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Reynolds, Chevonne

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Synthesis of Potentially Biologically Active Aromatic and Hetero-aromatic Compounds

Chevonne Reynolds

Supervisors:
Dr. Moira Bode (CSIR), Prof. Charles B. de Koning and
Prof. Willem A. L. van Otterlo

A dissertation submitted to the Faculty of Science, University of the Witwatersrand, in fulfilment of the requirements for the Degree of Master of Science

October 2010





Declaration

I declare that the work presented in this dissertation is my own, unaided work and was carried out under the supervision of Dr. M. Bode, Prof. C. de Koning and Prof. W. van Otterlo. It is being submitted for the Degree of Master of Science in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination in any other University.

_____

Chevonne Reynolds
October 2010

Abstract

The first part of this dissertation deals with employing the use of multi-component coupling reactions (MCC) for the synthesis of large diverse compound libraries. A review of selected literature identified the growing need for more potent and selective HIV/AIDS drugs due to the extremely high mutation rate of the HI virus. We thus chose to test our synthesised compound library against the HIV enzyme, reverse transcriptase (RT) in the hopes of identifying a potential novel non-nucleoside reverse transcriptase inhibitor (NNRTI). Two different MCC approaches were used in order to give two different classes of compounds; firstly the Groebke-Blackburn reaction for the synthesis of imidazo[1,2-*a*]pyridines and secondly a reaction developed by Poigny and co-workers for the synthesis of 3-amino-1-cyano-indolizines. We were successful in utilizing the Groebke-Blackburn to synthesise a variety of imidazo[1,2-*a*]pyridines in varying yields. However, all of the compounds showed poor inhibition of the RT enzyme in the biological assay. We thus turned our attention to the synthesis of the 3-amino-1-cyano-indolizines, which proved to be very difficult. It was discovered that this reaction did not proceed to completion and the product generally isolated from this MCC reaction was the more stable aldol condensation intermediate. In some of the experiments we were able to isolate mostly small quantities of indolizine compound, but when tested against the RT enzyme the results once again were very poor.

A short review in the second section of this dissertation showed the lack of methodology available for the synthesis of the dihydrobenzo[*b*]phenanthridine motif which constitutes the backbone of a secondary metabolite known as Jadomycin B. The major aim of this segment of the project was thus to develop methodology to synthesise this biologically important scaffold. However, our methodology failed to yield the desired product as it was not possible to reduce the nitrile intermediate to the required amine. In an attempt to determine whether similar methodology could be used for the synthesis of pyranonaphthoquinone containing compounds an unexpected and novel reaction was discovered. It was found that treatment of [2-(1,4-dimethoxynaphthalen-2-yl)phenyl]methanol with brominating agent NBS results in the synthesis of a naphthopyranone ring system known as 12-methoxy-6*H*-dibenzo[*c,h*]chromen-6-one. Following this discovery it was attempted to elucidate the mechanism by which NBS performs this novel reaction. Unfortunately we were unable to determine the exact mechanism responsible for this transformation conclusively. The most likely mechanism shows NBS oxidising the benzylic alcohol to an aldehyde, which is then converted to an acid bromide facilitating ring closure. Finally we wished to determine if this strategy could be applied in the synthesis of related naphthopyranone ring systems, which was shown to be possible with the synthesis of 3-bromo-2-methoxy-6*H*-benzo[*c*]chromen-6-one.

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**If an experiment has worked,
something has gone wrong!**

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Appendix A: Selected NMR Spectra

Appendix B: Single-Crystal X-Ray Diffraction Data

List of Abbreviations

AcOH	acetic acid
AIBN	Azobisisobutyronitrile
AIDS	Acquired Immune Deficiency Syndrome
APCI	Atmospheric Pressure Chemical Ionisation
aq.	Aqueous
AZT	Azidothymidine
BBr_3	boron tribromide
BCl_3	boron trichloride
BOC	*tert*-butyl carbamate
Br_2	Bromine
$CaCl_2$	calcium chloride
CAN	ceric ammonium nitrate
CBr_4	carbon tetrabromide
$CDCl_3$	deuterated chloroform
CF_3CO_2H	trifluoroacetic acid
CH_2Cl_2	Dichloromethane
$CHCl_3$	Chloroform
DBU	1,8-diazabicycloundec-7-ene
DDQ	4-benzoquinone
DMAP	4-dimethylaminopyridine
DME	dimethyl ether
DMF	*N,N*-dimethylformamide
DNA	deoxyribonucleic acid
dsDNA	double stranded DNA
Et_3N	Triethylamine
Et_3SiH	Triethylsilane
EtOAc	ethyl acetate
EtOH	Ethanol
h	Hours
H_2	Hydrogen
H_2O	Water
H_2SO_4	sulfuric acid
HAART	Highly Active Antiretroviral Therapy
HCl	hydrochloric acid
HIV	Human Immunodeficiency Virus
HNO_3	nitric acid
HRMS	High Resolution Mass Spectroscopy

hv	Light
IR	Infra-red
K_2CO_3	potassium carbonate
K_3PO_4	potassium phosphate
$KOBu^t$	potassium *tert*-butoxide
$LiAlH_4$	lithium aluminium hydride
m.p.	melting point
MCC	multi component coupling
MCR	multi component reaction
Me_2SO_4	dimethyl sulphate
MeCN	Acetonitrile
MeOH	Methanol
$MgSO_4$	magnesium sulphate
min	Minutes
N_2	Nitrogen
Na_2CO_3	sodium carbonate
$Na_2S_2O_4$	sodium hydrosulfite
Na_2SO_3	sodium sulphite
Na_2SO_4	sodium sulphate
NaCl	sodium chloride
$NaHSO_3$	sodium bisulfite
NaN_3	sodium azide
NaOH	sodium hydroxide
NaOMe	sodium methoxide
NBS	*N*-bromosuccinimide
***n*-BuLi**	*n*-butyl lithium
NMR	Nuclear Magnetic Resonance
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
$Pd(dba)_2$	bis(dibenzylideneacetone)palladium
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium
Pd/C	palladium on carbon
PI	Protease Inhibitor
PPh_3	Triphenylphosphine
RNA	ribonucleic acid
RT	Reverse Transcriptase
rt	room temperature
SAR	Structure-Activity Relationship

ssDNA	single stranded DNA
^{t}BuLi	*tert*-butyl lithium
TFAA	trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	triisopropylsilyl (ethers)
TLC	thin layer chromatography
Wits	University of the Witwatersrand

Part A

Chapter 1: Introduction, Literature Review and Aims

Use of Multi-component Coupling Reactions for the Synthesis of Potential HIV Non-Nucleoside Reverse Transcriptase Inhibitors

Acquired Immune Deficiency Syndrome or AIDS is a disease caused by the Human Immunodeficiency Virus (HIV) and is responsible for more then 20 million deaths globally.[1, 2] With a further 70 million people infected with HIV and no viable cure we are facing one of the worst pandemics in our human history.[1] Although HIV is a devastating disease to suffer from it has further reaching implications in terms of economic, social and political stability.[1] For example the province of Kwa-Zulu Natal (KZN) in South Africa, one of the world's worst afflicted countries, shows 26.4% of the working age population to be HIV positive.[3] The predictions for KZN show that at the current infection rate, two-fifths of the adult population will die of AIDS related illness by 2025.[3] Thurlow *et al.* predicted that the collective effects of HIV over all economic sectors means that the KZN economy will be 43% smaller by 2025.[3] Combating the AIDS epidemic is thus of grave importance in securing our economic stability as well as addressing the devastating social decline which it elicits.[1]

1. Brief History of Human Immunodeficiency Virus (HIV)

Along with many discoveries in the science, the discovery of the virus HIV as the cause of AIDS, was also one not untouched by luck.[2] Human Immunodeficiency Virus (HIV) was first isolated in 1983 by Dr. Luc Montagnier.[2, 4] Had it not been for research into cancer-causing viruses in the same time period as the first identified AIDS patients, the knowledge and tools for the discovery of the HIV virus may not have existed.[2] Many factors including fungi, chemicals and autoimmune disease were thought to be the cause of AIDS, but it was the earlier discovery in 1970 by Temin and Baltimore which showed human T-cell leukaemia virus types 1 and 2 (HTLV-1 and HTLV2) to cause T-cell leukaemia which allowed researchers to eventually discover the cause to be a virus.[2, 5] Animal studies revealed that HLTV not only caused leukaemia and lymphoma, but an AIDS-like syndrome.[2, 5] This result, as well as the similar epidemiology of HTLV, also transmitted by blood and sexual activity, convinced scientists that a virus was the cause of AIDS.[2, 5]

From 1983-1985 rapid advancements including genome sequencing, understanding of pathogenesis, blood tests and development of AZT led to the expectation that AIDS would be quickly combated.[5] However, by the early 1990s it was clear that if a suitable vaccine was not developed HIV would probably become a permanent infection in our species.[5] The use of multiple drug routines over the last 15 years has significantly extended the period between infection with

the virus and the onset of AIDS symptoms, but it is no cure.[4, 5] Until a vaccine is discovered the production of more potent HIV drugs which can significantly inhibit viral load is vital to slowing the mortality rate of this horrific disease.[5]

2. Mode of Infection of HIV

It is widely accepted by scientists that AIDS is caused by the HIV retrovirus.[2] A retrovirus is a RNA virus containing an enzyme called reverse transcriptase which enables the virus to utilise its single strand RNA genome as a template for the production of an intermediate single DNA strand.[2, 4, 6] There are two subtypes of HIV, HIV-1 and HIV-2 which are thought to have originated from two different primate species.[5] HIV-1 is the more virulent sub-type and more easily transmitted and spread, HIV-1 thus accounts for the vast majority of global HIV infections.[7] Hence for the purposes of this discussion all information on the pathogenesis of HIV will pertain to the HIV-1 sub-type. Heterosexual transmission by unprotected sexual intercourse with an infected person is the main mode via which one can be infected with the HIV-1 virus and accounts for 80% of all HIV-1 positive people.[8] Other modes of infection include direct exposure to infected body fluids (blood, semen etc.), either by accident or intravenously, and direct mother to child infections.[1, 4]

Once the HIV-1 virus has entered the host, a protein on the outer envelope of the virus attaches to the CD4 receptor protein of the helper T cell, its primary target **(Figure 1)**.[4, 6, 9] This interaction results in the fusion of the virus envelope with the host cell's plasma membrane and allows the viral core or capsid containing the nucleic acid and enzymes to enter the T cell cytoplasm.[4, 6] Once in the cytoplasm, host enzymes remove the capsid releasing the viral RNA and viral enzymes into the cell.[4] A viral enzyme known as reverse transcriptase now catalyses the synthesis of single strand (ss) DNA which is complementary to the viral RNA.[4, 6] Host cell DNA polymerase now catalyses the synthesis of double stranded (ds) DNA from the complementary ssDNA.[4, 6] This dsDNA now migrates to the host cell's nucleus where the viral enzyme integrase integrates it into the host's chromosome.[4] Once incorporated into the chromosomal DNA of the host cell, the viral DNA can use host enzymes to synthesise viral proteins and to transcribe viral RNA.[4] This viral RNA then leaves the nucleus and initiates the synthesis of viral proteins on host ribosomes.[4] The viral RNA and new viral proteins are then assembled by host enzymes into new virus particles which then exit the cell using host plasma membrane to make the viral envelope.[4]

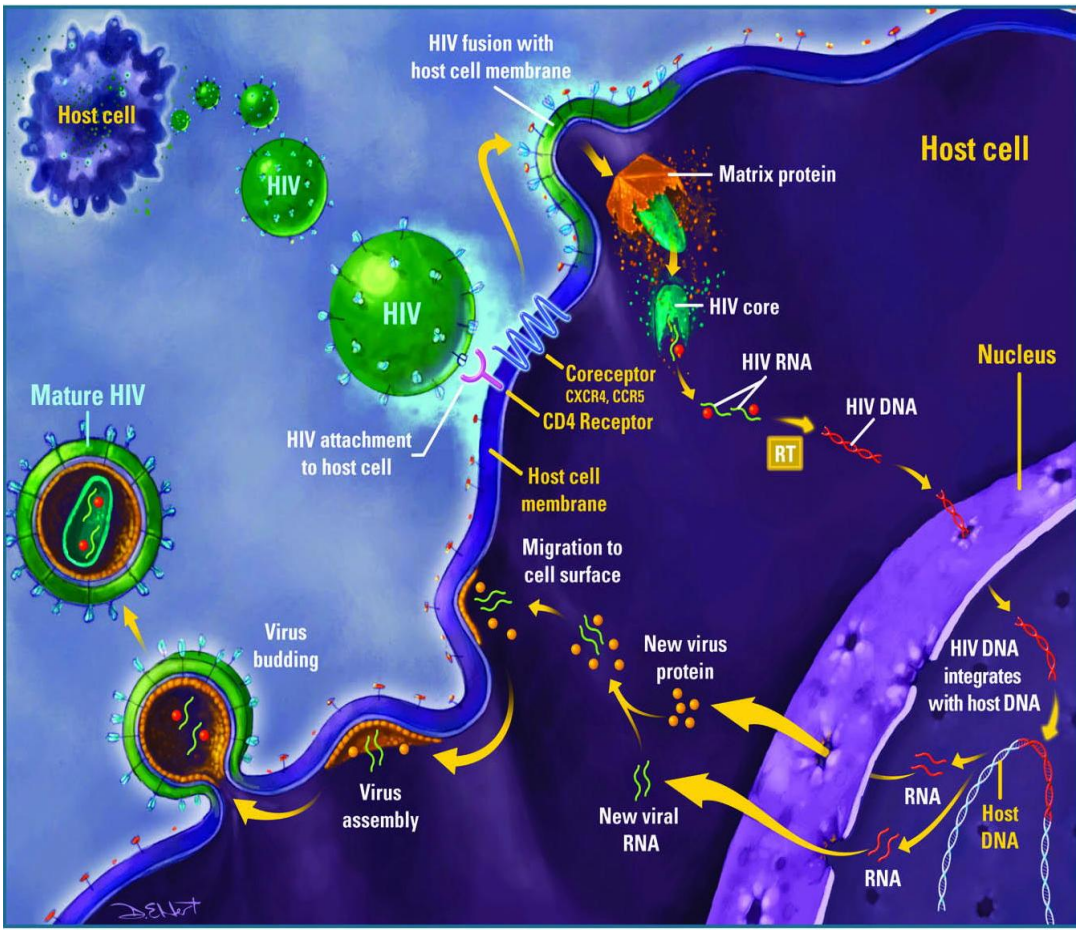


Figure 1 Schematic of HIV mode of infection and replication[9]

Since the virus utilises host proteins in its assembly process, normal cellular functioning and synthesis of essential proteins are inhibited and the cell eventually dies.[4] The newly synthesised virus moves off to infect and destroy more host cells, which eventually results in a progressive decline in the CD4 T-cell count and greatly inhibits the immune system's ability to defend against other infectious diseases.[4] It is at this point that HIV infected people may develop the disease AIDS as their immune systems are no longer able to combat opportunistic diseases caused mainly by bacteria, fungi and parasites.[4, 10] Diseases such as severe bacterial infections and tuberculosis have been identified as the leading causes of death amongst AIDS suffers as these individuals' severely undermined immune systems are incapable of defending themselves against these infections.[10]

3. In Search of a Treatment for HIV/AIDS

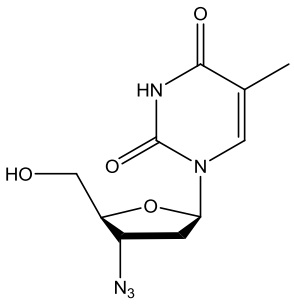
The response of an individual who is infected with HIV and the progression to AIDS depends on a combination of genetic, environmental and health factors and many individuals can live very healthy lives for a number of years.[10] Science has had some success in prolonging the life span of HIV positive people mostly through the development of anti-retroviral drugs.[1] However there is

unfortunately no cure for HIV/AIDS and new developments in HIV/AIDS research are crucial in order to combat this pandemic.[1] This section will address the various strategies for combating this disease; from the discovery of the first HIV drug, AZT to the current drug therapies used and finally new developments in HIV/AIDS research.

3.1 AZT: The proposed wonder drug

Azidothymidine or AZT **1 (Figure 2)** was the first drug approved by the United States Government for the treatment of HIV/AIDS.[5] AZT was first synthesised in 1964 by Dr. Jerome P. Horwitz for use as an anti-cancer agent.[11] He wanted to design a novel drug which would prevent the growth of cancer cells by preventing replication of the cells.[11] A group of compounds called dideoxythymidines were synthesised which could mimic DNA nucleosides and act as chain terminators in DNA synthesis, thus preventing the growth of cancer cells.[11] AZT was among the drugs synthesised and screened, but showed no activity and so was quickly forgotten.[11] In 1974 when AZT was revisited by Wolfram Ostertag at the Max Planck Institute who tested it against Friend Leukaemia Virus (FLV) and found it to successfully inhibit the virus in mice.[11] Burroughs Wellcome, a pharmaceutical company in the United States, bought AZT from Ostertag and conducted intensive animal tests, but ultimately decided not to develop the drug further as it did not seem to have applications for human use.[11] AZT was thus shelved away as Burroughs Wellcome compound 509US1 and did not make an appearance again until 1984 when pharmaceutical companies began screening their compound libraries in the hopes of finding a drug which could be used to treat the newly emerging disease, AIDS.[11]

On 29 October 1984 Dr Janet Rideout selected compound 509US1 for testing against retroviruses FLV and Harvey Sarcoma Virus (HaSV).[11] AZT showed good activity against these two retroviruses and was immediately sent for testing against live HIV at Duke University by Dr. Bolognesi who showed the drug to be active against HIV *in vivo*.[11] On 3 July 1985 a furniture salesman from Massachusetts named Joseph Rafuse became the first person to be given AZT for the treatment of HIV and after six weeks of administration of the drug his T-cell count had increased significantly.[11] The discovery of AZT and initial positive results of the clinical trial led many researchers to the expectation that AIDS would quickly be eradicated; however the rapid mutation rate of the HI virus and the subsequent resistance to AZT means that HIV/AIDS still remains an alarming problem today.[5, 11]



1

Figure 2 Representation of AZT[5]

3.2 Current Treatment Regimens

The reverse transcriptase enzyme of HIV makes a coding error every 3×10^5 bases, this translates to almost one mutation in each viral replication cycle.[12] These changes in the HIV genome allow drug resistant mutant forms of HIV to emerge as they are no longer inhibited by the current drug therapies and have hindered efforts to effectively block viral replication.[12, 13] AZT, the first drug approved for treatment of HIV infection, is on its own no longer able to significantly block the virus at clinically meaningful levels and Highly Active Antiretroviral Therapy (HAART) is used today to treat HIV.[14] HAART or triple therapy is able to radically increase the survival of HIV-infected individuals and generally consists of the use of two nucleoside reverse transcriptase inhibitors (NRTIs), plus either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI).[14]

Due to the essential role that reverse transcriptase plays in virus replication it is thus a major target for antiretroviral drugs.[15] There are two classes of reverse transcriptase (RT) inhibitors, the nucleoside (NRTIs) and non-nucleoside (NNRTIs) reverse transcriptase inhibitors, each affecting the RT enzyme in a different location.[15] NRTIs are analogs of deoxyribonucleosides which lack the hydroxyl group on the 3' carbon of the deoxyribose sugar.[15] In order for these compounds to have antiviral activity they must be metabolically converted by host cell proteins to the triphosphate form, which allows it to be mistaken by the virus as a natural nucleotide.[15, 16] These phosphorylated NRTIs can now function as chain-terminators in the synthesis of single stranded DNA.[15] AZT is an example of an NRTI, it mimics the nucleoside thymidine but replaces the 3'-OH group by a 3'-azide (N_3) group, thus stopping further inclusion of nucleotides and terminating DNA chain extension.[16] There are currently eight NRTIs which have been approved for clinical use including Azidothymidine **1** (AZT or Retrovir®), dideoxyinosine **2** (ddI or Videx®) and dideoxycytidine **3** (ddC or Hivid®) **(Figure 3)**.[15, 17]

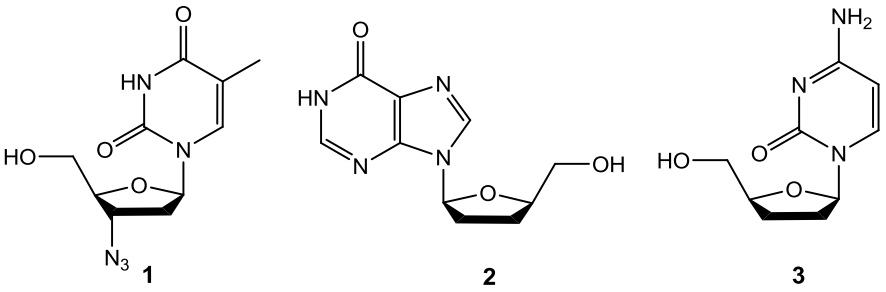


Figure 3 Some commercially available NRTIs[17]

NNRTIs on the other hand are small molecules that are chemically distinct from nucleosides and are not dependent on host cell metabolism to be converted to the active form.[15] NNRTIs are a group of diverse hydrophobic molecules which inhibit the HIV-1 RT reaction through interaction with an allosteric site of the enzyme.[15, 17] This allosteric site is located on the p66 subunit of the HIV-1 RT enzyme, a mere 10Å from the substrate or nucleoside binding site.[15, 17] The binding of an inhibitor in this allosteric site elicits a change in conformation of the substrate-binding site which means that nucleotides can no longer be bound in the active site of the enzyme and DNA synthesis cannot occur.[17] Four NNRTIs have been approved for clinical use including nevirapine **4** (Viramune®), delavirdine **5** (Rescriptor®), efavirenz **6** and etravirine **7 (Figure 4)** and several more have entered into clinical trials and development.[15, 17]

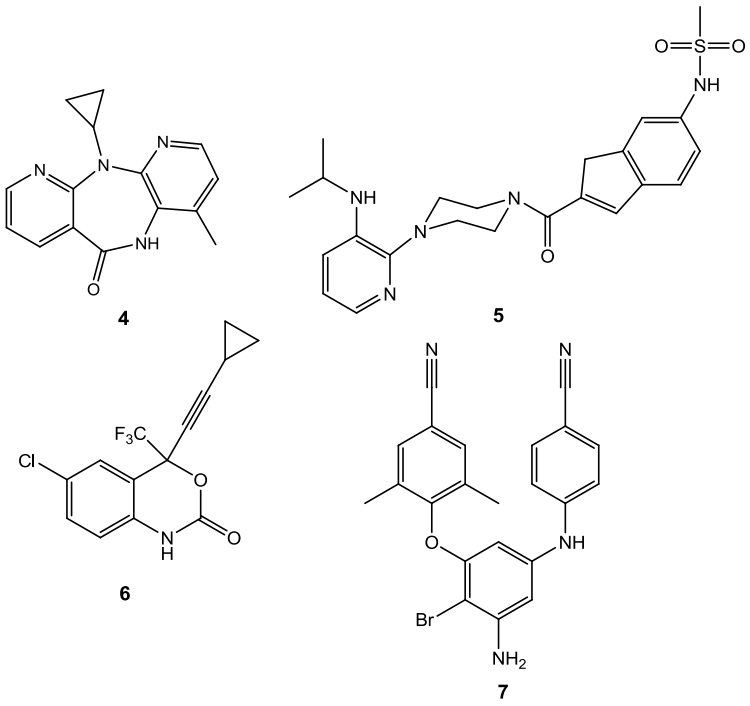


Figure 4 Commercially available NNRTIs[17]

The final class of therapeutic agents most commonly used in HAART are the HIV protease inhibitors. HIV protease plays a crucial role in the viral life cycle as it is essential for generating mature infectious virus particles by cleavage of peptide bonds of large proteins and polypeptides into smaller proteins.[18, 19] There are currently nine protease inhibitors approved for clinical use including saquinavir **8**, ritonavir **9**, indinavir **10** and lopinavir **11 (Figure 5)**.[18] The protease inhibitors act as competitive peptidomimetic inhibitors by imitating the natural substrate of the HIV protease enzyme.[18] These mimics contain a non-scissile hydroxyethylene core which prohibits the cleavage of the protease inhibitor by the protease enzyme, thus blocking the enzyme site and preventing maturation of viral particles.[18]

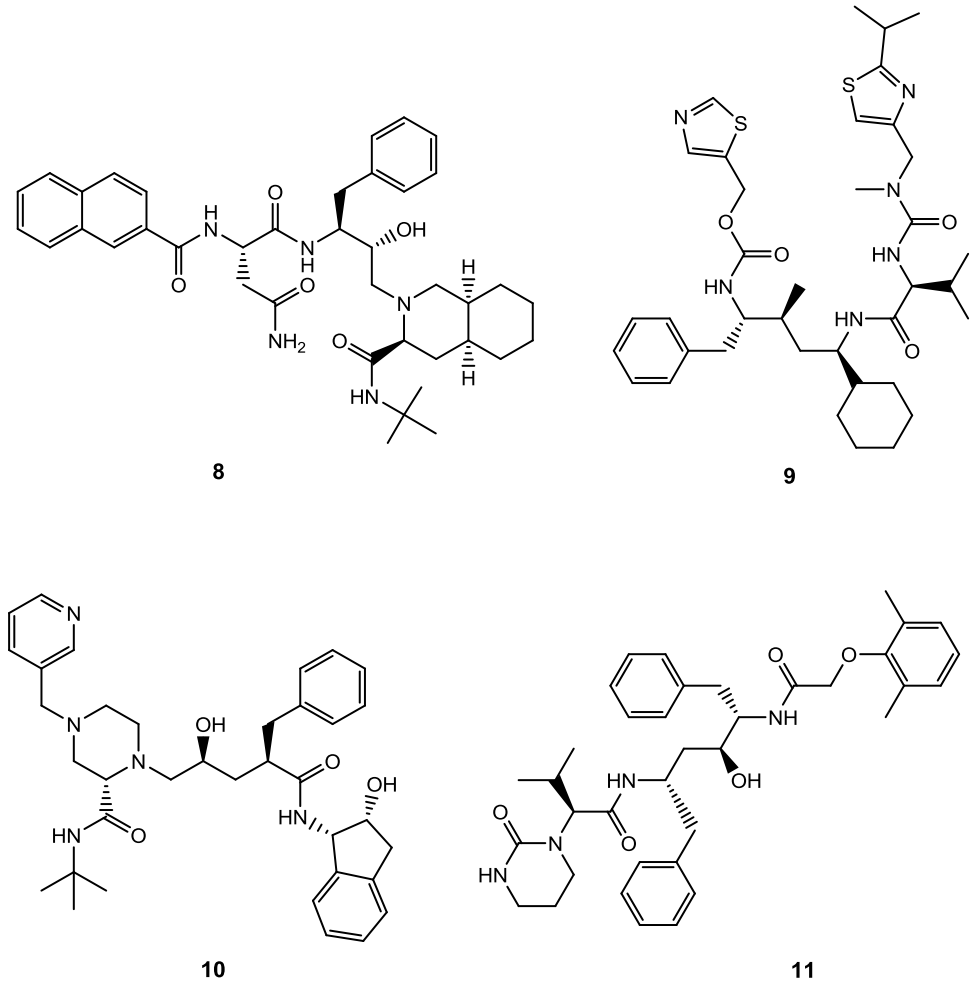


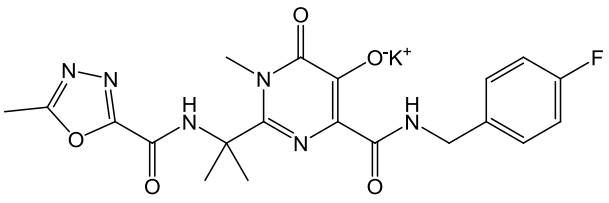
Figure 5 Some commercially available PIs[18]

3.3 Recent Developments and Strategies for Treating HIV

Although the use of HAART therapy has greatly prolonged the survival of HIV infected individuals, drug resistance due to the rapidly mutating HI virus still remains a huge problem.[14] Development and testing of more potent RT inhibitors and protease inhibitors remains a wide area of research, but due to the rapid rate at which the virus develops resistance to these drugs it is clear that new

drug targets need to be identified to efficiently combat the virus.[13] A new class of compounds known as integrase inhibitors has subsequently been developed.[13, 20] These drugs target the viral enzyme integrase which is responsible for the insertion of pro-viral DNA into the host-cell's genome.[20, 21]

HIV integrase is one of the three viral enzymes essential for viral replication (along with RT and protease); this reinforces integrase as an excellent drug target.[20, 22] Raltegravir (RAL) **12 (Figure 6)** was approved by the FDA on 12 October 2007 for use in antiretroviral therapy in patients with extreme drug resistance and was the first HIV integrase inhibitor to be used as an antiretroviral drug.[20] The integration of viral DNA into the human genome is a complex process starting with the binding of integrase to the viral DNA to form a stable pre-integration complex.[20, 22] This pre-integration complex then migrates from the cytoplasm of the host cell to the nucleus where the viral DNA is transferred and integrated into the host DNA.[20] RAL functions by blocking the active site in the pre-integrated enzyme complex, thus preventing the viral DNA strand from being incorporated into the host cell's genome.[20] HIV integrase inhibitors have just recently been included in the antiretroviral regime for treatment of individuals with multi-drug resistant HIV and have shown great success in boosting immune recovery in these patients.[20] However, this drug class is once again not impervious to mutations in the HI virus which render the drugs much less effective and once again highlights that the global control of AIDS will require an effective vaccine to stop the spread of the HIV virus.[4, 20]



12

Figure 6 Raltegravir, the first HIV integrase inhibitor[20]

It has already been widely established that a safe, effective and affordable HIV vaccine is needed if we wish to successfully combat AIDS.[23] The first HIV vaccine was developed in 1987 and since then over 35 different vaccines have been tested in phase I and II clinical trials.[23] Only 2 vaccines reached phase III trials and a third one is underway, but researchers believe we are still many years away from a successful HIV vaccine due to the seemingly insurmountable number of challenges scientists face when dealing with this disease.[4, 23] Why is it so difficult to develop a vaccine? When one considers the biology of HIV it becomes apparent what the complexities associated with an HIV vaccine are.[24] Perhaps the biggest hurdle which must be overcome is the ability of HIV to persist in the host's immune cells by crippling the immune system and avoiding an adaptive immune response.[24] These problems are further complicated by the rapid mutation of the HIV virus which aids in evading the immune response and seriously hampers progress in

developing an HIV vaccine.[24] The most recent advancement in the field of HIV vaccine development was reported by Jin and co-workers who recently submitted a novel polypeptide vaccine of HIV T helper epitopes (EP-1043) and a DNA vaccine of HIV CTL epitopes for phase I clinical trials.[25] The group demonstrated that 64% of their test subjects (non HIV-infected adults) had a positive CD4+ T response after two vaccinations.[25] Whether the vaccine can be used to prevent HIV infection or simply to slow disease progression was not established, but it is hoped that upon further study EP-1043, or a modified version of it, could be used as a novel HIV vaccine.[25]

While immunologists and scientists work to develop a successful vaccine and more effective drugs to treat HIV infected patients, the most effective solution for stopping the spread of HIV is that of education.[4] Educating the public on the facts of how HIV is transmitted and empowering women in rural communities is the best way of slowing the spread of HIV/AIDS.[4] Prevention is better then cure and if one can stop the spread of HIV by preaching safe sex, society may well be on its way to significantly reducing the number of AIDS patients and eradicating this human tragedy.[4]

4. The Use of NNRTIs as Drugs Targeting RT

Whilst we await the elusive HIV vaccine one of the main focuses in HIV treatment is the development of more potent drugs which target vital enzymes in the replication cycle of the virus.[4] NNRTIs are such drugs; these drugs target the RT enzyme in HIV preventing the synthesis of viral DNA from viral RNA.[15] With the advent of HAART therapy the use of NNRTIs has been firmly established in the treatment of HIV infection, but due to drug resistance the current NNRTIs are no longer as potent.[13] Thus the synthesis and development of novel NNRTIs with increased resistance selectivity has become the focus of many research groups in the fight against HIV/AIDS.[13]

4.1 The RT Enzyme and Mode of Action of NNRTIs

HIV-1 RT is a heterodimer consisting of p66 and p51 subunits **(Figure 7)**, where the p66 subunit is the larger of the two and contains both NRTI and NNRTI binding sites.[13, 26] The p66 subunit consists of RNA-dependent DNA polymerase (RDDP) and ribonuclease H (RNase H) domains, both of which are vital for the process of converting single-stranded RNA into double-stranded DNA.[13, 15] Reverse transcription is initiated when cellular tRNA is coupled by RDDP to viral RNA at the 3'-end and is then elongated towards the 5'-end of the viral RNA.[15] The resulting product is a DNA-RNA hybrid strand which is complimentary to the viral RNA.[15] RT RNase H activity is then responsible for hydrolysing the ssRNA from the DNA-RNA hybrid resulting in a single strand of DNA.[15] The single-stranded DNA can now be converted to the double-stranded proviral DNA by

the RT enzyme and can then be integrated into the host cell's genome using viral enzyme intergrase.[15]

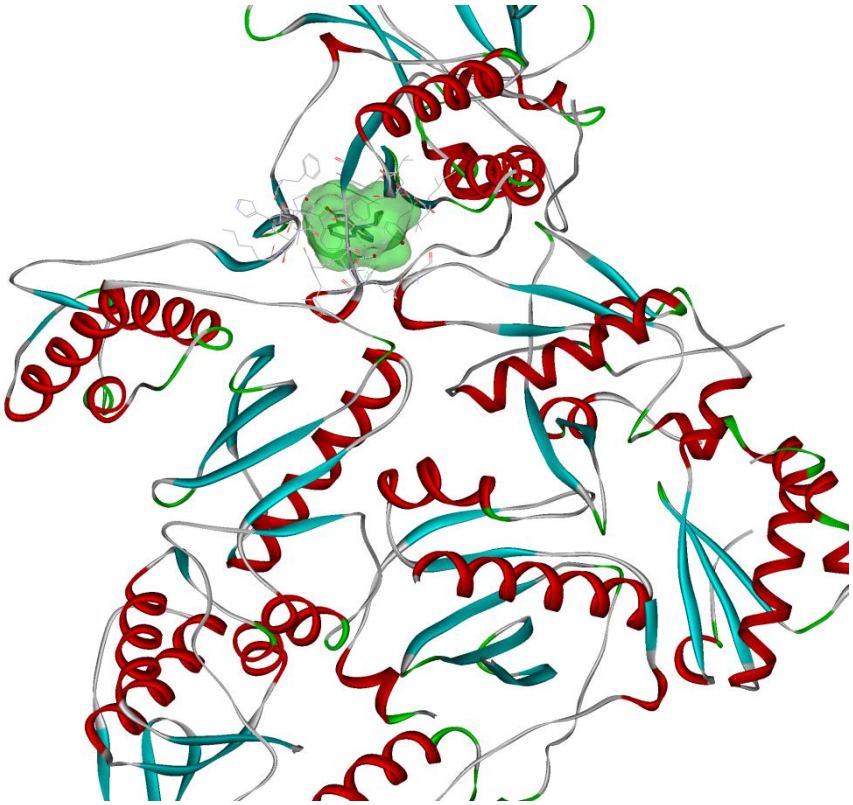


Figure 7 HIV-1 RT heterodimer showing Nevirapine bound in the allosteric site[26]

NNRTIs interact with the HIV-1 RT by binding to a site on the p66 subunit called the NNRTI binding pocket and is an allosteric site situated 10 Å from the RT polymerase and 60 Å from the RNase H active site.[13, 15] In contrast to NRTIs, which are competitive inhibitors and actively compete for the active site of the polymerase, NNRTIs are non-competitive inhibitors.[13] When unliganded and NNRTI-bound RT crystal structures are compared it is evident that the NNRTI binding pocket is only created by the binding of the inhibitor itself.[13] This event is characterised by the movement of the side chains of the key amino acids Tyr181 and Tyr188 from a 'down' position to an 'up' position.[13] The importance of these residues for binding of the inhibitor is shown by how favourably the virus selects for the mutated enzyme where these two residues are aliphatic so that favourable π-stacking interactions with aromatic inhibitors is avoided.[13] It is thus obvious that design of new NNRTIs should seek to avoid this key interaction in the hopes of significantly reducing the rate at which HIV becomes drug resistant.[13]

In order to design new and effective NNRTIs it is important to understand the mode of inhibition and the specific binding actions of the ligands in the enzyme.[13, 15] A number of different mechanisms have been proposed for NNRTI inhibition of RT.[13] Perhaps the simplest explanation is that the binding of the NNRTI in the allosteric site of the enzyme reduces the lability of the

enzyme and prevents the domain movements which are imperative to the catalytic cycle.[13] Perhaps a more likely suggestion is that on binding of the NNRTI in the allosteric site there is a significant and consistent movement of the β2-β3 chains which contain the important amino acids Asp110, Asp185 and Asp186.[13] It is thus deduced that when these amino acid residues are shifted in the active site by the change in conformation of the enzyme, the essential catalytic processes cannot occur.[13] It is generally accepted that binding of the NNRTI in the allosteric site brings about a change in conformation of the active site, preventing the nucleosides from being taken up by the enzyme and preventing the key process of synthesising viral DNA.[13, 15]

4.2 Current NNRTIs and the Mutations Which Confer Resistance

There is unfortunately a wide range of drug resistance mutations described in the literature for NNRTIs and this highlights the problem with the current NNRTIs available for use in HAART therapy.[13, 17] The Tyr181/Tyr188 mutation which has already been discussed, greatly reduces the efficacy of the NNRTI nevirapine.[13] This is due to the loss of favourable aromatic stacking between the pyridine ring of nevirapine and the aromatic side chains of the Tyr181/Tyr188 residues when they mutate to aliphatic residues such as cysteine.[13] The same mutation,not surprisingly, only confers a small loss in potency with the NNRTI efavirenz as the cyclopropyl group already has less effective contacts with the Try181/Try188 residues.[13] Perhaps newly designed NNRTIs should exploit this mutation and include aliphatic regions which could still efficiently bind with the mutated enzyme.

The most widely reported resistance mutation is that of K103N, or the mutation of the lysine residue at 103 to an asparagine residue.[13] Structural studies indicate that this mutation actually blocks the entry of NNRTIs into the allosteric site by producing favourable H-bonding interactions which stabilise the closed NNRTI binding site.[27] This mutation reduces the activity of many FDA approved NNRTIs (nevirapine **4**, delavirdine **5** and efavirenz **6**).[28] Delavirdine's activity is the most affected as this inhibitor actually forms favourable H-bonding contacts with the Lys103 residue; when this mutation occurs these H-bond contacts are removed, disfavouring the bonding of delavirdine in the allosteric site.[27] Efavirenz once again is the NNRTI which best overcomes this mutation and still remains up to 90% effective if this mutation occurs.[28]

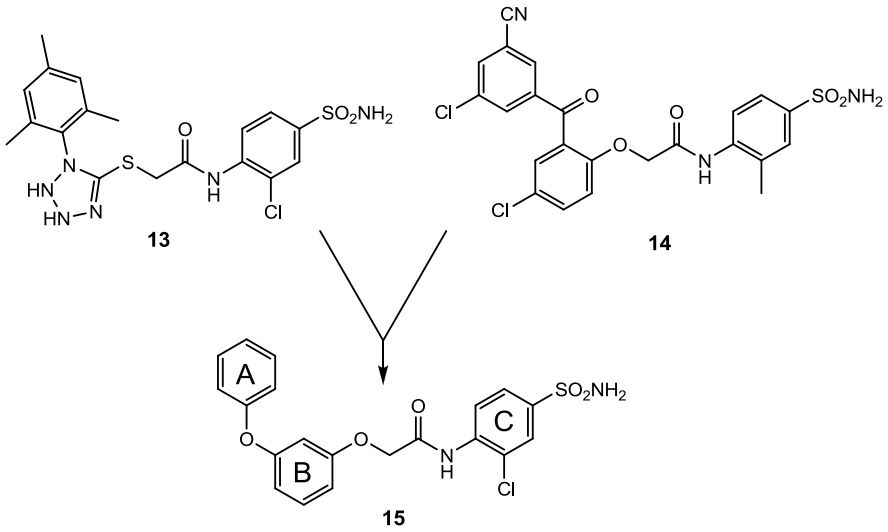
A further mutation which confers moderate resistance to a number of NNRTIs is a mutation at position 101 or 138.[13] The Lys101 residue does not have direct contact with the binding NNRTI, but there is generally a chain of three water molecules which link the inhibitor with the Lys101 residue.[13] The Lys101 residue can form a salt bridge with the Glu138 residue of the p51 subunit and a mutation at either of these residues can result in an inversion of charge.[13] Once this occurs the Lys101, water molecules and inhibitor may no longer have a favourable electrostatic interaction, thus destabilising the binding of the inhibitor in the NNRTI binding site.[13] Likewise a

mutation in the Glu138 residue may result in an unfavourable electrostatic interaction across the Lys101 and Glu138 salt bridge; again destabilising the binding of the NNRTI in the allosteric site.[13] There are many more mutations which can result in the resistance of HIV to the current NNRTI treatments.[13] Understanding the mechanisms by which these mutations confer resistance is therefore imperative in designing novel NNRTIs which may be more effective in treating HIV infections.[13, 17]

4.3 Developments in the Design and Synthesis of Novel NNRTIs

There are two schools of thought when it comes to the development of novel NNRTIs.[29] The first strategy focuses on the understanding of drug resistance mechanisms and development of drugs to effectively inhibit the mutant virus.[29] The second strategy focuses on targeting highly conserved areas in the enzyme where the least mutation has occurred and designing drugs to interact with this portion of the enzyme.[29] Both schools of thought have met with some success and second generation NNRTIs have shown increased ability to bind with mutated HIV-1 RT.[29] Although numerous new classes of compounds have been identified as potential novel NNRTIs, this section aims at highlighting only a few of the current successes in NNRTI design and development in combating HIV drug resistance.

One of the current successes in novel NNRTI design is the synthesis and development of second generation diaryl ethers as lead compounds.[30] Tucker *et al.* discovered lead compound **13** via high throughput screening (HTS), but the disappointing pharmacokinetic results forced the group into a different direction.[30] Using **13** as a lead compound and comparing it to an already known NNRTI **14** via a molecular modelling program they were able to identify a novel diphenyl ether substructure **15 (Scheme 1)** which had good docking results with the NNRTI binding site.[30] The molecular modelling study showed that the amide carbonyl was imperative in maintaining a critical hydrogen bond with the backbone NH of Lysine 103, which is crucial in maintaining good potency at the K103N postion.[30] The modelling study also indicated that a di-*meta* substitution pattern on the A and B aryl-rings as seen in compound **14** would help optimise interactions with the binding site and help to improve the potency of this series of compounds.[30] The model also indicated that the sulfonamide was situated at the enzyme/water interface and was thus fully solvent exposed, indicating the potential for various polar substitutions in this area.[30]



Scheme 1 Design of Novel Diaryl Lead Structures[30]

The group synthesised a variety of compounds based on the modelling study with an indazole compound **16 (Figure 8)** showing the best NNRTI activity.[30] The key carbonyl H-bonding interaction is replaced by the indazole moiety which is capable of forming two H-bonds with amino acid residue K103, thus increasing its potency.[30] The di-*meta* substitution on the A aryl-ring once again increased the potency of the compound and this is thought to be due to the improved π-π stacking of the A-aryl ring and the Y188 residue.[30] The chlorine atom on the B aryl-ring fits very well into a small lipophillic region behind the V179 residue and once again increases binding potency.[30] Unfortunately the compound showed low bioavailability and poor solubility, but the discovery of this compound has become a prototype for novel NNRTI synthesis and efforts for improving its solubility are being investigated.[30]

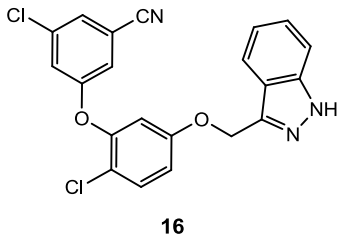


Figure 8[30]

A further success story in the quest for novel and more potent NNRTIs was published by Lui and co-workers whose previous work with triazole **17**, tetrazole **18** and 1,2,3-thiadiazole **19** thioacetanilides (TTAs) **(Figure 9)** had already exhibited significant anti-HIV-1 activity.[31] Based on this activity the group thought it worthwhile to synthesise new TTAs based on the SAR studies done for previously synthesised TTAs, in a bid to improve the interaction between the inhibitors and the RT enzyme and improve the biological activity.[31]

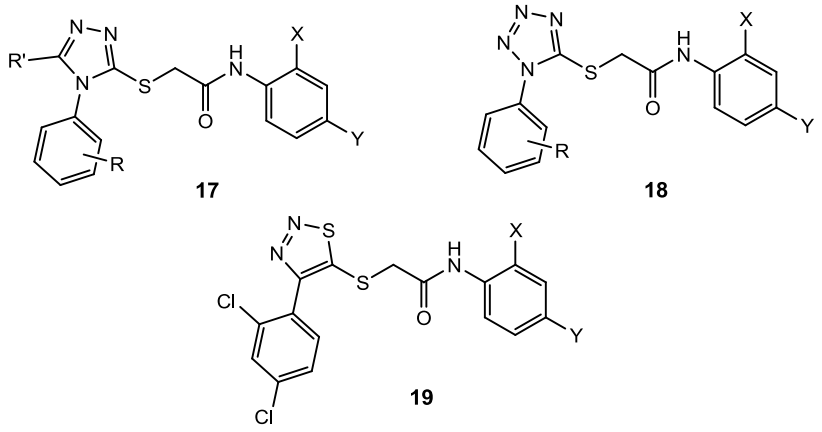


Figure 9 Triazole, Tetrazole and 1,2,3-Thiadiazole Thioacetanilide based NNRTIs[31]

The previous SAR and molecular modelling studies demonstrated that an increase in the volume of the substituted phenyl ring linked with the azole proved beneficial in strengthening the π-π stacking between the inhibitor and the Tyr181 and Tyr188 amino acid residues of the RT enzyme.[31] The group thus opted for a larger 2,4-dibromo substitution on the newly synthesised TTAs.[31] It was also noted from the SAR studies that the anilide phenyl moiety is located at the protein/solvent interface and in several of the newly synthesised TTAs this phenyl ring was replaced with several substituted heterocycles to improve the interaction between the inhibitor and solvent front.[31] The group discovered that of the newly synthesised TTAs the 2,4-dibromo derivative containing a 2-chloropyridin-3-yl heterocycle **20 (Figure 10)** was the most potent potential NNRTI and had an activity 7-fold that of Nevirapine and Delaviridine, two commercially available NNRTIs.[31] Molecular modelling studies of compound **20** showed that the 2,4-dibromophenyl ring fits into the aromatic-rich binding pocket, surrounded by the aromatic side chains of Tyr188, Phe227 and Trp229 amino acid residues.[31] The analysis showed that the binding mode of the phenyl ring was parallel to the Tyr188 side chain, giving rise to positive π-stacking interactions.[31] The inhibitor's amide carbonyl also forms a key H-bond with the backbone N-H of the Lys103 amino acid residue, also improving the binding of the inhibitor in the allosteric site.[31] Based on the biological testing results and SAR studies, these newly synthesised TTAs could serve as potent NNRTIs in the future and synthesis of new TTA derivatives and testing of these compounds is currently being conducted by this group.[31]

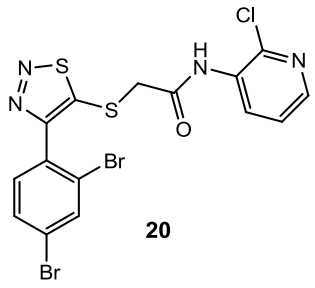


Figure 10[31]

The positive results displayed by both these groups highlights the importance of such processes as HTS, SAR studies and molecular modelling in finding compounds which can act as potent and selective NNRTIs. The successes of these groups in developing the potential NNRTIs shows how critical it is to use each and every available resource in drug design. The following sections will highlight the use of another one of these important tools in medicinal chemistry, the use of multi-component coupling reactions for the synthesis of high throughput screening libraries.

5. Multi-Component Coupling Reactions in Medicinal Chemistry

Drug discovery is a competitive field which requires constant innovation and development due to a combination of variable factors which include market, patient and regulatory issues.[32] Due to high failure rates of drugs in phase II and phase III clinical trials and the limited human resources, drug development is a slow and risky process.[32] Multi-component coupling chemistry emerged in the 1990s with the ability to address some of the major issues facing the pharmaceutical companies today and has since become important in modern drug discovery.[32]

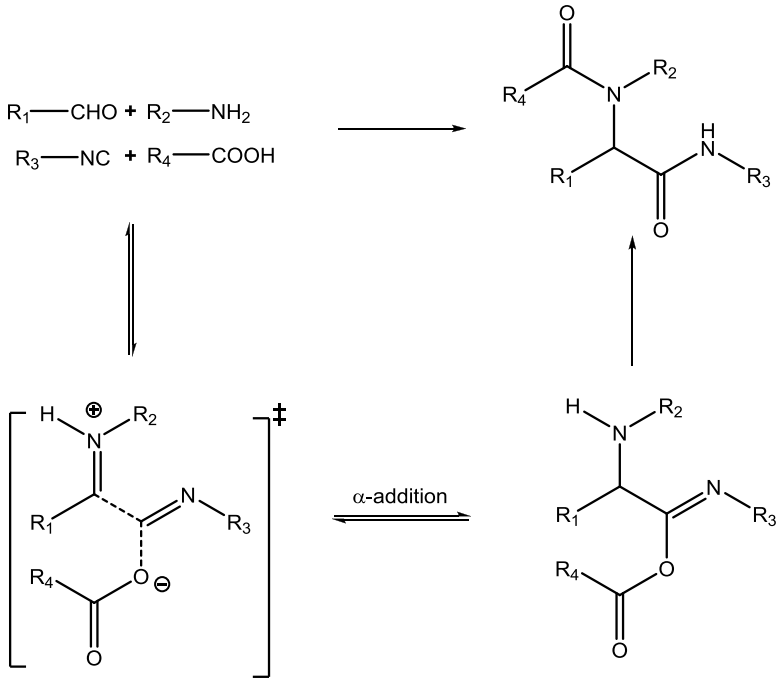
5.1 What Are Multi-Component Couplings?

Multi-component coupling reactions (MCCs) are powerful condensation reactions which occur in one pot and incorporate portions of three or more starting materials in the final product.[33] Perhaps the most attractive aspect of MCCs is the ability of these types of reactions to create structurally complex or highly substituted molecules in a single chemical step.[34] Multi-component condensations are atom economical in contrast to classical synthesis which requires multiple steps and reagents; MCC only require one step thus significantly reducing the generation of by-products.[34] As well as being an important means of generating structurally diverse molecules in an atom economical reaction an ideal multi-component reaction should also possess the ability to be modified in order to diversify the products.[35] This allows for the creation of large libraries of compounds which contain a certain privileged skeleton.[35] The new approach in medicinal chemistry is a scaffold-based approach whereby hundreds of derivatives of a certain core structure are prepared and biologically screened.[36] MCC allows medicinal chemists to create these large screening libraries either in one pot, by varying side chains on starting materials, or by way of post-MCC modifications.[36] It is the use of MCC in the almost effortless creation of these compound libraries which have cemented the use of MCC in medicinal chemistry.[33] There are numerous examples of MCCs in the literature and this section aims to demonstrate the elegance and efficiency of a few well known MCCs.

5.2 Specific Examples of MCCs

5.2.1 The Ugi Reaction

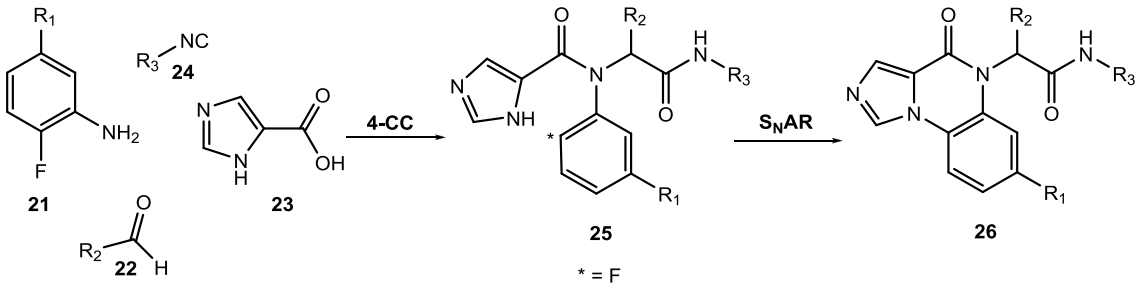
Perhaps one of the most famous and widely used MCCs is the Ugi reaction, which is a four component reaction of an amine, aldehyde, carboxylic acid and isocyanide to afford a peptide-like structure **(Scheme 2)**.[37] The Ugi reaction is generally initiated by the condensation of the amine with the aldehyde to form the intermediate imine, which subsequently reacts with the carboxylic acid and isocyanide to give the desired product.[37] Many researchers have focused on the Ugi reaction to prepare libraries of α-aminoacylamides, but recently the ability of these products to be modified post-condensation has become a key focus.[38, 39] These post-condensation modifications and cyclisations can be used to produce numerous pharmacologically important scaffolds by careful selection of the key Ugi-components.[39]



Scheme 2 Mechanism of Ugi 4-Component Coupling Reaction[37]

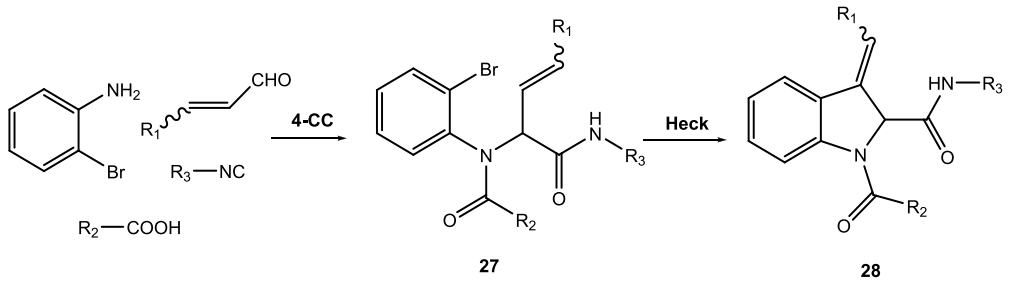
The use of the classical Ugi reaction, followed by a post-condensation cyclisation via nucleophilic aromatic substitution (S_NAr), leading to the novel and versatile two step synthesis of imidazo and pyrazolo[1,5-*a*]quinoxalines was demonstrated by Spatz and co-workers.[37] Imidazoquinoxalines are an important class of biological heterocycles which are found extensively in pharmaceutical agents.[37] They have been used as templates for GABA/benzodiazepine receptor agonists/antagonists and cAMP and cGMP phosphodiesterase inhibitors in addition to numerous other pharmacological applications.[40] The first step of the synthesis was the four-component Ugi-reaction yielding the product **25** as the intermediate for the subsequent cyclisation reaction

(Scheme 3).[37] The use of 2-fluoroaniline **21** and the heterocyclic carboxylic acid **23**, as bifunctional starting materials, enabled the nucleophillic aromatic substitution reaction to occur in which the nitrogen of the heterocyclic acid component acts as a nucleophile and the fluorine as the leaving group to give compounds such as **26**.[37] The group was also able to demonstrate this methodology using a variety of fluoro-substituted amines, aldehydes and isocyanides leading to compounds with three points of variable diversity.[37]



Scheme 3 Schematic of 4-oxo-4*H*-imidazo-[1,5-*a*]quinoxaline synthesis[37]

A further example of the Ugi reaction products undergoing post condensation modifications was reported by Kalinski *et al.* who demonstrated the combined use of the Ugi and Heck reactions for the synthesis of highly substituted dihydroindoles.[39] Their synthesis involved the use of 2-bromoanilines and acrylic aldehydes as starting materials for the Ugi reaction **(Scheme 4)**.[39] The acyclic intermediate, Ugi-product **27**, was then subjected to an intermolecular Heck-reaction to give the final dihydroindole **28**.[39]

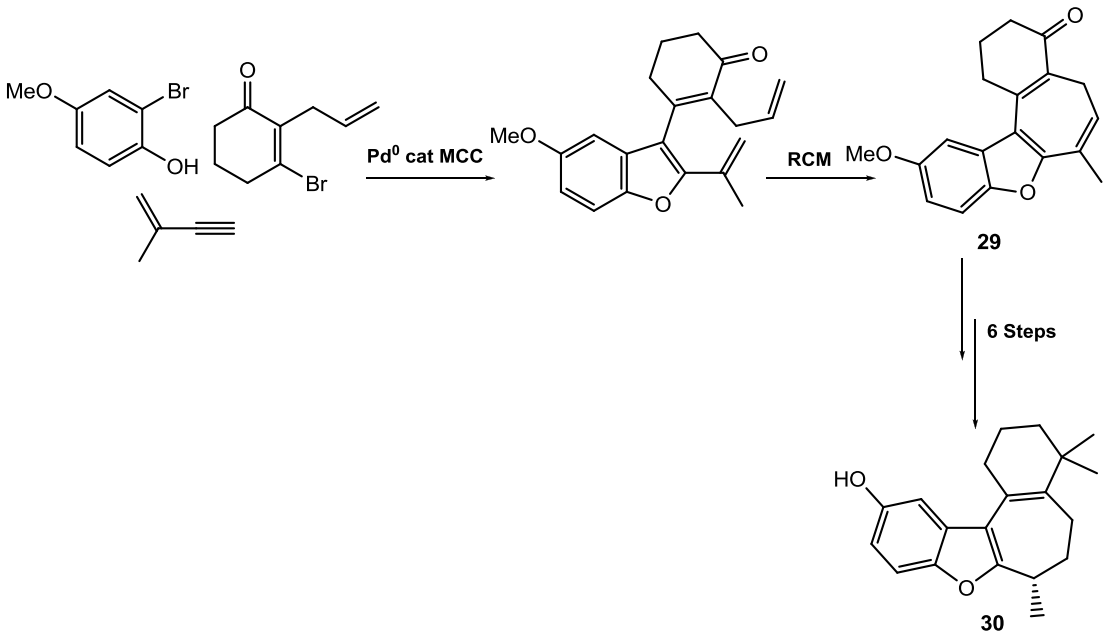


Scheme 4 Ugi-Heck Synthesis of Substituted Indoles[39]

5.2.2 MCC based on Transition Metal Catalysis

A recent review showed a transition metal catalysed MCC as the key step in the synthesis of (+)-frondosin B **30**, a marine alkaloid active as an interleukin-8 antagonist.[35] The approach utilised a Pd-catalysed MCC between a 2-bromomphenol, alkyne and bromoenone to provide the intermediated functionalized benzofuran derivative which was successfully cyclised using ring

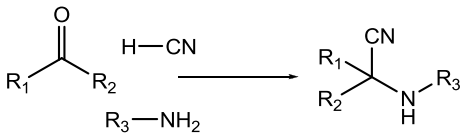
closing metathesis to afford the basic core of frondosin B **29 (Scheme 5)**.[35] The final product was obtained in a further six steps with an overall yield of 32%.[35]



Scheme 5 Total Synthesis of Frondosin B using Pd-catalysed MCC reaction[35]

5.2.3 The Strecker reaction

The Strecker reaction, which was discovered in 1850, was the first MCC reaction to be published and is of great importance in medicinal chemistry.[41] The reaction demonstrates the coupling of an amine, carbonyl compound and either hydrogen cyanide or an alkaline metal cyanide to afford α-amino nitriles **(Scheme 6)** which are important products *en route* to the synthesis of α-amino acids.[41] The Strecker reaction has also been used as an important step in the synthesis of natural products as shown by Zhu and co-workers when they demonstrated the use of the asymmetric Strecker reaction in the synthesis of D-(*R*)-4-methoxy-3,5-bisbutyldimethylsiloxy phenylglycine as a key intermediate in the synthesis of the antibiotic vancomycin.[41, 42]

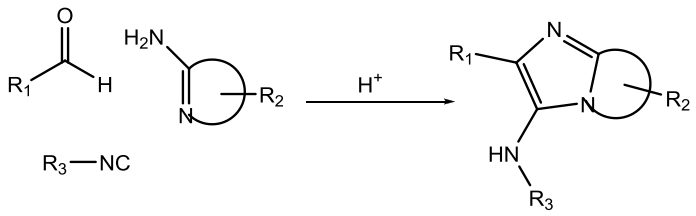


Scheme 6 Schematic of Strecker Reaction[41]

6. Multi-Component Couplings for the Development of Imidazo[1,2-*a*]pyridines

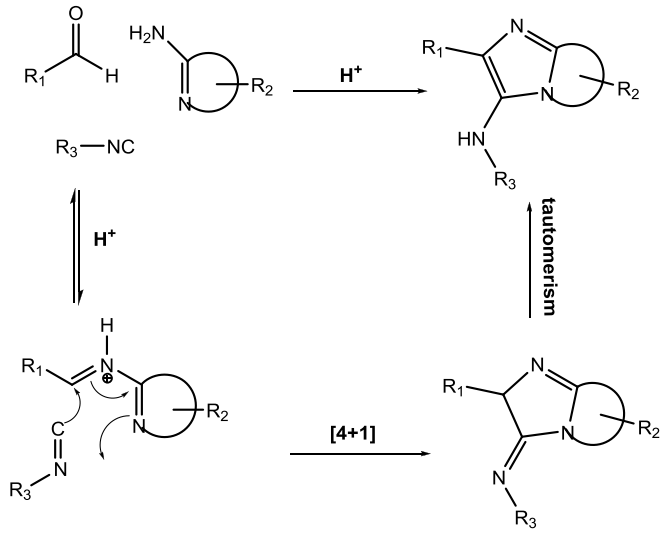
6.1 Groebke-Blackburn Reaction

In 1998, a four-centre, three-component reaction involving 2-aminoazines and 2-aminoazoles to form fused imidazoles was reported independently by three different research groups.[43] This reaction which involves the condensation of a 2-aminoazine or 2-aminoazole with an isocyanide and aldehyde, in the presence of catalytic acid **(Scheme 7)** became known as the Groebke-Blackburn reaction.[44a] The original success of the Groebke-Blackburn reaction being high yielding, experimentally simple and the originality of the 3-aminoimidazo[1,2-*a*]pyridine ring system led to further exploration of this unusual transformation.[44b] Preliminary studies showed that aldehydes (1.2 - 3.0 equiv) and isocyanides (1.2 - 1.5 equiv) are best used in slight excess to the 2-aminoazine component and that the reactions were not sensitive to either oxygen or moisture.[44b] Further studies highlighted the tolerance of the MCC reaction for structural variations of the three components; aldehydes and isocyanides (aromatic, electron-rich and electron-poor, hetero-aromatic, aliphatic and sterically encumbered) showed little effect on the high yields of the reactions.[44b] Many hetero-aromatic amidines can be used in the reaction, but the use of electron-poor amidines tended to slow the reaction down significantly and resulted in many more side-products.[44b] Thus the simple and highly efficient synthesis of imidazo[1,2-*a*]azines by way of the Groebke-Blackburn reaction has led to numerous efforts to develop compound libraries based on this drug-like core and further highlights the importance of effective MCC in medicinal chemistry.[44a, 45]



Scheme 7 Schematic of Groebke-Blackburn Reaction[43]

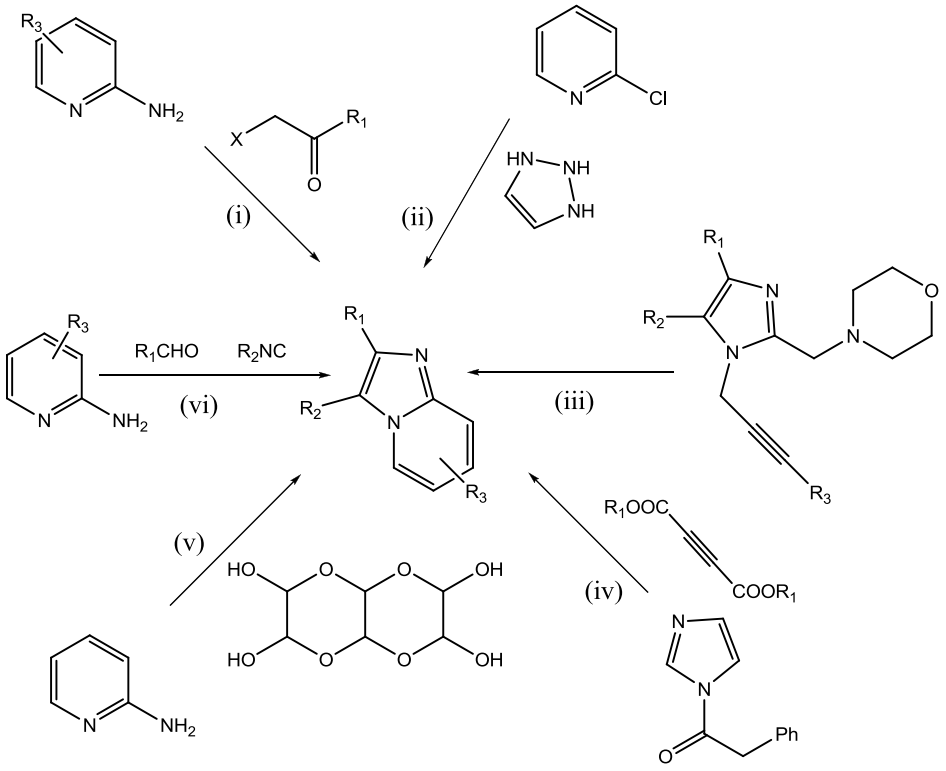
A probable mechanism **(Scheme 8)** for the formation of the imidazo[1,2-*a*]azine core involves a non-concerted [4+1] cycloaddition between the protonated Schiff base (which holds both the nucleophilic and electrophilic character) and the isocyanide (which behaves as a vinylidene carbenoid).[43] Under acidic conditions an aldehyde and a primary amine can react to form what is known as an iminium ion or Schiff base.[46] It is this iminium ion which contains both the nucleophilicity and electrophilicty which is essential for the [4+1] cycloaddition of the isocyanide.[46] The final step in the formation of the 3-aminoimidazole is a prototropic shift forming the final aromatic product.[44a, 44b]



Scheme 8 Suggested Mechanism of Groebke-Blackburn Reaction[44a]

6.2 Synthesis of Imidazo[1,2-a]pyridines and the Efficacy of MCC

There are a number of synthetic routes for the synthesis of imidazo[1,2-*a*]pyridines and imidazo[1,2-a]pyrimidines **(Scheme 9)**.[47] These include: (i) coupling reactions of 2-aminopyridines with α-halocarbonyl compounds; (ii) reaction of 2-chloropyridine with 1,2,3-triazoline and subsequent elimination of nitrogen; (iii) cyclizations of 1-(2-alkynyl)-2-aminomethylimidazoles, which are obtained from substituted imidazoles via six steps; (iv) reactions of (arylacetyl)imidazoles with acetylenedicarboxylic esters; (v) condensation of 2-aminopyridine with glyoxal trimer dehydrate in aqueous $NaHSO_3$ and (vi) one-pot condensations of aldehydes, isonitriles and 2-aminopyridines.[47]



Scheme 9 Various Approaches to the Synthesis of Imidazo[1,2-*a*]pyrimidine and Imidazo[1,2-*a*]pyridine[47]

Of all the methods which can be employed to synthesise the imidazo[1,2-*a*]pyridine core, only (i) and (vi) allow for diversity in the final products.[47] Method (i) is a popular approach for synthesising the imidazo[1,2-*a*]azine core as a variety of substituted 2-aminopyridines and α-halocarbonyl compounds are commercially available or can be readily synthesised.[47] However, one of the biggest drawbacks with this methodology is the inability to form 3-amino monosubstituted imidazo[1,2-*a*]pyridines or imidazo[1,2-*a*]pyrimidines with this ring closing procedure.[47] Hence the Groebke-Blackburn MCC reaction is the method of choice for the synthesis of 3-aminoimidazo[1,2-*a*]pyri(mi)dine ring systems as it is the only method know to date to allow for significant diversity at the 3-position.[48]

The simplest way in which huge libraries of diverse 3-aminoimidazo[1,2-*a*]pyri(mi)dine compounds can be synthesised is to make use of the variety of commercially available aldehydes, isocyanides and substituted 2-aminopyri(mi)dines.[43] However, although the diversity of aldehydes is quite substantial, there are only a few commercially available isocyanides.[43] This problem is easily overcome by using an isocyanide with a side chain which can be easily converted to the primary amine and further modified at the amino group by, for example acylation or *N*-arylation.[45] Krasavin and co-workers demonstrated that *t*-butyl isocyanide can be used as a convertible isocyanide with the *tert*-butyl group being cleaved in neat TFA under reflux and gave the corresponding trifluoroacetamides.[49] The latter were then subjected to alkaline hydrolysis to afford the primary

amines in excellent yields.[49] The subsequent primary amine was then derivatized via Palladium catalyzed arylation, acylation, carbamoylation and reductive alkylation.[49] In this way the Groebke-Blackburn multi-component coupling reaction can be used to synthesise large numbers of structurally diverse imidazo[1,2-*a*]azines without being limited by the isocyanide component.[49]

6.3 Biological Application of Imidazo[1,2-a]pyridines

Imidazo[1,2-*a*]pyridines and the related imidazo[1,2-*a*]pyrimidines have received significant attention from the pharmaceutical industry owing to their interesting biological applications.[48] These compounds have been known to display bioactivity over a broad range of therapeutic classes and have shown antibacterial, antifungal, antiviral and anti-inflammatory properties.[48] There are also several therapeutic agents currently on the market which contain the imidazo[1,2-*a*]pyridine core **(Figure 11)** including alpidem **31** (anxiolytic), zolpidem **32** (hypnotic) and zolimidine **33** (antiulcer).[48] This section aims to illustrate a few of the recent developments in the use of novel imidazo[1,2-*a*]pyridines as biological agents.

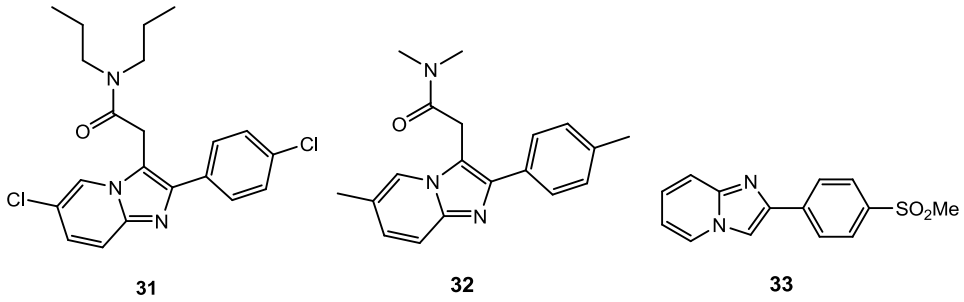


Figure 11 Therapeutic Agents containing the Imidazo[1,2-*a*]pyridine core[48]

6.3.1 Anti-viral Applications of Imidazo[1,2-a]pyridines

The human cytomegalovirus (HCMV) is a β-herpes virus which can cause severe illness in immuno-compromised people such as AIDS patients or organ transplant recipients.[50] The drugs which are currently used to treat this disease are Ganciclovir, Foscarnet and Cidofovir, but these drugs have many side effects and the drug Ganciclover has been shown to have a toxic effect on the bone marrow of patients.[50] Gueiffier and co-workers, as part of a study on nitrogen bridgehead heterocycles, reported the synthesis and antiviral activity of 7- and 8-methyl-3-benzylthiomethyl-imidazo[1,2-*a*]pyridine **34** and **35 (Figure 12)** as novel HCMV inhibitors.[50, 51] The biological assays demonstrated that these compounds had high selectivity for the CMV-infected cells *in vivo* and thus a high selectivity for viral enzymes.[51]

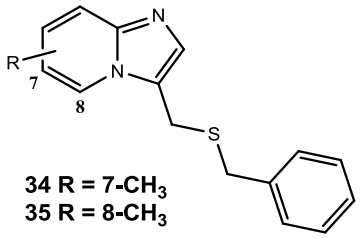


Figure 12[51]

A further example of the biological applications of imidazo[1,2-*a*]pyridines was shown by Hamdouchi and co-workers, who developed a series of 2-amino-3-substituted-6-[(*E*)-1-phenyl-2-(*N*-methylcarbamoyl)vinyl]imidazo[1,2-*a*]pyridines **36a-f (Figure 13)** which showed excellent potential as anti-rhinovirus agents.[52] Human rhinoviruses are a group of viruses responsible for the common cold, bronchitis, and sinusitis and exacerbate chronic asthma and emphysema.[52] A wide range of compounds have been shown to exhibit anti-rhinovirus activity, but most compounds have been rejected due to problems with toxicity, unfavourable pharmacology and poor bioavailability.[52] Two synthetic potential rhinovirus benzimidazole inhibitors, enviroxime **37** and enviradene **38 (Figure 13)** show good *in vitro* activity.[52] However further development of both compounds has been discontinued due to their insignificant therapeutic benefit and undesirable side effects.[52] The newly synthesised imidazo[1,2-*a*]pyridines showed improved antiviral activity and reduced cellular toxicity when compared to enviroxime and enviradene.[52] Since the anti-rhinoviral activity found in this new class of compounds is promising, it is hoped that further biological evaluation including bioavailability and broad-spectrum activity will be valuable in finding a potential treatment for the common cold.[52]

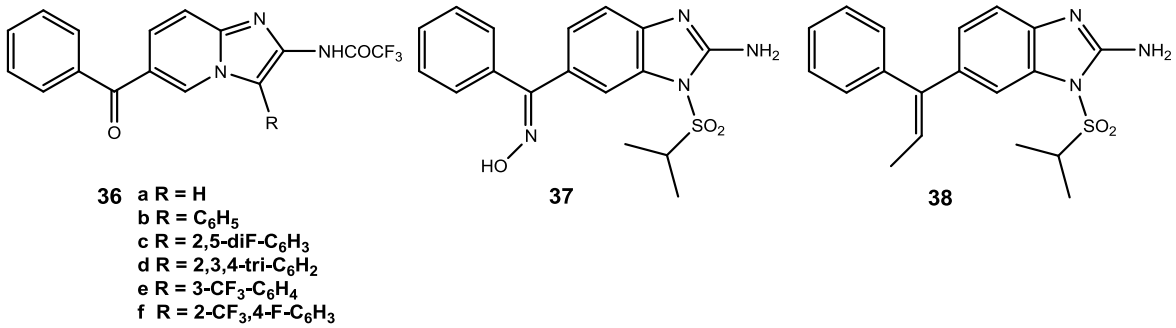
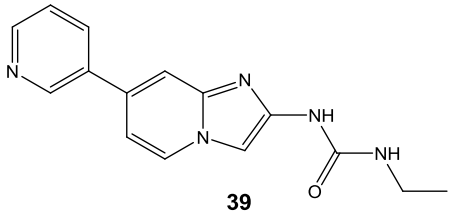


Figure 13[52]

6.3.2 Anti-Bacterial Applications of Imidazo[1,2-a]pyridines

The type II bacterial topoisomerases DNA gyrase and topoisomerase IV, which are responsible for the control of chromosome function, are important drug targets of the quinolone/fluoroquinolone class of anti-bacterial agents.[53] These therapeutic agents interact with the catalytic subunits of

DNA gyrase (GyrA) and topoisomerase IV (ParC).[53] The ATPase subunits of these enzymes GyrB and ParE have also been identified as targets for small molecule inhibitors; however, the anti-bacterial agents used to date have many downfalls including resistance, toxicity and permeability, which limited the scope of these drugs.[53] East and co-workers identified an imidazo[1,2-*a*]pyridine scaffold to demonstrate anti-bacterial activity through inhibition of the GyrB and ParE ATPase subunits.[53] The imidazopyridine **39 (Figure 14)** was the most active compound tested against Gram-positive *Staphylococcus aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212 as well as Gram-negitive *E. coli* N43 bacterial strains.[53] Further SAR studies and investigations into the pharmacokinetics and efficacies are being investigated by this group.[53]



39

Figure 14[53]

6.3.3 Anti-Parasitic Activity of Imidazo[1,2-a]pyridines

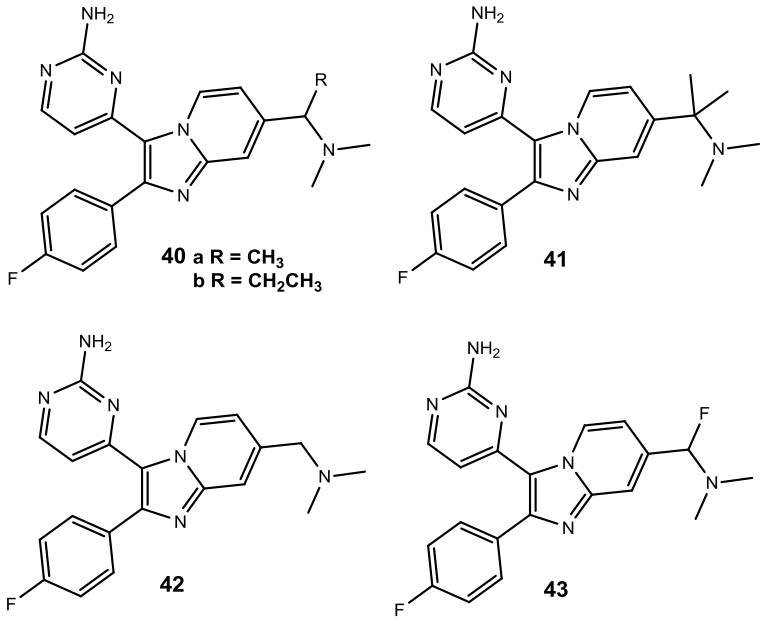


Figure 15[54]

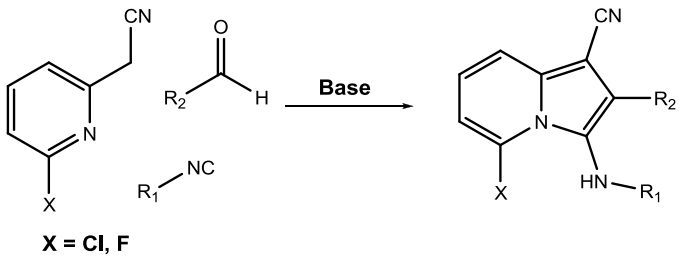
Coccidiosis is a parasitic disease which is caused by the invasion of the avian intestinal lining by a protozoan parasite of the genus *Eimeria* and is a major cause of mortality in the poultry industry.[54] Over 35 billion chickens are raised worldwide and the major poultry operations administer anti-

coccidial agents prophylactically; however, increased resistance to current coccidiostats means a new range of drugs needs to be developed in order to target novel biochemical pathways.[54] A recent study indicated that cCMP-dependent protein kinase (PKG) is essential to the survival of the parasite and thus represents a good drug target.[54] HTS of known kinase inhibitors identified imidazo[1,2-*a*]pyridines as potential PKG inhibitors and broad spectrum anti-coccidial agents.[54] Scribner prepared a variety of 2-aryl-3-(2-aminopyrimidin-4-yl)imidazopyridines with different alkyl amine substituents at the 7-postion of the imidazopyridine moiety to test as anti-coccidial agents.[54] The most active compounds **40a, 40b, 41, 42** and **43 (Figure 15)** all showed *in vivo* potency against all four species of *Eimeria* at, or below, 12.5ppm, but due to potential genotoxicity these compounds were not developed further.[54] The synthesis of less toxic imidazopyridine derivatives is currently being continued by the group.[54]

7. Multi-Component Couplings for the Synthesis of 3-amino-1-cyano-indolizines

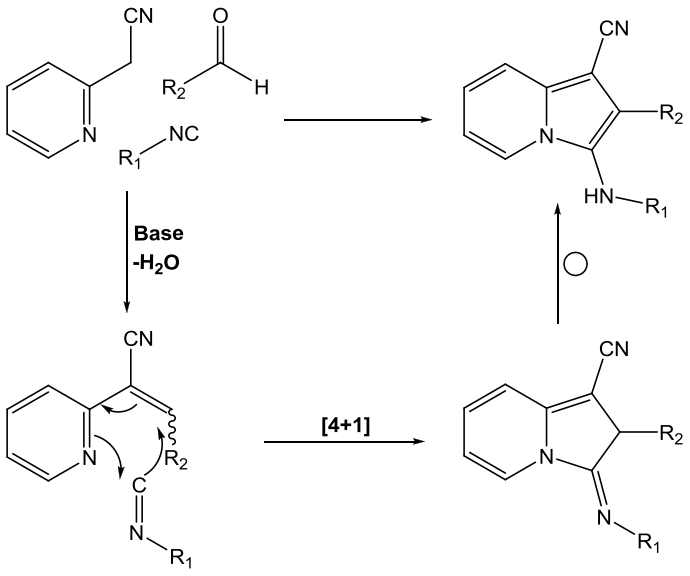
7.1 3-Amino-1-cyano-indolizine by MCC

The synthesis of 3-amino-1-cyano-indolizines by using a MCC was first reported by Poigny and co-workers as part of an effort to synthesise small molecule inhibitors which could inhibit protein-protein binding in an attempt to develop a novel prostate cancer treatment.[34] As part of the study, the group screened approximately 20 000 small molecules of which 11 800 were purchased and 8160 were synthesised in-house using exclusively different multi-component coupling reactions.[34] Of all the molecules screened, only three different MCC-based scaffolds showed any activity in the biological screening and among those scaffolds the 3-amino-1-cyano-indolizines were the most potent antagonists.[34] The synthesis of 3-amino-1-cyano-indolizines is similar to the Groebke-Blackburn reaction and involves the condensation of an isocyanide, an aldehyde and cyano-2-methylene-pyridine in the presence of a catalytic amount of base **(Scheme 10)** to give the desired products in moderately good yields.[34] As in the case with the Groebke-Blackburn reaction, by making use of the wide variety of commercially available starting materials, both aldehyde and isocyanide components could be varied to increase the diversity in the 3-amino-1-cyano-indolizines.[34] In this way large diverse compound libraries of these indolizines can be synthesized for high throughput screening against various diseases and pathogens.



Scheme 10 Schematic of 3-amino-1-cyano-indolizine synthesis[34]

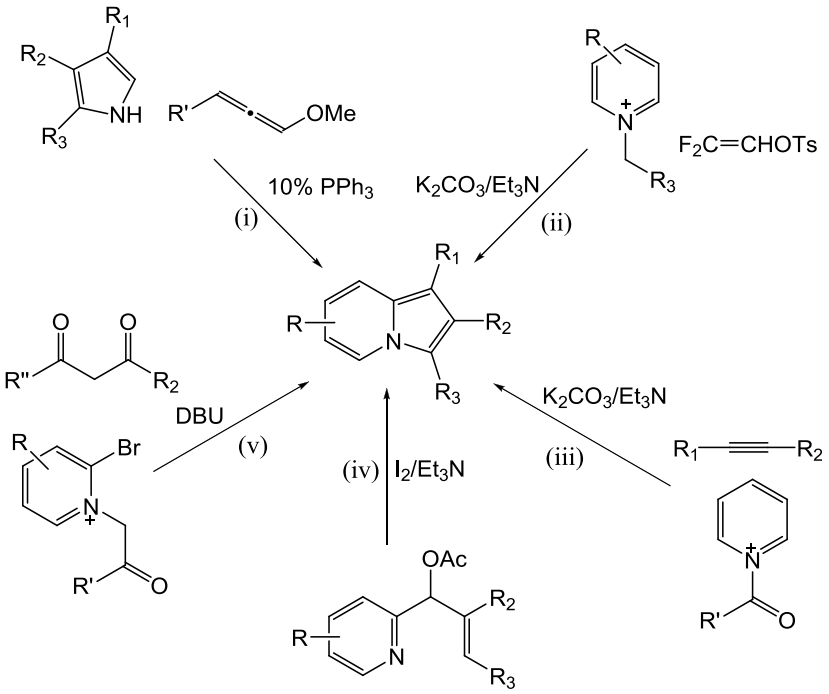
The mechanism of this MCC reaction has not been fully elucidated, but the authors suggest that a possible mechanism is through the cheletropic addition of the isocyanide moiety to the Knoevenagel-type hetero-diene intermediate **(Scheme 11)** as in the Groebke-Blackburn mechanism.[34] The protons which are α- to the nitrile are acidic and can easily be removed by a base, thus generating an anion in the α-position.[46] The carbonyl carbon of the aldehyde being electrophilic then undergoes nucleophilic attack from the α-anion and with subsequent elimination of water forms the hetero-diene.[46] It is then suggested that a non-concerted [4+1] cycloaddition between the hetero-diene and the isocyanide, followed by a prototropic shift to regain aromaticity, forms the 3-amino-1-cyano-indolizine scaffold.[34]



Scheme 11 Proposed Mechanism for the Synthesis of 3-amino-1-cyano-indolizines[34]

7.2 Synthesis of Indolizines; Why MCC is so efficient

Pyrrolo[1,2-*a*]pyridine, known as indolizine, is an important scaffold found in natural products and has been used as a key motif in the pharmaceutical industry due to the broad spectrum of biological activities with which it is associated.[55] It is thus not surprising that there are many synthetic approaches for the development of this privileged scaffold in the literature.[55] Syntheses of the indolizine ring system include, as shown in **Scheme 12**: (i) the phosphine catalysed nucleophilic addition of azoles to allenes,[56] (ii) 1,3-dipolar reaction of *N*-ylides with fluorinated vinyl tosylates,[57] (iii) 1,3-dipolar cycloaddition of pyridiniums and alkynes,[58] (iv) 5-*endo*-*trig* iodocyclization[55] and (v) reaction of α-halo pyridinium salts with β-dicarbonyl species[59].



Scheme 12 Schematic of key steps in the syntheses of the indolizine scaffold[55 - 59]

Although many of these syntheses appear to be simple one pot syntheses (ii,iii,v), they do however require preparation of the starting materials. The pyridinium salts and *N*-ylides need to be prepared from the appropriate pyridines and α-halo species (ii,iii,v) and the fluorinated alkenyl tosylates need to be prepared from the corresponding fluorinated alcohols (ii), making these syntheses less efficient and atom economical than the MCC reaction.[57, 58, 59] The diversity of the indolizine compounds synthesised by these methods is also limited by the starting materials, as although various alkynes (iii) and β-dicarbonyl (v) compounds are commercially available there is not a wide variety of highly substituted species found and preparation of these compounds may then be necessary.[58, 59] The iodocyclization starting material (iv) first needs to be prepared from the reaction between the corresponding 2-pyridinyl lithium and α,β-unsaturated aldehyde to give the allylic alcohol, which is turn is converted to the allylic acetate, making the synthesis far less efficient than the MCC reaction.[55] Synthesis (i) is the only true one-pot synthesis, but the diversity of the final indolizine compounds is seriously hampered by the lack of functionalized allenes and azoles which are commercially available.[56]

When reviewing the syntheses presented in **Scheme 12** it becomes obvious why multi-component condensations are amongst the most useful chemical reactions. The MCC reaction for the synthesis of 3-amino-1-cyano-indolizines is not only synthetically efficient, but allows for the development of structurally diverse indolizine products.[34] The simplest way in which large libraries of structurally diverse 3-amino-1-cyano–indolizine compounds can be synthesised is to make use of the variety of commercially available aldehydes and isocyanides.[34] However, although the

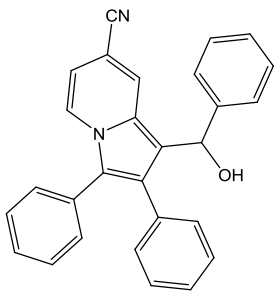
diversity of aldehydes is quite substantial, there are only a few commercially available isocyanides.[43] This problem is easily overcome by using a convertible isocyanide which is converted to the primary amine and further modified at the amino group by way of, for example acylation or *N*-arylation[45], as is the case with the imidazo[1,2-*a*]pyridine compounds.

7.3 Biological Applications of Indolizines

It has already been mentioned that the indolizine scaffold is an important one in nature and in the pharmaceutical industry.[55] This privileged scaffold has been found to have a variety of biological activities including anti-inflammatory, antiviral, analgesic, antitumor and cardiovascular activity.[60] Thus indolizines have become important synthetic targets in the development of novel pharmaceuticals for the treatment of cancer, cardiovascular disease and HIV infections.[60] This section will illustrate a few of the biological applications of compounds containing the indolizine motif and recent developments in the synthesis of novel indolizines as potential biological agents.

7.3.1 Antibacterial Activity of Indolizines

There are approximately 1.6 million deaths annually worldwide due to tuberculosis (TB).[61] Current treatments for TB must be taken for a period of 6-9 months and due to the lengthy time period many patients stop taking the drugs leading to the growing problem of multi-drug resistant strains of TB.[61] The increased resistance of the micro-organism against antibacterial compounds calls for research and development into producing novel TB agents which are effective against the drug resistant TB strains.[61] Gundersen *et al.* began screening indolizine derivatives which had been previously studied for their anti-oxidant properties and came across the antimycobacterial properties of (±)-1-(hydroxyphenylmethyl)-2,3-diphenylindolizine-7-carbonitrile **44 (Figure 16)**.[61] The indolizine compound was screened against *M. tuberculosis* $H_{37}Rv$ and showed excellent results *in vitro* and with continued development may prove to be a potent and selective antimycobacterial agent.[61]



44

Figure 16[61]

7.3.2 Cardiovascular Activity of Indolizines

Calcium channel blockers or calcium antagonists have been found to be the most effective treatment for ischemic heart disease and hypertension.[62, 63] These drugs selectively inhibit Ca^{2+} influx into the heart muscles by blocking the slow inward channels for Ca^{2+} or inhibit Ca^{2+} influx into vascular smooth muscle causing the muscles to relax.[62] There are currently three clinically available calcium channel blockers: a 1,4-dihydropyridine, nifedipine **45**, a phenylalkylamine, verapamil **46** and a benzothiazepine, diltiazem **47 (Figure 17)**.[62] A new class of calcium channel blockers has recently been discovered; the 1-[[4-(aminoalkoxyphenyl]sulfonyl] indolizines **48** with most compounds being as active as verapamil **46** and diltiazem **47**.[63] The compound fantoforone or SR 33537 **49** was discovered to be as potent as nifedipine **45** and has been selected for clinical development for the treatment of hypertension.[63]

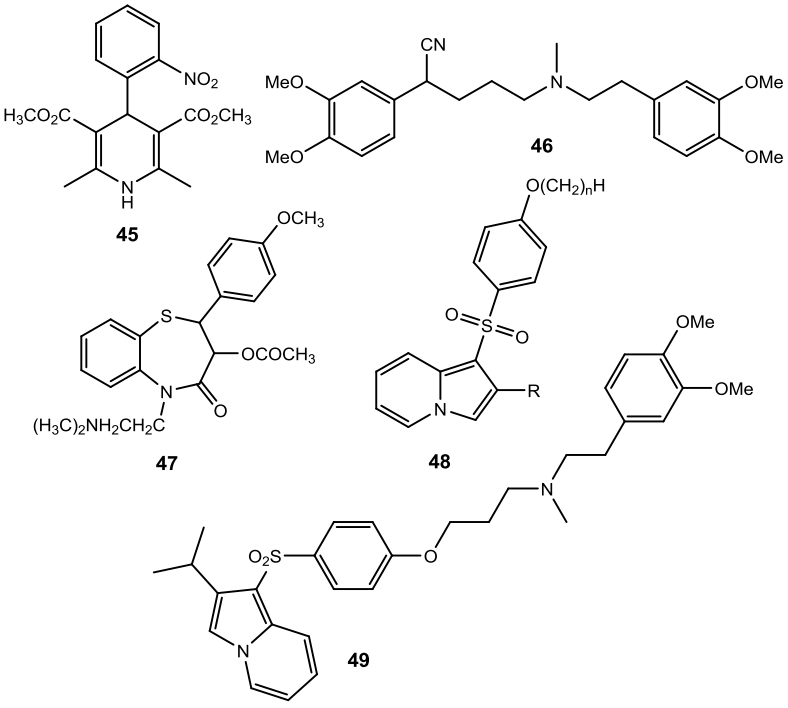


Figure 17[62, 63]

7.3.3. Anticancer Activity of Indolizines

Inhibitors of the cytochrome P450 aromatase are therapeutic agents for the treatment of estrogen dependent diseases such as breast cancer.[64] Several inhibitors of aromatase have been reported and are either clinically available or under clinical evaluation; however, many of these inhibitors are not as potent as expected *in vivo* or have terrible side effects.[64] Thus the synthesis and development of more powerful and specific aromatase inhibitors is of great importance for the treatment of breast cancers.[64] Molecular modelling studies carried out by Sonnet *et al.* led to the design of a novel hypothetical aromatase inhibitor.[64] The group synthesised an array of indolizine compounds based on the indolizine pharmacophore and were tested for aromatase inhibition in

human placental microsomes.[64] The *in vitro* biological evaluation of these compounds led to the identification of two new and potent non-steroidal aromatase inhibitors MR 20494 **50** and MR 20492 **51 (Figure 18)** which are undergoing clinical development.[64]

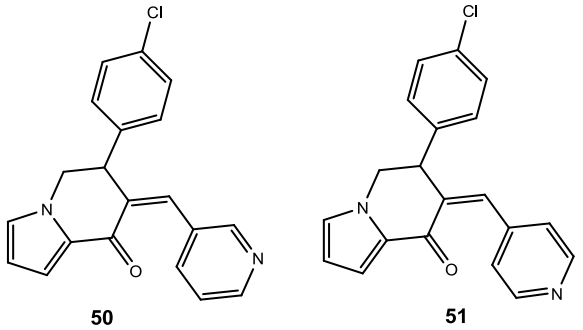
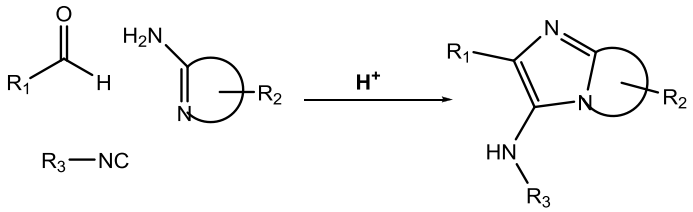


Figure 18[64]

8. Aims of this Section

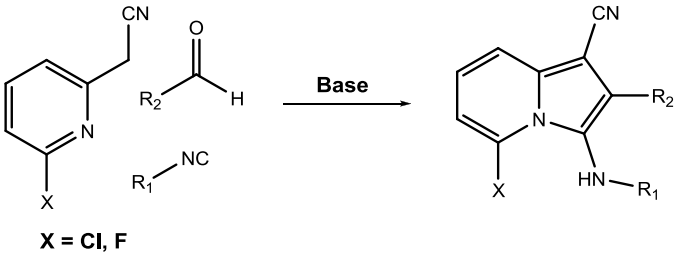
The selected review in Chapter 1 highlights the growing need for novel NNRTIs with improved potency and activity to combat drug resistant forms of the HIV-1 virus. The review also highlights the remarkable ability of MCC reactions to create large libraries of structurally diverse compounds in few steps. This section of the project aims to combine the synthetic efficacy of MCC reactions with the mounting need for novel NNRTIs in an effort to identify compounds showing potential anti-HIV activity. We thus wish to use MCC reactions to synthesise an imidazo[1,2-*a*]pyridine and 3-amino-1-cyano indolizine library which can be tested for activity against the RT enzyme of HIV-1.

- To synthesise a library of imidazo[1,2-*a*]pyridines via the Groebke-Blackburn reaction **(Scheme 7)**[43] making use of different commercially available aldehydes, isocyanides and 2-aminopyridines to diversify the products.



Scheme 7 Schematic of Groebke-Blackburn Reaction[43]

- To synthesise a library of 3-amino-1-cyano-indolizines via the multi-component coupling approach **(Scheme 10)**[34] making use of the variety of commercially available aldehydes, isocyanides and cyano-2-methylene-pyridines.



Scheme 10 Schematic of 3-amino-1-cyano-indolizine synthesis[34]

- Biological testing of the synthetic libraries with a HIV reverse transcriptase kit to identify any potential NNRTI activity.

Chapter 2: Results and Discussion

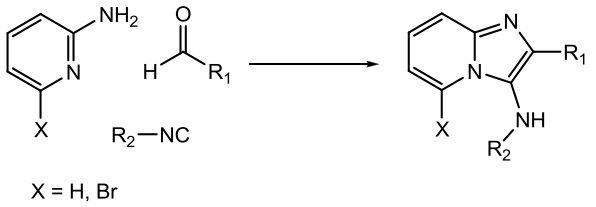
Synthesis of imidazo[1,2-*a*]pyridines and 3-amino-1-cyano indolizines

1. Introduction

This chapter concerns the results of the preparation of imidazo[1,2-*a*] pyridines and 3-amino-1-cyano-indolizines in accordance with the aims as outlined in Chapter 1. The overview highlighted the great need for novel NNRTIs with improved potency against HIV-1 and we thus wished to synthesise a variety of compounds which could be tested against HIV-1 RT. The following sections will discuss the use of multi-component coupling reactions in the creation of diverse compound libraries which were then tested for reverse transcriptase activity. Important aspects such as compound characterisation, synthetic issues, mechanistic detail and finally biological testing results will be addressed within this chapter for the synthesised compounds.

2. Synthesis and Attempted Synthesis of imidazo[1,2-*a*]pyridines 52-62

2.1 The Groebke-Blackburn Reaction

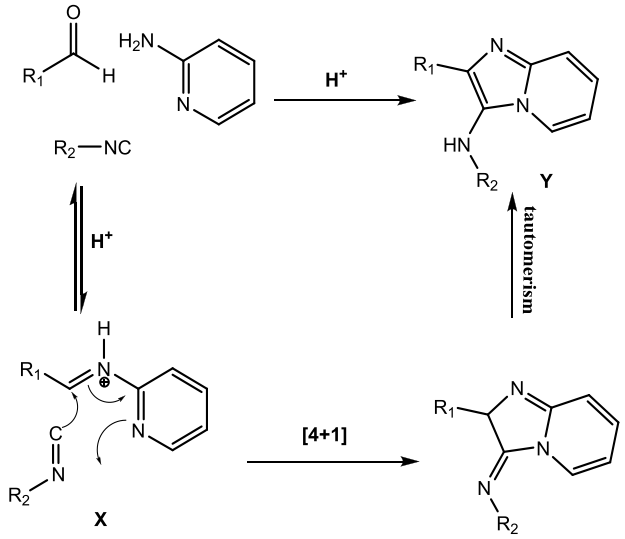


Scheme 13 Groebke-Blackburn MCC Reaction *Reagents and Conditions*: K-10 Montmorillonite clay, 1,4-dioxane, reflux, 60-90 h

The Groebke-Blackburn three-component coupling reaction is a well documented reaction involving the condensation of an aldehyde, an isocyanide and a 2-aminopyridine to afford an imidazo[1,2-*a*]pyridine compound in the presence of a catalytic acid.[48] This versatile reaction **(Scheme 13)** was employed in the synthesis of imidazo[1,2-*a*]pyridines **52-60 (Table 1)** and in the attempted synthesis of imidazo[1,2-*a*]pyridines **61** and **62 (Table 1)**, making use of commercially available aldehydes, isocyanides and 2-aminopyridines. A variety of acid catalysts including scandium(III) triflate, ammonium chloride, acetic acid and perchloric acid have been utilised in the Groebke-Blackburn reaction[48] but ongoing work at the CSIR suggested the use of K-10 montmorillonite clay as the best promoter for our purposes. The condensation reactions were carried out in 1,4-dioxane and heated at reflux for 60-90 h, after which time the montmorillonite clay was removed and the solvent removed *in vacuo* to afford the imidazo[1,2-*a*]pyridines as crude

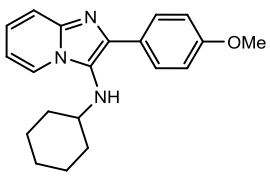
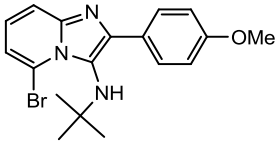
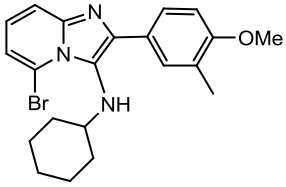
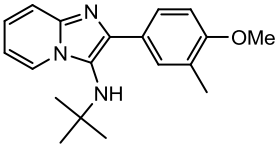
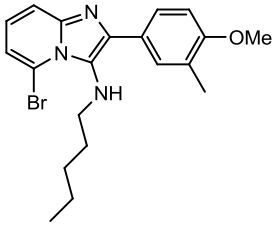
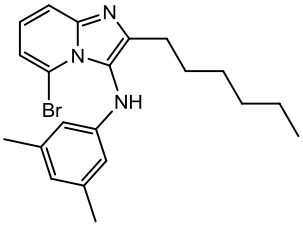
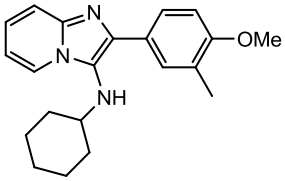
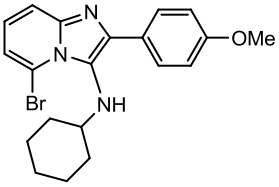
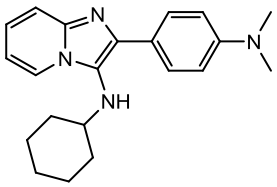
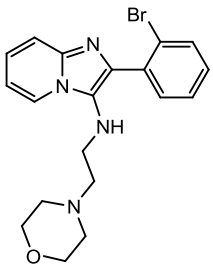
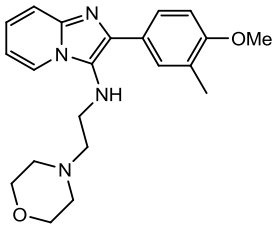
black oils. These crude products were then purified by column chromatography to afford the pure compounds **52-60** in varying yields **(Table 1)**, as well as the aldehyde and 2-aminopyridine starting materials.

The mechanism **(Scheme 8)** of the Groebke-Blackburn reaction is believed to proceed via a non-concerted [4+1] cycloaddition between the protonated Schiff base and the isocyanide moiety.[43] In this case under the acidic reaction conditions, brought about by the montmorillonite clay, the aldehyde and the primary amine of the 2-aminopyridine moiety condense to form what is knows as an iminium ion or Schiff base **X**. This iminium ion has both nucleophilic and electrophilic character and is a key intermediate allowing the [4+1] cycloaddition to occur with the isocyanide moiety. [43, 46] The concluding step in the formation of the imidazo[1,2-*a*]pyridine backbone is a prototropic shift which forms the final conjugated product **Y**.[46] Throughout the reaction both the aldehyde and isocyanide side chains are conserved, thus by varying the starting aldehydes and isocyanides we can confer much diversity to the imidazo[1,2-*a*]pyridine scaffold.



Scheme 8 Suggested Mechanism of Groebke-Blackburn Reaction

Table 1: Preparation of imidazo[1,2-*a*]pyridines **52-62**

Entry	Imidazo[1,2-*a*]pyridine	Yield (%)	Entry	Imidazo[1,2-*a*]pyridine	Yield (%)
52		28	**53**		31
54		33	**55**		15
56		79	**57**		46
58		37	**59**		61
60		13	**61**		0
62		0			

Following the purification of the synthesised imidazo[1,2-*a*]pyridines by column chromatography, compounds **52-60** were characterised by NMR spectroscopy and all integrated for the correct

number of aromatic and aliphatic protons and showed the correct number of carbon signals. The spectroscopic data of compound **52** compared favourably with that found in the literature.[48] A characteristic feature of the compounds in the ^{1}H NMR spectrum is the presence of an N-*H* singlet in the region of 3.08 - 2.07 ppm. An exception to this were compounds **56** and **59** which showed the N-*H* as multiplets at 3.00 ppm and 3.02 ppm respectively, due to overlap with the adjacent pentyl CH_2 group or cyclohexyl CH group, whilst compound **57** showed the N-*H* singlet at 5.01 ppm due to de-shielding from the aromatic ring causing the signal to move further downfield.

Another key identification aspect was the presence of the amine side chain in the ^{1}H NMR spectrum. Compounds **52, 54, 58, 59** and **60**, which contain the cyclohexyl moiety, show a multiplet at approximately 2.96 ppm which corresponds to the C*H* signal adjacent to the NH, as well as a large multiplet at approximately 1.89 – 1.05 ppm which integrates for the remainder of the protons of the cyclohexyl side chain. The inclusion of the cyclohexyl ring into these five imidazo[1,2-*a*]pyridines is further substantiated by the ^{13}C NMR spectrum with the presence of the deshielded NH*C*H signal at 56.7 ppm and *C*H_2 signals at 34.1 ppm, 25.7 ppm and 24.8 ppm respectively. Since the cyclohexyl moiety has the ability to rotate freely around the CH-NH single bond, two different sets of carbon atoms are equivalent; namely the signals at 34.1 ppm and 24.8 ppm. Compounds **53** and **55** which incorporate a *t*-butyl side chain show the presence of a large singlet at approximately 0.98 ppm which integrates for 9 protons and corresponds to the 3 methyl groups present in the *t*-butyl moiety. The ^{13}C NMR spectra for these compounds show two characteristic signals at approximately 55.3 ppm and 30.3 ppm which correspond to the quaternary NH*C*$(CH_3)_3$ and the C(*C*$H_3)_3$ carbon atoms respectively. The *n*-pentyl side chain of compound **56** was clearly present as evidenced by the N*HCH*$_2$ signal at 3.00 ppm, a C*H*$_2$ at 1.56 ppm, the C*H*$_2$-C*H*$_2$ at 1.45 ppm and the C*H*$_3$ at 0.90 ppm. This observation is again mirrored in the ^{13}C NMR spectrum by the presence of signals at 48.1 ppm, 30.3ppm, 29.2 ppm, 22.5 ppm and 14.01 ppm which correspond to the five carbon atoms of the *n*-pentyl side chain. The inclusion of the side chain of compound **57** is verified by the observed singlet at 1.89 ppm, integrating for 6 protons and corresponding to the presence of the aromatic methyl groups of the 3,5-xylyl moiety. The ^{13}C NMR spectrum shows the analogous signal at 18.3 ppm corresponding to the aromatic methyl groups.

Further evidence for the synthesis of the desired imidazo[1,2-*a*]pyridine compounds was obtained from the ^{1}H and ^{13}C NMR spectra which verified the incorporation of the aldehyde side chains into the products. The ^{1}H NMR spectra of compounds **52, 53** and **59** all showed a characteristic OC*H*$_3$ singlet at approximately 3.86 ppm whilst compounds **54, 55, 56** and **58** show the same characteristic OC*H*$_3$ signal at approximately 3.82 ppm, as well as the aromatic C*H*$_3$ signal at approximately 2.23 ppm. The ^{13}C NMR spectra for the same compounds displayed the O*C*H_3 signal at approximately 55.2 ppm and the aromatic *C*H_3 signal at approximately 16.3 ppm. The ^{1}H NMR spectrum of compound **60** showed a characteristic singlet at 2.89 ppm which integrates for 6 protons and corresponded to the N(C*H*$_3)_2$ moiety. The incorporation of this aldehyde side chain is

demonstrated by an analogous signal at 40.5 ppm in the ^{13}C NMR spectrum which corresponded to the carbon atoms of the $N(CH_3)_2$ moiety. Inclusion of the *n*-hexyl side chain of compound **57** was supported by the presence of the CH_2 signals at 2.28 ppm, 1.45 ppm and 1.17 ppm and a CH_3 at 0.72 ppm. Signals found in the aliphatic region of the ^{13}C NMR spectrum at 31.5 ppm, 29.2 ppm, 28.6 ppm, 27.1 ppm, 22.5 ppm and 4.04ppm confirmed the presence of the six carbon atoms of the *n*-hexyl side chain. The above data provides strong evidence to support that the Groebke-Blackburn MCC reaction was successfully employed to synthesise the desired imidazo[1,2-*a*]pyridines.

HRMS provided added evidence for the synthesis of the desired imidazo[1,2-*a*]pyridines as it confirmed the presence of the required molecular ion in all cases. Compounds **55, 58** and **60** with molecular formulae $C_{19}H_{23}ON_3$, $C_{21}H_{23}ON_3$ and $C_{21}H_{26}N_4$ showed molecular ion peaks at 309.1836, 335.1990 and 334.2152 respectively, which compare favourably to their calculated molecular masses of 309.1841, 355.1998 and 334.2152. The compounds **53, 54, 56** and **57** with molecular formulae $C_{18}H_{20}N_3Br$, $C_{21}H_{24}ON_3Br$, $C_{20}H_{24}ON_3Br$ and $C_{21}H_{26}N_3Br$ all contain a bromine atom, and thus displayed two molecular ion peaks corresponding to the two bromine isotopes, ^{79}Br and ^{81}Br. Compound **53** exhibited peaks at 373.0788 and 375.0775; compound **54** at 413.1094 and 415.1082, compound **56** at 401.1071 and 403.110 and compound **57** at 399.1280 and 401.1273, which compared favourably with the calculated values. For compound **59** ($C_{20}H_{22}ON_3Br$) a molecular ion peak could not be obtained using EI HRMS; however, the APCI did show both the ^{79}Br and ^{81}Br M^+ peaks. IR spectroscopy was also employed in the characterisation of these compounds and provided a very useful piece of information when determining if the desired condensation reactions had occurred. The IR spectra for compounds **53-60** showed the presence of a broad signal at between 3185 cm^{-1} – 3292 cm^{-1} which corresponded to the N-H stretch in the molecules.

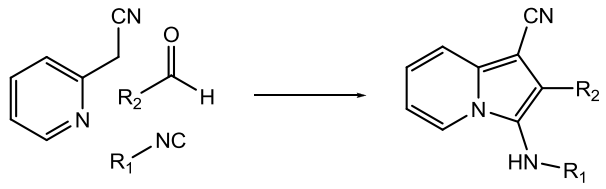
After evaluating all the characterisation data there is strong evidence to suggest that compounds **52-60** were synthesised and that the Groebke-Blackburn reaction could be applied for the development of large libraries of structurally diverse imidazo[1,2-*a*]pyridines. However one of the major drawbacks of the reaction appears to be the low yields obtained for most of the synthesised compounds. Compounds **61** and **62** decomposed during column chromatography and this is probably attributed to the instability of the morpholino side chain on the slightly acidic silica medium. Chromatography remains a serious problem with these types of compounds and may account for some of the losses in yield as co-elution of imidazo[1,2-*a*]pyridines, side products and starting materials often occurs. During the course of the project it was discovered that the best method for obtaining pure compounds was by a pre-column to remove as many side products as possible, followed by recrystallisation from diethyl ether.

However, chromatography alone cannot be blamed for the low yields; perhaps the reaction conditions themselves play an integral role in the yields of compounds **52-60**. Many of the isocyanides are volatile substances, possibly evaporating during the reaction and thus not allowing the [4 +1] addition to occur, resulting in low yields. Literature[48] suggests that shorter reaction times may increase some of the yields by reducing the number of side reactions which could occur during the long reaction times. Microwave irradiation is also suggested in the literature[48] as a means of improving the yields as the solvent may reach higher temperatures, transferring more energy to the starting materials. Optimisation of the reaction conditions could allow the Groebke-Blackburn reaction to be employed in the synthesis of a number of diverse imidazo[1,2-*a*]pyridines in higher yields, however due to time constraints on the project this was unfortunately not attempted.

3. Synthesis and Attempted Synthesis of 3-Amino-1-cyano indolizines 63-79

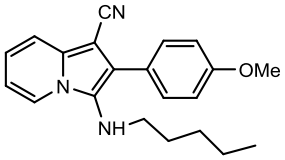
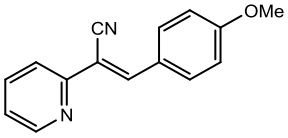
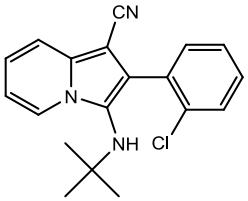
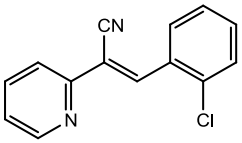
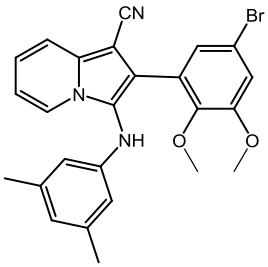
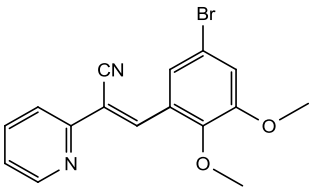
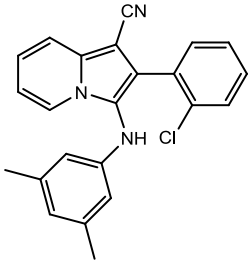
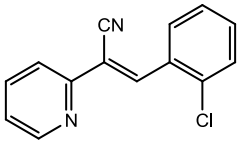
*3.1 Method A: Attempted Synthesis of 3-Amino-1-cyano-indolizines **63-70***

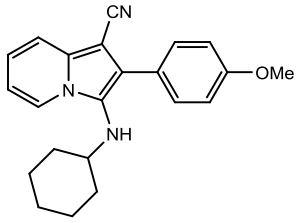
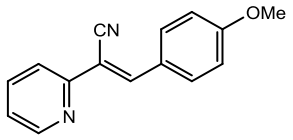
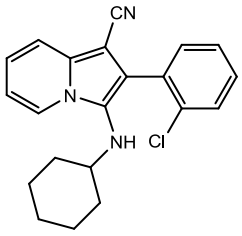
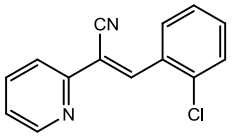
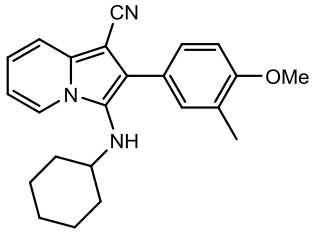
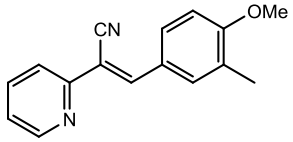
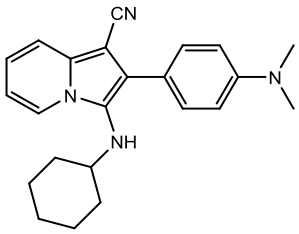
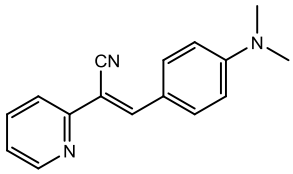
In accordance with a literature procedure first described by Poigny and co-workers[34] we set out to synthesise a variety of related compounds, the 3-amino-1-cyano-indolizines which could also be tested for activity against HIV-1 reverse transcriptase. This three-component coupling reaction **(Scheme 14)** is very similar to the Groebke-Blackburn reaction and involves the condensation of an isocyanide, an aldehyde and a 2-cyanomethylpyridine in the presence of a catalytic amount of base to afford the 3-amino-1-cyano-indolizine compound. In order to begin building our compound library for biological testing we made use of commercially available aldehydes, isocyanides and 2-cyanomethylpyridine for the reactions. These condensation reactions were carried out at 100˚C in 1,4-dioxane for a period of 60-90 h, using DBU as the catalytic base. After this time the solvent was removed *in vacuo* to afford the crude products which were further purified by column chromatography and/or recrystalisation. The pure compounds were then characterised by NMR spectroscopy, infra red and HRMS and proved to be the corresponding intermediate aldol condensation products **63a – 65a, 69a** and **70a (Table 2)**. A crystal structure determined of intermediate aldol condensation compound **64a** shows it to be the *E*-isomer. Since all the intermediate aldol condensation products synthesised throughout were obtained as a single gemometric isomer as indicated by NMR spectroscopy, we will assume the geometry of these products to be the *E*-isomer. This reaction unfortunately failed to synthesise any of the desired 3-amino-1-cyano-indolizines **63-70 (Table 2)** and the possible reason for this will be addressed later in this discussion.



Scheme 14 3-Amino-1-cyano-indolizine synthesis *Reagents and Conditions:* 10% DBU, 1,4-dioxane, 100˚C, 60-90 h

Table 2: Attempted Preparation of 3-Amino-1-cyano-indolizines **63-70** and the Resultant Intermediate Aldol Products **63a-65a, 69a** and **70a**

Entry	Desired Product	Entry	Actual Product	Yield (%)
63		**63a**		28
64		**64a**		78
65		**65a**		51
66		**64a**		59

67		**63a**		60
68		**64a**		68
69		**69a**		43
70		**70a**		26

Compounds **63a-65a**, **69a** and **70a** were all characterised by ^{1}H and ^{13}C NMR spectroscopy which clearly indicated that the desired 3-amino-1-cyano indolizine compounds **63-70** had not been synthesised. There was a distinct lack of signals desired from the isocyanide reagent in both the ^{1}H and ^{13}C NMR spectra and a lack of the characteristic N-*H* signal in the ^{1}H NMR spectra. The ^{1}H NMR spectra of compounds **63a-65a**, **69a** and **70a** corresponded to the aldol products, with integration giving the correct number of protons and the ^{13}C NMR spectra showing the correct number of carbon signals. Another key identifying feature was the presence of a singlet between 8.33 – 8.80 ppm integrating for a single proton in all the ^{1}H NMR spectra which corresponded to the hydrogen of the alkene bond. This observation was verified by the presence of the corresponding alkene carbon signal between 141.8 – 149.9 ppm in the ^{13}C NMR spectra. A final characteristic peak was that of the *C*N bond which was also present in the ^{13}C NMR spectra of the aldol compounds between 117.1 – 119.5 ppm. Formation of the products could readily be explained by an aldol condensation between the carbon atom α- to the nitrile and the aldehyde.

This occurs readily because of the acidic nature of the protons α- to the nitrile. The reaction apparently stopped at this point and no subsequent reaction with the isocyanide was observed.

Other key features which could be discerned from the NMR spectra were specific to a synthesised aldol compound, i.e. compound **63a** which contained a *p*-methoxy group displays a clear singlet at 3.86 ppm which integrated for 3 protons in the ^{1}H NMR spectrum. The corresponding carbon signal of the O-*C*H$_3$ was found at 55.5 ppm. Compound **65a** showed two close singlets at 3.88 ppm which collectively integrated for 6 protons and corresponded to the two OC*H*$_3$ groups found on the aldehyde side chain. Once again the ^{13}C NMR spectrum mirrored these observations and the corresponding carbon signals of the two O*C*H$_3$ groups were found at 61.75 ppm and 56.21 ppm. Compound **69a** showed the presence of a singlet at 3.90 ppm and at 2.22 ppm which corresponded to the OC*H*$_3$ and Ar-C*H*$_3$ respectively, whilst the carbon signals were found at 55.5 ppm for the O*C*H$_3$ and at 16.3 ppm for the Ar-*C*H$_3$. The ^{1}H NMR spectrum of compound **70a** indicated the presence of the N(C*H*$_3$)$_2$ in the aldol product as a singlet integrating for 6 protons at 3.02 ppm and the related carbon signal is found at 40.0 ppm.

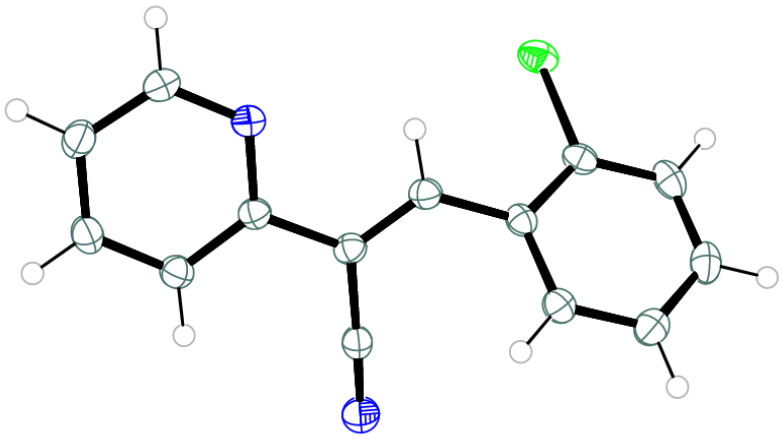


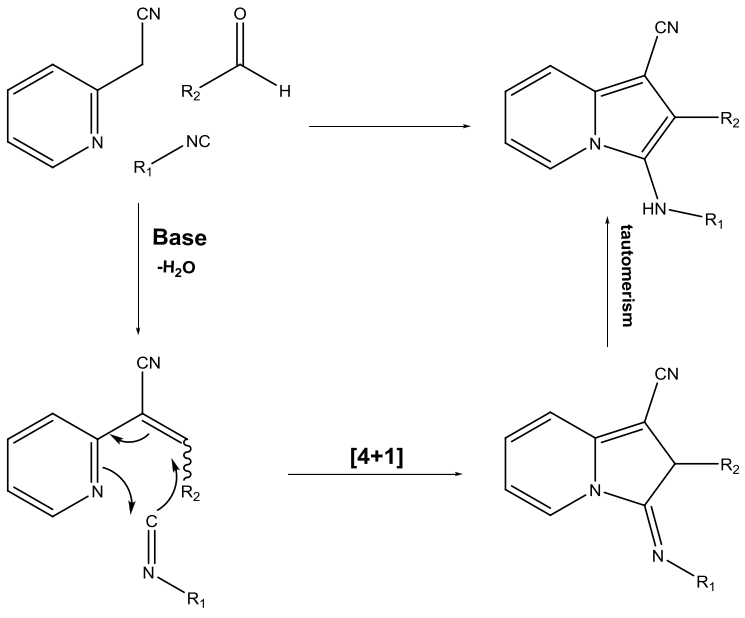
Figure 19: Ortep Diagram of Compound **64a**
(Showing the 50% probability thermal ellipsoids for all non-hydrogen atoms.)

Conclusive evidence that the desired 3-amino-1-cyano-indolizine compounds had not been synthesised was obtained by means of a crystal structure determination of compound **64a (Figure 19)**. The crystallographic data showed that the intermediate aldol product was what we were indeed isolating, as no amine side chain from the isocyanide starting material could be observed in the product.

HRMS provided additional evidence for the identity of the aldol compounds **63a, 64a, 65a, 69a** and **70a**. Compounds **63a, 69a** and **70a** with molecular formulae $C_{13}H_{12}ON_2$, $C_{16}H_{14}ON_2$ and $C_{16}H_{15}N_3$ respectively showing the corresponding molecular ion peaks at 236.0924, 250.1081 and 249.1257, which corresponded well with the calculated values. Compound **65a** with molecular formula

$C_{16}H_{13}O_2N_2Br$ contains a bromine atom and thus displays two molecular ion peaks, each one corresponding to a different bromine isotope; ^{79}Br at 344.0124 and ^{81}Br at 346.0133. For compound **64a** an anomaly occurs whereby no molecular ion could be obtained for the molecular formula $C_{14}H_9N_2Cl$; however a peak at 239.0378 is obtained which corresponds to a molecular formula of $C_{14}H_8N_2Cl$ and depicts the loss of a proton from the molecule. IR spectroscopy of the aldol compounds **63a, 64a, 65a, 69a** and **70a** was performed and showed the presence of the alkene proton between 3168 - 3012cm^{-1} shifting upfield or downfield depending on what functional groups are found on the aromatic ring of the starting aldehyde side chain. The IR spectra of these compounds also show the presence of the –CN nitrile stretch as a weak signal near 2213cm^{-1}.

Subsequent to analysing all the characterisation data and conclusively deciding that compounds **63a-65a, 69a** and **70a** were indeed the aldol products, a rationale for the failure of this reaction to synthesise the desired 3-amino-1-cyano-indolizine compounds needed to be addressed. A possible reason for the failure of this multi-component coupling reaction to yield the desired products can be elucidated from the mechanism of the reaction. Although a definite reaction mechanism has not been fully determined, the proposed mechanism is thought to proceed via the cheletropic addition of the isocyanide moiety to the Knoevenagel-type hetero-diene intermediate **(Scheme 11)**.[34] The first step in the mechanism is proposed to be the removal of the acidic protons which are α- to the nitrile by the base, which in this case is DBU.[34, 46] The carbonyl carbon of the aldehyde moiety then undergoes nucleophillic attack from the α-anion, followed by elimination of water to form the Knoevenagel-type hetero-diene intermediate.[34, 46] If the reaction were to proceed to completion it is at this point that a non-concerted [4+1] cycloaddition between the hetero-diene and the isocyanide would occur, followed by a protototropic shift to form the desired 3-amino-1-cyano indolizine scaffold.[34]

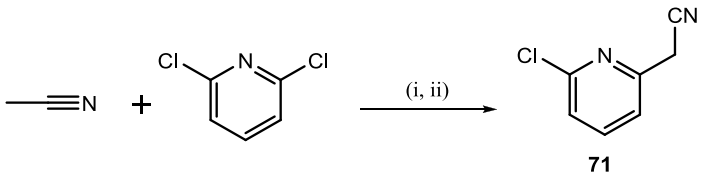


Scheme 11 Proposed Mechanism for the Synthesis of 3-amino-1-cyano indolizines

From the mechanistic scheme **(Scheme 11)** it is clear that our reaction proceeded well to the formation of the hetero-diene intermediate, but the non-concerted [4+1] cycloaddition did not occur. Upon inspecting the literature it was found that there was one major difference between our reaction conditions and those used by Poigny and co-workers.[34] The literature procedure utilised the solvent *n*-butanol which is a protic solvent, as opposed to the solvent 1,4-dioxane used in our procedure. It is thought that through hydrogen bonding of the alcohol proton of *n*-butanol with the lone pairs of the nitrile nitrogen, the electron density is more confined to the nitrile.[46] This may give the the Knoevenagel-type intermediate more of a diene character by preventing the dispersion of electron density throughout the conjugated system and thus allowing the [4+1] cycloaddtion to occur. The alkene bond is also perhaps slightly weakened, making it more electrophilic by the reduced delocalisation of electrons into the nitrile. The aldol product formed here is much more stable than the corresponding Schiff base product for the Groebke-Blackburn reaction, which means that the subsequent reaction with the isocyanide reagent is not as favourable when compared to the Groebke-Blackburn reaction. Thus it was decided that the subsequent attempts at the synthesis of 3-amino-1-cyano-indolizines would be carried out in *n*-butanol and not 1,4-dioxane.

*3.2 Synthesis of Starting Material 2-(6-Chloropyridin-2-yl)acetonitrile **71** and the Synthesis and Attempted Synthesis of 3-Amino-1-cyano Indolizines **68, 72-76***

*3.2.1 Synthesis of 2-(6-Chloropyridin-2-yl)acetonitrile **71***



71

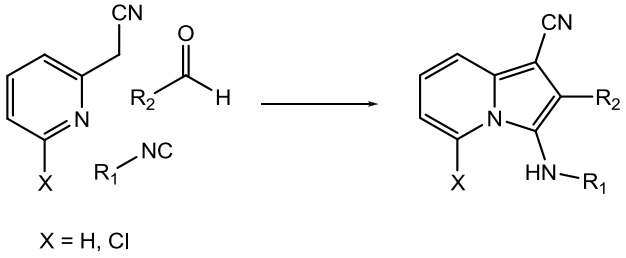
Scheme 15 Synthesis of 2-(6-Chloropyridin-2-yl)acetonitrile *Reagents and Conditions*: i) *n*-BuLi (1.4M/hexane), THF, -78˚C, 1 h; ii) 2,6-dichloropyridine, THF, -78˚C, 1 h

In addition to the use of *n*-butanol as a solvent instead of 1,4-dioxane another major difference between our procedure and the literature procedure[34] was their use of 2-(6-chloropyridin-2-yl)acetonitrile **71** as opposed to cyano-2-methylpyridine. Compound **71** is not a commercially available starting material and needed to be synthesised from the commercially available 2,6-dichloropyridine **(Scheme 15)**. In accordance with a procedure stipulated by Skerlj and co-workers CH_3CN was added dropwise to a stirring solution of *n*-BuLi (1.4M/hexane) at -78˚C which resulted in a milky white suspension.[65] Since the α-hydrogens of the CH_3CN are acidic, the *n*-BuLi

abstracts a proton to form the organo-metallic $LiCH_2CN$ species.[65] After 1 hour, 2,6-dichloropyridine was added to the stirring white suspension at which point nucleophilic displacement of the chloride occurred to form the (6-chloropyridin-2-yl)acetonitrile **71**, marked by a change in the colour of the solution from milky white to yellow.[46, 65] The reaction mixture was quenched with H_2O, worked up and the organic solvent removed *in vacuo* to give a yellow oil, which was further purified by column chromatography to afford the desired product, (6-chloropyridin-2-yl)acetonitrile **71**, as a yellow solid in 84% yield.

The compound was characterised by NMR spectroscopy and the spectroscopic data was in agreement with that of the literature.[65] A key feature of the ^1H NMR spectrum was the presence of a singlet at 3.94 ppm which corresponded to the α-protons of the cyanomethyl group. The ^{13}C NMR spectrum gave clear signals at 116.29 ppm and 26.13 ppm which corresponded to the *C*N and *C*H_2CN groups respectively.

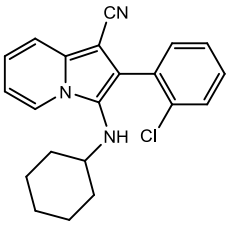
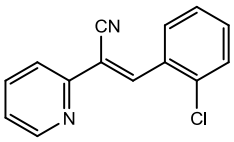
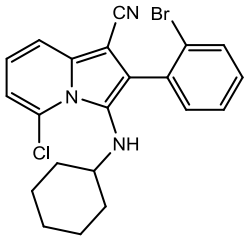
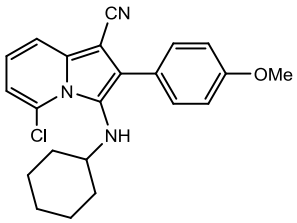
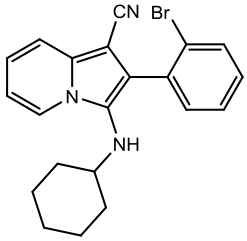
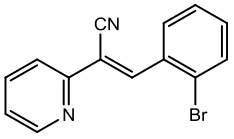
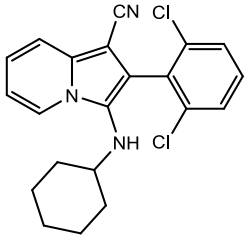
*3.2.2 Method B: Synthesis and Attempted Synthesis of 3-Amino-1-cyano indolizines **68** and **72-76***

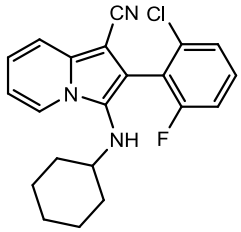
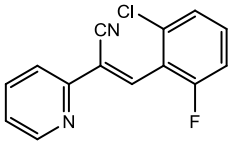


Scheme 16 3-amino-1-cyano-indolizine synthesis *Reagents and Conditions:* 10% DBU, *n*-butanol, 100˚C, 43 h

Following the synthesis of (6-chloropyridin-2-yl)acetonitrile **71**, we once again attempted to synthesise a variety of 3-amino-1-cyano-indolizine compounds in accordance with the multi-component coupling procedure stipulated by Poigny and co-workers.[34] In an attempt to synthesise compounds **68** and **72-76**; 2-pyridylacetonitrile or (6-chloropyridin-2-yl)acetonitrile **71**, a variable aldehyde and an isocyanide were dissolved in *n*-butanol **(Scheme 16)**. Catalytic base, DBU was added to the solution and the reaction was then stirred at 100˚C for 43 h, after which time the solvent was removed *in vacuo* to afford the crude products. These crude products were then purified by flash chromatography and/or recrystallisation to afford the pure compounds **68, 72, 73** and **75 (Table 3)** in varying yields as well as two aldol products **74a** and **76a (Table 3)**. It appears that changing the solvent from 1,4-dioxane to *n*-butanol greatly improved the yield of the desired 3-amino-1-cyano-indolizine compounds; however, some of the reactions still did not proceed to completion and once again aldol products **68a, 74a** and **76a** were isolated.

Table 3: Synthesis and Attempted Synthesis of 3-Amino-1-cyano-indolizine compounds **68** and **72-76**

Entry	3-amino-1-cyano indolizine	Yield (%)	Entry	Aldol Product	Yield (%)
68		23	**68a**		42
72		75			
73		38			
74		0	**74a**		13
75		7			

76  0 **76a**  8

The above compounds were all characterised by NMR spectroscopy, with the exception of compound **68** which was unstable in a variety of deuterated solvents and we could thus not obtain any useful NMR data for this sample. A distinct N-*H* signal is present in compounds **72, 73** and **75** at 3.36 ppm, 3.56 ppm and 2.89 ppm respectively, and was a good indication that the isocyanide reagent had been incorporated into the new compounds. These compounds showed a definitive signal at approximately 2.77 ppm which correlated with NHC*H*$(CH_2)_5$ as well as a group of signals at approximately 1.76-0.93 ppm which correlated with the remainder of the cyclohexyl protons. These observations were substantiated by the ^{13}C NMR spectra of these compounds which show the corresponding carbon signals at approximately 58.5 ppm for NH*C*H$(CH_2)_5$ and 32.8, 25.4 and 24.6 ppm for the rest of the cyclohexyl carbon atoms. Furthermore, all three compounds displayed the C-*C*N signal between 115.9 ppm and 118.6 ppm in their ^{13}C NMR spectra. The ^{1}H NMR spectrum for compound **73** showed a clear singlet at 3.87 ppm which corresponded to the OCH_3 group of the aldehyde side chain, with the corresponding carbon signal found at 55.2 ppm. Compounds **72** and **75** show 7-aromatic proton signals in their ^{1}H NMR spectra; which is the expected number of signals and confirms the inclusion of the aromatic aldehyde reagent. The NMR spectroscopic data of compounds **72, 73** and **75** was a good indication that the desired 3-amino-1-cyano-indolizine compounds had been synthesised.

Despite being unable to obtain any viable NMR spectral data for compound **68**, a definite identification of the product was obtained by means of X-ray crystal determination of the compound **(Figure 20)**. The product was recrystalised from diethyl ether to yield fine yellow crystals from which an X-ray crystal structure was obtained. From the Ortep diagram of compound **68** we see that the product has been co-crystallised with the solvent, diethyl ether. The Ortep diagram also indicates very clearly the incorporation of the cyclohexyl isocyanide starting material to afford the desired 3-amino-1-cyano-indolizine **68**.

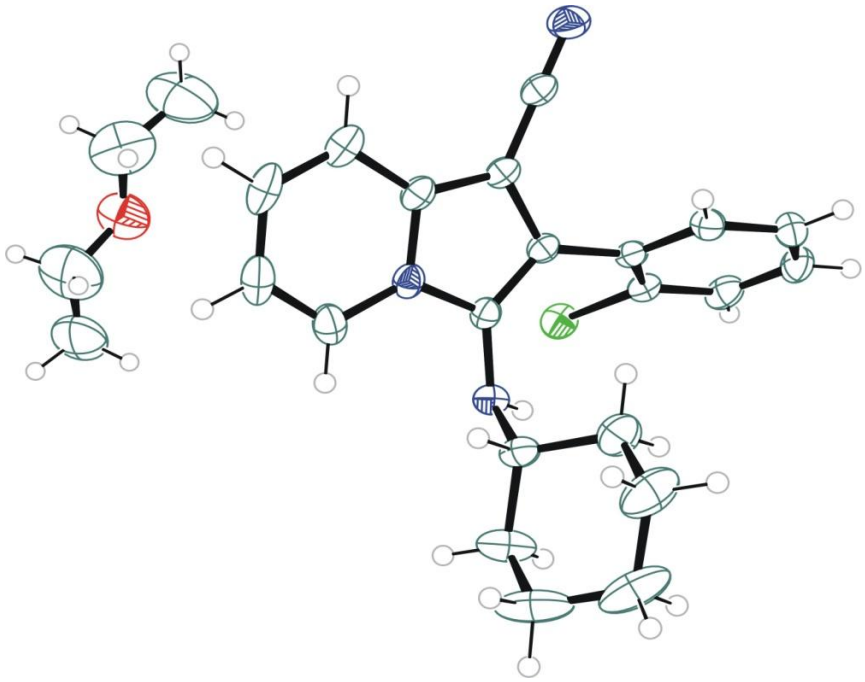


Figure 20 Ortep Diagram of Compound **68**
(Showing the 50% probability thermal ellipsoids for all non-hydrogen atoms)

HRMS was performed on the synthesised 3-amino-1-cyano-indolizine compounds **68, 72, 73** and **75** and further corroborated that the three component coupling reaction had indeed occurred. Compounds **68** and **75** showed molecular ion peaks at 349.1339 and 383.0946 respectively, which corresponded to their molecular formulae $C_{21}H_{20}N_3{}^{35}Cl$ and $C_{21}H_{19}N_3{}^{35}Cl_2$. The M+2 peaks associated with the heavier chlorine isotope for compounds **68** and **75** were found at 351.1327 and 387.0918 respectively and correspond to the molecular formulae $C_{21}H_{20}N_3{}^{37}Cl$ and $C_{21}H_{19}N_3{}^{37}Cl_2$. Compound **72** contains a bromine atom and thus showed two molecular ion peaks; one at 427.0463 corresponding to molecular formula $C_{21}H_{19}N_3Cl^{79}Br$ and one at 429.0443 with molecular formula $C_{21}H_{19}N_3Cl^{81}Br$. Chlorine-containing compound **73** displays the same isotopic trend and showed two molecular ion peaks at 379.1456 and 381.1444 corresponding to $C_{22}H_{22}N_3O^{35}Cl$ and $C_{22}H_{22}N_3O^{37}Cl$ respectively. IR spectroscopy of the compounds **68, 72, 73** and **75** showed the diagnostic N-H stretch as a broad signal between 3293cm^{-1} - 3373cm^{-1}. The IR spectra also indicated the presence of the CN functional group in the compounds by a signal found at approximately 2200cm^{-1} for all four indolizine products.

Compounds **74a** and **76a** did not show the distinct N-H signal and this was the first indication that the desired 3-amino-1-cyano-indolizine had not been synthesised. Other evidence to suggest that this was the case was that the ^{1}H NMR spectra for both of these compounds did not show the correct proton integration and the ^{13}C NMR spectra showed fewer signals than expected from the indolizine products. What is evident in the ^{1}H NMR spectra is the presence of the alkene C-*H* proton for these compounds at approximately 8.58 ppm, which is indicative of the aldol product.

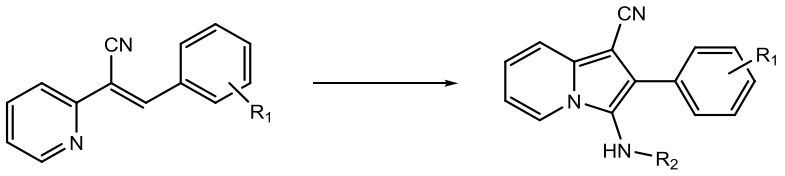
Once again HRMS was used to confirm that these molecules were indeed only the aldol condensation products. Compound **76a** showed a molecular ion peak at 258.0345, which compares favourably to the calculated value of 258.0360 for molecular formula $C_{14}H_8N_2ClF$. The aldol product **74a** shows two molecular ion peaks each one corresponding to the two different bromine isotopes, $C_{14}H_9N_2{}^{79}Br$ and $C_{14}H_9N_2{}^{81}Br$, and found at 283.9938 and 285.9918. IR spectroscopy of aldol compounds **74a** and **76a** indicated the C-H stretch of the alkene at 3065cm^{-1} and 3016cm^{-1} respectively and further indicated that these products were in fact the aldol condensation products.

It appears that changing the solvent used for the reaction greatly improved the yield of 3-amino-1-cyano-indolizine from zero, when only aldol product was isolated, to fair yields of the desired products. It is not fully understood why this should be the case, but as explained above the protic nature of *n*-butanol may provide a crucial hydrogen bonding interaction in the reaction.

When inspecting the yields of these varying 3-amino-1-cyano indolizine compounds, it becomes clear that the yields of the 5-chloro substituted products were greater than the unsubstituted products. Compounds **72** and **73** had yields of 75% and 38% respectively, whilst compounds **68** and **75** had yields of only 23% and 7%. We will attempt once again to explain this phenomenon in terms of the mechanism **(Scheme 11)**. The chlorine atom is an electron withdrawing substituent and can withdraw electron density from the *ortho* and *para* positions by the inductive effect.[46] If the chlorine substituent were to withdraw electron density from the pyridine ring system it may be probable that it could confer further diene-character to the Knoevenagel-type intermediate.[46] This stabilised hetero-diene may be more favourable in the [4+1] cycloaddition step and allow the reaction to go further to completion, resulting in higher yields for the 5-chloro substituted compounds. This inductive effect may also explain why compounds **74a** and **76a** were isolated as aldol compounds, as both lacked the 5-chloro substituent. A more stable hetero-diene intermediate may well have been crucial to the success of these two reactions.

The overall yields of these reactions were not very good, with the exception of compound **72**. This could be attributed to the fact that the chromatography is difficult, with compounds overlapping with starting materials and side products, leading to isolation of only small amounts of pure products. However the literature also shows much the same trend in yields and reports very low yields for most of the synthesised compounds.[34] Thus, despite this reaction allowing for the creation of diverse libraries of 3-amino-1-cyano-indolizine compounds, it is not very synthetically efficient. Perhaps optimisation of the reaction conditions or the use of a microwave may produce better yields, but until then a more classical synthetic approach may be needed if we are to obtain the desired products in acceptable yields.

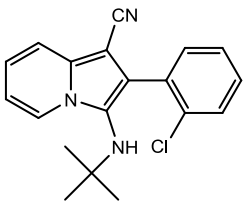
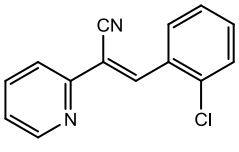
*3.3 Method C: Attempted Synthesis of 3-Amino-1-cyano indolizines **64, 77-75***

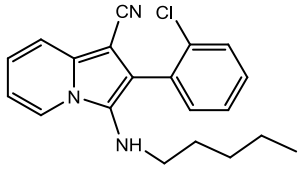
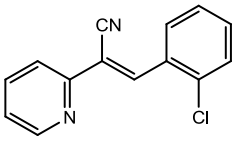
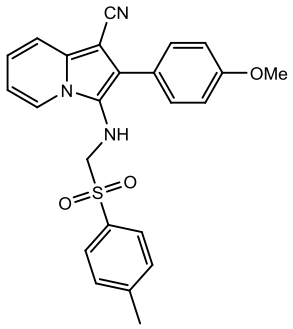
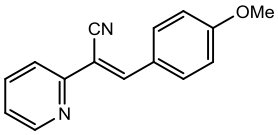
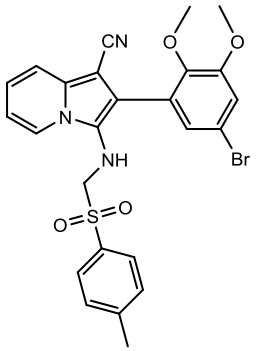
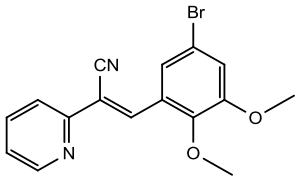


Scheme 17 Attempted 3-Amino-1-cyano-indolizine Synthesis *Reagents and Conditions*: variable isocyanides, Montmorillonite K-10 clay, 1,4-dioxane, 100˚C, 73 h

Our final effort at synthesising a variety of 3-amino-1-cyano indolizine compounds focused on utilising the already synthesised aldol products and attempted to force the [4+1] cycloaddition reaction to occur by using acid promotion **(Scheme 17)**. It was thought that by using an acid promoter we could prevent the delocalisation of the nitrile electrons to an even greater extent than when using a protic solvent. It was hoped that this would confer enough electrophilc character to the alkene bond and allow for the cycloaddtion reaction to occur more easily, enabling us to isolate the desired 3-amino-1-cyano indolizine compounds. Previously synthesised aldol products **63a, 64a** and **65a (Table 2, pg. 42)** were thus dissolved in 1,4-dioxane, which was chosen as it was used successfully in the synthesis of the imidazo[1,2-*a*]pyridine compounds by means of acid catalysis. A variable isocyanide and one mass equivalent of Montmorillonite K-10 clay were added to this solution and the reaction was heated at 100˚C for 73 hours. After this time, the reaction was cooled, filtered through celite and the solvent removed *in vacuo* to afford the crude products. These crude products were purified by flash chromatography and characterised by NMR spectroscopy. Unfortunately none of the desired 3-amino-1-cyano indolizine compounds **64, 77, 78** and **79** were isolated and the NMR spectroscopy data showed the products to be starting aldol compounds **63a-65a (Table 4)**.

Table 4: Attempted Synthesis of 3-Amino-1-cyano Indolizine Compounds **64, 77-79** from the Corresponding Aldol Products

Entry	Desired Product	Entry	Corresponding Aldol Product	Yield (%)
64		**64a**		84

77		**64a**		90
78		**63a**		78
79		**65a**		60

From the interpretation of the ^{1}H NMR spectra of the products it was clear that the desired 3-amino-1-cyano-indolizine compounds **64, 77, 78** and **79** had not been synthesised. There was no evidence in the ^{1}H NMR to suggest that the isocyanide starting material had been included in the products, as there were no signals for the amine side chains and no distinct N-H signal. When compared to the ^{1}H NMR spectra of the aldol starting materials it was clear that the isolated products were in fact the aldol compounds **63a, 64a** and **65a**. The loss in yield of the starting material was probably due to retention of some of the organic compounds in the montmorillonite clay, as well as due to column chromatography. We could still attempt this reaction in *n*-butanol to determine if the "two-step one-pot" synthesis may still afford the desired indolizine compounds.

Three different methods for the preparation of 3-amino-1-cyano-indolizines are presented in the above discussion. Method A was only able to yield the aldol products formed from the base-catalysed condensation of cyano-2-methylene-pyridine and aldehyde starting materials. This methodology could have been salvaged had method C shown any success in allowing the non-concerted [4+1] cycloaddition reaction to occur with the aldol products and an isocyanide under acidic conditions. We might then have been able to synthesise the desired indolizine compounds

in a “two-step one-pot” synthesis and potentially avoid the host of side reactions that occur from the true multi-component coupling reaction. Method B showed some success in synthesising the required 3-amino-1-cyano indolizines, although the chromatography remains tedious and the yields poor. We could however, utilise this method to create a series of diverse 3-amino-1-cyano indolizine compounds, but the literature suggests that the yields would still be very poor.[34] It appears that despite the limited success of method B in synthesising the indolizine products, it may be more efficient to utilise another method to prepare these types of compounds in better yields.

4. Biological Testing Results of Imidazo[1,2-*a*]pyridines 52–60 and 3-Amino-1-cyano Indolizines 68, 73 and 75

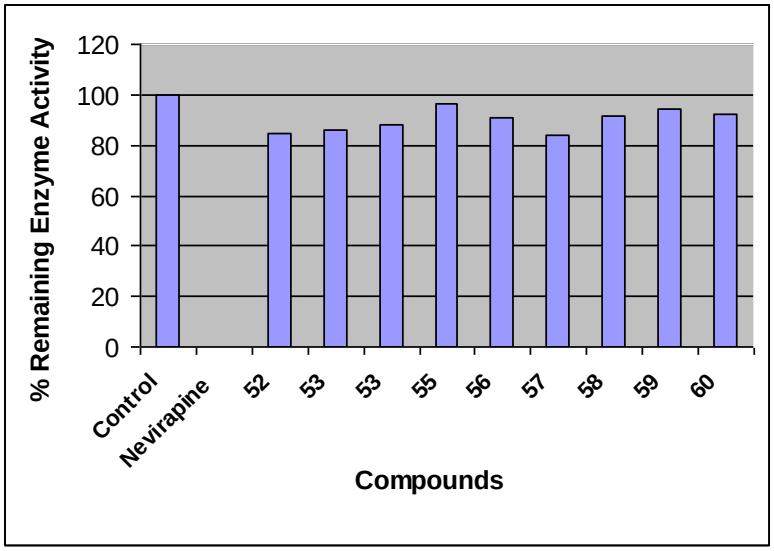
The following discussion pertains to the biological testing results of a variety of imidazo[1,2-*a*]pyridines and 3-amino-1-cyano indolizines. These compounds were tested for inhibition of an HIV-1 enzyme, reverse transcriptase in the hope of identifying a viable compound which can be further developed as a potent and effective NNRTI. The biological testing was carried out by the CSIR Biosciences Pharmacology Group using an HIV reverse transcriptase kit, which is available from Roche Pharmaceuticals. To assess the inhibitory activity of the test compounds they were incubated with HIV-1 reverse transcriptase and the residual percentage enzyme activities expressed, relative to a control test without inhibitor. For a full explanation of the inhibitory HIV-1 reverse transcriptase testing procedure the reader is referred to the experimental section general procedures **(pg. 134)**.

*4.1 Biological Testing Results of imidazo[1,2-a]pyridines **52–60** as HIV-1 Reverse Transcriptase Inhibitors*

Imidazo[1,2-*a*]pyridines **52–60** were dissolved in DMSO to give a concentration of 10mM and later diluted to 50µM for the assay. They were then tested for inhibitory activity against HIV-1 reverse transcriptase, using a nevirapine reference standard and a positive control containing only reverse transcriptase enzyme with no inhibitor. The control showed 100% remaining enzyme activity and Nevirapine showed 0.2% remaining enzyme activity, demonstrating that it is an excellent inhibtor of HIV-1 reverse transcriptase. The nine imidazo[1,2-*a*]pyridines which we sent for evaluation showed extremely poor inhibition of the reverse transcriptase enzyme and showed residual enzyme activities of > 80% **(Graph 1) (Table 5)**. In order to be considered a promising inhibitor the compounds need to show at least 80% suppression of RT enzyme activity, which was not achieved by any of our tested imidazo[1,2-*a*]pyridines. In conclusion, this set of compounds can be abandoned as potential HIV-1 reverse transcriptase inhibitors. However, the possibility still remains that these compounds may show promising biological applications when tested for anti-tumour, anti-bacterial and anti-malarial activities, which are possibilities suggested by the multitude of variable biological applications presented in Chapter 1.

Table 5: Percentage Residual Enzyme Activity for Imidazo[1,2-*a*]pyridines **52-60**

Compound	% Enzyme Activity
Control	100.0
Nevirapine	0.2
52	84.4
53	86.1
54	87.9
55	96.4
56	91.2
57	84.0
58	91.6
59	94.3
60	92.5



Graph 1: Biological Test Results of the Inhibitory Activity of Imidazo[1,2-*a*]pyridines against HIV-1 Reverse Transcriptase

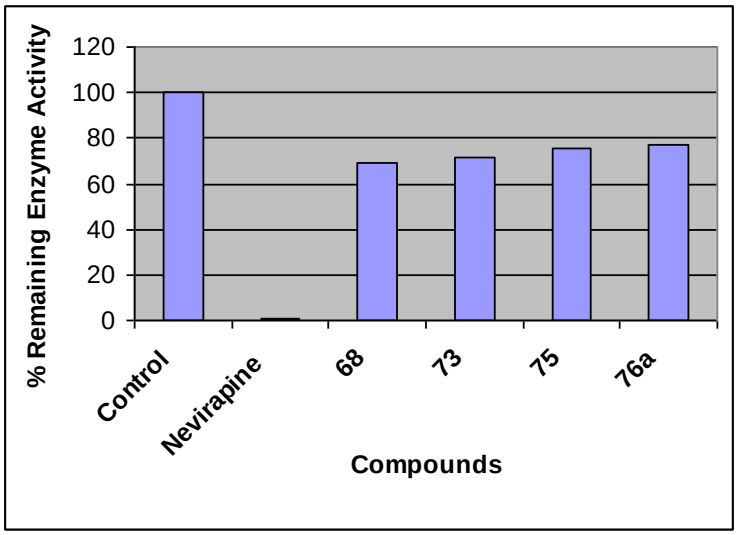
*4.2 Biological Testing Results of 3-Amino-1-cyano Indolizines **68, 73** and **75** as HIV-1 Reverse Transcriptase Inhibitors*

3-Amino-1-cyano-indolizines **68, 73** and **75** and aldol compound **76a** were dissolved in DMSO to give a concentration of 10mM and tested in the same way as the imidazo[1,2-*a*]pyridines at a final concentration of 50μM of inhibitor. Once again these compounds showed poor inhibition of the

HIV-1 reverse transcriptase enzyme with compounds **73, 75** and **76a** showing >70% residual enzyme activity and compound **68** showing 69.4% residual enzyme activity **(Graph 2) (Table 6)**. Although these results are slightly better then the results of the imidazo[1,2-*a*]pyridines, they are nowhere near the percentage needed to be considered promising inhibitors. It is obvious that these compounds cannot be considered for development as novel and potent NNRTIs, but once again may show other interesting biological applications in the anti-tumor, cardiovascular and anti-bacterial class of inhibitors.

Table 6: Percentage Residual Enzyme Activity for 3-Amino-1-cyano Indolizines **68, 73** and **75** and Aldol Compound **76a**

Compound	% Enzyme Activity
Control	100.0
Nevirapine	0.5
68	69.4
73	71.8
75	75.8
76a	77.1



Graph 2: Biological Test Results of the Inhibitory Activity of 3-Amino-1-cyano-Indolizines against HIV-1 Reverse Transcriptase

Chapter 3: Conclusions and Future Work

Synthesis of imidazo[1,2-*a*]pyridines and 3-amino-1-cyano Indolizines

1. Conclusions and Future Work

Chapter 1 briefly introduced a number of increasingly drug-resistant forms of the HIV-1 due to the virus' extremely high mutation rate. These mutations have led to a great need for novel HIV-1 inhibitors with improved potency against the virus. The main aim of this section of the project was to use the highly efficient synthetic methods of MCC reactions to develop a small molecule library. This collection of compounds could then be tested against HIV-1 reverse transcriptase in the hopes it would uncover a potentially novel NNRTI.

1.1 Synthesis of Imidazo[1,2-a]pyridines

The first aim of this project was the use of the well known Groebke-Blackburn three-component coupling reaction **(Scheme 13, pg 32)** in the synthesis of a library of imidazo[1,2-*a*]pyridines.[43] We chose this reaction as it can be successfully employed with a variety of different aldehydes and isocyanides and we could thus create a structurally diverse compound library. The Groebke-Blackburn reaction was successfully used for the synthesis of imidazo[1,2-*a*]pyridines **52-60**, which were isolated in various yields ranging from fair to good. This three-component coupling reaction was also utilized in the attempted synthesis of imidazo[1,2-*a*]pyridines **61** and **62** which we suspect were probably synthesised, but decomposed during column chromatography.

As we were able to synthesise a small imidazo[1,2-*a*]pyridine library we could conclude that the Groebke-Blackburn reaction is an efficient means of developing a structurally diverse library of these types of compounds. However, one of the major drawbacks with this reaction were the low yields for some of the isolated compounds. Many factors may be responsible for the low yields and we cannot identify one factor as the main cause. This reaction undergoes many side reactions, which in turn makes the chromatography of these compounds extremely tedious and difficult. Many of the products were isolated as mixed fractions with a side-product or starting material and so may have to be re-columned or recrystallised; leading to losses in yield. The isocyanide starting materials were often volatile liquids and were prone to evaporation before and during the reaction. This means that the MCC reactions could not proceed to completion and the yields will inevitably be lower.

Literature suggests that shorter reaction times may increase some of the yields of the isolated products by reducing the number of side reactions which can occur during the longer reaction times.[48] For future experiments it is also notable that microwave irradiation can be used as a

means of doing these experiments on a shorter time scale and with improved yields.[48] Microwave experiments are usually completed within 1 hour as opposed to our reaction time of 60-90 hours.[48]

1.2 Synthesis of 3-Amino-1-cyano-indolizines

Our second major aim was to synthesise a library of 3-amino-1-cyano-indolizine compounds also using a multi-component coupling approach. We utilised a method first described by Poigny *et al*. which made use of an aldehyde, isocyanide and cyano-2-methylpyridine for synthesising a variety indolizine compounds.[34] Over the course of the project we made use of thee different variations of this multi-component coupling reaction and only one method had marginal success in synthesising the desired 3-amino-1-cyano indolizine compounds.

The first method which we employed for the synthesis of a variety of 3-amino-1-cyano-indolizine compounds utilised an isocyanide, an aldehyde and 2-cyanomethylpyridine in 1,4-dioxane in the presence of catalytic base DBU **(Scheme 14, pg 38)**. We were unable to isolate any of the desired indolizine compounds with this method and instead only isolated intermediate aldol condensation products **63a, 64a, 65a, 69a** and **70a**. It was thought that the use of 1,4-dioxane as a solvent, and not *n*-butanol as described in the literature,[34] was responsible for the failure of this method to isolate any of the desired indolizine compounds. The use of *n*-butanol may provide a key hydrogen-bonding interaction with the intermediate Knoevenagel-type diene, which prevents the dispersion of electron density throughout the conjugated system and allows the [4+1] cycloaddtion to occur. It is for this reason that the subsequent attempt at the synthesis of 3-amino-1-cyano indolizines was carried out using *n*-butanol as a solvent.

Our second attempt at synthesising a variety of 3-amino-1-cyano-indolizine compounds utilised an aldehyde, an isocyanide and either 2-cyanomethylpyridine or (6-chloropyridin-2-yl)acetonitrile in *n*-butanol in the presence of catalytic base **(Scheme 16, pg 43)**. This time the reaction did afford some of the desired indolizine compounds **68, 72, 73** and **75**, but once again intermediate aldol product **74a** and **76a** were also isolated. It appears that changing the solvent from 1,4-dioxane to *n*-butanol greatly improves the ability of the multi-component reaction to yield the desired indolizine compounds, although some of the reactions still do not proceed to completion. Once again in the cases where we did isolate the desired indolizine products the yields are poor (7%-32%), with exception of compound **72**. This may be due to the chromatography of these compounds being extremely difficult, with compounds overlapping with starting material and by products leading to minimal isolation of pure products. The literature reports much the same trend and shows very low yields for most of their synthesised compounds. It can be concluded that despite this reaction in some cases allows for the synthesis of structurally diverse 3-amino-1-cyano-indolizine products, it

is not a synthetically useful reaction. We may have to use longer and more classical synthetic methods for the creation of these types of compounds in the future.

Our final effort at synthesising a variety of 3-amino-1-cyano-indolizine compounds focused on using the already synthesised intermediate aldol products and attempting to drive the [4+1] cycloaddtion forward using acid promotion and an isocyanide **(Scheme 17, pg 45)**. The rationale was that by using an acid promoter we could prevent the delocalisation of the nitrile electrons more efficiently than if we used only a protic solvent. Unfortunately this reaction did not yield any of the desired indolizine compounds and only the starting aldol compounds **63a, 64a** and **65a** were isolated from the reaction. This was a very disappointing result as it was hoped that should this methodology have any success in isolating 3-amino-1-cyano-indolizines, we could then develop a 'two-step one-pot' synthesis. This synthesis would potentially avoid the host of side reactions that occur during the multi-component reaction and perhaps improve yields of the desired indolizines.

In conclusion, none of the methods presented above show any real synthetic value for preparing 3-amino-1-cyano-indolizines efficiently and in good yields. Despite the very limited success of the second method **(Scheme 16)** it is definitely advisable to attempt to synthesise these types of compounds following some better methodology in the future.

1.3 Biological Testing Results

The final aim for this section of the project was the biological testing of the imidazo[1,2-*a*]pyridine and 3-amino-1-cyano indolizine libraries against HIV reverse transcriptase. We wished to determine if any of our synthesised compounds showed any potential NNRTI activity in the hope of determining a viable compound which can be further developed as a novel HIV drug. Unfortunately all nine of the imidazo[1,2-*a*]pyridines which were sent for biological testing showed extremely poor inhibition of the reverse transcriptase enzyme and showed residual enzyme activities of >80%. This set of imidazo[1,2-*a*]pyridines can thus be abandoned as potential NNRTIs, but these compounds should still be tested as anti-tumor, anti-bacterial and anti-malarial agents as they may still demonstrate interesting biological applications. Synthesised 3-amino-1-cyano-indolizines **68, 73** and **75**, as well as intermediate aldol product **76a** were also sent for biological testing. Once again these compounds also demonstrated poor inhibition of the HIV-1 reverse transcriptase enzyme and showed >70% remaining enzyme activity **(Graph 3)**. These compounds thus cannot be considered for use as NNRTIs, but once again should also be tested for anti-tumor, anti-bacterial and anti-malarial applications. One further aspect that could be investigated with these 3-amino-1-cyano-indolizine compounds would be whether removal of the nitrile functional group would improve the efficacy of these compounds as NNRTIs. It is thought that cleaving the nitrile group will change a key substrate-enzyme interaction i.e. a hydrogen

acceptor will be replaced with a π-π stacking interaction. It will be interesting to note if this post synthetic modification would provide more promising biological testing results.

Part B

Chapter 4: Introduction, Literature Review and Aims

Development of Methodology for the Synthesis of Benzo-fused Heteroaromatic Naphthoquinone and Naphthopyranone Ring Systems using Palladium Mediated Suzuki-Miyaura Coupling as a Key Step

Aromatic polyketides which feature both the benzo-fused naphthoquinone and nahpthopyranone structural motifs represent one of the largest families of secondary metabolites found in nature and are of considerable interest due to their biological activities and structural intricacies.[66, 67] These compounds have a wide range of biological applications including antibacterial, antitumor, antiviral and enzyme inhibitory activities and have thus become a very important class of therapeutic agents.[66, 67] These aromatic polyketides are thus popular synthetic targets due to their extensive pharmaceutical applications.[66, 67] However due to the challenging synthetic nature of these motifs, syntheses tend to be long, laborious and inefficient and often result in low yields.[68] Thus, as part of our research program, a methodology study was undertaken to develop a new, synthetically efficient and reliable method for the synthesis of these two structural motifs using Suzuki coupling as a key step in building these important scaffolds.

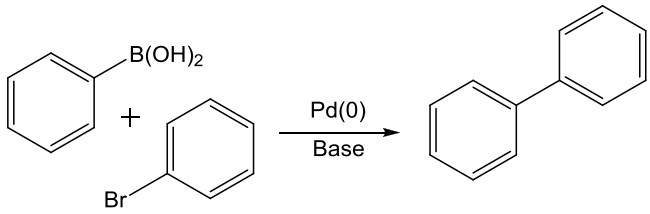
1. Palladium Mediated Suzuki-Miyaura Cross-Coupling Reaction

In 1979 Miyaura, Yamada and Suzuki laid the ground work for what has become one of the most important and useful methods for the construction of carbon-carbon bonds in organic chemistry.[69a] Their original coupling reactions reported the use of alkenyl boronates with alkenyl bromides; however, the immense amount of research which has been conducted over the past 30 years has led to vast improvements in what is now known as the Suzuki-Miyaura cross-coupling reaction.[69a] These improvements have led to the use of a variety of starting substrates, room temperature reactions, low catalyst loadings and the ability to work with sterically hindered substrates.[69b] The immeasurable applications of the Suzuki-Miyaura cross coupling reaction in the synthesis of carbon-carbon bonds in pharmaceuticals, fine chemicals and industrials has firmly cemented it as one of the most important reactions in modern organic chemistry.[69b]

1.1 Suzuki-Miyaura Cross-Coupling Reaction

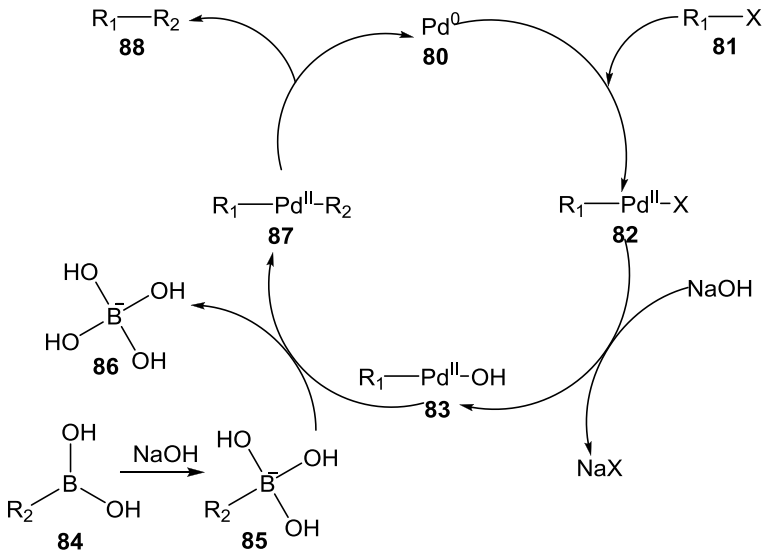
The Suzuki-Miyaura cross-coupling reaction is a powerful transformation which allows the coupling of alkenyl- or aryl-boronic acids with an alkenyl- or aryl-halide catalyzed by a palladium(0) complex in the presence of a base to form C-C bonds **(Scheme 18)**.[70] The key advantages of the Suzuki

coupling reactions are the use of mild reaction conditions and the commercially availability of the diverse boronic acids which are environmentally safer than many of the other organometallic reagents.[71] The reaction relies on a palladium catalyst such as $Pd(PPh_3)_4$ known as tetrakis (the most commonly used catalyst), which can be prepared beforehand or *in situ* to bring about C-C bond formation.[71] One of the major drawbacks of the Suzuki reaction is that all oxygen must be excluded from the system to prevent the oxidation of the palladium(0) species, which is key to the cross coupling reaction mechanism.[71] As mentioned before, developments over the last 30 years have allowed a large variety of substrates to be utilised in the Suzuki coupling reaction.[69] Potassium trifluoroborates, organoboranes and boronate esters may be used in place of boronic acids and pseudo-halides such as triflates may also be used as coupling partners, but are generally more expensive to prepare or purchase.[69, 71]



Scheme 18 Schematic of Suzuki-Miyaura Cross Coupling Reaction for the Formation of the Bi-aryl Axis[70]

The mechanism of the Suzuki-Miyaura cross coupling reaction is best explained by a catalytic cycle involving three key steps involving the transition metal, palladium **(Scheme 19)**.[72] The first step of the mechanism involves the oxidative addition of the carbon electrophile **81** to the zerovalent palladium species **80** to form the organo-palladium species **82**, which on reaction with the base gives key intermediate **83**.[72] This highlights one of the very important functions of the base in the Suzuki reaction in 'mopping up' the halide ion preventing the reverse reaction.[73] The second key step is a transmetallation of the nucleophilic carbon from the boronate complex **85** to the organo-palladium species **83** to form intermediate **87**.[72] A second important function of the base is highlighted by this transmetallation step. As the organic groups of the organoboron compounds **84** are weakly nucleophilic, the coordination of the negatively charged base to the boron atom **85** is used as an efficient way of improving the nucleophilicity of the organic group to be transferred.[73] The final step in the catalytic cycle is the reductive elimination of the desired cross-coupling product **88** and the regeneration of the palladium(0) catalyst **80**.[72]

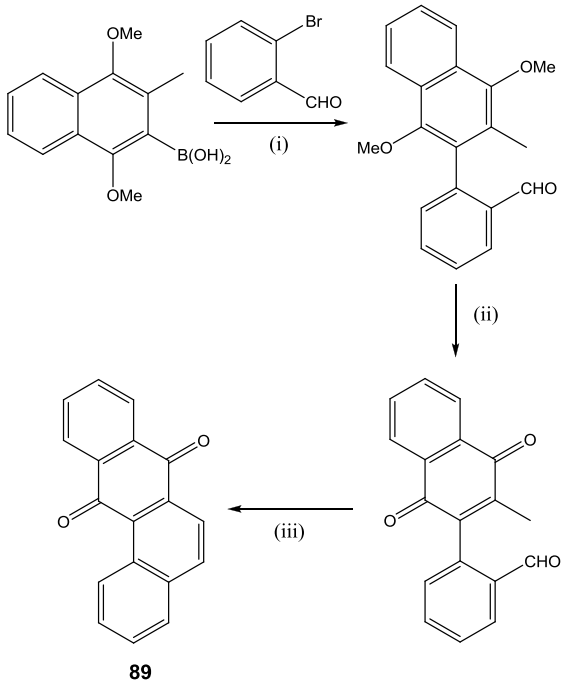


Scheme 19 Catalytic Cycle of Suzuki-Miyaura Cross-Coupling Reaction[72]

1.2 Suzuki-Miyaura Cross-Coupling: The Wits Approach

1.2.1 The Synthesis of Angularly Fused Polyaromatic Compounds

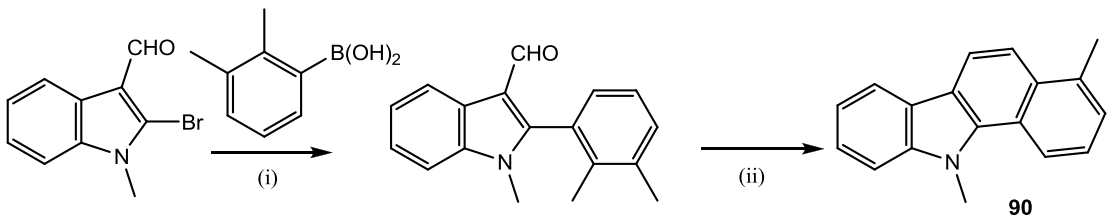
The Suzuki-Miyaura cross-coupling reaction has been used extensively in our labs, mainly for the construction of a biaryl axis. The first example is the use of the Suzuki-Miyaura cross coupling reaction as a key step in the synthesis of Polycyclic Aromatic Hydrocarbons (PAHs).[74] This large class of compounds is primarily recognised for their carcinogenic activities, but recently these compounds have been investigated for other reasons and have found a niche as large ligands in transition metal catalysis. The synthesis of benzo[*a*]anthracene-7,12-dione **89 (Scheme 20)** in an 82% yield is amongst one of the PAHs synthesised by de Koning and co-workers using Suzuki-Miyaura coupling as a key step in building these large scaffolds.[74]



Scheme 20 The Synthesis of Benzo[*a*]anthracene-7,10-dione *Reagents, Conditions and Yields* (i) 10% mol $Pd(PPh_3)_4$, 2M aq. Na_2CO_3, DME/EtOH, 100%; (ii) CAN, H_2O/MeCN, 87%; (iii) $KOBu^t$, DMF, 80°C, h*v*, 82%.[74]

1.2.2 The Synthesis of Benzo[a]carbazoles

Benzo- or pyrido-fused carbazoles are also of great interest to synthetic chemists as these systems are often found as scaffolds of biologically active products and are being developed as potential antitumor agents.[75] The same methodology as illustrated in **Scheme 20** could also be adopted for the synthesis of these potentially bioactive carbazole molecules.[75] *N*-Methyl 2-bromoindole-3-carbaldehyde underwent Suzuki-Miyaura cross-coupling with boronic acids in the presence of palladium(0) **(Scheme 21)**.[75] Treatment of these coupled products with potassium-*t*-butoxide in the presence of light afforded the same ring-closure as previously seen in the PAH systems, but instead formed the benzo[*a*]carbazole compound **90**.[75]



Scheme 21 The synthesis of Benzo[*a*]carbazoles *Reagents, Conditions and Yields* (i) 10% mol $Pd(PPh_3)_4$, 2M aq. Na_2CO_3, DME/EtOH, 93%; (ii) $KOBu^t$, DMF, 80°C, h*v*, 78%.[75]

2. The Naphthoquinone Derivatives

As mentioned earlier, the naphthoquinone motif is a very important one as it is found in a vast number of secondary metabolites and constitutes a chief class of therapeutic agents.[66] Whilst these naphthoquinone-containing compounds show a wide range of biological activities from antiviral to anti-inflammatory agents, their use as antitumor and antibiotic agents is the most common.[76] The reason for the potency of compounds containing this motif against bacteria and tumours is to do with the chemical properties of the quinone itself.[76] In a system such as that found for rapidly dividing cells and bacteria, oxygen is being rapidly used up, creating an oxygen deficient or reductive area in the body.[76] The ability of the quinone to be reduced to the hydroquinone *in vivo* allows it to act as a bisalkylating agent attacking the rapidly dividing cells responsible for the reductive system.[76] This means that quinones are potent and selective pharmaceutical agents for the treatment of cancers and bacterial infections.[76] This highlights the need for development of novel methodology for the efficient synthesis of quinone-containing compounds which could be used as potential bioactive compounds. The following section aims to demonstrate the vast biological applications of naphthoquinones as therapeutic agents and also the synthetic strategies employed for the creation of this extremely important privileged scaffold.

2.1 Biological Applications and Synthetic Strategies for Pyranonaphthoquinones

Pyranonaphthoquinones display the characteristic biological activities expected of the naphthoquinone substructure.[76] For example, nanaomycin A **91**, francolin **92**, kalafungin **93** and medermycin **94 (Figure 21)** have been shown to be extremely active against many strains of the Gram-positive bacterial species of *Staphylococcus* and *Bacillus* as well as being active against fungi and mycoplasms.[76, 77] Many synthetic routes to these pyranonaphthoquinones have been reported[76] and this section will illustrate a number of the methodologies employed to synthesise these natural product antibiotics.

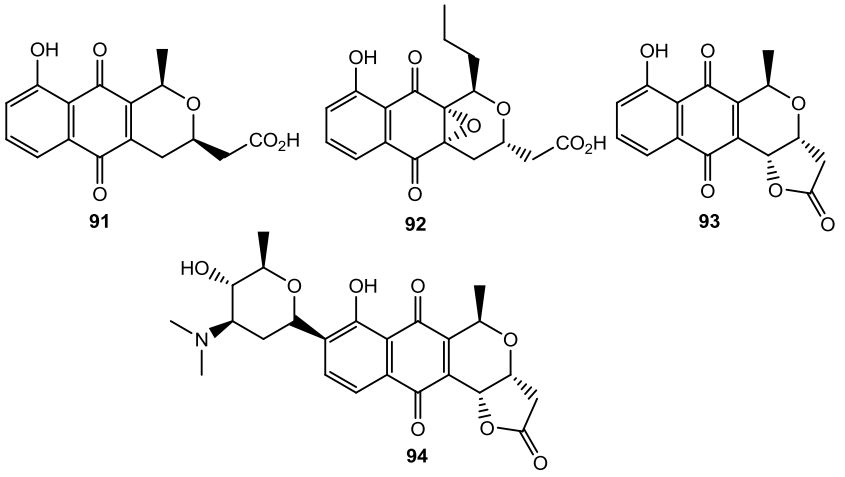
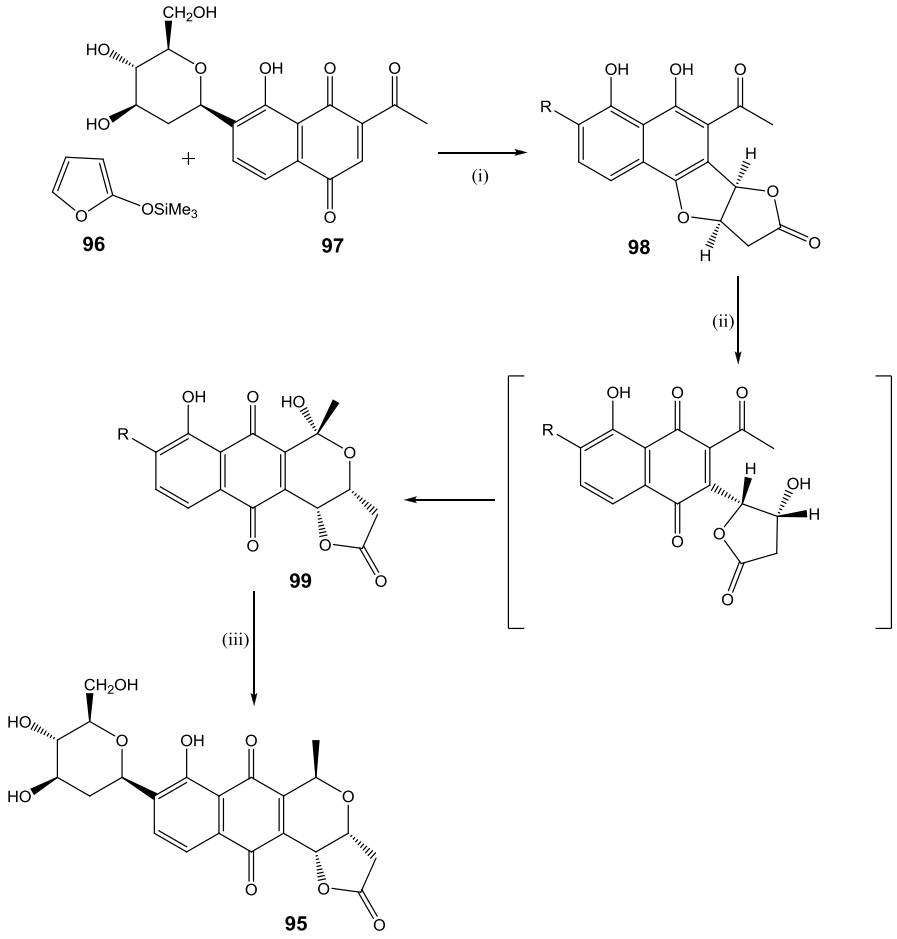


Figure 21 Some Bioactive Pyranonaphthoquinones[76]

2.1.1 Synthesis of Pyranonaphthoquinone Motif by Furonaphthofuran Annulation-Oxidative Rearrangement

The pyranonaphthoquinone antibiotic medermycin **94** was isolated from *Streptomyces tanashiensis* and was found to be active against gram positive organisms, antibiotic resistant cell lines of L5178Y lymphoblastoma and Ehrlich carcinoma in mice and human leukaemia K562 cells.[78] However, despite the obvious biological application of this molecule only one total synthesis of it has been reported to date.[78] Brimble and Brenstrum designed a synthetic strategy for the synthesis of the 2-deoxyglycosyl analogue of medermycin **95**, which is flexible at the point of introduction of the *C*-glycoside so that a range of medermycin derivatives can be synthesised **(Scheme 17)**.[78] The group successfully synthesised the 2-deoxyglycosyl analogue of medermycin **95** using a furonaphthofuran annulation-oxidative rearrangement strategy **(Scheme 17)** to form the pyranonaphthoquinone ring system.[77, 78] This strategy involves the conversion of one tri-cyclic system into another tri-cyclic system.[77, 78, 79] The reaction proceeds via an uncatalysed 1,4-addition of 2-trimethylsiloxyfuran **96** to the C-glycoside linked 2-acetyl-1,4-naphthoquinone **97** and gives the furo[3,2-*b*]naphtho[2,1-*d*]furan **98**, which then undergoes oxidative rearrangement with cerium(IV) ammonium nitrate to give the desired furo[3,2-*b*]naphtho[1,3-*d*]pyran **99**.[77, 78, 79] The final step is the reduction of the hemiacetal **99** to the cyclic ether **95** which is prepared using triethylsilane in trifluoroacetic acid.[79]



Scheme 17 The Synthesis of Medermycin Derivative *Reagents and conditions:* (i) MeCN; (ii) CAN, H_2O, room temp; (iii) Et_3SiH, CF_3CO_2H, -78^oC to room temp.[77, 78, 79]

2.1.2 Synthesis of Pyranonaphthoquinone Motif by Intramolecular Michael Addition

The pyranonaphthoquinones nanaomycin A **91** and francolin **92** show characteristic biological activities and are active against Gram-positive bacteria, fungi and mycoplasms.[76] It is due to their wide range of biological activities that many synthetic routes have been reported for the synthesis of these pyranonaphthoquinone containing compounds.[76] Uno also established an efficient synthetic strategy which led to the total synthesis of four natural products containing the pyranonaphthoquinone motif: eleutherin **100**, isoeleutherin **101**, nanaomycin A **91** and deoxyfrenolicin **102 (Figure 22)**.[76]

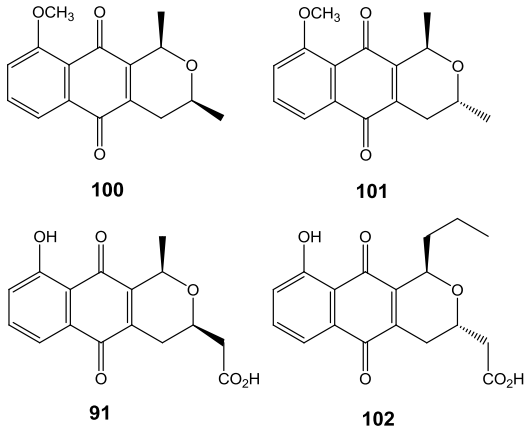
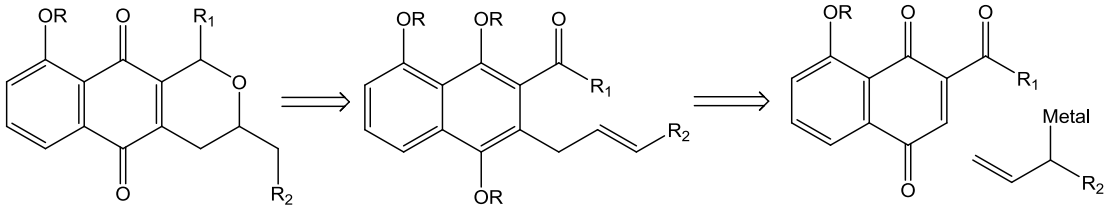


Figure 22 Natural Products containing the Pyranonaphthoquinone motif[76]

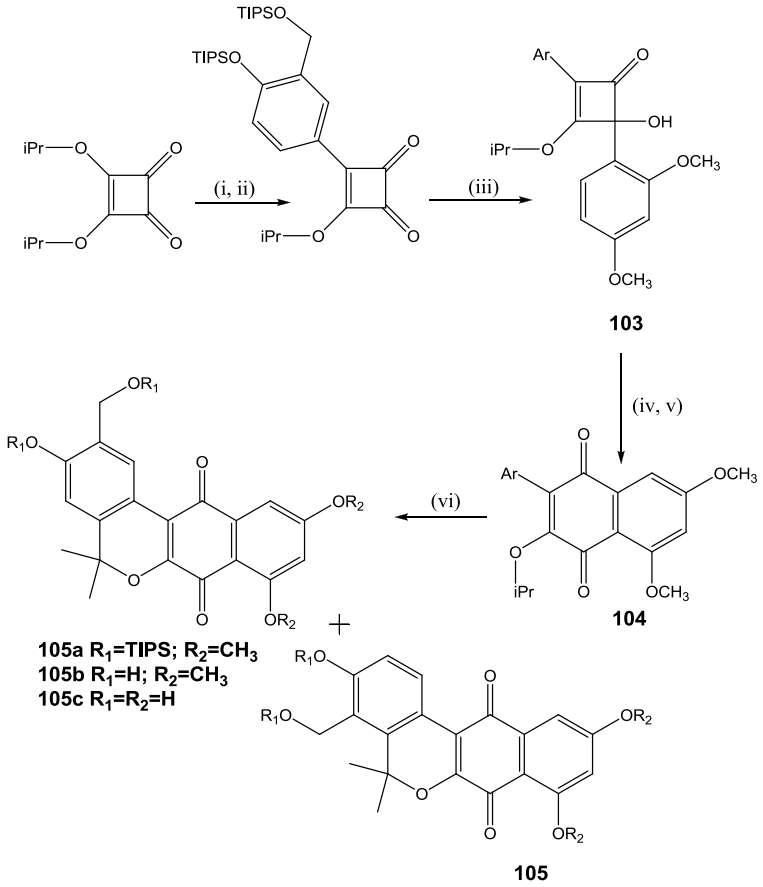
This retrosynthetic route **(Scheme 23)** shows that the construction of the pyran ring system could be achieved by intramolecular Michael addition or etherification.[76] The required carbon chains for the ring closure are prepared from the reaction of alkanoylnaphthoquinones with simple or modified allylmetals.[76] The group also demonstrated that the tin allyl reagents gave the best yields (nearly 100%) for the intramolecular Michael addition precursors.[76]



Scheme 23 Retrosynthetic Strategy for Synthesis of Pyranonaphthoquinone-containing Products[76]

2.1.3 Synthesis of Pyranonaphthoquinone motif by Photoannulation Reaction

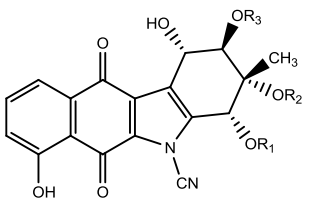
The final synthetic approach to be highlighted in this review is employed in the synthesis of pyranonaphthoquinone **105b** which is an analogue of naphthgeranine E **105c**, a member of a family of bioactive naturally-occurring naphthoquinones found in *Streptococcus violaceus*.[80] This is the first and only reported synthesis in the literature where a direct analogue of the naphthgeranine family of natural products has been synthesised.[80] The key steps of this synthetic strategy are the thermally induced ring expansion of the 4-arylcyclobutenone **103** to the 2-aryl-3-isopropoxy-1,4-naphthoquinone **104** and the subsequent photoannulation reaction of the quinone **104** for the construction of the pyranonaphthoquinone nucleus **105a** and its regioisomer **105 (Scheme 24)**, in an 82% yield as a 1:1 mixture.[80]



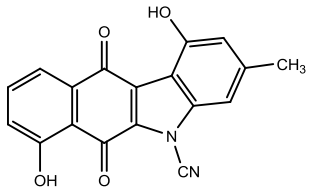
Scheme 24 Synthesis of Naphthgeranine E Derivatives, *Reagents and conditions:* i) LiC_6H_3-4-OTIPS-3CH_2OTIPS, THF, -78^{o}C; ii) TFAA; iii) LiC_6H_3-2,4-$(OCH_3)_2$, -78^{o}C, THF; iv) *p*-xylene, 138^{o}C; v) Ag_2O, K_2CO_3; vi) h*v*, DDQ, benzene.[80]

2.2 Biological Applications and Synthetic Strategies for Kinamycin Antibiotics

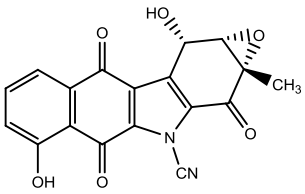
The kinamycin antibiotics were first isolated from *Streptomyces murayamaensis* and were originally characterised by Omura and co-workers as being benzo[*b*]carbazole cyanamides **106 (Figure 23)**.[81] This group of compounds have been shown to possess activity against Gram-positive and Gram-negative bacteria, Ehrlich ascites carcinoma and sarcoma-180.[81] Subsequently four additional biologically active metabolites have been isolated from the same organism; kinamycin E **107**, kinamycin F **108**, prekinamycin **109** and ketoanhydrokinamycin **110 (Figure 23)**.[82] Recently, 3-*O*-isobutyrylkinamycin **111** and 4-deacetyl-4-*O*-isobutyrylkinamycin **112 (Figure 23)** were isolated from a *Saccharothrix* species.[82] These compounds show activity against Gram-positive bacteria, L1210 leukemia, IMC carcinoma, LX-1 human lung carcinoma and SC-6 human stomach carcinoma.[82]



	R_1	R_2	R_3
106	Ac	H	Ac
107	H	H	Ac
108	H	H	H
111	Ac	CO*i*-bu	H
112	CO*i*-bu	H	H



109

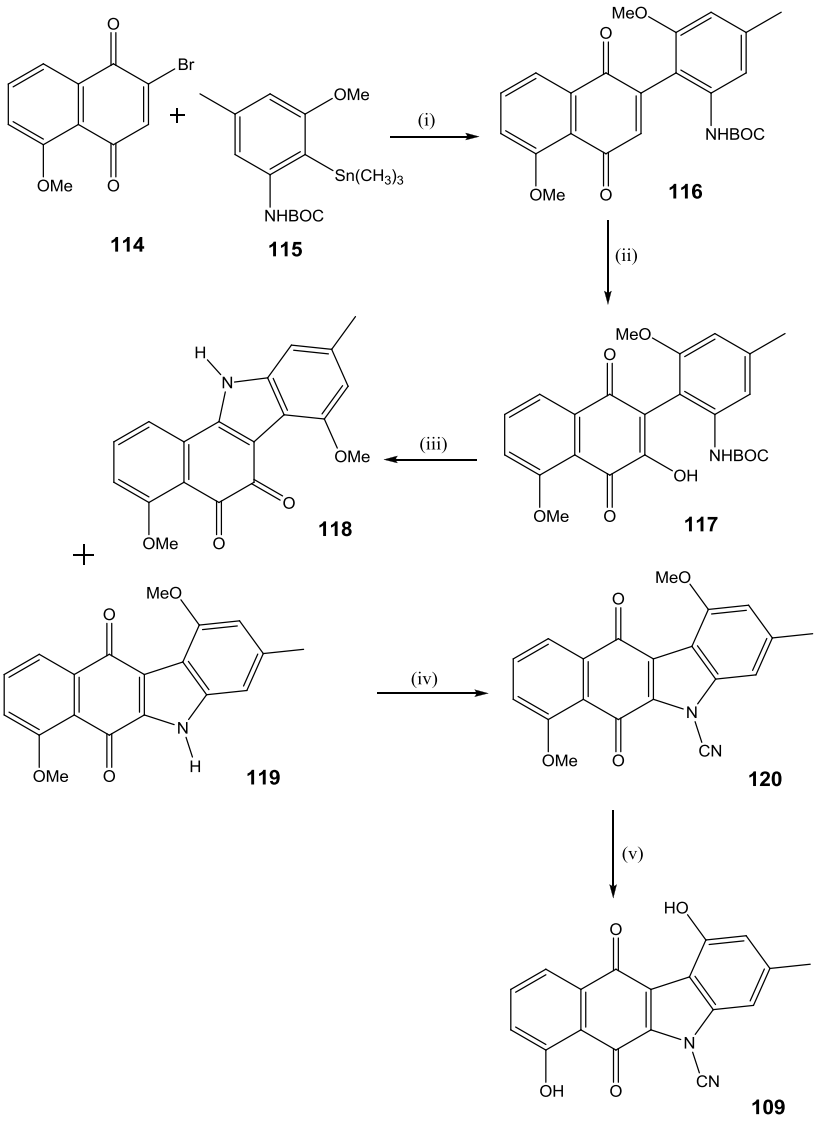


110

Figure 23 Kinamycin Antibiotics[82]

2.2.1 Synthesis of Benzo[b]carbazoloquinones by Coupling of Organostannanes with Bromoquinones

Echavarren *et al.* set out to synthesise prekinamycin **109** relying on the coupling of 2-bromonapthoquinone with stannanes, in the presence of palladium or copper catalyst as a key step.[83] The coupling of the naphthoquinone **114** with arylstannane **115** with $Pd(PPh_3)_4$ and CuBr (5 mol% each) as the catalysts, gave the desired coupled product **116** in excellent yield **(scheme 25)**.[83] Hydroxylation of **116** afforded **117** in a quantitative yield and removal of the BOC protecting group by heating at reflux in H_2SO_4 resulted in ring-closure and gave a 1:1 ratio of products **118** and **119** in an overall yield of 80%.[83] The desired regioisomer **119** was finally *N*-cyanated with excess BrCN in the presence of Et_3N and DMAP to give product **120** in a quantitative yield.[83] Finally demethylation of **120** with BBr_3 gave the desired prekinamycin **109** in a yield of 90%.[83]



Scheme 25 Synthesis of Prekinamycin *Reagents and Conditions*: i) 5 mol% $Pd(PPh_3)_4$, 5 mol% CuBr,1,4-dioxane, reflux (90%); ii) TFA, TFAA, aq. THF, 23^oC (100%); iii) MeOH, cat. H_2SO_4, reflux (80%) iv) excess BrCN, Et_3N, DMAP, CH_2Cl_2, 23^oC (100%); v) BBr_3 (90%)[83]

2.3 Biological Applications and Synthetic Strategies for Jadomycin Antibiotics

The final class of naphthoquinone-containing compounds with interesting biological activities are the jadomycin antibiotics. The jadomycins are a unique family of angucycline-derived antibiotics because of their pentacyclic 8*H*-benz[*b*]oxazolo[3,2-*f*] phenanthridine backbone and is distinctive to the jadomycin antibiotics.[84] The jadomycins are active against both Gram-positive and Gram–negative bacteria and yeast.[66, 84] Jadomycin B **121 (Figure 24)** is the principal product produced when *Streptomyces venezuelae* ISP5230 is fermented under stress conditions, such as heat shock, ethanol treatment or phage infection. Although the biosynthetic pathway for the synthesis of jadomycin B **121** has not been fully elucidated, some of the important steps in the synthesis are known.[84] The key step of the jadomycin biosynthesis is the oxidative opening of the 5,6-bond of an

angucyclinone intermediate and the subsequent incorporation of the isoleucine amino acid from which the nitrogen heteroatom is derived.[84] It is not known if the incorporation of this amino acid is catalyzed by an enzyme and to date no responsible enzyme candidate has been identified in the jadomycin gene cluster.[84] By replacing isoleucine in the jadomycin B production medium with other amino acids, eleven new jadomycin derivatives have been generated.[66]

Jadomycin B **121** and five of its derivatives; jadomycins A **122**, F **123**, V **124**, S **125** and T **126** **(Figure 24)**, which incorporate alanine, phenylalanine, valine, serine and threonine, were tested against four different cancer cell lines (HepG2, IM-9, IM-9/Bcl-2 and H460).[66] It was found that jadomycin S **125** was most potent against HepG2, IM-9 and IM-9/Bcl-2, whilst jadomycin F **123** was most potent against H460, as these derivatives caused the most apoptosis in the specific cancer cell line.[66] The jadomycins are known to elicit a wide range of antibacterial activities, but now their antitumor activities are of interest.[66] The fact that various amino acids with varying side chains can be incorporated into the jadomycin skeleton makes these compounds of further value, as jadomycin thus offers an ideal scaffold to exploit for novel bioactive compounds.[66]

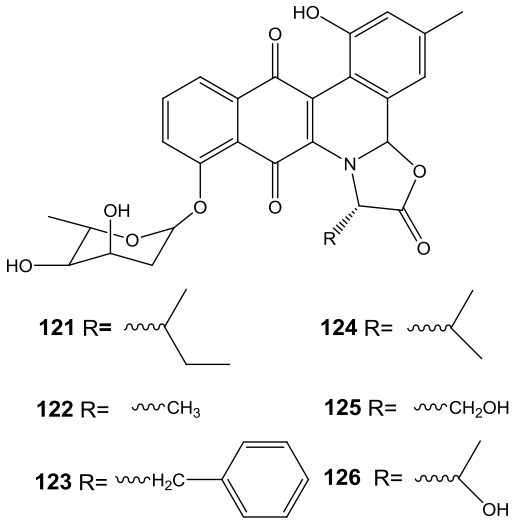
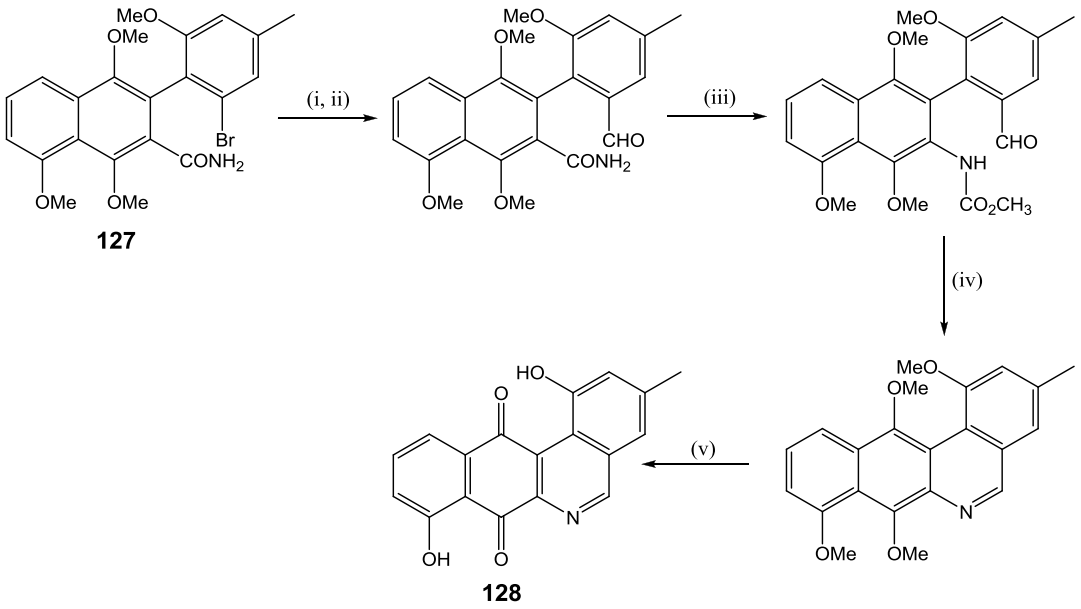


Figure 24 Structures of Jadomycin Derivatives[66]

2.3.1 Synthesis of Phenanthroviridin aglycon

There are no reported syntheses of the dihydrobenzo[*b*]phenanthridine motif as found in the skeleton on jadomycin. There is however a reported synthesis of a very closely related compound, phenanthroviridin aglycon **128**, which is a natural product isolated from *Streptomyces virdiochromogenes* DSM 397.[82] The product was synthesised by Gould and co-workers as part of a study on the synthesis of kinamycin antibiotics which are discussed above.[82] The group was able to prepare the phenanthroviridin compound from a (bromoaryl)naphthamide compound **127**

(Scheme 26), which was a key intermediate in their synthesis of prekinamycin.[82] The desired phenanthroviridin aglycon **128** was then obtained in good yield by way of a sequence of metal-halogen exchange, formylation, Hofmann rearrangement, cyclisation, deprotection and oxidation to 1,4-quinone **(Scheme 26)**.[82]



Scheme 26 Synthesis of Phenanthroviridin Aglycon *Reagents and Conditions:* i) 2.5 equiv *t*-BuLi, -89^{0}C; ii) DMF; iii) NaOMe/Br_2 (-54^{o}C – 55^{o}C); iv) H_2O/reflux (NaOH); v) BBr_3/CH_2Cl_2.[82]

3. The Naphthopyranone Derivatives

Another group of aromatic polyketides which are of considerable interest are compounds containing the oxygenated benzonaphthopyranone motif.[67] They are of interest not only because they display a variety of biological activities, but are also structurally intricate and thus of significance to synthetic chemists.[67] Chartreusin **129**, chrymutasin A **130**, arnottin 1 **131**, hayumicinone **132** and gilvocarcin V **133 (Figure 25)** are a few selected aromatic polyketide antibiotics which share a benzonaphthopyranone moiety and demonstrate a variety of antibiotic and antitumor activities.[67] Despite their obvious biological importance there are very few reported syntheses of these types of systems, mainly due to their challenging structural features as demonstrated by the chartreusin and chrymutasin compounds.[67, 85] This section will further highlight the biological relevance of these polyketide antibiotics as well as elucidate some of the synthetic strategies employed for the synthesis of the benzonaphthopyranone motif.

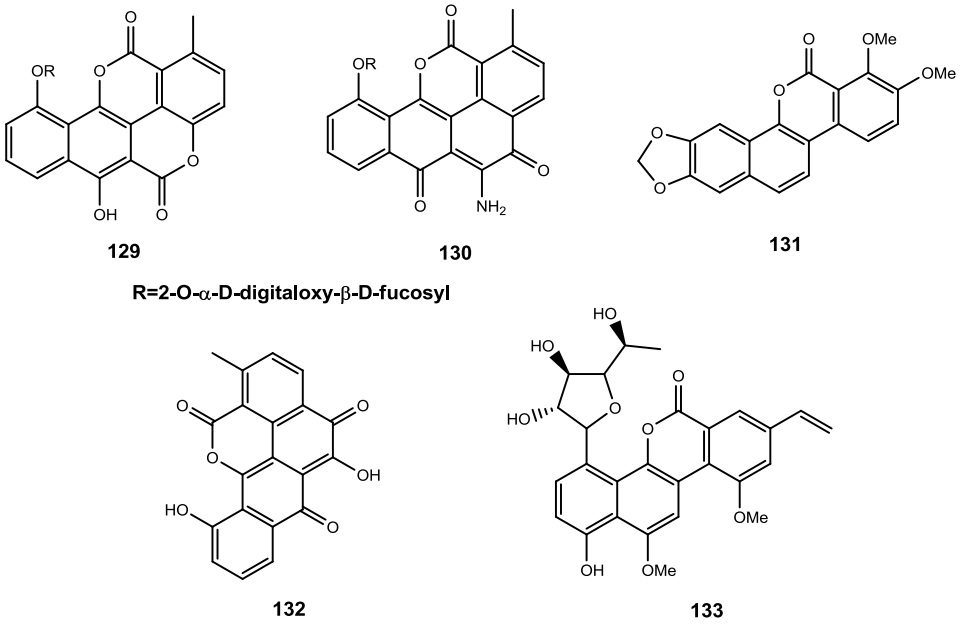
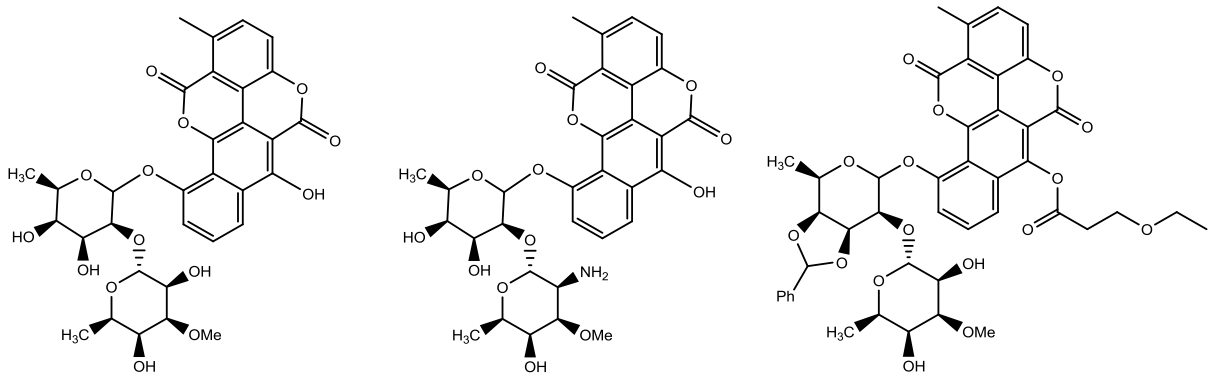


Figure 25 Structures of Benzonaphthopyranone Antibiotics[67]

3.1 Biological Applications and Synthetic Approaches to the Chartreusin Antibiotics

Chartreusin **129** is the most studied member of the benzonaphthopyranone antibiotics and was first isolated in 1953 from the culture broth and mycelial cake of *Streptomyces chartreuses*, and fully characterised in 1964.[67] The compound was first investigated because of its antibacterial activity, but further studies revealed chartreusin **129** to have significant chemotherapeutic activity against several mouse cancers *in vivo*.[86] Chartreusin **129** shows excellent activity against tumour cell lines such as murine P388, L1210 leukemia and B16 melanoma; however the development of chartreusin **129** as a pharmaceutical has been hampered due to its unfavourable pharmacokinetics.[86] The compound has very slow gastrointestinal absorption, poor water solubility and rapid biliary excretion, which limits its ability to be an effective anticancer drug.[86]

Due to the excellent antitumor activity shown *in vitro* by chartreusin much attention has been directed at addressing these poor pharmacokinetic shortcomings and both natural and semisynthetic chartreusin analogues have been identified with improved *in vivo* properties.[86] A natural derivative of chartreusin **129**, elsamicin A **134 (Figure 26)** which is produced by an unidentified actinomycete strain has improved water solubility due to the amino sugar moiety.[86] A semisynthetic derivative of chartreusin, IST-622 **135** has also been identified as a pro-drug with greatly improved pharmacokinetic properties.[86] Currently both elsamicin A **134** and IST-622 **135** are undergoing phase II clinical trials for breast cancer in Japan.[86]

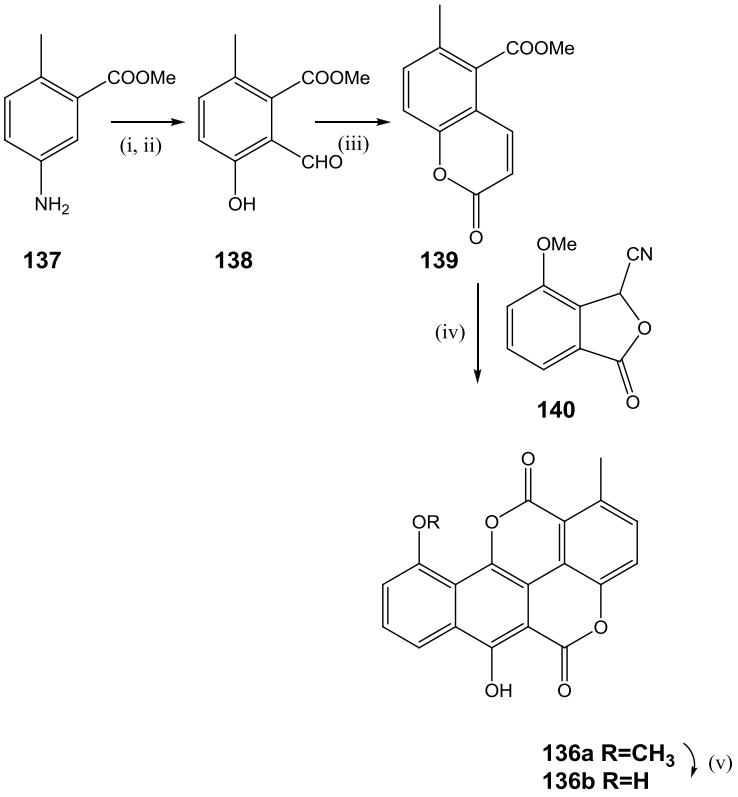


129 **134** **135**

Figure 26 Structures of Antitumor Agents; Chartreusin **129**, Elsamicin A **134** and IST-622 **135**[86]

3.1.1 Synthesis of Benzonaphthopyranones by Hauser-Kraus Annulation

There is only one reported synthesis for the production of the benzonaphthopyranone motif as found in the chartreusin antibiotic. Work done by Mal *et al.* showed the use of Hauser-Kraus annulation for the synthesis of the chartarin **136b (Scheme 27)**, which is the analogue of chartreusin **129** without the sugar moiety.[67] For the total synthesis of chartarin, the required coumarin **139** was prepared in three steps from the aminotoluate **137**.[67] The crucial annulation of coumarin **139** with cyanophthalide **140** was performed to give **136a** in an 86% yield.[67] The use of HBr promoted the demethylation of **136a** to give chartarin **136b** in an 81% yield.[67] The group was also able to extend the methodology to the synthesis of the benzonaphthopyranone cores as found in chrymutasins and hayumicins, and later to the gilvocarcin antibiotics.[67]



Scheme 27 Synthesis of chartarin *Reagents and Conditions*: i) 5.4 vol% H_2SO_4, $NaNO_2$, 0°C – reflux (66%); ii) $(CH_2)_6N_4$, PPA, reflux (30%); iii) Ph_3P=CHCOOEt, Et_2NPh, reflux (95%); iv) LiO*t*-Bu, -60°C – rt (86%); v) HBr, AcOH, reflux (81%).[67]

3.2 Biological Applications and Synthetic Approaches to the Gilvocarcin Antibiotics

Gilvocarcin V **133**, defucogilvocarcin V **141**, and its methyl **142** and ethyl **143** derivatives **(Figure 27)**, represent an important group of benzonaphthopyranone natural products which have been isolated from various strains of *Streptomyces*, and in addition show significant antibacterial and antitumor activity.[85] Gilvocarcin V is the most widely used compound and shows excellent antitumor activity and extremely low toxicity.[87]

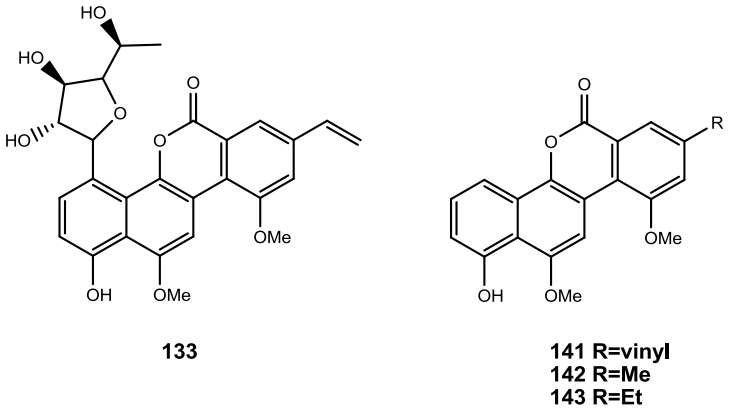
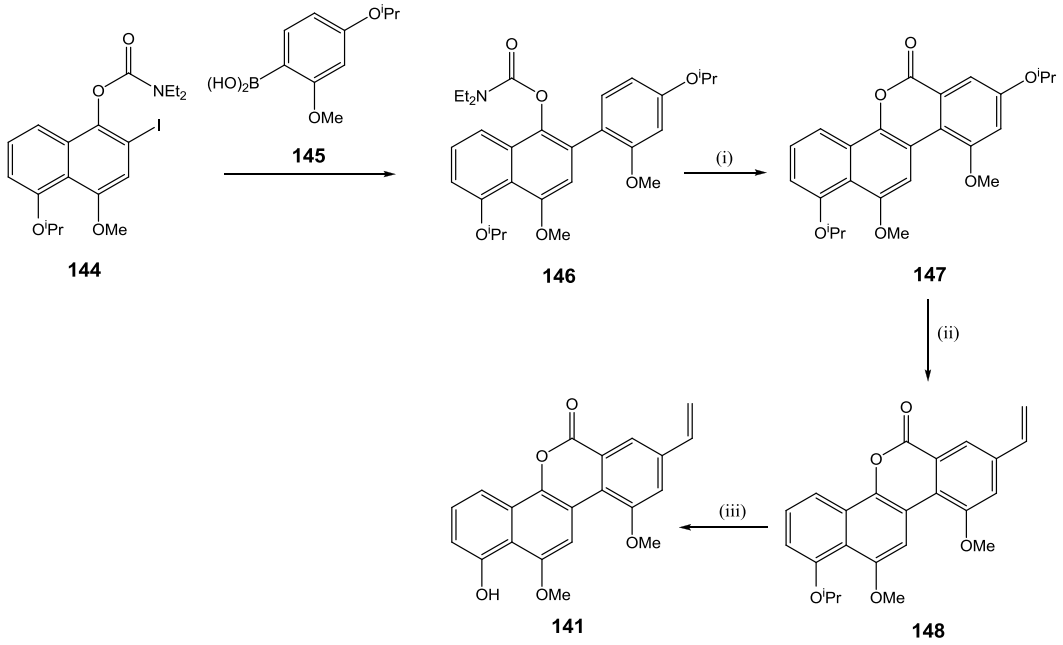


Figure 27 Structure of Gilvocarcin Antibiotics[87]

3.2.1 Cross Coupling Strategies for the Synthesis of Gilvocarcin Antibiotics

Snieckus and co-workers reported the total synthesis of defucogilvocarcin V **141**, and its methyl **142** and ethyl **143** derivatives **(Figure 27)**, in a continued attempt to demonstrate the synthetic advantages of transition metal-catalysed cross-coupling reactions.[85] This section will demonstrate the synthetic strategy employed for the production of the defucogilvocarcin V analogue **141**. To initiate the synthesis an iodinated trioxygenated naphthalene species **144 (Scheme 28)** was cross-coupled with the arylboronic acid **145** in a Pd(0)-catalysed Suzuki-Miyaura reaction to give the biaryl compound **146** in excellent yield.[85] Compound **146** then underwent an anionic Fries rearrangement under standard conditions of treatment with LDA, followed by an acid workup, to give the tetracyclic lactone **147** in a modest yield.[85] Stille coupling with vinyltributyltin converted compound **147** to the desired vinyl analogue **148** in a 69% yield and selective deprotection of the isopropyl ether with BCl_3 gave the final product, defucogilvocarcin V **141** in an overall yield of 14%.[85]

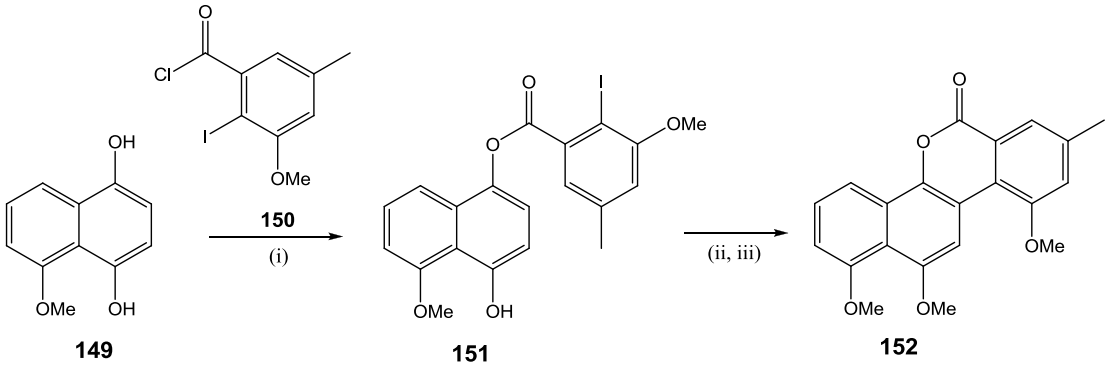


Scheme 28 Synthesis of Defucogilvocarcin V *Reagents and Conditions:* i) i. 3 equiv LDA, THF, reflux, 1hr; ii. HOAc, reflux, 10min; ii) 2mol % $Pd_2(dba)_3$, LiCl, $(2\text{-furyl})_3P$, NMP, rt/5hr; iii) BCl_3, CH_2Cl_2, 0^oC, 10 min.[85]

3.2.2 Palladium-Catalysed Ring Closure for the Synthesis of Gilvocarcin Antibiotics

As part of a study on the use of palladium-catalysed intramolecular ring-closures as an approach to benzo[*b*]fluorenes, Qabaja and Jones published the synthesis of a benzonaphthopyranone closely related to the methyl derivative of defucogilvocarcin **142**.[88] The group synthesised this compound

as an intermediate in the synthesis of a WS-5995C antibiotic which is isolated from a bacterium *Steptomyces acidizcabies* and also shows excellent antitumor activity.[88] Unfortunately their proposed synthesis never gave the desired WS-5995C antibiotic, but it did provide an efficient synthetic strategy for the production of gilvocarcin antibiotics.[88] The synthesis of the benzonaphthopyranone proceeded by way of the reaction of the hydroquinone **149** with the acyl chloride **150 (Scheme 24)**, to give the resulting ester **151** in a 71% yield.[88] The ester product **151** was first methylated and then subjected to Pd-catalysed intramolecular ring-closure to give the benzonaphthopyranone product **152** in a 75% yield.[88]



Scheme 29 Synthesis of Benzonaphthopyranone Motif *Reagents and Conditions*: i) DMAP, *i*-Pr_2NEt, THF; ii) Me_2SO_4, K_2CO_3, acetone; iii) $PdCl_2(PPh_3)_2$, NaOAc, DMA.[88]

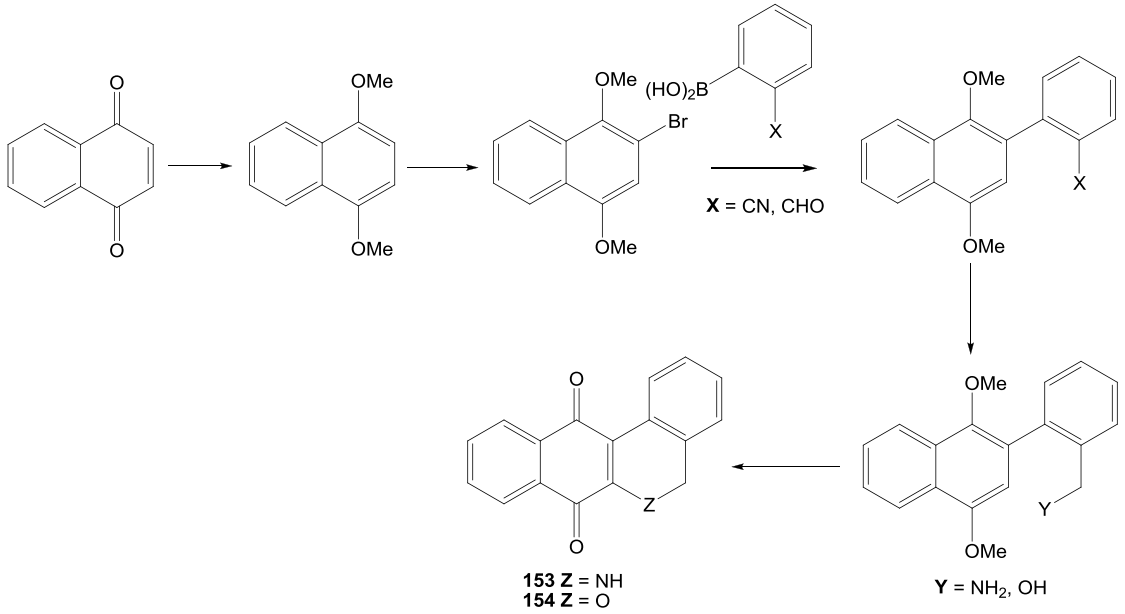
4. Aims of this Section

From the above selected review we can see the biological relevance and applications of naphthoquinone and naphthopyranone containing antibiotics. The overview also highlights the limited methodology for the synthesis of some of these types of structures, particularly the dihydrobenzo[*b*]phenanthridine motif as found in the jadomycin antibiotics. The main aim of this section is the development of methodology for the synthesis of this dihydrobenzo[*b*]phenanthridine motif. We then hope to expand this methodology for the synthesis of related naphthoquinone-containing compounds and other natural products containing these important scaffolds.

- *To develop methodology for the synthesis of the benzo-fused naphthoquinone motif as found in jadomycin antibiotics.*

The main aim of this section is the use of the Suzuki-Miyaura cross-coupling reaction to create the biaryl axis needed for the development of methodology for the synthesis of the dihydrobenzo[*b*]phenanthridine **153** motif and the dihydrobenzo[*c,g*]chromene motif **154 (Scheme 30)**. The starting point of the synthesis is the protection of the 1,4-naphthoquinone, followed by bromination at the *ortho*-postion, and then the Pd(0)-catalysed Suzuki-Miyaura cross-coupling

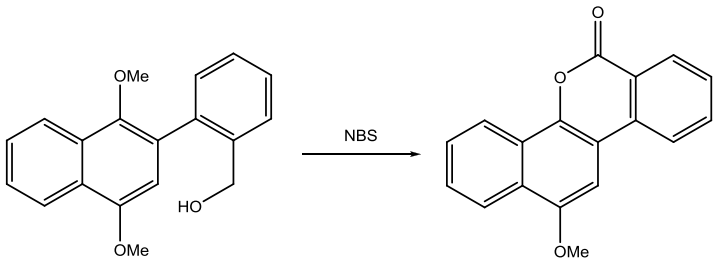
reaction with the relevant boronic acid to create the required biaryl product **(Scheme 30)**. Reduction of nitrile or aldehyde, oxidation back to the quinone and intra-molecular Michael addition are then hoped to create the desired benzo-fused naphthoquinone-containing products. Once the methodology has been successfully employed for the synthesis of the desired naphthoquinones, we wish to extend it to more complex starting materials in the hope that we develop a general procedure for the synthesis of a variety of naphthoquinone-containing products.



Scheme 30 Proposed Synthesis of the Naphthoquinone Motif

- *To develop reproducible methodology for the synthesis of the naphthopyranone motif as found in the gilvocarcin antibiotics.*

It was discovered during the course of this project that NBS could perform an interesting and unexpected ring-closing reaction on one of the substrates required for the synthesis of the dihyrobenzo[*c,g*]chromene motif **154 (Scheme 30)**. This unforeseen result led to the synthesis of 12-methoxy-6*H*-dibenzo[*c,h*]chromen-6-one **155 (Scheme 31)**, which is the scaffold found in a range of biologically important naphthopyranone antibiotics known as the gilvocarcin antibiotics **(Figure 27)**. With this unpredicted product in hand we wished to determine if this reaction could be reproduced and extended to related naphthopyranone scaffolds. We also aimed to elucidate the mechanism by which NBS performs this ring-closing transformation.



155

Scheme 31 Synthesis of 12-Methoxy-6*H*-dibenzo[*c*,*h*]chromen-6-one

Chapter 5: Results and Discussion

Synthesis of Benzo-fused Hetero-aromatic Naphthoquinone and Naphthopyranone Ring Systems

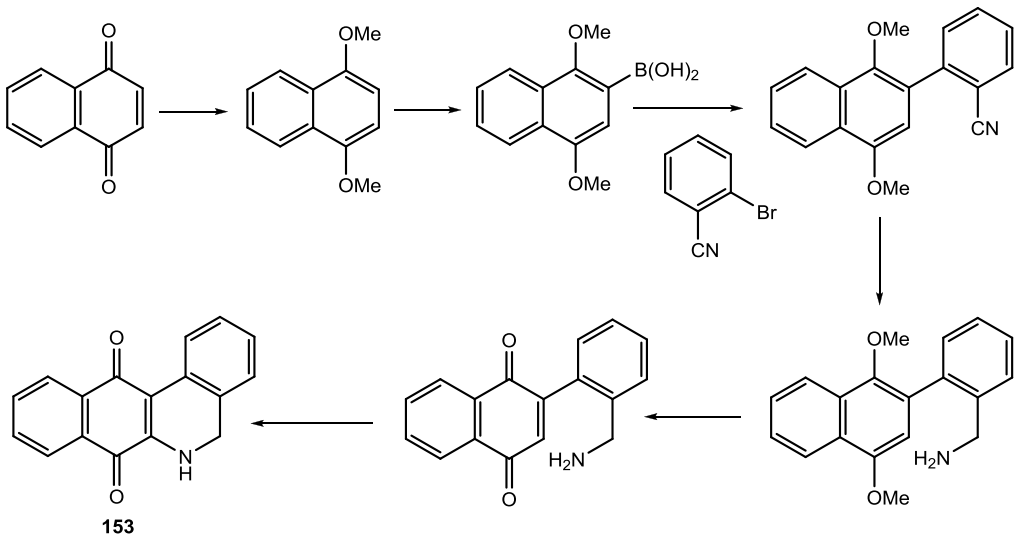
1. Introduction

The following discussion will address matters in the synthesis of the dihydrobenzo[*b*]phenanthridine motif **153** which constitutes the backbone of an important secondary metabolite, jadomycin B **121**. To date no known syntheses of this scaffold have been reported, which made this motif an extremely valuable target for this project. Jadomycin B **121** and its derivatives show a remarkable capacity for biological applications and are known to be active against both Gram-positive and Gram–negative bacteria, with their antitumor activities recently becoming of great interest.[66, 84] This discussion will address the results in accordance with the attempts at the synthesis of this important scaffold, as well as characterisation of the synthesised compounds. In addition we will also examine the results of the attempts to extend the synthetic methodology to other systems in order to form a range of related benzo-fused hetero-aromatic naphthoquinone products. Finally, this section will introduce an extremely interesting novel result which unexpectedly occurred during the course of what we believed would be a standard aromatic bromination reaction. The product from this reaction culminated in the introduction of the second major aim of this project; the synthesis of 12-methoxy-6*H*-dibenzo[*c,h*]chromen-6-one **155** and other related naphthopyranone ring systems.

2. Attempted Synthesis of 5,6-Dihydrobenzo[*b*]phenanthridine-7,12-dione 153 and 5,6-Dihydrophenanthridine-1,4-dione 161

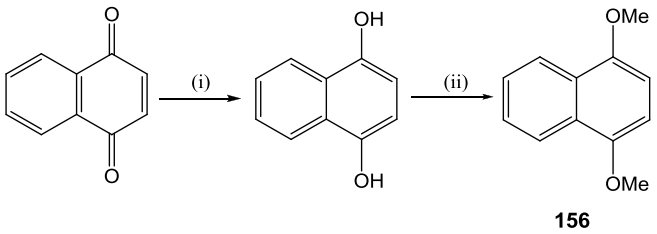
*2.1 Attempted Synthesis of 5,6-Dihydrobenzo[b]phenanthridine-7,12-dione **153***

The synthesis presented below **(Scheme 32)** details how we hope to achieve the synthesis of compound **153**, the motif of jadomycin B **121**. Starting from commercially available 1,4-naphthoquinone we wished to protect the staring material as 1,4-dimethoxynaphthalene and subsequently mono-brominate in the *ortho*-position using known literature procedures.[89, 90] By converting the brominated product to the corresponding boronic acid and coupling it with a relevant aryl-halide we hoped to create a biaryl axis from which we can develop the methodology for the synthesis of **153**. A simple method of achieving this desired biaryl axis is to invoke the use of Suzuki-Miyaura cross-coupling which is a palladium(0)-catalyzed coupling reaction forming C-C bonds.[70] The ensuing reduction of the nitrile to the amine and oxidation of the naphthalene motif to the naphthoquinone will hopefully create conditions for an intra-molecular Michael addition to occur resulting in the synthesis of 5,6-dihydrobenzo[*b*]phenanthridine-7,12-dione **153**.



Scheme 32 Proposed Synthetic Stratergy for the Synthesis of 5,6-Dihydrobenzo[*b*] phenanthridine-7,12-dione **153**

*2.1.1 Synthesis of 1,4-Dimethoxynaphthalene **156***



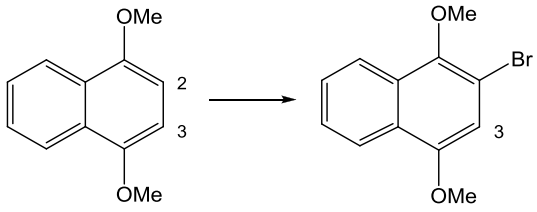
Scheme 33 Synthesis of 1,4-Dimethoxynaphthalene **156** *Reagents and Conditions*; i) $Na_2S_2O_4$, diethyl ether, H_2O, rt, 1 h ii) K_2CO_3, dimethyl sulphate, acetone, reflux, 22 h

The first major aim of this project was the use of Suzuki-Miyaura cross-coupling to create the biaryl axis needed for the development of methodology for the synthesis of the dihydrobenzo[*b*]phenanthridine motif **153 (Scheme 32)**. The starting point of the synthesis was the protection of commercially available 1,4-naphthoquinone as the analogous ether, 1,4-dimethoxynaphthalene **156 (Scheme 33)**. To achieve this, 1,4-naphthoquinone and the reducing agent $Na_2S_2O_4$ were dissolved in diethyl ether and H_2O, and shaken together vigorously in a separating funnel for 1 hour. The $Na_2S_2O_4$ reduces the 1,4-naphthoquinone to the 1,4-dihydroquinone, which is unstable to oxygen and so used directly in the following step without characterisation. The intermediate 1,4-dihydroquinone was quickly dissolved in acetone and K_2CO_3 and dimethyl sulfate were added to the solution, and the reaction was heated at reflux for 22 hours. The K_2CO_3 base removes the protons of the 1,4-dihydroquinone and allows the methylating agent, dimethyl sulfate, to deliver the desired methyl groups. Subsequent to a work-up, the crude brown oily product was purified by column chromatography to yield the desired 1,4-

dimethoxynaphthalene **156** as an off-white solid in a 79% yield. The losses in yield are most probable due to the poor quality of the starting 1,4-naphthoquinone and purification of the starting material may have resulted in higher yields.

The product was characterised by ^{1}H and ^{13}C NMR spectroscopy and the spectroscopic data was in agreement with that of the reported values in the literature.[89] A key identifying feature was the presence of a singlet at 3.93 ppm in the ^{1}H NMR spectrum which integrated for 6 protons and was a result of the two OCH_3 groups. The corresponding carbon signal was found in the ^{13}C NMR spectrum at 55.7 ppm.

*2.1.2 Synthesis of 2-Bromo-1,4-dimethoxynaphthalene **157***



156 **157**

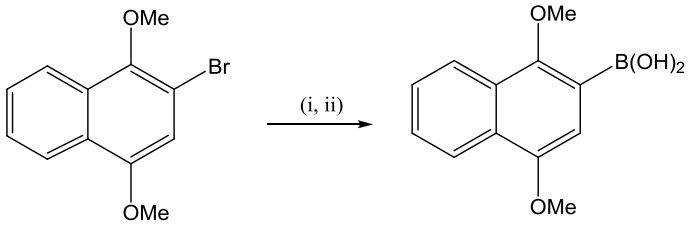
Scheme 34 Synthesis of 2-Bromo-1,4-dimethoxynaphthalene **157** *Reagents and Conditions*; NBS, CH_2Cl_2, rt, 21 h

Having successfully synthesised compound **156**, the following step in the synthesis was the mono-bromination of the compound in a position *ortho* to the methoxy group **(Scheme 34)**. This was achieved by dissolving 1,4-dimethoxynaphthalene **156** in CH_2Cl_2 and reacting it with 1 equivalent of NBS at room temperature for 21 hours. The resultant solution was subjected to a work-up procedure and purified by column chromatography to yield the desired 2-bromo-1,4-dimethoxynaphthalene **157** as a white solid in a 65% yield. Although the yield of this reaction is not very high, the mild reaction conditions and the ease with which the bromination is achieved, makes this method highly favourable compared to other bromination strategies.

The spectroscopic data of compound **157** were in agreement with that of Bloomer and Zheng.[90] The ^{1}H NMR spectrum of compound **156** showed a distinct singlet at 6.66 ppm which integrated for 2 protons and corresponded to hydrogen atoms H^2 and H^3 which are both *ortho* to the methoxy groups. However, the ^{1}H NMR spectrum of compound **157** showed the presence of only one of these protons, H^3, as a clear singlet at 6.88 ppm was found which only integrated for 1 proton. The absence of this second proton signal confirms that the mono-bromination in the *ortho*-position was successful. Another clear indication that the bromination reaction had occurred was that both the ^{1}H and ^{13}C NMR spectra of compound **157** showed a marked increase in the number of signals

found. This relates to the fact that the newly synthesised compound **157** is no longer symmetrical, unlike its parent compound 1,4-dimethoxynaphthalene **156**. The ^{1}H NMR spectrum of **156** showed both OCH_3 groups as a singlet at 3.93 ppm due to the symmetrical nature of the molecule, but the ^{1}H spectrum of compound **157** shows two distinct OCH_3 signals at 3.96 and 3.95 ppm, respectively.

*2.1.3 Synthesis of 1,4-Dimethoxynaphthalen-2-yl boronic acid **158***

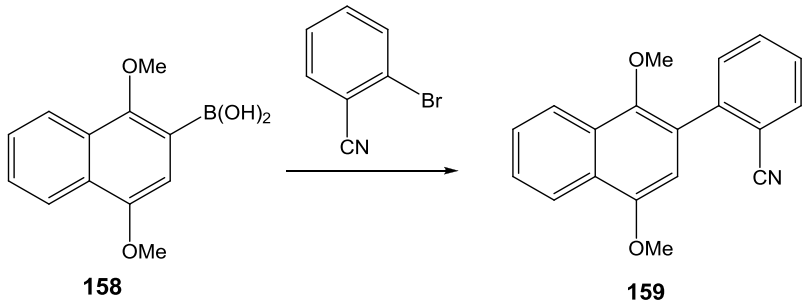


157 **158**

Scheme 35 Synthesis of 1,4-dimethoxynaphthalen-2-yl boronic acid **158** *Reagents and Conditions*; i) *n*-BuLi, THF, -78˚C, 40 min ii) trimethyl borate, THF, -78˚C, 1 h

Before the Suzuki-Miyaura cross-coupling reaction could be achieved, we needed to synthesise the corresponding boronic acid of 2-bromo-1,4-dimethoxynaphthalene **157**. The synthesis of 1,4-dimethoxynaphthalen-2-yl boronic acid **158 (Scheme 35)** was accomplished by dissolving compound **157** in dry THF in a two-necked flask and thoroughly degassing the solution with N_2 gas. The reaction solution was then cooled to -78˚C using a liquid N_2 and acetone bath. Three equivalents of *n*-BuLi were added slowly to the reaction mixture and the solution was left stirring for a further 40 minutes at -78˚C, before the addition of three equivalents of trimethyl borate. The solution was stirred for a further 1 h at -78^{o}C and then quenched with 10% HCl solution. The organic extracts were collected and the solvent removed *in vacuo* to give a clear oil, which upon the addition of acetone afforded the desired boronic acid **158** as a white solid in a yield of 76%. The boronic acid product **158** was not characterised as it is unstable, and insoluble in a variety of deuterated solvents and was thus used directly in the following synthetic step.

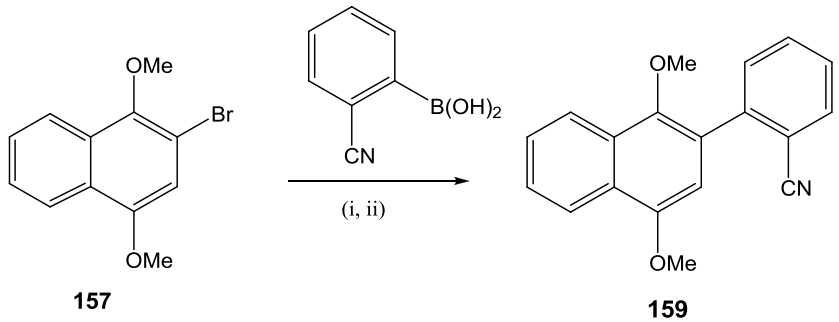
*2.1.4 Synthesis of 2-(1,4-Dimethoxynaphthalen-2-yl)benzonitrile **159***



158 **159**

Scheme 36 Synthesis of 2-(1,4-Dimethoxynaphthalen-2-yl)benzonitrile **159** *Reagents and Conditions*; $Pd(PPh_3)_4$, 2M aq. Na_2CO_3, DME, EtOH, reflux, 23 h

Having 1,4-dimethoxynaphthalen-2-yl boronic acid **158** in hand we could now build the biaryl axis required for the synthesis of dihydrobenzo[*b*]phenanthridine motif **153 (Scheme 32)**. This was done by using the palladium mediated Suzuki-Miyaura cross-coupling reaction which will couple the synthesised boronic acid **158** with commercially available 2-bromobenzonitrile **(Scheme 36)**. 15% of tetrakis [$Pd(PPh_3)_4$], which is the catalyst used for the Suzuki-Miyaura cross-coupling reaction, was placed in a 3-neck round bottom flask. The catalyst is very sensitive to oxygen and so the reaction mixture must first be evacuated of all oxygen and then carried out under an inert N_2 atmosphere. Next the 1,4-dimethoxynaphthalen-2-yl boronic acid **158** and 2-bromobenzonitrile were dissolved in DME and EtOH, degassed and added to the $Pd(PPh_3)_4$ in the reaction vessel via a dropping funnel. Finally an aqueous 2M Na_2CO_3 solution was also degassed and added to the reaction vessel via a dropping funnel and the resultant solution was then heated at reflux for 23 hours. The reaction was then quenched with H_2O, the organic extracts collected and the solvent removed *in vacuo* to afford a pale residue. The crude product was finally purified by column chromatography to give the desired Suzuki product, 2-(1,4-dimethoxynaphthalen-2-yl)benzonitrile **159** as a white solid in a 50% yield.



157 **159**

Scheme 37 Synthesis of 2-(1,4-Dimethoxynaphthalen-2-yl)benzonitrile **159** *Reagents and Conditions;* i) $Pd(PPh_3)_4$, 2M aq. Na_2CO_3, DME, EtOH, reflux, 19 h ii) $Pd(PPh_3)_4$, K_3PO_4, DMF, reflux, 47 h

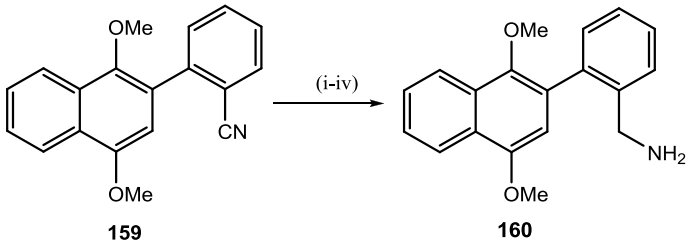
The 50% yield of compound **159** from the Suzuki reaction was disappointing and could have been due to impure boronic acid **158**. Since compound **158** was not characterised by NMR spectroscopy we had no way of knowing what the ratio of starting material to product was or how pure the boronic acid actually was. This may have led to the low yields as there may have been insufficient boronic acid **158** in the reaction mixture to allow the reaction to go to completion. With this in mind, we decided that we would couple commercially available 2-cyanophenylboronic acid with previously synthesised 2-bromo-1,4-dimethoxynaphthalene **157 (Scheme 37)** in the hopes of improving the yields. This would also have the added benefit of reducing the number of synthetic steps required for the synthesis of target molecule dihydrobenzo[*b*]phenanthridine **153**. The reaction procedure for the Suzuki-Miyaura cross-coupling of 2-cyanophenylboronic acid with 2-bromo-1,4-dimethoxy naphthalene **157**, used the same reaction conditions as previously discussed **(Scheme 36)**, in spite of the coupling partners being exchanged **(Scheme 37)**. After 19 hours of heating at reflux the product was purified by column chromatography to yield the desired product **159** as a white solid in a 56% yield.

The yield of this reaction was only marginally better than our first attempt and one last method was tried to improve the Suzuki cross-coupling yields, before settling on the conclusion that the reaction does not proceed to completion. For our last effort we decided to use anhydrous Suzuki conditions so that the reaction could occur in only one homogenous solvent phase instead of at the interface of the organic and aqueous layers. Previously synthesised 2-bromo-1,4-dimethoxynaphthalene **157** and commercially available 2-cyanophenylboronic acid were placed in a 3-neck round bottom flask and dissolved in DMF **(Scheme 37)**. The solution was degassed to exclude all oxygen from the system and 0.2 mol% $Pd(PPh_3)_4$ and 4 equivalents of K_3PO_4 were then added to the reaction solution under flowing N_2 gas. The reaction mixture was then heated at reflux for 47 hours before being quenched with brine. The organic products were extracted, the solvent removed *in vacuo* and the crude product purified by column chromatography to yield the desired 2-(1,4-dimethoxynaphthalen-2-yl)benzonitrile **159** as a white solid in a 45% yield. Unfortunately the anhydrous Suzuki conditions had little influence in improving the yields, and despite using three different reaction conditions the yields remained at about 50% conversion.

In all cases the cross-coupled compound **159** was characterised by NMR spectroscopy and both the ^{1}H and ^{13}C NMR spectra verified that the Suzuki-Miyaura reaction had been successful as there was the correct number of expected proton and carbon signals. The presence of four extra proton signals in the aromatic region of the ^{1}H NMR spectra corresponded well with the occurrence of four extra hydrogen atoms as found on the benzonitrile motif. Perhaps the key identifying feature was a signal at 118.5 ppm in the ^{13}C NMR spectrum which coincided with the carbon of the nitrile group. HRMS failed to give conclusive evidence that the coupling had occurred as a molecular ion for $C_{19}H_{15}O_2N$ could not be obtained. However a fragment with molecular formula

$C_{12}H_{12}O_2$ and mass 188.0837 was found and this corresponds to the 1,4-dimethoxynaphthalene portion of the compound. IR spectroscopy helped to confirm that the Suzuki reaction had occurred as we observe a signal at 2330cm^{-1} which corresponds to the nitrile functional group.

*2.1.5 The Attempted Synthesis of 2-(1,4-Dimethoxynaphthalen-2-yl)phenyl) Methanamine **160***



159 **160**

Scheme 38: Attempted Synthesis of 2-(1,4-Dimethoxynaphthalen-2-yl)phenyl) Methanamine **160** *Reagents and Conditions;* i) 5% Pd/C, conc. HCl, H_2, CH_2Cl_2, rt, 16 h; ii) 2.5 eq $LiAlH_4$, THF, 0˚C – rt, 1 h; iii) 20.0 eq $LiAlH_4$, THF, 0˚C – rt, 22 h; iv) 2N aq. NaOH, Raney alloy, EtOH, EtOAc, rt, 3 h.

Being confident from the characterisation data that we had in fact synthesised 2-(1,4-dimethoxynaphthalen-2-yl)benzonitrile **159**, although only in moderate yields, we attempted to undertake the next step of the synthesis. This step involved the attempted reduction of the nitrile to the benzylic amine to afford the desired product 2-(1,4-dimethoxynaphthalen-2-yl)phenyl)methanamine **160 (Scheme 38)**. Our first attempt at performing this reduction step involved the use of hydrogenation with H_2 gas and 5% Pd/C catalyst. Starting material **159** was dissolved in CH_2Cl_2 and placed in the hydrogenation vessel along with 5% Pd/C and 3 drops of conc. HCl which activates the hydrogenation catalyst **(Scheme 38)**. The reactants were then stirred at room temperature for 16 h under a 4.5kPa H_2 atmosphere, after which time the Pd/C was removed by filtering the solution through celite. The organic filtrate was collected, subjected to a work-up procedure and the solvent removed *in vacuo* to afford a white product which was characterised by NMR spectroscopy to be the starting material **159**. The ^{1}H NMR spectrum showed no presence of the benzylic protons or of an N-H stretch and we safely concluded that the reduction reaction had not been effective.

Having failed in our first attempt at reducing the nitrile to the benzylic amine we thought that by varying the hydrogenation conditions we would eventually achieve the desired effect. It was thought that a higher Pd/C catalyst loading, increased pressures and longer reaction times would force the reaction forward so as to obtain the required amine. Unfortunately, all other attempts at reducing the nitrile to the amine using the hydrogenation vessel failed and yielded only starting material **159** as confirmed by NMR spectroscopy. The table below **(Table 7)** highlights the varying pressure, time, solvent, catalyst and yields of starting material obtained during the subsequent reduction attempts.

Table 7: Conditions for the Attempted Reduction of Compound **159**

Pressure/kPa	Time/h	Solvent	Catalyst	Recovery of Starting Material (%)
5	20	CH_2Cl_2	10% Pd/C and 0.1eq	98
7	20	MeOH	10% Pd/C And 0.5eq	99
8	94	MeOH	10% Pd/C and 1.0eq	97

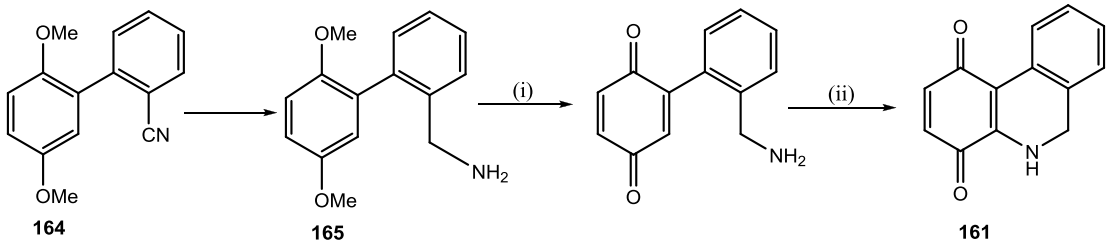
It appears that the reduction conditions used may have been too mild as the nitrile is stabilised due to conjugation with the aromatic ring. It was considered that perhaps the use of a harsher chemical reducing agent may afford the desired reduction. With this in mind we attempted to reduce the nitrile to the amine using $LiAlH_4$ as the reducing agent. Starting material **159** was dissolved in THF and the solution was cooled to 0˚C before the addition of 2.5 equivalent of $LiAlH_4$ **(Scheme 38)**. On addition of the reducing agent the reaction mixture effervesced, which was a positive indication that a reaction was occurring. The reaction was stirred for 1 hour at room temperature before being quenched with H_2O, the organic products extracted and the solvent removed *in vacuo* to afford a white solid. A crude ^1H NMR spectrum showed that the extracted white solid was again the starting material **159**, which was recovered in a 99% yield. The same reaction was attempted once more, but this time using 20 equivalents of $LiAlH_4$ **(Scheme 38)** and once again the isolated product was none other than starting material **159**. To satisfy ourselves that we were not incorrectly interpreting the NMR spectra, an infra red was performed and clearly showed the presence of the nitrile at 2225cm^{-1}.

One final attempt at the reduction of compound **159** was performed, this time using a literature procedure used in our laboratories and known to give the primary amine from a nitrile.[91] As per this procedure, compound **159** was dissolved in ethanol and ethyl acetate. Aqueous NaOH (2N) was added to the solution and the reaction mixture was stirred for 10 minutes, before the addition of 2.0 mass equivalents of Raney nickel alloy **(Scheme 38)**. The reaction mixture was stirred for a further 3 hours after which time the organic products were extracted and the solvent removed *in vacuo* to afford a white solid, which was once again characterised by NMR spectroscopy to be starting material **159**.

It is not fully understood why the reduction of this nitrile does not afford the desired primary amine **160**, but perhaps the extra stability conferred due to conjugation with the aromatic system is a possibility.[46] In any event, it does not seem likely that the hydrogenation reactions will give any

worthwhile results, especially if the nitrile is being stabilised by electron donation from the aromatic ring. The use of reducing agent $LiAlH_4$ may still be an option, as even though the reactions did not show any positive results we could still attempt these reactions at higher temperatures. The nitrile carbon may not be electrophilic enough as it is once again stabilised by conjugation, but if the reaction was to be heated we may be able to overcome this activation energy barrier and force the reaction to proceed. The same reasoning can be applied to the attempted Raney nickel reduction and we can once again attempt this reaction at a higher temperature to see if we obtain some positive results.

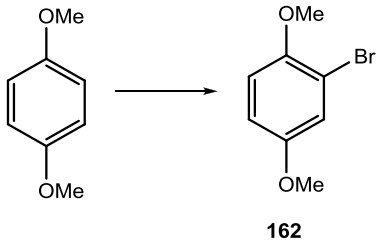
*2.2 Attempted Synthesis of 5,6-Dihydrophenanthridine-1,4-dione **161***



Scheme 39 Proposed Synthesis of 5,6-Dihydrophenanthridine-1,4-dione **161**; i) Oxidation, ii) Intra-molecular Michael addition

Having been unable to reduce 2-(1,4-dimethoxynaphthalen-2-yl)benzonitrile **159** to the corresponding amine **160**, we decided to determine if the proposed methodology for the synthesis of 5,6-dihydrobenzo[*b*]phenanthridine-7,12-dione **153** was worthwhile pursuing. Starting from commercially available 1,4-dimethoxybenzene we wished to synthesise 5,6-dihydrophenanthridine-1,4-dione **161** by employing a similar synthetic strategy to that of the attempted synthesis of compound **153 (Scheme 32)**. If we could effectively reduce nitrile **164** of this simpler system to the corresponding amine **165**, we would have a means of testing whether the proposed oxidation reaction and intra-molecular Michael addition were a viable way of completing the synthesis of these dihydrophenanthridine scaffolds **(Scheme 39)**.

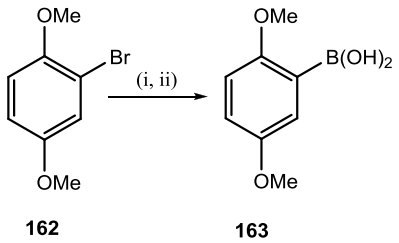
*2.2.1 Synthesis of 2-Bromo-1,4-dimethoxybenzene **162***



Scheme 40 Synthesis of 2-Bromo-1.4-dimethoxybenzene **162** *Reagents and Conditions*; NBS, CH_2Cl_2, reflux, 52 h

The first step in the attempted synthesis of 5,6-dihydrophenanthridine-1,4-dione **161** was the bromination in the 2-position of commercially available 1,4-dimethoxybenzene. The starting material was dissolved in CH_2Cl_2 and brominating agent NBS was added to the solution, which was set to reflux for 52 hours **(Scheme 40)**. The crude product was purified by column chromatography to give the desired product **162** as a clear oil in an 86% yield. The product was characterised by NMR spectroscopy and the spectroscopic data was in agreement with those obtained by Bloomer and Zheng.[90]

*2.2.2 Synthesis of 2,5-Dimethoxyphenylboronic acid **163***

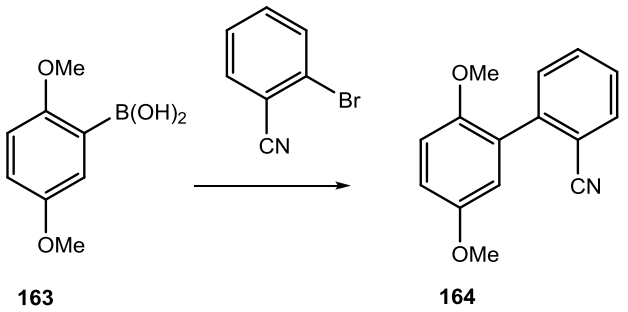


Scheme 41 Synthesis of 2,5-Dimethoxyphenylboronic acid **163** *Reagents and Conditions*; i) *n*-BuLi, THF, -78˚C, 1 h; ii) Trimethyl borate, THF, -78˚C, 1 h

Having successfully synthesised 2-bromo-1,4-dimethoxybenzene **162**, we wished to synthesise the corresponding boronic acid **163 (Scheme 41)**, so as to later attempt the Suzuki coupling to build the required biaryl axis. Starting material **162** was dissolved in dry THF, thoroughly degassed and cooled to -78˚C, before the addition of 2.0 equivalents of organometallic reagent, *n*-BuLi. The resultant solution was stirred for a further hour at -78˚C, trimethyl borate was then added and the solution was stirred for a further hour at -78˚C. The solution quenched with 10% aqueous HCl solution, the organic products extracted and the solvent removed *in vacuo* to afford the boronic acid **163** as a white solid in a 38% yield. The product was not characterised due to solubility and

stability problems and was used directly in the following synthetic step. Although the yield of this reaction was extremely poor, we made no subsequent attempts to improve it as this was meant as merely a model study.

*2.2.3 Synthesis of 2',5'-Dimethoxybiphenyl-2-carbonitrile **164***



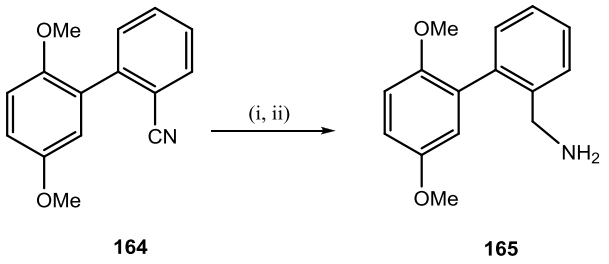
163 **164**

Scheme 42 Synthesis of 2',5'-dimethoxybiphenyl-2-carbonitrile **164** *Reagents and Conditions;* $Pd(PPh_3)_4$, 2M aq. Na_2CO_3, DME, EtOH, reflux, 27 h

Having the required boronic acid **163** in hand, although in poor yield, we now attempted the Suzuki-Miyaura cross-coupling using the same aqueous conditions as previously discussed **(Scheme 36)**. Synthesised 2,5-dimethoxyphenyl boronic acid **163** and commercially available 2-bromobenzonitrile were dissolved in EtOH and DME and added to a reaction vessel containing Suzuki catalyst, $Pd(PPh_3)_4$ under flowing N_2 gas **(Scheme 42)**. 2M Aqueous Na_2CO_3 was then added to the stirring solution and the reaction mixture was set to reflux for 27 hours. The desired product, 2',5'-dimethoxybiphenyl-2-carbonitrile **164**, was isolated as a yellow oil in 57% yield after purification by column chromatography. Although the yield of this reaction is quite poor, it would probably benefit from the use of a purer boronic acid **163** coupling partner. Alternatively to improve the yield, we could also exchange the Suzuki coupling partners and use 2-bromo-1,4-dimethoxybenzene **162** and commercially available 2-cyanophenylboronic acid as previously shown **(Scheme 37)**.

The Suzuki product **164** was characterised by ^{1}H and ^{13}C NMR spectroscopy and the spectroscopic data was in agreement with Al-Fakhri *et al*.[92] A defining characteristic of the ^{1}H NMR spectrum was the presence of 4 additional proton signals, which corresponded well to the inclusion of the benzonitrile motif. The ^{13}C NMR spectrum verifies this observation as there are an additional 4 Ar*C*-H signals in the spectrum as well as 2 new quaternary signals. A signal at 118.6 ppm in the ^{13}C NMR corresponds to the presence of a nitrile functional group in the compound.

*2.2.4 Attempted Synthesis of (2',5'-Dimethoxybiphenyl-2-y)Methanamine **165***



164 **165**

Scheme 43 Attempted Synthesis of (2',5'-Dimethoxybiphenyl-2-y)Methanamine **165** *Reagents and Conditions;* i) 10% Pd/C, conc. HCl, MeOH, rt, 37 h ii) $LiAlH_4$, THF, 0˚C – rt, 2 h

Having successfully synthesised 2',5'-dimethoxybiphenyl-2-carbonitrile **164** we could now attempt the crucial reduction reaction, in the hopes of obtaining (2',5'-dimethoxybiphenyl-2-y)methanamine **165**. The success of this reaction was vital if we wanted to pursue the oxidation reaction and intra-molecular Michael addition to ascertain if this methodology would afford the desired product **161**. Our first attempt saw starting material **164** dissolved in MeOH and treated with 10% Pd/C and conc. HCl in the hydrogenator **(Scheme 43)**. The reaction was stirred for 37 hours at room temperature under a 7kPa atmosphere of H_2 gas. After work-up and purification by column chromatography the yellow oil obtained was characterised by NMR spectroscopy and identified as starting material **164**, which was recovered in a yield of 99%. The ^{1}H NMR spectrum showed no presence of either the benzylic protons or of an N-H and we safely concluded that the isolated product was indeed starting material **164**.

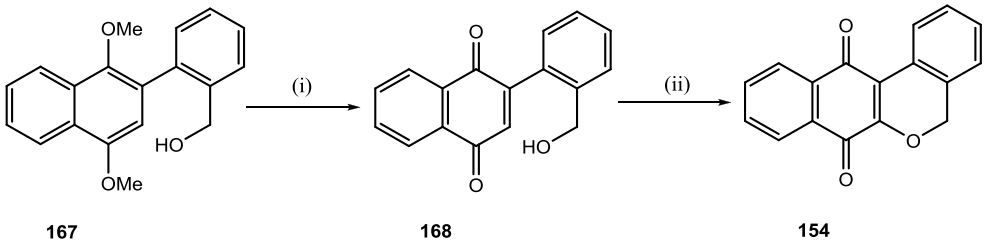
The hydrogenation attempt once again failed to reduce the nitrile to the primary amine as it had done previously when trying to reduce 2-(1,4-dimethoxynaphthalen-2-yl) benzonitrile **159**. This failed reduction effort is probably once more attributed to the stability of the nitrile conferred by conjugation with the aromatic ring. Since we had no way of trying the hydrogenation reactions at higher temperatures, use of the hydrogenator for this transformation was abandoned in favour of other methods.

Our second attempt at reducing compound **164** to the desired primary amine **165**, made use of reducing agent $LiAlH_4$ **(Scheme 43)**. Starting material **164** was dissolved in THF at 0˚C and treated with 20 equivalents of $LiAlH_4$, before being allowed to stir at room temperature for 2 hours. Following the work-up procedure, a yellow oil was isolated which was spectroscopically pure, and once again was identified as starting material **164**.

With this crucial reduction step in the synthesis still proving to be elusive it appears that the only remaining options for perhaps isolating the desired amines **160** and **165** is to try chemical reducing agents at high temperatures. Without obtaining these amine products we will not be able to establish if the oxidation reaction and subsequent intra-molecular Michael addition will be successful in forming the 5,6-dihydro benzo[*b*]phenanthridine-7,12-dione **153** and 5,6-dihydrophenanthridine-1,4-dione **161** scaffolds.

3. Synthesis of 5-*H*-dibenzo[*c,g*]chromene-7,12-dione 154

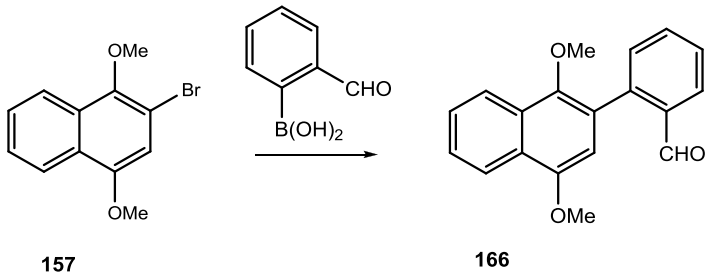
In a final attempt to determine if the proposed methodology **(Scheme 32)** would yield the desired product 5,6-dihydrobenzo[*b*]phenanthridine-7,12-dione **153**, should we obtain the required amine, we turned our focus to the synthesis of the oxygen derivative 5-*H*-dibenzo[*c,g*]chromene-7,12-dione **154**. Feeling certain that we could easily synthesise [2-(1,4-dimethoxynaphthalen-2-yl)phenyl]methanol **167** by following similar synthetic procedures as already discussed, we could then verify if the proposed oxidation reaction and intra-molecular ring closure would give the correct product **154 (Scheme 44)**. Should this attempt yield the desired product, we could then decide if the methodology is worthwhile applying to the phenathridine derivatives **153** and **161**.



167 **168** **154**

Scheme 44 Proposed Methodology for the Synthesis of 5-*H*-dibenzo[*c,g*]chromene-7,12-dione **154** i) oxidation; ii) Michael addition

*3.1 Synthesis of 2-(1,4-Dimethoxynaphthalen-2-yl)benzaldehyde **166***



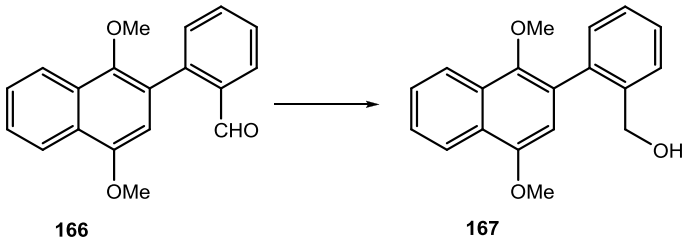
157 **166**

Scheme 45 Synthesis of 2-(1,4-Dimethoxynaphthalen-2-yl)benzaldehyde **166** *Reagents and Conditions;* $Pd(PPh_3)_4$, 2M aq. Na_2CO_3, DME, EtOH, reflux, 73 h

The first step in the synthesis of 5-*H*-dibenzo[*c,g*]chromene-7,12-dione **154** was to construct a biaryl axis from which we could synthesise the rest of the molecule. Once again aqueous Suzuki-Miyaura cross-coupling methodology was used. Previously synthesised 2-bromo-1,4-dimethoxynaphthalene **157** and commercially available 2-formylphenylboronic acid dissolved in EtOH and DME were placed with Suzuki catalyst, $Pd(PPh_3)_4$, in a round bottom flask under an inert atmosphere **(Scheme 45)**. 2 M aqueous Na_2CO_3 was added to the reaction mixture and the solution was heated at reflux for 73 hours. We isolated a white solid from the reaction which was characterised by NMR spectroscopy to be desired product **166**, and was obtained in a 63% yield.

The synthesis of product **166** was confirmed from the ^{1}H NMR spectrum, which showed a clear aldehyde peak at 9.90 ppm. The corresponding carbon signal was found in the ^{13}C NMR spectrum at 192.4 ppm. Other evidence from the NMR spectral data is the presence of 4 additional aromatic proton signals in the ^{1}H spectrum, which coincides with the coupling of the naphthalene motif to the benzaldehyde. These additional signals were also found in the ^{13}C NMR spectrum, along with two new quaternary signals. HRMS shows the exact mass to be 292.1100, for a molecular ion with formula $C_{19}H_{16}O_3$, which compares favourably with the calculated mass of 292.1099. The IR spectrum also showed the clear presence of the aldehyde as signals at 2861cm^{-1}, corresponding to the aldehyde proton and at 1726cm^{-1}, indicating the carbonyl stretch.

*3.2 Synthesis of [2-(1,4-Dimethoxynaphthalen-2-yl)phenyl]methanol **167***



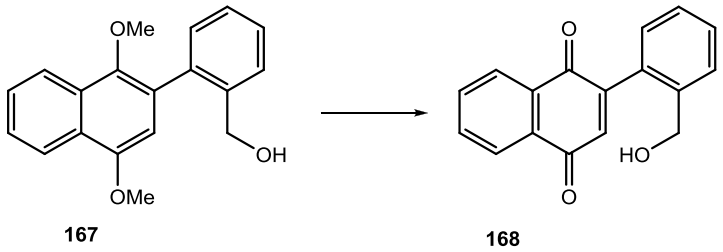
166 **167**

Scheme 46 Synthesis of [2-(1,4-dimethoxynaphthalen-2-yl)phenyl]methanol **167** *Reagents and Conditions;* $LiAlH_4$, THF, 0˚C – rt, 40 min

The next step in the reaction was crucial and involved the reduction of the aldehyde group of 2-(1,4-dimethoxynapthalen-2-yl)benzaldehyde **166** to the benzylic alcohol of [2-(1,4-dimethoxynaphthalen-2-yl)phenyl]methanol **167**. Should this reaction be successful we would finally be able to test whether oxidation and subsequent intra-molecular Michael addition would yield the desired 5-H-dibenzo[*c,g*]chromene-7,12-dione **154** motif **(Scheme 44)**. Starting material **166** was dissolved in dry THF and the solution was cooled to 0˚C before the addition of 3 equivalents of the reducing agent $LiAlH_4$ **(Scheme 46)**. After workup and purification by column chromatography we isolated the desired compound **167** as a white solid in a yield of 98%.

Compound **167** was characterised by NMR spectroscopy, which showed the clear presence of a broad OH signal at 3.56 ppm in the ^1H NMR spectrum. Two distinct doublets at 4.40 ppm were also observed which correspond to the two benzylic protons (CH_2OH). It is thought that there may be some restricted rotation about the biaryl axis, making the two hydrogens diastereotopic and resulting in the observed doublet. The coupling constant of 13.0Hz is further evidence of non-equivalent hydrogens and supports germinal coupling. Further information from the NMR data that the reduction had occurred was the disappearance of the characteristic aldehyde signals in both ^1H and ^{13}C NMR spectra. Compound **167** has a calculated molecular mass of 294.1256 and HRMS showed a clear molecular ion with chemical formula $C_{19}H_{18}O_3$ and a mass of 294.1256. Confirmation that the reduction reaction had in fact occured was the replacement of the aldehyde signals in the IR spectrum with a broad O-H stretch at 3251cm^{-1}.

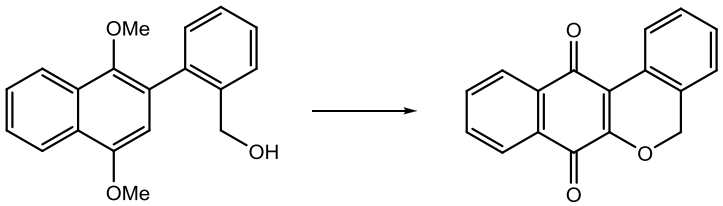
*3.3 Synthesis of 5-H-Dibenzo[c,g]chromene-7,12-dione **154***



167 **168**

Scheme 47 Attempted synthesis of 2-(2-(Hydroxymethyl)phenylnaphthalene-1,4-dione **168** *Reagents and Condtions;* CAN, CH_3CN, CH_3Cl, H_2O, rt - 63˚C, 91 h

Having successfully synthesised [2-(1,4-dimethoxynaphthalen-2-yl)phenyl]methanol **164**, we now wished to determine an appropriate oxidation method to afford 2-(2-(hydroxymethyl)phenylnaphthalene-1,4-dione **168 (Scheme 44)**. Two different strategies were employed in an attempt to bring about this transformation. In our first attempt, starting material **167** was dissolved in CH_3CN and CH_3Cl before the addition of 3 equivalents of oxidant CAN dissolved in H_2O **(Scheme 47)**. The yellow solution was stirred at room temperature for 68 hours after which time a TLC of the reaction mixture revealed only starting material to be present. An additional 3 equivalents of CAN were then added to the solution and the reaction was heated at 63˚C for a further 23 hours. A TLC of the reaction mixture showed the formation of two new products and the reaction was cooled and the organic products extracted. Purification of the reaction mixture by column chromatography isolated two oily products which were characterised by NMR spectroscopy. The NMR spectra however, revealed the products to be unidentifiable compounds which were probably decomposed starting material.



167 **154**

Scheme 48 Synthesis of 5-*H*-dibenzo[*c,g*]chromene-7,12-dione **154** *Reagents and Conditions;* Ag_2O, 6M aq. HNO_3, THF, rt, 30 min

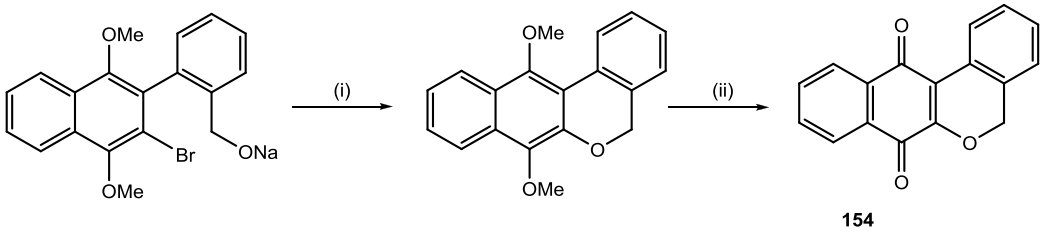
Having been unable to isolate a discernable product from our first oxidation attempt, we tried a different approach. This time starting material **167** was dissolved in dry THF and 6 equivalents of Ag_2O were added to the clear solution **(Scheme 48)**. A 6M aqueous HNO_3 solution was then added to the stirring reaction at which point the Ag_2O was solubilised and the clear solution turned

bright orange. The reaction was stirred for 30 minutes at room temperature after which time the organic solvent was removed *in vacuo* to give a dark red residue. The crude residue was purified by column chromatography to afford a dark red product which was characterised by NMR spectroscopy. From the NMR spectral data it was clear that we had not synthesised desired product **168,** but we had gone one step further and actually isolated the 5-*H*-dibenzo[*c,g*]chromene-7,12-dione **154** in a 60% yield.

Compound **154** is a known compound and comparison of our spectroscopic data with that of Onofrey *et al*. showed good agreement.[80] Perhaps the most obvious evidence that this transformation had occurred was the absence of the two OCH_3 signals in both the ^{1}H and ^{13}C NMR spectra. The ^{13}C NMR now also showed two distinct carbonyl signals at 179.17ppm and 177.19ppm. Another good indication that the ring closure had occurred was the absence of the broad O-H signal in the ^{1}H NMR spectrum. To be absolutely sure that we had isolated compound **154**, a HRMS was performed and showed the desired molecular ion of $C_{17}H_{10}O_3$ at 262.0625, which correlates very well to the calculated mass of 262.0630.

This was an unexpected, but exciting, result as it gave some indication that the ring closing methodology we wished to employ for the synthesis of 5,6-dihydro benzo[*b*]phenanthridine-7,12-dione **153** and 5,6-dihydrophenanthridine-1,4-dione **161** scaffolds may be effective. It was clear that on oxidation of compound **167** the intra-molecular Michael addition occurred spontaneously to afford compound **154**.

4. Synthesis and Mechanistic Studies of 12-Methoxy-6*H*-dibenzo[*c,h*]chromen-6-one 170



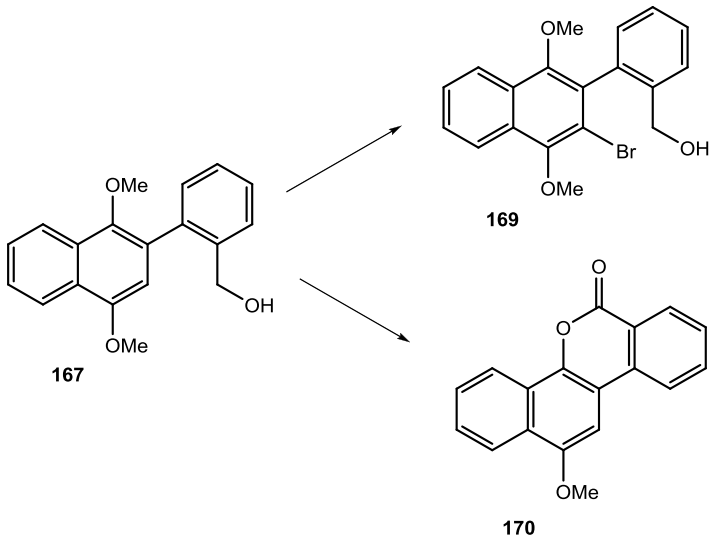
Scheme 49 Proposed Cu(I)Br Catalysed Ring-Closure for the Synthesis of Compound **154** ; i) Cu(I)Br; ii) Oxidation

As a second approach we thought that if we could first close the ring to form the desired polyaromatic scaffold, we could then oxidise it to form the 5-*H*-dibenzo[*c,g*]chromene-7,12-dione **154** with less chance of side reactions occurring **(Scheme 49)**. To perform this transformation we first needed to brominate in the remaining *ortho*-position of compound **167** before removing the alcohol proton and replacing it with a Na^{+} ion.[93] We could then attempt a copper(I)halide-catalysed ring-closure where the *ortho*-bromine is replaced with the oxygen atom, forming the polyaromatic

scaffold.[93] Oxidation of this compound will then hopefully yield the desired product **154 (Scheme 49)**.

*4.1 Synthesis of 12-Methoxy-6H-dibenzo[c,h]chromen-6-one **170***

Before attempting a Cu(I)Br-catalysed ring-closure, we needed to first synthesise the *ortho*-brominated starting material **169 (Scheme 50)**. To a stirring solution of [2-(1,4-dimethoxynaphthalen-2-yl)phenyl]methanol **167** in dry CH_2Cl_2 was added 1 equivalent of NBS. The reaction mixture was stirred at room temperature for 21 h during which time the reaction changed from clear to dark red in colour. After the work-up, the crude product was purified by column chromatography and the white solid was characterised by NMR spectroscopy. From the NMR data it was clear that we had not isolated desired product **169**, but had instead synthesised 12-methoxy-6*H*-dibenzo[*c,h*]chromen-6-one **170** in an 86% yield **(Scheme 50)**.



Scheme 50 Synthesis of 12-Methoxy-6*H*-dibenzo[*c,h*]chromen-6-one **170** *Reagents and Conditions;* NBS, CH_2Cl_2, rt, 21 h

Our spectroscopic data was in agreement with those of Qabaja and Jones and showed clearly that we had in fact synthesised compound **170**.[88] The ^{1}H NMR spectrum showed only one OCH_3 peak at 4.10 ppm; likewise, in the ^{13}C NMR spectrum which showed this signal at 52.3 ppm. The carbonyl signal of the ester was seen clearly at 161.4 ppm in the ^{13}C NMR spectrum. Other evidence to suggest that this was indeed compound **170** was the presence of a clear singlet at 7.21 ppm in the ^{1}H NMR spectrum which corresponded to aromatic proton H^3. We could also no longer see the benzylic protons or the O-H signal in the ^{1}H spectrum, verifying that this ring closure had occurred.

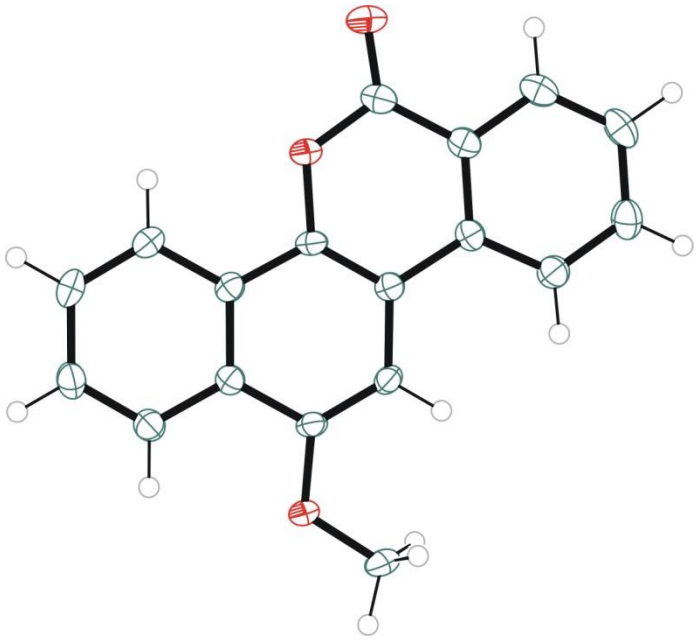


Figure 28 Ortep Diagram of Compound **170**
(Showing the 50% probability thermal ellipsoids for all non-hydrogen atoms).

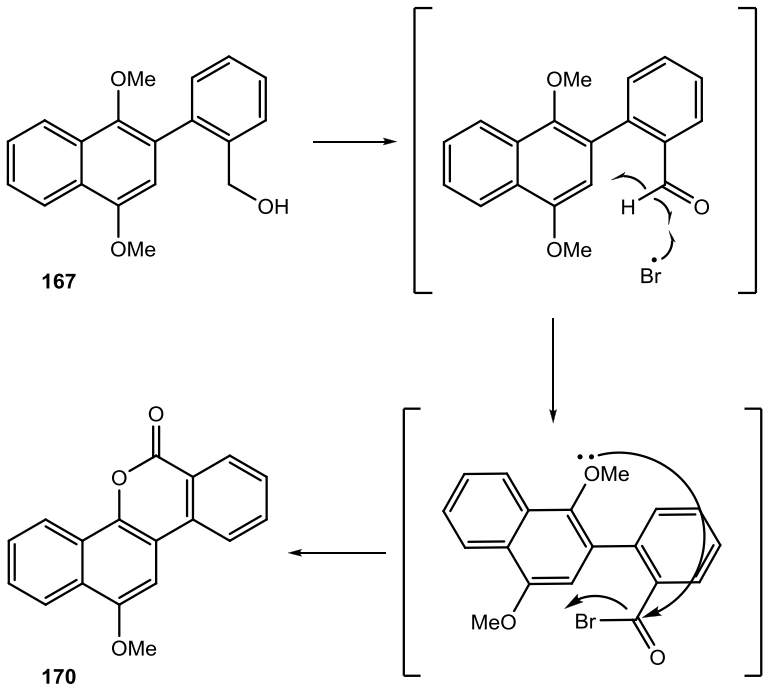
Further evidence that we had indeed synthesised the unexpected compound 12-methoxy-6*H*-dibenzo[*c,h*]chromen-6-one **170** was that an X-ray crystal structure for the compound was obtained **(Figure 28)**. The Ortep diagram of compound **170** clearly shows the benzonaphthopyranone scaffold and corroborates our NMR spectroscopy and HRMS data.

Although we never managed to synthesise the desired compound **169**, this is a far more interesting and novel result and also proved to be highly reproducible. NBS is known to oxidise aldehydes to acid bromides in the presence of a radical initiator, so it not impossible that NBS is firstly oxidising the benzylic alcohol to the aldehyde and then converting the aldehyde to an acid bromide, thereby facilitating the observed ring closure to occur.[94] We will also make an attempt at elucidating the mechanism of this novel result in the discussion to follow. It was this exciting new discovery that led to the second major aim of this project as 12-methoxy-6*H*-dibenzo[*c,h*]chromen-6-one **170** is a scaffold found in a group of natural product antibiotics.[67] These benzonaphthopyranone-containing antibiotics also show some interesting biological applications and the synthesis of these types of compounds is virtually unexplored in the literature.[67] Our second major aim was to thus see if we could extend this NBS oxidation and ring-closing methodology to a variety of other structurally related substrates in the hope of providing a general reaction procedure for the synthesis of a range of benzonaphthopyranone molecules.

*4.2 Mechanistic Studies on the Synthesis of 12-Methoxy-6H-dibenzo[c,h]chromen-6-one **170***

*4.2.1 Mechanistic Study 1: Attempted Synthesis of 12-Methoxy-6H-dibenzo[c,h] chromen-6-one **170** from Aldehyde Intermediate **166***

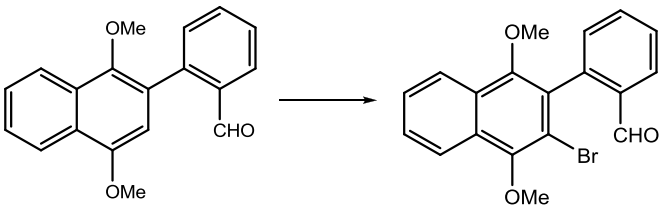
The proposed mechanism for the novel NBS ring-closure, which resulted in the synthesis of 12-methoxy-6*H*-dibenzo[*c,h*]chromen-6-one **170** from 2-(1,4-dimethoxynaphthalen-2-yl)phenyl)methanol **167**, is thought to proceed from the use of NBS as an oxidising agent **(Scheme 51)**. It is speculated that NBS oxidises the benzylic alcohol to an aldehyde releasing radicals into the solution. NBS is known to oxidise aldehydes to acid bromides under radical mediation, and it is believed that this is what is occurring during our reaction.[94] Once the activated acid bromide intermediate has been formed, nucleophilic attack of the methoxy group on the carbonyl of the acid bromide will result in the ring-closure as the halide is an excellent leaving group. There is literature precedent for this type of substitution reaction and numerous examples show the use of the activated acid bromide as an intermediate on route to the synthesis of esters or amides.[94, 95]



Scheme 51 Proposed Mechanism for the Synthesis of **170** Using NBS as a Radical Oxidising Agent

In order to determine if the proposed mechanism is a viable one we wished to see if treatment of the aldehyde intermediate **166** with NBS under radical mediation would afford the final ring-closed product **170**. Should this reaction succeed in yielding product **170** we could conclude that the benzylic alcohol of compound **167** is indeed being oxidised by NBS to the aldehyde, before being converted to the acid bromide and undergoing ring closure. To test this hypothesis 2-(1,4-

dimethoxynaphthalen-2-yl)benzaldehyde **166** was dissolved in CH_2Cl_2 and treated with NBS and AIBN **(Scheme 52)**. After 21 hours a TLC of the reaction solution revealed only starting material and an extra equivalent of NBS and AIBN were added to the stirring solution. The reaction was stirred for a further 23 hours before being quenched with saturated aqueous Na_2SO_3. The organic products were extracted and the solvent removed *in vacuo* to afford a white solid which was purified by column chromatography. The purified white solid was characterised by NMR spectroscopy and was identified, not as desired product **170**, but as *ortho*-brominated product 2-(3-bromo-1,4-dimethoxynaphthalen-2-yl)benzaldehyde **171** in 88% yield **(Scheme 52)**.



166 **171**

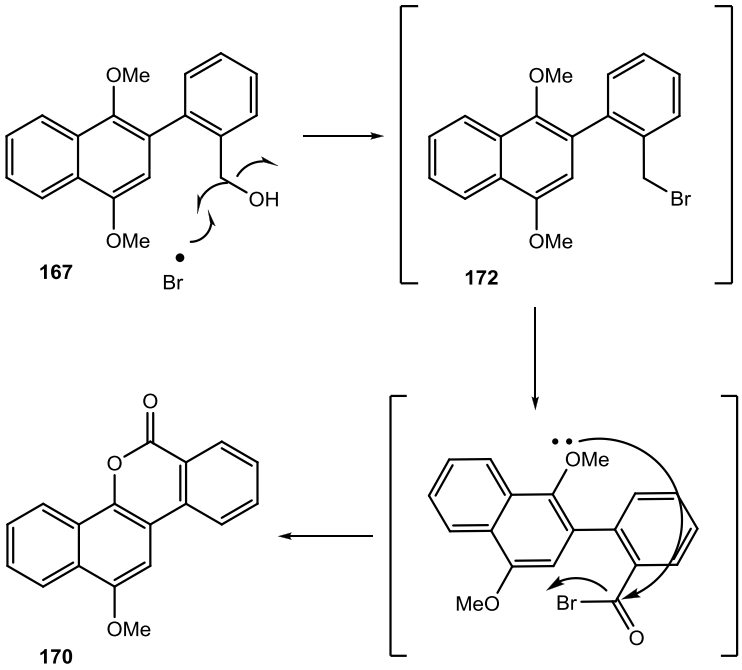
Scheme 52 Synthesis of 2-(3-Bromo-1,4-dimethoxynaphthalen-2-yl)benzaldehyde **171** *Reagents and Conditions;* NBS, AIBN, CH_2Cl_2, rt, 44 h

The NMR data confirmed that we had not synthesised the desired compound **170**, but rather brominated compound **171**. This product was characterised by the disappearance of the singlet aromatic hydrogen in the ^{1}H NMR spectrum due to bromination in the position *ortho* to the methoxy group. No ring-closure had occurred as we could still observe two methoxy signals in the ^{1}H NMR spectrum at 4.02 ppm and 3.48 ppm and the corresponding carbon signals were found at 150.8 ppm and 150.3 ppm in the ^{13}C NMR spectrum. There was also the presence of the aldehyde proton in the ^{1}H NMR spectrum, which was conclusive evidence that the aldehyde had not been converted to the acid bromide. HRMS showed the presence of two molecular ions, each one corresponding to a different bromine isotope. The molecular ions have masses of 370.0201 and 372.0162 corresponding to the two isotopes $C_{19}H_{15}O_3{}^{79}Br$ and $C_{19}H_{15}O_3{}^{81}Br$ respectively. These values compare favourably with the calculated values. The IR spectrum of compound **171** showed the presence of the aldehyde C-H stretch at 2850cm^{-1} and the C=O stretch at 1727cm^{-1}. As these signal stretches are still visible in the IR spectrum we can conclude that the ring closure from the aldehyde to the ester did not occur.

*4.2.2 Mechanistic Study 2: Attempted Synthesis of 12-Methoxy-6H-dibenzo[c,h]chromen-6-one **170** from Benzylic Bromide Intermediate **172***

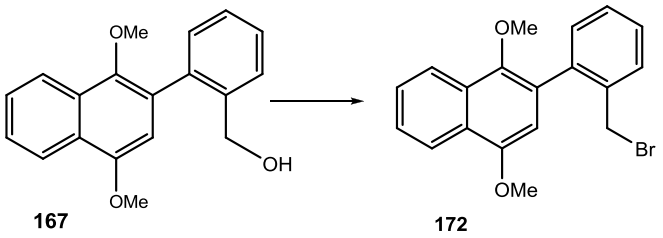
Having been unable to show that the mechanism for the NBS ring-closure proceeded from the aldehyde intermediate **166** to the desired compound **170**, we proposed another mechanism which advanced via a benzylic bromide intermediate **172 (Scheme 53)**. It was thought that the benzylic

alcohol of compound **167** was perhaps being converted to a benzylic bromide intermediate **172** under radical conditions. NBS could then perhaps oxidise this intermediate to the required acid bromide needed for the ring-closure to occur, affording 12-methoxy-6*H*-dibenzo[*c,h*]chromen-6-one **170**.



Scheme 53 Proposed Mechanism for the Synthesis of 12-methoxy-6*H*-dibenzo[*c,h*]chromen-6-one **170** via a Benzylic Bromide Intermediate

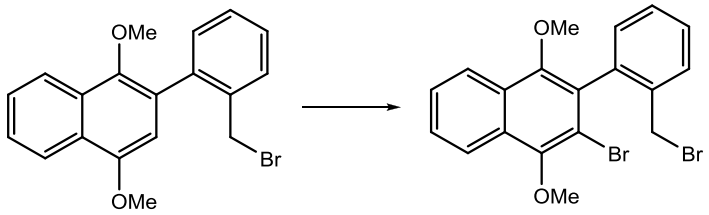
Before we could test if this was a viable reaction mechanism we first needed to synthesise the benzyl bromide intermediate **172**. Previously synthesised [2-(1,4-dimethoxynaphthalen-2-yl)phenyl]methanol **167** was dissolved in dry CH_2Cl_2 in a 2-neck round bottom flask fitted with a $CaCl_2$ drying tube. It was important to exclude all moisture from the reaction as we did not want the reverse reaction to occur once we had synthesised 2-[2-(bromomethyl)phenyl]-1,4-dimethoxy naphthalene **172**. Next, 5 equivalents of both PPh_3 and CBr_4 were added to the solution and the reaction was left to stir at room temperature for 3 hours **(Scheme 54)**. After this time the solvent was removed *in vacuo* and the resultant orange residue was purified by column chromatography to afford the product **172** as a yellow oil in a 95% yield.



Scheme 54 Synthesis of 2-[2-(Bromomethyl)phenyl]-1,4-dimethoxynaphthalene **172** *Reagents and Conditions;* PPh_3, CBr_4, CH_2Cl_2, rt, 3 h

Compound **172** was characterised by NMR spectroscopy and strong evidence that the benzylic alcohol had indeed been converted to the benzylic bromide was the absence of an O-H signal in the ^{1}H NMR spectrum. Further evidence to support this transformation was an upfield shift of the *C*H_2Br signal which was now found at 32.6 ppm in the ^{13}C NMR spectrum. As the bromine atom is less electronegative than the oxygen atom we expected the benzylic carbon to shift upfield, which it did in comparison to the *C*H_2OH signal which was found at 64.1 ppm in the ^{13}C NMR spectrum. Since there was only a small difference between the NMR spectra of compound **167** and compound **172**, an HRMS was performed to determine if the bromination reaction had occurred. Strong evidence for the presence of the bromine atom was that two molecular ions were observed in the HRMS spectrum each one corresponding to a different bromine isotope. HRMS shows the exact mass for $C_{19}H_{17}O_2{}^{79}Br$ to be 356.0391 and for $C_{19}H_{17}O_2{}^{81}Br$ to be 358.0374, which compared very well to the calculated values of 356.0412 and 358.0392. The IR spectrum for compound **167** no longer showed an O-H stretch, this confirms the disappearance of the alcohol group.

Having successfully synthesised the required benzylic bromine intermediate **172**, we now set out to test whether treatment of this intermediate with NBS and a radical initiator would give us the desired 12-methoxy-6*H*-dibenzo[*c,h*]chromen-6-one **170**. To a stirring solution of 2-[2-(bromomethyl)phenyl]-1,4-dimethoxy naphthalene **172** in CH_2Cl_2 was added NBS and AIBN and the resulting yellow solution was allowed to stir at room temperature for 64 hours **(Scheme 55)**. Following this time the organic products were extracted and the organic solvent was removed *in vacuo* to yield an off-white solid which was spectroscopically pure and needed no further purification. Unfortunately the isolated product was not the desired compound **170**, but was again identified as having been brominated in the position *ortho* to the methoxy group, affording compound **173** in an 88% yield.



172 **173**

Scheme 55 Synthesis of 2-Bromo-3-[2-(bromomethyl)phenyl]-1,4-dimethoxy naphthalene **173** *Reagents and Conditions;* NBS, AIBN, CH_2Cl_2, rt, 64 h

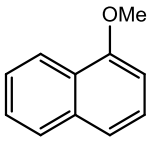
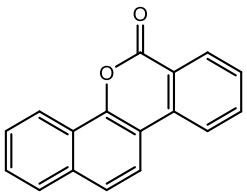
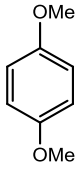
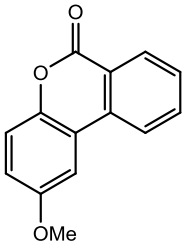
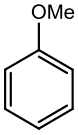
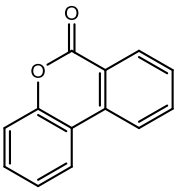
Compound **173** was once again characterised by NMR spectroscopy and perhaps the only evidence that bromination *ortho* to the methoxy on the naphthalene had occurred was the disappearance of the singlet proton signal from the ^{1}H NMR spectrum. It is also clear from the NMR spectra that no desired ring-closure had occurred as we could still see the presence of both OCH_3 groups in the ^{1}H and ^{13}C NMR spectra. Also the benzylic protons were still evident in the ^{1}H NMR spectrum at 4.44ppm - 4.30ppm and this indicated that oxidation to the acid bromide had not occurred. HRMS further confirmed that additional bromination had occurred as this time the spectrum showed the presence of three molecular ions corresponding to the three bromine isotope patterns we were likely to see, namely: $^{79}Br^{79}Br$, $^{79}Br^{81}Br$ and $^{81}Br^{81}Br$. These molecular ions were found at 433.9511, 435.9491 and 347.9467 and corresponded to compounds of molecular formulae $C_{19}H_{16}O_2{}^{79}Br_2$, $C_{19}H_{16}O_2{}^{79}Br^{81}Br$ and $C_{19}H_{16}O_2{}^{81}Br_2$, respectively.

Although we were unable to conclusively prove either one of our proposed reaction mechanisms it is still thought that mechanism 1 **(Scheme 51)**, which proceeds via an aldehyde intermediate, is a more viable approach. This is due to the fact that NBS is known to oxidise aldehydes to the corresponding acid bromides under radical conditions.[94] Perhaps we need to vary the reaction conditions in order to test whether the aldehyde intermediate **166** will give the desired ring-closed product 12-methoxy-6*H*-dibenzo[*c,h*]chromen-6-one **170**. Literature suggests that the use of benzoyl peroxide as a radical initiator, as opposed to AIBN, may lead to the conversion of the aldehyde to the acid bromide, allowing the ring-closure to occur.[95] We could also attempt the conversion of the aldehyde to the acid bromide using a much higher boiling solvent, e.g. $CHCl_3$ or chlorobenzene, and actually heat the reaction in the hope of isolating compound **170**.[94] Another means of verifying that reaction mechanism 1 is responsible for the synthesis of compound **170** is to try to do the NBS ring closure on the *ortho*-brominated aldehyde intermediate **171**. Seeing that the more favourable bromination reaction has already been performed, it may be possible that treatment of compound **171** with NBS and a radical initiator would oxidise the aldehyde to the acid bromide and ring-closure could then occur. Unfortunately due to time constraints on the project these strategies were never tested and the actual mechanism for the transformation of benzylic alcohol **167** to 12-methoxy-6*H*-dibenzo[*c,h*]chromen-6-one **170** remains to be elucidated.

5. Expansion of the NBS Radical Oxidation Ring Closing Methodology for the Synthesis of Related Naphthopyranone Scaffolds

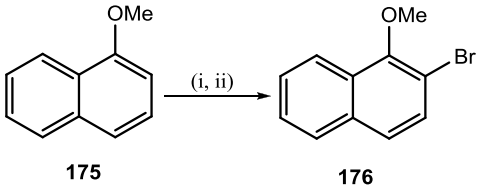
Having been able to synthesise compound **170** from the benzylic alcohol **167** using NBS, we wished to determine if we could extend this methodology to the synthesis of a variety of related naphthopyranone scaffolds **(Table 8)**. As part of this study we wished to ascertain if this methodology could be applied in a reproducible fashion to different substrates, in the hope of determining an efficient method for the synthesis of napthopyranone scaffolds. We also wished to test which functional groups of the compound **167** were crucial to the synthesis of compound **170**. Our subsequent starting materials thus focused on determining if the 1,4-dimethoxy aromatic system and/or a naphthalene system were crucial to the success of the reaction as illustrated in **Table 8**.

Table 8: Different Starting Substrate and the Desired Naphthopyranone Motif

Starting Material	Naphthopyranone Product
 **175**	 **174**
	 **177**
	 **181**

*5.1 Attempted Synthesis of 6H-Dibenzo[c,h]chromen-6-one **174***

*5.1.1 Attempted Synthesis of 2-Bromo-1-methoxynaphthalene **176***



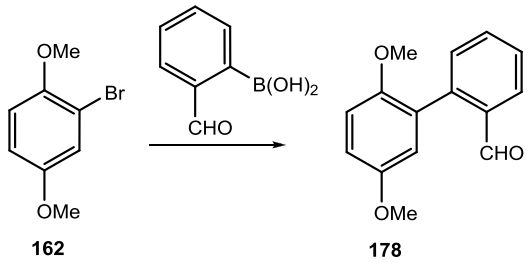
Scheme 56 Attempted Synthesis of 2-Bromo-1-methoxynaphthalene **176** *Reagents and Conditions;* i) *n*-BuLi, THF, 0˚C, 1 h; ii) Br_2, THF, 0˚C – rt, 1 h

Before we could begin building the required ring-closing substrate to test whether the presence of a single methoxy group on the naphthalene motif would allow for the synthesis of naphthopyranone **174 (Table 8)** under the radical oxidation conditions, we needed to brominate in the *ortho*-position. Knowing that the use of a brominating agent such as NBS would only afford the *para*-brominated product, we attempted to use directed-*ortho* metallation (DOM) to synthesise the desired *ortho*-brominated product **176 (Scheme 56)**. To achieve this starting material 1-methoxynaphthalene **175**, dissolved in THF, was placed under an inert N_2 atmosphere in a two-neck round bottom flask. The solution was cooled to 0˚C before the addition of *n*-BuLi which saw the yellow solution turn dark green, indicating that metallation had occurred. The solution was then stirred at 0˚C for 1 h after which time Br_2, which was dissolved in dry THF, was added dropwise to the solution by way of a dropping funnel until a dark orange colour was obtained. The reaction was subsequently allowed to heat to room temperature and stirred for a further 1 h before being quenched with saturated aqueous Na_2SO_3. The organic products were extracted and the solvent removed *in vacuo* to afford a crude brown oil, which was further purified by column chromatography to yield a yellow oil which was identified to be starting material **175**.

NMR spectroscopy confirmed that no bromination had occurred as all seven protons were still visible in the ^{1}H NMR spectrum. A literature survey revealed that no previous syntheses of *ortho*-bromination of this compound had been reported and it was also impossible to obtain compound **176**, or its corresponding boronic acid, as commercially available compound from a fine chemicals supplier. We had to thus abandon this synthesis and could not establish if the NBS radical oxidation methodology would work in the case of the synthesis of compound **174**.

*5.2 Attempted Synthesis of 2-Methoxy-6H-benzo[c]chromen-6-one **177***

*5.2.1 Synthesis of 2',5'-Dimethoxybiphenyl-2-carbaldehyde **178***



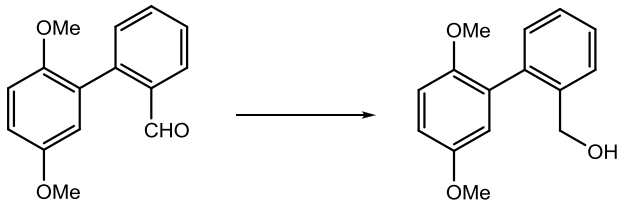
162 **178**

Scheme 57 Synthesis of 2',5'-Dimethoxybiphenyl-2-carbaldehyde **178** *Reagents and Conditions;* $Pd(dba)_2$, PPh_3, 2M aq. Na_2CO_3, DME, EtOH, reflux, 19 h

Before we could test whether the NBS radical oxidation ring-closing procedure would afford the desired compound **177 (Table 8)** we needed to build the biaryl axis from which we could acquire the pre-ring closing substrate. Suzuki-Miyaura cross coupling was once again employed to afford the desired compound **178 (Scheme 57)**. Having depleted our available supply of $Pd(PPh_3)_4$ we decided to attempt the synthesis of $Pd(PPh_3)_4$ *in situ* from $Pd(dba)_2$ and then adding the compounds needing to be coupled in Suzuki fashion. $Pd(dba)_2$ was then dissolved in DME in a round bottom flask and the resultant purple solution was degassed with N_2 and placed under an inert atmosphere. Next PPh_3 was dissolved in DME, degassed and added to the reaction mixture and the solution was stirred at room temperature for 30 minutes during which time the solution changed from purple to yellow in colour, indicating that $Pd(PPh_3)_4$ had been synthesised. Previously synthesised 2-bromo-1,4-dimethoxybenzene **162** and commercially available 2-formylphenylboronic acid were then dissolved in DME and EtOH, degassed and added to the yellow solution **(Scheme 57)**. Finally an aqueous 2M Na_2CO_3 solution was degassed, added to the stirring solution and the reaction mixture was set to reflux for 19 hours before being quenched with H_2O. The organic products were extracted and the solvent removed *in vacuo* to afford a crude brown oil, which was purified by column chromatography to afford product **178** as a light brown oil in a 64% yield.

Compound **178** was characterised by NMR spectroscopy and the spectroscopic data was in agreement with Zhao *et al*.[96] The compound was identified by the presence of the aldehyde proton at 9.79 ppm in the ^1H NMR spectrum and the aldehyde carbonyl carbon at 192.5 ppm in the ^{13}C NMR spectrum. Further evidence to suggest that the Suzuki-coupling had occurred was the occurrence of four additional proton signals in the ^1H NMR spectrum, which was confirmed by the presence of four additional aromatic C-H signals in the ^{13}C NMR spectrum.

*5.2.2 Synthesis of (2',5'-Dimethoxybiphenyl-2-yl)methanol **179***



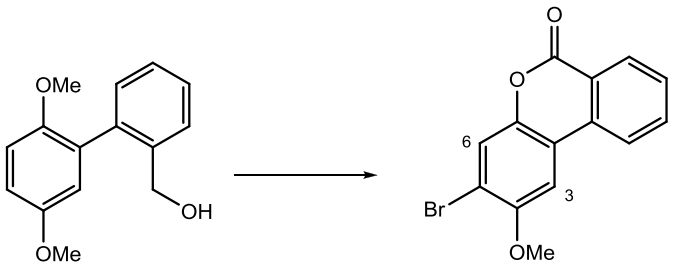
178 **179**

Scheme 58 Synthesis of (2',5'-Dimethoxybiphenyl-2-yl)methanol **179** *Reagents and Conditions;* $LiAlH_4$, THF, rt, 2 h

Having successfully synthesised compound **178**, we could now reduce the aldehyde to the benzylic alcohol to afford the pre-ring closure product **179 (Scheme 58)**. Starting material 2',5'-dimethoxybiphenyl-2-carbaldehyde **178** was dissolved in dry THF and treated with 3.0 equivalents of $LiAlH_4$. The resulting solution was stirred at room temperature for 2 h before being quenched with H_2O, the organic products extracted and the organic solvent removed *in vacuo* to afford an oily residue. Purification of the crude product by flash chromatography afforded the desired compound **179** as a clear oil in an 80% yield.

The compound was characterised by NMR spectroscopy and both the ^{1}H and ^{13}C NMR spectra no longer showed the presence of the aldehyde moiety in the molecule. In addition the ^{1}H NMR spectrum showed a broad singlet at 2.78 ppm corresponding to the O-H group and a signal at 4.39 ppm which corresponded to the benzylic protons. The ^{13}C NMR spectrum verified this observation and showed a signal at 63.5 ppm coinciding with the benzylic carbon, CH_2OH. HRMS further verified that the reduction had occurred and showed a molecular ion at 244.1031 corresponding to a molecular formula of $C_{15}H_{16}O_3$. IR spectroscopy of compound **179** confirmed that the reduction reaction had occurred by the disappearance of the aldehyde signals and the presence of an O-H stretch at 3420cm^{-1}.

*5.2.3 Attempted Synthesis of 2-Methoxy-6H-benzo[c]chromen-6-one **177***



179 **180**

Scheme 59 Synthesis of 3-Bromo-2-methoxy-6*H*-benzo[*c*]chromen-6-one **180** *Reagents and Conditions;* NBS, AIBN, $CHCl_3$, rt – reflux, 21 h

Having the pre-ring closure product **179** in hand we now wished to determine whether treatment of this compound with NBS would yield the desired 2-methoxy-6*H*-benzo[*c*]chromen-6-one **177 (Table 8)**. Starting material (2',5'-dimethoxybiphenyl-2-yl)methanol **179** was dissolved in $CHCl_3$ and 1.0 equivalent of NBS and 0.2 equivalents of AIBN were added to the solution **(Scheme 59)**. The AIBN was added for this reaction as the same synthesis attempted using only NBS failed to afford the desired product. After stirring at room temperature for 16 hours a TLC revealed only starting material to be present and the reaction was thus set to reflux for 3 hours, after which time the clear solution had turned orange. The organic products were then extracted, the solvent removed *in vacuo* and purified by column chromatography to yield a white solid. This white solid was characterised by NMR spectroscopy and revealed not to be desired compound **177 (Table 8)**, but rather the desired brominated compound 3-bromo-2-methoxy-6*H*-benzo[*c*]chromen-6-one **180 (Scheme 59)** which was isolated in a 32% yield.

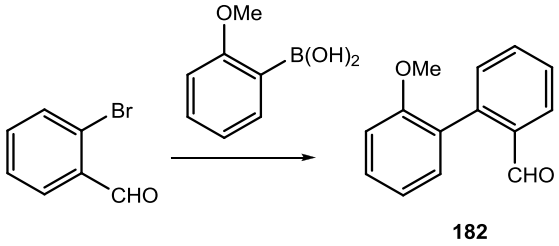
Both the ^{1}H and ^{13}C NMR spectra provide strong evidence that compound **180** had been synthesised, as we see the presence of only one methoxy peak in both spectra. A clear carbonyl signal was seen at 160.7 ppm in the ^{13}C NMR which corresponded to the ester carbonyl carbon and indicated that oxidation had in fact occurred. We are also certain that bromination in an *ortho*-position to a methoxy group did occur as the ^{1}H NMR spectrum does not integrate for the required number of protons in compound **177**. The clear singlet at 7.46 ppm in the ^{1}H NMR spectrum was another good indication that this *ortho*-bromination had occurred. We suspect that bromination occurred in the 5-position and not in the 6- or 3-positions as we would not have seen the clear singlet, but rather a doublet with a *ortho*-coupling constant of at least 8.0 Hz or a doublet with a *meta*-coupling constant of about 1.2 Hz respectively. HRMS confirmed that compound **180** had been synthesised as it showed two clear molecular ion peaks each corresponding to one of the bromine isotopes, ^{79}Br and ^{81}Br. These molecular ion peaks were found at 303.9741 and 305.9720 and coincided with compounds of molecular formulae $C_{14}H_9O_3{}^{79}Br$ and $C_{14}H_9O_3{}^{81}Br$. The IR

spectrum of compound **180** provided some evidence that the ring closure had occurred, as the O-H stretch of compound **179** had disappeared and was replaced by the C=O stretch of an ester at 1734cm^{-1}.

It was thought that since NBS is known to oxidise aldehydes to acid bromides under radical conditions we decided to use a radical initiator for this reaction, as opposed to just treatment with NBS.[94] A higher boiling solvent than CH_2Cl_2 was also used should we require added activation energy to afford the desired transformation, which was the case during our reaction. It appears that the NBS radical oxidation ring-closure can be applied to different substrates which contain a di-methoxy motif, as indicated by the synthesis of compound **180**. Although the yield of this reaction was quite poor it is believed that this yield can be improved upon. Our reaction was performed on a 30mg scale with potential for losses during work-up and column chromatography procedures, and had this reaction been performed on a larger scale we may have isolated the product in a higher yield. Furthermore it may be impossible to synthesise compound **180** without the NBS brominating in the *ortho*-position to one of the methoxy groups as well. This due to the fact that NBS is a known brominating agent and bromination *ortho* to a methoxy group is the first desired reaction. This has two important consequences; one it may lead to losses in the yield of isolated product **180** and we may need to use two equivalents of NBS for compounds which can still undergo bromination reactions; and two, we could use this brominated scaffold as a handle for further Suzuki-coupling reactions which may allow us to build larger and more complex naphthopyranone products. One may be asking why bromination did not occur at the 3-position of compound **170 (Scheme 50)** and it is believed that classic steric hindrance may be a factor.[46] The 5-position in compound **180** provided a sterically unhindered position where bromination could occur, and this is another reason why we believe that bromination occurred at this site and not in the 3- or 6-postions.

*5.3 Attempted Synthesis of 6H-Benzo[c]chromen-6-one **181***

*5.3.1 Synthesis of 2-Methoxybiphenyl-2-carbaldehyde **182***



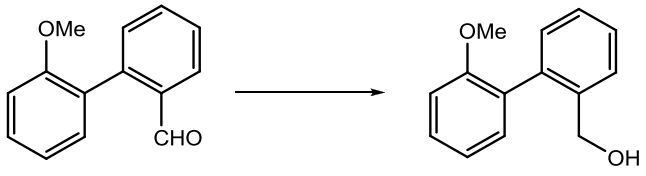
182

Scheme 60 Synthesis of 2-Methoxybiphenyl-2-carbaldehyde **182** *Reagents and Conditions;* $Pd(dba)_2$, PPh_3, 2M aq. Na_2CO_3, DME, EtOH, reflux, 26 h

We also wished to determine whether NBS could be used to synthesise 6*H*-benzo[*c*]chromen-6-one **181**, if we started with anisole **(Table 8)**. This synthesis would play an integral part in determining whether the NBS ring-closure could only be applied to di-methoxy containing substrates, or if this transformation was a completely general reaction. In order to begin the synthesis of compound **181 (Table 8)**, we once more first needed to build the biaryl axis of the pre-ring closure compound. Once again $Pd(dba)_2$ and PPh_3 were dissolved in DME, degassed and allowed to stir under an inert atmosphere for 30 minutes to produce $Pd(PPh_3)_4$ *in situ*. After this time, commercially available starting materials 2-methoxyphenylboronic acid and 2-bromobenzaldehyde were dissolved in DME and EtOH, degassed and added to the now yellow solution **(Scheme 60)**. A degassed 2M aqueous Na_2CO_3 solution was then added to the reaction mixture and the reaction was heated at reflux for 26 h. The organic products were extracted and the solvent removed *in vacuo* to give a crude brown oil, which was further purified by flash chromatography to afford the product **182** as a yellow oil in a 99% yield.

The compound **182** was characterised by NMR spectroscopy and the spectroscopic data was in agreement with those of Zhao *et al*.[96] A defining characteristic of the synthesised compound was the presence of the aldehyde proton in the ^{1}H NMR spectrum at 9.79 ppm and the aldehyde carbonyl in the ^{13}C NMR spectrum at 192.6 ppm. Further evidence that the Suzuki-coupling reaction had occurred was that the ^{1}H NMR spectrum integrated for the correct number of aromatic protons and also showed the OCH_3 signal as a clear singlet at 3.73 ppm.

*5.3.2 Synthesis of (2'-Methoxybiphenyl-2-yl)methanol **183***



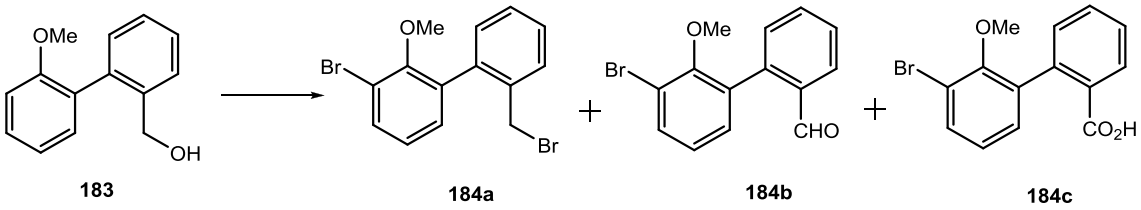
182 **183**

Scheme 61 Synthesis of (2'-Methoxybiphenyl-2-yl)methanol **183** *Reagents and Conditions;* $LiAlH_4$, THF, rt, 15 min

Having successfully synthesised compound **182** we could now reduce the aldehyde to the benzylic alcohol **183 (Scheme 61)**, which we required for the NBS radical oxidation reaction. To a stirring solution of 2-methoxybiphenyl-2-carbaldehyde **182** in dry THF was added 3.0 equivalents of $LiAlH_4$ and the resultant solution was left to stir at room temperature for 15 min. The extracted organic product was purified by flash chromatography to give the desired product **183** as a clear oil in a 76% yield.

Compound **183** was characterised by NMR spectroscopy and both the ^{1}H and ^{13}C NMR spectra showed that the aldehyde had indeed been reduced to the benzylic alcohol as there was no evidence of the aldehyde proton or carbonyl. The ^{1}H NMR spectrum showed a broad singlet at 2.60 ppm which corresponded to the O-H and a signal at 4.36ppm which corresponded to the benzylic protons. The benzylic carbon signal CH_2OH is found in the ^{13}C NMR spectrum at 63.4 ppm. HRMS further corroborated that the correct compound had been synthesised as there was a molecular ion peak at 214.0986 which corresponded to $C_{14}H_{14}O_2$ molecular formula of compound **183**. Further evidence that the reduction reaction had occurred was provided by the presence of an O-H stretch at 3219cm^{-1} in the IR spectrum of compound **183**.

*5.3.3 Attempted Synthesis of 6H-Benzo[c]chromen-6-one **181***



Scheme 62 Attempted Synthesis of 6*H*-Benzo[*c*]chromen-6-one **181** *Reagents and Conditions;* NBS, AIBN, $CHCl_3$, reflux – rt, 53 h

Having successfully synthesised compound **183** we wanted now to determine if treatment with NBS and a radical initiator would lead to the synthesis of 6*H*-benzo[*c*]chromen-6-one **181 (Table 8)**. To a stirring solution of starting material **183** dissolved in $CHCl_3$ were added 1.0 equivalent of NBS and 0.2 equivalents of radical initiator AIBN **(Scheme 62)**. The solution was heated at reflux for 6 hours, cooled and stirred at room temperature for a further 47 hours. After this time the solution was quenched with saturated aqueous Na_2SO_3, the organic products were extracted and the solvent removed *in vacuo* to give a crude residue. This residue was purified by flash chromatography to afford two products, an off-white solid which was characterised to be product **184a** in a 22% yield, and a white solid which was thought to be products **184b** or **184c (Scheme 62)**. The compounds were inseparable by chromatography or recrystallisation and made characterisation of these compounds very difficult.

Compound **184a** was characterised by NMR spectroscopy and both the ^{1}H and ^{13}C NMR spectra provided strong evidence that this was not the desired compound **181**. The presence of the methoxy group in the ^{1}H NMR at 3.73ppm and in the ^{13}C NMR at 55.76ppm verified that the oxidation and ring-closure had not occurred. The OH group of compound **183** has also been replaced by a bromine atom; this is shown by the disappearance of the O-H signal in the ^{1}H NMR spectrum and the upfield shift of the benzylic carbon CH_2Br to 31.85ppm, as opposed to 63.40ppm for the CH_2OH. It was also observed that bromination has occurred as the ^{1}H NMR spectrum only

integrates for 7 aromatic protons as opposed to 8 expected aromatic protons. HRMS was also performed, but provided no valuable information about the compound as a molecular ion or a discernable fragment was not obtained. IR spectroscopy also helped confirm that the benzylic alcohol of compound **183** had been replaced by a bromine atom, as the spectrum of **184a** did not show the presence of the O-H stretch.

We also attempted to characterise the compounds **184b** and **184c** by NMR spectroscopy, but as these compounds were inseparable the NMR spectra were not very helpful in properly identifying the molecules. Certain key characteristics were present in the ^{1}H NMR spectrum and were used to give some direction to our assignment of the white solid as compounds **184b** and **184c**. The presence of an aldehyde proton was seen at 9.77 ppm, which corresponded to the characterisation of one of these compounds as an aldehyde. We could also see what may be an O-H signal at 1.73 ppm and leads to the characterisation of the other compound as a carboxylic acid. This O-H signal is more probably from a carboxylic acid and not a benzylic alcohol as the ^{1}H NMR spectrum shows no presence of these benzylic protons. IR spectroscopy proved very helpful in this instance as it helped to confirm the suspicion that the inseparable compounds **184b** and **184c** may indeed be aldehyde and carboxylic acid respectively. The IR spectrum showed an O-H stretch at 3071cm^{-1}, which likely corresponds to a carboxylic acid. It also showed two C=O stretches at 1727cm^{-1} and 1694cm^{-1}; which correspond to the carbonyl groups of an aldehyde and a carboxylic acid respectively. HRMS was also used as a characterisation tool and it was hoped that we would obtain molecular ions for both compound **184b** and **184c**; however, the spectrum only showed the molecular ions of compound **184b**. Two molecular ions were shown for compound **184b** corresponding to the two bromine isotopes, these were found for $C_{14}H_{11}O_2{}^{79}Br$ at 289.9941 and for $C_{14}H_{11}O_2{}^{81}Br$ at 291.9928.

It is important to note that many assumptions were made in the assignment of structures **184a-c** to the compounds isolated as no characterisation evidence was conclusive. It must also be noted that it is not known if these compounds underwent bromination in the position *ortho* or *para* to the methoxy group as both cases are equally as likely. However it is clear that the NBS ring-closing procedure has not given us the desired compound **181**, but it has provided us with some insight into the mechanism. From our results it is observed that NBS can convert a benzylic alcohol to a benzylic bromide under radical conditions and provides some credit to proposed mechanism 2 **(Scheme 53)**. However since the second fraction was isolated in a much higher yield it is perhaps more likely that mechanism 1 **(Scheme 51)** is being followed, i.e. the oxidation of the benzylic alcohol to an aldehyde. In this case NBS takes this oxidation one step further and may actually oxidise the aldehyde to the carboxylic acid. It appears unlikely that NBS is able to elicit the ring-closure on compounds which only contain a single methoxy group. This may be due to electronic enriching factors of an added methoxy group, but the reason is not fully understood. This may seem disappointing at first, but in order to synthesise most of the naphthopyranone-containing

natural products we would require the presence of both methoxy groups. There exists only one natural product which does not require the presence of the extra methoxy group, that compound is arnottin 1 **131 (Figure 25)**.[67]

Chapter 6: Conclusions and Future Work

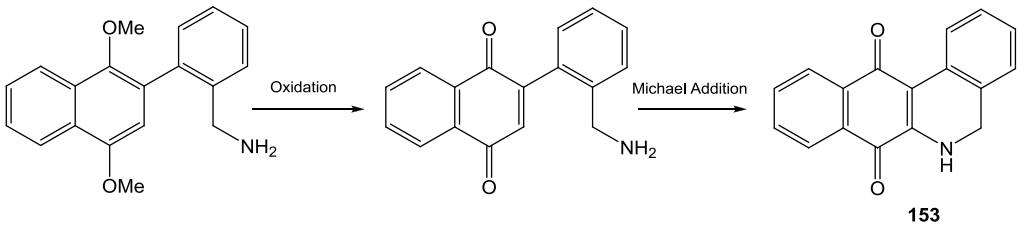
Synthesis of Benzo-fused Hetero-aromatic Naphthoquinone and Naphthopyranone Ring Systems

1. Summaries and Conclusions

The selected overview in Chapter 4 highlighted some of the biological relevance and applications of naphthoquinone and naphthopyranone containing antibiotics. It also exposed the limited methodology available for the synthesis of these types of structures; particularly the dihydrobenzo[*b*]phenanthridine motif **153**, as found in the jadomycin antibiotics **(Figure 24)**. There have been no reported syntheses of this motif **153** in the literature and it was thus the main objective of the project to develop methodology for the synthesis of this dihydrobenzo[*b*]phenanthridine backbone **(Scheme 30)**.

*1.1 Synthesis of 5,6-Dihydrobenzo[b]phenanthridine-7,12-dione **153** and 5,6-Dihydrophenanthridine-1,4-dione **161***

In accordance with the first major aim of this project we wished to develop methodology for the synthesis of the dihdrobenzo[*b*]phenanthridine motif **153 (Scheme 30, pg. 75)**. Unfortunately we were unable to synthesise compound **153** due to the fact that we were unable to reduce the nitrile functional group of compound **159** to the benzylic amine of compound **169 (Scheme 39, pg. 85)**. All of the reduction attempts, both hydrogenation and chemical, failed to yield the desired compound 2-[(1,4-dimethoxynaphthalene-2-yl)phenyl]methanamine **160**. It is not fully understood why the reduction of the nitrile did not afford the desired amine, but it is suspected that the conjugated nature of compound **159** confers extra stability to the nitrile. Having been unable to synthesise amine **160** we were unable to determine whether oxidation, followed by intra-molecular Michael addition would afford the dihydrobenzo[*b*]phenanthridine motif **153 (Scheme 63)**.



Scheme 63 Proposed Methodology for the Synthesis of the Dihdrobenzo[*b*] phenanthridine motif **153**

Having been unable to synthesise the desired dihydrobenzo[*b*]phenanthridine backbone **153**, as we could not reduce compound **159** to the corresponding amine **160**, we decided to test the

proposed methodology on a simpler system. Following a similar synthetic strategy as that used for the synthesis of 2-(1,4-dimethoxynaphthalen-2-yl)benzonitrile **159**, we set out to synthesise 2',5'-dimethoxybiphenyl-2-carbonitrile **164**, from which we could test the planned reduction, oxidation and intra-molecular Michael addition synthetic steps. Unfortunately following the synthesis of compound **164**, we were once again unable to reduce the nitrile functional group of compound **164** to the corresponding amine **165** under the reduction conditions discussed. This meant that we could not determine whether the subsequent oxidation and intra-molecular ring-closure steps would yield the desired 5,6-dihydrophenanthridine-1,4-dione scaffold **161 (Scheme 39).**

*1.2 Synthesis of 5H-Dibenzo[c,g]chromene-7,12-dione **154***

For our final attempt at determining whether the methodology shown in **Scheme 30** would yield the desired product 5,6-dihydrobenzo[*b*]phenanthridine-7,12-dione **153** should we obtain the required amine, we synthesised the oxygen derivative 5*H*-dibenzo[*c,g*]chromene-7,12-dione **154**. Having successfully reduced the aldehyde functional group of 2-(1,4-dimethoxynapthalene-2-yl)benzaldehyde **166** to the benzylic alcohol **167** using $LiAlH_4$, we were able to test whether oxidation of compound **167** would give the Michael addition precursor **168 (Scheme 47, pg. 92)**. To our surprise, oxidation of compound **167** with Ag_2O did not give compound **168**, but rather yielded the final ring-closed product, 5*H*-dibenzo[*c,g*]chromene-7,12-dione **154 (Scheme 48, pg. 92)**. This exciting result gave some indication that the ring-closing strategy we wished to employ in the synthesis of phenanthridine scaffolds **153** and **161** may be effective should we yield the desired amine precursors **160** and **165**.

*1.3 Synthesis of 12-Methoxy-6H-dibenzo[c,h]chromen-6-one **170***

During an attempt at formulating a different ring closing strategy for the synthesis of 5*H*-dibenzo[*c,g*]chromene-7,12-dione **154**, which would result in less side reactions, a novel and interesting reaction occurred. In an effort to brominate the 3'-position of compound **167** we used a standard brominating reagent, NBS. NBS did not perform the bromination as expected, but instead performed a ring-closure on compound **167** which resulted in the synthesis of 12-methoxy-6*H*-dibenzo[*c,h*] chromen-6-one **170 (Scheme 50, pg. 94)**. This exciting discovery led to the second major aim of this project, the extension of this NBS oxidative ring-closure to a variety of structurally related substrates in the hope of forming a general reaction procedure for the synthesis of a range of benzonaphthopyranone molecules.

Before we could begin extending this methodology to related substrates it was important that we elucidate the mechanism for this novel transformation. Two different attempts at determining the mechanism were undertaken and both failed to conclusively identify the correct mechanism. The

first mechanistic study proposed that NBS was oxidising the benzylic alcohol to an aldehyde and releasing radicals into the solution. Under these radical conditions it was thought that NBS was oxidising the aldehyde to an acid bromide facilitating the ring-closure **(Scheme 51, pg. 96)**. However, when we tested this hypothesis by starting from what would be the aldehyde intermediate none of the expected product **170** was isolated. Characterisation of the compound showed that under the NBS and AIBN reaction conditions, bromination had occurred in the 3'-position **(Scheme 52, pg. 97)**. The second mechanistic study then proposed that the benzylic alcohol of compound **167** was being converted to a benzylic bromide intermediate **172**, which under radical conditions was oxidised to the acid bromide required for the ring-closure **(Scheme 53, pg. 98)**. However, when we tested this hypothesis using the benzylic bromide intermediate **172**, it was found once again that bromination had occurred in the 3'-position of compound **172 (Scheme 55, pg. 100)** and no ring-closure had happened. Neither of the mechanistic studies allowed us to fully elucidate the mechanism for the synthesis of 12-methoxy-6*H*-dibenzo[*c,h*]chromen-6-one **170**, however we still believe that mechanism 1 is the correct mechanism **(Scheme 51, pg. 96)** as NBS is known to oxidise aldehydes to the corresponding acid bromides.

1.4 Expansion of the NBS Radical Oxidation Ring Closing Methodology

In accordance with the final aim of this project we wished to determine if the novel NBS reaction methodology which resulted in compound **170** could be applied to different related starting substrates. We also wished to test which functional groups of compound **167** were crucial in the synthesis of the naphthopyranone motif **170** and develop an efficient method for the synthesis of naphthopyranone scaffolds.

*1.4.1 Synthesis of 6H-Dibenzo[c,h]chromen-6-one **174***

This substrate was chosen to determine whether the NBS reaction could be carried out on a naphthalene system which contains only one methoxy group. Unfortunately we could not test this as brominating in the *ortho*-position to the methoxy group of compound **175** was impossible **(Scheme 56, pg. 102)** and thus the subsequent reaction steps could not be carried out.

*1.4.2 Synthesis of 2-Methoxy-6H-benzo[c]chromen-6-one **177***

This substrate was chosen to test whether the NBS ring-closing methodology could be extended to a benzene system. Under radical conditions NBS completed the desired transformation, but it was also noted that bromination had occurred in one of the positions *ortho* to the methoxy group **(Scheme 59, pg. 105)**. We could conclude that the NBS oxidative ring-closure can be applied to different substrates which contain a di-methoxy motif as indicated by the successful synthesis of

compound **180**. It may however be impossible to perform this reaction on this type of substrate without bromination in addition to the ring-closure. NBS is a known brominating agent and will probably perform the bromination reaction first if there is position available. However, this may also be of interest as we could use the bromine atom as a handle for further Suzuki-coupling reactions which may allow us to build larger and more complex naphthopyranone products.

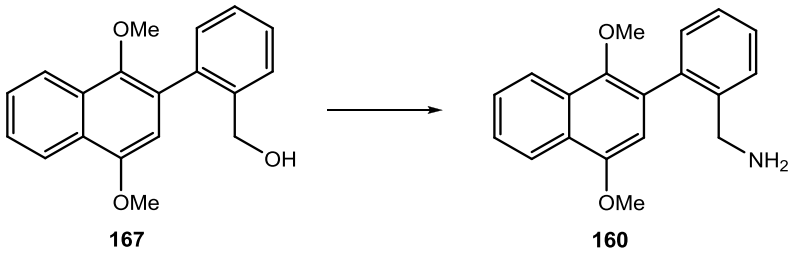
*1.4.3 Synthesis of 6H-Benzo[c]chromen-6-one **181***

This final substrate was chosen to determine whether a benzene ring with a single methoxy group would be able to undergo the NBS transformation. Our results suggest that this is not the case and that a di-methoxy motif is essential for ring closure. Treatment of the benzylic alcohol containing compound **183** with NBS under radical conditions led to the isolation of three different compounds **(Scheme 62, pg. 108)**, none of which had undergone ring-closure. This reaction did give us some important information about the mechanism as from the results in can be seen that NBS can convert a benzylic alcohol to a benzylic bromide under radical conditions, which gives some credit to proposed mechanism 2 **(Scheme 53, pg. 98)**. However compounds **184b** and **184c** were isolated in a much higher yield which suggests that the NBS is acting as an oxidising agent converting the benzylic alcohol to an aldehyde as per mechanism 1 **(Scheme 51, pg. 96)**.

2. Future Work

Although we were unable to synthesise the desired compound 5,6-dihydrobenzo[*b*] phenanthridine-7,12-dione **153**, it is still worthwhile pursuing this methodology as demonstrated by the synthesis of 5*H*-dibenzo[*c,g*]chromene-7,12-dione **154**. Should we obtain the desired amine precursors we may then be able to obtain compound **153** and **161**, which are extremely valuable synthetic targets. We could perhaps force the reduction of the nitrile functional group to the amine by performing the reduction reactions at higher temperatures. The reduction reactions using $LiAlH_4$ and Raney nickel were done only at low temperatures and it is thought that should we heat the reactions sufficiently we may be able to overcome the activation energy barrier conferred to the nitrile by conjugation. Should these attempts still fail to yield the required amine precursors, literature suggests that a benzylic alcohol can be converted to a benzylic amine via a one step process.[97] This means that previously synthesised [2-(1,4-dimethoxynaphthalen-2-yl)phenyl]methanol **167** can be converted to the required amine **160** by treatment with sodium azide and triphenyl phosphine **(Scheme 64)**.[97] We could then proceed with the proposed oxidation and intra-molecular Michael addition steps, which will hopefully yield 5,6-dihydrobenzo[*b*]phenanthridine-7,12-dione **153**. The same strategy can be adopted for the synthesis of 5,6-dihydrophenanthridine-1,4-dione **161**, as the benzylic alcohol of easily synthesised (2',5'-dimethoxybiphenyl-2-yl)methanol **179** can similarly be converted to the benzylic amine by treatment with sodium azide and triphenyl phosphine. Once again we can then test if treatment

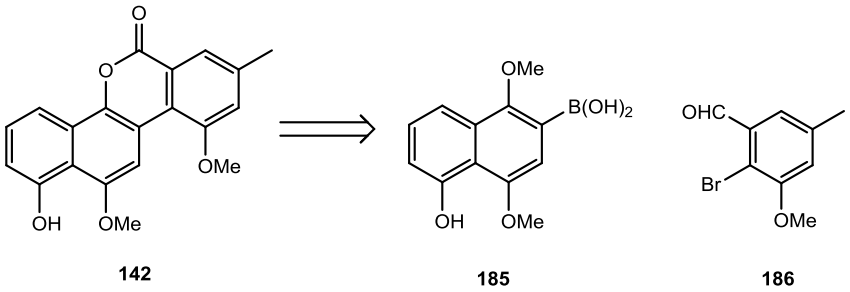
with an oxidising agent followed by intra-molecular Michael addition will afford the desired compound **161**.



Scheme 64: Proposed Conversion of Compound **167** to Desired Amine Product **160** *Reagents and Conditions*; i) NaN_3, PPh_3, CH_2Cl_2, DMF, 90˚C, 4 h [97]

Another important aspect of this project which needs still needs to be addressed in the future is the full elucidation of the mechanism for the ring-closure which resulted in the synthesis of 12-methoxy-6*H*-dibenzo[*c,h*]chromen-6-one **170**. It is thought that we may need to vary the reaction conditions in order to test whether the aldehyde intermediate **166** will give the desired ring-closed product **170**, thus showing the reaction to proceed via mechanism 1. We could do this by perhaps using a higher boiling solvent or a different radical initiator, such as benzoyl peroxide.[94] Another way of verifying that mechanism 1 is the correct mechanism is to attempt the NBS ring-closure on the *ortho*-brominated aldehyde intermediate **171 (Scheme 52, pg. 97)**. As the more favourable bromination reaction has already occurred it may mean that treatment of **171** with NBS and a radical initiator would easily oxidise the aldehyde to the acid bromide allowing ring-closure to occur.

Finally having determined that NBS and a radical initiator can be used effectively and reproducibly to synthesise the naphthopyranone scaffold we wish to extend this methodology to a variety of natural products in the future. Many of the natural products can be retro-synthesised back to easily prepared or commercially available Suzuki-Miyaura cross-coupling precursors from which we can build the required biaryl axis. An example is that of the defucogilvocarcin antibiotics, where defucogilvocarcin M **142 (Figure 27)** is thought can be easily prepared from boronic acid **185** and aryl halide **186 (Scheme 65)**. The synthesis of the aromatic bromine precursor of compound **185** has been described by Jung *et al*.[98] and is a good building block from which other naphthopyranone containing natural products can be synthesised.



142 **185** **186**

Scheme 65 Retro-synthetic Approach to the Synthesis of defucogilvocarcin M **142**

Chapter 7: Experimental Procedures

1. General Experimental Procedures

1.1 Purification of Solvents and Reagents

All solvents used for chromatographic purposes and work-up procedures were distilled prior to use by means of conventional distillation procedures. Solvents used in reactions were pre-dried in their reagent bottles and then distilled over the appropriate drying mediums under a nitrogen atmosphere. Solvents n-butanol, 1,4-dioxane and ethanol (EtOH) were not pre-dried or distilled. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium wire using benzophenone as an indicator. Acetonitrile (MeCN), dichloromethane (CH_2Cl_2) and *N,N*-dimethyl formamide (DMF), methanol (MeOH) and triethylamine were distilled from calcium hydride. Chloroform ($CHCl_3$) was dried over 4Å molecular sieves.

1.2 General Procedures

Where indicated reactions were performed under an inert atmosphere of nitrogen using a standard manifold line and connected to a vacuum pump. The nitrogen was dehydrated by bubbling the gas through sulphuric acid, and then neutralizing by passing the gas over sodium hydroxide pellets.

Concentration or evaporation *in vacuo* refers to the removal of solvent under reduced pressure (approximately 20mmHg, 40-50˚C) on a rotary evaporator and final drying on an oil pump (approximately 1-2mmHg) at room temperature.

Hydrogenations were set up in a Bűchi*gl*asuster picoclave “Parr Hydrogenator” with a built in stirrer and a maximum pressure of 8 bar.

1.3 Chromatographic Separations

Separation of compounds by column chromatography was performed using Merck or Fluka silica-gel (particle size 0.200-0.063mm). The silica was packed into a suitable size column; the product was loaded onto the silica surface and then covered in acid washed sand or cotton wool. The elution process was performed using the indicated solvent mixture. R_f values quoted are for thin layer chromatography (TLC) which was performed using Merck silica-gel 60 F_{254} coated aluminium sheets. Compounds on the TLC plates were viewed under UV light or by staining the plates with basic potassium permanganate.

1.4 Spectroscopic and Physical Data

^{1}H NMR spectra were recorded either on a Bruker AVANCE 300 spectrometer or on a Bruker DRX-400 spectrometer 300.13 and 400.13MHz respectively using standard pulse sequences. The probe temperature for all experiments was 300±1K. All spectra were recorded in deuterated chloroform ($CDCl_3$) in 5mm NMR tubes. Chemical shifts are reported in parts per million (ppm) relative to the tetramethylsilane as the internal standard. The ^{1}H NMR chemical shifts are reported as follows: value (number of hydrogens, multiplicity of signal, coupling constants in hertz (Hz) where applicable and assignment). Abbreviations used: s=singlet, d=doublet, t=triplet, q=quartet and m=multiplet.

Decoupled carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on either a Bruker AVANCE 300 spectrometer or on a Bruker DRX-400 spectrometer at frequencies of 75MHz or 101MHz respectively. Chemical shifts are reported on the δ scale relative to the central signal of deuterated chloroform taken as δ 77.00. The ^{13}C chemical shifts are reported as follows: value (assignment). The ^{1}H and ^{13}C NMR spectroscopic assignments with the *superscript are interchangeable. CH-correlated spectra were routinely run to enable more complete assignment of the signals.

Infra-red spectra were recorded on a Bruker Tensor 27 Fourier Transform spectrometer with diamond ATR attachment. The absorptions are reported on the wavenumber (cm^{-1}) scale in the 600-3500cm^{-1} range. Abbreviations used in describing the signals are: s (strong), m (medium), w (weak) and br (broad). Assignments are only indicated for key signals and functional groups.

Melting points were recorded using a JM 626 melting-point apparatus with microscope and digital thermometer.

High-resolution mass spectra were recorded either on a VG70 MS (Mass spectrum CC Pyramid data system), a VG70 SEQ (VG 11-205J or Mar II data system), or on a DFS High Resolution Magnetic Sector mass spectrometer.

Intensity data were collected on a Bruker APEX II CCD area detector diffractometer with graphite monochromated Mo K_α radiation (50kV, 30mA) using the APEX 2[99] data collection software. The collection method involved ω-scans of width 0.5° and 512x512 bit data frames. Data reduction was carried out using the program *SAINT+*[100] and face indexed absorption corrections were made using *XPREP* [100]. The crystal structure was solved by direct methods using *SHELXTL* [101]. Non-hydrogen atoms were first refined isotropically followed by anisotropic refinement by full matrix least-squares calculations based on F^2 using *SHELXTL*. Hydrogen atoms were first located in the

difference map then positioned geometrically and allowed to ride on their respective parent atoms. Diagrams and publication material were generated using SHELXTL, PLATON[102] and ORTEP-3[103].

1.5 Biological Testing

The *in vitro* HIV reverse transcriptase assays were performed by the CSIR Biosciences Pharmacology group. The assay is based on a sandwich-ELISA protocol employing the ROCHE colorimetric reverse transcriptase kit. Biotin and DIG-labelled nucleotides are incorporated into cDNA strands polymerized on an RNA template by the action of HIV-1 reverse transcriptase. The cDNA products are bound to the streptavidin-coated wells of 96-well plate inserts, and their associated DIG-moieties detected by incubation with the anti-DIG antibodies conjugated to horseradish peroxidase (HRP). The amount of bound antibody is quantified by incubation with a colorimetric HRP substrate, followed by absorbance reading at 405nm using a multiwell spectrophotometer. To assess the inhibitory activity of the test compounds they are incubated with HIV-1 reverse transcriptase and substrate and the residual percentage enzyme activity expressed relative to a control without inhibitor.

1.6 Nomenclature and Compound Numbering

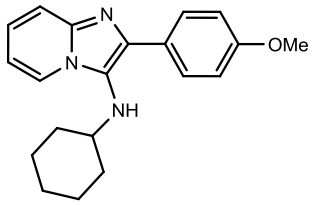
The compounds prepared during the course of this project are named in the following experimental section according to systematic nomenclature. However, the numbering system used in the diagrams of these compounds is one adopted for convenience and is not meant to reflect the systematic numbering of these compounds.

2. Experimental Procedures: Synthesis of Imidazo[1,2-*a*]pyridines and 3-Amino-1-cyano Indolizines

2.1 General Procedure for the Synthesis of Imidazo[1,2-a]pyridines ***52-62***

2-Aminopyridine (1.0eq, 1.6mmol, 0.15g) or 2-amino-5-bromopyridine (1.0eq, 0.86mmol, 0.15g) were dissolved in 1,4-dioxane (8.0cm^3) and treated with the aldehyde (1.2eq), isocyanide (1.5eq) and montmorillonite clay (1.0eq by mass of 2-aminopyridine or 2-amino-5-bromopyridine) and then heated at reflux for 60-90 h. After this time the reaction mixture was filtered through a celite plug to remove the montmorillonite clay and the solvent was removed *in vacuo* to yield a crude black oil.

2.1.1 Synthesis of N-cyclohexyl-2-(4-methoxypheny)imidazo[1,2-a]pyridine-3-amine ***52***

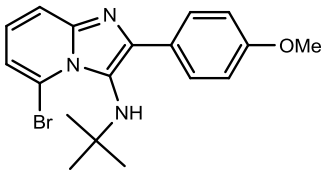


52

The reagents; *p*-methoxybenzaldehyde (1.2eq, 1.9mmol, 0.26g), cyclohexyl isocyanide (1.5eq, 2.4mmol, 0.31cm^3) and montmorillonite clay (0.15g) were added together and reacted as per the general procedure. The crude black oil was adsorbed onto silica gel and purified by column chromatography (30% – 70% EtOAc-Hexane) to yield an impure yellow oil. The yellow oil was recrystallised from diethyl ether to yield the product **52** as an off white solid (0.45mmol, 0.15g, 28% yield). The spectroscopic data of this known compound was in agreement with that of Rousseau *et al*.[48]

R_f = 0.53 (70% EtOAc-Hexane); **δ_H (300 MHz, $CDCl_3$)** 8.10 (1H, d, *J*=6.8Hz, Ar-H), 8.04 – 7.93 (2H, m, 2 Ar-H), 7.55 (1H, d, *J*=9.0Hz, Ar-H), 7.12 (1H, ddd, *J*=8.9, 6.7 and 1.2Hz, Ar-H), 7.03 – 6.95 (2H, m, 2 Ar-H), 6.78 (1H, td, *J*=6.8 and 1.0Hz, Ar-H), 3.86 (3H, s, OCH_3), 3.08 (1H, broad s, $NHCH(CH_2)_5$), 2.96 (1H, m, $NHCH(CH_2)_5$), 1.89 – 1.05 (10H, m, $NHCH(CH_2)_5$); **δ_C (75 MHz, $CDCl_3$)** 158.94 ($ArCOCH_3$), 141.48 (ArC), 136.60 (ArC), 128.34 (2 Ar*C*-H), 127.08 (ArC), 124.11 (ArC), 123.70 (Ar*C*-H), 122.61 (Ar*C*-H), 117.02 (Ar*C*-H), 113.93 (2 Ar*C*-H), 111.40 (Ar*C*-H), 56.78 ($NHCH(CH_2)_5$, 55.22 (OCH_3), 34.14 (2 CH_2), 25.74 (CH_2), 24.80 (2 CH_2).

2.1.2 Synthesis of 5-Bromo-N-tert-butyl-2-(4-methoxyphenyl)imidazo[1,2-a]pyridine-3-amine ***53***

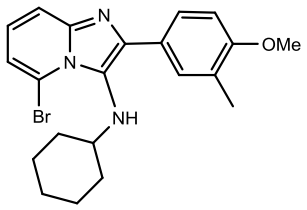


53

The reagents; *p*-methoxybenzaldehyde (1.2eq, 1.9mmol, 0.26g), *t*-butyl isocyanide (1.5eq, 1.3mmol, 0.15cm^3) and montmorillonite clay (0.15g) were added together and reacted as per the general procedure. The crude black oil was adsorbed on silica and purified by flash chromatography (25% EtOAc-Hexane) to give the pure product **53** as an off-white solid (0.27mmol, 0.10g, 31% yield).

R_f = 0.54 (50% EtOAc-Hexane); ***m.p.*** 189-192˚C; **I.R. (*v*/cm^{-1})** 3281 (m, CH*N*-*H*C(CH$_3$)$_3$), 3047 – 3010 (m, Ar*C*-*H*), 2963 – 2834 (m, C(*C*-*H*$_3$)$_3$), 1613 (m, *C*=*N*-C), 1579 – 1454 (m - s, Ar*C*=*C*), 1250 (s, Ar*C*-*O*CH$_3$); **δ_H (300 MHz, CDCl$_3$)** 8.39 – 8.27 (1H, m, Ar-H), 7.89 – 7.70 (2H, m, 2 Ar-H), 7.41 (1H, dd, *J*=9.4 and 0.6Hz, Ar-H), 7.17 (1H, dd, *J*=9.4 and 1.9Hz, Ar-H), 7.05 – 6.90 (2H, m, 2 Ar-H), 3.86 (3H, s, OC*H*$_3$), 3.05 (1H, s, N*H*), 1.05 (9H, s, C(C*H*$_3$)$_3$); **δ_C (75 MHz, CDCl$_3$)** 159.26 (Ar*C*OCH$_3$), 140.28 (ArC), 129.50 (ArC), 129.39 (2 Ar*C*-H), 127.36 (Ar*C*-H), 127.13 (ArC), 123.61 (Ar*C*-H), 123.28 (ArC), 117.71 (ArC), 115.55 (Ar*C*-H), 113.83 (2 Ar*C*-H), 56.49 (O*C*H$_3$), 55.25 (NH*C*(CH$_3$)$_3$, 30.32 (C(*C*H$_3$)$_3$); **MS *m/z* (%)** 375 (M$^+$ ^{81}Br, 61), 373 (M$^+$ ^{79}Br, 78), 320 (25), 316 (100), 302 (20), 291 (89), 289 (61), 274 (22), 259 (4), 264 (12), 222 (6), 210 (28), 207 (8), 179 (6), 172 (14), 157 (82); ***HRMS*** calculated mass for $C_{18}H_{20}ON_3{}^{79}Br$: 373.0787 and for $C_{18}H_{20}ON_3{}^{81}Br$: 375.0769; exact mass for $C_{18}H_{20}ON_3{}^{79}Br$: 373.0788 and for $C_{18}H_{20}ON_3{}^{81}Br$: 375.0775

2.1.3 Synthesis of 5-Bromo-N-cyclohexyl-2-(4-methoxy-3-methylphenyl)imidazo[1,2-a]pyridine-3-amine ***54***



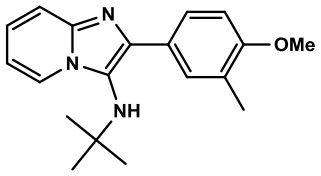
54

As per the general procedure 3-methyl-anisaldehyde (1.2eq, 1.0mmol, 0.15cm^3), cyclohexyl isocyanide (1.5eq, 1.3mmol, 0.17cm^3) and montmorillonite (0.15g) were reacted together. The crude black oil was adsorbed on silica and flash chromatography (25% EtOAc-Hexane) gave an

impure yellow solid which was recrystallised from diethyl ether to give and the pure product **54** as an off-white solid (0.29mmol, 0.12g, 33% yield).

R_f = 0.62 (50% EtOAc-Hexane); ***m.p.*** 84-86˚C; **I.R. (*v*/cm^{-1})** 3292 (m, C*N*-*H*CH$(CH_2)_5$), 2925 - 2851 (m, NHCH(*C*-*H*$_2)_5$), 1611 (m, C-*C*=*N*), 1500 – 1463 (m-s, Ar*C*=*C*), 1271 (s, Ar*C*-*O*CH_3); **δ_H (300 MHz, $CDCl_3$)** 8.12 (1H, d, *J*=1.1Hz, Ar-H), 7.81 – 7.60 (2H, m, 2 Ar-H), 7.31 (1H, d, *J*=9.4Hz, Ar-H), 7.06 (1H, dd, *J*=9.4 and 1.9Hz, Ar-H), 6.80 (1H, d, *J*=8.5Hz, Ar-H), 3.80 (3H, s, O*CH*$_3$), 2.97 (1H, s, N*H*CH$(CH_2)_5$), 2.88 (1H, m, NHC*H*$(CH_2)_5$), 2.21 (3H, s, Ar-CC*H*$_3$), 1.80 –1.13 (10H, m, NHCH(C*H*$_2)_5$); **δ_C (75 MHz, $CDCl_3$)** 157.41 (Ar*C*OCH_3), 139.81 (ArC), 137.83 (ArC), 129.54 (Ar*C*-H), 126.83 (Ar*C*-H), 126.76 (ArC), 126.10 (ArC), 125.41(Ar*C*-H), 124.36 (Ar*C*-H), 122.75 (Ar*C*-H), 117.74 (ArC), 109.87 (Ar*C*-H), 106.22 (ArC), 56.81 (NH*C*H$(CH_2)_5$), 55.33 (O*C*H$_3$), 34.13 (2 CH_2), 25.69 (CH_2), 24.76 (2 CH_2), 16.34 (Ar-C*C*H$_3$); **MS *m/z* (%)** 415 (M^+ ^{81}Br, 70), 413 (M^+ ^{79}Br, 58), 411 (9), 332 (85), 330 (48), 316 (3), 305 (92), 303 (64), 293 (20), 167 (20), 157 (60), 148 (100), 127 (23), 103 (11); ***HRMS*** calculated mass for $C_{21}H_{24}ON_3{}^{79}Br$: 413.1103 and $C_{21}H_{24}ON_3{}^{81}Br$: 415.1082; exact mass for $C_{21}H_{24}ON_3{}^{79}Br$: 413.1094 and $C_{21}H_{24}ON_3{}^{81}Br$: 415.1082

*2.1.4 Synthesis of N-tert-butyl-2-(4-methoxy-3-methylphenyl)imidazo[1,2-a]pyridine-3-amine **55***

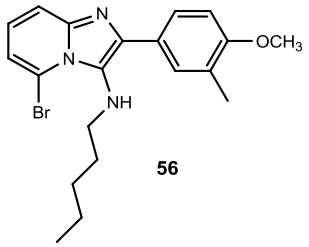


55

3-Methyl-anisaldehyde (1.2eq, 1.0mmol, 0.15cm^3), *t*-butyl isocyanide (1.5eq, 2.4mmol, 0.27cm^3) and montmorillonite (0.15g) were reacted together as per the general reaction procedure. The crude product was adsorbed onto silica gel and column chromatography (30%-65% EtOAc-Hexane) gave the pure product **55** as a yellow oil (0.24mmol, 0.08g, 15% yield).

R_f = 0.35 (35% EtOAC-Hexane); **I.R. (*v*/cm^{-1})** 3273 (broad, CH*N*-*H*C$(CH_3)_3$), 2963 – 2901 (m, C(*C*-*H*$_3)_3$), 1612 (m, *C*=*N*-C), 1557 – 1442 (m - s, Ar*C*=*C*), 1247 (s, Ar*C*-*O*CH_3); **δ_H (300 MHz, $CDCl_3$)** 8.08 (1H, d, *J*=6.8Hz, Ar-H), 7.72 – 7.55 (2H, m, 2 Ar-H), 7.41 (1H, d, *J*=9.0Hz, Ar-H), 7.08 – 6.90 (1H, m, Ar-H), 6.75 (1H, d, *J*=8.4Hz, Ar-H), 6.61 (1H, t, *J*=6.6Hz, Ar-H), 3.75 (3H, s, O*CH*$_3$), 2.99 (1H, s, N*H*C$(CH_3)_3$), 2.19 (3H, s, Ar-CC*H*$_3$), 0.94 (9H, s, C(C*H*$_3)_3$); **δ_C (75 MHz, $CDCl_3$)** 157.17 (Ar*C*OCH_3), 141.86 (ArC), 139.50 (ArC), 130.49 (Ar*C*-H), 127.29 (ArC), 126.51 (Ar*C*-H), 126.30 (ArC), 123.65 (Ar*C*-H), 123.31 (Ar*C*-H), 122.82 (ArC), 116.99 (Ar*C*-H), 111.02 (Ar*C*-H) , 109.54 (Ar*C*-H), 56.24 (O*C*H$_3$), 55.25 (NH*C*$(CH_3)_3$), 30.37 (NHC(*C*H$_3)_3$), 16.23 (Ar-C*C*H$_3$); **MS *m/z* (%)** 309 (M^+, 9), 252 (25), 225 (28), 149 (100), 147 (8), 135 (37), 133 (7), 119 (15), 107 (54); ***HRMS*** calculated mass for $C_{19}H_{23}ON_3$: 309.1841; exact mass for $C_{19}H_{23}ON_3$: 309.1836

2.1.5 Synthesis of 5-Bromo-2-(4-methoxy-3-methylphenyl)-N-pentylimidazo[1,2-a]pyridine-3-amine ***56***

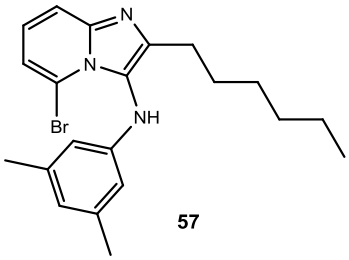


56

As per the general reaction procedure; 3-methyl-anisaldehyde (1.2eq, 1.0mmol, 0.15cm^3) and *n*-pentyl isocyanide (1.5eq, 1.3mmol, 0.16cm^3) were reacted together. The crude product was adsorbed onto silica gel and column chromatography (35% EtOAc-Hexane) gave the desired pure product **56** as a green solid (0.79mmol, 0.32g, 79% yield).

R_f = 0.63 (40% EtOAc-Hexane); ***m.p.*** 102-104˚C; **I.R. (*v*/cm^{-1})** 3254 (m, CH*N*-*H*C(CH$_3$)$_3$), 2959 – 2839 (m, NH(*C*-*H*$_2$)$_4$*C*-*H*$_3$), 1608 (m, *C*=*N*-C), 1558 – 1467 (s, Ar*C*=*C*), 1243 (s, Ar*C*-*O*CH$_3$); **δ_H (300 MHz, CDCl$_3$)** 8.08 (1H, d, *J*=0.9Hz, Ar-H), 7.85 – 7.59 (2H, m, 2 Ar-H), 7.38 (1H, d, *J*=9.4Hz, Ar-H), 7.12 (1H, dd, *J*=9.4 and 1.7Hz, Ar-H), 6.85 (1H, d, *J*=8.5Hz, Ar-H), 3.86 (3H, s, OC*H*$_3$), 3.00 (3H, m, N*HCH*$_2$CH$_2$), 2.28 (3H, s, Ar-CC*H*$_3$), 1.56 – 1.52 (2H, m, NHCH$_2$C*H*$_2$CH$_2$), 1.45 – 1.21 (4H, m, CH$_2$C*H*$_2$C*H*$_2$CH$_3$), 0.90 (3H, t, *J*=6.9Hz, CH$_2$C*H*$_3$); **δ_C (75 MHz, CDCl$_3$)** 157.43 (Ar*C*OCH$_3$), 139.60 (ArC), 136.88 (ArC), 129.40 (Ar*C*-H), 126.81 (ArC), 126.69 (Ar*C*-H), 125.94 (ArC), 125.77 (ArC), 125.36 (Ar*C*-H), 122.41 (Ar*C*-H), 117.76 (Ar*C*-H), 109.90 (Ar*C*-H), 106.25 (ArC), 55.31 (O*C*H$_3$), 48.12 (NH*C*H$_2$CH$_2$), 30.34, 29.20 and 22.52 (NHCH$_2$(*C*H$_2$)$_3$CH$_3$), 16.30 (Ar-C*C*H$_3$), 14.01 (CH$_2$*C*H$_3$); **MS *m/z* (%)** 403 (M$^+$ ^{81}Br, 34), 401 (M$^+$ ^{79}Br, 50), 399 (13), 344 (8), 332 (40), 328 (9), 305 (100), 303 (80), 252 (21), 239 (8), 225 (24), 157 (30), 149 (58), 135 (30), 114 (36), 110 (43); ***HRMS*** calculated mass for C$_{20}$H$_{24}$ON$_3$^{79}Br: 401.103 and C$_{20}$H$_{24}$ON$_3$^{81}Br: 403.1082; exact mass for C$_{20}$H$_{24}$ON$_3$^{79}Br: 401.1071 and C$_{20}$H$_{24}$ON$_3$^{81}Br: 403.1095

2.1.6 Synthesis of 5-Bromo-N-(3,5-dimethylphenyl)-2-hexylimidazo[1,2-a]pyridine-3-amine ***57***



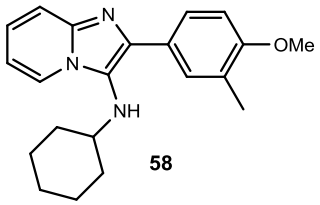
57

Reagents; n-heptaldehyde (1.2eq, 1.0mmol, 0.14cm^3) and 1-xylyl isocyanide (1.5eq, 1.3mmol, 0.17g) were reacted together according to the general reaction procedure. The crude black oil was

adsorbed on silica gel and column chromatography (20%-55% EtOAc-Hexane) gave the pure product **57** as an orange solid (0.52mmol, 0.21g, 46% yield).

R_f = 0.61 (40% EtOAc-Hexane); ***m.p.*** 132-133˚C; **I.R. (*v*/cm^{-1})** 3185 (m, CH*N*-*H*C$(CH_3)_3$), 2916 – 2855 (m, C(*C*-*H*$_2$)$_5$*C*-*H*$_3$) 1623 (m, *C*=*N*-C), 1565 – 1470 (s, Ar*C*=*C*); **δ_H (300 MHz, $CDCl_3$)** 8.04 (1H, d, *J*=0.7Hz, Ar-H), 7.23 (1H, d, *J*=9.4Hz, Ar-H), 7.03 (1H, dd, *J*=9.4 and 1.6Hz, Ar-H), 6.89 (2H, d, *J*=7.4Hz, 2 Ar-H), 6.79 – 6.69 (1H, m, Ar-H), 5.01 (1H, s, N*H*), 2.28 – 2.18 (2H, m, CC*H*$_2$CH$_2$), 1.89 (6H, s, 2 Ar-CC*H*$_3$), 1.45 – 1.31 (2H, m, CH$_2$C*H*$_2$CH$_3$), 1.17 – 0.95 (6H, m, CH$_2$(C*H*$_2$)$_3$CH$_2$), 0.72 (3H, m, CH$_2$C*H*$_3$); **δ_C (75 MHz, $CDCl_3$)** 141.90 (ArC), 141.49 (ArC), 139.54 (ArC), 129.38 (Ar*C*-H), 126.94 (Ar*C*-H), 126.34 (Ar*C*-H), 122.12 (Ar*C*-H), 121.81 (Ar*C*-H), 121.65 (ArC), 117.48 (Ar*C*-H), 106.51 (ArC), 31.46, 29.23, 28.59 and 22.48 (CH$_2$(*C*H$_2$)$_4$CH$_3$), 27.09 (C*C*H$_2$(CH$_2$)$_5$), 18.26 (Ar-C*C*H$_3$), 4.04 (CH$_2$*C*H$_3$); **MS *m/z* (%)** 399 (M$^+$ ^{79}Br, 17), 397 (2), 370 (2), 355 (2), 342 (4), 329 (4), 314 (14), 281 (2), 267 (6), 239 (7), 211 (6), 205 (100), 203 (8), 177 (8), 158 (18); ***HRMS*** calculated mass for $C_{21}H_{26}N_3{}^{79}Br$: 399.1310 and $C_{21}H_{26}N_3{}^{81}Br$: 401.1290; exact mass for $C_{21}H_{26}N_3{}^{79}Br$: 399.1280 and $C_{21}H_{26}N_3{}^{81}Br$: 401.1273

*2.1.7 Synthesis of N-cyclohexyl-2-(4-methoxy-3methylphenyl)imidazo[1,2-a}pyridine-3-amine **58***

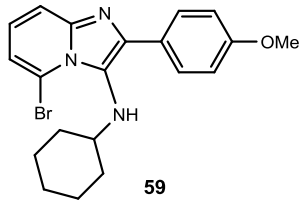


58

In accordance with the general reaction procedure 3-methyl anisaldehyde (1.2eq, 1.9mmol, 0.23cm^3) and cyclohexyl isocyanide (1.5eq, 2.4mmol, 0.31cm^3) were reacted. The crude product was adsorbed on silica gel and column chromatography (50% EtOAc-Hexane) gave the desired pure product **58** as a yellow oil (0.58mmol, 0.20g, 37% yield).

R_f = 0.47 (50% EtOAc-Hexane); **I.R. (*v*/cm^{-1})** 3229 (w, C*N*-*H*CH(CH$_2$)$_5$), 2978 – 2851 (m, NHCH(*C*-*H*$_2$)$_5$), 1591 (w, C-*C*=*N*), 1499 (m, Ar*C*=*C*), 1247 (s, ArC*C*-*O*CH$_3$); **δ_H (300 MHz, $CDCl_3$)** 8.09 (1H, d, *J*=6.8Hz, Ar-H), 7.92 – 7.76 (2H, m, 2 Ar-H), 7.53 (1H, d, *J*=9.0Hz, Ar-H), 7.20 – 6.98 (1H, m, Ar-H), 6.88 (1H, d, *J*=8.4Hz, Ar-H), 6.74 (1H, dd, *J*=6.7 and 5.8Hz, Ar-H), 3.87 (3H, s, OC*H*$_3$), 3.02 (1H, s, N*H*CH(CH$_2$)$_5$), 2.96 (1H, m, NHC*H*(CH$_2$)$_5$), 2.29 (3H, s, Ar-CC*H*$_3$), 1.71 - 1.03 (10H, m, NHCH(C*H*$_2$)$_5$); **δ_C (75 MHz, $CDCl_3$)** 157.21 (Ar*C*OCH$_3$), 141.24 (ArC), 136.35 (ArC), 129.54 (Ar*C*-H), 126.61 (Ar*C*-H), 126.27 (ArC), 125.42 (Ar*C*-H), 124.13 (ArC), 123.80 (Ar*C*-H), 122.65 (ArC), 116.88 (Ar*C*-H), 111.46 (Ar*C*-H), 109.84 (Ar*C*-H), 56.85 (NH*C*H(CH$_2$)$_5$), 55.31 (O*C*H$_3$), 34.17, 25.74 and 24.80 (NHCH(*C*H$_2$)$_5$, 16.34 (Ar-C*C*H$_3$); **MS *m/z* (%)** 335 (M$^+$, 88), 334 (70), 252 (74), 238 (26), 226 (100), 210 (73), 195 (11), 181 (16), 160 (7), 149 (23), 131 (14), 115 (10); ***HRMS*** calculated mass for $C_{21}H_{23}ON_3$: 335.1998; exact mass for $C_{21}H_{23}ON_3$: 335.1990

*2.1.8 Synthesis of 5-Bromo-N-cyclohexyl-2-(4-methoxyphenyl)imidazo[1,2-a]pyridine-3-amine **59***

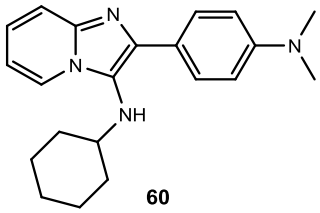


59

Reagents *p*-methoxybenzaldehyde (1.2eq, 1.0mmol, 0.12cm^3) and cyclohexyl isocyanide (1.5eq, 1.3mmol, 0.17cm^3) were reacted according to the general reaction procedure. The crude product was adsorbed on silica gel and column chromatography (30% EtOAc-Hexane) gave the desired pure product **59** as an off-white solid (0.70mmol, 0.28g, 61% yield).

R_f = 0.58 (50% EtOAc-Hexane); ***m.p.*** 202-204˚C; **I.R. (*v*/cm^{-1})** 3247 (m, C*N*-*H*CH$(CH_2)_5$), 2921 – 2853 (m, NHCH(*C*-*H*$_2)_5$), 1610 (s, C-*C*=*N*), 1504 – 1455 (m-s, Ar*C*=*C*), 1248 (s, ArC*C*-*O*CH_3); **δ_H (300 MHz, $CDCl_3$)** 8.22 – 8.05 (1H, m, Ar-H), 7.96 – 7.77 (2H, m, 2 Ar-H), 7.32 (1H, d, *J*=9.4Hz, Ar-H), 7.08 (1H, dd, *J*=9.4 and 1.9Hz, Ar-H), 6.91 (2H, d, *J*=8.9Hz, Ar-H), 3.79 (3H, s, OC*H*$_3$), 3.03 – 2.81 (2H, m, N*HCH*$(CH_2)_5$), 1.81 – 1.00 (10H, m, NHCH(C*H*$_2)_5$); **δ_C (75 MHz, $CDCl_3$)** 159.11 (Ar*C*OCH_3), 139.82 (ArC), 137.73 (ArC), 128.26 (Ar*C*-H), 126.89 (Ar*C*-H), 126.64 (ArC), 124.33 (ArC), 122.76 (Ar*C*-H), 117.76 (Ar*C*-H), 113.96 (Ar*C*-H), 106.25 (ArC), 56.71 (NH*C*H$(CH_2)_5$, 55.25 (O*C*H$_3$), 34.07, 25.67 and 24.76 (NHCH(*C*H$_2)_5$; **MS *m/z* (%)** 399 (M^+ ^{79}Br, 4), 326 (19), 311 (18), 283 (12), 252 (41), 225 (59), 207 (21), 205 (56), 181 (18), 179 (24), 165 (36), 149 (100), 135 (37), 123 (43), 109 (74); ***HRMS*** HRMS could not identify a molecular ion for $C_{20}H_{22}ON_3Br$.

*2.1.9 Synthesis of N-cyclohexyl-2-(4-(dimethylamino)phenyl)imidazo[1,2-a]pyridine-3-amine **60***

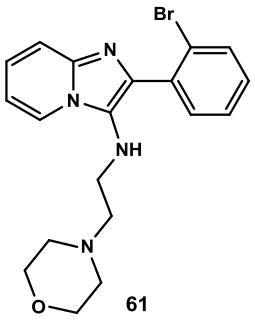


60

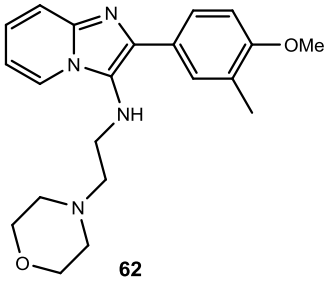
The reagents; 4-dimethylaminobenzaldehyde (1.2eq, 1.9mmol, 0.29g) and cyclohexyl isocyanide (1.5eq, 2.4mmol, 0.31cm^3) were reacted together as per the general reaction procedure. The resulting crude black oil was adsorbed onto silica gel and column chromatography (30%-70% EtOAc-Hexane) gave the desired pure product **60** as a bright yellow solid (0.20mmol, 0.07g, 13% yield).

R_f = 0.45 (70% EtOAc-Hexane); ***m.p.*** 179-181˚C; **I.R. (*v*/cm^{-1})** 3277 (m, C*N*-*H*CH$(CH_2)_5$), 2920 (m – s, N(*C*-*H*$_3)_2$), 2851 (m, NHCH(*C*-*H*$_2)_5$), 1612 (s, C-*C*=*N*), 1551 – 1439 (s, Ar*C*=*C*), 1228 (s, ArC*C*-*O*CH_3), 1197 (Ar*C*-*N*-$(CH_3)_2$); **δ_H (300 MHz, $CDCl_3$)** 7.97 (1H, d, *J*=6.7Hz, Ar-H), 7.85 (2H, d, *J*=8.6Hz, 2 Ar-H), 7.40 (1H, d, *J*=8.9Hz, Ar-H), 7.11 – 6.86 (1H, m, Ar-H), 6.71 (2H, d, *J*=8.6Hz, 2 Ar-H), 6.61 (1H, t, *J*=6.6, Ar-H), 2.98 (1H, s, N*H*CH$(CH_2)_5$), 2.89 (6H, s, N(C*H*$_3)_2$), 2.05 (1H, m, NHC*H*$(CH_2)_5$), 1.73 – 0.8 (10H, m, CH(C*H*$_2)_5$); **δ_C (75 MHz, $CDCl_3$)** 149.69 (ArC), 141.42 (ArC), 137.20 (ArC), 127.87 (2 Ar*C*-H), 123.56 (ArC), 123.26 (Ar*C*-H), 122.68 (ArC), 122.51 (Ar*C*-H), 116.78 (Ar*C*-H), 112.33 (2 Ar*C*-H), 111.08 (Ar*C*-H), 56.78 (NH*C*H$(CH_2)_5$), 40.45 (N(*C*H$_3)_2$), 34.13, 25.79 and 24.83 (CH(*C*H$_2)_5$); **MS *m/z* (%)** 334 (M^+, 82), 332 (20), 227 (10), 251 (96), 237 (12), 224 (100), 208 (28), 181 (6), 167 (6), 148 (38), 110 (10); ***HRMS*** calculated mass for $C_{21}H_{26}N_4$: 334.2158; exact mass for $C_{21}H_{26}N_4$: 334.2152

*2.1.10 Attempted Synthesis of 2-(2-Bromophenyl)-N-(2-morpholinoethyl)imidazo[1,2-a]pyridine-3-amine **61** and 2-(4-Methoxy-3-methylphenyl)-N-(2-morpholinoethyl) imidazo[1,2-a]pyridine-3-amine **62***



61



62

For the first reaction 2-bromobenzaldehyde (1.2eq, 1.9mmol, 0.22cm^3) and 2-morpholinoethyl isocyanide (1.5eq, 2.4mmol, 0.33cm^3) were reacted together as per the general reaction procedure. The same procedure was adopted for the attempted synthesis of **62**, but this time 3-methyl anisaldehyde (1.2eq, 1.9mmol, 0.24cm^3) was used as the variable aldehyde reagent. The crude products were adsorbed onto silica gel and loaded onto a silica gel column (30% EtOAc-Hexane). The products decomposed on the column and no discernible compounds were isolated from the column chromatography fractions.

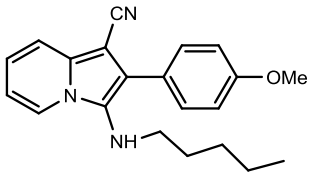
*2.2 General Procedures for the Synthesis of 3-Amino-1-cyano-indolizines **63-79***

*2.2.1 Method A: General Procedure for the Attempted Synthesis of 3-Amino-1-cyano-indolizines **63-70***

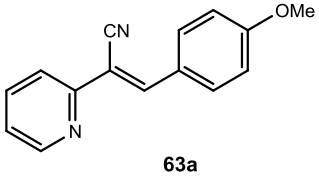
2-Pyridylacetonitrile (1.0eq, 1.3mmol, 0.15g, 0.14cm^3), an aldehyde (1.2eq) and an isocyanide (1.2eq) were dissolved in 1,4-dioxane (8.0cm^3) and treated with DBU (0.1eq, 0.13mmol, 0.02g).

The reaction mixture was heated at reflux from 60-90 h after which time the solution had turned black. After this time the solvent was removed *in vacuo* and 10% aqueous HCl (30cm^3) was added to the crude black oil. The organic products were extracted with CH_2Cl_2 (3 x 30cm^3) and dried over anhydrous $MgSO_4$. The solvent was once again removed *in vacuo* to afford a crude yellow oil. Further purification of this crude oil via column chromatography and/or recrystallisation revealed that the reaction had not gone to completion and NMR spectral analysis verified the isolated products to be aldol condensation products of the 2-pyridylacetonitrile and the various aldehydes.

2.2.1.1 Attempted Synthesis of 2-(4-Methoxyphenyl)-3-(pentylamino)indolizine-1-carbonitrile ***63***



63

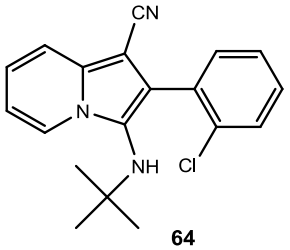


63a

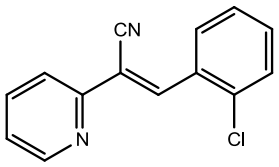
For this reaction *p*-methoxybenzaldehyde (1.2eq, 1.5mmol, 0.19cm^3) and *n*-pentyl isocyanide (1.2eq, 1.5mmol, 0.18cm^3) were reacted together as per the general reaction procedure. The crude yellow oil was adsorbed onto silica gel and purified by flash chromatography (30% EtOAc-Hexane) to give starting aldehyde and an impure yellow oil. Recrystallisation of the impure yellow oil in 96% aqueous ethanol, gave a fine yellow powder (0.36mmol, 0.08g, 28%) which is identified by NMR spectroscopy to be the aldol product 3-(4-methoxyphenyl)-2-(pyridin-2-yl)acrylonitirile **63a**.

R_f = 0.39 (20% EtOAc-Hexane); ***m.p.*** 89-92˚C; **I.R. (*v*/cm^{-1})** 3168 (m, C=*C*-*H*), 2221 (w, C-*CN*), 1623 (s, C-*C*=*N*), 1587 – 1439 (s , Ar*C*=*C*), 1258 (m, Ar*C*-*O*-*C*H$_3$); **δ_H (300 MHz, $CDCl_3$)** 8.61 (1H, d, *J*=4.4Hz, Ar-H), 8.39 (1H, s,-C=C*H*-), 7.99 (2H, d, *J*=8.8Hz, 2 Ar-H), 7.88 – 7.61 (2H, m, 2 Ar-H), 7.24 (1H, ddd, *J*=6.6, 5.2 and 2.8Hz, Ar-H), 6.98 (2H, d, *J*=8.9Hz, Ar-H), 3.86 (3H, s, OC*H*$_3$); **δ_C (75 MHz, $CDCl_3$)** 161.97 (ArC), 151.53 (Ar-C), 149.53 (Ar*C*-H), 144.68 (-C=*C*H-), 137.30 (Ar*C*-H), 132.08 (2 ArC), 126.13 (ArC), 123.02 (Ar*C*-H), 120.88 (Ar*C*-H), 118.41(C-*C*N), 114.45 (2 Ar*C*-H), 106.99 (*C*-CN), 55.45 (O*C*H$_3$); **MS *m/z* (%)** 235 (M$^+$, 100), 222 (3), 221 (16), 220 (27), 210 (7), 205 (6), 193 (16), 192 (97), 191 (7), 177 (2), 166 (10), 151 (5), 139 (8), 123 (4), 111 (6); ***HRMS*** calculated mass for $C_{15}H_{12}ON_2$: 236.0950 exact mass for $C_{15}H_{12}ON_2$: 236.0924

2.2.1.2 Attempted Synthesis of 3-(tert-butylamino)-2-(2-chlorophenyl)indolizine-1-carbonitrile ***64***



64

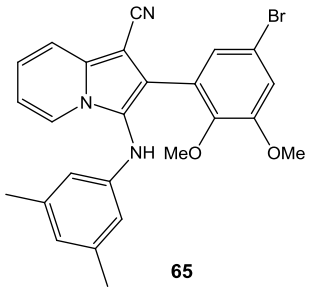


64a

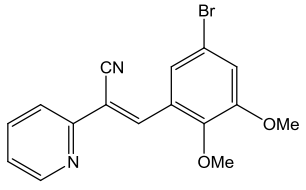
As per the general reaction procedure, 2-chlorobenzaldehyde (1.2eq, 1.5mmol, 0.17cm^3) and *t*-butyl isocyanide (1.2eq, 1.5mmol, 0.17cm^3) were reacted together. The crude yellow oil was recrystallised from diethyl ether to afford yellow crystals (0.99mmol, 0.24g, 78%) which were characterised by NMR spectroscopy to be the aldol product 3-(2-chlorophenyl)-2-(pyridin-2-yl)acrylonitrile **64a**.

R_f = 0.66 (20% EtOAc-Hexane); ***m.p.*** 147-149˚C; **I.R. (*v*/cm^{-1})** 3068 (w, C=*C*-*H*), 2219 (w, C-*CN*), 1608 (s, C-*C*=*N*), 1579 – 1430 (s , Ar*C*=*C*), 742 (s, Ar*C*-*Cl*); **δ_H (300 MHz, $CDCl_3$)** 8.80 (1H, s, -C=C*H*-), 8.67 (1H, d, *J*=4.5Hz, Ar-H), 8.17 (1H, dd, *J*=5.3 and 4.1Hz, Ar-H), 7.92 – 7.65 (2H, m, Ar-H), 7.58 – 7.21 (4H, m, Ar-H); **δ_C (75 MHz, $CDCl_3$)** 150.68 (ArC), 149.92 (Ar*C*-H), 141.79 (-C=*C*H-), 137.37 (Ar*C*-H), 135.45 (ArC), 132.00 (ArC), 131.76 (Ar*C*-H), 129.99 (Ar*C*-H), 129.48 (Ar*C*-H), 127.22 (Ar*C*-H), 123.90 (Ar*C*-H), 121.45 (Ar*C*-H), 117.12 (C-*C*N), 113.58 (*C*-CN); **MS *m/z* (%)** 242 ($M^{+\,37}$Cl, 36), 241 (58) 240 ($M^{+\,35}$Cl, 96), 239 (80), 235 (16), 214 (26), 207 (64), 206 (74), 205 (100), 203 (98), 202 (16), 180 (6), 179 (36), 178 (66), 176 (72), 175 (18), 153 (26), 152 (64), 151 (81), 150 (41), 148 (29), 139 (90, 127 (19), 125 (50), 124 (32), 119 (15); ***HRMS*** Could not obtain a molecular ion for $C_{14}H_9N_2Cl$.

2.2.1.3 Attempted Synthesis of 2-(5-Bromo-2,3-dimethoxyphenyl)-3-(3,5-dimethyl phenylamino)indolizine-1-carbonitrile ***65***



65



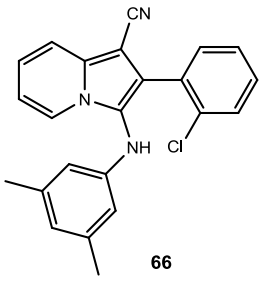
65a

In accordance with the general reaction procedure, 5-bromo-2,3-dimethoxybenzaldehyde (1.2eq, 1.5mmol, 0.37g) and 1-xylyl isocyanide (1.2eq, 1.5mmol, 0.20g) were reacted. The crude yellow oil was adsorbed onto silica gel and purified by column chromatography (35% EtOAc-Hexane) to

yield a greenish-yellow solid. This solid was dissolved in 96% aqueous ethanol and on standing a white solid (0.64mmol, 0.22g, 51%) precipitated out of the solution which was collected and dried. Characterisation of the product shows the white solid to be the aldol compound 3-(5-bromo-2,3-dimethoxyphenyl)-2-(pyridin-2-yl)acrylonitrile **65a**.

R_f = 0.31 (10% EtOAc-Hexane); ***m.p.*** 165-166˚C; **I.R. (*v*/cm^{-1})** 3052 (w, C=*C*-*H*), 2217 (w - m, C-*CN*), 1608 (m, C-*C*=*N*), 1584 – 1465 (s , Ar*C*=*C*), 1266 (m, Ar*C*-*O*-*C*H_3); **δ_H (300 MHz, $CDCl_3$)** 8.67 (2H, m, -C=C*H*- and Ar-H), 7.94 (1H, d, *J*=2.0Hz), 7.88 – 7.70 (2H, m, 2 Ar-H), 7.41 – 7.21 (1H, m, Ar-H), 7.14 (1H, d, *J*=2.1Hz, Ar-H), 3.88 (6H, 2s, 2 OC*H*$_3$); **δ_C (75 MHz, $CDCl_3$)** 153.35 (ArC), 150.95 (ArC), 149.83 (-C=*C*H-), 148.06 (ArC), 138.68 (Ar*C*-H), 137.32 (Ar*C*-H), 129.14 (ArC), 123.76 (Ar*C*-H), 122.62 (Ar*C*-H), 121.37 (Ar*C*-H), 118.17 (Ar*C*-H), 117.15 (C-*C*N), 116.71 (*C*-CN), 112.82 (ArC), 61.75 (O*C*H_3), 56.21 (O*C*H_3); **MS *m/z* (%)** 346 ($M^{+\ 81}$Br, 92) 344 ($M^{+\ 79}$Br, 100), 268 (1), 267 (6), 266 (32), 241 (1); ***HRMS*** calculated mass for $C_{16}H_{13}ON_2{}^{79}Br$: 344.0160 and for $C_{16}H_{13}ON_2{}^{81}Br$: 346.0140, exact mass for $C_{16}H_{13}ON_2{}^{79}Br$: 344.0124 and for $C_{16}H_{13}ON_2{}^{81}Br$: 346.0133.

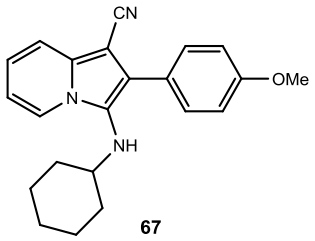
*2.2.1.4 Attempted Synthesis of 2-(2-Chlorophenyl)-3-(3,5-dimethylphenylamino)indolizine-1-carbonitrile **66***



66

2-Chlorobenzaldehyde (1.2eq, 1.5mmol, 0.17cm^3) and 1-xylyl isocyanide (1.2eq, 1.5mmol, 0.20g) were reacted in accordance with the general reaction procedure. The crude yellow oil was dissolved in hot diethyl ether and upon standing yellow crystals (0.74mmol, 0.18g, 59%) precipitated from the solution, which were identified by NMR spectroscopy to be the same aldol product as **64a**.

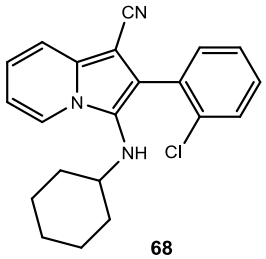
2.2.1.5 Attempted Synthesis of 3-(Cyclohexylamino)-2-(4-methoxyphenyl)indolizine-1-carbonitrile ***67***



67

As per the general reaction procedure *p*-methoxybenzaldehyde (1.2eq, 1.5mmol, 0.18cm^3) and cyclohexyl isocyanide (1.2eq, 1.5mmol, 0.19cm^3) were reacted together. The crude yellow oil was adsorbed onto silica gel and purified by flash chromatography (30% EtOAc-Hexane) to give a yellow oil. Recrystallisation of the impure oil in 96% aqueous ethanol yielded a fine yellow powder (0.76mmol, 0.18g 60%) which was characterised by NMR spectroscopy to be the same aldol product as **63a**.

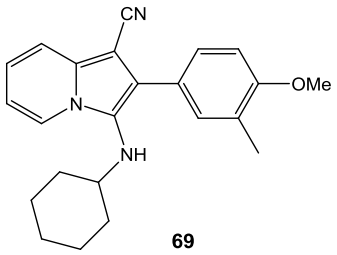
2.2.1.6 Attempted Synthesis of 2-(2-Chlorophenyl)-3-(cyclohexylamino)indolizine-1-carbonitrile ***68***



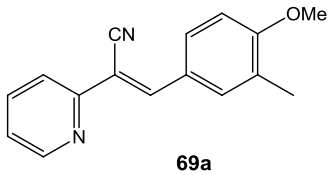
68

The reagents; 2-chlorobenzaldehyde (1.2eq, 1.5mmol, 0.17cm^3) and cyclohexyl isocyanide (1.2eq, 1.5mmol, 0.19cm^3) were reacted together in accordance with the general reaction procedure. The crude oil was purified by column chromatography (20% EtOAc-Hexane) to give a yellow oil, which was dissolved in hot diethyl ether and allowed to cool. Upon cooling yellow crystals (0.86mmol, 0.21g, 68%) precipitated out of the solution and NMR spectral characterisation of this product revealed it to be the same aldol product as **64a**.

2.2.1.7 Attempted Synthesis of 3-(Cyclohexylamino)-2-(4-methoxy-3-methylphenyl) indolizine-1-carbonitrile ***69***



69

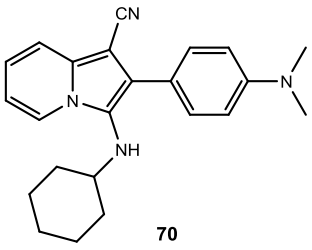


69a

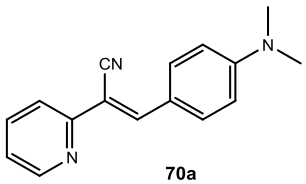
In accordance with the general reaction procedure; 3-methyl anisaldehyde (1.2eq, 1.5mmol, 0.22cm^3) and cyclohexyl isocyanide (1.2eq, 1.5mmol, 0.19cm^3) were reacted together. The crude product was purified by column chromatography (30% EtOAc-Hexane) to give a white solid (0.53mmol, 0.13g, 42%) which was identified to be aldol product 3-(4-methoxy-3-methylphenyl)-2-(pyridin-2-yl)acrylonitirile **69a**.

R_f = 0.51 (20% EtOAc-Hexane); ***m.p.*** 95-98˚C; **I.R. (*v*/cm^{-1})** 3012 (w, C=*C*-*H*), 2922 – 2842 (w, ArC*C*-*H*$_3$) 2213 (m, C-*CN*), 1582 – 1463 (s , Ar*C*=*C*), 1255 (s, Ar*C*-*O*-*C*H$_3$); **δ_H (300 MHz, $CDCl_3$)** 8.62 (1H, d, *J*=4.7Hz, Ar-H), 8.37 (1H, s, -C=C*H*-), 8.02 – 7.65 (4H, m, 4 Ar-H), 7.36 – 7.10 (1H, m, Ar-H), 6.91 (1H, d, *J*=8.6Hz, Ar-H), 3.90 (3H, s, OC*H*$_3$), 2.22 (3H, s, ArC-C*H*$_3$); **δ_C (75 MHz, $CDCl_3$)** 160.33 (Ar*C*OCH$_3$), 151.71 (ArC) , 149.49 (Ar*C*-H), 144.99 (-C=*C*H-), 137.25 (Ar*C*-H), 132.59 (Ar*C*-H), 129.99 (Ar*C*-H), 127.35 (ArC), 125.69 (ArC), 122.88 (Ar*C*-H), 120.80 (Ar*C*-H), 118.50 (C-*C*N), 110.05 (Ar*C*-H), 106.54 (*C*-CN), 55.49 (O*C*H$_3$), 16.29 (ArC-*C*H$_3$); **MS *m/z* (%)** 249 (M$^+$, 100), 234 (16), 208 (2), 207 (8), 205 (14), 192 (12), 179 (6), 165 (6), 149 (10), 135 (6), 128 (5), 114 (10), 109 (10); ***HRMS*** calculated mass for $C_{16}H_{14}ON_2$: 250.1106; exact mass for $C_{16}H_{14}ON_2$: 250.1081

2.2.1.8 Attempted Synthesis of 3-(Cyclohexylamino)-2-(4-(dimethylamino)phenyl) indolizine-1-carbonitrile ***70***



70



70a

4-Dimethylaminobenzaldehyde (1.2eq, 1.5mmol, 0.23g) and cyclohexyl isocyanide (1.2eq, 1.5mmol, 0.19cm^3) were reacted together according to the general reaction procedure. The crude product was purified by column chromatography (30% EtOAc-Hexane) to give a green solid

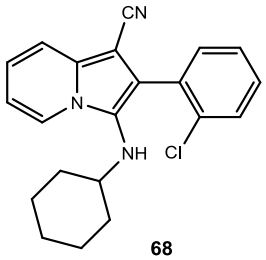
(0.33mmol, 0.08g, 26%) which was characterised by NMR spectroscopy to be aldol product 3-(4-(dimethylamino)phenyl)-2-(pyridin-2-yl)acrylonitrile **70a**.

R_f = 0.34 (30% EtOAc-Hexane); ***m.p.*** 60-63˚C; **I.R. (*v*/cm^{-1})** 3013 (w, C=*C-H*), 2904 – 2713 (w, -N-*C-H*$_3$) 2203 (m, C-*C*N), 1659 (s, C-*N*=*C*), 1579 – 1464 (s , Ar*C*=*C*), 1231 (s, *N*-*C*H$_3$); **δ_H (300 MHz, $CDCl_3$)** 8.59 (1H, d, *J*=4.4Hz, Ar-H), 8.33 (1H, s, -C=C*H*-), 7.97 (2H, d, *J*=9.0Hz, 2 Ar-H), 7.71 (2H, m, 2 Ar-H), 7.18 (1H, dd, *J*=8.4 and 3.2Hz, Ar-H), 6.72 (2H, d, *J*=9.0Hz, 2 Ar-H), 3.02 (6H, s, Ar-N(C*H*$_3$)$_2$); **δ_C (75 MHz, $CDCl_3$)** 152.47 (ArC), 152.14 (ArC), 149.36 (Ar*C*-H), 145.25 (-C=*C*H-), 137.15 (Ar*C*-H), 132.32 (2 Ar*C*-H), 122.17 (Ar*C*-H), 121.17 (ArC), 120.43 (Ar*C*-H), 119.46 (C-*C*N), 111.56 (Ar*C*-H), 102.81(*C*-CN) , 40.02 (N(*C*H$_3$)$_2$); **MS *m/z* (%)** 249 (M$^+$, 84), 248 (100), 232 (28), 205 (21), 203 (14), 192 (7), 177 (8), 165 (8), 151 (9), 148 (36), 143 (6), 135 (6), 123 (10), 114 (21); ***HRMS*** calculated mass for $C_{16}H_{15}N_3$: 249.1266; exact mass for $C_{16}H_{15}N_3$: 249.1257

2.2.2 Method B: General Procedure for the Synthesis and Attempted Synthesis of 3-Amino-1-cyano-indolizines ***68,72-76***

2-pyridylacetonitrile (1.0eq, 1.3mmol, 0.15g, 0.14cm^3) or 6-chloro-2-pyridylacetonitrile (1.0eq, 0.98mmol, 0.15g) a variable aldehyde (1.2eq) and a variable isocyanide (1.2eq) were dissolved in *n*-butanol (5cm^3). DBU (0.1eq, 0.13mmol, 0.02g) was then added to the reaction mixture and the solution was heated to 100^{o}C and left to stir for 43 h under an argon atmosphere. After this time the solvent was removed *in vacuo* to afford a crude black oil which was further purified by flash chromatography.

2.2.2.1 Synthesis of 2-(2-Chlorophenyl)-3-(cyclohexylamino)indolizine-1-carbonitrile ***68***



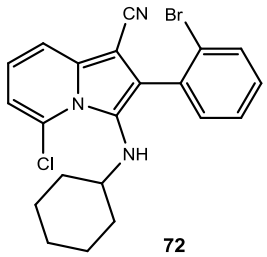
68

In accordance with the general reaction procedure 2-chlorobenzaldehyde (1.2eq, 1.5mmol, 0.17cm^3) and cyclohexyl isocyanide (1.2eq, 1.5mmol, 0.19cm^3) were reacted together. The crude black oil was absorbed onto silica gel and purified via flash chromatography (30% EtOAc-Hexane) to give two products; a white solid (0.54mmol, 0.13g, 42%) which was identified from NMR spectroscopy to be the aldol product **64a** and a yellow oil. The yellow oil was dissolved in hot diethyl ether and placed in the freezer for overnight recrystallisation and the desired product **68** was isolated as bright yellow crystals (0.30mmol, 0.10g, 23%).

R_f = 0.54 (20% EtOAc-Hexane); ***m.p.*** 91-94˚C; **I.R. (*v*/cm^{-1})** 3293 (m, C*N*-*H*CH(CH_2)$_5$), 2904 – 2714 (m, NHCH(*C*-*H*$_2$)$_5$), 2203 (w, C-*CN*) 1660 (m, C-*C*=*N*), 1580 – 1465 (m-s, Ar*C*=*C*), 727 (Ar*C*-*Cl*); **δ_H** and **δ_c***; **MS *m/z* (%)** 350 (M^+, 100), 348 (46), 346 (15), 314 (3), 266 (1). ***HRMS*** calculated mass for $C_{21}H_{20}N_3{}^{35}Cl$: 349.1346 and for $C_{21}H_{20}N_3{}^{37}Cl$: 351.1316; exact mass for $C_{21}H_{20}N_3{}^{35}Cl$: 349.1339 and for $C_{21}H_{20}N_3{}^{37}Cl$: 351.1327

*****The compound is unstable in a variety of deuterated solvents thus no useful NMR spectral data was obtained, however we did obtain an x-ray crystal structure for this compound which is discussed in Chapter 2

*2.2.2.2 Synthesis of 2-(2-Bromophenyl)-5-chloro-3-(cyclohexylamino)indolizine-1-carbonitrile **72***

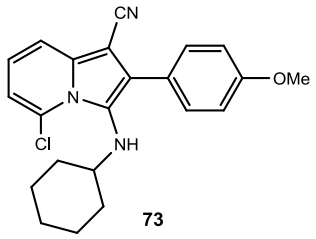


72

Commercially available 2-bromobenzaldehyde (1.2eq, 1.2mmol, 0.14cm^3) and cyclohexyl isocyanide (1.2eq, 1.2mmol, 0.15cm^3) were reacted together according to the general reaction procedure. On cooling a lightly coloured crystalline substance precipitated from the crude product oil. This was collected and adsorbed onto silica gel and purified further by flash chromatography (15% EtOAc-Hexane). A yellow solid was isolated from the column which was identified as the desired product **72** (0.68mmol, 0.29g, 75%)

R_f = 0.33 (15% EtOAc-Hexane); ***m.p.*** 191-194˚C; **I.R. (*v*/cm^{-1})** 3341 (m, C*N*-*H*CH(CH_2)$_5$), 2923 (m, NHCH(*C*-*H*$_2$)$_5$), 2206 (w, C-*CN*) 1660 (m, C-*C*=*N*), 1488 (s, Ar*C*=*C*), 753 (Ar*C*-*Cl*); **δ_H (300 MHz, $CDCl_3$)** 7.71 (1H, d, *J*=8.0Hz, Ar-H), 7.55 (1H, d, *J*=8.8Hz, Ar-H), 7.40 (2H, m, 2 Ar-H), 7.34 – 7.21 (1H, m, Ar-H), 6.96 – 6.84 (1H, m, Ar-H), 6.75 (1H, d, *J*=7.0Hz, Ar-H), 3.36 (1H, s, N*H*CH(CH_2)$_5$), 2.77 (1H, m, NHC*H*(CH_2)$_5$), 1.76 – 0.93 (10H, m, NHCH(C*H*$_2$)$_5$); **δ_C (75 MHz, $CDCl_3$)** 137.25 (ArC), 133.52 (ArC), 133.04 (Ar*C*-H), 132.70 (Ar*C*-H), 129.79 (Ar*C*-H), 129.69 (ArC), 127.46 (Ar*C*-H), 127.19 (ArC), 124.99 (ArC), 124.21 (ArC), 121.38 (Ar*C*-H), 116.82 (Ar*C*-H), 115.92 (C-*C*N), 115.56 (Ar*C*-H), 83.13 (ArC), 58.55 (NH*C*H(CH_2)$_5$), 33.08, 32.80, 25.66, 24.67 and 24.47 (NHCH(*C*H$_2$)$_5$); **MS *m/z* (%)** 430 (M^+ ^{81}Br, 100), 428 (M^+ ^{79}Br, 78), 394 (4), 346 (6), 314 (18), 310 (2); ***HRMS*** calculated mass for $C_{21}H_{19}N_3Cl^{79}Br$: 427.0451 and for $C_{21}H_{19}N_3Cl^{81}Br$: 429.0430; exact mass for $C_{21}H_{19}N_3Cl^{79}Br$: 427.0463 and for $C_{21}H_{19}N_3Cl^{81}Br$: 429.0443

2.2.2.3 Synthesis of 5-Chloro-3-(cyclohexylamino)-2-(4-methoxyphenyl)indolizine-1-carbonitrile ***73***

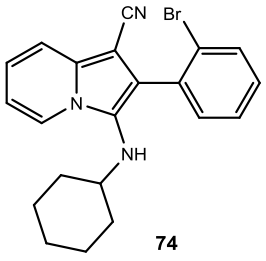


73

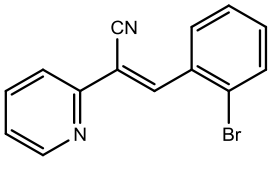
In accordance with the general reaction procedure *p*-methoxybenzaldehyde (1.2eq, 1.2mmol, 0.14cm^3) and cyclohexyl isocyanide (1.2eq, 1.2mmol, 0.15cm^3) were reacted together. The crude product was adsorbed onto silica gel and purified by flash chromatography (10% EtOAc-Hexane) to yield the product **73** as a yellow solid (0.49mmol, 0.19g, 38%).

R_f = 0.37 (10% EtOAc-Hexane); ***m.p.*** 123-124˚C; **I.R. (*v*/cm^{-1})** 3373 (w, C*N*-*H*CH(CH$_2$)$_5$), 2923 – 2852 (m, NHCH(*C*-*H*$_2$)$_5$), 2203 (m, C-*CN*) 1612 (m, C-*C*=*N*), 1577 – 1447 (s, Ar*C*=*C*), 1249 (s, Ar*C*-*O*-*C*H$_3$), 737 (Ar*C*-*Cl*); **δ_H (400 MHz,CDCl$_3$)** 7.90 – 7.56 (2H, m, 2 Ar-H), 7.53 (1H, dd, *J*=8.8 and 1.2Hz, Ar-H), 7.14 – 6.94 (2H, m, 2 Ar-H), 6.87 (1H, dd, *J*=8.7 and 7.1Hz, Ar-H), 6.71 (1H, dd, *J*=7.1 and 1.2Hz, Ar-H), 3.87 (3H, s, OC*H*$_3$), 3.56 (1H, s, N*H*), 2.90 – 2.52 (1H, m, NHC*H*(CH$_2$)$_5$), 1.80 – 0.65 (10H, m, NHCH(C*H*$_2$)$_5$); **δ_C (101 MHz, CDCl$_3$)** 159.06 (Ar*C*OCH$_3$), 137.68 (ArC), 130.47 (2 Ar*C*-H), 128.50 (ArC), 126.62 (ArC), 125.81 (ArC), 124.77 (ArC), 121.07 (Ar*C*-H), 116.71 (C-*C*N), 116.57 (Ar*C*-H), 115.29 (Ar*C*-H), 113.97 (Ar*C*-H), 81.76 (*C*-CN), 58.76 (NH*C*H(CH$_2$)), 55.22 (O*C*H$_3$), 32.82, 25.64 and 24.69 (NHCH(*C*H$_2$)$_5$); **MS *m/z* (%)** 380 (M$^+$, 100), 344 (20), 337 (12), 327 (2), 262 (2); ***HRMS*** calculated mass for $C_{22}H_{22}N_3O^{35}Cl$: 379.1451 and for $C_{22}H_{22}N_3O^{37}Cl$: 381.1422; exact mass for $C_{22}H_{22}N_3O^{35}Cl$: 379.1456 and for $C_{22}H_{22}N_3O^{37}Cl$: 381.1444

2.2.2.4 Attempted Synthesis of 2-(2-Bromophenyl)-3-(cyclohexylamino)indolizine-1-carbonitrile ***74***



74

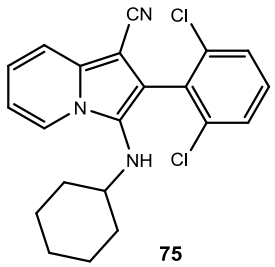


74a

2-Bromobenzaldehyde (1.2eq, 1.5mmol, 0.18cm^3) and cyclohexyl isocyanide (1.2eq, 1.5mmol, 0.19cm^3) were reacted according to the general reaction procedure. Purification of the crude product by flash chromatography (10% EtOAc-Hexane) afforded a white solid which was identified as aldol product 3-(2-bromophenyl)-2-(pyridin-2-yl)acrylonitrile **74a** (0.16mmol, 0.05g, 13%).

R_f = 0.50 (10% EtOAc-Hexane); ***m.p.*** 143-145˚C; **I.R. (*v*/cm^{-1})** 3065 (w, C=*C*-*H*), 2219 (w, C-*CN*), 1644 (s, C-*C*=*N*), 1578 – 1464 (s , Ar*C*=*C*); **δ_H (400 MHz, $CDCl_3$)** 8.79 – 8.58 (2H, m, Ar-*H* and -C=C*H*-), 8.25 – 8.01 (1H, m, Ar-H), 7.87 – 7.75 (2H, m, 2 Ar-H), 7.69 (1H, dd, *J*=8.0 and 1.2Hz, Ar-H), 7.58 – 7.38 (1H, m, Ar-H), 7.39 – 7.23 (2H, m, 2 Ar-H); **δ_C (75 MHz, $CDCl_3$)** 150.65 (ArC), 149.95 (Ar*C*-H), 144.37 (-C=*C*H-), 137.37 (Ar*C*-H), 133.84 (ArC), 133.22 (Ar*C*-H), 131.81 (Ar*C*-H), 129.76 (Ar*C*-H), 127.81 (Ar*C*-H), 125.60 (ArC), 123.89 (Ar*C*-H), 121.44 (Ar*C*-H), 117.00 (C-*C*N), 113.77 (*C*-CN); **MS *m/z* (%)** 286 (^{81}Br M$^+$, 66), 285 (100), 284 (^{79}Br M$^+$, 66), 283 (92), 282 (2), 280 (6), 278 (4), 276 (1); ***HRMS*** calculated mass for $C_{14}H_9N_2{}^{79}Br$: 283.9949 and for $C_{14}H_9N_2{}^{81}Br$: 285.9929; exact mass for $C_{14}H_9N_2{}^{79}Br$: 283.9938 and for $C_{14}H_9N_2{}^{81}Br$: 285.9918

*2.2.2.5 Synthesis of 3-(Cyclohexylamino)-2-(2,6-dichlorophenyl)indolizine-1-carbo-nitrile **75***

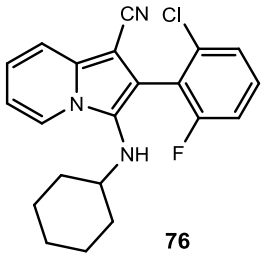


75

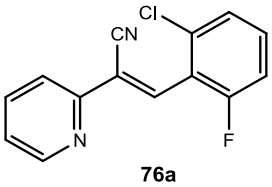
In accordance with the general reaction procedure; 2,6-dichlorobenzaldehyde (1.2eq, 1.5mmol, 0.27g) and cyclohexyl isocyanide (1.2eq, 1.5mmol, 0.19cm^3) were reacted together. On cooling a brownish solid precipitated out of the crude product oil, was collected and purified by flash chromatography (5% EtOAc-Hexane) to afford the desired product **75** as a yellow solid (0.08mmol, 0.03g, 7%).

R_f = 0.56 (20% EtOAc-Hexane); ***m.p***. 138-141˚C; **I.R. (*v*/cm^{-1})** 3351 (w, C*N*-*H*CH$(CH_2)_5$), 2932 – 2853 (m, NHCH(*C*-*H*$_2)_5$), 2195 (m, C-*CN*) 1633 (m, C-*C*=*N*), 1558 – 1470 (s, Ar*C*=*C*), 745 (Ar*C*-*Cl*); **δ_H (400 MHz, $CDCl_3$)** 8.24 – 8.17 (1H, m, Ar-H), 7.59 (1H, dd, *J*=8.9 and 1.0Hz, Ar-H), 7.48 – 7.42 (2H, m, 2 Ar-H), 7.31 (1H, dd, *J*=8.6 and 7.5Hz, Ar-H), 7.04 (1H, ddd, *J*=8.9, 6.6 and1.0Hz, Ar-H), 6.78 (1H, td, *J*=6.9 and 1.1Hz, Ar-H), 2.89 (1H, m, NHC*H*$(CH_2)_5$), 2.76 – 2.58 (1H, broad, NH), 1.57 - 1.05 (10H, m, NHCH(C*H*$_2)_5$); **δ_C (101 MHz, $CDCl_3$)** 136.00 (Ar-*C*Cl), 134.49 (ArC), 130.56 (ArC), 130.20 (Ar*C*-H), 128.23 (2 Ar*C*-H), 127.16 (ArC), 123.12 (Ar*C*-H), 122.09 (Ar*C*-H), 118.61 (C-*C*N), 117.54 (Ar*C*-H), 116.52 (ArC), 112.35 (Ar*C*-H), 80.64 (*C*-CN), 56.28 (NH*C*H$(CH_2)_5$), 33.64, 25.52 and 24.51 (NHCH(*C*H$_2)_5$); **MS *m/z* (%)** 384 (M$^+$, 100), 382 (32), 380 (10), 346 (5), 275 (2); ***HRMS*** calculated mass for $C_{21}H_{19}N_3{}^{35}Cl_2$: 383.0956 and for $C_{21}H_{19}N_3{}^{37}Cl_2$: 387.0927; exact mass for $C_{21}H_{19}N_3{}^{35}Cl_2$: 383.0946 and for $C_{21}H_{19}N_3{}^{37}Cl_2$: 387.0918

2.2.2.6 *Attempted Synthesis of 2-(2-Chloro-6-fluorophenyl)-3-(cyclohexylamino) indolizine-1-carbonitrile* ***76***



76



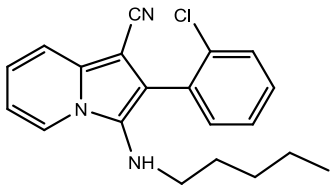
76a

In accordance with the general reaction procedure reagents 2-chloro-6-flourobenzaldehyde (1.2eq, 1.5mmol, 0.24g) and cyclohexyl isocyanide (1.2eq, 1.5mmol, 0.19cm^3) were reacted together. The crude black product was adsorbed onto silica gel and purification by flash chromatography (5% EtOAc-Hexane) afforded a white solid which was identified to be the aldol product 3-(2-chloro-6-fluorophenyl)-2-(pyridin-2-yl)acrylonitrile **76a** (0.10mmol, 0.03g, 8%).

R_f = 0.37 (5% EtOAc-Hexane); ***m.p.*** 155-157˚C; **I.R. (*v*/cm^{-1})** 3016 (w, C=*C*-*H*), 2226 (w, C-*CN*), 1614 (m, C-*C*=*N*), 1580 – 1439 (s , Ar*C*=*C*), 1099 (m, Ar*C*-*F*), 774 (s, Ar*C*-*Cl);* **δ_H (400 MHz, $CDCl_3$)** 8.68 (1H, ddd, *J*=4.7, 1.7 and 1.0Hz, Ar-H), 8.40 (1H, s, -C=C*H*-), 7.90 – 7.70 (2H, m, 2 Ar-H), 7.44 – 7.27 (3H, m, 3 Ar-H), 7.26 – 7.07 (1H, m, Ar-H); **δ_C (75 MHz, $CDCl_3$)** 161.69 (ArC), 158.32 (ArC), 149.95 (Ar*C*-H), 149.84 (ArC), 137.4 (Ar*C*-H), 136.40 (Ar*C*-H), 135.27 (ArC), 131.50 (Ar*C*-H), 131.38 (Ar*C*-H), 125.52 (Ar*C*-H), 124.24 (Ar*C*-H), 121.66 (Ar*C*-H), 115.13 (C-*C*N), 114.83 (*C*-CN); **MS *m/z* (%)** 259 (M^+, 100), 225 (5); ***HRMS*** calculated mass for $C_{14}H_8N_2ClF$: 258.0360; exact mass for $C_{14}H_8N_2ClF$: 258.0345

2.2.3 Method C: Attempted Synthesis of 3-Amino-1-cyano Indolizines ***64, 77-79***

2.2.3.1 Attempted Synthesis of 2-(2-Chlorophenyl)-3-(phentylamino)indolizine-1-carbonitrile ***77***

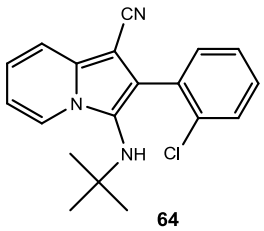


77

3-(2-chlorophenyl)-2-(pyridin-2-yl)acrylonitrile **64a** (1.0eq, 0.10mmol, 0.24g) and montmorillonite clay (1.0eq, 0.24g) were added to a round bottom flask containing 1,4-dioxane (5cm^3) and stirred at room temperature. To this solution was added 1-pentyl isocyanide (1.2eq, 1.2mmol, 0.15cm^3) and the reaction mixture was heated to 100^{o}C and left stirring for 73 h. After this time the reaction mixture was allowed to cool and the solution was filtered through a celite plug to remove the Montmorillonite clay. The filtrate was collected and the solvent was removed *in vacuo* to afford a

yellow oil which was purified by flash chromatography (5% EtOAc-Hexane) to give a solid white product (0.84mmol, 0.20g, 84%) which was identified by NMR spectroscopy as starting material **64a**.

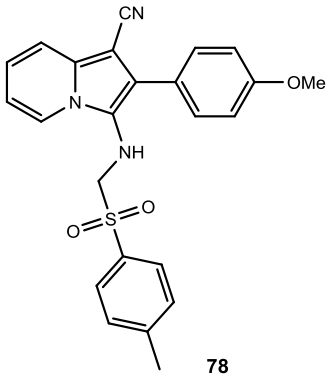
*2.2.3.2 Attempted Synthesis of 3-(tert-butylamino)-2-(2-chlorophenyl)indolizine-1-carbonitrile **64***



64

To a stirring solution of 3-(2-chlorophenyl)-2-(pyridin-2-yl)acrylonitrile **64a** (1.0eq, 1.5mmol, 0.36g) and montmorillonite clay (1.0eq, 0.36g) in 1,4-dioxane (8cm^3) was added *t*-butyl isocyanide (1.2eq, 1.8mmol, 0.2cm^3). The reaction mixture was then heated to 100^{o}C and stirred for a further 73 h, after which time the solution was allowed to cool. The reaction mixture was then filtered though a celite plug to remove the inorganic residues and the filtrate was collected and the solvent removed *in vacuo* to afford a yellow oil. The crude product was purified by flash chromatography (5% EtOAc-Hexane) to give a white solid (1.3mmol, 0.32g, 90%) which was identified as the starting material **64a**.

*2.2.3.3 Attempted Synthesis of 2-(4-Methoxyphenyl)-3-(tosylmethylamino)indolizine-1-carbonitrile **78***

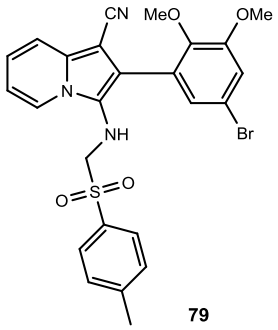


78

To a stirring solution of 3-(4-methoxyphenyl)-2-(pyridin-2-yl)acrylonitrile **63a** (1.0eq, 0.42mmol, 0.10g) in 1,4-dioxane (5cm^3) was added montmorillonite clay (1.0eq, 0.10g) and *p*-toluenesulfonyl methyl isocyanide (1.2eq, 0.51mmol, 0.10g). The reaction mixture was then stirred for 73 h at 100^{o}C, after which time the solution was allowed to cool and then filtered through a celite plug to remove the solid inorganic material. The filtrate was collected and the solvent removed *in vacuo* to

afford a crude off-white oil which was purified by flash chromatography (10% EtOAc-Hexane) to give an off-white solid (0.33mmol, 0.08g, 78%) which was identified as the starting material **63a**.

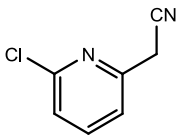
*2.2.3.4 Attempted Synthesis of 2-(5-Bromo-2,3-dimethoxyphenyl)-3-(tosylmethyl-amino)indolizine-1-carbonitrile **79***



79

Montmorillonite clay (1.0eq, 0.10g) and *p*-toluenesulfonyl methyl isocyanide (1.2eq, 0.35mmol, 0.07g) were added to a stirred solution of 3-(5-bromo-2,3-dimethoxypheny)-2-(pyridin-2-yl)acrylonitirile **65a** (1.0eq, 0.29mmol, 0.10g) in 1,4-dioxane (5cm^3). The reaction mixture was then heated to 100^{o}C and stirred for 73 h before being allowed to cool and filtered through celite. The filtrate was collected and the solvent removed *in vacuo* to afford a crude off-white oil. The crude product was adsorbed onto silica gel and purified by flash chromatography (10% EtOAc-Hexane) to yield a white solid (0.17mmol, 0.06g, 60%) which was identified as starting material **65a**.

*2.3 Synthesis of 2-(6-Chloropyridin-2-yl)acetonitrile **71***



71

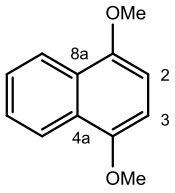
To a stirred solution of *n*-BuLi (1.4 M/hexane, 1.0eq, 35.4mmol, 25.3cm^3) at -78^{o}C under an inert atmosphere was rapidly added dry THF (250cm^3), followed immediately by the dropwise addition of dry MeCN (1.1eq, 39mmol, 2.0cm^3) in dry THF (3cm^3). The reaction mixture was stirred for 1 h at -78^{o}C during which time the clear solution turned to a milky white suspension. The reaction solution was then treated with 2,6-dichloropyridine (1.0eq, 10.83mmol, 1.602g) dissolved in dry THF (10cm^3) upon which time the solution turned from milky white to pale yellow. The reaction mixture was stirred for a further 1 h at -78^{o}C and then allowed to warm slowly to room temperature before being quenched with H_2O (50cm^3). The organic solvent was removed *in vacuo* to give a residual yellow solid, which was then dissolved in CH_2Cl_2 and washed with saturated aq. NaCl. The organic extracts were collected, dried over $MgSO_4$, filtered and the organic solvent removed *in*

vacuo to afford a yellow oil. The crude product was absorbed onto silica gel and purified by column chromatography (50% EtOAc-Hexane) to yield the product **71** as a yellow solid (9.09mmol, 1.39g, 84%). Spectroscopic data was in agreement with that of Skerlj *et al*.[65]

R_f = 0.32 (50% EtOAc-Hexane); **δ_H (400 MHz, $CDCl_3$)** 7.73 (1H, t, *J*=7.8Hz, Ar-H), 7.41-7.39 (1H, m, Ar-H), 7.37 – 7.28 (1H, m, Ar-H), 3.94 (2H, s, CCH_2CN); **δ_C (101 MHz, $CDCl_3$)** 151.06 (Ar*C*-CH_2), 139.96 (Ar*C*-Cl), 123.75 (2 Ar*C*-H), 120.75 (Ar*C*-H), 116.29 (CH_2CN), 26.13 (CCH_2CN).

3. Experimental Procedures: Synthesis of Benzo-fused Heteroaromatic Naphthoquinone and Napthopyranone Ring Systems

*3.1 Synthesis of 1,4-Dimethoxynaphthalene **156***

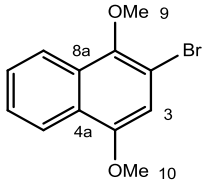


156

Commercially available 1,4-naphthoquinone (1.0eq, 0.588mol, 9.30g), $Na_2S_2O_4$ (10.0eq, 0.5881mol, 102.3g), H_2O (300cm^3) and Diethyl ether (500cm^3) were added together in a separating funnel and shaken vigorously for a period of 1 h. The ethereal layer was then collected, washed with brine (2 x 200cm^3), dried over Na_2SO_4, filtered and the organic solvent removed *in vacuo* to yield the naphthalene-1,4-diol as a brown solid. The intermediate product was not characterised as it is sensitive to air and was used directly in the next step. Dry acetone (250cm^3) was added to the naphthalene-1,4-diol intermediate followed by K_2CO_3 (4.0eq, 0.2352mol, 32.51g) and dimethyl sulphate (7.0eq, 0.4116mol, 51.92g). The now orange reaction mixture was heated and left to reflux for 22 h, after which time the solution was allowed to cool and filtered to remove the K_2CO_3. The filtrate was collected and the solvent was removed *in vacuo* to give a brown oil which was dissolved in diethyl ether and allowed to stir. 25% Ammonia solution (200cm^3) was added slowly to the stirring solution until the evolution of gas had stopped and was then transferred to a separating funnel where the organic layer was collected. The organic extracts were then washed with H_2O (150cm^3), 15% HCl (2 x 150cm^3) and brine (150cm^3), collected and dried over $MgSO_4$. The filtrate was collected and the solvent removed *in vacuo* to afford a light brown oil which was purified by column chromatography (20% EtOAc-Hexane) to yield the product **156** as a off white solid (0.046mol, 8.69g, 79%). Spectroscopic data was in agreement with that of Wege and co-workers.[89]

R_f = 0.62 (10% EtOAc-Hexane); **δ_H (300 MHz, $CDCl_3$)** 8.21 (2H, dd, *J*=6.4 and 3.3Hz, 2 Ar-H), 7.49 (2H, dd, *J*=6.4 and 3.3Hz, 2 Ar-H), 6.66 (2H, s, H^2 and H^3), 3.93 (6H, s, 2 O*C*H_3); **δ_C (75 MHz, $CDCl_3$)** 149.51 (C^1 and C^4), 126.36 (C^{4a} and C^{8a}), 125.89 (2 Ar*C*-H), 121.80 (2 Ar*C*-H), 103.18 (2 Ar*C*-H), 55.73 (O*C*H_3).

*3.2 Synthesis of 2-Bromo-1,4-dimethoxynaphthalene **157***



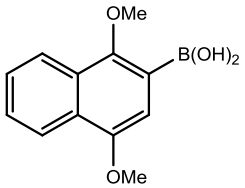
157

1,4-dimethoxynaphthalene **156** (1.0eq, 0.040mol, 7.58g) and NBS (1.0eq, 0.040mol, 7.17g) were dissolved in dry CH_2Cl_2 (100cm^3) and allowed to stir at room temperature for 21 h. The reaction mixture was then transferred to a separating funnel and washed with a saturated aqueous $NaSO_3$ solution. The organic layer was collected, dried over $MgSO_4$, filtered and the solvent removed *in vacuo* to afford a brown oil. The crude product was purified by column chromatography (10% EtOAc-Hexane) to yield the pure product **157** as a white solid (0.026mol, 6.98g, 65%). Spectroscopic data was in agreement with that of Bloomer and Zheng.[90]

R_f = 0.72 (10% EtOAc-Hexane); **δ_H (300 MHz, $CDCl_3$)** 8.40 – 7.84 (2H, m, 2 Ar-H), 7.70 – 7.39 (2H, m, 2 Ar-H), 6.88 (1H, s, H^3), 3.96 (3H, s, O*C*$H_3{}^9$)*, 3.95 (3H, s, O*C*$H_3{}^{10}$)*; **δ_C (75 MHz, $CDCl_3$)** 152.28 (C^1)*, 146.77 (C^4)*, 129.00 (ArC), 127.39 (Ar*C*-H), 125.81 (2 Ar*C*-H), 122.60 (Ar*C*-H), 121.85 (Ar*C*-H), 111.92 (ArC), 107.92 (ArC), 61.44 (C^9)*, 55.89 (C^{10})*.

* Assignments with superscripts can be interchanged

*3.3 Synthesis of 1,4-Dimethoxynaphthalen-2-yl boronic acid **158***

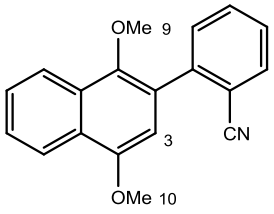


158

The 2-bromo-1,4-dimethoxynaphthalene **157** (1.0eq, 1.488mmol, 0.3528g) was dissolved in dry THF (30cm^3) in a dry two-necked flask fitted with a septum. All air was removed from the solution by bubbling N_2 gas though the reaction mixture for approximately 10 min. The reaction solution

was then cooled to -78^{o}C and n-BuLi (1.6M/hexane, 3.0eq, 4.5mmol, 1.5cm^{3}) was added slowly to the reaction via a syringe. The solution was left to stir at -78^{o}C for 40 min before the addition of the trimethyl borate (3.0eq, 4.5mmol, 0.50cm^{3}). The solution was stirred for a further 1 h at -78^{o}C and was then allowed to warm to room temperature before being quenched with 10% aqueous HCl solution (60cm^{3}) and extracted with diethyl ether (3 x 40cm^{3}). The organic extracts were collected and the solvent removed *in vacuo* to give a clear oil which yielded a white solid on addition of acetone. The solid was filtered, collected and dried to afford the boronic acid **158** as a flaky white solid (1.138mmol, 0.2641g, 76%). The product was not characterised due to solubility and stability problems and was used directly in the following synthetic step.

*3.4 Synthesis of 2-(1,4-Dimethoxynaphthalen-2-yl)benzonitrile **159***



159

3.4.1 Method A:

$Pd(PPh_3)_4$ (0.15eq, 0.1144mmol, 0.1322g) was placed in a 3-neck round bottom flask which was evacuated of all O_2 and placed under an inert N_2 atmosphere. Next 1,4-dimethoxynaphthalen-2-yl boronic acid **158** (1.5eq, 0.7625mmol, 0.1540g) and commercially available 2-bromobenzonitrile (1.0eq, 0.5083mmol, 0.0910g) were dissolved in DME (5cm^{3}) and EtOH (10cm^{3}) in a dropping funnel and degassed by bubbling N_2 though the solution for 10 min. This solution was then added to the $Pd(PPh_3)_4$ in the reaction vessel under a closed system so as to prevent the introduction of any O_2 to the system. The yellow solution was stirred for 10 min at room temperature while 2M aqueous Na_2CO_3 (10cm^{3}) solution was degassed for 10 min in the dropping funnel. The 2M aqueous Na_2CO_3 solution was then added to the stirring reaction mixture once again careful to exclude all O_2 from the system. The resultant solution was then refluxed for 23 h after which time the yellow solution turned milky white. The milky reaction mixture was quenched with H_2O (50cm^{3}) and the organic products were extracted into CH_2Cl_2 (3 x 50cm^{3}) and dried over $MgSO_4$. Once the extracts were sufficiently dry they were filtered, collected and the solvent removed *in vacuo* to afford a pale residue. The crude product was purified via column chromatography (20% EtOAc-Hexane) to afford the product **159** as a white solid (0.2561mmol, 0.0741g, 50%) and debrominated starting material, benzonitrile (0.0402g, 8%).

3.4.2 Method B:

Once again $Pd(PPh_3)_4$ (0.2eq, 0.0748mmol, 0.0864g) was placed in a 3-neck round bottom flask, evacuated of all O_2 and placed under an N_2 atmosphere as in Method A. Previously synthesised 2-bromo-1,4-dimethoxynaphthalene **157** (1.0eq, 0.3822mmol, 0.1021g) and commercially available 2-cyanophenylboronic acid (1.0eq, 0.3821mmol, 0.0561g) were dissolved in DME ($5cm^3$) and EtOH ($5cm^3$) in a dropping funnel and degassed by bubbling N_2 though the solution for 10 min. The degassed solution was then added quickly to the $Pd(PPh_3)_4$ in the reaction vessel being careful to exclude all O_2 from the system. The yellow reaction mixture was then stirred at room temperature whilst a 2M aqueous Na_2CO_3 solution ($10cm^3$) was degassed for 10 min in the dropping funnel. Finally the 2M aqueous Na_2CO_3 solution was added to the stirring solution and the reaction mixture was refluxed for 19 h upon which time the solution changed form a yellow colour to milky white. The reaction was quenched with H_2O ($50cm^3$) and the organic products were extracted with CH_2Cl_2 (3 x $40cm^3$) and dried over $MgSO_4$. The dried organic extracts were filtered, collected and the solvent removed *in vacuo* to afford a crude oil, which was further purified by column chromatography (20% EtOAc-Hexane) to yield the product **159** as a white solid (0.2146mmol, 0.0621g, 56%).

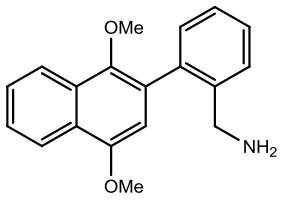
3.4.3 Method C:

Synthesised 2-bromo-1,4-dimethoxynaphthalene **157** (1.0eq, 0.3743mmol, 0.1001g) and commercially available 2-cyanophenylboronic acid (2.0eq, 0.0.7488mmol, 0.1103g) were placed in a 3-neck round bottom flask and dissolved in DMF ($4cm^3$). The solution was degassed for 10 min by bubbling N_2 through the reaction mixture and then placed under an inert atmosphere to exclude O_2 from the system. $Pd(PPh_3)_4$ (0.2eq, 0.1498mmol, 0.1730g) and K_3PO_4 (4.0eq, 2.9952mmol, 0.0620g) were then added to the reaction solution under flowing N_2 gas to give a yellow reaction mixture. The reaction was then refluxed for 47 h during which time the solution changed from yellow to dark brown in colour. The reaction was quenched with brine ($25cm^3$) and the organic products were extracted with Diethyl ether (3 x $25cm^3$). The organic extracts were once again dried over $MgSO_4$, collected and the solvent removed *in vacuo* to afford an orange oil. The crude product was purified by column chromatography (20% EtOAc-Hexane) to yield the product **159** as a white solid (0.1680mmol, 0.0486g, 45%).

R_f = 0.44 (20% EtOAc-Hexane); ***m.p.*** 86-88˚C; **I.R. (*v*/cm^{-1})** 2959 – 2830 (w, ArCO-*C*-H_3), 2330 (w, ArC-*CN*), 1631 – 1590 (s, Ar*C*=*C*), 1263 – 1240 (s, Ar*C*-*O*-*C*H_3); **δ_H (300 MHz, $CDCl_3$)** 8.23 (2H, m, 2 Ar-H), 7.91 – 7.37 (6H, m, 6 Ar-H), 6.73 (1H, s, H^3), 4.00 (3H, s, OCH_3^9)*, 3.52 (3H, s, OCH_3^{10})*; **δ_C (75 MHz, $CDCl_3$)** 151.79 (C^1)*, 147.26 (C^4)*, 142.85 (ArC), 133.23 (Ar*C*-H), 132.41 (Ar*C*-H), 131.38 (Ar*C*-H), 128.77 (ArC), 127.72 (Ar*C*-H), 127.05 (Ar*C*-H), 126.87 (ArC), 126.31 (Ar*C*-H), 126.21 (ArC), 122.47 (Ar*C*-H), 122.42 (Ar*C*-H), 118.54 (Ar-*C*N), 112.96 (ArC), 105.42 (Ar*C*-H),

61.90 (OCH_3^9)*, 55.84 (OCH_3^{10})*; **MS *m/z* (%)** 189 (60), 188 (100), 174 (56). 146 (16), 145 (86), 143 (20), 129 (72), 127 (18), 118 (12), 116 (28), 115 (86), 114 (52), 113 (14), 105 (2), 103 (22), 102 (76); ***HRMS*** could not obtain a molecular ion for $C_{19}H_{15}O_2N$

*3.5 Attempted Synthesis of 2-(1,4-Dimethoxynaphthalene-2-yl)phenyl)methanamine **160***



160

3.5.1 Method A: Attempted Hydrogenation in the Hydrogenator

2-(1,4-Dimethoxynaphthalen-2-yl)benzonitrile **159** (1.0eq, 0.35mmol, 0.10g) was dissolved in CH_2Cl_2 (5cm^3) in the hydrogenation vessel. The hydrogenation catalyst 5% Pd/C (0.1eq by mass, 0.01g) was then added to the reaction vessel followed by conc. HCl (3 drops). The reactants were then stirred at room temperature for 16 h under a 4.5kPa H_2 atmosphere. The resultant solution was filtered through celite to remove the Pd/C and the organic filtrate was collected, washed with H_2O (20cm^3) and the organic products were extracted with CH_2Cl_2 (3 x 10cm^3). The organic extracts were dried over $MgSO_4$, collected and the solvent removed *in vacuo* to afford a white product (0.342mmol, 0.990g, 99%) which was characterised by NMR spectroscopy to be starting material **159**.

All other attempts at reducing the nitrile to the amine using varying pressures, solvents and catalyst loadings in the hydrogenator yielded only starting material **159** and are discussed in Chapter 5.

3.5.2 Method B: Attempted Hydrogenation using $LiAlH_4$ as a Reducing Agent

3.5.2.1 Method B1

2-(1,4-Dimethoxynaphthalen-2-yl)benzonitrile **159** (1.0eq, 0.55mmol, 0.16g) was dissolved in THF (20cm^3) and cooled to 0^oC whilst stirring. $LiAlH_4$ (2.5eq, 1.38mmol, 0.053g) was added slowly to the solution to avoid a vigorous reaction and once the addition was completed the reaction was allowed to warm to room temperature and stir for 1 h. After this time the reaction was quenched with H_2O (20cm^3) and 10% aqueous HCl (20cm^3) and the organic solvent was removed *in vacuo*. The organic products were then extracted with diethyl ether (3 x 30cm^3), dried over $MgSO_4$, collected and the solvent was once again removed *in vacuo* to yield a white solid. A crude NMR showed the white solid to be starting material **159** (0.5480mmol, 0.1586g, 99%).

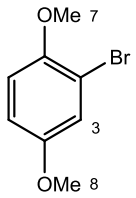
3.5.2.2 Method B2

Once again 2-(1,4-dimethoxynaphthalen-2-yl)benzonitrile **159** (1.0eq, 1.2mmol, 0.29g) was dissolved in THF (30cm^3) and cooled to 0^{o}C whilst stirring. $LiAlH_4$ (20.0eq, 0.02mol, 0.92g) was then added slowly to the stirring solution. After the addition of $LiAlH_4$ was complete the reaction was allowed to warm to room temperature and was stirred for 22 h after which time it was quenched with H_2O (50cm^3) and 10% aqueous HCl (20cm^3). The organic solvent was removed *in vacuo* and the organic products were then extracted with diethyl ether (3 x 50cm^3), dried over $MgSO_4$ and collected. The organic solvent was removed *in vacuo* to afford a white solid which was characterised by NMR spectroscopy to be starting material **159** (1.204mmol, 0.2881g, 99%).

3.5.3 Method C: Attempted Hydrogenation using Raney-Nickel

2-(1,4-Dimethoxynaphthalen-2-yl)benzonitrile **159** (1.0eq, 0.1728mmol, 0.0502g) was dissolved in EtOH (5cm^3) and EtOAc (5cm^3) and to this clear solution was added 2N NaOH (10cm^3). The solution was stirred at room temperature for 10 min before the Raney alloy (2.0eq by mass, 0.10g) was added in one portion causing the clear solution to become black. The reaction mixture was stirred for a further 3 h after which time the organic solvent was removed *in vacuo* and the organic products were extracted with CH_2Cl_2 and dried over $MgSO_4$. The organic extracts were collected and the solvent removed *in vacuo* to afford a white solid which was characterised by NMR spectroscopy to be starting material **159** (0.1701mmol, 0.0491g, 98%).

*3.6 Synthesis of 2-Bromo-1,4-dimethoxybenzene **162***

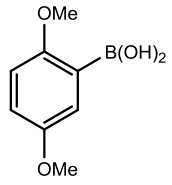


162

Commercially available 1,4-dimethoxybenzene (1.0eq, 0.022mol, 3.02g) and NBS (1.0eq, 0.022mol, 3.89g) were dissolved in CH_2Cl_2 (30cm^3) and refluxed for 52 h. After which time the reaction was transferred to a separating funnel and quenched with saturated aqueous $NaSO_3$ solution. The organic layer was collected and dried over $MgSO_4$ to afford a clear solution. The solvent was removed *in vacuo* to give a crude oil which was purified by column chromatography (20% EtOAc-Hexane) to yield the product **162** as a clear oil (0.019mol, 4.08g, 86%). Spectroscopic data was in agreement with Bloomer and Zheng.[90]

R_f = 0.66 (20% EtOAc-Hexane); **δ_H (300 MHz, $CDCl_3$)** 7.13 (1H, d, *J*=1.7Hz, H^3), 6.83 (2H, m, 2 Ar-H), 3.84 (3H, s, OCH_3^7)*, 3.76 (3H, s, OCH_3^8)*; **δ_C (75 MHz, $CDCl_3$)** 154.02 (C^1)*, 150.28 (C^4)*, 119.01 (Ar*C*-H), 118.92 (ArC), 113.39 (Ar*C*-H), 112.89 (Ar*C*-H), 56.98 (OCH_3^7)*, 55.88 (OCH_3^8)*.

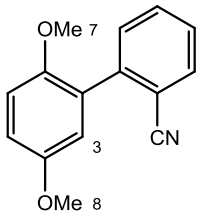
*3.7 Synthesis of 2,5-Dimethoxyphenylboronic acid **163***



163

2-Bromo-1,4-dimethoxybenzene **162** (1.0eq, 9.26mmol, 2.01g) was dissolved in dry THF (50cm^3) in a two-necked flask fitted with a septum. The solution was degassed for 10 min and placed under an inert N_2 atmosphere to exclude moisture. The reaction solution was then cooled to -78^{o}C using an acetone and liquid N_2 bath and *n*-BuLi (1.2M/hexane, 2.0eq, 0.019mol, 15.5cm^3) was added slowly to the reaction via a syringe. The solution was left to stir at -78^{o}C for 1 h before trimethyl borate (3.0eq, 0.03mol, 3.1cm^3) was added to the reaction. The solution was stirred for a further 1 h at -78^{o}C and was then allowed to warm to room temperature over night before being quenched with 10% aqueous HCl solution (100cm^3) and extracted with diethyl ether (3 x 100cm^3). The organic extracts were collected, dried over $MgSO_4$, filtered and the solvent removed *in vacuo* to give a clear oil which yielded a white solid on addition of acetone. The solid was collected and dried to afford the boronic acid **163** as a flaky white solid (3.561mmol, 0.6480g, 38%). The product was not characterised due to solubility and stability problems and was used directly in the following synthetic step.

*3.8 Synthesis of 2',5'-Dimethoxybiphenyl-2-carbonitrile **164***



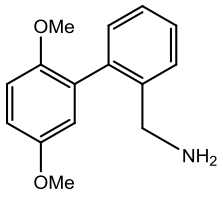
164

$Pd(PPh_3)_4$ (0.1eq, 0.1923mmol, 0.2219g) was placed in a 3-neck round bottom flask which was evacuated of all oxygen and placed under an inert N_2 atmosphere. Commercially available 2-bromobenzonitrile (1.0eq, 1.923mmol, 0.3506g) and previously synthesised 2,5-dimethoxyphenylboronic acid **163** (1.0eq, 1.9mmol, 0.35g) were dissolved in EtOH (7cm^3) and DME (7cm^3) in dropping funnel. The solution was degassed by bubbling N_2 through the solution

for 10 min and then added to the $Pd(PPh_3)_4$ in the round bottom flask being careful to maintain the inert atmosphere. The resulting yellow solution was allowed to stir at room temperature for 10 min whilst a 2M aqueous Na_2CO_3 solution was being degassed in the dropping funnel. The degassed aqueous Na_2CO_3 was then added to the stirring yellow solution and the reaction mixture was set to reflux for 27 h. After this time the reaction was quenched with H_2O ($30cm^3$) and the organic products were extracted with CH_2Cl_2 (3 x $30cm^3$), dried over $MgSO_4$ and the solvent was removed *in vacuo* to afford a yellow oil. The yellow oil was further purified by column chromatography (10% EtOAc-Hexane) to yield the product **164** as a yellow oil (1.103mmol, 0.2640g, 57%). Spectroscopic data was in agreement with Al-Fakhri *et al*.[92]

R_f = 0.61 (20% EtOAc-Hexane); **δ_H (300 MHz, $CDCl_3$)** 7.28 – 7.03 (4H, m, 4 Ar-H), 6.80 (2H, m, 2 Ar-H), 6.72 – 6.61 (1H, d, *J*=1.71Hz, H^3), 3.71 (3H, s, OCH_3^7)*, 3.62 (3H, s, OCH_3^8)*; **δ_C (75 MHz, $CDCl_3$)** 153.54 (C^1)*, 150.65 (C^4)*, 142.33 (ArC), 132.79 (Ar*C*-H), 132.51 (Ar*C*-H), 130.86 (Ar*C*-H), 127.98 (ArC), 127.54 (Ar*C*-H), 118.66 (Ar-*C*N), 116.74 (Ar*C*-H), 114.98 (Ar*C*-H), 113.34 (ArC), 112.48 (Ar*C*-H), 55.97 (OCH_3^7)*, 55.78 (OCH_3^8)*.

*3.9 Attempted Synthesis of (2',5'-Dimethoxybiphenyl-2-yl)methanamine **165***



165

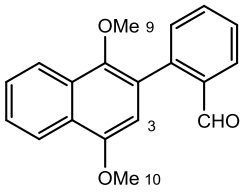
3.9.1 Method A:

2',5'-Dimethoxybiphenyl-2-carbonitrile **164** (1.0eq, 0.3762mmol, 0.0903g) was dissolved in MeOH ($7cm^3$) in the hydrogenation vessel and 10% Pd/C (0.1eq, 0.0090g) and conc. HCl (3 drops) were then added to this solution. The reaction mixture was then set up to stir at room temperature for 37 h at 7 kPa in the hydrogenator. After which time the pressure was released and the reaction mixture was filtered through celite to remove the solid Pd/C. The organic products were collected, washed with H_2O, dried over $MgSO_4$ and the solvent was removed *in vacuo* to afford a crude oil. The crude product was purified by column chromatography (10% EtOAc-Hexane) to yield a yellow oil, which was identified by NMR spectroscopy to be starting material **164** (0.3744mmol, 0.0891g, 99%).

3.9.2 Method B:

2',5'-Dimethoxybiphenyl-2-carbonitrile **164** (1.0eq, 1.046mmol, 0.2503g) was dissolved in THF (10cm^3) and cooled to 0^{o}C in an ice bath. $LiAlH_4$ (20.0eq, 0.0209mol, 0.7940g) was then added slowly to the stirring solution after which time the reaction was allowed to warm to room temperature. The reaction was stirred at room temperature for 2 h before it was quenched with H_2O (30cm^3) and 10% aqueous HCl solution (20cm^3). The organic solvent was removed *in vacuo* and the organic products were then extracted with diethyl ether (3 x 40cm^3), dried over $MgSO_4$ and collected. The organic solvent was removed *in vacuo* to afford a yellow oil which was pure enough to be characterised by NMR spectroscopy as starting material **164** (1.034mmol, 0.2474g, 99%).

*3.10 Synthesis of 2-(1,4-Dimethoxynaphthalen-2-yl)benzaldehyde **166***



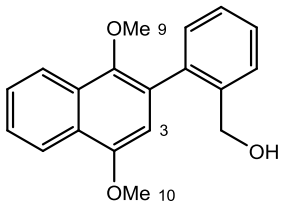
166

$Pd(PPh_3)_4$ (0.2eq, 2.05mmol, 2.37g) was placed under an inert N_2 atmosphere in a 3-necked round bottom flask. 2-bromo-1,4-dimethoxynaphthalene **157** (1.0eq, 0.010mol, 2.74g) and 2-formylphenylboronic acid (2.0eq, 0.021mol, 3.07g) were dissolved in EtOH (20cm^3) and DME (20cm^3) and the solution was degassed using N_2 for 10 min. The degassed solution was then added to the round bottom flask and the mixture was stirred at room temperature for 10 min whilst a 2M aqueous Na_2CO_3 solution (20cm^3) was degassed in the same way. Once the aqueous Na_2CO_3 solution had been added to the mixture the reaction was set to reflux for 73 h, after which time the reaction was quenched with H_2O (100cm^3). The organic products were extracted with CH_2Cl_2 (3 x 100cm^3), dried over $MgSO_4$ and the organic solvent removed *in vacuo* to afford a yellow oil. The crude product was further purified by column chromatography (5%-25% EtOAc-Hexane) to yield the product **166** as a white solid (6.43mmol, 1.88g, 63%).

R_f = 0.63 (20% EtOAc-Hexane); ***m.p.*** 190-192˚C; **I.R. (*v*/cm^{-1})** 2935 (w, ArCO-*C*-*H*$_3$), 2861 (w, -*CH*O), 1726 (m, -H*C*=*O*), 1625 – 1469 (s, Ar*C*=*C*), 1263 – 1224 (s, Ar*C*-*O*-*C*H$_3$); **δ_H (300 MHz, $CDCl_3$)** 9.90 (1H, s, C*H*O), 8.42 – 8.20 (1H, m, Ar-H), 8.25 – 7.97 (2H, m, 2 ArH), 7.83 – 7.45 (5H, m, 5 Ar-H), 6.74 (1H, s, H^3), 4.01 (3H, s, OC*H*$_3^9$)*, 3.40 (3H, s, OC*H*$_3^{10}$)*; **δ_C (75 MHz, $CDCl_3$)** 192.48 (*C*HO), 152.06 (C^1)*, 146.98 (C^4)*, 141.93 (ArC), 133.74 (ArC), 133.60 (Ar*C*-H), 131.02 (Ar*C*-H), 128.39 (ArC), 127.97 (ArC), 127.26 (Ar*C*-H), 127.09 (Ar*C*-H), 126.63 (ArC), 126.27 (Ar*C*-H), 125.39 (ArC), 122.39 (Ar*C*-H), 122.36 (Ar*C*-H), 105.84 (Ar*C*-H), 60.96 (O*C*H$_3^9$)*, 55.81 (O*C*H$_3^{10}$)*; **MS *m/z* (%)** 292 (M$^+$, 67), 279 (2), 277 (67), 276 (6), 263 (18), 262 (76), 261 (99), 249

(60), 246 (52), 249 (52), 234 (100), 221 (22), 219 (48), 218 (80), 205 (56), 202 (32), 190 (40), 189 (78), 178 (65), 163 (10), 152 (16), 151 (22), 148 (37), 138 (14), 130 (21), 128 (11), 117 (7), 114 (34); ***HRMS*** calculated mass for $C_{19}H_{16}O_3$: 292.1099; exact mass for $C_{19}H_{16}O_3$: 292.1100

*3.11 Synthesis of (2-(1,4-Dimethoxynaphthalen-2-yl)phenyl)methanol **167***

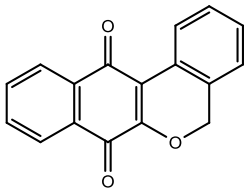


167

To a solution of synthesised 2-(1,4-dimethoxynaphthalen-2-yl)benzaldehyde **166** (1.0eq, 0.27mmol, 0.08g) in dry THF (5cm^3) was slowly added $LiAlH_4$ (3.0eq, 0.8210mmol, 0.0312g). The resulting reaction mixture was stirred for 40 min at room temperature before being quenched with H_2O (10cm^3). The organic products were extracted into diethyl ether (3 x 30cm^3), dried over $MgSO_4$ and the solvent removed *in vacuo* to afford a crude oil. The crude product was further purified by column chromatography (30% EtOAc-Hexane) to yield the product **167** as a white solid (0.2684mmol, 0.0790g, 98%).

R_f = 0.31 (20% EtOAc-Hexane); **m.p.** 114-115˚C; **I.R. (*v*/cm^{-1})** 3251 (m broad, CH_2*O*-*H*), 2838 (m, ArC-*C*-*H*$_2$OH), 1625 – 1454 (s, Ar*C*=*C*), 1273 – 1229 (s, Ar*C*-*O*-*C*H_3); **δ_H (300 MHz, $CDCl_3$)** 8.29 (1H, d, *J*=7.8Hz, Ar-H), 8.10 (1H, d, *J*=7.7Hz, Ar-H), 7.74 – 7.30 (6H, m, 6 Ar-H), 6.62 (1H, s, H^3), 4.40 (2H, d, *J*=13.0Hz, C*H*$_2$OH), 3.95 (3H, s, OC*H*$_3^9$)*, 3.56 (1H, broad s, CH_2O*H*), 3.48 (3H, s, OC*H*$_3^{10}$)*; **δ_C (75 MHz, $CDCl_3$)** 152.00 (C^1)*, 146.16 (C^4)*, 139.49 (ArC), 137.96 (ArC), 130.09 (Ar*C*-H), 129.96 (ArC), 129.14 (ArC), 128.33 (Ar*C*-H), 128.31 (Ar*C*-H), 127.88 (Ar*C*-H), 127.12 (ArC), 126.15 (Ar*C*-H), 125.85 (Ar*C*-H), 122.36 (Ar*C*-H), 122.10 (Ar*C*-H), 106.32 (Ar*C*-H), 64.13 (*C*H_2OH), 61.66 (OCH_3^9)*, 55.75 (OCH_3^{10})*; **MS *m/z* (%)** 294 (M$^+$, 86), 292 (28), 279 (7), 278 (12), 276 (6), 263 (17), 262 (58), 261 (78), 250 (20), 249 (100), 247 (45), 235 (24), 234 (92), 221 (36), 218 (71), 206 (12), 205 (46), 202 (46), 191 (44), 189 (90), 178 (40), 165 (40), 152 (26), 149 (30), 131 (18), 123 (19), 115 (43); ***HRMS*** calculated mass for $C_{19}H_{18}O_3$: 294.1256; exact mass for $C_{19}H_{18}O_3$: 294.1256

*3.12 Synthesis of 5-H-dibenzo[c,g]chromene-7,12-dione **154***



154

3.12.1 Method A:

To a solution of (2-(1,4-dimethoxynaphthalen-2-yl)phenyl)methanol **167** (1.eq, 0.17mmol, 0.05g) in CH_3CN ($2cm^3$) and CH_3Cl ($2cm^3$) was added CAN (3.0eq, 0.5096mmol, 0.2790g) dissolved in H_2O ($8cm^3$). The milky yellow solution was stirred at room temperature for 68 h after which time a TLC revealed only starting material to be present. Additional CAN (3.0eq, 0.5096mmol, 0.2786g) was added to the reaction mixture and the solution was heated to 63^oC and stirred for a further 23 h. The reaction mixture was then allowed to cool and the organic products were extracted with EtOAc, dried over $MgSO_4$ and the solvent removed *in vacuo* to afford a brown oil. The crude product was purified by column chromatography (10%-50% EtOAc-Hexane) to afford two oily products which when characterised by NMR spectroscopy appeared to be nothing more than decomposition of the starting material.

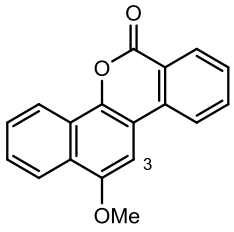
3.12.2 Method B:

To a stirred clear solution of (2-(1,4-dimethoxynaphthalen-2-yl)phenyl)methanol **167** (1.eq, 0.14mmol, 0.04g) in dry THF ($3cm^3$) was added Ag_2O (6.0eq, 0.82mmol, 0.10g). Addition of 6M HNO_3 ($1.5cm^3$) solubilised the Ag_2O the clear solution became orange. The reaction was stirred for 30 min at room temperature after which time the organic solvent was removed *in vacuo* to give a dark red residue which was dissolved in CH_2Cl_2 ($20cm^3$) and H_2O ($20cm^3$). The organic products were extracted with CH_2Cl_2 (3 x $30cm^3$), dried over $MgSO_4$ and the solvent removed *in vacuo* to afford a crude red oil. The crude product was purified by column chromatography (25%-80% EtOAc-Hexane) to afford the product **154** as a dark red amorphous solid (0.0774mmol, 0.0203g, 60%). Spectroscopic data was in agreement with that of Onofrey *et al*.[80]

R_f = 0.47 (50% EtOAc-Hexane); **δ_H (300 MHz, $CDCl_3$)** 8.47 (1H, d, *J*=7.9Hz, Ar-H), 8.12 (1H, d, *J*=7.5Hz, Ar-H), 7.94 (1H, d, *J*=7.8Hz, Ar-H), 7.70 (1H, t, *J*=7.6Hz, Ar-H), 7.58 (1H, t, *J* =7.6Hz, Ar-H), 7.37 (2H, m, 2 Ar-H), 7.14 (1H, d, *J*=7.3Hz, Ar-H), 5.42 (2H, s, O-C*H*$_2$-C); **δ_C (75 MHz, $CDCl_3$)** 179.17 (C^1=O)*, 177.19 (C^4=O)*, 164.15 (ArC), 135.18 (Ar*C*-H), 131.67 (ArC), 131.60 (Ar*C*-H), 130.29 (ArC), 129.07 (Ar*C*-H), 128.92 (Ar*C*-H), 128.42 (Ar*C*-H), 126.84 (ArC), 126.65 (ArC),

125.94 (Ar*C*-H), 124.84 (Ar*C*-H), 123.85 (Ar*C*-H) 113.84 (ArC), 70.20 (O-*C*H_2-C); **MS *m/z* (%)** 263 (M^+, 100); ***HRMS*** calculated mass for $C_{17}H_{10}O_3$: 262.0630; exact mass for $C_{17}H_{10}O_3$: 262.0625

*3.13 Synthesis of 12-Methoxy-6H-dibenzo[c,h]chromen-6-one **170***

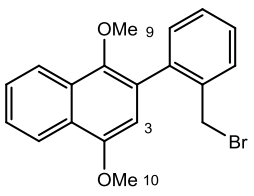


170

To a stirring solution of (2-(1,4-dimethoxynaphthalen-2-yl)phenyl)methanol **167** (1.0eq, 0.1698mmol, 0.0503g) in dry CH_2Cl_2 (5cm^3) was added NBS (1.0eq, 0.1698mmol, 0.0302g). The reaction mixture was stirred at room temperature for 21 h during which time the reaction had changed from clear to dark red in colour. The reaction was quenched with saturated aqueous Na_2SO_3 solution (15cm^3) and the organic products were extracted with CH_2Cl_2 (3 x 20cm^3), dried and the solvent removed *in vacuo* to yield a brown solid. The crude product was purified by column chromatography (20% EtOAc-Hexane) to afford a brown solid. This solid was dissolved in hot diethyl ether and placed in the freezer overnight to yield the product **170** as a pure white crystalline substance (0.1466mmol, 0.0405g, 86%). Spectroscopic data was in agreement with the of Jones and Qabaja.[88]

R_f = 0.24 (20% EtOAc-Hexane); **δ_H (300 MHz, $CDCl_3$)** 8.52-8.46 (2H, m, 2 Ar-H), 8.26 (1H, d, *J*=7.5Hz, Ar-H), 8.11 (1H, d, *J*=7.8Hz, Ar-H), 7.84 (1H, dt, *J*=7.6 and 1.2Hz, Ar-H), 7.62 (3H, m, 3 Ar-H), 7.21 (1H, s, H^3), 4.10 (3H, s, O*C*H_3); **δ_C (75 MHz, $CDCl_3$)** 161.40 (C=O), 152.36 (C^4), 141.78 (C^1), 135.44 (ArC), 134.76 (Ar*C*-H), 130.68 (Ar*C*-H), 128.45 (Ar*C*-H), 127.64 (Ar*C*-H), 127.35 (Ar*C*-H), 126.73 (ArC), 124.72 (ArC), 122.12 (Ar*C*-H), 122.05 (Ar*C*-H), 121.85 (Ar*C*-H), 121.36 (ArC), 112.64 (ArC), 95.71 (Ar*C*-H), 55.77 (O*C*H_3).

*3.14 Synthesis of 2-[2-(Bromomethyl)phenyl]-1,4-dimethoxynaphthalene **172***



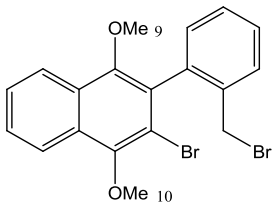
172

The previously synthesised (2-(1,4-dimethoxynaphthalen-2-yl)phenyl)methanol **167** (1.0eq, 0.6795mmol, 0.2004g) was dissolved in dry CH_2Cl_2 (15cm^3) in a 2-neck round bottom flask fitted with a $CaCl_2$ drying tube. PPh_3 (5.0eq, 3.397mmol, 0.8913g) and CBr_4 (5.0eq, 3.397mmol, 1.133g) were then added to the clear solution which turned dark orange and was then left to stir at room temperature for 3 h. After this time the solvent was removed *in vacuo* and the orange residue was purified by column chromatography (5% EtOAc-Hexane) to afford the product **172** as a yellow oil (0.6438mmol, 0.2310g, 95%).

R_f = 0.31 (5% EtOAc-Hexane); **I.R. (*v*/cm^{-1})** 2931.73 (w, -*C*H_2Br), 1625.34 – 1458.12 (m - s, Ar*C*=*C*), 1271.46 – 1225.43 (s, Ar*C*-*O*-*C*H_3); **δ_H (300 MHz, $CDCl_3$)** 8.12 (2H, m, 2 Ar-H), 7.71 – 7.21 (6H, m, 6 Ar-H), 6.68 (1H, s, H^3), 4.43 (2H, q, *J*=10.1, CH_2Br), 3.92 (3H, s, OCH_3^9)*, 3.41 (3H, s, OCH_3^{10})*; **δ_C (75 MHz, $CDCl_3$)** 151.48 (C^1)*, 146.51 (C^4)*, 138.62 (ArC), 136.21 (ArC), 130.91 (Ar*C*-H), 130.80 (Ar*C*-H), 128.74 (ArC), 128.36 (Ar*C*-H), 128.24 (Ar*C*-H), 127.88 (ArC), 126.91 (Ar*C*-H), 126.31 (ArC), 125.85 (Ar*C*-H), 122.43 (Ar*C*-H), 122.29 (Ar*C*-H), 106.34 (Ar*C*-H), 61.63 (O*C*H$_3^9$)*, 55.91 (O*C*H$_3^{10}$)* , 32.61 (*C*H$_2$Br); **MS *m/z* (%)** 314 (1), 308 (2), 294 (1), 200 (2), 279 (1), 278 (6), 277 (21), 276 (100), 274 (15), 262 (2), 261 (8), 260 (27), 245 (7), 236 (), 230 (1); ***HRMS*** calculated mass for $C_{19}H_{17}O_2{}^{79}Br$: 356.0412 and $C_{19}H_{17}O_2{}^{81}Br$: 358.0392; exact mass for $C_{19}H_{17}O_2{}^{79}Br$: 356.0391 and $C_{19}H_{17}O_2{}^{81}Br$: 358.0374

*3.15 Attempted Synthesis of 12-Methoxy-6H-dibenzo[c,h]chromen-6-one **170***

*3.15.1 Attempted Synthesis from 2-[2-(Bromomethyl)phenyl]-1,4-dimethoxy naphthalene **172***



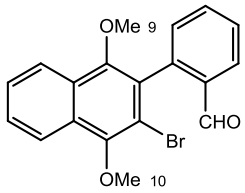
173

To a stirring solution of 2-(2-(bromomethyl)phenyl)-1,4-dimethoxy naphthalene **172** (1.0eq, 0.5598mmol, 0.2012g) in dry CH_2Cl_2 (25cm^3) was added NBS (1.0eq, 0.5598mmol, 0.1004g) and AIBN (0.1eq, 0.06mmol, 0.01g) and the resulting yellow solution was allowed to stir at room temperature for 64 h. Following this time the reaction was quenched with saturated aqueous Na_2SO_3 solution (30cm^3). The organic products were extracted with CH_2Cl_2 (3 x 40cm^3), dried over $MgSO_4$ and the organic solvent was removed *in vacuo* to yield an off-white solid which was identified as product **173** (0.4907mmol, 0.2140g, 88%).

R_f = 0.46 (10% EtOAc-Hexane); ***m.p.*** 103-104˚C; **I.R. (*v*/cm^{-1})** 2994 – 2843 (w, -*C*H_2r and O-*C*-*H*$_3$), 1664 – 1451 (m - s, Ar*C*=*C*), 1266 – 1220 (s, Ar*C*-*O*-*C*H_3); **δ_H (300 MHz, $CDCl_3$)** 8.22 – 8.10

(2H, m, 2 Ar-H), 7.65 – 7.57 (3H, m, 3 Ar-H), 7.44 (2H, m, 2 Ar-H), 7.27 (1H, dd, *J*=7.8 and 2.2Hz, Ar-H), 4.44 (1 H, d, *J*=10.5Hz, C*H*HBr), 4.30 (1 H, d, *J*=10.5Hz, CH*H*Br), 4.02 (3H, s, OCH_3^9)*, 3.56 (3H, s, OCH_3^{10})*; **δ_C (75 MHz, $CDCl_3$)** 150.46 (C^1)*, 150.29 (C^4)*, 136.84 (ArC), 136.37 (ArC), 131.25 (Ar*C*-H), 130.50 (Ar*C*-H), 129.96 (ArC), 129.02 (ArC), 128.78 (Ar*C*-H), 128.17 (ArC), 127.41 (Ar*C*-H), 126.90 (Ar*C*-H), 123.15 (Ar*C*-H), 122.77 (Ar*C*-H), 122.58 (Ar*C*-H), 115.50 (ArC), 61.98 (O*C*H_3^9)*, 61.46 (O*C*H_3^{10})*, 31.77 (*C*H_2Br); **MS *m/z* (%)** 435 (M^+, 16), 420 (7), 395 (2), 356 (6), 345 (60), 330 (100), 326 (7), 276 (10), 261 (25), 246 (30), 234 (68), 206 (70), 180 (42), 171 (28), 155 (10), 130 (28), 113 (29), 100 (41), 74 (32), 69 (50); ***HRMS*** calculated mass for $C_{19}H_{16}O_2{}^{79}Br_2$: 433.9517 and $C_{19}H_{16}O_2{}^{79}Br^{81}Br$: 435.9497; exact mass for $C_{19}H_{16}O_2{}^{79}Br_2$: 433.9511; for $C_{19}H_{16}O_2{}^{79}Br^{81}Br$: 435.9491 and for $C_{19}H_{16}O_2{}^{81}Br_2$: 437.9467

*3.15.2 Attempted Synthesis from 2-(1,4-Dimethoxynaphthalen-2-yl)benzaldehyde **166***

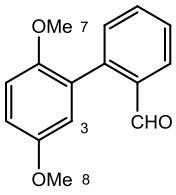


171

2-(1,4-dimethoxynaphthalen-2-yl)benzaldehyde **166** (1.0eq, 0.41mmol, 0.12g) was dissolved in CH_2Cl_2 (20cm^3) to afford a clear solution. NBS (2.0eq, 0.8210mmol, 0.1460g) and AIBN (0.2eq, 0.0821mmol, 0.0143g) were added to the reaction mixture and the resulting solution was allowed to stir at room temperature for 44 h after which time the reaction was quenched with saturated aqueous Na_2SO_3 solution (15cm^3). The organic products extracted with CH_2Cl_2, dried over $MgSO_4$ and the solvent removed *in vacuo* to afford a white solid. The white solid was purified by column chromatography (20% EtOAc-Hexane) to yield a white product which was identified by NMR spectroscopy to be product **171** (0.3610mmol, 0.1340g, 88%).

R_f = 0.68 (20% EtOAc-Hexane); ***m.p.*** 95-98˚C; **I.R. (*v*/cm^{-1})** 2997 – 2932 (w, -O-*C*-H_3), 2850 – 2758 (w, *CH*O), 1727 (s, H*C*=*O*), 1595 – 1456 (m - s, Ar*C*=*C*), 1261 – 1229 (s, Ar*C*-*O*-*C*H_3); **δ_H (300 MHz, $CDCl_3$)** 9.82 (1H, s, C*H*O), 8.30 – 8.04 (3H, m, 3 Ar-H), 7.66 (4H, m, 4 Ar-H), 7.42 (1H, d, *J*=7.3Hz, Ar-H), 4.02 (3H, s, OCH_3^9)*, 3.48 (3H, s, OCH_3^{10})*; **δ_C (75 MHz, $CDCl_3$)** 191.54 (*C*HO), 150.83 (C^1)*, 150.38 (C^4)*, 140.33 (ArC), 134.10 (ArC), 133.53 (Ar*C*-H), 132.06 (Ar*C*-H), 129.21 (ArC), 128.68 (Ar*C*-H), 128.23 (ArC), 127.95 (ArC), 127.63 (Ar*C*-H), 127.20 (Ar*C*-H), 123.10 (Ar*C*-H), 122.62 (Ar*C*-H), 119.11 (Ar*C*-H), 114.73 (ArC), 61.55 (O*C*H_3^9)*, 61.48 (O*C*H_3^{10})*; **MS *m/z* (%)** 372 (M^+, 4), 291 (100), 276 (24), 261 (81), 233 (22), 231 (3), 205 (11), 202 (5), 189 (12), 176 (24), 163 (3), 151 (6), 138 (6), 114 (3); ***HRMS*** calculated mass for $C_{19}H_{15}O_3{}^{79}Br$: 370.0205 and for $C_{19}H_{15}O_3{}^{81}Br$: 372.0184; exact for $C_{19}H_{15}O_3{}^{79}Br$: 370.0201 and for $C_{19}H_{15}O_3{}^{81}Br$: 372.0162

*3.16 Synthesis of 2',5'-Dimethoxybiphenyl-2-carbaldehyde **178***

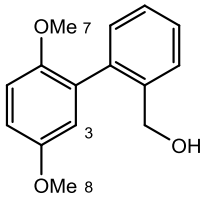


178

$Pd(dba)_2$ (0.15eq, 0.8295mmol, 0.4770g) was dissolved in DME ($8cm^3$) in a 3-neck round bottom flask and the resultant purple solution was degassed with N_2 and placed under an inert atmosphere. PPh_3 (0.8eq, 4.42mmol, 1.15g) was dissolved in DME ($8cm^3$), degassed with N_2 for 10min and added to the stirring reaction mixture via a dropping funnel. The solution was allowed to stir at room temperature for 30 min during which time the solution changed from purple to yellow in colour. Previously synthesised 2-bromo-1,4-dimethoxybenzene **162** (1.0eq, 5.52mmol, 1.20g) and commercially available 2-formylphenylboronic acid (1.2eq, 6.63, 1.77g) were dissolved in DME ($10cm^3$) and EtOH ($10cm^3$) in the dropping funnel and degassed for 10 min before being added to the stirring yellow solution. A 2M aqueous Na_2CO_3 solution ($20cm^3$) was degassed in the same way for 10 min and then added to the stirring solution. The reaction mixture was set to reflux for 19 h before being quenched with H_2O. The organic solvent was removed *in vacuo* and the organic products were extracted from the residue with CH_2Cl_2 (3 x $50cm^3$), dried over $MgSO_4$ and once again the solvent was removed *in vacuo* to afford a crude brown oil. The crude product was purified by column chromatography (10% EtOAc-Hexane) to yield the product **178** as a light brown oil (3.537mmol, 0.8570g, 64%). Spectroscopic data was in agreement with Zhao and co-workers.[96]

R_f = 0.40 (20% EtOAc-Hexane); **δ_H (300 MHz, $CDCl_3$)** 9.79 (1H, s, C*H*O), 7.98 (1H, dd, *J*=7.8 and 1.1Hz, Ar-H), 7.62 (1H, m, Ar-H), 7.52 – 7.30 (2H, m, 2 Ar-H), 6.98 – 6.83 (3H, m, 3 Ar-H), 3.79 (3H, s, OCH_3^7)*, 3.66 (3H, s, OCH_3^8)*; **δ_C (75 MHz, $CDCl_3$)** 192.53 (*C*HO), 153.80 (C^1)*, 150.74 (C^4)*, 141.60 (ArC), 134.02 (ArC), 133.68 (Ar*C*-H), 131.04 (Ar*C*-H), 127.85 (Ar*C*-H), 127.67 (ArC), 126.58 (Ar*C*-H), 117.30 (Ar*C*-H), 114.41 (Ar*C*-H), 111.81 (Ar*C*-H), 55.90 (OCH_3^7)*, 55.78 (OCH_3^8)*.

*3.17 Synthesis of (2',5'-Dimethoxybiphenyl-2-yl)methanol **179***

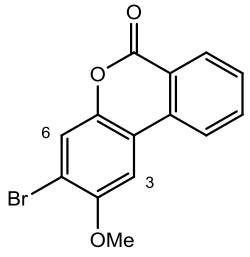


179

To a stirring solution of 2',5'-dimethoxybiphenyl-2-carbaldehyde **178** (1.0eq, 0.74mmol, 0.18g) in dry THF (10cm^3) was added $LiAlH_4$ (3.0eq, 2.229mmol, 0.0851g). The resulting solution was stirred at room temperature for 2 h before being quenched with H_2O (20cm^3) and 10% aqueous HCl (30cm^3). The organic products were extracted with diethyl ether (3 x 30cm^3), dried over $MgSO_4$ and the solvent removed in *vacuo* to afford an oily residue. Flash chromatography (20% EtOAc-Hexane) afforded the product **179** as a clear oil (0.5936mmol, 0.1450g, 80%).

R_f = 0.30 (20% EtOAc-Hexane); **I.R. (*v*/cm^{-1})** 3420 (broad, CH_2*O*-*H*) 2999 – 2835 (w, -*C*-H_2-OH and -O-*C*-H_3), 1600 – 1461 (m - s, Ar*C*=*C*), 1261 – 1211 (s, Ar*C*-*O*-*C*H_3); **δ_H (300 MHz, $CDCl_3$)** 7.51 (1H, dd, *J*=7.3 and 1.5Hz, Ar-H), 7.41 – 7.26 (2H, m, 2 Ar-H), 7.19 (1H, dd, *J*=7.3 and 1.6Hz, Ar-H), 6.87 (2H, m, 2 Ar-H), 6.73 (1H, dd, *J*=2.5 and 0.8Hz, Ar-H), 4.39 (2H, 2s, C*HH*OH), 3.73 (3H, s, OCH_3^7)*, 3.62 (3H, s, OCH_3^8)*, 2.78 (1H, broad s, CH_2O*H*); **δ_C (75 MHz, $CDCl_3$)** 153.89 (C^1)*, 150.63 (C^4)*, 139.38 (ArC), 137.34 (ArC), 131.05 (ArC), 130.12 (Ar*C*-H), 128.54 (Ar*C*-H), 128.07 (Ar*C*-H), 127.62 (Ar*C*-H), 117.07 (Ar*C*-H), 113.63 (Ar*C*-H), 112.79 (Ar*C*-H), 63.54 (*C*H_2OH), 56.61 (O*C*H_3^7)*, 55.72 (O*C*H_3^8)*; **MS *m/z* (%)** 240 (10), 226 (21) 224 (100); ***HRMS*** calculated for $C_{15}H_{16}O_3$: 244.1099; exact for $C_{15}H_{16}O_3$: 244.1093.

*3.18 Synthesis of 3-Bromo-2-methoxy-6H-benzo[c]chromen-6-one **180***



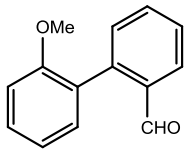
180

Previously synthesised compound (2',5'-dimethoxybiphenyl-2-yl)methanol **179** (1.0eq, 0.1244mmol, 0.0304g) was dissolved in $CHCl_3$ (7cm^3). To this stirred solution was added NBS (1.0eq, 0.1244mmol, 0.0222g) and radical initiator AIBN (0.2eq, 0.0249mmol, 0.0048g) and the clear solution was left to stir at room temperature for 16 h. Marking no distinct change in the starting material the reaction was set to reflux for 3 h upon which time the solution turned orange in colour. The reaction solution was quenched with saturated aqueous Na_2SO_3 solution (20cm^3) and the organic products extracted with CH_2Cl_2 (3 x 30cm^3). The organic extracts were dried over $MgSO_4$, the solvent removed *in vacuo* and purified by column chromatography (10% EtOAc-Hexane) to yield the product **180** as a white solid (0.0393mmol, 0.0120g, 32%).

R_f = 0.32 (10% EtOAc-Hexane); ***m.p***. 233-235˚C; **I.R. (*v*/cm^{-1})** 2921 – 2851 (w, -O-*C*-H_3), 1734 (s, C-O-*C*=*O*), 1605 – 1449 (m - s, Ar*C*=*C*); **δ_H (300 MHz, $CDCl_3$)** 8.42 (1H, d, *J*=7.9Hz, Ar-H), 8.08 (1H, d, *J*=8.1Hz, Ar-H), 7.85 (1H, t, *J*=7.8Hz, Ar-H), 7.72 – 7.53 (2H, m, 2 Ar-H), 7.46 (1H, s, Ar-H),

4.03 (3H, s, OC*H*$_3$); **δ_C (75 MHz, $CDCl_3$)** 160.72 (C=O), 153.02 (C^1)*, 145.45 (C^4)*, 134.90 (Ar*C*-H), 134.15 (ArC), 130.91 (Ar*C*-H), 129.26 (Ar*C*-H), 122.64 (Ar*C*-H), 121.56 (Ar*C*-H), 121.27 (ArC), 117.72 (ArC), 114.34 (ArC), 104.32 (Ar*C*-H), 56.85 (O*C*H$_3$); **MS *m/z* (%)** 307 (M$^+$ ^{81}Br, 56), 305 (M$^+$ ^{79}Br, 58), 285 (4), 279 (6), 261 (4), 259 (8), 241 (4), 229 (4), 228 (30), 227 (100); ***HRMS*** calculated for $C_{14}H_9O_3{}^{79}Br$: 303.9735 and for $C_{14}H_9O_3{}^{81}Br$: 305.9715; exact for $C_{14}H_9O_3{}^{79}Br$: 303.9741 and exact for $C_{14}H_9O_3{}^{81}Br$: 305.9720

3.19 Synthesis of 2'-Methoxybiphenyl-2-carbaldehyde ***182***

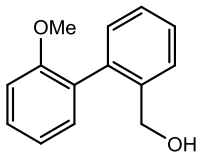


182

$Pd(DBA)_2$ (0.15eq, 0.4935mmol, 0.2841g) was dissolved in DME (5cm^3) and degassed by bubbling N_2 through the solution for 10 min. The solution was placed under an inert atmosphere to exclude all oxygen from the system. The PPh_3 (0.8eq, 2.6mmol, 0.69g) was dissolved in DME (5cm^3) in a dropping funnel and degassed by passing N_2 through the solution for 10 min. The PPh_3 solution was then added to the stirring purple solution in the flask and allowed to stir at room temperature for 30 min. After this time commercially available starting materials 2-methoxyphenylboronic acid (1.0eq, 3.3mmol, 0.50g) and 2-bromo benzaldehyde (1.0eq, 3.3mmol, 0.60g) were dissolved in DME (10cm^3) and EtOH (10cm^3), degassed with N_2 for 10 min and added to the now yellow solution. A 2M aqueous Na_2CO_3 solution (15cm^3) was degassed for 10 min in a dropping funnel and added to the reaction mixture. The reaction was refluxed for 26 h after which time H_2O (30cm^3) was added to quench the reaction and the organic solvent was removed *in vacuo* to afford a dark brown residue. The organic products were extracted from the residue with CH_2Cl_2 (3 x 40cm^3), dried over $MgSO_4$ and the solvent removed *in vacuo* to give a crude brown oil. The crude product was further purified by flash chromatography (5% EtOAc-Hexane) to yield the product **182** as a yellow oil (3.251mmol, 0.6902g, 99%). Spectroscopic data was in agreement with Zhao *et al*.[96]

R_f = 0.39 (5% EtOAc-Hexane); **δ_H (300 MHz, $CDCl_3$)** 9.79 (1H, s, C*H*O), 7.99 (1H, dd, *J*=7.7 and 1.2Hz, Ar-H), 7.64 (1H, td, *J*=7.5 and 1.5Hz, Ar-H), 7.53 – 7.23 (4H, m, 4 Ar-H), 7.05 (2H, m, 2 Ar-H), 3.73 (3H, s, OC*H*$_3$); **δ_C (75 MHz, $CDCl_3$)** 192.60 (*C*HO), 156.54 (Ar*C*-OCH$_3$), 141.83 (ArC), 134.06 (ArC), 133.63 (Ar*C*-H), 131.41 (Ar*C*-H), 131.19 (Ar*C*-H), 129.97 (Ar*C*-H), 127.72 (Ar*C*-H), 126.87 (ArC), 126.60 (Ar*C*-H), 121.00 (Ar*C*-H), 110.68 (Ar*C*-H), 55.38 (O*C*H$_3$).

*3.20 Synthesis of (2'-Methoxybiphenyl-2-yl)methanol **183***

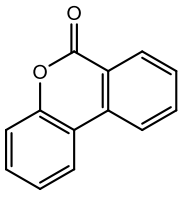


183

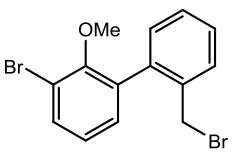
$LiAlH_4$ (3.0eq, 4.240mmol, 0.1611g) was added slowly to a stirring solution of 2'-methoxybiphenyl-2-carbaldehyde **182** (1.0eq, 1.413mmol, 0.3012g) in dry THF (15cm^3) and stirred at room temperature for 15 min. The reaction was then quenched with H_2O (20cm^3) and the organic solvent removed *in vacuo* to afford a white residue. This residue was dissolved in 5% aqueous HCl solution (30cm^3) and the organic products were extracted with diethyl ether (3 x 30cm^3). The organic extracts were collected, dried over $MgSO_4$ and the solvent was removed *in vacuo* to give crude residue. The crude product was purified by flash chromatography (5% EtOAc-Hexane) to yield the desired product **183** as a clear oil (1.1mmol, 0.23g, 76%).

R_f = 0.16 (5% EtOAc-Hexane); **I.R. (*v*/cm^{-1})** 3219 (broad, CH_2*O-H*) 2949 – 2836 (w, *CH_2*OH), 1594 – 1455 (m - s, Ar*C*=*C*), 1230 (s, Ar-*C*-*O*-*C*H_3); **δ_H (300 MHz, $CDCl_3$)** 7.54 – 7.45 (1H, m, Ar-H), 7.30 (3H, m, 3 Ar-H), 7.13 (2H, m, 2 Ar-H), 6.96 (2H, m, 2 Ar-H), 4.36 (2H, 2 s, C*HH*OH), 3.64 (3H, s, OC*H_3*), 2.60 (1H, broad s, CH_2O*H*); **δ_C (75 MHz, $CDCl_3$)** 156.48 (Ar*C*-OCH_3), 139.56 (ArC), 137.44 (ArC), 131.31 (Ar*C*-H), 130.30 (Ar*C*-H), 129.95 (ArC), 129.11 (Ar*C*-H), 127.93 (Ar*C*-H), 127.50 (Ar*C*-H), 126.54 (Ar*C*-H), 121.07 (Ar*C*-H), 111.20 (Ar*C*-H), 63.40 (*C*H_2OH), 55.70 (O*C*H_3). **MS *m/z* (%)** 215 (M^+, 2), 214 (12), 205 (2), 195 (22), 180 (100), 168 (10), 164 (32), 151 (72), 138 (16), 127 (10), 114 (20), 107 (12); ***HRMS*** calculated for $C_{14}H_{14}O_2$: 214.0994; exact for $C_{14}H_{14}O_2$: 214.0986.

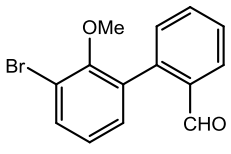
*3.21 Attempted Synthesis of 6H-Benzo[c]chromen-6-one **181***



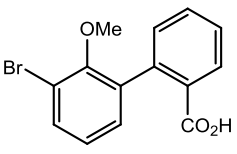
181



184a



184b



184c

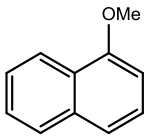
To a stirring solution of starting material (2'-methoxybiphenyl-2-yl)methanol **183** (1.0eq, 0.9335mmol, 0.2006g) dissolved in $CHCl_3$ (15cm^3) was added NBS (1.0eq, 0.9335mmol, 0.1660g) and AIBN (0.2eq, 0.1867mmol, 0.0315g). The solution was refluxed for 6 h and then cooled and stirred at room temperature for a further 47 h. After this time the solution was quenched with

saturated aqueous Na_2SO_3 solution (20cm^3) and the organic products were extracted with CH_2Cl_2 (3 x 30cm^3) and dried over $MgSO_4$. The solvent was removed *in vacuo* to give a crude residue which was purified by flash chromatography (15% EtOAc-Hexane) to afford three products; an off-white solid which was characterised to be product **184a** (0.2091mmol, 0.0740g, 22%) and a white solid which are thought to be products **184b** and **184c**, were inseparable by chromatography methods or recrystallisation and a clear NMR spectrum could not be obtained (0.1620g).

184a: **R_f** = 0.59 (15% EtOAc-Hexane); ***m.p.*** 125-127˚C; **I.R. (*v*/cm^{-1})** 2913 – 2837 (w, *C*H_2Br), 1590 – 1464 (m - s, Ar*C*=*C*), 1237 (s, Ar-*C*-*O*-*C*H_3); **δ_H (300 MHz, $CDCl_3$)** 7.57 – 7.43 (2H, m, 2 Ar-H), 7.42 – 7.28 (3H, m, 3 Ar-H), 7.21 – 7.11 (1H, m, Ar-H), 6.85 (1H, d, *J*=8.8Hz, Ar-H), 4.34 (2H, 2d, *J*=10.1Hz, C*H*$_2$OH), 3.73 (3H, s, OC*H*$_3$); **δ_C (75 MHz, $CDCl_3$)** 155.63 (Ar*C*-OCH$_3$), 136.98 (ArC), 136.16 (ArC), 133.71 (Ar*C*-H), 131.87 (Ar*C*-H), 130.90 (ArC), 130.60 (Ar*C*-H), 130.35 (Ar*C*-H), 128.44 (Ar*C*-H), 128.38 (Ar*C*-H), 112.75 (ArC), 112.48 (Ar*C*-H), 55.76 (O*C*H$_3$), 31.85 (*C*H$_2$Br) ; **MS *m/z* (%)** 315 (1); 306 (8), 291 (48), 276 (64), 261 (76), 248 (10), 212 (100), 180 (94), 151 (80), 138 (26), 114 (10; ***HRMS*** could not obtain a molecular ion for $C_{14}H_{13}OBr_2$

184b and 184c: **R_f** = 0.54 (15% EtOAc-Hexane); ***m.p.*** 108-117˚C; **I.R. (*v*/cm^{-1})** 3071 (broad w, -CO*O-H),* 2860 (w, -*CH*O), 1727 (s, -H*C*=*O*), 1694 (s, (OH)*C*=*O*), 1596 – 1459 (m - s, Ar*C*=*C*); **MS *m/z* (%)** 309 (M^+ $C_{14}H_{11}O_3{}^{81}Br$, 18), 307 (M^+ $C_{14}H_{11}O_3{}^{79}Br$, 100), 293 (M^+ $C_{14}H_{11}O_2{}^{81}Br$, 21), 291 (M^+ $C_{14}H_{11}O_3{}^{79}Br$, 24), 279 (14), 274 (10), 261 (5), 258 (10), 242 (4), 241 (20), 227 (16), 198 (6), 197 (32), 195 (6), 178 (22); ***HRMS*** calculated for $C_{14}H_{11}O_2{}^{79}Br$: 289.9942 and for $C_{14}H_{11}O_2{}^{81}Br$: 291.9922; exact mass for $C_{14}H_{11}O_2{}^{79}Br$: 289.9941 and for $C_{14}H_{11}O_2{}^{81}Br$: 291.9928; could not obtain a molecular ion for $C_{14}H_{11}O_3Br$.

*3.22 Synthesis of 1-Methoxynaphthalene **175***



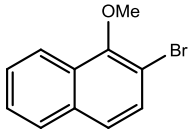
175

Commercially available starting material 1-naphthol (1.0eq, 0.022mol, 3.15g) was dissolved in dry acetone (100cm^3) and placed under an inert N_2 atmosphere. Dimethyl sulfate (3.0eq, 0.07mol, 6.2cm^3) and K_2CO_3 (2.0eq, 0.044mol, 6.04g) were added to the stirring dark brown solution. The solution was then refluxed for 67 h after which time the solution was allowed to cool and then filtered to remove the solid K_2CO_3. The filtrate was collected and the solvent removed in vacuo to afford a brown oil which was dissolved in diethyl ether and allowed to stir. 25% Ammonia solution (100cm^3) was added slowly to the stirring solution until the evolution of gas has stopped and was then transferred to a separating funnel where the ammonia solution was run off and collected. The

remaining organic layer was then washed with H_2O (50cm^3), 10% aqueous HCl (50cm^3) and brine (50cm^3), collected and dried over Na_2SO_4. The solvent was removed *in vacuo* to afford the product **175** as a yellow oil (0.021mol, 3.27g, 95%), which was spectroscopically pure and required no further purification. The spectroscopic data was in agreement with that of Adkin and Musser.[97]

R_f = 0.67 (20% EtOAc-Hexane); **δ_H (300 MHz, $CDCl_3$)** 8.36 – 8.16 (1H, m, Ar-H), 7.90 – 7.62 (1H, m, Ar-H), 7.57 – 7.25 (4H, m, 4 Ar-H), 6.76 (1H, d, *J*=7.3Hz, Ar-H), 3.90 (3H, s, OC*H*$_3$); **δ_C (75 MHz, $CDCl_3$)** 156.05 (Ar*C*-OCH_3), 135.11 (ArC), 128.07 (Ar*C*-H), 127.00 (Ar*C*-H), 126.48 (Ar*C*-H), 126.24 (ArC), 125.78 (Ar*C*-H), 122.60 (Ar*C*-H), 120.83 (Ar*C*-H), 104.38 (Ar*C*-H), 56.03 (O*C*H_3).

*3.23 Attempted Synthesis of 2-Bromo-1-methoxynaphthalene **176***



176

1-Methoxynaphthalene **175** (1.0eq, 6.76mmol, 1.07g) was placed under an inert N_2 atmosphere in a two-neck round bottom flask fitted with a septum and dissolved in dry THF (50cm^3). The stirring solution was then cooled to 0^{o}C using and ice bath before the addition of n-BuLi (1.3M/hexane, 1.5eq, 0.01mol, 8.0cm^3) to the reaction via a syringe. The yellow solution turned dark green on addition of the n-BuLi and was stirred at 0^{o}C for 1 h. After this time Br_2 (1.5eq, 0.01mol, 1.0cm^3) was dissolved in dry THF (5cm^3) in a dropping funnel and added dropwise to the solution until a dark orange colour was obtained. The reaction was allowed to heat to room temperature and stirred for a further 1 h before being quenched with saturated aqueous Na_2SO_3 (50cm^3). The organic solvent was removed *in vacuo* to afford a dark orange residue and the organic products were extracted with diethyl ether (3 x 50cm^3). The organic extracts were dried and the solvent removed *in vacuo* to afford a crude brown oil which was purified by column chromatography to yield a yellow oil which was identified to be starting material **175** (6.46mmol, 1.02g, 95%).

Chapter 8: References

1. R.C. Gallo and L. Montagnier, *Science*, 2002, **298**, 1730-1731.
2. R.C. Gallo and L. Montagnier, *N. Engl. J. Med.*, 2003, **349**, 2283-2285.
3. J. Thurlow, J. Gow and G. George, *Journal of the International AIDS Society*, 2009, **12**, 18-31.
4. E.P. Solomon, L.R. Berg and D.W. Martin, *Biology Sixth Edition*, Thomson Learning, Inc, United States of America, 2002.
5. R.C. Gallo, *Retrovirology*, 2006, **3**, 72-78.
6. E.M. Campbell and T.J. Hope, *Trends Microbiol.*, 2008, **16**, 580-587.
7. M. Ndour, P.S. Sow, A.M. Coll-Seck, S. Badiane, C.T. Ndour, N. Diakhate, B. Diop, M. Faye, M. Soumare and G. Diouf, *Tropical Medicine and International Health*, 2000, **5**, 687-691.
8. R.J. Shattock and J.P. Moore, *Nat. Rev. Microbiol.*, 2003, **1**, 25-34.
9. Northwest Association for Biomedical Research, Accessed 19 July 2008, 2004, *www.nwabr.org/education/hivrequest.html*.
10. S. Jaffer, A.D. Grant, J. Whitworth, P.G. Smith and H. Whittle, *Bulletin of the World Health Organisation*, 2004, **82**, 462-469.
11. The Story of AZT: Partnership and Conflict, Accessed 31 November 2009, 2006, *www.scribd.com/doc/1049/The-History-of-AZT*.
12. L.M. Mansky and L.C. Bernard, *J. Virol.*, 2000, **74**, 9532-9539.
13. R. Jingshan and D.K. Stammers, *Virus Res.*, 2008, **134**, 157-170.
14. F. Maggiolo, *J. Antimicrob. Chemother.*, 2009, **64**, 910-928.
15. N. Sluis-Cremer and G. Tachedjian, *Virus Res.*, 2008, **134**, 147-156.
16. G. Wang, N. Boyle, F. Chen, V. Rajappan, P. Fagan, J.L. Brooks, T. Hurd, J.M. Leeds, V.K. Rajwanshi, Y. Jin, M. Prhavc, T.W. Bruice and P.D. Cook, *J. Med. Chem.*, 2004, **47**, 6902-6913.
17. E. De Clercq, *Antiviral Res.*, 1998, **38**, 153-179.
18. A.M.J. Wensing, N.M. van Maarseveen and M. Nijhuis, *Antiviral Res.*, 2007, **75**, 93-103.
19. K.D. Phillips, *Journal of the Association of Nurses in AIDS Care*, **7**, 57-71.
20. J. Cocohoba and B.J. Dong, *Clin. Ther.*, 2008, **30**, 1747-1765.
21. V.R. de Soultrait, P.-Y. Lozach, R. Altmeyer, L. Tarrago-Litvak, S. Litvak and M.L. Andréola, *J. Mol. Biol.*, 2002, **324**, 195-203.
22. S. Lee-Huang, P.L. Huang, D. Zhang, J.W. Lee, J. Bao, Y. Sun, Y.-T. Chang, J. Zhang and P.L. Huang, *Biochem. Biophys. Res. Commun.*, 2007, **354**, 879-884.
23. M.P. Girard, S.K. Osmanov and M.P. Kieny, *Vaccine*, 2006, **24**, 4062-4081.
24. P. Mooij and J.L. Heeney, *Vaccine*, 2001, **20**, 304-321.

25. X. Jin, M.J. Newman, S. De-Rosa, C. Cooper, E. Thomas, M. Keefer, J. Fuchs, W. Blattner, B.D. Livingston, D.M. McKinney, E. Noonan, A. deCamp, O.D. Defawe and M. Wecker, *Vaccine*, 2009, **27**, 7080-7086.

26. R. Jingshan, E.N. Charles, S. Anna, P.C. Phillip, F. Robert, L.W. Kurt, A.S. Steven and K.S. David, *FEBS*, 2006, **273**, 3850-3860.

27. R.A. Domaoal and L.M. Demeter, *Int. J. Biochem. Cell Biol.*, 2004, **36**, 1735-1751.

28. M. Udier-Blagovic, E.K. Watkins, J. Tirado-Rives and W.L. Jorgensen, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 3337-3340.

29. D.G. Prajapati, R. Ramajayam, M.R. Yadav and R. Giridhar, *Bioorg. Med. Chem.*, 2009, **17**, 5744-5762.

30. T.J. Tucker, S. Saggar, J.T. Sisko, R.M. Tynebor, T.M. Williams, P.J. Felock, J.A. Flynn, M.-T. Lai, Y. Liang, G. McGaughey, M. Liu, M. Miller, G. Moyer, V. Munshi, R. Perlow-Poehnelt, S. Prasad, R. Sanchez, M. Torrent, J.P. Vacca, B.-L. Wan and Y. Yan, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 2959-2966.

31. P. Zhan, X. Liu, Z. Li, Z. Fang, Z. Li, D. Wang, C. Pannecouque and E. De Clercq, *Bioorg. Med. Chem.*, 2009, **17**, 5920-5927.

32. C.W. Lindsley, J.P. Kennedy, L. Williams, T.M. Bridges, R.N. Daniels and D. Weaver, *J. Comb. Chem.*, 2008, **10**, 345-354.

33. I. Akritopoulou-Zanze, *Curr. Opin. Chem. Biol.*, 2008, **12**, 324-331.

34. S. Poigny, K. Bedjeguelal, H. Bienayme, A. Dumoulin, P. Schmitt and E. Tam, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 3998-4001.

35. A. Ulaczyk-Lesanko and D.G. Hall, *Curr. Opin. Chem. Biol.*, 2005, **9**, 266-267.

36. J.D. Sunderhaus, C. Dockendorff and S.F. Martin, *Tetrahedron*, 2009, **65**, 6454-6469.

37. J.H. Spatz, M. Umkehrer, C. Kalinski, G. Ross, C. Burdack, J. Kolb and T. Bach, *Tetrahedron Lett.*, 2007, **48**, 8060-8064.

38. T. Lindhorst, H. Bock and I. Ugi, *Tetrahedron*, 1999, **55**, 7411-7420.

39. C. Kalinski, M. Umkehrer, J. Schmidt, G. Ross, J. Kolb, C. Burdack, W. Hiller and S.D. Hoffmann, *Tetrahedron Lett.*, 2006, **47**, 4683-4686.

40. P. Chen, J.C. Barrish, E. Iwanowicz, J. Lin, M.S. Bednarz and B.-C. Chen, *Tetrahedron Lett.*, 2001, **42**, 4293-4295.

41. R. Martínez, D.J. Ramón and M. Yus, *Tetrahedron Lett.*, 2005, **46**, 8471-8474.

42. J. Zhu, J.-P. Bouillon, G.P. Singh, J. Chastanet and R. Bengelmans, *Tetrahedron Lett.*, 1995, **36**, 7081-7084.

43. K. Groebke, L. Weber and F. Mehlin, *Synlett.*, 1998, 661-663

44a. Y. Sandulenko, A. Komarov, K. Fufanow and M. Krasavin, *Tetrahedron Lett.*, 2008, **49**, 5990-5993.

44b. H. Bienaymé and K. Bouzid, *Angew. Chem. Int. Ed.*, 1998, **37**, 2234-2237.

45. Y. Sandulenko, A. Komarov and M. Krasavin, *Lett. Org. Chem.*, 2009, **6**, 491- 495.

46. J. Clayden, N. Greeves, S. Warren and P. Wothers, *Organic Chemisty*, Oxford University Press, New York, 2001.
47. A.R. Katritzky, Y.-J. Xu and H. Tu, *J. Org. Chem.*, 2003, **68**, 4935-4937.
48. A.L. Rousseau, P. Matlaba, C.J. Parkinson, *Tetrahedron Lett.*, 2007, **48**, 4079-4082.
49. S. Tsirulnikov, M. Krasavin, M. Nikulmikov, Y. Sandulenko and K. Bukhryakov, *Tetrahedron Lett.*, 2008, **49**, 7318-7321.
50. O. Chavignon, M. Lhassani, J.M. Chezal, J.C. Teulade, J.P. Chapat, R. Snoeck, G. Andrei, J. Blazarim, E. De Clercq, A. Gueiffier, *Eur. J. Med. Chem.*, 1999, **34**, 271-274.
51. A. Gueiffier, M. Lhassani, A. Elhakmaoui, R. Snoeck, G. Andrei, O. Chavignon, J.-C. Teulade, A. Kerbal, E.M. Essassi, J.-C. Debouzy, M. Witvrouw, Y. Blache, J. Balzarini, E. De Clercq and J.-P. Chapat, *J. Med. Chem.*, 1996, **39**, 2856-2859.
52. C. Hamdouchi, J. de Blas, M. del Prado, J. Gruber, B.A. Heinz and L. Vance, *J. Med. Chem.*, 1998, **42**, 50-59.
53. S.P. East, C.B. White, O. Barker, S. Barker, J. Bennett, D. Brown, E.A. Boyd, C. Brennan, C. Chowdhury, I. Collins, E. Convers-Reignier, B.W. Dymock, R. Fletcher, D.J. Haydon, M. Gardiner, S. Hatcher, P. Ingram, P. Lancett, P. Mortenson, K. Papadopoulos, C. Smee, H.B. Thomaides-Brears, H. Tye, J. Workman and L.G. Czaplewski, *Bioorg. Med. Chem.*, 2009, **19**, 894-899.
54. A. Scribner, R. Dennis, S. Lee, G. Ouvry, D. Perrey, M. Fisher, M. Wyvratt, P. Leavitt, P. Liberator, A. Gurnett, C. Brown, J. Mathew, D. Thompson, D. Schmatz and T. Biftu, *Eur. J. Med. Chem.*, 2008, **43**, 1123-1151.
55. I. Kim, H.K. Won, J. Choi and G.H. Lee, *Tetrahedron*, 2007, **63**, 12954-12960.
56. D. Virieux, A.-F. Guillouzic and H.-J. Cristau, *Tetrahedron*, 2006, **62**, 3710-3720.
57. X. Fang, Y.-M. Wu, J. Deng and S.-W. Wang, *Tetrahedron*, 2004, **60**, 5487-5493.
58. Y. Shang, M. Zhang, S. Yu, K. Ju, C. Wang and X. He, *Tetrahedron Lett.*, 2009, **50**, 6981-6984.
59. R.A. Nugent and M. Murphy, *J. Org. Chem.*, 1986, **52**, 2206-2208.
60. Y. Lui, H. Hu, Q. Lui and H.-W.Hu, *Synlett,* 2006, 2985-2988.
61. L.-L. Gundersen, C. Charnock, A.H. Negussie, F. Rise and S. Teklu, *Eur. J. Pharm. Sci.*, 2007, **30**, 26-35.
62. S.P. Gupta, A.N. Mathur, A.N. Nagappa, D. Kumar and S. Kumaran, *Eur. J. Med. Chem.*, 2003, **38**, 867-873.
63. J. Gubin, H. de Vogelaer, H. Inion, C. Houben, J. Lucchetti, J. Mahaux, G. Rosseels, M. Peiren and M. Clinet, *J. Med. Chem.*, 2002, **36**, 1425-1433.
64. P. Sonnet, P. Dallemagne, J. Guillon, C. Enguehard, S. Stiebing, J. Tanguy, R. Bureau, S. Rault, P. Auvray, S. Moslemi, P. Sourdaine and G.-E. Séralini, *Bioorg. Med. Chem.*, 2000, **8**, 945-955.
65. D. Bogucki, R.T. Skerlj and G.J. Bridger, *Synlett*, 2000, 1488-1490.

66. U. Rix, J.-T. Zheng, L. Zhao, C. Mattingly, V. Adams, Q. Chen, J. Rhor and K.-Q. Yang, *J. Antibiot.*, 2005, **58**, 405-408.
67. A. Patra, S. Ray and D. Mal, *Tetrahedron*, 2008, **64**, 3253-3267.
68. P. Pahari, A. Patra, S. Ray and D. Mal, *J. Org. Chem.*, 2005, **70**, 9017-9020.
69a. N. Miyaura, K. Yamada and A. Suzuki, *Tetrahedron Lett.*, 1976, **36**, 3437-3440
69b. T.E. Barder, S.D. Walker, J.R. Martinelli and S.L. Buchwald, *J. Am. Chem. Soc.*, 2005, **127**, 4685-4696.
70. B.H. Ridgeway and K.A. Woerpel, *J. Org. Chem.*, 1998, **63**, 458-460.
71. K. Sambasivarao, L. Kakali and D. Kashinath, *Tetrahedron*, 2002, **58**, 9633-9695.
72. K. Matos and J.A. Soderquist, *J. Org. Chem.*, 1998, **63**, 461-470.
73. N. Miyaura and A. Suzuki, *Chem. Rev.*, 2002, **95**, 2457-2483.
74. R. Pathak, K. Vandayar, W.A.L. van Otterlo, J.P. Michael, M.A. Fernandes and C.B. de Koning, *Org. Biomol. Chem.,* 2004, **2**, 3504-3509.
75. C.B. de Koning, J.P. Michael and A.L. Rousseau, *Tetrahedron Lett.*, 1998, **39**, 8725-8728.
76. H. Uno, *J. Org. Chem.*, 1985, **51**, 350-358.
77. M.A. Brimble and T.J. Brenstrum, *J. Chem. Soc. Perkin Trans. 1*, 2001, **2001**, 1612-1623.
78. M.A. Brimble and T.J. Brenstrum, *Tetrahedron Lett.*, 1999, **41**, 1107-1110.
79. M.A. Brimble and S.J. Stuart, *J. Chem. Soc. Perkin Trans. 1*, 1990, 881-886.
80. T.J. Onofrey, D. Gomez, M. Winters and H.W. Moore, *J. Org. Chem.*, 1997, **62**, 5658-5659.
81. W. Williams, X. Sun and D. Jebaratnam, *J. Org. Chem.*, 1997, **62**, 4364-4369.
82. M.P. Gore, S.J. Gould and D.D. Weller, *J. Org. Chem.*, 2002, **57**, 2774-2783.
83. A.M. Echavarren, N. Tamayo, Ó. de Frutos and A. García, *Tetrahedron*, 1997, **53**, 16835-16846.
84. U. Rix, J. Zheng, L.L. Remsing-Rix, L. Greenwall, K. Yang and J. Rohr, *J. Am. Chem. Soc.*, 2004, **126**, 4496-4497.
85. C.A. James and V. Snieckus, *Tetrahedron Lett.*, 1997, **38**, 8149-8152.
86. Z. Xu, K. Jakobi, K. Welzel and C. Hertweck, *Chem. Biol.*, 2005, **12**, 579-588.
87. C. Hertweck, A. Luzhetskyy, Y. Rebets and A. Bechthold, *Nat. Prod. Rep.*, 2006, **24**, 162-190.
88. G. Qabaja and G.B. Jones, *J. Org. Chem.*, 2000, **65**, 7187-7194.
89. K. Karichiappan and D. Wege, *Aust. J. Chem.*, 2000, **53**, 743-747.
90. J.L. Bloomer and W. Zheng, *Synth. Commun.*, 1998, **28**, 2087-2095.
91. B. Staskun and T. van Es, *J. Chem. Soc. C*, 1966, 531-532.
92. K.A.K. Al-Fakhri, A.C. Mowatt and A.C. Pratt, *J. Chem. Soc. Chem. Commun.*, 1980, **12**, 566-568.
93. M. A. Keegstra, T.H. Peters and L. Brandsma, *Tetrahedron* 1992, **48**, 3633-3652.
94. I.E. Marko and A Mekhalfia, *Tetrahedron Lett.*, 1990, **31**, 7237-7240.
95. D. H. Kang, T.Y. Joo, W. Chavasiri and D. O. Jang, *Tetrahedron Lett.*, 2007, **48**, 285-287.

96. Y. Zhou, Y. Zhao, D. Ma, J. Liu, L. Li, T.Y. Zhang and H. Zhang, *Org. Biomol. Chem.*, 2003, **1**, 1643-1646.

97. J.F. Adkins and J.M. Musser, *J. Am. Chem. Soc.*, 1938, **60**, 664-666.

98. M.E. Jung and J.A. Hagenah , *J. Org. Chem.*, 1986, **52**, 1889-1902.

99. M. Bruker (2005a). APEX2. Version 2009.1-0. Bruker AXS Inc., Wisconsin, USA.

100. M. Bruker (2005b). SAINT+. Version 7.60A. (includes XPREP and SADABS) Bruker AXS Inc., Wisconsin, USA.

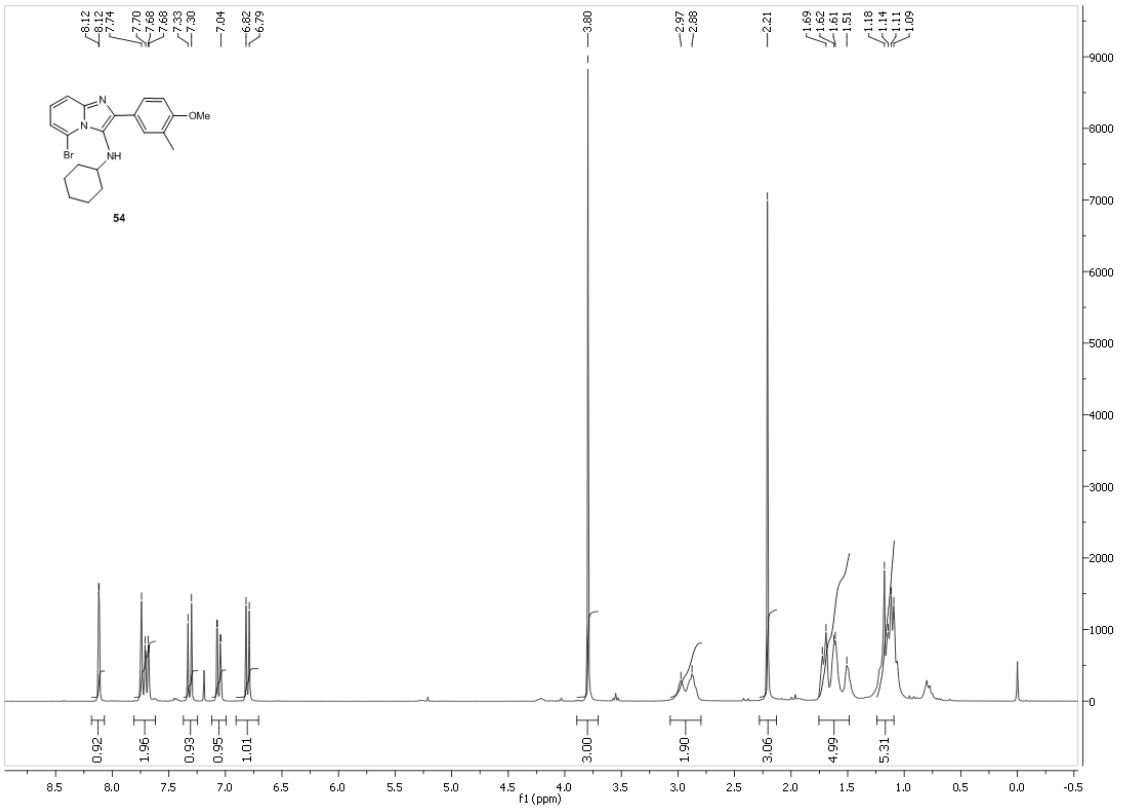
101. X. Bruker (1999). SHELXTL. Version 5.1. (includes XS, XP, XSHELL) Bruker AXS Inc., Madison, Wisconsin, USA.

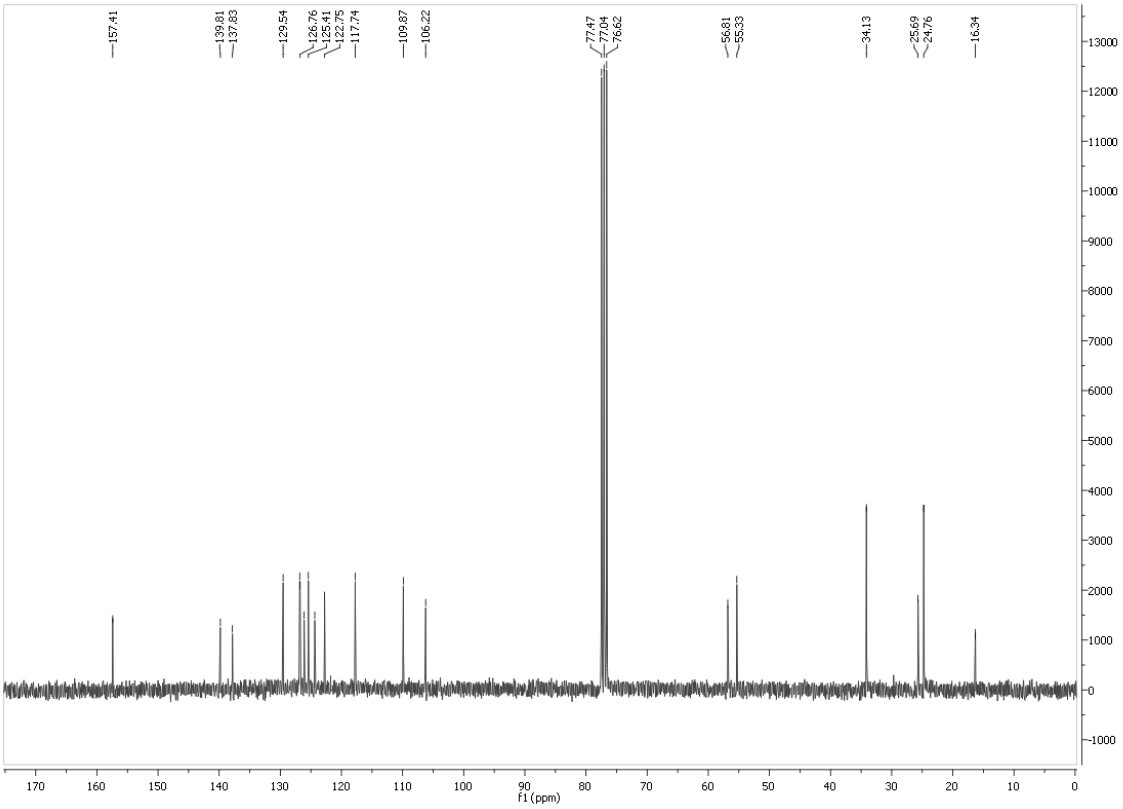
102. A.L. Spek, *J. Appl. Cryst.*, 2003, **36**, 7-13.

103. L.J. Farrugia, *J. Appl. Cryst.*, 1997, **30**, 565.

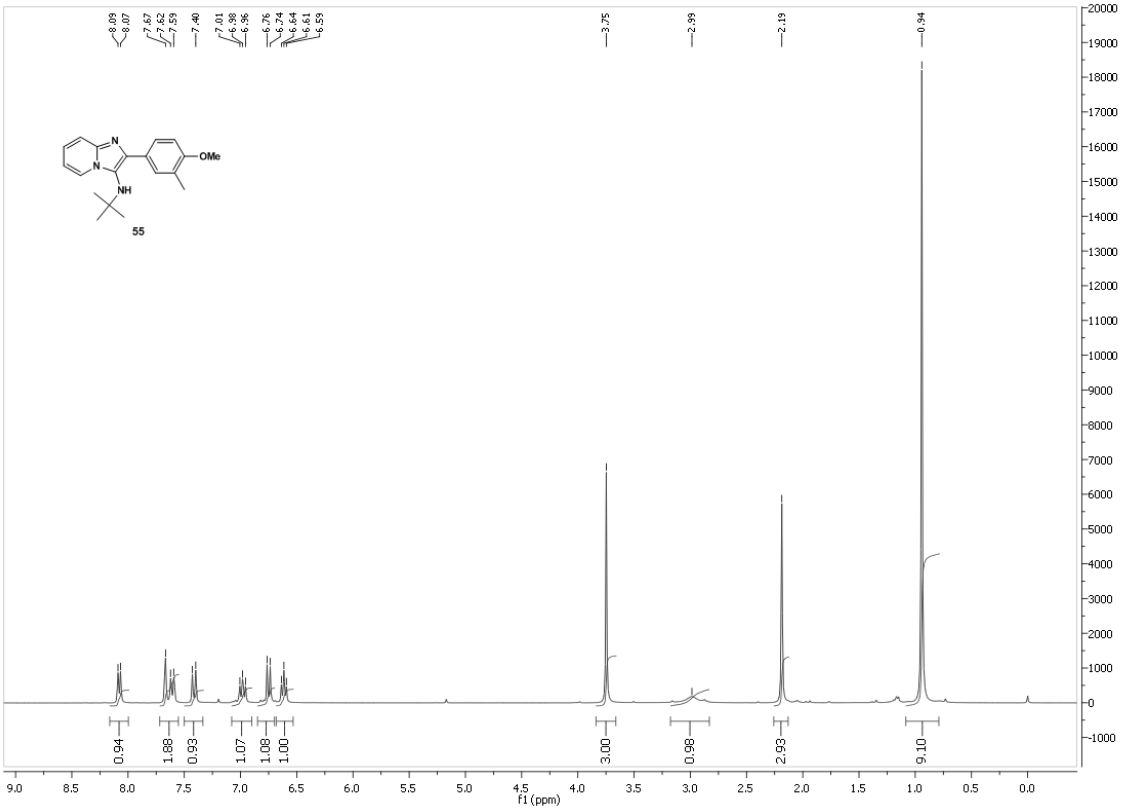
Appendix A: Selected NMR Spectra

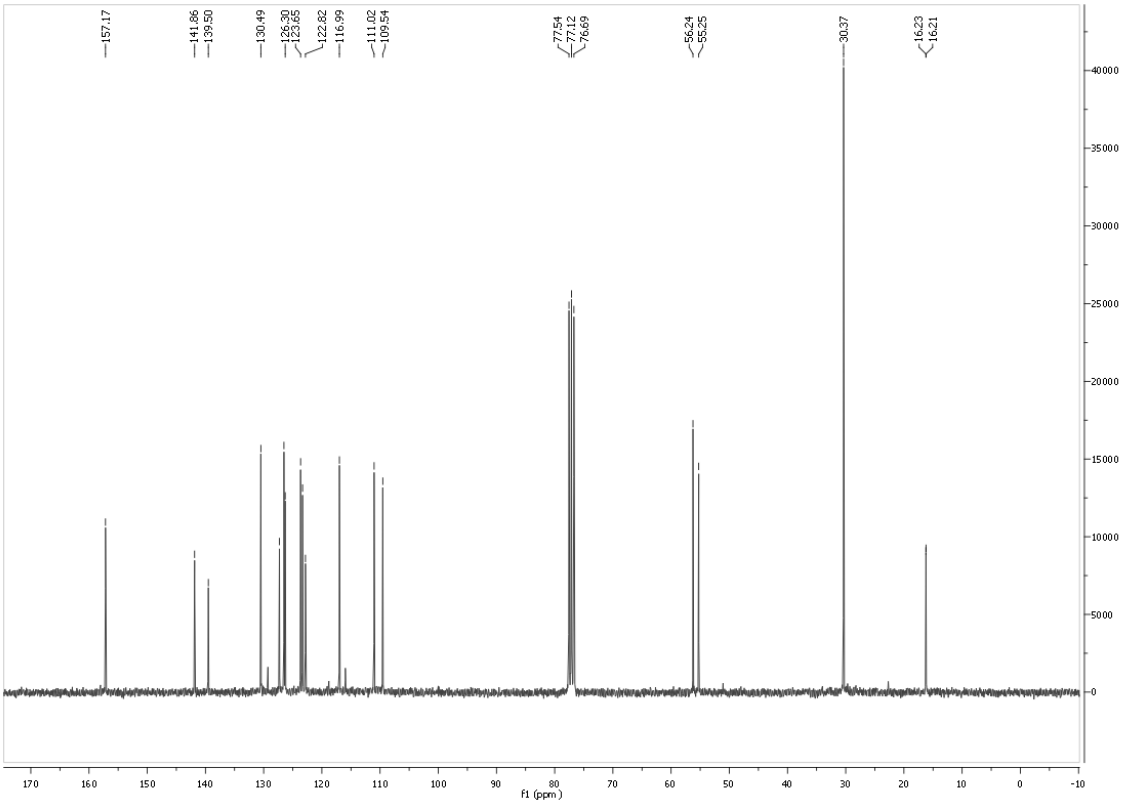
5-bromo-*N*-cyclohexyl-2-(4-methoxy-3-methylphenyl)imidazo[1,2-*a*]pyridine-3-amine 54



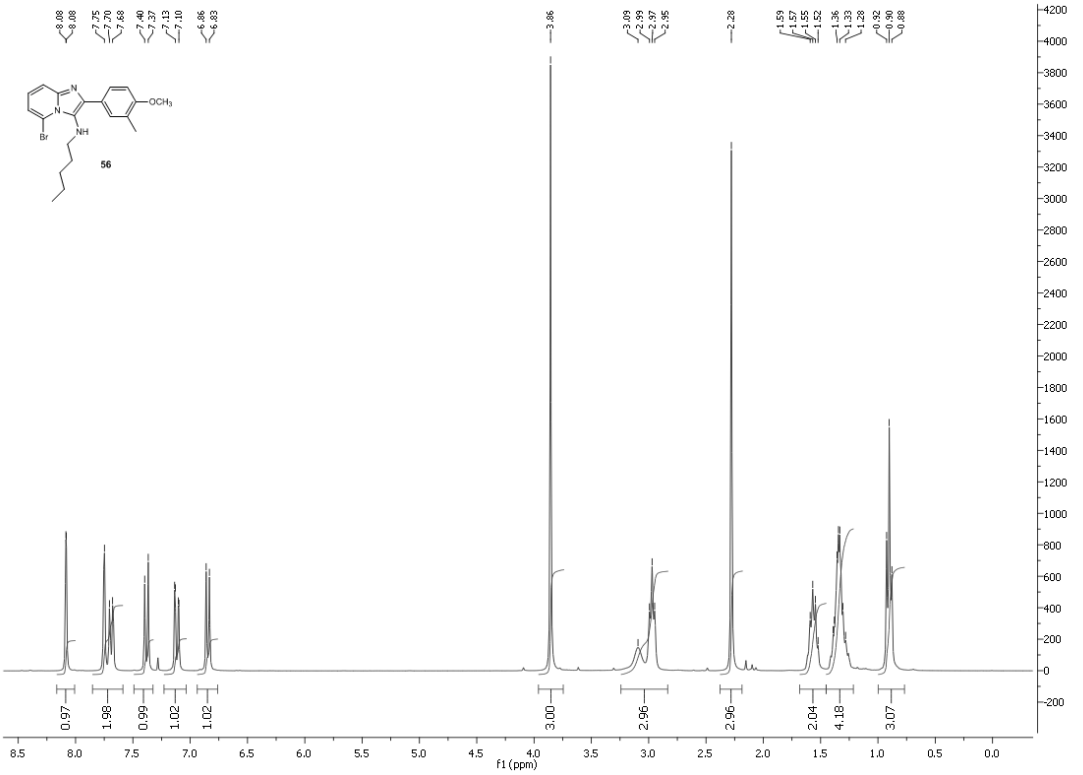


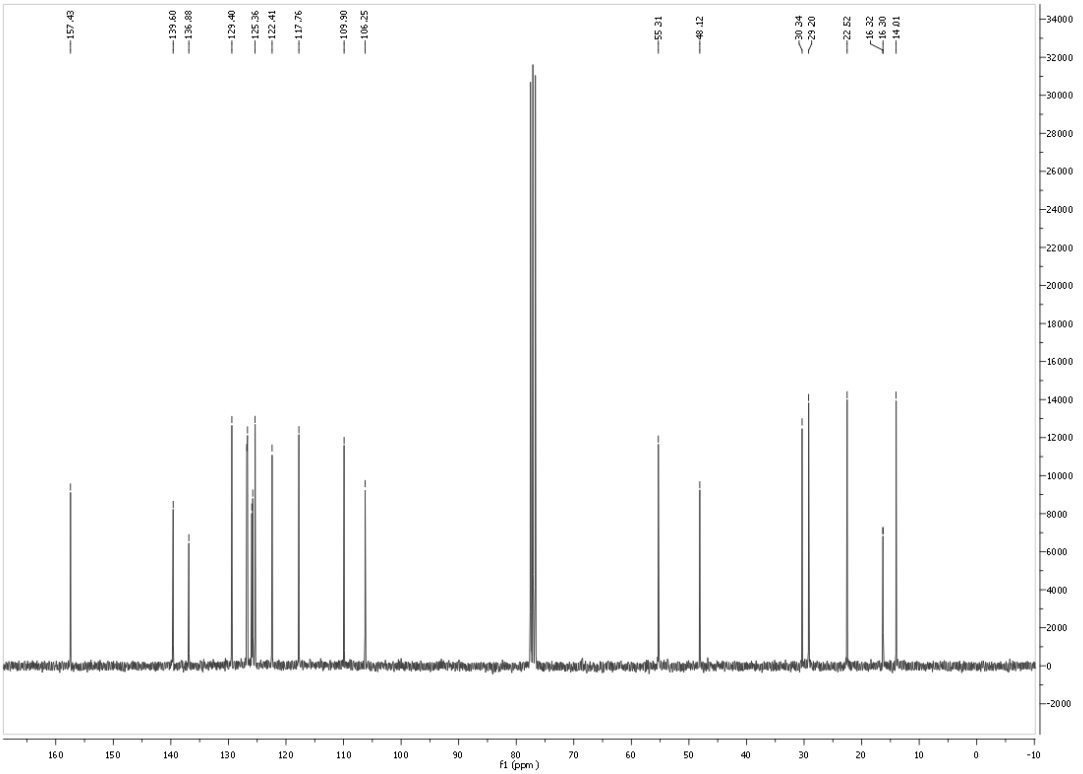
_N_-tert-butyl-2-(4-methoxy-3-methyl-phenyl)imidazo[1,2-_a_]pyridine-3-amine 55



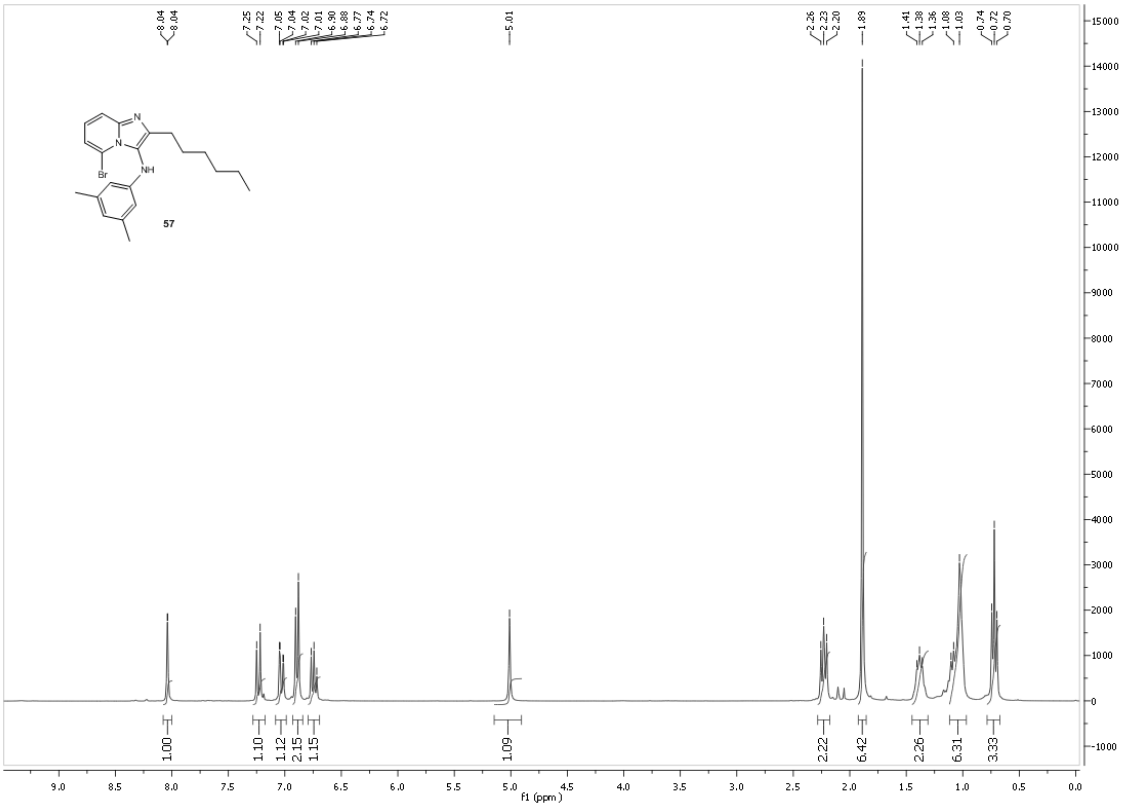


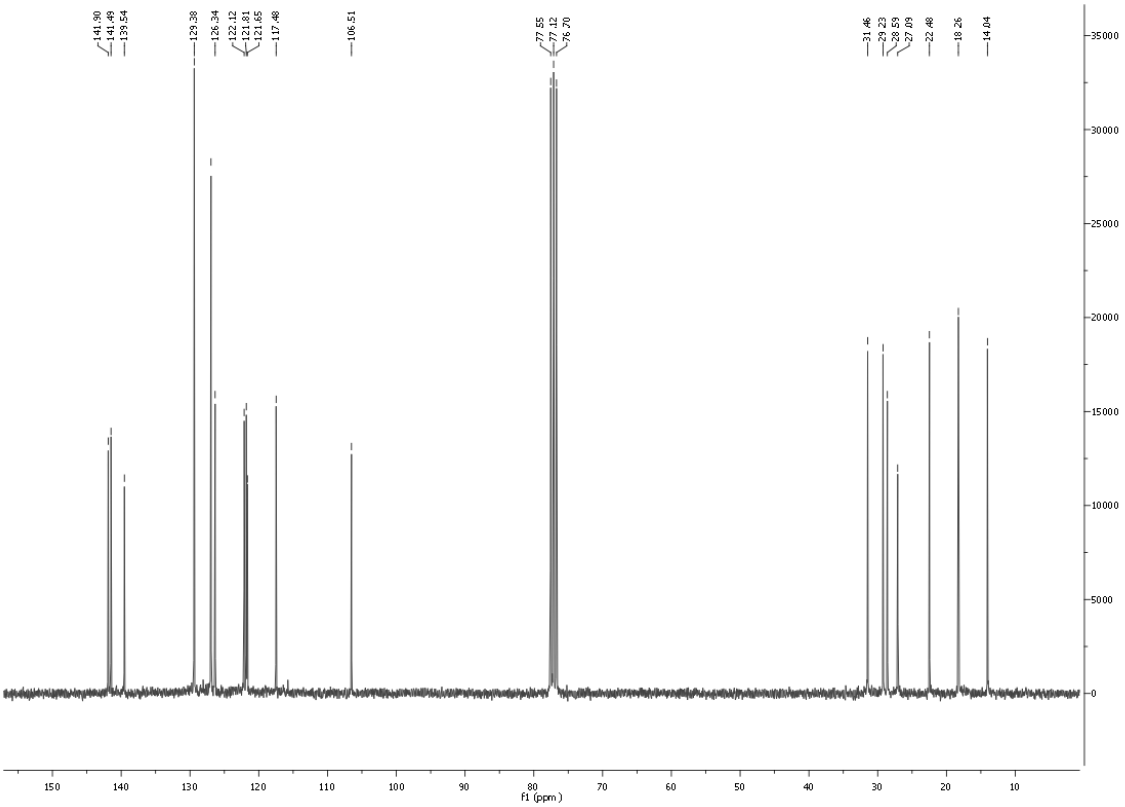
5-bromo-2-(4-methoxy-3-methylphenyl)-*N*-pentylimidazo[1,2-*a*]pyridine-3-amine 56



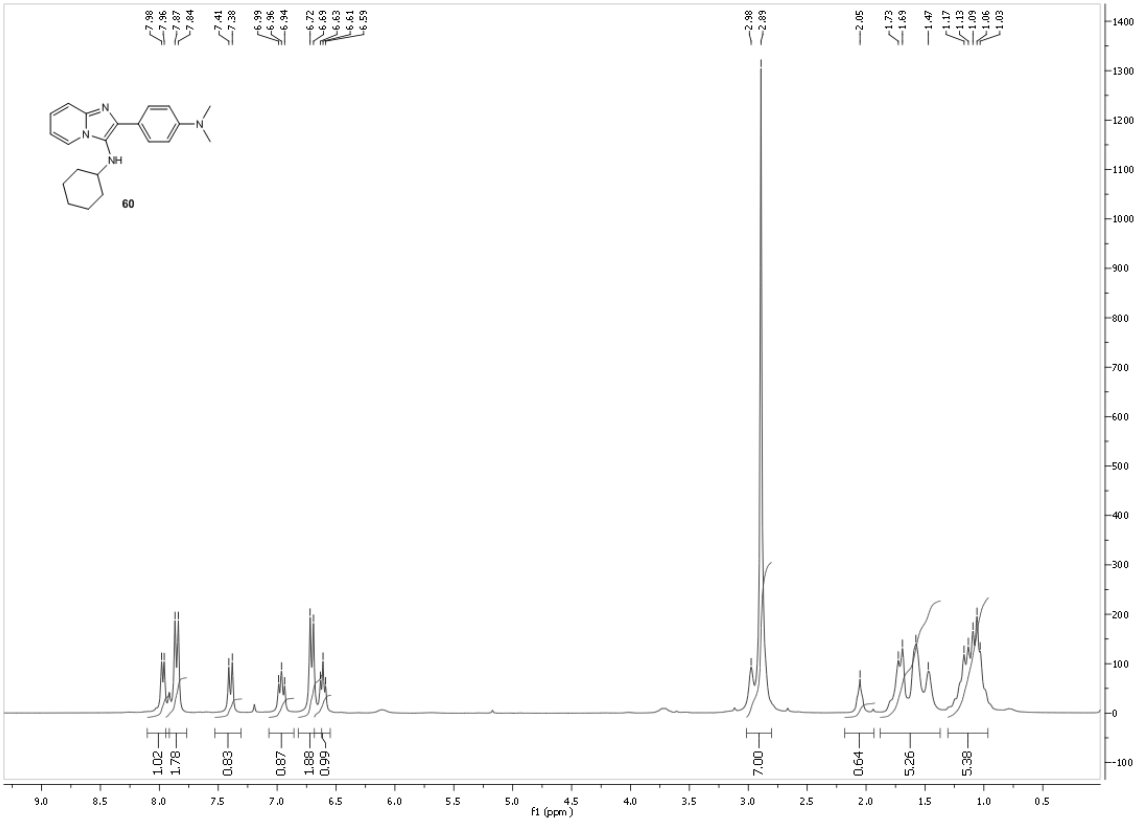


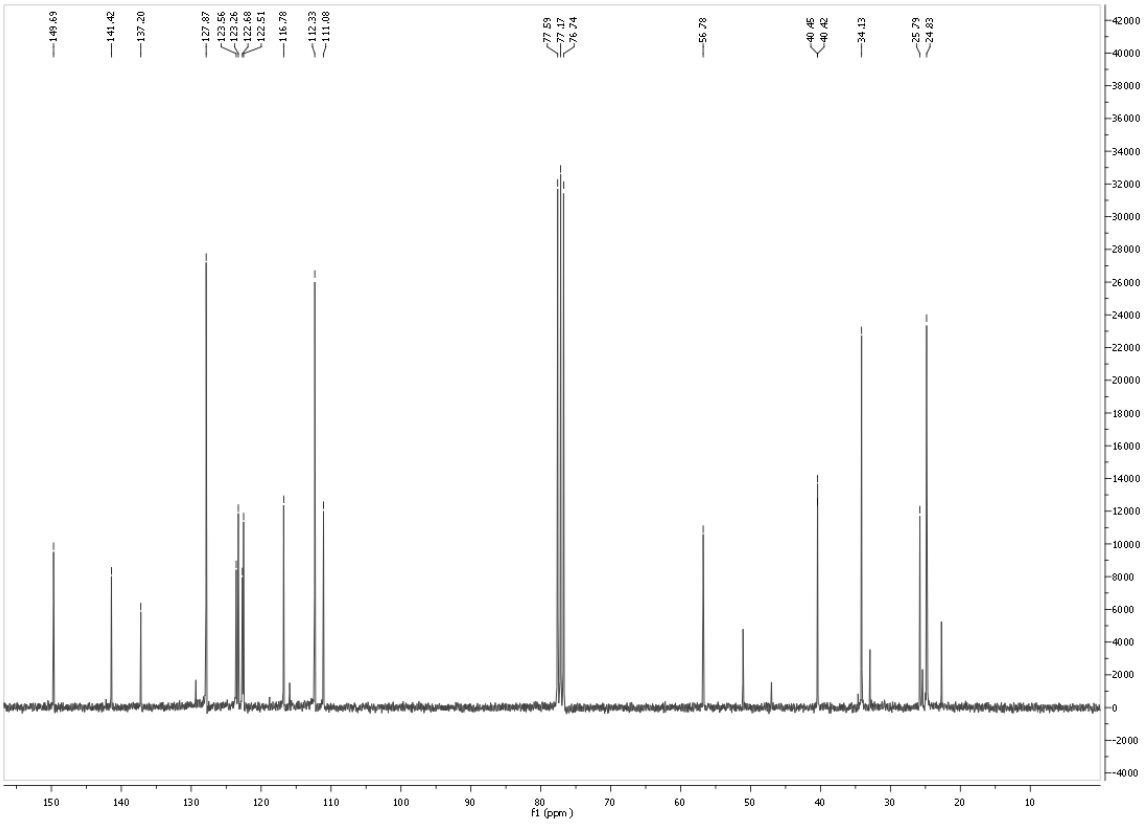
5-bromo-*N*-(3,5-dimethylphenyl)-2-hexylimidazo[1,2-*a*]pyridine-3-amine 57



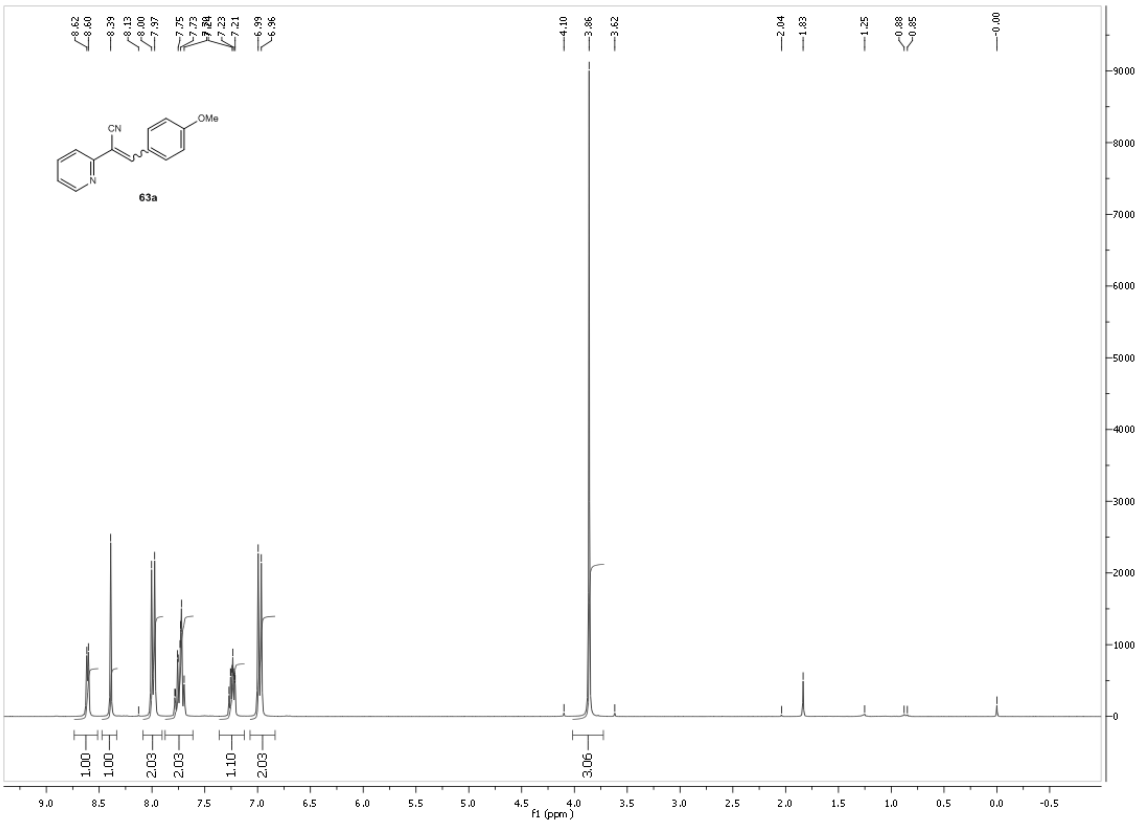


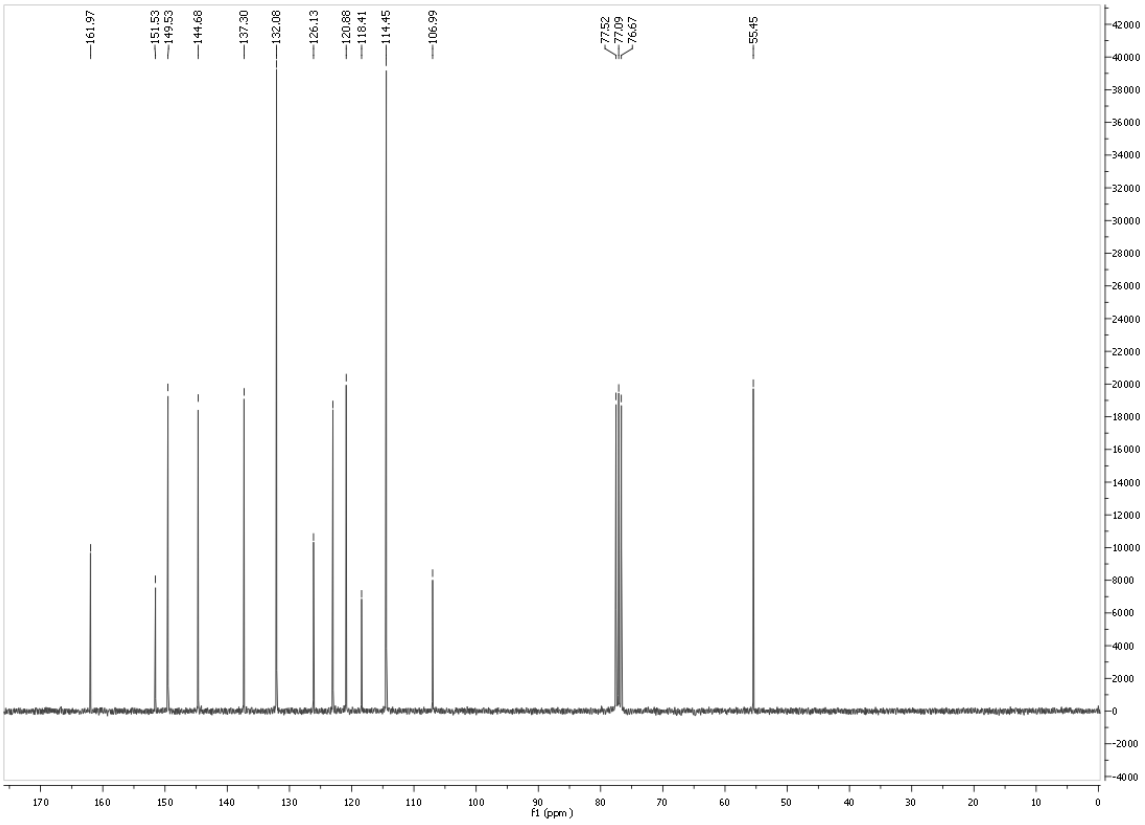
***N*-cyclohexyl-2-(4-(dimethylamino)phenyl)imidazo[1,2-*a*]pyridine-3-amine 60**



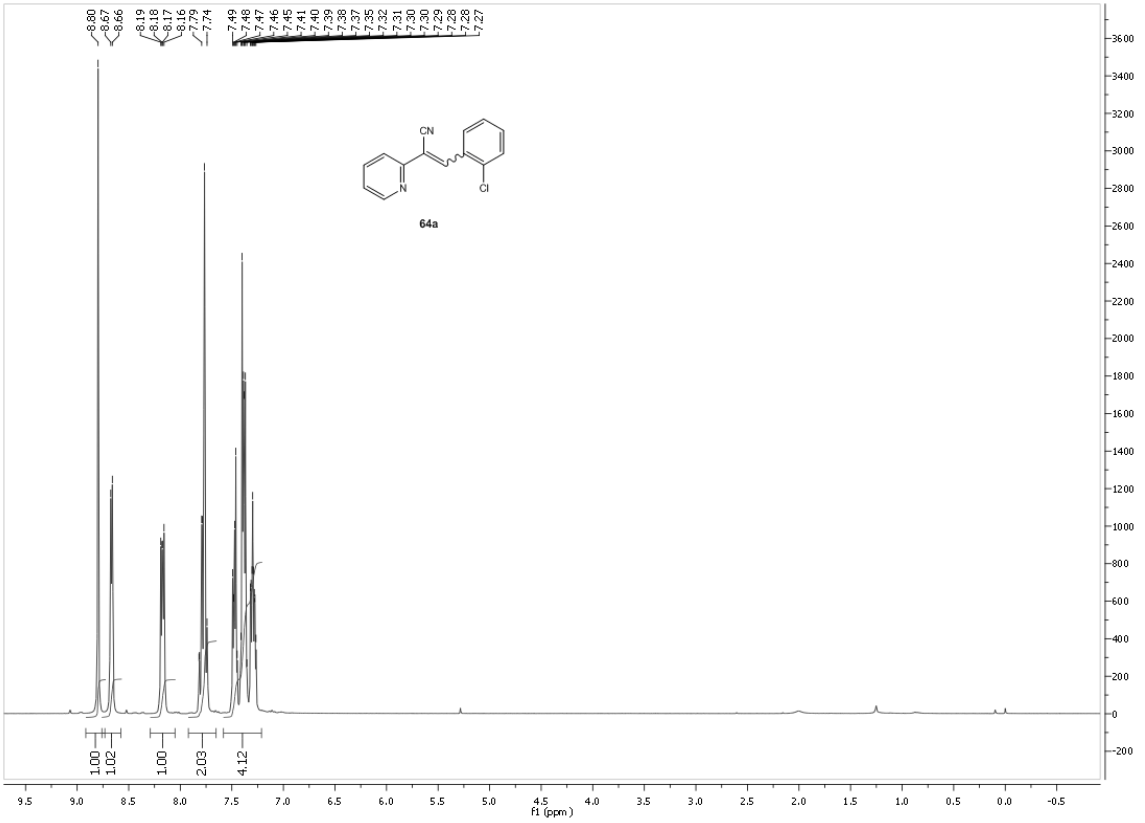


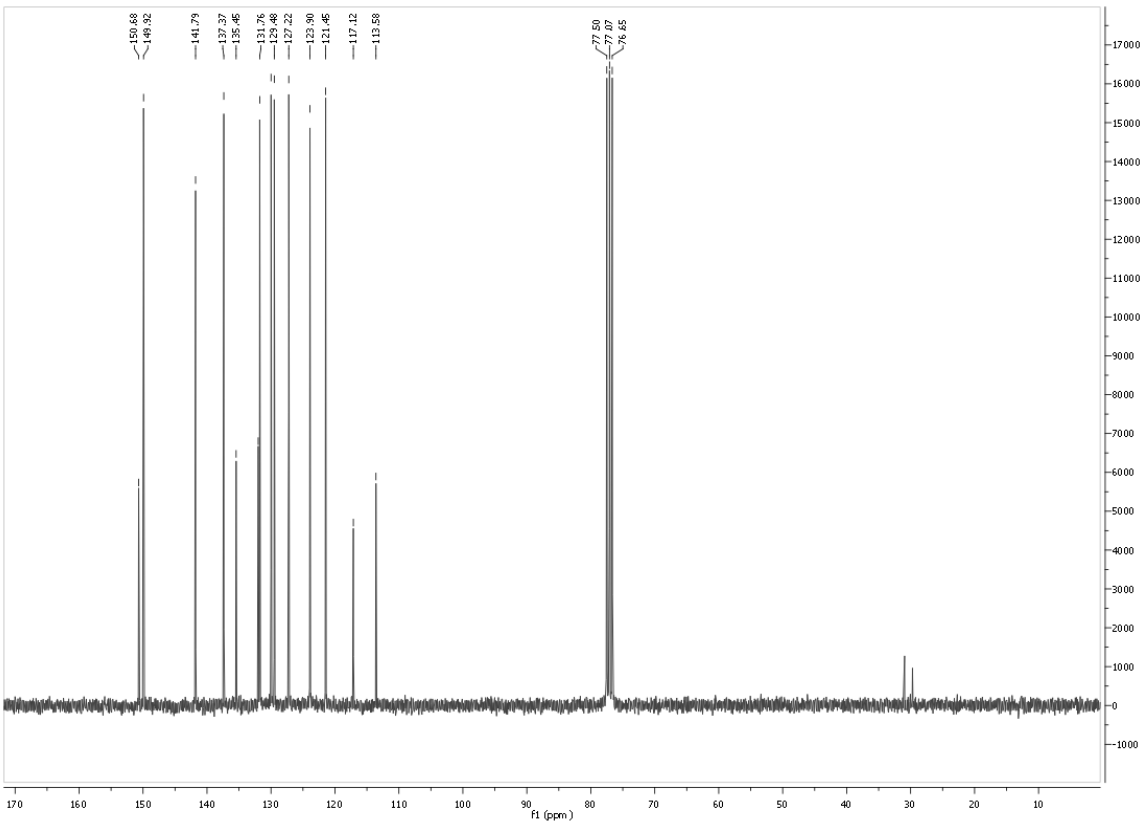
3-(4-methoxyphenyl)-2-(pyridin-2-yl)acrylonitirile 63a



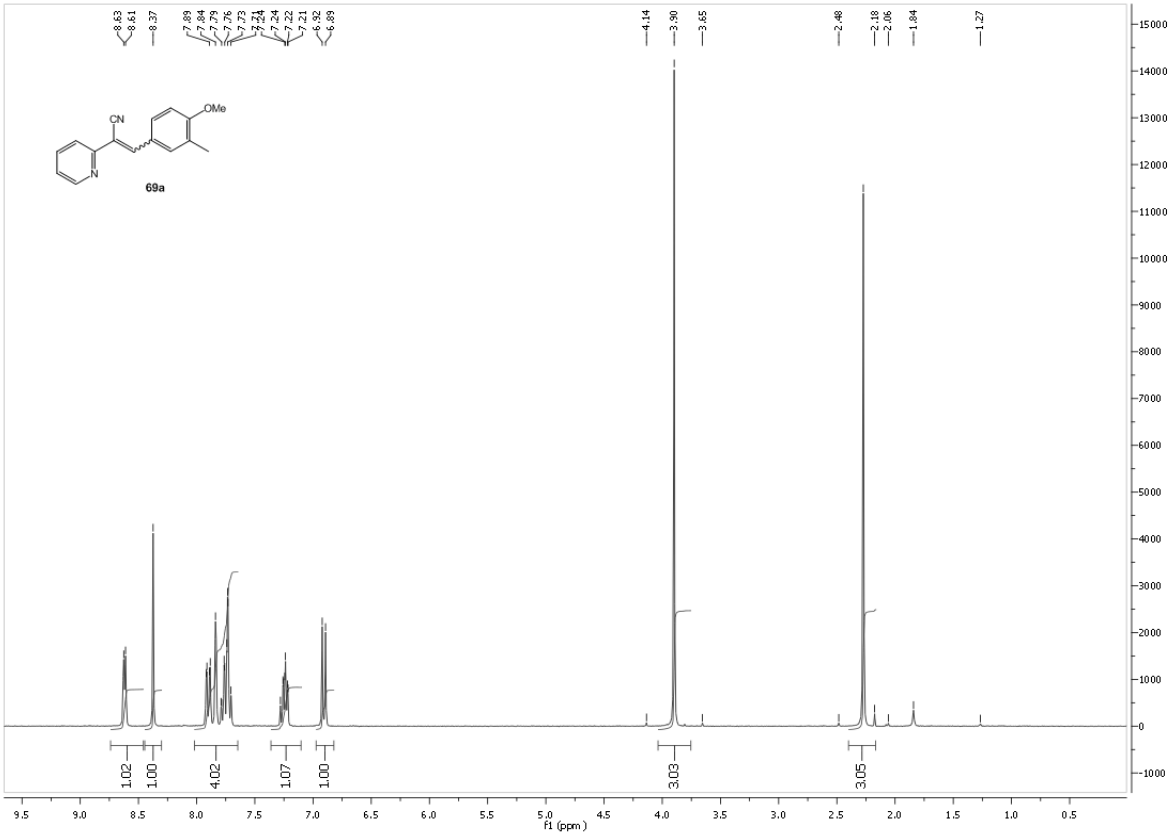


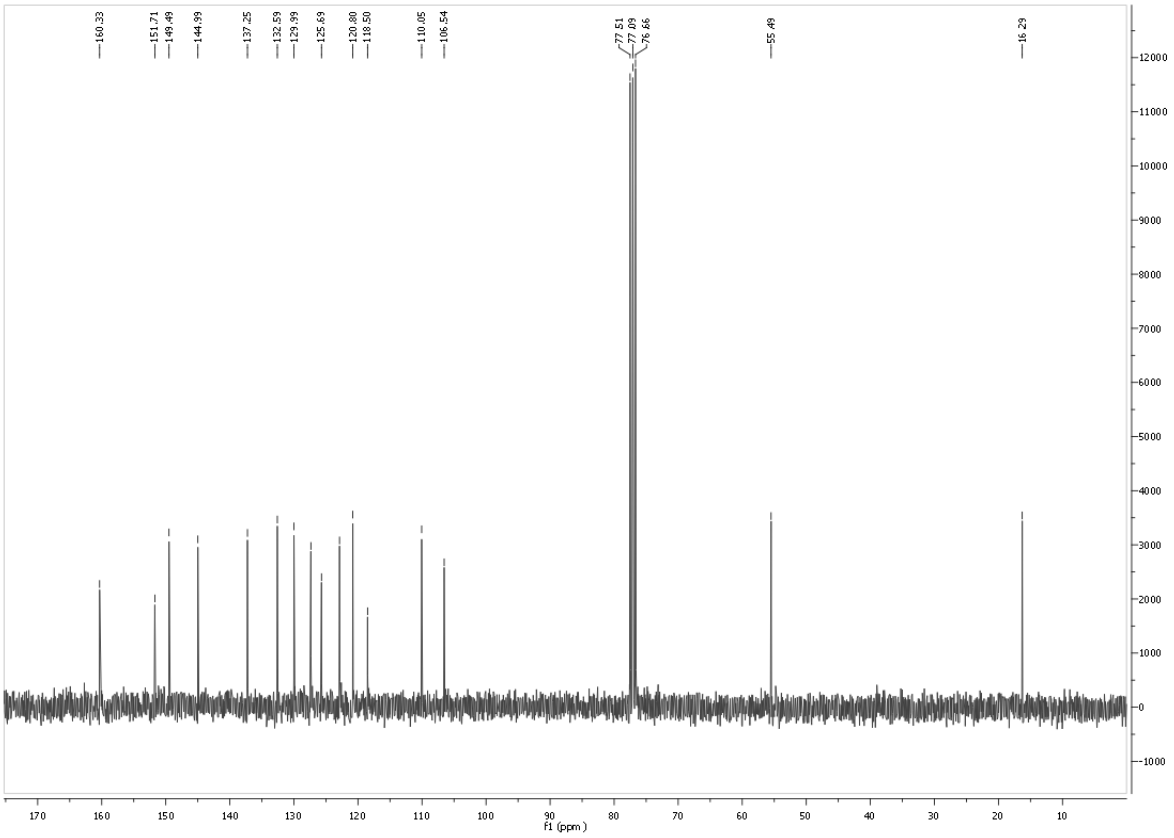
3-(2-chlorophenyl)-2-(pyridin-2-yl)acrylonitrile 64a



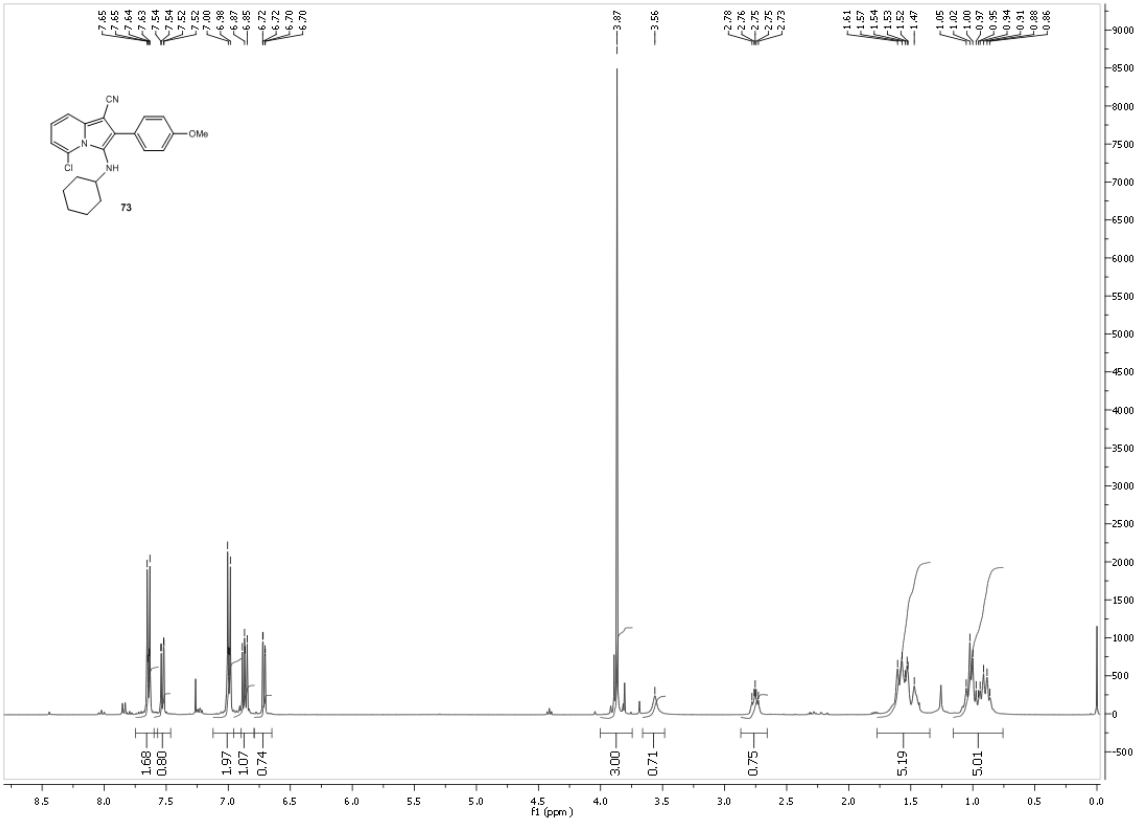


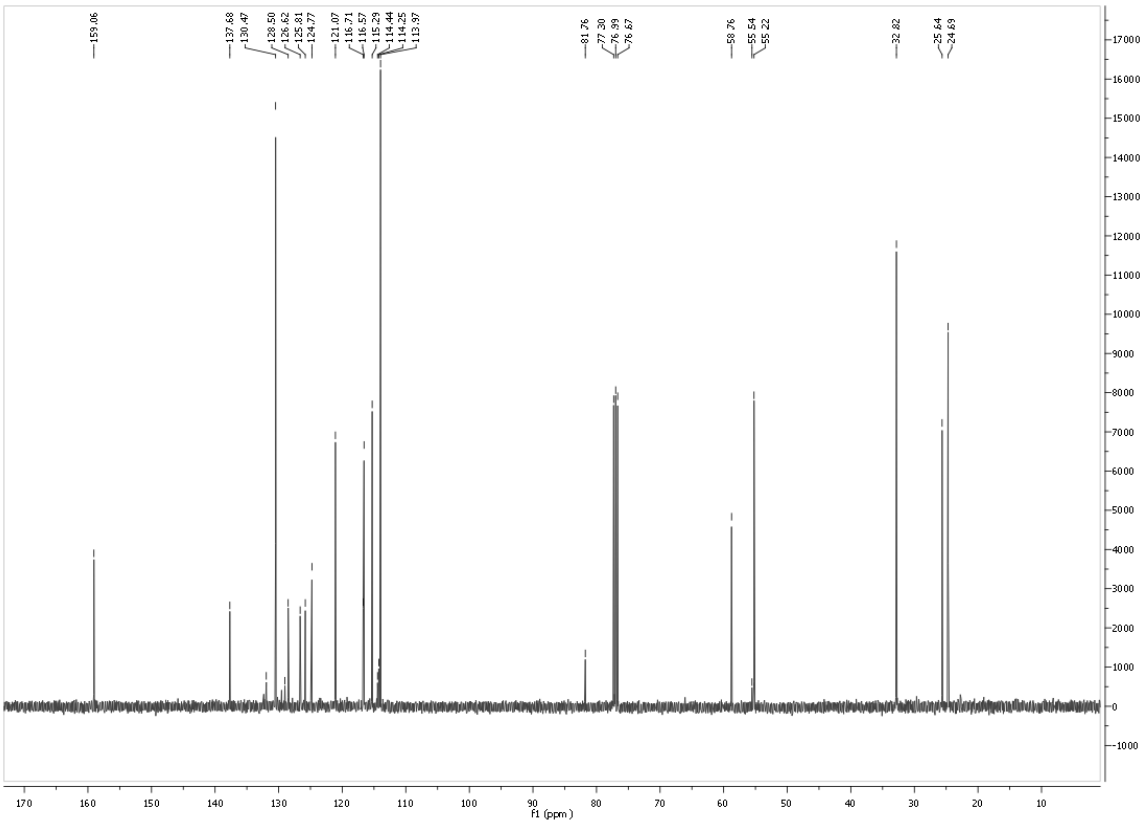
3-(4-methoxy-3-methylphenyl)-2-(pyridin-2-yl)acrylonitirile 69a



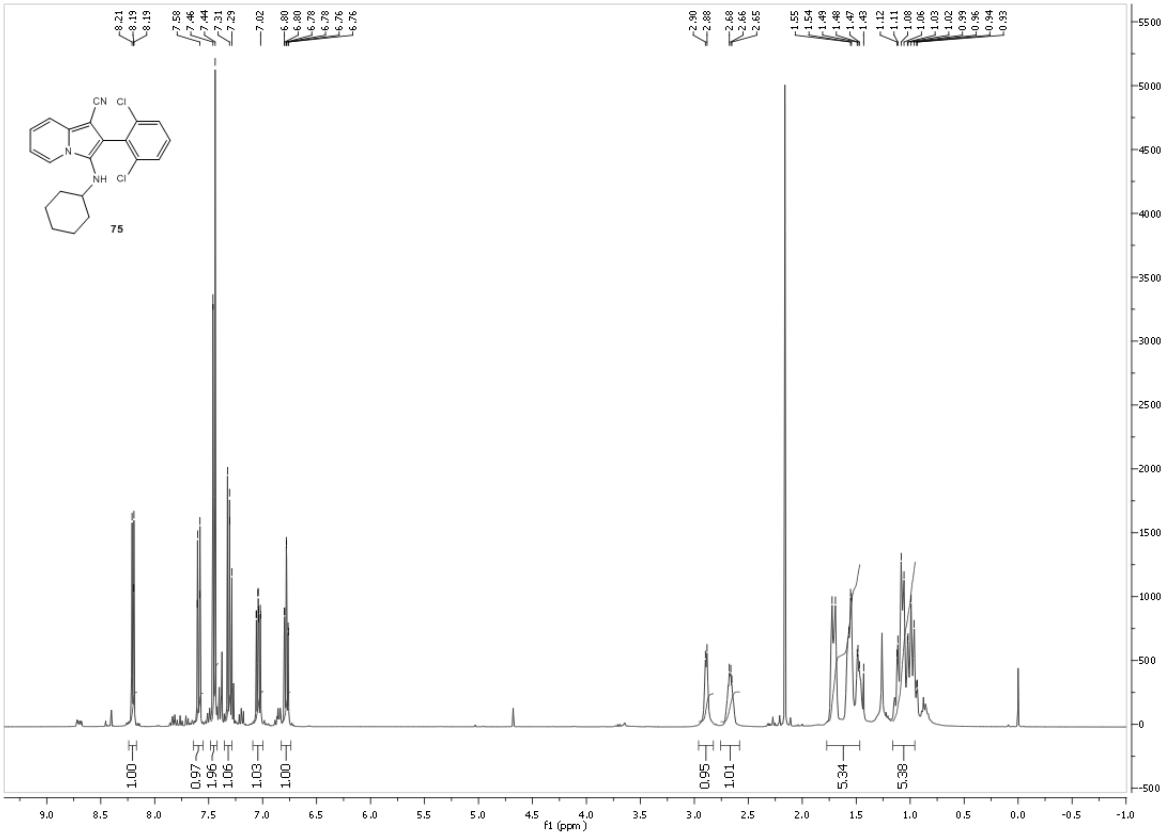


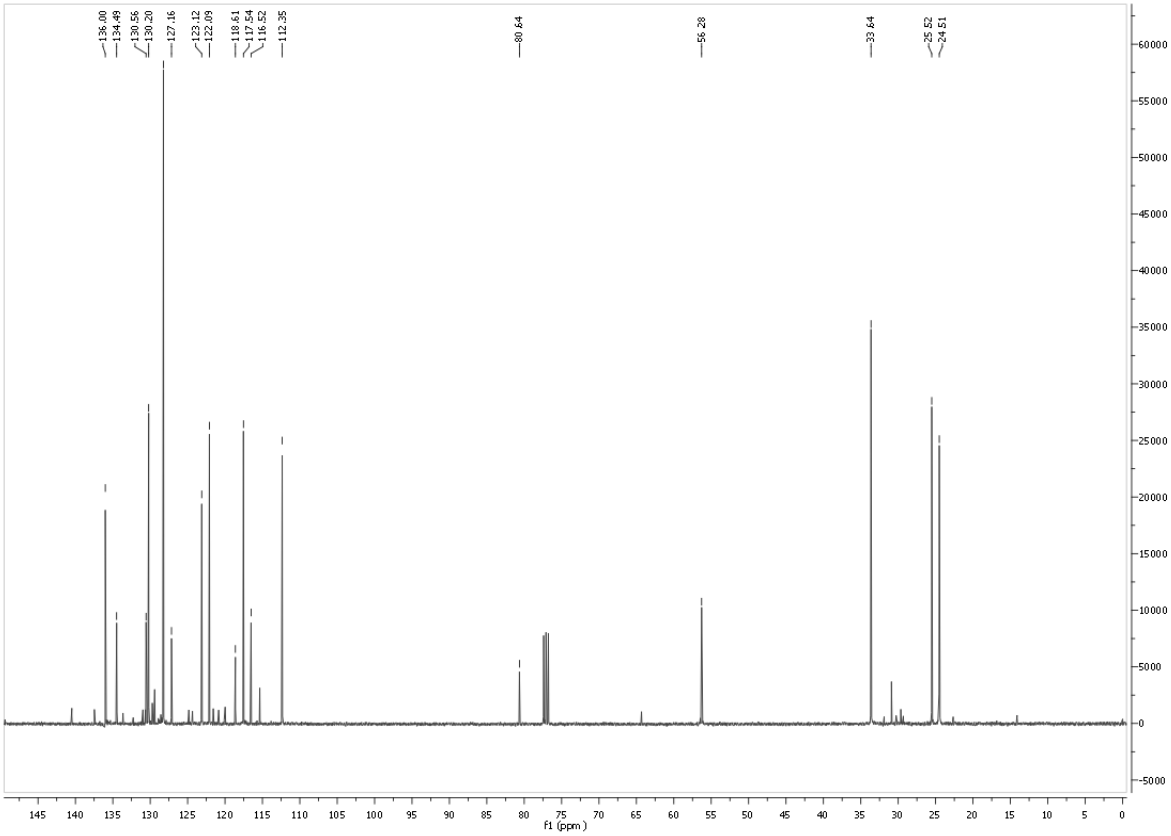
5-chloro-3-(cyclohexylamino)-2-(4-methoxyphenyl)indolizine-1-carbonitrile 73



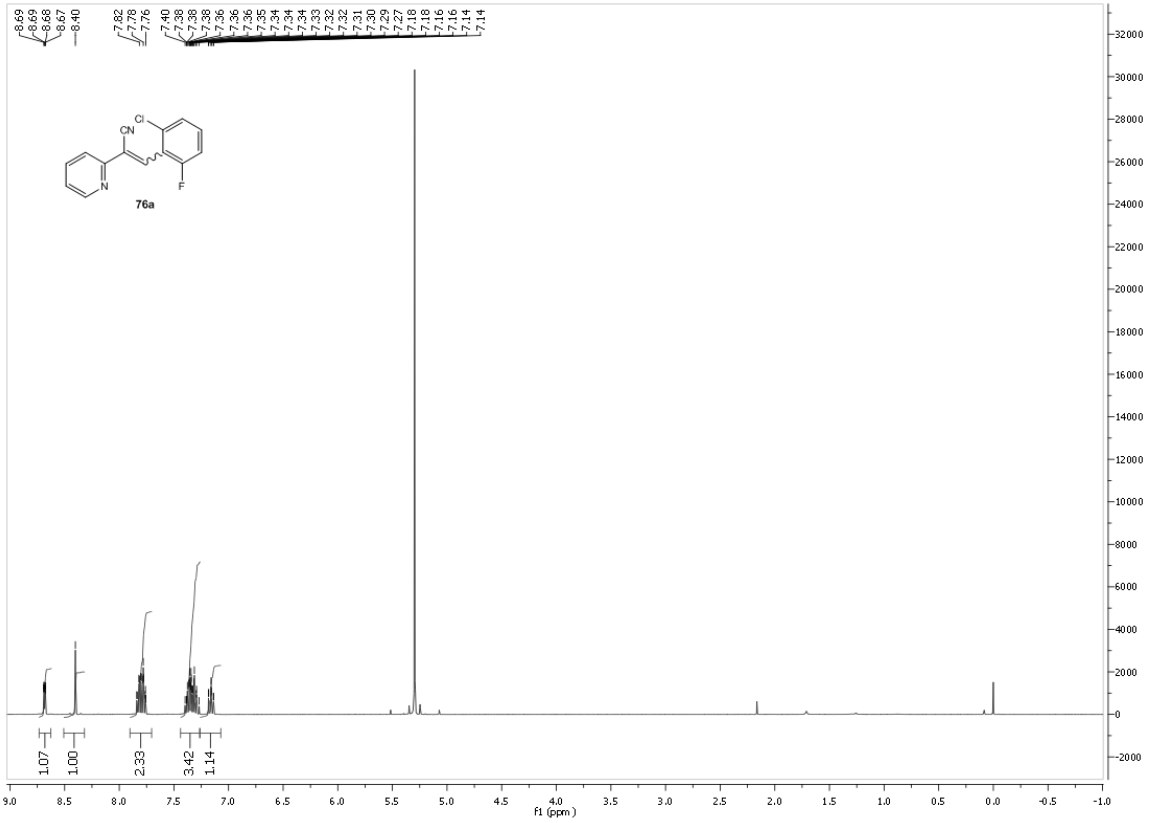


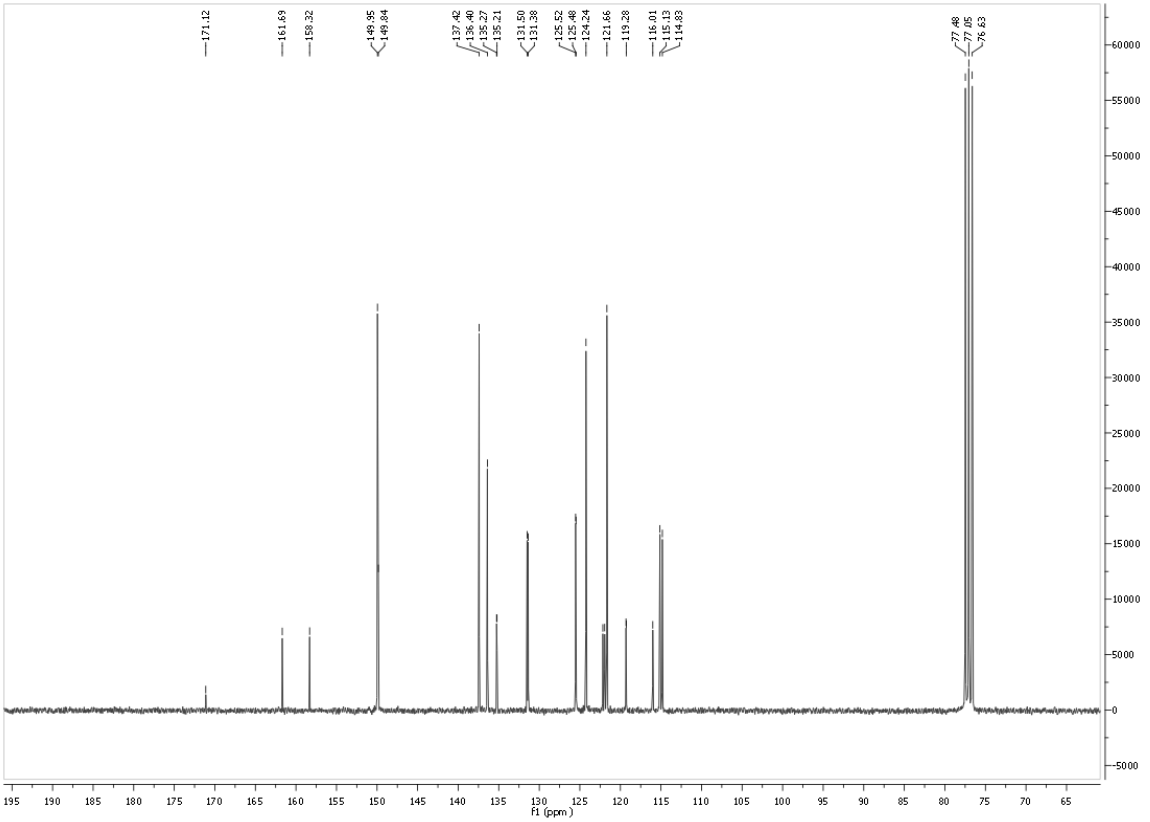
3-(cyclohexylamino)-2-(2,6-dichlorophenyl)indolizine-1-carbo-nitirle 75



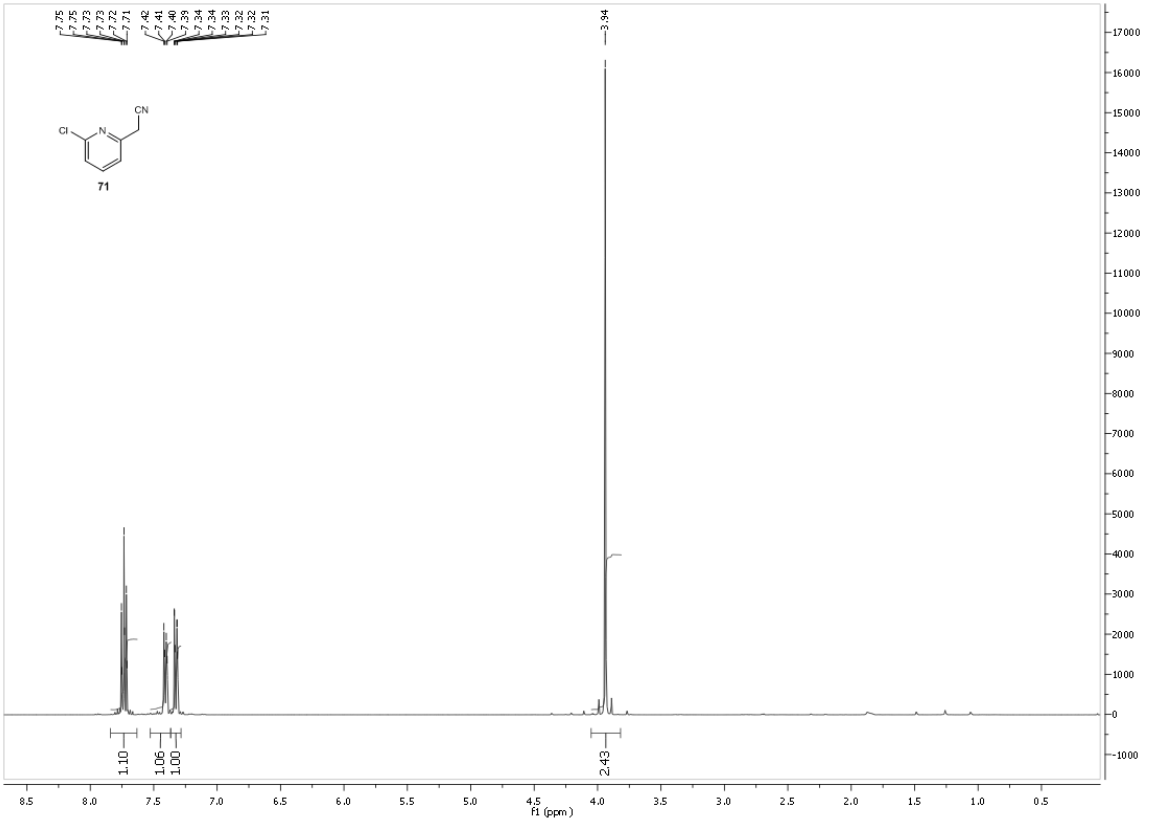


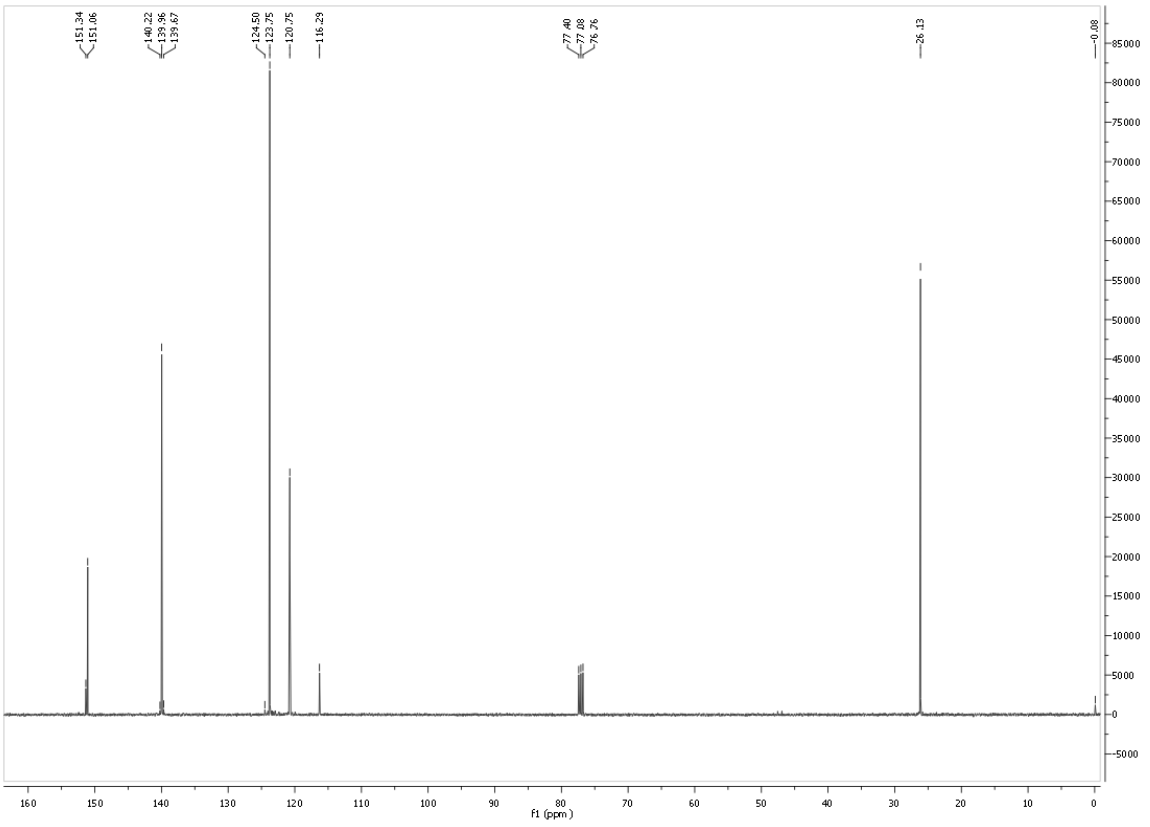
3-(2-chloro-6-fluorophenyl)-2-(pyridin-2-yl)acrylonitrile 76a



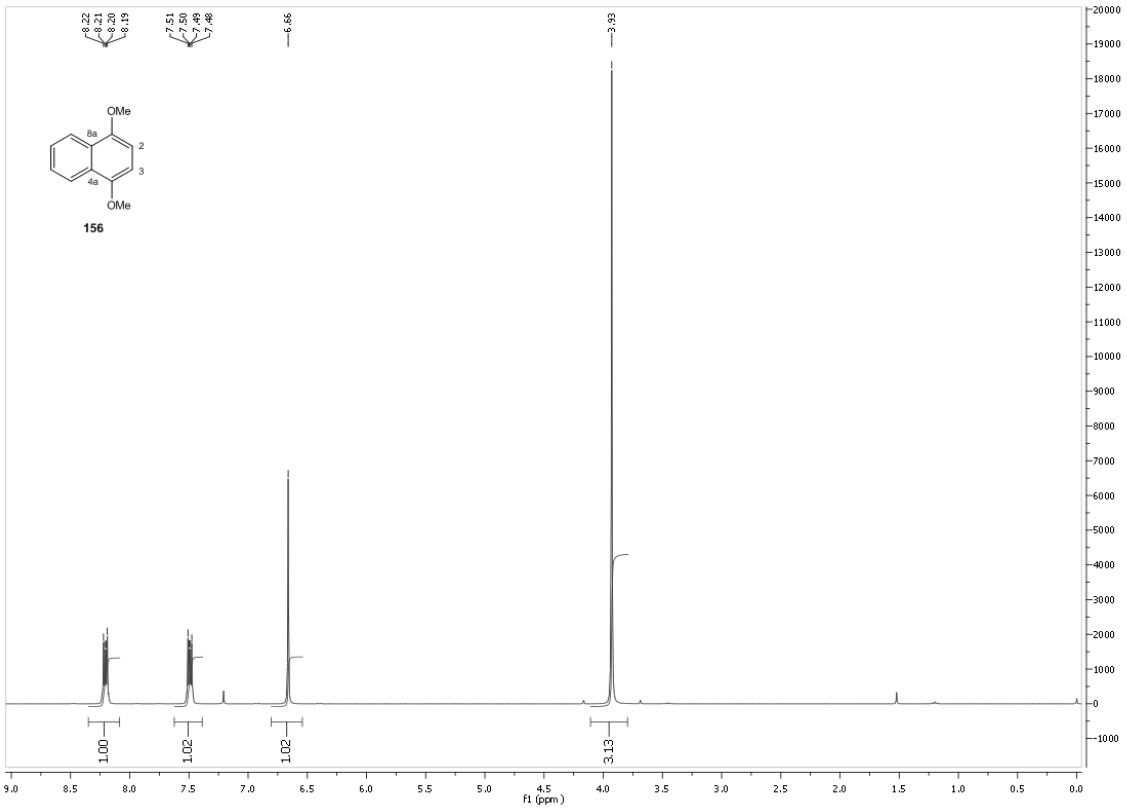


2-(6-chloropyridin-2-yl)acetonitrile 71

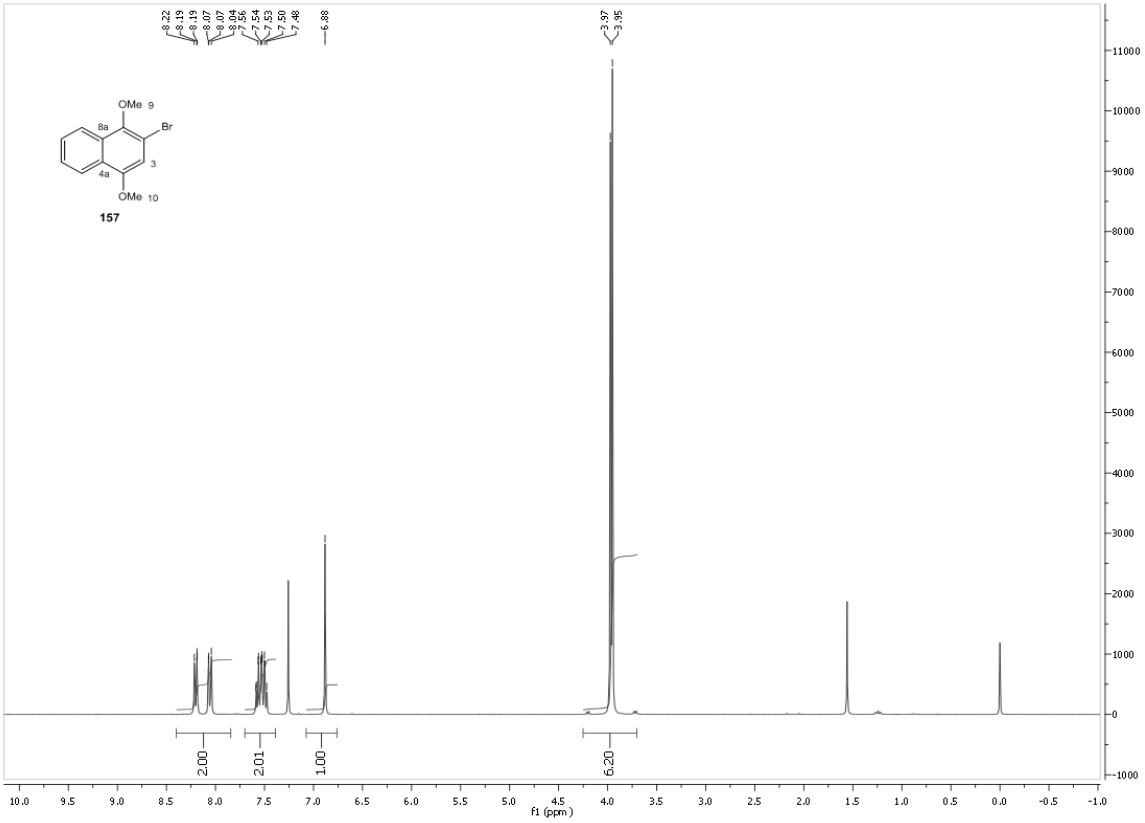


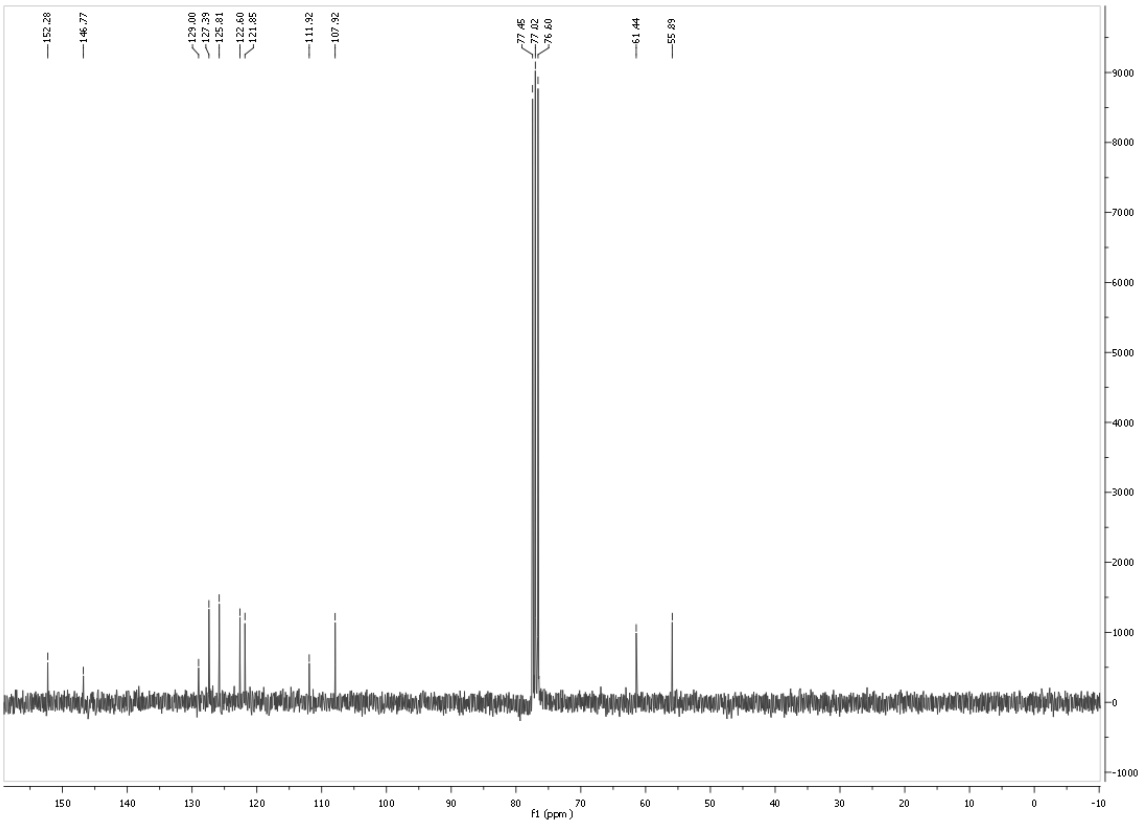


1,4-dimethoxynaphthalene 156

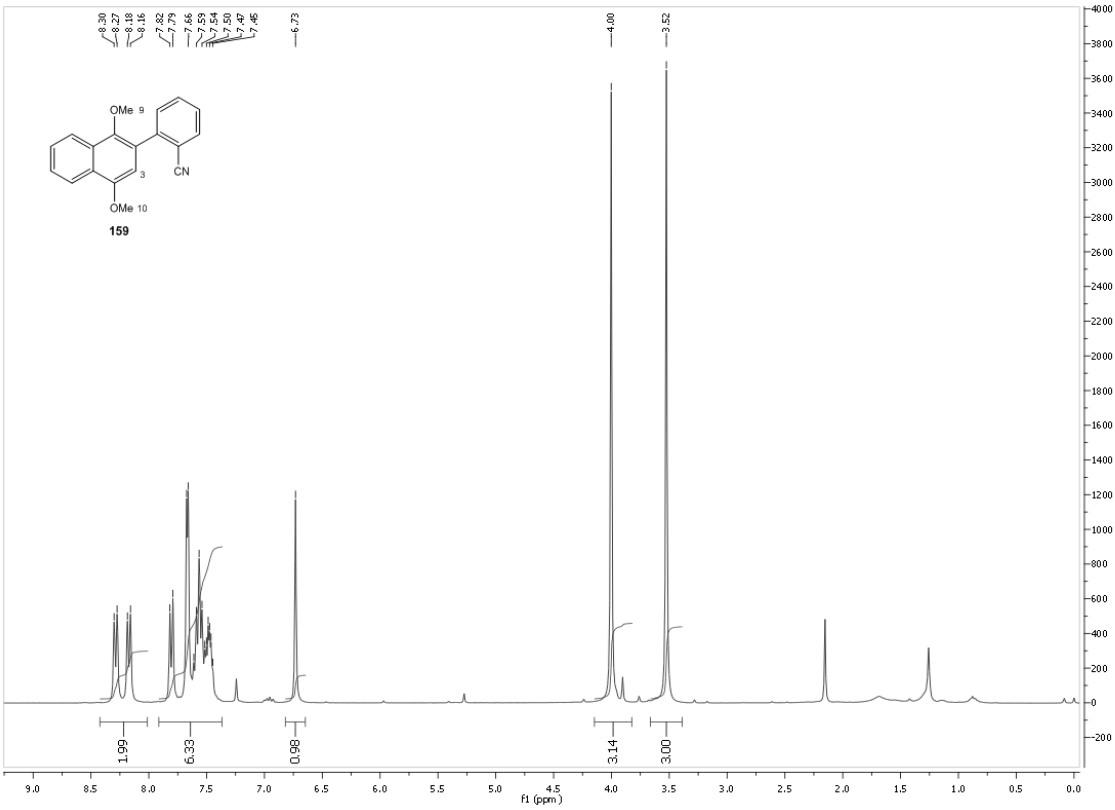


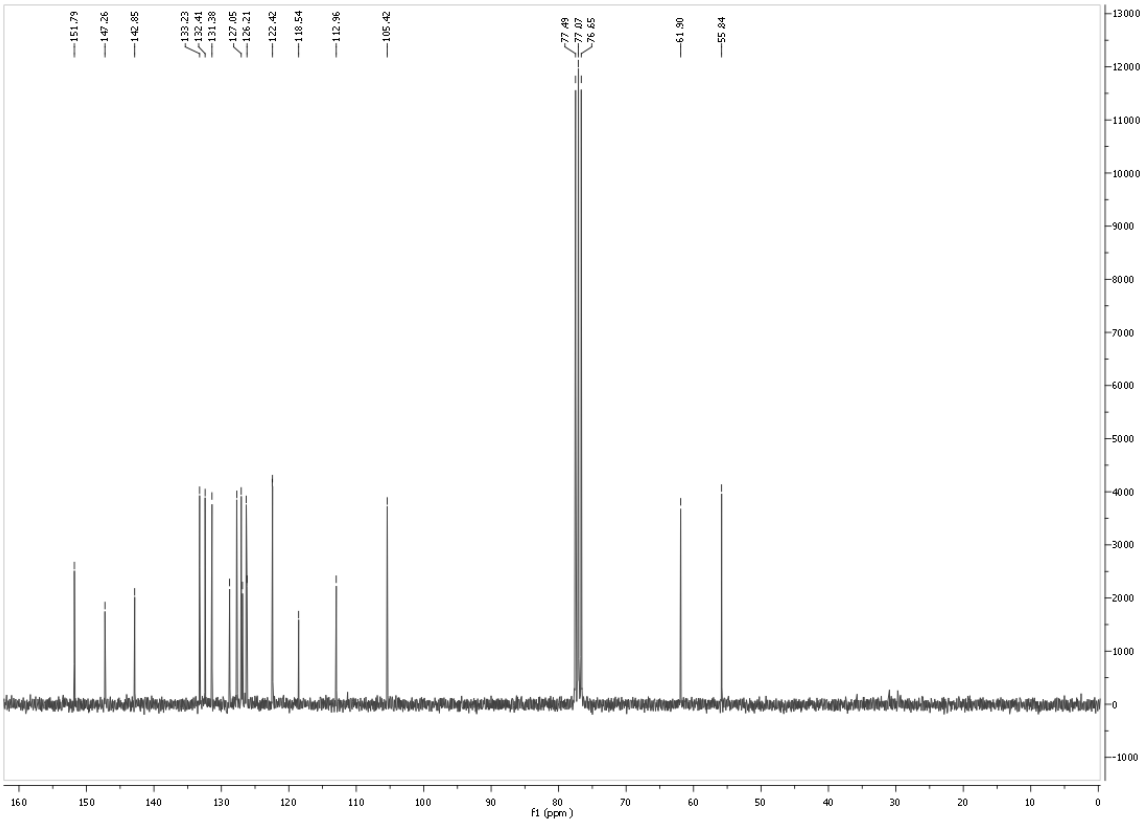
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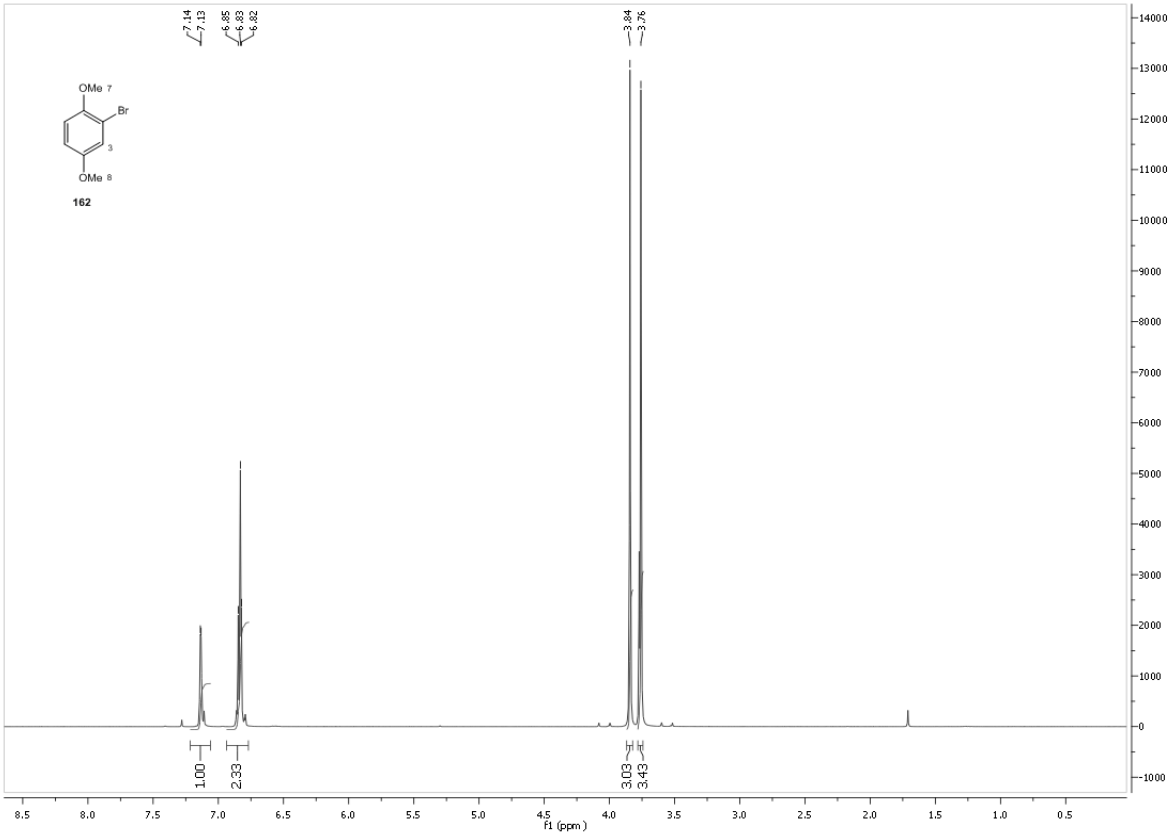


2-(1,4-dimethoxynaphthalen-2-yl)benzonitirle 159

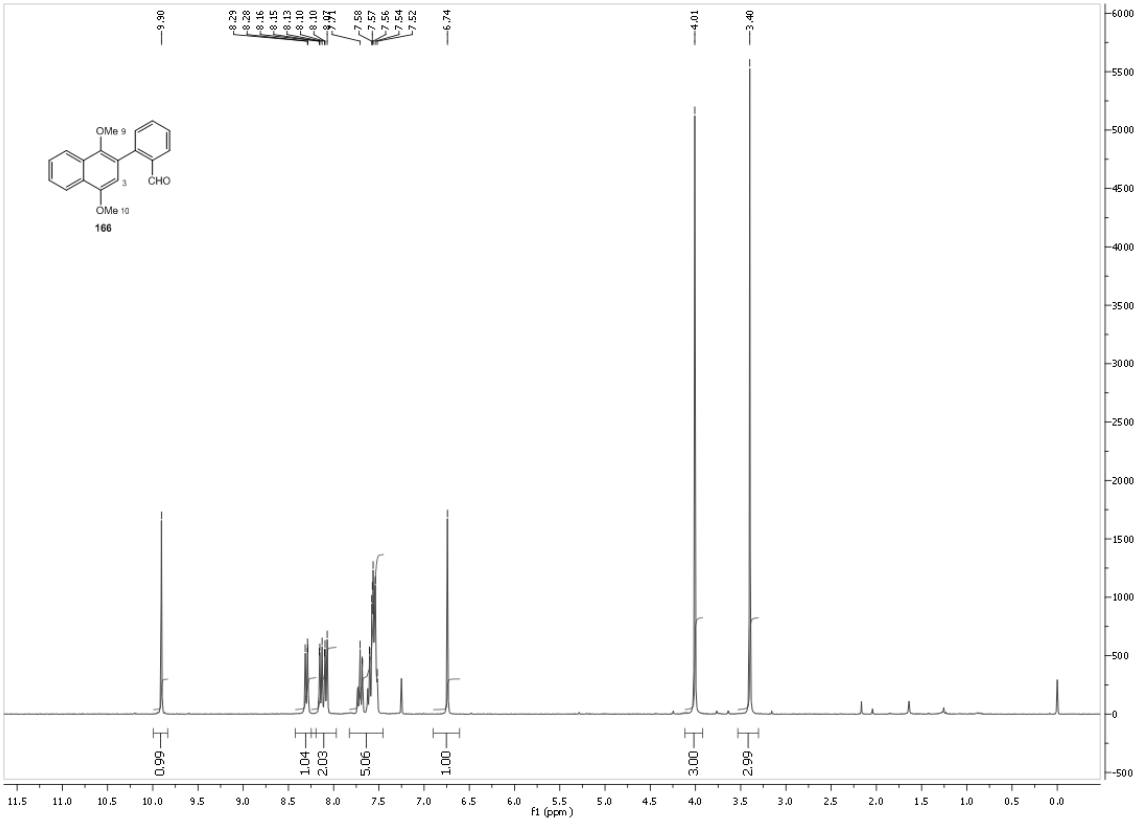


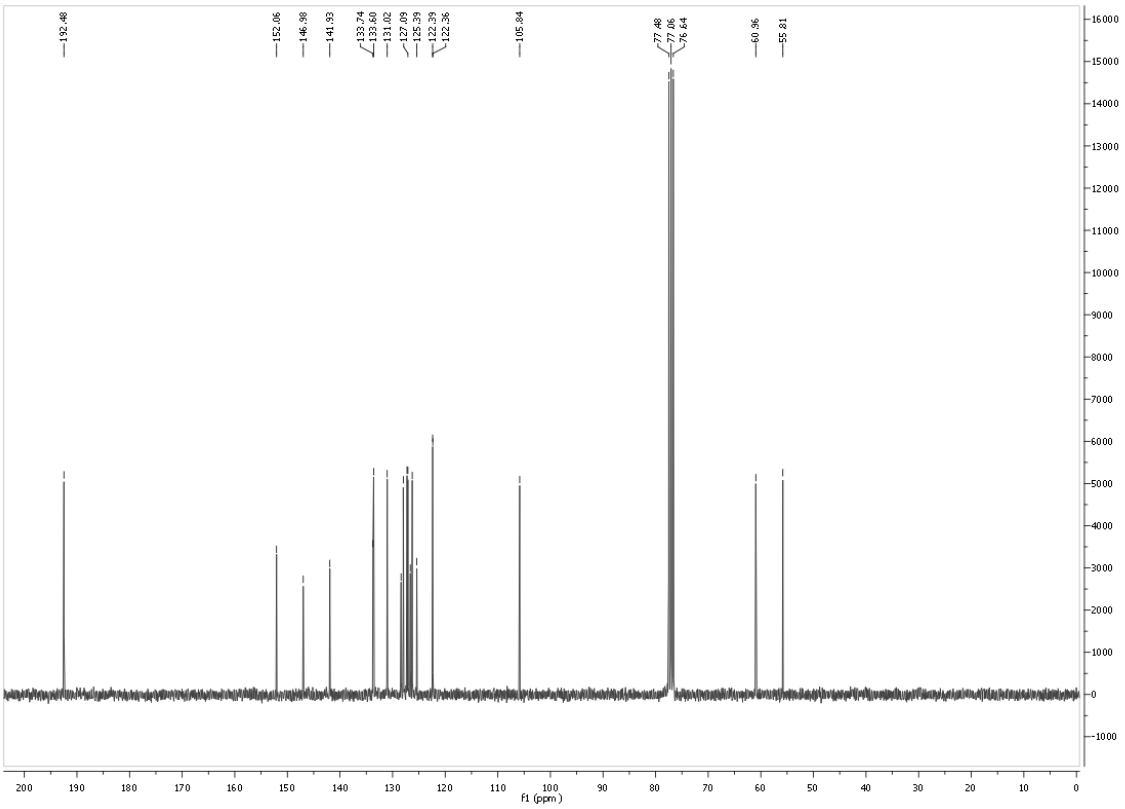


2-bromo-1,4-dimethoxybenzene 162

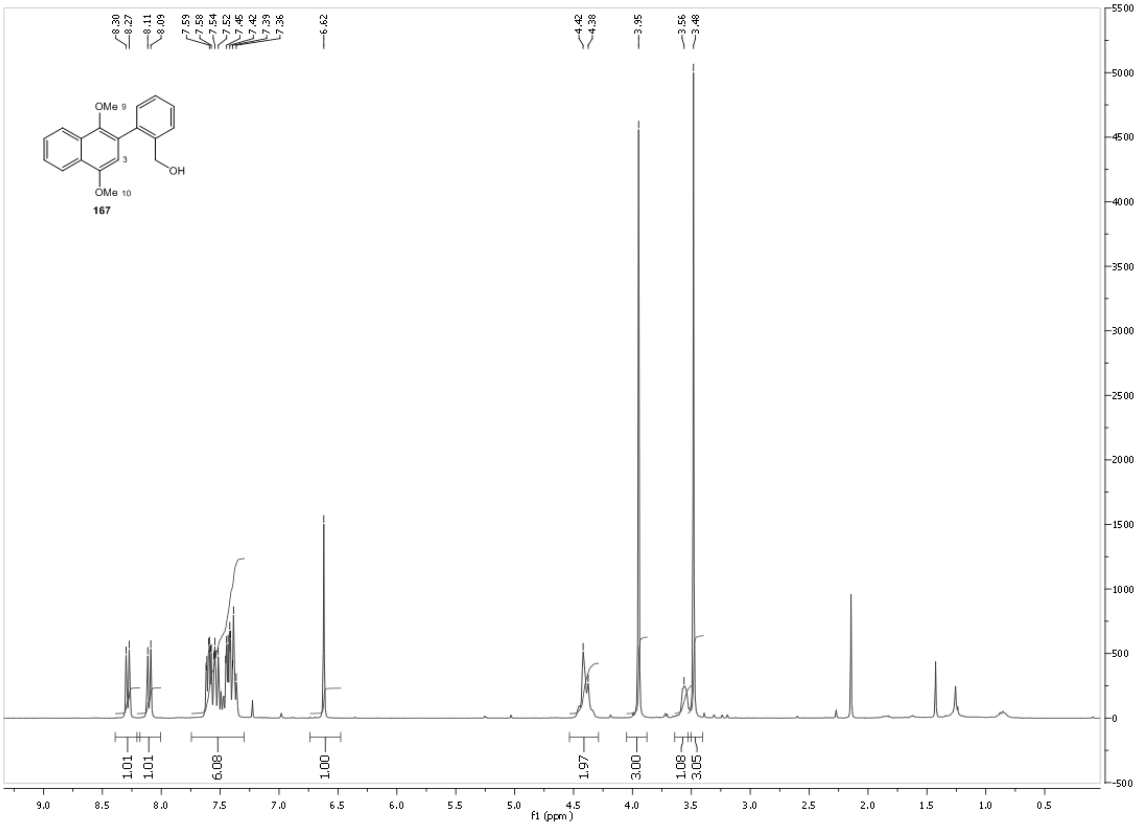


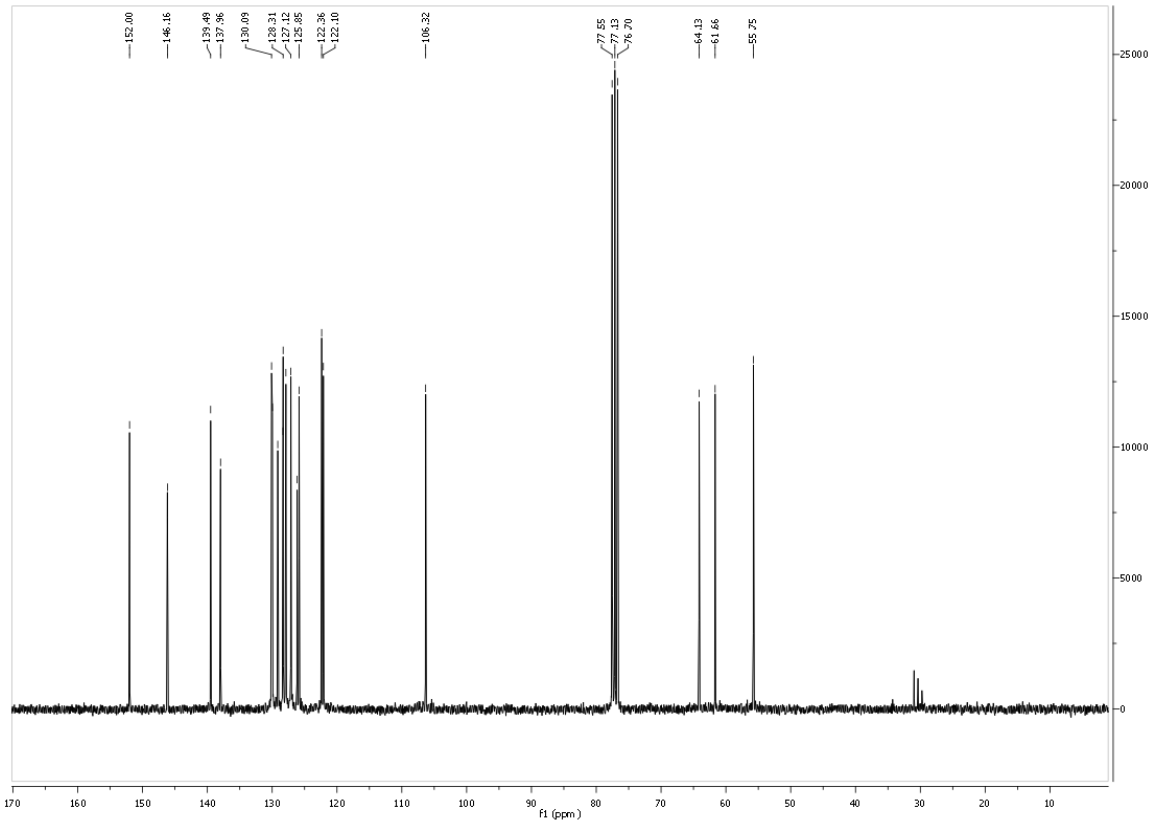
2-(1,4-dimethoxynaphthalen-2-yl)benzaldehyde 166



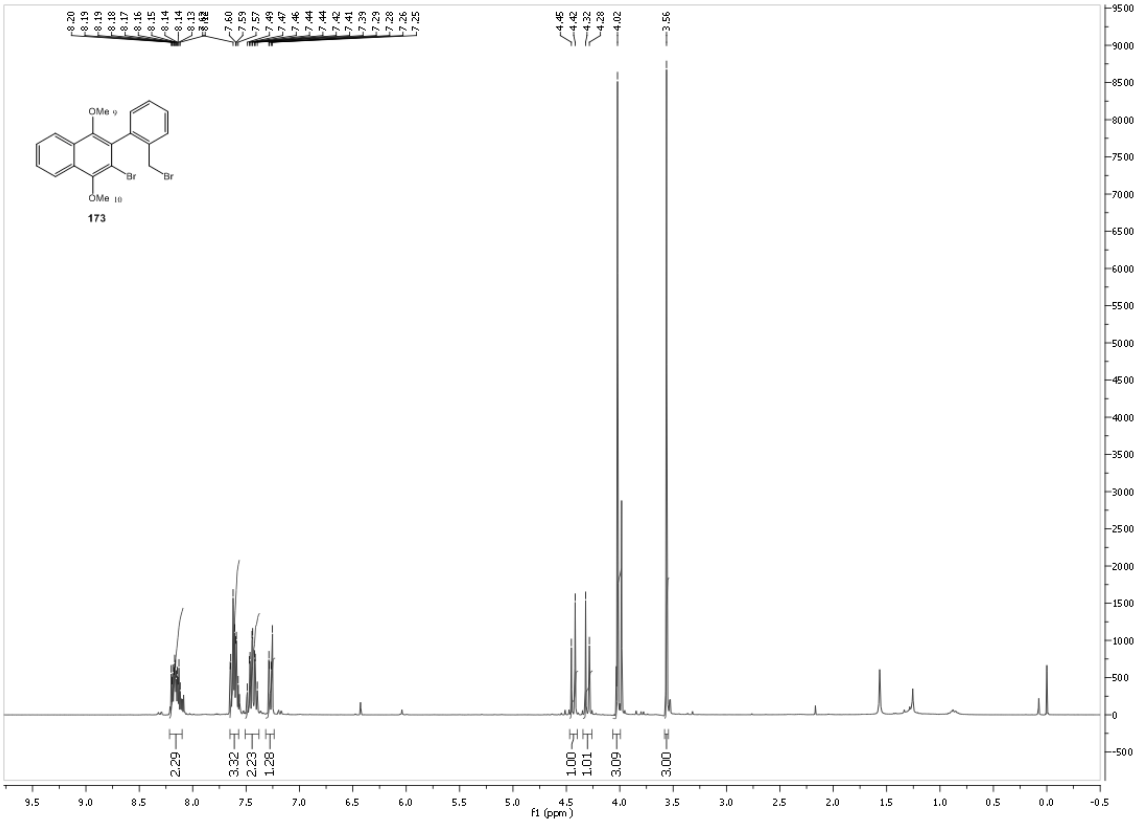


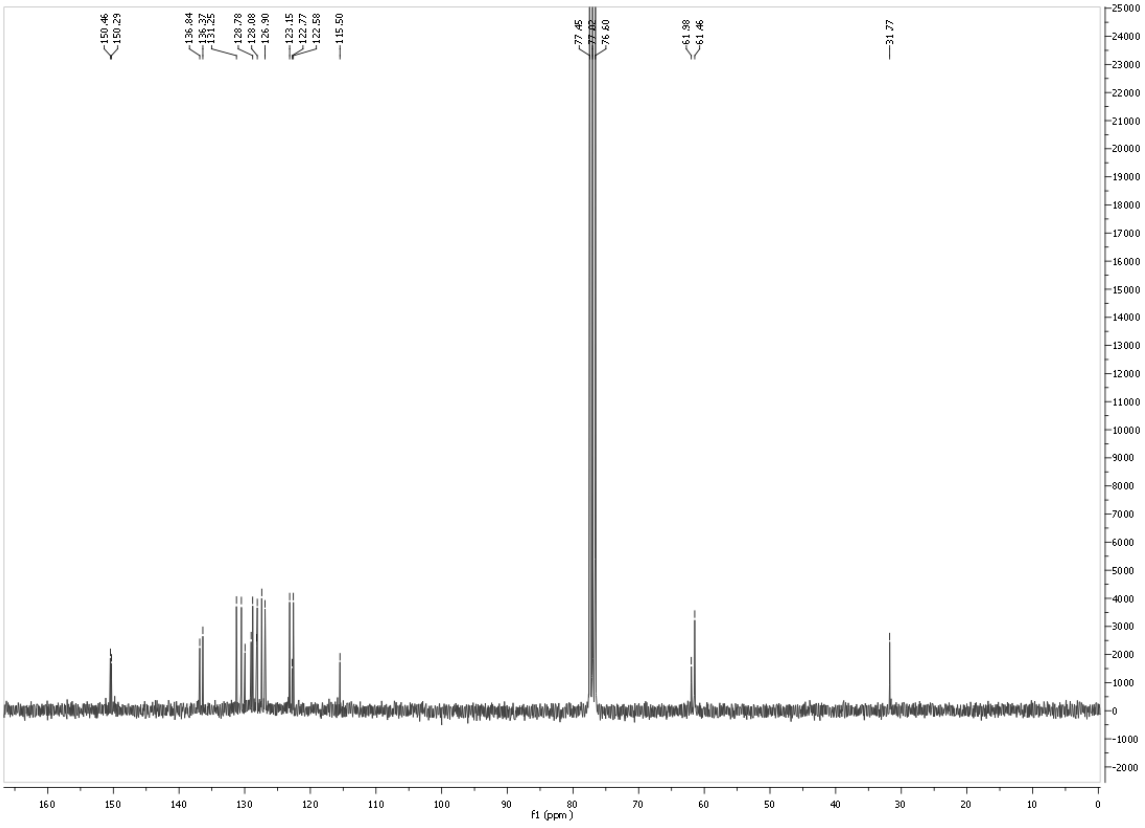
(2-(1,4-dimethoxynaphthalen-2-yl)phenyl)methanol 167



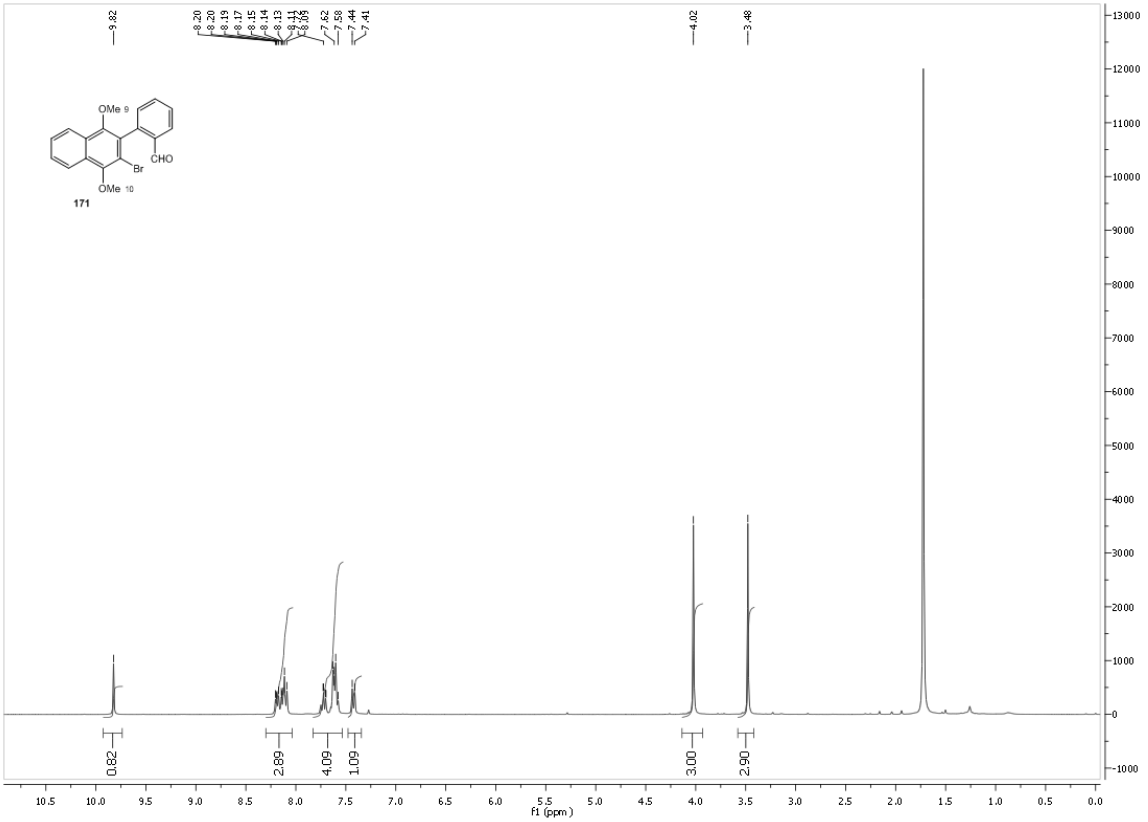


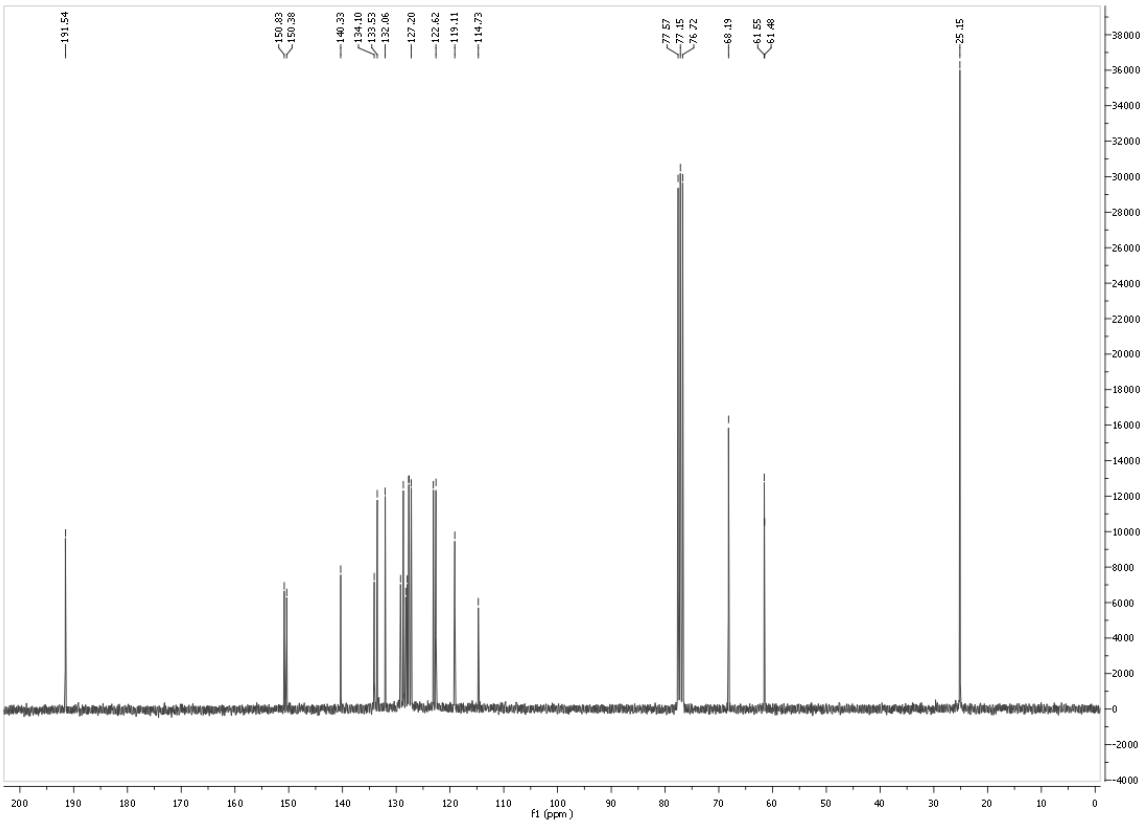
2-bromo-3-(2-(bromomethyl)phenyl)-1,4-dimethoxynaphthalene 173



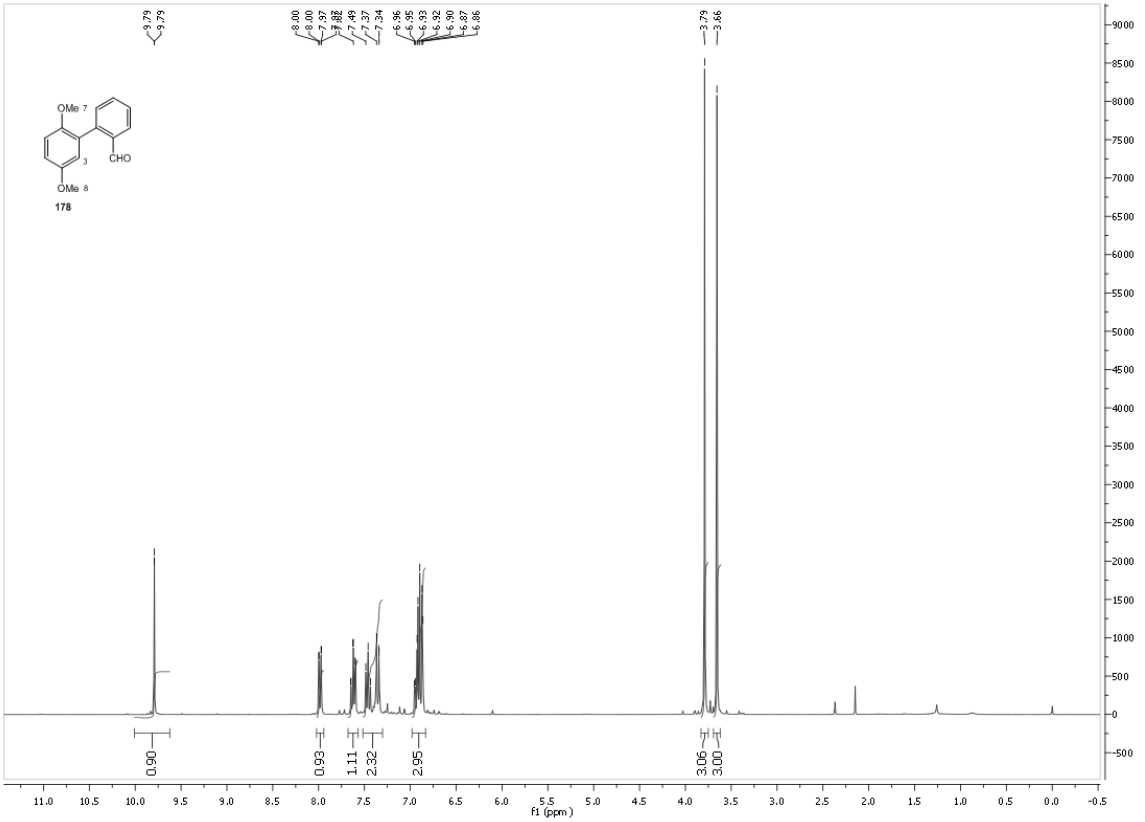


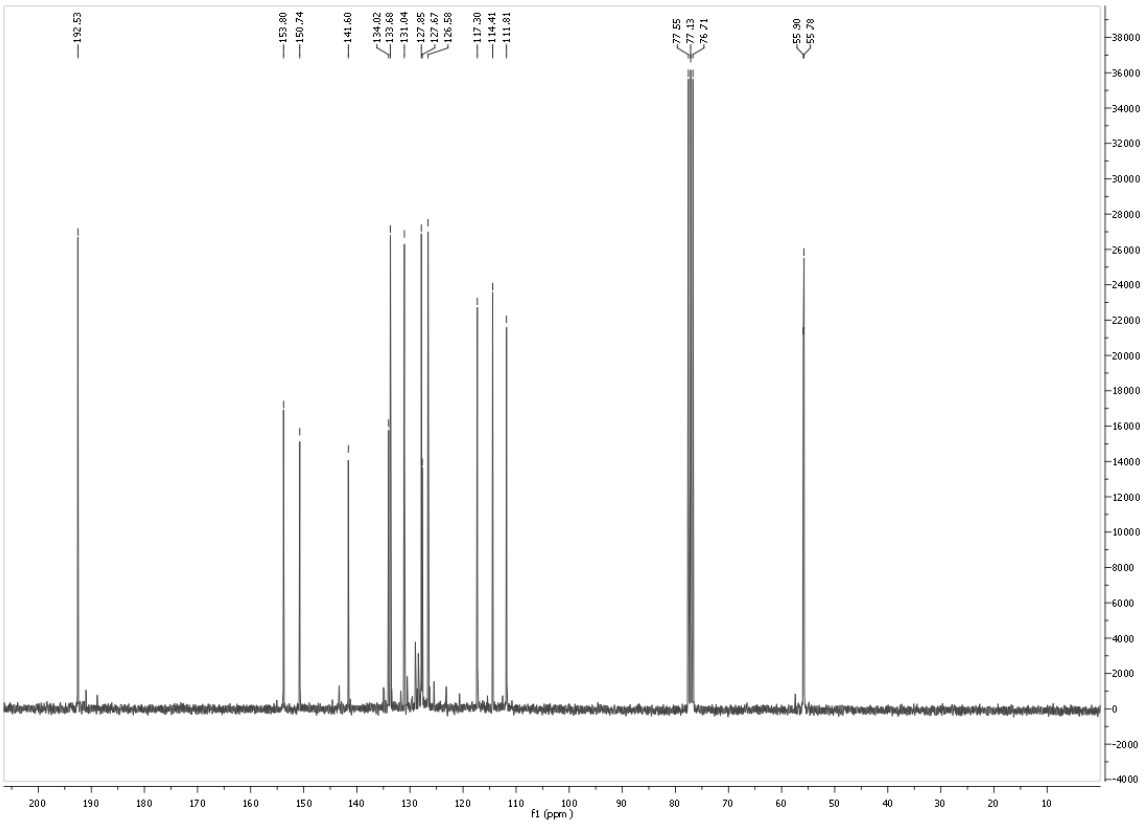
2-(3-bromo-1,4-dimethoxynaphthalen-2-yl)benzaldehyde 171



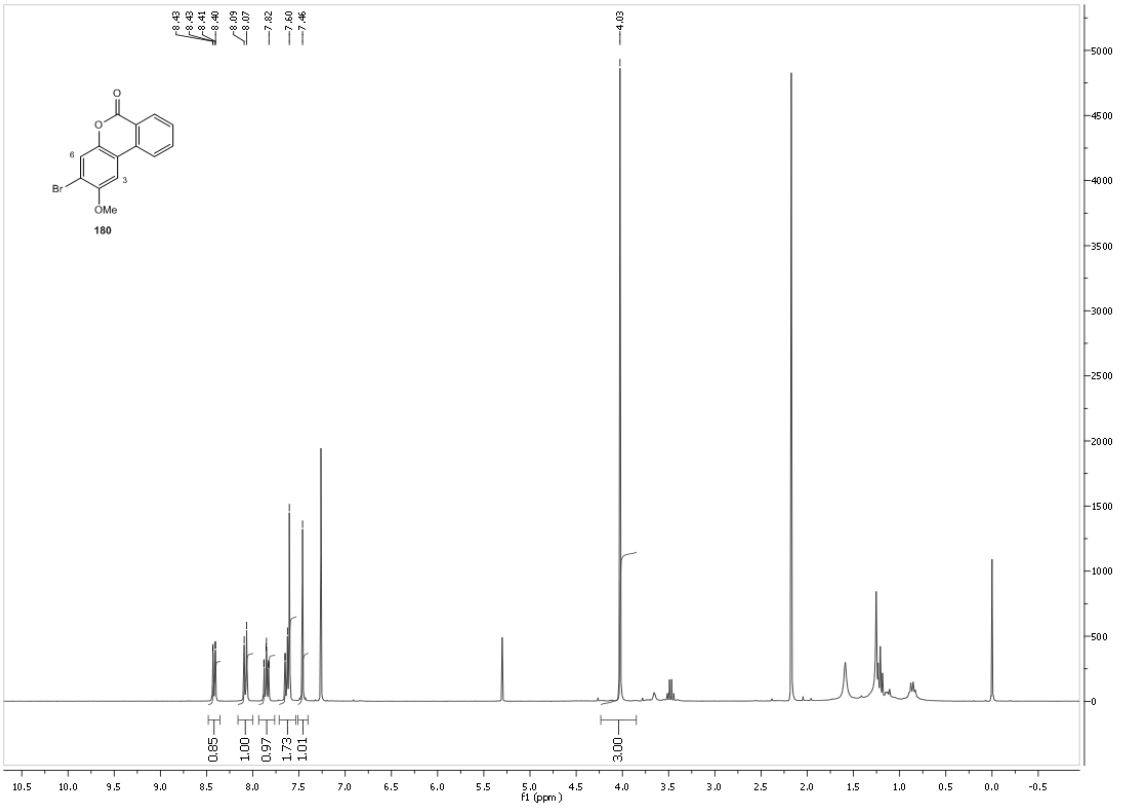


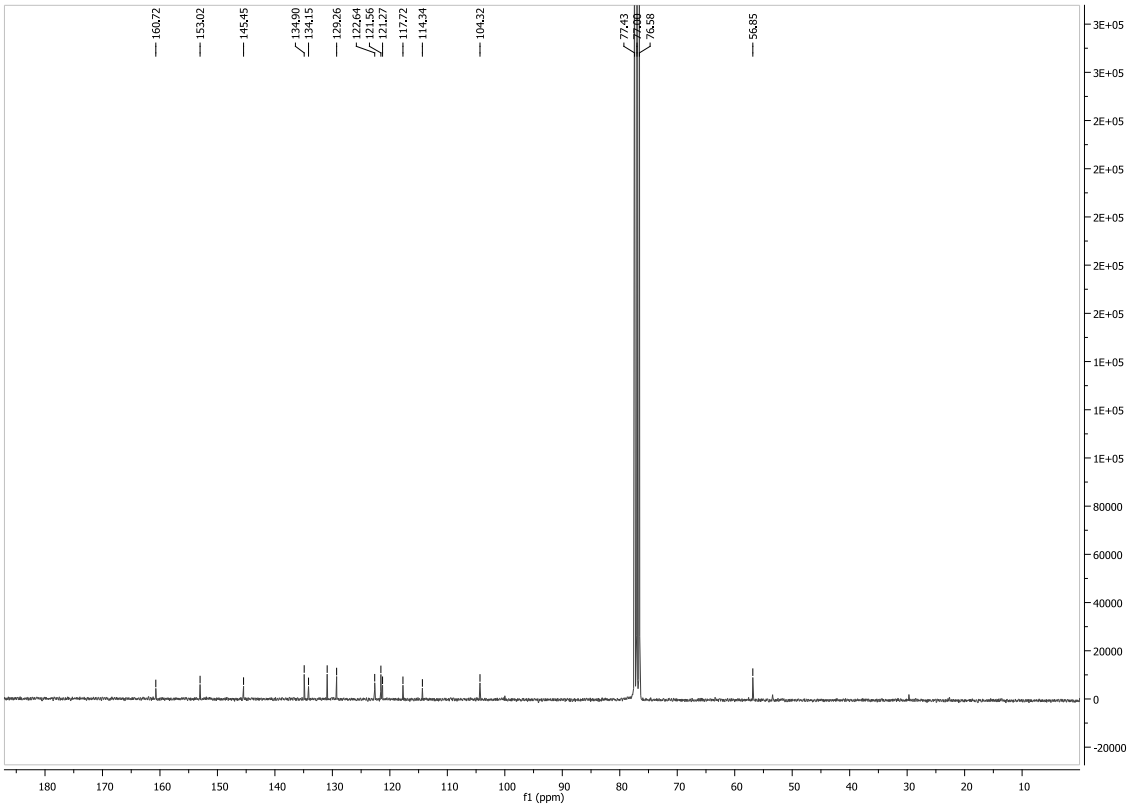
2’,5’-dimethoxybiphenyl-2-carbaldehyde 178



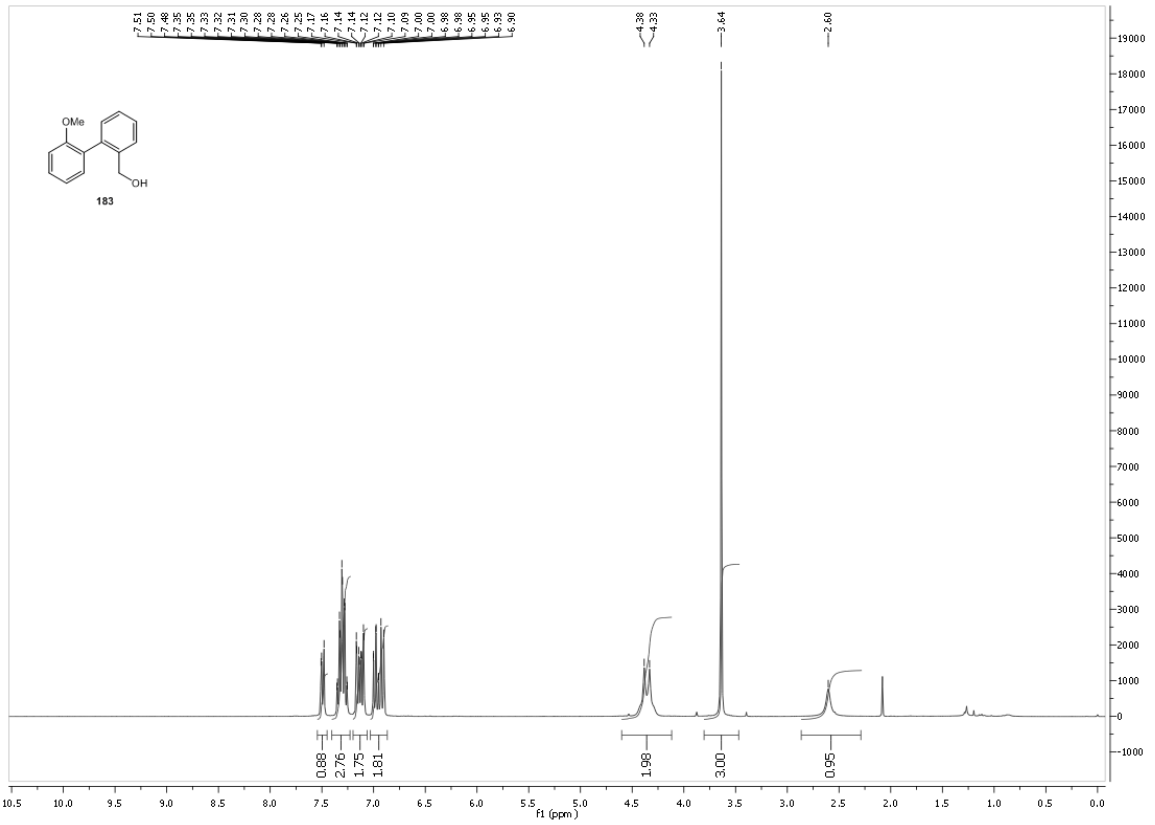


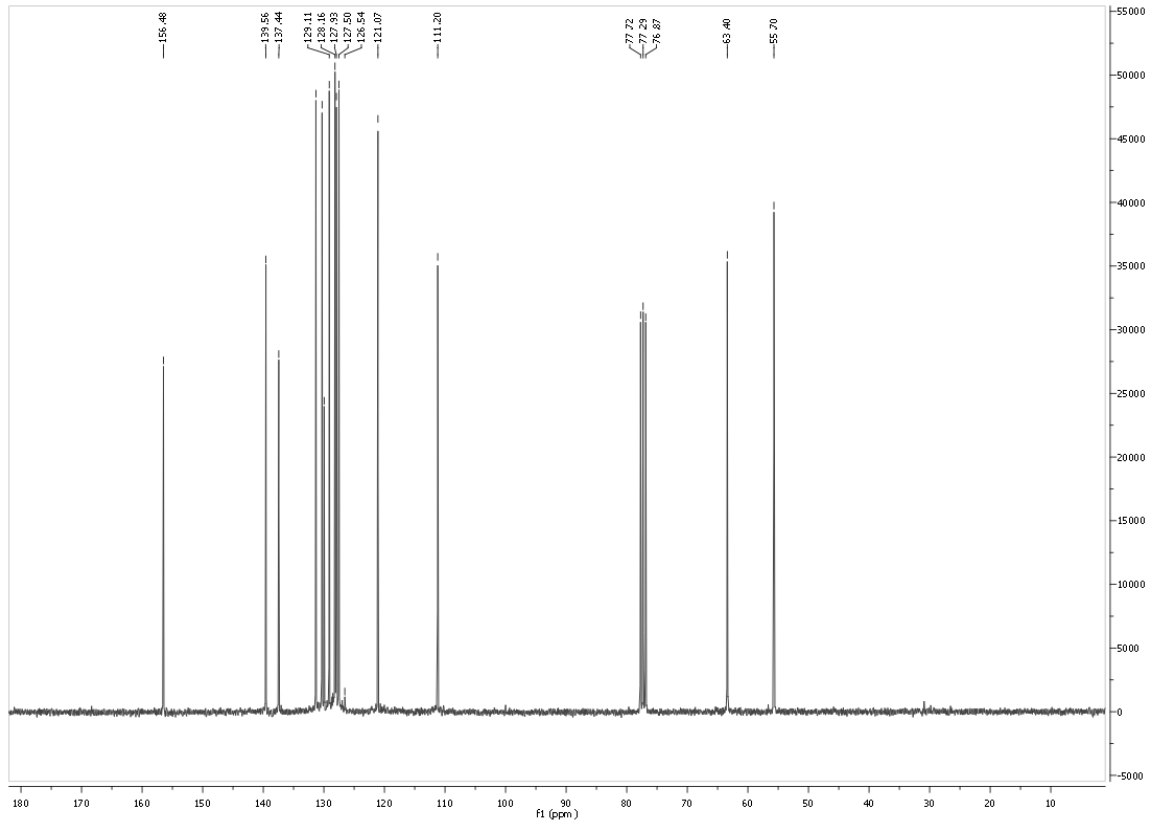
3-bromo-2-methoxy-6*H*-benzo[*c*]chromen-6-one 180



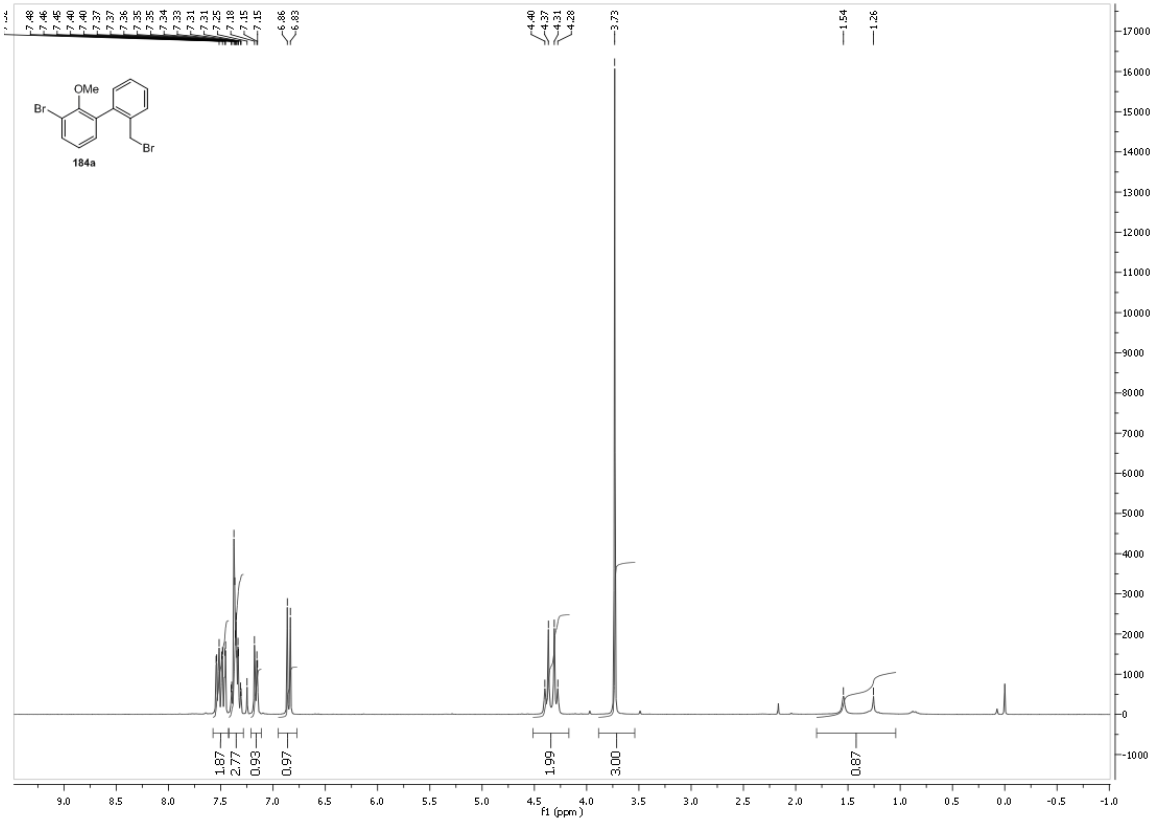


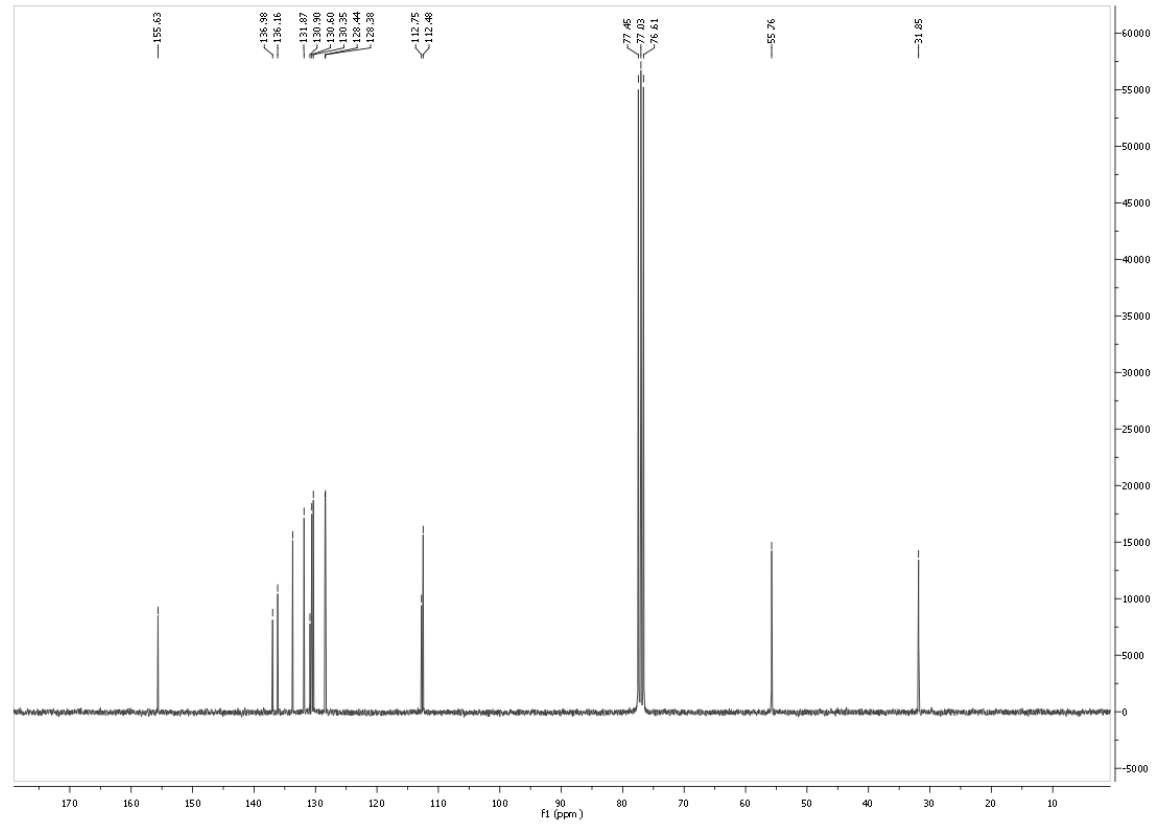
(2’-methoxybiphenyl-2-yl)methanol 183





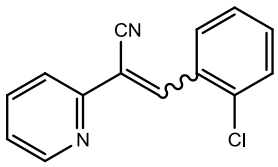
3-bromo-2'-(bromomethyl)-2-methoxybiphenyl 184a





Appendix B: Single-Crystal X-ray Diffraction Data

1.1 Crystal Structure Data for 3-(2-chlorophenyl)-2-(pyridin-2-yl)acrylonitrile **64a**

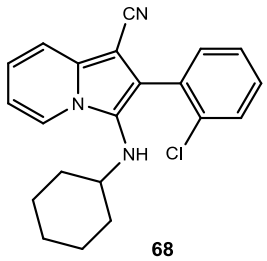


64a

Table 1: Crystal Data and Structure Refinement for Compound **64a**

Empirical formula	C14 H9 Cl N2	
Formula weight	240.68	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 3.80440(10) Å	α= 98.634(2)°.
	b = 12.2280(4) Å	β= 90.676(2)°.
	c = 12.2766(4) Å	γ =93.692(2)°.
Volume	563.33(3) $Å^3$	
Z	2	
Density (calculated)	1.419 Mg/m^3	
Absorption coefficient	0.314 mm^{-1}	
F(000)	248	
Crystal size	0.48 x 0.18 x 0.10 mm^3	
Theta range for data collection	1.68 to 28.00°.	
Index ranges	-4≤h≤5, -14≤k≤16, -16≤l≤16	
Reflections collected	8849	
Independent reflections	2693 [R(int) = 0.0522]	
Completeness to theta = 28.00°	100.0 %	
Absorption correction	None	
Max. and min. transmission	0.9693 and 0.8640	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2693 / 0 / 154	
Goodness-of-fit on F^2	1.064	
Final R indices [I>2sigma(I)]	R1 = 0.0410, wR2 = 0.0873	
R indices (all data)	R1 = 0.0560, wR2 = 0.0944	
Largest diff. peak and hole	0.289 and -0.259 $e.Å^{-3}$	

*1.2 Crystal Structure Data for 2-(2-chlorophenyl)-3-(cyclohexylamino)indolizine-1-carbonitrile **68***



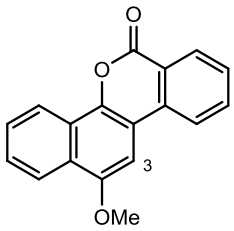
68

Table 2: Crystal Data and Structure Refinement for Compound **68**

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Empirical formula	C25 H30 Cl N3 O	
Formula weight	423.97	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 9.1055(2) Å	α= 90°.
	b = 18.7282(4) Å	β= 108.48°.
	c = 14.3646(3) Å	γ= 90°.
Volume	2323.30(9) $Å^3$	
Z	4	
Density (calculated)	1.212 Mg/m^3	
Absorption coefficient	0.185 mm^{-1}	
F(000)	904	
Crystal size	0.46 x 0.45 x 0.29 mm^3	
Theta range for data collection	1.85 to 28.00°.	
Index ranges	-12≤h≤12, -24≤k≤17,	
	-18≤l≤18	
Reflections collected	29802	
Independent reflections	5596 [R(int) = 0.0448]	
Completeness to theta = 28.00°	100.0 %	
Absorption correction	None	
Max. and min. transmission	0.9483 and 0.9197	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5596 / 0 / 277	
Goodness-of-fit on F^2	1.055	
Final R indices [I>2sigma(I)]	R1 = 0.0464, wR2 = 0.1240	
R indices (all data)	R1 = 0.0576, wR2 = 0.1307	
Largest diff. peak and hole	0.435 and -0.416 $e.Å^{-3}$	

*1.3 Crystal Structure Data for 12-methoxy-6H-dibenzo[c,h]chromen-6-one **170***



170

Table 3: Crystal data and structure refinement for Compound **170**

Empirical formula	C18 H12 O3
Formula weight	276.28
Temperature	173(2) K
Wavelength	0.71069 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 7.1970(7) Å α=103.237(3)°.
	b = 9.0700(9) Å β=105.722(3)°.
	c = 10.8400(11) Å γ=104.026(3)°.
Volume	627.07(11) $Å^3$
Z	2
Density (calculated)	1.463 Mg/m^3
Absorption coefficient	0.100 mm^{-1}
F(000)	288
Crystal size	0.62 x 0.14 x 0.04 mm^3
Theta range for data collection	2.06 to 27.00°.
Index ranges	-9≤h≤9, -11≤k≤10, -13≤l≤13
Reflections collected	6387
Independent reflections	2743 [R(int) = 0.0758]
Completeness to theta = 27.00°	100.0 %
Absorption correction	None
Max. and min. transmission	0.9960 and 0.9409
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2743 / 0 / 191
Goodness-of-fit on F^2	0.874
Final R indices [I>2sigma(I)]	R1 = 0.0479, wR2 = 0.1016
R indices (all data)	R1 = 0.0902, wR2 = 0.1190
Largest diff. peak and hole	0.229 and -0.271 $e.Å^{-3}$