Synthetic Approaches to Novel Pyridine and Indole Derivatives as Potential Agents for the Treatment of Neurodegenerative Disorders

Neil Colgin

A thesis submitted in partial fulfilment of the
requirements of the University of Sunderland
for the degree of Doctor of Philosophy

This research programme was carried out
in collaboration with Institut de Recherches Servier

May 2009

Acknowledgements

I would like to express my gratitude to my supervisor Dr. Adrian Moore for his support and guidance. I am grateful to our collaborators at Institut de Recherches Servier for financial support and also Dr. Pierre Lestage and Dr. Denis Guedin at Servier for the pharmacological data. Thanks also to Dr. Yongxue Huang for helpful discussion and ChemiSPEC, University of Sunderland for NMR and elemental data.

Table of Contents

Chapter 3

Chapter 4

Abbreviations

ACh	Acetylcholine
AChE	Acetylcholine esterase
AD	Alzheimer's Disease
n-BuLi	n-Butyllithium
t-BuLi	t-Butyllithium
CBS	Corey-Bakshi-Shibata catalyst
CNS	Central nervous system
DCM	Dichloromethane
DMF	*N,N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5-tetrahydro-2(1*H*)-pyrimidione
DMSO	Dimethyl sulphoxide
HMPA	Hexamethylphosphoramide
HMPT	Hexamethylphosphorus triamide
HPLC	High performance liquid chromatography
IPA	Isopropyl alcohol
IR	Infrared
LBD	Lewy Body Disease
LDA	Lithium diisopropylamide
MS	Mass spectrometry
nAChR	Nicotinic acetylcholine receptor
NADPH	Nicotinamide adenine dinucleotide phosphate
NAM	Negative allosteric modulator
NICE	National Institute for Clinical Excellence
NMDA	*N*-methyl-D-aspartate

NMR	Nuclear magnetic resonance
NSAID	Non-steroidal anti-inflammatory drug
PAM	Positive allosteric modulator
PCC	Pyridinium chlorochromate
PD	Parkinson’s Disease
THF	Tetrahydrofuran
TLC	Thin layer chromatography

Abstract

Alzheimer's Disease (AD), Parkinson's Disease (PD) and Lewy Body Disease (LBD) are some of the many neurodegenerative disorders associated with dementia, for which there is no ultimate cure. It is widely accepted that central nervous system (CNS) nicotinic acetylcholine receptors (nAChRs) may be strongly implicated in the pathology of these devastating disorders, and that stimulation of nAChRs can enhance cognitive behaviour in animals and humans. Nicotine and other nicotinic receptor binding compounds have, over many years, been explored as potential therapies for disorders such as AD and PD. This thesis describes the preparation and pharmacological investigation of a series of 3-substituted and 3,5-disubstitued pyridine derivatives as potential novel and selective nictotinic receptor agonists.

Chapter Two details the synthesis of targeted compounds using the generation of [(pyridin-3-yl)methyl]lithium and [(5-methylpyridin-3-yl)methyl]lithium, respectively and subsequent reaction with various electrophiles. Unsuccessful attempts at the synthesis of enantiomerically pure 4-substituted arylpyridin-3-yl-ethanol derivatives by reduction of pro-chiral 4-substituted arylpyridin-3-yl-ethanone derivatives were made using both catalytic and enzymatic approaches; however, a pair of enantiomerically pure alcohols were isolated *via* the resolution of diastereomeric esters (prepared by reaction with (*S*)-*O*-acetyl mandelic acid) and subsequent hydrolysis.

Chapter Three explores the synthesis of targeted compounds using halogen-lithium exchange reactions of 3-bromopyridine using n-BuLi and ring-opening by the resultant pyridin-3-yllithium of 4-substituted aryl epoxides. As an extension, Sonogashira cross-coupling of 3-bromopyridine and 4-substituted arylacetylenes and subsequent hydration as an approach to 4-substituted pyridin-3-yl-ethanone derivatives is described. A series of indole derivatives were synthesised using identical approaches.

Using methodology developed in previous Chapters, Chapter Four describes approaches to symmetrical and asymmetrical 3,5-bis(arylethynyl)pyridine derivatives, the corresponding bis(ketones), alcohols and 3,5-disubstituted keto-alcohol products.

Chapter Five details preliminary pharmacological data (binding and functional assays) performed by our collaborators at Institut de Recherches Servier.

Chapter 1

1.1 Dementia Related Disorders of the Central Nervous System

Dementia can be defined as a syndrome which features the deterioration of previously acquired intellectual abilities, sufficiently severe to hinder social or occupational functioning. The most common forms of dementia related disorders of the central nervous system include Alzheimer's Disease, Parkinson's Disease, Huntingdon's Disease and Dementia with Lewy Bodies.

Dementia is currently estimated to affect seven hundred thousand people in the UK and this figure is estimated to rise to over one million by 2025.[1] Alzheimer's Disease (AD) is the most common form of dementia diagnosed and is becoming even more prevalent in developed countries as a result of increasing life expectancies. AD is a progressive brain disorder that gradually destroys memory and the ability to learn; eventually, communication becomes almost impossible and a sufferer will, in time, be unable to complete simple day-to-day tasks and will, almost certainly, require full-time care.

The primary cause of AD dementia appears to be the disruption of the regulation, expression or scavenging of abnormal proteins present in the neuronal cell-membrane.[2] This is thought to be due to a defect on chromosome 21; this defect affects amyloid precursor protein (APP) resulting in fibrillary aggregates of β-amyloid protein, which are toxic to

neurons.[3] The neurotoxicity of β-amyloid protein leads to the degeneration of a large number of neurotransmitter systems responsible for cognitive expression.[4] Perry *et al.*[5] demonstrated that the entorhinal cortex, which has a high concentration of nicotinic receptors, is vulnerable to amyloid plaque induced loss of receptors. Patients suffering from AD show a marked reduction in nicotinic cholinergic receptor binding relative to age matched healthy subjects.[2,6] AD is also characterised neuropathologically by the presence of neurofibrillary tangles formed by aggregates of hyperphosphorylated tau protein inside the neurons. In AD, tau proteins bind to each other and grow to form Paired Helical Filaments (PHF). PHF do not degrade normally and grow to such an extent that they fill the cytoplasm, eventually causing the death of a cell.[7]

Nicotinic receptor loss also appears to be linked to the primary pathology of Parkinson's Disease (PD).[6] A loss of cholinergic cells in the basal forebrain similar to that seen in AD has also been witnessed in PD.[8] Parkinson's Disease patients suffer from muscular rigidity, tremors, poor balance and bradykinesia (difficulty in the initiation of movement), but usually show no signs of the mental deterioration seen in AD. It is believed that PD results from the degeneration of dopamine-producing nerve cells in the *substantia nigra* region of the brain. Dopamine is a neurotransmitter that stimulates the motor neurones which control muscle movement - depletion of dopamine, therefore, causes impairment of motor function.

In rare PD cases where dementia exists, Lewy bodies (spherical protein deposits found inside neurons) are often found in the cerebral cortex and

substantia nigra and this is commonly known as Lewy Body Disease (LBD). LBD was often misdiagnosed as either AD or PD, but is now recognised as a disease in its own right. Sufferers of LBD display symptoms of both AD, *e.g.* language disturbances, and the tremors and rigidity which are classic symptoms of PD.

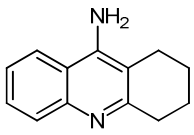
1.2.1 Current Treatments for Neurodegenerative Disorders

No cures currently exist for neurodegenerative disorders such as AD and PD, and current therapies only serve to alleviate some of the life-affecting symptoms of the disorders.

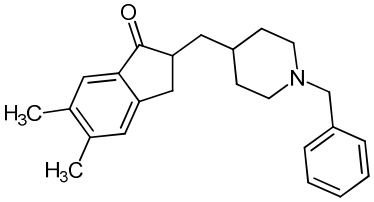
Several pharmaceuticals have been licenced for the short-term relief of the symptoms of AD. These include**,** tacrine (Cognex®, Sciele Pharma) **1,** donepezil (Aricept®, Pfizer) **2,** rivastigmine (Exelon®, Novartis) **3,** galantamine (Reminyl®, Shire Pharmaceuticals) **4** and memantine (Ebixa®, Lundbeck) **5**.

Donepezil, galantamine and rivastigmine are all broadly termed 'Second-Generation' Acetylcholine Esterase Inhibitors (AChEIs), however, their structure, pharmacokinetics and pharmacology differ significantly. With the exception of memantine, these pharmaceuticals act *via* inhibition of the enzyme acetylcholine esterase (AChE).

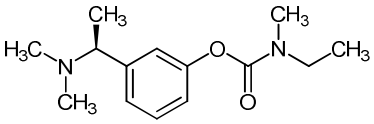
AChE is found in the brain, muscles and cholinergic neurons, where it hydrolyses acetylcholine (ACh) **6** upon its release at the synaptic cleft, thereby reducing cholinergic function. The inhibition of AChE prevents the breakdown of acetylcholine, increasing cerebral acetylcholine concentrations and producing some improvement in cognitive performance.



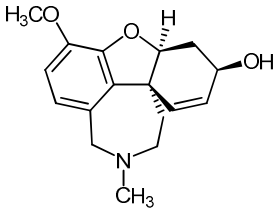
Tacrine, 1



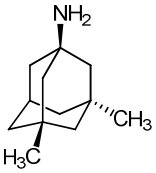
Donepezil, 2



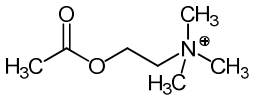
Rivastigmine, 3



Galantamine, 4



Memantine, 5



Acetylcholine, 6

In 1993, Tacrine **1** was the first of the AChEIs approved for treatment of AD.[9] Tacrine has been shown to be useful in the stabilisation and improvement of symptoms in AD.[10-12] Initial trials of tacrine with LBD sufferers[13] and PD patients[14,15] have, thus far, proven promising. However, in recent years the clinical use of tacrine has become uncommon in response to findings that therapeutic concentrations can cause hepatoxicity.[16,17]

Donepezil **2**, a piperidine based compound, selectively inhibits AChE. It is metabolised in the liver by cytochrome P-450 isoenzymes. Donepezil has been proven to have beneficial effects on cognitive function and aspects of

daily living of AD patients.[18,19] Aarsland *et al.*[20] have demonstrated that donepezil also has the ability to improve cognition in PD patients; however, more recent studies contradict this work and report a worsening in Parkinsonism.[21] Similar contradictory evidence exists for the use of donepezil on patients suffering from LBD; several studies have shown that LBD responds well to AChEIs such as donepezil,[22,23] whereas some groups have reported observable improvement in overall function, but some worsening of symptoms (primarily motor function).[24,25]

Rivastigmine **3** is a slowly reversible AChEI and butyrylcholine esterase inhibitor (BChEI).[26] Rivastigmine is not metabolised in the liver but is hydrolysed during the process of inhibition of AChE; unlike other AChEIs it is, therefore, not involved in a hepatic cyctochrome P-450 cycle, reducing unwanted drug interactions.[27] Recently, Bullock *et al.*[28] performed a clinical comparison of rivastigmine and donepezil and, although both are similarly effective AChEIs with similar cognitive efficacy, the authors concluded that rivastigmine gave better results with respect to improvements in the activities of daily living. In common with the other AChEIs described here, rivastigmine has also shown some promise for the treatment of LBD[29-31] and PD.[32]

Galantamine **4** posseses selective AChE inhibitive, as well as nicotinic allosteric agonist properties.[33] Allosterically potentiating ligands (APLs) have a distinct advantage over agonist or antagonists in that they interact with different binding sites to agonist or antagonists and are, therefore, not

involved in processes such as receptor desensitisation.[34] Galantamine has been used successfully for the treatment of mild to moderate AD and is well tolerated by most patients.[35,36] Galantamine has also been suggested as a potential agent in the cholinergic approach to PD therapy and may be a useful strategy in the alleviation of cognitive and psychiatric symptoms.[37,38] The efficacy of galantamine has also been assessed against LBD with some success. Initial trials suggest that galantamine improves a patient's independence and allows them to continue their activities of daily living; for these reasons galantamine may also be a suitable candidate for clinical use in LBD.[39,40]

Memantine **5** is a partial antagonist at the *N*-methyl-D-aspartate (NMDA) receptor. NMDA receptor activation causes a net flow of Ca^{2+} into neurons and this intracellular influx of Ca^{2+} leads to death of the affected neurons.[41] Memantine is also a moderate affinity NMDA antagonist at the central phenylcyclidine binding ion channel of NMDA; administration of memantine has proven effective for neuroprotection from glutamate-mediated excitotoxicity, whilst not activating the NMDA receptor.[42] Memantine has also been shown to slow neurodegeneration in PD.[43,44] Mixed results have, however, been reported when memantine was administered to LBD sufferers, suggesting that the efficacy of memantine for the treatment of LBD is variable at best. For example, Marwan *et al.* reported that seven out of eleven patients showed improvement (or stability) of symptoms upon administration of memantine.[45] In contrast, Menendez-Gonzalez *et al.* described a worsening of motor and cognitive

function which subsided when the drug was withdrawn;[46] moreover, Ridha *et al.* reported delusions and hallucinations in some patients administered with memantine.[47]

In summary, studies have shown that the AChEIs **1**-**4** and the NMDA antagonist memantine **5** have some proven benefit for patients suffering from differing forms of dementia. Both short-term cognitive and long-term neuroprotective effects have been described. However, some contradictory evidence is also reported along with side-effects such as hepatoxicity,[16,17] dizziness, nausea and malaise.[48]

In recent years, the cost-effectiveness and efficacy of AChEI and NMDA drugs has been questioned. A recent appraisal of donepezil, rivastigmine, galantamine and memantine for the treatment of Alzheimer's disease was conducted by the National Institute for Health and Clinical Excellence (NICE) and it was concluded, based on cost-effectiveness, that donepezil, rivastigmine and galantamine should only be prescribed for patients with moderate AD and that memantine should not be recommended for patients with moderate to severe AD.[49] Contradictory to the NICE survey, a number of international studies have concluded that treatment with AChEIs can be cost effective.[50-52] Nevertheless, further clinical trials and cost-effectiveness studies of AChEIs remains to be undertaken in order to establish their overall efficacy and their realistic long-term clinical use for the treatment of dementia patients.

1.2.2 Non-Steroidal Anti-Inflammatory Drugs

Senile plaques and neurofibrillary tangles are classic neuropathological hallmarks of AD. Senile plaques are composed of extracellular aggregates of β-amyloid protein (Aβ) and neurofibrillary tangles of intracellular aggregates of tau protein. Inflammation develops around these β-amyloid deposits and it has been suggested that this inflammation may play a role in inducing neuronal damage in AD.[53]

Several studies[54-59] have shown that the incidence of AD was reduced with long-term use of non-steroidal anti-inflammatory drugs (NSAIDs), such as indomethacin and ibuprofen, suggesting that NSAIDs may have some neuroprotective effect against AD. For example, Lim *et al.,* reported that chronic administration of oral ibuprofen over six months decreased plaque inflammation and β-amyloid concentration in mice.[58] Similar neuroprotective effects have been described when NSAIDs were administered to PD patients.[59]

Unfortunately, NSAIDs are associated with a number of adverse effects, such as gastrointestinal ulceration and bleeding[60] which may compromise their long-term use in patients. Research into NSAID therapy for neurodegenerative disorders is still at a relatively early stage; nevertheless, the NSAID approach appears promising and controlled clinical trials are required to fully establish the benefits of NSAIDs.

1.2.3 Cleavage of Amyloid Precursor Protein

β-Amyloid (Aβ) protein is known to play an important role in the pathogenesis of AD. Approaches for the treatment of AD that aim to prevent the build-up of Aβ through cleavage of amyloid precursor protein (APP) is an emerging area.

Aβ peptides are generated by processing of APP (encoded by a gene on chromosome 21). Two metabolic pathways are thought to be involved in the metabolism of APP (Figure 1). The first is a non-amyloidogenic pathway (*i.e*. preventing Aβ formation) involving the activation of α-secretase; α-secretase cleaves APP within the Aβ domain and prevents the generation of Aβ peptide.[61] The second is an amyloidogenic pathway (*i.e*. leading to the generation of Aβ) involving both β - and γ-secretases. APP is initially cleaved by β-secretase (BACE1; β-site APP-cleaving enzyme) at the *N*-terminus, generating a 99 amino acid *C*-terminal fragment; this fragment is subsequently cleaved by γ-secretase (consisting of presenilin, nicastrin, PEN-2 and APH-1) within the transmembrane domain of APP to release Aβ.[62]

In particular, the β and γ-secretases are thought to be plausible molecular targets for AD treatment with a number of pharmaceutical companies reporting a range of structurally diverse and potent secretase inhibitors. Much of this work has focussed on γ-secretase as this is the last biological step in Aβ production and determines its length.

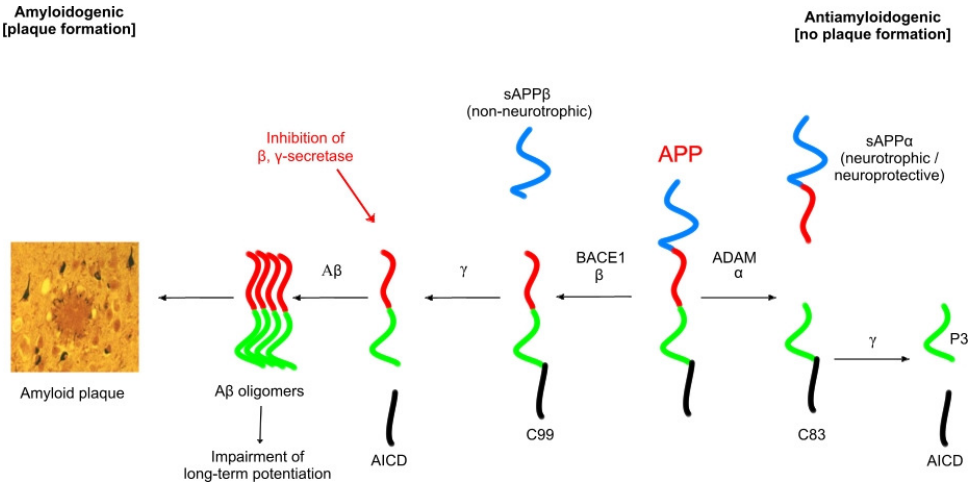
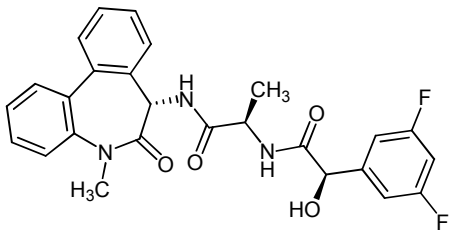
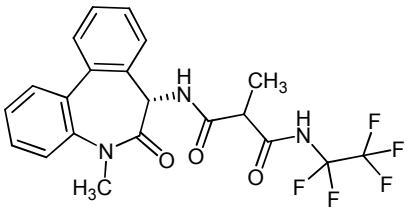


Figure 1. *Illustration of APP cleavage (adapted from Lichtenthaler et al.)* [61]

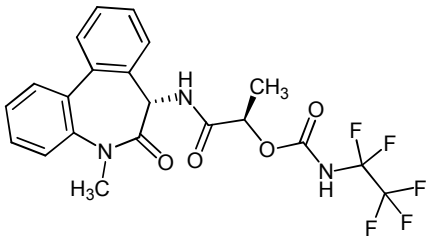
γ-Secretase inhibitors have been shown to reduce Aβ in animal[63] and human models. Notably, LY411575 **7** and its derivatives (*e.g.* **8** and **9**) have been shown to possess good inhibitory activities in humans.[64]



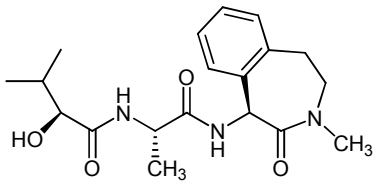
LY411575, 7



8



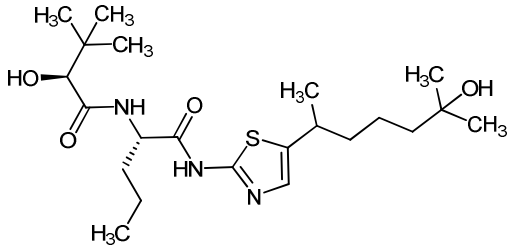
9



LY450139, 10

Perhaps the most promising γ-secretase inhibitor to emerge in recent years is LY450139 **10**, which has been demonstrated to reduce Aβ in AD patient's blood by up to 38%.[65] LY450139, currently in phase II clinical trials, is well tolerated by patients and produces a good dose-dependent

response in Aβ. Chen *et al*.[66] have very recently reported the synthesis of highly potent γ-secretase inhibitors incorporating similar 'bis(amide)' functionality of LY450139 into a series of thiazole-based compounds *e.g.* **11** (IC_{50} 0.22 nM).



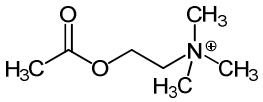
11

The synthesis of novel γ-secretase inhibitors is fast becoming an important area of research and appears to be a promising approach to the treatment of AD and other neurodegenerative diseases which possess similar neuropathology.

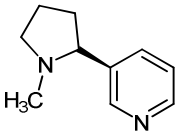
1.2.4 The Nicotinic Approach

Acetylcholine **6** is an endogenous neurotransmitter that acts upon various types of receptors found in the body. It is a simple quaternary amine biosynthesised from choline and acetylcoenzyme A and subsequently released by neurons at synapses. Acetylcholine receptors are classified as either Muscarinic or Nicotinic and are named for their preferential affinity for either nicotine **12** or muscarine **13** respectively. For example, receptors

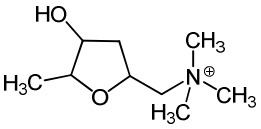
that are activated by acetylcholine and the tobacco alkaloid nicotine are referred to as nicotinic receptors.



Acetylcholine, 6



(S)- Nicotine, 12



Muscarine, 13

Nicotinic acetylcholine receptors (nAChRs) have a long history of study and were one of the first receptors to be cloned. nAChRs present in the autonomic system, and especially those present in muscle, have been studied extensively. However, only in recent years have the central nervous system (CNS) nAChRs become the subject of intensive research with the improving knowledge of how neuronal nAChRs can mediate a wide variety of behavioural and neurochemical functions. Although it is widely recognised that CNS nAChRs may be implicated in the pathology of a wide range of debilitating disorders,[67] the binding mechanisms, regulation and subunit composition are not, as yet, fully understood. Progress made in the understanding of the distribution, function and structure of CNS nAChRs will no doubt, in time, lead to nicotinic agents with therapeutic potential.

1.3 Structure and Subtypes of Nicotinic Acetylcholine Receptors

Nicotinic acetylcholine receptors (nAChRs) are pentameric integral membrane proteins belonging to a 'superfamily' of ligand-gated ion-

channel receptors[69] that include γ -aminobutyric acid A ($GABA_A$), glycine, glutamate and serotonin 3 ($5\text{-}HT_3$) receptors.[69,70] nAChRs are found in a variety of tissue types including those of the autonomic nervous system, the neuromuscular junction and in brain tissue of vertebrates.

Early elucidation of the nicotinic receptor structure was performed in the 1970s and was facilitated by the natural abundance of nAChRs in the electric ray *Torpedo californica* and in the eel *Electrophorus electricus.* Extraction and solubilisation of the receptor using anionic surfactants, followed by passage through an affinity column containing the snake neurotoxin, α-bungarotoxin, allowed the efficient isolation of the pure receptor[71] (α-Bungarotoxin binds irreversibly and competitively at acetylcholine receptors and is also able to act as a highly selective antagonist at α7 nAChRs). More recently, molecular biological techniques and research with cDNA and monoclonal antibodies has allowed the subunits to be cloned and sequenced, yielding further structural information.[72]

The nAChRs consist of five subunits labelled α, β, γ and δ (ε in adults) with a stoichiometry of two α to each of the other two subunits. When the endogenous neurotransmitter acetylcholine **6** binds to the two α subunits, it produces a conformational change in the ion-channel allowing cations (such as Ca^{2+}, Na^+ and K^+) to pass across the cell membrane. The five subunits are arranged around the central ion channel in a 'barrel-like' formation (Figure 2). Each subunit consists of a protein approximately 500

amino acids in length, which crosses back and forth across the cell membrane giving four transmembrane spanning segments (Figure 3).

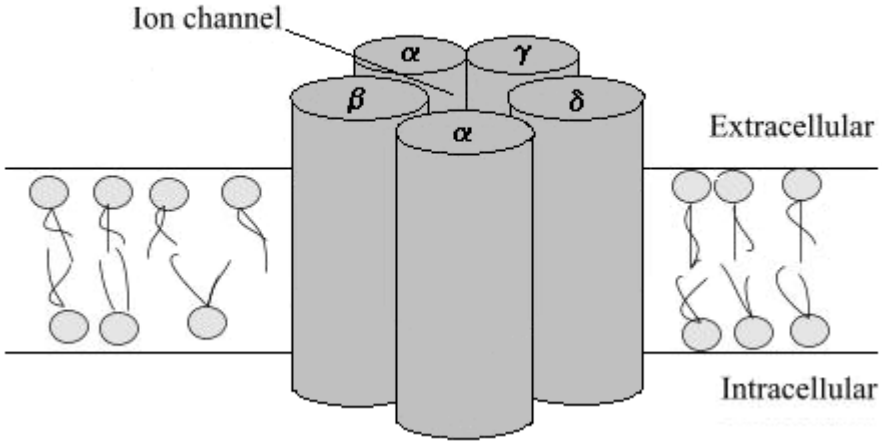


Figure 2. *3-D representation of a pentameric nAChR*

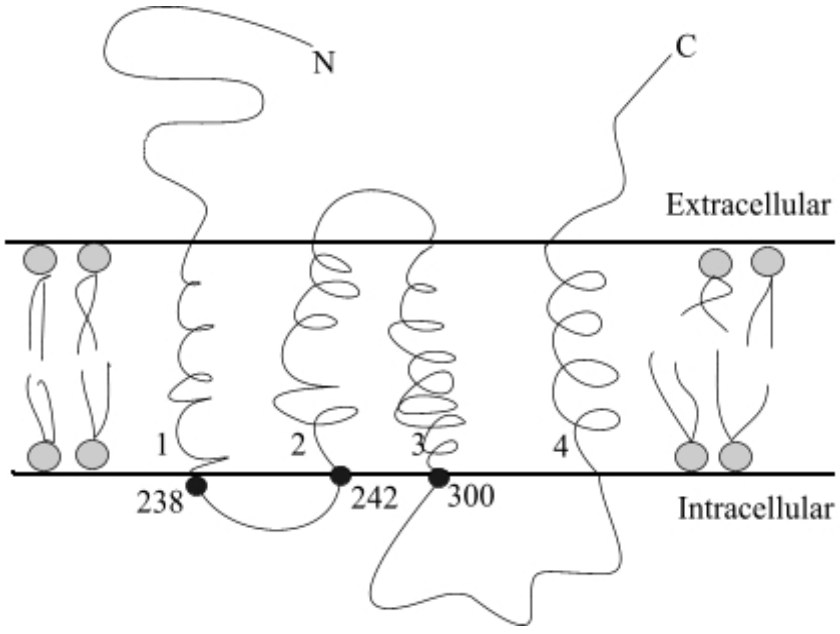


Figure 3. *Four transmembrane segments of the nAChR*

The nicotinic receptors found in the autonomic nervous system and in the brain have more diversity than those of the neuromuscular junction, due to the greater number of α and β subunits present. To date, eleven neuronal nAChR subunits have been identified in mammals (α2-α7, α9, α10 and β2-β4).[73] The various combinations of these different subtypes into a pentameric form results in a large variety of nAChRs with differing pharmacological, electrophysical and behavioural properties.[74] The receptors that are formed may be either heteromeric in αβ combination (*e.g.* α4β2) or homomeric (*e.g.* α7) (Figure 4).[75] The α4β2 and α7 subtypes are the two most common subtypes present in the mammalian brain to be affected by the normal aging processes and also by neurodegenerative diseases, such as AD and LBD.

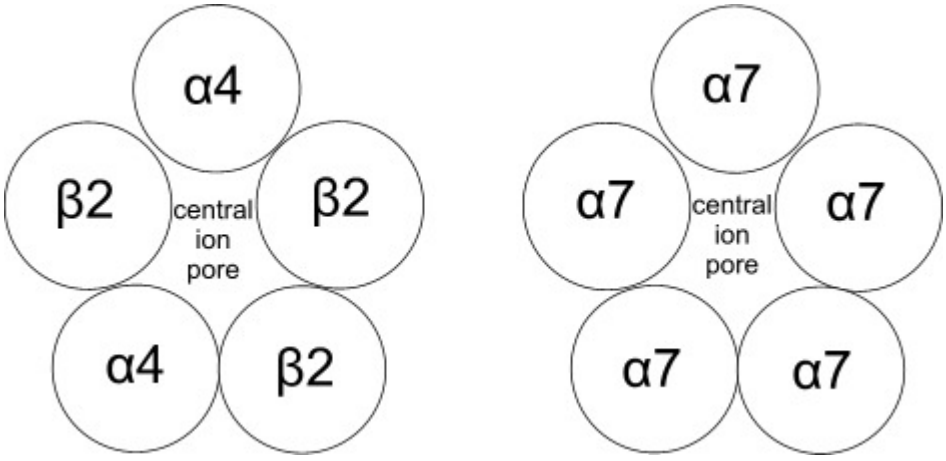


Figure 4. *Receptor subtypes showing (i) heteromeric α4β2 and (ii) homomeric α7 combinations*

Homomeric subunits such as α7 or α9 display little, or no, affinity for nicotine and are inhibited by the antagonist α-bungarotoxin,[76] whereas

heteromeric nAChRs are characterised as having a very high affinity for nicotine but do not bind to α-bungarotoxin.[69]

Such diverse possibilities for receptor combination gives rise to a multitude of functions in the CNS, making these receptors prime targets for a wide variety of therapeutic agents. Figure 5 illustrates some of the possible binding sites and function of the pentameric nAChRs suggested to date.[77]

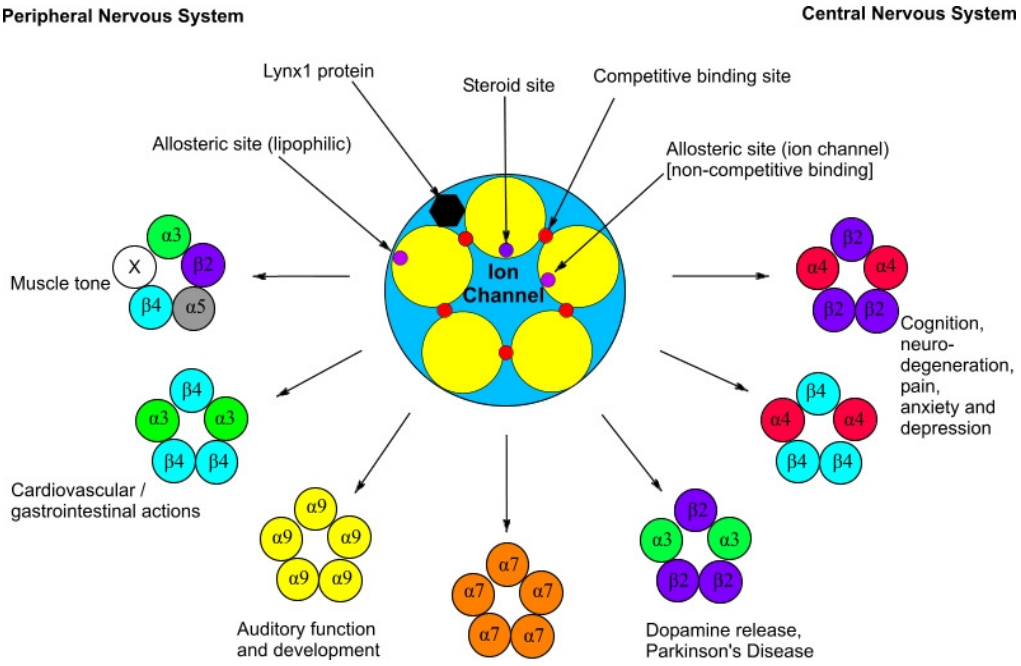


Figure 5. *Possible functions of the various pentameric nAChR subtypes (adapted from Lloyd et al.)* [77]

1.4 Nicotine and its Analogues in the Treatment of Dementia

It is widely recognised that central nervous system nAChRs play a major role in a wide range of cognitive, motor and behavioural systems. Nicotine has been investigated extensively for its usefulness in increasing cognitive

function and improving memory function and learning.[78] Nicotinic mechanisms are thought to be heavily involved in the pathology of disease states, such as PD, AD, LBD and even Attention Deficit Disorder.[77]

Nicotine is one of around four thousand compounds identified from the tobacco plant, *Nicotiana tabacum*, and is the major psychoactive compound present. Other constituents of tobacco, such as cyanide, heavy metals and carcinogenic compounds (*e.g.* benzopyrene) are responsible for the negative health effects associated with smoking such as heart disease, emphysema and cancer.

The usefulness of tobacco products can, therefore, only be very limited for the treatment of dementia unless delivered by other, safer, routes (*e.g.* transdermal patches are common in the treatment of nicotine dependency); this approach to nicotine administration in the treatment of dementia may yet prove useful.

A number of studies have shown that the incidence of Alzheimer's Disease and Parkinson's Disease[79] is decreased amongst smokers. Furthermore, it has been demonstrated that smoking not only provides a long-term neuroprotective effect, but can also provide short-term effects on patients, such as improved attention and arousal.[80] Nicotine was first examined for the treatment of PD as long ago as the 1920's.[81] A variety of studies with both animals[82] and humans[83] have shown that nicotine can improve cognitive performance. Some studies are however, contradictory,

suggesting that this improvement in cognition is restricted to smokers suffering from withdrawal - re-administration serving only to either restore performance lost during deprivation[84] or even failing to have any discernable effect on memory or cognition. The reason for these disparate opinions may be due, in part, to the inability of nicotine to bind selectively to nAChR subtypes, leading to effects which may nullify some of its positive therapeutic benefits. Additionally, side-effects such as gastrointestinal and cardiovascular toxicity have been observed.

1.4.1 Nicotinic Acetylcholine Receptor Agonists

Nicotinic agonists interact with the AChR agonist site to produce a conformational change in the receptor, leading to the opening of the cation conducting pore in much the same way as acetylcholine.[85,86] This so-called cholinergic approach is currently of great interest to pharmaceutical companies and a concerted effort is being made to discover agonists that possess the potency of nicotine but exhibit none of its toxicity or other undesired properties. If nicotinic stimulation is to provide an effective treatment for neurodegenerative diseases such as AD, it is important that novel and highly subtype selective nAChR agonists are discovered so their neuroprotective and cognitive efficacy can be determined.

Until recent years, selective nAChR ligands for the study of receptor function were scarce. However, as it has become increasingly clear that a relationship exists between neuronal nicotinic receptors and increasingly

prevalent disease states such as Alzheimer's disease, many new compounds have been synthesised over the past two decades, some of which have subsequently progressed to clinical trials. A selection of reported nAChR agonists **14-27** investigated recently are shown in Figure 6 emphasising the structural diversity of compounds considered

Like nicotine, many of the compounds that have shown promise as nicotinic acetylcholine receptor (nAChR) selective agonists contain a substituted pyridine ring. RJR-2403 **14** is formed by the ring opening of nicotine and is naturally present in tobacco. RJR-2403 has a similar potency to nicotine at α4β2 receptors and exhibits very similar cognitive enhancement properties. It is, however, much less potent in its effect on cardiovascular function and locomotor activity[93] which are significant side effects of nicotine. SIB-1508Y **15** is more potent and selective than nicotine at α4β2 sites and also appears to improve cognitive and motor function deficits in certain models of PD.[91,92]

Epibatidine **16** is a potent nAChR agonist isolated from the skin of the Ecuadorian frog *E. tricoloris* and is a potent natural nAChR agonist,[87,88] epibatidine is, however, not useful therapeutically as it shows poor selectivity for the various nAChRs.[89] Interestingly epibatidine also possesses potent analgesic effects (~ 100 - 200 times more potent than morphine).

One of the most promising non-aromatic heterocycles studied is ABT-418 **21**. ABT-418 is a full agonist at α4β2 sites and shows improved receptor

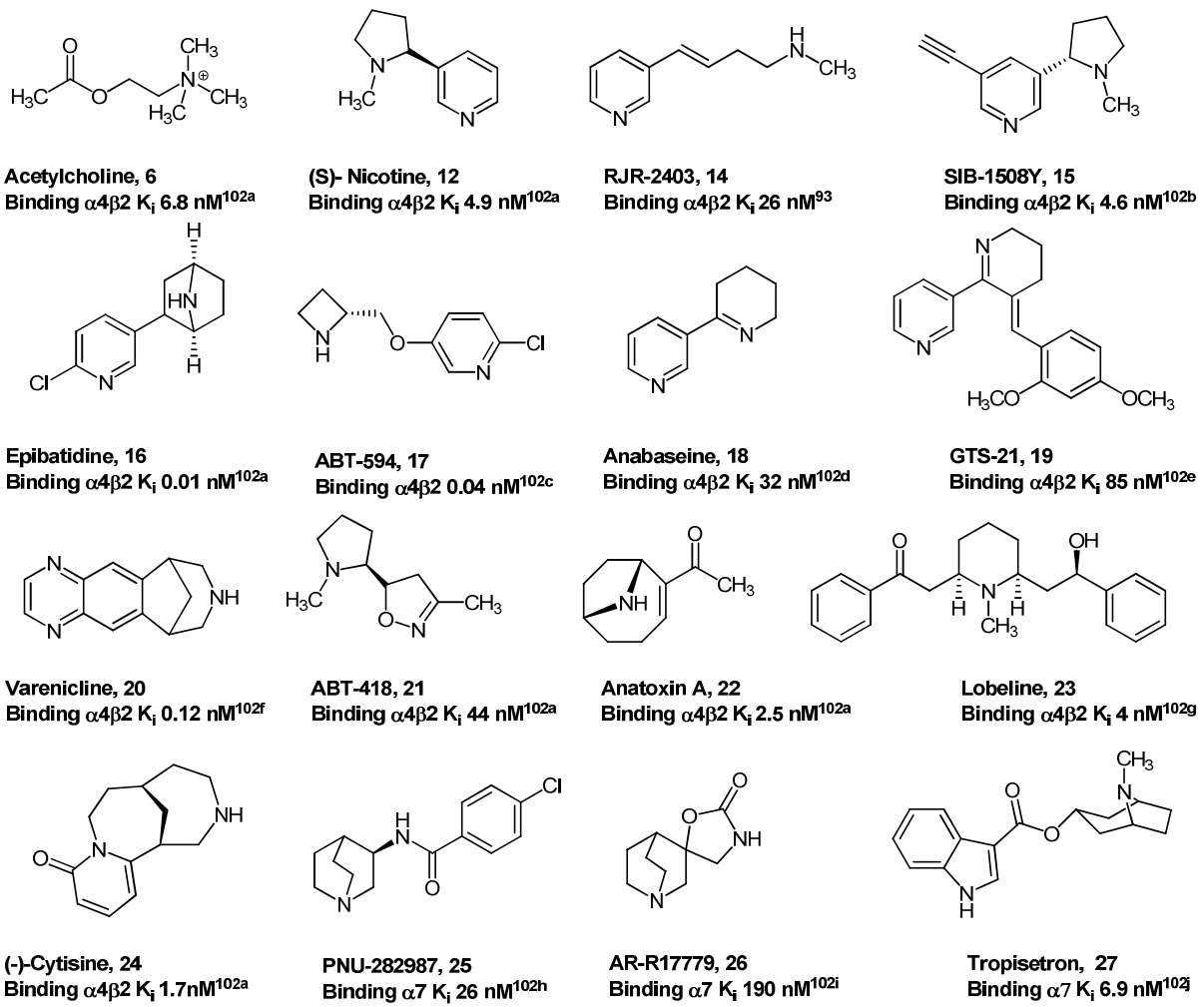
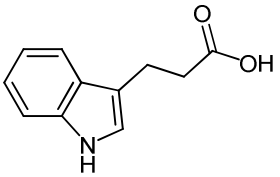


Figure 6. *Selected structures and binding affinities of reported nicotinic receptor agonists*

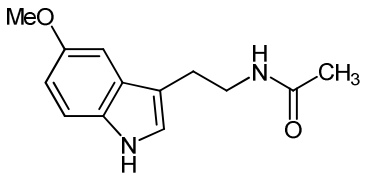
selectivity when compared to nicotine. Notably, ABT-418 has shown cognitive enhancing properties in animals and also appears to have separate cardiovascular and CNS function.[90]

Lobeline **23** is the most biologically active compound produced by the plant *Lobelia inflata.* Lobeline has a very high affinity for α4β2 nAChRs and is now believed to possess both agonist and antagonist properties.[94,95] Lobeline has been studied extensively as a potential agent for treatment of CNS disorders; this will be further discussed in Section 1.4.2.

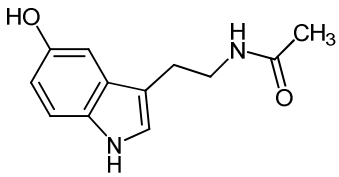
To date, a number of nAChR selective agonists possessing an indole framework have been reported.[96,97] Tropisetron **27** possesses $5HT_3$ antagonist properties, however, recent studies have also shown **27** to be a potent and selective α7 nAChR partial agonist.[98] Although not known to be an nAChR agonist, indole propanoic acid (IPA) (Oxigon™) **28** is a naturally occurring anti-oxidant and has undergone clinical trials for the treatment of Alzheimer's Disease.



28



29



30

Alongside having significant beneficial neuroprotective effects, IPA **28** is believed to be a powerful inhibitor of β-amyloid fibril formation.[99] Similarly, melatonin **29** has also shown good efficacy in the inhibition of β-amyloid fibril formation.[100] Interestingly, Carter *et al.* have demonstrated that the neuroprotective effect of melatonin **29** is dependent on the presence of the 5-methoxy group - when this group is absent, as in *N*-acetyl serotonin (NAS) **30**, the compound possesses no neuroprotective properties.[101]

The nicotinic agonists shown in Figure **6** display a marked difference in structure, functional group types and spatial arrangements of the potential binding sites into the pharmacological receptor, whilst often having very similar activities or selectivities at nAChRs. As the precise geometry of the nicotinic receptor sites have not yet been elucidated, potential molecules must be modelled around compounds that are known to be biologically active. This involves the mimicking of promising inter-atomic distances, functional group interactions and other structural likenesses with the aim of designing selective nAChR agonists with equivalent or better potency than nicotine, yet without its toxicity. This approach has been explored by Institut de Reserches Servier for several years, but, as yet, no reliable structure-activity relationship has been revealed

1.4.2 Lobeline and Sedamine

Lobelia inflata is native to North America and is an annual or bi-annual plant that thrives in dry soils. It grows up to two feet tall and produces white or pale blue flowers (Figure 7). The plant is named in honour of the botanist Matthias De Lobel (1570-1616) and after its inflated seed pods. Sometimes known as Indian Tobacco or Wild Tobacco, *Lobelia inflata* is thought to have been smoked by North American Indian tribes, such as the Penobscot. The Lobelia family consists of over 50 species that include *Lobelia kalamis*, *Lobelia spitaca* and *Lobelia erinus*. Of the 47 compounds extracted from Lobelias, 29 are piperidines (see Figure 7 for structures) with the greatest concentration being found in *Lobelia inflata*; of these, (-)-lobeline is the most abundant and most biologically active compound.[103]

Sedum is a large genus of crassulaceae which contains around 400 species. These include *Sedum adolphii*, *Sedum aizoon*, *Sedum albomarginatum* and perhaps the most interesting, *Sedum acre* (sometimes known as biting stonecrop). *Sedum acre* (Figure 8) was often used in ancient Greece to treat skin disorders and epilepsy. Figure 8 shows the piperidine based structures isolated from *sedum acre*.

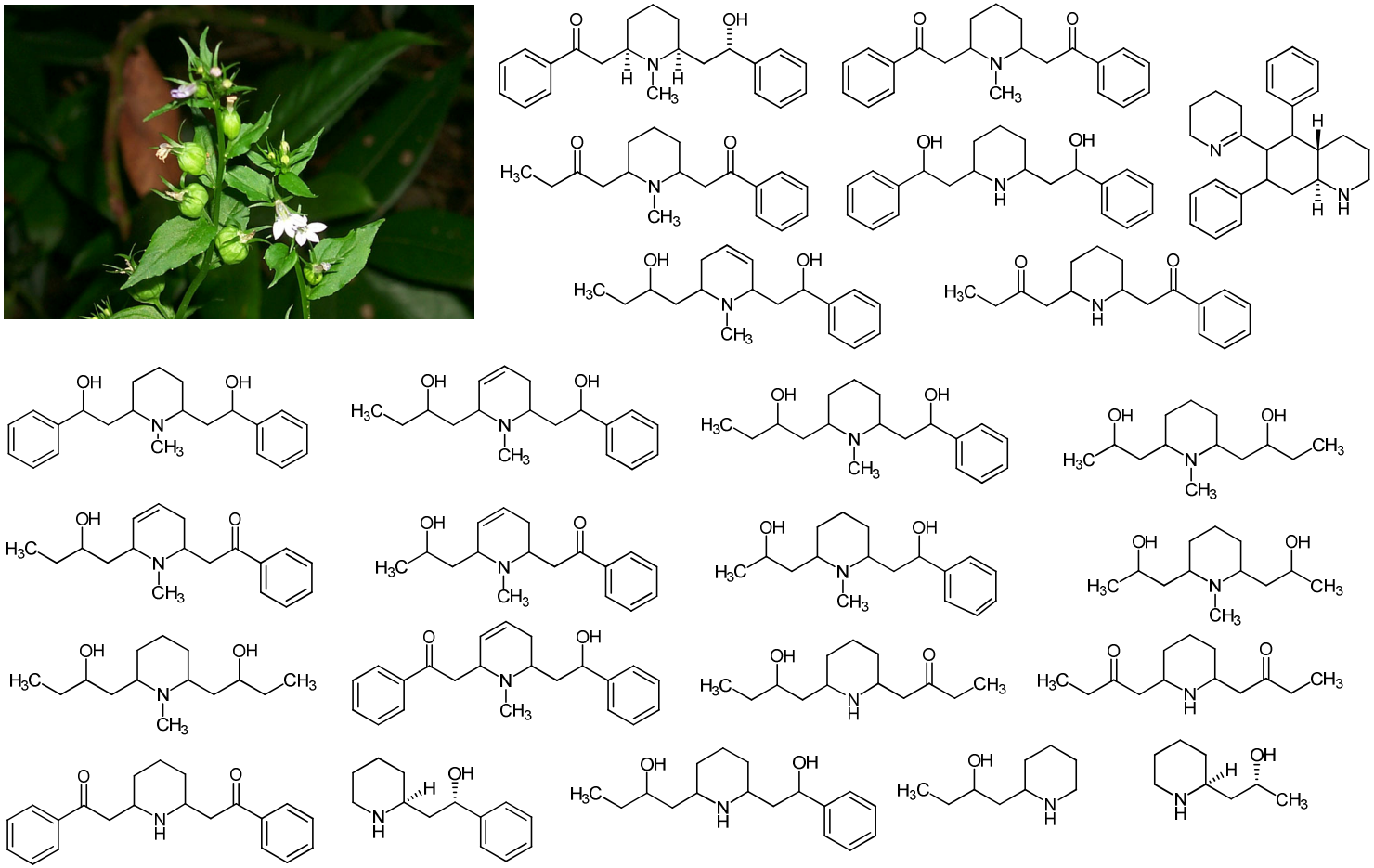


Figure 7. *Structures of piperidine based compounds isolated from Lobelia inflata*[103] *and Lobelia inflata* [104] *(inset)*

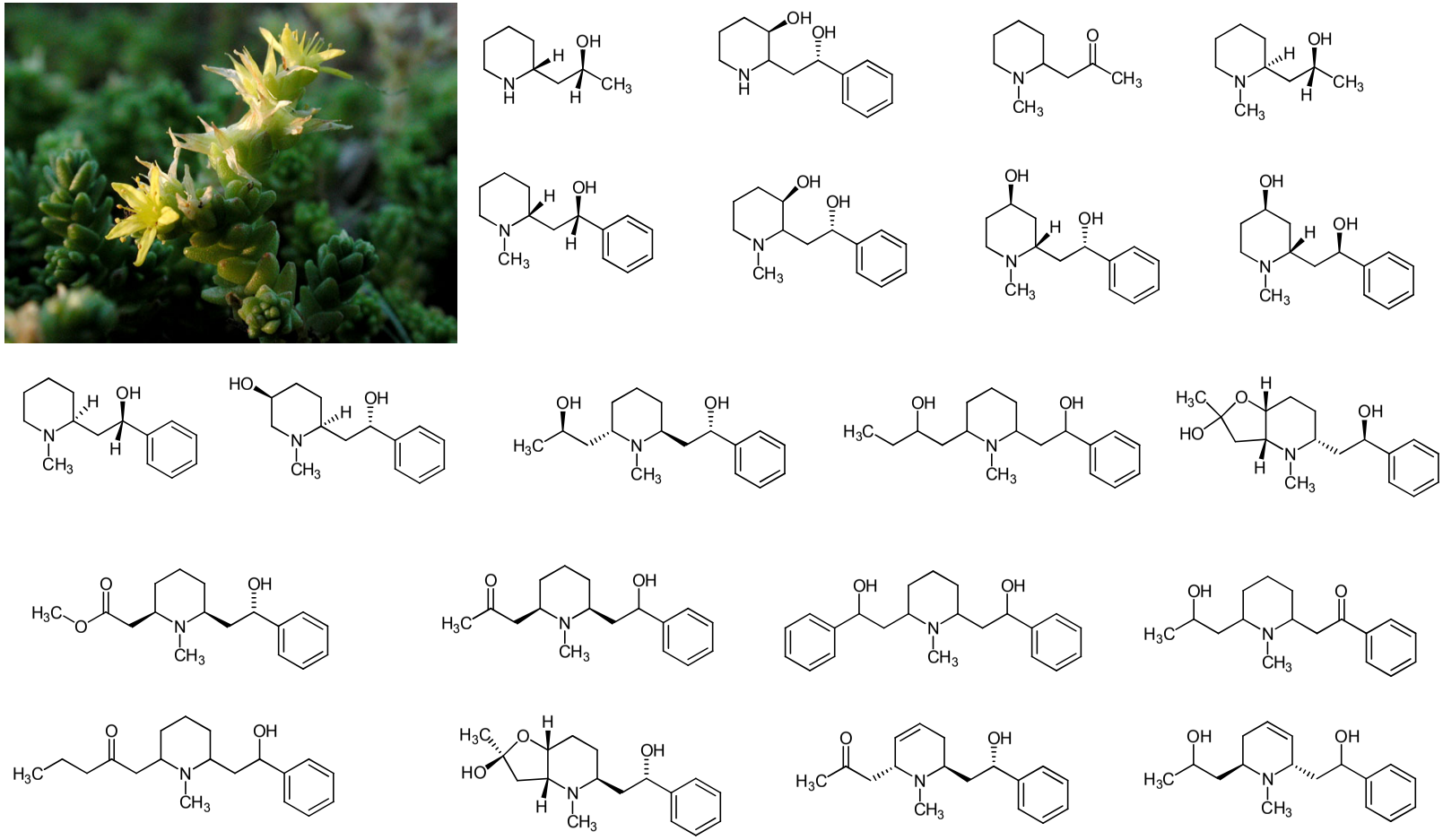


Figure 8. *Structures of piperidine based compounds isolated from Sedum acre*[106] *and Sedum acre*[105] *(inset)*

Lobeline **23** possess a variety of useful pharmacological properties. In the late 1960s lobeline was used as a respiratory stimulant.[107] In small doses, lobeline activates carotid and aortic body chemoreceptors, whilst larger doses have been shown to induce coughing.[108]

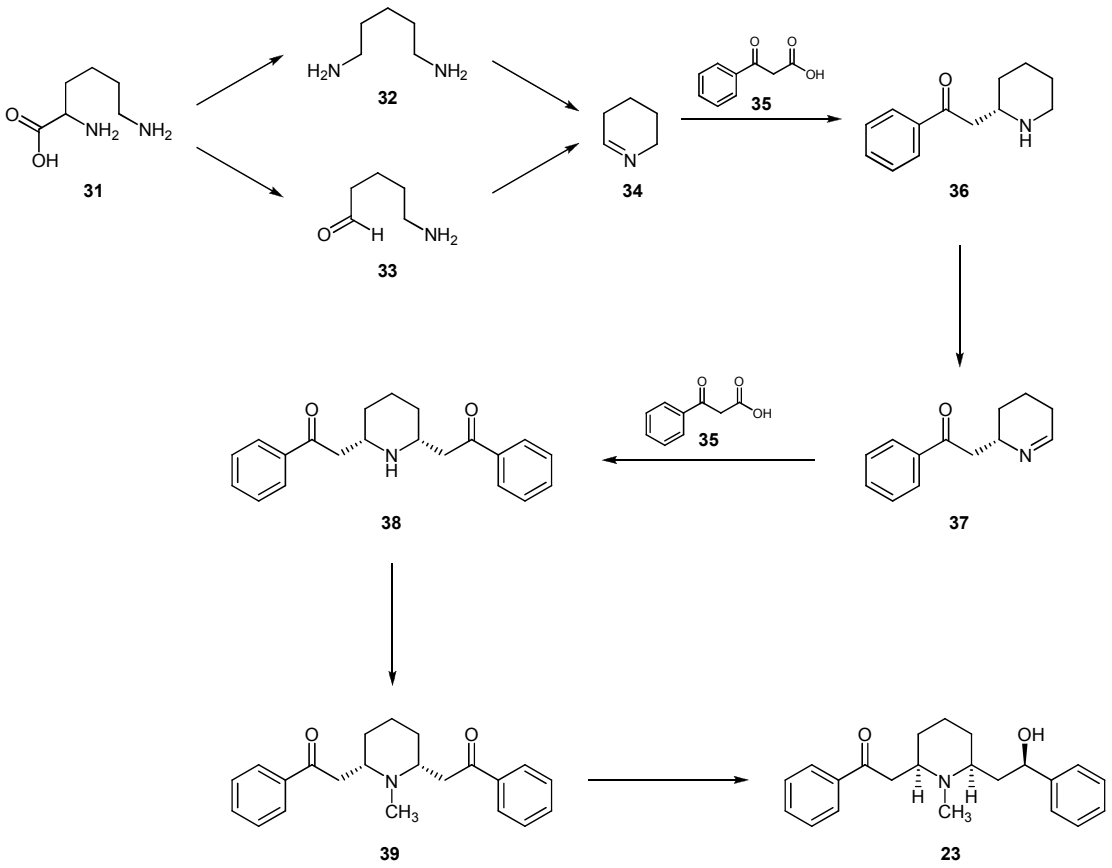
Perhaps the most promising biological aspect of lobeline is its potential for use in the therapy of various CNS conditions including PD, LBD, Tourette's syndrome and schizophrenia. Lobeline possesses a number of properties in common with nicotine; these include the ability to stimulate autonomic ganglia[109] and to improve memory.[110] Lobeline does not, however, up-regulate nicotinic receptors with chronic use[111] or desensitise central nicotinic receptors (a significant drawback of nicotine).

Although the active site of the nAChR is not yet fully mapped, some essential properties of the potential nAChR agonist have been suggested from binding data. Beers and Reich[112] initially suggested that compounds which display nAChR binding activity possess a quaternised nitrogen and a hydrogen bond acceptor (*e.g*. a carbonyl group) which is able to form a hydrogen bond with a donor group in the receptor. Subsequent modelling studies of known nicotinic agonists structures by Sheridan *et al*. suggested these two binding elements should be separated by between 4.6 and 6.3 Å.[113] Barlow and Johnson[114] claimed that lobeline **23** is able to assume a conformation which agrees with this model. It is thought that lobeline has mixed agonist and antagonist activity and this has been attributed to site selective binding in the nAChR through either the ketone or hydroxyl

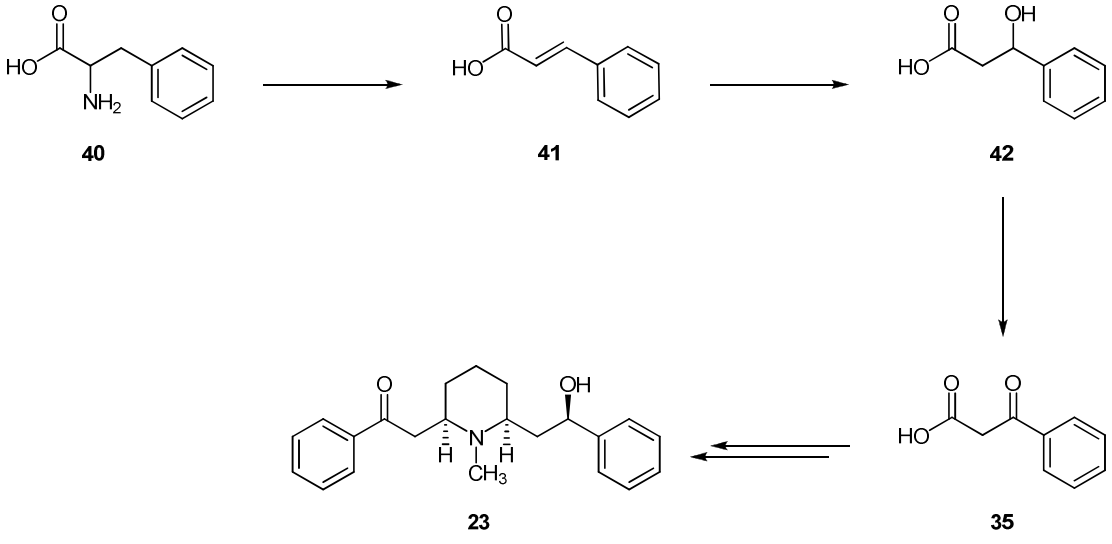
functionality, respectively[115] (see section 5.2.1 for a further discussion of the pharmacophore).

The biosynthesis of lobeline has been extensively studied since the 1960s and is not yet fully determined. Indeed, certain enzymes involved in the final stages of the biosynthesis still remain unknown. As early as 1917, Robinson[116] proposed that lysine **31** was the common precursor of the piperidinic alkaloids, such as lobeline and sedamine.

The currently accepted biosynthesis of lobeline and sedamine is shown in Scheme 1. It is suggested that 2,3,4,5-tetrahydropyridine **34** is formed from lysine **31** *via* 5-aminopentanal **33**. A route *via* cadaverine **32** has also been proposed but tracer studies suggested that this route is less likely.[117] Condensation of **34** with benzoylacetic acid **35** gives the ketone **36**. Oxidation of **36** to **37** and subsequent condensation with a further molecule of benzoylacetic acid, furnishes the bis(ketone) **38**. **38** Then undergoes *N*-methylation and stereoselective reduction of one ketonic group to give (-)-lobeline **23**. Feeding studies with radiolabelled phenylalanine **40**, cinnamic acid **41** and 3-hydroxy-3-phenyl propionic acid **42** have shown their intermediacy in the biosynthesis of benzoylacetic acid **35** and that they are also precursors for lobeline biosynthesis (Scheme 2).[118] In addition, feeding studies[119] have shown that lobeline **23** can be biosynthesised in good yield by administration of radiolabelled lobelanine **39**, providing further evidence for the proposed biosynthetic pathway.[120]



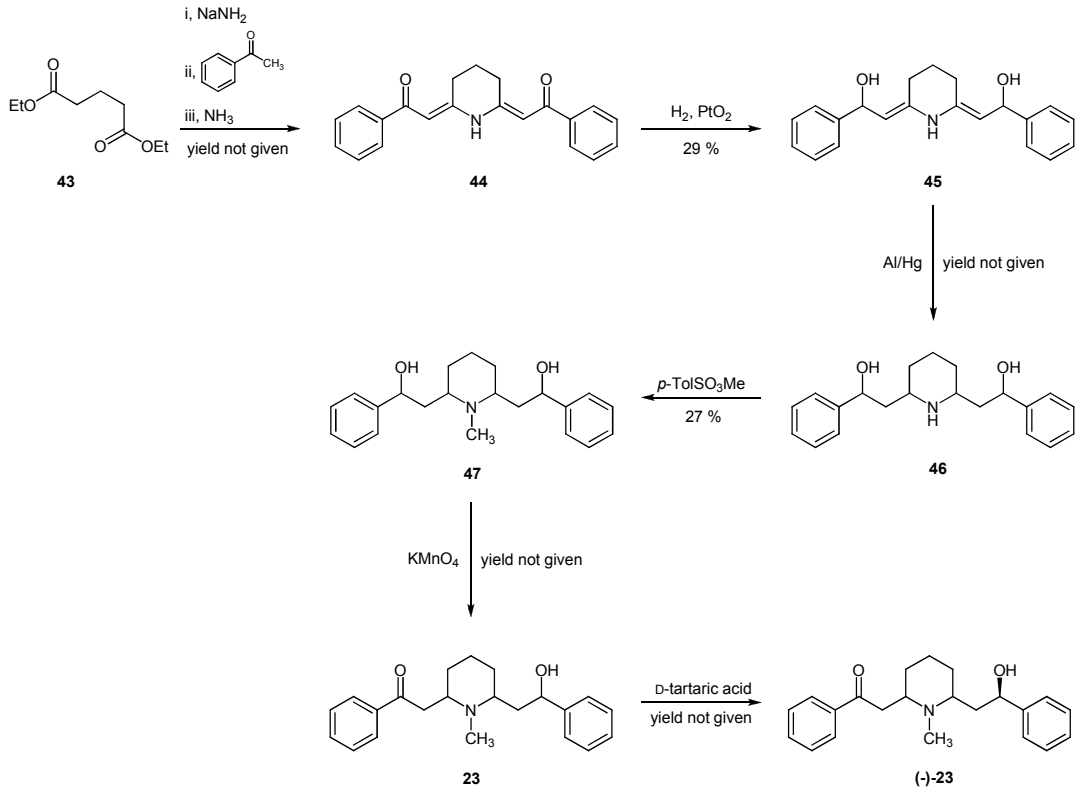
Scheme 1. *Proposed biosynthesis of (-)-lobeline **23***



Scheme 2. *Precursors in the biosynthesis of (-)-lobeline **23***

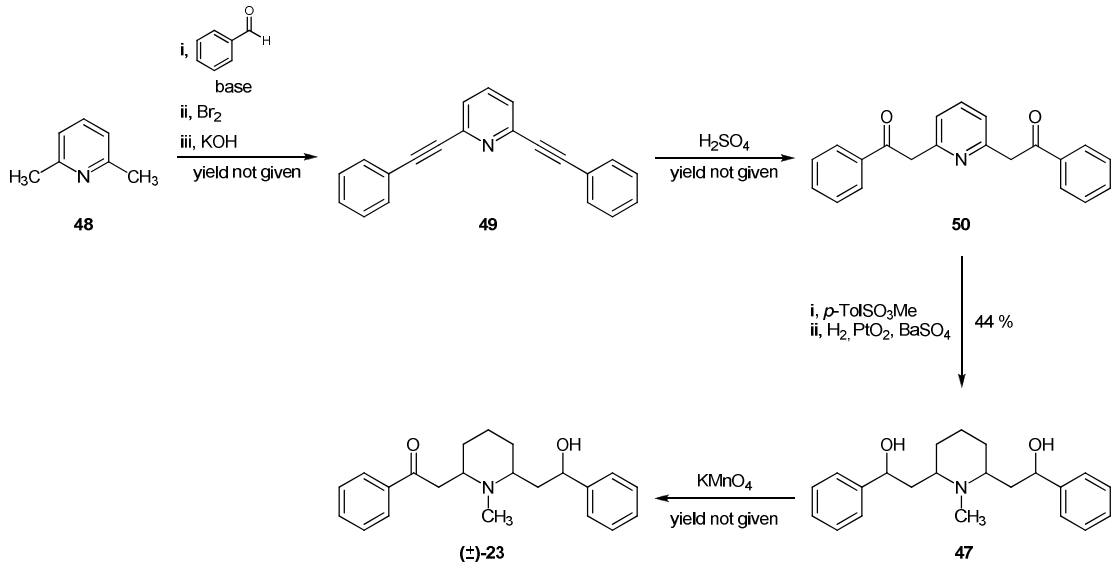
1.5 Reported Synthetic Strategies for the Synthesis of Lobeline and Sedamine Analogues

The synthesis of lobeline was first reported in 1929 by Wieland *et al.*[121] (Scheme 3), who utilised a double Claisen condensation between diethyl pentanedioate **43** and acetophenone followed by addition of NH_3 to give the piperidine-based ring structure **44**. In the next steps, the carbonyl groups were reduced using H_2 / PtO_2 and the diastereoisomers separated by crystallisation; treatment with Al/Hg gave norlobelanidine **46**. **46** was subsequently *N*-methylated with methyl *p*-toluenesulphonate to give **47** and oxidised using $KMnO_4$ to give racemic lobeline **23**; (-)-lobeline **23** was finally resolved using D-tartaric acid.



Scheme 3. *Wieland synthesis of (-)-lobeline **23** (1929)*

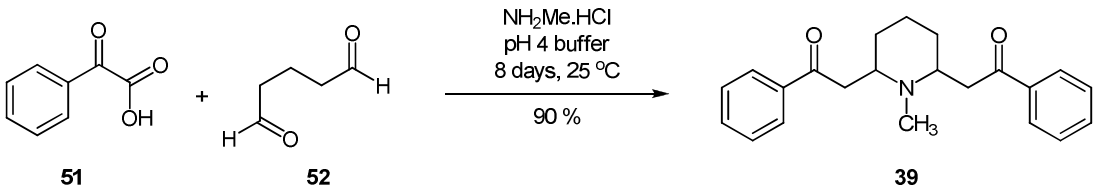
Also in 1929, a full synthesis of (±)-lobeline from 2,6-lutidine **48** was described by Scheung and Winterhalder (Scheme 4).[122] Initially, 2,6-bis(phenylethynyl)pyridine **49** was synthesised using a method described by Shaw in 1924.[123] Hydration of the alkyne **49** with concentrated H_2SO_4 produced the bis(ketone) **50**, which was *N*-methylated and subsequently reduced using H_2 / Pt / $BaSO_4$ to give **47**. Oxidation using $KMnO_4$ furnished racemic lobeline **23**, which was not subjected to optical resolution.



Scheme 4. *Synthesis of racemic (±)-lobeline **23** by Scheung and Winterhalder (1929)*

In 1935, Schopf and Lehmann[124] described a remarkable high yielding, one-pot synthesis of lobelanine **39**, the bis(ketone) derivative of lobeline (Scheme 5). In their synthesis, a mixture of benzoyl acetic acid **51**, glutaric dialdehyde **52** and methylamine hydrochloride was simply stirred at room

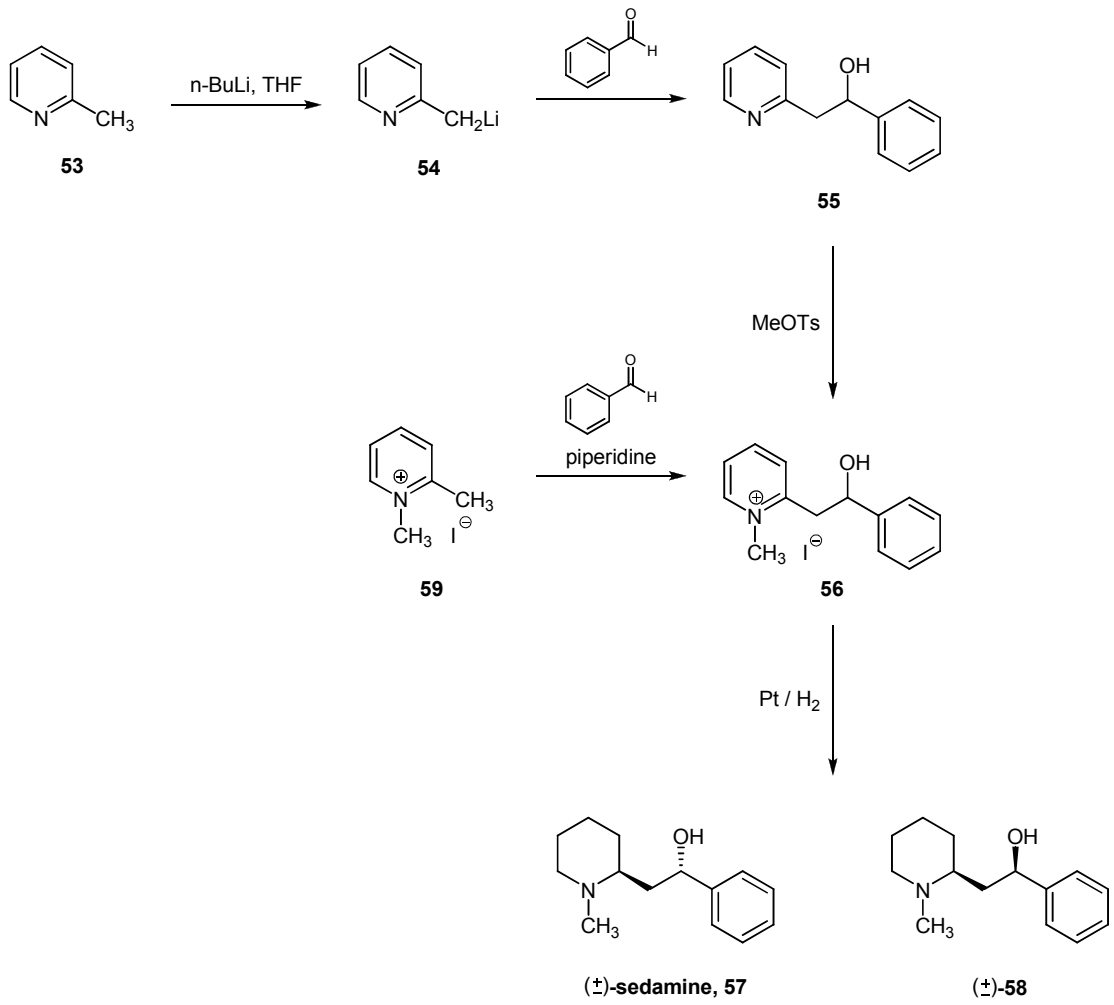
temperature for eight days in pH 4 buffered solution to give lobelanine **39** in 90% yield.



Scheme 5. *The Schopf and Lehhmann one-pot synthesis of lobelanine **39** (1935)*

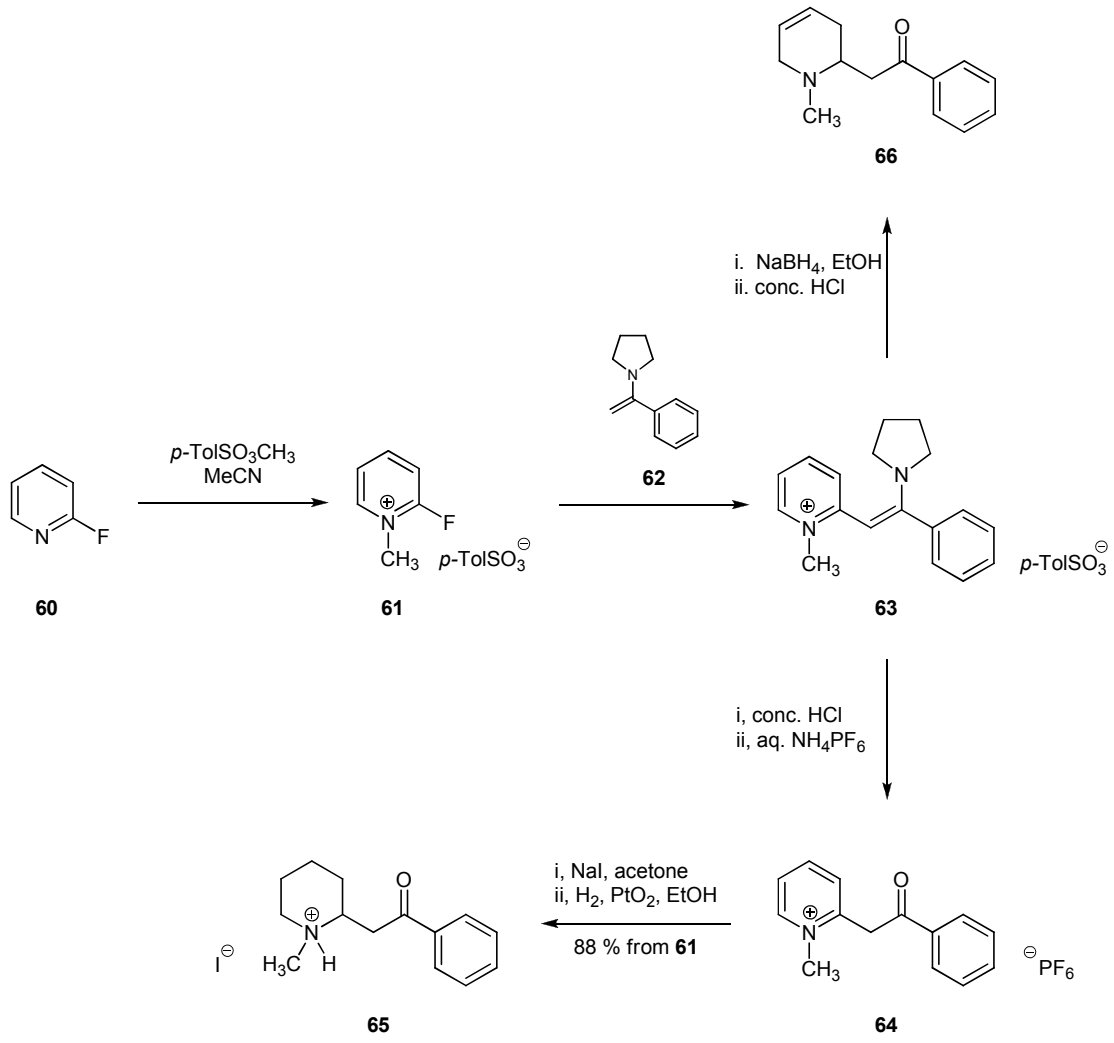
Few other syntheses of racemic lobeline have been reported in recent years. However, several multi-step, highly enantioselective syntheses have recently been reported by Compère *et al.*[125] and Felpin *et al*.[103] These, along with a number of other approaches, are discussed comprehensively in a recent review of *Lobelia inflata* alkaloids.[103]

A number of strategies have been employed for the synthesis of sedamine and its related alkaloids. The simplest of those described involves attachment of an aromatic component to a pyridine derivative followed by reduction. The first synthesis of sedamine was reported in 1956 by Beyerman *et al*.[126] using the addition of (pyridin-2-ylmethyl)lithium **54** (generated from 2-methylpyridine **53** and n-BuLi) to benzaldehyde to give, after work-up, the alcohol **55** (Scheme 6). Subsequent *N*-methylation and hydrogenation over Pt gave (±)-sedamine **57** and its diastereoisomer (±)-allosedamine **58** (also present in *Lobelia inflata*). An analogous preparation has also been reported by Beyerman using [(1-methylpyridinium-2-yl)methyl]lithium iodide **59** as the starting reagent (Scheme 6).[127]



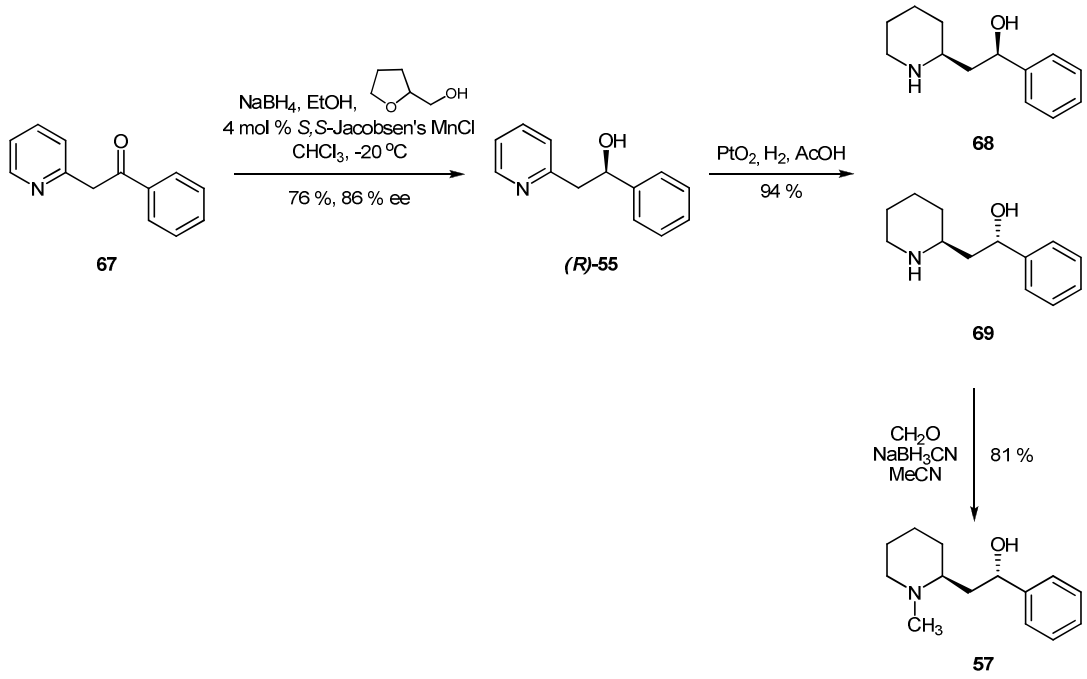
Scheme 6. *Approaches of Beyerman to the synthesis of (±)-sedamine **57***

Meth-Cohn *et al.*[128] and Chu-Yu *et al.*[129] synthesised ketone **65** by displacement of the halogen from 2-fluoro-1-methylpyridinium salt **61** using pyrrolidinoenamine **62** (Scheme 7). The resulting adduct **63** was easily hydrolysed under acidic conditions to give the corresponding ketone **64** which was subsequently hydrogenated using PtO_2 to give the ketone species **65**. Reduction of **63** using $NaBH_4$ gave the tetrahydropyridine **66**.



Scheme 7. *Chu-Yu et al. synthesis of sedamine based ketone derivatives*

Meth-Cohn and co-workers also tackled the problem of obtaining enantiomerically pure sedamine analogues by investigating the reduction of the ketone **67** using both *R*,*R* and *S*,*S* Jacobsen's catalyst.[130] For example, reduction of ketone **67** with modified $NaBH_4$ and (*S,S)*-Jacobsen's catalyst gave the (*R*)-alcohol **55** in both good yield and enantiomeric excess (76 %, 86 % ee) (Scheme 8). Subsequent reduction and separation of diastereoisomers gave **68** and **69**; methylation of **69** gave sedamine **57**.



Scheme 8. *Meth-Cohn & Chu-Yu synthesis of enantiomerically pure sedamine **57***

A comprehensive review by Bates and Kanicha covering the synthesis of sedamine and related compounds was published recently.[106] Unlike the approaches described above, many of the strategies described are piperidine based, and are often complex involving syntheses consisting of ten steps (or more).

1.6 Preamble to Synthetic Work

The work reported in this thesis forms part of a wide-ranging collaborative project between the University of Sunderland and Institut de Recherches Servier. This research programme began in 1996 (originally instigated by Prof. Otto Meth-Cohn) with the aim of developing heterocyclic derivatives as potential agents for treatment of neurodegenerative diseases. The

project arose from the reported observations of neuroprotective effects seen in lobeline and sedamine administration and has targeted a broad spectrum of compounds that can be loosely represented by the schematic illustration in Figure 9. A representative selection of compounds synthesised and investigated pharmacologically to date is shown in Figure 10.[131]

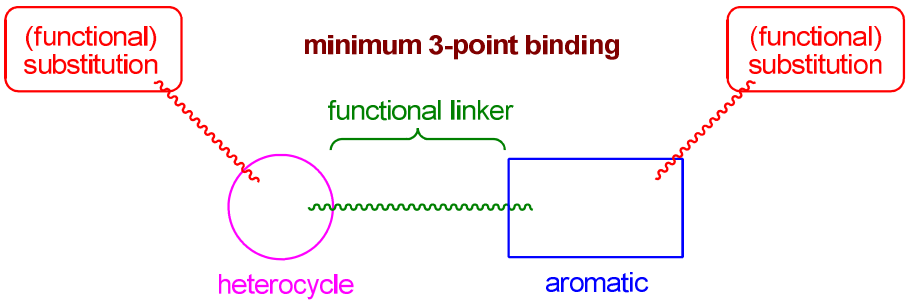


Figure 9. *Schematic representation of the target compounds in the University of Sunderland –Institut de Recherches Servier research collaboration*

Of the many compounds prepared at the University of Sunderland and investigated pharmacologically by Institut de Recherches Servier, compounds **70** and **71** (Figure 11) have been of particular interest.[132] Both **70** (S24795-1) and **71** (S24806-1) were shown to be negative allosteric modulators at nicotinic receptors with wide-spectrum pro-cognitive and pro-psychobehavioural activity. Notably, both **70** and **71** have excellent membrane permeability, borderline-acceptable metabolic stability and good binding at nicotinic receptors (Figure 11).

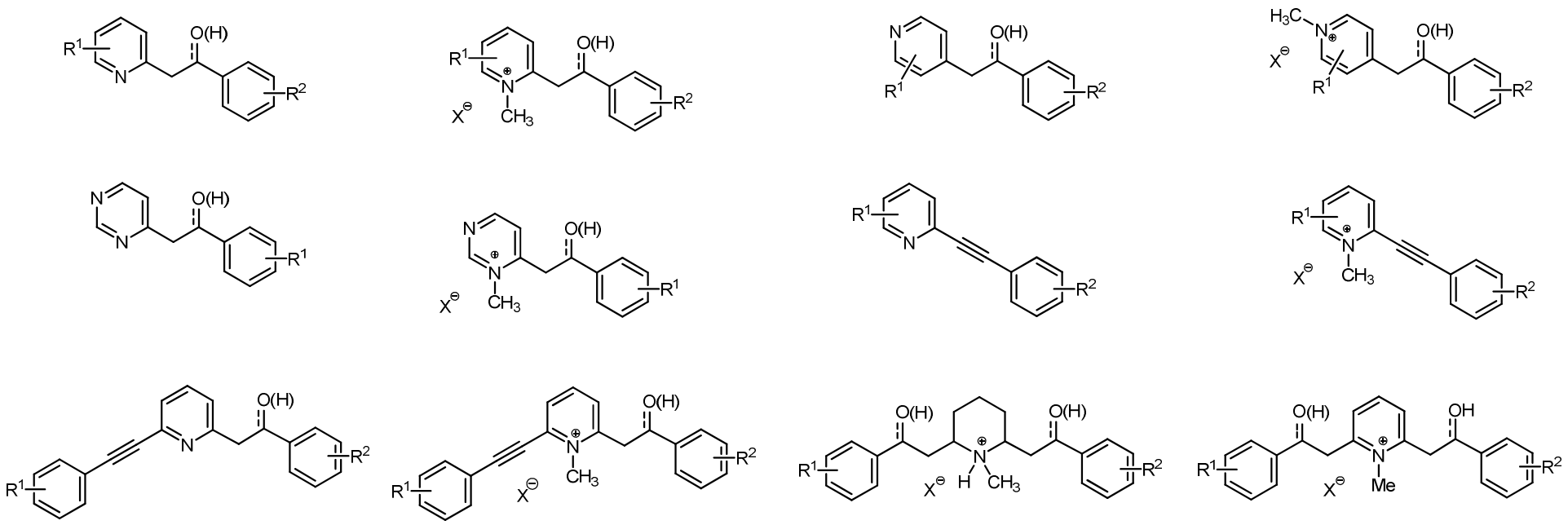
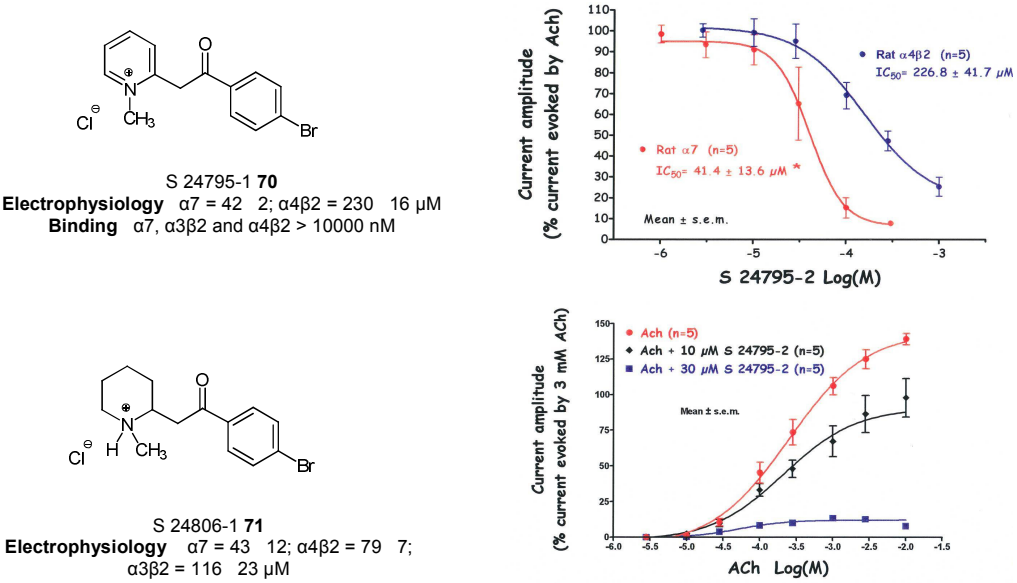


Figure 10. *Representative selection of compounds synthesised and investigated pharmacologically in the research collaboration between the University of Sunderland and Institut de Recherches Servier*

Compound **70** completed Phase I Clinical Studies during the course of this project, notably with no negative interactions at the eighty alternative physiological binding sites investigated; unfortunately however, **70** has not progressed into Phase II Clinical Studies due to metabolite related *in vitro* clastogenotoxicity. Compound **71** has been studied intensively in pre-clinical trials but has recently been shown to have unacceptable blocking at the human *ether-à-go-go related gene* potassium ion (hERG K^+) channel, precluding further investigation. Blocking at the hERG K^+ channel has been shown to cause acquired long QT syndrome (acquired LQTS) that can, under certain circumstances, lead to potentially fatal cardiac arrhythmias.



S 24795-1 **70**
Electrophysiology α7 = 42 2; α4β2 = 230 16 μM
Binding α7, α3β2 and α4β2 > 10000 nM

S 24806-1 **71**
Electrophysiology α7 = 43 12; α4β2 = 79 7; α3β2 = 116 23 μM
Binding α7, α3β2 and α4β2 > 10000 nM

Figure 11. *Pharmacological data for S 24795-1 and S 24806-1*

Through structure-activity relationships developed from studying the many compounds previously synthesised in the research programme, the 4-substituted 3-pyridin-yl ketone and alcohol compounds (and their

respective *N*-methylated derivatives) depicted in Figure 12a were the primary targets for investigation in this project. Chapters 2, 3 and 4 detail our endeavours to synthesise bis-ketone, bis- alcohol and keto-alcohol compounds (Figure 12b). Chapter 3 also details the synthesis of indole derivatives (Figure 12c).

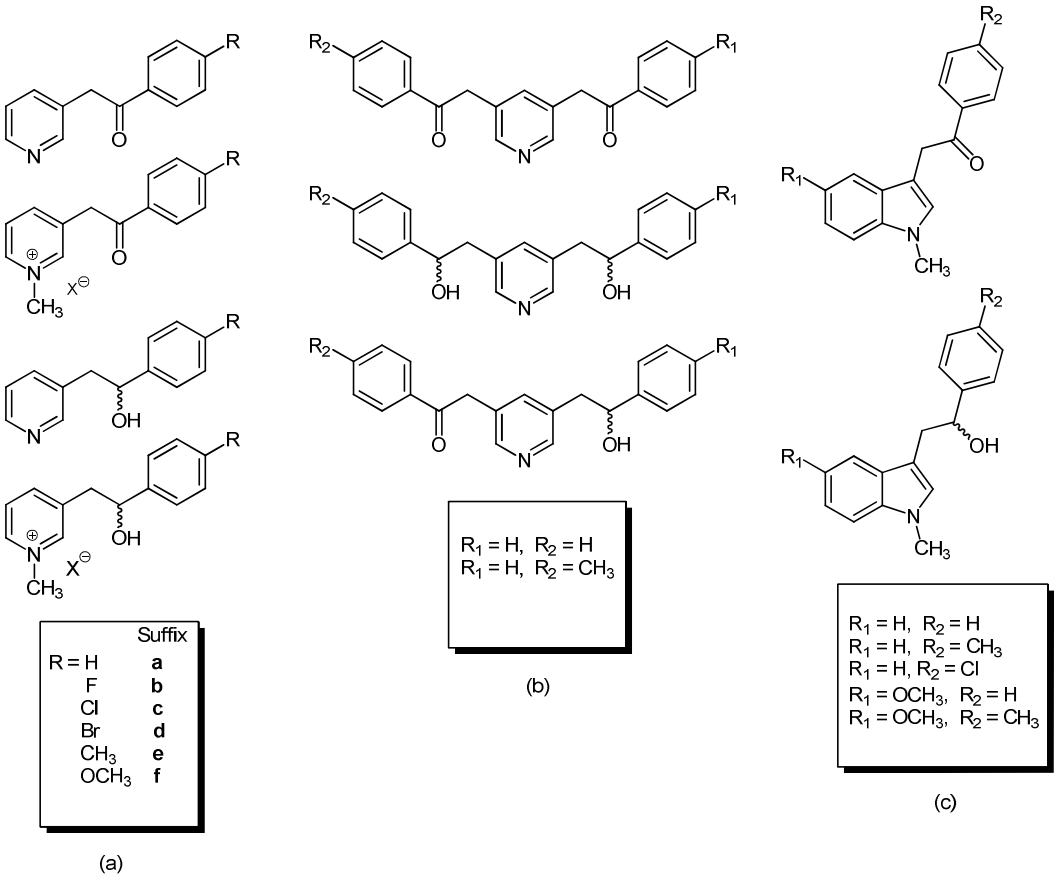


Figure 12. *Primary targets of investigation in this project*

The compounds synthesised in this project have been sent to our collaborators at Institut de Recherches Servier for pharmacological evaluation. Chapter 5 details some of the pre-clinical pharmacological investigations performed, giving a brief summary of the initial results

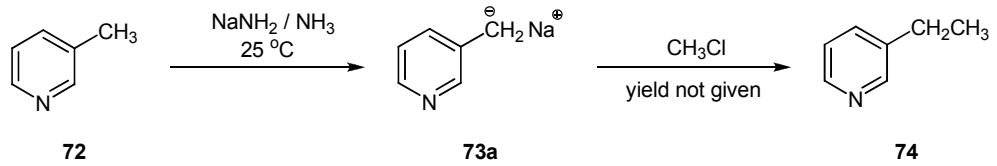
obtained to date. Pharmacological data obtained from compounds synthesised in this project will be of great value to aid further refinement of the structure-activity database and provide great insight for designing future targets for the research programme. Naturally, it was hoped that the compounds prepared in this project could provide candidates for detailed pre-clinical pharmacological investigation and, ultimately perhaps, agents for treatment of neurodegenerative disease.

Chapter 2

This chapter details our approach to 3-pyridin-yl ketone and alcohol compounds using synthetic approaches that involve metallation reactions of 3-methylpyridine.

2.1 Reported Methodology for the Metallation of 3-Methylpyridine

The reaction of 3-methylpyridine **72** with strong bases has been known since the early 1950s. The first report by Brown and Murphy (1951)[133] used sodium amide / liq. ammonia to generate **73a**; subsequent trapping with methylchloride afforded 3-ethylpyridine **74** (Scheme 9).

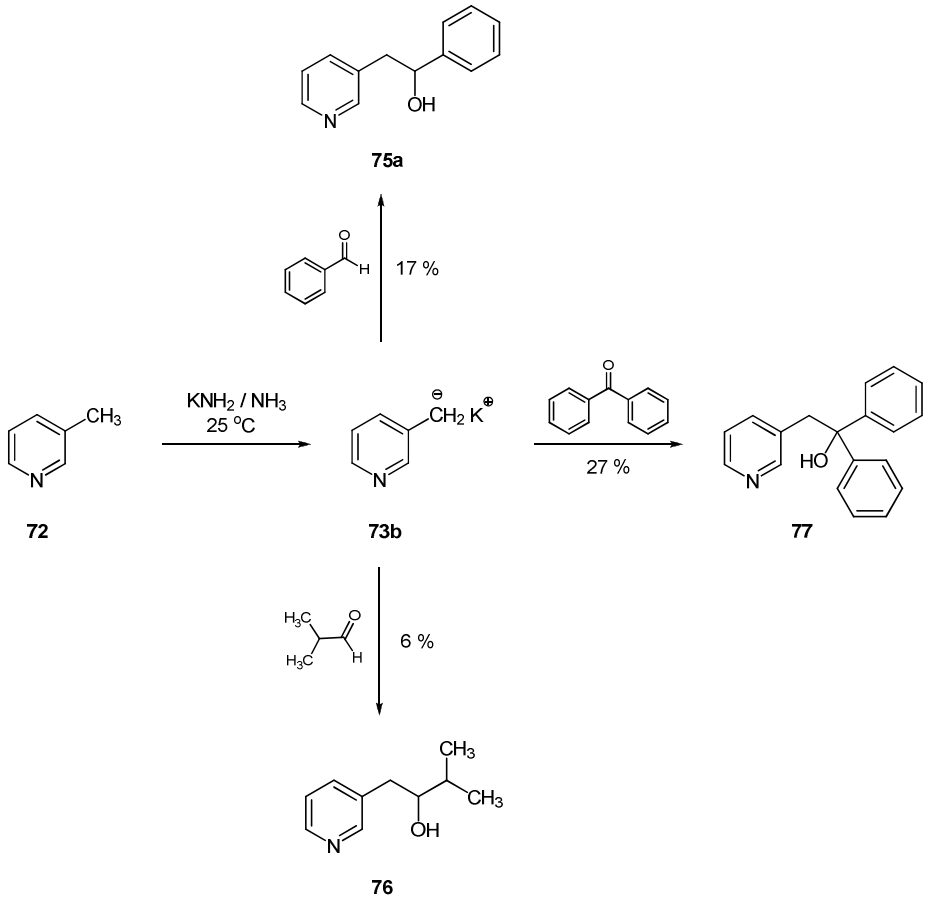


72 **73a** **74**

Scheme 9. *Brown and Murphy metal-amide metallation procedure*

In a later report, Miller and Levine (1959)[134] used benzaldehyde and 2-methylpropanal to trap **73b** generated by treating **72** with potassium amide / liq. ammonia to give the corresponding secondary alcohols **75a** and **76** (17 % and 6 % respectively); it is noteworthy that the structural motif of compound **75a** is of interest in this study. In an analogous reaction, tertiary alcohol **77** was isolated when **73b** was intercepted when benzophenone was employed as electrophile (27 % yield) (Scheme 10). The use of these metal amide / ammonia systems is, however, inconvenient with poor yields

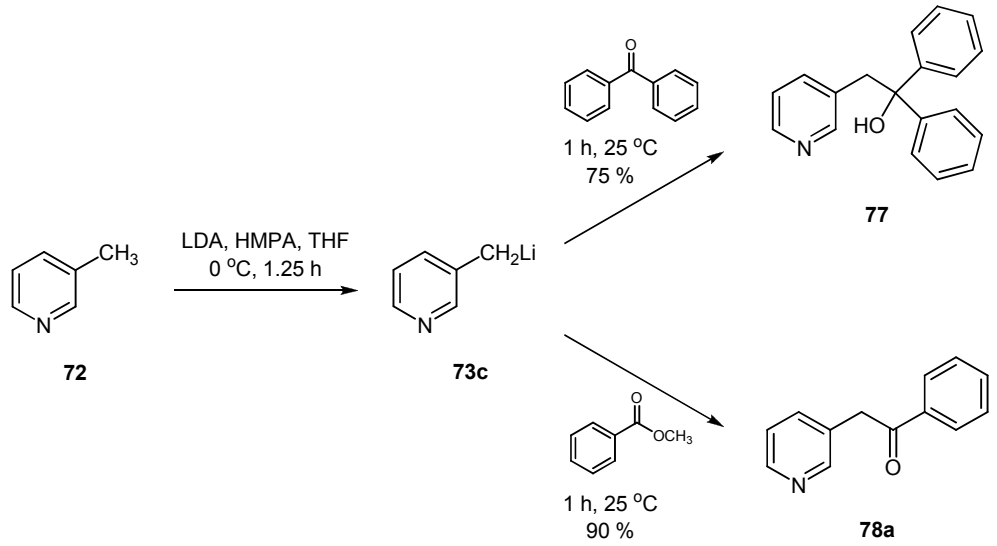
seen (typically < 20 %); no suggestions have been offered to account for the poor isolated yields and no significant optimisation of reaction conditions have been reported.



Scheme 10.

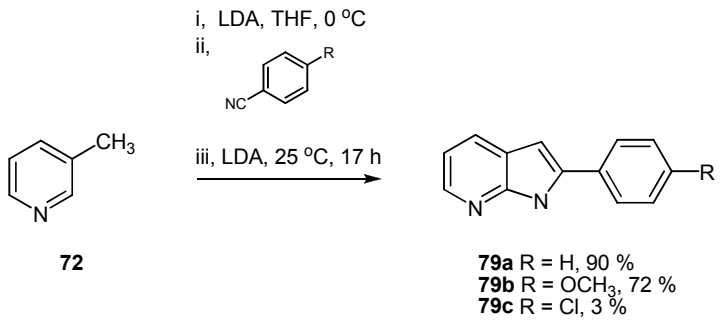
An improved lithiation procedure was reported by Kaiser *et al.* in 1975,[135] who were able to generate (pyridin-3-ylmethyl)lithium **73c** in THF at 0 °C using lithium diisopropylamide (LDA) and hexamethylphosphoric acid triamide (HMPT) as a chelating co-solvent (Scheme 11); subsequent trapping of **73c** with either benzophenone or methyl benzoate gave the respective alcohol **77** (75 %) and ketone **78a** (90 % yield). Comparatively, for reactions of benzophenone as electrophile this methodology appears

to show a marked improvement in yield to the approach reported by Miller and Levine for synthesis of the same compound (75 versus 27 % from 3-methylpyridine).[134]



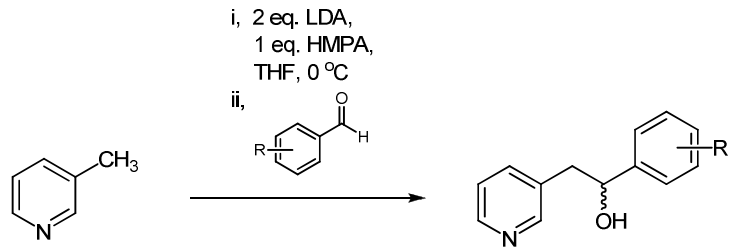
Scheme 11.

More recently, Davis *et al.*[136] have successfully synthesised a number of pyrrolopyridines (**79a-c**) by deprotonation of 3-methylpyridine using LDA in the absence of any stabilising co-solvent (Scheme 12) (see later for a more detailed discussion).



Scheme 12.

Koller *et al.*[137] investigated the use of LDA in the presence of hexamethylphosphoramide (HMPA) in THF at 0 ^{o}C to metallate 3-methylpyridine (Scheme 13); reported yields for trapping reactions with aromatic aldehydes as electrophile were in the range 3-45 %. A significant drawback of methods employing phosphoramide co-solvents is that HMPA and HMPT, like many other phosphoramides, are known to be highly carcinogenic compounds[138] and their use is obviously undesirable.

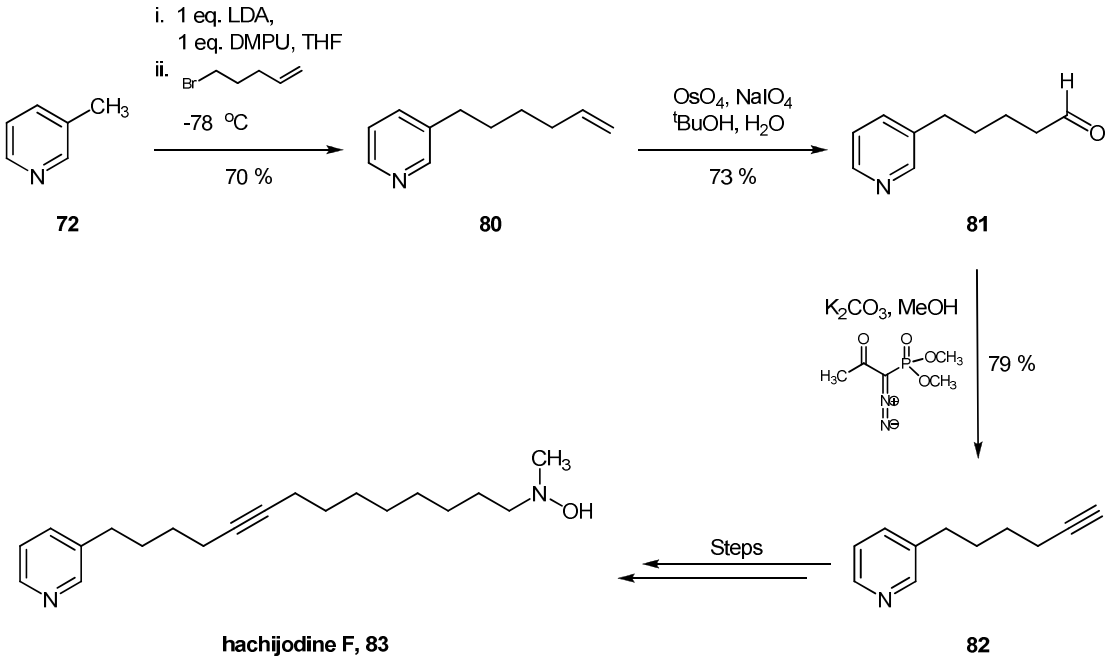


72

75g R = 4-OH, 19 %
75h R = 3-OH, 3 %
75i R = 2-OH, 45 %

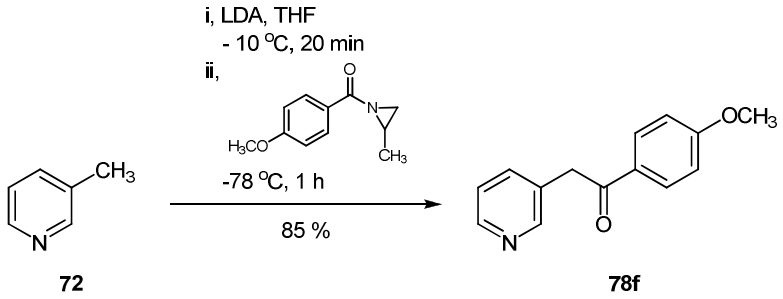
Scheme 13.

Baldwin and co-workers[139a-d] demonstrated that 3-methylpyridine was efficiently lithiated using LDA in THF in the presence of 1,3-dimethyl-3,4,5-tetrahydro-2(1H)-pyrimidione (DMPU). DMPU is a dipolar, aprotic solvent which, in recent years, has been used to some success as a replacement for phosphoramide solvents.[140] The Baldwin group reported that reactions of **73c** (from **72**) with various primary alkyl halides proceeded smoothly, with yields of between 55 and 70 %.[139d] This approach was employed as a key step in the synthesis of a number of marine sponge alkaloids, for example, hachijodines F and G and pyrinodemin A. The synthesis of hachijodine F is outlined in Scheme 14.



Scheme 14.

Since the inception of this project Miwatashi *et al.*[141] have reported the synthesis of a series of 2, 3 and 4- substituted pyridylketones *via* trapping reactions of (pyridin-3-ylmethyl)lithium with substituted tertiary amides (*e.g.* Scheme 15).



Scheme 15.

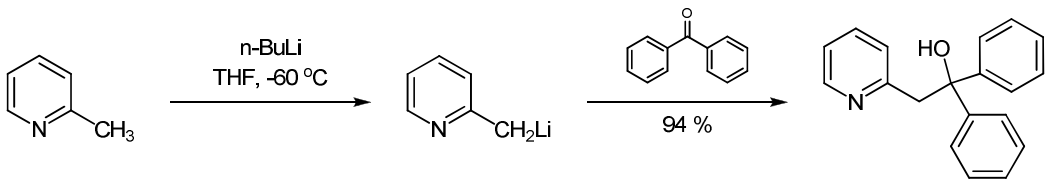
Metallated 3-methylpyridine has been trapped with aldehydes, ketones,[134,135,137,142] arylnitriles,[136] acylhalides / esters[135,141,143-145] and alkyl halides.[133,139d,146-150] The specific method of metallation and subsequent reaction with electrophiles differs significantly in each of these examples. For example, Davis *et al.*,[136] Kaiser *et al.*[135] and Koller *et al.*[137] have reported the generation of the organometallic by maintaining the mixture of 3-methylpyridine and base at 0 °C, followed by addition of the electrophile, also at 0 °C. In contrast, Davies-Coleman *et al.*[151] performed reactions entirely at -78 °C, whereas, Baldwin *et al.*[139d] described a hybrid reaction, first generating the organometallic at 0 °C, then cooling the solution to -78 °C before addition of the electrophile.

Organometallic generation times also appear to vary widely. For example, Miller and Levine[134] Kaiser *et al.*[135] Baldwin *et al.*[139d] and Davis *et al.*[136] all report stirring for 30 min. at 0 °C. However, organometallic generation required just 20 min. at -78 °C in the hands of Morimoto *et al.*[152] who report comparable yields for similar reactions.

Although several authors have reported achieving moderate yields through reaction of metallated 3-methylpyridines **73a-c** with various electrophiles, it is clear that the methodology for the generation of these organometallics is not well defined or consistent and reported organometallic generation times and reaction temperatures often vary without explanation. The range of electrophiles explored thus far could be extended to provide further

insight into the metallation of 3-methylpyridine and establish a clearer general metallation method.

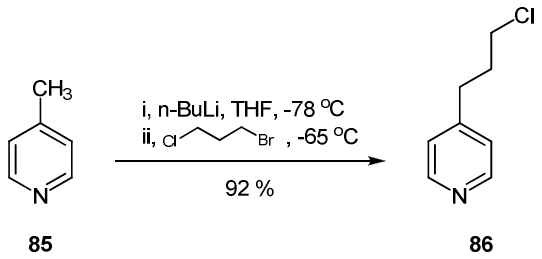
In contrast to the apparent problems with deprotonation of 3-methylpyridine, it should be noted that deprotonation of both 2- and 4-methylpyridine is possible both by using either weak bases (*e.g.* hydroxides, alkoxides and amines) in protic media or strong bases (*e.g.* alkali metal amides, organolithium compounds) in aprotic media; subsequent reaction with a wide-variety of electrophiles generally proceeds cleanly, often occuring in high yield (typically > 70%).[153-155] For example, in an analogous reaction to those reported by Miller and Levine[134] and subsequently Kaiser *et al*. using 3-methylpyridine,[135] benzophenone reacted smoothly with (pyridin-2-ylmethyl)lithium **54** to give alcohol **84** in 94 % yield (Scheme 16).[156]



53 **54** **84**

Scheme 16.

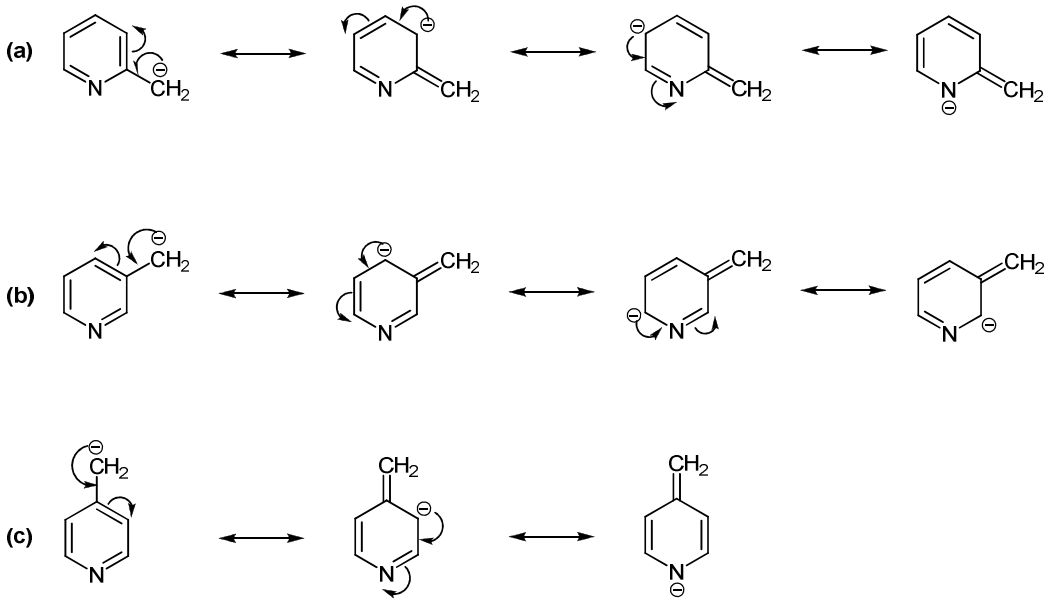
Similarly, good yields have been reported for compounds synthesised *via* the metallation of 4-methylpyridine.[141,157] For example, Jiang *et al.*[158] were able to able to carry out the deprotonation and subsequent alkylation of 4-methylpyridine **85** using n-BuLi to give **86** in excellent yield 92 % (Scheme 17).



85 **86**

Scheme 17.

The improved ease of formation of 2- and 4-metallomethylpyridines compared to 3-metallomethylpyridines may be attributed to the favourable resonance stabilisation (with participation of the ring nitrogen) afforded to anions derived from both 2- and 4-methylpyridine (Scheme 18). H / D-exchange experiments of 2-, 3-, and 4-methylpyridine with a relative exchange rate of 130: 1 : 1810 (MeOD / MeONa at 20 °C, *c.f.* toluene ~10^{-5}) demonstrate this point. [159]



Scheme 18. *Resonance structures for carbanions derived from deprotonation of (a) 2-methylpyridine, (b) 3-methylpyridine and (c) 4-methylpyridine.*

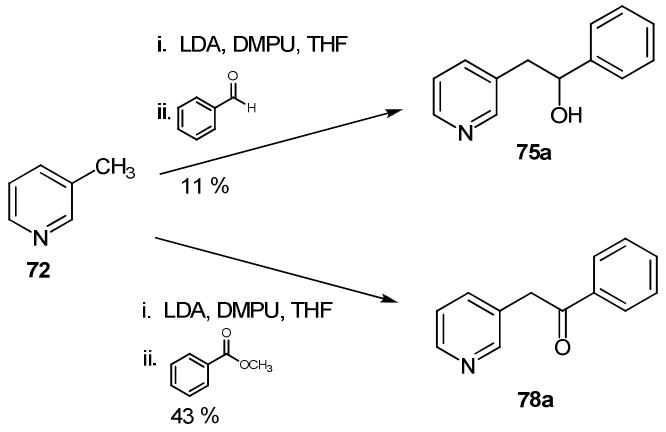
2.2 Synthetic Approaches to Target Compounds 75 and 78

As part of our synthetic strategy, approaches *via* lithiation of 3-methylpyridine were appealing, offering a potentially simple one-step entry into the target compounds 1-phenyl-2-(pyridin-3-yl)ethanol **75** and 1-phenyl-2-(pyridin-3-yl)ethanone **78**. To begin our investigation we sought to establish reliable reaction conditions for efficient metallation of 3-methylpyridine.

Our initial investigations focused on reproducing the methodology of Kaiser and Petty[135] who synthesised the alcohol **77** and ketone **78a**, by trapping (pyridin-3-ylmethyl)lithium **73c** with benzophenone and methyl benzoate, respectively (Scheme 11) (compound **78a** has been identified as a compound of pharmacological interest in this study). In our work, the co-solvent HMPT employed by Kaiser and Petty[135] was replaced with DMPU, successfully utilised by Baldwin *et al*. (Scheme 14) for the reasons described previously.

In our hands, the formation of (pyridin-3-ylmethyl)lithium using LDA / DMPU and its subsequent reaction with benzaldehyde proved testing. A maximum isolated yield of only 11 % was achieved despite extensive alteration of the reaction stoichiometry (*i.e*. the ratio of 3-methylpyridine : LDA : chelating agent : electrophile, *e.g*. 1:2:2:1.2 or 1:3:3:1.2) in attempts to improve the reaction yield. As a varying range of organometallic generation times and reaction temperatures have been described in the

literature, these variations were also explored; (pyridin-3-ylmethyl)lithium generation times of 15, 30 and 45 min were investigated with reactions being carried out at both -78 and 0 °C. However, no improvement in isolated yield was achieved. The maximum yields obtained using our methodology are given in Scheme 19. Comparatively, the modest yield of **75a** (11%) is consistent with that reported by Miller and Levine[134] utilising the metal amide / ammonia procedure (17 %), but somewhat lower than that detailed by Kaiser and Petty, who used LDA and HMPT (40 %).[135]

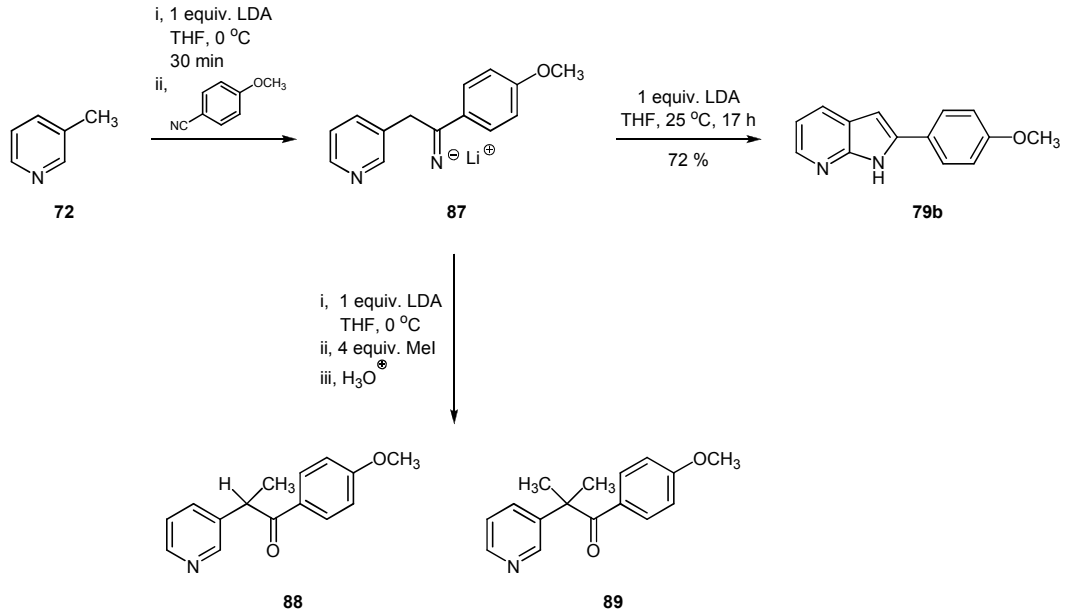


Scheme 19.

The reaction of (pyridin-3-ylmethyl)lithium (Scheme 19) generated using LDA in the presence of DMPU with methyl benzoate appeared more promising with, a maximum isolated yield obtained in our hands of 43 %. However, Kaiser *et al*.[135] reported a yield of 90 % for the synthesis of the same compound using HMPT (and not DMPU) as co-solvent, suggesting that DMPU may not be as efficient as a chelating agent when compared with HMPT. This was illustrated under our conditions by an improved yield (67 %) when DMPU was replaced by HMPT as the co-solvent. It was,

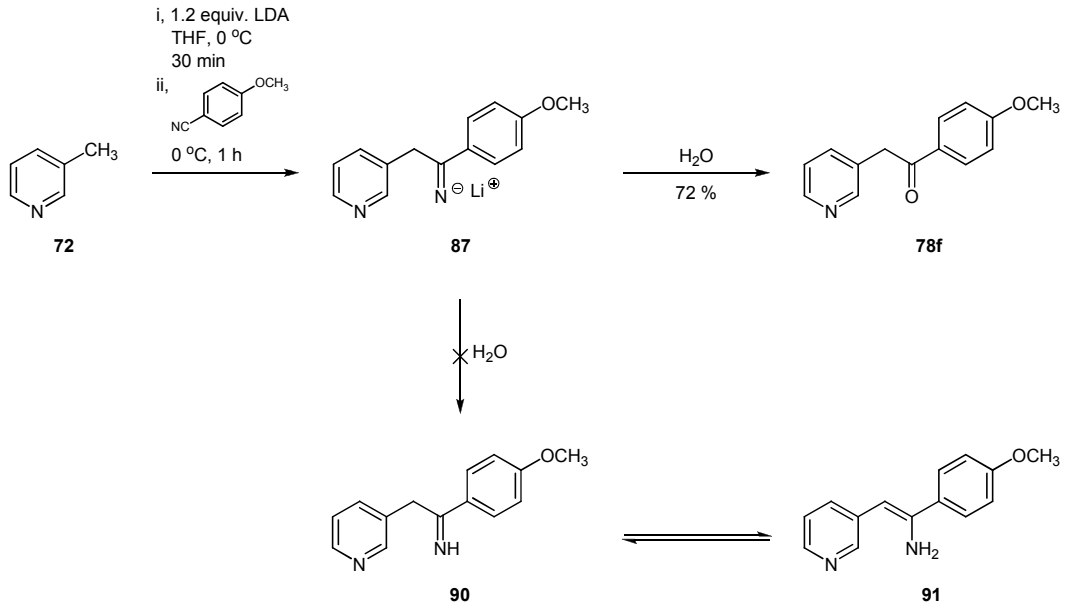
however, noted that reactions with, for example, Weinreb amides, arylnitriles and alkyl halides did not proceed in our hands using this methodology. Nevertheless, it was encouraging that in all trial reactions of (pyridin-3-ylmethyl)lithium using either HMPT or DMPU, no evidence of side-reactions was observed, with only products and / or starting materials ever recovered.

As our initial attempts to improve upon reported methods for the generation and trapping of the (pyridin-3-ylmethyl)lithium using LDA / DMPU under various reaction conditions had proven difficult, we next turned our attention to the work reported by Davis *et al.*[136] in an attempt to identify an alternative method for efficient metallation of 3-methylpyridine. In a reaction of interest to us, this group used 1 equiv. of LDA to deprotonate 3-methylpyridine at 0 °C in THF, followed by the addition of 4-methoxybenzonitrile, to give the intermediate **87** (Scheme 20). A further equivalent of LDA and warming to room temperature effected deprotonation at the α-position and induced cyclisation to the pyrrolopyridine **79b** (72 % yield). Davis *et al*.[136] suggested that good evidence for this mechanistic rationale is provided by the isolation of **88** and **89** on trapping with methyliodide (their yields or respective ratios were, however, not reported).



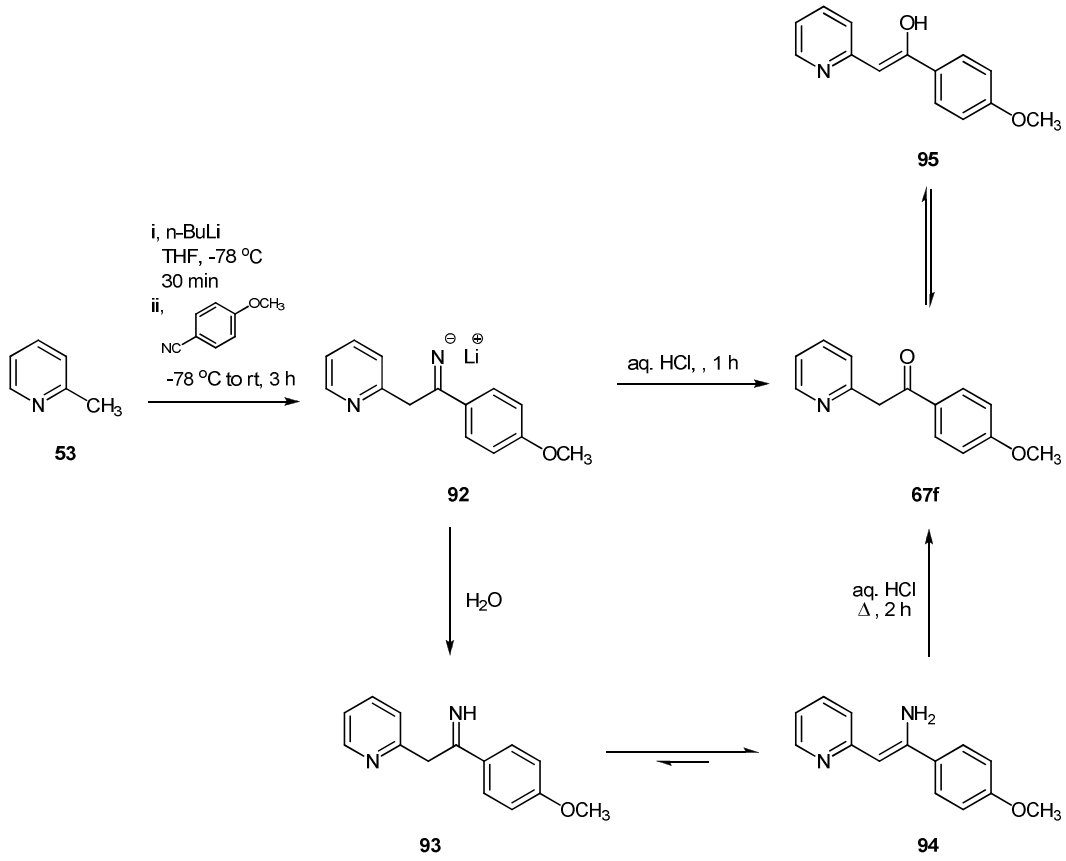
Scheme 20.

From the work of Davis *et al*. it is apparent that initial deprotonation of 3-methylpyridine with LDA in THF at 0 °C to afford intermediate imine **87** must be reasonably efficient. It was expected that (acidic) hydrolysis of **87** could readily furnish the target ketone **78f** (Scheme 21). Interestingly, in the work by Davis *et al.* the ketone **78f** was never isolated. Thus, following the procedure detailed by Davis *et al.*,[136] treating 3-methylpyridine in THF at 0 °C with 1.2 equivalents of LDA with subsequent addition of 4-methoxybenzonitrile and aqueous work-up, the desired ketone **78f** was obtained in an isolated yield of 66 %. Procedurally, once the benzonitrile had been added, stirring was continued at 0 °C for 1 h prior to reaction work-up (however in our experience, from monitoring of the reaction by TLC, the reaction appeared to be complete in approximately 30 min).



Scheme 21.

On reaction work-up, hydrolysis of the intermediate imine **87** occurred rapidly by simply quenching the reaction with water. In comparison, it is interesting to note that analogous reaction with 2-methylpyridine afforded, on aqueous work-up, the stable enamine **94** with no evidence for hydrolysis to ketone **67f** found. In this case, only acidic hydrolysis of intermediate **92** or enamine **94** afforded ketone **67f** (in solution (DMSO) this exists as a mixture of keto / enol tautomers, with a ratio of 3 keto to 1 enol, Scheme 22, Figure 13).[160] Carey *et al*. have studied the keto-enol equlibria for a range of 1-(4-substituted phenyl)-2-(pyridin-2-yl)ethanone[161a] and 1-phenyl-2-(quinolin-2-yl)ethanone derivatives.[161b]



Scheme 22.

In contrast, ^{1}H (Figure 14) and ^{13}C NMR showed that compound **78f** does not exist with a contribution from the enol form in the solution state in either $CDCl_3$ or DMSO-d_6.

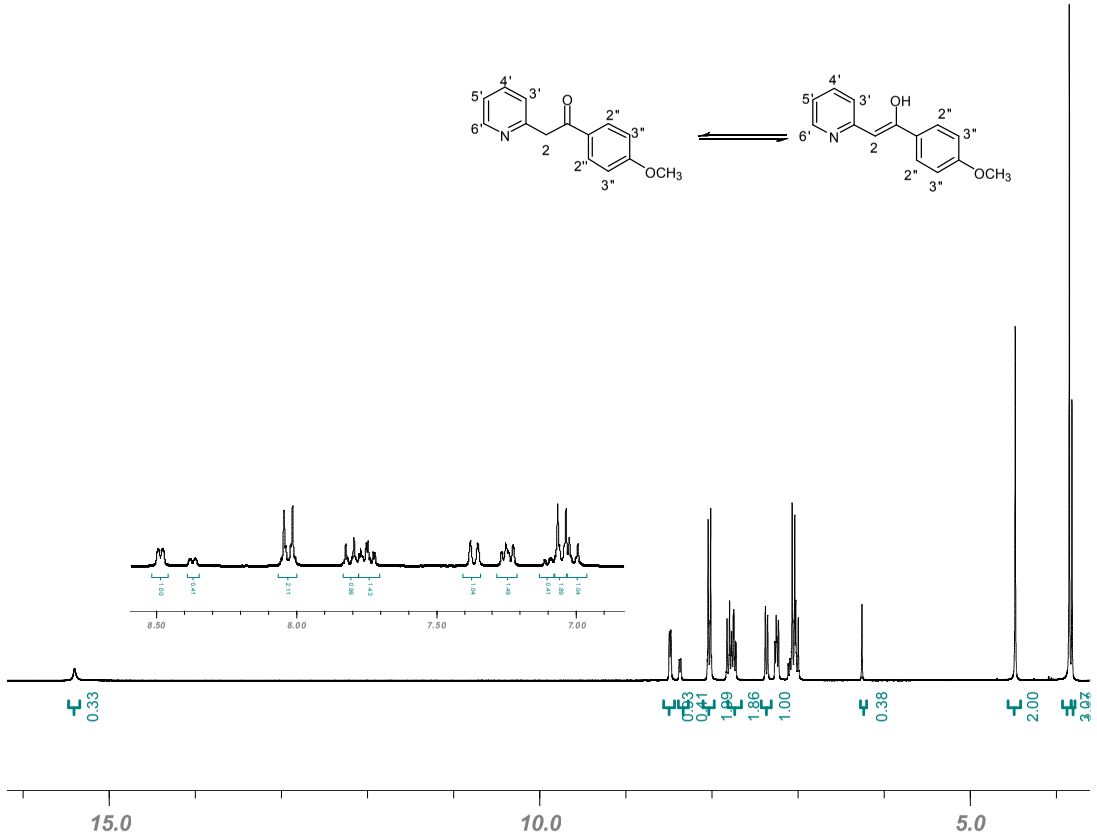


Figure 13. ^{1}H spectrum of 1-(4-methoxyphenyl)-2-(pyridin-2-yl)ethanone in DMSO-d_6; Keto: δ 8.48 (bd, *J* = 4.8, 1H, H6'), 8.03 (d, *J* = 8.7, 2H, H2''), 7.75 (td, *J* = 7.8, 1.8, 1H, H4'), 7.37 (bd, *J* = 7.8, 1H, H5'), 7.27-7.23 (m, 1H, H3'), 7.05 (d, *J* = 8.7, 2H, H3''), 4.48 (s, 2H, H2), 3.85 (s, 3H, OCH_3); Enol: 15.40 (s, 1H, OH), 8.37 (bd, *J* = 4.8, 1H, H6'), 7.81 (d, *J* = 8.7, 2H, H2''), 7.78-7.72 (m, 1H, H5'), 7.26 (bd, *J* = 7.8, 1H, H3'), 7.12-7.09 (m, 1H, H4'), 7.01 (d, *J* = 8.7, 2H, H3''), 6.26 (s, 1H, H2), 3.82 (s, 3H, OCH_3).

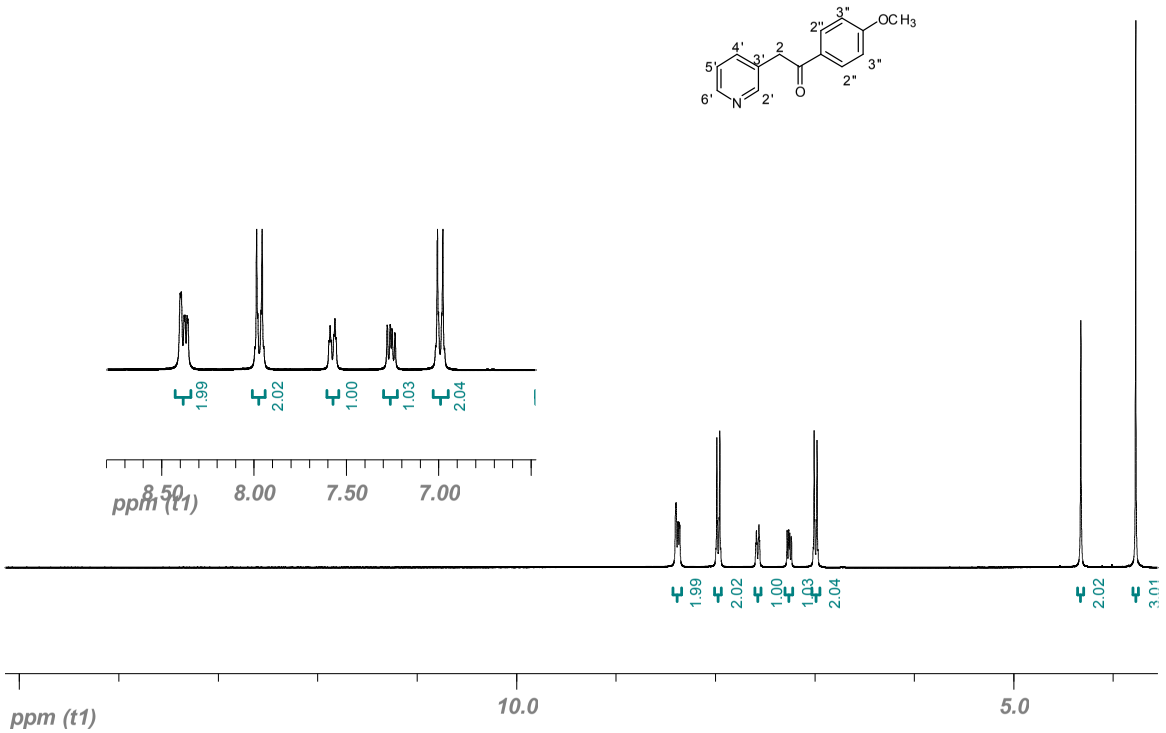


Figure 14. ^{1}H spectrum of 1-(4-methoxyphenyl)-2-(pyridin-3-yl)ethanone in DMSO-d_6; δ 8.40 (d, *J* = 1.8, 1H, H2'), 8.37 (dd, *J* = 4.8, 1.8, 1H, H6'), 7.97 (d, *J* = 9.0, 2H, H2''), 7.58 (dt, *J* = 7.8, 1.8, 1H, H4'), 7.26 (dd, *J* = 7.8, 4.8, 1H, H5'), 6.99 (d, *J* = 9.0, 2H, H3''), 4.33 (s, 2H, H2), 3.77 (s, 3H, 4''-OCH_3).

As a methodological improvement, we were able to obtain compound **78f** using a greater excess of LDA (2 equiv.) and a reduced (pyridin-3-ylmethyl)lithium generation time (5 min.) at 0 °C without witnessing any loss in yield; all other parameters remained true to the methodology described above. Interestingly, using an organometallic generation time of 5 min. at 0 °C and the original 1.2 equiv. of LDA, the isolated yield of **78f** was approximately halved (35 %). In all attempts, no products of cyclisation (*cf.* Davis *et al*.[136]), or other side-products, were ever witnessed in these reactions.

For completeness, the above methodology was also attempted in the presence of varying concentrations of the chelating agent DMPU. On these occasions, no improvement in yield was noted with yields of ketone **78f** being similar to those obtained in the absence of DMPU. In these reactions, the DMPU presented problems in the purification of the reaction product; DMPU has a similar polarity to compound **78f** and was, therefore, often difficult to remove by column chromatography or re-crystallisation.

Having developed a reliable, reproducible methodology for the formation of (pyridin-3-ylmethyl)lithium and subsequent reaction with 4-methoxybenzonitrile to give the ketone **78f**, we investigated application of this approach to reactions of (pyridin-3-ylmethyl)lithium with a range of commercially available electrophiles; these results are summarised in Table 1.

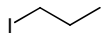
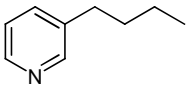
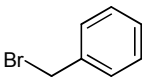
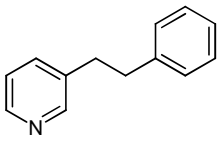
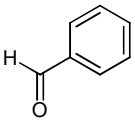
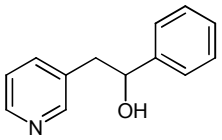
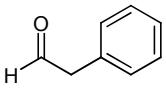
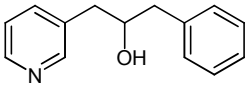
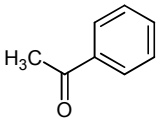
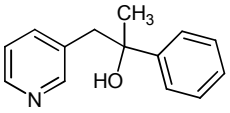
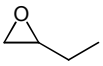
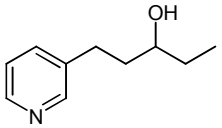
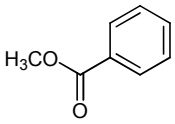
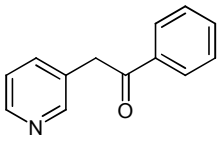
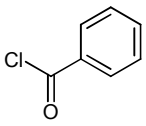
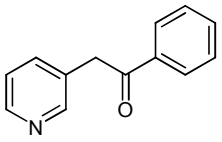
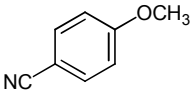
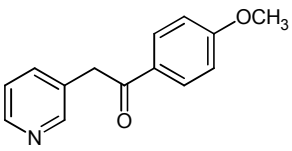
Entry	Electrophile	Product		Yield (%)
1.			**96a**	58
2.			**96b**	37
3.			**75a**	11
4.			**96c**	32
5.			**96d**	28
6.			**96e**	59
7.			**78a**	43
8.			**78a**	26
9.			**78f**	66

Table 1. *Reactions of (pyridin-3-ylmethyl)lithium with various electrophiles Reagents and Conditions: i, 3-methylpyridine* ***72****, 2 equiv. LDA, THF, 0 °C, 5 min; ii, electrophile, 0 °C, 1h; iii,* H_2O *or* NH_4Cl*. Yields are quoted after work-up and purification by column chromatography and / or recrystallisation.*

Alkylation of **73c** with iodopropane (entry 1) or benzyl bromide (entry 2) gave the expected products **96a** (58 %) and **96b** (37 %). The isolated yield of **96a** was consistent with that reported by Baldwin *et al.*[139d] who reported reactions of (pyridin-3-ylmethyl)lithium **73c** with a range of alkyl halides that proceeded in yields of 55-70 %, (although these were largely the somewhat less reactive bromoalkanes). To our knowledge, reaction of (pyridin-3-ylmethyl)lithium with a benzylic halide has not been reported to date; however, Alunni *et al.* have recently reported the reaction of (pyridin-2-ylmethyl)lithium **54** with benzyl bromide using similar methodology.[162]

Regioselective ring-opening of an aliphatic epoxide (entry 6) with (pyridin-3-ylmethyl)lithium was also demonstrated, giving the corresponding alcohol **96e** (59 % yield). To our knowledge, no examples of the ring-opening of epoxides by (pyridin-3-ylmethyl)lithium have been reported previously.

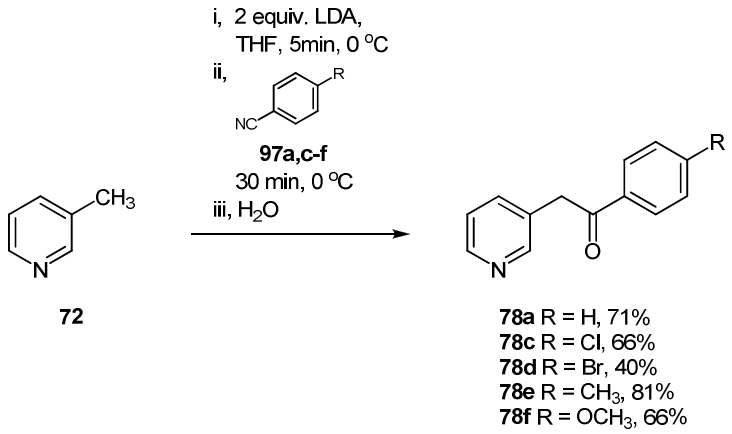
Given the lack of reactivity of 4-substituted benzaldehydes with **73c** it was perhaps surprising that alcohol **96d** could be obtained from reaction of **73c** with acetophenone (28 %) (entry 5). Reaction of (pyridin-3-ylmethyl)lithium **73c** with phenylacetaldehyde gave the secondary alcohol **96c** (32 %) (entry 4). Unfortunately, in our hands, reaction of **73c** with benzaldehyde was unsuccessful (even after stir-out at room temperature for up to 4 h) with starting materials being recovered essentially quantitatively. A similar

lack of reactivity was noted with other 4-substituted benzaldehydes (*e.g.* 4-fluoro, 4-bromo and 4-nitro).

Acylation of (pyridin-3-ylmethyl)lithium using either benzoyl chloride (entry 8) or methyl benzoate (entry 7) as electophile to give ketone **78a** in 26 and 43 % yields, respectively, was also possible. In the reactions of acetophenone, phenyacetaldehyde and benzoyl chloride with **73c**, products other than the expected target compounds were always witnessed by TLC (perhaps accounting for reduced isolated yields). The more reactive benzoyl chloride, in particular, gave a complex mixture of highly polar compounds making purification of the desired reaction product **78a** extremely difficult (the side-products were, however, never isolated or identified).

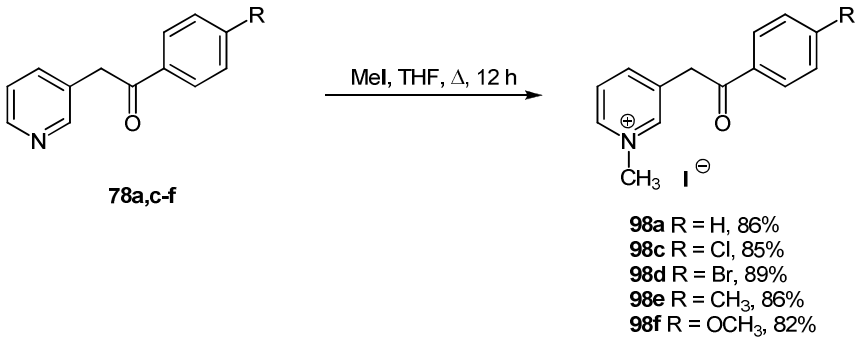
The above investigation into the general reactions of (pyridin-3-ylmethyl)lithium, although brief, provided evidence that a methodology had been developed that could be widely applicable and reasonably efficient, with potential for optimisation. We rapidly demonstrated that a compound of interest, **78f**, could be synthesised in reasonable yield, from the reaction of **73c** with 4-methoxybenzonitrile by employing a modified version of a procedure originally reported by Davis *et al*.[136] This significant result indicated that this methodology could be a useful approach towards the synthesis of compounds of interest in this study.

Target ketones **78a,c-f** (Scheme 23), were readily prepared, with most isolated in good yield (40 - 81%). It is noteworthy that, although these reactions have been performed many times, the yields reported here are unoptimised and with further work, greater yields could be achievable.



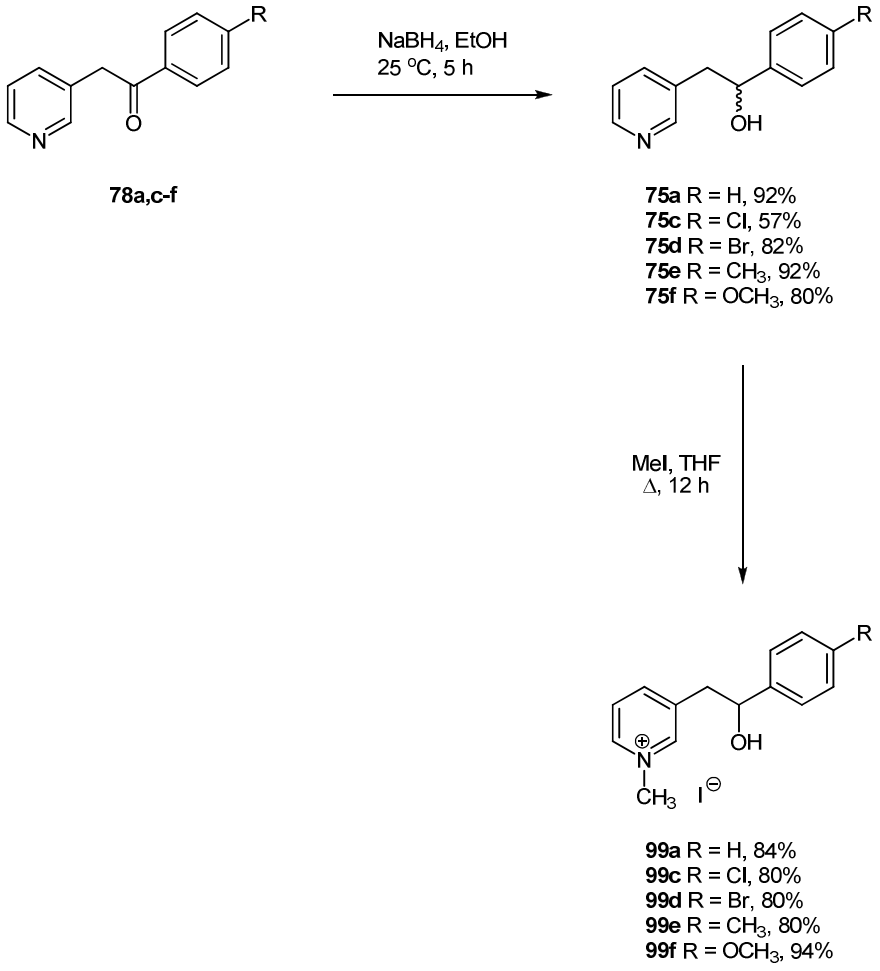
Scheme 23.

With the target ketones in hand, *N*-methylation of **78a,c-f** with excess methyl iodide in refluxing THF smoothly afforded pyridinium salts **98a,c-f** in excellent yield (Scheme 24).



Scheme 24.

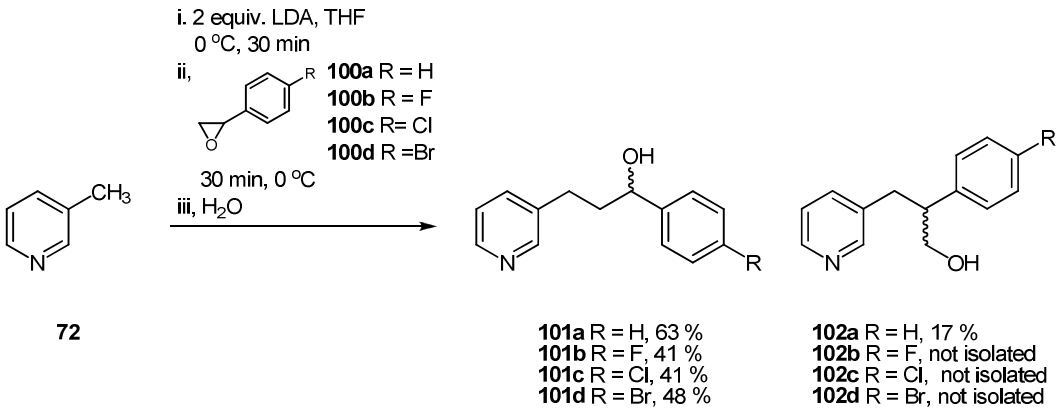
Ketones **78a,c-f** could be easily reduced using $NaBH_4$ in ethanol at room temperature to give target alcohols **75a,c-f** (57 - 92 %) (in our experience, this two-step approach to **75a,c-f** *via* **78a,c-f** offers better yields than reaction of **73c** with 4-substituted benzaldehydes). As with ketones **78a,c-f**, the alcohol derivatives **75a,c-f** could be readily *N*-alkylated with methyl iodide to furnish salts **99a,c-f** (80 - 94 %) (Scheme 25).



Scheme 25.

To act as a direct comparison with alcohols **75a,c-f** for pharmacological assessment, a series of novel propane based secondary alcohols were

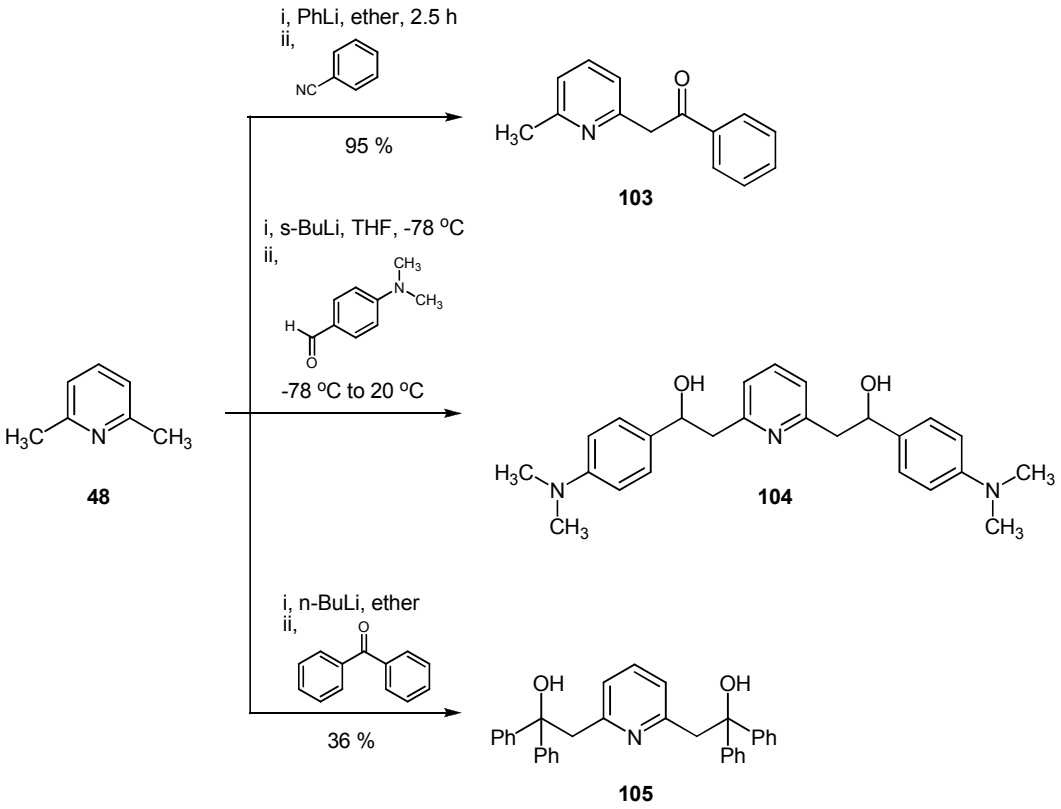
prepared *via* the ring opening of commercially available aromatic epoxides **100a-d** with (pyridin-3-ylmethyl)lithium (Scheme 26). Interestingly, in the reaction of **73c** with **100a**, the desired product **101a** (63 %) was isolated along with the more polar primary alcohol **102a** (17 %). TLC of the crude reaction mixtures from reactions of **73c** with **100b-d** also indicated competition by this side-reaction; however, in these cases isolation and purification of **102b-d** was never accomplished due to other interfering impurities. The formation of product **102a** can be rationalised through ring-opening of the corresponding epoxide by (pyridin-3-ylmethyl)lithium **73c** at the more sterically hindered carbon; there was no evidence for this ring-opening in the reaction of **73c** with with an aliphatic epoxide (entry 6, Table 1).



Scheme 26.

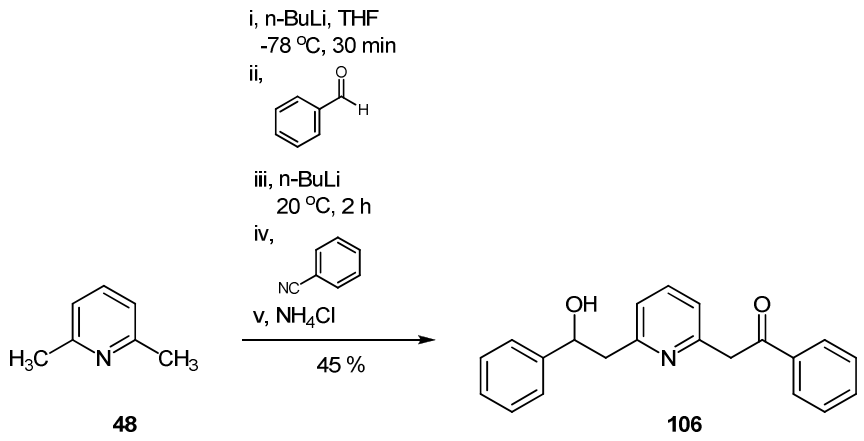
2.3 Metallation of 3, 5-Dimethylpyridine

Our work on the lithiation of 3-methylpyridine was further extended to the metallation and subsequent trapping of 3,5-dimethylpyridine with arylnitriles. In this instance, we were particularly interested in the possibility of deprotonation of the second pyridyl methyl group. It has been demonstrated that 2,6-dimethylpyridine **48** is able to undergo both single[163] and double deprotonation[164,165] followed by trapping with various electrophiles (Scheme 27).

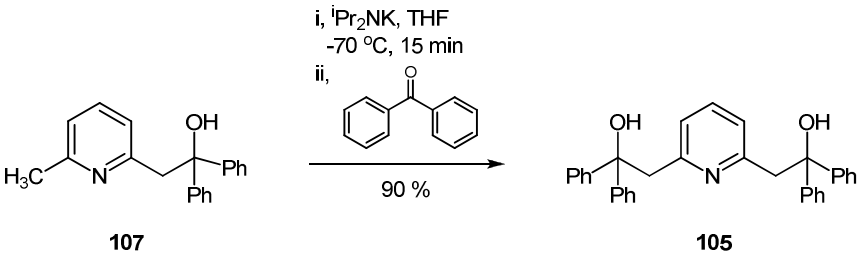


Scheme 27.

Additionally, efficient sequential deprotonation followed by sequential trapping with a range of benzaldehydes and / or benzonitriles to furnish 2,2'-(pyridine-2,6-diyl)bis(1-phenylethanone), 2,2'-(pyridine-2,6-diyl)bis(1-phenylethanone) or 2-(6-(2-hydroxy-2-phenylethyl)pyridin-2-yl)-1-phenylethanone derivatives (*e.g.* Scheme 28) has been demonstrated in both a 'one-pot'[166] and 'two-pot'[166] manner (a literature example is given in Scheme 29).[156] A similar sequence of reactions using 3,5-dimethylpyridine as substrate could provide a versatile methodology for the synthesis of a large variety of 3,5-disubstitutedpyridine analogues.

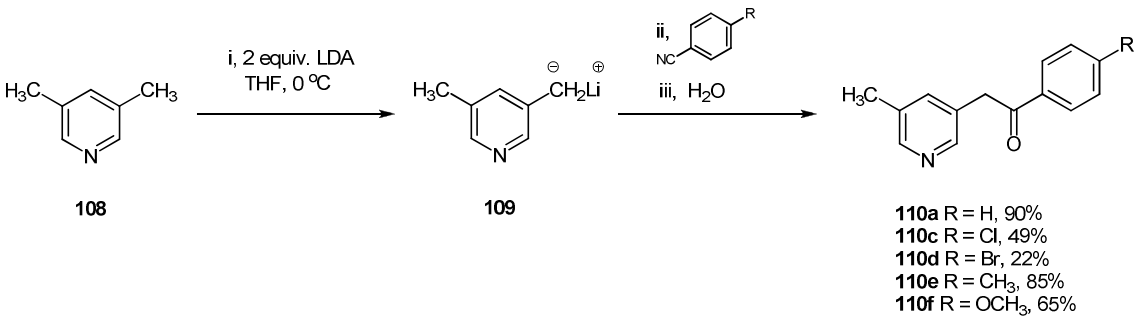


Scheme 28.



Scheme 29.

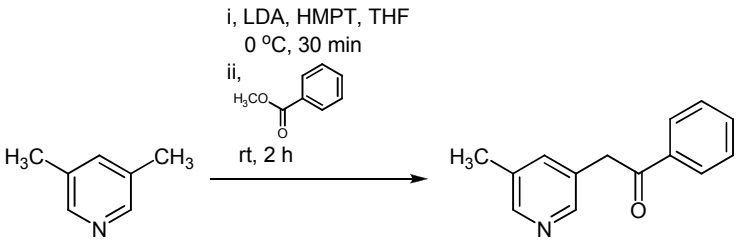
Using our general procedure established for preparation and reactions of (pyridin-3-ylmethyl)lithium **73c**, treatment of 3,5-dimethylpyridine **108** with 2 equiv. of LDA followed by addition of substituted benzonitriles **95a,c-f** gave the expected compounds **110a,c-f** arising from mono-metallation. Derivatives **110a,c-f** were obtained in good-excellent unoptimised yields (90 %, 85 % and 65 %, respectively), whereas halogenated benzonitriles **97c-d**, gave products **110c** and **110d** in somewhat disappointing yields (49 % and 22 %, respectively) (Scheme 30). This pattern of reactivity is similar to reactions between (pyridin-3-ylmethyl)lithium and benzonitriles described earlier in this Chapter. Indeed, as for 3-methylpyridine, reactions of **108** with LDA followed by addition of benzaldehydes gave no detectable reaction in our hands, with only starting materials ever recovered (essentially quantitatively).



Scheme 30.

Compounds **110c-f** have, to our knowledge, not been reported to date and provide a further series of novel compounds for pharmacological testing. Unsubstituted derivative **110a** has been synthesised previously by Baradarani *et al*.[167] In this case, 3,5-dimethylpyridine was deprotonated

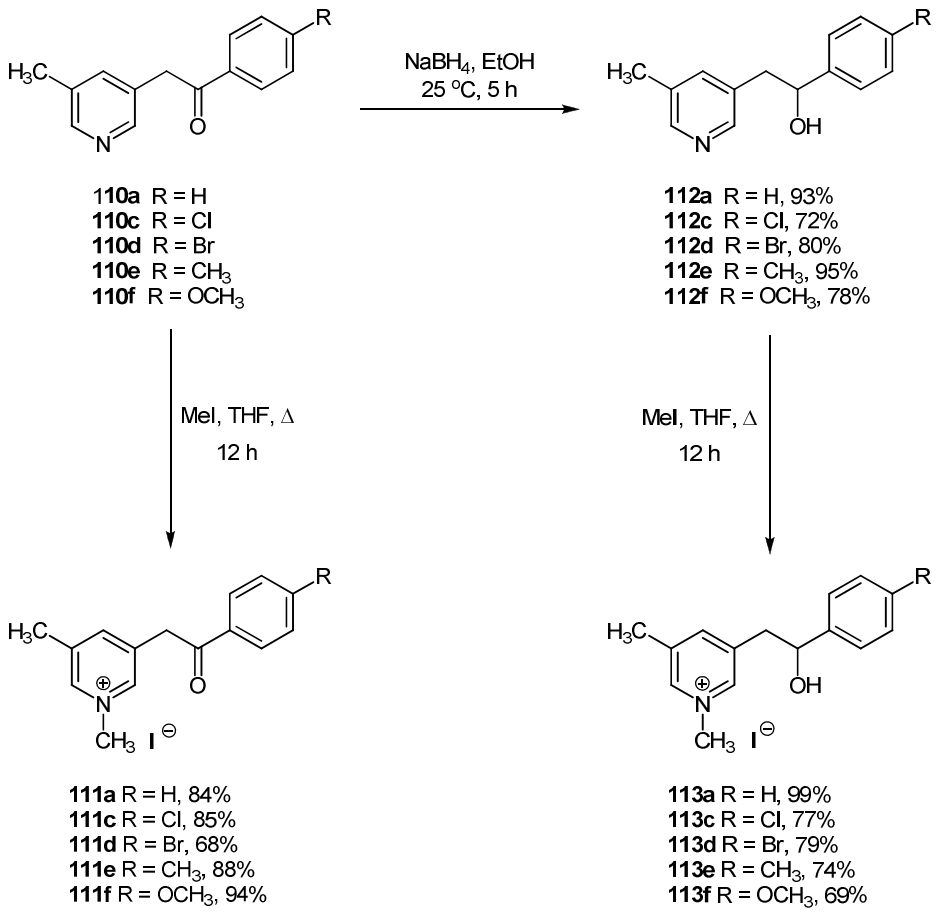
using LDA in the presence of HMPT and the resultant ((5-methylpyridin-3-yl)methyl)lithium trapped with methylbenzoate (Scheme 31).



108 **110a**

Scheme 31.

Compounds **110a,c-f** were easily converted to their *N*-methylated salts **111a,c-f** on refluxing with excess iodomethane in THF (68 – 94 % yields) (Scheme 32). Reduction of ketones **110a,c-f** with $NaBH_4$ at room temperature proceeded smoothly and the alcohols **112a,c-f** were obtained in good yields (72 – 95 %). Subsequent *N*-alkylation of **112a-e** with methyliodide furnished the expected pyridinum alcohols salts **113a,c-f** (69 – 99 %).



110a R = H
110c R = Cl
110d R = Br
110e R = CH_3
110f R = OCH_3

112a R = H, 93%
112c R = Cl, 72%
112d R = Br, 80%
112e R = CH_3, 95%
112f R = OCH_3, 78%

111a R = H, 84%
111c R = Cl, 85%
111d R = Br, 68%
111e R = CH_3, 88%
111f R = OCH_3, 94%

113a R = H, 99%
113c R = Cl, 77%
113d R = Br, 79%
113e R = CH_3, 74%
113f R = OCH_3, 69%

Scheme 32.

Attempts to effect a double deprotonation in a one-step procedure using up to 4 equiv. LDA followed by addition of benzonitrile yielded only 2-(5-methylpyridin-3-yl)-1-phenylethanone **110a**.

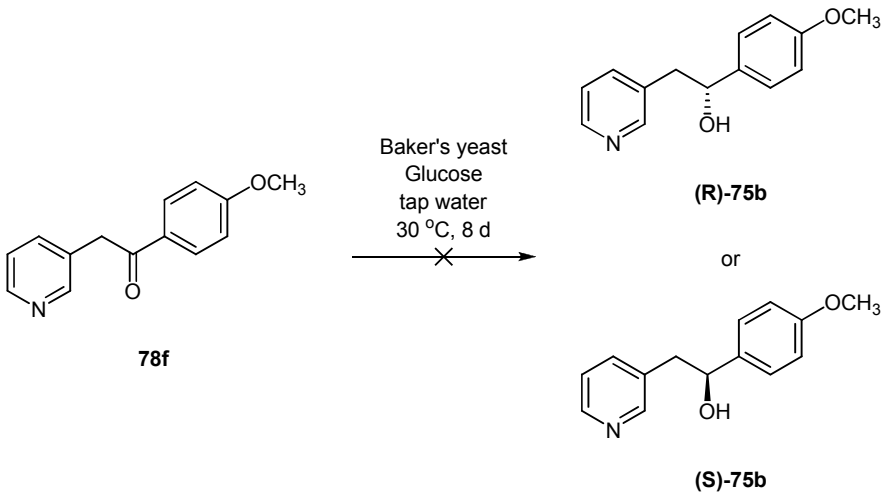
Attempts to deprotonate both alcohol **112a** and ketone **110a** using excess LDA or t-BuLi in THF at both 0 °C and -78 °C with subsequent addition of either benzaldehyde, benzonitrile or methyl iodide were all unsuccessful; on each occasion only unreacted starting materials were ever recovered suggesting that deprotonation had not occurred under the reaction conditions employed or that the generated lithiospecies were unreactive towards the electrophile employed. Similarly, Baradarani *et al.*[166] provided

no evidence for a second proton abstraction in their investigation of lithiation reactions of 3,5-dimethylpyridine; no other literature exists to suggest that it has been achieved to date for 3,5-dimethylpyridine. With this in mind, we did not further explore metallation reactions of 3,5-dimethylpyridine as an approach to the bis-substituted derivatives targetted at the outset of this project. However, future work in this area could explore further the necessary reaction conditions to effect a one-step or sequential double-lithiation successfully.

2.4 Synthesis of Optically Pure Alcohols

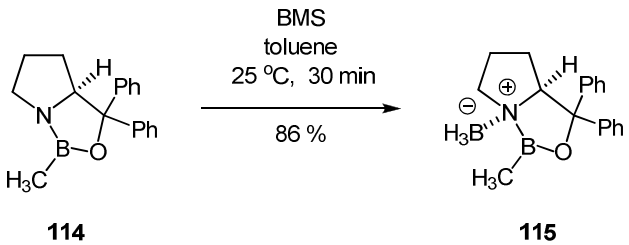
As a reliable synthetic method had been developed for the synthesis of the target ketones **78a,c-f** and their reduced products **75a,c-f** (isolated in a racemic mixture from $NaBH_4$ reduction), we became interested in the possibility of an asymmetric reduction of ketones **78** to afford enantiomerically pure alcohols **75**.

First to be investigated was the stereoselective reduction of ketone **78f** using baker's yeast (*Saccharomyces cerevisiae*) and glucose in tap water as described by Fantin *et al*. (Scheme 33)[168] – after the mixture had been stirred at 30 $^{\circ}$C for 8 days, no reduction of ketone **78f** had occurred and no other products were visible by TLC.



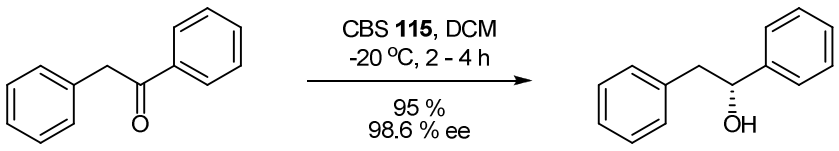
Scheme 33.

Asymmetric reduction was next attempted using **115**, commonly referred to as the CBS reagent. CBS **115** is a borane complex, based on (*S*)-proline, developed by Corey *et al*.[169] and is a highly efficient enantioselective reducing agent, particularly useful for prochiral ketones. The unstable 'inactive' reducing agent **114** is available commercially. The active reducing agent was prepared following a literature procedure by treating **114** with borane-dimethyl sulphide complex (BMS) in dry toluene at room temperature for 30 min.; addition of dry heptane precipitated **115** as a white crystalline solid (86% yield) (Scheme 34). **115** is the more stable form and is preferred to **114** for long-term storage.[170]



Scheme 34.

Reduction of ketone **78f** was, subsequently, attempted using CBS **115** following the method of Mathre *et al.*[170] Ketone **78f** was added to a catalytic amount of **115** in dry DCM at -20 °C and the mixture stirred for 3h at this temperature.[170] Unfortunately, after work-up, no reduced product was evident by TLC, with only the unchanged starting material being observed. This result was, perhaps, surprising as Mathre *et al.*[170] achieved both an excellent yield (95 %) and ee (98.6 %) for the reduction of the structurally similar compound **116** to **117** when using both a stoichiometric and catalytic amount of **115** (Scheme 35). This group did not, however, attempt reduction of ketones possessing substituted aromatic rings or heterocycles. The reason for our result, reproduced on several occasions, is unclear. It is known that good complexation is important for effective hydride transfer by CBS as it is a relatively weak hydride source; the presence of the pyridine ring, or the electron donating effects of the methoxy group, may affect the outcome of the reaction investigated in this work.



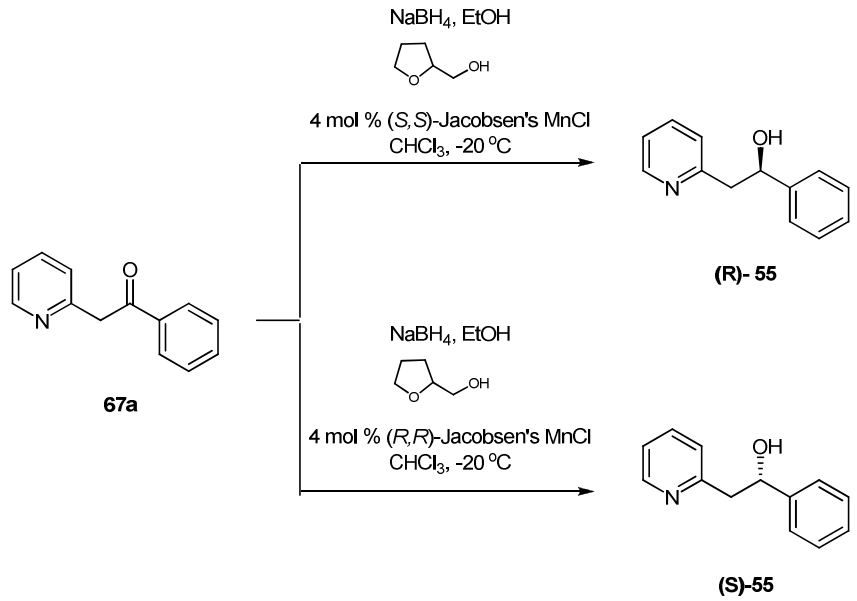
116 **117**

Scheme 35.

The work by Mathre *et al.* does, however, suggest that the two groups adjacent to the prochiral carbonyl in **78f** are sufficiently different sterically

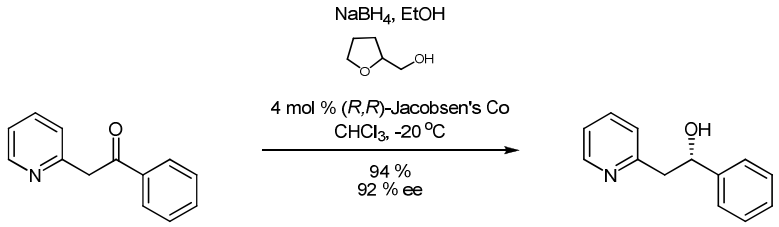
for hydride delivery to occur preferentially from one face. Clearly, further work for the asymmetric reduction of ketones **78a,c-f** using this methodology is worthwhile as Mathre *et al.*[170] have shown that structurally similar compounds can be reduced with excellent yield and enantiomeric excess.

Paralleling our results, Chu-Yi *et al.*[130] reported that baker's yeast and CBS did not affect the stereoselective reduction of the 1-phenyl-2-(pyridin-2-yl)ethanone **67a**. Excellent yields and ee were, however, achieved by this group using (*S,S*) or (*R,R*)-(-)-Jacobsen's MnCl with modified $NaBH_4$ ($NaBH_4$ / ethanol / tetrahydrofurfuryl alcohol)[170] in chloroform (Scheme 36).



Scheme 36.

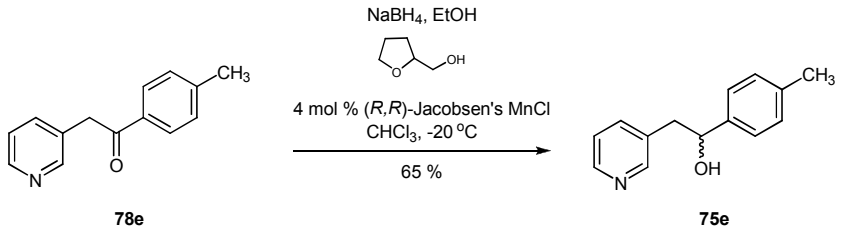
Subsequently Ohtsuka *et al.*[172] reported an analogous reduction using the (*S,S*)-Jacobsen's Co (III) complex with modified $NaBH_4$ to obtain the (*S*)-alcohol **55** in 94 % yield (92 % ee) (Scheme 37). Interestingly, the (*R*)-product was obtained when the (*S,S*)-Manganese complex modified with $NaBH_4$ was employed by Chu-Yi *et al.*[130]



67a **(S)-55**

Scheme 37.

Given these excellent reported results, an enantioselective reduction of ketone **78c** was attempted, using (*S,S*)-Jacobsen's MnCl complex modified with $NaBH_4$. Initial reactions following the procedure by Chu-Yi *et al.*[130] did not produce a selective reduction and only the racemic alcohol **75e** was ever obtained (typically ~ 65 % yield) as determined by chiral HPLC or polarimetry. Initially it was believed that this may be due to poor modification of the $NaBH_4$ as a solid had precipitated from the modified $NaBH_4$ solution at -20 °C; performing the reaction at 0 °C prevented precipitation, but again gave only racemic alcohol in similar yield.



78e **75e**

Scheme 38.

Similarly, (*R,R*)-Jacobsen's Cobalt complex modified with $NaBH_4$ gave only racemic **75e** (following the procedure by Ohtsuka *et al.*).[172] The reason for the lack of enantioselectivity in the reduction of **78e** is unclear. However, assuming that the $NaBH_4$ complex had been adequately modified, and that free $NaBH_4$ had not been introduced, the problem may lie in the poor formation of the pyridyl-Jacobsen's complex, precluding preferential face-selective hydride delivery.

The catalytic mechanism for the enantioselective reduction using Jacobsen's catalyst modified with $NaBH_4$ is not yet fully understood. However, Chu-Yi *et al.*[130] speculated that in their work 1-phenyl-2-(pyridin-2-yl)ethanone **67a** in its enol form may complex with Jacobsen's catalyst. This may explain a lack of complexation of the 3-position analogue **78e**, as we have shown that these derivatives exist only in the keto form in solution.

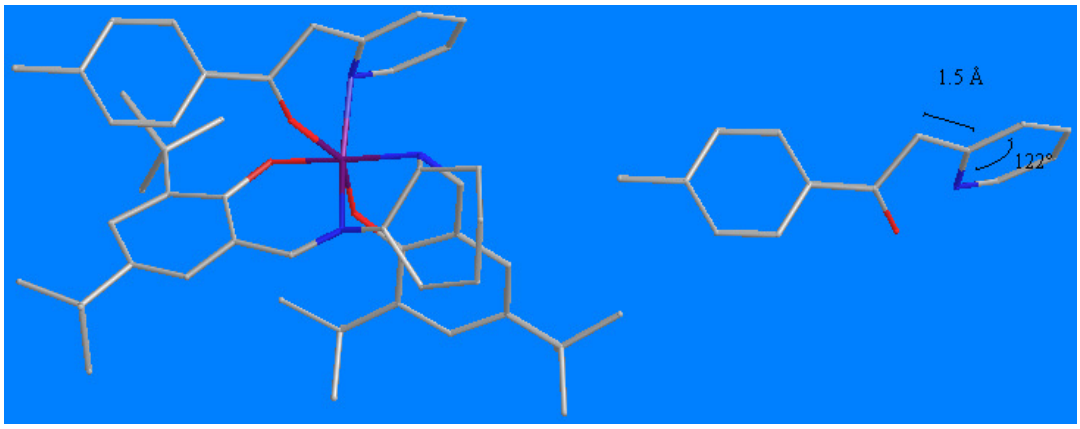


Figure 15a. *Molecular model of the octahedral complex formed by coordination of 2-pyridin-2-yl-1-(4-methylphenyl)-ethanone* ***67e*** *[minimised energy in Chem3D®].*

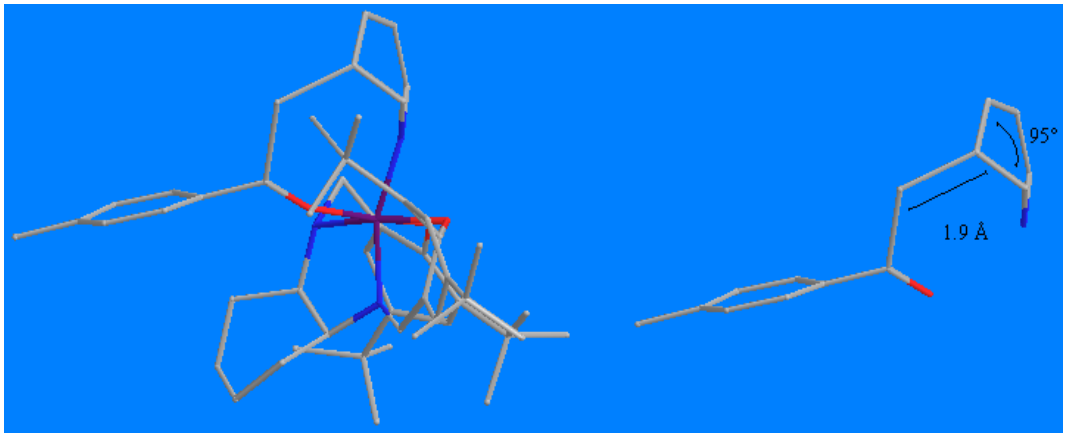


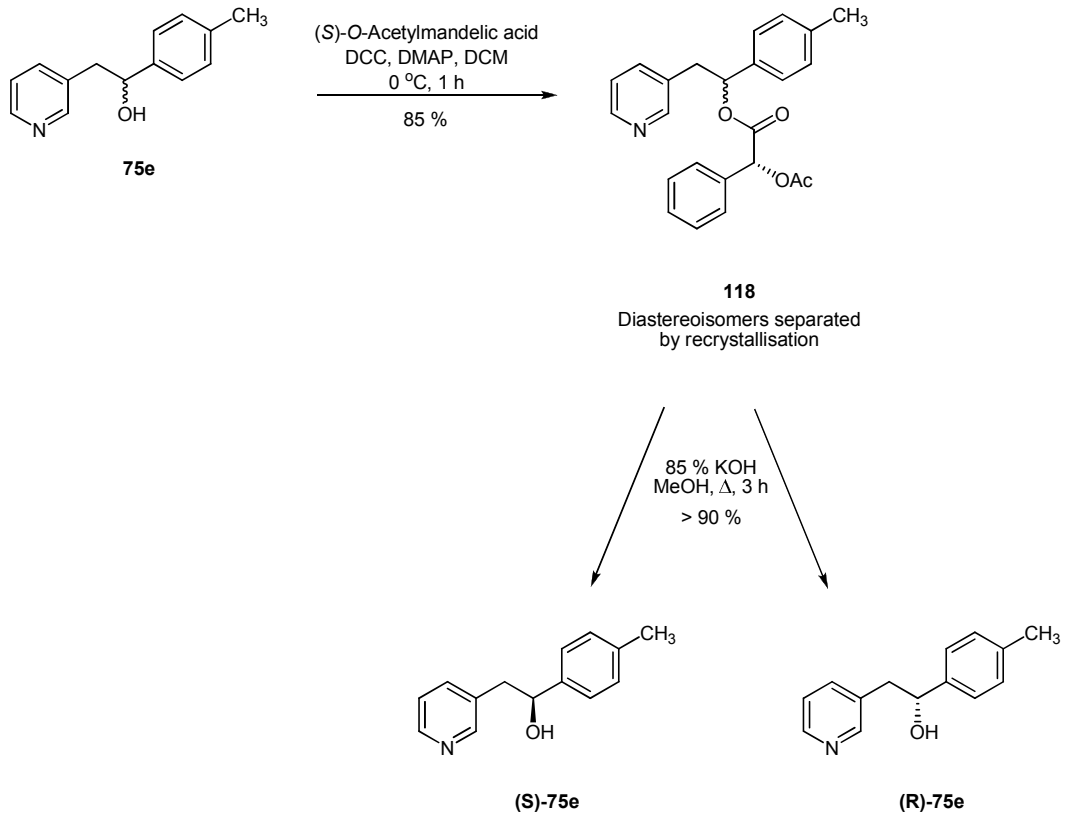
Figure 15b. *Molecular model of the octahedral complex formed by coordination of 2-pyridin-3-yl-1-(4-methylphenyl)-ethanone* ***78e*** *with Jacobsen's catalyst [minimised energy in Chem3D®].*

An alternative explanation may lie in the molecular geometry of **78e**. Molecular modelling suggests that coordination of 2-pyridin-2-yl-1-(4-methylphenyl)-ethanone **67e** through the pyridine nitrogen and carbonyl oxygen to the manganese (III)-salen Schiff base complex produces a favourable octahedral complex with minimum distortion to the substrate

geometry (it remains effectively planar) (Figure 15a) [calculations suggests the optimum bond length between the α-carbon and pyridine carbon to be 1.50 Å and the actual to be 1.54 Å; the internal angle between the two pyridine carbons was found to be 122.32° compared to an optimum angle of 120.0°]. However, to adopt a similar conformation in an octahedral complex with the manganese (III)-salen Schiff base complex, the pyridine ring of 1-phenyl-2-(pyridin-3-yl)ethanone **78e** would be required to twist unfavourably about C-3 of the pyridine ring (Figure 15b). Modelling suggests the bond length between α-carbon and pyridine carbon to be 1.94 Å and the internal angle between pyridine carbons to be 95.18°, indicating significant deformation of the molecule, and in particular, the pyridine ring.

As catalytic asymmetric reduction to obtain enantiomerically pure alcohol derivatives **75a,c-f** had proven unsuccessful in our hands, we next attempted the formation and subsequent resolution of diastereoisomers prepared from the racemic alcohol **75e** (Scheme 39). Thus, using (*S*)-*O*-acetylmandelic acid it was possible to prepare a mixture of a pair of diastereomeric esters **118** (Scheme 39) in excellent yield (85 %) using a procedure described by Hutchison *et al*.[173] [who used the more expensive (*R*) and (*S*)-Mosher's acids]. Recrystallisation of **118** afforded one diastereoisomer as a colourless oil (99 % de, Figure 16b) and the second as a white crystalline solid (99 % de, Figure 16c). Hydrolysis of each ester occurred readily under basic conditions[174] and furnished the enantiomerically pure alcohols (*S*)-**75e** and (*R*)-**75e** (Figures 16e and 16f)

also in excellent yield ($[\alpha]_D$ = +/- 16.2). Unfortunately, the absolute stereochemistry of each enantiomer / diastereoisomer has not yet been determined.



Scheme 39.

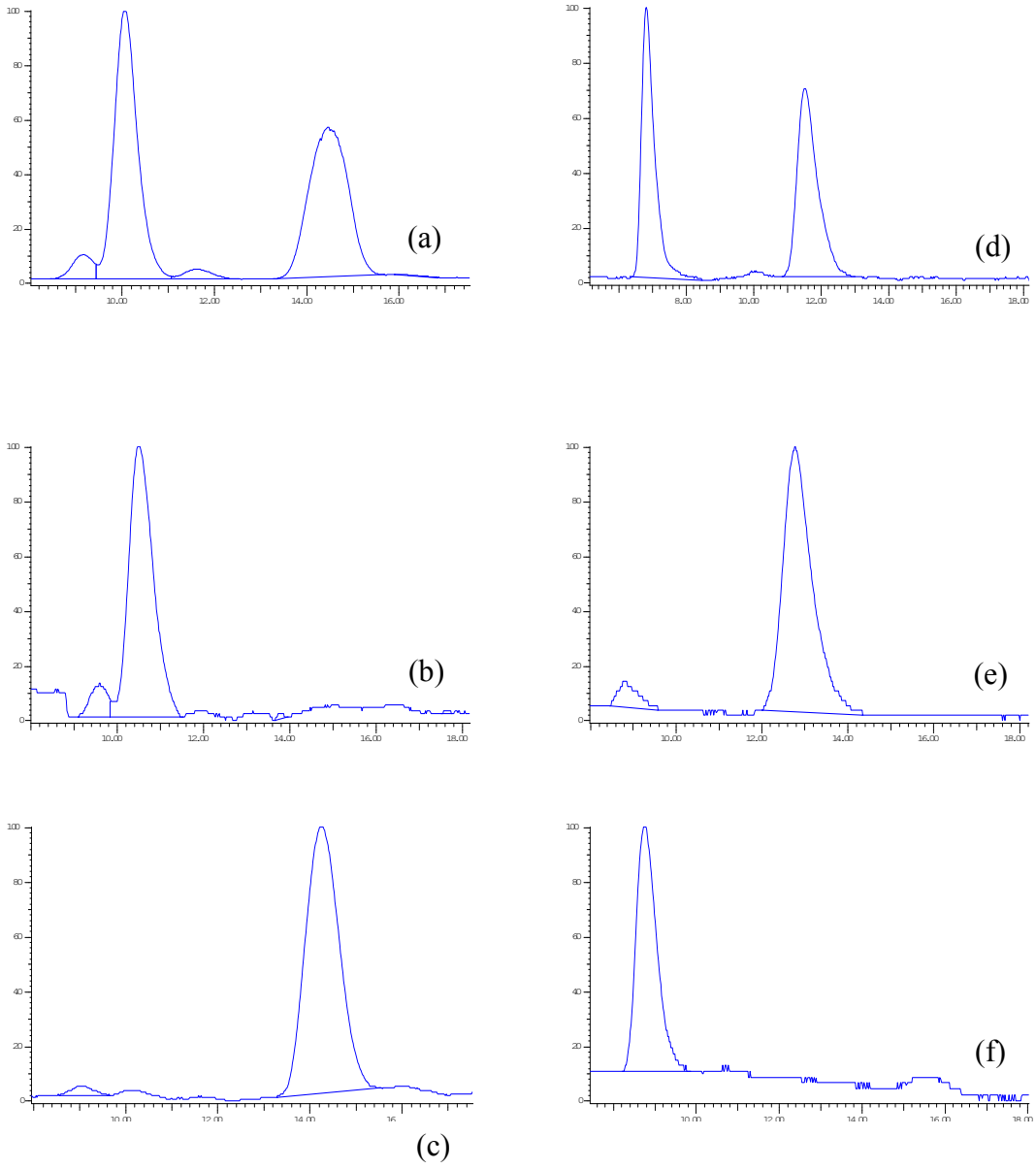


Figure 16. *Chromatograms of (a) mixture of diastereoisomers **118**; (b) separated diastereoisomer (oil); (c) separated diastereoisomer (solid); (d) racemic alcohol **75e**; (e) (R) or (S)- alcohol **75e** (oil); (f) (R) or (S)- alcohol **75e** (solid); HPLC Conditions: mobile phase: 90 / 10, Hexane / IPA; samples: 1 mg mL^{-1} in mobile phase; flow rate: 1 mL / min; detection: UV 254 nM; Loop: 10 µL.*

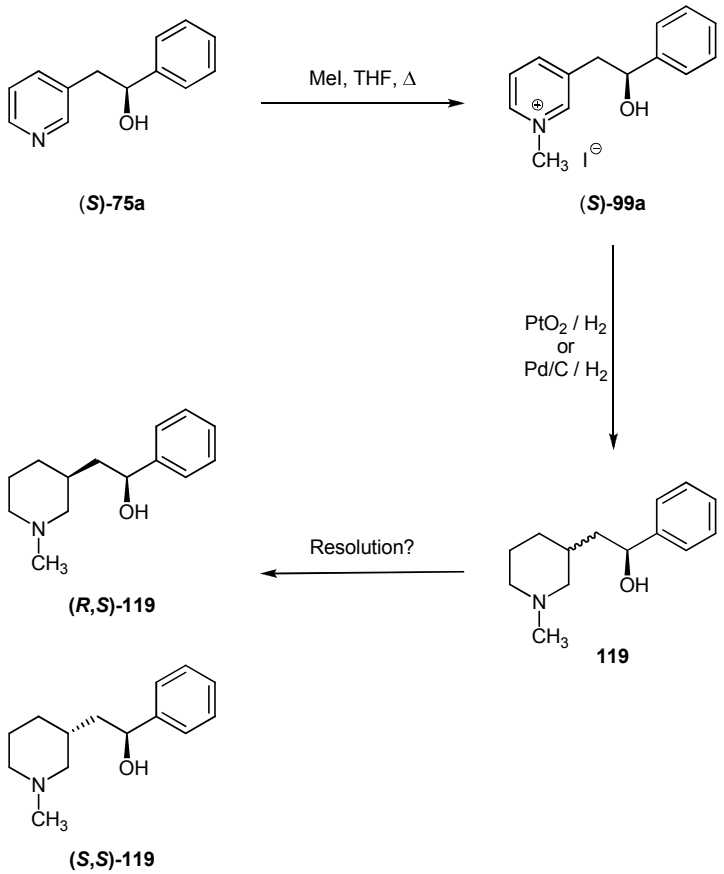
2.5 Conclusion

In summary, the ability to generate (pyridin-3-yl)methyl)lithium **73c** and ((5-methylpyridin-3-yl)methyl)lithium **109** by the addition of 3- or 3,5-dimethylpyridine, respectively, to LDA in THF at 0 °C has been demonstrated. Subsequent reaction of **73c** and **109** with various electrophiles afforded compounds of sufficient purity for pharmacological testing; preliminary pharmacological data for these compounds are presented in Chapter 5. The synthetic protocol developed in this Chapter was a modification of published literature procedures, and the methodology still has scope for further optimisation. Compared to current literature procedures for the lithiation of 3- or 3,5-dimethylpyridine, the method described in this Chapter has the advantages of (i) a simpler reaction procedure, (ii) a shorter reaction time, and (iii) no requirement for a chelating co-solvent (*e.g.* DMPU or HMPT).

A number of methods to enable the preparation of enantiomerically pure alcohols by asymmetric reduction of prochiral ketone derivatives **78a,c-f** were assessed. However, the various methodologies investigated (enzymatic and catalytic) proved to be unsuitable. Despite this, enantiomerically pure alcohols (*S*)-**75e** and (*R*)-**75e** could be prepared *via* the resolution of the diastereomeric esters **118** [prepared by reaction of (±)-**75e** with (*S*)-*O*-acetyl mandelic acid] and subsequent hydrolysis. This strategy should be equally applicable to all the alcohol derivatives **75a,c-f**

described in this Chapter, allowing access to single enantiomers of each for pharmacological testing, if required.

With an established synthetic methodology in place, future work in this area could focus around the synthesis of derivatives which possess alternate substitution patterns around the aromatic ring for pharmacological comparison. Additionally, an extension to the work described in this Chapter could investigate the synthesis of novel, enantiomerically pure piperidine derivatives **119** (piperidin-3-yl analogues of sedamine) (*e.g.* using the methodology shown in Scheme 40).



Scheme 40.

Chapter 3

This chapter details our approaches to target compounds **75a-d**, **78a-d**, **144a,c-e** and **159a-e** employing 3-bromopyridine **120** as starting reagent using either halogen-lithium exchange reactions (Section 3.1.1) or metal-mediated cross-coupling reactions (Sonogashira, Section 3.2.1.1; Heck, Section 3.2.1.2) as the key synthetic step. These approaches were successfully extended to prepare compounds **170-171a-e** from either 3-bromo-1-methyl-1*H*-indole **169a**, 3-iodo-1-methyl-1*H*-indole **169b** or 3-iodo-5-methoxy-1-methyl-1*H*-indole **169c** (Section 3.3).

3.1 Reactions of 3-Bromopyridine

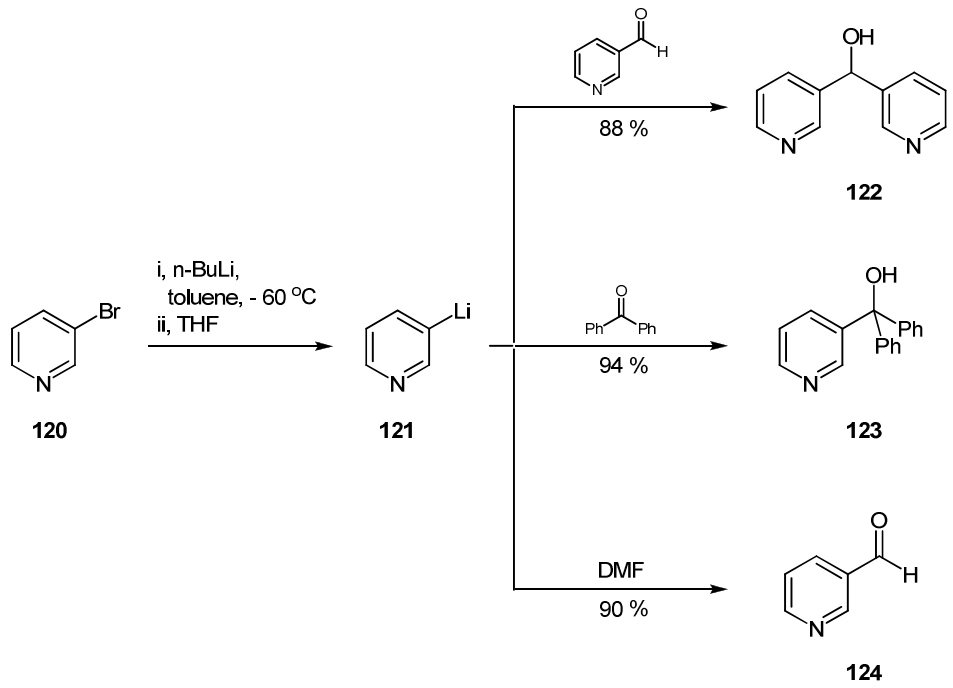
3.1.1 Halogen-Lithium Exchange Reactions of 3-Bromopyridine

3.1.1.1 Introduction

As an alternative to the synthetic approach to alcohols **75a,c-f** described in Chapter 2, a single step synthesis of racemic alcohol derivatives **75a-d** was explored *via* halogen-lithium exchange reactions of 3-bromopyridine.

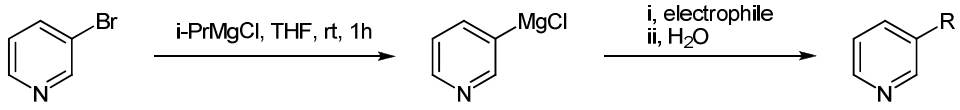
The exchanges of lithium[175] and magnesium[176] for halogens on pyridine have been reported extensively. Several authors have reported that (pyridin-3-yl)lithium **121** may be generated easily from 3-bromopyridine **120** using n-BuLi in either THF[180] or toluene[180] at low temperatures. Cai *et al*.[175] in particular, have reported the efficient bromine-lithium exchange

reaction of **120** using n-BuLi in toluene at -60 ^{o}C to give **121** (which was relatively stable at this temperature); subsequent trapping of **121** using various electrophiles gave the expected products in good-to-excellent yields (Scheme 41).



Scheme 41.

Trecourt *et al.* have reported an efficient bromine–magnesium exchange reaction on 3-bromopyridine using i-PrMgCl in THF at room temperature to give pyridin-3-ylmagnesium chloride **125**; **125** subsequently reacted with a range of electrophiles to give various 3-substituted pyridines **126a-i** in moderate-to-high yields (Scheme 42).[176]

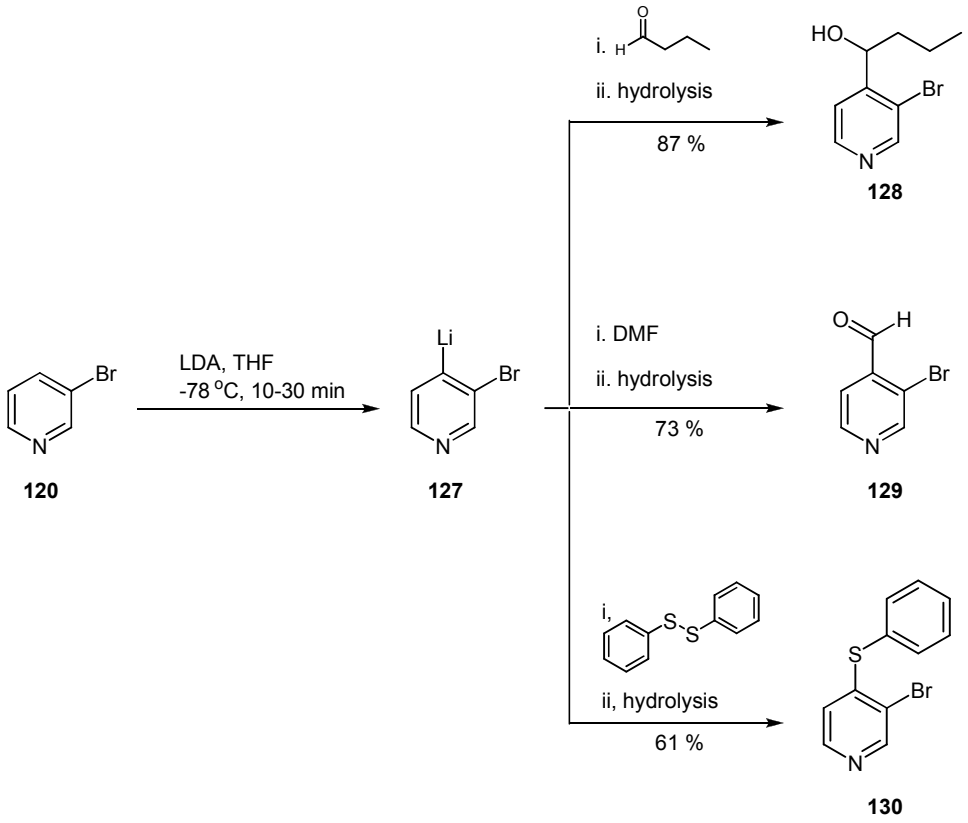


120 **125** **126a-i**

Entry	Electrophile	R	Product	Yield (%)
1.	PhCHO	CH(OH)Ph	**126a**	84
2.	$(CH_3)_3CCHO$	$CH(OH)C(CH_3)_3$	**126b**	78
3.	CH_3CHO	$CH(OH)CH_3$	**126c**	51
4.	PhCOPh	$C(OH)Ph_2$	**126d**	51
5.	EtCOEt	$C(OH)Et_2$	**126e**	58
6.	PhCOCl	COPh	**126f**	35
7.	$(CH_3)_2CHCOCl$	$COCH(CH_3)_2$	**126g**	12
8.	CH_3SSCH_3	SCH_3	**126h**	49
9.	I_2	I	**126i**	78

Scheme 42.

It is also worthwhile noting that metallation of 3-bromopyridine with LDA at temperatures above -78 °C has been shown to promote halogen migration to afford 4-bromo-3-substituted pyridines as the major products after addition of an electrophile.[177] At temperatures below -78 °C no bromine migration was observed and either 3-bromo-4-substituted pyridines (Scheme 43)[178a-c] or 3-bromo-2,4-disubstituted pyridines were obtained.[179]



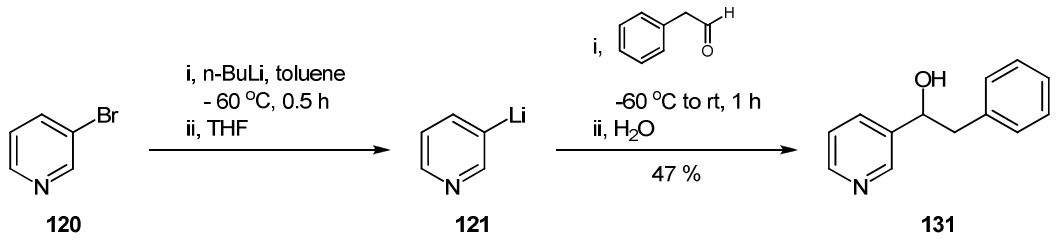
Scheme 43.

3.1.1.2 Results and Discussion

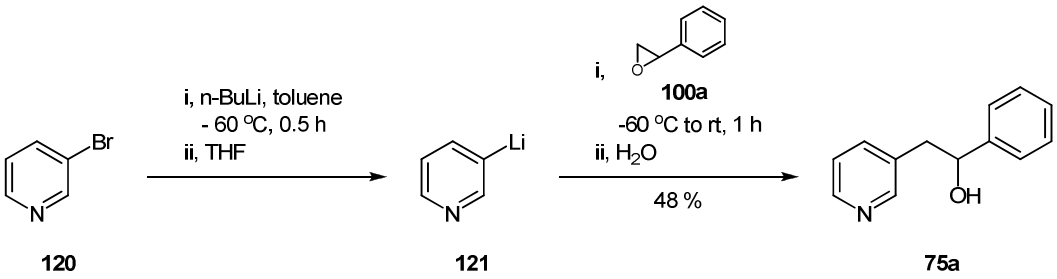
To our knowledge, reactions involving the ring-opening of aromatic epoxides using pyridin-3-yllithium **121** have not, to date, been reported. Our successful investigation of the synthesis of 1-(4-substituted-phenyl)-2-pyridin-3-yl-ethanol derivatives **75** *via* the halogen-lithium exchange reaction of 3-bromopyridine **120** using n-BuLi and subsequent reaction with aromatic epoxides **100a-d** (Scheme 44) is discussed below.

An initial test reaction using 3-bromopyridine **120** as substrate was carried out based on the halogen-lithium exchange methodology reported by Cai *et al*.[175] with subsequent reaction using phenylacetaldehyde as the electrophile (Scheme 44). In our hands, the addition of

phenylacetaldehyde to pyridin-3-yllithium **121**, generated from **120** in toluene by slow addition of n-BuLi at -60 °C, furnished the alcohol **123** in moderate yield after work-up and purification (47 %); the only other constituents of the reaction mixture were identified as starting materials (the presence of unchanged 3-bromopyridine was indicative of incomplete halogen-lithium exchange under the reaction conditions employed). Similarly, application of this methodology using 2-phenyloxirane **100a** as the electrophile afforded the desired alcohol **75a** in 48 % yield with only unreacted starting materials and product again isolated after chromatography.



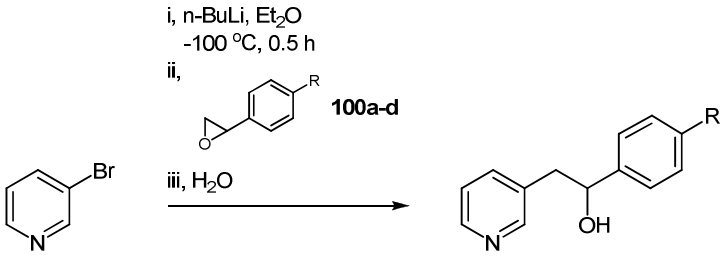
Scheme 44.



Scheme 45.

In order to optimise the isolated yield of **75a**, variation of the reaction conditions was, investigated. Specifically, (i) the addition time of n-BuLi to the cooled solution (-60 °C) of 3-bromopyridine in toluene (10 – 60 min);

(ii) the (pyridin-3-yl)lithium generation time (15 – 60 min); and, (iii) the addition time of the electrophile (5 - 30 min) were varied, whilst the final stir-out time (1 h), reaction temperature and work-up procedure remained the same as the reported methodology of Cai *et al*. Additionally, the reaction mixture was allowed to warm to room temperature immediately after the addition of the epoxide. In all cases, no detectable improvement in the isolated yield of **75a** was found. It was noted that all these reactions suffered from solubility problems and the addition of THF to the reaction mixture was often required. Repeating reactions at -60 °C in either THF or diethyl ether as the sole solvent improved solubility, but offered no improvement in isolated yield of **75a**. However, reactions carried out in diethyl ether at -100 °C gave an improved isolated yield (61 %) with no solubility issues noted. Thus, reaction of 3-bromopyridine with n-BuLi in ether at -100 °C followed by addition of 2-(4-substitutedphenyl)oxiranes **75a-d** afforded, after work-up and purification, alcohols **75a,d-f** (31 - 61 % yield) (Scheme 46).



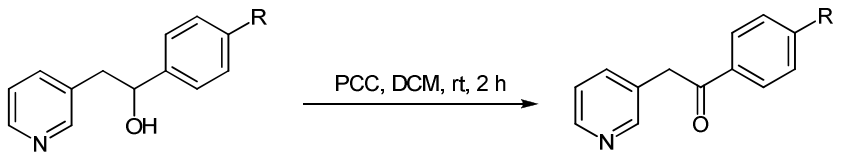
120

75a R = H, 61 %
75b R = F, 51 %
75c R = Cl, 54 %
75d R = Br, 31 %

Scheme 46.

Interestingly, employing the methodology of Trecourt *et al.,*[176] we did not observe a reaction between pyridin-3-ylmagnesium chloride and 2-phenyloxirane, despite extensive modification of the reaction conditions.

Oxidation of alcohols **75a-d** to ketones **78a-d** was readily achieved using pyridinium chlorochromate (PCC) in DCM (70-83 % yield) (Scheme 47).[181]



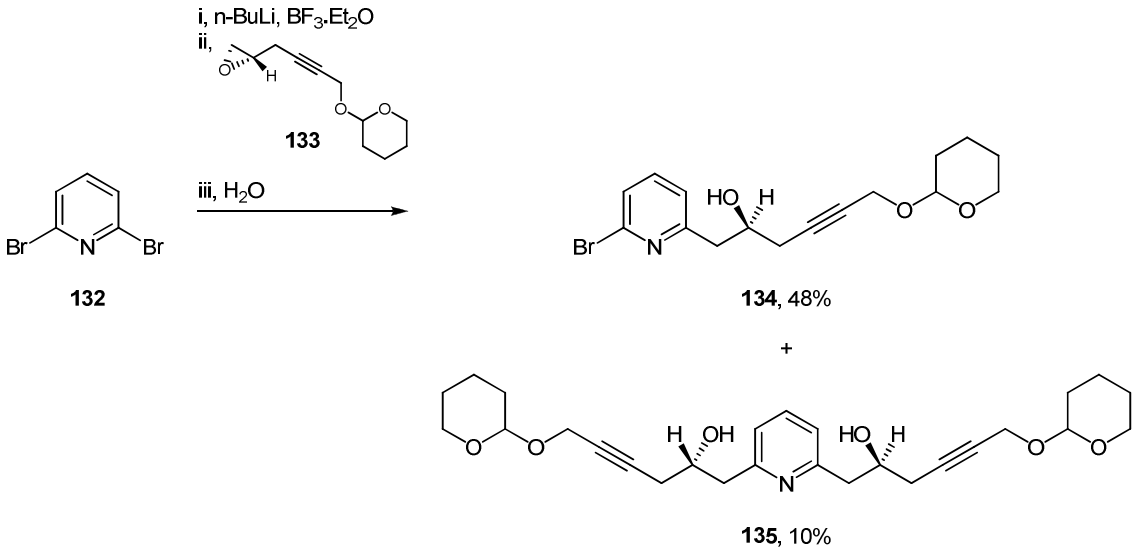
75a R = H
75b R = F
75c R = Cl
75d R = Br

78a R = H, 82 %
78b R = F, 74 %
78c R = Cl, 83 %
78d R = Br, 70 %

Scheme 47.

3.1.1.3 Summary

To our knowledge, this work describes the first example of the ring-opening of an epoxide with the organolithium derived from 3-bromopyridine and n-BuLi. Indeed, no examples could be found in the literature of the analogous reactions with either 2-bromopyridine or 4-bromopyridine and only one relevant example using 2,6-dibromopyridine **132**. In this latter case, (*S*)-alcohol **134** was obtained as the major product with retention of configuration (> 98 % ee, 48 % yield) by boron-trifluoride assisted ring-opening of (*S*)-epoxide **133** by (6-bromopyridin-2-yl)lithium (Scheme 48).[182] Alongside (*S*)-alcohol **134**, (*S,S*)-bis-alcohol **135** (10 %) was also isolated arising from formation and reaction of pyridin-2,6-diyllithium. Ring-opening of the enantiomeric (*R*)-epoxide similarly gave the (*R*)-alcohol (> 98 % ee).



Scheme 48.

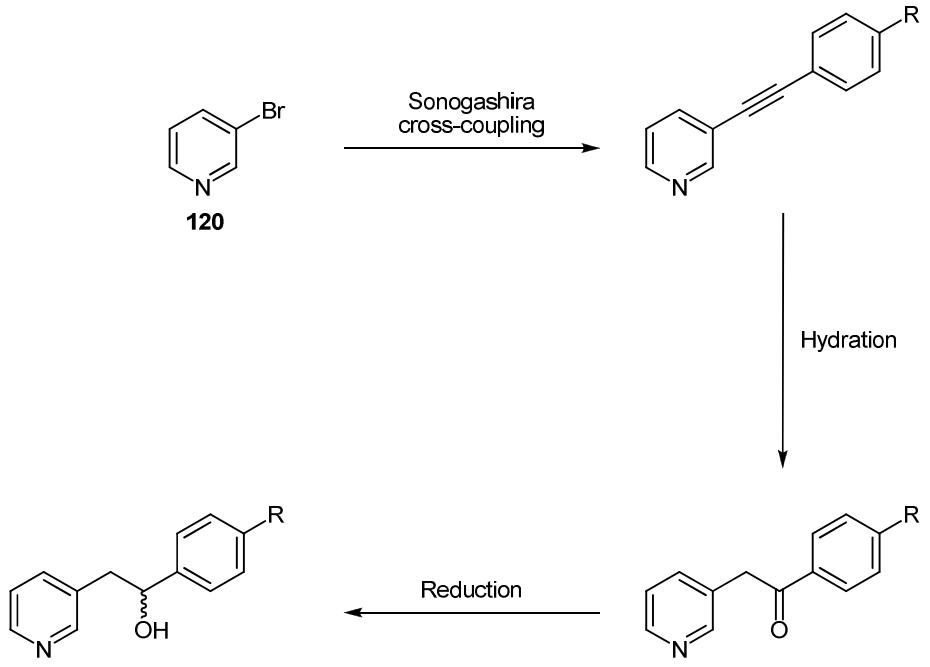
The ring-opening of epoxides **100a-d** with pyridin-3-yllithium allowed the direct entry to target alcohol derivatives **75a-d**; this methodology has the potential to be extended to prepare a wide range of derivatives by variation of the electrophile - this may prove valuable in the future if the compounds studied in this work are shown to exhibit interesting pharmacological activity. Perhaps the most interesting application of this methodology lies in the potential one-step synthesis of enantiomerically pure alcohol derivatives **75** by reaction of pyridin-3-yllithium with enantiomerically pure epoxides following the strategy of Burgos *et al*.[182] However, a notable disadvantage of this synthetic route in the preparation of a series of derivatives for rapid pharmacological evaluation is that only a limited number of enantiomerically pure, substituted aromatic epoxides are commercially available, with some being extremely expensive.

3.1.2 Metal Mediated Reactions of 3-Bromopyridine

3.1.2 .1 Sonogashira Cross-Coupling Reactions

3.1.2.1.1 Preamble

This section describes our investigation of Sonogashira cross-coupling reactions of 3-bromopyridine **120** with a range of 4-substitutedarylalkynes **147a,c-f** to give 3-((4-substitutedphenyl)ethynyl)pyridine derivatives **144a,c-f**. Functional group interconversion *via* the acidic hydrolysis of the alkyne and subsequent reduction gave ketones **78a,c-f** (compounds previously described in Chapter 2) (Scheme 49). This approach has already proven successful and versatile for the synthesis and elaboration of 2-(4-substitutedphenylethynyl)pyridine derivatives.[183-185]



Scheme 49.

3.1.2.1.2 Introduction

The Sonogashira reaction is one of the most widely employed palladium catalysed cross-coupling reactions; it involves the reaction of a terminal alkyne with a vinyl or aryl halide in the presence of a palladium (0) or palladium (II) ligand, a co-catalyst (often CuI) and a base (most commonly Et_2NH or Et_3N) (Figure 16).[186]

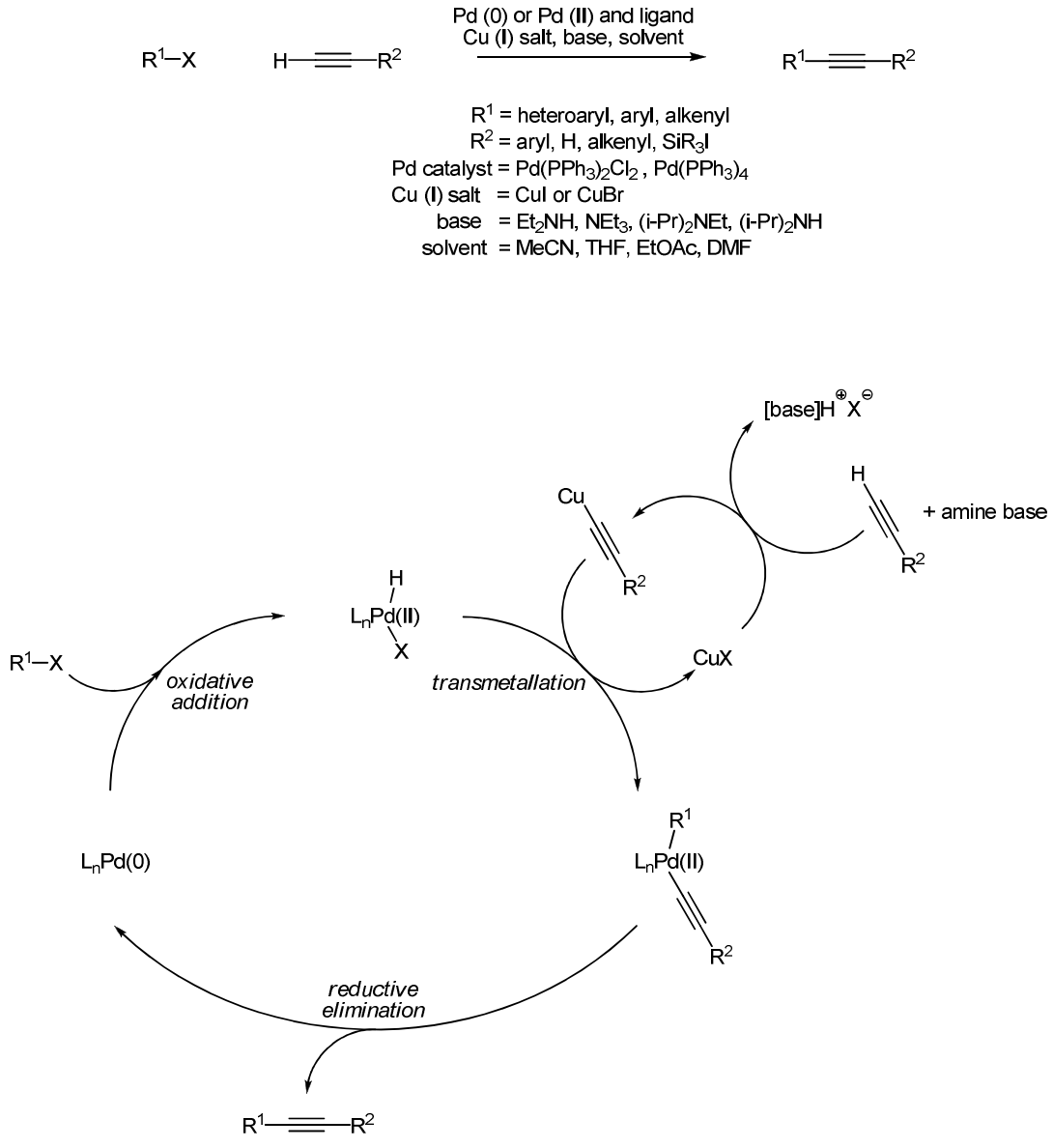
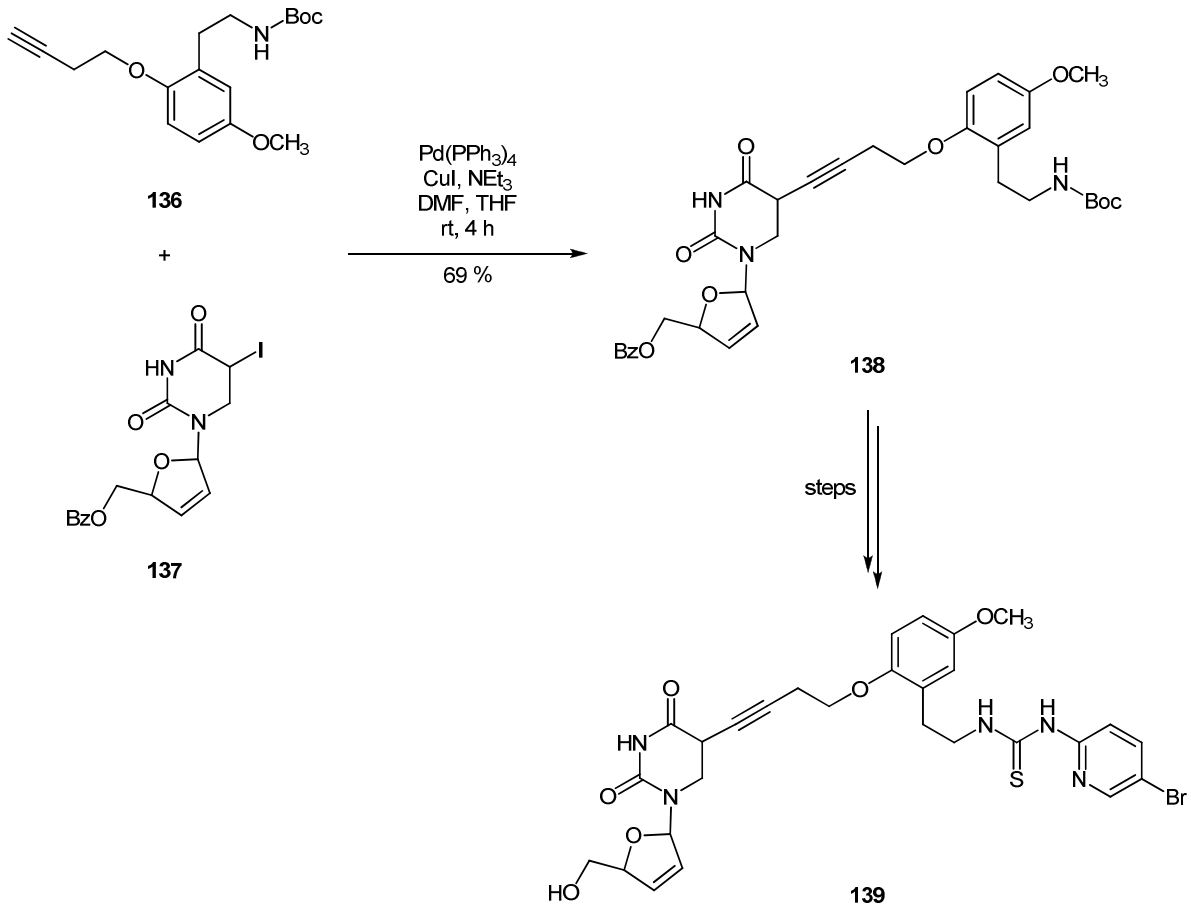
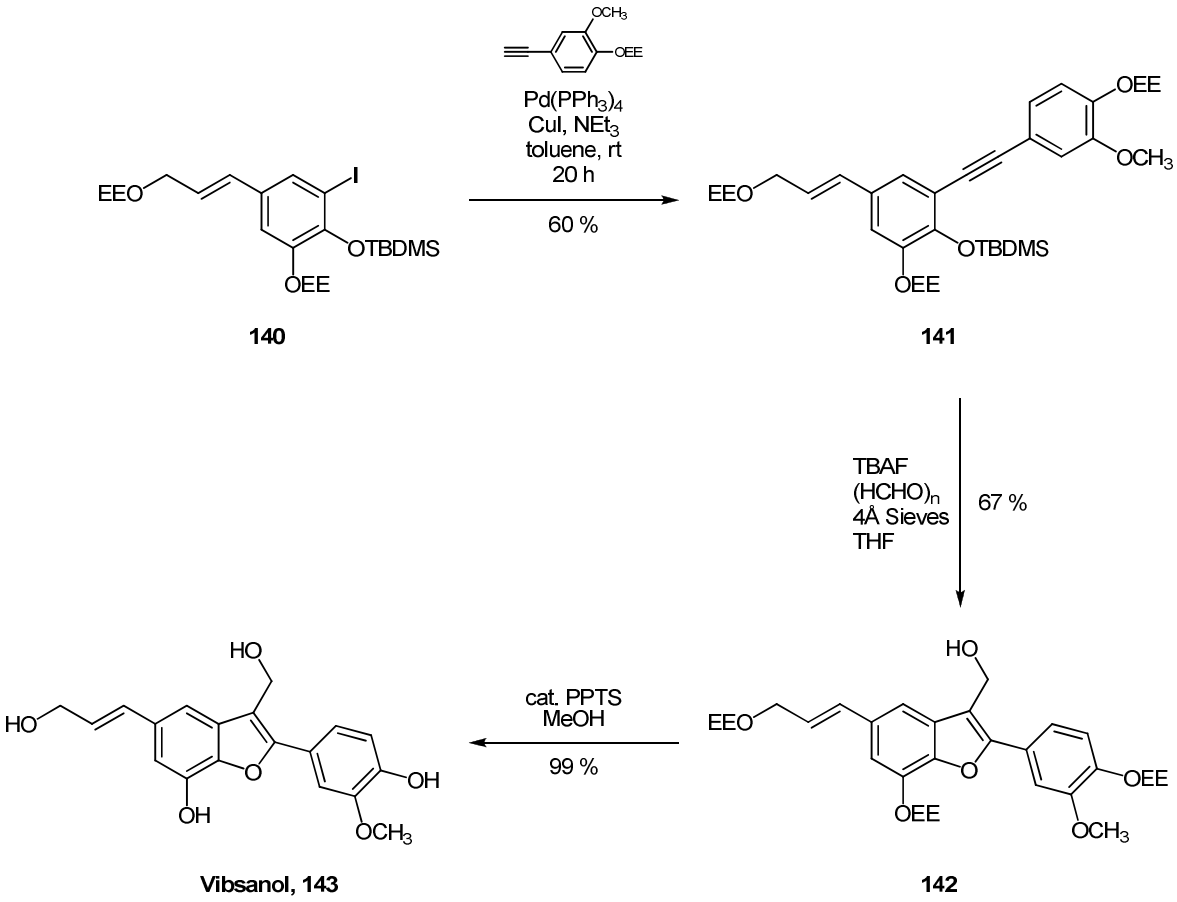


Figure 16. *Catalytic cycle for Sonogashira cross-coupling*

There are many literature examples citing the use of the Sonogashira reaction as a pivotal step in the synthesis of compounds of, for example, pharmacological interest.[187a-j] For example, the synthesis of reverse-transcriptase inhibitor **139** (Scheme 50)[187a] and the synthesis of Vibsanol **143** (Scheme 51)[187c] both employed Sonogashira methodology as a main synthetic step.

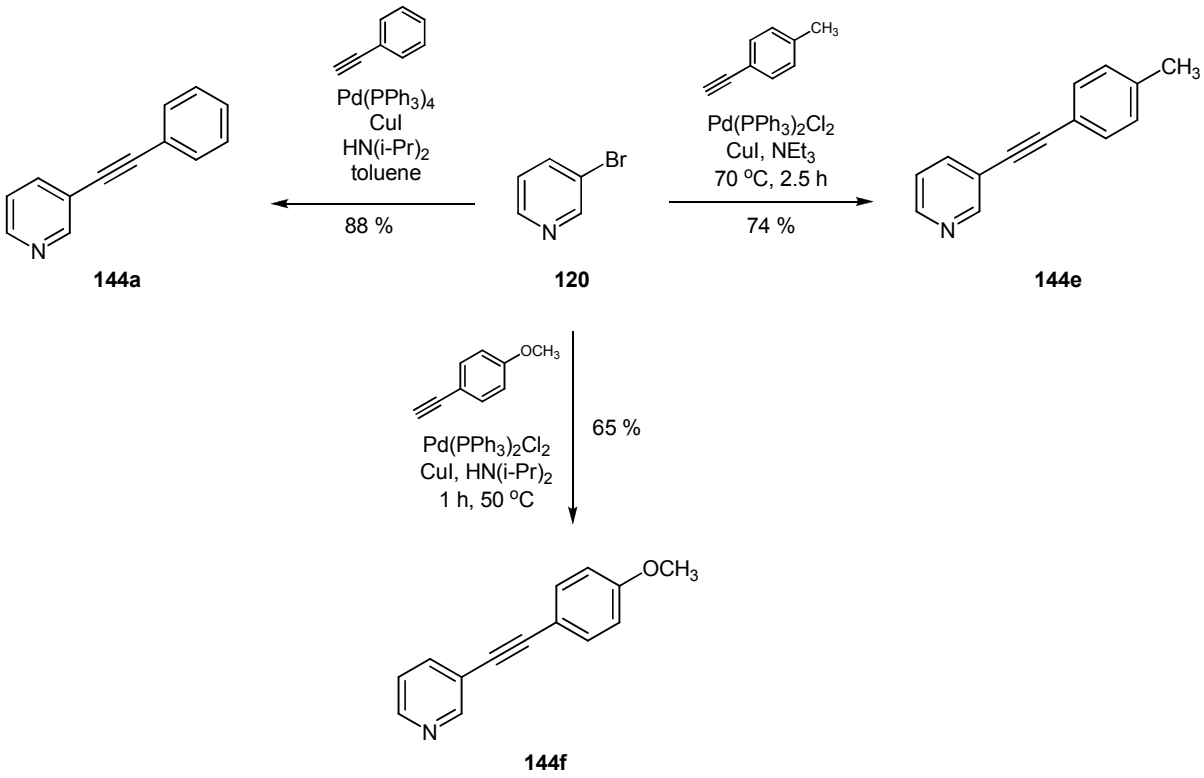


Scheme 50.



Scheme 51.

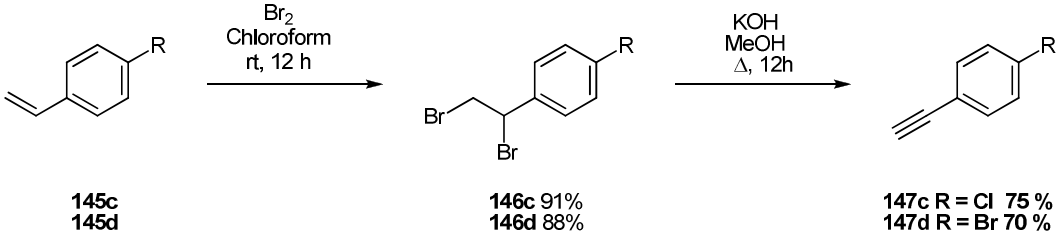
Additionally, Sonogashira reactions of 2-bromopyridine,[184a,b,188,189] 3-bromopyridine[190-192] and 4-bromopyridine[189] have been reported. Notably for this project, **144a**,[190] **144f**[192] and **144e**,[191] have been synthesised using Sonogashira methodology from 3-bromopyridine **120** in good yield (Scheme 52).



Scheme 52.

3.1.2.1.3 Results and Discussion

Terminal alkynes **147a,e,f** were available commercially and were relatively inexpensive; others of interest, **147c** and **147d**, could also be purchased commercially but were, however, somewhat more expensive. In this work, compounds **147c** and **147d** were prepared in two steps from the significantly cheaper 1-chloro-4-vinylbenzene **145c** and 1-bromo-4-vinylbenzene **145d**, respectively, as starting reagents by modification of a literature procedure (Scheme 53).[193] Thus, bromination of **145c,d** in chloroform followed by base-catalysed dehydrobromination at elevated temperature gave terminal alkynes **147c** and **147d**, which were readily purified by fractional distillation (83 % and 79 % yield, respectively, over two steps).



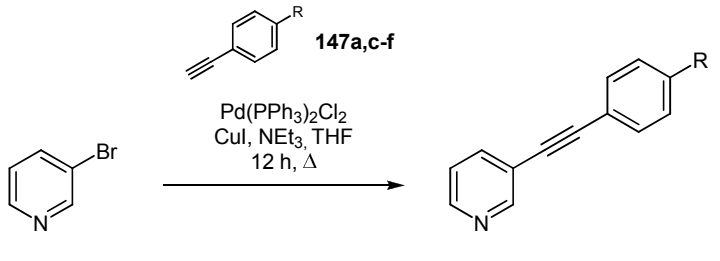
145c
145d

146c 91%
146d 88%

147c R = Cl 75 %
147d R = Br 70 %

Scheme 53.

The synthesis of acetylene **147a** (R = H) was initially investigated through Sonogashira cross-coupling of **120** with **147a** in the presence of ($Pd(PPh_3)_2Cl_2$ (5 mol.%, CuI (2 mol.%), NEt_3 (1.5 equiv.) in THF at room temperature (40 % yield). No by-products were ever witnessed in the reaction mixture, with only starting materials and product being detected by TLC. Elevation of the reaction temperature (to reflux) gave an improved conversion, with **144a** isolated in 72% yield. Compounds **144c-f** were similarly prepared in acceptable yields (20 – 98 %) (Scheme 54). In contrast, it is notable that for reaction of **120** with **147d**, despite repeated attempts and wide-ranging modification to the reaction conditions, a maximum isolated yield for **144d** of 20 % was only ever achieved the remainder being a complex mixture of unidentified side products.

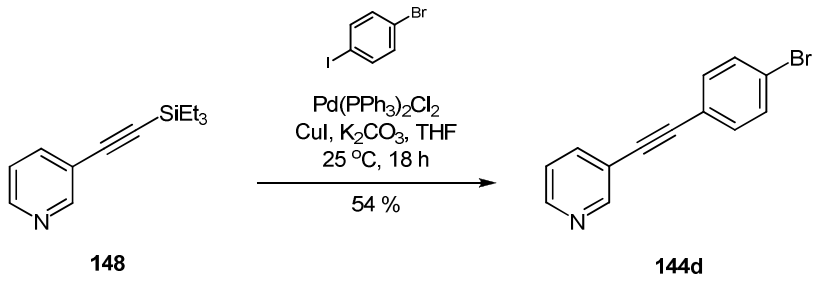


120

144a R = H, 72%
144c R = Cl, 41%
144d R = Br, 20 %
144e R = CH_3, 98%
144f R = OCH_3, 63%

Scheme 54.

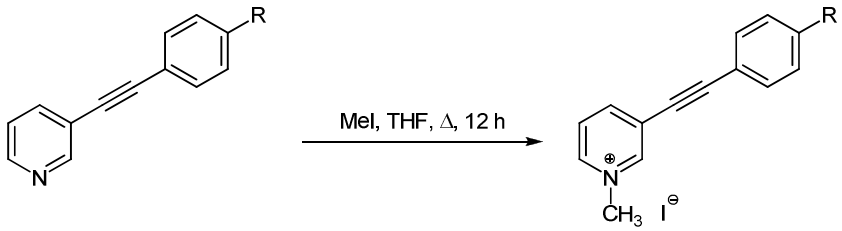
As an improvement, however, when commercially available 3-((triethylsilyl)ethynyl)pyridine **136** was stirred with 1-bromo-4-iodobenzene in the presence of ($Pd(PPh_3)_2Cl_2$ (4 mol.%, CuI (2 mol.%), K_2CO_3 (3 equiv.) in THF at room temperature for 18 h, **144d** was obtained in an unoptimised yield of 54 % (Scheme 55). Notably, alongside the reaction product, only unreacted starting materials were recovered from the reaction mixture, suggesting that an improved yield of **144d** may be achievable by modification of the reaction conditions (for example, by raising the reaction temperature or by employing a stronger base).



148 **144d**

Scheme 55.

Efficient *N*-methylation of the acetylenes **144a,c-f** to give pyridinium salts **149a,c-f** (Scheme 56) was demonstrated by simply refluxing overnight in THF in a sealed vessel with 5 equivalents of iodomethane (72 – 97 % yields).

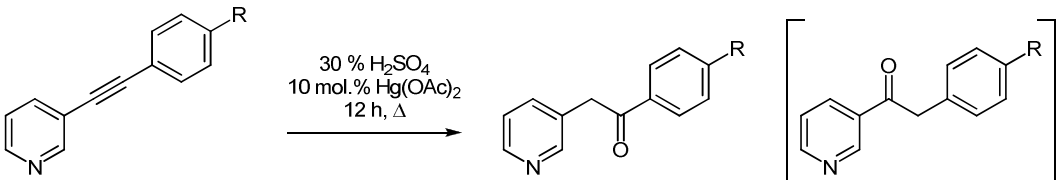


144a R = H
144c R = Cl
144d R = Br
144e R = CH_3
144f R = OCH_3

149a R = H, 77%
149c R = Cl, 86%
149d R = Br, 97 %
149e R = CH_3, 78%
149f R = OCH_3, 72%

Scheme 56.

Hydration of alkynes **144a,c-f** [30 % H_2SO_4 , 10 mol.% $Hg(OAc)_2$, reflux, 12 h] proceeded smoothly and in good yield (Scheme 57) to afford, after work-up and purification, the corresponding ketones **78a,c-f** (66 - 77 % isolated yields). In all cases, no evidence for the alternate regioproduct **150** was ever observed during hydration reactions. Hydration reactions of **144a,c-f** to give **78a,c-f** could also be accomplished under analogous reaction conditions in the absence of $Hg(OAc)_2$, although in slightly reduced yield. This may be of particular importance for future development purposes, as the synthesis of pharmaceuticals using mercury salts is undesirable.



144a R = H
144c R = Cl
144d R = Br
144e R = CH_3
144f R = OCH_3

78a R = H, 77%
78c R = Cl, 71%
78d R = Br, 74%
78e R = CH_3, 66%
78f R =O CH_3, 69%

150a R = H
150c R = Cl
150d R = Br
150e R = CH_3
150f R = OCH_3

Scheme 57.

3.1.2.1.4 Summary

In conclusion, this section of work demonstrates an alternative synthetic approach to that detailed in Chapter 2 for the preparation of ketones **78a,c-f** using a palladium catalysed cross-coupling reaction of 3-bromopyridine **120** with various terminal alkynes **147a,c-f**, followed by acidic hydrolysis. However, for the synthesis of ketones **78a,c-f**, this two-step methodology presents no distinct advantage over the reaction of (pyridin-2-ylmethyl)lithium with arylnitriles described in Chapter 2. Notably, (i) an additional synthetic step is required; (ii) the combination of starting reagents is significantly more expensive; and, (iii) relatively few terminal alkynes are available commercially. However, the methodology developed has proven important for the synthesis of other novel 3-substituted and 3,5-disubstituted pyridine derivatives (Chapter 4).

3.1.2.2 Heck Coupling Reactions of 3-Bromopyridine

This section describes our investigation of Heck cross-coupling reactions of 3-bromopyridine **120** with a range of 4-substituted arylalkenes **145a-e** to give (*E*)-3-(1-(4-substitutedphenyl)ethen-2-yl)pyridine derivatives **159a-e**, another series of unsaturated derivatives which may have intrinsic value as pharmacologically active compounds. More significantly using **159a-e**, functional group interconversion has the potential to deliver novel derivatives appropriate for pharmacological testing as nicotinic receptor antagonists.

3.1.2.2.1 Introduction

The Heck reaction is the palladium-catalysed arylation or alkenylation of olefins (Figure 17).[194]

As with the Sonogashira approach described above, the Heck reaction is well known and there are again many literature examples citing the use of the Heck reaction as reaction steps in the preparation of compounds of, for example, pharmacological interest.[195]

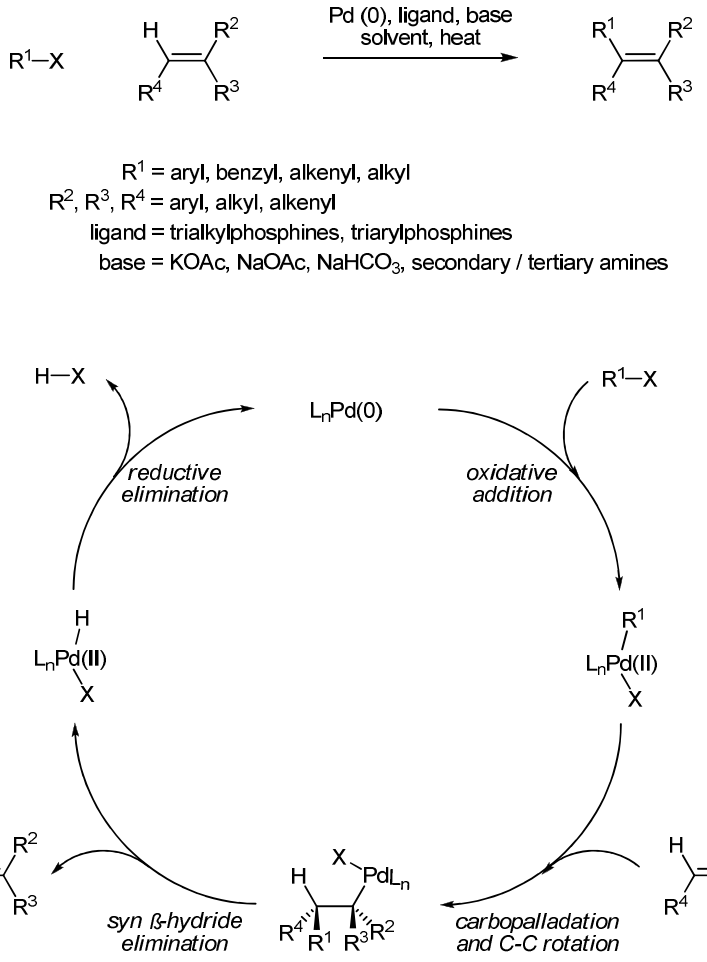
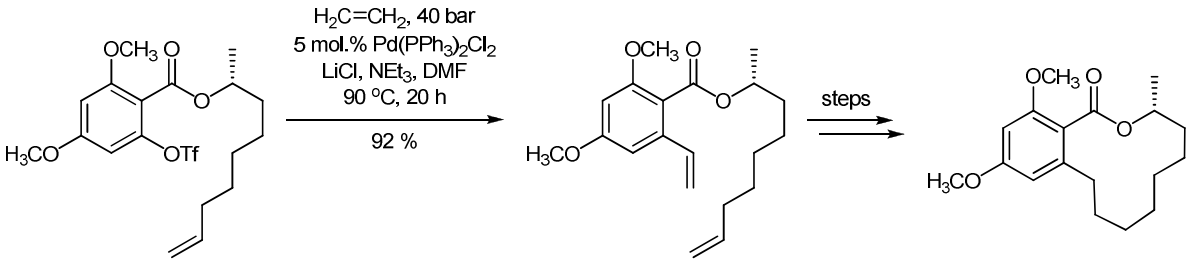
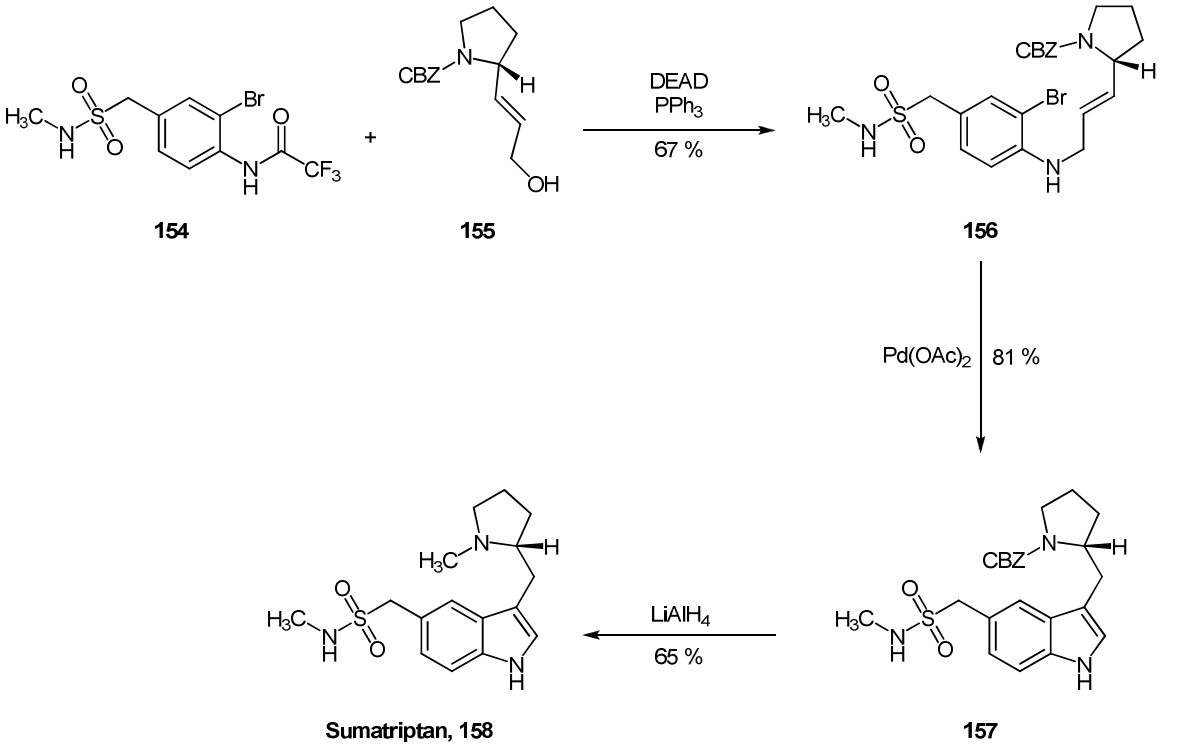


Figure 17. *Heck catalytic cycle*

Schemes 58 and 59 illustrate steps in the synthesis of lasiodiplodin[195a] **153** and sumatriptan[195b] **158** which possess anti-cancer and anti-migraine activity respectively.

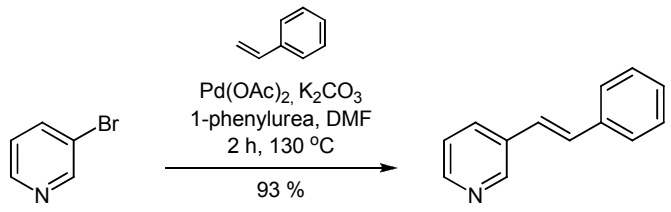


Scheme 58.



Scheme 59.

A number of Heck reactions using 3-bromopyridine as a substrate have been reported.[196a-d] Significant to this project is the synthesis of **159a** obtained in excellent yield (93 %) by Cui *et al.* (Scheme 60).[197]



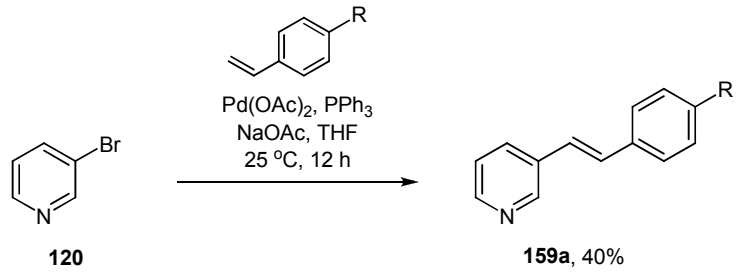
120 **159a**

Scheme 60.

3.1.2.2.2 Results and Discussion

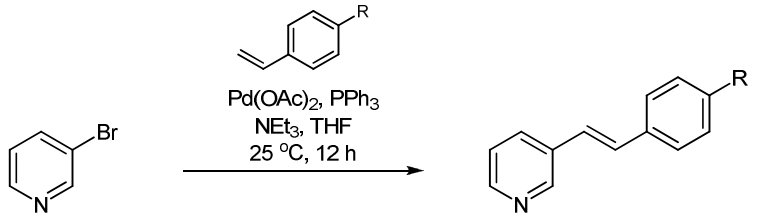
An initial reaction Heck reaction using 3-bromopyridine **120** was carried out based on the reaction conditions of a literature example;[198] thus reaction of 3-bromopyridine **120** with the inexpensive, styrene **145a** [$Pd(OAc)_2$ (1 mol%), PPh_3 (2 mol%) KOAc (1.5 Equiv.)] in THF at room temperature gave, after purification, alkene **159a** (40 % yield) (Scheme 61). As with the Sonogashira reaction, the yield was further improved (54 %) by repeating the reaction at reflux. When dry triethylamine replaced the relatively insoluble potassium acetate (under the same reaction conditions) compound **159a** was obtained in 70% yield. These conditions were subsequently adopted to give a series of (*E*)-3- (1-(4-substituted-phenyl)eth-1-en-2-yl)pyridine derivatives **159a-e** (43 – 70 % yield) (Scheme 62). For compounds **159a-e**, a trans orientation for the alkene

was confirmed by the ^{3}J coupling constant of the ethenylic protons (15-18 Hz).



120 **159a**, 40%

Scheme 61.

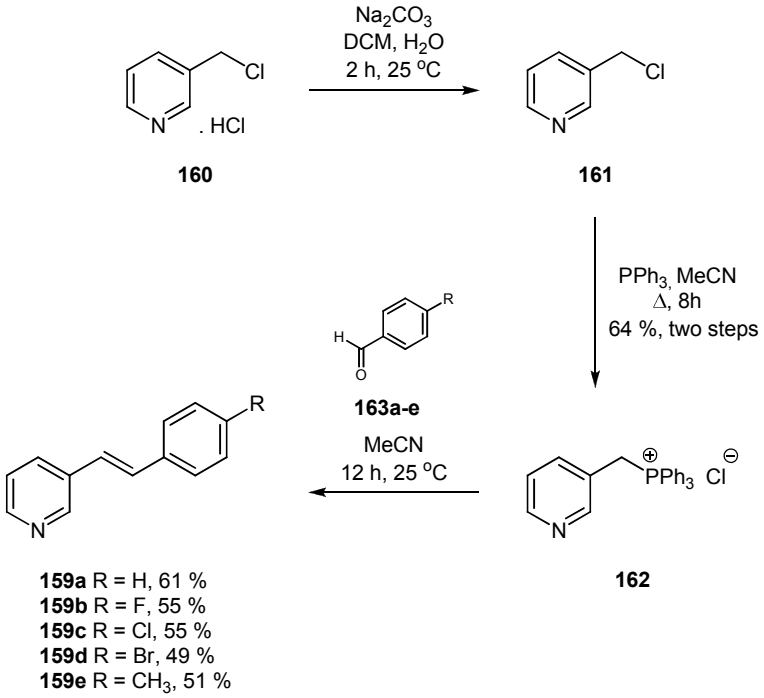


120

159a R = H, 70%
159b R = F, 55%
159c R = Cl, 65%
159d R = Br, 51 %
159e R = CH_3, 43%

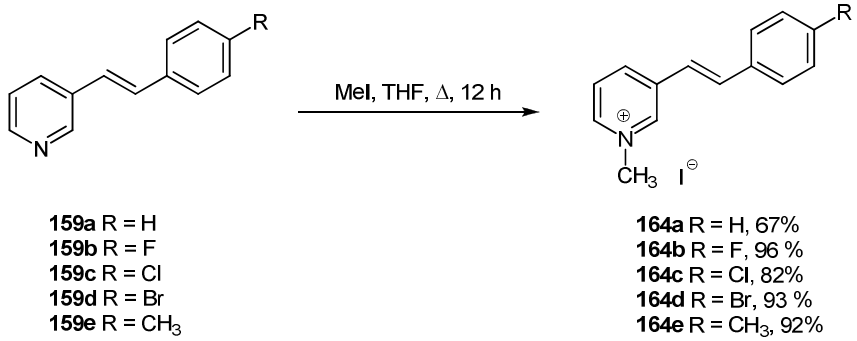
Scheme 62.

A similarly efficient, but potentially more cost effective route into alkenes **159a-e** was also explored, *via* a Wittig reaction (Scheme 63). The commercially available 3-(chloromethyl)pyridine hydrochloride salt 1**60** was first converted to the unstable free base **161** in a biphasic system (aq. Na_2CO_3 / DCM) (95 %, crude yield). The phosphonium salt **162** was simply prepared by refluxing crude **161** with excess PPh_3 in MeCN (64 % yield).[199] Subsequent treatment of **162** with n-BuLi followed by addition of 4-substitutedbenzaldehydes **163a-e** afforded, after work-up and purification, the desired products **159a-e** (49 - 61 % yields).



Scheme 63.

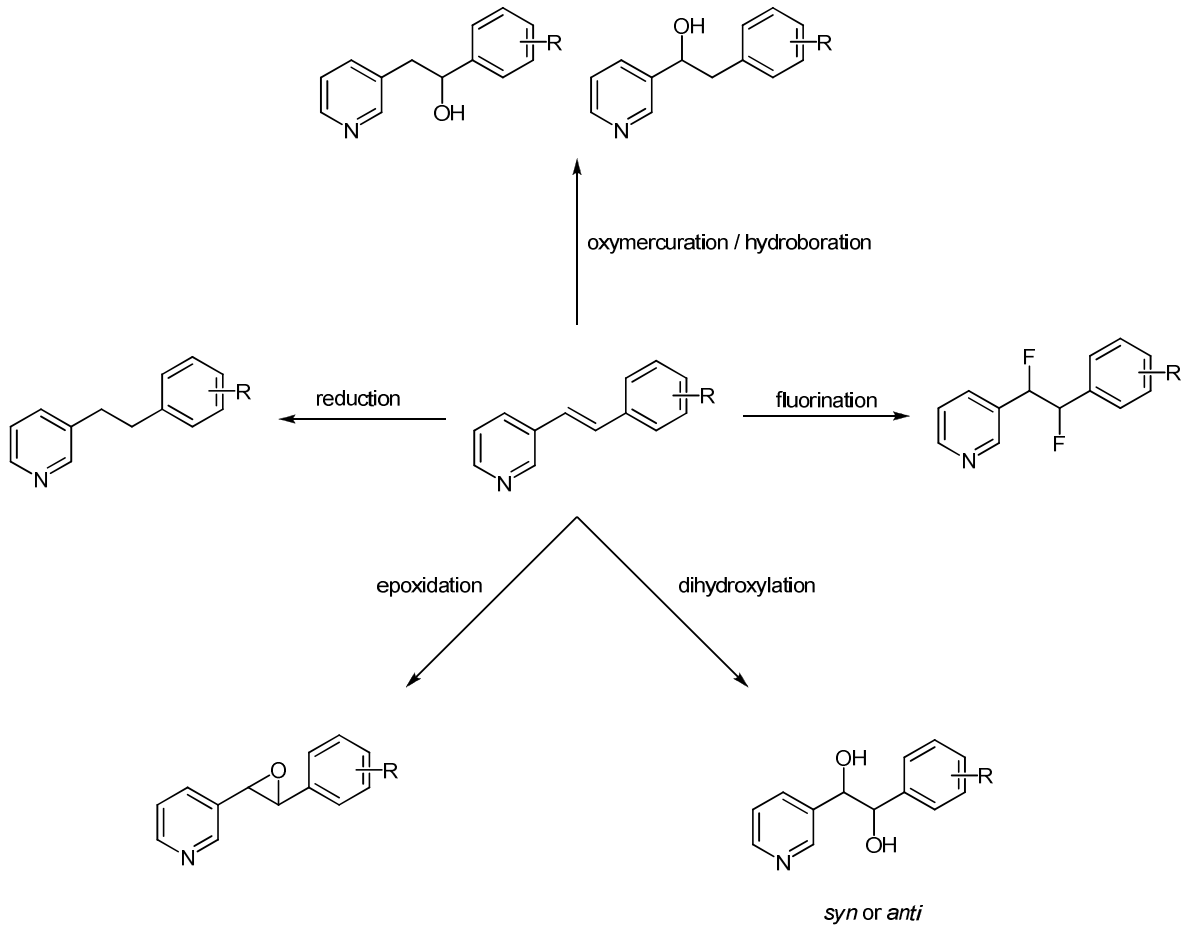
Compounds **159a-e** could be easily converted into their corresponding *N*-alkylated salts by refluxing with methyl iodide in THF (67 – 92 % yields) (Scheme 64).



Scheme 64.

3.1.2.2.3 Summary

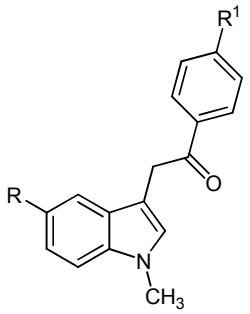
In conclusion, we have demonstrated two simple strategies to prepare alkenyl derivatives **159a-e** using either a Heck reaction or a Wittig reaction. Alkenyl derivatives **159a-e** offer a building block for the development of a wide-range of derivatives by simple functional group manipulation using established literature methodology. Scheme 65 shows a selection of transformations that have been identified for future investigation to access additional compounds with potential pharmacological application.



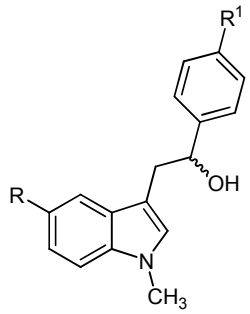
Scheme 65.

3.2 Reactions of 3-Bromo-1-methyl-1*H*-indole 154a, 3-Iodo-1-methyl 1*H*-indole 154b or 3-Iodo-5-methoxy-1-methyl-1*H*-indole 154c

Using minor adaptations of either the Sonogashira methodology or halogen-lithium exchange methodology developed above, novel indole compounds **171a-e** and **177** could be synthesised from either 3-bromo-1-methyl-1*H*-indole **169a**, 3-iodo-1-methyl-1*H*-indole **169b** or 3-iodo-5-methoxy-1-methyl-1*H*-indole **169c** as detailed in the following Section.



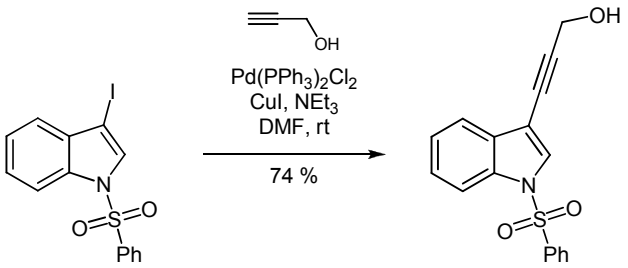
171a R = H, R^1 = H,
171b R = H, R^1 = CH_3,
171c R = H, R^1 = Cl,
171d R = OCH_3 R^1 = H,
171e R = OCH_3 R^1 = CH_3,



177 R = H, R^1 = H

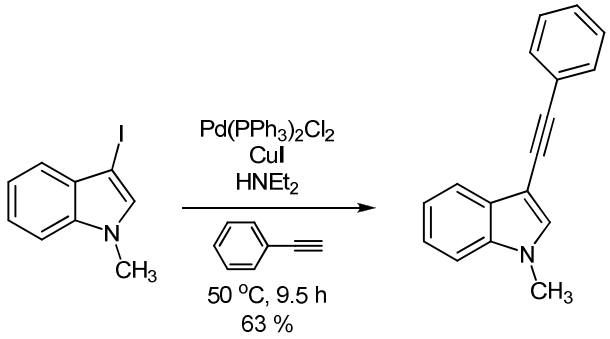
3.2.1 Sonogashira Reactions

The Sonogashira cross-coupling of indoles has, to date, not been extensively reported. The majority of report thus far involve the coupling of variously *N*-substituted 2[200,201] or 3-iodoindoles.[201,202] Two examples of the Sonogashira coupling of *N*-substituted-3-iodoindoles are given in Schemes 66[202] and 67.[201]



165 **166**

Scheme 66.

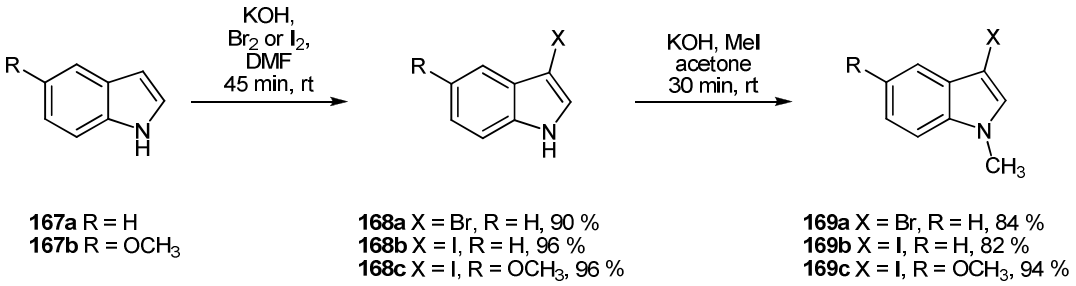


169b **170a**

Scheme 67.

Halogenated indoles **169a**, **169b** and **169c** were not available commercially and were synthesised according to the procedure of Bocchi *et al.*[203] without modification. Thus, bromination of **167a** using Br_2 in DMF / KOH at room temperature occurred in almost quantitative yield (96 %) to give 3-bromo-1*H*-indole **168a**. Subsequent *N*-methylation of **168a** occurred rapidly with MeI in acetone / KOH at room temperature to give 3-bromo-1-methyl-1*H*-indole **169a** (84 % yield). Analogously, 3-iodo-1-methyl-1*H*-indole **169b** and 3-iodo-5-methoxy-1-methyl-1*H*-indole **169c** were synthesised from indole and 5-methoxyindole, respectively, in two steps in good overall yield (Scheme 68). In our hands, **168a**, **168b** and **168c** were quite unstable, decomposing within four or five days even with refrigeration or freezing; *N*-methylation afforded some stability and

compounds **169a**, **169b** and **169c** could be successfully stored for several weeks in a freezer without significant decomposition.



167a R = H
167b R = OCH_3

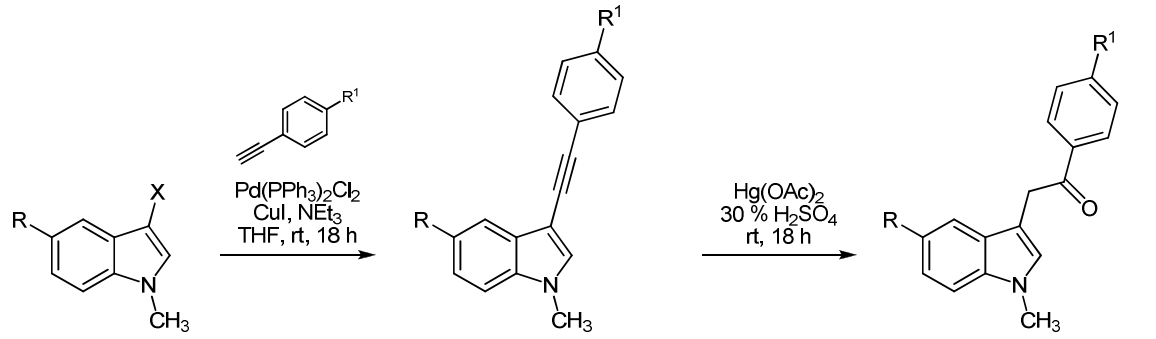
168a X = Br, R = H, 90 %
168b X = I, R = H, 96 %
168c X = I, R = OCH_3, 96 %

169a X = Br, R = H, 84 %
169b X = **I**, R = H, 82 %
169c X = **I**, R = OCH_3, 94 %

Scheme 68.

In our hands, Sonogashira reactions of 3-bromo-1*H*-indole **169a**, 3-iodo-1*H*-indole **169b** and 3-iodo-5-methoxy-1*H*-indole **169c** with arylalkynes **147a** using the methodology described in Section 3.1.2.1.3 [($Pd(PPh_3)_2Cl_2$ (5 mol.%, CuI (2 mol.%), Et_3N (3 equiv.) in THF at elevated temperature (50 °C – reflux)] gave only negligible yields of the desired products (typically < 5%). In these reactions, significant decomposition of the indoles **151a-c** was observed (consistent with the storage problems noted above) producing highly complex reaction mixtures. Analogous reaction of 3-bromo-1-methyl-1*H*-indole **169a** with arylalkyne **147a** at room temperature proceeded sluggishly, affording alkyne **171a** in 41 % yield after 2 days. However, when employing the more reactive 3-iodo-1-methyl-1*H*-indole **169b** and 3-iodo-5-methoxy-1-methyl-1*H*-indole **169c** with arylalkynes **147a,c,e** reactions proceeded cleanly at room temperature to give acceptable yields of 58 - 81 % in 12 h (Scheme 69). Hydration of the alkynes **170a-e** using 10 mol.% $Hg(OAc)_2$ in 30% H_2SO_4 at room temperature gave, after work-up and purification, ketones **171a-e** in good

yield (57 - 91 %). Hydration of alkynes **170a-e** at elevated temperature gave only poor yields of ketones **171a-e** (typically < 10 %); in these reactions, significant decomposition was noted.



169b X = I, R = H
169c X = I, R = OCH_3

170a R = H, R^1 = H, 79 %
170b R = H, R_1 = CH_3, 81 %
170c R = H, R_1 = Cl, 58 %
170d R = OCH_3, R_1 = H, 81 %
170e R = OCH_3, R_1 = CH_3, 61 %

171a R = H, R_1 = H, 61 %
171b R = H, R_1 = CH_3, 91 %
171c R = H, R_1 = Cl, 57 %
171d R = OCH_3 R_1 = H, 72 %
171e R = OCH_3 R_1 = CH_3, 69 %

Scheme 69.

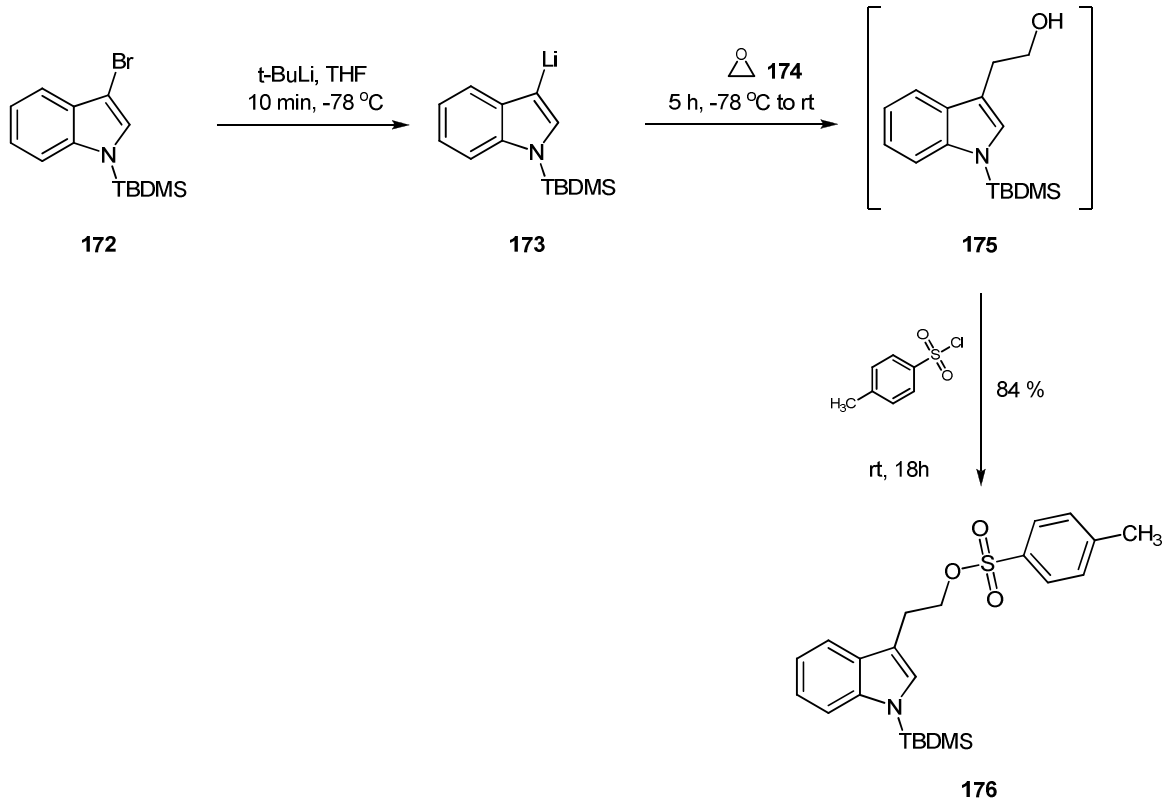
Thus, using only a minor modification to methodology developed in Section 3.1.2.1, we were able to convert **170a-e** into ketones **171a-e** in two-steps. Unfortunately, however, attempts at hydride reduction (sodium borohydride in ethanol at room temperature or reflux; lithium aluminium hydride in diethyl ether at room temperature or reflux) of ketones **171a-e** gave none of the expected alcohol products. In all cases, ketone starting materials were recovered unchanged. Further work is required to establish whether the reduction of **171a-e** to give alcohol products is possible.

3.2.2 Halogen-lithium Exchange of 1-Methyl-3-bromo-1*H*-indole

As reduction of ketones **171a-c** was not successful in our hands, we considered a halogen-lithium exchange of 1-methyl-3-bromo-*1H*-indole **169a** followed by ring-opening of aryl epoxides.

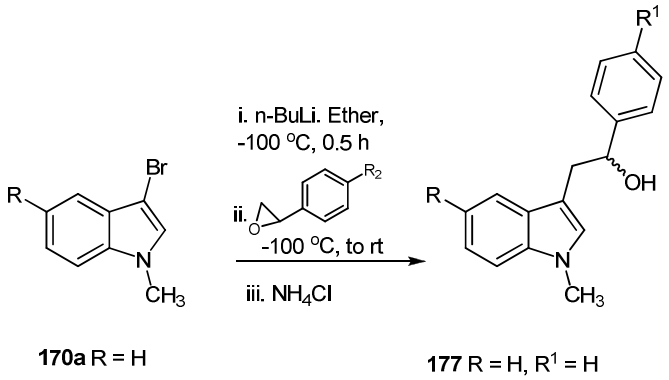
To our knowledge, no halogen-lithium exchange reactions of 1-methyl-3-bromo-*1H*-indole have been reported to date. However, there are several reports detailing the halogen-lithium exchange reaction of 3-bromo-*N*-silylprotected indoles and subsequent reaction of the generated organolithium with, for example, amides,[204] aldehydes[205] esters[204a] or alkylating agents.[204a]

Notably, the first step in their synthesis of the sulphonic acid derivative **176** Ma *et al.*[206] described the bromine-lithium exchange of **173** using t-BuLi, followed by ring-opening of oxirane **174** to give the primary alcohol **175** which was then reacted *in situ* to give the tosyl derivative **176** in 84 % overall yield (Scheme 70).



Scheme 70.

Employing the methodology established for halogen-lithium exchange using 3-bromopyridine as substrate (Chapter 3.1.1), we were able to demonstrate the synthesis of alcohol **177** by treatment of **169a** with n-BuLi at -100 °C and subsequent addition of phenyloxirane (Scheme 71). Alcohol derivative **177** was obtained in an unoptimised yield of 22 % after work-up and purification. Additional work is required to determine optimum conditions so that this reaction may be further extended to use a range of arylepoxides as electophiles.



170a R = H

177 R = H, R^1 = H

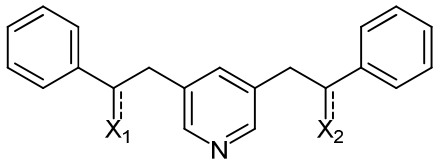
Scheme 71.

3.2.3 Summary

In summary we have successfully prepared indole derivatives **171a-e** and **177** using minor adaptations of the Sonogashira and alkyne hydrolysis methodology developed in Chapter 3.1.1.2. Hydride reduction of ketones **171** was, unfortunately, unsuccessful and additional work is required to develop halogen-lithium exchange reactions using 3-bromo-1-methyl-1*H*-indole as substrate as an alternative approach to analogues of alcohol **177**.

Chapter 4

After establishing robust synthetic approaches to a range of 3-substituted pyridine analogues with potential pharmacological activity as described in Chapters 2 and 3, we next turned our attention to developing these methodologies for the synthesis of 3,5-disubstituted pyridine derivatives typified by the general stuctures given in Figure 18. It should be noted that attempts to prepare these compounds *via* lithiation methodology using 3,5-dimethylpyridine as a starting reagent were unsuccessful in our hands (Chapter 2.3). This Chapter details our approaches to prepare 3,5-disubstituted derivatives using the commercially available 3,5-dibromopyridine **178** as starting reagent.



X^1 = OH, X^2 = OH
X^1 = O, X^2 = O
X^1 = OH, X^2 = O

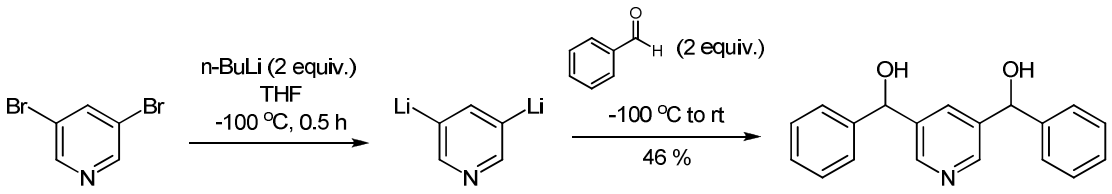
Figure 18.

4.1 Halogen-Lithium Exchange Reactions of 3,5-Dibromopyridine

4.1.1 Introduction

Very few examples exist in the literature for the formation of pyridin-3,5-yldilithium **179** by halogen-lithium exchange using 3,5-dibromopyridine **178** as substrate. Encouragingly, however, Mysliborski *et al.*[207] recently described a successful bis(halogen-lithium) exchange reaction of 3,5-

dibromopyridine with n-BuLi in THF, followed by reaction with benzaldehyde as electrophile to give the bis(alcohol) **180** (46 %) (Scheme 72).

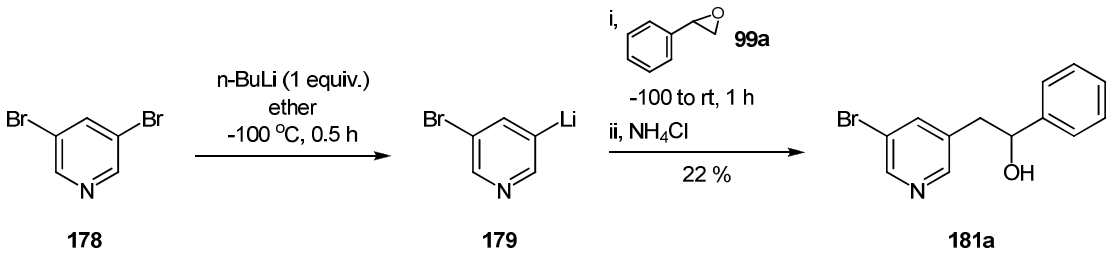


178 **179** **180**

Scheme 72.

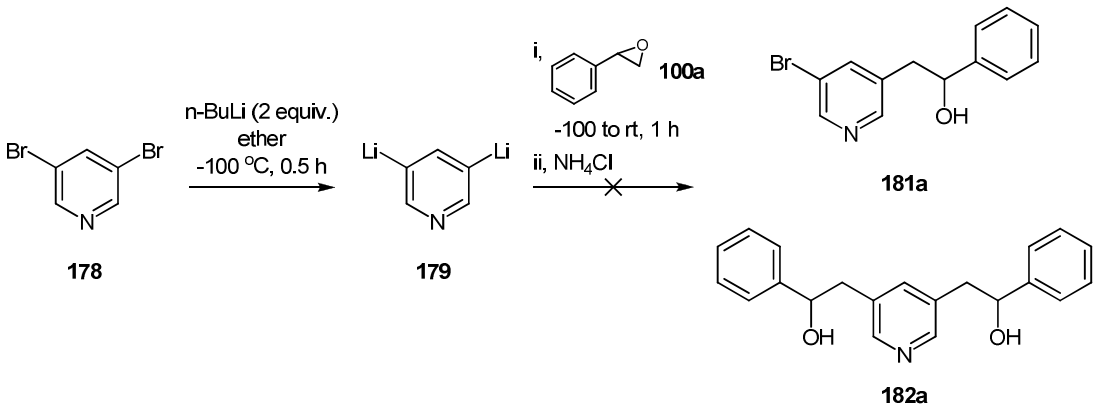
4.1.2 Results and Discussion

Attempted bromine-lithium exchange reaction of 3,5-dibromopyridine **178** using 1 equiv. n-BuLi in toluene at both -60 °C and -100 °C (solubility issues were noted at this lower temperature), followed by addition of 1 equiv. of epoxide **100a** (revisiting the methodology employed for the synthesis of alcohols **75a-e** in Chapter 3.1.1.2) gave only a highly complex mixture of starting materials and products from which no identifiable reaction products could be isolated. However, by performing a similar reaction at -100 °C in diethyl ether we were able to isolate, after work-up and purification of the complex reaction mixture, the desired mono(alcohol) **181a**, in an unoptimised 22 % yield (Scheme 73). Unfortunately, no other reaction products could be identified.



Scheme 73.

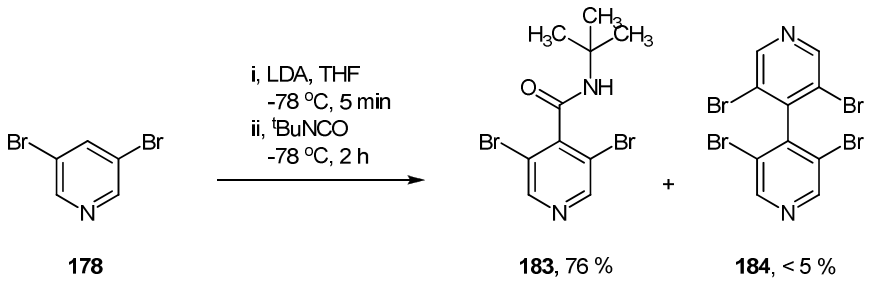
Perhaps not surprisingly, in an attempt to prepare and react pyridin-3,5-yldilithium **179** by first treating **178** with 2 equiv. of n-BuLi at -100 °C in diethyl ether followed by addition of 2 equiv. epoxide **100a**, neither bis(alcohol) **182a** (GC/MS evidence) or even mono(alcohol) **181a** were ever witnessed after work-up; again, only a complex mixture of starting materials and unidentified products was obtained (Scheme 74). Further reactions were not attempted.



Scheme 74.

There is literature precedent for *ortho*-lithiation at the 4-position of 3,5-dibromopyridine using LDA and subsequent reaction with a range of electrophiles (*e.g.* Scheme 75);[208] it is possible that similar *ortho*-lithiations

complicated the reactions of 3,5-dibromopyridine with n-BuLi, thus leading to the observed complex reaction mixtures.



Scheme 75.

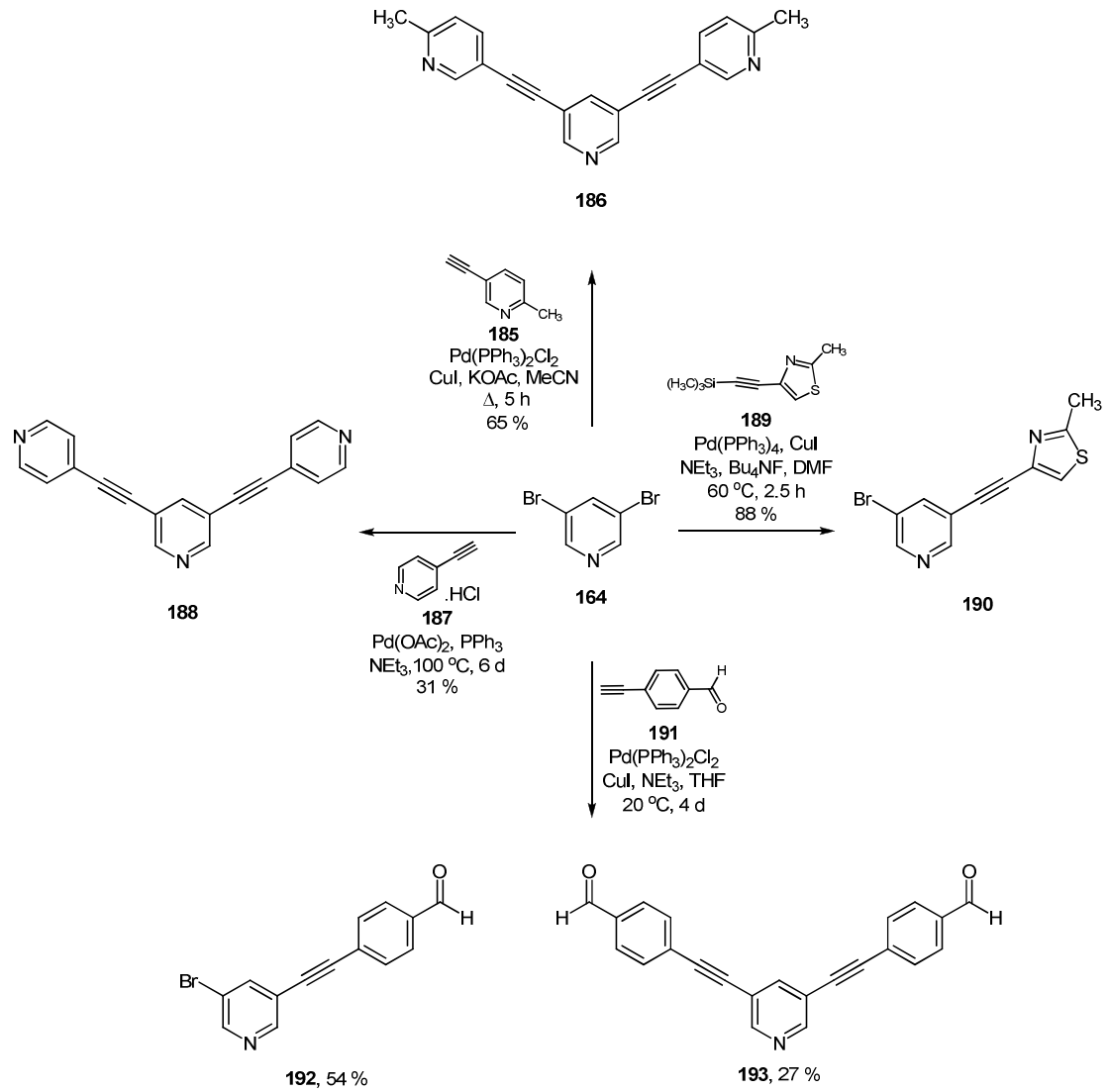
4.2 Sonogashira Reactions of 3,5-Dibromopyridine

4.2.1 Introduction

In light of the results achieved in this project using the Sonogashira cross-coupling reaction of 3-bromopyridine **120** and arylalkynes **147a,c-f** and subsequent acid-catalysed hydration of the products **144a,c-f** to give ketones **78a,c-f** (Chapter 3), this methodology was further investigated using 3,5-dibromopyridine as a substrate. We envisaged that this could offer an adaptable route from which a number of novel 3,5-substituted pyridine derivatives with varying functionality could be derived.

To our knowledge, reports of Sonogashira cross-coupling of 3,5-dibromopyridine **178** in the literature are limited; relevant examples are given in Scheme 76. Karchava *et al*.[209] and Yamamoto *et al*.[210] described the coupling of 2-methyl-5-ethynylpyridine **185** and 4-ethynylpyridine hydrochloride **187** with **178** to give the bis(alkynes) **186** and **188**,

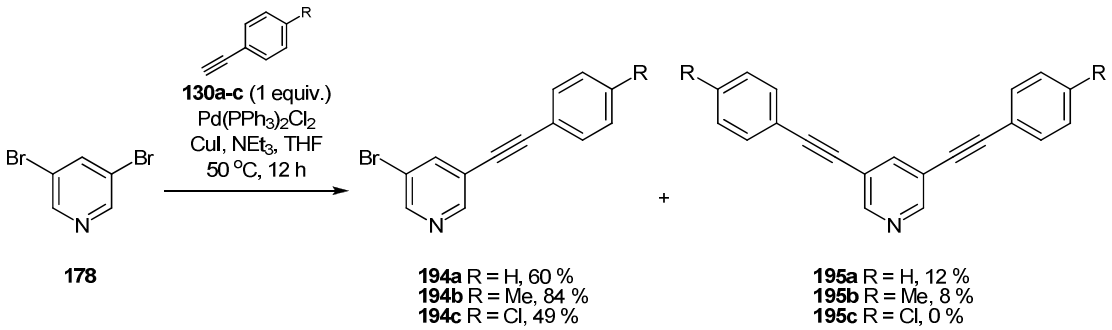
respectively. Rajadurai *et al*.[211] synthesised the mono(alkyne) **192** in acceptable yield by Sonogashira coupling of 4-ethynylbenzaldehyde **191** with **178**, however, this group also obtained a significant amount of the corresponding bis(alkyne) **193**. More recently, Roppe *et al*. reported the synthesis of the glutamate receptor antagonist **190** in excellent yield; noteworthy in this report is the Bu_4NF mediated *in situ* demasking of the terminal alkyne **189**.[212]



Scheme 76.

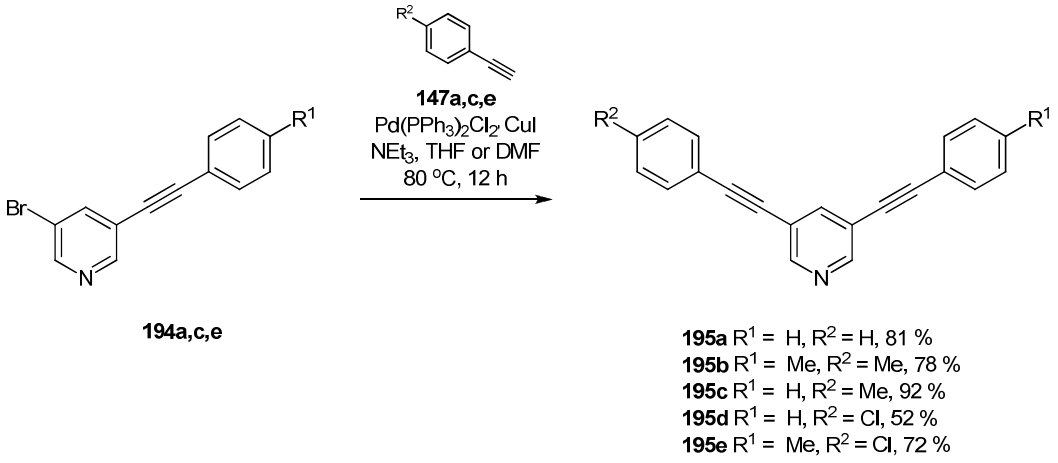
4.2.2 Results and Discussion

The pivotal intermediates **194a-c** were readily synthesised, alongside some bis(alkyne) **195**, by the Sonogashira cross-coupling of 3,5-dibromopyridine **178** with 1 equiv. of arylalkynes **147a,c,e** in the presence of $Pd(PPh_3)_2Cl_2$ (4 mol.%), CuI (2 mol.%), Et_3N (3 equiv.) in THF at 50 °C (Scheme 77). It is notable that, even when these reactions were performed at room temperature with less than 1 equiv. of arylalkynes, some bis(alkyne) **195** was usually always obtained (typically ~ 10%).



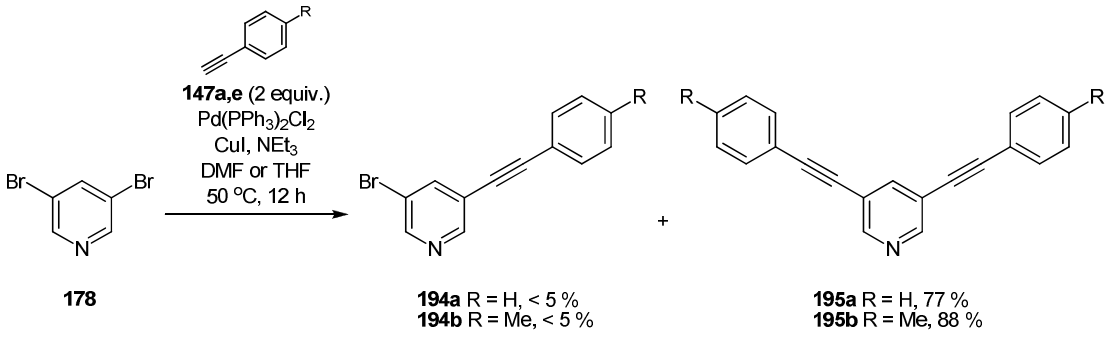
Scheme 77.

The isolated mono(alkynes) **194a-d** were readily converted to the symmetrical or asymmetrically substituted bis(alkynes) **195a-e** by a further Sonogashira coupling reaction at elevated temperature in either THF or DMF (80 °C) (52 – 92 % yields) (Scheme 78, Method A). Analogous reactions performed at temperatures below 80 °C gave somewhat lower isolated yields (in the range of 50 - 60 %) and no improvement in isolated yield was noted at reaction temperatures above 80 °C.



Scheme 78.

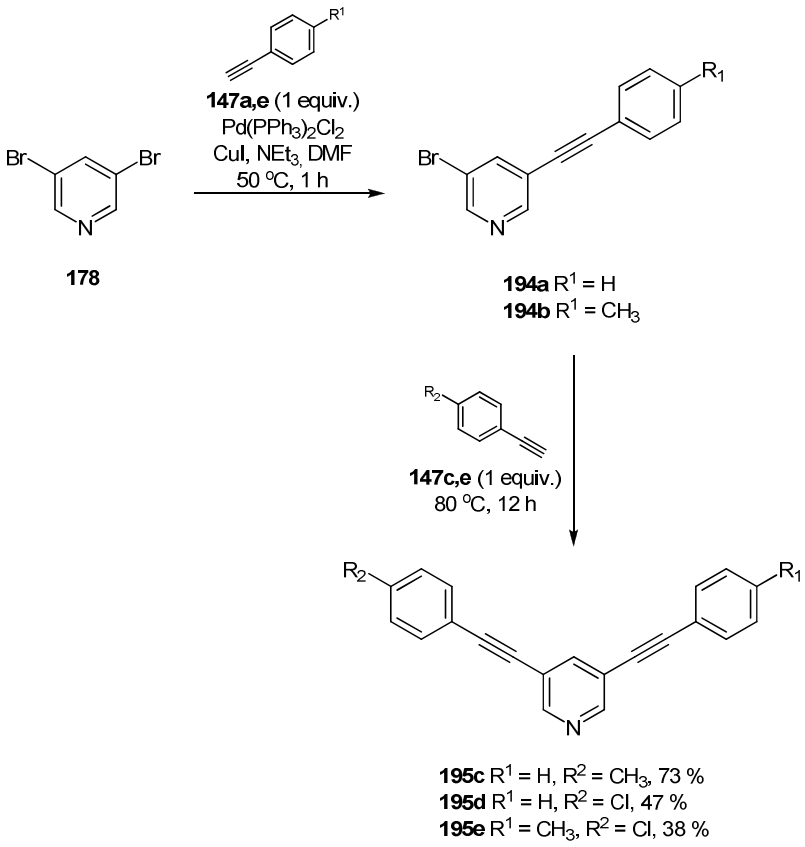
As expected, the symmetrically substituted bis(alkynes) **195a** and **195b** were easily obtained in one step under Sonogashira conditions by cross-coupling of 3,5-dibromopyridine **178** with 2 equiv. of arylalkynes **147a,e** in the presence of $Pd(PPh_3)_2Cl_2$ (5 mol.%), CuI (2 mol.%), Et_3N (3 equiv.) in THF or DMF at 80 °C (Scheme 79, Method B). In these reactions, only trace amounts of the mono(alkyne) **194** was ever isolated (< 5 %).



Scheme 79.

Additionally, we were able to achieve the synthesis of asymmetrically substituted bis(alkynes) **195c-e** using a two-step 'one-pot' methodology

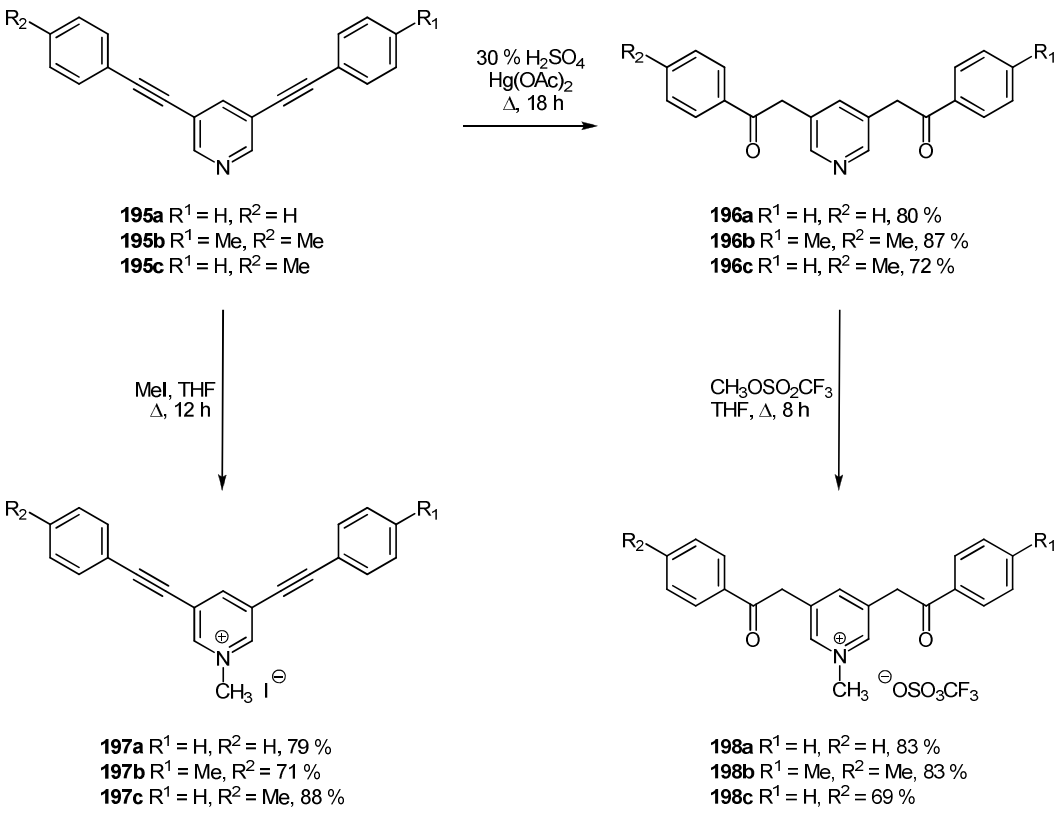
(Scheme 80, Method C). Interestingly, symmetrically substituted bis(alkynes) **195a** and **195b** were not observed and, therefore, complications in purification were not encountered. Yields obtained *via* this approach were comparable to those achieved by a second Sonogashira coupling reaction of the isolated mono(alkyne) (Scheme 78). This 'one-pot' strategy is advantageous in terms of reduced reaction and purification times and also in terms of cost (the quantity of expensive palladium catalyst employed can be reduced).



Scheme 80.

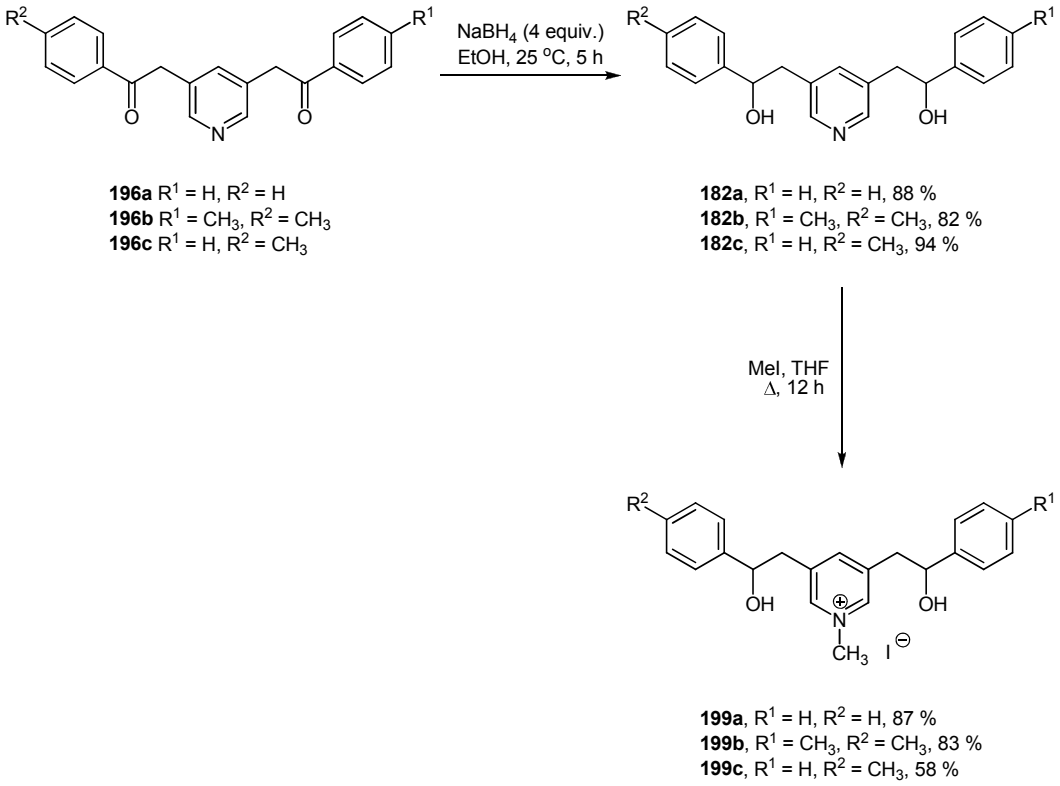
Bis(alkynes) **195a-c** were key compounds for the preparation of bis(ketones) **196a-c**, (bis)alcohols **182a-c** and their respective alkylated derivatives **198a-c** and **183a-c** (Schemes 81 and 82). *N*-Alkyation of

bis(alkynes) **195a-c** with excess methyl iodide in refluxing THF furnished salts **197a-c** in good yield. Hydration of bis(alkynes) **195a-c** into their corresponding bis(ketones) **195a-c** was readily accomplished by refluxing in 30 % $^{w}/_{v}$ H_2SO_4 in the presence of 10 mol.% $Hg(OAc)_2$ (no alternative regioisomeric products were obtained). In our hands, *N*-alkylation of bis(ketones) **196a-c** using excess methyl iodide in refluxing THF gave, on each occasion attempted, a semi-solid product which we were unable to sufficiently purify for elemental analysis. However, *N*-alkylation of bis(ketones) **196a-c** proceeded smoothly by reaction at elevated temperature with methyl trifluoromethanesulfonate to afford trifluoromethanesulfonate salts **198a-c** in good yield (69 - 83 %).



Scheme 81.

As expected, bis(ketones) **196a-c** underwent smooth hydride reduction using 4 equiv. of $NaBH_4$ in EtOH at room temperature to afford bis(alcohols) **182a-c** in high yield; subsequent *N*-methylation of **182a-c** with excess methyl iodide in refluxing THF led to the pyridinium derivatives **199a-c** (Scheme 82).



196a R^1 = H, R^2 = H
196b R^1 = CH_3, R^2 = CH_3
196c R^1 = H, R^2 = CH_3

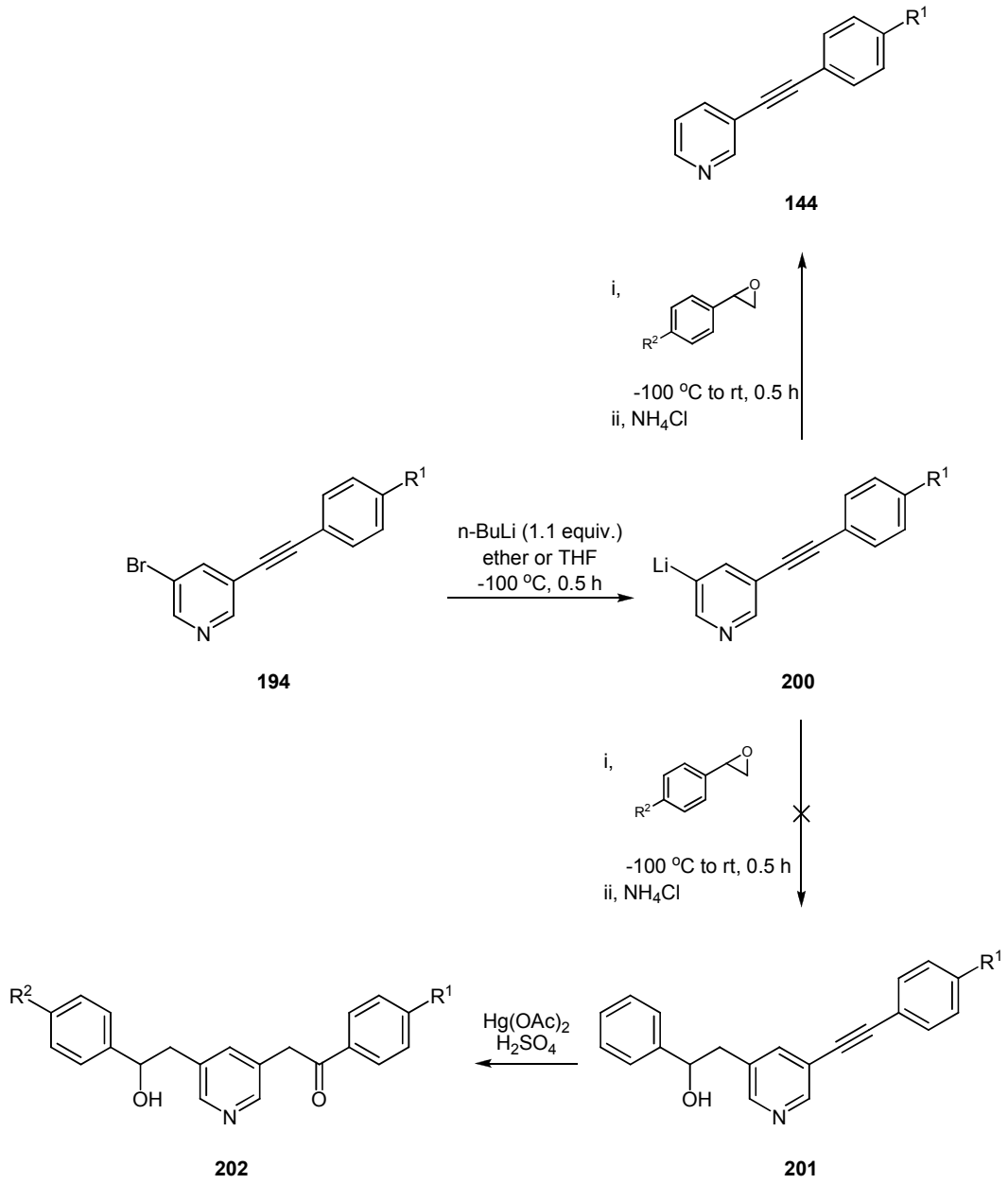
182a, R^1 = H, R^2 = H, 88 %
182b, R^1 = CH_3, R^2 = CH_3, 82 %
182c, R^1 = H, R^2 = CH_3, 94 %

199a, R^1 = H, R^2 = H, 87 %
199b, R^1 = CH_3, R^2 = CH_3, 83 %
199c, R^1 = H, R^2 = CH_3, 58 %

Scheme 82.

After having prepared bis(ketones) **196a-c** and bis(alcohols) **199a-c**, we next investigated approaches to target compounds **202**. Initially, we anticipated that **202** could be prepared in two-steps by an initial halogen-lithium exchange reaction of the key intermediate **194** using n-BuLi (in a similar fashion to that described in Chapter 3) to give [5-(4-substituted-phenylethynyl)pyridin-3-yl]lithium species **201**; trapping of **201** with the

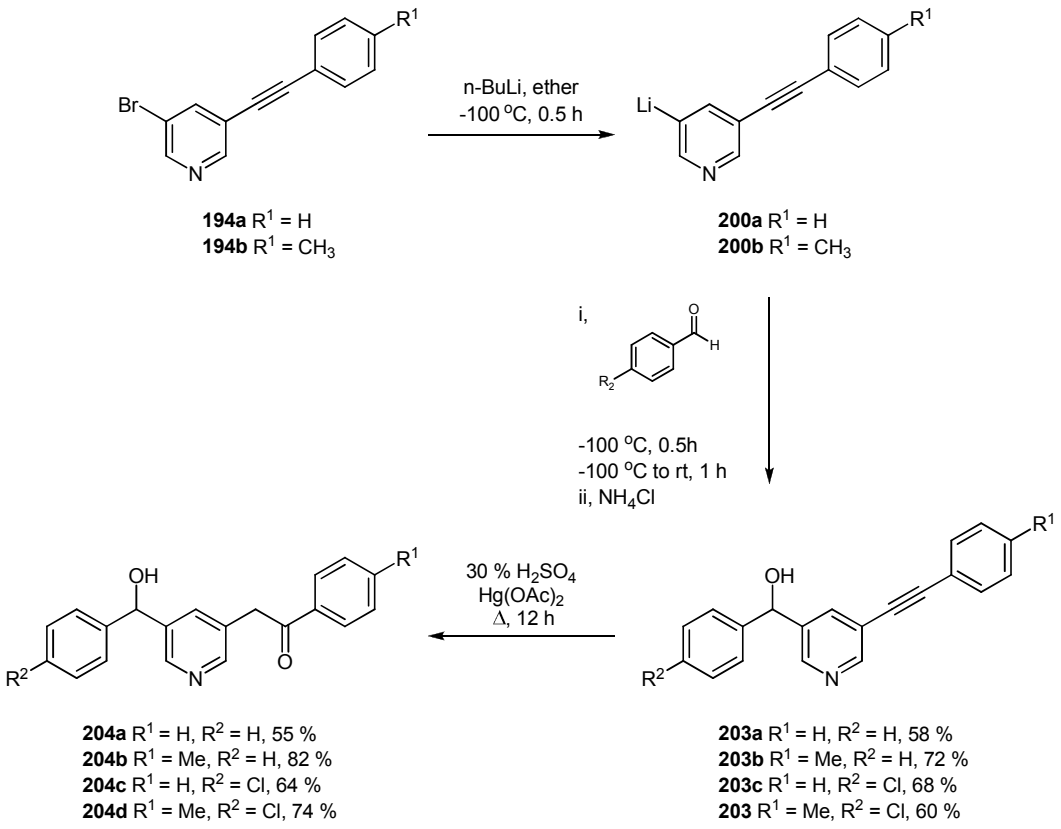
epoxide **100**, followed by hydration of alkyne **202** was then expected to furnish the target derivative **203** (Scheme 83). Unfortunately, despite repeated attempts, we were unable to effect ring-opening of the epoxide **100** using the organometallic **200** under a variety of reaction conditions (reactions were carried out at both -78 °C and -100 °C in various solvents *e.g*. toluene, THF and ether). However, we believed that a halogen-lithium exchange reaction had occurred as the dehalogenated compound **144** was recovered in all cases from reaction mixtures (50 - 70 % yield) (in addition, a distinctive colour change from yellow to orange was witnessed upon the addition of n-BuLi to a cooled solution of **194** in either toluene, THF or ether).



Scheme 83.

This observation can only be rationalised by a successful halogen-lithium exchange reaction followed by quenching of the resultant organometallic **200** on addition of water (the organometallic **200** is suggested to be of insufficient reactivity to ring-open the epoxide **100**).

To confirm that organometallic **200** had been generated under the reaction conditions employed, we attempted to react **200** with an alternate electrophile. Pleasingly, the addition of benzaldehyde to a solution of **200a** in ether at -100 °C proceeded smoothly and afforded phenyl(5-(phenylethynyl)pyridin-3-yl)methanol **203a** (58 %). Similarly, we were able to prepare compounds **203b-d** in consistently good yields (60 – 72 %) (Scheme 84). Hydration of **203a-d** in 30% $^{w}/_{v}$ H_2SO_4 in the presence of 10 mol.% $Hg(OAc)_2$ gave compounds **204a-d** (55 – 82 % yield).



194a R^1 = H
194b R^1 = CH_3

200a R^1 = H
200b R^1 = CH_3

204a R^1 = H, R^2 = H, 55 %
204b R^1 = Me, R^2 = H, 82 %
204c R^1 = H, R^2 = Cl, 64 %
204d R^1 = Me, R^2 = Cl, 74 %

203a R^1 = H, R^2 = H, 58 %
203b R^1 = Me, R^2 = H, 72 %
203c R^1 = H, R^2 = Cl, 68 %
203 R^1 = Me, R^2 = Cl, 60 %

Scheme 84.

As an alternative approach to compounds **202a-c**, the pathways shown in Scheme 85 were investigated. Ketones **189a,b** were readily obtained through mercury catalysed hydration of the alkynes **177a,b** and sodium

borohydride reduction of ketones **205a,b** smoothly afforded the corresponding alcohols **181a,b**.

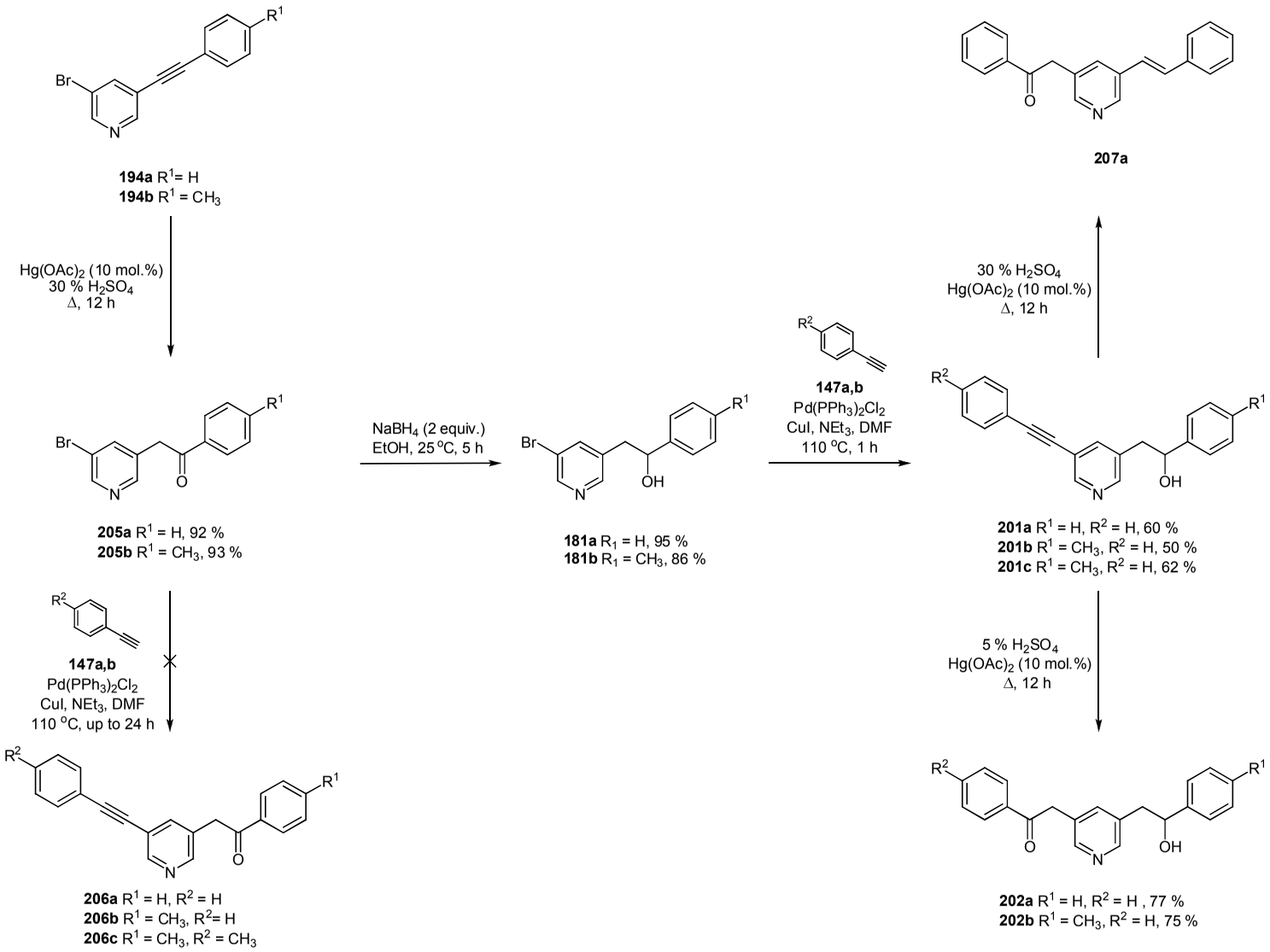
Sonogashira coupling reactions of arylalkynes **147a,b** with alcohols **181a,b** [($Pd(PPh_3)_2Cl_2$ (5 mol.%), CuI (2 mol.%), Et_3N (4 equiv.)] at 110 °C in DMF was rapid and efficient (1 h, 50-62 % isolated yield); TLC analysis indicated that, under these reaction conditions, conversion was complete in under 1 h. Unfortunately, using similar reaction conditions for Sonogashira coupling of ketones **205a,b** and arylalkynes **147a,b** resulted only in the recovery of unreacted starting materials. Also, Sonogashira coupling reactions of arylalkynes **147a,b** with alcohols **181a,b** was ineffective at 80 °C, and resulted only in the recovery of unreacted starting materials, even after greater than 48 h at 80 °C.

Initial attempts to hydrate the alkyne functionality present in **201a** using 10 mol.% $Hg(OAc)_2$ in 30 % $^{w}/_{v}$ H_2SO_4 at reflux gave only dehydrated product **207a** after work-up and purification. After varying the reaction conditions, we successfully achieved a hydration of **201a** using 10 mol.% $Hg(OAc)_2$ in 3 % $^{w}/_{v}$ H_2SO_4 to afford the **202a** (50 % yield), with no dehydration product **207** isolated. However, under these conditions, reaction times were greater than 48 h and significant quantities of recovered starting material were obtained (~50 %). A more optimum hydration reaction using 10 mol.% $Hg(OAc)_2$ in 5 % $^{w}/_{v}$ H_2SO_4 at reflux gave the desired products **203a-c** in only 12 h (65 - 77 %) [in these reactions, starting material was

again recovered (~10 %) and there was no evidence for dehydration products **207a-c**] (Scheme 85).

4.3 Summary

In summary, robust methodology for the synthesis of 3,5-disubstituted pyridine derivatives **182**, **195**-**199**, **201** and **202**-**204** has been developed. All compounds were prepared of sufficient purity for pharmacological evaluation by Institut de Recerches Servier (Chapter 5 gives a brief overview of the pharmacological data obtained). The methodology described herein is ripe for expansion; additional work could rapidly deliver further examples in each class and, thus, aid development of structure-activity relationships that may be used to inform the development of future synthetic targets to further the course of the project.


194a R1= H
194b R1 = CH3
Hg(OAc)2 (10 mol.%)
30 % H2SO4
Δ, 12 h
205a R1 = H, 92 %
205b R1 = CH3, 93 %
147a,b
Pd(PPh3)2Cl2
CuI, NEt3, DMF
110 °C, up to 24 h
206a R1 = H, R2 = H
206b R1 = CH3, R2= H
206c R1 = CH3, R2 = CH3
NaBH4 (2 equiv.)
EtOH, 25 °C, 5 h
181a R1 = H, 95 %
181b R1 = CH3, 86 %
147a,b
Pd(PPh3)2Cl2
CuI, NEt3, DMF
110 °C, 1 h
201a R1 = H, R2 = H, 60 %
201b R1 = CH3, R2 = H, 50 %
201c R1 = CH3, R2 = H, 62 %
30 % H2SO4
Hg(OAc)2 (10 mol.%)
Δ, 12 h
207a
5 % H2SO4
Hg(OAc)2 (10 mol.%)
Δ, 12 h
202a R1 = H, R2 = H , 77 %
202b R1 = CH3, R2 = H, 75 %

Scheme 85.

Chapter 5

5.1 Pharmacological Testing

The aim of this project was to develop heterocyclic derivatives as potential agents for treatment of neurodegenerative diseases. During the course of the project, the compounds described in Chapters 2-4 were sent to our collaborators at Institut de Recherches Servier for pharmacological evaluation. This Chapter gives a brief summary of the initial results obtained from *in vitro* pharmacological investigations of the α7-neuronal nicotinic receptor binding affinities of these compounds.

As the project was synthetic in nature, a detailed discussion of the relevant pharmacological techniques utilised by our co-workers is beyond the scope of this work. The contribution of Dr. Denis Guedin and Dr. Pierre Lestage, Institut de Reserches, Croissy-sur-Seine, France for providing the data presented in this Chapter is gratefully acknowledged.

5.1.1 Binding and Functional Assays

The compounds synthesised in Chapters 2-4 were tested at the α7 neuronal nicotinic receptor for their binding relative (in competition) to a radiolabelled tracer ([^{125}I] α-bungarotoxin). The receptor used for the studies was a chimera of the human α7 receptor extracellular domain and the transmembrane section of the mouse 5HT3 receptor. As closing of the

cloned receptor (by desensitisation) occurs at a much slower rate than in native human α7 alone, the active state is easier to detect.

Functional assays were performed using a fluorescence membrane potential assay which is a highly sensitive and rapid technique, and is preferred over an electrophysiological technique such as 'patch clamping' for high throughput screening and determination of subtype specificity.

In general terms, transefected cells (which express the nicotinic α7 subtype) are loaded with a membrane potential sensitive dye. The dye serves to give an indication of ionic flux in the cells upon application of the test compound, hence, the measurement of fluorescence (both pre and post application) gives a measure of nicotinic receptor activation.

For the α7-nAChR functional assay data (Table 2) obtained in this study:

(i) Agonism was determined by detecting the receptor response to the investigated compound alone.

(ii) Antagonism was determined by the modification of the receptor response elicited by acetylcholine when both the investigated compound and 60 μM acetylcholine were applied.

(iii) Partial agonism was detected by the addition of the investigated compound with 1 mM 5-hydroxyindole, a positive allosteric modulator (PAM) which boosts agonist response, thus allowing detection.

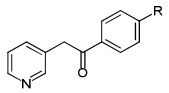
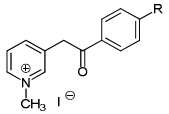
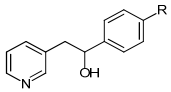
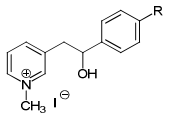
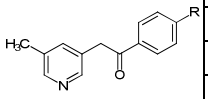
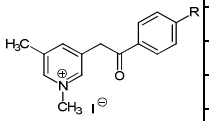
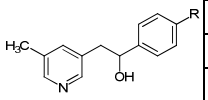
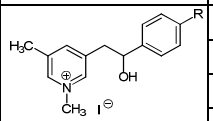
	R	Cpd.	Fluorescence Membrane Potential Assay			R	Cpd.	Fluorescence Membrane Potential Assay	
			IC_{50} (μM)	Comments				IC_{50} (μM)	Comments
	H	**78a**	>200	Inactive		H	**98a**	>200	Inactive
	Cl	**78c**	>200	Inactive		Cl	**98c**	90	H
	Br	**78d**	>200	Inactive		Br	**98d**	80	H
	Me	**78e**	>200	Inactive		Me	**98e**	120	H
	OMe	**78f**	NT	NT		OMe	**98f**	120	H
	H	**75a**	>200	Inactive		H	**99a**	>200	Inactive
	Cl	**75c**	>200	Inactive		Cl	**99c**	200	NAM
	Br	**75d**	NT	NT		Br	**99d**	150	NAM
	Me	**75e**	>200	Inactive		Me	**99e**	>200	Inactive
	OMe	**75f**	>200	Inactive		OMe	**99f**	>200	Inactive
	H	**110a**	>200	Inactive		H	**111a**	100	H
	Cl	**110c**	100	NAM		Cl	**111c**	NT	NT
	Br	**110d**	NT	NT		Br	**111d**	30	H
	Me	**110e**	>200	Inactive		Me	**111e**	150	H
	OMe	**110f**	>200	Inactive		OMe	**111f**	80	H
	H	**112a**	NT	NT		H	**113a**	>200	Inactive
	Cl	**112c**	120	NAM		Cl	**113c**	NT	NT
	Br	**112d**	150	NAM		Br	**113d**	NT	NT
	Me	**112e**	>200	Inactive		Me	**113e**	>200	Inactive
	Ome	**112f**	NT	NT		OMe	**113f**	NT	NT
Key: NT = Not tested; NAM = Negative Allosteric Modulator; H = Hyperpolarizing Compound									

Table 2. *Fluorescence membrane potential assay measurements using an α7 transefected cell line.*

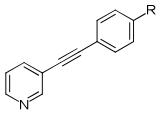
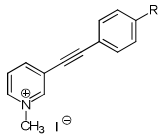
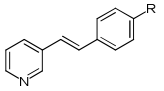
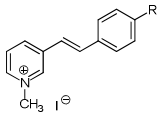
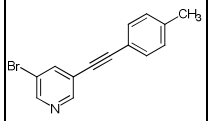
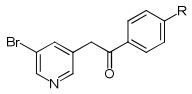
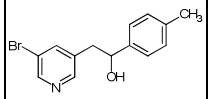
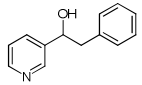
	R	Cpd.	Fluorescence Membrane Potential Assay			R	Cpd.	Fluorescence Membrane Potential Assay	
			IC_{50} (μM)	Comments				IC_{50} (μM)	Comments
	H	**144a**	NT	NT		H	**149a**	NT	NT
	Cl	**144c**	NT	NT		Cl	**149c**	6	H
	Br	**144d**	>200	Inactive		Br	**149d**	5	H
	Me	**144e**	NT	NT		Me	**149e**	8	H
	OMe	**144f**	>200	Inactive		OMe	**149f**	4	H
	H	**159a**	EC_{50} 8	PAM		H	**164a**	NT	NT
	F	**159b**	>200	Inactive		F	**164b**	NT	NT
	Cl	**159c**	>200	Inactive		Cl	**164c**	NT	NT
	Br	**159d**	>200	Inactive		Br	**164d**	NT	NT
	Me	**159e**	>200	Inactive		Me	**164e**	3	H
	Me	**194b**	>200	Inactive		H	**205a**	120	NAM
						Me	**205b**	80	NAM
	Me	**181b**	80	H		H	**131**	>200	Inactive

Table 2.*(cont.)*

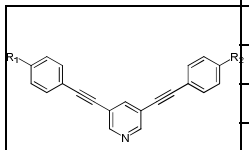
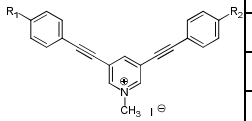
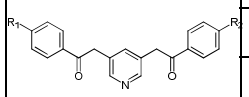
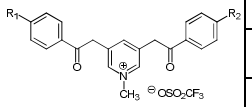
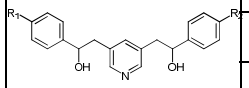
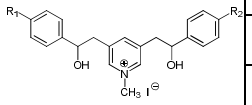
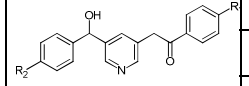
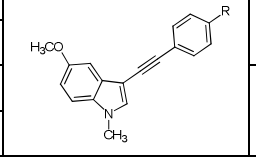
	R_1	R_2	Cpd.	Fluorescence Membrane Potential Assay			R_1	R_2	Cpd.	Fluorescence Membrane Potential Assay	
				IC_{50} (μM)	Comments					IC_{50} (μM)	Comments
	H	H	**195a**	>200	Inactive		H	H	**197a**	70	H
	Me	Me	**195b**	>200	Inactive		Me	Me	**197b**	NT	NT
	H	Cl	**195d**	>200	Inactive		H	Cl	**197d**	NT	NT
	Me	Cl	**195e**	>200	Inactive		Me	Cl	**197e**	NT	NT
	H	H	**196a**	60	H		H	H	**198a**	150	H
	Me	Me	**196b**	60	H		Me	Me	**198b**	60	H
	H	Me	**196c**	NT	NT		H	Me	**198c**	60	H
	H	H	**182a**	>200	Inactive		H	H	**199a**	>200	Inactive
	Me	Me	**182b**	NT	NT		Me	Me	**199b**	>200	Inactive
	H	Me	**182c**	NT	NT		H	Me	**199c**	>200	Inactive
	H	H	**204a**	>200	Inactive		H	Me	**170b**	>200	Inactive
	Me	H	**204b**	>200	Inactive						
	H	Cl	**204c**	30	H		OMe	Me	**170e**	>200	Inactive
	Me	Cl	**204d**	>200	Inactive						

Table 2.*(cont.)*

5.2 Discussion of Biological Data

5.2.1 α7 Neuronal Nicotinic Receptor Binding Affinities

The following definitions apply to the final classification and discussion of the compounds investigated pharmacologically:

Orthosteric Ligand

A compound which binds to the active site of the α7 neuronal nicotinic chimera receptor and produces a quantifiable binding and functional response.

Inactive

A compound for which binding at the α7 neuronal nicotinic chimera receptor and other functional properties cannot be measured.

Negative Allosteric Modulator (NAM)

A compound which does not bind to the neuronal nicotinic orthosteric (native) receptor site and does not display any other functional effects (*e.g*. down-regulation or antagonism of the AChR).

Hyperpolarizing compound

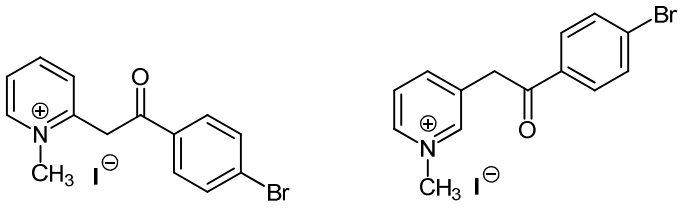
A compound which exhibits no binding affinity for the neuronal nicotinic receptor orthosteric site, but does display measurable functional parameters (*e.g.* down-regulation or antagonism of the AChR).

Positive Allosteric Modulator (PAM)

A compound which exhibits no binding at the α7 neuronal nicotinic receptor but may stabilise the receptor in the active state, increasing the response of the agonist.

The compounds tested in this project (Table 2) showed no measurable binding affinity for the α7 neuronal nicotinic chimera receptor at concentrations of up to 200 μM, regardless of the functional group present or whether the pyridine ring existed as the free base or the *N*-alkylated form. When compared to compound **70** (IC_{50} 38 μM) (the direct 2-position analogue of **98d**), and other active 2-position ligands, it is clear that, for the compounds investigated, all affinity for the α7 AChR is removed when substitution occurs at the 3-position of the pyridine ring.

Sheridan *et al*.,[113] suggested that compounds should possess, as essential parts of their pharmacophore, a hydrogen bond acceptor (carbonyl) and a positively charged nitrogen separated by between 4.6 and 6.3 Å for the compound to show reasonable binding affinity at nAChRs. Basic calculations (Figure 19, minimised energy, Chem3D®) suggest that both the orthosteric ligand **70** and the 3-position analogue **98d** have separations between the carbonyl oxygen (hydrogen bond acceptor) and the pyridine nitrogen which fulfil this requirement (**70**, 4.6 Å; **98d**, 5.9 Å); it is perhaps noteworthy that compounds **70** and **98d** have carbonyl- pyridinium nitrogen separations at the lower and upper limit, respectively.



70 **98d**

Figure 19. *Minimised representation of compounds **70** and **98d** (Chem3D®).*

Through functional assays a number of compounds (**110c**, **112c,d**, **99c,d**, **205a,b**) have been identified as NAMs which do not have an intrinsic effect. These compounds may bind to similar or distinct allosteric sites on the receptor as other NAMs; however, although binding occurs, no functional modulation of the nAChR could be detected. NAMs (or non-competitive binders) bind to a site on the receptor away from the active binding site and, without interaction with the receptor, cause a perturbation or alteration in the conformation of the nAChR. In this case, binding at the allosteric site reduced the response of the agonist probe for the allosterically modulated (conformationally altered) nAChR. For our

purposes, these compounds can be considered to be allosteric 'antagonists'.

One compound **159a** possesses positive allosteric modulation (PAM) properties without exhibiting any intrinsic effects. This compound may also bind allosterically but, unfortunately, no functional response (*i.e.* upregulation of nAChR response) could be detected. PAMs are of increasing interest for the treatment of cognitive neurodegenerative disorders such as AD for their ability to modulate the release of neurotransmitters and increase sensitivity of the receptor response to ACh.[213]

The remainder of the compounds tested have been identified as hyperpolarising compounds. Hyperpolarising compounds cause an increase in cell membrane potential, effecting an opening of ion channels allowing the efflux of K^+ ions from the cell; this results in a net decrease in the membrane potential and subsequent hyperpolarisation. Disappointingly, further testing, using a cell line untransfected by the α7 receptor (chinese hamster ovary cell line) showed the same dose-dependent hyperpolarisation response to the original cell line, implying that the hyperpolarisation effect of these compounds is not due to the target α7 receptor.

5.2.2 Further Testing

In the course of the initial pharmacological investigations on this project, candidates showing promising α7-neuronal nicotinic receptor binding affinities would routinely undergo *in vitro* safety studies as well as ADME (Adsorbtion; Distribution; Metabolism; Excretion) studies to establish suitability for further investigation and development. This testing initially consists of:

- cardiac safety profile by monitoring affinity for the hERG channel;
- Ames test to indicate potential mutagenicity;
- biomembrane permeability tests using Caco-2 cells;
- initial *in vitro* metabolic stability screening using liver microsomes from mice, rats and humans.

5.2.2.1 hERG Affinity

The hERG (*human ether-a-go-go related gene*), or KCHN2, is responsible for encoding of the cardiac potassium ion channel $K_v11.1$ which is intimately involved in the timing of ventricular repolarisation. Unfortunately, however, the hERG channel is known to be blocked by a wide range of structurally diverse small molecules due mainly to:- (i) the large central ion channel and (ii) the presence of two aromatic rings from aromatic amino

acid side chains within the channel which can interact (π-cation) with a positively charged nitrogen (these are commonly present in molecules which interact strongly with hERG).[214a,b] It is these unwanted interactions that can often lead to reduced potassium levels and resultant physiological conditions such as acquired long Q-T (the interval denoted by the electrocardiogram) syndrome and potentially fatal arrhythmia (commonly known as torsades de pointes). It is for these reasons that, in 2005, the regulatory authorities recommended that preclinical studies must first establish the cardiac safety of potential pharmaceuticals.[215] Over the last 15 years several widely-prescribed drugs including Propulsid® (cisapride, Janssen), Raxar® (grepafloxacin, GSK) and Seldane® (terfenadine, Merrell Dow Pharmaceuticals) have been withdrawn from the market due to their hERG binding properties.[216]

Determination of hERG affinity is commonly performed using a 'patch clamp' assay on HEK293 cells which have expressed the hERG channel gene.[217] hERG affinity of the test compound is determined at a series of concentrations.

5.2.2.2 Permeability Profiling *in vitro*

Initial permeability studies are often performed *in vitro* using the Caco-2 permeability assay in order to assess the transit of the test compound across the intestinal epithelial cell barrier and, hence, predict the extent to

which the compound may be absorbed intestinally.[218] Caco-2 cells are human colonic adenocarcinoma cells and are cultured over a 21 day period to form a mono-layer around a microporous membrane. The membrane is suspended in a microwell and the compound of interest placed in the upper chamber of the microwell; aliquots are then removed from the lower chamber at regular intervals. Analysis of the samples using UV or HPLC/MS/MS, for example, allows the quantification of the test substance which has crossed the mono-layer. In common with other pre-clinical screening tests this type of assay is easily automated to allow high throughput screening of libraries of potential drug substances.

5.2.2.3 Ames Testing

The Ames test is a rapid bacterial assay based on the *Salmonella typhimurium* bacterial strain which carry a mutation in the gene responsible for the synthesis of the essential amino acid histidine. The Ames test is used for the rapid screening of potential drug substances to determine mutagenicity and, indirectly, carcinogenicity (as a strong correlation exists between mutagenicity and carcinogenicity).

In practice, the bacteria and a limiting amount of histidine are applied to an agar plate, after which the test compound is introduced (often absorbed on blotting paper) and the plate incubated. Compounds which possess mutagenic properties can induce mutation of the bacteria; the mutated

bacteria then revert to producing their own histidine, allowing division and the formation of colonies. Conversely, if the bacteria are exposed to non-mutagenic compounds, once the small amount of histidine is expended, they cannot divide any further or produce colonies, as they remain unable to synthesise their own histidine.[219] An adaptation of this technique, which is often employed by pharmaceutical companies, involves the addition of S9 liver enzymes to the agar plate containing the bacteria. Monitoring of the metabolism of the test compound gives an indication of the potential mutagenicity of both the parent compound and its metabolites.

Ames II, a second generation Ames test, is in routine use by most pharmaceutical companies and is based on the same principle as the original Ames test, also using *Salmonella typhimurium*. Ames II, however, employs a liquid culture media; this reduces the quantity of test compound and reagents required and, more importantly, allows for automated preparation and reading using microwell plates.

5.2.2.4 Metabolic Stability

Metabolic stability testing is commonly performed using rat, mouse and human liver microsomes. Microsomes are subcellular fractions responsible for phase I metabolism (*i.e.* oxidation, hydrolysis and reduction) and involve enzymes such as the cytochrome P450 enzymes.

For analysis, the compound is exposed to liver microsomes and an enzyme co-factor (NADPH) and compared to a control sample, prepared using the test compound, microsomes but no co-factor. Samples are removed at various time intervals and analysed, often by a mass spectrometry technique such as LC/MS/MS to determine the percentage of parent compound remaining and hence give an indication of systemic metabolic stability.

5.3 Summary of Pharmacological Testing

In summary, the intention of this project was to synthesise novel 3-substituted pyridine based compounds which displayed orthosteric binding for neuronal nicotinic acetylcholine receptors. Several compounds were found to be negative allosteric modulators, *i.e.* the compounds bind to a receptor at a site other than the active site, causing a perturbation in the conformation of the receptor and, thus, prevent binding of the probe (in this case [^{125}I] α- bungarotoxin). Unfortunately, little therapeutic benefit can be derived from this type of compound; however, recent work has suggested that these compounds may have some benefit in the treatment of nicotine addiction.[220]

A number of compounds synthesised in this project have a hyperpolarising effect, which upon further investigation was found (by observation of identical dose-dependent hyperpolarisation response in the transefected

and an untransefected cell line) to be independent of the α7 receptor. At this point the target through which hyperpolarisation proceeds is unknown.

Unfortunately, in this study no useful biological activity was observed at the neuronal nicotinic acetylcholine receptor subtype tested in terms of nicotinic receptor agonism. Hence, it can be concluded that the 3-substituted pyridine derivatives synthesised in this project, although meeting Barlow's criteria in terms of internuclear separation, do not adopt a conformation appropriate for efficient binding at the active site of the α7 nAChR.

To progress this project, further work should focus around the synthesis and pharmacological testing of the analogous, novel and somewhat less conformationally restricted 3-substituted piperidine derivatives identified in Scheme 40 (Section 2.5). Such derivatives have hydrogen bond acceptor - hydrogen bond donor separations within the 4.6 and 6.5 Å range suggested by Barlow *et al*. Additionally, it is worthwhile noting that the highly selective and potent α7 agonist PNU-282987 **25** (Figure 6.) possesses a similar (although conformationally restricted) structure to those identified in Scheme 40.

Chapter 6 - Experimental

6.1 General

IR spectra were collected on a Perkin-Elmer Spectrum BX FT-IR instrument fitted with a PIKE MIRacle clamp. Reaction progress was monitored using pre-coated aluminium TLC plates (Merck silica gel type 60 HF_{254}). Melting points were determined using a Stuart SMP10 or Reichart and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz respectively on a Brüker Avance with deuterated chloroform unless stated otherwise. 'Petrol' refers to the fraction boiling at 60-80 ^{o}C, 'ether' refers to diethyl ether. Elemental analyses were performed by Medac Ltd, Brunel Science Centre or ChemiSPEC, University of Sunderland. THF was dried over sodium / benzophenone ketyl under nitrogen and stored over 3Å molecular sieves. Toluene was dried over calcium hydride. 3-Methylpyridine was distilled over calcium hydride onto 3Å molecular sieves. DMPU was distilled and stored over 3Å molecular sieves, all other reagents were reagent grade and used as supplied. All glassware was flame dried under vacuum. Reactions requiring anhydrous conditions were performed under argon or nitrogen. Chemical shifts, given in ppm, are relative to tetramethylsilane (TMS). Spin multiplicities are described as b (broad), bs (broad singlet), s (singlet), d (doublet), t (triplet), dd (doublet of doublets), dt (doublet of triplets), td (triplet of doublets), tt (triplet of triplets), ddd (doublet of doublet of doublets). NMR spectra were fully assigned using a combination of ^{1}H, ^{13}C, DEPT-135, COSY, HMBC and HMQC.

6.2 General Synthetic Procedures

6.2.1 General Procedure 1 (GP 1) - formation of (pyridin-3-ylmethyl)lithium 73c and subsequent reaction with electrophiles

To a stirred solution of LDA (10 mL, 2.0 M, 20 mmol) in dry THF (60 mL) maintained at 0 °C under an atmosphere of argon was added 3-methylpyridine **72** (10 mmol) dropwise over 5 min. The mixture was stirred for a further 5 min, followed by dropwise addition over 5 min of the electrophile (11 mmol) in dry THF (10 mL). The resulting solution was stirred at 0 °C for 1 h then quenched with water (60 mL), the phases separated and the aqueous phase extracted using DCM (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure to yield red / brown residues which were purified by column chromatography (SiO_2; EtOAc / petrol, 60 / 40 $^{v}/_{v}$) and recrystallisation, as appropriate.

6.2.2 General Procedure 2 (GP 2) - Sodium borohydride reduction of ketones

To a stirred solution of ketone (10 mmol) in ethanol (40 mL), was added sodium borohydride (0.76 g, 20 mmol). The resulting solution was stirred at room temperature for 2 h followed by the addition of water (90 mL). The aqueous layer was extracted with DCM (3 x 40 mL) and the organic extracts combined, washed with brine (50 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure to yield the crude products which were subsequently purified by recrystallisation from EtOAc.

GP 2 was used for the synthesis of alcohols **75a,c-f**, **112a,c-f** and **181a,b**.

6.2.3 General Procedure 3 (GP 3) - pyridine *N*-alkylation

To a stirred solution of pyridine substrate (5 mmol) in dry THF (3 mL) was added iodomethane (1.6 mL, 25 mmol). The mixture was stirred at reflux overnight. After cooling, the resulting precipitate was filtered to give crude *N*-alkylated products, which were subsequently purified by recrystallisation from ethanol.

GP 3 was used for the synthesis of pyridinium salts **98a,c-f, 99a,c-f, 111a,c-f**, **113a,c-f**, **149a,c-f** and **164a-e**.

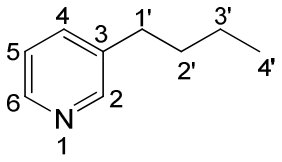
General Procedure 4 (GP4) – Hydration of Alkynes

Acetylene (10 mmol) and $Hg(OAc)_2$ (0.32 g, 1 mmol, 10 mol.%) were dissolved in a mixture of 30 % $^{w}/_{v}$ H_2SO_4 (8 mL) and acetone (4 mL). The mixture was stirred at reflux for 12 h. After cooling, the mixture was diluted with water (80 mL), neutralised with 10 % NaOH and extracted with EtOAc (3 x 25 mL). The combined organic extracts were dried ($MgSO_4$), evaporated under reduced pressure, and the residue purified by column chromatography (SiO_2; EtOAc:petrol, 70:30) and the solid obtained recrystallised.

GP4 was used for the synthesis of ketones **78a-d**, **205a,b** and **196a-c**

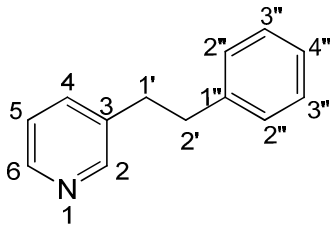
6.3 Synthetic Work, Chapter 2

6.3.1. 3-Butylpyridine (96a)



Using **GP 1** with butyl iodide (1.87 g) as electrophile; (0.74 g, 53 %); colourless oil; FTIR (neat) 2957, 2929, 2859, 1574, 1421, 712 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.47 (d, *J* = 2.1, 1H, H2), 8.42 (dd, *J* = 4.8, 2.1, 1H, H6), 7.51 (dt, *J* = 7.8, 2.1, 1H, H4), 7.22 (dd, *J* = 7.8, 4.8, 1H, H5), 2.63 (t, *J* = 7.5, 2H, H1'), 1.64 (p, *J* = 7.5, 2H, H2'), 1.38 (tt, *J* = 7.5, 7.2, 2H, H3'), 0.96 (t, *J* = 7.2, 3H, H4'); ^{13}C NMR ($CDCl_3$) δ 149.9 (C6), 147.1 (C2), 138.0 (q, C3), 135.8 (C4), 123.2 (C5), 33.2 (C2'), 32.7 (C1'), 22.2 (C3'), 13.8 (C4'). Spectroscopic data were identical to that reported in literature.[228]

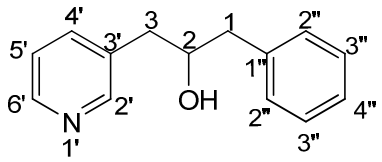
6.3.2. 3-Phenylethylpyridine (96b)



Using **GP 1** with benzyl bromide (1.88 g) as electrophile. (0.68 g, 37 %); colourless oil; FTIR (neat) 3026, 1494, 1452, 1422, 1027, 758, 713, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.41 (dd, *J* = 4.8, 1.8, 1H, H6), 8.28 (d, *J* = 1.8,

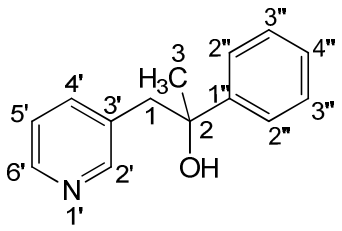
1H, H2), 7.31-7.19 (m, 4H, H3'', H4'', H4'), 7.13-7.06 (m, 3H, H2'', H5'), 3.06- 2.94 (m, 4H, H1', H2'); ^{13}C NMR ($CDCl_3$) δ 150.2 (C2), 147.1 (C6), 143.3 (q, C1''), 135.9 (q, C3), 136.7 (C4), 128.5 (C2'' or C3''), 128.4 (C2'' or C3''), 126.5 (C4''), 123.0 (C5), 42.8 (C2'), 39.4 (C1'). Spectroscopic data were identical to that reported in literature.[229]

6.3.3. 1-Phenyl-3-pyridin-3-yl-propan-2-ol (96c)



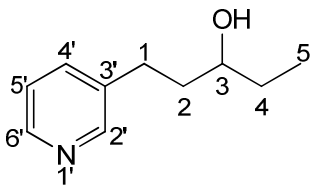
Using **GP 1** with phenylacetaldehyde (1.32 g) as electrophile. (0.68 g, 32 %); cream solid; m.p. 67-68 °C (from EtOAc); FTIR (neat solid) 3149 br, 2919, 1578, 1425, 1071, 1047, 747, 711, 700, 618 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.38 (s, 1H, H2'), 8.34 (d, *J* = 3.3, 1H, H6'), 7.55 (d, *J* = 7.8, 1H, H4'), 7.30-7.10 (m, 6H, H2'', H3'', H4'', H5'), 3.99 (tt, *J* = 8.1, 4.5, 1H, H2), 3.57 (bs, 1H, OH), 2.79 (dd, *J* = 14.1, 4.5, 1H, $H3_A$ or $H1_A$), 2.79 (dd, *J* = 13.2, 4.5, 1H, $H3_A$ or $H1_A$), 2.69 (dd, *J* = 13.2, 8.1, 1H, $H3_B$ or $H1_B$), 2.68 (dd, *J* = 14.1, 8.1, 1H, $H3_B$ or $H1_B$); ^{13}C NMR ($CDCl_3$) δ 149.8 (C2'), 146.8 (C6'), 138.0 (2C; C4' and q, C1''), 134.9 (q, C3'), 129.4 (C2''), 128.7 (C3''), 126.7 (C4''), 123.6 (C5'), 72.9 (C2), 43.8 (C1), 40.3 (C3). HRMS calcd for $C_{14}H_{15}NO$ $(M + H)^+$ required 214.1233, found 214.1224.

6.3.4. 2-Phenyl-1-pyridin-3-yl-propan-2-ol (96d)



Using **GP 1** with acetophenone (1.32 g) as electrophile. (0.59 g, 28 %); colourless oil; FTIR (neat) 3216 br, 1578, 1492, 1425, 1067, 764, 699 cm^{-1} ^1H NMR ($CDCl_3$) δ 8.26 (dd, *J* = 4.5, 1.2, 1H, H6'), 8.14 (d, *J* =1.2, 1H, H2'), 7.30-7.13 (m, 6H, H2'', H3'', H4'', H4'), 7.01 (dd, *J* = 7.8. 4.5, 1H, H5'), 3.05 (bs, 1H, OH), 2.97 (d, *J* = 13.5, 1H, $H1_A$), 2.93 (d, *J* = 13.5, 1H, $H1_B$), 1.50 (s, 3H, C3); ^{13}C NMR ($CDCl_3$) δ 151.1 (C2), 147.2 (C6), 147.1 (q, C1''), 138.3 (C4), 133.1 (q, C3'), 128.2 (C3''), 126.9 (C4''), 125.0 (C2''), 122.8 (C5'), 74.3 (q, C2), 47.8 (C1), 29.4 (C3). HRMS calcd for $C_{14}H_{15}NO$ $(M + H)^+$ required 214.1233, found 214.1229.

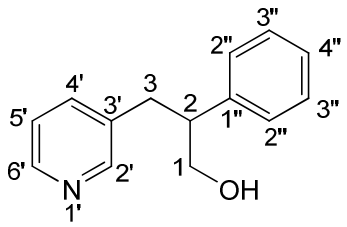
6.3.5. 1-Pyridin-3-yl-pentan-3-ol (96e)



Using **GP 1** with 1,2-epoxybutane (0.79 g) as electrophile. (0.98 g, 59 %); colourless oil; FTIR (neat) 3289, 2959, 2924, 2873, 1578, 1423, 712 cm^{-1};

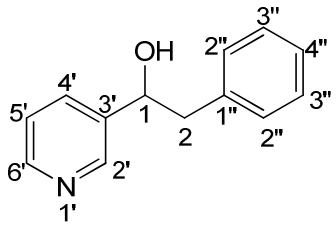
^{1}H NMR ($CDCl_3$) δ 8.39 (s, 1H, H2'), 8.34 (d, *J* = 5.1, 1H, H6'), 7.47 (d, *J* = 7.8, 1H, H4'), 7.14 (dd, *J* = 7.2, 5.1, 1H, H5'), 3.49- 3.43 (m, 1H, H3), 2.89 (s, br, 1H, OH), 2.81-2.57 (m, 2H, H1), 1.72-1.65 (m, 2H, H2), 1.50-1.36 (m, 2H, H4), 0.87 (t, *J* = 7.5, 3H, H5); ^{13}C NMR ($CDCl_3$) δ 149.6 (C2'), 146.9 (C6'), 137.9 (q, C3'), 136.2 (C4'), 123.4 (C5'), 72.0 (C3), 38.2 (C2), 30.4 (C1), 29.2 (C4), 9.9 (C5). Spectroscopic data were identical to that reported in literature.[230]

6.3.6. 2-Phenyl-3-pyridin-3-yl-propan-1-ol (102a)



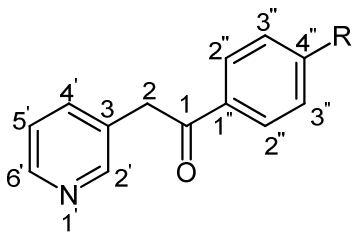
Using **GP 1** with (±)-**100a** (1.32 g) as electrophile. (0.36 g, 17%); colourless solid; m.p. 91 °C (from EtOAc / petrol); IR (neat solid) 3216, 1577, 1423, 1068, 1030, 761, 704 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.25 (dd, *J* = 4.8, 1.8, 1H, H6'), 8.20 (d, *J* = 1.8, 1H, H2'), 7.23 (dt, *J* = 7.8, 1.8, 1H, H4'), 7.12-7.06 (m, 3H, H44'', H3''), 7.02 (dd, *J* = 7.8, 4.8, 1H, H5'), 3.72 (d, *J* = 6.0, 2H, H1), 3.05 (dd, *J* = 12.9, 6.3, 1H, $H3_A$), 2.95 (dd, *J* = 13.8, 6.3, 1H, H2), 2.78 (dd, *J* = 12.9, 7.8, 1H, $H3_B$), 2.42 (bs, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 150.2 (C2'), 147.3 (C6'), 141.1 (q, C1''), 136.6 (C4'), 135.5 (q, C3'), 128.7 (C3''), 128.1 (C2''), 127.0 (C4''), 123.1 (C5'), 66.1 (C1), 50.1 (C2), 35.7 (C3); Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.81; H, 7.10; N, 6.50.

6.3.7 2-Phenyl-1-pyridin-3-yl-ethanol (131)



Using **exchange** with phenylacetaldehyde (1.32 g) as electrophile. (0.94 g, 47 %); white solid; m.p. 101-102 °C (from EtOAc); FTIR (neat solid) 3157 br, 2904, 1580, 1492, 1424, 1065, 700, 544 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.30 (d, *J* = 1.8, 1H, H2'), 8.28 (dd, *J* = 4.8, 1.8, 1H, H6'), 7.57 (dt, *J* = 7.8, 1.8, 1H, H4'), 7.22-7.11 (m , 4H, H5', H3'', H4''), 7.06 (dd, *J* = 7.8, 1.5, 2H, H2''), 4.81 (t, *J* = 6.6, 1H, H1), 3.45 (bs, 1H, OH), 2.92 (d, *J* = 6.6, 2H, H2); ^{13}C NMR ($CDCl_3$) δ 148.4 (C2), 147.6 (C6), 139.6 (q, C3), 137.4 (q, C1''), 134.0 (C4'), 129.6 (C2''), 128.6 (C3''), 126.8 (C4''), 123.4 (C5), 72.9 (C1), 46.0 (C2). Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.40; H, 6.60; N, 7.19.

6.3.8 Synthesis of compounds 78a-e



Compounds **78a,c-f** were synthesised using **GP 1**. There was obtained:

1-Phenyl-2-pyridin-3-yl-ethanone (78a), using **97a** (1.13 g). (1.41 g, 71%); pale yellow solid; m.p. 41-42 °C (from EtOAc); lit. 43 °C.[221] FTIR (neat solid) 3031, 1679, 1592, 1577, 1107, 993, 761, 713 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.51 (d, *J* = 1.5, 1H, H2'), 8.49 (dd, *J* = 5.0, 1.5, 1H, H6'), 8.00 (dd, *J* = 7.2, 1.2, 2H, H2''), 7.59 (tt, *J* = 7.2, 1.2, 1H, H4''), 7.58 (dt, *J* = 7.6, 1.2, 1H, H4'), 7.48 (t, *J* = 7.2, 6.3 2H, H3''), 7.25 (dd, *J* = 7.6, 5.0 1H, H5'), 4.29 (s, 2H, H2); ^{13}C NMR ($CDCl_3$) δ 196.5 (q, C1), 150.7 (C2'), 148.4 (C6'), 137.3 (C4'), 136.4 (q, C1''), 133.6 (C4''), 130.3 (q, C3'), 128.9 (C3''), 128.5 (C2''), 123.5 (C5'), 42.4 (C2); Anal. Calcd for $C_{13}H_{11}NO$: C, 79.17; H, 5.62; N, 7.10. Found: C, 78.51; H, 5.59; N, 7.10.

1-(4-Chlorophenyl)-2-pyridin-3-yl-ethanone (78c), using **97c** (1.51 g). (1.52 g, 66 %); pale yellow solid; m.p. 64-65 °C (from EtOAc); lit. 65 – 68 °C;[227] FTIR (neat solid) 3047, 1687, 1592, 1481, 839 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.55 (d, *J* = 4.8, 1.8, 1H, H6'), 8.54 (d, J = 1.8, 1H, H2'), 7.97 (d, *J* = 8.7, 2H, H2''), 7.62 (dt, *J* = 7.8, 1.8 1H, H4'), 7.48 (d, *J* = 8.7, 2H, H3''), 7.30 (dd, *J* = 7.8, 4.8 1H, H5'), 4.29 (s, 2H, H2); ^{13}C NMR ($CDCl_3$) δ 194.3 (q, C1), 149.6 (C2'), 147.5 (C6'), 139.2 (q, C4''), 136.3 (C4'), 133.7 (q, C1'), 129.8 (C2''), 129.0 (q, C3'), 128.3 (C3''), 122.6 (C5'), 41.4 (C2); Anal. Calcd for $C_{13}H_{10}ClNO$: C, 67.40; H, 4.35; N, 6.05. Found: C, 67.51, H, 4.40; N, 6.03.

1-(4-Bromophenyl)-2-pyridin-3-yl-ethanone (78d), using **97d** (2.00 g). (1.10 g, 40 %); yellow solid; m.p. 88-89 °C (from EtOAc); FTIR (neat solid) 3047, 1677, 1585, 1479, 817 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.48 (dd, *J* = 5.4,

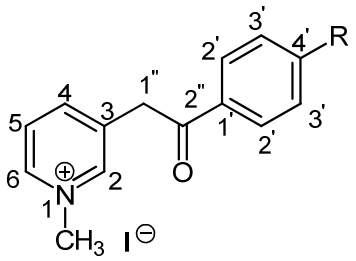
1.8, 1H, H6'), 8.45 (d, *J* = 1.8, 1H, H2'), 7.80 (d, *J* = 6.9, 2H, H2''), 7.56 (d, *J* = 6.9, 2H, H3''), 7.53 (dt, *J* = 8.4, 1.8 1H, H4'), 7.21 (dd, J = 8.4, 5.4 1H, H5'), 4.19 (s, 2H, H2); ^{13}C NMR ($CDCl_3$) δ 195.8 (q, C1), 150.9 (C2'), 148.8 (C6'), 137.6 (C4'), 135.4 (q, C1''), 132.6 (C3''), 130.3 (C2''), 130.3 (q, C3'), 129.2 (q, C4''), 123.9 (C5'), 42.7 (C2); Anal. Calcd for C_{13} H_{11}BrNO: C, 56.55; H, 3.65; N, 5.07; Found: C, 56.72; H, 3.75; N, 5.11.

2-Pyridin-3-yl-1-(4-methylphenyl)-ethanone (78e), using **97e** (1.29 g). (1.71 g, 81%); pale yellow solid; m.p. 76-77 °C (from EtOAc); FTIR (neat solid) 3035, 1683, 1602, 1482, 819 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.43 (d, *J* = 1.8, 1H, H2'), 8.42 (dd, *J* = 5.0, 1.8, 1H, H6'), 7.83 (d, *J* = 8.2, 2H, H2''), 7.52 (dt, *J* = 7.8, 1.8 1H, H4'), 7.15 – 7.21 (m, 3H, H5', H3''), 4.18 (s, 2H, H2), 2.34 (s, 3H, 4''-CH_3); ^{13}C NMR ($CDCl_3$) δ 196.4 (q, C1), 151.0 (C2'), 148.7 (C6'), 144.8 (q, C4''), 137.5 (C4'), 134.2 (q, C1''), 130.8 (q, C3'), 129.8 (C3''), 129.0 (C2''), 123.7 (C5'), 42.6 (C2), 22.0 (C4''-CH_3); Anal. Calcd for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.50; H, 6.18; N, 6.59.

1-(4-Methoxyphenyl)-2-pyridin-3-yl-ethanone (78f), using **97f** (1.46 g). (1.50g, 66%); pale yellow solid; m.p. 73-74 °C (from EtOAc); FTIR (neat solid) 3047, 1677, 1598, 1509, 835 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.44 (d, *J* = 1.8, 1H, H2'), 8.41 (dd, *J* = 4.8, 1.8, 1H, H6'), 7.91 (d, *J* = 8.7, 2H, H2''), 7.52 (dt, *J* = 7.8, 1.8 1H, H4'), 7.17 (dd, *J* = 7.8, 4.8 1H, H5'), 6.86 (d, *J* = 8.7, 2H, H3''), 4.15 (s, 2H, H2), 3.78 (s, 3H, 4''-OCH_3); ^{13}C NMR ($CDCl_3$) δ 195.4 (q, C1), 164.2 (q, C4''), 151.0 (C2'), 148.6 (C6'), 137.5 (C4'), 131.2

(C2''), 131.0 (q, C3'), 129.7 (q, C1''), 123.8 (C5'), 114.4 (C3''), 55.9 (C4''-OCH_3), 42.4 (C2); Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16 %. Found: C, 73.89; H, 5.72; N, 6.15.

6.3.9 Synthesis of compounds 98a-e



Compounds **98a,c-f** were prepared using **GP 3**. There was obtained:

1-Methyl-3-(2-oxo-2-phenylethyl)pyridinium iodide (98a), using **78a** (0.99 g). (1.47 g, 86 %); yellow solid; m.p. 122-123 °C (from EtOH); FTIR (neat solid) 3031, 1673, 1604, 1504 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.95 (bs, 1H, H2), 8.93 (d, *J* = 6.0, 1H, H6), 8.50 (d, *J* = 8.1, 1H, H4), 8.15 (dd, *J* = 7.8, 6.0 1H, H5), 8.09 (d, *J* = 6.9, 2H, H2'), 7.71 (tt, *J* = 7.8, 6.9, 1H, H4'), 7.62 (t, *J* = 7.8, 2H, H3'), 4.81 (s, 2H, H1''), 4.38 (s, 3H, 1-CH_3); ^{13}C NMR (DMSO-d_6) δ 195.3 (q, C2''), 146.6 (C4), 145.8 (C2), 143.6 (C6), 135.9 (q, C3), 135.7 (q, C1'), 133.7 (C4'), 128.8 (C3'), 128.1 (C2'), 126.8 (C5), 47.8 (1-CH_3), 41.1 (C1''); Anal. Calcd for C_{14} H_{14}INO: C, 49.58; H, 4.16; N, 4.13. Found: C, 49.67; H, 4.16; N, 4.02.

3-[2-(4-Chlorophenyl)-2-oxoethyl]-1-methylpyridinium iodide (98c), using **78c** (1.16 g). (1.59 g, 85 %); yellow solid; m.p. 183-184 °C (from EtOH); FTIR (neat solid) 3010, 1688, 1587, 1511 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.96 (bs, 1H, H2), 8.94 (d, *J* = 6.6, 1H, H6), 8.49 (d, *J* = 8.1, 1H, H4), 8.15 (dd, *J* = 8.1, 6.6 1H, H5), 8.13 (d, *J* = 7.6, 2H, H2'), 7.69 (d, *J* = 7.6, 2H, H3'), 4.81 (s, 2H, H1''), 4.38 (s, 3H, 1-CH_3); ^{13}C NMR (DMSO-d_6) δ 195.0 (q, C2'), 147.3 (C4), 146.5 (C6), 144.3 (C2), 139.3 (q, C4'), 136.2 (q, C1'), 135.0 (q, C3), 130.7 (C2'), 129.5 (C3'), 127.5 (C5), 48.5 (1-CH_3), 41.8 (C1''); Anal. Calcd for $C_{14}H_{13}ClINO$: C, 45.01; H, 3.55; N, 3.77. Found: C, 45.07; H, 3.52; N, 3.78.

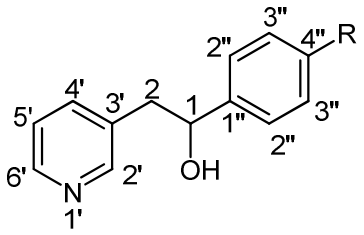
3-[2-(4-Bromophenyl)-2-oxo-ethyl]-1-methylpyridinium iodide (98d), using **78d** (1.38 g). (1.86 g, 89 %); pale yellow crystals; m.p. 215-216 °C (from EtOH); FTIR (neat solid) 3015, 1691, 1583, 1511, 817 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.95 (s, br, 1H, H2), 8.94 (d, *J* = 6.6, 1H, H6), 8.50 (d, *J* = 7.8, 1H, H4), 8.15 (dd, *J* = 7.8, 6.6 1H, H5), 8.03 (d, *J* = 8.7, 2H, H2'), 7.83 (d, *J* = 8.7, 2H, H3'), 4.80 (s, 2H, H1''), 4.38 (s, 3H, 1-CH_3); ^{13}C NMR (DMSO-d_6) δ 194.6 (q, C2'), 146.6 (C4), 145.8 (C6), 143.7 (C2), 135.6 (q, C3), 134.7 (q, C1'), 131.8 (C2'), 130.1 (C3'), 127.8 (q, C4'), 126.9 (C5), 47.9 (1-CH_3), 41.1 (C1''); Anal. Calcd for $C_{14}H_{13}BrINO$: C, 40.22; H, 3.12; N, 3.35. Found: C, 40.49; H, 3.20; N, 3.32.

1-Methyl-3-[2-oxo-2-(4-methylphenyl)-ethyl]pyridinium iodide (98e), using **78e** (1.06 g). (1.52 g, 86 %); yellow solid; m.p. 158-159 °C (from EtOH); FTIR (neat solid) 3018, 1675, 1606, 1506 cm^{-1}; ^1H NMR (DMSO-

d_6) δ 9.29 (bs, 1H, H2), 9.01 (d, *J* = 6.0, 1H, H6), 8.32 (d, *J* = 8.1, 1H, H4), 7.95 (dd, *J* = 7.8, 6.0 1H, H5), 7.88 (d, *J* = 8.3, 2H, H2'), 7.22 (d, *J* = 8.1, 2H, H3'), 4.68 (s, 2H, C1''), 4.51 (s, 3H, 1-CH_3), 2.35 (s, 3H, 4'-CH_3); ^{13}C NMR (DMSO-d_6) δ 194.0 (q, C2''), 147.1 (C4), 146.5 (C2), 145.3 (q, C4'), 143.2 (C6), 136.5 (q, C3), 132.9 (q, C1'), 129.7 (C3'), 128.7 (C2'), 127.3 (C5), 49.2 (1-CH_3), 41.5 (C1''), 21.7 (4'-CH_3); Anal. Calcd for $C_{15}H_{16}INO$; C, 51.01; H, 4.57; N, 3.96. Found: C, 51.00; H, 4.56; N, 3.84.

3-[2-(4-Methoxyphenyl)-2-oxo-ethyl]-1-methylpyridinium iodide (98f), using **78f** (1.14 g). (1.52 g, 82 %); yellow solid; m.p. 184-185 °C (from EtOH); FTIR (neat solid) 3016, 1673, 1602, 1511 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.95 (bs, 1H, H2), 8.92 (d, *J* = 6.3, 1H, H6), 8.48 (d, *J* = 8.1, 1H, H4), 8.12 (dd, *J* = 8.1, 6.3 1H, H5), 8.09 (d, *J* = 9.0, 2H, H2'), 7.13 (d, *J* = 9.0, 2H, H3'), 4.73 (s, 2H, H1''), 4.39 (s, 3H, 1-CH_3), 3.87 (s, 3H, 4'-OCH_3); ^{13}C NMR (DMSO-d_6) δ 193.5 (q, C2''), 163.5 (q, C4'), 146.6 (C4), 145.8 (C6), 143.5 (C2), 136.1 (q, C3), 130.5 (C2'), 128.5 (q, C1'), 126.8 (C5), 114.0 (C3'), 55.6 (C4'-OCH_3), 47.8 (1-CH_3), 40.7 (C1''); Anal. Calcd for $C_{15}H_{16}INO_2$: C, 48.80; H, 4.37; N, 3.79. Found: C, 48.80; H, 4.33; N, 3.64.

6.3.10. Synthesis of compounds 75a,c-f



Compounds **75a,c-f** were synthesised using **GP 2**. There was obtained:

1-Phenyl-2-pyridin-3-yl-ethanol (75a), using **78a** (1.97 g). (1.83 g, 92 %); yellow solid; m.p. 117-118 °C (from EtOAc); lit. 120–121 °C;[135] FTIR (neat solid) 3194, 3059, 1577, 1452, 1065 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.34 (dd, *J* = 4.8, 1.8, 1H, H6'), 8.30 (d, *J* = 1.8, 1H, H2'), 7.46 (dt, *J* = 7.8, 1.8, 1H, H4'), 7.28-7.39 (m, 5H, H2", H3", H4"), 7.17 (dd, *J* = 7.5, 4.8, 1H, H5'), 4.89 (dd, *J* = 7.5,5.7, 1H, H1), 3.51 (bs, 1H, OH), 3.05 (dd, *J* = 13.8, 7.5, 1H, $H2_A$), 3.00 (dd, *J* = 13.8, 7.5, 1H, $H2_B$); ^{13}C NMR ($CDCl_3$) δ 150.5 (C2'), 147.4 (C6'), 143.8 (q, C1"), 137.4 (C4'), 134.0 (q, C3'), 128.5 (C3'"), 127.7 (C4"), 126.0 (C2"), 123.2 (C5'), 74.7 (C1), 43.0 (C2); Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.28; H, 6.59; N, 7.16.

1-(4-Fluorophenyl)-2-pyridin-3-yl-ethanol (75b) using **78b** (1.37 g, 63 %); pale yellow solid; m.p. 126 °C (from EtOAc); FTIR (neat solid) 3180 (br), 2918, 1601, 1508, 1427, 1209, 1063, 831, 824, 712 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.40 (dd, *J* = 4.8, 1.5, 1H, H6'), 8.36 (d, *J* = 1.5, 1H, H2'), 7.60 (dt, *J* = 7.8, 1.5, 1H, H4'), 7.35 (dd, *J* = 8.4, 5.7, 2H, H2"), 7.29 (dd, *J* = 7.8, .48, 1H, H5'), 7.12 (t, *J* = 8.7, 2H, H3"), 5.44 (bs, 1H, OH), 4.81 (t, *J* = 6.6, 1H, H1), 2.91 (d, *J* = 6.6, 2H, H2); ^{13}C NMR ($CDCl_3$) δ 161.6 (q, J_{C-F} = 242, C4"), 150.7 (C2'), 147.3 (C6'), 141.8 (q, J_{C-F} = 3, C1"), 137.8 (C4'),

134.9 (q, C3'), 128.3 (J_{C-F} = 8, C2''), 123.6 (C5'), 115.1 (J_{C-F} = 21, C3''), 72.8 (C1), 42.9 (C2). Anal. Calcd for $C_{13}H_{12}FNO$: C, 71.88; H, 5.57; N, 6.45. Found: C, 71.74; H, 5.74; N, 6.18.

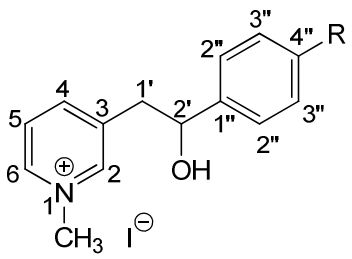
1-(4-Chlorophenyl)-2-pyridin-3-yl-ethanol (75c), using **78c** (2.32 g). (1.33 g, 57 %); yellow solid; m.p. 119-121 °C (from EtOAc); FTIR (neat solid) 3176, 2923, 1600, 1509, 1211, 1064 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.20 (d, *J* = 4.2, 1H, H6'), 8.15 (s, 1H, H2'), 7.34 (d, *J* = 7.8, 1H, H4'), 7.20 (d, *J* = 8.4, 2H, H3''), 7.12 (d, *J* = 8.4, 2H, H2''), 7.06 (dd, *J* = 7.5, 4.8, 1H, H5'), 4.76 (dd, *J* = 7.2, 6.0, 2H, H2''), 3.60 (s, br, 1H, OH), 2.88 (dd, *J* = 13.8, 7.2, 1H, $H2_A$), 2.86 (dd, *J* = 13.8, 6.0, 1H, $H2_B$); ^{13}C NMR ($CDCl_3$) δ 150.4 (C2'), 147.4 (C6'), 142.4 (q, C1''), 137.5 (C4'), 133.7 (q, C3'), 133.3 (q, C4''), 128.6 (C3''), 127.3 (C2''), 123.3 (C5'), 73.9 (C1), 43.0 (C2); Anal. Calcd for $C_{13}H_{12}ClNO$: C, 66.81; H, 5.18; N, 5.99. Found: C, 66.96; H, 5.22; N, 5.92.

1-(4-Bromophenyl)-2-pyridin-3-yl-ethanol (75d), using **78d** (2.76 g). (2.28 g, 82 %); yellow solid; m.p. 114 °C (from EtOAc); FTIR (neat solid) 3260, 2971, 1567, 1487, 1058 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.18 (s, 1H, H6'), 8.14 (s, 1H, H2'), 7.36 – 7.33 (m, 3H, H3'', H4'), 7.08 – 7.03 (m, 3H, H2'', H5'), 4.76 (m, 1H, H1), 3.77 (s, br, 1H, OH), 2.89 (m, 2H, H2); ^{13}C NMR ($CDCl_3$) δ 150.4 (C2'), 147.4 (C6'), 143.9 (q, C1''), 137.5 (C4'), 133.7 (q, C3'), 131.5 (C3''), 127.7 (C2''), 123.2 (C5'), 121.2 (q, C4''), 73.9 (C1), 43.0 (C2); Anal. Calcd for $C_{13}H_{12}BrNO$: C, 56.14; H, 4.35; N, 5.04. Found: C, 56.02; H, 4.30; N, 4.94.

2-Pyridin-3-yl-1-(4-methylphenyl)ethanol (75e), using **78e** (2.11 g). (1.96 g, 92 %); white solid; m.p. 127-128 °C (from EtOAc); FTIR (neat solid) 3188, 3050, 1578, 1459, 1067 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.39 (dd, *J* = 5.7, 1.8, 1H, H6'), 8.34 (d, *J* = 1.8, 1H, H2'), 7.49 (dt, *J* = 7.8, 1.8, 1H, H4'), 7.16-7.24 (m, 5H, H2'', H3'', H5'), 4.87 (dd, *J* = 7.5, 5.7, 1H, H1), 3.05 (dd, *J* = 13.8, 7.5, 1H, $H2_A$), 2.96 (dd, *J* = 13.8, 5.7, 1H, $H2_B$), 2.85 (bs, 1H, OH), 2.38 (s, 3H, 4''-CH_3); ^{13}C NMR ($CDCl_3$) δ 150.6 (C2'), 147.5 (C6'), 140.7 (q, C1''), 137.5 (q, C4''), 137.3 (C4'), 134.0 (q, C3'), 129.2 (C3''), 125.9 (C2''), 123.2 (C5'), 74.7 (C1), 42.9 (C2), 21.1 (4''-CH_3); Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.12; N, 6.56 %. Found: C, 78.84; H, 7.10; N, 6.54.

1-(4-Methoxyphenyl)-2-pyridin-3-yl-ethanol (75f), using **78f** (2.27 g). (1.83 g, 80 %); pale yellow solid; m.p. 123-124 °C (from EtOAc); FTIR (neat solid) 3158, 3028, 1509, 1236, 1028, 824, 712 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.31 (dd, *J* = 4.8, 1.8, 1H, H6'), 8.26 (d, *J* = 1.8, 1H, H2'), 7.39 (dt, *J* = 7.8, 1.8, 1H, H4), 7.14 (d, *J* = 8.4, 2H, H2''), 7.11 (dd, *J* = 8.1, 5.1, 1H, H5'), 6.78 (d, *J* = 8.4, 2H, H3''), 4.76 (dd, *J* = 7.5, 5.7, 1H, H1), 3.72 (s, 3H, 4''-OCH_3), 2.92 (dd, *J* = 13.8, 7.5, 1H, $H2_A$), 2.87 (dd, *J* = 13.8, 5.7, 1H, $H2_B$); ^{13}C NMR ($CDCl_3$) δ 159.2 (q, C4''), 150.1 (C2'), 147.1 (C6'), 137.7 (C4'), 135.7 (q, C3'), 134.1 (q, C1''), 127.2 (C2''), 125.3 (C5'), 113.9 (C3''), 74.5 (C1), 55.3 (4''-OCH_3), 42.8 (C2); Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.18; H, 6.60; N, 6.07.

6.3.11. Synthesis of compounds 99a,c-f



Compounds **99a,c-f** were prepared using **GP 3**. There was obtained:

3-(2-Hydroxy-2-phenylethyl)-1-methylpyridinium iodide (99a) using **75a** (1.00 g). (1.43 g, 84 %); white solid; m.p. 162 °C (from EtOH); FTIR (neat solid) 3343, 3036, 1050, 798, 702, 674 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.92 (bs, 1H, H2), 8.85 (d, *J* = 6.1, 1H, H6), 8.39 (d, *J* = 7.8, 1H, H4), 8.05 (dd, *J* = 7.8, 6.1, 1H, H5), 7.41-7.27 (m, 5H, H2", H3", H4"), 5.56 (d, *J* = 4.5, 1H, OH), 4.89 (m, 1H, H2), 4.34 (s, 3H, 1-CH_3), 3.16 (dd, *J* = 13.5, 3.6, 1H, H1'$_A$), 3.01 (dd, *J* = 13.5, 8.7, 1H, H1'$_B$); ^{13C} NMR (DMSO-d_6) δ 146.3 (C4), 146.1 (C2), 145.0 (q, C3), 143.6 (C6), 140.2 (q, C1"), 128.6 (C3"), 127.7 (C5), 127.3 (C4"), 126.3 (C2"), 72.3 (C1'), 48.3 (1-CH_3), 42.2 (C2'); Anal. Calcd for $C_{14}H_{16}INO$: C, 49.28; H, 4.73; N, 4.10. Found: C, 49.34; H, 4.77; N, 4.01.

3-[2-(4-Chlorophenyl)-2-hydroxyethyl]-1-methylpyridinium iodide (99c), using **75c** (1.17 g). (1.50 g, 80 %); yellow solid; m.p.152-153 °C (from EtOH); FTIR (neat solid) 3328, 3050, 1603, 1485, 1062, 823 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.95 (s, 1H, H2), 8.86 (d, *J* = 6.3, 1H, H6), 8.38 (d, *J* = 7.8, 1H, H4), 8.05 (dd, *J* = 7.8, 6.3, 1H, H5), 7.41 (s, 4H, H2", H3"), 5.63

(d, *J* = 4.8, 1H, OH), 4.92 (ddd, *J* = 8.7, 4.8, 3.6, 1H, H2'), 4.35 (s, 3H, 1-CH_3), 3.11 (dd, *J* = 13.5, 8.7, 1H, H1'$_A$), 2.99 (dd, *J* = 13.5, 3.6, 1H, H1'$_B$); ^{13}C NMR (DMSO-d_6) δ 146.3 (C4), 146.1 (C2), 143.9 (q, C1''), 143.7 (C6), 139.9 (q, C3), 132.1 (q, C4''), 128.6 (C3''), 128.2 (C2''), 127.3 (C5), 71.6 (C2'), 48.3 (1-CH_3), 41.9 (C1'); Anal. Calcd for $C_{14}H_{15}ClINO$: C, 44.77; H, 4.02; N, 3.73. Found: C, 44.84; H, 4.02, N, 3.66.

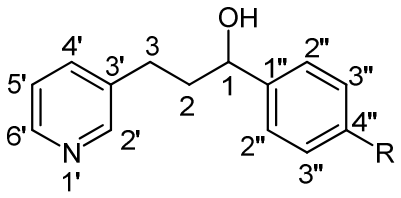
3-[2-(4-Bromophenyl)-2-hydroxy-ethyl]-1-methylpyridinium iodide (99d), using **75d** (1.39 g). (1.68 g, 80 %); yellow solid; m.p. 172-173 °C (from EtOH); FTIR (neat solid) 3319, 3034, 1588, 1481, 1061, 820 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.93 (bs, 1H, H2), 8.86 (d, *J* = 5.7, 1H, H6), 8.39 (d, *J* = 7.8, 1H, H4), 8.05 (dd, *J* = 7.8, 5.7, 1H, H5), 7.55 (d, *J* = 8.4, 2H, H3''), 7.35 (d, *J* = 8.4, 2H, H2''), 5.65 (d, *J* = 3.9, 1H, OH), 4.89 (m, 1H, H1'), 4.33 (s, 3H, 1-CH_3), 3.16 (dd, *J* = 13.5, 3.6, 1H, H1'$_A$), 2.96 (dd, *J* = 13.5, 8.7, 1H, H1'$_B$); ^{13}C NMR (DMSO-d_6) δ 146.3 (C4), 146.1 (C2), 144.4 (q, C1''), 143.7 (C6), 139.9 (q, C3), 131.5 (C3''), 128.6 (C2''), 127.3 (C5), 120.6 (q, C4''), 71.6 (C2'), 48.3 (1-CH_3), 41.9 (C1'); Anal. Calcd for $C_{14}H_{15}BrINO$: C, 40.03; H, 3.60; N, 3.35. Found: C, 39.57; H, 3.57; N, 3.32.

3-[2-Hydroxy-2-(4-methylphenyl)-ethyl]-1-methylpyridinium iodide (99e), using **75e** (1.07 g). (1.42 g, 80 %); pale yellow solid; m.p. 172-173 °C (from EtOH); FTIR (neat solid) 3338, 3053, 1632, 1504, 1062, 819, 677 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.92 (s, br, 1H, H2), 8.84 (d, *J* = 6.0, H6), 8.37 (d, *J* = 7.8, 1H, H4), 8.04 (dd, *J* = 7.8, 6.0, 1H, H5), 7.26 (d, *J* = 7.8, 2H,

H2''), 7.16 (d, *J* = 7.8, 2H, H3''), 4.84 (dd, *J* = 8.7, 4.2, 1H, H2'), 4.34 (s, 3H, 1-CH_3), 3.25 (s, br, 1H, OH), 3.13 (dd, *J* = 13.8, 4.2, 1H, H1'$_A$), 2.99 (dd, *J* = 13.8, 8.7, 1H, H1'$_B$), 2.30 (s, 3H, 4''-CH_3); ^{13}C NMR (DMSO-d_6) δ 146.2 (C4), 146.0 (C2), 143.6 (C6), 142.0 (q, C1''), 140.2 (q, C4''), 136.7 (q, C3), 129.1 (C3''), 127.3 (C5), 126.2 (C2''), 72.2 (C2'), 48.3 (CH_3), 42.2 (C1'), 21.2 (4''-CH_3); Anal. Calcd for $C_{15}H_{18}INO$: C, 50.72; H, 5.11; N, 3.94. Found: C, 50.79; H, 5.11; N, 3.83.

3-[2-Hydroxy-2-(4-methoxyphenyl)ethyl]-1-methylpyridinium iodide (99f), using **75f** (1.15 g). (1.74 g, 94 %); yellow solid; m.p. 153 °C (from EtOH); FTIR (neat solid) 3368, 3037, 1608, 1510, 1241, 1054, 678 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.91 (bs, 1H, H2), 8.84 (d, *J* = 6.0, 1H, H6), 8.36 (d, *J* = 8.1, 1H, H4), 8.04 (dd, *J* = 8.1, 6.3, 1H, H5), 7.30 (d, *J* = 8.7, 2H, H2''), 6.91 (d, *J* = 8.7, 2H, H3''), 5.45 (d, *J* = 4.5, OH), 4.84 (ddd, *J* = 8.7, 4.5, 4.2, 1H, H2'), 4.34 (s, 3H, 1-CH_3), 3.75 (s, 3H, 4''-OCH_3), 3.10 (dd, *J* = 13.5, 4.2, 1H, H1'$_A$), 3.00 (dd, *J* = 13.5, 8.7, 1H, H1'$_B$); ^{13}C NMR (DMSO-d_6) δ 158.9 (q, C4''), 146.2 (C4), 146.0 (C2), 143.6 (C6), 140.2 (q, C1''), 136.9 (q, C3), 127.5 (C2''), 127.3 (C5), 114.0 (C3''), 71.9 (C2'), 55.6 (4''-OCH_3), 48.3 (1-CH_3), 42.2 (C1'); Anal. Calcd for $C_{15}H_{18}INO_2$: C, 48.53; H, 4.89; N, 3.77. Found: C, 48.52; H, 4.85; N, 3.78.

6.3.12 Synthesis of compounds 101a-e



Compounds **101a-e** were prepared using **GP 1**. There was obtained:

1-Phenyl-3-pyridin-3-yl-propan-1-ol (101a), using (±)-**100a** (1.32 g). (1.34 g, 63 %); colourless solid; m.p. 74 °C (from EtOAc / petrol); FTIR (neat solid) 3178 (br), 3024, 2907, 1578, 1426, 1059, 714, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.21 (d, *J* = 1.8, 1H, H2'), 8.18 (dd, *J* = 4.8, 1.8, 1H, H6'), 7.37 (dt, *J* = 7.8, 1.8, 1H, H4'), 7.25-7.14 (m, 5H, H2", H3", H4"), 7.05 (dd, *J* = 4.8, 1.8, 1H, H5), 4.54 (dd, *J* = 8.1, 5.4, 1H, H1), 4.05 (s, br, OH), 2.57-2.68 (m, 2H, $H3_A$, $H3_B$), 2.09-1.88 (m, 2H, H2);^{13}C NMR ($CDCl_3$) δ 149.6 (C2'), 146.9 (C6'), 144.9 (q, C1"), 137.4 (q, C3'), 136.0 (C4'), 128.4 (C3"), 127.4 (C4"), 125.9 (C2"), 123.3 (C5'), 73.0 (C1), 40.2 (C2), 29.2 (C3); Anal. Calcd for $C_{14}H_{15}NO$: C, 78.85; H, 7.13; N, 6.45. Found: C, 78.84; H, 7.09; N, 6.57.

1-(4-Fluorophenyl)-3-pyridin-3-ylpropan-1-ol (101b). Using (±)-**100b** (1.52 g) (0.95 g, 41 %); colourless oil; FTIR (neat) 3188 (br), 2924, 2863, 1603, 1508, 1424, 1219, 1069, 836, 712 cm^{-1}; ^{1}H NMR (DMSO-d6) δ 8.35 (d, J = 1.5, 1H, H2'), 8.32 (dd, *J* = 4.5, 1.5, 1H, H6'), 7.54 (dt, *J* = 7.8, 1.5, 1H, H4'), 7.31 (dd, *J* = 9.0, 5.7,2H, H2"), 7.22 (dd, *J* = 7.8, 4.8, 1H, H5'),

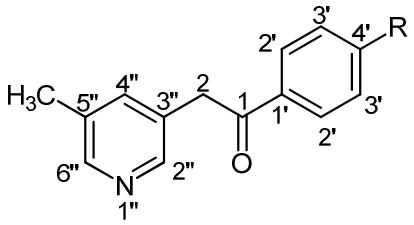
7.07 (t, *J* = 9.0, 2H, H3''), 5.28 (d, *J* = 4.5, 1H, OH), 4.48 (td, J = 6.3, 4.5, 1H, H1), 2.63 (dd, *J* = 14.1, 7.8, 1H, $H3_A$), 2.53 (dd, *J* =14.1, 7.8, 1H, $H3_B$), 1.86-1.79 (m, 2H, H2); ^{13}C NMR (DMSO-d6) δ 161.6 (q, J_{C-F} = 242, C4''), 150.0 (C2'), 147.5 (C6'), 142.6 (q, J_{C-F} = 3, C1''), 137.8 (q, C3'), 136.2 (C4'), 128.1 (J_{C-F} = 8, C2''), 123.9 (C5'), 115.1 (J_{C-F} = 21, C3''), 71.4 (C1), 41.0 (C2), 29.1 (C3). HRMS calcd for $C_{14}H_{14}FNO$ $(M + H)^+$ required 232.1138, found 232.1139.

1-(4-Chlorophenyl)-3-pyridin-3-ylpropan-1-ol (101c), using (±)-**100c** (1.70 g). (1.02 g, 41 %); pale yellow solid; m.p. 54-55 °C (from EtOAc / petrol); FTIR (neat solid) 3181 (br), 2916, 1482, 1421, 1070, 1016, 826, 813, 707 cm^{-1}; ^1H NMR (DMSO-d6) δ 8.42 (d, *J* = 1.5, 1H, H2'), 8.39 (dd, *J* = 4.5, 1.5, 1H, H6'), 7.62 (dt, *J* = 7.8, 1.5, 1H, H4'), 7.38 (s, 4H, H2'', H3''), 7.29 (dd, *J* = 7.8, 4.5, 1H, H5), 5.41 (d, *J* = 4.8, 1H, OH), 4.56 (td, J = 6.3, 4.8, 1H, H1), 2.71 (dd, *J* = 14.1, 7.8, 1H, $H3_A$), 2.60 (dd, *J* = 14.1, 7.8, 1H, $H3_B$), 1.93-1.86 (tt, J = 7.8, 6.3, 2H, H2); ^{13}C NMR (DMSO-d6) δ 150.0 (C2'), 147.5 (C6'), 145.4 (q, C4''), 137.8 (q, C3'), 136.2 (C4'), 131.6 (q, C1''), 128.4 (C2'' or C3''), 128.1 (C2'' or C3''), 123.9 (C5'), 71.3 (C1), 40.8 (C2), 29.0 (C3); HRMS calcd for $C_{14}H_{14}ClNO$ $(M + H)^+$ required 248.0843, found 248.0844.

1-(4-Bromophenyl)-3-pyridin-3-ylpropan-1-ol (101d), using (±)-**100d** (2.19 g). (1.39 g, 48 %); yellow solid; m.p. 72 °C (from EtOAc / petrol); FTIR (neat solid) 3234 (br), 2959, 2919, 1578, 1480, 1427, 1068, 1010, 821, 810, 712 cm^{-1}; ^1H NMR (DMSO-d6) δ 8.43 (d, *J* = 1.5, 1H, H2'), 8.39

(d, *J* = 4.8, 1.5, 1H, H6'), 7.62 (dt, *J* = 7.8, 1.5, 1H, H4'), 7.52 (d, *J* = 8.4, 2H, H3''), 7.32 (d, *J* = 8.4, 2H, H2''), 7.29 (dd, *J* = 7.8, 4.8, 1H, H5'), 5.42 (d, *J* = 4.5, 1H, OH), 4.55 (td, J = 6.0, 4.5, 1H, H1), 2.71 (dd, *J* = 14.1, 7.8, 1H, $H3_A$), 2.60 (dd, *J* = 14.1, 7.8, 1H, $H3_B$), 1.89 (tt, J = 7.8, 6.0, 2H, H2); ^{13}C NMR (DMSO-d6) δ 150.0 (C2'), 147.5 (C6'), 145.9 (q, C1''), 137.8 (q, C3'), 136.2 (C4'), 131.4 (C3''), 128.5 (C2''), 123.9 (C5'), 120.1 (q, C4''), 71.3 (C1), 40.8 (C2), 29.0 (C3). HRMS calcd for $C_{14}H_{14}BrNO$ $(M + H)^+$ required 292.0338, found 292.0344.

6.3.13. Synthesis of compounds 110a,c-f



To a stirred solution of LDA (10 mL, 2.0 M, 20 mmol) in dry THF (60 mL) maintained at 0 °C under an atmosphere of argon was added 3,5-dimethylpyridine **108** (1.07 g, 10 mmol) dropwise over 5 min. The mixture was stirred for a further 5 min, followed by dropwise addition over 5 min of the electrophile **97a,c-f** (11 mmol) in dry THF (10 mL). The resulting solution was stirred at 0 °C for 1 h then quenched with water (60 mL), the phases separated and the aqueous phase extracted using DCM (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure to yield red / brown residues which were

subjected to column chromatography (SiO_2; EtOAc / petrol, 60 / 40 $^{v}/_{v}$) and the solids obtained recrystallised. There was obtained:

2-(5-Methylpyridin-3-yl)-1-phenyl-ethanone (110a), using **97a** (1.13 g) (1.90 g, 90 %); pale yellow crystals; m.p. 59-60 $^{\circ}$C (from EtOAc); lit. 54–55 $^{\circ}$C[167]; FTIR (neat solid) 3028, 1682, 1596, 1456, 753, 691 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.38 (d, *J* = 1.8, 1H, H2''), 8.37 (d, *J* = 1.8, 1H, H6''), 8.05 (dd, *J* = 7.2, 1.5, 2H, H2'), 7.64 (tt, *J* = 7.2, 1.5, 1H, H4'), 7.49 (td, *J* = 7.2, 1.5, 2H, H3'), 7.45 (t, *J* = 1.8, 1H, H4''), 4.29 (s, 2H, H2), 2.82 (s, 3H, 5''-CH_3); ^{13}C NMR ($CDCl_3$) δ 196.6 (q, C1), 148.8 (C2''), 147.7 (C6''), 137.8 (C4''), 136.3 (q, C1'), 133.4 (C4'), 132.9 (q, C5''), 129.7 (q, C3''), 128.8 (C3'), 128.4 (C2'), 42.2 (C2), 18.3 (5''-CH_3); Anal. Calcd for $C_{12}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.52; H, 6.24; N, 6.60.

1-(4-Chlorophenyl)-2-(5-methylpyridin-3-yl)ethanone (110c), using **97c** (1.51 g). (1.20 g, 49 %); yellow solid; m.p. 78-79 $^{\circ}$C (from EtOAc); FTIR (neat solid) 3024, 1680, 1587, 1488, 824 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.27 (d, *J* = 1.8, 1H, H6''), 8.23 (d, *J* = 1.8, 1H, H2''), 7.86 (d, *J* = 8.7, 2H, H2'), 7.37 (d, *J* = 8.7, 2H, H3'), 7.31 (t, *J* = 1.8, 1H, H4''), 4.23 (s, 2H, H2), 2.33 (s, 3H, 5''-CH_3); ^{13}C NMR ($CDCl_3$) δ 195.4 (q, C1), 149.0 (C6''), 147.7 (C2''), 140.0 (q, C4'), 137.7 (C4''), 134.6 (q, C1'), 133.1 (q, C5''), 129.9 (C2'), 129.3 (q, C3''), 129.1 (C3'), 42.2 (C2), 18.3 (5''-CH_3); Anal. Calcd for $C_{14}H_{12}ClNO$: C, 68.44; H, 4.92; N, 5.70. Found: C, 68.63; H, 4.98; N, 5.90.

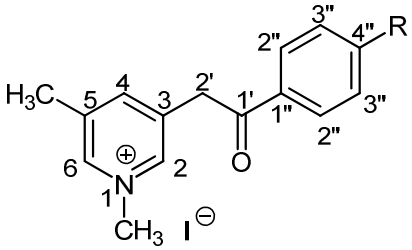
1-(4-Bromophenyl)-2-(5-methylpyridin-3-yl)ethanone (110d), using **97d** (2.00 g). (0.64 g, 22 %); yellow solid; m.p. 74 °C (from EtOAc); FTIR (neat solid) 3085, 1683, 1583, 1483 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.26 (d, *J* = 1.5, 1H, H6''), 8.22 (d, *J* = 1.5, 1H, H2''), 7.79 (d, *J* = 8.7, 2H, H2'), 7.56 (d, *J* = 8.7, 2H, H3'), 7.32 (t, *J* = 1.5, 1H, H4''), 4.14 (s, 2H, H2), 2.24 (s, 3H, 5''-CH_3); ^{13}C NMR ($CDCl_3$) δ 195.6 (q, C1), 148.9 (C2''), 147.5 (C6''), 137.8 (C4''), 135.0 (q, C1'), 133.2 (q, C5''), 132.1 (C3'), 130.4 (q, C3''), 130.0 (C2'), 129.6 (q, C4'), 42.2 (C2), 18.3 (5''-CH_3); HRMS calcd for $C_{14}H_{12}BrNO$ $(M + H)^+$ required 290.0181, found 290.0190.

2-(5-Methylpyridin-3-yl)-1-(4-methylphenyl)ethanone (110e). using **97e** (1.29 g). (1.91 g, 85 %); pale yellow solid; m.p. 67-68 °C (from EtOAc); FTIR (neat solid) 3027, 1681, 1604, 811 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.34 (bs, 2H, H2'', H6''), 7.94 (d, *J* = 8.1, 2H, H2'), 7.48 (bs, 1H, H4''), 7.30 (d, *J* = 8.1, 2H, H3'), 4.27 (s, 2H, H2), 2.45 (s, 3H, 5''-CH_3), 2.36 (s, 3H, 4'-CH_3); ^{13}C NMR ($CDCl_3$) δ 196.2 (q, C1), 148.9 (C6''), 147.7 (C2''), 144.4 (q, C4'), 137.6 (C4''), 133.9 (q, C1'), 132.9 (q, C5''), 129.8 (q, C3''), 129.5 (C3'), 128.6 (C2'), 42.1 (C2), 21.7 (4'-CH_3), 18.3 (5''-CH_3); Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.85; H, 6.75; N, 6.16.

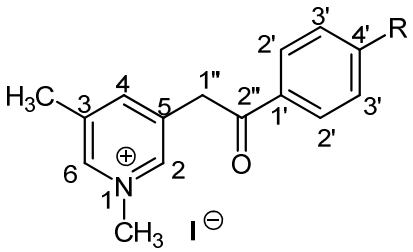
1-(4-Methoxyphenyl)-2-(5-methylpyridin-3-yl)ethanone (110f), using **97f** (1.46 g). (1.57 g, 65 %); pale yellow solid; m.p. 85-86 °C (from EtOAc); FTIR (neat solid) 3071, 1675, 1601, 1508, 831 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.33 (s, 2H, H2'', H6''), 8.00 (d, *J* = 8.9, 2H, H2'), 7.41 (s, 1H, H4), 6.95 (d, *J* = 8.7, 2H, H3'), 4.20 (s, 2H, H2), 3.87 (s, 3H, 4'-OCH_3), 2.31 (s, 3H, 5''-

CH_3); ^{13}C NMR ($CDCl_3$) δ 195.4 (q, C1), 160.0 (q, C4'), 149.1 (C6''), 147.7 (C2''), 137.6 (C4''), 136.8 (q, C1'), 134.6 (q, C3''), 133.0 (q, C5''), 129.9 (C2'), 129.2 (C3'), 55.3 (4'-OCH_3), 42.2 (C2), 18.3 (5''-CH_3); Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.80. Found: C, 74.70; H, 6.30; N, 5.91.

6.3.1.4. Synthesis of compounds 111a,c-f



R = Cl, Br, OCH_3



R = H, CH_3

Compounds **111a,c-f** were prepared using **GP 3**. There was obtained:

1,3-Dimethyl-5-(2-oxophenylethyl)pyridinium iodide (111a), using **110a** (1.06 g). (1.48 g, 84 %); pale yellow solid; m.p. 153-154 °C (from EtOH); FTIR (neat solid) 3017, 1684, 1211, 764, 690, 666 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.87 (s, 1H, H6), 8.80 (s, 1H, H2), 8.35 (s, 1H, H4), 8.01 (d, *J* = 7.2, 2H, H2'), 7.76 (t, *J* = 7.2, 1H, H4'), 7.60 (t, *J* = 7.2, 2H, H3'), 4.77 (s, 2H, H1''), 4.33 (s, 3H, 1-CH_3), 2.50 (s, 3H, 3-CH_3); ^{13}C NMR (DMSO-d_6) δ 196.0 (q, C2''), 147.5 (C4), 143.9 (C2 or C6), 143.8 (C2 or C6), 137.9 (q, C3), 136.3 (q, C1'), 135.8 (q, C5), 134.4 (C4'), 129.4 (C2'), 128.7 (C3'), 48.3 (1-CH_3), 41.7 (C1''), 18.2 (3-CH_3); Anal. Calcd for $C_{15}H_{16}INO$: C, 51.01; H, 4.57; N, 3.97. Found: C, 50.88; H, 4.54; N, 3.73.

3-[2-(4-Chlorophenyl)-2-oxoethyl]-1,5-dimethylpyridinium iodide (111c), using **110c** (1.23 g). (1.65 g, 85 %); yellow solid; m.p. 168-169 °C (from EtOH); FTIR (neat solid) 3020, 1694, 1585, 1497, 821 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.89 (s, 1H, H6), 8.80 (s, 1H, H2), 8.35 (s, 1H, H4), 8.11 (d, *J* = 6.9, 2H, H2''), 7.69 (d, *J* = 6.9, 2H, H3''), 4.76 (s, 2H, H1'), 4.34 (s, 3H, 1-CH_3), 2.50 (s, 3H, 5-CH_3); ^{13}C NMR (DMSO-d_6) δ 195.1 (q, C2'), 147.5 (C4), 143.9 (C2 or C6), 143.8 (C2 or C6), 139.2 (q, C4''), 138.0 (q, C5), 135.6 (q, C3), 135.0 (q, C1''), 130.7 (C2''), 129.5 (C3''), 48.3 (1-CH_3), 41.7 (C1'), 18.2 (5''-CH_3); Anal. Calcd for $C_{15}H_{15}ClINO$: C, 46.48; H, 3.90; N, 3.61. Found: C, 46.26; H, 3.90; N, 3.54.

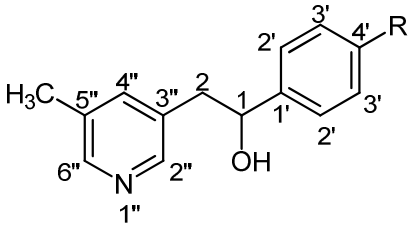
3-[2-(4-Bromophenyl)-2-oxoethyl]-1,5-dimethylpyridinium iodide (111d), using **110d** (1.45 g). (1.47 g, 68 %); yellow solid; m.p. 210-211 °C (from EtOH); FTIR (neat solid) 3027, 1676, 1582, 1488, 1068, 753, 688 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.87 (s, 1H, H6), 8.79 (s, 1H, H2), 8.34 (s, 1H, H4), 8.02 (d, *J* = 8.7, 2H, H3''), 7.83 (d, *J* = 8.7, 2H, H2''), 4.75 (s, 2H, H2'), 4.33 (s, 3H, 1-CH_3), 2.50 (s, 3H, 5-CH_3); ^{13}C NMR (DMSO-d_6) δ 195.3 (q, C1'), 147.5 (C4), 143.9 (C2 or C6), 143.8 (C2 or C6), 138.0 (q, C5), 135.6 (q, C4''), 135.3 (q, C3), 132.5 (C2''), 130.7 (C3''), 128.5 (q, C1''), 48.3 (1-CH_3), 41.7 (C2'), 18.2 (5-CH_3); Anal. Calcd for $C_{15}H_{15}BrINO$: C, 41.70; H, 3.50; N, 3.24. Found: C, 41.53; N, 3.48; N, 3.15.

1,3-Dimethyl-5-[2-oxo-2-(4-methylphenylethyl]pyridinium iodide (111e), using **110e** (1.13 g). (1.62 g, 88 %); pale yellow solid; m.p. 147-148 °C (from EtOH); FTIR (neat solid) 3018, 1681, 1606, 816, 677 cm^{-1}; ^1H

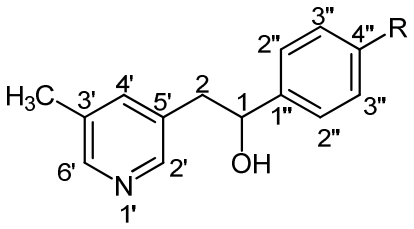
NMR (DMSO-d_6) δ 8.87 (s, 1H, H6), 8.80 (s, 1H, H2), 8.35 (s, 1H, H4), 8.00 (d, *J* = 8.1, 2H, H2'), 7.42 (d. *J* = 8.1, 2H, H3'), 4.73 (s, 2H, H1''), 4.34 (s, 3H, 1-CH_3), 2.52 (s, 3H, 3-CH_3), 2.43 (s, 3H, 4'-CH_3); ^{13}C NMR (DMSO-d_6) δ 195.5 (q, C2'), 147.5 (C4), 144.9 (q, C4''), 143.8 (C2 + C6), 143.8 (C2), 137.9 (q, C3), 135.9 (q, C5), 133.8 (q, C1''), 129.9 (C3''), 128.9 (C2''), 48.3 (1-CH_3), 41.5 (C1'), 21.7 (4''-CH_3), 18.2 (3-CH_3); Anal. Calcd for $C_{16}H_{18}INO$: C, 52.33; H, 4.94; N, 3.81. Found: C, 51.86; H, 4.90; N, 3.85.

3-[2-(4-Methoxyphenyl)-2-oxoethyl]-1,5-dimethylpyridinium iodide (111f), using **110f** (1.21 g). (1.80 g, 94 %); yellow solid; m.p. 217 °C (from EtOH); FTIR (neat solid) 3039, 1679, 1598, 1470, 1170, 844 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.86 (s, 1H, H6), 8.79 (s, 1H, H2), 8.34 (s, 1H, H4), 8.08 (d, *J* = 9.0, 2H, H2''), 7.12 (d, *J* = 9.0, 2H, H3''), 4.69 (s, 2H, H2'), 4.33 (s, 3H, 1-CH_3), 3.88 (s, 3H, 4''-OCH_3), 2.50 (s, 3H, 5-CH_3); ^{13}C NMR (DMSO-d_6) δ 194.2 (q, C1'), 164.2 (q, C4''), 147.5 (C4), 143.8(C2 + C6), 137.9 (q, C5), 136.1 (q, C3), 131.1 (C2''), 129.2 (q, C1''), 114.6 (C3''), 56.2 (4''-OCH_3), 48.2 (1-CH_3), 41.3 (C2'), 18.2 (5-CH_3); Anal. Calcd for $C_{16}H_{18}ClINO_2$: C, 50.15; H, 4.73; N, 3.65. Found: C, 50.13; H, 4.71; N, 3.52.

6.3.15. Synthesis of compounds 112a-e



R = H, CH_3



R = OCH_3, Br, Cl

Compounds **112a,c-f** were synthesised using **GP 2**. There was obtained:

2-(5-Methylpyridin-3-yl)-1-phenylethanol (112a), using **111a** (2.11 g). (1.98 g, 93 %); white solid; m.p. 117 °C (from EtOAc); FTIR (neat solid) 3440-3050, 3029, 1636, 1447, 1063, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.21 (d, *J* = 1.5, 1H, H6''), 8.15 (d, *J* = 1.5, 1H, H2''), 7.38 – 7.31 (m, 6H, H2', H3', H4'), 4.90 (d, *J* = 7.5, 1H, H1), 3.14 (s, br, 1H, OH), 2.99 (d, *J* = 7.5, 2H, H2); ^{13}C NMR ($CDCl_3$) δ 148.0 (C6''), 147.6 (C2''), 143.9 (q, C1'), 138.0 (C4''), 133.6 (q, C3''), 132.7 (q, C5''), 128.5 (C3'), 127.7 (C4'), 125.9 (C2'), 74.8 (C1), 42.9 (C2), 18.3 (5''-CH_3); Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.65; H, 7.06; N, 6.62.

1-(4-Chlorophenyl)-2-(5-methylpyridin-3-yl)ethanol (112c), using **111c** (2.46 g). (1.78 g, 72 %); yellow solid; m.p. 94-95 °C (from EtOAc); FTIR (neat solid) 3450-3050, 2915, 1567, 1487, 1058, 1012, 836, 710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.67 (s, 1H, H6'), 8.60 (s, 1H, H2'), 8.30 (s, 1H, H4'), 7.40 (bs, 4H, H2'', H3''), 4.88 (dd, *J* = 8.7, 6.3, 1H, H1), 3.92 (s, br, 1H, OH), 3.15 (dd, *J* = 12.8, 6.3, 1H, $H2_A$), 2.97 (dd, *J* = 12.8, 8.7, 1H, $H2_B$), 2.46 (s, 3H, 5'-CH_3); ^{13}C NMR ($CDCl_3$) δ 147.7 (C4'), 144.2 (q, C1''), 139.6 (C2'),

139.3 (C6'), 138.8 (q, C5'), 137.4 (q, C3'), 132.0 (q, C4''), 128.5 (C3''), 128.2 (C2''), 71.7 (C1), 41.8 (C2), 18.2 (5'-CH_3); Anal. Calcd for $C_{14}H_{14}ClNO$: C, 67.88; H, 5.70; N, 5.65. Found: C, 67.81; H, 5.84; N, 5.73.

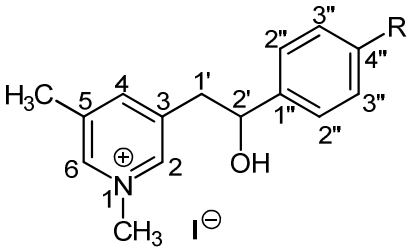
1-(4-Bromophenyl)-2-(5-methylpyridin-3-yl)ethanol (112d), using **111d** (2.90 g). (2.33 g, 80 %); pale yellow solid; m.p. 113 °C (from EtOAc); FTIR (neat solid) 3260 b, 3074, 1567, 1487, 1058, 1012 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.16 (bs, 1H, H6'), 8.11 (bs, 1H, H2'), 7.38 (d, *J* = 7.8, 2H, H3''), 7.19 (bs, 1H, H4'), 7.10 (d, *J* = 7.8, 2H, H3''), 4.78 (t, *J* = 6.6, 1H, H1), 2.92 (s, br, 1H, OH), 2.89 (d, *J* = 6.6, 2H, H2), 2.21 (s, 3H, 5'-CH_3); ^{13}C NMR ($CDCl_3$) δ 147.2 (C6'), 146.8 (C2'), 142.8 (q, C1''), 138.4 (C4'), 133.5 (q, C5'), 131.2 (q, C3'), 131.6 (C3''), 127.6 (C2''), 121.5 (q, C4''), 73.9 (C1), 42.8 (C2), 18.3 (5'-CH_3); Anal. Calcd for $C_{14}H_{14}BrNO$: C, 57.55; H, 4.83; N, 4.79. Found: 57.28; H, 4.79; N, 4.51.

2-(5-Methylpyridin-3-yl)-1-(4-methylphenyl)-ethanol (112e), using **111e** (2.25 g). (2.16 g, 95 %); white solid; m.p. 107-108 °C (from EtOAc); FTIR (neat solid) 3400-3100, 3028, 1585, 1441, 814 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.97 (s, 1H, H6''), 7.93 (s, 1H, H2''), 7.17 (s, 1H, H4''), 7.14 (d, *J* = 7.8, 2H, H2'), 7.02 (d, *J* = 7.8, 2H, H3'), 4.69 (dd, *J* = 7.5, 5.4, 1H, H1), 2.84 (dd, *J* = 12.9, 7.5, 1H, $H2_A$), 2.77 (dd, J = 12.9, 5.4, 1H, $H2_B$), 2.49 (s, br, 1H, OH), 2.23 (s, 3H, 4'-CH_3), 2.12 (s, 3H, 5''-CH_3); ^{13}C NMR ($CDCl_3$) δ 147.6 (C2'' or C6''), 147.5 (C2'' or C6''), 141.2 (q, C1'), 138.0 (C4''), 137.1 (q, C4'), 133.7 (q, C3''), 132.5 (q, C5''), 129.0 (C3'), 125.9 (C2'), 74.4 (C1),

42.9 (C2), 21.1 (4'-CH_3), 18.2 (5''-CH_3); Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; 6.16. Found: C, 79.01; H, 7.56; N, 6.11.

1-(4-Methoxyphenyl)-2-(5-methylpyridin-3-yl)ethanol (112f), using **111f** (2.41 g). (1.90 g, 78 %); pale yellow solid; m.p. 99-100 $^{\circ}$C (from EtOAc); FTIR (neat solid) 3260, 3074, 1569, 1487, 1059, 1013, 840 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.05 (bs, 1H, H6'), 8.03 (bs, 1H, H2'), 7.24 (bs, 1H, H4'), 7.13 (d, *J* = 8.7, 2H, H2''), 6.76 (d, *J* = 8.7, 2H, H3''), 4.73 (dd, *J* = 7.5, 5.4, 1H, H1), 4.08 (s, br, 1H, OH), 3.70 (s, 3H, 4''-OCH_3), 2.88 (dd, *J* = 12.9, 7.5, 1H, $H2_A$), 2.82 (dd, *J* = 12.9, 5.4, 1H, $H2_B$), 2.17 (s, 3H, 5'-CH_3); ^{13}C NMR ($CDCl_3$) δ 159.1 (q, C4''), 146.7 (C6' and C2'), 138.9 (C4'), 136.0 (q, C1''), 133.2 (q, C3'), 131.1 (q, C5'), 127.1 (C2''), 113.8 (C3''), 74.2 (C1), 55.3 (4''-OCH_3), 42.8 (C2), 18.3 (5'-CH_3); Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.84; H, 7.11; N, 5.71.

6.3.16. Synthesis of compounds 113a,c-f



Compounds **113a,c-f** were prepared using **GP 3**. There was obtained:

3-(2-Hydroxy-2-phenylethyl)-1,5-dimethylpyridinium iodide (113a), using **112a** (1.07 g). (1.76 g, 99 %); yellow solid; m.p. 117-118 °C (from EtOH); FTIR (neat solid) 3254, 3039, 1497, 1038, 758, 689 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.78 (s, 1H, H6), 8.76 (s, 1H, H2), 8.27 (s, 1H, H4), 7.41-7.27 (m, 5H, H2'', H3'', H4''), 5.54 (d, *J* = 4.5, 1H, OH), 4.88 (dd, *J* = 9.0, 4.5, 3.8, 1H, H2'), 4.29 (s, 3H, 1-CH_3), 3.09 (dd, *J* = 13.8, 3.9, 1H, H1'$_A$), 2.95 (dd, *J* = 13.8, 9.0, 1H, H1'$_B$), 2.50 (s, 3H, 5-CH_3); ^{13}C NMR (DMSO-d_6) δ 146.7 (C4), 145.1 (q, C1''), 143.4 (C2), 143.2 (C6), 139.6 (q, C3), 137.7 (q, C5), 128.6 (C3''), 127.7 (C4''), 126.2 (C2''), 72.4 (C2'), 48.1 (1-CH_3), 42.2 (C1'), 18.2 (5-CH_3); Anal. Calcd for $C_{15}H_{18}INO$: C, 50.72; H, 5.11; N, 3.94. Found: C, 50.71; H, 5.30; N, 3.54.

3-[2-(4-Chlorophenyl)-2-hydroxyethyl]-1,5-dimethylpyridinium iodide (113c), using **112c** (1.24 g). (1.50 g, 77 %); pale yellow solid; m.p. 139-140 °C (from EtOH); FTIR (neat solid) 3314, 2948, 2362, 1488, 1062, 848, 674 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.79 (s, 1H, H2), 8.77 (s, 1H, H6), 8.29 (s,

1H, H4), 7.42 (s, 4H, H2'', H3''), 5.61 (d, *J* = 4.5, 1H, OH), 4.91 (ddd, *J* = 8.7, 4.5, 3.6, 1H, H2'), 4.30 (s, 3H, 1-CH_3), 3.11 (dd, *J* = 13.5, 3.6, 1H, H1'$_A$), 2.92 (dd, *J* = 13.5, 9.0, 1H, H1'$_B$), 2.45 (s, 3H, 5-CH_3); ^{13}C NMR (DMSO-d_6) δ 146.7 (C4), 144.1 (q, C1''), 143.4 (C6), 143.3 (C2), 139.3 (q, C5), 137.8 (q, C3), 132.1 (q, C4''), 128.6 (C3''), 128.1 (C2''), 71.7 (C2'), 48.1 (1-CH_3), 41.9 (C1'), 18.2 (5-CH_3); Anal. Calcd for $C_{15}H_{17}ClINO$: C, 46.24; H, 4.40; N, 3.59. Found: C, 46.22; H, 4.36; N, 3.68.

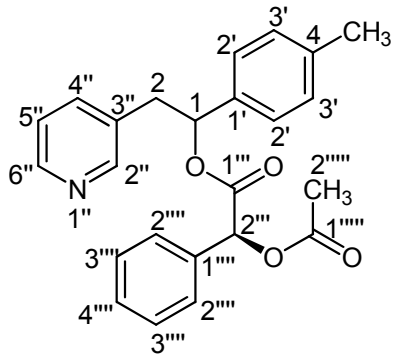
3-[2-(4-Bromophenyl)-2-hydroxyethyl]-1,5-dimethylpyridinium iodide (113d), using **112d** (1.46 g). (1.71 g, 79 %); pale yellow solid; m.p.177 °C (from EtOH); FTIR (neat solid) 3319, 3005, 2363, 1485, 1063, 839, 668, 579 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.79 (s, 1H, H2), 8.77 (s, 1H, H6), 8.30 (s, 1H, H4), 7.57 (d, *J* = 8.1, 2H, H3''), 7.37 (d, *J* = 8.1, 2H, H2''), 5.63 (d, *J* = 4.2, 1H, OH), 4.89 (ddd, *J* = 9.0, 4.5, 2.7, 1H, H2'), 4.30 (s, 3H, 1-CH_3), 3.11 (dd, *J* = 13.2, 2.7, 1H, H1'$_A$), 2.95 (dd, *J* = 13.2, 9.0, 1H, H1'$_B$), 2.51 (s, 3H, 5-CH_3); ^{13}C NMR (DMSO-d_6) δ 146.7 (C4), 144.5 (q, C1''), 143.4 (C6), 143.3 (C2), 139.3 (q, C3), 137.8 (q, C5), 131.5 (C2''), 128.5 (C3''), 120.6 (q, C4''), 71.7 (C1'), 48.1 (1-CH_3), 41.9 (C2'), 18.2 (5-CH_3); Anal. Calcd for $C_{15}H_{17}BrINO$: C, 41.50; H, 3.95; N, 3.23. Found: C, 41.46; H, 3.91; N, 3.20.

3-[2-Hydroxy-2-(4-methylphenyl*)*-ethyl]-1,5-dimethylpyridinium iodide (113e), using **112e** (1.14 g). (1.37 g, 74 %); white solid; m.p. 156 °C (from EtOH); FTIR (neat solid) 3327, 3026, 1635, 1506, 1030, 824 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.78 (s, 1H, H2), 8.76 (s, 1H, H6), 8.28 (s, 1H, H4), 7.28 (d, *J*

= 7.8, 2H, H2''), 7.16 (d, *J* = 7.8, 2H, H3''), 5.45 (d, *J* = 4.5, 1H, OH), 4.84 (ddd, *J* = 9.0, 4.5, 3.9, 1H, H2'), 4.30 (s, 3H, 1-CH_3), 3.08 (dd, *J* = 13.8, 3.9, 1H, H1'$_A$), 2.96 (dd, *J* = 13.8, 9.0, 1H, H1'$_B$), 2.45 (s, 3H, 5-CH_3), 2.30 (s, 3H, 4''-CH_3); ^{13}C NMR (DMSO-d_6) δ 146.7 (C4), 143.3 (C6), 143.1 (C2), 142.1 (q, C1''), 139.7 (q, C3), 137.7 (q, C5), 136.7 (q, C4''), 129.1 (C3''), 126.2 (C2''), 72.2 (C1'), 48.1 (1-CH_3), 42.2 (C2'), 21.2 (4''-CH_3), 18.2 (5-CH_3); Anal. Calcd for $C_{16}H_{20}INO$: C, 52.05; H, 5.46; N, 3.79. Found: C, 51.97; H, 5.44; N, 3.75.

3-[2-Hydroxy-2-(4-methoxyphenyl)ethyl]-1,5-dimethylpyridinium iodide (113f), using **112f** (1.22 g). (1.33 g, 69 %); pale yellow solid; m.p. 178-179 °C (from EtOH); FTIR (neat solid) 3319, 3035, 1624, 1499, 825 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.77 (s, 1H, H2), 8.74 (s, 1H, H6), 8.26 (s, 1H, H4), 7.31 (d, *J* = 8.7, 2H, H2''), 6.92 (d, *J* = 8.7, 2H, H3''), 5.43 (d, *J* = 4.5, 1H, OH), 4.82 (ddd, *J* = 8.7, 4.5, 3.9, 1H, H2'), 4.29 (s, 3H, 1-CH_3), 3.75 (s, 3H, 4''-OCH_3), 3.08 (dd, *J* = 12.5, 3.9, 1H, H1'$_A$), 2.93 (dd, *J* = 13.5, 8.7, 1H, H1'$_B$), 2.45 (s, 3H, 5-CH_3); ^{13}C NMR (DMSO-d_6) δ 158.9 (q, C4''), 146.6 (C4), 143.3 (C6), 143.1 (C2), 139.7 (q, C1''), 137.7 (q, C5), 137.1 (q, C3), 127.4 (C2''), 114.0 (C3''), 72.0 (C1'), 55.6 (4''-OCH_3), 48.1 (1-CH_3), 42.3 (C2'), 18.2 (5-CH_3); Anal. Calcd for $C_{16}H_{20}INO_2$: C, 49.88; H, 5.23; N, 3.64. Found: C, 49.87; H, 5.22; N, 3.55.

6.3.17. (S,S) or (R,S) Acetoxyphenylacetic acid 2-pyridin-3-yl-1-(4-methylphenyl)ethyl ester (118).

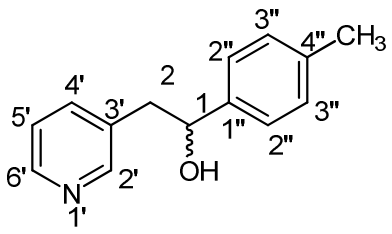


To a stirred solution of 2-pyridin-3-yl-1-(4-methylphenyl)ethanol **75c** (1.28 g, 6 mmol) and DMAP (2.20 g, 18 mmol) in dry DCM (35 mL) under an atmosphere of argon was added DCC (12.4 g, 60 mmol) and (*S*)-*O*-acetyl mandelic acid (2.33 g, 12 mmol) in DCM (60 mL) *via* cannula. The resulting white suspension was allowed to warm to room temperature and stirred for a further 3 h, after which time the suspended urea was removed by filtration and the filtrate concentrated *in vacuo* to give a yellow oil. Subsequent column chromatography (SiO_2; ether, 100 %) furnished the title compound **118** as a colourless oil (2.00 g, 85 %). Recrystallisation from EtOAc / petrol gave a single diastereomer as a white solid; de > 98 %; m.p. 76 – 77 $^{\circ}$C; FTIR (neat solid) 3028, 1748, 1203, 1218, 1168, 1050, 808, 746, 711, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.42 (dd, *J* = 4.8, 1.5, 1H, H6''), 8.16 (d, *J* = 1.5, 1H, H2''), 7.44-7.39 (m, 5H, H2'''', H3'''', H4''''), 7.17 (bs, 4H, H2', H3'), 7.14 (dt, *J* = 7.8, 1.5, 1H, H4''), 7.02 (dd, *J* = 7.8, 4.8, 1H, H5''), 5.98 (dd, *J* = 7.8, 5.4, 1H, H1), 5.98 (s, 1H, H2'''), 3.09 (dd, *J* = 14.1, 7.8, 1H, $H2_A$), 3.02 (dd, *J* = 14.1, 5.4, 1H, $H2_B$), 2.37 (s, 3H, 4'-CH_3),

2.18 (s, 3H, H2''''); ^{13}C NMR ($CDCl_3$) δ 170.1 (q, C1''''), 167.9 (q, C1'''), 149.9 (C2''), 147.3 (C6''), 138.2 (q, C4'), 137.3 (C4''), 135.5 (q, C1''''), 133.8 (q, C1'), 132.3 (q, C3''), 129.3 (C3'), 128.9 (C2'''' or C3''''), 128.8 (C2'''' or C3''''), 127.7 (C4'''' and C3''''), 126.2 (C2'), 123.2 (C5''), 77.1 (C1), 74.4 (C2'''), 39.7 (C2), 21.2 (4'-CH_3), 20.7 (C2''''). Anal. Calcd for $C_{23}H_{23}NO_4$: C, 73.19; H, 61.4; N, 3.71. Found: C, 73.13; H, 6.01; N, 3.59.

de > 98 %; Colourless oil; FTIR (neat) 3026, 1751, 1202, 1218, 1168, 1048, 808, 745, 711, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.28 (bs, 1H, H6''), 8.04 (bs, 1H, H2''), 7.27-7.23 (m, ^H, H2'''', H3'''', H4'''', H4''), 6.88 (d, J = 8.1, 2H, H2'), 6.86 (J = 7.8, 4.8, H, H5''), 6.69 (d, J = 8.1, 2H, H3'), 5.86 (s, 1H, H2''), 5.83 (dd, J = 7.8, 5.4, 1H, H1), 2.97 (dd, J = 14.1, 7.8, 1H, $H2_A$), 2.90 (dd, J = 14.1, 5.4, 1H, $H2_B$), 2.19 (s, 3H, 4'-CH_3), 2.05 (s, 3H, H2''''); ^{13}C NMR ($CDCl_3$) δ 170.2 (q, C1''''), 167.8 (q, C1'''), 150.9 (C2''), 148.1 (C6''), 138.2 (q, C4'), 137.0 (C4''), 135.3 (q, C1''''), 133.5 (q, C1'), 131.9 (q, C3''), 129.2 (C3'), 128.9 (C2'''' or C3''''), 128.7 (C2'''' or C3''''), 127.8 (C4''''), 126.0 (C2'), 123.0 (C5''), 77.3 (C1), 75.5 (C2'''), 39.9 (C2), 21.1 (4'-CH_3), 20.7 (C2''''); HRMS calcd for $C_{24}H_{23}NO_4$ $(M + H)^+$ required 390.1706, found 390.1707.

6.3.18. 2-Pyridin-3-yl-1-(4-methylphenyl)ethanol (*R*) or (*S*)-75e.

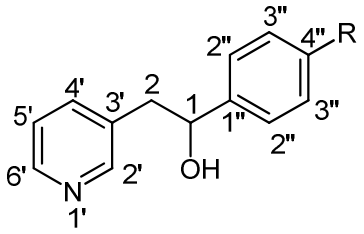


A solution of KOH (88 mg, 1.6 mmol) and compound **118** (0.24 g, 0.6 mmol) in MeOH (3 mL) was stirred at room temperature overnight. Filtration and removal of the solvent *in vacuo,* followed by recrystallisation from EtOAc furnished single enantiomers of the product **75c** as a white solids (0.13 g, 98 %); m.p. 105 -106 °C (EtOAc); $[\alpha]^{24}$ = + 16.2° (c = 0.34, $CHCl_3$); (0.12 g, 87 %); m.p. 103 °C (EtOAc); $[\alpha]^{22}$ = - 14.8° (c = 0.19, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.43 (bs, 1H, H2'), 8.40 (bs, 1H, H6'), 7.66 (dt, *J* = 7.8, 1.8, 1H, H4'), 7.34 (dd, *J* = 7.8, 5.1, 1H, H5'), 7.24 (d, *J* = 8.1, 2H, H2''), 7.15 (d, *J* = 8.1, 2H, H3''), 5.36 (bs, 1H, OH), 4.79 (t, *J* = 6.6, 1H, H1), 2.96 (bs, 1H, $H2_A$), 2.94 (d, *J* = 1.5, 1H, $H2_B$), 2.32 (s, 3H, 4''-CH_3); ^{13}C NMR ($CDCl_3$) δ 150.5 (C2'), 147.1 (C6'), 142.7 (q, C3'), 138.0 (C4'), 136.3 (q, C4''), 135.2 (q, C1''), 128.9 (C3''), 126.4 (C2''), 123.7 (C5'), 73.3 (C1), 42.9 (C2), 21.2 (4''-CH_3).

6.4 Synthetic Work, Chapter 3

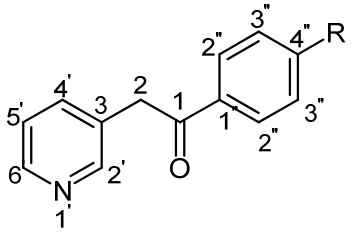
Procedure for Halogen-Lithium Exchange of 3-Bromopyridine

Synthesis of 75a-e



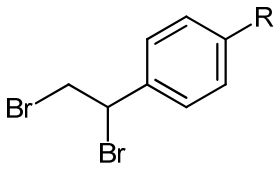
A solution of 3-bromopyridine **120** (1.58 g, 10 mmol) in dry ether (60 mL) was cooled to -100 ^{o}C followed by the dropwise addition of n-BuLi (4.4 mL, 2.5M, 11 mmol) in ether (10 mL) over 15-20 min. The resulting bright yellow solution was stirred at -100 ^{o}C for a further 30 min. and a solution of **100a** (1.32 g, 11 mmol), **100b** (1.52 g, 11 mmol), **100c** (1.70 g, 11 mmol) or **100d** (2.19 g, 11 mmol) in ether (15 mL) added dropwise over 10 min. The reaction mixture was stirred at -100 ^{o}C for 30 min., allowed to warm to room temperature for a further 1h and poured into water (80 mL). The phases were separated and the aqueous phase extracted with EtOAc (3 x 30 mL). The combined organic phases were washed with brine (40 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; EtOAc / petrol, 90 / 10 $^{v}/_{v}$) and recrystallisation from EtOAc gave **75a-e**. There was obtained compounds **78a** (1.22 g, 61 %), **78b** (1.11 g, 51 %), **78c** (1.26 g, 54 %) and **78d** (0.86 g, 31 %). Analytical data were identical to those described in 6.4.1.

Synthesis of 78a-d by oxidation of 75a-d



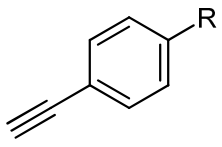
To a suspension of PCC (1.62 g, 7.5 mmol), in DCM (50 mL) was added **75a** (0.99 g, 5 mmol), **75b** (1.08 g, 5 mmol) **75c** (1.16 g, 5 mmol) or **75d** (1.38 g, 5 mmol) and the resulting mixture stirred at room temperature for 2h. whereupon 10 % aqueous NaOH solution was added (15 mL), the phases separated and the aqueous phase extracted with DCM (2 x 20 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. Column chromatography of the resulting residues (SiO_2; EtOAc / petrol, 90 / 10 $^{v}/_{v}$) gave compounds **78a-d**. **78a** (0.81 g, 82 %), **78b** (0.80 g, 74 %), **78d** (0.96 g, 83 %) and **78e** (0.97, 70 %). Analytical data were identical to those described in 6.3.8.

Synthesis of 146c and 146d



Bromine (5.3 mL, 104 mmol.) was added dropwise to a stirred solution of **145c** (11.1 g, 80 mmol) or **145c** (14.6 g, 80 mmol) in chloroform (150 mL) at room temperature. The resulting mixture was stirred at room temperature overnight. A 5 % aq. sodium metabisulphite solution was added until the bromine colour had dissipated. The phases were separated and the aqueous phase extracted with DCM (3 x 60 mL) and the combined organic extracts dried ($MgSO_4$), filtered, concentrated *in vacuo* and the resulting solids recrystallised from EtOAc /. petrol. Analytical data were identical to literature reports.[231]

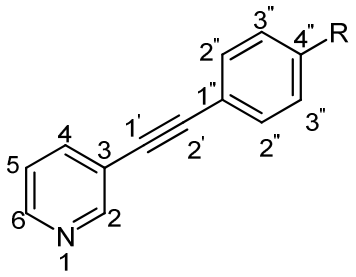
Synthesis of 147c and 147d



146c (14.9 g, 50 mmol) or **146d** (17.3 g, 50 mmol) and KOH (16.8 g, 300 mmol) were placed in a flask containing MeOH (300 mL) and the mixture heated at reflux for 12h. The mixture was concentrated under reduced pressure at room temperature, the resulting residue dissolved in water

(150 mL) and extracted using DCM (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$) and the volatiles removed which were recrystallised from 40/60 petrol. Analytical data were identical to literature reports.[232]

6.4.1 Preparation of alkynes 144a,c-f



To a stirred solution of 3-bromopyridine **120** (2.93 mL, 30 mmol) in dry THF under an atmosphere of N_2 was sequentially added one of terminal alkyne **147a** (3.22 g, 31.5 mmol), **147c** (4.30 g, 31.5 mmol), **147d** (5.70 g, 31.5 mmol), **147e** (3.66 g, 31.5 mmol) or **147f** (4.16 g, 31.5 mmol), bis(triphenylphosphine) palladium (II) chloride (1.05 g, 1.5 mmol, 5 mol.%), triethylamine (6.27 mL, 45 mmol), and copper iodide (0.11 g, 0.6 mmol, 2 mol.%) The resulting solution was stirred at reflux overnight. After cooling, the solvent was evaporated to give a brown residue which was chromatographed (SiO_2; petrol : ether, 70 : 30 $^{v}/_{v}$) and the solid obtained recrystallised to yield the products. There was obtained:

3-Phenylethynylpyridine (147a). (3.86 g, 72 %); pale yellow solid; m.p. 49 $^{\circ}$C (from petrol / EtOAc); lit. 50-51 ^{o}C;[222] FTIR (neat solid) 3027, 2210, 1597, 1488, 1421, 890, 754, 689 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.78 (s, 1H, H2),

8.55 (dd, *J* = 5.1, 1.8, 1H, H6), 7.80 (dt, *J* = 7.8, 1.8, 1H, H4), 7.58-7.54 (m, 2H, H2''), 7.38 – 7.36 (m, 3H, H4'', H3''), 7.27 (dd, *J* = 7.8, 5.1, 1H, H5); ^{13}C NMR ($CDCl_3$) δ 152.7 (C2), 149.0 (C6), 138.8 (C4), 132.1 (C2''), 129.2 (C4''), 128.8 (C3''), 123.4 (C5), 123.0 (q, C1''), 120.9 (q, C3), 93.1 (q, C2'), 86.4 (q, C1'); Anal. Calcd for $C_{13}H_9N$: C, 87.12; H, 5.06; N, 7.81. Found: C, 86.62; H, 5.01; N, 7.75.

3-(4-Chlorophenylethynyl)pyridine (147c). (2.62 g, 41 %); pale yellow solid; m.p. 87 °C (from petrol / EtOAc); FTIR (neat solid) 3026, 2219, 1488, 1089, 824 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.70 (bs, 1H, H2), 8.50 (dd, *J* = 4.8, 1.2, 1H, H6), 7.74 (dt, *J* = 7.8, 1.8, 1H, H4), 7.40 (d, *J* = 8.4, 2H, H3''), 7.26 (d, *J* = 8.4, 2H, H2''), 7.23 (dd, *J* = 7.8, 4.8, 1H, H5); ^{13}C NMR ($CDCl_3$) δ 152.5 (C2), 149.0 (C6), 138.9 (C4), 133.3 (q, C4''), 132.9 (C2''), 128.9 (q, C1''), 128.9 (C3''), 123.5 (C5), 121.0 (q, C3), 91.6 (q, C2'), 86.8 (q, C1'); Anal. Calcd for $C_{13}H_8ClN$: C, 73.08; H, 3.77; N, 6.56. Found: C, 73.01; H, 3.88; N, 6.48.

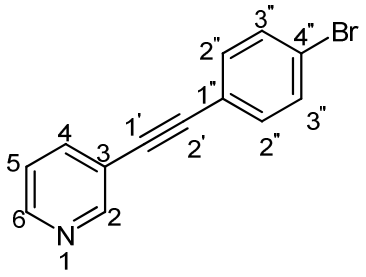
3-(4-Bromophenylethynyl)pyridine (147d). (1.55 g, 20 %); cream solid; m.p. 97 °C (from petrol / EtOAc); FTIR (neat solid) 2926, 2217, 1484, 1405, 1186, 1069, 1008, 818, 804, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.69 (d, *J* = 1.5, 1H, H2), 8.50 (dd, *J* = 5.1, 1.5, 1H, H6), 7.77 (dt, *J* = 7.8, 1.5, 1H, H4), 7.43 (d, *J* = 8.4, 2H, H3''), 7.33 (d, *J* = 8.4, 2H, H2''), 7.25 (dd, *J* = 7.8, 5.1, 1H, H5); ^{13}C NMR ($CDCl_3$) δ 151.6 (C2), 148.1 (C6), 139.0 (C4), 133.1 (C2''), 131.8 (C3''), 128.6 (q, C4''), 123.3 (C5), 121.4 (q, C1''), 120.5

(q, C3), 92.0 (q, C2'), 86,8 (q, C1'). Anal. Calcd for $C_{13}H_8BrN$: C, 60.49; H, 3.12; N, 5.43. Found: C, 60.35; H, 3.16; N, 5.34.

3-(4-Methylphenylethynyl)pyridine (147e). (5.50 g, 95 %); white or pale yellow solid; m.p. 90 °C (from petrol / EtOAc); lit. 87-88 °C;[191a] FTIR (neat solid) 3018, 2219, 1573, 1508, 1400, 1011, 879, 821, 692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.68 (bs, 1H, H2), 8.46 (dd, *J* = 5.1, 1.5, 1H, H6), 7.71 (dt, *J* = 7.8, 1.5, 1H, H4), 7.38 (d, *J* = 8.1, 2H, H2''), 7.20 (dd, *J* = 7.8, 5.1, 1H, H5), 7.10 (d, *J* = 8.1, 2H, H3''), 2.31 (s, 3H, 4''-CH_3); ^{13}C NMR ($CDCl_3$) δ 152.6 (C2), 148.8 (C6), 139.4 (q, C4''), 138.7 (C4), 132.0 (C2''), 129.6 (C3''), 123.4 (C5), 119.9 (q, C3), 119.9 (q, C1''), 93.3 (q, C2'), 85.7 (q, C1'), 21.9 (4''-CH_3); Anal. Calcd for $C_{14}H_{11}N$: C, 87.01; H, 5.74; N, 7.24. Found: C, 86.26; H, 5.75; N, 7.05.

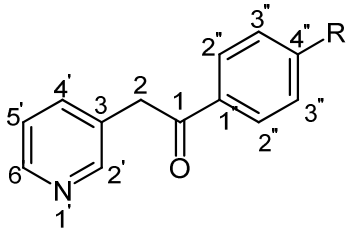
3-(4-Methoxyphenylethynyl)pyridine (147f). (3.95 g, 63 %); pale yellow solid; m.p. 53 °C (from petrol / EtOAc); lit 46 – 48 °C;[192] FTIR (neat solid) 3046, 2217, 1602, 1506, 1244, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.69 (bs, 1H, H2), 8.47 (dd, *J* = 5.1, 1.8, 1H, H6), 7.72 (dt, *J* = 8.1, 1.8, 1H, H4), 7.40 (d, *J* = 9.0, 2H, H2''), 7.24 (dd, *J* = 7.8, 5.1, 1H, H5), 6.82 (d, *J* = 9.0, 2H, H3''), 3.77 (s, 3H, 4''-CH_3); ^{13}C NMR ($CDCl_3$) δ 160.1 (q, C4''), 151.9 (C2), 147.9 (C6), 138.6 (C4), 133.3 (C2''), 123.2 (C5), 121.2 (q, C3), 114.5 (q, C1''), 114.2 (C3''), 93.1 (q, C2'), 84.5 (q, C1'), 55.4 (4''-OCH_3); Anal. Calcd for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.37; H, 5.36; N, 6.49.

6.4.2. Alternate procedure for the synthesis of 3-(4-bromophenylethynyl)pyridine (147d).



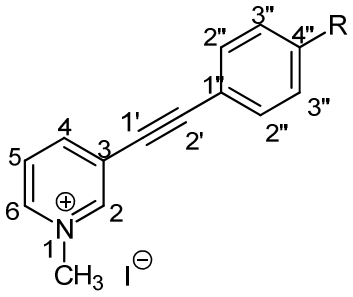
3-[(Triethylsilyl)ethynyl]pyridine 148 (3.4 mL, 18 mmol) was added to a stirred solution of bis(triphenylphosphine) palladium (II) chloride (0.63 g, 0.9 mmol, 5 mol.%), copper iodide (69 mg, 0.36 mmol, 2 mol.%), potassium carbonate (7.46 g, 54 mmol) and 1-bromo-4-iodobenzene (4.2 g, 15 mmol) in DMF (30 mL) and the mixture stirred at room temperature for 12 h. The mixture was then poured into H_2O (100 mL) and extracted into ether (4 x 20 mL). The combined organic extracts were dried ($MgSO_4$), the solvent removed under reduced pressure and the residue purified by column chromatography (SiO_2; petrol : ether, 70 : 30 $^{v}/_{v}$) to furnish the title product as a yellow solid (2.56 g, 54 %). Analytical data were identical to those described in Section 6.4.1.

6.4.4. Alternate synthesis of compounds 78a,c-f (from compounds 147a,c-f)



Compounds **78a,c-f** were synthesised using **GP 4**. There was obtained: **78a** using **147a** (1.79 g, 10 mmol). (1.52 g, 77 %); **78c** using **147c** (2.14 g, 10 mmol). (1.64 g, 71 %); **78d** using **147d** (2.58 g, 10 mmol).(2.04 g, 74 %); **78e** using **147e** (1.93 g, 10 mmol). (1.39 g, 66 %); **78f** using (2.09 g, 10 mmol). (1.57 g, 69 %).

6.4.5. Preparation of compounds 149a,c-f



Compounds **149a,c-f** were prepared using **GP 3**. There was obtained:

1-Methyl-3-phenylethynyl pyridinium iodide (149a), using **147a** (0.90 g). (1.37 g, 85 %); yellow solid; m.p. 172 °C (from EtOH); FTIR (neat solid)

3072, 2223, 1504, 756, 670 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.38 (s, 1H, H2), 9.00 (d, *J* = 6.0, 1H, H6), 8.72 (d, *J* = 8.1, 1H, H4), 8.18 (dd, *J* = 8.1, 6.0, 1H, H5), 7.68-7.65 (m, 2H, H2''), 7.54-7.51 (m, 3H, H3'', H4''), 4.37 (s, 3H, 1-CH_3); ^{13}C NMR (DMSO-d6) δ 148.2 (C2), 146.8 (C4), 145.3 (C6), 132.3 (C2''), 130.8 (C4''), 129.6 (C3''), 128.1 (C5), 123.1 (q, C3), 120.8 (q, C1''), 95.5 (q, C2'), 83.1 (q, C1'), 48.7 (1-CH_3); Anal. Calcd for $C_{14}H_{12}IN$: C, 52.36; H, 3.77; N, 4.36. Found: C, 52.30; H, 3.69; N, 4.33.

3-(4-Chlorophenylethynyl)-1-methylpyridinium iodide (149c), using **147c** (1.07 g). (1.53 g, 86 %); pale yellow crystals; m.p. 189-190 °C (from EtOH); FTIR (neat solid) 3064, 3052, 2220, 1503, 1086, 1008, 830, 819, 721, 670 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.38 (s, 1H, H2), 9.01 (d, *J* = 6.3, 1H, H6), 8.74 (d, *J* = 8.1, 1H, H4), 8.19 (dd, *J* = 8.1, 6.3, 1H, H5), 7.70 (d, *J* = 8.7, 2H, H2''), 7.60 (d, *J* = 8.7, 2H, H3''), 4.37 (s, 3H, 1-CH_3); ^{13}C NMR (DMSO-d_6) δ 148.3 (C2), 146.9 (C4), 145.5 (C6), 135.7 (q, C4''), 134.0 (C2''), 129.8 (C3''), 128.2 (C5), 122.9 (q, C3), 119.7 (q, C1''), 95.2 (q, C2'), 84.0 (q, C1'), 48.7 (1-CH_3); Anal. Calcd for $C_{14}H_{11}ClIN$: C, 47.29; H, 3.12; N, 3.94. Found: C, 47.23; H, 3.10; N, 3.75.

3-(4-Bromophenylethynyl)-1-methyl-pyridinium iodide (149d), using **147d** (1.29 g). (1.94 g, 97 %); yellow solid; m.p. 193-194 °C (from EtOH); FTIR (neat solid) 3069, 2219, 1573, 1501, 1064, 1006, 826, 819, 713, 670 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.40 (s, 1H, H2), 9.02 (d, *J* = 5.7, 1H, H6), 8.75 (d, *J* = 7.8, 1H, H4), 8.20 (dd, *J* = 7.8, 5.7, 1H, H5), 7.74 (d, *J* = 8.4, 2H, H3''), 7.62 (d, *J* = 8.4, 2H, H2''), 4.38 (s, 3H, 1-CH_3); ^{13}C NMR (DMSO-

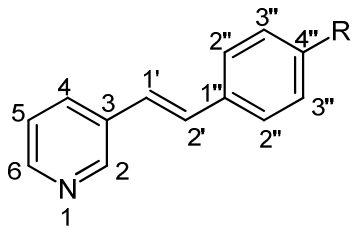
d_6) δ 148.3 (C2), 146.9 (C4), 145.5 (C6), 134.2 (C2''), 132.7 (C3''), 128.2 (C5), 124.5 (q, C4''), 122.9 (q, C3), 120.1 (q, C1''), 95.3 (q, C2'), 84.2 (q, C1'), 48.7 (1-CH_3); Anal. Calcd for $C_{14}H_{11}BrNI$: C, 42.03; H, 2.77; N, 3.50. Found: 41.95; H, 2.77; N, 3.42.

1-Methyl-3-(4-methylphenyl)ethynylpyridinium iodide (149e), using **147e** (0.97 g). (1.29 g, 77 %); pale yellow solid; m.p. 217 °C (from EtOH); FTIR (neat solid) 3030, 2929, 2216, 1514, 810, 667 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.35 (s, 1H, H2), 8.99 (d, *J* = 6.0, 1H, H6), 8.70 (d, *J* = 8.4, 1H, H4), 8.17 (dd, *J* = 8.4, 6.1, 1H, H5), 7.54 (d, *J* = 8.1, 2H, H2''), 7.32 (d, *J* = 8.1, 2H, H3''), 4.37 (s, 3H, 1-CH_3), 2.37 (s, 3H, 4''-CH_3); ^{13}C NMR (DMSO-d_6) δ 148.1 (C2), 146.7 (C4), 145.1 (C6), 140.9 (q, C4''), 132.2 (C2''), 130.2 (C3''), 128.1 (C5), 123.3 (q, C3), 117.8 (q, C1''), 96.9 (q, C2'), 82.6 (q, C1'), 48.7 (1-CH_3), 21.7 (s, 3H, 4''-CH_3); Anal. Calcd for $C_{15}H_{14}IN$: C, 53.75; H, 4.21; N, 4.18. Found: C, 53.70; H, 4.20; N, 4.11.

3-(4-Methoxyphenylethynyl)-1-methylpyridinium iodide (149f), using **147f** (1.05 g). (1.26 g, 72 %); yellow solid; m.p. 222-223 °C (from EtOH); FTIR (neat solid) 3003, 2215, 1581, 1513, 818, 665 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.32 (s, 1H, H2), 8.95 (d, *J* = 6.0, 1H, H6), 8.67 (d, *J* = 8.1, 1H, H4), 8.15 (dd, *J* = 8.1, 6.3, 1H, H5), 7.60 (d, *J* = 8.7, 2H, H2''), 7.07 (d, *J* = 8.7, 2H, H3''), 4.35 (s, 3H, 1-CH_3), 3.83 (s, 3H, 4''-OCH_3); ^{13}C NMR (DMSO-d_6) δ 161.2 (q, C4''), 147.9 (C2), 146.5 (C4), 144.8 (C6), 134.1 (C2''), 128.1 (C5), 123.6 (q, C3), 112.6 (q, C1''), 115.3 (C3''), 97.2 (q, C2'),

82.1 (q, C1'), 56.0 (4''-OCH_3), 48.6 (1-CH_3); Anal. calcd for $C_{15}H_{14}NOI$: C, 51.30; H, 4.02; N, 3.99. Found: C, 51.31; H, 4.02; N, 4.01.

6.4.6. Synthesis of compounds 159a-e



Styrene **145a** (2.60 g, 25 mmol), **145b** (3.05 g, 25 mmol), **145c** (3.46 g, 25 mmol), or **145d** (2.95 g, 25 mmol), 3-bromopyridine (1.95 mL, 20 mmol), palladium (II) acetate (44 mg, 0.2 mmol, 1 mol.%), triphenylphosphine (0.10 g, 0.4 mmol, 2 mol.%) and triethylamine (4.18 mL, 30 mmol) were dissolved in dry THF (60 mL) and the mixture stirred overnight under N_2 at reflux. After cooling, ether (60 mL) was added and the solution washed with water (2 x 200 mL). The organic phases were dried ($MgSO_4$) and the solvent removed under vacuum to yield brown / yellow solids which were purified by chromatography (SiO_2; EtOAc / petrol, 60 : 40 $^{v}/_{v}$) and subsequent recrystallisation. There was obtained:

3-[(*E*)-Phenylvinyl]pyridine (159a). (2.54 g, 70 %); pale yellow solid; m.p. 81-82 $^{\circ}$C (from petrol / EtOAc); lit. 80 $^{\circ}$C;[223] FTIR (neat solid) 3024, 1564, 1492, 1448, 1409, 1022, 963, 800, 752 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.78 (s, 1H, H2), 8.54 (d, *J* = 3.9, 1H, H6), 7.89 (d, *J* = 7.8, 1H, H4). 7.58 (d, *J* = 7.2, 2H, H2''), 7.43 (t, *J* = 7.2, 2H, H3''), 7.37-7.34 (m, 2H, H5, H4''), 7.21 (d, *J* = 16.2, 1H, H2'), 7.10 (d, *J* = 16.2, 1H, H1'); ^{13}C NMR ($CDCl_3$) δ

148.2 (C2 and C6), 136.6 (q, C1''), 133.2 (q, C3), 133.0 (C4), 131.1 (C2'), 128.8 (C3''), 128.3 (C4''), 126.7 (C2''), 124.8 (C1'), 123.7 (C5); Anal. Calcd for $C_{13}H_{11}N$: C, 86.15; H, 6.12; N, 7.22. Found: C, 86.21; H, 6.10; N, 7.70.

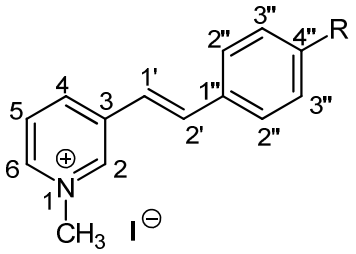
3-[(*E*)-2-(4-Fluorophenyl)vinyl]pyridine (159b). (2.19 g, 55 %); palye yellow solid; m.p. 59-60 °C (from petrol / EtOAc); FTIR (neat solid) 3023, 1595, 1507, 1411, 1227, 1214, 1157, 965, 823, 701 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.63 (s, 1H, H2), 8.41 (bd, J = 3.9, 1H, H6), 7.73 (dt, *J* = 8.1, 1.5, 1H, H4), 7.41 (dd, *J* = 8.4, 5.1, 2H, H2''), 7.20 (dd, *J* = 8.1, 3.9, 1H, H5), 7.03 (d, *J* = 16.2, 1H, H1'), 6.98 (dt, *J* = 6.6, 2H, H3''), 6.89 (d, *J* = 16.2, 1H, H2'); ^{13}C NMR ($CDCl_3$) δ 162.8 (d, *J* = 249, C4''), 148.3 (C2), 148.2 (C2), 133.0 (q, C1''), 132.9 (C4), 132.8 (q, C3), 129.8 (C1'), 128.3 (d, *J* = 8, C2''), 124.6 (C2'), 123.7 (C5), 115.8 (d, *J* = 22, C3''); Anal. Calcd for $C_{13}H_{10}FN$: C, 78.37; H, 5.06; N, 7.03. Found: C, 78.39; H, 5.07; N, 6.95.

3-[(*E*)-2-(4-Chlorophenyl)vinyl]pyridine (159c). (2.81 g, 65 %); yellow solid; m.p. 84-85 °C (from petrol / EtOAc); FTIR (neat solid) 3120, 1567, 1489, 1419, 1088, 965, 821, 711, 529 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.64 (d, *J* = 1.5, 1H, H2), 8.41 (dd, *J* = 4.8, 1.5, 1H, H6), 7.73 (dt, *J* = 8.1, 1.5, 1H, H4), 7.35 (d, *J* = 8.4, 2H, H2''), 7.24 (d, *J* = 8.4, 2H, H3''), 7.21 (dd, *J* = 8.1, 4.8, 1H, H5), 7.02 (d, *J* = 16.5, 1H, H2'), 6.93 (d, *J* = 16.5, 1H, H1'); ^{13}C NMR ($CDCl_3$) δ 148.5 (C6), 148.2 (C2), 135.2 (q, C1''), 134.0 (q, C4''), 133.0 (C4), 132.9 (q, C3), 129.7 (C2'), 129.0 (C3''), 127.9 (C2''), 125.4 (C1'), 123.7 (C5); Anal. Calcd for $C_{13}H_{10}ClN$: C, 72.40; H, 4.67; N, 6.49. Found: C, 72.42; H, 4.69; N, 6.39.

3-[(*E*)-2-(4-Bromophenyl)-vinyl]pyridine (159d). (2.65 g, 51 %); yellow solid; m.p. 94-95 °C (from petrol / EtOAc); FTIR (neat solid) 3022, 1488, 1073, 874, 820, 708 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.65 (d, *J* = 1.8, 1H, H2), 8.43 (dd, *J* = 4.5, 1.8, 1H, H6), 7.75 (dt, *J* = 7.8, 1.8, 1H, H4), 7.42 (d, *J* = 8.7, 2H, H3''), 7.30 (d, *J* = 8.7, 2H, H2''), 7.22 (dd, *J* = 7.8, 4.5, 1H, H5), 7.02 (d, *J* = 16.2, 1H, H2'), 6.95 (d, *J* = 16.2, 1H, H1'); ^{13}C NMR ($CDCl_3$) δ 148.4 (C6), 148.2 (C2), 135.6 (q, C1''), 133.1 (C4), 132.9 (q, C3), 132.0 (C3''), 129.8 (C2'), 128.2 (C2''), 125.5 (C1'), 123.7 (C5), 122.2 (q, C4''). Anal. Calcd for $C_{14}H_{13}BrN$: C, 41.82; H, 3.26; N, 3.48. Found: 41.61; H, 3.40; N, 3.14.

3-[(*E*)-2-(4-Methylphenyl)vinyl]pyridine (159e). (1.68 g, 43 %); cream solid; m.p. 106-107 °C (from petrol / EtOAc) ; FTIR (neat solid) 3024, 1508, 1421, 1174, 1022, 972, 816, 714 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.63 (d, *J* = 1.8, 1H, H2), 8.39 (dd, *J* = 4.8, 1.8, 1H, H6), 7.75 (dt, *J* = 8.1, 1.8, 1H, H4), 7.34 (d, *J* = 8.1, 2H, H2''), 7.21 (dd, *J* = 8.1, 4.8, 1H, H5), 7.10 (d, *J* = 8.1, 2H, H3''), 7.06 (d, *J* = 16.2, 1H, H2'), 6.93 (d, *J* = 16.2, 1H, H1'); ^{13}C NMR ($CDCl_3$) δ 148.0 (C2), 147.9 (C6), 138.4 (q, C4''), 133.9 (q, C1''), 133.5 (q, C3), 133.0 (C4), 131.1 (C2'), 129.6 (C3''), 126.7 (C2''), 123.7 (C5 and C1'), 21.3 (4''-CH_3); Anal. Calcd for $C_{14}H_{13}N$: C, 86.12; H, 6.71; N, 7.17. Found: C, 86.03; H, 6.73; N, 7.14.

6.4.7. Synthesis of compounds 164a-e



Compounds **164a-e** were synthesised using **GP 3**. There was obtained:

1-Methyl-3-((*E*)-styryl)-pyridinium iodide (164a), from **159a** (0.91 g). (1.08 g, 67 %); pale yellow solid; m.p. 216-217 °C (from EtOH); FTIR (neat solid) 3026, 1642, 1627, 1508, 1224, 804, 747, 691, 670 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.32 (s, 1H, H2), 8.86 (d, *J* = 6.0, 1H, H6), 8.77 (d, *J* = 8.4, 1H, H4), 8.13 (dd, *J* = 8.4, 6.0, 1H, H5), 7.73 (d, *J* = 16.5, 1H, H2'), 7.69 (d, *J* = 7.2, 2H, H2''), 7.50 (t, *J* = 7.2, 2H, H3''), 7.43 (d, *J* = 16.5, 1H, H1'), 7.40 (t, *J* = 7.2, 1H, H4''), 4.39 (s, 3H, 1-CH_3); ^{13}C NMR (DMSO-d_6) δ 143.7 (C2 and C6), 141.5 (C4), 137.6 (q, C3), 136.0 (q, C1''), 135.8 (C2'), 129.8 (C4''), 129.5 (C3''), 128.0 (C5), 127.7 (C2''), 121.9 (C1'), 48.6 (1-CH_3). Anal. Calcd for $C_{14}H_{14}NI$: 52.03; H, 4.37; N, 4.33. Found: C, 51.86; H, 4.34; N, 4.13.

3-[(*E*)-2-(4-Fluorophenyl)vinyl]-1-methylpyridinium iodide (164b), from **159b** (1.00 g). (1.64 g, 96 %); cream solid; m.p. 242-243 °C (from EtOH); FTIR (neat solid) 3026, 1642, 1627, 1594, 1508, 1224, 1157, 972, 826, 668 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.30 (s, 1H, H2), 8.86 (d, *J* = 5.7, 1H, H6),

8.75 (d, *J* = 8.1, 1H, H4), 8.13 (dd, *J* = 8.1, 5.7, 1H, H5), 7.74 (dd, *J* = 8.4, 5.4, 2H, H2''), 7.73 (d, *J* = 16.5, 1H, H2'), 7.38 (d, *J* = 16.5, 1H, H1'), 7.32 (t, *J* = 8.4, 2H, H3''), 4.39 (s, 3H, 1-CH_3); ^{13}C NMR (DMSO-d_6) δ 163.0 (q, J_{C-F} = 246, C4''), 143.7 (C2 or C6), 143.6 (C2 or C6), 141.4 (C4), 137.5 (q, C3), 134.6 (C2'), 132.7 (q, J_{C-F} = 3, C1''), 129.8 (J_{C-F} = 8, C2''), 128.0 (C5), 121.8 (C1'), 116.5 (J_{C-F} = 22, C3''), 48.6 (1-CH_3). Anal. Calcd for $C_{14}H_{13}FNI$: C, 49.29; H, 3.84; N, 4.11. Found: C, 49.12; H, 3.84; N, 3.99.

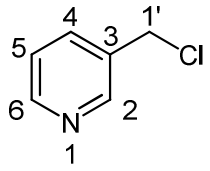
3-[(*E*)-2-(4-Chlorophenyl)vinyl]-1-methylpyridinium iodide (164c), using **159c** (1.08 g). (1.47 g, 82 %); yellow solid; m.p. 196-197 °C (from EtOH); FTIR (neat solid) 3030, 1644, 1625, 1509, 1487, 1158, 1086, 968, 810, 666 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.31 (s, 1H, H2), 8.91 (d, *J* = 5.7, 1H, H6), 8.79 (d, *J* = 8.4, 1H, H4), 8.17 (dd, *J* = 8.4, 5.7, 1H, H5), 7.74 (d, *J* = 16.5, 1H, H2'), 7.74 (d, *J* = 8.4, 2H, H2''), 7.58 (d, *J* = 8.4, 2H, H3''), 7.48 (d, *J* = 16.5, 1H, H1'), 4.42 (s, 3H, 1-CH_3); ^{13}C NMR (DMSO-d_6) δ 143.9 (C2 or C6), 143.8 (C2 or C6), 141.5 (C4), 137.4 (q, C3''), 135.0 (q, C1''), 134.4 (C2'), 134.2 (q, C4''), 129.6 (C3''), 129.4 (C2''), 128.0 (C5), 122.8 (C1'), 48.6 (1-CH_3). Anal. Calcd for $C_{14}H_{13}ClNI$: 47.02; H, 3.66; N, 3.92. Found: C, 46.75; H, 3.84; N, 4.01.

3-[(*E*)-2-(4-Bromophenyl)vinyl]-1-methylpyridinium iodide (164d), using **159d** (1.30 g). (1.97 g, 98 %); yellow solid; m.p. 231-232 °C; FTIR (neat solid) 3032, 1644, 1624, 1510, 968, 808, 666 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.30 (s, 1H, H2), 8.87 (d, *J* = 5.7, 1H, H6), 8.76 (d, *J* = 8.4, 1H, H4), 8.14 (dd, *J* = 8.4, 5.7, 1H, H5), 7.73-7.61 (m, 5H, H2'', H3'', H2'), 7.46 (d, *J*

= 16.5, 1H, H1'), 4.39 (s, 3H, 1-CH_3); ^{13}C NMR (DMSO-d_6) δ 143.9 (C2 or C6), 143.8 (C2 or C6), 141.6 (C4), 137.3 (q, C3), 135.3 (q, C1''), 134.5 (C2'), 132.5 (C3''), 129.6 (C2''), 128.0 (C5), 122.9 (q, C4''), 122.8 (C1'), 48.6 (1-CH_3). Anal. Calcd for $C_{14}H_{13}BrIN$: C, 41.82; H, 3.26; N, 3.48. Found: 41.62; H, 3.40; N, 3.14.

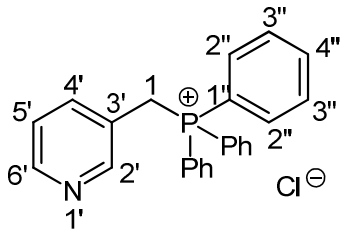
1-Methyl-3-[(*E*)-2-4-methylphenylvinyl]-pyridinium iodide (164e), from **159e** (0.98 g). (1.55 g, 92 %); pale yellow solid; m.p. 247 °C (from EtOH); FTIR (neat solid) 3026, 3008, 1640, 1625, 1507, 1208, 969, 859, 665 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.28 (s, 1H, H2), 8.84 (d, *J* = 6.0, 1H, H6), 8.74 (d, *J* = 8.4, 1H, H4), 8.12 (dd, *J* = 8.4, 6.0, 1H, H5), 7.68 (d, *J* = 16.5, 1H, H2'), 7.58 (d, *J* = 8.1, 2H, H2''), 7.35 (d, *J* = 16.5, 1H, H1'), 7.29 (d, *J* 8.1, 2H, H3''), 4.38 (s, 3H, 1-CH_3), 2.30 (s, 3H, 4''-CH_3); ^{13}C NMR (DMSO-d_6) δ 143.5 (C2), 143.4 (C6), 141.3 (C4), 139.6 (q, C4''), 137.8 (q, C3), 135.8 (C2'), 133.3 (q, C1''), 130.1 (C3''), 128.0 (C5), 127.7 (C2''), 120.9 (C1'), 48.6 (1-CH_3), 21.5 (4''-CH_3). Anal. Calcd for $C_{15}H_{16}IN$: C, 53.43; H, 4.78; N, 4.15; Found: C, 53.40; H, 4.77; N, 4.13.

6.4.8. 3-(Chloromethyl)pyridine (161)



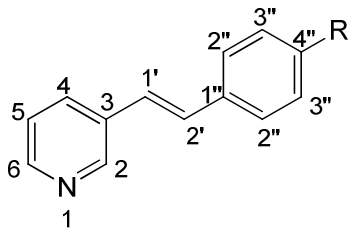
3-Chloromethylpyridinium hydrochloride **160** (3.28 g, 20 mmol) was added portionwise over 2 min to a solution of sodium hydrogen carbonate (2.18 g, 26 mmol) in a mixture of DCM (60 mL) and water (60 mL). The mixture was stirred vigorously for 1 h after which time the phases were separated and the aqueous phase extracted using DCM (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo* to furnish the desired product as a pale yellow liquid which was used without further purification; (2.42 g, 95 %); FTIR (neat solid) 3033, 1577, 1479, 1423, 1027, 824, 710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.65 (d, *J* = 1.8, 1H, H2), 8.59 (dd, *J* = 4.8, 1.8, 1H, H6), 7.76 (dt, *J* = 8.1, 1.8, 1H, H4), 7.33 (dd, *J* = 8.1, 4.8, 1H, H5), 4.61 (s, 2H, H1'); ^{13}C NMR ($CDCl_3$) δ 149.6 (C2), 149.5 (C6), 136.3 (C4), 133.3 (q, C3), 123.6 (C5), 43.1 (C1').

6.4.9. Triphenyl(pyridine-3-ylmethyl)phosphonium chloride (162).



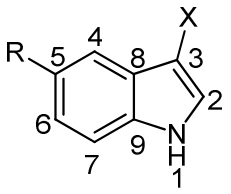
To a solution of **161** (2.42 g, 19 mmol) in acetonitrile (80 mL) was added triphenylphosphine (4.98 g, 19 mmol) and the mixture refluxed overnight. After cooling, the resulting precipitate was collected by filtration and washed thoroughly with ether to yield the title compound **162** as a pale cream solid, which could be used without further purification; (4.70 g, 64 %); m.p. 297 °C; FTIR (neat solid) 2845, 1435, 1110, 717, 692 cm^{-1}; ^{1}H NMR (D_2O) δ 8.46 (dd, *J* = 4.5, 1.8, 1H, H6'), 8.05 (d, *J* = 1.8, 1H, H2'), 7.93-7.88 (m, 3H, H4), 7.71-7.64 (m, 12H, H2, H3), 7.51 (dt, *J* = 7.8, 1.8, 1H, H4'), 7.32 (dd, *J* = 7.8, 4.5, 1H, H5'), 4.86 (d, J_{H-P} = 14.7, 2H, H1); ^{13}C NMR (D_2O) δ 150.3 (d, J_{C-P} = 6, C2'), 148.8 (d, J_{C-P} = 4, C6'), 139.7 (d, J_{C-P} = 5, C4'), 135.6 (d, J_{C-P} = 3, C4''), 134.1 (d, J_{C-P} = 10, C3''), 130.3 (d, J_{C-P} = 13, C2''), 124.8 (q, d, J_{C-P} = 8, C3'), 124.5 (d, J_{C-P} = 3, C5'), 116.7 (q, d, J_{C-P} = 87, C1''), 27.2 (d, J_{C-P} = 50, C1); Anal. Calcd for $C_{24}H_{21}ClNP$: C, 73.94; H, 5.43; N, 3.59. Found: C, 73.67; H, 5.34; N, 4.07.

6.4.10. Alternative synthesis of alkenes (159a-e) *via* Wittig methodology



To a stirred solution of triphenyl(pyridine-3-ylmethyl) phosphonium chloride **162** (1.56 g, 4 mmol) in dry THF (20 mL) at -10 °C under argon was added n-BuLi (1.6 mL, 2.5 M, 4 mmol). The resulting mixture was stirred at -10 °C for 30 min. The mixture was cooled to -78 °C and arylaldehyde **163a-e** (4 mmol) in dry THF (5 mL) added; the mixture was allowed to warm to room temperature overnight with stirring. The reaction was quenched with sat. NH_4Cl (50 mL) and extracted into ether (3 x 30 mL). The combined ethereal extracts were dried ($MgSO_4$), and the solvent removed *in vacuo* to yield the desired products. There was obtained **159a** (0.44 g, 61 %), **159b** (0.44 g, 55 %), **159c** (0.47 g, 55 %), **159d** (0.38 g, 49 %) and **159e** (0.43 g, 51 %). Analytical data were identical to those described in 6.4.6.

6.4.11. Synthesis of compounds 168a-c



152a X = Br, R = H
152b X = **I**, R = H
152c X = I, R = OCH_3

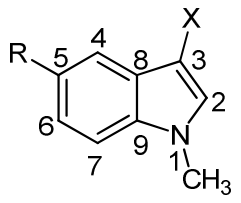
To a vigorously stirred solution of powdered potassium hydroxide (5.62 g, 100 mmol), and either 1*H*-indole **167a** (4.68 g, 40 mmol) or 5-methoxy-1*H*-indole **167b** (5.89 g, 40 mmol) in DMF (70 mL) at room temperature was added dropwise over 5 min either iodine (10.25 g, 40.4 mmol) or bromine (2.08 mL, 40.4 mmol) in DMF (60 mL). The mixture was stirred for a further 45 min at room temperature and then poured into iced aqueous sodium metabisulphite (400 mL, 0.1 % $^{w}/_{v}$). The resulting precipitate was filtered, washed with cold water (100 mL) and dried under vacuum to yield the products. The products were highly unstable and could not be stored for significant periods and were used immediately in the next reaction step. There was obtained.[233]

3-Bromo-1*H*-indole (168a). (7.05 g, 90 %); tan solid; m.p. 68-69 $^{\circ}$C; lit. 65 ^{o}C [Hugon]FTIR (neat solid) 3400, 1656, 1452, 977, 811, 736 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.15 (bs, 1H, N-H), 7.51 (dd, *J* = 8.4, 1.2, 1H, H4), 7.26 (dd, *J* = 8.4, 1.2, 1H, H7), 7.18-7.10 (m, 3H, H5, H6, H2); ^{13}C NMR ($CDCl_3$) δ 135.4 (q, C9), 126.9 (q, C8), 123.4 (C5 or C6), 123.2 (C5 or C6), 120.7 (C2), 19.2 (C4), 111.5 (C7), 91.7 (q, C3).

3-Iodo-1*H*-indole (168b). (9.33 g, 96%); tan solid; m.p. 71 °C (dec.); literature 66 °C (dec.);[225] FTIR (neat solid) 3382, 3051, 1653, 1450, 1236, 1083, 957, 735 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.52 (bs, 1H, NH), 7.54 (d, *J* = 2.7, 1H, H2), 7.45 (dd, 1H, *J* = 7.2, 1.5, H4), 7.29 (dd, *J* = 7.2, 1.5, 1H, H7), 7.17 (td, *J* = 7.2, 1.5, 1H, H6), 7.11 (td, *J* = 7.2, 1.5, 1H, H5); ^{13}C NMR (DMSO-d_6) δ 136.4 (q, C9), 130.1 (C2), 129.8 (q, C8), 122.6 (C4), 120.4 (C6), 120.2 (C5), 112.4 (C7), 56.3 (q, C3).

3-Iodo-5-methoxy-1*H*-indole (168c). (10.49 g, 96%); tan solid; m.p. 78-79 °C (dec); FTIR (neat solid) 3329, 3108, 1484, 1435, 1289, 1211, 1160, 1025, 820, 918, 797 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.38 (bs, 1H, N-H), 7.49 (d, *J* = 2.4, 1H, H2), 7.33 (d, *J* = 8.7, 1H, H7), 6.82 (dd, *J* = 8.7, 2.4, 1H, H6), 6.74 (d, *J* = 2.4, 1H, H4), 3.80 (s, 3H, 5-OCH_3); ^{13}C NMR (DMSO-d_6) δ 154.7 (q, C5), 131.4 (q, C9), 130.5 (C2), 130.2 (q, C8), 113.3 (C6), 113.1 (C7), 101.6 (C4), 55.8 (2C, q, C3 and 5-OCH_3).

6.4.12 Synthesis of compounds 169a-c



152a X = Br, R = H
152b X = **I**, R = H
152c X = I, R = OCH_3

Either compound **168a** (5.88 g, 30 mmol), **168b** (7.29 g, 30 mmol) or **168c** (8.19 g, 30 mmol), was dissolved in acetone (90 mL). The mixture was

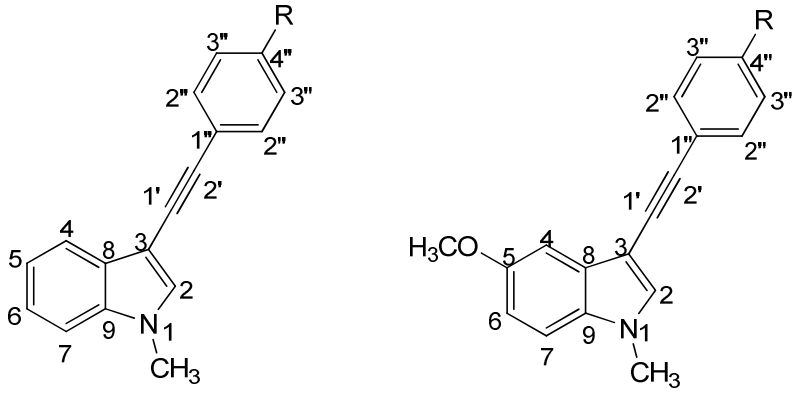
cooled to 0 °C and powdered potassium hydroxide (8.42 g, 150 mmol) added portionwise over 5 min. Iodomethane (3.8 mL, 60 mmol) was added and the mixture stirred vigorously at room temperature for 30 min; after which, petrol (60 mL) was then added and the solution filtered. The filtrate was washed with brine (60 mL), dried ($MgSO_4$) and the solvent removed to yield a deep red residue. Column chromatography of the residue (SiO_2, 100 % petrol) afforded the title compounds. The title compounds could be stored in a freezer for approx. 30 days without significant decomposition. There was obtained:

3-Bromo-1-methyl-1*H*-indole (169a). (5.30 g, 84 %); cream solid; m.p. 77-78 °C; FTIR (neat solid) 2900, 1505, 1460, 1237, 1106, 740 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.50 (s, 1H, H2), 7.48-7.47 (m, 1H, H4), 7.45-7.44 (m, 1H, H7), 7.26 (td, *J* = 6.9, 1.2, 1H, H6), 7.17 (td, *J* = 6.9, 1.2, 1H, H5), 3.77 (s, 3H, 1-CH_3); ^{13}C NMR (DMSO-d_6) δ 136.5 (q, C9), 129.1 (C2), 127.0 (q, C8), 122.7 (C4), 120.4 (C6), 118.7 (C5), 110.7 (C7), 88.0 (q, C3), 33.2 (1-CH_3).

3-Iodo-1-methyl-1*H*-indole (169b). (6.32 g, 82%); cream solid; m.p. 56 °C; literature 58-59 °C;[226] FTIR (neat solid) 2905, 1502, 1455, 1236, 1102, 931, 743 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.52 (s, 1H, br, H2), 7.44 (dd, *J* = 7.8, 1.2, 1H, H4), 7.29 (dd, *J* = 7.8, 1.2, 1H, H7), 7.23 (td, *J* = 7.8, 1.2, 1H, H6), 7.14 (td, *J* = 7.8, 1.2, 1H, H5) 3.80 (s, 3H, 1-CH_3); ^{13}C NMR (DMSO-d_6) δ 137.1 (q, C9), 133.9 (C2), 130.3 (q, C8), 122.7 (C4), 120.6 (C6), 120.5 (C5), 110.6 (C7), 54.9 (q, C3), 33.2 (1-CH_3).

3-Iodo-5-methoxy-1-methyl-1*H*-indole (169c). (8.10 g, 94 %); cream solid; m.p. 75-76 °C (dec.); FTIR (neat solid) 2971, 2359, 1362, 1215, 1178, 1150, 1129, 1028, 806, 782 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.51 (s, 1H, H2), 7.41 (d, *J* = 9.0, 1H, H7), 6.90 (dd, *J* = 9.0, 2.4, 1H, H6), 6.76 (d, *J* = 2.4, 1H, H4), 3.84 (s, 3H, 5-OCH_3), 3.81 (s, 3H, 1-CH_3); ^{13}C NMR (DMSO-d_6) δ 154.8 (q, C5), 134.2 (C2), 132.3 (q, C9), 130.7 (q, C8), 113.0 (C6), 111.7 (C7), 102.0 (C4), 55.9 (5-OCH_3), 54.2 (q, C3), 33.4 (1-CH_3).

6.4.13. Synthesis of compounds 170a-e



A solution of either compound **169a** (1.94 g, 10 mmol) or **169b** (2.43 g, 10 mmol) or **169c** (2.73 g , 10 mmol) bis(triphenylphosphine)palladium (II) chloride (0.35 g, 0.5 mmol, 5 mol.%), copper iodide (38 mg, 0.2 mmol, 2 mol.%), triethlyamine (5.6 mL, 40 mmol) and either arylalkyne **147a** (1.12 g, 11 mmol), **147c** (1.50 g, 11 mmol), or **147e** (1.28 g, 11 mmol) in THF (20 mL) was stirred under an atmosphere of argon at room temperature. for 18 h. Water (60 mL) was subsequently added, the phases separated and the aqueous phase extracted with ether (3 x 30 mL). The combined ethereal extracts were dried ($MgSO_4$), concentrated and the residue

purified by column chromatography (SiO_2; 80:20, petrol: ether). There was obtained:

1-Methyl-3-phenylethynyl-1*H*-indole (170a). (1.83 g, 79 %); pale yellow crystals; m.p. 106 °C; FTIR (neat solid) 2925, 2208, 1538, 1487, 1471, 1381, 1234, 818, 759, 742, 689 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.72 (d, *J* = 7.5, 1H, H4), 7.47 (dd, *J* = 8.4, 1.8, 2H, H2''), 7.26-7.14 (m, 7H, H2, H3'', H4'', H7, H5, H6), 3.70 (s, 3H, 1-CH_3); ^{13}C NMR ($CDCl_3$) δ 136.3 (q, C9), 132.2 (C2), 131.3 (C2''), 129.2 (q, C8), 128.3 (C3''), 127.5 (C4''), 124.4 (q, C1''), 122.7 (C5 or C6), 120.4 (C4 or C5), 120.2 (C4 or C5), 109.6 (C7), 97.2 (q, C3), 91.1 (q, C2'), 83.2 (q, C1'), 33.1 (1-CH_3).Anal. Calcd for $C_{17}H_{13}N$: C, 88.28; H, 5.67; N, 6.06. Found: C, 88.07; H, 5.44; N, 6.36.

1-Methyl-3-(4-methylphenylethynyl)-1*H*-indole (170b). (1.99 g, 81 %); pale yellow solid; m.p. 117 °C; FTIR (neat solid)) 3044, 2204, 1504, 1382, 814, 736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.73 (dd, *J* = 8.1, 1.8, 1H, H4), 7.36 (d, *J* = 7.8, 2H, H2''), 7.24 (td, *J* = 8.1, 1.8, 1H, H5), 7.21 (dd, *J* = 8.1, 1.8, 1H, H7), 7.18 (s, 1H, H2), 7.13 (td, *J* = 8.1, 1.8, 1H, H6), 7.05 (d, *J* = 7.8, 2H, H3''), 3.69 (s, 3H, 1-CH_3), 2.28 (s, 3H, 4''-CH_3); ^{13}C NMR ($CDCl_3$) δ 137.6 (q, C4''), 136.4 (q, C9), 132.3 (C2), 131.2 (C2''), 129.3 (q, C8), 129.2 (C3''), 122.8 (C6), 121.4 (q, C1''), 120.4 (C5), 120.4 (C4), 109.6 (C7), 97.4 (q, C3), 91.2 (q, C2'), 82.4 (q, C1'), 33.2 (1-CH_3), 21.6 (4''-CH_3); Anal. Calcd for $C_{18}H_{15}N$: C, 88.13; H, 6.16; N, 5.71. Found: C, 88.11; H, 6.20; N, 5.77.

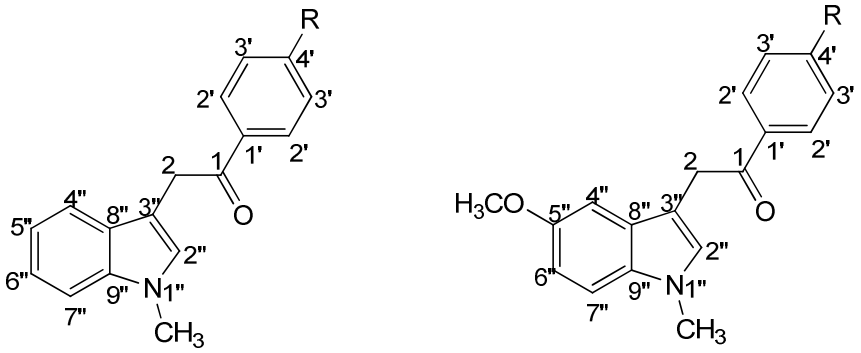
3-(4-Chlorophenylethynyl)-1-methyl-1*H*-indole (170c). (1.54 g, 58 %); pale yellow solid; m.p. 141 ^{o}C; FTIR (neat solid) 3053, 2212, 1487, 1462, 1382, 822, 743 cm^{-1}; ^{1}H NMR (DMSO-d$_6$) δ 7.83 (s, 1H, H2), 7.75 (dd, *J* = 7.8, 1.2, 1H, H4), 7.62 (d, *J* = 8.7, 2H, H2''), 7.58 (dt, *J* =7.2, 1.2, 1H. H7), 7.53 (d, *J* =8.7, 2H, H3''), 7.33 (td, *J* = 7.2, 1.2, 1H, H6), 7.24 (td, *J* = 7.2, 1.2, 1H, H5), 3.89 (s, 3H, 1-CH$_3$); ^{13}C NMR (DMSO-d$_6$) δ 136.5 (q, C9), 134.2 (C2), 132.9 (C2''), 132.8 (q, C4''), 129.3 (C3''), 128.9 (q, C8), 123.0 (q, C1''), 123.0 (C6), 120.9 (C5), 119.7 (C4), 111.1 (C7), 95.3 (q, C3), 90.2 (q, C2'), 85.7 (q, C1'), 33.3 (1-CH$_3$).

5-Methoxy-1-methyl-3-phenylethynyl-1*H*-indole (170d). (2.12 g, 81 %); pale yellow solid; m.p. 126 $^{\circ}$C; FTIR (neat solid) 2916, 2214, 1490, 1217, 1062, 783, 750, 691 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.47 (dd, *J* = 8.4, 1.8, 2H, H2''), 7.27-7.23 (m, 3H, H3'', H4''), 7.20 (s, 1H, H2), 7.16 (d, *J* = 2.4, 1H, H4), 7.14 (d, *J* = 9.0, 1H, H7), 6.85 (dd, *J* = 9.0, 2.4, 1H, H6), 3.82 (s, 3H, 5-OCH$_3$), 3.68 (s, 3H, 1-CH$_3$); ^{13}C NMR (CDCl$_3$) δ 155.0 (q, C5), 132.6 (C2), 131.6 (q, C9), 131.3 (C2''), 129.7 (q, C8), 128.3 (C3''), 127.4 (C4''), 124.4 (q, C1''), 113.2 (C6), 110.4 (C7), 101.7 (C4), 96.6 (q, C3), 91.1 (q, C2'), 83.3 (q, C1'), 55.9 (5-OCH$_3$), 33.3 (1-CH$_3$); Anal. Calcd for $C_{18}H_{15}NO$: C, 82.73; H, 5.79; N, 5.36. Found: C, 82.79; H, 5.83; N, 5.31.

5-Methoxy-1-methyl-3-(4-methylphenylethynyl)-1H-indole (170e). (1.68 g, 61 %); pale yellow crystals; m.p. 127 $^{\circ}$C; FTIR (neat solid) 2906, 2205, 1489, 1214, 1060, 816, 797 cm^{-1}; ^{1}H NMR (DMSO-d$_6$) δ 7.68 (s, 1H, H2), 7.46 (d, J = 7.8, 2H, H3''), 7.42 (d, J = 8.7, 1H, H7), 7.23 (d, J = 7.8, 2H,

H2''), 7.12 (d, J = 2.1, 1H, H4), 6.90 (dd, J = 8.7, 2.1, 1H, H6), 3.84 (s, 3H, 5-OCH_3), 3.80 (1-CH_3), 2.35 (s, 3H, 4''-CH_3); ^{13}C NMR (DMSO-d_6) δ 155.0 (q, C5), 137.7 (q, C4''), 134.0 (C2), 131.7 (q, C9), 131.2 (C3''), 129.7 (C2''), 129.5 (q, C8), 121.2 (q, C1''), 113.0 (C6), 111.9 (C7), 101.2 (C4), 95.4 (q, C3), 91.3 (q, C2'), 83.8 (q, C1'), 56.0 (5-OCH_3), 33.4 (1-CH_3), 21.5 (4''-CH_3). Anal. Calcd for $C_{19}H_{17}NO$: C, 82.88; H, 6.22; N, 5.09. Found: C, 82.84; H, 6.24; N, 5.11.

6.4.14. Synthesis of compounds 171a-e



Either compound **170a** (0.69 g, 3 mmol), **170b** (0.74 g, 3 mmol), **170c** (0.80 g, 3 mmol), **170d** (0.78 g, 3 mmol) or **170e** (0.83 g, 3 mmol) and $Hg(OAc)_2$ (0.095 g, 0.3 mmol, 10 mol.%) were dissolved in 30 % $^{w}/_{v}$ H_2SO_4 (6 mL) and acetone (3 mL). The resulting solution was stirred at room temperature for 12 h. The reaction mixture was diluted with water (60 mL), neutralised with 10 % aq. NaOH and the aqueous phase extracted with EtOAc (3 x 15 mL). The compbined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and the solvent removed under vacuum. The crude product was purified by column chromatography (SiO_2; petrol :

ether, 80 : 20 $^{v}/_{v}$) and recrystallised to give the title products. There was obtained:

2-(1-Methyl-1*H*-indol-3-yl)-1-phenyl ethanone (171a). (0.46 g, 61 %); orange-brown solid; m.p. 119 °C (from EtOAc / petrol); FTIR (neat solid) 2933, 1631, 1528, 1464, 1371, 1230, 1128, 1090, 747, 722, 693 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.55 (s, 1H, H2''), 8.20 (dd, *J* = 7.8, 1.2, 1H, H4''), 7.55 (dd, *J* = 7.8, 1.2, 1H, H7''), 7.37-7.19 (m, 7H, H2', H3', H4', H5'', H6''), 4.13 (s, 2H, H2), 3.90 (s, 3H, 1''-CH_3); ^{13}C NMR (DMSO-d_6) δ 192.5 (q, C1), 138.7 (C2''), 137.9 (q, C9''), 136.9 (q, C1'), 129.9 (C2' or C3'), 128.7 (C2' or C3'), 126.7 (C4'), 126.5 (q, C8''), 123.4 (C5''), 122.6 (C6''), 122.0 (C4''), 115.4 (q, C3''), 111.1 (C7''), 46.2 (C2), 33.7 (1''-CH_3). Anal. Calcd for $C_{17}H_{11}NO$: C, 81.90; H, 6.06; N, 5.70. Found: C, 81.67; H, 6.12; N, 5.71.

2-(1-Methyl-1*H*-indol-3-yl)-1-(4-methylphenyl) ethanone (171b). (0.72 g, 91%); orange-brown solid; m.p. 130 °C (from EtOAc / petrol); FTIR (neat solid) 2905, 1650, 1524, 1383, 1371, 1214, 1077, 932, 784, 742, 569 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.34-8.31 (m, 1H, H4''), 7.61 (s, 1H, H2''), 7.23-7.20 (m, 3H, H5'', H6'', H7''), 7.13 (d, *J* = 7.8, 2H, H2'), 7.02 (d, *J* = 7.8, 2H, H3'), 3.99 (s, 2H, H2), 3.70 (s, 3H, 1-CH_3), 2.22 (s, 3H, 4'-CH_3); ^{13}C NMR ($CDCl_3$) δ 192.9 (q, C1), 137.6 (q, C4'), 136.3 (q, C9''), 135.8 (C2''), 133.0 (q, C1'), 129.4 (C2' or C3'), 129.2 (C2' or C3'), 126.8 (q, C8''), 123.5 (C5'' or C6''), 122.9 (C5'' or C6''), 122.7 (C4''), 116.3 (q, C3''), 109.6 (C7), 46.7 (C2), 33.6 (1''-CH_3), 21.2 (4'-CH_3); Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 81.88; H, 6.52; N, 5.42.

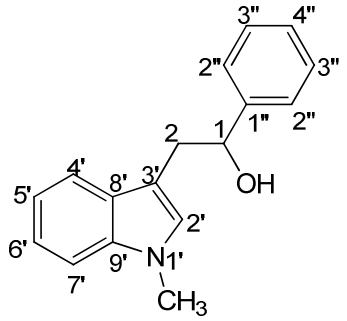
1-(4-Chlorophenyl)-2-(1-methyl-1H-indol-3-yl) ethanone (171c). (0.49 g, 57 %); orange-brown solid; m.p. 110 °C (from EtOAc / petrol); FTIR (neat solid) 2922, 1682, 1648, 1627, 1467, 1376, 2122, 1086, 805, 746, 569 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.32-8.27 (m, 1H, H4''), 7.61 (s, 1H, H2'), 7.22-7.19 (m, 3H, H5'', H6'', H7''), 7.17 (d, *J* = 8.7, 2H, H2''), 7.15 (d, *J* = 8.7, 2H, H3'), 3.98 (s, 2H, H2), 3.71 (s, 3H, 1-CH_3); ^{13}C NMR ($CDCl_3$) δ 191.9 (q, C1), 137.6 (q, C4'), 135.7 (C2''), 134.3 (q, C9''), 132.6 (q, C1'), 130.8 (C2' or C3'), 128.7 (C2' or C3'), 126.6 (q, C8''), 123.6 (C5'' or C6''), 122.8 (C5''or C6'), 122.7 (C4''), 116.1 (q, C3''), 109.7 (C7''), 46.0 (C2), 33.6 (1''-CH_3); Anal. Calcd for $C_{17}H_{14}ClNO$: C, 71.96; H, 4.97; N, 4.94; O, 5.64. Found: C, 71.74; H, 4.88; N, 4.99.

2-(5-Methoxy-1-methyl-1*H*-indol-3-yl)-1-phenyl-ethanone (171d). (0.60 g, 72 %); orange-brown solid; m.p. 128 °C; FTIR (neat solid) 2933, 1631, 1527, 1464, 1370, 1089, 747, 722 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.47 (s, 1H, H2''), 7.71 (d, *J* = 2.4, 1H, H4''), 7.44 (d, *J* = 9.0, 1H, H7''), 7.35 (dd, *J* = 7.2, 1.5, 2H, H2'), 7.30 (t, *J* = 7.2, 2H, H3'), 7.21 (tt, *J* = 7.2, 1.5, 1H, H4'), 6.90 (dd, *J* = 9.0, 2.4, 1H, H6''), 4.09 (s, 2H, H2), 3.86 (s, 3H, 1''-CH_3), 3.77 (s, 3H, 5''-OCH_3); ^{13}C NMR (DMSO-d_6) δ 192.3 (q, C1), 156.3 (q, C5''), 138.7 (C2''), 136.9 (q, C1'), 132.9 (q, C9''), 129.8 (C2'), 128.7 (C3'), 127.3 (q, C8''), 126.7 (C4'), 115.0 (q, C3''), 113.2 (C6''), 111.9 (C7''), 103.7 (C4''), 55.8 (5''-OCH_3), 46.2 (C2), 33.9 (1''-CH_3).

2-(5-Methoxy-1-methyl-1*H*-indol-3-yl)-1-(4-methylphenyl)-ethanone (171e). (0.61 g, 69 %); pale yellow crystals; m.p. 187-188 °C (from EtOAc /

petrol); FTIR (neat solid) 2910, 1646, 1613, 1522, 1482, 1368, 1221, 1073, 812, 773, 722 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.85 (d, *J* = 2.4, 1H, H4''), 7.60 (s, 1H, H2''), 7.14 (d, *J* = 7.8, 2H, H3'), 7.10 (d, *J* = 9.0, 1H, H7''), 7.04 (d, *J* = 7.8, 2H, H2'), 6.85 (dd, *J* = 9.0, 2.4, 1H, H6''), 3.99 (s, 2H, H2), 3.78 (s, 3H, 5''-OCH_3), 3.70 (s, 3H, 1''-CH_3), 2.23 (s, 3H, 4'-CH_3); ^{13}C NMR ($CDCl_3$) δ 192.9 (q, C1), 156.6 (q, C5''), 136.2 (q, C4'), 135.6 (C2''), 132.9 (q, C1' or C9''), 132.6 (q, C1 or C9''), 129.3 (C2' or C3'), 129.2 (C2' or C3'), 127.5 (q, C8''), 115.9 (q, C3''), 114.1 (C6''), 110.4 (C7''), 103.9 (C4''), 55.8 (5''-OCH_3), 46.4 (C2), 33.7 (1''-CH_3), 21.1 (4'-CH_3); Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.16; H, 6.49; N, 4.70.

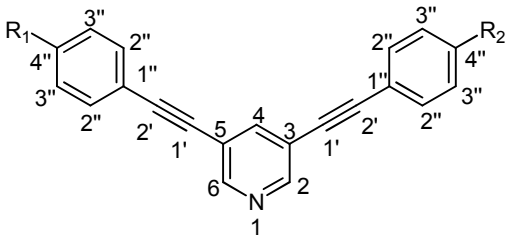
6.4.15. 2-(1-Methyl-1*H*-indol-3-yl)-1-phenylethanol (177).



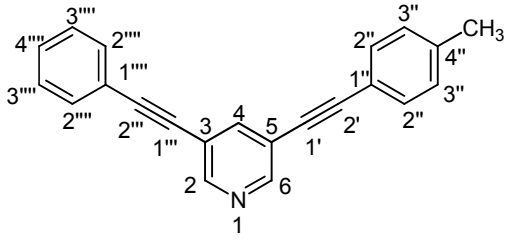
To dry THF (20 mL) at -78 °C under an atmosphere of argon was added n-BuLi (4.2 mL, 2.5M, 10.5 mmol). The resulting mixture was stirred for 5 min at this temperature followed by the addition of 3-bromo-1-methyl-1*H*-indole **169a** (2.10 g, 10 mmol) in dry THF (20 mL) *via* cannula. The reaction mixture was stirred at -78 C for a further 30 min followed by

addition over 5 min of aryl epoxide **100a** (1.3 mL, 12 mmol) in dry THF (10 mL). The solution was allowed to warm to room temperature over 1 h and stirred for a further 20 min. The reaction mixture was quenched with water (60 mL) and extracted with ether (3 x 30 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography of the residue (SiO_2; petrol : ether, 80 : 20 $^{v}/_{v}$) furnished compound **159**. (0.55 g, 22 %); tan solid; m.p.110 $^{\circ}$C; FTIR (neat solid) 3404 (br), 2927, 1682, 1471, 1326, 1246, 1044, 737, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.72 (d, *J* = 7.5, 1H, H4''), 7.57-7.23 (m 8H, H2', H5'', H6'', H7'', H3', H4'), 6.98 (s, 1H, H2''), 5.08 (dd, *J* = 8.7, 4.2, 1H, H1), 3.81 (s, 3H, 1-CH_3), 3.33 (dd, *J* = 9.0, 4.2, 1H, $H2_A$), 3.23 (dd, *J* = 9.0, 8.7, 1H, $H2_B$), 2.25 (bs, 1H, OH); ^{13}C NMR δ 144.5 (q, C1'), 137.3 (q, C9''), 128.7 (q, C8''), 128.4 (C3'), 128.0 (C2''), 127.5 (C4'), 126.0 (C2'), 121.9 (C6'' and C5''), 119.1 (C4''), 110.6 (q, C3''), 109.4 (C7''), 74.1 (C1), 36.0 (C2), 32.7 (1-CH_3).

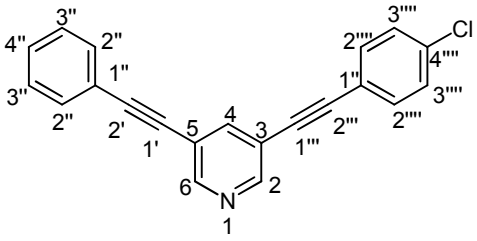
6.5. Synthetic Work, Chapter 4



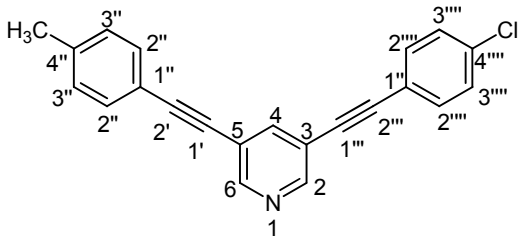
195a R_1 = H, R_2 = H,
195b R_1 = CH_3, R_2 = CH_3



195c



195d



195e

6.5.1. Synthesis of compounds 195a-e, Method A

To dry THF (40 mL) or DMF (25 mL) under an inert atmosphere was sequentially added: bis(triphenylphosphine) palladium (II) chloride (0.07 g, 0.1 mmol, 5 mol %), copper iodide (0.04 g, 0.2 mmol, 2 mol %), triethylamine (4.2 mL, 30 mmol), either 3-bromo-5-pyridyl acetylene **194a** (2.58 g, 10 mmol) [for **195a,b** or **d**] or **194b** (2.72 g, 10 mmol) [for **195c** and **195e**] followed by arylacetylene **147a** (1.12 g, 11 mmol) [for **195a**], **147c** (1.50 g, 11 mmol) [for **195d** or **195e**] or **147e** (1.28 g, 11 mmol) [for **195b** or **195c**] and the resulting black solution stirred at 80 ^{o}C for 12-18 h. After cooling, the mixture was poured into cold water (80 mL) then extracted with ether (4 x 50 mL). The ethereal extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo* to yield brown residues which, after column chromatography and recrystallisation from petrol, yielded

195a-e as white needles or pale yellow solids.**195a** (2.26 g, 81 %), **195b** (2.40 g, 78 %), **195c** (2.70 g, 92 %), **195d** (1.63 g, 52 %) and **195e** (2.36 g, 72 %).

6.5.2. Synthesis of compounds 195a and 195b, Method B

3,5-Dibromopyridine **120** (1.18 g, 5 mmol), bis(triphenylphosphine) palladium (II) chloride (0.18 g, 0.25 mmol, 5 mol %), copper iodide (20 mg, 0.05 mmol, 2 mol %), triethylamine (2.9 mL, 20 mmol) and acetylene **147a** (1.07 g, 10.5 mmol) [for **195a**] or **147e** (1.22 g 10.5 mmol) [for **195b**] were added to dry THF (40 mL) under a blanket of argon and the resulting black mixture stirred at 80 ^{o}C for 12 h. After cooling, the reaction mixture was poured into water (80 mL), the phases separated and the aqueous phase extracted with EtOAc (3 x 20 mL). The combined organic phases were dried ($MgSO_4$) and the volatiles removed *in vacuo.* The crude product was purified by column chromatography (SiO_2; petrol: ether, 90 : 10 $^{v}/_{v}$) followed by recrystallisation from petrol. **195a** (1.08 g, 77 %), **195b** (1.35 g, 88 %).

6.5.3. Synthesis of compounds 195c, 195d, 195e, Method C

To dry DMF (10 mL) under an atmosphere of argon was added 3,5-dibromopyridine (2.37 g, 10 mmol), bis(triphenylphosphine) palladium (II) chloride (0.40 g, 0.6 mmol, 6 mol%), copper iodide (0.20 g, 1.1 mmol, 11

mol%), triethylamine (6 mL) and **147a** (1.10 mL, 10 mmol) [for **195c** or **195d**] or **147e** (1.16 g, 10 mmol) [for **195e**]. The resulting black solution was stirred at 25 ^{o}C for 3 h after which time the solution became lighter in colour. **147e** (1.28 g, 11 mmol) [for **195c**] or **147c** (1.50 g, 11 mmol) [for **195d** or **195e**] was added and the mixture heated at 110 ^{o}C overnight. The solution was cooled, poured into water (100 mL) and extracted into ether (3 x 40 mL). The ethereal extracts were dried ($MgSO_4$) and the solvent removed under vacuum to yield a brown residue. Subsequent chromatography (SiO_2; petrol : ether, 90 / 10 $^{v}/_{v}$) and recrystallisation from petrol afforded the title compounds **195c** (2.14 g, 73 %), **195d** (1.47 g, 47 %) and **195e** (1.25 g, 38 %).

3,5-Bis(phenylethynyl)pyridine (195a); white needles m.p. 126 ^{o}C (from petrol / EtOAc); FTIR (neat solid) 3025, 2209, 1487, 1420, 889, 753, 688 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.60 (d, *J* = 1.8, 2H, H2, H6), 7.86 (t, *J* = 1.8, 1H, H4), 7.49-7.40 (m, 4H, H2''), 7.32- 7.28 (m, 6H, H3'', H4''); ^{13}C NMR ($CDCl_3$) δ 150.8 (C2, C6), 140.6 (C4), 131.8 (C2''), 129.0 (C4''), 128.5 (C3''), 122.4 (q, C1''), 120.2 (q, C3, C5), 93.3 (q, C2'), 85.2 (q, C1'); Anal. Calcd for $C_{21}H_{13}N$: C, 90.30; H, 4.69; N, 5.01. Found: C, 90.23; H, 4.74; N, 4.81.

3,5-Bis-[(4-methylphenyl)ethynyl]pyridine (195b); voluminous white solid; m.p. 182 ^{o}C (from petrol / EtOAc); FTIR (neat solid) 3020, 2210, 1506, 814, 763 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.57 (m, br, 2H, H2, H6), 7.82 (t, *J* = 1.8, 1H, H4), 7.35 (d, *J* = 8.0, 4H, H2''), 7.10 (d, *J* = 7.8, 4H, H3''), 2.30

(s, 6H, 4''-CH_3); ^{13}C NMR ($CDCl_3$) δ 150.6 (C2 or C6), 150.5 (C2 or C6), 140.4 (C4), 139.2 (q, C4''), 131.7 (C2''), 129.3 (C3''), 120.3 (q, C3, C5), 119.3 (q, C1''), 93.5 (q, C2'), 84.7 (q, C1'), 21.6 (4''-CH_3); Anal. Calcd for $C_{23}H_{17}N$: C, 89.87; H, 5.57; N, 4.56. Found: C, 89.65; H, 5.62; N, 4.36.

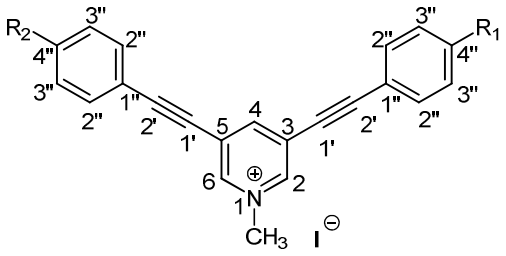
3-Phenylethynyl-5-[(4-methylphenyl)ethynyl]pyridine (195c); voluminous white solid; m.p. 143-144 ^oC; FTIR (neat solid) 3027, 2212, 1419, 818, 754, 701, 686 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.59 (m, br, 2H, H2, H6), 7.84-7.82 (m, 1H, H4), 7.48-7.45 (m, 2H, H2''''), 7.35 (d, *J* = 7.9, 2H, H2''), 7.30-7.28 (m, 3H, H3'''', H4''''), 7.10 (d, *J* = 7.9, 2H, H3''), 2.30 (s, 3H, 4''-CH_3); ^{13}C NMR ($CDCl_3$) δ 150.6 (C2 or C6), 150.5 (C2 or C6), 140.6 (C4), 139.3 (q, C4''), 131.8 (C2''''), 131.7 (C2''), 129.3 (C3''), 129.0 (C4''''), 128.5 (C3''''), 122.4 (q, C1''''), 122.5 (q, C3 or C5), 122.4 (q, C3 or C5), 119.3 (q, C1''), 93.7 (q, C2'), 93.3 (q, C2'''), 85.3 (q, C1'''), 84.6 (q, C1'), 21.6 (4''-CH_3); Anal. Calcd for $C_{22}H_{15}N$: C, 90.07; H, 5.15; N, 4.77. Found: C, 90.22; H, 5.18; N, 4.78.

3-(4-Chlorophenylethynyl)-5-phenylethynyl-pyridine (195d); pale yellow solid; m.p. 131-132 ^oC; FTIR (neat solid) 3027, 2212, 1487, 1090, 832, 756, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.61-8.58 (m, br, 2H, H2, H6), 7.86-7.82 (m, 1H, H4), 7.48-7.45 (m, 2H, H2''), 7.40 (d, *J* = 8.7, 2H, H2''''), 7.32-7.29 (m, 3H, H3'', H4''), 7.27 (d, *J* = 8.7, 2H, H3''''); ^{13}C NMR ($CDCl_3$) δ 150.9 (C2 or C6), 150.7 (C2 or C6), 140.7 (C4), 135.2 (q, C4''''), 133.0 (C2''''), 131.8 (C2''), 129.1 (C4''), 128.9 (C3''''), 128.5 (C3''), 122.3 (q, C1''), 120.8 (q, C1''''), 120.3 (q, C5), 119.9 (q, C3), 93.5 (q, C2'), 92.2 (q, C2'''),

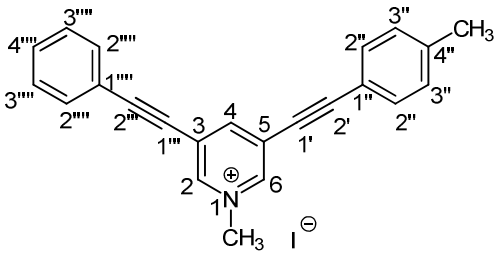
86.2 (q, C1'), 85.1 (q, C1'''); Anal. Calcd for $C_{21}H_{12}ClN$: C, 80.38; H, 3.85; N, 4.46. Found: C, 80.35; H, 3.89; N, 4.36.

3-(4-Chlorophenylethynyl)-5-[(4-methylphenyl)ethynyl]pyridine (195e); pale yellow solid; m.p.189 ^{o}C; FTIR (neat solid) 3026, 2210, 1578, 1507, 1487, 1087, 819 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.59 (m, br, 1H, H2, H6), 7.83 (t, *J* = 1.8, 1H, H4), 7.38 (d, *J* = 8.7, 2H, H2''''), 7.36 (d, *J* = 8.1, 2H, H2''), 7.27 (d, *J* = 8.7, 2H, H3''''), 7.10 (d, *J* = 8.1, 2H, H3''), 2.30 (s, 3H, 4''-CH_3); ^{13}C NMR ($CDCl_3$) δ 150.9 (C2 or C6), 150.5 (C2 or C6), 140.5 (C4), 139.3 (q, C4''), 135.1 (q, C4''''), 133.0 (C2''), 131.7 (C2''''), 129.3 (C3''), 128.9 (C3''''), 120.9 (q, C1''''), 120.8 (q, C3 and C5), 119.3 (q, C1''), 93.7 (q, C2'''), 92.0 (q, C2'), 86.3 (q, C1'''), 84.6 (q, C1'), 21.6 (4''-CH_3); Anal. Calcd for $C_{22}H_{14}ClN$: C, 80.61; H, 4.30; N, 4.27. Found: C, 80.38; H, 4.39; N, 4.18.

Synthesis of compounds 197a-c



197a, R^1 = H, R^2 = H
197b, R^1 = Me, R^2 =H



197c

Compounds **197a-c** were prepared using **GP 3**. There was obtained:

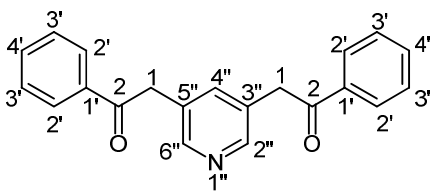
1-Methyl-3,5-bis(phenylethynyl)pyridinium iodide (197a), using **195a** (1.40 g, 5 mmol). (1.66 g, 79 %); pale yellow solid; m.p. 226-227 °C (from EtOH); FTIR (neat solid) 2996, 2216, 1599, 1585, 1493, 1442, 756, 748, 687, 662 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.38 (s, 2H, H2, H6), 8.97 (s, 1H, H4), 7.68 (dd, *J* = 6.9, 1.5, 4H, H2''), 7.58-7.55 (m, 6H, H3'', H4''), 4.37 (s, 3H, 1-CH_3); ^{13}C NMR (DMSO-d_6) δ 148.0 (C4), 147.3 (C2, C6), 132.3 (C2''), 131.0 (C4''), 129.6 (C3''), 123.2 (q, C3), 120.7 (q, C1''), 97.2 (q, C2'), 82.7 (q, C1'), 48.9 (1-CH_3); Anal. Calcd for $C_{22}H_{16}IN$: C, 62.72; H, 3.83; N, 3.32. Found: C, 62.38; H, 3.81; N, 3.22.

1-Methyl-3,5-bis[(4-methylphenyl)ethynyl]pyridinium iodide (197b), using **195b** (1.54 g, 5 mmol). (1.60 g, 71 %); yellow solid; m.p. 218-219 °C (from EtOH); FTIR (neat solid); 2993, 2210, 1584, 1482, 1071, 818 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.34 (s, 2H, H6, H2), 8.91 (s, 1H, H4), 7.56 (d, *J* = 8.1, 4H, H2''), 7.35 (d, *J* = 8.1, 4H, H3''), 4.35 (s, 3H, 1-CH_3), 2.40 (s, 6H, 4''-CH_3); ^{13}C NMR (DMSO-d_6) δ 147.7 (C4), 146.9 (C2, C6), 141.2 (q,

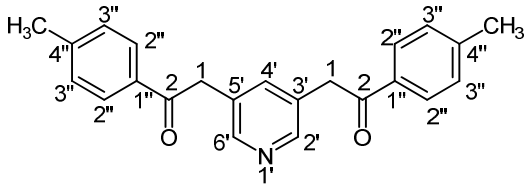
C4''), 132.3 (C2''), 130.2 (C3''), 123.4 (q, C3), 117.7 (q, C1''), 97.6 (C2'), 82.3 (C1'), 48.8 (1-CH_3), 21.7 (4''-CH_3); Anal. Calcd for $C_{24}H_{20}IN$: C, 64.15; H, 4.49; N, 3.12. Found: C, 63.96; H, 4.55; N, 3.23.

1-Methyl-3-phenylethynyl-5-[(4-methylphenyl)ethynylpyridinium] iodide (197c), using **195c** (1.47 g, 5 mmol). (1.92 g, 88 %); yellow solid; m.p. 211 ^{o}C (from EtOH); FTIR (neat solid) 2990, 2211, 1590, 1478, 810, 748 cm^{-1}; 1H NMR (DMSO-d_6) δ 9.36 (s, 2H, H2, H6), 8.94 (s, 1H, H4), 7.68 (dd, *J* = 7.2, 1.8, 2H, H2''''), 7.58-7.55 (m, 5H, H2'', H3'''', H4''''), 7.35 (d, *J* = 7.8, 2H, H3''), 4.36 (s, 3H, 1-CH_3), 2.40 (s, 3H, 4''-CH_3); ^{13}C NMR (DMSO-d_6) δ 147.9 (C4), 147.1 (C2 or C6), 147.0 (C2 or C6), 141.2 (q, C4''), 132.3 (C2'', C2''''), 131.0 (C4''''), 130.2 (C3''), 129.6 (C3''''), 123.5 (q, C3 or C5), 123.2 (q, C3 or C5), 120.7 (q, C1''''), 117.7 (q, C1''), 97.6 (q, C2'), 97.1 (q, C2'''), 82.7 (q, C1'), 82.3 (q, C1'''), 48.8 (1-CH_3), 21.7 (4''-CH_3); Anal. Calcd for $C_{23}H_{18}IN$: C, 63.46; H, 4.17; N, 3.22. Found: C, 63.64; H, 4.21; N, 3.30.

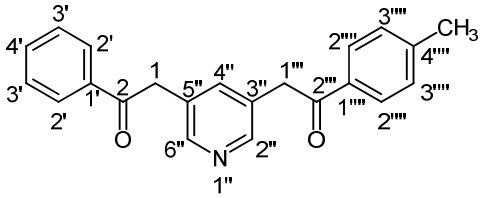
Synthesis of compounds 196a-c



196a



196b



196c

Compounds **196a-c** were prepared using **GP 4**. There was obtained:

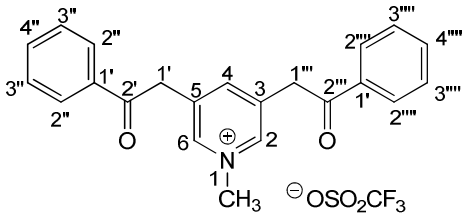
2-[5-(2-Oxo-2-phenylethyl)pyridin-3-yl]-1-phenylethanone (196a), using **195a** (2.79 g, 10 mmol). (2.52 g, 80 %); white solid; m.p. 105-106 °C (from EtOAc); FTIR (neat solid) 3026, 2924, 1680, 1208, 1014, 756, 688 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.41 (bs, 2H, H2'', H6''), 8.11 (dd, *J* = 7.2, 2.1, 4H, H2'), 7.71 (tt, *J* = 7.2, 2.1, 2H, H4'), 7.60 (t, *J* = 7.2, 4H, H3'), 7.58 (s, 1H, H4''), 4.47 (s, 4H, H1); ^{13}C NMR ($CDCl_3$) δ 196.3 (q, C2), 149.1 (C2'', C6''), 138.8 (C4''), 136.3 (q, C1'), 133.6 (C4'), 130.1 (q, C3'', C5''), 128.8 (C3'), 128.4 (C2'), 42.2 (C1); Anal. Calcd for $C_{21}H_{17}NO_2$: C, 79.98; H, 5.43; N, 4.44. Found: C, 79.80; H, 5.49; N, 4.32.

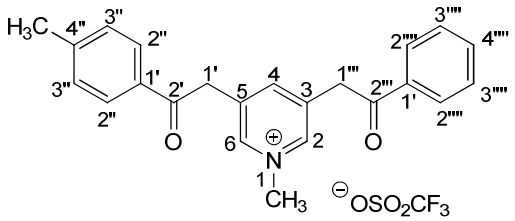
2-[5-(2-Oxo-2-(4-methylphenyl)ethyl)-pyridin-3-yl]-1-(4-methylphenyl) ethanone (196b), using **195b** (3.07 g, 10 mmol)**.** (2.99 g, 87 %); pale yellow solid; m.p. 134 °C (from EtOAc); FTIR (neat solid) 3026, 2917,

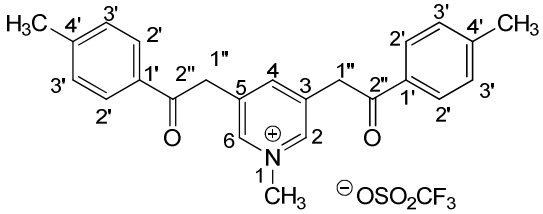
1676, 1603, 1409, 1324, 1221, 1204, 1182, 812, 771 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.37 (bs, 2H, H2', H6'), 7.83 (d, *J* = 7.5, 4H, H2''), 7.47 (s, 1H, H4'), 7.20 (d, *J* = 7.5, 4H, H3''), 4.19 (s, 4H, H1), 2.34 (s, 6H, 4''-CH_3); ^{13}C NMR ($CDCl_3$) δ 196.0 (q, C2), 149.1 (C2', C6'), 144.4 (q, C4''), 138.5 (C4'), 133.9 (q, C1''), 129.5 (C3''), 129.4 (q, C3', C5'), 128.6 (C2''), 42.1 (C1), 21.7 (4''-CH_3); Anal. Calcd for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.08. Found: C, 80.35; H, 6.16; N, 4.05.

2-[5-(2-Oxo-2-(4-methylphenyl)ethyl)pyridin-3-yl]-1-phenylethanone (196c), using **195c** (2.93 g, 10 mmol). (2.37 g, 72 %); pale yellow solid; m.p. 77 °C (from EtOAc); FTIR (neat solid) 2924, 1680, 1605, 1325, 1209, 755, 690, 571 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.35 (bs, 2H, H2'', H6''), 7.92 (dd, *J* = 7.6, 1.0, 2H, H2'), 7.82 (d, *J* = 8.1, 2H, H2''''), 7.51 (tt, *J* = 7.6, 1.0, 1H, H4'), 7.46 (bs, 1H, H4''), 7.40 (t, *J* = 7.6, 2H, H3'), 7.18 (d, *J* = 8.1, 2H, H3''''), 4.21 (s, 2H, H2), 4.18 (s, 2H, H2'''), 2.33 (s, 3H, 4''''-CH_3); ^{13}C NMR ($CDCl_3$) δ 196.4 (q, C1 or C1'''), 196.0 (q, C1 or C1'''), 149.2 (C2''), 149.1 (C6''), 144.5 (q, C4''''), 138.6 (C4''), 136.6 (q, C1'), 133.9 (q, C1''''), 133.5 (C4'), 130.3 (q, C3'' or C5''), 130.0 (q, C3'' or C5''), 129.5 (C3''''), 128.8 (C3'), 128.6 (C2''''), 128.5 (C2'), 42.2 (C2), 42.1 (C2'''), 21.7 (4''''-CH_3); Anal. Calcd for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 80.03; H, 5.89; N, 4.21.

Synthesis of compounds 198a-c







Either compound **196a** (1.58 g, 5 mmol), **196b** (1.72 g, 5 mmol) or **196c** (1.65 g, 5 mmol) and methyl trifluoromethanesulfonate (1.23 g, 0.85 mL, 7.5 mmol) were added to a pressure tube containing dry THF (3 mL) and the resultant mixture stirred at 80 °C for 12 h. The reaction mixture was allowed to cool and was then diluted with cold ether (15 mL). The resulting precipitate was collected by filtration and recrystallised to give the products. There was obtained:

1-methyl-3,5-bis(2-oxo-2-phenylethyl)pyridinium trifluoromethanesulfonate (198a); (2.06 g, 83 %); white solid; m.p. 134 °C (from EtOH); FTIR (neat solid) 3069, 1686, 1598, 1260, 1214, 1149, 1026, 752, 636, 571 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 8.90 (s, 2H, H2), 8.42 (s, 1H, H4), 8.11 (dd, *J* = 7.5, 2.1, 4H, H2''), 7.75 (tt, *J* = 7.5, 2.1, 2H, H4''), 7.63 (t, *J* = 7.5, 4H, H3''), 4.82 (s, 4H, H2'), 4.41 (s, 3H, 1-CH_3); ^{13}C-NMR (DMSO-d_6) δ 196.0 (C1'), 148.8 (C2), 144.8 (C4), 136.3 (q, C3 or C1''),

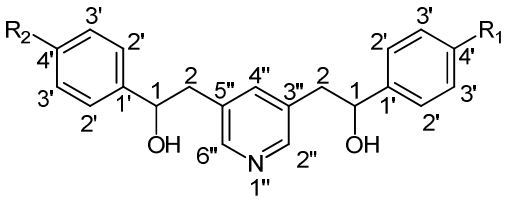
135.9 (q, C3 or C1''), 134.4 (C4''), 129.4 (C3''), 128.8 (C2''), 48.5 (1-CH_3), 41.7 (C2'). Anal. Calcd for $C_{23}H_{20}F_3NO_5S$: C, 57.62; H, 4.20; N, 2.92. Found: C, 57.44; H, 4.18; N, 2.83.

1-Methyl-3,5-bis[2-oxo-2-(4-methylphenyl)ethyl]pyridinium trifluoromethanesulphonate (198b); (2.17 g, 83 %); pale yellow solid; m.p. 165 °C (from EtOH); FTIR (neat solid) 3070, 1685, 1598, 1259, 1218, 1150, 1027, 753, 636, 571 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 8.90 (s, 2H, H2), 8.40 (s, 1H, H4), 8.02 (d, *J* = 8.1, 4H, H3''), 7.43 (d, *J* = 8.1, 4H, H2''), 4.78 (s, 4H, H1'), 4.40 (s, 3H, 1-CH_3), 2.44 (s, 6H, 4''-CH_3); ^{13}C-NMR (DMSO-d_6) δ 195.5 (q, C2'), 148.7 (C4), 144.9 (q, C4''), 144.8 (C2), 135.9 (q, C3), 133.9 (q, C1''), 129.9 (C2''), 128.9 (C3''), 48.5 (1-CH_3), 41.6 (C1'), 21.7 (4''-CH_3); Anal. Calcd for $C_{25}H_{24}F_3NO_5S$: C, 59.16, H, 4.77; N, 2.76. Found: C, 58.98; H, 4.75; N, 2.76.

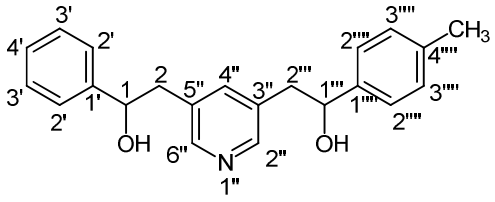
1-Methyl-3-(2-oxo-2-phenylethyl)-5-(2-oxo-2-(4-methylphenyl)ethylpyridinium trifluoromethanesulphonate (198c). (1.77 g, 69 %); pale yellow solid; m.p. 132 °C (from EtOH); FTIR (neat solid) 3064, 1685, 1607, 1258, 1223, 1212, 1152, 1029, 809, 753, 637, 570 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 8.90 (s, 2H, H2 + H6), 8.41 (s, 1H, H4), 8.12 (d, *J* = 7.8, 2H, H2''''), 8.02 (d, *J* = 8.1, 2H, H3''), 7.75 (t, *J* = 7.8, 1H, H4''''), 7.63 (t, *J* = 7.8, 2H, H2''''), 7.43 (d, *J* = 8.1, 2H, H2''), 4.83 (s, 2H, H1'''), 4.79 (s, 2H, H1'), 4.40 (s, 3H, 1-CH_3), 2.44 (s, 3H, 4''-CH_3); ^{13}C-NMR (DMSO-d_6) δ 196.0 (q, C2'''), 195.5 (q, C2'), 148.8 (C4), 144.9 (q, C4''), 144.8 (C2 and C6), 136.3 (q, C1''''), 135.9 (q, C5), 135.8 (q, C3),

134.4 (C4""), 133.9 (q, C1"), 129.9 (C2"), 129.4 (C2""), 128.9 (C2"), 128.8 (C2""), 48.5 (1-CH_3), 41.7 (C1'"), 41.6 (C1'), 21.7 (4"-CH_3); Anal. Calcd for $C_{24}H_{22}F_3NO_5S$: C, 58.41; H, 4.49; N, 2.83. Found: C, 58.26; H, 4.47; N, 2.74.

Synthesis of compounds 182a-c



196a, R^1 = H, R^2 = H
196b, R^1 = CH_3, R^2 = CH_3



196c

To a stirred solution of either **196a** (3.15 g, 10 mmol) **196b** (3.43 g, 10 mmol) or **196c** (3.29 g, 10 mmol) in MeOH (15 mL) at room temperature was added $NaBH_4$ (1.51 g, 40 mmol) in 3 portions. The reaction mixture was stirred at room temperature for 5 h. The solvent was removed under reduced pressure and the residue re-dissolved in water (20 mL). The aqueous phase was extracted with DCM (3 x 15 mL) and the combined organic extracts washed with brine (15 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The resultant residue was recrystallised to afford the products. There was obtained:

2-[5-(2-Hydroxy-2-phenylethyl)-1-pyridin-3-yl]-1-phenylethanol (196a). (2.81 g, 88 %); white solid; m.p. 148-149 $^{\circ}$C (from EtOAc); FTIR (neat solid) 3340 (br), 3030, 2854,1586, 1493, 1453, 1433, 1029, 755, 714, 700 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.09 (bs, 2H, H6", H2"), 7.36 (bs, 1H, H4"),

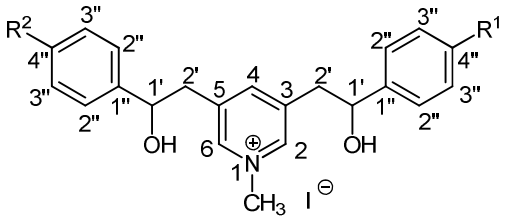
7.30-7.20 (m, 10H, H2', H3', H4'), 5.33 (d, *J* = 3.6, 2H, OH), 4.72 (td, *J* = 6.6, 3.6, 2H, H1), 2.83 (d, *J* = 6.6, 4H, H2); ^{13}C NMR (DMSO-d_6) δ 148.5 (C2'', C6''), 145.8 (q, C1'), 138.3 (C4''), 133.9 (q, C3''), 128.4 (C3'), 127.3 (C4'), 126.4 (C2'), 73.7 (C1), 43.0 (C2); Anal. Calcd for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63; N, 4.39. Found: C, 78.79; H, 6.67; N, 4.46.

2-[5-(2-Hydroxy-2-4-methyl-ethyl)-pyridin-3-yl]-1-(4-methylphenyl)-ethanol (196b). (2.85 g, 82 %); white solid; m.p. 103 °C (from EtOAc); FTIR (neat solid) 3332 br, 3029, 2924, 1512, 1053, 814, 783 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.14 (bs, 2H, H6'', H2''), 7.26 (bs, 1H, H4''), 7.17 (d, *J* = 8.4, 4H, H2'), 7.13 (d, *J* = 8.4, 4H, H3'), 4.73 (td, *J* = 6.3, 3.6, 2H, H1), 2.90 (d, *J* = 6.3, 4H, H2), 2.72 (bs, 2H, OH), 2.34 (s, 6H, 4'-CH_3); ^{13}C NMR ($CDCl_3$) δ 148.4 (C6'', C2''), 140.7 (q, C4'), 138.6 (C4''), 137.5 (q, C1'), 133.5 (q, C3''), 129.2 (C3'), 125.8 (C2'), 74.6 (C1), 42.8 (C2), 21.1 (4'-CH_3); Anal. Calcd for $C_{23}H_{25}NO_2$: C, 79.51; H, 7.25; N, 4.03. Found: 79.74; H, 7.33; N, 4.11.

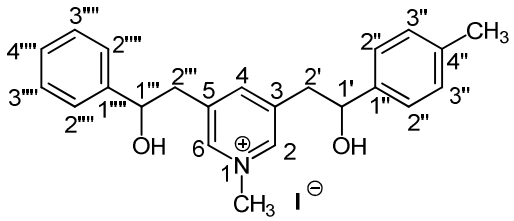
2-[5-(2-Hydroxy-2-(4-methylphenyl)ethyl)pyridin-3-yl]-1-phenylethanol (196c). (3.13 g, 94 %); white solid; m.p.106-107 °C (from EtOAc); FTIR (neat solid) 3352 (br), 3056, 2924, 1451, 1431, 1039, 818, 753, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.04 (bs, 2H, H2'', H6''), 7.25-7.18 (m, 6H, H2', H3', H4', H4''), 7.09 (d, *J* = 8.4, 2H, H2''''), 7.04 (d, *J* = 8.4, 2H, H3''''), 4.66 (m, 2H, H1, H1'''), 2.92 (s, br, 2H, OH), 2.83 (m, 4H, H2, H2'''); ^{13}C NMR ($CDCl_3$) δ 148.3 (C6'', C2''), 143.7 (q, C1'), 140.7 (q, C1''''), 138.8 (C4''), 137.5 (q, C4''''), 137.4 (q, C1'''), 133.6 (q, C3'' or C5''), 133.5 (q, C3'' or

C5''), 129.2 (C3''''), 128.5 (C3'), 127.7 (C4'), 125.9 (C2'), 125.8 (C2''''), 74.7 (C2 or C2'''), 74.6 (C2 or C2'''), 42.8 (C1 or C1'''), 42.8 (C1 or C1'''), 21.1 (4''''-CH_3); Anal. Calcd for $C_{22}H_{23}NO_2$: C, 79.25; H, 6.95; N, 4.20. Found: C, 79.21; H, 7.14; N, 4.12.

Synthesis of compounds 199a-c



199a, R^1 = H, R^2 = H
199b, R^1 = CH_3, R^2 = CH_3



199c

Dry THF (2 mL), either compound **196a** (0.96 g, 3 mmol)**, 196b** (1.04 g, 3 mmol) or **196c** (1.00 g, 3 mmol) and methyl iodide (0.31 mL, 5 mmol) were sequentially placed in an oven dried pressure tube. The reaction mixture was stirred at 80 °C for 12 h. After cooling, the resulting precipitate was collected by filtration, washed with ether (10 mL) and recrystallised to furnish the products. There was obtained:

3,5-Bis-(2-hydroxy-2-phenylethyl)-1-methylpyridinium iodide (199a). (1.20 g, 87 %); white solid; m.p. 169-170 °C (from EtOH); FTIR (neat solid) 3378 (br), 3016, 1451, 1417, 1053, 764, 706, 686 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.78 (bs, 2H, H6, H2), 8.27 (t, *J* = 2.1, 1H, H4), 7.42-7.35 (m, 8H, H2'', H3''), 7.32-7.27 (m, 2H, H4''), 5.55 (d, *J* = 4.2, 2H, OH), 4.89-4.85 (m, 2H, H2'), 4.32 (s, 3H, 1-CH_3), 3.14-2.95 (m, 4H, H1'); ^{13}C NMR (DMSO-d_6) δ 147.1 (C4), 145.1 (q, C1''), 143.7 (C2, C6), 139.4 (q, C3, C5), 128.7

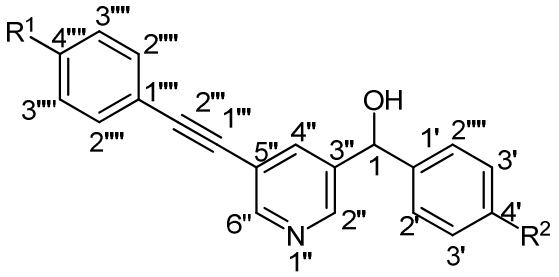
(C3''), 127.7 (C4''), 126.3 (C2''), 72.5 (C2'), 48.1 (1-CH_3), 42.3 (C1'); Anal. Calcd for $C_{22}H_{24}INO_2$: C, 57.28; H, 5.24; N, 3.04. Found: C, 57.18; H, 5.20; N, 2.93.

3,5-Bis-[2-hydroxy-2-(4-methylphenyl)ethyl]-1-methylpyridinium iodide (199b). (1.22 g, 83 %); white solid; m.p. 182-183 °C (from EtOH); FTIR (neat solid) 3375, 3026, 1686, 1508, 1210, 1063, 812, 684 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.76 (s, 2H, H2, H6), 8.24 (br, 1H, H4), 7.27 (d, *J* = 7.5, 4H, H2''), 7.18 (d, *J* = 7.5, 4H, H3''), 5.48 (d, *J* = 3.6, 2H, OH), 4.83-4.80 (m, 2H, H2'), 4.31 (s, 3H, 1-CH_3), 3.10-2.91 (m, 4H, H1'), 2.31 (s, 6H, 4''-CH_3); ^{13}C NMR (DMSO-d_6) δ 147.0 (C4), 143.7 (C2, C6), 142.1 (q, C4''), 139.4 (q, C3, C5), 136.7 (q, C1''), 129.2 (C3''), 126.2 (C2''), 72.4 (C2'), 48.1 (1-CH_3), 42.3 (C1'), 21.2 (4''-CH_3); Anal. Calcd for $C_{24}H_{28}INO_2$: C, 58.90; H, 5.77; N, 2.86. Found: C, 58.76; H, 5.73; N, 2.76.

3-(2-Hydroxy-2-phenylethyl)-5-[2-hydroxy-2-(4-methylphenyl)ethyl]-1-methylpyridinium iodide (199c). (0.83 g, 58%); white solid; m.p. 160-161 °C (from EtOH); FTIR (neat solid) 3382 (br), 3018, 1496, 1056, 818, 761, 706 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.81 (br, 2H, H2, H6), 8.30 (br, 1H, H4), 7.44-7.38 (m, 5H, H2'''', H3'''', H4''''), 7.35 (d, *J* = 8.1, 2H, H2''), 7.23 (d, *J* = 8.1, 2H, H3''), 5.60 (d, *J* = 4.2, 1H, 2''' OH), 5.52 (d, *J* = 4.2, 1H, 2' OH), 4.93-4.86 (m, 2H, H2', H2''), 4.36 (s, 3H, 1-CH_3), 3.18-2.98 (m, 4H, H1', H1'''), 2.36 (s, 3H, 4''-CH_3); ^{13}C NMR (DMSO-d_6) δ 147.0 (C4), 145.1 (q, C1''''), 143.7 (C2, C6), 142.1 (q, C4''), 139.4 (q, C3), 139.3 (q, C5), 136.7 (q, C1''), 129.2 (C3''), 128.6 (C3''''), 127.7 (C4''''), 126.3 (C2''''), 126.2

(C2''), 72.5 (C2'), 72.4 (C2'), 72.3 (C2'''), 72.3 (C2'''), 48.1 (1-CH_3), 42.3 (C1, C1''''), 21.2 (4''-CH_3); Anal. Calcd for $C_{23}H_{26}INO_2$: C, 58.11; H, 5.51; N, 2.95. Found: C, 58.13; H, 5.55; N, 2.90.

Synthesis of compounds 203a-d



203a, R_1 = H, R_2 = H
203b, R_1 = Me, R_2 = H
203c, R_1 = H, R_2 = Cl
203d, R_1 = Me, R_2 = Cl

A solution of either **194a** (1.55 g, 6 mmol) [for **203a** or **203c**] or **194b** (1.63 g, 6 mmol) [for **203b** or **203d**, in dry ether (100 mL) was cooled to -78 °C under an atmosphere of argon, followed by the dropwise addition of n-BuLi (2.6 mL, 2.5 M, 6.6 mmol) in ether (30 mL) over 15 min. The resulting bright orange solution was stirred at -78 °C for 30 min and a solution of benzaldehyde **163a** (0.70 g, 6.6 mmol) [for **203a** or **203b**] or 4-chlorobenzaldehyde **163c** (0.93 g, 6.6 mmol) [for **203c** or **203d**] in ether (30 mL) added dropwise over 10 min. The reaction mixture was allowed to warm to room temperature over 0.5 h and stirred for a further 1 h, quenched with water (100 mL), the phases separated, and the aqueous phase extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure. Subsequent purification of the residue by column chromatography (SiO_2;

ether : petrol, 90 : 10 $^{v}/_{v}$) and recrystallisation as appropriate furnished the products. There was obtained:

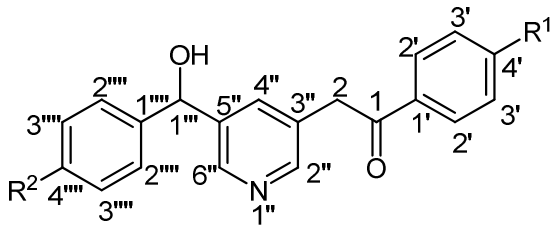
Phenyl-(5-phenylethynylpyridin-3-yl)methanol (203a). (0.99 g, 58 %); colourless oil; FTIR (neat) 3188 (br), 2215, 1491, 1443, 1024, 754, 698, 689 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.59 (br, 1H, H6''), 8.53 (br, 1H, H2''), 7.91 (t, *J* = 1.8, 1H, H4''), 7.59 –7.55 (m, 2H, H2'''), 7.42-7.35 (m, 8H, H3'''', H4'''', H2'''', H3''', H4'''), 5.90 (s, 1H, H1), 3.95 (bs, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 150.2 (C6'), 146.3 (C2'), 142.8 (q, C1''''), 139.6 (q, C3'), 137.2 (C4'), 131.8 (C2'''), 129.0 (C4'''), 128.9 (C3''''), 128.5 (C3'''), 128.2 (C4''''), 126.7 (C2''''), 122.4 (q, C1'''), 120.6 (q, C5'), 93.2 (q, C2'''), 85.7 (q, C1'''), 73.7 (C1). HRMS calcd for $C_{20}H_{15}NO$ $(M + H)^{+}$ required 286.1233, found 286.1232.

Phenyl-[5-(4-methylphenyl)-ethynyl-pyridin-3-yl]methanol (203b). (1.29 g, 72 %); pale yellow solid; m.p. 47-48 $^{\circ}C$ (EtOAc / petrol); FTIR (neat solid) 3193 (br), 2214, 1509, 1044, 1023, 814, 709, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.43 (br, 1H, H6'), 8.35 (br, 1H, H2'), 7.75 (t, *J* = 1.8, 1H, H4'), 7.32 (d, *J* = 8.1, 2H, H2'''), 7.27-7.17 (m, 5H, H2'''', H3'''', H4''''), 7.06 (d, J = 8.1, 2H, H3'''), 5.74 (s, 1H, H1), 3.75 (s, 1H, OH), 2.28 (s, 3H, 4''-CH_3); ^{13}C NMR ($CDCl_3$) δ 150.4 (C6'), 146.3 (C2'), 142.9 (q, C1''''), 139.4 (q, C3'), 139.2 (q, C4'''), 136.9 (C4'), 131.7 (C2'''), 129.3 (C3'''), 128.9 (C3''''), 128.1 (C4''''), 126.7 (C2''''), 120.7 (q, C1'''), 119.4 (q, C5'), 93.3 (q, C2''), 85.2 (q, C1''), 73.7 (C1), 21.6 (4''-CH_3).

(4-Chlorophenyl)-(5-phenylethynylpyridin-3-yl)methanol (203c). (1.31 g, 68 %); white solid; m.p. 108 °C (from EtOAc / petrol); FTIR (neat solid) 3128 (br), 3052, 1487, 1439, 1086, 1013, 787, 753, 687 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.50 (br, 1H, H6'), 8.38 (br, 1H, H2'), 7.73 (t, *J* = 1.5, 1H, H4), 7.46-7.43 (m, 2H, H2'''), 7.30-7.21 (m, 5H, H3''', H4''', H3''''), 5.76 (s, 1H, H1), 3.49 (s, br, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 150.8 (C6'), 146.5 (C2'), 141.2 (q, C1''''), 138.9 (q, C3'), 136.8 (C4'), 134.0 (q, C4''''), 131.8 (C2'''), 129.1 (C3''''), 129.0 (C4'''), 128.5 (C2''''),, 128.0 (C3'''), 122.3 (q, C1'''), 118.2 (q, C5'), 93.3 (q, C2'), 85.6 (q, C1'), 73.1 (C1); Anal. Calcd for $C_{20}H_{14}ClNO$: C, 75.12; H, 4.41; N, 4.38. Found: C, 74.91; H, 4.49; N, 4.40.

(4-Chlorophenyl)-[5-(4-methylphenyl)ethynylpyridin-3-yl]methanol (203d). (1.20 g, 60 %); white solid; m.p. 151-152 °C (from EtOAc / petrol); FTIR (neat solid) 3133, 2214, 1508, 1088, 1058, 815 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.45 (d, *J* = 1.5, 1H, H6'), 8.35 (d, *J* = 1.5, 1H, H2'), 7.71 (t, *J* = 1.5, 1H, H4'), 7.33 (d, *J* = 8.1, 2H, H2'''), 7.25 (d, *J* = 9.0, 2H, H3''''), 7.21 (d, *J* = 9.0, 2H, H2''''), 7.07 (d, *J* = 8.1, 2H, H3'''), 5.74 (s, 1H, H1), 3.81 (s, 1H, OH), 2.29 (s, 3H, 4'''-CH_3); ^{13}C NMR ($CDCl_3$) δ 150.5 (C6'), 146.1 (C2'), 141.2 (q, C1''''), 139.3 (q, C4'''), 139.1 (q, C3'), 137.0 (C4'), 134.0 (q, C4''''), 131.7 (C2'''), 129.3 (C3'''), 129.0 (C3''''), 128.0 (C2''''), 120.9 (q, C1'''), 119.2 (q, C5'), 93.7 (q, C2''), 85.0 (q, C1''), 73.0 (C1), 21.6 (4'''-CH_3); Anal. Calcd for $C_{21}H_{16}ClNO$: C, 75.56; H, 4.83; N, 4.20. Found: C, 75.25; H, 4.89; N, 4.07.

Synthesis of compounds 204a-d



204a, R^1 = H, R_2 = H
204b, R^1 = Me, R_2 = H
204c, R^1 = H, R_2 = Cl
204d, R^1 = Me, R_2 = Cl

Compounds **204a-d** were prepared using **GP 4**. There was obtained:

2-[5-(Hydroxyphenylmethyl)pyridin-3-yl]-1-phenylethanone (204a), using **203a** (0.86 g, 3 mmol). (0.50 g, 55 %); white solid; m.p. 102-103 °C (from EtOAc / petrol); FTIR (neat solid) 3143 (br), 1684, 1449, 1327, 1209, 1052, 743, 716, 702, 686 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.48 (d, *J* = 1.8, 1H, H6''), 8.35 (d, *J* = 1.8, 1H, H2''), 8.06 (dd, *J* = 7.8, 1.8, 2H, H2'), 7.70-7.65 (m, 2H, H4'', H4'), 7.56 (t, *J* = 7.8, 2H, H3'), 7.39 (dd, *J* = 7.8, 1.2, 2H, H2'''), 7.33 (t, *J* = 7.8, 2H, H3'''), 7.24 (tt, *J* = 7.8, 1.8, 1H, H4'''), 6.06 (d, *J* = 3.9, 1H, OH), 5.79 (d, *J* = 3.9, 1H, H1''''), 4.48 (s, 2H, H2); ^{13}C NMR (DMSO-d_6) δ 197.7 (q, C1), 149.8 (C2''), 146.5 (C6''), 145.4 (q, C1''''), 140.8 (q, C5'), 136.8 (q, C1'), 135.6 (C4''), 133.9 (C4'), 130.9 (q, C3''), 129.2 (C3'), 128.8 (C2'), 128.7 (C3'''), 127.5 (C4'''), 126.7 (C2'''), 72.6 (C1''''), 42.2 (C2); Anal. Calcd for $C_{20}H_{17}NO_2$: C, 79.19; H, 5.65; N, 4.62. Found: C, 79.05; H, 5.67; N, 4.63.

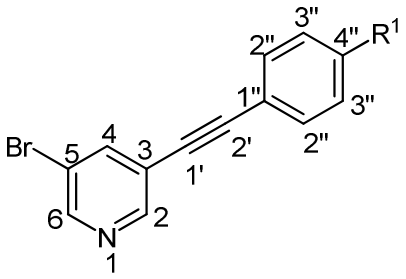
2-[5-(Hydroxyphenylmethyl)pyridin-3-yl]-1-(4-methylphenyl)ethanone (204b), using **203b** (0.90 g, 3 mmol). (0.78 g, 82 %); white solid; m.p. 139-140 °C (from EtOAc / petrol); FTIR (neat solid) 3125, 1683, 1605, 1327, 1049, 809, 744, 716, 705 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.47 (d, *J* = 1.8, 1H, H6''), 8.34 (d, *J* = 1.8, 1H, H2''), 7.96 (d, *J* = 8.1, 2H, H2'), 7.66 (t, *J*= 1.8, 1H, H4''), 7.41-7.30 (m, 7H, H3', H2''', H3''', H4'''), 6.07 (d, *J* = 4.1, 1H, OH), 5.79 (d, *J* = 3.9, 1H, H1''''), 4.43 (s, 2H, H2), 2.40 (s, 3H, 4'-CH_3); ^{13}C NMR (DMSO-d_6) δ 197.1 (q, C1), 149.8 (C2''), 146.5 (C6''), 145.4 (q, C4'), 144.3 (q, C1'), 140.8 (q, C1'''), 135.5 (C4''), 134.3 (q, C5''), 131.1 (q, C3''), 129.8 (C3'), 128.9 (C2'), 128.7 (C3'''), 127.5 (C4'''), 126.7 (C2'''), 72.7 (C1''''), 42.1 (C2), 21.6 (4'-CH_3); Anal. Calcd for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03; N, 4.41. Found: C, 79.04; H, 6.12; N, 4.27.

2-{5-[(4-Chloro-phenyl)hydroxymethyl]pyridin-3-yl}-1-phenylethanone (204c), using **203c** (0.96 g, 3 mmol). (0.65 g, 64 %); white solid; m.p. 107 °C (EtOAc / petrol); FTIR (neat solid) 3125 (br), 1686, 1488, 1325, 1208, 1063, 1014, 756, 726, 686 570 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.48 (d, *J* = 1.2, 1H, H6''), 8.36 (d, *J* = 1.2, 1H, H2''), 8.06 (dd, *J* = 7.8, 1.2, 2H, H2'), 7.68 (tt, *J* = 7.8, 1.2, 1H, H4'), 7.64 (t, *J* = 1.2, 1H, H4''), 7.56 (t, *J* = 7.8, 2H, H3'), 7.43 (d, *J* = 9.0, 2H, H3''''), 7.38 (d, *J* = 9.0, 2H, H2''''), 6.17 (d, *J* = 4.2, 1H, OH), 5.81 (d, *J* = 4.2, 1H, H1), 4.48 (s, 2H, H2); ^{13}C NMR (DMSO-d_6) δ 197.6 (q, C1), 150.0 (C2''), 146.5 (C6''), 144.3 (q, C1''''), 140.4 (q, C5''), 136.8 (q, C1'), 135.6 (C4''), 133.9 (C4'), 132.0 (q, C4''''), 131.0 (q, C3''), 129.2 (C3'), 128.8 (C2'), 128.7 (C3'''' or C2''''), 128.5 (C2''''

or C3""), 71.9 (C1""), 42.2 (C2); Anal. Calcd for $C_{20}H_{16}ClNO_2$: C, 71.11; H, 4.77; N, 4.15. Found: C, 71.12; H, 4.78; N, 4.12.

2-{5-[4-Chlorophenyl)hydroxymethyl]pyridin-3-yl}-1-(4-methylphenyl)ethanone (204d), using **203d** (1.00 g, 3 mmol). (0.79 g, 74 %); white solid; m.p. 144-145 °C (from EtOAc / petrol); FTIR (neat solid) 3108 (br), 1685, 1604, 1487, 1323, 1062, 1013, 807, 793, 766, 725, 566 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.48 (br, 1H, H6''), 8.35 (br, 1H, H2''), 7.95 (d, *J* = 8.1, 2H, H2'), 7.63 (br, 1H, H4''), 7.35 (m, 6H, H3', H2"", H3""), 6.16 (d, *J* = 4.2, 1H, OH), 5.80 (d, *J* = 4.2, 1H, H1'"), 4.43 (s, 2H, H2), 2.40 (s, 3H, 4'-CH_3); ^{13}C NMR (DMSO-d_6) δ 197.1 (q, C1), 150.0 (C2''), 146.5 (C6''), 144.4 (q, C1"" or q, C4'), 144.3 (q, C1"" or q, C4'), 140.4 (q, C5'), 135.6 (C4''), 134.3 (q, C1'), 132.0 (q, C4""), 131.2 (q, C3''), 129.8 (C3'), 128.9 (C2'), 128.7 (C3""), 128.5 (C2""), 71.9 (C1'"), 42.1 (C2), 21.6 (4'-CH_3); Anal. Calcd for $C_{21}H_{18}ClNO_2$: C, 71.69; H, 5.16; N, 3.98. Found: C, 71.73; H, 5.15; N, 3.97.

Synthesis of compounds 194a,c,e



To dry THF (8 mL) was added 3,5-dibromopyridine (2.37 g, 10 mmol), either terminal acetylene **147a** (0.92 g, 9 mmol), **147c** (1.23 g, 9 mmol), or **147e** (1.05 g, 9 mmol), bis(triphenylphosphine)palladium (II) chloride (0.4 g, 0.6 mmol, 5 mol.%), copper iodide (0.2 g, 1.1 mmol, 2 mol.%) and triethylamine (6 mL, 40 mmol). The mixture was stirred for 12 h at 50 °C (110 °C for **147c**) under an atmosphere of argon. After cooling, the reaction mixture was washed with water, dried ($MgSO_4$) and the volatiles removed under reduced pressure to afford a brown residue. Purification by column chromatography (SiO_2, 100% petrol) and recrystallisation afforded the products. There was obtained:

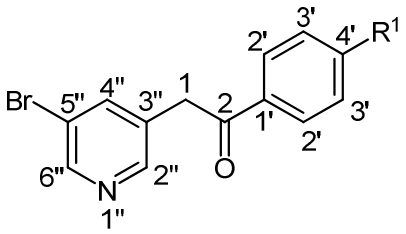
3-Bromo-5-phenylethynylpyridine (194a). (1.39 g, 60 %); pale yellow solid; m.p. 97 °C (from petrol / EtOAc); FTIR (neat solid) 3030, 2209, 1580, 1397, 754, 689 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.59 (d, *J* = 1.8, 1H, H2), 8.54 (d, *J* = 1.8, 1H, H6), 7.89 (t, *J* = 1.8, 1H, H4), 7.47 (dd, *J* = 7.5, 2.1, 2H, H2''), 7.32-7.30 (m, 3H, H3'', H4''); ^{13}C NMR ($CDCl_3$) δ 150.2 (C2), 149.7 (C6), 140.7 (C4), 131.8 (C2''), 129.2 (C4''), 128.5 (C3''), 122.1 (q, C1''), 121.9 (q,

C3), 120.1 (q, C5), 94.0 (q, C2'), 84.5 (q, C1'); Anal. Calcd for $C_{13}H_8BrN$: C, 60.49; H, 3.12; N, 5.43. Found: C, 60.65; H, 3.14; N, 5.32.

3-Bromo-5-(4-methylphenyl)ethynylpyridine (194b). (2.06 g, 84 %); pale yellow solid; m.p. 121-122 °C (from petrol / EtOAc); FTIR (neat solid) 3022, 2210, 1572, 1406, 1109, 828 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.58 (d, *J* = 1.8, 1H, H2), 8.52 (d, *J* = 1.8, 1H, H6), 7.87 (t, *J* = 1.8, 1H, H4), 7.35 (d, *J* = 7.8, 2H, H2''), 7.11 (d, *J* = 7.8, 2H, H3''), 2.31 (s, 3H, 4''-CH_3); ^{13}C NMR ($CDCl_3$) δ 150.1 (C2), 149.5 (C6), 140.6 (C4), 139.5 (q, C4''), 131.7 (C2''), 129.3 (C3''), 122.2 (q, C1''), 120.1 (q, C5), 119.0 (q, C3), 94.3 (q, C2'), 83.9 (q, C1'), 21.6 (4''-CH_3); Anal. Calcd for $C_{14}H_{10}BrN$: C, 61.79; H, 3.70; N, 5.15. Found: C, 61.79; H, 3.73; N, 5.09.

3-Bromo-5-(4-chlorophenylethynyl)pyridine (194c). (1.29 g, 49 %); pale yellow solid 113-114 °C; FTIR (neat solid) 3017, 1484, 1404, 1091, 880, 824 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.60 (br, 1H, H6), 8.56 (br, 1H, H6), 7.88 (s, 1H, H4), 7.38 (d, *J* = 8.7, 2H, H2''), 7.26 (d, *J* = 8.7, 2H, H3''); ^{13}C NMR ($CDCl_3$) δ 150.0 (C6), 149.8 (C2), 140.7 (C4), 135.4 (q, C4''), 133.0 (C2''), 128.9 (C3''), 120.5 (q, C3, q, C5, q, C1''), 92.9 (q, C2'), 85.4 (q, C1'); EA calc. for $C_{13}H_{17}ClBrN$: C, 53.37; H, 2.41; N, 4.79. Found: C, 53.29; H, 2.50; N, 4.24.

Synthesis of compounds 205a and 205b



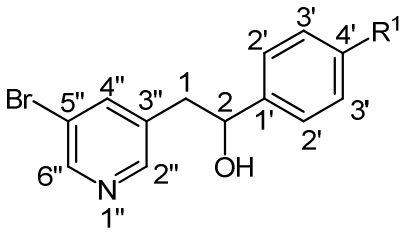
Compounds **205a and 205b** were synthesised using **GP 4**. There was obtained: (15 mmol **194a** and **194b**).

2-(5-Bromopyridin-3-yl)-1-phenylethanone (205a). (3.81 g, 92 %); pale yellow solid; m.p. 51-52 °C (from EtOAc); FTIR (neat solid) 3050, 2970, 1674, 1423, 1330, 1207, 755, 684 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.57 (d, *J* = 1.8, 1H, H2''), 8.42 (d, *J* = 1.8, 1H, H6''), 8.00 (dd, *J* = 8.1, 1.2, 2H, H2'), 7.77 (t, *J* = 1.8, 1H, H4''), 7.60 (tt, *J* = 8.1, 1.8, 1H, H4'), 7.49 (t, *J* = 8.1, 2H, H3'), 4.28 (s, 2H, H2); ^{13}C NMR ($CDCl_3$) δ 195.6 (q, C1), 149.4 (C2''), 148.8 (C6''), 140.0 (C4''), 136.1 (q, C1'), 133.8 (C4'), 131.9 (q, C3''), 128.9 (C2'), 128.4 (C3'), 120.6 (q, C5''), 41.6 (C2); Anal. Calcd for $C_{13}H_{10}BrNO$: C, 56.55; H, 3.65; N, 5.07. Found: C, 56.39; H, 3.64; N, 4.88.

2-(5-Bromopyridin-3-yl)-1-(4-methylphenyl)ethanone (205b). (4.05 g, 93 %); white solid; m.p. 102-103 °C (from EtOAc); FTIR (neat solid) 3020, 2919, 1681, 1603, 1338, 1203, 1182, 809, 697, 568 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.60 (br, 1H, H2''), 8.44 (br, 1H, H6''), 7.92 (d, *J* = 8.1, 2H, H2'), 7.79 (t, *J* = 1.8, 1H, H4''), 7.31 (d, *J* = 8.1, 2H, H3'), 4.27 (s, 2H, H2), 2.45 (s, 3H, 4'-CH_3); ^{13}C NMR ($CDCl_3$) δ 195.2 (q, C1), 149.4 (C2''), 148.8 (C6''), 148.8

(q, C4'), 139.8 (C4''), 133.6 (q, C1'), 131.2 (q, C3''), 129.6 (C2'), 128.5 (C3'), 120.1 (q, C5''), 41.6 (C2), 21.7 (4'-CH_3); Anal. Calcd for $C_{14}H_{12}BrNO$: C, 57.95; H, 4.17; N, 4.83. Found: C, 57.79; H, 4.18; N, 4.74.

Synthesis of compounds 181a and 181b

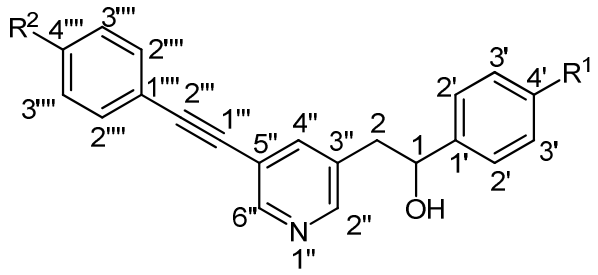


Compounds **181a and 181b** were synthesised using **GP 1**. There was obtained: (10 mmol **205a,b**)

2-(5-Bromopyridin-3-yl)-1-phenylethanol (181a). (2.64 g, 95 %); white solid; m.p. 77-78 ^{o}C (from EtOAc); FTIR (neat solid) 3263 (br), 3029, 1581, 1423, 1050, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.33 (d, *J* = 1.8, 1H, H6''), 8.13 (d, *J* = 1.8, 1H, H2''), 7.57 (t, *J* = 1.8, 1H, H4''), 7.20-7.18 (m, 5H, H2', H3', H4'), 4.78 (dd, *J* = 7.2, 5.4, 1H, H1), 2.91 (dd, *J* = 13.2, 7.2, 1H, $H2_A$), 2.85 (dd, *J* = 13.2, 5.4, 1H, $H2_B$), 2.84 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 148.7 (C2''), 148.6 (C6''), 143.4 (q, C1'), 140.0 (C4''), 135.8 (q, C3''), 128.6 (C3'), 128.1 (C4'), 125.8 (C2'), 120.4 (q, C5''), 74.5 (C1), 42.3 (C2); Anal. Calcd for $C_{13}H_{12}BrNO$: C, 56.14; H, 4.35; N, 5.04. Found: C, 56.23; H, 4.55; N, 4.78.

2-(5-Bromo-pyridin-3-yl)-1-(4-methylphenyl) ethanol (181b). (2.51 g, 86 %); white solid; m.p. 100-101 °C (from EtOAc); FTIR (neat solid) 3402, 3031, 1598, 1507, 1420, 1041 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.38 (br, 1H, H6''), 8.18 (br, 1H, H2''), 7.59 (t, *J* = 2.1, 1H, H4''), 7.08 (d, *J* = 8.4, 2H, H2'), 7.05 (d, *J* = 8.4, 2H, H3'), 4.76 (dd, *J* = 7.5, 5.4, 1H, H1), 2.92 (dd, *J* = 13.8, 7.5, 1H, $H2_A$), 2.84 (dd, *J* = 13.8, 5.4, 1H, $H2_B$), 2.27 (s, 3H, 4'-CH_3); ^{13}C NMR ($CDCl_3$) δ 148.6 (C2''), 148.4 (C6''), 140.3 (C4''), 140.1 (q, C1'), 137.8 (q, C4'), 136.0 (q, C3''), 129.3 (C3'), 125.8 (C2'), 120.4 (q, C5''), 74.4 (C1), 42.3 (C2), 21.1 (4'-CH_3); Anal. Calcd for $C_{14}H_{14}BrNO$: C, 57.55; H, 4.83; N, 4.79. Found: C, 57.55; H, 4.85; N, 4.68.

Synthesis of compounds 201a-c



To dry DMF (20 mL) under a steady stream of argon was added either **181a** (2.78 g, 10 mmol) [for **202a** or **202c**] or **181b** (2.92 g, 10 mmol) [for **202b**], bis(triphenylphosphine) palladium (II) chloride (0.35 g, 0.5 mmol, 5 mol.%), copper iodide (0.19 g, 0.1 mmol, 2 mol.%), triethylamine (6 mL, 40 mmol) and either arylacetylene **147a** (1.12 g, 11 mmol) [for **202a** or **202b**] or **147e** (1.28 g, 11 mmol) [for **202c**]. After 2 h at 110 °C, the reaction mixture was cooled, diluted with water (150 mL) and extracted with ether

(4 x 30 mL). The combined ethereal extracts were washed with water (2 x 50 mL), brine (30 mL), dried ($MgSO_4$), the solvent removed under reduced pressure and the resultant residue purified by column chromatography (SiO_2; EtOAc : petrol, 60 : 40 $^{v}/_{v}$) to afford the products **202a-c**. There was obtained:

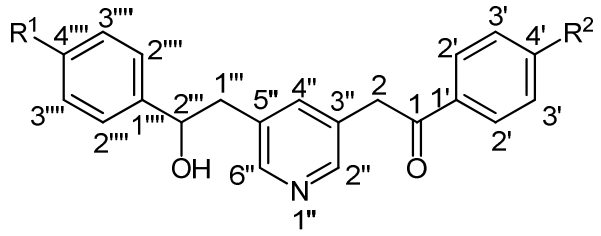
1-Phenyl-2-(5-phenylethynylpyridin-3-yl)ethanol (201a). (1.80 g, 60 %); white solid; m.p. 125-126 $^{\circ}$C (from EtOAc / petrol); FTIR (neat solid) 3167 br, 2850, 1489, 1441, 1065, 754, 702, 698 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.57 (br, 1H, H6'), 8.36 (br, 1H, H2'), 7.81 (br, 1H, H4'), 7.61-7.56 (m, 2H, H2'''), 7.46-7.44 (m, 3H, H3''', H4'''), 7.38-7.32 (m, 4H, H2'''', H3''''), 7.26-7.21 (m, 1H, H4''''), 5.43 (d, *J* = 4.5, 1H, OH), 4.83 (ddd, *J* = 8.1,4.8, 4.5, 1H, H1), 2.97 (dd, *J* = 13.5, 4.8, 1H, $H2_A$), 2.89 (dd, *J* = 13.5, 8.7, 1H, $H2_B$); ^{13}C NMR (DMSO-d_6) δ 150.6 (C2'), 149.6 (C6'), 145.6 (q, C1''''), 139.8 (C4'), 135.0 (q, C3'), 131.9 (C2'''), 129.6 (C4'''), 129.3 (C3'''), 128.4 (C3''''), 127.4 (C4''''), 126.4 (C2''''), 122.3 (q, C1'''), 119.0 (q, C5'), 92.4 (q, C2''), 86.8 (q, C1''), 73.2 (C1), 42.5 (C2); Anal. Calcd for $C_{21}H_{17}NO$: C, 84.25; H, 5.72; N, 4.68. Found: C, 83.97; H, 5.80; N, 4.68.

2-(5-Phenylethynylpyridin-3-yl)-1-(4-methylphenyl)ethanol (201b). (1.57 g, 50 %); cream solid; m.p. 126 $^{\circ}$C (from EtOAc / petrol); FTIR (neat solid) 3285 (br), 2212, 1490, 1443, 1419, 1071, 840, 758, 705, 693, 577 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.56 (s, br, 1H, H6''), 8.34 (s, br, 1H, H2''), 7.80 (t, *J* = 1.8, 1H, H4''), 7.60-7.57 (m, 2H, H2''''), 7.46 (t, *J* = 3.0, 3H, H3'''', H4''''), 7.23 (d, *J* = 7.8, 2H, H2'), 7.17 (d, *J* = 7.8, 2H, H3'), 5.32 (d, *J*

= 4.5, 1H, OH), 4.78 (ddd, *J* = 7.8, 5.1, 4.5, 1H, H1), 2.93 (dd, *J* = 12.9, 5.1, 1H, $H2_A$), 2.86 (dd, *J* = 12.9, 7.8, 1H, $H2_B$), 2.28 (s, 3H, 4'-CH_3); ^{13}C NMR (DMSO-d_6) δ 150.6 (C2), 149.6 (C6), 142.7 (q, C4'), 139.7 (C4), 136.3 (q, C1'), 135.0 (q, C3''), 131.9 (C2''''), 129.6 (C4''''), 129.3 (C3''''), 129.0 (C3'), 126.3 (C2'), 122.3 (q, C1''''), 119.0 (q, C5''), 92.4 (q, C2'''), 86.9 (q, C1'''), 73.0 (C1), 42.5 (C2), 21.2 (4'-CH_3); HRMS calcd for $C_{22}H_{19}NO$ $(M + H)^+$ required 314.1546, found 314.1541.

1-Phenyl-2-[5-(4-methylphenyl)ethynylpyridin-3-yl]ethanol (201c). (1.94 g, 62 %); pale yellow or white solid; m.p. 132-133 °C (from EtOAc); FTIR (neat solid) 3174 (br), 2210, 1507, 1450, 1415, 1066, 816, 747, 701 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.70-8.30 (br, 2H, H6'', H2''), 7.79 (s, 1H, H4''), 7.49 (d, *J* = 8.1, 2H, H2'''), 7.38-7.23 (m, 7H, H2', H3', H4', H3''''), 5.40 (d, *J* = 4.5, 1H, OH), 4.83 (ddd, *J* = 7.8, 4.8, 4.5 1H, H1), 2.96 (dd, *J* = 13.8, 4.8, 1H ,$H2_A$), 2.88 (dd, *J* = 13.8, 8.1, 1H, $H2_B$), 2.35 (s, 3H, 4''''-CH_3); ^{13}C NMR (DMSO-d_6) δ 150.4 (C6''), 149.5 (C2''), 145.7 (q, C1'), 139.6 (C4), 139.5 (q, C3''), 139.5 (q, C4''''), 131.8 (C2''''), 129.9 (C3''''), 128.4 (C3'), 127.3 (C4'), 126.4 (C2'), 119.3 (2C; C5'', q, C1''''), 92.6 (q, C2'''), 86.3 (q, C1'''), 73.2 (C1), 42.5 (C2), 21.6 (4''''-CH_3); Anal. Calcd for $C_{22}H_{19}NO$: C, 84.31; H, 6.11; N, 4.47. Found: C, 84.09; H, 6.16; N, 4.38.

Synthesis of compounds 202a-c



$Hg(OAc)_2$ (0.16 g, 0.5 mmol, 10 mol.%) and either **201a** (1.50 g, 5 mmol) **201b** (1.57 g, 5 mmol) **201c** (1.57 g, 5 mmol) were dissolved in 10 % $^{w}/_{v}$ aq. H_2SO_4 (40 mL) and acetone (15 mL) and the mixture heated to reflux. After 12 h the reaction mixture was allowed to cool, poured into water (50 mL), neutralised with 10 % NaOH and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried ($MgSO_4$), and the solvent removed *in vacuo*. The crude material was purified by column chromatography (SiO_2; EtOAc : petrol, 80 : 20 $^{v}/_{v}$) There was obtained:

2-[5-(2-Hydroxy-2-phenyl-ethyl)-pyridin-3-yl]-1-phenylethanone (202a). (1.24 g, 75 %); white solid; m.p. 89 ^{o}C (from EtOAc); FTIR (neat solid) 3212, 2919, 1684, 1595, 1447, 1210, 1048, 752, 699, 689 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.29 (bd, *J* = 1.5, 1H, H6''), 8.21 (bd, *J* = 1.5, 1H, H2''), 8.08-8.05 (m, 2H, H2'), 7.67 (tt, *J* = 7.3, 1.2, 1H, H4'), 7.56 (t, *J* = 7.3, 2H, H3'), 7.50 (dt, *J* = 1.5, 1H, H4''), 7.32-7.25 (m, 4H, H2'''', H3''''), 7.23-7.20 (m, 1H, H4''''), 5.37 (d, *J* = 4.5, 1H, OH), 4.76 (td, *J* = 7.2, 5.7, 4.5, 1H, H2'''), 4.42 (s, 2H, H2), 2.90 (dd, *J* = 13.2, 5.7, 1H, H1'''$_A$), 2.84 (dd, *J* = 13.2, 7.2, 1H, H1'''$_B$);^{13}C NMR (DMSO-d_6) δ 197.6 (q, C1), 149.1 (C2''), 148.8 (C6''), 145.8 (q, C1''''), 138.7 (C4''), 136.8 (q, C1'), 134.5 (q, C5''),

133.9 (C4'), 130.5 (q, C3''), 129.3 (C3'), 128.8 (C2'), 128.4 (C3''''), 127.3 (C4''''), 126.4 (C2''''), 73.6 (C1'''), 42.9 (C2'''), 42.2 (C2). HRMS calcd for $C_{21}H_{19}NO_2$ $(M + H)^+$ required 318.1495, found 318.1491.

2-[5-(2-Hydroxy-2-phenylethyl)pyridin-3-yl]-1-(4-methylphenyl)ethanone (202c). (1.22 g, 77 %); colourless oil; FTIR (neat) 3223, 2919, 1680, 1605, 1436, 1180, 1052, 754, 700 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.34 (br, 1H, H6''), 8.33 (br, 1H, H2''), 8.01 (d, *J* = 8.1, 2H, H2'), 7.54 (br, 1H, H4''), 7.41 (d, *J* = 8.1, 2H, H3'), 7.37-7.30 (m, 4H, H2'''', H3''''), 7.28-7.23 (m, 1H, H4''''), 5.39 (d, *J* = 4.5, 1H, OH), 4.80 (td, *J* = 7.2, 4.5, 1H, H2'''), 4.41 (s, 2H, H2), 2.90 (d, *J* = 7.2, 2H, H1'''), 2.44 (s, 3H, 4'-CH_3); ^{13}C NMR (DMSO-d_6) δ 197.1 (q, C1), 149.1 (C2''), 148.7 (C6''), 145.8 (q, C1''''), 144.3 (q, C4'), 138.6 (2C; C4'', q, C5''), 134.3 (q, C1'), 130.8 (q, C3''), 129.8 (C3'), 128.9 (C2'), 128.3 (C3''''), 127.3 (C4''''), 126.3 (C2''''), 73.6 (C2'''), 42.9 (C2), 42.1 (C1'''), 21.6 (4'-CH_3). HRMS calcd for $C_{22}H_{21}NO_2$ $(M + H)^+$ required 332.1651, found 332.1653.

References

1. www.alzheimers.org.uk/Facts_about_dementia/Statistics/index.htm, (accessed on14/09/07).
2. Newhouse, P. A.; Potter, A.; Kelton, M.; Corwin, *J. Biol. Psychiatry* **2001**, 49, 268-278.
3. Amenta, F.; Parnetti, L.; Gallai, V.; Wallin, A. *Mech. Ageing. Dev.* **2001**, 122, 2025-2040.
4. Dani, J. A. *Biol. Psychiatry* **2001**, 49, 166-174.
5. Perry, E. K.; Court, J. A.; Lloyd. S. Johnson, M.; Griffiths, M. H.; Spurden, D.; Piggott, M. A.; Turner, J.; Perry. R. H. *Ann. NY Acad. Sci.* **1996**, 777, 388-392.
6. Rusted, J. M.; Newhouse, P. A.; Levin, E. D. *Behav. Brain Res*. **2000**, 113, 121-129.
7. Kosik, K. S.; Joachim, C. L.; Selkoe, D. J. *Proc. Nati. Acad. Sci.* **1986**, 83, 4044-4048.
8. Whitehouse, P. J; Hedreen, J. C.; White, C. L.; Price, D. L. *Ann. Neurol*. **1983**, 13, 243-248.
9. Summers, W. K.; Majovski, L. V.; Marsh, G. M.; Tachiki, K.; Kling, A. *New Engl. J. Med.* **1986**, 315, 1241-1245.
10. Farlow, M.; Gracon, S. I.; Hershey, L. A.; Lewis, K. W.; Sadowsky, C. H.; Dolan-Ureno, J. *J. Am. Med. Ass.* **1992**, 268, 2523-2529.
11. Raskind, M. A.; Sadowsky, C. H.; Sigmund, W. R.; Beitler, P. J.; Auster, S. B. *Arch. Neurol*. **1997**, 54, 836-840.
12. Lebert, F.; Pasquier, F.; Souliez, L.; Petit, H. *Int. J. Geriatr. Psych.* **1998** 13, 516-519.

13. Querfurth, H. W.; Allam, G. J.; Geffroy, M. A.; Schiff, H. B.; Kaplan, R. F *Dement. Geriatr. Cogn. Disord.* **2000**, 11, 314-321.

14. Werber, E. A.; Rabey, J. M. *J. Neural. Transm*. **2001**, 108, 11.

15. Liepelt, I.; Maetzler, W.; Blaicher, H-P.; Gasser, T.; Berg, D. *Dement. Geriatr. Cogn. Disord*. **2007**, 23, 351-367.

16. Watkins, P. B.; Zimmerman, H. J.; Knapp, J. M.; Gracon, S. I.; Lewis, K. W. J. *J. Am. Med. Ass.* **1994**, 271, 992-998.

17. Blackard, W. G. Jr.; Sood, G. K.; Crowe, D. R.; Fallon, M. B. *J. Clin. Gastroenterol.* **1998**, 26, 57-59.

18. Sramko, C. A.; Berger, F.; Calabrese, P.; Frölich, L. *Eur. Neuropsychopharmacol.* **2000**, 10, 368.

19. Winblad, B.; Engedal, K.; Soininen, H.; Verhey, F.; Waldemar, G.; Wimo, A.; Wetterholm, A. L.; Zhang, R.; Haglund, A.; Subbiah, P. *Neurology* **2001**, 57, 489-495.

20. Aarsland, D.; Laake, K.; Larsen, J. P.; Janvin, C. *J .Neurol. Neurosurg. Psychiatry* **2002**, 72, 708-712.

21. Samuel, M.; Maidment, I.; Boustani, M.; Fox, C. *Adv. Psychiatr Treat.* **2006**, 12, 121-129.

22. Rojas-Fernandez, C. H. *Ann. Pharmacother.* **2001**, 35, 202-205.

23. Skjerve, A.; Nygaard, H. A. *Int J. Geriatr. Psych*. **2000**, 15, 1147-1151.

24. Shea, C.; MacKnight, C.; Rockwood, K. *Int. Psychogeriatr*. **1998**, 10, 229-238.

25. Alwahhabi, F. K. *J. Psychopharmacol*, **2005**, 19, 214-216.

26. Eskander, M. F.; Nagykery N. G.; Leung, E. Y.; Khelghati, B.; Geula, C. *Brain Res*. **2005**, 1060, 144-152.

27. Polinsky, R.J. *Clin. Ther*. 20, **1998**, 634-647.

28. Bullock, R.; Touchon, J.; Bergman, H.; Gambina, G.; Yunsheng, R.; Rapaz, G.; Nagel, J.; Lane, R. *Curr. Med. Res. Opin*. **2005**, 21, 1317-1328.

29. McKeith, I. G.; Grace, J. B.; Walker, Z.; Byrne, E. J.; Wilkinson , D.; Stevens , T.; Perry, E. K. *Int. J. Geriatr. Psych.* **2000**, 15, 387 - 392.

30. Maclean, L. E.; Collins, C. C.; Byrne, E. J. *Int. Psychogeriatr.* **2001**, 13, 277-288.

31. McKeith, I.; Del Ser, T.; Spano, P. F.; Emre, M.; Wesnes, K.; Anand, R.; Cicin-Sain, A.; Ferrara, R.; Spiegel, *R. Lancet* **2000**, 356, 2031-2036.

32. Korczyn, A. D. *J. Neurol*. **2001**, 248, 3.

33. Raskind, M. A.; Peskind, E. R.; Wessel, T.; Yuan, W. *Neurology* **2000**, 54, 2261-2268.

34. Maelicke, A.; Samochock, M.; Jostock, R.; Fehrenbacher, A.; Ludwig, J.; Albuquerque, E. X.; Zerlin, M. *Biol. Psychiat*. **2001**, 49, 279-288.

35. Wilcock, G. K.; Lilienfeld, S.; Gaens, E. *BMJ* **2000**, 321, 1445.

36. Tariot, P. N.; Solomon, P. R.; Morris, J. C.; Kershaw, P.; Lilienfeld, S.; Ding, C. *Neurology* **2000**, 54, 2269-2276.

37. McNamara, P.; Durso, R. *Behav. Neurol*. **2006**, 17, 43-51.

38. Aarsland, D. *Eur. Neuropsychopharmacol.* **2002**, 12, (Suppl. 3), 378-379.

39. Edwards, K. R.; Hershey, L.; Wray, L.; Bednarczyk, E. M.; Lichter, D.; Farlow, M.; Johnson, S. *Dement. Geriatr. Cogn.* **2004**, 17, (Suppl. 1), 40-48.

40. Collins, C. C.; Mitchell, L. E.; Byrne, E. J. *Neurobiol. Aging* **2000**, 21, (Suppl. 1), 158.

41. Greenamyre, J. T.; Porter, R. H. *Neurology* **1994**, 44, S7-13.

42. Scarpini, E.; Scheltens, P.; Feldman, H. *Lancet Neurology* **2003**, 2, 539-547.

43. Danysz, W.; Parsons, C. G.; Kornhuber, J.; Schmidt, W. J.; Quack, G. *Neurosci Biobehav. Rev.* **1997**, 21, 455-468**.**

44. Chen, H. S.; Pellegrini, J. W.; Aggarwal, S. K.; Lei, S. Z.; Warach, S.; Jensen, F. E.; Lipton, S. A. *J. Neurosci.* **1992**, 12, 4427-4436.

45. Marwan, S. N.; Hake, A. M.; Ahmed, S.; Farlow, M. R. *J. Alzheimer's Dis.* **2005**, 7, 285-289.

46. Menendez-Gonzalez, M.; Calatayud, M. T.; Blazquez-Menes, B. *J. Alzheimer's Dis*. **2005**, 8, 289-291.

47. Ridha, B. H.; Josephs, K. A.; Rossor, M. N. *Neurology* **2005**, 65, 481-482.

48. Dunn, N.; Pearce, G. L.; Shakir, S. A. W. *J. Psychopharmacol*. **2000**, 14, 406-408.

49. http://guidance.nice.org.uk/TA111 (accessed on 15/07/07).

50. Khang, P.; Weintraub, N.; Espinoza, R. T. *J. Am. Med. Dir. Assoc.* **2004**, 5, 249-255.

51. Neumann, P. J.; Hermann, R. C.; Kuntz, K. M.; Araki, S. S.; Duff, S. B.; Leon, J.; Berenbaum, P. A.; Goldman, P. A.; Williams, L. W.; Weinstein, M. C. *Neurology* **1999**, 52, 1138-1138.

52. Jönsson, L.; Lindgren, P.; Wimo, A.; Jönsson, B.; Winblad, B. *Clin Ther.* **1999**, 21, 1230-1240.

53. Akiyama, H.; Barnum, S.; Bradt, B.; Bauer, J.; Cole, G. M. *Neurobiol. Aging* **2000**, 21, 383-421.

54. McGreer, P. L.; Schulzer, M.; McGreer, E. G. *Neurology* **1996**, 47, 425-432.

55. McGreer, P. L.; McGreer, E.; Rogers, J.; Sibley, J. *Lancet* **1990**, 335, 1037.

56. Rich, J. B.; Rasmusson, D. X.; Folstein, M. F.; Carson, K. A.; Kawas, C.; Brandt, J. *Neurology* **1995**, 45, 51-55.

57. Stewart, W. F.; Kawas, C.; Corrada, M.; Metter, J. E. *Neurology* **1997**, 48, 626-632.

58. Lim, G.P.; Yang, F.; Chu, T.; Chen, P.; Beech, W.; Teter, B.; Tran, T.; Ubeda, O.; Ashe, K. H.; Frautschy, S. A.; Cole, G. M. *J. Neurosci.* **2000**, 20, 5709-5714.

59. Asanuma, M.; Miyazaki, I.; Ogawa, N. *Curr. Pharm. Design* **2004**, 10, 695-700.

60. Fortun, P.; Hawkey, C. J. *Medicine* **2007**, 35, 4, 210-215.

61. Lichtenthaler, S. F.; Haas, C. *J. Clin. Invest*. **2004**, 113, 1384-1387.

62. Haas, C. *EMBO J.* **2004**, 23, 3, 483-488.

63. Dovey, H. F.; John, V.; Anderson, J. P.; Chen, L. Z.; de Saint Andrieu, P.; Fang, L. Y.; Freedman, S. B.; Folmer, B.; Goldbach, E.;

Holsztynska, E. J.; Hu, K. L.; Johnson-Wood, K. L.; Kennedy, S. L.; Kholodenko, D.; Knops, J. E.; Latimer, L. H.; Lee, M.; Liao, Z.; Lieberburg, I. M.; Motter, R. N.; Mutter, L. C.; Nietz, J.; Quinn, K. P.; Sacchi, K. L.; Seubert, P. A.; Shopp, G. M.; Thorsett, E. D.; Tung, J. S.; Wu, J.; Yang, S.; Yin, C. T.; Schenk, D. B. *J. Neurochem*. **2001**, 76, 173-181.

64. Peters, J-U.; Galley, G.; Jacobsen, H.; Czech, C.; David-Pierson, P.; Kitas E. A.; Ozmen, L. *Bioorg. Med. Chem. Lett*. **2007**, 17, 5918-5923.

65. Siemers, E. R.; Quinn, J. F.; Kaye, J.; Farlow, M. R.; Porsteinsson, A.; Tariot, P.; Zoulnouni, P.; Galvin, J. E.; Holtzman, D.M.; Knopman, D. S.; Satterwhite, J.; Gonzales, C.; Dean, R. A.; May, P. C. *Neurology*. **2000**, 66, 4, 602-604.

66. Chen, Y. L.; Cherry, K.; Corman, M. L.; Ebbinghaus, C. F.; Gamlath, C. B.; Liston, D.; Martin, B-A.; Oborski, C. E.; Sahagan, B. G.; *Bioorg. Med. Chem. Lett*. **2007**, 17, 5518-5522.

67. Whitehouse, P. J.; Price, D. L.; Struble, R. G.; Clark, A. W.; Coyle, J. T.; Delon, M. R.; *Science* **1982**, 215, 1237-1239.

68. Rafferty, M. A.; Hunkapiller, M. W.; Srader, C. D; Hood, L. E. *Science* **1980**, 208, 1454.

69. Gotti, C.; Clementi, F.; *Prog. Neurobiol*. **2004**, 74, 363-396.

70. Wonnacott, S. *Trends Neurosci*. **1997**, 20, 92-98.

71. Deneris, E. S.; Connolly, J.; Rogers, S. W.; Duvoisin, R. *Trends Pharmac. Sci.* **1991**, 12, 34-41.

72. Picciotto, M. R.; Caldarone, B, J.; King, S. L.; Zachariou, V. *Neuropsychopharmacol.* **2000***,* 22, 451-465.

73. Lukas, R. J.; Changeux, J-P.; le Novere, N.; Albuquerque, E. X.; Balfour, D. J. K.; Berg, D. K.; Bertrand, D.; Chiappinelli, V. A.; Clarke, P. B. S.; Collins, A. C.; Dani, J. A.; Grady, S. R.; Kellar, K. J.; Lindstrom, J. M.; Marks, M. J.; Quik, M.; Taylor, P. W.; Wonnacott, S. *Pharmacol. Rev*. **1999**, 51, 397-401.

74. Court, J. A.; Martin-Ruiz, C.; Graham, A.; Perry, E. *J. Chem. Neuroanat.* **2000**, 20, 281-298.

75. Gotti, C.; Zoli, M.; Clementi, F. *Trends Pharmac. Sci*. **2006**, 27, 482-491.

76. Clarke, P. B. *Trends Pharmacol. Sci*. **1992**, 13, 407-413.

77. Lloyd, K. G.; Williams, M. *J. Pharmacol. Exp. Ther.* **2000**, 292, 461-467.

78. Newhouse, P. A.; Potter, A.; Singh, A. *Curr. Opin. Pharmacol.* **2004**, 4, 36-46.

79. Perry, E. K.; Morris, C. M.; Court, J. A.; Cheng, A.; Fairbairn, A. F.; McKeith, I. G.; Irving, D.; Brown, A.; Perry, R. H. *Neuroscience* **1995***,* 64, 385-395.

80. White, H. K.; Levin, E. D. *Psychopharmacol.* **1999**, 143, 158-165.

81. Moll, H. *Br. Med. J.* **1926**, 1, 1079-1081.

82. Levin, E. D.; Rose, J. E. *Brain Res. Bull*. **1991**, 27, 125-128.

83. (a) Foulds, J.; Stapleton, J.; Feyerabend, C.; Vesey, C.; Jarvis, M.; Russell, M. A. H. *Psychopharmacol.* **1992**, 106, 3, 421-427.

(b) Heishman, S. J.; Taylor, R. C.; Henningfield, J. E. *Exp. Clin. Psychopharmacol*. **1994**, 2, 355-395.

84. Heishman, S. J.; Henningfield, J. E.; Singleton, E. G. *Nicotine Tob. Res.* **2002**, 4, 3-4.

85. Lester, H. A.; Dibas, M. I.; Dahan, D. S.; Leite, J. F.; Dougherty, D. A. *Trends Neurosci.* **2004**, 27, 329-336.

86. Boyd, N. D.; Cohen, J. B.; *Biochemistry* **1980**, 19, 5344-5353.

87. Gerzanich, W.; Peng, X.; Wang, F.; Wells, G.; Anand, R.; Fletcher, S.; Lindstrom, J. *Mol. Pharmacol.* **1995**, 48, 774-782.

88. Spande, T. F.; Garraffo, H. M.; Edwards, M. W.; Yeh, H. J. C.; Pannell, L.; Daly, J. W. *J. Am. Chem. Soc.* **1992**, 114, 3475-3478.

89. Badio, B.; Daly, J. W. *Mol. Pharmacol.* **1994**, 45, 563-569.

90. Holladay, M. W.; Dart, M. J.; Lynch, J. K. *J. Med. Chem.* **1997***,* 40, 4169-4194.

91. Menzaghi, F.; McClure, D. A.; Lloyd, G.K.; Subtype-selective nAChR agonists for the treatment of neurological disorders: SIB-1508Y and SIB-1553A, in *Neuronal Nicotinic Receptors: Pharmacology and Therapeutic Opportunities;* Arneric, S.P. and Brioni, J.D., Eds.; Wiley-Liss, New York*,* **1999**, 379-394.

92. Schneider, J. S.; Van Velson, M.; Menzaghi, F.; Lloyd. G. K. *Ann. Neurol.* **1998***,* 43, 311-317.

93. Bencherif, M.; Lovette, M. E.; Fowler, K. W.; Arrington, S.; Reeves, L.; Caldwell, W. S.; Lippiello, P.M. *Pharmacology* **1996**, 279, 1413-1421.

94. Decker, M. W.; Brioni, J. D.; Bannon, A. W.; Arneric, S. P. *Life Sci*. **1995**, 56, 545-570.

95. Dwoskin, L. P.; Crooks, P. A. *Biochem. Pharmacol*. **2002**, 63, 89-98.

96. Papke, J. K.; Papke, J. K. P.; Rose, G. M. *Bioorg. Med. Chem. Lett*. **2004**, 14, 1849-1853.

97. Sala, F.; Mulet, J.; Reddy, K. P.; Bernal, J. A.; Wikman, P.; Valor, L. M.; Peters, L.; Konig, G. M.; Criado, M.; Sala*, S. Neurosci. Lett.* **2005**, 373, 144-149.

98. Haskimoto, K.; Fujita, Y.; Ishima, T.; Hagiwara, H.; Lyo, M. *Eur. J. Pharmacol*. **2006**, 553, 191-195.

99. Chyan, J. Y.; Poeggeler, B.; Rawhi, O. A.; Chain, D. G.; Frangione, B.; Ghiso, J.; Pappolla, M. A. *J. Biol. Chem.* **1999**, 274, 21937-21942.

100. Feng, Z.; Zhang, J-T. *Radical Biology and Medicine* **2004**, 37, 1790-1801.

101. Carter, M. D.; Weaver, D. F. *J. Mol. Struct.* **2003**, 626, 279-285.

102. (a) Whiteaker, P.; Sharples, C. G. V.; Wonnacott, S.; *Mol. Pharmacol*. **1998**, 53, 950-962.

(b) Cosford, N. D. P.; Bleicher, L.; Herbaut, A.; McCallum, J. S.; Vernier, J.-M.; Dawson, H.; Whitten, J. P.; Adams, P.; Chavez-Noriega, L.; Correa, L. D.; Crona, J. H.; Mahaffy, L. S.; Menzaghi, F.; Rao, T. S.; Reid, R.; Sacaan, A. I.; Santori, E.; Stauderman, K. A.; Whelan, K.; Lloyd, G. K.; McDonald, I. A. *J. Med. Chem*. **1996**, 39, 3235-3237.

(c) Donnelly-Roberts, D.L.; Puttfarcken, P. S.; Kuntzweiler, T. A.; Briggs, C. A.; Anderson, D. J.; Campbell,J. E.; Piattoni-Kaplan, M.; Mckenna, D. G.; Wasicak, J. T.; Holladay, M. W.; Williams, M.; Arneric, .S. P. *J. Pharm. Exp. Ther.* **1998**, 285, 777-786.

(d) Kem, W. R. *J. Pharmacol. Exp. Ther*. **1997**, 283, 979-992.

(e) de Fiebre,C. M.; Meyer, E. M.; Henry, J. C.; Muraskin, S. I.; Kem, W. R.; Papke, R. L. *Mol. Pharmacol.* **1995**, 47, 164-171.

(f) Carroll, F. I.; Yokota, Y.; Ma, W.; Lee, J. R.; Brieaddy, L. E.; Burgess, J. P.; Navarro, H. A.; Damaj, M. I.; Martin, B. R. *Bioorg. Med. Chem.* **2008**, 16, 746-754.

(g) Flammia, D.; Dukat, M.; Imad Damaj, M.; Martin, B.; Glennon , R. A. *J. Med. Chem.* **1999**, 42, 3726-3731.

(h) Hajo´ s, M.; Hurst, R. S.; Hoffmann, W. E.; Krause, M.; Wall, T. M.; Higdon, N. R.; Groppi, V. E. *J. Pharmacol. Exp. Ther*. **2005**, 312, 1213-1222.

(i) Mullen, G.; Napier, J.; Balestra, M.; DeCory, T.; Hale, G.; Macor, J.; Mack, R.; Loch, J.; Wu, E.; Kover, A.; Verhoest, P.; Sampognaro, A.; Phillips, E.; Zhu, Y.; Murray, R.; Griffith, R.; Blosser, J.; Gurley, D.; Machulskis, A.; Zongrone, J.; Rosen, A.; Gordon, J. *J. Med. Chem*. **2000**, 43, 4045-4050.

(j) Macor, J. E.; Gurley, D.; Lanthorn, T.; Loch, J.; Mack, R.A.; Mullen, G.; Tran, O.; Wright, N.; Gordon, J.C. *Bioorg. Med. Chem. Lett*., **2001**, 11, 3, 319-321.

103. Felpin, F-X.; Lebreton, J. *Tetrahedron* **2004**, 60, 10127-10153.

104. http://web.vet.cornell.edu/CVM/HANDOUTS/plants/lobelia%20Inflata%20Sep02.jpg (accessed on 21/07/07)

105. http://www.delawarewildflowers.org/sedum_acre.jpg (accessed on 21/07/07)

106. Bates, R. W.; Kanicha Sa-Ei. *Tetrahedron* **2002**, 58, 5957-5978.

107. Dwoskin, L. P.; Crooks, P. A. *Biochem. Pharmacol.* **2002**, 63, 89-98.

108. Robb, G. P.; Weiss, S. *Am. Heart J.* **1934**, 9, 742-763.

109. Muhtadi, F. J., *Anal. Profiles Drug Subst*., **1990**, 19, 261-313.

110. Decker, M. W.; Majchzark, M. J.; Arneric, S. P. *Pharmacol. Biochem. Behav*. **1993**, 45, 571-576.

111. Collins, A. C.; Romm, E.; Wehner, J. M., *Brain Res. Bull*. **1990**, 25, 373-379.

112. Beers, W. H.; Reich, E. *Nature*, **1970**, 228, 917-922.

113. Sheridan, R. P.; Nilakantan, R.; Dixon, J. S.; Venkataraghavan, R. *J. Med. Chem*. **1986**, 29, 899-906.

114. Barlow, R. B.; Johnson, O. *Br. J. Pharmacol*. **1989**, 98, 799-808.

115. Abood, L. G.; Shahid Salles, K.; Maiti, A. *Pharmacol. Biochem. Behav.* **1988**, 30, 403-408.

116. Robinson, R. *J. Chem. Soc.* **1917**, 111, 876-899.

117. Leete, E. *J. Am. Chem. Soc*. **1956**, 78, 14, 3520-3523.

118. O'Donovan, D. G.; Long, D. J.; Forde, E.; Geary, P. *J. Chem. Soc., Perkin Trans. 1* **1975**, 5, 415-419.

119. O'Donovan, D. G.; Forde, T. *J. Chem.* Soc. C. **1971**, 2889-2890.

120. (a) Zenk, M. H.; In Biosynthesis of Aromatic Compounds, Proceedings of the 2nd meeting of F. E. B. S., Billek, G.; Ed.; Pergamon Press, Oxford, **1966**; Vol. 3, p. 45.

(b) M. H. Zenk, M.H.; In 'Pharmacognosy and Phytochemistry', ed. H. Wagner, H.; Horhammer, L.; Eds.; Springer-Verlag, Berlin, **1971**; p. 314.

(c) Gupta, R. N.; Spenser, I. D. *Can. J. Chem.* **1967**, 45, 1275.

121. (a) Wieland, H.; Drishaus, I., *Liebigs Ann. Chem.* **1929**, 473, 102-118.

(b) Wieland, H.; Koschara, W.; Dane, E.*, Liebigs Ann. Chem*., **1929**, 473, 118-126.

122. Scheuing, G.; Winterhalder, L. *Liebigs Ann. Chem*. **1929**, 473, 126-136.

123. Shaw, B. D. *J. Chem. Soc.* **1924**, 125, 2363-2365.

124. Schopf, C.; Lehmann, G., *Liebigs Ann. Chem*. **1935**, 518, 1-37.

125. Compère, D.; Marazano, C.; Das, B.C. *J. Org. Chem.* **1999**, 64, 4528-4532.

126. Beyerman, H. C.; Eveleens, W.; Muller, Y. M. F. *Rec. Trav. Chim. Pays-Bas,* **1956**, 75, 63.

127. Beyerman H. C.; Eenshuistra J.; Eveleens W.; Zweistra A. *Rec. Trav. Chim. Pays-Bas*. **1959**, 78, 43.

128. Meth-Cohn, O.; Yau, C.C.; Yu, C-Y. *J. Heterocycl. Chem*. **1999**, 36, 1549-1553.

129. Yu, C-Y.; Meth-Cohn, O. *Tetrahedron Lett*. **1999**, 40, 6661-6664.

130. Yu, C-Y.; Meth-Cohn, O. *Tetrahedron Lett*. **1999**, 40, 6665-6668.

131. Unpublished results; Moore, A. J.; Huang, Y.; Ashton, M. University of Sunderland.

132. Unpublished results; Meth-Cohn, O.; Yu, C.-Y.; Lestage, P.; Guedin, D.; Moore, A. University of Sunderland.

133. Brown, H. C.; Murphy, W. A. *J. Am. Chem. Soc*. **1951**, 73, 3308-3312.

134. Miller, A. D.; Levine, R. *J. Org. Chem*. **1959**, 24, 1364-1366.

135. Kaiser E. M.; Petty J. D. *Syn. Comm.* **1975**, 705-706.

136. Davis, M. L.; Wakefield, J. B.; Wardell, J. A. *Tetrahedron* **1991**, 48, 939-952.

137. Koller, M. U.; Peariso, K. L.; Guion, T. S. Martinez, S. S.; Beam, C. F. *Synth. Commun.* **1995**, 25, 2963-2974.

138. (a) Ashby, J.; Styles, J.A.; Anderson, D. *Br. J. Cancer* **1977**, 36, 564-571.

(b) Ashby, J.; Styles, J. A.; Paton, D. *Br. J. Cancer* **1978**, 38, 418-427.

139. (a) Baldwin, J. E.; Romeril, S. P.; Lee, V.; Claridge, T. D. W. *Org Lett*. **2001**, 3, 1145-1148.

(b) Romeril, S. P.; Lee, V.; Claridge, T. D. W.; Baldwin J. E. *Tetrahedron Lett.* **2002**, 43, 327-329.

(c) Romeril, S. P.; Lee, V.; Baldwin, J. E.; Claridge, T. D.; Odell, B. *Tetrahedron Lett.* **2003**, 44, 7757-7761.

(d) Goundry, W. R. F.; Baldwin, J. E.; Lee, V. *Tetrahedron* **2003**, 59, 1719-1729.

140. Mukhopadhyay, T.; Seebach, D. *Helv. Chim. Acta* **2004**, 65, 385-391.

141. Miwatashi, S.; Arikawa, Y.; Naruo, K.; Igaki, K.; Watanabe, Y.; Kimura, H.; Kawamoto,T.; Ohkawa, S. *Chem. Pharm. Bull.* **2005**, 53, 410-418.

142. Scribner, A. W.; Haroutounian, S. A.; Carlson, K. E.; Katzenellenbogen, J. A. *J. Org. Chem*. **1997**, 62, 1043-1057.

143. Biftu T.; Feng, D.; Ponpipom, M.; Girotra, N.; Liang, G-B.; Qian, X.; Bugianesi, R.; Simeone, J.; Chang, L.; Gurnett, A.; Liberator, P.; Dulski, P.; Leavitt, P.S.; Crumley, T.; Misura, A.; Murphy, T.; Rattray, S.; Samaras, S.; Tamas, T.; Mathew, J.; Brown, C.; Thompson, D.; Schmatz, D.; Fisher, M.; Wyvratt, M. *Bioorg. Med. Chem. Lett*. **2005**; 15; 3296-3301.

144. Miller, A. D.; Levine, R. *J. Am. Chem. Soc*. **1960**, 82, 472-475.

145. Miller, A. D.; Osuch, C.; Goldberg, N. N.; Levine, R. *J. Am. Chem. Soc*. **1956**, 78, 674-676.

146. Morimoto, Y.; Yokoe, C. *Tetrahedron Lett.* **1997**, 38, 8981-8984.

147. Kaiser E. M., *Tetrahedron* **1983**, 39, 2055-2064.

148. Shorey, B. J.; Lee, V.; Baldwin, J. E.; *Tetrahedron* **2007**, 63, 5587-5592.

149. Kiehne, V.; Bunzen, J.; Staats, H.; Luetzen, A. *Synthesis* **2007**, 7, 1061-1069.

150. Miller, A. D.; Levine, R. *J. Org. Chem*. **1957**, 22, 168-170.

151. Davies-Coleman, M. T.; Faulkner, J. D.; Dubowchik, G.M.; Roth, G. P.; Polson, C.; Fairchild, C. *J. Org. Chem.* **1993**, *58*, 5925-5930.

152. Morimoto, Y.; Yokoe, C.; Kurihara, H.; Kinoshita, T. *Tetrahedron* **1998**, 54, 12197-12214.

153. Meyers, M. J.; Carlson, K. E.; Katzenellenbogen, J. A. *Biorg. Med. Chem. Lett*. **1998**, 8, 3589-3594.

154. Niwa, T.; Yorimitsu, H.; Oshima, K. Angew. Chem., Int. Ed. Engl**.** **2007**, 46, 2643-2645.

155. Natarajan, S. R.; Chen, M-H.; Heller, S. T.; Tynebor, R. M.; Crawford, E. M.; Minxiang, C.; Kaizheng, H.; Dong, J.; Hu, B.; Hao, W.; Chen, S-H. *Tetrahedron. Lett*. **2006**, 47, 5063-5067.

156. Koning, B.; Buter, J.; Hulst, R.; Stroetinga, R.; Kellogg, R. M.; *Eur. J. Org. Chem.* **2000**, 15, 2735-2744.

157. Alcaraz, L.; Baxter, A.; Bent, J.; Bowers, K.; Braddock, M.; Cladingboel, D.; Donald, D.; Fagura, M.; Furber, M.; Laurent, C.; Lawson, M.; Mortimore, M.; McCormick, M.; Roberts, N.; Robertson, M. *Bioorg. Med. Chem. Lett*. **2003**, 13, 4034-4046.

158. Jiang, J.; Wang, W.; Sane, D. C.; Wang, B. *Bioorg. Chem*. **2001**, 29, 357-379.

159. The Chemistry of Heterocycles; Eicher, T.; Hauptmann, S., Eds.; Wiley-VCH, 2003; pp 281.

160. Unpublished results. Meth-Cohn, O.; Yu, C.-Y.; Ashton, M.; Moore, A. University of Sunderland

161. (a) Carey, A. R. E.; Eustace, S.; O'Ferrall, R. A. M.; Murray, B. A. D. *J. Chem.* Soc., *Perkin Trans. 2,* **1993**, 2285-2296.

(b) Carey, A. R. E.; Fukata, G.; O'Ferrall, R. A. M.; Murphy, M. G. *J. Chem. Soc., Perkin Trans. 2*, **1985**, 1711-1722.

162. Alunni, S.; De Angelis, F.; Ottavi, L.; Papavasileiou, M.; Tarantelli, F., *J. Am. Chem. Soc.* **2005**, 127, 15151-15160.

163. Compagnon, P-L.; Gasquez, F.; Compagnon, O.; Kimny, T.; *Bull Soc. Chim. Belg.* **1982**, 91, 931-946.

164. Berg, J. M.; Holm, R. H., *J. Am. Chem. Soc.* **1984**, 106, 3035-3036.

165. Wang, H.; Helgeson, R.; Ma, B.; Wudl, F. *J. Org. Chem*. **2000**, 65, 5862-5867.

166. Unpublished results. Moore, A.; Huang, Y. University of Sunderland.

167. Baradarani, M. M.; Joule, J. A. *J. Chem. Soc*., *Perkin Trans 1* **1980**, 72-77.

168. Fantin, G.; Fogagnolo, M.; Guerzoni, E. M.; Medici, A.; Pedrini, P.; Poli, S. *J. Org. Chem.* **1994**, 59, 924-925.

169. Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C. P.; Singh, V. K. *J. Am. Chem. Soc*,. **1987**, 109, 7925-7926.

170. Mathre, D. J.; Thompson, A. S.; Douglas, A. W.; Hoogsteen, K.; Carroll, J. D.; Corley, E. G.; Grabowski, E. J. J. *J. Org. Chem*. **1993**, 58, 2880-2888.

171. Sugi, K. D.; Nagata, T.; Yamata, T.; Mukaiyama, T. *Chem. Lett*. **1997**, 26, 493-494.

172. Ohtsuka, Y.; Ikeno, T.; Yamada, T. *Tetrahedron: Asymmetry*, **2000**, 11, 3671-3674.

173. Hutchison, P. C.; Heightman, T. D.; Procter, D. J.; *J. Org. Chem*. **2004**, *69*, 790 - 801.

174. Basavaiah, D.; Krishna, P. R. *Tetrahedron* **1995**, 51, 2403-2416.

175. Cai, D.; Larsen, R. D.; Reider, P. J. *Tetrahedron Lett*. **2002**, 43, 4285-4287.

176. Trecourt, F.; Breton, G.;. Bonnet, V.; Mongin, F.; Marsais, F.; Queguiner, G. *Tetrahedron* **2000**, 56, 1349-1360.

177. Quéguiner, G.; Marsais, F.; Snieckus, V.;Epsztajn, J. *Adv. Heterocycl. Chem.*, **1991**, *52*, 187–304.

178. (a) Jones, K.; Fiumana, A.; Escudero-Hernandez, M.L. *Tetrahedron*, **2000**, 397-406.

(b) Corey, E. J.; Pyne, S. G. *Tetrahedron Lett*. **1983**, 3291-3294.

(c) Gribble, G. W.; Saulnier, M. G. *Tetrahedron Lett*. **1980**, 4137-4140.

179. Effenberger, F.; Daub, W. *Chem. Ber.*, **1991**, 124, 2119–2125.

180. Cai, D.; Hughes, D. L.; Verhoeven, T. R. *Tetrahedron Lett*. **1996**, 37, 2537-2540.

181. Hudlicky, T.; Olivo, H. F.; Natchus, M. G. *J. Org. Chem.* **1990**, 55; 4767-4770.

182. Burgos, C. E.; Nidy, E. G.; Johson, A. *Tetrahedron Lett.* **1989**, 30, 5081-5084.

183. Unpublished results. Moore, A.; Huang, Y.; Meth-Cohn, O. University of Sunderland.

184. (a) Bookham, J. L.; Smithies, D. M.; *J. Organomet. Chem*. **1999**, 577; 305 - 315.

(b) Kim, D-K.; Kim, J.; Park, H. J. *Bioorg. Med*. *Chem. Lett*. **2004** 14, 2401–2405.

(c) Nishiwaki, N.; Ariga, M.; Komatsu, M.; Oshiro, Y. *Heterocycles*, **1996**, 43, 1179-1184.

185. Smith, J. M.; Stewart, H. W.; Roth, B. *J. Am. Chem. Soc*. **1948**, 70, 3997-3998.

186. (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett*. **1975,** 16, 4467-4470.

(b) Chinchilla, R.; Nájera, C. *Chem. Rev*. **2007**, 107, 874 - 922.

187. (a) Hunter, R.; Muhanji, C. I.; Hale, I.; Bailey, C. M.; Basavapathrunib, A.; Anderson, K. S. *Bioorg., Med. Chem. Lett*. **2007**, 17, 2614-2617.

(b) Graham, A. E.; McKerrecher, D.; Davies, D. H.; Richard J. K. Taylor, R. J. K. *Tetrahedron Lett.* **1996**, 37, 7445-7448.

(c) Sakai, A.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1999**, 40, 4211-4214.

(d) Yoshimura, F.; Kawata, S.; Hirama, M. *Tetrahedron Lett*. **1999**, 40, 8281-8285.

(e) Basak, A.; Kar, M. *Bioorg. Med. Chem.* **2008**, 16, 4532–4537.

(f) Taylor, E. C.; Young, W. B.; Spanka, C. *J. Org. Chem.*, **1996**, 61, 1261 -1266.

(g) Kawai, S. H.; Hambalek, R. J.; Just, G. *J. Org. Chem.* **1994,** 59, 2620-2622.

(h) Miller, M.W.; Johnson, C. R. *J. Org. Chem.* **1997**, 62, 1582-1583.

(i) Toyota, M.; Komori, C.; Ihara, M. *J. Org. Chem.,* **2000**, 65, 7110 - 7113.

(j) Brooks, C. D.; Stewart, A. O.; Basha, A.; Bhatia, P.; Ratajczyk, J. D.; Martin, J. G.; Craig, R. A.; Kolasa, T.; Bouska, J. B.; Lanni, C.; Harris, R. R.; Malo, P. E.; G. C. Carter, G. C.; Bell, R. L. *J. Med. Chem.* **1995**, 38, 4768-4775.

188. Karpov, A. S.; Rominger, F.; Mueller, T. J. J. *J. Org. Chem*. **2003**, 68, 1503-1511.

189. Lautens, M.; Yoshida, M. *J. Org. Chem*. **2003**, 68, 762-769.

190. Walsh, C.; Mandal, B. K. *J. Org. Chem.,* **1999**, 64, 6102-6105.

191. (a) Hiraoka, S.; Harano, K.; Shiro, M.; Shionoya, M. *Angew Chem. Int. Ed*. Engl. 44, **2005**, 2727-2731.

(b) Hiraoka, S.; Harano, K.; Shiro, M.; Shionoya, M. *Angew Chem. Int. Ed*. Engl. **2005**, 117, 2787-2791.

192. Novak, Z.; Nemes, P.; Kotschy, A.; *Org. Lett*. **2004**, 6; 4917 - 4920.

193. Taft, R. W.; Price, E.; Fox, I. R.; Lewis, I. C.; Andersen, K. K.; Davis, G. T. *J. Am. Chem. Soc.* **1963**, 85, 3146-3156.

194. (a) Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972***,* 37, 2320-2322

(b) Heck, R. F.; *Org. React.* **1982***,* 27, 345-390.

195. (a) Furstner, A.; Thiel, O. R.; Kindler, N.; Bartkowska, B.; *J. Org. Chem*. **2000**, 65, 7990-7995.

(b) Macor, J. E.; Blank, D. H.; Post, R. J.; Ryan, K. *Tetrahedron Lett.* **1992**, 33, 8011-8014.

(c) Andrus, M. B.; Liu, J.; Meredith, E. L.; Nartey, E. *Tetrahedron Lett.* **2003**, 44, 4819–4822.

(d) Labelle, M.; Belley, M.; Gareau, Y.; Gauthier, J. Y.; Guay, D.; Gordon, R.; Grossman, S. G.; Jones, T. R.; Leblane, Y.; McAuliffe,

M.; McFarlane, C.; Massun, P.; Metters, K. M.; Onimet, N.; Patrick, D. H.; Piechuta, H.; Roebette, C.; Sawyer, N.; Xiang, Y. B.; Pickett, C. B.; A. W. Ford-Hutehinsun, A. W.; Zamboni, R. J.; Young, R. N. *Bioorg. Med. Chem. Lett.* **1995**, 5, 283-288.

(e) Ashimori, A.; Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Org. Chem.* **1993**, 58, 6949-6951.

(f) Or, Y. S.; Clark, R. F.; Wang, S.; Chu, D. T. W.; Nilius, A. M.; Flamm, R. K.; Mitten, M.; Ewing, P.; Alder, J.; Ma, Z. *J. Med. Chem.* **2000**, 43, 1045-1049.

(g) Pastre, J. C.; Correia, C. R. D. *Org. Lett.,* **2006**, 8, 1657 -1660.

(h) Comins, D. L.; Nolan, J. M.; Comins, D. L.; Nolan, J. M. *Org. Lett.* **2001**, *3*, 4255 – 4257.

196. (a) Rao, A. V.; Reddy, G. R.; *Tetrahedron Lett*. **1993**, 34, 8329-8332.

(b) Sakamoto, T.; Kondo, Y.; Yasuhara, A.; Yamanaka, H. *Heterocycles*, **1990**, 31, 219-221.

(c) Katritzky, A. R.; Ferwanah, A.; Denisenko, S. *Heterocycles*, **1999**, 50, 767-778.

(d) Li, J.; Zhang, Z-P.; Fu, Y.; Liu, L, Guo, Q-X. *J. Org. Chem*. **2007**, 72, 9342-9345.

197. Cui, X.; Zhou, Y.; Wang, N.; Liu, L.; Guo, Q-X. *Tetrahedron Lett*. **2007**, 163-167.

198. Based on general conditions given in text book. Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. Organic Chemistry; Oxford University Press, **2001**; 1321-1323.

199. Doria, G.; Passarotti, C.; Sala, R.; Magrini, R.; Sberze, P , *Farmaco Ed. Sci.*, **1986**, 41, 417-429.

200. Sakamoto, T.; Numata, A.; Saitoh, H.; Kondo, Y. *Chem. Pharm. Bull*. **1999**, 47, 1740-1743.

201. Prikhodko, T. A.; Kurilenko, V. M.; Khlienko, Z. N; Vasilevskii, S. F; Scvartsberg, M. S, *Bull. Acad. Sci. USSR* **1990**, 39, 134-141.

202. Sakamoto, T.; Takao, N.; Tatsuo, K.; Yamanaka, H. *Chem. Pharm. Bull*. **1988**, 36, 2248-2252.

203. Bocchi, V.; Palla, G. *Synth.Comm*, **1982**, 12, 1097-1099.

204. (a) Amat, M; Hadida, S.; Sathyanarayana, S.; Bosch, J. *J. Org. Chem*, **1994**, 59, 1, 10-11.

(b) Shinohara, K.; Suzuki, K. *Tetrahedron Lett.* **2002**, 43, 6937-6940.

205. Hansen, D. B.; Lewis, A. S.; Gavalas, S. J.; Joullie, M. M. *Tetrahedron Asymmetry*, **2006**, 17, 15-21.

206. Ma, C.; Yu, S.; He, X.; Liu, X.; Cook, J. M. *Tetrahedron Lett.* **2000**, 41, 2781-2785.

207. Mysliborski, R.; Latos-Grazynski, L. *Eur. J. Org. Chem.* **2005***, 23,* 5039-5048.

208. Gu, Y. G.; Bayburt, E. K. *Tetrahedron Lett.* **1996**, 37, 2565-2568.

209. Karchava, A. V.; Maksimova, F. V.; Yurovskaya, M. A. *Chem. Heterocycl. Compd*. **1994**, 30, 1195-1199.

210. Yamamoto, T.; Arif, A.; Atta, M.; Stang, P. J. *J. Am. Chem. Soc*. **2003**, 125, 12309-12317.

211. Rajadurai, C.; Ivanova, A.; Enkelmann, V.; Baumgarten, M. *J. Org. Chem.* **2003**, 68, 9907-9915.

212. Roppe, J. R.; Wang, B.; Huang, D.; Tehrani, L.; Kamenecka, T.; Schweiger, E. J.; Anderson, J. J.; Brodkin, J.; Jiang, X.; CrAm, M.; Chung, J.; Reyes-Manalo, G.; Munoza, B.; Cosford, N. D. P. *Bioorg. Med. Chem. Lett*. **2004**, 14, 3993-3996.

213. (a) Hurst, R. S.; Hajos, M.; Raggenbass, M.; Wall, T. M.; Higdon, N. R.; Lawson, J. A.; Rutherford-Root, K. L.; Berkenpas, M. B.; Hoffmann, W. E.; Piotrowski, D. W.; Groppi, V. E.; Allaman, G.; Ogier, R.; Bertrand, S.; Bertrand, D.; Arneric, S. P. *J. Neurosci.* **2005**, 25, 4396-4405.

(b) Bitner, R. S.; Bunnelle, W. H.; Anderson, D. J.; Briggs, C. A.; Buccafusco, J.; Curzon, P.; Decker, M. W.; Frost, J. M.; Gronlien, J. H.; Gubbins, E.; Li, J.; Malysz, J.; Markosyan, S.; Marsh, K.; Meyer, M. D.; Nikkel, A. L.; Radek, R. J.; Robb, H. M.; Timmermann, D.; Sullivan, J. P.; Gopalakrishnan, M. *J. Neurosci*. **2007**, 27, 10578-10587.

(c) Bartus, R.T., Dean, R.L., Beer, B., and Lippa, A.S. *Science*, **1982**, 217, 408–417.

(d) Maelicke, A., Schrattenholz, A., Samochocki, M., Radina, M., Albuquerque, E. X. *Behav. Brain Res*. **2000**, 113, 199–206.

(e) Bodnar, A. L.; Cortes-Burgos, L. A.; Cook, K. K.; Dinh, D. M.; Groppi, V. E.; Hajos, M.; Higdon, N. R.; Hoffmann, W. E.; Hurst, R. S.; Myers, J. K.; Rogers, B. N.; Wall, T. M.; Wolfe, M. L.; Wong, E. *J. Med. Chem*. **2005**, 48, 905-908.

214. (a) Crumb. W.; Cavero. I. *Pharm. Sci. Technol. Today*, **1999**, 270-280.

(b) Dennis, A.; Wang, I.; Wan , X.; Ficker, E. *Biochem. Soc. Trans.* **2007**, 35, 1060-1063.

215. http://www.ich.org/LOB/media/MEDIA2192.pdf (accessed on 02/07/08).

216. Brown, A. M. *Cell Calcium*, **2004**, 35, 543-547.

217. http://www.cellular-dynamics.com/products/glp_herg.html (accessed on 04/08/08).

218. http://pubs.acs.org/subscribe/journals/mdd/v03/i08/html/10toolbox.html (accessed on 10/07/08).

219. http://ntp-server.niehs.nih.gov/?objectid=16D6D969-A9F4-0B6F-2B81F2FB53BBFD3E (accessed on 10/07/08).

220. Yoshimura, R. F.; Hogenkamp, D. J.; Li, W. Y.; Tran, M. B.; Belluzzi, J. D.; Whittemore, E. R.; Leslie, F. M.; Gee, K. W. *J. Pharmacol. Exp. Ther.* **2007**, 323, 907-915.

221. Klose, W; Schwarz, K. *J. Het. Chem*. **1985**, 22, 669-671.

222. Yoshikazu, M.; Masahiko, S. *J. Org. Chem*. **2003**, 68, 1571-1574.

223. Horner, L; Hoffmann, H.; Klink, W.; Ertel, H.; Toscano, V. G. *Chem. Ber*. **1962**, 95, 581-601.

224. Hugon, B.; Pfeiffer, B.; Renard, P.; Prudhomme, M. *Tetrahedron Lett*. **2003**, 44, 3927-3930.

225. Gribble, G. W.; Liu, Y. *Org. Prep. Proced. Int*. **2001**, 33; 6; 615 – 620.

226. Shvartsberg, M. S.; Vasilevskii, S. F.; Prikhod'ko, T. A. *Bull. Acad. Sci. USSR*, **1982**, 11; 2226-2229.

227. LaMontagne, M.P; Ao, M.S, Markovac, A; Menke, J.R. *J. Med. Chem*. **1976**, 19, 360-365.

228. Tamao, S.; Kodama, S.; Nakajima, I.; Kumada, M. *Tetrahedron* **1982**, 38, 3347-3354.

229. Chami, Z.; Gareil, M.; Pinson, J.; Saveant, J-M.; Thiebault, A. *J. Org. Chem.* **1991**, 56, 586-595.

230. Iglesias, B.; Alvarez, R.; de Lera, A.R. *Tetrahedron* **2001**, 3125-3130.

231. (a) Dakka, J.; Sasson, Y. *J. Org. Chem*. **1989**, 54, 3224-3226.
(b) Cope, A. C.; Burg, M. *J. Amer. Chem. Soc*. **1952**, 74, 168, 171.
(c) Nair, V.; Panicker, S. B.; Augustine, A; George, T. G.; Thomas, S.; Vairamani, M. *Tetrahedron* **2001**, 57, 7417-7422.

232. Kuang, C.; Yang, Q.; Senboku, H.; Tokuda, M. *Tetrahedro*n **2005**, 61, 4043-4052.

233. Witulski, B.; Buschmann, N.; Uwe Bergstrasser, U. *Tetrahedron* **2000**, 56, 8473-8480.