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Design, Synthesis and Evaluation of Indazoles as Antiproliferative Agents

A thesis submitted to the University of Dublin for the degree of doctor of philoscopy

By

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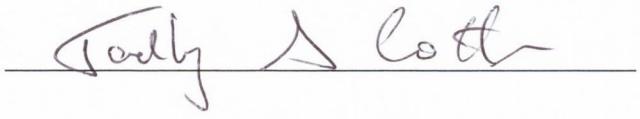
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Abstract

Cancer is a leading cause of death in most countries, second only to the diseases of the circulatory system. In relation to Ireland, cancer accounted for 29.6 % of all the deaths reported in 2012. After non-melanoma skin cancer, breast cancer is the most common cancer suffered by women in Ireland. In 2012, there were 2,899 reported new cases of breast cancer while 704 female deaths were associated with this disease. Ireland has one of the highest rates of incidence of breast cancer in Europe.

This thesis describes the synthesis and biochemical evaluation of potentially dual acting tumour targeting compounds, based on the indazole scaffold. The indazole based scaffold, identified by the Meegan group, represents "first in class" dual Hsp90/tubulin binding compound. Tubulin and Hsp90 are the targets for the dual acting indazole compounds contained in this thesis. It is proposed that the dual acting Hsp90/tubulin molecules offer a combined approach to the treatment of breast cancer and related malignancies. Tubulin is recognized a valid target for cancer chemotherapeutic agents and compounds which interfere with microtubule dynamics are clinically available. Despite initial apprehension from the scientific community, Hsp90 is now considered a valid target for cancer chemotherapeutic agents as cancer cells have a higher dependence on Hsp90 than normal cells. A significant amount of detail is contained within chapter 1 on cancer chemotherapeutic agents, tubulin, Hsp90 and the synthesis and biological activity of selected indazoles. Chapter 2 is comprised of nine separate chemistry sections. Sections 2.2 – 2.6 describe the synthesis of indazole analogues of the lead compound with modified linkers at *N*-1. Section 2.7 describes the synthesis of 5- and 6-arylindazole analogues of the lead compound together with the preparation of 6-aroylated indazole analogues. Sections 2.8 and 2.9 describe the design and synthesis of a library of 3-aryl and 3-heterocyclic substituted indazoles respectively. In section 2.10, the synthetic chemistry required for introduction of a pyrrole or pyridone ring at C-5 or C-6 of indazole is described. Chapter 3 reviews the biochemical evaluation a number of selected indazoles while chapter 4 contains the results of the molecular modelling that was performed on a selection of the synthetic indazoles in order to provide a rationalisation of the antiproliferiative activities. 6-Amino-1-(3,4,5-trimethoxybenzoyl)-1*H*-indazole (**209**) was identified as a potent antiproliferative agent with significant activity against a panel of human tumour cell lines including kidney, breast, ovarian, CNS, melanoma, prostate, leukemia, colon and lung.

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The PhD journey has been an experience, both demanding and enjoyable. A PhD is like a battle and sometimes no matter how hard you fight, you will lose and typically there will be more losses than wins. In order to survive after every loss, you have to remind yourself that this battle is not over.

To my late brother Dermot and to all those who die before their time:
"In our hearts you will always stay, loved and remembered everyday"

Abbreviations

ADP	Adenosine diphosphate
AHR	Aryl hydrocarbon receptor
AIDS	Acquired immunodeficiency syndrome
AKT	
AML	Acute myeloid leukemia
ATP	Adenosine triphosphate
BMS	Bristol-Myers Squibb
CA1	Combretastatin A1
CA4	Combretastatin A4
cm^{-1}	Wavenumber
^{13}C NMR	Carbon 13 NMR
CNS	Central nervous system
ClogP	Partition coefficient
COSY	Correlation spectroscopy
CsF	Cesium fluoride
DCC	Dicyclohexylcarbodiimide
DCM	Dichloromethane
DEPT	Distortionless Enhancement by Polarization Transfer
DHFR	Dihydrofolate reductase
DIW	Deionised water
DMF	Dimethylformamide
DNA	Deoxyribonucleic acid
EGRF	Epidermal growth factor receptor
EtOAc	Ethyl acetate
EtOH	Ethanol
FDA	Food and Drug Administration
GA	Geldanamycin
GI	Growth inhibition
GIST	Gastrointestinal stromal tumour
GTP	Guanosine-5'-triphosphate
h	Hours
Hex	Hexane
HCl	Hydrochloric acid
HIV	Human immunodeficiency virus
HIF	Hypoxia-inducible factor
HMBC	Heteronuclear multiple-bond correlation spectroscopy
^{1}H NMR	Proton NMR
HSQC	Heteronuclear Single Quantum Coherence
HRMS	High resolution mass spectroscopy
Hsp90	Heat shock protein 90
HTS	High throughput screening
IC_{50}	Concentration where 50 % growth is inhibited

IR	Infrared
J	Coupling constant
Lit.	Literature
LC_{50}	Concentration where 50 % of the cells are killed
M	Molar
M.P.	Melting point
MCF-7	ER-positive human breast cancer cell line
MCH	Melanain concentrating hormone
MDR	Multiple drug resistance
MDS	Myelodysplastic syndromes
MeOH	Methanol
MEME	Minimum essential medium Eeagle
MOAS	Microwave assisted organic synthesis
MOE	Molecule Operating Environment
mW	Microwave power
*n*BuLi	*n*-Butyllithium
NCI	National Cancer Institute
NMR	Nuclear magnetic resonace
NOE	Nuclear Overhauser Effect
PAR	Protease-activated receptor
PARP	Poly(ADP-ribose) polymerase
Pd/C	Palladium on carbon
ppm	Parts per million
PSA	Polar surface area
Rf	Retention factor
RNA	Ribonucleic acid
ROCK1	Rho-associated, coiled-coil-containing protein kinase 1
rt	Room termperature
SAR	Structure activity relationships
*t*BuLi	*t*-Butyllithium
TGI	Total growth inhibition
THF	Tetrahydrofuran
TLC	Thin layer chromatrography
VEGF	Vascular endothelial growth factor
VS	Virtual screening
VTA	Vascular-targeting agent

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Chapter 1

Introduction

1.0 Introduction to the thesis

The synthesis and biochemical evaluation of potentially dual acting tumour targeting compounds, based on the indazole scaffold, is described within this thesis. This work develops the research initially performed by the Meegan research group which identified an indazole based scaffold that represents the "first in class" dual Hsp90/tubulin binding compound[1]. It is proposed that the dual acting Hsp90/tubulin molecules may offer a combined approach to the treatment of breast cancer and related malignancies. Tubulin is recognised as a valid target for cancer chemotherapeutic agents and compounds which interfere with microtubule dynamics are clinically available (see section 1.4.1). Despite initial apprehension from the scientific community, Hsp90 is now considered a valid target for cancer chemotherapeutic agents as cancer cells have a higher dependence on Hsp90 than normal cells. Hsp90 inhibitors are now in various clinical trials (see section 1.6.5).

The following sections will provide a summary of cancer chemotherapeutic agents, the relevant cancer protein targets and will conclude with a review of biologically active indazole compounds.

1.1 Cancer

Cancer is a leading cause of death in most countries, second only to the diseases of the circulatory system[2]. In relation to Ireland, cancer accounted for 29.6% of all the deaths reported in 2012[3]. This figure places cancer second in the principal causes of death, with diseases of the circulatory system first with 34.3% and diseases of the respiratory system third with 11.7%. These three principal causes of death are in the same order when sex of the deceased is taken into consideration.

In terms of cancer incidence for Ireland, the most common cancers in 2012, are as follows[4]: non-melanoma skin cancer – 20,808 reported cases, prostate cancer – 3,788 reported cases, breast cancer – 2,899 reported cases, bowel cancer – 2,560 reported cases and lung cancer – 2,273 reported cases.

The most frequent form of cancer for Irish males and females are listed in table 1[5]. The number of reported cases of cancer in Ireland is increasing each year for both males and females[5], which is significantly disturbing.

Table 1: Forms of cancer and number of reported cases factoring in gender (2012)

Males			Females	
Cancer type	**Numbers of reported Cases**		**Cancer Type**	**Number of reported cases**
Non-melanoma skin cancer	11,304		Non-melanoma skin cancer	9504
Prostate cancer	3,788		Breast cancer	2,899
Bowel cancer	1,478		Bowel cancer	1082
Lung cancer	1,246		Lung cancer	1027
Melanoma	402		Melanoma	457
Testicular cancer	142		Gynae cancer	992

In the United State of America, it was estimated that 1,660,290 cases of cancer will be reported and 580,350 Americans will die from cancer in 2013[6]. The American Cancer Society estimated that 12,667,500 new cases of cancer would be reported in 2008 globally. Also cancer is the cause of one in eight deaths worldwide, which is greater than AIDS, tuberculosis and malaria combined. The serious threat posed by cancer was once described by Dr. Gro Brundtland, former Director-General of the World Health Organisation, in the following statement: "The global burden of cancer continues to increase. In the year 2000, 5.3 million men and 4.7 million women developed a malignant tumour and 6.2 million died from the disease. The number of new cases is expected to grow by 50% over the next 20 years to reach 15 million by 2020"[7].

1.2 Breast Cancer: Incidence and Treatment

After non-melanoma skin cancer, breast cancer is the most common cancer suffered by women in Ireland[5]. In 2012, there were 2,899 reported new cases of breast cancer while 704 female deaths were associated with this disease. Irish women are not alone in suffering the burden of breast cancer. In Europe, it was estimated that 463,819 women (94.2 per 100,000) would be diagnosed with breast cancer and 131,169 women (23.1 per 100,000) would die from this disease[8]. However Ireland has one of the highest rates of incidence of breast cancer in Europe, figure 1.

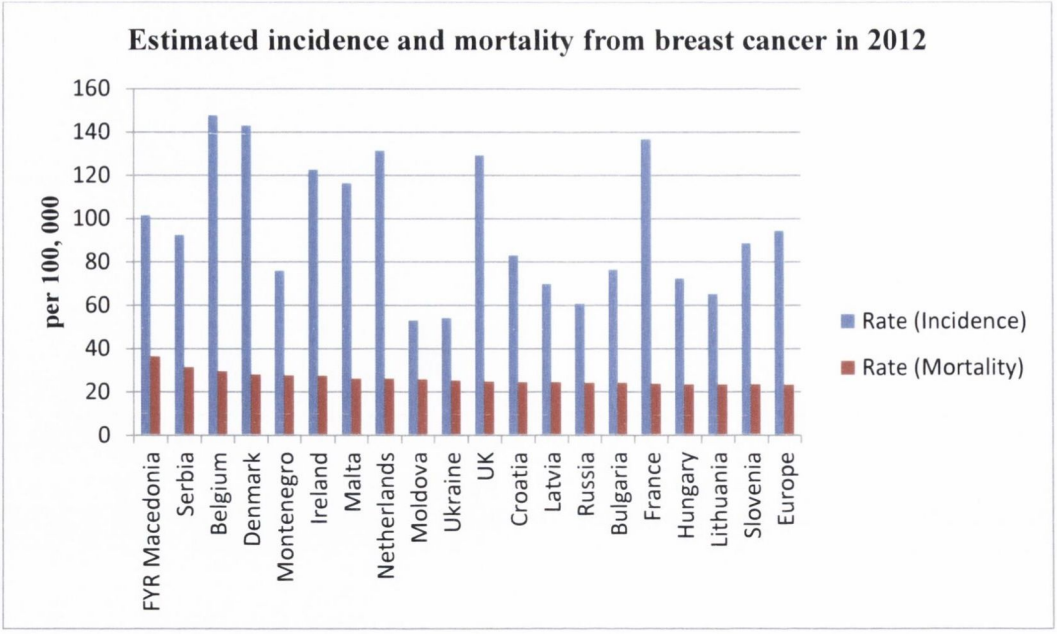


Figure 1: Estimated incidence and mortality from breast cancer in 2012

1.3 Cancer chemotherapy

The three most frequently used methods in treating cancer are surgery, radiotherapy and chemotherapy. Cancer chemotherapy is a treatment using drugs that cure or control cancer. The drugs mainly used are cytotoxic, which means that they can kill both cancer cells and healthy cells in the body. Normal cells like those in the lining of the mouth, bone marrow etc. are also affected by these drugs. Healthy cells usually repair the damage caused by chemotherapy but cancer cells cannot and so eventually die. Chemotherapy helps to (i) reduce the size of the tumour, (ii) cure cancer, (iii) prevent cancer recurring, (iv) control cancer and (v) ease cancer symptoms. Historically, anticancer agents have been classified according to the phase of the cell cycle which they target. Classification according to their mode of action is considered far more relevant[9]. Chemotherapeutic agents act either by (i) damaging DNA, (ii) inhibiting DNA synthesis or (iii) interfering with the various signalling events in cell replication. Chemotherapeutic agents can be divided into (a) alkylating agents, (b) antimetabolites, (c) topoisomerase inhibitors or (d) mitotic inhibitors.

Alkylating Agents

Alkylating agents can be defined as compounds capable of covalently introducing an alkyl group to a biomolecule under physiological conditions. Interference with cell replication, achieved most simply by DNA alkylation, still remains the mechanism of action of many clinically relevant anticancer drugs. These were the first drugs to successfully treat cancer and

actually the nitrogen mustard compound used in World War I, was shown to be an alkylating agent[10].

Base alkylation significantly affects the structure and activity of DNA, which leads to several types of effects. In the first place, alkylation prevents DNA replication and RNA transcription from the affected DNA. It also leads to the fragmentation of DNA by hydrolytic reactions and also by the action of repair enzymes when attempting to remove alkylated bases. Alkylation also induces the mispairing of the nucleotides by alteration of the normal hydrogen bonding between bases. Some alkylating agents have two available alkyl groups and these form bridges within a single DNA strand (intrastrand cross linkage). These type of alkylating agents also lead to cross-linking between DNA and associated proteins or between two complementary DNA strands (interstrand cross linkage), preventing their separation during DNA replication or transcription. However bi-functional alkylating agents have been shown to be more cytotoxic than their mono-functional counterparts.

Alkylating agents[11] include nitrogen mustards (e.g. mephalan, chlorambucil), azirdines (e.g. thiotepa), triazenes (e.g. dacarbazine) and nitrosureas (e.g. carmustine), figure 2.

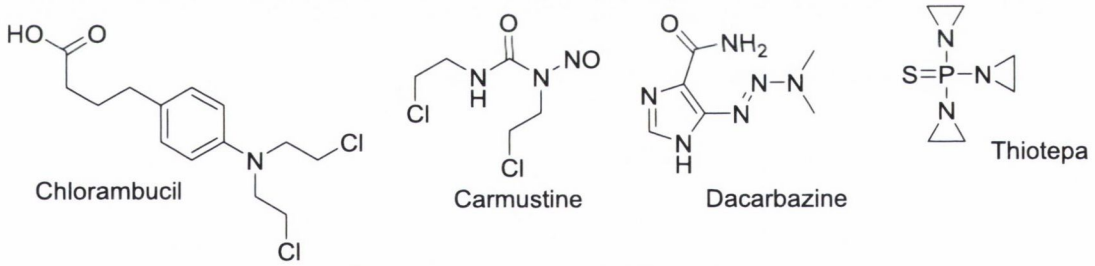


Figure 2: Some common alkylating agents

It should be noted that even though all of the above agents are considered alkylating agents, their mode of action can vary. Chlorambucil contains two bischloroethyl groups which are characteristic of all the common nitrogen mustard compounds. At neutral or alkaline pH, one of the chloroethyl groups cyclises, to form an aziridinium intermediate. This intermediate is very reactive and is susceptible to attack by nucleophilic groups such as amino, carboxyl, sulfhydryl or imidazole moieties in proteins and nucleic acids. The formation of a covalent bond between the aziridine and the 7-nitrogen of guanine contributes significantly to the cycotoxic effects of chlorambucil. Since chlorambucil contains two chloroethyl groups, it behaves as a bi-functional alkylating agent. After forming a covalent bond with one molecule,

chlorambucil undergoes similar cyclisation with the second chloroethyl group and forms a covalent bond with another nucleophilic group such as guanine[12, 13], figure 3.

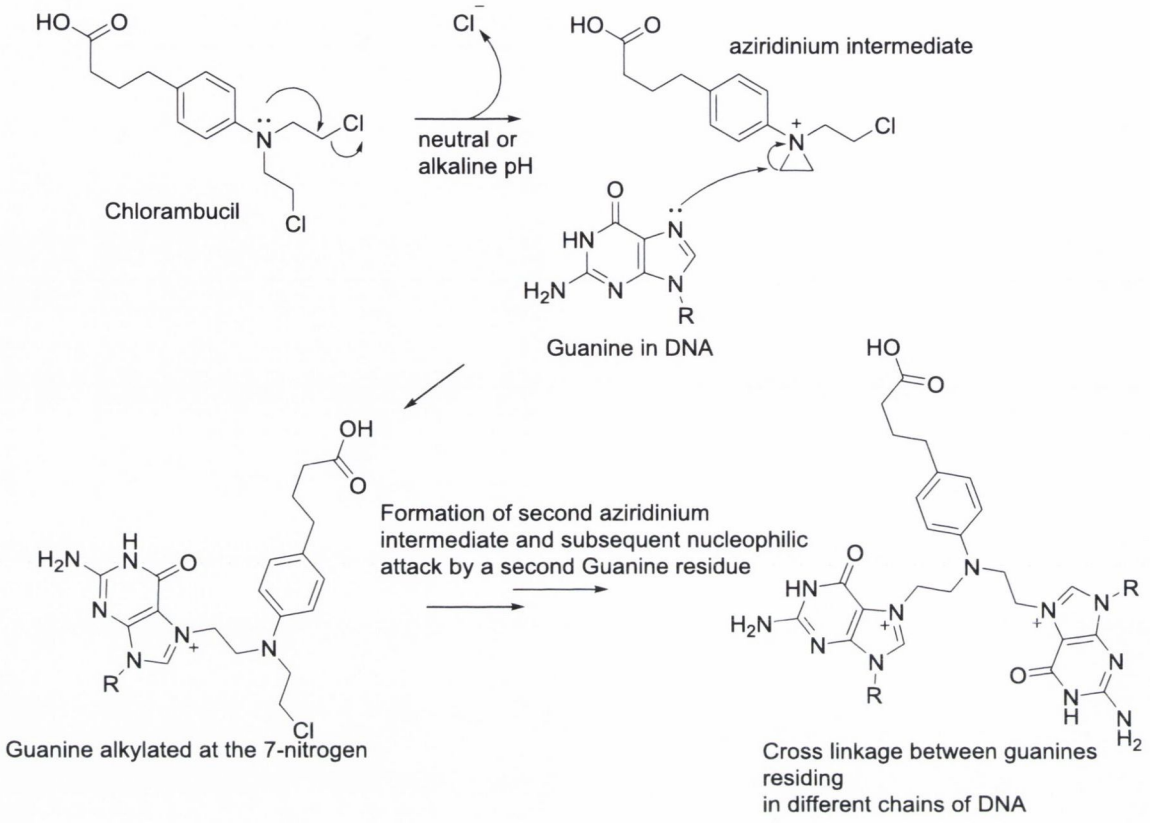


Figure 3: Reaction of chloroambucil with guanine bases in DNA[13]

Aziridines such as thiotepa presumably alkylate by the same mechanism as the aziridinium intermediates produced by the nitrogen mustards, but the aziridine rings in these compounds are uncharged and less reactive than aziridinium compounds[12]. Dacarbazine is recognised as a methylating agent of the guanine bases within the major groove of DNA predominantly at the O-6 position. It was initially evaluated as a potential inhibitor of purine biosynthesis but it was later demonstrated that *N*-demethylation occurs *in vivo* to afford 5-aminoimidazole-4-carboxamide and a transient methyl diazonium ion. Through radiolabelling experiments, it was demonstrated that the methyl diazonium ion methylates DNA at guanine *N*-7 in the minor groove[14], figure 4.

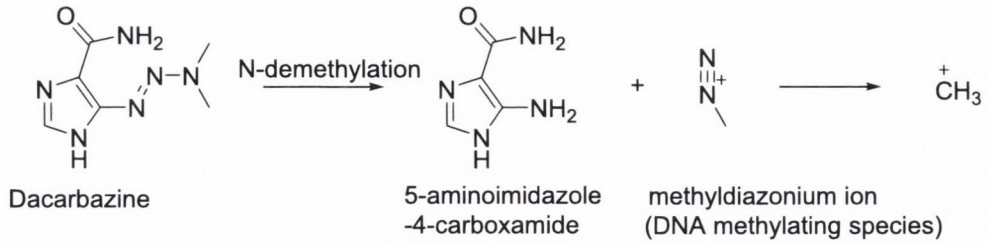


Figure 4: Methylation of DNA by dacabazine[14]

Nitrosoureas are compounds that produce alkylating agents under physiological conditions. The predominant mechanism of action is a base catalysed decomposition to a chloroethyl diazonium moiety which alkylates DNA[12], figure 5.

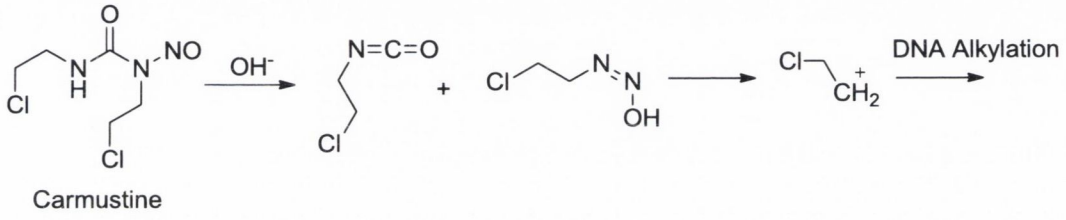


Figure 5: Mechanism of nitrosourea activation

Antimetabolites

Antimetabolites structurally resemble the naturally occurring purines and pyrimidines involved in nucleic acid synthesis[15]. Due to the structural similarity, they are mistaken by cells for normal metabolites and they have two modes of action[16]: (i) inhibition of key enzymes required for DNA synthesis or (ii) incorporation into the DNA and RNA, therefore producing incorrect codes and cause strand breaks or premature chain terminations. Even though the enzymes inhibited by antimetabolites are present in normal cells, some selectivity towards cancer cells is possible due to their faster division rates. Antimetabolites can be divided into four groups[17], figure 6.

(i) *Folate antagonists*: Methotrexate is an example of a folate antagonist. It inhibits dihydrofolate reductase (DHFR), an essential enzyme in folate metabolism. Methotrexate is structurally related to folic acid but has a greater affinity for DHFR, to which it binds and inactivates.

(ii) *Arabinosides*: Cytosine arabinoside is a competitive inhibitor of the enzyme DNA polymerase. Its principal action is as a false nucleotide competing for the conversion of cytidine to deoxycytidine and for incorporation of deoxycytidine into DNA.

(iii) *Antipyrimidines*: 5-Fluorouracil is a fluoro-pyrimidine that inhibits DNA synthesis by inhibiting the main enzymes involved in the synthesis of cytosine and thymine, which are two of the four bases in DNA and RNA.

(iv) *Antipurines*: Purine antagonists (e.g. 6-thioguanine) inhibit purine synthesis by being mistakenly incorporated into DNA and thus interfering with DNA replication.

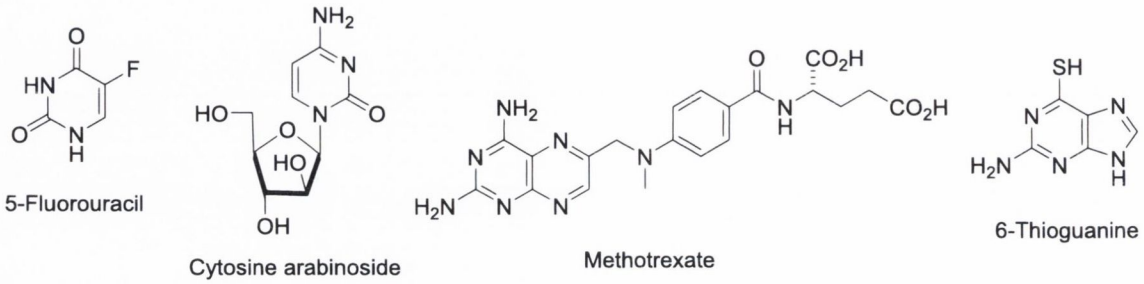


Figure 6: Some common antimetabolites

1.4 Antimitotic agents

Antimitotic agents are a class of cancer chemotherapeutic agents whose mechanism of action is the inhibition of microtubule function. The M phase, the last stage in the cell cycle where cell division and separation occurs, is dependent on microtubule polymerisation and depolymerisation for successful completion. The following will describe the structure of microtubule and how its inhibition negatively affects cell division i.e. mitosis[18].

1.4.1 Microtubules

Microtubules are long and relatively stiff hollow tubes of protein that can rapidly disassemble in one location and rapidly assemble in another. This behavoiur, known as dynamic instability, is central for mitosis. Microtubules are composed of molecules of tubulin. Tubulin is a heterodimer consisting of α tubulin and β tubulin. These heterodimers stack together, in a head to tail arrangement, forming a protofilament, figure 7.

Microtubules are composed of 13 profilaments, creating a hollow cylindrical tube. The polarity of each end of the protofilaments is not the same, with the β tubulin exposed end designated the plus end and the other end, the α tubulin end, designated the minus end.

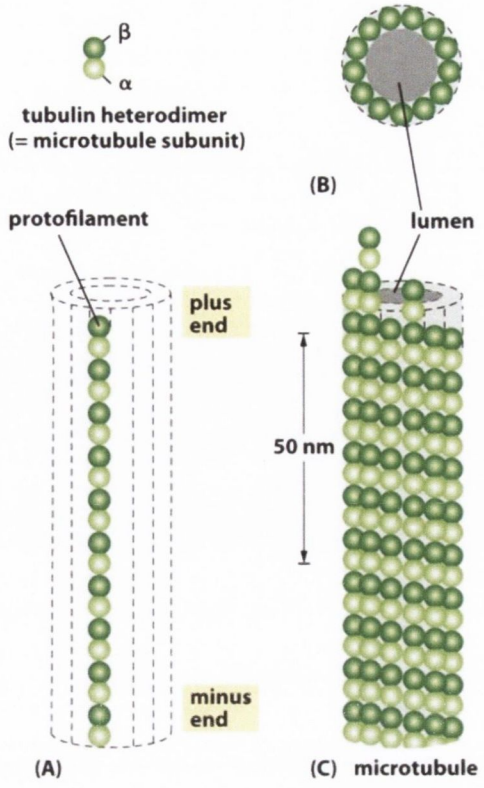


Figure 7: (A) Protofilament, (B) Top view of a microtubule, (C) Side view of a microtubule[18]

Microtubules are in a constant state of growth and shrinkage i.e. assembly and diassembly. Dynamic instability is caused from the ability of tubulin molecules to hydrolyse GTP. Each free tubulin dimer contains one tighly bound GTP molecule that is hydrolysed to GDP shortly after the subunit is added to the growing mircotubule. Tubulin molecules containing GTP pack efficiently together in the wall of the microtuble while tubulin molecules carrying GDP have a different conformation and bind less strongly to each other. When assembly/polymerisation is progressing rapidly, tubulin molecules add to the end of the microtubule faster than the rate at the which the attached GTP can hydroylze. The end of the growing micrtubule is therefore composed of GTP tubulin subunits. This end is known as a GTP cap. However once GTP is hydrolyzed to GDP in the tubulin at the free end of microtubule, the free ends of the protofilaments are now composed of GDP-tubulin subunits. Disassmbely/depolymerisation is now favoured and once started, the microtubule will shrink and disappear[18], figure 8.

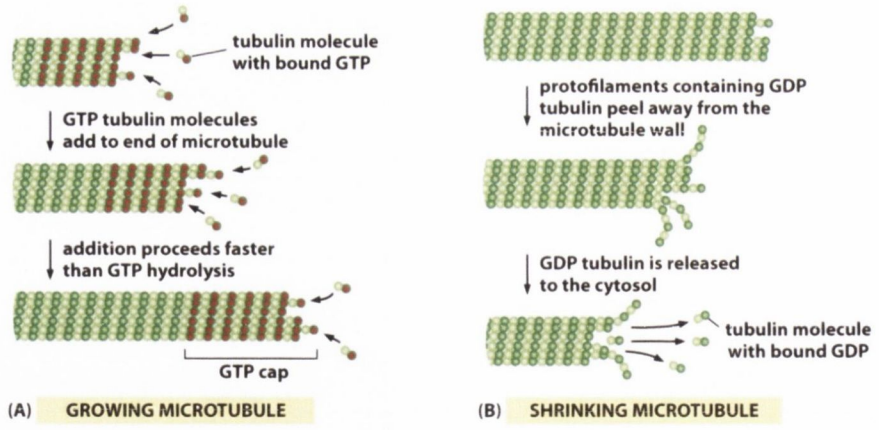


Figure 8: (A) Polymerization and (B) Depolymerization of microtubule[18]

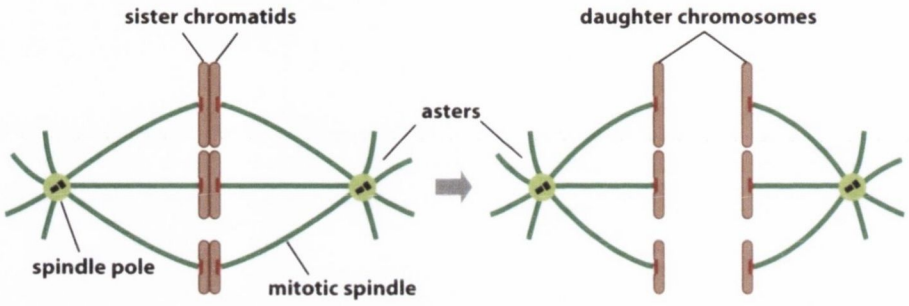
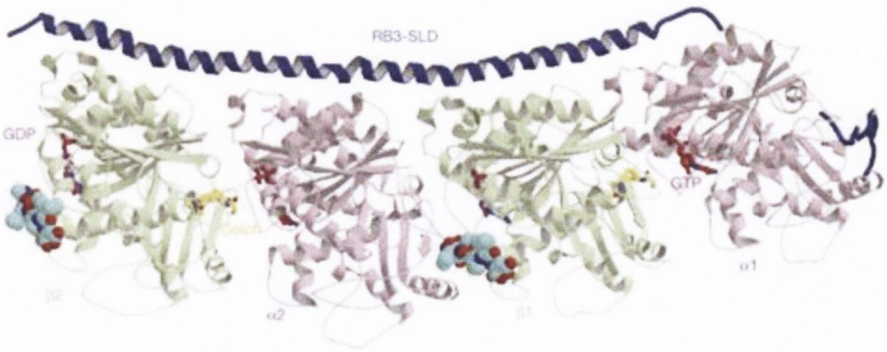


Figure 9: Separation of daughter chromsomes to the poles by the mitotic spindle, during the anaphase[18]

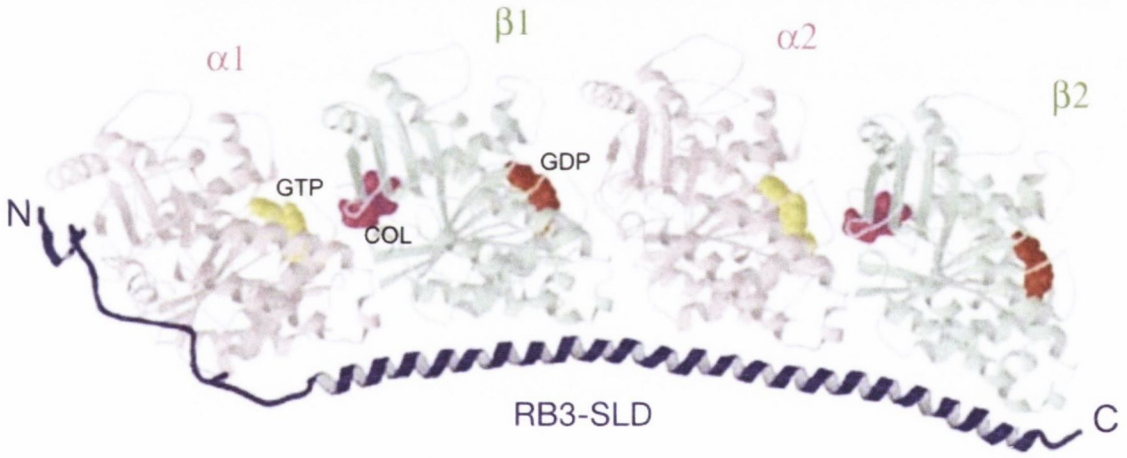
Microtubules have important functions within the cell which include cell signalling, migration, signal transduction and mitosis. Mitosis along with cytokinesis constitute the M phase. Mitosis itself consists of five phases: Prophase, Prometaphase, Metaphase, Anaphase and Telophase. Mitosis is performed by the mitotic spindle which is composed of microtubules and the various proteins that interact with microtubules. The mitotic spindle is responsible for separating the replicated chromosomes and allocating one copy of each chromosome to each daughter cell, figure 9. The assembly of the mitotic spindle and its ability to segregate the sister chromatids is dependent both on the dynamic instability of microtubules and the activity of associated motor protiens.

Antimotitic agents, also referred to antimicrotubule agents or tubulin inhibitors, are divided into two major classes, depending on their mode of action. Microtubules are in a constant state of polymerisation and depolymerisation. Tubulin polymerisation inhibitors are agents that bind preferentially to α/β-tubulin heterodimers and this inhibits microtubule polymerisation. Tubulin depolymerisation inhibitors are agents when bound to microtubule, stabilise it and thus preventing depolymerisation.

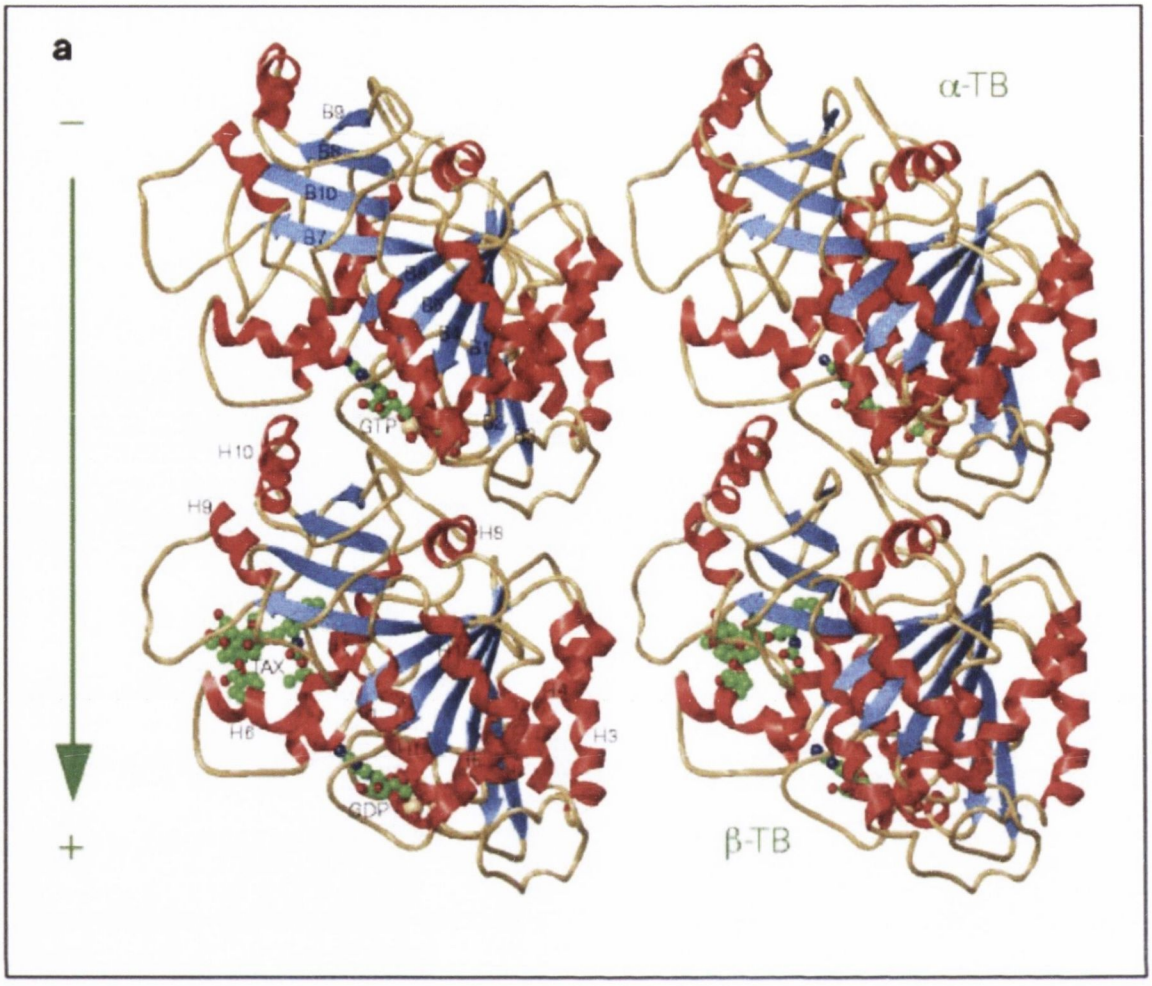
Tubulin depolymerisation inhibitors bind to the pacliatxel binding site within tubulin, figure 10 (C). However for tubulin polymerisation inhibitors, there exist two distinct binding sites: the *Vinca* alkaloid binding site and the colchicine binding site, figure 10 (A) and (B) respectively.



(A)[19]



(B)[20]



(C)[21]

Figure 10: Location of (A) *vinca* binding site, (B) colchicine binding site and (C) taxol binding site in tubulin

1.4.2 Tubulin Depolymerisation Inhibitors

A screening program set up by the NCI to examine the anticancer activity of both synthetic compounds and compounds isolated from natural sources resulted in the discovery of a potent naturally occuring anticancer agent. This diterpene agent, paclitaxel, was isolated from the bark of the yew tree *Taxus brevifolia* and later became known as Taxol®[22], figure 11.

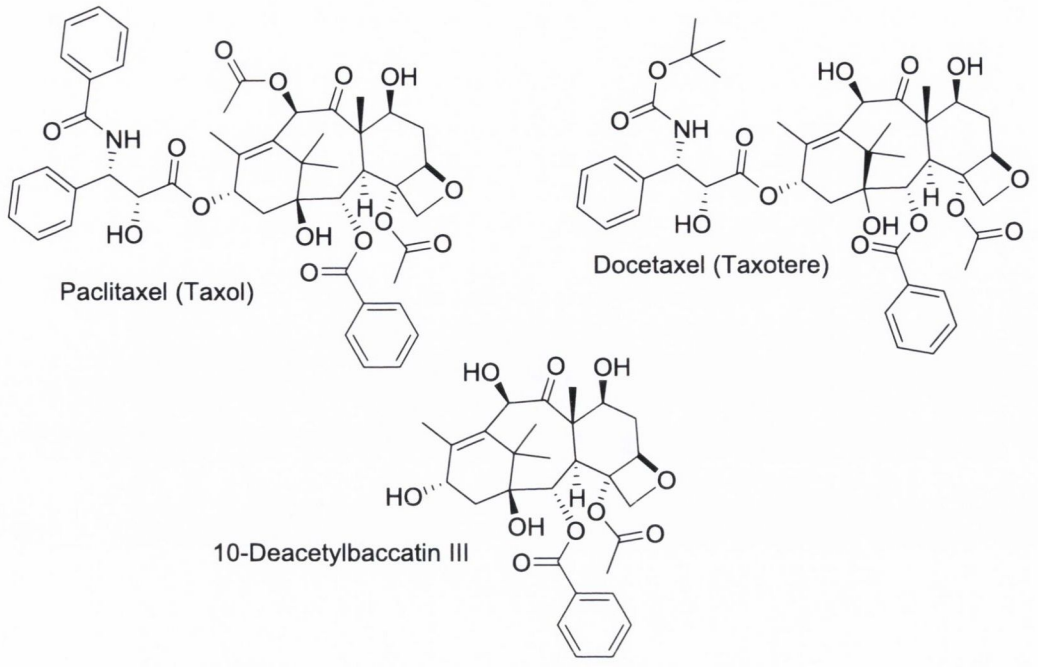


Figure 11: Paclitaxel, Docetaxel, 10-deacetylbaccatin III

Taxol displayed activity in L-1210, P-388, and P-1534 leukemia cell lines, being highly active in the latter two systems and was also highly active as an inhibitor of WM-256 carcinosarcoma. Taxol, more commonly known as its generic name paclitaxel, was only present in the *Taxus brevifolia* in small quantities and formulation was difficult due to its poor water solublity. Despite these issues, further research proved fruitful as taxol displayed excellent activity against various solid tumour xenografts in nude mice. However it was taxol's unique mechanism of action which ensured ongoing interest. Taxol was first recognised as a microtubule targeting agent but unlike clinically used drugs such as vinblastine and vincristine which were known to act as inhibitors of tubulin polymeristaion, taxol was the first compound shown to promote tubulin depolymerisation[23, 24]. Bristol Myers Squibb (BMS) later acquired the rights to taxol but the limited availablity of the drug from its natural source, forced BMS to search for an alternative supply. Taxol was instead prepared using a semisynthetic process from 10-deacetylbaccatin III, which is found to be abundant in the European yew, *Taxus baccata*[25].

The search for alternative supply of taxol led to the discovery of another taxoid drug docetaxel, an analogue of taxol. Docetaxel was prepared using a semisynthetic process again using 10-deacetylbaccatin III[26]. There are two structural differences between paclitaxel and docetaxel. Docetaxel has an hydroxy functional group on carbon 10 instead of an acetate ester and a *tert*-butyl carbamate ester is present on the phenylpropionate side chain instead of the benzyl amide,

figure 11. The problems associated with the current formulations of paclitaxel[27] led to the development of abraxane™. Abraxane™ is a newly derivatized formulation where paclitaxel is bound to albumin nanoparticles allowing the drug to be administered at a higher maximum-tolerated dose and without Cremophor-EL™, thereby eliminating the need for pre-medication. Paclitaxel, docetaxel, and abraxane™ are approved for clinical use. Paclitaxel and docetaxel share a broad spectrum of antitumor activity including breast, lung, ovarian, bladder, and prostate cancer. Both drugs also have activity against lymphoid malignancies.

The success of paclitaxel and docetaxel intensified the search for additional natural products that could stabilize microtubules. *Bollag et al*[28] reported that two naturally occurring compounds, isolated from the fermentation broth of a soil *Myxobacterium, Sorangium cellulosum* strain 90, inhibited microtubule depolymerization. These two polyketide compounds, Epothilone A and Epothilone B, were shown to act as competitive inhibitors of paclitaxel binding to microtubule. This confirmed that they share the microtubule binding site. Epothilone A and Epothilone B, figure 12, represented a new class of microtubule stabilizing compounds, the first since the discovery of paclitaxel. There are currently six epothilones in either preclinical or clinical trials[29, 30] and one of these, (BMS-247550, ixabepilone) has been approved by the FDA for the treatment of breast cancer[31]. It is also in various clinical trials for kidney cancer, advanced kidney cancer and progressive advanced solid tumours.

(+)-Discodermolide is a polyketide natural product which inhibited microtubule depolymerization, figure 12. It was isolated from the deep sea sponge *Discodermia dissoluta* in 1990[32]. (+)-Discodermolide expresses activity in paclitaxel resistant cell lines which over-express P-glycoprotein, the multidrug-resistant transporter. In 2002, five new naturally analogues of Discodermolide isolated from the marine sponge *Discodermia* species were reported[33]. These analogues exhibited a range of cytotoxicity against the cultured murine P-388 leukemia and A-549 human adenocarcinoma cells. There is also on-going research into synthetic analogues of discodermolide[34-36], some of which have demonstrated to be tumour growth suppression agents *in vivo*[37]. The efficacy of several discodermolide analogues was examined as standalone anti-tumour agents and in the case of (+)-2,3-anhydrodiscodermolide, as a chemical component of a combination bacteriolytic therapy. It was shown that the use of (+)-2,3-anhydrodiscodermolide plus *Clostridium novyi*-NT lead to a robust and rapid obliteration of HCT116 xenograft tumours[37].

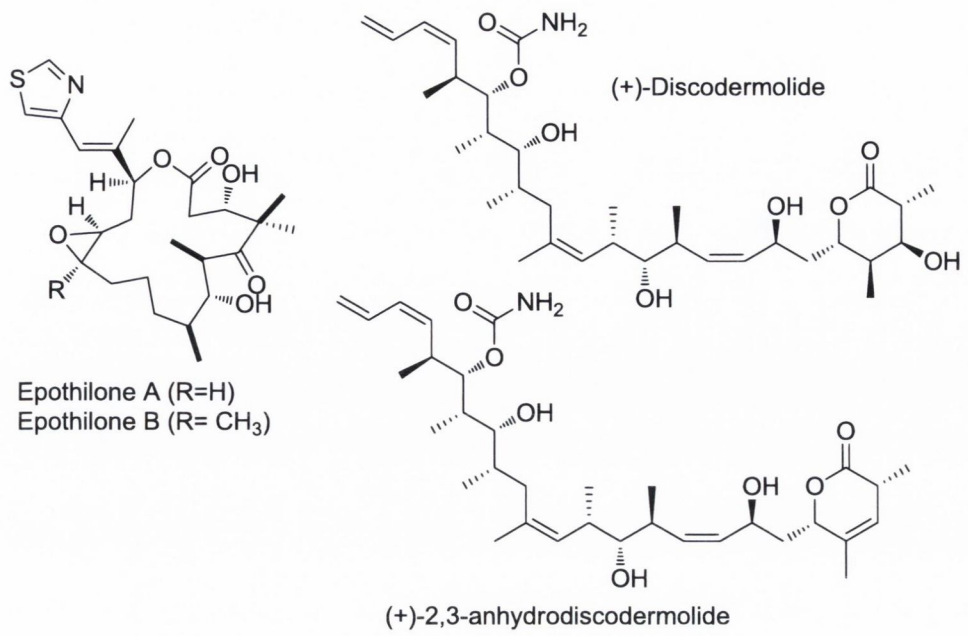


Figure 12: Epothilone A, Epothilone B, (+)-Discodermolide, (+)-2,3-anhydrodiscodermolide

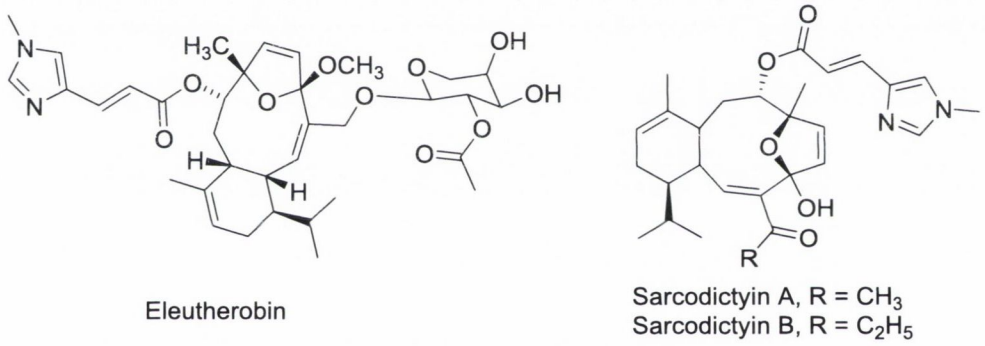


Figure 13: Eleutherobin and Saracodictyins

Eleutherobin[38] represents another diterpene glycoside natural product which inhibited microtubule depolymerization, figure 13. Eleutherobin was isolated from an *Eleutherobia* species of soft, red coral found near Western Australia. It is an extremely potent inducer of tubulin polymerization *in vitro* and is cytotoxic for cancer cells with IC_{50} values similar to that of paclitaxel[38]. IC_{50} values of 10.7 and 13.7 nM were recorded for eleutherobin in cancer cell lines HCT116 and A2780 respectively while IC_{50} values of 4.6 and 6.7 nM were recorded for paclitaxel in the same two cancer cell lines. The closely related sarcodictyins, isolated from Mediterranean stolonifer *Sarcodictyin roseum*, were shown to stabilize microtubules with potency similar to that of paclitaxel[39], figure 13.

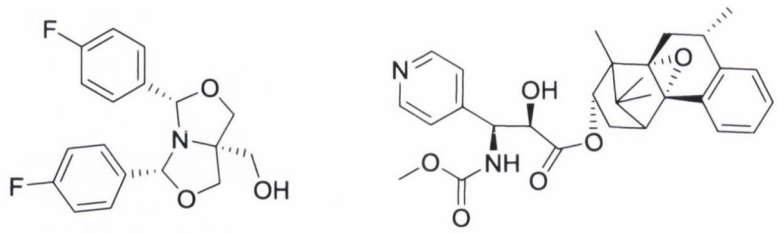


Figure 14: Synthetic small molecules that promote tubulin polymerisation

Several synthetic small molecules that inhibit tubulin depolymerization have been identified[40, 41], figure 14. The borneol ester molecule was reported to be a more potent microtubule stabilizer than paclitaxel while GS-164 has been shown to cause cellular effects that are typically associated with microtubule stabilizing agents, although its potency is significantly lower than that of paclitaxel e.g. for the cancer cell lines HeLa, MCF-7 and H-69, IC_{50} values of 9, 5 and 24.6 μM were recorded for GS-164 while for same cell lines paclitaxel demonstrated IC_{50} values of 0.023, 0.0009 and 0.009 μM respectively.

More recently, *Reddy et al*[42] reported a series of (*Z*)-1-aryl-3-arylamino-2-propen-1-one molecules, such as (**1**), that induce apoptotic death of a wide variety of human tumour cell lines at nanomolar concentrations by promoting tubulin polymerization and stabilizing microtubules, figure 15. A series of 6-(substituted)phenyltriazolopyrimidine compounds e.g. (**2**) was developed by *Zhang et al*[43] to act as tubulin polymerization promoters as anticancer agents for tumours that express multiple drug resistance (MDR) or are resistant because of MDR, figure 15.

Dyrager et al[44] reported the first known chalcone derivative with microtubule stabilizing ability. As an example, compound (**3a**) was shown to inhibit tubulin polymerization which is in accordance with previous reports concerning chalcones[45, 46]. It is believed that these compounds inhibit tubulin polymerization by binding to the colchicine binding site of tubulin. However (**3b**) behaved as a promoter of tubulin polymerization and it was similar to docetaxel in its microtubule stabilizing activity. Molecular modelling studies performed by *Drager et al* revealed that (**3b**) interacts with the paclitaxel binding site. The discovery of (**3b**) as a promoter of tubulin polymerization could see the chalcone scaffold being used in the development of novel small molecule tubulin stabilizing agents. *Cao et al*[47] used a pyranochalcone scaffold to synthesise a series of novel microtubule stabilising agents. In several human tumour cell lines, including multidrug resistant human cell lines, compound (**4**) from this series was the most potent in antiproliferative activity. IC_{50} values of 0.09, 0.24 and 0.16 μM were recorded in

cancer cell lines HepG2, A375 and K562 respectively. (**4**) displayed the similar tubulin polymerisation activity as taxol.

One of the more interesting synthetic microtubule stabilising agents are the cyclopropylamide analogues of combretastatin-A4 (CA4) developed by *Chen et al*[48], figure 15. CA4 is a known microtubule destabilising agent, see section 1.5, however these cyclopropylamide analogues behave as microtubule stabilising agents. The most potent of these cyclopropylamide analogues, compound (**5**), showed good activity against A549 and HeLa cell lines that were resistant to paclitaxel. Thus the CA4 scaffold, with the 3,4,5-trimethoxyphenyl moiety, could lead to the development of an extremely novel class of microtubule stabilising agents. These examples highlight that stabilization of microtubule is possible with relatively simple synthetic molecules and is not restricted to complex natural products.

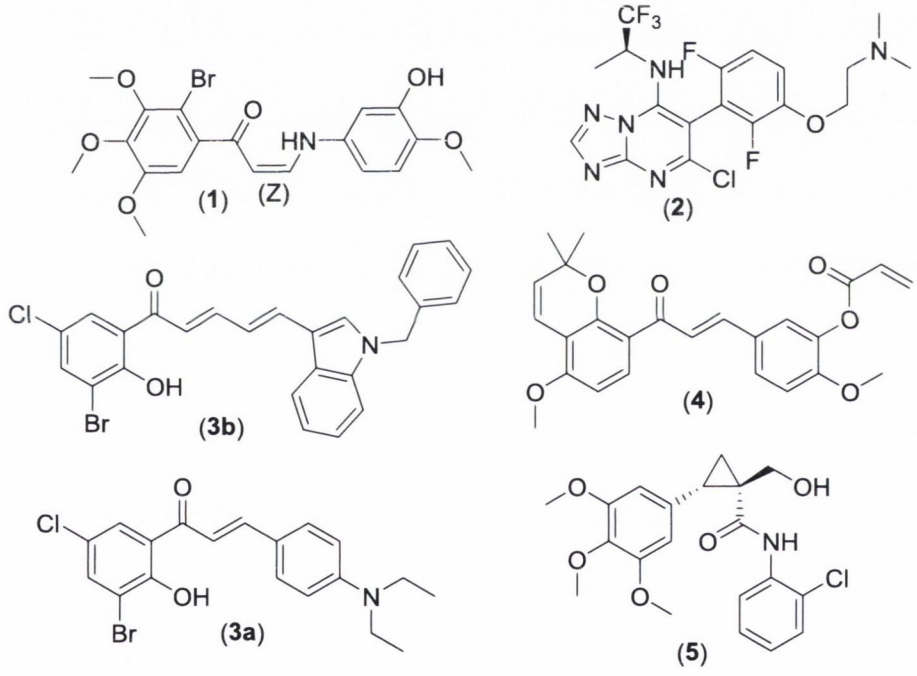


Figure 15: Recently developed synthetic microtubule stabilizing agents

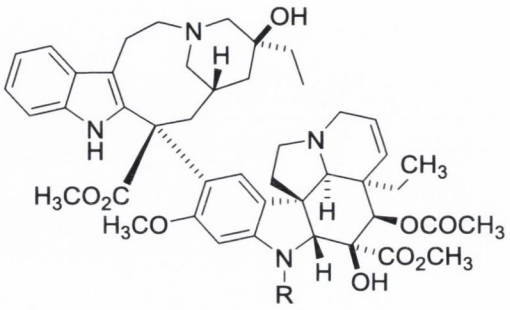
1.4.3 Tubulin Polymerisation Inhibitors

Tubulin polymerisation inhibitors are divided into two categories: (i) compounds that bind to the *Vinca* alkaloid binding site of tubulin and (ii) compounds which bind to the colchicine binding site of tubulin.

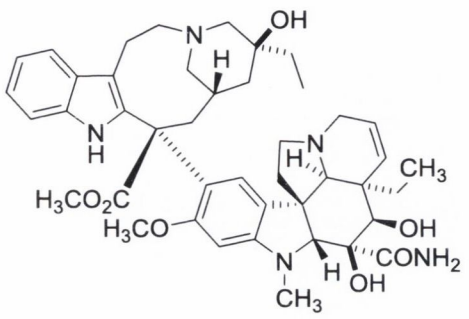
1.4.3.1 Compounds binding at the *Vinca* alkaloid site

The *Vinca* alkaloids are a family of macrocyclic compounds isolated from the Madagascar periwinkle *Catharanthus roseus*. *Nobel et al*[49] isolated the bisindole alkaloid

vincaleukoblastine, later renamed as vinblastine, while leurocristine was isolated by *Svoboda et al*[50], later renamed as vincristine. Both alkaloids have become an important part of many potential curative regimens used in the treatment of leukaemia, lymphoma and testicular cancer. Vindesine, a semi-synthetic analogue (see figure 16), is in clinical use, mainly in the treatment of melanoma and lung carcinomas[51].



R = CHO Vincristine
R = CH_3 Vinblastine



Vindesine

Figure 16: *Vinca* alkaloids

A marine derived natural product that also binds at the *Vinca* domain is halichondrin B, figure 17. It is a complex polyether macrolide isolated from the marine sponge *Halichondria okadai*. It has an extraordinarily high potency as an antitumor agent and a high therapeutic index. However the development of halichondrin B as a new anticancer agent was hindered due to scarcity in natural sources but structurally similar analogues, e.g. (**6**) Eribulin and (**7**) ER-076349, figure 17, have been prepared. These fully synthetic analogues[52] have retained the same high potency as the parent compound.

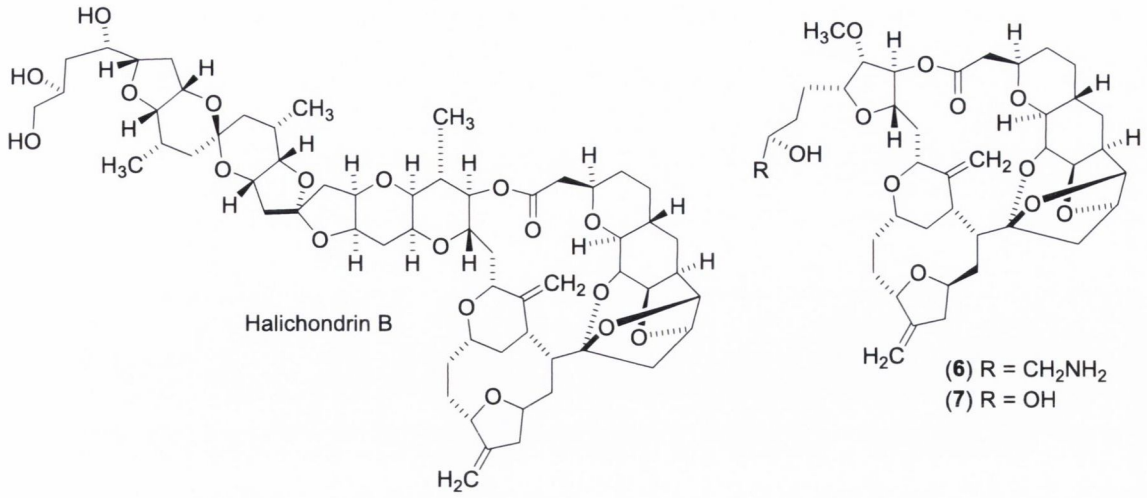


Figure 17: Halichondrin B and analogues

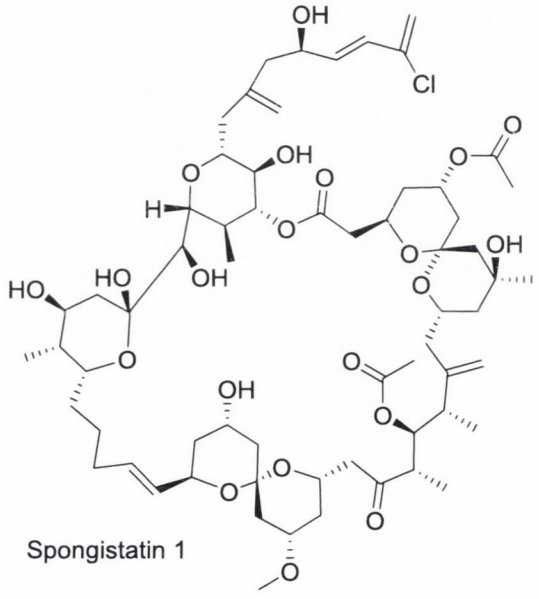


Figure 18: Spongistatin 1

Spongistatin 1 is a natural marine derived product which binds to the *Vinca* domain of tubulin, figure 18. It was isolated from an Eastern Indian Ocean sponge in the genus *Spongia*[53] and displayed potent activity against selected human tumor cell types in the NCI's primary screen. *Bai et al*[54] reported that Spongistatin 1 did not bind to the colchicine binding site of tubulin but it was a potent inhibitor of the binding of vinblastine and GTP to tubulin. It is believed that the *Vinca* domain in tubulin is composed of a series of overlapping domains rather than a single unit and there are three distinct binding sites within the *Vinca* domain[54, 55]. To our knowledge,

there appears to be currently no research into the development of synthetic small molecule inhibitors of microtubule polymerization which bind to the *Vinca* domain.

1.4.3.2 Compounds binding at the colchicine site

Compounds which bind to the colchicine binding site of tubulin represent the second class of inhibitors of tubulin polymerization. The first known drug to bind to tubulin and inhibit microtubule formation was colchicine[56, 57]. The specific binding site/region of tubulin where colchicine binds to is called the colchicine binding site and compounds which bind to the same site of tubulin are referred to as colchicine site inhibitors. Colchicine is a plant alkaloid isolated from the autumn crocus, *Colchicum autumnale*[58]. In addition to behaving as a tubulin inhibitor, it demonstrated anti-vascular activity. Clinical development of colchicine was halted due to its significant toxicity and efficacy only at doses approaching the maximum tolerated doses. Due to gastrointestinal side-effects, colchicine is not clinically available for the treatment of cancer[59] but is prescribed for the short term treatment of gout but only at low doses[60].

Podophyllotoxin is another natural product which inhibits mitotic assembly. It is an aryltetrainlactone cyclolignan and is a major constituent of *Podophyllin*[61]. It is thought that the podophyllotoxin binding site of tubulin overlaps with the colchicine binding site as it competitively inhibits the binding of colchicine. The anti-cancer properties of pollophyllotoxin were demonstrated by the American Indians who used extracts from the roots of *Podophyllum peltatum* (American Mayapple)[62]. However podophyllotoxin is not used clinically for the treatment of cancer due to unacceptable side effects. Other natural products which inhibit microtubule polymerization by binding to the colchicine active include steganacin[63], 2-methoxyestradiol[64] and curacin A[65], figure 19. Steganacin was isolated from the plant *Steganotaenia araliacea* by *Kupchan et al* in 1973[66]. This lignan lactone showed significant antileukemic activity against P-388 leukemia in the mouse, and cytotoxicity against a KB cell culture at 10^{-1} to 10^{-3} mg/mL. This natural product also contains the 3,4,5-trimethoxyphenyl system as in colchicine and podophyllotoxin. 2-Methoxyestradiol is a natural metabolite of estradiol. It underwent phase I clinical trials for advanced solid tumours[67] in order to determine the maximum-tolerated dose. There is no obvious structural similarity between 2-methoxyestradiol and colchicine/podophyllotoxin/steganacin. 2-Methoxyestradiol does not contain the trimethoxyphenyl ring however it does bind to the colchicine binding site. It has been suggested that the term colchicine binding region is more appropriate. This statement is further substantiated by the natural product curacin A. Curacin A was isolated from the cyanobacterium *Lyngbya majuscula* collected off the coast of Curaçao[68]. Curacin A and 2-

methoxyestradiol represent a class of colchicine binding site compounds which do not possess the trimethoxyphenyl ring.

From the list of natural products which inhibit microtubule polymerization by binding to the colchicine active site of tubulin, the combretastatins have been the focus of a considerable amount of research. Combretastatin A4 is one of the most potent of all the naturally available combretastatins. The following section will focus on combretastatins.

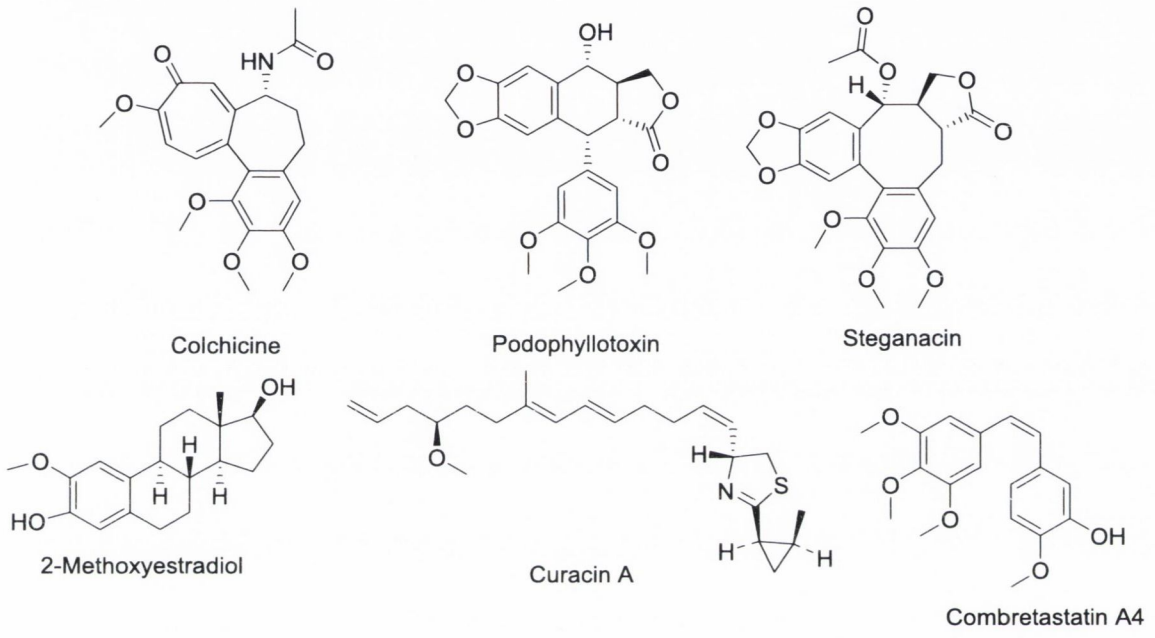


Figure 19: Natural products which bind in the colchicine active site of tubulin

1.5 Combretastatins

Combretastatins are a family of natural products first isolated from the bark of the South African tree *Combretum caffrum*[69]. The first member of this family, combretastatin, produced prominent astrocyte reversal in the NCI astrocytoma bioassay. Two further combretastatins, combretastatin A-1 and combretastatin B-1, were isolated from *Combretum caffrum* in 1987[70]. Both were significantly more potent than the original combretastatin, with combretatastin A-1 being more potent than combretatastin B-1. Further investigation of *Combretum caffrum* lead to the discovery of combretastatin A-2[71], combretastatin A-3[71], combretastatin A-4[72, 73], combretastatin A-5[73], combretastatin A-6[73], combretatastin B-2[71], combretatastin B-3[74] and combretatastin B-4[74], figure 20.

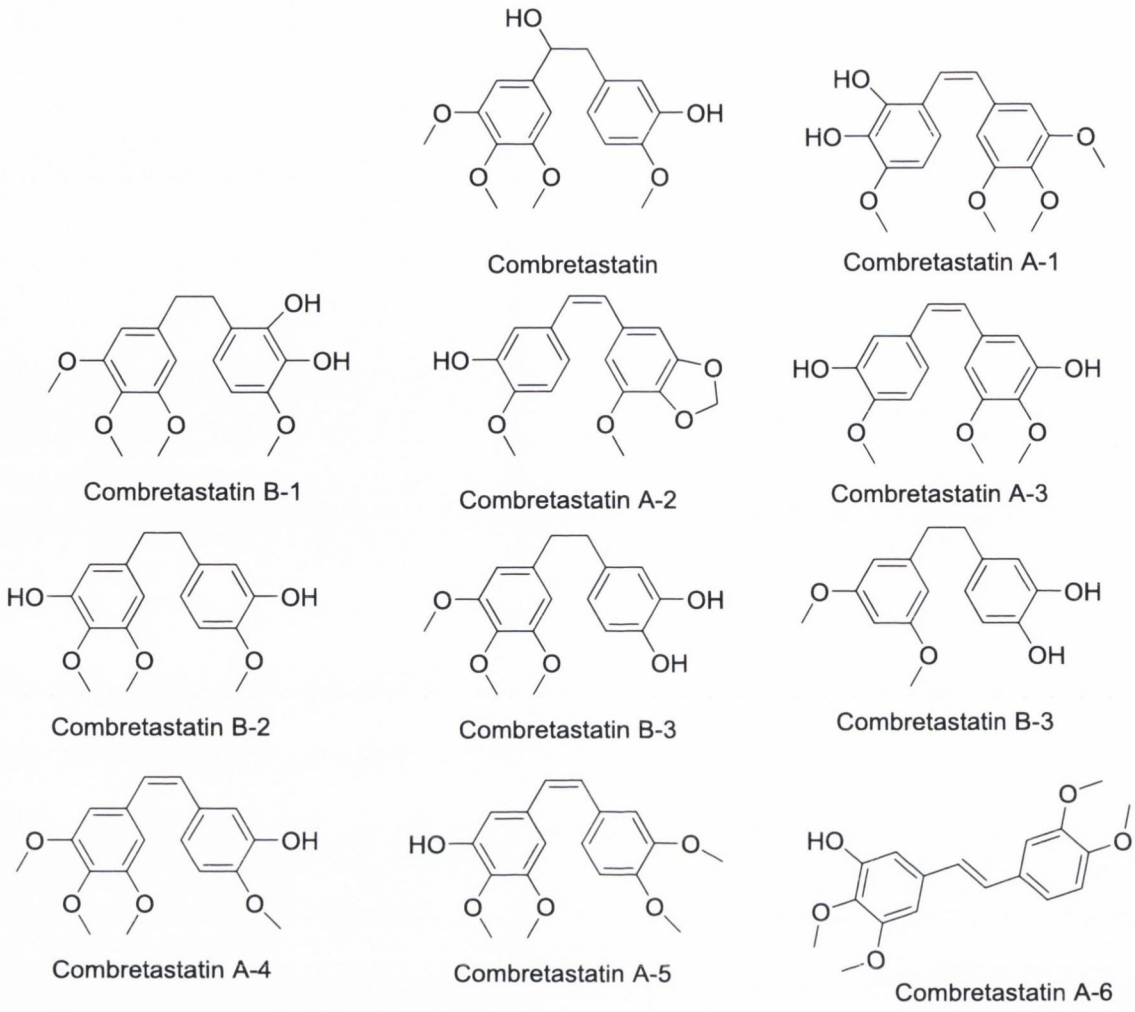


Figure 20: Combretastatins isolated from combretum caffrum

All the naturally derived combretastatins inhibit tubulin polymerisation and bind to the colchicine active site of tubulin. In addition to behaving as antimitotic agents, combretastatins behave as tumour vascular targeting agents (VTA)[59]. One of the requirements for the growth of a tumour is the provision of necessary nutrients and oxygen, delivered by the vasculature system. The aim of VTA is to cause the rapid and selective shutdown of the blood vessels of the tumour. VTA essentially starve the tumour by obstructing the network of pre-existing blood vessels resulting in tumour cell death[75].

Combretastatin A-1, commonly referred as CA1, and Combretastatin A-4, commonly referred as CA4, are among the most potent cancer chemotherapeutic of the naturally occurring combretastatins[73, 76, 77]. CA4 exhibited excellent cytotoxicity against murine P388, L1210 lymphocytic leukemia cells and various human cell lines. Despite their early promise as anticancer agents, CA1 and CA4 has not entered clinical I trials due to formulation difficulties,

leading to the development of CA1 and CA4 analogues and prodrugs having increased water solubility.

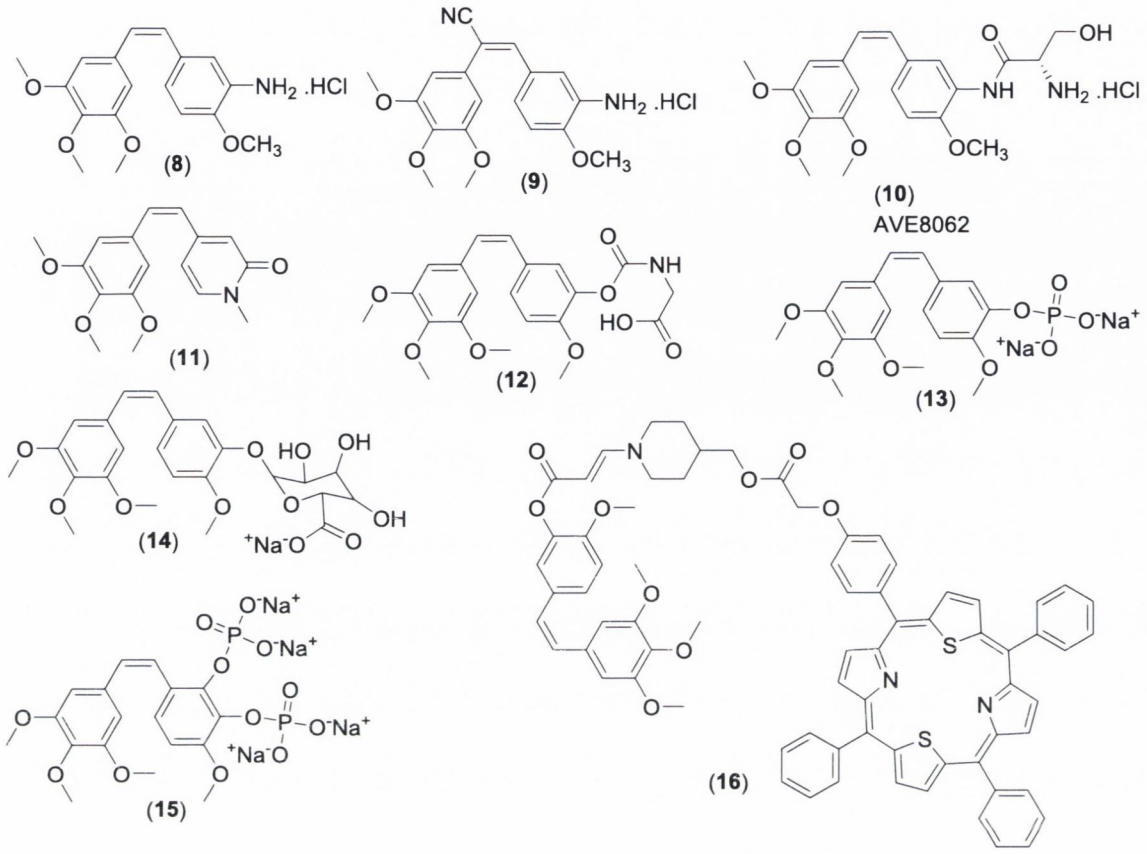


Figure 21: Combretastatin analogues and prodrugs

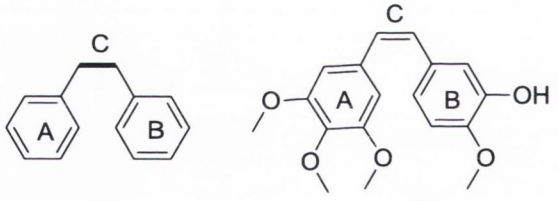
CA4 analogues (**8**)[78], (**9**)[78], (**10**)[79-81]and (**11**)[82] were all developed by Ajinomoto, a Japanese research institute, figure 21. All four compounds had improved water solubility. The replacement of the 3-hydroxy group on the B ring with an amine group had a positive effect on water solubility. In Colon 26, Colon 38 and 3LL murine models in mice, both (**8**) and (**9**) displayed potent antitumor activity. (**10**) had an IC_{50} value of 19.2 nM in colon 26 adenocarinoma cells. (**10**) is a serine prodrug of (**8**) and showed antitumor activity against advanced solid tumors. Prodrugs are bioreversible derivatives of pharmacologically active agents that must undergo an enzymatic and/or chemical transformation *in vivo* to release the active parent drug which can then produce its pharmacological effect[83], (**10**) showed improved water solubility over parent compound (**8**). It was also shown to restrict tumour blood flow and inhibit the growth of tumours developing in various tissues and organs[84]. It is currently

involved in clinical trials, under the new designation AVE8062, for advanced stage soft tissue sarcoma.

Brown et al (**14**)[85], *Pettit et al* (**13**)[86], and *Bedford et al* (**12**)[87] developed water soluble CA4 pro-drugs, but only the sodium phosphate pro-drug (**13**) has entered clinical trials[88-90]. (**15**)[91], a sodium phosphate CA1 prodrug, is currently undergoing phase I clinical trials for relapsed and refractory AML and MDS, under the designation OXi4503[92]. (**16**) is a novel low energy light activated CA4 prodrug[93]. (**16**), CMP-L-CA4, consisted of a dithiaporphyrin, a photosensitizer, an aminoacrylate linker L and CA4. After exposure to tissue-penetrable far-red light (690 nm), the aminoacrylate linker of the prodrug is cleaved, releasing CA4.

1.5.1 Combretastatin Analogues

The emergence of combretastatins, particularly CA4, as potent cancer chemotherapeutic agents has led to the development of diverse range of related analogues. As seen from figure 22, combretastatins are composed of two aryl rings, labelled A ring and B ring respectively, and a bridge/linker, labelled C. For CA4, the 3,4,5-trimethoxyphenyl ring corresponds to the A ring, the 3-hydroxy-4-methoxy phenyl ring corresponds to the B ring while the ethylene bond corresponds to bridge C. The *Z* arrangement of these rings is responsible for CA4's potency[73]. Many CA4 analogues have been designed and evaluated having either a different A ring, B ring, bridge C or a combination of all three.



(i) (ii)

Figure 22: (i) Identification of A ring, B ring and bridge C, (ii) Labelled components of CA4

1.5.1.1 Combretastatin analogues with modified B ring

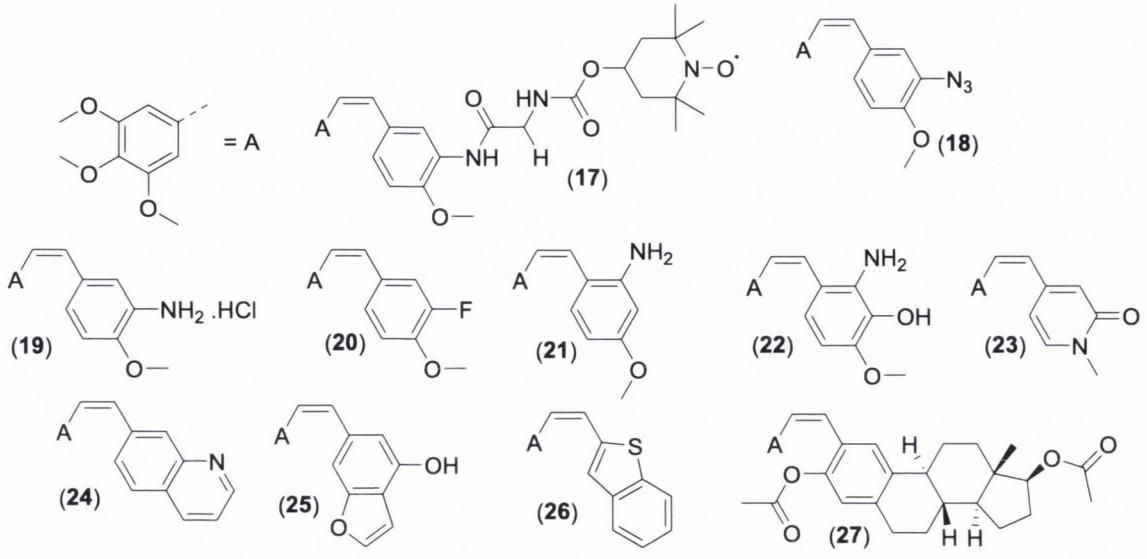


Figure 23: Combretastatin analogues with modified B rings

A selection of CA4 analogues with modified B rings is shown in figure 23. Analogues (**17**)[94], (**18**)[95], (**19**)[78] and (**20**)[96] have replaced the 3-hydroxy substituent on the B ring with a spin labeled oxygen, azide, amine or a flouro substituent respectively. (**17**) was a strong inhibitor of tubulin polymerization and IC_{50} values of 0.41, 0.39 and 0.98 μM were measured in tumour cell lines Hela, BGC-832 and HEPG-2 respectively. (**18**) was also a strong inhibitor of tubulin polymerization and demonstrated excellent *in vitro* cytotoxicity against human cancer cell lines e.g. BXPC-3. (**19**) showed improved water solubility and displayed potent antitumour activity against Colon 26, Colon 38 and 3LL murine tumour models in mice. (**20**) recorded an IC_{50} value of 4 nM against the K562 human myelogenous leukaemia cell-line. Compounds (**21**)[97] and (**22**)[98] both have an amine substituent in the 2 position of B ring but only (**22**) retains the 3-hydroxy substituent. (**21**) was a strong inhibitor of tubulin polymerisation with an IC_{50} value of 1.6 μM and displayed antiproliferative activity with IC_{50} values ranging from 11 to 20 nM in a variety of human cell lines. (**22**) was also a strong inhibitor of tubulin polymerisation and had significant *in vivo* blood flood shutdown capability.

Compounds (**23**)[82], (**24**)[99], (**25**)[100] and (**26**)[101] possess different heterocyclic B rings. Instead of the 3-hydroxy-4-methoxy phenyl ring, (**23**), (**24**), (**25**) and (**26**) have a pyridone ring, quinolone ring, benzofuran ring and a benzo[*b*]thiophene ring respectively. (**23**) demonstrated enhanced water solubility and an IC_{50} value of 19.2 nM in colon 26 adenocarinoma cells while CA4 had an IC_{50} value of 8.7 nM. (**24**) inhibited tubulin polymerization and had similar cytotoxicity to CA4 when assayed against different tumour cell lines (P-388, HT-29). (**25**) displayed

antiproliferative activity with IC_{50} values ranging from 31-70 nM in a variety of human cell lines. (**26**) displayed similar activity as colchicine in the inhibition of tubulin polymerisation and an IC_{50} value of 16 nM was measured when it was assayed in the HaCaT keratinocyte cell line. Compound (**27**) is a CA4 analogue with a steroidal B ring. (**27**) was found to have IC_{50} values in the low μM range when assayed in the breast cancer lines, MCF-7 and MDA-MB-231. Compounds (**17**) – (**27**) demonstrate that, with retention of the 3,4,5-trimethoxyphenyl ring and the ethylene bridge, the B ring of CA4 can be modified affording equally potent analogues.

1.5.1.2 Combretastatin analogues with modified A ring

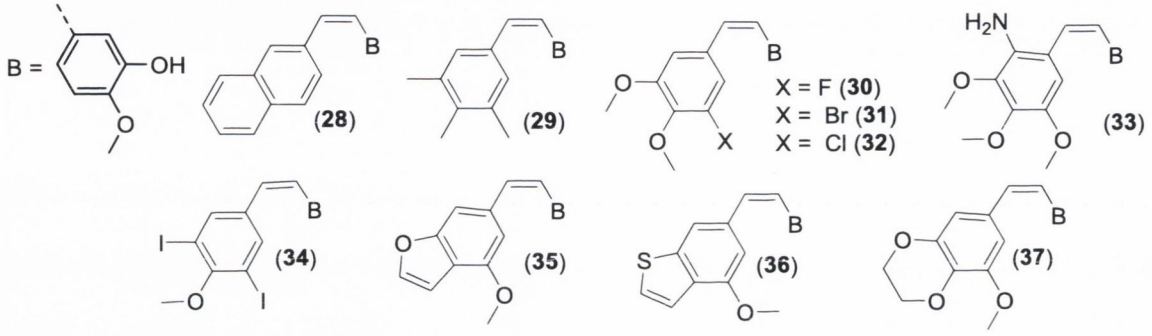


Figure 24: CA4 analogues with modified A ring

A selection of CA4 analogues with modified A rings are shown in figure 24. Instead of 3,4,5 trimethoxyphenyl ring, (**28**)[102] contained a naphthalene ring. It was initially thought that the naphthalene ring could replace either the A or B rings of CA4 and still have a similar cytotoxic potency. However further research by *Maya et al*[103] revealed that while naphthalene is a good surrogate for the B ring, the cytotoxic activity is largely decreased when naphthalene replaces the A ring. Compounds (**30**)-(**32**)[104] and (**34**)[105] are examples of halo-substituted A rings. In the case of (**30**)-(**32**), the 3-methoxy group was replaced with either a flouro, bromo or chloro substituent. This substitution was well tolerated in that these halo derivatives were nearly equivalent to CA4 as inhibitors of tubulin polymerization. In the case of (**34**), the 3-methoxy and 5-methoxy groups are replaced by iodo substituents. This di-iodo derivative was found to be a potent inhibitor of colchicine binding.

Compound (**33**)[97] contains an additional substituent, an amine group, on the A ring. (**33**) was a strong inhibitor of tubulin polymerization and displayed IC_{50} values of 19 – 39 nM in a variety of human cell lines from different organs. The introduction of the amine substituent in the 2 position of the A ring is thought to have an important role in its activity. Compound (**29**)[106] contains a 3,4,5-trimethylphenyl ring instead of the 3,4,5-trimethoxyphenyl ring and was

shown to be a potent inhibitor of tubulin polymerisation. Compounds (**35**)[107], (**36**)[107] and (**37**)[108] possess heterocyclic A rings. (**35**) and (**36**) were found to have a binding affinity for the colchicine active site five times that of CA4. IC_{50} values in the nM range were obtained against HT-29 and H-46 cancer cell lines. (**37**) is structurally similar to CA2 but instead of methylenedioxy substituent, it has an ethylenedioxy substituent. Compounds (**28**) – (**37**) demonstrate that, with retention of the ring B isovanillin moiety and the ethylene bridge, the A ring of CA4 can be modified affording equally potent analogues.

1.5.1.3 Combretastatin analogues with modified bridges

The modification of the ethylene bridge in CA4 has been also investigated in the search of alternative CA4 analogues. This has been achieved by (i) the introduction of substituents onto the ethylene bridge, see figure 25, or (ii) using an alternative scaffold core while still incorporating the A/B ring system of CA4, figure 26. Substituents and modifications introduced onto the ethylene bridge include amide (**38**)[109], methyl (**40**)[110], fluoro (**39**)[111] and aryl groups (**41**)[112].

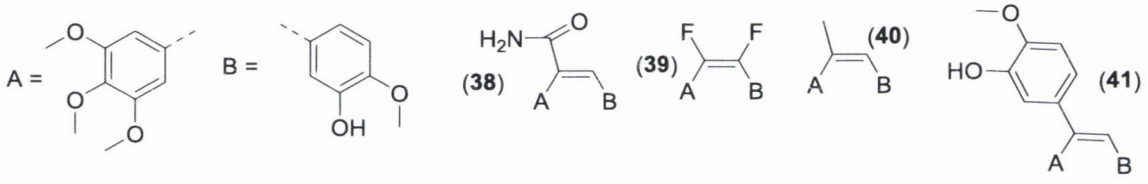


Figure 25: Double bond substituted combretastatins

By using alternative scaffold cores, more elaborate combretastatin anlogues have been synthesized e.g. tetrazole analogues (**42**)[79], combretazolones (**43**)[113], benzo[*b*]thiophene analogues (**44**)[114], thiophene analogues (**45**)[115], indole analogues (**46**)[116], furan analogues (**47**)[117], 3,4-diaryl-2(5*H*)-furanone analogues (**48**)[118], combretocyclopentenones (**49**)[119], pyridine analogues (**50**)[120], combretafurazans (**51**)[121], pyrrole analogues (**52**)[122], chromone analogues (**53**)[123], isoxazole analogues (**54**)[124], indanone analogues (**55**)[125], 1,2,3-thiadiazoles (**56**)[126], furo[2,3-*d*]pyrimidin-2(1*H*)-one analogues (**57**)[127], pyrrole-2,5-dione analogues (**58**)[128], pyrazolone analogues (**59**)[129], benzoxepin analogues (**60**)[130], β-lactam analogues (**62**)[131], cyclopentene analogues (**61**)[132] and 3,4-diaryl squaric acid analogues (**63**)[133].

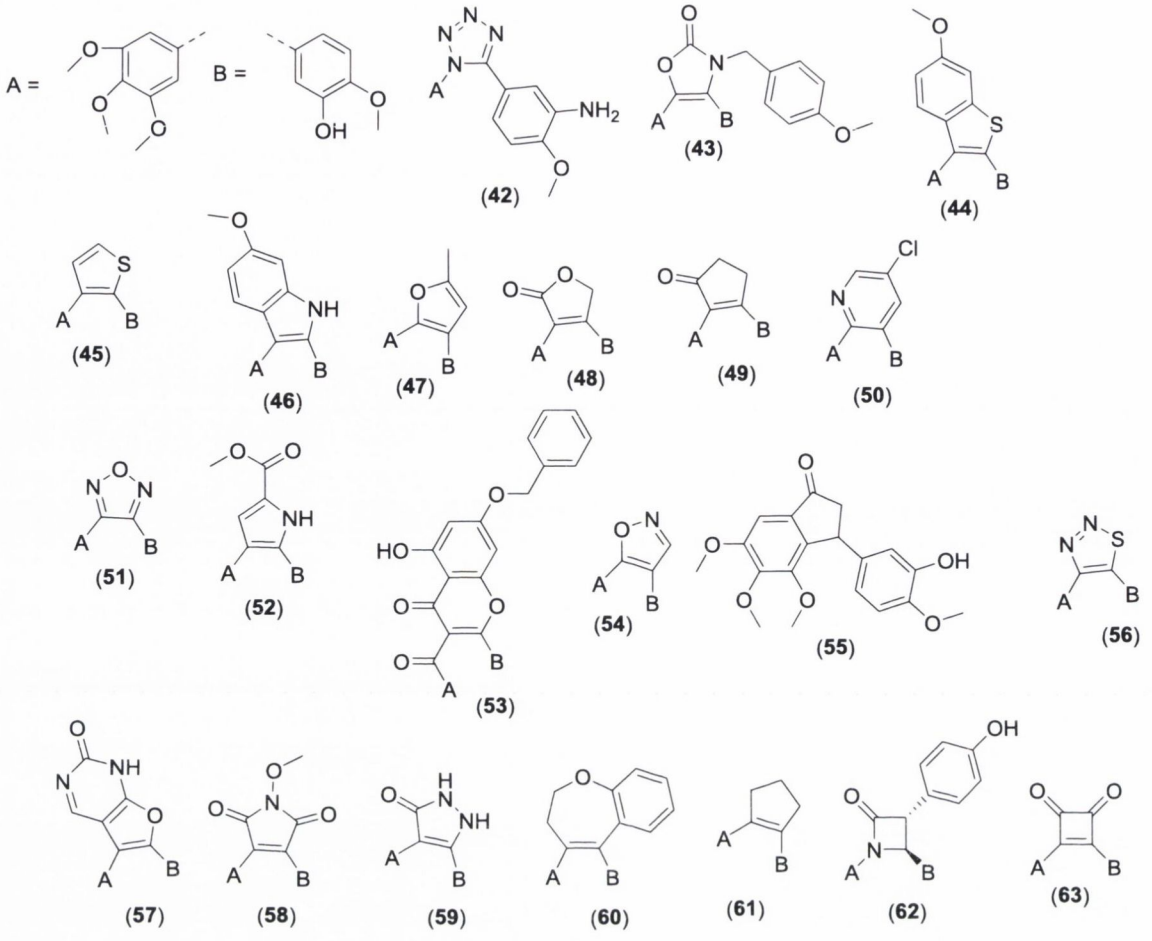
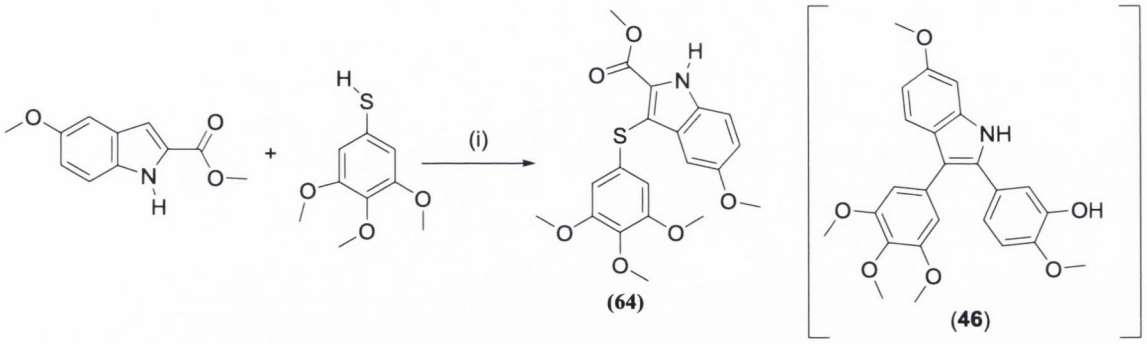


Figure 26: Combretastatin anlogues with novel cyclic scaffold cores

As seen from figure 26, the indole scaffold (**46**) was used to design combretastatin analogues. This scaffold is significant as the compound initially identified by *Knox et al*[1] to illustrate the commonalities between a Hsp90 inhibitor, bearing a 3',4',5-trimethoxyphenyl moiety, was the 3-arylthioindole compound (**64**), figure 27. These commonalities initiated the search to identify a single molecule that would inhibit both Hsp90 and tubulin, section 1.8. In terms of activity, an IC_{50} value of 2 μM was measured for (**64**) for the inhibition of tubulin polymerization and it inhibited colchicine binding by 93 %. When assayed in MCF-7 cells, an IC_{50} of 13 nM was recorded. (**64**) was synthesized by *Martino et al* who were investigating arylthio/sulfonylindoles as potential inhibitors of tubulin polymerization[134].



(i) -78°C, N-chlorosuccinimide, CH_2Cl_2

Figure 27: Synthesis of (64)

1.6 Heat Shock Protein 90: A Molecular Chaperone

When cells are exposed to heat or other environmental stresses, a rapid increase in stress proteins/heat shock proteins occurs. Some of these proteins are molecular chaperones that defend against proteotoxic damage and guard against undesirable misfolding and promiscuous interactions with other cell proteins[135]. Amongst the most important of these heat shock proteins is heat shock protein 90, Hsp90. In unstressed conditions, Hsp90, along with a host of other co-chaperones, is responsible for the correct late stage folding, stability, regulation, maintenance and degradation of proteins[135]. The most interesting aspect of Hsp90 is its list of client proteins, many of which are oncogenic proteins. These client proteins include kinases, steroid hormone receptors and transcription factors. Hsp90 assists in the folding of these proteins, aids the translocation of proteins to their correct intracellular location and when proteins become damaged, facilitates their folding or directs them to proteasomal degradation[136], figure 28[137] & table 2[138].

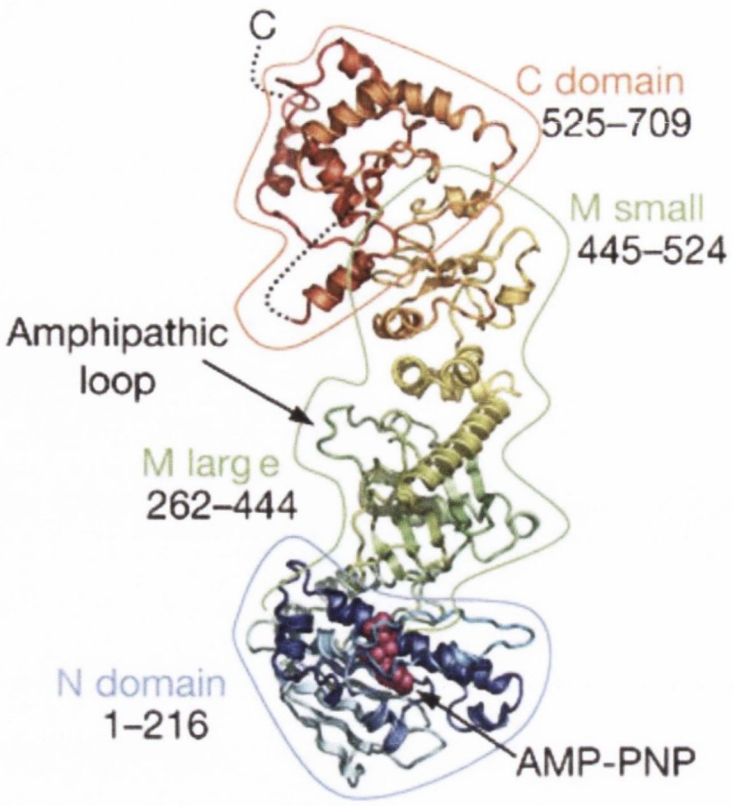


Figure 28: Structure of Hsp90

Table 2: A selection of Hsp90 client proteins, their mechanism of action and cancers associated with these client proteins

Class of protein	Client protein or interacting protein of Hsp90	Mechanism of action of client protein	Associated cancers
Receptor tyrosine kinase	EGFR mutant ErbB2/HER-2 Kit	Activation of downstream pro-survival pathways	NSCLC and globlastama Breast cancer GIST
Signaling molecules or kinases	AKT	Activation of pro-survival proteins and suppression of proapoptotic proteins	Various cancers
Transcriptional factors	HIF-Iα ERα-receptors	Promoting angiogenesis Regulating genes involved in cellular proliferation	Renal cancer Breast cancer

1.6.1 Origins of Heat Shock Response and Hsp90

The existence of heat shock proteins was first noted by Ferruccio Ritossa in 1962[139]. Ritossa was experimenting with *Drosophila*, examining nucleic acid synthesis in puffs of the salivary glands of this organism. When the cells were accidently placed at the wrong temperature,

Ritossa noticed the development of new chromosomal puffs. Upon repeating the experiments, using different *Drosophila* species and exposing the cells to anaerobic conditions and to dinitrophenol and salicylate (uncouplers of ATPase), the same new genes were activated[140]. Ritossa hypothesised that this cellular response was directly correlated with energy production. However his findings were initially dismissed by the scientific community. This phenomenon, called heat-shock response, was also investigated by *Tissieres et al*[141] and *McKenzie et al*[142] using the salivary glands and other tissues from *Drosophila melanogaster*. When *Drosophila melanogaster* tissue culture cells were subjected to heat treatment, drastic changes in the pattern of protein synthesis and the size distribution of polysomes were observed.

1.6.2 Establishment of Hsp90 as a credible therapeutic target

There was considerable scepticism in the scientific community towards the initial proposal that Hsp90 was a useful target for drugs. It was believed that inhibition of Hsp90 would be unfeasible as it was critical to the survival of both normal and malignant cells. Dr. Susan Lindquist, who has been described as a pioneer in the study of protein folding[143], recognized the potential link between Hsp90 and cancer. However in 1992, when she shared this idea at her college's intellectual-property office, the then intellectual-property project manager called Lindquist's idea as "ridiculous" as it arose from experiments in yeast[144].

It is now known that while normal cells are dependent on Hsp90, tumour cells may be more dependent and they express higher levels of Hsp90 than normal cells[136, 145]. Geldanamycin, a natural product Hsp90 inhibitor, and 17-allyaminogeldanamycin, a related analogue, were found to exhibit a 100 fold higher affinity for Hsp90 derived from tumour cells over Hsp90 from normal cells[146]. The difference in affinity is due to the Hsp90 in tumour cells which is present in a highly active complexed state and has a high ATPase activity. As mentioned earlier, Hsp90's client protein list is quite extensive and furthermore a large number of these client proteins are involved in the regulation of all the phenotypic hallmark features of the cancer cell e.g. resistance to apoptosis, invasion/metastasis[147]. Hsp90 inhibition would result in simultaneous combinatorial elimination of multiple oncogenic proteins, blockade of a plethora of cancer associated pathways and a broad attack on all of the biological features of the malignant cell[148, 149]. It is this multifarious action that makes Hsp90 such an exciting therapeutic target for the treatment of cancer[145].

1.6.3 Structure and isoforms of Hsp90

Hsp90 consists of three flexibly linked domains. The ATP binding site is situated in the *N*-terminal domain, a middle domain regulates the ATPase activity of the *N*-terminal and binds client domains while the C-terminal contains the dimerization domain[150, 151]. The understanding of the conformation of the ATP-binding site's location was aided by X-ray structural studies on Hsp90.

Five isoforms of Hsp90 have been identified. Hsp90α and Hsp90β are the two major cytoplasmic forms and share 85% sequence identity at protein level. The other isoforms are glucose related protein 94 (GRP94) in the endoplasmic reticulum, THF-receptor association protein 1 (TRAP1) in the mitochondria and the recently discovered Hsp90N[152]. Hsp90N is different to the other four isoforms as they all possess the three domains and hydrolyse ATP, but at different rates. Studies have shown that selective inhibition of these isoforms is possible. Radicicol, a natural product Hsp90 inhibitor, binds to all Hsp90 iosforms except for Hsp90N. However the binding to other four isoforms is not equal and there is a 5 and 10 fold greater affinity for Hsp90α and Hsp90β respectively compared to GRP94 and TRAP1.

1.6.4 The ATPase activity of Hsp90

Hsp90 is a dimer, with each dimer consisting of three domains mentioned earlier. The dimer subunits are joined by their C-terminal domains, figure 29. For the Hsp90 chaperone client protein cycle to proceed, the association and dissociation of several co-chaperones are required which regulate the cycle. For instance AHA1 stimulates the ATPase activity whereas CDC37 inhibits the ATPase activity. p23 stabilizes the dimerized form of Hsp90 before ATP hydrolysis while HOP inhibits *N*-terminal dimerization. ATP binding leads to the dimerization of the N-terminal domains, forming the Hsp90 molecular clamp. The compaction of the Hsp90 dimer occurs causing the individual subunits to twist around each other. After the hydrolysis of ATP to ADP, the Hsp90 monomers separate *N*-terminally. The once bound substrate i.e. client protein is now activated and released, figure 29. Hsp90 inhibitors such as geldanamycin act as nucleotide mimetics, inhibiting the ATPase function of Hsp90 and thus blocking the formation of the mature complex[153].

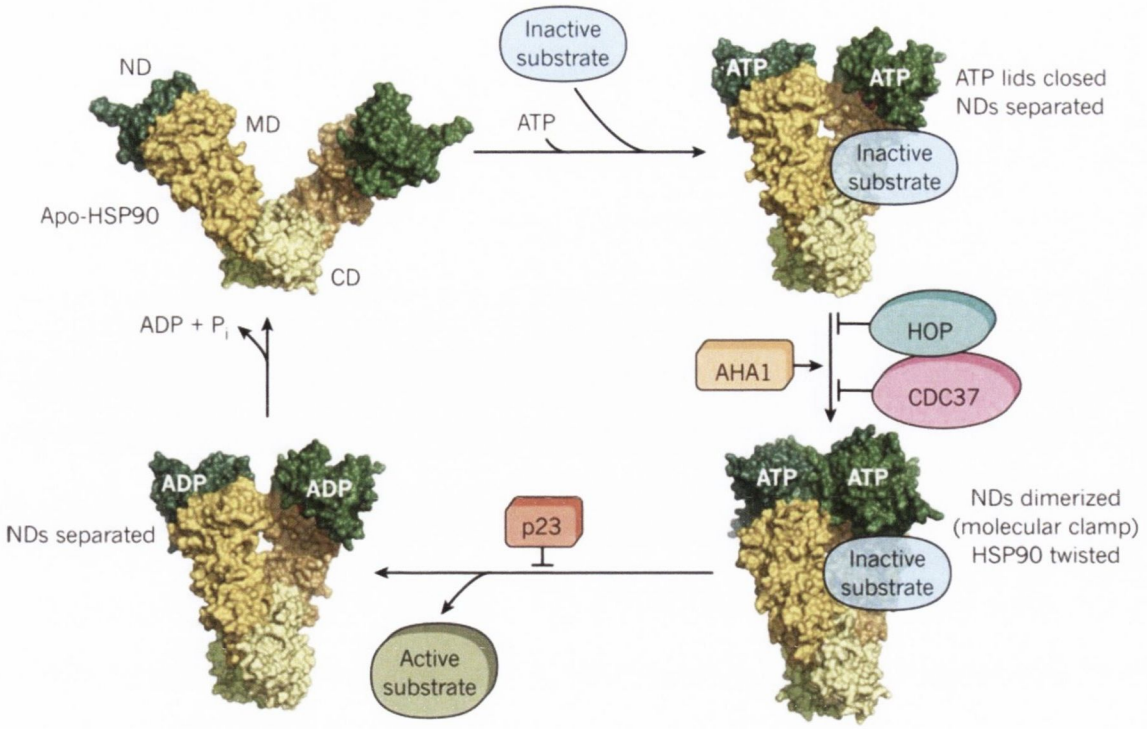
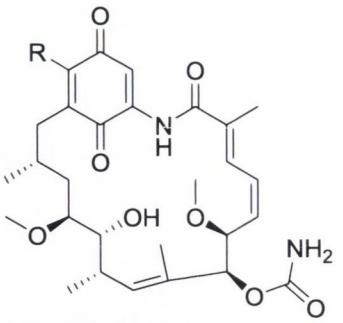


Figure 29: ATPase cycle of the Hsp90 chaperone system

1.6.5 Heat Shock Protein 90 Inhibitors

1.6.5.1 Natural product inhibitors – Geldanamycin and analogues

The first known Hsp90 inhibitor was the ansamycin antibiotic geldanamycin, figure 30. It was first isolated from the organism *Streptomyces hygroscopicus* var *geldanus* in 1970[154]. It was originally thought that geldanamycin was a kinase inhibitor[155] but *Whitesell et al* revealed that geldanamycin inhibits the association of the Hsp90 and v-Src oncogene, which suggested that Hsp90 plays an integral part in oncogenic transformation[156]. X-ray crystallographic studies demonstrated that geldanamycin inhibits Hsp90 function by interacting with the N-terminal ATP-binding domain of Hsp90 resulting in the proteasomal degradation of several oncogenic client proteins. Geldanamycin binds in the ATP pocket adopting a folded C-shape conformation, enabling it to mimic the natural bound nucleotide[157].



Geldanamycin R = OCH_3
17-AAG R = $NHCH_2CH{=}CH_2$
17-DMAG R = $NHCH_2CH_2N(CH_3)_2$

Figure 30: Geldanamycin, 17-AAG and 17-DMAG

In the NCI 60 human cancer cell line panel, geldanamyicn demonstrated broad activity[158] but early clinical trials were discontinued due to severe hepatotoxicity[159]. Since geldanamycin showed great promise, research focused on the development of analogues with reduced toxicity. Studies performed by *Schnur et al*[160, 161] looked at alternative substituents to the 17-methoxy group in geldanamycin, as it could be easily replaced. One of these analogues, 17-AAG, was less toxic than geldanamycin and displayed similar cellular effects. There was significant interest in the effects of 17-AAG on tumour cell progression. Human breast cells with high levels of ERBB2, were shown to be sensitive to 17-AAG. In SK-BR-3 human breast cells, an IC_{50} value of 31 nM for the depletion of ERBB2 was recorded. In the same study, differentiation of breast cancer cells by 17-AAG was observed[162, 163]. In Phase I clinical trials, 17-AAG showed a response in prostate cancer, breast cancer and in multiple myeloma[164, 165]. Following these results, it entered several Phase II clinical trials in metastatic kidney, melanoma and refractory advanced breast cancers and more recently it had entered Phase III clinical trials for replased-refractory multiple myeloma[166]. However these trials are now closed and there is no active 17-AAG trial at present. Problems associated with 17-AAG include limited solubility, polymorphic metabolism by cytochrome P450 CYP3A4[167] and various toxic side effects such as hepatotoxicity[168].

Another analogue of geldanamycin, 17-DMAG, was developed by the NCI and Kosan Biosciences. The 17-methoxy group of geldanamycin is replaced with dimethylethane-1,2-diamine substituent affording 17-DMAG. In comparison to 17-AAG, 17-DMAG had similar biological activity and more importantly due to its greater solubility, formulation was not an issue[169, 170]. 17-DMAG is currently in phase I clinical trials for metastatic or unresectable solids tumours or lymphomas[31].

1.6.5.2 Natural product inhibitors - Radicicol and analogues

Radicicol, also known as monorden[171], is also a natural product Hsp90 inhibitor, figure 31. Radicicol is a macrocyclic antibiotic, originally isolated from the fungus *Monosporium bonordenin* 1953[172]. Radicicol was shown to compete with GA for binding to Hsp90, suggesting that it also binds to the N-terminal domain, inhibiting the ATPase cycle[173]. This result was in contrast to earlier suggestions that radicicol behaved as a kinase inhibitor[174]. *Roe et al* firmly established that radicicol binds to Hsp90 by releasing a crystal structure of radicicol bound to Hsp90[157]. Despite having promising *in vitro* activity, radicicol was inactive *in vivo* due to its instability in serum. This instability was attributed to its reactive epoxide moiety and the ability of the dienone to behave as a Michael acceptor, resulting to reaction with a variety of biological nucleophiles[175].

Soga et al[176] synthesised a series of oxime derivatives (**65**) of radicicol in order to avoid the Michael acceptor problems. The chemical liability is removed as oximes are significantly less electrophilic than the parent ketones. These oxime derivatives possessed excellent anti-tumour activity in human tumour xenografts[175]. The clinical development of oxime derivatives has not progressed due to toxicity to the eye[177].

The replacement of the epoxide motif in radicicol with a cyclopropane ring (**66**) was reported by *Yamamoto et al*[178]. These compounds displayed good anti-proliferative activity. *Day et al* reported a series of novel resorcylic acid macrolactams (**67**)[179]. It was hypothesized that the replacement of the lactone unit with a lactam unit would result in compounds that were more metabolically stable. Hsp90 inhibition was still retained with the macrolactams and protein crystallography showed that (**67**), the most potent compound from the series, opened a hydrophobic pocket in the *N*-terminal ATP site by displacing the loop between Leu93 and Lys98. Even though this effect was seen previously with synthetic small molecule Hsp90 inhibitors, it is unique for radicicol based chemical class of inhibitors[179].

The discovery of radicicol and the subsequent synthesis of radicicol analogues have not yielded a candidate compound suitable for clinical trials. However two synthetic Hsp90 inhibitors, containing the resorcinol motif, (**68**)[180] and (**69**)[181] are in clinical trials. When (**69**) was investigated in both *in vitro* and *in vivo* GIST models, (**69**) inhibited the proliferation of imatinib-sensitive (GIST882, GIST-T1) and -resistant (GIST430, GIST48) cell lines, including those resistant to the geldanamycin analogue Hsp90 inhibitor, 17-AAG[182].

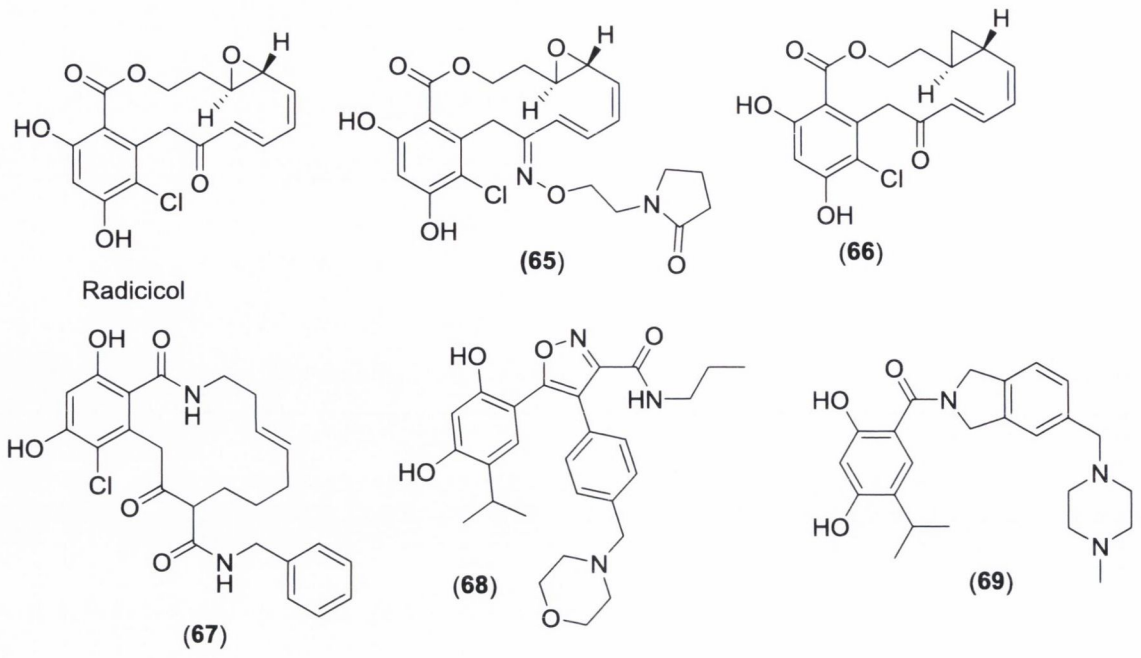


Figure 31: Radicicol, Radicicol analogues and Hsp90 inhibitors containing the resorcinol motif

1.6.5.3 Synthetic Hsp90 Inhibitors

Two different scaffolds have emerged in the development of small molecule Hsp90 inhibitors. These are the purine scaffold and the resorcinol pyrazole scaffold. Small molecules featuring other heterocyclic moieties have been also identified as Hsp90 inhibitors.

1.6.5.4 Purines

Chiosis et al used the structure of the co-crystals of Hsp90 and it ligands (geldanamycin, radicicol and adenine nucleotides) to facilitate the design of a novel compound that would interact with the Hsp90 nucleotide binding pocket. The study of co-crystals revealed that a number of factors had to be considered in the design of this novel Hsp90 ligand[183]. Figure 32 shows the following key ligand interactions for geldanamycin bound to Hsp90:

- a key interaction between the inhibitor and the Asp93/Ser52 at the base of the pocket
- interactions at the top of the pocket involving Lys112, Lys58 and hydrogen acceptor functionalities on the inhibitor
- an hydrophobic pocket that lies midway in the binding site and that is constituted by Met98, Val150, Leu107, Leu103, Phe138 and Val186 (the amino acid numbering as in human Hsp90α).

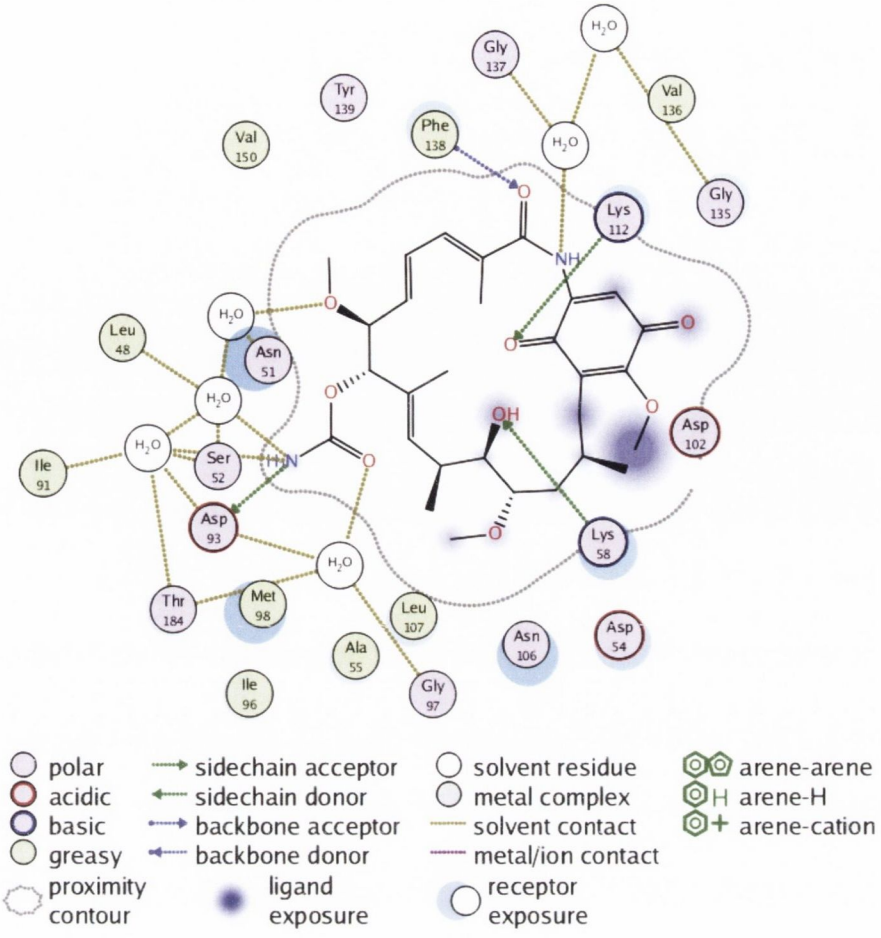
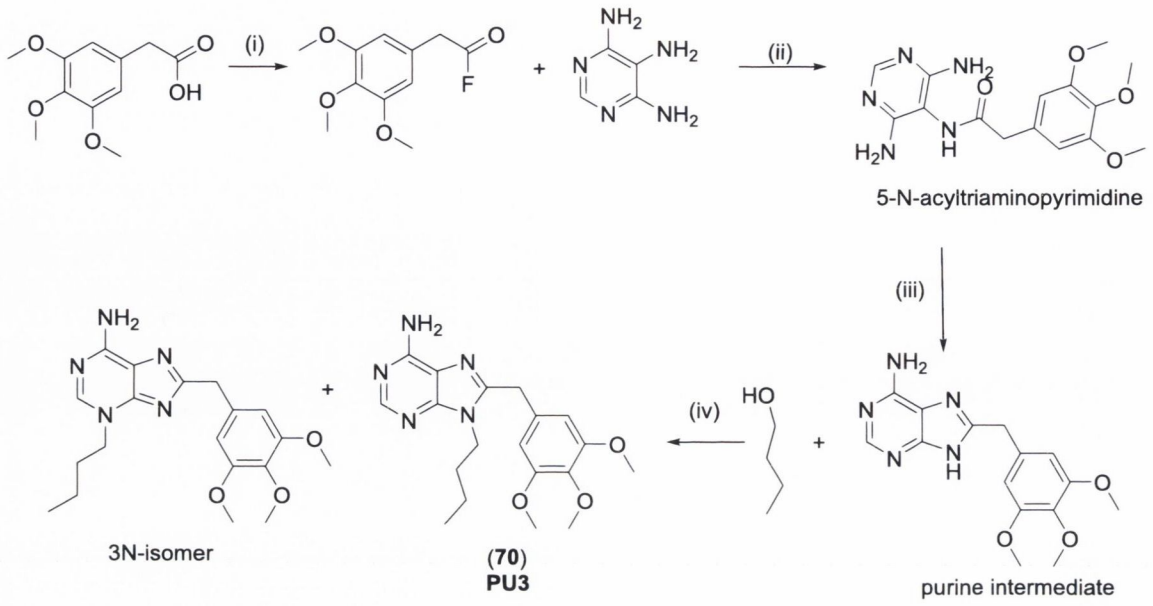


Figure 32: Ligand interaction for geldanamycin bound to Hsp90[183]

This structure based modelling approach identified the purine containing molecule, PU3 (**70**), figure 33. (**70**) competed with geldanamycin with a relative IC_{50} value of 15-20 μM. PU3 causes the degradation of HER kinases, estrogen receptor and Raf kinase, which are known client proteins of Hsp90. Even though (**70**) was less potent than geldanamycin, it had improved water solubility and could be easily synthesised[183]. (**70**) was prepared as follows, figure 32: 3,4,5-Trimethoxyphenylacetic acid is treated with cyanuric fluoride affording 2-(3,4,5-trimethoxyphenyl)acetyl fluoride which is reacted with 4,5,6-triaminopyrimidine affording the desired 5-*N*-acyltriaminopyrimidine intermediate. Cyclisation of the 5-*N*-acyltriaminopyrimidine intermediate using sodium methoxide yields the purine intermediate which then alkylated using Mitsunobu methodology which then affords both the desired 9-*N* alkylated purine (**70**) and the 3-N alkyl isomer. As seen from figure 33, (**70**) contains a 3',4',5'-trimethoxyphenyl moiety which is commonly associated with compounds which bind to the colchicine active site of tubulin. The occurrence of the 3',4',5'-trimethoxyphenyl moiety in the

Hsp90 inhibitor (**70**) initiated the research by *Knox et al*[1] to identify a single molecule that would inhibit both Hsp90 and tubulin.



(i) cyanuric fluoride, pyridine, CH_2Cl_2 (ii) Pr_2NEt, DMAP (iii) NaOMe, MeOH (iv) PPh_3, DEAD, toluene/DCM

Figure 33: Synthesis of (70)[184]

The identification of (**70**) as a novel Hsp90 inhibitor directed the development of the purine scaffold in the search of more potent analogues[185]. *Chiosis et al* investigated the purine scaffold (**71**), figure 34. From the SAR of the 70 analogues that were synthesised in the study by *Chiosis et al*[185], (**73**) was found to the most potent and was 30-fold more active than (**70**). It also displayed binding to Hsp90 comparable to 17AAG. (**73**) induces the degradation of Her2 tyrosine kinase and when assayed in the MCF-7 breast cancer cell, an IC_{50} value of 2 μM was measured. (**73**) was shown to have a 10 to 50 times higher affinity for tumour Hsp90 compared for Hsp90 from normal cells and when assayed against various cancer types (breast, prostate, colon etc.), submicromolar antiproliferative potency was measured[186].

The purine scaffold was also used by other research groups for the development of synthetic Hsp90 inhibitors. *Llauger et al* reported libraries of 8-arylsufanyl, 8-sulfoxyl and 8-sulfonyl adenine derivatives[187]. The most potent compound, (**74**), had an IC_{50} of 30 nM for binding to Hsp90. It was also extremely more selective for tumour versus normal cells. The Biogen Idec research group synthesised a series of 2-amino-6-halopurine derivatives[188]. From this series, (**72**) is currently undergoing phase II clinical trials for gastrointestinal stromal tumors (GIST)[189, 190]. When assayed in cancer cell lines that were 17-AAG resistant e.g. H295R

(adrenal), T47D (breast), IE8 (AML), it was more potent than 17-AAG. The success of (**72**) directed the development of second generation Hsp90 inhibitors by Biogen Idec[191]. The replacement of substituents R_1 – R_6 and the replacement of atoms X and Y with carbon in scaffold structure (**76**), figure 34, caused a drop in potency. They decided to use a pyrrolo[2,3-*d*]pyrimidine scaffold which allowed the retention of the important functional groups of (**72**). From this set of compounds, (**75**) was identified as being the most potent. (**75**) was more potent than (**72**) *in vitro* and *in vivo*. In an Hsp90 binding assay, (**75**) had an IC_{50} value of 1.1 nM versus an IC_{50} value of 5.5 nM for (**72**) and inhibited tumour growth *in vivo*.

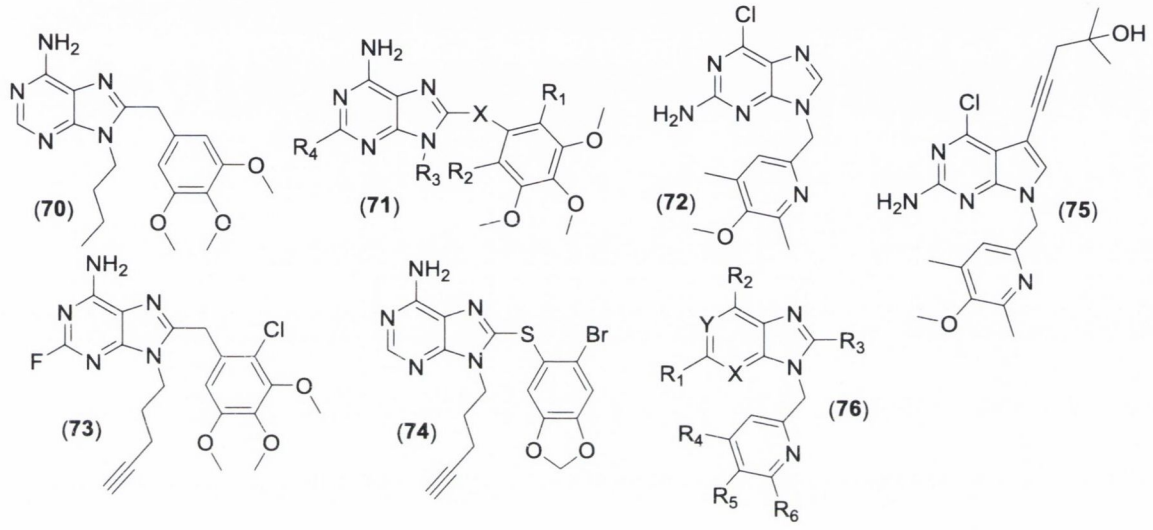


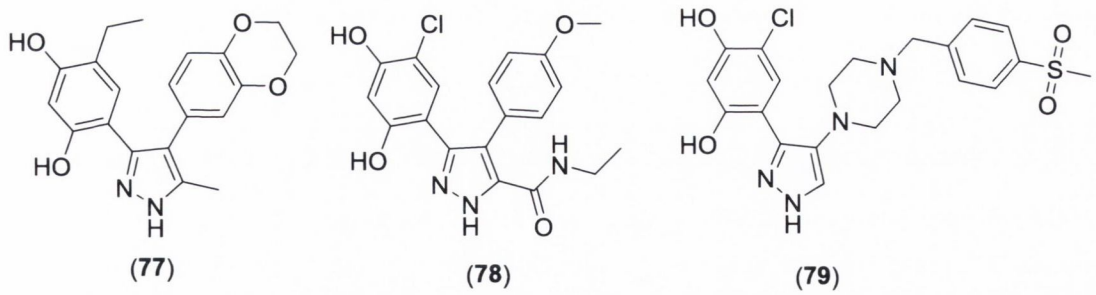
Figure 34: Purine based Hsp90 inhibitors

1.6.5.5 Pyrazoles

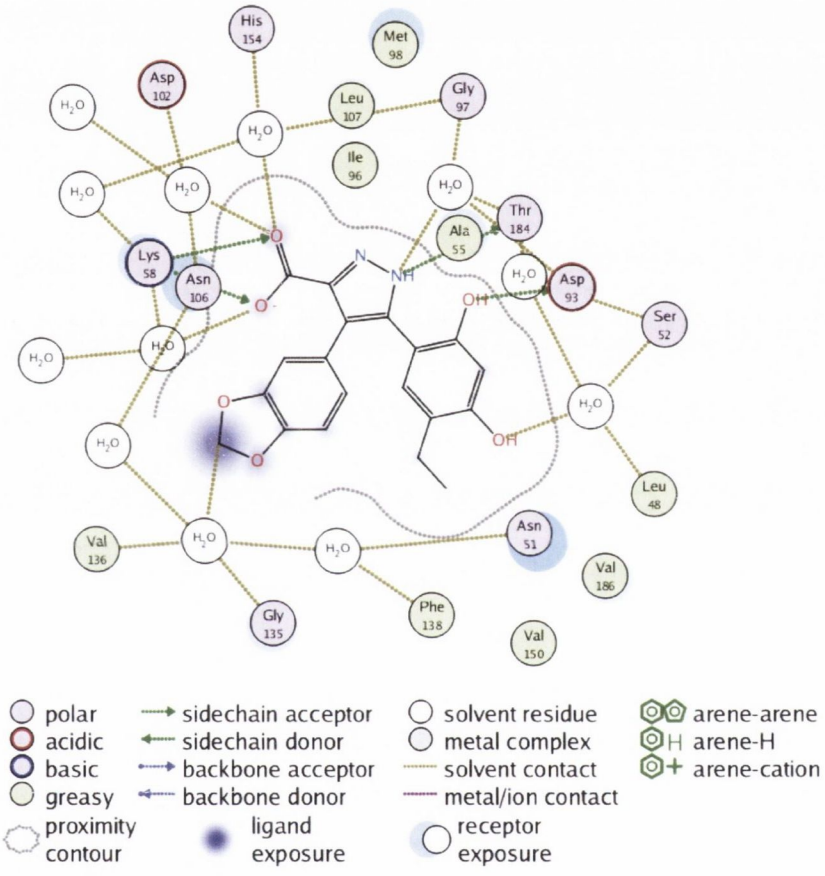
A high-throughput screen was developed by *Rowlands et al* to identify small-molecule inhibitors of Hsp90 ATPase activity that could be developed as therapeutic agents with improved pharmacological properties. *Rowlands et al*, using a colorimetric malachite green assay, screened ~56,000 compounds to screen for inhibitors of yeast Hsp90 ATPase[192]. The most potent compound, (77), had an IC_{50} value of 8.9 μM (figure 35). In the same assay, geldanamycin and 17-AAG recorded IC_{50} values of 4.8 μM and 8.7 μM respectively. (77) is comprised of three different heterocyclic rings: a resorcinol ring, a pyrazole ring and a benzodioxan ring. The resorcinol ring has observed in Hsp90 inhibitors such as radicicol and related analogues. A series of closely related analogues of (77) were synthesised by the same research group to provide structure activity relationship information[193].

The knowledge from this exercise was used in conjunction with information gained from the X-ray crystal structure of (**77**) bound to the N-terminal domain of human Hsp90[194]. It was hypothesised that additional hydrogen bonding interactions could be achieved *via* the 5-position of the pyrazole ring. A series of analogues were then prepared and evaluated. The most potent of these compounds, (**78**), incorporated the structural changes suggested by *Cheung et al*[193]. A chlorine atom now replaced the ethyl group in the 5-position of the resorcinol ring and the dioxan ring was replaced with a methoxy group at the C-4 of the aryl ring. Also a carboxamide group was now included instead of the methyl group in the 5 position of the pyrazole ring. In terms of activity, an IC_{50} value of 0.26 μM was observed in HCT-116 cells while (**77**) displayed an IC_{50} value of 4.1 μM. The X-ray structure of (**78**) bound to the N-terminal domain of human Hsp90α revealed the 5-carboxamide group forms hydrogen bonds with Gly97 and interactions with Lys58[194], thus rationalising the improved binding activity.

The development of further analogues of (**77**) was investigated by the same research group[195]. The substituted aryl at C-4 of the pyrazole ring was replaced with a series of cyclic amines generating piperazinyl, morpholino and piperidyl derivatives. It was hypothesised that this would improve water solubility with minimal impact on potency. The most potent of these products, (**79**), resulted in an IC_{50} value of 3.1 μM in HCT-116 cells and caused depletion of Raf-1 and up-regulation of Hsp70.



(a)



(b)

Figure 35: (a) Rescorinol pyrazole Hsp90 inhibitors and (b) ligand interaction diagram for (77) bound to Hsp90

1.6.5.6 Miscellaneous small molecule Hsp90 Inhibitors

The success of the pyrazole and purine scaffolds intensified the development of alternative novel Hsp90 inhibitors. A number of Hsp90 inhibitors, not based on aforementioned scaffolds, are shown in figure 36. *Barril et al* identified the 1-(2-phenol)-2-naphthol scaffold using a docking based virtual screening method. (**80a**) and (**80b**) were the two most active compounds of this series and exhibited IC_{50} values of 600-700 nM when assayed by the FP competitive

binding assays. However when assayed in HCT-116 cells, they displayed poor antiproliferative activity[196] and the development of this scaffold has not progressed.

Using a combination of fragment based lead discovery, virtual and structure based drug design, *Miura et al* identified a 2-amino-6-(1*H*,3*H*-benzo[*de*]isochromen -6-yl)-1,3,5-triazine compound as a new class of Hsp90 inhibitor[197]. (**81**) showed a high binding affinity for N-terminal Hsp90 and *in vitro* cell growth inhibition against human cancer cell lines e.g. HCT-116 (IC_{50} = 0.46 μM), NCI-N87 (IC_{50} = 0.57 μM). However it had poor water solubility and limited oral bioavailability. In order to improve affinity and physiochemical properties, the transformation of the methyl group on the sulphur atom at the triazine ring was investigated[197]. From these analogues, (**82**) showed improved water solubility and retained affinity. (**82**) reduced the phosphorylation and protein level of multiple Hsp90 client proteins such as EGFR, HER2, Raf1, and AKT. This result indicates that (**82**) inhibits proliferation of cancer cells by inducing degradation of multiple Hsp90 client proteins. (**82**) demonstrated high oral bioavailability in mice and potent antitumor efficacy in a human NCI-N87 gastric cancer xenograft mouse model.

Two different research groups identified the resorcinol isoxazole scaffold for the development of synthetic Hsp90 inhibitors, (**68**)[180] and (**84**)[198]. (**68**) displayed excellent potency against Hsp90 in a FP binding assay with an IC_{50} value of 21 nM. (**68**) inhibited proliferation in wide range of human cancer cell lines e.g. HCT-116 (colon), PC3M (prostate), SF268 (glioma). (**68**) is now in clinical trials for non-small cell lung cancer.

Using a fragment based drug discovery, *Brasca et al* identified the fragment (**85**) as a potential starting point for their research[198] (figure 36). By comparing the crystal structure of (**85**) bound to the ATPase N-terminal domain of Hsp90 with the crystal structures of other known Hsp90 inhibitors, they decided to modify the C-4 position of (**85**) by introducing the isoxazole 3-carboxamide moiety. The aim here was to increase binding affinity through additional interactions with the protein. (**84**) was the most potent of these compounds. It showed nanomolar affinity to Hsp90 and high selectivity towards a panel of kinases. Further investigation of (**84**)[199] shows that it inhibited cell proliferation in range of different cancer cell lines e.g. DU-4475 (carcinoma breast), MOLM-13 (leukemia acute myeloid), A2780 (adenocarcinoma ovary), RKO (adenocarcinoma colon). IC_{50} values in the nanomolar range were obtained for the cell lines that were tested. (**84**) induced tumour shrinkage in different human tumour xenografts and is highly active in models of resistance to kinase inhibitors. Also

it was shown to cross the blood brain barrier which is an uncommon feature of compounds described so far. (**68**) and (**84**) could give rise a new class of synthetic Hsp90 inhibitors based on the resorcinol isoxazole scaffold.

Using fragment based drug design, *Woodhead et al* identified a potent 2,4-dihydroxybenzamide compound (**83**). (**83**) was a potent inhibitor of Hsp90, k_d = 0.54 nM, and when assayed in HCT-116 cells, an IC_{50} value of 31 nM was measured[200]. Further optimisation of this compound was investigated by the same research group[181]. It was discovered that modification of the 2,4-dihydroxybenzamide core, while retaining the isoindoline ring, adversely affected activity. The 2,4-dihydroxybenzamide core was retained while different substituents were introduced onto the isoindoline ring. (**69**) was the most potent of these derivatives with affinity (k_d = 0.5 nM) in binding at the ATPase site at the N-terminus of Hsp90. (**69**) displayed activity against a range of human tumour cell lines and has proceeded into clinical trial development for prostate cancer.

The β-lactam unit was also identified, by the Meegan research group, as a suitable scaffold for the development of synthetic Hsp90 inhibitors[201]. Molecular modelling studies revealed a good overlay between the lead β-lactam (**86**) and the pyrazole containing Hsp90 inhibitor (**77**) and that (**86**) displayed the necessary ligand interactions with Asp93, Phe138 and Thr184. (**86**) was the most potent of the β-lactams that were synthesised with an IC_{50} of 48 μM in MCF-7 cells and an IC_{50} value of 5.63 μM in Hsp90α binding assay.

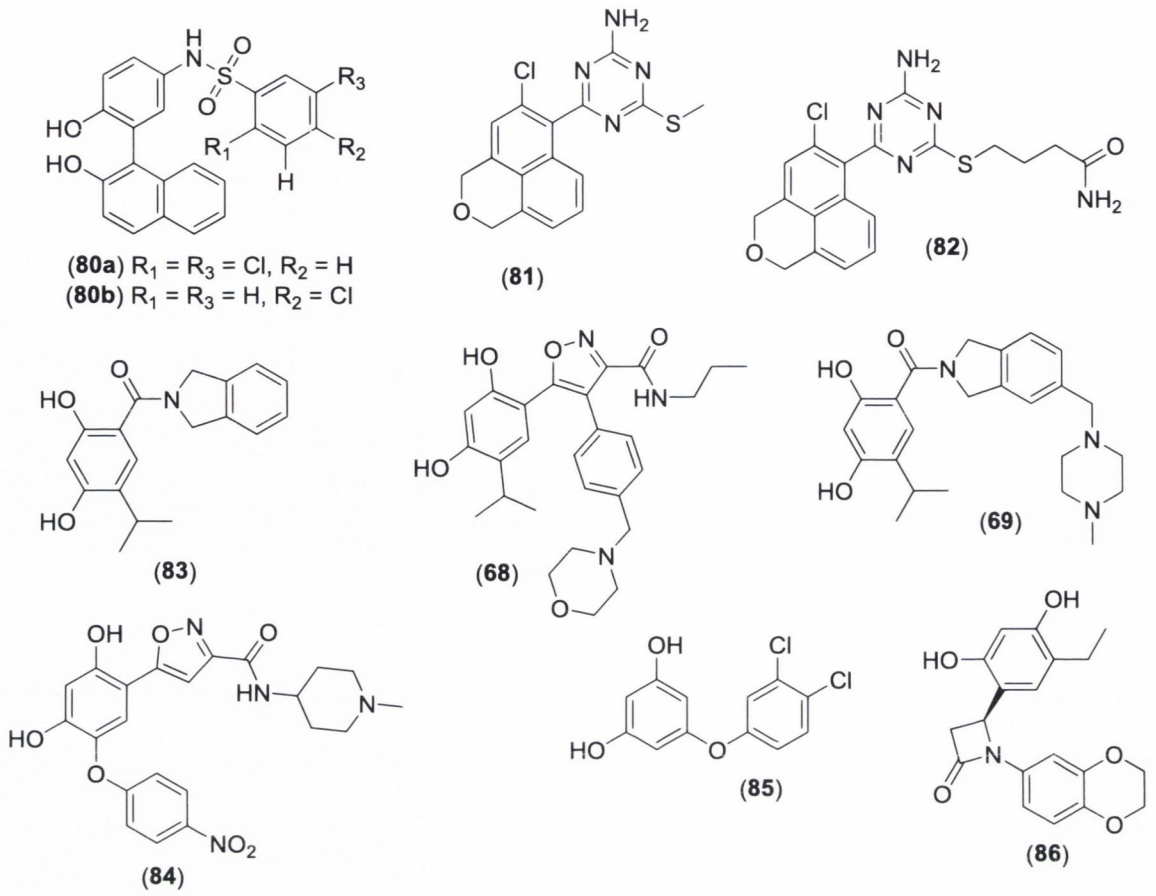


Figure 36: Miscellaneous Hsp90 inhibitors

1.6.5.7 Agents that bind to C terminal/middle domain of Hsp90

Novobiocin, an aminocoumarin-containing antibiotic, binds to the second proposed ATP-binding site in the C terminal domain of Hsp90[202], figure 37. This binding disrupts the interaction of both p23 and Hsp70 co-chaperones with the Hsp90 complex. The ATP binding site in the C terminal domain is involved in the autophosphorylation of Hsp90. When novobiocin was tested *in vitro* and *in vivo*, the results were consistent with Hsp90 inhibition, namely the degradation of client proteins such as erbB-2 and c-Raf occurred[202]. It has been shown that both novobiocin and coumermycin A1, a more potent analogue, have the ability to alter Hsp90's chaperone function and co-chaperone interaction. Another active novobiocin analogue, A4, is reported to deplete wild type and mutant androgen receptors in prostate cancer cell lines[203]. More recently *Zhao et al*, with the aid of molecular modelling studies, identified a scaffold containing a biphenyl moiety *in lieu* of the coumarin ring system found in novobiocin for development of new Hsp90 C-terminal inhibitors[204]. Compound (**87**) was the most potent compound from this series. When assayed in cancer cells lines, SK-BR-3 and MCF-7, IC_{50} values of 1.94 and 0.88 μM respectively were recorded. After treatment of MCF-7 cells with

(**87**), western blot analysis revealed that Hsp90 dependent client proteins Her2, Raf-1 and p-Akt were degraded in a concentration-dependent manner. In contrast to N-terminal inhibitors, C-terminal inhibitors do not induce the pro-survival heat shock response and therefore inhibition of Hsp90 C-terminal function should be more advantageous[205, 206].

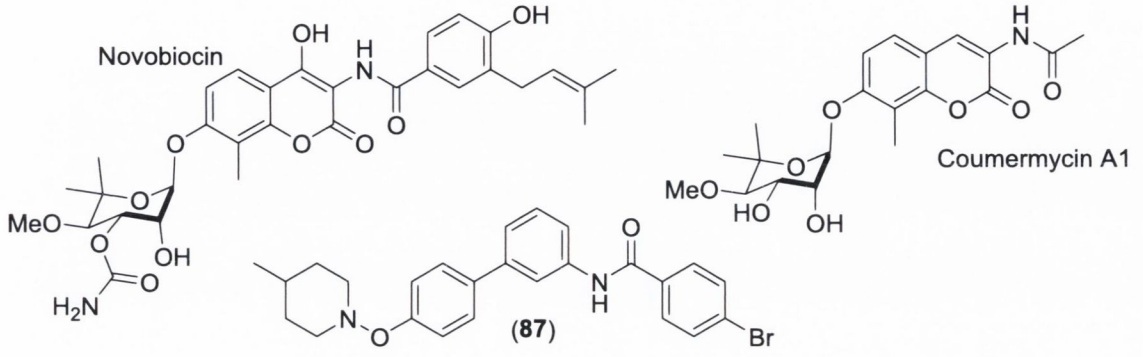
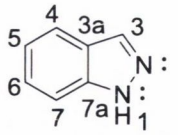


Figure 37: C-terminal/middle domain Hsp90 inhibitors

1.7 Indazole

The lead dual tubulin/Hsp90 binding compound which prompted this thesis project featured an indazole ring (see section 1.8). The indazole scaffold is used extensively in the project for the synthesis of analogues of the lead compound. Indazole is a heterocyclic aromatic organic compound consisting of a benzene ring fused with a pyrazole ring[207], figure 38. Indazole is a basic compound with $pK_a = 1.25$ but is less basic than pyrazole, $pK_a = 2.57$, but stronger NH acid. The following three sections will review naturally occurring indazoles, synthetic methods available to prepare the indazole ring and the chemistry and therapeutic applications of indazoles.



1*H*-Indazole

Figure 38: Structure and numbering of indazole ring

1.7.1 Naturally occurring indazoles

Only four naturally occurring indazole based products have been isolated to date. The first one, Nigellicine, was isolated from the seeds of the *Nigella savita* in 1985[208]. *Atta-ur-Rahman et al* had noted, at the time, that there was no other natural product similar to Nigellicine[208]. Two other naturally occurring alkaloids, with molecular formulas $C_{12}H_{13}NO_2$ and $C_{19}H_{20}N_2O_2$ respectively, were also isolated in limited quantities. Nigellidine had a structure similar to

Nigellicine but instead of a carboxylic acid substituent attached at the imine carbon, it had a *para*-phenol substituent[209], figure 39.

The third naturally indazole alkaloid, Nigeglanine, was isolated from the seeds of the *Nigella glandulifera*[210]. This plant is commonly found in the southwest and western parts of China. Nigeglanine has the same ring system as Nigellicine and Nigellidine but there is no substituent at the imine carbon. The fourth naturally occurring indazole alkaloid, Nigellidine-4-*O*-sulfite, was isolated in 2008[211], again from the seeds of the *Nigella savita*. It is believed that during the extraction process, Nigellidine-4-*O*-sulfite is hydrolyzed to Nigellidine and that Nigellidine-4-*O*-sulfite is the true natural product, not Nigellidine. None of the four indazole alkaloids are in clinical use but the therapeutic properties of both plant species are well documented. The *Nigella glandulifera* plant has been traditionally used as a remedy for colds, cough and insomnia while the seeds are believed to have diuretic, analgesic, spasmolytic and bronchodilator properties[212]. The active components of the *Nigella savita* seed have been shown to have anti-cancer activity[213].

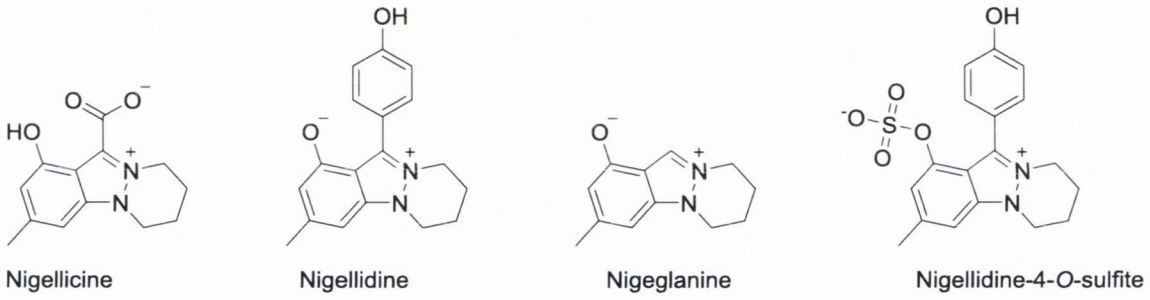
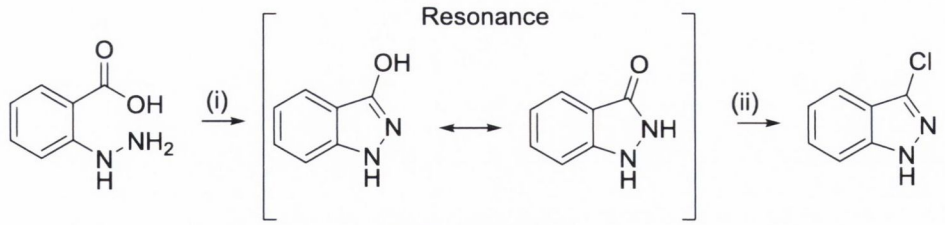


Figure 39: Nigellicine, Nigellidine, Nigeglanine and Nigellidine-4-*O*-sulfite

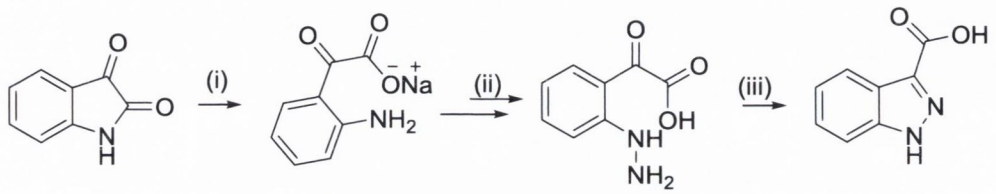
1.7.2 Synthesis of Indazole

Fischer et al reported the synthesis of one of the earliest synthetic indazoles, 3-chloro-1*H*-indazole from 2-hydrazinylbenzoic acid[214]. The reaction first involves refluxing in HCl in order to form 1*H*-indazol-3-ol which is then reacted with phosphorous oxychloride ($POCl_3$) affording the desired product, figure 40. This method was also used by Stephenson[215], where 2-hydrazinylbenzoic acid is first prepared from anthranilic acid. Stephenson also reported the dehalogenation of 3-choroindazole, using red phosphorous and hydrogen iodide, affording indazole. *Snyder et al* reported the one pot synthesis of 1*H*-indazole-3-carboxylic acid from isatin[216]. Isatin was first heated in sodium hydroxide which opened the pyrrolidine-2,3-dione ring of isatin. Subsequent additions of sodium nitrite, sulfuric acid and tin chloride afforded 1*H*-indazole-3-carboxylic acid, figure 41.



(i) HCl, (ii) $POCl_3$

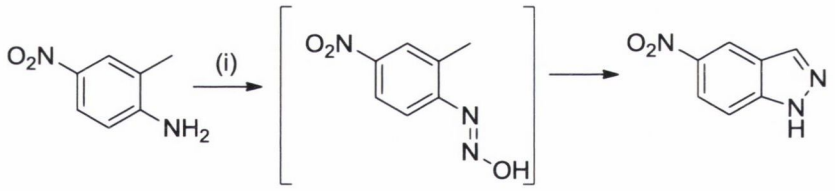
Figure 40: Synthesis of 3-chloroindazole



(i) NaOH (ii) $NaNO_2$ (iii) $SnCl_2$, HCl

Figure 41: Synthesis of 1H-indazole-3-carboxylic acid from isatin

One of the most widely used synthetic methods for indazole synthesis is the diazotization of a suitably substituted 2-methylaniline in protic solvents followed by spontaneous cyclisation. 5-Nitroindazole is synthesized using this method[217] which is limited to 2-methylanilines with either electron withdrawing group on the arene ring or in the alkyl side chain[218]. Indazole and indazole derivatives with electron donating groups cannot be obtained using this method, figure 42.



(i) $NaNO_2$, aq. AcOH

Figure 42: Synthesis of 5-nitroindazole

Huisgen et al reported the synthesis of indazole from 2-methylaniline[219], which is first reacted with acetic anhydride. The acetylated product is then treated with sodium nitrite forming *N*-nitroso-*o*-acetotoluidide. Deacetylation affords the desired indazole product. The synthesis of indazole using this method is referred to as Jacobson indazole synthesis[220]. This method can also be applied to substituted 2-aminotoluenes ($R_1 = CH_3$)[221], ($R_1 = OH$)[222], ($R_1 = I$)[223] , figure 43.

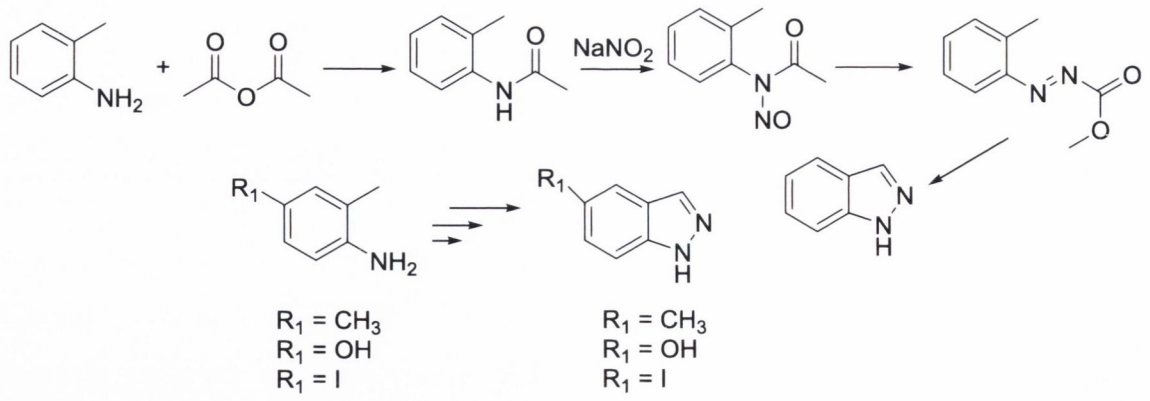
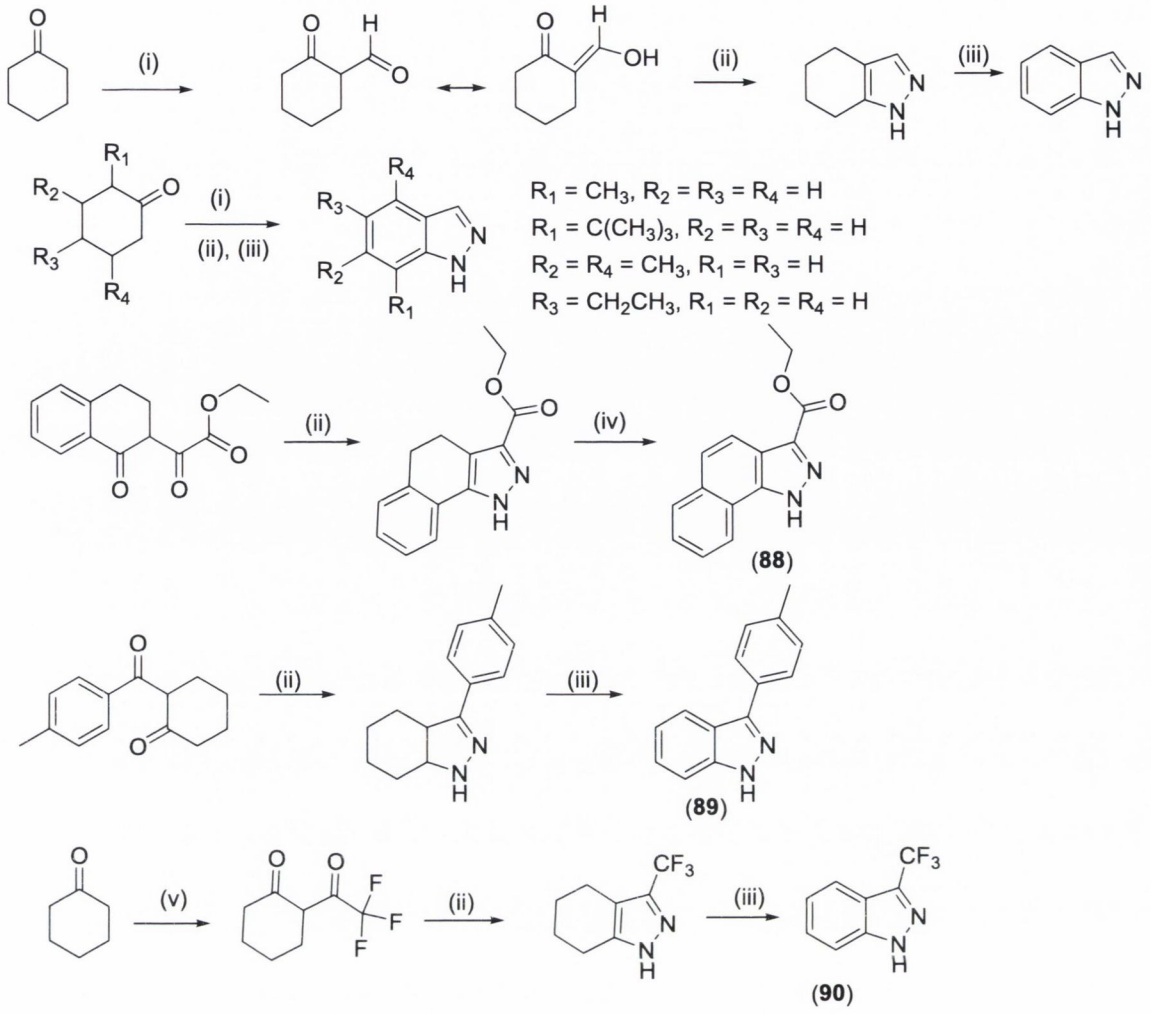


Figure 43: Jacobson indazole synthesis

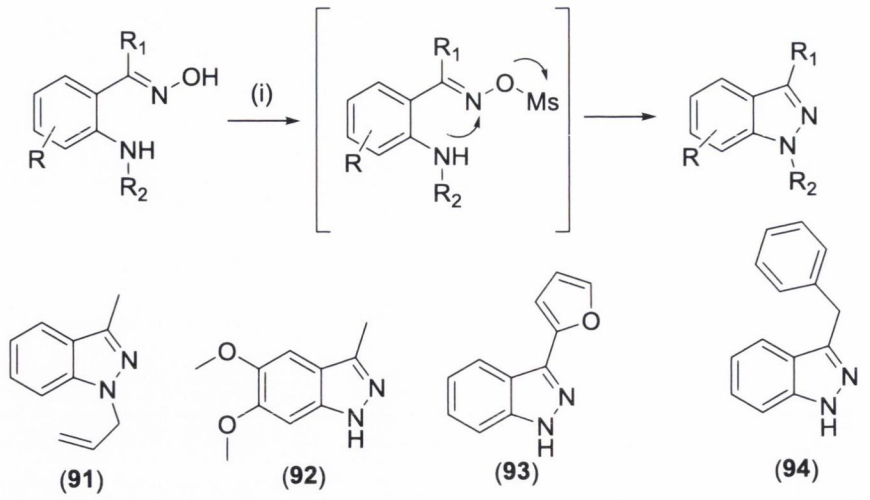
Ainsworth reported the synthesis of indazole from cyclohexanone in 1959[224]. Cyclohexanone is first reacted with ethyl furamate affording 2-oxocyclohexanecarbaldehyde which is then treated with hydrazine to form 4,5,6,7-tetrahydro-1*H*-indazole. In the last step, 4,5,6,7-tetrahydro-1*H*-indazole is heated in the presence of *trans*-decalin and palladium on carbon. This results in the dehydrogenation/aromatization of the cyclohexene ring affording indazole. The same chemistry can be used for alkyl substituted cyclohexanones affording indazole derivatives[225]. Cyclohexanone derivatives with carbonyl substituents in the 2-position generate 3-substituted indazole derivatives (**88**)[226], (**89**)[227, 228], (**90**)[229], figure 44.



(i) NaOEt, ethyl furamate (ii) hydrazine (iii) decalin, Pd/C, reflux (iv) CH_2Cl_2, 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), rt (v) NaH, CF_3CO_2Et

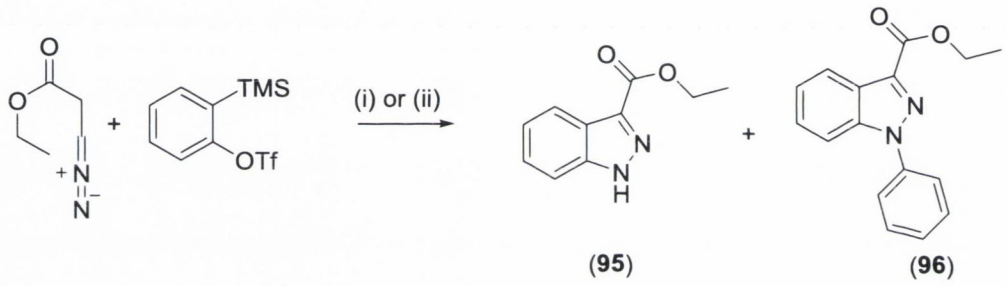
Figure 44: Synthesis of indazole from cyclohexanone

Current research into indazole synthesis has identified methods which do not require harsh reaction conditions[230, 231]. *Counceller et al* obtained a series of indazole derivatives from *o*-aminobenzoximes by the selective activation of the oxime in the presence of the amino group[230], figure 45. It was hypothesized that selective activation of an oxime can occur over an arylamino group, which would then prompt an intramolecular attack onto this activated oxime by the amino group and produce the desired 1*H*-indazole. The combination of methanesulfonyl chloride and triethylamine, using the molar equivalent shown in figure 45, directly formed the desired 1*H*-indazole in a fast and reliable manner. Compounds (**91**) – (**94**) highlight the range of indazole derivatives prepared by *Counceller et al.*



(i) MsCl (1.2 molar eq), NEt_3 (2.0 molar eq), DCM, 0 – 23 °C

Figure 45: Metal-free synthesis of 1*H*-indazole by *Counceller et al*[230]



(i) CsF (4.0 molar eq), 2.4 molar eq of *o*-(trimethylsilyl)phenyl triflate, MeCN, rt (ii) TBAF (1.2 molar eq), THF, -78° C to rt

Figure 46: Reaction used by *Liu et al* to determine optimum reaction conditions

Liu et al synthesised a series of indazole derivatives by the (3+2) cycloaddition of diazo compounds with *o*-(trimethylsilyl)aryl triflates[231], figure 46. *Liu et al* discovered that when ethyl diazoacetate was treated with *o*-(trimethylsilyl)phenyl triflate using reaction conditions (i), (**96**) was the only product afforded in 97% yield. If 2.0 molar eq of CsF and 1.0 molar eq of *o*-(trimethylsilyl)phenyl triflate are used, (**95**) was obtained in 55 % yield and (**96**) in 17% yield. However the reaction was repeated using reaction conditions (ii), (**95**) was obtained in 85 % yield and (**96**) in less than 5 % yield. In the reaction, the corresponding benzyne intermediate is generated *in situ* by the reaction of *o*-(trimethylsilyl)phenyl triflate with the fluoride source, cesium fluoride or tetra-*n*-butylammonium fluoride, figure 47.

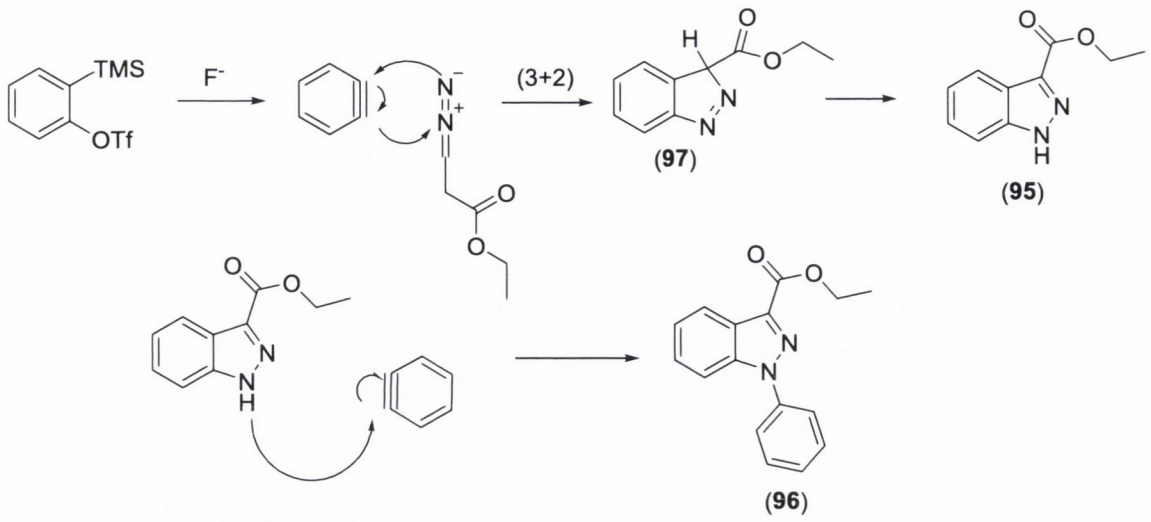
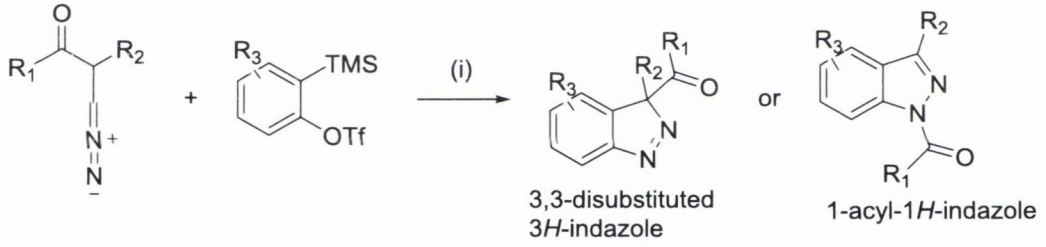


Figure 47: Proposed mechanism for the formation of (94) and (95)[231]

The benzyne reacts with ethyl diazoacetate generating (**97**) which undergoes a 1,3-hydrogen or two 1,5-hydrogen shifts to afford (**95**). If an excess of the benzyne is employed, (**95**) reacts further with the benzyne to afford the N-arylated product (**96**).



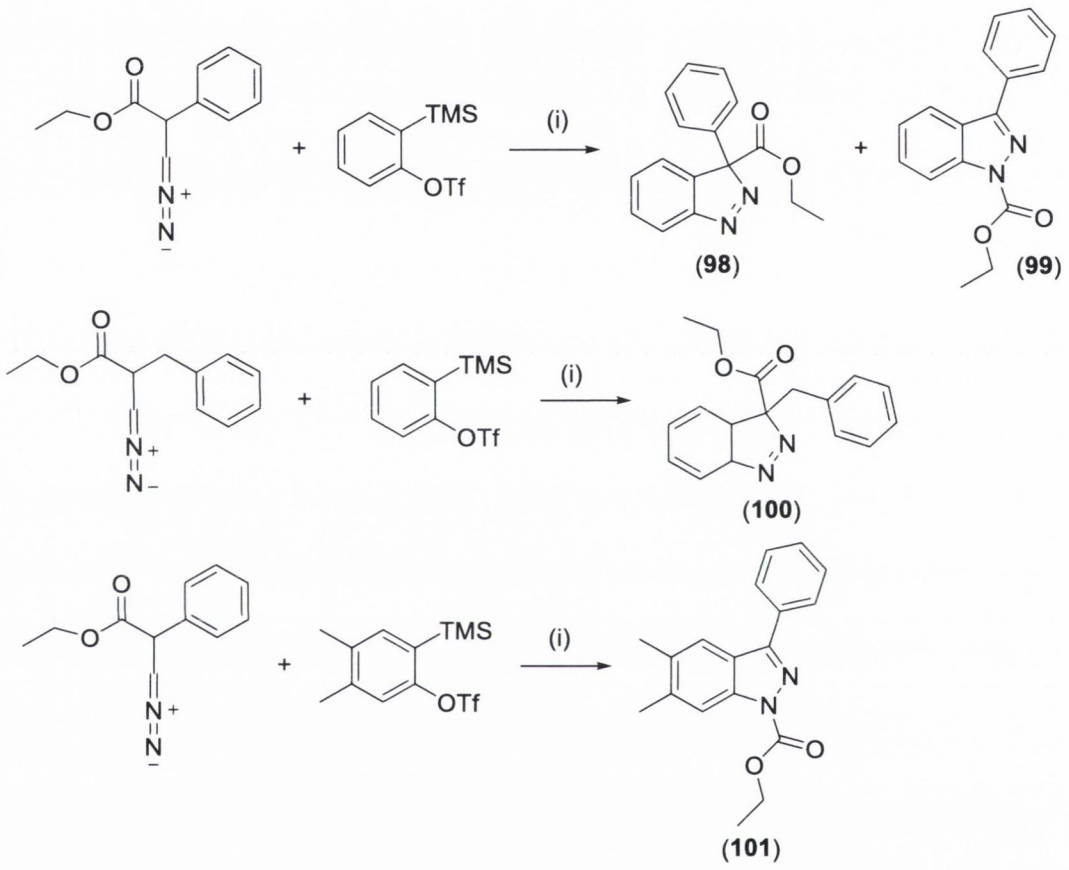
(i) CsF (2 molar eq), MeCN, rt

Figure 48: Cycloaddition with disubstituted diazomethane derivatives and subsequent acyl migration[231]

Liu et al also reacted a series of di-substituted diazo compounds with different *o*-(trimethylsilyl)aryl triflates, figure 48. Since there is no hydrogen on the diazo carbon and hence no hydrogen shift can occur, it was expected that products would be nonaromatized 3,3-disubstituted 3*H*-indazoles. Also if the di-substituted diazo compounds contain an aryl group on the diazo carbon, acyl migration should generate 2-acyl-2*H*-indazoles or 1-acyl-1*H*-indazoles[232], figure 49. However the 2-acyl-1*H*-indazoles was not observed by *Liu et al*. In one case, a mixture of the 3,3-disubstituted 3*H*-indazole (**98**) and 1-acyl-1*H*-indazole (**99**) was obtained while in other examples either the 3,3-disubstituted 3*H*-indazole (**100**) or 1-acyl-1*H*-indazole (**101**) were obtained as the sole product, figure 50.



Figure 49: Acyl migration



(i) CsF (2 molar eq), MeCN, rt

Figure 50: Cycloaddition with disubstituted diazoesters derivatives and subsequent acyl migration[231]

This section has highlighted the extensive research into indazole synthesis which has been performed over the years. Initially harsh condition reactions and high reaction temperatures were required for the preparation of indazole derivatives, figures 40-44. Many examples of the preparation of indazole derivatives using mild reaction conditions are now available, figures 45-50.

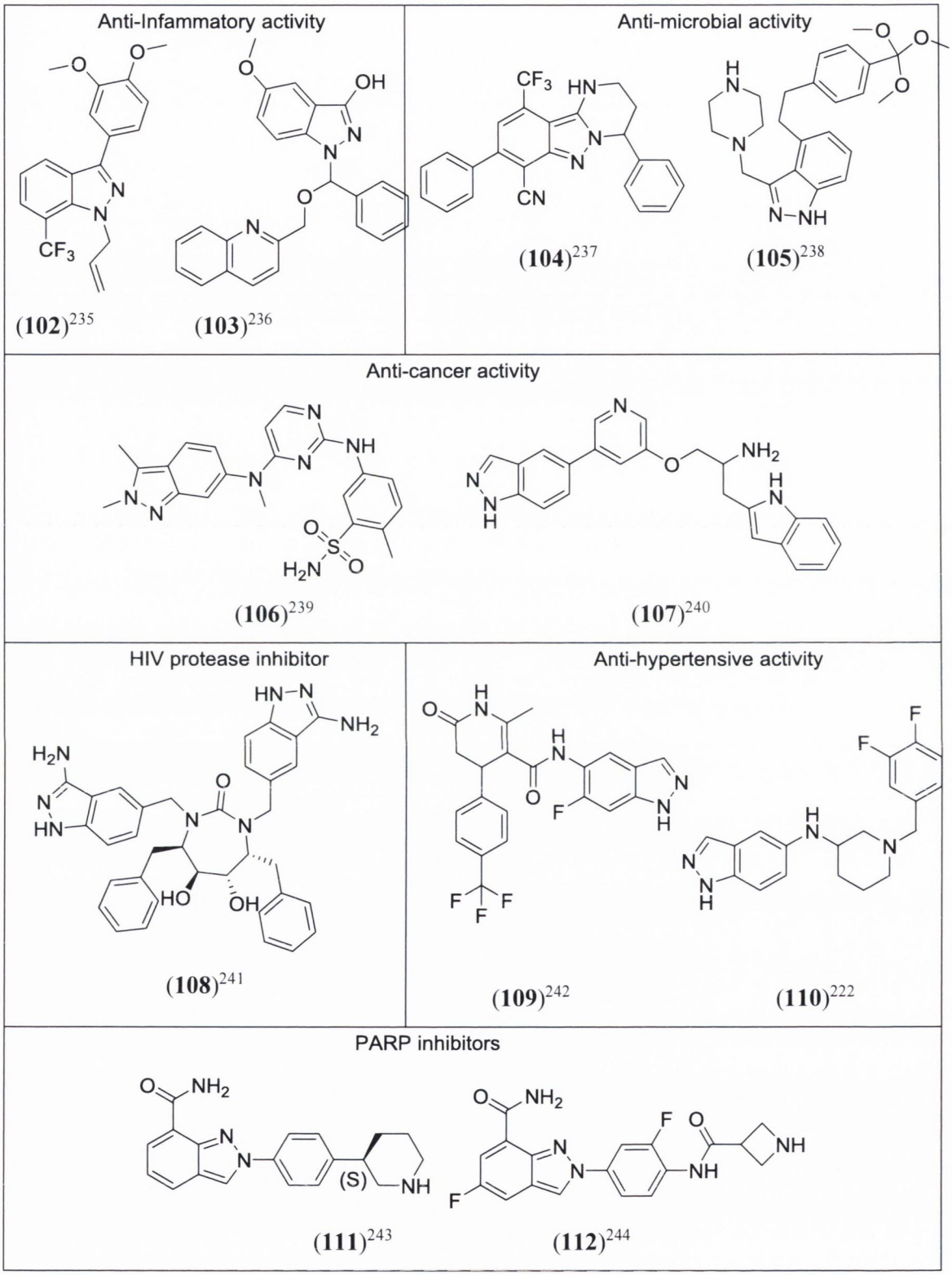
1.7.3Biological activities of indazole derivatives

Thangadurai et al[233] and *Shafakat*[234] recently reviewed the chemistry and biology of indazole moiety, highlighting it as a medicinally important heterocyclic scaffold. The indazole moiety is found in a diverse range of synthetic molecules which have various therapeutic applications listed below.

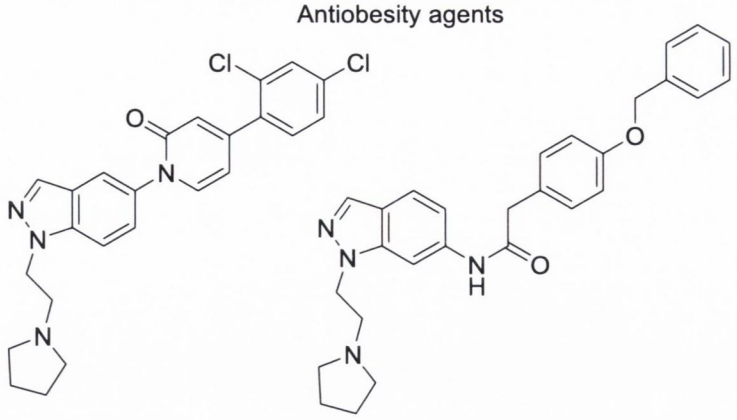
- Anti-inflammatory agents
- Anti-microbial agents
- Anti-cancer agents
- HIV protease inhibitors
- Anti-hypertensive agents
- PARP inhibitors
- Anti-obesity agents
- Thrombin receptor antagonists

Specific examples of each category are now discussed together with details of the relevant synthetic chemistry. A selection of indazole derivatives and their corresponding therapeutic effect are shown in table 3.

Table 3: Structures and bioactivity of selected indazoles

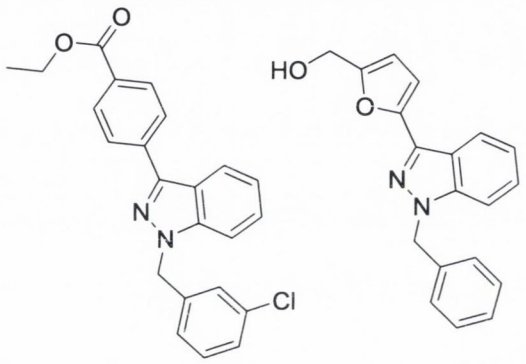


Antiobesity agents



(**113**)[245] (**114**)[246]

Thrombin receptor antagonists

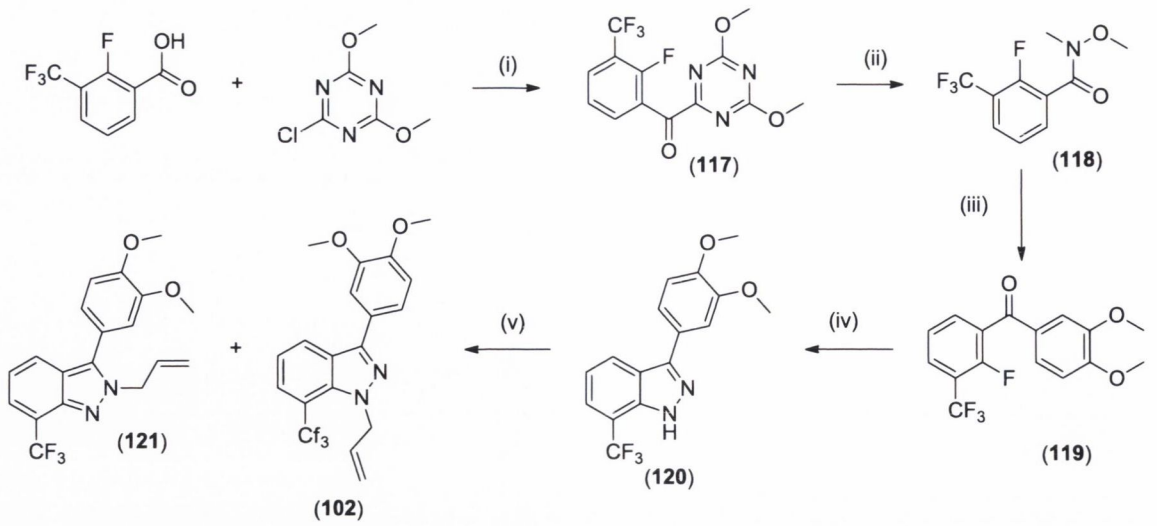


(**115**)[247] (**116**)[248]

Anti-inflammatory activity

The aryl hydrocarbon receptor (AHR) is a ligand-activated transcription factor that mediates the toxicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin[249]. However little is known about its role in normal physiology and thus is subject to intensive research. However this receptor plays an important role in certain immune responses and mediates repression of acute-phase genes in the liver[250]. It was thus necessary to selectively activate AHR in order for this observation to be therapeutically useful. A series of compounds, containing the indazole moiety, were synthesised by *Murray et al.* They were evaluated in a 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-mediated ear inflammatory edema model using C57BL6/J and *Ahr-/-* mice.

Compound (**102**) was shown to significantly inhibit TPA-mediated ear swelling and induction of a number of inflammatory genes. (**102**) was shown also to be a selective ARH receptor modulator[235].



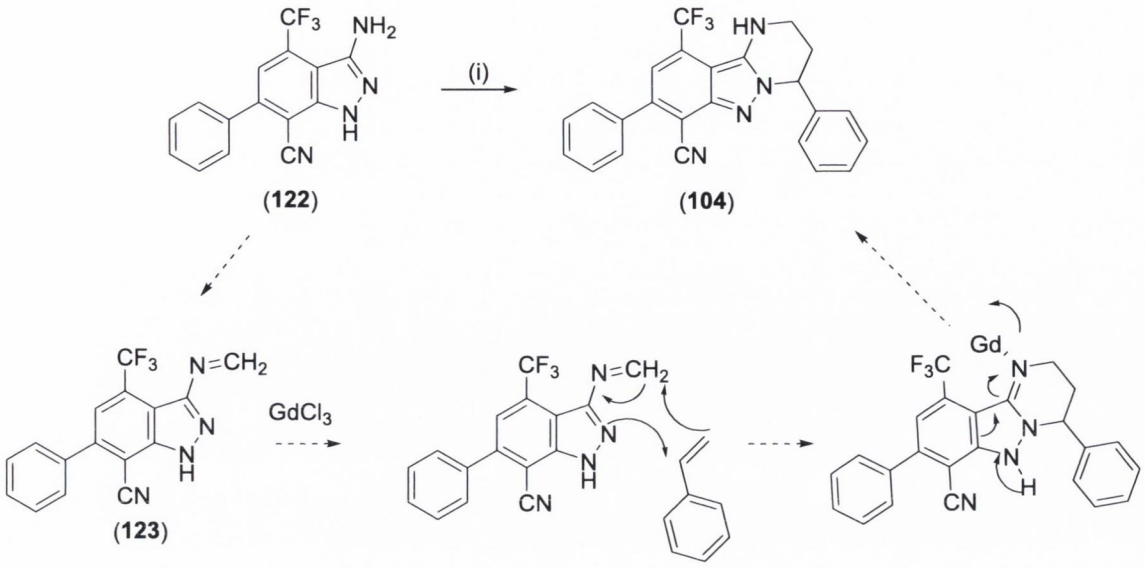
(i) *N*-Methylmorpholine, THF, rt, 1 h; (ii) *N,O*-dimethylhydroxylamine hydrochloride, rt, 8 h; (iii) 3,4-dimethoxyphenylmagnesium bromide, THF, 0 °C, 2 h; (iv) anhydrous H_2NNH_2, pyridine, microwave, 250 W (MAOS), 100 °C, 1 h; (v) NaH, DMF, rt to 60 °C, 30 min, allyl bromide, 60 °C, 4 h

Figure 51: Synthesis of (102)[235]

The preparation of (**102**) is shown in figure 51. 2-Fluoro-3-(trifluoromethyl)benzoic acid is reacted with 2-chloro-4,6-dimethoxy-1,3,5-triazine, a peptide coupling agent, to afford (**117**). (**117**) is then reacted with *N,O*-dimethylhydroxylamine hydrochloride yielding (**118**). A Grignard reaction is performed with (**118**) and 3,4-dimethoxyphenylmagnesium bromide to afford (**119**) which is then reacted with anhydrous hydrazine to give the indazole derivative (**120**). Alkylation with allyl bromide affords the desired product (**102**) and the corresponding regioisomer (**121**).

Anti-microbial activity

The terms antimicrobial, antibiotic, and anti-infective encompass a wide variety of pharmaceutical agents that include antibacterial, antifungal, antiviral, and anti-parasitic drugs. Of these, antibacterial agents are by far the most commonly encountered[251]. *Yakaiah et al* were interested in pyrimidine fused indazoles as they were considered to have promising activity against many infections.



(i) HCHO, CH_3CN, rt, $GdCl_3$, stryene

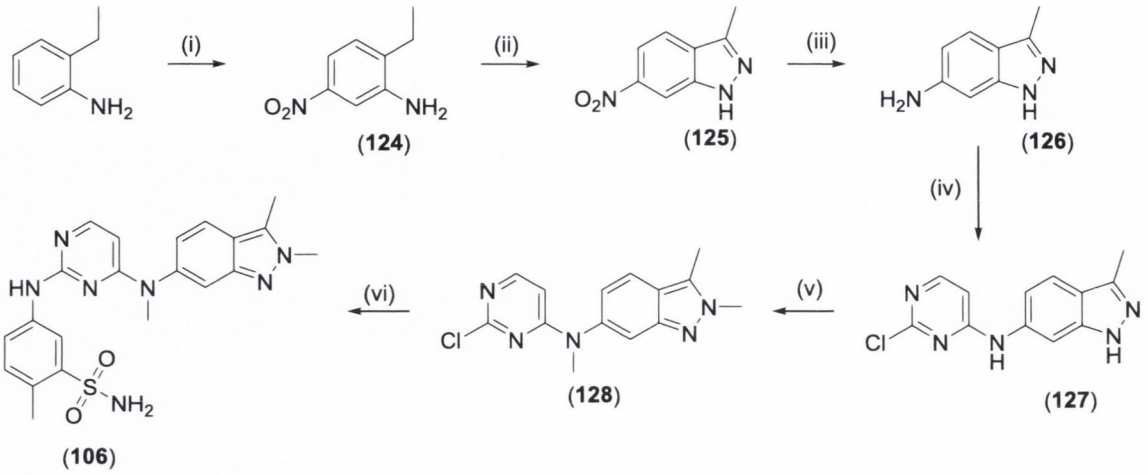
Figure 52: Synthesis of (104)

Yakaiah et al synthesised a series of annulated pyrimidine fused indazole derivatives in a single pot reaction[237], figure 52. The most potent compound of this series was identified as compound (**104**) which was obtained by reaction of 3-amino-4-(trifluoromethyl)-6-phenyl-1*H*-indazole-7-carbonitrile (**122**) with formaldehyde in acetonitrile at room temperature. This reaction generates the corresponding Schiff base (**123**) *in situ*. (**123**) can be described as a diazadiene due to conjugation of the new $N{=}CH_2$ bond and the imine bond present in the pyrazole ring of indazole. Gadolinium(III) chloride and stryene are then introduced to the reaction mixture and the 1,3-dipolar cycloaddition reaction afforded (**104**). The anti-bacterial activity of (**104**) was tested against Gram-positive (*B. subtilis*, *S. aureus*) and Gram-negative (*P. aeruginosa*, *E. coli*) bacteria *in vitro*. (**104**) showed significant activity against all species of Gram-positive and Gram-negative bacteria with reference to penicillin as well as streptomycin.

Anti-cancer activity

The growth of solid tumours is dependent on nutrients and oxygen that they receive *via* angiogenesis. This is facilitated by a number of endogenous proteins among which VEGF is thought to be key[252]. VEGF is secreted by tumours and induces a mitogenic response through its binding to one of three tyrosine kinase receptors (VEGFR-1 to -3) on nearby endothelial cells[253]. Thus inhibition of this signaling pathway should block angiogenesis and subsequent tumour growth. *Harris et al* synthesized a series of indazole derivatives that would inhibit VEGF[239]. Compound (**106**) was the most potent of these compounds. It displayed good activity against all the human VEGFR receptors with an IC_{50} value of 10, 30, and 47 nM for VEGFR-

1, -2, and -3, respectively. The ability of compound (**106**) to inhibit angiogenesis was shown in two separate animal studies, mouse matrigel plug assay and mouse corneal micropocket assay. Following successful clinical trials, (**106**) was approved by the FDA for the treatment for advanced soft tissue sarcoma[254].



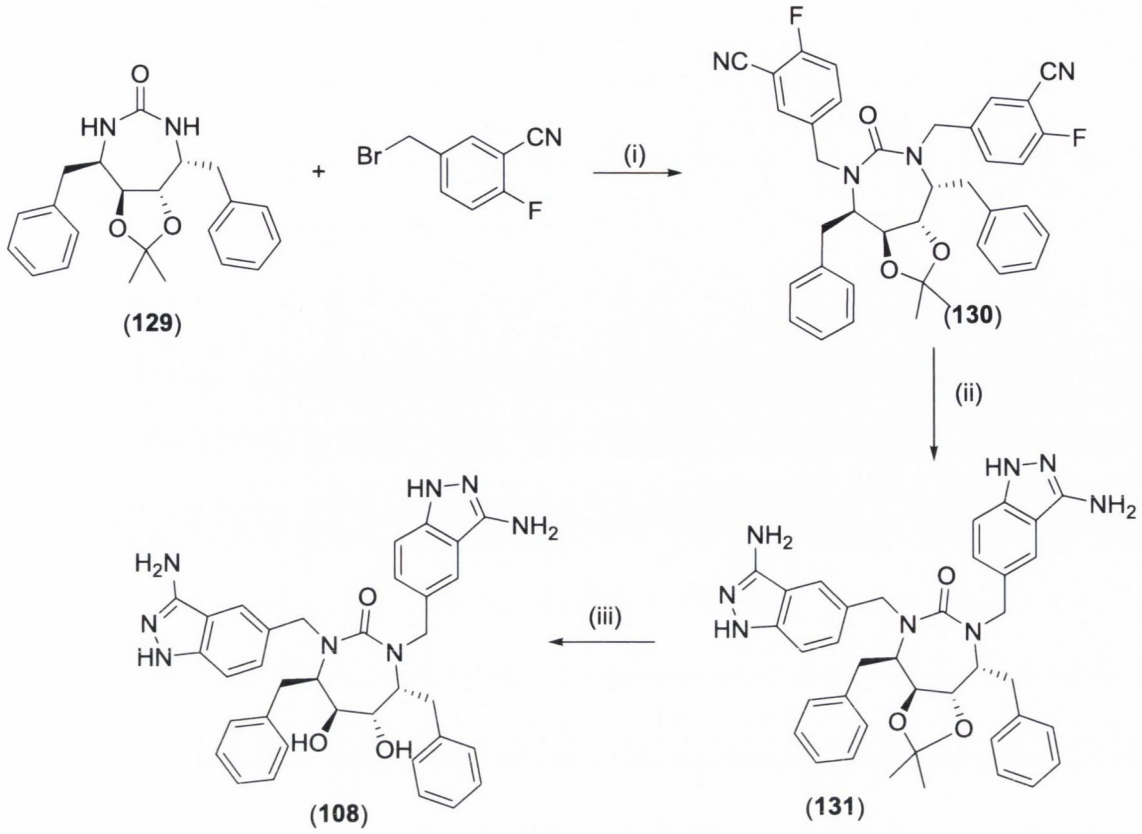
(i) fuming HNO_3, conc. H_2SO_4 (ii) isoamyl nitrite, AcOH (iii) $SnCl_2$, conc HCl, glyme (iv) 2,4-dichloropyrimidine, $NaHCO_3$, EtOH, THF, rt (v) NaH, iodomethane, (vi) 5-amino-2-methylbenzenesulfonamide, *i*PrOH, HCl, 80 °C

Figure 53: Synthesis of (106)

The preparation of (**106**) is illustrated in figure 53. (**124**) was obtained from the nitration of 2-ethylbenzenamine. Intramolecular cyclization of (**124**) with isoamyl nitrite in acetic acid afforded the indazole derivative (**125**). The nitro group in (**125**) was reduced using tin chloride yielding (**126**) which was then reacted 2,4-dichloropyrimidine, yielding (**127**). The methylation of (**127**) using iodomethane afforded the 2*H*-indazole derivative (**128**) which was condensed with 5-amino-2-methylbenzenesulfonamide to give the required product (**106**).

HIV protease inhibitors

Acquired immunodeficiency syndrome (AIDS) is caused by the HIV retrovirus. The mechanisms associated with HIV replication have been studied in great detail and are now well understood. One method for combating AIDS is the inhibition of HIV protease[255]. The protease enzyme plays a crucial role at the end of the viral life cycle. It cleaves encoded poly-peptide chains into their individual constituents that are required for a fully functional virus. In the presence of inhibitors, the cleavage process is inhibited and non-infectious particles are formed resulting in a full blockage of the viral replication[255]. The indazole containing compound (**108**) is an example of the many HIV protease inhibitors which have been reported[241].



(i) NaH, DMF (ii) H_2NNH_2, nBuOH, (iii) HCl, THF

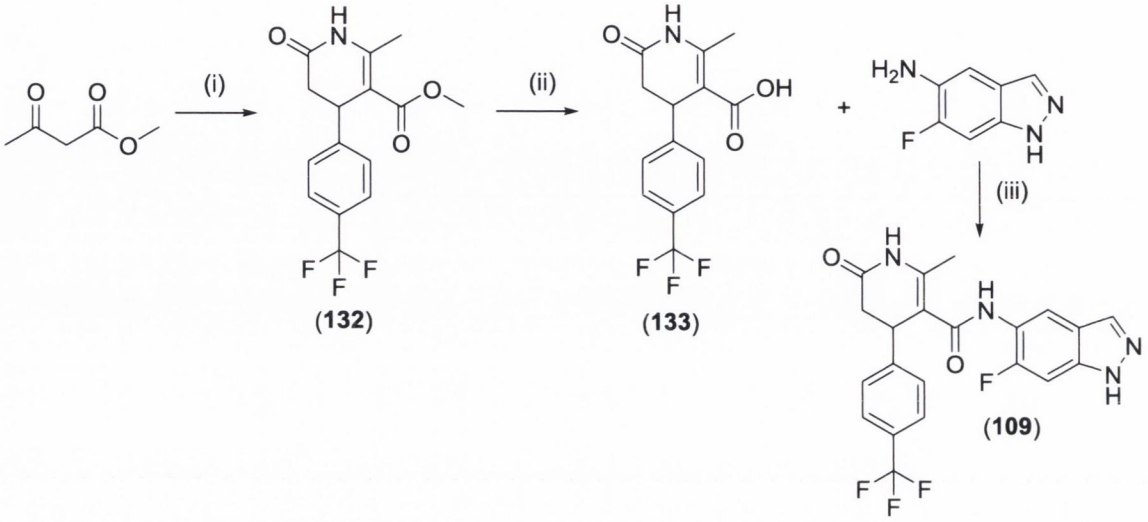
Figure 54: Synthesis of (108)

The prepararion of (**108**) is illustrated in figure 54. Benzylation of (**129**) using 5-(bromomethyl)-2-fluorobenzonitrile affords (**130**). The treatment of (**130**) with hydrazine results in the isolation of cyclized indazole product (**131**). The 1,3-dioxolane protecting group was removed using mild acid which afforded the desired product (**108**). (**108**) was demonstrated to be extremely potent against HIV protease with $K_i < 0.01$ nM.

Anti-hypertensive activity

Rho-associated kinase (ROCK1) is a serine/threonine kinase that has been implicated in a variety of cellular processes including vascular smooth muscle contraction, stress-fiber formation, cell migration, and gene expression[256]. In vascular smooth muscle contraction, ROCK1 plays a central role in the calcium-sensitization pathway[257]. Activation of ROCK1 indirectly regulates the phosphorylation state of myosin light chain, leading to increased vascular smooth muscle contraction. Inhibition of this pathway represents a promising strategy for the treatment of a variety of cardiovascular diseases, including hypertension. *Goodman et al* sought to develop a potent, selective ROCK1 inhibitor for use as an antihypertensive agent[242]. Dihydropyridone indazole amides, such as (**109**), were evaluated for potency in

ROCK1 and other kinases such as RSK1 and p70S6K. IC_{50} values of 8 nM, 90 nM and 590 nM were recorded for these kinases respectively for (**109**). Spontaneously hypertensive rats were treated with (**109**). (**109**) dramatically reduced mean arterial pressure after oral administration.



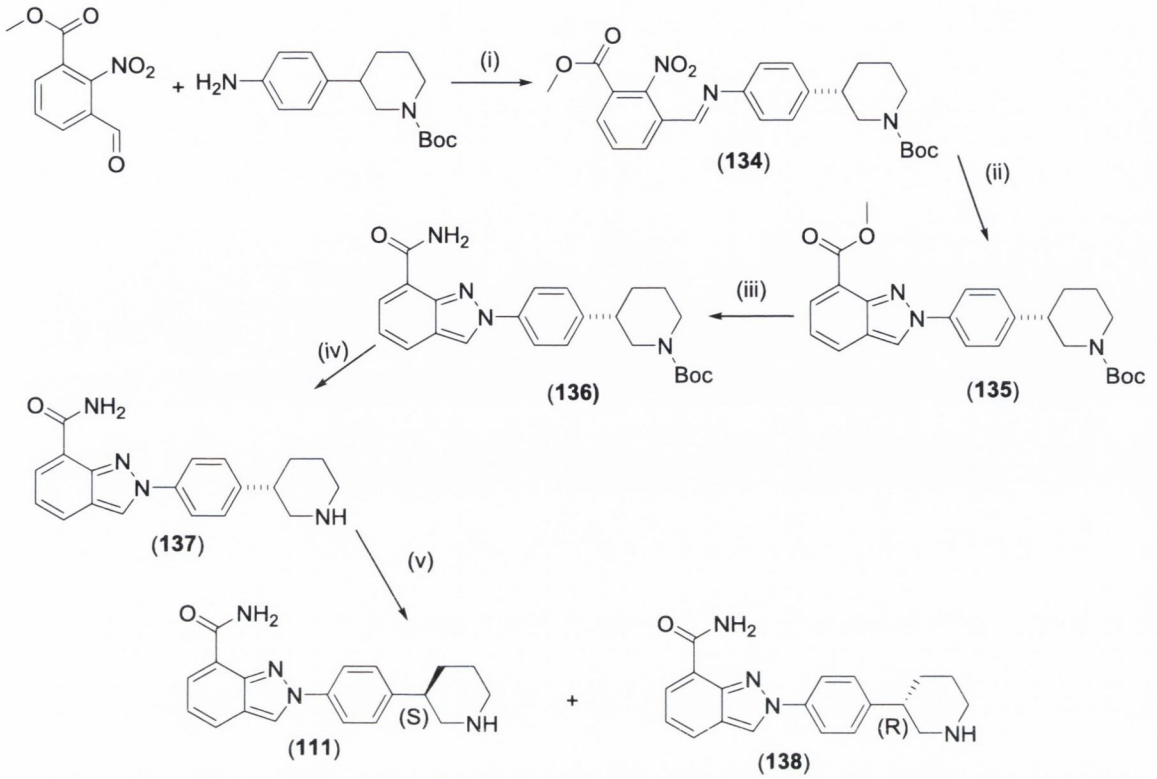
(i) Meldrum's acid, 4-(trifluoromethyl)benzaldehyde, NH_4OAc, HOAc; (ii) NaOH, MeOH, H_2O (iii) EDC, Et_3N, DMF

Figure 55: Synthesis of (109)

Methyl 3-oxobutanoate was reacted with the necessary benzaldehyde forming the dihydropyridone compound (**132**), figure 55. Subsequent hydrolysis of the methyl ester of (**132**) affords (**133**). EDC coupling of (**133**) with 6-fluoro-1*H*-indazol-5-amine affords the product (**109**).

PARP inhibitors

Poly(ADP-ribose) polymerase (PARP)-1 is the first identified and most abundant member of poly(ADP-ribosyl)ating proteins, a family of some 18 proteins. PARP-1 and the closely related PARP-2 are nuclear proteins and possess DNA binding domains. Due to their involvement in DNA repair, PARP-1 and PARP-2 have been promising targets for chemotherapeutic agents[258]. The cytotoxic effects of ionizing radiation and DNA-damaging chemotherapy agents have been shown to be enhanced by PARP inhibition. *Jones et al* synthesised a series of 2-phenyl-2*H*-indazole-7-carboxamides as PARP-1 and PARP-2 inhibitors[243]. Compound (**111**) displayed exceptional PARP-1 and PARP-2 inhibition activities, recording IC_{50} values of 3.8 and 2.1 nM respectively. In a whole cell assay, it inhibited PARP activity with EC_{50} value = 4 nM and inhibited proliferation of cancer cells with mutant BRCA-1 and BRCA-2 with IC_{50} values in the 10-100 nM range.



(i) EtOH, reflux (ii) NaN_3, DMF, 90 °C (iii) NH_3, MeOH, sealed tube, 60 °C (iv) HCl, dioxane (v) supercritical fluid chromatography

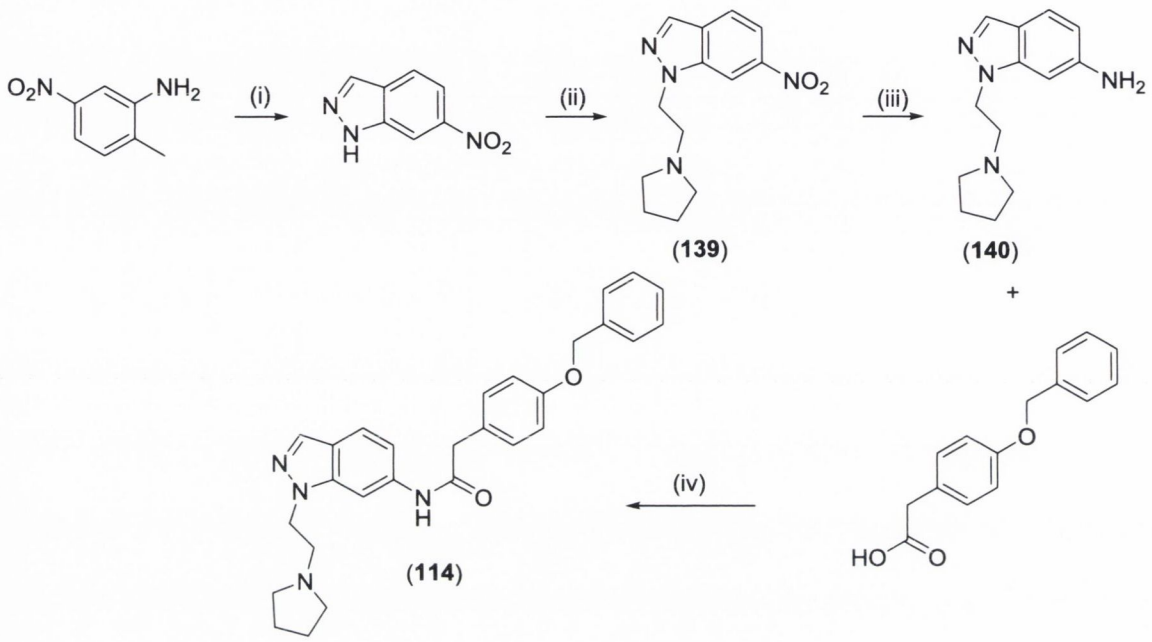
Figure 56: Synthesis of (111)

The preparation of (**111**) is illustrated in figure 56. Racemic *N*-Boc-3-(4-aminophenyl)piperidine was condensed with methyl 3-formyl-2-nitrobenzoate affording the imine (**134**). Cyclization of (**134**) using sodium azide in DMF afforded (**135**). The amide (**136**) was afforded on treatment of (**135**) with ammonia in a sealed tube at 60 °C. The Boc protecting group was removed with HCl affording (**137**). The separation by chiral supercritical fluid chromatography of racemic (**137**) afforded the desired *S*-enantiomer (**111**) and the *R*-enantiomer (**138**)[243].

Anti-obesity agents

Melanain concentrating hormone (MCH) is a 19 amino acid cyclic neuropeptide that is expressed in cell bodies in the lateral hypothalamus and zona incerta of the central nervous system. The correlation between the overexpression of MCH and food intake/body weight regulation has been investigated[259]. Using mouse models, it was shown that disruption of MCH gene leads to a lean phenotype while eutopic overexpression, leads to susceptibility to hyperphagia, obesity, and to a dysregulation of glucose homeostasis. *Souers et al* synthesised

a series of *N*-1-(2-aminoethyl)indazoles and investigated them for melanain concentrating hormone-1 (MCHr-1) antagonism in both binding and functional assays[246]. Compound (**114**) was found to be a high-affinity ligand for MCHr1 and a potent inhibitor of MCH-mediated Ca^{2+} release, showed good plasma and CNS exposure upon oral dosing in diet-induced obese mice, and is the first reported MCHr1 antagonist that is efficacious upon oral dosing in a chronic model of weight loss.



(i) $NaNO_2$, AcOH, rt (ii) chloroethylpyrrolidine hydrochloride, K_2CO_3, DMF, 60 °C (iii) Fe, NH_4Cl, 65 °C; (iv) EDCI, HOBt, DMF, NMM

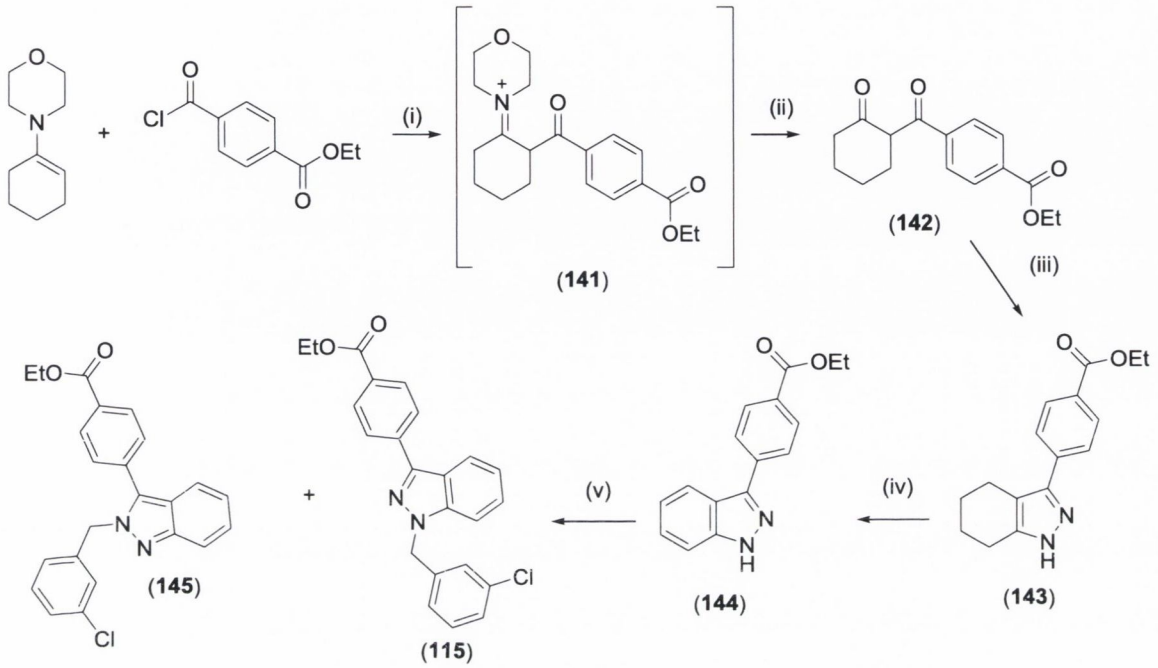
Figure 57: Synthesis of (114)

The preparation of (**114**) is illustrated in figure 57. 2-Methyl-5-nitrobenzenamine was treated with sodium nitrite affording 6-nitroindazole. Alkylation of 6-nitroindazole with chloroethylpyrrolidine hydrochloride yielded (**13**). (**140**) was afforded by the reduction of (**139**) using iron and ammonium chloride and was then coupled with 4-benzyloxy-4-phenylacetic acid to afford the desired amide compound (**114**).

Thrombin receptor antagonists

The protease activated receptors PAR1 and PAR4 are seen as promising targets for development of new antithrombotic drugs due to their involvement in signal platelet activation. In animal models, the inhibition of arterial thrombosis was observed by pharmacological and genetic blockade of PAR1 and PAR4. Also in comparison to thrombin inhibitors, PAR antagonists do not affect the ability of thrombin to cleave fibrinogen which is believed to result in fewer bleeding complications. *Chen et al* had already identified ethyl 4-(1-benzyl-1*H*-

indazol-3-yl)benzoate, the first non-peptide protease-activated receptor 4 (PAR4) antagonist, and used it as the lead compound in their of development of novel anti-PAR4 agents[247]. Compound (**115**) showed the most potent inhibitory effect on PAR4-mediated platelet aggregation, ATP release, and P-selectin expression.



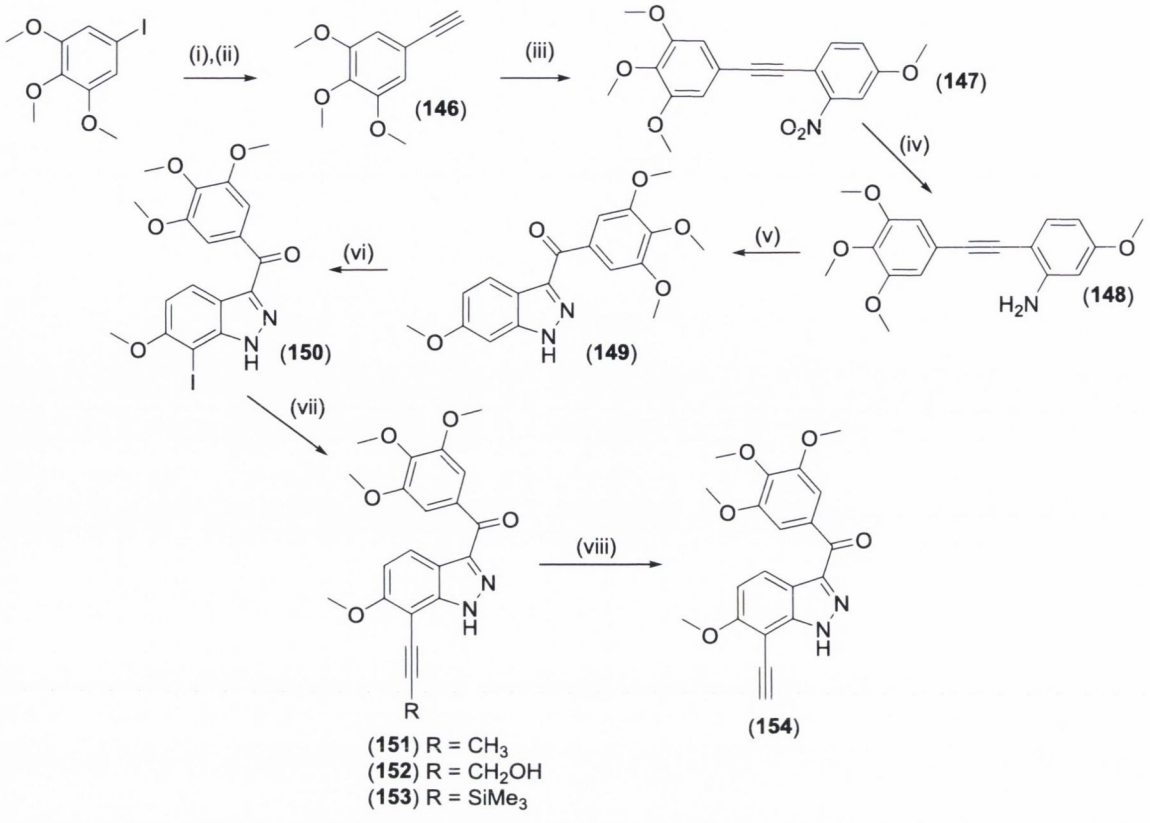
(i) Et_3N, $CHCl_3$, reflux, 3 h (ii) 20% HCl, reflux, 5 h (iii) 98% NH_2NH_2 H_2O, MeOH, reflux, 30 min; (iv) *trans*-decalin, 10 % Pd/C, reflux, 24 h (v) EtONa, 3-chlorobenzyl bromide, EtOH, rt, 12 h

Figure 58: Synthesis of (115)

The preparation of (**115**)[247] is illustrated in figure 58. 4-Cyclohexenylmorpholine is reacted with ethyl 4-(chlorocarbonyl)benzoate yielding (**141**). Refluxing (**141**) in HCl affords the dione (**142**) which is then treated with hydrazine which to give the 3-aryl 4,5,6,7-tetrahydro-1*H*-indazole compound (**143**). The 3-aryl indazole derivative (**144**) is afforded by refluxing (**143**) in *trans*-decalin in the presence of 10% palladium on carbon. Benzylation of (**142**) using 3-chlorobenzyl bromide affords (**115**) and its N2 isomer (**145**).

Tubulin Inhibitors

Duan et al synthesized a series 3-aroyl indazoles as tubulin inhibitors, binding to the colchicine active site of tubulin[260], figure 59.



(i) $PdCl_2(PPh_3)_2$, CuI, Et_3N, trimethylsilylacetylene. (ii) NBu_4F, THF. (iii) $PdCl_2(PPh_3)_2$, CuI, Et_3N, 4-iodo-3-nitroanisole. (iv) Fe, HCl/EtOH. (v) $NaNO_2$, HCl. (vi) *N*-iodosuccinimide, AcOH. (vii)$PdCl_2(PPh_3)_2$, CuI, Et_3N, terminal alkyne. (viii) NBu_4F, THF.

Figure 59: Synthesis of tubulin inhibitors containing an indazole core

Using Sonogashira reaction conditions, 5-iodo-1,2,3-trimethoxybenzene is first coupled with trimethylsilylacetylene rather than acetylene to prevent further coupling reactions. The resulting coupled product is then desilylated with *tetra*-n-butylammonium fluoride (NBu_4F) affording (**146**). Sonogashira reaction conditions were again used to couple (**146**) with 4-iodo-3-nitroanisole to yield (**147**). The nitro group in (**147**) was reduced using Bechamp reduction conditions obtaining (**148**). Diazotization of (**148**), using sodium nitrite, transforms it into an ortho-(arylethynyl)benzene diazonium salt which subsequently underwent cyclisation yielding (**149**). Iodination of (**149**) using *N*-iodosuccinimide afforded (**150**) which was then coupled with prop-1-yne, prop-2-yn-1-ol or trimethylsilylacetylene to form (**151**), (**152**) and (**153**) respectively. (**153**) was then desilylated using tetra-*n*-butylammonium fluoride affording (**154**).

When evaluated for cytotoxicity toward H460 cells (a human non-small lung cancer cell line) IC_{50} values of 1 nM, 8nM and 3 nM were recorded for compounds (**151**), (**152**) and (**154**) respectively. These analogues were significantly more active than the core compound (**149**) which recorded an IC_{50} value of 64 nM. It should be noted that (**149**) is structurally similar to

the BPR0L075, which has an indole core[261], figure 60. BPR0L075 was shown to have a broad spectrum of activity against human leukemia, glioblastoma, oral, nasopharyngeal, breast, gastric, colorectal, and liver cancer cells *in vitro* and strongly inhibits tubulin polymerization through binding at tubulin's colchicine-binding site. In a separate study[262], BPR0L075 caused rapid, albeit, temporary tumor vascular shutdown and led to reduction of tumour perfusion in orthotopic human breast cancer xenografts, suggesting that this antimitotic agent may be useful as a vascular-disrupting cancer therapy. When BPR0L075 and its propyne analogue (**155**) were evaluated on the same non-small cell lung cancer cell line, IC_{50} values of 16 nM and > 1000 nM were recorded respectively.

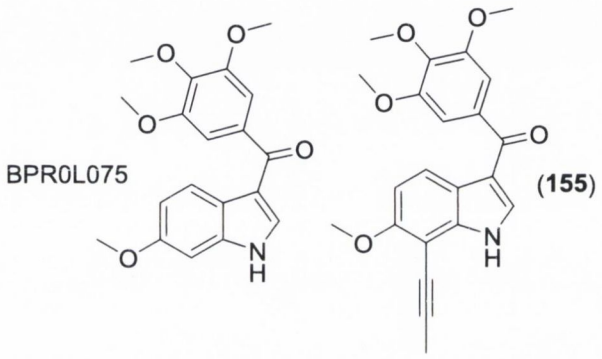
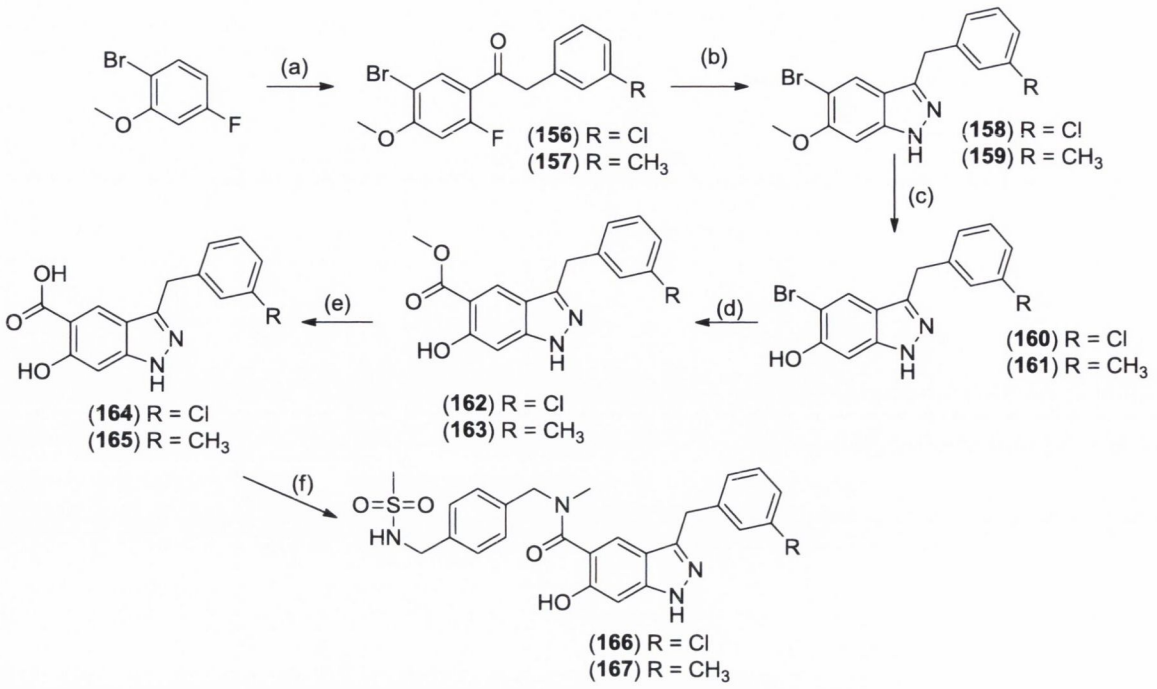


Figure 60: BPR0L075 and its propyne analogue (155)

Potent indazole compounds (**151**), (**152**) and (**154**) were then tested in cancer lines HT-29, PC3 and HeLa. Low nanomolar IC_{50} values were recorded for these compounds. CA4 was used a control and demonstrated similar low nanomolar potency except against Hela cell, where it was virtually inactive. When evaluated against cell lines possessing the well characterized drug resistance efflux pumps, all three compounds exhibited potent antiproliferative activities.

Hsp90 inhibitors

Buchstaller et al synthesized a series of 3-benzylindazole derivatives which bound to the ATP binding site of Hsp90[263], figure 61.



(a) (i) $ArCH_2COCl$, $AlCl_3$, CH_2Cl_2, (ii) 1 N HCl, 0 °C (b) $(NH_2)_2.H_2O$, dioxane, reflux, 1.5–3 h; (c) BBr_3, CH_2Cl_2 rt, 16–60 h; (d) $Pd(dppf)_2Cl_2CH_2Cl_2$, 4bar CO, Et_3N, MeOH/toluene, 100 °C, overnight; (e) NaOH, dioxane, reflux, 1 h; (f) (i) $SOCl_2$, THF, rt; (ii) *N*-(4-((methylamino)methyl)benzyl)methanesulfonamide, DIPEA, THF, rt, 1 h.

Figure 61: Synthesis of Hsp90 inhibitors containing the indazole core

Friedel-Crafts acylation of 1-bromo-4-fluoro-2-methoxybenzene with the necessary phenylacetyl chloride afforded (**156**) and (**157**). Intramolecular cyclization with hydrazine in dioxane yielded (**158**) and (**159**). Demethylation of the methoxy group gave (**160**) and (**161**). Compounds (**162**) and (**163**) was obtained *via* palladium-catalyzed methoxy-carbonylation using $Pd(dppf)_2Cl_2CH_2Cl_2$; the hydrolysis of (**162**) afforded (**164**), while the hydrolysis of (**163**) afforded (**165**). The carboxylic acid compounds (**164**) and (**165**) were treated with thionyl chloride yielding the corresponding acid chlorides which were then reacted with the necessary secondary amine affording the desired compounds (**166**) and (**167**). In the Hsp90 binding assay, IC_{50} values of 0.06 μM and 0.15 μM were obtained for (**166**) and (**167**) respectively. When evaluated in cancer lines A2780, PC-3, MCF-7 and Colo-205, sub-micromolar IC_{50} values were obtained for both (**166**) and (**167**).

1.8 Background to the Project

This project evolved from research performed in the Meegan group by *Knox et al* which had identified, from *in silico* high throughput screening (HTS), an indazole based scaffold that represents the "first in class" dual Hsp90/tubulin binding compound[1]. This dual Hsp90/tubulin binding compound, (**168**) figure 62, contains an amine group in the 5 position of the indazole

ring and an amide bond to a 3,4,5-trimethoxyphenyl ring from the *N*-1 nitrogen. A recent structure of a Hsp90 inhibitor[264], compound **(70)**, was released which contained a 3',4,5' - trimethoxyphenyl moiety, which is observed being required for binding of ligands in the colchicine binding site of tubulin[106]. Figure 62 illustrates the commonalities between the 3-arylthionindole tubulin binding compound **(64)**[265], the purine based analogue (**70**) that binds to Hsp90 and the dual Hsp90/tubulin binding compound (**168**).

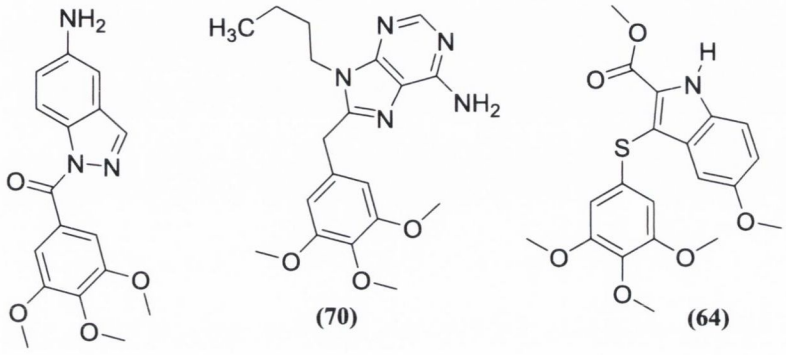


Figure 62: Common 3',4',5'- trimethoxyphenyl pharmacophore: (168) - dual Hsp90/tubulin binding compound, (70) - PU3 analogue Hsp90 inhibitor, (64) - tubulin inhibitor 3-arylthioindole

It was hypothesized that building for this structural commonality, it might be possible to identify a single molecular scaffold that would inhibit both targets, using virtual screening (VS) techniques. To advance this hypothesis, the relative regions that Hsp90 and colchicine-site actives occupy within medicinal chemistry space were mapped. Principal component analysis (PCA) allowed the reduction in dimensionality, preserving the major differences and similarities between molecules but removing redundancy between them. In Figure 63, 165-dimensional space was reduced into three-dimensional space for a database containing 129 Hsp90/49 tubulin actives selected from literature and a set of 10,000 randomly selected molecules representing generic medicinal chemistry space extracted from the ZINC database[266]. The discovery of the lead compound (**168**) is now outlined.

From the VS protocol, which was developed in-house, the SPECS database of ~160,000 compounds was reduced and 51 potential candidates were identified. 20 of these candidates were visually selected and tested for their ability to bind to Hsp90 and to also de-polymerize tubulin. Two displayed modest binding affinity to Hsp90 and were carried forward for testing in a tubulin polymerization assay. (**168**) displayed binding to the ATP site of Hsp90 with an IC_{50} value of 80.76 $\pm$ 0.0235 μM and also displayed the ability to depolymerise tubulin.

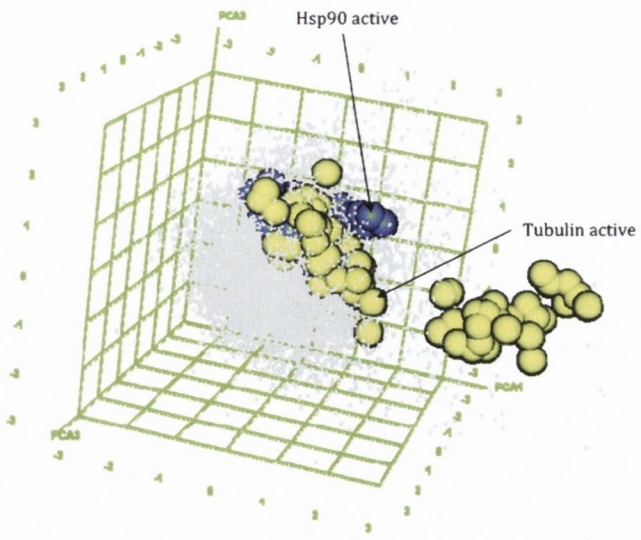


Figure 63: Hsp90 and tubulin binders overlap in the medicinal chemistry space: grey, med. chem. space; yellow, Hsp90; blue, antitubulin[1]

The ability of (**168**) to interact with the Hsp90 ATP-binding site and induce protesomal degradation of Hsp90 client proteins was performed using a cell based assay. After MCF-7 cells were treated with 200 μM (**168**), western blotting demonstrated significant degradation of ERα, a known Hsp90 client protein, compared to the vehicle control. 17-AAG also induces ERα degradation at lower concentrations. However when MCF-7 cells were treated with nocodazole, a ligand of the colchicine binding site, the level of degradation of ERα was not significant. This indicates that (**168**) can induce Hsp90 client protein degradation which is facilitated through its ability to bind to the Hsp90 ATP-binding site and is not associated to its ability to bind to the colchicine active site of tubulin.

In terms of its ability to depolymerize tubulin, (**168**) displayed a dose-response depolymerizing effect with 75 μM being equivalent to 10 μM nocodazole treatment. Even though **(168)** displayed modest tubulin binding and Hsp90 activity, it was the dual action which was most interesting and warranted further investigation.

1.9 Objectives of this project

The objective of the research described in this thesis was to optimise the antiproliferative effect of the lead indazole containing compound (**168**). A number of libraries based on the core scaffold structure (**168**) were designed, synthesised and initial biochemical screening investigated.

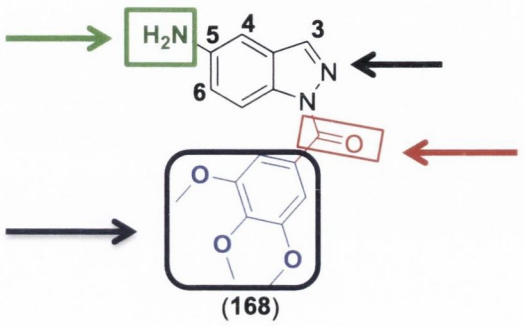


Figure 64: Functional groups of (168)

The different functional groups of the dual binding Hsp90/tubulin compound (**168**) are highlighted in figure 64. It contains an amine group (green), in the 5-position of the indazole ring and has a carbonyl linker (red) from the *N*-1 nitrogen to a 3,4,5-trimethoxyphenyl ring (blue). The specific objectives of this thesis project are:

- To synthesize indazoles related in structure to (**168**) which contain the amine in either the 5 position or the 6 position. These modified products will also contain different linkers in between the N1 atom and the aryl ring. The effect in amine position and linker type on biochemical activity will be investigated.
- To modify the amine group of (**168**) by replacing it with different aryl substituents
- To synthesize derivatives of (**168**) by introducing aryl and heterocyclic substituents in the 3 position of the indazole ring
- To introduce nitrogen heterocyclic substituents onto the scaffold of (**168**) by modification of the amine group
- To evaluate a number of synthesized compounds in a biochemical assay for anti-proliferative activity in MCF-7 cells
- To rationalize the observed cell proliferative effects using molecular modelling

Chapter 2

Synthetic studies with Indazoles

2.1 Introduction

The first section of this chapter describes the synthesis of analogues of the lead compound (**168**) which explored the nature of the aryl amide together with the modifications of the linker between the N-1 atom of the indazole and the aryl ring, figure 65.

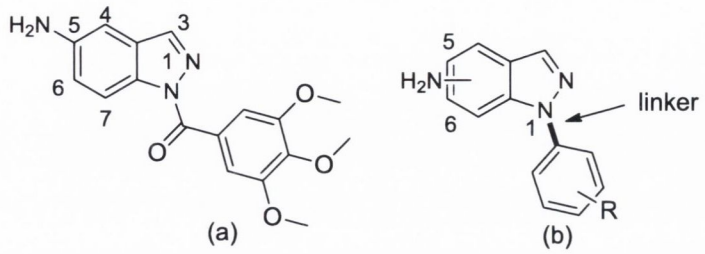
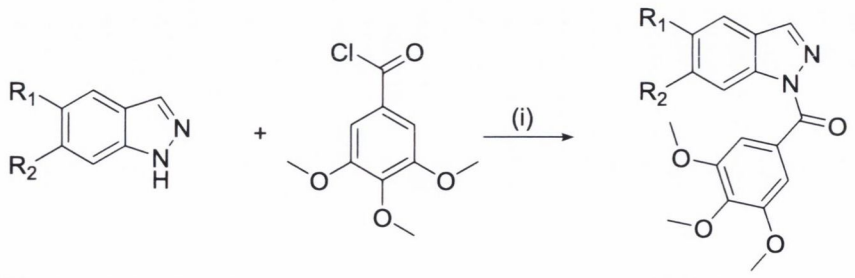


Figure 65: (a) lead compound (168) (b) general structure of compounds in this chapter

The lead compound (**168**) contained a carbonyl linker between N-1 and the 3,4,5-trimethoxyphenyl ring together with an amine in the 5-positon, figure 65. The library of analogues were synthesised by first reacting 5-nitroindazole with benzoyl chlorides, phenylacetyl chlorides, benzyl/alkyl bromides, phenylboronic acids and aliphatic acid chlorides. These 5-nitroindazole products were then reduced to give the corresponding 5-aminoindazole derivatives. An investigation between potency and the change in linker could be undertaken with these 5-aminoindazoles. 6-Nitroindazole was also investigated and these 6-nitroindazole derivatives were subsequently reduced to the corresponding 6-aminoindazoles. These 6-aminoindazoles would enable us to investigate what effect the location of the amine position, C-5 or C-6, would have on potency.

2.2 Preparation of (168) and related aroylated indazoles

It was initially desired to synthesise the dual binding compound (**168**) identified from the *in silico* study[1]. In order to prepare (**168**), the nitro precursor (**171**) was obtained by reacting 5-nitroindazole (**169**) with 3,4,5-trimethoxybenzoyl chloride, figure 66.



(**169**) $R_1 = NO_2$, $R_2 = H$
(**170**) $R_1 = H$, $R_2 = NO_2$

(**171**) $R_1 = NO_2$, $R_2 = H$ (54%)
(**172**) $R_1 = H$, $R_2 = NO_2$ (55%)

(i) Et_3N, CH_2Cl_2, reflux for (**171**), 20 °C for (**172**)

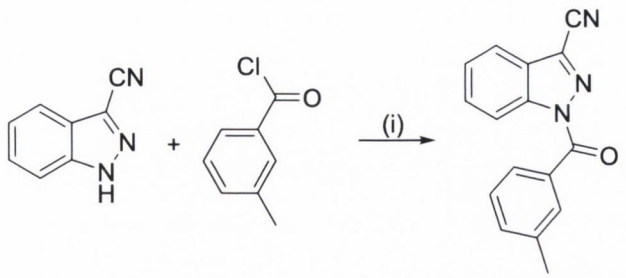
Figure 66: Synthesis of nitro precursors (171) and (172)

Compound (**172**) was similarly prepared and its preparation is now discussed. The procedure for the preparation of (**172**) from (**170**) involved refluxing the reactants in anhydrous benzene for 14 hours followed re-crystallisation from benzene[267]. This reaction was attempted in anhydrous toluene due to the toxicity of benzene. Also a few drops of Et_3N were added to the reaction mixture. The product was obtained in 63 % yield. Since toluene is difficult to remove due to its high boiling point[268], the same reaction was repeated using anhydrous dichloromethane (DCM) and the product was obtained in 55 % yield. Since the reaction proceeds well in DCM, it was decided to use this solvent for synthesis of all other 5 and 6-nitroindazole derivatives as it has a much lower boiling point[269]. For (**172**), it was discovered the reaction proceeded at room temperature, 20 °C, while for (**171**), refluxing was required. Also (**172**) was prepared using microwave assisted organic synthesis (MOAS). Within the research group, two microwave reactors are available, a Biotage Initiator and CEM Discover. (**172**) was obtained from (**170**) in 65 % yield using the reaction conditions described highlighted in table 4.

Table 4: Optimization of the reaction conditions for (172)

Reaction Conditions	Anhydrous Solvent	Temperature and method of heating	Time	% Yield
1	Toluene	~ 120°C, refluxing	14 hours	63%
2	Dichloromethane	~39.6 °C, refluxing	14 hours	55%
3	Dichloromethane	50 °C, CEM microwave	20 minutes	57%
4	**Dichloromethane**	**50 °C, CEM microwave**	**40 minutes**	**65%**

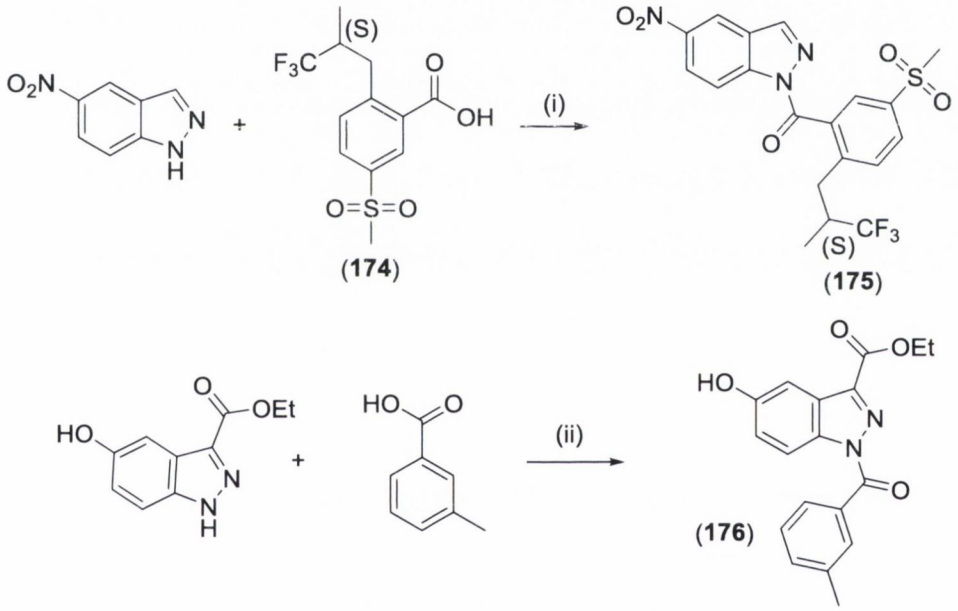
Acid chlorides, such as 3,4,5-trimethoxybenzoyl chloride, undergo amide bond forming reactions in which a nitrogen nucleophile displaces the halide leaving group from the benzoyl halide substrate. Amides can also be prepared by reacting amines with carboxylic acids, anhydrides or esters[270]. The benzoylation of indazole derivatives has been previously reported using acid chlorides (figure 67), carboxylic acids (figure 68), anhydrides (figure 69), benzoxazin-4-one derivative (figure 70) and ring transformations (figure 71).



(i) NEt_3, CH_2Cl_2, 0 °C, 2 h and then rt, 2 – 12 h[271]

Figure 67: Benzoylation of indazole derivative using acid chlorides

Crocetti et al synthesised a series of *N*-benzoylindazole derivatives in order to inhibit human neutrophil elastase (HNE)[271] which is an important therapeutic target for treatment of pulmonary diseases.



(i)TBTU, EtN(Pr-*i*)$_2$, DMF, 25 °C[272] (ii) $(CH_3CH_2O)_2P(O)CN$, DMF, 0 °C – 25 °C[271]

Figure 68: Benzoylation of indazole derivative using carboxylic acids

Jolidon et al[272] prepared a series of heterocyclic substituted phenyl methanones as inhibitors of the glycine transporter 1, figure 68. Inhibition of the glycine transporter 1 has been used for the treatment of neurological and neuropsychiatric disorders. Benzoylation of 5-nitroindazole with carboxylic acid (**174**) afforded (**175**). The synthesis of amides and esters, using carboxylic acids requires the use of activating agents. *Jolidon et al* reported *O*-(benzotriazol-1yl)-*N*,*N*,*N*',*N*',-tetramethyluronium tetrafluoroborate (TBTU) as the coupling agent. *Crocetti et al* benzoylated ethyl 5-hydroxy-1*H*-indazole-3-carboxylate with *m*-toluic acid affording (**176**) using diethyl cyanophosphonate as the coupling agent[271].

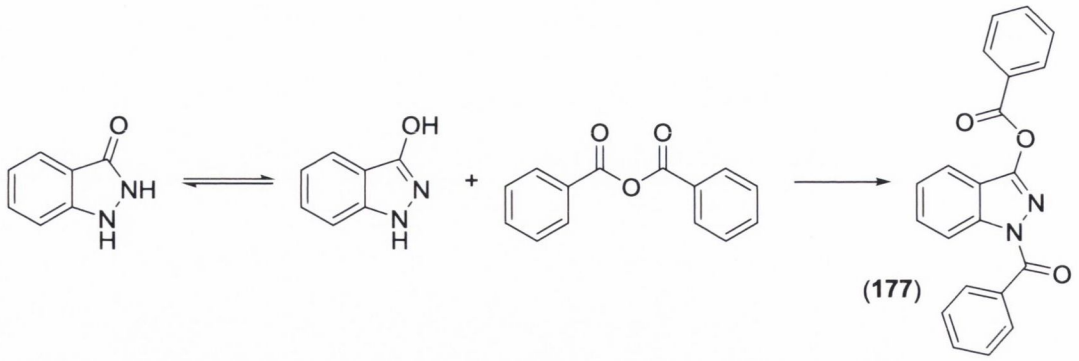
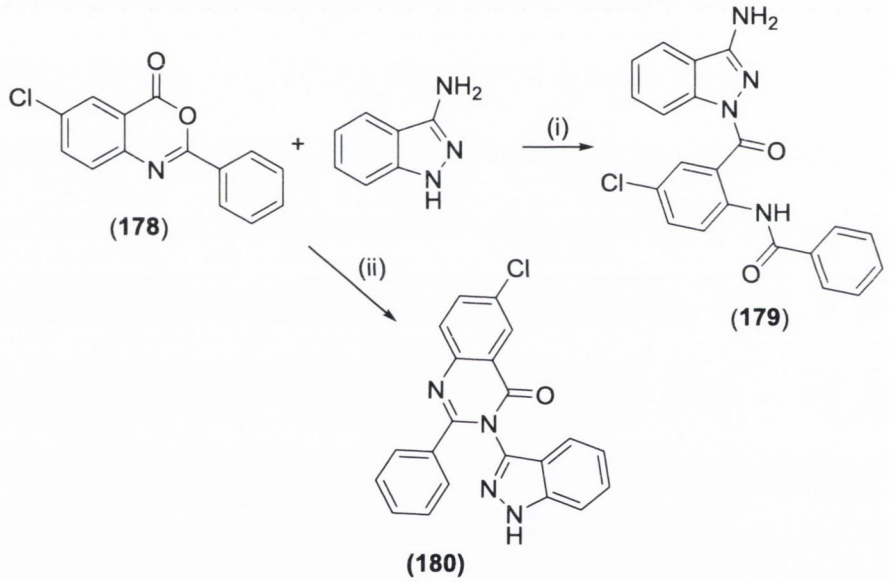


Figure 69: Benzoylation of indazole derivative using benzoic anhydride[273]

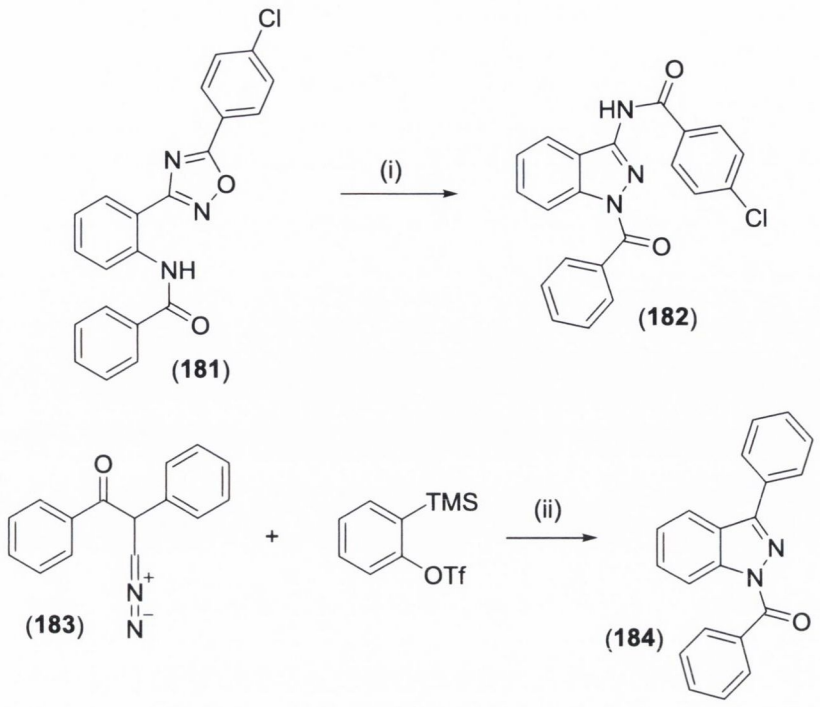
The synthesis of acyl derivatives of indazolin-3-one has been reported[273], figure 69. Indazolin-3-one exists in tautomeric forms with 1*H*-indazol-3-ol. 1*H*-indazol-3-ol is reacted with benzoic anhydride affording the di-benzoylated compound (**177**). Both the NH and OH in 1*H*-indazol-3-ol may react with benzoic anhydride.



(i) 160°C, 15 min (ii) 260°C, 15 min[274]

Figure 70: Benzoylation of 3-aminoindazole using benzoxazin-4-one derivative

Plescia et al synthesised a series of indazole derivatives and evaluated their antimicrobial, antiproliferative and COX inhibitory activities[274], figure 70. It was reported that if 3-aminoindazole was reacted with the benzoxazin-4-one (**178**) at 160 °C for 15 minutes, the benzoylated indazole (**179**) was afforded. However if the same two reactants were reacted at 260 °C for 15 minutes, the 4(3*H*)-quinazolinone derivative (**180**) was afforded.



(i) 150°C, DMF, H_2O[275] (ii) CsF, MeCN, rt[231]

Figure 71: Benzoylated indazoles from ring transformation

Continuing their research on the ring transformation of 3-(2-aminoethyl)-1,2,4-oxadiazoles into acylaminopyrazolines, *Korbonits et al* reported the ring transformation of 3-(2-aminophenyl)oxadiazoles (**181**) into 3-acylaminoindazoles (**182**), figure 71. This azole rearrangement was achieved by heating the necessary azole to 150 °C in anhydrous DMF[275]. *Liu et al* investigated the synthesis of indazoles by the (3+2) cycloaddition of diazo compounds with arynes and subsequent acyl migration[231]. The benzoylated indazole (**184**) was obtained by reacting the disubstituted diazomethane (**183**) with *o*-(trimethylsilyl)phenyl triflate. The resulting intermediate underwent acyl migration which afforded (**184**).

In the present work, the benzoylated products (**171**) and (**172**) were characterised by ^1H and ^{13}C NMR spectroscopy. The ^1H-NMR spectrum of (**171**) is shown in figure 72. The sharp singlet at 3.95 ppm, which integrates for 6 protons, corresponds to the symmetric methoxy groups at $C_{3'}$ & $C_{5'}$. The singlet at 3.98 ppm corresponds to the methoxy group at $C_{4'}$. The singlet at 7.45 ppm, which integrates for 2 protons, corresponds to the aromatic protons, $H_{2'}$ & $H_{6'}$. The singlet at 8.41 ppm is assigned to the imine proton, H_3. The double doublet at 8.51 ppm, $J = 9.03$, 2.01 Hz, corresponds to H_6. The doublet at 8.68 ppm, $J = 9.03$ Hz, corresponds to H_7. Finally the doublet at 8.76 ppm, $J = 2.01$ Hz, corresponds to H_4.

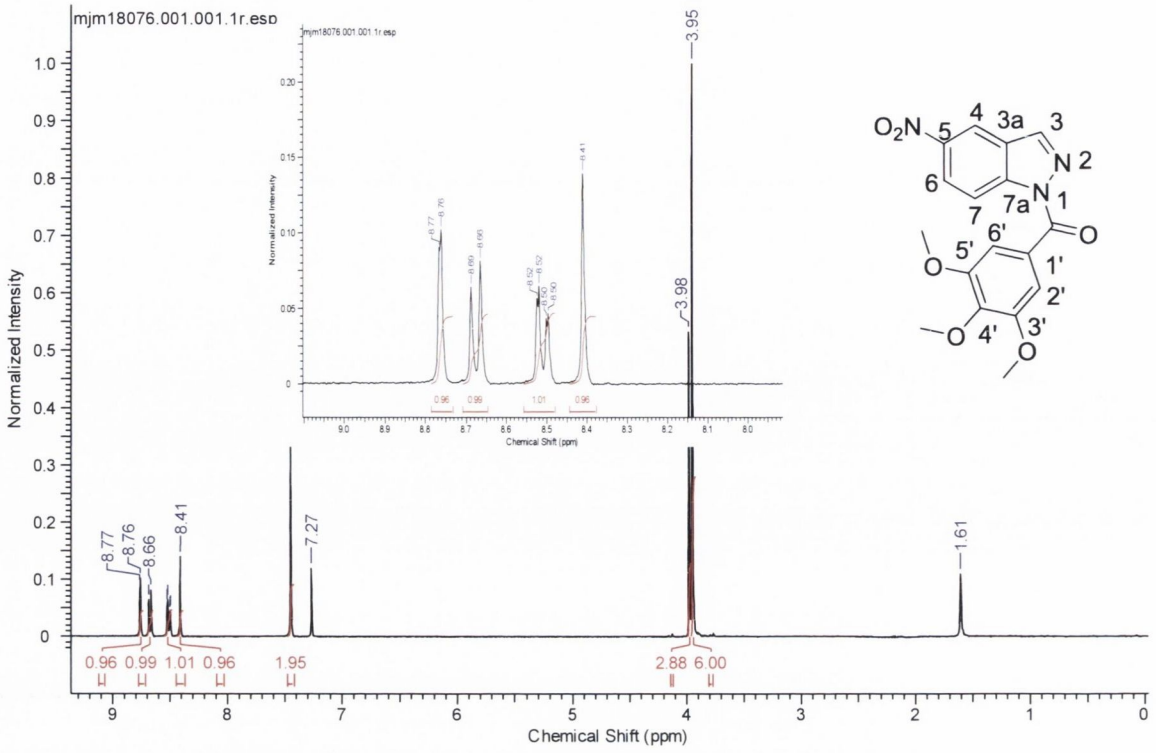


Figure 72: ^{1}H-NMR spectrum of (171)

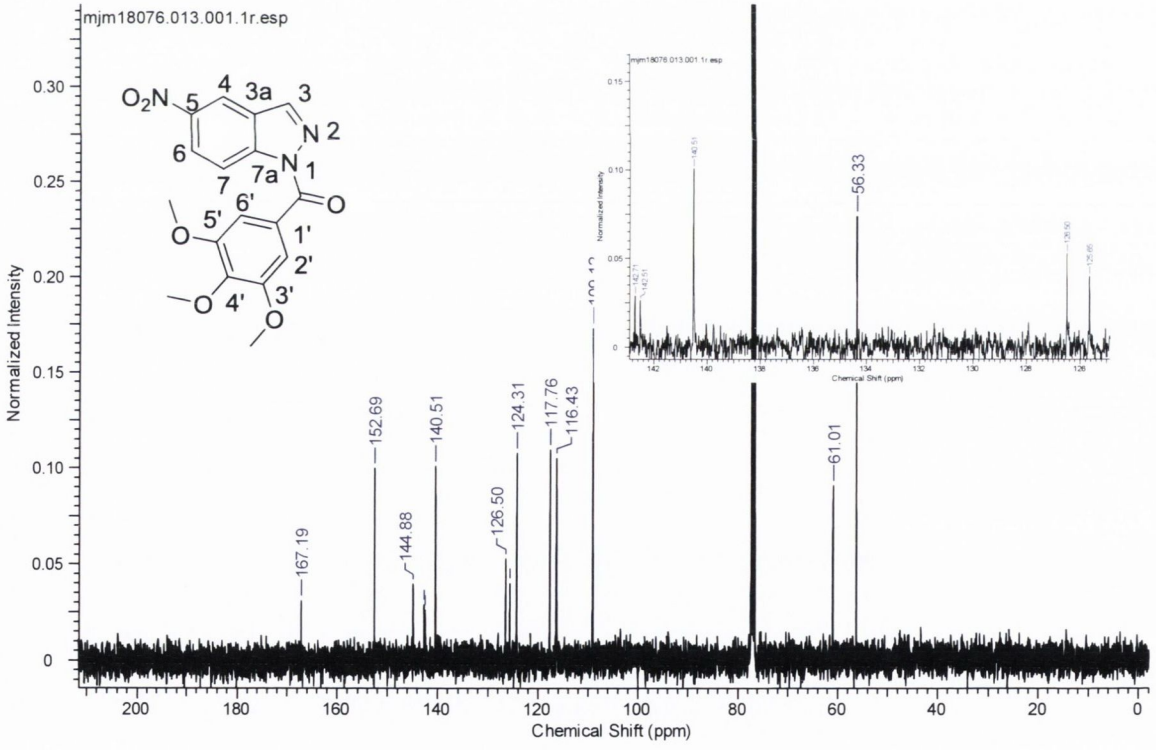


Figure 73: ^{13}C-NMR spectrum of (171)

The ^{13}C-NMR spectrum for (**171**) is shown in figure 73. The signal at 56.33 ppm is attributed to the carbons of the symmetric methoxy groups at $C_{3'}$ & $C_{5'}$. The signal at 61.00 ppm is

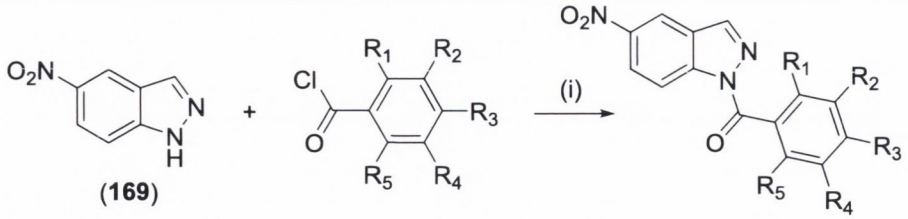
assigned to the carbon of the methoxy group at $C_{4'}$. The signal at 109.12 ppm corresponds to aromatic methine carbons, $C_{2'}$ and $C_{6'}$. The signals at 116.43, 117.75, 124.30 and 140.50 ppm correspond to C_4, C_7, C_6 and C_3 respectively. The signal 152.68 ppm represents the two *ipso* carbons, $C_{3'}$ and $C_{5'}$. These carbons are symmetric and so are magnetically equivalent. The signal at 167.18 ppm belongs to carbonyl carbon. The signals at 125.65, 126.30, 142.51, 142.71, 144.88 ppm correspond to *ipso* carbons, $C_{1'}$, C_{3a}, C_5 and $C_{4'}$ and C_{7a} respectively.

(**171**) was also analysed by IR and high resolution mass spectrometry ($[M+Na]^+$, found $C_{17}H_{15}N_3NaO_6$ = 380.0853). Since (**171**) is prepared by reacting an amine (**169**) with an acid chloride, this would result in the formation of an amide bond. The absorption for the amide carbonyl for (**172**) appears at 1697.6 cm^{-1}. The nitro group absorption appears at 1525.4 cm^{-1}, asymmetric stretch, and 1344.6 cm^{-1}, symmetric stretch.

The 6-nitroindazole isomer was synthesised also by reacting 6-nitroindazole with 3,4,5-trimethoxybenzoyl chloride which afforded (**172**) (55%), figure 66. Once these compounds were synthesised and obtained in satisfactory yields, (**169**) and (**170**) were then reacted with a variety of acid chlorides, table 5 and table 6. Note for all novel compounds synthesised in this project, an asterisk* is present next to the corresponding compound number while for non-novel compounds, the necessary literature reference is given.

Table 5 contains the benzoylated 5-nitroindazole products (**171**), (**185**) – (**192**) synthesised by reacting (**169**) with structurally varied acid chlorides. These compounds contain electron donating substituents on the aryl ring e.g. (**185**) and (**186**) and naphthalene rings e.g. (**190**) and (**191**). The yields are quite good (34 – 71 %). It should be expected that the amide carbonyl stretching vibration should be around the base value of 1690 cm^{-1}. Also since the carbonyl is attached to an aryl ring, conjugation effects should actually increase in frequency from the base value[278]. For all the compounds, except for (**185**), the amide carbonyl frequency increased from the base value of 1690 cm^{-1}.

Table 5: 5-Nitroindazoles with arylcarbonyl substituents at N1



(i) Et_3N, CH_2Cl_2, reflux

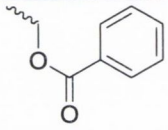
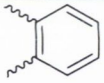
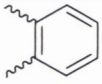
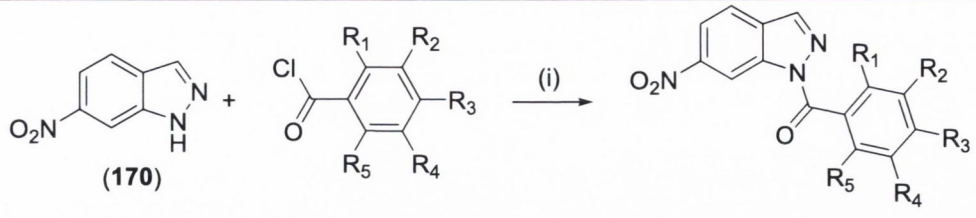
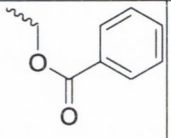
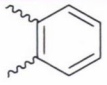
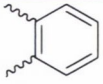
Compound Number	R_1	R_2	R_3	R_4	R_5	IRν_{max} (C=O) cm^{-1}	Yield (%)
(**171**)[276]	H	OCH_3	OCH_3	OCH_3	H	1697.6	54
(**185**)*	H	H	CH_3	H	H	1685.9	65
(**186**)*	H	H	OCH_3	H	H	1694.3	55
(**187**)*	H	OCH_2CH_3	H	OCH_2CH_3	H	1697.2	48
(**188**)*	OCH_2CH_3	H	H	OCH_2CH_3	H	1704.3	55
(**189**)*	H	H	H	H		1693.5, 1719.7	75
(**190**)[276]	H	H	H			1697.9	51
(**191**)*	H	H			H	1714.3	65
(**192**)[277]	H	H	H	H	H	1694.2	71

Table 6 contains the benzoylated 6-nitroindazole products (**172**), (**193**) – (**200**) obtained by reacting (**170**) with different aryl acid chlorides. The yields are comparable to the corresponding 5-nitroindazole derivatives in table 5.

Table 6: 6-Nitroindazoles with arylcarbonyl substituents at N1



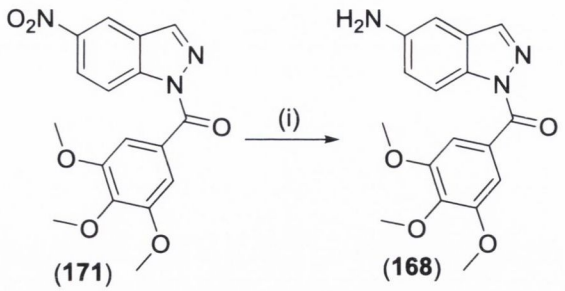
(i) Et_3N, CH_2Cl_2, 20 °C

Compound Number	R_1	R_2	R_3	R_4	R_5	IR (C=O) ν_{max} cm^{-1}	Yield (%)
(172)[267]	H	OCH_3	OCH_3	OCH_3	H	1676.4	55
(193)*	H	H	CH_3	H	H	1685.8	56
(194)[267]	H	H	OCH_3	H	H	1674.1	55
(195)*	H	OCH_2CH_3	H	OCH_2CH_3	H	1672.5	56
(196)*	OCH_2CH_3	H	H	OCH_2CH_3	H	1715.4	48
(197)*	H	H	H	H		1679.6, 1719.1	52
(198)[276]	H	H	H			1714.9	32
(199)*	H	H			H	1686.2	49
(200)*	H	H	H	H	H	1693.7	60

In order to obtain the lead compound (**168**), figure 65, the nitro group had to be reduced to the amine. There exist many methods of nitro reduction[279,280] and these include (i) catalytic or heterogeneous hydrogenation (involving the use of palladium on carbon or platinum oxide or raney nickel and hydrogen in methanol/ethyl acetate/ethanol) (ii) zinc in acetic acid and (iii) tin in hydrochloric acid (Sn/HCl).

The reduction of (**171**) to (**168**) was performed by catalytic hydrogenation using 10 % palladium on carbon in a 1:1 mixture of methanol and ethyl acetate at atmospheric pressure, figure 74. The reaction was monitored by TLC and following reaction completion, the

palladium suspension was filtered through sand/celite® using a sintered glass funnel. This method was used for all subsequent nitro reductions, tables 7 and 8.



(i) 10% Pd/C, 1:1 MeOH:EtOAc, H_2, atmospheric pressure, 20 °C

Figure 74: Preparation of (168)

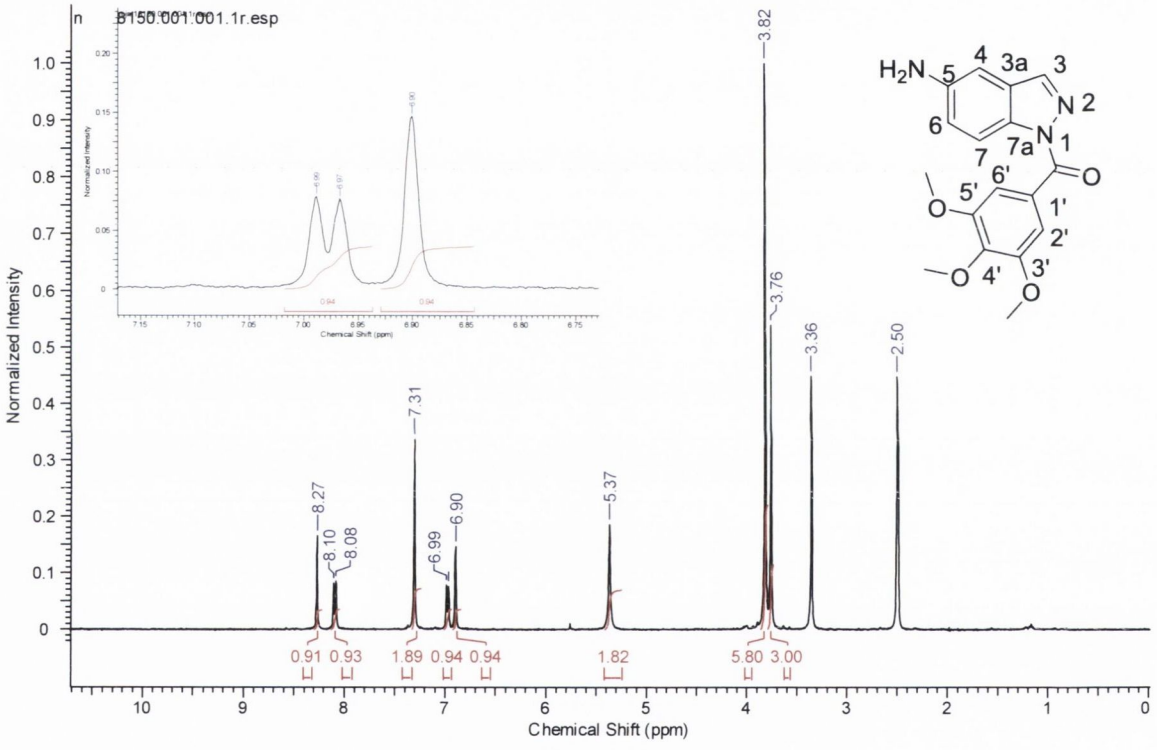


Figure 75: ^{1}H-NMR spectrum of (168)

The ^{1}H-NMR spectrum for (**168**) is shown in figure 75. The singlet at 3.76 ppm corresponds to the protons of the methoxy group at $C_{4'}$. The sharp singlet at 3.82 ppm, which integrates for 6 protons, corresponds to the protons of the two methoxy groups at $C_{3'}$ and $C_{5'}$. The broad singlet at 5.37 ppm, which integrates for 2 protons, corresponds to the amine group protons. The singlet at 6.90 ppm corresponds to H_4. The doublet at 6.98 ppm, J = 8.50 Hz, is assigned to H_6. The sharp singlet at 7.31 ppm corresponds to the protons, $H_{2'}$ and $H_{6'}$. The doublet at 8.09 ppm, J = 8.50 Hz, is assigned to H_7 while the singlet at 8.27 ppm corresponds to the imine proton, H_3.

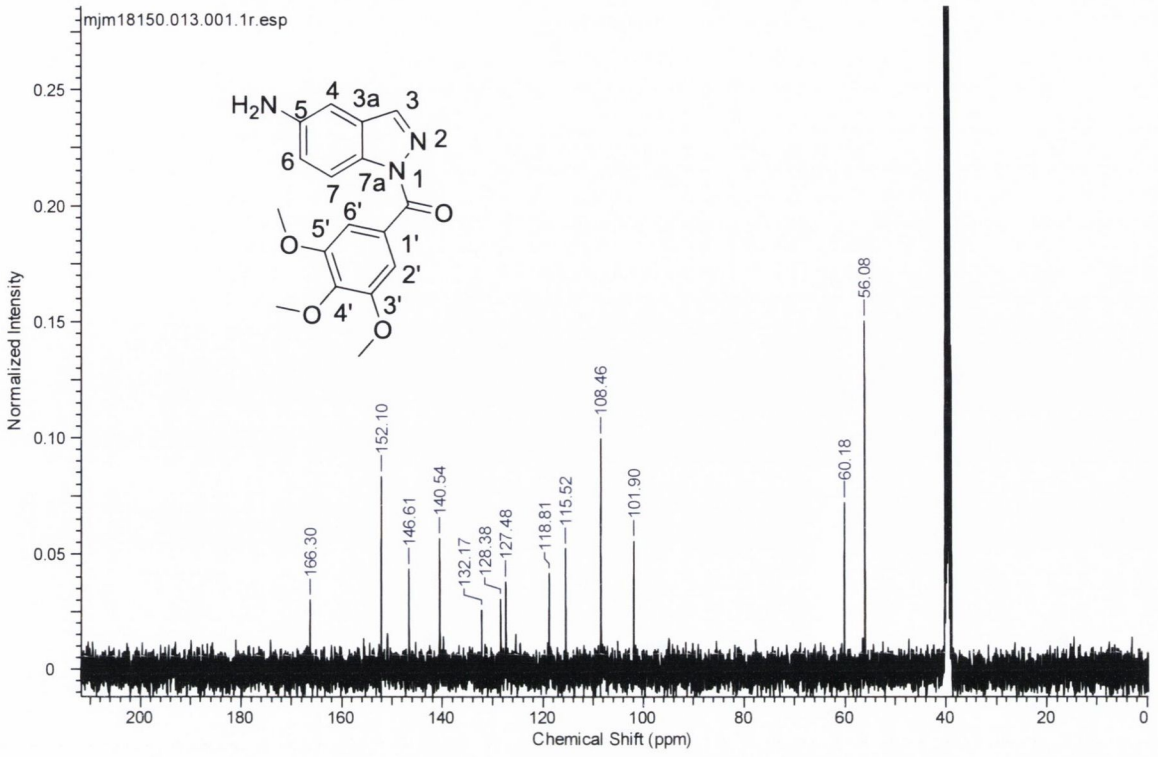
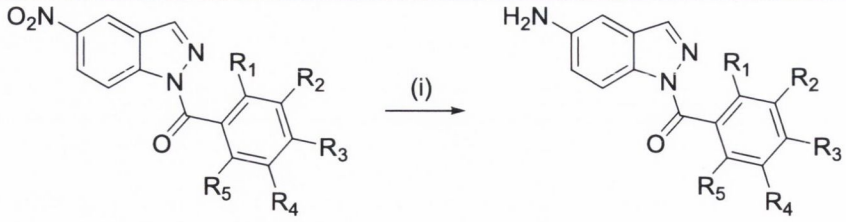


Figure 76: ^{13}C-NMR spectrum for (168)

The ^{13}C-NMR spectrum for (**168**) is shown in figure 76. The signal at 56.10 ppm corresponds to the methoxy carbons at $C_{3'}$ and $C_{5'}$ while the signal at 60.19 ppm corresponds to the methoxy carbon at $C_{4'}$. The signal at 108.23 ppm corresponds to the two aromatic methine carbons at positions $C_{1'}$ and $C_{6'}$. The signal at 101.91, 115.53, 118.83 and 140.55 ppm correspond to C_3, C_7 and C_6 and C_3 respectively. The signal at 166.31 ppm corresponds to the carbonyl group. The signal at 152.11 ppm corresponds to the two aromatic ipso carbons, C_3'and $C_{5'}$. The signals at 127.49, 128.40, 132.19 and 146.63 ppm correspond to C_{3a}, $C_{1'}$ and $C_{4'}$ respectively.

The complete series of 5-amino and 6-aminoindazole products (**168**) and (**201**) – (**217**) obtained from the reduction of the required nitroindazoles, (**171**) & (**185**) – (**192**) and (**172**), (**193**) – (**200**), are contained in tables 7 and 8 respectively. The % yields are quite satisfactory (35 – 98 %). The NH_2 absorption signals appear in the region of ~ 3350 and ~ 3450 cm^{-1} for nearly all the aminoindazoles in the IR spectrum.

Table 7: 5-Aminoindazoles with arylcarbonyl substituents at N1



(i) 10% Pd/C, 1:1 MeOH:EtOAc, H_2, atmospheric pressure, 20 °C

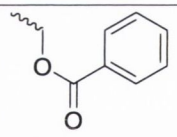
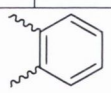
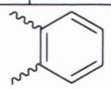
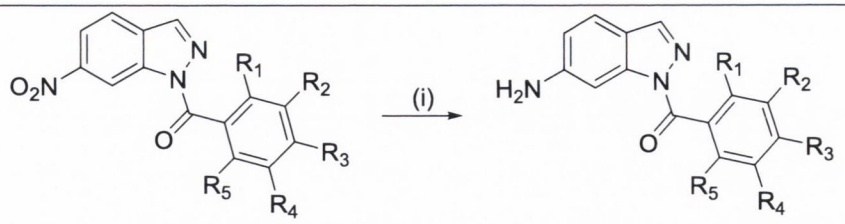
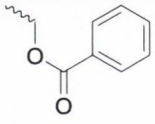
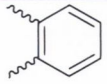
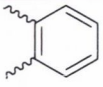
Compound Number	R_1	R_2	R_3	R_4	R_5	IR ν_{max} (NH_2) cm^{-1}	Yield (%)
(**168**)*	H	OCH_3	OCH_3	OCH_3	H	3454.1, 3352.7	90
(**201**)*	H	H	CH_3	H	H	3408.8, 3335.8	90
(**202**)*	H	H	OCH_3	H	H	3448.9, 3362.3	59
(**203**)*	H	OCH_2CH_3	H	OCH_2CH_3	H	3463.8, 3357.7	89
(**204**)*	OCH_2CH_3	H	H	OCH_2CH_3	H	3449.3, 3365.7	92
(**205**)*	H	H	H	H		3458.9, 3362.1	43
(**206**)*	H	H	H			3461.5, 3340.5	62
(**207**)*	H	H			H	3461.5, 3340.5	98
(**208**)*	H	H	H	H	H	3483.1, 3405.8	93

Table 8: 6-Aminoindazoles with arylcarbonyl substituents at N1

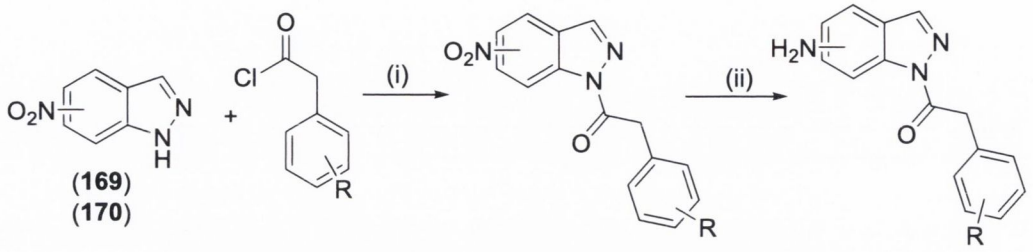


(i) 10% Pd/C, 1:1 MeOH:EtOAc, H_2, atmospheric pressure, 20 °C

Compound Number	R_1	R_2	R_3	R_4	R_5	IR (NH_2) ν_{max} cm^{-1}	Yield (%)
(**209**)*	H	OCH_3	OCH_3	OCH_3	H	3463.8, 3368.7	90
(**210**)*	H	H	CH_3	H	H	3458.9, 3357.5	95
(**211**)*	H	H	OCH_3	H	H	3458.9, 3363.7	87
(**212**)*	H	OCH_2CH_3	H	OCH_2CH_3	H	3463.8, 3370.7	92
(**213**)*	OCH_2CH_3	H	H	OCH_2CH_3	H	3463.8, 3365.1	84
(**214**)*	H	H	H	H		3473.4, 3377.8	53
(**215**)*	H	H	H			3463.7, 3347.8	30
(**216**)*	H	H			H	3463.8, 3367.1	87
(**217**)*	H	H	H	H	H	3425.1, 3343.0	35

2.3 Preparation of analogues of (168) using phenylacetyl chlorides

The next library of compounds was created by first reacting 5-nitroindazole (**169**) and 6-nitroindazole (**170**) with a variety of phenylacetyl chlorides and then reducing these nitro intermediates to the required amino indazole, figure 77. The chemistry used is similar to that in the first library (section 2.2).



(i) CH_2Cl_2, Et_3N (ii) H_2, 10 % Pd/C, MeOH/EtOAc, 20 °C

Figure 77: Synthesis of 5/6 amino indazoles with arylmethylene carbonyl substituents at N1

The compounds differ from the products in first library as they contain a methylene group (CH_2) linking the carbonyl and the aryl ring, rather than a direct N-carbonyl linking group as before, figure 78. The methylene group should affect the potential orientation of the aryl ring with respect to the indazole at the colchicine bonding site of tubulin. This positional change may have some effect on the biochemical potency of the compounds in this library.

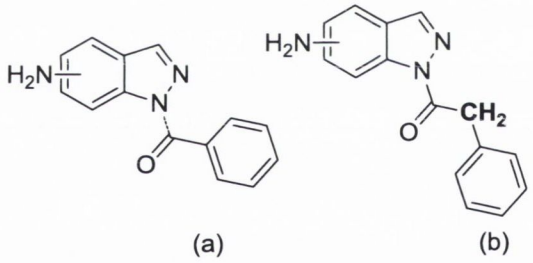
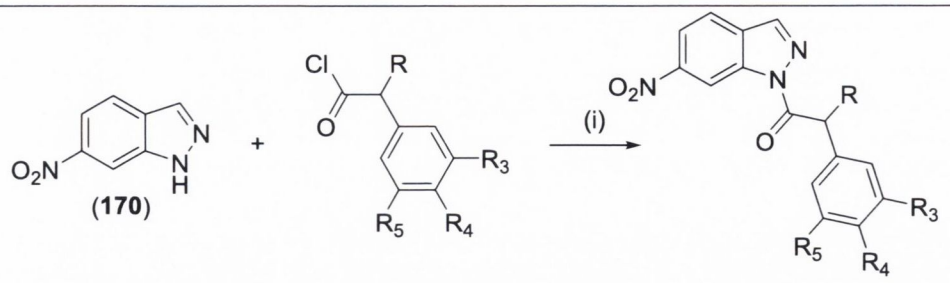


Figure 78: Structural difference between (a) compounds in section 2.2 and (b) compounds in section 2.3

Both (**169**) and (**170**) were reacted with a variety of phenyl acetyl chlorides yielding compounds (**222**) – (**225**), table 10, and (**218**) – (**221**), table 9.

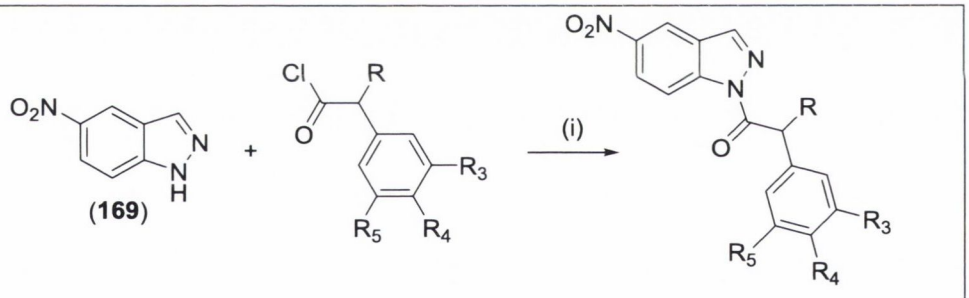
Table 9: 6-Nitroindazoles with aryl methylene carbonyl substituents at N1



(i) CH_2Cl_2, Et_3N, 20 °C

Compound Number	R	R_3	R_4	R_5	IR ν_{max} (C=O) cm^{-1}	% Yield
(**218**)*	H	OCH_3	OCH_3	H	1723.0	69
(**219**)[267]		H	H	H	1723.7	91
(**220**)*	H	H	OCH_3	H	1716.4	45
(**221**)*	H	H	H	H	1715.8	47

Table 10: 5-Nitroindazoles with aryl methylene carbonyl substituents at N1



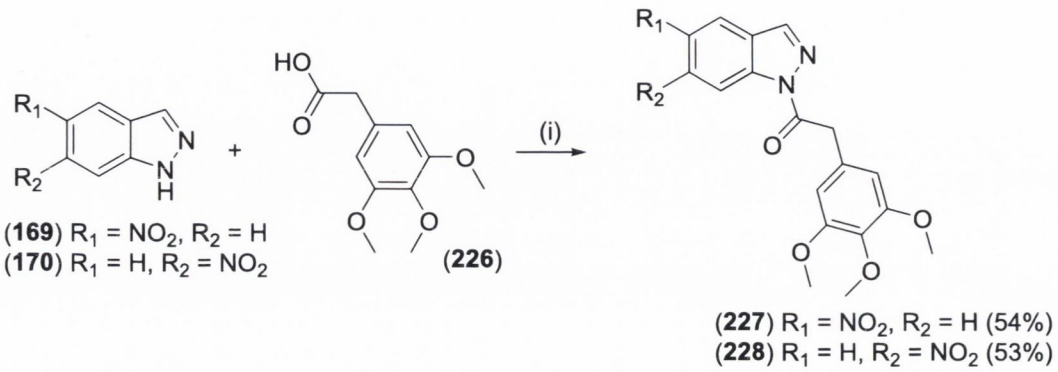
(i) CH_2Cl_2, Et_3N, reflux

Compound Number	R	R_2	R_3	R_4	IR (C=O) ν_{max} cm^{-1}	% Yield
(**222**)*	H	OCH_3	OCH_3	H	1717.2	50
(**223**)*		H	H	H	1725.2	50
(**224**)*	H	H	OCH_3	H	1725.5	33
(**225**)*	H	H	H	H	1721.2	21

* Previously unreported compounds

It was desired to synthesise 3,4,5-trimethoxyphenylacetyl analogues of (**168**) and (**209**) but the necessary phenylacetyl chloride, 2-(3,4,5-trimethoxyphenyl)acetyl chloride, was not

commercially available. However the carboxylic acid precursor, 3,4,5-trimethoxyphenylacetic acid (**226**), was reacted with both (**169**) and (**170**) using a DCC coupling reaction to afford the required products (**227**) and (**228**) , figure 79. DCC is a coupling reagent and it is required as the OH group of the carboxylic acid is a poor leaving group, figure 80.



(i) CH_2Cl_2, DCC, HOBt, 24 h, 20 °C

Figure 79: Synthesis of (227) and (228) using a DCC coupling reaction

The first step in the DCC amide coupling reaction involves the reaction of the carboxylic acid (**226**) with DCC to form the *O*-acylurea intermediate, figure 80. This intermediate then reacts with 1-hydroxy-1*H*-benzotriazole (HOBt), forming the activated ester and dicyclohexylurea (DCU). DCU is insoluble in the reaction mixture and can be removed by filtration[281]. The activated ester reacts with the amine, forming the desired compound (**227**).

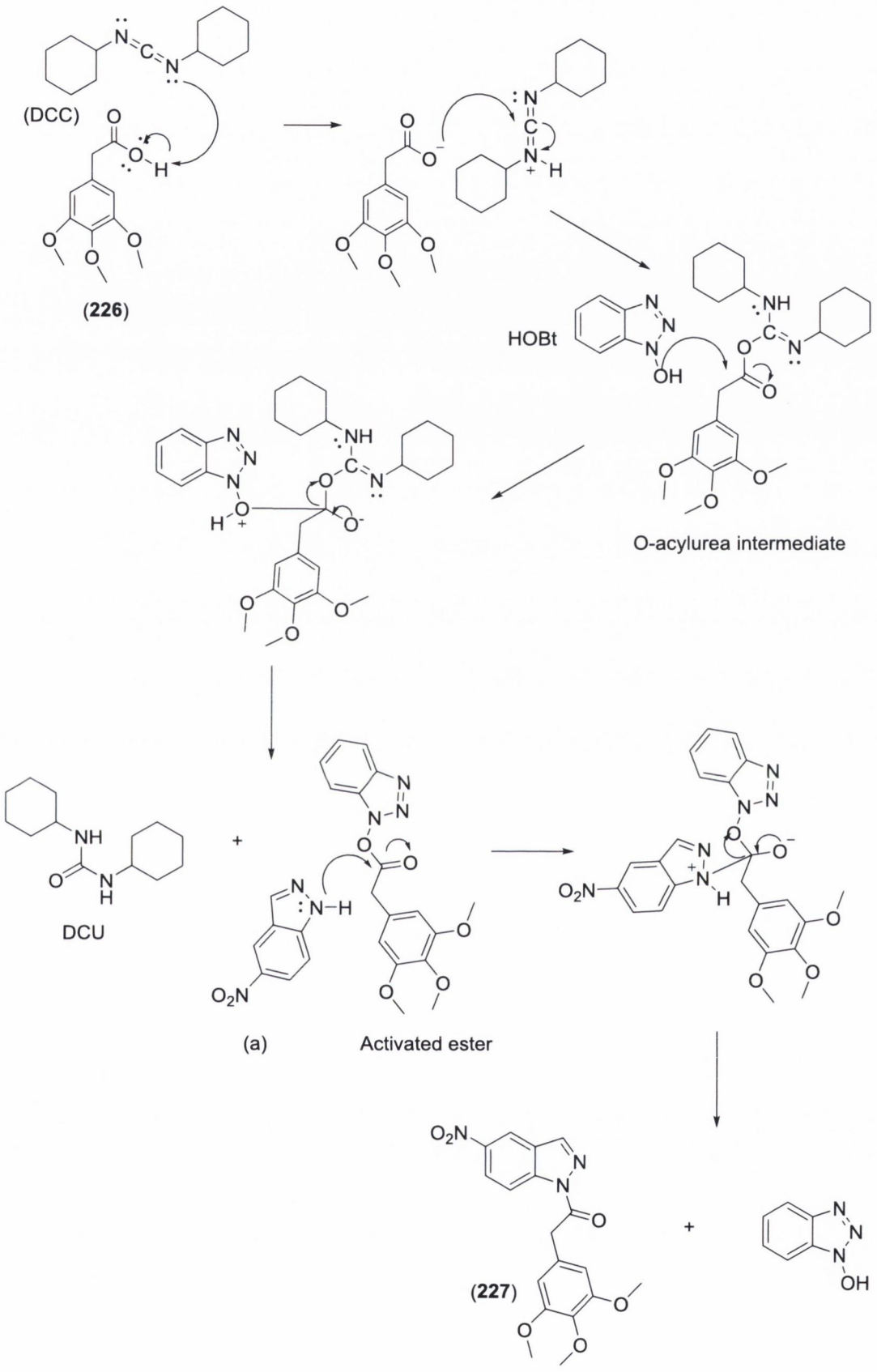


Figure 80: DCC coupling reaction

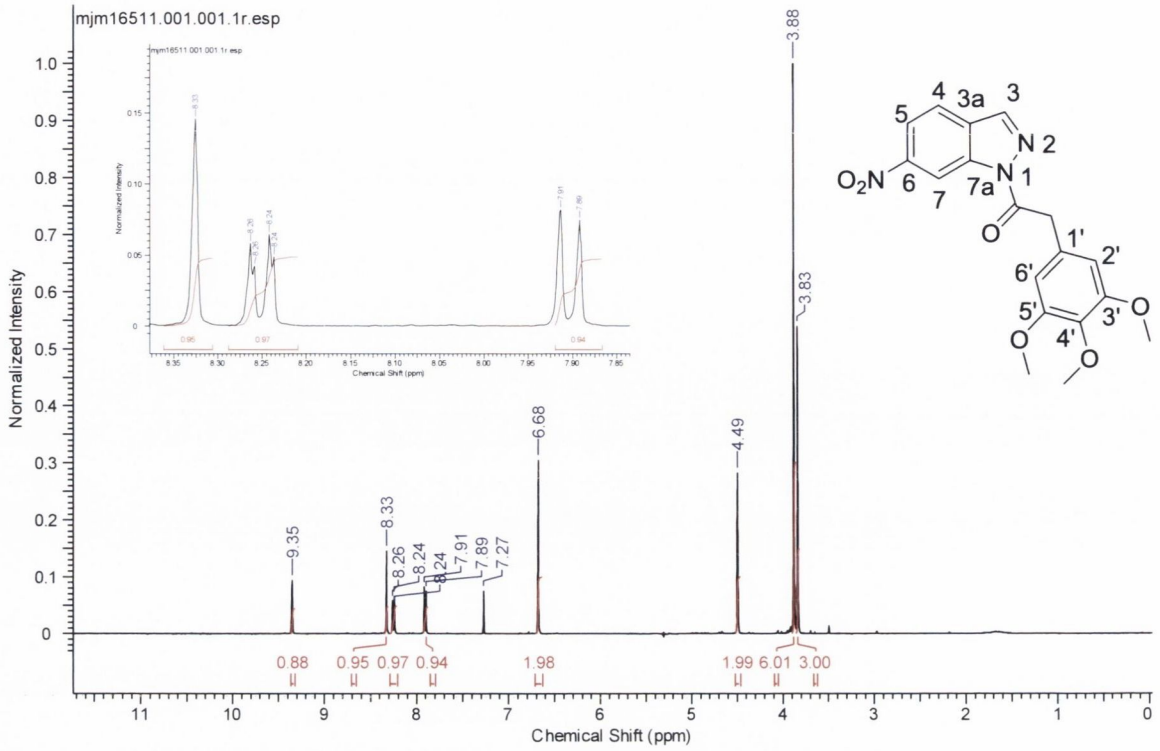


Figure 81: ^{1}H-NMR spectrum of (228)

The ^{1}H-NMR spectrum of (**228**) is shown in figure 81. The singlet at 3.83 ppm, which integrates for 3 protons, is assigned to the protons of the methoxy group at $C_{4'}$ while the sharp singlet at 3.88 ppm corresponds to the protons of the symmetric methoxy groups at $C_{3'}$ & $C_{5'}$. The singlet at 4.49 ppm corresponds to methylene protons. The singlet at 6.68 ppm corresponds to the aromatic protons, $H_{2'}$ and $H_{6'}$. The doublet at 7.90 ppm, J = 8.50 Hz, corresponds to H_4. The double doublet at 8.25 ppm, J = 8.50, 2.00 Hz, is assigned to H_5. The singlet at 8.32 ppm is assigned to H_3 while the singlet at 9.35 ppm is assigned to H_7.

The ^{13}C-NMR and DEPT spectra of (**228**) are shown in figures 82 and 83 respectively. The signal at 41.32 ppm corresponds to the methylene carbon as it has an opposite phase to the CH and CH_3 carbons. The signal at 55.78 ppm is assigned to the carbons of the symmetric methoxy groups at $C_{3'}$ & $C_{5'}$, while the signal at 60.48 ppm is assigned to the carbon of the methoxy group at $C_{4'}$. The signal at 106.45 ppm corresponds to the aromatic methine carbons, $C_{2'}$ and $C_{6'}$. The signals at 111.56, 119.31, 121.32 and 138.91 ppm correspond to C_7, C_5, C_4 and C_3 respectively. The signal at 152.98 ppm corresponds to the two aromatic *ipso* carbons, $C_{3'}$ and $C_{5'}$. The signal at 170.88 ppm is assigned to carbonyl carbon. The signals at 128.21, 129.29, 138.04 and 148.18 ppm correspond to C_{3a}, $C_{1'}$, $C_{4'}$ and C_5 respectively.

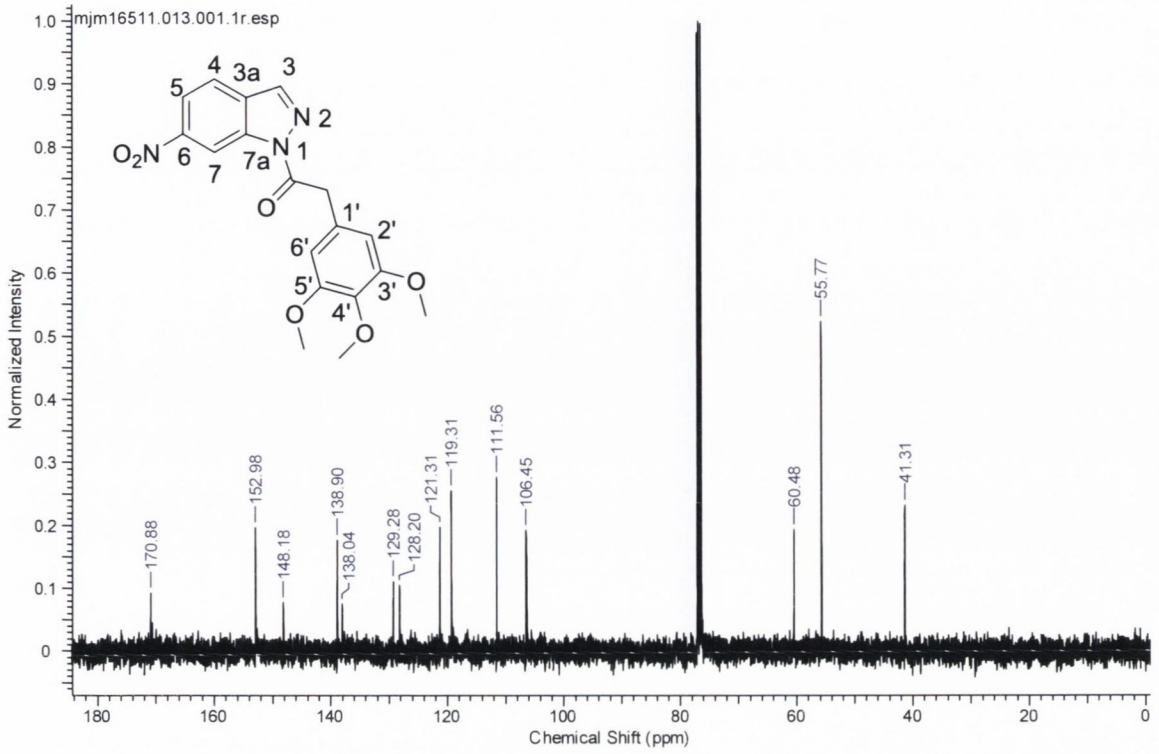


Figure 82: ^{13}C-NMR spectrum of (228)

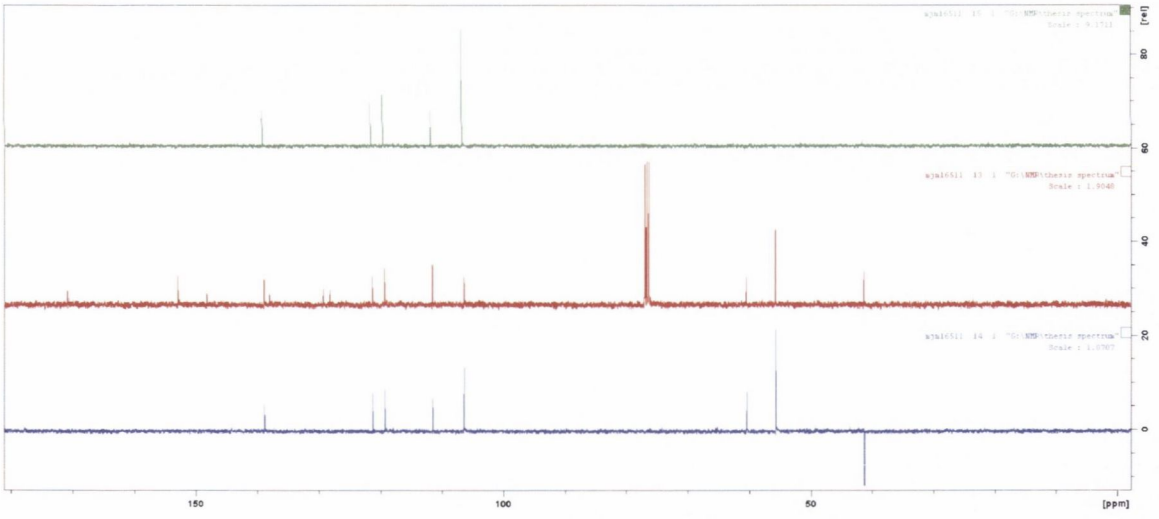
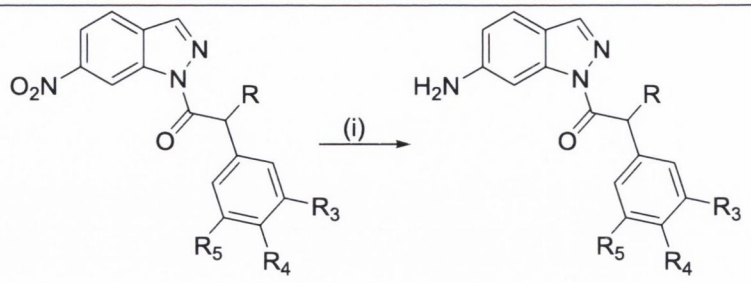


Figure 83: Dept 135, Dept 90 and ^{13}C-NMR spectra of (228)

The nitroindazoles in tables 9 and 10, (**218**) – (**221**) and (**222**) – (**225**), and compounds (**227**) and (**228**) were all reduced using the same hydrogenation method as described in section 2.2 (10% Pd/C, H_2) yielding compounds (**229**) – (**233**) and (**234**) – (**238**). The reduced final

compounds are shown in tables 11 and 12. The yields for all the reduced compounds were quite satisfactory (70 – 96 %).

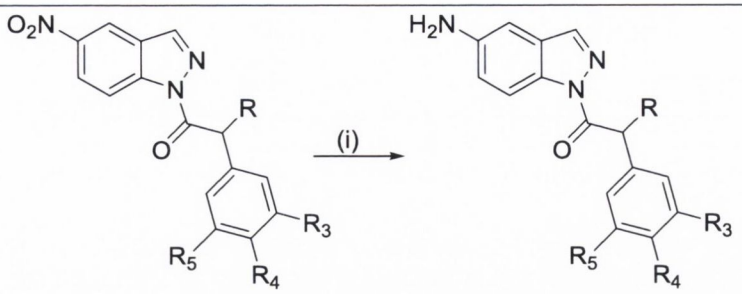
Table 11: 6-Aminoindazoles with aryl methylene carbonyl substituents at N-1



(i) H_2, 10 % Pd/C, 1:1 MeOH/EtOAc, 20 °C

Compound Number	R	R_3	R_4	R_5	IR (NH_2) ν_{max} cm^{-1}	% Yield
(**229**)*	H	OCH_3	OCH_3	H	3473.4, 3363.3	91
(**230**)*		H	H	H	3473.4, 3371.1	91
(**231**)*	H	H	OCH_3	H	3454.1, 3367.1	80
(**232**)*	H	H	H	H	3454.1, 3363.2	90
(**233**)*	H	OCH_3	OCH_3	OCH_3	3452.3, 3367.4	88

Table 12: 5-Aminoindazoles with aryl methylene carbonyl substituents at N-1



(i) H_2, 10% Pd/C, 1:1 MeOH/EtOAc, 20 °C

Compound Number	R	R_3	R_4	R_5	I.R. (NH_2) ν_{max} cm^{-1}	% Yield
(**234**)*	H	OCH_3	OCH_3	H	3454.1, 3366.8	93
(**235**)*		H	H	H	3458.9, 3373.0	96
(**236**)*	H	H	OCH_3	H	3449.3, 3365.0	83
(**237**)*	H	H	H	H	3449.3, 3366.2	70
(**238**)*	H	OCH_3	OCH_3	OCH_3	3452.4, 3367.4	85

As an example, the ^{1}H-NMR spectrum of (**233**) is shown in figure 84. The singlet at 3.64 ppm corresponds to the protons of the methoxy group at $C_{4'}$ while the sharp singlet at 3.74 ppm is assigned to the protons of the symmetric methoxy groups at $C_{3'}$ & $C_{5'}$. The singlet at 4.38 ppm corresponds to the methylene protons while the broad singlet at 5.84 ppm is assigned to the amine protons. The multiplet 6.65 – 6.70 ppm is comprised of protons, H_4 and $H_{2'}$& $H_{6'}$. The singlet at 7.44 ppm is assigned to H_7 while the doublet at 7.48, J = 8.54 Hz, corresponds to H_4. The singlet at 8.16 ppm is assigned to H_3.

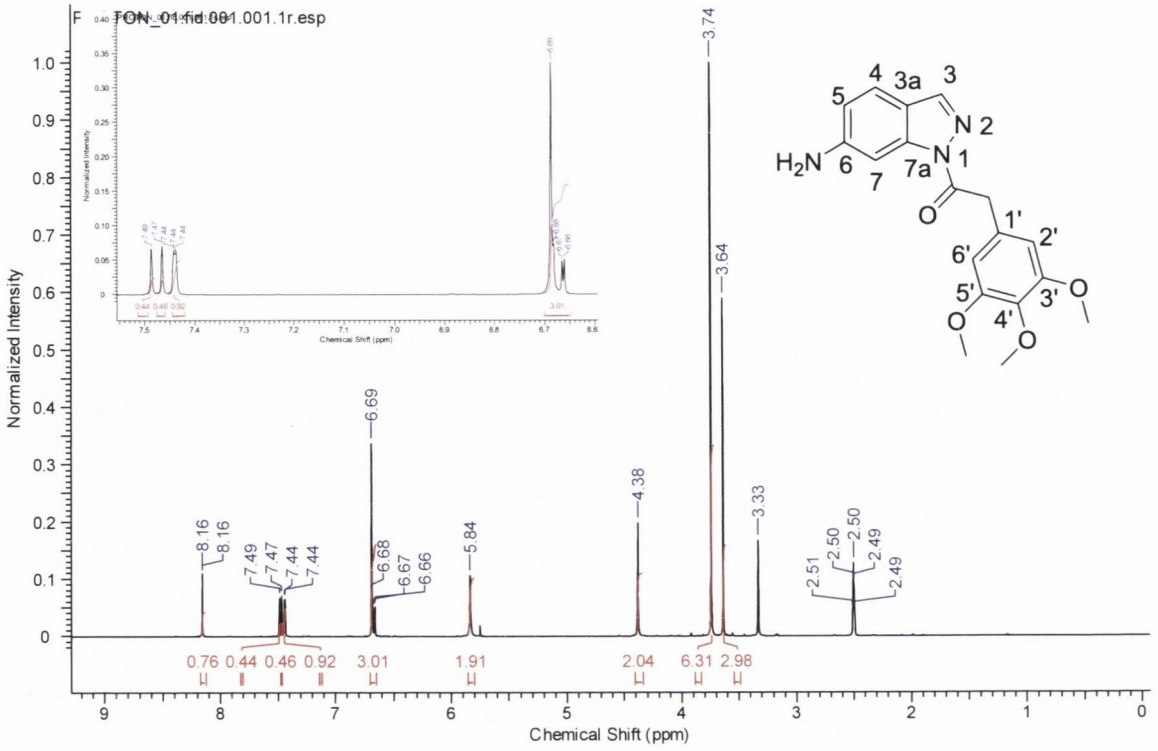


Figure 84: ^{1}H-NMR spectrum of (233)

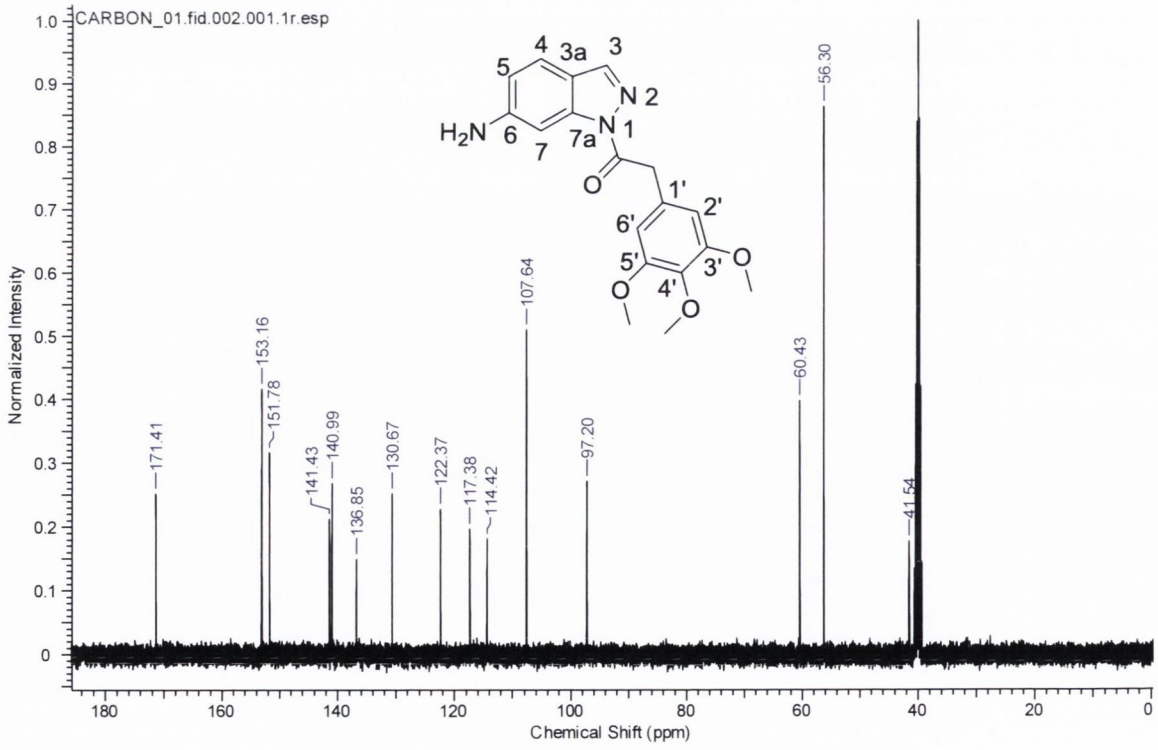


Figure 85: ^{13}C-NMR spectrum of (233)

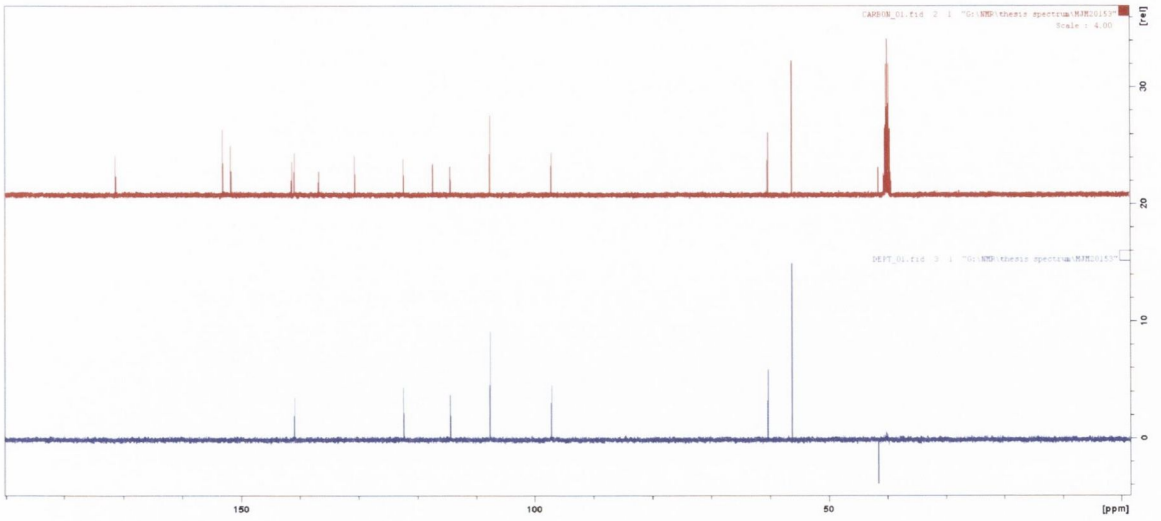


Figure 86: ^{13}C-NMR and DEPT 135 spectra of (233)

The ^{13}C-NMR and DEPT 135 spectra for (**233**) are shown in figures 85 and 86 respectively. The signal at 41.54 ppm corresponds to the methylene carbon, see figure 86. The signal at 56.30 ppm is assigned to the carbons of the symmetric methoxy groups at $C_{3'}$ & $C_{5'}$ while the signal at 60.43 ppm corresponds to the carbon of the methoxy group at $C_{4'}$. The signals at 97.21, 107.65, 114.42, 122.37 and 141.00 ppm are assigned to the aromatic methine carbons C_7, $C_{2'}$& $C_{6'}$, C_5, C_4 and C_3 respectively. The signal at 171.41 ppm is assigned to the amide carbonyl while the signal at 153.16 ppm is assigned to the aromatic *ipso* carbons $C_{3'}$ & $C_{5'}$. The signals at 117.39, 130.67, 136.85, 141.43 and 151.78 ppm are assigned to the aromatic ipso carbons C_{3a}. $C_{1'}$, $C_{4'}$, C_{7a} and C_6 respectively.

2.4 Preparation of 1-benzyl analogues of (168)

The modification of the bridge between the *N*-1 nitrogen and the aryl ring for the lead compound (**168**) was investigated further in this library. Compounds in section 2.3 contained a methylene (CH_2) group between the *N*-1 carbonyl and the aryl ring. It was desired to prepare indazole derivatives that would just have a methylene bridge between the *N*-1 atom and the aryl ring, figure 87. The methylene group should affect the potential orientation and also potential H-bonding of the aryl ring with respect to the indazole core at the colchicine binding site of tubulin. This positional change may have some effect on the potency of the compounds in this library

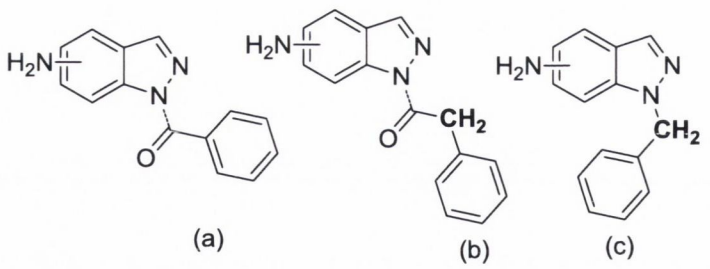
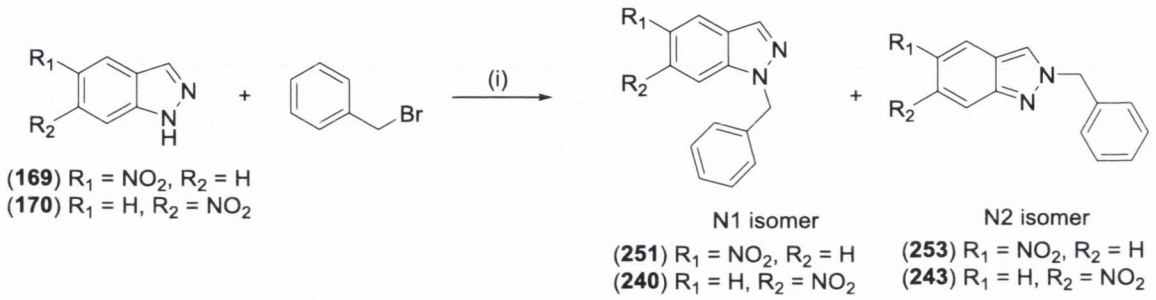


Figure 87: Structural differences between (a) section 2.2, (b) section 2.3 and (c) section 2.4

This library was prepared by reacting indazoles (**169**) and (**170**) with a variety of benzyl bromide or alkyl bromides and again reducing the nitro intermediates to the corresponding amine. However the first step in this reaction produced the desired products (**251**) and (**240**), the N1 regioisomers, and the N2 regioisomers, (**253**) and (**243**) for both (**169**) and (**170**)[282] respectively.



(i) Anhydrous DMF, Cs_2CO_3, 20 °C

Figure 88: Synthesis of 5-nitro and 6-nitroindazoles with benzyl substiutents at N-1 and N-2

Claramunt et al first observed the potential of indazole to form regioisomers on alkylation since it contained two nitrogen atoms capable of reacting with electrophiles[283]. It was suggested that the addition of aqueous base, heating the reaction or altering the electrophile could result in the regioselective synthesis of the *N*-1 regioisomer. From a recent study investigating the alkylation of indazole with alkyl halides, researchers discovered that when the alkylation reaction of (**170**) with methyl bromoacetate was carried out, in anhydrous DMF such that the final concentration of (**170**) was 0.3 M, using two molar equivalents of methyl bromoacetate and three molar equivalent of cesium carbonate, the N1: N2 ratio gradually increased with time. Their results suggested thermodynamic control for the alkylation by methyl bromoactetate. Further experiments involving alkylation of (**170**) with ethyl bromoacetate helped in the explanation of the mechanism, figure 89.

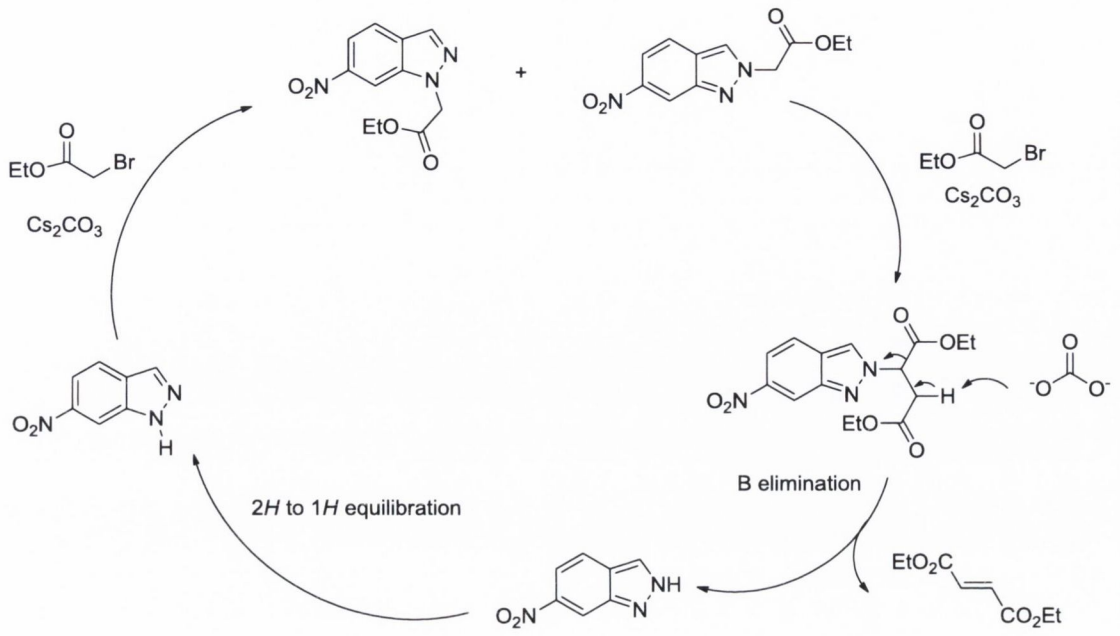
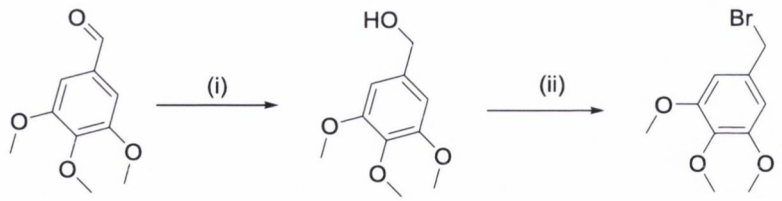


Figure 89: Reaction mechanism for the alkylation of 6-nitroindazole

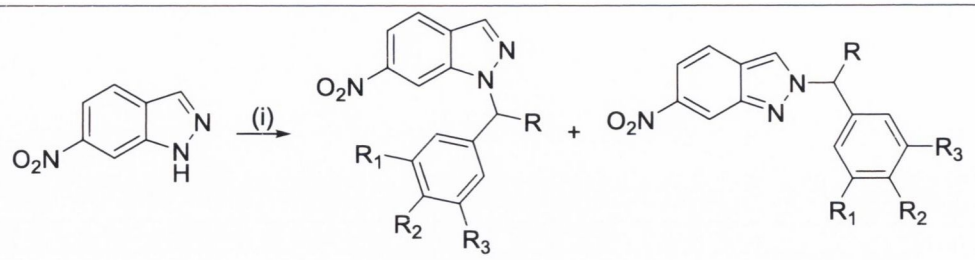
In the present work, the *N*-1:*N*-2 isomers were separated using flash column chromatography. In all cases, the *N*-1 regioisomer was less polar than the corresponding N-2 regioisomer. Tables 13 and 14 contain the products, (**239**) – (**248**) and (**249**) – (**258**), from the alkylation and benzylation of (**170**) and (**169**) respectively. As in the previous library, it was desired that an analogue of (**168**), with just a methylene group between the nitrogen and the aromatic ring, be synthesised for this library. However the necessary benzyl bromide, 3,4,5-trimethoxybenzyl bromide, was not available commercially; but it could be synthesized using the chemistry in figure 90.



(i) MeOH, $NaBH_4$ (ii) DCM, PBr_3

Figure 90: Preparation of 3,4,5-trimethoxybenzyl bromide

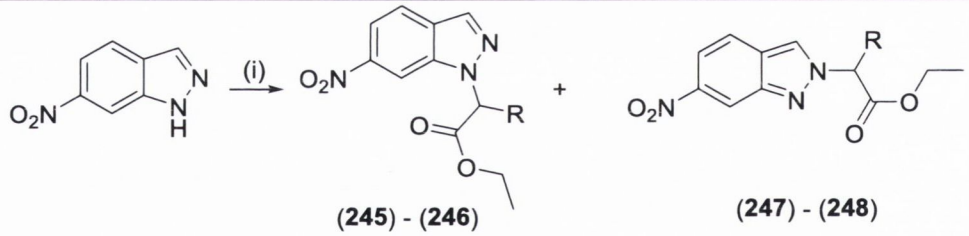
Table 13: 6-Nitroindazoles with alkyl ester or benzyl substituents at *N*-1 or *N*-2



(239) - (241) **(242) - (244)**

(i) Anhydrous DMF, Cs_2CO_3, 20 °C

Compound Number	R	R_1	R_2	R_3	Yield (%)
(239)*	H	OCH_3	OCH_3	OCH_3	37
(242)*					12
(240)[284]	H	H	H	H	32
(243)[284]					19
(241)*		H	H	H	12
(244)*					9

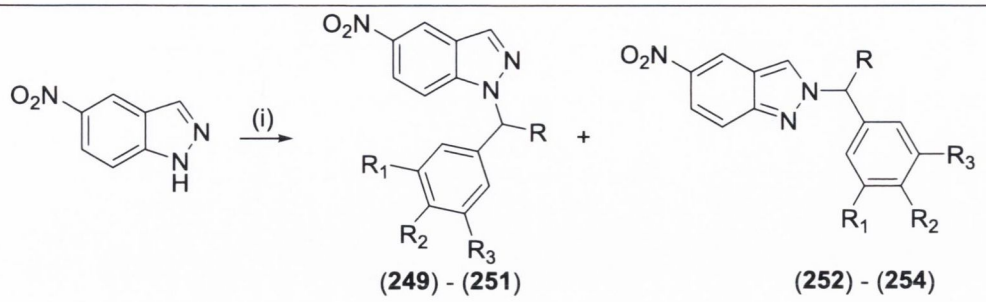


(245) - (246) **(247) - (248)**

(i) Anhydrous DMF, Cs_2CO_3, 20 °C

Compound Number	R	Yield (%)
(245)*	CH_3	42
(247)*		34
(246)[285]	H	40
(248)*		2

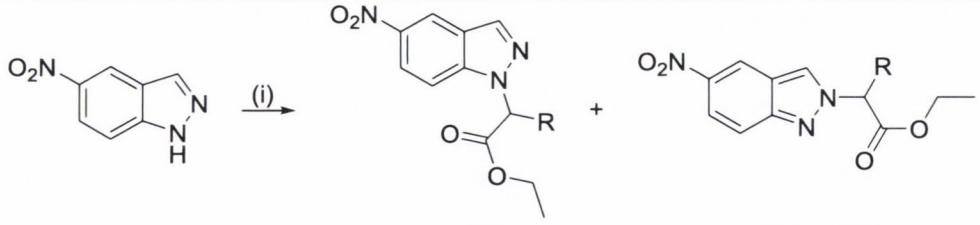
Table 14: 5-Nitroindazoles with alkyl ester or benzyl substituents at N1 or N2



(249) - (251) **(252) - (254)**

(i) Anhydrous DMF, Cs_2CO_3, 20 °C

Compound Number	R	R_1	R_2	R_3	Yield (%)
(249)*	H	OCH_3	OCH_3	OCH_3	44
(252)*					10
(250)[286]	H	H	H	H	49
(251)[286]					18
(253)*		H	H	H	40
(254)*					-



(255) - (256) **(257) - (258)**

(i) Anhydrous DMF, Cs_2CO_3, 20 °C

Compound Number	R	Yield (%)
(255)*	CH_3	13
(257)*		6
(246)[285]	H	46
(248)*		8

#Compound (**254**) could not be purified successfully by flash column chromatography and so % yield was not determined.

For all the alkylation and benzylation experiments performed in this project, the NMR technique Heteronuclear Multiple Bond Correlation (HMBC) was used to determine the

identity of the isolated products as the *N*-1 or *N*-2 regioisomers. This NMR technique measures long range coupling/connection between hydrogens and carbons that are within 2 to 3 bond lengths away[288]. The following explains the structural elucidation process using the benzylation of 6-nitroindazole (**170**) with benzyl bromide as an example.

The benzylation of (**170**) yielded two products, with the expected product (**240**) in 32 % yield and its *N*-2 regioisomer (**243**) in 19 % yield, figure 91.

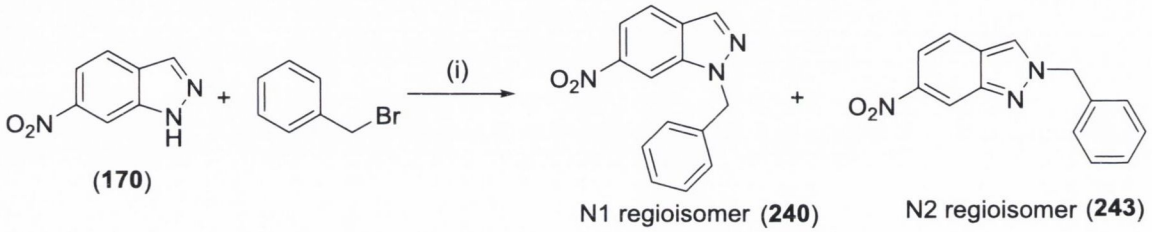


Figure 91: Reaction of 6-nitroindazole with benzyl bromide

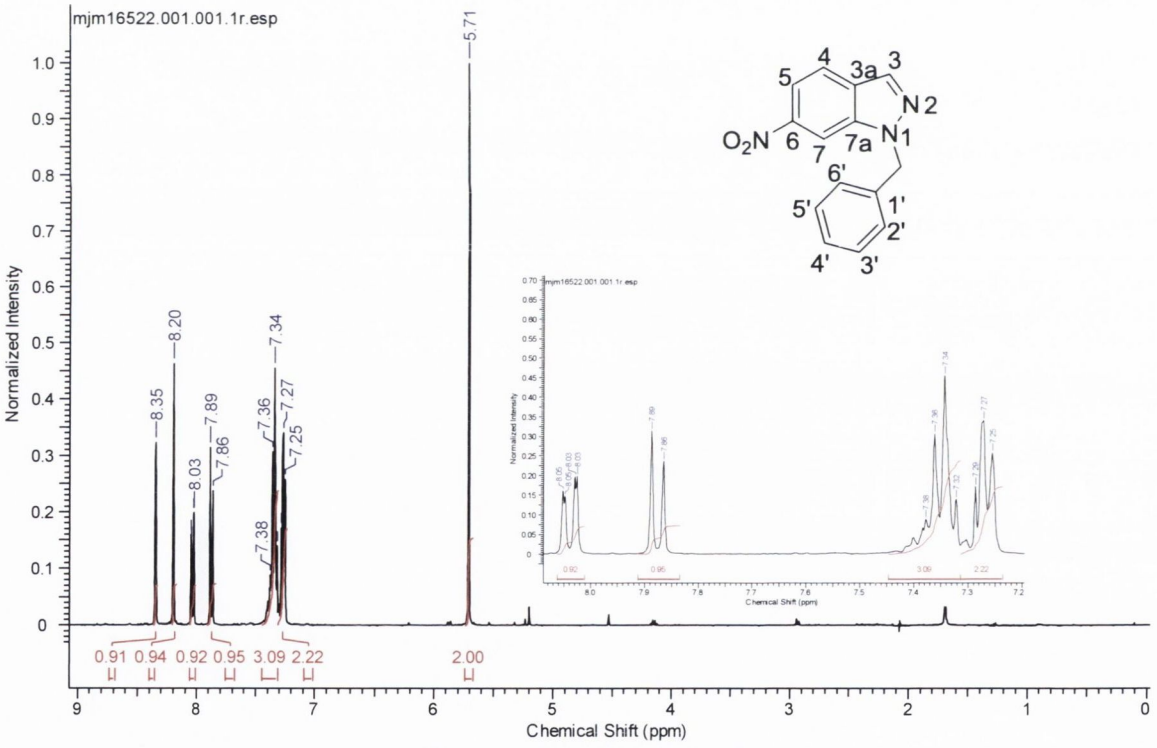


Figure 92: ^{1}H-NMR spectrum of (240)

The ^{1}H-NMR spectrum of the *N*-1 isomer (**240**) is shown in figure 92. The sharp singlet at 5.71 ppm corresponds to the methylene group. The multiplets from 7.25 ppm to 7.29 ppm and 7.32 ppm to 7.38 ppm are assigned to the aromatic protons, $H_{2'}$ to $H_{6'}$. The doublet at 7.88 ppm, *J*

= 9.00 Hz, corresponds to the proton H_4. This proton experiences *ortho* coupling to H_5. The double doublet at 8.04 ppm, J = 9.00, 1.50 Hz, is assigned to the proton H_5. The signal at 8.20 ppm is assigned to the imine proton, H_3. The signal at 8.35 ppm corresponds to the proton H_7.

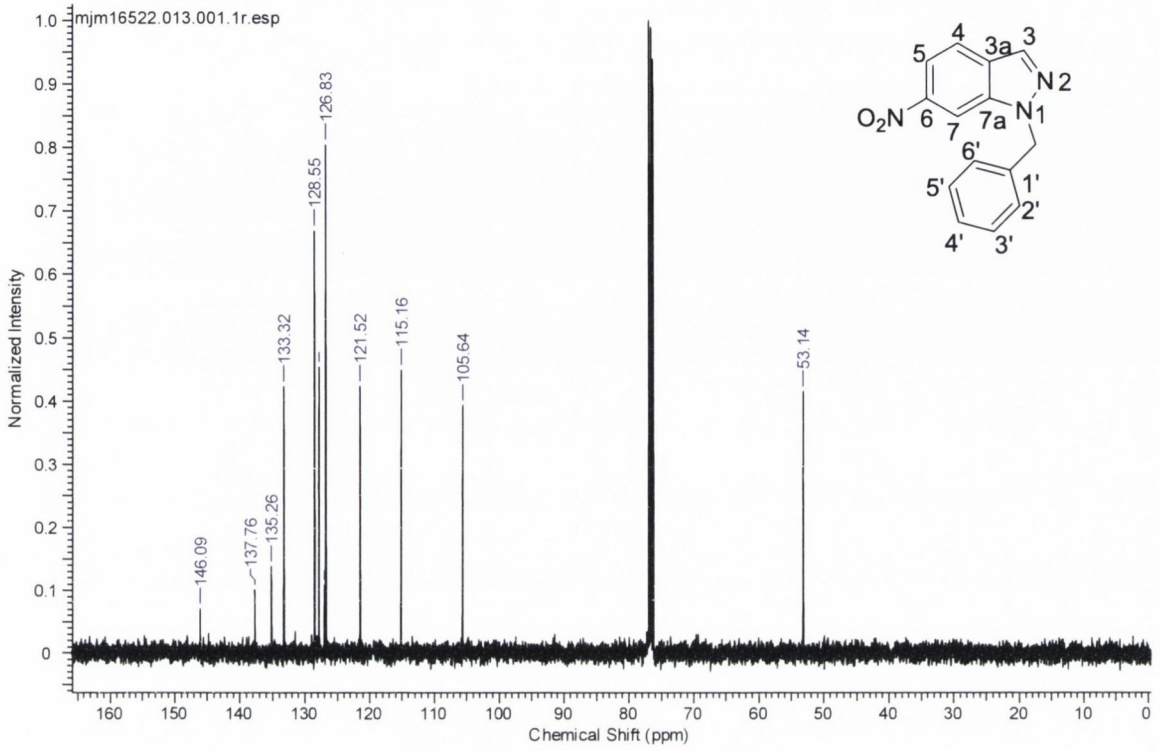


Figure 93: ^{13}C-NMR spectrum of (240)

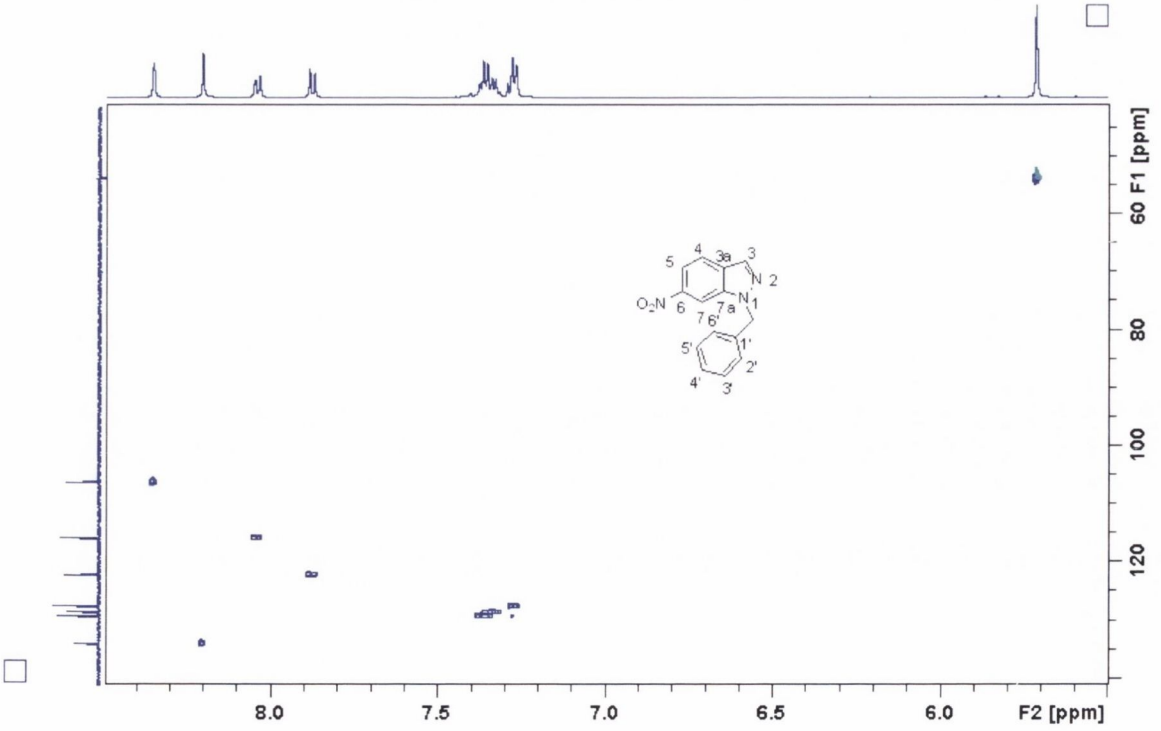


Figure 94: C-H COSY spectrum of (240)

The ^{13}C-NMR and C-H COSY spectra of the *N*-1 benzylated isomer (**240**), figures 93 and 94 respectively, enabled the assignment of the aromatic methine carbons. The C-H COSY is an example of a 2 dimensional NMR spectrum with the ^{1}H-NMR spectrum on the horizontal axis and the ^{13}C-NMR spectrum on the vertical axis. A series of cross peaks will be present along the diagonal for any carbon directly bonded to a proton[278]. Thus the signals at 105.65, 115.16, 121.53, 126.83, 127.87, 128.56 and 133.32 ppm correspond to carbons C_7, C_5, C_4, $C_{2'}$& $C_{6'}$, $C_{4'}$, $C_{3'}$& $C_{5'}$ and C_3 respectively.

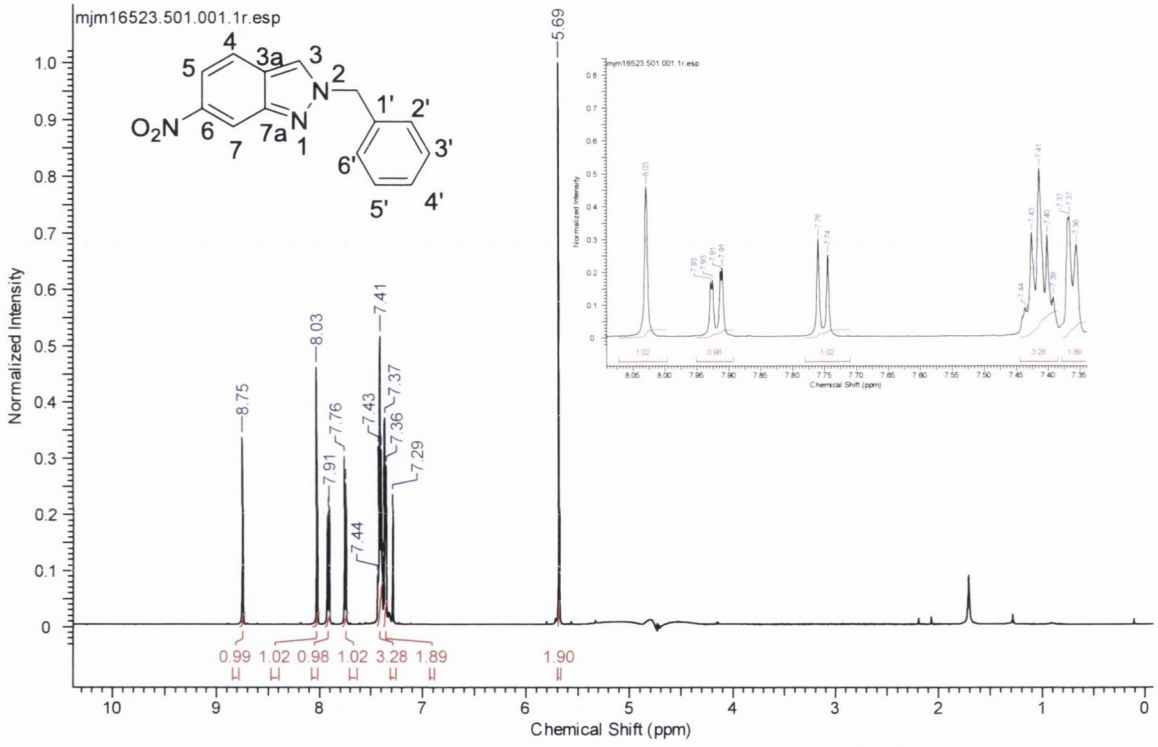


Figure 95: ^{1}H-NMR spectrum of (243)

The ^{1}H-NMR spectrum of the *N*-2 benzylated isomer (**243**) is shown in figure 95. The sharp singlet at 5.69 ppm corresponds to the methylene group protons. The multiplets from 7.34 – 7.37 ppm (2 protons) and 7.39 to 7.43 ppm (3 protons) are assigned to the aromatic protons, $H_{1'}$ to $H_{6'}$. The doublet at 7.75 ppm, J = 9.00 Hz, corresponds to the proton H_4. The double doublet at 7.92 ppm, J = 9.00, 1.80 Hz, is assigned to H_5. The signal at 8.03 ppm corresponds to the proton H_3 while the signal at 8.75 ppm corresponds to H_7.

The ^{13}C-NMR and C-H COSY spectra for the N-2 benzylated isomer (**243**), see figures 96 and 97 respectively, enabled the assignment of the aromatic methine carbons. As such, the signals

at 115.69, 115.86, 121.46, 123.71, 128.25, 128.88 and 129.15 ppm correspond to C_7, C_5, C_4, C_3, $C_{2'}$ & $C_{6'}$, $C_{4'}$ and $C_{3'}$ & $C_{5'}$ respectively.

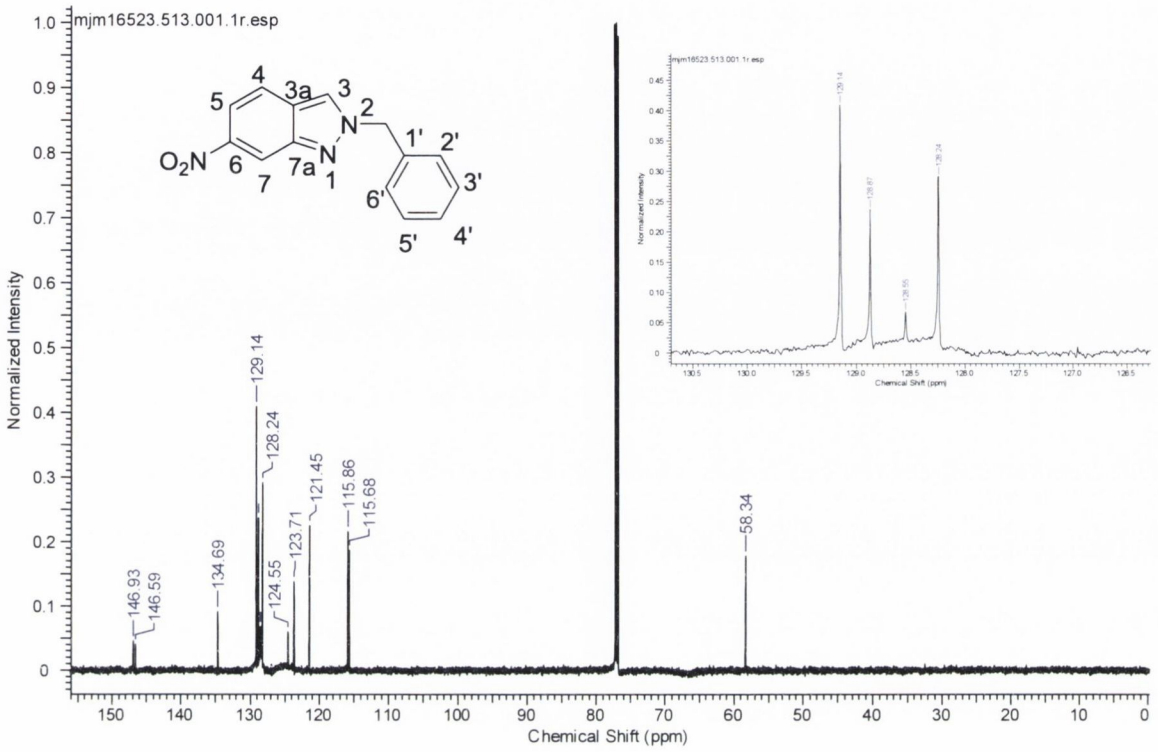


Figure 96: ^{13}C-NMR spectrum of (243)

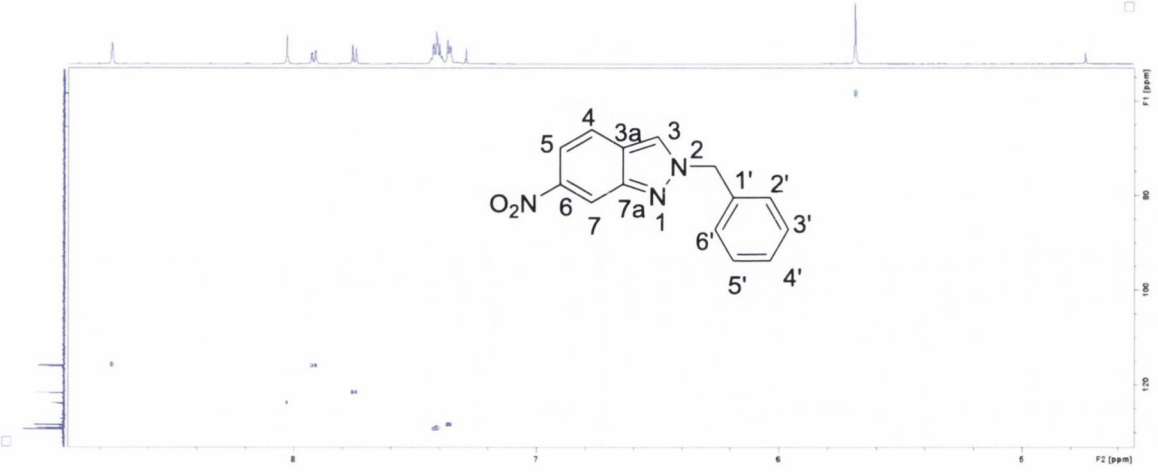


Figure 97: C-H COSY spectrum of (243)

Figures 98 and 99 illustrate the structural assignment for the *N*-1 and *N*-2 isomers (**240**) and (**243**) accomplished by the NMR experiments thus far.

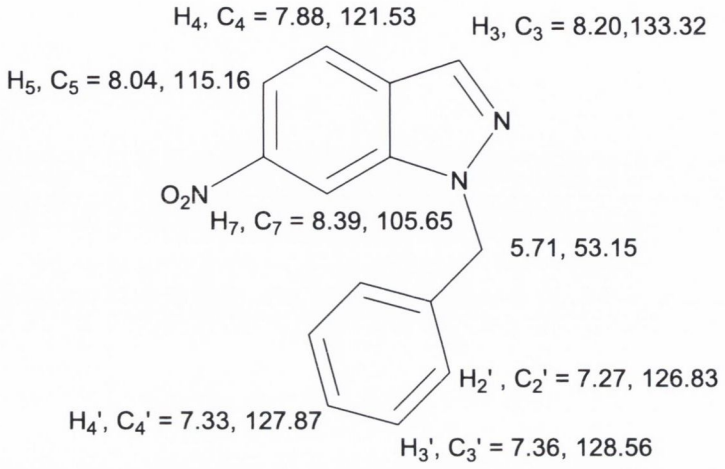


Figure 98: Proton NMR and carbon assignment of (240)

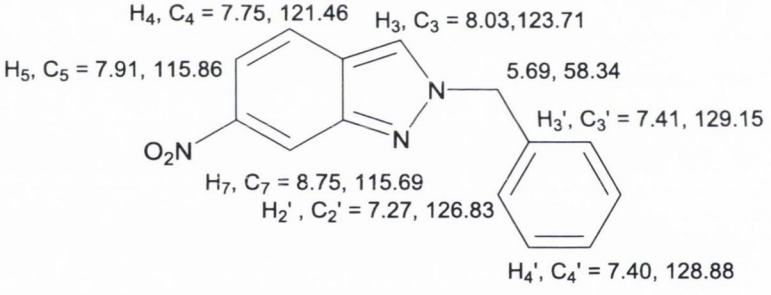


Figure 99: Proton NMR and carbon assignment of (243)

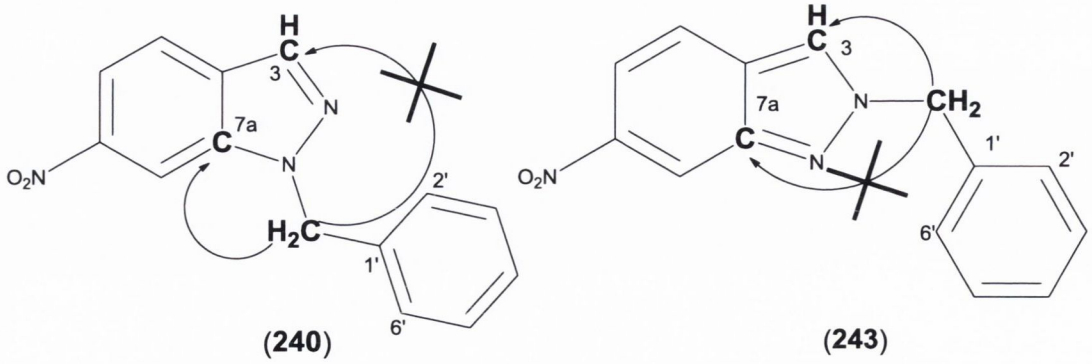


Figure 100: Possible long range coupling for the methylene group in (240) and (243)

Analysis of the HMBC spectra of compounds (**240**) and (**243**) was critical in the structural elucidation of the products. For the *N*-1 isomer (**240**), long range coupling is possible between the methylene group protons and the *ipso* carbon, carbon 7a, as they are within 3 bond lengths of each other. However no coupling should be evident between the methylene group protons and the imine carbon, carbon 3, as they are 4 bond lengths from each other, outside the range for HMBC. The opposite is the case for the (**243**) isomer, as seen from figure 100. It is this difference in long range coupling which will be used to distinguish between the isomers. It should be noted in both isomers, long range coupling exists between the methylene group and *ipso* carbon, C-1', and the aromatic CH carbons, C-2' and C-5'. Since this coupling is common to both isomers, it not possible to use this information to determine which isomer is present.

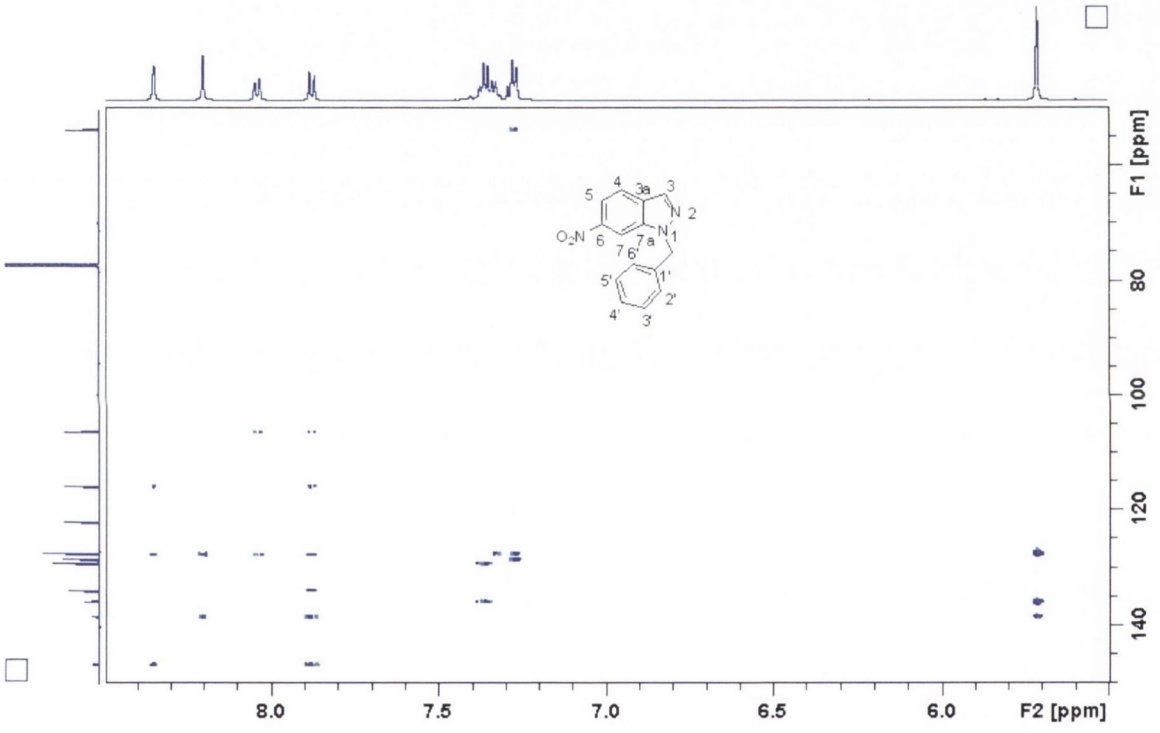


Figure 101: HMBC spectrum of the *N*-1 isomer (240)

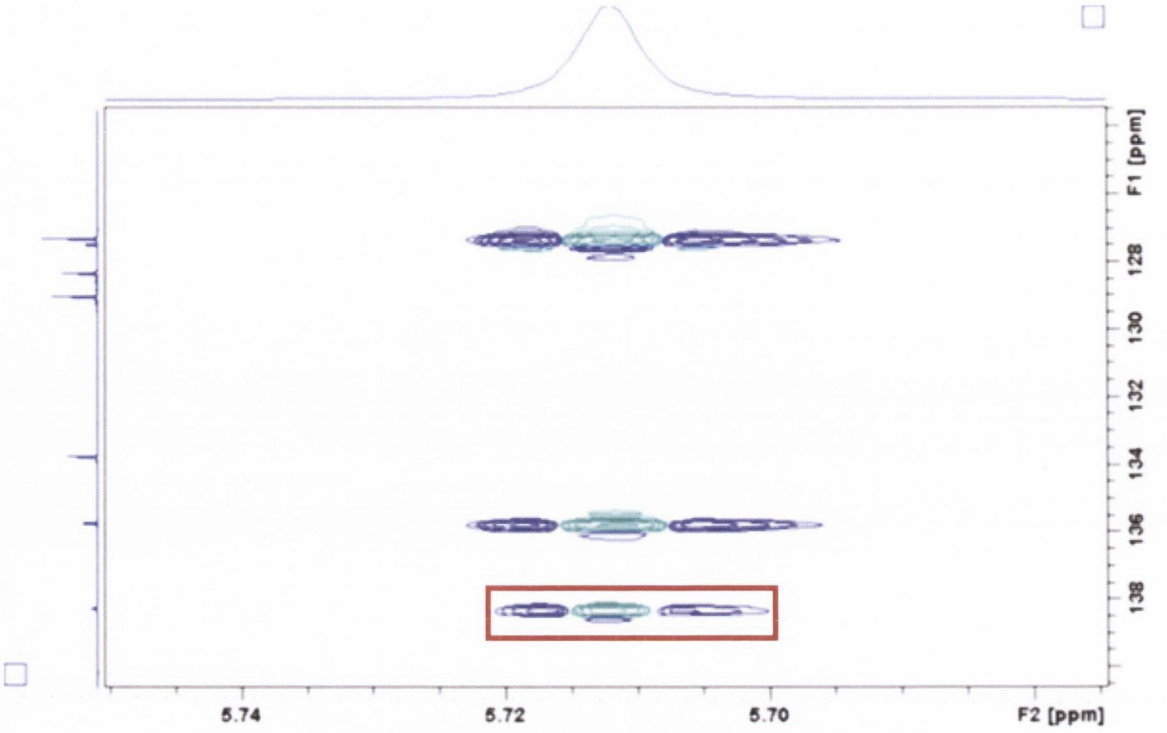


Figure 102: Highlighted area of the HMBC spectrum of the *N*-1 isomer (240)

The HMBC spectrum of the *N*-1 isomer (**240**) is shown in figure 101 and a segment of the HMBC spectrum is highlighted in figure 102. The segment illustrates the long range coupling observed for the methylene protons. The methylene protons should experience long coupling to carbons $C_{1'}$, $C_{2'}$ & $C_{6'}$ and C_{7a}, figure 100. If long range coupling is observed, cross peaks should be present. However cross peaks can be missing in HMBC spectra due to the lack of sensitivity and sometimes very small *J* values[289]. In order to reject the one bond correlations seen in HSQC/HMQC spectra, HMBC incorporates a "low pass" filter. "Low pass" relates to J_{CH} values between 0 – 10 Hz whereas $^{1}J_{CH}$, one bond correlations, are of the magnitude 125 – 175 Hz[289]. The signal at 137.77 was assigned to C_{7a} and seen from figure 102, long range coupling to the methylene protons is observed, as indicated by the cross peak contained in the red rectangle. Since this cross peak is present and the absence of a similar cross peak from C_3 to the methylene protons indicates that this compound (**240**) is the N1 isomer. There are similar cross peaks from $C_{1'}$ and $C_{2'}$ & $C_{6'}$ to the methylene protons, figure 102.

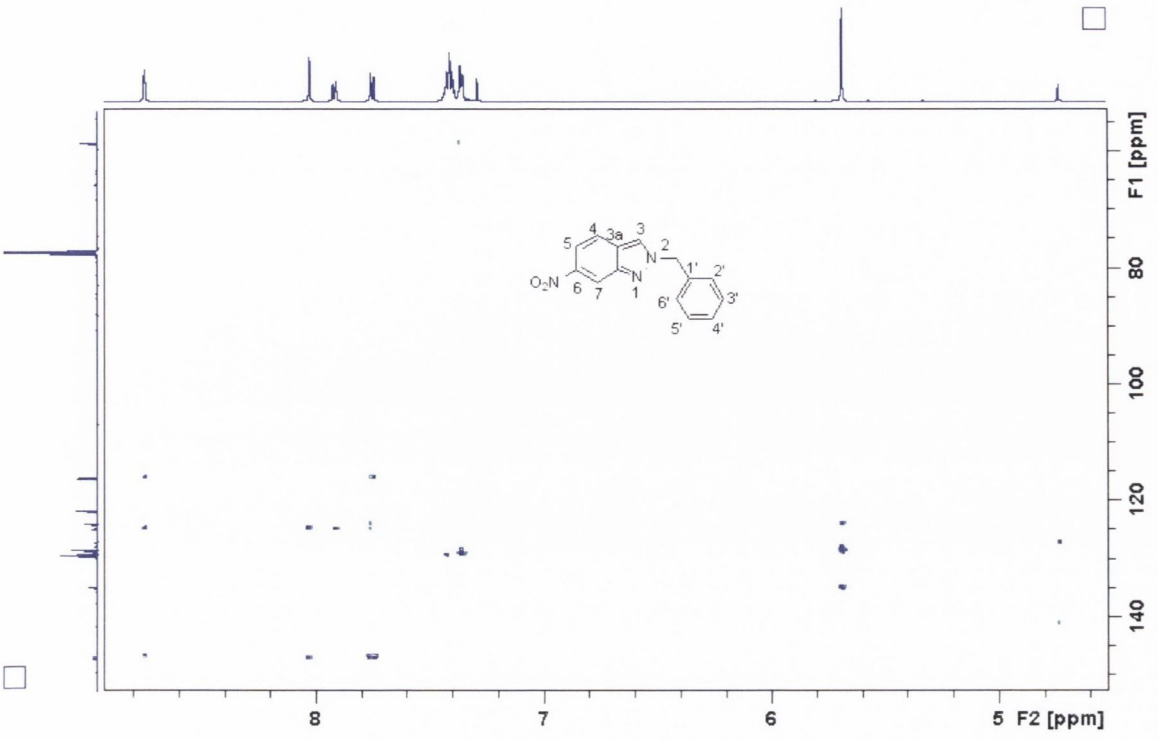


Figure 103: HMBC spectrum of N-2 isomer (243)

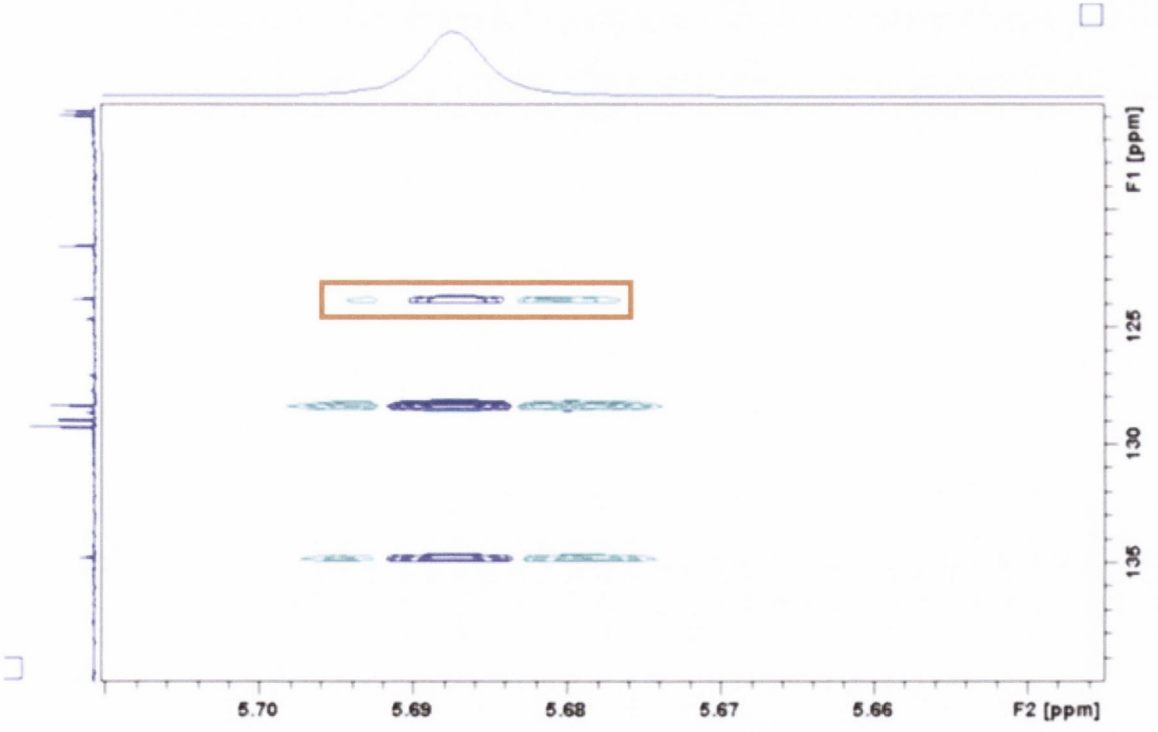


Figure 104: Highlighted area of HMBC spectrum of N-2 isomer (243)

The HMBC spectrum of the *N*-2 isomer (**243**) is shown in figure 103 and a segment of the HMBC is highlighted in figure 104. The segment illustrates the long range coupling observed for the methylene protons. For (**243**), the methylene protons should experience long range

coupling to carbons $C_{1'}$, $C_{2'}$ & $C_{6'}$ and more importantly to C_3. The signal at 123.71 ppm was assigned to C_3 and as seen from figure 104, a cross peak is present for the signal and the methylene protons. This cross peak and the absence of a cross peak between C_{7a} and the methylene protons, indicates that the isolated compound is the N2 isomer (**243**). The complete proton and carbon assignment is shown for (**240**) and (**243**) is shown in figure 105.

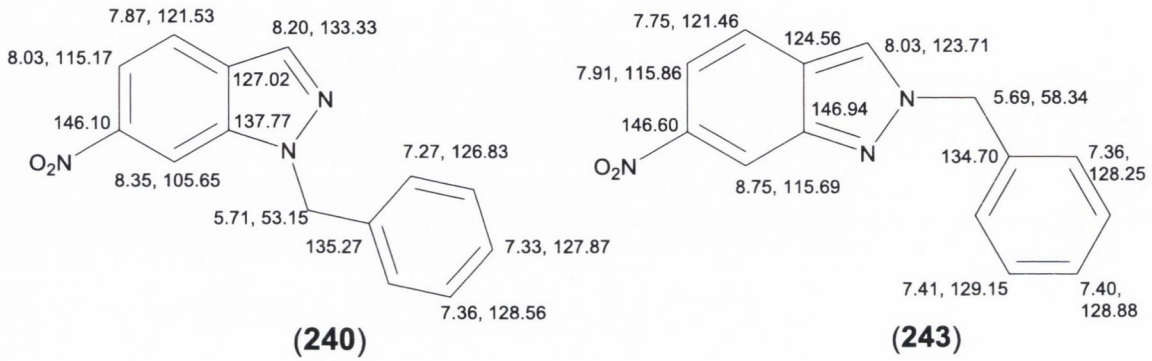
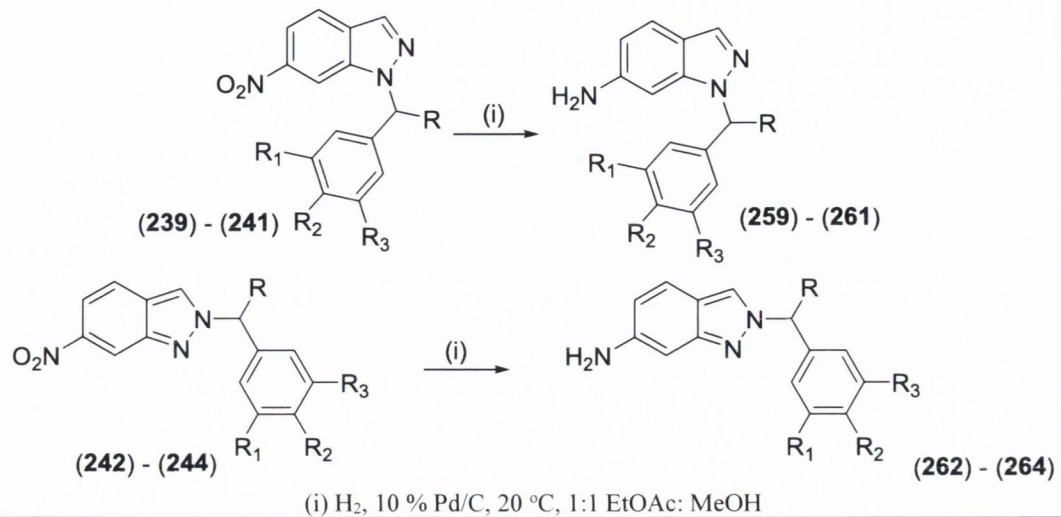


Figure 105: Complete proton and carbon NMR assignment for (240) and (243)

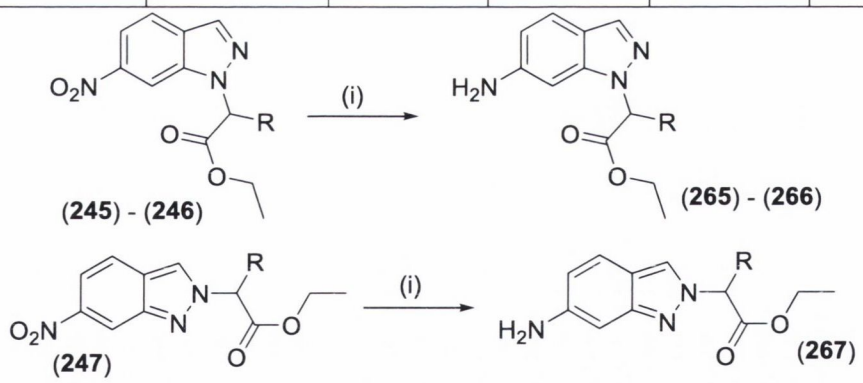
The *N*-1 and *N*-2 substituted nitroindazoles (**239**) – (**258**) in tables 13 and 14 were then reduced using the same hydrogenation method as described in section 2.2 (10 % Pd/C, H_2). The reduced final products are displayed in table 15, compounds (**259**) – (**267**) and table 16, compounds (**268**) – (**274**).

Table 15: 6-Aminoindazoles with alkyl ester or benzyl substituents at *N*-1 or *N*-2.



(i) H_2, 10 % Pd/C, 20 °C, 1:1 EtOAc: MeOH

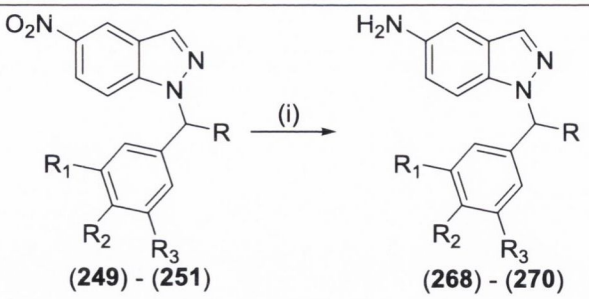
Compound Number	R	R_1	R_2	R_3	Yield (%)
(**259**)*	H	OCH_3	OCH_3	OCH_3	46
(**262**)*					42
(**260**)*		H	H	H	65
(**264**)*					52
(**261**)*	H	H	H	H	75
(**263**)*					98



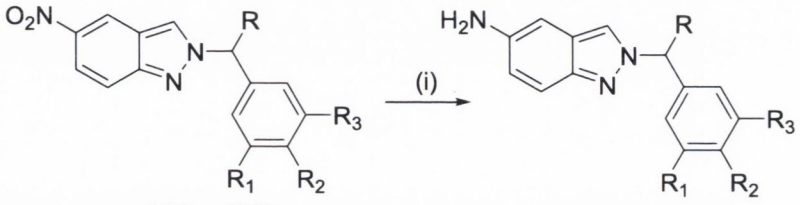
(i) H_2, 10 % Pd/C, 20 °C, 1:1 EtOAc: MeOH

Compound Number	R	Yield (%)
(**265**)*	CH_3	34
(**267**)*		74
(**266**)[285]	H	76

Table 16: 5-Aminoindazoles with either alkyl ester or benzyl substituents at *N*-1 or *N*-2



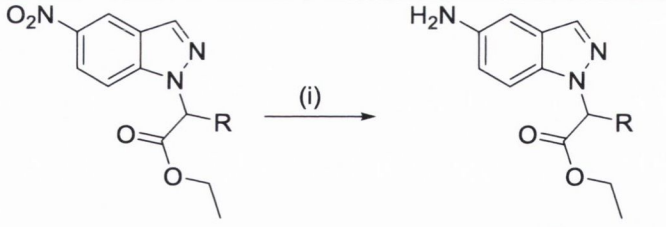
(249) - (251) **(268) - (270)**



(252) - (253) **(271) - (272)**

(i) H_2, 10 % Pd/C, 20 °C, 1:1 EtOAc: MeOH

Compound Number	R	R_1	R_2	R_3	Yield (%)
(268)*	H	OCH_3	OCH_3	OCH_3	55
(271)*					64
(270)[286]	H	H	H	H	91
(272)[290]					99
(269)*		H	H	H	80



(255) - (256) **(273) - (274)**

(i) H_2, 10 % Pd/C, 20 °C, 1:1 EtOAc: MeOH

Compound Number	R	Yield (%)
(273)*	CH_3	85
(274)*	H	94

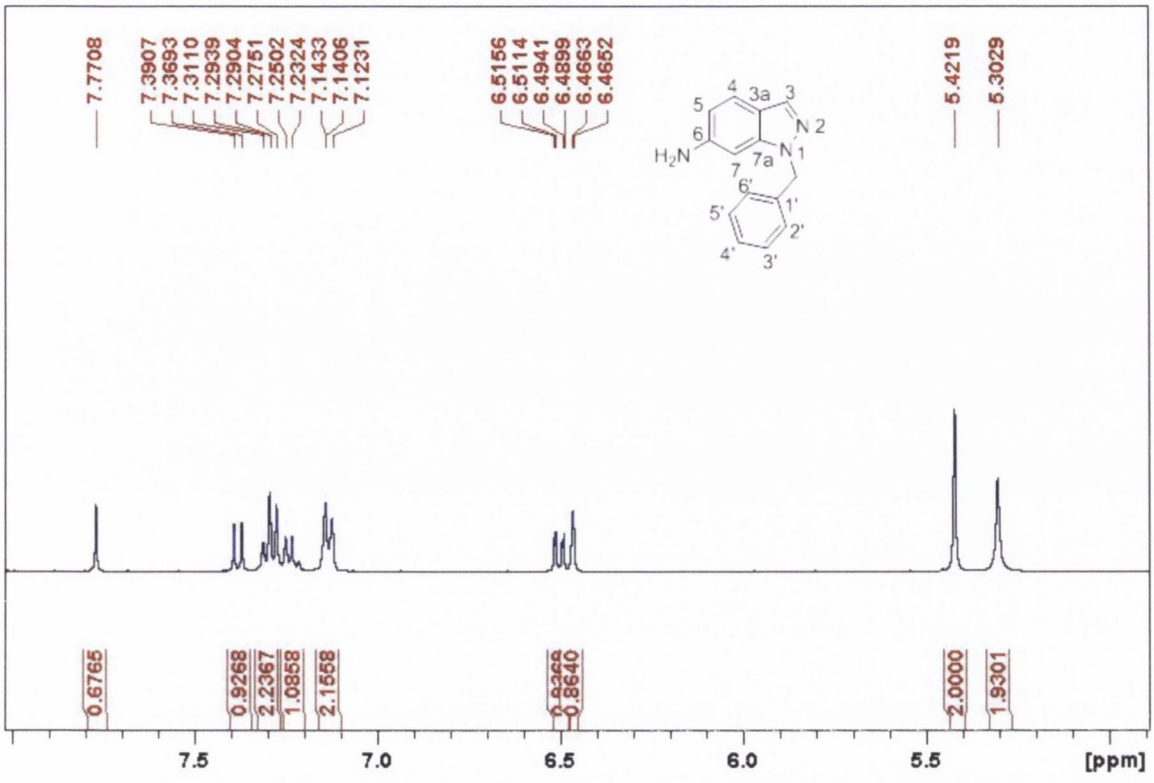


Figure 106: ^{1}H-NMR spectrum of (261)

As an example, the ^{1}H-NMR spectrum of (**261**) is shown in figure 106. The broad singlet at 5.30 ppm corresponds to the amine while the singlet at 5.42 ppm is assigned to the methylene protons. The doublet at 6.47 ppm, J = 1.68 Hz, is assigned to H_7, while the double doublet at 6.50 ppm, J = 8.58, 1.68 Hz, corresponds to H_5. The doublet at 7.13 ppm, J = 8.08 Hz, is assigned to the symmetric protons $H_{2'}$ & $H_{6'}$ while the multiplet 7.22-7.25 ppm is assigned to $H_{4'}$. The multiplet 7.28 – 7.31 ppm, integrating for 2 protons, is assigned to protons $H_{3'}$& $H_{5'}$. The doublet at 7.38 ppm, J = 8.58 Hz, is assigned to H_4 while the singlet at 7.77 ppm corresponds to H_3.

2.5 Preparation of analogues of (168) by direct *N*-arylation of indazole

The modification of the linker between the *N*-1 nitrogen of the indazole and the aryl ring was the focus of this library of compounds (see structure (d) (black box), figure 107). These compounds would have a direct link to the aryl ring unlike the previous sections, figure 107. The orientation of the aryl ring with respect to the indazole core will change when compared to the lead compound (**168**) and this positional change may have some effect on the biochemical potency of these compounds.

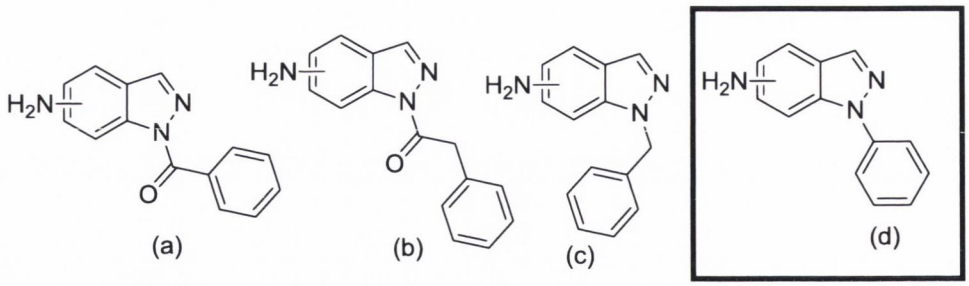
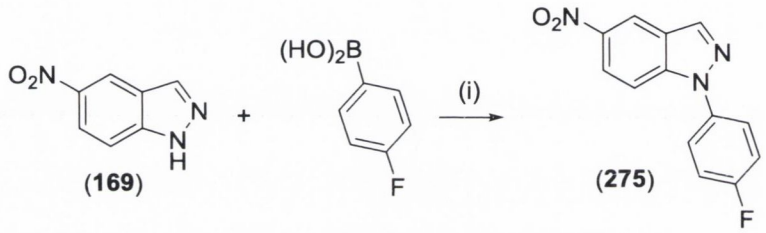


Figure 107: Structural differences between indazoles described in (a) section 2.2 (b) section 2.3 (c) section 2.4 and (d) section 2.5

Bai et al, who investigated the enantioselective synthesis of chiral β-aryloxy alcohols[291], reacted (**169**) with 4-fluorophenyl boronic acid, in the presence of copper acetate and pyridine, forming a direct link from *N*-1 and the aryl ring, (**275**) figure 108.



(i) $Cu(OAc)_2$ (0.92 molar eq.), pyridine (2 molar eq.), 4-flourophenyl boronic acid (2 molar eq.)

Figure 108: N-aryl coupling reaction

This type of cross coupling reaction, commonly referred to as Chan-Lam coupling, was reported by *Lam et al*[292] and *Chan et al*[293], who were investigating an alternative method of aryl/heteroaryl C-N bond formation involving arylboronic acid and copper actetate using mild reaction conditions Aryl/heteroaryl C-N bond formation was already possible using the Ullman reaction[294] and the Buchwald-Hartwig amination reaction[295, 296]. However limitations such as high reaction temperatures, variable yields, sensitivity to air or moisture were associated with these cross coupling reactions. Chan-Lam coupling can be performed at room temperature in air which is not possible with Buchwald-Hartwig cross coupling.

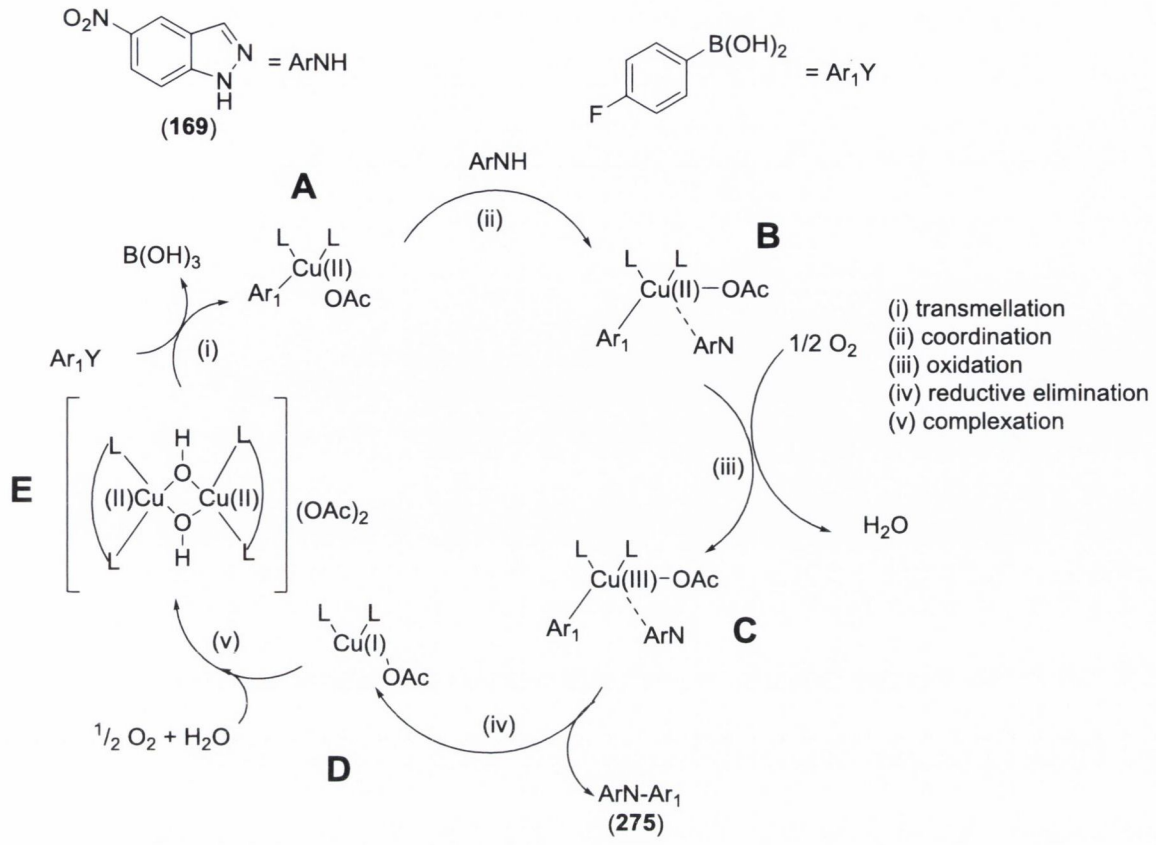
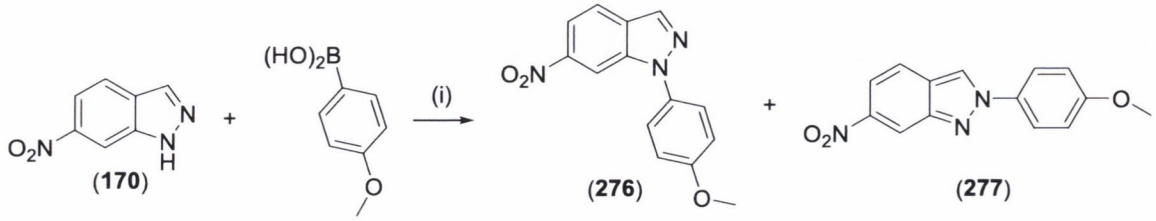


Figure 109: Mechanism for Chan-Lam coupling[297]

In the proposed general mechanism for Chan-Lam coupling reaction, illustrated in figure 109, the arylboronic acid (Ar_1Y) initially undergoes transmetalation with complex E to generate boric acid and intermediate A, which then coordinates the substrate (ArNH) (**169**), forming complex B. In the presence of dioxygen, complex B has been proposed to undergo oxidation, forming a putative Cu(III) intermediate C, which undergoes reductive elimination, yielding the coupled product (**275**) and complex D. The latter can be reconverted into bis-μ-hydroxo Cu(II) complex E in the presence of dioxygen and water.

In the present work, (**170**) was initially reacted with 4-methoxyphenylboronic acid, figure 110, in order to determine the optimum reaction conditions for this coupling reaction.



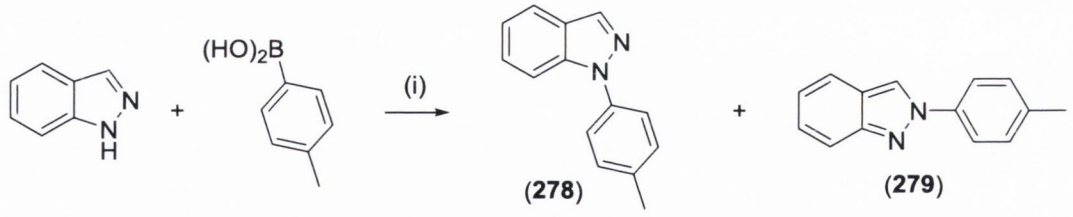
(i) $Cu(OAc)_2$, pyridine, CH_2Cl_2, 20 °C

Figure 110: Synthesis of (276) and (277)

Table 17: Optimisation for the Cham-Lam coupling reaction conditions for (276)

Reaction Number	$Cu(OAc)_2$ Molar Eq	pyridine Molar Eq	4-methoxyphenyl boronic acid Molar Eq	Anhydrous DCM (5 mL) Y/N	N_2 Y/N	Air Y/N	Yield (mg, %) (**276**)
1	2	2	2	Y	Y	N	85 mg, 32 %
2	1	2	2	Y	Y	N	110 mg, 41 %
3	1	1	2	Y	Y	N	165 mg, 61 %
4	0.5	0.5	2	Y	Y	N	60 mg, 22 %
5	1	1	1.5	Y	Y	N	121 mg, 45 %
6	1	1	2	Y	N	Y	131 mg, 49 %
7	1	1	2	N	N	Y	165 mg, 61 %

All the above reactions, in table 17, were performed at 20 °C for 24 hours using 1 mmol of 6-nitroindazole (**170**). The optimal conditions for the production of (**276**) are highlighted by in table 17. It should be noted that two products were obtained when (**170**) was reacted with 4-methoxyphenylboronic acid, the *N*-1 isomer (**276**) and the *N*-2 isomer (**277**). The yield for (**277**), using the conditions in the yellow row, was 37 mg (14 %). It is initially assumed that the dominant of the two products was the *N*-1 isomer (**276**) as *Lam et al* reported that following the reaction of indazole with 4-methylphenylboronic acid, two isomeric compounds were obtained[292], figure 111. The ratio of *N*-1 isomer, (**278**), to the *N*-2 isomer, (**279**), was 9:2. It was assumed that dominant product from figure 110 was the *N*-1 isomer, (**276**) which later confirmed by NMR spectroscopy (see figures 116 – 118). These conditions were used in subsequent library synthesis and development.



(i) pyridine (2.0 molar eq.), $Cu(OAc)_2$ (1.5 molar eq.), molecular sieves, CH_2Cl_2, rt, air

Figure 111:Reaction of indazole with 4-methylboronic acid[292]

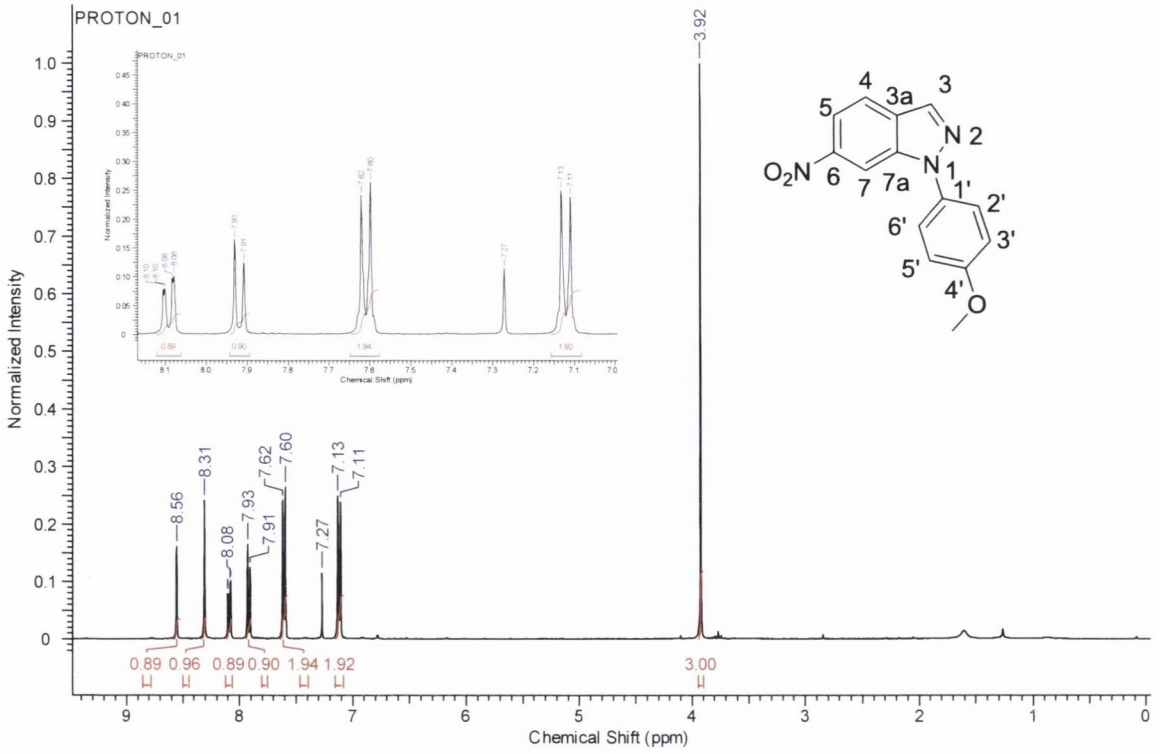


Figure 112: ^{1}H-NMR spectrum of (276)

The characterisation of the *N*-1 isomer (**276**) and the N-2 isomer (**277**) are now discussed.

The ^{1}H-NMR spectrum of the *N*-1 isomer (**276**) is shown in figure 112. The sharp singlet at 3.92 ppm corresponds to the methoxy protons. The doublet at 7.12 ppm, J = 9.20 Hz, corresponds to the symmetric protons, $H_{3'}$ & $H_{5'}$. These protons will be more up-field than the protons, $H_{2'}$ and $H_{5'}$, due to increased shielding from the methoxy substituent. The doublet at 7.61 ppm, J = 9.20 Hz, corresponds to the symmetric protons, $H_{2'}$ & $H_{6'}$. The doublet at 7.92 ppm, J = 8.50 Hz, is assigned to proton H_4. The double doublet at 8.09 ppm, J = 8.50, 1.80 Hz, is assigned to H_5. The signal at 8.31 ppm is assigned to the imine proton, H_3 while the doublet at 8.55 ppm, J = 1.80 Hz, is assigned to the proton H_7.

The ^{13}C-NMR spectrum of the *N*-1 isomer (**276**) is shown in figure 113. The signal at 55.67 ppm corresponds to the methoxy carbon. The signals at 107.10, 114.99, 116.09, 121.98, 124.89 and 134.83 ppm correspond to aromatic methine carbons C_7, $C_{3'}$, C_5, C_4, $C_{2'}$ and C_3 respectively. The signals at 127.84, 132.05, 137.90, 147.01, 159.31 ppm correspond to the aromatic quaternary carbons $C_{1'}$, C_{3a}, C_{7a}, C_6 and $C_{4'}$ respectively.

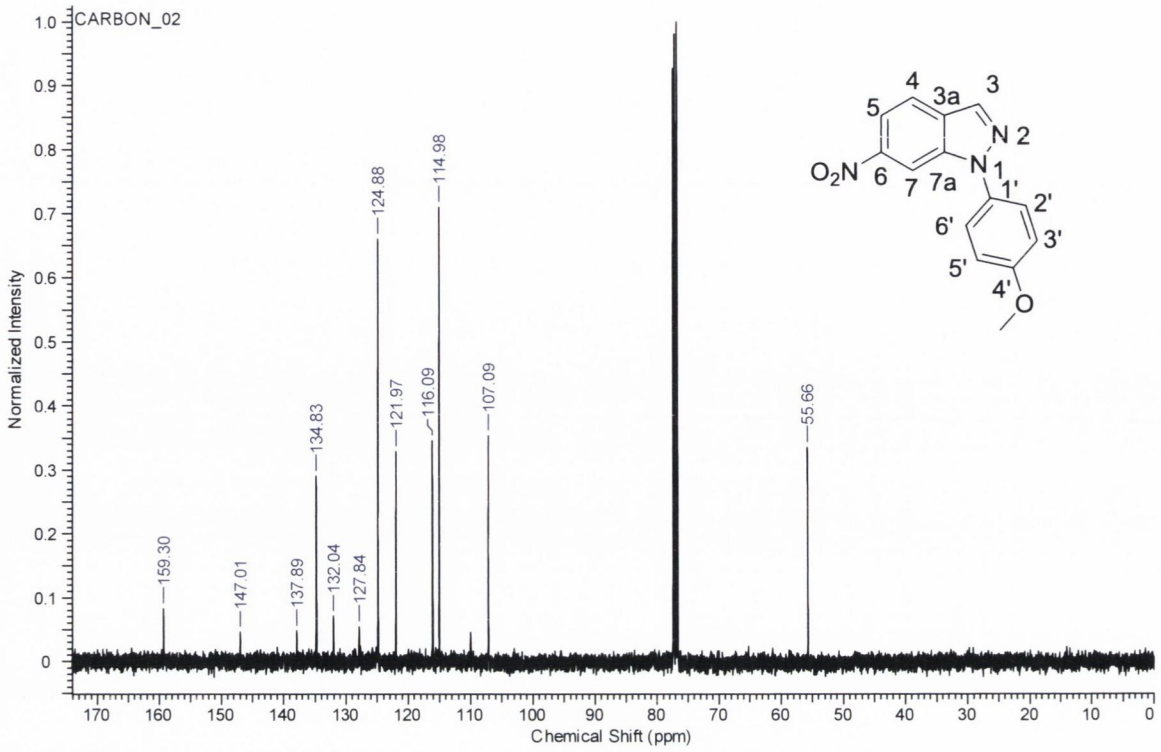


Figure 113: ^{13}C-NMR spectrum of (276)

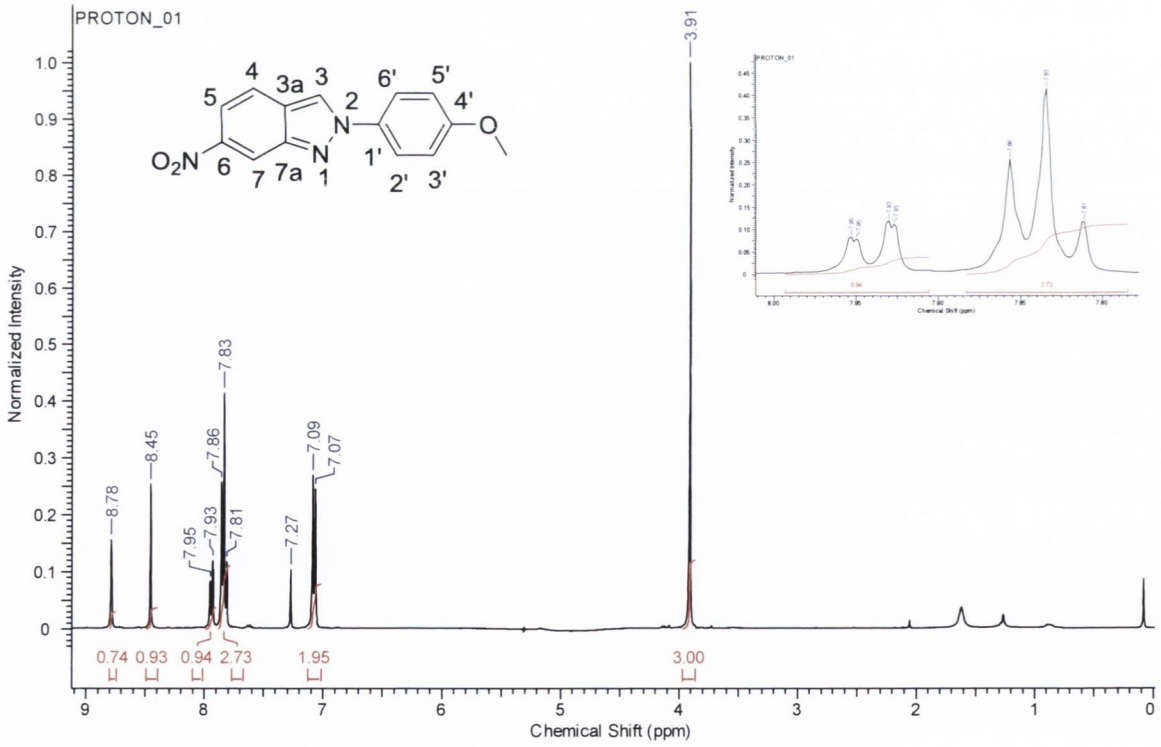


Figure 114: ^{1}H-NMR spectrum of (277)

The ^{1}H-NMR spectrum of the *N*-2 isomer (**277**) is shown in figure 114. The sharp singlet at 3.91 ppm corresponds to the methoxy protons. The doublet at 7.08 ppm, J = 9.20 ppm, corresponds to the symmetric protons, $H_{3'}$ & $H_{5'}$. The multiplet from 7.81 ppm to 7.85 ppm corresponds to protons, $H_{2'}$ & $H_{6'}$ and H_4. An H-H COSY spectrum was used to accurately assign protons $H_{2'}$ & $H_{6'}$ and H_4 in compound (**277**). Since the signal at 7.08 corresponds to symmetric protons $H_{3'}$ and $H_{5'}$, only the symmetric protons $H_{2'}$ & $H_{6'}$ should couple to this signal. Thus, by looking at the cross peaks along the diagonal, the symmetric protons $H_{3'}$ and $H_{5'}$ appear at 7.84 ppm. Also for the proton H_4, it should only couple to H_5 and by looking at the cross peaks along the diagonal, it appears at 7.82 ppm. The double doublet at 7.94 ppm, J = 9.20, 1.20 Hz, corresponds to H_5. The signal at 8.45 ppm is assigned to H_3 while the signal at 8.78 ppm is assigned to H_7.

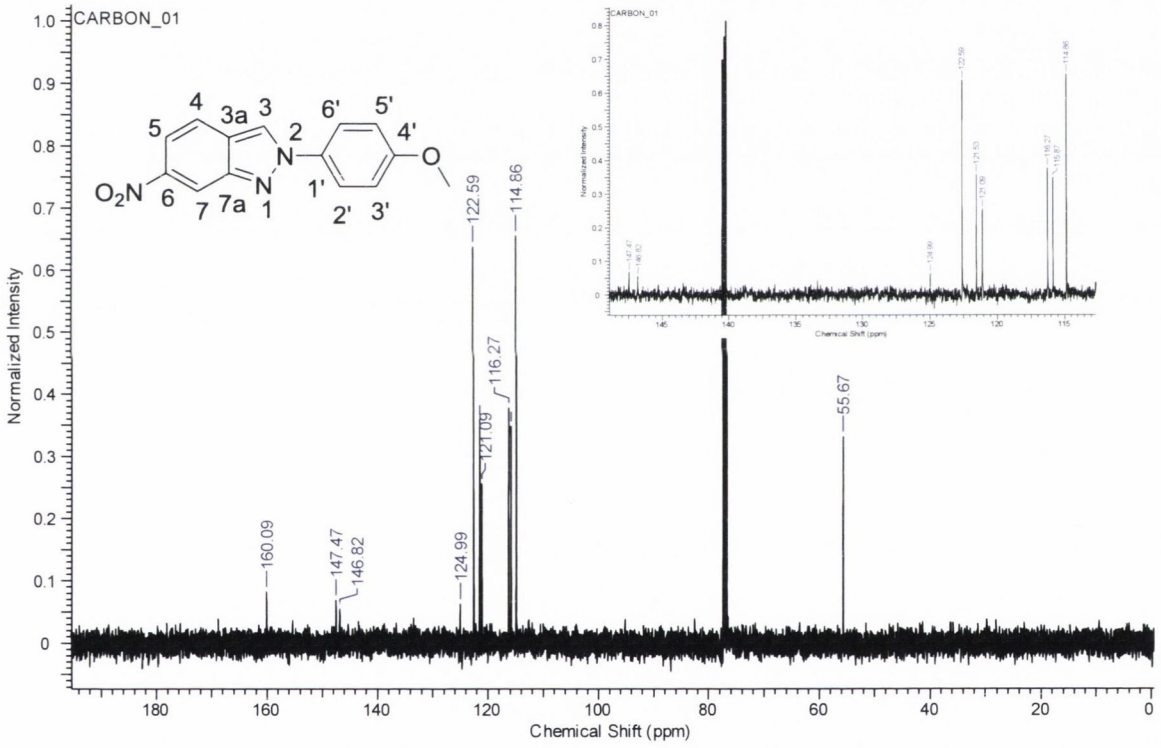


Figure 115: ^{13}C-NMR spectrum of (277)

The ^{13}C-NMR spectrum of the N-2 isomer (**277**) is shown in figure 115. The methoxy carbon appears at 55.67 ppm. The signals at 114.86, 115.86, 116.27, 120.59 121.52 and 122.59 ppm correspond to aromatic methine carbons $C_{3'}$ & $C_{5'}$, C_7, C_5, C_3, C_4 and $C_{2'}$& $C_{6'}$. The signals at 124.99, 146.82, 147.47 and 160.09 ppm correspond to aromatic *ispo* carbons C_{3a}, C_6, C_{7a} and $C_{4'}$ respectively.

Finally to distinguish between the two isomers, (**276**) and (**277**), nuclear Overhauser effect (NOE) difference spectroscopy was used. In this technique, a proton or group of protons are irradiated and any neighbouring protons, which are sufficiently near the irradiated proton(s), will interact *via* the nuclear Overhauser effect. The NOE difference spectrum would show a negative signal for irradiated proton(s), while a positive signal should be observed only for protons that interact with the irradiated protons by means of a dipolar mechanism. For this to occur, the neighbouring protons should be within about 3 to 4 angstroms of the irradiated protons. Thus for the *N*-1 isomer (**276**), if proton H_7 is irradiated, a positive signal should be present for the symmetric protons $H_{2'}$ & $H_{6'}$; if symmetric protons $H_{2'}$ & $H_{6'}$ are irradiated, a positive signal should be present for the proton H_7, figures 116 and 117.

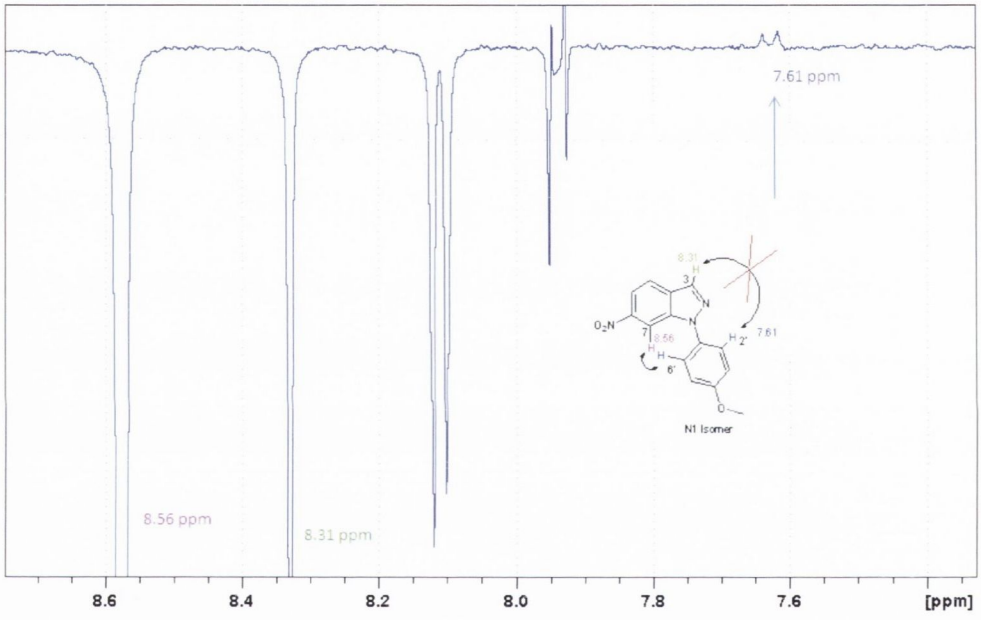


Figure 116: Resultant NOE spectrum for *N*-1 isomer (276) - irradition of proton H_7

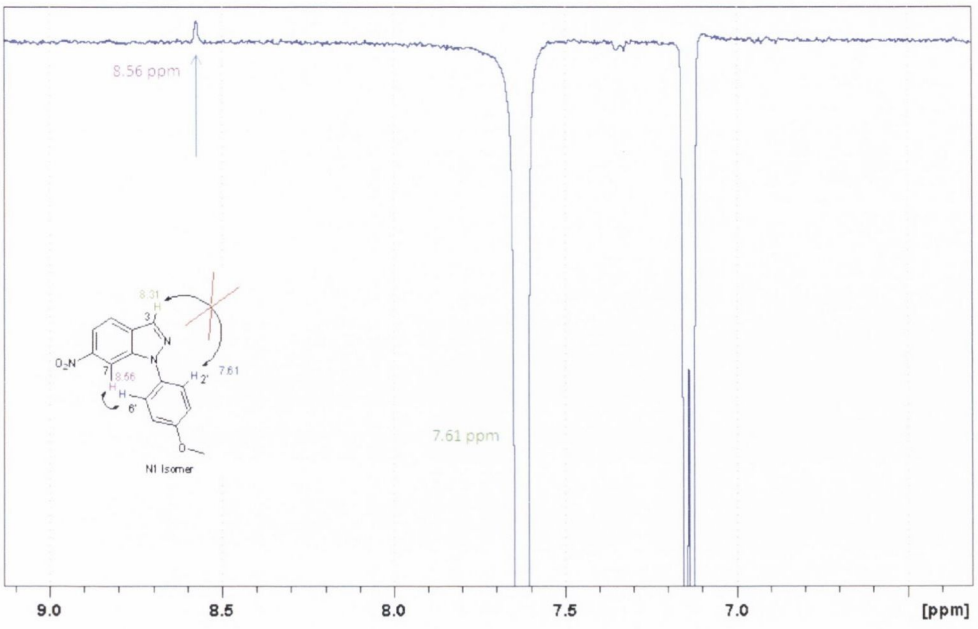


Figure 117: Resultant NOE spectrum of *N*-1 isomer (276) - irradiation of $H_{2'}$ proton

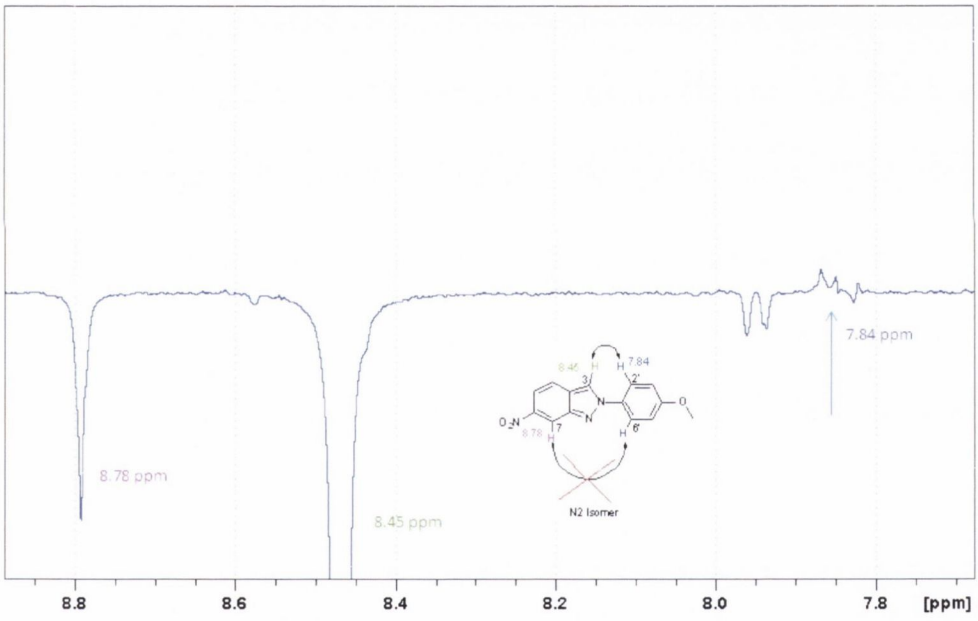


Figure 118: Resultant NOE spectrum for *N*-2 isomer (277) - irradiation of H_3 proton

A NOE experiment was performed for the *N*-2 isomer (**277**) also, figure 118. The H_3 proton, 8.45 ppm, was irradiated here. A negative signal is observed for the H_3 proton while the only observed positive signal is for the symmetric protons, $H_{2'}$ & $H_{5'}$, 7.84 ppm. Since the H_3 proton only interacts with these protons, we can conclude that (**277**) is the N-2 isomer.

Since it known that two isomeric products are obtained for the arylation of indazoles, it was not clear why it not mentioned by *Bai et al* when they reacted (**169**) with 4-fluorophenylboronic acid[291] (see figure 108). In the present work, this reaction was repeated, using the in-house optimised reaction conditions, table 17. TLC analysis revealed that two products were present, R_f = 0.42 and 0.35 (Hex:EtOAc 2:1) respectively. The intensity of the least polar compound was significantly greater than the more polar compound. The purification of these compounds by column chromatography was somewhat successful. A ^{1}H-NMR spectrum was obtained for the product (**275**) and is shown in figure 119. The major product is the *N*-1 isomer (**275**) and contains a small amount of the *N*-2 isomer.

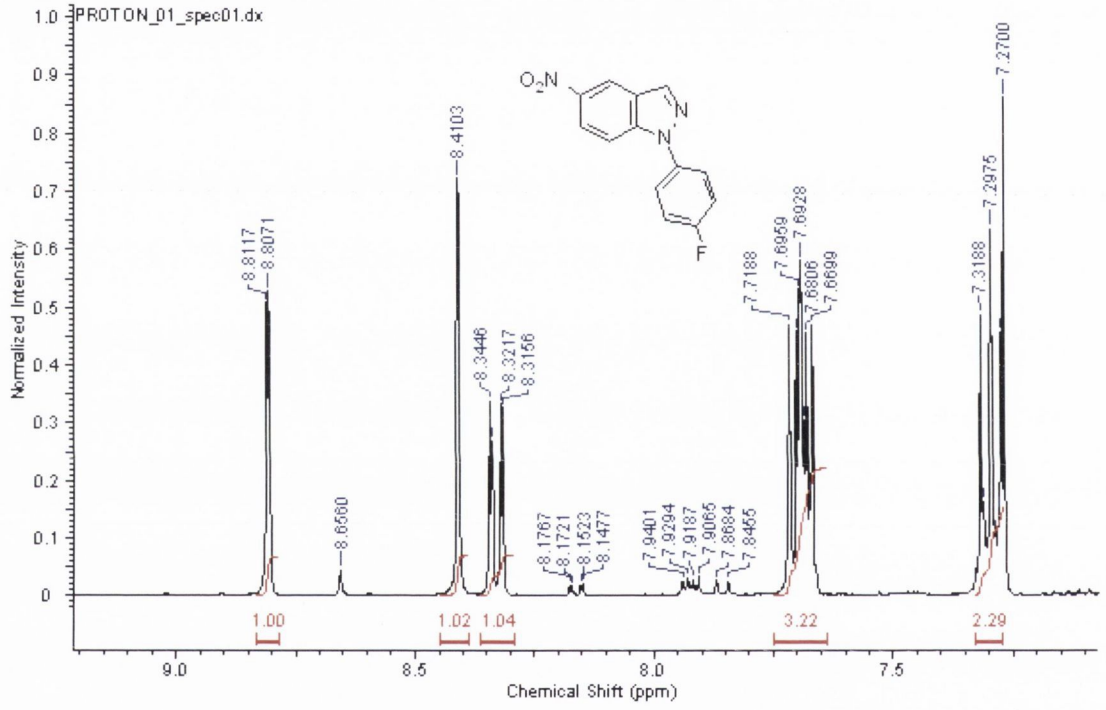


Figure 119: ^{1}H-NMR spectrum of (275)

The multiplet from 7.27 ppm to 7.32 ppm, which integrates for 2 protons, corresponds to the symmetric protons, $H_{3'}$ & $H_{5'}$. The multiplet from 7.67 ppm to 7.72 ppm, which integrates for 3 protons, is comprised of the proton H_7 and the symmetric protons, $H_{2'}$ & $H_{6'}$. The double doublet at 8.33 ppm, J = 9.20, 1.80 Hz, is assigned to H_6 since it experiences *ortho* coupling from H_7 and *meta* coupling from H_4. The singlet at 8.41 ppm corresponds to the imine proton, H_3. The small doublet at 8.81 ppm, J = 1.80 Hz, is assigned to H_4. If the region of the ^{1}H-NMR spectrum of (**275**) from 7.80 ppm to 8.70 ppm is magnified, a series of weaker signals is apparent (see figure 120) which can be assigned to a small amount of the corresponding *N*-2 isomer in the product.

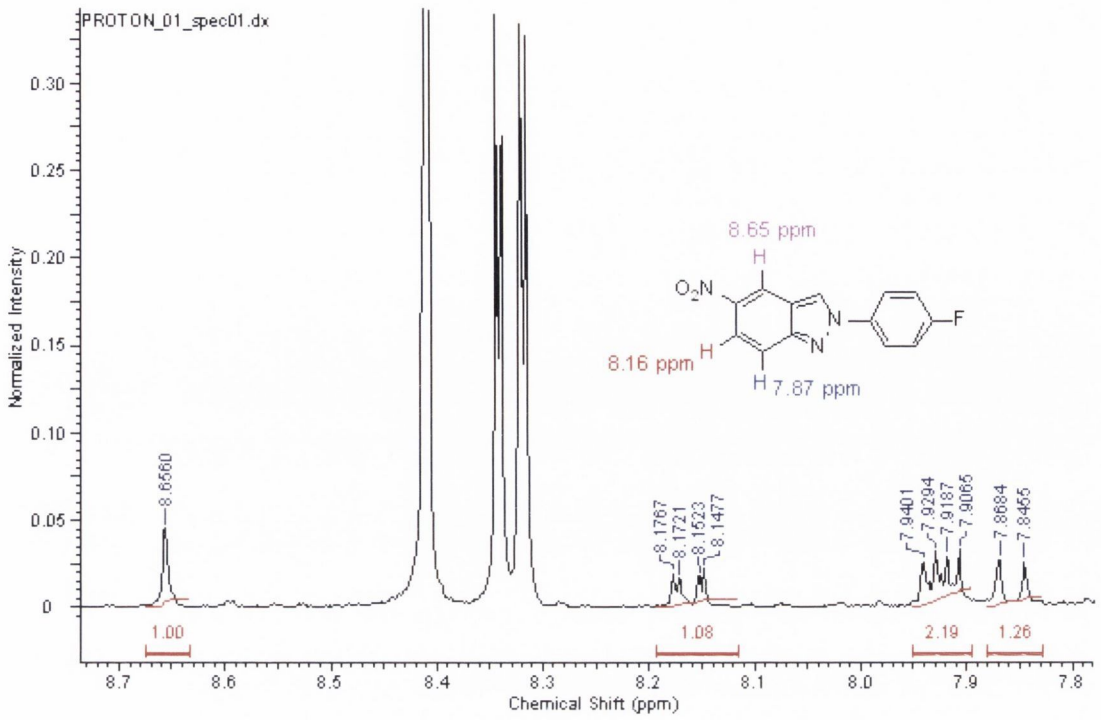
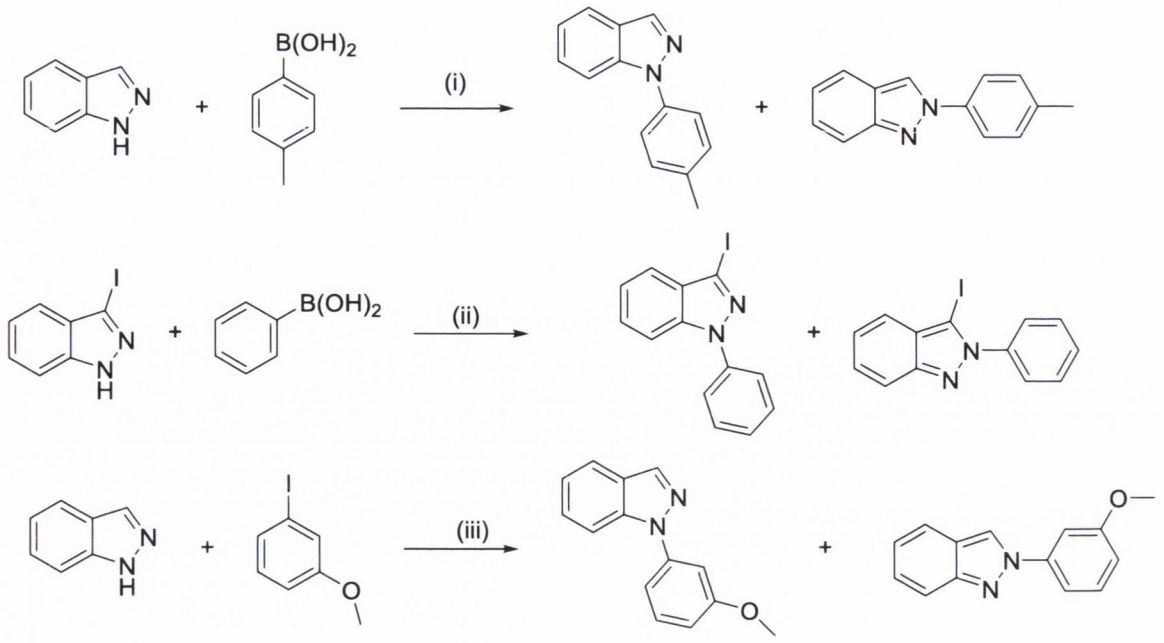


Figure 120: ^{1}H-NMR spectrum of (275) (7.80 ppm to 8.70 ppm)

The doublet at 7.87 ppm, $J = 9.20$ Hz, corresponds to H_7 of the N2 isomer. The double doublet at 8.16 ppm, $J = 9.20$, 1.84 Hz, is assigned to H_6. The singlet at 8.66 ppm is assigned to H_4. The multiplet from 7.91 ppm to 7.94 ppm corresponds to symmetric protons, $H_{2'}$ & $H_{6'}$ or $H_{3'}$ & $H_{5'}$. These weaker signals are due to N-2 isomer. If the integral of the H_6 proton of the N-2 isomer is set to 1 and the corresponding H_6 proton of (**275**) is integrated, an integral of 16 is obtained. Thus the ratio of *N*-1:*N*-2 is roughly 16:1. Since only trace amounts of *N*-2 are obtained, it must not have been observed by *Bai et al*[291]. Separation of the *N*-1 isomer and the *N*-2 isomer of (**275**) was not achieved in the present work.

Previous research, apart from the work of *Lam et al*[292], on C-N cross coupling have observed that isomeric products are obtained following the *N*-arylation of indazoles. Two studies were found using phenylboronic acids[298, 299] and one using aryl halides , figure 121.



(i) $Cu(OAc)_2$, Tempo, pyridine, anhydrous CH_2Cl_2, rt[298] (ii) $Cu(OAc)_2$, pyridine, activated molecular sieves, CH_2Cl_2, rt[299] (iii) CuI, N^1,N^2-dimethylcyclohexane-1,2-diamine, anhydrous toluene[300]

Figure 121: Reactions where isomeric products were obtained

However in one of the aforementioned C-N cross coupling studies, by *Hari et al*[299], revealed that *N*-arylation of 3-trimethylsilylindazoles yielded only the N-1 isomer, figure 122. It was suggested that the *N*-2 isomer was not observed due to steric hindrance caused by the trimethylsilyl group and that the electronic effect of the silicon atom accelerated the reaction rate of N-arylation at the 1-position.

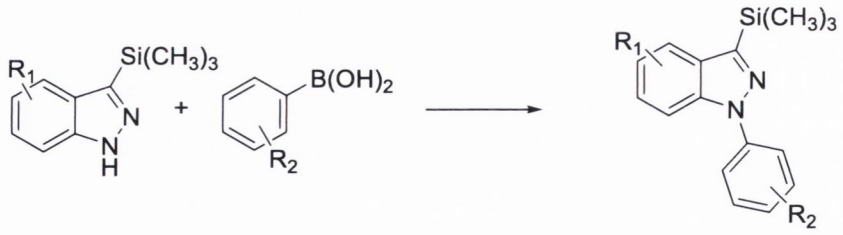
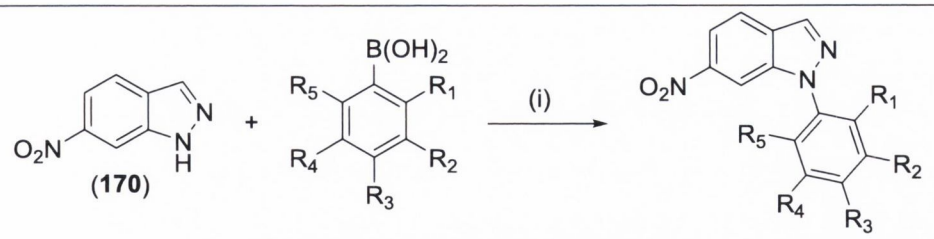


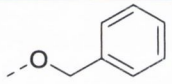
Figure 122: Regioselective N-arylation of 3-trimethylsilylindazole

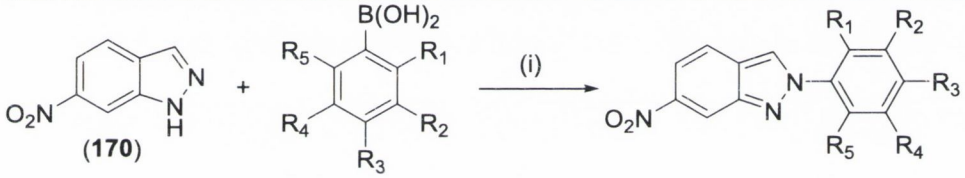
Tables 18 and 19 highlight the complete series of synthesised N-arylated 6-nitroindazoles, (**276**)-(**277**) and (**280**)-(**282**), and *N*-arylated 5-nitroindazoles, (**275**) and (**283**)-(**285**), respectively. Even though the *N*-2 isomer was observed in all Chan-Lam cross couplings performed in this thesis project, only the (**277**) and (**282**) were isolated and purified successfully by flash column chromatography.

Table 18: *N*-Arylated 6-nitroindazoles



(i) $Cu(OAc)_2$, pyridine, CH_2Cl_2, 20 °C, air

Compound Number	R_1	R_2	R_3	R_4	R_5	IRν_{max} (NO_2) cm^{-1}	Yield (%)
(**276**)[301]	H	H	OCH_3	H	H	1523.5, 1346.9	61
(**280**)*	H	OCH_3	OCH_3	OCH_3	H	1529.9, 1344.3	61
#(**281**)	H	H		H	H	1515.1, 1341.8	52

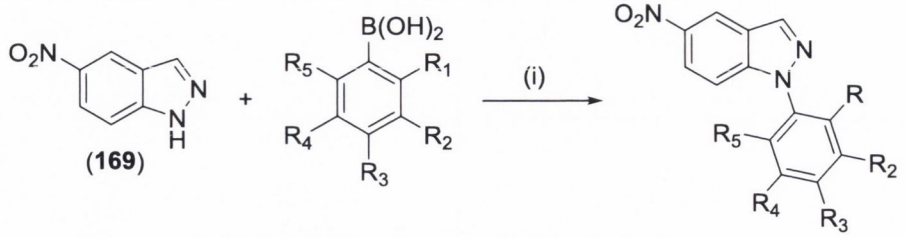


(i) $Cu(OAc)_2$, pyridine, CH_2Cl_2, 20 °C, air

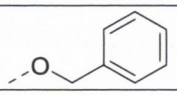
(**277**)*	H	H	OCH_3	H	H	1518.7, 1341.9	14
(**282**)*	H	OCH_3	OCH_3	OCH_3	H	1529.9, 1344.3	5

#Corresponding N2 isomer was present but was not purified successfully by column chromatography.

Table 19: N-Arylated 5-nitroindazoles



(i) $Cu(OAc)_2$, pyridine, CH_2Cl_2, 20 °C, air

Compound Number	R_1	R_2	R_3	R_4	R_5	IR ν_{max} (NO_2) cm^{-1}	Yield (%)
#(**283**)[301]	H	H	OCH_3	H	H	1523.5, 1346.9	59
#(**284**)*	H	OCH_3	OCH_3	OCH_3	H	1512.4, 1345.9	45
#(**285**)*	H	H		H	H	1514.9, 1340.8	55
#(**275**)[291]	H	H	F	H	H	1514.9, 1342.2	20

#Corresponding N2 isomer was present but was not purified successfully by column chromatography.

The reduction of the 6-nitroindazoles (**276**), (**280**), (**281**) and the 5-nitroindazoles (**275**), (**283**) – (**284**) was accomplished by hydrogenation using hydrogen and 10 % palladium on carbon to afford compounds (**286**) – (**289**), table 20, and (**290**) – (**292**), table 21 respectively. For (**281**) and (**285**), reduction of the nitro group was accomplished using zinc and acetic acid as hydrogenation would result in the removal of the benzyl group which was the case when this method was used on (**281**) which initially afforded (**288**).

The ^{1}H-NMR spectrum of (**286**) is shown in figure 123. The sharp singlet at 3.82 ppm corresponds to the methoxy protons. The broad singlet at 5.45 corresponds to the amine. The double doublet at 6.58 ppm, J = 8.90, 1.50 Hz, is assigned to H_5. This proton appears as a double doublet as it experiences *ortho* coupling from H_4 and *meta* coupling from H_7. The singlet 6.73 ppm is assigned to H_7. Due to the increased electronic shielding by the amine, both protons have more up-field signals. The doublet at 7.11 ppm, J = 8.00 Hz, corresponds to the symmetric protons, $H_{3'}$& $H_{5'}$. The doublet at 7.46 ppm, J = 8.90 Hz, is assigned to H_4. The doublet at 7.54 ppm, J = 8.00 Hz, is assigned to the symmetric protons, $H_{2'}$& $H_{6'}$. The singlet at 7.96 ppm is assigned to the imine proton, H_3.

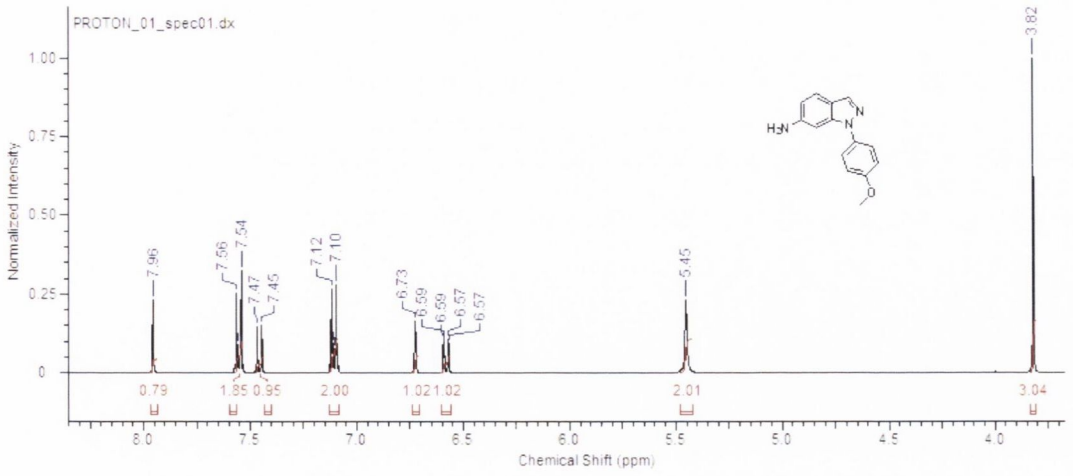


Figure 123: ^{1}H-NMR spectrum of (286)

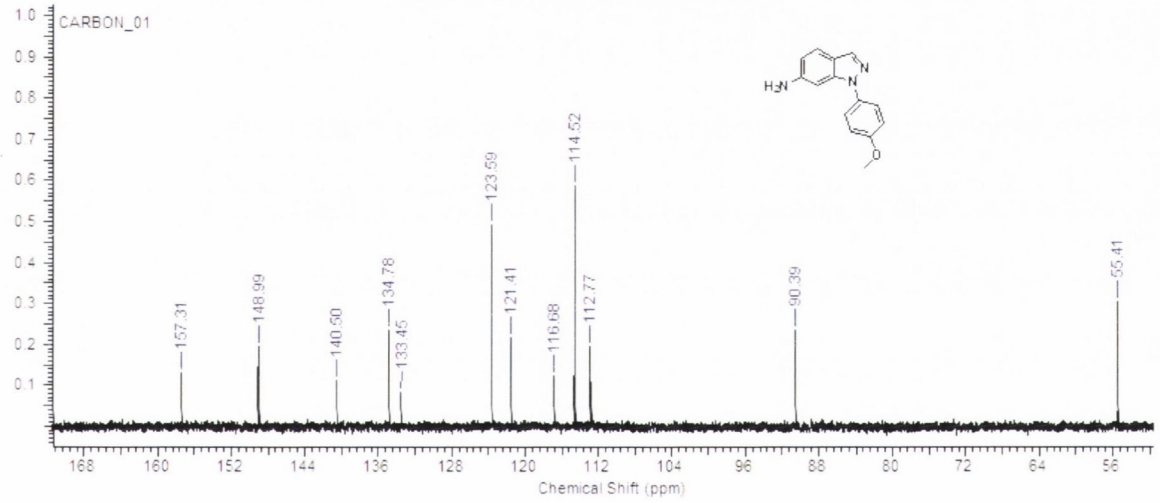
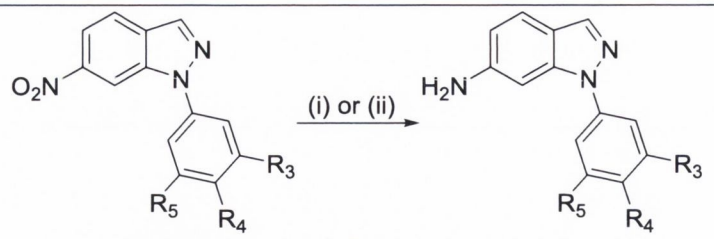


Figure 124: ^{13}C-NMR spectrum of (286)

The ^{13}C-NMR spectrum of (**286**) is shown in figure 124. The signal at 55.41 ppm corresponds to the methoxy carbon. The signals at 90.39, 112.77, 114.52, 121.41, 123.59 and 134.78 ppm correspond to aromatic methine carbons, C_7, C_5, $C_{3'}$, C_4, $C_{2'}$ and C_3 respectively. The signals at 116.68, 133.45, 140.50, 148.99 and 157.31 ppm correspond to aromatic *ipso* carbons C_{3a}, $C_{1'}$, C_{7a}, C_6 and $C_{4'}$ respectively.

The Cham-Lam coupling of 5 and 6-nitroindazoles has been successfully achieved to afford a library of N-1 aryl and N-2 arylindazoles for biochemical evaluation.

Table 20: N-Arylated 6-aminoindazoles



(i) 10% Pd/C, H_2, MeOH:EtOAc (ii) Zinc, acetic acid

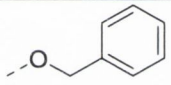
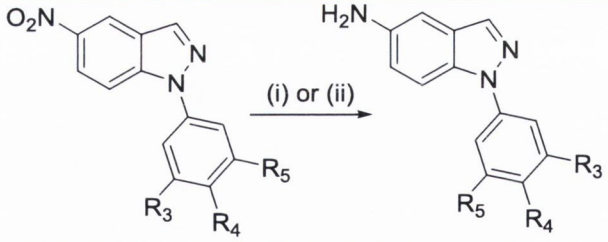
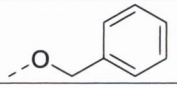
Compound Number	R_3	R_4	R_5	IR ν_{max} cm^{-1}	Yield (%)
(**286**)*	H	OCH_3	H	3463.1 (NH_2), 3382.7 (NH_2)	66
(**287**)*	OCH_3	OCH_3	OCH_3	3453.2 (NH_2), 3367.5 (NH_2)	77
(**288**)*	H	OH	H	3428.8 (OH)	98
(**289**)*	H		H	3455.1 (NH_2), 3361.4 (NH_2)	15

Table 21: N-Arylated 5-aminoindazoles

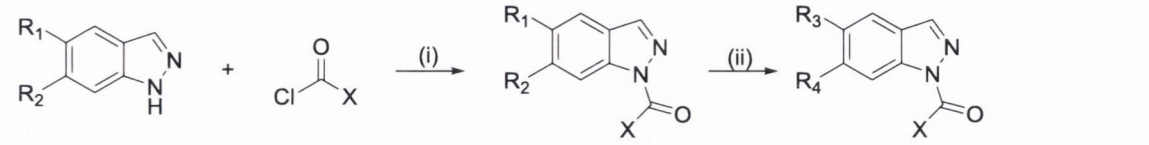


(i) 10% Pd/C, H_2, MeOH:EtOAc (ii) Zinc, acetic acid

Compound Number	R_2	R_3	R_4	IR (NH_2) ν_{max} cm^{-1}	Yield (%)
(**290**)*	H	OCH_3	H	3428.6, 3344.4	64
(**291**)*	OCH_3	OCH_3	OCH_3	3428.6, 3347.4	95
(**292**)[302]	H	F	H	3394.1, 3325.0	88
(**293**)*	H		H	3438.4, 3349.6	27

2.6 5- and 6-Aminoindazoles with *N*-1 amide substituents

This library is comprised of compounds related to the lead compound (**168**) which either have alkyl or alkylether type linkers between the *N*-1 nitrogen and a carbocyclic system. The compounds were synthesised by reacting (**169**) and (**170**) with the necessary acid chlorides using the same chemistry in sections 2.2 and 2.3, figure 125. The nitroindazole intermediates were subsequently reduced by hydrogenation which afforded the desired final products.



(**169**) $R_1 = NO_2$, $R_2 = H$
(**170**) $R_1 = H$, $R_2 = NO_2$

(**294**) - (**298**) $R_1 = NO_2$, $R_2 = H$
(**299**) - (**303**) $R_1 = H$, $R_2 = NO_2$

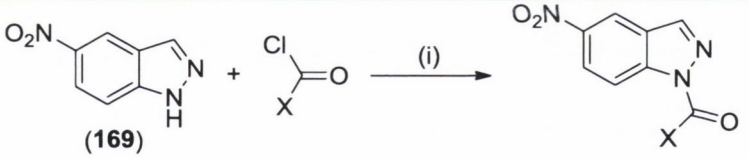
$R_3 = NH_2$, $R_4 = H$ (**304**) - (**308**)
$R_3 = H$, $R_4 = NH_2$ (**309**) - (**313**)

(i) Anhydrous CH_2Cl_2, Et_3N (ii) MeOH/EtOAc, H_2, 10% Pd/C

Figure 125: Synthesis of (304) – (313)

Tables 22 and 23 contain the nitroindazoles (**294**) – (**298**) and (**299**) – (**303**) obtained from the reaction of (**169**) and (**170**) with a variety of acid chlorides. These *N*-1 indazole amide derivatives contain alkyl or alkyl ether linkers between the *N*-1 nitrogen and the aryl ring or contain aliphatic rings instead of aryl rings.

Table 22: 5-Nitroindazoles with *N*-1 amide substituents



(i) Anhydrous CH_2Cl_2, Et_3N, reflux

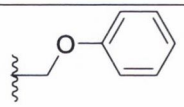
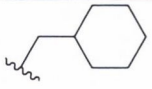
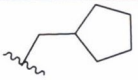
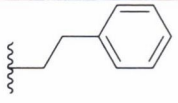
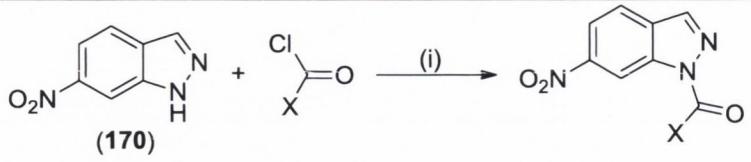
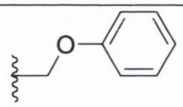
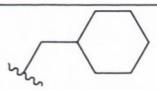
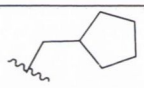
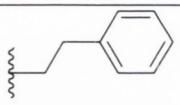
Compound Number	X	IR (C=O) ν_{max} cm^{-1}	Yield (%)
(**294**)*		1732.2	37
(**295**)*		1707.3	40
(**296**)*		1723.7	83
(**297**)*		1726.2	80
(**298**)*		1716.3	29

Table 23: 6-nitroindazoles with *N*-1 amide substituents



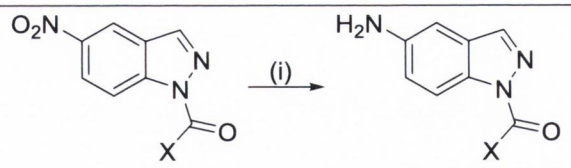
(i) Anhydrous CH_2Cl_2, Et_3N, 20 °C

Compound Number	X	IR (NO_2) ν_{max} cm^{-1}	Yield (%)
(**299**)*		1738.8	35
(**300**)*		1706.1	27
(**301**)*		1720.8	59
(**302**)*		1714.9	80
(**303**)*		1715.0	80

The 5-nitro and 6-nitroindazole *N*-1 amide derivatives (**294**) – (**298**) and (**299**) – (**303**) in tables 22 and 23 were reduced to their corresponding aminoindazole compound using 10 % palladium on carbon and hydrogen. The yields for these hydrogenations were quite high (33- 96 %) and the amine absorption occurred in the region ~ 3450 and ~ 3350 cm^{-1} in the infrared spectrum for these aminoindazoles, tables 24 (**304**) – (**308**) and 25 (**309**) – (**313**).

This library of 5 and 6-aminoindazoles will further expand the diversity of the indazoles structures prepared for biochemical evaluation.

Table 24: 5-Aminoindazoles with *N*-1 amide substituents



(294) - (298) **(304) - (308)**

(i) 1:1 MeOH:EtOAc, H_2, 10% Pd/C

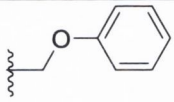
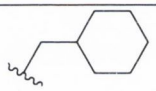
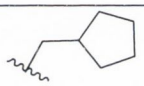
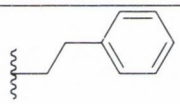
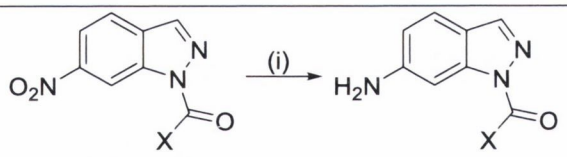
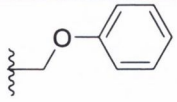
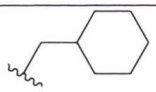
Compound Number	X	IR (NH_2) ν_{max} cm^{-1}	Yield (%)
(304)*		3453.7, 3365.0	85
(305)*		3454.9, 3366.5	33
(306)*		3453.7, 3365.0	94
(307)*		3455.4, 3345.7	96
(308)*		3414.97, 3348.74	72

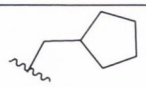
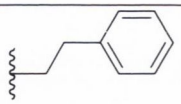
Table 25: 6-Aminoindazoles with *N*-1 amide substituents



(299) - (303) **(309) - (313)**

(i) 1:1 MeOH:EtOAc, H_2, 10% Pd/C

Compound Number	X	I.R. (NH_2) ν_{max} cm^{-1}	Yield (%)
(309)		3467.2, 3363.4	87
(310)		3472.5, 3371.7	54
(311)		3470.1, 3370.7	71

(**312**)		3468.9, 3369.1	95
(**313**)		3470.10, 3370.65	34

2.6.1 Conclusion

Sections 2.2 to 2.6 describe the preparation of analogues of the lead compound (**168**) which have various linkers from *N*-1 to an aryl/cyclic ring. The change in linker type could possibly affect the orientation of the aryl ring and thus have an effect on biological activity. Antiproliferative studies could highlight the potential difference in activity of these analogues and establish the optimal linker. Analogues of (**168**) were also prepared which contained the amine in the C-6 position instead of the C-5. The potential effect on biological activity due to the positional change of the amine could be highlighted in the antiproliferative studies.

2.7 Synthesis of 5 and 6 aryl substituted indazoles

2.7.1 Introduction

This chapter will describe the synthesis of analogues of the lead indazole compound (**168**) which contain either aryl, alkyne or vinyl substituents at the 5 or 6 position of the indazole ring, figure 127. The aim here was to investigate analogues of the lead compound (**168**) by modification of the C-5/C-6 amine substituent as some primary aromatic amines are known, upon metabolism, to form toxic metabolites. The carcinogenicity of aromatic amines was first discovered over 100 years ago due to the levels of urinary bladder cancer in men from occupational exposure to anilines in the dye industry[303]. The mutagenic nature of aromatic and heteroaromatic amines occurs following metabolic transformation by a series of reactions[304] which starts with *N*-hydroxylation by the 1A subfamily of cytochrome P450 enzymes, primarily by CYP1A2, figure 126. The formation of nitrenium ions may proceed by (i) direct hydrolytic dissociation of the resulting hydroxylamines or by (ii) further metabolism of the conjugates by Phase II enzymes leading to even more reactive bio-conjugates which eventually result in nitrenium ion formation. These nitrenium ions covalently modify nucleic bases of DNA. Reactive oxygen species (ROS) are formed by the interaction of Ar-NH_2 with P450 enzymes and peroxidases. Reactive oxygen species are believed to have important roles in the tumour progression due to their involvement in cell signalling and invasion[305], figure 126.

The following section will first describe the transformation of the amine substituent in (**168**) and (**209**) into the corresponding iodo and bromo analogues and the various palladium catalysed carbon-carbon coupling chemistry e.g. Suzuki, Sonogashira and Heck reactions which were applied with the halo analogues, figure 127.

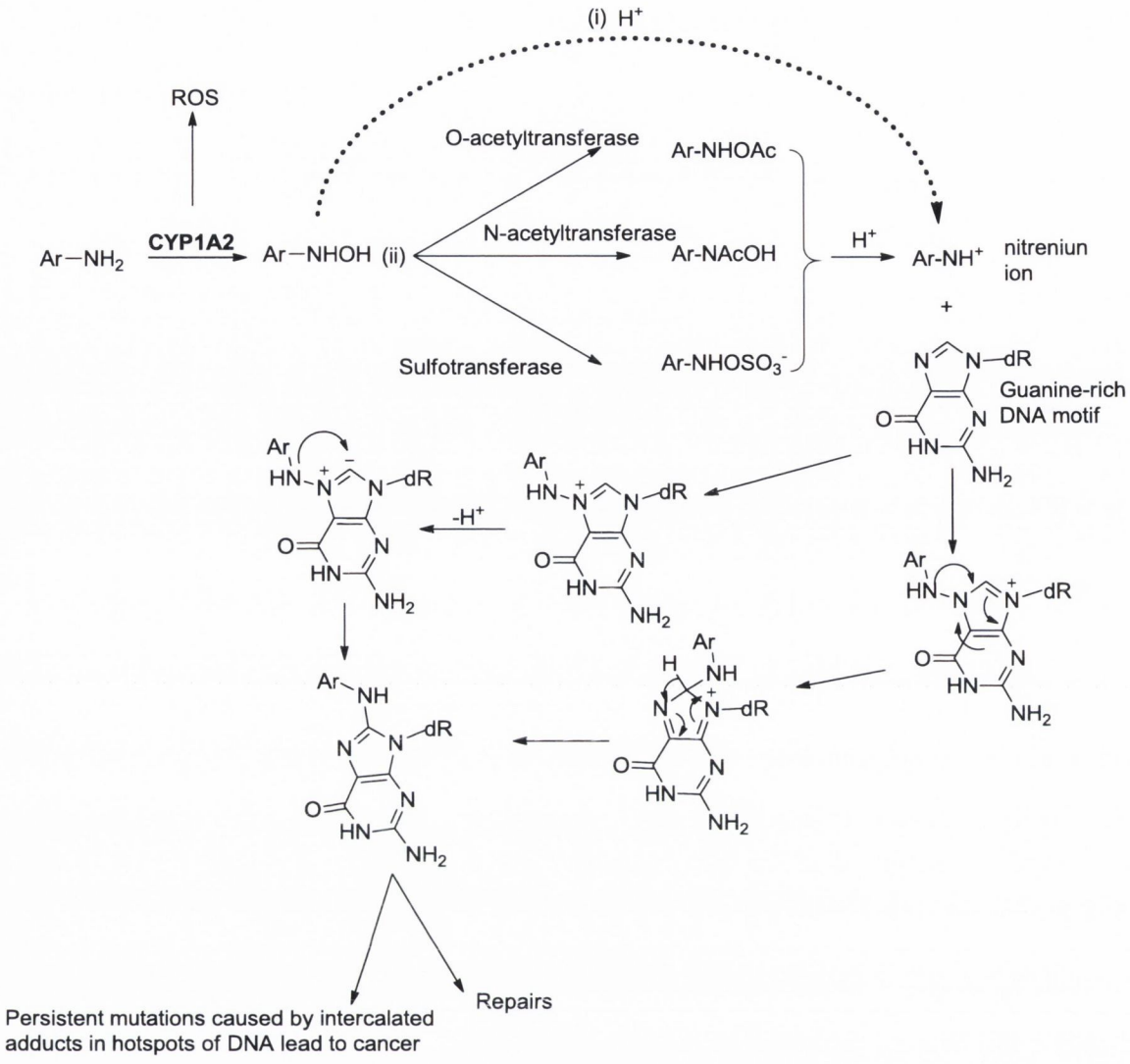


Figure 126: Two mutagenic pathways of aromatic amines by interactions with CYP1A2[304, 306]

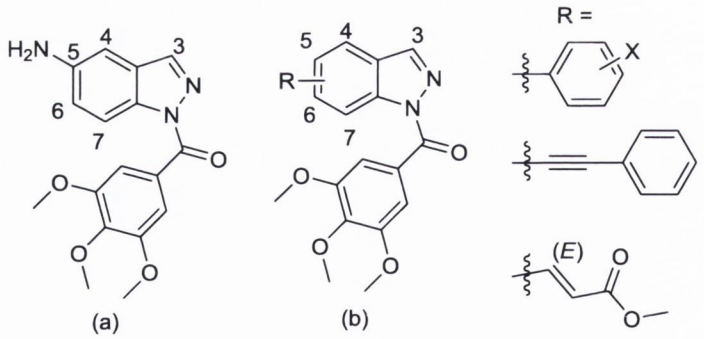


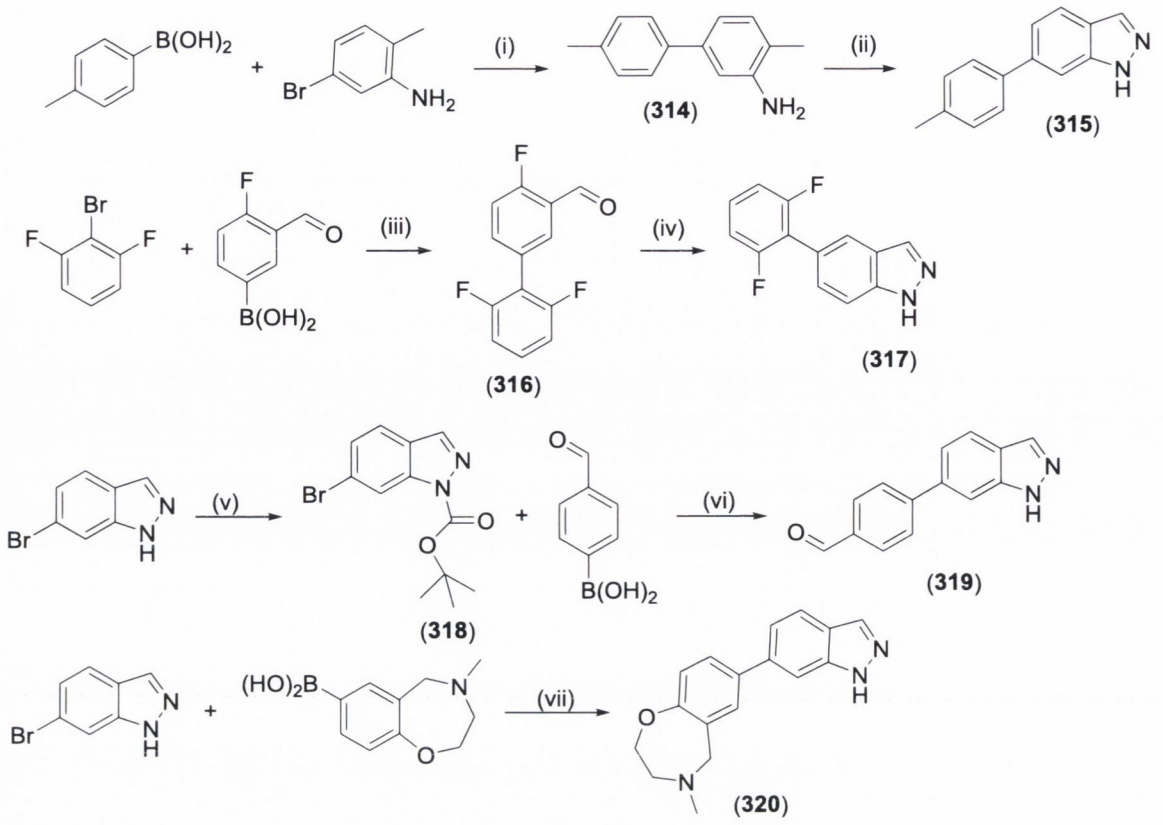
Figure 127: (a) Lead compound (168) and (b) analogues developed in this section

2.7.2 Literature review of 5-aryl and 6-aryl indazoles

Before the preparation of the specific indazoles contained in this section is described, the approaches reported to the synthesis of 5-aryl and 6-aryl indazoles in discussed (figure 128).

Thomas et al prepared a series of substituted indoles, indazoles and benzimidazoles as chemokine receptor CXCR4 and CCR7 inhibitors[307]. These compounds were designed for the treatment of cancer, inflammation and treatment of HIV infection. During the course of their work, *Thomas et al* synthesised a series of 6-arylindazole intermediates e.g. (**315**). Using Suzuki coupling, the bi-aryl compound (**314**) was prepared from 5-bromo-2-methylbenzenamine and 4-methoxyphenylboronic acid. Cyclisation of the (**314**) using sodium nitrite afforded the 6-arylindazole intermediate (**315**). The same synthetic approach was also used for 5-arylindazoles. *Wang et al*[308] prepared a series of 5-arylindazole intermediates by first synthesising the bi-aryl compound (**316**) using Suzuki coupling. Cyclisation of (**316**) using hydrazine afforded the 5-arylindazole intermediate (**317**). *Wang et al* were investigating cancer chemotherapeutic agents that behaved as PIM inhibitors. The proto-oncogene serine/threonine-protein kinase (PIM) family comprises PIM1, PIM2 and PIM3 which are often highly expressed in haematological malignancies. PIM1, for example, was shown to be involved in the tumour initiation or progression[309].

Alternatively 6-arylindazoles can be prepared, using Suzuki coupling, starting from 6-bromoindazoles. In one example, *N*-1 protection was first required followed by Suzuki coupling. The Suzuki coupling conditions were such that 6-arylation and *N*-1 de-protection occurred simultaneously. *Hallman et al* prepared a series of azabenimidazoles as potential cancer chemotherapeutic agents[310]. *N*-1 protection was achieved by reacting 6-bromoindazole with di-*tert*-butyl dicarbonate, affording (**318**), which was then coupled with 4-formylphenylboronic acid affording the 6-arylindazole (**319**). However there are examples of the preparation of 6-arylindazoles where *N*-1 protection is not required. *Takeuchi et al*, during their research into the preparation of compounds as inhibitors of the mammalian target of rapamycin[311], directly synthesised the 6-arylated indazole (**320**) without first protecting the N1 atom.



(i) $PdCl_2(PPh_3)_2$, KOtBu, dioxane/H_2O, 80 °C, 12 hrs (ii) HBF_4, H_2O, $NaNO_2$, 0 °C, AcOK, 18-crown-6[307] (iii) Na_2CO_3, $PdCl_2(PPh_3)_2$, H_2O, toluene, 100 °C, 8 h (iv) N_2H_4-H_2O, 120 °C, 8 h[308] (v) DMAP, Et_3N, MeCN, 5 °C to rt, 18 h (vi) aq. Cs_2CO_3, $Pd(PPh_3)_4$, dioxane, 100 °C[310] (vii) $Pd(dppf)Cl_2.CH_2Cl_2$, Et_3N, 1,4-dioxane, H_2O, 85 °C[311]

Figure 128: Synthesis of 5-aryl and 6-arylindazoles previously reported

2.7.3 Synthesis of bromo and iodo analogues of (168) and (209)

In the present work, the preparation of the required bromo- and iodoindazoles is first described. The transformation of a primary aromatic amine into the corresponding aromatic halide compound can be performed using a diazotization process[312]. At 0 °C, primary aromatic amines react with nitrous acid to yield aromatic diazonium ions. Nitrous acid is prepared by treating an aqueous solution of sodium nitrite with strong acid at 0-5 °C, figure 129 (a). This temperature is required as nitrous acid decomposes rapidly at room temperature but is reasonably stable at 0-5 °C. Protonation of nitrous acid and the subsequent loss of water yields the nitrosonium ion (NO^+), which is the reactive species of nitrous acid, figure 129 (b). Nucleophilic attack of the primary aromatic amine on the nitrosonium ion, followed by proton loss, yields a primary nitrosamine, figure 129 (c). The oxygen in the nitrosamine is protonated which results in the elimination of water, yielding the aromatic diazonium ion, figure 129 (d). The diazonium group is then replaced by the necessary nucleophile, figure 129 (e).

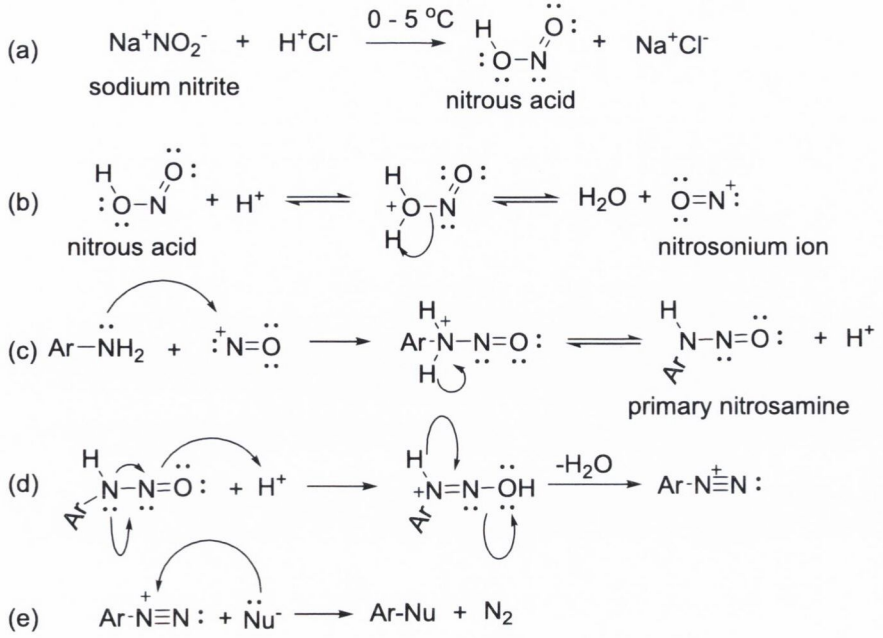
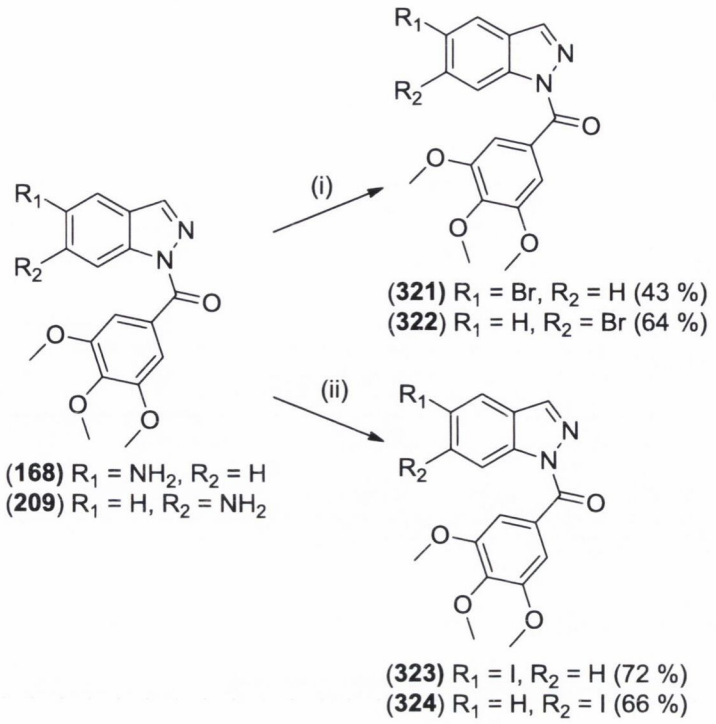


Figure 129: Diazotization process

Primary aromatic amines can be transformed into the corresponding aromatic halide, phenol analogue or cyano analogue depending on the nucleophile[312]. The bromo and iodo analogues of (**168**) and (**209**) were prepared in good yield, figure 130. In the literature, the preparation of 6-iodoindazole[313] and 6-bromoindazole[314] by the diazotization of 6-aminoindazole was reported as well as the preparation of 5-iodoindazole[315] and 5-bromoindazole[316] from 5-aminoindazole.



(i) HBr, $NaNO_2$, DIW, CuBr (ii) HCl, $NaNO_3$, DIW, KI

Figure 130: Synthesis of bromo and iodo analogues of (168) and (209) by diazotization

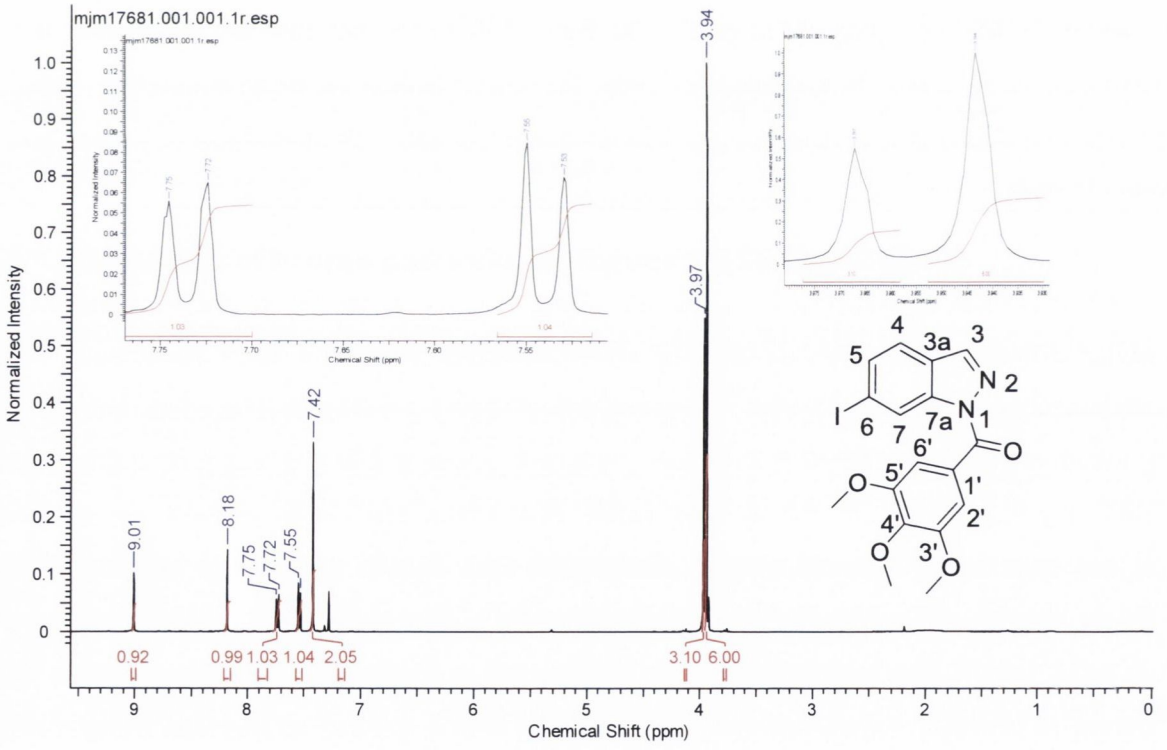


Figure 131: ^{1}H-NMR spectrum of (324)

As an example, the ^{1}H-NMR spectrum of (6-iodo-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (**324**) is shown in figure 131. The sharp singlet at 3.94 ppm, integrating for 6 protons, corresponds to the protons of the two symmetric methoxy groups while the singlet at 3.96 ppm is assigned to the protons of the methoxy group at $C_{4'}$. The singlet at 7.41 ppm is assigned to the symmetric protons, $H_{2'}$ & $H_{6'}$. The doublet at 7.54 ppm, $J = 8.32$ Hz, is assigned to H_5 while the doublet at 7.24 ppm, $J = 8.32$ Hz, is assigned to H_4. The singlet at 8.18 ppm is assigned to H_3 while the singlet at 9.01 ppm corresponds to H_7.

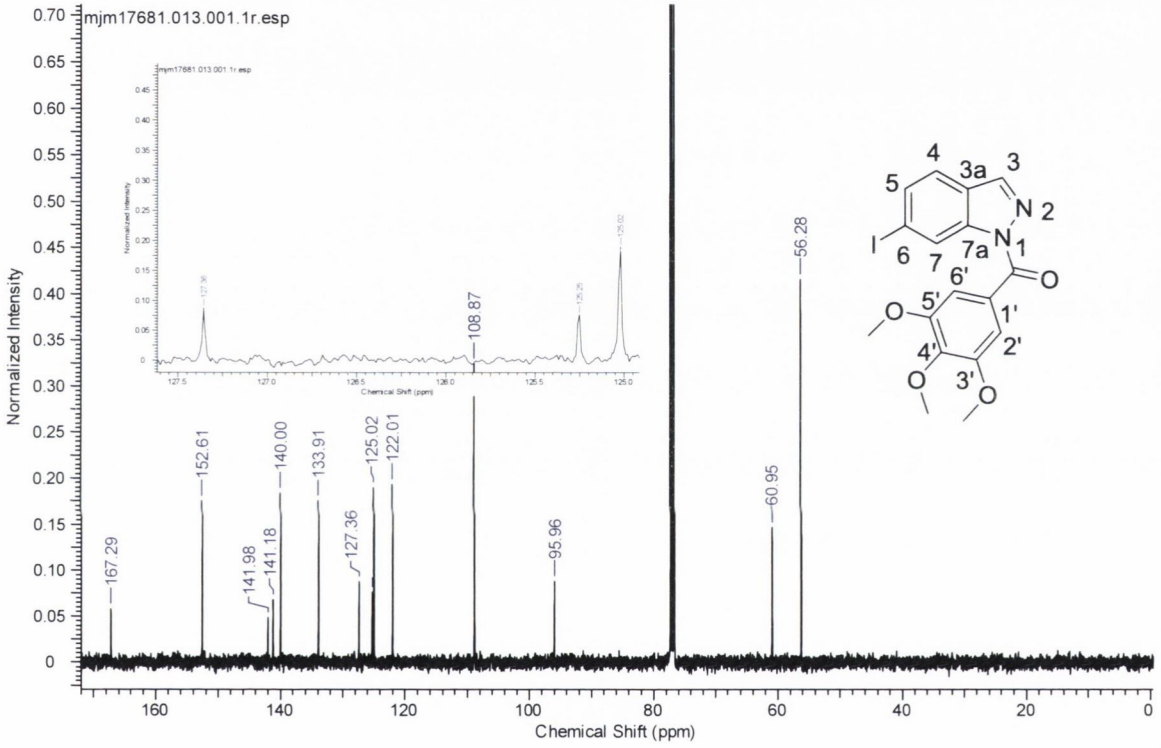


Figure 132: ^{13}C-NMR spectrum of (324)

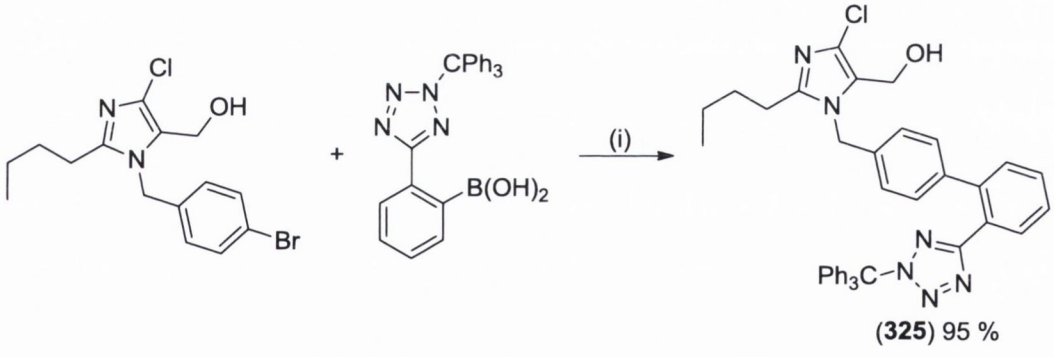
The ^{13}C-NMR spectrum of (**324**) is shown figure 132. The signal at 56.28 ppm corresponds to the carbons of the symmetric methoxy groups while the signal at 60.95 corresponds to the carbon of the methoxy group at $C_{4'}$. The signals at 108.86, 122.02, 125.03 and 133.91 and 140.00 ppm correspond to the aromatic methine carbons $C_{2'}$ & $C_{6'}$, C_{7a}, C_4, C_5 and C_3 respectively. The signal at 167.30 ppm is assigned to the carbonyl carbon while the signal at 152.61 ppm is assigned to the symmetric *ipso* carbons $C_{3'}$ and $C_{5'}$. The signals at 95.97, 125.26, 127.36, 141.18 and 141.98 ppm are assigned to aromatic *ipso* carbons C_6, C_{3a}, $C_{1'}$, C_{7a} and $C_{4'}$ respectively.

The halide indazoles (**321**) – (**324**) enabled the preparation of analogues of the lead compound (**168**) and (**209**) using various palladium catalysed carbon – carbon coupling chemistry, namely using the Suzuki, Heck and Sonogashira reactions.

2.7.4 Synthesis of 5-aryl and 6-aryl substituted indazoles

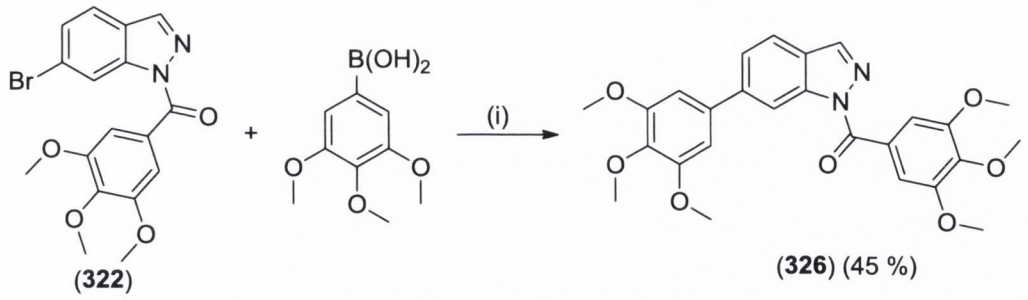
The 5-aryl and 6-aryl substituted indazoles synthesised in this section were obtained by the Suzuki reaction. The Suzuki reaction, often referred as Suzuki coupling or sometimes as Suzuki–Miyaura coupling, is a palladium catalysed cross coupling reaction of organoboron compound with an organic halide or organic triflate. This type of cross coupling reaction was reported by *Miyaura et al*[317] who were investigating alternative synthetic methods for the preparation of (*E*,*E*)- and (*E*,*Z*)-dienes. *Miyaura et al* reported a novel cross coupling reaction of 1-alkenylboranes with 1-alkenyl halides, using a catalytic amount of tetrakis(triphenylphosphine) palladium and base[318].

The Suzuki reaction is today one of the most widely used C-C coupling reactions. This is due to the mild reaction conditions and the extensive range of commercially available boronic acids that are environmentally safer than the other organometallic reagents[319]. The handling and removal of boron-containing byproducts is easy when compared to other organometallic reagents, especially in a large-scale synthesis. Suzuki coupling is used in the preparation of Losartan, a nonpeptide angiotensin II receptor antagonist, which affords the desired penultimate bi-aryl intermediate (**325**) in 95% yield[320] (see figure 133).



(i) $Pd(OAc)_2$, PPh_3, K_2CO_3, H_2O/THF/DME[320]

Figure 133: Example of Suzuki coupling in large scale synthesis



(i) THF, aq. 2M Na_2CO_3, 5 mol % $Pd(PPh_3)_4$, 100 °C, 6 h

Figure 134: Synthesis of 6-arylated indazole (326)

In the present work, the Suzuki coupling of (**322**) and 3,4,5-trimethoxyphenylboronic acid afforded (**326**), figure 134. The 6-arylated indazole (**326**) was obtained in 45 % yield using conventional refluxing.

The Suzuki coupling mechanism is shown in figure 135. In the first step, dissociation of two triphenylphosphines from the tetrakis(triphenylphosphine)palladium(0) yields the $Pd^0(PPh_3)_2$ species. A π complex is formed between the aryl bromide (**A**) and $Pd^0(PPh_3)_2$. Oxidative addition of (**A**) and $Pd^0(PPh_3)_2$ yields the organopalladium compound (**B**) which reacts with base to form (**C**). Base is required for the activation of the boronic acid also which enables transmetalation which yields (**D**). Reductive elimination of (**D**) yields the desired diaryl compound (**E**) and reconstitutes the original Pd^0 catalyst, $Pd^0(PPh_3)_2$[321, 322].

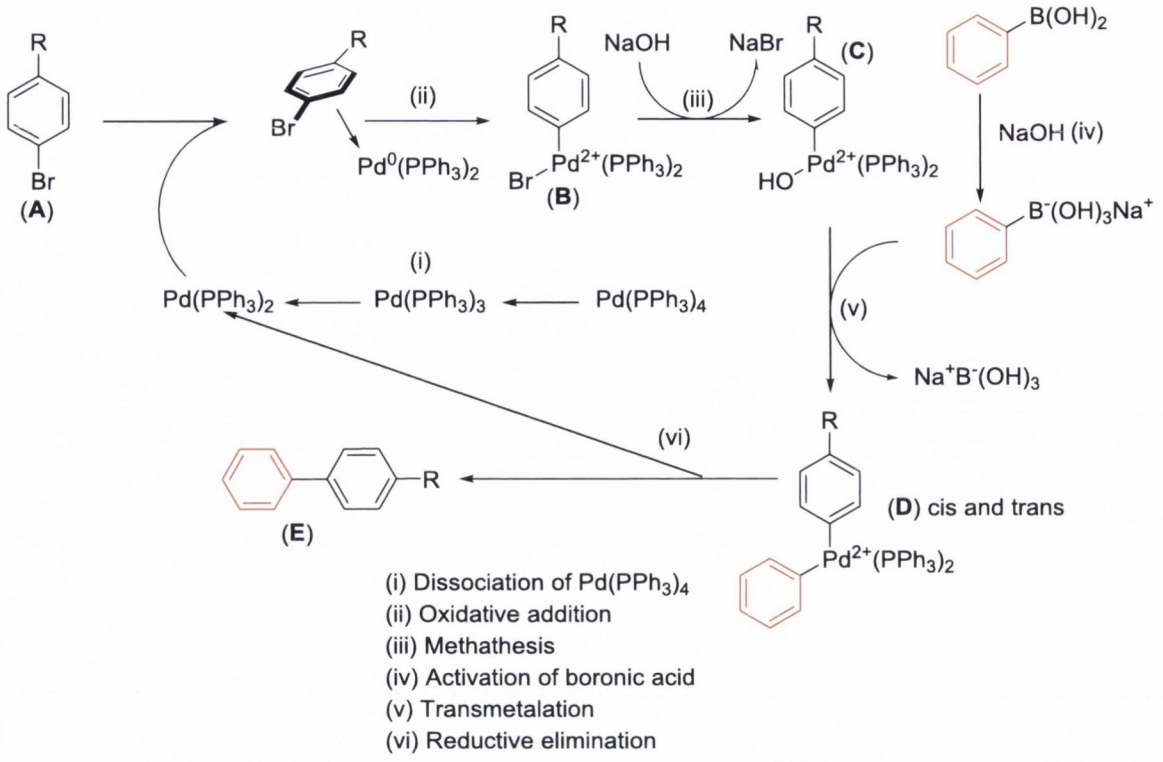


Figure 135: Mechanism for Suzuki coupling[321]

The ^{1}H-NMR spectrum of the coupled product (**326**) is shown in figure 136. The signals 3.93, 3.94, 3.96 and 3.97 ppm correspond to the protons of the methoxy groups. By comparing the ^{1}H-NMR spectra of (**322**) and (**326**), figure 137, the signal at 3.93 corresponds to the protons of the methoxy group at $C_{4''}$ while the sharp singlet at 3.94 ppm, integrating for 6 protons, is assigned to the protons of the symmetric methoxy groups at $C_{3'}$ and $C_{5'}$. The singlet at 3.96 ppm is assigned to the protons of the methoxy group at $C_{4'}$ while the sharp singlet at 3.97 ppm is assigned to the protons of the symmetric methoxy groups at $C_{3''}$ & $C_{5''}$. The singlet at 6.91 ppm, integrating for 2 protons, is assigned to the symmetric protons $H_{2''}$ & $H_{6''}$ while the singlet at 7.43 ppm, also integrating for 2 protons, is assigned to the symmetric protons $H_{2'}$ & $H_{6'}$ (figure 138). The double doublet at 7.64 ppm, J = 8.36, 1.16 Hz, is assigned to H_5 while the doublet at 7.84 ppm, J = 8.36 Hz, is assigned to H_4. The singlet at 8.25 ppm is assigned to H_3 while the singlet at 8.75 ppm is assigned to H_7.

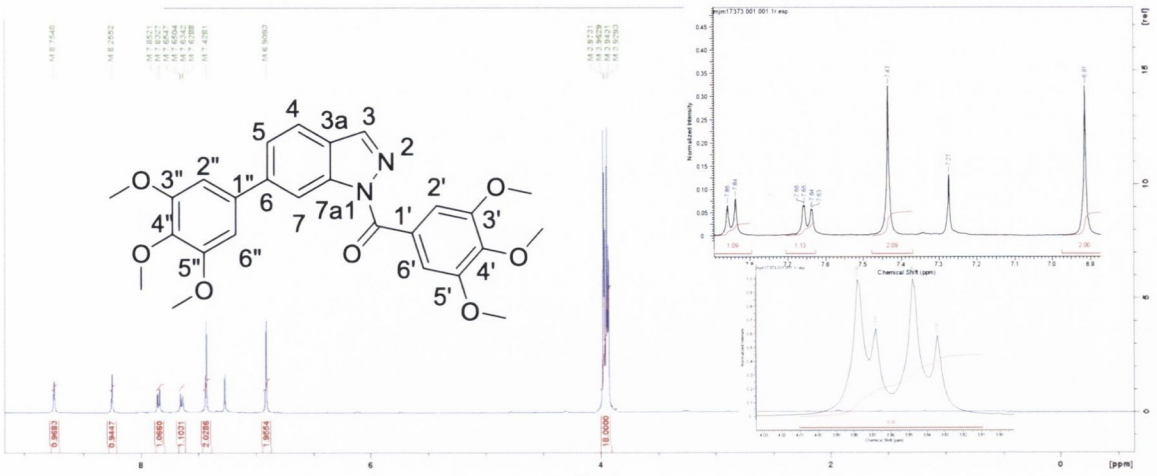


Figure 136: ^{1}H-NMR spectrum of (326)

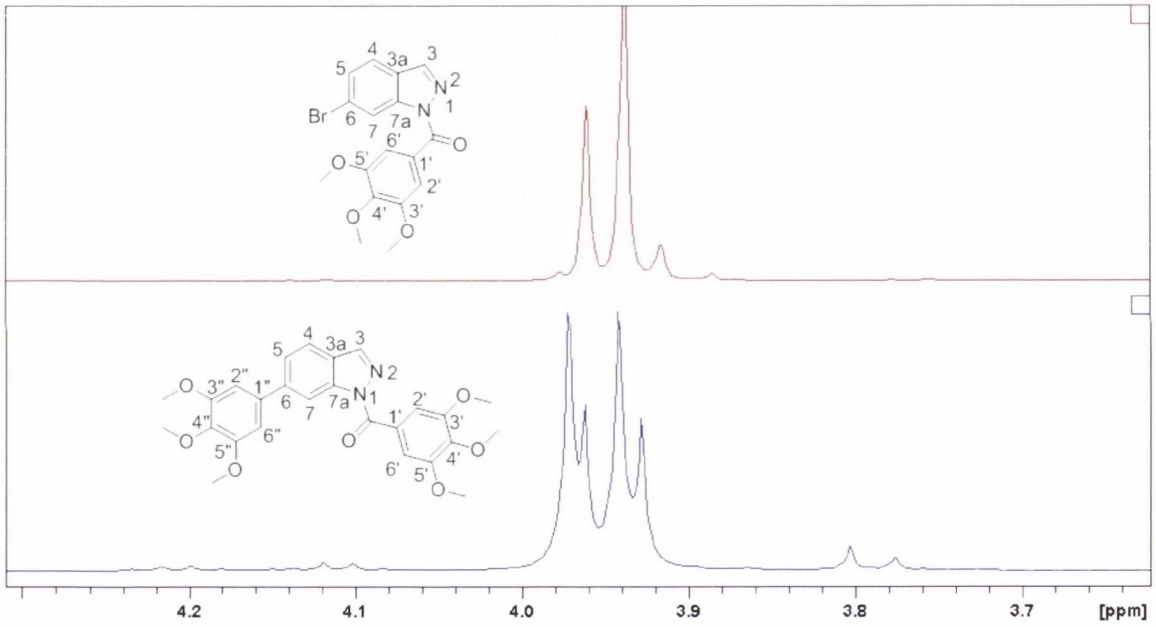


Figure 137: Overlay of ^{1}H-NMR spectra of (322) and (326) from 3.6 to 4.3 ppm

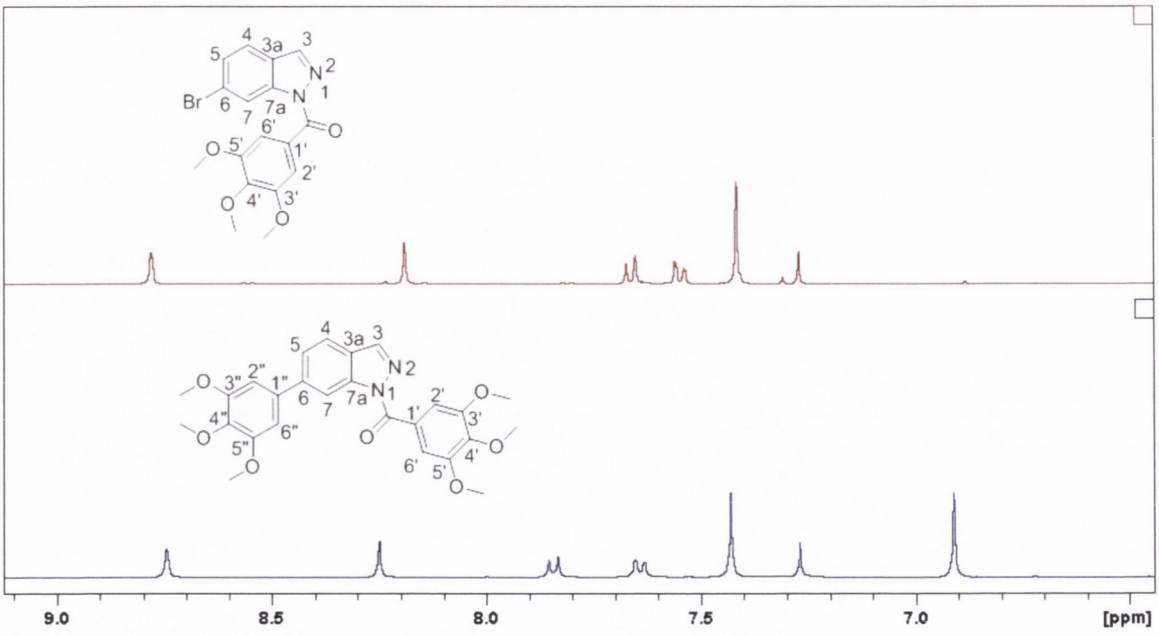


Figure 138: Overlay of ^{1}H-NMR spectra of (322) and (326) from 6.9 to 9.0 ppm

The ^{13}C-NMR and DEPT 90 spectra of (**326**) are shown is figures 139 and 140 respectively. Figure 141 compares the ^{13}C-NMR spectra of (**324**) and (**326**). The signal at 56.23 ppm is assigned to the carbons of the two symmetric methoxy groups at $C_{3'}$ & $C_{5'}$ and $C_{3''}$ & $C_{5''}$. The signals at 60.90 and 60.96 ppm are assigned to the carbons of the methoxy groups at $C_{4''}$ and $C_{4'}$ respectively. The signals at 104.95 and 108.79 ppm are assigned to the aromatic methine carbon pairs of $C_{2''}$ & $C_{6''}$ and $C_{3'}$ & $C_{5'}$ respectively, figure 141. The signals at 114.01, 121.72, 124.72 and 140.14 ppm are assigned to the aromatic methine carbons C_7, C_5, C_4 and C_3 respectively.The signal at 167.68 ppm is assigned to the carbonyl carbon while the signals at 152.59 and 153.52 ppm correspond to the aromatic *ipso* carbons $C_{3'}$& $C_{5'}$ and $C_{3''}$& $C_{5''}$ respectively, figure 141. The signals 125.12, 127.60, 136.59, 138.08, 140.94, 141.80 and 143.15 ppm correspond to the remaining aromatic *ipso* carbons C_{3a}, $C_{1'}$, $C_{1''}$, C_6, C_{7a}, $C_{4''}$ and $C_{4'}$ respectively.

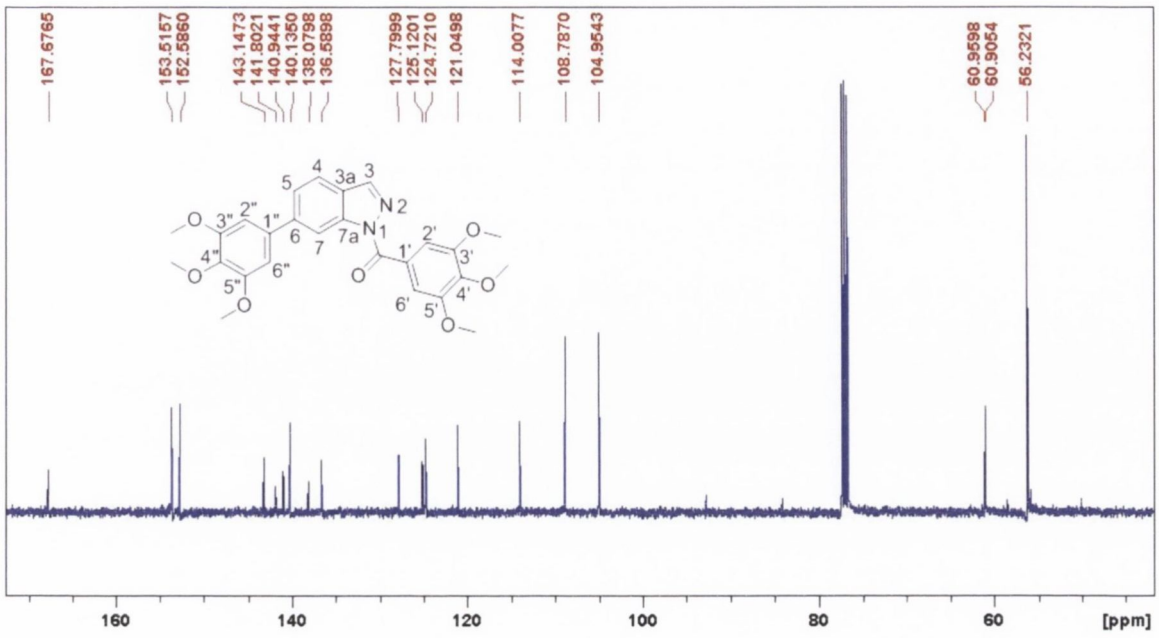


Figure 139: ^{13}C-NMR spectrum of (326)

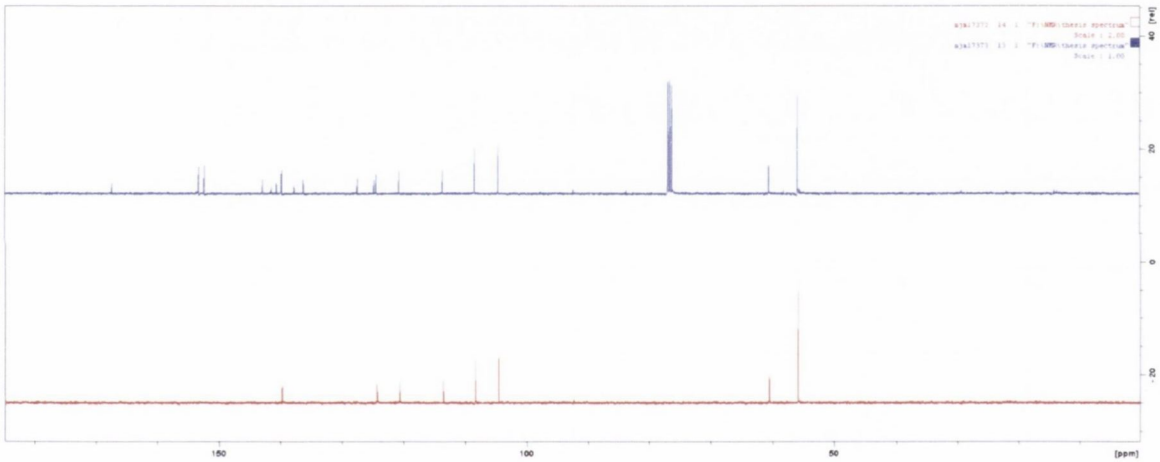


Figure 140: DEPT 90 and ^{13}C-NMR spectra of (326)

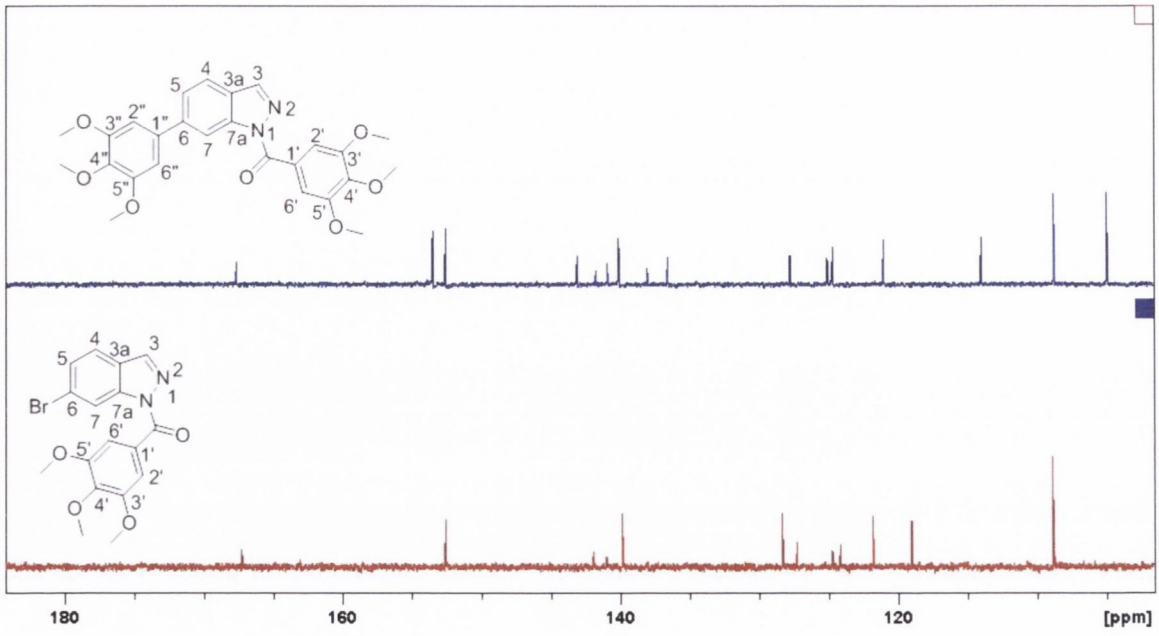


Figure 141: Overlay of ^{13}C-NMR spectra of (324) and (326)

Suzuki coupling has been performed successfully using microwave assisted organic synthesis (MAOS)[323-325]. The preparation of (**326**) was attempted on the same scale but using the CEM Discover microwave reactor. The power supplied by the microwave reactor was no greater than 300 watts. Once the reaction has commenced, the power is ramped up but is lowered once the pre-defined reaction temperature has been reached. The reaction temperature was set to 120 °C while reaction time was set to 1 hour. The work up was as before. TLC analysis revealed that the crude mixture possibly contained the desired 6-arylated product (**326**) while there also a significant amount of side products. The mixture was purified by flash column chromatography and fractions which contained the R_f 0.33 (eluent 1:1 EtOAc: Hexane), identified as (**326**), were combined. The ^{1}H-NMR spectrum of these combined fractions as well the ^{1}H-NMR spectrum of (**326**), obtained by normal refluxing, are shown in figure 142. The two ^{1}H-NMR spectra are identical and also mass spectrometry (Found $[M+Na]^+$ = 501.1632, $C_{26}H_{26}N_2NaO_7$ requires 501.1638) further confirmed the microwave reaction had been successful.

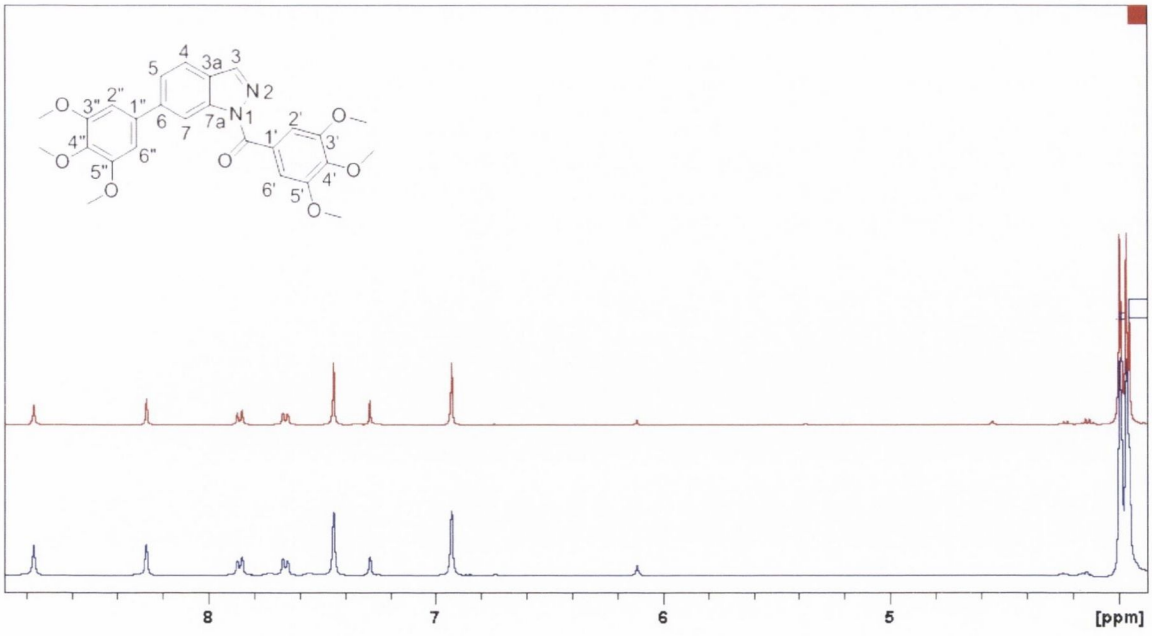
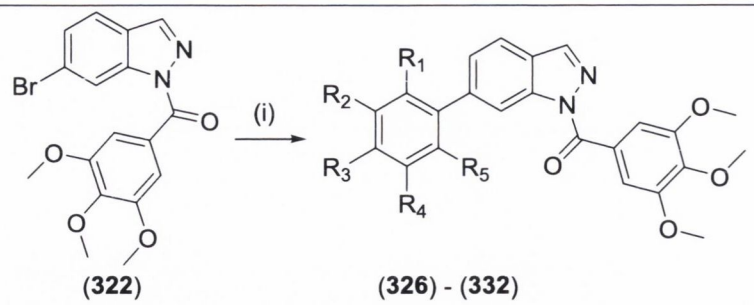


Figure 142: Overlay of ^{1}H-NMR spectra of (326) obtained by MOAS (red) and conventional refluxing (blue)

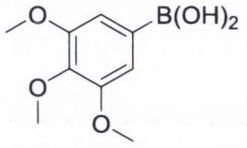
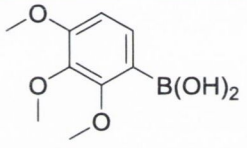
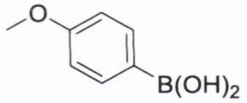
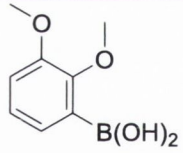
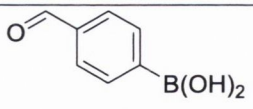
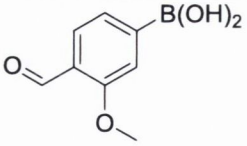
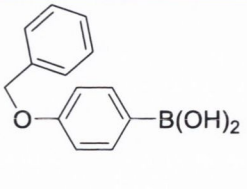
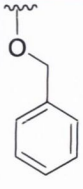
The 6-arylated product (**326**) was obtained in 16% yield using aforementioned microwave reaction conditions. Since there was a significant of side products in the first attempt and the yield was lower than the refluxing method, optimisation of the microwave reaction conditions was then performed. The reaction was repeated but the temperature was set first to 80 °C and reaction time set to 10 minutes. The reaction was attempted again at 90, 100, 110 and 120 °C while keeping the reaction time constant at 10 minutes. (**326**) was obtained in 40% yield at 80 °C and 10 minutes, which is comparable to the yield recorded for the refluxing method. The difference in yield between this temperature and the higher temperatures was negligible and there were significant amount of observed side products at higher temperatures. A 97% reduction in reaction time is obtained with the optimised microwave reaction conditions. A series of 6-arylindazoles (**326**) – (**332**) and 5-aryindazoles (**333**) – (**341**) were then prepared from the corresponding aryl bromides (**322**) and (**321**) using these optimised conditions, see tables 26 and 27 respectively.

Table 26: 6-Arylindazoles prepared by Suzuki coupling



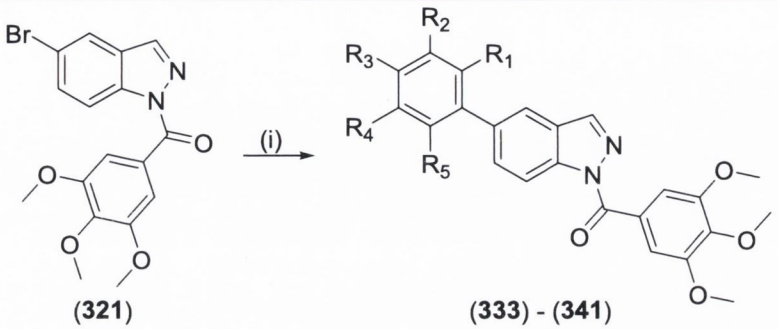
(322) **(326) - (332)**

(i) THF, aq. 2M Na_2CO_3, $Pd(PPh_3)_4$, 80 °C, 10 min, 300 W (MAOS)

Compound No.	Phenylboronic acid	R_1	R_2	R_3	R_4	R_5	% Yield	IR_{vmax} (NC=O) cm^{-1}
(**326**)*		H	OCH_3	OCH_3	OCH_3	H	40	1675.5
(**327**)*		H	H	OCH_3	OCH_3	OCH_3	48	1678.4
(**328**)*		H	H	OCH_3	H	H	38	1676.2
(**329**)*		OCH_3	OCH_3	H	H	H	25	1681.5
(**330**)*		H	H	HC=O	H	H	33	1678.2
(**331**)*		H	OCH_3	HC=O	H	H	14	1684.1
(**332**)*		H	H		H	H	12	1682.2

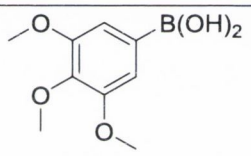
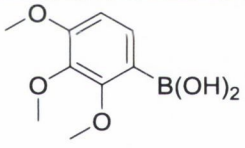
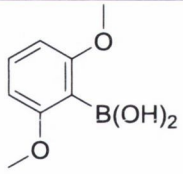
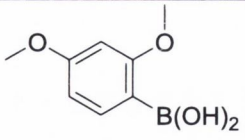
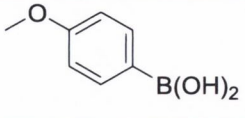
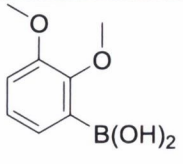
* Novel compound

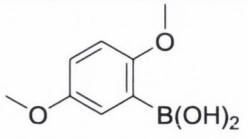
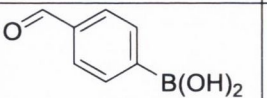
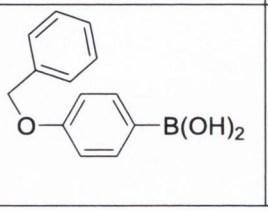
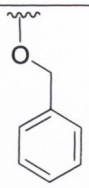
Table 27: 5-Arylindazoles prepared by Suzuki coupling



(321) **(333) - (341)**

(i) THF, aq. 2M Na_2CO_3, $Pd(PPh_3)_4$, 80 °C, 10 min, 300 W (MAOS)

Compound No.	Phenylboronic acid	R_1	R_2	R_3	R_4	R_5	% Yield	IR_{vmax} (NC=O) cm^{-1}
(**333**)*		H	OCH_3	OCH_3	OCH_3	H	43	1681.7
(**334**)*		H	H	OCH_3	OCH_3	OCH_3	40	1684.7
(**335**)*		OCH_3	H	H	H	OCH_3	33	1682.6
(**336**)*		OCH_3	H	OCH_3	H	H	53	1675.5
(**337**)*		H	H	OCH_3	H	H	43	1681.7
(**338**)*		OCH_3	OCH_3	H	H	H	51	1682.7

(**339**)*		OCH_3	H	H	OCH_3	H	44	1682.7
(**340**)*		H	H	HC=O	H	H	30	1703.5
(**341**)*		H	H		H	H	20	1679.2

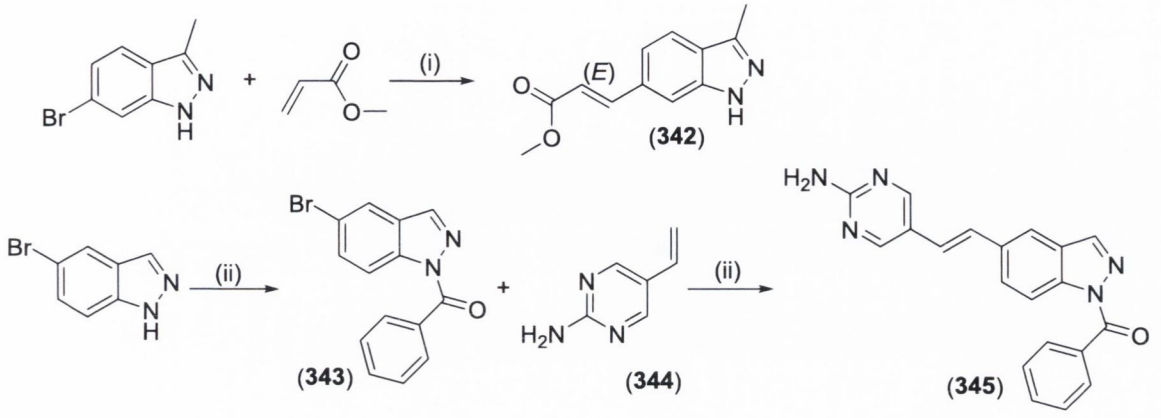
* Novel compound

The 6-arylindazoles and 5-arylindazoles that were prepared have electron donating substituents on the aryl ring (**326**) – (**329**), electron withdrawing substituents (**330**) and (**341**) or both as in (**331**). The yields for the arylindazoles are quite good, ranging from 25-43%. The novel arylated indazoles in tables 26 and 27 were all obtained as solids. For the corresponding 5-aryl and 6-aryl indazoles, there is a slight difference in % yields e.g. (**326**) – 40%, (**333**) – 43% and (**327**) – 32%, (**334**) – 40%.

2.7.5 Synthesis of 5 and 6-vinylindazoles *via* the Heck reaction

The preparation of 5- and 6-vinylindazoles has been previously reported[327,328], figure 143. The examples chosen are prepared by Heck reaction but it is possible to synthesise similar compounds using Suzuki coupling as alkenylboronic acids are widely available[326]. *Nagai et al* , who were investigating compounds having urate transporter 1 (URAT1) inhibitory activity, prepared the intermediate (**342**) by reacting 6-bromo-3-methyl-1*H*-indazole with methyl acrylate using palladium acetate and tri(*o*-tolyl)phosphine[327]. Since palladium acetate is a Pd^{2+} species, a triphenylphosphine ligand, such as tri(*o*-tolyl)phosphine, is required which generates bis(triphenylphosphine)palladium(0) acetate (**D**), the active palladium catalyst, *in situ*[322], figure 144. The bis(triphenylphosphane)palladium(II) diacetate (**A**) is formed from palladium acetate and two molecules of triphenylphosphine. Within (**A**), a triphenylphosphine transfers the initially free electron pair of its phosphorus atom to palladium and in its place, picks up the electron pair by which one of the acetate ligands was bound to palladium. This results in the formation of triphenylphosphane oxide (**B**) and (triphenylphosphane palladium) acetate (0) (**C**), which in turn irreversibly binds to a second ligand of triphenylphosphane forming the active palladium catalyst (**D**). However *Cao et al* coupled the aroylated 5-bromindazole (**343**) with the alkene (**344**) affording the 5-vinylindazole (**345**)[328] in the absence of a

triphenylphosphine ligand. An investigation by *Yao et al* into ligand free Heck reactions[329] demonstrated that palladium acetate, when used in combination of potassium phosphate as base and DMF as solvent, was an extremely active catalyst for the Heck reaction of aryl bromides.



(i) Et_3N, $Pd(OAc)_2$, (o-$MeC_6H_4)_3P$, DMF, 150 °C[327] (ii) Et_3N, CH_2Cl_2, benzoyl chloride, rt, 16 h (iii) Et_3N, $Pd(OAc)_2$, DMF, 110 °C, 16 h[328]

Figure 143: Examples of the preparation of 5 and 6-vinylindazoles

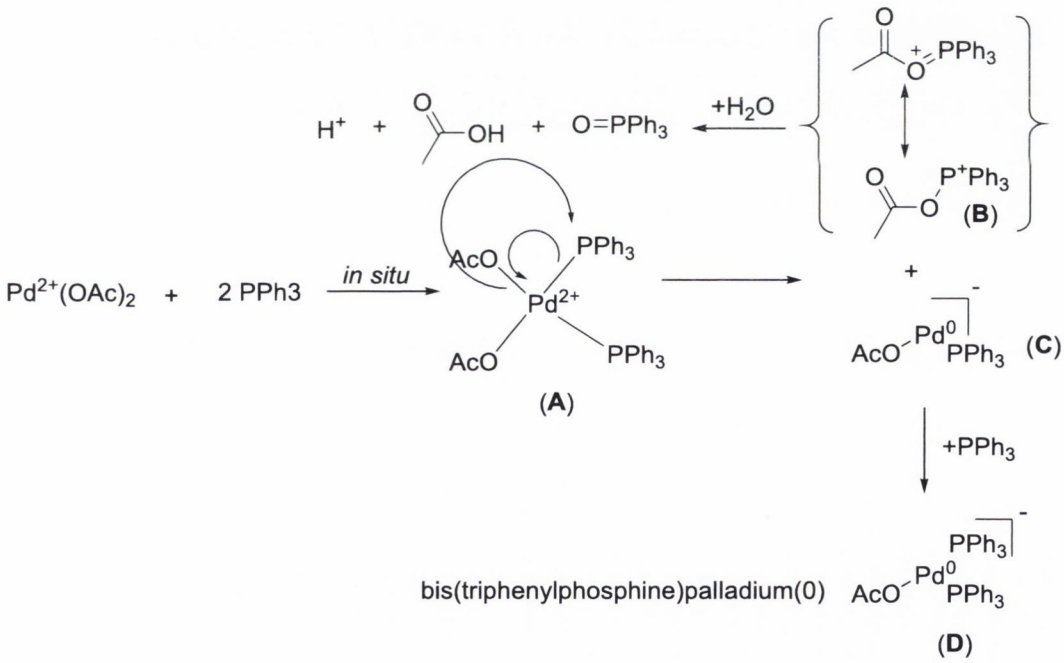
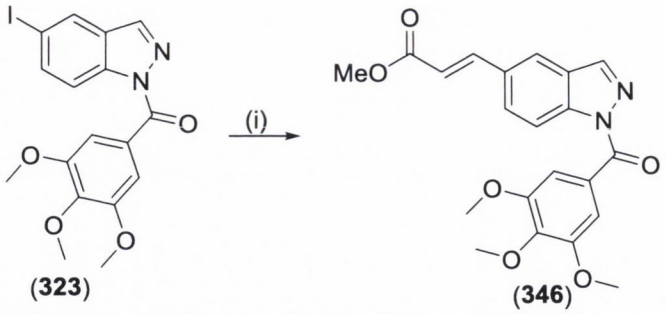


Figure 144: *In situ* generation of bis(triphenylphosphine)palladium(0)[322]



(i) $Pd(OAc)_2$ or Pd $(PPh_3)_4$ (5 mol %), methyl acrylate (2 molar eq), Et_3N, DMF, reflux, 18 h

Figure 145: Synthesis of 5-vinylindazole (346)

In the present work, the 5-vinylindazole (**346**) was prepared from (**323**) and methyl acrylate first using tetrakis(triphenylphosphine)palladium(0) and then using palladium acetate as the palladium catalyst, figure 145. The main mechanistic steps for the Heck reaction are similar for both palladium catalysts. Using the palladium acetate system, figure 146, the transient palladacycle (I) is first formed by the reaction of palladium acetate with the required olefin. The palladacycle (I) is expected to be able to undergo oxidative addition by the aryl halide, generating the Pd(IV) species (II). Base-promoted elimination of the acetate ion gives intermediate (III), which subsequently collapses to the Pd(II) species (IV) and releases the coupling product. Equilibration of Pd(IV) with the acetate ion then regenerates $Pd(OAc)_2$. Additionally, (IV) itself could participate in the catalytic cycle in a similar way to that of the first turnover.

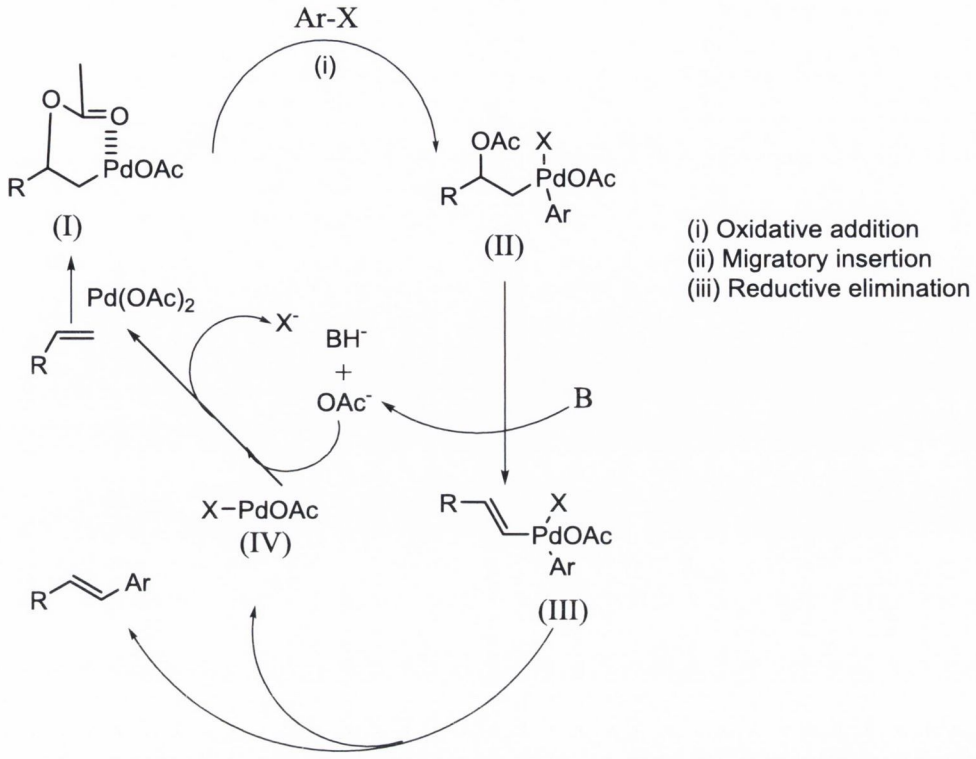
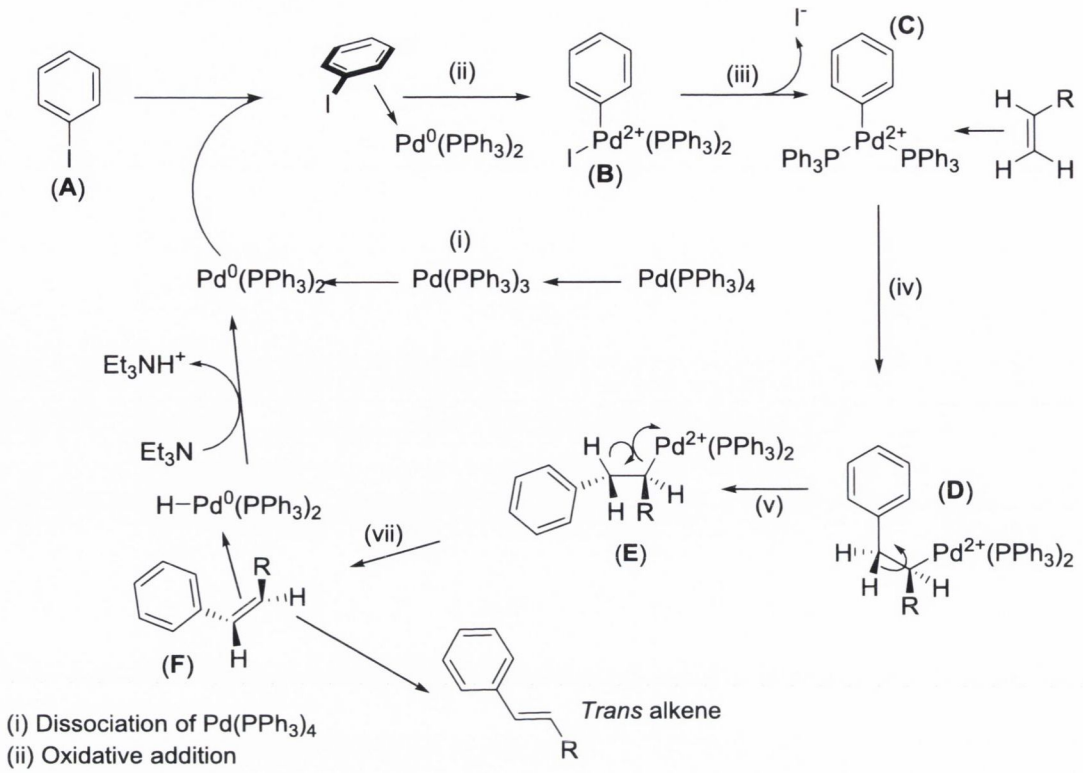


Figure 146: Ligand free $Pd(OAc)_2$ catalysed Heck reaction[329]

The mechanistic steps when tetrakis(triphenylphosphine)palladium(0) is used are shown in figure 147. In the first step, dissociation of two phenyl phosphine from the tetrakis(triphenylphosphine)palladium(0) yields the $Pd^0(PPh_3)_2$ species. A π complex is formed between the aryl iodide (**A**) and $Pd^0(PPh_3)_2$. Oxidative addition of (**A**) and $Pd^0(PPh_3)_2$ yields the organopalladium compound (**B**) which then yields (**C**), following the loss of the iodide ion. A π complex is then formed between (**C**) and the alkene. There is *cis* – selective addition of the aryl-Pd complex (**C**) to the C=C such that the organic moiety is bonded to the methylene carbon and Pd to the methine carbon i.e. carbopalladation of the double bond. Rotation of the C-C bond in (**D**) is required in order to orient the β–H atom and the $Pd^{2+}(PPh_3)_2$ into a *syn* relationship (**E**). This rotation is essential for the formation of a hydrido-Pd(II) complex (**F**) to occur by β-elimination of this β–H atom and the $Pd^{2+}(PPh_3)_2$ group. Dissociation of this complex (**F**) forms the *trans* alkene product and regenerates $Pd^0(PPh_3)_2$ catalyst[322, 330].



(i) Dissociation of $Pd(PPh_3)_4$
(ii) Oxidative addition
(iii) Loss of halide ion
(iv) Carbopalladation of the double bond
(v) Rotation of C-C bond
(vi) B-hydride elimination
(vii) Dissociation of hydrido-Pd(π) complex

Figure 147: $Pd^0(PPh_3)_4$ catalysed Heck reaction[322]

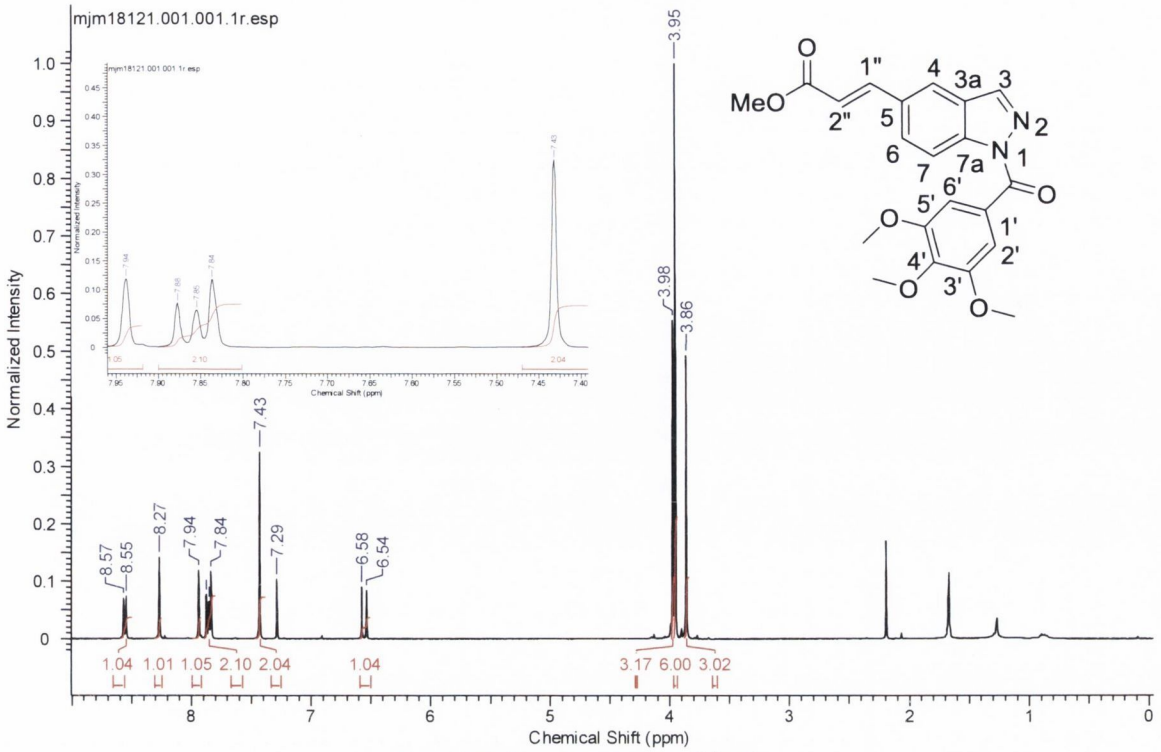


Figure 148: ^{1}H-NMR spectrum of (346)

The ^{1}H-NMR spectrum of (**346**) is shown in figure 148 confirming the structure of the product. The singlet at 3.86 ppm is assigned to the protons of the ester methoxy group. The sharp singlet at 3.95 ppm, integrating for 6 protons, is assigned to the protons of the symmetric methoxy groups at $C_{3'}$ and $C_{5'}$ while the singlet at 3.98 ppm corresponds to the protons of the methoxy group at $C_{4'}$. The doublet at 6.56 ppm, J = 16.04 Hz, is assigned to the vinyl proton at $C_{2''}$. The product of the Heck reaction is a *trans* alkene. $^3J_{trans}$ is in the order of 11 – 18 Hz[331] so the high splitting frequency of 16.04 Hz for this proton is indicative of a *trans* alkene. The singlet at 7.43 ppm is assigned to the symmetric aromatic protons, $H_{2'}$ & $H_{6'}$. The multiplet from 7.84 – 7.88 ppm, integrating for 2 protons, is assigned to H_6 and the proton at $C_{1''}$. By performing an H-H COSY, figure 149, and by observing the cross peaks along the diagonal, it is known that this multiplet comprises of the *trans* protons at $C_{1''}$ and the proton H_6. The singlet at 7.94 ppm corresponds to H_4 while the singlet at 8.27 Hz is assigned to H_3. The doublet at 8.56 Hz, J = 8.52 Hz, is assigned to H_7.

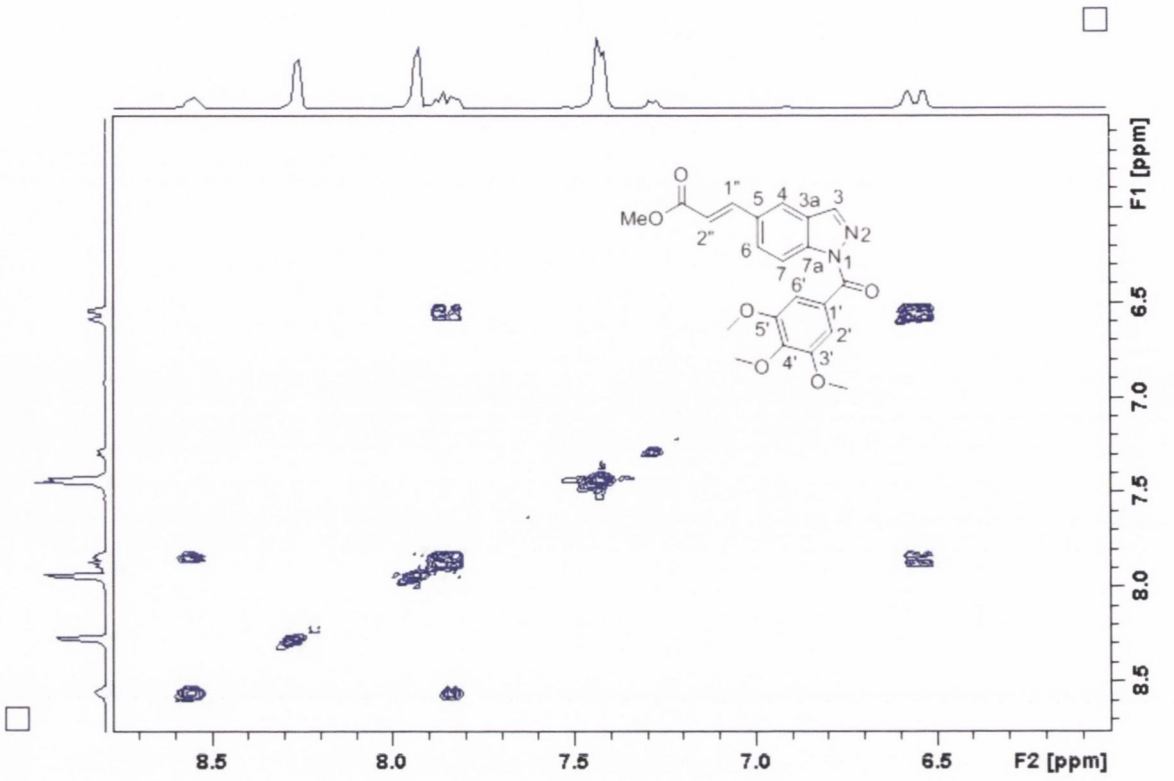


Figure 149: H-H COSY spectrum of (346)

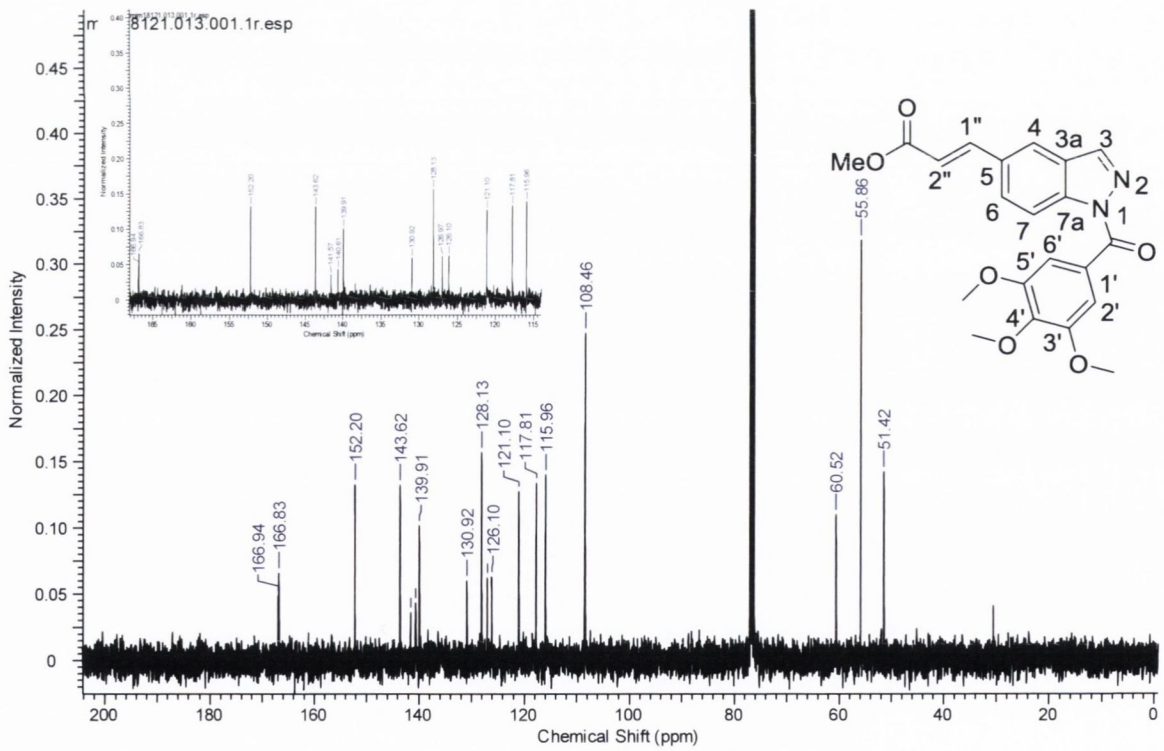


Figure 150: ^{13}C-NMR spectrum of (346)

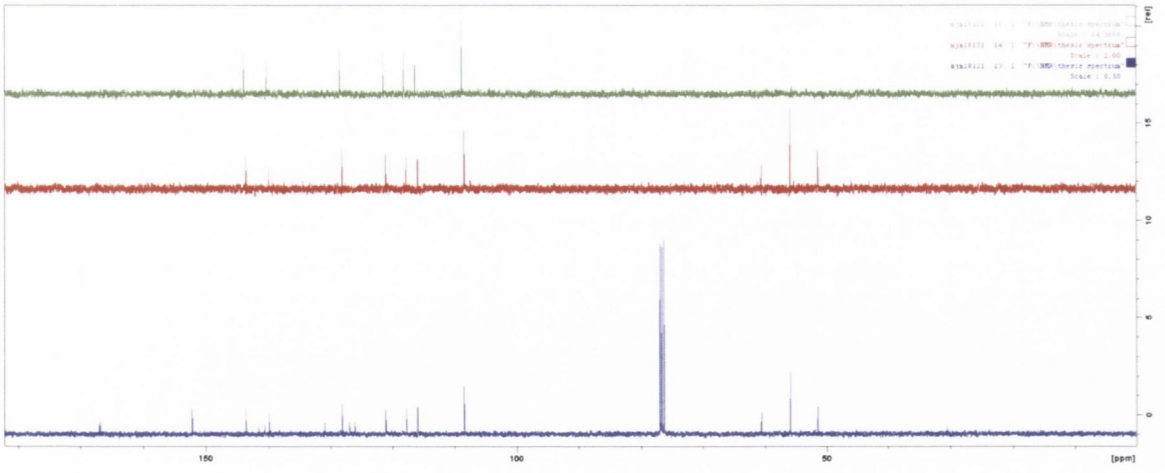


Figure 151: ^{13}C and DEPT spectra of (346)

The ^{13}C NMR, DEPT and C-H COSY spectra of (**346**) is shown in figures 150, 151 and 152 respectively. The signal at 51.58 ppm is assigned to the ester methoxy carbon while the signal at 55.96 ppm corresponds to the symmetric methoxy carbons at $C_{3'}$ & $C_{5'}$ and the signal at 60.53 ppm corresponds the methoxy carbon at $C_{4'}$. The assignment of the methine carbons was facilitated by a C-H COSY by observing cross peaks for protons to their corresponding carbons to which they were attached. Thus the signals at 108.45, 115.96, 117.81, 121.10, 128.13, 139.90 and 143.62 ppm correspond to the aromatic methine carbons $C_{2'}$ & $C_{6'}$, C_7, $C_{2''}$, C_4, C_6, C_3 and $C_{1''}$ respectively. The signals at 126.10, 126.97, 130.92, 140.62, 141.57 and 152.19 ppm are assigned to C_{3a}, $C_{1'}$, C_6, C_{7a}, $C_{4'}$, $C_{3'}$ & $C_{5'}$ respectively while the signals at 166.83 and 166.94 ppm correspond to the amide carbonyl and ester carbonyl respectively.

A nuclear Overhauser effect (NOE) spectrum, figure 153, was performed in order to confirm that the alkene bond in (**346**) was in *trans* configuration. The doublet at 6.56 ppm was irradiated and if a *cis* alkene was obtained a corresponding positive signal should be present at 7.86 ppm, which is approximately the chemical shift of the proton at $C_{2''}$. However no positive signal is present and so it can be concluded that (**346**) is in *trans* configuration, as is predicted with the Pd coupling reaction is performed in these conditions.

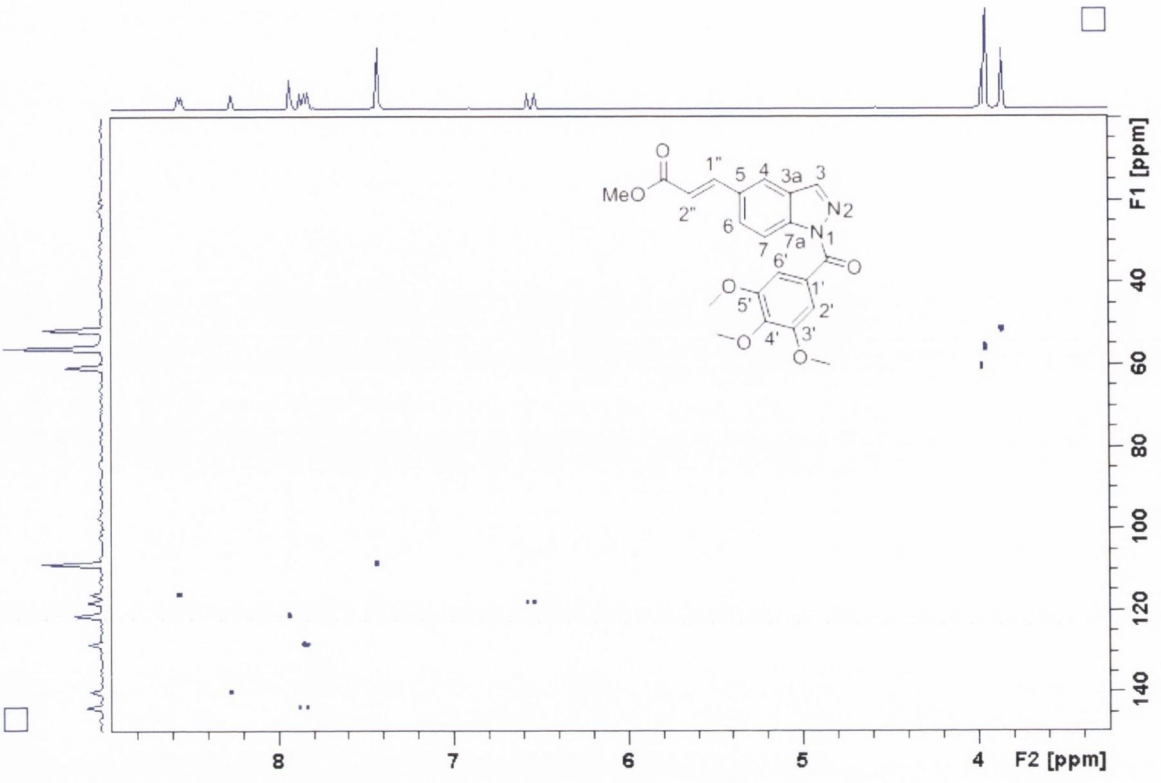


Figure 152: C-H COSY spectrum of (346)

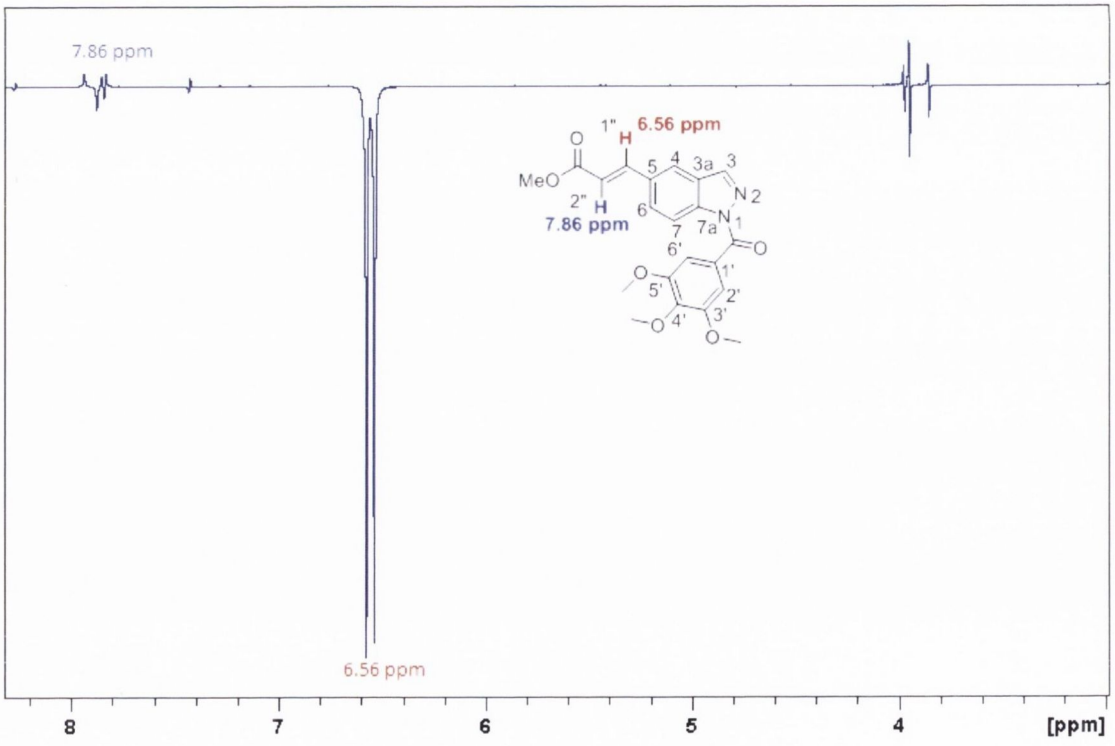
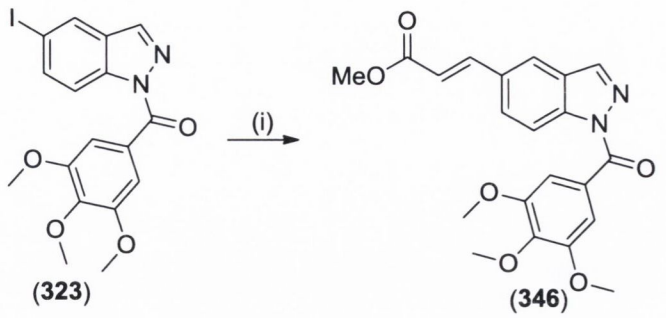


Figure 153: NOE spectrum of (346)

Table 28: Optimisation of Heck reaction conditions



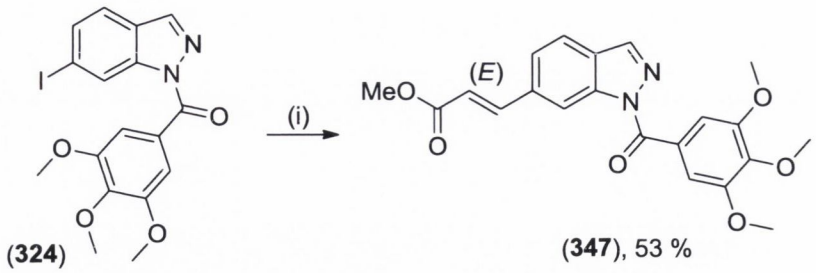
(323) (346)

Reaction Number*	Palladium catalyst (5 mol%)	Time	Method of heating	% Yield
1	$Pd(PPh_3)_4$	18 hours	Reflux	38
2	$Pd(OAc)_2$	18 hours	Reflux	44
3	$Pd(OAc)_2$	5 min	Microwave, 100 °C	39
4	$Pd(OAc)_2$	15 min	Microwave, 100 °C	59
5	$Pd(OAc)_2$	30 min	Microwave, 100 °C	56

*All five reactions were performed using 0.23 mmol of (**323**) and using anhydrous DMF as solvent

Optimisation of the Heck reaction condtions was next investigated. Table 28 contains the yield of (**346**) obtained when $Pd(PPh_3)_4$, line 1, and $Pd(OAc)_2$, line 2, was used as the palladium catalyst in the Heck coupling reaction. A 6 % increase in yield is observed when $Pd(OAc)_2$ was employed as the catalyst. (**346**) was then prepared using the CEM Discover microwave reactor, setting the temperature to 100 °C and initially setting the reaction to 5 minutes. The maximum wattage was 300 watts. (**346**) was obtained in 39 % yield, which is comparable to the refluxing method. The reaction was again attempted but setting the reaction time to 10 and 15 minutes. (**346**) was obtained in 59 % and 56 % yield for 10 and 15 minutes respectively. The decrease in yield for 15 minutes could be caused by product degradation. The optimum reaction conditions are highlighted in yellow. The reaction time has been reduced by 98 % while the yield has increased by 21 % in comparison to line 2. Using the same optimised reactions, (**347**) was prepared from (**324**) in 53 % yield, figure 154.

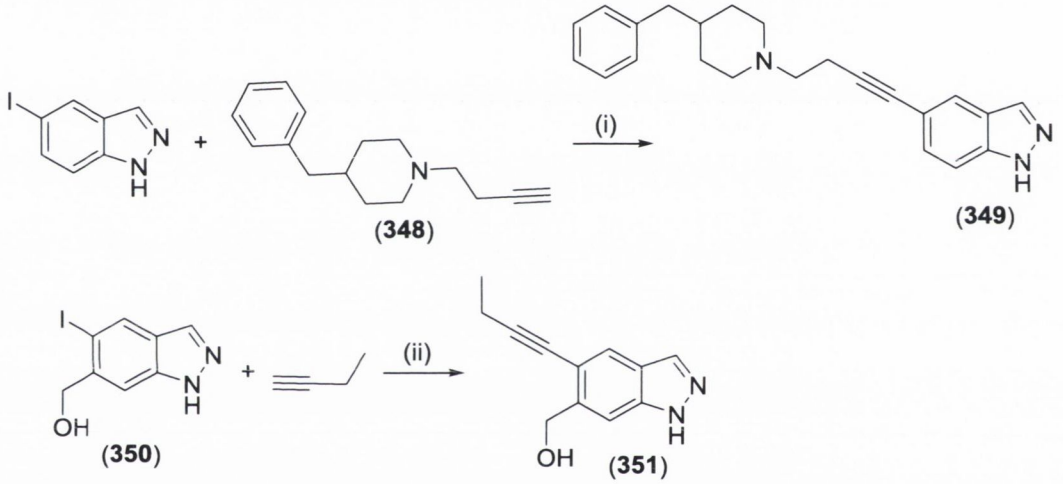
In conclusion, two novel vinylindazoles (**346**) and (**347**) have been prepared and the reaction conditions optimised using microwave assisted organic synthesis (MOAS).



(i) $Pd(OAc)_2$, DMF, Et_3N, 100 °C, μW

Figure 154: Preparation of (347)

2.7.6 Synthesis of 5 and 6-alkynylindazole *via* the Sonogashira reaction



(i) $Pd(PPh_3)_4$, pyrrolidine, 50 °C[332] (ii) Et_3N, CuI, $PdCl_2(PPh_3)_2$, DMF, 40 °C, 7 h[333]

Figure 155: Preparation of 5 and 6-alkynylindazoles

Wright et al reported the preparation of a series of 1-(heteroarylalkynyl)-4-benzylpiperidines as subtype selective *N*-methyl-D-aspartate receptor antagonists for the treatment of Parkinson's disease[332]. One of the compounds prepared was the 5-alkynylindazole (**349**) from the coupling of 5-bromoindazole with the terminal alkyne (**348**). The coupling was performed using $Pd(PPh_3)_4$ and pyrrolidine. These conditions are quite similar to Sonogashira coupling where copper iodide is used also as a co-catalyst[279, 334]. Copper free Sonogashira coupling has been successfully demonstrated previously by *Leadbeater et al*[335] and *Bohm et al*[336]. *Yamamoto et al* synthesised the 5-alkynylindazole (**351**) by coupling the 5-bromoindazole (**350**) with but-1-yne[333]. This reaction could be described as a typical Sonogashira coupling reaction.

The copper-cocatalyzed Sonogashira reaction is believed to take place through two independent catalytic cycles, figure 156.

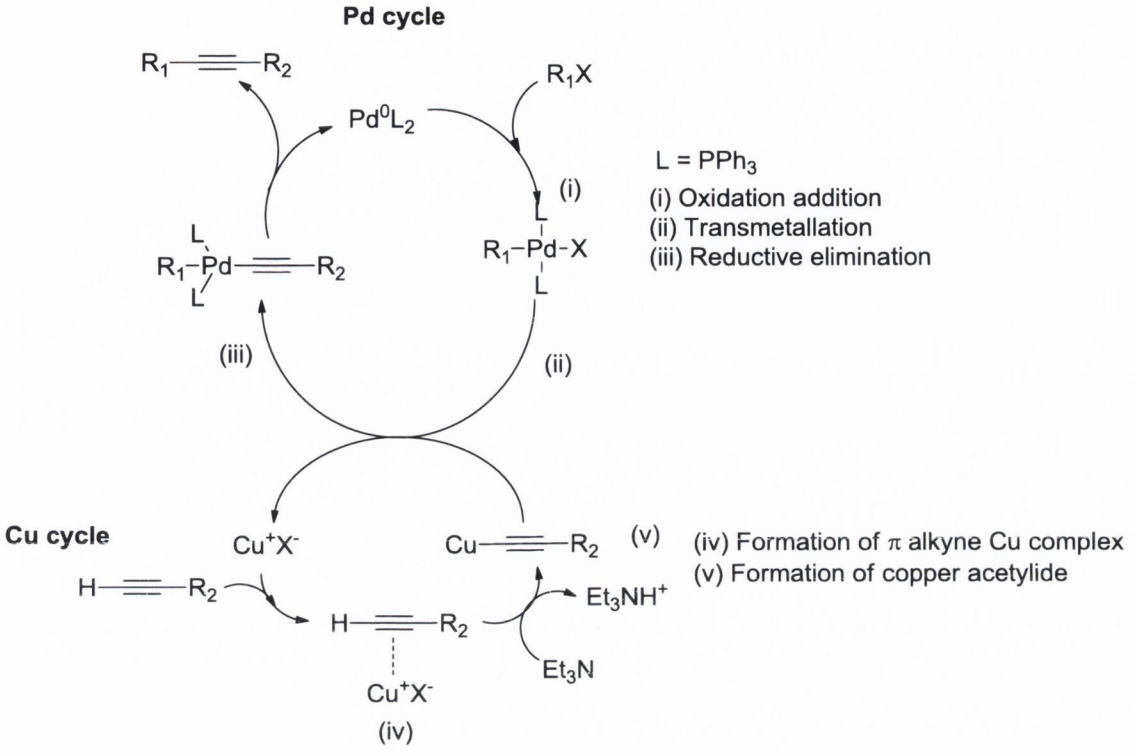
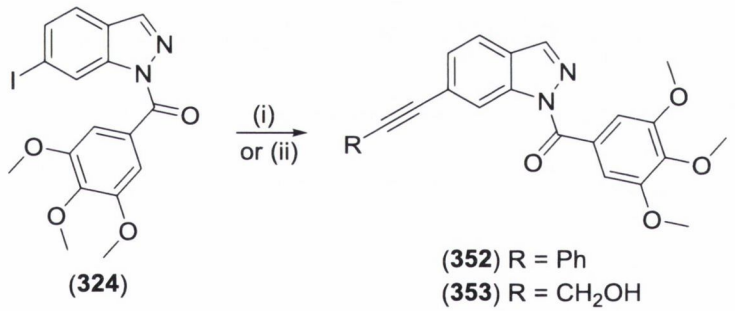


Figure 156:Copper co-catalysed Sonogashira reaction[334]



(i) 5 mol% $Pd(PPh_3)_4$, 5 mol % CuI, Et_3N, phenylacetylene, reflux or μW (ii) 5 mol % $Pd(PPh_3)_4$, 5 mol % CuI, propargyl alcohol μW

Figure 157: Preparation of (352) and (353)

In the present work, 6-alkynyindazoles (**352**) and (**353**) were prepared by reaction of the indazole (**324**) with phenylacetylene and propargyl alcohol respectively. The ^{13}C and DEPT NMR spectra for the product (**352**) are shown on figures 158 and 159 respectively. The alkyne carbons can be located at 89.26 and 91.13 ppm respectively.

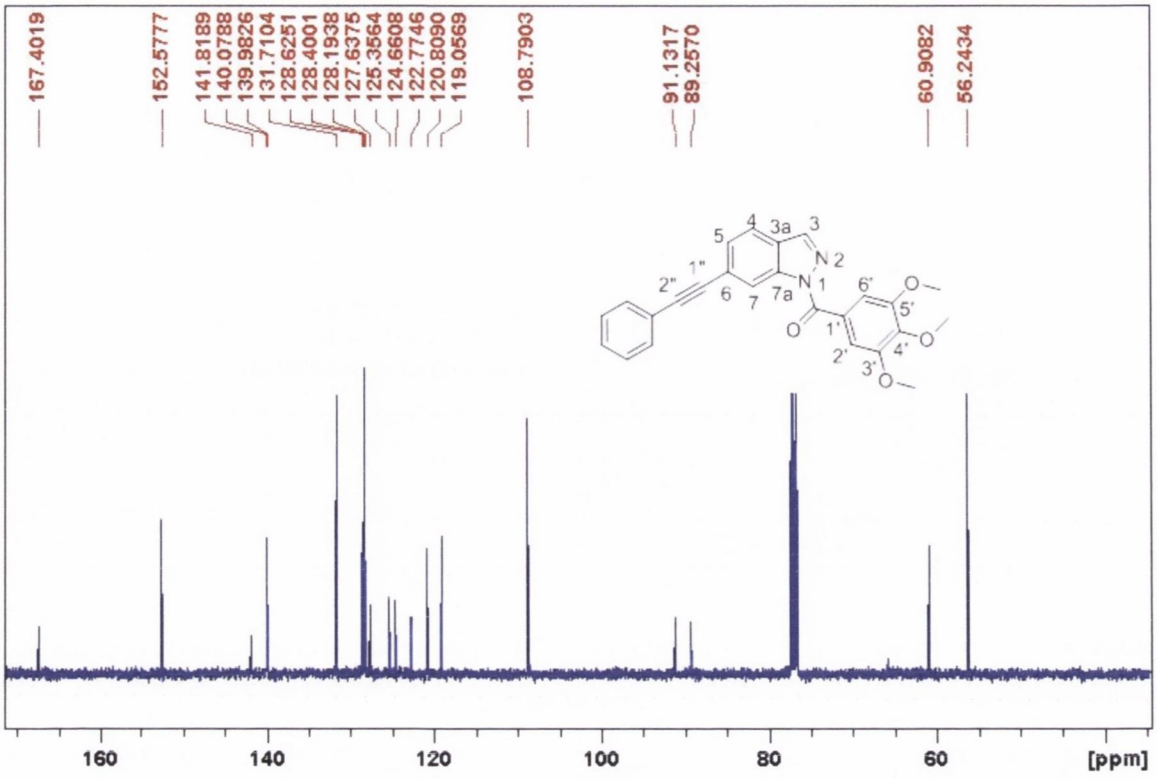


Figure 158: ^{13}C-NMR spectrum of (352)

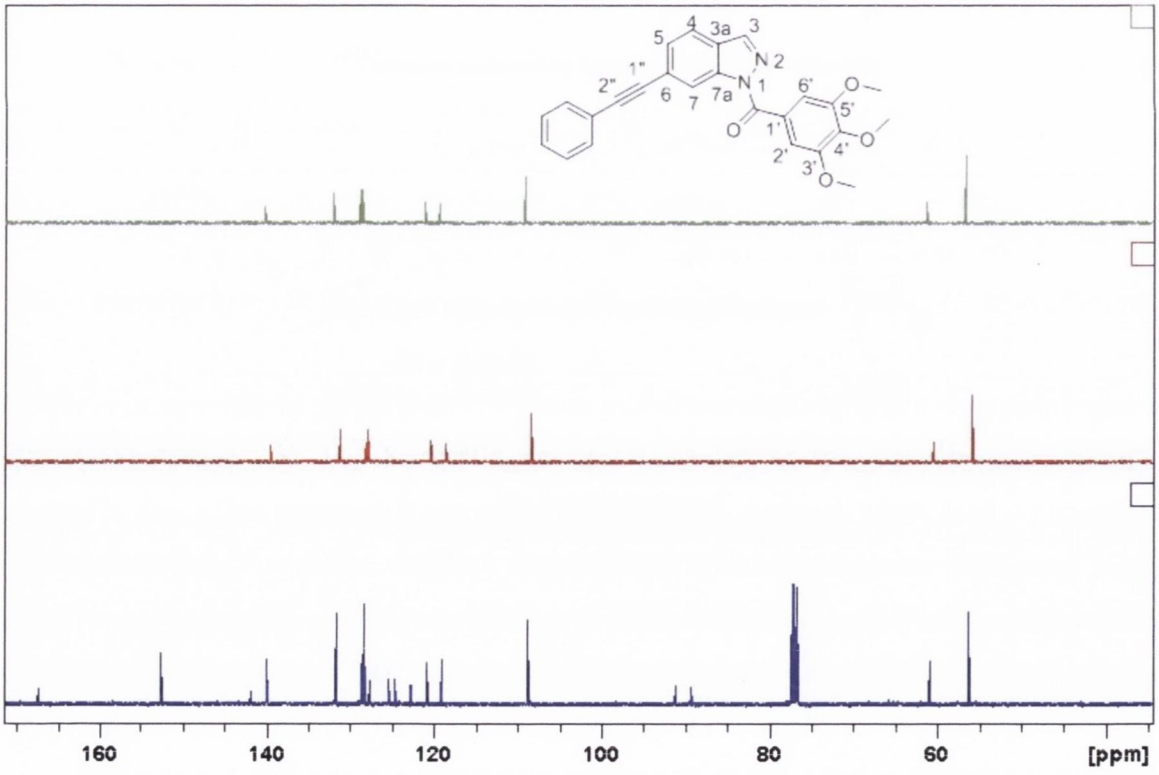


Figure 159: ^{13}C and DEPT spectra of (352)

2.7.7 Synthesis of 5-aroylated indazoles

This section will describe the synthesis of 5-aroylated analogues of the lead compound (**168**), figure 160. The aim here was to modify the amine substituent of (**168**) due to toxicity associated with metabolism of primary aromatic amines and introduce a benzoyl substituent on the indazole ring.

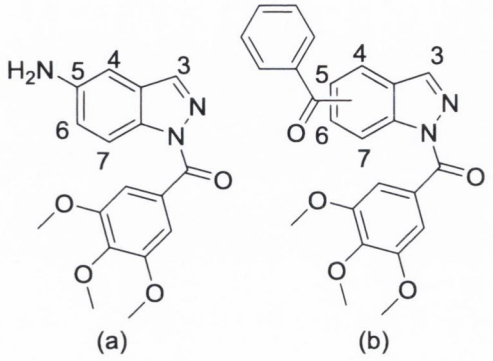
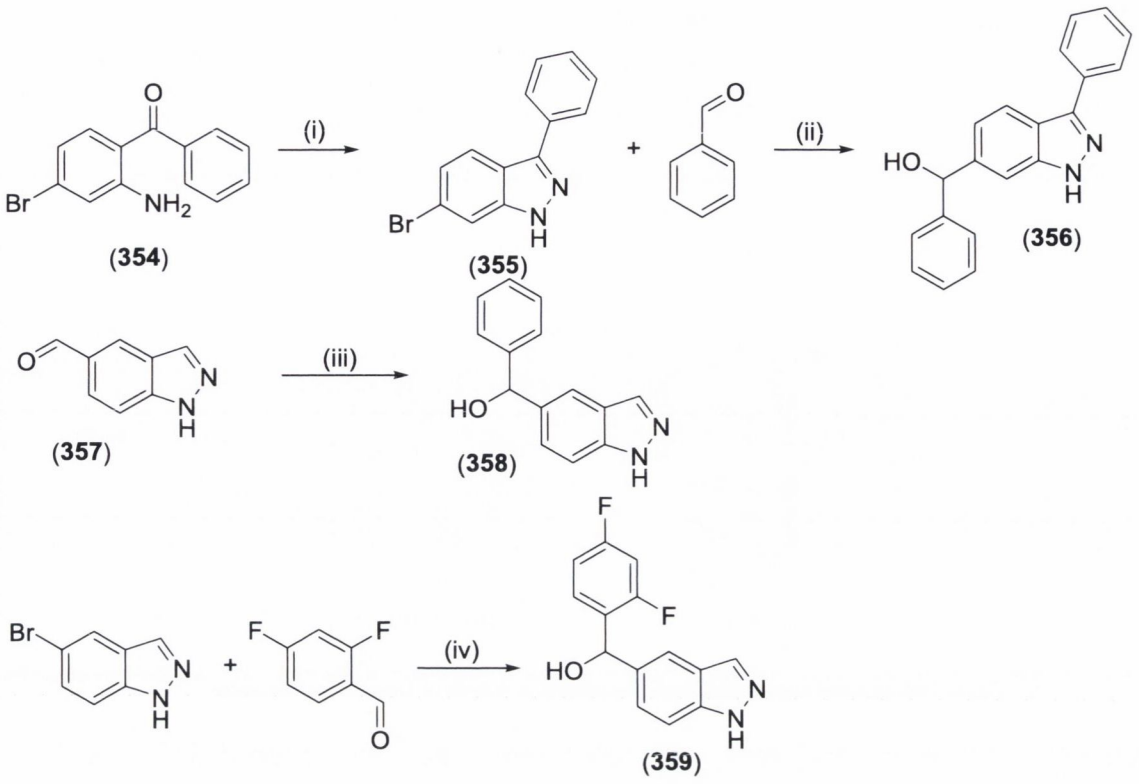


Figure 160: (a) Lead compound (168), (b) general structure of 5-aroylated indazoles

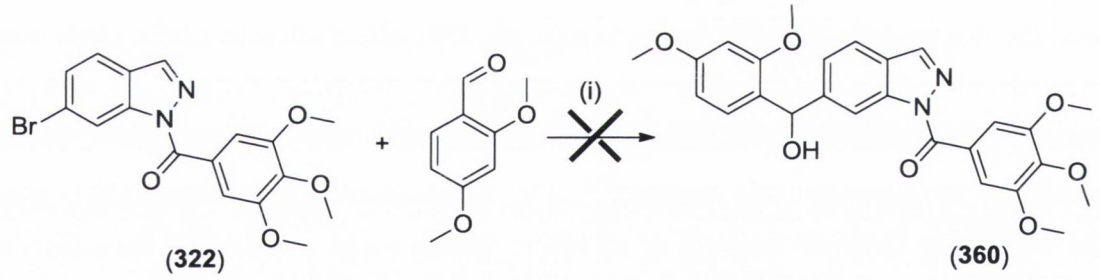
Before the synthesis of the specific 5-aroylated indazoles in this thesis is discussed, the synthesis of similar aroylated indazoles reported in the literature is presented (see figure 161).

Sheppeck et al, who were investigating non-steroidal compounds as effective modulators of the glucocorticoid receptor in treatment of inflammation or immune associated diseases[337], prepared the intermediate (**356**) by the cyclization of (**354**) which afforded (**355**). (**355**) was then treated with *n*-BuLi and benzaldehyde affording (**356**). *Sheppeck et al* also reported the synthesis of nonsteroidal indazoyl amides in a continuation of their research into effective modulators of the glucocorticoid receptor[338]. The 1*H*-indazole-5-carbaldehyde (**357**) was reacted with either Grignard reagents or alkyl/aryl lithium reagents affording the indazole intermediate (**358**). *Munson et al* prepared a series of compounds as p38 inhibitors for the treatment of inflammatory disease, autoimmune disease or neurodegenerative disease[339]. The intermediate (**359**) was prepared by treating 5-bromoindazole with *t*-BuLi and the 2,4-difluorobenzaldehyde.



(i) HCl, $NaNO_2$, H_2O, $SnCl_2$ (ii) nBuLi, anhydrous THF, - 78 °C to rt[337] (iii) Grignard reagent or alkyl/aryl lithium reagent[338] (iv) *t*-BuLi, THF, diethylether, -78 °C to rt, 72 h[339]

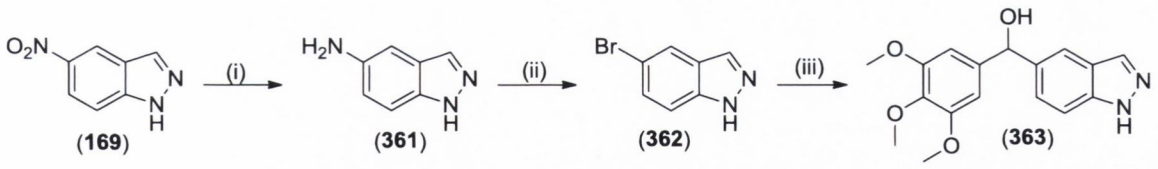
Figure 161: 5-Aroylated and 6-aroylated indazoles previously reported



(i) Anhydrous THF, *n*BuLi (2 molar eq), -78 °C to 20 °C

Figure 162: Attempted synthesis of (360)

The approaches towards the synthesis of 5 and 6-aroylated indazoles, prepared in this thesis, is now presented (figure 162). In the present work, 6-bromoindazole (**322**) was first treated with *n*-BuLi at -78 °C and 2,4-dimethoxybenzaldehyde was then added slowly and stirred at **-78 °C** for 1.5 hours and at 20 °C for 2 hours, figure 162. However, following purification by flash column chromatography, the desired product was not afforded. A significant amount of the unreacted aldehyde was recovered. Steric hindrance could have been a factor due to the 2-methoxy substituent. The synthetic route was changed slightly. It was decided to follow the same synthetic approach as *Munson et al*[339].



(i) 10 % Pd/C, EtOAc:MeOH (ii) 48% HBr, $NaNO_3$, CuBr, DIW, 0 °C to 80 °C (iii) Anhydrous THF, *n*-BuLi (3 molar eq), 3,4,5-trimethoxybenzaldehyde (2 molar eq), -78 °C to 20 °C

Figure 163: Attempted synthesis of (363)

5-Bromoindazole (**362**) was prepared from (**361**) which was then treated with *n*BuLi and 3,4,5-trimethoxybenzaldehyde, figure 163. The desired product (**363**) was not afforded. It was not clear if the reaction failure was due to the (a) THF not being anhydrous, (b) *n*-BuLi that used had expired or (c) experimental technique. The synthesis of the secondary alcohol (**359**), figure 161, was then attempted using the exact procedure by *Munson et al*[339]. This involved stirring 5-bromoindazole in anhydrous diethyl ether at – 78 °C for 10 minutes, then adding *t*-BuLi (3 molar eq) slowing *via* a syringe. After 30 minutes at -78 °C, 2,4-difluorobenzaldehyde (2 molar eq) was added slowly *via* a syringe. The resultant solution was stirred at -78 °C for 2 hours, warmed to 20 °C and stirred at this temperature for 3 days. After work up and purification by flash column chromatography, (**359**) was successfully prepared in 12 % yield.

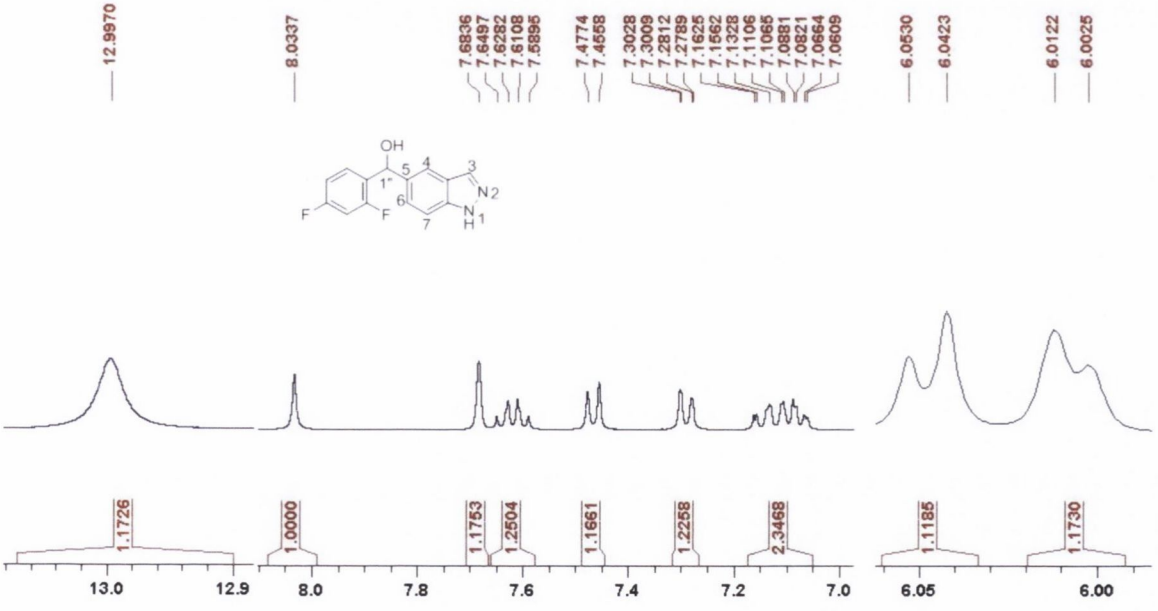


Figure 164: ^{1}H-NMR spectrum of (359)

The ^{1}H-NMR spectrum of (**359**) is shown in figure 164. The doublets at 6.00 and 6.04 ppm, both integrating for 1 proton each, correspond to the OH and the methine proton respectively.

Also mass spectrometry (found $[M+H]^+ = 261.0836$) confirmed the successful preparation of (**359**).

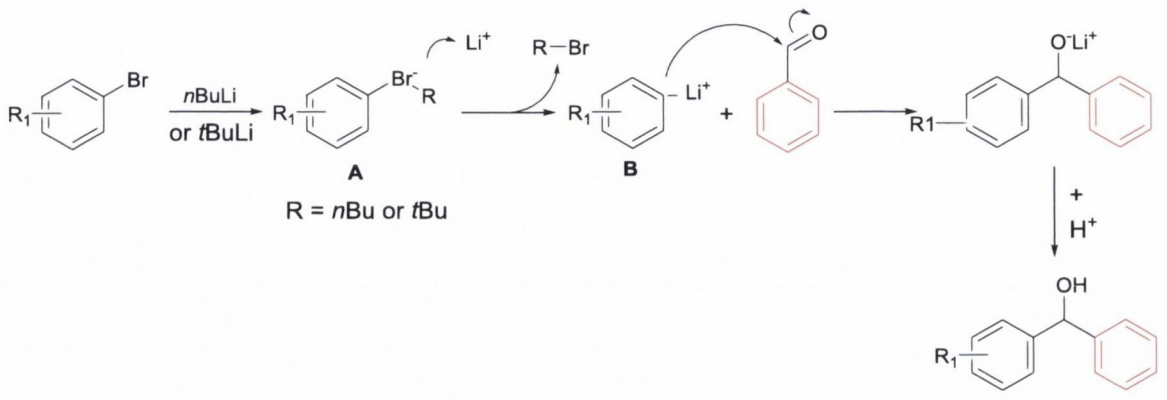
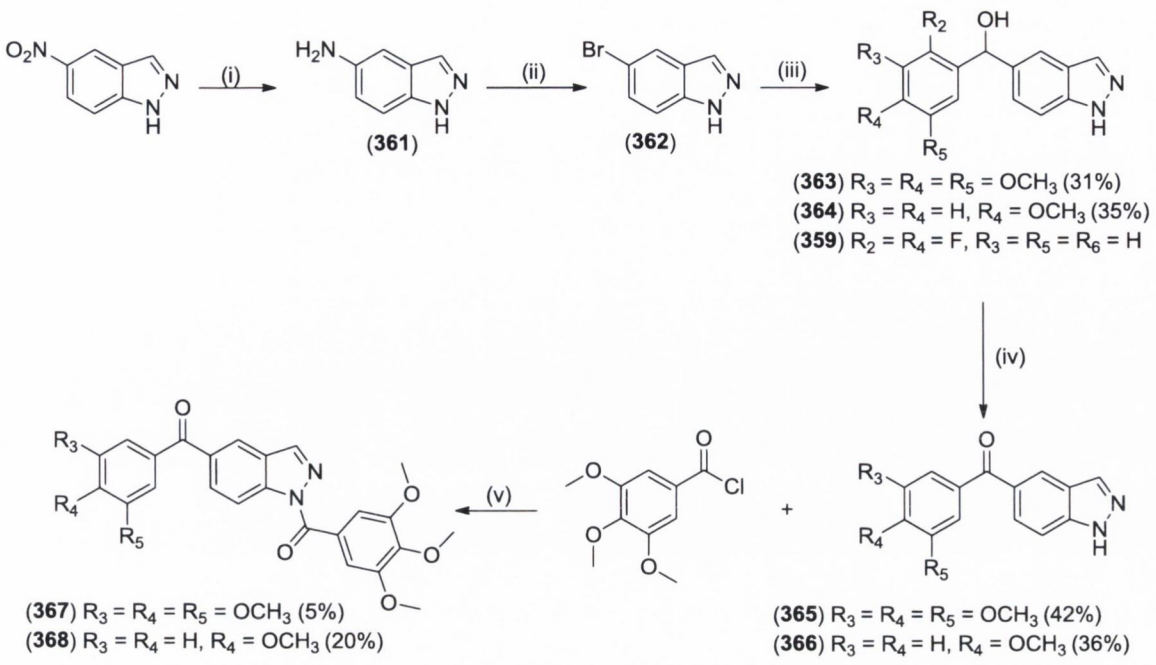


Figure 165: Preparation of secondary alcohols from BuLi and aryl bromides

The mechanism for the preparation of secondary alcohols is shown in figure 165. Firstly the aryl bromide and the *n*- or *tert*-BuLi yield the lithium salt **A**. This lithium salt **A** decomposes when the Li^+ reacts with the C-Br bond as an electrophile, forming the lithioaromatic salt **B**[340]. The salt **B** is actually comprised of a phenyl anion and lithium cation[279]. Nucleophilic attack of the aldehyde carbonyl by the phenyl anion takes place and following protonation, the desired secondary alcohol is generated.



(i) 10 % Pd/C, EtOAc:MeOH (ii) 48% HBr, $NaNO_3$, CuBr, DIW, 0 °C to 80 °C (iii) Anhydrous THF, tBuLi (3 molar eq), appropriate benzaldehyde (2 molar eq), -78 °C to 20 °C (iv) anhydrous THF, pyridinium chlorochromate (1.5 molar eq) (v) anhydrous CH_2Cl_2, Et_3N, 20 °C

Figure 166: Preparation of 5-aryolated analogues of (168)

Once the secondary alcohols, (**363**) and (**364**), were isolated, they were treated with pyrindinium chlorochormate which afforded the corresponding aryl ketones (**365**) and (**366**), figure 166. These aryl ketones were then reacted with 3,4,5-trimethoxybenzoyl chloride which yielded the desired N-1 benzoylated products (**367**) and (**368**), figure 166. The ^{1}H-NMR spectrum of (**364**) is shown in figure 167. The singlet at 3.70 ppm is assigned to the protons of the methoxy group at $C_{4''}$. The broad singlets at 5.75 and 5.79 ppm correspond to the OH and chiral methine proton. The doublet at 6.85 ppm, J = 7.92 Hz, is assigned to the symmetric aromatic protons, $H_{3''}$ & $H_{5''}$. The doublet at 7.28 ppm, J = 7.92 Hz, integrating for 3 protons, is assigned to H_6 and $H_{2''}$ & $H_{6''}$. The doublet at 7.44 Hz, J = 8.56 Hz, is assigned to H_7. The singlet at 7.71 ppm corresponds to H_4 while the singlet at 8.02 is assigned to H_3. The broad singlet at 12.97 ppm is due to the NH. The ^{13}C-NMR and DEPT spectra of (**364**) are shown in figure 168 and 169. The signals at 55.52 and 74.40 ppm correspond to the methoxy carbon and the chiral secondary carbon respectively. The signals at 110.27, 113.90, 117.73, 125.93, 127.97 and 134.02 ppm correspond to the aromatic methine carbons C_7, $C_{3''}$& $C_{5''}$, C_4, C_6, $C_{2''}$ & $C_{6''}$ and C_3 respectively. The signals at 123.67, 138.66, 138.70, 139.61, 158.50 ppm correspond to the C_{3a}, $C_{1''}$, C_6, C_{7a} and $C_{4''}$ respectively.

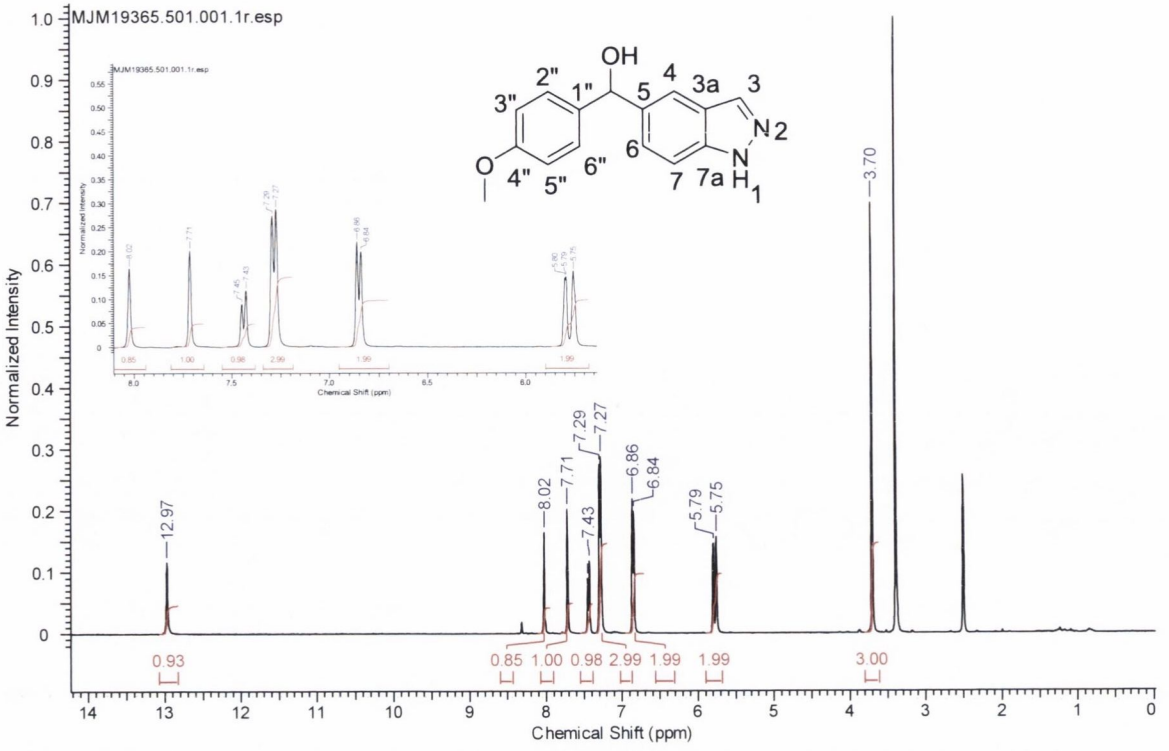


Figure 167: ^{1}H-NMR spectrum of (364)

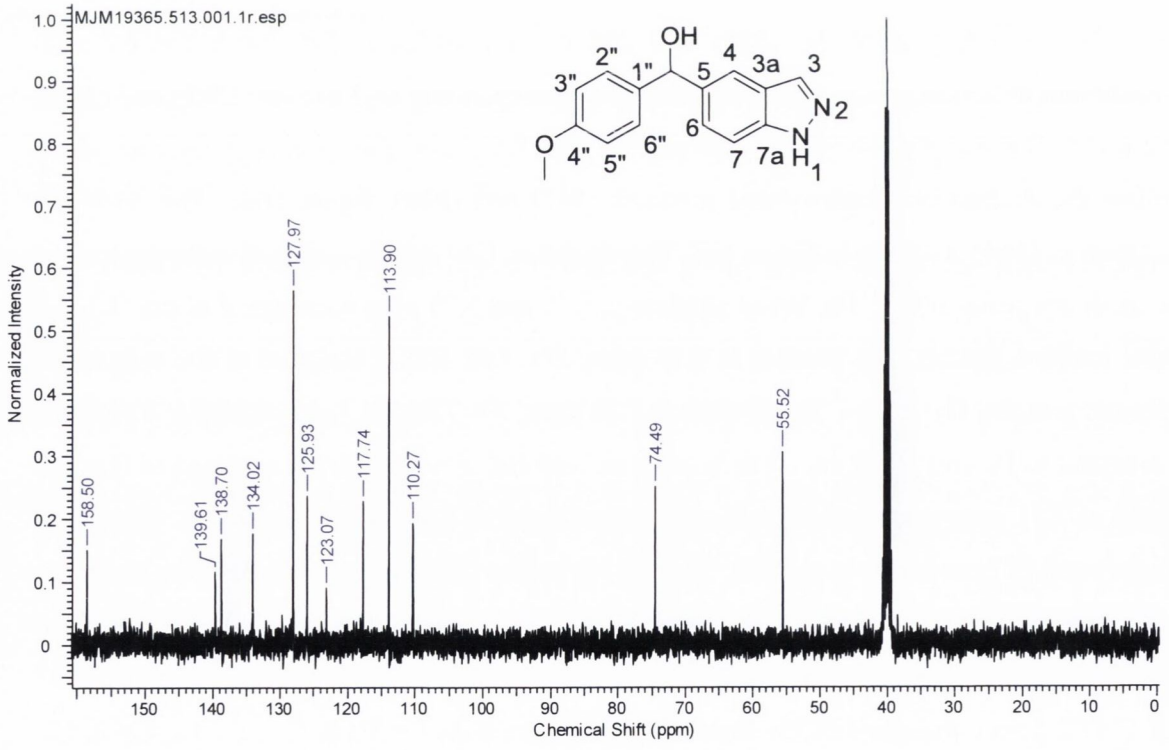


Figure 168: ^{13}C-NMR spectrum of (364)

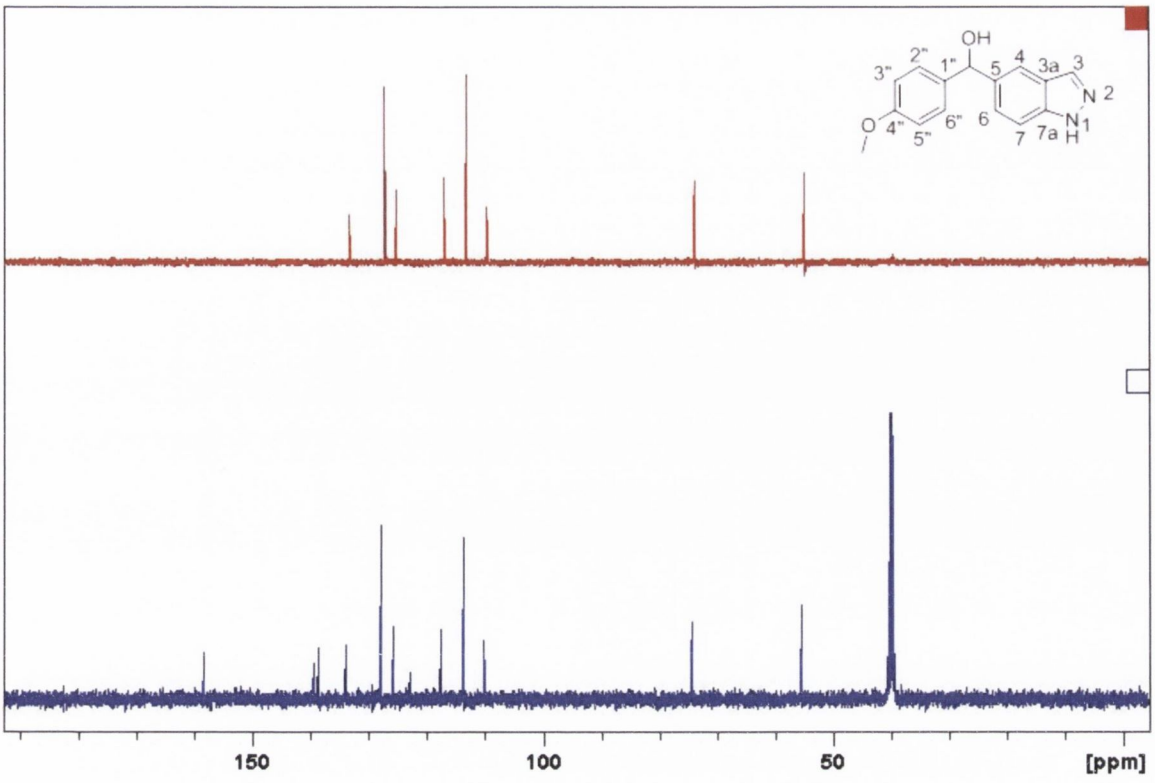
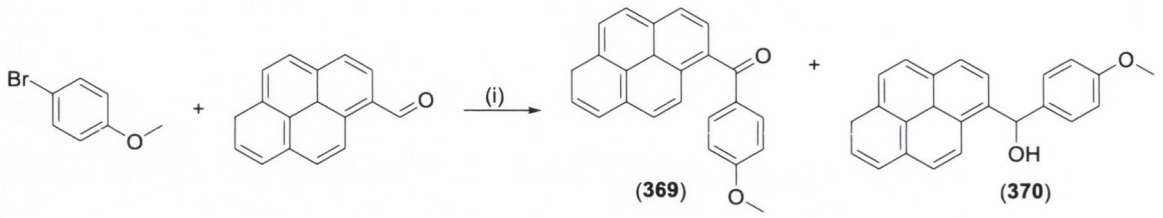


Figure 169: ^{13}C NMR and DEPT spectra of (364)

The preparation of (**364**) yielded two products, the desired secondary alcohol (**364**) in 35 % yield and unidentified compound in 11 % yield. The ^{1}H-NMR and ^{13}C-NMR spectra of this compound are shown in figure 171 and 172 respectively. The signal at 194.70 ppm in the ^{13}C-NMR spectrum, figure 172, is normally associated with aldehyde and ketone carbonyls[341]. It was believed that this compound was the oxidised product of (**364**) i.e. the corresponding ketone (**366**). To confirm this, (**364**) was treated with pyridinium chlorochromate which yielded (**366**). The ^{1}H-NMR spectrum of (**366**), obtained during the preparation of (**364**) and obtained following the oxidation of (**364**) using pyridinium chlorochromate are shown in figure 173. These spectra are identical so the unknown compound isolated during the preparation of (**364**) was (**366**). Thus *in situ* oxidation of (**364**) occurred during its preparation. *Telitel et al* reported the *in situ* oxidation of a secondary alcohol following the reaction of 4-bromoanisole with pyrene 1-carbaldehyde in anhydrous THF/nBuLi[342]. The ketone (**369**) was afforded in 63 % yield while the secondary alcohol (**370**) was obtained in 20 % yield, figure 170.



(i) anhydrous THF, *n*BuLi, - 78 °C to rt

Figure 170: Preparation of secondary alcohol with *in situ* oxidation of secondary alcohol[344]

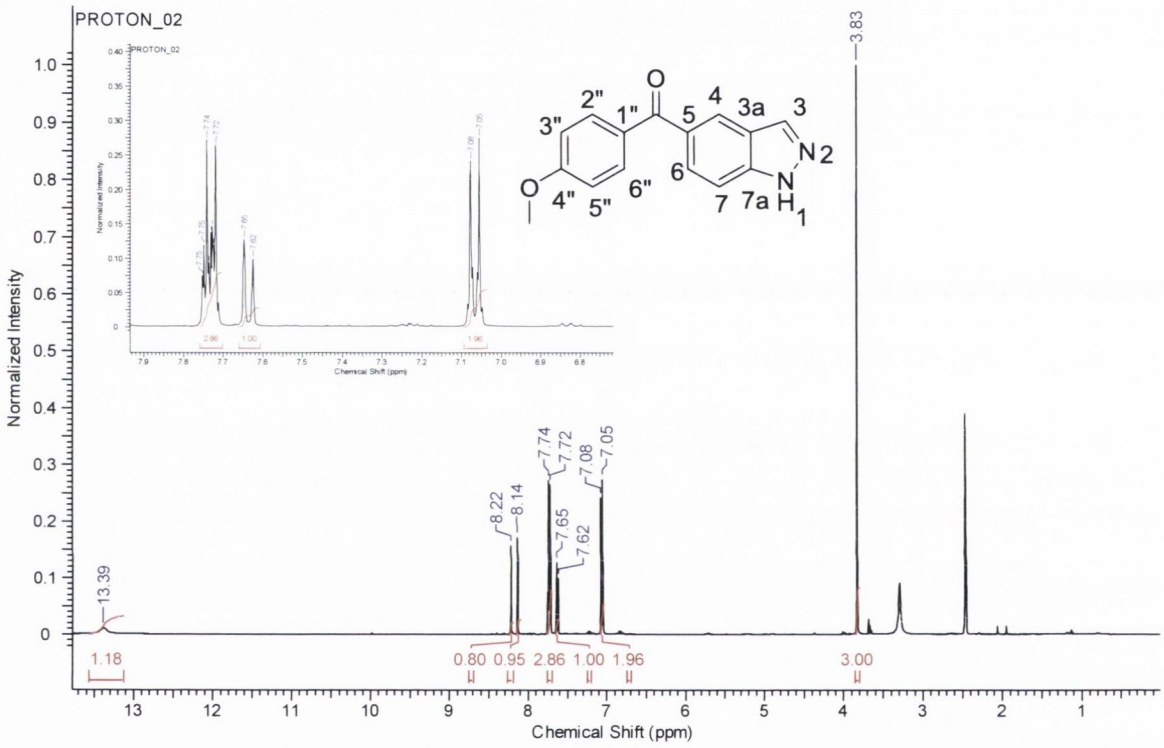


Figure 171: ^{1}H-NMR spectrum of (366)

The ^{1}H-NMR spectrum of (**366**) is shown in figure 171. The singlet at 3.83 ppm is assigned to the protons of the methoxy group at $C_{4''}$. The doublet at 7.06 ppm, J = 8.84 Hz, is assigned to the symmetric aromatic protons, $H_{3''}$ & $H_{6''}$. The doublet at 7.63 ppm, J = 7.63 Hz, corresponds to H_7. The multiplet 7.71 to 8.14 ppm is comprised of H_6 and $H_{2''}$ & $H_{6''}$. The singlet at 8.14 ppm is assigned to H_3 while the doublet at 8.22 ppm is assigned to H_4. The broad singlet at 13.38 ppm is assigned to the NH. The ^{13}C-NMR spectrum of (**366**) is shown in figure 172. The signal at 56.00 ppm is assigned to the methoxy carbon at $C_{4''}$ while the signals at 114.27 and 132.46 ppm correspond to the symmetric aromatic carbons, $C_{3''}$ & $C_{6''}$ and $C_{2''}$ & $C_{6''}$

respectively. The signal at 163.03 ppm is assigned to $C_{4''}$ while the signal at 194.70 ppm is corresponds to ketone carbonyl.

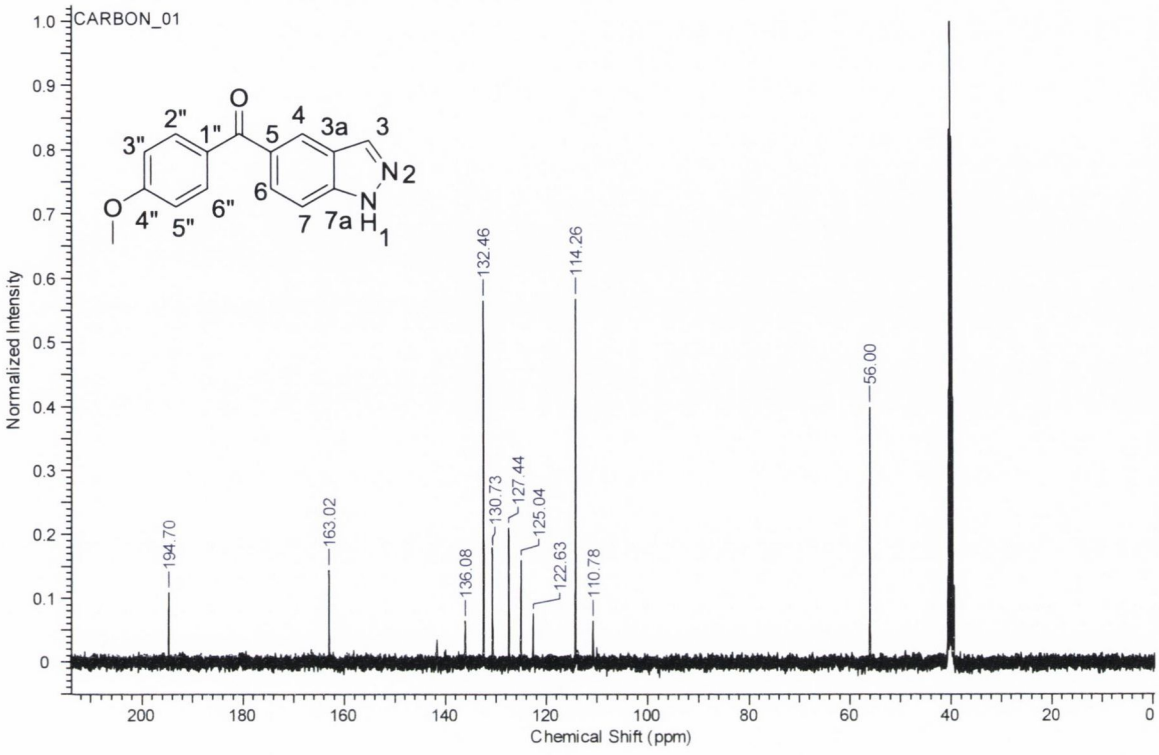


Figure 172: ^{13}C-NMR spectrum of (366)

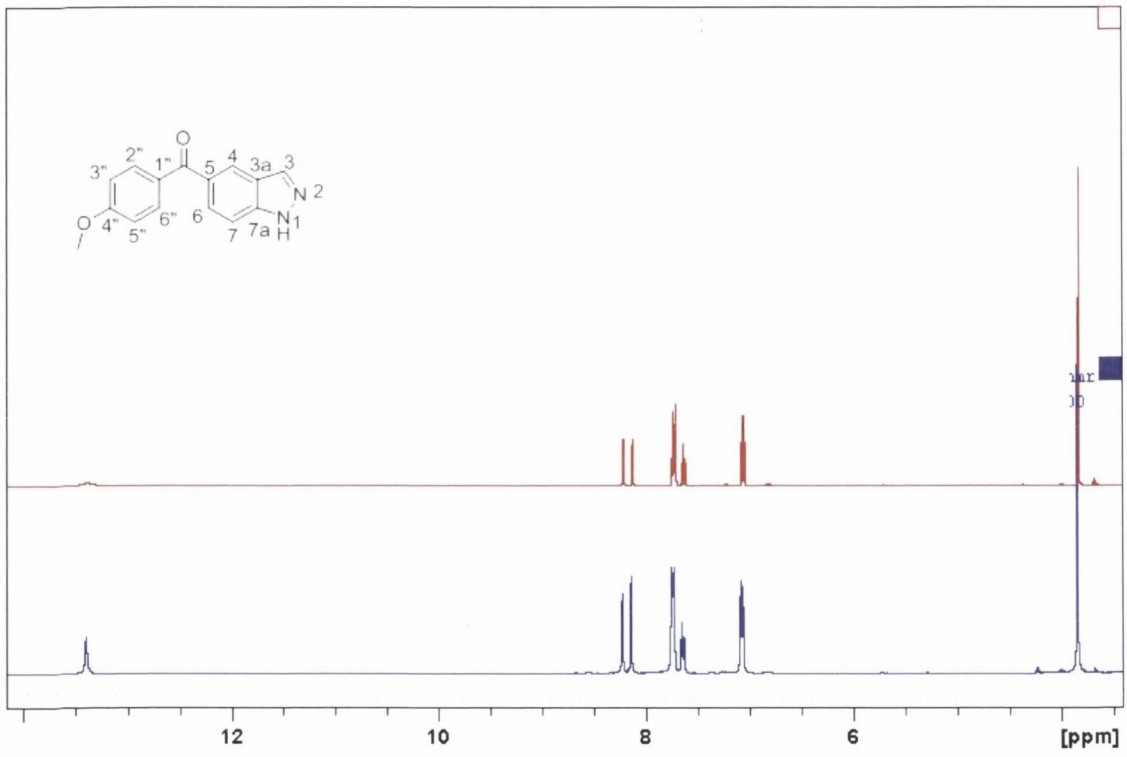


Figure 173: Overlay of ^{1}H-NMR spectra of (366) – red = oxidation of (364) using pyridinium chlorochromate and blue = *in situ* oxidation of (364)

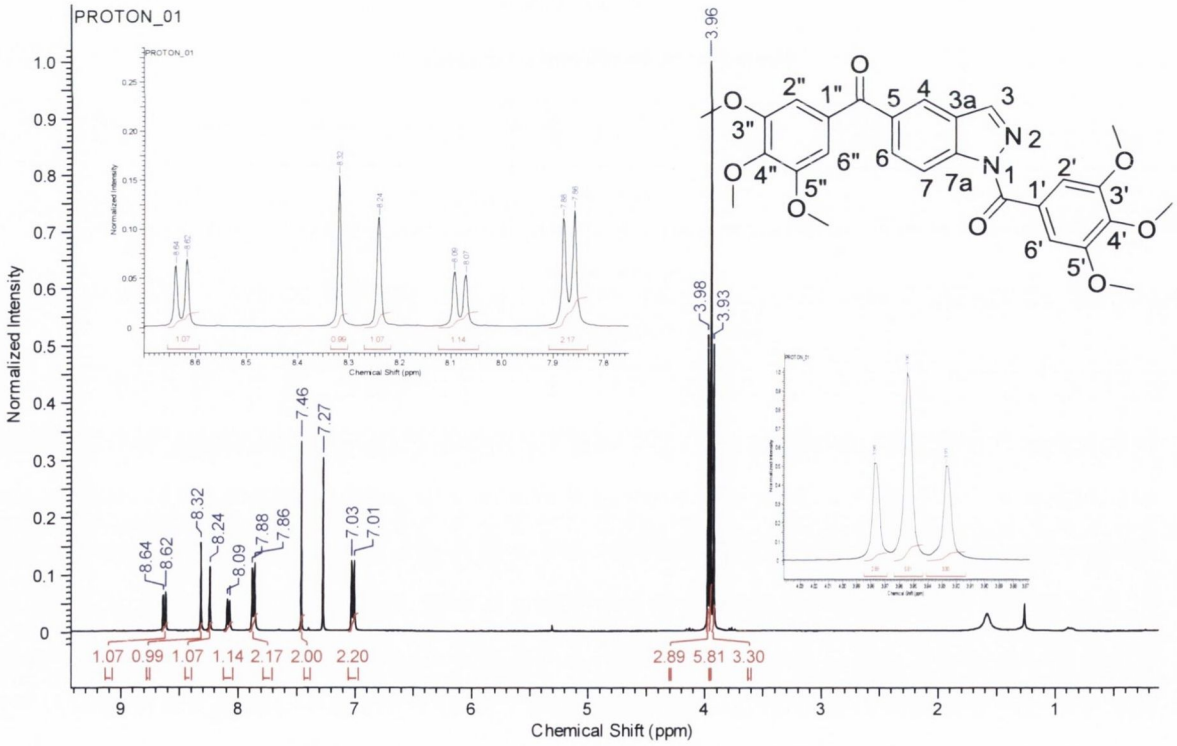


Figure 174: ^{1}H-NMR spectrum of (368)

Benzoylation of (**365**) and (**366**) with 3,4,5-trimethoxybenzoyl chloride afforded the desired products (**367**) and (**368**) respectively, figure 166. The ^{1}H-NMR spectrum of (**368**) is shown in figure 174. The singlet at 3.93 ppm is assigned to the protons of the methoxy group at $C_{4''}$. The sharp singlet at 3.95 ppm is assigned to the symmetric methoxy groups at $C_{3'}$ & $C_{5'}$ while the singlet at 3.98 ppm corresponds to the methoxy group at $C_{4'}$. The doublets at 7.01 and 7.87 ppm, J = 8.48 Hz, corresponds to the symmetric aromatic protons, $H_{3''}$ & $H_{5''}$ and $H_{2''}$ & $H_{6''}$ respectively. The singlet at 7.46 ppm is assigned to the symmetric aromatic protons $H_{2'}$ & $H_{6'}$. The doublet at 8.08 ppm, J = 9.08 Hz, is assigned to H_7. The singlets at 8.24 and 8.32 ppm correspond to H_3 and H_4 respectively. The doublet at 8.62 ppm, J = 9.08 Hz, is assigned to H_6.

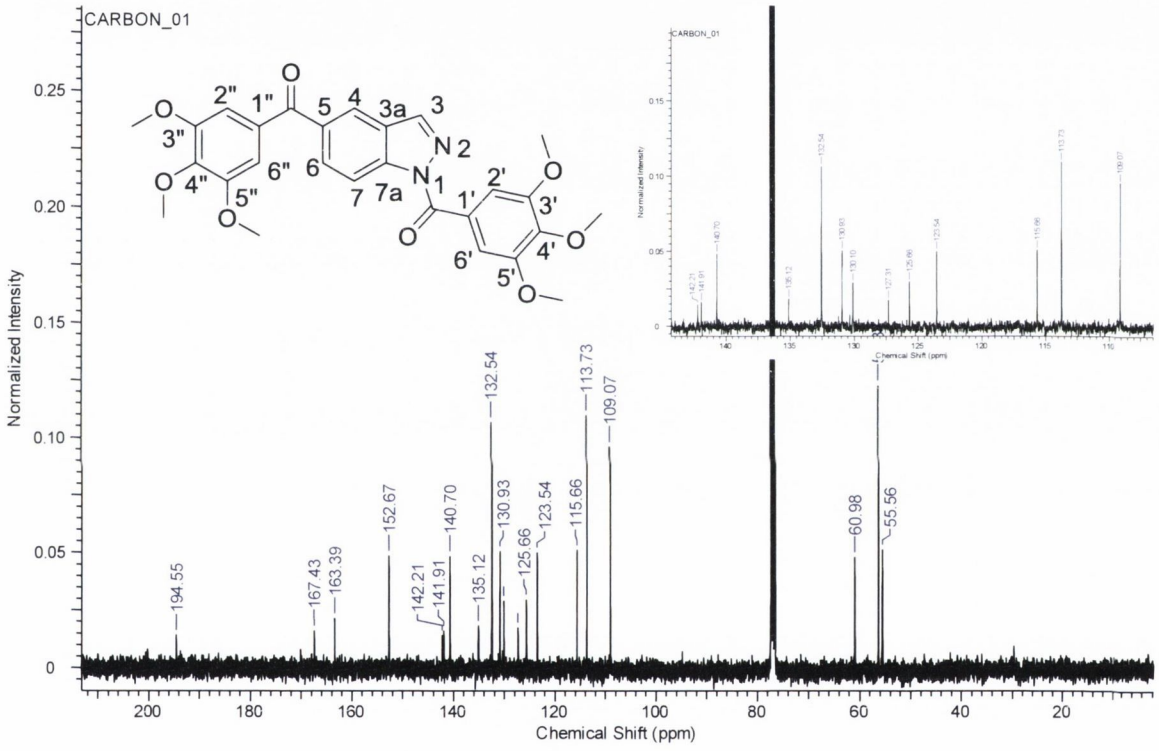


Figure 175: ^{13}C-NMR spectrum of (368)

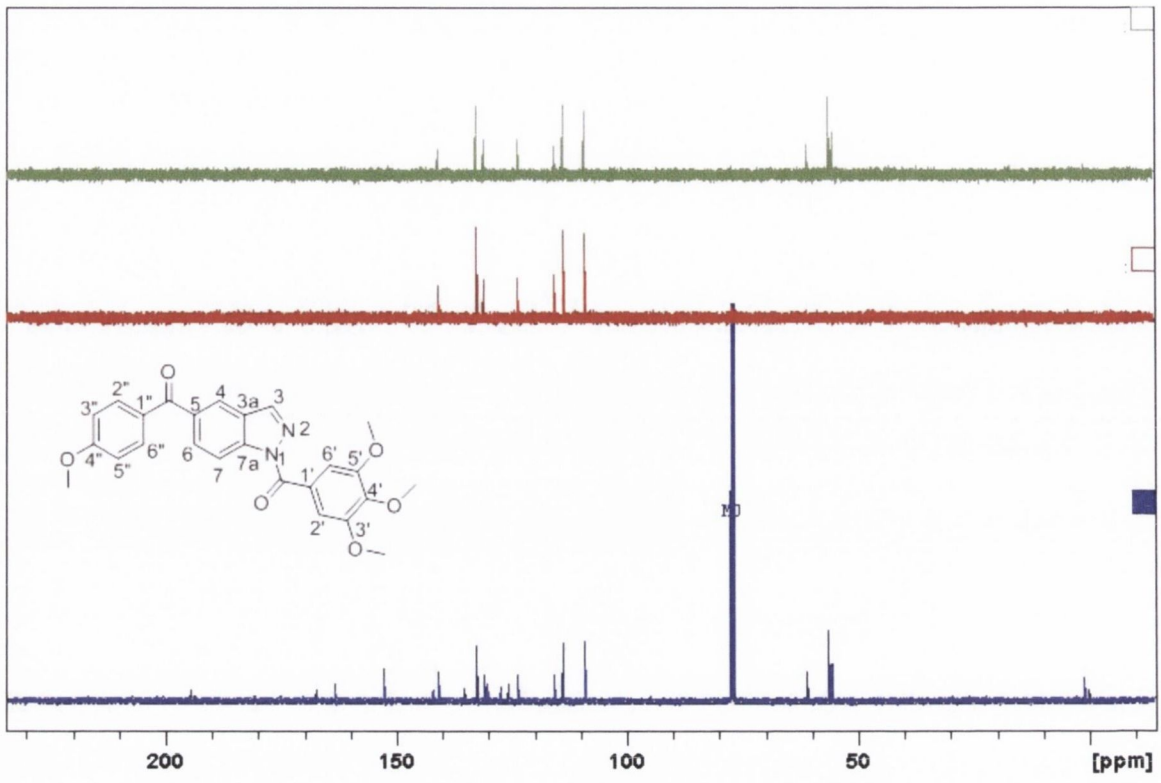


Figure 176: ^{13}C-NMR and DEPT spectra of (368)

The ^{13}C-NMR and DEPT spectra of (**368**) are shown in figures 175 and 176 respectively. The signals at 55.54, 56.33 and 60.97 ppm correspond to the methoxy carbons at $C_{4''}$, $C_{3'}$& $C_{5'}$ and $C_{4'}$. The signals at 109.07, 113.73, 115.66, 123.54, 130.92, 132.54 and 140.70 ppm correspond to the aromatic methine carbons $C_{2'}$, $C_{3''}$& $C_{5''}$, C_7, C_4, C_6, $C_{2''}$& $C_{6''}$ and C_3. The signals at 167.43 and 194.55 ppm correspond to the amide and ketone carbonyls respectively. The signals at 152.68 and 163.39 ppm corresponds to the aromatic *ipso* carbons $C_{3'}$ & $C_{5'}$ and $C_{4''}$ respectively. The signals at 125.66, 127.31, 130.10, 135.12, 141.91 and 142.21 ppm correspond to the aromatic *ipso* carbons C_{3a}, C_6, $C_{1'}$, $C_{1''}$, $C_{4'}$ and C_{7a}.

In conclusion, two 5-aryolated indazoles (**367**) and (**368**) have been successfully prepared using the synthetic route shown in figure 166. The secondary alcohols, (**363**) and (**364**), were afforded following the treatment of 5-bromoindazole (**362**) with *t*-BuLi and the required aldehyde. Oxidation of (**363**) and (**364**), using pyrindinium chlorochromate, afforded the corresponding aryl ketones (**365**) and (**366**) which then benzoylated with 3,4,5-trimethoxybenzoyl chloride providing (**367**) and (**368**). During the preparation of (**364**) from (**363**) and 4-methoxybenzaldehyde, figure 166 (iii), *in situ* oxidation afforded the corresponding aryl ketone (**366**). The presence of (**365**) was not observed during the preparation of (**366**) from (**362**) and 3,4,5-trimethoxybenzaldehyde.

2.8 Synthesis of 3-arylated indazoles

2.8.1 Introduction

This section will describe approaches to the synthesis of indazoles, like Axitinib, with 3-aryl substituents, figure 177. In comparison to the lead compound (**168**), these analogues will retain the amino substituent in either the 5 or 6 position but will contain an aryl group in the C-3 position. Also some of these analogues will contain the 3,4,5-trimethoxybenzoyl group or the 3,4,5-trimethoxybenzyl group at N-1.

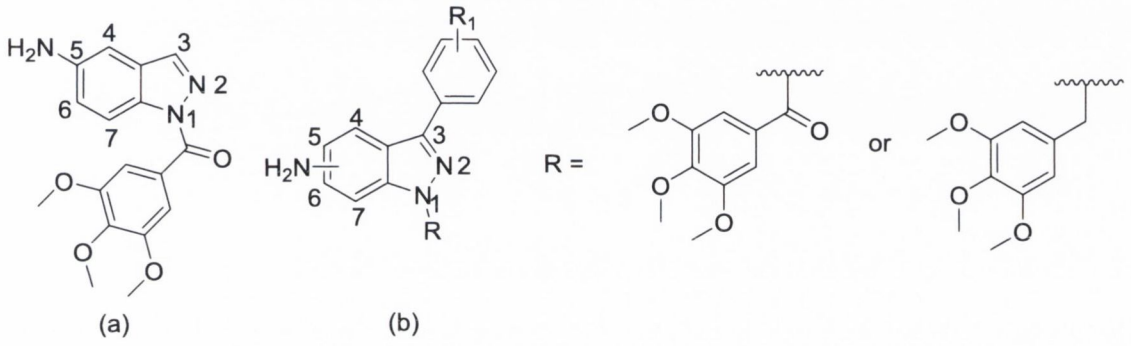
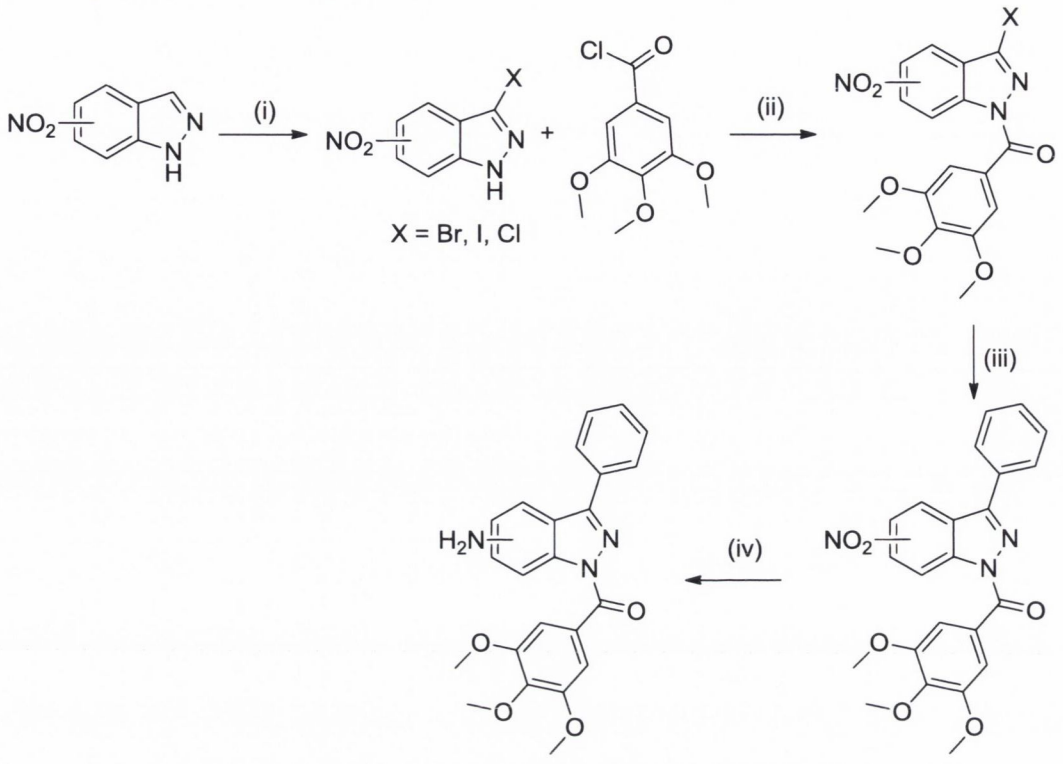


Figure 177: (a) Lead compound (168) and (b) general structure of 3-arylindazoles

The compounds described in this section still feature the indazole core but also contain 3-aryl substituents. These 3-aryl indazole derivatives could possibly provide improved tubulin binding when compared with the lead compound (**168**).

2.8.2 Preparation of 3-arylindazoles

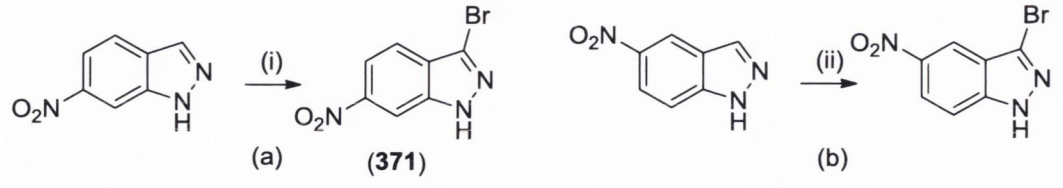


(i) Halogenation (ii) CH_2Cl_2, NEt_3 (iii) Suzuki reaction (iv) 10% Pd/C, MeOH:EtOAc

Figure 178: Initial proposed synthetic route for 3-arylindazoles

In this work, the initial synthetic route proposed is illustrated in figure 178. It known that, from section 3.0, the introduction of aryl substituents onto the indazole ring was possible using Suzuki coupling. In order to employ Suzuki coupling to introduce aryl groups in the C-3 position, halogenation of the C-3 position of the indazole ring was required. Once that was achieved, it was believed that the synthesis of 3-arylindazoles would proceed using the synthetic route outlined in figure 178.

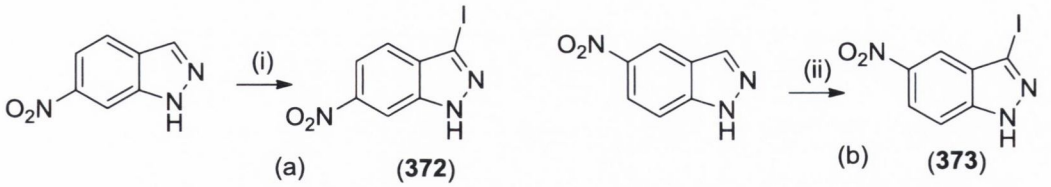
The halogenation of 6-nitroindazole and 5-nitroindazole in the C-3 position has been reported, figures 179 to 181.



(i) Br_2[343] **or** (i) NaOH, $C_5H_5.NBr.Br_3$, pH 7[344] **or** (i) NBS, MeCN, reflux[345]

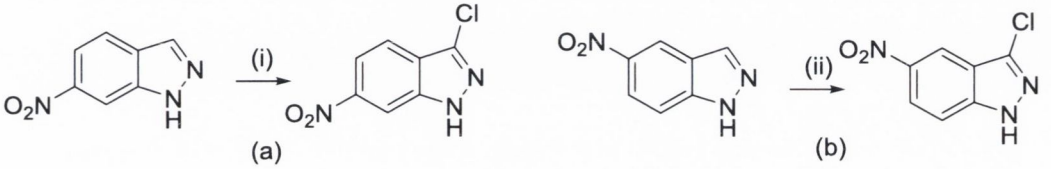
(ii)Br_2[343] **or** (ii) $C_5H_5.NBr.Br_3$, pH 7[346]

Figure 179: 3-Bromination of (a) 6-nitroindazole and (b) 5-nitroindazole



(i) KOH, I_2, DMF, rt[347] **or** (i) NaOH, Dioxane, I_2, rt[348] **or** (i) K_2CO_3, I_2, DMF[349]
(ii) I_2, KOH, DMF, rt[350] **or** I_2, DMF, 65°C[351]

Figure 180: 3-Iodation of (a) 6-nitroindazole and (b) 5-nitroindazole



(i) Cl_2, AcOH, $NaHCO_3$[343] **or** (i) *N*-chlorophthalimide, HCl[352] **or** (i) NaOH, NaClO[353]
(ii) Cl_2, AcOH, $NaHCO_3$[343] or (ii) NaOH, NaClO[357] **or** (ii) *N*-chlorosuccinimide, AcOH, 50°C[355]

Figure 181: 3-Chlorination of (a) 6-nitroindazole and (b) 5-nitroindazole

In the present work, 3-bromo-6-nitroindazole (**371**) was synthesised from 6-nitroindazole (**170**) using pyridinium tribromide. However, the crude product still contained unreacted 6-nitroindazole which required purification by flash column chromatography but were separable.

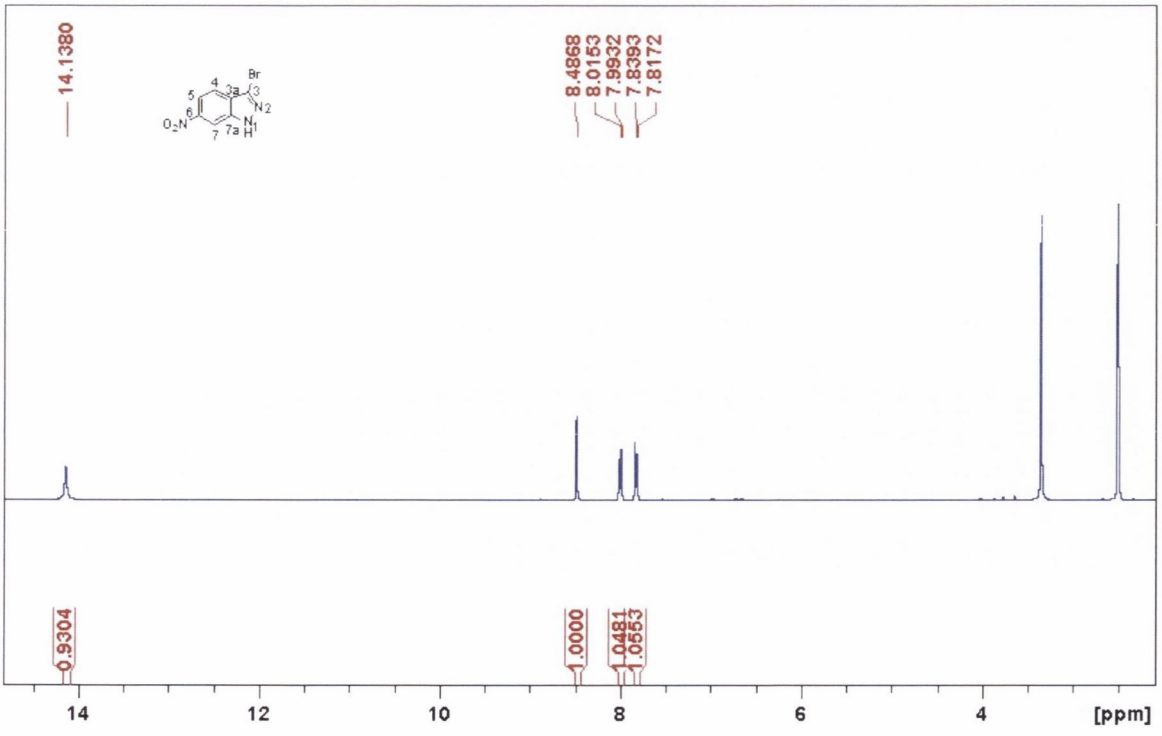
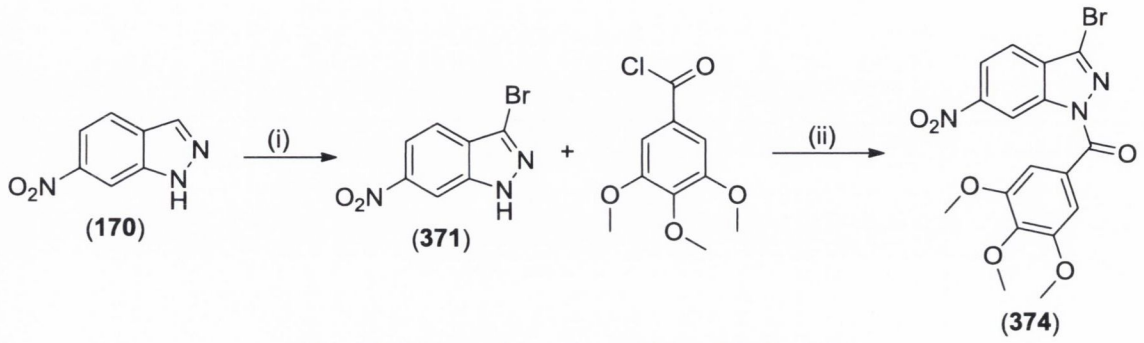


Figure 182: ^{1}H-NMR spectrum of 3-bromo-6-nitroindazole (371)

The ^{1}H-NMR spectrum of 3-bromo-6-nitroindazole (**371**) is shown figure 182. The doublet at 7.83 ppm, J = 8.84 Hz, corresponds to H_4 while the doublet at 8.00 ppm, J = 8.84 Hz, corresponds to H_7. The singlet at 8.49 ppm is assigned to H_7. The broad singlet at 14.14 ppm is assigned to the NH. (**371**) was benzoylated with 3,4,5-trimethoxybenzoyl chloride which afforded the N-1 benzoylated indazole (**374**), figure 183.



(i) NaOH, $C_5H_5HBr.Br_3$, pH 7 (ii) NEt_3, CH_2Cl_2, 20 °C

Figure 183: Synthesis of (374)

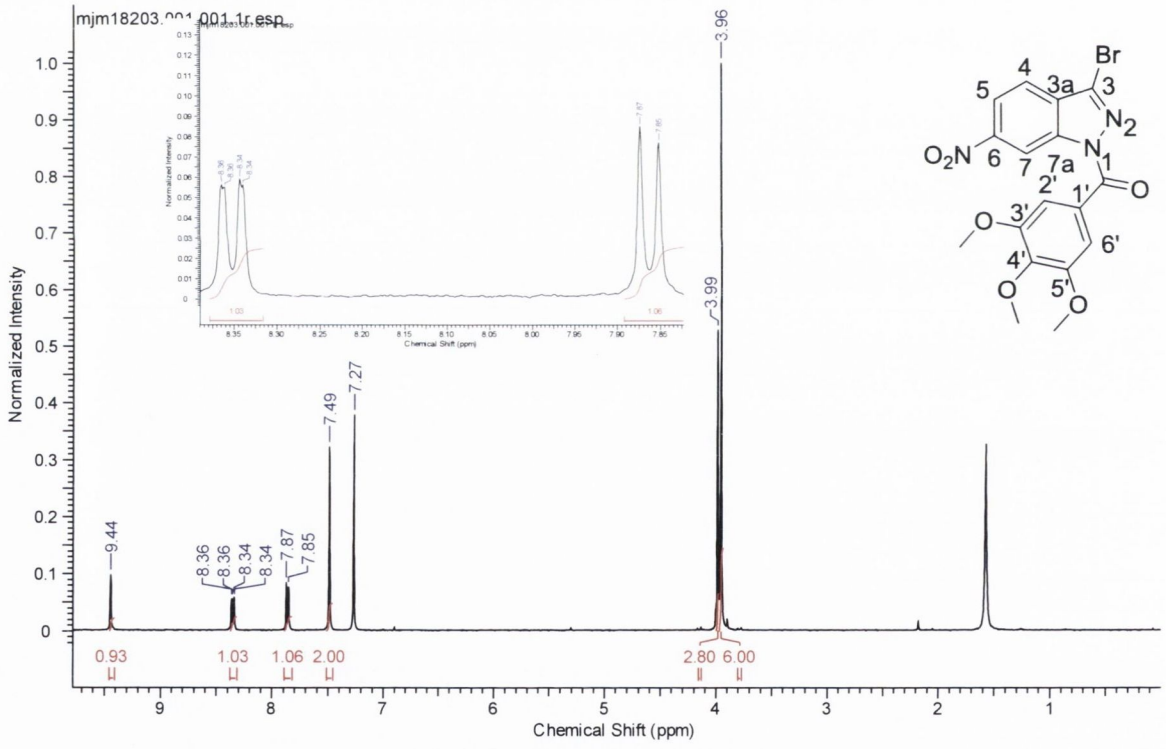


Figure 184: ^{1}H-NMR spectrum of (374)

The ^{1}H-NMR spectrum of (**374**) is shown in figure 184. The sharp singlet at 3.96 ppm, integrating for 6 protons, corresponds to the two symmetric methoxy groups on the aryl ring at $C_{3'}$ & $C_{5'}$. The singlet at 3.99 ppm corresponds to the methoxy group protons on the aryl ring at $C_{4'}$. The sharp singlet at 7.49 ppm, integrating for 2 protons, is assigned to the symmetric

protons, H_2' and H_6'. The doublet at 7.87 ppm, J = 8.76 Hz, is assigned to H_4. The doublet at 8.36 ppm, J = 8.76, 1.19 Hz, is assigned to H_5. The singlet at 9.45 ppm is assigned to H_7.

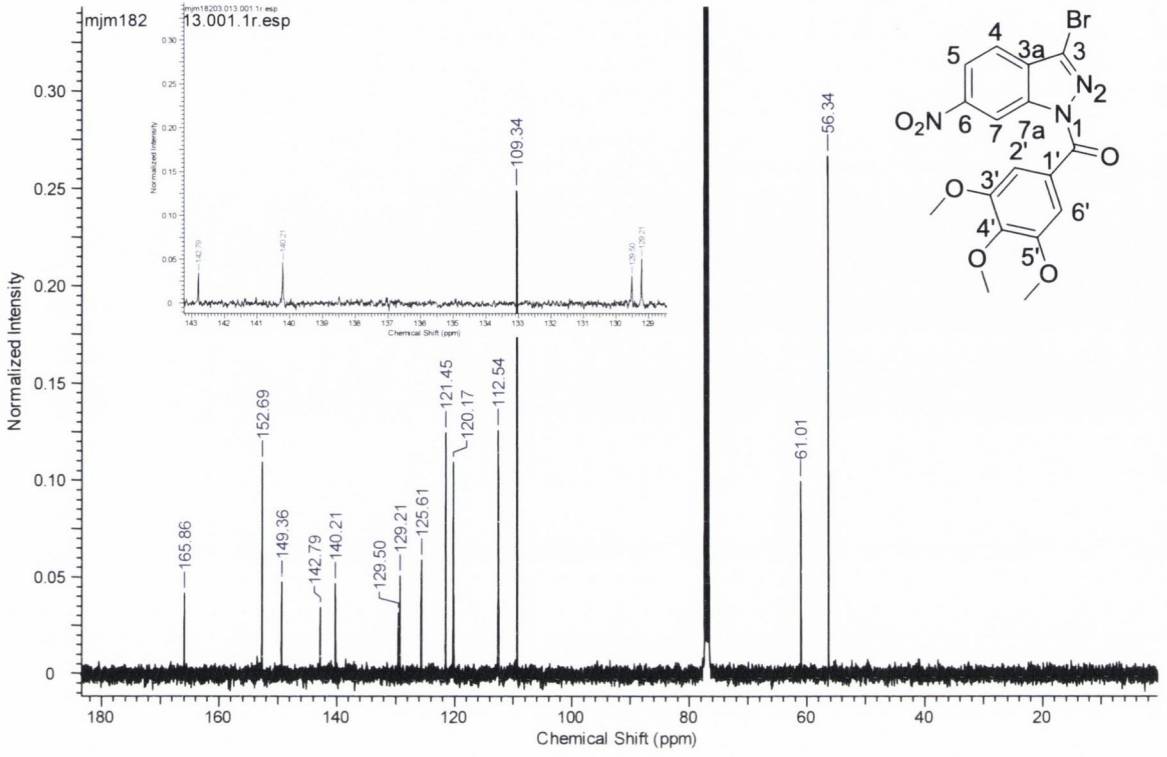
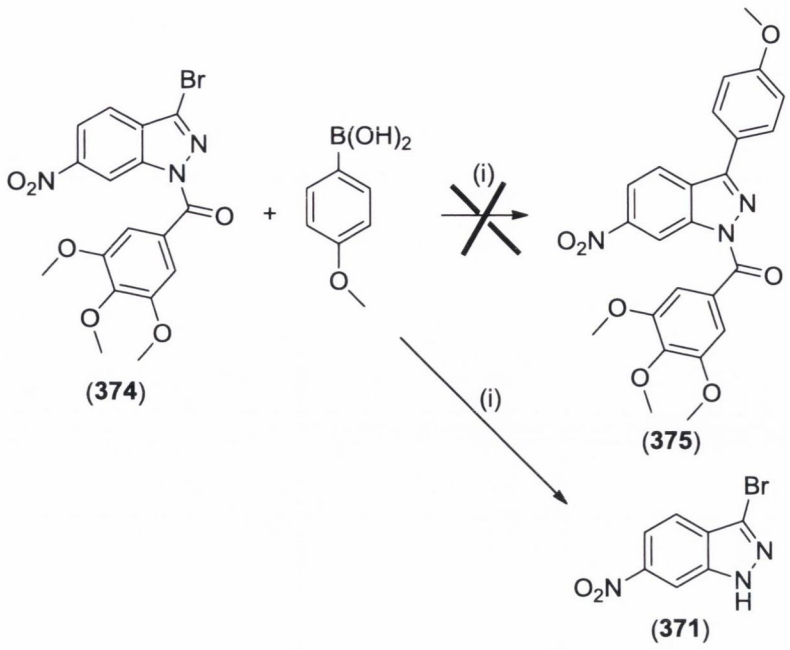


Figure 185: ^{13}C-NMR spectrum of (374)

The ^{13}C-NMR spectrum of (**374**) is shown in figure 185. The signal at 56.34 ppm is assigned to the carbons of the two symmetric methoxy groups on the aryl ring while the signal at 61.02 ppm is assigned the methoxy carbon at $C_{4'}$. The signals at 109.34, 112.54, 120.65 and 121.46 ppm are assigned to aromatic methine carbons $C_{2'}$ & C_6', C_7, C_5 and C_4 respectively. The signal at 165.86 ppm is assigned to the carbonyl carbon. The signals at 125.61, 129.21, 129.51, 140.21, 142.79, 149.36 and 152.70 is assigned to the *ipso* carbons C_3, C_{3a}, $C_{1'}$, C_{7a}, C_6, $C_{4'}$ and $C_{3'}$ respectively.



(i) 2 M Na_2CO_3, $Pd(PPh_3)_4$, THF

Figure 186: Attempted Synthesis of (374)

The aryl coupling of (**374**) using 4-methoxyphenylboronic acid was attempted using the Suzuki reaction conditions described in section 3.0, figure 186. However the 3-arylindazole compound (**375**) was not successfully obtained. After purification by flash column chromatography, it was determined that one of the products formed was 3-bromo-6-nitroindazole (**371**). This was obtained by base catalysed hydrolysis of the amide in (**374**). The normal stability associated with amides is diminished by the fact the lone pair of electrons on the N1 atom are delocalised with the pyrazole section of indazole instead of being delocalized on the carbonyl group, figure 187. Also since the 3-bromo substituent is electron withdrawing, this would further diminish the amide bond's stability.

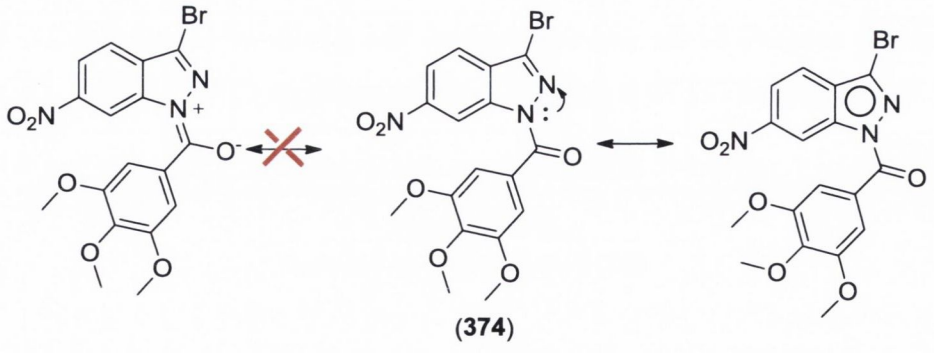
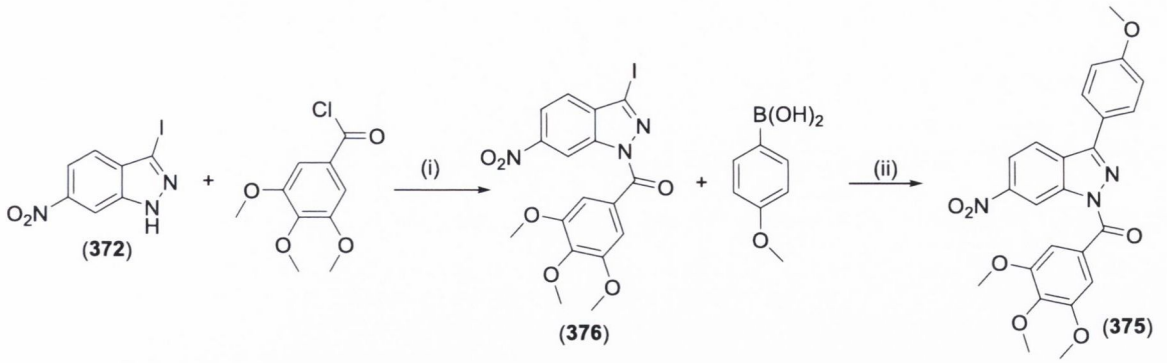


Figure 187: Resonance of the lone pair of N1 electons in (374)

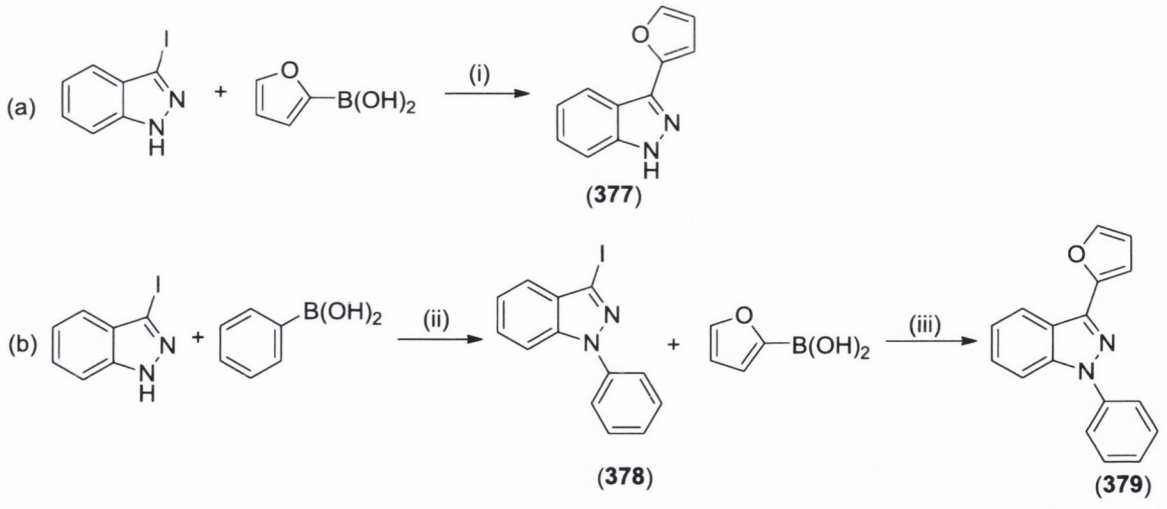


(i) Anhydrous CH_2Cl_2, NEt_3 (ii) 2 M Na_2CO_3, $Pd(PPh_3)_4$, THF

Figure 188: Attempted synthesis of (380) using (381) as the aryl halide substrate

The synthesis of (**375**) was again attempted but using 3-iodo-6-nitroindazole (**376**) instead of (**374**). However this also was not successful and 3-iodo-6-nitroindazole (**372**) was obtained as the sole product. Also using bis(triphenylphosphine)palladium (II) chloride instead of tetrakis(triphenylphosphine)palladium(0) as the palladium catalyst did not change the outcome of the reaction.

Upon reviewing the literature, it was discovered that the 3-arylation of 3-iodoindazole was reported by *Collot et al*[356].

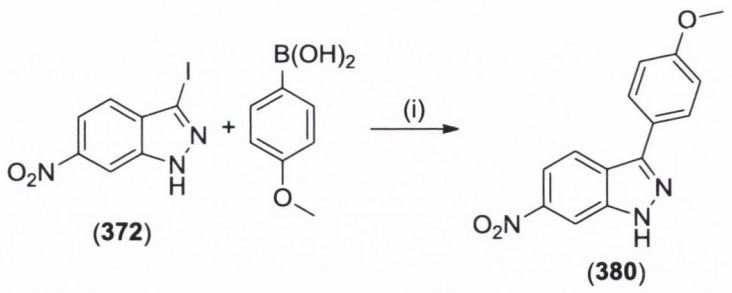


(i) $NaHCO_3$, $Pd(PPh_3)_4$, DME, 80°C (ii) $Pd(PPh_3)_4$, $Cu(OAc)_2$, NEt_3, $NaHCO_3$, rt, 2 h (iii) 80°C, 3h

Figure 189: (a) 3-arylation of 3-iodoindazole and (b) One pot N-arylation and 3-arylation of 3-iodoinazole

Collot et al had successfully 3-arylated 3-iodoindazole using the conditions described in figure 189 (a), yielding the compound (**377**) in 65% yield. Further research by *Collot et al* demonstrated that by the appropriate addition of the required reagents, the N-arylation of 3-iodoindazole would first yield (**378**) and then subsequently the compound (**379**) could be

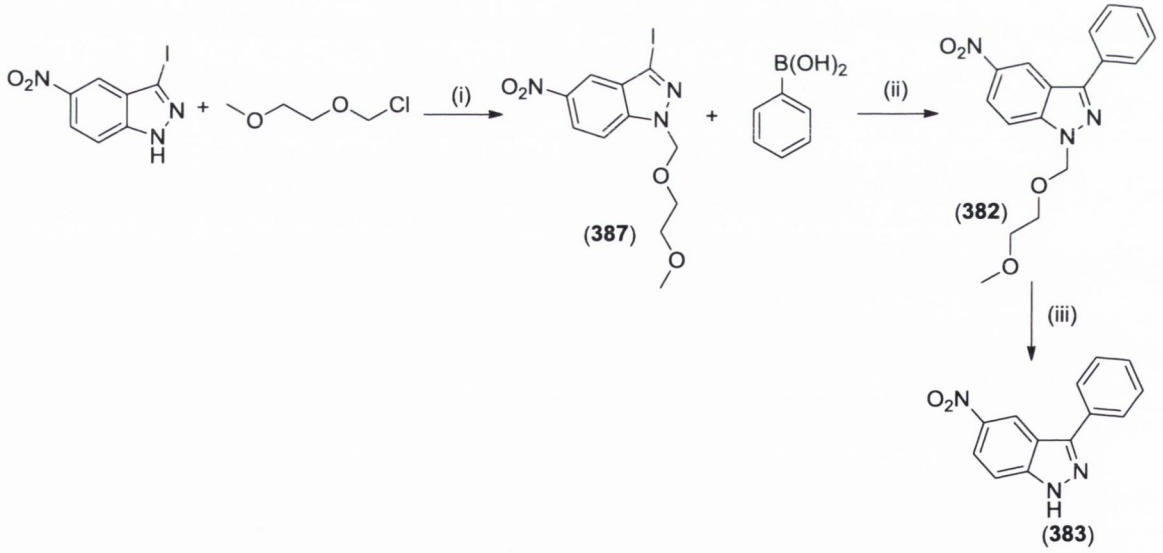
obtained[357] using Chan Lam coupling, figure 189 (b). This reaction was performed using a one pot synthesis.



(i) $NaHCO_3$, $Pd(PPh_3)_4$, DME, 80°C

Figure 190: Attempted 3-arylation of 3-iodo-6-nitroindazole

Following this observation, it was initially thought that the 3-arylation of 3-iodo-6-nitroindazole (**372**) could be performed first, yielding (**380**), figure 190, and then (**380**) could be reacted with 3,4,5-trimethoxybenzoyl chloride affording (**377**). However the arylation of (**372**) using the reaction conditions in figure 190 did not yield (**380**) and only starting material (**372**) was recovered. The literature was examined again and it was discovered that 3-arylation of (**373**) was successfully carried out by *Binch et al* who investigating indazole derivatives as protein kinase inhibitors[355].

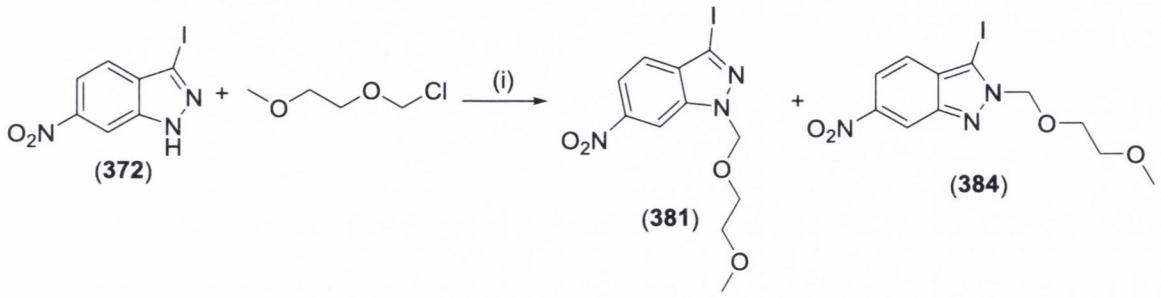


(i) sodium bis(trimethylsilyl)amide, THF, rt, 15 h (ii) potassium phosphate, DME, (1,1'-Bis(diphenylphosphino)ferrocene)palladium(II) dichloride, 85°C, 18 h (iii) HCl

Figure 191: 3-Arylation of 3-iodo-5-nitroindazole by *Binch et al*[355]

Binch et al first reacted 3-iodo-5-nitroindazole with 2-methoxyethoxymethyl chloride yielding the MEM protected compound (**387**), figure 191. The MEM protecting group is commonly used for the protection of OH groups[358]. The 3-arylation of (**387**) was carried out using the

palladium coupling catalyst bis(diphenylphosphino)ferrocene)palladium(II) dichloride yielding (**382**). The MEM protecting group was removed using HCl yielding (**3823**). In the present work, 3-iodo-6-nitroindazole (**372**) was therefore reacted with 2-methoxyethoxymethyl chloride which afforded the desired N-1 isomer (**381**) in 51 % yield and the N2 isomer (**384**) in 5 % yield, figure 192. The presence of the N-2 isomer (**384**) was not documented by *Binch et al*[355]. Characterisation of (**384**) was completed in the present work however the further development of the N-2 isomer product was not pursued due to small quantity of material.



(i) Anhydrous THF, DMF, NaH, 0 °C to 20 °C

Figure 192: Synthesis of (381) and (384)

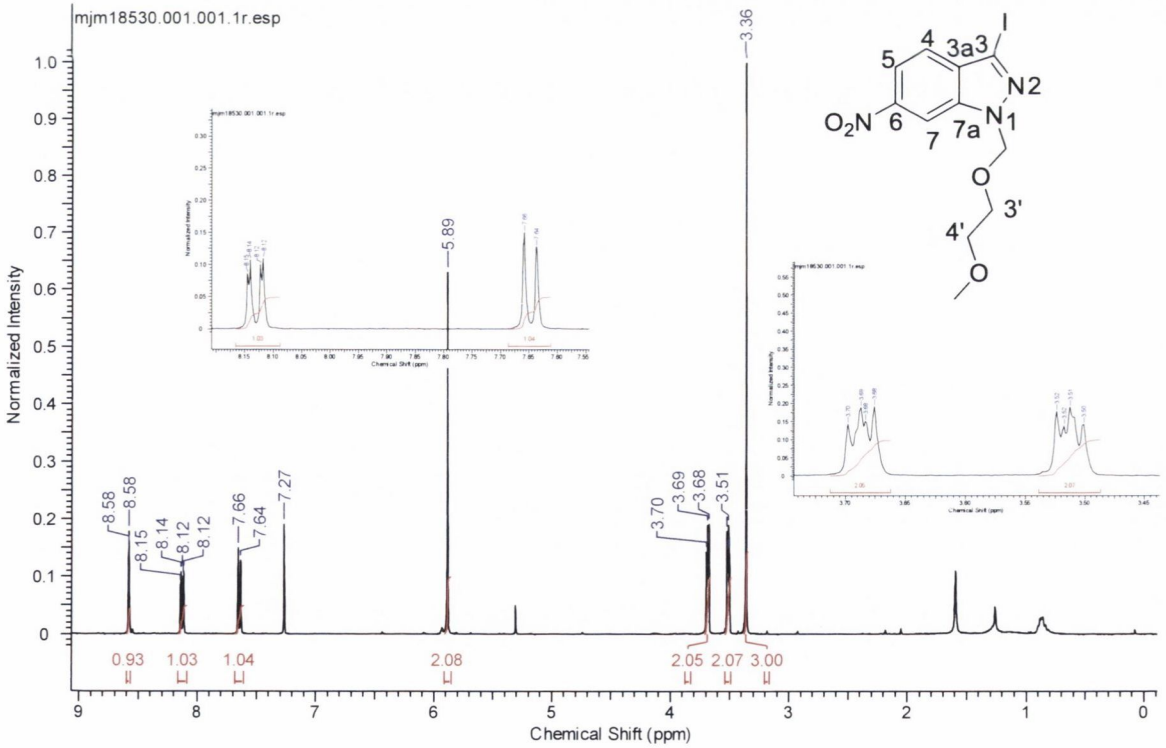


Figure 193: ^{1}H-NMR spectrum of (381)

The ^{1}H-NMR spectrum of (**381**) is shown in figure 193. The singlet at 3.36 ppm corresponds to the methoxy protons. The multiplets from 3.50 to 3.52 ppm and 3.68 to 3.70 ppm, which both integrate for 2 protons each, correspond to ethylene groups at 3' and 4' respectively. The singlet at 5.89 ppm is assigned to the ethylene group attached to the N1 atom. The doublet at 7.65 ppm, J = 8.84 Hz, is assigned to H_4. The double doublet at 8.13 ppm, J = 8.84, 1.84 Hz, is assigned to H_5.The doublet at 8.58 Hz, J = 1.84 Hz, is assigned to H_7.

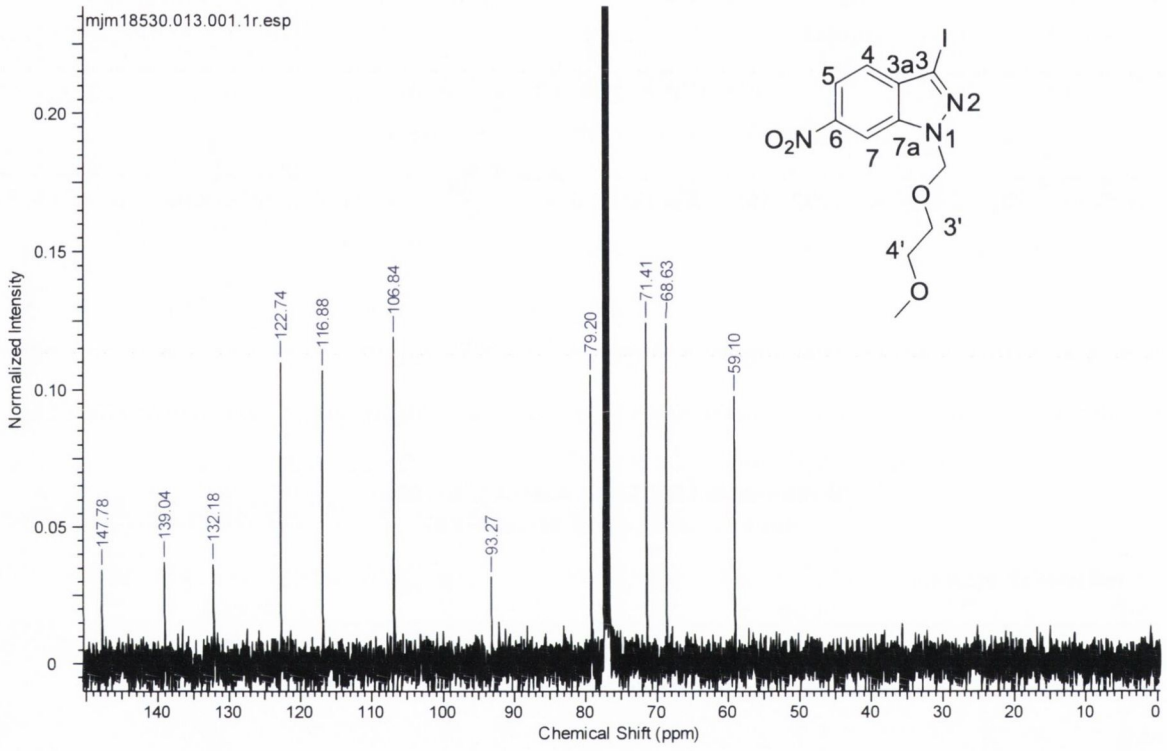


Figure 194: ^{13}C-NMR spectrum of (381)

The ^{13}C-NMR spectrum of (**381**) is shown in figure 194. The signal at 59.10 ppm is assigned to the methoxy carbon. The signals at 68.23 and 71.41 ppm are assigned to the ethylene carbons at 3' and 4' respectively. The signal at 79.19 ppm is assigned to the ethylene carbon directly attached to the N1 atom. The signals at 106.84, 116.88 and 122.74 ppm correspond to the aromatic methine carbons C_7, C_5 and C_4 respectively. The signals at 93.27, 132.18, 139.04, 147.78 ppm correspond to the aromatic *ipso* carbons C_3, C_{3a}, C_{7a} and C_6 respectively. The assignment of the carbons was facilitated by DEPT and HMBC spectroscopy.

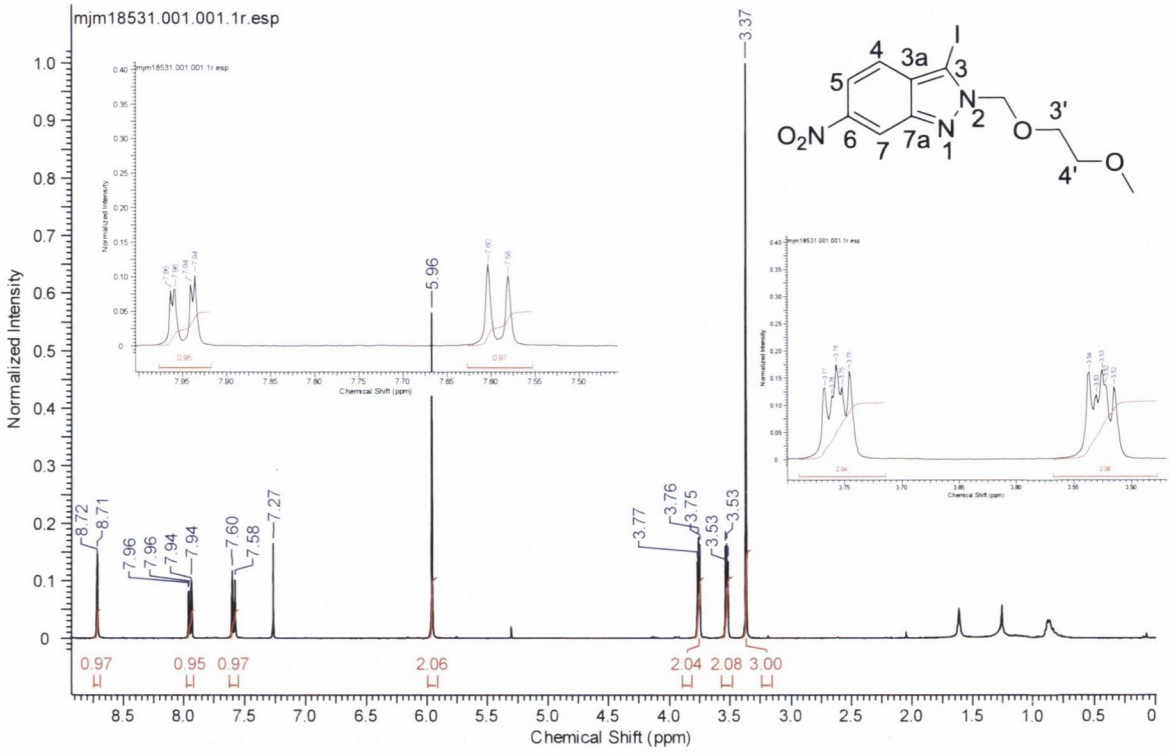
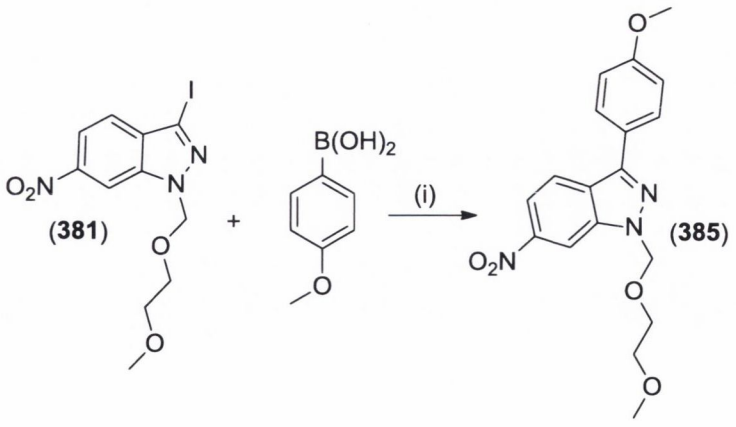


Figure 195: ^{1}H-NMR spectrum of (384)

The ^{1}H-NMR spectrum of the N-2 isomer (**384**) is shown in figure 195. The singlet at 3.38 ppm corresponds to the methoxy protons. The multiplets from 3.52 to 3.54 ppm and 3.75 to 3.77 ppm, which both integrate for 2 protons each, correspond to ethylene groups at 3' and 4' respectively. The singlet at 5.96 ppm is assigned to the ethylene group attached to N2. The doublet at 7.59 ppm, $J = 9.24$ Hz, is assigned to H_4. The double doublet at 7.95 ppm, $J = 9.24$, 1.72 Hz, is assigned to H_5.The doublet at 8.72 Hz, $J = 1.72$ Hz, is assigned to H_7.



(i) K_2CO_3, (1,1'-bis(diphenylphosphino)ferrocene)palladium(II) dichloride, anhydrous DME, 90 °C, 16 h

Figure 196: 3-Arylation of (381) yielding (385)

The reaction of (**381**) with 4-methoxyphenylboronic acid, using the reaction conditions in figure 196, successfully yielded the 3-arylated compound (**385**) in 53 % yield.

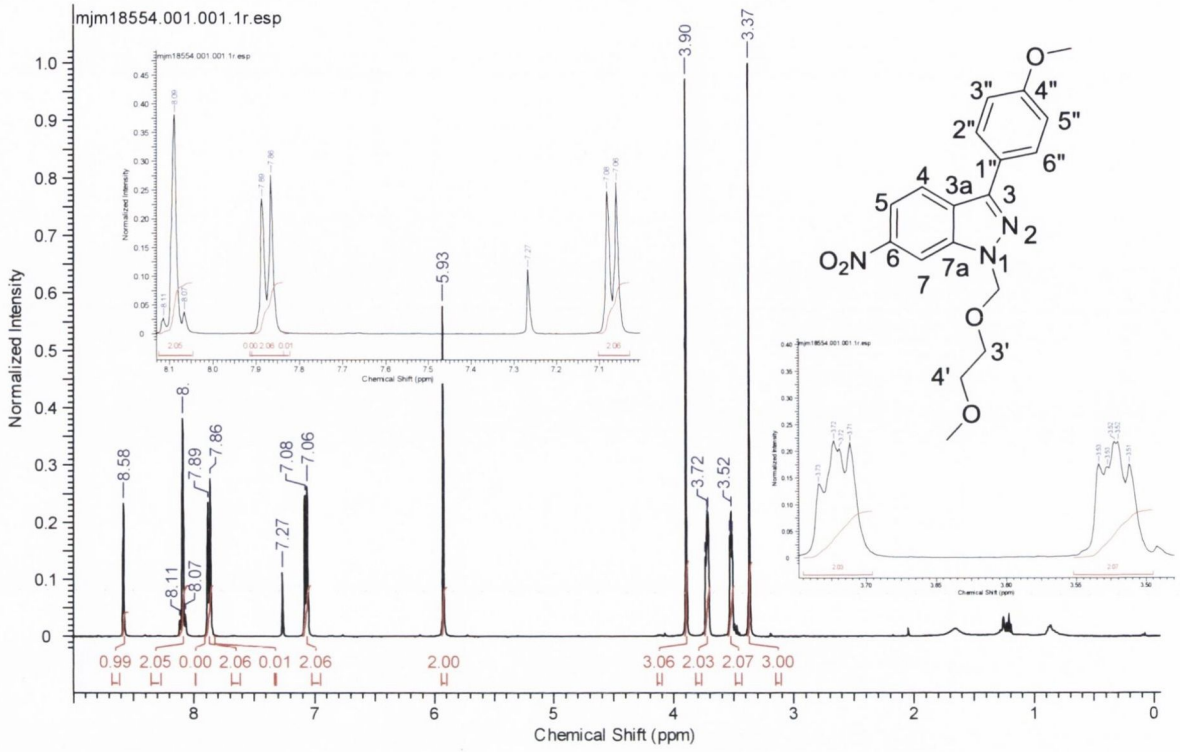


Figure 197: ^{1}H-NMR spectrum of (385)

The ^{1}H-NMR spectrum of (**385**) is shown in figure 197. The singlet at 3.37 ppm corresponds to the methoxy protons of the MEM protecting group while the singlet at 3.90 ppm, is assigned to the 4"-methoxyphenyl group protons. The multiplets 3.51 to 3.54 ppm and 3.71 to 3.74 ppm, each integrating for 2 protons, correspond to the ethylene group protons at 3' and 4' respectively. The doublets at 7.07 and 7.88 ppm correspond to the symmetric aromatic protons $H_{3"}$ & $H_{5"}$ and $H_{2"}$ & $H_{6"}$ respectively. The chemical shift of the protons H_4 and H_5 overlap resulting in the multiplet 8.07 to 8.12 ppm. The singlet at 8.58 is assigned to the proton H_7.

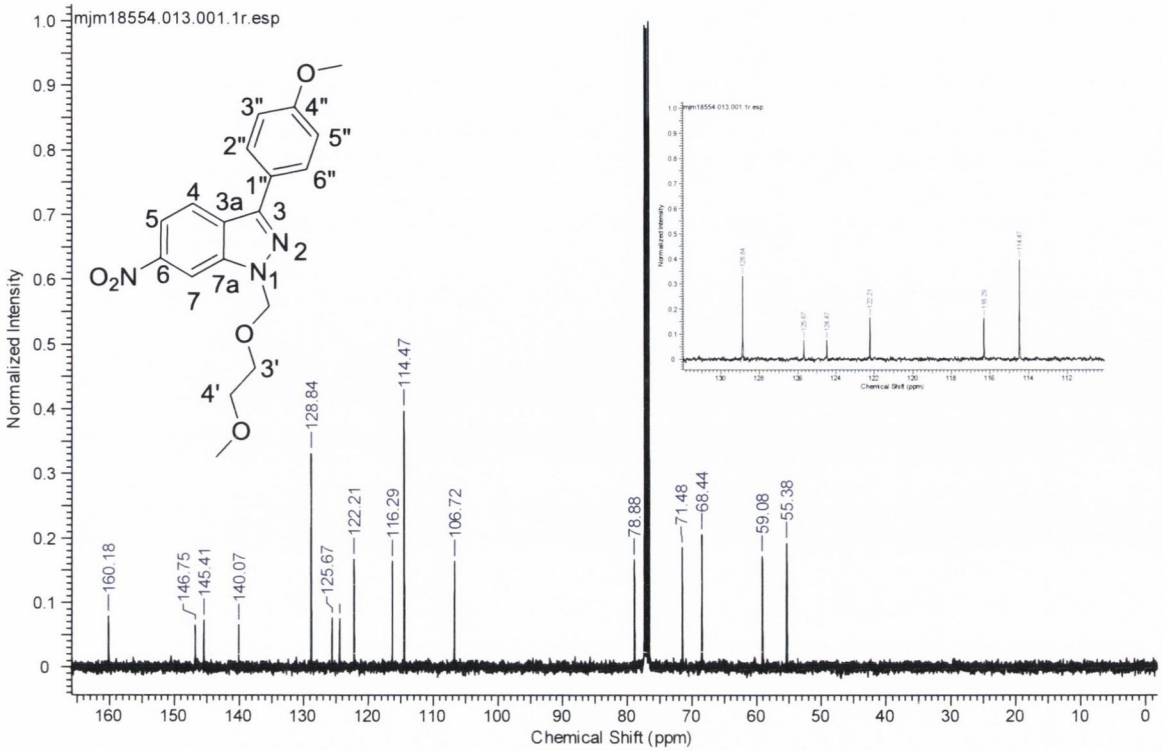


Figure 198: ^{13}C-NMR spectrum of (385)

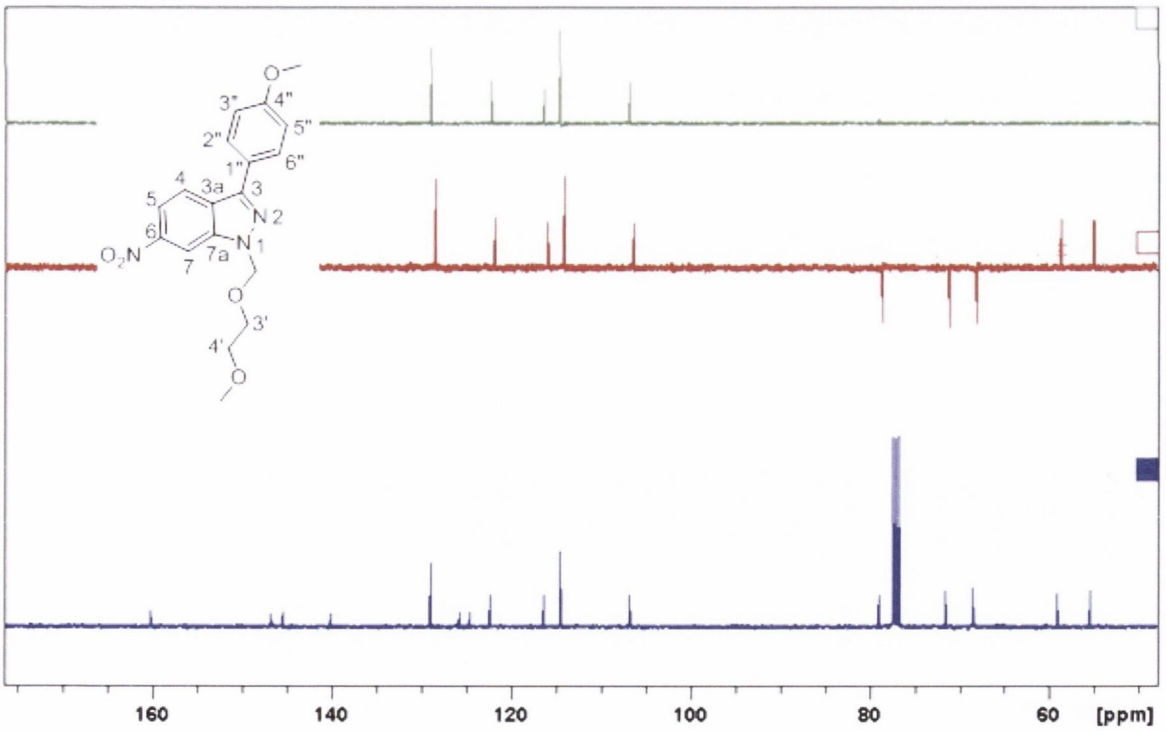
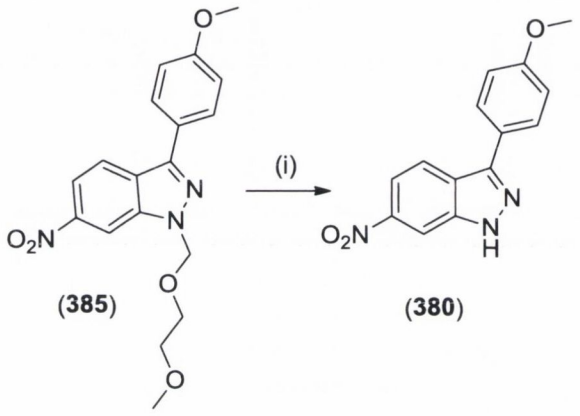


Figure 199: DEPT 90, DEPT 135 and ^{13}C-NMR spectra of (385)

The ^{13}C-NMR and DEPT spectra of (**385**) are shown in figures 198 and 199 respectively. The 4"-methoxy carbon is assigned the signal at 55.38 ppm while the methoxy carbon of the MEM protecting group is assigned to the signal 59.08 ppm. The signals at 68.43 and 71.47 ppm correspond to the ethylene carbons $C_{3'}$ and $C_{4'}$ respectively while the signal at 78.87 ppm corresponds to the ethylene attached to N1. The signals at 106.71, 114.46, 116.28, 122.20 and 128.84 ppm correspond to the aromatic methine C_7, $C_{3"}$& $C_{5"}$, C_5, C_4 and $C_{2"}$& $C_{6"}$ respectively. The signals at 124.46, 125.66, 140.06, 145.40, 146.75 and 160.18 ppm correspond to the aromatic ipso carbons $C_{1"}$, C_{3a}, C_{7a}, C_3, C_6 and $C_{4"}$.



(i) 6N HCl, 75 °C, 6 h

Figure 200: Synthesis of (385)

The next step in the new synthetic route was the removal of the MEM protecting group. This was achieved by refluxing (**385**) in HCl for 6 hours, figure 200, allowing the solution to cool to room temperature and filtering the precipitate. (**380**) was afforded in 55 % yield.

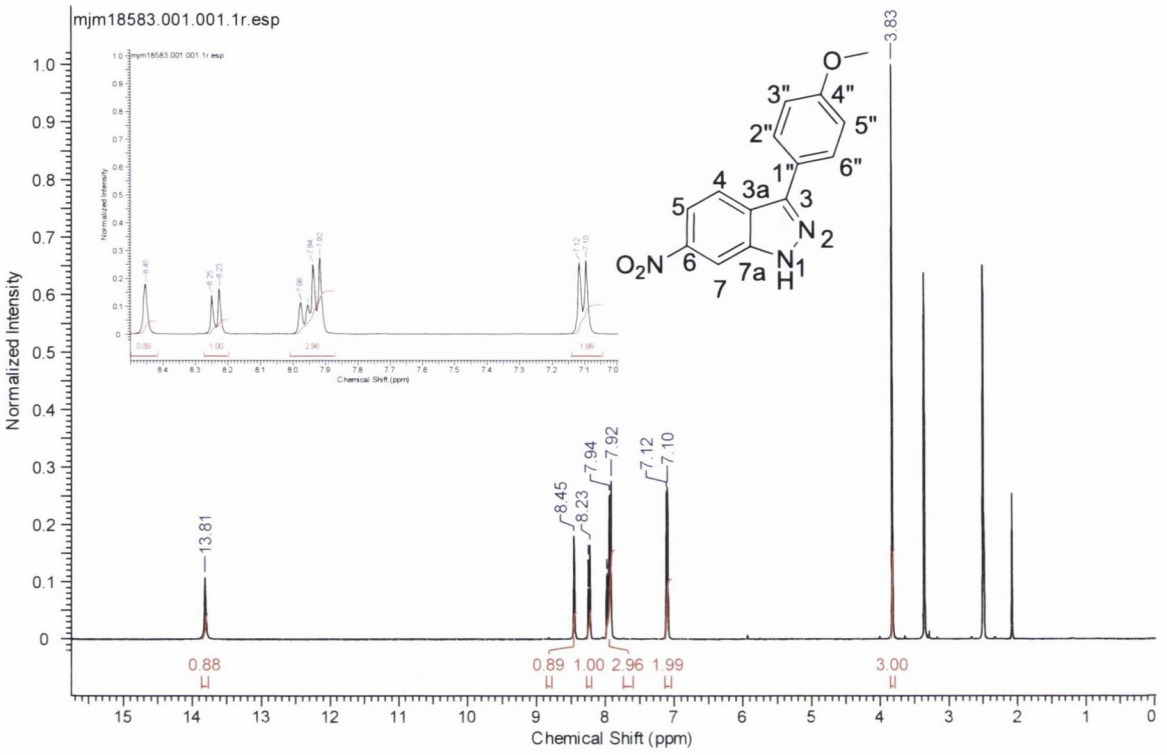


Figure 201: ^{1}H-NMR spectrum of (380)

The ^{1}H-NMR spectrum of (**380**) is shown in figure 201. The sharp singlet at 3.83 ppm is assigned to the methoxy protons. The doublet at 7.11 ppm, J = 8.48 Hz, is assigned to the symmetric aromatic protons $H_{3"}$& $H_{5"}$. The chemical shifts of the symmetric protons $H_{2"}$ & $H_{6"}$ and H_4 overlap, resulting in the multiplet 7.92 to 7.98 ppm, which integrates for 3 protons. The doublet at 8.24 ppm, J = 8.92 Hz, is assigned to H_5 while the singlet at 8.45 ppm is assigned to H_7. Both H_5 and H_7 would appear more downfield than H_4 due to their proximity to the electron deshielding nitro group. The broad singlet at 13.81 ppm is assigned to the NH.

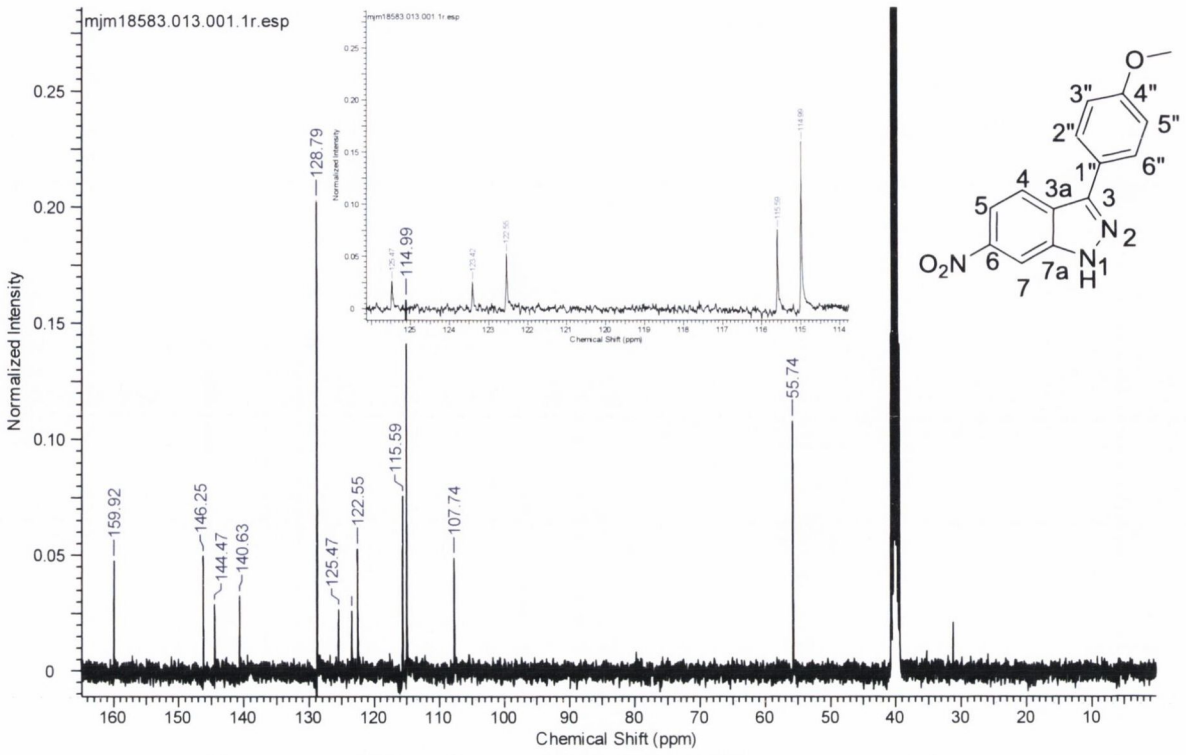
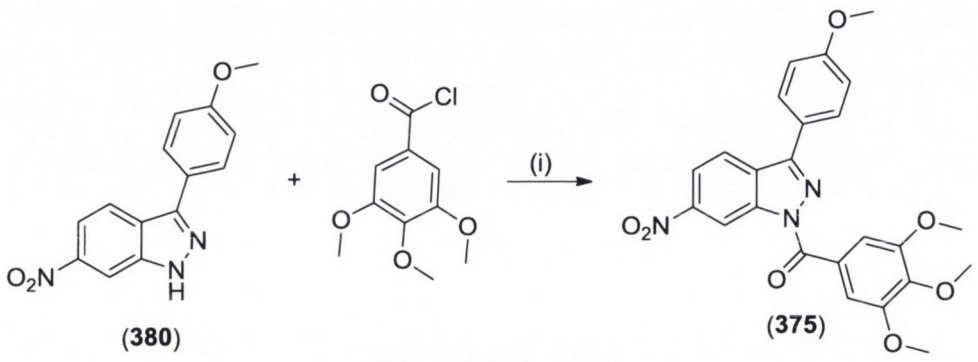


Figure 202: ^{13}C-NMR spectrum of (380)

The ^{13}C-NMR spectrum of (**380**) is shown in figure 201. The signal at 55.74 ppm is assigned to the methoxy carbon while the signals at 107.74, 114.99, 115.60, 122.55 and 128.70 are assigned to the aromatic methine carbons C_7, $C_{3"}$ & $C_{5"}$, C_5, C_4 and $C_{2"}$ & $C_{6"}$ respectively. The signals at 123.42, 125.48, 140.63, 144.48, 146.25 and 159.92 ppm are signed to the aromatic ispo carbons $C_{1"}$, C_{3a}, C_3, C_{7a}, C_6 and $C_{4"}$ respectively.

(**380**) was next benzoylated using the reaction conditions in figure 203, yielding the compound (**375**) in 25 % yield. The structure of (**375**) was successfully confirmed from infrared, MS and ^{1}H and ^{13}C NMR spectroscopy.



(i) NEt_3, CH_2Cl_2, 50 °C

Figure 203: Synthesis of (375)

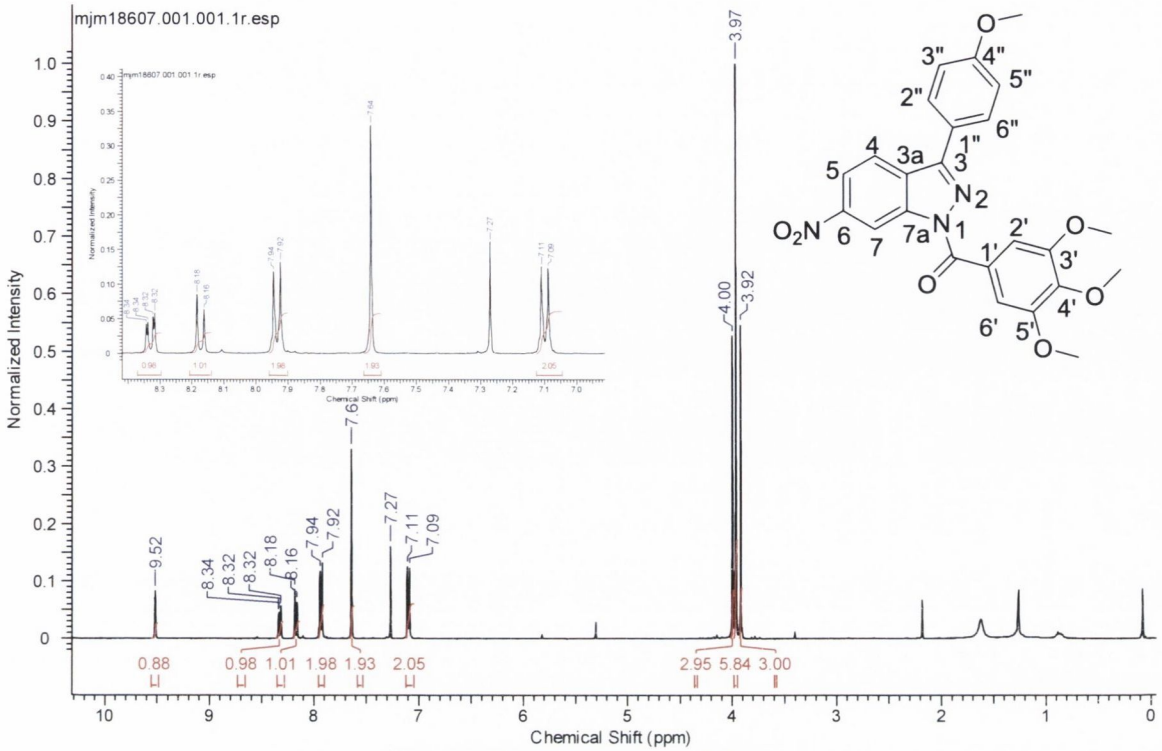


Figure 204: ^{1}H-NMR spectrum of (375)

The ^{1}H-NMR spectrum of (**375**) is shown in figure 204. The singlet at 3.92 ppm is assigned to the 4"-methoxy protons. The sharp singlet at 3.97 ppm, which integrates for 6 protons, is assigned to the symmetric methoxy groups at $C_{3'}$ & $C_{5'}$ while the singlet at 4.00 ppm is assigned to the protons of the methoxy group at $C_{4'}$. The doublet at 7.10 ppm, J = 8.72 Hz, is assigned to the symmetric protons $H_{3''}$ & $H_{5''}$ while the doublet at 7.93 ppm, J = 8.72 Hz, is assigned to the symmetric protons $H_{2''}$ & $H_{6''}$. The former symmetric pair would be more shielded than the latter due to the methoxy group. The sharp singlet at 7.64 ppm is assigned to the symmetric protons $H_{2'}$ & $H_{6'}$. The doublet at 8.17 ppm, J = 8.80 Hz, is assigned to H_4 while the double doublet at 8.33 ppm, J = 8.80, 1.76 Hz, is assigned to H_5. The doublet at 8.52 ppm, J = 1.76 Hz, is assigned to H_7.

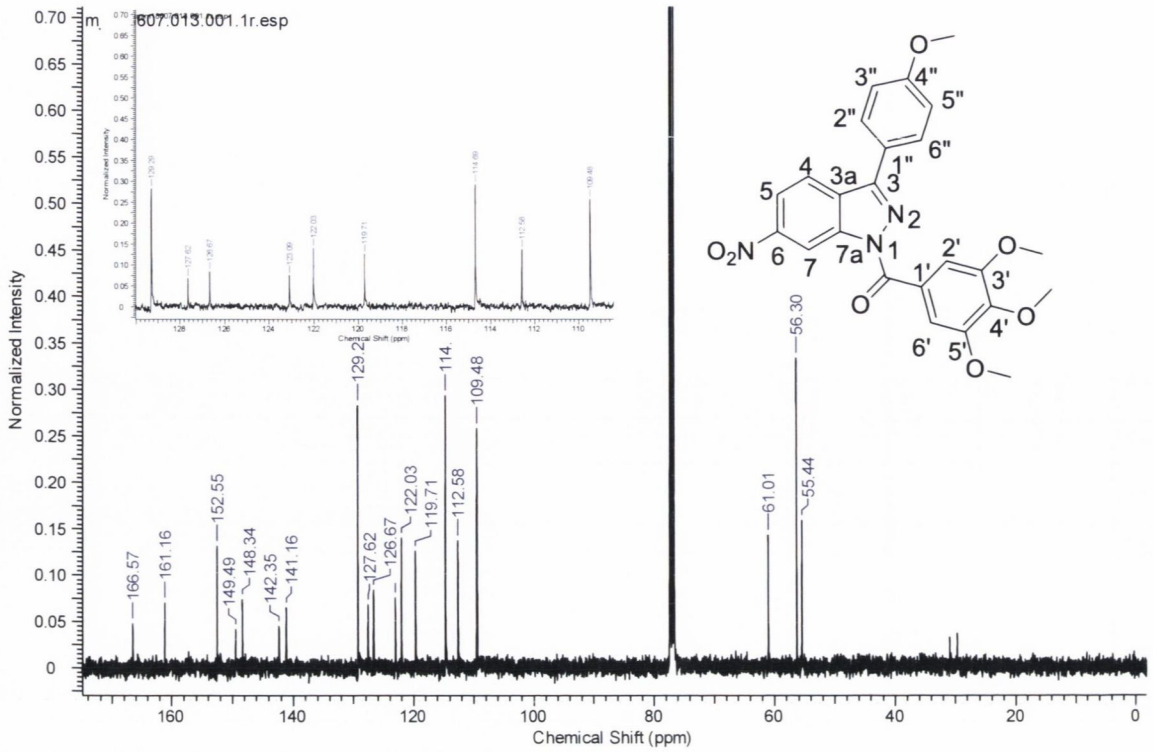


Figure 205: ^{13}C-NMR spectrum of (375)

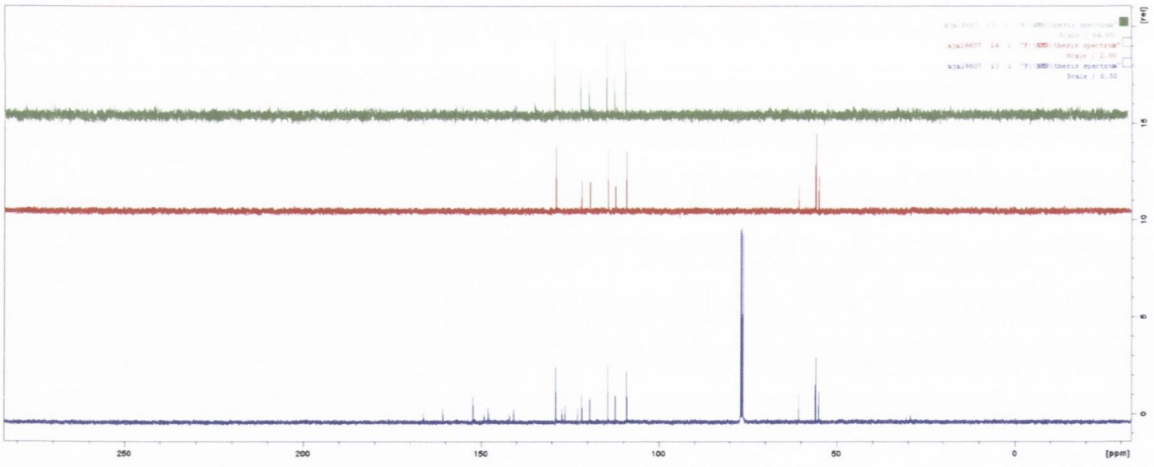
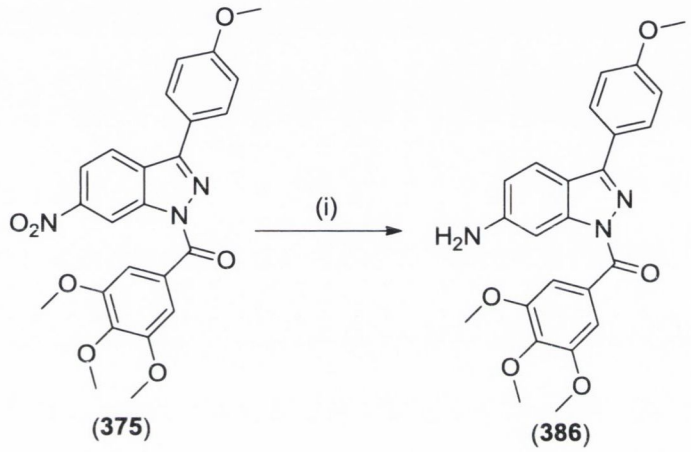


Figure 206: DEPT and ^{13}C-NMR spectra of (375)

The ^{13}C-NMR and DEPT spectra of (**375**) are shown in figures 205 and 206 respectively. The signal at 55.45 ppm corresponds to the 4"-methoxy carbon. The signal at 56.31 ppm is assigned to the symmetric methoxy carbons *ortho* to the amide bond while the signal at 61.01 ppm is assigned to the methoxy carbon *para* to the amide bond. The sharp signals at 109.48, 114.69 and 129.30 ppm correspond to the symmetric carbon pairs $C_{2'}$ & $C_{6'}$, $C_{3''}$ & $C_{5''}$ and $C_{2''}$ & $C_{6''}$ respectively. The signals at 112.59, 119.72 and 122.03 ppm correspond to the aromatic methine

carbons C_7, C_5 and C_4 respectively. The signal at 166.57 ppm is assigned to the C=O group. The signals at 126.76, 127.63, 141.17, 142.36, 148.34, 149.49, 152.56 and 161.56 ppm are assigned to the remaining *ipso* carbons $C_{1'}$, $C_{1''}$, C_{3a}, C_{7a}, $C_{4'}$, C_6, $C_{3'}$ & $C_{5'}$ and $C_{4''}$ respectively.

The final step in the synthetic sequence required the reduction of the nitro group in (**375**) by hydrogenation, figure 207, which yielded the desired final product (**386**). The presence of the aromatic amine was observed in the infrared spectrum and the molecular ion was confirmed in the HRMS.



(i) H_2, 10% Pd/C, 1:1 MeOH: EtOAc, 20 °C

Figure 207: Preparation of (386)

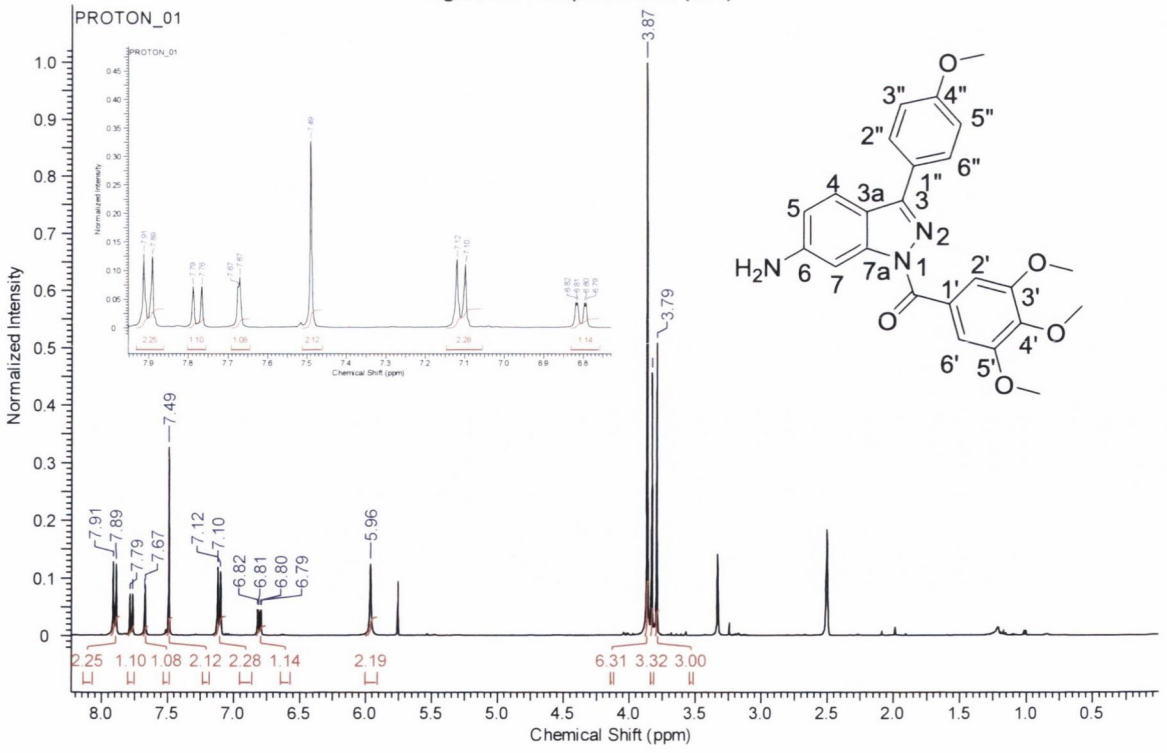


Figure 208: ^{1}H-NMR spectrum of (386)

The ^{1}H-NMR spectrum of (**386**) is shown in figure 208. The singlet at 3.79 ppm is assigned to the protons of the methoxy group at $C_{4'}$ while the singlet at 3.83 ppm corresponds to the protons of the methoxy group at $C_{4''}$. The sharp singlet at 3.86 ppm, integrating for 6 protons, corresponds to the symmetric methoxy groups at $C_{3'}$ & $C_{5'}$. The broad singlet at 5.96 ppm corresponds to the amine group. The double doublet at 6.80 ppm, J = 8.68, 1.80 Hz, is assigned to H_5. The doublet at 7.10 ppm, J = 8.80 Hz, is assigned to $H_{3''}$& $H_{5''}$ while the doublet at 7.80 ppm, J = 8.80 Hz, is assigned to $H_{2''}$ & $H_{6''}$. The singlet at 7.49 ppm is assigned to $H_{2'}$ & $H_{6'}$. The doublet at 7.67 ppm, J = 1.80 Hz, is assigned to H_7 while the doublet at 7.77 ppm, J = 8.80 Hz, corresponds to H_4.

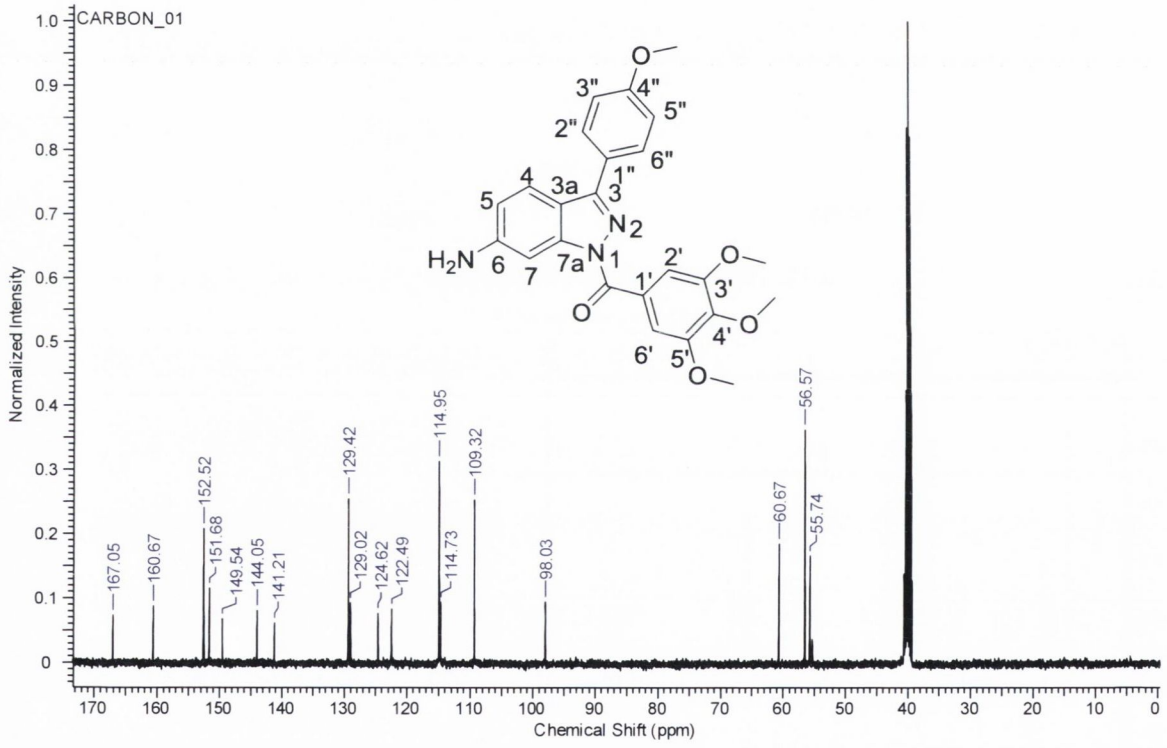


Figure 209: ^{13}C-NMR spectrum of (386)

The ^{13}C-NMR and DEPT spectra of (**386**) are shown in figures 208 and 209 respectively. The signal at 55.74 ppm corresponds to the methoxy carbon at $C_{4''}$. The signals at 56.57 and 60.67 ppm correspond to the methoxy carbons at $C_{3'}$ & $C_{5'}$ and $C_{4'}$ respectively. The signal at 98.03 ppm is assigned to C_7 while the signal at 109.32 ppm is assigned to $C_{2'}$ & $C_{5'}$. The signal at 122.49 ppm corresponds to C_7 while the signal at 129.42 ppm is assigned to $C_{2''}$ & $C_{6''}$. It appears the chemical shift of C_5 and $C_{3''}$ & $C_{5''}$ overlap and the signal at 114.95 ppm represents

these carbons. The signals at 152.52, 160.67 and 167.06 ppm correspond to $C_{4''}$, $C_{3'}$ & $C_{5'}$ and NC=O respectively. The signals at 114.73, 124.62, 129.02, 141.21, 144.05, 149.55 and 151.69 ppm correspond to the aromatic *ipso* carbons C_{3a}, $C_{1'}$, $C_{1''}$, C_{7a}, C_{3a}, $C_{4'}$ and C_6 respectively.

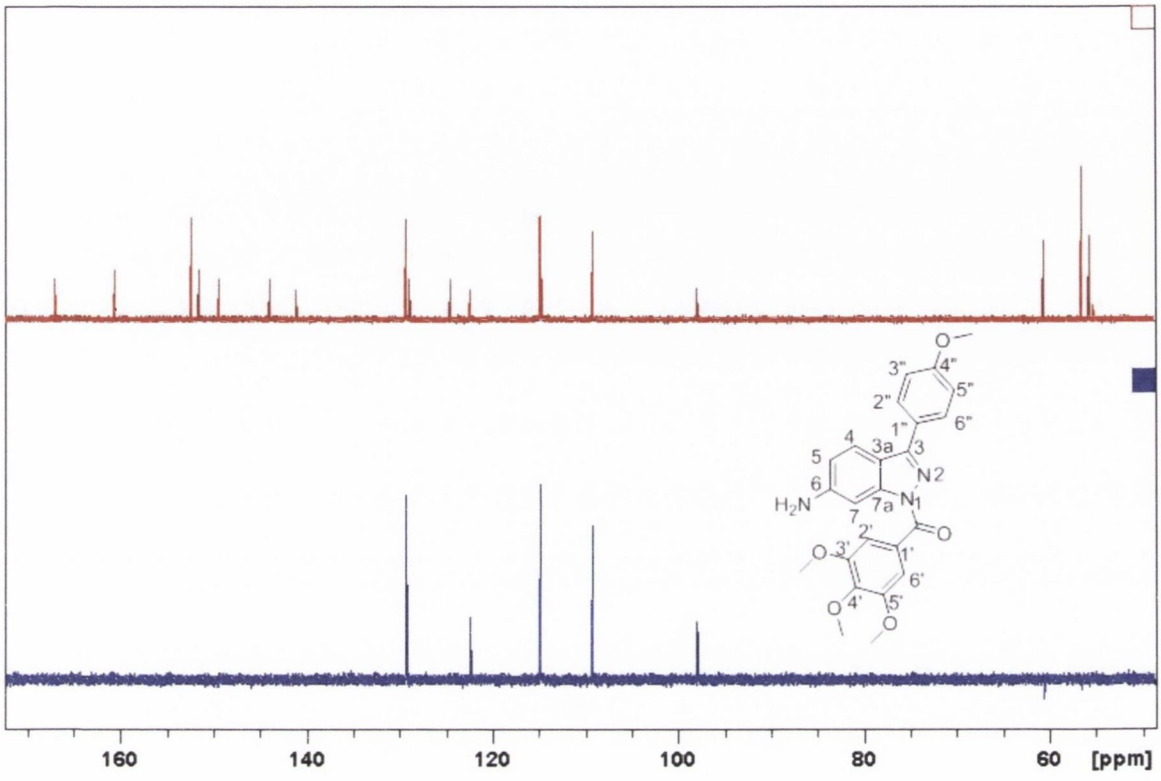
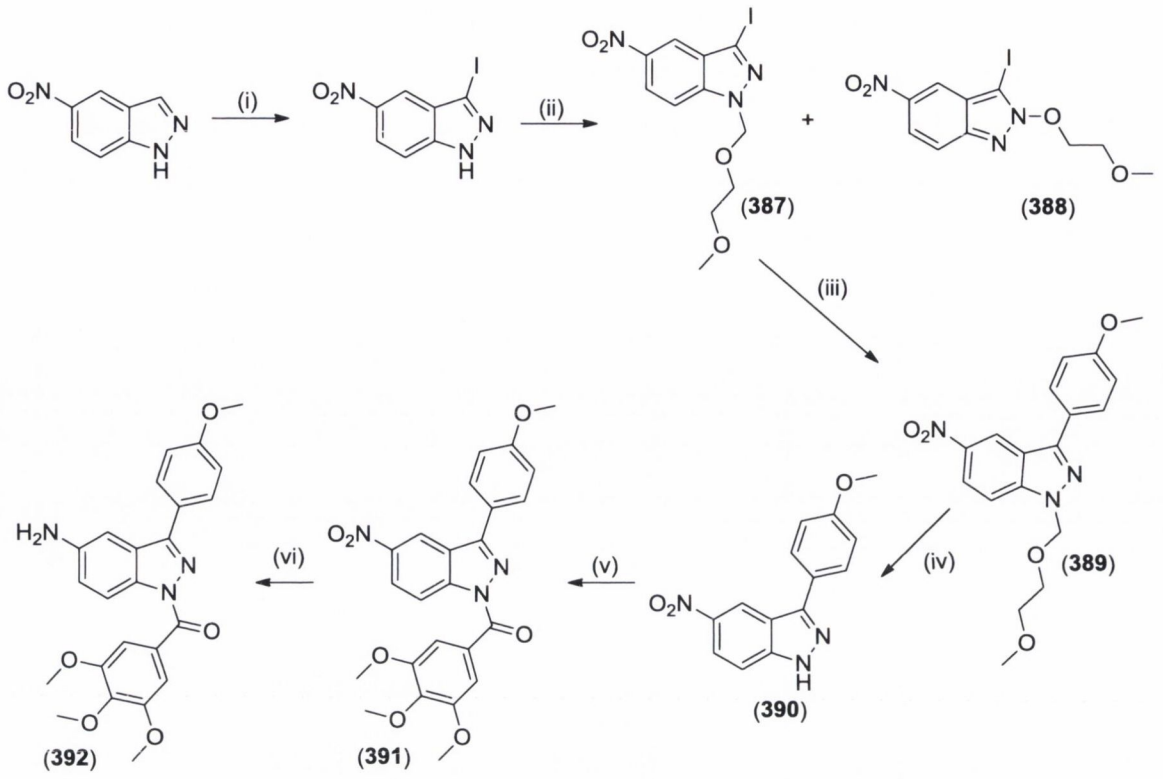


Figure 210: ^{13}C-NMR and DEPT spectra of (386)

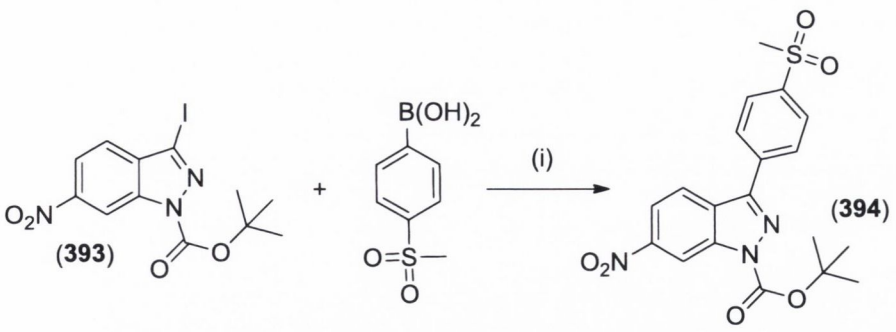
The preparation of the 1-benzoyl-3-aryl-6-aminoindazole (**386**) was successful using the chemistry described. The corresponding 3-aryl-5-aminoindazole (**392**) was prepared using the same chemistry and the complete synthetic scheme is shown in figure 211.



(i) I_2, NaOH, DMF, $Na_2S_2O_5$ 0 °C to 20 °C (ii) DMF, THF, NaH, 2-methoxyethoxymethyl chloride. 0 °C to 20 °C (iii) 4-methoxyphenylboronic acid, K_2CO_3, (1,1'-Bis(diphenylphosphino)ferrocene)palladium(II) dichloride, anhydrous DME, 90 °C, 16 h (iv) 6N HCl, 75 °C, 6 h (v) 3,4,5-trimethoxybenzoyl choride, NEt_3, CH_2Cl_2, 39.6 °C (vi) 10% Pd/C, H_2, 1:1 MeOH:EtOAc

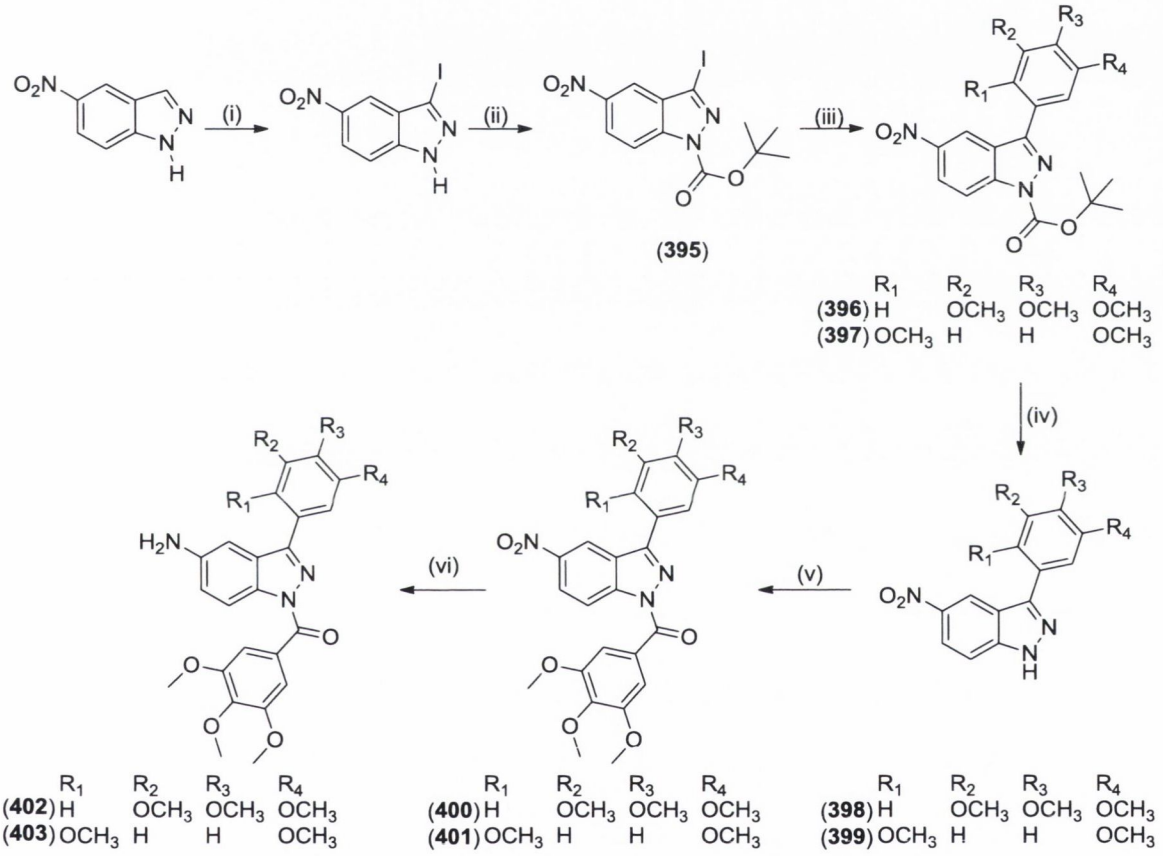
Figure 211: Synthesis of (392)

The *tert*-butyloxycarbonyl (BOC) group was also reported in the literature as a useful protecting group in the 3-arylation of 3-iodo-5-nitroindazole and 3-iodo-6-nitroindazole[359-361] to afford (**394**), figure 212 Once 3-arylation was completed, the BOC protecting group can be removed using HCl. In the present work, it was anticipated that the BOC protecting group could be used instead of the MEM protecting group for the synthesis of 3-arylated 5-aminoindazoles as the addition of the BOC group did not require purification while the addition of the MEM protecting group produced N-1 and N-2 isomers. Figure 213 illustrates the proposed preparation of 3-aryl 5-aminoindazoles using the BOC protecting group. The 3-arylation of (**395**), step (iii) figure 212, was achieved using microwave assisted organic synthesis (MOAS) with the CEM microwave reactor to afford (**396**) and (**397**). Both synthetic approaches have same number of steps but as mentioned earlier, the BOC protection step does not require purification unlike the MEM protection route, figure 211. Removal of the BOC protecting groups yielded (**398**) and (**399**). Subsequent benzoylation to (**400**) and (**401**) was followed by reduction (H_2, Pd/C) to afford the desired products (**402**) and (**403**) respectively.



(ii) $Pd(dppf)_2Cl_2$, DMF, 80°C, Na_2CO_3[360]

Figure 212: 3-arylation of N1 BOC protected 3-iodo-6-nitroindazole (393)



	R_1	R_2	R_3	R_4
(396)	H	OCH_3	OCH_3	OCH_3
(397)	OCH_3	H	H	OCH_3

	R_1	R_2	R_3	R_4
(398)	H	OCH_3	OCH_3	OCH_3
(399)	OCH_3	H	H	OCH_3

	R_1	R_2	R_3	R_4
(400)	H	OCH_3	OCH_3	OCH_3
(401)	OCH_3	H	H	OCH_3

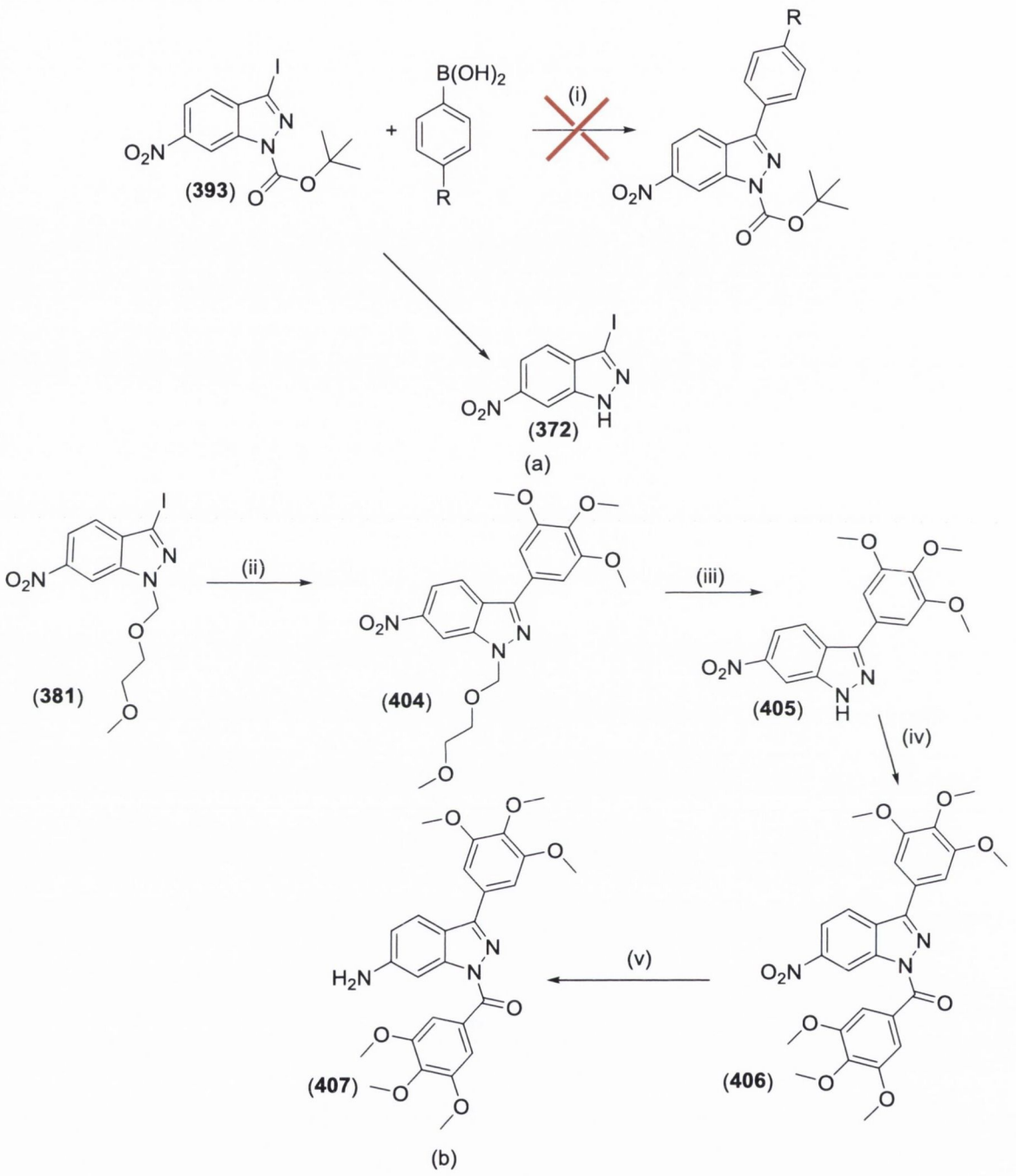
	R_1	R_2	R_3	R_4
(402)	H	OCH_3	OCH_3	OCH_3
(403)	OCH_3	H	H	OCH_3

(i) I_2, KOH, DMF, 0 °C to 20 °C (ii) Di-*tert*-butyl carbonate, Et_3N, DMAP, THF, 0 °C to 20 °C, overnight (iii) $Pd(dppf)_2Cl_2CH_2Cl_2$, Cs_2CO_3, THF, 100 °C, 30 min, μW (iv) HCl, EtOAc, 0 °C to 20 °C (v) 3,4,5-trimethoxybenzoyl chloride, Et_3N, CH_2Cl_2, 20 °C (vi) 10% Pd/C, 1:1 EtOAc:MeOH, 20 °C

Figure 213: Synthesis of 3-aryl-5-aminoindazoles

It was anticipated that a similar sequence of reactions could be employed for the preparation of the corresponding 3-aryl-6-nitro-1*H*-indazole. However when Suzuki 3-arylation of the N-BOC 3-iodo-6-nitro-1*H*-indazole (**393**) was attempted, cleavage of the BOC group occurred to give (**372**) and 3-arylation did not proceed, figure 214 (a). This could be possibly due to the

basic conditions. For the synthesis of 3-arylated 6-aminoindazole derivatives (**407**), the MEM protecting group was used instead, as outlined in figure 214 (b).

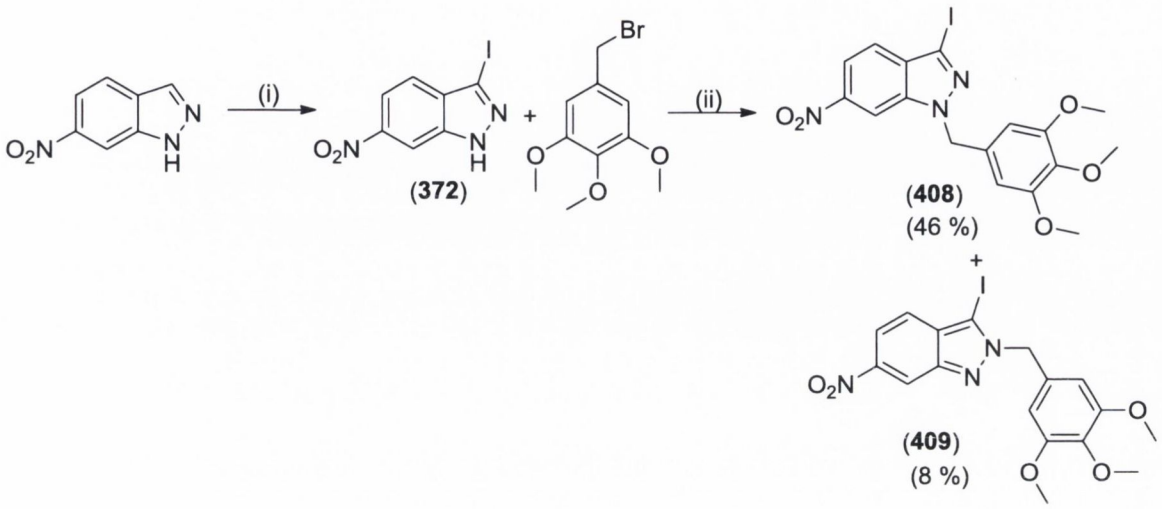


(i) $Pd(dppf)_2Cl_2CH_2Cl_2$, Cs_2CO_3, THF, 100 °C, 30 min, W (ii) 3,4,5-trimethoxyphenylboronic acid, K_2CO_3, (1,1'-Bis(diphenylphosphino)ferrocene)palladium(II) dichloride, anhydrous DME, 90 °C, 16 h (iii) 6N HCl, 75 °C, 6 h (iv) 3,4,5-trimethoxybenzoyl choride, NEt_3, CH_2Cl_2, 50 °C (v) 10% Pd/C, H_2, 1:1 MeOH:EtOAc

Figure 214: (a) Cleavage of BOC protecting group (b) Synthesis of (407)

An additional approach to the preparation of 3-arylindazoles, was to investigate the reaction of 3-iodo-6-nitroindazole (**372**) with 5-(bromomethyl)-1,2,3-trimethoxybenzene which yielded

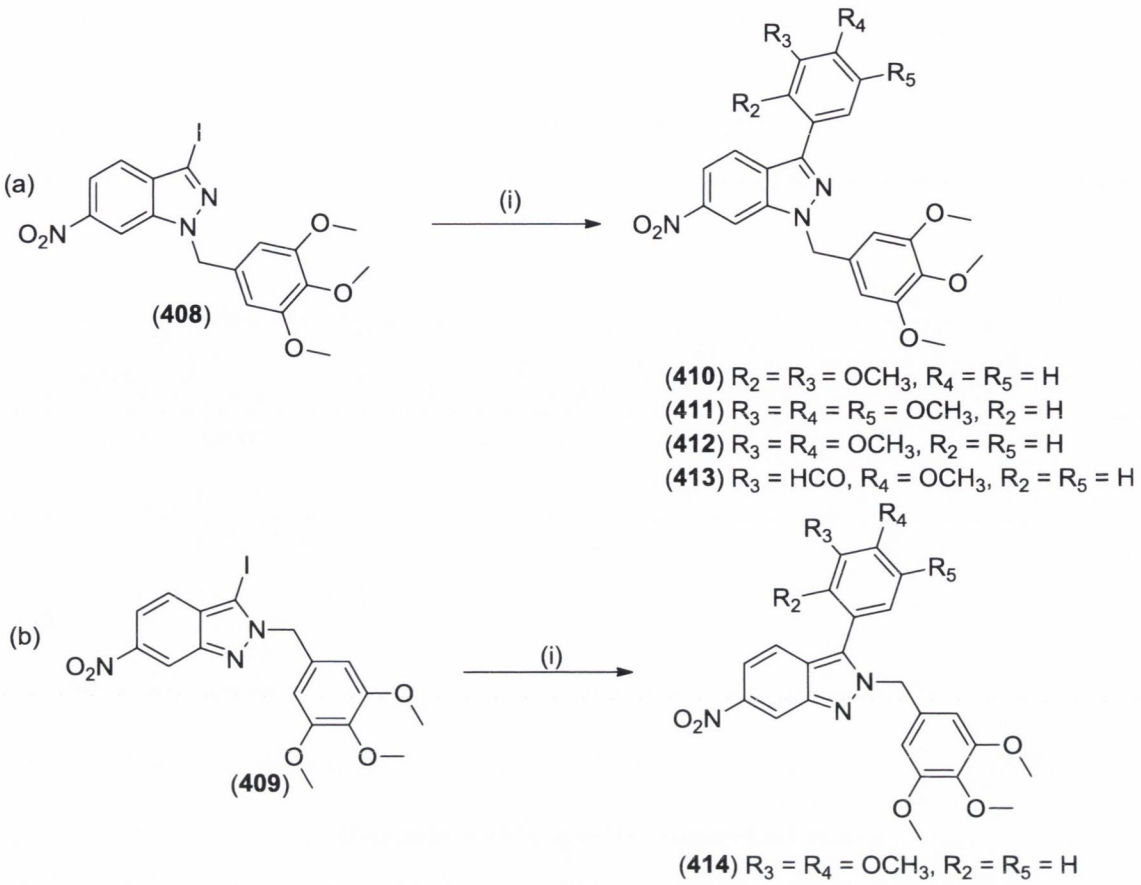
(**408**) and (**409**), figure 215. The 3,4,5-trimethoxybenzyl group would enable subsequent 3-arylation to proceed since it would behave as a benzyl type protecting group but removal of this group was not necessary as it had the required 3,4,5-trimethxoxyphenyl pharmacophore for potential colchicine site inhibitors.



(i) I_2, KOH, DMF, 0 °C to 20 °C (ii) DMF, Cs_2CO_3, 20 °C, 24 h

Figure 215: Benzylation of 3-iodo-6-nitroindazole (372)

The N-1 and N-2 isomers (**408**) and (**409**) could be identified by reference to the ^{1}H and ^{13}C NMR spectra as discussed earlier in section 2.3.



(i) K_2CO_3, (1,1'-Bis(diphenylphosphino)ferrocene)palladium(II) dichloride, anhydrous DME, 90 °C, 16 h

Figure 216: 3-Arylation of (408) and (409)

The 3-arylation of (**408**) and (**409**) was successfully achieved, figure 216, affording 3-arylated indazoles in (**410**) – (**414**) in 40 – 50 % yield.

The ^{1}H-NMR spectrum of (**413**) is shown in figure 217 while the signals in the region from 8.00 to 8.50 ppm are shown in figure 218. The sharp singlet at 3.82 ppm, integrating for 9 protons, is assigned to the methoxy group at $C_{3'}$ & $C_{5'}$ and $C_{4'}$ while the singlet at 4.04 ppm is assigned to the protons of the methoxy group at $C_{4''}$. The singlet at 5.63 ppm is assigned to the methylene protons while the singlet at 6.56 ppm is assigned to the aromatic protons, $H_{2'}$ & $H_{6'}$. The doublet at 7.19 ppm, J = 8.72 Hz, is assigned to $H_{5''}$ while the doublet doublet at 8.06, J = 8.72, 1.44 Hz, is assigned to $H_{6''}$. The doublet at 8.12 pp, J = 8.92 Hz, is assigned to H_4 while the double doublet at 8.20, J = 8.92, 2.20 Hz, is assigned to H_5. The doublet at 8.37, J = 1.44 Hz, is assigned to $H_{2''}$ while the doublet at 8.43 ppm, J = 2.20 Hz, is assigned to H_7. The singlet at 10.57 ppm is assigned to the aldehydic proton.

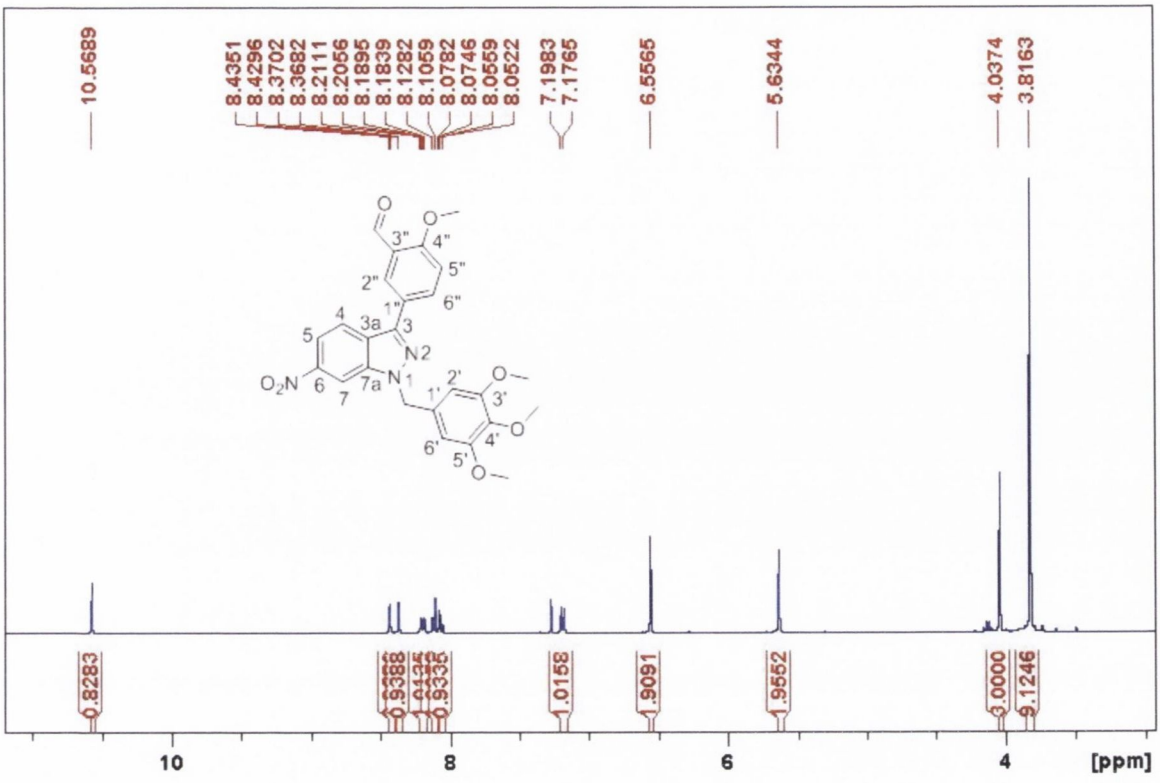


Figure 217: ^{1}H-NMR spectrum of (413)

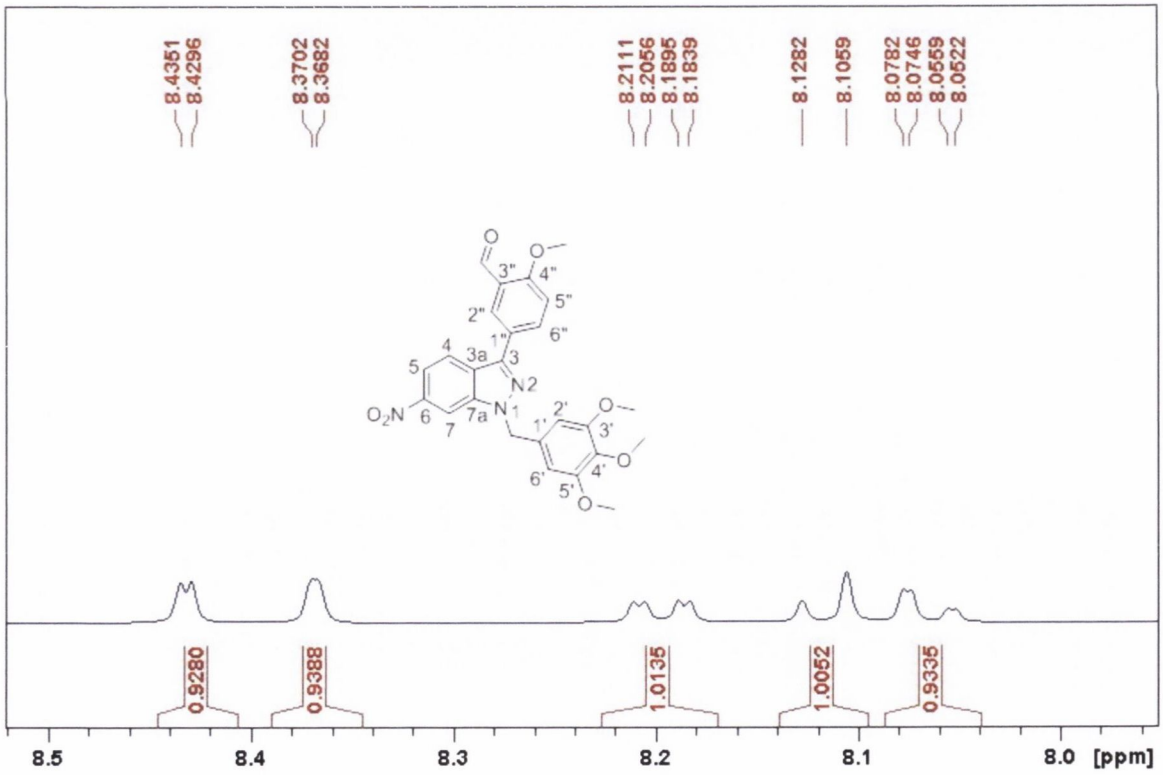


Figure 218: ^{1}H-NMR spectrum of (413) from 8.00 to 8.50 ppm

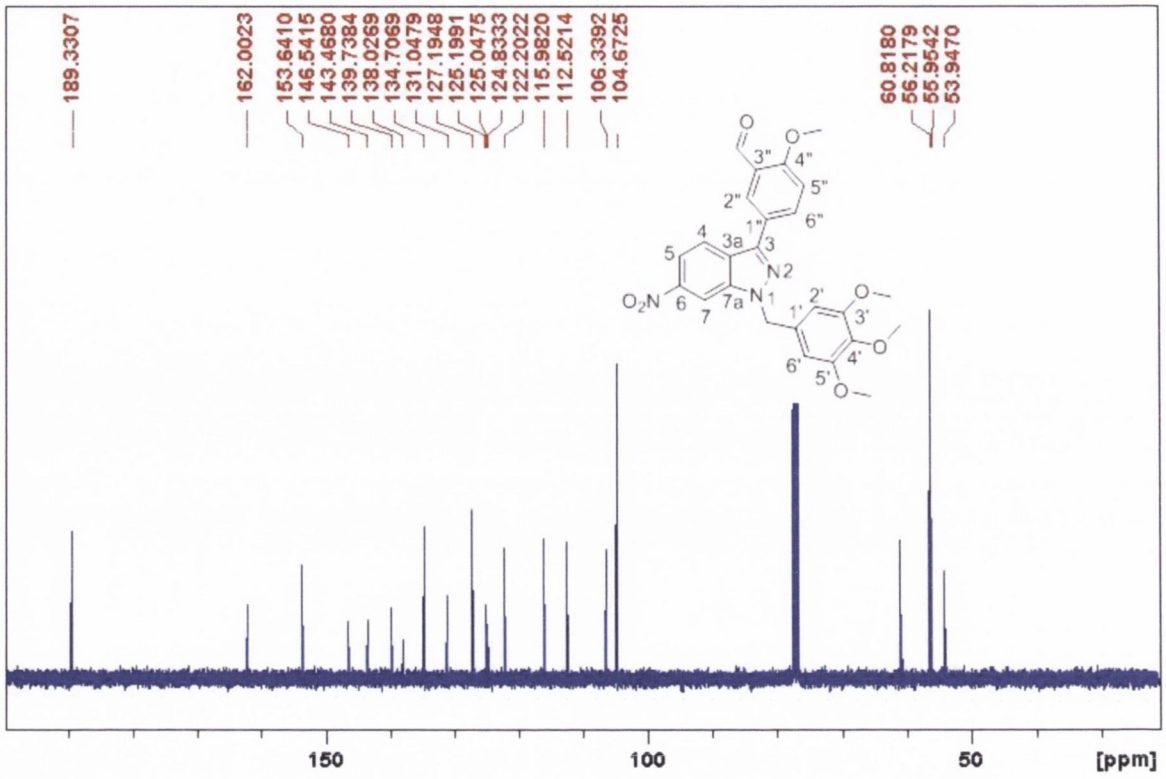


Figure 219: ^{13}C-NMR spectrum of (413)

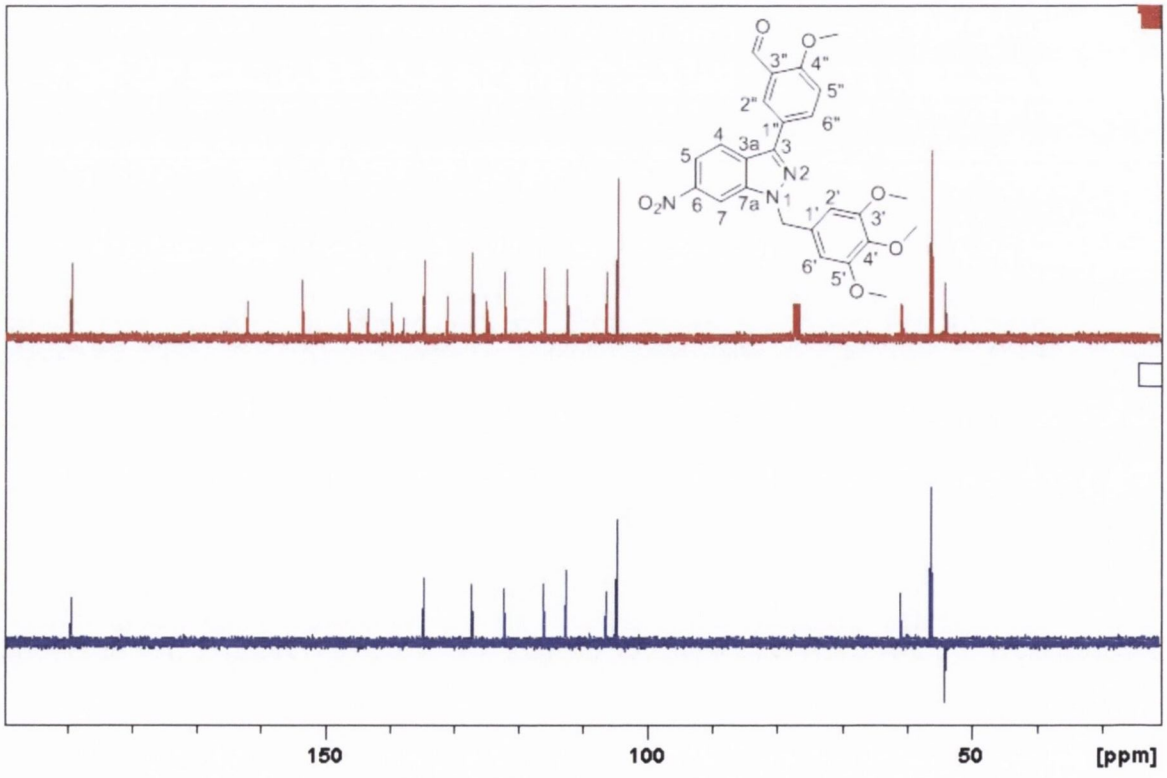
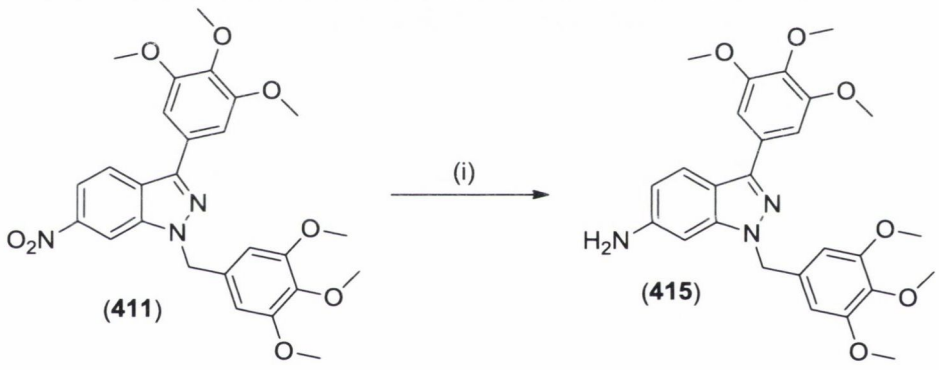


Figure 220: ^{13}C-NMR and DEPT 135 spectra of (413)

The ^{13}C-NMR and DEPT 135 spectra of (**413**) are shown in figures 219 and 220 respectively. The signal at 53.95 ppm corresponds to the methylene carbon. The signals at 55.95, 56.22 and 60.82 ppm correspond to the methoxy groups at $C_{2'}$& $C_{5'}$, $C_{4''}$ and $C_{4'}$. The signal at 104.67 ppm to the symmetric methine carbons $C_{2'}$ & $C_{6'}$. The signals at 112.52, 115.98, 122.20, 125.20 134.70 ppm are assigned to the aromatic methine carbons C_7, C_5, $C_{5''}$, $C_{6''}$, C_4 and $C_{2''}$ respectively. The signal at 189.33 is assigned to the aldehydic carbon. The signals 124.83, 125.05, 127.19, 131.05, 138.02, 139.74, 143.47, 146.54, 153.64 and 162.00 ppm are assigned to aromatic *ipso* carbons $C_{1''}$, $C_{3''}$, C_{3a}, $C_{1'}$, $C_{4'}$, C_{7a}, C_6, C_3, $C_{3'}$ & $C_{5'}$ and $C_{4''}$ respectively.

However the reduction (H_2, palladium on carbon) of the nitro group of the above indazoles proved quite difficult using the proven hydrogenation method. (**411**) was successfully reduced however purification by flash column chromatography over silica gel was required, figure 221. The same reaction conditions were applied to (**412**) and (**413**) but TLC analysis revealed that the reaction was not proceeding as a significant amount of starting material was still present.



(i) 10% Pd/C, H_2, 1:1 EtOAc: MeOH, 20 °C

Figure 221: Successful reduction of (411) affording (415)

2.8.3 Conclusion

In conclusion, a synthetic route for the efficient preparation of 1-benzoyl-3-aryl-6-aminoindazoles and 1-benzoyl-3-aryl-5-aminoindazoles has been described. The preparation of 3-arylindazole intermediates, for both of the 5- and 6-aminoindazoles, first required *N*-1 protection. The MEM and BOC protecting group were used successfully for the generation of 3-aryl-5-nitroindazoles (**389**), (**396**) and (**397**) while the generation of 3-aryl-6-nitroindazoles was only successful when the MEM protecting group (**385**) and (**404**) was used. When 3-arylation of N-1 BOC protected (**393**) was attempted, N-1 deprotection occurred and 3-arylation was not successful. An alternative approach to the synthesis of 3-aryl-6-nitroindazoles was attempted, figure 216, by first benzylating (**372**) with 5-(bromomethyl)-

1,2,3-trimethoxybenzene. The benzyl group enabled 3-arylation e.g. compounds (**410**) – (**414**) however reduction of the nitro group by hydrogenation was only successful for the preparation of (**415**) while the reduction of (**412**) and (**413**) did not proceed. It is not known why the hydrogenation was not successful as this method was used for similar compounds, (**259**) and (**262**) (see section 2.4). An alternative method of reduction e.g. zinc/acetic acid might be successful in reducing the nitro group in these compounds.

2.9 Preparation of 3-aminoindazoles

This section will describe the synthesis of analogues of the lead compound (**168**) which have amine substituents in the C-3 position. These N-substituted 3-aminoindazoles contain a C-N bond to the amine substituent at C-3 while still retaining the same structural features of the lead compound (**168**), figure 222.

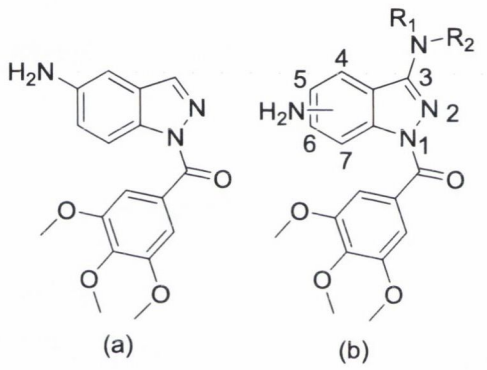
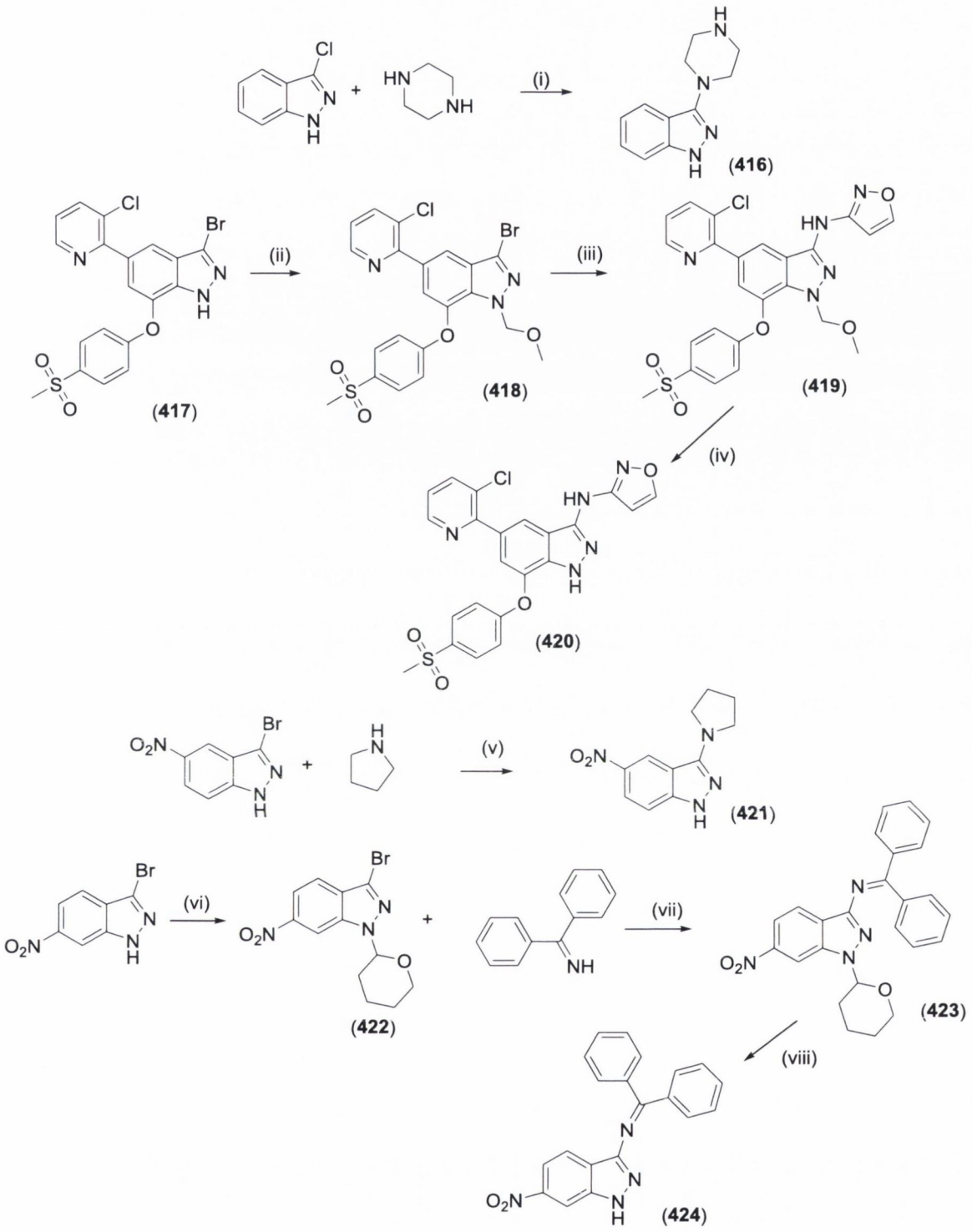


Figure 222: (a) Lead compound (168), (b) General structure of N-substituted 3-aminoindazoles

2.9.1 Introduction

Before the preparation of the specific 3-aminoindazoles contained in this chapter is described, the approaches to the synthesis of 3-aminoindazoles reported in the literature is briefly discussed, figure 223.



(i) 250 °C, 14 h[362] (ii) chloro(methoxy)methane, NaH, DMF, 0 °C (iii) isoxazol-3-amine , Cs_2CO_3, xantphos, $Pd_2(dba)_2$, dioxane, 100 °C (iv) HCl, 2h, 25 °C[363] (v) 87 °C, 40 h, sealed tube[364] (vi) EtOAc, PTSA, 3,4-dihydro-2*H*-pyrane, 80 °C (vii) diphenylmethanimine, xantphos, $Pd(OAc)_2$, dioxane, 100 °C (MAOS) (viii) Ethanolic HCl, 25 °C[365]

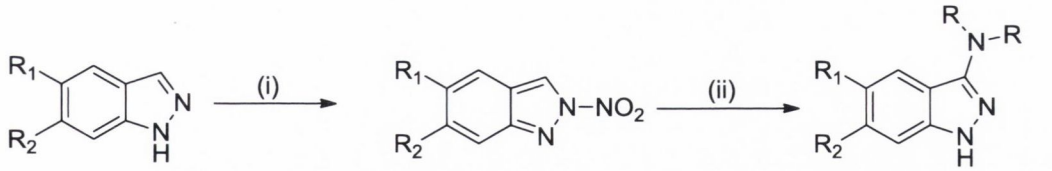
Figure 223: Synthesis of indazoles with amine substituents at the C-3

Cho et al prepared a series of phenylalkyl and pyridylalkyl piperazine derivatives as antagonists of dopamine D2 receptors and of serotonin 2A receptors. These compounds were investigated for the treatment of schizophrenia and other central nervous system disorders[362]. During the course of their work, *Cho et al* had treated 3-chloroindazole with piperazine, heating the mixture at 250 °C for 14 hours[362] to afford 3-piperazin-1-yl-1*H*-indazole (**416**) by nucleophilic substitution. *Yasuma et al* synthesised a series of indazole compounds for the treatment of diabetes and obesity[363]. The target of interest for these compounds was the glucose phosphorylating enzyme glucokinase[366]. Compound (**420**) was one of the subsequent indazole compounds prepared by *Yasuma et al*. Alkylation of (**417**) using chloro(methoxy)methane yielded the N-1 alkylated indazole (**418**). Using the Buchwald Hartwig amination reaction, (**418**) was reacted with isoxazol-3-amine yielding the indazole derivative (**419**). The N-1 alkyl substituent was removed with HCl to afford (**420**).

Cooper et al synthesised a series of indazole compounds designed to behave as extracellular signal induced regulated kinase (ERK) inhibitors[364]. Cellular processes such as proliferation, survival, differentiation and motility are mediated by the ERK signalling pathway. This pathway is often up-regulated in human tumours and as such is regarded as an attractive target for the development of anticancer drugs[367]. During the course of their work, *Cooper et al* treated 3-bromo-5-nitroindazole with pyrrolidine in a sealed tube for 40 hours. Upon work up of the reaction, 3-morpholine-4-yl-5-nitro-1*H*-indazole (**421**) was afforded. This procedure is similar for the synthesis of (**416**) by *Cho et al*. *Lohou et al* were investigating alternative methods for the synthesis of *N*-substituted 3-aminoindazoles[365]. Using (**424**) as an example, 3-bromo-6-nitroindazole was first protected using the tetrahydropyran-2-yl (THP) group yielding (**422**). In a Buchwald Hartwig amination reaction, (**422**) was coupled with diphenylmethanimine yielding the N-substituted 3-aminoindazole derivative (**423**) which was then treated with ethanolic HCl affording the deprotected indazole derivative (**424**).

2.9.2 Synthesis of N-substituted 3-aminoindazole derivatives from 5-nitroindazole and 6-nitroindazole

In the present work, the method chosen for the synthesis of *N*-substituted 3-aminoindazole derivatives from 5-nitroindazole and 6-nitroindazole first involved the nitration of 5-nitroindazole and 6-nitroindazole which yielded 2,5-dinitro-2*H*-indazole (**425**) and 2,6-dinitro-2*H*-indazole (**426**) respectively. These intermediates were isolated and then reacted with acyclic and cyclic amines forming products of the type (**A**) and (**B**) respectively[368, 369], figure 224.



(**169**) $R_1 = NO_2$, $R_2 = H$
(**170**) $R_1 = H$, $R_2 = NO_2$

(**425**) $R_1 = NO_2$, $R_2 = H$
(**426**) $R_1 = H$, $R_2 = NO_2$

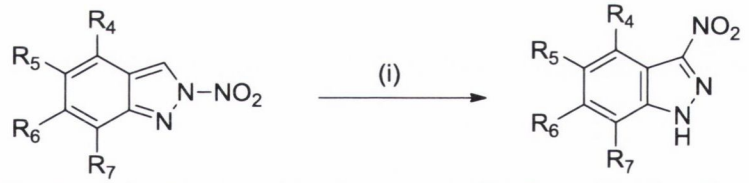
(**A**) $R_1 = NO_2$, $R_2 = H$
(**B**) $R_1 = H$, $R_2 = NO_2$

(i) HNO_3, $(CH_3CO)_2O$, CH_3COOH, -5°C (ii) Anhydrous THF, cyclic or acyclic amine, 0 °C

Figure 224: Synthesis of 5-nitroindazozle and 6-nitroindazoles with heterocylic substituents in the 3-position

2.9.3 Synthesis of 2,5-dinitro-2*H*-indazole (425) and 2,6-dinitro-2*H*-indazole (426)

Cohen-Fernandes el al reported a method for the nitration of indazole which afforded a mixture of 3-nitroindazole and 3,5-dinitroindazole[370]. This involved the treatment of a cold acetic acid solution of indazole, with nitric acid and acetic anhydride successively. When the same method was used on 5-nitroindazole (**169**), a mixture of 3,5-dinitroindazole (**430**) and 2,5-dinitro-2*H*-indazole (**425**) was reported. However for the nitration of 6-nitroindazole (**170**), only 3,6-dinitroindazole (**431**) was reported. For the nitration of 4-nitroindazole and 7-nitroindazole, only the *N*-nitro compounds, 2,4-dinitro-2*H*-indazole (**427**) and 2,7-dinitro-2*H*-indazole (**428**) respectively were reported. 2,6-Dinitro-2*H*-indazole (**426**) could be afforded if 6-nitroindazole is nitrated with acetylnitrate at room temperature in acetic acid. When the dinitro-2*H*-indazoles (**425**) – (**428**) were heated in anisole, they were converted into the corresponding 3-nitroindazole derivatives (**429**) – (**432**), see figure 225.



(**427**) $R_4 = NO_2$, $R_5 = R_6 = R_7 = H$
(**425**) $R_5 = NO_2$, $R_4 = R_6 = R_7 = H$
(**426**) $R_6 = NO_2$, $R_4 = R_5 = R_7 = H$
(**428**) $R_7 = NO_2$, $R_4 = R_5 = R_6 = H$

(**429**) $R_4 = NO_2$, $R_5 = R_6 = R_7 = H$
(**430**) $R_5 = NO_2$, $R_4 = R_6 = R_7 = H$
(**431**) $R_6 = NO_2$, $R_4 = R_5 = R_7 = H$
(**432**) $R_7 = NO_2$, $R_4 = R_5 = R_6 = H$

(i) Anisole, heat

Figure 225: Rearrangement of 2,X-dinitro-2H-indazoles into their corresponding 3,X-dinitroindazole derivatives

Cohen-Fernandes el al suggested that since acetic acid is weak acid, nitration will occur on the neutral molecule in a weak acid environment[370]. The most susceptible position in a neutral molecule for electrophilic attack is a nitrogen atom. This would explain the simultaneous formation of the N-nitro indazole derivative and the nitration in the 3 position, figure 226.

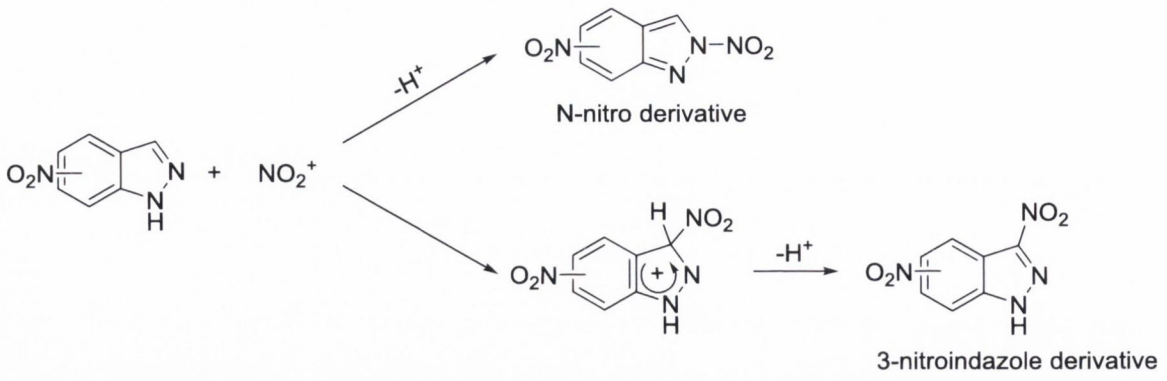
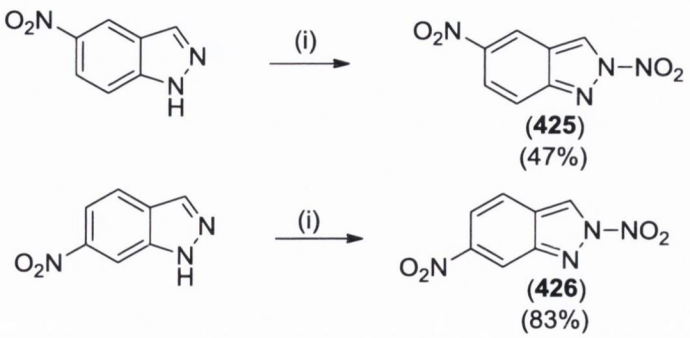


Figure 226: *N*-nitration of 2*H*-indazoles concurrent with the nitration on the 3 position

It was proposed that an attack of the free electron pair of a nitrogen atom of the neutral molecule on the NO_2^+ results in the N-nitration of indazoles. The resultant formation of a σ complex then may lead to the formation of a 3-nitroindazole derivative and direct loss of a proton from the adjacent nitrogen atom would result in the formation of the N-nitroindazole.

Alternative methods[369,371] for the synthesis of (**425**) and (**426**) have been developed and the method used by *Ronsheim et al* was used in this project. This method involved cooling a solution of nitric acid and acetic anhydride to -5 °C. To this solution, a suspension of 5-nitroindazole or 6-nitroindazole in acetic acid was added. The resultant solution was stirred at -5 °C for 5 minutes, then poured into ice and stirred for 30 minutes. The precipitate was collected by vacuum filtration. The precipitate contained unreacted starting material and it was purified using column chromatography affording the desired product, figure 227. Using this method, 2,5-dinitro-2*H*-indazole (**425**) and 2,6-dinitro-2*H*-indazole (**426**) were the only products afforded.



(i) HNO_3, $(CH_3CO)_2O$, CH_3COOH, -5 °C

Figure 227: Synthesis of (425) and (426)

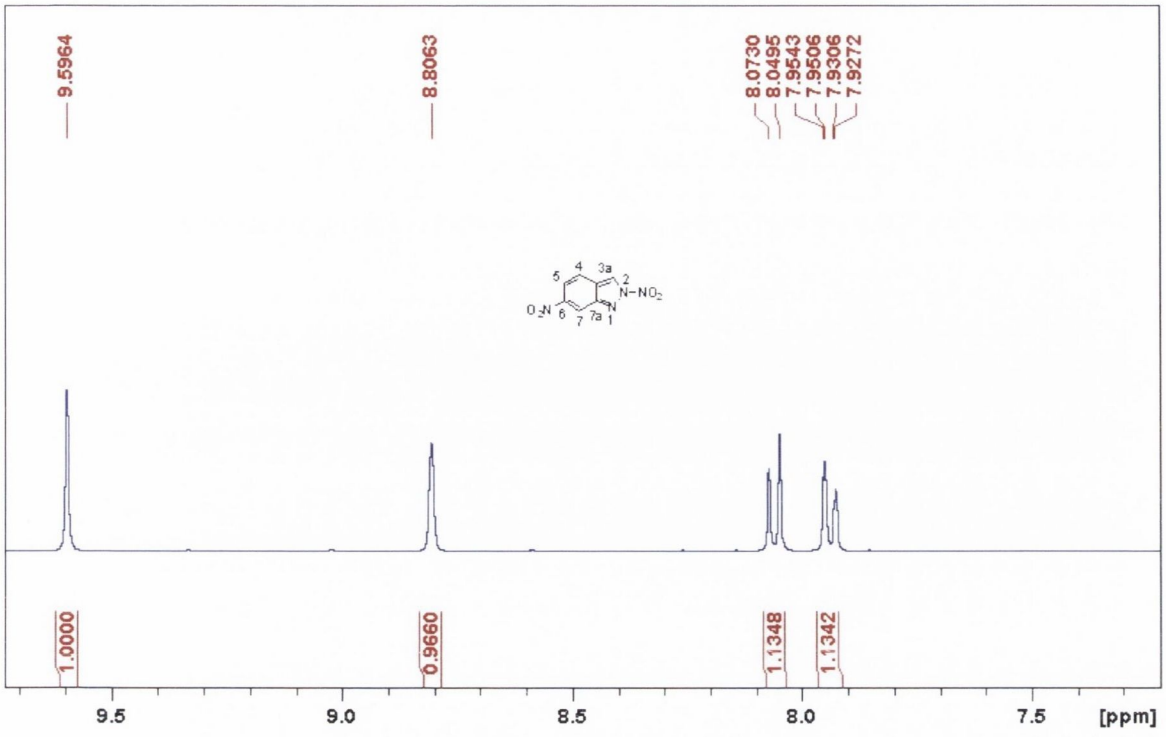


Figure 228: ^{1}H-NMR spectrum of (426)

The ^{1}H-NMR spectrum of (**426**) is shown in figure 228. The double doublet at 7.94 ppm, J = 9.40, 1.36 Hz, is assigned to H_5 while the doublet at 8.06 ppm, J = 9.40 Hz, is assigned to H_4. The singlet at 8.61 ppm is assigned to H_3 while the singlet at 9.60 ppm is assigned to H_7.

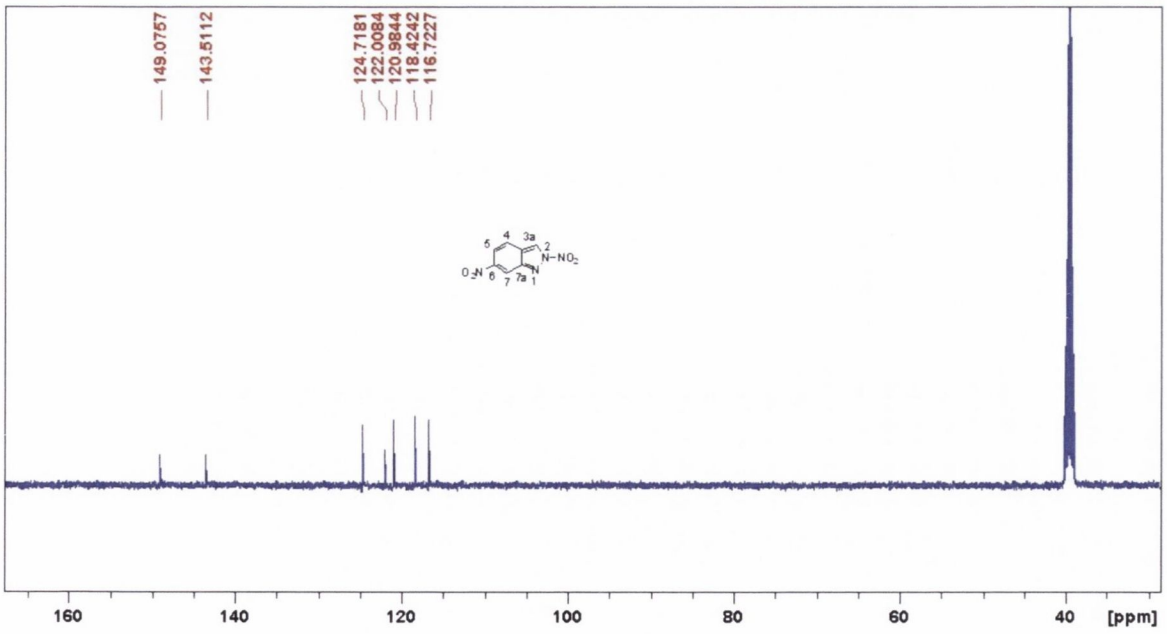


Figure 229: ^{13}C-NMR spectrum of (426)

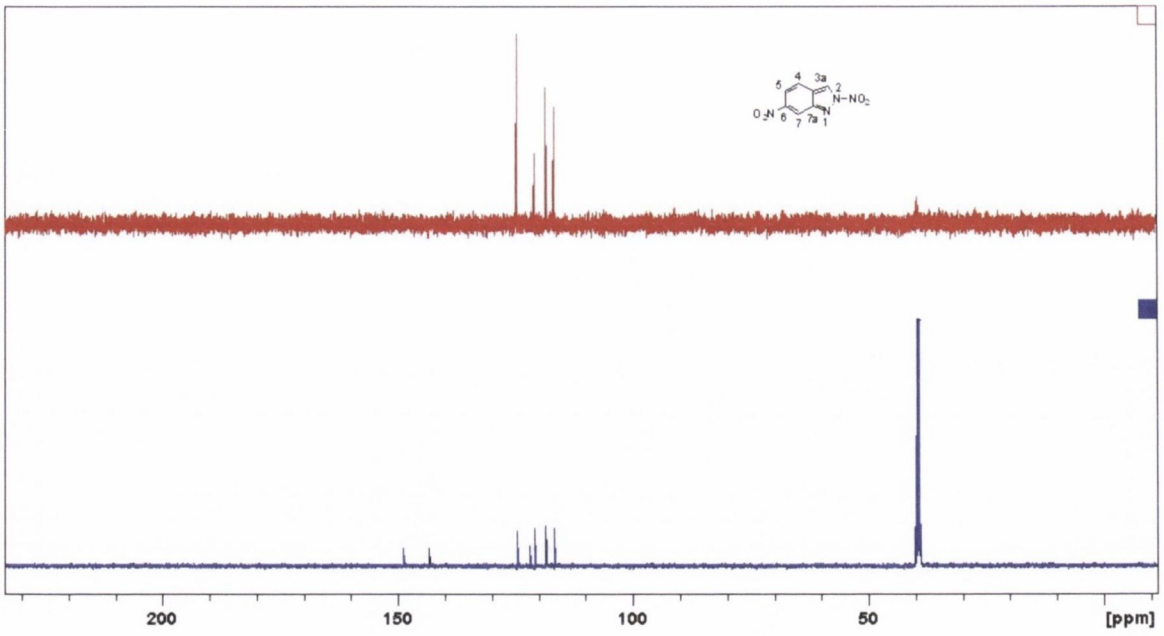


Figure 230: DEPT 90 and ^{13}C-NMR spectra of (426)

The ^{13}C-NMR and DEPT 90 spectra of (**426**) are shown in figures 229 and 230 respectively. The signals at 116.72, 118.42, 120.98 and 124.72 ppm are assigned to the aromatic methine carbons C_7, C_5, C_4 and C_3 respectively. The signals at 122.01, 143.51 and 149.08 ppm are assigned to the aromatic *ipso* carbons C_{3a}, C_{7a}, C_6 respectively.

2.9.4 Synthesis of *N*-substituted 3-aminoindazole derivatives from 2,5-dinitro-2*H*-indazole (425) and 2,6-dinitro-2*H*-indazole (426)

Wrzeciono et al first reported the synthesis of 5-nitro and 6-nitroindazole derivatives with heterocyclic substituents in the 3 position using (**425**) and (**426**) introducing a variety of cyclic amines[369]. The procedure developed by *Wrzeciono et al* was used exclusively in this project. A typical example is the synthesis of 3-morpholino-5-nitro-1*H*-indazole (**433**), figure 231. Typically a solution of (**425**) in anhydrous THF is reacted with morpholine at 0 °C to afford the product (**433**).

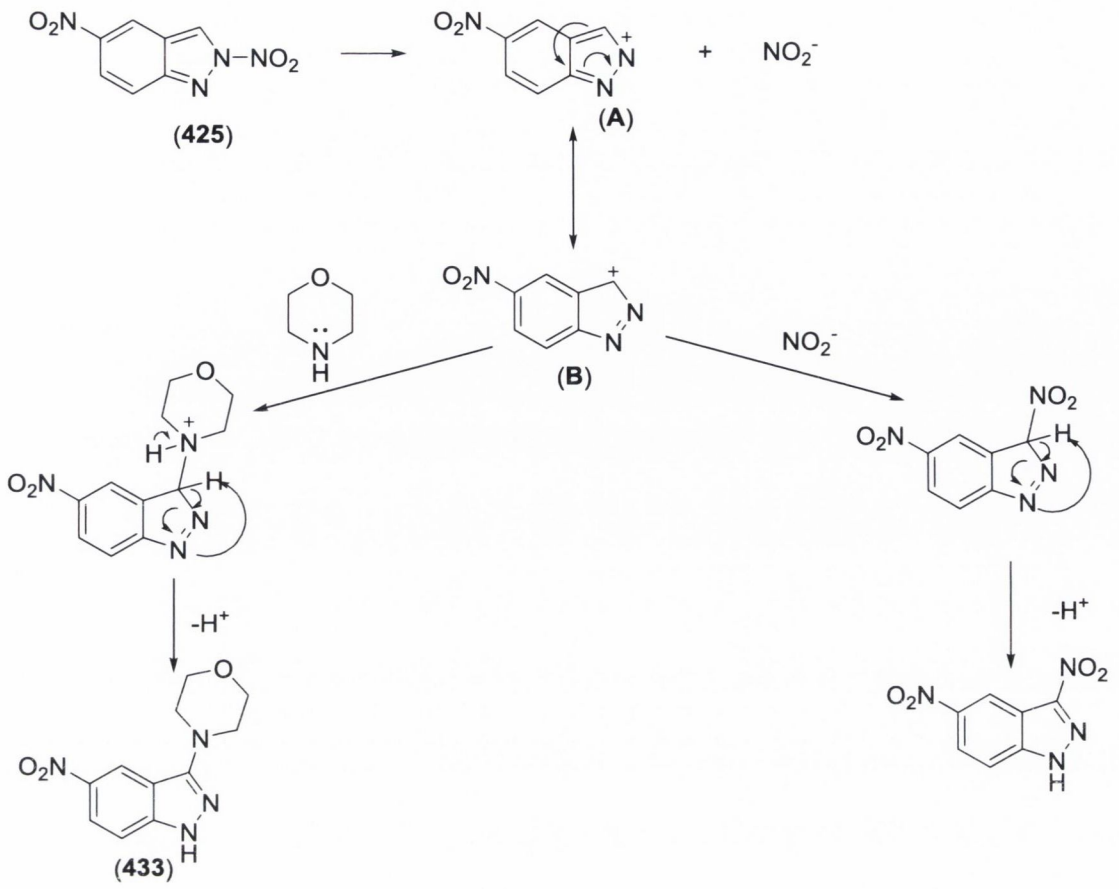
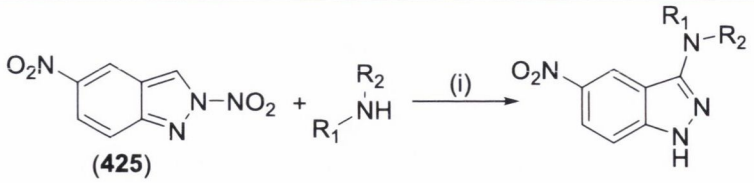


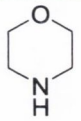
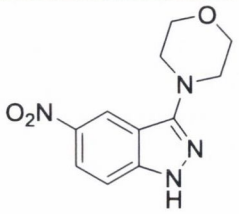
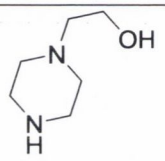
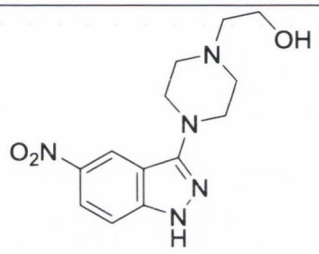
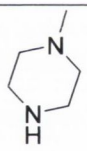
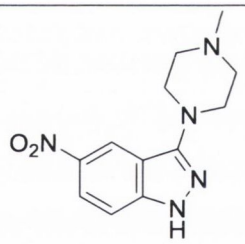
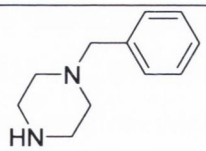
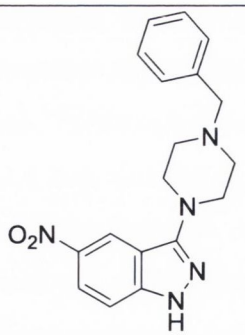
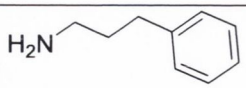
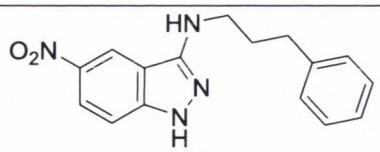
Figure 231: Synthesis of (433)

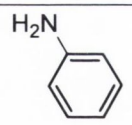
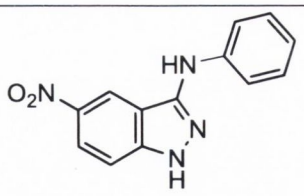
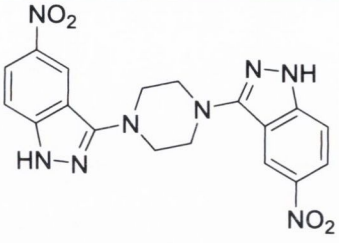
Wrzeciono et al also put forward the proposed mechanism for this reaction, figure 231. Using the synthesis of (**433**) as an example, (**425**) dissociates into (**A**) which then rearranges to (**B**). The 3-position of (**B**) is susceptible to nucleophilic attack as it bears a positive charge. Morpholine, with the lone pair of electrons on the nitrogen, attacks (**B**) in the 3-position and following a proton shift, (**433**) is afforded. It also noted that by *Wrzeciono et al* that such a reaction with either (**425**) and (**426**) with an amine should yield 3,5-dinitro-1*H*-indazole (**430**) and 3,6-dinitro-1*H*-indazole respectively (**431**)[369]. However in the similar reactions performed in this thesis, both 3,5-dinitro-1*H*-indazole and 3,6-dinitro-1*H*-indazole were not observed. Tables 29 and 30 contain the 5-nitro-3-aminoindazoles (**433**) – (**439**) and 6-nitro-3-aminoindazoles, (**442**) – (**447**) respectively, synthesised in this thesis following the reaction with the amines such as morpholine, piperazine, aniline and benzylamine.

Table 29: 5-Nitro-3-aminoindazoles

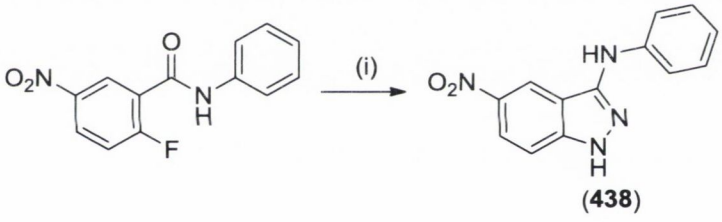


(i) Anhydrous THF, 0 °C, 2 h

Compound No.	Amine	Structure	IR ν_{max} cm^{-1} (NO_2)	% Yield
(**433**) [372]			1528.1, 1324.4	57
(**434**)*			1522.7, 1320.6	60
(**435**) [371]			1530.9, 1324.6	50
(**436**)*			1529.9, 1324.4	53
(**437**)*			1515.8, 1337.2	35

(**438**)[373]			1525.1, 1336.4	37
(**439**)*			1528.5, 1346.2	26

(**433**)[369] and (**435**)[371] were reported previously in the literature and both were synthesised from 2,5-dinitro-2*H*-indazole (**425**) while it was also reported that (**433**) could be synthesised by treating 3-bromo-5-nitroindazole with morpholine[364,372]. (**438**) was also reported previously in the literature but it was synthesised from the intramolecular cyclisation of 2-fluoro-5-nitro-*N*-phenylbenzamide using hydrazine monohydrate[373], figure 232.



(**438**)

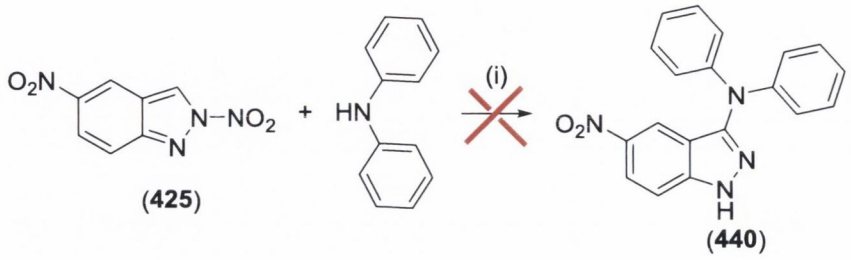
(i) N_2H_4-H_2O, EtOH, $POCl_3$, 50 °C

Figure 232: Synthesis of (22) from the intramolecular cyclisation of 2-fluoro-5-nitro-*N*-phenylbenzamide

Compounds (**433**) – (**436**) and (**439**) were obtained from cyclic secondary amines while (**437**) and (**438**) were synthesised from aromatic primary amines. When (**425**) was treated with piperazine, the novel di-substituted compound (**439**) was afforded. When (**425**) was treated 1-(2-hydroxyethyl)piperazine, the corresponding N-substituted 3-aminoindazole derivative (**434**) was afforded. Since the OH group of 1-(2-hydroxyethyl)piperazine could behave as a nucleophile, it was initially unclear what the structure of the resultant product would be. However the recovered product was analysed by infra spectroscopy, a broad OH band at 3325.24 cm^{-1} was present indicating that (**434**) was afforded rather the *O*-substituted product.

It should be noted that all acyclic and cyclic amines used in the preparation of the compounds in tables 29 and 30 were liquids. Diphenylamine is a solid at room temperature and so a

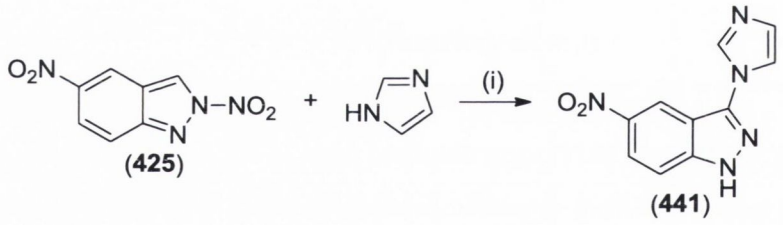
solution of diphenylamine was prepared in anhydrous THF and was added to (**425**) *via* a syringe and the reaction was performed using the general procedure, figure 233. But the corresponding N-substituted 3-aminoindazole derivative (**440**) was not obtained. Only unreacted (**425**) was recovered. Steric hindrance could have a factor in the failure if the reaction here.



(i) Anhydrous THF, 0 °C

Figure 233: 2,5-Dinitro-2*H*-indazole treated with diphenylamine

Upon reviewing the literature, *Ronsheim et al* reported the synthesis of 3-(1*H*-imidazol-1-yl)-5-nitro-1*H*-indazole[371] (**441**), figure 234. Their procedure for the synthesis of (**441**) differed considerably from anhydrous conditions that was used in this thesis in that it required that 2,5-dinitro-2*H*-indazole and imidazole, a solid at room temperature, to be stirred in DIW and THF at room temperature for 15 hours. This reaction was attempted using the quoted reaction conditions but the recovered product was too impure to be used.

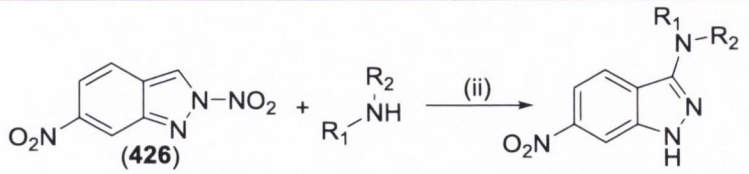


(i) DIW, THF, 25 °C[371]

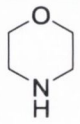
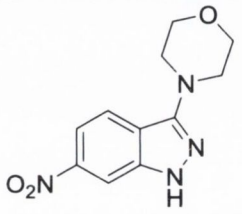
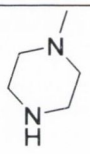
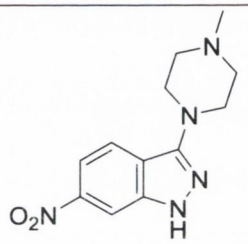
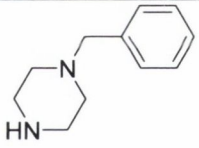
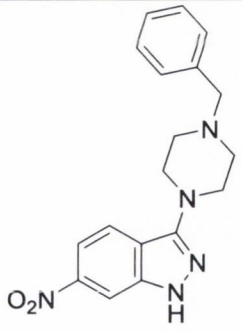
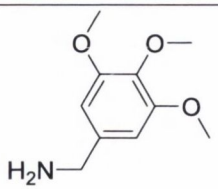
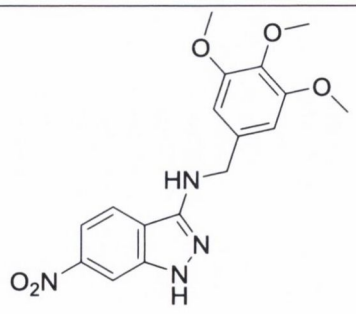
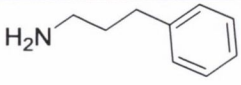
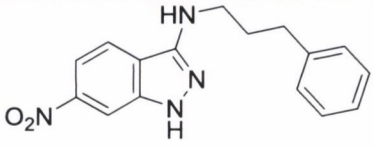
Figure 234: Synthesis of (441)

Table 30 contains the 6-nitro-3-aminoindazoles (**442**)-(**445**) that were prepared. The % yields are satisfactory (42%-72%). The preparation of 6-nitro analogues of (**437**) and (**438**) was attempted but the desired compounds (**446**) and (**447**) were not successfully synthesised.

Table 30: 6-Nitro-3-aminoindazoles



(i) Anhydrous THF, 0 °C, 2 h

Compound No.	Amine	Compound Structure	IR ν_{max} (KBr) cm^{-1} (NO_2)	% Yield
(**442**)*			1523.5, 1350.1	57
(**443**)[371]			1521.5, 1346.2	65
(**444**)*			1523.1, 1346.1	72
(**445**)*			1528.1, 1343.3	42
(**446**)			-----	0

(**447**)	H_2N	O_2N, HN, N, N, H	-----	0

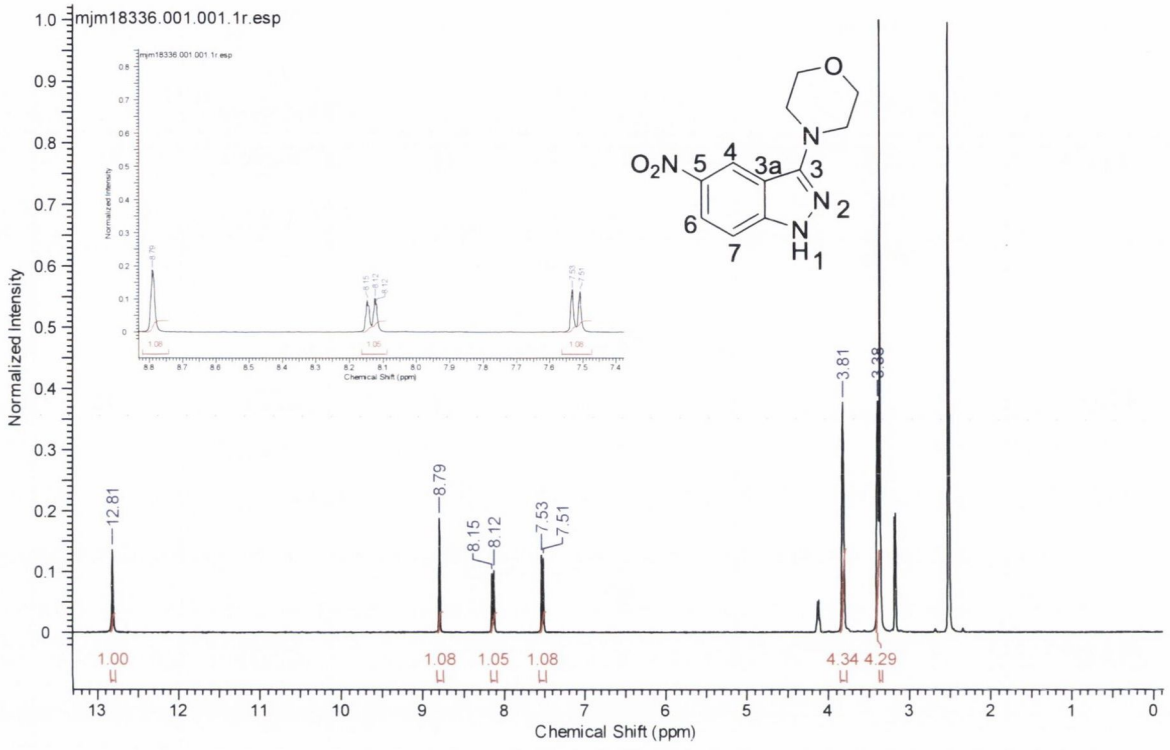


Figure 235: ^{1}H-NMR spectrum of (433)

As an example, the ^{1}H-NMR spectrum of the morpholine compound (**433**) is shown in figure 235. The broad singlet at 3.38 ppm is assigned to the two symmetric methylene groups adjacent to the nitrogen atom. The broad singlet at 3.81 ppm belongs to the other two symmetric groups which are adjacent to the oxygen atom. In this type of ring system, the protons on each methylene group of the morpholine ring are not identical, figure 236.

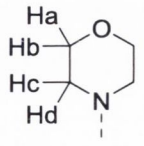


Figure 236: Labelling of the methylene protons in the morpholine ring for (433)

H_a will experience geminal coupling from H_b and vicinal coupling from both H_c and H_d. The splitting here would be complicated and the symmetric methylene groups both appear as broad singlets. The doublet at 7.52 ppm, $J = 9.20$ Hz, is assigned to H_7 while the double doublet at 8.13 ppm, $J = 9.20, 1.56$ Hz, is assigned to H_6. The singlet at 8.79 ppm corresponds to H_4 while the broad singlet at 12.81 ppm is corresponds to the NH.

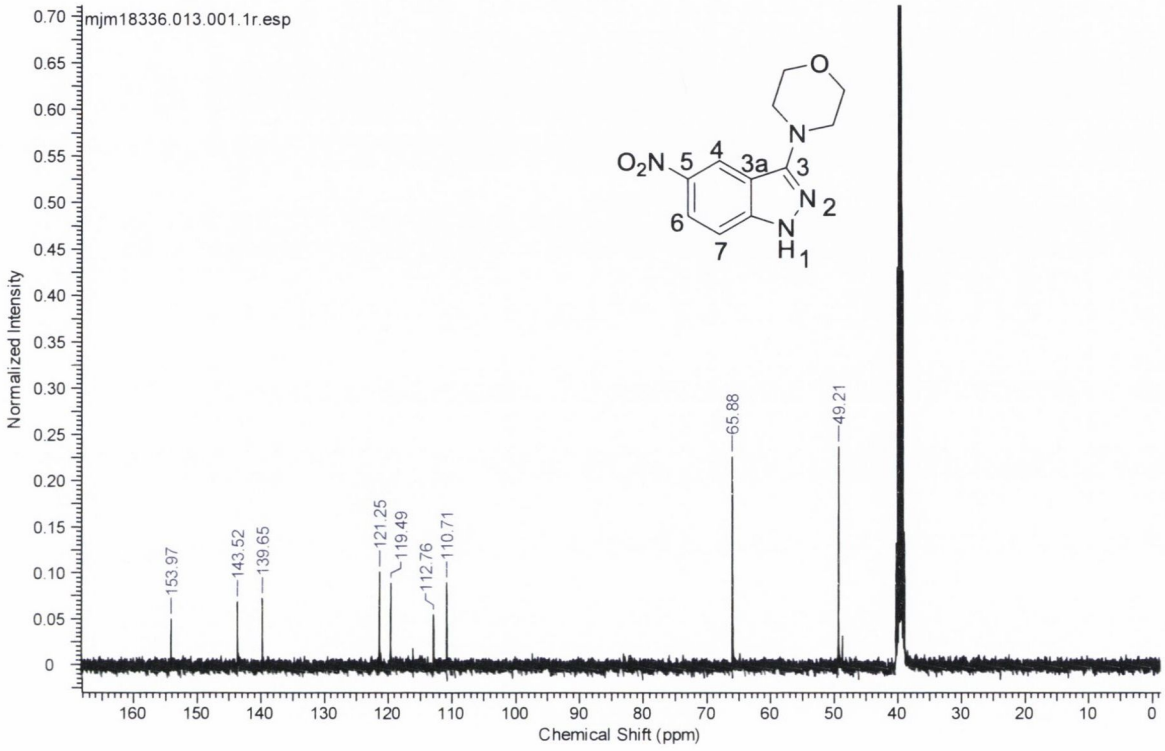


Figure 237: ^{13}C-NMR spectrum of (433)

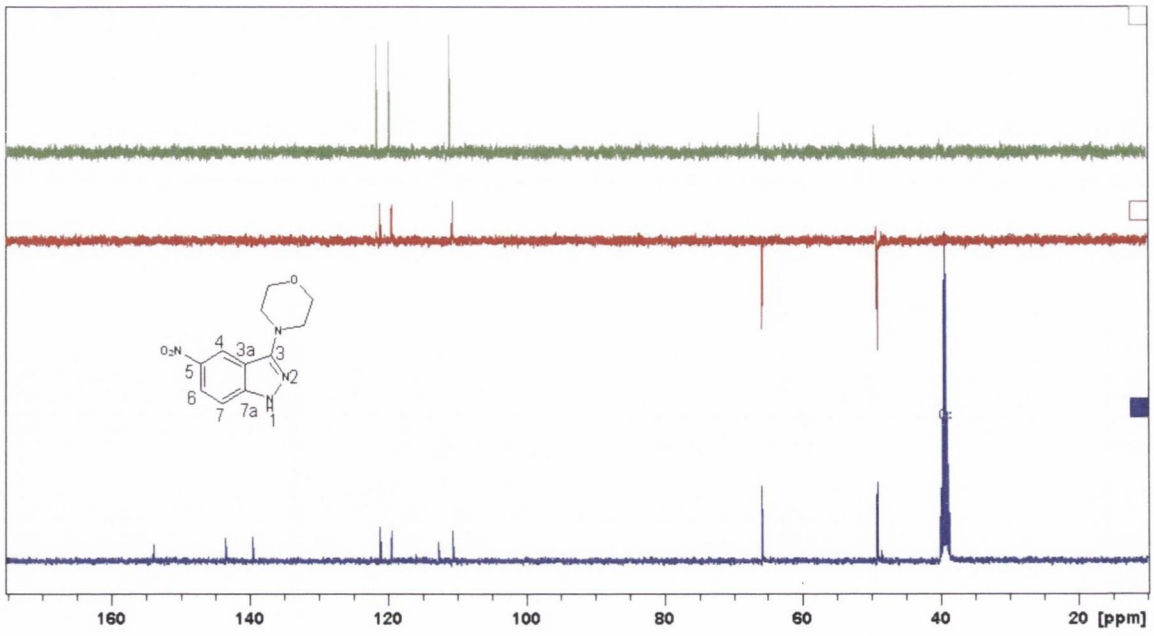
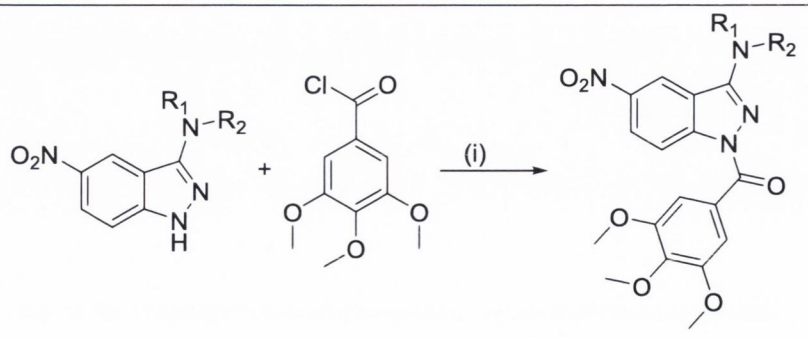


Figure 238: DEPT and ^{13}C-NMR spectra of (433)

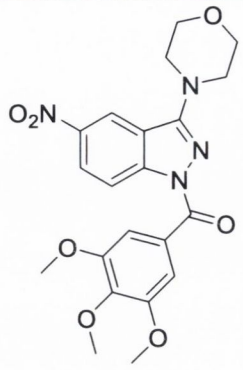
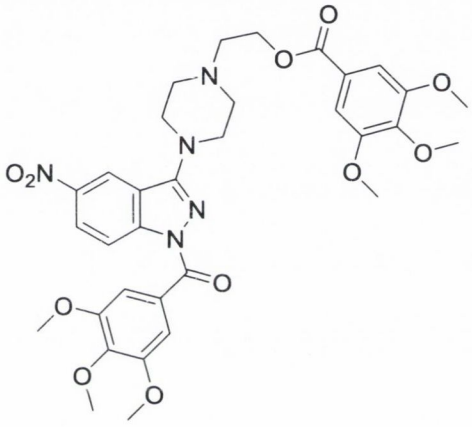
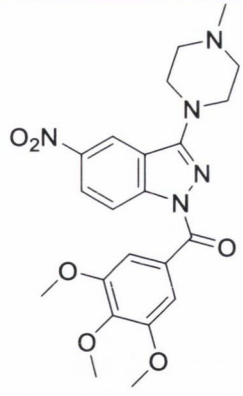
The ^{13}C-NMR and DEPT spectra of (**433**) are shown in figures 237 and 238 respectively. The signal at 49.21 ppm is assigned to the methylene carbons adjacent to the N atom while the signal at 65.87 ppm is assigned to the methylene carbons adjacent to the O atom. The signals at 110.71, 119.49 and 121.25 ppm are assigned to the aromatic methine carbons C_7, C_4 and C_6 respectively. The signals at 112.75, 139.65, 143.52 and 153.98 ppm are assigned to the aromatic *ipso* carbons C_{3a}, C_5, C_{7a} and C_3 respectively.

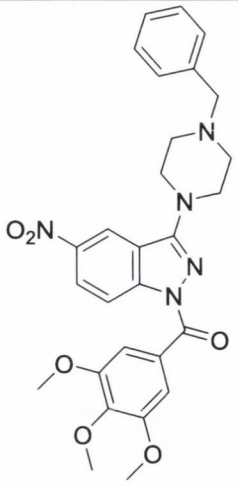
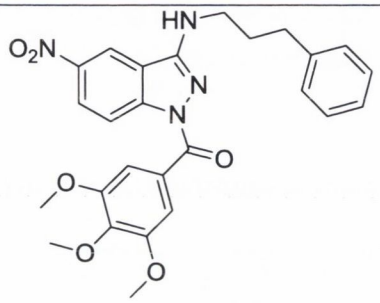
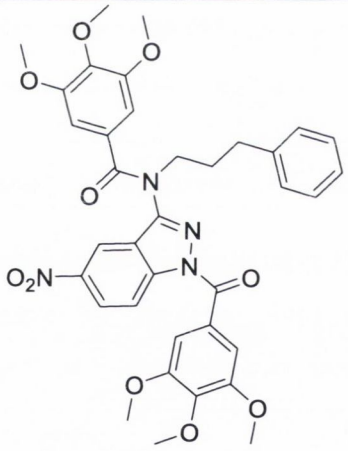
A selection of the 5-nitro-3-aminoindazole derivatives in table 29 (**433**) – (**438**) and the 6-nitro-3-aminoindazole derivatives in table 30 (**442**) – (**445**) were aroylated using 3,4,5-trimethoxybenzoyl chloride yielding N-1 aryl carbonyl compounds, table 31 (**448**) – (**453**) and table 32 (**454**) – (**457**).

Table 31: Aroylated 5-nitro-3-aminoindazoles



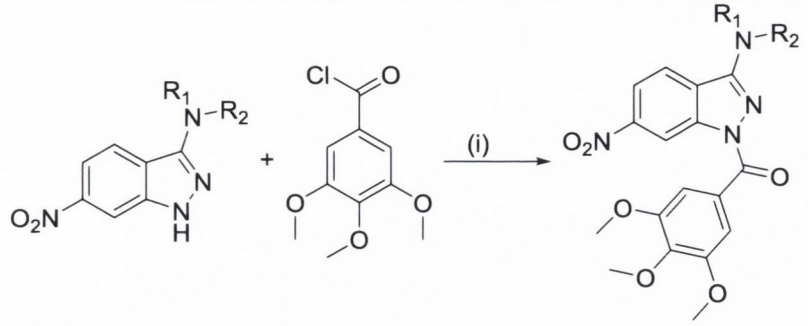
(i) Anhydrous CH_2Cl_2, Et_3N, reflux

Compound No.	Starting material	Structure	IR ν_{max} (NaCl film) cm^{-1} (C=O)	% Yield
(448)*	**(433)**		1685.65	68
(449)*	**(434)**		1667.9	50
(450)*	**(435)**		1687.0	40

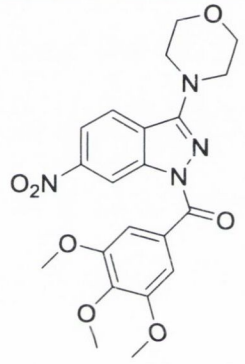
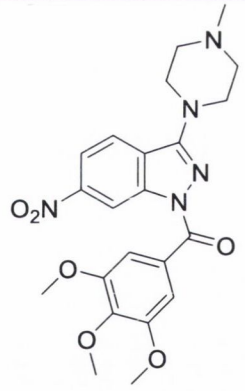
(**451**)*	(**436**)		1682.37	50
(**452**)*	(**437**)		1686.5	14
(**453**)*	(**437**)		1667.0	5

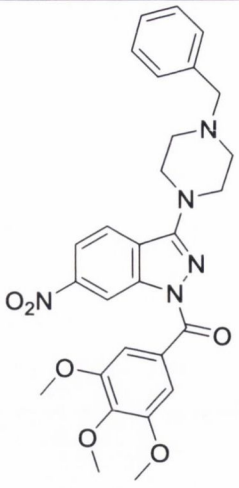
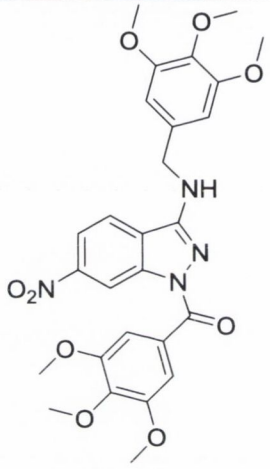
As seen from table 31, benzoylation of (**434**) yielded the di-trimethoxyphenyl substituted compound (**449**). The alcohol OH group of (**434**) readily reacts with the acid chloride yielding the corresponding ester product so the benzyolation of (**434**) was performed at 0 °C for 12 hours in order to limit ester formation. However due to the reactivity of acid chlorides, (**449**) was obtained in all attempts. Also the benzyolation of (**437**) produced the desired N-1 aryl carbonyl compound (**452**) in 14 % yielded together with the di-trimethoxyphenyl substituted compound (**453**) in 5 % yield. The benzyolation of (**445**) yielded only the desired N-1 aryl carbonyl compound (**457**), table 32.

Table 32: Aroylated 6-nitro-3-aminoindazoles



(i) Anhydrous CH_2Cl_2, Et_3N, reflux

Compound No.	Starting material	Structure	IR ν_{max} (NaCl film) cm^{-1} (C=O)	% Yield
(**454**)*	(**442**)		1678.6	36
(**455**)*	(**443**)		1666.7	41

(**456**)*	(**444**)		1666.9	50
(**457**)*	(**445**)		1681.4	39

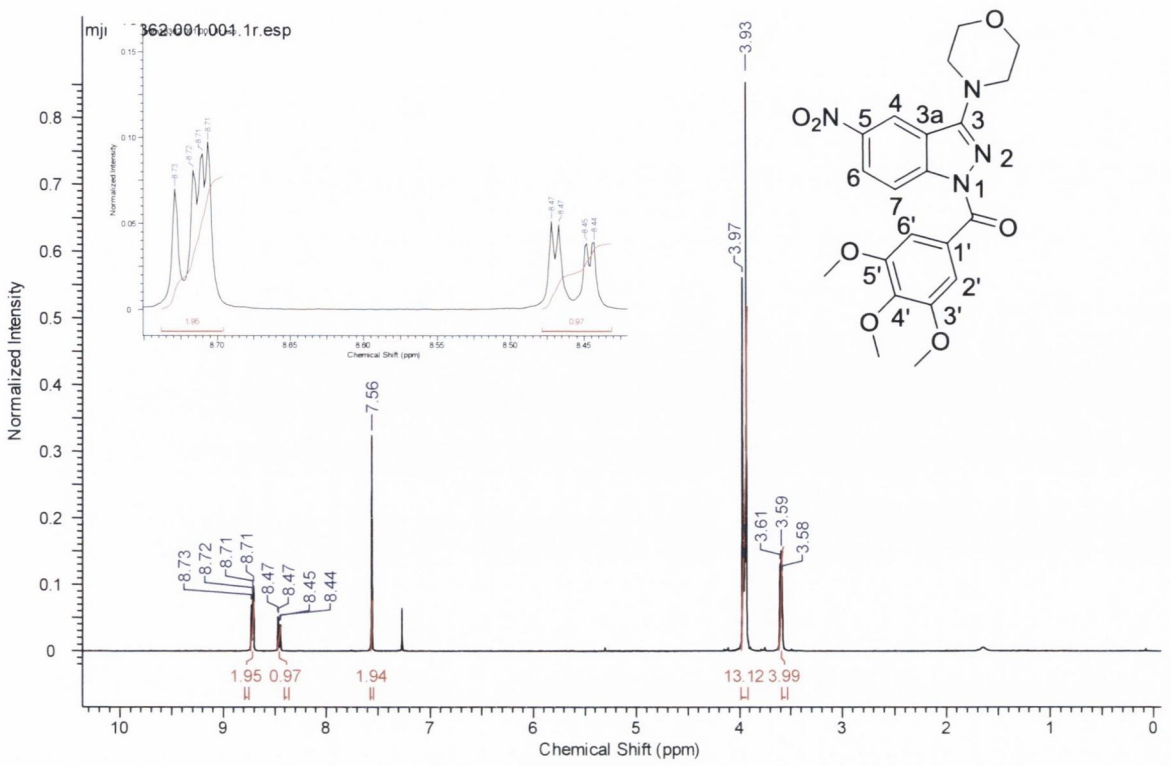


Figure 239: ^{1}H-NMR spectrum of (448)

As an example, the ^{1}H-NMR spectrum of (**448**) shown in figure 239 is now discussed. The multiplet from 3.58 ppm to 3.61 ppm is assigned to the morpholine symmetric methylene protons adjacent to nitrogen atom. The sharp singlet, which integrates for 6 protons, at 3.93 ppm is assigned to the two methoxy groups at $C_{3'}$ & $C_{5'}$. The singlet at 3.97 ppm corresponds to the methoxy group on the same aryl ring, *para* to the amide bond. The protons from the morpholine symmetric methylene groups adjacent to the oxygen atom overlap with these two singlets and hence the integration of 13 protons is observed. The singlet at 7.56 ppm is assigned to $H_{2'}$ and $H_{6'}$. The double doublet at 8.46 ppm, J = 9.32, 1.96 Hz, is assigned to H_6. The multiplet, integrating for 2 protons, from 8.71 to 8.73 ppm corresponds to H_4 and H_7.

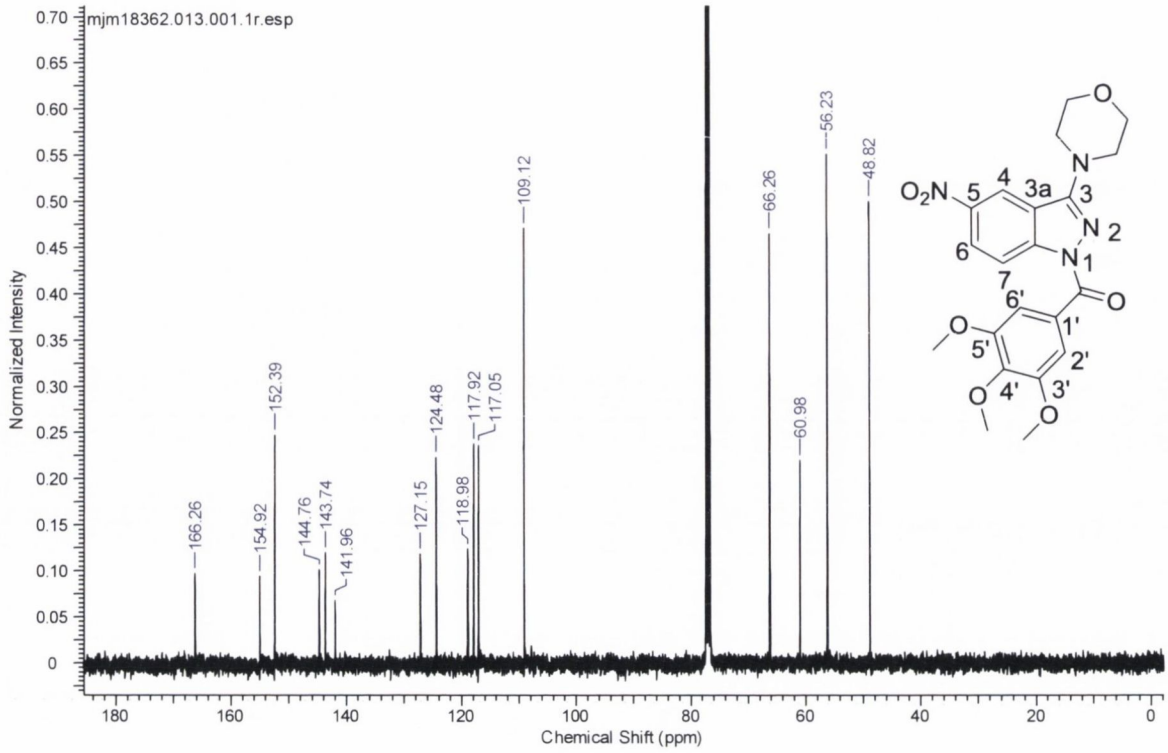


Figure 240: ^{13}C-NMR of (448)

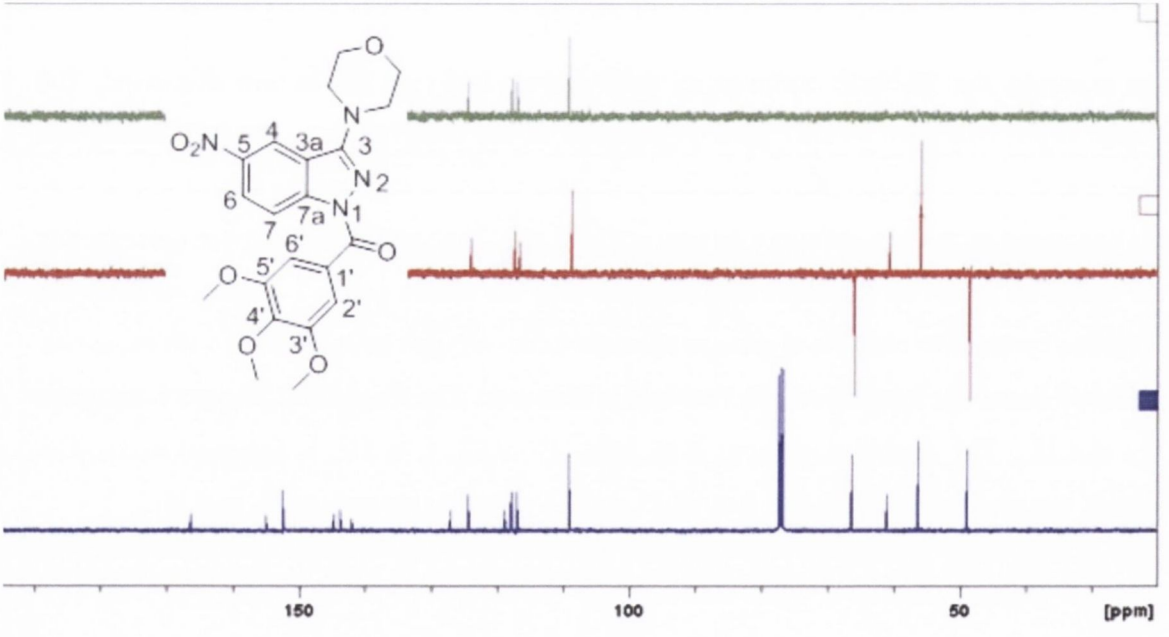


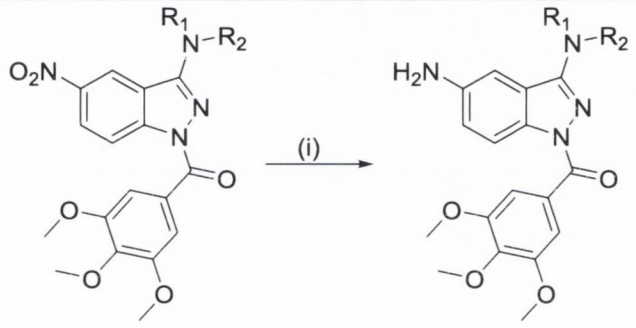
Figure 241: DEPT and ^{13}C-NMR spectra of (448)

The ^{13}C-NMR and DEPT spectra of (**448**) are shown in figures 240 and 241 respectively. The signals at 48.82 ppm and 66.26 ppm are assigned to the morpholine methylene carbons adjacent to the nitrogen atom and oxygen atom respectively. The signal at 56.23 ppm corresponds to the carbons of the two symmetric methoxy groups at $C_{3'}$ and $C_{5'}$. The signal at 60.98 ppm is

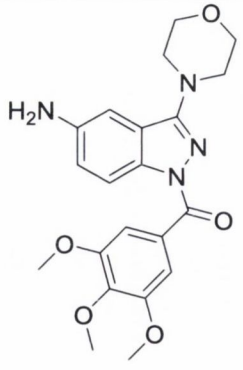
assigned to the methoxy carbon at $C_{4'}$. The signal at 109.12 ppm is assigned to $C_{2'}$ and $C_{6'}$. The signals at 117.05, 117.92 and 124.48 ppm are assigned to aromatic methine carbons C_7, C_4 and C_6. The signal at 166.27 ppm corresponds to the carbonyl carbon. The signals at 109.12, 118.98, 127.16, 141.96, 143.74, 144.76, 152.40 and 154.93 ppm correspond to the aromatic *ipso* carbons C_{3a}, $C_{1'}$, C_5, $C_{4'}$, C_{7a}, $C_{3'}$ & $C_{5'}$ and C_3 respectively.

The nitro substituted indazoles (**448**) – (**452**) and (**454**) – (**457**) were reduced to the corresponding aminoindazole products (**458**) – (**462**) and (**463**) – (**466**) using the heterogeneous catalysis method of 10 % palladium on carbon and hydrogen. The recovered aminoindazoles were obtained in satisfactory yield of up to 96 %.

Table 33: 5-Amino-3-aminoindazoles



(i) EtOAc:MeOH, 10% Pd/C, 20 °C

Compound No.	Starting material	Structure	IR ν_{max} (KBr) cm^{-1} (NH_2)	% Yield
(458)*	**(448)**		3450.6, 3362.8	93

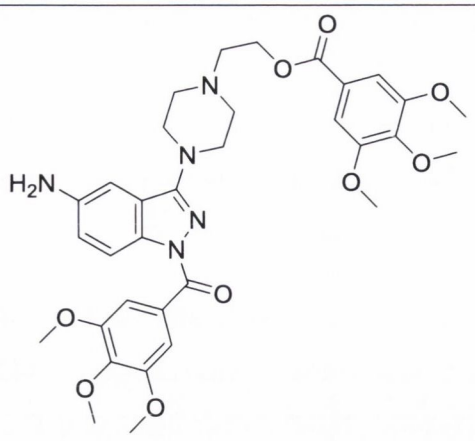
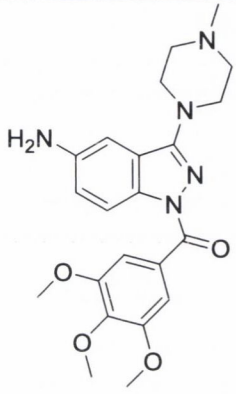
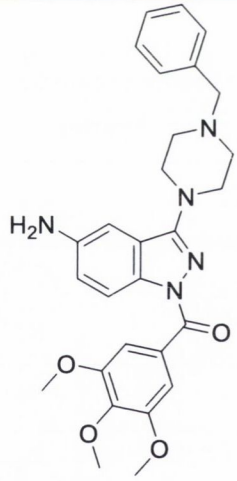
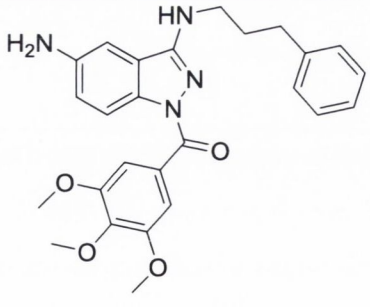
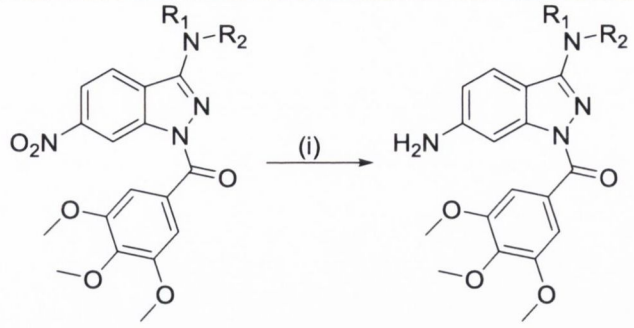
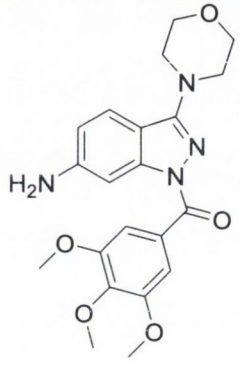
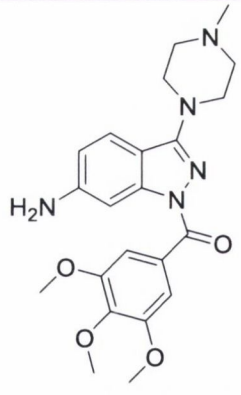
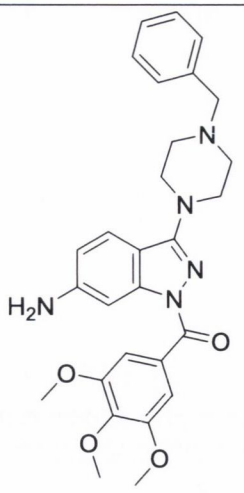
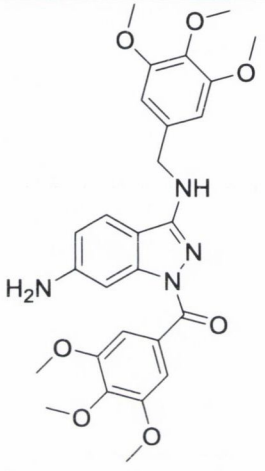
(**459**)*	(**449**)		3458.1, 3367.4	85
(**460**)*	(**450**)		3457.2, 3357.1	90
(**461**)*	(**451**)		3448.3 3362.7	89
(**462**)*	(**452**)		3457.2, 3367.9	96

Table 34: 6-Amino-3-aminoindazoles



(iv) 1:1 EtOAc:MeOH, 10% Pd/C, 20 °C

Compound No.	Starting material	Structure	IR ν_{max} (KBr) cm^{-1} (NH_2)	% Yield
(463)*	**(454)**		3457.81, 3365.54	72
(464)*	**(455)**		3456.7, 3371.1	86

(465)*	**(456)**		3462.0, 3374.4	87
(466)	**(457)**		3453.2, 3367.5	90

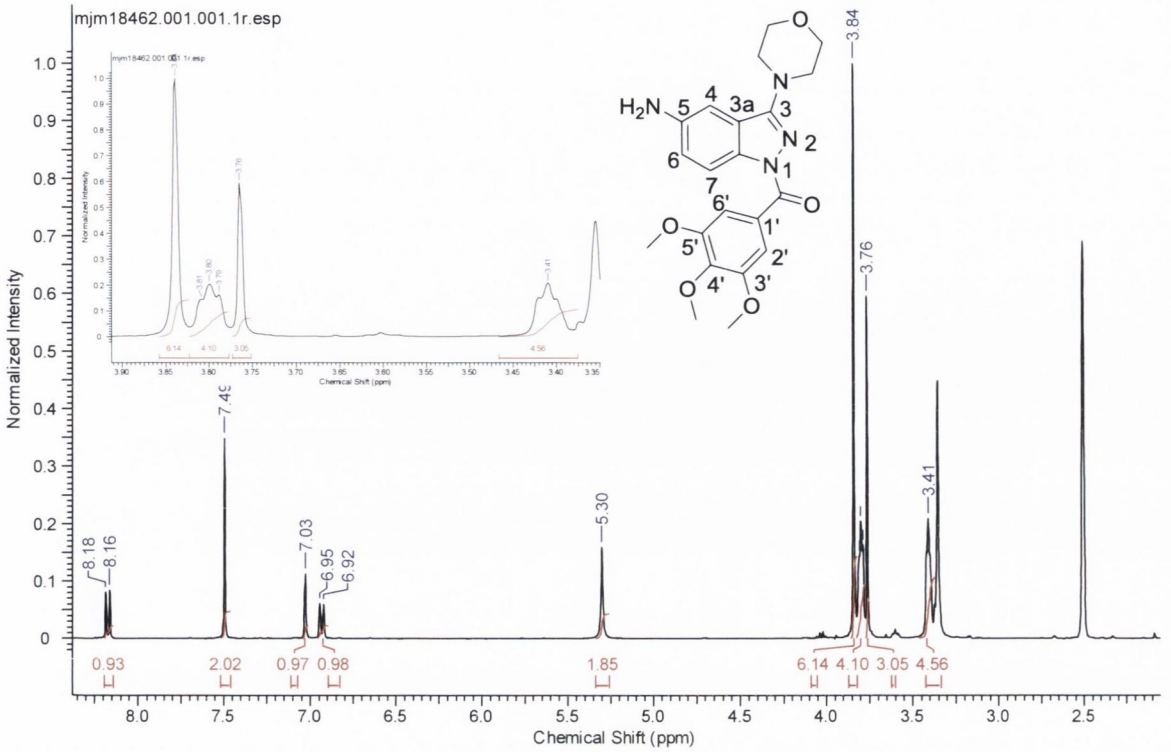


Figure 242: ^{1}H-NMR spectrum of (458)

The ^{1}H-NMR spectrum of the 3-morpholine product (**458**) is shown in figure 242. The multiplet from 3.40 ppm to 3.42 ppm is assigned to the protons of the symmetric methylene groups adjacent to the nitrogen atom. The singlet at 3.76 ppm corresponds to the methoxy group protons at $C_{4'}$ on the aryl ring, at $C_{3'}$ & $C_{5'}$. The sharp singlet at 3.84 ppm, which integrates for 6, is assigned to the protons of the two methoxy groups at $C_{3'}$ and $C_{5'}$. The multiplet from 3.79 ppm to 3.81 ppm is assigned to the morpholine protons of the symmetric methylene groups adjacent to the oxygen atom. The broad singlet at 5.30 ppm is aassigned to the amine group. The doublet at 6.93 ppm, J = 8.92 Hz, corresponds to H_6 while the singlet at 7.03 ppm is assigned to H_4. These protons more up-field than H_7 since they are more shielded due to their proximity to the amine. The singlet at 7.49 ppm corresponds to the symmetric aromatic protons $H_{2'}$ and $H_{6'}$ while the doublet at 8.17 ppm, J = 8.92 Hz, is assigned to H_7.

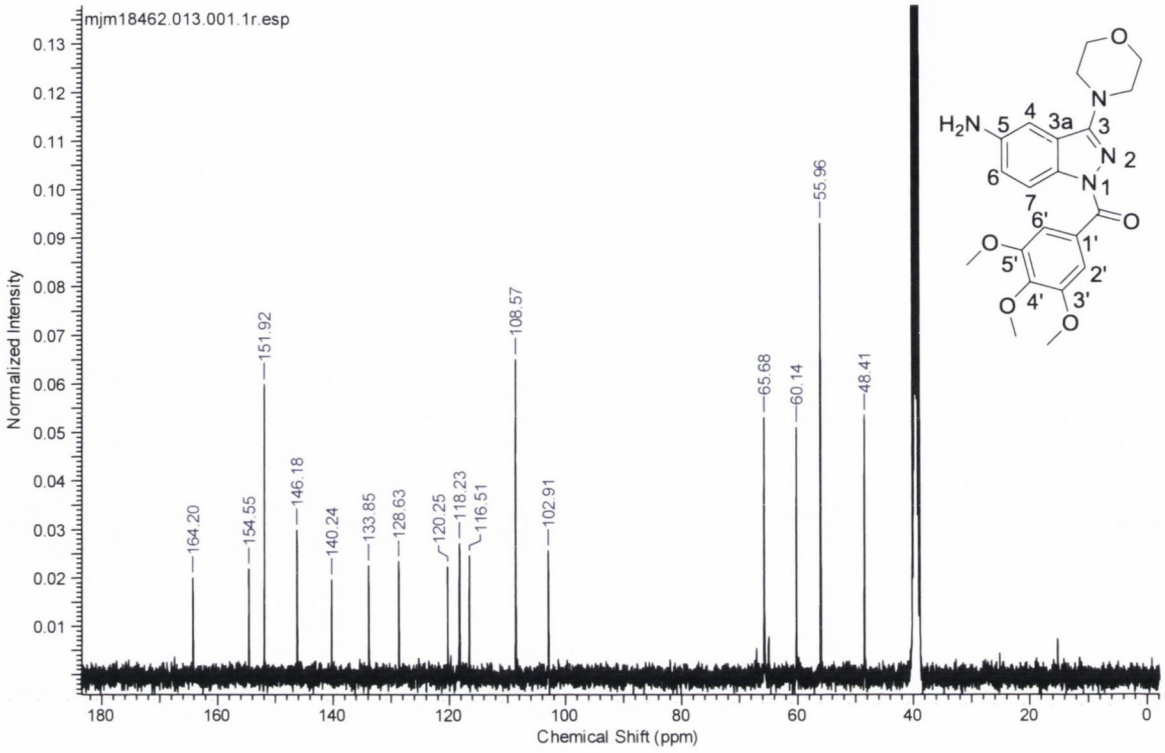


Figure 243: ^{13}C-NMR spectrum of (458)

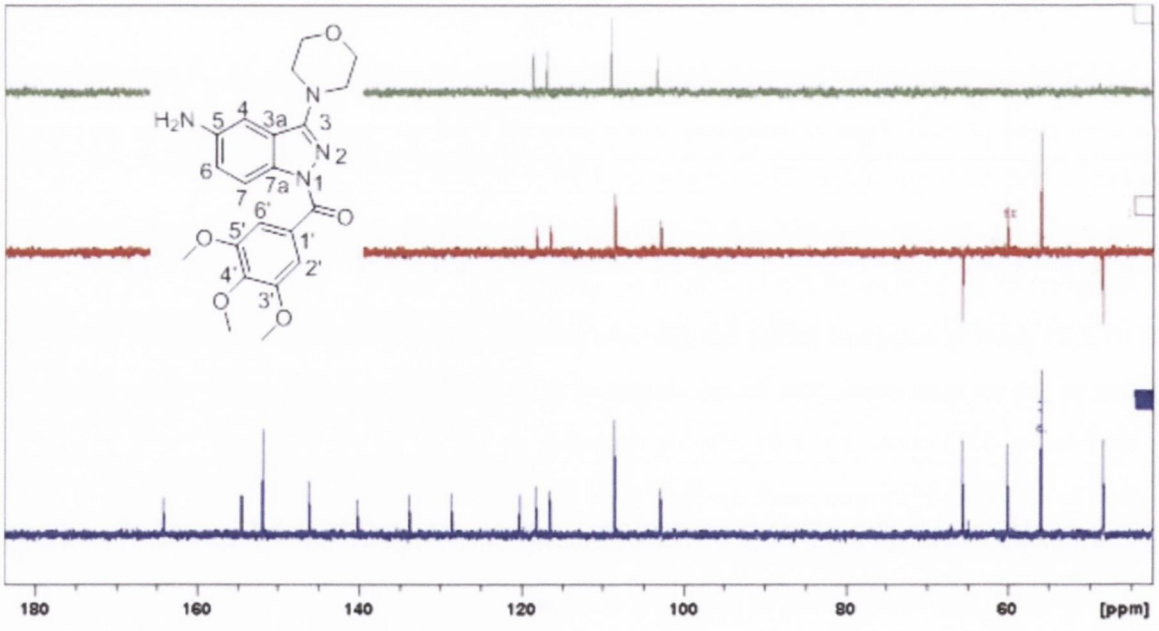


Figure 244: DEPT and ^{13}C-NMR spectra of (458)

The ^{13}C-NMR and DEPT 90 spectra of (**458**) are shown in figures 243 and 244 respectively. The signals at 48.41 ppm and 65.68 ppm correspond to the morpholine carbons of the methylene groups adjacent to the nitrogen atom and oxygen atom respectively. The signal at 55.95 is assigned to the methoxy carbon groups at $C_{4'}$ while the signal at 60.14 ppm

corresponds to the carbons of the symmetric methoxy groups at $C_{3'}$ and $C_{5'}$. The signal at 108.47 ppm is assigned to the aromatic methine carbons at $C_{2'}$ and $C_{5'}$ while the signals at 102.91, 116.52 and 118.24 ppm correspond to C_4, C_7 and C_6 respectively. The signal at 164.20 ppm is assigned to the carbonyl while the signal at 152.37 ppm belongs to the aromatic *ipso* carbons *meta* to the amide bond, attached to the methoxy groups at $C_{3'}$ & $C_{5'}$. The remaining signals correspond to the other aromatic *ipso* carbons.

In conclusion, a total of nine indazoles containing a secondary or tertiary amine substituent at C-3 were prepared using a four step synthetic route. Theses indazoles contain different heterocyclic rings at the C-3 position of the indazole ring. The heterocyclic rings include a morpholine e.g. (**463**), a 4-methylpiperazine e.g. (**455**) and a 4-benzylpiperazine e.g. (**450**).

The required synthetic steps were relatively straightforward and the yield for each was quite satisfactory (23 – 98%). It was shown that, in the case of the reaction of (**425**) with 1-(2-hydroxyethyl)piperazine, the N-substituted 5-nitro-3-aminoindazole (**434**) was afforded in preference to the O-substituted product. However benzoylation of (**434**) afforded the di-trimethoxyphenyl compound (**449**). It could be possible to react (**425**) with 1-(2-(benzyloxy)ethyl)piperazine, the OH benzyl protected analogue of 1-(2-hydroxyethyl)piperazine), benzoylate the corresponding the *N*-substituted 5-nitro-3-aminoindazole and reduce the indazole nitro group and simultaneously obtain the required alcohol product by debenzylation by hydrogenation.

All the acyclic and cyclic amines that were successfully used in the amination reactions (step 2) were liquids. Two amines which were solid at room temperature, diphenylamine and imidazole, were reacted with (**425**). The preparation of the 5-nitro-aminoindazole (**440**), when diphenylamine was used (see figure 233), was not successful while imidazole did generate the desired 5-nitro-aminoindazole (**441**). However the recovered product was quite impure.

2.10 Indazoles substituted with heterocycles at C-5 and C-6

In section 2.7, analogues of the lead compound (**168**) were prepared by modification of the C-5 amine substituent. This approach was investigated as it is known that some primary aromatic amines can be transformed into toxic metabolites. The chemical modification of the amine substituent is also the focus of this section which will describe the transformation of the amine substituent in the lead compound (**168**), or related analogues, into various heterocyclic substituents such as pyrrole and pyridone. Examples of indazoles with *N*-substituted heterocyclic substituents at C-5 and C-6 include (**467**)[375], (**468**)[376], (**469**)[377] and (**470**)[378] and their corresponding therapeutic application are shown in figure 245.

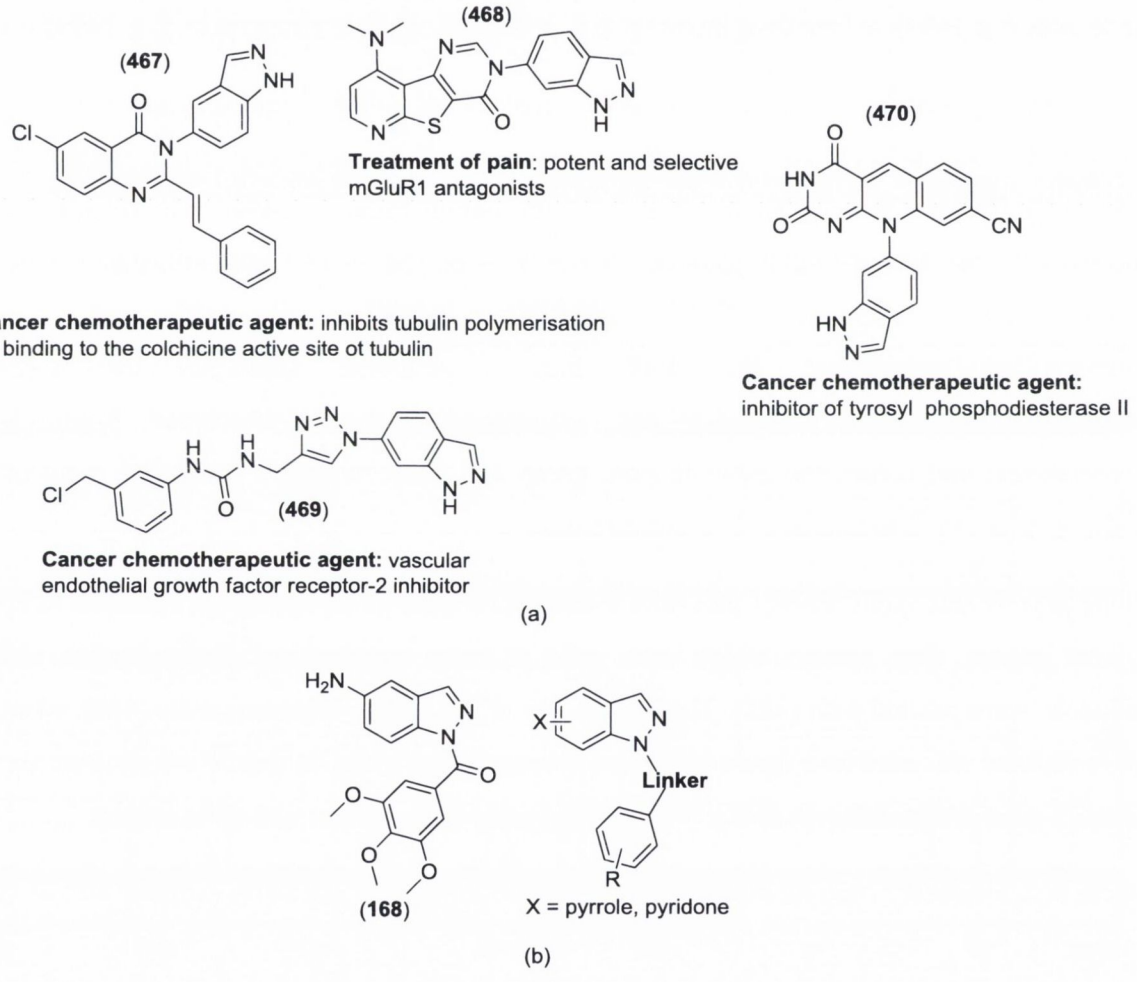


Figure 245: (a) Indazoles with 5- and 6- heterocyclic substiteunts (b) Lead compound (168) and general structure of indazoles with 5- and 6- heterocyclic substituents prepared in this thesis

2.10.1 Naturally occurring and synthetic pyrroles

In this thesis, one of the methods investigated involving transformation of the indazole C-5 and C-6 primary amine substituent was the Clauson-Kass pyrrole synthesis. The conversion of the amine into a pyrrole not only eliminates the toxicity associated with primary aromatic amines

but pyrrole itself is an important heterocycle. The pyrrole motiety is found in numerous natural products such as Ageladine A[379], Routiennoin[380], Rhazinilian[381], Indanoycin[382] and Halitulin[383], figure 246. The pyrrole moiety can also be found in numerous synthetic molecules of biological and pharmaceutical interest (**471**)[384], (**472**)[385], (**473**)[386] and (**474**)[387], figure 247.

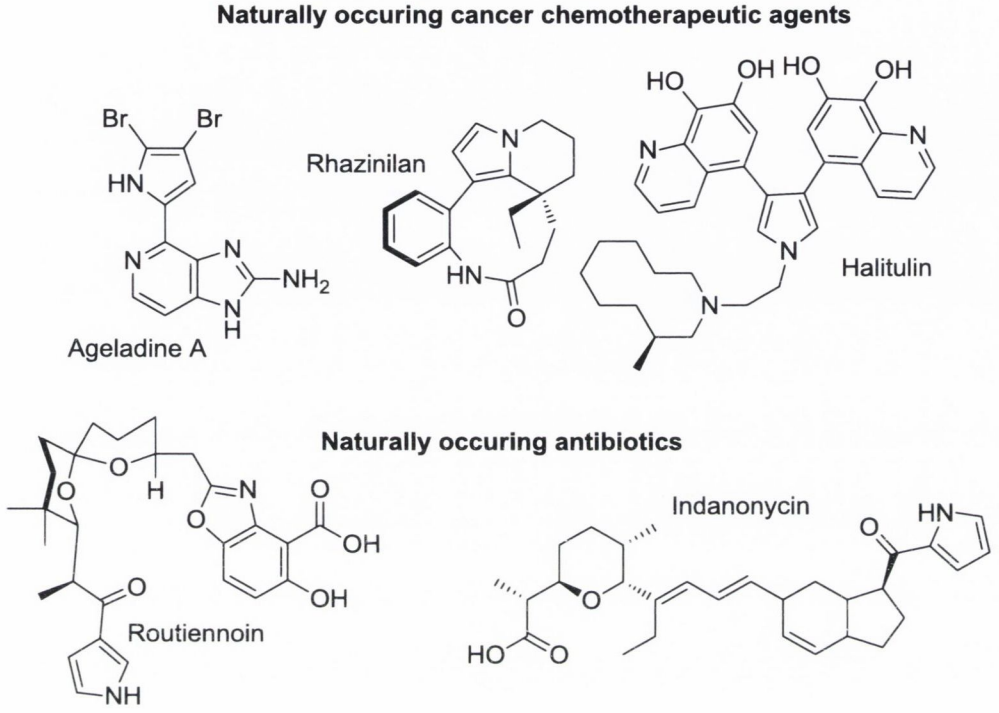


Figure 246: Natural products containing the pyrrole ring

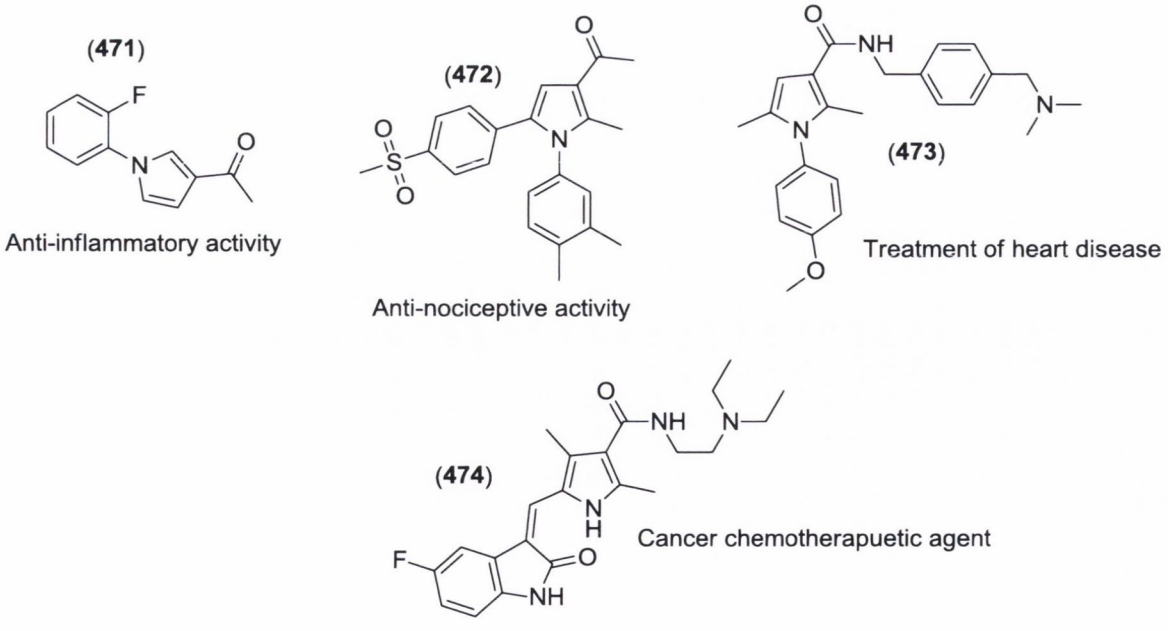
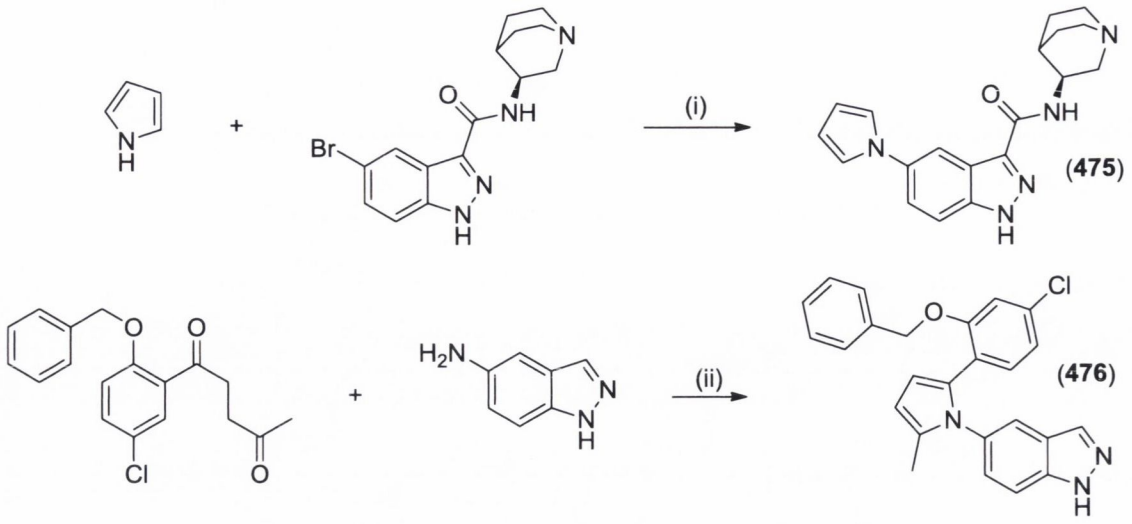


Figure 247: Synthetic molecules of biological interest that contain the pyrrole ring

2.10.2 Synthesis of indazoles with pyrrole substituents at C-5 and C-6

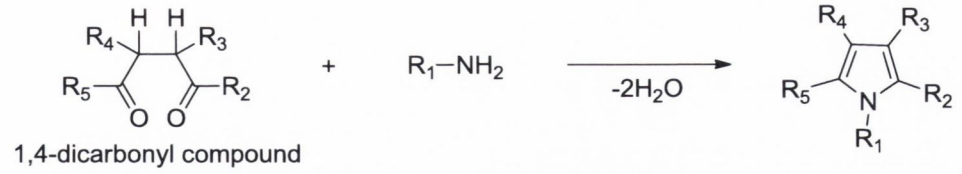


(i) Buchwald-Hartwig reaction (ii) Paal-Knorr pyrrole reaction

Figure 248: Synthesis of indazoles with pyrrole substituents

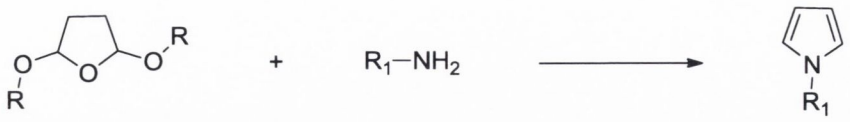
Compounds (**475**) [388] and (**476**) [389] are synthetic indazole derivatives with pyrrole substituents, figure 248. (**475**) was prepared using the Buchwald-Hartwig reaction, a palladium catalysed cross coupling reaction while (**476**) was prepared using the Paal-Knorr pyrrole reaction. The latter method involves the reaction of ammonia or a primary amine with a 1,4-dicarbonyl compound[207,390].

In this thesis, the Clauson-Kaas pyrrole synthesis was used exclusively for the transformation of 5-amino or 6-aminoindazoles into the corresponding 5-pyrrole or 6-pyrrole indazoles, see tables 35 and 36. The Clauson-Kaas method involves the acid-catalysed cyclization of a primary amine and a dialkoxytetrahydrofuran to form an N-substituted pyrrole[391,392]. There are essentially two routes available for the direct synthesis of pyrroles from primary aromatic amines, figure 249. Alternatively the Buchwald-Hartwig reaction could be used if the primary aromatic amine is first transformed into the corresponding aromatic halide through diazotization. As seen from figure 249, the Paal Knorr method generates multi-substituted pyrroles while the Clauson-Kass method generates non-substituted pyrroles when 2,5-dimethoxytetrahydrofuran is used as precursor. However it is possible to generate substituted pyrroles using Clauson-Kass pyrrole synthesis by first modifying 2,5-dimethoxytetrahydrofuran[392], figure 250.



1,4-dicarbonyl compound

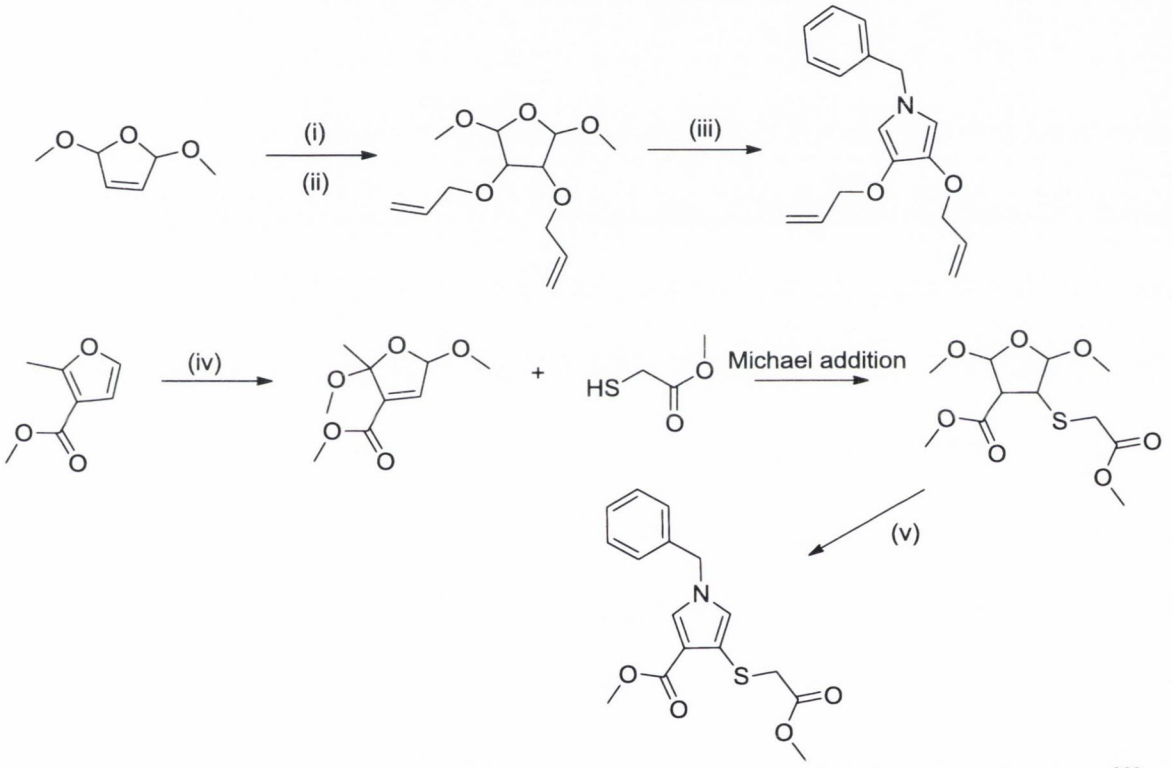
Paal-Knorr pyrrole synthesis



2,5-Dialkoxytetrahydrofuran

Clauson-Kaas pyrrole synthesis

Figure 249: Pyrrole synthesis from primary aromatic amine



(i) $KMnO_4/H_2O$ (ii) Allyl bromide (iii) TFA/H_2O, benzylamine (iv) Br_2, MeOH (v) AcOH, benzylamine[392]

Figure 250: Generation of substituted pyrroles using the Clauson-Kaas pyrrole reaction

Even though the Clauson-Kaas pyrrole synthesis is defined as an acid-catalysed cyclization of a primary amine and a dialkoxytetrahydrofuran, there are examples in the literature where Paal-Knorr pyrrole synthesis was used to describe such reactions conditions[393,394]. This is probably due to the mechanism for Clauson-Kass pyrrole synthesis, figure 251.

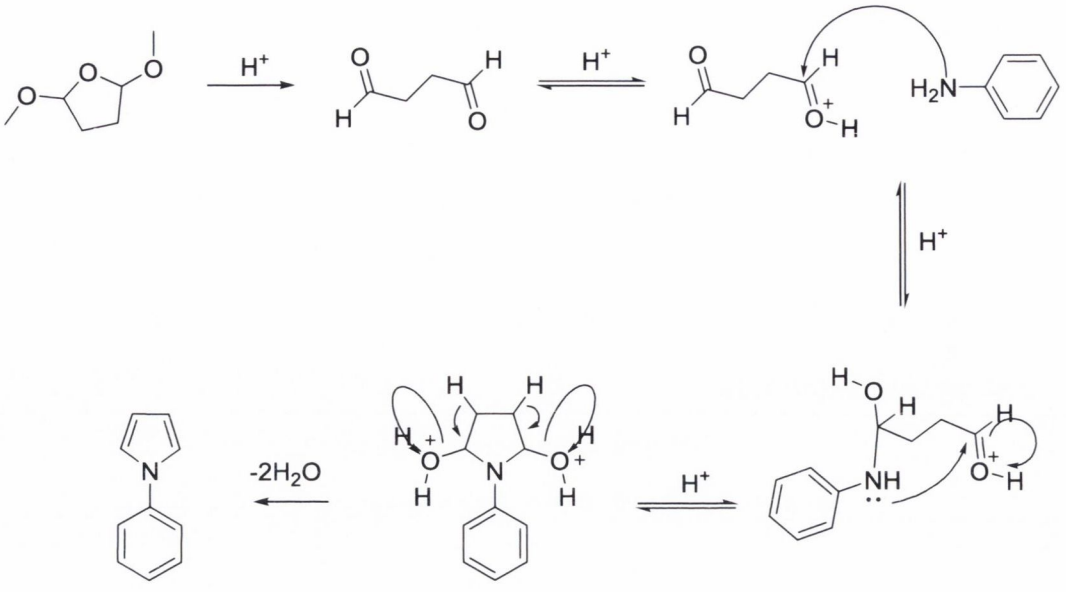


Figure 251: Clauson-Kaas pyrrole synthesis following the Paal-Knorr reaction pathway

Acid-catalysed hydrolysis of the 2,5-dimethoxytetrahydrofuran releases succindialdehyde, a 1,4-dicarbonyl compound. Succindialdehyde then enters into the Paal-Knorr reaction pathway[396]. Once the di-aldehyde is revealed, the acid catalyst aids the attack of the nucleophilic nitrogen to one of the carbonyls forming a hemiaminal. The nitrogen is then free to attack the second carbonyl after which two dehydrations generate the pyrrole ring system. An alternative mechanism exists which results in the formation of an imine intermediate[397], illustrated in figure 252. The first step is the partial decomposition of 2,5-dimethoxytetrahydrofuran forming the cyclic aldehyde cation. The carbon of the carbonyl bond is susceptible to nucleophilic attack by the amine. Nucleophilic attack by the amine results in the opening of the furan ring. A proton shift results in the loss of a methanol molecule and the formation of another aldehyde type cation. Intra-molecular nucleophilic attack by the nitrogen on the carbonyl carbon results in ring formation and the loss of water forms the pyrrole ring.

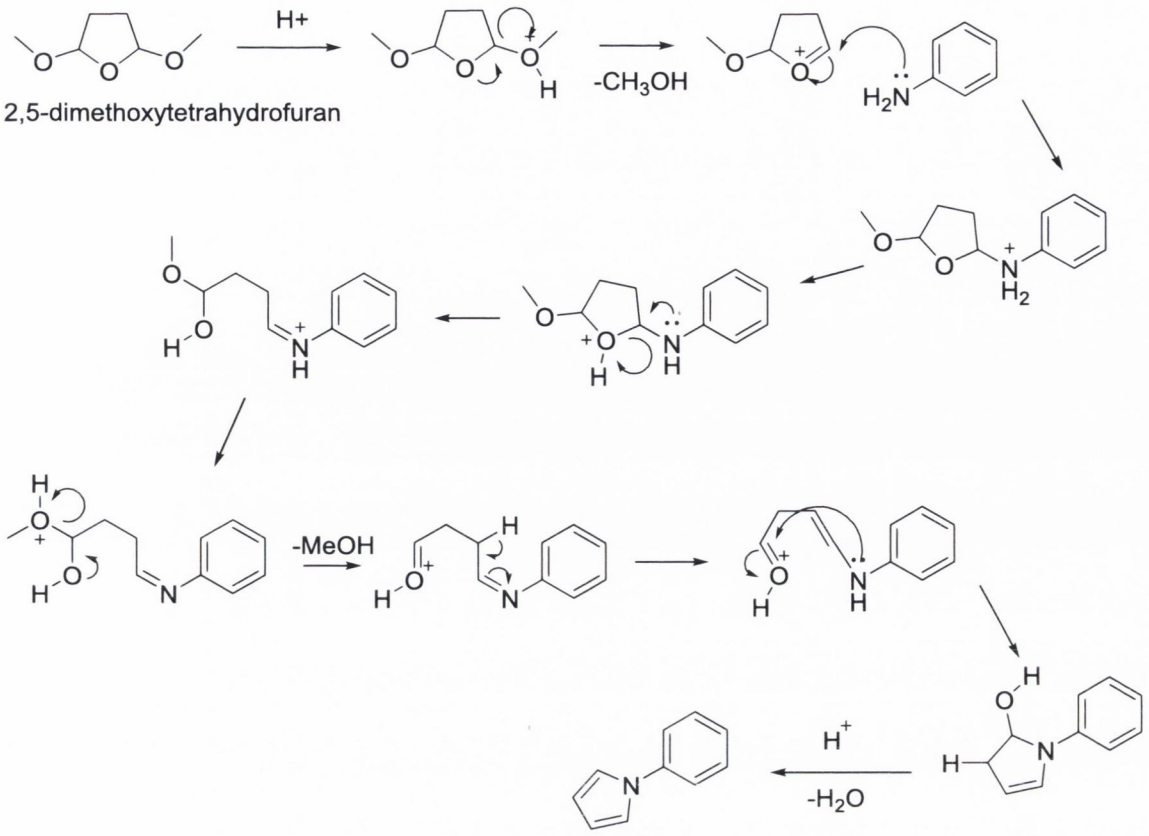
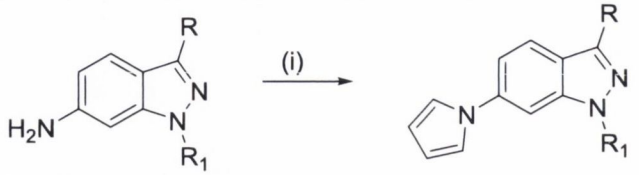


Figure 252: Clauson-Kaas mechanism for the synthesis of pyrroles

In this thesis, the preparation of a library of indazoles containing a pyrrole ring substituent at C-5 and C-6 was achieved by reaction of the corresponding 5- and 6-aminoindazole with 2,5-dimethoxytetrahydrofuran in the presence of acetic acid. Tables 35 and 36 contain details of the indazole derivatives with pyrrole substituents (**477**) – (**497**) that were synthesised. The pyrrole indazoles were obtained in yields ranging from 15% - 52%, containing different type of *N*-1 linkers e.g. (**477**), (**478**) and C-3 substituents (**481**) and (**485**).

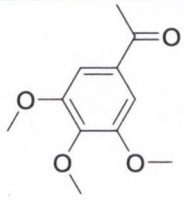
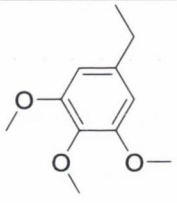
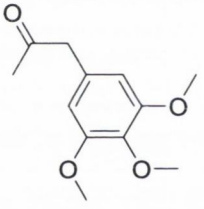
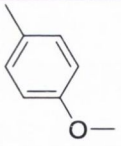
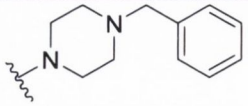
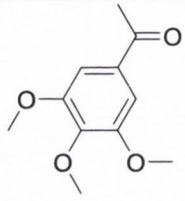
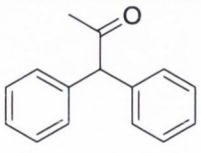
Table 35: Indazoles with pyrrole substituents at C-6



(209), (211), (217) , (229)
(230), (272), (286) (463),(465),(478)

(477) - (486)

(i) 2,5-dimethoxytetrahydrofuran, acetic acid, DIW, rt to 80 °C

Compound Number	R	R_1	Yield (%)
(477)*	H		26
(478)*	H		57
(479)*	H		32
(480)*	H		40
(481)*			15
(482)*	H		35

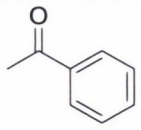
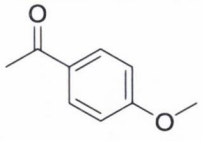
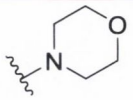
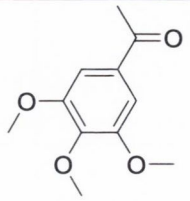
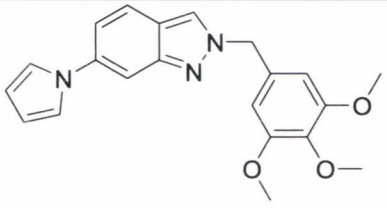
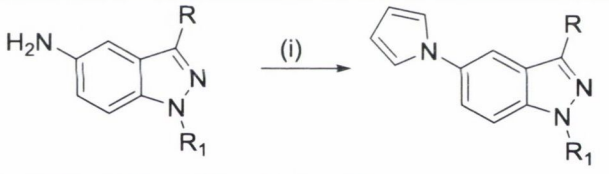
(**483**)*	H		31
(**484**)*	H		14
(**485**)*			51
(**486**)*			29

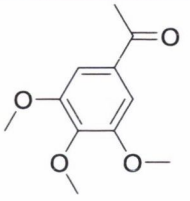
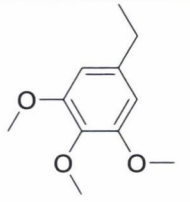
Table 36: Indazoles with pyrrole substituents at C-5

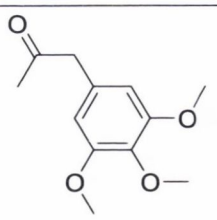
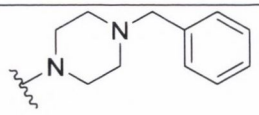
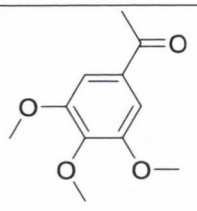
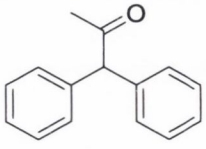
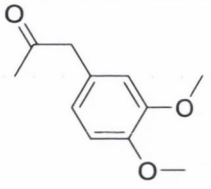
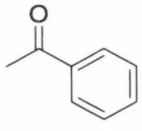
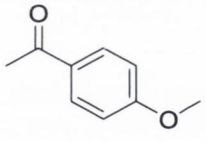
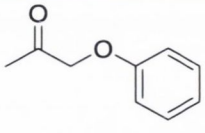
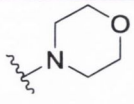
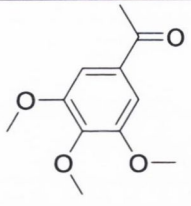
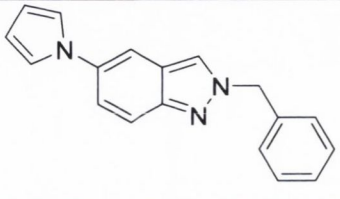


(**168**), (**202**), (**208**), (**229**), (**234**) , (**235**)
(**259**), (**268**), (**304**) (**458**),(**461**)

(**487**) - (**497**)

(i) 2,5-dimethoxytetrahydrofuran, acetic acid, DIW, rt to 80 °C

Compound Number	R	R_1	Yield (%)
(**487**)*	H		33
(**488**)*	H		52

(**489**)*	H		24
(**490**)*			29
(**491**)*	H		40
(**492**)*	H		21
(**493**)*	H		26
(**494**)*	H		34
(**495**)*	H		15
(**496**)*			51
(**497**)*			27

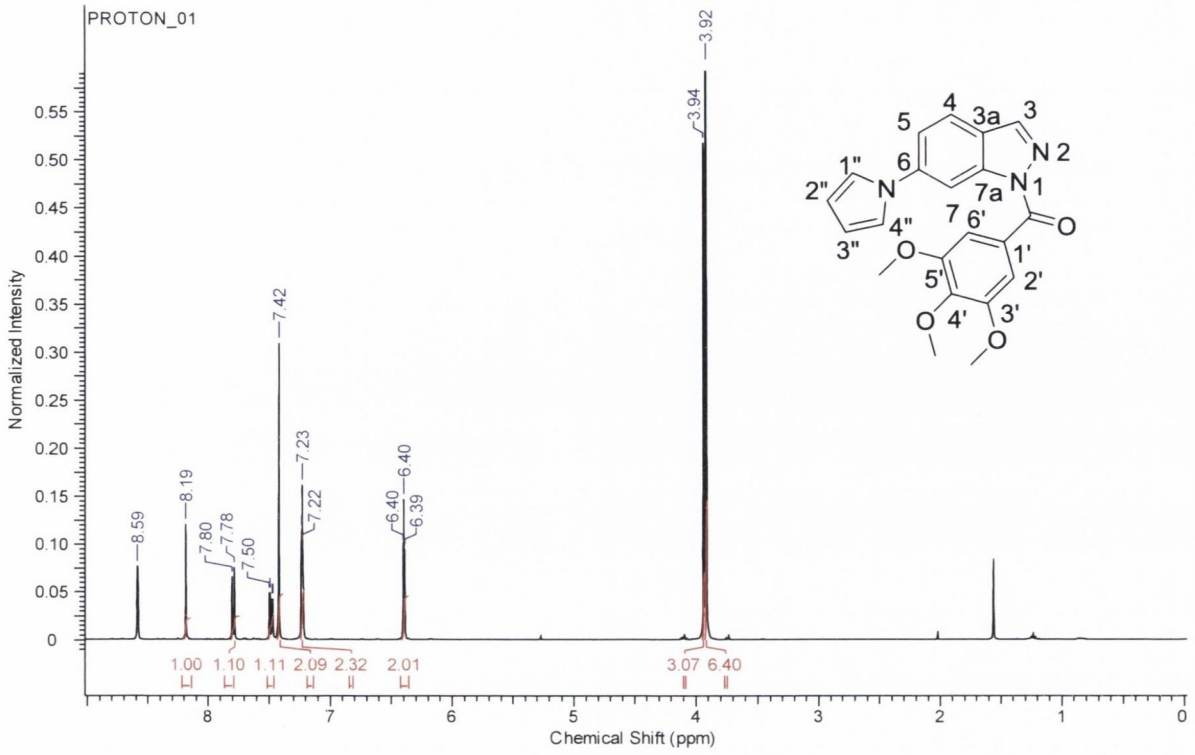


Figure 253: ^{1}H-NMR spectrum of (477)

The ^{1}H-NMR spectrum of (**477**) is shown in figure 253. The sharp singlet at 3.92 ppm corresponds to the two symmetric methoxy group protons at $C_{3'}$ & $C_{5'}$. The singlet at 3.94 ppm is assigned to the protons of the methoxy group at $C_{4'}$. The singlet at 7.42 ppm corresponds to the symmetric aromatic protons, $H_{2'}$ & $H_{6'}$. The double doublet at 7.48 ppm, J = 8.50, 1.80 Hz, is assigned to proton H_5. The doublet at 7.79 ppm, J = 8.50 Hz, is assigned to the proton H_4. The singlet at 8.18 ppm is assigned to the imine proton H_3 and the singlet at 8.59 ppm is assigned to the proton H_7.

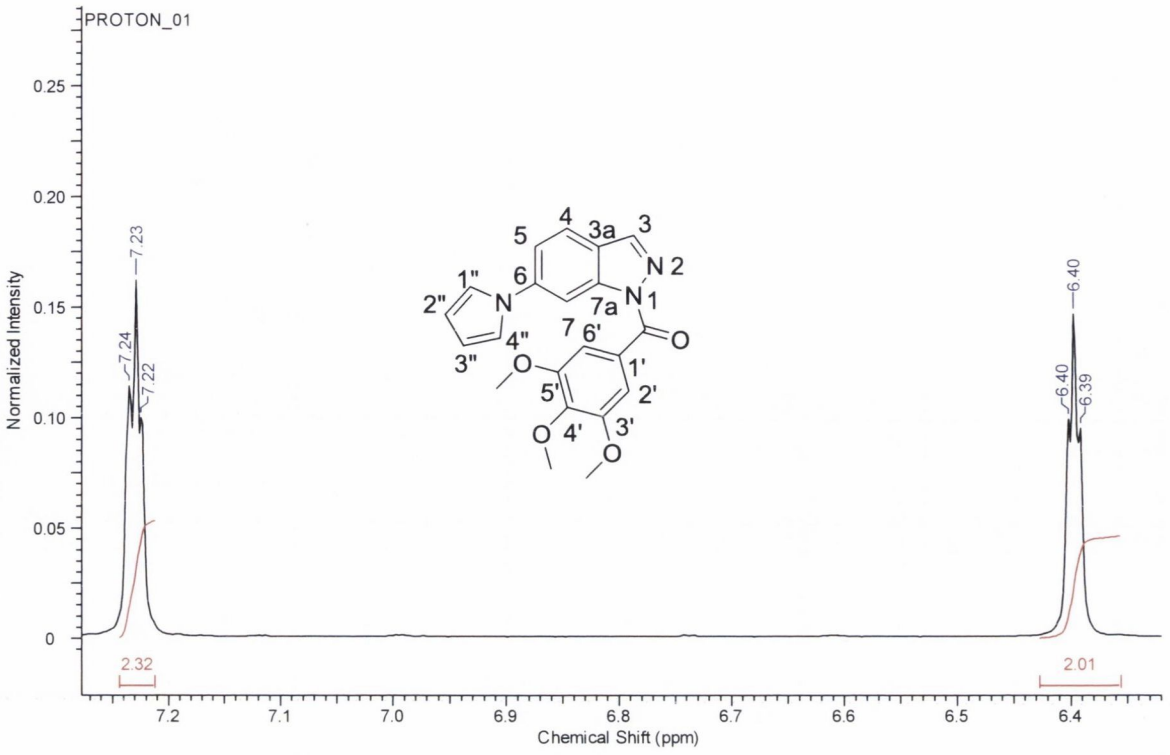


Figure 254: ^{1}H-NMR spectrum of pyrrolic protons in (477)

The apparent triplets at 6.40 ppm and 7.23 ppm correspond to the pyrrolic protons, $H_{2''}$ & $H_{3''}$ and $H_{1''}$ & $H_{4''}$ respectively, figure 254. Due to the degree of symmetry of the pyrrole ring, the pyrrolic protons $H_{1''}$ & $H_{4''}$ and $H_{2''}$ & $H_{3''}$ have the same chemical shift. Even though the pyrrole ring is symmetric, this is not reflected in the observed proton coupling. The vicinal vinylic proton coupling observed in pyrrole and other five membered rings such as furan, thiophene, selenophene, tellurophene and cyclopentadiene is of a smaller magnitude observed for benzene, ~7.6 Hz, due in part to the greater separation of the protons[414]. Electronegativity of the heteroatom and double bond character in the five membered ring affect coupling sizes in $J_{2,3}$ and $J_{3,4}$. The known coupling constants observed for pyrrole[414] are shown in figure 255 (a), as well as the possible coupling in the pyrroleindazoles prepared in this thesis project.

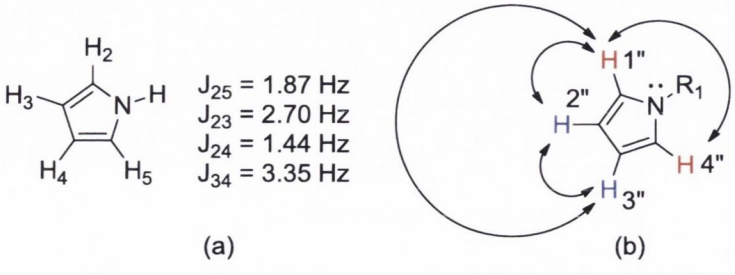


Figure 255: (a) Coupling constants for the pyrrole (b) Proton coupling for pyrrolylindazoles[414]

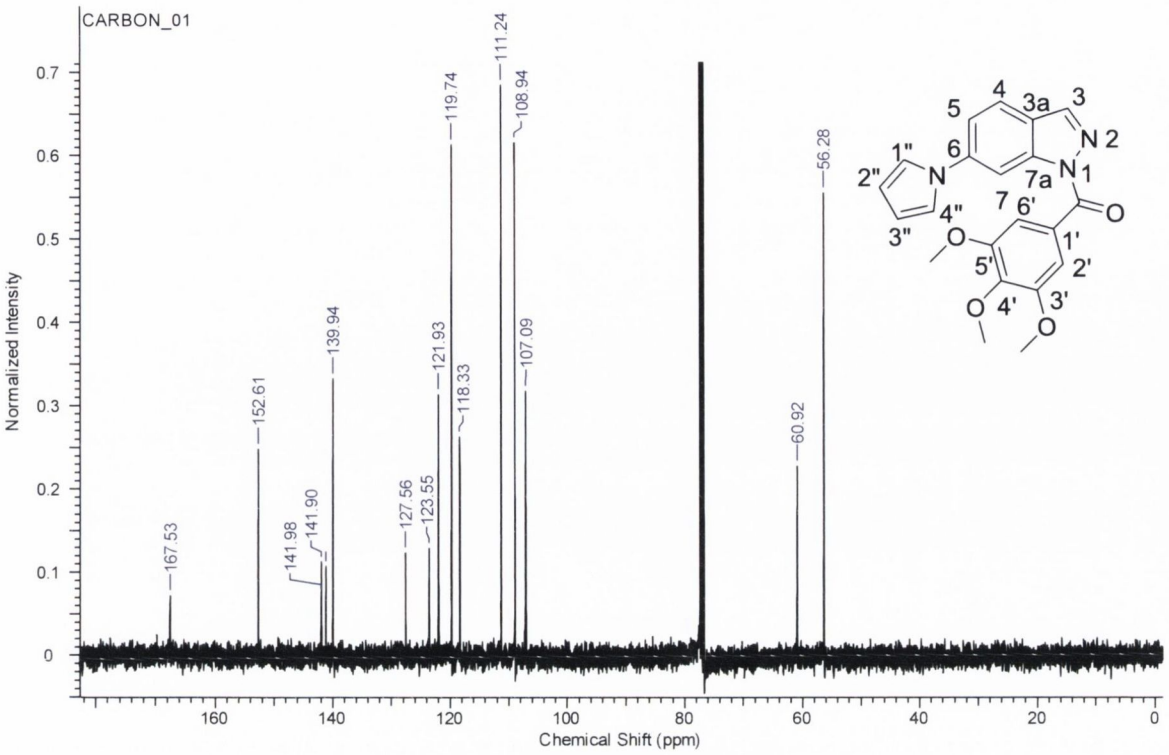


Figure 256: ^{13}C-NMR spectrum of (477)

The ^{13}C-NMR spectrum of (**477**) is shown in figure 256. The signal at 56.26 ppm is assigned to the symmetric methoxy group carbons on the aryl ring, attached at positions, $C_{3'}$ and $C_{5'}$. The signal at 60.92 ppm corresponds to the methoxy group carbon at position $C_{4'}$. The signals at 107.09, 108.94, 111.24, 118.33, 119.74, 121.93 and 139.95 ppm correspond to the aromatic methine carbons C_7, $C_{1''}$ & $C_{4''}$, $C_{2'}$& $C_{6'}$, C_5, $C_{2''}$ & $C_{4''}$, C_4 and C_3 respectively. The signal at 167.54 ppm is assigned to the carbonyl while the signals at 123.55, 127.56, 141.19, 141.90, 141.99 and 152.62 ppm are assigned to the aromatic *ipso* carbons C_{3a}, $C_{1'}$, C_6, C_{7a} , C_4 and $C_{3'}$& $C_{5'}$ respectively.

In conclusion, 21 pyrrole substituted indazole compounds were synthesised using the Clauson-Kass pyrrole ring froming reaction and were obtained in yields ranging from 15% - 51%. These compounds contain C-3 substituents e.g. (**481**) and (**485**), variable N-1 linkers and as well two unique pyrrole substitueted 2*H*-indazoles, (**486**) and (**497**), were obtained. The transformation of the primary aromatic amine in its corresponding pyrrole analogue removes the potential formation of toxic metabolites from bioactive compounds. Also the pyrrole products provide novel structures for biochemical investigation.

2.10.3: Preparartion of indazoles with pyridone substituents at C-6

This section will describe approaches to the synthesis of indazoles with pyridone, dihydroisquinoline and related heterocyclic substituents in the C-6 position of the indazole ring. *Ghorab et al* reported the synthesis of a series dihydropyridines, dihydroisoquinolines and other heterocyclic compounds from a primary aromatic amine[398]. Since the lead indazole compound (**168**) and (**209**) are primary aromatic amines, it was envisaged that pyridone substituted indazoles could be prepared using the indazole scaffolds in this thesis.

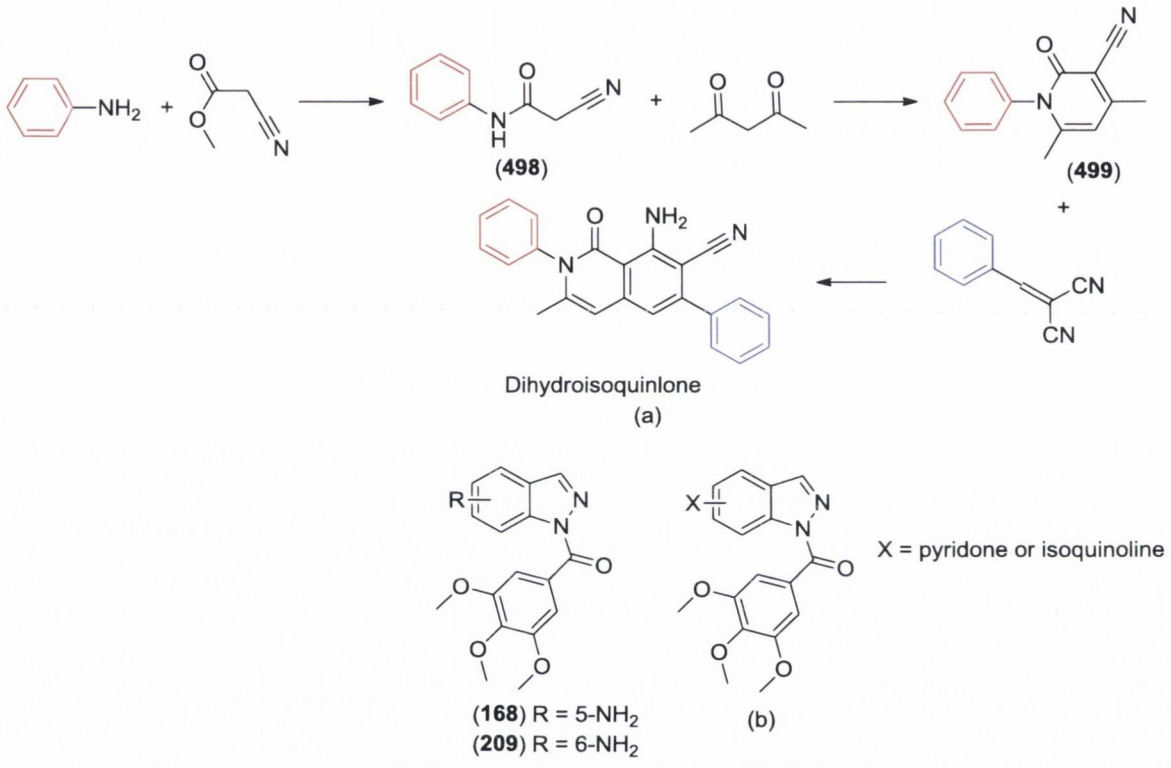
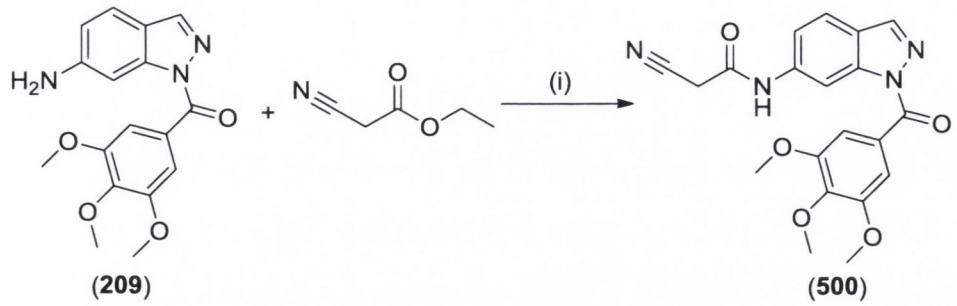


Figure 257: (a) General synthetic route for the preparation of dihydroisoquinolines and (b) general structure of compounds in this section

The synthetic route for the preparation of the pyridones and dihydroisoquinolines is shown in figure 257. The necessary primary aromatic amine is first reacted with ethyl cyanoacetate yielding the corresponding 2-cyano-*N*-phenylacetamide (**498**) which is then reacted with acetylacetone which yields the 2-pyridone (**499**). (**499**) can be further reacted with 2-benzylidenemalononitrile affording the desired dihydroisoquinoline.

In the present work, the approaches to the preparation of pyridone and dihydroisoquinoline substituted indazoles are now discussed. The initial reaction required the preparation of the 2-cyano-*N*-arylacetamide (**500**) from the indazole (**209**), figure 258.



(209) (500)

(i) 190 °C, 30 minutes, μW

Figure 258: Synthesis of (500)

A fusion method using solvent free conditions, excess ethyl cyanoacetate and heat is a common method for the preparation of these acetamide compounds[399]. A review by *Fadda et al* reported that 2-cyano-*N*-phenylacetamide could be prepared using microwave assisted organic synthesis (MAOS)[400]. The reaction between (**209**) and ethyl cyanoacetate was thus performed using the CEM Discover microwave reactor and the results are displayed in table 37.

The initial temperature used for the reaction was 220 °C and the reaction time was set to 30 minutes. The power limit was set to 35 watts. This restricted the amount of power the microwave reactor could use to heat the reaction. This was only a precautionary measure in order to limit possible product degradation from high wattage. Using these reaction conditions, a yield of 26% was obtained for compound (**500**). The reaction was repeated but the temperature was reduced to 190 °C. The molar amounts of the reactants remained the same along with the reaction time and the power limit. The yield increased from 26% to 43%. The reaction was repeated again however the reaction time was reduced to 15 minutes and the temperature was set to 190 °C. Using these conditions, the yield actually decreased to 20%.

Table 37: Reaction optimisation for (500)

Reaction number	Reaction Conditions				
	Power, watts	Temperature, °C	Reaction time, minutes	Molar equivalents of ethyl cyanoacetate	% Yield (**500**)
1	35	220	30	6	26
2	35	190	30	6	43
3	35	190	15	6	20

In all three cases, purification of the crude product (**500**) by column chromatography was difficult as a secondary product was present very close to the product. Using 1:2 Hexane:Ethyl

Acetate as mobile phase, the R_f of the product (**500**) was 0.41 while the secondary product had a R_f of 0.51. An alternative method using refluxing was then investigated, one which might enable cleaner synthesis, table 38. Here only 1 molar equivalent of ethyl cyanoacetate was used and the mixture was refluxed in *m*-xylene or ethanol for 4 hours. For our reaction, *m*-xylene was replaced with toluene, tetrahydrofuran and ethanol and 1.5 molar equivalents of ethyl cyanoacetate were used. Each reaction was heated to reflux for 6 hours.

Table 38: Refluxing conditions for product (500)

Reaction munber	Reaction Conditions		
	Molar equivalents of ethyl cyanoacetate	Solvent	Reaction time, hours
4	1.5	Toluene	6
5	1.5	Tetrahydrofuran	6
6	1.5	Ethanol	6

However all three different conditions failed to synthesize the desired product. When analyzed by TLC, the product was not present and starting material was still observed. From this, it was believed that higher temperatures were required together with excess ethyl cyanoacetate for the efficient synthesis of (**500**). It was hypothesized that higher temperatures were required as toluene has a boiling point of 111 °C, the highest of all three solvents in table however the reaction did not proceed. It was decided to revert back to the microwave neat method for the synthesis of (**500**), attempting the reaction at a temperature of 175 °C and 155 °C but keeping the reaction time to 30 minutes and using 6 molar equivalents of ethyl cyanoacetate, table 39.

Table 39: Alternative microwave reaction conditions for (500)

Reaction number	Reaction Conditions				
	Power, watts	Temperature, °C	Reaction time, minutes	Molar equivalents of ethyl cyanoacetate	% Yield (**500**)
7	35	175	30	6	30
8	35	155	30	6	25

It was noticed that after purifying product (**500**) from reaction numbers (7) and (8) (table 39), a considerable amount of starting material was still present. When the temperature was set to 190 °C, all the starting was consumed. The secondary product close to the product spot on TLC

was also present in both reaction conditions. It was decided to leave the temperature at 190 °C as at this temperature, complete reaction was achieved. The secondary product at R_f 0.51 was then investigated further as it thought that maybe this compound was caused by the excess ethyl cyanoacetate. The ^{1}H-NMR spectrum of this secondary product (**501**) is shown in figure 259.

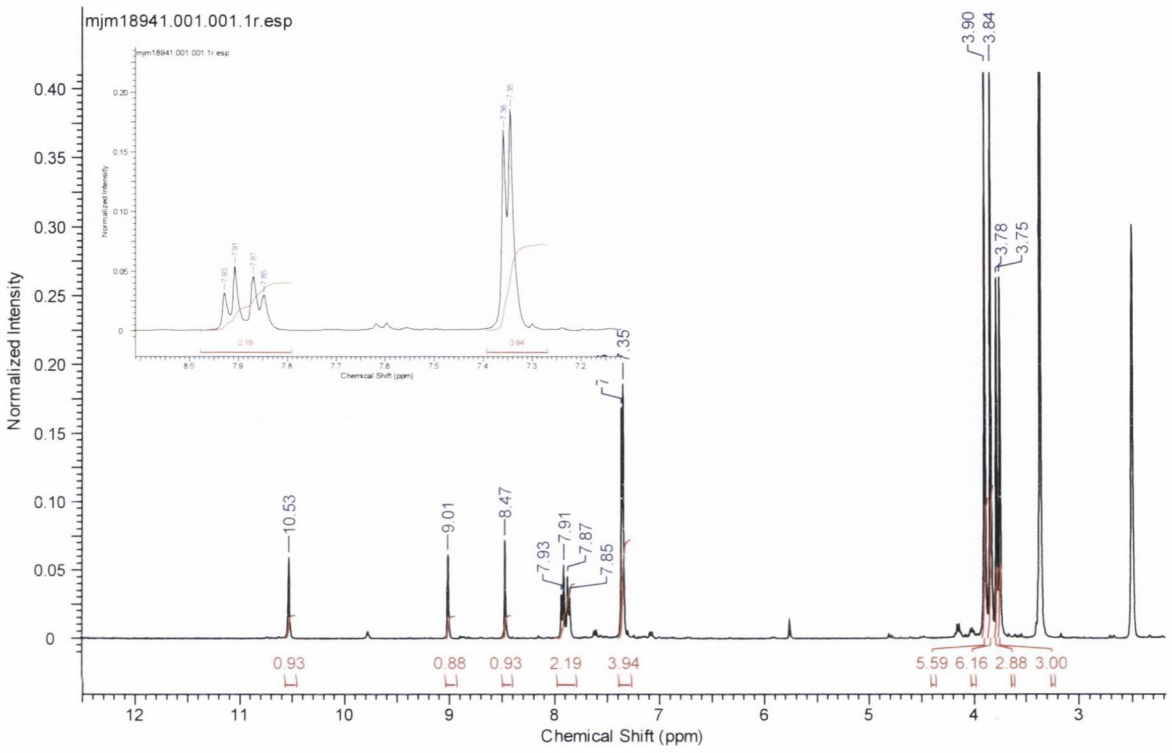


Figure 259: ^{1}H-NMR spectrum of secondary product (501)

As seen from figure 259, four singlets are present at 3.75 ppm (3H), 3.78 ppm (3H), 3.84 ppm (6H), 3.90 ppm (6H) and the doublet at 7.36 ppm (4H). These signals correspond to the 3,4,5-trimethoxyphenyl ring or more precisely two such rings.

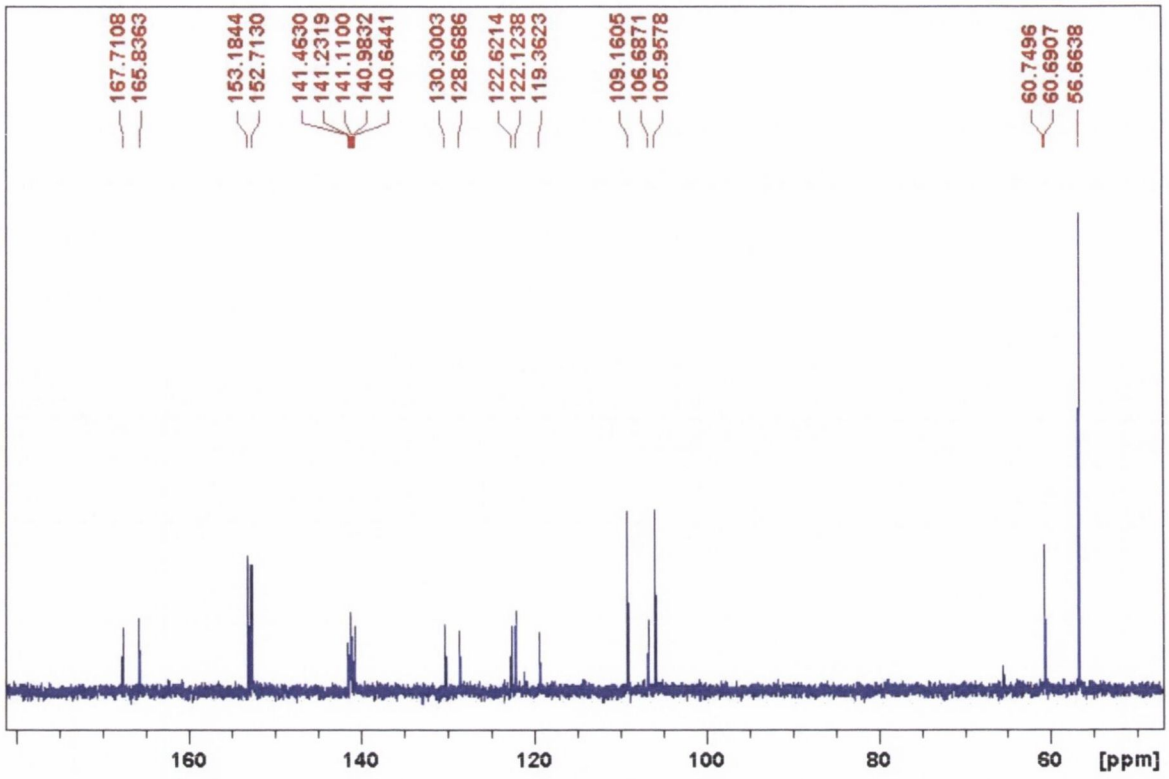


Figure 260: ^{13}C-NMR spectrum of secondary product (501)

From the ^{13}C-NMR spectrum, figure 260, it appears that there are two carbonyl groups present in the secondary product (**501**), one at 165.84 ppm and the second at 167.71 ppm. The signals at 56.66 ppm, 60.69 ppm and 60.75 ppm correspond to the methoxy carbons on the two phenyl rings. The signals at 105.96 ppm and 109.16 ppm are due to the equivalent carbons on the same phenyl rings.

Also the secondary product was further analyzed by ^{13}C-NMR using Distortional Enhancement by Polarization Transfer (DEPT). This technique is used to determine the presence of primary, secondary and tertiary carbons. According to the DEPT 135, there is no methylene group in the secondary product (**501**). This was interesting as this suggested that the impurity was not due to a side reaction between the excess ethyl cyanoacetate and (**209**). The secondary product was also analyzed by infrared spectroscopy, figure 261.

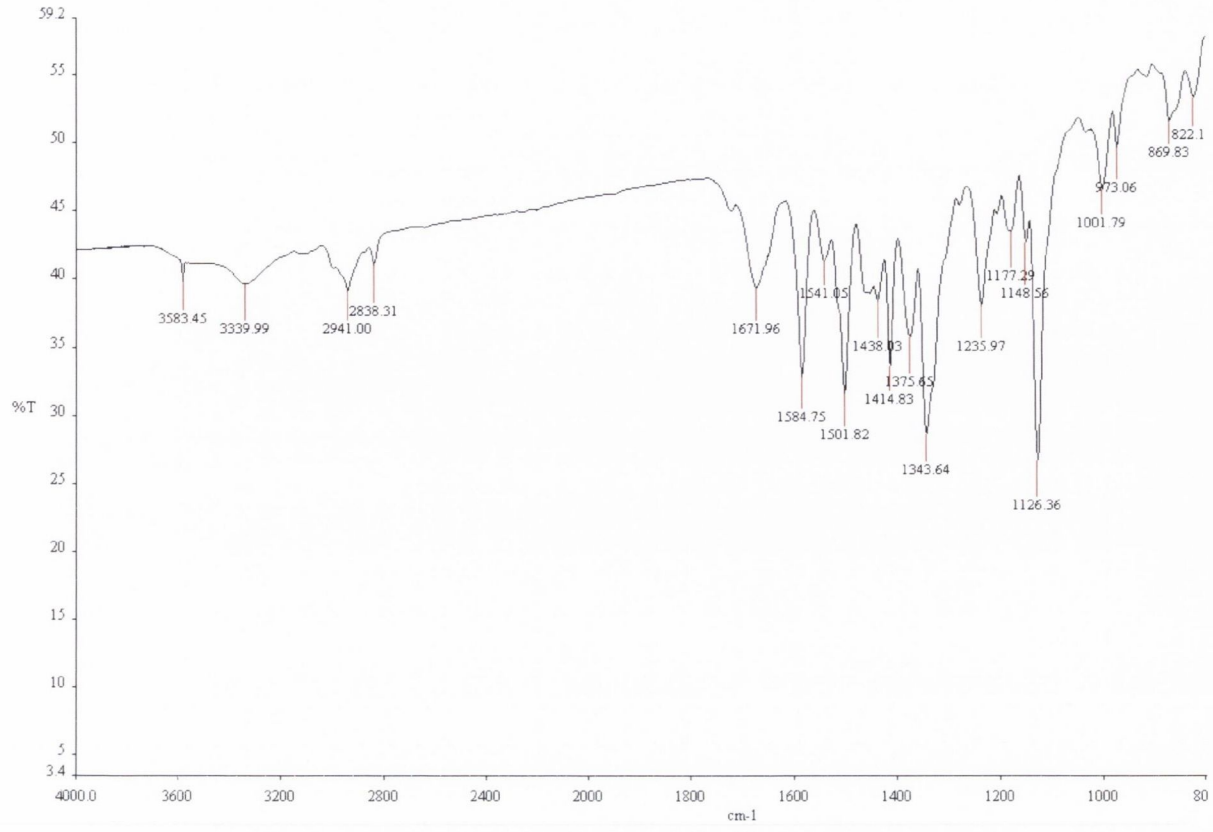


Figure 261: IR spectrum of secondary product (501)

As seen from the IR spectrum, figure 261, there is no absorption present at 2250 cm^{-1}, the usual wavenumber at which the cyano group appears. Thus the secondary product at R_f 0.51 is believed to have the following structure (**501**) from initial analysis performed:

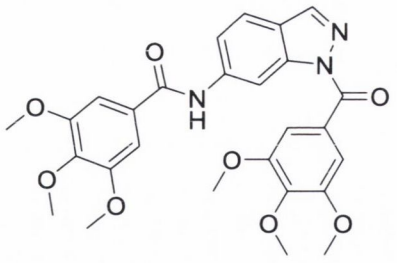


Figure 262: Structure of secondary product (501)

The formation of this secondary product is not related to the excess of ethyl cyanoacetate but due to the stability, rather the lack of, of the amide bond in the starting material (**209**). Other 6-aminoindazoles (**259**), (**262**) and (**286**) prepared in this thesis were reacted with ethyl cyanoactetate yielding the corresponding 2-cyano-*N*-arylacetamides (**502**) – (**504**) which contained a benzyl or aryl substituent at *N*-1 of the indazole ring. In all three cases, no

secondary product was observed. This further substantiates the conclusion the instability/reactivity of the amide bond in (**209**) is the reason for the formation of the secondary product (**501**).

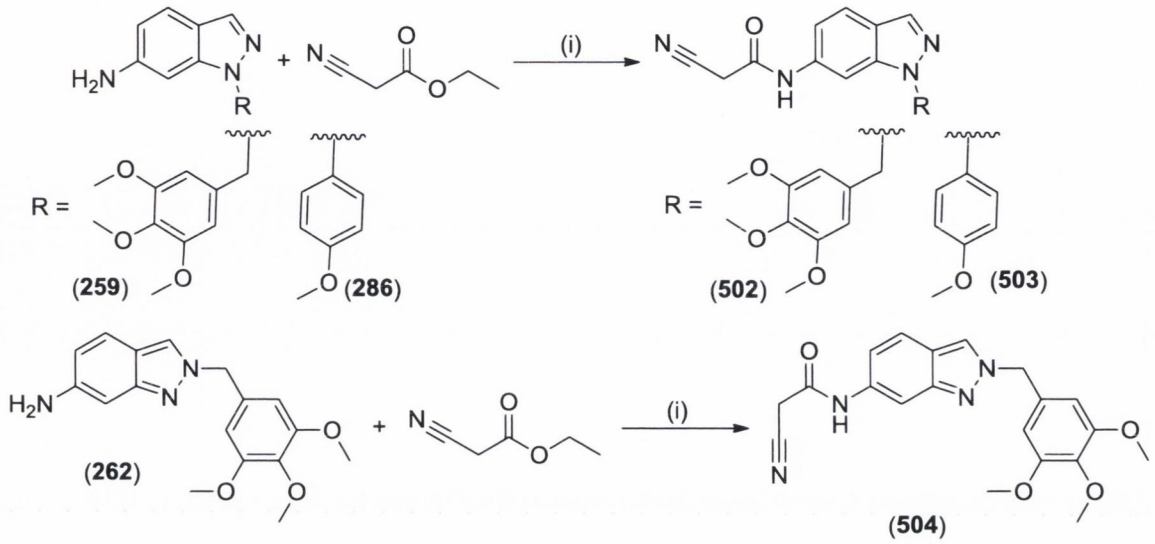
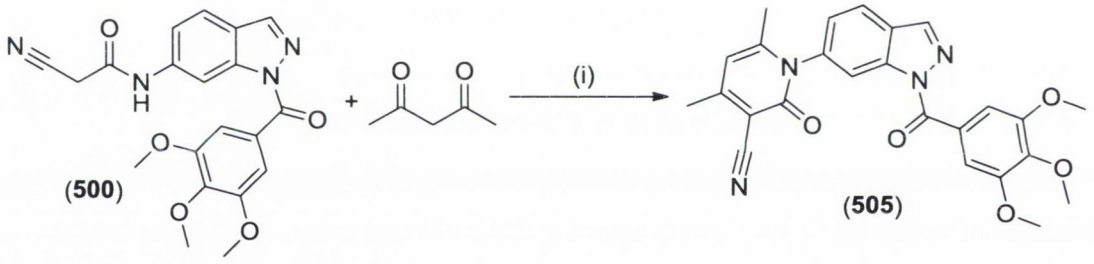


Figure 263: 2-Cyano-N-phenylacetamides (502) – (504)



(i) Ethanol, piperidine, 80 °C

Figure 264: Preparation of (505)

The next step was the reaction of 2-cyano-*N*-arylacetamide (**500**) with acetylacetone to yield the 2-pyridone (**505**), figure 264. The proposed mechanism is shown in figure 265. The hydrogens on the *alpha* carbon on (**500**) are weakly acidic and so can be removed with a base. The resulting carbanion attacks one the of the carbonyl bonds in acetylacetone forming a new bond. Since there is no good leaving group in acetylacetone, the carbon oxygen bond is not reformed and so the oxygen is protonated, forming an aldol adduct. A cyclocondensation reaction occurs *via* nucleophilic attack from the lone pair electrons on the nitrogen to the carbonyl bond. Two molecules of water are lost yielding the desired product (**505**).

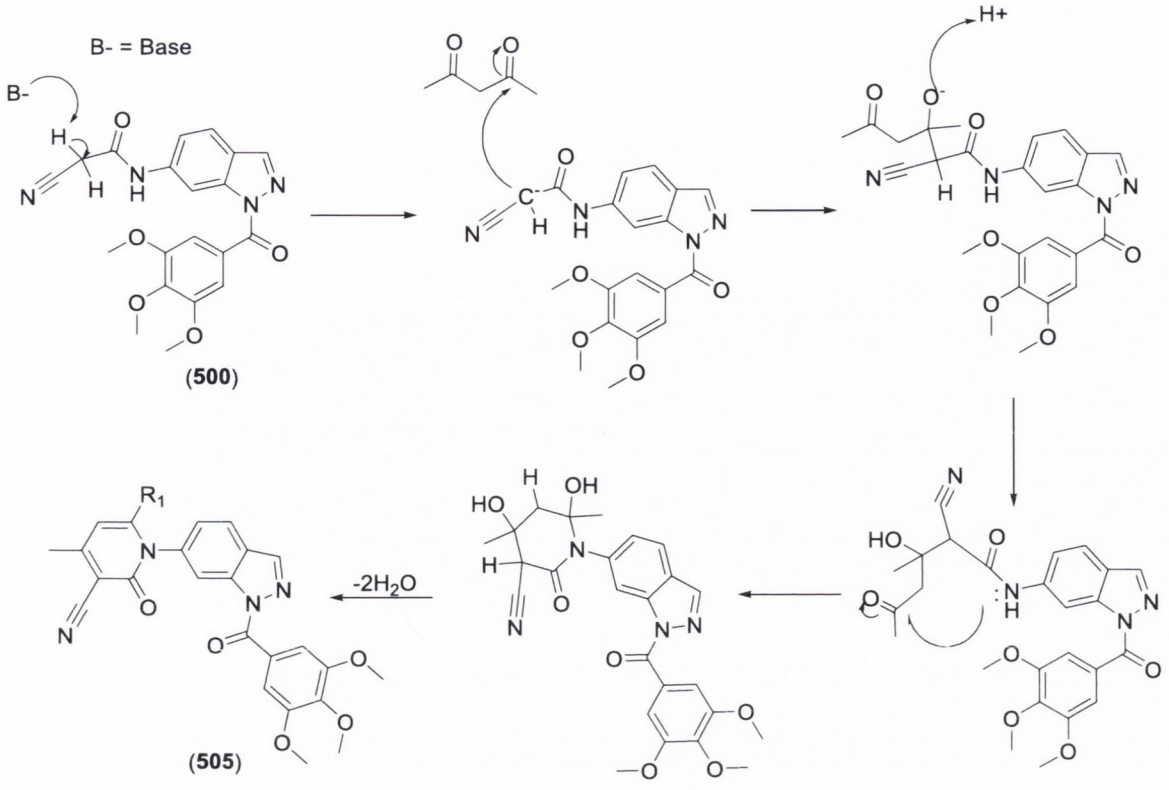


Figure 265: Proposed mechanism for the preparation of (505)

In the present work, (**500**) was refluxed in ethanol for 5 hours with a catalytic amount of piperidine and left stirring at room temperature overnight. When this reaction was first attempted, a surprising result was obtained. When the crude product was analyzed by TLC, all the starting material (**500**) was consumed and four different compounds were present. All four (R_f 0.74, R_f 0.55, R_f 0.28, R_f 0.18, 1:2 hexane: ethyl acetate) were separated by flash column chromatography but none of them corresponded to the expected product (**505**) when analyzed by ^{1}H-NMR spectroscopy.

From analysis the ^{1}H-NMR spectrum of the compound at R_f 0.74, it was identified that the unknown compound contained a 3,4,5-trimethoxyphenyl ring due to the singlet at 3.93 ppm (9H) and the singlet at 7.32 ppm (2H). It also contained an ethyl group due to the triplet at 1.42 ppm (3H) and the quartet at 4.39 ppm (2H). The structure of this product was believed to be ethyl 3,4,5-trimethoxybenzoate. A reference ^{1}H-NMR spectrum was obtained and this confirmed the compound as ethyl 3,4,5-trimethoxybenzoate.

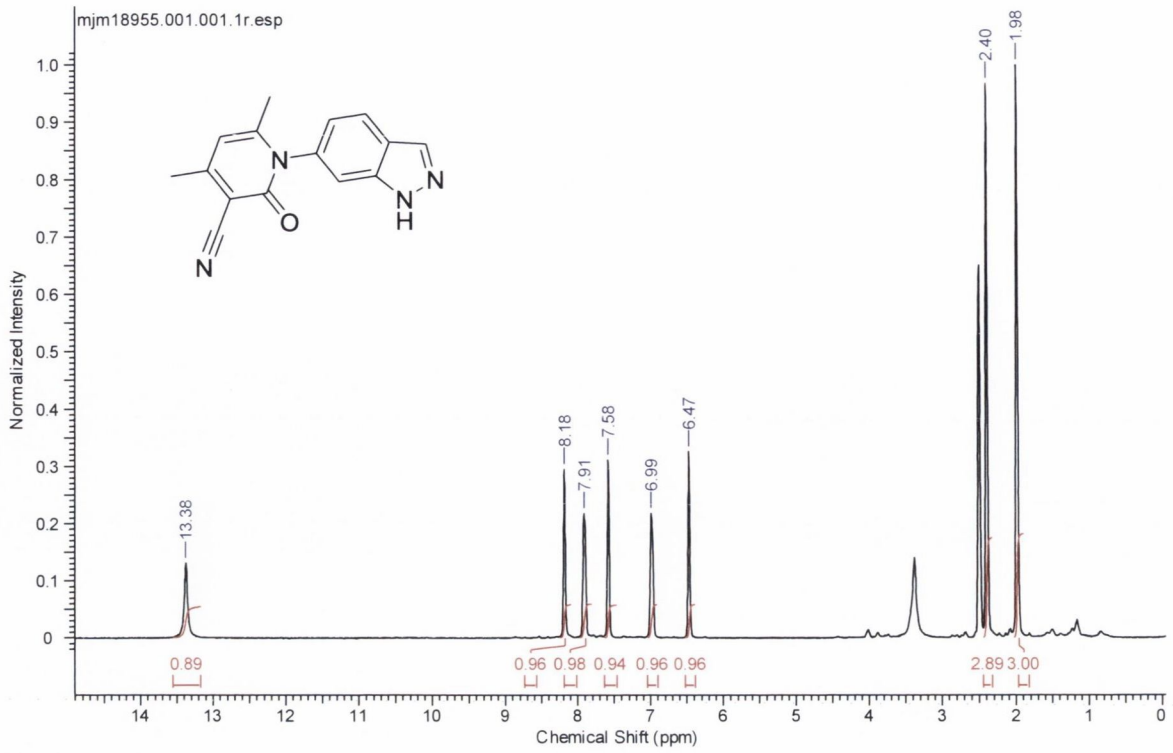


Figure 266: ^{1}H-NMR spectrum of compound with R_f 0.18 (506)

From the ^{1}H-NMR spectrum of the compound with R_f 0.18, it was confirmed that it contained two methyl groups, at 1.98 ppm and at 2.40 ppm. Also the broad singlet at 13.38 ppm was due to the N-H of the indazole indazole. Thus it was believed that this compound could be assigned the following structure (**506**):

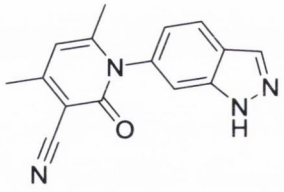
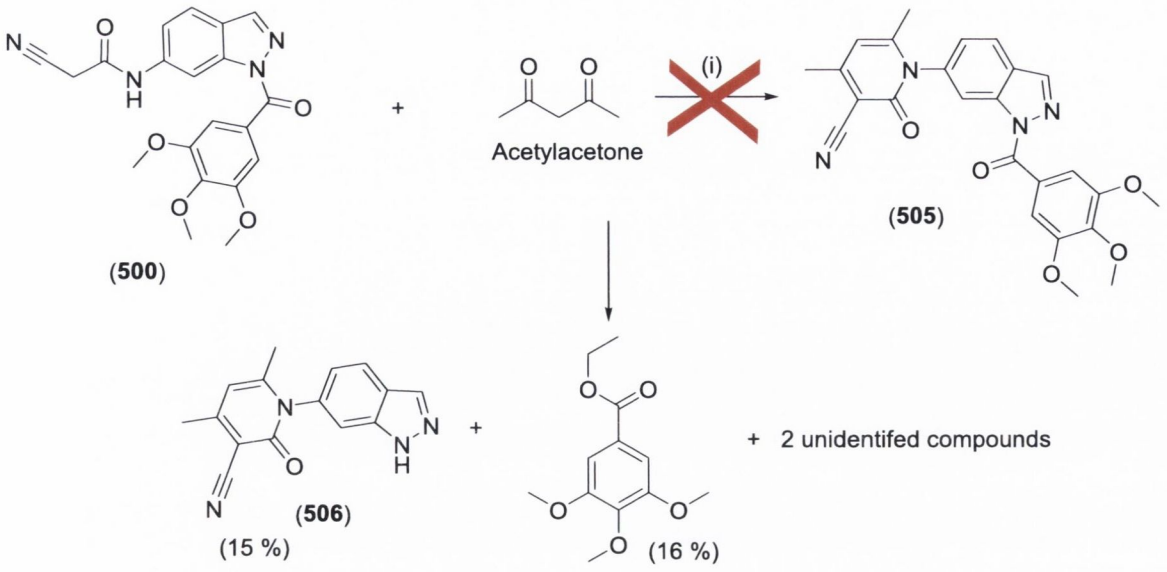


Figure 267: Structure of compound (506) with R_f 0.18



(i) Ethanol, piperidine, 80 °C

Figure 268: Outcome from initial attempt to synthesise pyridone product (505)

Therefore the pyridone ring was successfully synthesized in compound (**506**) but cleavage of the amide bond at *N*-1 occured as well, figure 268. Nucleophilic attack by the ethoxide anion, formed from ethanol and piperidine, on the amide carbonyl results in the cleavage of the 3,4,5-trimethoxyphenyl ring. The same reaction in figure 268 was performed again but chloroform was used instead of ethanol as solvent. It was believed that since hydrolysis of the amide bond was caused by the ethoxide anion, no such anion could be formed using chloroform as solvent. The reaction was successful and the desired product (**505**) was isolated in 26% yield. . However (**506**) was still obtained (5% yield) when chloroform was used as solvent. The ^{1}H-NMR spectrum of (**505**) is shown in figure 269.

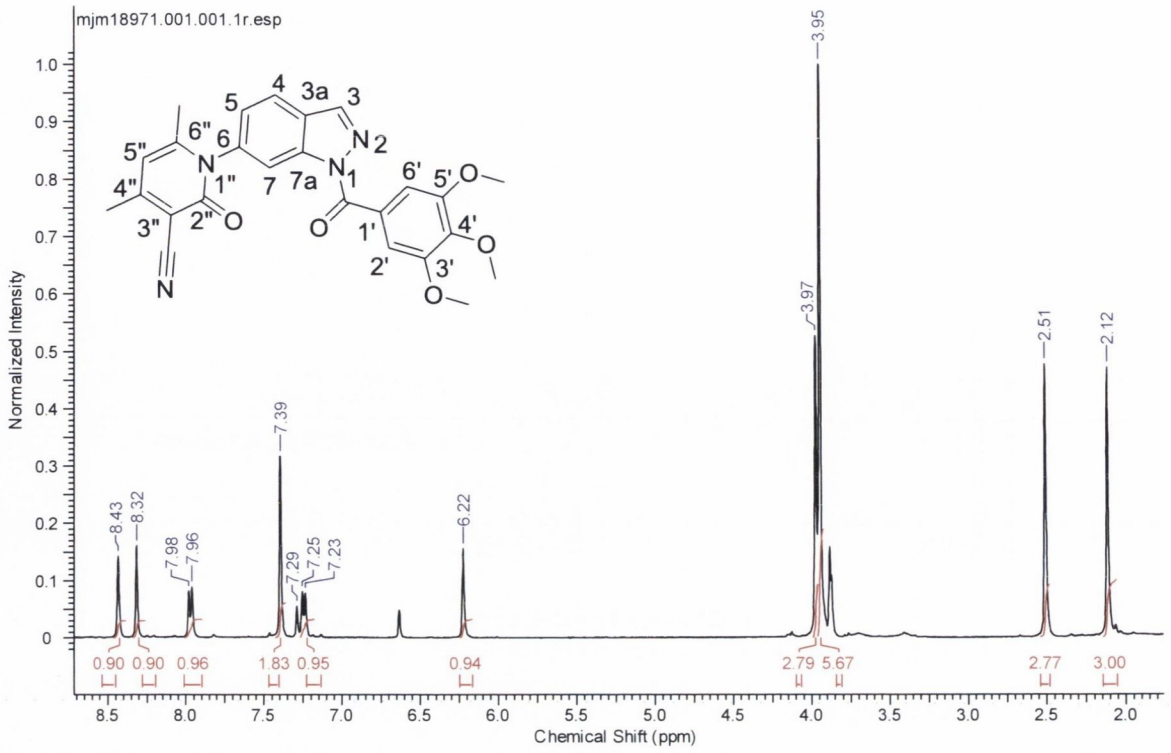


Figure 269: ^{1}H-NMR spectrum of (505)

The singlets at 2.12 and 2.51 ppm correspond to the methyl groups at $C_{6''}$ and $C_{4''}$ respectively on the pyridone ring. The sharp singlet at 3.95 ppm correspond to the protons of the two symmetric methoxy groups at $C_{3'}$ & $C_{5'}$. The singlet at 6.22 ppm is assigned to the $H_{5''}$ proton on the pyridone ring. The doublet at 7.24 ppm, $J = 8.52$ Hz, corresponds to the proton H_5 while the singlet at 7.39 ppm is assigned to the protons $H_{2'}$ & $H_{6'}$. The doublet at 7.97 ppm, $J = 8.52$ Hz, is assigned to H_4. The singlets at 8.32 and 8.43 ppm are assigned to protons H_3 and H_7 respectively.

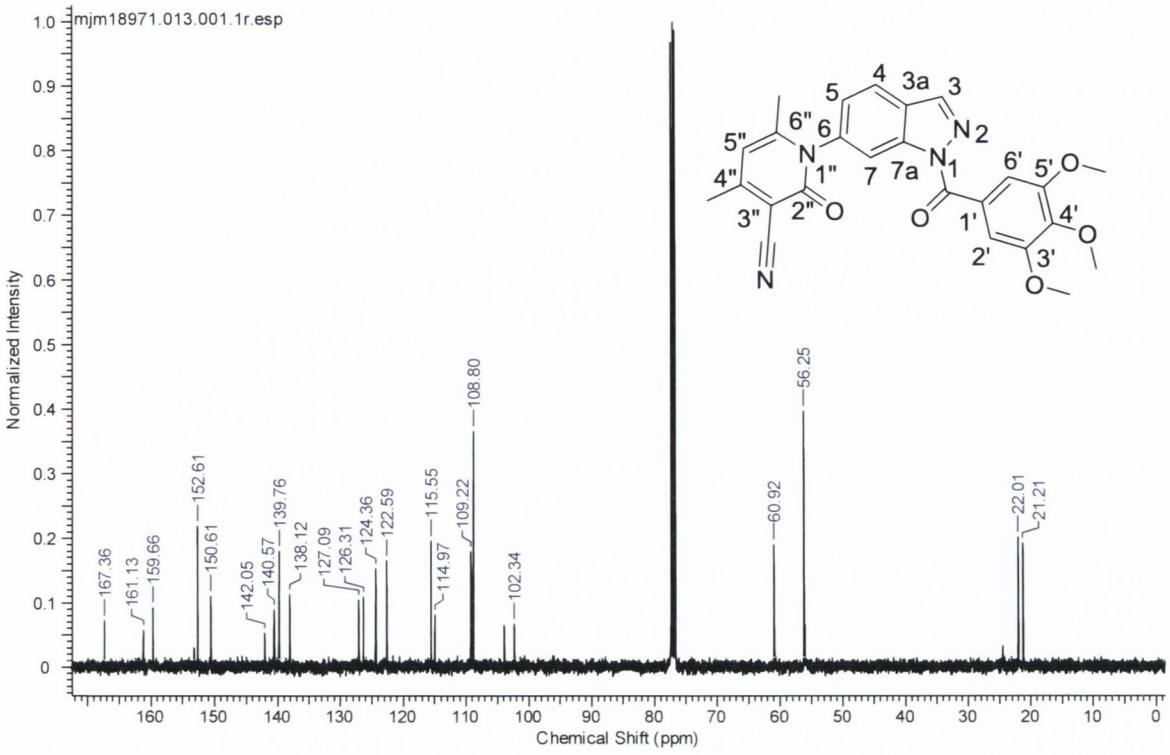


Figure 270: ^{13}C-NMR spectrum of (505)

The ^{13}C-NMR and DEPT spectra of (**505**) are shown in figures 270 and 271 respectively. The signals at 21.21 and 22.01 ppm correspond to the methyl groups on the pyridone ring. The signal at 56.26 ppm is assigned to the carbons of the methoxy groups at $C_{3'}$& $C_{5'}$ while the 60.92 is assign to the methoxy group at $C_{4'}$. The signals at 108.00, 109.21, 115.56, 122.48, 124.09 and 139.76 ppm correspond to the aromatic methine carbons $C_{2'}$& $C_{6'}$, C_7, $C_{5''}$, C_5, C_4 and C_3 respectively. The signals at 161.13 and 167.36 ppm correspond to the amide carbonyl at $C_{2''}$ and *N*-1 respectively.

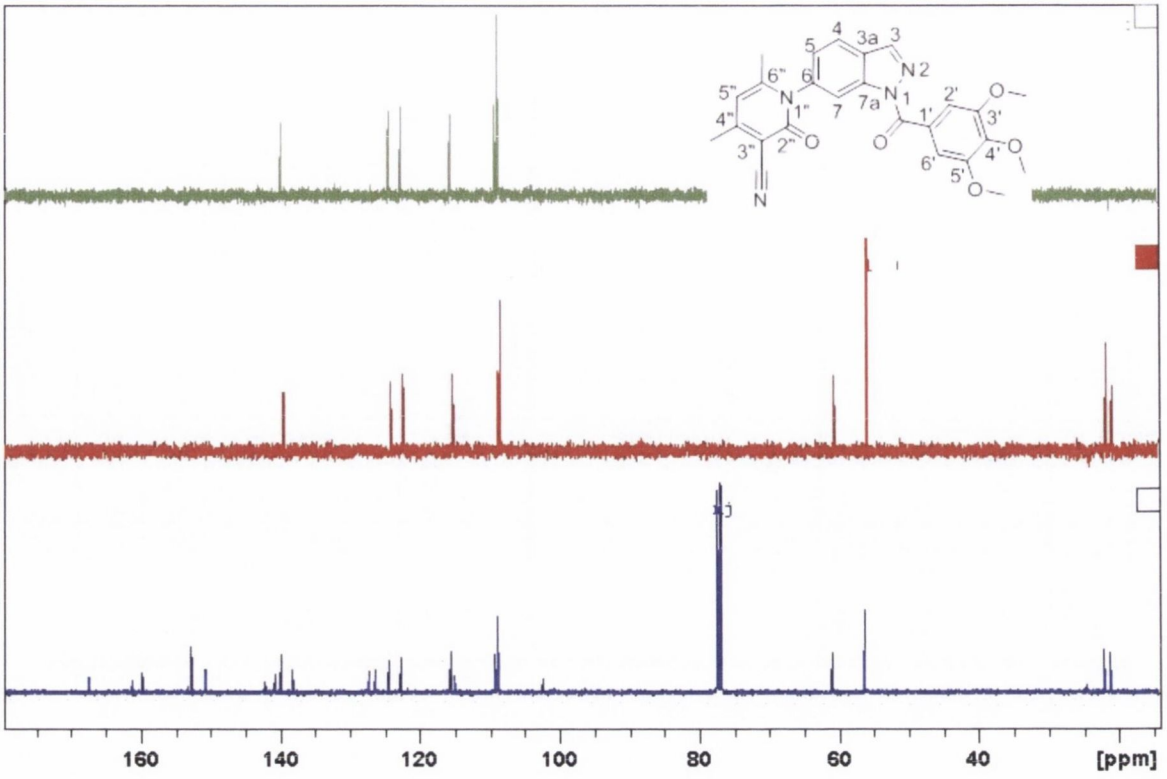
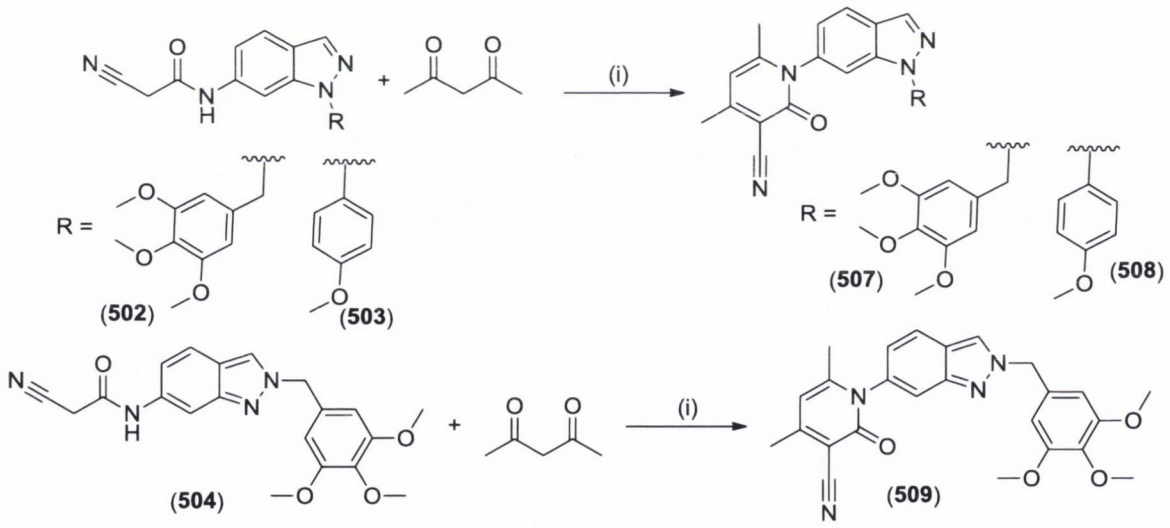


Figure 271: ^{13}C-NMR and DEPT spectra of (505)

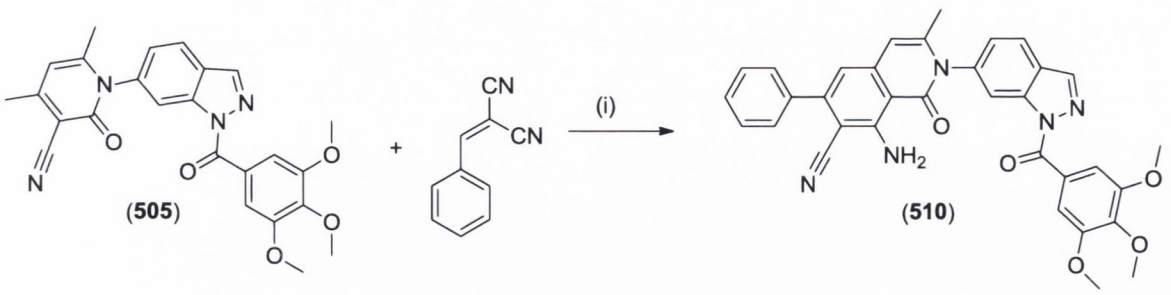


(i) Ethanol, piperidine, 80 °C

Figure 272: Preparation of 6-pyridone substituted indazoles (507) – (509)

As a further extension of this work, the 2-cyano-*N*-arylacetamides (**502**) – (**504**) in figure 264 were all reacted with acetylacetone, yielding the desired pyridone ring, figure 272. In all three cases (**507**) – (**509**), cleavage of the *N*-1 or *N*-2 substiteunt was not observed since of 2-cyano-*N*-arylacetamides did not have amide bonds at *N*-1.

The preparation of the isoquinolone product (**510**) by the reaction of (**505**) with 2-benzylidenemalononitrile was next investigated, figure 273.



(i) $CHCl_3$, piperidine, reflux

Figure 273: Proposed preparation of isoquinolone ring

The procedure involves refluxing the pyridone (**505**) and benzylidenemalononitrile in ethanol in the presence of piperidine. However, the combination of ethanol and piperidine would hydrolyse the amide bond in (**505**) therefore the reactants were refluxed in chloroform with piperidine.

The synthesis of (**510**) is an example of a Michael addition reaction. The mechanism propsed fro the reaction is shown below in figure 274.

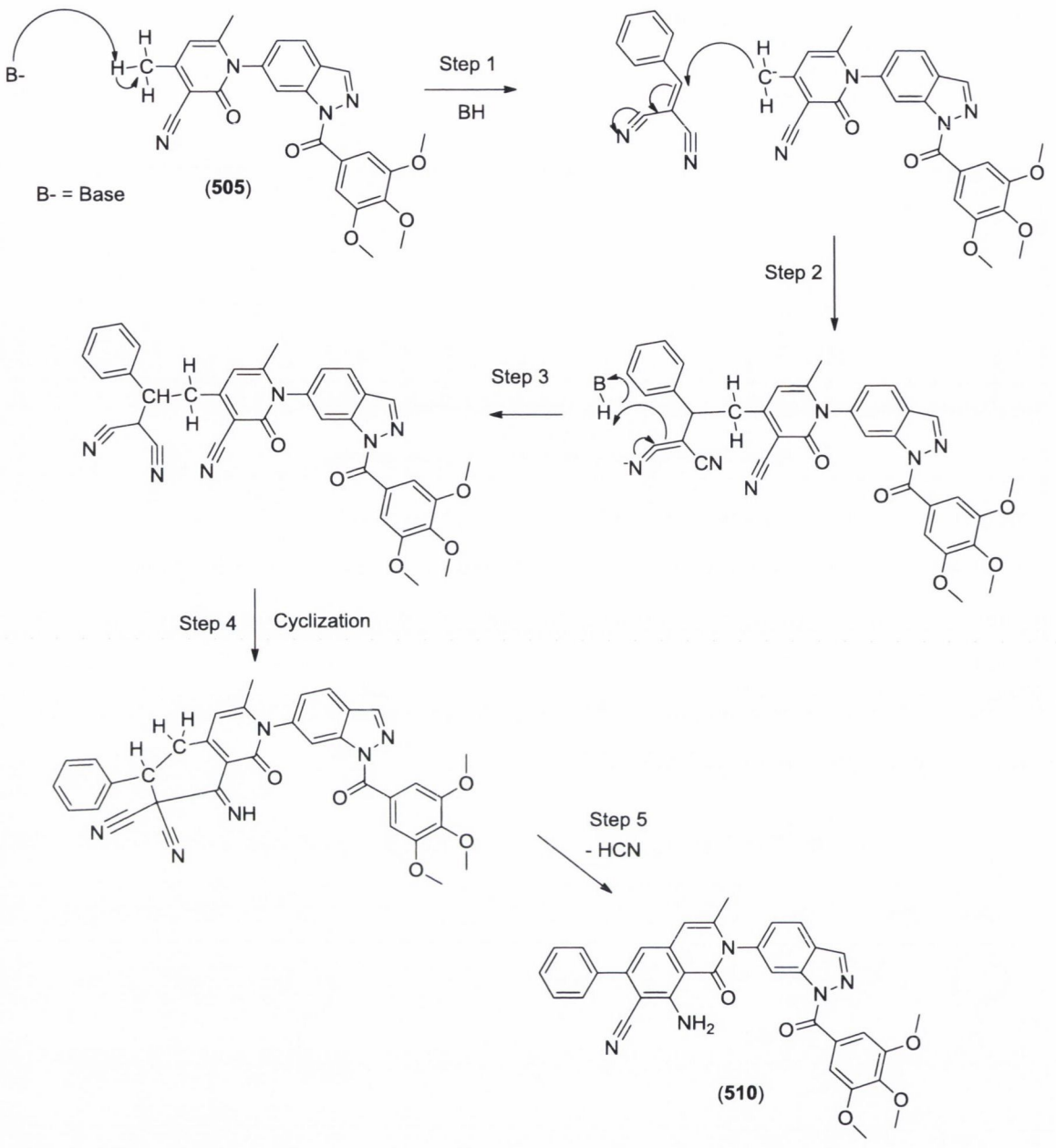


Figure 274: Proposed mechanism for the synthesis of isoquinolone (510)

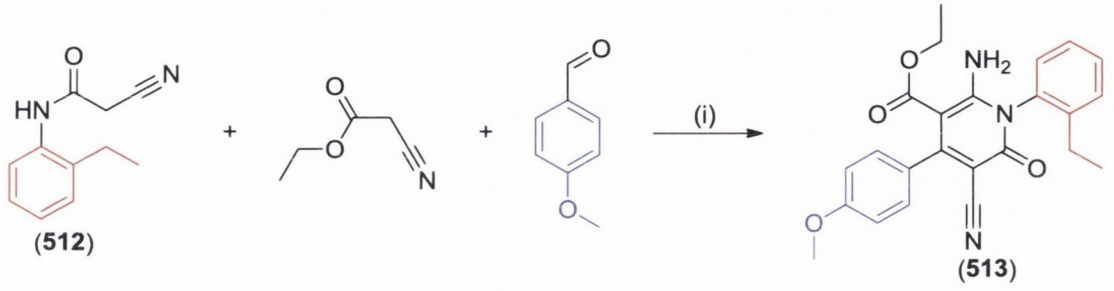
Step 1: The methyl group *alpha* to the cyano group in (**505**) is weakly acidic and can be deprotonated to form a carbanion. This is possible due to the electron withdrawing effect of the cyano group, stabilising the negative charge

Steps 2 & 3: Michael addition of the carbanion to the 2-benzylidenemalononitrile. 2-benzylidenemalononitrile is an α,β unstaturated compound and so addition occurs in the β position. Following addition, protonation at the α carbon occurs.

Steps 4 & 5: Cyclisation followed by loss of hydrogen cyanide affords the desired isoquinolne ring.

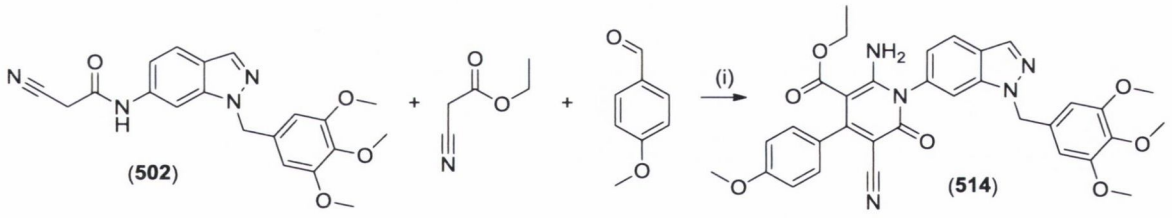
Upon work up of this reaction, figure 273, TLC revealed that all 2-benzylidenemalononitrile was consumed; however the desied product (**510**) was not isolated.

An alternative approach was now investigated for the preparation of indazoles containing C-6 heterocycles. *Ammar et al* had reported the preparation a series of 2-amino-5-cyano-1,6-dihydro-6-oxopyridine-3-carboxylate compounds such as (**513**), figure 275, in a one pot reaction by refluxing the required 2-cyano-*N*-phenylacetamide (**512**) , ethyl cyanoacetate and the required benzaldehyde in ethanol in the presence of piperidine[401].



(i) ethanol, piperidine, 80 °C

Figure 275: 2-Amino-5-cyano-1,6-dihydro-6-oxopyridine-3-carboxylate (513) as prepared by *Ammar et al*



(i) ethanol, piperidine, 80 °C

Figure 276: 2-Amino-5-cyano-1,6-dihydro-6-oxopyridine-3-carboxylate (514)

A similar reaction was attempted in this thesis using (**502**) as the required 2-cyano-*N*-arylacetamide compound. The reaction was performed using 0.62 mmol of (**502**) and equal molar amount of the ethyl cyanoacetate and *p*-methoxybenzaldehyde. TLC analysis (eluent 1:4 Hexane:EtOAc) revealed that all *p*-methoxybenzaldehyde was consumed but there was small quantity of (**502**) and ethyl cyanoacetate detected. Two new compounds were present, one at the baseline of the TLC and a second compound with R_f 0.68. However the compound at R_f 0.68 was identified as ethyl 2-cyano-3-(4-methoxyphenyl)acrylate (**515**) which was formed

from the Knoevenagel condensation of ethyl cyanoacetate with *p*-methoxybenzaldehyde. The ^{1}H-NMR spectrum of the baseline compound (**516**) is displayed in figures 277 amd 278.

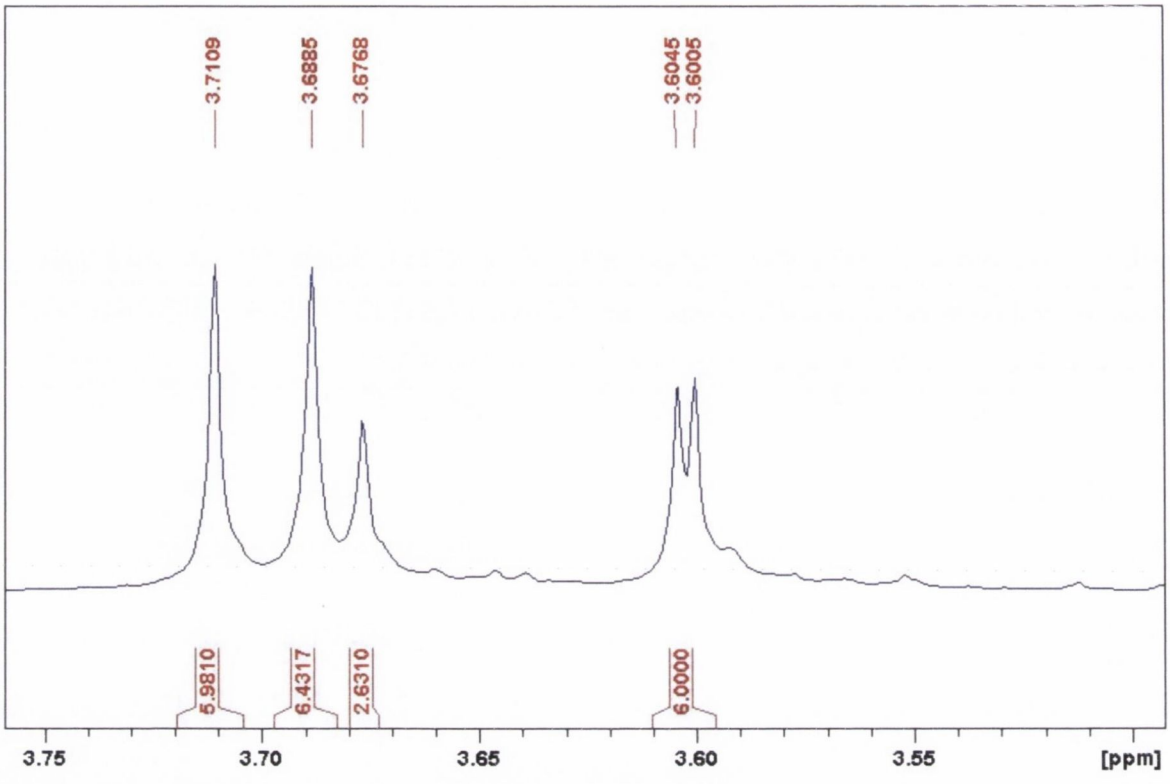


Figure 277: ^{1}H-NMR spectrum of baseline compound (516) from 3.55 - 3.75 ppm

Inspection of the ^{1}H-NMR spectrum determined that the baseline compound was not the desired 2-amino-5-cyano-1,6-dihydro-6-oxopyridine-3-carboxylate (**514**). However it was apparent that the compound had 7 methoxy groups, four of which were symmetric. Also the singlets at 6.54 ppm and 6.73 ppm, both integrating for 2 protons, indicated that this compound contained two separate symmetric aromatic protons. The following scheme, figure 279, shows the possible structure of this compound (**516**) and proposed synthetic route for its formation.

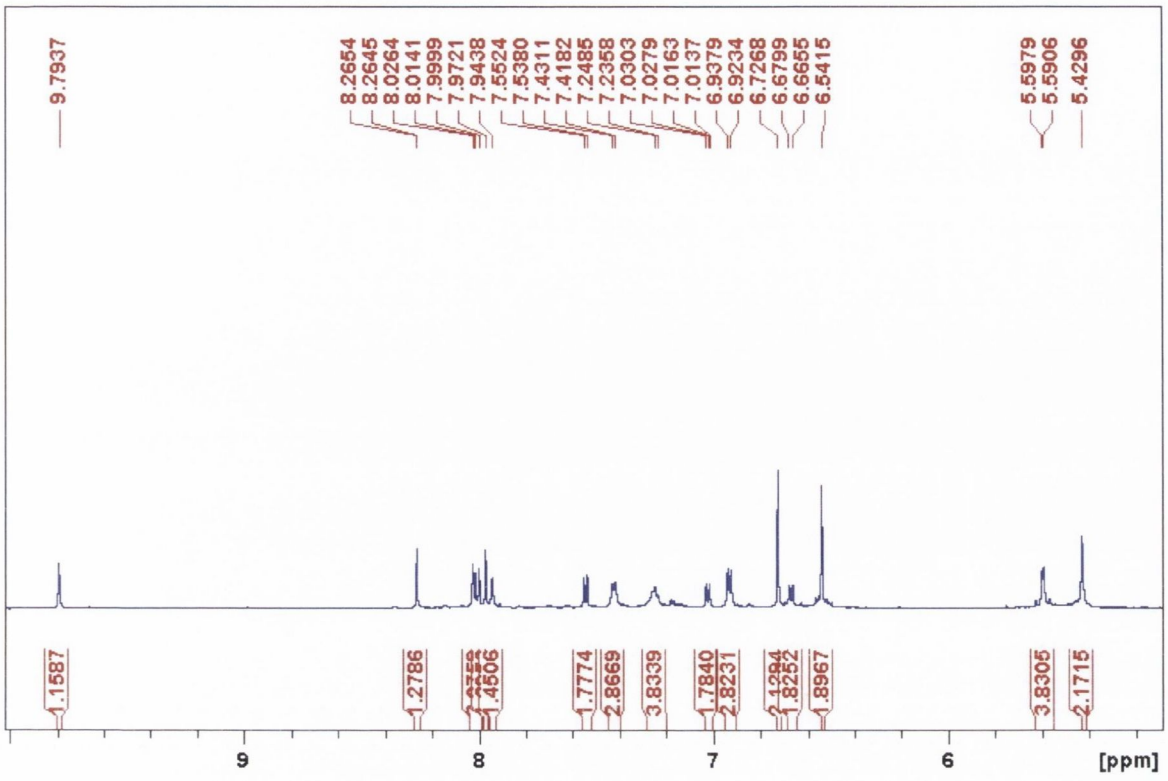


Figure 278: ^{1}H-NMR spectrum of baseline compound (516) showing aromatic region

It is proposed that (**502**) reacts with *p*-methoxybenzaldehyde forming the intermediate (**517**), figure 279. This intermediate is attacked by a second molecule of (**502**) and following Michael addition and cyclization, the baseline compound (**516**) is formed. A sample of baseline compound was sent for HRMS analysis and the $[M+Na]^+$ ion, 899.3099, was detected. Also in the same sample, trace amounts of the $[M+H]^+$ ion (Found: 610.2300, $C_{33}H_{32}N_5O_7$ requires 610.2302) of the desired product (**514**) were detected. Thus this first attempt was somewhat successful.

It was then decided to try a stepwise synthetic approach to the pyridone (**514**), figure 280. Since ethyl 2-cyano-3-(4-methoxyphenyl)acrylate (**515**) was formed during the preparation of (**514**), it believed that reacting (**502**) with ethyl 2-cyano-3-(4-methoxyphenyl)acrylate (**515**) would not only afford (**514**) but constitute a cleaner synthetic route. Alternatively (**502**) could be reacted with *p*-methoxybenzaldehyde forming (**518**). If (**518**) is isolated and then reacted with ethyl cyanoacetate, (**514**) should be formed. Thus there was two potential stepwise synthetic approaches available, route A and route B, illustrated in figure 280. *Khalifa et al* reported a stepwise synthetic plan, similar to route B, for the synthesis of a series pyridone type compounds[402].

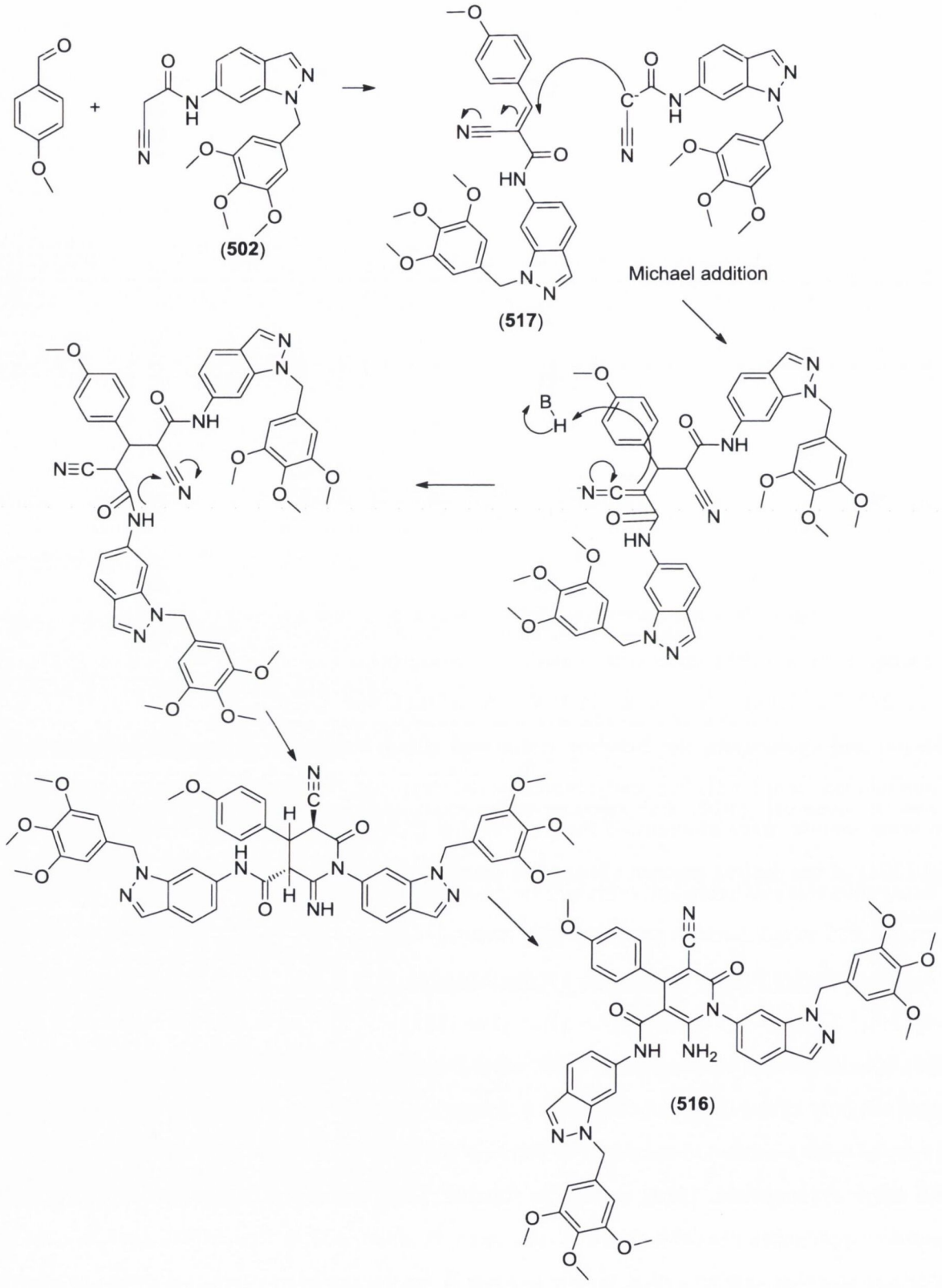


Figure 279: Proposed mechanism for the synthesis of pyridone compound (516)

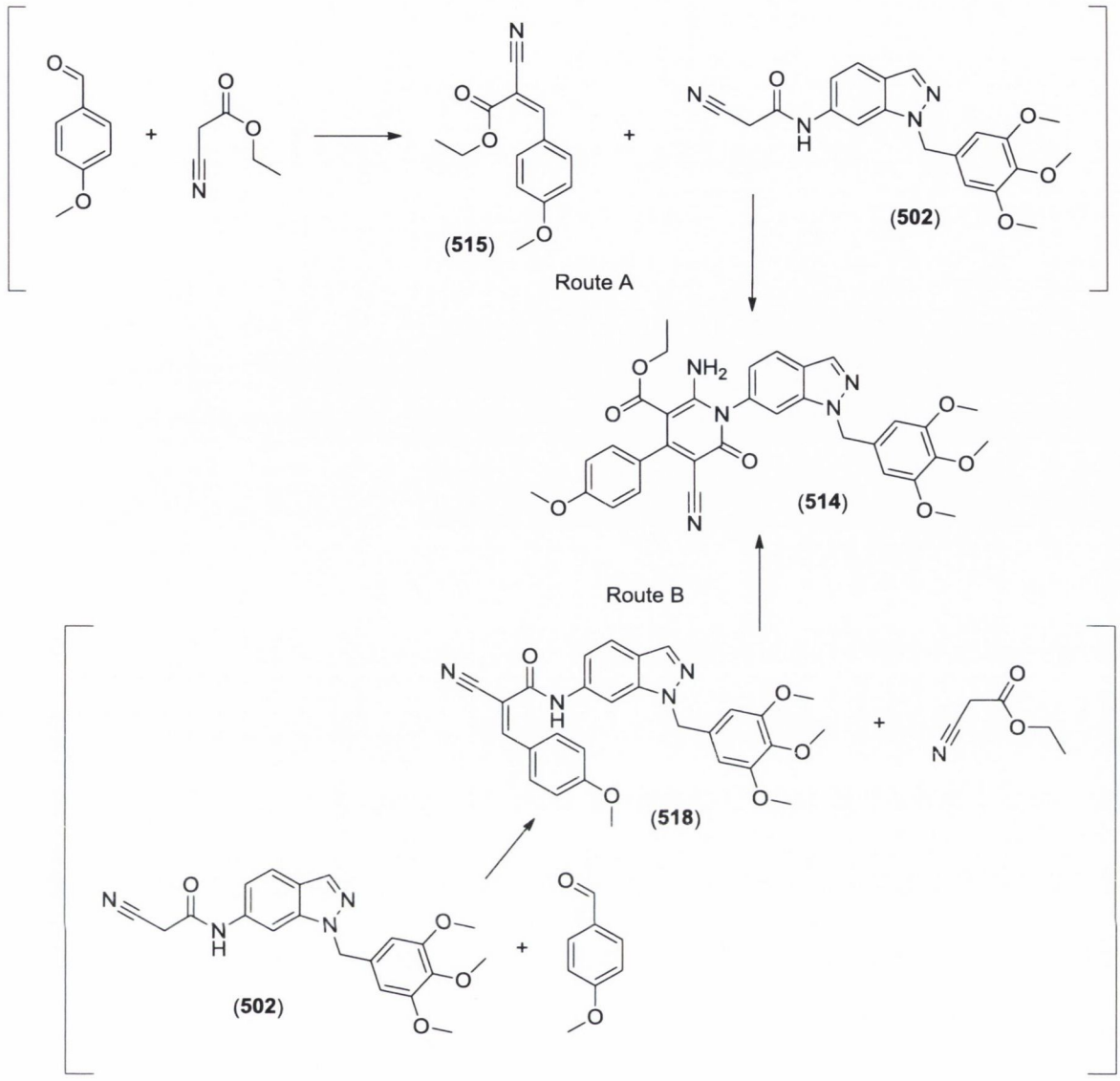


Figure 280: Two possible synthetic approaches to (514)

In the present work, the cyanoacrylate (**515**) was prepared from *p*-methoxybenzaldehdye and ethyl cyanoacetate and then was reacted with (**502**) in ethanol, using a catalytic amount of piperidine, at room temperature. After 1 h, a yellow precipitate formed. After 5 h of stirring at room temperature, the solution was filtered and the yellow precipitate collected. This precipitate was not the desired pyridone product (**514**) but was identified as (**518**). The ^{1}H-NMR spectrum for (**518**) is identical to the ^{1}H-NMR spectrum of the product formed from the reaction of 4-methoxybenzaldehyde with (**502**). Route B was then attempted but (**502**) and (**515**) were formed. The actual products obtained from route A and route B are shown in figure 281.

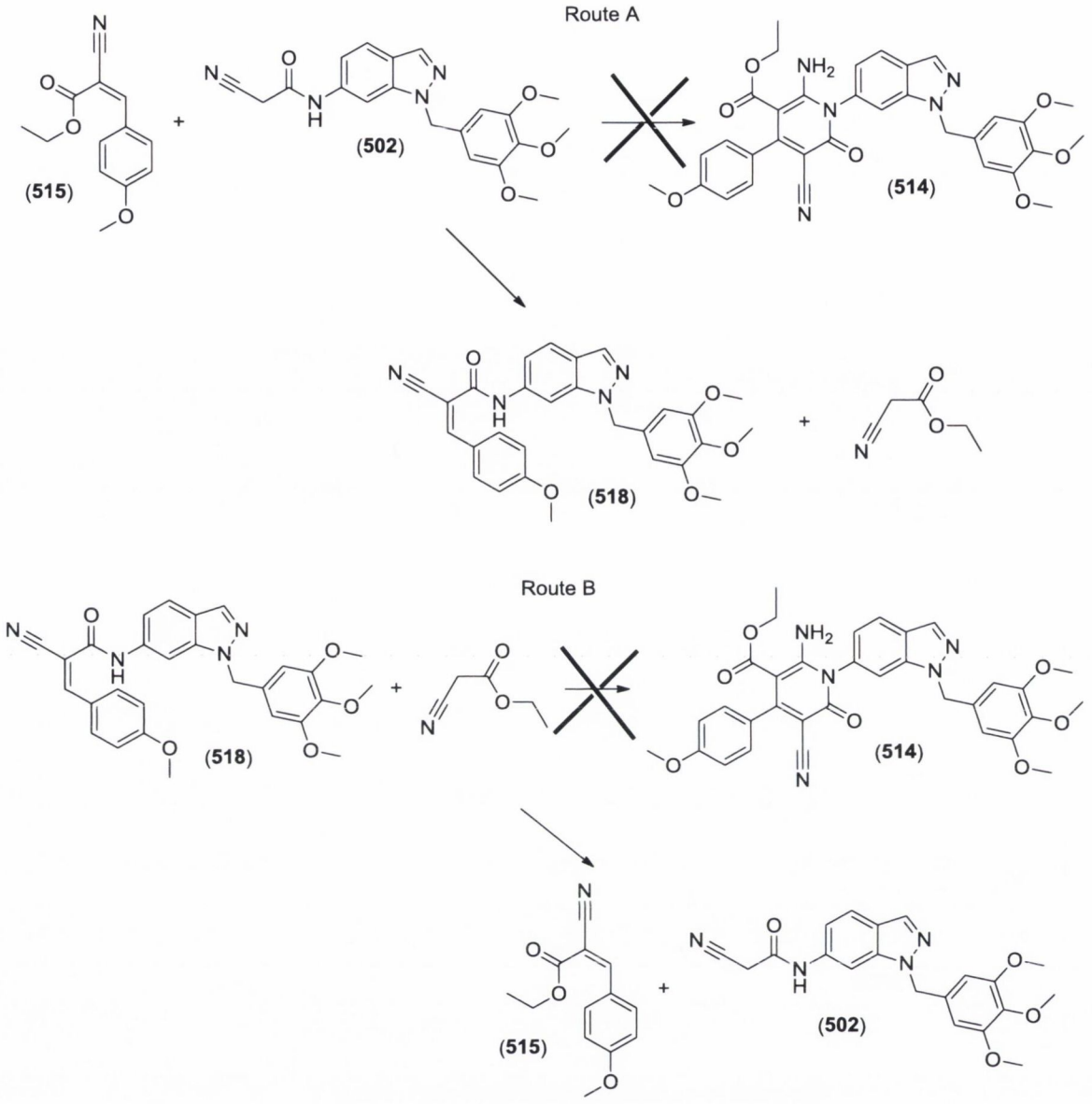
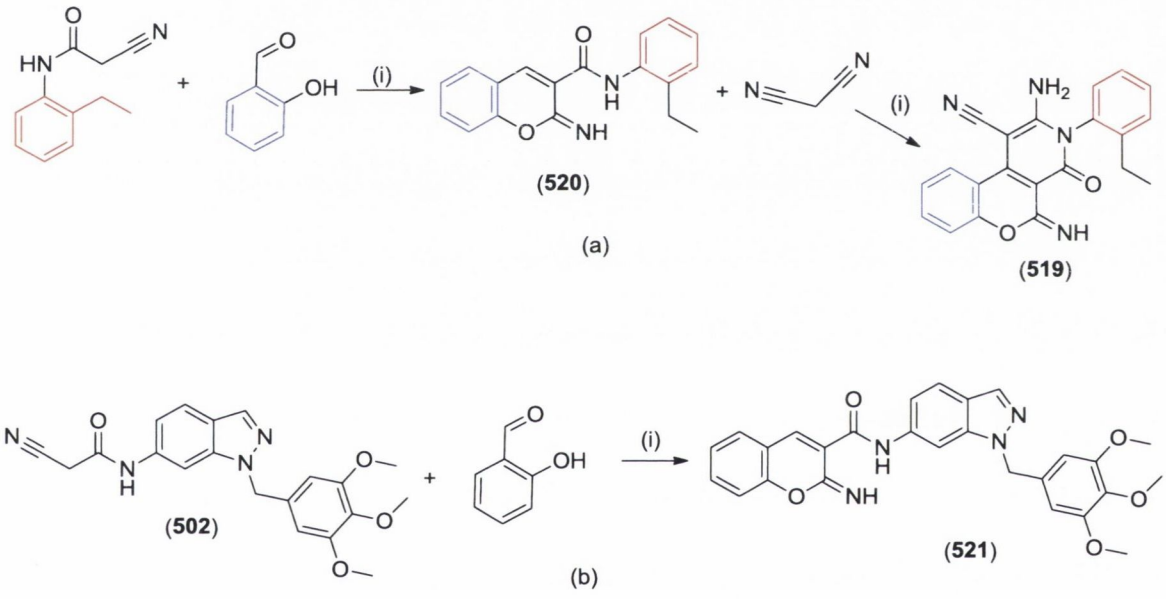


Figure 281: Products obatined from route A and route B

A final attempt to prepare the pyridone (**514**) using a one pot synthetic method from the cyanoacetamide (**502**), *p*-methoxybenzaldehdye and ethyl cyanoacetate was performed. The reaction was closely monitored by TLC. Equimolar amounts (0.62 mmol) of each reactant were refluxed in ethanol (4 mL), in the presence of a catalytic amount of piperidine. After 1 hour, a yellow precipitate was observed. The reaction was cooled to room temperature and TLC showed the presence of significant amount of (**518**), the yellow precipitate, and trace amounts of (**502**), (**515**) and ethyl cyanoacetate. No *p*-methoxybenzaldehdye was present. It seems that the formation of (**518**) is kinetically favourable. Since (**518**) was present is in the reaction mixture, 2 molar equivalents of ethyl cynaoacetate was added in order to drive the reaction to

completion. Purification by flash column chromatography showed the presence of ethyl cyanoacetate, ethyl 2-cyano-3-(4-methoxyphenyl)acrylate, (**502**) and (**516**). Further attempts to obtain the pyridone (**514**) were not pursued.

A further extension of the chemistry of 2-cyano-N-phenylacetamides resulting in the formation of chromene substituted indazoles was investigated. *Ismail et al* had reported a series of chromeno(3,4-c)pyridines such as (**519**) from the required 2-cyano-*N*-phenylacetamides[407], figure 282 (a). The chromene intermediate (**520**) was obtained by refluxing the required 2-cyano-*N*-phenylacetamide with salicylaldehyde, in ethanol, in the presence of ammonium actetate. (**520**) was then further reacted with malononitrile, in the presence of ammonium acetate, yielding the chromeno(3,4-*c*)pyridine (**519**).



(i) NH_4OAc, ethanol, reflux

Figure 282: (a) Chromeno(3,4-*c*)pyridones prepared by *Ismail et al* (b) Synthesis of chromene (521)

In the present work, the chromene (**521**) was successfully prepared from (**502**) and salicylaldehyde. (**512**) was characterised by ^{1}H-NMR, ^{13}C-NMR, IR and MS. In the IR spectrum, the NH and C=O absorptions appear at 3299.5 and 1692.7 cm^{-1} respectively while the C=O appears at 160.230 ppm in the ^{13}C-NMR spectrum. HRMS detected the $[M+Na]^+$ ion (Found: 507.1627, $C_{27}H_{24}N_4NaO_5$ requires 507.1644). The indazole scaffold has not been mentioned previously in the preparation of chromeno(3,4-*c*)pyridones and so future research would yield a novel series of compounds.

2.10.3 Conclusion

It was initially desired to synthesise a series of a dihydropyridines, dihyroisoquinolines and related compounds using the indazole scaffold. Such compounds were of interest due to their potential biological activity and the fact that the indazole scaffold has not been previously used in the preparation of these compounds. Even though the desired dihydroisoquinline (**510**) was not prepared, methods have been developed for the efficient synthesis of 2-cyano-*N*-phenylacetamide precursors (**500**), (**502**), (**503**) and (**504**) using MAOS. During the course of this work, the instability of amide bond in (**500**) was encountered as a secondary product (**501**) was obtained. No secondary products were obtained during the preparation of (**502**), (**503**) and (**504**) as they contain benzyl or aryl group at N-1. The pyridone compound (**505**) was eventually prepared from (**500**) after the solvent was changed from ethanol to chloroform. The change of solvent was required as the amide bond in (**500**) was susceptible to hydrolysis. Since (**502**), (**503**) and (**504**) did not contain N-1 amide bonds, hydrolysis was not an issue and ethanol was used in the preparation of the corresponding novel pyridones (**507**), (**508**) and (**509**). An attempt was made to prepare alternative pyridone compounds (**514**) using one pot reaction from (**502**), ethyl cyanoacetate and 4-methoxybenzaldehyde but this reaction proved only somewhat successful. The desired pyridone (**514**) was only obtained in trace amounts together with a novel *bis*indazole substituted product (**516**). A stepwise synthetic approach to (**514**) was attempted but was not successful. However a novel chromene/benzopyran compound (**521**) was successfully prepared from (**502**) and salicyaldehyde. The preparation of the aforementioned heterocycles, using the indazole scaffold, has not been previously attempted and represent an extremely novel segment of work.

Chapter 3
Biochemistry

3.0 Introduction

The chapter describes the biochemical evaluations performed in this thesis project. The AlamarBlue (viability) assay was used to evaluate a selection of the indazole compounds. Compounds were evaluated for antiproliferative activity in the MCF-7 human breast cancer cell. Within this chapter, the details of materials and methods for the AlamarBlue assay is provided together with a discussion of the biochemical results obtained for the compounds innestigation.

3.1 Materials for Biochemical analysis

Materials	Supplier
Alamar Blue	Biosource
DMSO	Sigma
Dulbecco's Modified Eagle's Medium	Gibco
Eagle's Minimum Essential Medium	Sigma/Gibco
L-glutamine	Gibco
MCF-7 Cells	E.C.A.C.C.
Non-essential amino acids	Sigma
Penicillin/streptomycin	Sigma
Phosphate Buffer Saline	Oxoid Ltd.

3.2 MCF-7 human breast cancer cell

The MCF-7 cell line is a human breast cancer cell derived from a 69 year old Caucasian woman in 1970[404]. This cell line was used to evaluate the antiproliferative properties of a selection of the synthesised indazoles contained in this thesis.

3.3 Storage and breaking out of cells

When cells were not in use, they were stored in a liquid nitrogen vapour phase environment at approximately -180 °C. When preserving cells, they were suspended in 10 % DMSO/90 % foetal bovine serum in a cryotube, placed in a freezer at -78 °C overnight and transferred into liquid nitrogen after 24 hours. Cells that were required for anti-profileration studies, were thawed at 37 °C, diluted with complete growth medium and centrifuged at 1250 rpm for 5 minutes. The supernatant containing DMSO was poured off, the cells were re-suspended in

complete growth medium and were transferred into a 25 cm^3 flask. 10 mL of the appropriate growth medium was added to the flask and it was incubated at 5 % CO_2/95 % air and 37 °C until confluency was reached. The cells were then be transferred to a 75 cm^3 culture flask.

3.4 Growth and maintenance of cells

MCF-7 cells were grown in Minimum Essential Medium Eagle (MEME) supplemented with non-essential amino acids, FBS, L-glutamine and penicillin/streptomycin. Cell culture flasks were stored in an incubator at 5 % CO_2/95 % air and at 37 °C. When cells reached confluency, they were split to prevent cell death. To split the cells, the growth media was decanted and 3 mL of trypsin-EDTA solution 10X was added. When trypsinization was complete, the cells were in suspension and are round in shape. 10 mL of complete growth medium was added, the mixture was centrifuged at 1000 rpm for 5 minutes after the supernantant was decanted. The pellet of cells remaining was re-suspended in 2 – 4 mL of complete growth media.

3.5 Counting cells

A haemocytometer was used to count cells. It is etched with 5 x 5 grid of squares. The cells in the four corner and in the centre square were counted. Cells touching the top and left hand sides of these squares were included on the count, but cells touching the bottom and right hand sides were excluded. The total number of cells counted in the five squares is multiplied by 5 to give the number of cells in the grid. This is equivalent to the number of cells by 10^4 per mL of medium. The process was repeated and the average was used to calculate the number of cells per mL.

3.6 AlamarBlue

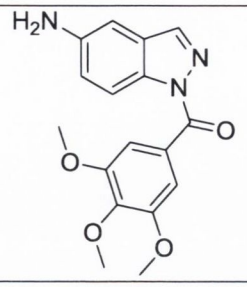
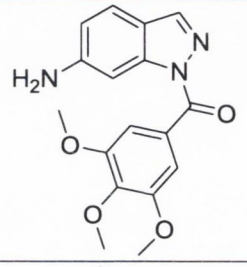
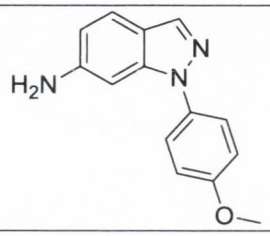
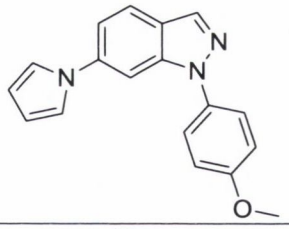
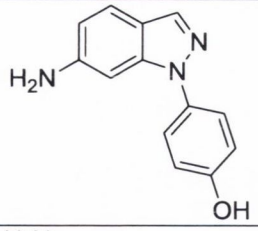
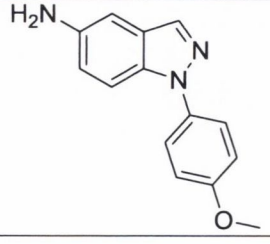
A dye known as AlamarBlue was used to measure the growth inhibitory effects. As with the tetrazolium dyes, AlamarBlue monitors the reducing environment of the cell. The internal environment of the proliferating cell is more reduced than that of a non-proliferating cell[405]. As the dye is reduced, it changes from an oxidised indigo-blue, non-fluorescing state to a fluorescent pink. There are two ways to measure alamar Blue reduction, either by measuring the absorbance spectrophotometrically at 570 nm and 600 nm, either by measuring the fluorescence with excitation at 530 – 560 nm and emission at 590 nm. The 96 well plates were treated with compounds and were incubated at 5 % CO_2/95 % air at 37 °C. After 72 hours. Each well was treated with 20 µL of alamar Blue, prewarmed to 37 °C, and left to incubate in the dark for 4 hours and followed by measuring the flourescence at emission 590 nm and excitation

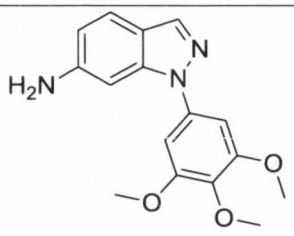
544 nm. The background fluorescence of the media without cells was deducted from each group, and the control untreated cells represented 100% cell viability.

3.7 Results and Discussion

Compounds (**168**), (**209**), (**286**), (**480**), (**288**), (**290**) and (**287**) were chosen as a representative selection for an initial screen, at 100 μM, to evaluate cell proliferation in the MCF-7 human breast cancer cell line. Each compound was diluted to a volume of 1 mL by first adding 100 μL of DMSO and then 900 μL of ethanol, giving an initial concentration of 100 mM. The cells were then dosed to 2 μL of the required solution so the final concentration of the compound and DMSO concentration in the well was 100 μM and 0.1% respectively. The results are displayed in table 40.

Table 40: Compounds selected for initial screening at 100 μM

Compound Number	Compound	% Cells remaining after 72 h	% Inhibition at 100 μM
(**168**)		56	44
(**209**)		39	61
(**286**)		83	17
(**480**)		29	71
(**288**)		36	64
(**290**)		38	62

(**287**)		15	85

From the compounds evaluated, compound (**287**) was clearly the most potent with 85 % inhibition of proliferation after 72 hours. The pyrrole compound (**480**) also showed encouraging effects with 71 % inhibition of proliferation. The lead indazole compound (**168**) showed 44 % inhibition of growth while the 6-amino analogue (**209**) demonstrated 61 % inhibition of proliferation.

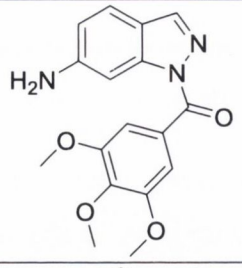
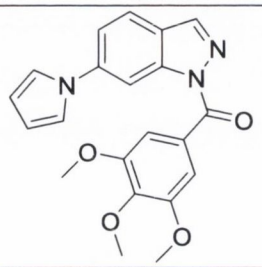
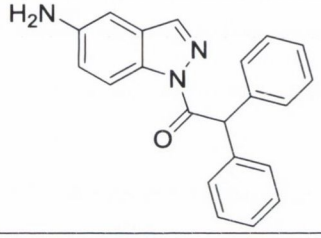
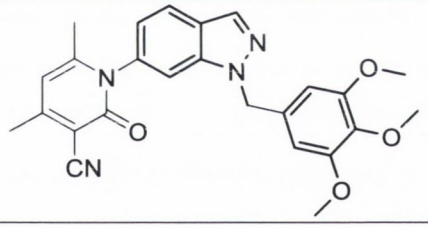
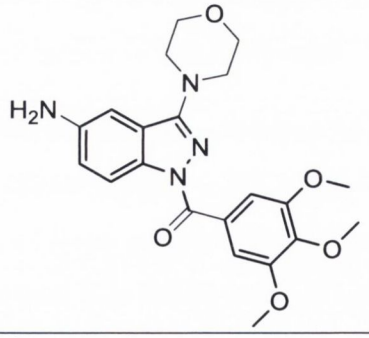
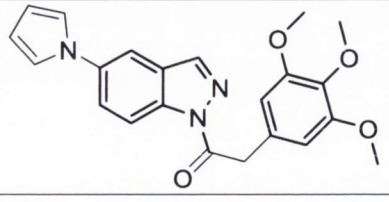
A group of 14 compounds were accepted by the NCI for evaluation in the NCI 60 cancer cell line screening program[410], table 41. These cancer cell lines cover a range of cancers including breast cancer, CNS cancer, leukemia, non-small cell lung cancer, prostate cancer, melamoma, ovarian cacer and renal cancer. The selected compounds were evaluated using an initial one dose screen at a concentration of 10 μM. The lowest mean growth percent overall was observed for compound (**209**) of 24.5 % over the 60 cancer cell line screen. The structure of compound (**209**) is similar to the lead compound (**168**) but differs in the position of the aromatic amine substituent at C-6 rather than C-5 in (**168**). The observed % growth in the leukemia panel and colon cancer panel for (**209**) and the other compounds, screened at 10 μM, are shown in figures 283 and 284 respectively. The % growth of various leukemia cell lines was the lowest for (**209**) indicating potential for further investigation of this compound.

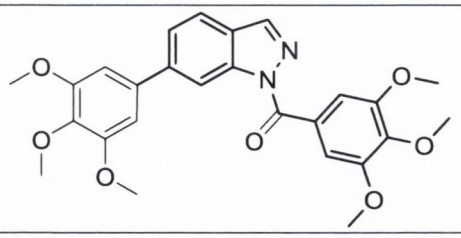
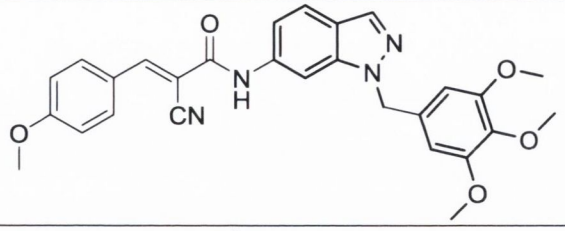
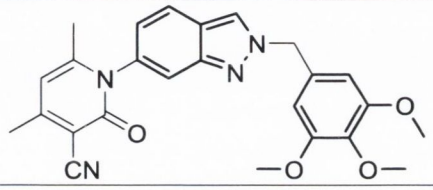
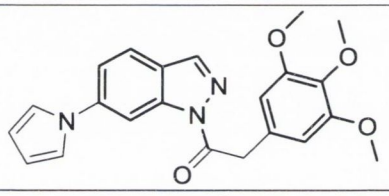
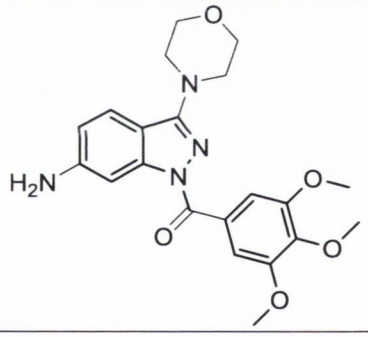
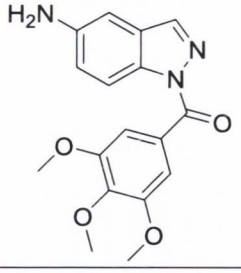
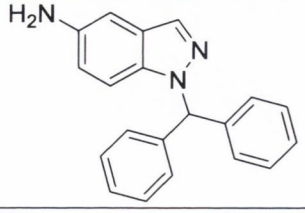
(**209**) satisfied the threshold requirements and proceeded to the NCI five dose screening. The result from the five dose screen is shown in figures 285 - 288. IC_{50} values in the low and sub μM were observed for the cancer cell lines, particularly the leukemia panel and colon cancer panel. Compound (**209**) had the lowest IC_{50} values in the HL-60 cell line (Leukemia, IC_{50} = 0.324 μM), NCI-H460 cell line (non-small cell lung cancer, IC_{50} = 0.408 μM), HT29 cell line (colon cancer, IC_{50} = 0.376 μM), SNB-75 cell line (CNS cancer, IC_{50} = 0.292 μM), MDA-MB-435 cell line (melanoma, IC_{50} = 0.158 μM), OVCAR-3 cell line (ovarian cancer, IC_{50} = 0.400 μM), A498 cell line (renal cancer, IC_{50} = 0.115 μM), PC-3 cell line (prostate cance, IC_{50} = 1.3 μM) and MDA-MB-468 cell line (breast cancer, IC_{50} = 0.753 μM), figure 286.

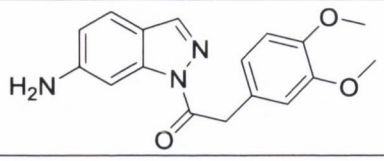
The detailed results obtained for compound (**209**) in the 60 cell line screen are shown in figures 285 – 288. The 5 dose viability result for compound (**209**) over the 60 cell lines is presented in figure 285. The GI_{50}, LC_{50} and TGI results for the 60 cancer cell lines is given in figure 286. The individual results for the various cancer cell lines is presented in figure 285 while the mean GI_{50}, LC_{50} and TGI results for the 60 cell lines is displayed in figure 288.

In figure 288, the mean logarithmic GI value, - 5.8, is subtracted from the logarithmic GI values observed for the cancer cell lined which were dosed with (**209**). The results of which are displayed by the first bar graph. Cancer cell line more sensitive to (**209**) have bars deflecting to the right e.g. HL-60, HCT-15, A498 while cancer cell lines more resistant to (**209**) have bars deflecting to the left e.g. NCI-H226, UACC-257, OVCAR-4, TK-10.

Table 41: Mean growth precentage for compounds assayed by NCI

Compound Number (NCI Code)	Compound Structure	Mean Growth Percent
(**209**) (779302)		24.50
(**477**) (778764)		96.89
(**235**) (779305)		97.41
(**507**) (778762)		99.26
(**458**) (778761)		71.93
(**487**) (778760)		98.02

(**326**) (778759)		76.41
(**518**) (779299)		98.23
(**509**) (770298)		97.81
(**479**) (779301)		97.48
(**465**) (779300)		49.66
(**168**) (779303)		97.15
(**269**) (779305)		91.94

(**229**) (779304)		93.04

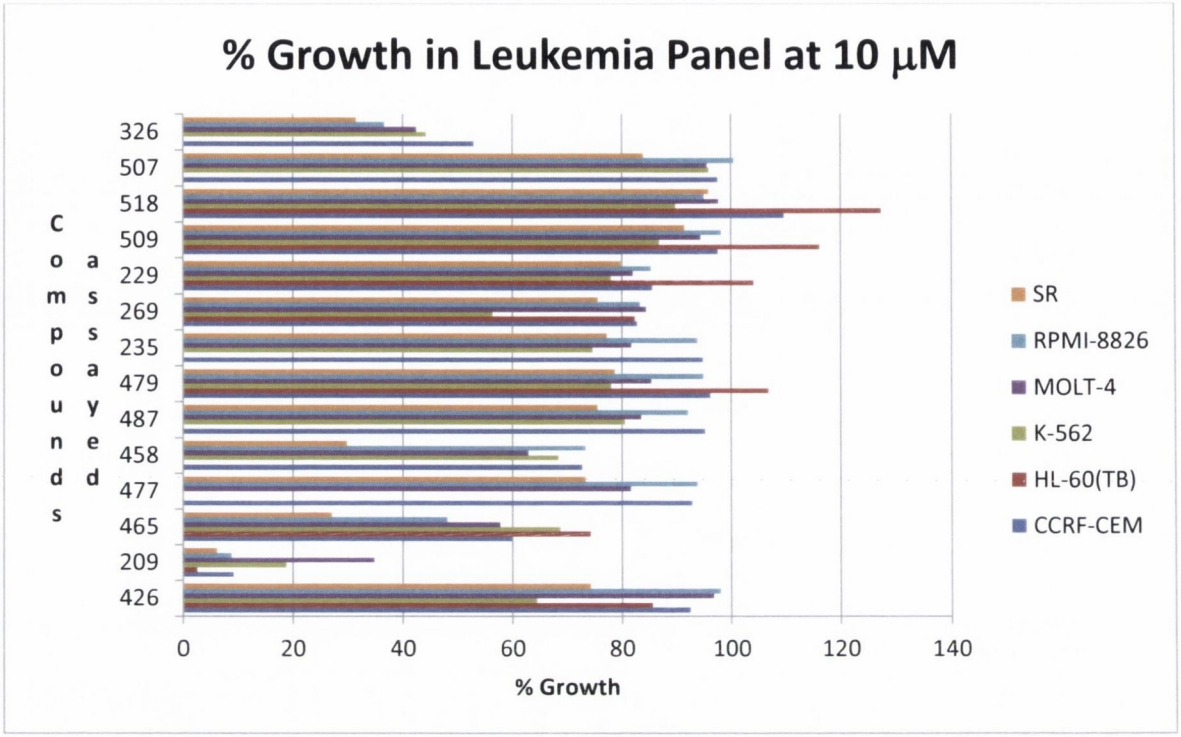


Figure 283: % Growth in leukemia panel for selected indazoles

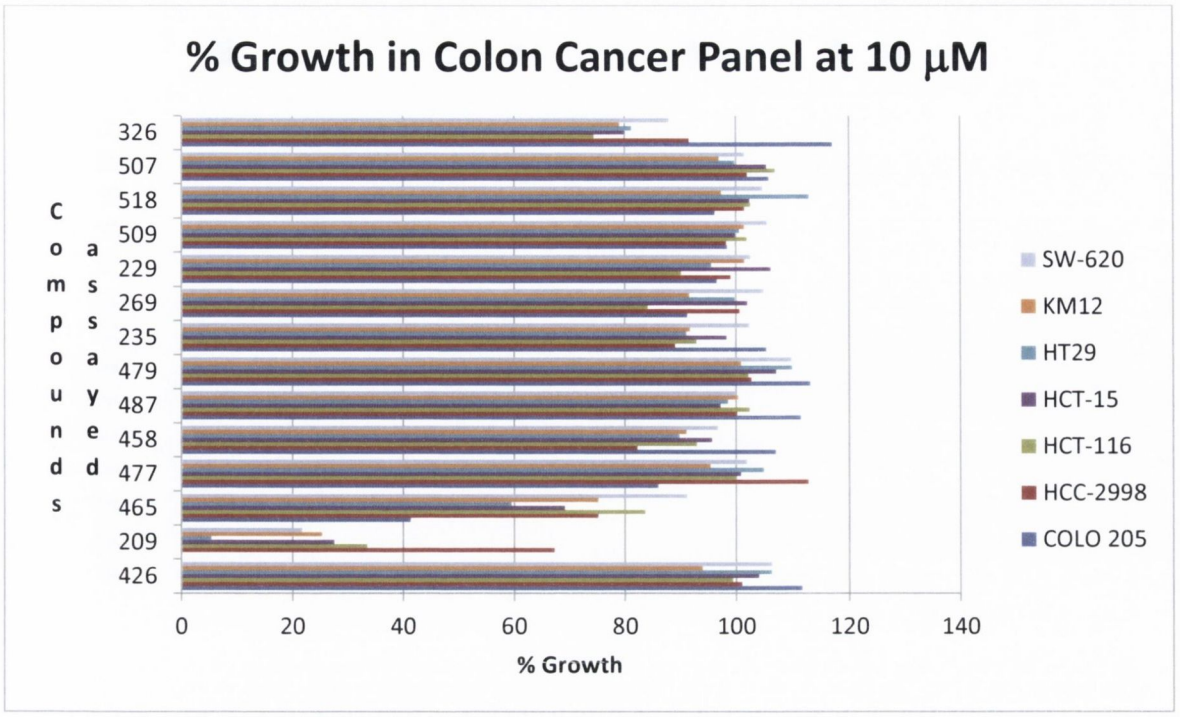


Figure 284: % Growth in colon cancer panel for selected indazoles

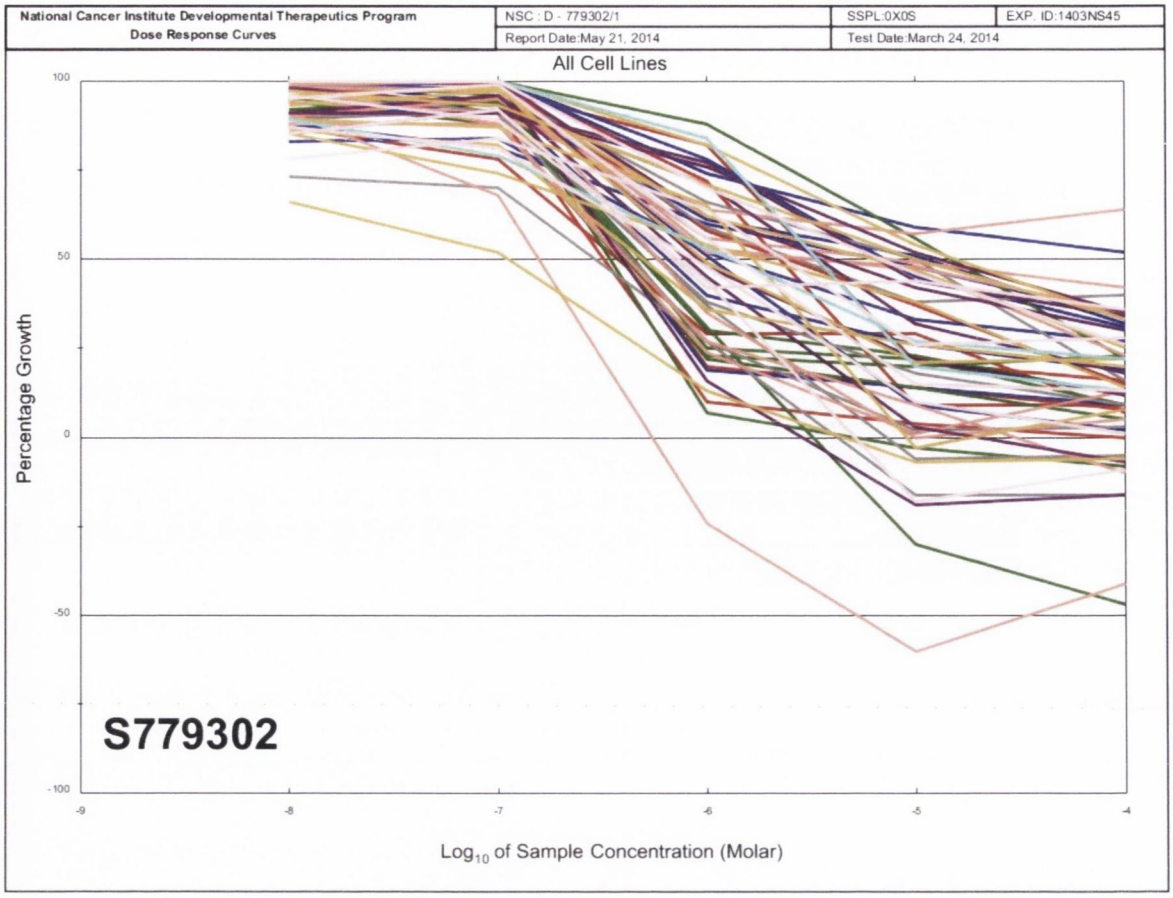


Figure 285: Five dose NCI results for (209) for 60 cell lines

National Cancer Institute Developmental Therapeutics Program
In-Vitro Testing Results

NSC : D - 779302 / 1	Experiment ID : 1403NS45	Test Type : 08	Units : Molar
Report Date : May 21, 2014	Test Date : March 24, 2014	QNS :	MC :
COMI : MJMTC094 (136935)	Stain Reagent : SRB Dual-Pass Related	SSPL : 0X0S	

			Log10 Concentration											
	Time		Mean Optical Densities					Percent Growth						
Panel/Cell Line	Zero	Ctrl	-8.0	-7.0	-6.0	-5.0	-4.0	-8.0	-7.0	-6.0	-5.0	-4.0	GI50	TGI	LC50
Leukemia															
CCRF-CEM	0.438	2.389	2.435	2.434	1.852	0.618	0.606	102	102	72	9	9	2.27E-6	> 1.00E-4	> 1.00E-4
HL-60(TB)	0.739	2.756	2.826	2.582	0.950	0.825	0.742	103	91	10	4	.	3.24E-7	> 1.00E-4	> 1.00E-4
K-562	0.315	1.973	2.015	1.959	0.642	0.547	0.449	103	99	20	14	8	4.16E-7	> 1.00E-4	> 1.00E-4
MOLT-4	0.659	2.532	2.605	2.779	1.746	1.347	0.946	104	113	58	37	15	2.38E-6	> 1.00E-4	> 1.00E-4
RPMI-8226	1.155	2.993	2.944	2.946	2.656	1.534	1.450	97	97	82	21	16	3.30E-6	> 1.00E-4	> 1.00E-4
SR	0.455	1.938	1.740	1.613	0.878	0.880	0.560	87	78	29	29	7	3.69E-7	> 1.00E-4	> 1.00E-4
Non-Small Cell Lung Cancer															
A549/ATCC	0.473	2.098	2.101	2.006	1.128	0.899	0.789	100	94	40	26	19	6.61E-7	> 1.00E-4	> 1.00E-4
HOP-62	0.707	1.661	1.501	1.509	1.199	1.018	0.960	83	84	52	33	27	1.21E-6	> 1.00E-4	> 1.00E-4
HOP-92	0.971	1.616	1.537	1.491	1.358	1.282	1.189	88	81	60	48	34	7.07E-6	> 1.00E-4	> 1.00E-4
NCI-H226	0.863	2.125	1.989	2.048	1.627	1.502	1.266	89	94	61	51	32	1.08E-5	> 1.00E-4	> 1.00E-4
NCI-H23	0.611	1.992	2.018	2.010	1.684	1.236	1.036	102	101	78	45	31	7.15E-6	> 1.00E-4	> 1.00E-4
NCI-H322M	0.749	2.009	1.989	2.085	1.686	1.492	1.408	98	106	74	59	52	> 1.00E-4	> 1.00E-4	> 1.00E-4
NCI-H460	0.308	2.847	2.807	2.797	0.799	0.658	0.531	98	98	19	14	9	4.08E-7	> 1.00E-4	> 1.00E-4
NCI-H522	1.325	2.517	2.514	2.482	1.928	1.434	1.347	100	97	51	9	2	1.03E-6	> 1.00E-4	> 1.00E-4
Colon Cancer															
COLO 205	0.502	1.607	1.518	1.554	0.840	0.351	0.265	92	95	31	-30	-47	5.01E-7	3.19E-6	> 1.00E-4
HCC-2998	0.761	2.396	2.529	2.700	2.192	1.676	1.120	108	119	88	56	22	1.50E-5	> 1.00E-4	> 1.00E-4
HCT-116	0.387	2.390	2.215	2.279	0.833	0.669	0.481	91	94	22	14	5	4.13E-7	> 1.00E-4	> 1.00E-4
HCT-15	0.277	2.120	2.033	1.984	0.826	0.693	0.491	95	93	30	23	12	4.77E-7	> 1.00E-4	> 1.00E-4
HT29	0.304	1.432	1.501	1.526	0.382	0.295	0.280	106	108	7	-3	-8	3.76E-7	5.01E-6	> 1.00E-4
KM12	0.433	2.028	2.104	1.963	0.840	0.790	0.574	105	96	25	22	9	4.49E-7	> 1.00E-4	> 1.00E-4
SW-620	0.302	2.297	2.181	2.061	0.755	0.702	0.759	94	88	23	20	23	3.83E-7	> 1.00E-4	> 1.00E-4
CNS Cancer															
SF-268	0.713	1.919	1.894	1.887	1.504	1.313	0.907	98	97	66	50	16	9.64E-6	> 1.00E-4	> 1.00E-4
SF-295	0.519	2.574	2.368	2.384	1.068	0.551	0.577	90	91	27	2	3	4.33E-7	> 1.00E-4	> 1.00E-4
SF-539	0.840	2.692	2.493	2.536	1.530	0.792	0.796	89	92	37	-6	-5	5.82E-7	7.36E-6	> 1.00E-4
SNB-19	0.620	2.340	2.317	2.290	1.628	1.277	1.302	99	97	59	38	40	2.63E-6	> 1.00E-4	> 1.00E-4
SNB-75	0.923	1.727	1.509	1.486	1.140	0.780	0.779	73	70	27	-16	-16	2.92E-7	4.31E-6	> 1.00E-4
U251	0.453	1.912	1.884	1.774	1.006	0.716	0.583	98	91	38	18	9	5.88E-7	> 1.00E-4	> 1.00E-4
Melanoma															
LOX IMVI	0.275	2.009	1.997	2.003	1.196	1.099	0.680	99	100	53	47	23	3.57E-6	> 1.00E-4	> 1.00E-4
M14	0.422	1.510	1.374	1.376	0.681	0.428	0.560	88	88	24	1	13	3.89E-7	> 1.00E-4	> 1.00E-4
MDA-MB-435	0.537	2.781	2.581	2.069	0.408	0.217	0.315	91	68	-24	-60	-41	1.58E-7	5.49E-7	.
SK-MEL-2	1.437	2.405	2.535	2.512	1.778	1.439	1.483	113	111	35	.	5	6.39E-7	> 1.00E-4	> 1.00E-4
SK-MEL-28	0.747	2.074	1.940	2.012	1.491	1.391	1.305	90	95	56	49	42	6.39E-6	> 1.00E-4	> 1.00E-4
SK-MEL-5	0.636	2.856	2.803	2.597	1.237	0.830	0.571	98	88	27	9	-10	4.22E-7	2.89E-5	> 1.00E-4
UACC-257	1.156	2.322	2.250	2.222	1.904	1.815	1.901	94	91	64	57	64	> 1.00E-4	> 1.00E-4	> 1.00E-4
UACC-62	0.876	3.040	2.991	2.979	2.008	1.914	1.635	98	97	52	48	35	3.37E-6	> 1.00E-4	> 1.00E-4
Ovarian Cancer															
IGROV1	0.611	2.227	2.356	2.416	1.618	1.291	1.101	108	112	62	42	30	4.05E-6	> 1.00E-4	> 1.00E-4
OVCAR-3	0.553	1.690	1.741	1.708	0.735	0.448	0.465	105	102	16	-19	-16	4.00E-7	2.86E-6	> 1.00E-4
OVCAR-4	0.689	1.712	1.622	1.616	1.464	1.216	1.044	91	91	76	52	35	1.23E-5	> 1.00E-4	> 1.00E-4
OVCAR-5	0.586	1.421	1.299	1.357	1.229	0.953	0.873	85	92	77	44	34	6.56E-6	> 1.00E-4	> 1.00E-4
OVCAR-8	0.717	2.551	2.509	2.420	2.019	1.298	1.041	98	93	71	32	18	3.42E-6	> 1.00E-4	> 1.00E-4
NCI/ADR-RES	0.492	1.802	1.861	1.832	1.119	0.774	0.646	105	102	48	22	12	9.14E-7	> 1.00E-4	> 1.00E-4
SK-OV-3	0.837	1.511	1.452	1.485	1.141	0.856	0.777	91	96	45	3	-7	8.01E-7	1.91E-5	> 1.00E-4
Renal Cancer															
786-0	0.587	2.066	2.012	2.041	1.315	0.900	0.913	96	98	49	21	22	9.65E-7	> 1.00E-4	> 1.00E-4
A498	1.276	1.744	1.585	1.521	1.338	1.192	1.199	66	52	13	-7	-6	1.15E-7	4.64E-6	> 1.00E-4
ACHN	0.406	1.779	1.688	1.739	1.252	1.051	0.754	93	97	62	47	25	6.17E-6	> 1.00E-4	> 1.00E-4
CAKI-1	0.591	2.796	2.479	2.395	1.396	1.154	1.029	86	82	36	26	20	5.03E-7	> 1.00E-4	> 1.00E-4
RXF 393	0.952	1.785	1.691	1.675	1.491	0.925	1.018	89	87	65	-3	8	1.65E-6	.	> 1.00E-4
SN12C	0.582	2.449	2.391	2.311	1.899	1.510	1.197	97	93	71	50	33	9.64E-6	> 1.00E-4	> 1.00E-4
TK-10	1.032	1.976	2.029	2.037	1.803	1.540	1.342	106	106	82	54	33	1.51E-5	> 1.00E-4	> 1.00E-4
UO-31	0.780	2.179	1.963	1.817	1.534	1.314	0.976	85	74	54	38	14	1.76E-6	> 1.00E-4	> 1.00E-4
Prostate Cancer															
PC-3	0.503	1.927	1.771	1.630	1.257	0.882	0.813	89	79	53	27	22	1.30E-6	> 1.00E-4	> 1.00E-4
DU-145	0.487	1.536	1.570	1.638	1.370	0.694	0.623	103	110	84	20	13	3.39E-6	> 1.00E-4	> 1.00E-4
Breast Cancer															
MCF7	0.322	1.881	1.807	1.865	1.203	0.551	0.524	95	99	56	15	13	1.43E-6	> 1.00E-4	> 1.00E-4
MDA-MB-231/ATCC	0.607	1.538	1.580	1.563	1.257	1.036	0.851	104	103	70	46	26	6.83E-6	> 1.00E-4	> 1.00E-4
HS 578T	1.177	2.137	2.009	1.957	1.637	1.272	1.185	87	81	48	10	1	8.66E-7	> 1.00E-4	> 1.00E-4
BT-549	1.199	2.054	1.926	1.989	1.561	1.571	1.508	85	92	42	44	36	7.03E-7	> 1.00E-4	> 1.00E-4
T-47D	0.721	1.357	1.217	1.253	1.130	0.884	0.899	78	84	64	26	28	2.34E-6	> 1.00E-4	> 1.00E-4
MDA-MB-468	0.750	1.686	1.652	1.587	1.166	0.616	0.681	96	89	44	-18	-9	7.53E-7	5.17E-6	> 1.00E-4

Figure 286: GI_{50}, TGI, LC_{50} results for (209) for the 60 cancer cell lines

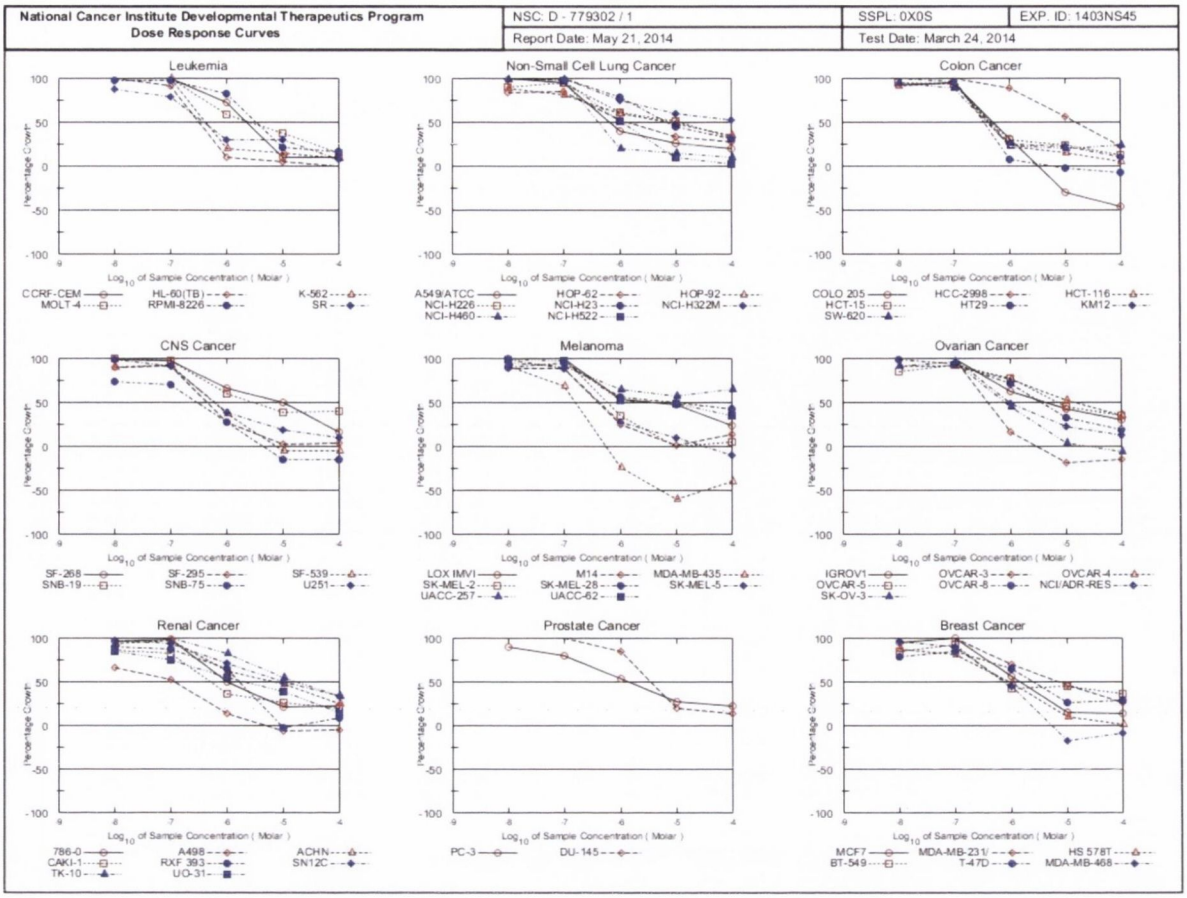


Figure 287: Growth precentage results for (209) on the 9 different cancer cell panels

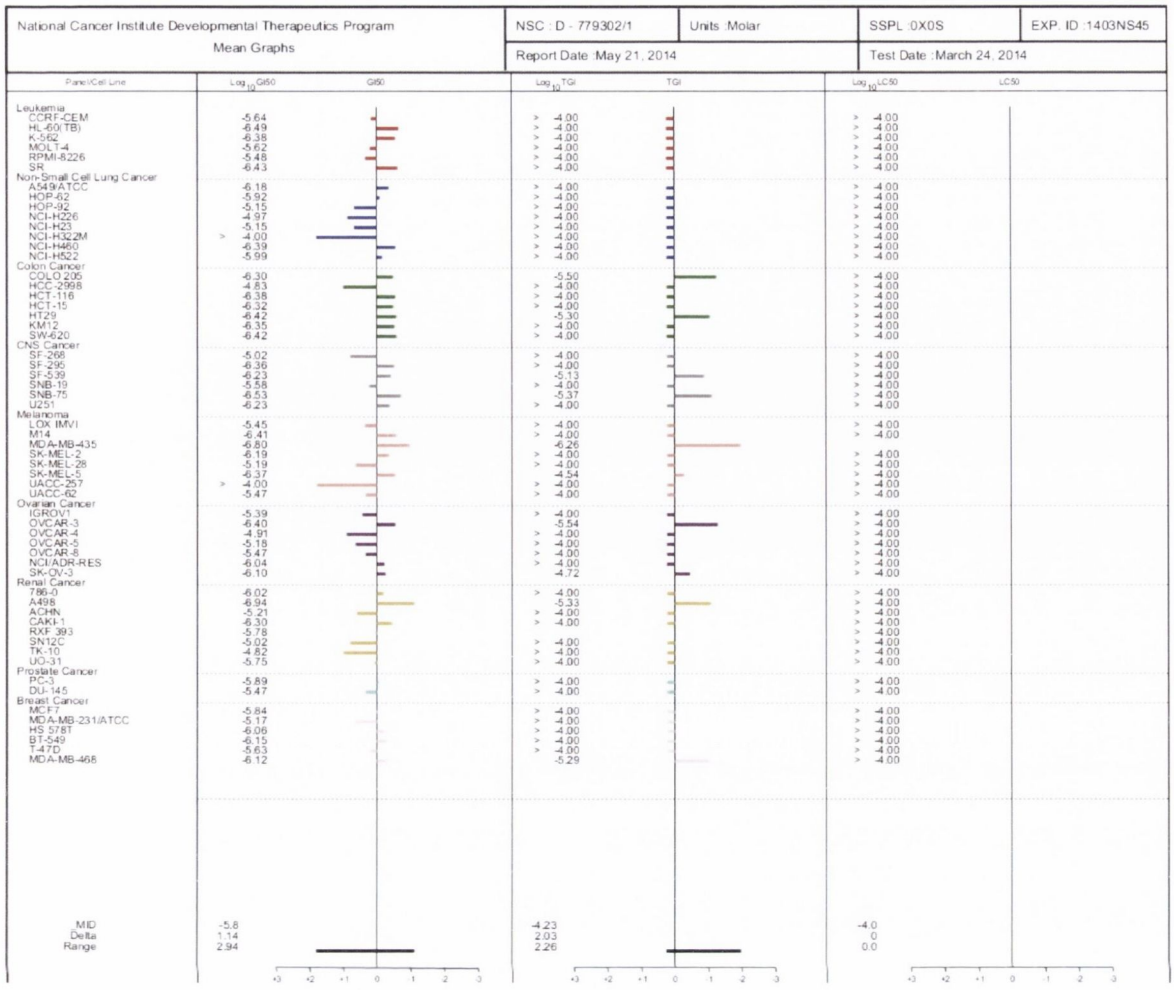


Figure 288: Mean GI50, TGI and LC50 results on 60 cell line for compound (209)

3.8 Conclusion

The (6-amino-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone compound (**209**) demonstrated useful antiproliferative activity in the 60 cancer cell line assay with IC_{50} values in the low micromolar and submicromolar region. Compounds (**326**), (**458**) and (**465**) displayed useful antiproliferative activity with mean growth percentages of 71.9 %, 76.41 % and 49.66 % respectively, indicating that the 6-amino and 5-amino group is important for maintaining the antiproliferative effect in compounds (**458**) and (**465**) and the replacement of the 5 or 6-amino group in (**168**) by the 3,4,5-trimethoxybenzoyl ring is well tolerated and maintains activity. Surprisingly the lead compound (**168**) did not perform well in the initial one dose screen (10 μM) with the 6-amino isomer (compound (**209**)) was identified as the most potent compound evaluated.

Chapter 4

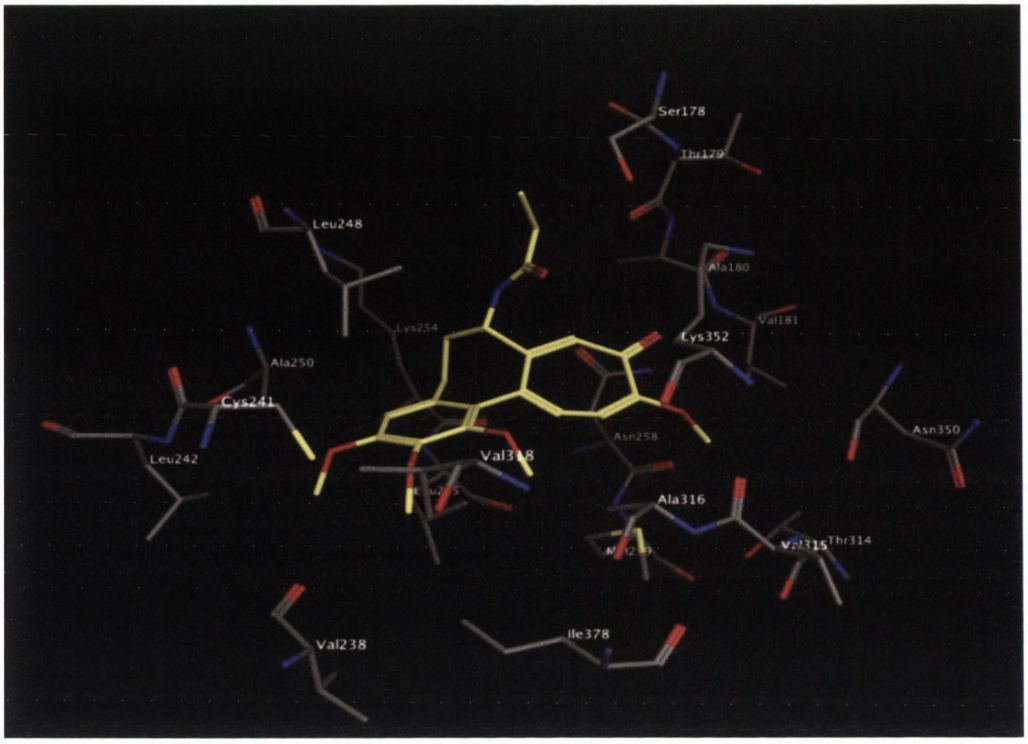
Molecular Modelling

4.0 Molecular Modelling

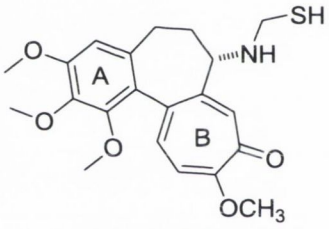
The section will attempt to rationalize the biochemical results from section 7.0 by performing molecular modelling studies using Molecular Operating Environment (MOE). A selection of the synthesised compounds in this thesis were docked into the colchicine active site of tubulin in order to observe any possible interactions/conformation of these compounds with the amino acid residues which constitute the colchicine active site of tubulin. In this thesis project, consistent modelling strategies were used. The lowest energy conformer of a compound was created and a set of conformers were generated and then this set of conformers was docked and scored to determine the highest ranking docked solution. MOE is a software system designed by the Chemical Computing Group[407] to support Cheminformatics, Molecular Modelling, Bioinformatics, Virtual Screening and Structure based desugn.

4.1 Docking studies in the colchicine active site of tubulin

The crystallographic structure of tubulin bound to the colchicine derivative *N*-deacetyl-*N*-(2-mercaptoacetyl)-colchicine (DAMA-colchicine) (1SA0)[408] had been previously determined. This X-ray structure has been used to dock a vast variety of tubulin polymerisation inhibitors within the colchicine site. The colchicine binding pocket within tubulin is well understood and this has enabled the identification of key amino acid residues within the binding pocket, figure 289 and 290.



(a)



DAMA colchicine

(b)

Figure 289: (a) DAMA-Colchicine in its active site of tubulin and the amino residues which constitute the colchicine binding pocket and (b) DAMA-Colchicine

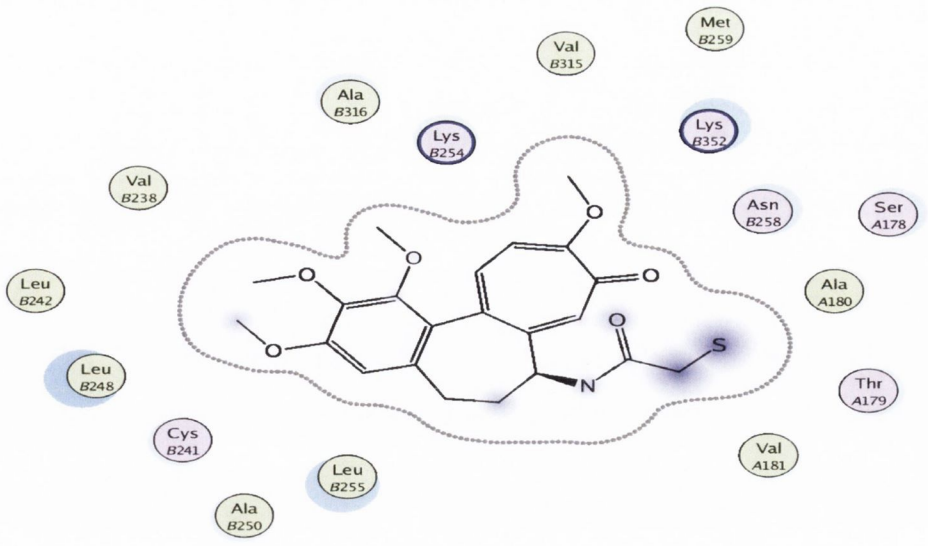


Figure 290: Interactions between DAMA-Colchicine and tubulin.

As seen from figure 290, no hydrogen bond interactions are present between DAMA-colchicine and tubulin, specifically there was no interactions between the trimethoxyphenyl ring (ring A) and tubulin. It has been shown that selective elimination of the ring A methoxy groups of colchicine cause a decrease in tubulin binding and a decrease in the inhibition of microtubule assembly. The A ring is believed to serve as a complex stabilising agent. Of the three methoxy groups, the 4-methoxy group of ring A (highlighted in red) is believed to function as key attachment for the binding of drugs on the protein[409], figure 291. It has been also that promixity to amino acid residues Val318 and Cys241 is important for compounds to bind to the colchicine binding site of tubulin.

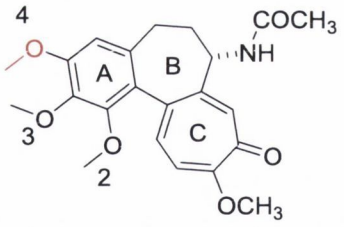
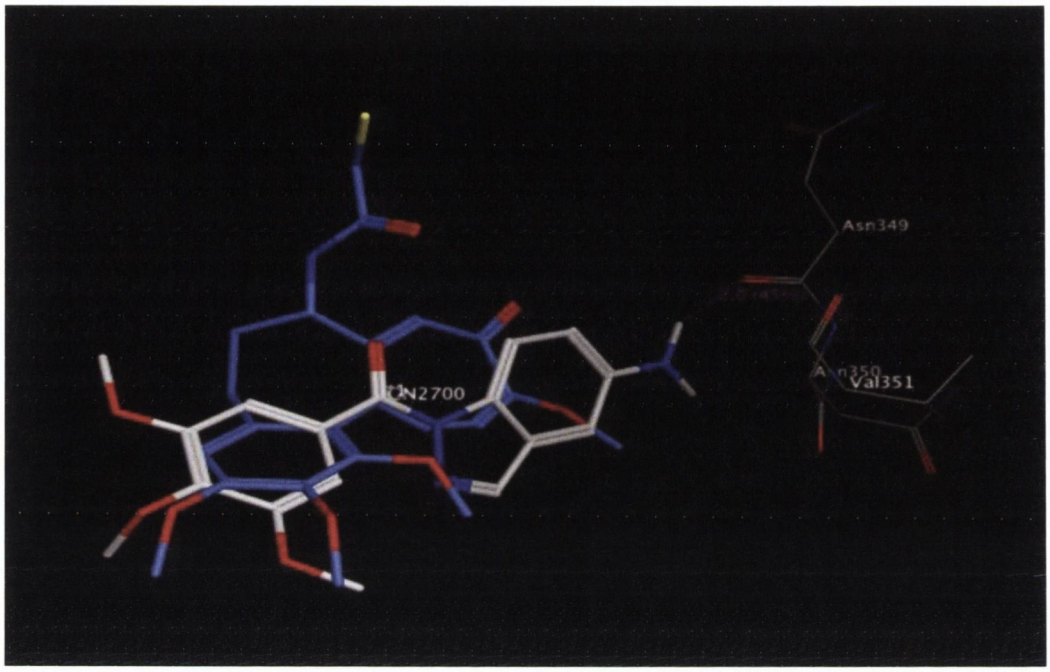


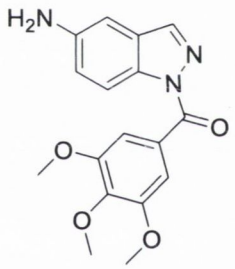
Figure 291: Colchicine – 4-methoxy group highlighted in red

4.2 Molecular docking results for lead compound (168)

The conformation of the lead compound (**168**), identified as the dual tubulin/Hsp90 binding compound, in the colchicine active site of tubulin is presented in figure 292 and the corresponding ligand interaction diagram is shown in figure 293. The trimethoxyphenyl ring of (**168**) overlaps significantly well with the A ring of colchicine while the indazole section of (**168**) occupies the same section of the binding pocket of the B ring of colchicine. A hydrogen

bond interaction is observed between the 5-amino group and Asnβ349. The 6-aminoindazole (**209**) would also be expected to demonstrate similar interactions at the colchicine binding sit, thus rationalising the biochemical activity observed.





(**168**)

Figure 292: Docked conformation of (168) in the colchicine binding site of tubulin

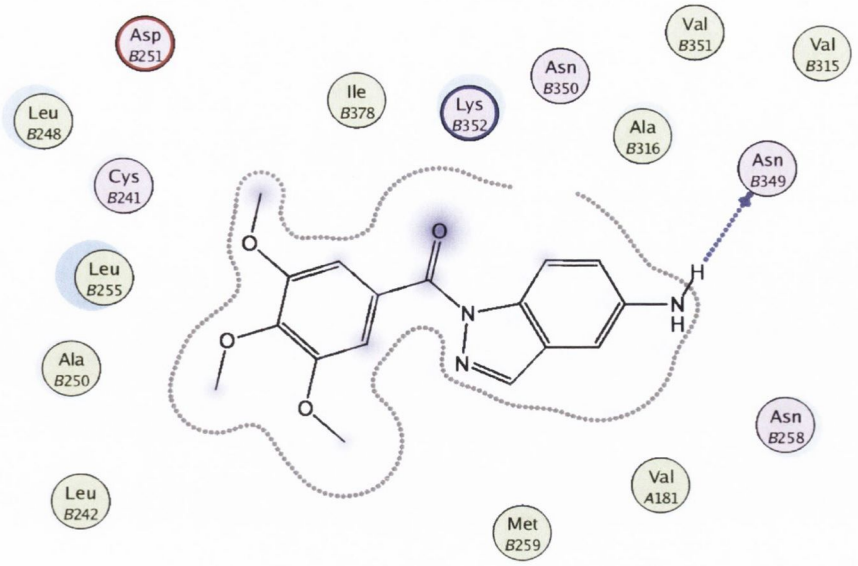


Figure 293: Ligand interaction diagram for lead compound (168)

4.3 Molecular modelling for *N*-arylated indazoles

To investigate the possible binding sites of selected biologically active indazole molecules to tubulin, three *N*-arylated indazoles were initially docked into the colchicine active site of tubulin, figure 294. (**480**) (pink) is the pyrrole derivative of compound (**286**) (orange), while (**287**) (blue) is the only example of the three compounds to contain the 3,4,5-trimethoxyphenyl group. This particular motif is deemed to be a requirement for binding of compounds in the colchicine active site. Since (**287**) has the 3,4,5-trimethoxyphenyl motif while (**286**) has only a 4-methoxyphenyl ring, it was hypothesised that (**287**) would exhibit more binding than (**286**).

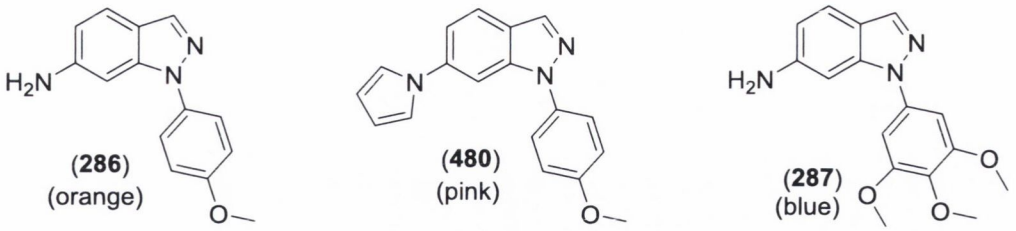


Figure 294: *N*-arylated indazoles chosen for molecular modeling studies

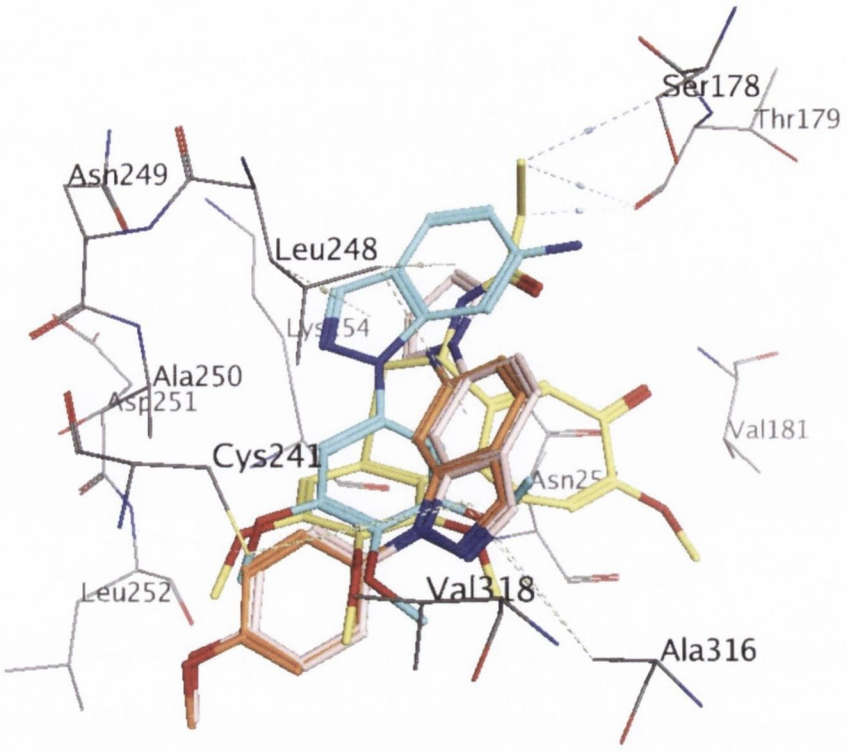


Figure 295: Docked orientations of (286) (orange), (287) (blue) and (480) (pink) in the colchicine (yellow) active site of tubulin

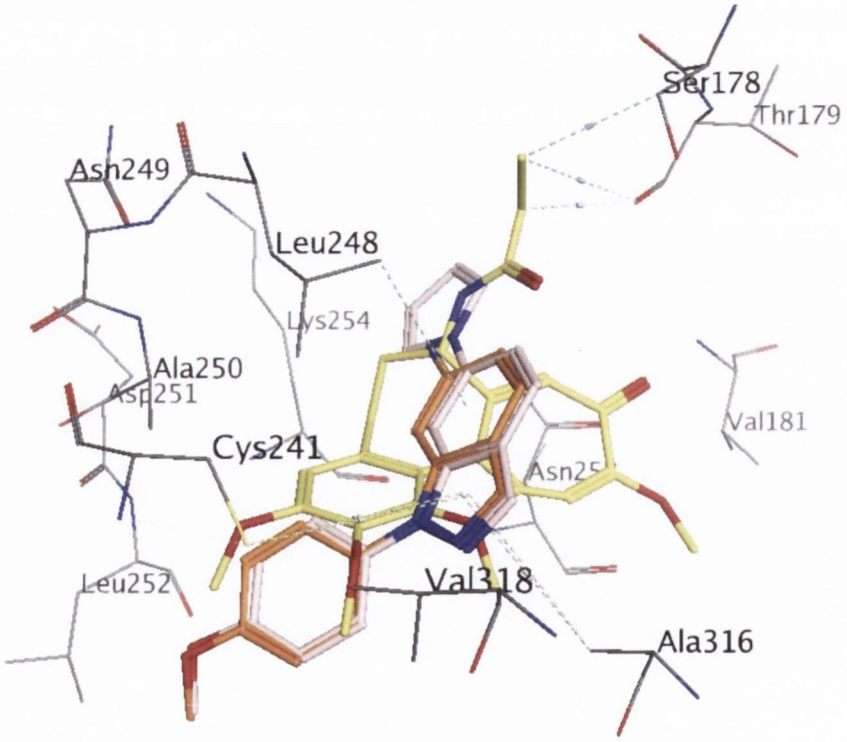


Figure 296: Docked conformation of (286) and (480)

As seen from figure 296, both (**286**) and (**480**) have the same conformation in the colchicine active site, although there is a slight misalignment. This initial result suggests that there is no difference in binding between (**286**), a primary aromatic amine and (**480**), the pyrrole derivative of (**286**).

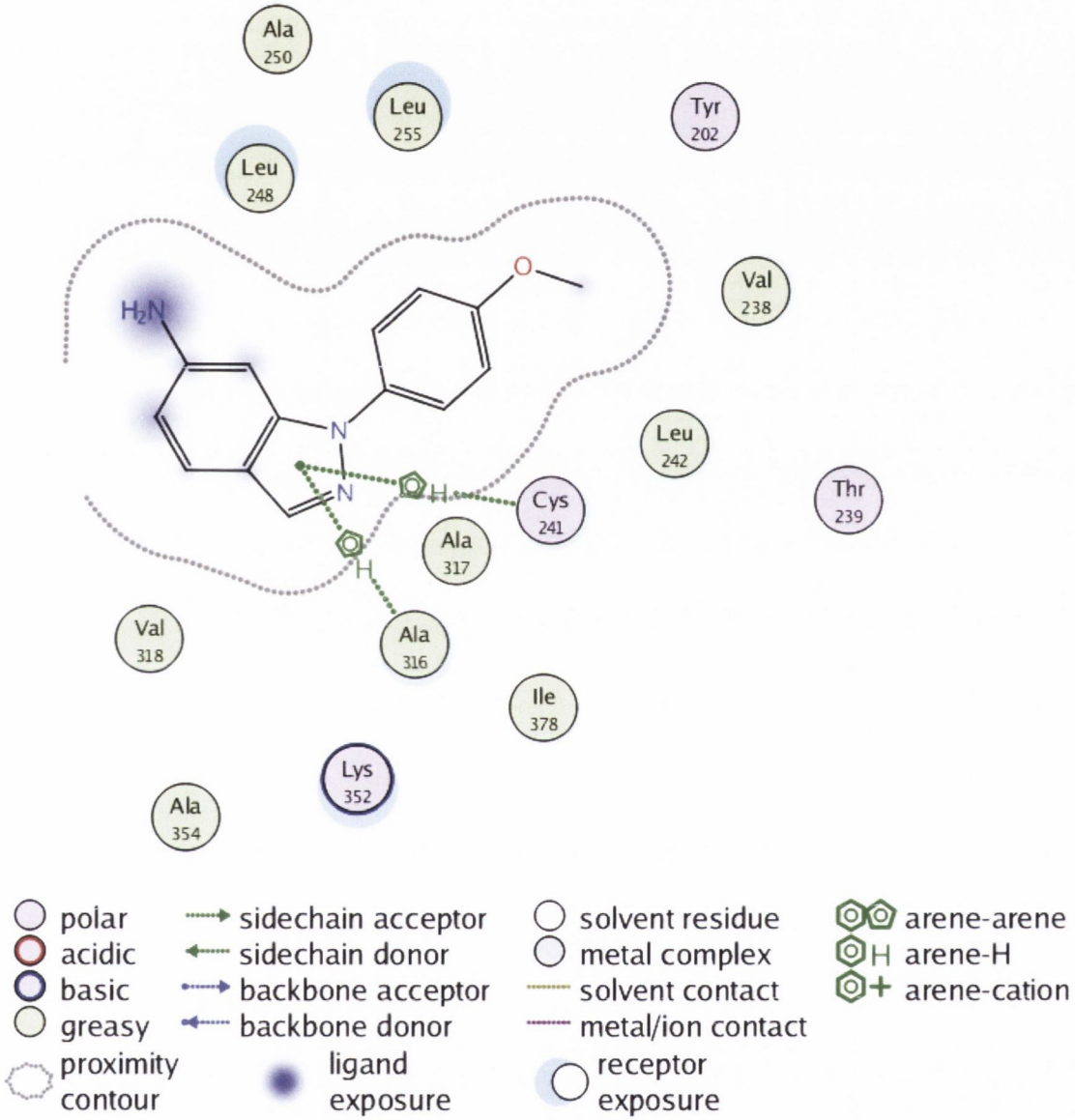


Figure 297: Ligand interaction diagram for (286)

For (**286**), there two different arene or pi interactions present, one with cysteine 241, Cysβ241 and another with alanine 316, (Ala316), figure 297. For (**480**), there is only arene or pi interaction present, to Cysβ241, figure 298. The Cysβ241 interaction is of particular importance as this amino acid and Valβ318 are considered the two important residues for the

binding of compounds in the colchicine active site of tubulin[408]. These results suggest that both compounds could be bind to tubulin.

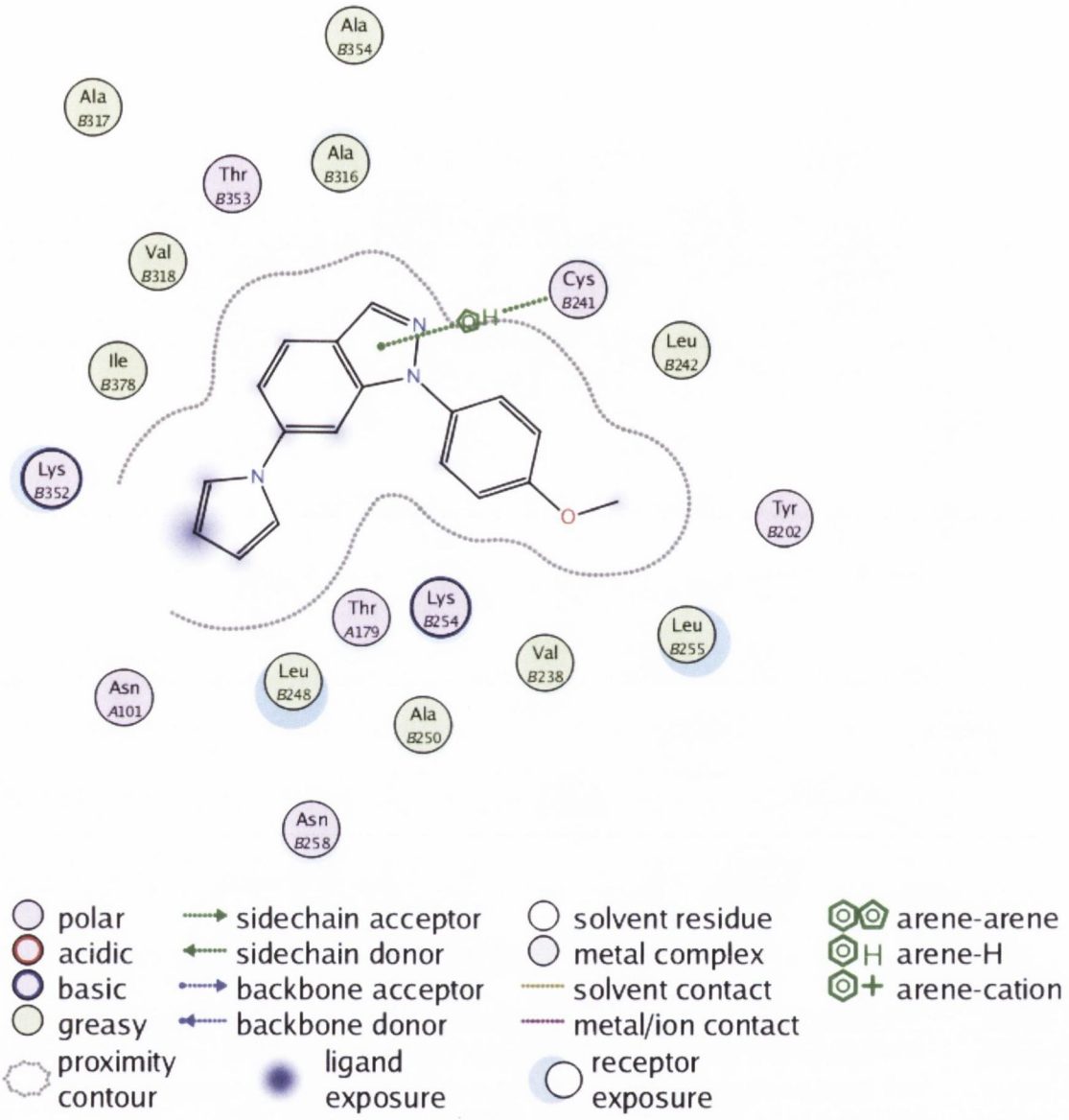


Figure 298: Ligand interaction diagram for (480)

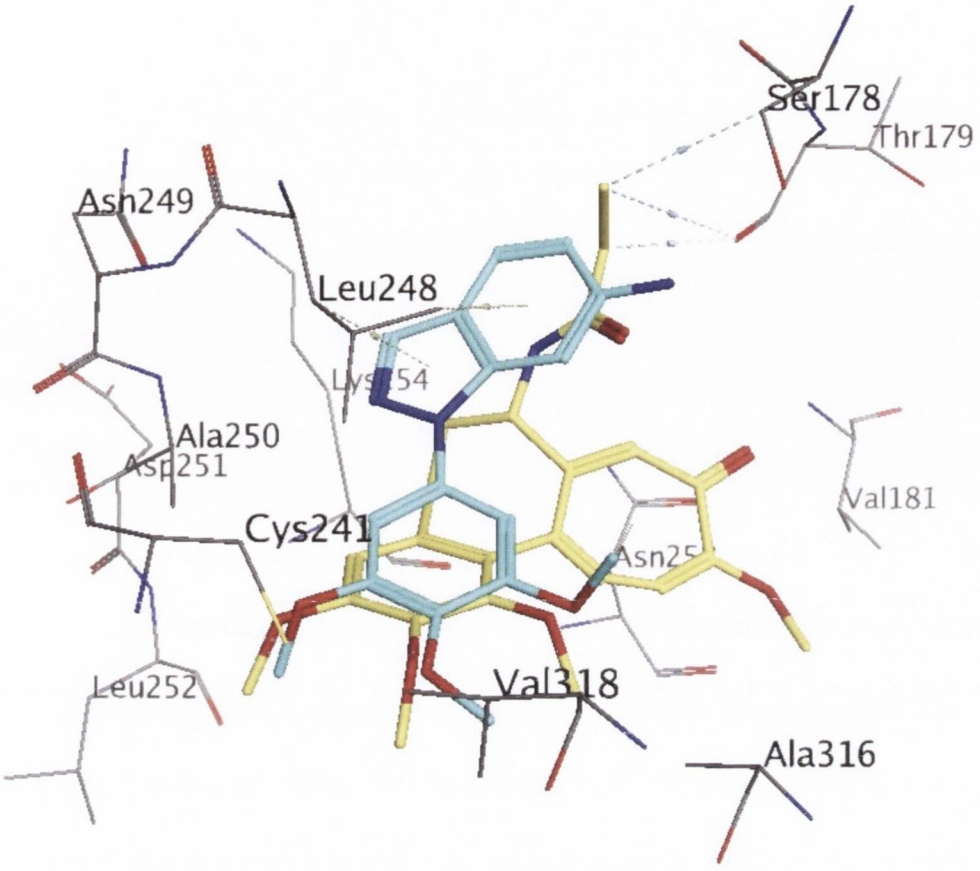


Figure 299: Docked conformation of (287)

Figure 299 shows the docked conformation of (**287**) in the colchicine active site. The 3,4,5-trimethoxypheny ring of (**287**) (blue) overlaps significantly well with the A-ring of colchicine (yellow). Compound (**287**) would be predicted to demonstrate good interaction *in vitro* with tubulin.

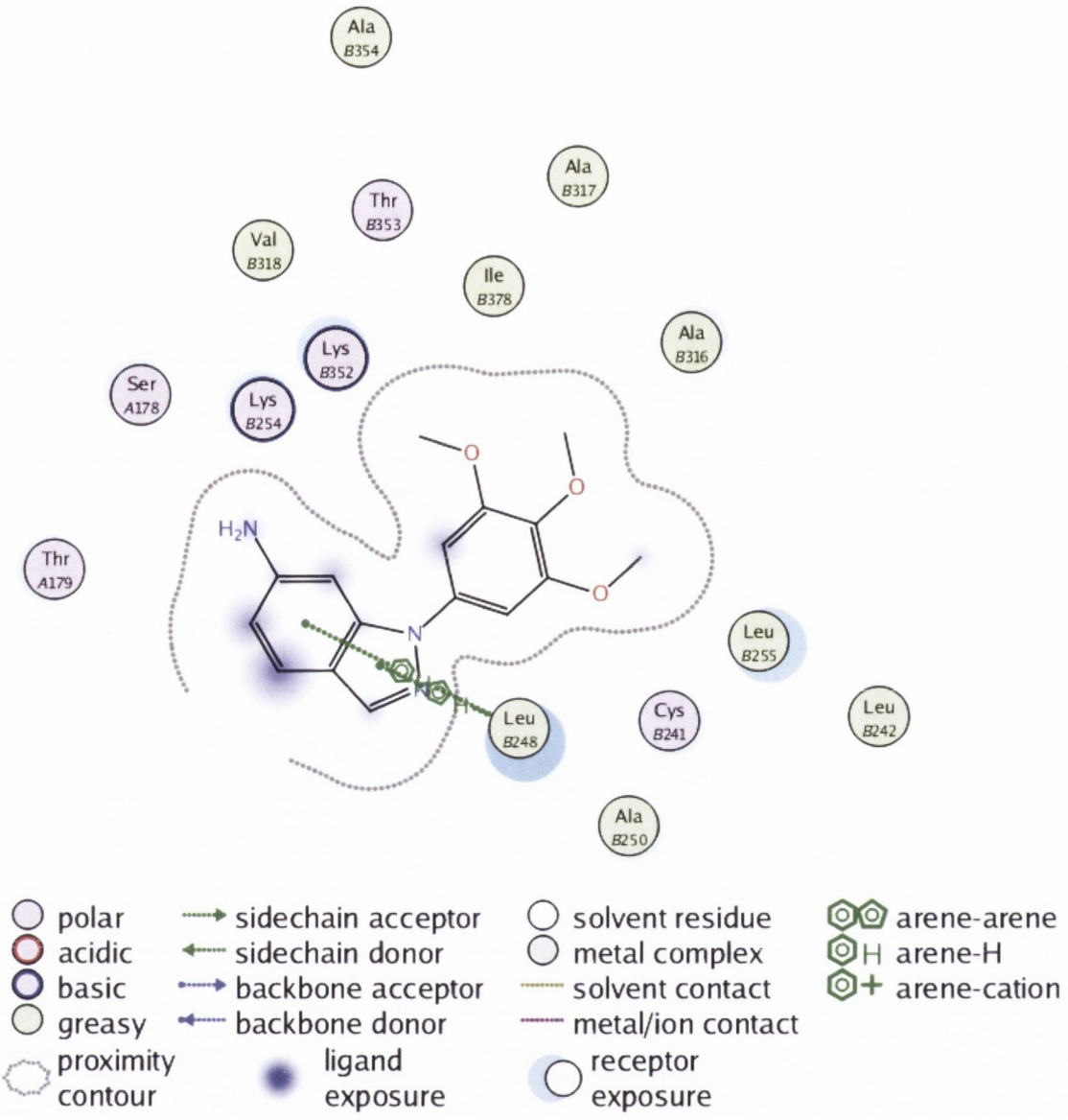
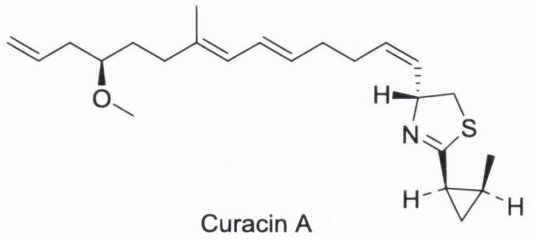


Figure 300: Ligand interaction diagram for (287)

From the ligand interaction diagram of (**287**), figure 300, two separate arene interactions are present, both to Leuβ248. The pyrazole ring and the phenyl ring of (**287**), which constitute indazole, interact with Leuβ248. The side chain of this particular amino acid, along with the side chains of Valβ238, Leuβ248, Alaβ250, Leuβ255 and Alaβ354 form a hydrophobic pocket within the colchicine active site and facilitate the hydrophobic interactions indicated in figure 300.

This particular hydrophobic interaction was observed by *Nguyen et al* for Curacin A[410]. Curacin A, figure 301, is a natural marine product and a potent tubulin polymerisation inhibitor that binds to the colchicine active site. The IC_{50} for Curacin A in MCF-7 breast cancer cells at was found to be 0.038 μM. The presence of this interaction and the significant overlap of the trimethoxyphenyl ring of (**287**) with the A ring of colchicine initially indicate this compound will bind to tubulin and could be particularly potent.



Curacin A

Figure 301: Curacin A

4.4 Molecular modelling of 6-arylindazole

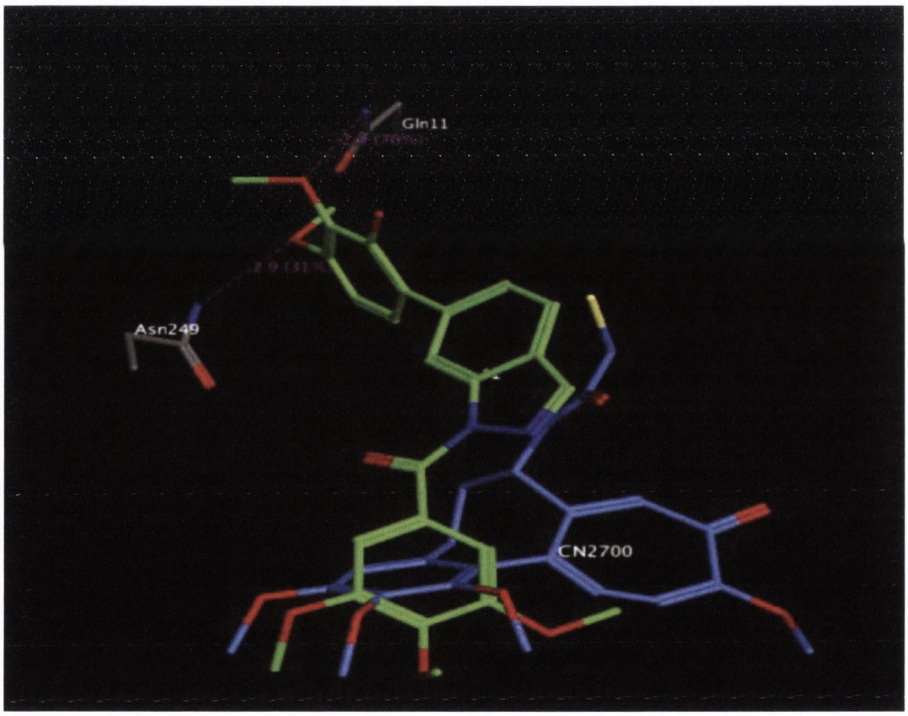


Figure 302: Docked conformation of 6-arylated indazole (327)

The interaction of the 6-arylindazole (**327**) with the colchicine binding site is illustrated in figure 302. The 3,4,5-trimethoxyphenyl of **(327)** (green) does overlap to the ring A of DAMA-colchicine (blue) somewhat but two H-bonds are present, Asn β249 and Gln α11, (figure 302, figure 303) One hydrogen bond is observed between 4-methoxy of **(337)** and Asn β249 and

the other between 3-methoxy of (**327**) and Gln α11. Potential tubulin interactions may indicate further development of these compounds as antiproliferative agents would be of interest.

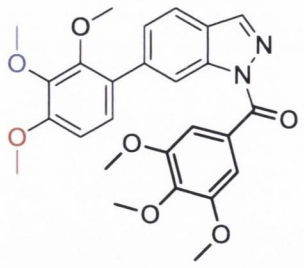


Figure 303: Compound (327), 4-methoxy in red and 3-methoxy in blue

The latter hydrogen bonding interaction has been previously reported by *Romagnoli et al*[411]. The research here focused on the synthesis of tubulin binding compounds using the molecular skeleton of 2-amino-3-(3,4,5-trimethoxybenzoyl)-thiophene. The most potent of these benzoylthiophene compounds, figure 304, exhibited a hydrogen bond between the 3-methoxy group of the molecule and Gln α11.

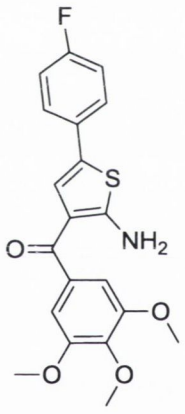


Figure 304: Benzoylthiophene which exhibited hydrogen interaction with Glnα11

Chapter 5

Overall Summary and Conclusion

5.1 Summary and Conclusion

The aim of this project was the synthesis of analogues of the lead dual tubulin/Hsp90 binding compound (**168**), figure 305, identified by *Knox et al*[1] in order to optimise the antiproliferative activity and to obtain more biologically active analogues. The lead compound contained an indazole core with a 3,4,5-trimethoxyphenyl ring attached to N-1 *via* a carbonyl bond and having an amine substituent on the indazole core at C-5. This compound was identified as having interesting antiproliferative (antitubulin) and Hsp90 binding properties. The library of analogues that were prepared were based on the indazole core structure (**168**).

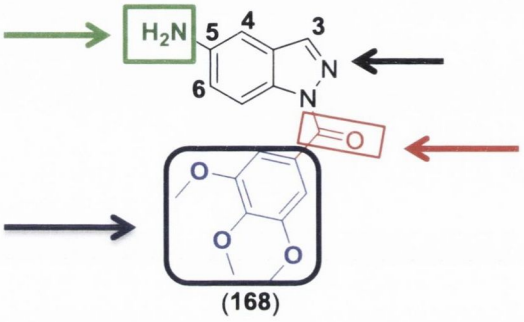


Figure 305: Functional groups of (168)

Chapter 2, sections 2.2 to 2.6 described the synthesis of analogues of (**168**) which were designed to contain various different linkers between N-1 and the aryl ring, different substituents on the aryl ring and having the primary aromatic amine located at the C-6 position or the C-5 position on the indazole core (Type 1, figure 306). These analogues were efficiently synthesised by reacting the required nitroindazoles, (**169**) and (**170**), with a variety of acid chlorides, phenylacetyl chlorides, benzyl bromides and phenylboronic acids. The reaction of (**169**) and (**170**) with benzyl bromides and phenylboronic acids generated two structurally isomeric products, a N-1 isomer and N-2 isomer. NOE spectroscopy was used to identity which of the isolated products was the N-1 isomer when (**169**) and (**170**) was reacted with phenylboronic acids. For the reaction with benzyl bromides, HMBC was used to identify which of the isolated products was the N-1 isomer and N-2 isomer. However in all cases the N-1 isomer was less polar than the corresponding N-2 isomer and was present in higher yield. Once the required nitroindazole intermediates were prepared, the reduction of nitro group to the required amine was achieved by hydrogenation, using 10 % palladium on carbon as catalyst. The yields for these hydrogenations were quite satisfactory after the work-up and afforded a library of structurally diverse aminoindazoles.

Section 2.7 described the preparation of 5- and 6- arylated analogues of (**168**), (Type 2, figure 306). The aim here was to modify the amine substituent because primary aromatic amines are known, upon metabolism, to possibly form toxic metabolites. The synthesis first required the diazotization of (**168**) and (**209**) which generated the corresponding C-5 and C-6 bromo and iodo analogues respectively. These halide analogues allowed the application of palladium catalysed carbon coupling chemistry, namely Suzuki coupling, Heck coupling and Sonogashira coupling. These coupling reactions were optimised using microwave assisted organic synthesis (MOAS). The reaction time for Suzuki coupling was reduced from 6 hours using conventional refluxing to 10 minutes using the CEM Discover microwave with good yield.

The synthesis of 3-arylated indazoles (Type 4, figure 306) is described in section 2.8. The C-3 halogenation of nitroindazoles (**169**) and (**170**) has been previously investigated and it was believed that following the preparation of a C-3 bromo analogue (**374**), the Suzuki reaction conditions that were used in section 2.7 for the synthesis of 5- and 6- arylated indazole, could be useful. Unforunately Suzuki coulpling was not successful. A literature search revealed that C-3 arylation of (**372**) and (**373**) first required N1 protection. This was accomplished using the MEM protecting group or the *t*-BOC protecting group. C-3 arylation was then successfully achieved *via* Suzuki coupling. The 3-arylated indazole was then deprotected, reacted with necessary acid chloride followed by reduction of the nitro group by hydrogenation. An alternative approach to 3-arylated indazole was attempted. Benzylation of the required C-3 iodoindazole (**373**) using 5-(bromomethyl)-1,2,3-trimethoxybenzene yielded (**408**) and (**409**). The trimethoxybenzyl group in (**408**) and (**409**) behaved as a protecting group and allowed C-3 arylation to occur without the requirement of subsequent deprotection. However the reduction of the nitro group by hydrogenation of these indazoles was only successful in (**411**) which afforded (**415**). Reduction of similar N1 benzyl indazoles was accomplished using hydrogenation so it is not clear why reduction did not proceed for these compounds.

The synthesis of *N*-substitued 3-aminoindazole was discussed in section 2.9, (Type 5, figure 306). The preparation of these indazoles followed a four step synthetic route. The first step required the preparation of 2,5-dinitro-2*H*-indazole (**425**) and 2,6-dinitro-2*H*-indazole (**426**) which then reacted with a variety of cyclic and acyclic amines to afford a series of 5-nitro-3-aminoindazoles. These compounds were then benzoylated with the required acid chlorides and subsequently hydrogenated to afford the required aminoindazoles.

Section 2.10 of the chemisty chapter describes the design and characterisation of indazoles with pyrrole substituents at C-5 or C-6, (Type 3, figure 306). The preparation of these 5- and 6-pyrrolylindazoles was achieved using the Clauson-Kaas synthesis reaction and a total of 21 5- and 6-pyrrolylindazoles were prepared. The transformation of a primary aromatic amine into the corresponding pyrrole analogue eliminated the possible formation of toxic metabolites. Also pyrrole is an important heterocyclic moiety in pharmaceutically active compounds. The synthesis of indazoles with 6-pyridone and 6-amidocoumarin substituents is also described in section 2.10. Pyridones (**505**), (**507**) – (**509**) were successfully prepared. Even though the pyridone (**510**) was not successfully obtained, methods have been established which would aid in the future development of indazoles with pyridone susbtituents. Indazole compounds with pyridone substituents have not been previously reported and this work would compliment the ongoing synthetic research involving the indazole scaffold. Figure 305 illustrates the diverse range of compounds prepared in this thesis project.

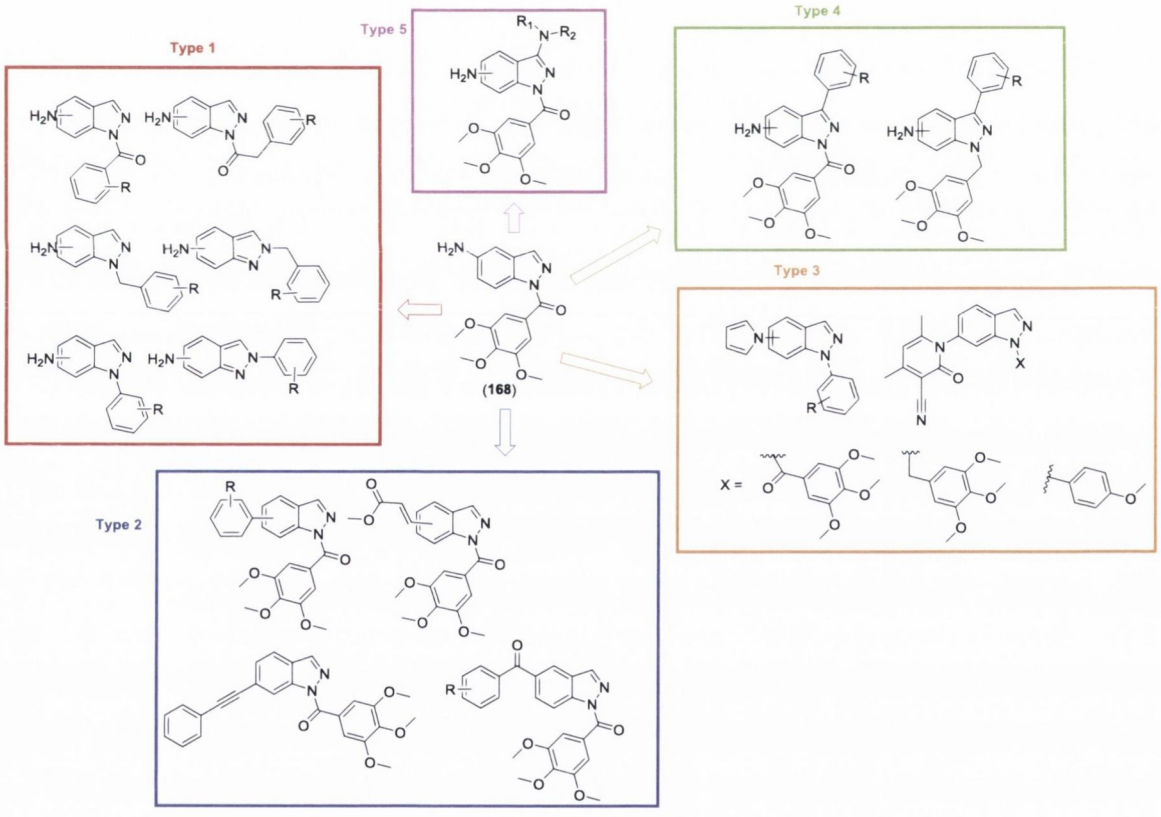


Figure 306: Lead compound and analogues prepared in this thesis project

Chapter 3 describes the preliminary biochemical evaluation of a selection of synthetic indazoles. Antiproliferative studies, using the MCF-7 human breast cancer cell line, on compounds (**168**), (**209**), (**286**), (**480**), (**288**), (**290**) and (**287**) were performed, only dosing at

100 μM and incubating for 72 hours. The 6-aminoindazoles (**209**) and (**287**) showed significant inhibition of proliferation, with 61 % and 85 % inhibition of proliferation respectively. Compounds (**168**), (**209**), (**229**), (**235**), (**269**), (**326**), (**458**), (**465**), (**477**), (**479**), (**487**), (**507**), (**509**), (**518**) and (**519**) were accepted by the NCI and screened in their 60 cancer cell line program. Surprisingly the lead compound (**168**), which initated the work contained in thesis project, was less active than the isomeric 6-aminoindazole compound (**209**). (**209**) was selected by the NCI five dose screening and IC_{50} values in the low and sub μM region were observed, particularly in the leukemia and colon cancer cell lines. A comprehensive antiproliferative study should be performed on the indazoles contained in this thesis project in order to highlight other potentially potent compounds while gaining valuable structure-activity relationship data.

Table 42: Cheminformatic data for selected indazoles

Compound No.	Type	Molecular Formula	Molecular Weight	[a]ClogP	[b]H-Bond acceptors	[b]H-Bond donors	[b]PSA Å^2	[b]Rotatable Bonds
(**168**)	1	$C_{17}H_{17}N_3O_4$	327.33	2.4531	7	2	88.622	4
(**209**)	2	$C_{17}H_{17}N_3O_4$	327.33	2.3491	7	2	88.622	4
(**326**)	3	$C_{26}H_{26}N_2O_4$	478.49	4.8682	9	0	90.301	8
(**458**)	5	$C_{21}H_{24}N_4O_5$	412.44	2.2731	9	2	101.094	5
(**465**)	5	$C_{21}H_{24}N_4O_5$	412.44	2.2731	9	5	101.094	5
(**477**)	3	$C_{21}H_{19}N_3O_4$	377.39	4.6986	7	0	67.533	5
(**479**)	3	$C_{22}H_{21}N_3O_4$	391.42	4.2576	7	0	67.533	6
(**487**)	3	$C_{22}H_{21}N_3O_4$	391.42	4.2576	7	0	67.533	6
(**235**)	1	$C_{21}H_{17}N_3O$	327.38	4.06	4	2	60.92	3
(**269**)	1	$C_{20}H_{17}N_3$	299.37	3.86.37	3	2	43.849	3
(**239**)	1	$C_{17}H_{17}N_3O_3$	311.34	2.37	6	2	79.388	4
(**507**)	3	$C_{25}H_{24}N_4O_4$	444.48	3.4690	8	0	91.325	6
(**509**)	3	$C_{25}H_{24}N_4O_4$	444.48	3.4690	8	0	91.325	6
(**518**)	3	$C_{28}H_{26}N_4O_5$	498.53	3.7781	9	1	107.652	9

[a] ClogP values calculated from Chemdraw 12 Ultra, [b] Generated using Molinspiration Cheminfomratics software, http://www.molinspiration.com/

Table 42 contains cheminformatic data on the indazole compounds that were screened by the NCI in their 60 cancer cell line. The selected indazoles obey the Lipinski's rule of five, which is used to determine the "druglikeness" of a particular compound[416] i.e. molecular weight less than 500 g/mol, ClogP not greater than 5 (an indication of oral absorption capability), hydrogen bond donors not greater 5, hydrogen bond acceptors not greater than 10 and polar surface are no greater than 140 Å^2. The parameters are estimated from the molecular structure of the particular compound and are used as a guide to the drug's water and fat solubility/diffusion capability.

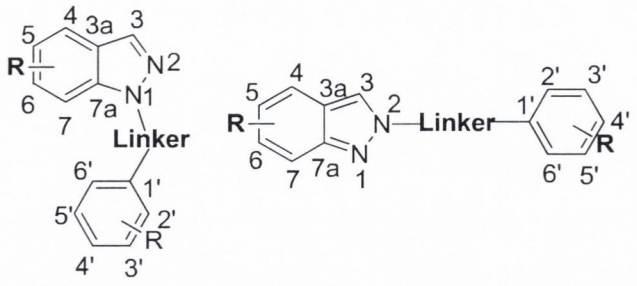
The molecular modelling performed on selected indazole compounds synthesised is outlined in chapter 5. The possible binding conformation and ligand interactions, in the colchicine active site of tubulin, is observed for a selection of indazole compounds. The molecular modelling together with a comprehensive antiproliferative study may highlight alternative structural modification that could be introduced on the indazole scaffold to identify the optimised structures for progression to tubulin binding evaluation.

Chapter 6

Experimental

Experimental note

Uncorrected melting points were measured on a Gallenkamp apparatus. Infra-red (IR) spectra were recorded on a Perkin Elmer FT-IR Paragon 1000 spectrometer. ^{1}H, ^{13}C and ^{19}F nuclear magnetic resonance (NMR) were recorded at 27 °C on a Brucker DPX 400 spectrometer (400.13 MHz, ^{1}H; 100.61 MHz, ^{13}C; 376.47 MHz, ^{19}F) in either $CDCl_3$ (internal standard tetramethylsilane (TMS)) or CD_3OD or DMSO-d_6. 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 middle $CDCl_3$ peak at 77.0 ppm. For CD_3OD, ^{1}H and ^{13}C-NMR spectra were assigned relative to the center peaks of the CD_3OD multiplets at 3.30 δ and 49.00 ppm respectively. ^{19}F-NMR were not calibrated. Coupling constants are reported in Hertz. For ^{1}H-NMR assignments, chemical shifts are reported: shift value (number of protons, description of absorption, coupling constant(s) where applicable). Electrospray ionisation mass spectrometry (ESI-MS) was performed in the positive ion mode on a liquid chromatography time-of-flight mass spectrometer (Micromass LCT, Waters Ltd., Manchester, UK). The samples were introduced to the ion source by an LC system (Waters Alliance 2795, Waters Corporation, USA) in acetonitrile:water (60:40 %v/v) at 200µl/min. The capillary voltage of the mass spectrometer was at 3kV. The sample cone (de-clustering) voltage was set at 40V. For exact mass determination, the instrument was externally calibrated for the mass range m/z 100 to m/z 1000. A lock (reference) mass (m/z 556.2771) was used. Mass measurement accuracies of $<\pm 5$ ppm were obtained. R_f values are quoted for thin layer chromatography on silica gel Merck F-254 plates, unless otherwise stated. Flash column chromatography was carried out on Merck Kieselgel 60 (particle size 0.040-0.063mm), Aldrich aluminium oxide (activated, neutral, Brockmann I, 50 mesh) or Aldrich aluminium oxide (activated, acidic, Brockmann I, 50 mesh). Microwave experiments were carried out using the Discover CEM microwave synthesiser on standard power setting if otherwise stated. On standard power setting, the maximum power supplied is 300 watts.



Numbering scheme for N1 and N2 substituted indazoles

General procedure A: *N*-Acylation and *N*-benzoylation of 6-nitroindazole

To a suspension of 6-nitroindazole (2 mmol, 1eq) and the appropriate acid chloride (2 mmol, 1 eq) in anhydrous DCM (20 mL), triethylamine (2.2 mmol, 1.1 eq) was added. The resulting solution was stirred at 20 °C under nitrogen for 12 h. The solution was then washed with DIW (20 mL), a saturated brine solution (20 mL), dried using anhydrous sodium sulphate and then filtered. The filtrate was concentrated to dryness *in vacuo*. The crude product was re-crystallised from methanol affording the desired product.

Note: The masses of the 6-nitroindazole and the appropriate acid chloride correspond to 2 mmol unless stated differently.

(3,4,5-Trimethoxyphenyl)(6-nitro-1*H*-indazol-1-yl)methanone (172)

As per general procedure A, (3,4,5-trimethoxyphenyl)(6-nitro-1*H*-indazol-1-yl)methanone (**172**) was prepared from 6-nitroindazole (326 mg) and 3,4,5-trimethoxybenzoyl chloride (461 mg) as a yellow solid (386 mg, 54%) following recrystallisation from methanol.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.97 (s, 6H, 2 x OCH_3), 4.00 (s, 3H, OCH_3). 7.49 (s, 2H, 2 x ArH, $H_{2'}$ & $H_{6'}$), 7.97 (d, 1H, ArH, J = 9.04 Hz, H_4), 8.32 (dd, 1H, ArH, J = 2.00, 9.04 Hz, H_5), 8.38 (s, 1H, ArH, H_3), 9.46 (s, 1H, ArH, H_7)

^{13}C-NMR (101 MHz, $CDCl_3$) δ 55.91 (OCH_3), 60.58 (2 x OCH_3), 108.72 (ArCH, $C_{2'}$ & $C_{5'}$), 111.88 (ArCH, C_7), 119.29 (ArCH, C_5), 121.21 (ArCH, C_4), 126.08 (C_q, $C_{1'}$), 128.73 (C_q, C_{3a}), 138.97 (ArCH, C_3), 139.18 (C_q, C_{7a}), 142.05 (C_q, $C_{4'}$), 148.10 (C_q, C_6), 152.27(C_q, $C_{3'}$ & $C_{5'}$), 166.50 (C=O)

M.P.: 195-198 °C Lit. M.P.: 195 °C[267]

IRν_{max} (NaCl film) cm^{-1}: 3025.8, 2963.6, 2937.7, 2867.4, 2838.3, 1682.4 (C=O), 1584.9, 1537.9 (NO_2), 1467.7, 1352.4 (NO_2), 1238.5, 1184.9, 1132.3, 997.9

HRMS: Found 380.0870 $[M+Na]^+$, $C_{17}H_{15}N_3NaO_6$ requires 380.0859, (+2.9 ppm)

(6-Nitro-1*H*-indazol-1-yl)(*p*-tolyl)methanone (193)

As per general procedure A, (6-nitro-1*H*-indazol-1-yl)(*p*-tolyl)methanone (**193**) was prepared from 6-nitroindazole (326 mg) and *p*-tolylbenzoyl chloride (309 mg) as a cream solid (315 mg, 56%) following recrystallisation from methanol.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.50 (s, 3H, CH_3), 7.38 (d, 2H, ArH, J = 8.04 Hz), 7.95 (d, 1H, ArH, J = 8.52 Hz, H_4), 8.05 (d, 2H, ArH, J = 8.04 Hz), 8.30 (dd, 1H, ArH, J = 2.00, 8.52 Hz, H_5), 8.35 (s, 1H, ArH, H_3), 9.48 (s, 1H, ArH, H_6)

^{13}C-NMR (101 MHz, $CDCl_3$) δ 21.31 (CH_3), 111.82 (ArCH, C_7), 119.19 (ArCH, C_5), 121.14 (ArCH, C_4), 128.51 (ArCH), 128.68 (C_q), 128.79 (C_q, C_{3a}), 130.97 (ArCH), 138.76 (ArCH, C_3), 139.00 (C_q. C_{7a}), 143.56(C_q), 148.03 (C_q, C_6), 167.31 (C=O)

M.P.: 169-172 °C

IRν_{max} (NaCl film) cm^{-1}: 3060.4, 2924.5, 2850.9, 1685.8 (C=O), 1492.9 (NO_2), 1639.4, 1452.3, 1348.1 (NO_2), 1182.1

HRMS: Found 282.0870 $[M+H]^+$, $C_{15}H_{12}N_3O_3$ requires 282.0879, (-3.2 ppm)

(4-Methoxyphenyl)(6-nitro-1*H*-indazol-1-yl)methanone (194)

As per general procedure A, (4-methoxyphenyl)(6-nitro-1*H*-indazol-1-yl)methanone (**194**) was prepared from 6-nitroindazole (326 mg) and 4-methoxybenzoyl chloride (342 mg) as an orange solid (327 mg, 55%) following recrystallisation from methanol.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.93 (s, 3H, OCH_3), 7.05 (d, 2H, ArH, J=7.93 Hz), 7.93 (d, 1H, ArH, J = 9.16 Hz, H_4), 8.21 (d, 2H, J = 7.93 Hz), 8.29 (d, 1H, J = 9.16 Hz, H_5), 8.34 (s, 1H, H_3), 9.47 (s, 1H, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 55.56 (OCH_3), 112.34 (ArCH), 113.62 (ArCH), 119.48 (ArCH), 121.49 (ArCH), 123.95(C_q), 133.92 (ArCH), 138.92 (ArCH), 139.58 (C_q), 148.49(C_q), 163.59 (C=O)

M.P.: 165-167 °C[267]

IRν_{max} (NaCl film) cm^{-1}: 3055.6, 2920.9, 2856.9, 1674.1 (C=O), 1606.2, 1525.3 (NO_2), 1411.9, 1361.9, 1341.9 (NO_2), 1200.8, 1155.3

HRMS: Found 297.0755 $[M+H]^+$, $C_{15}H_{11}N_3O_4$ requires 297.0750, (+1.7 ppm)

(3,5-Diethoxyphenyl)(6-nitro-1*H*-indazol-1-yl)methanone (195)

As per general procedure A, (3,5-diethoxyphenyl)(6-nitro-1*H*-indazol-1-yl)methanone (**195**) was prepared from 6-nitroindazole (57 mg, 0.35 mmol) and 3,5-diethoxybenzoyl chloride (81 mg, 0.35 mmol) as an orange solid (70 mg, 56%) following recrystallisation from methanol.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (t, 6H, J = 7.03 Hz, 2 x $OCH_2\underline{CH_3}$), 4.10 (q, 4H, J=7.03 Hz, 2 x $O\underline{CH_2}CH_3$), 6.72 (app t., dd, 1H, ArH, J = 2.01 Hz), 7.21 (d, 2H, ArH, J = 2.01 Hz), 7.94 (d, 1H, ArH, J = 8.53 Hz, H_5), 8.30 (dd, 1H, ArH, J = 1.76, 8.53 Hz, H_5), 8.34 (s, 1H, H_3), 9.46 (s, 1H, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 14.72 (2 x $OCH_2\underline{CH_3}$), 63.87 (2 x $O\underline{CH_2}CH_3$), 106.09 (ArCH), 109.49 (ArCH), 112.27 (ArCH, C_7), 119.75 (ArCH, C_5), 121.60 (ArCH, C_4), 129.29 (C_q), 133.47 (C_q), 139.41 (ArCH, C_3), 148.49 (C_q, C_6), 159.66 (C_q, CO), 167.43 (C=O)

M.P.: 169-171 °C

IRν_{max} (NaCl film) cm^{-1}: 3149.0, 3140.2, 2985.3, 1673.0 (C=O), 1594.7, 1555.5 (NO_2), 1411.5, 1375.3, 1349.4 (NO_2), 1302.8, 1174.7

HRMS: Found 378.1060 $[M+Na]^+$, $C_{18}H_{17}N_3NaO_5$ requires 378.1066, (-1.6 ppm)

(2,5-Diethoxyphenyl)(6-nitro-1*H*-indazol-1-yl)methanone (196)

As per general procedure A, (2,5-diethoxyphenyl)(6-nitro-1*H*-indazol-1-yl)methanone (**196**) was prepared from 6-nitroindazole (57 mg, 0.35 mmol) and 2,5-diethoxybenzoyl chloride (81 mg, 0.35 mmol) as a cream solid (60 mg, 48%) following recrystallization from methanol.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.12 (t, 3H, CH_3, J = 7.00 Hz), 1.43 (t, 3H, CH_3, J = 7.04 Hz), 3.99 – 4.07 (m, 4H, 2 x CH_2), 6.98 (d, 1H, J = 9.56 Hz), 7.07 – 7.09 (m, 2H), 7.92 (d, 1H, ArH, J = 8.52 Hz, H_4), 8.27 (s, 1H, ArH, H_3) 8.31 (dd, 1H, ArH, J = 2.00, 8.52 Hz, H_5), 9.47 (s, 1H, ArH, H_7)

^{13}C-NMR (101 MHz, $CDCl_3$) δ 14.25 (CH_3), 14.43 (CH_3), 63.75 (CH_2), 64.41 (CH_2), 111.43 (ArCH), 113.60 (ArCH), 114.58 (ArCH), 118.59 (ArCH), 119.23(ArCH), 121.08 (ArCH), 123.68 (C_q), 129.08 (C_q), 138.04 (C_q), 138.82 (ArCH, C_3), 148.03 (C_q), 150.16 (C_q), 152.15 (C_q), 167.53 (C=O)

M.P.: 127-130 °C

IRν_{max} (NaCl film) cm^{-1}: 2985.3, 2914.7, 2943.6, 2873.8, 1715.4 (C=O), 1594.7, 1532.5 (NO_2), 1443.9, 1346.1 (NO_2), 1302.8, 1174.7, 1153.2, 1113.3 1060.9, 1049.2

HRMS: Found 378.1049 $[M+Na]^+$, $C_{18}H_{17}N_3NaO_5$ requires 378.1066, (-4.5 ppm)

2-[(6-Nitro-1*H*-indazol-1-yl)carbonyl]benzyl benzoate (197)

As per general procedure A, 2-[(6-nitro-1*H*-indazol-1-yl)carbonyl]benzyl benzoate (**197**) was prepared from 6-nitroindazole (77 mg, 0.48 mmol) and 2-(benzoyloxymethyl)benzoyl chloride (130 mg, 0.48 mmol) as a colourless solid (90 mg, 52%) following recrystallization from methanol.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.50 (s, 2H, CH_2), 7.19 (app t., dd, 2H, ArH, J = 7.63 Hz), 7.36 - 7.43 (m, ArH, 1H), 7.50 - 7.71 (m, ArH, 6H), 7.83 (d, 1H, ArH, J = 9.16 Hz, H_4), 8.18 - 8.23 (m, 2H, ArH, H_3 & H_5), 9.21 (d, 1H, ArH, J = 1.83 Hz, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 65.22 (CH_2), 111.86 (ArCH), 119.78 (ArCH), 121.53 (ArCH), 128.01 (ArCH), 128.08 (ArCH), 128.76(ArCH), 129.03 (C_q), 129.29 (ArCH), 129.41 (C_q), 129.44 (ArCH), 131.30 (ArCH), 132.66 (C_q), 133.03 (ArCH), 135.24 (C_q), 138.54 (C_q), 139.98 (C_q), 148.36 (C_q), 165.60 (NC=O), 169.12 (OC=O)

M.P.: 174-176 °C

IRν_{max} (NaCl film) cm^{-1}: 3161.4, 3130.4, 2956.5, 2917.9, 1719.1 (OC=O), 1679.6 (NC=O) 1599.7, 1531.0 (NO_2), 1348.1 (NO_2). 1452.3, 1410.2, 1266.2

HRMS: Found 424.0891 $[M+Na]^+$, $C_{14}H_7N_3NaO_3$ requires 424.0909, (-4.2 ppm)

6-Nitro-1*H*-indazol-1-yl)(naphthalen-1-yl)methanone (198)

As per general procedure A, (6-nitro-1*H*-indazol-1-yl)(naphthalen-1-yl)methanone (**198**) was prepared from 6-nitroindazole (326 mg) and 1-naphthoyl chloride (381 mg) as a colourless solid (200 mg, 32%) following recrystallization from methanol.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.52 – 7.58 (m, 2H, ArH), 7.59 – 7.64 (m, 1H, ArH), 7.83 (d, 1H, ArH, J = 7.10 Hz), 7.94 – 8.00 (m, 3H, ArH), 8.09 (d, 1H, ArH, J = 8.5 Hz), 8.25 (s, 1H, ArH, H_3), 8.34 (dd, 1H, ArH, J = 8.5, 1.9 Hz), 9.60 (d, 1H, ArH, J = 1.0 Hz, H_7),

^{13}C-NMR (101 MHz, DMSO-d_6) δ 112.2 (ArCH), 120.1 (ArCH), 121.8 (ArCH), 124.4 (ArCH), 124.9 (ArCH), 126.7 (C_q), 127.6 (C_q), 128.5 (ArCH), 128.7 (ArCH), 129.7 (ArCH), 130.5 (ArCH), 130.7 (ArCH), 132.1 (C_q), 133.5 (C_q), 139.1 (ArCH, C_3), 139.8 (C_q), 148.7 (C_q), 169.0 (C=O)

M.P.: 194-196 °C Lit. M.P.:190-191 °C[276]

IRν_{max} (KBr) cm^{-1}: 3120.4, 2950.1, 2913.8, 1704.9 (C=O), 1640.2, 1535.3 (NO_2), 1504.7, 1344.7 (NO_2), 1241.6, 1129.5

HRMS: Found 318.0890 $[M+H]^+$, $C_{18}H_{12}N_3O_3$ requires 318.0879, (+3.5 ppm

(Naphthalen-3-yl)(6-nitro-1*H*-indazol-1-yl)methanone (199)

As per general procedure A, (naphthalen-3-yl)(6-nitro-1*H*-indazol-1-yl)methanone (**199**) was prepared from 6-nitroindazole (326 mg) and 2-naphthoyl chloride (381 mg) as a colourless solid (311 mg, 49%) following recrystallization from methanol.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 - 7.69 (m, 2H, ArH), 7.92 - 8.00 (m, 2H, ArH), 8.00 - 8.05 (m, 2H, ArH), 8.15 (d, 1H, ArH, J = 8.55 Hz), 8.32 (d, 1H, ArH, J = 8.55 Hz), 8.39 (s, 1H, ArH), 8.74 (s, 1H, ArH), 9.53 (s, 1H, ArH, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 112.34 (ArCH), 119.78 (ArCH), 121.62 (ArCH), 126.53 (ArCH), 126.93 (ArCH), 127.79 (C_q), 127.90 (C_q), 128.76 (ArCH), 129.17 (C_q), 129.27 (C_q), 129.58 (ArCH), 132.16 (C_q), 133.27 (ArCH), 135.33 (C_q), 139.42 (ArCH), 167.60 (C=O)

M.P.: 239-241 °C

IRν_{max} (KBr) cm^{-1}: 3125.3, 3100.4, 3119.3, 1686.2 (C=O), 1514.9 (NO_2), 1347.5 (NO_2), 1290.9, 1125.7, 1091.6

HRMS: Found 318.0890 $[M+H]^+$, $C_{18}H_{12}N_3O_3$ requires 318.0879, (+3.5 ppm)

(6-Nitro-1*H*-indazol-1-yl)(phenyl)methanone (200)

As per general procedure A, (6-nitro-1*H*-indazol-1-yl)(phenyl)methanone (**200**) was prepared from 6-nitroindazole (326 mg) and benzoyl chloride (281 mg) as an orange solid (323 mg, 60%) following recrystallization from methanol.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.58 (ap t, 2H, ArH, J = 7.52 Hz), 7.68 (app t., dd, , 1H, ArH, J = 7.52 Hz), 7.96 (d, 1H, ArH, J = 8.52 Hz, H_4), 8.13 (d, 2H, ArH, J = 7.52 Hz), 8.31 (dd, 1H, ArH, J = 2.00, 8.52 Hz, H_5), 8.37 (s, 1H, ArH, H_3), 9.48 (s, 1H, ArH, H_7)

^{13}C-NMR (101 MHz, $CDCl_3$) δ 111.80 (ArCH, C_7), 119.32 (ArCH, C_5), 121.18 (ArCH, C_4), 127.75 (ArCH), 128.84 (C_q), 130.79 (ArCH), 131.60 (C_q), 132.54 (ArCH), 138.98 (ArCH, C_3), 148.11 (C_q, C_6), 167.39 (C=O)

M.P.: 163-166 °C

IRν_{max} (NaCl film) cm^{-1}: 3143.3, 3102.5, 3129.3, 1693.7 (C=O), 1615.86, 1598.9, 1581.6, 1532.8 (NO_2), 1483.8, 1448.6, 1409.6, 1342.2 (NO_2), 1296.9, 1118.68, 1093.2

HRMS: Found 290.0536 $[M+Na]^+$, $C_{14}H_9N_3NaO_3$ requires 290.0542, (-1.6 ppm)

General procedure B: *N*-1 benzoylation of 5-nitroindazole

To a suspension of 5-nitroindazole (2 mmol, 1 eq) and the appropriate acid chloride (2 mmol, 1eq) in anhydrous DCM (20 mL), triethylamine (2.2 mmol, 1.1 eq) was added. The resulting solution was refluxed under nitrogen for 12 h. The solution was then washed with DIW (20 mL), a saturated brine solution (20 mL), dried using anhydrous sodium sulphate and then filtered. The filtrate was concentrated to dryness *in vacuo*. The crude product was re-crystallized in methanol affording the desired product.

Note: The masses of the 5-nitroindazole and the appropriate acid chloride correspond to 2 mmol unless stated differently.

3,4,5-Trimethoxyphenyl)(5-nitro-1*H*-indazol-1-yl)methanone (171)

As per general procedure B, (3,4,5-trimethoxyphenyl)(5-nitro-1*H*-indazol-1-yl)methanone (**171**) was prepared from 5-nitroindazole (326 mg) and 3,4,5-trimethoxybenzoyl chloride (461 mg) as a colourless solid solid (393 mg, 55%) following recrystallization from methanol.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.97 (s, 6H, 2xOCH_3), 4.00 (s, 3H, OCH_3). 7.47 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 8.54 (dd, 1H, ArH, J = 2.00, 9.00 Hz, H_7), 8.70 (d, 1H, ArH, J = 9.00 Hz, H_6), 9.79 (d, 1H, J = 2.00 Hz, ArH, H_4)

^{13}C-NMR (101 MHz, $CDCl_3$) δ 55.91 (2 x OCH_3), 60.58 (OCH_3), 108.71 (ArCH, $C_{2'}$ & $C_{5'}$), 116.01 (ArCH, C_4), 117.34 (ArCH, C_7), 123.87 (ArCH, C_6), 125.23 (C_q, $C_{1'}$), 126.07 (C_q, C_{3a}), 140.10 (ArCH, C_3), 142.10 (C_q, C_5), 142.30 (C_q, $C_{4'}$), 144.45 (C_q, C_{7a}), 152.27 (C_q, $C_{3'}$ & $C_{5'}$), 166.75 (C=O)

M.P.: 204-206 °C Lit. M.P. : 209-210 °C[276]

IRν_{max} (NaCl film) cm^{-1}: 1697.6 (C=O), 1525.35 (NO_2), 1344.6 (NO_2)

HRMS: Found 380.0853 $[M+Na]^+$, $C_{17}H_{15}N_3NaO_6$ requires 380.0859, (-1.6 ppm)

(5-Nitro-1*H*-indazol-1-yl)(*p*-tolyl)methanone (185)

As per general procedure B, (5-nitro-1*H*-indazol-1-yl)(p-tolyl)methanone (**185**) was prepared from 5-nitroindazole (326 mg) and *p*-tolylbenzoyl chloride (309 mg) as a colourless solid (366 mg, 65%) following recrystallization from methanol.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48 (s, 3H), 7.37 (d, 2H, ArH, J = 7.93 Hz), 8.03 (d, 2H, ArH, J = 7.93 Hz), 8.38 (s, 1H, ArH, H_3), 8.50 (dd, 1H, ArH, J = 9.16, 2.44 Hz, H_6), 8.70 (d, 1H, ArH, J = 9.16 Hz, H_4), 8.75 (d, ArH, J = 1.83 Hz, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 21.75 (CH_3), 116.40 (ArCH, C_7), 117.71 (ArCH, C_4), 124.20 (ArCH, C_6), 125.70 (C_q, C_{3a}), 128.93 (C_q), 129.15 (C_q), 131.41 (C_q), 140.30 (ArCH, C_3), 142.59 (C_q, C_6), 144.06 (C_q), 144.86 (C_q, C_{7a}), 167.95 (C=O)

M.P.: 171-173 °C

IRν_{max} (NaCl film) cm^{-1}: 3060.1, 2924.2, 1685.9 (C=O), 1601.1, 1514.7 (NO_2), 1492.8, 1452.2, 1347.4 (NO_2), 1155.5, 1076.0, 1027.9

HRMS: Found 282.0879 $[M+H]^+$, $C_{15}H_{12}N_3O_3$ requires 282.0879, (0.0 ppm)

(4-Methoxyphenyl)(5-nitro-1*H*-indazol-1-yl)methanone (186)

As per general procedure B, (4-methoxyphenyl)(5-nitro-1*H*-indazol-1-yl)methanone (**186**) was prepared from 5-nitroindazole (326 mg) and *p*-methoxybenzoyl chloride (341 mg) as a colourless solid (327 mg, 55%) following recrystallization from methanol.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (s, 3H, OCH_3), 6.92 - 7.06 (m, 3H), 8.03 (s, 1H, ArH), 8.12 (d, 2H, J = 7.32 Hz), 8.35 (d, 1H, J = 8.55 Hz)

^{13}C NMR (101 MHz, $CDCl_3$) δ 55.45 (OCH_3), 103.58 (ArCH, C_7), 113.31 (ArCH), 116.67 (ArCH, C_4), 119.48 (ArCH, C_6), 127.28 (C_q), 133.35 (ArCH), 139.31 (ArCH, C_3), 143.66 (C_q), 147.30 (C_q), 162.75 (C=O)

M.P.: 273-275 °C

IRν_{max} (NaCl film) cm^{-1}: 2929.1, 2875.8, 1694.3 (C=O), 1614.1, 1589.2, 1589.2, 1523.4 (NO_2), 1472.4, 1445.5, 1385.3, 1334.6 (NO_2), 1261.0, 1192.8, 1152.8, 1071.6

HRMS: Found 297.0760 $[M+H]^+$, $C_{15}H_{11}N_3O_4$ requires 297.0750, (+3.7 ppm)

(3,5-Diethoxyphenyl)(5-nitro-1H-indazol-1-yl)methanone (187)

As per general procedure B, (3,5-diethoxyphenyl)(5-nitro-1H-indazol-1-yl)methanone (**187**) was prepared from 5-nitroindazole (57 mg, 0.35 mmol) and 3,5-diethoxybenzoyl chloride (81 mg, 0.35 mmol) as a white solid (45 mg, 35%) following recrystallization from methanol.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (t, 6H, J = 7.02 Hz, 2 x CH_3), 4.09 (q, 4H, J = 6.71 Hz, 2 x CH_2), 6.72 (s, ArH, 1H), 7.20 (s, ArH, 2H), 8.38 (s, ArH, 1H, H_3), 8.50 (d, 1H, ArH, J = 8.55 Hz, H_6), 8.68 (d, 1H, ArH, J = 8.55 Hz, H_7), 8.75 (s, 1H, ArH, H_4)

M.P.: 271-273 °C

IRν_{max} (NaCl film) cm^{-1}: 3095.1, 3077.1, 2984.6, 2941.7, 2898.7, 1697.2 (C=O), 1610.9, 1529.6 (NO_2), 1441.9, 1425.8, 1397.3, 1380.7, 1346.6 (NO_2), 1319.8, 1260.9, 1223.9, 1197.9, 1061.4

HRMS: Found 378.1060 $[M+Na]^+$, $C_{18}H_{17}N_3NaO_5$ requires 378.1066, (-1.6 ppm)

(2,5-Diethoxyphenyl)(5-nitro-1*H*-indazol-1-yl)methanone (188)

As per general procedure B, (2,5-diethoxyphenyl)(5-nitro-1*H*-indazol-1-yl)methanone (**188**) was prepared from 5-nitroindazole (57 mg, 0.35 mmol) and 3,5-diethoxybenzoyl chloride (81 mg, 0.35 mmol) as a white solid (70 mg, 55%) following recrystallization from methanol.

^{1}H-NMR (400MHz, $CDCl_3$) δ 1.11 (t, 3H, CH_3, J = 7.04 Hz), 1.43 (t, 3H, CH_3, J = 7.04 Hz), 3.99 – 4.08 (m, 4H, CH_2) 6.71 (d, 1H, ArH, J = 9.76 Hz), 7.07 – 7.10 (m, 2H, ArH), 8.32 (s, 1H, H_3), 8.52 (dd, 1H, ArH, J = 2.00, 9.04 Hz, H_6), 8.70 (d, 1H, ArH, J = 9.04 Hz, H_7), 8.74 (d, 1H, ArH, J = 2.00 Hz, H_4)

^{13}C NMR (101 MHz, $CDCl_3$) δ 14.66 (CH_3), 14.85 (CH_3), 64.20 (CH_2), 64.84 (CH_2), 114.03 (ArCH), 115.04 (ArCH), 115.94 (ArCH), 117.66 (ArCH), 119.14 (s ArCH), 124.12 (C_q), 124.22 (ArCH), 125.96 (C_q), 140.33 (ArCH, C_3), 141.59 (C_q), 144.89 (C_q), 150.65 (C_q), 152.61 (C_q), 168.17 (C=O)

M.P.: 268-270 °C

IRν_{max} (NaCl film) cm^{-1}: 2978.2, 2929.6, 2885.1, 1704.3 (C=O), 1615.6, 1599.1, 1589.2, 1523.9 (NO_2), 1474.4, 1445.5, 1395.3, 1334.6 (NO_2), 1264.0, 1212.8, 1152.8, 1073.6, 1045.4

HRMS: Found 378.1070 $[M+Na]^+$, $C_{18}H_{17}N_3NaO_5$ requires 378.1066, (+1.1 ppm)

2-(5-Nitro-1*H*-indazole-1-carbonyl)benzyl benzoate (189)

As per general procedure B, 2-(5-nitro-1*H*-indazole-1-carbonyl)benzyl benzoate (**189**) was prepared 5-nitroindazole (77 mg, 0.48 mmol) and 2-(benzoyloxymethyl)benzoyl chloride (130 mg, 0.48 mmol) as a colourless solid (140 mg, 75%) following recrystallization from methanol.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.51 (s, 2H, CH_2), 7.18 (app t., dd, 2H, J=7.93 Hz), 7.37 - 7.44 (m, 1H), 7.49 - 7.56 (m, 1H, ArH), 7.59 - 7.70 (m, 4H, ArH), 8.23 (s, 1H, ArH, H_3), 8.36 (d, 1H, ArH, J = 9.16, 1.83 Hz, H_6), 8.53 (d, 1H, ArH, J = 9.16 Hz, H_7), 8.64 (d, 1H, ArH, J = 1.83 Hz, H_4)

^{13}C NMR (101 MHz, $CDCl_3$) δ 65.33 (CH_2), 116.38 (ArCH), 117.95 (ArCH), 124.59 (ArCH), 126.30 (C_q), 128.26 (ArCH), 128.37 (ArCH), 129.26 (ArCH), 129.48 (C_q), 129.62 (ArCH), 129.67 (ArCH), 131.65 (ArCH), 133.01 (C_q), 133.30 (ArCH), 135.57 (C_q), 141.34 (ArCH), 142.06 (C_q), 145.27 (C_q), 165.95 (NC=O), 169.52 (OC=O)

M.P.: 159-162 °C

IRν_{max} (NaCl film) cm^{-1}: 1719.7 (OC=O), 1693.5 (NC=O), 1525.9 (NO_2), 1450.7, 1427.0, 1341.2 (NO_2), 1268.8, 1152.7

HRMS: Found $[M+Na]^+$ 424.0919, $C_{22}H_{15}N_3NaO_5$ requires 424.0909. (+2.4 ppm)

(Naphthalen-1-yl)(5-nitro-1*H*-indazol-1-yl)methanone (190)

As per general procedure B, naphthalen-1-yl(5-nitro-1*H*-indazol-1-yl)methanone (**190**) was prepared from 5-nitroindazole (326 mg) and 1-naphthoyl chloride (381 mg) as a colourless solid (323 mg, 51%) following recrystallization from methanol.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.64 (m, 3H, ArH), 8.23 (d, 1H, ArH, *J*= 7.04 Hz), (d, 2H, ArH, *J* = 8.00 Hz), 8.10 (d, 1H, ArH, *J* = 8.00 Hz), 8.29 (s, 1H, ArH), 8.56 (dd, 1H, ArH, *J* = 2.00 Hz, *J* = 9.04 Hz), 8.75 (d, 1H, ArH, *J* = 2.00 Hz), 8.82 (d, 1H, ArH, *J* = 9.56 Hz)

^{13}C-NMR (101 MHz, $CDCl_3$) δ 115.92 (ArCH), 117.44 (ArCH), 123.90 (ArCH), 124.09 (ArCH), 124.37 (ArCH), 125.76 (C_q), 126.20 (ArCH), 127.18 (ArCH), 128.03 (ArCH), 128.27 (ArCH), 130.00 (C_q), 130.16 (C_q), 131.73 (ArCH), 133.00 (C_q), 140.46 (ArCH), 141.62 (C_q), 144.67 (C_q), 168.75 (C=O)

M.P.: 189-191 °C Lit. M.P.: 186-187 °C [276]

IRν_{max} (NaCl film) cm^{-1}: 1697.9 (C=O), 1510.4 (NO_2), 1338.7 (NO_2)

HRMS: Found 340.0694 $[M+Na]^+$, $C_{18}H_{11}N_3NaO$ requires 340.0698, (-1.2 ppm)

(Naphthalen-3-yl)(5-nitro-1*H*-indazol-1-yl)methanone (191)

As per general procedure B, (naphthalen-3-yl)(5-nitro-1*H*-indazol-1-yl)methanone (**191**) was prepared from 5-nitroindazole (326 mg) and 2-napthoyl chloride (381 mg) as a colourless solid (412 mg, 65%) following recrystallization from methanol.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 - 7.70 (m, ArH, 2H), 7.91 - 8.04 (m, ArH, 3H), 8.13 (d, 1H, ArH, *J* = 8.54 Hz), 8.43 (s, 1H, ArH, H_3), 8.53 (dd, 1H, ArH, *J* = 9.16, 1.83 Hz), 8.73 (m, 1H, ArH), 8.75 - 8.79 (m, 1H, ArH)

^{13}C NMR (101 MHz, $CDCl_3$) δ 116.47 (ArCH), 117.76 (ArCH), 124.32 (ArCH), 125.77 (C_q), 126.49 (ArCH), 126.95 (ArCH), 127.80 (ArCH), 127.90 (ArCH), 128.81 (ArCH), 129.17 (C_q),

129.58 (ArCH), 132.16 (C_q), 133.32 (ArCH), 135.36 (C_q), 140.55 (ArCH, C_3), 142.66 (C_q), 144.96 (C_q), 168.05 (C=O)

M.P.: 221-224 °C

IRν_{max} (NaCl film) cm^{-1}: 1714.3 (C=O), 1601.0, 1527.1 (NO_2), 1492.7, 1452.1, 1339.6 (NO_2

HRMS: Found 340.0694 $[M+Na]^+$, $C_{18}H_{11}N_3NaO$ requires 340.0698, (-1.2 ppm)

(5-Nitro-1*H*-indazol-1-yl)(phenyl)methanone (192)

As per general procedure B, (5-nitro-1*H*-indazol-1-yl)(phenyl)methanone (**192**) was prepared from 5-nitroindazole (326 mg) and benzoyl chloride (281 mg) as a colourless solid (380 mg, 71%) following recrystallization from methanol.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 2H, ArH), 7.67 (s, 1H, ArH), 8.11 (d, 2H, ArH, J = 7.03 Hz), 8.40 (s, 1H, ArH, H_3), 8.52 (d, 1H, ArH, J = 9.03 H), 8.65 - 8.81 (m, 2H, ArH)

^{13}C-NMR (101 MHz, $CDCl_3$) δ 115.98 (ArCH, H_7), 117.29 (ArCH, H_4), 123.87 (ArCH, H_6), 125.33 (C_q), 127.75 (ArCH), 130.79 (ArCH), 131.62 (C_q), 132.60 (ArCH), 140.08 (ArCH, H_3), 142.12 (C_q), 144.52 (C_q), 167.63 (C=O)

M.P.: 195-198 °C Lit. M.P.: 192-193 °C [277]

IRν_{max} (NaCl film) cm^{-1}: 1694.2 (C=O), 1613.6, 1599.7, 1536.7 (NO_2), 1514.9, 1451.8, 1443.6, 1346.8 (NO_2), 1283.9, 1238.8, 1199.9, 1187.4, 1153.3, 1074.4, 1002.1

HRMS: Found 290.0550 $[M+Na]^+$, $C_{14}H_9N_3NaO_3$ requires 290.0542, (+2.8 ppm)

General procedure C: Reduction of the nitro indazoles

To a suspension of nitro derivative in 1:1 MeOH:EtOAc (50 mL), a spatula tip full of 10% palladium on carbon was added. The reaction was stirred under hydrogen atmosphere at 20 °C. Upon reaction completion, the solution was filtered through celite. The filtrate was concentrated to dryness *in vacuo*, affording the desired product. No further purification was required.

(6-Amino-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (209)

As per general procedure C, (6-amino-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (**209**) was prepared from (**172**) (379 mg, 1 mmol) and obtained as a brown solid (295 mg, 90%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.77 (s, 3H, OCH_3), 3.83 (s, 6H, 2 x OCH_3), 5.92 (s, 2H, NH_2), 6.73 (d, 1H, ArH, J = 8.56 Hz, H_4), 7.30 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 7.52 (d, 1H, ArH, J = 8.56 Hz), 7.56 (s, 1H, ArH, H_7), 8.16 (s, 1H, ArH, H_3)

^{13}C-NMR (101 MHz, DMSO-d_6) δ 56.09 (2 x OCH_3), 60.18 (OCH_3), 97.12 (ArCH, C_7), 108.40 (ArCH, $C_{2'}$ & $C_{6'}$), 114.14 (C_q, C_{3a}), 116.67 (ArCH, C_5), 121.86 (ArCH, C_4), 128.75 (C_q, C_{3a}) , 140.93 (C_q, C_{7a}), 141.92 (C_q, $C_{4'}$), 151.32 (C_q, C_6), 152.08 (C_q, $C_{3'}$ & $C_{5'}$), 167.17 (C=O)

M.P.: 145-149 °C

IR ν_{max} (KBr) cm^{-1}: 3464.8 (NH_2), 3368.7.79 (NH_2), 1675.7 (C=O), 1616.0, 1492.5, 1415.2, 1388.3, 1330.7, 1355.9, 1124.1

HRMS: Found 328.1300 $[M+H]^+$, $C_{17}H_{18}N_3O_6$ requires 328.1297, (+0.9 ppm)

(5-Amino-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (168)

As per general procedure C, (5-amino-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (**168**) was prepared from (**171**) (379 mg, 1 mmol) and obtained as a brown solid (295 mg, 90%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.77 (s, 3H, OCH_3), 3.83 (s, 6H, 2 x OCH_3), 5.34 (s, 2H, NH_2), 6.91 (s, 1H, ArH, H_4), 6.99 (d, 1H, ArH, J = 8.52 Hz, H_6), 7.32 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 8.10 (d, 1H, ArH, J = 8.56 Hz, H_7), 8.28 (s, 1H, H_3)

^{13}C-NMR (101 MHz, DMSO-d_6) δ 56.09 (2 x OCH_3), 60.18 (OCH_3), 101.90 (ArCH, C_3), 108.47 (ArCH, $C_{2'}$ & $C_{6'}$), 115.52 (ArCH, C_7), 118.82 (ArCH, C_6), 127.48 (C_q, $C_{4'}$), 128.39 (C_q, $C_{4'}$), 132.18 (C_q, $C_{4'}$), 140.54 (ArCH, C_3), 146.62 (C_q, $C_{4'}$), 152.10 (C_q, $C_{3'}$ & $C_{5'}$), 166.30 (C=O)

M.P.: 155-175 °C

IRν_{max} (KBr) cm^{-1}: 3454.1 (NH_2), 3352.7 (NH_2), 1672.2 (NC=O), 1583.9, 1519.4, 1415.1, 1351.4, 1331.1, 1151.7

HRMS: Found 328.1297 $[M+H]^+$, $C_{17}H_{18}N_3O_6$ requires 328.1297, (+0.0 ppm)

2-(6-Amino-1*H*-indazole-1-carbonyl)benzyl benzoate (214)

As per general procedure C, 2-(6-amino-1*H*-indazole-1-carbonyl)benzyl benzoate (**214**) was prepared from (**197**) (65 mg, 0.16 mmol) and obtained as a cream solid (32 mg, 53%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 5.37 (s, 2H, CH_2), 5.84 (s, 2H, NH_2), 6.68 – 7.00 (m, 1H, ArH), 7.24 - 7.28 (m, 2H, ArH), 7.45 – 7.62 (m, 8H, ArH), 8.02 (s, 1H, ArH)

^{13}C NMR (101 MHz, DMSO-d_6) δ 64.97 (CH_2), 97.24 (ArCH), 114.28 (ArCH), 117.00, 122.05 (ArCH), 127.97 (ArCH), 128.51 (ArCH), 128.93 (ArCH), 128.96 (ArCH), 129.03 (ArCH), 129.11 (ArCH), 130.26 (ArCH), 133.38 (ArCH), 134.01 (C_q), 134.74 (C_q), 141.41 (C_q), 141.60 (ArCH, C_3), 151.47(C_q), 165.27 (NC=O), 168.99 (OC=O)

M.P.: 134-136 °C

IRν_{max} (KBr) cm^{-1}: 3473.4 (NH_2), 3377.8 (NH_2), 1715.3(OC=O), 1685.5 (NC=O), 1617.4, 1491.8, 1396.6, 1301.3, 1269.7, 1316.9, 1109.4

HRMS: Found $[M+Na]^+$ 394.1165, $C_{22}H_{17}N_3NaO_3$ requires 394.1168, (-0.8 ppm)

2-(5-Amino-1*H*-indazole-1-carbonyl)benzyl benzoate (205)

As per general procedure C, 2-(5-amino-1*H*-indazole-1-carbonyl)benzyl benzoate (**205**) was prepared from (**189**) and obtained as a cream solid (40 mg, 43%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 5.31 (s, 2H, CH_2), 5.38 (s, 2H, NH_2), 6.85 (s, 1H, ArH, H_7), 6.89 (dd, 1H, ArH, J = 9.16, 1.83 Hz, H_6), 7.24 - 7.30 (m, 2H, ArH), 7.47 - 7.64 (m, 7H, ArH), 8.00 (d, 1H, ArH, J = 8.54 Hz), 8.15 (s, 1H, ArH, H_3)

^{13}C NMR (101 MHz, DMSO-d_6) δ 64.81 (CH_2), 101.96 (ArCH), 115.20 (ArCH), 118.68 (ArCH), 127.79 (ArCH), 128.33 (ArCH), 128.73 (ArCH), 128.84 (C_q), 128.86 (ArCH), 129.14 (ArCH), 130.18 (C_q), 131.48 (C_q), 133.22 (ArCH), 134.07 (C_q), 134.27 (C_q), 141.02 (ArCH), 146.66 (C_q), 165.03 (NC=O), 167.96 (OC=O)

M.P.: 171-173 °C

IRν_{max} (KBr) cm^{-1}: 3458.9 (NH_2), 3362.3 (NH_2), 1716.4 (OC=O), 1686.6 (NC=O), 1518.8, 1434.9, 1392.8, 1352.9, 1323.7, 1152.4

HRMS: Found 394.1157 $[M+Na]^+$, $C_{22}H_{17}N_3NaO_3$ requires 394.1168, (-2.8 ppm)

6-Amino-1*H*-indazol-1-yl)(2,5-diethoxyphenyl)methanone (213)

As per general procedure C, (6-amino-1*H*-indazol-1-yl)(2,5-diethoxyphenyl)methanone (**213**) was prepared from (**196**) (57 mg, 0.16 mmol) and obtained as a brown solid (44 mg, 84%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.02 (t, 3H, J=6.71 Hz, CH_3), 1.30 (t, 3H, J = 6.71 Hz, CH_3), 3.90 - 4.02 (m, 4H, 2 x CH_2), 5.88 (s, 2H, NH_2), 6.71 (dd, 1H, ArH, J = 8.54, 1.22 Hz, H_5), 6.97 (d, 1H, ArH, J = 1.22 Hz. H_7), 7.00 - 7.04 (m, 2H, ArH), 7.47 (d, 1H, ArH, J = 8.54 Hz, H_4), 7.56 (s, 1H, ArH), 8.00 (s, 1H, ArH, H_3)

^{13}C NMR (101 MHz, DMSO-d_6) δ 14.59 (CH_3), 14.69 (CH_3), 63.60 (CH_2), 64.43(CH_2), 96.90 (ArCH), 113.95 (ArCH), 114.31 (ArCH), 114.33 (ArCH), 116.82 (ArCH), 116.87, 121.77 (ArCH), 126.48 (C_q), 140.64 (ArCH, C_3), 140.96 (C_q), 149.45 (C_q), 151.20 (C_q), 151.88 (C_q), 167.45 (C=O)

M.P.: 159-162 °C

IRν_{max} (KBr) cm^{-1}: 3463.8 (NH_2), 3365.1 (NH_2), 2979.3, 2928.8, 1689.5 (NC=O), 1615.9, 1496.9, 1423.4, 1392.2, 1357.3, 1298.7, 1222.7, 1197.6, 1046.9

HRMS: Found 348.1336 $[M+Na]^+$, $C_{18}H_{19}N_3NaO_3$ requires 348.1324, (+3.4 ppm)

(6-Amino-1*H*-indazol-1-yl)(naphthalen-1-yl)methanone (215)

As per general procedure C, (6-amino-1*H*-indazol-1-yl)(naphthalen-1-yl)methanone (**215**) was prepared from (**198**) as brown solid (35 mg, 30%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 5.69 (s, 2H, NH_2), 6.17 (s, 1H), 6.68 (dd, 1H, ArH, J = 9.16, 1.83 Hz, H_5), 7.48 (d, 1H, ArH, J = 9.16 Hz), 7.52 - 7.72 (m, 3H, ArH), 7.77 (d, 1H, ArH, J = 7.93 Hz), 7.84 (dd, 1H, ArH, J = 6.71, 1.22 Hz), 8.05 - 8.11 (m, 1H, ArH), 8.19 (d, 1H, ArH, J = 8.54 Hz), 8.82 (s, 1H, ArH)

^{13}C NMR (101 MHz, DMSO-d_6) δ 90.66 (ArCH), 117.78, 121.63 (ArCH), 122.16 (ArCH), 124.11 (ArCH), 124.58 (ArCH), 124.69 (ArCH), 126.52 (ArCH), 127.46 (ArCH), 128.29 (ArCH), 128.49 (ArCH), 130.03 (C_q), 130.72 (C_q), 131.31 (ArCH), 132.80 (C_q), 149.59 (C_q), 153.40 (C_q), 168.02 (C=O)

M.P.: 143-146 °C

IRν_{max} (KBr) cm^{-1}: 3463.8 (NH_2), 3347.8 (NH_2), 1705.9 (NC=O), 1641.1, 1486.6, 1132.9

HRMS: Found 310.0970 $[M+Na]^+$, $C_{18}H_{13}N_3NaO$ requires 310.0956, (+4.5 ppm)

(6-Amino-1*H*-indazol-1-yl)(phenyl)methanone (217)

As per general procedure C, (6-amino-1*H*-indazol-1-yl)(phenyl)methanone (**217**) was prepared from (**200**) (160 mg, 0.60 mmol) and obtained as a yellow solid (50 mg, 35%).

^1H NMR (400 MHz, DMSO-d_6) δ 5.93 (s, 2H, NH_2), 6.74 (d, 1H, ArH, J= 8.52 Hz, H_5), 7.51 – 7.56 (m, 3H, ArH), 7.61 – 7.64 (m, 2H, ArH), 7.94 (d, 1H, ArH, J = 7.00 Hz), 8.15 (s, 1H, H_3)

^{13}C NMR (101 MHz, DMSO-d_6) δ 97.18 (ArCH), 114.17 (ArCH), 116.63 (C_q), 121.91 (ArCH), 127.82 (ArCH), 130.42 (ArCH), 131.75 (ArCH), 133.78 (C_q), 141.05 (ArCH), 141.79 (C_q), 151.38 (C_q), 167.91 (C=O)

M.P.: 153-155 °C

IRν_{max} (KBr) cm^{-1}: 3425.1 (NH_2), 3342.9 (NH_2), 1667.9 (NC=O), 1611.9, 1484.1, 1398.6, 1299.3

HRMS: Found 260.0793 $[M+Na]^+$, $C_{14}H_{11}N_3NaO$ requires 260.0800, (-2.7 ppm)

(5-Amino-1*H*-indazol-1-yl)(naphthalen-2-yl)methanone (207)

As per general procedure C, (5-amino-1*H*-indazol-1-yl)(naphthalen-2-yl)methanone (**207**) was prepared from (**191**) (100 mg, 0.32 mmol) and obtained as a brown solid (90 mg, 98%)

^1H NMR (400 MHz, DMSO-d_6) δ 5.37 (s, 2H, NH_2), 6.93 (d, 1H, ArH, J = 1.83 Hz, H_4), 7.01 (dd, 1H, ArH, J = 8.54, 1.83 Hz, H_6), 7.59 - 7.71 (m, 2H, ArH), 7.96 - 8.07 (m, 3H, ArH), 8.10 (d, 1H, ArH, J = 7.93 Hz), 8.17 (d, 1H, ArH, J = 8.55 Hz), 8.30 (s, 1H, ArH), 8.60 (s, 1H, ArH)

^{13}C NMR (101 MHz, DMSO-d_6) δ 101.96 (ArCH), 115.58 (ArCH), 118.85 (ArCH), 126.59 (ArCH), 126.83 (ArCH), 127.23 (ArCH), 127.53 (C_q), 127.62 (ArCH), 128.25 (ArCH), 129.16 (ArCH), 130.77 (C_q), 131.56 (ArCH), 131.67 (C_q), 132.10 (C_q), 134.19 (C_q), 140.74 (C_q), 146.69 (ArCH), 166.98 (C=O)

M.P.: 149-151 °C

IRν_{max} (KBr) cm^{-1}: 3461.5 (NH_2), 3340.5 (NH_2), 1702.5 (NC=O), 1631.1, 1476.6, 1138.9

HRMS: Found 310.0956 $[M+Na]^+$, $C_{18}H_{13}N_3NaO_3$ requires 310.0956, (0.0 ppm)

(6-Amino-1*H*-indazol-1-yl)(naphthalen-2-yl)methanone (216)

As per general procedure C, (6-amino-1*H*-indazol-1-yl)(naphthalen-2-yl)methanone (**216**) was prepared from (**199**) (100 mg, 0.32 mmol) and obtained as a yellow solid (80 mg, 87%)

^1H NMR (400 MHz, DMSO-d_6) δ 5.93 (s, 2H, NH_2), 7.57 - 7.76 (m, 4H), 7.91 - 8.23 (m, 6H), 8.51 - 8.66 (m, 1H)

^{13}C NMR (101 MHz, DMSO-d_6) δ 97.21 (ArCH), 114.20 (ArCH), 116.64, 121.90 (ArCH), 126.59 (ArCH), 126.80 (ArCH), 127.16 (ArCH), 127.61 (ArCH), 128.21 (ArCH), 129.14 (C_q), 131.42 (ArCH), 131.66 (C_q), 134.17 (C_q), 141.13 (ArCH), 151.39 (C_q), 167.83 (C=O)

M.P.: 194-196 °C

IRν_{max} (KBr) cm^{-1}: 3463.8 (NH_2), 3367.1 (NH_2), 1675.5 (NC=O), 1616.7, 1488.9, 1401.1, 1299.9

HRMS: Found 310.0956 $[M+Na]^+$, $C_{18}H_{13}N_3NaO$ requires 310.0956, (0.0 ppm)

(6-Amino-1*H*-indazol-1-yl)(*p*-tolyl)methanone (210)

As per general procedure C, (6-amino-1*H*-indazol-1-yl)(*p*-tolyl)methanone (**210**) was prepared from (**193**) and obtained as a brown solid (103 mg, 95%).

^1H NMR (400 MHz, DMSO-d_6) δ 2.40 (s, 3H, CH_3), 5.87 (s, 2H, NH_2), 6.72 (dd, 1H, ArH, J = 8.54, 1.83 Hz, H_5), 7.34 (d, 2H, ArH, J = 7.93 Hz), 7.51 (d, 1H, ArH, J = 8.54 Hz, H_4), 7.58 (s, 1H, ArH, H_7), 7.88 (d, 2H, ArH, J = 7.93 Hz), 8.13 (s, 1H, ArH, H_3)

^{13}C NMR (101 MHz, DMSO-d_6) δ 21.13 (CH_3), 97.18 (ArCH), 114.10 (C_q), 116.60 (ArCH), 121.81 (ArCH), 128.36 (ArCH), 130.71 (ArCH), 140.79 (ArCH), 141.85 (C_q), 142.03 (C_q), 151.27 (C_q), 167.63 (C=O)

M.P.: 134-137 °C

IRν_{max} (KBr) cm^{-1}: 3483.1 (NH_2), 3405.8 (NH_2), 1676.8 (NC=O), 1518.9, 1433.2, 1395.7, 1355.4, 1322.9, 1152.8

HRMS: Found 274.0960 $[M+Na]^+$, $C_{15}H_{13}N_3NaO$ requires 274.0956, (+1.5 ppm)

(6-Amino-1*H*-indazol-1-yl)(4-methoxyphenyl)methanone (211)

As per general procedure C, (6-amino-1*H*-indazol-1-yl)(4-methoxyphenyl)methanone (**211**) was prepared from (**194**) (127 mg, 0.43 mmol) as a brown solid (100 mg, 87%).

^1H NMR (400 MHz, DMSO-d_6) δ 3.86 (s, 3H, OCH_3), 5.86 (s, 2H, NH_2), 6.71 (dd, 1H, ArH, J = 8.54, 1.83 Hz, H_5), 7.07 (d, 2H, J = 9.16Hz), 7.50 (d, 1H, ArH, J = 8.54 Hz, H_4), 7.57 (d, 1H, ArH, J = 1.83 Hz, H_7), 8.04 (d, 2H, J = 9.16Hz), 8.14 (s, 1H, H_3)

^{13}C NMR (101 MHz, DMSO-d_6) δ 55.47 (OCH_3), 97.17 (ArCH), 113.22 (ArCH), 114.05 (ArCH), 116.55 (C_q), 121.74 (ArCH), 125.45 (C_q), 133.14 (ArCH), 140.54 (ArCH), 141.96 (C_q), 151.18 (C_q), 162.21 (C_q), 166.85 (C=O)

M.P.: 149-151 °C

IR$_{vmax}$ (KBr) cm^{-1}: 3458.9 (NH_2), 3363.7 (NH_2), 1662.4 (NC=O), 1613.9, 1490.8, 1420.2, 1358.1, 1300.3, 1256.4, 1173.6

HRMS: Found 290.0921 $[M+Na]^+$, $C_{15}H_{13}N_3NaO_2$ requires 290.0905, (+5.5 ppm)

(5-Amino-1*H*-indazol-1-yl)(4-methoxyphenyl)methanone (202)

As per general procedure C, (5-amino-1*H*-indazol-1-yl)(4-methoxyphenyl)methanone (**202**) was prepared from (**186**) (150 mg, 0.51 mmol) and obtained as a colourless solid (80 mg, 59%).

^1H NMR (400 MHz, DMSO-d_6) δ 3.86 (s, 3H, OCH_3), 5.31 (s, 2H, NH_2), 6.90 (d, 1H, ArH, J = 2.14 Hz, H_4), 6.97 (dd, 1H, ArH, J = 8.54, 2.14 Hz, H_6), 7.08 (d, 2H, ArH, J = 9.16 Hz), 8.03 (d, 2H, ArH, J = 9.16 Hz), 8.10 (d, 1H, ArH, J = 8.54 Hz, H_7), 8.25 (s, 1H, ArH, H_3)

^{13}C NMR (101 MHz, DMSO-d_6) δ 55.48 (OCH_3), 101.81 (ArCH), 113.28 (ArCH), 115.56 (ArCH), 118.79 (ArCH), 125.13 (C_q), 127.30 (C_q), 132.33 (C_q), 133.15 (ArCH), 140.07 (ArCH), 146.40 (C_q), 162.26 (C_q), 166.07 (C=O)

M.P.: 175-177 °C

IRν_{max} (KBr) cm^{-1}: 3448.9 (NH_2), 3362.3 (NH_2), 1669.4 (C=O), 1615.9, 1491.8, 1425.7, 1358.1, 1305.3, 1216.4, 1183.6

HRMS: Found 290.0923 $[M+Na]^+$, $C_{15}H_{13}N_3NaO_2$ requires 290.0905,(+6.2 ppm)

(6-Amino-1*H*-indazol-1-yl)(3,5-diethoxyphenyl)methanone (212)

As per general procedure C, (6-amino-1*H*-indazol-1-yl)(3,5-diethoxyphenyl)methanone (**212**) was prepared from (**194**) (52 mg, 0.15 mmol) and obtained as a brown solid (44 mg, 92%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.33 (t, 6H, J = 6.71 Hz, $OCH_2\underline{CH_3}$), 4.06 (q, 4H, J = 6.71 Hz, $O\underline{CH_2}CH_3$), 5.89 (s, 2H, NH_2), 6.62 - 6.80 (m, 2H, ArH), 7.02 (s, 2H, ArH), 7.50 (d, 1H, ArH, J = 8.54 Hz, H_4), 7.57 (s, 1H, ArH), 8.12 (s, 1H, ArH, H_3)

^{13}C NMR (101 MHz, DMSO-d_6) δ 14.55 ($OCH_2\underline{CH_3}$), 63.43 ($O\underline{CH_2}CH_3$), 97.21 (ArCH), 104.13 (ArCH), 108.71 (ArCH), 114.13 (ArCH), 116.63 (C_q), 121.85 (ArCH), 135.52 (C_q), 141.01 (ArCH), 141.80 C_q), 151.34 (C_q), 158.91 (C_q), 167.45 (C=O)

M.P.: 163-165 °C

IRν_{max} (KBr) cm^{-1}: 3463.8 (NH_2), 3370.7 (NH_2), 2979.3, 2929.3, 1679.5 (NC=O), 1615.6, 1592.4, 1491.7, 1443.6, 1390.4, 1355.4, 1320.6, 1172.3, 1058.9

HRMS: Found 348.1329 $[M+Na]^+$, $C_{18}H_{19}N_3NaO_3$ requires 348.1324, (+1.4 ppm)

(5-Amino-1*H*-indazol-1-yl)(2,5-diethoxyphenyl)methanone (204)

As per general procedure C, (5-amino-1*H*-indazol-1-yl)(2,5-diethoxyphenyl)methanone (**204**) was prepared from (**188**) (30 mg, 0.08 mmol) as a brown solid (24 mg, 92%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.01 (t, 3H, J = 6.71 Hz, CH_3), 1.30 (t, 3H, J = 6.71 Hz, CH_3), 3.89 - 4.04 (m, 4H, 2x $O\underline{CH_2}CH_3$), 5.32 (s, 2H, NH_2), 6.87 (s, 1H, ArH, H_4), 6.91 - 7.10 (m, ArH, 4H), 8.06 (d, 1H, ArH, J = 9.16 Hz), 8.11 (s, 1H, ArH, H_3)

^{13}C NMR (101 MHz, DMSO-d_6) δ 14.58 ($OCH_2\underline{CH_3}$), 14.68 ($OCH_2\underline{CH_3}$), 63.60 ($O\underline{CH_2}CH_3$), 64.38 ($O\underline{CH_2}CH_3$), 102.02 (ArCH), 114.29 (ArCH), 114.46 (ArCH), 115.03 (ArCH), 117.01 (ArCH), 118.56 (ArCH), 126.11 (C_q), 127.73 (C_q), 131.31 (C_q), 140.21 (ArCH), 146.56 (C_q), 149.52 (C_q), 151.88 (C_q), 166.63 (C=O)

M.P.: 118-121 °C

IRν_{max} (KBr) cm^{-1}: 3463.8 (NH_2), 3357.7 (NH_2), 1677.9 (NC=O), 1593.7, 1519.7, 1440.0, 1390.5, 1351.5, 1172.1, 1060.4

HRMS: Found 348.1330 $[M+Na]^+$, $C_{18}H_{19}N_3NaO_3$ requires 348.1324, (+1.7 ppm)

(5-Amino-1*H*-indazol-1-yl)(3,5-diethoxyphenyl)methanone (203)

As per general procedure C, (5-amino-1*H*-indazol-1-yl)(3,5-diethoxyphenyl)methanone (**203**) was prepared from (**186**) (47 mg, 0.13 mmol) and obtained as a brown solid (38 mg, 89%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.33 (t, 6H, J = 7.12 Hz, $OCH_2\underline{CH_3}$), 4.06 (q, 4H, J = 7.12 Hz, $O\underline{CH_2}CH_3$), 5.35 (s, 2H, NH_2), 6.71 (app t, dd, 1H, ArH, J=1.83 Hz), 6.90 (d, 1H, ArH, J = 2.14 Hz, H_4), 6.97 (dd, 1H, ArH, J = 8.85, 2.14 Hz, H_6), 7.02 (d, 2H, ArH, J = 1.83 Hz), 8.09 (d, 1H, ArH, J = 8.54 Hz, H_7), 8.24 (s, 1H, ArH, H_3)

^{13}C NMR (101 MHz, DMSO-d_6) δ 14.55 ($OCH_2\underline{CH_3}$), 63.43 ($O\underline{CH_2}CH_3$), 101.96 (ArCH), 104.21 (ArCH), 108.76 (ArCH), 115.52 (ArCH), 118.76 (ArCH), 127.54 (C_q), 132.02 (C_q), 135.19 (C_q), 140.63 (ArCH), 146.65 (C_q), 158.93 (C_q), 166.62 (C=O)

M.P.: 149-152 °C

IRν_{max} (KBr) cm^{-1}: 3449.3 (NH_2), 3365.7 (NH_2), 2979.2, 2928.3, 1687.3 (NC=O), 1628.1, 1586.2, 1499.5, 1429.3, 1391.2, 1226.2, 1152.8

HRMS: Found 348.1334 $[M+Na]^+$, $C_{18}H_{19}N_3NaO_3$ requires 348.1324, (+2.9 ppm)

(5-Amino-1*H*-indazol-1-yl)(phenyl)methanone (208)

As per general procedure C, (5-amino-1*H*-indazol-1-yl)(phenyl)methanone (**208**) was prepared from (**192**) (150 mg, 0.56 mmol) and obtained as a brown solid (123 mg, 93%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 5.35 (s, 2H, NH_2), 6.91 (s, 1H, ArH, H_4), 6.99 (d, 1H, J = 9.16 Hz, H_6), 7.49 - 7.58 (m, 2H, ArH), 7.59 - 7.67 (m, 1H, ArH), 7.94 (d, 2H, ArH, J=7.93 Hz), 8.12 (d, J = 9.16 Hz, H_7), 8.26 (s, 1H, ArH, H_3)

^{13}C NMR (101 MHz, DMSO-d_6) δ 101.92 (ArCH, C_4), 115.52 (ArCH, C_7), 118.79 (ArCH, C_6), 127.52 (C_q, C_{3a}), 127.83 (ArCH), 130.44 (ArCH), 131.76 (ArCH, $C_{4'}$), 132.01 (C_q, $C_{1'}$), 133.46 (C_q, C_{7a}), 140.60 (ArCH, C_3), 146.64 (C_q, C_6), 167.02 (C=O)

M.P.: 136-139 °C

IRν_{max} (KBr) cm^{-1}: 3483.2 (NH_2), 3405.8 (NH_2), 1676.8 (NC=O), 1518.9, 1433.2, 1395.7, 1355.4, 1322.9, 1152.9

HRMS: Found 238.0980 $[M+H]^+$, $C_{14}H_{12}N_3O$ requires 238.0980, (0.0 ppm)

(5-Amino-1H-indazol-1-yl)(*p*-tolyl)methanone (201)

As per general procedure C, (5-amino-1*H*-indazol-1-yl)(*p*-tolyl)methanone (**201**) was prepared from (**185**) (100 mg, 0.36 mmol) and obtained as a brown solid (80 mg. 90%).

^1H NMR (400 MHz, DMSO-d_6) δ 2.40 (s, 3H, CH_3), 5.33 (s., 2H, NH_2), 6.91 (d, 1H, ArH, *J*=1.83 Hz, H_4), 6.98 (dd, 1H, ArH, *J* = 8.85, 1.83 Hz, H_6), 7.34 (d, 2H, ArH, *J*=8.54 Hz), 7.88 (d, 2H, ArH, *J*=8.54 Hz), 8.12 (d, 1H, ArH, *J*=8.55 Hz, H_7), 8.25 (s, 1H, ArH, H_3)

^{13}C NMR (101 MHz, DMSO-d_6) δ 21.10 (CH_3), 101.87 (ArCH, C_4), 115.53 (ArCH, C_7), 118.78 (ArCH, C_6), 127.42 (C_q, C_{3a}), 128.40 (C_q, $C_{1'}$), 130.47 (ArCH), 130.74 (ArCH), 132.13 (C_q, C_{7a}), 140.34 (ArCH, C_3), 142.08 (C_q, C_6), 146.52 (C_q, $C_{4'}$), 166.79 (C=O)

M.P.: 137-139 °C

IRν_{max} (KBr) cm^{-1}: 3408.79 (NH_2), 3335.8 (NH_2), 1672.5 (NC=O), 1519.5, 1458.4, 1390.6, 1354.9, 1321.7, 1279.8, 1152.8

HRMS: Found 252.1137 $[M+Na]^+$, $C_{15}H_{14}N_3O$ requires 252.1137, (0.0 ppm)

(5-Amino-1*H*-indazol-1-yl)(naphthalen-1-yl)methanone (206)

As per general procedure C, (5-amino-1*H*-indazol-1-yl)(naphthalen-1-yl)methanone (**206**) was prepared from (**190**) (105 mg, 0.33 mmol) and obtained as a brown solid (60 mg, 62%).

^1H NMR (400 MHz, DMSO-d_6) δ 5.39 (s, 2H, NH_2), 6.91 (d, 1H, ArH, *J* = 1.83 Hz, H_7), 7.05 (dd, 1H, ArH, *J* = 8.54, 1.83 Hz, H_6), 7.49 - 7.56 (m, 1H, ArH), 7.57 - 7.61 (m, 1H, ArH), 7.63 (d, 1H, ArH, *J* = 7.93 Hz), 7.70 (d, 1H, ArH, *J* = 7.93 Hz), 7.76 (d, 1H, ArH, *J* = 6.10 Hz), 8.04 (d, 1H, ArH, *J* = 7.93 Hz), 8.10 - 8.15 (m, 2H, ArH), 8.23 (d, 1H, ArH, *J* = 8.54 Hz)

^{13}C NMR (101 MHz, DMSO-d_6) δ 102.09 (ArCH), 115.42 (ArCH), 118.79 (ArCH), 124.70 (ArCH), 124.71 (ArCH), 126.30 (ArCH), 126.88 (ArCH), 127.13 (ArCH), 127.89 (C_q), 128.35 (ArCH), 129.78 (C_q), 130.27 (ArCH), 131.56 (C_q), 132.55 (C_q), 132.72 (C_q), 140.97 (ArCH, C_3), 146.88 (C_q), 168.02 (C=O)

M.P.: 195-197 °C

IRν_{max} (KBr) cm^{-1}: 3452.4 (NH_2), 3367.4 (NH_2), 2939.4, 2836.9, 1702.3 (NC=O), 1617.3, 1590.6, 1507.4, 1462.5, 1395.9, 1359.7, 1343.6, 1320.3, 1242.2, 1194.0, 1151.0, 1003.7

HRMS: Found 310.0949 $[M+Na]^+$, $C_{18}H_{13}N_3NaO$ requires 310.0956, (-2.3 ppm)

1-(6-Nitro-1*H*-indazol-1-yl)-2,2-diphenylethanone (219)

As per general procedure A, 1-(6-nitro-1*H*-indazol-1-yl)-2,2-diphenylethanone (**219**) was prepared from 6-nitroindazole (326 mg) and 2,2-diphenylacetyl chloride (461 mg) as an orange solid (650 mg, 91%) following recrystallization from methanol.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.66 (s, 1H, CH), 7.31 (app t., dd, 2H, ArH, J = 7.00 Hz), 7.38 (app t, dd, 4H, ArH, J = 7.04, 7.52 Hz), 7.48 (d, 1H, ArH, J = 7.52 Hz), 7.89 (d, 1H, ArH, J = 8.52 Hz), 8.25 – 8.28 (m, 2H, ArH), 9.45 (s, 1H, ArH, H_7)

^{13}C-NMR (101 MHz, $CDCl_3$) δ 54.63 (CH), 111.65 (ArCH), 119.27 (ArCH), 121.19 (ArCH), 127.14 (ArCH), 128.35 (ArCH), 128.52 (ArCH), 129.32 (C_q), 137.56 (C_q), 138.10 (C_q), 138.91 (ArCH, C_3), 148.13 (C_q), 171.83 (C=O)

M.P.: 119-122 °C Lit. M.P.: 135 °C[267]

IRν_{max} (NaCl film) cm^{-1}: 1723.7 (C=O), 1496.2, 1450.4, 1532.6 (NO_2), 1410.7, 1347.7 (NO_2), 1165.9

HRMS: Found 380.1028 $[M+Na]^+$, $C_{21}H_{15}N_3NaO_3$ requires 380.1011, (+4.5 ppm)

2-(3,4-Dimethoxyphenyl)-1-(6-nitro-1*H*-indazol-1-yl)ethanone (218)

As per general procedure A, 2-(3,4-dimethoxyphenyl)-1-(6-nitro-1*H*-indazol-1-yl)ethanone (**218**) was prepared from 6-nitroindazole (326 mg) and 3,4-dimethoxyphenylacetyl chloride (429.3 mg) as a brown solid (471 mg, 69%) following recrystallization from methanol.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.89 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.52 (s, 2H, CH_2), 6.87 (d, 1H, ArH, J = 8.00 Hz), 7.00 – 7.02 (m, 2H, ArH), 7.90 (d, 1H, ArH, J = 9.04 Hz, H_4), 8.25 (dd, 1H, J = 2.00 Hz, 9.04 Hz, H_5), 8.33 (s, 1H. ArH, H_3), 9.35 (d, 1H, ArH, J = 2.00 Hz, H_7)

^{13}C-NMR (101 MHz, $CDCl_3$) δ 40.60 (CH_2), 55.46 (2 x OCH_3), 110.88 (ArCH), 111.48 (ArCH), 112.38 (C_q), 119.15 (ArCH), 121.16 (ArCH), 121.56 (ArCH), 124.99 (C_q), 129.16 (C_q), 137.96, 138.74 (ArCH, C_3), 148.06 (C_q), 148.61 (C_q), 171.10 (C=O)

M.P.: 149-151 °C

IRν_{max} (NaCl film) cm^{-1}: 3106.3, 2932.4, 1717.8 (C=O), 1592.2, 1515.5 (NO_2), 1461.4, 1410.3, 1346.9(NO_2), 1261.8, 1157.7

HRMS: Found 364.0909 $[M+Na]^+$, $C_{17}H_{15}N_3O_5Na$ requires 364.0907, (-0.7 ppm)

2-(3,4-Dimethoxyphenyl)-1-(5-nitro-1*H*-indazol-1-yl)ethanone (222)

As per general procedure B, 2-(3,4-dimethoxyphenyl)-1-(5-nitro-1*H*-indazol-1-yl)ethanone (**222**) was prepared from 5-nitroindazole (326 mg) and 3,4-dimethoxyphenylacetyl chloride (429.3 mg) as a colourless solid (341 mg, 50%) following recrystallization from methanol.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.87 (s, 3H, CH_3), 3.90 (s, 3H, CH_3), 4.50 (s, 2H, CH_2), 6.86 (d, 1H, ArH, J = 8.04 Hz), 6.97 – 6.99 (m, 2H, ArH), 8.36 (s, 1H, ArH, H_3), 8.44 (dd, 1H, ArH, J = 2.00 Hz, 9.00 Hz, H_6), 8.57 (d, 1H, ArH, 9.00 Hz, H_7), 8.70 (d, 1H, ArH, J = 2.00 Hz, H_4)

^{13}C-NMR (101 MHz, $CDCl_3$) δ 41.28 (CH_2), 56.02 (2 x CH_3), 111.47 (ArCH), 113.04 (ArCH), 116.20 (C_q), 117.83 (ArCH), 122.16 (ArCH), 124.50 (ArCH), 125.53 (C_q), 126.20 (C_q), 140.44 (C_q), 141.62 (ArCH), 141.62 (C_q), 144.96 (C_q), 148.59 (C_q), 149.19 (C_q), 171.88 (C=O)

M.P.: 186-188 °C

IRν_{max} (NaCl film) cm^{-1}: 1725.2 (C=O), 1611.9, 1517.5 (NO_2), 1423.9, 1342.1 (NO_2), 1262.4, 1153.9

HRMS: Found 364.0905 $[M+Na]^+$, $C_{17}H_{15}N_3NaO_5$ requires 364.0909, (-1.2 ppm)

1-(5-Nitro-1*H*-indazol-1-yl)-2,2-diphenylethanone (223)

As per general procedure B, 1-(5-nitro-1*H*-indazol-1-yl)-2,2-diphenylethanone (**223**) was prepared from 5-nitroindazole (326 mg) and 2,2-diphenylacetyl chloride (461 mg) as a colourless solid (357 mg, 50%) following recrystallization from methanol.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.62 (s, 1H, CH), 7.25 - 7.30 (m, 2H), 7.34 (app t, dd, 4H, J = 7.02 Hz,), 7.43 (d, 4H, J = 7.02 Hz), 8.27 (s, 1H), 8.42 (d, 1H, J = 9.16 Hz), 8.59 - 8.68 (m, 2H)

^{13}C NMR (101 MHz, $CDCl_3$) δ (CH), 116.21 (ArCH), 117.69 (ArCH), 124.43 (ArCH), 126.23 (C_q), 127.57 (ArCH), 128.77 (ArCH), 128.96 (ArCH), 137.94 (C_q), 140.45 (ArCH), 141.62 (C_q), 144.88 (C_q), 172.46 (C=O)

M.P.: 180-183 °C

IRν_{max} (NaCl film) cm^{-1}: 3088.8, 1725.20 (C=O), 1615.1, 1524.4 (NO_2), 1495.8, 1426.9, 1340.7 (NO_2), 1152.7

HRMS: Found 380.1030 $[M+Na]^+$, $C_{21}H_{15}N_3O_3Na$ requires 380.1011, (+5.0 ppm)

1-(5-Nitro-1*H*-indazol-1-yl)-2-phenylethanone (225)

As per general procedure B, 1-(5-nitro-1*H*-indazol-1-yl)-2-phenylethanone (**225**) was prepared from 5-nitroindazole (326 mg) and phenylacetyl chloride (309 mg) as a colourless solid (118 mg, 21%) following recrystallization from methanol.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.57 (s, 2H, CH_2), 7.28 - 7.34 (m, 1H, ArCH), 7.38 (app t, dd, 2H, J = 7.32 Hz, ArH), 7.42 - 7.47 (m, 2H, ArH), 8.35 (s, 1H, H_3), 8.44 (dd, 1H, J = 9.16, 2.44 Hz, H_7), 8.57 (d, 1H, ArH, J = 9.16 Hz, H_6), 8.70 (d, 1H, ArH, J = 2,44 Hz, H_4)

^{13}C NMR (101 MHz, $CDCl_3$) δ 41.61 (CH_2), 116.06 (ArCH), 117.70 (ArCH), 124.38 (ArCH), 126.09 (C_q), 127.47 (ArCH), 128.73 (ArCH), 129.75 (ArCH), 133.06 (C_q), 140.35 (ArCH), 141.46 (C_q), 144.82 (C_q), 171.54 (C=O)

M.P.: 171-174 °C

IRν_{max} (NaCl film) cm^{-1}: 1721.2 (C=O), 1624.1, 1525.1 (NO_2), 1495.8, 1426.9, 1343.6 (NO_2), 1151.5

HRMS: Found 304.0696 $[M+Na]^+$, $C_{15}H_{11}N_3O_3Na$ requires 304.0698, (-0.7 ppm)

2-(3,4-Dimethoxyphenyl)-1-(6-amino-1*H*-indazol-1-yl)ethanone (229)

As per general procedure C, 2-(3,4-dimethoxyphenyl)-1-(6-amino-1*H*-indazol-1-yl)ethanone (**229**) was prepared from (**218**) (112 mg, 0.35 mmol) and obtained as a brown solid (98 mg, 91%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.72 (6H, 2 x OCH_3), 4.36 (s, 2H, CH_2), 5.84 (s, 2H, NH_2), 6.67 (dd, 1H, ArH, J = 8.53, 1.51 Hz), 6.83 - 6.91 (m, 2H, ArH), 6.98 (d, 1H, ArH, J = 1.51 Hz), 7.44 (s, 1H, ArH), 7.47 (d, 1H, ArH, J = 8.53 Hz), 8.15 (s, 1H, H_3)

^{13}C NMR (101 MHz, DMSO-d_6) δ 40.17 (CH_2), 55.42 (OCH_3), 55.49 (OCH_3), 96.71 (ArCH), 111.78 (ArCH), 113.54 (ArCH), 113.90 (ArCH), 116.89 (C_q), 121.70 (ArCH), 121.84 (ArCH), 126.96 (C_q), 140.45 (ArCH), 140.93 (C_q), 147.72 (C_q), 148.51 (C_q), 151.25 (C_q), 171.21 (C=O)

M.P.: 152-154 °C

IR ν_{max} (KBr) cm^{-1}: 3473.4 (NH_2), 3363.3 (NH_2), 1701.1 (C=O), 1616.7, 1513.1, 1419.1, 1390.5, 1257.5

HRMS: Found 312.1335 $[M+H]^+$, $C_{17}H_{18}N_3O_3$ requires 312.1348, (-4.2 ppm)

1-(6-Amino-1*H*-indazol-1-yl)-2-phenylethanone (232)

As per general procedure C, 1-(6-Amino-1*H*-indazol-1-yl)-2-phenylethanone (**232**) was prepared from (**221**) (300 mg, 1.07 mmol) and obtained as a brown solid (240 mg, 90%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 4.44 (s, 2H, CH_2), 5.84 (s, 2H, NH_2), 6.67 (d, 1H, J = 8.54 Hz), 7.21 - 7.39 (m, 5H), 7.43 (s, 1H), 7.47 (1 H, d, J = 8.54 Hz), 8.15 (s, 1H, H_3)

^{13}C NMR (101 MHz, DMSO-d_6) δ 40.97 (CH_2), 96.68 (ArCH), 113.93 (ArCH), 116.89 (C_q), 121.87 (ArCH), 126.72 (ArCH), 128.32 (ArCH), 129.62 (ArCH), 134.74 (C_q), 140.57 (ArCH), 140.90 (C_q), 151.30 (C_q), 171.00 (C=O)

M.P.: 136-140 °C

IRν_{max} (KBr) cm^{-1}: 3454.1 (NH_2), 3363.2 (NH_2), 1701.7 (C=O), 1618.3, 1493.0, 1422.2, 1396.7, 1360.1, 1194.9, 1124.6

HRMS: Found 252.1134 $[M+H]^+$, $C_{15}H_{14}N_3O$ requires 252.1137, (-1.1 ppm)

1-(6-Amino-1*H*-indazol-1-yl)-2-(4-methoxyphenyl)ethanone (231)

As per general procedure C, 1-(6-amino-1*H*-indazol-1-yl)-2-(4-methoxyphenyl)ethanone (**231**) was prepared from (**230**) (350 mg, 1.12 mmol) ands obtained as white solid (250 mg, 80%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.72 (s, 3H, OCH_3), 4.35 (s, 2H, CH_2), 5.82 (s, 2H, NH_2), 6.66 (d, 1H, ArH, J = 8.54 Hz), 6.88 (d, 2H, ArH, J = 7.93 Hz), 7.27 (d, 2H, ArH, J = 7.93 Hz), 7.42 (s, 1H, ArH), 7.47 (s, 1H, ArH, J = 8.54 Hz), 8.14 (s, 1H, ArH, H_3)

^{13}C NMR (101 MHz, DMSO-d_6) δ 40.03 (CH_2), 55.00 (OCH_3), 96.68 (ArCH), 113.76 (ArCH), 113.90 (ArCH), 116.89 (C_q), 121.84 (ArCH), 126.53 (C_q), 130.65 (ArCH), 140.48 (ArCH), 151.25 (C_q), 158.12 (C_q), 171.30 (C=O)

M.P.: 149-151 °C

IRν_{max} (KBr) cm^{-1}: 3454.1 (NH_2), 3367.1 (NH_2), 1701.1 (C=O), 1616.7, 1511.7, 1246.2

HRMS: Found 304.1049 $[M+Na]^+$, $C_{16}H_{15}N_3NaO_2$ requires 304.1062, (-4.3 ppm)

1-(6-Amino-1*H*-indazol-1-yl)-2,2-diphenylethanone (230)

As per general procedure C, 1-(6-amino-1*H*-indazol-1-yl)-2,2-diphenylethanone (**230**) was prepared from (**219**) (300 mg, 0.84 mmol) and obtained as a brown solid (250 mg, 91%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 5.88 (s, 2H, NH_2), 6.57 (s, 1H, ArH, H_7), 6.68 (d, 1H, ArH, J = 8.54 Hz, H_5), 7.22 - 7.29 (m, 2H, ArH), 7.30 - 7.40 (m, 8H, ArH), 7.45 (d, 1H, ArH, J = 8.54 Hz, H_4), 7.51 (s, 1H, ArH), 8.10 (s, 1H, H_3)

^{13}C NMR (101 MHz, DMSO-d_6) δ 54.36 (CH), 96.89 (ArCH), 114.03 (ArCH), 116.92 (C_q), 121.97 (ArCH), 127.02 (ArCH), 128.51 (ArCH), 128.76 (ArCH), 139.02 (ArCH), 140.88 (C_q), 141.01 (C_q), 151.45 (C_q), 171.50 (C=O)

M.P.: 182-185 °C

IRν_{max} (KBr) cm^{-1}: 3473.4 (NH_2), 3371.1 (NH_2), 1701.2 (C=O), 1623.4, 1493.9, 1421.2, 1393.8

HRMS: Found 350.1267 $[M+Na]^+$, $C_{21}H_{17}N_3NaO$ requires 350.1267, (0.0 ppm)

1-(5-Amino-1*H*-indazol-1-yl)-2,2-diphenylethanone (235)

As per general procedure C, 1-(5-amino-1*H*-indazol-1-yl)-2,2-diphenylethanone (**235**) was prepared from (**223**) (350 mg, 0.98 mmol) and obtained as a brown solid (310 mg, 96%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 5.31 (s, 2H), 6.57 (s, 1H), 6.85 (s, 1H), 6.90 - 6.97 (m, 1H, ArH), 7.22 - 7.28 (m, 2H, ArH), 7.30 - 7.40 (m, 8H, ArH), 8.05 (d, 1H, ArH, J = 8.54 Hz), 8.22 (s, 1H, ArH)

^{13}C NMR (101 MHz, DMSO-d_6) δ 54.09 (CH), 102.03 (ArCH), 115.20 (ArCH), 118.88 (ArCH), 127.04 (ArCH), 127.88 (C_q), 128.52 (ArCH), 128.75 (ArCH), 131.28 (C_q), 138.98 (C_q), 140.43 (ArCH), 146.58 (C_q), 170.70 (C=O)

M.P.: 173-176 °C

IRν_{max} (KBr) cm^{-1}: 3458.9 (NH_2), 3372.9 (NH_2), 1698.2 (C=O), 1627.1, 1519.7, 1436.1, 1392.3, 1321.4, 1149.8

HRMS: Found 350.1264 $[M+Na]^+$, $C_{21}H_{17}N_3NaO$ requires 350.1267, (-0.9 ppm)

1-(5-Amino-1*H*-indazol-1-yl)-2-(3,4-dimethoxyphenyl)ethanone (234)

As per general procedure C, 1-(5-amino-1*H*-indazol-1-yl)-2-(3,4-dimethoxyphenyl)ethanone (**234**) was prepared from (**222**) (200 mg, 0.59 mmol) and obtained as a brown solid (170 mg, 93%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.72 (s, 6H, 2 x OCH_3), 4.37 (s, 2H, CH_2), 5.27 (s, 2H, NH_2), 6.86 (d, J=3.05 Hz, 2H, ArH), 6.89 - 6.94 (m, 1H, ArH), 6.98 (s, 1H, ArH), 7.98 (d, J=8.54 Hz, 1H, ArH), 8.25 (s, 1H, ArH, H_3)

^{13}C NMR (101 MHz, DMSO-d_6) δ 40.64 (CH_2), 55.42 (OCH_3), 55.50 (OCH_3), 101.93 (ArCH), 111.79 (ArCH), 113.57 (ArCH), 115.04 (ArCH), 118.87 (ArCH), 121.73 (ArCH), 126.90 (C_q), 127.69 (C_q), 131.39 (C_q), 139.87 (ArCH), 146.28 (C_q), 147.74 (C_q), 148.52 (C_q), 170.49 (C=O)

M.P.: 139-142 °C

IRν_{max} (KBr) cm^{-1}: 3454.1 (NH_2), 3366.8 (NH_2), 1700.1 (C=O), 1629.3, 1516.0, 1433.3, 1324.0, 1149.1, 1026.8

HRMS: Found 334.1165 $[M+Na]^+$, $C_{17}H_{17}N_3NaO_3$ requires 334.1168, (-0.9 ppm)

2-(4-Methoxyphenyl)-1-(5-nitro-1*H*-indazol-1-yl)ethanone (224)

As per general procedure B, 2-(4-methoxyphenyl)-1-(5-nitro-1*H*-indazol-1-yl)ethanone (**224**) was prepared from 5-nitroindazole (326 mg) and 4-methoxyphenylacetyl chloride (369 mg) as a colourless solid (205 mg, 33%) folllowing recrystallisation from methanol.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3H, OCH_3), 4.50 (s, 2H, CH_2), 6.91 (d, 2H, ArH, J = 8.53 Hz), 7.36 (d, 2H, ArH, J = 8.53 Hz), 8.35 (s, 1H, ArH, H_3), 8.43 (dd, 1H, ArH, J = 9.29, 2.91 Hz, H_6), 8.57 (d, 1H, ArH, J = 9.29 Hz, H_7), 8.70 (d, 1H, ArH, J = 2.91 Hz, H_4)

^{13}C NMR (101 MHz, $CDCl_3$) δ 40.75 (CH_2), 55.26 (OCH_3), 114.15 (ArCH), 116.05 (ArCH, C_7), 117.71 (ArCH, C_4), 124.36 (ArCH, C_6), 124.96 (C_q), 126.03 (C_q), 130.81 (ArCH), 140.32 (ArCH, C_3), 141.48 (C_q), 144.75 (C_q), 158.93 (C_q, $C_{4'}$), 171.90 (ArCH)

M.P.: 142-145 °C

IRν_{max} (NaCl film) cm^{-1}: 1725.5 (C=O), 1609.5, 1516.2 (NO_2), 1435.9, 1421.5, 1340.9 (NO_2), 1250.7, 1179.3, 1146.4, 1036.3,

HRMS: Found 334.0.0818 $[M+Na]^+$, $C_{16}H_{13}N_3O_4Na$ requires 334.0804, (+4.3 ppm)

1-(5-Amino-1*H*-indazol-1-yl)-2-(4-methoxyphenylethanone (236)

As per general procedure C, 1-(5-amino-1*H*-indazol-1-yl)-2-(4-methoxyphenylethanone (**236**) was prepared from (**224**) (150 mg, 0.48 mmol) and obtained as a brown solid (112 mg, 83%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.72 (s, 3H, OCH_3), 4.37 (s, 2H, CH_2), 5.29 (s, 2H, NH_2), 6.88 (d, 3H, ArH, J = 8.53 Hz), 6.92 (dd, 1H, ArH, J = 9.03, 2.01 Hz), 7.27 (d, 2H, ArH, J = 8.53 Hz), 7.97 (d, 1H, ArH, J = 9.03 Hz), 8.25 (s, 1H, ArH)

^{13}C NMR (101 MHz, DMSO-d_6) δ 39.72 (CH_2), 55.01 (OCH_3), 101.95 (ArCH), 113.78 (ArCH), 115.05 (ArCH), 118.89 (ArCH), 126.48 (C_q), 127.72 (C_q), 130.71 (ArCH), 131.40 (C_q), 139.94 (ArCH), 146.31 (C_q), 158.16 (C_q), 170.62 (C=O)

M.P.: 73-76 °C

IRν_{max} (KBr) cm^{-1}: 3449.3 (NH_2), 3365.0 (NH_2), 1700.8 (C=O), 1629.0, 1519.4, 1434.1, 1394.8, 1320.3, 1322.2, 1147.8, 1109.6

HRMS: Found 304.1059 $[M+Na]^+$, $C_{16}H_{15}N_3O_2Na$ requires 304.1062, (-1.0 ppm)

1-(5-Amino-1*H*-indazol-1-yl)-2-phenylethanone (237)

As per general procedure C, 1-(5-amino-1*H*-indazol-1-yl)-2-phenylethanone (**237**) was prepared from (**225**) (120 mg, 0.48 mmol) as a brown solid (95 mg, 70%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 4.45 (s, 2H, CH_2), 5.29 (s, 2H, NH_2), 6.87 (s, 1H, ArH, H_4), 6.92 (dd, 1H, ArH, J = 8.78, 1.76 Hz), 7.22 - 7.28 (m, 1H, ArH), 7.29 - 7.39 (m, 4H, ArH), 7.97 (d, 1H, ArH, J = 8.78 Hz, H_7), 8.26 (s, 1H, ArH, H_3)

^{13}C NMR (101 MHz, DMSO-d_6) δ 40.60 (CH_2), 101.96 (ArCH), 115.06 (ArCH), 118.91 (ArCH), 126.78 (ArCH), 127.75 (C_q), 128.36 (ArCH), 129.70 (ArCH), 131.36 (C_q), 134.68 (C_q), 140.05 (ArCH), 146.37 (C_q), 170.31 (C=O)

M.P.: 151-155 °C

IRν_{max} (KBr) cm^{-1}: 3449.3 (NH_2), 3366.2 (NH_2), 1701.6 (C=O), 1628.4, 1513.5, 1432.88, 1320.3, 1149.3, 1178.7, 1109.2

HRMS: Found 252.1133 $[M+H]^+$, $C_{15}H_{14}N_3Na$ requires 252.1137, (-1.6 ppm)

2-(4-Methoxyphenyl)-1-(6-nitro-1*H*-indazol-1-yl)ethanone (220)

As per general procedure A, 2-(4-methoxyphenyl)-1-(6-nitro-1*H*-indazol-1-yl)ethanone (**220**) was 6-nitroindazole (490 mg, 3 mmol) and 4-methoxyphenylacetyl chloride (554 mg, 3 mmol) as an orange solid (420 mg, 45%) following recrystallisation from metanol.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H, OCH_3), 4.50 (s, 2H, CH_2), 6.90 (d, 2H, ArH, J = 8.53 Hz, , $H_{3'}$ & $H_{5'}$), 7.36 (d, 2H, ArH, J = 8.53 Hz, $H_{2'}$ & $H_{6'}$), 7.88 (d, 1H, ArH, J=8.53 Hz, H_4), 8.23 (dd, 1H, ArH, J = 8.78, 1.76 Hz, H_5), 8.30 (s, 1H, ArH, H_3), 9.33 (d, 1H, ArH, J = 1.76 Hz, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 40.60 (CH_2), 55.26 (OCH_2), 111.88 (ArCH, C_7), 114.13 (ArCH), 119.52 (ArCH, C_6), 121.57 (ArCH, C_4), 125.00 (C_q), 129.56 (C_q), 130.78 (ArCH), 138.35 (C_q), 139.16 (ArCH, C_3), 148.43 (C_q), 158.91 (C_q), 171.66 (C=O)

M.P.: 134-137 °C

IRν_{max} (NaCl film) cm^{-1}: 1716.4 (C=O), 1609.5, 1511.7 (NO_2), 1436.9, 1411.5, 1335.9 (NO_2), 1251.7, 1180.5, 1136.4, 1036.3

HRMS: Found 334.0804 $[M+Na]^+$, $C_{16}H_{13}N_3O_4Na$ requires 334.0810, (+1.9 ppm)

1-(6-Nitro-1*H*-indazol-1-yl)-2-phenylethanone (221)

As per general procedure A, 1-(6-nitro-1*H*-indazol-1-yl)-2-phenylethanone (**221**) was prepared from 6-nitroindazole (326 mg) and phenylacetyl chloride as a orange solid (264 mg, 47%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.57 (s, 2H, CH_2), 7.29 - 7.34 (m, 1H, ArH), 7.38 (app t, dd, 2H, J = 7.53 Hz), 7.43 - 7.47 (m, 2H, ArH), 7.89 (d, 1H, ArH, J = 8.53 Hz, H_4), 8.25 (dd, 1H, ArH, J=8.53, 2.01 Hz, H_5), 8.31 (s, 1H, ArH, H_3), 9.34 (s, 1H, ArH, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 41.49 (CH_2), 111.90 (ArCH, C_7), 119.59 (ArCH, C_6), 121.59 (ArCH, C_4), 127.45 (ArCH), 128.73 (ArCH), 129.72 (C_q), 133.08 (ArCH), 138.37 (C_q), 139.21 (ArCH, C_3), 171.33 (C=O)

M.P.: 117-120 °C

IRν_{max} (NaCl film) cm^{-1}: 3086.9, 3067.4, 3032.2, 1715.8 (C=O), 1594.9, 1527.2 (NO_2), 1497.9, 1454.9, 1412.0, 1345.9 (NO_2), 1316.4, 1286.8, 1171.2, 1128.8, 1111.8, 1061.9

HRMS: Found 304.0684 $[M+Na]^+$, $C_{15}H_{11}N_3O_3Na$ requires 304.0698, (-4.6 ppm)

General Procedure D: DCC coupling

A suspension of 6-nitroindazole or 5-nitroindazole (163 mg, 1 mmol), DCC (103 mg, 1 mmol), HOBt (135 mg) and 3,4,5-trimethoxyphenylacetic acid (226 mg, 1 mmol) in anhydrous CH_2Cl_2 (15 mL) was stirred under nitrogen at 20 °C for 24 hours. The suspension was filtered and the filtrate was washed with DIW (10 mL), a saturated brine solution, dried using sodium sulphate, filtered and concentrated to dryness in *vacuo*. Hot filtration and recrystallization in MeOH afforded the desired product.

2-(3,4,5-Trimethoxyphenyl)-1-(5-nitro-1*H*-indazol-1-yl)ethanone (227)

As per general procedure D, 2-(3,4,5-trimethoxyphenyl)-1-(5-nitro-1*H*-indazol-1-yl)ethanone (**227**) was prepared from 5-nitroindazole and 3,4,5-trimethoxyphenylacetic acid as a colourless solid (223 mg, 60%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (s, 3H, OCH_3), 3.87 (s, 6H, 2 x OCH_3), 4.49 (s, 2H, CH_2), 6.67 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 8.37 (s, 1H, ArH, H_3), 8.45 (d, 1H, ArH, J = 9.16 Hz, H_7), 8.58 (d, 1H, ArH, J = 9.16 Hz, H_6), 8.71 (d, 1H, ArH, J = 1.22 Hz, H_4)

^{13}C NMR (101 MHz, $CDCl_3$) δ 41.77 (CH_2), 56.13 (2 x OCH_3), 60.82 (OCH_3), 106.87 (ArCH, $H_{2'}$ & $H_{6'}$), 116.08 (ArCH, C_7), 117.72 (ArCH, C_4), 124.43 (ArCH, C_6), 126.47 (C_q,C_{3a}), 128.49 (C_q, $C_{1'}$), 137.34 (C_q, $C_{4'}$), 140.38 (ArCH, C_3), 141.47 (C_q, , C_6), 144.86 (C_q, C_{7a}), 153.33 (C_q, $C_{3'}$ & $C_{5'}$), 171.44 (C=O)

M.P.: 166-169 °C

IRν_{max} (NaCl film) cm^{-1}: 1721.8 (C=O), 1591.1, 1534.8 (NO_2), 1518.1, 1460.6, 1460.6, 1341.0 (NO_2), 1241.7, 1159.2, 1124.8

HRMS: Found 394.1003 $[M+Na]^+$, $C_{18}H_{17}N_3O_6Na$ requires 394.1015, (-3.1 ppm)

2-(3,4,5-Trimethoxyphenyl)-1-(6-nitro-1*H*-indazol-1-yl)ethanone (228)

As per general procedure D, 2-(3,4,5-trimethoxyphenyl)-1-(6-nitro-1*H*-indazol-1-yl)ethanone (**228**) was prepared from 6-nitroindazole and 3,4,5-trimethoxyphenyl acetic acid as an orange solid (212 mg, 57%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (s, 3H, OCH_3), 3.88 (s, 6H, 2 x OCH_3), 4.49 (s, 2H, CH_2), 6.68 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 7.90 (d, 1H, ArH, *J*=8.50 Hz, H_4), 8.25 (dd, 1H, ArH, *J* = 8.50, 2.00 Hz, H_5), 8.32 (s, 1H, ArH, H_3), 9.35 (s, 1H, ArH, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 41.32 (CH_2), 55.78 (2 x OCH_3), 60.48 (OCH_3), 106.36 (ArCH, $H_{2'}$ & $H_{6'}$), 111.56 (ArCH), 119.22, 121.23, 128.11, 129.20, 137.95 (ArCH, C_3), 138.82 (C_q), 148.09 (C_q), 152.89 (C_q, $C_{3'}$ & $C_{5'}$), 170.79 (C=O)

M.P.: 178-180 °C

IRν_{max} (NaCl film) cm^{-1}: 1723.0 (C=O), 1591.1, 1531.8 (NO_2), 1508.1, 1460.6, 1460.6, 1346.0 (NO_2), 1242.7, 1154.2, 1125.8

HRMS: Found 394.1003 $[M+Na]^+$, $C_{18}H_{17}N_3O_6Na$ requires 394.1015, (-3.1 ppm)

1-(6-Amino-1*H*-indazol-1-yl)-2-(3,4,5-trimethoxyphenyl)ethanone (233)

As per general procedure C, 1-(6-amino-1*H*-indazol-1-yl)-2-(3,4,5-trimethoxyphenyl)ethanone (**233**) was prepared from (**228**) (150 mg, 0.4 mmol) and obtained as a brown solid (120 mg, 88%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.64 (s, 3H, OCH_3), 3.74 (s, 6H, 2 x OCH_3), 4.38 (s, 2H, CH_2), 5.84 (s, 2H, NH_2), 6.65 - 6.70 (m, 3H, ArH, H_4, $H_{2'}$ & $H_{6'}$), 7.44 (s, 1H, ArH, H_7), 7.48 (d, 1H, ArH, J=8.54 Hz, H_4), 8.16 (s, 1H, ArH,)

^{13}C NMR (101 MHz, DMSO-d_6) δ 41.04 (CH_2), 55.80 (2 x OCH_3), 59.94 (OCH_3), 96.71 (ArCH, C_7), 107.15 (ArCH, $C_{2'}$ & $C_{6'}$), 113.92 (ArCH, C_5), 116.89 (C_q, C_{3a}), 121.87 (ArCH, C_4), 130.18 (C_q, $C_{1'}$), 136.35 (C_q, $C_{4'}$), 140.49 (ArCH, C_3), 140.93 (C_q, C_{7a}), 151.28 (C_q, C_6), 152.66 (C_q, $C_{3'}$ & $C_{5'}$), 170.91 (C=0)

M.P.: 147-149 °C

IRν_{max} (KBr) cm^{-1}: 3452.3 (NH_2), 3367.4 (NH_2), 2939.4, 2836.9, 1702.3 (C=O), 1617.3, 1590.6, 1507.4, 1462.5, 1422.4, 1395.9, 1359.7, 1272.7, 1125.5, 1003.7

HRMS: Found 342.1454 $[M+H]^+$, $C_{18}H_{20}N_3O_4$ requires 342.1454, (0.0 ppm)

1-(5-Amino-1*H*-indazol-1-yl)-2-(3,4,5-trimethoxyphenyl)ethanone (238)

As per general procedure C, 1-(5-amino-1*H*-indazol-1-yl)-2-(3,4,5-trimethoxyphenyl)ethanone (**238**) was prepared from (**227**) (150 mg, 0.4 mmol) and obtained as a colourless solid (117 mg, 85%) .

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.64 (s, 3H, OCH_3), 3.74 (s, 9H, 2 x OCH_3), 4.39 (s, 2H, CH_2), 5.28 (s, 2H, NH_2), 6.68 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 6.88 (d, 1H, ArH, J = 1.83 Hz, H_4), 6.92 (dd, 1H, ArH, J = 8.85, 1.83 Hz, H_6), 7.98 (d, 1H, ArH, J = 8.85 Hz, H_7), 8.27 (s, 1H, ArH, H_3)

^{13}C NMR (101 MHz, DMSO-d_6) δ 40.69 (CH_2), 55.80 (2 x OCH_3), 59.94 (OCH_3), 101.96 (ArCH, C_4), 107.18 (ArCH, $C_{2'}$ & $C_{6'}$), 115.05 (ArCH, C_7), 118.88 (ArCH, C_6), 127.70 (C_q, C_{3a}), 130.11 (C_q, $C_{1'}$), 131.38 (C_q, C_{7a}), 136.37 (C_q, $C_{4'}$), 139.93 (ArCH, C_3), 146.31 (C_q, C_5), 152.67 (C_q, $C_{2'}$ & $C_{6'}$), 170.19 (C=O)

M.P.: 125-128 °C

IRν_{max} (KBr) cm^{-1}: 3452.4 (NH_2), 3367.4 (NH_2), 2931.5, 2832.9, 1701.0 (C=O), 1617.3, 1591.6, 1503.1, 1451.4, 1422.4, 1385.9, 1353.7, 1262.7

HRMS: Found 342.1460 $[M+H]^+$, $C_{18}H_{20}N_3O_4$ requires 342.1454., (+1.8 ppm)

General Procedure E: *N*-1 and *N*-2 direct arylation of indazoles using Cham-Lam coupling

To a solution of 6-nitroindazole or 5-nitroindazole (1 mmol, 163 mg) and copper acetate (1 mmol, 182mg) in CH_2Cl_2 (5 mL), pyridine (1 mmol, 0.08 mL) was added slowly. After 15 minutes of stirring at 20 °C under air, the necessary phenylboronic acid (2 mmol) was added. The resultant solution was left stirring at 20 °C under air for 24 h. It was then diluted with CH_2Cl_2 (20 mL), filtered through celite, washed once with 1M HCl (15 mL), brine (15 mL), dried using anhydrous sodium sulfate and filtered. The filtrate was concentrated to dryness *in vauco*. The crude mixture was purified using flash column chromatography over silica gel (eluent EtOAc: Hexane gradient) which afforded the desired product. The *N*-2 regioisomer was isolated as well where possible.

Note: The masses of 6-nitroindazole and 5-nitroindazole and the phenylboronic acid correspond to the molar amounts used in the general procedure D unless stated otherwise.

1-(4-Methoxyphenyl)-6-nitro-1*H*-indazole (276)

As per general procedure E, 1-(4-methoxyphenyl)-6-nitro-1*H*-indazole (**276**) was prepared from 6-nitroindazole (163 mg) and 4-methoxyphenyl boronic acid (304 mg) as a yellow solid (165 mg, 61%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (s, 3H, OCH_3), 7.12 (d, 2H, ArH, *J*=9.03 Hz, $H_{3'}$ & $H_{5'}$), 7.61 (d, 2H, ArH, *J* = 8.53 Hz, $H_{2'}$ & $H_{6'}$), 7.92 (d, 1H, ArH, *J* = 9.03 Hz, H_4), 8.09 (dd, 1H, ArH, *J*=9.03, 1.51 Hz, H_5), 8.31 (s, 1H, ArH, H_3), 8.55 (s, 1H, ArH, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 55.65 (OCH_3), 107.09 (ArCH), 114.95 (ArCH), 116.07 (ArCH), 121.98 (ArCH), 124.86 (ArCH), 127.82 (C_q), 132.00 (C_q), 134.82 (ArCH, C_3), 137.85 (C_q), 146.96 (C_q), 159.27 (C_q)

M.P.: 130-132 °C Lit. M.P.: 128-130 °C[301]

IRν_{max} (NaCl film) cm^{-1}: 1523.5 (NO_2), 1346.9 (NO_2)

HRMS: Found 270.0873 $[M+H]^+$, $C_{14}H_{12}N_3O_3$ requires 270.0879, (-2.2 ppm)

2-(4-Methoxyphenyl)-6-nitro-2*H*-indazole (277)

As per general procedure E, 2-(4-methoxyphenyl)-6-nitro-2*H*-indazole (**277**) was prepared from 6-nitroindazole (163 mg) and 4-methoxyphenyl boronic acid (304 mg) as a yellow solid (37 mg, 14%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (s, 3H, OCH_3), 7.07 (d, 2H, *J*=8.53 Hz), 7.77 - 7.88 (m, 3H), 7.93 (d, 1H, *J*=9.54 Hz), 8.45 (s, 1H), 8.77 (s, 1H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 55.97 (OCH_3), 115.16 (ArCH), 116.15 (ArCH), 116.55 (ArCH), 121.42 (ArCH), 121.85 (ArCH), 122.88 (ArCH), 125.30 (C_q), 133.67 (C_q), 147.09 (C_q), 147.75 (C_q), 160.38 (C_q)

M.P.: 135-137 °C

IRν_{max} (NaCl film) cm^{-1}: 1518.7 (NO_2), 1341.9 (NO_2)

HRMS: Found 270.0873 $[M+H]^+$, $C_{14}H_{12}N_3O_3$ requires 270.0879, (-2.2 ppm)

1-(4-Methoxyphenyl)-1*H*-indazol-6-amine (286)

As per general procedure C, 1-(4-methoxyphenyl)-1*H*-indazol-6-amine (**286**) was prepared from (**276**) (204 mg, 0.76 mmol) and obtained as a brown solid (120 mg, 66%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.82 (s, 3H, OCH_3), 5.45 (s, 2H, NH_2), 6.58 (dd, 1H, ArH, *J*=8.54, 1.53 Hz, H_5), 6.73 (s, 1H, ArH, H_7), 7.11 (d, 2H, ArH, *J* = 9.24 Hz, $H_{3'}$ & $H_{5'}$), 7.46 (d, 1H, ArH, *J*=8.54 Hz, H_4), 7.55 (d, 2H, ArH, *J* = 9.24 Hz, $H_{2'}$ & $H_{6'}$), 7.96 (s, 1H, ArH, H_3)

^{13}C NMR (101 MHz, DMSO-d_6) δ 55.41 (OCH_3), 90.39 (ArCH), 112.77 (ArCH), 114.52 (ArCH), 116.68, 121.41 (ArCH), 123.59 (ArCH), 133.45 (C_q), 134.78 (ArCH), 140.50 (C_q), 148.99 (C_q), 157.31 (C_q)

M.P.: 175 -177 °C

IRν_{max} (KBr) cm^{-1}: 3463.1 (NH_2), 3382.7 (NH_2), 1626.7, 1514.4, 1481.7, 1241.9

HRMS: Found 240.1131 $[M+H]^+$, $C_{14}H_{14}N_3O$ requires 240.1137, (-2.5 ppm)

1-(4-Methoxyphenyl)-5-nitro-1*H*-indazole (301)

As per general procedure E, 1-(4-methoxyphenyl)-5-nitro-1*H*-indazole (**301**) was prepared from 5-nitroindazole (163 mg) and 4-methoxyphenyl boronic acid (304 mg) as a yellow solid (160 mg, 59%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (s, 3H, OCH_3), 7.10 (d, 2H, ArH, *J*=8.54 Hz), 7.60 (d, 2H, ArH, *J*=8.54 Hz), 7.67 (d, 1H, ArH, *J*=9.16 Hz, H_7), 8.29 (dd, 1H, ArH, *J*=9.16, 2.44 Hz, H_6), 8.38 (s, 1H, ArH, H_3), 8.79 (d, 1H, ArH, *J*=2.44 Hz, H_4)

^{13}C NMR (101 MHz, $CDCl_3$) δ 55.33 (OCH_3), 110.21 (ArCH), 114.54 (ArCH), 118.63 (ArcH), 121.65 (ArCH), 123.69 (C_q), 124.61 (ArCH), 131.71 (C_q), 136.72 (ArCH), 140.42 (C_q), 142.38 (C_q), 158.96 (C-O, C_q)

M.P.: 97-99 °C Lit. M.P.: 94-96 °C[301]

IRν_{max} (NaCl film) cm^{-1}: 1612.93, 1523.48 (NO_2), 1346.89 (NO_2)

HRMS: Found 270.0879 $[M+H]^+$, $C_{14}H_{12}N_3O_3$ requires 270.0879, (0.0 ppm)

1-(4-Fluorophenyl)-5-nitro-1*H*-indazole (275)

As per general procedure E, 1-(4-fluorophenyl)-5-nitro-1*H*-indazole (**275**) was prepared from 5-nitroindazole (163 mg) and 4-flourophenyl boronic acid (280 mg) as a yellow solid (100 mg, 20%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 - 7.32 (m, 2H), 7.66 - 7.73 (m, 3H), 8.33 (dd, 1H, *J* = 9.16, 2.44 Hz), 8.41 (s, 1H), 8.81 (d, 1H, *J* = 2.44 Hz)

^{13}C NMR (100 MHz, $CDCl_3$) δ 110.39 (ArCH), 116.72 (d, *J*=8.39 Hz, ArCH), 118.99 (ArCH), 122.31 (ArCH), 125.13 (d, *J* = 8.39 Hz, ArCH), 137.51 (ArCH), 163.09 (C_q)

IRν_{max} (NaCl film) cm^{-1}: 1616.32, 1514.88 (NO_2), 1342.15 (NO_2)

M.P.: 186-189 °C[291]

HRMS: Found 256.0522 $[M-H]^-$, $C_{13}H_7FN_3O_2$ requires 256.0522, (0.0 ppm)

6-Nitro-1-(3,4,5-trimethoxyphenyl)-1*H*-indazole (280)

As per general procedure E, 6-nitro-1-(3,4,5-trimethoxyphenyl)-1*H*-indazole (**280**) was prepared from 6-nitroindazole (163 mg) and 3,4,5-trimethxoxyphenylboronic acid (424 mg) as a yellow solid (200 mg, 61%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.95 (s, 3H, OCH_3), 3.96 (s, 6H, 2 x OCH_3), 6.91 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 7.94 (d, 1H, ArH, J = 9.16 Hz, H_4), 8.11 (dd, 1H, ArH, J = 9.16, 1.83 Hz, H_5), 8.32 (s, 1H, ArH, H_3), 8.65 (s, 1H, ArH, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 56.77 (2 x OCH_3), 61.38 (OCH_3), 101.44 (ArCH), 107.50 (ArCH), 116.67 (ArCH), 121.18 (C_q), 122.44 (ArCH), 128.37 (C_q), 135.01 (C_q), 135.45 (ArCH), 138.11 (C_q), 147.44 (C_q), 154.35 (C_q)

M.P.: 166-167 °C

IRν_{max} (NaCl film) cm^{-1}: 1600.99, 1529.95 (NO_2), 1509.42, 1464.25, 1344.34 (NO_2)

HRMS: Found 330.1095 $[M+H]^+$, $C_{16}H_{16}N_3O_5$ requires 328.1090, (+1.5 ppm)

6-Nitro-2-(3,4,5-trimethoxyphenyl)-2*H*-indazole (282)

As per general procedure E, 6-nitro-2-(3,4,5-trimethoxyphenyl)-2*H*-indazole (**282**) was prepared from 6-nitroindazole (163 mg) and 3,4,5-trimethxoyphenylboronic acid (424mg) as a yellow solid (16 mg, 5%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.93 (s, 3H, OCH_3), 4.00 (s, 6H, 2 x OCH_3), 7.15 (s, 2H, ArH, $H_{2'}$ & H_5), 7.83 (d, 1H, ArH, J = 9.16 Hz, H_4), 7.95 (dd, 1H, ArH, J = 9.16, 1.83 Hz, H_5), 8.50 (s, 1H, ArH, H_3), 8.79 (s, 1H, ArH, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 56.81 (2 x OCH_3), 61.41 (OCH_3), 99.45 (2 x ArCH), 116.24 (ArCH), 116.81 (ArCH), 121.85 (ArCH), 121.96 (ArCH), 125.23 (C_q), 136.14 (C_q), 139.05 (C_q), 147.84 (C_q), 154.28 (C_q)

M.P.: 205-207 °C

IRν_{max} (NaCl film) cm^{-1}: 1600.99, 1529.95 (NO_2), 1509.42, 1464.25, 1344.34 (NO_2)

HRMS: Found 330.1085 $[M+H]^+$, $C_{16}H_{16}N_3O_5$ requires 328.1090, (-1.5ppm)

5-Nitro-1-(3,4,5-trimethoxyphenyl)-1*H*-indazole (284)

As per general procedure E, 5-nitro-1-(3,4,5-trimethoxyphenyl)-1*H*-indazole (**284**) was prepared from 5-nitroindazole (163 mg) and 3,4,5-trimethxoyphenyl boronic acid (424 mg) as a yellow solid (150 mg, 45%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94 (s, 3H, OCH_3), 3.95 (s, 6H, 2 x OCH_3), 6.91 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 7.77 (d, 1H, ArH, J = 9.16 Hz, H_7), 8.33 (dd, 1H, ArH, J = 9.16, 1.83Hz, H_6), 8.40 (s, 1H, ArH, H_3), 8.80 (d, 1H, ArH, J = 1.83 Hz, H_4)

^{13}C NMR (101 MHz, $CDCl_3$) δ 56.44 (2xOCH_3), 61.07 (OCH_3), 99.16, 101.24 (2xArCH), 110.70 (ArCH), 119.01 (ArCH), 121.05 (C_q), 122.24 (ArCH), 134.68 (C_q), 137.28 (ArCH), 142.50 (C_q), 153.98 (C_q)

M.P.: 191-192 °C

IRν_{max} (NaCl film) cm^{-1}: 1607.03, 1512.37 (NO_2), 1457.16, 1345.95 (NO_2), 1133.51

HRMS: Found 329.0939 $[M-H]^-$, $C_{16}H_{14}N_3O_5$ requires 328.0939, (0.0 ppm)

1-(3,4,5-Trimethoxyphenyl)-1*H*-indazol-6-amine (287)

As per general procedure E, 1-(3,4,5-trimethoxyphenyl)-1*H*-indazol-6-amine (**287**) was prepared from (**280**) (100 mg, 0.3 mmol) and obtained as a brown solid (70 mg, 77%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.72 (s, 3H, OCH_3), 3.87 (s, 6H, 2 x OCH_3), 5.51 (s, 2H, NH_2), 6.59 (dd, 1H, ArH, J = 8.54, 1.83 Hz, H_5), 6.89 - 6.94 (m, 3H, ArH, H_7, $H_{2'}$ & $H_{6'}$), 7.47 (d, 1H, ArH, J = 8.54 Hz, H_4), 7.98 (s, 1H, ArH, H_3)

^{13}C NMR (101 MHz, DMSO-d_6) δ 56.03 (2 x OCH_3), 60.16 (OCH_3), 91.00 (ArCH), 99.63 (ArCH), 112.84 (ArCH), 116.91 (C_q), 121.53 (ArCH), 135.24 (ArCH), 135.31 (C_q), 136.21 (C_q), 140.43 (C_q), 149.21 (C_q), 153.22 (C_q)

M.P.: 144-145 °C

IRν_{max} (KBr) cm^{-1}: 3453.2 (NH_2), 3367.5 (NH_2) 1625.4, 1598.2, 1507.7, 1423.8, 1229.1

HRMS: Found 300.1341 $[M+H]^+$, $C_{16}H_{18}N_3O_3$ requires 300.1348, (-2.3 ppm)

1-(3,4,5-Trimethoxyphenyl)-1*H*-indazol-5-amine (291)

As per general procedure C, 1-(3,4,5-trimethoxyphenyl)-1*H*-indazol-5-amine (**291**) was prepared from (**284**) (150 mg, 0.3 mmol) and obtained as a brown solid (130 mg, 95%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.71 (s, 3H, OCH_3), 3.86 (s, 6H, 2 x OCH_3), 5.00 (s, 2H, NH_2), 6.85 (s, 1H, ArH, H_7), 6.90 (d, 1H, ArH, J = 9.16 Hz, H_6), 6.95 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 7.64 (d, 1H, ArH, J = 9.16 Hz, H_7), 8.01 (s, 1H, ArH, H_3)

^{13}C NMR (101 MHz, DMSO-d_6) δ 56.04 (2 x OCH_3), 60.17 (OCH_3), 99.26 (ArCH, $C_{2'}$ & $C_{6'}$), 101.01 (ArCH), 111.05 (ArCH), 118.82 (ArCH), 126.39 (C_q), 132.44 (C_q), 133.64 (ArCH), 135.39 (C_q), 136.11 (C_q), 143.64 (C_q), 153.33 (C_q)

M.P.: 127-129 °C

IR ν_{max} (KBr) cm^{-1}: 3428.57 (NH_2), 3347.41 (NH_2) 1628.65, 1598.78, 1509.85, 1229.66

HRMS: Found 300.1358 [M+H], $C_{16}H_{18}N_3O_3$ requires 300.1348, (+3.3 ppm)

General procedure F: Zinc/acetic acid reduction of nitroindazoles

To a suspension of (**285**) or (**288**) in acetic acid (10 mL), was added zinc powder 10 μm (15 mmol) which was then stirred at 20 °C under nitrogen for 7 days. The suspension was filtered through celite. A saturated sodium bicarbonate solution was added to the filtrate until efferverence was not observed. The aqueous layer was extracted with EtOAc (3 x 20 mL), the organic layers collected, washed with saturated sodium bicarbonate (2 x 20 mL), a saturated brine solution (20 mL), dried using sodium sulphate, filtered and concentrated to dryness *in vacuo*. Purification by flash column chromatography over silica gel (eluent EtOAc: Hex gradient) afforded the desired product.

1-(4-(Benzyloxy)phenyl)-1*H*-indazol-5-amine (293)

Using the general procedure F, 1-(4-(benzyloxy)phenyl)-1*H*-indazol-5-amine (**293**) was prepared from (**285**) (410 mg, 1.19 mmol), zinc and acetic acid as a brown solid (100 mg, 27%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 4.97 (s, 2H, NH_2), 5.17 (s, 2H, CH_2), 6.84 (s, 1H, ArH), 6.85 - 6.90 (m, 1H, ArH), 7.18 (d, 2H, ArH, J = 9.16 Hz), 7.35 (d, 1H, ArH, J = 7.32 Hz), 7.41 (app t., dd, 2H, ArH, J = 7.32 Hz), 7.45 - 7.51 (m, 2H, ArH), 7.60 (d, 2H, ArH, J = 9.16 Hz), 7.98 (s, 1H, ArH)

^{13}C NMR (101 MHz, DMSO-d_6) δ 69.53 (CH_2), 100.92 (ArCH), 110.55 (ArCH), 115.55 (2xArCH), 118.65 (ArCH), 122.98 (2 x ArCH), 126.07 (C_q), 127.71 (2 x ArCH), 127.87

(ArCH), 128.45 (2 x ArCH), 132.51 (C_q), 133.17 (ArCH), 133.58 (C_q), 136.95 (C_q), 143.42 (C_q), 156.35(C_q)

M.P.: 147-149 °C

IRν_{max} (KBr) cm^{-1}: 3438.42 (NH_2), 3349.59 (NH_2) 1629.42, 1514.22, 1243.98

HRMS: Found 316.1442 $[M+H]^+$, $C_{20}H_{18}N_3O$ requires 316.1450, (-2.5 ppm)

1-(4-(Benzyloxy)phenyl)-1*H*-indazol-6-amine (289)

Using the general procedure F, 1-(4-(benzyloxy)phenyl)-1*H*-indazol-6-amine (**289**) was prepared from (**285**) (410 mg, 1.19 mmol), zinc and acetic acid as a brown solid (100 mg, 27%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 5.18 (s, 2H, CH_2), 5.46 (br. s., 2H, NH_2), 6.58 (d, 1H, ArH, J = 8.54 Hz), 6.73 (s, 1H, ArH), 7.18 (d, 2H, ArH, J = 8.54 Hz), 7.30 - 7.62 (m, 8H, ArH), 7.96 (s, 1H, ArH)

^{13}C NMR (101 MHz, DMSO-d_6) δ 69.51 (CH_2), 90.42 (ArCH), 112.77 (ArCH), 115.45 (ArCH), 116.70 (C_q), 121.42 (ArCH), 123.51 (ArCH), 127.69 (ArCH), 127.87 (C_q), 128.45 (ArCH), 133.64 (C_q), 134.84 (ArCH), 136.96 (C_q), 140.47 (C_q), 149.02 (C_q), 156.36 (C_q)

M.P.: 151-153 °C

IRν_{max} (KBr) cm^{-1}: 3435.5 (NH_2), 3349.2 (NH_2) 1629.4, 1511.2, 1237.9

HRMS: Found 316.1442 $[M+H]^+$, $C_{20}H_{18}N_3O$ requires 316.1450, (-2.5 ppm)

1-(4-(Benzyloxy)phenyl)-5-nitro-1*H*-indazole (285)

As per general procedure E, 1-(4-(benzyloxy)phenyl)-5-nitro-1*H*-indazole (**286**) was prepared from 5-nitroindazole and 1-(4-(benzyloxy)phenylboronic acid as yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) 5.17 (s, 2H, CH_2), 7.17 (d, 2H, J = 8.54 Hz), 7.34 - 7.40 (m, 1H), 7.43 (app t., dd, 2H, J = 7.63 Hz), 7.46 - 7.50 (m, 2H), 7.60 (d, 2H, J = 8.54 Hz), 7.68 (d, 1H, J = 9.16 Hz), 8.29 (dd, 1H, J = 9.16, 1.83 Hz), 8.38 (s, 1H), 8.79 (d, 1H, J = 1.83 Hz)

^{13}C NMR (101 MHz, $CDCl_3$) δ 70.72 (CH_2), 110.86 (ArCH), 116.15 (ArCH), 119.26 (ArCH), 122.29 (ArCH), 124.33 (2xArCH), 125.20, 127.78 (2xArCH), 128.51 (ArCH), 129.01, 132.56, 136.71(ArCH), 137.38, 141.00, 143.02, 158.71

M.P.: 140-141 °C

IRν_{max} (NaCl film) cm^{-1}: 2945.5, 1716.4, 1514.9 (NO_2), 1453.2, 1340.8 (NO_2), 1245.0

HRMS: Found 346.1200 $[M+H]^+$, $C_{20}H_{16}N_3O_3$ requires 326.1192, (+2.5 ppm)

4-(6-Amino-1*H*-indazol-1-yl)phenol (288)

As per general procedure C, 4-(6-amino-1*H*-indazol-1-yl)phenol (**288**) was prepared from (**281**) (75mg, 0.23 mmol) and obtained as a brown solid (50 mg, 98%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 5.41 (s, 2H, NH_2), 6.56 (dd, 1H, ArH, J=8.24, 1.53 Hz, H_5), 6.68 (s, 1H, ArH, H_7), 6.92 (d, 1H, ArH, J = 8.54 Hz, H_4), 7.38 - 7.46 (m, 4H, ArH), 7.92 (s, 1H, ArH, H_3), 9.66 (br. s., 1H, OH)

^{13}C NMR (101 MHz, DMSO-d_6) δ 90.42 (ArCH), 112.69 (ArCH), 115.72 (2 x ArCH), 116.60, 121.31 (ArCH), 123.89 (2 x ArCH), 132.00, 134.39 (ArCH), 140.55, 148.82, 155.71

M.P.: 235-238 °C

IRν_{max} (NaCl film) cm^{-1}: 3428.83 (OH), 1641.56

HRMS: Found 226.0982 $[M+H]^+$, $C_{13}H_{12}N_3O$ requires 226.0980, (+0.9 ppm)

1-(4-(Benzyloxy)phenyl)-6-nitro-1*H*-indazole (281)

As per general procedure E, 1-(4-(benzyloxy)phenyl)-6-nitro-1*H*-indazole (**281**) was prepared from 6-nitroindazole (163mg) and 4-benzyloxybenzeneboronic acid (456 mg) as a yellow solid (110 mg, 52%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.18 (s, 2H, CH_2), 7.19 (d, 2H, J = 8.00 Hz), 7.35 - 7.40 (m, 1H), 7.44 (app t., dd, 2H, J = 7.32 Hz), 7.47 - 7.52 (m, 2H), 7.59 - 7.63 (m, 2H, ArH), 7.92 (d, 1H, ArH, J=8.54 Hz), 8.09 (dd, 1H, ArH, J=8.54, 1.83 Hz), 8.31 (s, 1H, ArH), 8.56 (s, 1H, ArH)

^{13}C NMR (101 MHz, $CDCl_3$) δ 70.44 (ArCH), 107.11 (ArCH), 115.96 (2xArCH), 116.11 (ArCH), 121.98 (C_q), 124.86 (2 x ArCH), 127.48 (2 x ArCH), 128.20 (ArCH), 128.70 (2 x ArCH), 132.26 (C_q), 134.86 (ArCH), 136.43 (C_q), 137.86 (C_q), 147.01 (C_q), 158.44 (C_q)

M.P.: 139-141 °C

IRν_{max} (NaCl film) cm^{-1}: 1607.74, 1515.08, 1380.53, 1341.81, 1250.13

HRMS: Found 346.1202 $[M+H]^+$, $C_{20}H_{16}N_3O_3$ requires 326.1192, (+3.1 ppm)

1-(4-Fluorophenyl)-1*H*-indazol-5-amine (292)

As per general procedure C, 1-(4-fluorophenyl)-1*H*-indazol-5-amine (**292**) was prepared from (**275**) (80 mg, 0.31mmol) and obtained as a brown solid (62 mg, 88%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 5.02 (s, 2H, NH_2), 6.86 (s, 1H, ArH), 6.90 (d, 1H, J = 8.54 Hz), 7.37 (app t, dd, 2H, ArH, J = 8.85 Hz), 7.55 (d, 1H, ArH, J = 8.54 Hz), 7.74 (dd, 2H, ArH, J = 8.55, 4.88 Hz), 8.03 (s, 1H, ArH)

^{13}C NMR (101 MHz, DMSO-d_6) δ 101.06 (ArCH), 110.61 (ArCH), 116.13 (ArCH), 116.36 (ArCH), 118.79 (ArCH), 123.12 (ArCH), 123.20 (C_q), 126.40 (C_q), 132.32 (C_q), 134.01 (ArCH), 136.61 (C_q), 143.73 (C_q), 158.55 (C_q), 160.97 (C_q)

M.P.: 138-140 °C[302]

IRν_{max} (KBr) cm^{-1}: 3394.1 (NH_2), 3325.0 (NH_2) 1635.9, 1516.6, 1225.7

HRMS: Found 228.0929 $[M+H]^+$, $C_{13}H_{11}FN_3$ requires 288.0937, (-2.8 ppm)

1-(4-Methoxyphenyl)-1*H*-indazol-5-amine (290)

As per general procedure C, 1-(4-methoxyphenyl)-1*H*-indazol-5-amine (**290**) was prepared from (**283**) (130 mg, 0.48 mmol) and obtained as a brown solid (83 mg, 64%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.82 (s, 3H, OCH_3), 4.96 (s, 2H, NH_2), 6.84 (s, 1H, ArH, H_4), 6.88 (dd, 1H, ArH, J=9.16, 1.83 Hz, H_6), 7.10 (d, 2H, ArH, J = 8.54 Hz), 7.47 (d, 1H, ArH, J = 9.16 Hz, H_7), 7.60 (d, 2H, ArH, J = 8.54 Hz), 7.98 (s, 1H, ArH, H_3)

^{13}C NMR (101 MHz, DMSO-d_6) δ 55.39 (OCH_3), 100.91 (ArCH), 110.52 (ArCH), 114.62 (2xArCH), 118.64 (ArCH), 123.04 (2xArCH), 126.05 (C_q), 132.55 (C_q), 133.10 (ArCH), 133.39 (C_q), 143.40 (C_q), 157.28 (C_q)

M.P.: 126-128 °C

IRν_{max} (KBr) cm^{-1}: 3428.6 (NH_2), 3344.4 (NH_2) 1629.8, 1459.8, 1249.3

HRMS: Found 240.1127 $[M+H]^+$, $C_{14}H_{14}N_3O$ requires 240.1137, (-4.6 ppm)

1-(6-Nitro-1*H*-indazol-1-yl)-2-phenoxyethanone (299)

As per general procedure A, 1-(6-nitro-1*H*-indazol-1-yl)-2-phenoxyethanone (**299**) was prepared from 6-nitroindazole (326 mg) and phenoxyacetyl chloride (341 mg) as a colourless solid (208 mg, 35%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 5.69 (CH_2), 7.00 (app t., dd, 1H, J = 7.00 Hz, ArH), 7.08 (d, 2H, J = 8.00 Hz, ArH), 7.32 (app t., dd, 2H, J = 7.56 Hz, 8.52 Hz, ArH), 8.23 (d, 1H, J = 8.52 Hz, ArH), 8.30 (dd, 1H, J = 2.00 Hz, 8.56 Hz, ArH), 8.80 (s, 1H, ArH, H_3), 9.01 (s, 1H, ArH)

^{13}C-NMR (101 MHz, DMSO-d_6) δ 70.60 (CH_2), 114.65 (ArCH), 119.41 (ArCH), 124.41 (ArCH), 126.04 (ArCH), 128.21 (ArCH), 134.17, 134.30 (ArCH), 142.24, 145.67 (ArCH), 152.79, 162.46, 173.11 (C=O)

M.P.: 205-209 °C

IRν_{max} (KBr) cm^{-1}: 1738.8 (C=O), 1531.7 (NO_2), 1335.7 (NO_2)

HRMS: Found 320.0652 $[M+Na]^+$, $C_{15}H_{11}N_3NaO_4$ requires 320.0647, (+1.6 ppm)

1-(5-Nitro-1*H*-indazol-1-yl)-2-phenoxyethanone (294)

As per general procedure B, 1-(5-nitro-1*H*-indazol-1-yl)-2-phenoxyethanone (**294**) was prepared from 5-nitroindazole (326 mg) and phenoxyacetyl chloride (341 mg) as a colourless solid (220 mg, 37%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 5.67 (s, 2H, CH_2) 6.99 (t, 1H, J=7.28 Hz) 7.06 (d, 2H, J = 8.53 Hz), 7.27 - 7.36 (m, 2H, ArH), 8.41 - 8.47 (m, 1H, ArH), 8.48 - 8.53 (m, 1H, ArH), 8.79 (s, 1H, ArH), 8.94 (d, 1H, ArH, J = 2.01 Hz)

^{13}C-NMR (101 MHz, DMSO-d_6): δ 65.99 (CH_2), 114.63, 115.04, 119.06, 121.27, 124.75, 125.77, 129.55, 140.74, 142.01, 144.40, 157.71, 168.42 (C=O)

M.P.: 215-218 °C

IRν_{max} (KBr) cm^{-1}: 1732.2 (C=O), 1525.1 (NO_2), 1337.8 (NO_2)

HRMS: Found 320.0655 $[M+Na]^+$, $C_{15}H_{11}N_3NaO_4$ requires 320.0647, (+2.5 ppm)

1-(6-Nitro-1*H*-indazol-1-yl)-3-phenylpropan-1-one (303)

As per general procedure A, 1-(6-nitro-1*H*-indazol-1-yl)-3-phenylpropan-1-one (**303**) was prepared from 6-nitroindazole (326mg) and hydrocinnamoyl chloride (337 mg) as an orange solid (472 mg, 8%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.22 (t, 2H, J = 7.52 Hz, CH_2), 3.62 (t, 2H, J = 7.52 Hz, CH_2), 7.24 – 7.29 (m, 1H, ArH), 7.33 – 7.34 (m, 4H, ArH), 7.90 (d, 1H, ArH, J = 8.56 Hz, H_4), 8.26 (dd, 1H, ArH, J = 8.56, 2.00 Hz, H_5), 9.37 (s, 1H, ArH, H_7)

^{1}H NMR (101 MHz, $CDCl_3$) δ 29.78 (CH_2), 36.16 (CH_2), 111.37, 119.01, 121.16, 125.99, 128.03, 128.16, 128.98, 137.72, 138.56, 139.75, 148.03, 172.22 (C=O)

IRν_{max} (NaCl film) cm^{-1}: 3025.48, 2927.70, 1715.00 (C=O), 1595.15, 1531.56 (NO_2), 1497.43, 1416.47, 1337.80 (NO_2), 1206.31, 1172.88

M.P.: 148-150 °C

HRMS: Found 318.0855 $[M+Na]^+$, $C_{16}H_{13}N_3O_3Na$ requires 318.0855, (0.0 ppm)

1-(5-Nitro-1*H*-indazol-1-yl)-3-phenylpropan-1-one (298)

As per general procedure B, 1-(5-nitro-1*H*-indazol-1-yl)-3-phenylpropan-1-one (**298**) was prepared from 5-nitroindazole (326 mg) and hydrocinnamoyl chloride (337 mg) as a colourless solid (169 mg, 29%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.19 (t, 2H, J = 7.78 Hz, CH_2), 3.60 (t, 2H, J = 7.78 Hz, OC$\underline{CH_2}$), 7.20 - 7.26 (m, 1H), 7.30 - 7.34 (m, 4H, ArH), 8.30 (s, 1H, ArH, H_3), 8.45 (d, 1H, ArH, J = 9.03 Hz, H_7), 8.60 (d, 1H, ArH, J = 9.03 Hz, H_5), 8.70 (s, 1H, ArH, H_4)

^{13}C NMR (101 MHz, $CDCl_3$) δ 29.89 (CH_2), 36.42 (OC$\underline{C}H_2$), 115.63 (ArCH), 117.41 (ArCH), 123.99 (ArCH), 126.10 (ArCH), 128.11 (ArCH), 128.26 (ArCH), 139.80 (C_q), 139.85 (ArCH), 140.92 (C_q), 144.38 (C_q), 172.56 (C=O)

M.P.: 148-151 °C

IRν_{max} (NaCl film) cm^{-1}: 1716.3 (C=O), 1615.58, 1520.3 (NO_2), 1497.36, 1403.75, 1389.82, 1350.0 (NO_2), 1155.49

HRMS: Found 318.0845 $[M+Na]^+$, $C_{16}H_{13}N_3O_3Na$ requires 318.0855, (-3.1 ppm)

Cyclopropyl(6-nitro-1*H*-indazol-1-yl)methanone (300)

As per general procedure A, cyclopropyl(6-nitro-1*H*-indazol-1-yl)methanone (**300**) was prepared from 6-nitroindazole (326 mg) and cyclopropane carbonyl chloride (209 mg) as a cream solid (126 mg, 27%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (dq, 2H, J = 7.84, 3.74 Hz, CH_2), 1.39 (quin, 2H, J = 3.89 Hz, CH_2), 3.19 - 3.28 (m, 1H, CH), 7.90 (d, 1H, ArH, J = 8.53 Hz, H_4), 8.24 (dd, 1H, ArH, J = 8.53, 2.01 Hz, H_5), 8.32 (s, 1H, AtH, H_3), 9.35 (s, 1H, ArH, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 11.32 (2 x CH_2), 12.74 (CH), 111.91 (ArCH), 119.25 (ArCH), 121.47 (ArCH), 129.36 (C_q, C_{3a}), 138.08 (C_q, C_{7a}), 138.92 (ArCH, C_3), 148.34 (C_q, C_6), 174.23 (C=O)

M.P.: 190-191 °C

IRν_{max} (NaCl film) cm^{-1}: 1706.1 (C=O), 1530.4 (NO_2), 1407.23, 1348.96, 1366.83, 1329.8 (NO_2), 1166.66, 1058.51

HRMS: Found 232.0712 $[M+H]^+$, $C_{11}H_{10}N_3O_3$ requires 232.0722, (-4.3 ppm)

2-Cyclohexyl-1-(6-nitro-1*H*-indazol-1-yl)ethanone (301)

As per general procedure A, 2-cyclohexyl-1-(6-nitro-1*H*-indazol-1-yl)ethanone (**301**) was prepared from 6-nitroindazole (326 mg) and cyclohexylacetyl chloride (321 mg) as a yellow solid (340 mg, 59%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 - 1.40 (m, 5H), 1.62 - 1.79 (m, 3H), 1.83 – 1.86 (m, 2H), 1.99 - 2.16 (m, 1H), 3.12 (d, 2H, J = 7.03 Hz), 7.89 (d, 1H, ArH, J = 8.53 Hz, H_4), 8.19 - 8.31 (m, 2H, ArH, H_3, H_5), 9.38 (s, 1H, ArH, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 26.01 (2 x CH_2), 26.09 (CH_2), 33.13 (2 x CH_2), 34.73 (CH), 42.26 (CH_2), 111.92 (ArCH), 119.33 (ArCH), 121.50 (ArCH), 129.41 (C_q, C_{3a}), 138.13(C_q, C_{7a}), 138.73 (ArCH, C_3), 148.41 (C_q, C_6), 173.02 (C=O)

M.P.: 122-124 °C

IRν_{max} (NaCl film) cm^{-1}: 3112.85, 2924.7, 2839.8, 1720.8 (C=O), 1532.9 (NO_2), 1449.60, 1410.61, 1344.2 (NO_2), 1165.44

HRMS: Found 288.1356 $[M+H]^+$, $C_{15}H_{18}N_3O_3$ requires 288.1348, (+2.8 ppm)

Cyclopropyl(5-nitro-1*H*-indazol-1-yl)methanone (295)

As per general procedure B, cyclopropyl(5-nitro-1*H*-indazol-1-yl)methanone (**295**) was prepared from 5-nitroindazole (326mg) and cyclopropane carbonyl chloride (209 mg) as a cream solid (185 mg, 40%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 – 1.26 (m, 2H, CH_2), 1.39 – 1.41 (m, 2H, CH_2), 3.23 – 3.29 (m, 1H, CH), 8.38 (s, 1H, ArH, H_3), 8.46 (dd, 1H, ArH, J = 9.04, 2.00 Hz, H_6), 8.60 (s, 1H, ArH, J = 9.04 Hz, H_7), 8.74 (d, 1H, J = 2.00 Hz, H_4)

^{1}H NMR (101 MHz, $CDCl_3$) δ 11.04 (2xCH_2), 12.45 (CH), 115.61 (ArCH), 117.27 (ArCH), 123.74 (ArCH), 125.49, 125.43, 139.73 (ArCH), 140.73, 144.14, 174.07 (C=O)

M.P.: 98-100 °C

IRν_{max} (NaCl film) cm^{-1}: 1707.3 (C=O), 1518.7 (NO_2), 1442.2, 1423.8, 1396.1, 1326.3 (NO_2), 1150.2, 1061.1

HRMS: Found 232.0724 $[M+H]^+$, $C_{11}H_{10}N_3O_3$ requires 232.0722, (+0.9 ppm)

2-Cyclohexyl-1-(5-nitro-1*H*-indazol-1-yl)ethanone (296)

As per general procedure B, 2-cyclohexyl-1-(5-nitro-1*H*-indazol-1-yl)ethanone (**296**) was prepared from 5-nitroindazole (326mg) and cyclohexylacetyl chloride (321 mg) as a colourless solid (479mg, 83%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 - 1.40 (m, 5H), 1.64 - 1.78 (m, 3H), 1.80 - 1.88 (m, 2H), 2.07 (dtt, 1H, J=14.65, 7.42, 7.42, 3.58, 3.58 Hz), 3.12 (d, 2H, J=7.03 Hz), 8.31 (s, 1H, ArH, H_3), 8.44 (dd, 1H, ArH, J=9.54, 2.01 Hz, H_5), 8.61 (d, 1H, ArH, J=9.54 Hz, H_7), 8.70 (d, 1H, ArH, J=2.01 Hz, H_4)

^{13}C NMR (101 MHz, $CDCl_3$) δ 25.68 (2 x CH_2), 25.76 (CH_2), 32.81 (2xCH_2), 34.35 (CH), 42.10 ($OCCH_2$), 115.73 (ArCH), 117.35 (ArCH), 123.89 (ArCH), 125.54 (C_q), 139.61 (C_q), 140.92 (C_q), 144.31 (C_q), 172.92 (C=O)

M.P.: 98-100 °C

IRν_{max} (NaCl film) cm^{-1}: 3127.7, 2927.0, 2853.0, 1723.7 (C=O), 151967 (NO_2), 1448.3, 1424.8, 1383.2, 1327.3 (NO_2), 1149.4

HRMS: Found 288.1335 $[M+H]^+$, $C_{15}H_{18}N_3O_3$ requires 288.1348, (-4.5 ppm)

1-(6-Amino-1*H*-indazol-1-yl)-3-phenylpropan-1-one (313)

As per general procedure C, 1-(6-amino-1*H*-indazol-1-yl)-3-phenylpropan-1-one (**313**) was prepared from (**303**) (104 mg, 0.35 mmol) as a brown solid (32 mg, 34%,)

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.02 (t, 2H, J = 7.78 Hz, CH_2), 3.42 (t, 2H, J = 7.78 Hz, CH_2), 6.68 (dd, 1H, ArH, J = 8.53, 2.01 Hz, H_5), 7.15 - 7.22 (m, 1H, ArH), 7.26 - 7.30 (m, 4H, ArH), 7.43 - 7.51 (m, 1H, ArH), 8.10 (s, 1H, ArH, H_3)

^{13}C NMR (101 MHz, DMSO-d_6) δ 29.90 (CH_2), 36.12 ($OCCH_2$), 97.10 (ArCH), 114.05 (ArCH), 117.05 (ArCH), 121.90 (ArCH), 126.04 (2xArCH), 128.36 (2xArCH), 140.38 (ArCH), 140.68 (C_q), 140.88 (C_q), 150.67 (C_q), 172.31 (C=O)

M.P.: 108-112 °C

IRν_{max} (KBr) cm^{-1}: 3421.0 (NH_2), 3344.7 (NH_2), 3051.8, 2912.4, 1691.6 (C=O), 1439.73, 1277.9, 946.0

HRMS: Found 266.1293 $[M+H]^+$, $C_{16}H_{16}N_3O$ requires 266.1293, (0.0 ppm)

3-Cyclopentyl-1-(6-nitro-1*H*-indazol-1-yl)propan-1-one (302)

As per general procedure A, 3-cyclopentyl-1-(6-nitro-1*H*-indazol-1-yl)propan-1-one (**302**) was prepared from 6-nitroindazole (326 mg) and 3-cyclopropionyl chloride (321 mg) as an orange solid (460 mg, 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 - 1.27 (m, 2H), 1.49 - 1.70 (m, 4H, 2 x CH_2), 1.79 - 1.92 (m, 4H, 2 x CH_2), 3.26 (t, 2H, J = 8.00Hz, $OC\underline{CH_2}$), 7.89 (d, 1H, ArH, J=8.53 Hz,), 8.24 (dd, 1H, ArH, J = 8.53, 1.76 Hz), 8.27 (s, 1H, ArH), 9.36 (d, 1H, ArH, J = 1.76Hz)

^{13}C NMR (101 MHz, $CDCl_3$) δ 25.15 (2 x CH_2), 30.65 (CH_2), 32.50 ($2xCH_2$), 34.29 (CH_2), 39.65 (CH), 111.87 (ArCH), 119.33 (ArCH), 121.51 (ArCH), 129.38 (C_q, C_{3a}), 138.17 (C_q, C_{7a}), 138.78 (ArCH, C_3), 148.42 (C_q, C_6), 173.85 (C=O)

M.P.: 88-91 °C

IRν_{max} (NaCl film) cm^{-1}: 3131.6, 2950.8, 2866.5, 1715.0 (C=O), 1529.6 (NO_2), 1344.77 (NO_2), 1360.1, 1381.1, 1173.3, 1111.1

HRMS: Found 288.1335 $[M+H]^+$, $C_{15}H_{18}N_3O_3$ requires 288.1348, (-4.9 ppm)

3-Cyclopentyl-1-(5-nitro-1*H*-indazol-1-yl)propan-1-one (297)

As per general procedure B, 3-cyclopentyl-1-(5-nitro-1*H*-indazol-1-yl)propan-1-one (**297**) was prepared from 5-nitroindazole (326 mg) and 3-cyclopropionyl chloride (321 mg) as an orange solid (466 mg, 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 - 1.24 (m, 2H, CH_2), 1.49 - 1.69 (m, 4H, 2xCH_2), 1.79 - 1.92 (m, 5H, 2 x CH_2, CH), 3.22 - 3.29 (m, 2H, CH_2), 8.31 (s, 1H, ArH, H_3), 8.44 (dd, 1H, ArH, J = 9.54, 2.01 Hz, H_6), 8.60 (d, 1H, ArH, J = 9.54 Hz, H_7), 8.70 (d, 1H, ArH, J = 2.01 Hz, H_4)

^{13}C NMR (101 MHz, $CDCl_3$) δ 25.14 (2 x CH_2), 30.60 (CH_2), 32.49 (2xCH_2), 34.44 (CH_2), 39.63 (CH), 115.99 (ArCH), 117.69 (ArCH), 124.24 (ArCH), 125.81 (C_q, C_{3a}), 139.99 (ArCH), 141.25 (C_q, C_{7a}), 144.62 (C_q, C_6), 174.09 (C=O)

M.P.: 95-97 °C

IRν_{max} (NaCl film) cm^{-1}: 3135.5, 2950.2, 2866.5, 1726.2 (C=O), 1519.3 (NO_2), 1442.3, 1386.7, 1335.0 (NO_2), 1156.2, 1138.5

HRMS: Found 288.1336 $[M+H]^+$, $C_{15}H_{18}N_3O_3$ requires 288.1348, (-4.2 ppm)

1-(5-Amino-1*H*-indazol-1-yl)-3-phenylpropan-1-one (308)

As per general procedure C, 1-(5-amino-1*H*-indazol-1-yl)-3-phenylpropan-1-one (**308**) was prepared from (**298**) (106 mg, 0.36 mmol) and obtained as a light brown solid (69 mg, 72%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.02 (t, 2H, J = 7.53 Hz, CH_2), 3.43 (t, 2H, J = 7.53 Hz, OC$\underline{CH_2}$), 5.28 (s, 2H, NH_2), 6.85 (s, 1H, ArH, H_4), 6.89 - 6.96 (m, 1H, ArH, H_6), 7.13 - 7.22 (m, 1H, ArH), 7.28 (d, 4H, ArH, J = 4.02 Hz), 7.99 (d, 1H, ArH, J = 9.03 Hz, H_7), 8.19 (s, 1H, ArH, H_3)

^{13}C NMR (101 MHz, DMSO-d_6) δ 29.93 (CH_2), 35.67 (O$\underline{C}\underline{CH_2}$), 101.97 (ArCH), 115.05 (ArCH), 118.92 (ArCH), 126.07 (ArCH), 127.56(2 x ArCH), 128.36(2 x ArCH), 128.39 (C_q), 131.33 (C_q), 139.79 (ArCH, C_3), 140.84 (C_q), 146.19 (C_q), 171.62 (C=O)

M.P.: 139-142 °C

IRν_{max} (KBr) cm^{-1}: 3415.0 (NH_2), 3348.7 (NH_2), 3054.9, 2919.5, 1690.6 (C=O), 1449.73, 1277.9, 946.0

HRMS: Found 288.1100 $[M+Na]^+$, $C_{16}H_{15}N_3NaO$ requires 288.1113, (-4.5 ppm)

(6-Amino-1*H*-indazol-1-yl)(cyclopropyl)methanone (310)

As per general procedure C, (6-amino-1*H*-indazol-1-yl)(cyclopropyl)methanone (**310**) was prepared from (**300**) (100 mg, 0.43 mmol) and obtained as a brown solid (54 mg, 61%).

^1H NMR (400 MHz, MeOD) δ 1.05 - 1.11 (m, 2H, CH_2), 1.14 - 1.20 (m, 2H, CH_2), 3.13 - 3.22 (m, 1H, CH), 4.90 (s, 2H, NH_2), 6.75 (dd, 1H, ArH, J = 8.53, 1.51 Hz), 7.47 (d, 1H, ArH, J = 8.53 Hz), 7.59 (s, 1H, ArH), 8.02 (s, 1H, ArH)

^{13}C NMR (101 MHz, MeOD) δ 10.81 (CH_2), 13.80 (CH), 99.98 (ArCH), 115.99 (ArCH), 120.02 (C_q), 123.02 (ArCH), 139.71 (ArCH), 140.54 (C_q), 150.12 (C_q), 174.03 (C=O)

M.P.: 134-137 °C

IRν_{max} (KBr) cm^{-1}: 3472.5 (NH_2), 3371.7 (NH_2), 3012.0, 1691.8 (C=O), 1487.35, 1370.6, 1318.4, 1161.2

HRMS: Found 224.0800 $[M+Na]^+$, $C_{11}H_{11}N_3NaO$ requires 224.0800, (0.0 ppm)

1-(6-Amino-1*H*-indazol-1-yl)-2-cyclohexylethanone (311)

As per general procedure C, 1-(6-amino-1*H*-indazol-1-yl)-2-cyclohexylethanone (**311**) was prepared from (**301**) (100 mg, 0.35 mmol) and obtained as a brown solid (64 mg, 71%)

^1H NMR (400 MHz, DMSO-d_6) δ 0.96 - 1.29 (m, 5H), 1.54 - 1.76 (m, 5H), 1.82 - 2.00 (m, 1H, CH), 2.95 (d, 2H, J = 7.03 Hz, $OCCH_2$), 5.82 (s, 2H, NH_2), 6.66 (d, 1H, ArH, J = 8.53 Hz), 7.39 - 7.50 (m, 2H, ArH), 8.07 (s, 1H, ArH)

^{13}C NMR (101 MHz, DMSO-d_6) δ 26.05 (CH_2), 26.22 (CH_2), 33.02 (CH_2), 34.85 (CH), 42.30 (CH_2), 97.28 (ArCH), 114.31 (ArCH), 117.31, 122.23 (ArCH), 140.64 (ArCH), 141.19, 151.65, 172.89 (C=O)

M.P.: 121-123 °C

IRν_{max} (KBr) cm^{-1}: 3470.1 (NH_2), 3370.7 (NH_2), 2922.1, 2845.5, 1693.7 (C=O),

HRMS: Found 280.1415 $[M+Na]^+$, $C_{15}H_{19}N_3NaO$ requires 280.1426, (-3.9 ppm)

1-(5-Amino-1*H*-indazol-1-yl)-3-cyclohexylpropan-1-one (306)

As per general procedure C, 1-(5-amino-1*H*-indazol-1-yl)-3-cyclohexylpropan-1-one (**306**) was prepared from (**296**) (100mg, 0.35 mmol) and obtained as a yellow oil (85 mg, 94%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 0.96 - 1.32 (m, 5H), 1.54 - 1.76 (m, 5H), 1.90 (dtt, 1H, J=10.89, 7.23, 7.23, 3.89, 3.89 Hz, CH), 2.97 (d, 2H, J = 7.03 Hz, CO$\underline{CH_2}$CH), 5.27 (s, 2H, NH_2), 6.85 (d, 2H, J = 2.01 Hz, ArCH), 6.91 (dd,1H, J = 8.78, 2.01 Hz), 8.01 (d, 1H, ArH, J = 8.78 Hz), 8.18 (s, 1H, ArH)

^{1}H NMR (101 MHz, DMSO-d_6) δ 26.04 (CH_2), 26.21 (CH_2), 33.02 (CH_2), 34.91 (CH), 102.36 (ArCH), 115.58 (ArCH), 119.31 (ArCH), 128.04 (C_q), 131.76 (C_q), 140.03 (ArCH), 146.62 (C_q), 172.16 (C=O)

M.P.: N/A

IRν_{max} (NaCl film) cm^{-1}: 3453.7 (NH_2), 3365.0 (NH_2), 2923.8, 2851.1, 1699.1 (C=O), 1630.0, 1519.2, 1355.0, 1151.8

HRMS: Found 280.1412 $[M+Na]^+$, $C_{15}H_{19}N_3NaO$ requires 280.1426, (-5.0 ppm)

1-(6-Amino-1*H*-indazol-1-yl)-3-cyclopentylpropan-1-one (312)

As per general procedure C, 1-(6-amino-1*H*-indazol-1-yl)-3-cyclopentylpropan-1-one (**312**) was prepared from (**302**) (300 mg, 1 mmol) and obtained as a brown solid (254 mg, 95%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.04 - 1.17 (m, 2H), 1.42 - 1.60 (m, 4H), 1.66 - 1.87 (m, 5H), 3.07 (t, 2H, J = 7.63 Hz, CH$\underline{CH_2}$), 5.81 (s, 2H, NH_2), 6.66 (dd, 1H, ArH, J = 8.54, 1.83 Hz, H_5), 7.43 - 7.48 (m, 2H, ArH, H_4 & H_7), 8.08 (s, 1H, ArH, H_3)

^{13}C NMR (101 MHz, DMSO-d_6) δ 24.71 (CH_2), 30.57 (CH_2), 32.02 (CH_2), 33.78 (CH_2), 39.21 (CH_2), 96.72 (ArCH, C_7), 113.78 (ArCH), 116.79 (C_q), 121.72 (ArCH), 140.15 (ArCH, C_3), 140.74 (C_q), 151.15 (C_q), 173.24 (C=O)

M.P.: 88-90 °C

IRν_{max} (KBr) cm^{-1}: 3468.9 (NH_2), 3369.1 (NH_2), 2946.8, 2865.2, 1696.8 (C=O), 1618.1, 1485.7, 1421.2, 1399.9, 1358.9, 1281.5, 1247.9, 1195.2, 1124.6

HRMS: Found 258.1610 $[M+H]^+$, $C_{15}H_{20}N_3O$ requires 258.1606, (+1.5 ppm)

1-(5-Amino-1*H*-indazol-1-yl)-3-cyclopentylpropan-1-one (307)

As per general procedure C, 1-(5-amino-1*H*-indazol-1-yl)-3-cyclopentylpropan-1-one (**307**) was prepared from (**297**) and obtained as a brown solid (257 mg, 96%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.04 - 1.17 (m, 2H), 1.41 - 1.61 (m, 4H), 1.66 - 1.87 (m, 5H), 3.09 (t, 2H, J = 7.63 Hz, CH$\underline{CH_2}$), 5.24 (s, 2H, NH_2), 6.85 (d, 1H, ArH, J = 2.14 Hz, H_4), 6.92 (dd, 1H, ArH, J = 8.54, 2.14 Hz, H_6), 8.00 (d, 1H, ArH, J = 8.54 Hz, H_7), 8.18 (s, 1H, ArH, H_3)

^{13}C NMR (101 MHz, DMSO-d_6) δ 24.71 (CH_2), 30.61 (CH_2), 32.01 (CH_2), 33.33 (CH_2), 39.16 (CH), 101.84 (ArCH, C_4), 115.02 (ArCH, C_6), 118.82 (ArCH. C_7), 127.50 (C_q), 131.31 (C_q), 139.53 (ArCH, C_3), 146.11 (C_q), 172.51 (C=O)

M.P.: 85-87 °C

IRν_{max} (KBr) cm^{-1}: 3455.4 (NH_2), 3345.7 (NH_2), 1717.7 (C=O), 1628.9, 1516.5, 1456.8, 1412.7, 1391.9, 1318.1, 1276.2, 1182.0, 1153.4, 1113.5, 950.0

HRMS: Found 258.1606 $[M+H]^+$, $C_{15}H_{20}N_3O$ requires 258.1606, (0.0 ppm)

(5-Amino-1*H*-indazol-1-yl)(cyclopropyl)methanone (305)

As per general procedure C, (5-amino-1*H*-indazol-1-yl)(cyclopropyl)methanone (**305**) was obtained from (**295**) (113 mg, 0.49 mmol) and obtained as a brown solid (32.3 mg, 33%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.09 (d, 4H, J = 6.10 Hz, 2 x CH_2), 3.10 (quin, 1H, J = 6.05 Hz, CH), 5.26 (s, 2H, NH_2), 6.87 (d, J = 1.83 Hz, H_4), 6.91 (dd, 1H, ArH, J = 8.85, 2.14 Hz, H_6), 7.98 (d, 1H, ArH, J = 8.54 Hz, H_7), 8.25 (s, 1H, ArH, H_3)

^{13}C NMR (101 MHz, DMSO-d_6) δ 9.76 (2 x CH_2), 12.15 (CH), 101.75, 115.04, 118.86, 127.52, 131.31, 139.91 (ArCH, C_3), 146.15 (C_q), 172.74 (C=O)

M.P.: 98-102 °C

IRν_{max} (KBr) cm^{-1}: 3454.9 (NH_2), 3366.5 (NH_2), 3009.4, 1688.7 (C=O), 1628.4, 1519.3, 1360.4, 1341.9, 1315.4, 1275.7, 1152.2, 1110.2, 1080.7 1028.8

HRMS: Found 202.0976 $[M+H]^+$, $C_{11}H_{12}N_3O$ requires 202.098, (-2.0 ppm)

1-(6-Amino-1*H*-indazol-1-yl)-2-phenoxyethanone (309)

As per general procedure C, 1-(6-amino-1*H*-indazol-1-yl)-2-phenoxyethanone (**309**) was prepared from (**299**) (297 mg, 1 mmol) and obtained as a white solid (233 mg, 87%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 5.54 (s, 2H, NH_2), 5.93 (s, 2H, CH_2), 6.70 (dd, 1H, J = 1.52 Hz, 8.52 Hz, ArH), 6.95 – 7.00 (m, 3H, ArH), 7.30 (app t, dd, 2H, ArH, J = 7.52 Hz, 8.52 Hz, H_5), 7.40 (s, 1H, ArH), 7.51 (d, 1H, ArH, J = 8.52 Hz, H_4), 8.20 (s, 1H, ArH, H_3)

^{13}C-NMR (101 MHz, DMSO-d_6) δ 65.82 (CH_2), 96.20 (ArCH), 114.10 (ArCH), 114.56 (ArCH), 116.42 (C_q), 121.07 (ArCH), 122.11 (ArCH), 129.52 (ArCH), 140.85 (C_q), 141.22 (ArCH), 151.52 (C_q), 157.87 (C_q), 167.70 (C=O)

M.P.: 169-172 °C

IRν_{max} (KBr) cm^{-1} : 3467.2 (NH_2), 3363.4 (NH_2), 1719.8 (C=O)

HRMS: Found 290.0898 $[M+Na]^+$, $C_{15}H_{13}N_3NaO_2$ requires 290.0905, (-2.4 ppm)

1-(5-Amino-1*H*-indazol-1-yl)-2-phenoxyethanone (306)

As per general procedure C, 1-(5-amino-1*H*-indazol-1-yl)-2-phenoxyethanone (**304**) was prepared from (**294**) (297 mg, 1 mmol) as a brown solid (227 mg, 85%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 5.36 (s, 2H, NH_2), 5.58 (s, 2H, CH_2), 6.91 (s, 1H, ArH), 6.95 -7.01 (m, 4H, ArH), 7.30 (app t., dd, 2H, J = 7.04 Hz, 8.52 Hz, ArH), 7.95 (d, 1H, J = 9.00 Hz, ArH), 8.31 (s, 1H, ArH)

^{13}C-NMR (101 MHz, DMSO-d_6) δ 65.50 (CH_2), 102.12 (ArCH), 114.52 (ArCH), 114.63 (ArCH), 119.03 (ArCH), 121.07 (ArCH), 127.39 (C_q), 129.52 (ArCH), 131.16 (C_q), 140.69 (ArCH), 146.60 (C_q), 157.86 (C_q), 166.99 (C=O)

M.P.: 176-179 °C

IRν_{max} (KBr) cm^{-1}: 3421.4 (NH_2), 3341.3 (NH_2), 1725.1 (C=O)

HRMS: Found 290.0901 $[M+Na]^+$, $C_{15}H_{13}N_3NaO_2$ requires 290.0905, (-1.4 ppm)

(3,4,5-Trimethoxyphenyl)methanol

To a solution of 3,4,5-trimethoxybenzaldehyde (3 g, 15.3 mmol) in MeOH (50 mL), sodium borohydride (637 mg, 16.8 mmol) was added slowly. The resultant solution was stirred at 20 °C for 2 hours. Acetic acid (2 mL) was added followed by aqueous 10% sodium hydrogen carbonate solution (30 mL). The MeOH was removed *in vacuo* and product was extracted with EtOAc (3 x 30 mL). The organic layers were combined, washed with a saturated brine solution (30 mL), dried using sodium sulphate, filtered and concentrated to dryness *in vacuo*. The desired product was afforded as an orange oil (2.99 g, 99%). No further purification was required.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H, OCH_3), 3.81 (s, 6H, 2 x OCH_3), 4.57 (s, 2H, CH_2), 6.55 (s, 2H, ArH), OH not observed

^{13}C NMR (101 MHz, $CDCl_3$) δ 55.85 (2 x OCH_3), 60.67 (OCH_3), 65.09 (CH_2), 103.48 (ArCH), 136.72 (C_q, CO), 136.81 (C_q, $\underline{C}CH_2$), 153.05 (C_q, 2 x CO)

M.P.: N/A

IRν_{max} (NaCl film) cm^{-1}: 3350, 3112.3, 2956.3, 1622.4, 1614.3, 1552.1, 1467.9, 1455.0, 1436.1, 1387.6, 1373.8, 1336.0

HRMS: Found 221.0799 $[M+Na]^+$, $C_{10}H_{14}O_4Na$ requires 221.0790, (+4.2 ppm)

3,4,5-Trimethoxybenzyl bromide

To a stirred solution of (3,4,5-trimethoxyphenyl)methanol (2.99 g, 15.1 mmol) in CH_2Cl_2 (40 mL) at 0 °C, triphosphorous tribromide (4.09 g, 15.1 mmol) was added slowly. The resultant solution was stirred at 0°C for 15 minutes, warmed to 20 °C and stirred at this temperature for 2 hours. 10% aqueous sodium hydrogen carbonate (15 mL) was then added slowly and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL), the organic layers were combined, washed with a saturated brine solution (25 mL), dried using sodium sulphate, filtered, and concentrated to dryness *in vacuo*. The desired product was afforded as colourless solid (3.04 g, 77%). No further purification was required.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 3H, OCH_3), 3.88 (s, 6H, 2 x OCH_3), 4.47 (s, 2H, CH_2), 6.62 (s, 2H, ArH)

^{13}C NMR (101 MHz, $CDCl_3$) δ 34.28 (CH_2), 56.07 (2 x OCH_3), 60.84 (OCH_3), 105.98 (ArCH), 133.15 (C_q, CO), 138.00 (C_q, $\underline{C}CH_2$), 153.23 (C_q, 2 x CO)

M.P.: 78-80 °C Lit. M.P.: 74-75 °C[416]

IRν_{max} (NaCl film) cm^{-1}: 3114.1, 2951.6, 1623.4, 1614.3, 1522.1, 1481.9, 1450.0, 1416.1, 1397.6, 1373.8, 1270.1

HRMS: Found 282.9957 $[M+Na]^+$, $C_{10}H_{13}O_3Na$ requires 282.9946, (+4.0 ppm)

General procedure G: N1-benzylation and N-1 alkylation of (169) and (170)

To a solution of (**169**, 0.49 g, 3 mmol) or (**170**, 0.49 g, 3 mmol) in anhydrous DMF (10 mL), was added cesium carbonate (2.93 g, 9 mmol, 3 eq) and the appropriate benzyl bromide (6 mmol, 2 eq) or alkyl bromide (6 mmol, 2 eq). The resultant solution was stirred at 20 °C for 12 hours. EtOAc (30 mL) was then added and the organic layer was washed with a saturated brine solution (6 x 15 mL), dried using sodium sulphate, filtered and concentrated to dryness *in vacuo*. Purification by flash column chromatography over silica gel (eluent EtOAc: Hexane gradient) afforded the desired *N*-1 and *N*-2 regioisomers.

Note: The masses of the appropriate benzyl bromide and alkyl bromide correspond to 2 mmol unless stated differently.

1-Benzyl-6-nitro-1*H*-indazole (240)

As per the general procedure G, 1-benzyl-6-nitro-1*H*-indazole (**240**) was prepared from 6-nitroindazole and benzyl bromide (1.03 g) as an orange solid (243 mg, 32%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.69 (s, 2H, CH_2), 7.27 (d, 2H, ArH, J = 6.53 Hz, $H_{2'}$ & $H_{6'}$), 7.30 - 7.36 (m, 3H, ArH, $H_{4'}$, $H_{3'}$ & $H_{5'}$), 7.86 (d, 1H, ArH, J = 9.03 Hz, H_4), 8.02 (dd, 1H, ArH, J = 9.03, 1.51 Hz, H_5), 8.19 (s, 1H, ArH, H_3), 8.33 (s, 1H, ArH, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 53.15 (CH_2), 105.65 (ArCH, C_7), 115.17 (ArCH, C_5), 121.53 (ArCH, C_4), 126.83 (ArCH, $C_{2'}$ & $C_{6'}$), 127.01 (C_q, C_{3a}), 128.27 (ArCH, $C_{4'}$), 128.96 (ArCH, $C_{3'}$ & $C_{5'}$), 133.33 (ArCH, C_3), 135.27 (C_q, $C_{1'}$), 137.77 (C_q, C_{7a}), 146.10 (C_q, C_6)

M.P.: 114-116 °C Lit. M.P.: 124-125 °C[284]

IR ν_{max} (NaCl film) cm^{-1}: 3117.8, 2956.3, 1622.4, 1604.3, 1562.1, 1524.9 (NO_2), 1487.9, 1455.0, 1436.1, 1397.6, 1373.8, 1336.0 (NO_2), 1275.1, 1233.6, 1206.2, 1065.1, 1006.4

HRMS: Found 254.0935 $[M+H]^+$, $C_{14}H_{12}O_2$ requires 254.0930, (+2.2 ppm)

2-Benzyl-6-nitro-2*H*-indazole (243)

As per the general procedure G, 2-benzyl-6-nitro-2*H*-indazole (**243**) was prepared from 6-nitroindazole and benzyl bromide (1.03 g) as a light yellow solid (144 mg, 19%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.69 (s, 2H, CH_2), 7.32 - 7.36 (m, 2H, ArH, $H_{2'}$ & $H_{6'}$), 7.36 - 7.41 (m, 3H, ArH, $H_{4'}$, $H_{3'}$ & $H_{5'}$), 7.75 (d, 1H, ArH, J = 9.03 Hz, H_4), 7.91 (dd, 1H, ArH, J = 9.29, 1.76 Hz, H_5), 8.03 (s, 1H, ArH, H_3), 8.75 (s, 1H, ArH, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 58.34 (CH_2), 105.65 (ArCH, C_7), 115.86 (ArCH, C_5), 121.46 (ArCH, C_4), 124.56 (C_q, C_{3a}), 128.25 (ArCH, $C_{2'}$ & $C_{6'}$), 128.88 (ArCH, $C_{4'}$), 129.15 (ArCH, $C_{3'}$ & $C_{5'}$), 134.70 (C_q, $C_{1'}$), 146.60 (C_q, C_6)

M.P.: 131-133 °C Lit. M.P.: 121-123[284]

IRν_{max} (NaCl film) cm^{-1}: 3099.3, 3032.09, 1617.9, 1603.6, 1585.7, 1520.7 (NO_2), 1455.8, 1440.6, 1392.3, 1369.7, 1350.4 (NO_2), 1276.9, 1239.4, 1205.7, 1089.5, 1027.9

HRMS: Found 254.0938 $[M+H]^+$, $C_{14}H_{12}O_2$ requires 254.0930, (+3.1 ppm)

1-Benzhydryl-6-nitro-1*H*-indazole (241)

As per the general procedure G, 1-benzhydryl-6-nitro-1*H*-indazole (**241**) was prepared from 6-nitroindazole and bromodiphenylmethane (1.48 g) as an orange solid (130 mg, 12 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (s, 1H, CH), 7.20 - 7.25 (m, 4H, ArH), 7.34 - 7.39 (m, 6 H, ArH), 7.87 (d, 1H, ArH, J = 9.03 Hz, H_4), 8.03 (dd, 1H, ArH, J = 9.03, 1.51 Hz, H_5), 8.23 (s, 2H, ArH, H_3 & H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 67.16 (CH), 106.42 (ArCH), 115.76 (ArCH), 121.90 (ArCH), 127.38 (C_q), 128.29 (ArCH), 128.35 (ArCH), 128 (ArCH), 134.14 (ArCH), 138.47 (C_q), 138.72 (C_q), 146.47 (C_q)

M.P.: 159-162 °C

IRν_{max} (NaCl film) cm^{-1}: 3059.1, 3034.5, 2857.2, 1599.99, 1524.99 (NO_2), 1496.38, 1454.60, 1421.72, 1346.88 (NO_2),

HRMS: Found 352.1063 $[M+Na]^+$, $C_{20}H_{15}N_3O_2Na$ requires 352.1062, (+0.3 ppm)

1-Benzhydryl-5-nitro-1*H*-indazole (250)

As per the general procedure G, 1-benzhydryl-5-nitro-1*H*-indazole (**250**) was prepared from 5-nitroindazole and bromodiphenylmethane (1.48 g) as a yellow solid (150 mg, 14%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (s, 1H, ArH), 7.21 – 7.23 (m, 4H, ArH), 7.27 – 7.29 (m, 2H, ArH), 7.37 – 7.39 (m, 6H, ArH), 8.19 (dd, 1H, ArH, J = 9.52, 2.00 Hz), 8.35 (s, 1H, ArH), 8.77 (d, 1H, ArH, J = 2.00 Hz)

^{13}C NMR (101 MHz, $CDCl_3$) δ 66.99 (CH), 109.67 (ArCH), 118.54 (ArCH), 121.09 (ArCH), 123.16 (C_q), 127.87 (ArCH), 127.95 (ArCH), 128.35 (ArCH), 135.98 (ArCH), 137.93 (C_q), 141.25 (C_q), 142.01 (C_q)

M.P.: 141-143 °C

IRν_{max} (NaCl film) cm^{-1}: 1616.96, 1519.13 (NO_2), 1494.51, 1450.63, 1428.16, 1340.74 (NO_2)

HRMS: Found 352.1065 $[M+Na]^+$, $C_{20}H_{15}N_3O_2Na$ requires 352.1062, (+0.9 ppm)

Ethyl 2-(6-nitro-2*H*-indazol-2-yl)propanoate (247)

As per the general procedure G, ethyl 2-(6-nitro-2*H*-indazol-2-yl)propanoate (**247**) was prepared from 6-nitroindazole and ethyl 2-bromopropanoate (1.09 g) as a brown solid (270 mg, 34%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, 3H, J = 7.02 Hz, $CH_2\underline{CH_3}$), 1.98 (d, 3H, J = 7.32 Hz, $CH\underline{CH_3}$), 4.25 (q, 2H, J = 7.02Hz, $\underline{CH_2}CH_3$), 5.46 (q, 1H, J = 7.32 Hz, $\underline{CH}CH_3$), 7.80 (d, 1H, ArH, J = 9.16 Hz, H_4), 7.92 (dd, 1H, ArH, J = 9.16, 1.83 Hz, H_5), 8.23 (s, 1H, ArH, H_3), 8.72 (s, 1H, ArH, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 13.99 (CH_3), 17.99 (CH_3), 61.85 (CH), 62.44 (CH_2), 115.74 (ArCH), 115.98 (ArCH), 121.78 (ArCH), 123.21 (ArCH), 124.14 (C_q), 146.47 (C_q), 146.82 (C_q), 169.23 (C_q) (C=O)

M.P.: 132-135 °C

IRν_{max} (NaCl film) cm^{-1}: 3055.1, 3032.5, 2856.2, 1733.4 (OC=O), 1595.9, 1524.99 (NO_2), 1496.38, 1451.6, 1422.7, 1341.3 (NO_2)

HRMS: Found 264.0990 $[M+H]^+$, $C_{12}H_{14}N_3O_4$ requires 264.0984, (+2.3 ppm)

Ethyl 2-(6-nitro-1*H*-indazol-1-yl)propanoate (245)

As per the general procedure G, ethyl 2-(6-nitro-1*H*-indazol-1-yl)propanoate (**245**) was prepared from 6-nitroindazole and ethyl 2-bromopropanoate (1.09 g) as a yellow solid (339 mg, 42%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (t, 3H, *J* = 7.02 Hz, $CH_2\underline{CH_3}$), 2.00 (d, 3H, *J* = 7.32 Hz, $CH\underline{CH_3}$), 4.21 (q, 2H, *J* = 7.12 Hz, $\underline{CH_2}CH3$), 5.44 (q, 1H, *J*=7.32 Hz, $\underline{CH}CH_3$), 7.87 (d, 1H, ArH, *J* = 9.16 Hz, H_4), 8.06 (dd, 1H, ArH, *J* = 9.16, 1.83 Hz, H_5), 8.18 (s, 1H, ArH, H_3), 8.40 (s, 1H, ArH, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 14.04 (CH_3), 16.59 (CH_3), 57.39 (CH), 62.13 (CH_2), 106.02 (ArCH), 115.85 (ArCH), 122.00 (ArCH), 127.56 (C_q), 134.11 (ArCH), 138.48 (C_q), 146.62 (C_q), 169.70 (C=O)

M.P.: 105-106 °C

IRν_{max} (NaCl film) cm^{-1}: 2970.4, 1737.4 (OC=O), 1527,.6 (NO_2), 1476.1, 1377.1, 1336.9 (NO_2), 1297.0, 1237.2, 1199.1, 1070.9, 1027.5

HRMS: Found 264.0994 $[M+H]^+$, $C_{12}H_{14}N_3O_4$ requires 264.0984, (+3.8 ppm)

Ethyl 2-(5-nitro-2*H*-indazol-2-yl)propanoate (257)

As per the general procedure G, ethyl 2-(5-nitro-2*H*-indazol-2-yl)propanoate (**257**) was prepared from 5-nitroindazole and ethyl 2-bromopropanoate (1.09 g) as a yellow oil (50 mg, 6%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, 3H, *J* = 7.02 Hz, $CH_2\underline{CH_3}$), 1.98 (d, 3H, *J* =7.32 Hz, $CH\underline{CH_3}$), 4.22 - 4.28 (q, 2H, *J* = 7.02Hz, $\underline{CH_2}CH_3$), 5.43 (q, 1H, *J* =7.32 Hz, $\underline{CH}CH_3$), 7.76 (d, 1H, ArH, *J* = 9.16 Hz, H_5), 8.11 (dd, 1H, ArH, *J* = 9.16, 2.14 Hz, H_6), 8.40 (s, 1H, ArH, H_3), 8.75 (d, 1H, ArH, *J* = 1.83 Hz, H_4)

^{13}C NMR (101 MHz, $CDCl_3$) δ 13.98 (CH_3), 17.94 (CH_3), 61.71 (CH), 62.45 (CH_2), 118.63 (ArCH), 119.64 (ArCH), 120.08 (C_q), 120.55 (ArCH), 126.53 (ArCH), 143.29 (C_q), 149.41 (C_q), 169.19 (C=O)

M.P.: N/A

IRν_{max} (NaCl film) cm^{-1}: 1711.0 (OC=O), 1625.9, 1561.1 (NO_2), 1481.2, 1334.9 (NO_2)

HRMS: Found 264.0977 $[M+H]^+$, $C_{12}H_{14}N_3O_4$ requires 264.0984, (-2.7 ppm)

Ethyl 2-(5-nitro-1*H*-indazol-1-yl)propanoate (255)

As per the general procedure G, ethyl 2-(5-nitro-1*H*-indazol-1-yl)propanoate (**255**) was prepared from 5-nitroindazole and ethyl 2-bromopropanoate (1.09 g) as a colourless solid (100 mg, 13%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (t, 3H, J =7.02 Hz, $CH_2\underline{CH_3}$), 1.98 (d, 3H, J = 7.32 Hz, $CH\underline{CH_3}$), 4.20 (q, 2H, J = 7.02 Hz, $\underline{CH_2}CH_3$), 5.39 (q, J = 7.12 Hz, $\underline{CH}CH_3$), 7.48 (d, 1H, ArH, J = 9.16 Hz, H_7), 8.26 (s, 1H, ArH, H_3), 8.29 (dd, 1H, ArH, J = 9.16, 1.83 Hz, H_6), 8.75 (d, 1H, ArH, J =1.83 Hz, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 14.03 ($CH_2\underline{CH_3}$), 16.49 ($CH\underline{CH_3}$), 57.43 (CH_2), 62.10 (CH), 109.51 (ArCH), 118.98 (ArCH), 121.63 (ArCH), 123.65 (C_q), 136.28 (ArCH), 141.42 (C_q), 142.60 (C_q), 169.64 (C=O)

M.P.: 113-116 °C

IRν_{max} (NaCl film) cm^{-1}: 1711.0 (OC=O), 1618.9, 1561.1 (NO_2), 1486.2, 1334.9 (NO_2)

HRMS: Found 264.0977 $[M+H]^+$, $C_{12}H_{14}N_3O_4$ requires 264.0984, (-2.7 ppm)

Ethyl 2-(5-nitro-2*H*-indazol-2-yl)acetate (258)

As per general procedure G, ethyl 2-(5-nitro-2*H*-indazol-2-yl)acetate (**258**) was prepared from 5-nitroindazole and ethyl bromoacetate (1.0 g) as yellow solid (60 mg, 8%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, 3H, J = 7.12 Hz, CH_3), 4.30 (q, J = 7.12 Hz, $\underline{CH_2}CH_3$), 5.27 (s, 2H, CH_2), 7.77 (d, 1H, ArH, J = 9.46 Hz, H_7), 8.12 (dd, 1H, ArH, J = 9.46, 2.14 Hz, H_6), 8.35 (s, 1H, ArH, H_3), 8.76 (d, 1H, ArH, J = 2.14 Hz, H_4)

^{13}C NMR (101 MHz, $CDCl_3$) δ 14.06 (CH_3), 54.93 (CH_2), 62.58 (CH_2), 118.66 (ArCH), 119.57 (ArCH), 120.46 (C_q), 120.71 (ArCH), 128.73 (ArCH), 143.44 (C_q), 149.90 (C_q), 166.35 (C=O)

M.P.: 119-122 °C

IRν_{max} (NaCl film) cm^{-1}: 1714.0 (OC=O), 1623.9, 1566.1 (NO_2), 1486.2, 1338.9 (NO_2)

HRMS: Found 250.0828 $[M+H]^+$, $C_{11}H_{12}N_3O_4$ requires 250.0828, (0.0 ppm)

Ethyl 2-(5-nitro-1*H*-indazol-1-yl)acetate (256)

As per general procedure G, ethyl 2-(5-nitro-1*H*-indazol-1-yl)acetate (**256**) was prepared from 5-nitroindazole and ethyl bromoacetate (1.0 g) as a white solid.(340 mg, 46%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, 3H, *J*=7.02 Hz, CH_3), 4.25 (q, 2H, *J* = 7.02 Hz, $\underline{CH_2}CH_3$), 5.22 (s, 2H, CH_2), 7.42 (d, 1H, ArH, *J* = 9.16 Hz, H_7), 8.27 (s, 1H, ArH, H_3), 8.31 (dd, 1H, ArH, *J* = 9.16, 1.83 Hz, H_6), 8.76 (d, 1H, ArH, *J* = 1.83 Hz, H_4)

^{13}C NMR (101 MHz, $CDCl_3$) δ 14.07 (CH_3), 50.68 (CH_2), 62.20 (CH_2), 109.29 (ArCH), 119.00 (ArCH), 121.96 (ArCH), 123.57 (C_q), 136.72 (ArCH), 142.02 (C_q), 142.73 (C_q), 167.06 (C=O)

M.P.: 263-265 °C Lit. M.P.: 264-266 °C[288]

IRν_{max} (NaCl film) cm^{-1}: 2935.2, 2835.7, 1711.0 (OC=O), 1591.9, 1523.7 (NO_2), 1507.3, 1461.4, 1423.8, 1347.1 (NO_2), 1240.9, 1121.3

HRMS: Found 250.0830 $[M+H]^+$, $C_{11}H_{12}N_3O_4$ requires 250.0828, (+0.8 ppm)

6-Nitro-1-(3,4,5-trimethoxybenzyl)-1*H*-indazole (239)

As per the general procedure G, 6-nitro-1-(3,4,5-trimethoxybenzyl)-1*H*-indazole (**239**) was prepared from 6-nitroindazole and 3,4,5-trimethoxybenzyl bromide (1.57 g) as a yellow solid (381 mg, 37%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 6H, 2 x OCH_3), 3.81 (s, 3H, OCH_3), 5.61 (s, 2H, CH_2), 6.49 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 7.87 (d, 1H, ArH, *J* = 8.54 Hz, H_4), 8.03 (dd, 1H, ArH, *J* = 8.54, 1.83 Hz, H_5), 8.19 (s, 1H, ArH, H_3), 8.38 (s, 1H, ArH, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 54.13 (OCH_3), 56.42 (2 x OCH_3), 61.10 (CH_2), 104.74 (ArCH), 106.39 (ArCH), 115.93 (ArCH), 122.30 (ArCH), 127.73 (C_q), 131.50 (C_q), 134.05 (ArCH), 138.13 (C_q), 138.44 (C_q), 146.82 (C_q), 153.87 (C_q)

M.P.: 131-134 °C

IRν_{max} (NaCl film) cm^{-1}: 2939.7, 2837.7, 1591.9, 1524.8 (NO_2), 1507.3, 1462.8, 1421.8, 1350.9 (NO_2), 1240.9, 1127.3, 1005.7

HRMS: Found 366.1049 $[M+Na]^+$, $C_{17}H_{19}N_3NaO_3$ requires 366.1066, (-4.6 ppm)

6-Nitro-2-(3,4,5-trimethoxybenzyl)-2*H*-indazole (242)

As per the general procedure G, 6-nitro-2-(3,4,5-trimethoxybenzyl)-2*H*-indazole (**242**) was prepared from from 6-nitroindazole and 3,4,5-trimethoxybenzyl bromide (1.57 g) as a yellow solid (124 mg, 12%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 6H, 2 x OCH_3), 3.81 (s, 3H, OCH_3), 5.53 (s, 2H, CH_2), 6.38 (app t., dd, 3H, ArH, J = 2.14 Hz), 6.45 (s, 2H, ArH), 7.11 (app t., dd, 2H, ArH, J = 2.14 Hz), 7.27 (dd, 1H, ArH, J = 8.56,1.84 Hz), 7.30 (s, 1H, ArH), 7.79 (d, 1H, ArH, J = 9.16 Hz), 8.07 (s, 1H, ArH)

^{13}C NMR (101 MHz, $CDCl_3$) δ 53.18 (CH_2), 56.08 (2 x OCH_3), 60.75 (OCH_3), 100.52 (ArCH), 104.24 (ArCH), 110.68 (ArCH), 115.63 (ArCH), 119.84 (ArCH), 122.31 (ArCH), 132.08 (C_q), 133.57 (ArCH), 137.61 (C_q), 139.64 (C_q), 153.50 (C_q)

M.P.: 165-167 °C

IRν_{max} (NaCl film) cm^{-1}: 2935.2, 2835.7, 1591.9, 1523.7 (NO_2), 1501.1, 1453.1, 1413.8, 1345.1 (NO_2), 1220.1, 1122.7

HRMS: Found 366.1051 $[M+Na]^+$, $C_{17}H_{19}N_3NaO_3$ requires 366.1066, (-4.1 ppm)

5-Nitro-1-(3,4,5-trimethoxybenzyl)-1*H*-indazole (249)

As per the general procedure G, 5-nitro-1-(3,4,5-trimethoxybenzyl)-1*H*-indazole (**249**) was prepared from 5-nitroindazole and 3,4,5-trimethoxybenzyl bromide (1.57 g) as a colourless solid (453 mg, 44%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 6H, 2 x OCH_3), 3.80 (s, 3H, OCH_3) 5.59 (s, 2H, CH_2) 6.43 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$) 7.46 (d, 1H, ArH, J = 9.35 Hz, H_7) 8.26 - 8.29 (m, 2H, ArH, H_3 & H_6) 8.77 (d, 1H, J = 1.75 Hz, H_4)

^{13}C NMR (101 MHz, $CDCl_3$) δ 53.34 (CH_2), 55.69 (2 x OCH_3), 60.79 (OCH_3), 103.88 (2xArCH), 109.18 (ArCH), 118.60 (ArCH), 121.22 (ArCH), 123.06 (C_q), 130.80 (C_q), 135.69 (ArCH), 137.40 (C_q), 140.77 (C_q), 142.04 (C_q), 153.18 (C_q)

M.P.: 137-139 °C

IRν_{max} (NaCl film) cm^{-1}: 1515.9 (NO_2), 1336.8 (NO_2)

HRMS: Found 366.1074 $[M+Na]^+$, $C_{17}H_{19}N_3NaO_3$ requires 366.1066, (+2.2 ppm)

5-Nitro-2-(3,4,5-trimethoxybenzyl)-2*H*-indazole (252)

As per the general procedure G, 5-nitro-2-(3,4,5-trimethoxybenzyl)-2*H*-indazole (**252**) was prepared from from 5-nitroindazole and 3,4,5-trimethoxybenzyl bromide (1.57 g) as a brown solid (102 mg, 10%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 6H, 2 x OCH_3), 3.81 (s, 3H, OCH_3), 5.55 (s, 2H, CH_2) 6.57 (s, 2H, $H_{2'}$ & $H_{6'}$), 7.74 (d, 1H, ArH, J = 9.54 Hz, H_7), 8.05 (dd, 1H, ArH, J = 9.54, 2.01 Hz, H_6), 8.22 (s, 1H, ArH, H_3), 8.66 (1H, d, ArH, J = 2.01 Hz, H_4)

^{13}C NMR (101 MHz, $CDCl_3$) δ 55.72 (2 x OCH_3), 57.95 (CH_2), 60.37 (OCH_3), 105.06 (2xArCH), 117.99 (ArCH), 119.04 (ArCH), 119.84 (ArCH), 126.71 (ArCH), 129.54 (C_q), 137.85 (C_q), 142.59 (C_q), 149.42 (C_q), 153.24 (C_q)

M.P.: 115-118 °C

IRν_{max} (NaCl film) cm^{-1}: 1505.23 (NO_2), 1333.7 (NO_2)

HRMS: Found 366.1051 $[M+Na]^+$, $C_{17}H_{19}N_3NaO_3$ requires 366.1066, (-4.1 ppm)

1-Benzyl-5-nitro-1*H*-indazole (251)

As per the general procedure G, 1-benzyl-5-nitro-1*H*-indazole (**251**) was prepared from 5-nitroindazole and benzyl bromide (1.03 g) as a colourless solid (372 mg, 49%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66 (s, 2H, CH_2), 7.22 (d, 2H, ArH, J = 7.53 Hz), 7.29 - 7.35 (m, 3H, ArH), 7.41 (d, 1H, ArH, J = 9.03 Hz, H_7), 8.22 (dd, 1H, ArH, J = 9.03, 2.01 Hz, H_6), 8.26 (s, 1H, ArH, H_3), 8.74 (d, 1H, ArH, J = 2.01 Hz, H_4)

^{13}C NMR (101 MHz, $CDCl_3$) δ 53.54 (CH_2), 109.58 (ArCH, C_7), 118.96 (ArCH, C_4), 121.53 (ArCH, C_6), 123.46 (C_q, C_{3a}), 127.18 (ArCH), 128.25 (ArCH), 128.93 (ArCH), 135.61 (C_q, $C_{1'}$), 136.04 (ArCH, C_3), 141.16 (C_q, C_6), 142.37 (C_q, C_{7a})

M.P.: 104-107 °C Lit. M.P.: 102-103 °C[286]

IRν_{max} (NaCl film) cm^{-1}: 2936.2, 2835.7, 1592.9, 1523.4 (NO_2), 1511.1, 1451.8, 1423.8, 1341.1 (NO_2), 1228.1, 1121.7

HRMS: Found 254.0939 $[M+H]^+$, $C_{14}H_{12}O_2$ requires 254.0930, (+3.5 ppm)

1-Benzyl-5-nitro-2*H*-indazole (253)

As per the general procedure G, 1-benzyl-5-nitro-2*H*-indazole (**253**) was prepared from 5-nitroindazole and benzyl bromide (1.03 g) as a yellow solid (140 mg, 18%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.65 (s, 2H, CH_2), 7.32 - 7.36 (m, 2H, ArH), 7.38 - 7.42 (m, 3H, ArH), 7.77 (d, 1H, ArH, J = 9.03 Hz, H_7), 8.10 (dd, 1H, ArH, J = 9.03, 2.01 Hz, H_6), 8.18 (s, 1H, ArH, H_3), 8.70 (d, 1H, ArH, J = 2.01 Hz, H_4)

^{13}C NMR (101 MHz, $CDCl_3$) δ 58.15 (CH_2), 118.47 (ArCH, C_7), 119.38 (ArCH, C_4), 120.30 (ArCH, C_6), 127.00 (ArCH, C_3), 128.25 (ArCH), 128.90 (ArCH), 129.15 (ArCH), 134.49 (C_q), 143.08 (C_q), 149.87 (C_q)

M.P.: 134-137 °C [286]

IRν_{max} (NaCl film) cm^{-1}: 2935.2, 2836.7, 1598.4, 1521.4 (NO_2), 1521.1, 1443.1, 1413.8, 1339.1 (NO_2), 1229.1,

HRMS: Found 254.0939 $[M+H]^+$, $C_{14}H_{12}O_2$ requires 254.0930, (+3.5 ppm)

2-Benzhydryl-5-nitro-2*H*-indazole (254)

As per the general procedure G, 2-benzhydryl-5-nitro-2*H*-indazole (**254**) was prepared from 5-nitroindazole and bromodiphenylmethane (1.48 g). This compound was not purified successfully by flash chromatography and no experimental data is present for this compound.

2-Benzhydryl-6-nitro-1*H*-indazole (244)

As per the general procedure G, 2-benzhydryl-6-nitro-1*H*-indazole (**244**) was prepared from 6-nitroindazole and bromodiphenylmethane (1.48 g) as a brown solid (100 mg, 9%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (s, 5H, ArH), 7.39 (s, 6H, ArH, CH), 7.73 (d, 1H, J = 9.16 Hz, ArH), 7.91 (d, 2H, ArH, J = 6.71 Hz), 8.74 (s, 1H, ArH)

^{13}C NMR (101 MHz, $CDCl_3$) δ 71.87 (CH), 115.86 (ArCH), 115.89 (ArCH), 121.72 (ArCH), 124.36 (C_q 128.26 (ArCH), 128.73 (ArCH), 128.98 (ArCH), 138.07 (C_q), 146.70 (C_q), 146.91 (C_q)

M.P.: 198-200 °C

IRν_{max} (NaCl film) cm^{-1}: 2931.2, 2825.4, 1592.8, 1526.7 (NO_2), 1501.1, 1453.1, 1413.8, 1345.1 (NO_2), 1220.1,

HRMS: Found 352.1063 $[M+Na]^+$, $C_{20}H_{15}N_3O_2Na$ requires 352.1062, (+0.3 ppm)

Ethyl 2-(6-nitro-2*H*-indazol-2-yl)acetate (248)

As per the general procedure G, ethyl 2-(6-nitro-2*H*-indazol-2-yl)acetate (**248**) was prepared from 6-nitroindazole and ethyl bromoacetate (1.0 g) as a yellow solid (15 mg, 2 %). No experimental data is present for this compound.

Ethyl 2-(6-nitro-1*H*-indazol-2-yl)acetate (246)

As per the general procedure G, ethyl 2-(6-nitro-1*H*-indazol-2-yl)acetate (**246**) was prepared from 6-nitroindazole and ethyl bromoacetate (1.0 g) as a yellow solid (300 mg, 40%).

^1H NMR (400 MHz, $CDCl_3$) δ 1.30 (t, 3H, J = 7.02 Hz, $CH_2\underline{CH_3}$), 4.27 (q, 2H, J = 7.02Hz, $\underline{CH_2}CH_3$), 5.26 (s, 2H, CH_2), 7.88 (d, 1H, ArH, J = 8.54 Hz, H_4), 8.07 (dd, 1H, ArH, J = 8.54, 1.83 Hz, H_5), 8.19 (s, 1H, ArH, H_3), 8.33 (s, 1H, ArH, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 14.08 (CH_3), 50.65 (CH_2), 62.22 ($\underline{CH_2}CH_3$), 105.73 (ArCH, C_7), 115.92 (ArCH, C_5), 122.09 (ArCH, C_4), 127.50 (C_q, C_{3a}), 134.58 (ArCH, C_3), 139.07 (C_q, C_{7a}), 146.84 (C_q, C_6), 167.15 (C=O)

M.P.: 128-130 °C Lit M.P.: 98-99 °C[285]

IRν_{max} (NaCl film) cm^{-1}: 2935.2, 2828.9, 1740.1 (OC=O), 1595.9, 1523.4 (NO_2), 1511.1, 1443.1, 1412.8, 1345.1 (NO_2), 1220.1, 1121.7

HRMS: Found 250.0820 $[M+H]^+$, $C_{11}H_{12}N_3O_4$ requires 250.0828, (-3.1 ppm)

Ethyl 2-(5-amino-1*H*-indazol-1-yl)acetate (274)

As per general procedure C, ethyl 2-(5-amino-1*H*-indazol-1-yl)acetate (**274**) was prepared from (**256**) (205 mg, 0.82 mmol) and obtained as a brown solid (170 mg, 94%).

^1H NMR (400 MHz, DMSO-d_6) δ 1.19 (t, 3H, J = 7.02 Hz, CH_3), 4.12 (q, 2H, J = 7.32 Hz, CH_2), 4.83 (s, 2H, NH_2), 5.21 (s, 2H, CH_2), 6.76 (s, 1H, ArH), 6.80 (d, 1H, ArH, J = 8.54 Hz), 7.31 (d, 1H, ArH, J = 9.16 Hz), 7.75 (s, 1H, ArH)

^{13}C NMR (101 MHz, DMSO-d_6) δ 14.03 (CH_3), 49.76 (CH_2), 60.85 (CH_3), 100.61 (ArCH), 109.85 (ArCH), 118.09 (ArCH), 124.80 (C_q), 131.61 (ArCH), 134.71 (C_q), 142.79 (C_q), 168.49 (ArCH)

M.P.: 101-103 °C

IRν_{max} (KBr) cm^{-1}: 3361.3 (NH_2), 2981.4, 1740.7 (OC=O), 1515.4, 1463.2, 1410.0, 1373.5, 1309.9, 1225.5 1162.4, 1026.9

HRMS: Found 220.1096 $[M+H]^+$, $C_{11}H_{14}N_3O_2$ requires 220.1086, (+4.5 ppm)

Ethyl 2-(5-amino-1*H*-indazol-1-yl)propanoate (273)

As per general procedure C, ethyl 2-(5-amino-1*H*-indazol-1-yl)propanoate (**273**) was prepared from (**255**) (82 mg, 0.31 mmol) and obtained as a dark oil (60 mg, 83%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.09 (t, 3H, J = 6.71 Hz, $\underline{CH_2}CH3$), 1.69 (d, 3H, J = 6.71 Hz, $CH\underline{CH_3}$), 4.06 (d, 2H, J = 6.71Hz, J = 6.00 Hz, $\underline{CH_2}CH_3$), 4.84 (s, 2H, NH_2), 5.52 (q, 1H, J = 6.71Hz, $\underline{CH}CH_3$), 6.76 (s, 1H, ArH), 6.81 (d, 1H, ArH, J = 8.54 Hz), 7.24 - 7.41 (m, 2H, ArH), 7.75 (s, 1H, ArH)

^{13}C NMR (101 MHz, DMSO-d_6) δ 13.96 (CH_3), 16.44 (CH_3), 55.42 (CH), 60.87 (CH_2), 100.69 (ArCH), 109.77 (ArCH), 117.97 (ArCH), 124.86 (C_q), 128.02 (C_q), 131.38 (ArCH), 134.17 (C_q), 142.81 (C_q), 170.41 (C=O)

M.P.: N/A

IRν_{max} (NaCl film) cm^{-1}: 3449.2 (NH_2), 3341.9 (NH_2), 3029.6, 2926.3, 1738.7 (OC=O), 1629.1 1482.9, 1454.3, 1275.7, 1127.1

HRMS: Found 256.1070 $[M+Na]^+$, $C_{12}H_{15}N_3O_2Na$ requires 256.1062, (+3.1 ppm)

1-Benzyl-1*H*-indazol-6-amine (261)

As per general procedure C, 1-benzyl-1*H*-indazol-6-amine (**261**) was prepared from (**240**) (365 mg, 1.4 mmol) and obtained as a brown solid (241 mg, 75%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 5.30 (s, 2H, NH_2), 5.42 (s, 2H, CH_2), 6.47 (s, 1H, ArH), 6.50 (dd, 1H, ArH, J = 8.54, 1.83 Hz), 7.13 (d, 2H, ArH, J = 6.71 Hz), 7.20 - 7.32 (m, 3H, ArH), 7.38 (d, 1H, ArH, J = 8.54 Hz), 7.77 (s, 1H, ArH)

^{13}C NMR (101 MHz, DMSO-d_6) δ 51.43 (CH_2), 89.76 (ArCH), 112.44 (ArCH), 116.26, 121.09 (ArCH), 126.94 (ArCH), 127.22 (ArCH), 128.43 (ArCH), 132.80 (ArCH), 137.95 (C_q), 141.37 (C_q), 148.01 (C_q)

M.P.: 115-117 °C

IRν_{max} (KBr) cm^{-1}: 3453.2 (NH_2), 3342.9 (NH_2), 3029.6, 2916.3, 1629.1 1481.1, 1454.3, 1280.7, 1127.6, 947.3

HRMS: Found 224.1180 $[M+H]^+$, $C_{14}H_{14}N_3$ requires 224.1188, (-3.6 ppm)

2-Benzyl-2*H*-indazol-6-amine (263)

As per general procedure C, 2-benzyl-2*H*-indazol-6-amine (**263**) was prepared from (**243**) (220 mg, 0.87 mmol) and obtained as a brown solid (191 mg, 98%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 5.03 (s, 2H, NH_2), 5.45 (s, 2H, CH_2), 6.45 (d, 1H, J = 1.22 Hz), 6.51 (dd, 1H, ArH, J = 9.16, 1.83 Hz), 7.22 - 7.39 (m, 1H, ArH), 8.14 (s, 1H, ArH)

^{13}C NMR (101 MHz, DMSO-d_6) δ 55.65 (CH_2), 93.93 (ArCH), 115.64, 116.06 (ArCH), 120.52 (ArCH), 123.46 (ArCH), 127.60 (ArCH), 127.71(ArCH), 128.45 (ArCH), 137.49 (C_q), 146.43 (C_q), 150.31 (C_q)

M.P.:137-139 °C

IRν_{max} (KBr) cm^{-1}: 3423.2 (NH_2), 3309.6 (NH_2), 3211.8, 2935.9, 1637.2, 1485.1, 1397.3, 1337.9, 1397.7, 1213.5, 1138.9

HRMS: Found 224.1190 $[M+H]^+$, $C_{14}H_{14}N_3$ requires 224.1188, (+0.9 ppm)

Ethyl (6-amino-1*H*-indazol-1-yl)acetate (266)

As per the general procedure C, ethyl (6-amino-1*H*-indazol-1-yl)acetate (**266**) was prepared from (**246**) (450 mg, 1.81 mmol) and obtained as a brown solid (166 mg, 76%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.20 (t, 3H, J = 7.32 Hz, CH_3), 4.13 (q, 2H, J = 6.92 Hz, CH_2), 5.09 (s, 2H, CH_2), 5.34 (s, 2H, NH_2), 6.42 (s, 1H, ArH, H_7), 6.52 (dd, 1H, ArH, J = 8.85, 1.53 Hz, H_5), 7.37 (d, 1H, ArH, J = 8.54 Hz, H_4), 7.75 (s, 1H, ArH, H_3)

^{13}C NMR (101 MHz, DMSO-d_6) δ 14.06 (CH_3), 49.50 (CH_2), 60.87 (CH_2), 89.73 (ArCH), 112.41 (ArCH), 116.05 (C_q), 121.00 (ArCH), 133.38 (ArCH), 142.12 (C_q), 148.16 (C_q), 168.49 (C=O)

M.P.: 151-154 °C[285]

IRν_{max} (NaCl film) cm^{-1}: 3423.2 (NH_2), 3309.6 (NH_2), 3211.8, 2935.9, 1637.2, 1485.1, 1397.3, 1337.9, 1397.7, 1213.5, 1138.9

HRMS: Found 242.0893 $[M+Na]^+$, $C_{11}H_{13}N_3NaO_2$ requires 242.0905, (-5.0 ppm)

1-(3,4,5-Trimethoxybenzyl)-1*H*-indazol-6-amine (259)

As per the general procedure C, 1-(3,4,5-trimethoxybenzyl)-1*H*-indazol-5-amine (**259**) was prepared from (**239**) (500 mg, 1.46 mmol) and obtained as a brown solid (210 mg, 46%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.60 (s, 3H, OCH_3), 3.67 (s, 6H, 2 x OCH_3), 5.31 (s, 2H, NH_2), 5.33 (s, 2H, CH_2), 6.47 - 6.52 (m, 4H, ArH), 7.37 (d, 1H, ArH, J = 9.16 Hz), 7.77 (s, 1H, ArH)

^{13}C NMR (101 MHz, DMSO-d_6) δ 51.70 (CH_2), 55.80 (2 x OCH_3), 59.94 (OCH_3), 89.88 (ArCH), 104.54 (ArCH), 112.44 (ArCH), 116.27 (C_q), 121.08 (ArCH), 132.77 (ArCH), 133.52 (C_q), 136.70 (C_q), 141.35 (C_q), 147.97 (C_q), 152.87 (C_q)

M.P.: 111-114 °C

IRν_{max} (KBr) cm^{-1}: 3458.1 (NH_2), 3367.2 (NH_2), 2935.9, 2832.5, 1630.2, 1592.9, 1507.1, 1481.5, 1460.8, 1422.4, 1328.7, 1236.9, 1124.3, 1004.0

HRMS: Found 366.1076 $[M+Na]^+$, $C_{17}H_{17}N_3NaO_5$ requires 366.1066, (+2.7 ppm)

2-(3,4,5-Trimethoxybenzyl)-2*H*-indazol-6-amine (262)

As per the general procedure C, 2-(3,4,5-trimethoxybenzyl)-2*H*-indazol-6-amine (**262**) was prepared from (**242**) (194 mg, 0.57 mmol) and obtained as a brown solid (74 mg, 42%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.62 (s, 3H, OCH_3), 3.72 (s, 6H, 2 x OCH_3), 5.05 (s, 2H, NH_2), 5.35 (s, 2H, CH_2), 6.46 (s, 1H, ArH, H_7), 6.51 (dd, 1H, ArH, J = 9.16, 1.83 Hz, H_5), 6.67 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 7.36 (d, 1H, ArH, J = 8.54 Hz, H_4), 8.12 (s, 1H, ArH, H_3)

^{13}C NMR (101 MHz, DMSO-d_6) δ 55.87 (2 x OCH_3), 55.91 (CH_2), 59.94 (OCH_3), 93.95 (ArCH), 105.62 (ArCH), 115.62 (C_q), 115.99 (ArCH), 120.52 (ArCH), 123.22 (ArCH), 132.78 (C_q), 146.31 (C_q), 152.82 (C_q)

M.P.: 190-191 °C

IRν_{max} (KBr) cm^{-1}: 3433.5 (NH_2), 3354.7(NH_2), 2931.0, 2827.6, 1637.9, 1593.0, 1507.0, 1460.7, 1422.8, 1329.4, 1239.1, 1124.5

HRMS: Found 366.1056 $[M+Na]^+$, $C_{17}H_{17}N_3NaO_5$ requires 366.1066, (-2.7 ppm)

2-(3,4,5-Trimethoxybenzyl)-2*H*-indazol-5-amine (271)

As per the general procedure C, 2-(3,4,5-trimethoxybenzyl)-2*H*-indazol-5-amine (**271**) was prepared from (**252**) (240 mg, 0.7 mmol) and obtained as a brown solid (140 mg, 64%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.62 (s, 3H, OCH_3), 3.73 (s, 6H, 2 x OCH_3), 4.78 (s, 2H, NH_2), 5.39 (s, 2H, CH_2), 6.56 (d, 1H, ArH, J = 1.83 Hz, H_4), 6.68 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 6.74 (dd, 1H, ArH, J = 9.16, 2.44 Hz, H_6), 7.33 (d, 1H, ArH, J = 9.16 Hz, H_7), 7.98 (s, 1H, ArH, H_3)

^{13}C NMR (101 MHz, DMSO-d_6) δ 55.88 (2 x OCH_3), 56.25 (CH_2), 59.95 (OCH_3), 97.06 (ArCH), 105.64 (ArCH), 117.47 (ArCH), 120.18 (ArCH), 120.40 (ArCH), 122.75 (C_q), 132.70 (C_q), 137.07 (C_q), 142.39 (C_q), 144.13 (C_q), 152.84 (C_q)

M.P.: 140-143 °C

IRν_{max} (KBr) cm^{-1}: 3418.7 (NH_2), 3359.6 (NH_2), 2935.9, 2832.5, 1593.6, 1530.9, 1507.3, 1462.2, 1239.4, 1125.2

HRMS: Found 366.1071 $[M+Na]^+$, $C_{17}H_{17}N_3NaO_5$ requires 366.1066, (+1.4 ppm)

2-Benzhydryl-2*H*-indazol-6-amine (264)

As per the general procedure C, 2-benzhydryl-2*H*-indazol-6-amine (**264**) was prepared from (**244**) (80 mg, 0.24 mmol) and obtained as a grey solid (38 mg, 52%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 5.07 (s, 2H, NH_2), 5.75 (s, 1H, CH), 6.45 (s, 1H, ArH, H_7), 6.53 (d, 1H, ArH, J=8.54 Hz, H_6), 7.03 (s, 1H, ArH), 7.19 (d, 4H, ArH, J = 7.32 Hz), 7.27 - 7.42 (m, 6H, ArH), 7.95 (s, 1H, ArH, H_3)

^{13}C NMR (101 MHz, DMSO-d_6) δ 68.73 (CH), 93.78 (ArCH, C_7), 115.14 (C_q), 116.32 (ArCH, C_5), 120.72 (ArCH, C_4), 123.53 (ArCH, C_3), 127.75 (ArCH, $C_{1'}$), 128.16 (ArCH), 128.42 (ArCH), 139.92 (C_q), 146.63 (C_q), 150.21 (C_q)

M.P.: 163-165 °C

IRν_{max} (KBr) cm^{-1}: 3461.2 (NH_2), 3339.5 (NH_2), 3216.9, 3029.2, 2922.8, 1638.9, 1557.7, 1494.6, 1482.1, 1397.6, 1227.3, 1130.8

HRMS: Found 322.1325 $[M+Na]^+$, $C_{17}H_{17}N_3NaO_5$ requires 322.1320, (+1.6 ppm)

1-Benzhydryl-1*H*-indazol-6-amine (260)

As per the general procedure C, 1-benzhydryl-1*H*-indazol-6-amine (**261**) was prepared from (**241**) (112 mg, 0.34 mmol) and obtained as a grey solid (76 mg, 75%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 5.29 (s, 1H, CH), 6.52 (d, 1H, ArH, J=8.54 Hz, H_5), 6.56 (s, 1H, ArH, H_7), 6.97 (s, 1H, CH), 7.21 (d, 4H, ArH, J = 7.32 Hz), 7.26 - 7.35 (m, 6H, ArH), 7.39 (d, 1H, ArH, J = 8.54 Hz, H_4), 7.79 (s, 1H, ArH, H_3)

^{13}C NMR (101 MHz, DMSO-d_6) δ 64.00 (CH), 90.12 (ArCH, C_7), 112.59 (ArCH, C_5), 116.06 (C_q), 121.04 (ArCH, C_4), 127.31 (ArCH, C_3), 128.16 (ArCH), 128.32 (ArCH), 133.14 (ArCH), 140.40 (C_q), 142.00 (C_q), 147.98 (C_q)

M.P.: 155-157 °C

IRν_{max} (KBr) cm^{-1}: 3467.9 (NH_2), 3345.3 (NH_2), 3221.7, 1626.9, 1480.7, 1451.7, 1276.1, 1236.6, 1030.6

HRMS: Found 322.1315 $[M+Na]^+$, $C_{17}H_{17}N_3NaO_5$ requires 322.1320, (-1.6 ppm)

1-Benzhydryl-1*H*-indazol-5-amine (269)

As per the general procedure C, 1-benzhydryl-1*H*-indazol-5-amine (**269**) was prepared from (**250**) (400 mg, 1.2 mmol) and obtained as a red oil (290 mg, 80%).

^{1}H NMR (400 MHz DMSO-d_6) δ 4.83 (s, 2H, NH_2), 6.74 - 6.81 (m, 2H, ArH, H_4 & H_6), 7.16 (s, 1H, CH), 7.19 - 7.37 (m, 10H, ArH), 7.42 (d, 1H, ArH, J = 9.16 Hz, H_7), 7.80 (s, 1H, ArH, H_3)

^{13}C NMR (101 MHz, DMSO-d_6) δ 64.15 (CH), 100.57 (ArCH, C_4), 110.08 (ArCH, C_7), 117.97 (ArCH, C_6), 124.79 (C_q, C_{3a}), 127.36 (ArCH, $C_{4'}$), 128.20 (ArCH), 131.44 (ArCH, C_3), 134.70 (C_q, C_{7a}), 140.43 (C_q, $C_{1'}$), 142.88 (C_q, C_5)

M.P.: N/A

IRν_{max} (NaCl film) cm^{-1}: 3433.8.8 (NH_2), 3347.4 (NH_2), 3221.3, 3060.7, 3029.1, 1629.7, 1511.5, 1494.9, 1454.4, 1411.0, 1373.7, 1323.3, 1274.2, 1235.9, 1201.1, 1159.6, 1078.14, 1031.51

HRMS: Found 322.1330 $[M+Na]^+$, $C_{17}H_{17}N_3NaO_5$ requires 322.1320, (+3.1 ppm)

Ethyl 2-(6-amino-2*H*-indazol-2-yl)propanoate (267)

As per the general procedure C, ethyl 2-(6-amino-2*H*-indazol-2-yl)propanoate (**267**) was prepared from (**247**) (230 mg, 0.87 mmol) and obtained as a black oil (150 mg, 74%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.14 (t, 3H, J = 7.02 Hz, $CH_2\underline{CH_3}$), 1.72 (d, 2H, J = 6.71 Hz, $CH\underline{CH_3}$), 4.10 (q, 2H, J = 7.02 Hz, $\underline{CH_2}CH_3$), 5.07 (s, 2H, NH_2), 5.36 (q, 1H, J = 6.71 Hz, , $\underline{CH}CH_3$), 6.44 (s, 1H, ArH, H_7), 6.53 (d, 1H, ArH, J = 8.54 Hz, H_5), 7.37 (d, 1H, ArH, J = 8.54 Hz, H_4), 8.13 (s, 1H, ArH, H_3)

^{13}C NMR (101 MHz, DMSO-d_6) δ 13.92 (CH_3), 17.18 (CH_3), 59.39 (CH), 61.13 (CH_2), 93.69 (ArCH, C_7), 115.33 (C_q), 116.31 (ArCH, C_5), 120.65 (ArCH, C_4), 123.03 (ArCH, C_3), 146.62 (C_q), 149.93 (C_q), 170.05 (C=O)

M.P.: N/A

IRν_{max} (NaCl film) cm^{-1}: 3449.1 (NH_2), 3351.1 (NH_2), 3222.1, 3128.5, 2940.5, 1740.0 (C=O), 1640.2, 1558.3, 1519.5, 1487.8, 1397.9, 1381.7, 1321.4, 1303.0, 1238.5, 1202.6, 1110.3

HRMS: Found 234.1250 $[M+H]^+$, $C_{12}H_{16}N_3O_2$ requires 234.1243, (+3.0 ppm)

Ethyl 2-(6-amino-1*H*-indazol-2-yl)propanoate (265)

As per the general procedure C, ethyl 2-(6-amino-1*H*-indazol-2-yl)propanoate (**265**) was prepared from (**245**) (250 mg, 0.95 mmol) and obtained as a red oil (76 mg, 34%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.11 (t, 3H, J = 7.02 Hz, $CH_2\underline{CH_3}$), 1.67 (d, 3H, J = 6.71 Hz, $CH\underline{CH_3}$), 4.04 - 4.13 (m, 2H, $\underline{CH_2}CH_3$), 5.34 (br. s., 3H, CH & NH_2), 6.46 (s, 1H, ArH, H_7), 6.51 (d, 1H, ArH, J = 8.54 Hz, H_5), 7.37 (d, 1H, ArH, J = 8.54 Hz, H_4), 7.74 (s, 1H, ArH, H_3)

^{13}C NMR (101 MHz, DMSO-d_6) δ 13.99 (CH_3), 16.29 (CH_3), 55.24 (CH), 60.85 (CH_2), 89.77 (ArCH, C_7), 112.44 (ArCH, C_5), 116.11 (C_q), 121.05 (ArCH, C_4), 133.11 (ArCH, C_3), 141.5 (C_q), 148.05 (C_q), 170.47 (C=O)

M.P.: N/A

IRν_{max} (NaCl film) cm^{-1}: 3455.1 (NH_2), 3359.2 (NH_2), 3227.1, 2985.9, 2940.4, 1737.5 (C=O), 1630.1,1577.8, 1513.7, 1483.5, 1423.6, 1377.3, 1338.1, 1285.1, 1244.3, 1244.3, 1185.2, 1071.2

HRMS: Found 256.1062 $[M+Na]^+$, $C_{12}H_{16}N_3O_2$ requires 256.1062, (0.0 ppm)

1-(3,4,5-Trimethoxybenzyl)-1*H*-indazol-5-amine (268)

As per the general procedure C, 1-(3,4,5-trimethoxybenzyl)-1*H*-indazol-5-amine (**268**) was prepared from (**249**) (514 mg, 1.50 mmol) and obtained as a red solid (258 mg, 55%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.59 (s, 3H, OCH_3), 3.67 (s, 6H, 2 x OCH_3), 4.81 (s, 2H, NH_2), 5.42 (s, 2H, CH_2), 6.55 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 6.75 (d, 1H, ArH, J = 1.83 Hz, H_4), 6.79 (dd, 1H, ArH, J = 8.85, 1.83 Hz, H_5), 7.40 (d, 1H, ArH, J = 8.14 Hz, H_7), 7.75 (s, 1H, ArH, H_3)

^{13}C NMR (101 MHz, DMSO-d_6) δ 52.01 (CH_2), 55.79 (2 x OCH_3), 59.94 (OCH_2), 100.63 (ArCH, C_4), 104.81 (ArCH, $C_{1'}$), 110.05 (ArCH, C_7), 118.08 (ArCH, C_6), 124.99 (C_q), 130.87 (ArCH, C_3), 133.45 (C_q), 133.94 (C_q), 136.74 (C_q), 142.65 (C_q), 152.80 (C_q, $C_{3'}$ & $C_{5'}$)

M.P.: 173-175 °C

IRν_{max} (KBr) cm^{-1}: 3430.8 (NH_2), 3353.6 (NH_2), 3227.3, 2938.5, 2838.0, 1633.5, 1593.2, 1511.2, 1460.4, 1423.2, 1328.3, 1237.2, 1126.0, 1004.1

HRMS: Found 314.1508 $[M+H]^+$, $C_{17}H_{20}N_3O_3$ requires 314.1505, (+1.0 ppm)

1-Benzyl-1*H*-indazol-5-amine (270)

As per the general procedure C, 1-benzyl-1*H*-indazol-5-amine (**270**) was prepared from (**251**) (250 mg, 1 mmol) and obtained as a pink solid (201 mg, 91%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 4.81 (s, 2H, NH_2), 5.51 (s, 2H, CH_2), 6.76 (s, 1H, ArH, H_4), 6.79 (dd, 1H, ArH, J = 8.54, 1.83 Hz, H_6), 7.17 (d, J = 7.32 Hz, 2H), 7.22 - 7.31 (m, 3H, ArH), 7.35 (d, 1H, ArH, J = 8.54 Hz, H_7), 7.75 (s, 1H, ArH, H_3)

^{13}C NMR (101 MHz, DMSO-d_6) δ 51.76 (CH_2) 100.61 (ArCH, C_4), 109.96 (ArCH, C_7), 118.08 (ArCH, C_6), 124.97 (C_q, C_{3a}), 127.19 (ArCH), 127.30 (ArCH), 128.39 (ArCH), 130.88 (ArCH, C_3), 133.98 (C_q, C_{7a}), 137.92 (C_q, $C_{1'}$), 142.66 (C_q, C_5)

M.P.: 131-133 °C Lit M.P.: 147-148 °C[286]

IRν_{max} (KBr) cm^{-1}: 3339.9, 3224.3, 2931.0, 1648.0, 1510.5, 1454.3, 1376.3, 1324.3, 1236.4, 1170.6

HRMS: Found 224.1188 $[M+H]^+$, $C_{14}H_{14}N_3$ requires 224.1880, (0.0 ppm)

2-Benzyl-2*H*-indazol-5-amine (272)

As per the general procedure C, 2-benzyl-2*H*-indazol-5-amine (**272**) was prepared from (**253**) (250 mg, 0.88 mmol) and obtained as a black solid (191 mg, 99%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 4.79 (s, 2H, NH_2), 5.49 (s, 2H, CH_2), 6.56 (s, 1H, ArH, H_4), 6.74 (d, 1H, ArH, J = 9.16 Hz, H_6), 7.23 - 7.38 (m, 6H, ArH), 7.98 (s, 1H, ArH, H_3)

^{13}C NMR (101 MHz, DMSO-d_6) δ 55.95 (CH_2), 97.01 (ArCH, C_4), 117.47 (ArCH, C_7), 120.39 (ArCH, C_6), 120.43 (ArCH, C_3), 122.77 (C_q), 127.65 (ArCH, $C_{4'}$), 127.74 (ArCH), 128.46 (ArCH), 137.40 (C_q), 142.44 (C_q), 144.24 (C_q)

M.P.: 114-117 °C[290]

IRν_{max} (KBr) cm^{-1}: 3433.5 (NH_2), 3335.5 (NH_2), 3019.7, 2931.0, 1641.2, 1530.5, 1496.7, 1469.6, 1455.1, 1353.2, 1216.7, 1136.4

HRMS: Found 224.1186 $[M+H]^+$, $C_{14}H_{14}N_3$ requires 224.1880, (+2.7 ppm)

General procedure H: Preparation of 5-bromo and 6-bromo indazoles

To a suspension, cooled to 0 °C, of **(168)** or (**209**) (4.28 mmol, 1 eq) in 48% hydrobromic acid (2.5 mL) and DIW (10 mL), sodium nitrite (4.71 mmol, 1.1 eq) in DIW (5 mL) was added slowly. The resultant solution was stirred at 0 °C for 15 minutes. Urea (2.87 mmol, 0.67 eq) was added slowly to neutralize excess nitrous acid. After a further 15 minutes of stirring on

ice, the solution was taken off ice and allowed to stir at room temperature for 15 minutes. The solution was then added slowly (dropwise) to a solution containing copper bromide (12.82 mmol, 3 eq), 48% hydrobromic acid (4.5 mL) and DIW (10 mL). The resultant solution was heated to 80 °C for 2 h, cooled to 20 °C and basified with ammonium hydroxide to a pH of 11 – 12. The aqueous layer was extracted with chloroform (3 x 50 mL), the organic layers were combined, washed with a saturated brine solution (40 mL), dried using sodium sulphate, filtered and concentrated to dryness *in vacuo*. Purification by flash column chromatography over silica gel (eluent CH_2Cl_2) afforded the desired aryl bromide compound.

(5-Bromo-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (321)

As per general procedure H, (5-bromo-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (**321**) was prepared from (**186**) and obtained as a colourless solid (719 mg, 43%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.95 (s, 6H, 2 x OCH_3), 3.98 (s, 3H, OCH_3), 7.42 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 7.74 (d, 1H, ArH, J = 8.52 Hz, H_6), 7.97 (s, 1H, ArH, H_3), 8.19 (s, 1H, ArH, H_3), 8.45 (d, 1H, ArH, J = 8.52 Hz, H_4)

^{13}C NMR (101 MHz, $CDCl_3$) δ 55.86 (2 x OCH_3), 60.54 (OCH_3), 108.45 (ArCH, $H_{2'}$ & $H_{6'}$), 116.85 (ArCH, C_7), 117.50 (C_q) , 123.13 (ArCH, C_4), 126.92 (C_q), 127.14 (C_q), 132.14 (ArCH, C_6), 138.67 (ArCH, H_3), 138.71 (C_q), 141.57 (C_q), 152.20 (C_q, $C_{3'}$ & $C_{5'}$), 166.89 (C=O)

MP: 139-143 °C

IRν_{max} (NaCl film) cm^{-1}: 3111.4, 2990.9, 2963.1, 2832.4, 1682.92 (C=O), 1603.3, 1586.1, 1518.2, 1461.4, 1454.9, 1412.7, 1358.1

HRMS: Found 413.0101 $[M+Na]^+$, $C_{17}H_{15}BrN_2O_4Na$ requires 413.0113, (-2.9 ppm)

6-Bromo-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (322)

As per general procedure H, (6-bromo-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (**324**) was prepared from (**209**) and obtained as a pale yellow solid (1.07 g, 64%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.96 (s, 6H, 2 x OCH_3), 3.98 (s, 3H, OCH_3), 7.43 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 7.57 (d, 1H, ArH, J = 8.80 Hz, H_5), 7.68 (d, 1H, ArH, J = 8.80 Hz, H_4), 8.21 (s, 1H, ArH, H_3), 8.80 (s, 1H, ArH, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 55.86 (2 x OCH_3), 60.54 (OCH_3), 108.44 (ArCH, $H_{2'}$ & $H_{6'}$), 118.62 (ArCH, C_7), 121.45 (ArCH, C_4), 123.80 (C_q), 124.35 (C_q), 126.92 (C_q), 127.99 (ArCH, C_5), 139.50 (ArCH, H_3), 149.59 (C_q), 141.57 (C_q), 152.19 (Cq, $C_{3'}$ & $C_{5'}$), 166.89 (C=O)

MP: 147-151 °C

IRν_{max} (NaCl film) cm^{-1}: 3117.4, 2998.9, 2968.9, 2835.4, 1675.95 (C=O), 1606.8, 1586.1, 1508.2, 1468.4, 1452.9, 1415.7, 1368.1, 1320.1, 1241.5, 1177.1, 1132.6, 1089.5, 996.1

HRMS: Found 415.0125 $[M+Na]^+$, $C_{17}H_{15}BrN_2O_4Na$ requires 413.0113, (+2.9 ppm)

General procedure I: Preparation of 5-iodo and 6-iodo indazoles

To a suspension, cooled to 0 °C, of (**168**) or (**209**) (5.12 mmol, 1 eq) and 6N HCl (14 mL), sodium nitrite (10.24 mmol, 2 eq) in DIW (10 mL) was added slowly. The resultant solution was stirred at 0 °C for 10 minutes. Potassium iodide (21.5 mmol, 4.2 eq) in DIW (15 mL) was added slowly to the chilled solution. **Note**: The rate of addition of the aqueous potassium iodide solution was such that the temperature of the chilled solution did not rise above 5 °C. The resultant solution was stirred at 20 °C for 3 h. The resultant solution was extracted with EtOAc (3 x 40 mL), the organic layers combined, washed with a saturated aqueous sodium thiosulphate solution (30 mL), a saturated brine solution (30 mL), dried using sodium sulphate, filtered and concentrated to dryness *in vacuo*. Purification by flash column chromatography over silica gel (eluent CH_2Cl_2) afforded the desired aryl iodide compound.

(5–Iodo-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (323)

As per general procedure I, (5–iodo-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (**324**) was prepared from (**168**) and obtained as a pale yellow solid (1.6 g, 72%).

^{1}H – NMR (400 MHz, $CDCl_3$) δ 3.95 (s, 6H, 2 x OCH_3), 3.98 (s, 3H, OCH_3), 7.42 (s, 2H), 7.90 (dd, 1H, ArH, J = 1.52 Hz, 9.04 Hz, H_6), 8.16 – 8.18 (m, 2H, ArH, H_3 & H_4), 8.34 (d, 1H, ArH, J = 9.04 Hz, H_7)

^{13}C- NMR (101 MHz, $CDCl_3$) δ 55.86 (2 x OCH_3), 60.53 (OCH_3), 88.14 (C_q, C_5), 108.46 (ArCH, $C_{2'}$ & $C_{6'}$), 117.14 (ArCH, C_7), 126.95 (C_q), 127.76 (C_q), 129.46 (ArCH, C_4), 137.55 (ArCH, C_6), 138.42 (ArCH, C_3), 139.18 (C_q), 141.58 (C_q), 152.19 (C_q, $C_{3'}$ & $C_{5'}$), 166.90 (C=O)

MP: 138-142 °C

IRν_{max} (NaCl film) cm^{-1}: 3036.0, 2835.9, 1686.16 (C=O), 1585.9, 1504.9, 1453.3, 1415.7, 1376.4, 1324.8, 1282.5, 1213.8, 1173.6, 1148.4, 1042.8, 998.6

HRMS: Found 460.9977 $[M+Na]^+$, $C_{17}H_{15}IN_2O_4Na$ requires 460.9974, (+0.7 ppm)

6–Iodo-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (324)

As per general procedure I, (6–iodo-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (**324**) was prepared from (**209**) and obtained as a yellow solid (1.5 g, 66%).

^1H NMR (400 MHz, $CDCl_3$) δ 3.95 (s, 6H, 2 x OCH_3), 3.98 (s, 3H, OCH_3), 7.43 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 7.55 (d, 1H, ArH, J = 8.52 Hz, H_4), 7.74 (d, 1H, J = 8.52 Hz, H_5), 8.19 (s, 1H, ArH, H_3), 9.02 (s, 1H, ArH, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 55.86 (2 x OCH_3), 60.52 (OCH_3), 95.55 (C_q, C_6), 108.44 (ArCH, $C_{2'}$ & $C_{6'}$), 121.60 (ArCH, C_7), 124.60 (ArCH, C_4), 124.83 (C_q, C_{3a}), 126.94(C_q, $C_{1'}$), 133.49 (ArCH, C_5), 139.59 (ArCH, H_3), 140.76 (C_q, C_{7a}), 141.57 (C_q, $C_{4'}$), 152.19 (C_q, $C_{3'}$ & $C_{5'}$), 166.87 (C=O)

MP: 148-151 °C

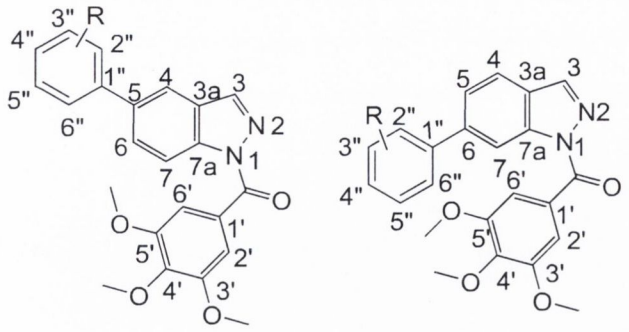
IRν_{max} (NaCl film) cm^{-1}: 2938.8, 2836.3, 1685.14 (C=O), 1599.4, 1583.2, 1504.7, 1452.2, 1414.8, 1400.2, 1362.4, 1330.8, 1285.4, 1239.0, 1183.5, 1226.8, 1002.5

HRMS: Found 460.9975 $[M+Na]^+$, $C_{17}H_{15}IN_2O_4Na$ requires 460.9974, (+0.2 ppm)

General procedure J: Preparation of 5-aryl and 6-aryl indazoles by microwave assisted Suzuki coupling

To a microwave vial containing a solution of **(321)** or **(322)** (150 mg, 0.38 mmol, 1 eq), the appropriate phenyl boronic acid (0.77 mmol, 2 eq) and tetrakis(triphenylphosphine)palladium (5 mol %, 0.019 mmol) in tetrahydrofuran (5 mL), 2M aq. sodium carbonate (1.05 mL) was added. The resultant solution was irradiated for 10 minutes at 120 °C, on standard power setting, using the CEM Discover microwave reactor. On standard power setting, the maximum power supplied is 300 watts. DIW (10 mL) was added to the reaction mixture and the aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL). The organic layers were combined, washed with a saturated brine solution (10 mL), dried using anhydrous sodium sulphate, filtered and

concentrated to dryness *in vacuo*. Purification by flash column chromatography over silica gel (eluent EtOAc: Hexane gradient) afforded the desired arylated indazole.



Numbering scheme for 5-aryl and 6-aryl indazoles

(3,4,5-Trimethoxyphenyl)(5-(3,4,5-trimethoxyphenyl)-1*H*-indazol-1-yl)methanone (333)

As per general procedure J, (3,4,5-trimethoxyphenyl)(5-(3,4,5-trimethoxyphenyl)-1*H*-indazol-1-yl)methanone **(333)** was prepared from **(321)** and 3,4,5-trimethoxyphenylboronic acid (163 mg) and obtained as a colourless solid (80 mg, 44%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.95 (s, 3H, OCH_3), 3.97 (s, 6H, 2 x OCH_3), 3.99 (s, 9H, OCH_3), 6.87 (s, 2H, ArH, $H_{2"}$ & $H_{6"}$), 7.46 (s, 2H, $H_{2'}$ & $H_{6'}$), 7.87 (d, 1H, ArH, J = 8.52 Hz), 7.97 (s, 1H, ArH. H_4), 8.30 (s, 1H, ArH, H_3), 8.61 (d, 1H, ArH, J = 8.52 Hz)

^{13}C NMR (101 MHz, $CDCl_3$) δ 55.84 (2 x OCH_3), 55.86 (2 x OCH_3), 60.53 (OCH_3), 60.59 (OCH_3), 104.23 (ArCH), 108.42 (ArCH), 115.68 (ArCH), 118.45 (ArCH), 126.25, 127.32, 128.82 (ArCH), 136.04 (C_q), 137.36 (C_q), 138.07 (C_q), 139.02 (C_q), 140.06 (ArCH, C_3), 141.42 (C_q), 152.2 (C_q), 153.17 (C_q), 167.03 (C=O)

MP: 151-153 °C

IRν_{max} (NaCl film) cm^{-1}: 2933.0, 2832.8, 1681.7 (C=O), 1609.9, 1574.2, 1504.3, 1423.5, 1375.7

HRMS: Found 501.1648 $[M+Na]^+$, $C_{26}H_{26}N_2O_7Na$ requires 501.1638, (+2.0 ppm)

(3,4,5-Trimethoxyphenyl)(5-(4-methoxyphenyl)-1*H*-indazol-1-yl)methanone (337)

As per general procedure J, (3,4,5-trimethoxyphenyl)(5-(4-methoxyphenyl)-1*H*-indazol-1-yl)methanone (**337**) was prepared from **(321)** and 4-methoxyphenylboronic acid (117 mg) as a colourless solid (68 mg, 43%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.94 (s, 3H, 4" - OCH_3), 3.96 (s, 6H, 2 x OCH_3), 3.98 (s, 3H, OCH_3), 7.05 (d, 2H, ArH, J = 8.52 Hz, $H_{3"}$ & $H_{6"}$), 7.44 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 7.62 (d, 2H, J = 8.52 Hz, $H_{2"}$ & $H_{6"}$), 7.86 (dd, 1H, ArH, J = 2.00 Hz, 9.04 Hz, H_6), 7.94 (s, 1H, ArH, H_4), 8.28 (s, 1H, ArH, H_3), 8.58 (d, 1H, J = 9.04 Hz, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 54.97 (4"-OCH_3), 55.85 (2 x OCH_3), 60.52 (OCH_3), 108.36 (ArCH, $C_{2'}$ & $C_{6'}$), 113.96 (ArCH, $C_{3"}$ & $C_{5"}$), 115.62 (ArCH), 117.93 (ArCH), 126.36 (C_q), 127.46 (C_q), 128.00 (ArCH, $C_{2"}$ & $C_{6"}$), 128.63 (ArCH), 132.57 (C_q), 137.64 (C_q), 138.88 (C_q), 140.14 (ArCH, C_3), 141.31 (C_q), 152.18 (C_q, $C_{3'}$ & $C_{5'}$), 158.90 (C_q, $C_{4"}$), 167.03 (C=O)

MP: 143-146 °C

IRν_{mav} (NaCl film) cm^{-1}: 2943.0, 2836.8, 1681.7 (C=O), 1609.9, 1584.2, 1505.1, 1413.9, 1375.7, 1305.6, 1240.0, 1165.1, 1127.1, 1040.2, 1004.2

HRMS: Found 441.1426 $[M+Na]^+$, $C_{24}H_{22}N_2O_5Na$ requires 441.1426, (0.0 ppm)

(3,4,5-Trimethoxyphenyl)(5–(2,3,4-trimethoxyphenyl)-1*H*-indazol-1-yl)methanone (334)

As per general procedure J, (3,4,5-trimethoxyphenyl)(5–(2,3,4-trimethoxyphenyl)-1*H*-indazol-1-yl)methanone (**334**) was prepared from **(321)** and 2,3,4-trimethoxyphenylboronic acid (163 mg) as a pale yellow solid (72 mg. 40%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 3.96 (s, 6H, 2 x OCH_3), 3.98 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 6.82 (d, 1H, ArH, J = 8.52 Hz), 7.13 (d, 1H, ArH, J = 8.52 Hz), 7.44 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 7.82 (d, 1H, ArH, J = 8.52 Hz), 7.94 (s, 1H, ArH, H_4), 8.28 (s, 1H, ArH, H_3), 8.57 (d, 1H, ArH, J = 8.52 Hz)

^{13}C NMR (101 MHz, $CDCl_3$) δ 55.65 (OCH_3), 55.84 (2 x OCH_3), 60.52 (OCH_3), 60.56 (OCH_3), 60.66 (OCH_3), 107.16 (ArCH), 108.36 (ArCH, C_2 & C_6), 114.95 (ArCH), 120.62 (ArCH), 124.55 (ArCH), 125.90, 127.41 (C_q), 127.51 (C_q), 130.90 (Ar-CH), 134.76, 138.82, 140.17 (ArCH, H_3), 141.31 (C_q), 142.16 (C_q), 150.95 (C_q), 152.19 (C_q, $C_{3'}$ & $C_{5'}$), 152.99 (C_q), 167.09 (C=O)

M.P.: 157-161 °C

IRν_{max} (NaCl film) cm^{-1} : 3138.1, 2946.4, 2837.7, 1694.68 (C=O), 1664.7, 1583.2, 1492.8, 1467.5, 1414.9, 133.9, 1292.2, 1130.9, 1080.6, 1008.2, 972.9

HRMS: Found 501.1619 $[M+Na]^+$, $C_{26}H_{26}N_2O_7Na$ requires 501.1638, (-3.8 ppm)

(3,4,5-Trimethoxyphenyl)(5–(2,6-dimethoxyphenyl)-1*H*-indazol-1-yl)methanone (337)

As per general procedure J, (3,4,5-trimethoxyphenyl)(5–(2,6-dimethoxyphenyl)-1*H*-indazol-1-yl)methanone (**337**) was prepared from **(323)** and 2,6-dimethoxyphenylboronic acid and obtained as a colourless solid (56 mg, 33%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 6H, 2 x OCH_3), 3.96 (s, 6H, 2 x OCH_3), 3.98 (s, 3H, OCH_3), 6.73 (d, 2H, ArH, J = 8.52 Hz, $H_{3''}$ & $H_{6''}$), 7.34–7.38 (m, 1H, ArH, $H_{4''}$), 7.42 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 7.64 (dd, 1H, ArH, J = 1.52 Hz, 8.52 Hz, H_6), 7.79 (s, 1H, ArH, H_4), 8.25 (s, 1H, ArH, H_3), 8.57 (d, 1H, ArH, J = 8.52 Hz, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 55.47 (2 x OCH_3), 55.84 (2 x OCH_3), 60.50 (OCH_3), 103.71 (ArCH), 108.32 (ArCH, $C_{2'}$ & $C_{6'}$), 114.57 (ArCH, $C_{3''}$ & $C_{5''}$), 118.07 (C_q), 122.63 (Ar-CH), 125.68 (C_q), 127.71 (C_q), 128.68 (ArCH), 130.59 (C_q), 132.64 (ArCH), 138.83 (C_q), 140.18 (ArCH, H_3), 141.23 (C_q), 152.18 (C_q, $C_{3'}$& $C_{5'}$), 157.26 (C_q, $C_{2''}$ & $C_{6''}$), 167.09 (C=O)

M.P.: 136-139 °C

IRν_{max} (NaCl film) cm^{-1}: 3036.0, 2834.9, 1682.6 C=O) 1581.9, 1503.9, 1454.3, 1411.7, 1374.4, 1323.8, 1272.5, 1213.8,

HRMS: Found 449.1719 $[M+H]^+$, $C_{25}H_{25}N_2O_6$ requires 449.1713, (+1.3 ppm)

(3,4,5-Trimethoxyphenyl)(6–(2,3,4-trimethoxyphenyl)-1*H*-indazol-1-yl)methanone (327)

As per general procedure J, (3,4,5-trimethoxyphenyl)(6–(2,3,4-trimethoxyphenyl)-1*H*-indazol-1-yl)methanone (**327**) was prepared from **(322)** and 2,3,4-trimethoxyphenylboronic acid (163 mg) and obtained as a pale yellow solid (90 mg, 48%).

^{1}H – NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H, OCH_3), 3.96 (s, 9H, 3 x OCH_3), 3.98 (s, 6H, 2 x OCH_3), 6.82 (d, 1H, ArH, J = 8.52 Hz, $H_{5''}$), 7.19 (d, 1H, ArH, J = 8.52 Hz, $H_{6''}$), 7.29 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 7.64 (d, 1H, ArH, J = 8.00 Hz, H_5), 7.82 (d, 1H, ArH, J = 8.00 Hz, H_4), 8.26 (s, 1H, ArH, H_3), 8.67 (s, 1H, ArH, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 56.12 (OCH_3), 56.32 (2 x OCH_3), 60.96 (OCH_3), 61.05 (OCH_3), 61.19 (OCH_3), 107.58 (ArCH), 108.89 (ArCH, $C_{2'}$ & $C_{6'}$), 116.06 (ArCH), 120.23 (ArCH), 124.75 (C_q), 126.89 (ArCH), 128.09 (C_q), 128.13 (C_q), 131.22 (ArCH), 140.21 (ArCH, C_3),

140.69, 141.81 (C_q), 142.61 (C_q), 142.61 (C_q), 151.56 (C_q), 152.65 (C_q, $C_{3'}$ & $C_{5'}$), 153.72 (C_q), 167.64 (C=O)

M.P.: 143-146 °C

IRν_{max} (NaCl film) cm^{-1}: 3033.0, 2845.9, 1678.4 (C=O), 1585.9, 1514.9, 1443.3, 1415.7, 1377.4, 1322.8, 1281.3, 1211.4

HRMS: Found 501.1658 $[M+Na]^+$, $C_{26}H_{26}N_2O_7Na$ requires 501.1638, (+4.0 ppm)

(3,4,5-Trimethoxyphenyl)(6–(3,4,5-trimethoxyphenyl)-1*H*-indazol-1-yl)methanone (326)

As per general procedure J, (3,4,5-trimethoxyphenyl)(6–(3,4,5-trimethoxyphenyl)-1*H*-indazol-1-yl)methanone (**326**) was prepared from **(322)** and 3,4,5-trimethoxyphenylboronic acid (163 mg) and obtained as a colourless solid (75 mg, 40%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.93 (s, 3H, OCH_3), 3.94 (s, 6H, 2 x OCH_3), 3.96 (s, 3H, OCH_3), 3.97 (s, 6H, 2 x OCH_3), 6.91 (s, 2H, ArH, $H_{2''}$ & $H_{6''}$), 7.43 (s, 2H, ArH, $H_{2''}$ & $H_{6''}$), 7.64 (dd, 1H, ArH, J = 8.03, 1.25 Hz, H_5), 7.84 (d, 1H, ArH, J = 8.03 Hz, H_4), 8.25 (s, 1H, ArH, H_3), 8.75 (s, 1H, ArH, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 56.23 (3 x OCH_3), 60.91 (OCH_3), 60.96 (OCH_3), 104.96 (ArCH, $C_{2''}$ & $C_{6''}$), 108.79 (ArCH, $C_{2'}$ & $C_{6'}$), 114.01 (ArCH), 121.05 (ArCH), 124.72 (ArCH), 125.13 (C_q), 127.80 (C_q), 136.59 (C_q), 138.08 (C_q), 140.14 (ArCH, C_3), 140.95 (C_q), 141.81 (C_q), 143.15 (C_q), 152.59 (C_q, $C_{3'}$ & $C_{5'}$), 153.52 (C_q, $C_{3''}$ & $C_{5''}$), 167.68 (C=O)

M.P.: 174-177 °C

IRν_{max} (NaCl film) cm^{-1}: 3117.4, 2990.9, 1675.5 cm^{-1} (C=O), 1603.3, 1586.1, 1518.2, 1461.4, 1412.7, 1358.1

HRMS: Found 501.1632 $[M+Na]^+$, $C_{26}H_{26}N_2O_7Na$ requires 501.1638, (-1.2 ppm)

(3,4,5-Trimethoxyphenyl)(5-(2,3-dimethoxyphenyl)-1*H*-indazol-1-yl)methanone (338)

As per general procedure J, (3,4,5-trimethoxyphenyl)(5-(2,3-dimethoxyphenyl)-1*H*-indazol-1-yl)methanone (**338**) was prepared from **(321)** and 2,3-dimethoxyphenylboronic acid (140 mg) and obtained as a colourless solid (88 mg, 51%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.60 (s, 3H, OCH_3), 3.95 (s, 9H, 2 x OCH_3), 3.97 (s, 3 H OCH_3), 7.69 (d, 1H, ArH, J = 8.80 Hz), 7.02 (d, 1H, ArH, J = 7.8Hz) 7.13 - 7.21 (m, 1H, ArH), 7.43 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 7.85 (d, 1H, ArH, J = 8.80 Hz), 7.98 (s, 1H, ArH, H_4), 8.27 (s, 1H, ArH, H_3), 8.57 (d, 1H, ArH, J = 8.80 Hz)

^{13}C NMR (101 MHz, $CDCl_3$) δ 55.92 (OCH_3), 56.24 (2 x OCH_3), 60.57 (OCH_3), 60.91 (OCH_3), 108.76 (ArCH, $C_{2'}$ & $C_{6'}$), 111.78 (ArCH), 115.34 (ArCH), 121.33 (ArCH), 122.65 (ArCH), 124.26 (ArCH), 126.22 (C_q), 127.90 (C_q), 131.33 (C_q), 135.11 (C_q), 139.42 (C_q), 140.59 (ArCH, C_3), 141.73 (C_q), 146.51 (C_q), 152.60 (C_q, $C_{3'}$ & $C_{5'}$), 153.18 (C_q), 167.50 (C=O)

M.P.: 123-126 °C

IRν_{max} (NaCl film) cm^{-1}: 2941.8, 2836.4, 1682.7 (C=O), 1575.0, 1529.2, 1442.9, 1424.1, 1373.4, 1325.2, 1231.2

HRMS: Found 449.1727 $[M+H]^+$, $C_{25}H_{25}N_2O_7$ requires 449.1713, (+3.1 ppm)

(3,4,5-Trimethoxyphenyl)(5-(2,4-dimethoxyphenyl)-1*H*-indazol-1-yl)methanone (336)

As per general procedure J, (3,4,5-trimethoxyphenyl)(5-(2,4-dimethoxyphenyl)-1*H*-indazol-1-yl)methanone (**336**) was prepared from **(321)** and 2,4-dimethoxyphenylboronic acid (140 mg) and obtained as a colourless solid (90 mg, 53%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.94 (s, 6H, 2 x OCH_3), 3.96 (s, 3H, OCH_3), 6.59 - 6.65 (m, 2H, ArH), 7.31 (d, 1H, ArH, J = 8.53 Hz), 7.42 (s, 2H, $H_{2'}$ & $H_{6'}$), 7.78 (dd, 1H, ArH, J = 8.53, 1.51 Hz, H_6), 7.89 (s, 1H, ArH, H_4), 8.24 (s, 1H, ArH, H_3), 8.53 (d, 1H, ArH, J = 8.53 Hz, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 55.04 (OCH_3), 55.15 (OCH_3), 55.84 (2 x OCH_3), 60.51 (OCH_2), 98.59 (ArCH), 104.30 (ArCH), 108.35 (ArCH, $C_{2'}$ & $C_{6'}$), 114.74 (ArCH), 120.84 (ArCH), 122.28 (C_q), 125.83 (C_q), 127.61 (C_q), 131.03 (ArCH), 131.29 (ArCH), 134.97 (C_q), 138.66 (C_q), 140.18 (ArCH, C_3), 141.27 (C_q), 152.18 (C_q), 157.02 (C_q, $C_{3'}$ & $C_{5'}$), 160.15 (C_q), 167.05 (C=O)

M.P.: 149-151 °C

IRν_{max} (NaCl film) cm^{-1}: 2941.9, 2837.4, 1675.5 (C=O) 1582.1, 1503.3, 1452.4, 1424.4, 1381.4, 1334.6, 1232.8, 1153.0, 1129.5, 1005.2

HRMS: Found 471.1538 $[M+Na]^+$, $C_{25}H_{24}N_2O_6Na$ requires 471.1532, (+1.3 ppm)

(3,4,5-Trimethoxyphenyl)(5-(2,5-dimethoxyphenyl)-1*H*-indazol-1-yl)methanone (339)

As per general procedure J, (3,4,5-trimethoxyphenyl)(5-(2,5-dimethoxyphenyl)-1*H*-indazol-1-yl)methanone (**339**) was prepared from **(321)** and 2,5-dimethoxyphenylboronic acid (140 mg) and obtained as a colourless solid (74 mg, 44%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.95 (s, 6H, 2 x OCH_3), 3.96 (s, 3H, OCH_3), 6.89 - 6.93 (m, 1H, ArH), 6.95 - 6.99 (m, 2H, ArH), 7.42 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 7.81 (d, 1H, ArH, J = 9.03 Hz, H_6), 7.94 (s, 1H, ArH, H_4), 8.26 (s, 1H, ArH, H_3), 8.56 (d, 1H, ArH, J = 9.03 Hz, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 55.39 (OCH_3), 55.85 (2 x OCH_3), 60.51 (OCH_3), 108.38 (ArCH, $C_{2'}$ & $C_{6'}$), 112.21 (ArCH), 112.86 (ArCH), 114.84 (ArCH), 116.59 (ArCH), 121.06 (ArCH), 125.76 (C_q), 127.52 (C_q), 130.37 (C_q), 131.14 (ArCH), 134.91 (C_q), 138.96 (C_q), 140.16 (ArCH, C_3), 141.32 (C_q), 150.31 (C_q), 152.19 (C_q), 153.37 (C_q, $C_{3'}$ & $C_{5'}$), 167.05 (C=O)

M.P.: 151-153 °C

IRν_{max} (NaCl film) cm^{-1}: 2940.9, 2837.4, 1682.7 (C=O), 1585.0, 1513.2, 1444.9, 1424.1, 1372.5, 1335.2, 1232.9, 1153.7, 1121.4, 1003.1

HRMS: Found 471.1537 $[M+Na]^+$, $C_{25}H_{24}N_2O_6Na$ requires 471.1532, (+0.6 ppm)

(5-(4-(Benzyloxy)phenyl)-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (341)

As per general procedure J, (5-(4-(benzyloxy)phenyl)-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (**341**) was prepared from **(321)** and 4-(benzyloxy)phenylboronic acid (176 mg) and obtained as a colourless solid (37 mg, 20%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 - 4.01 (m, 9H, 3 x OCH_3), 5.15 (s, 2H, CH_2), 7.11 (d, 2H, ArH, J = 7.93 Hz), 7.33 - 7.52 (m, 7H, ArH), 7.60 (d, 2H, ArH, J = 7.93 Hz), 7.84 (d, 1H, ArH, J=8.54 Hz, H_6), 7.92 (s, 1H, ArH, H_4), 8.25 (s, 1H, ArH, H_3), 8.57 (d, 1H, ArH, J = 8.54 Hz, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 56.28 (2 x OCH_3), 60.91 (OCH_3), 70.10 (CH_2), 108.88 (ArCH), 115.33 (ArCH), 116.04 (ArCH), 118.33 (ArCH), 126.77 (C_q), 127.44 (ArCH), 127.85 (C_q),

128.02 (ArCH), 128.42 (ArCH), 128.61 (ArCH), 129.01 (ArCH), 133.25 (C_q), 136.82 (C_q), 138.00 (C_q), 139.33 (C_q), 140.49 (ArCH, C_3), 141.83 (C_q), 152.60 (C_q), 158.53 (C_q), 167.39 (C=O)

M.P.: 139-142 °C

IRν_{max} (NaCl film) cm^{-1}: 2940.9, 2837.4, 1679.2 (C=O), 1583.0, 1503.3, 1454.4, 1414.4, 1371.4, 1332.8, 1242.3, 1163.9, 1126.8, 1005.2

HRMS: Found 495.1924 (M+H), $C_{30}H_{27}N_2O_5$ requires 495.1920, (+0.8 ppm)

(5-(4-Formylphenyl)-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (340)

As per general procedure J, (5-(4-formylphenyl)-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (**340**) was prepared from **(321)** and 4-formylphenylboronic acid (116 mg) and obtained as a colourless solid (47 mg, 30%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.95 (s, 6H, 2 x OCH_3), 3.97 (s, 3H, OCH_3), 7.46 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 7.84 (d, 2H, ArH, J = 7.93 Hz, $H_{2''}$ & $H_{6''}$), 7.92 (d, 1H, ArH, J = 9.16 Hz, H_6), 8.01 (d, 2H, ArH, J = 7.93 Hz, $H_{3''}$ & $H_{5''}$), 8.00 (s, 1H, ArH, H_4), 8.30 (s, 1H, ArH, H_3), 8.64 (d, 1H, ArH, J = 9.16 Hz, H_7), 10.10 (s, 1H, HC=O)

^{13}C NMR (101 MHz, $CDCl_3$) δ 56.32 (2 x OCH_3), 60.94 (OCH_3), 109.00 (ArCH, $C_{2'}$ & $C_{6'}$), 116.47 (ArCH), 119.58 (ArCH), 126.77 (C_q), 127.53 (C_q), 127.95 (ArCH), 129.15 (ArCH), 130.39 (ArCH), 135.35 (C_q), 136.79 (C_q), 140.21 (C_q), 140.39 (ArCH, C_3), 142.05 (C_q), 146.43 (C_q), 152.64 (C_q, $C_{3'}$ & $C_{5'}$), 167.39 (NC=O), 191.76 (HC=O)

M.P.:184-187 °C

IRν_{max} (NaCl film) cm^{-1}: 2935.9, 2837.4, 1703.5 (C=O), 1605.4, 1505.9, 1453.4, 1415.5, 1373.5, 1332.4, 1241.4, 1209.4, 1164.1, 1130.8

HRMS: Found 439.1279 $[M+Na]^+$, $C_{24}H_{20}N_2O_5Na$ requires 439.1270, (+2.0 ppm)

(6-(4-(Benzyloxy)phenyl)-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (332)

As per general procedure J, (6-(4-(benzyloxy)phenyl)-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (**332**) was prepared from **(322)** and 4-(benzyloxy)phenylboronic acid (176 mg) and obtained as a colourless solid (22 mg, 12%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.95 (s, 6H, 2 x OCH_3), 3.97 (s, 3H, OCH_3), 5.16 (s, 2H, CH_2), 7.11 (d, 2H, ArH, J = 8.54 Hz, $H_{3''}$ & $H_{6''}$), 7.35 - 7.51 (m, 7H, ArH), 7.64 (d, 1H, ArH, J = 7.93 Hz), 7.68 (d, 2H, ArH, J = 8.54 Hz, $H_{2''}$ & $H_{6''}$), 7.82 (d, 1H, ArH, J = 8.54 Hz), 8.22 (s, 1H, ArH, H_3), 8.75 (s, 1H, ArH, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 56.29 (2 x OCH_3), 60.94 (OCH_3), 70.13 (CH_2), 108.89 (ArCH, $C_{2'}$ & $C_{6'}$), 113.63 (ArCH), 115.31 (ArCH), 121.01 (ArCH), 124.39 (ArCH), 124.76 (C_q), 127.48 (ArCH), 127.98 (C_q), 128.04 (ArCH), 128.63 (ArCH), 128.85 (ArCH), 133.35 (C_q), 136.81 (C_q), 140.15 (ArCH, C_3), 141.18 (C_q), 141.83 (C_q), 142.68 (C_q), 152.62 (C_q, $C_{3'}$ & $C_{5'}$), 158.90 (C_q), 167.61 (C=O)

M.P.: 172-174 °C

IRν_{max} (NaCl film) cm^{-1}: 2938.9, 2832.5 1682.2 (C=O), 1606.0, 1583.71, 1518.0, 1504.6, 1454.5, 1414.8, 1400.1, 1373.9, 1340.6, 1240.8, 1179.7, 1126.7, 1004.6

HRMS: Found 495.1930 $[M+H]^+$, $C_{30}H_{27}N_2O_5$ requires 495.1920, (+2.0 ppm)

(6-(4-Formylphenyl)-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (330)

As per general procedure J, (6-(4-formylphenyl)-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (**330**) was prepared from **(322)** and 4-formylphenylboronic acid (116 mg) and obtained as a colourless solid (52 mg, 33%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.95 (s, 6H, 2 x OCH_3), 3.97 (s, 3H, OCH_3), 7.47 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 7.71 (dd, 1H, ArH, J = 8.54, 1.22 Hz, H_5), 7.91 (d, 3H, ArH, J = 8.54 Hz, H_4, $H_{2''}$ & $H_{6''}$), 8.03 (d, 2H, ArH, J = 8.55 Hz, $H_{3''}$ & $H_{5''}$), 8.28 (s, 1H, ArH, H_3), 8.86 (s, 1H, ArH, H_7), 10.11 (s, 1H, HC=O)

^{13}C NMR (101 MHz, $CDCl_3$) δ 56.32 (2 x OCH_3), 60.97 (OCH_3), 109.01 (ArCH, $C_{2''}$ & $C_{6''}$), 114.77 (ArCH), 121.46 (ArCH), 124.63 (ArCH), 125.83 (C_q), 127.61 (C_q), 128.40 (ArCH), 130.34 (ArCH), 135.66 (C_q), 140.03 (ArCH, C_3), 141.44 (C_q), 146.63 (C_q), 152.66 (C_q, $C_{3'}$ & $C_{5'}$), 167.58 (NC=O), 191.82 (HC=O)

M.P.: 175-177 °C

IRν_{max} (NaCl film) cm^{-1}: 2949.9, 2837.4 1700.2 (HC=O), 1678.7 (C=O), 1587.1, 1509.1, 1404.8, 1369.2, 1331.4, 1194.7, 1128.8

HRMS: Found 439.1281 $[M+Na]^+$, $C_{24}H_{20}N_2O_5Na$ requires 439.1270, (+2.5 ppm)

(6-(4-Formyl-3-methoxyphenyl)-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (331)

As per general procedure J, (6-(4-formyl-3-methoxyphenyl)-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (**331**) was prepared from **(322)** and 4-formyl-3-methoxyphenylboronic acid (139 mg) and obtained as a colourless solid (23 mg, 14%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.95 (s, 6H, 2 x OCH_3), 3.97 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 7.14 (d, 1H, ArH, J = 8.54 Hz), 7.45 (s, 2H, ArH, $H_{2'}$ & $H_{3'}$), 7.66 (d, 1H, ArH, J = 8.54 Hz), 7.84 (d, 1H, ArH, J = 8.54 Hz), 7.96 (dd, 1H, ArH, J=8.54, 1.83 Hz), 8.20 (d, 1H, ArH, J = 1.83 Hz), 8.24 (s, 1H, ArH, H_3), 8.76 (s, 1H, ArH), 10.55 (s, 1H, HC=O)

^{13}C NMR (101 MHz, $CDCl_3$) δ 55.92 (OCH_3), 56.29 (OCH_3), 60.93 (OCH_3), 108.92 (ArCH, $C_{2'}$ & $C_{6'}$), 112.34 (ArCH), 113.72 (ArCH), 121.26 (ArCH), 124.31 (ArCH), 124.99 (C_q), 125.11 (C_q), 127.53 (ArCH), 127.82 (C_q), 133.25 (C_q), 134.92 (ArCH), 140.10 (ArCH, C_3), 141.09 (C_q), 141.37 (C_q), 141.90 (C_q), 152.62 (C_q, $C_{3'}$ & $C_{5'}$), 161.69 (C_q), 167.58 (NC=O), 189.54 (HC=O)

M.P.: 167-169 °C

IRν_{max} (NaCl film) cm^{-1}: 2940.9, 2832.5 1684.1 (NC=O), 1608.2, 1585.8, 1506.7, 1474.4, 1416.2, 1374.4, 1339.9, 1272.5, 1183.3, 1126.9

HRMS: Found 447.1556 $[M+H]^+$, $C_{25}H_{23}N_2O_6$ requires 447.1556, (0.0 ppm)

(3,4,5-Trimethoxyphenyl)(6-(4-methoxyphenyl)-1*H*-indazol-1-yl)methanone (328)

As per general procedure J, (3,4,5-trimethoxyphenyl)(6-(4-methoxyphenyl)-1*H*-indazol-1-yl)methanone **(328)** was prepared from **(322)** and 4-methoxyphenylboronic acid (117 mg) as a colourless solid (60 mg, 38%).

^{1}H NMR (400 MHz, , $CDCl_3$) δ 3.89 (s, 3H, OCH_3), 3.95 (s, 6H, 2 x OCH_3), 3.97 (s, 3H, OCH_3), 7.04 (d, 2H, ArH, J = 8.53 Hz, $H_{3''}$ & $H_{5''}$), 7.44 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 7.64 (d, 1H, ArH, J = 8.53 Hz, H_6), 7.68 (d, 2H, ArH, J = 8.53 Hz, $H_{2''}$ & $H_{6''}$), 7.81 (d, 1H, ArH, J=8.03 Hz, H_4), 8.22 (s, 1H, ArH, H_3), 8.75 (s, 1H, ArH, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 55.36 (OCH_3), 56.24 (2 x OCH_3), 60.91 (OCH_3), 108.78 (ArCH, $C_{2'}$ & $C_{6'}$), 113.54 (ArCH), 114.34 (ArCH, $C_{3''}$ & $C_{5''}$), 121.00 (ArCH), 124.37 (ArCH), 124.70 (C_q), 127.96 (C_q), 128.80 (ArCH, $C_{2''}$ & $C_{6''}$), 133.04 (C_q), 140.17 (ArCH, C_3), 141.13 (C_q), 142.69 (C_q), 152.58 (C_q, $C_{3'}$ & $C_{5'}$), 159.66 (C_q), 167.62 (C=O)

M.P.: 165-169 °C

IRν_{max} (NaCl film) cm^{-1}: 2938.7, 2837.7, 1676.2.1 (C=O), 1588.1, 1503.2, 1459.2, 1412.9, 1397.1, 1377.1, 1285.9, 1234.8, 1184.8, 1126.4, 1108.1, 1010.3,

HRMS: Found 441.1419 $[M+Na]^+$, $C_{24}H_{22}N_2O_5Na$ requires 441.1426, (-1.6 ppm)

General Procedure K: Preparation of 5-vinyl and 6-vinyl indazole *via* Heck coupling

To a solution containing **(323)** (100 mg, 0.23 mmol, 1 eq), $Pd(PPh_3)_4$ (5 mol%, 13 mg) **or** $Pd(OAc)_2$ (5 mol %, 3 mg) and dimethylformamide (5 mL), triethylamine (0.16 mL) and methylacrylate (40 mg, 0.46 mmol, 2 eq) was added. The resultant solution was heated to 100 °C for 18 hours and then cooled to 20 °C. CH_2Cl_2 (20 mL) was added to the cooled reaction mixture and the organic layer was washed with DIW (5 x 15 mL), washed a saturated brine solution (15 mL), dried using anhydrous sodium sulphate, filtered and concentrated to dryness *in vacuo*. Purification by flash column chromatography over silica gel (eluent EtOAc: Hexane gradient) afforded the desired product.

General Procedure L: Preparation of 5-vinyl and 6-vinyl indazole using microwave assisted Heck coupling

To a microwave vial solution containing (**323**) or (**324**) (100 mg, 0.23 mmol, 1 eq), $Pd(OAc)_2$ (5 mol %, 3 mg) and dimethylformamide (5 mL), triethylamine (0.16 mL) and methylacrylate (40 mg, 0.46 mmol, 2 eq) was added. The resultant solution was irradiated at 100 °C for 5/15/30 minutes using the CEM Discover microwave reactor, at standard power setting and then cooled to 20 °C. CH_2Cl_2 (20 mL) was added to the cooled reaction mixture and the organic layer was washed with DIW (5 x 15 mL), washed a saturated brine solution (15 mL), dried using anhydrous sodium sulphate, filtered and concentrated to dryness *in vacuo*. Purification by flash column chromatography over silica gel (eluent EtOAc: Hexane gradient) afforded the desired product.

***(E)*-Methyl 3-(1-(3,4,5-trimethoxybenzoyl)-1*H*-indazol-5-yl)acrylate (346)**

As per general procedure L, (*E*)-methyl 3-(1-(3,4,5-trimethoxybenzoyl)-1*H*-indazol-5-yl)acrylate was prepared from (**323**) and methyl acrylate as a colourless solid (54 mg, 59%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (s, 3H, OCH_3), 3.96 (s, 6H, 2 x OCH_3), 3.98 (s, 3H, OCH_3), 6.56 (d, 1H, J = 16.04 Hz, CH=CH), 7.43 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 7.84-7.88 (m, 2H, ArH), 7.94 (s, 1H, ArH, H_4), 8.27 (s, 1H, ArH, H_3), 8.56 (d, 1H, ArH, J = 8.52 Hz)

^{13}C NMR (101 MHz, $CDCl_3$) δ 51.42 (OCH_3), 55.86 (2 x OCH_3), 60.53 (OCH_3), 108.46 (ArCH, $C_{2'}$ & $C_{6'}$), 115.97 (ArCH), 117.81 (ArCH), 121.11 (ArCH), 126.10 (C_q), 128.14 (HC=C), 130.92, 139.91 (HC=C), 140.62 (C_q), 141.48 (C_q), 143.62 (ArCH, C_3), 152.20 (C_q, $C_{3'}$ & $C_{6'}$), 166.84 (NC=O), 166.94 (OC=O)

M.P.: 168-171 °C

IRν_{max} (NaCl film) cm^{-1}: 2953.4, 2839.3, 1717.7 (OC=O), 1692.8 (NC=O), 1637.2, 1588.9, 1507.9, 1453.6, 1435.3, 1415.1, 1380.7, 1353.7, 1239.7, 1185.6, 1129.7, 1002.9

HRMS: Found 419.1223 $[M+Na]^+$, $C_{20}H_{18}N_2O_6Na$ requires 419.1219, (+1.0 ppm)

(*E*)-Methyl 3-(1-(3,4,5-trimethoxybenzoyl)-1*H*-indazol-6-yl)acrylate (347)

As per general procedure L, (*E*)-methyl 3-(1-(3,4,5-trimethoxybenzoyl)-1*H*-indazol-6-yl)acrylate (**349**) was prepared from (**324**) and methyl acrylate as a colourless solid (49 mg, 53%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 3H, OCH_3), 3.94 (s, 6H, 2 x OCH_3), 3.96 (s, 3H, OCH_3), 6.64 (d, 1H, J = 16.06 Hz, CH=CH), 7.42 (s, 2H, $H_{2'}$ & $H_{6'}$), 7.60 (d, 1H, ArH, J = 8.03 Hz, H_5), 7.80 (d, 1H, ArH, J = 8.03 Hz, H_4), 7.89 (d, 1H, J = 16.06 Hz, CH=CH), 8.23 (s, 1H, ArH, H_3), 8.72 (s, 1H, ArH, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 51.86 (OCH_3), 56.25 (2 x OCH_3), 60.92 (OCH_3), 108.83 (ArCH, $C_{2'}$ & $C_{6'}$), 115.95 (ArCH), 119.79 (ArCH), 121.32 (ArCH), 124.15 (ArCH), 126.92 (C_q), 127.48 (C_q), 135.79 (C_q), 139.90 (ArCH), 140.70 (C_q), 141.91 (Cq), 144.37 (ArCH, C_3), 152.59 (C_q, $C_{3'}$ & $C_{6'}$), 167.06 (NC=O), 167.43 (OC=O)

M.P.: 165-167 °C

IRν_{max} (NaCl film) cm^{-1}: 1720.7 (OC=O), 1645.1 (NC=O)

HRMS: Found 419.1210 $[M+Na]^+$, $C_{20}H_{18}N_2O_6Na$ requires 419.1219, (-2.1 ppm)

General Procedure M: Preparation of 6-alkynylindazoles using Sonogashira coupling

To a solution containing **(324)** (100 mg, 0.23 mmol, 1 eq), $Pd(PPh_3)_4$ (5 mol %, 13 mg), CuI (5 mol%, 2.2 mg) in triethylamine (3 mL) and phenylacetylene (35 mg, 0.36 mmol, 1.5 eq) was added. The resultant solution was refluxed for 4 hours and then cooled to 20 °C. DIW (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined, washed a saturated brine solution (10 mL), dried using sodium sulphate, filtered and concentrated to dryness *in vacuo*. Purification by flash column chromatography over silica gel (eluent EtOAc: Hexane gradient) afforded the desired product.

General Procedure N: Preparation of 6-vinylalkynylindazoles using microwave assisted Sonogashira coupling

To a microwave vial containing a solution of **(324)** (100 mg, 0.23 mmol, 1 eq), $Pd(PPh_3)_4$ (5 mol%, 13 mg), CuI (5 mol %, 2.2 mg) in triethylamine (3 mL) and phenylacetylene (35 mg, 0.36 mmol, 1.5 eq) was added. The resultant solution was irradiated at 120 °C for 20 minutes using the CEM Discover microwave reactor at standard power setting and then cooled to 20 °C. DIW (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined, washed a saturated brine solution (10 mL), dried using sodium sulphate, filtered and concentrated to dryness *in vacuo*. Purification by flash column chromatography over silica gel (eluent EtOAc: Hexane gradient) afforded the desired product.

(6-(Phenylethynyl)-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (352)

Using the general reflux procedure M, (6-(phenylethynyl)-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (**352**) was prepared from (**324**) and phenylacetylene as a yellow solid (37 mg, 40%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.96 (s, 6H, 2 x OCH_3), 3.98 (s, 3H, OCH_3), 7.39 - 7.43 (m, 3H, ArH), 7.45 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 7.58 - 7.64 (m, 3H, ArH), 7.78 (d, 1H, ArH, J = 8.53 Hz), 8.23 (s, 1H, ArH, H_3), 8.77 (s, 1H, ArH, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 56.24 (2 x OCH_3), 60.91 (OCH_3), 89.26 (C_q, C≡C), 91.13 (C_q, C≡C), 108.79 (ArCH, $C_{2'}$ & $C_{6'}$), 119.06 (ArCH), 120.81 (ArCH), 122.78 (C_q), 124.66 (C_q), 125.36 (C_q), 127.64 (C_q), 128.20 (ArCH), 128.40 (ArCH), 128.62 (ArCH), 131.71 (ArCH), 139.98 (ArCH), 140.08 (C_q), 141.82 (C_q), 152.58 (C_q, $C_{3'}$ & $C_{5'}$), 167.41 (C=O)

M.P.: 112-114 °C

IRν_{max} (NaCl film) cm^{-1}: 2938.4, 2832.5, 1685.3 (C=O), 1610.3, 1583.9, 1504.4, 1462.9, 1403.7, 1373.3, 1334.6, 1287.9, 1239.1, 1183.9, 1127.8, 1002.9

HRMS: Found 411.1352 $[M+H]^+$, $C_{25}H_{19}N_2O_4$ requires 411.1345, (+1.7 ppm)

(6-(3-Hydroxyprop-1-yn-1-yl)-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (353)

As per general microwave procedure N, (6-(3-hydroxyprop-1-yn-1-yl)-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (**353**) was prepared from (**323**) and progaryl alcohol as a yellow oil (21 mg, 25%).

^1H NMR (400 MHz, $CDCl_3$) δ 3.93 (s, 3H, OCH_3) 3.93 (s, 9H, 2 x OCH_2), 5.19 (s, 2H, CH_2), 7.25 - 7.29 (m, 1H, ArH, H_5), 7.37 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 7.66 (s, 1H, ArH, H_7), 7.71 (d, 1H, ArH, J = 8.53 Hz, H_4), 8.12 (s, 1H, ArH, H_3), OH not observed

^{13}C NMR (101 MHz, $CDCl_3$) δ 53.37 (OCH_3), 56.25 (2 x OCH_3), 60.94 (CH_2), 83.38 (C_q, C≡C), 86.80 (C_q, C≡C), 106.99 (ArCH, $C_{2'}$ & $C_{6'}$), 120.47 (s), 120.97 (br. s.), 124.46 (ArCH), 124.67 (ArCH), 142.42 (C_q), 152.93 (C_q, $C_{3'}$), 165.61 (C=O)

M.P.: N/A

IRν_{max} (NaCl film) cm^{-1}: 3338.4 (OH), 2940.5, 1718.0 (C=O), 1589.6, 1504.5, 1463.1, 1416.3, 1372.4, 1332.8, 1217.9, 1173.7, 1127.5, 1001.8

HRMS: Found 389.1108 $[M+H]^+$, $C_{20}H_{18}N_2O_4Na$ requires 389.1113, (-1.3 ppm)

General procedure O: Preparation of secondary alcohols

To a solution of 5-bromoinadazole (0.5 g, 2.6 mmol) in anhydrous diethyl ether (8 mL) at – 78 °C, under nitrogen, *tert*-BuLi (4.5 mL) was added slowly *via* a syringe. The resultant solution was stirred under nitrogen for 30 minutes at -78 °C. *p*-methoxybenzaldehyde (0.62 mL, 5.1 mmol) was added slowly *via* a syringe. The resultant solution was stirred under nitrogen at -78 °C for 2 h, warmed to 20 °C and stirred at this temperature for 3 days. DIW (10 mL) was then added and the aqueous layer was extracted with chloroform (6 x 15 mL). The organic layers were combined, washed with a saturated brine solution (20 mL), dried using sodium sulphate, filtered and concentrated to dryness *in vacuo*. The product was obtained by flash column chromatography over silica gel (eluent gradient EtOAc:Hexane) as a colourless solid.

(1*H*-Indazol-5-yl)(4-methoxyphenyl)methanol (364)

As per general procedure O, (1*H*-Indazol-5-yl)(4-methoxyphenyl)methanol (**364**) was obtained from 5-bromoinadazole and *p*-methoxy benzaldehyde as a colourless solid (231 mg, 35%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.70 (s, 3H, OCH_3), 5.75 (br. s., 1H, OH), 5.79 (d, 1H, *J*=2.01 Hz, CH), 6.85 (d, 2H, ArH, *J* = 8.03 Hz), 7.28 (d, 3H, ArH, *J* = 7.53 Hz), 7.44 (d, 1H, ArH, *J* = 8.53 Hz), 7.71 (s, 1H, ArH), 8.02 (s, 1H, ArH), 12.97 (br. s., 1H, NH)

^{13}C NMR (101 MHz, DMSO-d_6) δ 55.03 (OCH_3), 74.01 (CH), 109.78 (ArCH), 113.41 (ArCH), 117.25 (ArCH), 122.58 (C_q), 125.44 (ArCH), 127.48 (ArCH), 133.53 (ArCH), 138.17 (C_q), 139.12 (C_q), 158.02 (C_q)

M.P.: 163-165 °C

IRν_{max} (NaCl film) cm^{-1}: 3433.49 (OH), 1614.1, 1496.5, 1422.4, 1360.9, 1267.6, 1135.4, 1091.2, 962.6

HRMS: Found 255.1140 $[M+H]^+$, $C_{15}H_{15}N_2O_2$ requires 255.1134, (+2.4 ppm)

(1*H*-Indazol-5-yl)(4-methoxyphenyl)methanone (366)

As per general procedure O, (1*H*-indazol-5-yl)(4-methoxyphenyl)methanone (**366**) was obtained from 5-bromoinadazole and *p*-methoxy benzaldehyde as a colourless solid (72 mg, 11%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.41 (s, 3H, OCH_3), 6.64 (d, 2H, ArH, J = 8.00 Hz), 7.21 (d, 1H, ArH, *J* = 8.54 Hz), 7.29 - 7.33 (m, 3H, ArH), 7.71 (s, 1H, ArH), 7.80 (s, 1H, ArH)

^{13}C NMR (101 MHz, DMSO-d_6) δ 55.51 (OCH_3), 110.29, 113.77 (ArCH), 122.14, 124.55, 126.95, 130.14, 130.24, 131.97, 162.53 (C_q), 194.21 (C=O)

M.P.: 182-185 °C

IRν_{max} (NaCl film) cm^{-1}: 1638.7 (C=O), 1509.6, 1508.4, 1323.1, 1256.0, 1169.8, 1112.7, 1021.8

HRMS: Found 255.1140 $[M+H]^+$, $C_{15}H_{15}N_2O_2$ requires 255.1134, (+2.4 ppm)

General procedure P: Preparation of secondary alcohols

To a solution of 5-bromoinadazole (0.4 g, 2.1 mmol) in anhydrous diethyl ether (7 mL) at – 78 °C, under nitrogen, *tert*-BuLi (3.7 mL) was added slowly *via* a syringe. The resultant solution

was stirred under nitrogen for 30 minutes at -78 °C. A solution of 3,4,5-trimethoxybenzaldehyde (801 mg, 4.2 mmol) in anhydrous THF, minimum amount, was added slowly *via* a syringe. The resultant solution was stirred under nitrogen at - 78 °C for 2 hours, warmed to 20 °C and stirred at this temperature for 3 days. DIW (10 mL) was then added and the aqueous layer was extracted with chloroform (6 x 15 mL). The organic layers were combined, washed with a saturated brine solution (20 mL), dried using sodium sulphate, filtered and concentrated to dryness *in vacuo*. The product was obtained by flash column chromatography over silica gel (eluent gradient EtOAc:Hexane) as a colourless solid.

(1*H*-Indazol-5-yl)(3,4,5-trimethoxyphenyl)methanol (363)

As per general procedure P, 1*H*-indazol-5-yl)(3,4,5-trimethoxyphenyl)methanol (**363**) was obtained from 5-bromoinadazole and 3,4,5-trimethoxybenzaldehyde as a colourless solid (204 mg, 31%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.61 (s, 3H, OCH_3), 3.73 (s, 6H, 2 x OCH_3), 5.73 (d, 1H, *J* = 3.66 Hz, OH), 5.85 (d, 1H, *J*=3.66 Hz, CH), 6.72 (s, 2H, ArH), 7.32 - 7.38 (m, 1H, ArH), 7.42 - 7.48 (m, 1H, ArH), 7.74 (s, 1H, ArH), 8.03 (s, 1H, ArH), 12.96 (br. s., 1H, NH)

^{13}C NMR (101 MHz, DMSO-d_6) δ 55.79 (2 x OCH_3), 59.94 (OCH_3), 74.48 (CH), 103.38 (ArCH), 109.74 (ArCH), 117.38 (ArCH), 122.53 (C_q), 125.37 (ArCH), 133.54 (ArCH), 136.07 (C_q), 137.75 (C_q), 139.14 (C_q), 141.75 (C_q), 152.60 (C_q)

M.P.: 89-91 °C

IRν_{max} (NaCl film) cm^{-1}: 3327.7 (OH), 2935.9, 2837.4, 1592.4, 1504.9, 1461.5, 1418.1, 1329.1, 1169.8, 1232.8, 1125.3, 1001.4

HRMS: Found 337.1170 $[M+Na]^+$, $C_{17}H_{18}N_2NaO_2$ requires 337.1164, (+1.8 ppm)

General procedure Q: Preparation of 5-aroylated indazole - 1*H*-indazol-5-yl)(3,4,5-trimethoxyphenyl)methanone

To a solution of (**363**) (170 mg, 0.54 mmol) in anhydrous THF (3 mL), cooled to 0 °C, a solution of pyridinium chlorochromate (180 mg) in anhydrous THF was added slowly *via* a syringe. The resultant solution was stirred under nitrogen at 20 °C for 2 hours. The solution was diluted with diethyl ether and filtered through celite. The filtrate was concentrated to dryness *in vacuo* which afforded the desired product (1H-indazol-5-yl)(3,4,5-

trimethoxyphenyl)methanone (**365**) as a colourless solid (70 mg, 42%). No further purification was required.

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.69 - 3.88 (m, 9H, 3 x OCH_3), 7.03 (br. s., 2H, ArH), 7.68 (s, 1H, ArH), 7.83 (br. s., 1H), 8.27 (br. s., 2H), 13.43 (br. s., 1H, NH)

^{13}C NMR (101 MHz, DMSO-d_6) δ 56.01 (2 x OCH_3), 60.09 (OCH_3), 107.12 (ArCH), 110.33 (ArCH), 121.94 (C_q), 124.42 (ArCH), 126.75 (ArCH), 132.51 (C_q), 135.73 (ArCH), 140.88 (C_q), 141.32 (C_q), 149.60 (C_q), 152.51 (C_q), 194.42 (C=O)

M.P.: 141-143 °C

IRν_{max} (NaCl film) cm^{-1}: 3324.6, 2936.32, 2837.4, 1648.1 (C=O), 1613.1, 1580.9, 1502.1, 1461.8, 1461.8, 1413.2, 1337.5, 1232.9, 1168.2, 1126.6.8, 1002.9

HRMS: Found 335.1008 $[M+Na]^+$, $C_{17}H_{16}N_2NaO_2$ requires 335.1008, (0.0 ppm)

General procedure R: *N*-1 benzolyation of 5 aroylated indazoles

To a solution of 5-aroylated indazole and 3,4,5-trimethoxybenzoyl chloride in anhydrous CH_2Cl_2 (5 mL), triethylamine was added. The resultant solution was refluxed under nitrogen for 10 hours. It was cooled to 20 °C, washed with DIW, a saturated brine solution, dried using anhydrous sodium sulphate, filtered and concentrated to dryness *in vacuo*. Hot filtration of the crude product in hot methanol afforded the desired product.

(5-(4-Methoxybenzoyl)-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (368)

As per general procedure R, (**368**) was obtained from (**366**) (100 mg, 0.4 mmol) and 3,4,5-trimethoxybenzoyl chloride (91 mg, 0.4 mmol) as a colourless solid (35 mg, 20%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.93 (s, 3H, OCH_3), 3.95 (s, 6H, 2 x OCH_3), 3.98 (s, 3H, OCH_3), 7.02 (d, 2H, ArH, *J*=8.54 Hz), 7.46 (s, 2H, ArH), 7.87 (d, 2H, ArH, *J*=8.54 Hz), 8.08 (d, 1H, ArH, *J* = 9.16 Hz), 8.24 (s, 1H, ArH), 8.32 (s, 1H, ArH), 8.62 (d, 1H, ArH, *J* = 8.54 Hz)

^{13}C NMR (101 MHz, $CDCl_3$) δ 55.56 (OCH_3), 56.34 (2 x OCH_3), 60.97 (OCH_3), 109.07 (ArCH), 113.73 (ArCH), 115.66 (ArCH), 123.54 (ArCH), 125.66 (C_q), 127.27 (C_q), 127.31 (C_q) 130.10 (C_q), 130.93 (ArCH), 132.54 (ArCH), 140.70 (ArCH), 152.67 (C_q), 167.33 (NC=O), 194.54 (C=O)

M.P.: 148-151 °C

IRν_{max} (NaCl film) cm^{-1}: 2935.9, 2837.4, 1697.7, 1685.4 (NC=O), 1639.2, 1602.6, 1507.1, 1416.3, 1375.5, 1343.2, 1255.7, 1174.6, 1129.4

HRMS: Found 469.1370 $[M+Na]^+$, $C_{25}H_{22}N_2NaO_6$ requires 469.1376, (-1.2 ppm)

(1*H*-Indazole-1,5-diyl)*bis*((3,4,5-trimethoxyphenyl)methanone) (367)

As per general procedure R, (**367**) was obtained from (**365**) (60 mg, 0.19 mmol) and 3,4,5-trimethoxybenzoyl chloride (44 mg, 0.19 mmol) as a colourless solid (5 mg, 5%).

^1H NMR (400 MHz, $CDCl_3$) δ 3.90 (s, 6H, 2 x OCH_3), 3.95 (s, 6H, 2 x OCH_3), 3.98 (s, 6H, 2 x OCH_3), 7.10 (s, 2H, ArH), 7.47 (s, 2H, ArH), 8.11 (dd, 1H, ArH, *J*=8.55, 1.22 Hz), 8.29 (s, 1H, ArH), 8.34 (s, 1H, ArH), 8.65 (d, 1H, ArH, *J*=8.55 Hz)

^{13}C NMR (101 MHz, $CDCl_3$) δ 56.35 (2 x OCH_3), 56.38 (2 x OCH_3), 60.98 (OCH_3), 61.03 (OCH_3), 107.79 (ArCH), 109.11 (ArCH), 115.68 (ArCH), 123.77 (ArCH), 126.94 (C_q), 130.90 (ArCH), 132.32 (C_q), 134.44 (C_q), 140.67 (ArCH), 152.69 (C_q), 152.99 (C_q) 167.33 (NC=O), 194.54 (C=O)

M.P.: Not enough sample

IRν_{max} (NaCl film) cm^{-1}: 2933.2, 2831.4, 1695.1, 1681.4 (NC=O), 1629.2, 1612.3, 1517.9, 1416.3, 1375.5, 1323.8, 1226.7, 1164.6, 1129.4

HRMS: Found 529.1577 $[M+Na]^+$, $C_{27}H_{26}N_2NaO_8$ requires 529.1587, (-1.9 ppm)

General procedure S: Preparation of 3-bromo-6-nitroindazole (371)

6-Nitroindazole (1.0 g, 6.13 mmol) in an aqueous NaOH solution (1 g, 30 mL) was heated to 100 °C until a persistent red colour appeared. The resultant red solution was then cooled to 0 °C. A solution of pyridinium tribromide (2.35 g, 7.35 mmol) in MeOH (10 mL) was then added slowly and the resultant solution was stirred at 0°C for 5 hours. It was then warmed to 25°C and the pH adjusted to pH 7 with 1 M HCl. The aqueous solution was extracted with EtOAc (3 x 30 mL). The organic layers were combined and washed with (2 x 30 mL), a saturated brine solution (30 mL), dried using anhydrous sodium sulphate, filtered and concentrated to dryness *in vacuo*. The crude product was purified by flash column chromatography over silica gel (eluent DCM) which afforded 3-bromo-6-nitroindazole as a yellow solid (0.93 g, 63%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.83 (d, 1H, ArH, J = 8.84 Hz, H_4), 8.00 (d, 1H, ArH, J = 8.84 Hz, H_7), 8.49 (s, 1H, ArH, H_7), 14.14 (br. s, 1H, NH)

^{13}C NMR (101 MHz, DMSO-d_6) δ 107.79 (ArCH), 115.84 (ArCH), 120.76 (ArCH), 125.14 (C_q), 125.87 (C_q), 139.52 (C_q), 146.85 (C_q)

M.P.: 226-229 °C Lit M.P.: 222-224 °C[344]

IRν_{max} (KBr) cm^{-1}: 3349, 1591, 1526, 1339, 1019, 882, 786, 657

HRMS: Found 241.9555 $[M+H]^+$, $C_7H_5BrN_3O_2$ requires 241.9565, 2.2 ppm, (-4.1 ppm)

3-Bromo-6-nitro-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (374)

As per general procedure A, 3-bromo-6-nitro-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (**374**) was obtained from (**374**) (484 mg, 2.0 mmol) and 3,4,5-trimethoxybenzoyl chloride (461 mg, 2.0 mmol) as a yellow solid (679 mg, 78%) following recrystallization from methanol.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.96 (s, 6H, 2 x OCH_3), 3.99 (s, 3H, OCH_3), 7.49 (s, 2H, H_2' & H_6'), 7.87 (d, 1H, J= 8.76 Hz, H_4), 8.36 (d, 1H, J=8.76, 1.19 Hz, H_5), 9.45 (s, 1H, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 56.35 (2 x OCH_3), 61.02 (OCH_3), 109.35 (C_2' & C_6'), 112.55 (C_7), 120.18 (C_5), 121.46 (C_4), 125.62 (s C_3), 129.22 (s C_{3a}), 129.51 (s $C_{1'}$), 140.22 (s C_{7a}), 142.80 (C_6), 149.37 ($C_{4'}$), 152.70 ($C_{3'}$), 165.87 (C=O)

M.P.: 185-187 °C

IRν_{max} (NaCl film) cm^{-1}: 3114.3, 2936.0, 2875.3, 2831.4, 1693.8 (C=O), 1581.1, 1530.6 (NO_2), 1517.6, 1452.2, 1354.3, 1337.8 (NO_2), 1242.2, 1205.8, 1150.3, 997.4

HRMS: Found 436.0140 $[M+H]^+$, $C_{17}H_{15}BrN_3O_6$ requires 436.0144, (-0.9 ppm)

General procedure T: Iodination of 5-nitroindazle and 6-nitroindazole

To a solution of 5-nitronindazole or 6-nitroindazole (1 g, 6.13 mmol) in DMF, at 0 °C, KOH (1.27 g, 22.63 mmol) was added slowly followed by the slow addition I_2 pellets (3.07 g, 12.10 mmol). The resultant solution was stirred at 0 °C and warmed to 20 °C and stirred at this temperature for 2 hours. It was then poured into 10% aqueous sodium metabisulfite (150 mL)

and stirred for 30 minutes. The resultant suspension was collected by vacuum filtration, washed with DIW (3 x 100 mL) and left to air dry. No further purification was required.

3-Iodo-6-nitroindazole (372)

As per general procedure T, 3-iodo-6-nitroindazole (**372**) was prepared from 6-nitroindazole and obtained as a yellow solid (1.59 g, 90%)

^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.67 (d, 1H, ArH, J=9.16 Hz, H_4), 7.98 (dd, 1H, ArH, J = 9.16, 1.83 Hz, H_5), 8.46 (d, 1H, ArH, J = 1.83 Hz, H_7), 14.16 (br. s., 1H, NH)

^{13}C-NMR (101 MHz, DMSO-d_6) δ 94.60 (C_q, C_3), 107.90 (ArCH, C_7), 116.04 (ArCH, C_5), 122.40 (ArCH, C_4), 130.36 (C_q, C_{3a}), 139.45 (C_q, C_{7a}), 147.18 (C_q, C_6)

M.P.: 258-260 °C M.P.: 259-261 °C[347]

IRν_{max} (KBr) cm^{-1}: 3348.1, 1591.3, 1526.4, 1339.8, 1019.5

HRMS: Found 287.9282 [M-H]$^-$, $C_7H_3INO_2$ requires 287.9275, (+2.4 ppm)

3-Iodo-5-nitroindazole (373)

As per general procedure T, 3-iodo-5-nitroindazole (**373**) was prepared from 5-nitroindazole and obtained as a yellow solid (1.65 g, 93%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.75 (d, 1H, J = 9.03 Hz, H_7), 8.24 (dd, 1H, J = 9.03, 2.01 Hz, H_6), 8.31 (d, J = 2.01 Hz, H_4), 14.14 (br s., 1H, NH)

^{13}C NMR (101 MHz, DMSO-d_6) δ 97.42 (C_q, C_3), 111.80 (ArCH, C_7), 118.20 (ArCH, C_4), 122.03 (ArCH, C_6), 126.37 (C_q, C_3), 142.11 (C_q, C_5), 142.57 (C_q, C_{7a})

M.P.: 210-212 °C Lit M.P.: 214 °C[350]

IRν_{max} (KBr) cm^{-1}: 3336.1, 1591.3, 1526.4 (NO_2), 1338.1 (NO_2), 1021.4

HRMS: Found 287.9279 [M-H]$^-$, $C_7H_3INO_2$ requires 287.9275, (+1.4 ppm)

(3-Iodo-6-nitro-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (376)

As per general procedure A, (3-iodo-6-nitro-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (**376**) was obtained from 3-iodo-6-nitroindazole (578 mg, 2.0

mmol) and 3,4,5-trimethoxybenzoyl chloride (461 mg, 2.0 mmol) as a yellow solid (609 mg, 63%) following recrystallization from methanol.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.96 (s, 6H, 2 x OCH_3), 3.99 (s, 3H, OCH_3), 7.51 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 7.72 (d, 1H, ArH, J = 8.78 Hz, H_4), 8.34 (dd, 1H, ArH, J = 8.78, 1.51 Hz, H_5), 9.42 (d, 1H, ArH, J = 1.51 Hz, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 56.33 (2 x OCH_3), 61.03 (OCH_3), 101.92 (C_3), 109.41 ($C_{2'}$ & $C_{6'}$), 112.33 (C_7), 120.03 (C_5), 122.73 (C_4), 125.71 ($C_{1'}$), 133.32 (C_{3a}), 139.52 (C_{7a}), 142.74 ($C_{4'}$), 149.32 (C_7), 152.67 ($C_{3'}$ & $C_{5'}$), 165.74 (C=O)

M.P.: 183-185 °C

IRν_{max} (NaCl film) cm^{-1}: 3117.8, 2946.0, 2877.7, 2839.7, 1696.1 (C=O), 1587.4, 1530.6 (NO_2), 1507.1, 1454.4, 1364.3, 1337.8 (NO_2), 1242.2, 1205.8, 1150.3, 997.4

HRMS: Found 505.9836 $[M+Na]^+$, $C_{17}H_{14}IN_3NaO_6$ requires 505.9836, (+2.2 ppm)

General procedure U: Preparation of *N*-1 and *N*-2 MEM protected indazoles

To a stirred solution of sodium hydride (95mg, 2.37 mmol, 1.1 eq) in anhydrous THF (1 mL), a solution of (**372**) (621 mg, 2.15 mmol, 1.0 eq) in anhydrous DMF (6 mL) was added slowly. The resultant solution was stirred at 25 °C for 1 h. It was then cooled to 0 °C and 2-methoxyethoxymethyl chloride (268 mg, 2.15 mmol, 1.0 eq) was dropwise *via* a syringe. The resultant solution was warmed to 25 °C and stirred at this temperature for 2 hours. It was then poured into water/ice (25 mL) and then extracted with diethyl ether (3 x 25 mL). The organic layers were combined, washed once with DIW (25 mL), saturated brine solution (25 mL), dried using anhydrous sodium sulphate, filtered and concentrated to dryness *in vacuo*. The crude product was purified using flash column chromatography over silica gel (eluent EtOAc: Hexane gradient) yielding 1-((2-methoxyethoxy)methyl)-3-iodo-6-nitro-1*H*-indazole (410 mg, 51%) and 2-((2-methoxyethoxy)methyl)-3-iodo-6-nitro-2*H*-indazole (47 mg, 6%).

1-((2-Methoxyethoxy)methyl)-3-iodo-6-nitro-1*H*-indazole (381)

As per general procedure U, 1-((2-methoxyethoxy)methyl)-3-iodo-6-nitro-1*H*-indazole **(381)** was prepared from 3-iodo-6-nitroindazole (**372**) and 2-methoxyethoxymethyl chloride as a colourless solid (410 mg, 51%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.36 (s, 3H, OCH_3), 3.49 - 3.54 (m, 2H, $O\underline{CH_2}CH_2OCH_3$), 3.68 - 3.70 (m, 2H, CH_2, $OCH_2\underline{CH_2}OCH_3$), 5.89 (s, 2H, $N\underline{CH_2}$), 7.65 (d, 1H, ArH, J = 9.03 Hz, H_4), 8.13 (dd, 1H, ArH, J = 9.03, 1.51 Hz, H_5), 8.58 (d, 1H, ArH, J = 1.51 Hz, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 59.10 (OCH_2), 68.62 ($O\underline{CH_2}CH_2OCH_3$), 71.41 ($OCH_2\underline{CH_2}OCH_3$), 79.19 ($N\underline{C}H_2$), 93.27 ($C_q$, C_3), 106.84 (ArCH, C_7), 116.88 (ArCH, C_5), 122.74 (ArCH, C_4), 132.18 (C_q, C_{3a}), 139.04 (C_q, C_{7a}), 147.78 (C_q ,C_6)

M.P.: 167-169 °C[355]

IRν_{max} (NaCl): 3091.5, 3055.3, 2940.9, 2877.7, 2849.9, 2816.1, 1632.3, 1585.8, 1524.8 (NO_2), 1459.3, 1351.9, 1340.3 (NO_2), 1311.1, 1240.2, 1195.2, 1134.4, 1094.3

HRMS: Found 399.9764 $[M+Na]^+$, $C_{11}H_{12}IN_3NaO_4$ requires 399.9770, (-1.5 ppm)

2-((2-Methoxyethoxy)methyl)-3-iodo-6-nitro-2*H*-indazole (384)

As per general procedure U, 2-((2-methoxyethoxy)methyl)-3-iodo-6-nitro-2*H*-indazole (**384**) was prepared from 3-iodo-6-nitroindazole (**372**) and 2-methoxyethoxymethyl chloride as a colourless solid (47mg, 6%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.37 (s, 3H, OCH_3), 3.52 – 3.54 (m, 2H, $O\underline{CH_2}CH_2OCH_3$), 3.74 - 3.78 (m, 2H, $OCH_2\underline{CH_2}OCH_3$), 5.96 (s, 2H, $N\underline{CH_2}$), 7.59 (d, 1H, ArH, J = 9.54 Hz, H_4), 7.95 (dd, 1H, ArH, J = 9.54, 1.76 Hz, H_5), 8.72 (d, 1H, ArH, J = 1.76 Hz, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 59.08 ($O\underline{C}H_3$), 69.16 ($OCH_2\underline{C}H_2OCH_3$), 71.19 ($O\underline{C}H_2CH_2OCH_3$), 82.88 ($N\underline{C}H_2$), 116.54 (ArCH, C_7), 116.89 (ArCH, C_5), 122.60 (ArCH, C_4), 130.13 (C_q, C_{3a}), 147.43 (C_q, C_{7a}), 147.72 (C_q, C_6), C_3 not observed.

M.P.: 165-167 °C

IRν_{max} (NaCl film) cm^{-1}: 3064.8, 2949.9, 2870.7, 2841.8, 2806.3, 1632.3, 1585.8, 1522.4 (NO_2), 1484.2, 1449.7, 1381.8, 1343.9 (NO_2), 1301.9, 1236.8, 1201.0, 1173.9, 1096.8

HRMS: Found 399.9767 $[M+Na]^+$, $C_{11}H_{12}IN_3NaO_4$ requires 399.9770, (-0.8 ppm)

1-((2-Methoxyethoxy)methyl)-3-iodo-5-nitro-1*H*-indazole (387)

As per general procedure U, 1-((2-methoxyethoxy)methyl)-3-iodo-5-nitro-1*H*-indazole (**387**) was prepared from 3-iodo-5-nitroindazole (**373**) (767 mg, 2.7 mmol) and 2-methoxyethoxymethyl chloride (330 mg, 2.7 mmol) as a colourless solid (472 mg, 47%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.35 (s, 3H, OCH_3), 3.51 – 3.53 (m, 2H, $O\underline{CH_2}CH_2OCH_3$), 3.64 - 3.71 (m, 2H, $OCH_2\underline{CH_2}OCH_3$), 5.85 (s, 2H, NCH_2), 7.69 (d, 1H, ArH, J = 9.03 Hz, H_7), 8.37 (d, 1H, ArH, J = 9.54 Hz, H_6), 8.51 (s, 1H, H_4)

^{13}C NMR (101 MHz, $CDCl_3$) δ 59.06 (OCH_3), 68.63 ($OCH_2\underline{CH_2}OCH_3$), 71.32 ($O\underline{CH_2}CH_2OCH_3$), 79.17 ($NCH_2$), 95.82 ($C_q$, C_3), 110.65 (ArCH, C_7), 119.42 (ArCH, C_4), 123.02 (ArCH, C_6), 128.80 (C_q, C_{3a}), 142.31 (C_q, C_{7a}), 143.42 (C_q, C_5)

M.P.: 164-166 °C[355]

I.R.ν_{max} (NaCl film) cm^{-1}: 3097.3, 2929.0, 2888.7, 1614.1, 1586.4, 1520.9 (NO_2), 1483.9, 1449.2, 1395.5, 1339.5 (NO_2), 1299.6, 1269.8, 1188.6, 1080.2

HRMS: Found 399.9763 $[M+Na]^+$, $C_{11}H_{12}IN_3NaO_4$ requires 399.9770, (-1.8 ppm)

2-((2-Methoxyethoxy)methyl)-3-iodo-5-nitro-2*H*-indazole (388)

As per general procedure U, 2-((2-methoxyethoxy)methyl)-3-iodo-5-nitro-2*H*-indazole (**388**) was prepared from 3-iodo-5-nitroindazole (**373**) (767 mg, 2.7 mmol) and 2-methoxyethoxymethyl chloride (330 mg, 2.7 mmol) as a colourless solid (60 mg, 6%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.37 (s, 3H, OCH_3), 3.50 - 3.56 (m, 2H, CH_2), 3.75 - 3.79 (m, 2H, CH_2), 5.95 (s, 2H, CH_2), 7.78 (d, 1H, ArH, J = 9.54 Hz), 8.15 (dd, 1H, ArH, J=9.54, 2.51 Hz), 8.55 (d, 1H, ArH, J=1.51 Hz)

^{13}C NMR (100 MHz, $CDCl_3$) δ 59.10 (OCH_3), 69.26 ($OCH_2\underline{CH_2}OCH_3$), 71.22 ($O\underline{CH_2}CH_2OCH_3$), 82.81 ($NCH_2$), 119.73 (ArCH, C_7), 120.28 (ArCH, C_4), 121.68 (ArCH, C_6), 126.67 (C_q, C_{3a}), 144.00 (C_q, C_5), 150.56 (C_q, C_{7a}), C_3 not observed.

M.P.: 165-168°C

IRν_{max} (NaCl film) cm^{-1}: 3105.1, 2939.9, 2890.3, 2821.1, 1619.5, 1563.7, 1511.1 (NO_2), 1493.4, 1447.9, 1380.7, 1335.5 (NO_2), 1296.5, 1237.1, 1197.3, 1024.4

HRMS: Found 399.9756 $[M+Na]^+$, $C_{11}H_{12}IN_3NaO_4$ requires 399.9770, (-3.5 ppm)

General procedure V: Preparation of *N*-1 Boc protected indazoles

(**373**) (0.5 g, 1.73 mmol), di-*tert* butyl dicarbonate (567 mg, 2.60 mmol, 1.5 eq) and DMAP (21 mg, 0.18 mmol, 0.1 eq) in anhydrous THF (10 mL), cooled to 0°C, Et_3N (181 mg, 1.73 mmol, 1.0 eq) was added slowly via a syringe. The resultant solution was stirred at 0°C for 30 minutes and warm to 25°C and stirred at this temperature for 24 hours. DIW (10 mL) was added to quench the reaction and the aqueous layer was extracted with EtOAc (3 x 15 mL). The organic layers were combined and washed with 1M HCl (20 mL), a saturated brine solution (2 x 15 mL), dried using sodium sulphate, filtered and concentrated to dryness *in vacuo*. *tert*-Butyl 3-iodo-5-nitro-1H-indazole-1-carboxylate was afforded was a colourless solid (606 mg, 90%). No further purification was required.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.74 (s, 9H, C($\underline{CH_3}$)$_3$), 8.30 (d, 1H, ArH, *J*=10.04 Hz, H_7), 8.45 - 8.49 (m, 2H, ArH, H_4 & H_6)

^{13}C NMR (101 MHz, $CDCl_3$) δ 28.02 (C($\underline{C}H_3$)$_3$), 86.96 ($\underline{C}$(CH$_3$)$_3$), 102.91 (C_3), 115.37 (ArCH, C_7), 118.91 (ArCH, C_4), 124.65 (ArCH, C_6), 130.25 (C_{3a}), 142.11 (C_q, C_5), 144.57 (C_q, C_{7a}), 147.60 (OC=O)

M.P.: 161-163 °C[417]

IRν_{max} (NaCl film) cm^{-1}: 2998.0, 2935.7, 2838.2, 1745.0 (OC=O), 1607.5, 1588.7, 1528.5 (NO_2), 1474.7, 1438.0, 1406.8, 1382.1, 1346.9 (NO_2), 1298.7, 1255.8, 1159.7, 1150.8., 1038.5

HRMS: Found 411.9780 [M+Na]$^+$, $C_{12}H_{12}IN_3O_4$ requires 411.9770, (+2.4 ppm)

General procedure W: 3-Arylation of MEM-protected indazoles

To a solution of (**381**) (410 mg, 1.1 mmol, 1.0 eq) in anhydrous dimethoxyethane (6 mL), was added (1,1'-Bis(diphenylphosphino)ferrocene)palladium(II) dichloride (100 mg, 0.12 mmol, 0.1 eq), potassium carbonate (751 mg, 5.4 mmol, 5.0 eq) and the appropriate arylboronic acid (1.63 mmol, 1.5 eq). The resultant solution was refluxed under nitrogen 16 h. It was then cooled to room temperature and the reaction quenched with DIW (15 mL). The aqueous layer was extracted with chloroform (3 x 20 mL). The organic layers were combined, washed with brine (15 ml), dried using anhydrous sodium sulphate and concentrated to dryness *in vacuo*. The crude product was purified using flash column chromatography over silica gel (eluent EtOAc:

Hexane gradient) yielding 1-((2-methoxyethoxy)methyl)-3-aryl-6-nitro-1*H*-indazole as an orange solid.

1-((2-Methoxyethoxy)methyl)-3-(4-methoxyphenyl)-6-nitro-1*H*-indazole (385)

As per general procedure W, 1-((2-methoxyethoxy)methyl)-3-(4-methoxyphenyl)-6-nitro-1*H*-indazole (**385**) was prepared from (**381**) (410 mg, 1.1 mmol) and 4-methoxyphenylboronic acid (248 mg, 1.63 mmol) as an orange solid (206 mg, 53%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.37 (s, 3H, $CH_2O\underline{CH_3}$), 3.50 - 3.54 (m, 2H, $O\underline{CH_2}CH_2OCH_3$), 3.71 – 3.74 (m, 2H, $OCH_2\underline{CH_2}OCH_3$), 3.90 (s, 3H, OCH_3), 5.93 (s, 2H, $N\underline{CH_2}$), 7.07 (d, 2H, ArH, J = 8.53 Hz, $H_{3''}$ & $H_{5''}$), 7.88 (d, 2H, ArH, J = 8.53 Hz, $H_{2''}$ & $H_{6''}$), 8.04 - 8.14 (m, 2H, ArH, H_4 & H_5), 8.58 (s, 1H, ArH, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 55.37 ($CH_2O\underline{CH_3}$), 59.07 (OCH_3), 68.43 ($OCH_2\underline{CH_2}OCH_3$), 71.47 ($O\underline{CH_2}CH_2OCH_3$), 78.87 ($N\underline{CH_2}$), 106.71 (ArCH, C_7), 114.46 ($C_{3''}$ & $C_{5''}$), 116.28 (ArCH, C_5), 122.20 (ArCH, C_4), 124.46 (C_q, $C_{1''}$), 125.66 (C_q, C_{3a}), 128.83 (ArCH, $C_{2''}$ & $C_{6''}$), 140.06 (C_q, C_{7a}), 145.40 (C_q, C_3), 146.74 (C_q, C_6), 160.17 (C_q, $C_{4''}$)

M.P.: 171-173 °C

IRν_{max} (NaCl film) cm^{-1}: 3077.8, 2933.6, 2889.7, 2837.5, 1613.5, 1591.6, 1524.1 (NO_2), 1484.3, 1417.3, 1386.2, 1345.2 (NO_2), 1305.4, 1250.9, 1199.6, 1181.7, 1031.0

HRMS: Found 380.1206 $[M+Na]^+$, $C_{18}H_{19}N_3NaO_5$ requires 380.1222, (-4.2 ppm)

1-((2-Methoxyethoxy)methyl)-3-(3,4,5-trimethoxyphenyl)-6-nitro-1*H*-indazole (407)

Using the general procedure V, 1-((2-methoxyethoxy)methyl)-3-(3,4,5-trimethoxyphenyl)-6-nitro-1*H*-indazole (**407**) was prepared from (**381**) (410 mg, 1.1 mmol) and 3,4,5-trimethoxyphenylboronic acid (350 mg) as an orange solid (243 mg, 53%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.38 (s, 3H, OCH_3), 3.51 - 3.56 (m, 2H, CH_2), 3.73 (dd, 2H, J=5.49, 3.66 Hz, CH_2), 3.94 (s, 3H, OCH_3), 3.99 (s, 6H, 2 x OCH_3), 5.95 (s, 2H, CH_2), 7.14 (s, 2H, ArH), 8.06 - 8.10 (m, 1H, ArH), 8.11 - 8.15 (m, 1H, ArH), 8.61 (s, 1H, ArH)

^{13}C NMR (101 MHz, $CDCl_3$) δ 56.35 (2 x OCH_3), 59.10 (OCH_3), 60.99 (OCH_3), 68.52 (CH_2), 71.53 (CH_2), 79.03 (CH_2), 105.01 (ArCH), 106.90 (ArCH), 116.55 (ArCH), 122.04 (ArCH), 125.63 (C_q), 127.41 (C_q), 140.16 (C_q), 145.56 (C_q), 146.87 (C_q), 153.79 (C_q)

M.P.: 151-154 °C

IRν_{max} (NaCl film) cm^{-1}: 3047.3, 2921.0, 2898.7, 1624.1, 1589.1, 1521.8 (NO_2), 1473.9, 1429.2, 1395.5, 1334.1 (NO_2), 1279.1

HRMS: Found 418.1604 $[M+H]^+$, $C_{20}H_{24}N_3O_7$ requires 418.1614, (-2.4 ppm)

General procedure W: 1-((2-Methoxyethoxy)methyl)-3-(4-methoxyphenyl)-5-nitro-1*H*-indazole (389)

To a solution of 1-((2-methoxyethoxy)methyl)-3-iodo-5-nitro-1*H*-indazole (**387**) (429 mg, 1.14 mmol, 1.0 eq) in anhydrous dimethoxyethane (6 mL), was added (1,1'-Bis(diphenylphosphino)ferrocene)palladium(II) dichloride (103 mg, 0.13 mmol, 0.1 eq), potassium carbonate (787 mg, 5.9 mmol, 5.0 eq) and 4-methoxyphenyl boronic acid (260 mg, 1.71 mmol, 1.5 eq). The resultant solution was refluxed under nitrogen 16 hours. It was then cooled to room temperature and the reaction quenched with DIW (15 mL). The aqueous layer was extracted with chloroform (3 x 20 mL). The organic layers were combined, washed with brine (15 ml), dried using anhydrous sodium sulphate and concentrated to dryness *in vacuo*. The crude product was purified by flash column chromatography over silica gel (eluent Hex: EtOAc gradient) yielding the product (**389**) as an orange solid (261 mg, 64%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.36 (s, 3H, $CH_2O\underline{CH_3}$), 3.51 (dd, 2H, *J*=5.02, 4.02 Hz, $O\underline{CH_2}CH_2OCH_3$), 3.72 (dd, *J*=5.02, 4.02 Hz, $OCH_2\underline{CH_2}OCH_3$), 3.91 (s, 3H, OCH_4), 5.89 (s, 2H, $N\underline{CH_2}$), 7.09 (d, 2H, ArH, *J* = 8.53 Hz, $H_{3''}$ & $H_{5''}$), 7.69 (d, 1H, ArH, *J* = 9.03 Hz, H_6), 7.90 (d, 2H, ArH, *J* = 8.53 Hz, $H_{2''}$ & $H_{6''}$), 8.34 (d, 1H, ArH, *J* = 9.03 Hz, H_7), 8.95 (s, 1H, ArH, H_4)

^{13}C NMR (101 MHz, $CDCl_3$) δ 55.41 ($CH_2O\underline{CH_3}$), 59.05 (OCH_3), 68.46 ($OCH_2\underline{C}H_2OCH_3$), 71.40 ($O\underline{C}H_2CH_2OCH_3$), 78.87 ($NCH_2$), 110.32 (ArCH, C_7), 114.58 (ArCH, $C_{3''}$ & $C_{5''}$), 119.30 (ArCH, C_4), 121.94 (C_q, C_{3a}), 122.01 (C_q, C_6), 124.09 (C_q, $C_{1''}$), 128.92 ($C_{2''}$ & $C_{6''}$), 143.01 (ArCH, C_5), 143.06 (C_q, C_{7a}), 147.46 (C_q, C_3), 160.43 (C_q, $C_{4''}$)

M.P.: 175-179 °C

IRν_{max} (NaCl film) cm^{-1}: 3087.7, 2933.5, 2889.6, 2837.2, 1613.9, 1573.9, 1523.4 (NO_2), 1491.9, 1463.4, 1413.9, 1393.2, 1330.3 (NO_2), 1306.3, 1252.1, 1199.8, 1176.6, 1100.2, 1077.9, 1030.4

HRMS: Found 380.1234 $[M+Na]^+$, $C_{18}H_{19}N_3NaO_5$ requires 380.1222, (+3.2 ppm)

General Procedure X: 3-Arylation of *N*-1 Boc protected 3-iodo-5-nitroindazole

A solution of (**395**) (389 mg, 1 mmol), cesium carbonate (489 mg, 1.5 mmol, 1.5 eq), (1,1'-bis(diphenylphosphino)ferrocene)palladium(II) dichloride (90 mg, 0.11 mmol, 0.11 eq) and the necessary phenylboronic acid (1.5 mmol, 1.5 eq) in anhydrous THF (8 mL) were heated to 80°C for 4 hours under nitrogen. It was cooled to 25°C and DIW (15 ml) was added. The aqueous layer was extracted with chloroform (3 x 15 mL). The organic layers were combined, washed with a saturated brine solution (20 mL), dried using anhydrous sodium sulphate, filtered and concentrated to dryness *in vacuo*. The crude product was purified by flash column chromatography over silica gel (eluent EtOAc: Hex gradient).

***tert*-Butyl 3-(3,4,5-trimethoxyphenyl)-5-nitro-1*H*-indazole-1-carboxylate (396)**

As per general procedure X, *tert*-butyl 3-(3,4,5-trimethoxyphenyl)-5-nitro-1*H*-indazole-1-carboxylate (**396**) was prepared from (**395**) and 3,4,5-trimethoxyphenylboronic acid (318 mg, 1.5 mmol) as a yellow solid (180 mg, 42%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.77 (s, 9H, $C(\underline{CH_3})_3$), 3.95 (s, 3H, OCH_3), 3.99 (s, 6H, 2 x OCH_3), 7.16 (s, 2H, ArH, $H_{2''}$ & $H_{2''}$), 8.35 (d, 1H, ArH, J = 9.03, H_7), 8.46 (dd, 1H, ArH, J = 9.03, 2.01 Hz, H_6), 8.88 (d, 1H, ArH, J = 2.01 Hz, H_4)

^{13}C NMR (101 MHz, $CDCl_3$) δ 28.09 ($C(CH_3)_3$), 56.44 (2 x OCH_3), 61.02 (OCH_3), 86.43 ($\underline{C}(CH_3)_3$), 105.55 (ArCH, $C_{2''}$ & $C_{6''}$), 115.47 (ArCH, C_7), 118.30 (ArCH, C_4), 123.76 (ArCH, C_6), 123.99 (C_q, C_{3a}), 139.82 (C_q, $C_{1''}$), 143.29 (C_q, $C_{4''}$), 144.40 (C_q, C_5), 148.57 (C_q, C_3), 150.87 (C_{7a}), 153.83 (C_q, $C_{3''}$ & $C_{5''}$)

M.P.: 166-169 °C

IRν_{max} (NaCl film) cm^{-1}: 2912.5, 2887.5, 2775.4, 1740.7 (OC=O), 1580.8, 1527.9 (NO_2), 1494.0, 1466.6, 1386.8, 1339.6 (NO_2), 1293.7, 1238.7, 1153.0, 1128.1., 1060.5

HRMS: Found 452.1445 $[M+Na]^+$, $C_{21}H_{23}N_3NaO_7$ requires 452.1434, (+2.4 ppm)

***tert*-Butyl 3-(2,5-dimethoxyphenyl)-5-nitro-1*H*-indazole-1-carboxylate (397)**

As per general procedure X, *tert*-butyl 3-(2,5-dimethoxyphenyl)-5-nitro-1*H*-indazole-1-carboxylate (**397**) was prepared from (**395**) and 3,4,5-trimethoxyphenyl boronic acid (273 mg, 1.5 mmol) as a colourless solid (160 mg, 35%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.77 (s, 9H, C($\underline{CH_3}$)$_3$), 3.82 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 7.01 - 7.09 (m, 2H, ArH, $H_{4''}$ & $H_{5''}$), 7.26 - 7.29 (m, 1H, ArH, $H_{2''}$), 8.31 (d, 1H, ArH, J = 9.03 Hz, H_7), 8.41 (dd, 1H, ArH, J = 9.03, 2.01 Hz, H_6), 8.69 (d, 1H, ArH, J = 2.01 Hz, H_4)

^{13}C NMR (101 MHz, $CDCl_3$) δ 28.09 (C($\underline{C}H_3$)$_3$), 55.93 (OCH_3), 56.04 (OCH_3), 86.01 ($\underline{C}$(CH$_3$)$_3$), 112.65 ($C_{2''}$), 114.98 (C_7), 116.47 (ArCH, $C_{4''}$), 116.99 (C_q, $C_{5''}$), 120.06 (ArCH, C_4), 123.32 (C_6), 125.31 (C_q, C_3), 142.82 (C_q, C_5), 143.89 (C_{3a}), 148.67 (C_q, C_{7a}), 149.93 (OC=O), 151.59 (ArCH, $C_{6''}$), 153.79 (ArCH, $C_{3''}$), $C_{1''}$ not observed

M.P.: 188-191 °C

IRν_{max} (NaCl film) cm^{-1}: 2982.2, 29427.2, 2835.6, 1730.2 (OC=O), 1614.6, 1523.4 (NO_2), 1487.4, 1469.2, 1423.6, 1386.9, 1331.9 (NO_2), 1283.8, 1267.3, 1245.9, 1225.4, 1152.5, 1120.4., 1053.9

HRMS: Found 422.1328 [M+Na]$^+$, $C_{20}H_{21}N_3NaO_9$ requires 422.1328, (0.0 ppm)

General procedure Y: Removal of MEM protecting group

To a solution of 3-aryl *N*-1 MEM protected indazole (0.5 mmol) in MeOH (4 mL), was added 6N HCl (4 mL). The resultant solution was heated to 75 °C for 6 hours, cooled to 25 °C and stirred overnight. The precipitate was collected by vaccum filtration and air dried which afforded the desired *N*-1 deprotected 3-aryl indazole. No further purification was required.

3-(4-Methoxyphenyl)-6-nitro-1*H*-indazole (380)

As per general procedure Y, 3-(4-methoxyphenyl)-6-nitro-1*H*-indazole (**380**) was afforded from (**385**) (180 mg, 0.5 mmol) as an orange solid (75 mg, 55%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.83 (s, 3H, OCH_3), 7.11 (d, 2H, ArH, J=8.53 Hz, $H_{3''}$ & $H_{5''}$), 7.87 - 8.00 (m, 3H, H_4, ArH, $H_{2''}$ & $H_{4''}$), 8.24 (d, 1H, ArH, J = 9.03 Hz, H_5), 8.45 (s, 1H, ArH, H_7), 13.81 (br. s., 1H, NH)

^{13}C NMR (101 MHz, DMSO-d_6) δ 55.25 (OCH_3), 107.24 (ArCH, C_7), 114.50 (ArCH, $C_{3''}$ & $C_{5''}$), 115.10 (ArCH, C_5), 122.05 (ArCH, C_4), 122.92 (C_q, $C_{1''}$), 124.98 (C_q, C_{3a}), 128.29 (ArCH, $C_{2''}$ & $C_{6''}$), 140.14 (C_q, C_3), 143.98 (C_q, C_{7a}), 145.76 (C_q, C_6), 159.43 (C_q, $C_{4''}$)

M.P.: 175-178 °C

IRν_{max} (NaCl film) cm^{-1}: 2934.6, 2889.6, 2811.3, 1623.7, 1573.9, 1526.1 (NO_2), 1492.7, 1453.1, 1423.5, 1383.1, 1331.8 (NO_2)

HRMS: Found 268.0734 $[M+H]^+$, $C_{14}H_{10}N_3O_3$ requires 268.0728, (+2.2 ppm)

3-(4-Methoxyphenyl)-5-nitro-1*H*-indazole (390)

As per general procedure Y, 3-(4-methoxyphenyl)-5-nitro-1*H*-indazole (**390**) was afforded from (**389**) (261 mg, 0.73 mmol) as an orange solid (125 mg, 63%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.84 (s, 3H, OCH_3), 7.13 (d, 2H, ArH, J=8.53 Hz, $H_{3''}$ & $H_{5''}$), 7.75 (d, 1H, ArH, J = 9.03 Hz, H_7), 7.93 (d, 2H, ArH, J = 8.53 Hz, $H_{2''}$ & $H_{6''}$), 8.22 (dd, 1H, ArH, J = 9.03, 1.51 Hz, H_6), 8.85 (s, 1H, ArH, H_4), NH not observed

^{13}C NMR (101 MHz, DMSO-d_6) δ 55.27 (OCH_3), 111.53 (ArCH, C_7), 114.64 (ArCH, $C_{3''}$ & $C_{5''}$), 118.68 (ArCH, C_4), 119.10 (ArCH, C_6), 121.08 (ArCH, $C_{2''}$ & $C_{6''}$), 124.64 (C_{3a}), 128.49 (ArCH, C_4), 141.85 (C_q, C_5), 143.45 (C_q, C_3), 146.30 (C_q, C_{7a}), 159.69 (C_q, $C_{4''}$)

M.P.: 181-184 °C

IRν_{max} (NaCl film) cm^{-1}: 3170.4, 3122.7, 2973.2, 1630.7, 1526.0, 1515.1 (NO_2), 1482.9, 1422.5, 1342.5 (NO_2)

HRMS: Found 270.0885 $[M+H]^+$, $C_{14}H_{12}N_3O_3$ requires 270.0879, (+2.2 ppm)

3-(3,4,5-Trimethoxyphenyl)-6-nitro-1*H*-indazole (405)

As per general procedure Y, 3-(3,4,5-trimethoxyphenyl)-6-nitro-1*H*-indazole (**405**) was afforded from (**404**) as an orange solid (125 mg, 63%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.74 (s, 3H, OCH_3), 3.91 (s, 6H, 2 x OCH_3), 7.19 (s, 2H, ArH), 7.97 (dd, 1H, ArH, J = 9.16, 1.83 Hz), 8.30 (d, 1H, ArH, J = 9.16 Hz), 8.47 (d, 1H, ArH, J = 1.83 Hz), 13.67 (s, 1H, NH)

^{13}C NMR (101 MHz, DMSO-d_6) δ 55.98 (2 x OCH_3), 60.11 (OCH_3), 104.34 (ArCH), 107.26 (ArCH), 115.25 (ArCH), 122.19 (ArCH), 122.94 (C_q), 128.01 (C_q), 137.80 (C_q), 145.78 (C_q), 153.35 (C_q)

M.P.: 191-194 °C

IRν_{max} (NaCl film) cm^{-1}: 3177.4, 3124.5, 2973.2, 1629.3, 1536.0, 1517.3 (NO_2), 1482.9, 1428.9, 1344.9 (NO_2)

HRMS: Found 328.0943 $[M-H]^-$, $C_{16}H_{15}N_3O_5$ requires 328.0934, (+3.4 ppm)

General procedure Z: Deprotection of *t*-Boc *N*-1 protected 3-arylated 5-nitroindazoles

To a solution of 3-arylated indazole (0.42 mmol) in EtOAc (3 mL), cooled first to 0 °C, a solution of 12 M HCl:EtOAc (3:3 mL) was added slowly. The resultant solution was warmed to 25°C and stirred at this temperature for 5 hours. EtOAc (10 mL) was then added and the organic layer was washed with a saturated sodium bicarbonate solution (5 x 10 mL). The organic was washed with a saturated brine solution (10 mL), dried using anhydrous sodium sulphate, filtered and concentrated to dryness *in vacuo*. No further purification was required.

3-(3,4,5-Trimethoxyphenyl)-5-nitro-1*H*-indazole (398)

As per general procedure Z, 3-(3,4,5-trimethoxyphenyl)-5-nitro-1*H*-indazole (**398**) was prepared from (**396**) as a yellow solid (130 mg, 94%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.75 (s, 3H, OCH_3), 3.90 (s, 6H, 2 x OCH_3), 7.20 (s, 2H, ArH, $H_{2''}$ & $H_{6''}$), 7.77 (d, 1H, ArH, J = 9.03 Hz, H_7), 8.23 (dd, 1H, ArH, J=9.03, 1.51 Hz, H_6), 8.87 (d, 1H, ArH, J = 1.51 Hz, H_4), 13.86 (br. s., 1H, NH)

^{13}C NMR (101 MHz, DMSO-d_6) δ 56.08 (2 x OCH_3), 60.17 (OCH_3), 104.64 (ArCH, $C_{2''}$ & $C_{6''}$), 111.50 (ArCH, C_7), 118.79 (ArCH, C_4), 119.23 (C_q, C_{3a}), 121.16 (ArCH, C_6), 127.72 ($C_{1''}$), 138.10 (C_q, $C_{4''}$), 141.99 (C_q, C_5), 143.39 (C_q, C_{3a}), 145.58 (C_q, C_{7a}), 153.45 (C_q, $C_{3''}$ & $C_{5''}$)

M.P.: 195-200 °C

IRν_{max} (NaCl film) cm^{-1}: 3087.5, 3009.8, 2969.3, 2834.1, 1620.8, 1592.9, 1575.3, 1531.7 (NO_2), 1480.8, 1408.3, 1337.7 (NO_2), 1266.6, 1234.7, 1184.9, 1136.8., 1025.8

HRMS: Found 352.0922 $[M+Na]^+$, $C_{16}H_{15}N_3NaO_5$ requires 352.0909, (+3.7 ppm)

3-(2,5-Dimethoxyphenyl)-5-nitro-*1H*-indazole (399)

As per general procedure Z, 3-(2,5-dimethoxyphenyl)-5-nitro-1*H*-indazole (**399**) was prepared from (**397**) (168 mg) as a yellow solid (90 mg, 72%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.77 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 7.06 (dd, 1H, ArH, J = 8.00, 1.50 Hz, $H_{4''}$), 7.15 - 7.20 (m, 2H, ArH, $H_{2''}$ & $H_{5''}$), 7.74 (d, 1H, ArH, J = 9.03 Hz, H_7), 8.20 (dd, 1H, ArH, J = 9.03, 2.01 Hz, H_6), 8.63 (d, 1H, ArH, J=2.01 Hz, H_4), 13.82 (br. s., 1H, NH)

^{13}C NMR (101 MHz, DMSO-d_6) δ 55.55 (OCH_3), 55.92 (OCH_3), 111.30 (C_q), 113.30 (ArCH), 115.42 (ArCH), 115.86 (ArCH), 119.95 (ArCH), 120.76 (ArCH), 141.32 (C_5), 142.99 (C_{3a}), 145.09 (C_{7a}) 150.74 ($C_{6''}$), 153.28 ($C_{3''}$)

M.P.: 190-192 °C

IRν_{max} (NaCl film) cm^{-1}: 3568.33 (NH), 3187.5, 3124.5, 2953.2, 1624.3, 1537.0, 1518.3 (NO_2), 1481.9, 1422.9, 1344.9 (NO_2), 1308.1, 1272.9, 1229.0, 1107.3, 1062.3, 1049.3, 1024.1

HRMS: Found 322.0819 $[M+Na]^+$, $C_{16}H_{15}N_3NaO_5$ requires 322.0804, (+4.7 ppm)

(3,4,5-Trimethoxyphenyl)(3-(4-methoxyphenyl)-6-nitro-1*H*-indazol-1-yl)methanone (375)

Using the general procedure B, 3,4,5-trimethoxyphenyl)(3-(4-methoxyphenyl)-6-nitro-1*H*-indazol-1-yl)methanone (**375**) was prepared from (**380**) (60 mg, 0.22 mmol) and 3,4,5-trimethoxybenzoyl chloride (52 mg, 0.22 mmol) as a yellow solid (26 mg, 25%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (s, 3H, OCH_3), 3.97 (s, 6H, 2 x OCH_3), 4.00 (s, 3H, OCH_3), 7.10 (d, 2H, ArH, J = 8.53 Hz, $H_{3''}$ & $H_{5''}$), 7.64 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 7.93 (d, 2H, ArH, J = 8.53 Hz, $H_{2''}$ & $H_{6''}$), 8.17 (d, 1H, ArH, J = 8.53 Hz, H_4), 8.33 (dd, 1H, ArH, J = 8.53, 1.51 Hz, H_5), 9.52 (d, 1H, ArH, J=1.51 Hz, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 55.45 (OCH_3), 56.31 (2xOCH_3), 61.01 (OCH_3), 109.49 ($C_{2'}$ & $C_{6'}$), 112.59 (C_7), 114.69 ($C_{3''}$ & $C_{5''}$), 119.72 (C_5), 122.03 (C_4), 123.10 ($C_{1'}$), 126.67 ($C_{1''}$), 127.63 (s), 129.30 ($C_{2''}$ & $C_{6''}$), 141.17 (C_{3a}), 142.36 (C_{7a}), 148.35 ($C_{4'}$), 149.50 (C_6), 152.56 ($C_{3'}$ & $C_{5'}$), 161.17 ($C_{4''}$), 166.58 (C=O)

M.P.: 181-184 °C

IRν_{max} (NaCl film) cm^{-1}: 2998.0, 2935.7, 2838.2, 1690.0 (NC=O), 1613.9, 1585.7, 1527.2 (NO_2), 1507.9, 1487.7, 1417.7, 1380.6, 1343.0 (NO_2), 1298.5, 1254.9, 1178.8, 1133.1, 1030.9

HRMS: Found 268.0734 $[M-H]^-$, $C_{14}H_{10}N_3O_3$ requires 268.0728, (+2.2 ppm)

(3,4,5-Trimethoxyphenyl)(3-(3,4,5-trimethoxyphenyl)-6-nitro-1*H*-indazol-1-yl)methanone (406)

Using the general procedure B, (3,4,5-trimethoxyphenyl)(3-(3,4,5-trimethoxyphenyl)-6-nitro-1*H*-indazol-1-yl)methanone (**406**) was prepared from (**405**) (60 mg, 0.22 mmol) and 3,4,5-trimethoxybenzoyl chloride (52 mg, 0.22 mmol) as a yellow solid (26 mg, 25%).

^1H NMR (400 MHz, $CDCl_3$) δ 3.95 - 3.98 (m, 15H, 5 x OCH_3), 3.99 (s, 3H, OCH_3), 7.17 (s, 2H, ArH), 7.65 (s, 2H, ArH), 8.15 (d, 1H, ArH, J = 9.16 Hz), 8.34 (dd, 1H, ArH, J = 9.16, 1.83 Hz), 9.52 (d, 1H, ArH, J = 1.83 Hz)

^{13}C NMR (101 MHz, $CDCl_3$) δ 56.32 (2 x OCH_3), 56.39 (2 x OCH_3), 61.04 (2 x OCH_3), 105.49 (ArCH), 109.65 (ArCH), 112.72 (ArCH), 119.88 (ArCH), 121.87 (ArCH), 126.01 (C_q), 126.49 (C_q), 127.52 (C_q), 140.08 (C_q), 141.26 (C_q), 142.60 (C_q), 148.47 (C_q), 149.74 (C_q), 152.62 (C_q), 153.92 (C_q), 166.50 (C=O)

M.P.: 212-214 °C

IRν_{max} (NaCl film) cm^{-1}: 2988.8, 2925.75, 2848.2, 1695.3 (NC=O), 1613.9, 1575.9, 1525.2 (NO_2), 1517.9, 1477.8, 1414.8, 1381.4, 1341.5 (NO_2), 1297.5,

HRMS: Found 546.1477 $[M+H]^+$, $C_{26}H_{25}N_3O_9$ requires 546.1488, (-2.0 ppm)

(3,4,5-Trimethoxyphenyl)(3-(3,4,5-trimethoxyphenyl)-5-nitro-1*H*-indazol-1-yl)methanone (400)

As per general procedure B, (3,4,5-trimethoxyphenyl)(3-(3,4,5-trimethoxyphenyl)-5-nitro-1*H*-indazol-1-yl)methanone (**400**) was prepared from (**398**) (0.33 mmol) and 3,4,5-trimethoxybenzoyl chloride (77 mg, 0.33 mmol) as a yellow solid (37 mg, 21%)

^1H NMR (400 MHz, $CDCl_3$) δ 3.94 - 4.01 (m, 18H, 6 x OCH_3), 7.17 (s, 2H, ArH, $H_{2''}$ & $H_{6''}$), 7.63 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 8..55 (dd, 1H, ArH, J = 9.54, 2.01 Hz, H_6), 8.76 (d, 1H, ArH, J = 9.54 Hz, H_7), 8.96 (s, 1H, H_4)

^{13}C NMR (101 MHz, $CDCl_3$) δ 56.29 (2 x OCH_3), 56.37 (2 x OCH_3), 61.04 (2 x OCH_3), 105.33 (ArCH, $C_{2''}$ & $C_{6''}$), 109.54 (ArCH, $C_{2'}$ & $C_{6'}$), 116.90 (ArCH, C_7), 118.03 (ArCH, C_4), 123.71 (C_{3a}), 124.12 (ArCH, C_6), 124.34 ($C_{1'}$), 126.50 ($C_{4''}$), 142.55 (C_5), 144.31 (C_3), 145.05 ($C_{4'}$), 150.88 (C_{7a}), 152.59 ($C_{3'}$ & $C_{5'}$), 153.94 ($C_{3''}$ & $C_{5''}$), 166.81 (C=O)

M.P.: 243-245 °C

IRν_{max} (NaCl film) cm^{-1}: 3093.4, 2925.8, 2857.3, 1692.7 (C=O), 1585.2, 1530.4 (NO_2), 1494.6, 1470.9, 1418.89, 1382.8, 1342.7 (NO_2), 1247.2, 1135.9

HRMS: Found 546.1484 $[M+Na]^+$, $C_{26}H_{25}N_3NaO_9$ requires 546.1488, (-0.8 ppm)

(3,4,5-Trimethoxyphenyl)(3-(2,5-dimethoxyphenyl)-5-nitro-1*H*-indazol-1-yl)methanone (401)

As per general procedure B, (3,4,5-trimethoxyphenyl)(3-(2,5-dimethoxyphenyl)-5-nitro-1*H*-indazol-1-yl)methanone (401) was prepared from (**399**) (99 mg, 0.33 mmol) and 3,4,5-trimethoxybenzoyl chloride (77 mg, 0.33 mmol) as a yellow solid (50 mg, 30%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.95 (s, 6H, 2 x OCH_3), 3.97 (s, 3H, OCH_3), 7.07 (s, 2H, ArH), 7.20 (s, 1H, ArH), 7.60 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 8.479 (dd, 1H, ArH, J = 9.54, 1.50 Hz, H_6), 8.70 (d, 1H, ArH, J = 9.54 Hz, H_7), 8.75 (s, 1H, ArH, H_4)

^{13}C NMR (101 MHz, $CDCl_3$) δ 55.84 (OCH_3), 56.00 (OCH_3), 56.29 (2 x OCH_3), 60.97 (OCH_3), 109.47 ($C_{2'}$ & $C_{6'}$), 112.72 ($C_{2''}$), 116.35 (C_7), 116.54 ($C_{4''}$), 116.67 ($C_{5''}$), 119.81 (C_4), 119.91 ($C_{1''}$), 123.90 (C_6), 125.53 (C_{3a}), 126.69 ($C_{1'}$), 142.39 (C_5), 143.73 (C_{3a}), 144.57 (C_4), 150.11 (C_{7a}), 151.66 ($C_{6''}$), 152.56 ($C_{3'}$ & $C_{5'}$), 153.78 ($C_{3''}$), 166.90 (C=O)

M.P.: 134-137 °C

IRν_{max} (NaCl film) cm^{-1}: 3075.4, 2923.2, 2787.5, 1675.5 (C=O), 1612.4, 1581.7, 1525.7 (NO_2), 1508.0, 1485.5, 1415.2, 1378.0, 1341.5 (NO_2), 1271.8, 1228.3, 1136.2, 1120.9, 1052.7

HRMS: Found 494.1548 $[M+H]^+$, $C_{25}H_{24}N_3O_8$ requires 494.1563, (-3.0 ppm)

(6-Amino-3-(4-methoxyphenyl)-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (392)

As per general procedure C, 6-amino-3-(4-methoxyphenyl)-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (**392**) was prepared from (**375**) (200 mg, 0.43 mmol) and obtained as a brown solid (175 mg, 94%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.79 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.86 (s, 6H, 2 x OCH_3), 5.96 (s, 2H, NH_2), 6.80 (dd, 1H, ArH, *J*=8.54, 1.83 Hz), 7.11 (d, 2H, *J* = 8.54 Hz), 7.49 (s, 2H, ArH), 7.67 (d, 1H, ArH, *J* = 1.83 Hz), 7.77 (d, 1H, ArH, *J*=9.16 Hz, 1 H), 7.90 (d, 2H, *J* = 8.54 Hz)

^{13}C NMR (101 MHz, DMSO-d_6) δ 55.25 (OCH_3), 56.08 (2 x OCH_3), 60.18 (2 x OCH_3), 97.54 (ArCH), 108.83 (ArCH), 114.24 (C_q), 114.46 (ArCH), 114.46 (s), 122.00 (ArCH), 124.14 (C_q), 128.53 (C_q), 128.93 (ArCH), 140.72 (C_q), 143.56 (C_q), 149.05 (C_q), 151.19 (C_q), 152.03 (C_q), 160.18 (C_q), 166.56 (C=O)

M.P.: 203-205 °C

IRν_{max} (NaCl film) cm^{-1}: 3451.8 (NH_2), 3352.4 (NH_2), 2921.5, 2842.9, 1671.4 (C=O), 1621.8, 1525.6, 1481.3, 1448.7, 1444.9, 1366.8

HRMS: Found 434.1734 $[M+H]^+$, $C_{24}H_{14}N_3O_5$ requires 434.1716, (+2.2 ppm)

(6-Amino-3-(3,4,5-trimethoxyphenyl)-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (407)

As per general procedure C, (5-amino-3-(3,4,5-trimethoxyphenyl)-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (**407**) was prepared from (**406**) (155 mg, 0.30 mmol) as a brown solid (130 mg, 89%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.73 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.85 – 3.87 (m, 6H, 2 x OCH_3), 5.98 (s, 2H, NH_2), 6.82 (dd, 1H, ArH, *J*=8.54, 1.83 Hz), 7.15 (s, 2H, ArH), 7.55 (s, 2H, ArH), 7.67 (d, 1H, ArH, *J* = 1.83 Hz), 7.80 (d, 1H, ArH, *J* = 8.54 Hz)

^{13}C NMR (101 MHz, DMSO-d_6) δ 55.89 (2 x OCH_3), 56.07 (2 x OCH_3), 60.13 (OCH_3), 60.20 (OCH_3), 97.48 (ArCH), 104.98 (ArCH), 109.03 (ArCH), 114.25 (C_q), 114.66 (ArCH), 122.09 (ArCH), 127.18 (C_q), 128.23 (C_q), 140.90 (C_q), 143.64 (C_q), 149.58 (C_q), 151.35 (C_q), 152.07 (C_q), 153.23 (C_q), 166.43 (C=O)

M.P.: 201-203 °C

IRν_{max} (NaCl film) cm^{-1}: 3453.2 (NH_2), 3355.9 (NH_2), 2922.8, 2844.9, 1675.8 (C=O), 1626.8, 1588.2, 1515.2, 1489.5, 1468.7, 1424.9, 1377.6, 1277.8

HRMS: Found 494.1939 $[M+H]^+$, $C_{26}H_{28}N_3O_7$ requires 494.1927, (+2.4 ppm)

(5-Amino-3-(2,5-dimethoxyphenyl)-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (403)

As per general procedure C, (5-amino-3-(2,5-dimethoxyphenyl)-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (**403**) was prepared (**401**) (130 mg) as brown solid (40 mg, 33%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.70 - 3.78 (m, 9H, 3 x OCH_3), 3.85 (s, 6H, 2 x OCH_3), 5.33 (br. s., 2H, NH_2), 6.73 (s, 1H, ArH, H_4), 6.98 (d, 1H, ArH, J = 8.53 Hz, H_6), 7.05 - 7.12 (m, 2 H, ArH), 7.13 - 7.19 (m, 1H, ArH), 7.47 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 8.14 (d, 1H, ArH, J = 8.53 Hz, H_7)

^{13}C NMR (101 MHz, DMSO-d_6) δ 55.55 (OCH_3), 56.09 (2 x OCH_3), 56.20 (OCH_3), 60.22 (OCH_3), 102.76 (ArCH, C_4), 108.87 (ArCH, $C_{2'}$ & $C_{6'}$), 113.37 (ArCH, $C_{2''}$), 115.61 (ArCH, C_7), 115.93 (ArCH, $C_{4''}$), 116.23 ($C_{5''}$), 118.71 (C_6), 121.07 ($C_{1''}$), 127.02 ($C_{1'}$), 128.21 (C_{3a}), 132.85 (C_{7a}), 140.75 (C_5), 146.64 (C_3), 148.40 ($C_{4'}$), 151.59 ($C_{6''}$), 152.11 ($C_{3'}$ & $C_{5'}$), 153.11 ($C_{3''}$), 166.00 (C=O)

M.P.: 137-139 °C

IRν_{max} (NaCl film) cm^{-1}: 3453.2 (NH_2), 3368.46 (NH_2), 2938.4, 2835.2, 1670.5 (C=O), 1626.2, 1582.2, 1505.2, 1482.5, 1461.7, 1414.9, 1385.2, 1267.3, 1238.9, 1222.4, 1181.5, 1126.5, 1103.4, 1044.8

HRMS: Found 464.1814 $[M+H]^+$, $C_{25}H_{26}N_3O_6$ requires 464.1822, (-1.7 ppm)

(5-Amino-3-(3,4,5-trimethoxyphenyl)-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (402)

As per general procedure C, (5-amino-3-(3,4,5-trimethoxyphenyl)-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (**402**) was prepared from (**400**) (136 mg) as a brown solid (126 mg, 92%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.75 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.88 (s, 12H, 4 x OCH_3), 5.45 (br. s., 2H, NH_2), 7.03 (d, 1H, ArH, J = 9.16 Hz, H_6), 7.13 - 7.27 (m, 3H, ArH, $H_{4'}$, $H_{2''}$ & $H_{6''}$), 7.56 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 8.21 (d, 1H, ArH, J = 9.16 Hz)

^{13}C NMR (101 MHz, DMSO-d_6) δ 55.95 (2 x OCH_3), 56.07 (x OCH_3), 60.16 (OCH_3), 60.20 (OCH_3), 102.03 (ArCH, C_4), 105.01 (ArCH, $C_{2''}$ & $C_{6''}$), 109.05 (ArCH, $C_{2'}$ & $C_{6'}$), 116.14 (ArCH, C_7), 118.76 (ArCH, C_4), 125.21 (C_q, C_{3a}), 127.09 (C_q, $C_{1'}$), 127.86 (C_q, $C_{1''}$), 133.75 (C_q, C_{7a}), 138.61 (C_q, $C_{4''}$), 147.17 (C_q, C_5), 148.77 (C_q, $C_{4'}$), 152.10 (C_q, $C_{3'}$ & $C_{5'}$), 153.27 (C_q, $C_{3''}$ & $C_{5''}$), 165.62 (C=O)

M.P.: 189-191 °C

IRν_{max} (NaCl film) cm^{-1}: 3451.1 (NH_2), 3365.4 (NH_2), 2933.5, 2835.2, 1671.5 (C=O), 1626.2, 1586.3, 1511.2, 1422.5, 1462.7, 1411.5, 1385.2, 1255.8, 1237.9, 1223.4, 1182.1, 1124.6

HRMS: Found 494.1944 $[M+H]^+$, $C_{26}H_{28}N_3O_7$ requires 494.1927, (+3.4 ppm)

General Procedure AA: Benzylation of 3-iodo-6-nitroindazole (372)

To a solution of (**372**) (870 mg, 3.0 mmol. 1.0 eq) in anhydrous DMF (10 mL), was added Cs_2CO_3 (2.93 g, 9.0 mmol, 3.0 eq) and 5-(bromomethyl)-1,2,3-trimethoxybenzene (1.57 g, 6.0 mmol, 2 eq). The resultant solution was stirred at 25°C for 24 hours. EtOAc (30 mL) was added to the reaction mixture and the organic layer was washed with DIW (6 x 20 mL), a saturated brine solution (20 mL), dried using anhydrous sodium sulphate, filtered and concentrated to dryness *in vacuo*. The crude product was purified by flash column chromatography over-silica (eluent EtOAc: Hexane gradient) which afforded the N1 isomer 1-(3,4,5-trimethoxybenzyl)-3-iodo-6-nitro-1*H*-indazole (**408**) as a yellow solid (650 mg, 46%) and the N2 isomer 2-(3,4,5-trimethoxybenzyl)-3-iodo-6-nitro-2*H*-indazole (**409**) as a yellow solid (113 mg, 8%).

1-(3,4,5-Trimethoxybenzyl)-3-iodo-6-nitro-1*H*-indazole (408)

As per general procedure AA, 1-(3,4,5-trimethoxybenzyl)-3-iodo-6-nitro-1*H*-indazole (**408**) was prepared from (**372**) and 5-(bromomethyl)-1,2,3-trimethoxybenzene as yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 – 3.82 (m, 9H, 3 x OCH_3), 5.60 (s, 2H, CH_2), 6.53 (s, 2H, $H_{2'}$ & $H_{6'}$), 7.63 (d, 1H, J = 9.16 Hz, H_4), 8.07 (dd, 1H, J = 9.16, 1.53 Hz, H_5), 8.34 (d, 1H, J = 1.53 Hz, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 54.59 (CH_2), 56.26 (2 x OCH_3), 60.83 (OCH_3), 91.60 (C_q, C_3), 104.82 (ArCH, $C_{2'}$ & $C_{6'}$), 106.32 (ArCH, C_7), 116.21 (ArCH, C_5), 122.90 (ArCH, C_4), 130.56 (C_q, $C_{1'}$), 131.81 (C_q, C_{3a}), 138.20 (C_q, $C_{4'}$), 138.77 (C_q, C_{7a}), 147.45 (C_q, C_5), 153.68 (C_q, $C_{3'}$ & $C_{5'}$)

M.P.: 211-213 °C

IRν_{max} (NaCl film) cm^{-1}: 3009.8, 2955.3, 2832.1, 1621.9, 1582.1, 1570.3, 1532.7 (NO_2), 1479.8, 1418.3, 1335.7 (NO_2)

HRMS: Found 492.0039 $[M+Na]^+$, $C_{17}H_{16}INaN_3O_7$ requires 492.0032, (+1.4 ppm)

2-(3,4,5-Trimethoxybenzyl)-3-iodo-6-nitro-2*H*-indazole (409)

As per general procedure AA, 2-(3,4,5-trimethoxybenzyl)-3-iodo-6-nitro-2*H*-indazole (**409**) was prepared from (**372**) and 5-(bromomethyl)-1,2,3-trimethoxybenzene as yellow solid.

^1H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3H, OCH_3), 3.83 (s, 6H, 2 x OCH_3), 5.69 (s, 2H, CH_2), 6.63 (s, 2H, $H_{2'}$ & $H_{6'}$), 7.55 (d, 1H, J = 9.16 Hz, H_4), 7.94 (dd, 1H, J = 9.16, 1.53 Hz, H_5), 8.72 (s, 1H, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 56.19 (2 x OCH_3), 58.12 (CH_2), 60.81 (OCH_3), 105.34 (ArCH, $C_{2'}$ & $C_{6'}$), 116.14 (ArCH, C_7), 116.65 (ArCH, C_4), 122.23 (ArCH, C_4), 129.93 (C_q, C_3), 130.01 (C_q, C_{3a}), 138.23 (C_q, C_6), 147.54 (C_q, C_{7a}), 153.52 (C_q, $C_{3'}$ & $C_{5'}$), $C_{1'}$ not observed

M.P.: 201-204 °C

IRν_{max} (NaCl film) cm^{-1}: 3077.5, 3019.8, 2969.3, 2833.1, 1622.8, 1532.9, 1574.3, 1532.7 (NO_2), 1471.2, 1398.3, 1337.7 (NO_2), 1251.1

HRMS: Found 492.0044 $[M+Na]^+$, $C_{17}H_{16}INaN_3O_7$ requires 492.0032, (+2.4 ppm)

General procedure AB: 3-Arylation of (408)

To a solution of (**408**) (350 mg, 0.75 mmol), K_2CO_3 (520 mg, 3.76 mmol, 5 eq), appropriate phenylboronic acid (1.13 mmol, 1.5 eq) in anhydrous DME (5 mL), was added (1,1'-bis(diphenylphosphino)ferrocene)palladium(II) dichloride (68 mg, 83 μmol. 0.11 eq). The resultant solution was refluxed under nitrogen for 8 hours. It was then cooled to 20 °C and DIW (10 mL) was added. The aqueous layer was extracted with $CHCl_3$ (3 x 10 mL). The organic

layers were combined, washed with a saturated brine solution (10 mL), dried using anhydrous sodium sulphate, filtered and concentrated to dryness *in vacuo*. The crude product was purified using flash column chromatography over silica gel (eluent EtOAc: Hexane gradient)

1-(3,4,5-Trimethoxybenzyl)-3-(3,4-dimethoxyphenyl)-6-nitro-1*H*-indazole (412)

As per general procedure AB, 1-(3,4,5-trimethoxybenzyl)-3-(3,4-dimethoxyphenyl)-6-nitro-1*H*-indazole (**412**) was prepared from (**408**) and 3,4-dimethoxyphenyl boronic acid (205 mg, 1.13 mmol) as a yellow solid (200 mg, 56%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 - 3.83 (m, 9H, 3 x OCH_3), 3.98 (s, 3H, OCH_3), 4.01 (s, 3H, 2 x OCH_3), 5.64 (s, 2H, CH_2), 6.56 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 7.04 (d, 1H, ArH, J = 8.54 Hz, $H_{5''}$), 7.47 - 7.53 (m, 2H, ArH, $H_{2''}$ & $H_{6''}$), 8.05 (dd, 1H, ArH, J = 8.25, 2.00 Hz, H_5), 8.10 (d, 1H, ArH, J = 8.25 Hz, H_4), 8.34 (s, 1H, ArH, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 53.84, 56.00, 56.05, 56.19, 60.81, 104.62, 106.27, 110.55, 111.41, 115.70, 120.15, 122.32, 125.02, 125.05, 137.96, 139.72, 144.79, 146.47, 149.50, 149.70, 153.60

M.P.: 177-179 °C

IRν_{max} (NaCl film) cm^{-1}: 3054.2, 3032.1, 2857.8, 1597.9, 1527.9 (NO_2), 1496.9, 1452.6, 1422.7, 1341.9 (NO_2)

HRMS: Found 502.1590 $[M+Na]^+$, $C_{25}H_{25}NaN_3O_7$ requires 502.1590, (0.0 ppm)

5-(1-(3,4,5-Trimethoxybenzyl)-6-nitro-1*H*-indazol-3-yl)-2-methoxybenzaldehyde (413)

Using general procedure AB, 5-(1-(3,4,5-trimethoxybenzyl)-6-nitro-1*H*-indazol-3-yl)-2-methoxybenzaldehyde (**413**) was prepared from (**408**) and 3-formyl-4-methoxyphenylboronic acid (205 mg, 1.13 mmol) as a dark oil (240 mg, 67%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 9H, 3 x OCH_3), 4.04 (s, 3H, OCH_3), 5.63 (s, 2H, CH_2), 6.56 (s, 2H, $H_{2'}$ & $H_{6'}$), 7.19 (d, 1H, J = 9.16 Hz, $H_{5''}$), 8.05 - 8.09 (m, 1H, $H_{6''}$), 8.10 - 8.14 (m, 1H, $H_{4'}$), 8.20 (dd, 1H, J = 8.54, 2.44 Hz, H_5), 8.37 (s, 1H, $H_{2''}$), 8.43 (d, 1H, J = 2.44 Hz, H_7), 10.57 (s, 1H, HC=O)

^{13}C NMR (101 MHz, $CDCl_3$) δ 53.95 (CH_2), 55.96 (2 x OCH_3), 56.22 (OCH_3), 60.82 (OCH_3), 104.67 (ArCH, $C_{2'}$ & $C_{6'}$), 106.34 (ArCH, C_7), 112.52 (ArCH, C_5), 115.98 (ArCH, $C_{5''}$), 122.20

(ArCH, $C_{6''}$), 124.83 (C_q, $C_{1''}$), 125.05 (C_q, $C_{3''}$), 125.20 (C_q, C_{3a}), 127.19 (C_q, C_{3a}), 131.05 (C_q, $C_{1'}$), 134.70 (ArCH, $C_{2''}$), 138.02 (C_q, $C_{4'}$), 139.74 (C_q, C_{7a}), 143.47 (C_q, C_6), 146.54 (C_q, C_3), 153.64 (C_q, $C_{3'}$ & $C_{5'}$), 162.00 (C_q, $C_{4''}$), 189.32 (C=O)

M.P.: N/A

IRν_{max} (NaCl film) cm^{-1}: 3054.1, 3032.5, 2866.2, 1702.1 (HC=O), 1598.9, 1526.7 (NO_2), 1497.8, 1459.6, 1421.7, 1342.9 (NO_2)

HRMS: Found 500.1449 $[M+Na]^+$, $C_{25}H_{23}NaN_3O_7$ requires 500.1434, (+3.0 ppm)

6-Nitro-1-(3,4,5-trimethoxybenzyl)-3-(3,4,5-trimethoxyphenyl)-1*H*-indazole (411)

Using general procedure AB, 5-(1-(3,4,5-trimethoxybenzyl)-6-nitro-1*H*-indazol-3-yl)-2-methoxybenzaldehyde (**411**) was prepared from (**408**) and 3,4,5-trimethoxyphenylboronic acid (205 mg, 1.13 mmol) as a yellow solid (199 mg, 52%).

^1H NMR (400 MHz, $CDCl_3$) δ 3.80 - 3.83 (m, 9H, 3 x OCH_3), 3.94 (s, 3H, OCH_3), 3.99 (s, 6H, 2 x OCH_3), 5.66 (s, 2H, CH_2), 6.56 (s, 2H, ArH), 7.16 (s, 2H, ArH), 7.40 (d, 1H, J = 7.32 Hz, ArH), 8.08 (s, 1H), 8.36 (s, 1H, ArH)

^{13}C NMR (101 MHz, $CDCl_3$) δ 53.95 (CH_2), 56.21 (2 x OCH_3), 56.34 (2 x OCH_3), 60.82 (OCH_3), 60.98 (OCH_3), 104.66 (ArCH), 104.92 (ArCH), 106.41 (ArCH), 115.90 (ArCH), 122.17 (ARCH), 125.03 (C_q), 131.07 (C_q), 138.01 (C_q), 138.80 (C_q), 139.72 (C_q), 144.83 (C_q), 146.51 (C_q), 153.62 (C_q), 153.78 (C_q)

M.P.: 212-214 °C

IRν_{max} (NaCl film) cm^{-1}: 3050.5, 3033.5, 2856.2, 1595.9, 1525.9 (NO_2), 1490.6, 1451.6, 1425.8, 1341.7 (NO_2)

HRMS: Found 532.1702 $[M+Na]^+$, $C_{26}H_{27}NaN_3O_7$ requires 532.1696, (+1.1 ppm)

3-(2,3-Dimethoxyphenyl)-6-nitro-1-(3,4,5-trimethoxybenzyl)-1*H*-indazole (410)

Using general procedure AB, 3-(2,3-dimethoxyphenyl)-6-nitro-1-(3,4,5-trimethoxybenzyl)-1*H*-indazole (**410**) was prepared from (**408**) and 3,4,5-trimethoxyphenylboronic acid (205 mg, 1.13 mmol) as a yellow solid (176 mg, 49%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 6H, 2 x OCH_3), 3.82 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 5.68 (s, 2H, CH_2), 6.54 (s, 2H, ArH), 7.22 (app t, 1H, ArH, *J*=7.93 Hz), 7.28 - 7.31 (m, 1H, ArH), 7.41 (d, 1H, ArH, *J*=6.71 Hz), 7.97 - 8.02 (m, 1H, ArH), 8.02 - 8.06 (m, 1H, ArH), 8.36 (s, 1H, ArH)

^{13}C NMR (101 MHz, $CDCl_3$) δ 53.83 (CH_2), 55.97 (OCH_3), 56.13 (2 x OCH_3), 60.80 (OCH_3), 61.03 (OCH_3), 104.44 (ArCH), 105.91 (ArCH), 112.92 (ArCH), 115.32 (ArCH), 115.78 (ArCH), 122.63 (ArCH), 124.20 (C_q), 127.34 (C_q), 131.37 (C_q), 139.20 (C_q), 146.48 (C_q), 147.13 (C_q), 153.24 (C_q), 153.57 (C_q)

M.P.: 177-179 °C

IRν_{max} (NaCl film) cm^{-1}: 2935.1, 2833.7, 1591.9, 1520.1 (NO_2), 1504.1, 1453.2, 1423.7, 1342.1 (NO_2), 1221.1, 1122.8

HRMS: Found 502.1602 $[M+Na]^+$, $C_{25}H_{25}NaN_3O_7$ requires 502.1590, (+2.4 ppm)

General procedure AC: 3-Arylation of (409)

To a solution of 2-(3,4,5-trimethoxybenzyl)-3-iodo-6-nitro-2*H*-indazole (**409**) (400 mg, 0.85 mmol), K_2CO_3 (520 mg, 4.34 mmol, 5 eq), 3,4-dimethoxyphenylboronic acid (250 mg, 1.37 mmol, 1.5 eq) in anhydrous DME (7 mL), was added (1,1'-bis(diphenylphosphino)ferrocene)palladium(II) dichloride (80 mg, 98 μmol. 0.11 eq). The resultant solution was refluxed under nitrogen for 8 hours. It was then cooled to 25°C and DIW (12 mL) was added. The aqueous layer was extracted with $CHCl_3$ (3 x 15 mL). The organic layers were combined, washed with a saturated brine solution (10 mL), dried using anhydrous sodium sulphate, filtered and concentrated to dryness *in vacuo*. The crude product was purified using flash column chromatography which afforded 2-(3,4,5-trimethoxybenzyl)-3-(3,4-dimethoxyphenyl)-6-nitro-2*H*-indazole (**414**) as a yellow solid (229 mg, 56%).

2-(3,4,5-Trimethoxybenzyl)-3-(3,4-dimethoxyphenyl)-6-nitro-2*H*-indazole (414)

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 6H, 2 x OCH_3), 3.78 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 5.60 (s, 2H, CH_2), 6.38 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 6.85 (s, 1H, ArH, $H_{2''}$), 6.98 - 7.09 (m, 2H, ArH, $H_{5''}$ & $H_{6''}$), 7.66 (d, 1H, ArH, *J* = 8.55 Hz, H_5), 7.91 (d, 1H, ArH, *J* = 8.55 Hz, H_4), 8.77 (s, 1H, ArH, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 55.46 (CH_2), 55.97 (OCH_3), 56.09 (OCH_3), 56.13 (2 x OCH_3), 60.81 (OCH_3), 104.55 (ArCH, $C_{2'}$ & $C_{6'}$), 111.58 (ArCH, C_7), 112.72 (ArCH, $C_{2''}$), 115.36 (ArCH, C_5), 115.86 (ArCH, $C_{5''}$), 120.43 (C_q, $C_{1''}$), 121.87 (ArCH, $C_{6''}$), 122.78 (ArCH, C_4), 123.78 (C_q, C_{3a}), 131.39 (C_q, $C_{1'}$), 137.66 (C_q, $C_{4'}$), 137.88 (C_q, C_3), 145.84 (C_q, C_6), 147.14 (C_q, C_{7a}), 149.43 (C_q, $C_{3''}$), 150.34 (C_q, $C_{4''}$), 153.51 (C_q, $C_{3'}$ & $C_{5'}$)

M.P.: 195-198 °C

IRν_{max} (NaCl film) cm^{-1}: 2934.2, 2835.7, 1592.9, 1522.1 (NO_2), 1501.1, 1443.5, 1422.7, 1342.0 (NO_2)

HRMS: Found 502.1612 $[M+Na]^+$, $C_{25}H_{25}NaN_3O_7$ requires 502.1590, (+4.4 ppm)

1-(3,4,5-Trimethoxybenzyl)-3-(3,4,5-trimethoxyphenyl)-1*H*-indazol-6-amine (415)

As per general procedure C, 1-(3,4,5-trimethoxybenzyl)-3-(3,4,5-trimethoxyphenyl)-1*H*-indazol-6-amine (**415**) from (**411**) (150 mg, 0.29 mmol) as a dark oil (40 mg, 29%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.61 (s, 3H, OCH_3), 3.69 (s, 6H, 2 x OCH_3), 3.72 (s, 3H, OCH_3), 3.87 (s, 6H, 2 x OCH_3), 5.40 – 5.42 (m, 4H, CH_2, NH_2), 6.54 (s, 1H, ArH), 6.57 - 6.65 (m, 3H, ArH), 7.12 (s, 2H, ArH), 7.71 (d, 1H, ArH, J = 8.54 Hz)

^{13}C NMR (101 MHz, DMSO-d_6) δ 51.73 (CH_2), 55.84 (2 x OCH_3), 55.88 (2 x OCH_3), 59.95 (OCH_3), 60.09 (OCH_3), 90.10 (ArCH), 103.89 (ArCH), 104.66 (ArCH), 113.19 (ArCH), 113.42 (C_q), 121.38 (ArCH), 129.43 (C_q), 133.31 (C_q), 136.78 (C_q), 137.18 (C_q), 142.53 (C_q), 143.12 (C_q), 148.09 (C_q), 152.89 (C_q), 153.16 (C_q)

M.P.: N/A

IRν_{max} (NaCl film) cm^{-1}: 3452.8 (NH_2), 3359.1 (NH_2), 2945.1, 2824.1, 1625.1, 1587.4, 15112.2, 1425.5, 1462.5, 1412.4

HRMS: Found 480.2145 $[M+H]^+$, $C_{26}H_{30}N_3O_6$ requires 480.2135, (+2.1 ppm)

General procedure AD: Preparation of 2,5-dinitro-2*H*-indazole (425) and 2,6-dinitro-2*H*-indazole (426)

A suspension of 5-nitroindazole (**169**) or 6-nitroindazole (**170**) (1.74 g, 10.7 mmol) in acetic acid (15 mL) was poured in a solution of HNO_3 (3 mL) and Ac_3O (7 mL), which was cooled to -5°C, and stirred at this temperature for 2 minutes. It was poured onto ice and stirred for 30

minutes. The precipitate was collected by vacuum filtration and left to dry air. The crude product was purified by flash column chromatography over silica gel (eluent 2:1 CH_2Cl_2:Hexane) which afforded the desired di-nitro compound.

2,5-Dinitro-2*H*-indazole (425)

As per general procedure AD, 2,5-dinitro-2*H*-indazole (**425**) was prepared from (**169**) (1.74 g, 10.7 mmol) and obtained as a yellow solid (1.05 g, 47%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, 1H, ArH, J = 9.54, 1.00 Hz, H_6), 8.25 (d, 1H, ArH, J = 9.54 Hz, H_7), 8.79 (s, 1H, ArH, H_3), 9.16 (s, 1H, ArH, H_4)

^{13}C NMR (101 MHz, $CDCl_3$) δ 120.2 (ArCH, C_7), 121.5 (ArCH, C_4), 118.4 (C_q, C_{3a}), 123.7 (ArCH, C_6), 124.3 (ArCH, C_3). 144.5 (C_q, C_5), 145.8 (C_q, C_{7a})

M.P.: 150-151 °C [368, 369]

IRν_{max} (KBr) cm^{-1}: 3102.6, 1554.1, 1525.8 (NO_2) , 1512.3, 1336.3 (NO_2) , 1292.8, 1285.0, 1237.1, 1039.9, 1069.8, 945.9

HRMS: Found 207.0161 [M-H]$^-$, $C_7H_3N_4O_4$ requires 207.0155, (+2.9 ppm)

2,6-Dinitro-2*H*-indazole (426)

As per general procedure AD, 2,6-dinitro-2*H*-indazole (**425**) was prepared from (**170**) (1.74 g, 10.7 mmol) and obtained as a yellow solid (1.83 g, 83%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (dd, 1H, J = 9.56, 1.52 Hz, H_5), 8.06 (d, 1H, J = 9.56 Hz, H_4), 8.81 (s, 1H, H_3), 9.60 (s, 1H, H_4)

^{13}C NMR (101 MHz, DMSO-d_6) δ 116.75 (ArCH, C_7), 118.45 (ArCH, C_5), 121.01 (C_q, C_{3a}), 122.03 (ArCH, C_4), 124.74 (ArCH, C_3), 143.54 (C_q, C_{7a}), 149.10 (C_q, C_6)

M.P.: 155-157 °C[368, 369]

IRν_{max} (KBr) cm^{-1}: 3102.6, 1556.7, 1528.2 (NO_2), 1502.3, 1346.3 (NO_2), 1292.8, 1281.0, 1237.1, 1039.9, 1069.8, 945.9

HRMS: Found 207.0161 [M-H]$^-$, $C_7H_3N_4O_4$ requires 207.0155, (+2.9 ppm)

General Procedure AE: Preparation of N-substituted 3-aminoindazoles

To a solution of (**425**) or (**426**) (1.07g, 5.14mmol) in anhydrous THF (8 mL), which was cooled to 0 °C, the required amine (10.28 mmol) was added slowly *via* a syringe. The resultant solution was stirred for 2 h at 0 °C. The resultant precipitate was collected by vacuum filtration and re-crystallized in methanol. The THF filtrate was concentrated to dryness *in vacuo* and re-crystallized in methanol. These crystals were added to the re-crystallized precipitate affording the desired product.

4-(5-Nitro-1*H*-indazol-3-yl)morpholine (433)

As per general procedure AE, 4-(5-nitro-1*H*-indazol-3-yl)morpholine (**433**) was prepared from (**425**) (1.07g, 5.14 mmol) and morpholine (0.9 mL, 10.28 mmol) as an orange solid (730 mg, 57%) following recrystallization from methanol.

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.38 (br s, 4H, 2 x CH_2), 3.81 (br s, 4H, 2 x CH_2), 7.51 (d, 1H, ArH, J = 9.54 Hz, H_7), 8.13 (dd, 1H, ArH, J = 9.54, 1.51 Hz, H_6), 8.79 (s, 1H, ArH, H_4), 12.81 (s, 1H, NH)

^{13}C NMR (101 MHz, DMSO-d_6) δ 49.25 (2 x CH_2,), 65.91 (2 x CH_2), 110.74 (ArCH, H_7), 112.79 (C_q, C_{3a}), 119.52 (ArCH, H_4), 121.28 (ArCH, H_6), 139.68 (C_q, C_5), 143.56 (C_q, C_{7a}), 154.01 (C_q, C_3)

M.P.: 189-191 °C Lit. M.P.: 185-187°C[372]

IRν_{max} (KBr) cm^{-1}: 2911.3, 2852.2, 1616.6, 1579.7, 1528.1 (NO_2), 1477.8, 1353.6, 1324.4 (NO_2), 1107.9, 911.9

HRMS: Found 249.0985 $[M+H]^+$, $C_{11}H_{13}N_4O_3$ requires 249.0988, (-1.2 ppm)

2-(4-(5-Nitro-1*H*-indazol-3-yl)piperazin-1-yl)ethanol (434)

As per general procedure AE, 2-(4-(5-nitro-1*H*-indazol-3-yl)piperazin-1-yl)ethanol (**434**) was prepared from (**425**) (1.07 g, 5.14 mmol) and 1-(2-hydroxyethyl)-piperazine (1.26 mL, 10.28 mmol) as an orange solid (887 mg, 60%) following recrystallization from methanol.

^{1}H NMR (400 MHz, DMSO-d_6) δ 2.46 (t, 2H, J = 6.27 Hz, $\underline{CH2}CH_2OH$), 2.55 - 2.68 (m, 4H), 3.38 (dd, 4H, J = 9.79, 5.27 Hz), 3.55 (d, 2H, J = 4.52 Hz, $CH_2\underline{CH_2}OH$), 4.47 (s, 1H, OH), 7.49 (d, 1H, ArH, J = 9.03 Hz, H_7), 8.11 (dd, 1H, ArH, J = 9.03, 2.01 Hz, H_6), 8.71 (d, 1H, ArH, J = 2.01 Hz, H_4), 12.75 (s, 1H, NH)

^{13}C NMR (101 MHz, DMSO-d_6) δ 48.94 (CH_2), 52.84 (CH_2), 58.54 (CH_2), 60.41 (CH_2), 110.69 (ArCH, C_7), 112.89 (C_q, C_{3a}), 119.53 (ArCH, C_4), 121.19 (ArCH, C_6), 139.53 (C_q, C_5), 143.56(C_q, C_{7a}), 154.01 (C_q, C_3)

M.P.: 198-201 °C

IRν_{max} (KBr) cm^{-1}: 3470.5 (NH), 3325.2 (OH), 3098.8, 2958.0, 2890.9, 2856.3, 2817.3, 1614.1, 1584.3, 1522.7 (NO_2), 1464.6, 1435.9, 1391.1, 1369.6, 1320.6 (NO_2), 1303.0, 1237.0, 1224.2, 1160.8, 1147.8, 1131.6, 1063.3, 1014.2

HRMS: Found 292.1396 $[M+H]^+$, $C_{13}H_{18}N_5O_3$ requires 292.1410, (-4.8 ppm)

4-(6-Nitro-1*H*-indazol-3-yl)morpholine (442)

As per general procedure AE, 4-(6-nitro-1*H*-indazol-3-yl)morpholine (**442**) was prepared from (**426**) (1.07 g, 5.14 mmol) and morpholine (0.9 mL, 10.28 mmol) as an orange solid (642 mg, 57%) following recrystallization from methanol.

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.30 - 3.35 (m, 4H, 2 x CH_2), 3.75 - 3.83 (m, 4H, 2 x CH_2), 7.75 (d, 1H, ArH, J = 9.03 Hz, H_4), 8.04 (d, 1H, ArH, J = 9.03 Hz, H_6), 8.25 (s, 1H, ArH, H_7), 12.77 (s, 1H, NH)

^{13}C NMR (101 MHz, DMSO-d_6) δ 49.52 (2 x CH_2), 65.92 (2 x CH_2), 106.65 (ArCH, C_7), 112.64 (ArCH, C_6), 116.67 (C_q, C_{3a}), 122.29(ArCH, C_4), 140.39 (C_q, C_{7a}), 145.90 (C_q, C_6), 152.05 (C_q, C_3)

M.P.: 164-166 °C

IRν_{max} (KBr) cm^{-1}: 3291.96, 2958.9, 1629.8, 1523.5 (NO_2), 1445.9, 1350.1 (NO_2), 1308.0, 1272.99, 1260.16, 1243.9, 1165.8, 1107.3, 1035.6

HRMS: Found 249.0983 $[M+H]^+$, $C_{11}H_{13}N_4O_3$ requires 249.0988, (-2.0 ppm)

3-(4-Methylpiperazin-1-yl)-6-nitro-1*H*-indazole (443)

As per general procedure AE, (**443**) was prepared from (**426**) (1.07 g, 5.14 mmol) and 1-methylpiperazine (1.2 mL, 10.28 mmol) as an orange solid (874 mg, 65%) following recrystallization from methanol.

^{1}H NMR (400 MHz, DMSO-d_6) δ 2.24 (s, 3H, CH_3), 2.51 (s, 4H, 2 x CH_2), 3.35 (s, 4H, 2 x CH_2), 7.74 (d, 1H, ArH, J = 9.03 Hz, H_4), 8.01 (d, 1H, ArH, J = 9.03 Hz, H_6), 8.23 (s, 1H, ArH, H_7), 12.73 (s, 1H, NH)

^{13}C NMR (101 MHz, DMSO-d_6) δ 45.90 (CH_3), 49.01 (2 x CH_2), 54.32 (2 x CH_2), 106.59 (ArCH, C_7), 112.53 (ArCH, C_6), 116.78 (C_q, C_{3a}), 122.36 (ArCH, C_4), 140.38 (C_q, C_{7a}), 145.84 (C_q, C_6), 152.07 (C_q, C_3)

M.P.: 225-228 °C[371]

IRν_{max} (KBr) cm^{-1}: 3394.1 (NH), 2931.0, 2832.5, 1521.5 (NO_2), 1442.1, 1346.2 (NO_2), 1279.9

HRMS: Found 262.1302 $[M+H]^+$, $C_{12}H_{16}N_5O_2$ requires 262.1304, (-0.8 ppm)

3-(4-Methylpiperazin-1-yl)-5-nitro-1*H*-indazole (435)

As per general procedure AE, 3-(4-methylpiperazin-1-yl)-5-nitro-1*H*-indazole (**435**) was prepared from (**425**) (1.07 g, 5.14 mmol) and 1-methylpiperazine (1.2 mL, 10.28 mmol) as an orange solid (673 mg, 50%) following recrystallization from methanol.

^{1}H NMR (400 MHz, DMSO-d_6) δ 2.25 (s, 3H, CH_3), 2.51 – 2.53 (m, 4H, 2 x CH_2), 3.25 - 3.49 (m, 4H, 2 x CH_2), 7.49 (d, 1H, ArH, J = 9.03 Hz, H_7), 8.12 (dd, 1H, ArH, J = 9.03, 2.01 Hz, H_6), 8.72 (d, 1H, ArH, J = 2.01 Hz, H_4), 12.76 (s, 1H, NH)

^{13}C NMR (101 MHz, DMSO-d_6) δ 45.91 (CH_3), 48.78 (2 x CH_2), 54.27 (2 x CH_2), 110.72 (ArCH, C_7), 112.90 (C_q, C_{3a}), 119.55 (ArCH, C_4), 121.24 (ArCH, C_6), 139.57 (C_q, C_5), 143.57 (C_q, C_{7a}), 154.01(C_q, C_3)

M.P.: 183-186 °C[371]

IRν_{max} (KBr) cm^{-1}: 3364.5 (NH), 2940.9, 2837.4, 1617.2, 1530.9 (NO_2), 1477.3, 1371.9, 1324.6 (NO_2), 1131.6, 914.6

HRMS: Found 262.1295 $[M+H]^+$, $C_{12}H_{16}N_5O_2$ requires 262.1304, (-3.4 ppm)

3-(4-Benzylpiperazin-1-yl)-5-nitro-1*H*-indazole (436)

As per general procedure AE, 3-(4-benzylpiperazin-1-yl)-5-nitro-1*H*-indazole (**436**) was prepared from (**425**) (1.07 g, 5.14 mmol) and 1-benzylpiperazine (1.6 mL, 7.72 mmol) as an orange solid (918 mg, 53%) following recrystallization from methanol.

^{1}H NMR (400 MHz, DMSO-d_6) δ 2.58 (br s, 4H, 2 x CH_2), 3.40 (br s, 4H, 2 x CH_2), 3.55 (s, 2H, CH_2, NCH_2), 7.23 - 7.31 (m, 1H, ArH), 7.34 – 7.36 (m, 4H, ArH), 7.49 (m, 1H, ArH), 8.10 – 8.13 (m, 1H, ArH), 8.72 (s, 1H, ArH, H_7), 12.75 (s, 1H, NH)

^{13}C NMR (101 MHz, DMSO-d_6) δ 48.94 (2 x CH_2), 52.25 (2 x CH_2), 62.22 (CH_2, NCH_2), 110.70 (ArCH, C_7), 112.90 (C_q, C_{3a}), 119.54 (ArCH, C_4), 121.21 (ArCH, C_6), 127.02 (ArCH), 128.24 (ArCH), 128.99 (ArCH), 138.02 (C_q) , 139.55 (C_q, C_5), 143.56 (C_q, C_{7a}), 153.96 (C_q, C_3)

M.P.: 199-201 °C

IRν_{max} (KBr) cm^{-1}: 3368.6 (NH), 2817.7, 1617.6, 1579.7, 1529.9 (NO_2), 1478.1, 1451.9, 1324.4 (NO_2), 1277.4, 1157.6

HRMS: Found 338.1614 $[M+H]^+$, $C_{18}H_{20}N_5O_2$ requires 338.1617, (-0.9 ppm)

3-(4-Benzylpiperazin-1-yl)-6-nitro-1*H*-indazole (444)

As per general procedure AE, 3-(4-benzylpiperazin-1-yl)-6-nitro-1*H*-indazole (**444**) was prepared from (**426**) (0.7 g, 3.36 mmol) and 1-benzylpiperazine (1.2 mL, 7.72 mmol) as an orange solid (820 mg, 72%) following recrystallization from methanol.

^{1}H NMR (400 MHz, DMSO-d_6) δ 2.58 (br. s, 4H, 2xCH_2), 3.36 (br. s, 4H, 2 x CH_2), 3.56 (s, 2H, CH_2), 7.26 – 7.31 (m, 1H, $H_{4'''}$), 7.34 – 7.35 (m, 4H, $H_{2'''}$ & $H_{6'''}$, $H_{3'''}$ & $H_{5'''}$), 7.75 (dd, 1H, J = 9.04, 1.44 Hz, H_6), 8.02 (d, 1H, J = 9.04 Hz, H_4), 8.25 (d, 1H, J = 1.44 Hz, H_7), 12.72 (s, 1H, NH)

^{1}H NMR (101 MHz, DMSO-d_6) δ 49.13 (2 x CH_2), 52.27 (2 x CH_2), 62.18 (CH_2), 106.58 (ArCH, C_7), 112.53 (ArCH, C_5), 116.78 (C_q, C_{3a}) 122.35 (ArCH, C_4), 127.00 (ArCH), 128.22 (ArCH), 128.94 (ArCH), 138.02 (C_q), 140.36 (C_q, C_{7a}), 145.83(C_q, C_6), 152.02 (C_q, C_3)

M.P.: 196-199 °C

IRν_{max} (KBr) cm^{-1}: 2827.6, 1616.6, 1523.1 (NO_2), 1449.65, 1346.1 (NO_2), 1068.5

HRMS: Found 338.1610 $[M+H]^+$, $C_{18}H_{20}N_5O_2$ requires 338.1617, (-2.1 ppm)

5-Nitro-3-(4-(5-nitro-1*H*-indazol-3-yl)piperazin-1-yl)-1*H*-indazole (439)

As per general procedure AE, 5-nitro-3-(4-(5-nitro-1*H*-indazol-3-yl)piperazin-1-yl)-1*H*-indazole (**439**) was prepared from (**425**) (1.07 g, 5.14 mmol) and piperazine (884 mg, 10.28 mmol) as an orange solid (550 mg, 26%) following recrystallization from methanol.

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.65 (s, 8H, 4 x CH_2), 7.53 (d, 2H, J = 9.03 Hz, 2 x H_7), 8.14 (dd, 1H, J = 9.03, 2.01 Hz, 2 x H_6), 8.83 (d, 2H, ArH, J = 2.01 Hz, 2 x H_4), 12.30 - 13.31 (br. s, 2H, 2 x NH)

^{13}C NMR (101 MHz, DMSO-d_6) δ 48.68 (CH_2), 110.81 (ArCH, C_7), 112.90 (C_q, C_{3a}), 119.53 (ArCH, C_4), 121.30 (ArCH, C_6), 139.69 (C_q, C_5), 143.59 (C_q, C_{7a}), 153.93 (C_q, C_3)

M.P.: 230-232 °C

IRν_{max} (KBr) cm^{-1}: 1623.9, 1557.6, 1584.6, 1528.5 (NO_2), 1483.9, 1346.2 (NO_2), 1261.9, 1156.9, 1026.7

HRMS: Found 4071210 [M-H]$^-$, $C_{18}H_{15}N_5O_2$ requires 407.1217, (-1.7 ppm)

5-Nitro-N-(3-phenylpropyl)-1*H*-indazol-3-amine (437)

As per general procedure AE, 5-nitro-N-(3-phenylpropyl)-1*H*-indazol-3-amine (**437**) was prepared from (**425**) (563 mg, 2.71 mmol) and 3-phenylpropylamine (0.78 mL, 5.42 mmol) as an orange solid (280 mg, 35%) following recrystallization from methanol.

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.94 (quin, 2H, J = 7.28 Hz, $CH_2\underline{CH_2}CH_2$ NH), 2.71 (t, 2H, J = 7.78 Hz, $\underline{CH_2}CH_2CH_2$ NH), 3.27 (q, 2H, J = 6.53 Hz, $CH_2CH_2\underline{CH_2}$ NH), 6.71 (t, 1H, J = 5.27 Hz, $CH_2CH_2CH_2$ $\underline{NH}$), 7.14 - 7.20 (m, 1H, ArH), 7.22 - 7.31 (m, 4H, ArH), 7.34 (d, 1H, ArH, J = 9.03 Hz, H_7), 8.06 (dd, 1H, ArH, J = 9.03, 1.51 Hz, H_6), 8.94 (s, 1H, ArH, H_7), 12.22 (br. s, 1H, NH)

^{13}C NMR (101 MHz, DMSO-d_6) δ 30.59 ($CH_2\underline{CH_2}CH_2$ NH), 32.75 ($\underline{CH_2}CH_2CH_2$ NH), 42.36 ($CH_2CH_2\underline{CH_2}$ NH), 109.63 (ArCH, C_5), 112.98 (C_q, C_{3a}), 119.48 (ArCH, C_7), 121.54 (ArCH, C_6), 125.74 (ArCH), 128.32 (ArCH), 128.36 (ArCH), 138.64 (C_q), 141.95(C_q, C_5), 143.00 (C_q, C_{7a}), 152.35 (C_q, C_3)

M.P.: 174-177 °C

IRν_{max} (KBr) cm^{-1}: 3390.5 (NH), 1619.0, 1584.6, 1515.8 (NO_2), 1466.7, 1337.2 (NO_2), 1282.3, 1164.4

HRMS: Found 297.1359 $[M+H]^+$, $C_{16}H_{17}N_4O_2$ requires 297.1352, (+2.4 ppm)

5-Nitro-N-phenyl-1*H*-indazol-3-amine (438)

As per general procedure AE, 5-nitro-N-phenyl-1*H*-indazol-3-amine (**438**) was prepared from (**425**) (700 mg, 3.36 mmol) and aniline (1.02 mL, 6.73 mmol) as an orange solid (282 mg, 33%) following recrystallization from methanol.

^{1}H NMR (400 MHz, DMSO-d_6) δ 6.88 (app t, dd, 1H, ArH, J = 7.03 Hz), 7.31 (app t, dd, 2H, ArH, J = 7.78 Hz), 7.50 (d, 1H, ArH, J = 9.54 Hz, H_7), 7.75 (d, 2H, ArH, J = 8.03 Hz), 8.17 (dd, 1H, J = 9.54, 2.01 Hz, H_6), 9.23 (s, 1H, ArH, H_4), 9.42 (s, 1H, NH), 12.73 (s, 1H, N_1H)

^{13}C NMR (101 MHz, DMSO-d_6) δ 110.10 (ArCH, C_7), 113.76 (C_q, C_{3a}), 116.23 (ArCH), 119.23 (ArCH), 119.74 (ArCH, C_4), 121.94 (ArCH, C_6), 128.87 (ArCH), 139.57 (C_q, C_6), 141.97 (C_q), 147.57 (C_q, C_{7a}), C_3 not observed

M.P.: 210-212 °C[373]

IRν_{max} (KBr) cm^{-1}: 3364.5, 1623.9, 1601.8, 1525.1 (NO_2), 1336.4 (NO_2), 1316.7, 1272.5, 1137.3, 1024.3

HRMS: Found 255.0873 $[M+H]^+$, $C_{13}H_{11}N_4O_2$ requires 255.0882, (-3.5 ppm)

***N*-(3,4,5-Trimethoxybenzyl)-6-nitro-1*H*-indazol-3-amine (445)**

As per general procedure AE, *N*-(3,4,5-trimethoxybenzyl)-6-nitro-1*H*-indazol-3-amine (**445**) was prepared from (**426**) (700 mg, 3.36 mmol) and 3,4,5-trimethoxybenzyl amine (1.15 mL, 6.73 mmol) as an orange solid (506 mg, 42%) following recrystallization from methanol.

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.59 (s, 3H, OCH_3), 3.71 (s, 6H, 2 x OCH_3), 4.39 (d, 2H, J = 6.10 Hz, CH_2), 6.72 (s, 2H, ArH), 6.76 - 6.82 (m, 1H, $CH_2\underline{NH}$), 7.70 (dd, 1H, ArH, J = 9.16, 1.83 Hz, H_5), 7.98 (d, 1H, ArH, J = 9.16 Hz, H_5), 8.11 (d, 1H, ArH, J = 1.83 Hz, H_7), 12.13 (s, 1H, NH)

^{13}C NMR (101 MHz, DMSO-d_6) δ 47.08 (CH_2), 55.79 (2 x OCH_3), 59.94 (OCH_3), 104.93 (ArCH), 105.80 (ArCH, C_7), 111.78 (ArCH, C_5), 116.41 (C_q), 121.48 (ArCH, C_4), 135.94 (C_q), 136.28 (C_q), 139.93 (C_q), 146.31 (C_q), 150.08 (C_q), 152.73 (C_q)

M.P.: 175-177 °C

IRν_{max} (KBr) cm^{-1}: 3364.5 (NH), 2931.0, 2842.4, 1601.8, 1528.1 (NO_2), 1343.3 (NO_2), 1230.7, 1125.4

HRMS: Found 259.1355 $[M+H]^+$, $C_{17}H_{19}N_4O_5$ requires 359.1355, (0.0 ppm)

5-Nitro-*N*,*N*-diphenyl-1*H*-indazol-3-amine (440)

To a solution of (**425**) (700 mg, 3.36 mmol) in anhydrous THF (8 mL), which was cooled to 0 °C, a solution of diphenylamine (1.14 g, 6.73) in minimal anhydrous THF was added slowly *via* a syringe. The resultant solution was stirred for 2 h at 0 °C. The resultant precipitate was collected by vacuum filtration and re-crystallized in methanol. 5-Nitro-*N*,*N*-diphenyl-1*H*-indazol-3-amine (**440**) was not afforded.

6-Nitro-*N*-phenyl-1*H*-indazol-3-amine (447)

To a solution of (**426**) (700 mg, 3.36 mmol) in anhydrous THF (8 mL), which was cooled to 0 °C, aniline (1.02 mL, 6.73 mmol) was added slowly *via* a syringe. The resultant solution was stirred for 2 h at 0 °C. The resultant precipitate was collected by vacuum filtration and re-crystallized in methanol. 6-Nitro-N-phenyl-1*H*-indazol-3-amine (**447**) was not afforded.

6-Nitro-*N*-(3-phenylpropyl)-1*H*-indazol-3-amine (437)

To a solution of (**426**) (700 mg, 3.36 mmol) in anhydrous THF (8 mL), which was cooled to 0 °C, 3-phenylpropylamine (1.0 mL, 6.73 mmol) was added slowly *via* a syringe. The resultant solution was stirred for 2 h at 0 °C. The resultant precipitate was collected by vacuum filtration and re-crystallized in methanol. 6-Nitro-N-(3-phenylpropyl)-1*H*-indazol-3-amine (**437**) was not afforded.

3-(1*H*-Imidazol-1-yl)-5-nitro-1*H*-indazole (441)

A suspension of (**425**) (700 mg, 3.36 mmol) and imidazole (460 mg) in THF:DIW (5: 5 mL) was stirred at 20 °C for 15 h and then *vacuum* filtered. The collected precipitate was titurated with DIW and collected was collected by *vaccum* filtration and left to air dry. 1.0 g of crude product was afforded. The presence of (**441**) was confirmed by mass spectrometry.

HRMS: Found 230.0670 $[M+H]^+$, $C_{10}H_8N_5O_2$ requires 230.0678, (-3.5 ppm)

General procedure AF: *N*-1 benzoylation of 3-(heterocycle)-indazole

To a solution of 3-(heterocycle)-indazole (2.0 mmol, 1.0 eq) and 3,4,5-trimethoxybenzoyl chloride (461 mg, 2.0 mmol, 1.0 eq) in anhydrous CH_2Cl_2 (30 mL), Et_3N (223 mg, 2.2 mmol, 1.1 eq) was added *via* a syringe. The resultant solution was refluxed at 39.6 °C under nitrogen for 12 h. It was cooled to 20 °C, washed with DIW (15 mL), a saturated brine solution (15 mL), dried using anhydrous sodium sulphate, filtered and concentrated to dryness in *vacuo*. Hot filtration of the crude product from hot MeOH afforded the desired product.

(3-Morpholino-5-nitro-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (448)

As per general procedure AF, (3-morpholino-5-nitro-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone was prepared from (**433**) (497 mg, 2 mmol) and 3,4,5-trimethoxybenzoyl chloride (462 mg, 2 mmol) as a yellow solid (600 mg, 68%) following hot filtration and recrystallization from methanol.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.56 - 3.62 (m, 4H, 2 x CH_2), 3.91 - 4.00 (m, 13H, 2 x CH_2, 3 x OCH_3), 7.56 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 8.46 (dd, 1H, ArH, J = 9.54, 2.01 Hz, H_6), 8.71 - 8.73 (m, 2H, ArH, H_4 & H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 49.14(2 x CH_2), 56.55 (2 x OCH_3), 61.30 (OCH_3), 66.58 (2 x CH_2), 109.44 (ArCH, $C_{2'}$ & $C_{6'}$), 117.37 (ArCH, C_7), 118.24 (ArCH, C_4), 119.30 (C_q ,C_{3a}) 124.80 (ArCH, C_6), 127.47 (C_q, $C_{1'}$), 142.28 (C_q, C_5), 144.06 (C_q ,$C_{4'}$), 145.08 (C_q ,C_{7a}), 152.71 (C_q , $C_{3'}$ & $C_{5'}$), 155.24 (C_q , C_3), 166.58 (C=O)

M.P.: 237-239 °C

IRν_{max} (NaCl film) cm^{-1}: 3101.4, 3006.28, 2949.0, 2838.75, 1685.65 (C=O), 1609.4, 1588.4, 1542.1, 1515.4 (NO_2), 1468.6, 1433.6, 1393.2, 1340.7 (NO_2), 1259.2, 1226.2, 1136.7, 1081.2

HRMS: Found 443.1549 $[M+H]^+$, $C_{21}H_{23}N_4O_7$ requires 443.1567, (-4.1 ppm)

(3-(4-Methylpiperazin-1-yl)-6-nitro-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (455)

As per general procedure AF, (3-(4-methylpiperazin-1-yl)-6-nitro-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (**455**) was prepared from (**443**) (523 mg, 2.0mmol) and 3,4,5-trimethoxybenzoyl chloride (461 mg 2.0 mmol) as an orange solid (373 mg, 41%) following hot filtration and recrystallization from methanol.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (s, 3H, CH_3), 2.61 - 2.71 (m, 4H, 2 x CH_2, $H_{3''}$ & $H_{5''}$), 3.57 - 3.66 (m, 4H, 2 x CH_2, $H_{3''}$ & $H_{5''}$), 3.93 (s, 6H, 2 x OCH_3), 3.97 (s, 3H, OCH_3), 7.62 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 7.90 (d, 1H, ArH, J = 8.53 Hz, H_4), 8.18 (dd, 1H, ArH, J = 8.53, 2.01 Hz, H_6), 9.46 (d, 1H, ArH, J = 2.01 Hz, H_7)

^{1}H NMR (101 MHz, $CDCl_3$) δ 45.75 (CH_3), 48.17 (2 x CH_2), 53.91(2 x CH_2), 55.79 (2 x OCH_3), 60.56 (OCH_3), 108.73 (ArCH, $C_{2'}$ & $C_{5'}$), 112.37 (ArCH, C_7) 118.17 (ArCH, C_5), 121.30 (ArCH, C_3), 122.44 (C_q, C_{3a}), 126.82 (C_q, $C_{1'}$), 141.19 (C_q, C_{7a}), 141.37 (C_q, $C_{4'}$), 147.88 (C_q, C_6), 151.96 (C_q, $C_{3'}$ & $C_{5'}$), 153.76 (C_q , C_{3a}), 165.41 (C=O)

M.P.: 183-185 °C

IRν_{max} (NaCl film) cm^{-1}: 2999.29, 2940.28, 2840.60, 1666.69 (C=O), 1581.57, 1542.07 (NO_2), 1452.82, 1414.64, 1399.38, 1343.21 (NO_2), 1220.61

HRMS: Found 456.1892 $[M+H]^+$, $C_{22}H_{26}N_5O_6$ requires 456.1892, (+2.0 ppm)

(3-(4-Methylpiperazin-1-yl)-5-nitro-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (450)

As per procedure AF, (3-(4-methylpiperazin-1-yl)-5-nitro-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (**450**) was prepared from (**435**) (523 mg, 2.0 mmol) and 3,4,5-trimethoxybenzoyl chloride (462 mg, 2.0 mmol) as an orange solid (360 mg, 40%) following hot filtration and recrystallization from methanol.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3H, CH_3), 2.69 (t, 4H, J = 4.48 Hz, 2 x CH_2), 3.66 (t, 4H, J = 4.48 Hz, 2 x CH_2), 3.95 (s, 6H, 2 x OCH_3), 3.99 (s, 3H, OCH_3), 7.61 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 8.46 (dd, 1H, ArH, J = 9.48, 2.00 Hz, H_6), 8.72 – 9.74 (m, 2H, ArH, H_4 & H_7)

^{1}H NMR (101 MHz, $CDCl_3$) δ 45.77 (CH_3), 48.06 (2 x CH_2), 53.94 (2 x CH_2), 55.80 (2 x OCH_3), 60.58 (OCH_3), 108.74 (ArCH, $C_{2'}$ & $C_{6'}$), 116.59 (ArCH, C_7), 117.70 (ArCH, C_4), 118.81 (C_q, C_{3a}), 123.98 (ArCH, C_6), 126.83 (C_q, $C_{1'}$), 141.45 (C_q, C_5), 143.28 (C_q, $C_{4'}$), 144.48, 151.96 (C_q, $C_{3'}$ & $C_{5'}$), 154.49 (C_q, C_{3a}), 165.80 (C=O)

M.P.: 213-215 °C

IRν_{max} (NaCl film) cm^{-1}: 3102.4, 3008.8, 2930.2, 2837.2, 2807.8, 1687.0 (C=O), 1609.1, 1589.2, 1546.5, 1513.9 (NO_2), 1467.99, 1414.99, 1398.59, 1343.3 (NO_2), 1227.6, 1134.2, 1004.7

HRMS: Found 456.1878 $[M+H]^+$, $C_{22}H_{26}N_5O_6$ requires 456.1883, (-1.1 ppm)

(3-Morpholino-6-nitro-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (454)

As per general procedure AF, (3-morpholino-6-nitro-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (**454**) was prepared from (**442**) 497 mg, 2 mmol) and 3,4,5-trimethoxybenzoyl chloride (461 mg, 2 mmol) as a yellow solid (631 mg, 36%) following hot filtration and recrystallization from methanol.

^1H NMR (400 MHz, $CDCl_3$) δ 3.53 - 3.59 (m, 4H, 2 x CH_2), 3.92 - 3.96 (m, 10H, 2 x CH_2, 2 x OCH_3), 3.97 (s, 3H, OCH_3), 7.59 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 7.89 (d, 1H, ArH, J = 8.53 Hz, H_4), 8.20 (dd, 1H, ArH , J = 8.53,1.51 Hz, H_5), 9.48 (s, 1H, ArH, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 49.31 (2 x CH_2), 56.54 (2 x OCH_3), 61.30 (OCH_3), 66.57 (2 x CH_2), 109.41 (ArCH, $C_{2'}$ & $C_{6'}$), 113.17 (ArCH,C_7), 119.00 (ArCH, C_5), 121.88 (ArCH, C_4), 122.94 (C_q, C_{3a}), 127.49 (C_q, $C_{1'}$), 141.93 (C_q, C_{7a}), 142.17 (C_q, $C_{4'}$), 148.69 (C_q, C_6), 152.72 (C_q, $C_{3'}$ & $C_{5'}$), 154.51(C_q, C_3), 166.24 (C=O)

M.P.: 190-192 °C

IRν_{max} (NaCl film) cm^{-1}: 3097.3, 2998.9, 2954.3, 2837.8, 1678.6 (C=O), 1586.3, 1544.26 (NO_2), 1505.7, 1465.1, 1450.4, 1397.7, 1377.8, 1346.1 (NO_2), 1266.6, 1223.8, 1129.4, 1065.7, 1026.5, 1001.1

HRMS: Found 465.1368 $[M+H]^+$, $C_{21}H_{22}N_4O_7Na$ requires 465.1386, (-3.9 ppm)

(3-(4-Benzylpiperazin-1-yl)-5-nitro-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (451)

As per general procedure AF, (3-(4-benzylpiperazin-1-yl)-5-nitro-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (**451**) was prepared from (**436**) (657 mg, 2.0 mmol) and 3,4,5-trimethoxybenzoyl chloride (462 mg 2 mmol) as a yellow solid (523 mg, 50%) following hot filtration and recrystallization from methanol.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.71 (br s, 4H, 2xCH_2), 3.63 (br s, 6H, 3 x CH_2), 3.93 (s, 6H, 2 x OCH_3), 3.97 (s, 3H, OCH_3), 7.28 - 7.34 (m, 1H, ArH), 7.35 – 7.37 (m, 4H, $H_{2'''}$ & $H_{6'''}$, $H_{3'''}$ & $H_{5'''}$), 7.59 (s, 2H, ArH, $H_{2'}$ &$H_{6'}$), 8.45 (d, 1H, ArH, J = 9.54 Hz, H_7), 8.67 - 8.75 (m, 2H, ArH, H_4 & H_6)

^{13}C NMR (101 MHz, $CDCl_3$) δ 48.82 (2 x CH_2), 52.66 (2 x CH_2), 56.55 (2 x OCH_3), 61.29 (OCH_3), 63.36 (CH_2), 109.47 (ArCH, $C_{2'}$ & $C_{6'}$), 117.31 (ArCH, C_7), 118.46 (ArCH, C_4), 119.58 (C_q, C_{3a}) , 124.68 (ArCH, C_6), 127.59 (C_q, $C_{1'}$) , 127.70 (ArCH), 128.70 (ArCH), 129.53 (ArCH), 142.16 (C_q), 143.99 (C_q, C_5), 145.12 (C_q, C_{7a}), 152.67 (C_q, $C_{3'}$ & $C_{5'}$), 155.22 (C_q, C_{3a}) 166.53 (C=O)

M.P.: 190-193 °C

IRν_{max} (NaCl film) cm^{-1}: 2938.74, 2837.48, 1682.37 (C=O), 1587.96, 1523.43 (NO_2), 1453.01, 1414.11, 1374.04, 1332.44 (NO_2), 1222.54

HRMS: Found 532.2215 $[M+H]^+$, $C_{28}H_{30}N_5O_6$ requires 532.2196, (+3.6 ppm)

(3-(3-Phenylpropylamino)-5-nitro-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (452)

As per general procedure AF, (3-(3-phenylpropylamino)-5-nitro-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (**452**) was prepared from (**437**) (250 mg, 0.84 mmol) and 3,4,5-trimethoxybenzoyl chloride (195 mg, 0.84 mmol) as a yellow solid (57 mg, 14%) following flash column chromatography over silica gel (eluent EtOAc:Hexane gradient).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.11 - 2.22 (m, 2H, $CH_2\underline{CH_2}CH_2NH$), 2.84 (t, 2H, J=7.28 Hz, $\underline{CH_2}CH_2CH_2NH$), 3.57 (t, 2H, J = 6.78 Hz, $CH_2CH_2\underline{CH_2}NH$), 3.93 (s, 6H, 2 x OCH_3), 4.02 (s, 3H, OCH_3), 4.57 (br. s, 1H, $CH_2CH_2CH_2$ $\underline{NH}$), 7.23 - 7.38 (m, 5H, ArH), 7.66 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 8.43 - 8.53 (m, 2H, ArH, H_4 & H_6), 8.68 (d, 1H, ArH, J=9.03 Hz, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 30.42, 33.45, 43.07, 56.14, 60.96, 109.09, 115.62, 116.96, 119.09, 124.84, 126.28, 127.52, 128.32, 128.62, 141.11, 141.66, 143.82, 144.02, 152.35, 166.20

M.P.: 210-212 °C

IRν_{max} (NaCl film) cm^{-1}: 3095. 3, 2937.7, 2863.9, 2836.2, 1686.5 (C=O), 1663.9, 1604.7, 1580.5, 1517.8 (NO_2), 1507.0, 1462.3, 1453.4, 1414.7, 1389.5, 1332.5 (NO_2), 1266.6, 1223.2, 1165.9, 1126.5

HRMS: Found 513.1733 $[M+Na]^+$, $C_{26}H_{26}N_4NaO_6$ requires 513.1750, (-3.3 ppm)

3,4,5-Trimethoxy-N-(5-nitro-1-(3,4,5-trimethoxybenzoyl)-1*H*-indazol-3-yl)-N-(3-phenylpropyl)benzamide (453)

As per general procedure AF, (**453**) was prepared from (**437**) (250 mg, 0.84 mmol) and 3,4,5-trimethoxybenzoyl chloride (195 mg, 0.84 mmol) as a yellow solid (19 mg, 5%) following flash column chromatography over silica gel (eluent EtOAc:Hexane gradient)..

^1H NMR (400 MHz, $CDCl_3$) δ 2.13 (t, 2H, J = 7.28 Hz, $CH_2\underline{CH_2}CH_2N$), 2.68 (t, 2H, J=7.78 Hz, $\underline{CH_2}CH_2CH_2N$), 3.65 (s, 6H, 2 x OCH_3), 3.74 (s, 3H, OCH_3), 3.87 (s, 6H, 2 x OCH_3), 3.98 (s, 3H, OCH_2), 4.17 (t, 2H, J = 7.53 Hz, $CH_2CH_2\underline{CH_2}N$), 6.73 (s, 2H, ArH), 7.04 (d, 2H, ArH), 7.11 - 7.23 (m, 3H, ArH), 7.39 (s, 2H, ArH), 8.33 (d, 1H, J = 1.51 Hz, H_4), 8.40 (dd, 1H, J = 9.03, 1.51 Hz, H_6), 8.61 (d, 1H, J = 9.03 Hz, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 30.24 ($CH_2\underline{CH_2}CH_2N$), 33.06 ($\underline{CH_2}CH_2CH_2N$), 50.16 ($CH_2CH_2\underline{CH_2}N$), 56.10 (2 x OCH_3), 56.32 (2 x OCH_3), 60.86 (OCH_3), 61.04 (OCH_3), 106.00 (ArCH), 109.30 (ArCH, $C_{2'}$ & $C_{6'}$), 116.94 (ArCH, C_7), 116.98 (ArCH, C_4), 121.41 (C_q, C_{3a}), 124.72 (ArCH, C_6), 125.93 (C_q), 126.16 (ArCH), 128.03 (ArCH), 128.43 (ArCH), 129.65 (C_q), 140.55 (C_q, C_5), 142.86 (C_q), 143.41 (C_q, $C_{4'}$), 144.61 (C_q, C_{7a}), 150.82 (C_q, C_3), 152.65 (C_q), 152.94 (C_q, $C_{3'}$ & $C_{5'}$), 166.34 (C=O), 170.10 (C=O)

M.P.: 221-225 °C

IRν_{max} (NaCl film) cm^{-1}: 3086. 3, 3063.7, 3001.9, 2863.9, 2939.4, 2838.3, 1667.0 (C=O), 1612.6, 1584.8, 1522.1 (NO_2), 1504.9, 1463.5, 1432.2, 1415.1, 1382.2, 1335.4 (NO_2), 1238.5, 1238.5, 1169.7, 1128.6, 1002.98

HRMS: Found 707.2357 $[M+Na]^+$, $C_{36}H_{36}N_4NaO_{10}$ requires 707.2329, (+4.0 ppm)

(3-(4-Benzylpiperazin-1-yl)-6-nitro-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (456)

As per general procedure AF, (3-(4-benzylpiperazin-1-yl)-6-nitro-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (**456**) was prepared from (**444**) (600 mg, 1.78 mmol) and 3,4,5-

trimethoxybenzoyl chloride (410 mg 1.78 mmol) as a yellow solid (570 mg, 50%) following hot filtration and recrystallization from methanol.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.71 (br. s, 4H, 2 x CH_2), 3.64 (br. s, 6H, 3xCH_2), 3.95 (s, 6H, 2 x OCH_3), 3.98 (s, 3H, OCH_3), 7.32 - 7.39 (m, 5H, ArH), 7.63 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 7.90 (d, 1H, ArH, J = 9.04 Hz, H_4), 8.20 (dd, 1H, ArH, J = 9.04, 2.00 Hz, H_5) 9.50 (d, 1H, ArH, J = 2.00 Hz, H_7)

^{1}H NMR (101 MHz, $CDCl_3$) δ 48.23 (2 x CH_2), 51.91 (2 x CH_2), 55.82 (2 x OCH_3), 60.56 (OCH_3), 62.64 (NCH_2), 108.72 (ArCH, $C_{2'}$ & $C_{6'}$), 112.40 (ArCH, C_7), 118.18 (ArCH, C_5), 121.33 (ArCH, C_4), 122.50 (C_q, $C_{1'}$), 126.87 (C_q, $C_{1'''}$), 126.96 (ArCH, $C_{4'''}$), 127.96 (ArCH, $C_{3'''}$ & $C_{5'''}$), 128.78 (ArCH, $C_{2'''}$ & $C_{6'''}$), 141.22(C_q, C_{7a}) , 141.36 (C_q, $C_{4'}$), 147.89 (C_q, C_6), 151.96 (C_q, $C_{3'}$ & $C_{5'}$), 153.78 (C_q, C_3) 165.42 (C=O)

M.P.: 144-147 °C

IRν_{max} (NaCl film) cm^{-1}: 3061.9, 3001.2, 2939.5, 2836.3, 1666.9 (C=O), 1587.96, 1523.43 (NO_2), 1504.6, 1453.6, 1414.6, 1398.7, 1332.6 (NO_2), 1240.5, 1219.9, 1165.9, 1128.3, 1005.0

HRMS: Found 532.2190 $[M+H]^+$, $C_{28}H_{30}N_5O_6$ requires 532.2196, (-1.1 ppm)

2-(4-(5-Nitro-1-(3,4,5-trimethoxybenzoyl)-1*H*-indazol-3-yl)piperazin-1-yl)ethyl 3,4,5-trimethoxybenzoate (449)

As per general procedure AF, 2-(4-(5-nitro-1-(3,4,5-trimethoxybenzoyl)-1*H*-indazol-3-yl)piperazin-1-yl)ethyl 3,4,5-trimethoxybenzoate (**449**) was prepared from (**434**) (519 mg, 1.78 mmol) and 3,4,5-trimethoxybenzoyl chloride (410 mg 1.78 mmol) as a yellow solid (570 mg, 50%) following hot filtration and recrystallization from methanol.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.86 (br. s., 6H, 3 x CH_2), 3.66 (br. s., 4H, 2 x CH_2), 3.92 (s, 9H, 3 x OCH_3), 3.93 (s, 6H, 2 x OCH_3), 3.97 (s, 3H, OCH_3), 4.42 - 4.66 (m, 2H, CH_2), 7.31 (s, 2H, ArH), 7.57 (s, 2H, ArH), 8.45 (dd, 1H, ArH, J = 9.16, 1.83 Hz, H_6), 8.69 - 8.74 (m, 2H, ArH, H_4 & H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 56.31 (4 x OCH_3), 60.92 (OCH_3), 60.99 (OCH_3), 106.98 (ArCH), 109.23 (ArCH), 117.10 (ArCH), 124.49 (ArCH), 143.79 (C_q), 144.78 (C_q), 152.44 (C_q), 152.99 (C_q), 166.00 (C=O), 166.25 (C=O)

M.P.: 100-104 °C

IRν_{max} (NaCl film) cm^{-1}: 2949.1, 2836.3, 1667.9 (C=O), 1588.4, 1523.4 (NO_2), 1514.6, 1451.6, 1414.7, 1398.7, 1333.6 (NO_2), 1241.5, 1219.8

HRMS: Found 680.2568 $[M+H]^+$, $C_{33}H_{38}N_5O_{11}$ requires 680.2568, (0.0 ppm)

(3-(3,4,5-Trimethoxybenzylamino)-6-nitro-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (457)

As per general procedure AF, ((3-(3,4,5-trimethoxybenzylamino)-6-nitro-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (**457**) was prepared from (**445**) (250 mg, 0.7 mmol) and 3,4,5-trimethoxybenzoyl chloride (161 mg 0.7 mmol) as a yellow solid (150 mg, 39%) following hot filtration and recrystallization rom methanol.

^1H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 6H, 2 x OCH_3), 3.84 (s, 3H, OCH_3), 3.90 (s, 6H, 2 x OCH_3), 3.96 (s, 3H, OCH_3), 4.59 (s, 2H, CH_2), 6.63 (s, 2H, ArH), 7.66 (s, 2H, ArH), 7.72 (d, 1H, ArH, J = 8.54 Hz, H_4), 8.20 (dd, 1H, ArH, J = 8.54, 1.83 Hz, H_5), 9.43 (d, 1H, ArH, J=1.83 Hz, H_7), NH not observed

^{13}C NMR (101 MHz, $CDCl_3$) δ 48.00 (CH_2), 56.07 (2 x OCH_3), 56.20 (2 x OCH_3), 60.83 (OCH_3), 60.94 (OCH_3), 105.06 (ArCH), 109.19 (ArCH, $C_{2'}$ & $C_{6'}$), 112.94 (ArCH, C_7), 118.90 (ArCH, C_5), 119.25 (ArCH, C_4), 122.26 (C_q), 127.49 (C_q), 133.52 (C_q), 137.54 (C_q), 140.96 (C_q), 141.75 (C_q), 149.00 (C_q), 151.47 (C_q), 152.41 (C_q), 153.47 (C_q), 165.83 (C=O)

M.P.: 123-125 °C

IRν_{max} (NaCl film) cm^{-1}: 2967.7, 2877.1, 2848.3, 1681.4 (C=O), 1574.9, 1534.8 (NO_2), 1477.7, 1352.1 (NO_2), 1234.5, 1211.8

HRMS: Found 553.1945 $[M+H]^+$, $C_{27}H_{29}N_4O_9$ requires 553.1935, (+1.8 ppm)

(5-Amino-3-morpholino-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (458)

As per the general procedure C, (5-amino-3-morpholino-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (**458**) was prepared from (**448**) (300 mg, 0.68 mmol) as a brown solid (260 mg, 93%)

^1H NMR (400 MHz, DMSO-d_6) δ 3.38 - 3.43 (m, 4H, 2 x CH_2, $H_{2''}$ & $H_{6''}$), 3.76 (s, 3H, OCH_3), 3.77 - 3.81 (m, 4H, 2 x CH_2, $H_{3''}$ & $H_{5''}$), 3.83 (s, 6H, 2 x OCH_3), 5.29 (s, 2H, NH_2), 6.93 (d,

1H, ArH, J = 8.77 Hz, H_6), 7.02 (s, 1H, ArH, H_4), 7.49 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 8.17 (d, 1H, ArH, J = 8.77 Hz, H_7)

^{13}C NMR (101 MHz, DMSO-d_6) δ 48.44 (2 x CH_2, $C_{2''}$ & $C_{6''}$), 55.98 (2 x OCH_3), 60.16 (OCH_3), 65.71 (2 x CH_2, $C_{3''}$ & $C_{5''}$), 102.94 (ArCH, C_4), 108.60 (ArCH, $C_{2'}$ & $C_{6'}$), 116.54 (ArCH, C_7), 118.26 (ArCH, C_6), 120.28 (C_q, C_{3a}), 128.65 (C_q, $C_{1'}$), 133.88 (C_q, C_{7a}), 140.27(C_q, C_5) , 146.20 (C_q, $C_{4'}$), 151.94 (C_q, $C_{3'}$ & $C_{5'}$), 154.58 (C_q, C_3), 164.23 (C=O)

M.P.: 109-112 °C

IRν_{max} (KBr) cm^{-1}: 3450.6 (NH_2), 3362.8 (NH_2), 2690.1, 2836.6, 1648.1 (C=O), 1580.3, 1538.6, 1490.4, 1504.4, 1552.3, 1414.1, 1383.0, 1342.9, 1248.8, 1124.5, 1069.8

HRMS: Found 435.1636 (M+Na), $C_{21}H_{24}N_4O_5Na$ requires 435.1644, (-1.8 ppm)

(6-Amino-3-morpholino-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (463)

As per general procedure C, (6-amino-3-morpholino-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (**463**) was prepared from (**454**) (300 mg, 0.68 mmol) as a brown solid (200 mg, 72%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.37 - 3.42 (m, 4H, 2 x CH_2, $H_{2''}$ & $H_{6''}$), 3.72 - 3.79 (m, 7H, 2 x CH_2, $H_{3''}$ & $H_{6''}$, OCH_3), 3.83 (s, 6H, 2 x OCH_3), 5.87 (s, 2H, NH_2), 6.60 - 6.67 (m, 1H, ArH), 7.48 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 7.62 (m, 2H, ArH)

^{13}C NMR (101 MHz, DMSO-d_6) δ 48.20 (2 x CH_2, $C_{2''}$ & $C_{6''}$), 55.98 (2 x OCH_3), 60.16 (OCH_3), 65.77 (2 x CH_2, $C_{3''}$ & $C_{6''}$), 98.29 (ArCH, C_4), 108.61 (ArCH, $C_{2'}$ & $C_{6'}$), 108.86 (C_q, C_{3a}), 112.88 (ArCH, C_5), 122.34 (ArCH, C_4), 128.96 (C_q, $C_{1'}$), 140.26 (C_q, C_{7a}), 143.94 (C_q, $C_{4'}$), 151.10 (C_q, C_6), 151.90 ($C_{3'}$ & $C_{5'}$), 155.02 (C_q, C_3), 165.14 (C=O)

M.P.: 186-189 °C

IRν_{max} (KBr) cm^{-1}: 3457.81 (NH_2), 3365.54 (NH_2), 2960.70, 2836.89, 1654.48 (C=O), 1582.81, 1503.55, 1443.90, 1413.87, 1387.07, 1332.49

HRMS: Found 435.1640 (M+Na), $C_{21}H_{24}N_4O_5Na$ requires 435.1644, (-0.9 ppm)

(6-Amino-3-(4-methylpiperazin-1-yl)-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (464)

As per general procedure C, (6-amino-3-(4-methylpiperazin-1-yl)-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (**464**) was prepared from (**455**) (300 mg, 0.66 mmol) as a brown solid (240 mg, 86%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 2.22 (s, 3H, CH_3), 3.35 (br. s., 4H, 2 x CH_2), 3.39 - 3.49 (m, 4H, 2 x CH_2), 3.76 (s, 3H, OCH_3), 3.84 (s, 6H, 2 x OCH_3), 5.85 (s, 2H. NH_2), 6.81 (d, 1H, ArH, *J*=8.53 Hz), 7.53 (s, 2H, ArH), 7.76 (d, 1H, ArH, *J*=8.53 Hz), 7.97 (s, 1H, ArH)

^{13}C NMR (101 MHz, DMSO-d_6) δ 45.82 (CH_3), 47.65 (2 x CH_2), 54.10 (2 x CH_2), 55.94 (2 x OCH_3), 60.13 (OCH_3), 97.75 (ArCH), 98.29 (ArCH), 108.69 (ArCH), 110.62 (C_q), 121.80 (C_q), 122.19 (ArCH), 140.14 (C_q), 141.95 (C_q), 143.15 (C_q), 143.84 (C_q), 151.84 (C_q), 153.82 (C_q), 164.93 (C=O)

M.P.: 88-90 °C

IRν_{max} (KBr) cm^{-1}: 3456.7 (NH_2), 3371.1 (NH_2), 2955.7, 2831.8, 1671.7 (C=O), 1545.9, 1513.9, 1484.2, 1451.7, 1329.0

HRMS: Found 426.2133 $[M+H]^+$, $C_{22}H_{28}N_5O_4$ requires 426.2141, (-1.9 ppm)

2-(4-(5-Amino-1-(3,4,5-trimethoxybenzoyl)-1*H*-indazol-3-yl)piperazin-1-yl)ethyl 3,4,5-trimethoxybenzoate (459)

As per general procedure C, 2-(4-(5-amino-1-(3,4,5-trimethoxybenzoyl)-1*H*-indazol-3-yl)piperazin-1-yl)ethyl 3,4,5-trimethoxybenzoate (**459**) was prepared from (**449**) (100 mg, 0.15 mmol) as a brown solid (81 mg, 85%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 2.72 (br. s., 4H, 2 x CH_2), 2.79 (t, 2H, *J* = 5.49 Hz, CH_2), 3.44 (br. s., 4H, 2 x CH_2), 3.74 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.83 (s, 12H, 4 x OCH_3), 4.42 (t, 2H, *J* = 5.80 Hz, CH_2), 5.28 (br. s., 2H, NH_2), 6.92 (dd, 1H, ArH, *J* = 9.16, 1.83 Hz, H_6), 7.01 (d, *J* = 1.83 Hz, H_4), 7.25 (s, 2H, ArH), 7.50 (s, 2H, ArH), 8.16 (d, 1H, ArH, *J* = 9.16 Hz, H_7)

^{13}C NMR (101 MHz, DMSO-d_6) δ 48.07 (CH_2), 52.26 (CH_2), 55.91 (OCH_3), 55.97 (OCH_3), 60.12 (OCH_3), 62.37 (CH_2), 103.00 (ArCH), 106.46 (ArCH), 108.65 (ArCH), 116.49 (ArCH), 118.11 (ArCH), 120.36 (C_q), 124.85 (C_q), 128.63 (C_q), 133.85 (C_q), 141.69 (C_q), 146.11 (C_q), 151.88 (C_q), 152.73 (C_q), 154.43 (C_q), 164.02 (C=O), 165.22 (C=O)

M.P.: 91-94 °C

IRν_{max} (KBr) cm^{-1}: 3458.1 (NH_2), 3367.4 (NH_2), 2938.7, 2836.1, 1713.3 (C=O), 1647.9, 1583.6, 1537.9, 1503.9, 1454.2, 1414.7, 1333.0, 1224.3, 1126.9 1003.4

HRMS: Found 650.2837 $[M+H]^+$, $C_{33}H_{40}N_5O_9$ requires 650.2826, (+1.7 ppm)

(5-Amino-3-(4-methylpiperazin-1-yl)-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (460)

As per general procedure C, (5-amino-3-(4-methylpiperazin-1-yl)-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (**460**) was prepared from (**450**) (150 mg, 0.33 mmol) as a brown solid (126 mg, 90%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 2.23 (s, 3H, NCH_3), 2.49 – 2.51 (m, 4H, 2 x CH_2) 3.40 - 3.46 (m, 4H, 2 x CH_2), 3.76 (s, 3H, OCH_3), 3.83 (s, 6H, 2 x OCH_3), 5.29 (s, 2 H), 6.92 (dd, 1H, ArH, J = 9.16, 1.83 Hz, H_6), 7.01 (d, 1H, ArH, J = 1.83 Hz, H_4), 7.51 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 8.16 (d, 1H, ArH, J = 9.16 Hz, H_7)

^{13}C NMR (101 MHz, DMSO-d_6) δ 45.80 (NCH_3), 47.87 (2 x CH_2), 54.02 (2 x CH_2), 55.92 (2 x OCH_3), 60.13 (OCH_3), 103.02 (ArCH, C_4), 108.66 (ArCH, $C_{2'}$ & $C_{6'}$), 116.49 (ArCH, C_7), 118.10 (ArCH, C_6), 120.39 (C_q), 128.64 (C_q), 133.86 (C_q), 140.27 (C_q), 146.12 (C_q), 151.88 (C_q, C_{3a}), 154.49 (C_q, $C_{3'}$ & $C_{5'}$), 164.00 (C=O)

M.P.: 95-98 °C

IRν_{max} (KBr) cm^{-1}: 3457.2 (NH_2), 3357.1 (NH_2), 2834.2, 1711.3 (C=O), 1642.8, 1573.9, 1534.4, 1513.8, 1459.2, 1424.4, 1323.8, 1224.3, 1126.9

HRMS: Found 448.1970 $[M+Na]^+$, $C_{22}H_{27}N_5O_4Na$ requires 448.1961, (+2.0 ppm)

(3-(3-Phenylpropylamino)-5-amino-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (462)

As per general procedure C, (3-(3-phenylpropylamino)-5-amino-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (**462**) was prepared from (**452**) (80 mg, 0.16 mmol) as a brown solid (72 mg, 96%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.93 - 2.02 (m, 2H, CH_2), 2.67 (t, 2H, J = 7.32 Hz, CH_2), 3.23 - 3.31 (m, 2H, CH_2), 3.75 (s, 3H, OCH_3), 3.78 (s, 6H, 2 x OCH_3), 5.28 (s, 2H, NH_2), 6.88

(dd, 1H, ArH, J = 8.85, 2.44 Hz, H_6), 6.93 (t, 1H, J = 5.49 Hz, NH), 6.97 (d, 1H, ArH, J = 2.44 Hz, H_4), 7.12 - 7.21 (m, 3H, ArH), 7.23 - 7.28 (m, 2H, ArH), 7.53 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 8.08 (d, 1H, ArH, J = 8.55 Hz, H_7)

^{13}C NMR (101 MHz, DMSO-d_6) δ 30.15 (CH_2), 32.64 (CH_2), 41.99 (CH_2), 55.80 (2 x OCH_3), 60.08 (OCH_3), 102.13 (ArCH, C_4), 108.54 (ArCH, $C_{2'}$ & $C_{6'}$), 116.40 (ArCH, C_6), 117.94 (ArCH, C_7), 120.93 (C_q), 125.68 (ArCH), 128.23 (ArCH), 129.26 (C_q), 132.89 (C_q), 139.92 (C_q), 141.66 (C_q), 145.98 (C_q), 151.79 (C_q), 152.92 (C_q), 163.33 (C=O)

M.P.: 68-72 °C

IRν_{max} (KBr) cm^{-1}: 3457.2 (NH_2), 3367.9 (NH_2), 2931.0, 2832.5, 1634.8 (C=O), 1567.9, 1455.1, 1458.7, 1415.0, 1347.9, 1237.5, 1126.1

HRMS: Found 483.2011 $[M+Na]^+$, $C_{26}H_{28}N_4O_4Na$ requires 483.2008, (+0.6 ppm)

(3-(3,4,5-Trimethoxybenzylamino)-6-amino-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (466)

As per general procedure C, (3-(3,4,5-trimethoxybenzylamino)-6-amino-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (**466**) was prepared from (**457**) (100 mg, 0.18 mmol) as a brown solid (85 mg, 90%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.61 (s, 3H, OCH_3), 3.64 (s, 6H, 2 x OCH_3), 3.74 (s, 3H, OCH_3), 3.77 (s, 6H, 2 x OCH_3), 4.39 (d, 2H, J = 6.10 Hz, CH_2), 5.74 (s, 2H, NH_2), 6.25 (s, 1H, ArH, H_7) 6.60 (dd, 1H, ArH, J = 8.54, 1.83 Hz, H_5), 6.67 (s, 2H, ArH), 7.54 (s, 2H, ArH), 7.57 (d, 1H, ArH, J = 8.54 Hz, H_4)

^{13}C NMR (101 MHz, DMSO-d_6) δ 46.31 (CH_2), 55.61 (2 x OCH_3), 55.82 (2 x OCH_3), 59.91 (OCH_3), 60.07 (OCH_3), 98.79 (ArCH), 104.99 (ArCH), 108.65 (ArCH), 109.35 (ArCH), 120.77 (ArCH), 129.36 (C_q), 135.42 (C_q), 136.31 (C_q), 140.05 (C_q), 143.04 (C_q), 151.79 (s), 152.68 (C_q), 153.14 (C_q), 164.51 (C=O)

M.P.: 102-104 °C

IRν_{max} (KBr) cm^{-1}: 3453.2 (NH_2), 3367.55 (NH_2), 2937.2, 2832.5, 1633.8 (C=O), 1573.3, 1504.7, 1458.7, 1458.7, 1415.8, 1332.3, 1235.1, 1168.9, 1126.1, 1002.2

HRMS: Found 435.1640 $[M+Na]^+$, $C_{21}H_{24}N_4O_5Na$ requires 435.1644, (-0.9 ppm)

(6-Amino-3-(4-benzylpiperazin-1-yl)-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (465)

As per general procedure C, (6-amino-3-(4-benzylpiperazin-1-yl)-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (**465**) was prepared from (**457**) (110 mg, 0.21 mmol) as a brown solid (90 mg, 87%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 2.52 – 2.54 (m, 4H, 2 x CH_2), 3.44 (br. s., 4H, 2 x CH_2), 3.52 (s, 2H, CH_2), 3.75 (s, 3H, OCH_3), 3.83 (s, 6H, 2 x OCH_3), 5.83 (s, 2H, NH_2), 6.63 (dd, 1H, ArH, J = 8.54, 1.83 Hz), 7.22 - 7.30 (m, 1H, ArH), 7.30 - 7.35 (m, 3H, ArH), 7.47 - 7.52 (m, 2H, ArH), 7.59 (d, 1H, ArH, J = 8.54 Hz), 7.65 (d, 1H, ArH, J = 1.83 Hz)

^{13}C NMR (101 MHz, DMSO-d_6) δ 47.77 (2 x CH_2), 52.10 (2 x CH_2), 55.93 (2 x OCH_3), 60.10 (OCH_3), 62.13 (CH_2), 98.35 (ArCH), 108.66 (ArCH), 108.98 (C_q), 112.78 (ArCH), 122.32 (ArCH), 126.97 (ArCH), 128.17 (ArCH), 128.91 (ArCH), 137.89 (C_q), 140.27 (C_q), 143.91 (C_q), 150.95 (C_q), 151.83 (C_q), 164.91 (C=O)

M.P.: 98-101 °C

IRν_{max} (KBr) cm^{-1}: 3462.0 (NH_2), 3374.4 (NH_2), 2935.9, 2832.5, 1654.9 (C=O), 1579.7, 1537.9, 1498.6, 1451.2, 1431.0, 1331.3, 1126.5

HRMS: Found 502.2466 $[M+H]^+$, $C_{23}H_{23}N_4O_4$ requires 502.2454, (+2.4 ppm)

(5-Amino-3-(4-benzylpiperazin-1-yl)-1H-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (461)

As per general procedure C, (5-amino-3-(4-benzylpiperazin-1-yl)-1H-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (**461**) was prepared from (**451**) (200 mg, 0.38 mmol) as a brown solid (170 mg, 89%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 2.54 - 2.59 (m, 4H, 2 x CH_2), 3.44 (br. s., 4H, 2 x CH_2), 3.54 (s, 2H, CH_2), 3.75 (s, 3H, OCH_3), 3.82 (s, 6H, 2 x OCH_3), 5.27 (br. s., 2H, NH_2), 6.92 (dd, 1H, ArH, J = 9.16, 1.83 Hz), 6.98 - 7.03 (m, 1H, ArH), 7.24 - 7.30 (m, 1H, ArH), 7.31 - 7.36 (m, 3H, ArH), 7.49 - 7.53 (m, 1H, ArH), 8.16 (d, 1H, ArH, J = 9.16 Hz)

^{13}C NMR (101 MHz, DMSO-d_6) δ 47.99 (2 x CH_2), 51.98 (2 x CH_2), 55.93 (OCH_3), 60.10 (2 x OCH_3), 62.09 (CH_2), 103.02 (ArCH), 108.63 (ArCH), 116.49 (ArCH), 118.10 (ArCH),

120.40 (C_q), 126.99 (ArCH), 128.18 (ArCH), 128.62 (ArCH), 128.94 (C_q), 133.86 (C_q), 137.79 (C_q), 140.27 (C_q), 146.09 (C_q), 151.88 (C_q), 154.44 (C_q), 164.01 (C=O)

M.P.: 91-93 °C

IRν_{max} (KBr) cm^{-1}: 3448.3 (NH_2), 3362.7 (NH_2), 2931.0, 2827.6, 1647.3 (C=O), 1579.5, 1538.3, 1452.5, 1413.8, 1342.9, 1236.3, 1126.2, 1003.9

HRMS: Found 502.2454 $[M+H]^+$, $C_{23}H_{23}N_4O_4$ requires 502.2454, (0.0 ppm)

General Procedure AG: Preparation of 5-pyrrolyl and 6-pyrrolyl indazoles

A solution of the appropriate 5 or 6-aminoindazole (1 mmol) in DIW: acetic acid (1:9, 6 mL) was left stirring at 20 °C for 1 hour. A solution of 2,5-dimethoxytetrahydrofuran (1 eq, 1 mmol, 0.13 mL) in acetic acid (2 mL) was added slowly. The resultant solution was heated to reflux for 40 minutes and then cooled to 20 °C. EtOAc (10 mL) was added to the reaction mixture and the organic layer was washed with a saturated sodium hydrogen carbonate solution (5 x 6 mL), DIW (5 mL), a saturated brine solution (7 mL), dried using sodium sulphate, filtered and then concentrated to dryness *in vacuo*. Purification by flash column chromatography over silica gel (eluent EtOAc: Hexane gradient) afforded the desired pyrrolyl indazole.

(6-(1*H*-Pyrrol-1-yl)-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (477)

As per general procedure AG, (6-(1*H*-pyrrol-1-yl)-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (**477**) was prepared from (**209**) (327 mg, 1 mmol) and obtained as a colourless solid (100 mg, 26%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.96 (s, 6H, 2 x OCH_3), 3.98 (s, 3H, OCH_3), 6.44 (app t, 2H, J = 2.14 Hz, $H_{2''}$ & $H_{3''}$), 7.27 (app t, 2H, J = 2.14 Hz, $H_{1''}$ & $H_{4''}$), 7.46 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 7.52 (dd, 1H, ArH, J = 8.54, 1.83 Hz, H_5), 7.83 (d, 1H, ArH, J = 8.54 Hz, H_4), 8.23 (s, 1H, ArH, H_3), 8.63 (s, 1H, ArH, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 56.29 (2 x OCH_3), 60.94 (OCH_3), 107.10 (ArCH), 108.95 (ArCH, $C_{2'}$ & $C_{6'}$), 111.25 (ArCH), 118.35 (ArCH), 119.75 (ArCH), 121.94 (ArCH), 123.56 (C_q), 127.57 (C_q), 139.96 (ArCH, C_3), 141.20 (C_q), 141.91 (C_q), 142.00 (C_q), 152.63 (C_q, $C_{3'}$ & $C_{5'}$), 167.54 (C=O)

M.P.: 149-152 °C

IRν_{max} (NaCl film) cm^{-1}: 3137.9, 2939.9, 2832.5, 1684.9 (C=O), 1618.9, 1584.5, 1502.1,1463.2, 1415.1, 1376.7, 1353.2, 1335.5, 1289.8, 1239.9, 1184.4, 1126.8, 1084.1, 1003.0

HRMS: Found 400.1277 $[M+Na]^+$, $C_{21}H_{19}N_3NaO_4$ requires 400.1273, (+1.0 ppm)

(5-(1*H*-Pyrrol-1-yl)-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (487)

As per general procedure AG, (5-(1*H*-pyrrol-1-yl)-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (**487**) was prepared from (**168**) (327 mg, 1 mmol) and obtained as a colourless solid (125 mg, 33%)

^1H NMR (400 MHz, $CDCl_3$) δ 3.95 (s, 6H, 2 x OCH_3), 3.97 (s, 3H, OCH_3), 6.42 (app t, 2H, J = 2.14 Hz, $H_{2''}$ & $H_{3''}$), 7.17 (app t, 2H, J = 2.14 Hz, $H_{1''}$ & $H_{4''}$), 7.45 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 7.71 (dd, 1H, ArH, J = 9.16, 1.83 Hz, H_6), 7.76 (d, 1H, ArH, J = 1.83 Hz, H_4), 8.26 (s, 1H, ArH), 8.61 (d, 1H, ArH, J = 9.16 Hz, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 56.29 (2 x OCH_3), 60.93 (OCH_3), 108.95 (ArCH), 110.83 (ArCH), 111.79 (ArCH), 116.93 (ArCH), 119.79 (ArCH), 123.34 (ArCH), 126.75 (s), 127.48 (C_q), 138.01 (C_q), 138.29 (C_q), 139.99 (ArCH, C_3), 142.00 (C_q), 152.63 (C_q, $C_{3'}$ & $C_{5'}$), 167.26 (C=O)

M.P.: 167-169 °C

IRν_{max} (NaCl film) cm^{-1}: 3000.0, 2940.9, 2837.4, 1682.6 (C=O), 1583.6, 1583.4, 1520.3, 1452.2, 1414.6, 1375.7, 1339.0, 1239.3, 1169.8, 1126.5, 1018.7

HRMS: Found 400.1269 $[M+Na]^+$, $C_{21}H_{19}N_3NaO_4$ requires 400.1273, (-1.0 ppm)

1-(3,4,5-Trimethoxybenzyl)-6-(1*H*-pyrrol-1-yl)-1*H*-indazole (478)

As per general procedure AG, 1-(3,4,5-trimethoxybenzyl)-6-(1*H*-pyrrol-1-yl)-1*H*-indazole **(478)** was prepared from (**259**) (92 mg, 0.3 mmol) and obtained as a colourless solid (61 mg, 57%)

^1H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 6H, 2 x OCH_3), 3.81 (s, 3H, OCH_3), 5.53 (s, 2H, CH_2), 6.38 (app t, 2H, J = 2.14 Hz, $H_{2''}$ & $H_{3''}$), 6.45 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 7.11 (app t, 2H, J = 2.14 Hz, $H_{2''}$ & $H_{4''}$), 7.27 (dd, 1H, ArH, J = 9.16, 1.80 Hz, H_5), 7.30 (s, 1H, ArH, H_7), 7.79 (d, 1H, ArH, J = 9.16 Hz, H_4), 8.07 (s, 1H, ArH, H_3)

^{13}C NMR (101 MHz, $CDCl_3$) δ 53.18 (CH_2), 56.08 (2 x OCH_3), 60.75 (OCH_3), 100.52 (ArCH), 104.24 (ArCH, $C_{2'}$ & $C_{6'}$), 110.68 (ArCH), 115.63 (ArCH), 119.84 (ArCH), 122.31 (ArCH), 132.08 (C_q), 133.57 (ArCH, C_3), 137.61 (C_q), 139.64 (C_q), 153.50 (C_q, $C_{3'}$ & $C_{5'}$)

M.P.: 118-121 °C

IRν_{max} (NaCl film) cm^{-1}: 2941.6, 2837.4, 1583.6, 1585.4, 1521.3, 1452.2, 1424.7, 1374.6, 1335.1, 1240.3, 1171.2

HRMS: Found 364.1674 $[M+Na]^+$, $C_{21}H_{22}N_3O_3$ requires 364.1661, (+3.6 ppm)

1-(3,4,5-Trimethoxybenzyl)-5-(1*H*-pyrrol-1-yl)-1*H*-indazole (488)

As per general procedure AG, 1-(3,4,5-trimethoxybenzyl)-5-(1*H*-pyrrol-1-yl)-1*H*-indazole (**488**) was prepared from (**268**) (230 mg, 0.7 mmol) and obtained as a colourless solid (140 mg, 52%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 6H, 2 x OCH_3), 3.82 (s, 3H, OCH_3), 5.55 (s, 2H, CH_2), 6.37 (app t, 2H, J = 2.14 Hz, $H_{2''}$ & $H_{2''}$), 6.47 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 7.07 - 7.10 (m, 2H, $H_{1''}$ & $H_{4''}$), 7.40 - 7.44 (m, 1H, ArH, H_7), 7.44 - 7.48 (m, 1H, ArH, H_6), 7.71 (d, 1H, ArH, J = 1.83 Hz, H_4), 8.09 (s, 1H, ArH, H_3)

^{13}C NMR (101 MHz, $CDCl_3$) δ 53.47 (CH_2), 56.11 (2 x OCH_3), 60.79 (2 x OCH_3), 104.36 (ArCH, $C_{2'}$ & $C_{6'}$), 110.14 (ArCH), 110.23 (ArCH), 112.63 (ArCH), 120.11 (ArCH), 121.80 (ArCH), 124.50 (C_q), 132.06 (C_q), 133.38 (ArCH, C_3), 135.11 (C_q), 137.66 (C_q), 153.51 (C_q, C3' & $C_{5'}$)

M.P.: 134-136 °C

IRν_{max} (NaCl film) cm^{-1}: 2947.6, 2837.4, 1584.6, 1580.4, 1512.3, 1451.9, 1424.7, 1347.9, 1329.1, 1243.1, 1172.1

HRMS: Found 364.1661 $[M+Na]^+$, $C_{21}H_{22}N_3O_3$ requires 364.1661, (0.0 ppm)

1-(4-Methoxyphenyl)-6-(1*H*-pyrrol-1-yl)-1*H*-indazole (480)

As per general procedure AG, 1-(4-methoxyphenyl)-6-(1*H*-pyrrol-1-yl)-1*H*-indazole (**480**) was prepared from (**286**) (239 mg, 1 mmol) and obtained as a colourless solid (115 mg, 40%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (s, 3H, OCH_3), 6.39 (app t, 2H, J = 2.14 Hz, $H_{2''}$ & $H_{3''}$), 7.08 (d, 2H, ArH, J = 8.54 Hz), 7.14 (app t, 2H, J = 2.14 Hz, $H_{1''}$ & $H_{4''}$), 7.32 (dd, 1H, ArH, J = 8.54, 1.83 Hz, H_5), 7.58 (s, 1H, ArH, H_7), 7.61 (d, 2H, ArH, J = 8.54 Hz), 7.83 (d, 1H, ArH, J = 8.54 Hz, H_4), 8.19 (s, 1H, ArH, H_3)

^{13}C NMR (101 MHz, $CDCl_3$) δ 55.59 (OCH_3), 101.55 (ArCH), 110.68 (ArCH), 114.73 (ArCH), 116.08 (ArCH), 119.92 (ArCH), 122.32 (ArCH), 122.84 (C_q), 124.72 (ArCH), 132.87 (C_q), 134.75 (ArCH, C_3), 139.49 (C_q), 140.13 (C_q), 158.67 (C_q)

M.P.: 94-95 °C

IRν_{max} (NaCl film) cm^{-1}: 3183.4, 2835.4, 1623.92, 1516.04, 1113.8

HRMS: Found 290.1300 $[M+H]^+$, $C_{18}H_{16}N_3O$ requires 290.1293, (+2.4 ppm)

1-(6-(1*H*-Pyrrol-1-yl)-1*H*-indazol-1-yl)-2-(3,4,5-trimethoxyphenyl)ethanone (479)

As per general procedure AG, 1-(6-(1*H*-pyrrol-1-yl)-1*H*-indazol-1-yl)-2-(3,4,5-trimethoxyphenyl)ethanone (**479**) was prepared from (**229**) (273 mg, 0.8 mmol) and obtained as a colourless solid (100 mg, 32%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (s, 3H, OCH_3), 3.88 (s, 6H, 2 x OCH_3), 4.48 (s, 2H, CH_2), 6.39 (app t, 2H, J = 2.14 Hz, $H_{2''}$ & $H_{3''}$), 6.68 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 7.20 (app t, 2H, J = 2.14 Hz, $H_{1''}$ & $H_{4''}$), 7.46 (dd, 1H, ArH, J = 8.54, 1.83 Hz, H_5), 7.78 (d, 1H, ArH, J=8.54 Hz, H_4), 8.18 (s, 1H, ArH, H_3), 8.52 (s, 1H, ArH, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 41.79 (CH_2), 56.10 (2 x OCH_3), 60.80 (OCH_3), 106.69 (ArCH), 106.85 (ArCH, $C_{2'}$ & $C_{6'}$), 111.24 (ArCH), 118.08 (ArCH), 119.64 (ArCH), 121.96 (ArCH), 123.92 (C_q), 129.20 (C_q), 137.18 (C_q), 139.74 (ArCH), 140.09 (C_q), 141.90 (C_q), 153.26 (C_q, $C_{3'}$ & $C_{5'}$), 171.56 (C=O)

M.P.: 128-131 °C

IRν_{max} (NaCl film) cm^{-1}: 2945.8, 2837.4, 1715.1, 1619.2, 1590.8, 1505.2, 1419.3, 1330.9, 1241.2, 1126.5

HRMS: Found 414.1436 $[M+Na]^+$, $C_{22}H_{21}N_3O_4Na$ requires 414.1430, (+1.4 ppm)

1-(5-(1*H*-Pyrrol-1-yl)-1*H*-indazol-1-yl)-2-(3,4,5-trimethoxyphenyl)ethanone (489)

As per general procedure AG, 1-(5-(1*H*-pyrrol-1-yl)-1*H*-indazol-1-yl)-2-(3,4,5-trimethoxyphenyl)ethanone (**489**) was prepared from (**229**) (110 mg, 0.3 mmol) and obtained as a colourless solid (30 mg, 24%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (s, 3H, OCH_3), 3.88 (s, 6H, 2 x OCH_3), 4.48 (s, 2H, CH_2), 6.40 (s, 2H, $H_{2''}$ & $H_{3''}$), 6.69 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 7.13 (s, 2H, $H_{1''}$ & $H_{4''}$), 7.64 (d, 1H, ArH, J = 8.54 Hz), 7.71 (s, 1H, ArH, H_4), 8.22 (s, 1H, ArH, H_3), 8.50 (d, 1H, ArH, J = 8.54 Hz)

^{13}C NMR (101 MHz, $CDCl_3$) δ 41.67 (CH_2), 56.11 (2 x OCH_3), 60.80 (OCH_3), 106.86 (ArCH, $C_{2'}$ & $C_{6'}$), 110.81 (ArCH), 111.87 (ArCH), 116.62 (ArCH), 119.79 (ArCH), 123.43 (ArCH), 127.18 (C_q), 129.21 (C_q), 137.19 (C_q), 137.22 (C_q), 137.94 (C_q), 139.76 (ArCH, C_3), 153.27 (C_q, $C_{3'}$ & $C_{5'}$), 171.23 (C=O)

M.P.: 180-183 °C

IRν_{max} (NaCl film) cm^{-1}: 3099.1, 2936.5, 2836.7, 1709.7, 1591.2, 1520.4, 1487.8, 1463.4, 1424.3, 1390.3, 1336.0, 1241.8, 1164.1, 1127.0, 1068.9

HRMS: Found 414.1430 $[M+Na]^+$, $C_{22}H_{21}N_3O_4Na$ requires 414.1430, (+0.0 ppm)

(3-(4-Benzylpiperazin-1-yl)-5-(1*H*-pyrrol-1-yl)-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (490)

As per general procedure AG, (3-(4-benzylpiperazin-1-yl)-5-(1*H*-pyrrol-1-yl)-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (**490**) was prepared from (**461**) (100 mg, 0.20 mmol) and obtained as a colourless solid (32 mg, 29%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.73 (br. s., 4H, 2 x CH_2), 3.64 (br. s., 6H, 3 x CH_3), 3.93 (s, 6H, 2 x OCH_3), 3.96 (s, 3H, OCH_3), 6.40 (br. s., 2H, $H_{2''}$ & $H_{3''}$), 7.11 (br. s., 2H, $H_{1''}$ & $H_{4''}$), 7.28 - 7.50 (m, 5H, ArH), 7.55 - 7.73 (m, 4H, ArH), 8.67 (d, 1H, ArH, J = 8.54 Hz)

^{13}C NMR (101 MHz, $CDCl_3$) δ 48.39 (CH_2), 52.24 (CH_2), 56.25 (2 x OCH_3), 60.94 (OCH_3), 62.81 (CH_2), 109.09 (ArCH), 110.73 (ArCH), 112.81 (ArCH), 117.81 (ArCH), 120.01 (ArCH), 123.55 (ArCH), 128.09 (ArCH), 128.48 (ArCH), 129.42 (C_q), 137.31 (C_q), 140.33 (C_q), 141.44 (C_q), 152.32 (C_q, $C_{3'}$ & $C_{5'}$), 165.91 (C=O)

M.P.: 85-88 °C

IRν_{max} (NaCl film) cm^{-1}: 3123.2, 2936.7, 2834.8, 1662.2, 1581.2, 1539.7, 1496.9, 1452.5, 1413.7, 1363.2, 1331.6, 1237.6, 1166.9, 1188.1, 1128.0, 1069.4, 1005.8

HRMS: Found 574.2442 $[M+Na]^+$, $C_{32}H_{33}N_5O_4Na$ requires 574.2430, (+2.1 ppm)

(3-(4-Benzylpiperazin-1-yl)-6-(1*H*-pyrrol-1-yl)-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (481)

As per general procedure AG, (3-(4-benzylpiperazin-1-yl)-6-(1*H*-pyrrol-1-yl)-1*H*-indazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (**481**) was prepared from (**465**) (124 mg, 0.25 mmol) and obtained as a colourless solid (20 mg, 15%)

^1H NMR (400 MHz, $CDCl_3$) δ 2.72 (br. s., 4H, 2 x CH_2), 3.66 (br. s., 6H, 3 x CH_2), 3.93 (s, 3H, OCH_3), 3.96 (s, 6H, 2 x OCH_3), 6.41 (br. s., 2H, $H_{2''}$ & $H_{3''}$), 7.25 (br. s., 2H, $H_{1''}$ & $H_{4''}$), 7.29 - 7.45 (m, 6H, ArH), 7.63 (s, 2H, ArH), 7.77 (d, 1H, ArH, J = 8.54 Hz), 8.71 (s, 1H, ArH)

^{13}C NMR (101 MHz, $CDCl_3$) δ 48.21 (CH_2.), 52.27 (CH_2), 56.23 (2 x OCH_3), 60.93 (OCH_3), 62.93 (CH_2.), 107.87 (ArCH), 109.11 (ArCH), 111.18 (ArCH), 116.93 (ArCH), 119.61 (ArCH), 122.09 (ArCH), 128.18 (C_q), 128.45 (ArCH), 129.42 (ArCH), 141.42 (C_q), 141.71 (C_q), 143.31 (C_q), 152.29 (C_q, $C_{3'}$ & $C_{5'}$), 166.13 (C=O)

M.P.: 99-103 °C

IRν_{max} (NaCl film) cm^{-1}: 2936.9, 2834.6, 1662.8, 1581.2, 1539.8, 1496.9, 1452.9, 1413.6, 1363.0, 1331.7, 1236.77, 1128.0, 1069.5, 1005.9

HRMS: Found 574.2421 $[M+Na]^+$, $C_{32}H_{33}N_5O_4Na$ requires 574.2430, (-1.6 ppm)

1-(6-(1*H*-Pyrrol-1-yl)-1*H*-indazol-1-yl)-2,2-diphenylethanone (482)

As per general procedure AG, 1-(6-(1*H*-pyrrol-1-yl)-1*H*-indazol-1-yl)-2,2-diphenylethanone (**482**) was prepared from (**230**) (200 mg, 0.61 mmol) and obtained as a colourless solid (80 mg, 35%)

^1H NMR (400 MHz, $CDCl_3$) δ 6.39 (s, 2H), 6.68 (s, 1H, CH), 7.21 (s, 2H), 7.30 (d, 2H, ArH, J = 7.32 Hz), 7.36 (app t, 4H, ArH, J = 7.63 Hz), 7.46 (d, 5H, ArH, J = 7.32 Hz), 7.74 (d, 1H, ArH, J = 8.54 Hz, H_4), 8.12 (s, 1H, ArH), 8.61 (s, 1H, ArH)

^{13}C NMR (101 MHz, $CDCl_3$) δ 55.11 (CH), 106.90 (ArCH), 111.21 (ArCH), 118.07 (ArCH), 119.64 (ArCH), 121.94 (ArCH), 124.03 (C_q), 127.34 (ArCH), 128.66 (ArCH), 129.01 (ArCH), 138.54 (C_q), 139.86 (ArCH), 140.21 (C_q), 141.91 (C_q), 172.54 (C=O)

M.P.: 198-201 °C

IRν_{max} (NaCl film) cm^{-1}: 3059.1, 3019.7, 2921.2, 2847.3, 1713.9 (C=O), 1618.8, 1496.1, 1453.5, 1415.9, 1355.4, 1333.2, 1312.5, 1167.9, 1123.5, 1102.0

HRMS: Found 400.1411 $[M+Na]^+$, $C_{25}H_{19}N_3ONa$ requires 400.1426, (-3.7 ppm)

1-(5-(1*H*-Pyrrol-1-yl)-1*H*-indazol-1-yl)-2-(3,4-dimethoxyphenyl)ethanone (492)

As per general procedure AG, 1-(5-(1*H*-pyrrol-1-yl)-1*H*-indazol-1-yl)-2-(3,4-dimethoxyphenyl)ethanone (**492**) was prepared from (**234**) (144 mg, 0.47 mmol) and obtained as a colourless solid (35 mg, 21%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.49 (s, 2H, CH_2), 6.39 (app t, 2H, J = 2.14 Hz, $H_{2''}$ & $H_{3''}$), 6.84 - 6.88 (m, 1H, ArH), 6.97 - 7.02 (m, 2H, ArH), 7.12 (app t, 2H, J = 2.14 Hz, $H_{21''}$ & $H_{4''}$), 7.63 (dd, 1H, ArH, J = 8.85, 2.14 Hz, H_6), 7.71 (d, 1H, ArH, J = 2.14 Hz, H_4), 8.21 (s, 1H, ArH, H_3), 8.49 (d, 1H, ArH, J = 8.85 Hz, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 41.05 (CH_2), 55.89 (2 x OCH_3), 110.77 (ArCH), 111.30 (ArCH), 111.86 (ArCH), 112.91 (ArCH), 116.62 (ArCH), 119.80 (ArCH), 121.99 (ArCH), 123.39 (ArCH), 126.14 (C_q), 127.13 (C_q), 137.26 (C_q), 137.88 (C_q), 139.68 (ArCH), 148.28 (C_q), 148.98 (C_q), 171.56 (C=O)

M.P.: 189-191 °C

IRν_{max} (NaCl film) cm^{-1}: 3000.0, 2934.6, 2834.9, 1714.5 (C=O), 1590.9, 1516.8, 1486.6, 1463.1, 1435.9, 1420.6, 1384.3, 1338.9, 1307.2, 1262.3, 1237.8, 1157.5

HRMS: Found 362.1495 $[M+H]^+$, $C_{21}H_{20}N_3O_3$ requires 362.1505, (-2.8 ppm)

1-(5-(1*H*-Pyrrol-1-yl)-1*H*-indazol-1-yl)-2,2-diphenylethanone (491)

As per general procedure AG, 1-(5-(1*H*-pyrrol-1-yl)-1*H*-indazol-1-yl)-2,2-diphenylethanone (**491**) was prepared from (**235**) (265 mg, 0.81 mmol) and obtained as a colourless solid (123 mg, 40 %)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.40 (app t, 2H, J = 2.14 Hz, $H_{2''}$ & $H_{3''}$), 6.69 (s, 1H, CH), 7.09 - 7.15 (m, 2H, $H_{1''}$ & $H_{4''}$), 7.30 (d, 2H, ArH, J = 7.32 Hz), 7.36 (app t, dd, 4H, ArH, J = 7.32 Hz), 7.47 (d, 4H, ArH, J = 7.32 Hz), 7.64 (dd, 1H, ArH, J = 9.16, 1.83 Hz, H_6), 7.68 (s, 1H, ArH, H_4), 8.16 (s, 1H, ArH, H_3), 8.57 (d, 1H, ArH, J = 9.16 Hz, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 54.96 (CH), 110.78 (ArCH), 111.89 (ArCH), 116.76 (ArCH), 119.80 (ArCH), 123.38 (ArCH), 127.31 (C_q), 127.34 (ArCH), 128.66 (ArCH), 129.02 (ArCH), 137.32 (C_q), 137.97 (C_q), 138.54 (C_q), 139.86 (ArCH, C_3), 172.19 (C=O)

M.P.: 155-158 °C

I.R.ν_{max} (NaCl film): 3061.9, 3028.6, 2945.8, 2911.3, 1715.9, 1622.1, 1586.9, 1520.7, 1494.9, 1436.2, 1384.3, 1307.7, 1264.4, 1163.1, 1131.6, 1105.4, 1066.9

HRMS: Found 400.1426 $[M+Na]^+$, $C_{25}H_{19}N_3ONa$ requires 400.1426, (0.0 ppm)

(5-(1*H*-Pyrrol-1-yl)-1*H*-indazol-1-yl)(phenyl)methanone (493)

As per general procedure AG, (5-(1*H*-pyrrol-1-yl)-1*H*-indazol-1-yl)(phenyl)methanone (**493**) was prepared from (**208**) (80 mg, 0.34 mmol) and obtained as a colourless solid (25 mg, 26%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.42 (app t, 2H, J = 2.14 Hz), 7.17 (app t, 2H, J = 2.14 Hz, $H_{1''}$ & $H_{4''}$), 7.50 - 7.60 (m, 3H, ArH), 7.61 - 7.67 (m, 1H, ArH), 7.71 (dd, 1H, ArH, J = 8.55, 2.14 Hz, H_6), 7.76 (s, 1H, ArH, H_4), 8.10 (d, 2H, ArH, J = 8.73 Hz), 8.24 (s, 1H, ArH, H_3), 8.64 (d, 1H, ArH, J = 8.55 Hz, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 110.82 (ArCH), 111.87 (ArCH), 116.93 (ArCH), 119.84 (ArCH), 123.36 (ArCH), 128.04 (ArCH), 130.99 (ArCH), 132.43 (ArCH), 138.05 (C_q), 138.15 (C_q), 140.05 (ArCH), 168.14 (C=O)

M.P.: 191-194 °C

IRν_{max} (NaCl film) cm^{-1}: 2837.4, 1671.9 (C=O), 1626.7, 1602.1, 1524.6, 1412.5, 1380.7, 1353.4, 1329.4, 1323.9, 1261.9, 1174.8, 1127.7, 1072.1

HRMS: Found 288.1123 $[M+H]^+$, $C_{18}H_{14}N_3O$ requires 288.1137, (-4.9 ppm)

(5-(1*H*-Pyrrol-1-yl)-1*H*-indazol-1-yl)(4-methoxyphenyl)methanone (494)

As per general procedure AG, (5-(1*H*-pyrrol-1-yl)-1*H*-indazol-1-yl)(4-methoxyphenyl)methanone (**494**) was prepared from (**202**) (75 mg, 0.28 mmol) and obtained as a colourless solid (30 mg, 34%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.93 (s, 3H, OCH_3), 6.43 (s, 2H, $H_{2''}$ & $H_{3''}$), 7.05 (d, 2H, ArH, J = 9.16 Hz), 7.27 (br. s., 2H, $H_{1''}$ & $H_{4''}$), 7.51 (d, 1H, ArH, J = 8.54 Hz), 7.82 (d, 1H, ArH, J = 8.54 Hz), 8.14 - 8.23 (m, 3H, ArH), 8.64 (s, 1H, ArH)

^{13}C NMR (101 MHz, $CDCl_3$) δ 55.49 (OCH_3), 107.14 (ArCH), 111.14 (ArCH), 113.44 (ArCH), 118.18 (ArCH), 119.79 (ArCH), 121.84 (ArCH), 123.54 (C_q), 124.95 (C_q), 133.61 (C_q), 139.53 (ArCH), 141.16 (C_q), 141.76 (C_q), 163.11 (C_q), 167.52 (C=O)

M.P.: 188-191 °C

IRν_{max} (NaCl film) cm^{-1}: 3093.6, 2960.6, 2837.4, 1670.9 (C=O), 1616.7, 1602.1, 1504.7, 1414.9, 1380.7, 1353.4, 1329.4, 1313.9, 1260.9, 1173.8, 1117.3, 1072.0, 915.37

HRMS: Found 340.1062 $[M+Na]^+$, $C_{19}H_{15}N_3O_2Na$ requires 340.1062, (0.0 ppm)

1-(5-(1*H*-Pyrrol-1-yl)-1*H*-indazol-1-yl)-2-phenoxyethanone (495)

As per general procedure AG, 1-(5-(1*H*-pyrrol-1-yl)-1*H*-indazol-1-yl)-2-phenoxyethanone (**495**) was prepared from (**304**) (115 mg, 0.43 mmol) and obtained as a colourless solid (20 mg, 15 %)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.58 (s, 2H, CH_2), 6.41 (app t, 2H, J = 2.14 Hz, $H_{2''}$ & $H_{3''}$), 7.03 - 7.09 (m, 3H, ArH), 7.14 (app t, 2H, J = 2.14 Hz, $H_{1''}$ & $H_{4''}$), 7.32 - 7.37 (m, 2H), 7.68 (dd, 1H, ArH, J = 9.16, 1.83 Hz, H_6), 7.74 (d, 1H, ArH, J = 1.83 Hz, H_4), 8.23 (s, 1H, ArH, H_3), 8.50 (d, 1H, ArH, J = 8.55 Hz, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 66.41 (CH_2), 110.92 (ArCH), 112.05 (ArCH), 114.82 (ArCH), 116.23 (ArCH), 119.80 (ArCH), 121.82 (ArCH), 123.77 (ArCH), 126.78 (s), 129.62 (ArCH), 137.03 (C_q), 138.24 (C_q), 140.54 (ArCH), 157.93 (C_q), 167.73 (C=O)

M.P.: 189-191 °C

IRν_{max} (NaCl film) cm^{-1}: 2961.6, 2837.4, 1670.9 (C=O), 1616.7, 1602.1, 1514.9, 1424.9, 1381.7, 1343.4, 1330.1, 1261.9,

HRMS: Found 340.1062 $[M+Na]^+$, $C_{19}H_{15}N_3O_2Na$ requires 340.1062, (0.0 ppm)

(6-(1*H*-Pyrrol-1-yl)-1*H*-indazol-1-yl)(phenyl)methanone (483)

As per general procedure AG, (6-(1*H*-pyrrol-1-yl)-1*H*-indazol-1-yl)(phenyl)methanone (**483**) was prepared from (**217**) (90 mg, 0.38 mmol) and obtained as a colourless solid (34 mg, 31%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.43 (app t, 2H, J = 2.14 Hz, $H_{2''}$ & $H_{3''}$), 7.24 - 7.28 (m, 2H, $H_{1''}$ & $H_{4''}$), 7.49 - 7.58 (m, 3H, ArH), 7.60 - 7.66 (m, 1H, ArH), 7.82 (d, 1H, ArH, J = 8.54 Hz), 8.05 - 8.13 (m, 2H, ArH), 8.21 (s, 1H, ArH, H_3), 8.65 (s, 1H, ArH, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 107.14 (ArCH), 111.23 (ArCH), 118.38 (ArCH), 119.79 (ArCH), 121.93 (ArCH), 123.67 (C_q), 128.04 (ArCH), 130.96 (ArCH), 132.41 (ArCH), 133.03 (C_q), 140.00 (ArCH), 141.03 (C_q), 141.93 (C_q), 168.42 (C=O)

M.P.: 220-222 °C

IRν_{max} (NaCl film) cm^{-1}: 2687.8, 1619.6, 1494.3, 1444.2, 1416.7, 1375.9, 1351.9, 1327.7, 1155.3, 1118.5, 1072.9, 1014.5, 905.9

HRMS: Found 288.1130 $[M+H]^+$, $C_{18}H_{14}N_3O$ requires 288.1137, (-2.4 ppm)

(6-(1*H*-Pyrrol-1-yl)-1*H*-indazol-1-yl)(4-methoxyphenyl)methanone (484)

As per general procedure AG, (6-(1*H*-pyrrol-1-yl)-1*H*-indazol-1-yl)(4-methoxyphenyl)methanone (**484**) was prepared from (**211**) (130 mg, 0.50 mmol) and obtained as a colourless solid (23 mg, 14%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (s, 3H, OCH_3), 6.41 (br. s., 2H, $H_{2''}$ & $H_{3''}$), 7.04 (d, 2H, ArH, J=9.16 Hz), 7.16 (br. s., 2H, $H_{1''}$ & $H_{4''}$), 7.69 (d, 1H, ArH, J = 9.16 Hz), 7.74 (s, 1H, ArH), 8.18 (d, 2H, ArH, J = 9.16 Hz), 8.23 (s, 1H, ArH, H_3), 8.61 (d, 1H, ArH, J = 9.16 Hz)

^{13}C NMR (101 MHz, $CDCl_3$) δ 55.50 (OCH_3), 110.74 (ArCH), 111.78 (ArCH), 113.44 (ArCH), 116.93 (ArCH), 119.84 (ArCH), 123.22 (ArCH), 124.86 (s), 126.65 (s), 133.62 (ArCH), 137.83 (C_q), 138.32 (C_q), 139.58 (ArCH), 163.13 (C_q), 167.24 (C=O)

M.P.: 237-239 °C

IRν_{max} (NaCl film) cm^{-1}: 2677.8, 1619.6, 1494.3, 1434.9, 1426.7, 1373.6, 1352.9, 1323.7, 1151.7, 1129.1, 1075.9, 1011.5, 911.3

HRMS: Found 340.1072 $[M+Na]^+$, $C_{19}H_{15}N_3O_2Na$ requires 340.1062, (+2.9 ppm)

2-Benzyl-5-(1*H*-pyrrol-1-yl)-2*H*-indazole (497)

As per general procedure AG, 2-benzyl-5-(1*H*-pyrrol-1-yl)-2*H*-indazole (**497**) was prepared from (**272**) (117 mg, 0.52 mmol) and obtained as a colourless solid (38 mg, 27%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.62 (s, 2H, CH_2), 6.36 (d, 2H, J = 1.83 Hz, $H_{2''}$ & $H_{4''}$), 7.09 (d, 2H, J = 1.83 Hz, $H_{2''}$ & $H_{4''}$), 7.30 - 7.44 (m, 6H, ArH), 7.56 (s, 1H, ArH), 7.81 (d, 1H, ArH, J = 9.16 Hz), 7.92 (s, 1H, ArH)

^{13}C NMR (101 MHz, $CDCl_3$) δ 57.68 (CH_2), 110.60 (ArCH), 118.95 (ArCH), 119.98 (ArCH), 122.22 (ArCH), 123.24 (ArCH), 128.01 (ArCH), 128.51 (ArCH), 128.98 (ArCH), 135.47 (C_q), 135.50 (C_q), 147.30 (C_q)

M.P.: 133-136 °C

I.R.ν_{max} (NaCl film) cm^{-1}: 3124.9, 3062.5, 2925.6, 1637.1, 1529.1, 1484.9, 1455.9, 1443.2, 1427.3, 1385.7, 1344.6, 1298.5, 1264.2, 1221.5, 1142.9, 1076.9, 1065.0

HRMS: Found 296.1152 $[M+Na]^+$, $C_{19}H_{15}N_3O_2Na$ requires 296.1164, (-4.1 ppm)

(3,4,5-Trimethoxyphenyl)(3-morpholino-6-(1*H*-pyrrol-1-yl)-1*H*-indazol-1-yl)methanone (486)

As per general procedure, (3,4,5-trimethoxyphenyl)(3-morpholino-6-(1*H*-pyrrol-1-yl)-1*H*-indazol-1-yl)methanone (**486**) was prepared from (**463**) (190 mg, 0.46 mmol) and obtained as a colourless solid (95 mg, 45%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.54 - 3.60 (m, 4H, 2 x CH_2), 3.91 - 3.95 (m, 10H, 2 x OCH_3, 2 x CH_2), 3.97 (s, 3H, OCH_3), 6.41 (app t, 2H, J = 2.14 Hz, $H_{2''}$ & $H_{3''}$), 7.25 (app t, 2H, J = 2.14 Hz, $H_{1''}$ & $H_{4''}$), 7.42 (dd, 1H, ArH, J = 8.85, 2.14 Hz, H_5), 7.60 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 7.79 (d, 1H, ArH, J = 9.16 Hz, H_4), 8.71 (d, 1H, ArH, J = 1.83 Hz, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 48.94 (2 x CH_2), 56.21 (2 x OCH_3), 60.94 (OCH_3), 66.35 (2 x CH_2), 107.84 (ArCH), 109.08 (ArCH), 111.24 (ArCH), 116.70 (C_q), 117.00 (ArCH), 119.60 (ArCH), 121.97 (ArCH), 128.10 (C_q), 141.49 (C_q), 141.80 (C_q), 143.30 (C_q), 152.32 (C_q, $C_{3'}$ & $C_{5'}$), 154.63 (C_q), 166.22 (C=O)

M.P.: 251-254 °C

IRν_{max} (NaCl film) cm^{-1}: 3131.5, 2959.9, 2837.3, 1662.9, 1613.2, 1582.6, 1539.6, 1503.4, 1441.0, 1378.3, 1333.6, 1277.7, 1210.7, 1168.7, 1126.4, 1064.9

HRMS: Found 463.1973 $[M+H]^+$, $C_{25}H_{27}N_4O_5$ requires 463.1981, (-1.7 ppm)

(3,4,5-Trimethoxyphenyl)(3-morpholino-5-(1*H*-pyrrol-1-yl)-1*H*-indazol-1-yl)methanone (496)

As per general procedure AG, (3,4,5-trimethoxyphenyl)(3-morpholino-5-(1*H*-pyrrol-1-yl)-1*H*-indazol-1-yl)methanone (**496**) was prepared from (**458**) (135 mg, 0.33 mmol) and obtained as a colourless solid (78 mg, 51%)

^1H NMR (400 MHz, $CDCl_3$) δ 3.54 - 3.58 (m, 4H, 2 x CH_2), 3.92 - 3.96 (m, 10H, 2 x OCH_3, 2 x CH_2), 3.97 (s, 2H, OCH_3), 6.41 (app t, 2H, J =1.83 Hz, $H_{2''}$ & $H_{3''}$), 7.13 (app t, 2H, J = 2.14 Hz, $H_{1''}$ & $H_{4''}$), 7.59 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 7.65 (dd, 1H, ArH, J = 8.85, 1.83 Hz, H_6), 7.70 (d, 1H, ArH, J = 1.83 Hz, H_4), 8.67 (d, 1H, ArH, J = 8.85 Hz, H_7)

^{13}C NMR (101 MHz, $CDCl_3$) δ 49.16 (2 x CH_2), 56.22 (2 x OCH_3), 60.94 (OCH_3), 66.35 (2 x CH_2), 109.07 (ArCH), 110.77 (ArCH), 112.69 (ArCH), 117.83 (ArCH), 120.02 (ArCH), 123.66 (ArCH), 128.03 (C_q), 137.37 (C_q), 140.33 (C_q), 141.51 (C_q), 152.35 (C_q), 154.82 (C_q), 165.99 (C=O)

M.P.: 229-232 °C

IRν_{max} (NaCl film) cm^{-1}: 2958.7, 2837.3, 1662.97, 1580.8, 1539.8, 1539.4, 1497.9, 1450.6, 1413.6, 1376.7, 1359.5, 1331.6, 1249.1, 1187.9, 1164.9, 1125.9, 1069.0, 1026.8, 1003.8

HRMS: Found 463.1981 $[M+H]^+$, $C_{26}H_{28}N_3O_5$ requires 463.1981, (0.0 ppm)

General Procedure AH: Preparation of 2-Cyano-*N*-arylacetamides

To a microwave vial, the required 6-aminoindazole (1.53 mmol, 1 eq) and ethyl cyanoacetate (9.4 mmol, 6 eq) were added. This suspension was irradiated, using the CEM Discover microwave reactor, to a temperature of 190 °C for 30 minutes, setting the maximum wattage to 35 W. The resultant black oil was purified using flash column chromatography over silica (eluent EtOAc: Hexane gradient) affording the desired product.

2-Cyano-*N*-(1-(3,4,5-trimethoxybenzoyl)-1*H*-indazol-6-yl)acetamide (500)

Using the general procedure AH, 2-cyano-*N*-(1-(3,4,5-trimethoxybenzoyl)-1H-indazol-6-yl)acetamide was prepared from (**209**) and ethyl cyanoacetate as a colourless solid (160 mg, 43%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.78 (s, 3H, OCH_3), 3.83 (s, 6H, 2 x OCH_3), 4.00 (s, 2H, CH_2), 7.35 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 7.61 (d, 1H, ArH, J = 8.53 Hz), 7.89 (d, 1H, ArH, J = 8.52 Hz), 8.45 (s, 1H, ArH, H_3), 8.81 (s, 1H, ArH, H_7), 10.74 (s, 1H, NHCO)

^{13}C NMR (101 MHz, DMSO-d_6) δ 27.07 (CH_2), 56.16 (2 x OCH_3), 60.24 (OCH_3), 104.91 (ArCH), 108.67 (ArCH, $C_{2'}$ & $C_{6'}$), 115.86 (ArCH), 117.37 (ArCH), 122.14 (ArCH), 128.03, 139.80 (C_q), 140.09 (C_q), 140.67 (ArCH), 140.98 (C_q), 152.18(C_q, $C_{3'}$ & $C_{5'}$), 161.63 (C=O), 167.21 (C=O)

M.P.: 189-192 °C

IRν_{max} (NaCl film) cm^{-1}: 3583.4, 3233.0, 3104.0, 2942.1, 2828.9, 2258.8 (CN), 1683.3 (C=O), 1620.8, 1584.6, 1558.4, 1488.9, 1464.5, 1409.2, 1378.4, 1348.7, 1328.9, 12391, 1125.6, 1033.7, 999.9

HRMS: Found 417.1161 $[M+Na]^+$, $C_{20}H_{18}N_4NaO_5$ requires 417.1175, (-3.4 ppm)

3,4,5-Trimethoxy-*N*-(1-(3,4,5-trimethoxybenzoyl)-1*H*-indazol-6-yl)benzamide (501)

Using the general procedure AH, 3,4,5-trimethoxy-*N*-(1-(3,4,5-trimethoxybenzoyl)-1*H*-indazol-6-yl)benzamide **(501)** was prepared from (**209**) and ethyl cyanoacetate as a colourless solid (35 mg, 4%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.75 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.84 (s, 6H, 2 x OCH_3), 3.90 (s, 6H, 2 x OCH_3), 7.35 (s, 2H, ArH), 7.37 (s, 2H, ArH), 7.83 - 7.88 (m, 1H, ArH), 7.89 - 7.94 (m, 1H, ArH), 8.47 (s, 1H, ArH), 9.01 (s, 1H, ArH), 10.53 (s, 1H, NHC=O)

^{13}C NMR (101 MHz, DMSO-d_6) δ 56.18 (3 x OCH_3), 60.20 (OCH_3), 60.26 (OCH_3), 105.47 (ArCH), 106.20 ArCH), 108.67 (ArCH), 118.87, 121.64, 122.14, 128.19, 129.81, 140.16, 140.49, 140.63, 140.74, 140.98, 152.22 (C_q, 2 x CO), 152.70(C_q, 2 x CO), 165.36 (C=O), 167.23 (C=O)

M.P.: 191-193 °C

IRν_{max} (NaCl film) cm^{-1}: 3585.5, 3339.9, 2941.0, 2838.3, 1671.9, 1584.8, 1541.8, 1501.8, 1438.1, 1414.8, 1343.8, 1235.9, 1126.4, 1001.8

HRMS: Found 522.1887 $[M+H]^+$, $C_{27}H_{28}N_3O_8$ requires 522.1876, (+2.1 ppm)

2-Cyano-*N*-(1-(3,4,5-trimethoxybenzyl)-1*H*-indazol-6-yl)acetamide (502)

Using the general procedure AH, 2-cyano-N-(1-(3,4,5-trimethoxybenzyl)-1*H*-indazol-6-yl)acetamide (**502**) was prepared from (**259**) (313 mg, 1 mmol) and ethyl cyanoacoatete as a colourless solid (310 mg, 81%)

^{1}H NMR 400 MHz, DMSO-d_6) δ 3.60 (s, 3H, OCH_3), 3.69 (s, 6H, 2 x OCH_3), 3.93 (s, 2H, CH_2), 5.51 (s, 2H, CH_2), 6.55 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 7.07 (dd, 1H, ArH, J = 8.85, 1.53 Hz, H_5), 7.71 (d, 1H, ArH, J = 8.54 Hz, H_4), 8.04 (s, 1H, ArH), 8.12 (s, 1H, ArH), 10.46 (s, 1H, NH)

^{13}C NMR (101 MHz, DMSO-d_6) δ 26.84 (CH_2), 52.20 (CH_2), 55.76 (2 x OCH_3), 59.93 (OCH_3), 99.17 (ArCH), 104.77 (ArCH), 114.27 (ArCH), 115.83 (C_q), 120.56 (C_q), 121.41 (ArCH), 132.79 (C_q), 132.91 (ArCH), 136.69 (C_q), 136.80 (C_q), 139.30 (C_q), 152.88 (C_q), 161.25 (C=O)

M.P.: 100-101 °C

IRν_{max} (KBr) cm^{-1}: 3116.8, 2940.5, 2839.0, 2221.06.83 (CN), 1666.30 (C=O), 1584.0, 1540.6, 1504.3, 1480.0, 1458.7, 1410.9, 1368.7, 1343.0, 1292.8, 1238.1, 1189.3, 1148.2, 1126.7, 1003.2

HRMS: Found 381.1562 $[M+H]^+$, $C_{20}H_{21}N_4O_4$ requires 381.1563, (-0.3 ppm)

2-Cyano-*N*-(2-(3,4,5-trimethoxybenzyl)-2*H*-indazol-6-yl)acetamide (504)

Using the general procedure AH, 2-cyano-*N*-(2-(3,4,5-trimethoxybenzyl)-2*H*-indazol-6-yl)acetamide (**504**) was prepared from (**262**) (313 mg, 1 mmol) and ethyl cyanoacoatete as a colourless solid (100 mg, 26%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.62 (s, 3H, OCH_3), 3.73 (s, 6H, 2 x OCH_3), 3.92 (s, 2H, CH_2), 5.49 (s, 2H, CH_2), 6.73 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 7.02 (dd, 1H, ArH, J = 8.54, 1.83 Hz, H_5), 7.66 (d, 1H, ArH, J = 8.54 Hz, H_4), 8.00 (s, 1H, ArH), 8.40 (s, 1H, ArH), 10.28 (s, 1H, NH)

^{13}C NMR (101 MHz, DMSO-d_6) δ 26.79 (CH_2), 55.89 (2 x OCH_3), 56.46 (CH_2), 59.95 (OCH_3), 104.93 (ArCH), 105.82 (ArCH), 115.96 (C_q), 116.08 (ArCH), 118.63 (C_q), 121.22 (ArCH), 123.92 (ArCH), 132.22 (C_q), 135.72 (C_q), 137.19 (C_q), 148.17 (C_q), 152.89 (C_q), 161.03 (C=O)

M.P.: 151-154 °C

IRν_{max} (NaCl film) cm^{-1}: 2941.1, 2842.6, 2220.9 (CN), 1658.4 (C=O), 1583.3, 1542.8, 1517.6, 1461.3, 1425.0, 1319.2, 1249.2, 1121.4

HRMS: Found 381.1563 $[M+H]^+$, $C_{20}H_{21}N_4O_4$ requires 381.1563, (0.0 ppm)

2-Cyano-*N*-(1-(4-methoxyphenyl)-1*H*-indazol-6-yl)acetamide (503)

Using the general procedure AH, 2-cyano-*N*-(1-(4-methoxyphenyl)-1*H*-indazol-6-yl)acetamide (**503**) was prepared from (**286**) (1 mmol, 239 mg) and ethyl cyanoacetate (6 mmol, 0.64 mL) as a brown solid (240 mg, 78 %)

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.85 (s, 3H, OCH_3), 3.94 (s, 2H, CH_2), 7.17 (d, 2H, ArH, J = 9.16 Hz), 7.21 (d, 1H, ArH, J = 8.54 Hz), 7.59 (d, 2H, ArH, J = 8.54 Hz), 7.81 (d, 1H, ArH, J = 9.16 Hz), 8.22 (s, 1H, ArH), 8.24 (s, 1H, ArH), 10.55 (s, 1H, NH)

^{13}C NMR (101 MHz, DMSO-d_6) δ 26.91 (CH_2), 55.47 (OCH_3), 99.19 (ArCH), 114.70 (ArCH), 114.78 (2 x ArCH), 115.78 (C_q), 121.07 (C_q), 121.80 (ArCH), 124.20 (2 x ArCH), 132.60 (C_q), 134.83 (ArCH), 137.68 (C_q), 138.73 (C_q), 158.03 (C_q), 161.41 (C=O)

M.P.: 176-178 °C

IRν_{max} (KBr) cm^{-1}: 3275.36 (NH), 2260.86 (CN), 1672.63 (C=O), 1515.19, 1248.03, 830.7, 665.65.

HRMS: Found 307.1192 $[M+H]^+$, $C_{17}H_{15}N_4O_2$ requires 307.1195, (-1.0 ppm)

General Procedure AI: Preparation of pyridone ring

To a solution of 2-cyano-*N*-arylacetamide (0.47mmol, 1 eq) in $CHCl_3$ (5 mL), was added acetylacetone (0.56 mmol, 1.2 eq) and piperidine (0.35 mmol, 0.75 eq). The resultant solution was refluxed for 6h, cooled to 20 °C and concentrated to dryness *in vacuo*. The crude product was purified using flash column chromatography over silica gel (eluent EtOAc: Hexane gradient) affording the desired pyridone product.

4,6-Dimethyl-2-oxo-1-(1-(3,4,5-trimethoxybenzoyl)-1H-indazol-6-yl)-1,2-dihydropyridine-3-carbonitrile (505)

As per the general procedure AG, 4,6-dimethyl-2-oxo-1-(1-(3,4,5-trimethoxybenzoyl)-1H-indazol-6-yl)-1,2-dihydropyridine-3-carbonitrile (**505**) was prepared from (**500**) and acetylacetone as a white solid (56.2 mg, 26%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.10 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 3.93 (s, 6H, 2 x OCH_3), 3.96 (s, 3H, OCH_3), 6.21 (s, 1H, ArH), 7.23 (d, 1H, ArH, J = 8.03 Hz), 7.38 (s, 1H, ArH), 7.95 (d, 1H, ArH, J = 8.53 Hz), 8.30 (s, 1H, ArH), 8.42 (s, 1H, ArH)

^{13}C NMR (101 MHz, $CDCl_3$) δ 21.51 (CH_3), 22.33(CH_3), 56.58 (2 x OCH_3), 61.24 (OCH_3), 102.66 (C_q), 104.22 (C_q), 109.13 (ArCH), 109.53 (ArCH), 115.29 (C_q), 115.87 (ArCH), 122.90 (ArCH), 124.68 (ArCH), 126.63 (C_q), 127.40 (C_q), 138.44 (C_q), 140.08 (ArCH), 140.89 (C_q), 142.36 (C_q), 150.92 (C_q), 152.93 (C_q), 159.98 (C_q), 161.45 (C=O), 167.69 (C=O)

M.P.: 194-197 °C

IRν_{max} (NaCl film) cm^{-1}: 3116.8, 2940.5, 2839.0, 2221.06.83 (CN), 1666.30 (C=O), 1584.0, 1540.6, 1504.3, 1480.0, 1458.7, 1410.9, 1368.7, 1343.0, 1292.8, 1238.1, 1189.3, 1148.2, 1126.7, 1003.2

HRMS: Found 459.1655 $[M+H]^+$, $C_{25}H_{23}N_4O_5$ requires 459.1668, (-2.8ppm)

1-(1*H*-Indazol-6-yl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (506)

As per the general procedure AG, 1-(1*H*-indazol-6-yl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (**506**) was prepared from (**500**) and acetylacetone as a white solid (5%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.98 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 6.47 (s, 1H, ArH), 6.99 (s, 1H, ArH), 7.58 (s, 1H, ArH), 7.91 (s, 1H, ArH), 8.18 (s, 1H, ArH), 13.38 (s, 1H, ArH)

HRMS: Found 265.1099 $[M+H]^+$, $C_{15}H_{13}N_4O$ requires 265.1089, (-3.8 ppm)

4,6-Dimethyl-2-oxo-1-(1-(3,4,5-trimethoxybenzyl)-1*H*-indazol-6-yl)-1,2-dihydropyridine-3-carbonitrile (507)

As per the general procedure AI, 4,6-dimethyl-2-oxo-1-(1-(3,4,5-trimethoxybenzyl)-1*H*-indazol-6-yl)-1,2-dihydropyridine-3-carbonitrile (**507**) was prepared from (**502**) (280 mg, 0.74 mmol) from and acetylacetone (0.88 mmol) as a colourless solid (56.2 mg, 26%)

^{1}H NMR (400 MHz,$CDCl_3$) δ 1.94 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 3.77 (s, 6H, 2 x OCH_3), 3.79 (s, 3H, OCH_3), 5.17 (d, 1H, *J* = 15.26 Hz, benzylic CH), 5.41 (d, 1H, *J* = 15.26 Hz, benzylic CH), 6.92 (dd, 1H, ArH, *J* = 8.54, 1.53 Hz, H_5), 7.30 (s, 1H, ArH, H_7), 7.88 (d, 1H, ArH, *J* = 8.54 Hz, H_4), 8.11 (s, 1H, ArH, H_3)

^{13}C NMR (101 MHz,$CDCl_3$) δ 21.18 (CH_3), 21.84 (CH_3), 53.31 (CH_2), 56.18 (2 x OCH_3), 60.76 (OCH_3), 102.15 (s), 104.50 (ArCH, $C_{2'}$ & $C_{6'}$), 109.20 (ArCH), 109.43 (ArCH), 114.99 (C_q), 120.08 (ArCH), 122.90 (ArCH), 124.45 (C_q), 131.65 (ArCH), 133.46 (C_q), 135.46 (C_q), 137.58 (C_q), 150.98 (C_q), 153.46 (C_q), 159.43 (C_q), 161.19 (C=O)

M.P.: 169-172 °C

IRν_{max} (NaCl film) cm^{-1}: 3058.9, 2939.9, 2839.3, 2221.1, 1699.9 (C=O), 1625.1, 1592.6, 1540.9, 1507.4, 1474.8, 1460.4, 1424.5, 1407.9, 1369.2, 1328.4, 1154.9, 1127.3, 1006.3

HRMS: Found 467.1705 $[M+Na]^+$, $C_{25}H_{24}N_4NaO_4$ requires 467.1695, (+2.1 ppm)

1-(2-(3,4,5-Trimethoxybenzyl)-2*H*-indazol-6-yl)-1,2-dihydro-4,6-dimethyl-2-oxopyridine-3-carbonitrile (509)

As per the general procedure AI, 1-(2-(3,4,5-trimethoxybenzyl)-2*H*-indazol-6-yl)-1,2-dihydro-4,6-dimethyl-2-oxopyridine-3-carbonitrile (**509**) was prepared from (**504**) (552 mg, 1.37 mmol) and acetylacetone (0.16 mL, 1.51 mmol) as a colourless solid (200 mg, 33%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.08 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 3.84 (s, 9H, 3 x OCH_3), 5.46 - 5.51 (m, 1H, benzylic CH), 5.52 - 5.58 (m, 1H, benzylic CH), 6.15 (s, 1H, ArH), 6.59 (s, 2H, ArH, $H_{2'}$ & $H_{6'}$), 6.81 (dd, 1H, ArH, *J* = 8.85, 1.53 Hz, H_5), 7.53 (s, 1H, ArH, H_7), 7.75 (d, 1H, ArH, *J* = 8.85 Hz, H_4), 7.99 (s, 1H, ArH, H_3)

^{13}C NMR (101 MHz, $CDCl_3$) δ 21.12 (CH_3), 21.91 (CH_2), 56.24 (2 x OCH_3), 58.03 (CH_2), 60.81 (OCH_3), 102.21 (C_q), 105.51 (ArCH), 109.00 (ArCH), 115.20 (s), 116.73 (ArCH), 120.99 (ArCH), 121.89 (C_q), 122.54 (ArCH), 123.61 (ArCH), 130.58 (C_q), 135.18 (C_q), 138.20 (C_q), 148.21 (C_q), 151.19 (C_q), 153.61 (C_q), 159.23 (C_q), 161.24 (C=O)

M.P.: 231-233 °C

IRν_{max} (NaCl film) cm^{-1}: 2942.0, 2840.6, 2220.1 (CN), 1658.4(C=O), 1593.3, 1540.8, 1507.6, 1461.3, 1426.0, 1329.2, 1241.2, 1125.9, 1008.8

HRMS: Found 445.1881 $[M+H]^+$, $C_{25}H_{25}N_4O_4$ requires 445.1876, (+1.1 ppm)

1-(1-(4-Methoxyphenyl)-1*H*-indazol-6-yl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (508)

As per the general procedure AI, 1-(1-(4-methoxyphenyl)-1*H*-indazol-6-yl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (**508**) was prepared from (**503**) (200 mg, 0.65 mmol) and acetyl acetone (0.72 mmol, 0.08 mL) as a white solid (110 mg, 45%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.04 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 3.87 (s, 3H, OCH_3), 6.14 (s, 1H, ArH), 6.98 (dd, 1H, ArH, *J*=8.54, 1.22 Hz), 7.04 (d, 2H, ArH, *J*=9.16 Hz), 7.46 (s, 1H, ArH), 7.57 (d, 2H, ArH, *J*=9.16 Hz), 7.94 (d, 1H, ArH, *J*=8.54 Hz), 8.25 (s, 1Hm ArH)

^{13}C NMR (101 MHz, $CDCl_3$) δ 21.48 (CH_3), 22.28 ($\underline{C}H_3C$=CCN)), 55.93 (OCH_3), 102.68, 109.32 (ArCH), 110.06 (ArCH), 115.07 (ArCH), 115.33 (C_q), 120.89 (ArCH), 123.35 (ArCH), 125.08 (ArCH), 132.84 (C_q), 135.17 (ArCH), 136.34 (C_q), 139.49 (C_q), 151.23 (C_q), 159.18 (C_q), 159.66 (C_q), 161.53 (C=O)

M.P.: 251-253 °C

IRν_{max} (NaCl film) cm^{-1}: 2218.92 (CN), 1655.16 (C=O), 1590.10, 1540.30, 1515.29

HRMS: Found 371.1491 $[M+H]^+$, $C_{22}H_{19}N_4O_2$ requires 371.1508, (+4.6 ppm)

***N*-(1-(3,4,5-Trimethoxybenzyl)-1*H*-indazol-6-yl)-2-imino-2*H*-chromene-3-carboxamide (521)**

A solution of (**502**) (137 mg, 0.36 mmol), salicyladehyde (0.04 mL, 0.36 mmol), ammonium acetate (42 mg, 0.54 mmol) in EtOH (3 mL) was refluxed for 1 hour. The solution was cooled to room temperature and the yellow precipitate was collected by vacuum filtration, recrystallized in EtOH which afforded the desired product as a yellow solid (80 mg, 46%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H, OCH_3), 3.81 (s, 6H, 2 x OCH_3), 5.52 (s, 2H, CH_2), 6.54 (s, 2H, ArH), 7.08 (d, 1H, ArH, *J* = 8.54 Hz), 7.17 (d, 1H, ArH, *J* = 8.54 Hz), 7.21 - 7.27 (m, 1H, ArH), 7.48 - 7.58 (m, 2H, ArH), 7.67 (d, 1H, ArH, *J* = 8.54 Hz), 7.99 (s, 1H, ArH), 8.47 (s, 1H, ArH), 8.58 (s, 1H, ArH), 12.85 (br. s., 1H, NH)

^{13}C NMR (101 MHz, $CDCl_3$) δ 52.95 (CH_2), 56.07 (2 x OCH_3), 60.74 (OCH_3), 99.89 (ArCH), 104.60 (ArCH), 115.34 (ArCH), 115.37 (ArCH), 118.85 (C_q), 121.05 (C_q), 121.34 (ArCH), 124.39 (ArCH), 129.67 (C_q), 132.49 (C_q), 133.03 (ArCH), 133.35 (ArCH), 137.08 (C_q), 140.19 (C_q), 142.24 (C_q), 153.36 (C_q), 153.82 (C_q), 157.79 (C_q), 160.30 (C=O)

M.P.: 181-183 °C

IRν_{max} (NaCl film) cm^{-1}: 3299.5, 2932.2, 2826.1, 1692.7 (C=O), 1591.1, 1504.9, 1455.3, 1421.9, 1315.1, 1273.6, 1208.1, 1123.8, 1008.1

HRMS: Found 507.1627 $[M+Na]^+$, $C_{27}H_{24}N_4NaO_5$ requires 507.1644, (-3.4 ppm)

(*E*)-*N*-(1-(3,4,5-Trimethoxybenzyl)-1*H*-indazol-6-yl)-2-cyano-3-(4-methoxyphenyl)acrylamide (518)

To a solution of (**502**) (380 mg, 1 mmol) and *p*-methoxybenzaldehyde (0.12 mL, 1 mmol) in ethanol (5 mL), a catalytic amount of piperidine was added. The resultant solution was refluxed for 4 hours, cooled to 20 °C. The resultant yellow precipitate was collected by vaccum filtration and then recrystallized in ethanol which afforded the desired product as a yellow solid (340 mg, 69%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H, OCH_3), 3.81 (s, 6H, 2 x OCH_3), 3.91 (s, 3H, OCH_3), 5.53 (s, 2H, CH_2), 6.53 (s, 2H, ArH), 7.01 - 7.07 (m, 3H, ArH), 7.72 (d, 1H, ArH, J = 8.54 Hz), 7.99 - 8.04 (m, 3H, ArH), 8.14 (s, 1H, ArH), 8.27 (s, 1H, ArH), 8.35 (s, 1H, ArH)

^{13}C NMR (101 MHz, $CDCl_3$) δ 53.08 (CH_2), 55.63 (2 x OCH_3), 56.09 (OCH_3), 60.75 (sOCH_3), 100.27 (ArCH), 104.56 (ArCH), 114.84 (ArCH), 114.92 (ArCH), 117.61 (s), 121.87 (ArCH), 124.47 (C_q), 132.10 (C_q), 133.25 (ArCH), 133.39 (ArCH), 135.84 (C_q), 153.30 (ArCH), 153.42 (C_q), 158.96 (C_q), 163.77 (C=O)

M.P.: 151-153 °C

IRν_{max} (NaCl film) cm^{-1}: 2938.7, 2839.7, 2209.2 (CN), 1681.9 (C=O), 1625.7, 1588.5, 1540.8, 1463.8, 1425.2, 1350.6, 1310.7, 1264.9, 1174.9, 1124.6, 1025.8

HRMS: Found 499.1981 $[M+H]^+$, $C_{28}H_{27}N_4O_3$ requires 499.1981, (-2.0 ppm)

(*E*)-Methyl 2-cyano-3-(4-methoxyphenyl)acrylate (515)

To a solution of *p*-methoxybenzaldehyde (1.2 ml, 10 mmol) and ethyl cyanoacetate (1.1 ml, 10 mml) in ethanol (15 mL), a catalytic amount of piperidine was added. The resultant solution was stirred at 20 °C for 24 hours. The resultant precipitate was collected by *vaccum* filtration and re-crytallised in ethanol affording the desired product as a colourless solid (1.6 g, 70%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (t, 3H, J = 7.02 Hz, CH_3), 3.90 (s, 3H, OCH_3), 4.37 (q, 2H, J = 7.02 Hz, CH_2), 7.00 (d, 2H, ArH, J = 8.54 Hz), 8.01 (d, 2H, ArH, J = 8.54 Hz), 8.18 (s, 1H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 14.19 (CH_2CH_3), 55.60 (OCH_3), 62.42 (CH_2), 99.36 (C_q), 115.47 (ArCH), 116.21 (C_q), 124.36 (ArCH), 133.62 (C_q), 154.37 (ArCH), 163.11 (C_q), 163.76 (C=O)

M.P.: 92-94 °C Lit. M.P.: 86-88 °C[418]

IRν_{max} (NaCl film) cm^{-1}: 2983.2, 2939.1, 2843.2, 2221.3(CN), 1722.7(C=O), 1592.2, 1565.8, 1512.9, 1463.7, 1443.7, 1428.1, 1367.5, 1311.6, 1263.8, 1175.9, 1124.9, 1088.9, 1021.9

HRMS: Found 240.0640 $[M+Na]^+$, $C_{12}H_{11}NNaO_3$ requires 240.0637, (+1.2 ppm)

2-Amino-5-cyano-4-(4-methoxyphenyl)-6-oxo-*N*,1-bis(1-(3,4,5-trimethoxybenzyl)-1H-indazol-6-yl)-1,6-dihydropyridine-3-carboxamide (516)

A solution of (**502**) (236 mg, 0.62 mmol), ethyl cyanoacetate (70 mg, 0.62 mmol), *p*-methoxybenzaldehyde (84 mg, 0.62 mmol) and piperidine in ethanol (5 mL) were refluxed for 5 h, cooled to 20 °C and concentrated to dryness *in vacuo*. The crude mixture was purified by flash column chromatography over silica gel (eluent Hexane: EtOAc gradient) which afforded (**516**) (27 mg, 5%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.60 (app d, 6H, 2 x OCH_3), 3.68 (s, 3H, OCH3), 3.69 (s, 6H, 2 x OCH_3), 3.71 (s, 6H, 2 x OCH3), 5.43 (s, 2H, NH_2), 5.59 (s, 4H, 2 x CH_2), 6.54 (s, 2H, ArH), 6.68 (d, 2H, ArH, J = 5.80 Hz), 6.72 (s, 2H, ArH), 6.93 (d, 3H, ArH, J = 5.80 Hz), 7.01 – 7.03 (m, 2H, ArH), 7.23 – 7.25 (m, 4H, ArH), 7.41- 7.43 (m, 3H, ArH), 7.54 (s, 2H, ARH), 7.94 – 8.01 (m, 3H, ArH), 8.26 (s, 1H, ArH), 9.79 (s, 1H, ArH)

HRMS: Found 899.3099 $[M+Na]^+$, $C_{48}H_{44}N_8NaO_9$ requires 899.3129, (-3.3 ppm)

Bibilography

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Design, Synthesis and Evaluation of Indazoles as Antiproliferative Agents

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Abstract

Cancer is a leading cause of death in most countries, second only to the diseases of the circulatory system. In relation to Ireland, cancer accounted for 29.6 % of all the deaths reported in 2012. After non-melanoma skin cancer, breast cancer is the most common cancer suffered by women in Ireland. In 2012, there were 2,899 reported new cases of breast cancer while 704 female deaths were associated with this disease. Ireland has one of the highest rates of incidence of breast cancer in Europe.

This thesis describes the synthesis and biochemical evaluation of potentially dual acting tumour targeting compounds, based on the indazole scaffold. The indazole based scaffold, identified by the Meegan group, represents "first in class" dual Hsp90/tubulin binding compound. Tubulin and Hsp90 are the targets for the dual acting indazole compounds contained in this thesis. It is proposed that the dual acting Hsp90/tubulin molecules offer a combined approach to the treatment of breast cancer and related malignancies. Tubulin is recognized a valid target for cancer chemotherapeutic agents and compounds which interfere with microtubule dynamics are clinically available. Despite initial apprehension from the scientific community, Hsp90 is now considered a valid target for cancer chemotherapeutic agents as cancer cells have a higher dependence on Hsp90 than normal cells. A significant amount of detail is contained within chapter 1 on cancer chemotherapeutic agents, tubulin, Hsp90 and the synthesis and biological activity of selected indazoles. Chapter 2 is comprised of nine separate chemistry sections. Sections 2.2 – 2.6 describe the synthesis of indazole analogues of the lead compound with modified linkers at *N*-1. Section 2.7 describes the synthesis of 5- and 6-arylindazole analogues of the lead compound together with the preparation of 6-aroylated indazole analogues. Sections 2.8 and 2.9 describe the design and synthesis of a library of 3-aryl and 3-heterocyclic substituted indazoles respectively. In section 2.10, the synthetic chemistry required for introduction of a pyrrole or pyridone ring at C-5 or C-6 of indazole is described. Chapter 3 reviews the biochemical evaluation a number of selected indazoles while chapter 4 contains the results of the molecular modelling that was performed on a selection of the synthetic indazoles in order to provide a rationalisation of the antiproliferiative activities. 6-Amino-1-(3,4,5-trimethoxybenzoyl)-1*H*-indazole (**209**) was identified as a potent antiproliferative agent with significant activity against a panel of human tumour cell lines including kidney, breast, ovarian, CNS, melanoma, prostate, leukemia, colon and lung.