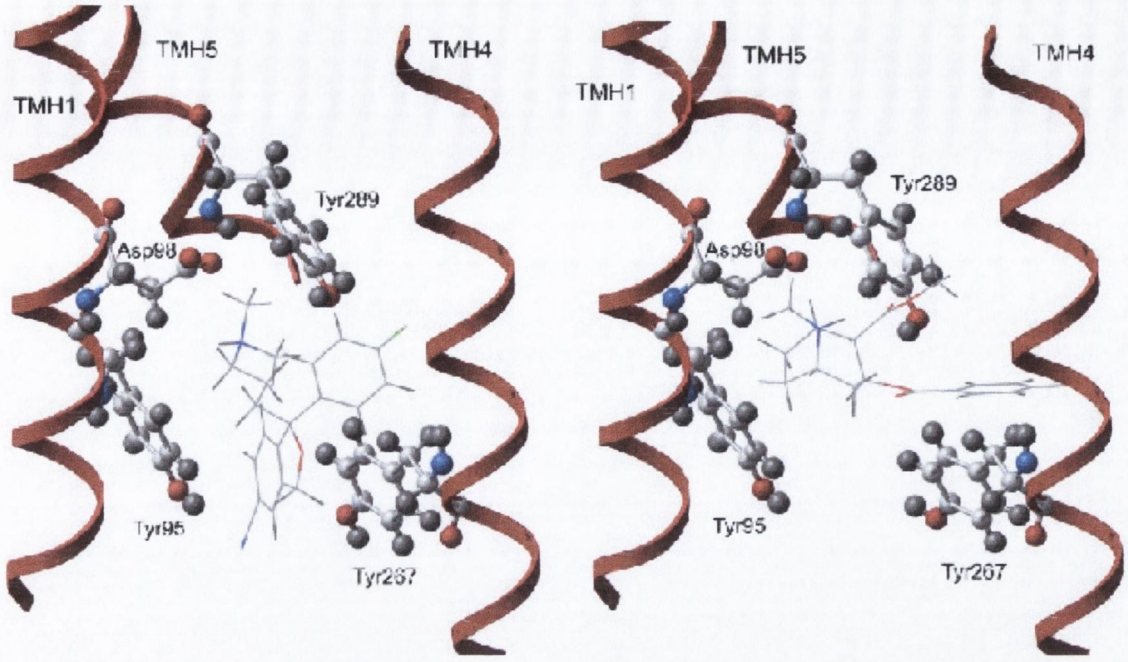
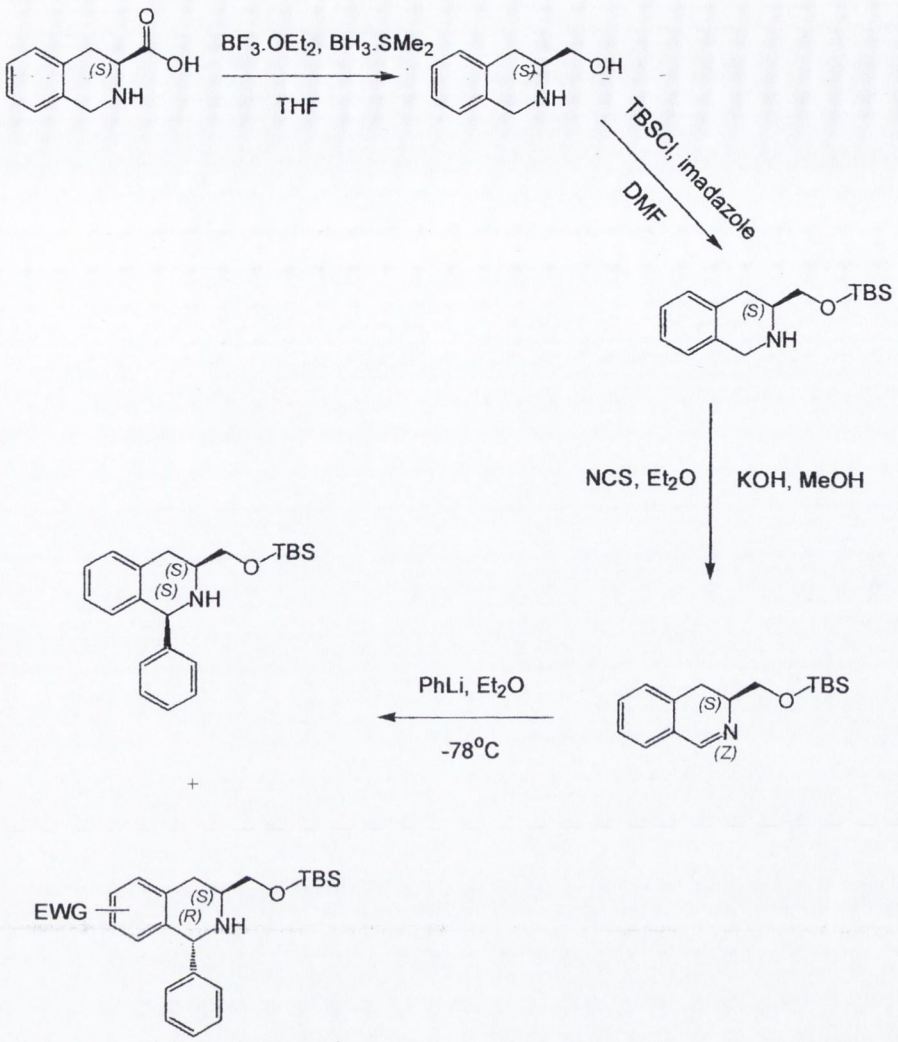


Figure 5-26: Docking results reported for SERT by Ravna *et al*[4]

5.4 Conclusions and future work

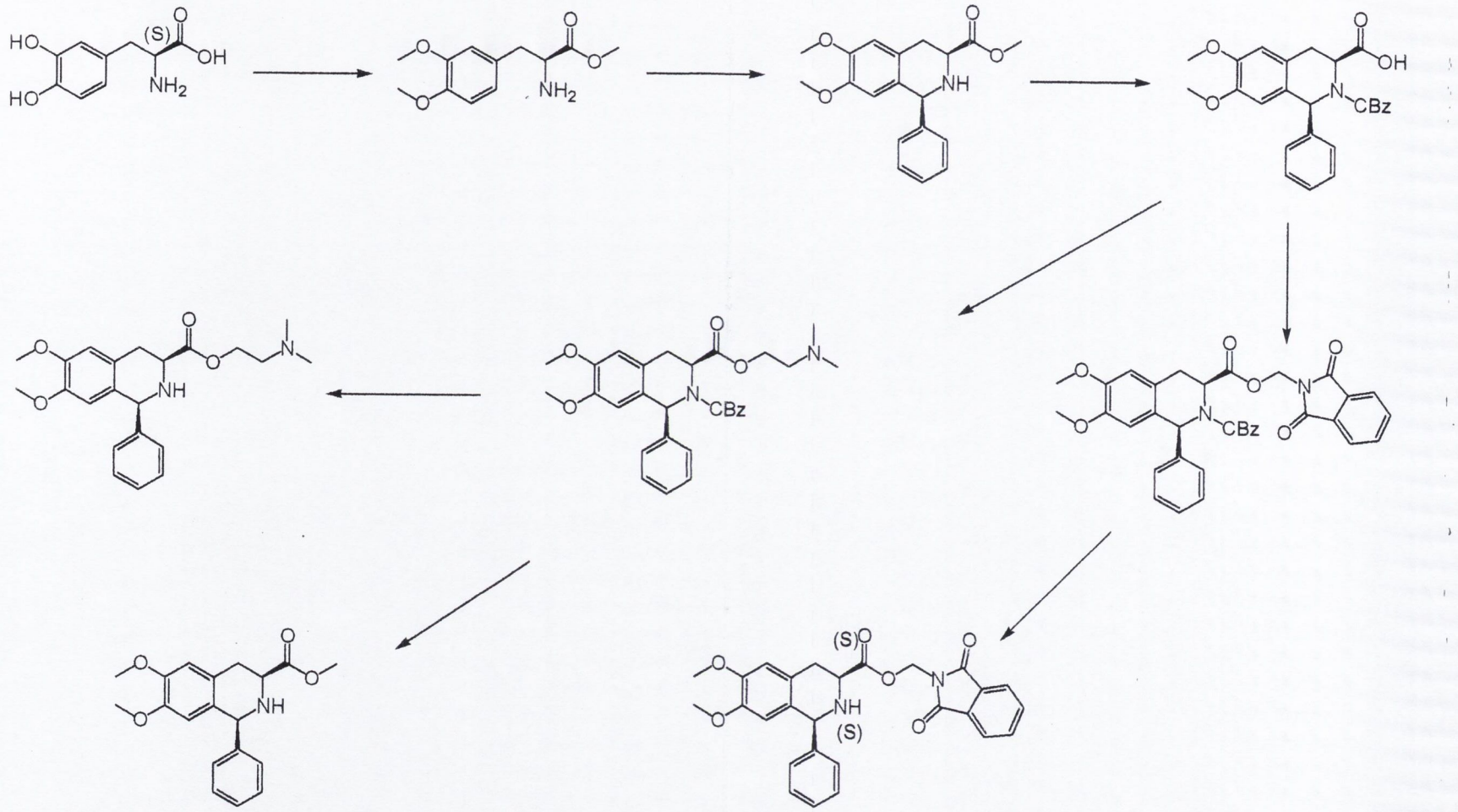
An appropriate synthetic route has established for the synthesis of various position-3 derivatives of 1-phenyltetrahydroisoquinolines as potentially *novel* SSRIs, summerised in Scheme 5-28 and Scheme 5-29. Several analogues with side chains extending from the amine at postion-2 have been produces in a minimal number of steps. The biochemical testing of these compounds using the TREX cell line expressing hSERT transporter proteins is proceeding presently.

Future work could be directed as follows: from the pharmacophoric studies described in Chapter one, it may be advantageous to produce a similar set of compounds having various electron-withdrawing groups in place of the methoxy groups at C6/C7 eventhough this causes difficulty in the initial Pictet-Spengler ring closing of tetrahydroisoquinolines. However, there has been a report of a phenyl group addition at position-1 of a ring unsubstituted dihydroisoquinoline using phenyl lithium to yield the relevant 1-phenyl substituted tetrahydroisoquinoline Scheme 5-25.[291] Subsequent aromantic substitution may then be attempted leaving the required alcohol at position-3 for further derivatisation.

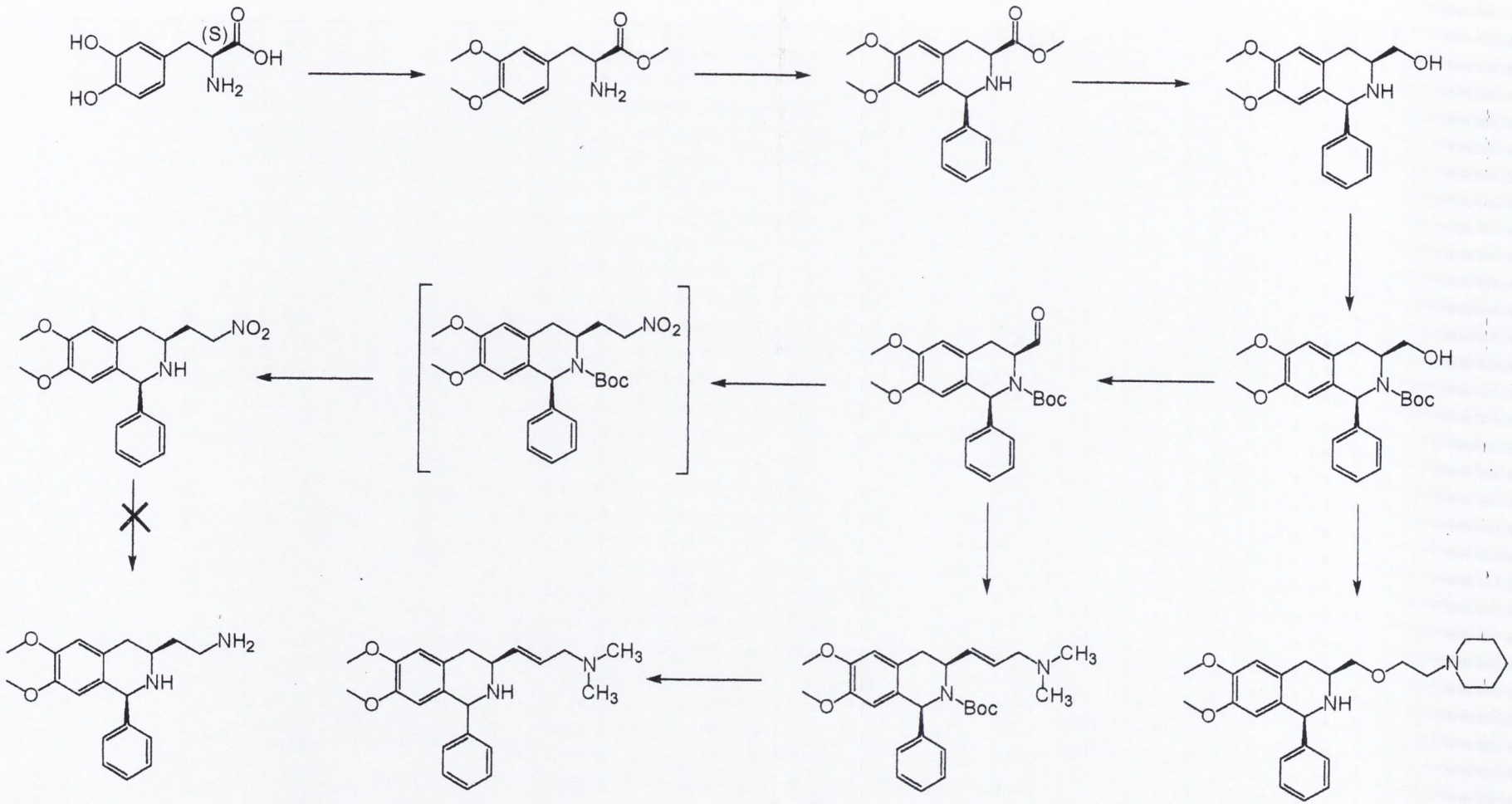


Scheme 5-25: Synthesis of 1-phenyl THIQ without substituents in the intial dihydroisoquinoline[291]

The stereoselectivity of the reaction was poor when using organolithiums with larger groups, the *cis/trans* ratio reported using phenyl lithium being 1:1.4 One potential avenue for exploration may lie in the extension of the Wittig chemistry at position-3 to introduce a variety of basic side chains. The allylic side chain could be subsequently reduced to provide a potential SERT modulator with an alkyl side chain. It would also be of interest to complete the alkylation reactions at position-2 of THIQ rings with a variety of electron withdrawing groups on the tetrahydroisoquinoline aromatic ring. With the chemistry now available to carry out a range of modifications to the tetrahydroisoquinoline scaffold (proven to form with the correct stereochemistry) at positions 2 and 3 a more comprehensive SERT SAR study for the series would be of interest. Scheme 5-26 and 5-27 summerize the synthesis carried out at the THIQ position-3.



Scheme 5-26: Summary of position-3 chemistry I



Scheme 5-27: Summary of position-3 chemistry II

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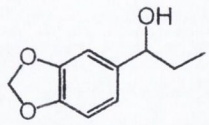
6. Experimental note.

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 Bruker 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 center peak of the CD_3OD multiplets at 3.30 δ and 49.00 δ respectively. ^{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 or protected as a carbamate functionality 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. Low resolution mass spectra (LRMS) were aquired on a Hewlett-Packard 5973 MSD GC-MS system in electron impact mode. High resolution molecular ion determinations (HRMS) were aquired on a Micro mass spectrometer (EI mode) at the Department of Chemistry, Trinity College Dublin. Elemental analyses were performed on an Exetor Analytical CE4400 CHN analyser in the microanalysis laboratory, Department of Chemistry, University College Dublin. Apart from DMF (which was purchased from Aldrich in anhydrous form), all other anhydrous solvents were prepared according to literature methods. The X-ray crystal structure data was collected by Tom McCabe Department of Chemistry, TCD .

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.

Experimental

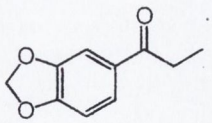
1-(3,4-Methylenedioxyphenyl)-propane-1-ol 154



The Grignard reagent was prepared by the dropwise of bromoethane (7.30 ml) to stirred Mg turnings (2.588 g) in 75 ml of dry diethylether under N_2 atmosphere. When the reaction had ceased, 13.295 g of piperonal dissolved in dry diethylether was added dropwise to the mixture, which was subsequently refluxed for three hours. The reaction was quenched by the addition of saturated ammonium chloride (200 ml). The organic phase was separated and washed with 10% HCl (3 x 75 ml). Solvent dried over anhydrous sodium sulphate and removed under vacuum leaving a clear yellow oil 92% yield.[1]

IRυ_{max} film 3436 (OH) cm^{-1}, 1103 (C-O) cm^{-1}, 814 (Ar) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 0.90 (t, J=7.5 Hz, 3H, H3), 1.74 (m, J=7.0 Hz, 2H, H2), 4.50 (t, J=7.0 Hz, 1H, H1), 5.94 (s, 2H, O$\underline{CH_2}$O), 6.77 (m, 2H, ArH2/H5), 6.86 (s,1H, ArH6). ^{13}C NMR ($CDCl_3$) δ: 9.64 (C3), 31.36 (C2), 75.37 (C1), 100.44 (O$\underline{C}H_2$O), 105.97 (ArC5), 107.50 (ArC2), 118.93 (ArC6), 138.30 (ArC1), 146.37 (ArC4), 147.27 (ArC3). m/z: (M^+) -180 (50), 163 (100).

1-(3,4-Methylenedioxyphenyl)-prop-1-one 150



Method A:

1-(3,4-Methylenedioxyphenyl)-prop-1-ol **154** dissolved in 50 ml dry DCM was added in one portion, to a suspension of 33.196 g of pyridiniumchlorochromate in 150 ml dry DCM. The reaction was initially self-refluxing, then heated to ensure reflux of three hours. Solvent decanted from the black gum which was ground under five 100

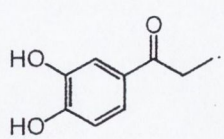
ml portions of diethylether. Etheral portions combined with DCM extract and solvent was removed under vacuum leaving a dark brown oil which was purified on silica-gel (65:35 (hexane:diethylether)) forming white crystals in ethanol/hexane. m.p. 38°C lit. 39°C[2]

Method B:

1,3-Benzodioxole (3.427 g, 28.10 mmol) and propionyl chloride (3.485 ml, 40.10 mmol) were dissolved in dry DCM (60 ml), under a nitrogen atmosphere the contents of the flask were adjusted to 0°C. $SnCl_4$ (6.401 ml, 54.72 mmol) was added dropwise and the reaction was allowed to stir at room temperature for 18 hours. The contents of the reaction were poured into 200 ml of ice-water and extracted with DCM (3 x 100 ml). The organic extracts were combined dried over anhydrous Na_2SO_4, filtered and removed under vacuum. Flash chromatography on silica gel, initially with 8:1 hexane:diethyl ether with a gradient to 1:1:1 hexane:DCM:diethyl ether. Isolated as a colourless solid that was recrystalised from ethanol to give colourless crystals in 67% yield.

M.p.- 38°C. IRυ_{max} (KBr) 1673 (C=O) cm^{-1}, 1252 (C-O) cm^{-1}, 794 (Ar) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.23 (t, J=7.2 Hz, 3H, H3), 2.93 (q, J=6.8 Hz, 2H, H2), 6.05 (s, 2H, $OC\underline{H}_2O$), 6.85 (d, J=8.0 Hz, 1H, ArH5), 7.46 (d, J=1.2 Hz, 1H, ArH2), 7.58 (dd, J=8.0, J=1.2, 1H, ArH6). ^{13}C NMR ($CDCl_3$) δ: 8.46 (C3), 31.52 (C2), 101.74 ($O\underline{C}H_2O$), 107.82 (ArC5), 107.89 (ArC2), 124.05 (ArC6), 131.88 (ArC1), 148.144 (ArC4), 151.54 (ArC3), 198.88 (C=O). LRMS $C_{10}H_{10}O_3$ requires m/z 178, found m/z 178.

1-(3,4-Dihydroxy-phenyl)-propan-1-one 151

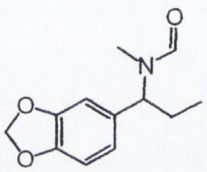


Benzodioxole (3.22 ml, 24.81 mmol) and propionyl chloride (3.657 ml, 42.08 mmol) were dissolved in dry DCM (50 ml) and adjusted to 0°C, under a nitrogen atmosphere, to which $AlCl_3$ (7.48 g, 56.10 mmol) was added, in four portions. The mixture was allowed to come to room temperature and stirred for 18 hours. Reaction was quenched by pouring onto crushed ice and extracting the resulting slush with DCM (4 x 100 ml). The organic extracts were combined, washed with brine (3 x 100

ml), followed by water (2 x 100ml), dried over anhydrous Na_2SO_4, filtered and removed under vacuum to leave a thick black tar. This gum was purified by flash chromatography to yield a dark solid which was recrystallised from ethanol to yield the title compound as grey needles (12%) m.p. 136-138°C lit. 137-138°C[3]

IRυ_{max} (KBr): 3347 (O-H) cm^{-1}, 1664 (C=O) cm^{-1}, 1283 (C-O) cm^{-1}, 794 (Ar) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.23 (t, J=7.2 Hz, 3H, H3), 2.93 (q, J=6.8 Hz, 2H, H2), 6.05 (s, 2H, $OC\underline{H}_2O$), 6.85 (d, J=8.0 Hz, 1H, ArH5), 7.46 (d, J=1.2 Hz, 1H, ArH2), 7.58 (dd, J=8.0, J=1.2, 1H, ArH6). ^{13}C NMR ($CDCl_3$) δ: 8.46 (C3), 31.52 (C2), 101.74 ($O\underline{C}H_2O$), 107.82 (ArC5), 107.89 (ArC2), 124.05 (ArC6), 131.88 (ArC1), 148.144 (ArC4), 151.54 (ArC3), 198.88 (C=O).

N-(1-Benzo[1,3]dioxol-5-yl-propyl)-N-methyl-formamide 159



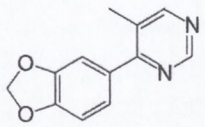
1-(3,4-Methylenedioxyphenyl)-prop-1-one **154** (4.090 g, 22.95 mmol), formic acid (1.281 g, 30.00 mmol) and N-Methyl formamide (4.406 g, 74.60 mmol) were heated to 150°C for 7 hours. The mixture was allowed to cool before the addition of 100 ml water and extraction with diethyl ether (3x100 ml). The organic extracts were combined and washed with water (2 x 50 ml) and 5% $NaHCO_3$ (3 x 100ml). The organic layer was dried over anhydous Na_2SO_4, filtered and removed *in vacuo*. The resulting brown oil was purified on silica gel using a diethyl ether mobile phase to leave a pale yellow oil (28%).

IRυ_{max} (film): 3278 (N-H) cm^{-1}, 2610 (C-C) cm^{-1}, 1659 (C=O), 1039 (C-O) cm^{-1}, 809, 638 (ArCH). ^1H NMR ($CDCl_3$) δ: 0.95 (t, J=7.5 Hz, 3H, H3), 1.81-2.06 (m, 2H, H2), 2.61 (s, 1.95H, $NC\underline{H}_3$ [R1]), 2.64 (s, 1.03H, NCH_3 [R2]), 4.32 (dd, J_1=9.5 Hz, J_2=6.0 Hz, 0.66H, H1 [R1]), 5.46 (dd, J_1=9.5 Hz, J_2=6.0 Hz, 0.33H, H1 [R2]), 5.94 (s, 0.65H, $OC\underline{H}_2O$ [R2]), 5.97 (s, 1.28H, OCH_2O [R1]), 6.72-6.81 (m, 3H, C_6H_3), 8.13 (s, 0.35H, CHO [R2]), 8.31 (s, 0.65H, CHO [R1]). ^{13}C NMR ($CDCl_3$) δ: 10.72 (C3 [R2]), 10.93 (C3 [R1]), 22.15 (C2 [R2]), 23.43 (C2 [R1]), 25.49 ($N\underline{C}H_3$ [R1]), 29.35 ($N\underline{C}H_3$ [R2]), 54.84 (C1 [R2]), 62.89 (C1), 101.01 ($O\underline{C}H_2O$ [R2]), 101.19 ($O\underline{C}H_2O$ [R1]), 107.55 (ArC2 [R1]), 108.03 (ArC2 [R2]), 108.18 (ArC5 [R1]), 108.39 (ArC5 [R2]), 120.47

(ArC6 [R1]), 121.09 (ArC6 [R2]), 132.63 (ArC1 [R1]), 132.70 (ArC1 [R2]), 146.90 (ArC4 [R2]), 147.20 (ArC4 [R1]), 147.81 (ArC3 [R2]), 148.05 (ArC3 [R1]), 162.56 (CHO [R1]), 162.92 (CHO [R2]). LRMS calculated for m/z $C_{12}H_{15}NO_3$: (M^+) 221 found 221.

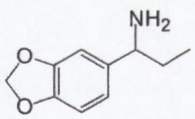
4-Benzo[1,3]dioxol-5-yl-5-methyl-pyrimidine 158

Isolated from the synthesis of **159** in 8% yield. No further characterisation was carried out.



^{1}H NMR ($CDCl_3$) δ: 2.40 (s, 3H, $CH_2C\underline{H}_3$), 6.03 (s, 2H, $OC\underline{H}_2O$), 6.91 (dd, J=8.6 Hz, J=1.9 Hz, 1H, ArH6) 7.13-7.16 (m, 2H, ArH2/H5), 8.58 (s, 1H, C2C<u>H</u>N), 9.07 (s, 1H, NC<u>H</u>N). ^{13}C NMR ($CDCl_3$) δ: 17.34 ($C\underline{C}H_3$), 101.38 ($O\underline{C}H_2O$), 108.15 (ArC5), 109.32 (ArC2), 123.32 (ArC6), 127.75 (C2), 131.76 (ArC1), 147.82 (ArC4), 148.67 (ArC3), 156.48 (C2<u>C</u>N), 158.73 (N<u>C</u>N), 164.21 (C1).

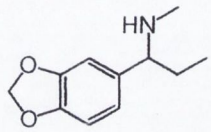
1-(3,4-Methylenedioxyphenyl)-1-aminopropane 161



To a dry three neck round bottom flask under a nitrogen atmosphere, fitted with septa, was added 1-(3,4-Methylenedioxyphenyl)-prop-1-one (1.000 g, 5.61 mmol) and hexamethyldisilazane (2.264 g, 14.00 mmol). $TiCl_4$ (1.062 ml, 5.61 mmol) was added dropwise and the reaction mixture was allowed to stir for twenty hours after which time $NaCNBH_3$ (1.500 g, 25.00 mmol) dissolved in freshly dried methanol was added dropwise. The reaction mixture was poured slowly over crushed ice. 200 ml of 15% NaOH was added and the mixture was extracted with DCM (5 x100 ml). The solvent was dried over anhydrous sodium sulphate and removed under vacuum the resulting residue was then purified on silica gel using a 100% methanol mobile phase. m.p. (HCl) 196-200°C (lit. 200-201)[4]

Amber oil (51%). IRυ_{max} (film): 2905 (NH_2) cm^{-1}, 1449 (C-H) cm^{-1}, 1256 (C-O) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.86 (t, J=7.0 Hz, 3H, H3), 1.57-1.73 (m, 4H, $N\underline{H_2}$/H2), 3.72 (t, J=6.4 Hz, 1H, H1), 5.94 (s, 2H, $OC\underline{H_2}O$), 6.75 (s, 2H, ArH2/H5), 6.84 (s, 1H, ArH6). ^{13}C NMR ($CDCl_3$) δ: 10.87 (C3), 32.38 (C2), 57.59 (C1), 100.77 ($O\underline{C}H_2O$), 106.63 (ArC5), 107.90 (ArC2), 119.51 (ArC6), 140.51 (ArC1), 146.26 (ArC4), 147.64 (ArC3). LRMS calculated for $C_{10}H_{13}NO_2$: (M^+) requires m/z: 179 (not observed), found 163 $C_{10}H_8O_2$ (M^+-16).

N-Methyl-1-(3,4-Methylenedioxyphenyl)-1-aminopropane 149



Method A:

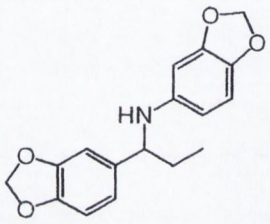
N-(1-Benzo[1,3]dioxol-5-yl-propyl)-N-methyl-formamide **159** (0.796 g, 3.60 mmol) was dissolved in 30ml of methanol, to which 40 ml 30% HCl was added. The solution was refluxed for 5 hours allowed to cool to room temperature and extracted (2 x50 ml) with diethyl ether. The aqueous layer was adjusted to pH 8-9 with 15% NaOH and extracted with DCM (3 x 100 ml). The DCM extracts were combined, dried over anhydrous Na_2SO_4, filtered and removed *in vacuo*. The HCl salt of the title compound was formed and recrystallised from 25 ml hot ethanol.

Method B:

To a dry three neck round bottomed flask, fitted with septa, under a nitrogen atmosphere was added 1-(3,4-Methylenedioxyphenyl)-prop-1-one **150** (0.700 g, 3.90 mmol), methylamine HCl (0.270 g, 4.00 mmol) and triethylamine (1.224 g, 12.00 mmol). $TiCl_4$ (0.738 ml, 3.90 mmol) was added dropwise and reaction mixture was allowed to stir for twenty hours after which time $NaCNBH_3$ (1.500 g, 25.00 mmol) dissolved in freshly dried methanol was added dropwise. The reaction mixture was poured slowly over crushed ice. 200 ml of 15% NaOH was added and the mixture was extracted with DCM (5 x 100 ml). The solvent was dried over anhydrous sodium sulphate and removed under vacuum resulting in a residue that was purified on silica gel with a 50:50 methanol:diethylether mobile phase. The free base was converted to the HCl salt (colourless powder) *via* the general method (48%) m.p. 216-218°C.

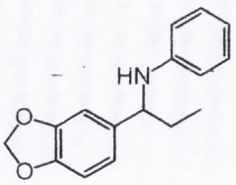
IRυ_{max} (KBr-HCl salt): 2897 (NH) cm^{-1}, 1497 (C-H) cm^{-1}, 1257, 1043 (C-O) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.81 (t, J=7.5 Hz, 3H, H3), 1.20-1.76 (m, 3H, NH/H2), 2.27 (s, 3H, NCH_3), 3.29 (m, 1H, H1), 5.94 (s, 2H, OCH_2O), 6.70-6.80 (m, 3H, ArH2, ArH5, ArH6). ^{13}C NMR ($CDCl_3$) δ: 10.71 (C3), 30.67 (C2), 34.41 (NCH_3), 66.91 (C1), 100.74 (OCH_2O), 107.14 (ArC5), 107.76 (ArC2), 120.68 (ArC6), 137.93 (ArC1), 146.33 (ArC4), 147.72 (ArC3). LRMS calculated for m/z $C_{11}H_{15}NO_2$: ($M^+ + H^+$) 193, (not observed) found 163 $C_{10}H_{11}O_2$ (M^+ - 30).

Benzo[1,3]dioxol-5-yl-(1-benzo[1,3]dioxol-5-yl-propyl)-amine 166 was converted to the HCl salt (colourless powder) *via* the general method as described for **161**. (87%) m.p. 174°C.



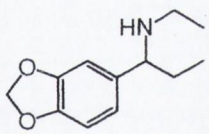
IRυ_{max} (KBr-HCl salt): 2889 (N-H) cm^{-1}, 2495 (C-C) cm^{-1}, 1501 (C-H) cm^{-1}, 1037 (C-O) cm^{-1}, 933, 651 (ArCH). ^1H NMR ($CDCl_3$) δ: 0.92 (t, J=7.3$_{ave}$ Hz, 3H, H3), 1.62-1.89 (m, 2H, H2), 3.86 (s, 1H, NH), 3.29 (t, J=6.5 Hz, 1H, H1), 5.81 (m, 2H, OCH_2O), 5.94 (2d, J=1.5 Hz, 2H, OCH_2O*), 5.98 (dd, J_o=8.0 Hz, J_m=2.0 Hz, 1H, ArH6*), 6.18 (d, J_m=2.0 Hz, 1H, ArH2*), 6.60 (d, J_o=8.0 Hz, 1H, ArH5*), 6.77 (d, J_o=8.0 Hz, 1H, ArH5), 6.81 (dd, J_o=8.0 Hz, J_m=1.5 Hz, 1H, ArH6), 6.85 (d, J_m=1.5 Hz, 1H, ArH2). ^{13}C NMR ($CDCl_3$) δ: 10.71 (C3), 31.72 (C2), 60.43 (C1), 96.28 (ArC2*), 100.41 (OCH_2O), 100.84 (OCH_2O*), 105.05 (ArC6*), 106.64 (ArC2), 108.11 (ArC5), 108.47 (ArC5*), 119.69 (ArC6), 138.05 (ArC4), 139.34 (ArC1*), 143.19 (ArC4*), 146.39 (ArC1), 147.88 (ArC3), 148.10 (ArC3*). Elemental analysis: $C_{17}H_{18}ClNO_4$ requires C, 60.81; H, 5.40; N, 4.17. Found C, 60.74; H, 5.49; N, 3.97.

(1-Benzo[1,3]dioxol-5-yl-propyl)-phenyl-amine 165 was converted to the HCl salt (colourless powder) *via* the general method as described for **161** (80%) m.p. 164°C.



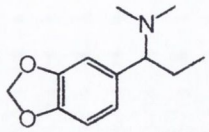
IRυ_{max} (KBr-HCl salt): 2868 (N-H) cm^{-1}, 2488 (C-C) cm^{-1}, 1487 (C-H) cm^{-1}, 1034 (C-O) cm^{-1}, 817, 692 (ArCH). ^{1}H NMR ($CDCl_3$) δ: 0.68 (t, J=7.3$_{ave}$ Hz, 3H, H3), 2.18-2.30, 2.51-2.61 (2m, 2H, H2), 4.10 (dd, J_1=11.5 Hz, J_2=4.0 Hz, 1H, H1), 5.91 (s, 2H, $OC\underline{H}_2O$), 6.62 (d, J_o=8.0 Hz, 1H, ArH5), 6.72 (dd, J_o=8.0 Hz, J_m=1.5 Hz, 1H, ArH6), 6.96 (d, J_m=1.5 Hz, 1H, ArH2), 7.21 (m, 3H, ArH3*/H4*/H5*) 7.32 (m, 2H, ArH2*/H6*), 11.65 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 10.31 (C3), 25.99 (C2), 70.71 (C1), 101.24 (OCH_2O), 108.18 (ArC5), 108.92 (ArC2), 123.46 (ArC6), 124.40 (ArC3*/5*), 126.77 (ArC1), 128.69 (ArC4*), 129.20 (ArC2*/C6*), 134.12 (ArC1*), 148.03 (ArC3), 148.19 (ArC4). Elemental analysis: $C_{16}H_{18}ClNO_4$ requires C, 65.86; H, 6.22; N, 4.80. Found C, 65.84; H, 6.19; N, 4.74.

(1-Benzo[1,3]dioxol-5-yl-propyl)-ethyl-amine 160 was converted to the HCl salt (colourless powder) *via* the general method as described for **161** (35%) m.p. 220-224 °C.



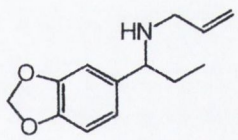
IRυ_{max} (KBr-HCl salt): 2971 (N-H), 2504 (C-C), 1039 (C-O) cm^{-1}, 930, 810 (ArCH). ^{1}H NMR ($CDCl_3$) δ: 0.79 (t, J=7.5 Hz, 3H, H3), 1.07 (t, J=7.0 Hz, 3H, $NCH_2C\underline{H}_3$) 1.54-1.81 (m, 2H, H2), 2.48 (q, J=7.0 Hz, 2H, $NC\underline{H}_2$), 3.42 (dd, J_1=8.0 Hz, J_2=5.5 Hz, 1H, H1), 5.94 (s, 2H, $OC\underline{H}_2O$), 6.71 (dd, J_o=8.0 Hz, J_m=1.5 Hz, 1H, ArH6), 6.76 (d, J=8.0 Hz, 1H, ArH5), 6.82 (d, J=1.5 Hz, 1H, ArH2). ^{13}C NMR ($CDCl_3$) δ: 10.72 (C3), 15.09 ($NCH_2\underline{C}H_3$), 30.63 (C2), 41.73 ($N\underline{C}H_2$), 64.85 (C1), 100.78 ($O\underline{C}H_2O$), 107.15 (ArC5), 107.81 (ArC2), 120.71 (ArC6), 137.79 (ArC1), 146.38 (ArC4), 147.75 (ArC3). Elemental analysis: $C_{12}H_{18}ClNO_2$ requires C, 59.13; H, 7.44; N, 5.75. Found C, 58.65; H, 7.36; N, 5.56.

(1-Benzo[1,3]dioxol-5-yl-propyl)-dimethyl-amine 159 synthesised via the general method as described for **161**, and was isolated as a pale yellow oil by flash chromatography on silica gel using a methanol mobile phase (76%).



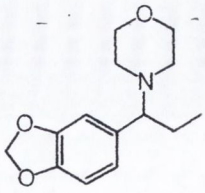
IRυ_{max} (film): 2771 (C-C), 1040 (C-O) cm^{-1}, 745, 647 (ArCH). ^{1}H NMR ($CDCl_3$) δ: 0.72 (t, J=7.5 Hz, 3H, H3), 1.60-1.95 (m, 2H, H2), 2.16 (s, 6H, $N(C\underline{H}_3)_2$), 2.95 (dd, J_1=4.5 Hz, J_2=9.5 Hz, 1H, H1), 5.94 (s, 2H, $OC\underline{H}_2O$), 6.65 (dd, J_o=8.0 Hz, J_m=1.5 Hz, 1H, ArH6),6.75 (2d, J_o=8.0 Hz, J_m=1.5 Hz, 2H, ArH5/H2). ^{13}C NMR ($CDCl_3$) δ: 10.89 (C3), 26.18 (C2), 42.87 ($N(\underline{C}H_3)_2$), 72.40 (C1), 100.76 ($O\underline{C}H_2O$), 107.57 (ArC5), 108.37 (ArC2), 121.96 (ArC6), 134.53 (ArC1), 146.38 (ArC4), 147.72 ($ArC3_q$). HRMS calculated for m/z $C_{12}H_{17}NO_2$: ($M^+ + H^+$) 208.1337, found 208.1338.

(1-Benzo[1,3]dioxol-5-yl-propyl)-but-2-enyl-amine 167 was converted to the HCl salt (colourless powder) *via* the general method as described for **161** (74%) m.p. 210-212 °C.



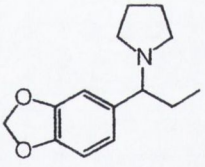
IRυ_{max} (Film) 2963 (N-H) cm^{-1}, 1503 (C=C) cm^{-1}, 1246/1040 (C-O) cm^{-1}, 808 (Ar) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 0.82 (t, J=7.5 Hz, 3H, H3), 1.28-1.79 (m, 3H, N$\underline{H}$/H2), 3.08 (ddd, J_1=11.4, J_2=6.5, J_3=14.0 Hz, 2H, $NC\underline{H}_2$), 3.47 (m, 1H, H1), 5.11 (dd, J_1=17.2, J_2=1.6, 2H, $CH=C\underline{H}_2$), 5.84-5.97 (m,3H, $OCH_2O/C\underline{H}=CH_2$), 6.65-6.88 (m, 3H, ArH2/H5/H6). ^{13}C NMR ($CDCl_3$) δ: 10.72 (C3), 30.89 (C2), 49.98 ($N\underline{C}H_2$), 64.03 (C1), 100.77 ($O\underline{C}H_2O$), 107.21 ($\underline{C}H=CH_2$), 120.75 (ArC2), 136.98 (ArC6), 137.92 (ArC1), 146.38 (ArC4), 147.76 (ArC3). Elemental analysis: $C_{13}H_{18}ClNO_2$ requires C, 61.05; H, 7.09; N, 5.48. Found C, 60.98; H, 7.06; N, 5.41.

4-(1-Benzo[1,3]dioxol-5-yl-propyl)-morpholine 162 was converted to the HCl salt (colourless powder) *via* the general method as described for **161** (55%) m.p. 241-242 °C.



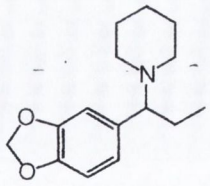
IRυ_{max} (KBr-HCl salt) cm^{-1}: 2464 (C-C), 1239 (N-C), 1068, 1113 (C-O) cm^{-1}, 813 (ArCH). ^{1}H NMR ($CDCl_3$) δ: 0.73 (t, J=7.5 Hz, 3H, H3), 1.54-1.96 (m, 2H, H2), 2.35 (m, 4H, $N(C\underline{H}_2)_2$), 3.02 (dd, J_1=4.5 Hz, J_2=9.5 Hz, 1H, H1), 3.68 (m, 4H, $O(CH_2)_2$), 5.95 (s, 2H, $OC\underline{H}_2O$), 6.67 (dd, J_o=8.0 Hz, J_m=1.5 Hz, 1H, ArH6), 6.75 (d, J_o=8.0 Hz, 1H, ArH5), 6.78 (d, J_m=1.5 Hz, 1H, ArH2). ^{13}C NMR ($CDCl_3$) δ: 10.54 (C3), 25.41 (C2), 52.23 ($N(CH_2)_2$), 67.22 ($O(CH_2)_2$), 71.82 (C1), 100.78 (OCH_2O), 107.56 (ArC5), 108.29 (ArC2), 121.98 (ArC6), 134.83 (ArC1), 146.42 (ArC4), 147.57 (ArC3). Elemental analysis: $C_{14}H_{20}ClNO_3$ requires C, 58.84; H, 7.05; N, 4.90. Found C, 58.70; H, 7.09; N, 4.73.

1-(1-Benzo[1,3]dioxol-5-yl-propyl)-pyrrolidine 164 was isolated as a pale yellow oil by flash chromatography on silica gel using a methanol mobile phase (60%).



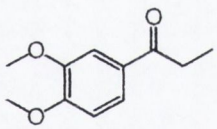
IRυ_{max} (film) cm^{-1}: 2523 (C-C), 1253 (N-C), 1038 (C-O) cm^{-1}, 889 (ArCH). ^{1}H NMR ($CDCl_3$) δ: 0.69 (t, J=7.5 Hz, 3H, H3), 1.61-1.78 (m, 5H, H2*, $N(CH_2)_2(C\underline{H}_2)_2$), 1.90-1.98 (m, 1H, H2), 2.37, 2.52 (m, 4H, $N(C\underline{H}_2)_2$), 2.89 (dd, J_1=4.0 Hz, J_2=10.0 Hz, 1H, H1), 5.93 (s, 2H, $OC\underline{H}_2O$), 6.72 (m, 2H, ArH5/6), 6.85 (s, 1H, ArH2). ^{13}C NMR ($CDCl_3$) δ: 10.43 (C3), 23.21 ($N(CH_2)_2(\underline{C}H_2)_2$), 28.47 (C2), 52.66 ($N(CH_2)_2$), 72.43 (C1), 100.71 ($OCH_2O$), 107.50 (ArC5), 108.06 (ArC2), 121.43 (ArC6), 137.18 (ArC1), 146.24 (ArC4), 147.53 (ArC3). LRMS: calculated for $C_{14}H_{20}NO_2$ m/z (M^+ + H^+) requires 234, found 234.

1-(1-Benzo[1,3]dioxol-5-yl-propyl)-piperidine 163 was isolated as a pale yellow oil by flash chromatography on silica gel using a methanol mobile phase (63%).



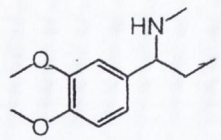
IRυ_{max} (film) cm^{-1}: 2523 (C-C), 1041 (C-O) cm^{-1}, 780 (ArCH). ^{1}H NMR ($CDCl_3$) δ: 0.73 (t, J=7.5 Hz, 3H, H3), 1.37-1.44 (m, 2H, $C\underline{H}_2(CH_2)_2$), 1.63-1.80 (m, 5H, H2*, $N(CH_2)_2(C\underline{H}_2)_2$), 1.89-1.99 (m, 1H, H2), 2.35-2.50 (m, 4H, $N(C\underline{H}_2)_2$), 2.89 (dd, J_1=4.0 Hz, J_2=10.3 Hz, 1H, H1), 6.01 (s, 2H, $OC\underline{H}_2O$), 6.70 (m, 2H, ArH5/6), 6.82 (d, J=1.2 Hz, 1H, ArH2). ^{13}C NMR ($CDCl_3$) δ: 10.88 (C3), 24.28 ($\underline{C}H_2(CH_2)_2$), 25.69 ($N(CH_2)_2(\underline{C}H_2)_2$), 28.42 (C2), 52.53 ($N(CH_2)_2$), 72.40 (C1), 100.75 ($OCH_2O$), 107.56 (ArC5), 108.27 (ArC2), 121.69 (ArC6), 136.88 (ArC1), 146.38 (ArC4), 147.70 (ArC3). LRMS: calculated for $C_{15}H_{22}NO_2$ m/z ($M^+ + H^+$) requires 248, found 248.

1-(3,4-Dimethoxy-phenyl)-propan-1-one 169 Isolated as a colourless solid *via* Friedel-Crafts acylation (as used for 1-(3,4-methylenedioxyphenyl)-prop-1-one **150** method B) was recrystalised from ethanol to give colourless crystals in (58%) m.p. 58-60 °C (lit. 61°C[5]).



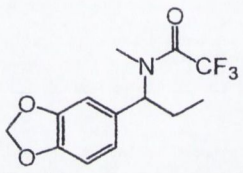
^{1}H NMR ($CDCl_3$) δ: 1.20 (t, J=7.3 Hz, 3H, H3), 2.93 (q, J=7.2 Hz, 2H, H2), 3.91, 3.92 (2s, 6H, (OCH_3 x 2), 6.86 (d, J_o=8.4 Hz, 1H, ArH5), 7.52 (d, J_m=1.7 Hz, 1H, ArH2), 7.56 (dd, J_o=8.4, J_m=1.2, 1H, ArH6). ^{13}C NMR ($CDCl_3$) δ: 8.45 (C3), 31.27 (C2), 55.91, 55.96 (OCH_3 x 2), 110.01 (ArC5), 110.21 (ArC2), 122.41 (ArC6), 130.13 (ArC1), 148.97 (ArC4), 153.06 (ArC3), 199.34 (C=O). LRMS: calculated for $C_{11}H_{14}O_3$ M^+ requires m/z 194, found 194.

[1-(3,4-Dimethoxy-phenyl)-propyl]-methyl-amine 170 was isolated (using *via* method as described for **150**) as a pale yellow oil by flash chromatography on silica gel using a methanol mobile phase (43%).[5]



IRυ_{max} (film) cm^{-1}: 2802 (C-C), 1516 (Ar), 1141 (C-O). ^1H NMR ($CDCl_3$). ^1H NMR ($CDCl_3$) δ: 0.82 (t, J_{ave}=7.3 Hz, 3H, $CH_2C\underline{H}_3$), 1.57-1.82 (m, 3H, $N\underline{H}/C\underline{H}_2CH_3$), 2.30 (s, 3H, $NC\underline{H}_3$), 3.33 (dd, J_1=7.5 Hz, J_2=6.0 Hz, 1H, $C\underline{H}CH_2$), 3.89, 3.91 (2s, 6H, OCH_3x2), 6.80-6.98 (m, 3H, ArH2/5/6). ^{13}C NMR ($CDCl_3$) δ: 10.82 (C3), 31.04 (C2), 34.39 ($N\underline{C}H_3$), 66.30 (C1), 106.77 (ArC5), 107.54 (ArC2), 119.11 (ArC6), 136.96 (ArC1), 147.61 (ArC4), 147.84 (ArC3). LRMS: calculated for $C_{12}H_{19}NO_2$ M^+ requires m/z 209 (not observed), found 179 (M^+ - 30 $C_{11}H_{15}O$).

N-Methyl-N-Trifluoroacetal-1-(3,4-Methylenedioxyphenyl)-1-aminopropane 171

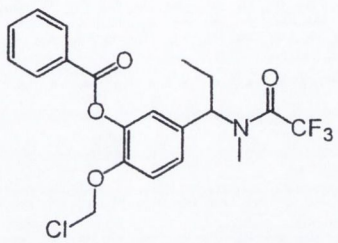


N-Methyl-1-(3,4-Methylenedioxyphenyl)-1-aminopropane (4) (1.407 g, 7.30 mmol) and triethylamine (0.911 g, 9.00 mmol) was dissolved in dry DCM and added to an oven-dried 250 ml round bottomed flask fitted with $CaCl_3$ moisture guard tube. The contents of the flask were adjusted to 0^0C at which point triflouroacetic anhydride (3.066 g, 14.60 mmol) was added very slowly. The mixture was allowed to stir slowly for three hours after which the reaction was quenched with washings of 10% HCl (4 x 75 ml). The organic phase was then washed with a saturated solution of $NaHCO_3$ (3 x 100 ml). Solvent was dried over anhydrous Na_2SO_4 and removed under vacuum leaving a fawn solid (80%) m.p. 70-72°C.

IRυ_{max} cm^{-1} (KBr): 3437 (N-H), 1144 (N-C), 1040 (C-O), 767 (ArCH). ^1H NMR ($CDCl_3$) δ: 0.98 (t, J=7.5 Hz, 3H, H3), 1.85-2.80 (m, 2H, H2), 2.80 (s, 3H, $NC\underline{H}_3$), 5.64 (t, J=6.0 Hz, 1H, H1), 5.99 (m, 2H, $OC\underline{H}_2O$), 6.80 (m, 3H, ArH2/H5/H6). ^{13}C NMR ($CDCl_3$) δ: 10.52 (C3), 22.23 (C2), 28.41 (q, J=4.1 Hz, $N\underline{C}H_3$), 58.42 (C1), 101.19 ($O\underline{C}H_2O$), 108.24 (ArC5/C2), 117.28 (q, J=287.8 Hz, $\underline{C}F_3$), 131.67 (ArC1), 147.37 (ArC4), 148.08 (ArC3), 157.84 (q, J=36.2 Hz, $\underline{C}OCF_3$). ^{19}F NMR ($CDCl_3$) δ: -70.13 ($C\underline{F}_3$). HRMS calculated for $C_{13}H_{14}NO_3F_3$: (M^+ + Na) 312.0823, found

312.0814. Elemental analysis: $C_{13}H_{14}F_3NO_3$ requires C, 53.98; H, 4.88; N, 4.84. Found C, 53.95; H, 4.74; N, 4.68.

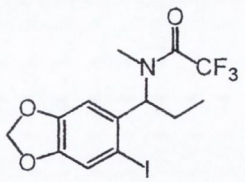
Benzoic acid 2-chloromethoxy-5-{1-[methyl-(2,2,2-trifluoro-acetyl)-amino]-propyl}-phenyl ester 181



N-Methyl-N-Trifluoroacetal-1-(3,4-Methylenedioxyphenyl)-1-aminopropane **154** (1.000 g, 2.55 mmol) was dissolved in dry DCM (40 ml) under a nitrogen atmosphere and cooled to 0°C. Benzoyl chloride (0.414 ml, 3.56 mmol) was added dropwise over 20 minutes. The reaction was allowed to rise to rt and stirred for 20 hours. The reaction was quenched by pouring the mixture into ice-water (200 ml). The aqueous layer was extracted with DCM (3 x 100 ml). The organic extracts were combined and washed with brine (4 x 100 ml). The organic extracts were combined and dried over anhydrous Na_2SO_4, filtered and removed under reduced pressure. The resulting residue was columned twice on silica gel using a mobile phase of 70:30 hexane:diethyl ether to yield the title compound in 8%, preliminary characterisation by nmr.

^{1}H NMR ($CDCl_3$) δ: 1.04 (2t, J=7.5 Hz, 3H, H3 [R1,R2]), 1.94-2.29 (m, 2H, H2), 2.81 (s, 0.63H, NC$\underline{H}_3$ [R2]), 2.87 (s, 2.32H, NC$\underline{H}_3$ [R1]), 5.03 (dd, J_1=8.5 Hz, J_2=6.5 Hz, 0.22H, H1 [R2]), 5.78 (dd, J_1=5.5 Hz, J_2=10.0 Hz, 0.81H, H1 [R1]), 5.85 (s, 2H, ClC$\underline{H}_2$O), 7.14 (dd, J_o=8.0 Hz, J_m=1.5 Hz, 1H, ArH4), 7.26 (d, J_o=8.5 Hz, 1H, ArH3). 7.27 (d, J_m=1.5 Hz, 1H, ArH6). ^{13}C NMR ($CDCl_3$) δ: 9.37 (H3), 22.06 (H2), 28.68 (N$\underline{C}H_3$ [R1]), 28.80 (N$\underline{C}H_3$ [R2]), 58.05 (C1 [R1]), 60.17 (C1 [R2]), 77.52 (O$\underline{C}H_2$Cl), 115.84 (ArC3), 119.56 (q, J=286.5 Hz, CF_3), 122.59 (ArC6), 123.80 (ArC4), 128.61 (ArC3*/5*), 128.78 (C5), 130.31 (ArC2*/6*), 137.05 (ArC4*), 140.69 (ArC1*), 147.53 (C2), 148.52 (C1), 157.31 (q, J=35.8 Hz, $\underline{C}OCF_3$), 164.39 (OC=O). ^{19}F NMR ($CDCl_3$) δ: -70.05 (COC$\underline{F}_3$).

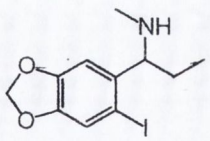
N-Methyl-N-Trifluoroacetal-1-(3,4-Methylenedioxy-6-iodophenyl)-1-aminopropane 192



N-Methyl-N-Trifluoroacetal-1-(3,4-Methylenedioxyphenyl)-1-aminopropane **171** (1.000 g, 3.46 mmol) was added to a mixture of iodine (1.755 g, 6.91 mmol) and silver(I)sulphate in ethanol at room temperature. The reaction flask was covered with aluminium foil avoiding exposure to light. The mixture was allowed to stir for twenty hours after which the yellow solid was removed by filtration. The ethanol was removed under vacuum and the resulting residue was dissolved in chloroform and washed with saturated $NaHCO_3$ (3 x 100 ml) followed by water (3 x 75 ml). Solvent was dried over anhydrous Na_2SO_4 and evaporated to dryness. The resulting residue was purified on silica gel with a 85:15 hexane:diethylether mobile phase to give a solid that was recrystallised from absolute ethanol to leave the title compound as colourless needles (54%) m.p. 96°C.

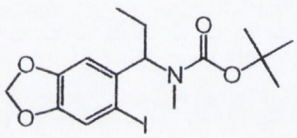
IRυ_{max} cm^{-1} (film): 1639 (C=O), 1478 (NCO), 1036 (C-O). ^{1}H NMR ($CDCl_3$) δ: 0.97 (t, J=7.5 Hz, 3H, H3), 1.93-2.01 (m, 2H, H2), 2.79 (s, 3H, $NC\underline{H}_3$), 5.38 (t, J=7.5 Hz, 1H, H1), 6.02 (s, 2H, $OC\underline{H}_2O$), 6.90 (s, 1H, ArH5), 7.36 (s, 1H, ArH2). ^{13}C NMR ($CDCl_3$) δ: 10.72 (C3), 23.67 (C2), 30.00 (q, J=4.1 Hz, $N\underline{C}H_3$), 63.89 (C1), 90.21 (ArC6), 101.99 ($O\underline{C}H_2O$), 109.30 (ArC5), 117.94 (q, J=288.5 Hz, $\underline{C}F_3$), 119.91 (ArC2), 132.30 (ArC1), 148.29 (ArC4), 148.56 (ArC3), 156.97 (q, J=36.4 Hz, $\underline{C}OCF_3$). HRMS calculated for $C_{13}H_{13}F_3INO_3$: (M^+ + Na) 437.9790, found 437.9799. Elemental analysis: $C_{13}H_{13}F_3INO_3$ requires C, 37.61; H, 3.16; N, 3.37. Found C, 37.57; H, 3.07; N, 3.16.

[1-(6-Iodo-benzo[1,3]dioxol-5-yl)-propyl]-methyl-amine 193. N-Methyl-N-Trifluoroacetal-1-(3,4-Methylenedioxy-6-iodophenyl)-1- aminopropane **192** (0.115g, 0.27 mmol) was dissolved in 4:1 methanol:water, to which K_2CO_3 was added to give a solution of pH 9. The mixture was stirred for 72 hours after which the title compound was isolated as a clear oil following an acid base extraction from DCM (150ml) (72%).



IRυ_{max} cm^{-1} (film): 2961 (N-H), 1472, 1039 (C-O). ^{1}H NMR ($CDCl_3$) δ: 0.97 (t, J_{ave}=7.3 Hz, 3H, H3), 1.53-1.66 (m, 3H, H2, NH), 2.28 (s, 3H, $NC\underline{H}_3$), 3.78 (dd, J_1=5.8 Hz, J_2=5.5 Hz, 1H, H1), 5.97 (2d, J=1.5 Hz, 2H, $OC\underline{H}_2O$), 6.92 (s, 1H, ArH5), 7.25 (s, 1H, ArH2). ^{13}C NMR ($CDCl_3$) δ: 10.41 (C3), 30.16 (C2), 34.20 ($N\underline{C}H_3$), 69.01 (C1), 88.42 (ArC6), 101.49 (OCH_2O), 107.39 (ArC5), 118.27 (ArC2), 125.87 (ArC1), 147.34 (ArC4), 148.89 (ArC3). LRMS calculated for $C_{11}H_{14}INO_2$: (M^+) requires m/z: 319 (not observed), found 289 $C_{10}H_{10}IO_2$ (M^+-30).

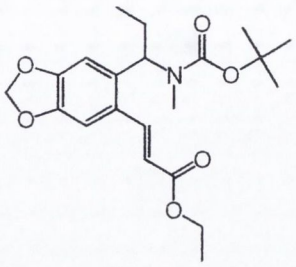
[1-(6-Iodo-benzo[1,3]dioxol-5-yl)-propyl]-methyl-carbamic acid tert-butyl ester 194



A mixture of [1-(6-Iodo-benzo[1,3]dioxol-5-yl)-propyl]-methyl-amine **193** (0.610 g, 1.91 mmol), triethyl amine added dropwise (0.459 g, 2.10 mmol) and Boc_2O (0.558 ml, 4.00 mmol) were stirred in dry DCM under a nitrogen atmomsphere for 6 hours. All volatiles were removed *in vacuo* and the resulting residue was columned directly on silica gel using a 70:30 hexane:diethyl ether mobile phase yielding the title compound as a pale yellow oil 85%.

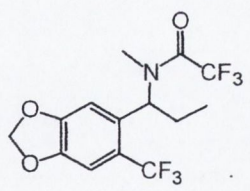
IRυ_{max} cm^{-1} (KBr): 1685 (C=O), 1230, 1027 (C-O), 1476, 918 (Ar). ^{1}H NMR ($CDCl_3$) δ: 0.97 (t, J_{ave}=7.3 Hz, 3H, H3), 1.47 (s, 9H, $C(CH_3)_3$), 1.79-1.90 (m, 2H, H2), 2.59 (s, 3H, $NC\underline{H}_3$), 4.98 (dd, J_1=7.2 Hz, J_2=6.8 Hz, 1H, H1), 5.99 (s, 2H, OCH_2O), 6.82 (s, 1H, ArH5), 7.31 (s, 1H, ArH2). ^{13}C NMR ($CDCl_3$) δ: 11.27 (C3), 24.93 (C2), 28.35 ($C(\underline{C}H_3)_3$), 29.21 ($N\underline{C}H_3$), 63.56 (C1), 79.49 ($\underline{C}(CH_3)_3$), 89.20 ($C6_q$), 101.49 (ArC2), 107.39 (ArC5), 118.27 (ArC2), 125.87 (ArC1), 147.34 (ArC4), 148.89 (ArC3). HRMS calculated for $C_{16}H_{22}INO_4$: (M^+ + Na) 442.0491, found 442.90482.

3-{6-[1-(tert-Butoxycarbonyl-methyl-amino)-propyl]-benzo[1,3]dioxol-5-yl}-acrylic acid ethyl ester 194a Prepared according to the general method from (0.177g, 0.42mmol) of the Boc protected iodide **194** isolated as a clear oil (49%).



IRυ_{max} film: 2933 (C-C) cm^{-1}, 1712, 1678 (C=O), 1179, 1040 (C-O) cm^{-1}, 1507, 933 (Ar) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.97 (t, J_{ave}=7.3 Hz, 3H, H3), 1.33 (t, J_{ave}=7.3 Hz, 3H, $OCH_2C\underline{H}_3$), 1.49 (s, 9H, $C(CH_3)_2$), 1.78-1.90 (m, 2H, H2), 2.50 (s, 3H, NCH_3), 4.24 (m, 2H, OCH_2), 5.37 (m, 1H, H1), 6.01 (s, 2H, OCH_2O), 6.19 (d, J_{trans}=15.7 Hz, 1H, CH=C$\underline{H}$CO), 6.85 (s, 1H, ArH2), 7.06 (s, 1H, ArH5), 8.03 (d, J_{trans}=15.7 Hz, 1H, C$\underline{H}$=CHCO). ^{13}C NMR ($CDCl_3$) δ: 14.32 (C3), 28.17 (C2), 28.26 (C($\underline{C}H_3)_3$), 28.51 (N$\underline{C}H_3$), 60.30 (O$\underline{C}H_2CH_3$), 63.54 (C1), 79.71 ($\underline{C}(CH_3)_3$), 101.54 (ArC2), 106.72 (ArC5), 107.57 (ArC2), 118.94 ($\underline{C}$HCO), 134.54 (ArC1), 138.51 (Ar$\underline{C}$H=C), 147.01 (ArC4), 148.05 (ArC3), 155.31 (NCO), 166.66 (COO). HRMS calculated for $C_{21}H_{29}NO_6$: (M^+ + Na) 414.1893, found 414.1884.

N-Methyl-N-Trifluoroacetal-1-(3,4-Methylenedioxy-6-trifluoromethylphenyl)-1-aminopropane 214

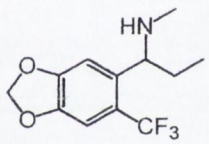


To an oven dried 25ml two neck round bottomed flask, fitted with a reflux condenser, was added CuI (0.498 g, 2.62 mmol), dry KF (0.153 g, 2.62 mmol) and N-Methyl-N-Trifluoroacetal-1-(3,4-Methylenedioxy-6-iodophenyl)-1- **192** (0.700 g, 1.68 mmol). The mixture was dissolved in anhydrous DMF and heated to 100^{0}C. Methylchlorodifluoroacetate (0.407 ml, 3.86 mmol) was injected over one hour. The reaction was heated to 120^{0}C for four hours after which time it was diluted with 100 ml of water and extracted with DCM (4 x 75 ml). The organic phase was filtered,

removing Cu salts, and washed with 10% HCl (3 x 75 ml). The solvent was dried over anhydrous Na_2SO_4 then removed under vacuum to leave a dark brown oil, which was columned on silica gel using a 90:10 hexane:diethylether mobile phase to give the title compound **214** as a brown oil (58%).

IRυ_{max} cm^{-1} (film): 1708, 1615 (C=O), 1038 (C-O), 1512, 886 (Ar). ^{1}H NMR ($CDCl_3$) δ: 0.95 (t, J=7.5 Hz, 3H, H3), 1.94-2.13 (m, 2H, H2), 2.82 (s, 3H, $NC\underline{H}_3$), 5.72 (t, J=7.6 Hz, 1H, H1), 6.10 (m, 2H, $OC\underline{H}_2O$), 7.12 (s, 1H, ArH5), 7.18 (s, 1H, ArH2). ^{13}C NMR ($CDCl_3$) δ: 10.70 (C3), 24.07 (C2), 30.44 (q, J=4.0 Hz, $NC\underline{H}_3$), 56.51 (C1), 102.43 ($OC\underline{H}_2O$), 107.30 (q, J=6.1 Hz, ArC6), 109.80 (ArC5), 116.53 (q, J=282.8 Hz, $CO\underline{C}F_3$), 123.74 (q, J=270.8 Hz, Ar-$\underline{C}F_3$), 130.21 (ArC1), 147.49 (ArC3), 150.35 (ArC4), 156.76 (q, J=35.5 Hz, $\underline{C}OCF_3$). LRMS: m/z (M^+-1) 356 (7), 328 (12), 288 (100). HRMS calculated for $C_{14}H_{13}F_3NO_3$: (M^+ + Na) 380.0697, found 380.0692.

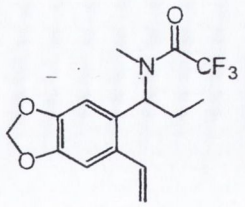
Methyl-[1-(6-trifluoromethyl-benzo[1,3]dioxol-5-yl)-propyl]-amine 215



Synthesised according to the general method described for the base hydrolysis of the TFA protecting group of **193**. (83%)

IRυ_{max} cm^{-1} (film): 3424 (N-H), 1039 (C-O), 1506, 859 (Ar). ^{1}H NMR (CD_3OD) δ: 0.86 (t, J=7.4 Hz, 3H, H3), 1.95-2.27 (2m, 2H, H2), 2.56 (s, 3H, $NC\underline{H}_3$), 4.38-4.41 (dd, J_1=10.0 Hz, J_2=4.3 Hz, 1H, H1), 6.21 (s, 2H, $OC\underline{H}_2O$), 7.29 (s, 1H, ArH5), 7.31 (s, 1H, ArH2). ^{13}C NMR (CD_3OD) δ: 10.10 (C3), 27.92 (C2), 31.78 ($NC\underline{H}_3$), 61.17 (C1), 104.43 ($OC\underline{H}_2O$), 107.49 (q, J=5.8 Hz, ArC6), 108.10 (ArC5), 123.55 (q, J=272.1 Hz, Ar$\underline{C}F_3$), 129.14 (ArC1), 150.34 (ArC3), 153.44 (ArC4). ^{19}F NMR (CD_3OD) δ: -57.07 (Ar$C\underline{F}_3$).

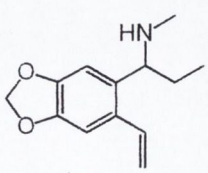
N-Methyl-N-Trifluoroacetal-1-(3,4-Methylenedioxy-6-ethenylphenyl)-1-aminopropane 195



N-Methyl-N-Trifluoroacetal-1-(3,4-Methylenedioxy-6-iodophenyl)-1- aminopropane **192** (1.000 g, 2.39 mmol) was dissolved in dry dioxane in a dry three neck 100 ml round bottomed flask. Pd[0]($(PPh_3)_4$) (0.140 g, 0.12 mmol) and tributylvinyltin (1.528 g, 4.77 mmol) was added and the reaction vessel was flushed with nitrogen. The mixture was refluxed for 100 hours, the solvent was removed under vacuum and the resulting residue was chromatographed directly on silica gel using a mobile phase of 80:20 hexane:diethylether to leave a yellow gummy solid that was recrystalised from ethanol to yield the title compound as yellow crystals (73%) m.p. 80-84°C.

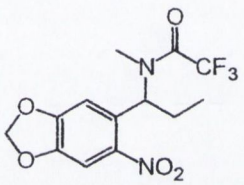
IRυ_{max} (KBr): 2983 (N-H), 1682 (C=O), 1503 (C=CH), 1253 (N-C) cm^{-1}, 1040 (C-O) cm^{-1}, 739 (ArCH) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.00 (t, J=7.5 Hz, 3H, H3), 1.90-2.02 (m, 2H, H2), 2.66 (s, 3H, $NC\underline{H}_3$), 5.23 (dd, J_v=9.5 Hz, J_g=1.5 Hz, 1H, CH=C$\underline{H}_2$, *cis*), 5.48 (dd, J_v=16.6 Hz, J_g=1.5 Hz, 1H, CH=C$\underline{H}_2$ *trans*), 5.77 (dt, J=7.0 Hz, 1H, H1), 6.00 (m, 2H, $OC\underline{H}_2O$), 6.79 (dd, J_{cis}=11.0 Hz, J_{trans}=17.0 Hz, 1H, C$\underline{H}$=CH_2), 6.86 (s, 1H, ArH5), 7.03 (s,1H, ArH2). ^{13}C NMR ($CDCl_3$) δ: 9.25 (C3), 23.10 (C2), 29.11 (q, J=4.2 Hz, $N\underline{C}H_3$), 55.46 (C1), 101.37 ($O\underline{C}H_2O$), 106.69 ($\underline{C}H=CH_2$), 107.52 (ArC5), 115.17 (CH=$\underline{C}H_2$), 115.55 (q, J=287.4 Hz, $CO\underline{C}F_3$), 127.93 (ArC1), 133.21 (ArC6), 133.67 (ArC2), 147.32 (ArC4), 147.59 (ArC3), 156.72 (q, J=36.5 Hz, $\underline{C}OCF_3$). m/z (M^+) 315 (70), 288 (28), 246 (38), 189 (100). HRMS calculated for $C_{15}H_{16}NO_3F_3$: (M^+ + Na) 338.0980, found 338.0977. Elemental analysis: $C_{15}H_{16}F_3NO_3$ requires C, 57.14; H, 5.12; N, 4.44. Found C, 56.84; H, 4.91; N, 4.32.

Methyl-[1-(6-vinyl-benzo[1,3]dioxol-5-yl)-propyl]-amine 196 isolated as a pale yellow oil according to the general procedure described in the synthesis of **193**. (75%).



IRυ_{max} cm^{-1} (film): 3436 (N-H), 1480 (C=CH), 1042 (C-O), 936 (ArCH). ^{1}H NMR ($CDCl_3$) δ: 0.83 (t, J=7.4 Hz, 3H, H3), 1.55-1.75 (m, 3H, H2, NH), 2.78 (s, 3H, $NC\underline{H}_3$), 3.80 (dd, J_1=6.9 Hz, J_2=6.7 Hz, 1H, H1), 3.81 (dd, J_v=10.9 Hz, J_g=1.3 Hz, 1H, CH=C$\underline{H}_2$, *cis*), 5.48 (dd, J_v=17.1 Hz, J_g=1.3 Hz, 1H, CH=C$\underline{H}_2$ *trans*), 6.00 (2d, J_v=1.2 Hz, 2H, $OC\underline{H}_2O$), 6.93 (s, 1H, ArH5), 6.97 (s,1H, ArH2), 7.02-7.09 (dd, J_{cis}=10.9 Hz, J_{trans}=17.2 Hz, 1H, C$\underline{H}$=CH_2). ^{13}C NMR ($CDCl_3$) δ: 10.55 (C3), 30.34 (C2), 34.36 ($N\underline{C}H_3$), 61.03 (C1), 100.89 ($O\underline{C}H_2O$), 105.54 ($\underline{C}H=CH_2$), 105.92 (ArC5), 114.35 (CH=$\underline{C}H_2$), 131.05 (ArC1), 134.18 (ArC6), 135.36 (ArC2), 146.36 (ArC4), 147.77 (ArC3). LRMS calculated for $C_{13}H_{17}NO_2$: (M^+) requires m/z: 219 (not observed), found 189, $C_{12}H_{13}O_2$ (M^+-30).

N-Methyl-N-Trifluoroacetal-1-(3,4-Methylenedioxy-6-Nitrophenyl)-1-aminopropane 185

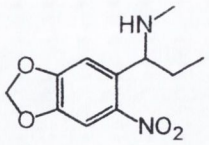


N-Methyl-N-Trifluoroacetal-1-(3,4-Methylenedioxyphenyl)-1-aminopropane **171** (2.000 g, 6.90 mmol) was dissolved in glacial acetic acid solution was cooled in an ice bath. 65% HNO_3 was added dropwise followed by the addition of a catalytic amount of sodium nitrite (65 mg). The reaction was stirred for three hours. Work up involved dilution with 150 ml water and extraction with DCM (4 x 75 ml). Organic phase was washed with $NaHCO_3$ (3 x 75 ml), dried over anhydrous sodium sulphate and removed under vacuum leaving a yellow oil that was purified on silica gel using a 60:40 hexane:diethylether mobile phase to leave the title compound as a yellow oil that solidifeid on standing (88%).

IRυ_{max} cm^{-1} (film): 1680, 1650 (C=O), 1519, 1347 (NO_2), 1096 (C-O). ^{1}H NMR ($CDCl_3$) δ: 1.02 (t, J=7.5$_{ave}$ Hz, 3H, H3), 1.93-2.19 (m, 2H, H2), 3.00 (s, 3H, $NC\underline{H}_3$), 5.75 (t, J=8.0 Hz, 1H, H1), 6.15 (s, 2H, $OC\underline{H}_2O$), 6.99 (s, 1H, ArH5,), 7.37 (s, 1H, ArH2). ^{13}C NMR ($CDCl_3$) δ: 10.94 (C3), 24.07 (C2), 32.55 (q, J=3.9 Hz, $N\underline{C}H_3$), 57.05 (C1), 103.11 ($O\underline{C}H_2O$), 105.85 (ArC5), 107.58 (ArC2), 116.36 (q, J=287.0 Hz, $\underline{C}F_3$), 144.67 (ArC1), 147.48 (ArC3), 151.28 (ArC4), 155.10 (q, J=35.0 Hz, $\underline{C}OCF_3$).

^{19}F NMR ($CDCl_3$) δ: -70.403 ($COC\underline{F}_3$). LRMS calculated for $C_{13}H_{14}F_3NO_5$: (M^+) requires m/z: 335, found 335.

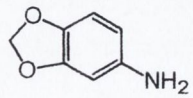
Methyl-[1-(6-nitro-benzo[1,3]dioxol-5-yl)-propyl]-amine 186



To a stirred solution of N-Methyl-N-Trifluoroacetal-1-(3,4-Methylenedioxy-6-Nitrophenyl)-1-aminopropane **185** (0.528 g, 1.60 mmol) in methanol (20 ml) was added water, dropwise (8 ml) until the start material was about to fall out of solution. A further 2 ml of methanol was added. K_2CO_3 was added in portions until the pH of the solution was at pH-10-11. The clear solution was stirred at room temperature for 4 days. The solution was made acidic with 10% HCl, extracted with diethyl ether (3 x 50 ml), basified to pH-9 with 15% NaOH and extracted with DCM (3 x 100 ml). The DCM extracts were dried over anhydrous Na_2SO_4, filtered and removed *in vacuo* to leave a colourless oil (96%) which was columned on a short silica column using a 100% methanol mobile phase.

IRυ_{max} cm^{-1} (film): 3235 (N-H), 1522, 1346 (NO_2), 1044 (C-O). ^1H NMR ($CDCl_3$) δ: 0.91 (t, J=7.3$_{ave}$ Hz, 3H, H3), 1.58 (s, 1H, NH), 1.62-1.76 (m, 2H, H2), 2.24 (s, 3H, $NC\underline{H}_3$), 5.75 (t, J=6.5 Hz, 1H, H1), 6.08 (2d, J=1.5 Hz, 2H, $OC\underline{H}_2O$), 7.17 (s, 1H, ArH5,), 7.32 (s, 1H, ArH2). ^{13}C NMR ($CDCl_3$) δ: 10.57 (C3), 30.35 (C2), 34.43 ($N\underline{C}H_3$), 60.68 (C1), 102.58 ($O\underline{C}H_2O$), 105.73 (ArC5), 106.91 (ArC2), 136.48 (ArC1), 144.17 (ArC6), 146.37 (ArC3), 151.75 (ArC4). HRMS m/z calculated for $C_{11}H_{15}N_2O_4$ ($M^+ + H^+$) 239.1032, found 239.1039.

Benzo[1,3]dioxol-5-ylamine 187

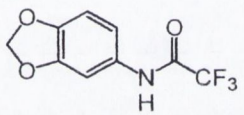


5-Nitro-benzo[1,3]dioxole (1.200 g, 7.2 mmol) was partially soluble in ethanol (60 ml), 10% Pd/C (0.2 g) added and the flask was flushed with H_2. The reaction was

stirred for 1 hour afterwhich TLC showed complete consumption of start material. The Pd/C catalyst was removed by filtration through a celite cake. The filtrate was collected and removed *in vacuo*. The product was chromatographed on silica gel using an initial mobile phase of 60:40 hexane:diethyl ether with a gradient towards a final mobile phase of 70:30 ether:hexane to yield the product as a dark grey solid (68%). 44-46°C. (lit. 44-46°C)[6]

IRυ_{max} cm^{-1} (film): 3328 (NH), 1039 (C-O), 877 (Ar). ^{1}H NMR ($CDCl_3$) δ: 3.49 (s, 2H, NH_2), 5.87 (s, 2H, OCH_2O), 6.14 (dd, J_o=8.3 Hz, J_m=2.5 Hz, 1H, ArH1), 6.30 (d, J_m=2.5 Hz, 1H, ArH5), 6.63 (d, J_o=8.1 Hz, 1H, ArH2). ^{13}C NMR ($CDCl_3$) δ: 97.90 (ArC5), 100.52 (OCH_2O), 106.69 (ArC1), 108.44 (ArC2), 140.15 (ArC3), 141.35 (ArC6), 148.06 (ArC4).

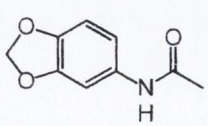
N-Benzo[1,3]dioxol-5-yl-2,2,2-trifluoro-acetamide 187b



General method for TFA protection as used in the synthesis of **171**. Benzo[1,3]dioxol-5-ylamine (1.300 g, 10.66 mmol), TFAA (3.16 ml, 22.38 ml) and triethyl amine (4 ml). M.p. 116-120 (lit 117-119)[7] (95%)

IRυ_{max} cm^{-1} (film): 1680, 1650 (C=O), 1519, 1347 (NO_2), 1096 (C-O). ^{1}H NMR ($CDCl_3$) δ: 6.01 (s, 2H, OCH_2O), 6.79 (d, J_o=8.0 Hz, 1H, ArH2), 6.90 (dd, J_o=8.0 Hz, J_m=2.0 Hz, 1H, ArH1), 7.21 (d, J_m=2.0 Hz, 1H, ArH5), 8.09 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 101.66 (OCH_2O), 103.00 (ArC5), 108.23 (ArC1), 114.20 (ArC2), 115.78 (q, J=288.64 Hz, CF_3), 128.94 (ArC6), 145.83 (ArC3), 148.05 (ArC4), 155.02 (q, J=37.91 Hz, $\underline{C}OCF_3$). ^{19}F NMR ($CDCl_3$) δ: -76.18 ($COC\underline{F}_3$).

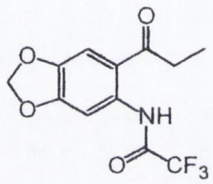
N-Benzo[1,3]dioxol-5-yl-acetamide 187a



Procedure carried out as described for TFA protection (Benzo[1,3]dioxol-5-ylamine **187**(0.728 g, 5.31 mmol), acetic anhydride (1.003 ml, 10.63 mmol), triethyl amine (1.48 ml, 10.63 mmol). 92% m.p. 122-125 (lit. 125)[8]

IRυ_{max} (KBr): 3327 (N-H), 1662 (C=O), 1237 (N-C) cm^{-1}, 1237, 1039 (C-O) cm^{-1}, 734 (ArCH) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.14 (s, 3H, $COCH_3$), 5.94 (s, 2H, OCH_2O), 6.72 (d, J_o=8.5 Hz, 1H, ArH2), 6.79 (dd, J_o=8.0 Hz, J_m=2.0 Hz, 1H, ArH1), 7.19 (d, J_m=2.0 Hz, 1H, ArH5), 7.67 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 24.24 ($CO\underline{C}H_3$), 101.18 (OCH_2O), 103.04 (ArC5), 107.93 (ArC1), 113.33 (ArC2), 132.06 (ArC6), 144.21 (ArC3), 147.65 (ArC4), 168.53 ($\underline{C}OCH_3$).

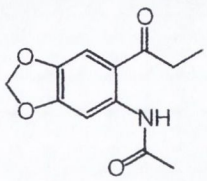
2,2,2-Trifluoro-N-(6-propionyl-benzo[1,3]dioxol-5-yl)-acetamide 188b



N-Benzo[1,3]dioxol-5-yl-2,2,2-trifluoro-acetamide **187b** (1.228 g, 5.27 mmol) was dissolved in dry 50 ml DCM, under a nitrogen atmosphere $SnCl_4$ (1.36 ml, 11.60 mmol) was added dropwise. The contents of the RBF were adjusted to 0°C with an ice bath and the propionyl chloride (1.15ml, 13.18 mmol) was added dropwise. The reaction was left to stir for 12 hours at rt. Reaction was then poured slowly onto crushed ice. The product was extracted with DCM (3 x 100 ml). The organic layer was washed with brine (4 x 100 ml), dried over anhydrous Na_2SO_4, filtered and removed *in vacuo* to give a yellow solid that was recrystallised from hot ethyl acetate to give a pale yellow solid in 68% yield.

IRυ_{max} (KBr): 3424 (N-H), 1721, 1651 (C=O), 1226 (CF_3), 1038 (C-O) cm^{-1}, 1514, 822 (Ar) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.24 (t, J_{ave}=7.1 Hz, 3H, H3), 3.00 (q, J_{ave}=7.1 Hz, 2H, H2), 6.11 (s, 2H, OCH_2O), 7.40 (s, 1H, ArH5), 8.30 (s, 1H, ArH2), 13.43 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 8.36 (C3), 33.12 (C2), 101.99 (OCH_2O), 102.55 (ArC5), 108.83 (ArC2), 115.64 (q, J=288.7 Hz, CF_3), 116.06 (ArC6), 136.09 (ArC3), 144.19 (ArC4), 152.66 (ArC1), 155.58 (q, J=37.90, $\underline{C}OCF_3$), 203.75 ($\underline{C}OCH_2$). ^{19}F NMR ($CDCl_3$) δ: 76.68 ($COC\underline{F}_3$). LRMS calculated for $C_{12}H_{10}F_3NO_4$: (M^+) requires m/z: 289, found 289.

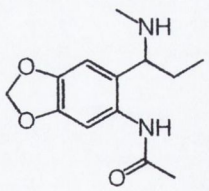
N-(6-Propionyl-benzo[1,3]dioxol-5-yl)-acetamide 188a



Proceedure carried out as described for the TFA analouge. N-Benzo[1,3]dioxol-5-yl-acetamide **188b** (0.358 g, 2.00 mmol), $SnCl_4$ (0.468 ml, 4.00 mmol), propionyl chloride (0.348 ml, 4.00 mmol). The product was purified on silica gel 60:40 diethyl ether:hexane mobile phase (32%)

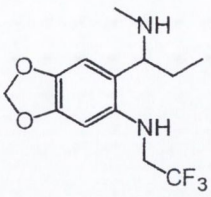
IRυ_{max} (film): 3447 (N-H), 1686 (C=O), 1200 (N-C) cm^{-1}, 1040 (C-O) cm^{-1}, 813 (ArCH) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.21 (t, J_{ave}=7.3 Hz, 3H, H3), 2.23 (s, 3H, $COCH_3$), 2.95 (q, J_{ave}=7.3 Hz, 2H, H2), 6.03 (s, 2H, OCH_2O), 7.30 (s, 1H, ArH5), 8.37 (s, 1H, ArH2), 12.18 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 8.50 (C3), 25.47 ($CO\underline{C}H_3$), 33.08 (C2), 101.54 (OCH_2O), 102.01 (ArC5), 108.60 (ArC2), 114.75 (ArC6), 138.99 (ArC3), 142.44 (ArC4), 152.54 (ArC1), 169.62 ($N\underline{C}O$), 203.17 ($\underline{C}OCH_2$). LRMS calculated for $C_{12}H_{13}NO_4$: (M^+) requires m/z: 235, found 235.

N-[6-(1-Methylamino-propyl)-benzo[1,3]dioxol-5-yl]-acetamide. 189 Isolated as a yellow oil in 28% yield via method described for **193**.



IRυ_{max} (film): 3434 (N-H), 1638 (C=O), 1035 (C-O) cm^{-1}, 932 (ArCH) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.80 (t, J_{ave}=7.2 Hz, 3H, H3), 1.51-1.84 (m, 2H, H2), 2.16 (s, 3H, $COCH_3$), 2.51 (s, 1H, NH), 3.05 (s, 3H, NCH_3), 4.29 (dd, J_1=6.1 Hz, J_2=3.4 Hz, 1H, H1), 5.90 (s, 2H, OCH_2O), 6.35 (s, 1H, ArH2), 6.62 (s, 1H, ArH5). ^{13}C NMR ($CDCl_3$) δ: 7.88 (C3), 21.88 ($CO\underline{C}H_3$), 27.81 (C2), 37.15 (NCH_3), 62.10 (C1), 100.66 (OCH_2O), 103.83 (ArC2), 104.84 (ArC5), 116.14 (ArC1), 137.42 (ArC6), 143.76 (ArC3), 146.98 (ArC4), 155.79 ($N\underline{C}O$). M^+ not observed in HRMS.

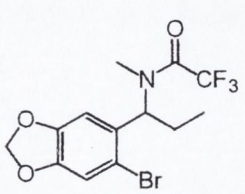
[6-(1-Methylamino-propyl)-benzo[1,3]dioxol-5-yl]-(2,2,2-trifluoro-ethyl)-amine 191



2,2,2-Trifluoro-N-(6-propionyl-benzo[1,3]dioxol-5-yl)-acetamide **188b** (0.455 g, 1.57 mmol) was stirred in dry methanol (20 ml), to which methylamine HCl (0.850 g, 12.59 mmol) and $NaCNBH_3$ (0.141 g, 2.24 mmol) was added. The mixture was stirred under a nitrogen atmosphere for 4 days. The reaction pH was maintained at pH 5-6 using methanolic HCl. The reaction was quenched by the addition of 10% HCl_{aq}, basified with 15% NaOH (to pH 8) and extracted with DCM (4 x 50 ml). The organic extracts were combined, dried over anhydrous Na_2SO_4, filtered and removed *in vacuo*. The resulting oil was purified on silica gel to yield the product as a pale yellow oil (36%).

IRυ_{max} (film): 3437 (N-H), 1039 (C-O) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.85 (t, J_{ave}=7.3 Hz, 3H, H3), 1.62-1.93 (m, 2H, H2), 1.51 (s, 1H, NH), 2.31 (s, 3H, NCH_3), 3.39 (dd, J_1=8.5 Hz, J_2=6.0 Hz, 1H, H1), 3.67 (2d, J=9.0 Hz, 2H, NCH_2CF_3), (s, 2H, OCH_2O), 6.31 (s, 1H, ArH5), 6.51 (s, 1H, ArH2), 7.62 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 11.38 (C3), 26.81 (C2), 34.01 (NCH_3), 45.90 (q, J=33.0 Hz, $\underline{C}H_2CF_3$), 68.94 (C1), 93.84 (ArC5), 100.53 (OCH_2O), 110.95 (ArC2), 117.05 (ArC1), 125.32 (q, J=280.9 Hz, CF_3), 138.78 (ArC3), 141.64 (ArC6), 147.26 (ArC4). LRMS calculated for $C_{13}H_{17}F_3N_2O_2$: (M^+) requires m/z: 290 (not observed), found m/z 260, $C_{12}H_{13}F_3NO_2$ (M^+-30).

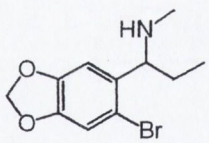
N-Methyl-N-Trifluoroacetal-1-(3,4-Methylenedioxy-6-Bromophenyl)-1-aminopropane 174



N-Methyl-N-Trifluoroacetal-1-(3,4-Methylenedioxyphenyl)-1-aminopropane **171** (1.800 g, 6.20 mmol) was dissolved in glacial acetic acid to which was added, dropwise, Br_2 (1.000 g, 7.44 mmol) dissolved in glacial acetic acid. Reaction mixture was stirred overnight and subsequently diluted with 150 ml water and extracted with DCM (4 x 75 ml). The organic extracts were then washed with a solution of saturated $NaHCO_3$ (4 x 75 ml). The solvent was removed under vacuum yielding a dark brown solid which was purified on silica gel with a 60:40 hexane:diethylether mobile phase to leave a fawn solid, which was recrystallised from ethanol to yield the title compound in 84% yield as pale brown crystals m.p 69-70°C.

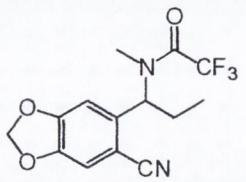
IRυ_{max} (KBr-HCl salt) cm^{-1}: 2939 (C-C), 1692 (C=O), 1242, 1034 (C-O), 926 (ArCH). ^1H NMR ($CDCl_3$) δ: 1.00 (t, J=7.5 Hz, 3H, H3), 1.92-2.01 (m, 2H, H2), 2.75 (s, 3H, $NC\underline{H}_3$), 5.58 (t, J=7.5 Hz, 1H, H1), 6.03 (s, 2H, $OC\underline{H}_2O$), 6.92 (s, 1H, ArH5,), 7.09 (s, 1H, ArH2). ^{13}C NMR ($CDCl_3$) δ: 10.64 (C3), 23.35 (C2), 29.61 (q, J=4.1 Hz, $N\underline{C}H_3$), 59.55 (C1), 101.86 ($O\underline{C}H_2O$), 109.18 (ArC5), 117.94 (q, J= 288.2 Hz, $\underline{C}F_3$), 113.66 (ArC2), 116.86 (ArC6), 129.08 (ArC1), 147.53 (ArC4), 148.19 (ArC3), 157.00 (q, J=35.5 Hz, $\underline{C}OCF_3$). ^{19}F NMR ($CDCl_3$) δ: -70.30 (CF_3). HRMS calculated for $C_{13}H_{13}BrF_3NO_3$: (M^+ + Na) 389.9929, found 389.9930.

[1-(6-Bromo-benzo[1,3]dioxol-5-yl)-propyl]-methyl-amine **175** synthesised according to the general procedure described in the synthesis of **193**. purified on a short silica gel column using 100% methanol mobile phase (57%).



IRυ_{max} (KBr-HCl salt) cm^{-1}: 2927 (N-H), 2476, 1497 (C-C), 1246, 1035 (C-O), 924, 846 (ArCH). ^1H NMR ($CDCl_3$) δ: 1.03 (t, J=7.4 Hz, 3H, H3), 1.73-1.82 (m, 3H, H2, NH), 2.32 (s, 3H, $NC\underline{H}_3$), 3.81 (dd, J_1=6.0 Hz, J_2=5.9 Hz, 1H, H1), 6.01 (2d, J=1.3 Hz, 2H, $OC\underline{H}_2O$), 6.92 (s, 1H, ArH5), 7.12 (s, 1H, ArH2). ^{13}C NMR ($CDCl_3$) δ: 10.57 (C3), 24.17 (C2), 33.20 ($N\underline{C}H_3$), 61.11 (C1), 102.03 (OCH_2O), 107.41 (ArC5), 116.42 (ArC6), 113.57 (ArC2), 128.12 (ArC1), 147.53 (ArC4), 148.19 (ArC3). Elemental analysis (HCl salt): $C_{11}H_{15}BrClNO_2$ requires C, 42.81; H, 4.90; N, 4.54. Found C, 42.36; H, 4.69; N, 4.29.

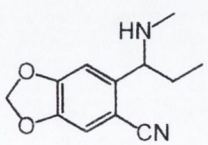
N-Methyl-N-Trifluoroacetal-1-(3,4-Methylenedioxy-6-Cyanophenyl)-1-aminopropane 183



N-Methyl-N-Trifluoroacetal-1-(3,4-Methylenedioxy-6-Bromophenyl)-1- aminopropane **174** (0.600 g, 1.63 mmol) was dissolved in anhydrous DMF (20 ml) in an oven dried 100 ml three-neck round bottomed flask. Cu(I)CN (0.365 g, 4.08 mmol) was added with caution and the reaction, under a nitrogen atmosphere, was refluxed for six hours. 200 ml DCM was added and the organic phase was filtered and washed thoroughly with water (6 x 500 ml). The volatiles were removed under vacuum and the remaining oil was purified by flash chromatography using a mobile phase of 60:40 hexane:diethylether to leave the title compound as a pale yellow oil (38%)

IRυ_{max} (Film) 2224 (C≡N) cm^{-1}, 1686 (C=O) cm^{-1}, 1246, 1038 (C-O) cm^{-1}, 893 (Ar) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.03 (t, J=7.5 Hz, 3H, H3), 2.01-2.19 (m, 2H, H2), 2.99 (s, 3H, $NC\underline{H}_3$), 5.44 (t, J=7.3$_{ave}$ Hz, 1H, H1), 6.11 (s, 2H, $OC\underline{H}_2O$), 7.04 (s, 1H, ArH5,) 7.07 (s, 1H, ArC2). ^{13}C NMR ($CDCl_3$) δ: 10.75 (C3), 23.42 (C2), 31.66 ($N\underline{C}H_3$), 60.07 (C1), 102.70 (OCH_2O), 108.99 (ArC6), 112.37 (ArC2), 117.35 ($\underline{C}\equiv N$), 117.82 (ArC5), 138.27 (ArC1), 147.37 (ArC4), 151.76 (ArC3). ^{19}F NMR ($CDCl_3$) δ: -70.37 ($COC\underline{F}_3$). HRMS calculated for $C_{14}H_{13}F_3N_2O_3$: (M^+ + Na) 337.0776, found 337.0775.

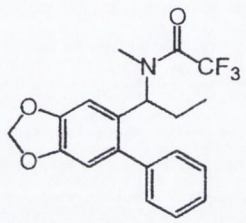
6-(1-Methylamino-propyl)-benzo[1,3]dioxole-5-carbonitrile 184. Synthesised according to the general procedure described in the synthesis of **193**. Isolated in 28% yield as a yellow oil from the basic deprotection of N-Methyl-N-Trifluoroacetal-1-(3,4-Methylenedioxy-6-Cyanophenyl)-1-aminopropane **183**.



IRυ_{max} cm^{-1} (Film): 2222 (C≡N) cm^{-1}, 1040 (C-O) cm^{-1}, 863 (Ar) cm^{-1}. ^{1}H NMR (CD_3OD) δ: 0.56 (t, J=7.5 Hz, 3H, H3), 2.09-2.26 (m, 2H, H2), 2.92 (s, 3H, $NC\underline{H}_3$),

3.32-3.34 (m, 1H, H1), 6.25 (s, 2H, $OC\underline{H}_2O$), 7.16 (s, 1H, ArH5,) 7.54 (s, 1H, ArC2). ^{13}C NMR (CD_3OD) δ: 7.34 (C3), 26.71 (C2), 29.91 ($N\underline{C}H_3$), 51.71 (C1), 102.53 (ArC6), 103.62 (ArC2), 104.75 (ArC5), 104.95 (OCH_2O), 122.41 ($\underline{C}\equiv N$), 140.44 (ArC1), 151.91 (ArC4), 155.74 (ArC3).

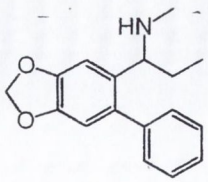
2,2,2-Trifluoro-N-methyl-N-[1-(6-phenyl-benzo[1,3]dioxol-5-yl)-propyl]-acetamide 176



To N-Methyl-N-Trifluoroacetal-1-(3,4-Methylenedioxy-6-Bromophenyl)-1-aminopropane **174** (0.600 g, 1.63 mmol) under a nitrogen atmosphere in dry THF (30 ml) was added $Pd[0](PPh_3)_4$ (0.094 g, 0,082 mmol). After 20 minutes stirring, $PhB(OH)_2$ (0.457 g, 3.75 mmol) and 2M aq Na_2CO_3 (5 ml) was added. The reaction was refluxed with stirring for 6 hours. The solvent was allowed to cool to room temperature and was diluted with 100 ml water. The aqueous mixture was then extracted with DCM (4 x 74 ml), the DCM dried over anhydrous Na_2SO_4, filtered and removed *in vacuo* to leave a dark brown oil. The product was purified on silica gel using a mobile phase of 85:15 hexane:diethyl ether, yielding a clear oil 66%.

IRυ_{max} cm^{-1} (Film): 2870 (CH), 1693 (C=O), 1483, 1040 (C-O). ^1H NMR ($CDCl_3$) δ: 0.91 (t, J=7.3$_{ave}$ Hz, 3H, H3), 1.81-2.01 (m, 2H, H3), 2.66 (s, 3H, $NC\underline{H}_3$), 5.42 (t, J=8.0 Hz, 1H, H1), 6.05 (s, 2H, OCH_2O), 6.74 (s, 1H, ArH5), 6.98 (s, 1H, ArH2), 7.15 (m, 2H, ArH2*/6*), 7.35-7.40 (m, 3H, ArH3*/5*, ArH4*). ^{13}C NMR ($CDCl_3$) δ: 10.68 (C3), 23.24 (C2), 29.60 ($N\underline{C}H_3$), 56.70 (C1), 101.41 (OCH_2O), 107.82 (ArC2), 111.02 (ArC5), 114.92 (q, J=288.6 Hz, CF_3), 127.44 (ArC4*), 127.95 (ArC6), 128.36 (ArC2*/6*), 128.55 (ArC3*/5*), 138.38 (ArC1), 140.12 (ArC1*), 146.89 (ArC4), 146.97 (ArC3), 158.32 (q, J=35.2 Hz, $\underline{C}OCF_3$). ^{19}F NMR ($CDCl_3$) δ: -70.18 ($COC\underline{F}_3$). HRMS calculated for $C_{19}H_{18}F_3NO_3$: (M^+ + Na) 388.1136, found 388.1131.

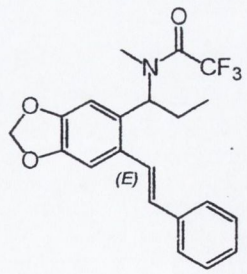
Methyl-[1-(6-phenyl-benzo[1,3]dioxol-5-yl)-propyl]-amine.177 Prepared according to the general procedure described in the synthesis of **193**. The title compound was isolated as a clear oil in 84% yield.



IRυ_{max} cm^{-1} (Film): 3414 (NH), 2870 (CH), 1141 (CH), 1484, 1037 (C-O), 932 (Ar). ^{1}H NMR ($CDCl_3$) δ: 0.82 (t, J=7.5 Hz, 3H, H3), 1.91-2.13 (m, 2H, H2), 2.32 (s, 3H, NCH_3), 5.42 (dd, J_1=10.2 Hz, J_2=4.8 Hz, 1H, H1), 6.05 (s, 2H, OCH_2O), 6.73 (s, 1H, ArH5), 7.17 (m, 2H, ArH2*/6*), 6.25 (s, 1H, ArH2), 7.43 (m, 3H, ArH3*/5*, ArH4*). ^{13}C NMR ($CDCl_3$) δ: 10.03 (C3), 26.84 (C2), 30.34 (NCH_3), 60.31 (C1), 101.41 (OCH_2O), 104.89 (ArC2), 110.17 (ArC5), 124.85 (ArC6), 127.62 (ArC2*/6*), 128.46 (ArC3*/5*), 129.28 (ArC4*), 138.05 (ArC1), 139.57 (ArC1*), 147.66 (ArC4), 148.32 (ArC3). LRMS calculated for $C_{17}H_{19}NO_2$: (M^+) requires m/z: 269 (not observed), found m/z 239, $C_{16}H_{15}F_3O_2$ (M^+-30).

2,2,2-Trifluoro-N-methyl-N-[1-(6-styryl-benzo[1,3]dioxol-5-yl)-propyl]-acetamide 182

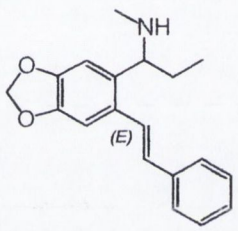
The proceedure for the synthesis of 2,2,2-Trifluoro-N-methyl-N-[1-(6-phenyl-benzo[1,3]dioxol-5-yl)-propyl]-acetamide **176** was used with the iodide **193** (0.176g, 0.42mmol), the phenylvinylboronic acid (0.126g, 0.85mmol), 0.42 ml of a 2M $_{aq}Na_2CO_3$ solution with 10 mol% Pd[0](PPH_3)$_4$ in dry THF under a nitrogen atmosphere. The product was isolated as colourless needles (73%) 118-122°C.



IRυ_{max} cm^{-1} (Film): 2878 (CH), 1644 (C=O), 1143 (C-O), 972 (Ar). ^{1}H NMR ($CDCl_3$) δ: 1.05 (t, J=7.5 Hz, 3H, H3), 1.95-2.06 (m, 2H, H2), 2.68 (s, 2.65H, NCH_3), 5.95 (t, J=7.5 Hz, 1H, H1), 6.03 (s, 2H, OCH_2O), 6.83 (d, J_{trans}=16.0 Hz, 1H, CH=C<u>H</u>C_6H_5), 6.90 (s, 1H, ArH5), 7.19 (s, 1H, ArH2), 7.25 (m, 1H, ArH4*), 7.26 (d, J_{trans}=16.0 Hz, 1H, C<u>H</u>=CHC_6H_5), 7.37 (dd, J_1=8.2 Hz, J_2=7.9 Hz, 2H, ArH3*/5*), 7.51 (d, J_o=7.5 Hz,

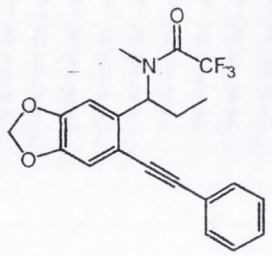
2H, ArH2*/6*). ^{13}C NMR ($CDCl_3$) δ: 10.67 (C3), 23.19 (C2), 28.72 (NCH_3), 55.50 (C1), 101.44 (OCH_2O), 106.30 (ArC5), 107.76 (ArC2), 119.91 (q, J=290.0 Hz, CF_3), 124.72 (CH=$\underline{C}HC_6H_5$), 126.70 (ArC2*/6*), 127.64 (ArC4*), 128.38 (ArC6), 128.65 (ArC3*/5*), 130.36 ($\underline{C}H=CHC_6H_5$), 132.59 (ArC1), 136.93 (ArC1*), 147.22 (ArC4), 147.71 (ArC3), 158.32 (q, J=35.2 Hz, $\underline{C}OCF_3$). ^{19}F NMR ($CDCl_3$) δ: -70.44 ($COCF_3$). Elemental analysis: $C_{21}H_{20}F_3NO_3$ requires C, 64.44; H, 5.15; N, 3.58. Found C, 64.15; H, 4.98; N, 3.47.

Methyl-[1-(6-styryl-benzo[1,3]dioxol-5-yl)-propyl]-amine.182a Prepared according to the general procedure described in the synthesis of **193**. Isolated in 28% yield, as a light brown coloured oil, from the basic deprotection of 2,2,2-Trifluoro-N-methyl-N-[1-(6-styryl-benzo[1,3]dioxol-5-yl)-propyl]-acetamide **182**.



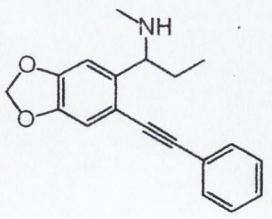
IRυ_{max} cm^{-1} (Film): 3435 (N-H), 1449 (C=C), 1040 (C-O). ^1H NMR (CD_3OD) δ: 0.82 (t, J_{ave}=7.3 Hz, 3H, H3), 1.74-2.05 (m, 2H, H2), 2.39 (s, 3H, NCH_3), 4.32 (m, 1H, H1), 6.01 (s, 2H, OCH_2O), 6.87 (d, J_{trans}=15.4 Hz, 1H, CH=C$\underline{H}C_6H_5$), 6.95 (s, 1H, ArH5), 7.10 (s, 1H, ArH2), 7.14 (d, J_{trans}=15.4 Hz, 1H, $\underline{C}H=CHC_6H_5$), 7.25 (m, 1H, ArH4*), 7.42-7.53 (m, 4H ArC2*/C6*, ArC3*/C5*). ^{13}C NMR (CD_3OD) δ: 8.76 (C3), 27.33 (C2), 30.78 (NCH_3), 59.35 (C1), 101.04 (OCH_2O), 104.52 (ArC5), 105.22 (Ar2), 124.72 (CH=$\underline{C}HC_6H_5$), 126.70 (ArC2*/6*), 127.64 (ArC4*), 128.38 (ArC6), 128.65 (ArC3*/5*), 130.36 ($\underline{C}H=CHC_6H_5$), 131.92 (ArC1), 136.89 (ArC1*), 147.46 (ArC4), 147.98 (ArC3).

2,2,2-Trifluoro-N-methyl-N-[1-(6-phenylethynyl-benzo[1,3]dioxol-5-yl)-propyl]-acetamide.211 Prepared *via* the general method for Sonogashira coupling as described in the synthesis of **210** and purified using flash chromatography with a 70:30 hexane:diethyl ether eluent to leave the title compound as a light brown oil (that solidified on standing) in 87% yield.



IRυ_{max} (film): 1696 (C=O), 1240 (N-C) cm^{-1}, 1039 (C-O) cm^{-1}, 757 (ArCH) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.98 (t, J=7.2$_{ave}$ Hz, 0.98H, H3 [R2]), 1.04 (t, J=7.2$_{ave}$ Hz, 1.92H, H3 [R1]), 1.85-2.07 (m, 2H, H2), 2.76 (s, 1.88H, NCH_3 [R1]), 2.79 (s, 1.09H, NCH_3 [R2]), 5.65 (dd, J_1=6.2 Hz, J_2=9.6 Hz, 0.35H, H1 [R2]), 5.88 (dd, J_1=7.5 Hz, J_2=7.4 Hz, 0.65H, H1 [R1]) 5.98 (s, 0.70H, OCH_2O [R2]), 6.04 (s, 1.30H, OCH_2O [R1]), 6.80 (s, 1H, ArH5), 6.93 (s, 0.68H, ArH2 [R1]), 7.07 (s, 0.35H, ArH2 [R2]), 7.32 (m, 3H, ArH4*, ArH3*/5*), 7.55-7.58 (m, 2H, ArH2*/6*). ^{13}C NMR ($CDCl_3$) δ: 10.52 (C3 [R2]), 10.71 (C3 [R1]), 22.14 (C2 [R2]), 23.02 (C2 [R1]), 28.52 (NCH_3 [R2]), 29.73 (NCH_3 [R1]), 58.01 (C1 [R1]), 58.23 (C1 [R2]), 86.50 (C≡$\underline{C}C_6H_5$), 93.97 ($\underline{C}$≡CC_6H_5), 101.17 (OCH_2O [R2]), 101.30 (OCH_2O [R1]), 108.20 (ArC2 [R1]), 108.29 (ArC2 [R2]), 112.82 (ArC5), 118.15 (ArC6), 119.41 (q, J=270.2 Hz, CF_3), 121.13 (ArC4*), 122.80 (ArC1*), 128.18 (ArC3*/5*), 131.69 (ArC2*/6*), 133.42 (C5), 147.01 (ArC4), 148.00 (ArC3). ^{19}F NMR ($CDCl_3$) δ: -70.25 ($COCF_3$ [R1]), -70.07 ($COCF_3$ [R2]). Elemental analysis: $C_{21}H_{18}F_3NO_3$ requires C, 64.78; H, 4.66; N, 3.60. Found C, 64.72; H, 4.66; N, 3.60.

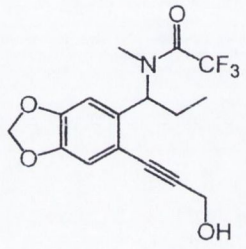
Methyl-[1-(6-phenylethynyl-benzo[1,3]dioxol-5-yl)-propyl]-amine 213 Isolated in 23% yield, as a light brown coloured oil, from the basic deprotection of 2,2,2-Trifluoro-N-methyl-N-[1-(6-phenylethynyl-benzo[1,3]dioxol-5-yl)-propyl]-acetamide **211**.



IRυ_{max} cm^{-1} (film): 3748 (N-H), 1590 (Ar), 1053 (C-O). ^1H NMR (CD_3OD) δ: 0.83 (t, J=7.5 Hz, 3H, H3), 1.64-1.96 (m, 2H, H2), 2.31 (s, 3H, NCH_3), 3.49 (dd, J_1=9.6 Hz, J_2=5.5 Hz, 1H, H1), 6.09 (s, 2H, OCH_2O), 6.88 (s, 1H, ArH5), 6.93 (s, 1H, ArH2),

7.34 (m, 3H, ArH4*, ArH3*/5*), 7.52 (m, 2H, ArH*2/6*). ^{13}C NMR (CD_3OD) δ: 10.92 (C3), 29.83 (C2), 33.38 (NCH_3), 67.30 (C1), 84.00 ($C{\equiv}\underline{C}C_6H_5$), 94.21 ($\underline{C}{\equiv}CC_6H_5$), 103.29 ($OCH_2O$), 105.65 (ArC2), 108.47 (ArC5), 117.30 (ArC6), 124.21 (ArC1*), 125.55 (ArC4*), 129.59 (ArC3*/5*), 132.50 (ArC2*/6*), 133.54 (ArC1), 149.58 (ArC4), 149.85 (ArC3). LRMS calculated for $C_{19}H_{19}NO_2$: (M^+) requires m/z: 293 (not observed), found m/z 263, $C_{16}H_{15}F_3O_2$ (M^+-30).

2,2,2-trifluoro-N-{1-[6-(3-hydroxy-prop-1-ynyl)-benzo[1,3]dioxol-5-yl]-propyl}-N-methyl-acetamide 210

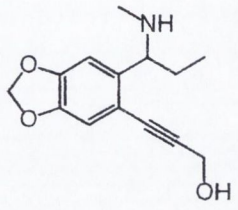


The start material N-Methyl-N-Trifluoroacetal-1-(3,4-Methylenedioxy-6-iodophenyl)-1- aminopropane **192** (1.500 g, 3.62 mmol) and reagents: $Pd(PPh_3)_4$ (0.209 g, 0.18 mmol), CuI (0.090 g, 0.45 mmol), propargyl alcohol (0.526 ml, 9.04 mmol) and triethylamine (50 ml, 357.00 mmol) were placed in an oven dried 100 ml three neck round bottomed flask, flushed with nitrogen and fitted with a reflux condenser. The mixture was refluxed for 15 hours and allowed to cool to room temperature. The volatiles were removed under vacuum and the contents of the flask were chromatographed on silica gel using a 50:50 hexane:diethylether mobile phase, the resulting solid was recrystallised from hexane/DCM (85:15) to yield the title product as fawn crystals (39%) m.p. 98-100°C.

IRυ_{max} (KBr) 3474 (O-H) cm^{-1}, 2350 (C≡C) cm^{-1}, 1669 (C=O) cm^{-1}, 1252, 1208 (C-O) cm^{-1}, 1489 (N-C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.00 (t, J=7.0 Hz, 3H, H3), 1.90-1.98 (m, 2H, H2), 2.71 (s, 3H, $NC\underline{H}_3$), 3.17 (t, J=6.0 Hz, 1H, H1), 4.36 (m, 2H, $C\underline{H}_2OH$), 5.91 (t, J=7.5 Hz, 1H, $O\underline{H}$), 6.02 (s, 2H, OCH_2O), 6.86 (s, 1H, ArH2,), 6.89 (s,1H, ArH5). ^{13}C NMR ($CDCl_3$) δ: 10.43 (C3), 22.71 (C2), 29.15 ($N\underline{C}H_3$), 51.11 ($C\underline{H}_2OH$), 57.31 (C1), 82.68 ($C{\equiv}\underline{C}CH_2$), 92.84 ($\underline{C}{\equiv}CCH_2$), 101.77 ($O\underline{C}H_2O$), 108.02 (ArC5), 111.94 (ArC2), 115.19 (q, J=287.6 Hz, $CO\underline{C}F_3$), 117.54 (ArC1), 133.91 (ArC6), 147.05 (ArC4), 147.94 (ArC3), 157.36 (q, J=36.3 Hz, $\underline{C}OCF_3$). ^{19}F NMR ($CDCl_3$) – 70.55 ($C\underline{F}_3$). HRMS calculated for $C_{16}H_{16}F_3NO_4$: (M^+ + Na) m/z 366.0929, found

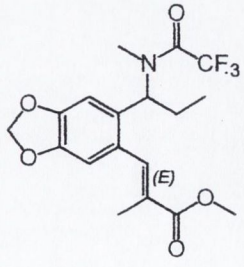
366.0943. Elemental analysis: $C_{16}H_{16}F_3NO_4$ requires C, 55.98; H, 4.70; N, 4.08. Found C, 55.78; H, 4.41; N, 3.93.

3-[6-(1-Methylamino-propyl)-benzo[1,3]dioxol-5-yl]-prop-2-yn-1-ol 212 Isolated from the basic deprotection of 2,2,2-trifluoro-N-{1-[6-(3-hydroxy-prop-1-ynyl)-benzo[1,3]dioxol-5-yl]-propyl}-N-methyl-acetamide **210** in 96% yield.



IRυ_{max} cm^{-1} (KBr) 3474 (O-H), 2350 (C≡C), 1669 (C=O), 1252, 1208 (C-O), 1489 (N-C=O). ^{1}H NMR (CD_3OD) δ: 1.00 (t, J_{ave}=7.3 Hz, 3H, H3), 1.88-2.15 (m, 2H, H2), 2.54 (s, 3H, NC<u>H</u>$_3$), 3.33 (m, 1H, OH), 3.97 (dd, J_1=10.2 Hz, J_2=4.1 Hz, 1H, H1), 4.43 (s, 2H, C<u>H</u>$_2$OH), 6.11 (s, 2H, OCH_2O), 6.94 (s, 1H, ArH2,), 6.98 (s, 1H, ArH5), 8.41 (s, 1H, NH). ^{13}C NMR (CD_3OD) δ: 10.43 (C3), 26.94 (C2), 31.43 (N<u>C</u>H$_3$), 51.12 (C<u>H</u>$_2$OH), 65.99 (C1), 78.58 (C≡<u>C</u>CH$_2$), 94.14 (<u>C</u>≡CCH$_2$), 103.80 (OCH_2O), 106.11 (ArC6), 108.57 (ArC2), 126.82 (ArC5), 129.09 (ArC1), 150.36 (ArC4), 151.17 (ArC3). LRMS $C_{14}H_{17}NO_3$ requires m/z 247, observed m/z 217 (M^+-$NHCH_3$) giving $C_{13}H_{13}O_3$

2-Methyl-3-(6-{1-[methyl-(2,2,2-trifluoro-acetyl)-amino]-propyl}-benzo[1,3]dioxol-5-yl)-acrylicacidmethylester. 200



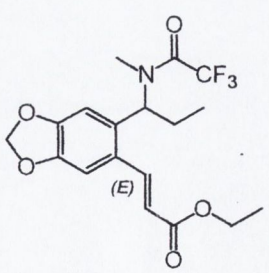
General method for the Heck coupling procedure in the synthesis of **200-204**

The reaction was carried out under a nitrogen atmosphere in an oven dried three neck round bottomed flask to which was added N-Methyl-N-Trifluoroacetal-1-(3,4-Methylenedioxy-6-Iodophenyl)-1-aminopropane **193** (0.500 g, 1.36 mmol),

triethylamine (0.947 ml, 6.80 mmol), Pd(II)Ac (0.050 g, 0.22 mmol) and 1,3-(diphenylphosphino)propane (0.082 g, 0.20 mmol). Anhydrous DMF (15 ml) was injected through a septum and the mixture was stirred for 18 hours at 100°C. Product was isolated by first adding 200 ml DCM which was filtered, washed with water (6 x 500 ml), dried over anhydrous sodium sulphate and removed under vacuum leaving a dark brown oil that was purified by flash chromatography with an 80:20 hexane:diethylether mobile phase to leave the rirle compound as a yellow oil (44%).

IRυ_{max} (KBr): 1638 (C=O), 1488 (CH vinylic), 1244, 1144 (C-O) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.99 (t, J=7.5 Hz, 3H, $CH_2C\underline{H}_3$), 1.89-2.04 (m, 5H, H2/C=C-C$\underline{H}_3$), 2.65 (s, 3H, NC$\underline{H}_3$), 3.81 (s, 3H, OC$\underline{H}_3$), 5.56 (t, J=7.8 Hz, 1H, $CHCH_2$), 6.04 (s, 2H, OC$\underline{H}_2$O), 6.74 (s,1H, ArH5), 6.93 (s,1H, ArH2), 7.52 (s, 1H, C=C$\underline{H}$). ^{13}C NMR ($CDCl_3$) δ: 10.52 (C3), 13.75 (C=C-$\underline{C}H_3$), 23.12 (C2), 29.08 (N$\underline{C}H_3$), 51.88 (O$\underline{C}H_3$), 56.39 (C1), 101.60 (O$\underline{C}H_2$O), 107.96 ($\underline{C}$H=C), 110.86 (ArC2), 116.90 (q, J=288.6 Hz, $\underline{C}F_3$), 129.65 (ArC1), 130.08 (CH=$\underline{C}(CH_3)$), 130.46 (ArC6), 136.75 (ArC5), 146.95 (ArC4), 147.64 (ArC3), 156.76 (q, J=35.1 Hz, $\underline{C}OCF_3$). ^{19}F NMR ($CDCl_3$) δ: -70.58 ($COCF_3$). HRMS calculated for m/z $C_{18}H_{20}F_3NO_5$: (M^+ + Na) 410.1191, found 410.1182

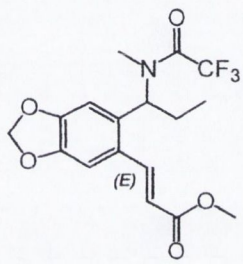
3-(6-{1-[Methyl-(2,2,2-trifluoro-acetyl)-amino]-propyl}-benzo[1,3]dioxol-5-yl)-acrylic acid ethyl ester 202 Prepared from the general Heck coupling proceedure in 62% yield m.p 122-124°C.



IRυ_{max} cm^{-1} (KBr): 2856 (C-H), 1735, 1698 (C=O), 1458 (CH vinylic), 1117 (C-O), 750 (Ar). ^1H NMR ($CDCl_3$) δ: 1.02 (t, J_{av}=7.3 Hz, 3H, H3), 1.35 (t, J=7.0 Hz, 3H, $OCH_2C\underline{H}_3$), 1.942-2.03 (m, 2H, H2), 2.66 (s, 3H, NCH_3), 4.18 (m, 2H, OCH_2), 5.81 (dd, J_1=8.0 Hz, J_2=7.5 Hz, 1H, H1), 6.04 (m, 2H, OCH_2O), 6.14 (d, J_{trans}=15.6 Hz, 1H, CH=C$\underline{H}$CO), 6.91 (s, 1H, ArH2), 7.06 (s, 1H, ArH5), 7.74 (d, J_{trans}=15.6 Hz, 1H,

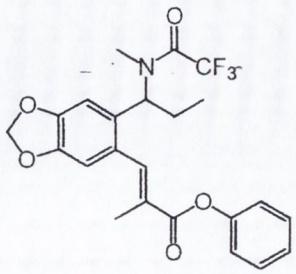
C<u>H</u>=CHCO). ^{13}C NMR ($CDCl_3$) δ: 10.57 (C3), 13.99 ($OCH_2\underline{C}H_3$), 23.21 (C2), 28.87 (NCH_3), 55.57 (C1), 60.55 (OCH_2), 101.81 (OCH_2O), 106.95 (ArC5), 107.98 (ArC2), 119.90 (ArCH=<u>C</u>H), 121.88 (q, J=288.5 Hz, CF_3), 129.40 (ArC1), 131.10 (ArC6), 140.47 (Ar<u>C</u>H=CH), 147.81 (ArC4), 149.23 (ArC3), 156.96 (q, J=35.1 Hz, <u>C</u>OCF_3), 166.22 (COO). ^{19}F NMR ($CDCl_3$) δ: -70.40 ($COCF_3$). Elemental analysis: $C_{18}H_{20}F_3NO_5$ requires C, 55.81; H, 5.20; N, 3.62. Found C, 55.50; H, 5.10; N, 3.50.

3-(6-{1-[Methyl-(2,2,2-trifluoro-acetyl)-amino]-propyl}-benzo[1,3]dioxol-5-yl)-acrylic acid methyl ester 201 Prepared from the general Heck coupling proceedure in 58% yield m.p 160-164°C.



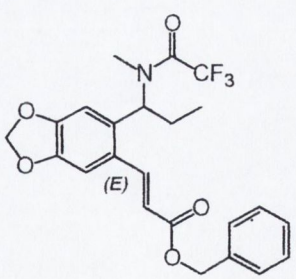
IRυ_{max} film: 2972 (C-C), 1687 (C=O), 1038 (C-O) cm^{-1}, 854 (ArCH). ^{1}H NMR ($CDCl_3$) δ: 1.02 (t, J_{av}=7.3 Hz, 3H, H3), 1.92-2.03 (m, 2H, H2), 2.67 (s, 3H, NCH_3), 3.79 (s, 3H, OCH_3), 5.80 (dd, J_1=8.0 Hz, J_2=7.5 Hz, 1H, H1), 6.12 (2d, J=1.0 Hz, 2H, OCH_2O), 6.14 (d, J_{trans}=16.1 Hz, 1H, CH=C<u>H</u>CO), 6.91 (s, 1H, ArH2), 7.05 (s, 1H, ArH5), 7.75 (d, J_{trans}=16.1 Hz, 1H, C<u>H</u>=CHCO). ^{13}C NMR ($CDCl_3$) δ: 10.58 (C3), 23.24 (C2), 28.90 (NCH_3), 51.55 (OCH_3), 55.65 (C1), 101.84 (OCH_2O), 106.96 (ArC5), 107.96 (ArC2), 119.38 (ArCH=<u>C</u>H), 117.95 (q, J=289.5 Hz, CF_3), 129.31 (ArC1), 131.26 (ArC6), 140.94 (Ar<u>C</u>H=CH), 147.83 (ArC4), 149.29 (ArC3), 156.52 (q, J=35.0 Hz, <u>C</u>OCF_3), 166.63 (COO). ^{19}F NMR ($CDCl_3$) δ: -70.52 ($COCF_3$). Elemental analysis: $C_{17}H_{18}F_3NO_5$ requires C, 54.69; H, 4.85; N, 3.75. Found C, 54.54; H, 4.67; N, 3.61.

2-Methyl-3-(6-{1-[methyl-(2,2,2-trifluoro-acetyl)-amino]-propyl}-benzo[1,3]dioxol-5-yl)-acrylic acid phenyl ester 204 Prepared from the general Heck coupling proceedure as a yellow oil in 28% yield.



IRυ_{max} film: 2885 (C-C), 1644 (C=O), 1486 (CH vinylic), 1091 (C-O) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.03 (t, J_{ave}=7.3 Hz, 3H, H3), 1.91-2.07 (m, 2H, H2), 2.01 (s, 3H, CH=C(C<u>H</u>$_3$)), 2.68 (s, 3H, NCH_3), 5.69 (dd, J_1=9.0 Hz, J_2=6.5 Hz, 1H, H1), 6.08 (s, 2H, OCH_2O), 6.82 (s, 1H, ArH2), 6.97 (s, 1H, ArH5), 7.24 (m, 3H, ArH3*/5*, ArH4*), 7.42 (m, 2H, ArH2*/6*), 7.81 (s, 1H, C<u>H</u>=C(CH_3)). ^{13}C NMR ($CDCl_3$) δ: 10.52 (C3), 13.86 (CH=C(CH_3)), 22.96 (C2), 28.90 (NCH_3), 56.10 (C1), 101.69 (OCH_2O), 108.06 (ArC5), 110.09 (ArC2), 116.82 (q, J=287.7 Hz, CF_3), 121.81 (ArC3*/5*), 125.55 (ArC4*), 129.30 (ArC2*/6*), 130.21 (ArC1), 130.30 (ArC6), 138.50 (Ar<u>C</u>H=C), 147.00 (ArC4), 147.81 (ArC3), 151.14 (CH=<u>C</u>(CH_3)), 156.72 (q, J=35.0 Hz, <u>C</u>OCF_3), 166.25 (COO). ^{19}F NMR ($CDCl_3$) δ: -70.23 ($COCF_3$). LRMS calculated for m/z $C_{23}H_{22}F_3NO_5$: (M^+ + Na) 449, found 449.

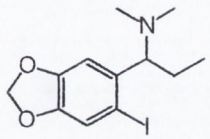
3-{6-{1-[Methyl-(2,2,2-trifluoro-acetyl)-amino]-propyl}-benzo[1,3]dioxol-5-yl)-acrylic acid benzyl ester 203 Prepared from the general Heck coupling proceedure as a yellow oil in 47% yield.



IRυ_{max} film: 2870 (C-C), 1688 (C=O), 1407 (CH vinylic), 1259, 1146 (ArC-O) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.72 (t, J_{av}=7.3 Hz, 3H, H3), 1.80-1.93 (m, 2H, H2), 2.57 (s, 3H, NCH_3), 5.15 (2d, J=12.2 Hz, 2H, OCH_2), 5.72 (t, J_1=7.6 Hz, 1H, H1), 6.12 (2d, J=1.2 Hz, 2H, OCH_2O), 6.09 (d, J_{trans}=15.3 Hz, 1H, CH=C<u>H</u>CO), 6.81 (s, 1H, ArH2), 6.94 (s, 1H, ArH5), 7.26 (m, 3H, ArH3*/5*, ArH4*), 7.36 (dd, J_o=7.2 Hz, J_m=1.8 Hz, 2H, ArH2*/6*), 7.75 (d, J_{trans}=15.3 Hz, 1H, C<u>H</u>=CHCO). ^{13}C NMR ($CDCl_3$)

δ: 10.56 (C3), 23.14 (C2), 28.88 ($N\underline{C}H_3$), 55.40 (C1), 66.23 (OCH_2), 101.81 (OCH_2O), 106.94 (ArC5), 107.92 (ArC2), 119.39 (ArCH=$\underline{C}$H), 119.96 (q, J=288.7 Hz, CF_3), 128.07 (ArC4*), 128.36 (ArC3/5*), 128.44 (ArC2*/6*), 129.18 (ArC1), 131.17 (ArC6), 136.18 (ArC1*), 141.15 (Ar$\underline{C}$H=CH), 147.74 (ArC4), 149.25 (ArC3), 156.49 (q, J=35.0 Hz, $\underline{C}OCF_3$), 165.96 ($\underline{C}OO$). ^{19}F NMR ($CDCl_3$) δ: -70.25 ($COCF_3$). HRMS calculated for $C_{23}H_{22}F_3NO_5$: (M^+ + Na) 472.1348, found 472.1350.

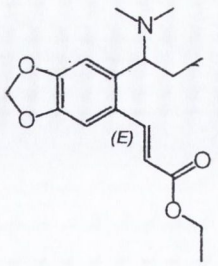
[1-(6-Iodo-benzo[1,3]dioxol-5-yl)-propyl]-dimethyl-amine 205



[1-(6-Iodo-benzo[1,3]dioxol-5-yl)-propyl]-methyl-amine **193** (0.676 g, 2.12 mmol) was stirred in formic acid (10 ml) for 40 minutes, then treated with formaldehyde (10 ml). The solution was heated to reflux and stirred for 10 hours. Volatiles were removed under reduced pressure and the resulting residue was dissolved in water, basified to pH 10 using 15% NaOH and extracted with DCM (3 x 50 ml). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and removed *in vacuo* to leave a light brown oil, which was columned on silica gel using a methanol mobile phase to yield a clear oil (93%).

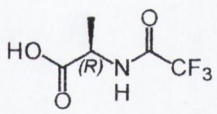
IRυ_{max} cm^{-1} film: 2832 (C-C), 1038 (C-O), 833 (Ar). ^1H NMR ($CDCl_3$) δ: 0.71 (t, J=7.5 Hz, 3H, H3), 1.53-2.23 (m, 2H, H2), 2.23 (s, 6H, $N(C\underline{H}_3)_2$), 3.40 (dd, J_1=4.8 Hz, J_2=9.2 Hz, 1H, H1), 5.96 (2d, J=1.4 Hz, 2H, $OC\underline{H}_2O$), 6.89 (s, 1H, ArH5), 7.25 (s, 1H, ArH2). ^{13}C NMR ($CDCl_3$) δ: 9.61 (C3), 26.57 (C2), 43.33 ($N(CH_3)_2$), 74.15 (C1), 89.80 (ArC5), 101.47 ($O\underline{C}H_2O$), 108.27 (ArC5), 118.05 (ArC2), 137.81 (ArC1), 147.21 (ArC4), 148.56 (ArC3). HRMS calculated for $C_{12}H_{17}INO_2$: (M^+ + H^+) 334.0304, found 334.0310.

3-[6-(1-Dimethylamino-propyl)-benzo[1,3]dioxol-5-yl]-acrylic acid ethyl ester. 206 Prepared from [1-(6-Iodo-benzo[1,3]dioxol-5-yl)-propyl]-dimethyl-amine **205** (0.350g, 1.05mmol) giving the title compound in 18% yield.



IRυ_{max} cm^{-1} film: 3428 (N-H), 2875 (C-C), 1713 (C=O), 1036 (C-O), 933 (Ar). ^{1}H NMR (CD_3OD) δ: 0.72 (t, J_{av}=7.2 Hz, 3H, H3), 1.33 (t, J=7.5 Hz, 3H, $OCH_2C\underline{H}_3$), 1.66-2.03 (m, 2H, H2), 2.20 (s, 6H, $N(CH_3)_2$), 3.08 (dd, J_1=10.2 Hz, J_2=4.2 Hz, 1H, H1), 4.25 (q, J=7.5 Hz, 2H, OCH_2), 6.12 (s, 2H, $OC\underline{H}_2O$), 6.66 (d, J_{trans}=16.4 Hz, 1H, CH=C<u>H</u>CO), 6.86 (s, 1H, ArH5), 6.90 (s, 1H, ArH2), 7.62 (d, J_{trans}=16.4 Hz, 1H, C<u>H</u>=CHCO). ^{13}C NMR (CD_3OD) δ: 9.37 (C3), 12.59 ($OCH_2\underline{C}H_3$), 24.80 (C2), 41.22 ($N(\underline{C}H_3)_2$), 59.66 (OCH_2), 71.57 (C1), 101.39 ($O\underline{C}H_2O$), 107.71 (ArCH=<u>C</u>), 115.56 (ArC6), 119.74 (ArC2), 122.24 (ArC5), 133.26 (ArC1), 138.39 (Ar<u>C</u>H=CH), 145.32 (ArC4), 147.87 (ArC3), 166.69 (C=O). HRMS calculated for $C_{17}H_{24}NO_4$: (M^+ + H^+) 306.1705, found 306.1710.

N-(R)-Trifluoroacetalalanine 232c



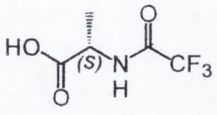
Triethylamine (24.66ml, 175.00 mmol) was added to (R)-alanine (15 g, 168.00 mmol) in dry methanol (200 ml). After 30 minutes ethyltrifluoroacetate (25 ml, 210.00 mmol) was added in two portions 20 minutes apart. The suspension was stirred vigorously over night under a nitrogen atmosphere. The solvents were removed under vacuum and the viscous oil was dissolved in water (200 ml), made acidic to litmus paper and extracted with ethylacetate (4 x 100 ml). The organic layers were combined, dried over anhydrous sodium sulphate and removed under vacuum. The pink oil was blown with N_2 gas resulting in a colourless hydroscopic solid (78%) that was stored under nitrogen m.p. 60-62°C (lit. 66°C)[9]

IRυ_{max} (KBr) 3305 (O-H) cm^{-1}, 3103 (N-H), 1711 (C=O) cm^{-1}, 1186 (C-O) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.60 (d, J=7.0 Hz, 3H, $CHC\underline{H}_3$), 4.69 (quin, J=7.5 Hz, 1H, C<u>H</u>CH_3), 7.07 (d, J=5 Hz, 1H, N<u>H</u>), 9.70 (s, 1H, O<u>H</u>,). ^{13}C NMR ($CDCl_3$) δ: 17.33 ($CH\underline{C}H_3$),

48.48 (CHCH$_3$), 115.87 (q, J=287.7 Hz, CF$_3$), 157.07 (q, J=37.9 Hz, COCF$_3$), 176.23 (COOH). ^{19}F NMR (CDCl$_3$) δ: -76.48.

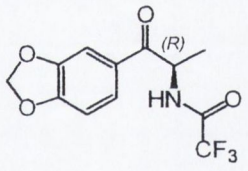
N-Trifluoroacetal-(S)-alanine 232b

Prepared as described for N-Trifluoroacetal-(R)-alanine in 71% yield. m.p. 58-62°C (lit. 66°C)[9]



IRυ_{max} (KBr) 3346 (O-H) cm^{-1}, 3100 (N-H), 1728 (C=O) cm^{-1}, 1107 (C-O) cm^{-1}. ^{1}H NMR (CDCl$_3$) 1.58 (d, J=7.5 Hz, 3H, CHCH$_3$), 4.69 (m, 1H, CHCH$_3$), 7.12 (d, J=6.0 Hz, 1H, NH), 10.11 (s, 1H, OH). ^{13}C NMR (CDCl$_3$) δ: 17.37 (CHCH$_3$), 48.52 (CHCH$_3$), 115.03 (q, J=287.7 Hz, CF$_3$), 156.61 (q, J=37.9 Hz, COCF$_3$), 175.97 (COOH). ^{19}F NMR (CDCl$_3$) δ: -76.56.

N-Trifluoroacetal-1-(3,4-Methylenedioxyphenyl)-2-(R)-amino-prop-1-one 231



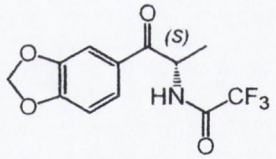
N-Trifluoroacetal-(R)-alanine **232c** (2.89 g, 15.53 mmol) was dissolved in 75 ml dry DCM and added to an oven dried 250 ml round bottomed flask under nitrogen. Temperature of the flask adjusted to -15^{0}C using an acetone ice bath. 3\4 drops of pyridine were added, oxalylchloride (4.3 ml, 49.00 mmol) was added dropwise to the stirred solution. Subsequent to addition of the oxalylchloride, the solution was allowed to rise to room temperature and left to stir for three hours. The volatiles were removed under vacuum at 30^{0}C and the orange oil was transferred to a dry three neck 100 ml round bottomed flask. 1,3-Benzodioxole (1.15 ml, 10 mmol) was injected through the septum followed by the dropwise addition of SnCl$_4$ (1.17 ml, 10 mmol). The reaction was kept under a nitrogen atmosphere for 18 hours afterwhich 150 ml water were added and the mixture was extracted with DCM (4 x 100 ml). Organic extracts were combined, dried over anhydrous sodium sulphate and

removed under vacuum. The resulting green residue was purified on silica gel using a mobile phase of 80:20 hexane:diethylether to give a colourless solid (18%) $[\alpha_D]_{20}$ = +48.1° (c = 0.015, ethanol) m.p. 142-144°C

IRυ_{max} (KBr) cm^{-1}: 3290 (N-H), 2917 (C-C), 1712, 1676 (C=O), 1552 (Ar), 1044 (ArC-O), 906, 746 (ArCH). ^{1}H NMR ($CDCl_3$) δ: 1.53 (d, J=7.0 Hz, 3H, H3), 5.46 (m, 1H, H2), 6.11 (s, 2H, O$\underline{C}H_2$O), 6.92 (d, J=8.2 Hz, 1H, ArH5), 7.45 (d, J=1.8 Hz, 1H, ArH2), 7.60 (dd, J_1=8.0 Hz, J_2=1.8 Hz, 1H, ArH6), 7.65 (s, 1H, N$\underline{H}$). ^{13}C NMR ($CDCl_3$) δ: 19.58 (C3), 50.50 (C2), 102.24 (O$\underline{C}H_2$O), 108.32 (ArC2/6), 115.73 (q, J=287.7 Hz, $\underline{C}F_3$), 125.43 (ArC5), 127.59 (ArC1), 148.70 (ArC4), 153.07 (ArC3), 156.41 (q, J=37.9 Hz, $\underline{C}OCF_3$), 194.99 (C=O). Elemental analysis: $C_{12}H_{10}F_3NO_4$ requires C, 49.84; H, 3.49; N, 4.84. Found C, 49.61; H, 3.19; N, 4.66.

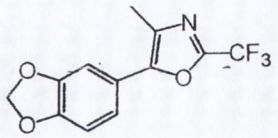
N-Trifluoroacetal-1-(3,4-Methylenedioxyphenyl)-2-(S)-amino-prop-1-one 233

Isolated as described for N-Trifluoroacetal-1-(3,4-Methylenedioxyphenyl)-2-(R)-amino-prop-1-one. colourless solid (12%).$[\alpha_D]_{20}$ = -48.5° (c = 0.015, ethanol) m.p. 138-142°C



IRυ_{max} (KBr) cm^{-1}: 3299 (N-H), 2917 (C-C), 1700, 1676 (C=O), 1201, (ArC-O), 888, 767 (ArCH). ^{1}H NMR ($CDCl_3$) δ: 1.50 (d, J=7.0 Hz, 3H, H3), 5.47 (m, 1H, H2), 6.09 (s, 2H, O$\underline{C}H_2$O), 6.92 (d, J=8.2 Hz, 1H, ArH5), 7.47 (d, J=1.8 Hz, 1H, ArH2), 7.61 (dd, J_1=8.0 Hz, J_2=1.8 Hz, 1H, ArH6), 7.78 (s, 1H, N$\underline{H}$). ^{13}C NMR ($CDCl_3$) δ: 19.56 (C3), 50.49 (C2), 102.24 (O$\underline{C}H_2$O), 108.32 (ArC2/C6), 116.10 (q, J=287.6 Hz, $\underline{C}F_3$), 125.43 (ArC5), 127.57 (ArC1), 148.70 (ArC4), 153.05 (ArC3), 156.19 (q, J=37.9 Hz, $\underline{C}OCF_3$), 194.99 (C=O). Elemental analysis: $C_{12}H_{10}F_3NO_4$ requires C, 49.84; H, 3.49; N, 4.84. Found C, 49.47; H, 3.15; N, 4.47.

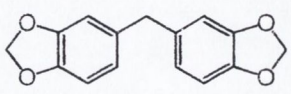
5-Benzo[1,3]dioxol-5-yl-4-methyl-2-trifluoromethyl-oxazole 235



N-Trifluoroacetal-(R)-alanine **231** (2.89 g, 15.53 mmol) was dissolved in 75ml dry DCM and added to an oven dried 250 ml round bottomed flask under nitrogen. Temperature of the flask adjusted to -15^{0}C using an acetone ice bath. 3\4 drops of pyridine were added, oxalylchloride (4.30 ml, 49.00 mmol) was added dropwise to the stirred solution. Subsequent to addition of the oxalylchloride, the solution was allowed to rise to room temperature and left to stir for three hours. The volatiles were removed under vacuum at 30^{0}C and the orange oil was transferred to a dry three neck 100 ml round bottomed flask. 1,3-Benzodioxole (1.15 ml, 10 mmol) was injected through the septum followed by the dropwise addition of $SnCl_4$ (1.17 ml, 10 mmol). The reaction was kept under a nitrogen atmosphere for 18 hours afterwhich 150 ml water were added and the mixture was extracted with DCM (4 x 100 ml). Organic extracts were combined, dried over anhydrous sodium sulphate and removed under vacuum. The resulting green residue was purified on silica gel using a mobile phase of 80:20 hexane:diethylether leaving an orange oil that solidified on standing (48%).

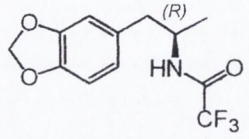
IRυ_{max} (Film): 1155 (C-O) cm^{-1}, 884 (Ar) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.45 (s, 3H, H3), 6.05 (s, 2H, O$\underline{C}H_2$O), 6.92 (d, J=8.0 Hz, 1H, ArH5), 7.11 (d, J=2.0 Hz, 1H, ArH2), 7.15 (dd, J_1=8.0 Hz, J_2=2.0 Hz, 1H, ArH6). ^{13}C NMR ($CDCl_3$) δ: 13.14 (C3), 104.49 (O$\underline{C}H_2$O), 106.42 (ArC2), 108.79 (ArC5), 116.64 (q, J=270.2 Hz, $\underline{C}F_3$), 120.49 (ArC6), 121.37 (ArC1), 131.56 (C1), 147.72 (q, J=43.7 Hz, $\underline{C}OCF_3$), 148.13 (C2), 148.30 (ArC4), 148.34 (ArC3). ^{19}F NMR ($CDCl_3$) δ: -66.27 (COC$\underline{F}_3$). GC-LRMS m/z (M^+) 271 (100), 202 (15), 149 (10), 121 (6). HRMS calculated for m/z $C_{12}H_8NO_3F_3$: ($M^+ + H^+$) 272.0535, found 272.0532.

6-Benzo[1,3]dioxol-5-ylmethyl-6-benzo[1,3]dioxole 236 Isolated in 8% (colourless solid m.p. 150-152°C (lit. 150-151)[10] yield from the synthesis of N-Trifluoroacetal-1-(3,4-Methylenedioxyphenyl)-2-(S)-amino-prop-1-one **231**



IRυ_{max} (Film): 1060 (C-O) cm^{-1}, 788 (Ar) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.82 (s, 2H, $ArCH_2$) 5.94 (s, 4H, $OC\underline{H_2}O$ x 2), 6.66-6.78 (m, 4H, ArH6/H2 x 2), 6.76 (d, J=8.0 Hz, 2H, ArH2 x 2). LRMS m/z (M^+) 256 (100), 225 (22), 196 (34), 168 (38). Elemental analysis: $C_{15}H_{12}O_4$ requires C, 70.31; H, 4.72. Found C, 70.09; H, 4.72.

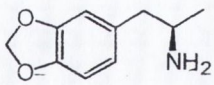
N-Trifluoroacetal-(R)-Methylenedioxyamphetamine 234



N-Trifluoroacetal-1-(3,4-Methylenedioxyphenyl)-2-amino-prop-1-one **231** (0.300 g, 1.20 mmol) was dissolved in 8ml trifluoroaceticacid. Triethylsilane (2 ml, 12.61 mmol) was added and the reaction was refluxed for nine hours and left to stir for twelve hours at room temperature. The reaction was quenched by the addition of a saturated solution of $NaHCO_3$ until the evolution of gas had subsided and the solution remained basic. Mixture was extracted with diethylether (3 x 75 ml). Solvent was combined dried over anhydrous sodium sulphate and removed under vacuum. Triethylsilane remnants could not be fully removed by columning on excess silica gel using a mobile phase of 80:20 hexane:diethylether pale yellow oil that solidified on standing (26%).

IRυ_{max} (KBr) cm^{-1}: 3302 (N-H), 2928 (C-C), 1701 (C=O), 1215 (CF_3), 1038 (C-O), 713 (ArCH). ^1H NMR ($CDCl_3$) δ: 1.23 (d, J=6.8 Hz, 3H, H3), 2.78 (m, 2H, H1), 4.24 (sept, J=6.8 Hz, 1H, H2), 5.96 (s, 2H, $OC\underline{H_2}O$), 6.62 (dd, J_1=7.8 Hz, J_2=2.0 Hz, 1H, ArH6), 6.67 (d, J=1.4 Hz, 1H, ArH2), 6.77 (d, J_1=7.5 Hz, 1H, ArH5), 6.81 (s, 1H, N$\underline{H}$). ^{13}C NMR ($CDCl_3$) δ: 19.30 (C3), 41.53 (C1), 47.36 (C2), 101.01 ($O\underline{C}H_2O$), 108.36 (ArC2), 109.56 (ArC6), 115.79 (q, J=288.6 $\underline{C}F_3$), 122.28 (ArC5), 138.27 (ArC1), 146.59 (ArC3), 147.91 (ArC4), 156.41 (q, J=36.9 Hz, $\underline{C}OCF_3$). Elemental analysis: $C_{12}H_{12}F_3NO_3$ requires C, 52.37; H, 4.39; N, 5.09. Found C, 52.37; H, 4.38; N, 4.87.

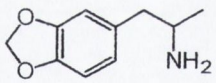
(R)-Methylenedioxyamphetamine 232a



Removal of the TFA protecting group from the above compound using general method described for the synthesis of **191**. The free base was converted to the HCl salt using the general method (53%).$[\alpha_D]_{20}$ = -24.3° (c = 0.02 H_2O) M.p (HCl) 200-202 (lit. 200-204)[11]

IRυ_{max} (KBr) cm^{-1}: 3302 (N-H), 2928 (C-C), 1701 (C=O), 1215 (CF_3), 1038 (C-O), 713 (ArCH).^{1}H NMR ($CDCl_3$) δ: 1.09 (d, J=6.0 Hz, 3H, H3), 1.82 (s, 2H, NH_2), 2.52 (2dd, J_{gem}=13.5 Hz, (H1*-H1), J_{vic}=8.0 Hz, (H1*-H2), J_{vic}=5.0 Hz (H1-H2), 2H, H1), 3.08 (m, 1H, H2), 5.91 (s, 2H, $OC\underline{H_2}O$), 6.62 (d, J_o=8.0 Hz, 1H, ArH6), 6.67 (s, 1H, ArH2), 6.73 (d, J_o=8.0 Hz, 1H, ArH5). ^{13}C NMR ($CDCl_3$) δ: 23.21 (C3), 46.05 (C1), 48.42 (C2), 100.67 (OCH_2O), 108.05 (ArC2), 109.36 (ArC6), 121.98 (ArC5), 133.25 (ArC1), 145.80 (ArC3), 147.48 (ArC4). LRMS calculated for m/z $C_{10}H_{13}NO_2$: (M^+) 179, found 179.

Methylenedioxyamphetamine 232b



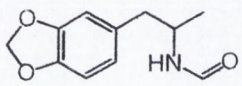
To a stirred solution of N-Trifluoroacetal-1-(3,4-Methylenedioxyphenyl)-2-(R)-amino-prop-1-one **234** (1.000 g, 3.46 mmol) in 20 ml of ethylene glycol was added KOH (0.660 g, 11.77 mmol) and hydrazine hydrate (2.50 ml, 50.17 mmol). The mixture was stirred under a nitrogen atmosphere at 150°C for 3.5 hours, then at 200°C for a further 3 hours. After cooling to near room temperature, the mixture was poured into a mixture of DCM (100 ml) and ice-water (100 ml). The aqueous layer was extracted with DCM (4 x 75ml). The organic extracts were combined, dried over anhydrous Na_2SO_4, filtered and removed under vacuum to yield a brown oil which was purified by flash chromatography on a short silica gel column, using a methanol mobile phase (62%).

^{1}H NMR ($CDCl_3$) δ: 1.09 (d, J=6.0Hz, 3H, H3), 1.88 (s, 2H, NH_2), 2.51 (2dd, J_{gem}=13.5Hz, (H1*-H1), J_{vic}=8.0Hz, (H1*-H2), J_{vic}=5.0Hz (H1-H2), 2H, H1),

3.08 (m, 1H, H2), 5.90 (s, 2H, $OC\underline{H_2}O$), 6.60 (d, J_o=8.0Hz, 1H, ArH6), 6.66 (s, 1H, ArH2), 6.72 (d, J_o=8.0Hz, 1H, ArH5). ^{13}C NMR ($CDCl_3$) δ: 23.16 (C3), 45.98 (C1), 48.40 (C2), 100.65 (OCH_2O), 108.01 (ArC2), 109.33 (ArC6), 121.94 (ArC5), 133.19 ($ArC1_q$), 145.77 ($ArC3_q$), 147.44 ($ArC4_q$).

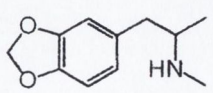
N-Formylmethylenedioxyamphetamine 232c

Methylenedioxyamphetamine **232a** (0.160 g, 0.89 μmol) was dissloved in fresh ethyl formate and refluxed for 5 hours. Volatiles were removed *in vacuo* and the resulting residue was columned directly on silica gel using a 60:40 ethyl acetate:hexane eluent to yeild the product as a clear oil. 64%[11]



^{1}H NMR ($CDCl_3$) δ: 1.11 (d, J=6.1 Hz, 2.3H, H3 [R1]), 1.23 (d, J=6.1 Hz, 0.7H, H3 [R2]), 2.54-2.75 (m, 2H, H1), 3.60 (m, 0.25H, H2 [R2]), 4.22 (m, 0.75H, H2 [R1]), 5.88 (s, 1.27H, $OC\underline{H_2}O$ [R1]), 5.89 (s, 0.64H, $OC\underline{H_2}O$ [R2]), 6.16 (d J=6.2 Hz, 0.75H, NH [R1]), 6.36 (m, 0.25H, NH [R2]), 6.58 (2d, J_o=7.5 Hz, J_m=1.4 Hz, 1H, ArH6 [R1/R2]), 6.65 (d, J_m=1.4 Hz, 1H, ArH2), 6.70 (2d, J_o=7.5 Hz, J_m=1.4 Hz, 1H, ArH5 [R1/R2]), 7.75 (d, 12.2 Hz, 0.25H, CHO [R2]), 8.03 (s, 0.75H, CHO [R1]). ^{13}C NMR ($CDCl_3$) δ: 19.73 (C3 [R1]), 21.60 (C3 [R2]), 41.87 (C1 [R1]), 43.88 (C1 [R2]), 45.06 (C2 [R1]), 50.05 (C2 [R2]), 100.67 (OCH_2O [R1]), 100.76 (OCH_2O [R2]), 107.95 (ArC2 [R1]), 108.17 (ArC2 [R2]), 109.41 (ArC6 [R2]), 109.47 (ArC6 [R1]), 122.08 (ArC5 [R1]), 122.26 (ArC5 [R2]), 130.99 ($ArC1_q$ [R2]), 131.35 ($ArC1_q$ [R1]), 145.95 ($ArC3_q$ [R1]), 146.14 ($ArC3_q$ [R2]), 147.39 ($ArC4_q$ [R1]), 147.57 ($ArC4_q$ [R2]), 160.53 (CHO [R1]), 163.75 (CHO [R2]).

Methylenedioxymethamphetamine 232d

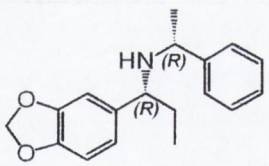


N-Formylmethylenedioxyamphetamine **232c** (0.066 g, 0.32 μmol), in dry THF (5 ml), was added dropwise to a stirred suspension of lithium aluminium hydride (0.043 g, 1.13 μmol) in dry THF (10 ml) under a nitrogen atmosphere. The mixture was

refluxed for 6 hours afterwhich time it was cooled to 0°C, 90/10 methanol/water (5 ml) was added dropwise followed by water (5 ml) and 15% NaOH (5 ml). The aqueous mixture was then extracted with ethyl actetate (4 x 50 ml). The organic extracts were combined, dried over anhydrous Na_2SO_4, filtered and removed *in vacuo* to leave a yellow oil, which was purified on silica gel to yield the product as a clear oil. 53%[11]

^{1}H NMR ($CDCl_3$) δ: 1.09 (d, J=6.2 Hz, 3H, H3), 2.44 (s, 3H, NCH_3), 2.61 (2dd, J_{gem}=13.6 Hz, (H1*-H1), J_{vic}=6.7 Hz, (H1*-H2), J_{vic}=6.2 Hz (H1-H2), 2H, H1), 2.80 (m, 1H, H2), 2.88 (s, 1H, NH), 5.95 (s, 2H, OCH_2O), 6.64 (dd, J_o=7.8 Hz, J_m=1.4 Hz, 1H, ArH6), 6.69 (d, J_m=1.4 Hz, 1H, ArH2), 6.75 (d, J_o=8.1 Hz, 1H, ArH5). ^{13}C NMR ($CDCl_3$) δ: 19.18 (C3), 33.57 (NCH_3), 42.73 (C1), 56.43 (C2), 100.82 (OCH_2O), 108.18 (ArC2), 109.46 (ArC6), 122.17 (ArC5), 132.79 ($ArC1_q$), 145.97 ($ArC3_q$), 147.63 ($ArC4_q$).

(1-Benzo[1,3]dioxol-5-yl-propyl)-(1-phenyl-ethyl)-amine 226a



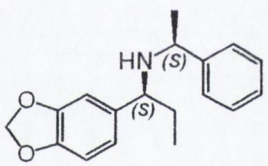
Method A: Attempted $TiCl_4$ catalysed imine formation followed by reduction to the amine resulted in a diastereomeric mixture 1:1, as described for the synthesis of **149**.

Method B: 1-(3,4-Methylenedioxyphenyl)-prop-1-one **150** (1.500 g, 8.42 mmol), (R)-phenylethylamine (1.10 g, 8.42 mmol) and pTSA (60 mg), were dissolved in 80 ml of dry toluene and refluxed under a nitrogen atmosphere for 36 hours. The mixture was cooled to –15°C with an acetone-ice bath, before slow dropwise additon to an ethanolic slurry of $NaBH_4$ at –30°C, under a nitrogen atmosphere. The resulting mixture was stirred at –30°C for 2 hours, adjusted to room temperature and all volatiles were removed under vacuum leaving a yellow oil with a diastereomeric ratio of 4:1. Any (R)-phenylethyl amine reagent was converted to the HCl-salt and removed by filtration. The diastereomeric ratio of the product was improved by flash

chromatography of the free base on excess silica gel with a 90:10 hexane:diethyl ether eluent to yield the product as the free base as a clear oil in 48% yield.

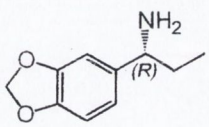
IRυ_{max} (film) cm^{-1}: 2865 (N-H), 1234, 1035 (C-O), 1487, 817, 918 (ArCH). ^1H NMR ($CDCl_3$) δ: 0.80 (t, J_{ave}=7.3 Hz, 3H, $CH_2C\underline{H}_3$), 1.36 (d, J=6.0 Hz, 3H, $CHC\underline{H}_3$), 1.53 (s, 1H, NH), 1.56-1.83 (m, 2H, $C\underline{H}_2CH_3$), 3.52 (dd, J_1=8.3 Hz, J_2=5.5 Hz, 1H, $C\underline{H}CH_2$), 3.74 (q, J=6.5 Hz, 1H, $C\underline{H}CH_3$), 5.95 (s, 2H, OCH_2O), 6.69 (d, J_o=7.6 Hz, 1H, ArH6), 6.76 (d, J_o=7.6 Hz, 1H, ArH5), 6.79 (s, 1H, ArH2), 7.29 (m, 5H, C_6H_5). ^{13}C NMR ($CDCl_3$) δ: 10.69 ($CH_2\underline{C}H_3$), 22.54 ($CH\underline{C}H_3$), 30.31 ($\underline{C}H_2CH_3$), 54.58 ($\underline{C}HCH_2$), 61.67 ($\underline{C}HCH_3$), 100.76 (OCH_2O), 107.29 (ArC5), 107.82 (ArC2), 120.56 (ArC6), 126.56 (ArC3/C5*), 126.69 (ArC4*), 128.29 (ArC2/6*), 138.40 ($ArC1_q$), 146.24 ($ArC4_q$), 146.27 ($ArC1^*_q$), 147.69 ($ArC3_q$). HRMS calculated for m/z $C_{18}H_{21}NO_2$: ($M^+ + H^+$) 284.1651, found 284.1646

(1-Benzo[1,3]dioxol-5-yl-propyl)-(1-phenyl-ethyl)-amine 226 Prepared as described for **226a** and isolated in 32% yield.



IRυ_{max} (film) cm^{-1}: 2964 (N-H), 1038 (C-O), 1502, 920 (ArCH). ^1H NMR ($CDCl_3$) δ: 0.77 (t, J_{ave}=7.3 Hz, 3H, $CH_2C\underline{H}_3$), 1.30 (d, J=6.5 Hz, 3H, $CHC\underline{H}_3$), 1.51-1.78 (m, 3H, $C\underline{H}_2CH_3$, NH), 3.20 (dd, J_1=7.6 Hz, J_2=6.8 Hz, 1H, $C\underline{H}CH_2$), 3.56 (q, J=6.5 Hz, 1H, $C\underline{H}CH_3$), 5.98 (s, 2H, OCH_2O), 6.61 (d, J_o=8.0 Hz, 1H, ArH6), 6.77 (d, J_o=8.0 Hz, 1H, ArH5), 6.80 (s, 1H, ArH2), 7.24-7.37 (m, 5H, C_6H_5). ^{13}C NMR ($CDCl_3$) δ: 10.84 ($CH_2\underline{C}H_3$), 25.02 ($CH\underline{C}H_3$), 31.46 ($\underline{C}H_2CH_3$), 54.78 ($\underline{C}HCH_2$), 61.44 ($\underline{C}HCH_3$), 100.74 (OCH_2O), 107.10 (ArC5), 107.78 (ArC2), 120.67 (ArC6), 126.63 (ArC3/C5*), 126.67 (ArC4*), 128.31 (ArC2/6*), 138.59 ($ArC1_q$), 145.85 ($ArC4_q$), 146.24 ($ArC1^*_q$), 147.74 ($ArC3_q$). HRMS calculated for $C_{18}H_{21}NO_2$: ($M^+ + H^+$) 284.1651, found 284.1650

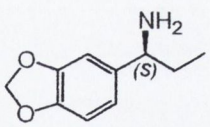
(R)-1-(3,4-Methylenedioxyphenyl)-1-aminopropane. 227



(1-Benzo[1,3]dioxol-5-yl-propyl)-(1-phenyl-ethyl)-amine (0.750 g, 2.67 mmol), was dissolved in methanol and added to a suspension of 10% Pd/C (0.160 g) in methanol under a H_2 atmosphere. The reaction was allowed to stir for 5 days afterwhich time it was filtered through a celite® cake. The cake was washed with a further 100 ml of methanol. The filtrate was taken and reduced to dryness under vacuum. The oil yielded was purified on a short silica column using a methanol mobile phase, the purified oil was dissolved in 2.50 ml IPA. 8 drops of conc HCl were added. Upon the addition of diethyl ether (6.0 ml) the product crashed out as a white fluffy solid (HCl-salt) $[\alpha_D]_{20}$ = -9.9° (c = 0.014, H_2O) 46% m.p. 204-206°C.

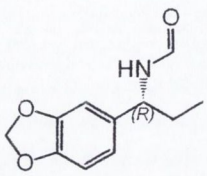
IRυ_{max} (KBr-HCl) cm^{-1}: 2962 (N-H), 1508 (Ar), 1042 (C-O), 814 (ArCH). ^1H NMR (CD_3OD-HCl salt) δ: 0.91 (t, J=7.5 Hz, 3H, H3), 1.86-2.07 (m, 2H, H2), 4.13 (dd, J_1=9.2 Hz, J_2=5.5 Hz, 1H, H1), 6.02 (s, 2H, $OC\underline{H_2}O$), 6.86 (d, J_o=8.1 Hz, 1H, ArH5), 6.89 (dd, J_o=8.0 Hz, J_m=2.0 Hz, 1H, ArH6), 6.98 (d, J_m=2.0 Hz, 1H, ArH2). ^{13}C NMR (CD_3OD HCl-salt) δ: 8.53 (C3), 26.58 (C2), 56.25 (C1), 100.90 ($O\underline{C}H_2O$), 106.23 (ArC5), 107.62 (ArC2), 120.63 (ArC6), 129.57 (ArC1), 147.76 (ArC4), 147.89 (ArC3). $[\alpha_D]_{20}$ = -9.9° (c = 0.014, H_2O). Elemental analysis: $C_{10}H_{14}ClNO_2$ requires C, 55.69; H, 6.54; N, 6.49. Found C, 55.63; H, 6.47; N, 6.44.

(S)-1-(3,4-Methylenedioxyphenyl)-1-aminopropane. 228 Isolated in 48% yield as the free base **226**. Converted to the HCl salt *via* the general method given in the experimental note. $[\alpha_D]_{20}$ = +10.2° (c = 0.012, H_2O) m.p. 208-210°C.



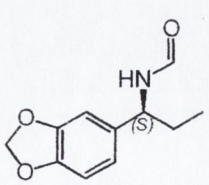
IRυ_{max} (KBr-HCl) cm^{-1}: 2981 (N-H), 1508 (Ar), 1040 (C-O). ^1H NMR (CD_3OD-HCl salt) ^1H NMR (CD_3OD-HCl salt) δ: 0.91 (t, J=7.5 Hz, 3H, H3), 1.87-2.09 (m, 2H, H2), 4.10 (dd, J_1=9.2 Hz, J_2=5.5 Hz, 1H, H1), 6.01 (s, 2H, $OC\underline{H_2}O$), 6.89 (d, J_o=8.1 Hz, 1H, ArH5), 6.93 (dd, J_o=8.0 Hz, J_m=2.0 Hz, 1H, ArH6), 6.97 (d, J_m=2.0 Hz, 1H, ArH2). ^{13}C NMR ($CDCl_3$) δ: 10.53 (C3), 28.58 (C2), 58.25 (C1), 102.93 ($O\underline{C}H_2O$), 108.19 (ArC5), 109.64 (ArC2), 122.59 (ArC6), 131.54 (ArC1), 149.82 (ArC4), 149.93 (ArC3). $[\alpha_D]_{50}$ = +10.2° (c = 0.012, H_2O). Elemental analysis: $C_{10}H_{14}ClNO_2$ requires C, 55.69; H, 6.54; N, 6.49. Found C, 55.67; H, 6.46; N, 6.42.

(R)-1-(3,4-Methylenedioxyphenyl)-1-(N-formyl)-aminopropane. 228a Preperation carried out as described for N-Formylmethylenedioxyamphetamine **232c**. Title compound formed in 64% yield isolated as a yello oil and was characterised by nmr and IR.



IRυ_{max} cm^{-1} (film): 2964 (N-H), 1670 (C=O), 1497 (ArCH), 1049 (C-O), 732 (ArCH). ^{1}H NMR ($CDCl_3$) δ: 0.90 (2t, J=7.5 Hz, 3H, H3 [R1/R2]), 1.69-1.84 (m, 2H, H2), 3.20 (dd, J_1=15.5 Hz, J_2=8.0 Hz, 0.25H, H1 [R2]), 4.82 (dd, J_1=15.5 Hz, J_2=8.0 Hz, 0.75H, H1 [R1]), 5.90 (s, 1.56H, OCH_2O [R1]), 5.93 (s, 0.43H, OCH_2O [R2]), 6.53 (s, 0.75H, NH [R1]), 6.63 (s, 0.25H, NH [R2]), 6.68 (dd, J_o=8.0 Hz, J_m=2.0 Hz, 0.25H, ArH6 [R2]), 6.74 (m, 2.75H, ArH2/5, ArH6 [R1]), 8.07 (d, J=12.0 Hz, 0.25H, CHO [R2]), 8.11 (s, 0.75H, CHO [R1]). ^{13}C NMR ($CDCl_3$) δ: 10.52 (C3), 29.01 (C2 [R1]), 30.11 (C2 [R2]), 53.47 (C1 [R1]), 57.96 (C1 [R2]), 100.88 ($O\underline{C}H_2O$ [R1]), 101.04 ($O\underline{C}H_2O$ [R2]), 106.48 (ArC5 [R2]), 106.88 (ArC5 [R1]), 108.10 (ArC2 [R1]), 108.21 (ArC2 [R2]), 119.48 (ArC6 [R2]), 119.84 (ArC6 [R1]), 135.68 (ArC1 [R1]), 135.78 (ArC1 [R2]), 146.62 (ArC4 [R1]), 146.92 (ArC4 [R2]), 147.74 (ArC3 [R1]), (ArC3 [R2]), 160.50 (CHO [R1]), 164.45 (CHO [R2]).

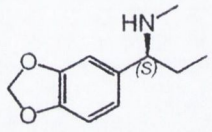
(S)-1-(3,4-Methylenedioxyphenyl)-1-(N-formyl)-aminopropane.228c Preperation carried out as described for N-Formylmethylenedioxyamphetamine **232c**. Title compound formed in 72% yield as a pale yellow oil and was characterised by nmr and IR.



^{1}H NMR ($CDCl_3$) δ: 0.90 (2t, J_{ave}=7.2 Hz, 3H, H3 [R1/R2]), 1.71-1.88 (m, 2H, H2), 3.20 (dd, J_1=15.0 Hz, J_2=8.0 Hz, 0.25H, H1 [R2]), 4.85 (dd, J_1=15.0 Hz, J_2=8.0 Hz, 0.75H, H1 [R1]), 5.94 (s, 1.56H, OCH_2O [R1]), 5.96 (s, 0.44H, OCH_2O [R2]), 6.18 (s,

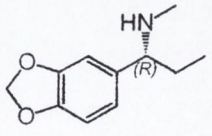
0.75H, NH [R2]), 6.52 (s, 0.25H, NH [R1]), 6.72 (dd, J_o=8.0 Hz, J_m=2.0 Hz, 0.25H, ArH6 [R2]), 6.77 (m, 2.75H, ArH2/5, ArH6 [R1]), 8.10 (d, J=12.0 Hz, 0.25H, CHO [R2]), 8.16 (s, 0.75H, CHO [R1]). ^{13}C NMR ($CDCl_3$) δ: 10.60 (C3 [R2]), 10.63 (C3 [R2]), 29.03 (C2 [R1]), 30.20 (C2 [R2]), 53.51 (C1 [R1]), 57.94 (C1 [R2]), 100.98 (O<u>C</u>H_2O [R1]), 101.12 (O<u>C</u>H_2O [R2]), 106.50 (ArC5 [R2]), 106.88 (ArC5 [R1]), 108.22 (ArC2 [R1]), 108.29 (ArC2 [R2]), 119.52 (ArC6 [R2]), 119.90 (ArC6 [R1]), 135.51 (ArC1 [R1]), 135.71 (ArC1 [R2]), 146.70 (ArC4), 147.79 (ArC3), 160.42 (CHO [R1]), 164.49 (CHO [R2]).

(S)-N-Methyl-1-(3,4-Methylenedioxyphenyl)-1-aminopropane 230 Preparation was carried out as described for methylenedioxymethamphetamine **232d**. Title compound formed in 78% yield as a pale yellow oil.



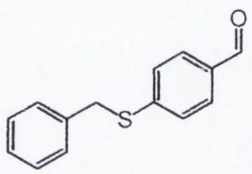
IRυ$_{max}$ cm^{-1} (film): 3434 (NH), 1040 (C-O), 887 (Ar). ^{1}H NMR ($CDCl_3$) δ: 0.80 (t, J=7.5 Hz, 3H, H3), 1.52-1.78 (m, 3H, NH/H2), 2.27 (s, 3H, NC<u>H</u>$_3$), 3.28 (dd, J_1=8.2 Hz, J_2=6.1 Hz, 1H, H1), 5.95 (s, 2H, OC<u>H</u>$_2$O), 6.71 (dd, J_o=7.8 Hz, J_m=1.4 Hz, 1H, ArH6), 6.76 (d, J_o=7.8 Hz, 1H, ArH5), 6.80 (d, J_m=1.4 Hz, 1H, ArH2). ^{13}C NMR ($CDCl_3$) δ: 10.76 (C3), 30.65 (C2), 34.42 (N<u>C</u>H_3), 66.90 (C1), 100.77 (O<u>C</u>H_2O), 107.11 (ArC5), 107.79 (ArC2), 120.73 (ArC6), 137.80 (ArC1), 146.32 (ArC4), 147.71 (ArC3). $[\alpha_D]_{50}$ = -11.9° (c = 0.019, ethanol). LRMS calculated for m/z $C_{11}H_{15}NO_2$: ($M^+ + H^+$) 193, (not observed) found 163 $C_{10}H_{11}O_2$ (M^+ - 30).

(R)-N-Methyl-1-(3,4-Methylenedioxyphenyl)-1-aminopropane 229 The title compound was prepared as described for methylenedioxymethamphetamine **232d** forming as a pale yellow oil in 70% yield.



IRυ_{max} cm^{-1} (film): 3428 (NH), 1257, 1039 (C-O), 930 (Ar). ^{1}H NMR ($CDCl_3$) δ: 0.80 (t, J=7.5 Hz, 3H, H3), 1.53-1.78 (m, 3H, NH/H2), 2.30 (s, 3H, $NC\underline{H}_3$), 3.24 (dd, J_1=8.2 Hz, J_2=6.1 Hz, 1H, H1), 6.00 (s, 2H, $OC\underline{H}_2O$), 6.71 (dd, J_o=7.8 Hz, J_m=1.4 Hz, 1H, ArH6), 6.75 (d, J_o=7.8 Hz, 1H, ArH5), 6.83 (d, J_m=1.4 Hz, 1H, ArH2). ^{13}C NMR ($CDCl_3$) δ: 10.83 (C3), 30.66 (C2), 34.38 ($N\underline{C}H_3$), 66.90 (C1), 100.77 ($O\underline{C}H_2O$), 107.10 (ArC5), 107.77 (ArC2), 120.74 (ArC6), 137.80 (ArC1), 146.38 (ArC4), 147.82 (ArC3). $[\alpha_D]_{50}$ = +11.3° (c = 0.014, ethanol). LRMS calculated for m/z $C_{11}H_{15}NO_2$: ($M^+ + H^+$) 193, (not observed) found 163 $C_{10}H_{11}O_2$ (M^+ - 30).

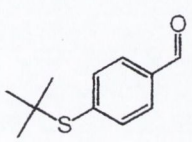
4-Benzylsulfanyl-benzaldehyde 252



To a solution of 4-fluorobenzaldehyde (3.000 g, 24.18 mmol) and benzylmercaptan (3.004 g, 24.18 mmol) in dry DMF (30 ml), under a nitrogen atmosphere, was added K_2CO_3 (4.020 g, 29.130 mmol). The reaction mixture was stirred at 140°C for 20 hours, cooled to room temperature, diluted with diethyl ether (150 ml) and washed with brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and removed under vacuum. The resulting oil was columned on silica gel using a 6:1 hexane/diethyl ether mobile phase to yield a clear oil. 87% yield. m.p. 68-70 (lit.70)[12]

IRυ_{max} (KBr) cm^{-1}: 2731 (C-C), 1692 (C=O), 1558, 838, 812 (ArCH). ^{1}H NMR ($CDCl_3$) δ: 4.26 (s, 2H, SCH_2), 7.28-7.42 (m, 7H, $SCH_2C_6\underline{H}_5$ + ArH2/H6), 7.76-7.78 (d, 2H, J=8.5 Hz, ArH3/H5), 9.94 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$) δ: 36.88 (SCH_2), 126.77 (ArC3/C5), 127.59 (ArC4*), 128.71 (ArC2*/C6*, ArC3*/C5*), 129.98 (ArC2/C6), 133.41 ($ArC4_q$), 135.86 ($ArC1^*_q$), 146.28 ($ArC1_q$), 191.22 (C1). Elemental analysis: $C_{14}H_{12}OS$ requires C, 73.65; H, 5.39. Found C, 73.61; H, 5.15.

4-tert-Butylsulfanyl-benzaldehyde 250

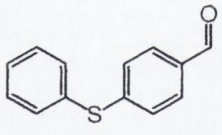


General proceedure for nucleophilic aromatic substitution using low boiling point thiols.

Reaction was divided into three ovendried pressure tubes, each containing 4-fluorobenzaldehyde (1.152 ml, 10.711 mmol), dry DMF (15 ml), 2-methyl-2-propanethiol (1.210 ml, 10.711 mmol) and K_2CO_3 (1.762 g, 12.853 mmol). Tubes were flushed with nitrogen, sealed and heated to 120°C for 4 hours. Reaction mixtures were combined, diluted with 200 ml diethyl ether. The organic phase was washed with brine (2 x 100 ml) and water (2 x 100 ml). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to dryness to yield a yellow oil in quantitative yield.[13]

IRυ_{max} (KBr) cm^{-1}: 1704 (C=O), 1591, 826 (ArCH). ^1H NMR ($CDCl_3$) δ: 1.34 (s, 9H, $C(CH_3)_3$), 7.67-7.69 (d, J=8.0 Hz, 2H, ArH3/H5), 7.82-7.84 (d, J=8.0 Hz, 2H, ArH2/H6), 10.03 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$) δ: 31.04 ($C(\underline{C}H_3)_3$), 47.07 ($\underline{C}(CH_3)_3$), 129.35 (ArH3/H5), 135.76 ($ArC4_q$), 136.94 (ArH2/H6), 141.19 ($ArC1_q$), 191.60 (C1). LRMS m/z calculated for $C_{11}H_{14}OS$: ($M^+ + H^+$) 195, found 195.

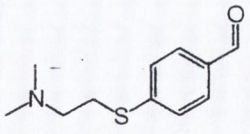
4-Phenylsulfanyl-benzaldehyde 251



Prepared *via* the general proceedure as described for the $SC(CH_3)_3$ derivative **250**. Product formed in quantitative yield as a waxy solid. m.p. 53-54°C (lit. 55-56°C)[12]

IRυ_{max} (KBr) cm^{-1}: 2734 (C-C), 1697 (C=O), 1592, 835 (ArCH). ^1H NMR ($CDCl_3$) δ: 7.24-7.26 (d, J=8.0 Hz, ArH3/H5), 7.44-7.45 (m, 3H, ArH2*/H6* + ArH4*), 7.54-7.56 (m, 2H, ArH3*/H5*), 7.23-7.75 (d, J=8.0 Hz, 2H, ArH2/H6), 9.93 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$) δ: 127.12 (ArC3*/C5*), 129.12 (ArC4*), 129.76 (ArC2*/C6*), 130.07 (ArC3/C5), 131.18 ($ArC1^*_q$), 133.62 ($ArC4_q$), 134.32 (ArC2/C6), 147.19 ($ArC1_q$), 191.13 (C1). LRMS m/z calculated for $C_{13}H_{10}OS$: (M^+) 214, found 214.

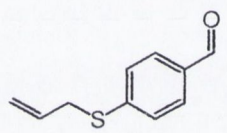
4-(2-Dimethylamino-ethylsulfanyl)-benzaldehyde 253



Prepared *via* the general proceedure as described for the $SC(CH_3)_3$ derivative **250**. Product formed in 89% yield as a brown oil.

IRυ_{max} (KBr) cm^{-1}: 1698 (C=O), 1590, 750 (ArCH). ^1H NMR ($CDCl_3$) δ: 2.30 (s, 6H, $N(CH_3)_2$), 2.61-2.64 (t, J=7.2 Hz, 2H, NCH_2), 3.11-3.15 (t, J=7.5 Hz, 2H, SCH_2), 7.35-7.37 (d, J=8.0 Hz, 2H, ArH3/H5), 7.75-7.77 (d, J=8.0 Hz, 2H, ArH1/H6), 9.91 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$) δ: 29.76 (NCH_2), 45.22 ($N(CH_3)_2$), 57.75 (SCH_2), 126.21 (ArH3/H5), 129.97 (ArH2/H6), 133.10 ($ArC4_q$), 146.48 ($ArC1_q$), 191.11 (C1). LRMS m/z calculated for $C_{11}H_{15}NOS$: ($M^+ + H^+$) 210, found 210.

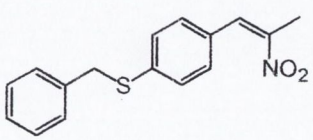
4-Allylsulfanyl-benzaldehyde



Prepared *via* the general proceedure as described for the $SC(CH_3)_3$ derivative **250**, product formed in quantitative yield as a yellow oil.

IRυ_{max} (KBr) cm^{-1}: 1694 (C=O), 1591, 836 (ArCH). ^1H NMR ($CDCl_3$) δ: 3.67-3.68 (d, J=6.5 Hz, 2H, SCH_2), 5.18-5.20 (dd, J_{cis}=10.0 Hz, J_{gem}=1.1 Hz, 1H, CH=C$\underline{H_2}$(cis)), 5.29-5.34 (dd, J_{trans}=17.1 Hz, J_{gem}=1.5 Hz, 1H, CH=C$\underline{H_2}$(trans)),5.86-5.92 (m, 1H, $SCH_2C\underline{H}$), 7.37-7.39 (d, J=8 Hz, 2H, ArH3/H4), 7.76-7.78 (d, J=8 Hz, 2H, ArH2/H6), 9.93 (s, 1H, C1). ^{13}C NMR ($CDCl_3$) δ: 35.00 (SCH_2), 118.63 (CH=$\underline{C}H_2$), 126.88 (ArH3/H5), 129.87 (ArH2/H6), 132.26 ($\underline{C}H=CH_2$), 133.33 ($ArC4_q$), 145.78 ($ArC1_q$), 191.16 (C1). LRMS m/z calculated for $C_{10}H_{10}OS$: (M^+) 178, found 178.

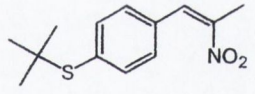
1-Benzylsulfanyl-4-(2-nitro-propenyl)-benzene 257



4-Benzylsulfanyl-benzaldehyde (1.445 g, 6.340 mmol) was dissolved in 20 ml of absolute ethanol. Nitroethane (0.456 ml, 6.340 mmol) was added followed by butylamine (8 drops). The solution was refluxed for 18 hours afterwhich it was concentrated and the residue was columned directly on silica gel using an eluent of 4:1 diethyl ether/hexane. 23% yield, yellow needles m.p. 84°C (lit. 74-75°C)[12]. Yield was increased to 72% utilising the general method for the synthesis of nitrostyrenes as used for the *tert*-butylthio derivative **225**.

IRυ_{max} (KBr) cm^{-1}: 1518, 1316 (conj-NO_2), 872, 718 (ArCH). ^1H NMR ($CDCl_3$) δ: 2.47 (s, 3H, CH_3), 4.22 (s, 2H, SCH_2), 7.28-7.39 (m, 10H, $SCH_2C_6\underline{H}_5$ + ArH2/H6/H3/H5), 8.06 (s, 1H, C$\underline{H}$=C). ^{13}C NMR ($CDCl_3$) δ: 14.13 (C3), 37.64 (SCH_2), 127.47 (ArC4*), 128.71 (ArC3*/C5*), 128.72 (ArC2*/C6*), 128.77 (ArC3*/C5*), 129.21 (ArC2/C6), 130.45 (ArC3/C5), 133.06 (C1), 135.08 ($ArC1^*_q$), 136.41 ($ArC4_q$), 140.25 ($ArC1_q$), 147.10 ($C2_q$). Elemental analysis: $C_{16}H_{15}NO_2S$ requires C, 67.34; H, 5.30; N, 4.91. Found C, 67.71; H, 5.14; N, 4.68.

1-tert-Butylsulfanyl-4-(2-nitro-propenyl)-benzene 255



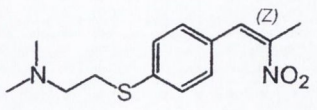
General method for the synthesis of nitrostyrenes **255, 256, 258**.

To an oven dried 100 ml round bottomflask, fitted with a Dean-Stark trap, containing 20 ml of dry toluene, nitroethane (10 ml), dimethylamine HCl (1.631 g, 20 mmol) and KF (0.090 g, 1.552 mmol) was added 4-tert-Butylsulfanyl-benzaldehyde **250** (1.943 g, 10.00 mmol) in 10 ml of dry toluene. The solution was refluxed at 148°C for 18 hours afterwhich the reaction was allowed to cool to room temperature. All volatiles were removed under reduced pressure and the yellow solid was purified on silica gel using a 4:1 hexane/diethyl ether mobile phase. The solid isolated was recrystallised from hot ethanol to give the title compound as yellow needles in 75% yield. m.p. 60-62

IRυ_{max} (KBr) cm^{-1}: 1511, 1318 (conj-NO_2), 836 (ArCH). ^1H NMR ($CDCl_3$) δ: 1.30 (s, 9H, $C(CH_3)_3$, 2.45 (s, 3H, CH_3), 7.37-7.39 (d, J=8.0 Hz, ArH3/H5), 7.58-7.60 (d, J=8.0 Hz, ArH2/H6), 8.05 (s, 1H, C$\underline{H}$=C). ^{13}C NMR ($CDCl_3$) δ: 13.78 (C3), 30.85

($C(\underline{C}H_3)_3$), 46.52 ($\underline{C}(CH_3)_3$), 129.73(ArC3/C5), 132.35 ($ArC4_q$), 132.56 (C1), 135.34 ($ArC1_q$), 137.24 (ArC2/C6), 147.86 ($C2_q$). Elemental analysis: $C_{13}H_{17}NO_2S$ requires C, 62.12; H, 6.82; N, 5.57. Found C, 62.05 H, 6.78; N, 5.51.

Dimethyl-{2-[4-(2-nitro-propenyl)-phenylsulfanyl]-ethyl}-amine 258

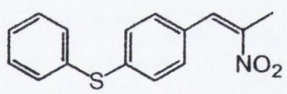


Prepared *via* the general proceedure as described for the $SC(CH_3)_3$ derivative **255**, product formed in 73% yield as a yellow oil.

IRυ_{max} (KBr) cm^{-1}: 1523, 1311 (conj-NO_2), 868 (ArCH). ^{1}H NMR ($CDCl_3$) δ: 2.28 (s, 6H, $N(CH_3)_2$, 2.44 (s, 3H, CH_3), 2.58-2.62 (t, J=7.0 Hz, 2H, $NCH\underline{2}$), 3.07-3.11(t, J=7.0 Hz, 2H, $SCH\underline{2}$), 7.28-7.36 (m, 4H, C_6H_4), 8.02 (s, 1H, $C\underline{H}$=C). ^{13}C NMR ($CDCl_3$) δ: 14.01 (C3), 30.21 (NCH_2), 45.16 ($N(CH_3)_2$), 57.94 (SCH_2),127.16 (ArC3/C5), 128.90 ($ArC4_q$), 130.43 (ArC2/C6), 132.97 (C1), 140.46 ($ArC1_q$), 146.81 ($C2_q$). LRMS m/z calculated for $C_{13}H_{18}N_2O_2S$: (M^++H^+) 267, found 267.

1-Phenylsulfanyl-4-(2-nitro-propenyl)-benzene 256

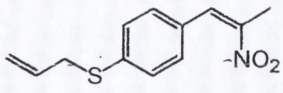
Prepared *via* the general proceedure as described for the $SC(CH_3)_3$ derivative **255**, product formed in 46% yield



IRυ_{max} (KBr) cm^{-1}: 1584, 1300 (conj-NO_2), 870, 825 (ArCH). ^{1}H NMR ($CDCl_3$) δ: 2.47 (s, 3H, CH_3), 7.27-7.29 (m, 2H, ArH3/H5), 7.34-7.36 (m, 2H, ArH2/H6), 7.41-7.44 (m, 3H, ArH2*/H6*/H4*), 7.50-7.52 (m, 2H, ArH3*/H4*), 8.05 (s, 1H, $C\underline{H}$=C). ^{13}C NMR ($CDCl_3$) δ: 14.12 (C3), 128.52 (ArC3/C5), 129.60 (ArC3*/C5*), 129.86 ($ArC1_q$*), 130.61(ArC2/C6), 132.63 ($ArC4_q$), 132.94 (C1), 133.36 (ArC2*/C6*), 140.84 ($ArC1_q$),147.25 ($C2_q$).

1-Allylsulfanyl-4-(2-nitro-propenyl)-benzene

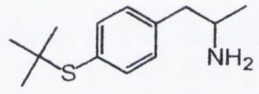
Prepared *via* the general proceedure as described for the $SC(CH_3)_3$ derivative **255**, product formed in 75% yield



IRυ_{max} (KBr) cm^{-1}: 1638 (C=C), 1509, 1320 (conj-NO_2), 870, 773 (ArCH). ^1H NMR ($CDCl_3$) δ: 2.47 (s, 3H, CH_3), 3.64-3.66 (d, J=7.0 Hz, 2H, SCH_2), 5.16-5.19 (dd, J_{cis}=10.0 Hz, J_{gem}=1.0 Hz, 1H, CH=C$\underline{H}_2$(cis)), 5.25-5.29 (dd, J_{trans}=17.1 Hz, J_{gem}=1.5 Hz, 1H, CH=C$\underline{H}_2$(trans)), 5.87-5.95 (m, 1H, $SCH_2C\underline{H}$), 7.35-7.38 (m, 4H, C_6H_4), 8.06 (s, 1H, C$\underline{H}$=C). ^{13}C NMR ($CDCl_3$) δ: 14.13 (C3), 35.77 (SCH_2), 118.36 (CH=$\underline{C}H_2$),128.14 (ArC3/C5), 129.40 ($ArC4_q$), 132.77 (CH_2=$\underline{C}H_2$), 133.08 (C1), 139.82 ($ArC1_q$), 147.08 ($C2_q$). Elemental analysis: $C_{12}H_{13}NO_2S$ requires C, 61.25; H, 5.57; N, 5.95. Found C, 60.96; H, 5.38; N, 5.81.

2-(4-tert-Butylsulfanyl-phenyl)-1-methyl-ethylamine 259

(4-tertbutlythioamphetamine)



To a stirred suspension of LAI (0.655 g, 17.259 mmol) in 20 ml of dry THF was added very slowly 1-tert-Butylsulfanyl-4-(2-nitro-propenyl)-benzene **255** (0.868 g, 3.45 mmol) in 10 ml of dry THF under a nitrogen atmosphere. The suspension was heated to reflux for 12 hours afterwhich TLC showed the complete consumption of start material. The reaction was quenched by the careful dropwise addition at 0°C of 10 ml of 20:1 methanol/H_2O followed by the addition of 50 ml 15% NaOH. The inorganic salts were removed by filtration on a buckner funnel. The filtrate was extracted with ethyl acetate (3 x 75 ml). The organic layer was washed with 10% HCl (4 x 50 ml), this acidic extract was basified with 15% NaOH to pH 8 and extracted with ethyl acetate (3 x 100 ml). The solvent was removed *in vacuo* to leave a yellow oil, that was further purified on a short silica column using a 100% methanol eluent to yield the title compound as a pale yellow oil (58%).

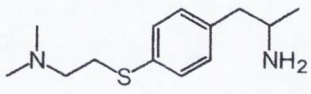
IRυ_{max} (KBr-HCl salt) cm^{-1}: 2956 (N-H), 1505, 797 (ArCH). ^1H NMR ($CDCl_3$) δ: 1.06-1.08 (d, J=6.0 Hz, 3H, CHC$\underline{H}_3$), 1.23 (s, 9H, $C(CH_3)_3$), 1.39 (s, 2H, NH_2), 2.47-2.68 (2dd, J_{gem}=13 Hz, J_{vic}=8.0 Hz ($C\underline{H}_2$CH), J_{gem}=13 Hz, J_{vic}=5.5 Hz ($C\underline{H}_2$*CH), 2H, $C\underline{H}_2$CH), 3.09-3.17 (m, 1H, $CH_2C\underline{H}$), 7.10-7.12 (d, J=8.0 Hz, 2H, ArH3/H5), 7.41-7.43 (d, J=8.0 Hz, 2H, ArH2/H6). ^{13}C NMR ($CDCl_3$) δ: 23.34 (C3), 30.71 ($C(\underline{C}H_3)_3$),

45.47 ($\underline{C}(CH_3)_3$), 46.07 (C1), 48.17 (C2), 129.17 (ArC3/C5), 129.97 ($ArC4_q$), 137.30 (ArC2/C6), 140.22 ($ArC1_q$). HRMS calculated for $C_{13}H_{22}NS$: (M^++H^+) 224.1473, found 224.1479.

2-[4-(2-Dimethylamino-ethylsulfanyl)-phenyl]-1-methyl-ethylamine 262

(4-(2-Dimethylaminoethyl)thioamphetamine).

Prepared *via* the general proceedure as described for the $SC(CH_3)_3$ amphetamine derivative **259**, product formed in 52% yield

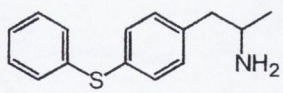


IRυ_{max} (film) cm^{-1}: 3438 (N-H), 2479 (C-C), 1511, 684 (ArCH). ^1H NMR ($CDCl_3$) δ: 1.10-1.12 (d, J=6.5 Hz, 3H, $CHC\underline{H}_3$), 1.26 (s, 2H, NH_2), 2.26 (s, 6H, $N(CH_3)_2$), 2.45-2.51 (dd, J_{gem}=13.0 Hz, J_{vic}=8.0 Hz, 1H, ($C\underline{H}_2CH$)), 2.53-2.57 (t, J=7.0 Hz, 2H, (NCH_2)), 2.64-2.69 (dd, J_{gem}=13.0 Hz, J_{vic}=5.5 Hz, 1H, ($C\underline{H}_2$*CH)), 2.98-3.03 (t, J=7.0 Hz, 2H, (SCH_2)), 3.09-3.18 (m, 1H, $CH_2C\underline{H}$), 7.10-7.12 (d, J=8.0 Hz, 2H, ArH3/H5), 7.28-7.30 (d, J=8.0 Hz, 2H, ArH2/H6). ^{13}C NMR ($CDCl_3$) δ: 23.51 (C3), 31.73 (C1), 45.28 ($N(CH_3)_2$), 46.08 (NCH_2), 48.35 (C2), 58.57 (SCH_2), 129.25 (ArC3/C5), 129.76 (ArC2/C6), 133.75 ($ArC4_q$), 137.61 ($ArC1_q$). HRMS calculated for $C_{13}H_{22}N_2S$: (M^++H^+) 239.1582, found 239.1580.

1-Methyl-2-(4-phenylsulfanyl-phenyl)-ethylamine 261

(4-Phenylthioamphetamine)

Prepared *via* the general proceedure as described for the $SC(CH_3)_3$ derivative **259**, product formed in 47% yield

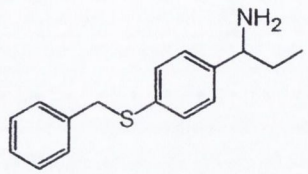


IRυ_{max} (KBr-HCl salt) cm^{-1}: 2905 (N-H), 2490 (C-C), 1496, 740 (ArCH). ^1H NMR ($CDCl_3$) δ: 1.13-1.15 (d, J=6.5 Hz, 3H, $CHC\underline{H}_3$), 1.95 (s, 2H, NH_2), 2.52-2.73 (2dd, J_{gem}=13.5 Hz, J_{vic}=7.5 Hz ($C\underline{H}_2CH$), J_{gem}=13.5 Hz, J_{vic}=5.5 Hz ($C\underline{H}_2$*CH), 2H, $C\underline{H}_2CH$), 3.14-3.20 (m, 1H, $CH_2C\underline{H}$), 7.14-7.16 (d, J=8.0 Hz, 2H, ArH3/H5), 7.25-7.32 (m, 7H, ArH2/H6 + C_6H_5). ^{13}C NMR ($CDCl_3$) δ: 23.21 (C3), 45.83 (C1), 48.29 (C2), 126.70 (ArC4*), 129.03 (ArC3/C5), 130.06 (ArC3*/C5*), 130.41 (ArC2*/C6*),

131.47 (ArC2/C6), 132.83 ($ArC4_q$), 136.13 ($ArC1^*_q$), 138.75 ($ArC1_q$). HRMS calculated for $C_{15}H_{17}NS$: (M^++H^+) 244.1160, found 244.1172.

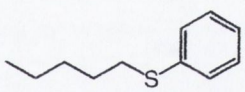
1-(4-Benzylsulfanyl-phenyl)-propylamine 257

Prepared *via* the general proceedure as described for the $SC(CH_3)_3$ derivative **259**, product formed in 71% yield



IRυ_{max} (KBr-HCl salt) cm^{-1}: 2936 (N-H), 2497 (C-C), 1494, 793 (ArCH). ^1H NMR ($CDCl_3$) δ: 1.12 (d, J=6.2 Hz, 3H, $CHC\underline{H}_3$), 1.58 (s, 2H, NH_2), 2.47-2.52 (dd, 1H, J_{gem}=13.3 Hz, J_{vic}=8.0 Hz ($C\underline{H}_2CH$), 3.11-3.19 (m, 1H, $CH_2C\underline{H}$), 4.11 (s, 2H, SCH_2), 7.08-7.10 (d, J=8.1 Hz, 2H, ArH3/H5), 7.25-7.32 (m, 7H, ArH2/H6, C_6H_5). ^{13}C NMR ($CDCl_3$) δ: 23.39 (C3), 39.33 (SCH_2), 46.02 (C1), 48.33 (C2), 127.06 ($ArC4^*$), 128.37 (ArC3/C5), 128.75 ($ArC3^*/C5^*$), 129.69 ($ArC2^*/C6^*$), 130.27 (ArC2/C6), 133.64 ($ArC4_q$), 137.48 ($ArC1^*_q$), 138.04 ($ArC1_q$). HRMS calculated for $C_{16}H_{19}NS$: (M^++H^+) 257.1238, found 257.1242

Pentylsulfanyl-benzene 247



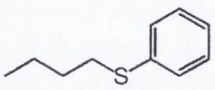
To a dry 3-neck 100 ml RBF was added, under nitrogen, thioanisole (0.497 g, 4.00 mmol) in dry THF (20 ml). The solution was cooled to –57°C and Sec-BuLi (5.714 ml (1.4M in C_6H_{12}), 4.10mmol) was added dropwise. The solution was stirred for 1.5 hours afterwhich, iodobutane (0.478 ml, 4.00 mmol) was added dropwise. The reaction mixture was allowed to rise to room temperature and was stirred for 3.5 hours before being poured slowly onto crushed ice and extracted with DCM (4 x 100 ml). The organic extracts were combined, dried over anhydrous Na_2SO_4, filtered and removed *in vacuo*. The resulting oil was purified on silica gel using a 95:5 hexane:diethyl ether mobile phase (76%).

IRυ_{max} (film) cm^{-1}: 1514, 729 (ArCH). ^1H NMR ($CDCl_3$) δ: 0.92-0.96 (t, J=7.0 Hz, 3H, $C\underline{H}_3CH_2$), 1.31-1.49 (m, 4H, $CH_3C_2\underline{H}_4$) 1.66-1.73 (m, 2H, $C\underline{H}_2CH_2S$), 2.94-2.97 (t,

J=7.5 Hz, 2H, CH_2SAr), 7.17-7.21 (m, 1H, ArH4), 7.28-7.38 (m, 4H, ArH2/6+ArH3/5). ^{13}C NMR ($CDCl_3$) δ: 13.93 (C1), 22.21 (C2), 28.78 (C3), 30.97 (C4), 33.44 (C5), 125.55 (ArC4), 128.73 (ArC2/C6), 128.76 (ArC3/C5), 137.00 ($ArC1_q$). LRMS m/z calculated for $C_{11}H_{16}S$: (M^+) 180, found 180.

Butylsulfanyl-benzene 248

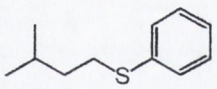
Prepared *via* the general proceedure as described for the **247**, product formed in 20% yield



IRυ_{max} (film) cm^{-1}: 2818 (CH), 1526, 731 (ArCH). ^1H NMR ($CDCl_3$) δ: 0.95-0.99 (t, J=7.2 Hz, 3H, $C\underline{H}_3CH_2$), 1.45-1.55 (m, 2H, $CH_3C\underline{H}_2$), 1.65-1.72 (m, 2H, $CH_3CH_2C\underline{H}_2$), 2.95-2.99 (t, J=7.6 Hz, 2H, CH_2SAr), 7.27-7.38 (m, 5H, C_6H_5). ^{13}C NMR ($CDCl_3$) δ: 13.60 (C1), 21.92 (C2), 31.16 (C3), 33.15 (C4), 125.54 (ArC4), 128.73 (ArC2/C6), 128.75 (ArC3/C5), 136.99 ($ArC1_q$). LRMS m/z calculated for $C_{10}H_{14}S$: (M^+) 166, found 166.

(3-Methyl-butylsulfanyl)-benzene 249

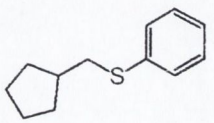
Prepared *via* the general proceedure as described for the **247**, product formed in 29% yield



IRυ_{max} (film) cm^{-1}: 1520, 733 (ArCH). ^1H NMR ($CDCl_3$) δ: 0.94-0.96 (d, J=6.1 Hz, 6H, $CH(C\underline{H}_3)_2$), 1.54-1.62 (m, 2H, $CHC\underline{H}_2$) 1.71-1.81 (m, 1H, $CH_2C\underline{H}$), 2.94-2.98 (t, J=8.0 Hz, 2H, SCH_2), 7.26-7.36 (m, 5H, C_6H_5). ^{13}C NMR ($CDCl_3$) δ: 22.22 (C1/C1*), 27.43 (C2), 31.49 (C3), 37.98 (C4), 125.55 (ArC4), 128.66 (ArC2/C6), 128.77 (ArC3/C5), 136.97 ($ArC1_q$). LRMS m/z calculated for $C_{11}H_{16}S$: (M^+) 180, found 180.

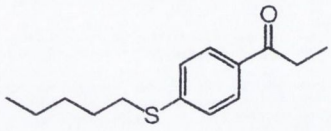
Cyclopentylmethylsulfanyl-benzene 246

Prepared *via* the general proceedure as described for the **247**, product formed in 12% yield



IRυ_{max} (film) cm^{-1}: 1522, 698 (ArCH). ^1H NMR ($CDCl_3$) δ: 1.57-1.70 (m, 4H, $CH_2(C\underline{H}_2)_2CH_2$), 1.84-1.91 (m, 4H, $CH(C\underline{H}_2)_2$), 2.09-2.19 (m, 1H, $C\underline{H}CH_2S$), 7.29-7.41 (m, 5H, C_6H_5). ^{13}C NMR ($CDCl_3$) δ: 25.20 (C1/1*), 32.37 (C2/2*), 39.32 (C3), 39.73 (C4), 125.48 (ArC4), 128.68 (ArC2/C6/C3/C5), 136.99 ($ArC1_q$). LRMS m/z calculated for $C_{12}H_{16}S$: (M^+) 192, found 192.

1-(4-Pentylsulfanyl-phenyl)-propan-1-one 245a

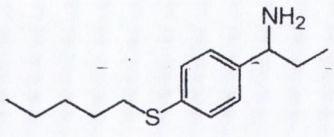


Pentylsulfanyl-benzene **247** (0.415 g, 2.31 mmol) was dissolved in dry DCM (30 ml) and the solution was cooled to 0°C with an ice bath. $AlCl_3$ (0.401 g, 3.00 mmol) was added, followed by the slow dropwise addition of propionyl chloride (0.361 ml, 4.16 mmol). After the addition of the acid chloride the reaction was allowed to warm to ambient temperature and stirred for a further 3 hours. The reaction was diluted with 200 ml DCM and poured slowly into 100 ml of ice-water. The organic phase was washed with water (6 x 100 ml). The organic layer was dried over anhydrous Na_2SO_4, filtered and removed under vacuum. The solid formed was recrystallised from hexane/ether to yield the title compound as colourless needles (94%).

IRυ_{max} film: 2931 (C-C), 1677 (C=O), 1592, 822 (Ar) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.90-0.94 (t, J=7.0 Hz, 3H, $COCH_2C\underline{H}_3$), 1.21-1.24 (t, J=7.5 Hz, 3H, $C\underline{H}_3C_4H_8$), 1.32-1.48 (m, 4H, $CH_3C_2\underline{H}_4$) 1.68-1.75 (m, 2H, $C\underline{H}_2CH_2S$), 2.94-3.01 (m, 4H, $C\underline{H}_2SAr$ + $COC\underline{H}_2$), 7.29-7.31 (d, J=8.5 Hz, 2H, ArH2/6), 7.86-7.89 (d, J=8.5 Hz, 2H, ArH3/5). ^{13}C NMR ($CDCl_3$) δ: 8.25 (C1), 13.89 (C8), 22.18 (C7), 28.38 (C6), 30.99 (C5), 31.50 (C2), 31.87 (C4), 126.19 (ArC3/C5), 128.34 (ArC2/C6), 133.36 ($ArC4_q$), 144.53 ($ArC1_q$), 199.81 (C1). Elemental analysis: $C_{14}H_{20}OS$ requires C, 71.14; H, 8.53. Found C, 70.97; H, 8.53.

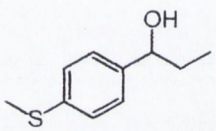
1-(4-Pentylsulfanyl-phenyl)-propylamine 245

Prepared *via* the general proceedure as described for the **149**, product formed as an oil that solidified on standing in 48% yield



IRυ_{max} (film) cm^{-1}: 3433 (N-H), 1528, 801 (ArCH). ^{1}H NMR ($CDCl_3$)^{1}H NMR ($CDCl_3$) δ: 0.78-0.83 (t, J=7.5 Hz, 3H, H3), 0.88-0.91 (t, J=7.0 Hz, 3H, H8), 1.26-1.44 (m, 4H, H7/H6), 1.61-1.72 (m, 4H, H5/H2), 2.81 (s, 2H, NH_2) 2.88-2.92 (t, J=7.5 Hz, 2H, H4), 3.73-3.76 (t, J=7.0 Hz, 1H, H1), 7.21-7.23 (d, J=8.0 Hz, 2H, ArH3/5), 7.26-7.29 (d, J=8.0 Hz, 2H, ArH2/6). ^{13}C NMR ($CDCl_3$) δ: 10.73 (C1), 13.87 (C8), 22.14 (C7), 28.75 (C6), 30.89 (C5), 31.76 (C2), 33.59 (C4), 57.12 (C1), 126.94 (ArC2/C6), 128.87 (ArC3/C5), 135.27 ($ArC4_q$), 142.92 ($ArC1_q$). LRMS $C_{14}H_{23}NS$ requires m/z 237, found (M^+ - 16); m/z 207, $C_{14}H_{21}S$.

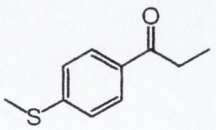
1-(4-Methylsulfanyl-phenyl)-propan-1-ol 246



Prepared *via* the general grignard alkylation proceedure as described for the **154**, product formed in 29% yield

^{1}H NMR ($CDCl_3$) δ: 0.91-0.94 (t, J=7.5 Hz, 3H, $CH_2C\underline{H}_3$), 1.65-1.90 (m, 2H, $C\underline{H}_2CH_3$), 2.50 (s, 3H, SCH_3), 4.56-4.60 (t, J=7.0 Hz, 1H, C<u>H</u>OH), 7.25-7.30 (m, 4H, C_6H_4). ^{13}C NMR ($CDCl_3$) δ: 10.21 (C3), 30.11 (C2), 33.18 (SCH_3), 72.80 (C1) 126.21 (ArC3/C5), 127.41 (ArC2/C6), 133.42 ($ArC4_q$), 143.39 ($ArC1_q$). LRMS m/z calculated for $C_{10}H_{14}OS$: (M^++H^+) 183, found 183.

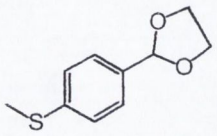
1-(4-Methylsulfanyl-phenyl)-propan-1-one 241



Prepared using the PCC oxidation method as described for **150**.

IRυ_{max} film 1672 (C=O) cm^{-1}, 1096 (C-O) cm^{-1}, 792 (Ar) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.22-1.26 (t, J=7.0 Hz, 3H, $CH_2C\underline{H}_3$), 1.65-1.90 (m, 2H, CH_2CH_3), 2.53 (s, 3H, SCH_3), 2.95-3.01 (q, J=7.0 Hz, 2H, $C\underline{H}_2CH_3$), 7.26-7.29 (d, J=8.0 Hz, 2H, ArH3/5), 7.88-7.90 (d, J=8.0 Hz, 2H, ArH2/6). ^{13}C NMR ($CDCl_3$) δ: 8.28 (C3), 14.74 (SCH_3), 31.53 (C2), 124.93 (ArC3/5), 128.36 (ArC2/6), 133.17 ($ArC4_q$), 145.44 ($ArC1_q$), 199.85 (C1). LRMS m/z calculated for $C_{10}H_{12}OS$: (M^+) 180, found 180.

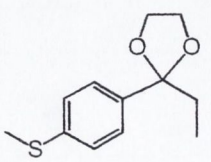
2-(4-Methylsulfanyl-phenyl)-[1,3]dioxolane 242a



4-Methylthiobenzaldehyde (7.983 ml, 60.00 mmol) was dissolved in toluene (200 ml) with ethylene glycol (43.50 ml, 780.00 mmol) and the mixture was refluxed with a Dean-Stark trap for 20 hours. The reaction mixture was allowed to cool to room temperature seperating into two layers. The ethylene glycol fraction was taken, diluted with water (150 ml) and extracted with toluene (3 x 100 ml). The toluene layers were combined and washed with saturated $NaHCO_3$ (4 x 100 ml). The organic layer was dried over anhydrous Na_2SO_4, filtered and removed under reduced pressure to leave a clear yellow oil, 100%.

IRυ_{max} film: 1039 (C-O) cm^{-1}, 898 (ArC-C) cm^{-1}, 734 (S-C). ^{1}H NMR ($CDCl_3$) δ: 2.51 (s, 3H, SCH_3), 4.03-4.06 (m, 2H, $OCH_2C\underline{H}_2O$), 4.12-4.16 (m, 2H, $OC\underline{H}_2CH_2O$), 5.80 (s, 1H, C$\underline{H}$), 7.27-7.29 (d, J=8.5 Hz, 2H, ArH2/6), 7.41-7.43 (d, J=8.5 Hz, 2H, Ar3/5). ^{13}C NMR ($CDCl_3$) δ: 15.77 (SCH_3), 64.48 ($O\underline{C}_2H_4O$), 109.39 (C1), 126.22 (ArC2/6), 126.32 (ArC3/5), 137.79 ($ArC4_q$), 139.52 ($ArC1_q$). LRMS calculated for $C_{10}H_{12}O_2S$: (M^++ H^+) requires m/z 197, found 197.

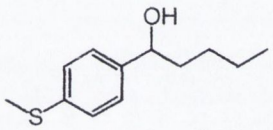
2-Ethyl-2-(4-methylsulfanyl-phenyl)-[1,3]dioxolane 242b



Prepared *via* the general proceedure as described for the **242a**, product formed in 95% yield

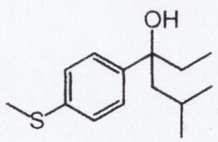
IRυ_{max} film: 1043 (C-O) cm^{-1}, 909 (ArC-C) cm^{-1}, 734 (S-C). ^{1}H NMR ($CDCl_3$) δ: 0.88-0.92 (t, J=7.0 Hz, 3H, $CH_2C\underline{H}_3$), 1.89-1.94 (q, J=7.0 Hz, 2H, $C\underline{H}_2CH_3$), 2.50 (s, 3H, SCH_3), 3.74-3.82 (m, 2H, $OCH_2C\underline{H}_2O$), 3.98-4.06 (m, 2H, $OC\underline{H}_2CH_2O$), 7.24-7.25 (d, J=8.5 Hz, 2H, ArH2/6), 7.37-7.39 (d, J=8.5 Hz, 2H, Ar3/5). ^{13}C NMR ($CDCl_3$) δ: 7.85 (C3), 15.78 (SCH_3), 33.36 (C2), 64.53 ($O\underline{C}_2H_4O$), 110.59 (C1), 126.19 (ArC2/6), 126.36 (ArC3/5), 137.84 ($ArC4_q$), 139.49 ($ArC1_q$). LRMS calculated for $C_{12}H_{16}O_2S$: ($M^+ + H^+$) requires m/z 225, found 225.

1-(4-Methylsulfanyl-phenyl)-pentan-1-ol 244



yellow oil 18% IRυ_{max} υ cm^{-1} film 3448 (OH), 1280 (C-O), 822 (Ar). ^{1}H NMR ($CDCl_3$) δ: 0.88-0.92 (t, J=7.0 Hz, 3H, H5), 1.20-1.42 (m, 4H, H4/H3), 1.64-1.83 (m, 2H, H2), 2.12 (s, 1H, OH), 2.49 (s, 3H, SCH_3), 4.60-4.63 (t, J=7.0 Hz, 1H, C$\underline{H}$OH), 7.23-7.26 (m, 4H, C_6H_4). ^{13}C NMR ($CDCl_3$) δ: 13.96 (C5), 15.86 (SCH_3), 22.53 (C4), 27.86 (C3), 38.64 (C2), 74.15 (C1), 126.42 (ArC2/6), 126.59 (ArC3/5), 137.26 ($ArC4_q$), 141.81 ($ArC1_q$). LRMS calculated for $C_{12}H_{18}OS$: ($M^+ + H^+$) requires m/z 211, found 211.

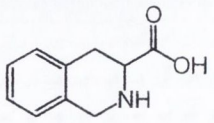
5-Methyl-3-(4-methylsulfanyl-phenyl)-hexan-3-ol 244a



Isolated as a clear oil in 62% from the dropwise addition of *sec*-BuLi (2.51 ml, 1.4M soln) to **242b** (0.393g, 1.755 mmol) in dry THF at -58°C. The mixture was allowed to stir 90 minutes afterwhich iodobutane (0.205ml, 1.80 mmol) was added dropwise. The reaction was brought slowley to room temperature and allowed to stir overnight. Reaction mixture was worked up in the same manner described in the synthesis of **247**.

IRυ_{max} (film) υ cm^{-1}: 3469 (O-H), 1098 (C-O) cm^{-1}, 816 (ArC-C) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 0.68-0.71 (t, J=7.5 Hz, 3H, $CH_2C\underline{H}_3$, [R1]), 0.72-0.75 (t, J=7.5 Hz, 3H, $CH_2C\underline{H}_3$, [R2]), 0.76-0.77 (d, J=7.0 Hz, 3H, $CHC\underline{H}_3$ [R1]), 0.82-0.84 (d, J=7.0 Hz, 3H, $CHC\underline{H}_3$* [R1]), 0.87-0.92 (m, 1H, $CHC\underline{H}_2$, [R1]), 0.90-0.91 (d, J=6.5 Hz, 3H, $CHC\underline{H}_3$ [R2]), 0.94-0.96 (d, J= 6.5 Hz, 3H, $CHC\underline{H}_3$* [R2]), 1.23-1.39 (m, 2H, $CHC\underline{H}_2$, [R2]), 1.65 (s, 2H, OH, [R1+R2]), 1.67-1.73 (m, 2H, $C\underline{H}(CH_3)_2$, [R1+R2]), 1.75-1.81 (m, 1H, $CHC\underline{H}_2$*, [R1]), 1.84-1.89 (q, J=6.7 Hz, 2H, $C\underline{H}_2CH_3$, [R1]), 1.89-1.93 (q, J=6.7 Hz, 2H, $C\underline{H}_2CH_3$, [R2]), 2.50 (s, 6H, SCH_3, [R1+R2]), 7.22-7.24 (d, J=8.5 Hz, 4H, ArH2/6, [R1+R2]), 7.29-7.31 (d, J=8.5 Hz, 4H, ArH3/5, [R1+R2]). ^{13}C NMR ($CDCl_3$) δ: 7.76 (C1, [R1]), 7.80 (C1, [R2]), 12.48, 12.54, 12.58 (C6*, [R1], $C6CH_3$, [R1+R2] 13.55 (C6, [R1]), 15.76 (SCH_3), 23.06 (C4, [R1]), 23.93 (C4, [R2]), 31.58 (C2, [R2]), 31.95 (C2, [R1]), 44.50, 44.69 (C5, [R1+R2]), 79.42, 79.61 (C3, [R1+R2]), 125.88, 125.95 (ArC2/6, [R1+R2]), 126.45, 126.59 (ArC3/5, [R1+R2]), 135.62, 135.65 ($ArC4_q$, [R1+R2]), 142.06, 142.43 ($ArC1_q$, [R1+R2]). HRMS m/z calculated for $C_{14}H_{22}OS$: requires 238.1391, found 238.1399.

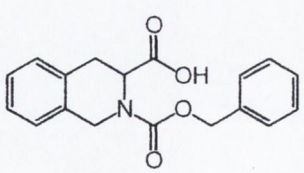
1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic acid 272



A mixture of (L)-phenylalanine (5 g, 30.27 mmol) and 40% formaldehyde 11.30 ml and 38 ml of concentrated HCl (added after 5 minutes) were heated with rigorous stirring to 100°C for 1.5 hours. A further 5 ml 40% formaldehyde plus 16 ml concentrated HCl were added and the mixture was heated for 3.5 hours. The reaction was cooled with an ice bath and the solids precipitated were collected by filtration and triturated with ethanol to leave a colourless solid (74%) m.p. 301°C (lit 309-310°C)[14].

IRυ_{max} (KBr): 2727-3243 (N-H, COOH), 1747 (C=O) cm^{-1}, 1196, 771 (Ar) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.84 (s, 1H, NH), 3.11-3.18 (dd, J_{gem}=16.6 Hz (H4*-H4), J_{vic}=11.6 Hz (H4*-H3), 1H, H4*), 3.28-3.34 (dd, J_{gem}=16.6 Hz, J_{vic}=5.0 Hz (H4-H3), 1H, H4), 4.31 (s, 2H, H1), 4.38-4.41 (dd, J_{gem}=5.0 Hz (H3-H4), J_{gem}=11.0 Hz (H3-H4*), 1H, H3), 7.26 (s, 4H, H5-8). 10.08 (s, 1H, COOH). ^{13}C NMR ($CDCl_3$) δ: 28.28 (C4), 43.87 (C1), 53.21 (C3), 126.05 (C6), 126.37 (C7), 126.96 (C8), 127.98 ($C5C_q$), 128.28 (C5), 130.34 ($C8C_q$), 169.35 (COOH). LRMS calculated for m/z $C_{10}H_{11}NO_2$: (M^+) 177, found m/z 177.

3,4-Dihydro-1H-isoquinoline-2,3-dicarboxylic acid 2-benzyl ester 272a



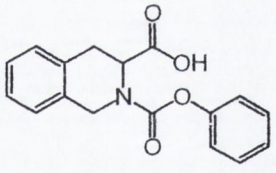
The 1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic acid.HCl **272** starting material (3.534 g, 16.59 mmol), was dissolved in water (150 ml). 20% NH_2OH was used to adjust the pH to 9. With vigorous stirring $NaHCO_3$ (3.903 g, 46.46 mmol) was added in small portions to avoid foaming. Benzylchloroformate (2.284 ml, 16.00 mmol) was added dropwise in 6 portions. The pH was maintained between pH 8 – 9 using 15% NaOH as necessary. When all the reagents were added the solution was stirred for

three hours afterwhich it was extracted with diethyl ether (4 x 50 ml). The pH was adjusted to pH 2.2 with 10% HCl and extracted with ethyl acetate (3 x 100 ml). The ethyl acetate was dried over anhydrous Na_2SO_4, filtered and removed *in vacuo* to yield the product as a clear oil (54%).

IRυ_{max} cm^{-1} (KBr): 2960-3031 (OH), 1753, 1703 (C=O), 739 (Ar). ^{1}H NMR ($CDCl_3$) δ: 3.17-3.32 (m, 2H, H4), 4.55-4.64 (m, 1H, H1 [R1]), 4.78-4.82 (m, 1H, H1 [R2]), 4.99-5.01 (m, 0.45H, H3 [R2]), 5.16-5.31 (m, 2.55H, H3 [R1] + O$\underline{C}H_2$Ar), 7.09-7.42 (m, 9H, H5-8 + $C_6\underline{H}_5$). 9.07 (s, 1H, COOH). ^{13}C NMR ($CDCl_3$) δ: 30.71 (C4, [R1]), 31.15 (C4, [R2]), 44.21 (C1, [R1]), 44.40 (C1, [R2]), 52.90 (C3, [R1]), 53.39 (C3, [R2]), 67.60 (O$\underline{C}H_2$Ar, [R1]), 67.76 (O$\underline{C}H_2$Ar, [R2]), 126.18 (C6, [R1]), 126.32 (C6, [R2]), 126.83 (C7, [R1]), 126.87 (ArC4*), 126.98 (C7, [R2]), 127.83, 127.94 (C8, [R1+R2]), 128.03, 128.12 (C5, [R1+R2]), 128.41 (ArC2/6*), 128.50 (ArC3/5*), 128.96 ($C5C_q$), 131.27 ($C8C_q$), 132.09 ($ArC1^*_q$, [R1]), 132.81 ($ArC1^*_q$, [R2]), 155.44 (N$\underline{C}$OO, [R2]), 156.30 (N$\underline{C}$OO, [R1]), 176.25 ($\underline{C}$OOH, [R1]), 176.53 ($\underline{C}$OOH, [R2]). HRMS calculated for $C_{18}H_{17}NO_4$: (M^+ + Na) 334.1055, found 334.1063.

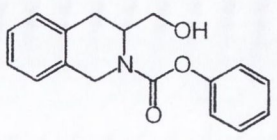
3,4-Dihydro-1H-isoquinoline-2,3-dicarboxylic acid 2-phenyl ester 272b

Prepared via the general proceedure as described for the **272a**, product formed in 47% yield



IRυ_{max} cm^{-1} (KBr): 3441 (OH), 2830 (CH), 1752, 1699 (C=O), 698 (Ar). ^{1}H NMR ($CDCl_3$) δ: 3.23-3.38 (m, 2H, H4), 4.65-4.69 (d, J=16.4 Hz, 0.40H, H1* [R1]), 4.82-4.87 (2d, J=4.7 Hz, 1H, H1 [R1+R2]), 5.00-5.04 (d, J=16.4 Hz, 0.60H, H1* [R2]), 5.19-5.25 (d, 1H, H3), 7.15-7.45 (m, 9H, H5-8 + $C_6\underline{H}_5$), 9.40 (s, 1H, COOH). ^{13}C NMR ($CDCl_3$) δ: 30.69 (C4, [R1]), 31.14 (C4, [R2]), 44.60 (C1, [R1]), 44.71 (C1, [R2]), 53.13 (C3, [R1]), 53.92 (C3, [R2]), 121.63 (ArC2/6*), 125.52 (ArC4*), 126.19 (C6, [R1]), 126.36 (C6, [R2]), 126.98 (C7), 128.04, 128.14 (C8, [R1+R2]), 128.53, (C5), 129.25 (ArC3/5*), 131.22 ($C5C_q$, [R1]), 131.26 ($C5C_q$, [R2]), 131.95 ($C8C_q$, [R1]), 132.59 ($C8C_q$, [R2]), 150.89 (ArC1*, [R2]), 151.00 (ArC1*, [R1]) 155.13 (N$\underline{C}$OO, [R2]), 154.85 (N$\underline{C}$OO, [R1]), 175.73 ($\underline{C}$OOH, [R1]), 175.89 ($\underline{C}$OOH, [R2]). HRMS calculated for m/z $C_{17}H_{15}NO_4$: (M^+) 297.1001, found m/z 298. 1016.

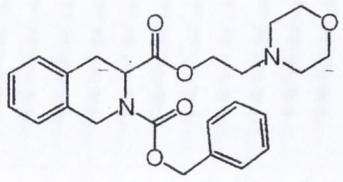
3-Hydroxymethyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid phenyl ester



To a stirred solution of 3,4-Dihydro-1H-isoquinoline-2,3-dicarboxylic acid 2-phenyl ester **272d** (0.459 g, 1.55 mmol) in dry DCM under a nitrogen atmosphere was added oxalyl chloride (0.549 g, 4.33 mmol) and three drops of anhydrous DMF at 0°C. The solution was allowed to warm to ambient temperature and was stirred for 3 hours. Volatiles were removed *in vacuo* and the acid chloride uncharacterised was dissolved in 50 ml of dry DCM added to a 100 ml dry RBF flushed with nitrogen. The solution was cooled to –50°C. A methanolic slurry of $NaBH_4$ (0.293 g, 7.72 mmol in 15 ml) was cooled to –20°C and added to the reaction mixture over 15 minutes. After three hours 20 ml of acetone was added slowly, followed by the dropwise addition of 10% HCl (15 ml). The mixture was then extracted with DCM (4 x 100 ml), which was dried over anhydrous Na_2SO_4, filtered and removed under vacuum. The resulting oil was purified on silica gel with a 60:40 hexane:diethyl ether mobile phase to yield the product as a waxy solid 32%.

IRυ_{max} cm^{-1} (KBr): 3424 (OH), 1716, 1699 (C=O), 1413 (C-N), 746 (Ar). ^{1}H NMR ($CDCl_3$) δ: 2.85-2.91 (m, 1H, H3), 3.09-3.17 (m, 2H, H4), 3.43-3.62 (m, 2H, C$\underline{H_2}$OH), 4.38-4.42 (d, J=16.5 Hz, 0.41H, H1* [R2]), 4.59-4.63 (d, J=16.5 Hz, 0.60H, H1* [R1]), 4.70 (m, 1H, OH), 4.89-4.92 (d, J=16.5 Hz, 0.39H, H1 [R2]), 4.99-5.03 (d, J=16.5 Hz, 0.61 Hz, H1 [R1]), 7.18-7.42 (m, 9H, H5-8 + $C_6\underline{H_5}$). ^{13}C NMR ($CDCl_3$) δ: 29.51 (C4, [R1]), 29.63 (C4, [R2]), 43.89 (C1, [R2]), 43.96 (C1, [R1]), 52.27 (C3, [R1]), 52.33 (C3, [R2]), 61.93 ($C3CH_2$ [R2]), 62.68 ($C3CH_2$ [R1]), 121.66 (ArC2/6*), 125.15 (C6, [R1]), 125.22 (C6, [R2]), 125.90 (ArC4*, [R1]), 126.08 (ArC4*, [R2]), 126.36 (C7), 126.78 (C8, [R2]), 126.99 (C8, [R1]), 128.69 (C5 [R2]), 128.83 (C5 [R2]), 129.13 (ArC3/5*), 132.15 ($C5C_q$, [R1]), 132.57 ($C5C_q$, [R2]), 137.69 ($C8C_q$), 151.05 (ArC1*, [R2]), 151.17 (ArC1*, [R2]) 154.57 (N$\underline{C}$OO, [R2]), 155.20 (N$\underline{C}$OO, [R1]). HRMS calculated for m/z $C_{17}H_{17}NO_3$: (M^++Na^+) 306.1106, found m/z 306.1095 $C_{17}H_{16}NO_3$.

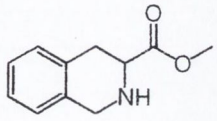
3,4-Dihydro-1H-isoquinoline-2,3-dicarboxylic acid 2-benzyl ester 3-(2-morpholin-4-yl-ethyl) ester 277



DCC (1.140 g, 5.528 mmol) and DMAP (60 mg) were added to a stirred solution of 3,4-Dihydro-1H-isoquinoline-2,3-dicarboxylic acid 2-benzyl ester **272a** (1.565 g, 5.026 mmol) dissolved in dry DCM (50 ml). After 10 minutes 2-morpholin-4-yl-ethanol (0.730 ml, 6.03 mmol) was added in one portion and the reaction mixture was stirred for 24 hours at room temperature. The solid material was filtered off using a celite® plug. The filtrate was washed with saturated NH_4Cl (3 x 50 ml), dried over anhydrous Na_2SO_4, filtered and the volatiles were removed under vacuum. The resulting oil was purified by flash chromatography on silica gel using a 90:10 diethyl ether:Methanol mobile phase to yield the product as a clear oil (85%).

IRυ_{max} cm^{-1} (film): 1742, 1701 (C=O),1515, 746 (Ar).^{1}H NMR ($CDCl_3$) δ: 2.28-2.38 (m, 5H, N($C\underline{H}_2$)$_2$, CH_2N [R1]), 2.44-2.47 (t, J=5.5 Hz, 1H, CH_2N [R2]), 3.15-3.32 (m, 2H, H4), 3.56-3.59 (m, 4H, $(CH_2)_2O$), 3.98-4.16 (m, 2H, $COOC\underline{H}_2$), 4.60-4.68 (m, 1H, H1 [R1]), 4.78-4.82 (m, 1H, H1 [R2]), 4.99-5.02 (m, 0.43H, H3 [R2]), 5.15-5.25 (m, 2.56H, H3 [R1] + $OC\underline{H}_2Ar$), 7.07-7.21 (m, 4H, H5-8), 7.29-7.43 (m, 5H, C_6H_5). ^{13}C NMR ($CDCl_3$) δ: 30.79 (C4, [R1]), 31.19 (C4, [R2]), 44.09 (C1, [R1]), 44.32 (C1, [R2]), 52.88 (C3, [R1]), 53.23 (N$(CH_2)_2$, [R1]), 53.26 (N$(CH_2)_2$, [R2]), 53.49 (C3, [R2]), 56.54 (CH_2N, [R1]), 56.61 (CH_2N, [R2]), 61.99 ($COO\underline{C}H_2$), 66.52 ($(CH_2)_2O$), 67.16 ($O\underline{C}H_2Ar$, [R1]), 67.31 ($O\underline{C}H_2Ar$, [R2]), 125.58 (C6), 125.95 (C7, [R1]), 126.06 (C7, [R2]), 126.50 (C8, [R1]), 126.57 (C8, [R2]), 126.61 (C5, [R1]), 126.70 (C5, [R2]), 127.66 (ArC3/5, [R1]), 127.69 (ArC3/5, [R2]), 127.85 (ArC4, [R1]), 127.89 (ArC4, [R2]), 128.23 (ArC2/6, [R1]), 128.28 (ArC2/6, [R2]), 131.25 ($C5C_q$, [R1]), 131.33 ($C5C_q$, [R2]), 132.05 ($C8C_q$, [R1]), 132.77 ($C8C_q$, [R2]), 136.10 ($ArC1_q$, [R1]), 136.16 ($ArC1_q$, [R2]), 155.12 (NCOO, [R2]), 155.87 (NCOO, [R1]), 170.68 (COOH, [R1]), 170.92 (COOH, [R2]). HRMS calculated for $C_{24}H_{29}N_2O_5$: (M^++H^+) 425.2076, found 425.2071.

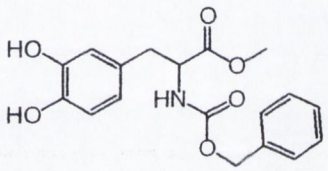
1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic acid methyl ester 278



Isolated from the attempted deprotection of **277** using 10% Pd/C with H_2 atmosphere.

white solid 63% IRυ_{max} cm^{-1} (KBr): 3466 (OH), 1949 (NH), 1747 (C=O), 771 (Ar). ^1H NMR ($CDCl_3$) δ: 2.97-3.04 (dd, J_{gem}=16.4 Hz (H4*-H4), J_{vic}=10.5 Hz (H4*-H3), 1H, H4*), 3.11-3.17 (dd, J_{gem}=16.4 Hz, J_{vic}=4.6 Hz (H4-H3), 1H, H4), 3.75-3.78 (dd, J_{vic}=10.5 Hz (H3-H4*), J_{vic}=4.6 Hz (H3-H4), 1H, H3), 3.83 (s, 3H, $COOCH_3$), 4.03-4.14 (2d, J_1=J_2=15.7 Hz, 2H, H1), 4.90 (s, 1H, NH), 7.08-7.20 (m, 4H, H5-8). ^{13}C NMR ($CDCl_3$) δ: 30.08 (C4), 45.67 (C1), 50.67 (C3), 54.52 ($COOCH_3$), 125.11 (C6), 125.21 (C7), 125.39 (C8), 127.95 (C5), 131.79 ($C5C_q$), 133.11 ($C8C_q$), 172.33 ($COOCH_3$).[15]

2-Benzyloxycarbonylamino-3-(3,4-dihydroxy-phenyl)-propionic acid methyl ester 273

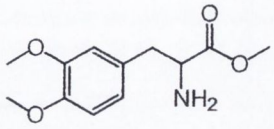


Racemic Dopa (5.000 g, 25.36 mmol) was dissolved in dry methanol, to which $SOCl_2$ (3.31 ml, 45.64 mmol) was added dropwise. The solution was stirred under nitrogen for three hours. All volatiles were removed *in vacuo* and the residue was dissolved in DCM (70 ml), to which triethyl amine (7.80 ml, 60.00 mmol) was added followed by the slow addition of benzyl chloroformate (4.28 ml, 30.00 mmol). The reaction mixture was stirred for a further 3 hours. Work-up involved washing the mixture with 10% HCl (3 x 75 ml), follwed by a wash with sat. K_2CO_3 (3 x 50 ml). The organic phase was dried over anhydrous Na_2SO_4, filtered and removed *in vacuo*. The resulting oil was purified on silica gel using a 60:40 diethyl ether:hexane mobile phase to leave a colourless solid (76%) m.p. 116-118 (lit. 116-118)[16]

IRυ_{max} cm^{-1} (KBr): 3351 (OH), 2953 (NH), 1734, 1692 (C=O), 1520 (Ar), 1280 (C-O). ^1H NMR ($CDCl_3$) δ: 2.89-3.03 (2dd, J_{gem}=14.2 Hz (H3*-H3), J_{vic}=6.2 Hz (H3*-H2), J_{gem}=14.2 Hz (H3-H3*), J_{vic}=5.4 Hz (H3-H2), 2H, H3/H3*), 3.69 (s, 0.64H, OCH_3 [R2]), 3.71 (s, 2.26H, OCH_3 [R1]), 4.48 (m, 0.24H, H2 [R2]), 4.61 (m, 0.78H, H2 [R1]), 5.09 (m, 2H, OCH_2), 5.45 (s, 1H, NH), 6.49 (dd, J_o=8.2 Hz, J_m=2.0 Hz, 1H, ArH6), 6.63 (d, J_m=2.0 Hz, 1H, ArH2), 6.72 (d, J_o=8.2 Hz, 1H, ArH5), 7.32 (m, 5H,

C_6H_5). ^{13}C NMR ($CDCl_3$) δ: 29.95 (C1 [R1]), 30.52 (C1 [R2]), 58.72 (C2), 68.20 (OCH_2Ar), 111.98 (ArC2), 113.43 (ArC5), 118.63 (ArC6), 129.17 (ArC1), 127.33 (OCH_2ArC4), 128.46 ($OCH_2ArC2/C6$), 129.96 ($OCH_2ArC3/C5$), 136.11 (OCH_2ArC1_q), 145.82 (ArC4), 146.92 (ArC5), 156.55 (NCOO). Elemental analysis: $C_{18}H_{19}NO_6$ requires C, 62.60; H, 5.55; N, 4.06. Found C, 62.45; H, 5.55; N, 3.96.

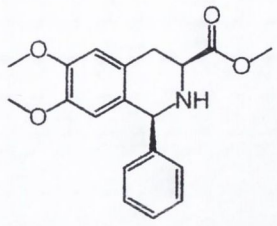
2-Amino-3-(3,4-dimethoxy-phenyl)-propionic acid methyl ester.HCl 275



L-Dopa (10 g, 50.75 mmol) , 96% formic acid (90 ml) and acetic anhydride (30 ml) were stirred at room temperature for three hours the mixture was concentrated. The resulting residue was dissolved in water (50 ml) and concentrated four times. To the final residue in water at 0°C, was added: 10N NaOH (15 ml) and dimethyl sulfate (9.5 ml). The reaction was stirred at room temperature. Every 30 minutes for two hours was added a further 9.50 ml of dimethyl sulfate. The temperature was kept below 40°C and the pH 5-9 (by addition of 10N NaOH as required). After all of the dimetyl sulfate was added, the reaction mixture was made basic by the addition of approximately 15 ml 10N NaOH, stirred for a further 30 minutes then acidified with 8N H_2SO_4 to pH 2. The mixture was subsequently extracted with ethyl acetate (3 x 100 ml). The organic extracts were combined and dried over anhydrous Na_2SO_4 and removed *in vacuo* to yield a pale red oil, which was stored overnight at –5°C. The oil was dissolved in absolute ethanol (130 ml) containing 56 ml of actetyl chloride and stirred at room temperature for 3 hours. The mixture was concentrated to form a fawn solid, that was recrystallised from ethanol/diethyl ether 150ml (2:1) to give the hydrochloride salt as a colourless powder (36%) m.p. 158-160°C (lit. 158-159.)[17].

IRυ_{max} cm^{-1} (KBr): 2944 (N-H), 1750 (C=O), 1266 (C-O), 759 (Ar). ^1H NMR ($CDCl_3$) δ: 3.12 (s, 3H, $COOCH_3$), 3.67 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 4.22-4.33 (m, 1H, $CHNH_2$), 6.14-6.45 (m, 4H, NH_2/ $ArCH_2$), 6.82-6.89 (dd, 1H, J_o=8.0 Hz, J_m=21.0 Hz, ArH6), 6.96-6.98 (d, 1H, J_m=8.0 Hz, ArH2), 7.03-7.09 (d, 1H, J_o= 21.0 Hz, ArH5). ^{13}C NMR ($CDCl_3$) δ: 45.14 (C1), 58.46 (C4), 62.52 (OCH_3), 63.37 (C2), 65.29 (OCH_3), 121.63 (ArC6), 123.06 (ArC5), 131.51 (ArC2), 136.61 ($ArC1_q$), 157.87 ($ArC4_q$), 158.44 ($ArC3_q$), 179.25 (C3). HRMS (free base) calculated for $C_{12}H_{18}NO_4$: (M^++H^+) 240.1236, found 240.1236.

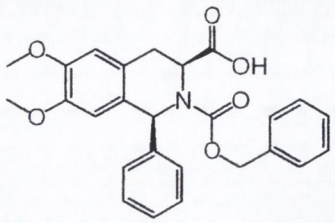
6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid methyl ester 274



2-Amino-3-(3,4-dimethoxy-phenyl)-propionic acid methyl ester.HCl **275** (0.839 g, 3.05 mmol) was dissolved in methanol (20 ml) with 10% K_2CO_3 (10 ml). The mixture was extracted with DCM (3 x 20 ml), which was dried over anhydrous Na_2SO_4 and removed *in vacuo*. The resulting free base was dissolved in 50 ml dry DCM and transferred to an oven dried 3-neck round bottomed flask, containing 0.60 g anhydrous Na_2SO_4. The flask was flushed with nitrogen and benzaldehyde (0.28 ml, 2.80 mmol) was added. The mixture was stirred for 20 hours at room temperature afterwhich the solvent was filtered and removed *in vacuo* to yield the imine, which was not characterised. The oil was dissolved in 10 ml of trifluoroacetic acid and refluxed for 2 hours. Reaction was quenched by the addition of water (100 ml). The solution was basified slowly and with stirring using 10% NaOH to pH 8-9. Solution was extracted with DCM (4 x 50 ml). The organic extracts were combined, dried over anhydrous Na_2SO_4 and removed under vacuum to leave an orange gummy solid which was purified on silica gel to yield colourless crystals (31%) m.p 120.

IRυ_{max} film cm^{-1}: 3345 (N-H), 1737 (C=O), 1202 (C-O), 1518, 829 (ArH) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.44 (s, 1H, NH), 3.05-3.16 (2dd, J_{gem}=15.2 Hz (H4*-H4), J_{vic}=5.0 Hz (H4*-H3), J_{gem}=15.1 Hz (H4-H4*), J_{vic}=10.0 Hz (H4-H3), 2H, H4/H4*), 3.18 (m, 1H, H3), 3.47-3.52 (dd, J_{gem}=11.0 Hz, J_{vic}=8.0 Hz (H9*-H3), 1H, CH_2*OH), 3.60 (s, 3H, OCH_3), 3.78 (s, 3H, $COOCH_3$), 3.87-3.91 (m, 4H, H3, OCH_3), 5.11 (s, 1H, H1), 6.19 (s, 1H, H5), 6.66 (s, 1H, H8), 7.31-7.36 (m, 5H, C_6H_5). ^{13}C NMR ($CDCl_3$) δ: 32.08 (C4), 52.08 (C3), 55.68, 55.74 (OCH_3x2), 56.40 ($COOCH_3$), 62.73 (C1), 110.33 (C8), 111.11 (C5), 125.91 (C5C_q), 127.71 (ArC4*), 128.47 (ArC3*/C5*), 128.91 (ArC2*/C6*), 130.07 (C8C_q), 143.75 (ArC1*$_q$), 147.22 (C7), 147.57 (C6). Details of the X-ray crystal structure are provided in Appendix 1.

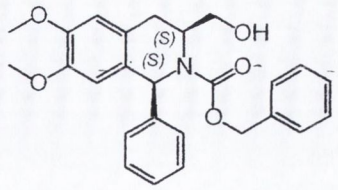
6,7-Dimethoxy-1-phenyl-3,4-dihydro-1H-isoquinoline-2,3-dicarboxylic acid 2-benzyl ester 276



6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid methyl ester **274** (0.941 g, 2.88 mmol) was dissolved in 100 ml of methanol. 40 ml of water was slowley added. NaOH pellets were ground to a powder and added slowley until pH 13 was reached. The mixture was refluxed for 3 hours TLC showing the consuption of the start material. The mixture was transferred to a 500 ml beaker and the pH was adjusted to pH 8 using 10% HCl and 20% NH_4OH. Benzyl chloroformate (0.37 ml, 2.60 mmol) added dropwise maintaining the pH 8. Mixture was stirred for 3 hours , extracted with diethyl ether (3 x 100 ml), pH adjusted to pH 2.7 and extracted with ethyl acetate (4 x 100 ml). Solvent was dried over anhydrous Na_2SO_4 filtered and removed *in vacuo* to yield a colourless oil (83%).

IRυ_{max} cm^{-1} (KBr): 1750, 1718 (C=O), 1518, 746 (Ar). ^{1}H NMR ($CDCl_3$) δ: 2.74-3.04 (m, 2H, H4/H4*), 3.90 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.43-4.47 (m, 0.56H, H3[R1]), 4.52-4.56 (m, 0.44H, H3[R2]), 5.18-5.29 (m, 2H, $OC\underline{H}_2Ar$ [R1+R2]), 6.26 (s, 0.42H, H1, [R2]), 6.46 (s, 0.58, H1, [R1]), 6.77 (s, 1.43H, H5 [R1+R2] + H8 [R2]), 6.87 (s, 0.57H, H8 [R1]), 7.17-7.33 (m, 10H, $(C_6\underline{H}_5)_2$), 9.46 (s, 1H, COO$\underline{H}$). ^{13}C NMR ($CDCl_3$) δ: 30.01 (C4 [R1]), 30.26 (C4 [R2]), 55.96, 56.03 ($O\underline{C}H_3$x2), 56.51 (C3 [R2]), 56.61 (C3 [R1]), 58.47 (C1 [R1]), 58.74 (C1 [R2]), 67.99 (OCH_2Ar), 110.93 (C8), 111.05 (C5), 125.36 (C5$\underline{C}_q$), 127.04 (ArC3*/C5*), 127.18 (ArC4*), 129.23 (C8$\underline{C}_q$), 135.85 (ArC1*$_q$ [R1]), 135.93 (ArC1*$_q$ [R2]), 140.59 ($OCH_2Ar\underline{C}1_q$), 147.80 ($C7_q$), 148.41 ($C6_q$), 156.37 (NCOO [R2]), 156.55 (NCOO [R1]), 176.40 (COOH [R2]), 177.03 (COOH [R1]). HRMS calculated for $C_{26}H_{25}NO_6$: (M^+ + Na) 470.1580, found 470.1581.

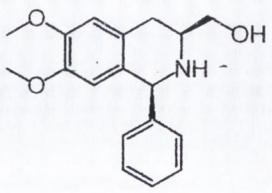
3-Hydroxymethyl-6,7-dimethoxy-1-phenyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid benzyl ester 282



6,7-Dimethoxy-1-phenyl-3,4-dihydro-1H-isoquinoline-2,3-dicarboxylic acid 2-benzyl ester **276** (1.000 g, 2.24 mmol) was dissloved in dry DCM (30 ml) and transferred to an oven-dried 3-neck 100 ml round bottomed flask under an nitrogen atmosphere. Oxalyl chloride (0.55 ml, 6.26 mmol) was added dropwise at room tempertature along with one drop of DMF. The reaction mixture was stirred for 2.5 hours, afterwhich the solvent was removed under vacuum, the resulting residue was dissolved in dry DCM (30 ml) and transferred to a dry 100 ml 3-neck flask under a nitrogen atmosphere. The reaction mixture was cooled to –60°C. $NaBH_4$ (0.423 g, 11.17 mmol) in 25ml dry ethanol (slurry) was cooled to –20°C and added dropwise to the reaction mixture. Reaction was brought to room temperature stirring for 2 hours and was quenched by the careful addition of 10% HCl at 0°C. The resulting mixture was extracted with DCM (4 x 70 ml). The organic extracts were combined and dried over anhydrous Na_2SO_4, filtered and removed *in vacuo* to leave an oily residue that was puified on silica gel with an initial 70:30 diethyl ether/hexane and ending with a 90:10 diethyl ether/methanol eluent (33%).

IRυ_{max} film: 3443 cm^{-1} (OH), 1684, 1661 cm^{-1} (C=O), 1296 cm^{-1} (C-O), 1117, 1106, 737 (Ar) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.48-2.62 (m, 1H, H4), 2.87-2.93 (dd, J_{gem}=15.7 Hz, J_{vic}=6.2 Hz, 1H, H4*), 3.01 (s, 1H, OH), 3.45-3.54 (m, 1H, CH_2*OH), 3.56-3.60 (dd, J_{gem}=11.0 Hz, J_{vic}=6.4 Hz, 1H, CH_2OH), 3.84 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.32-4.39 (m, 1H, H3), 5.16-5.35 (m, 2H, OCH_2Ar), 6.38 (s, 0.58H, H1, [R1]), 6.58 (s, 0.42, H1, [R2]), 6.72 (s, 1H, H5), 6.77 (s, 1H, H8), 7.17-7.40 (m, 10H, $(C_6H_5)_2$). ^{13}C NMR ($CDCl_3$) δ: 29.65 (C4 [R1]), 29.76 (C4 [R2]), 55.07 (C3), 55.96, 56.01 (OCH_3x2), 57.78 (C1), 66.18 (CH_2OH), 67.99 (OCH_2Ar), 110.94 (C5), 111.37 (C8), 126.55 ($C5C_q$), 127.16 (OCH_2ArC4), 127.43 (ArC4*), 127.97 (ArC2*/C6*), 128.16 ($OCH_2ArC2/C6$), 128.54 ($ArOCH_2C2$*/C6*), 128.60 ($OCH_2ArC2/C6$), 130.44 ($C8C_q$), 133.88 ($ArC1*_q$), 136.18 (OCH_2ArC1_q), 147.43 ($C7_q/C6_q$), 156.55 (NCOO). HRMS calculated for $C_{26}H_{27}NO_5$: (M^+ + Na) 456.1787, found 456.1789.

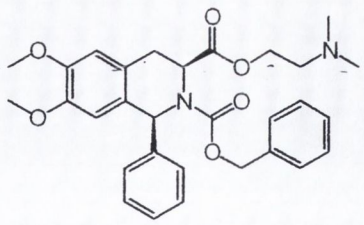
(6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydro-isoquinolin-3-yl)-methanol 283



To a stirred suspension of lithium aluminium hydride (0.520 g, 13.68 mmol) in dry THF (20 ml) under a nitrogen atmosphere, was added dropwise at 0°C: 6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid methyl ester **274** (3.109 g, 9.12 mmol) in 30 ml of dry THF. The mixture was stirred at room temperature for 2 hours, TLC showing the complete consumption of start material. At 0°C 10 ml of THF:water (4:1) was added dropwise (with caution). The thick suspension formed was stirred for 30 minutes at room temperature. The solid salts formed were filtered off and volatiles were removed *in vacuo*. The resulting residue was dissolved in DCM (200 ml) and washed with brine (3 x 100 ml). The organic layer was dried over anhydrous Na_2SO_4 and removed under vacuum the solid residue was dissolved in hot ethanol (100 ml) forming a clear amorphous solid on cooling to room temperature (84%).

IRυ_{max} film: 3591 (OH) cm^{-1}, 3260 (N-H), 1261 (C-O) cm^{-1}, 1514, 822 (Ar) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.21 (s, 1H, O<u>H</u>), 2.58-2.74 (2dd, J_{gem}=16.0 Hz (H4*-H4), J_{vic}=3.5 Hz (H4*-H3), J_{gem}=16.2 Hz (H4-H4*), J_{vic}=11.0 Hz (H4-H3), 2H, H4/H4*), 3.18 (m, 1H, H3), 3.47-3.52 (dd, J_{gem}=11.0 Hz, J_{vic}=8.0 Hz (H9*-H3), 1H, C<u>H</u>$_2$*OH), 3.60 (s, 3H, OCH_3), 3.71-3.74 (dd, J_{gem}=11.0 Hz, J_{vic}=3.0 Hz (H9-H3), 1H, C<u>H</u>$_2$OH), 3.87 (s, 3H, OCH_3), 5.01 (s, 1H, H1), 6.17 (s, 1H, H5), 6.61 (s, 1H, H8), 7.27-7.34 (m, 5H, C_6<u>H</u>$_5$). ^{13}C NMR ($CDCl_3$) δ: 31.38 (C4), 55.55 (C3), 55.73, 55.77 (O<u>C</u>H$_3$x2), 62.65 (C1), 65.88 (C9), 110.47 (C8), 111.24 (C5), 126.83 (C5<u>C</u>$_q$), 127.61 (ArC4*), 128.50 (ArC3*/C5*), 128.88 (ArC2*/C6*), 130.37 (C8<u>C</u>$_q$), 144.16 (ArC1*$_q$), 146.96 (C7), 147.53 (C6). HRMS m/z calculated for $C_{18}H_{22}NO_3$: (M^+ + H^+) 300.1600, found 300.1587

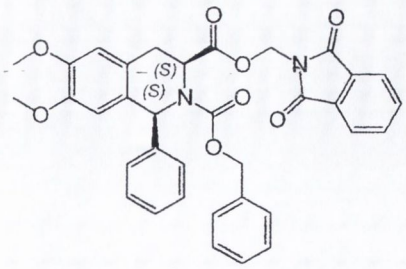
6,7-Dimethoxy-1-phenyl-3,4-dihydro-1H-isoquinoline-2,3-dicarboxylic acid 2-benzyl ester 3-(2-dimethylamino-ethyl) ester 279



To a stirred solution of 6,7-Dimethoxy-1-phenyl-3,4-dihydro-1H-isoquinoline-2,3-dicarboxylic acid 2-benzyl ester **276** (0.300 g, 0.671 mmol) in dry DCM (25 ml) under a nitrogen atmosphere was added: DCC (0.152 g, 0.738 mmol) and HOBT (0.100 g, 0.738 mmol), the suspension was stirred vigorously for 30 minutes. Dimethyl aminoethanol was added and the suspension was allowed to stir for 18 hours. The solid matter was filtered off using a buckner funnel. The proceedure was repeated on the filtrate, which was subsequently dried over anhydrous Na_2SO_4, filtered and removed *in vacuo*. The resulting residue was columned on silica gel using an eluent of diethyl ether/methanol (80/20) to yield a waxy solid (63%).

IRυ_{max} cm^{-1} (film): 3413 (NC), 1751, 1699 (C=O), 1106 (C-O), 1515, 746 (Ar). ^1H NMR ($CDCl_3$) δ: 2.17 (s, 3.5H, $N(CH_3)_2$ [R1]), 2.28 (s, 2.5H, $N(CH_3)_2$ [R2]), 2.31-2.34 (m, 1.31H, $C\underline{H}_2N(CH_3)_2$ [R1]), 2.50-2.61 (m, 0.74H, $C\underline{H}_2N(CH_3)_2$ [R2]), 2.73-3.03 (m, 2H, H4/H4*), 3.87-3.91 (m, 6H, 2xOCH_3), 3.98-4.23 (m, 2H, $OC\underline{H}_2CH_2$), 4.45-4.50 (dd, J_{vic1}=11.6 Hz (H3-H4*), J_{vic2}=5.5 Hz (H3-H4), 0.58H, H3[R1]), 4.57-4.61 (dd, J_{vic1}=11.6 Hz (H3-H4*), J_{vic2}=5.5 Hz (H3-H4), 0.38H, H3[R2]), 5.14-5.33 (m, 2H, OCH_2Ar), 6.29 (s, 0.37H, H1, [R2]), 6.50 (s, 0.56, H1, [R1]), 6.75 (s, 0.31H, H5 [R2]) 6.77 (s, 1H, H8 [R1+R2]), 6.86 (s, 0.71H, H5 [R1]), 7.20-7.37 (m, 10H, $(C_6\underline{H}_5)_2$). ^{13}C NMR ($CDCl_3$) δ: 29.54 (C4 [R2]), 29.87 (C4 [R2]), 44.95 ($N(CH_3)_2$), 55.93, 56.01 (OCH_3x2), 56.27 (C3 [R2]), 56.34 (C3 [R1]), 57.06 (OCH_2Ar), 58.18 (C1 [R1]), 58.36 (C1 [R2]), 67.81 ($O\underline{C}H_2CH_2$ [R2]), 67.88 ($O\underline{C}H_2CH_2$ [R1]), 110.86 (C8), 110.98 (C5), 125.44 (C5$\underline{C}_q$), 127.03 (ArC3*/C5*), 127.36 (ArC4*), 127.97, 127.98, 128.06, 128.39 ($(C_6\underline{H}_5)_2$), 128.94 (C8$\underline{C}_q$), 135.99 ($OCH_2Ar\underline{C}1_q$), 140.83 (ArC1*$_q$ [R1]), 141.04 (ArC1*$_q$ [R2]) 147.76 ($C7_q$), 148.37 ($C6_q$), 156.44 (NCOO), 171.53 ($COOCH_2$ [R2]), 171.71 ($COOCH_2$ [R1]). HRMS calculated for $C_{30}H_{34}N_2O_6$: ($M^+ + H^+$) 519.2495, found 519.2502.

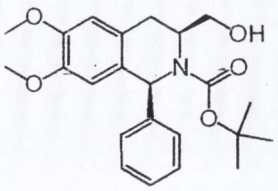
6,7-Dimethoxy-1-phenyl-3,4-dihydro-1H-isoquinoline-2,3-dicarboxylic acid 2-benzyl ester 3-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl) ester 280



To a stirred solution of 6,7-Dimethoxy-1-phenyl-3,4-dihydro-1H-isoquinoline-2,3-dicarboxylic acid 2-benzyl ester **276** (0.300 g, 0.671 mmol) in dry DCM (25 ml) under a nitrogen atmosphere was added: DCC (0.152 g, 0.738 mmol) and DMAP (0.020 g, 0.164 mmol), the suspension was stirred vigorously for 30 minutes. 2-(2-Hydroxy-ethyl)-isoindole-1,3-dione (0.143 g, 0.805 mmol) was added and the suspension was allowed to stir for 18 hours. The solid matter was filtered off using a buckner funnel and the filtrate was dried over anhydrous Na_2SO_4, filtered and removed *in vacuo*. The resulting residue was columned on silica gel using an eluent of diethyl ether/hexane (60/40) to yield a colourless oil (42%).

IRυ_{max} cm^{-1} (KBr): 1784, 1731, 1699 (C=O), 1403 (C-N), 725 (Ar). ^{1}H NMR ($CDCl_3$) δ: 2.73-3.01 (m, 2H, H4/H4*), 3.87-3.91 (m, 6H, 2xOCH_3), 4.40-4.44 (dd, J_{vic1}=11.8 Hz (H3-H4*), J_{vic2}=5.4 Hz (H3-H4), 0.64H, H3[R1]), 4.46-4.50 (dd, J_{vic1}=11.6 Hz (H3-H4*), J_{vic2}=5.4 Hz (H3-H4), 0.36H, H3[R2]), 5.12-5.27 (m, 2H, OCH_2Ar), 5.52-5.68 (m, 2H, OCH_2N), 6.24 (s, 0.34H, H1, [R2]), 6.45 (s, 0.66H, H1, [R1]), 6.75-6.76 (m, 1.36H, H8 [R1+R2] + H5 [R2]), 6.85 (s, 0.70H, H5 [R1]), 6.96-7.37 (m, 10H, ($C_6\underline{H}_5)_2$), 7.76-7.83 (m, 2H, (ArH2`/H5`)), 7.89-7.94 (m, 2H, (ArH3`/H4`)). ^{13}C NMR ($CDCl_3$) δ: 30.32 (C4), 55.97 (OCH_3x2), 56.85 (C3), 58.14 (C1), 61.10 (OCH_2Ar), 67.92 (OCH_2N), 110.88 (C8), 110.97 (C5), 123.84 ($OCH_2Ar\underline{C}3/\underline{C}5$), 125.29 ($C5\underline{C}_q$), 126.87 (ArC4*), 127.14 (ArC3*/C5*), 127.80 (ArC3`/C4`), 127.93 (OCH_2ArC4), 127.93 (ArC2*/C6*), 127.98 ($OCH_2ArC2/C6$), 128.44 (ArC2`/C5`), 129.04 ($C5\underline{C}_q$), 131.63 ($ArC1`_q/C6`_q$), 136.02 ($OCH_2Ar\underline{C}1_q$), 140.53 ($ArC1*_q$), 148.42 ($C7_q/C6_q$), 156.37 (NCOO), 166.29 (2x$CH_2N\underline{C}$=O), 170.76 (COOH). HRMS m/z calculated for $C_{35}H_{30}N_2O_8$: ($M^+ + Na^+$) 629.1900, found 629.1917.

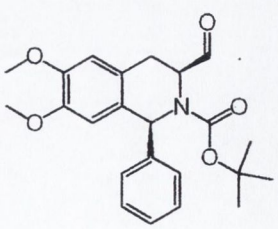
3-Hydroxymethyl-6,7-dimethoxy-1-phenyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butylester 285



A mixture of (6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydro-isoquinolin-3-yl)-methanol **283** (1.56 g, 6.69 mmol) and Boc-anhydride (2.34 g, 10.70 mmol), under a nitrogen atmosphere in 50 ml of chloroform, was stirred for four hours. TLC showed the formation of a small amount of possible product. Triethylamine (0.976 ml, 7.0 mmol) was added dropwise and the reaction was allowed to procced overnight (14 hours). TLC showed the complete consumption of start material. Volatiles were removed *in vacuo* and the residual oil was columned directly on silica gel with a diethyl ether/hexane (80/20) mobile phase (93%).

IRυ_{max} cm^{-1} (KBr): 3462 (OH), 1738, 1675 (C=O), 1101 (C-O).^{1}H NMR ($CDCl_3$) δ: 1.50 (s, 9H, C($C\underline{H}_3)_3$), 2.41-2.56 (m, 1H, H4),), 2.85-2.90 (dd, J_{gem}=15.5 Hz (H4*-H4), J_{vic}=6.5 Hz (H4*-H3), 1H, H4*), 3.46-3.56 (m, 2H, $C\underline{H}_2OH$), 3.84 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.27 (s, 1H, H3), 6.26 (s, 1H, H1), 6.70 (s, 1H, H5), 6.77 (s, 1H, H8), 7.16-7.34 (m, 5H, $C_6\underline{H}_5$). ^{13}C NMR ($CDCl_3$) δ: 28.33 ($C(\underline{C}H_3)_3$), 29.94 (C4), 54.52 (C3), 55.90, 55.95 ($O\underline{C}H_3$x2), 65.76 (C1), 81.58 ($\underline{C}(CH_3)_3$), 110.98 (C8), 111.27 (C5), 126.40 ($C5C_q$), 127.04 (ArC3*/C5*), 127.18 (ArC4*), 127.96 ($C8C_q$), 128.48 (ArC*2/C*6), 130.37 ($C8_qC$), 142.47 ($ArC1*_q$), 147.29 (C7), 148.30 (C6). HRMS m/z calculated for $C_{23}H_{29}NO_5$: ($M^+ + Na^+$) 422.1943, found 422.1954

3-Formyl-6,7-dimethoxy-1-phenyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester 286

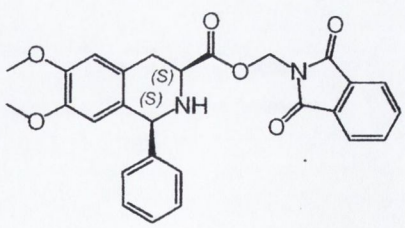


To an ovendried 3-neck round bottomed flask, covered in aluminium foil, under a nitrogen atmosphere, was added 3-Hydroxymethyl-6,7-dimethoxy-1-phenyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butylester **285** (0.519, 1.30 mmol) in 40 ml of dry DCM, the Dess-Martin periodinane (0.85 g, 1.94 mmol) was added in

one portion. The solution was stirred for 3 hours at ambient tempertature afterwhich 40 ml of 1M $NaHCO_3$ containing 0.352 g sodium thiosulfate solution was added carefully. The quenched reaction was stirred for 30 minutes, extracted with DCM (3 x 50 ml) and ethyl acetate (2 x 50 ml). The organic extracts were combined and dried over anhydrous Na_2SO_4 filtered and removed *in vacuo*. The solid residue was dissolved in 3 ml DMF, this solution was placed directly on a flash silica column and eluted with an initial mobile phase of 100% diethyl ether moving to a final eluent of (90/10) (diethyl ether/methanol), resulting solid was recrystallised from ethanol to leave the title compound as a colourless solid (96%). m.p 128-130°C.

IRυ_{max} film cm^{-1}: 2836 (C-C), 1732, 1693 (C=O), 1369 (C-N), 1229, 1101 (C-O), 1515, 877 (Ar). ^{1}H NMR ($CDCl_3$) δ: 1.50 (s, 9H, C($C\underline{H}_3$)$_3$), 2.55-2.93 (m, 2H, H4/H4*) 3.86 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.20 (s, 0.66H, H3 [R1]), 4.53 (s, 0.34H, H3 [R2]), 6.26 (s, 0.34H, H1 [R2]), 6.44 (s, 0.64H, H1 [R1]), 6.68-6.84 (m, 2H, H8/H5), 7.15-7.28 (m, 5H, $C_6\underline{H}_5$), 9.30-9.39 (m, 1H, C$\underline{H}$O). ^{13}C NMR ($CDCl_3$) δ: 27.38 (C4 [R2]), 27.56 (C4 [R1]), 28.16 (C($\underline{C}H_3$)$_3$), 55.88, 55.91 (O$\underline{C}H_3$x2), 56.62 (C3 [R1]), 57.50 (C3 [R2]), 60.25 (C1 [R2]), 61.95 (C1 [R1]), 81.61 ($\underline{C}$(CH$_3$)$_3$), 110.99 (C8), 111.09 (C5), 125.02 (C5C_q/C8C_q), 126.79 (ArC3*/C5*),127.21 (ArC*2/C*6), 128.40 (ArC4*), 141.91 (ArC1*$_q$ [R1]), 142.13 (ArC1*$_q$ [R2]), 147.70 (C7), 148.30 (C6), 155.47 (N$\underline{C}$OO), 200.33 ($\underline{C}$HO). Elemental analysis: $C_{23}H_{27}NO_5$ requires C, 69.50; H, 6.85; N, 3.52. Found C, 69.47; H, 6.88; N, 3.43.

6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid 1,3-dioxo-1,3-dihydro-isoindol-2-ylmethylester 281

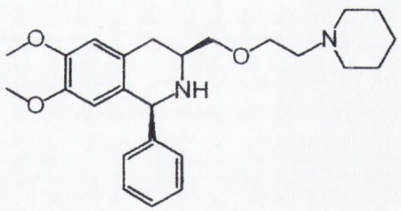


20 mg of 10% Pd/C added to 10 ml of ethyl acetate was stirred in a 50 ml 2-neck round bottomed flask. The suspension was flushed with H_2 and stirred for 30 minutes. 6,7-Dimethoxy-1-phenyl-3,4-dihydro-1H-isoquinoline-2,3-dicarboxylic acid 2-benzyl ester 3-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl) **280** ester (0.100 g, 0.165 mmol) was dissolved in 5 ml of ethyl acetate and added dropwise through a septum to the stirred suspension. Stirring was continued overnight afterwhich the

suspension was filtered through a celite® cake and the filtrate was removed *in vacuo*. The resulting residue was purified on silica gel using a 2:2:1 DCM/diethyl ether/hexane mobile phase to yield the product as a colourless solid (67%) m.p 184°C.

IRυ_{max} cm^{-1} 1752, 1723 (C=O), 1101 (C-O). ^{1}H NMR ($CDCl_3$) δ: 3.01-3.14 (2dd, J_{gem}=16.0 Hz (H4*-H4), J_{vic}=4.8 Hz (H4*-H3), J_{gem}=16.0 Hz (H4-H4*), J_{vic}=11.0 Hz (H4-H3), 2H, ArC$\underline{H}_2$), 3.58 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.89-3.93 (dd, J_{vic}=4.8 Hz (H3-H4*), J_{vic}=11.0 Hz (H3-H4),1H, $CH_2C\underline{H}N$), 5.08 (s, 1H, H1), 5.84 (s, 2H, O$C\underline{H}_2$N), 6.16 (s, 1H, H5), 6.62 (s, 1H, H8), 7.28-7.35 (m, 5H, $C_6\underline{H}_5$), 7.80-7.83 (m, 2H, NC=OArH2`,H5`), 7.94-7.96 (m, 2H, NC=OArH3`,H4`). ^{13}C NMR ($CDCl_3$) δ: 31.94 (C4), 55.69 (OCH_3), 55.74 (OCH_3), 56.22 (C3), 61.24 (OCH_2N), 62.58 (C1), 110.30 (C5), 111.06 (C8), 123.96 (ArC2`/5`), 125.66 ($C5C_q$) 127.76 (ArC4*), 128.49, 128.96 (ArC3*/C5*) + (ArC2*/C6*), 129.97 ($C8C_q$), 131.59 ($ArC1_q$`/$C6_q$`), 134.67 (ArC3`/C4`), 143.59 ($ArC1*_q$), 147.22 ($C7_q$), 147.57 ($C6_q$), 166.53 (2xNC=O), 171.44 (COO). LRMS m/z calculated for $C_{27}H_{24}N_2O_6$: (M^+ + Na^+) 495 found 495

6,7-Dimethoxy-1-phenyl-3-(2-piperidin-1-yl-ethoxymethyl)-1,2,3,4-tetrahydro-isoquinoline 287

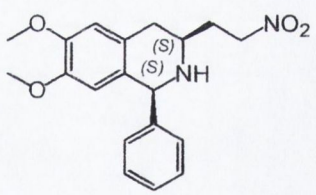


NaH (60% dispersion in oil) (0.22g, 5.50 mmol) was added to an ovendried 3-neck 100 ml RBF under a nitrogen atmosphere. Dry THF was added via syringe through a septum. The THF was removed thereby partially washing out some of the oil. A further 10 ml of dry THF was added followed by the dropwise addition of 3-Hydroxymethyl-6,7-dimethoxy-1-phenyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butylester **285** (1.00 g, 2.51 mmol). The suspension was heated to 70°C for 2 hours afterwhich chloroethyl piperidine was added as the free base (0.90 g, 5.00 mmol) in 10 ml of dry THF. The mixture was stirred for 3 hours at 70°C and the reaction was quenched by pouring it very slowly into ice-water (150 ml). This aqueous mixture was extracted with ethyl acetate (4 x 75 ml). The organic extracts

were combined and dried over anhydrous Na_2SO_4, removed *in vacuo* and the residue was columned on silica gel with a 4:1 methanol/DCM mobile phase (46%).

IRυ_{max} cm^{-1} (KBr): 3326 (NH), 2853 (CH), 1514 (Ar), 1114, 1066 (C-O), 828 (Ar). ^1H NMR ($CDCl_3$) δ: 1.38-1.45 (m, 2H, $N(CH_2)_2(CH_2)_2C\underline{H}_2$), 1.52-1.57 (m, 4H, $N(CH_2)_2(C\underline{H}_2)_2$), 2.33-2.44 (m, 4H, $N(C\underline{H}_2)_2$), 2.46 (s, 1H, N$\underline{H}$), 2.53-2.57 (dt, 2H, J_1=6 Hz, J_2=3 Hz, $OCH_2C\underline{H}_2N$), 2.60-2.75 (2dd, J_{gem}=15.4 Hz (H4*-H4), J_{vic}11.0 Hz (H4*-H3), J_{gem}=15.4 Hz (H4-H4*), J_{vic}=4 Hz (H4-H3), 2H, (H4/H4*)), 3.33-3.39 (m, 1H, H3), 3.45-3.49 (dd, J_{gem}=10.0 Hz, J_{vic}=8.0 Hz ($CHC\underline{H}_2$*O-H3), 1H, $CHC\underline{H}_2$*OH), 3.57-3.64 (m, 2H, $OC\underline{H}_2CH_2N$), 3.59 (s, 3H, OCH_3), 3.63-3.66 (dd, J_{gem}=10.0 Hz, J_{vic}=3.0 Hz ($C\underline{H}_2$O-H3), 1H, $CHC\underline{H}_2O$), 3.87 (s, 3H, OCH_3), 5.05 (s, 1H, H1), 6.17 (s, 1H, H5), 6.62 (s, 1H, H8), 7.28-7.35 (m, 5H, $C_6\underline{H}_5$). ^{13}C NMR ($CDCl_3$) δ: 24.18 ($N(CH_2)_2(CH_2)_2\underline{C}H_2$), 25.78 ($N(CH_2)_2(\underline{C}H_2)_2$), 31.96 (C4), 53.79 (C3), 54.92 ($N(CH_2)_2$), 55.73, 55.78 ($O\underline{C}H_3$x2), 58.29 ($OCH_2C\underline{H}_2N$), 62.82 (C1), 68.94 ($O\underline{C}H_2CH_2N$), 75.01 ($\underline{C}H_2OCH_2$), 110.59 (C8), 111.21 (C5), 126.69 (C5$\underline{C}_q$), 127.47 (ArC*4), 128.41 (ArC*3/C*5), 129.07 (ArC*2/C*6), 130.99 (C8$\underline{C}_q$), 144.58 (ArC1*$_q$), 146.89 ($C7_q$), 147.40 ($C6_q$). HRMS m/z calculated for $C_{25}H_{35}N_2O_3$: (M^+ + H^+) 411.2648 found 411.2639.

6,7-Dimethoxy-3-(2-nitro-ethyl)-1-phenyl-1,2,3,4-tetrahydro-isoquinoline 294

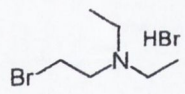


To a solution of 3-Formyl-6,7-dimethoxy-1-phenyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester **286** (0.334g, 0.84 mmol) in 1.5 ml IPA, was added KF (2.9mg, 0.05 mmol) and 0.12 ml nitromethane. After six hours reaction monitering with TLC showed the complete consumption of start material. The solvent was removed on the rotary evaporator and replaced with 4 ml of dry diethyl ether. Acetic anhydride (0.16 ml, 1.2 mmol) and DMAP (10mg, 0.09 mmol) were added and the mixture was stirred for twelve hours at ambient temperature. The ether was removed on the rotary evaporator leaving a residue to which 3 ml of 1M $NaBH_4$/EtOH solution was added dropwise and stirred for 1.5 hours. The mixture was acidifed to pH 5-6 using 10% HCl and extracted with ethyl acetate (3 x 20ml).

The extracts were dried over anhydrous Na_2SO_4, filtered and removed *invacuo*. The intermediate (Boc protected) had an R_f of 0.48 in a 4:1 diethyl ether:hexane mobile phase and was isolated by flash chromatography on silica gel using the aforementioned eluent. The resulting residue was dissolved in dry DCM 25 ml to which 10 ml TFA was added dropwise at 0°C and the solution was stirred fro two hours at ambient temperature. A colour change from orange to green was observed. All volatiles were removed under reduced pressure and the residue was purified by flash chromatography on silica gel using a 10:1 diethyl ether:methanol mobile phase to leave the title compound as a pale yellow oil in 54% yield.

IRυ_{max} (Film): 2946 (N-H) cm^{-1}, 1673, 1554, 1514 (NO_2) cm^{-1}, 1202 (C-O) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.11-2.27 (m, 2H, $C\underline{H}_2CH_2NO_2$), 2.64 (dd, J_{gem}=16.3 Hz (H4*-H4), J_{vic}=10.5 Hz (H4*-H3), 1H, H4*), 2.87 (dd, J_{gem}=16.3 Hz (H4-H4*), J_{vic}=4.5 Hz, (H4-H3), 1H, H4), 3.10 (s, 1H, NH), 3.04 (m, 1H, H3), 3.75 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.46 (m, 2H, CH_2NO_2), 5.22 (s, 1H, H1), 6.44 (s, 1H, H5), 6.66 (s, 1H, H8), 7.18 (d, J=7.8 Hz, ArH2/6*), 7.28 (m, 3H, ArH3/5*, ArH4*). ^{13}C NMR ($CDCl_3$) δ: 30.29 (C4), 34.00 (C3$\underline{C}H_2$), 45.70 (C3), 55.86, 55.88 (O$\underline{C}H_3$x2), 58.73 (C1), 72.61 (CH_2NO_2), 110.68 (C8), 111.35 (C5), 125.97 (C5$\underline{C}_q$), 127.52 (ArC4), 128.28 (ArC3/C5), 128.48 (C8$\underline{C}_q$), 128.91 (ArC2/C6), 144.23 (ArC1$_q$), 147.27 (C7$_q$), 147.60 (C6$_q$). HRMS m/z calculated for $C_{19}H_{23}N_2O_4$: ($M^+ + H^+$) 343.1658, found 343.1651.

(2-Bromo-ethyl)-diethyl-amine.HBr 299a

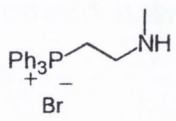


A solution of 2-Diethylamino-ethanol (10 ml, 0.78mmol) in 180 ml $_{aq}$HBr 48% was slowlet distilled over three hours until 100 ml of the distillate had been collected. The solution was refluxed for 12 hours, then concentrated under reduced pressure. The oily residue was triturated with acetone forming a pale brown powder in 53% yield m.p 210°C (lit. 208°C)[18].

IRυ_{max} cm^{-1} (Film): 2927 (N-H), 3593 (C-H), 1474 (C-C). ^{1}H NMR ($(CD_3)_2SO$) δ: 1.38 (t, 6H, J=7.3 Hz, $(CH_2C\underline{H}_3)_2$), 3.30-3.39 (m, 4H, $(C\underline{H}_2CH_3)_2$), 3.66 (t, 2H, J=6.8 Hz, $CH_2C\underline{H}_2N$), 3.81 (t, 2H, J=6.8 Hz, $BrCH_2$), 4.74 (s, 1H, NH). ^{13}C NMR

($((CD_3)_2SO$) δ: 7.11 ($((CH_2\underline{C}H_3)_2)$), 22.31 ($BrCH_2$), 47.05 ($N\underline{C}H_2CH_3$), 52.16 ($CH_2\underline{C}H_2N$).

(2-Methylamino-ethyl)-triphenyl-phosphonium bromide 299b

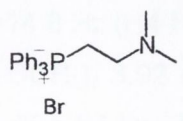


48% HBr was cautiously added to a stirred solution of 2-(methylamino)ethanol (9.4 ml, 93.5 mmol) and triphenylphosphine (24.45g, 93.5 mmol) in 38 ml benzene at such a rate not to allow the temperature of the solvent to rise above 10°C, cooling achieved using an acetone ice bath. The reaction mixture was then heated to 150°C removing the benzene to produce a melt. The temperature was held at 150°C for 90 minutes after which it was increase to 210°C for one hour, then cooled to 150°C for a further two hours. The mixture was allowed to cool to room temperature producing a thick glass that was extracted with the aid of a sonicator into 300 ml of a 1:1 mixture of ethyl acetate:water. The acidic *aqueous* layer was taken and extracted with ethyl acetate (2 x 100), the pH was adjusted to pH8 with a saturated $NaHCO_3/Na_2CO_3$ 1:1 solution and extracted with DCM (5 x 100ml). The DCM extracts were combined, dried over anhydrous Na_2SO_4, filtered and removed *invacuo* to yield a colourless solid in 72% yield.

IRυ_{max} cm^{-1} (Film): 2448 (N-H), 1111. ^1H NMR ($CDCl_3$) δ: 2.12 (s, 1.58H, NCH_3), 2.87-2.93 (m, 2H, $CH_2C\underline{H_2}N$), 3.78-3.85 (m, 2H, PCH_2), 5.94 (s, 1H, NH), 7.62-7.69 ($(C_6H_5)_3$). ^{13}C NMR ($CDCl_3$) δ: 20.98-21.48 (d, J=49.4 Hz, (PCH_2)), 42,09 (NCH_3), 48.82 (NCH_2), 117.50-118.36 (d, J=86.5 Hz, (P-$(ArC)_3$),130.11 ($(ArC2/C6)_3$), 133.78 ($(ArC3/C5)_3$), 134.68 ($(ArC4)_3$).

(2-Dimethylamino-ethyl)-triphenyl-phosphoniumbromide 299

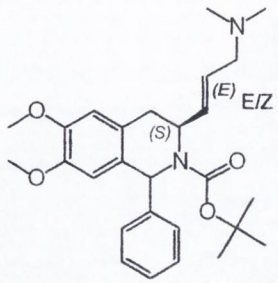
Prepared via the method described for **299b** m.p 188-190°C (lit. 191°C)[19]



IRυ_{max} cm^{-1} (Film): 1474 (C-C), 820 (Ar). ^1H NMR ($CDCl_3$) δ: 2.04 (s, 3.23H, $N(CH_3)_2$), 2.70-2.92 (m, 2H, $CH_2C\underline{H_2}N$), 3.79-3.98 (m, 2H, PCH_2), 7.64-7.85

($(C_6H_5)_3$). ^{13}C NMR ($CDCl_3$) δ: 21.11-21.61 (d, J=49.4 Hz, (PCH_2)), 44,90 ($N(CH_3)_2$), 50.80 (NCH_2), 118.32-119.18 (d, J=86.8 Hz, (P-(ArC)$_3$), 130.29 ((ArC2/C6)$_3$), 133.82 ((ArC3/C5)$_3$), 134.69 ((ArC4)$_3$).

3-(3-Dimethylamino-propenyl)-6,7-dimethoxy-1-phenyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester 300

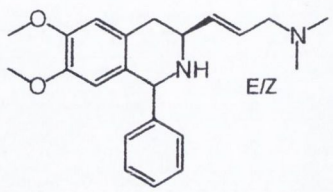


A suspension of (2-Dimethylamino-ethyl)-triphenyl-phosphoniumbromide **299** (1.28g (3.1 mmol) was stirred in anhydrous THF under an nitrogen atmosphere, to which *n*-BuLi (1.30 ml of a 2.5 M solution in hexane giving 3.1 mmol) was added dropwise at -15°C. After solution was achieved giving a deep red colour, 3-Formyl-6,7-dimethoxy-1-phenyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester **286** (1.128 g, 3.1 mmol) in 10 ml THF was added under nitrogen at -15°C. The dark red solution turned to a colourless suspension that was stirred overnight at ambient temperature. The reaction was diluted with 150 ml ethyl acetate and washed with brine (3 x 100 ml). The organic fraction was dried over anhydrous Na_2SO_4 and removed under vacuum leaving a residue that was purified on silica gel using a 4:1 diethyl ether:hexane mobile phase with a gradient to a 1:1 diethyl ether:methanol ending with a 100% methanol eluent to give the title compound in 52% yield as a colourless oil.

IRυ_{max} film cm^{-1}: 2974 (C-C), 1684 (C=O), 1382 (C-N), 1253, 1166 (C-O), 1514 (Ar). ^{1}H NMR ($CDCl_3$) δ: 1.48 (s, 9H, C($C\underline{H}_3$)$_3$), 2.14 (s, 0.82H, $N(CH_3)_2$ [R2]), 2.22 (s, 5.32H, $N(CH_3)_2$ [R1]), 2.42-2.48 (dd, 1H, J_{gem}=15.2 Hz (H4*-H4), J_{vic}=9.0 Hz (H4*-H3), H4*), 2.74-2.79 (dd, 1H, J_{gem}=14.8 Hz (H4-H4*), J_{vic}=4.2 Hz (H4-H3), H4), 2.96-3.07 (m, 2H, $C\underline{H}_2N$), 3.84 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.54 (m, 0.16H, H3 [R2]), 4.85 (m, 0.84H, H3 [R1]), 5.35-5.53 (m, 2H, $C\underline{H}$=$C\underline{H}$), 6.33 (s, 1H, H1), 6.73 (s, 1H, H8), 6.75 (s, 1H, H5), 7.16-7.21 (m, 5H, $C_6\underline{H}_5$). ^{13}C NMR ($CDCl_3$) δ: 28.32 (C($\underline{C}H_3$)$_3$), 33.47 (C4), 44.87 ($N(\underline{C}H_3)_2$ [R2]), 45.22 ($N(\underline{C}H_3)_2$ [R1]), 55.78 ($O\underline{C}H_3$x2),

56.23 ($\underline{C}H_2N$), 57.43 (C1), 79.95 ($\underline{C}(CH_3)_3$), 110.99 (C8), 111.09 (C5), 126.32 (C5$\underline{C}_q$), 126.52 (ArC4), 126.79 (ArC3/C5, CH=$\underline{C}H\underline{C}H_2$), 127.93 (ArC2/C6), 128.67 (C8$\underline{C}_q$), 134.38 ($\underline{C}H$=CHCH$_2$), 142.48 (ArC1$_q$), 147.22 (C7), 148.00 (C6), 155.49 (N$\underline{C}$OO). HRMS m/z calculated for $C_{27}H_{37}N_2O_4$: (M^+ + H^+) 453.2753, found 453.2730.

[3-(6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydro-isoquinolin-3-yl)-allyl]-dimethyl-amine 301

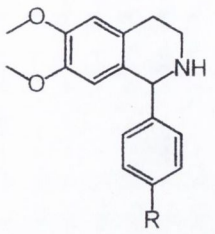


Prepared by stirring **300** (0.805g,) in 50 ml of 70/30 DCM/TFA for three hours. Reaction mixture was diluted with 100 ml DCM and washed with 10% NaOH (4x60ml). The organic layer was dried over anhydrous Na_2SO_4, filtered removed under vacuum and the resulting residue was columned on silica gel using a methanol eluent to yield the title compound in 96%.

IRυ_{max} film cm^{-1}: 3434 (N-H), 1513 (ArC-C), 1464 (C=C). ^{1}H NMR ($CDCl_3$) δ:1.93 (s, 2.26H, NH), 1.99 (s, 6H, N($\underline{C}H_3)_2$, [D1]), 2.26 (s, 4.85H, N($\underline{C}H_3)_2$, [D2]), 2.57-2.61 (dd, 1.82H, J_{gem}=6.7 Hz, J_{vic}=3.7 Hz, $\underline{C}H_2$N [D2]), 2.65-2.76 (m, 2.89H, H4 [D1], H4/H4* [D2]), 2.84-2.92 (m, 1H, H4* [D1]), 2.99-3.12 (2dd, 2H, J_1=13.6 Hz, J_2=6.2 Hz, J_3=5.8 Hz, $\underline{C}H_2$N [D1]), 3.61 (s, 2.49H, OCH_3 [D2]), 3.74 (s, 3H, OCH_3 [D1]), 3.82-3.88 (m, 3.72H, OCH_3 [D2], H3 [D1]), 3.91 (s, 3H, OCH_3 [D1]), 3.98-4.03 (m, 0.82H, H3 [D2]), 5.13 (s, 0.80H, H1 [D2]), 5.23 (s, 1H, H1 [D1]), 5.49-5.71 (m, 3.78H, $\underline{C}H$=$\underline{C}H$ [D1/D2]), 6.19 (s, 0.80H, H8 [D2]), 6.43 (s, 1H, H8 [D1]), 6.63 (s, 0.79H, H5 [D2]), 6.67 (s, 1H, H5 [D1]), 7.17-7.36 (m, 9.36H, $C_6\underline{H}_6$ [D1/D2]). ^{13}C NMR ($CDCl_3$) δ: 34.96 (C4 [D1]), 35.79 (C4 [D2]), 44.32 (C3 [D1]), 44.92 (N($CH_3)_2$ [D1]), 45.31 (N($CH_3)_2$ [D2]), 52.13 (C3 [D1]), 55.81 (OCH_3x2 [D1/D2]), 55.90 ($\underline{C}H_2$N [D2]), 56.51 ($\underline{C}H_2$N [D1]), 59.58 (C1 [D1]), 63.08 (C1 [D2]), 110.58 (H8 [D2]), 110.95 (H8 [D1]), 111.15 (H5 [D1/D2]), 127.09 (ArC4 [D2]), 127.25 (C5$\underline{C}_q$ [D1]), 127.38 (C5$\underline{C}_q$ [D2]), 127.62 (ArC4 [D1]), 128.15 (C8$\underline{C}_q$ [D2]), 128.46 (C8$\underline{C}_q$ [D1]), 128.21 (ArC3/C5 [D2]), 128.49 (ArC3/C5 [D1]), 128.67 (CH=$\underline{C}HCH_2$ [D1]), 128.91 (CH=$\underline{C}HCH_2$ [D1]), 128.99 (ArC2/C6 [D2]), 129.16 (ArC3/C5 [D1]), 130.26 (ArC1$_q$), 134.74 ($\underline{C}H$=CHCH$_2$ [D1]), 134.83 ($\underline{C}H$=CHCH$_2$ [D2]), 144.41 (ArC1$_q$ [D2]), 145.37 (ArC1$_q$ [D1]), 147.04

(C7 [D2]), 147.23 (C7 [D1]), 147.51 (C6 [D2]), 147.79 (C6 [D1]). HRMS m/z calculated for $C_{22}H_{29}N_2O_2$: ($M^+ + H^+$) 353.2229, found 353.2234.

6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydro-isoquinoline 302



R = H, **302**
NO_2, **302a**
SCH_3, **302b**
Br, **302c**
F. **302d**

General method for the synthesis of 1,2,3,4 tetrahydroisoquinolines **302, 302a-d**:

Benzaldehyde (1.273 g, 12.00 mmol) and 3,4-Dimethoxyphenethylamine (1.80 g, 10.00 mmol) were taken in dry toluene (50 ml) and refluxed under a nitrogen atmosphere using a Dean-Stark trap for four hours at 148°C, until no more water was collected. The solution was concentrated under vacuum. Thereafter, trifluoroacetic acid (10 ml) was added to the solution, and the solution was again refluxed for two hours at about 80°C. The reaction was quenched by adding water. The pH was adjusted to pH 8-9 using 15% sodium hydroxide solution and the isoquinoline product was extracted with DCM (3 x 100 ml). The DCM was dried over anhydrous Na_2SO_4, filtered and removed *in vacuo*. The crude solid product was recrystallised from ethanol, yielding the product as a colourless solid. Yield: 56%, m.p. 101°C (lit 102-103)[20]

6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydro-isoquinoline 302

IRυ_{max} film: 3325 (N-H) cm^{-1}, 1512 (ArC-C) cm^{-1}, 1109 (C-O) cm^{-1}, 828 (ArC-H) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.74-2.81 (m, 2H, H4 + N<u>H</u>), 2.92-2.99 (m, 1H, H4*), 3.03-3.09 (m, 1H, H3), 3.19-3.25 (m, 1H, H3*) 3.65 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 5.08 (s, 1H, H1), 6.26 (s, 1H, H5), 6.65 (s, 1H, H8), 7.28-7.35 (m, 5H, $C_6\underline{H}_5$). ^{13}C NMR ($CDCl_3$) δ: 28.95 (C4), 41.57 (C3), 55.78 ($O\underline{C}H_3$x2), 61.20 (C1), 110.81 (C8), 111.27 (C5), 127.36 (C5$\underline{C}_q$), 127.44 (C4*), 128.38 (C3*/C5*), 128.89 (C2*/C6*), 129.27 (C8$\underline{C}_q$), 144.23 ($C1_q$*), 147.03 ($C7_q$), 147.61 ($C6_q$). LRMS m/z calculated for $C_{17}H_{19}NO_2$: (M^+) 269, found 269.

6,7-Dimethoxy-1-(4-methylsulfanyl-phenyl)-1,2,3,4-tetrahydro-isoquinoline 302a

Title compound was synthesised according to the general method employed in the synthesis of **302** (53%).

IRυ_{max} film: 3259 (N-H) cm^{-1}, 1518 (ArC-C) cm^{-1}, 1096 (C-O) cm^{-1}, 750 (S-C) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.88 (s, 1H, NH), 2.48 (s, 3H, SCH_3), 2.72-2.77 (m, 1H, H4), 2.88-2.98 (m, 1H, H4*), 3.01-3.07 (m, 1H, H3), 3.18-3.24 (m, 1H, H3*) 3.66 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 5.01 (s, 1H, H1), 6.25 (s, 1H, H5), 6.64 (s, 1H, H8), 7.17-7.23 (m, 4H, C_6H_4),. ^{13}C NMR ($CDCl_3$) δ: 15.72 (SCH_3) 29.17 (C4), 41.71 (C3), 55.71, 55.76 (OCH_3x2), 60.82 (C1), 110.68 (C8), 111.27 (C5), 127.54 ($C5C_q$), 126.38 (C3*/C5*), 129.27 (C2*/C6*), 129.56 ($C8C_q$), 137.15 ($C4_q$*), 141.72 ($C1_q$*), 146.89 ($C7_q$), 147.47 ($C6_q$). Elemental analysis: $C_{18}H_{21}NO_2S$ requires C, 68.54; H, 6.71; N, 4.44. Found C, 68.48; H, 6.71; N, 4.30.

1-(4-Bromo-phenyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline 302c

Title compound was synthesised according to the general method employed in the synthesis of **302** (76%) m.p 140-142°C (lit. 140°C)[21]

IRυ_{max} film 3448 (N-H) cm^{-1}, 1517 (ArC-C) cm^{-1}, 1123 (C-O) cm^{-1}, 831 (C-Br) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.76-2.85 (m, 1H, H4), 3.02-3.15 (m, 3H, H4*, H3*, H3), 3.65 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 5.19 (s, 1H, H1), 6.17 (s, 1H, H5), 6.66 (s, 1H, H8), 6.97 (s, 1H, NH), 7.16-7.19 (d, 2H, J=8 Hz, (ArH2*/H6*)), 7.47-7.49 (d, 2H, J=8 Hz, (ArH3*/H5*)). ^{13}C NMR ($CDCl_3$) δ: 26.89 (C4), 40.73 (C3), 55.80, 55.84 (OCH_3x2), 59.68 (C1), 110.30 (C8), 111.13 (C5), 122.60 ($C4*_q$) 125.53 ($C5C_q$), 125.97 ($C1*_q$) 131.12 (ArC3*/C5*), 131.76 (ArC2*/C6*), 139.47 ($C8C_q$), 147.61 ($C7_q$), 148.41 ($C6_q$). HRMS m/z calculated for $C_{17}H_{19}NO_2Br$: ($M^+ + H^+$) 348.0599, found 348.0589.

1-(4-Fluoro-phenyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline 302d

Title compound synthesised according to the general method employed in the synthesis of **302**
(67%) m.p 148°C (lit. 145-150°C)[21]

IRυ_{max} cm^{-1} (KBr): 2935 (NH), 1517 (Ar), 1123, 1010 (C-O), 746 (Ar). ^1H NMR ($CDCl_3$) δ: 2.47 (s, 1H, NH), 2.71-2.77 (m, 1H, H4), 2.90-2.98 (m, 1H, H4*), 3.02-3.09 (m, 1H, H3), 3.17-3.23 (m, 1H, H3*) 3.65 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 5.04 (s, 1H, H1), 6.21 (s, 1H, H5), 6.64 (s, 1H, H8), 6.99-7.03 (dd, 2H, J_o=8.0 Hz, J_m=5.5 Hz, (ArH2*/H6*)), 7.22-7.25 (dd, 2H, J_o=8.0 Hz, J_m=5.5 Hz, (ArH3*/H5*)). ^{13}C NMR ($CDCl_3$) δ: 28.98 (C4), 41.69 (C3), 55.70, ($O\underline{C}H_3$x2), 60.54 (C1), 110.61 (C8), 111.28 (C5), 114.97, 115.18 (ArC3*/C5*), 127.41 (C5$\underline{C}_q$), 129.34 (C8$\underline{C}_q$), 130.33, 130.41 (ArC2*/C6*), 140.32 (ArC1*$_q$), 146.97 (C7*$_q$), 147.58 (C6*$_q$), 160.75 (ArC4*$_q$). HRMS m/z calculated for $C_{17}H_{19}NO_2F$: (M^+ + H^+) 288.1400, found 288.1393.

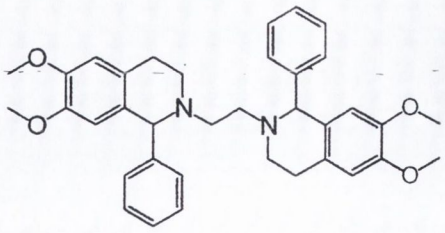
6,7-Dimethoxy-1-(4-nitro-phenyl)-1,2,3,4-tetrahydro-isoquinoline 302b

Title compound was synthesised according to the general method employed in the synthesis of **302** (58%).

IRυ_{max} film 3448 (N-H) cm^{-1}, 1544 (N-O) cm^{-1}, 1113 (C-O) cm^{-1}, 854 (ArC-H) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.06 (s, 1H, NH), 2.74-2.80 (m, 1H, H4), 2.90-2.98 (m, 1H, H4*), 3.04-3.10 (m, 1H, H3), 3.14-3.19 (m, 1H, H3*) 3.65 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 5.15 (s, 1H, H1), 6.17 (s, 1H, H5), 6.67 (s, 1H, H8), 7.45-7.47 (d, 2H, J=8.0 Hz, (ArH2*/H6*)), 8.16-8.19 (d, 2H, J=8 Hz, (ArH3*/H5*)). ^{13}C NMR ($CDCl_3$) δ: 28.96 (C4), 41.48 (C3), 55.76, 55.79 ($O\underline{C}H_3$x2), 60.52 (C1), 110.42 (C8), 111.56 (C5), 123.52, (ArC2*/C6*) 127.63 (C4$\underline{C}_q$), 128.03 (C1$\underline{C}_q$), 129.73 (ArC3*/C5*), 147.13 (C7$_q$), 147.16 (C6$_q$), 147.95 (ArC1*$_q$), 147.58 (ArC4*$_q$). HRMS m/z calculated for $C_{17}H_{19}N_2O_4$: (M^+ + H^+) 315.1345, found 315.1360.

2-[2-(6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydro-isoquinoline-1-yl)-ethyl]-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydro-isoquinoline 303

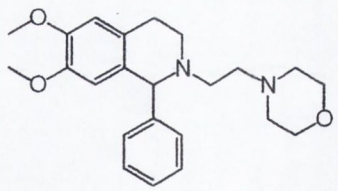
Start material **302** (3.142g, 11.68 mmol) was dissolved in dry acetonitrile to which 1M equivalent of dibromoethane was added with K_2CO_3 (1.613g, 11.68mmol). The reaction was refluxed for thre hours and filtered through a celite cake. Volitiles removed *in vacuo* residue recrystallised from DCM/MeOH to yield title compound as a colourless solid 56%.



IRυ_{max} cm^{-1} (film): 2812 (CH), 1515 (Ar), 1221, 1096 (C-O), 741 (ArH). ^{1}H NMR ($CDCl_3$) δ: 2.40-2.48, 2.52-2.60 (2m, 4H, H4, H4^), 2.65-2.84 (m, 4H, $NC\underline{H_2}C\underline{H_2}N$), 2.88-2.96, 2.98-3.09 (2m, 4H, H3, H3^), 3.61 (s, 6H, OCH_3), 3.86 (s, 6H, OCH_3), 4.43, 4.49 (2s, 2H, H1, H1^), 6.14 (s, 2H, H5, H5^), 6.59 (s, 2H, H8^), 7.16-7.29 (m, 10H, ($C_6\underline{H_5}$)x2). ^{13}C NMR ($CDCl_3$) δ: 28.08 (C4), 28.14 (C4^), 47.33 (C3), 47.47 (C3^), 51.50 ($NC\underline{H_2}C\underline{H_2}N$), 55.71 ($OC\underline{H_3}$x4), 67.56 (C1), 67.71 (C1^), 110.65 (C8/C8^), 111.53 (C5), 111.54 (C5^), 126.73 (C5$\underline{C_q}$), 126.78 (C5$\underline{C_q}$^), 126.98 (ArC4*/ArC4*^), 128.00 (ArC3*/C5*), 128.03 (ArC3*^/C5*^), 129.50 (ArC2*/C6*), 129.55 (ArC2*^/C6*^), 129.91 (C8$\underline{C_q}$), 130.00 (C8$\underline{C_q}$), 143.93 (Ar$C1_q$*), 144.12 (Ar$C1_q$*^), 146.85 ($C7_q$), 146.89 ($C7_q$^), 147.22 ($C6_q$^), 147.26 ($C6_q$*).
HRMS m/z calculated for $C_{36}H_{40}N_2O_4$: (M^+ + H) 565.3066, found 565.3052.

Symbol (^) denotes a second isoquinoline structure within the molecule.

6,7-Dimethoxy-2-(2-morpholin-4-yl-ethyl)-1-phenyl-1,2,3,4-tetrahydro isoquinoline 305



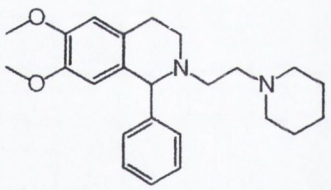
General method for the addition of side chains:

6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **302** (1.347 g, 5.00 mmol) was dissolved in anyhdrous DMF (20 ml) to which K_2CO_3 (2.760 g, 20 mmol) and KI (0.100 g, 0.60 mmol) were added. To this turbid solution, the free base of 4-(2-Chloro-ethyl)-morpholine (0.949g, 5.1mmol) in dry DMF (10 ml), was added dropwise. The reaction mixture was stirred for five days at 70°C under a nitrogen atmosphere. The reaction mixture was poured into 200 ml ethyl acetate and washed

with saturated sodium chloride solution (60 ml x 3). The organic layer was dried over anhydrous magnesium sulfate, and concentrated under vacuum. The crude oil was purified on a silica gel column. Elution with MeOH/DCM (4:1) yielded a pale yellow solid. Yield: 75%. m.p. 163°C.

IRυ_{max} film 2938 (N-C) cm^{-1}, 2009 (C-C) cm^{-1}, 1134 (C-O) cm^{-1}, 748 (ArC-H) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.31-2.32 (m, 4H, N($C\underline{H}_2$)$_2$), 2.40-2.50 (m, 2H, C1NC$\underline{H}_2$), 2.58-2.77 (m, 4H, H4*/H4/C1NCH$_2$C$\underline{H}_2$), 2.86-2.99 (m, 1H, H3), 3.11-3.17 (m, 1H, H3*), 3.55 (s, 3H, OCH_3), 3.58-3.60 (m, 4H, O(CH_2)$_2$), 3.80 (s, 3H, OCH_3), 4.52 (s, 1H, H1), 6.14 (s, 1H, H5), 6.56 (s, 1H, H8), 7.18-7.24 (m, 5H, $C_6\underline{H}_5$),. ^{13}C NMR ($CDCl_3$) δ: 27.74 (C4), 47.25 (C3), 50.95 (C1N$\underline{C}H_2$), 53.69 (N($\underline{C}H_2$)$_2$), 55.43, 55,47 (O$\underline{C}H_3$x2), 56.46 (C1NCH$_2$$\underline{C}H_2$), 66.56, 66.64 (O($\underline{C}H_2$)$_2$), 67.77 (C1), 110.50 (C8), 111.31 (C5), 126.43 (C5$\underline{C}_q$), 126.86 (ArC4*), 127.82 (ArC3*/C5*), 129.26 (ArC2*/C6*), 129.54 (C8$\underline{C}_q$), 143.69 (ArC1$_q$*), 146.70 (C6$_q$), 147.08 (C7$_q$). HRMS calculated for $C_{23}H_{30}N_2O_3$: (M^+ + H^+) 383.2335, found 383.2322. Elemental analysis: $C_{23}H_{30}N_2O_3$ requires C, 72.22; H, 7.91; N, 7.32. Found C, 71.99; H, 8.01; N, 7.27.

6,7-Dimethoxy-1-phenyl-2-(2-piperidin-1-yl-ethyl)-1,2,3,4-tetrahydro-isoquinoline 307



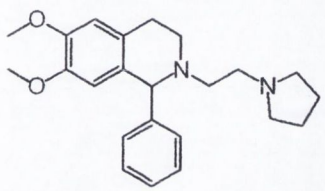
Synthesised according to the general method utilised in the synthesis of **305**. using the HCl salt of 4-(2-Chloro-ethyl)-piperidine and 7 equivalents of K_2CO_3 stirred in DMF for 5 days at 70ºC. (25%)

IRυ_{max} cm^{-1} (film): 3435 (N-C), 1513 (Ar), 1098 (C-O). ^{1}H NMR ($CDCl_3$) δ: 1.35-1.44 (m, 2H, N(CH_2)$_2$(CH_2)$_2$C$\underline{H}_2$), 1.50-1.55 (m, 4H, N(CH_2)$_2$($C\underline{H}_2$)$_2$), 2.28-2.35 (m, 4H, N($C\underline{H}_2$)$_2$), 2.38-2.55 (m, 4H, NC$\underline{H}_2$C$\underline{H}_2$N), 2.69-2.82 (m, 2H, H4/H4*), 2.92-2.97 (m, 1H, H3), 3.14-3.20 (m, 1H, H3*), 3.61 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.59 (s, 1H, H1), 6.20 (s, 1H, H5), 6.61 (s, 1H, H8), 7.22-7.31 (m, 5H, $C_6\underline{H}_5$),. ^{13}C NMR ($CDCl_3$) δ: 24.26 (N(CH_2)$_2$(CH_2)$_2$$\underline{C}H_2$), 25.84 (N($CH_2$)$_2$($\underline{C}H_2$)$_2$), 27.84 (C4), 47.29 (C3), 51.50 (C1N$\underline{C}H_2$), 54.87 (N($\underline{C}H_2$)$_2$), 55.66, 55.68 (O$\underline{C}H_3$x2), 57.10 (NCH$_2$$\underline{C}H_2$N),

67.78 (C1), 110.69 (C8), 111.54 (C5), 126.73 (C5$\underline{C}_q$), 126.97 (ArC4*), 127.99 (ArC3*/C5*), 129.48 (ArC2*/C6*), 129.79 (C8$\underline{C}_q$), 143.95 ($C1_q$*), 146.88 ($C7_q$), 147.27 ($C6_q$). HRMS calculated for $C_{24}H_{33}N_2O_2$: ($M^+ + H^+$) 381.2542, found 381.2548.

6,7-Dimethoxy-1-phenyl-2-(2-pyrrolidin-1-yl-ethyl)-1,2,3,4-tetrahydro-isoquinoline 306

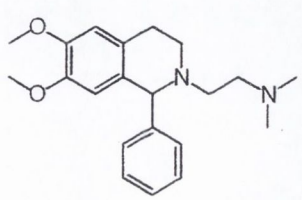
Title compound synthesised according to the general method employed in the synthesis of **305** (16%)



IRυ_{max} cm^{-1} (film): 2809 (C-H), 1518 (Ar), 1097 (C-O), 740 (ArC-H). ^{1}H NMR ($CDCl_3$) δ: 1.70-1.76 (m, 4H, $N(CH_2)_2(C\underline{H}_2)_2$), 2.40-2.45 (m, 4H, $N(C\underline{H}_2)_2$), 2.51-2.62 (m, 2H, $NCH_2C\underline{H}_2N$), 2.64-2.83 (m, 4H, H4, $NC\underline{H}_2CH_2N$), 2.95-3.03 (m, 1H, H3), 3.16-3.21 (m, 1H, H3*), 3.61 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.58 (s, 1H, H1), 6.19 (s, 1H, H5), 6.61 (s, 1H, H8), 7.22-7.32 (m, 5H, $C_6\underline{H}_5$). ^{13}C NMR ($CDCl_3$) δ: 23.27 ($N(CH_2)_2(\underline{C}H_2)_2$), 28.00 (C4), 47.48 (C3), 53.28 ($N\underline{C}H_2CH_2N$), 54.12 ($NCH_2\underline{C}H_2N$), 54.38 ($N(CH_2)_2$), 55.69, 55.72 ($O\underline{C}H_3$x2), 67.93 (C1), 110.68 (C8), 111.54 (C5), 126.74 (C5$\underline{C}_q$), 127.05 (ArC4*), 128.05 (ArC3*/C5*), 129.50 (ArC2*/C6*), 129.89 (C8$\underline{C}_q$), 143.92 ($C1_q$*), 146.89 ($C7_q$), 147.29 ($C6_q$).

[2-(6,7-Dimethoxy-1-phenyl-3,4-dihydro-1H-isoquinolin-2-yl)-ethyl]-dimethyl-amine 304

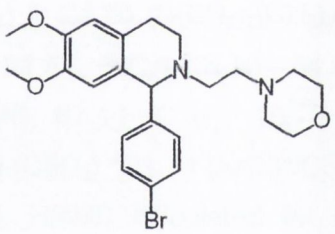
Title compound synthesised according to the general method employed in the synthesis of **302** (8%)



IRυ_{max} cm^{-1} (film): 2827 (C-H), 1513 (Ar), 1101 (C-O), 711 (ArC-H). ^{1}H NMR ($CDCl_3$) δ: 2.15 (s, 6H, $N(C\underline{H}_3)_2$), 2.40-2.49 (m, 3H, $NCH_2C\underline{H}_2N$, H4), 2.63-2.73 (m, 2H, $NC\underline{H}_2CH_2N$), 2.76-2.82 (m, 1H, H4*), 2.97-3.04 (m, 1H, H3), 3.16-3.21 (m, 1H, H3*), 3.61 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.58 (s, 1H, H1), 6.19 (s, 1H, H5), 6.61 (s, 1H, H8), 7.22-7.32 (m, 5H, $C_6\underline{H}_5$). ^{13}C NMR ($CDCl_3$) δ: 28.02 (C4), 45.72 ($N(CH_3)_2$) 47.43 (C3), 52.35 ($N\underline{C}H_2CH_2N$), 55.67, 55.69 ($O\underline{C}H_3$x2), 57.31 ($NCH_2\underline{C}H_2N$), 68.12 (C1), 110.65 (C8), 111.51 (C5), 126.71 ($C5\underline{C}_q$), 127.06 (ArC4*), 128.04 (ArC3*/C5*), 129.51 (ArC2*/C6*), 129.87 ($C8\underline{C}_q$), 143.89 ($ArC1_q$*), 146.88 ($C7_q$), 147.27 ($C6_q$). HRMS calculated for $C_{21}H_{28}N_2O_2$: ($M^+ + H^+$) 341.2229, found 341.2246.

6,7-Dimethoxy-1-phenyl-2-(2-pyrrolidin-1-yl-ethyl)-1,2,3,4-tetrahydro-isoquinoline 319

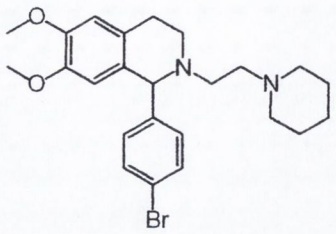
Title compound synthesised according to the general method employed in the synthesis of **305**
(19%)



IRυ_{max} cm^{-1} (film): 2831 (C-H), 1515 (Ar), 1118, (C-O), 1010 (ArC-H). ^{1}H NMR ($CDCl_3$) δ: 2.38-2.41 (m, 4H, $N(C\underline{H}_2)_2$), 2.45-2.55 (m, 2H, $NCH_2C\underline{H}_2N$), 2.63-2.71 (m, 3H, H4, $NC\underline{H}_2CH_2N$), 2.75-2.81 (m, 1H, H4*), 2.93-3.00 (m, 1H, H3), 3.13-3.18 (m, 1H, H3*), 3.64 (s, 3H, OCH_3), 3.66-3.68 (m, 4H, $O(CH_2)_2$), 3.86 (s, 3H, OCH_3) 4.55 (s, 1H, H1), 6.15 (s, 1H, H5), 6.61 (s, 1H, H8), 7.14-7.17 (d, 2H, J=8 Hz, (ArH2*/H6*)), 7.41-7.44 (d, 2H, J=8 Hz, (ArH3*/H5*)). ^{13}C NMR ($CDCl_3$) δ: 27.87 (C4), 47.31 (C3), 51.20 ($N\underline{C}H_2CH_2$), 54.02 ($N(\underline{C}H_2)_2$), 55.75, 55,78 ($O\underline{C}H_3$x2), 56.77 ($NCH_2\underline{C}H_2N$), 66.87 ($O(\underline{C}H_2)_2$), 67.29 (C1), 110.81 (C8), 111.34 (C5), 120.95 ($ArC4*_q$) 126.73 ($C5\underline{C}_q$), 129.03 ($ArC1*_q$) 131.14 (ArC3*/C5*), 131.21 (ArC2*/C6*), 143.22 ($C8\underline{C}_q$), 147.06 ($C7_q$), 147.49 ($C6_q$). HRMS calculated for $C_{23}H_{30}{}^{79}BrN_2O_3$: ($M^+ + H^+$) 461.1440, found 461.1429.

1-(4-Bromo-phenyl)-6,7-dimethoxy-2-(2-piperidin-1-yl-ethyl)-1,2,3,4-tetrahydro-isoquinoline 320

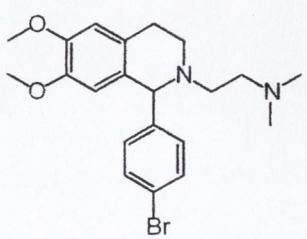
Title compound synthesised according to the general method employed in the synthesis of **305** (21%)



IRυ_{max} cm^{-1} (film): 1515 (Ar), 1118, (C-O), 766 (ArH). ^{1}H NMR ($CDCl_3$) δ: 1.36-1.44 (m, 2H, $N(CH_2)_2(CH_2)_2C\underline{H}_2$), 1.50-1.56 (m, 4H, $N(CH_2)_2(C\underline{H}_2)_2$), 2.30 (s, 4H, $N(C\underline{H}_2)_2$), 2.36-2.44 (m, 1H, H4), 2.48-2.54 (m, 2H, $NCH_2C\underline{H}_2N$), 2.63-2.68 (m, 2H, $NC\underline{H}_2CH_2N$), 2.69-2.80 (m, 1H, H4*), 2.89-2.95 (m, 1H, H3), 3.11-3.15 (m, 1H, H3*), 3.63 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3) 4.56 (s, 1H, H1), 6.16 (s, 1H, H8), 6.60 (s, 1H, H5), 7.14-7.16 (d, 2H, J=8 Hz, ArH2*/H6*), 7.40-7.43 (d, 2H, J=8 Hz, ArH3*/H5*). ^{13}C NMR ($CDCl_3$) δ: 24.26 ($N(CH_2)_2(CH_2)_2\underline{C}H_2$), 25.86 ($N(CH_2)_2(\underline{C}H_2)_2$), 27.79 (C-4), 47.20 (C-3), 51.52 ($N\underline{C}H_2CH_2N$), 54.92 ($N(\underline{C}H_2)_2$), 55.70, 55,73 ($O\underline{C}H_3$x2), 56.11 ($NCH_2\underline{C}H_2N$), 67.11 (C-1), 110.79 (C-8), 111.35 (C5), 120.82 ($C4^*_q$) 126.79 ($C5C_q$), 129.10 ($C8C_q$) 131.11 (ArC3*/C5*, ArC2*/C6*), 143.26 ($C1^*_q$), 146.99 ($C7_q$), 147.41 ($C6_q$). HRMS calculated for $C_{24}H_{31}{}^{79}Br\ N_2O_2$: ($M^+ + H^+$) 459.1647, found 459.1663.

{2-[1-(4-Bromo-phenyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-ethyl}-dimethyl-amine 318

Title compound synthesised from **302c** according to the general method employed in the synthesis of **305** (11%)

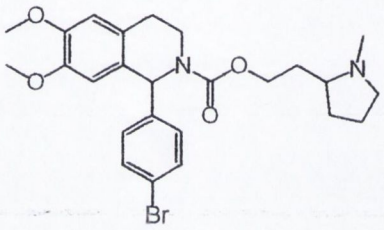


IRυ_{max} cm^{-1} (film): 1515 (Ar), 1464, 1118, (C-O), 703 (ArC-H). ^{1}H NMR ($CDCl_3$) δ: 2.15 (s, 6H, $N(C\underline{H}_3)_2$), 2.34-2.50 (m, 3H, H4/$NCH_2C\underline{H}_2N$), 2.60-2.69 (m, 2H,

$NC\underline{H}_2CH_2N$), 2.73-2.80 (m, 1H, H4*), 2.94-3.01 (m, 1H, H3), 3.12-3.21 (m, 1H, H3*), 3.63 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3) 4.51 (s, 1H, H1), 6.14 (s, 1H, H5), 6.60 (s, 1H, H8), 7.14-7.17 (d, 2H, J=8 Hz, (ArH2*/H6*)), 7.41-7.42 (d, 2H, J=8 Hz, (ArH3*/H5*)). ^{13}C NMR ($CDCl_3$) δ: 27.94 (C4), 45.75 ($N(C\underline{H}_3)_2$), 47.31 (C3), 52.33 ($NC\underline{H}_2CH_2N$), 55.70, 55,73 ($OC\underline{H}_3$x2), 57.29 ($NCH_2\underline{C}H_2N$), 67.46 (C1), 110.74 (C8), 111.32 (C5), 120.87 ($ArC4^*_q$) 126.76 ($C5C_q$), 129.15 ($C8C_q$) 131.13 (ArC3*/C5*, ArC2*/C6*), 143.20 ($ArC1^*_q$), 146.98 ($C7_q$), 147.41 ($C6_q$). HRMS calculated for $C_{21}H_{27}{}^{79}Br\ N_2O_2$: ($M^+ + H^+$) 419.1334, found 419.1323.

1-(4-Bromo-phenyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinoline-2-carboxylic acid 2-(1-methyl-pyrrolidin-2-yl)-ethyl ester 321

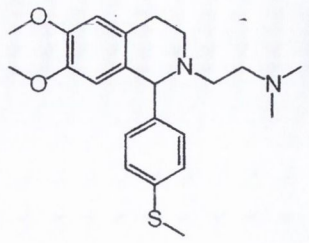
Title compound from **302c** synthesised according to the general method employed in the synthesis of **305** (18%)



IRυ_{max} cm^{-1} (film): 3434 (CON), 1641-1759 (C=O), 1519 (ArC-H), 1097 (C-O). ^1H NMR ($CDCl_3$) δ: 1.44-1.78 (m, 4H, $NCH_2C\underline{H}_2C\underline{H}_2$), 1.90-2.00 (m, 1H, $NC\underline{H}$), 2.04-2.13 (m, 4H, $CHNC\underline{H}_2$, $OCH_2C\underline{H}_2$), 2.30 (s, 3H, $NC\underline{H}_3$), 2.64-2.68 (m, 1H, H4), 2.86-2.98 (m, 1H, H4*), 3.02-3,14 (m, 2H, H3), 3.74 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.11-4.20 (m, 2H, $COOCH_2$), 6.14 (s, 1H, H1), 6.44 (s, 1H, H8), 6.66 (s, 1H, H5), 7.11-7.12 (d, 2H, J=8 Hz, ArH2*/H6*), 7.38-7.40 (d, 2H, J=8 Hz, ArH3*/H5*). ^{13}C NMR ($CDCl_3$) δ: 21.84 ($NCH_2CH_2\underline{C}H_2$), 27.79 (C4), 30.79 ($NCH_2\underline{C}H$), 33.21 ($OCH_2\underline{C}H_2$), 37.62 ($N(CH_3)\underline{C}H_2$), 40.41 ($NCH_3$), 55.78, 55.83 ($OCH_3$x2), 56.38 (C1), 56.97 (C3), 63.37 (NCH), 63.74 (OCH_2), 110.68 (C8), 111.12 (C5), 121.38 (ArC4*), 126.12 ($C5\underline{C}_q$), 130.20 ($ArC8\underline{C}_q$, ArC2*/C6*), 131.21 (ArC3*/C5*), 141.60 (ArC1*), 147.40 (C7), 148.03 (C6), 154.09 (NCO [R2]), 155.31 (NCO [R1]). HRMS calculated for $C_{22}H_{27}{}^{79}Br\ N_2O_4$: ($M^+ + H^+$) 503.1546, found 503.1574.

{2-[6,7-Dimethoxy-1-(4-methylsulfanyl-phenyl)-3,4-dihydro-1H-isoquinolin-2yl] ethyl}-dimethyl-amine 322

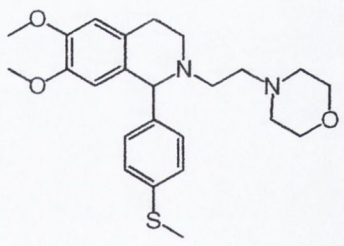
Title compound synthesised from **302b** according to the general method employed in the synthesis of **305** (10%)



IRυ_{max} cm^{-1} (film): 2827 (C-H), 1522 (Ar), 1112 (C-O), 631 (ArC-H). ^{1}H NMR ($CDCl_3$) δ: 2.18 (s, 6H, $N(CH_3)_2$), 2.43-2.47 (m, 2H, $NCH_2\underline{C}H_2N$,), 2.49 (s, 3H, SCH_3), 2.62-2.71 (m, 2H, $NC\underline{H}_2CH_2N$), 2.74-2.81 (m, 1H, H4), 2.94-3.02 (m, 2H, H3/H4*), 3.14-3.19 (m, 1H, H3*), 3.63 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.51 (s, 1H, H1), 6.18 (s, 1H, H5), 6.61 (s, 1H, H8), 7.14-7.21 (m, 4H, $C_6\underline{H}_4$). ^{13}C NMR ($CDCl_3$) δ: 15.83 (SCH_3), 28.01 (C4), 45.765 ($N(CH_3)_2$), 47.34 (C3), 52.20 ($NCH_2\underline{C}H_2N$), 55.75, 55.77 ($O\underline{C}H_3$x2), 57.19 ($N\underline{C}H_2CH_2N$), 67.63 (C1), 110.73 (C8), 111.33 (C5), 126.77 (C5$\underline{C}_q$), 129.67 (C8$\underline{C}_q$), 126.28 (ArC3*/C5*), 130.00 (ArC2*/C6*), 136.88 (ArC4*$_q$), 140.86 (ArC1$_q$*), 146.97 (C7$_q$), 147.39 (C6$_q$). LRMS m/z calculated for $C_{22}H_{30}N_2O_2S$: ($M^+ + H^+$) 386, found 386.

6,7-Dimethoxy-1-(4-methylsulfanyl-phenyl)-2-(2-morpholin-4-yl-ethyl)-1,2,3,4-tetrahydro-isoquinoline 323

Title compound was synthesised from **302b** according to the general method employed in the synthesis of **305** (17%)

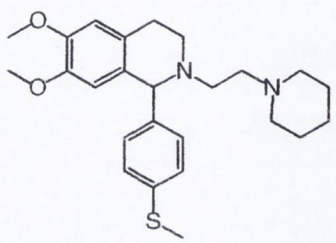


IRυ_{max} cm^{-1} (film): 2819 (C-H), 1520 (Ar), 1096 (C-O), 789 (ArC-H). ^{1}H NMR ($CDCl_3$) δ: 2.38-2.40 (m, 4H, $N(C\underline{H}_2)_2$), 2.43-2.47 (m, 2H, $NCH_2C\underline{H}_2N$,), 2.50 (s, 3H, SCH_3), 2.62-2.81 (m, 4H, H4/H4, $NC\underline{H}_2CH_2N$), 2.92-3.00 (m, 1H, H3), 3.14-3.19 (m, 1H, H3*), 3.64 (s, 3H, OCH_3), 3.66-3.68 (m, 4H, $O(CH_2)_2$), 3.86 (s, 3H, OCH_3), 4.54 (s, 1H, H1), 6.19 (s, 1H, H5), 6.61 (s, 1H, H8), 7.16-7.21 (m, 4H, $C_6\underline{H}_4$). ^{13}C NMR ($CDCl_3$) δ: 15.78 (SCH_3), 27.88 (C4), 47.29 (C3), 51.14 ($NCH_2\underline{C}H_2N$), 54.00 ($N(\underline{C}H_2)_2$), 55.74, 55.77 ($O\underline{C}H_3$x2), 56.75 ($N\underline{C}H_2CH_2N$), 66.86 ($O(\underline{C}H_2)_2$), 67.38 (C1),

110.74 (C8), 111.47 (C5), 125.88 (ArC3*/C5*), 126.21 (C5$\underline{C}_q$), 129.54 (C8$\underline{C}_q$), 129.95 (ArC2*/C6*), 136.90(ArC4$_q$*), 140.85 (ArC1$_q$*), 146.99 (C7$_q$), 147.39 (C6$_q$). LRMS m/z calculated for $C_{24}H_{32}N_2O_3S$: ($M^+ + H^+$) 429, found 429.

6,7-Dimethoxy-1-(4-methylsulfanyl-phenyl)-2-(2-piperidin-1-yl-ethyl)-1,2,3,4-tetrahydro-isoquinoline 325

Title compound synthesised from **302b** according to the general method employed in the synthesis of **305** (18%)

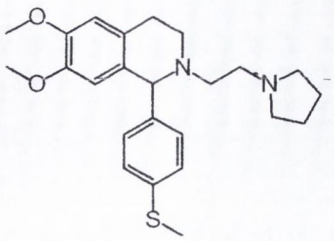


IRυ_{max} cm^{-1} (film): 2818 (C-H), 1520 (Ar), 1111 (C-O), 836 (ArC-H). ^{1}H NMR ($CDCl_3$) δ: 1.37-1.44 (m, 2H, N(CH$_2$)$_2$(CH$_2$)$_2$C$\underline{H}_2$), 1.51-1.57 (m, 4H, N(CH$_2$)$_2$(C$\underline{H}_2$)$_2$), 2.29-2.35 (m, 4H, N(C$\underline{H}_2$)$_2$), 2.49 (s, 3H, SCH_3), 2.51-2.54 (m, 2H, NCH$_2$C$\underline{H}_2$N,), 2.62-2.74 (m, 3H, H4, NC$\underline{H}_2$CH$_2$N), 2.75-2.82 (m, 1H, H4*), 2.90-2.98 (m, 1H, H3), 3.12-3.18 (m, 1H, H3*), 3.64 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.56 (s, 1H, H1), 6.20 (s, 1H, H5), 6.61 (s, 1H, H8), 7.14-7.20 (m, 4H, C$_6\underline{H}_4$). ^{13}C NMR ($CDCl_3$) δ: 15.86 (SCH_3), 24.29 (N(CH$_2$)$_2$(CH$_2$)$_2$$\underline{C}H_2$), 25.88 (N(CH$_2$)$_2$($\underline{C}H_2$)$_2$), 27.83 (C4), 47.18 (C3), 51.48 (NCH$_2$$\underline{C}H_2$N), 54.95 (N($\underline{C}H_2$)$_2$), 55.74, 55.77 (O$\underline{C}H_3$x2), 57.11 (N$\underline{C}H_2CH_2$N), 67.25 (C1), 110.75 (C8), 111.50 (C5), 126.28 (ArC3*/C5*),126.79 (C5$\underline{C}_q$), 129.62 (C8$\underline{C}_q$), 129.97 (ArC2*/C6*), 136.73 (ArC4*$_q$), 140.98 (ArC1$_q$*), 146.96 (C7$_q$), 147.35 (C6$_q$). LRMS m/z calculated for $C_{25}H_{34}N_2O_2S$: ($M^+ + H^+$) 427, found 427.

6,7-Dimethoxy-1-(4-methylsulfanyl-phenyl)-2-(2-pyrrolidin-1-yl-ethyl)-1,2,3,4-tetrahydro-isoquinoline 324

Title compound synthesised from **302b** according to the general method employed in the synthesis of **305**

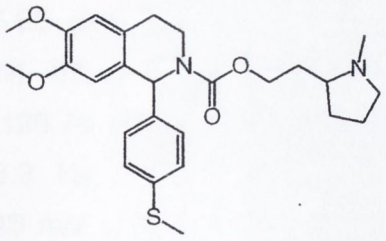
(15)



IRυ_{max} cm^{-1} (film): 2818 (C-H), 1527 (Ar), 1097 (C-O), 792 (ArC-H). ^{1}H NMR ($CDCl_3$) δ: 1.70-1.77 (m, 4H, $N(CH_2)_2(C\underline{H}_2)_2$), 2.41-2.46 (m, 4H, $N(C\underline{H}_2)_2$), 2.47 (s, 3H, SCH_3), 2.53-2.60 (m, 2H, $NCH_2C\underline{H}_2N$,), 2.63-2.73 (m, 3H, H4, $NC\underline{H}_2CH_2N$), 2.76-2.81 (m, 1H, H4*), 2.92-3.00 (m, 1H, H3), 3.13-3.19 (m, 1H, H3*), 3.63 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.53 (s, 1H, H1), 6.18 (s, 1H, H5), 6.60 (s, 1H, H8), 7.13-7.18 (m, 4H, $C_6\underline{H}_4$). ^{13}C NMR ($CDCl_3$) δ: 15.81 (SCH_3), 23.24 ($N(CH_2)_2(\underline{C}H_2)_2$), 27.95 (C4), 47.34 (C3), 53.11 ($NCH_2\underline{C}H_2N$), 54.01 ($N\underline{C}H_2CH_2N$), 54.32 ($N(\underline{C}H_2)_2$), 55.70, 55.73 ($O\underline{C}H_3$x2), 67.39 (C1), 110.71 (C8), 111.45 (C5), 126.26 (ArC3*/C5*), 126.73 ($C5\underline{C}_q$), 129.66 ($C8\underline{C}_q$), 129.94 (ArC2*/C6*), 136.77 ($ArC4^*_q$), 140.85 ($ArC1_q$*), 146.93 ($C7_q$), 147.33 ($C6_q$). LRMS m/z calculated for $C_{24}H_{32}N_2O_2S$: (M^+ + H^+) 413, found 413.

6,7-Dimethoxy-1-(4-methylsulfanyl-phenyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid 2-(1-methyl-pyrrolidin-2-yl)-ethyl ester 326

Title compound synthesised from **302c** according to the general method employed in the synthesis of **305** (15%)

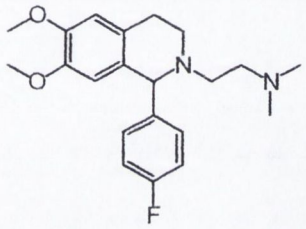


IRυ_{max} cm^{-1} (film): 3436 (CON), 1673 (C=O), 1520 (ArC-H), 1096 (C-O).^{1}H NMR ($CDCl_3$) δ: 1.49-1.60 (m, 2H, $NCHCH_2C\underline{H}_2$), 1.71-1.85 (m, 2H6, $NCHCH_2$), 1.97-2.03 (m, 1H, $NC\underline{H}$), 2.08-2.18 (m, 4H, $CHNC\underline{H}_2$, $OCH_2C\underline{H}_2$), 2.34 (s, 3H, $NC\underline{H}_3$), 2.66-2.70 (m, 1H, H4), 2.84-2.99 (m, 1H, H4*), 3.06-3,18 (m, 2H, H3), 3.77 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.13-4.21 (m, 2H, $COOCH_2$), 6.17 (s, 0.42H, H1 [R2]), 6.36 (s, 0.54H, H1 [R1]), 6.45 (s, 1H, H8), 6.67 (s, 1H, H5), 7.17 (s, 4H, ArH2*/H6*,

ArH3*/H5*). ^{13}C NMR ($CDCl_3$) δ: 21.88 ($NCH_2CH_2\underline{C}H_2$), 28.02 (C4), 30.83 ($NCH_2\underline{C}H$), 33.19 ($OCH_2\underline{C}H_2$), 37.78 ($N(CH_3)\underline{C}H_2$), 40.43 ($NCH_3$), 55.83, 55.90 ($OCH_3$x2), 56.49 (C1), 56.97 (C3), 63.41 (NCH), 63.93 (OCH_2), 110.62 (C8), 111.27 (C5), 129.32 (C5$\underline{C}_q$), 130.20 (ArC8$\underline{C}_q$), 130.85 (ArC2*/C6*), 131.09 (ArC3*/C5*), 131.38 (ArC4*) 139.77 (ArC1*), 147.16 (C7), 147.88 (C6), 154.16 (NCO [R2]), 155.50 (NCO [R1]). LRMS m/z calculated for $C_{26}H_{34}N_2O_4S$: ($M^+ + H^+$) 471, found 471.

{2-[1-(4-Fluoro-phenyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-ethyl}-dimethyl-amine 308

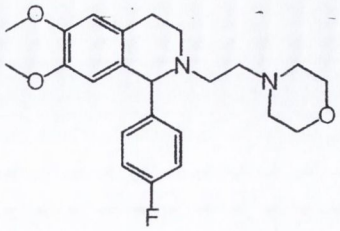
Title compound synthesised from **302d** according to the general method employed in the synthesis of **305** (12%)



IRυ_{max} cm^{-1} (film): 2861, (CH), 1527 (Ar), 1121, (C-O), 728 (ArC-H). ^1H NMR ($CDCl_3$) δ: 2.15 (s, 6H, $N(CH_3)_2$), 2.38-2.47 (m, 3H, H4/$NCH_2C\underline{H}_2N$), 2.61-2.67 (m, 2H, $NC\underline{H}_2CH_2N$), 2.74-2.81 (m, 1H, H4*), 2.95-3.03 (m, 1H, H3), 3.14-3.24 (m, 1H, H3*), 3.62 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.52 (s, 1H, H1), 6.14 (s, 1H, H5), 6.61 (s, 1H, H8), 6.97-7.02 (m, 2H, (ArH2*/H6*)), 7.22-7.26 (m, 2H, (ArH3*/H5*)). ^{13}C NMR ($CDCl_3$) δ: 28.00 (C4), 45.65 ($N(CH_3)_2$), 47.45 (C3), 52.21 ($NCH_2\underline{C}H_2N$), 55.71 (OCH_3), 57.25 ($N\underline{C}H_2CH_2N$), 67.45 (C1), 110.72 (C8), 111.41 (C5), 114.98 (d, J=21.2 Hz, ArC3*/C5*), 126.74 (C5$\underline{C}_q$), 129.67 (C8$\underline{C}_q$), 130.92 (d, J=7.9 Hz, ArC2*/C6*), 139.82 (d, J=3.3 Hz, ArC1$_q$*), 146.95 ($C7_q$), 147.38 ($C6_q$), 161.87 (d, J=243.8 Hz, ArC4*). HRMS m/z calculated for $C_{21}H_{27}N_2O_2F$: ($M^+ + H^+$) 359.2135, found 359.2135.

1-(4-Fluoro-phenyl)-6,7-dimethoxy-2-(2-morpholin-4-yl-ethyl)-1,2,3,4-tetrahydro-isoquinoline 309

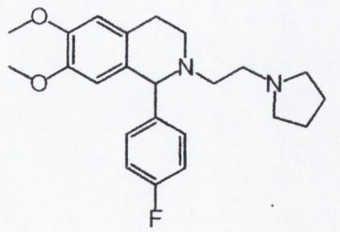
Title compound synthesised from **302d** according to the general method employed in the synthesis of **305** (17%)



IRυ_{max} cm^{-1} (film): 2848, (CH), 1518 (Ar), 728 (ArC-H).^{1}H NMR ($CDCl_3$) δ: 2.34-2.39 (m, 4H, $N(C\underline{H}_2)_2$), 2.42-2.52 (m, 2H, $NCH_2C\underline{H}_2N$), 2.61-2.68 (m, 2H, $NC\underline{H}_2CH_2N$), 2.71-2.82 (m, 2H, H4/H4*), 2.91-3.06 (m, 1H, H3), 3.12-3.20 (m, 1H, H3*), 3.61 (s, 3H, OCH_3), 3.63-3.65 (m, 4H, $O(CH_2)_2$), 3.84 (s, 3H, OCH_3), 4.55 (s, 1H, H1), 6.13 (s, 1H, H5), 6.59 (s, 1H, H8), 6.95-6.99 (m, 2H, (ArH2*/H6*)), 7.20-7.22 (m, 2H, (ArH3*/H5*)). ^{13}C NMR ($CDCl_3$) δ: 27.85 (C4), 47.36 (C3), 51.05 (NCH_2CH_2), 53.92 ($N(CH_2)_2$), 55.67, 55.72 (OCH_3x2), 56.71 (NCH_2CH_2N), 66.78 ($O(CH_2)_2$), 67.17 (C1), 110.71 (C8), 111.36 (C5), 114.95 (d, J=21.2 Hz, ArC3*/C5*), 126.64 ($C5C_q$), 129.46 ($C8C_q$), 130.89 (d, J=7.9 Hz, ArC2*/C6*), 139.81 (d, J=2.9 Hz, $ArC1_q$*), 146.95 ($C7_q$), 147.37 ($C6_q$), 161.86 (d, J=245.2 Hz, ArC4*). HRMS m/z calculated for $C_{23}H_{29}N_2O_3F$: ($M^+ + H^+$) 401.2240, found 401.2256.

1-(4-Fluoro-phenyl)-6,7-dimethoxy-2-(2-pyrrolidin-1-yl-ethyl)-1,2,3,4-tetrahydro-isoquinoline 310

Title compound synthesised from **302d** according to the general method employed in the synthesis of **305** (20%)

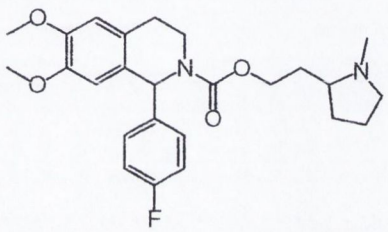


IRυ_{max} cm^{-1} (film): 2870, (CH), 1517 (Ar), 1119, (C-O), 819 (ArC-H). ^{1}H NMR ($CDCl_3$) δ: 1.71-1.75 (m, 4H, $N(CH_2)_2(C\underline{H}_2)_2$), 2.42-2.44 (m, 4H, $N(C\underline{H}_2)_2$), 2.48-2.59 (m, 2H, $NCH_2C\underline{H}_2N$), 2.62-2.78 (m, 2H, $NC\underline{H}_2CH_2N$), 2.75-2.80 (m, 2H, H4/H4*), 2.94-3.03 (m, 1H, H3), 3.14-3.19 (m, 1H, H3*), 3.62 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.55 (s, 1H, H1), 6.14 (s, 1H, H5), 6.60 (s, 1H, H8), 6.96-7.01 (m, 2H, ArH2*/H6*). ^{13}C NMR ($CDCl_3$) δ: 23.24 ($N(CH_2)_2(\underline{C}H_2)_2$), 27.99 (C4), 47.51 (C3), 53.14 ($N\underline{C}H_2CH_2N$),

54.05 ($NCH_2\underline{C}H_2N$), 54.32 ($N(CH_2)_2$), 55.71 ($O\underline{C}H_3$x2), 67.27 (C1), 110.73 (C8), 111.42 (C5), 114.96 (d, J=21.1 Hz, ArC3*/C5*), 126.74 ($C5\underline{C}_q$), 129.67 ($C8\underline{C}_q$), 130.92 (d, J=7.9 Hz, ArC2*/C6*), 139.82 (d, J=3.0 Hz, $ArC1_q$*), 146.95 ($C7_q$), 147.37 ($C6_q$), 161.86 (d, J=245.1 Hz, ArC4*). HRMS m/z calculated for $C_{23}H_{29}FN_2O_2$: ($M^+ + H^+$) 385.2291, found 385.2248.

1-(4-Fluoro-phenyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinoline-2-carboxylic acid 2-(1-methyl-pyrrolidin-2-yl)-ethyl ester 312

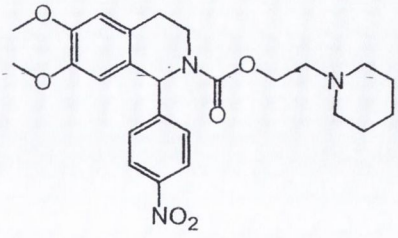
Title compound synthesised from **302d** according to the general method employed in the synthesis of **305** (15%)



IRυ_{max} cm^{-1} (film): 3434 (CON), 1643-1703 (C=O), 1508 (ArC-H), 1095 (C-O). ^1H NMR ($CDCl_3$) δ: 1.46-1.60 (m, 2H, $NCH_2CH_2\underline{C}H_2$), 1.66-1.82 (m, 2H, $NCH_2\underline{C}H_2CH_2$), 1.93-2.03 (m, 1H, $N\underline{C}H$), 2.06-2.17 (m, 4H, $CHN\underline{C}H_2$, $OCH_2\underline{C}H_2$), 2.32 (s, 3H, $N\underline{C}H_3$), 2.65-2.70 (m, 1H, H4), 2.86-2.99 (m, 1H, H4*), 3.05-3,15 (m, 2H, H3), 3.76 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.13-4.22 (m, 2H, $COOCH_2$), 6.21 (s, 0.42H, H1 [R2]), 6.37 (s, 0.52H, H1 [R1]), 6.46 (s, 1H, H8), 6.68 (s, 1H, H5), 6.95-6.99 (m, 2H, ArH2*/H6*), 7.14-7.24 (s, 2H, ArH3*/H5*). ^{13}C NMR ($CDCl_3$) δ: 21.89 ($NCH_2CH_2\underline{C}H_2$), 28.00 (C4), 30.85 ($NCH_2\underline{C}H_2$), 33.29 ($OCH_2\underline{C}H_2$), 37.53 ($N(CH_3)\underline{C}H_2$), 40.46 ($NCH_3$), 55.82, 55.89 ($OCH_3$x2), 56.47 (C1), 57.02 (C3), 63.51 (NCH), 63.77 (OCH_2), 110.80 (C8), 111.15 (C5), 114.92 (d, J=21.1 Hz, ArC3*/C5*), 126.59 ($C5\underline{C}_q$), 130.12 ($C8\underline{C}_q$), 129.38-129.83 (m, ArC2*/C6*), 138.43 (d, J=3.9 Hz, $ArC1_q$*), 147.43 ($C7_q$), 148.04 ($C6_q$), 162.02 (d, J=246.8 Hz, ArC4*). LRMS m/z calculated for $C_{25}H_{31}FN_2O_4$: ($M^+ + H^+$) 443, found 443.

6,7-Dimethoxy-1-(4-nitro-phenyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid 2-piperidin-1-yl-ethyl ester 316

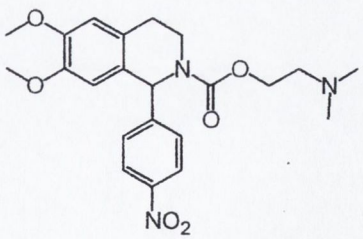
Title compound synthesised from **302a** according to the general method employed in the synthesis of **305** (32%)



IRυ_{max} cm^{-1} (film): 2875 (CH), 1681 (C=O), 1347, 1224 (NO_2), 1071 (C-O), 887 (Ar). ^1H NMR ($CDCl_3$) δ: 1.27-1.39 (m, 2H, $N(CH_2)_2(CH_2)_2C\underline{H}_2$), 1.43-1.55 (m, 4H, $N(CH_2)_2(C\underline{H}_2)_2$), 2.34-2.40 (m, 4H, $N(C\underline{H}_2)_2$), 2.53-2.56 (m, 2H, $OCH_2C\underline{H}_2N$), 2.59-2.66 (m, 1H, H4), 2.81-2.91 (m, 2H, H4*, H3), 2.97-3.13 (m, 1H, H3*), 3.67 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.04-4.28 (m, 2H, $COOC\underline{H}_2$), 6.24-6.34 (m, 1H, H1), 6.40 (s, 1H, H5), 6.63 (s, 1H, H8), 7.35-7.44 (m, 2H, (ArH2*/H6*)), 8.02-8.04 (d, 2H, J=8.5 Hz, (ArH3*/H5*)). ^{13}C NMR ($CDCl_3$) δ: 23.82 ($N(CH_2)_2(CH_2)_2\underline{C}H_2$), 25.64 ($N(CH_2)_2(\underline{C}H_2)_2$), 27.56 (C4), 38.05 (C3), 54.39 ($N(\underline{C}H_2)_2$), 55.52, 55,60 ($O\underline{C}H_3$x2), 56.29 (C1), 57.35 ($OCH_2\underline{C}H_2N$), 63.17 ($COO\underline{C}H_2$), 110.38 (C8), 111.11 (C5), 123.09 (ArC2*/C6*), 124.96 ($C5\underline{C}^*_q$), 126.78 ($C8\underline{C}_q$), 129.01 (ArC3*/C5*), 146.78 ($C7_q$), 147.36 ($C6_q$). 148.08 ($C1^*_q$), 149.55 ($C4^*_q$), 154.43 (NCOO [R1]), 155.24 (NCOO [R2]). HRMS m/z calculated for $C_{25}H_{31}N_3O_6$: ($M^+ + H^+$) 470.2292, found 470.2271.

6,7-Dimethoxy-1-(4-nitro-phenyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid 2-dimethylamino-ethyl ester 313

Title compound synthesised from **302a** according to the general method employed in the synthesis of **305** (26%)

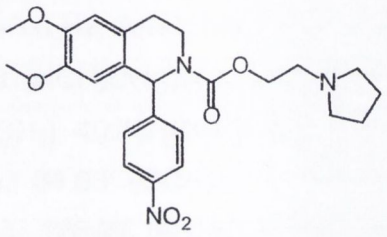


IRυ_{max} cm^{-1} (film): 1643-1733 (C=O), 1465, 1347 (NO_2), 1026 (C-O). ^1H NMR ($CDCl_3$) δ: 2.27 (s, 6H, $N(C\underline{H}_3)_2$), 2.52-2.62 (m, 3H, $OCH_2C\underline{H}_2N$, H4), 2.63-2.69 (m, 1H, H4*), 2.87-2.96 (m, 1H, H3), 3.05-3.18 (m, 1H, H3*), 3.73 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.18-4.33 (m, 2H, $OC\underline{H}_2$), 6.28-6.39 (m, 1H, H1), 6.44 (s, 1H, H5), 6.68 (s, 1H, H8), 7.42-7.44 (m, 2H, (ArH2*/H6*)), 8.09-8.11 (d, 2H, J=8.0 Hz,

(ArH3*/H5*)). ^{13}C NMR ($CDCl_3$) δ: 27.81 (C4), 37.66 (C3 [R2]), 38.22 (C3 [R1]), 45.63 ($N(\underline{C}H_3)_2$), 55.73, 55.81 ($O\underline{C}H_3$x2), 56.47 (C1), 57.78 ($OCH_2\underline{C}H_2N$), 63.28 ($O\underline{C}H_2$ [R2]), 63.75 ($O\underline{C}H_2$ [R1]), 110.49 (C8), 111.23 (C5), 123.31 (ArC2*/C6*), 125.29 ($C5\underline{C}^*_q$), 126.87 ($C8\underline{C}_q$), 129.19 (ArC3*/C5*), 147.00 ($C7_q$), 147.54 ($C6_q$). 148.27 ($ArC1^*_q$), 149.66 ($ArC4^*_q$), 154.80 (COO [R2]), 155.38 (COO [R1]). LRMS m/z calculated for $C_{22}H_{27}N_3O_6$: ($M^+ + H^+$) 430, found 430.

6,7-Dimethoxy-1-(4-nitro-phenyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid 2-pyrrolidin-1-yl-ethyl ester 315

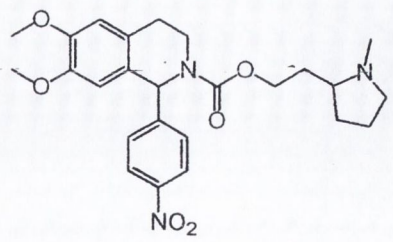
Title compound synthesised from **302a** according to the general method employed in the synthesis of **305** (36%)



IRυ_{max} cm^{-1} (film): 1641-1759 (C=O), 1519 (ArCH), 1491, 1358 (NO_2), 1096 (C-O). ^{1}H NMR ($CDCl_3$) δ: 1.79 (s, 4H, $N(CH_2)_2(\underline{C}H_2)_2$), 2.58 (s, 4H, $N(\underline{C}H_2)_2$), 2.67-2.77 (m, 4H, $OCH_2\underline{C}H_2N$, H3), 2.89-3.04 (m, 1H, H4), 3.08-3.17 (m, 1H, H4*), 3.76 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.16-4.38 (m, 2H, $COO\underline{C}H_2$), 6.31 (s, 0.48H, H1 [R2]), 6.43-6.46 (m, 1.53H, H1 [R1], H5), 6.70 (s, 1H, H8), 7.41-7.48 (m, 2H, ArH2*/H6*), 8.13 (d, 2H, J=8.9 Hz, ArH3*/H5*). ^{13}C NMR ($CDCl_3$) δ: 23.50 ($N(CH_2)_2(\underline{C}H_2)$), 27.87 (C4), 38.57 (C3), 54.60 ($OCH_2\underline{C}H_2N$), 54.74 ($N(\underline{C}H_2)_2$), 55.85, 55.92 ($O\underline{C}H_3$x2), 56.55 (C1), 65.07 ($COO\underline{C}H_2$), 110.58 (C8), 111.32 (C5), 123.42 (ArC2*/C6*), 125.26 ($C5\underline{C}^*_q$), 126.92 ($C8\underline{C}_q$), 129.30 (ArC3*/C5*), 147.14 ($C7_q$), 147.65 ($C6_q$), 148.38 ($ArC1^*_q$), 149.76 ($ArC4^*_q$), 154.82 (NCOO [R1]), 155.49 (NCOO [R2]). HRMS m/z calculated for $C_{24}H_{29}N_3O_6$: ($M^+ + H^+$) 456.2135, found 456.2161.

6,7-Dimethoxy-1-(4-nitro-phenyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid 2-(1-methyl-pyrrolidin-2-yl)-ethyl ester 317

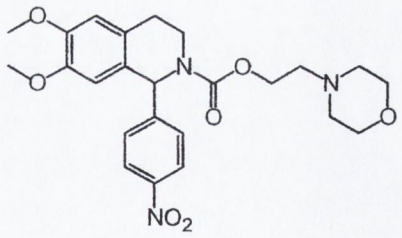
Title compound synthesised from **302a** according to the general method employed in the synthesis of **305** (18%)



IRυ_{max} cm^{-1} (film): 3437 (CON), 1663-1731 (C=O), 1448 (NO_2), 1097 (C-O). ^{1}H NMR ($CDCl_3$) δ: 1.45-1.79 (m, 4H, $NCH_2C\underline{H}_2C\underline{H}_2$), 1.91-2.00 (m, 1H, NC<u>H</u>), 2.07-2.16 (m, 4H, $CHNC\underline{H}_2$, $OCH_2C\underline{H}_2$), 2.30 (s, 3H, $NC\underline{H}_3$), 2.67-2.74 (m, 1H, H4), 2.84-2.97 (m, 1H, H4*), 3.03-3,18 (m, 2H, H3/H3*), 3.76 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.16-4.28 (m, 2H, $COOCH_2$), 6.24 (s, 0.42H, H1 [R2]), 6.45 (s, 1.58H, H1 [R2], H8), 6.69 (s, 1H, H5), 7.43 (d, 2H, J=8.0 Hz, ArH2*/H6*), 8.13 (d, 2H, J=8.0 Hz, ArH3*/H5*). ^{13}C NMR ($CDCl_3$) δ: 21.90 ($NCH_2CH_2\underline{C}H_2$), 28.21 (C4), 30.82 ($NCH_2\underline{C}H$), 33.16 ($OCH_2\underline{C}H_2$), 38.22 ($N(CH_3)\underline{C}H_2$), 40.45 ($NCH_3$), 55.87, 55.95 ($OCH_3$x2), 56.44 (C1), 57.00 (C3), 63.49 (NCH), 64.03 (OCH_2), 110.52 (C8), 111.32 (C5), 123.40 (ArC2*/C6*), 125.16 (C5$\underline{C}_q$), 126.97 (ArC8$\underline{C}_q$), 129.30 (ArC2*/C6*), 147.19 (C7), 147.72 (C6), 148.37 (ArC1*), 149.79 (ArC4*), 155.06 (NCO [R2]), 155.77 (NCO [R1]). HRMS m/z calculated for $C_{25}H_{31}N_3O_6$: ($M^+ + H^+$) 470.2292, found 470.2308

6,7-Dimethoxy-1-(4-nitro-phenyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid 2-morpholin-4-yl-ethyl ester 314

Title compound synthesised from **302a** according to the general method employed in the synthesis of **305** (21%)



IRυ_{max} cm^{-1} (film): 3436 (CON), 1676-1765 (C=O), 1514 (ArC-H), 1472, 1349 (NO_2), 1097 (C-O). ^{1}H NMR ($CDCl_3$) δ: 2.49 (m, 4H, $N(C\underline{H}_2)_2$), 2.61-2.73 (m, 4H, $OCH_2C\underline{H}_2N$, H3/H3*), 2.86-2.99 (m, 1H, H4), 3.04-3.18 (m, 1H, H4*), 3.62-3.68 (m, $O(CH_2)_2$), 3.73 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.16-4.34 (m, 2H, $COOC\underline{H}_2$), 6.27 (s, 0.43H, H1 [R2]), 6.40-6.45 (m, 1.61H, H1 [R1], H5), 6.67 (s, 1H, H8), 7.41-7.46 (m, 2H, ArH2*/H6*), 8.09 (d, 2H, J=8.5 Hz, ArH3*/H5*). ^{13}C NMR ($CDCl_3$) δ: 27.51 (C4 [R2]), 27.75 (C4 [R1]), 37.69 (C3 [R2]), 38.21 (C3 [R1]), 53.58 ($OCH_2\underline{C}H_2N$),

55.72, 55.80 ($O\underline{C}H_3$x2), 56.46 ($N(\underline{C}H_2)_2$), 57.25 (C1), 62.87 ($O(CH_2)_2$), 66.74 ($COO\underline{C}H_2$), 110.51 (C8), 111.22 (C5), 123.30 (ArC2*/C6*), 125.25 ($C5\underline{C}^*_q$), 126.78 ($C8\underline{C}_q$), 129.14 (ArC3*/C5*), 147.00 ($C7_q$), 147.56 ($C6_q$), 148.30 ($ArC1^*_q$), 149.60 ($ArC4^*_q$), 155.37 (NCOO). HRMS m/z calculated for $C_{24}H_{29}N_3O_7$: ($M^+ + H^+$) 472.2085, found 472.2086.

Experimental Bibiography

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Appendix 1.

X-ray crystal structure data for **274**.

Table 1. Crystal data and structure refinement for thig1m.

Identification code	thig1m	
Empirical formula	C19 H21 N O4	
Formula weight	327.38	
Temperature	292K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 5.4904(6) Å	α= 87.291(2)°.
	b = 11.8106(12) Å	β= 87.143(2)°.
	c = 13.0508(14) Å	γ =88.526(2)°.
Volume	844.05(16) $Å^3$	
Z	3	
Density (calculated)	1.433 Mg/m^3	
Absorption coefficient	0.097 mm^{-1}	
F(000)	371	
Crystal size	0.30 x 0.14 x 0.14 mm^3	
Theta range for data collection	1.56 to 28.29°.	
Index ranges	-7<=h<=7, -15<=k<=15, -17<=l<=17	
Reflections collected	11436	
Independent reflections	4147 [R(int) = 0.0436]	
Completeness to theta = 28.29°	98.6 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4147 / 0 / 228	
Goodness-of-fit on F^2	0.926	
Final R indices [I>2sigma(I)]	R1 = 0.0515, wR2 = 0.1376	
R indices (all data)	R1 = 0.0857, wR2 = 0.1628	
Largest diff. peak and hole	0.269 and -0.454 $e.Å^{-3}$	
Chiral Flag	Not set	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)

for thig1m. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(4)	-2536(3)	6325(2)	9552(2)	50(1)
O(4)	-3718(2)	10810(1)	7706(1)	51(1)
C(12)	-1926(3)	8905(1)	7814(1)	39(1)
N(1)	2192(2)	6341(1)	7660(1)	40(1)
C(8)	2811(3)	6416(1)	6559(1)	38(1)
O(1)	4794(3)	4639(1)	6834(1)	57(1)
C(11)	-136(3)	8123(1)	7469(1)	35(1)
O(3)	-400(3)	11472(1)	6332(1)	60(1)
C(7)	-127(3)	6917(1)	7930(1)	37(1)
C(13)	-2026(3)	10005(1)	7415(1)	39(1)
C(10)	1534(3)	8456(1)	6692(1)	38(1)
O(2)	6545(2)	5834(1)	5665(1)	60(1)
C(18)	4935(3)	5624(2)	6294(1)	41(1)
C(9)	3421(3)	7636(1)	6249(2)	42(1)
C(14)	-258(3)	10354(1)	6659(1)	44(1)
C(5)	-545(3)	6862(1)	9090(1)	36(1)
C(15)	1460(3)	9581(1)	6296(1)	44(1)
C(2)	-1276(4)	6742(2)	11211(2)	54(1)
C(6)	1065(3)	7345(2)	9708(1)	50(1)
C(3)	-2895(4)	6264(2)	10611(2)	59(1)
C(1)	694(4)	7286(2)	10765(2)	58(1)
C(21)	1611(4)	11893(2)	5716(2)	62(1)
C(19)	6714(4)	3808(2)	6632(2)	66(1)
C(22)	-5423(4)	10495(2)	8516(2)	68(1)

Table 3. Bond lengths [Å] and angles [°] for thig1m.

C(4)-C(5)	1.376(2)
C(4)-C(3)	1.385(3)
O(4)-C(13)	1.3655(19)
O(4)-C(22)	1.420(2)
C(12)-C(13)	1.378(2)
C(12)-C(11)	1.403(2)
N(1)-C(8)	1.460(2)
N(1)-C(7)	1.463(2)
C(8)-C(18)	1.512(2)
C(8)-C(9)	1.519(2)
O(1)-C(18)	1.334(2)
O(1)-C(19)	1.444(2)
C(11)-C(10)	1.383(2)
C(11)-C(7)	1.519(2)
O(3)-C(14)	1.370(2)
O(3)-C(21)	1.420(2)
C(7)-C(5)	1.518(2)
C(13)-C(14)	1.405(2)
C(10)-C(15)	1.403(2)
C(10)-C(9)	1.513(2)
O(2)-C(18)	1.199(2)
C(14)-C(15)	1.378(2)
C(5)-C(6)	1.378(2)
C(2)-C(3)	1.364(3)
C(2)-C(1)	1.364(3)
C(6)-C(1)	1.383(3)
C(5)-C(4)-C(3)	120.79(18)
C(13)-O(4)-C(22)	116.89(13)
C(13)-C(12)-C(11)	121.63(15)
C(8)-N(1)-C(7)	112.67(12)
N(1)-C(8)-C(18)	110.61(13)
N(1)-C(8)-C(9)	108.55(14)
C(18)-C(8)-C(9)	110.83(14)
C(18)-O(1)-C(19)	116.65(15)
C(10)-C(11)-C(12)	119.25(14)
C(10)-C(11)-C(7)	121.33(14)
C(12)-C(11)-C(7)	119.38(14)

C(14)-O(3)-C(21)	116.54(14)
N(1)-C(7)-C(5)	109.08(12)
N(1)-C(7)-C(11)	109.98(13)
C(5)-C(7)-C(11)	112.98(13)
O(4)-C(13)-C(12)	125.03(15)
O(4)-C(13)-C(14)	116.08(14)
C(12)-C(13)-C(14)	118.89(15)
C(11)-C(10)-C(15)	119.19(15)
C(11)-C(10)-C(9)	121.71(14)
C(15)-C(10)-C(9)	119.10(14)
O(2)-C(18)-O(1)	123.15(16)
O(2)-C(18)-C(8)	124.94(15)
O(1)-C(18)-C(8)	111.90(14)
C(10)-C(9)-C(8)	111.34(14)
O(3)-C(14)-C(15)	124.65(15)
O(3)-C(14)-C(13)	115.69(15)
C(15)-C(14)-C(13)	119.66(15)
C(4)-C(5)-C(6)	118.23(16)
C(4)-C(5)-C(7)	120.96(16)
C(6)-C(5)-C(7)	120.81(15)
C(14)-C(15)-C(10)	121.29(15)
C(3)-C(2)-C(1)	119.71(18)
C(5)-C(6)-C(1)	120.78(17)
C(2)-C(3)-C(4)	120.22(18)
C(2)-C(1)-C(6)	120.3(2)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for thig1m. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(4)	46(1)	53(1)	51(1)	4(1)	-1(1)	-12(1)
O(4)	52(1)	40(1)	59(1)	2(1)	11(1)	12(1)
C(12)	38(1)	40(1)	39(1)	1(1)	2(1)	0(1)
N(1)	45(1)	37(1)	38(1)	-1(1)	-2(1)	4(1)
C(8)	41(1)	37(1)	35(1)	-1(1)	-2(1)	4(1)
O(1)	75(1)	43(1)	50(1)	5(1)	11(1)	20(1)
C(11)	36(1)	33(1)	36(1)	0(1)	-3(1)	0(1)
O(3)	65(1)	35(1)	74(1)	13(1)	18(1)	8(1)
C(7)	36(1)	34(1)	39(1)	-1(1)	-1(1)	-1(1)
C(13)	39(1)	37(1)	42(1)	-2(1)	-2(1)	5(1)
C(10)	40(1)	36(1)	38(1)	-1(1)	0(1)	1(1)
O(2)	56(1)	51(1)	69(1)	-1(1)	16(1)	8(1)
C(18)	48(1)	40(1)	35(1)	-5(1)	-4(1)	2(1)
C(9)	45(1)	38(1)	41(1)	1(1)	5(1)	4(1)
C(14)	50(1)	33(1)	47(1)	5(1)	1(1)	1(1)
C(5)	37(1)	32(1)	39(1)	3(1)	-1(1)	2(1)
C(15)	48(1)	38(1)	44(1)	5(1)	8(1)	0(1)
C(2)	63(1)	58(1)	38(1)	6(1)	5(1)	11(1)
C(6)	44(1)	62(1)	44(1)	0(1)	1(1)	-12(1)
C(3)	53(1)	65(1)	55(1)	13(1)	14(1)	-8(1)
C(1)	60(1)	68(1)	46(1)	-5(1)	-8(1)	-6(1)
C(21)	68(1)	43(1)	73(1)	15(1)	9(1)	-5(1)
C(19)	84(2)	55(1)	57(1)	-3(1)	-1(1)	33(1)
C(22)	67(1)	60(1)	72(2)	1(1)	25(1)	18(1)

Table 5. Hydrogen coordinates ($x\ 10^4$) and isotropic displacement parameters ($Å^2 x\ 10^3$) for thig1m.

	x	y	z	U(eq)

H(12)	-3073	8674	8325	47
H(1A)	3387	6651	7994	48
H(1B)	2106	5606	7872	48
H(8)	1395	6201	6190	46
H(7)	-1438	6511	7635	44
H(15)	2593	9810	5779	53
H(20)	-1515	6697	11923	64
H(6)	2416	7716	9410	60
H(4)	-3651	6001	9147	60
H(3)	-4244	5896	10913	70
H(22)	1793	7618	11172	69
H(21A)	3090	11738	6066	93
H(21B)	1401	12697	5594	93
H(21C)	1704	11529	5073	93
H(19A)	6721	3615	5925	99
H(19B)	6439	3141	7066	99
H(19C)	8258	4118	6769	99
H(22A)	-6373	9880	8314	102
H(22B)	-6482	11131	8667	102
H(22C)	-4565	10261	9117	102
H(23)	3480(30)	7789(15)	5503(16)	50(5)
H(21)	5100(40)	7812(16)	6526(15)	59(6)

Table 6. Torsion angles [°] for thig1m.

Appendix 2.

LPC interactions calculated for the docking of **287** with SERT.

The analysis of ligand-protein contacts used in this page
is based upon the surface complementarity approach
developed in: Sobolev V., Wade R.C., Vriend G. and Edelman M.
PROTEINS (1996) 25, 120-129. The complementarity function
therein is defined as:

CF = SI - Si -E

Where, SI is the sum of all surface areas of legitimate
atomic contacts between ligand and receptor, Si is the
sum of all surface areas of illegitimate atomic
contacts, and E is a repulsion term.

Legitimacy depends on the hydrophobic-hydrophilic
properties of the contacting atoms. In order to
define it, for each inter-atomic contact,
eight atom classes have been introduced:

I Hydrophilic - N and O that can donate and accept hydrogen bonds (e.g., oxygen of hydroxyl group of Ser. or Thr)

II Acceptor - N or O that can only accept a hydrogen bond

III Donor - N that can only donate a hydrogen bond

IV Hydrophobic - Cl, Br, I and all C atoms that are not in aromatic rings and do not have a covalent bond to a N or O atom

V Aromatic - C in aromatic rings irrespective of any other bonds formed by the atom

VI Neutral - C atoms that have a covalent bond to at least one atom of class I or two or more atoms from class II or III; atoms; S, F, P, and metal atoms in all cases

VII Neutral-donor - C atoms that have a covalent bond with only one atom of class III

VIII Neutral-acceptor - C atoms that have a covalent bond with only one atom of class II

For each pair of contacts the state of legitimacy
is shown below.

Legend: +, legitimate; -, illegitimate

Atomic class	I	II	III	IV	V	VI	VII	VIII
I (Hydrophilic)	+	+	+	-	+	+	+	+
II (Acceptor)	+	-	+	-	+	+	+	-
III (Donor)	+	+	-	-	+	+	-	+
IV (Hydrophobic)	-	-	-	+	+	+	+	+
V (Aromatic)	+	+	+	+	+	+	+	+
VI (Neutral)	+	+	+	+	+	+	+	+
VII (Neutral-donor)	+	+	-	+	+	+	-	+
VIII (Neutral-acceptor)	+	-	+	+	+	+	+	-

Atom classes for ligands are automatically assigned
based on the atomic coordinates. However, in three
cases the automatic assignment is currently ambiguous
(due to low resolution). In these three cases, the user
is advised to manually analyze the full list of
contacts (Table IV):

1. Carbon atoms belonging to a 4-, 5- or 6-member
   ring are considered "aromatic" (Class V) if the ring
   is approximately planar, and "hydrophobic" (Class IV)
   or "neutral" (Classes VI, VII, VIII) if the ring is non-planar.
2. The oxygen atom of a carbonyl or hydroxy group is
   considered "hydroxy" (Class I) if the CO bond is
   longer than 1.29 A, and "carbonyl" (Class II) if shorter
3. Nitrogen atoms are considered "hydrophilic" (Class I).

IN YOUR STRUCTURE, the following atoms fall in
these ambiguous cases:

Ligand UNK 1

1. Carbon (in rings)

1 C11 2 C12 3 C13 4 C14 5 C15 6 C16
2 C12 3 C13 11 C21 12 C22 14 C24 15 C25
16 C26 17 C27 18 C28 19 C29 20 C30 26 C36
27 C37 28 C38 29 C39 30 C40

3. Nitrogen ("hydrophilic")

13 NP3 25 NP5

Ligand HID 61

1. Carbon (in rings)

6 CG 9 CE1 8 CD2

2. Oxygen ("hydroxy" or "carbonyl")

4 O

3. Nitrogen ("hydrophilic")

1 N 7 ND1 10 NE2

Ligand HID 75

1. Carbon (in rings)

6 CG 9 CE1 8 CD2

2. Oxygen ("hydroxy" or "carbonyl")

4 O

3. Nitrogen ("hydrophilic")

1 N 7 ND1 10 NE2

Ligand HID 143

1. Carbon (in rings)

6 CG 9 CE1 8 CD2

2. Oxygen ("hydroxy" or "carbonyl")

4 O

3. Nitrogen ("hydrophilic")

1 N 7 ND1 10 NE2

Ligand CYX 200

1. Carbon (in rings)

5 CB

2. Oxygen ("hydroxy" or "carbonyl")

4 O

3. Nitrogen ("hydrophilic")

1 N

Ligand CYX 209

1. Carbon (in rings)

5 CB

2. Oxygen ("hydroxy" or "carbonyl")

4 O

3. Nitrogen ("hydrophilic")

1 N

Ligand HID 223

1. Carbon (in rings)

6 CG 9 CE1 8 CD2

2. Oxygen ("hydroxy" or "carbonyl")

4 O

3. Nitrogen ("hydrophilic")

1 N 7 ND1 10 NE2

Ligand HID 235

1. Carbon (in rings)

6 CG 9 CE1 8 CD2

2. Oxygen ("hydroxy" or "carbonyl")

4 O

3. Nitrogen ("hydrophilic")

1 N 7 ND1 10 NE2

Ligand HID 240

1. Carbon (in rings)

6 CG 9 CE1 8 CD2

2. Oxygen ("hydroxy" or "carbonyl")

4 O

3. Nitrogen ("hydrophilic")

1 N 7 ND1 10 NE2

Ligand HID 456

1. Carbon (in rings)

6 CG 9 CE1 8 CD2

2. Oxygen ("hydroxy" or "carbonyl")

4 O

3. Nitrogen ("hydrophilic")

1 N 7 ND1 10 NE2

Please E-mail any questions and/or suggestions concerning this page to:
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