Synthesis of Novel Allosteric Agonists and Allosteric Modulators for Nicotinic Acetylcholine Receptors

A dissertation presented by

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Declaration

I, Persis Dhankher, confirm that the work presented in this thesis is my own. Where information is derived from other sources, I confirm that it has been indicated and acknowledged.

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Abstract

In healthy individuals, the α7 and α4β2 nAChRs are concentrated in regions of the brain involved with learning, cognition and memory, which are relevant to diseases such as Alzheimer's disease. Hence, these receptors have become significant from a pharmacological and drug discovery perspective. The tetrahydroquinoline compound 4BP-TQS has been reported to act as a potent allosteric agonist on the α7 nAChR. The natural product desformylflustrabromine is able to act as a positive allosteric modulator (PAM) on the α4β2 nAChR. This thesis describes the development of synthetic routes directed towards 4BP-TQS and desformyflustrabromine analogues, and their pharmacological effects on α7 and α4β2 nAChRs.

In the first half of the project a total of 51 analogues of 4BP-TQS were synthesized by performing a multicomponent reaction (MCR) between a substituted benzaldehyde, an aniline and an activated alkene. The pharmacological properties of these compounds were then studied by our collaborators in UCL pharmacology. These compounds exhibited interesting and wide ranging pharmacological properties with individual compounds acting as either allosteric agonists, antagonists, type I or type II positive allosteric modulators or allosteric antagonists of 4BP-TQS.

The second part of the project involved the development of new chemistry directed towards the synthesis of desformylflustrabromine analogues. Initial work focused on the investigation of a novel Pd-catalysed allylation procedure for introducing an allyl group at the C-2 position of indole. Although the desired transformation was not successfully achieved, a novel regioselective Pd-catalysed C-3 diallylation of substituted indoles was discovered. The diallylated products were shown to be versatile intermediates which could undergo a variety of different reactions. By subjecting the diallylated products to ring-closing metathesis, a series of spirocyclic alkaloid-like structures were obtained in excellent yields. It was also demonstrated that the diallylated products could be desymmetrized using a proline-catalysed Mannich reactions to give enantioenriched products.

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Finally last but certainly not least, I want to thank my husband and my family for their unconditional love and support.

Abbreviations

Ac	acetyl
aq	aqueous
9-BBN	9-borabicyclic[3.3.1]nonane
Bn	benzyl
Boc	tert-butoxycarbonyl
CAN	cerium ammonium nitrate
Cat	catalyst
DHF	dihydrofuran
DHP	dihydropyran
DIBAL	diisobutylaluminum hydride
DMAP	4-N,N-(dimethylamino)pyridine
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
DMA	dimethylacetamide
dr	diastereomeric ratio
ee	enantiomeric excess
er	enantiomeric ratio
HPLC	High Performance Liquid Chromatography
liq	liquid
***m*CPBA**	m-chloroperbenzoic acid
MS	molecular sieves
p	para
Py	pyridine
RCM	ring-closing metathesis
RT	room temperature
sat	saturated
tert	tertiary
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TQS	tetrahydroquinoline sulphonamide

Biological Abbreviations

ACh	Acetylcholine
CREB	Camp response element-binding protein
CNS	Central nervous system
GABA	γ-amino-butyric acid
5-HT	5-hydroxytryptamine
LGIC	Ligand gated ion channels

mAChRs	Muscarinic acetylcholine receptors
nAChRs	Nicotinic acetylcholine receptors
(NAMs)	Negative allosteric modulators,
(PAMs)	Positive allosteric modulators,
(TM)	Transmembrane.

Publications and Manuscripts

1) A Series of α7 Nicotinic Acetylcholine Receptor Allosteric Modulators with Close Chemical Similarity but Diverse Pharamacological Properties, JasKiran Gill, Persis Dhankher, Tom. D. Sheppard, Emanuelle Sher and Neil. S. Millar, *Molecular Pharmacology*, 2012, **81**, 710-718.

2) A Convenient Synthesis of Trimethyl and Tetramethyl Benzaldehydes from Readily Available Phenols, by Persis Dhankher and Tom D. Sheppard, *Manuscript given full consideration for publication in Synlett.*

Chapter 1

Introduction

1.1 Nicotinic Acetylcholine Receptors

The nervous system is an organ system, consisting of a network of specialized cells called neurons. It is through these neurons that messages are sent, received, and processed to coordinate the actions of animals and allow communication between cells.[1] The transmission of messages occurs from the pre-synaptic neuron to the post-synaptic neuron at a synaptic cleft, located between the axon terminal of the pre-synaptic neuron and dendrites of the postsynaptic neuron **(Figure 1)**.[1, 2] Two types of synapses co-exist electrical and chemical. In electrical synapses the pre- and post- synaptic neurons are separated by 3.5 nm[3] and so conduct nerve impulses faster than chemical synapses, where the pre- and post-synaptic neurons are separated by 20-40 nm.[1] Electrical impulses are found in the central nervous system (CNS) and the peripheral nervous system (PNS) to produce simple responses compared to the more complex chemical synapses. An important characteristic of electrical synapses is that they are bi-directional.[3]

In contrast, in a chemical synapse the message is transmitted between neurons *via* a chemical messenger or neurotransmitter.[4] The neurotransmitter, which is stored in synaptic vessels localised at the end of the pre-synaptic terminal, is released from the post-synaptic terminal into the synaptic cleft where it will bind onto specific receptors localised on the cell surface of the post-synaptic neuron. Neurotransmitters are often classified as either excitatory or inhibitory. Excitatory neurotransmitters cause depolarisation and promote the generation of action potentials whereas inhibitory neurotransmitters cause hyperpolarisation and suppress the generation of action potentials. Communication across the chemical synapse can normally only occur in one direction,that is from the pre-synaptic to the post-synaptic membrane.

When an action potential arrives at the synaptic knob it is depolarised which stimulates the release of the neurotransmitter from the synaptic vesicles.[2] The depolarisation opens voltage gated calcium channels allowing calcium ions to rapidly enter the cell.[2] This triggers exocytosis of the synaptic vesicles containing the neurotransmitter, and hence, its release into the synaptic cleft, which is

subsequently followed by binding onto the specific receptor on the post-synaptic neuron **(Figure 1).** This binding of the neurotransmitter at the post-synaptic neuron causes a conformational change of the receptor, which activates the receptor.

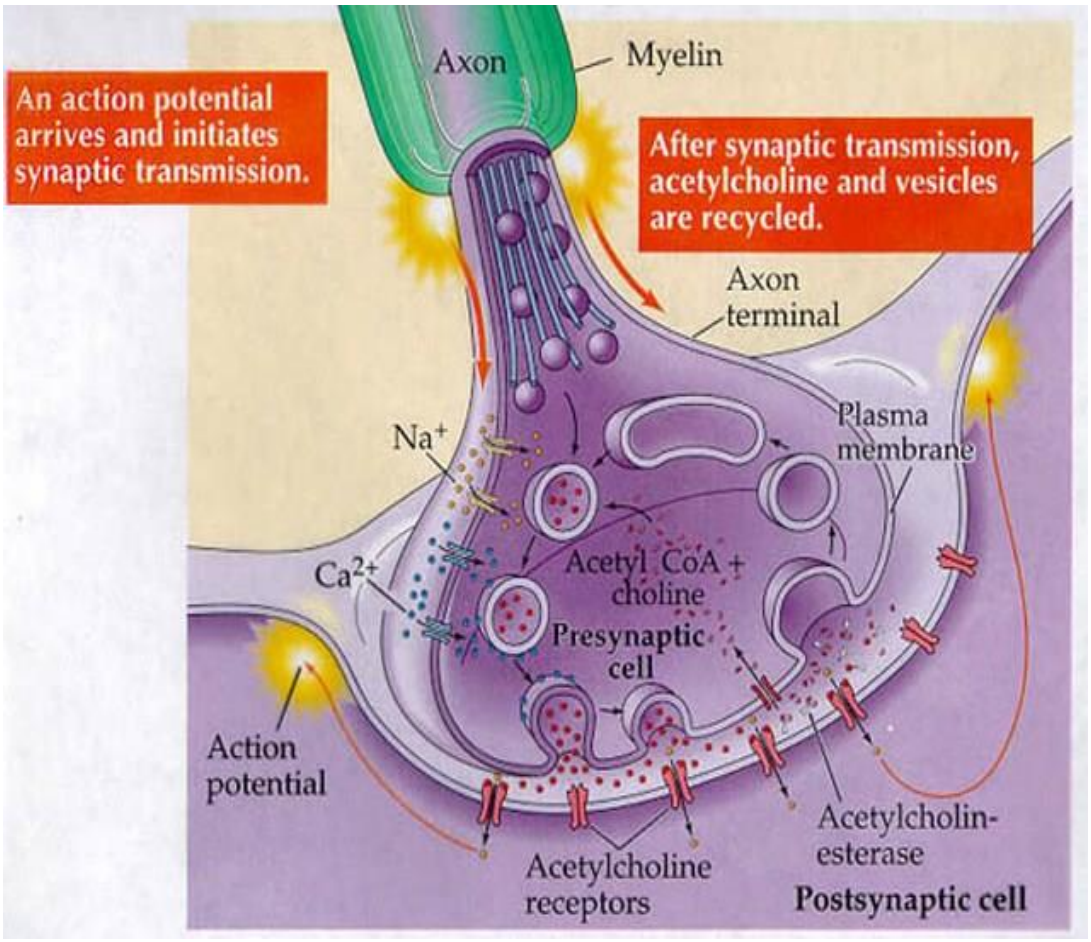
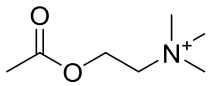


Figure 1. Diagram showing how messages are transmitted between neurons.[5]

On activation of ligand gated ion channels (LGIC), such as nAChRs, the opening of the ion channel which is part of the overall structure of these types of proteins, allows ions (Na^+, K^+ or Ca^{2+}) to move into and out of the ion channel according to the electrochemical gradient, resulting in either depolarisation or hyperpolarisation of the postsynaptic neurone.[2] In case of both excitatory and inhibitory neurotransmitters, the greater the amount of neurotransmitter in the membrane, the greater the depolarisation. However, a threshold potential exists in the membrane which regulates and propagates signalling in the CNS, an action potential is generated in the post-synaptic cell only when the membrane potential (-70 mV at resting state) is equal to or greater than the threshold potential (-40- -55 mV).[1]

Acetylcholine (ACh) was one of the first neurotransmitters to be discovered **(Figure 1a)**, playing a role in neurotransmission in the CNS and PNS. [1]



Acetylcholine

Figure 1a

It is formed from one acetyl-coenzyme A and one choline unit in a reaction catalysed by choline *O*–acetyltransferase (ChAT). Upon formation of ACh, it is then released from the nerve terminals in the cholinergic synapse. ACh release into the nerve terminals in the presynaptic cleft occurs if a high concentration of Ca^{2+} ions is present inside the cell. Once diffused into the synaptic cleft acetylcholine binds to nAChRs present on the post-synaptic neuron, which becomes activated.[2]

NAChRs are found on both pre- and post- synaptic neurons.[6] Pre-synaptic nAChRs are mainly found in the CNS whereas post-synaptic nAChRs are found mainly at the neuromuscular junction and autonomic ganglia.[6]

1.2 Structure and Function of nAChRs

NAChRs are members of the ligand gated ion channel (LGIC) superfamily.[7] They were the first neurotransmitter receptors and ion channels to be characterised in detail.[7] They are present in many tissues of the body and have a modulatory role.They contribute to the control of the resting membrane potential, modulation of synaptic transmission and mediation of fast excitatory transmission.[7]

There is a common structure amongst nAChRs, consisting of five polypeptide subunits assembled from a diverse collection of subunits which assemble together to form a pentameric transmembrane structure.[8, 9] At the centre of this structure the ion channel is formed.

The mechanism of nAChRs is similar for all receptors regardless of the different combinations of subtypes.[6, 9, 10] NAChRs are excitatory and are activated by ACh. The muscular nicotinic receptor of the *Torpedo californica* is considered the prototype for all the nAChRs, as receptors in this species of fish are very similar to those present in humans.[11]

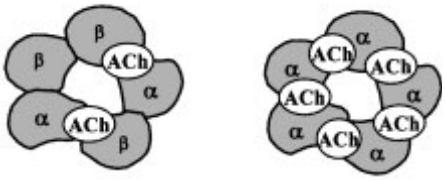


Figure 2: Schematic representation of nicotinic acetylcholine receptor. Bottom: Quaternary organization of the heteromeric (centre left) and homomeric (centre right) neuronal receptors.[10]

1.2.1 Subunit Subtypes

The four subunits are assigned the Greek letters α, β, γ and δ on the basis of their increasing apparent molecular weights.[11]

To date, 17 nAChR subunits have been identified in vertebrates, which are divided into muscle-type and neuronal-type subunits.[6] Of these, 12 subunits, α2-α10, and β2-β4 have been identified in neuronal receptor subtypes, which exist in various homomeric or heteromeric combinations.[6, 8]An example of a neuronal subtype is the $(\alpha 7)_5$ nAChR,[11] a receptor subtype this project has focused on.

In neuronal nAChRs the α subunits possess a pair of extracellular cysteines Cys 192 and Cys 193 which are believed to be required for acetylcholine binding whereas the β subunits do not.[6, 8] In general, each receptor subtype is defined by the combination of subunits it contains. This combination of subunits produces subtle changes in the ACh binding site and the ion channel, resulting in each receptor subtype exhibiting different levels of affinity for various drugs and cholinergic ligands.[11] Another effect of neuronal nAChR subtypes as a result of combination of subunits is the ability to selectively control the type of ions which flow through the receptor, such as differences in cation permeability,[11] typically much more calcium being allowed through the neuronal type than through the muscle type.[12]

1.2.2 Subunit structure of nAChRs

The nAChR subunits share the same transmembrane structure and similar amino acid sequences, which are 450-700 amino acids long. Each subunit is made up of a large extracellular amino-terminal (N-terminus) domain,[13] which consists of about 220 amino acids, four transmembrane domains and a small carboxy-terminal (C-terminus) domain of about 15 amino acids in the extracellular space **(Figure 3).**[13]

The terminus contains two cysteine molecules bound by a disulphide bond, which forms the characteristic Cys-loop.[13] The transmembrane domains of which there are four (M1, M2, M3 and M4) are about 20 amino acids long each, and are separated by loops.[13] The loop between M3 and M4 is larger than the loop between M1 and M2 by about 130 amino acids, being involved in the regulation of the channel activities and also containing phosphorylation sites.[13]

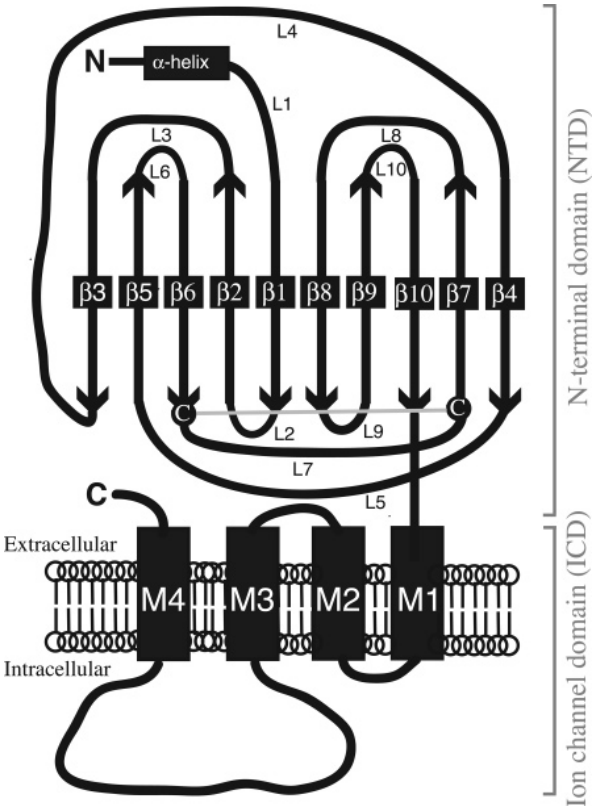


Figure 3.Common structure of a nAChR.[13]

The transmembrane domains are arranged anti-clockwise, with M2 facing into the ion channel pore and the amino acids in the M2 domain forming the main part of the ion channel.[14] There is strong evidence to suggest that the ion channel has mainly an α-helical structure, which is mainly negatively charged, as ion channels are only permeable to cations.[14]

The orthosteric binding domains are located at the interface of the subunits, and can range from two to five sites depending on the composition of the subunits. In addition, modulation of nAChRs can occur by binding to the allosteric domain that is distant from the primary active binding site.[12, 15 16, 17]

1.3 Heteromeric and Homomeric Receptors

Neuronal nAChRs form either in heteromeric or homomeric structures.[6] Heteromeric nAChRs are normally made up of α2-α6 and β2-β4 combinations, existing in many subunit arrangements to form functional channels, e.g. the α4β2 receptor.[6] In contrast homomeric receptors consist of five copies of a single type of subunit, α7, α8 and α9 have been shown to form functional homomeric pentamers, with an equal number of ACh binding sites, when expressed as recombinant receptors.[6] The subunit composition and arrangement of the subunits in the neuronal nAChRs is what gives them their distinct pharmacological and biophysical properties.[11] The most striking pharmacological characteristic of the α7 homomeric receptor is its marked permeability to calcium ions.[12]

A number of agonists bind to α7 nAChRs to activate the receptor's ion-channel, these include: ACh, nicotine, epibatidine, and cytosine.[18] In the brain, neuronal nAChRs are located in the hippocampus and cerebral cortex at the pre-synaptic membranes.[18] There they regulate the release of ACh and other important neurotransmitters. These receptors are involved in cognitive processes such as learning, memory and attention.[19-21] Changes in the functional activity of nAChRs have been implicated in a number of diseases, particularly Alzheimer's. Moreover, amyloid β released in Alzheimer's disease patients also extensively binds to α7 nAChRs in the brain and prevents their natural function. As the acetylcholine level is limited in the brain of a patient suffering from Alzheimer's disease, targeting the α7 nAChR was considered a promising way to enhance cognitive functions.[22]

An understanding of the functional and molecular properties of these receptors is important for understanding their functions in the brain, and to aid development of new drug therapies. The α7 nAChR subtype is currently of therapeutic interest, particularly, for Alzheimer's and schizophrenia.[23]

1.4. Orthosteric and Allosteric binding site

The site occupied by the natural ligand, ACh, which is typically located at the interface between subunits, is called the orthosteric site.[24] Depending on the composition of the subunits, the number of orthosteric binding sites present can

range from two to five binding sites. An allosteric binding site is a location distinct from the orthosteric site where the ligand binds to stabilise the protein in a preferential conformation .[24]

In α7 nAChRs there are 5 potential ACh binding sites. Not all binding sites need to be occupied to stabilize the open active state of the receptor, but the probability of the channel opening increases upon more orthosteric binding sites being occupied by the agonist. [13, 25] Different nAChR ligands can stabilize the conformational state of a receptor to which they preferentially bind. Agonists such as acetylcholine (ACh) and (-)-nicotine respectively stabilize the active and desensitized states.[13, 26]

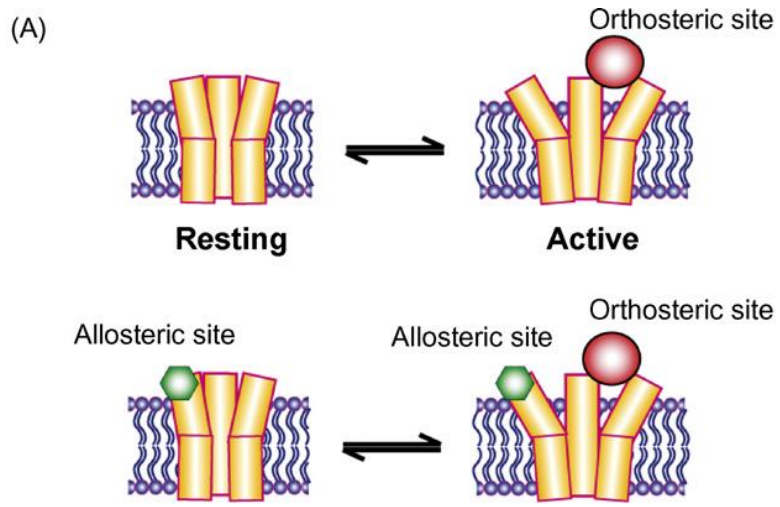


Figure 4a: Schematic diagram showing allosteric and orthosteric site of a protein with two conformational states, resting (close) and active (open).[24]

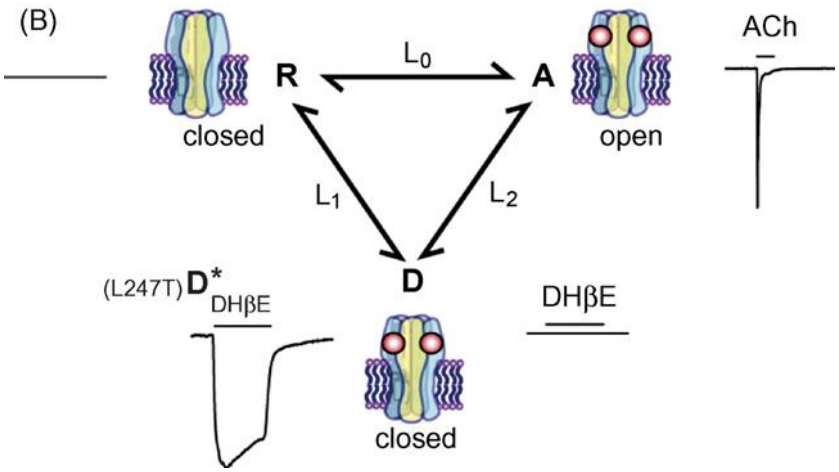


Figure 4b. A schematic diagram of the three state model in nAChRs.[24]

Binding of an agonist or a competitive antagonist to an orthosteric site of the nAChR stabilises its active and resting states, respectively, whereas binding of an effector at an allosteric site alters the overall properties by modifying the energy barriers between transitions resulting in a displacement of the equilibrium between states **(Figure 4b)**.[13, 24] Agonists are characterised by having higher affinity for the active state than for the resting state, and conversely antagonists have higher affinities for the resting/inactive receptor states.

Binding of a ligand to an allosteric site located at some distance from the orthosteric site of the receptor complex can also modulate the nAChR signalling via an effect on the equilibrium between the resting and active receptor states or on the desensitisation kinetics. [13, 25] For the description of an allosteric transition state model of nAChRs a three state model initially proposed by Heidmann and Changeux was developed that involves a resting state, an activated state and a desensitized closed channel state, which is a process by which receptors become insensitive to the agonist. The changes between these states can be monitored using electrophysiology methods.[24]

Structure functional studies carried out on nAChRs have revealed that the short amino acid segment between the second and third transmembrane domains is an important determinant in the gating process that takes place during receptor activation.[8]

1.5 Alzheimer's Disease (AD)

Alzheimer's disease (AD) is a progressive and fatal brain disorder that causes memory loss, deterioration of the cognitive centre of the brain, and dementia. Over 30 million people worldwide are afflicted with the disease. It is estimated that by 2050, there could be more than 100 million AD patients worldwide. AD dramatically affects the quality of life of the sufferers and their families, and despite massive investments, there are few, if any, effective treatments for AD. The AD pathogenesis involves a complex interplay of genetic and biochemical factors, including an increased production of β amyloid peptide and an increased phosphorylation of the micro-tubule-associated tau protein.

AD progression is associated with a significant disruption of several neurotransmitter systems, including the cholinergic, GABAergic, adrenergic, serotoninergic, and glutamatergic systems. Alterations of cholinergic and glutamatergic systems have been extensively studied, leading to many acetylcholineasterase (AChE) inhibitors.[13]

1.5.1 Current drug treatments for Alzheimer's Disease in USA (FDA) and UK

Acetylcholinesterase (AChE) is an enzyme responsible for catalysing the breakdown of acetylcholine into acetyl-COA and choline. This enzyme is significant for regulating neurotransmission at synapses in the nervous system. The significance of AD progression has been reported to be a result of deficits in the cholinergic neurotransmission. Donepezil hydrochloride **1**, rivastigamine tartrate **2**, galanthamine hydrobromide **3**, tacrine hydrochloride **4**, and memantine **5** are currently used to treat cognitive symptoms of Alzheimer's disease by acting as inhibitors for AChE. They are prescribed to patients suffering with mild to moderate stages of AD. These inhibitors are proposed to work by increasing the efficiency of cholinergic neurotransmission by preventing the hydrolysis of released ACh, thus making more ACh available at the cholinergic synapse.

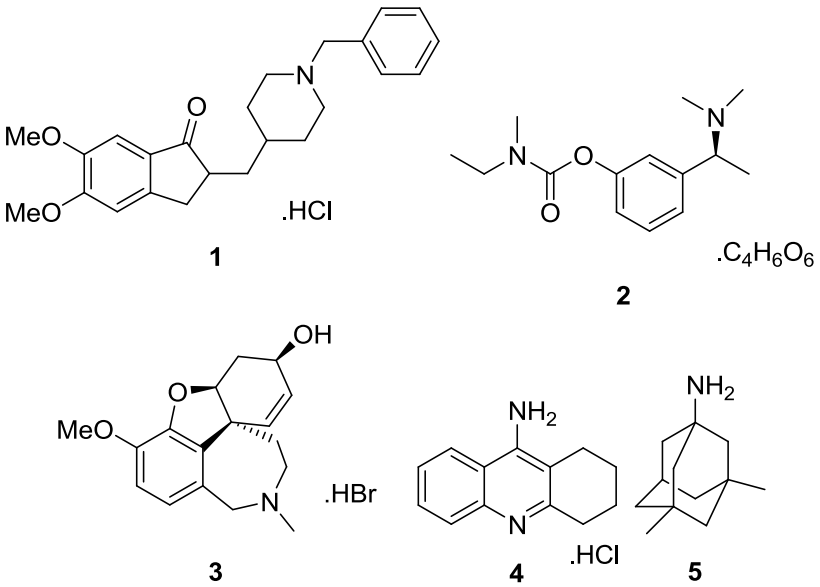


Figure 5. Structures of cholinesterase inhibitors currently prescribed to patients in USA and UK.

Despite alleviating effects of cholinesterase inhibitors for AD, inactivation of AChE on an excess level can lead to side effects that can be potentially life threatening to

any living organism with a nervous system. In fact, some irreversible organophosphate AChE inhibitors are used as insecticides and as chemical warfare agents.

1.6 Non-selective compounds for nAChRs

Many nicotinic ligands have come from a natural source, some having been obtained from sources such as nicotine from the plant *Nicotiana tabacum*, cytisine an alkaloid from *Cytisus* of the family Fabaceae and others from venoms or poisons obtained from reptiles or amphibians such as epibatidine, an alkaloid found on the skin of the endangered Ecuadorian frog, *Epipedobates tricolor*.

1.6.1 Agonists

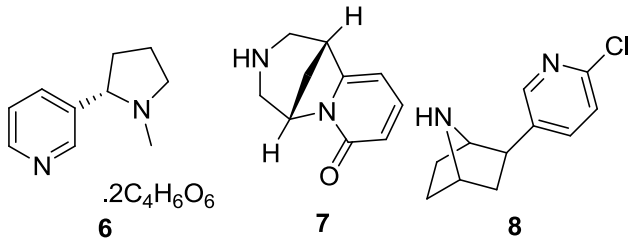


Figure 6. A few selected agonists

Nicotine ditartarte **6** a nicotinic acetylcholine receptor (nAChR) agonist exhibits binding affinity (K*i*) values of 1, > 1000, 4000 and 7130 nM at α4β2, α1β1δγ, rat α7 and human α7 receptors, respectively **(Figure 6)**.

Although (-)-cytisine **7** is considered to be selective for α4β2 (2000-fold higher than α7 subtype), selectivity towards heteromeric subtypes is lower with affinity ratios between α4β2, α2β2, α2β4, α3β2, α3β4, and α4β4 being 0.4, 5, 14, 56 and 1, respectively. Epibatidine **8** is known to be a very potent nicotinic agonist exhibiting K*i* values of 0.02 and 233 nM for α4β2 and α7 nicotinic receptors, respectively.[13]

A number of analogues derived from natural products such as epibatidine and nicotine show high potency but fail to exhibit subtype selectivity on nAChRs. As a result these compounds are unfit for clinical use due to the risk of unwanted metabolic reactions.

1.6.2 Antagonists

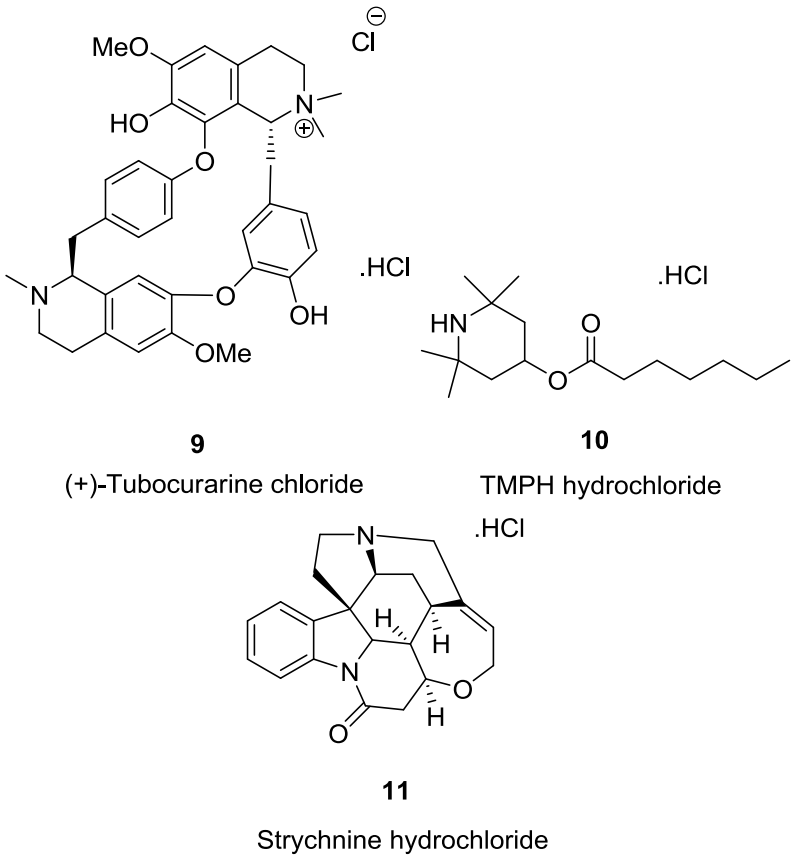


Figure 7. A few non-selective antagonists

Tubocurare is a mono–quaternary alkaloid found from the plant *Chondrodenron Tomentosum*. Its salt (+)-tubocurarine chloride **9** shows affinity with a number of receptors. TMPH hydrochloride **10** is a potent non-competitive antagonist of nAChRs. It produces long-lasting inhibition of neuronal nAChRs formed by the combination of the most abundant α and β subunits (i.e. α3, α4 and β2, β4 respectively). Little inhibition of muscle-type (α1β1γδ) or α7 receptors is displayed with **10**. Strychnine hydrochloride **11** was the first alkaloid to be identified in plants of *Strychnos*, family *Longaniaceaea.* It is a nicotinic receptor antagonist and displays competitive antagonism at α7 receptors and non-competitive antagonism at α4β2 receptors.

1.7 Ligands selective for α7 nAChRs

Rather than targeting the acetylcholinesterase enzyme, extensive research by academic and industrial institutes are finding alternative ways to understand how

agonists, antagonists, type I and type II PAMs can modulate the activity of α7 nAChRs selectively, which are heavily localised in the brain and has been reported to be associated with AD. The compounds mentioned above are being used as leads for a new generation of nAChR ligands to minimize cross-activities at mAChRs or other receptors.

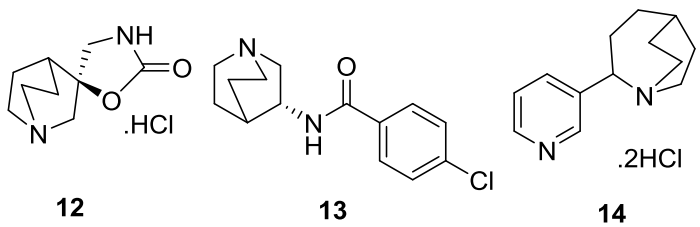
1.7.1 Agonists

In response to the challenges associated with the designs targeting specific neuronal α/β subtypes several α7 selective nAChR- selective agonists have been reported.

Agonists are characterised by having higher affinity for the active state than for the resting state, and conversely antagonists have higher affinity for the resting/inactive receptor states.

Choline, the endogenous precursor for ACh and metabolic product of ACh hydrolysis, has been shown to be a full agonist on native and recombinant α7 nAChRs with EC_{50} values around 1 mM, with little or no activity on α4β2, α3β4, α3β2, and muscle-type nAChRs.[13, 27, 28] However, due to the low potency of this compound, the synthesis and pharmacological characterisation has not sparked any interest in the development of analogues.

AR-R 17779 **12** a spirooxazolidinone, which is a conformationally restricted analogue of (CCh), is a full agonist at the α7 nAChR (K_i 90 nM) displaying pronounced selectivity against numerous heteromeric α/β nAChR combinations.[13, 29, 30] Due to the limitations of AR-R17779 **12** in *vivo*, attributed to poor pharmacokinetic characteristics, AR-R17779 **12** displays varying degrees of pharmacological effects in cognition models. [13, 31-35]



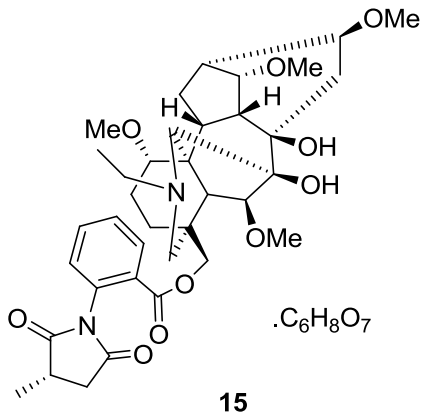
12 **13** **14**

Figure 8. A few selected examples of selective α7 nAChRs.

Quinuclidine structures containing cation centres where the bicyclic ring system is coupled directly to an aryl amide, bisarylamide, or a heteroarylamide group **(Figure 8)** have been a scaffold of choice for several α7 nAChRs ligands in the pharmaceutical industry.[29, 36] Due to its basic nitrogen, the bridgehead position occupied within an azabicyclic system are able to create maximal electrostatic interaction combined with minimal steric demand. Owing to the strong basicity of quinuclidine derivatives (pK_a 10-11), these α7 ligands exist under physiological conditions in the cationic form, with a well-defined orientation of the proton. The *p* – chlorobenzamide analogue PNU-282987 **13** has been shown to stimulate signalling through an α7/5-HT_3 chimera and through native α7 nAChRs with EC_{50} values of 128 nM and 3 nM, respectively and a of K_i 27 nM.[37, 38] TC-1698 **14** an analogue of nicotine by substitution of the pyrrolidine group for an azabicyclo[3.2.2]nonane ring is a full agonist at the α7 nAChR EC_{50} = 440 nM. TC-1698 has been shown to be neuroprotective.[13, 27, 39]

1.7.2 Antagonists

Analogous to nAChR agonists, most of the antagonists for the receptors have been obtained from natural sources. Methyllcaconitine **15** (MLA), isolated from *Delphinium* and *Consolida* species, is a highly selective competitive antagonist of the α7 nAChRs (K*i* = 1.4 nM). The molecule has also been subjected to small modifications which has resulted in elatine and nudicauline, which are equipotent to and slightly more potent than MLA as α7 antagonists, respectively. [13, 40]



15

Figure 9. Structure of MLA **15**

Conas peptides obtained from the venom of predatory cone snails provides an array of pharmacologically active peptides.[13, 41] These peptides containing 12-20 amino-acid residues have the potential to be interesting templates in the design of new nAChR ligands.[42, 43] α-Conotoxin is divided into subfamilies A, M, S, and O based on disulphide connectivity. α-Conotoxins possess four cysteine residues with disulphide bond formed between the first and third and between the second and fourth cysteine residues.The $\alpha_{4/3}$ –conotoxin ImI was the first α-conotoxin reported to inhibit neuronal nAChR signalling (IC_{50} = 100-200nM).[44] Recently, α-conotoxin ImII has been shown to inhibit α7 nAChR activity with an IC_{50} = 441 nM. In contrast to ImI, ImII does not displace [^{125} I]-α-bungarotoxin binding from the receptor, indicating that the two toxins bind to different sites of the receptor.[43] α-Bungarotoxin is another neurotoxin that blocks neuromuscular transmission via irreversible inhibition of nicotinic ACh receptors (nAChRs). It functions by preventing the opening of nicotinic receptor-associated ion channels and is selective for α7 receptors over α3β4 receptors (IC_{50} values are 1.6 nM and > 3 μM respectively).[10]

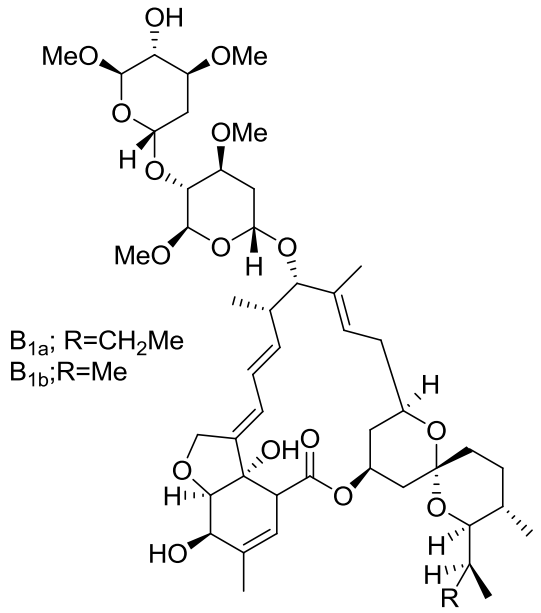
1.7.3 Allosteric modulation on α7-nAChRs

The initial functional characterization of the chick α7 nAChR revealed that this homomeric receptor displays a rather low sensitivity to ACh and an unusually fast desensitization.[24] Subsequently, numerous studies have confirmed that native α7 nAChRs of the mammalian central nervous system share similar functional properties. Another important feature is the high calcium permeability of the α7 nAChR.[24]

In addition to extensive studies aimed at characterizing nAChR subtype selective agonists and antagonists, considerable interest has been generated by the identification of a diverse group of allosteric modulators of nAChRs,[45-47] which bind to an allosteric site. These include positive allosteric modulators (PAMs), which increase the agonist responses by lowering the energy barrier between the resting state and active states. In contrast, allosteric ligands that increase the energy barrier causing a reduction of the agonist response are termed as negative allosteric modulators (NAMs or non-competitive antagonists).[8, 24] Several α7 selective PAMs have been identified and are divided into two types, type I and type II.[8, 24]

1.7.3.1 PAMs of α7 nAChRs

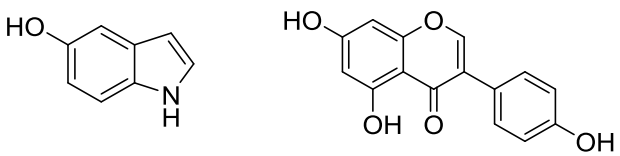
Currently, positive nAChR modulators at present are useful for the treatment of psychotic disorders.[26] The anthelminthic agent, ivermectin **16** (IVM) was identified as the first positive allosteric modulator of the α7 nAChR.[24] Ivermectin was found to increase maximal ACh-induced current, reduce desensitization and reduce the EC_{50} value of ACh.[24]



16

Figure 10. Structure of ivermectin.

It was also shown to increase the efficacy of partial agonists, such as dimethylphenylpiperazinium (DMPP) (a partial agonist at the α7 nAChR, which became almost a full agonist following exposure of the receptor to ivermectin).[24] Following this observation, several molecules have been reported to enhance the ACh-induced currents at the α7 nAChR. For example, 5-hydroxyindole (5-HI) **17k** causes a significant increase of subsequent ACh-evoked current.[24] However, high concentrations (1–20 mM) are required for potentiating the α7 nAChRs current, since 5-HI is a non-selective and weak ligand (5-HI also modulates the 5-HT_3 receptor).[24] Genistein **18**, a well-known tyrosine kinase inhibitor was found to act as an α7 PAM, which like 5-HI, predominantly affected apparent peak current.[24]

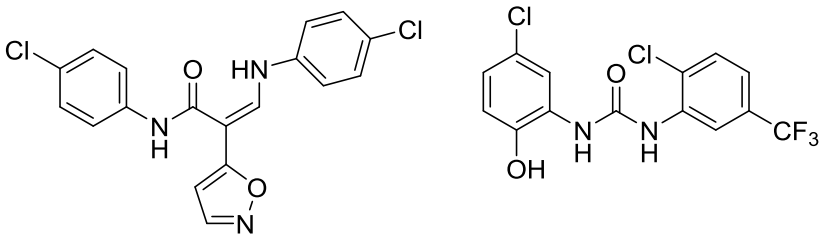


17 18

Figure 11. Positive allosteric modulators 5-hydroxyindole (5-HT) **17** and Genistein **18** at α7 nAChRs.[24]

1.7.3.2 Type I and Type II PAMs

In addition to compounds **17** and **18** above, a number of compounds have been recently reported as positive allosteric modulators with little effect on desensitisation kinetics. Ng *et al*. recently described compound **19 (Figure 12)**, derived from a chemical class previously exploited as GABAA modulators, to enhance α7 nAChR currents induced by ACh without affecting desensitization kinetics.[24] NS-1738 **20**, an analog from a biarylurea series was reported to enhance the potency of ACh as well as the maximal efficacy. NS-1738 also improved recognition memory performance in rats.[24]

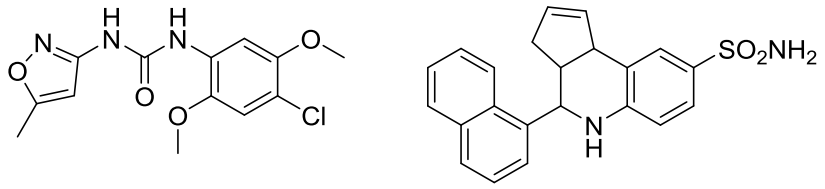


19 20

Figure 12. Structures of type I PAMs.[24]

Type I PAMs as mentioned above, behave by increasing the peak current amplitude response whereas type II PAMs, increase both the peak current response and the current decay profile. Hence, type II PAMs elicit a longer lasting action than type I PAMs towards receptor activation.

PNU-120596 **21** one of the better characterized urea analogs, not only increased the maximal amplitude and potency of ACh-induced α7 nAChR current by several fold (EC_{50} = 216 nM), but also almost suppressed desensitisation **(Figure 13)**. Another striking feature of **21** is its ability to restore responses in an otherwise desensitized receptor.[24] In other words, while continuous exposure to agonist (nicotine) desensitizes the α7 nAChR and reduces the response to a non-detectable level, application of **21** during continued exposure to the agonist is able to restore a current even larger than the peak current evoked by the agonist alone.[24] This phenomenon does not appear to be unique to **21**, but may be a common feature of Type II PAMs as revealed by analysis of structurally diverse compounds.[24]



21 **22**

1N-TQS

Figure 13.[24]

Studies have found that compounds with a type II agonist profile preferentially stabilizes a state of the receptor that differs from the state normally stabilized by agonists. Although both **21** and **20 (Figure 13)** are urea derivatives, **20** exhibited only minimal effects on the desensitisation kinetics of α7 nAChRs, unlike **21**, suggesting that these molecules may have different mechanisms or sites of action.[24] In vivo studies indicate that **21** improved performance in a rodent short-term recognition memory model and further increased the phosphorylation of camp response element-binding protein (CREB), a well-recognized biochemical process implicated in learning and memory. These observations collectively demonstrate that Type II PAMs also exhibit in vivo efficacy in models of cognition.

Analogs belonging to the tetrahydroquinoline series have also been described as α7 nAChR PAMs, useful for the treatment of conditions associated with reduced nAChR transmission.[24] Like **21**, a prototype **22** (TQS) **(Figure 13**), increased peak current and slowed desensitization of current responses.[24]

1.8 Advantages of α7 PAMs over α7 agonists

A key advantage of allosteric modulation is enhanced receptor activity only in the presence of the endogenous agonist, thereby preserving the overall integrity of neurotransmission. [48, 49]

Positive allosteric modulators (PAMs) have a long and successful clinical track record exemplified by the benzodiazepine family of drugs (e.g., diazepam), which function as allosteric modulators of GABAA receptors.[48, 50] The enhancement of α7 nAChR activity via positive allosteric modulation would provide the advantages of employing an allosteric modulatory approach to treat patients afflicted by CNS disorders.[48] It has been postulated that α7 nAChR PAMs might have advantages over orthosteric agonists in that they might modulate cholinergic responses and reduce receptor desensitisation more effectively. Because coordination of synaptic events is crucial in neuronal communication, an ideal therapeutic approach would be to enhance the strength of an existing synapse without disrupting overall control provided by the endogenous neurotransmitter. At the single ion channel level, this would require a drug that does not activate the channel by itself but instead modifies the agonist-induced responses.[51-53]

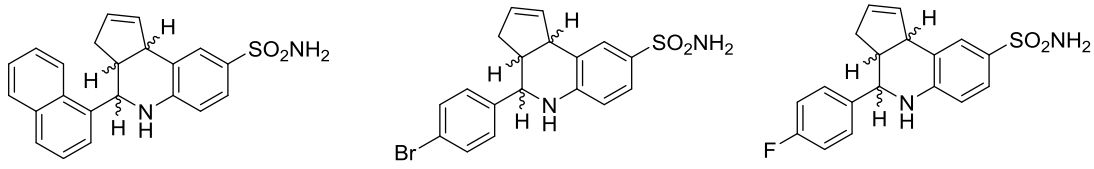
A number of subtype selective ligands have been developed but none alone offers the characteristics of an ideal α7 nAChR PAM where a high selectivity, potency and modulation, accompanied by the maintenance of rapid receptor desensitisation kinetics are observed.

Chapter 2

2 Synthesis of 4BP-TQS Analogues and Pharmacological Study on α7 nAChRs

2.1 Previous work

Recently work conducted by Millar and co-workers found that **23 (Figure 14)** acted as an allosteric agonist, which was able to activate the nAChR by binding at a transmembrane allosteric site in the absence of an endogenous agonist.[54] Becker and co-workers reported that tetrahydroquinoline sulphonamide compounds such as **22** and **24 (Figure 14)**, which are a closely related analogs of **23**, exhibited positive allosteric modulator activity at the α7 nAChR.[26] Becker reports the synthesis of **22** but not **23**. However, indirectly the synthesis of the halogenated tetrahydroquinoline compound **24**, is reported in the patent. The patent generally discusses the synthesis of halogenated TQS compounds where the halogen is either a chlorine, bromine or iodine, but no structure or experimental data are provided for these compounds.[26] The patent neither specifies nor separates the stereoisomers and nor does it assign the stereochemistry for compounds **22** and **24**. Nevertheless, they have shown a more detailed report on compound **25**, which is an analogue of **22**, they showed that the major diastereoisomer from the Pavarov reaction to form **25** was the *cis-cis* isomer **25b (Figure 14a)**, and in fact they even report separating enantiomers of **25b**, but do not indicate which stereoisomer(s) is/are biologically active.



22 1N-TQS

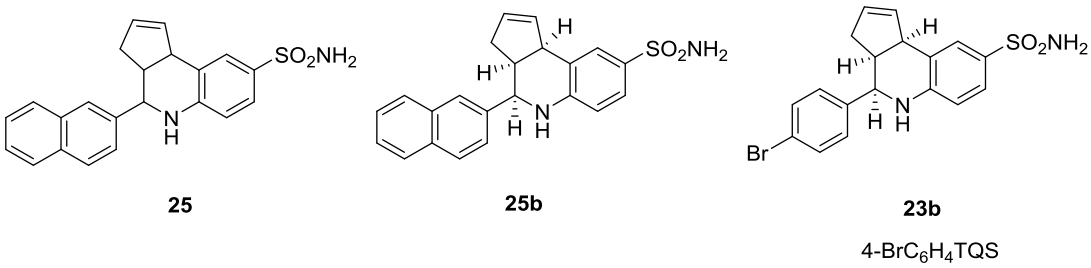
23 4-BrC_6H_4TQS

24 4-FC_6H_4TQS

Figure 14

Thus, prior to the start of our work it had not been proven which isomer(s) of **22** or **23** were biologically active, nor which was the biologically active enantiomer in each case. In the initial work carried out by our collaborators, samples of compound

23 were purchased commercially and the stereochemistry of the compound was not specified by the suppliers. Computational docking studies employed a 2D structure of **23** and the software arbitrarily modelled the cis-trans isomer. However, we believe that the stereochemistry of **23** originally used in Millar's study was likely to be the *cis-cis* isomer **23b**, on the basis of the observations reported by Becker and co-workers on the stereochemistry of **25** obtained from the Pavarov reaction.



25 **25b** **23b**

4-BrC_6H_4TQS

Figure 14a

As previously demonstrated by Couterier,[55] Millar and co-workers showed agonist activation on the receptor by ACh causes rapid desensitisation (**Figure 15 A, Left)**.[54] Similarly studies with **22** displayed no agonist activity on the nAChRs (not shown),[8, 46, 54] but **22** caused dramatic potentiation of agonist induced responses, together with a dramatic reduction in the rate of desensitisation when **22** was co-applied with ACh (**Figure 15 A** (right).[54] Despite the absence of agonist activity of **22**, a closely related compound **23** was found to act as a potent agonist of α7 nAChRs.

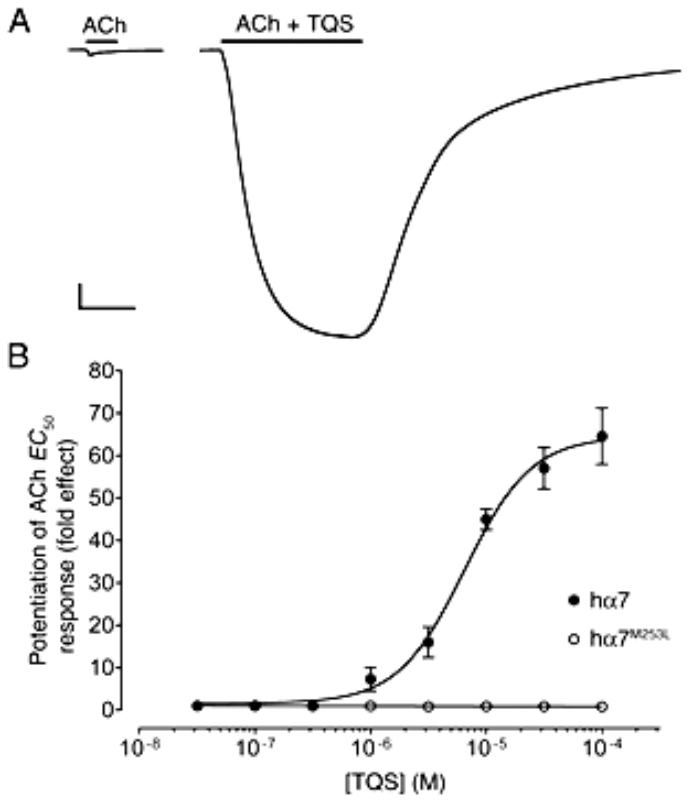


Figure 15.[54] Positive allosteric modulation of α7 nAChRs by TQS **22**, examined by two- electrode voltage-clamp recording in Xenopus oocytes. (A) Representative recordings are shown illustrating responses to the application of acetylcholine (100 μM) (Left) and of acetylcholine (100 μM) co-applied with TQS **22** (100 μM) (Right). The duration of agonist applications are indicated by a horizontal line. (Scale bars: vertical, 1 μA; horizontal, 5 s). (B) Dose-response data are presented for a range of concentrations of TQS **22** (0.03-100 μM) on responses evoked by a sub-maximal (EC_{50}) concentration of acetylcholine. Data were obtained with either wild type α7 nAChRs (filled circles) or α7 nAChRs containing the M253L mutation (open circles). Data are means ± SEM of at least three independent experiments, each from different oocytes.[54]

The agonist response induced by **23** displayed little evidence of desensitisation (**Figure 16 A (*Right*)**)[54], unlike the response observed with ACh (**Figure 16 A (*Left*)**.[54] The response that was generated by maximal concentration of **23** was larger (46 ± 9-fold) than the maximal acetylcholine responses recorded from the same oocyte (egg). An increase in the response was observed after agonist application ceased, which suggested channel blocking by **23**, in addition to its agonist action. Half maximal agonist activation required a lower concentration of **23** (EC_{50} = 10.1 ± 12.7 μM) than acetylcholine (EC_{50} = 128 ± 11.8 μM).[54]

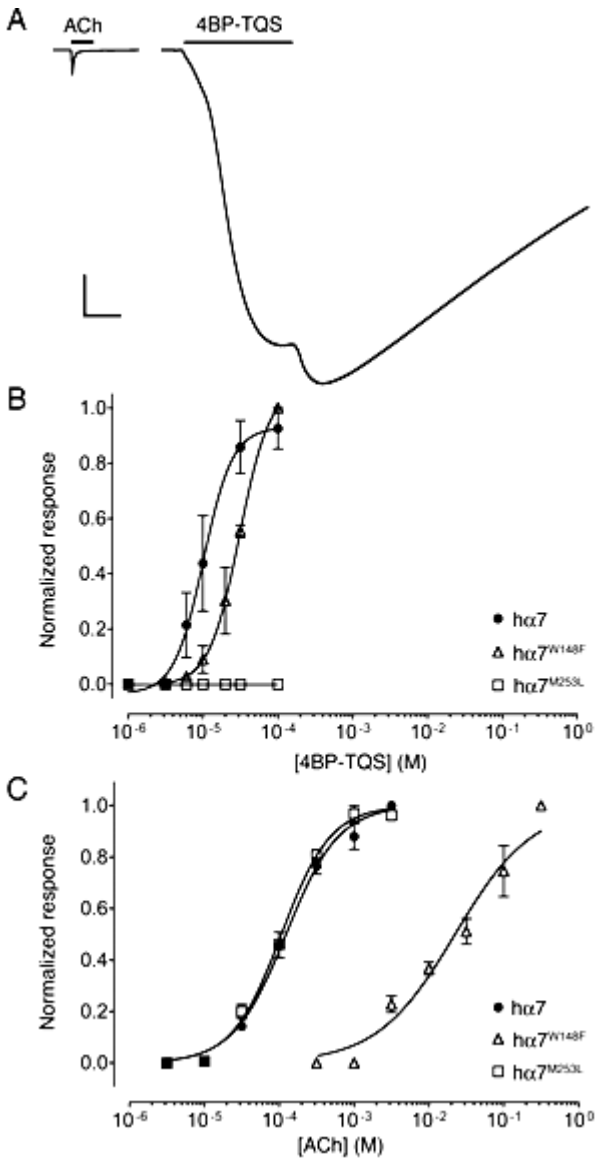


Figure 16.[54] Agonist activation of α7 nAChRs by acetylcholine and **23**, examined by two-electrode voltage-clamp recordings in *Xenopus* oocytes. (*A*) Representative recordings are shown illustrating responses to the application of acetylcholine (3 mM) (*Left*) and of **23** (60 μM) (*Right*) which were conducted 27 times. The duration of agonist applications are indicated by a horizontal line. (Scale bars: vertical, 1 μA; horizontal, 5 s). Dose- response data are presented for a range of concentrations of **23** (*B*) or acetylcholine (*C*) with wild type α7 nAChRs (filled circles) or with α7 nAChRs containing either the W148F mutation (open triangles) or the M253L mutation (open squares). Data are means ± SEM of at least three independent experiments, each from different oocytes.[54]

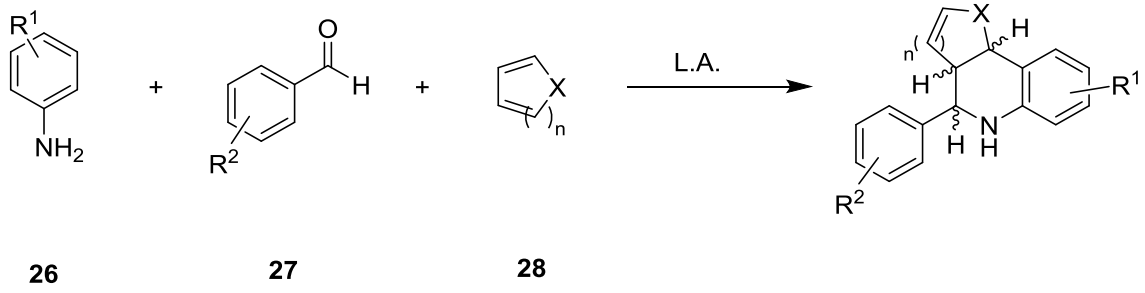
The differences in kinetics and the extent of receptor desensitisation were also observed with ACh and **23**.[54] In addition, mutagenic studies of the M253L mutation involving replacement of methionine for a leucine in the nAChR's transmembrane domain, led to complete loss of agonist induced response with **23 (Figure 16 B)**

whereas ACh showed agonist actiity on the mutant **(Figure 16 C)**. These studies, conducted by Millar and co-workers, supported the hypothesis that ACh and **23** activate α7 nAChRs through different binding sites. In contrast, a mutation known to be located close to the conventional agonist-binding site (W148F) had significantly greater effect on the agonist potency of ACh than **23 (Figure 16 B and C)**.[54] The site directed mutagenic studies support the hypothesis that **23** acts as an agonist by binding to the same allosteric site that is responsible for potentiation by PAMs such as **20** and **21**. It was suggested from computer docking simulations conducted with an α7 nAChR homology model that it is likely **23** acts as an agonist by binding at a similar location to **20**,[9] which has been previously reported to bind to an intrasubunit transmembrane cavity.[9, 56]

It has been reported that W148F is located close to the ACh binding site.[54] Similarly the M253L residue is located close to the binding site for **23**.[54] Further evidence that ACh and **23** bind to distinct sites comes from α7-selective antagonist studies with MLA **15**, which was found to be a competitive antagonist of ACh acting on α7 nAChRs,[57, 58] as demonstrated previously,[54] however, **15** was found to act as a non-competitive or reversible antagonist to responses induced by **22**.[8, 54] Taken together, these findings provided by Millar and co-workers suggested strong evidence that ACh and **23** cause agonistic activation of α7 nAChRs by binding to distinct orthosteric and allosteric sites, respectively.[8, 54]

2.1.1 Pavarov reaction

The Pavarov reaction is a variant of the hetero Diels-Alder reaction in which tetrahydroquinolines[59-61] are formed in a multicomponent fashion by the coupling of an aniline **26**, aldehyde **27**, and an alkene **28** *via* an in situ imine formation **(Scheme 9)**.



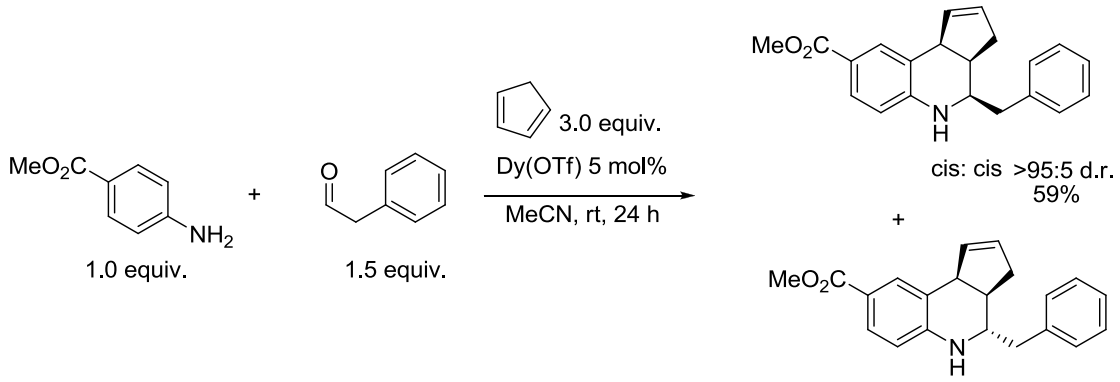
26 **27** **28**

Scheme 9. General scheme for the synthesis of tetrahydroquinoline compounds.

This reaction is proposed to follow by a [4 + 2] cycloaddition in a concerted process, or a stepwise intramolecular electrophilic aromatic substitution sequence.[59] Literature surrounding the Pavarov reaction have involved the use of expensive metal triflates,[62] triphenyl phosphonium perchlorate,[63] trifluoroacetic acid,[64] boron trifluoride diethyl ether,[59] and chiral lanthanide Lewis acids to catalyse the reaction.[65]

A wide variety of aniline and aldehydes are known to participate in the Pavarov reaction, however, the dienophile component is usually restricted to activated, electron rich alkenes, such as enol ethers and cyclic conjugated dienes.[59]

The stereochemical outcome of these reactions for example with cyclopentadiene as the dienophile have commonly observed a mixture of *cis*: *cis* and *cis*: *trans* diastereoisomers with no other isomer being detected **(Scheme 10)**.[66-68] The diastereoselectivity of the product formed has been associated with a number of factors such as temperature, solvent and the type of Lewis acid used. For example, Powell and Batey employed a mildly Lewis acidic lanthanide $DyOTf_3$ and maintained a low concentration of the imine upon addition of aldehyde **(Scheme 10)** to minimize competititve side reactions of these intermediates to maintain good yield and high diastereoselectivity.[69]



Scheme 10. Pavarov reaction catalysed by $Dy(OTf)_3$ showing selectivity for the *cis: cis* diastereoisomer as the major product over the *cis: trans* diastereoisomer.[69]

2.2 Aim and Objectives

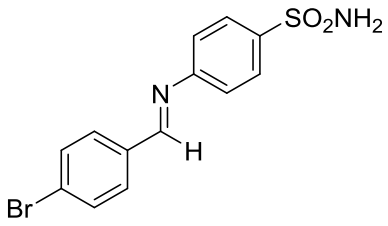
Having mentioned that the stereochemistry of **23** was unknown in Millar's study, it would therefore seem reasonable to prove which stereoisomers are formed in the Pavarov reaction, and thus to shed some light on which stereoisomer is biologically active. On establishing the stereochemistry of **23b**, which has been reported to bind to the intrasubunit transmembrane binding site,[54] analogues of compound **23b (Figure 16)** were synthesised in this project by applying a structure activity relationship (SAR) approach. This was to test for allosteric modulation and agonist activity at the α7 nAChR. The TQS analogues of **23b** can be readily synthesised *via* a Lewis-acid catalysed 3-component reaction between an aniline **26**, a substituted benzaldehyde **27** and a suitably activated alkene **28 (Scheme 9)**, most commonly known as the Pavarov reaction.[59]

Biological studies of these compounds will provide us with information to investigate their mode of binding at the α7 nAChRs, with a view to developing a detailed understanding of how subtype selective ligands interact with the α7 nAChR. These studies will provide us with information about whether these compounds could be used with the purpose of modulating the response of endogenous nAChR agonists, such as ACh. Compounds exhibiting allosteric behaviour at the α7 nAChR are currently being developed as possible treatments for Alzheimer's disease and

schizophrenia,[26] so there is scope for these compounds to be of therapeutic utility in the future.

2.3 Results and Discussion

The literature surrounding the synthesis of cyclopentaquinoline compounds are limited.[26, 67] In addition, the Lewis acids commonly used in the synthesis of other Pavarov reactions require long reaction times, some Lewis acids are expensive, too acidic or are moisture sensitive resulting in degradation, requiring excess amounts of Lewis acid to be employed. However, one of the major drawbacks with these Lewis acids is their limited substrate compatibility. A report by Perumal[67] and a patent by Becker *et al*. reported use of $InCl_3$ as the Lewis acid to be compatible with electron withdrawing groups, such as the sulphonamide functionality in sulphanilamide. Given that the stereochemistry of **23** was not known from Millar's study, using $InCl_3$, **23** was synthesised which was isolated as the *cis: cis* major isomer **23b** in 82% yield. The pharmacological response of **23** was found to be similar to the response initially reported for **23b** exhibiting 38 and 45 fold, respectively.[54, 71] This suggests that the stereochemistry of **23** might be the *cis: cis* isomer. Based on this study, this Lewis acid proved successful for the synthesis of **23b** from the preformed imine **29 (Figure 17)** and cyclopentaquinoline analogues of **23b** in the presence of cyclopentadiene as the dienophile and a substituted benzaldehyde in acetonitrile at room temperature.[26]



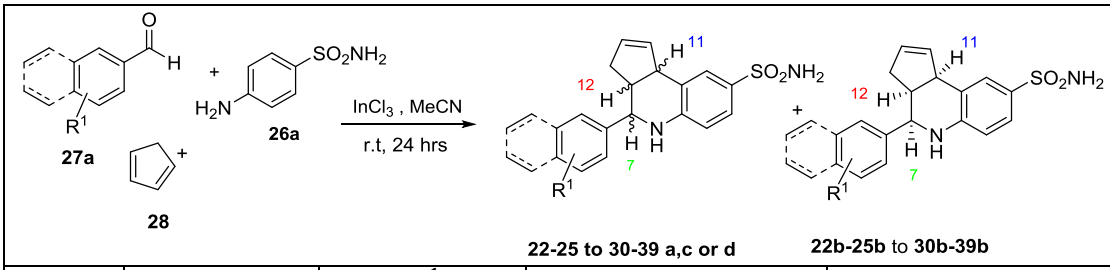
29

Figure 17

Our initial studies involved modifying the aldehyde component. The rationale behind synthesising these initial analogues was to compare the pharmacological response of **23b** with compounds when the position of the bromine atom is varied **(Table 2, Entry 3 and 13)** and when more than one bromine atom is present on the

phenyl ring **(Table 2, Entry 11).** The synthesis of analogues with increasing halogen atomic radii was also considered to be another approach to acquire interesting pharmacological data **(Table 2, Entry 2, 4 and 7)**. Modifications by incorporating a hydrogen **(Table 2, Entry 1),** methyl group **(Table 2, Entry 12)** and a hydroxyl group **(Table 2, Entry 5)** at the para position on the phenyl group, and a bioisostere of bromine such as a triflouromethyl group at the para position on the phenyl were also considered **(Table 2, Entry 10).** In addition, it seemed sensible to synthesise an analogue 2-Napthyl-TQS **25b (Table 2, Entry 9)** of the well documented 1-Napthyl-TQS **22b (Table 2, Entry 14)** given that it acts as a potent type II PAM as reported by Gill. It is worth mentioning that the diastereoisomer of the previously documented compound **22** was not known.[54]

In all cases the reaction proceeded smoothly to give the corresponding cyclopentaquinolines **(Table 2, Entry 1-14)** as the *cis: cis* diastereoisomer from the four possible conformations in **Scheme 11**.



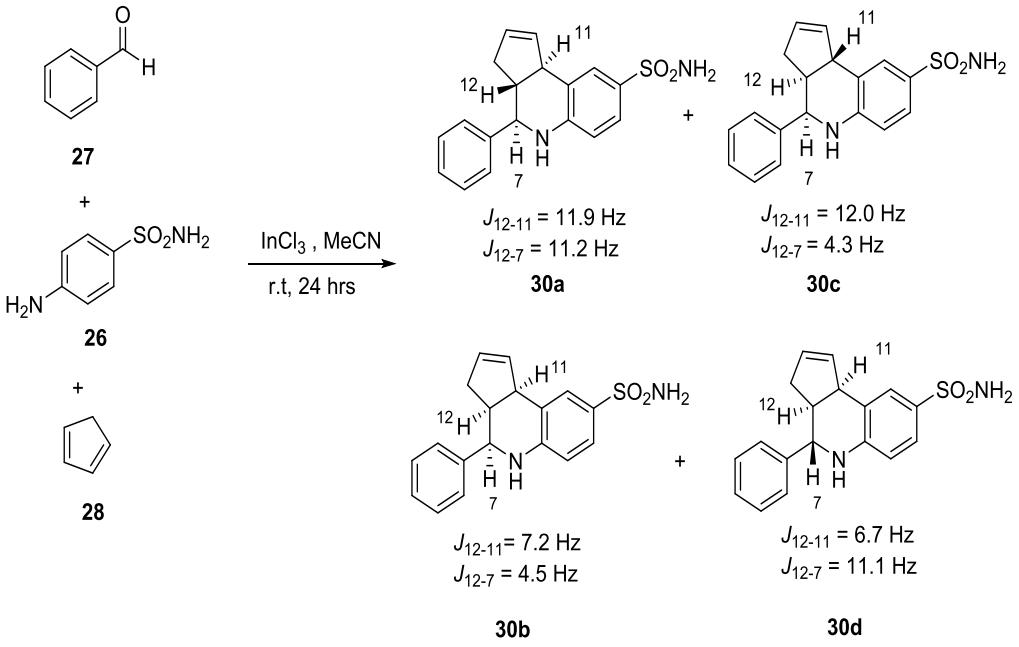
Entry	No.	R^1	dr (22-25b to 30b-39b: unknown[(b)])	Yield (%)
1	**30b**	4-H	95: 5	51
2	**23b**	4-Br	95: 5	82 [(a)]
3	**31b**	3-Br	95: 5	49
4	**32b**	4-Cl	95: 5	63
5	**33b**	4-OH	81 : 19	32
6	**24b**	4-F	89 : 11	2
7	**34b**	4-I	92 : 8	15
8	**35b[(c)]**	3-I	(c)	8
9	**25b**	2-Napth	92 : 8	9
10	**36b**	4-CF_3	95 :5	72
11	**37b**	3,4-DiBr	95 :5	37

12	**38b**	4-Me	95 :5	44
13	**39b**	2-Br	95 :5	60
14	**22b**	1-Napth	83: 17	22

Table 2 (a) Product made *via* the preformed imine **29** (b) Configuration of minor isomer not determined for **22b-25b** to **30b-39b**; (c) Ratio of isomers could not be determined from crude nmr as broad peaks were observed, however, after purification the isomer **35b** was observed.

The structural assignment of *cis*- and *trans*-isomers was made on the basis of comparing the measured coupling constant values between protons $-C_{12}H$ and $-C_{11}H$ and protons $-C_{12}H$ and $-C_{7}H$ **(Scheme 11)** by ^{1}H NMR and the calculated coupling csonstant values of the protons determined using PC model system v8.5 software, under the guidance of Dr. Abil Aliev.

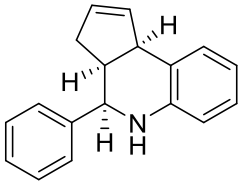
For example in **(Table 2, Entry 1),** ^{1}H NMR analysis of the reaction between benzaldehyde **27**, sulphanilamide **26** and cyclopentadiene **28** showed stereoselectivity for the *cis-cis* diastereoisomer **30b** entirely, out of the four possible stereoisomers.



Scheme 11. Structure of four possible diastereoisomers of **30** formed during the reaction with their calculated coupling constant values (Hz), determined by PC Model system v8.5 software.

The structural assignment of **27b** was made on the basis of the measured coupling constant values by ^{1}H NMR ($J_{12\text{-}11}$ = 8.7 Hz and $J_{12\text{-}7}$ = 3.2 Hz). The computer model

system showed that the coupling constant values were consistent with the *cis-cis* configuration **30b (Figure 19)** with calculated coupling constant values $J_{12\text{-}11}$= 7.2 Hz and $J_{12\text{-}7}$ = 4.5 Hz, respectively **(Table 3)**. This stereochemistry measured is further supported by Perumal and co-workers, reporting coupling constant values of $J_{12\text{-}11}$ = 8.6 and $J_{12\text{-}7}$ = 2.9 Hz, respectively for the structure shown below **40b (Figure 18)**.[67]



40b

Figure 18.

On using the computer model system to determine the torsion angle between protons (H-12-C-12-C-11-H-11) for the model structure for **Entry 1** was calculated to be -34.1˚, which is consistent with the measured coupling constant of $J_{12\text{-}11}$ = 8.7 Hz by ^{1}H NMR as mentioned before for **30b**. Similarly, torsion angle (H-12-C-C-7-H-7) for the model structure was calculated to be 53.8˚ which is consistent with the observed coupling constant $J_{12\text{-}7}$ = 3.1 Hz, with a syn relationship for these protons **(Figure 19)**. In contrast, coupling constant values calculated by the model system for isomers **30a** ($J_{12\text{-}11}$ = 11.9 Hz and $J_{12\text{-}7}$ = 11.2 Hz), **30c** ($J_{12\text{-}11}$ = 12.0 Hz and $J_{12\text{-}7}$ = 4.3 Hz and **30d** ($J_{12\text{-}11}$ = 6.7 Hz and $J_{12\text{-}7}$ = 11.1 Hz) did not correspond with the measured coupling constant values for **30b** determined by ^{1}H NMR.

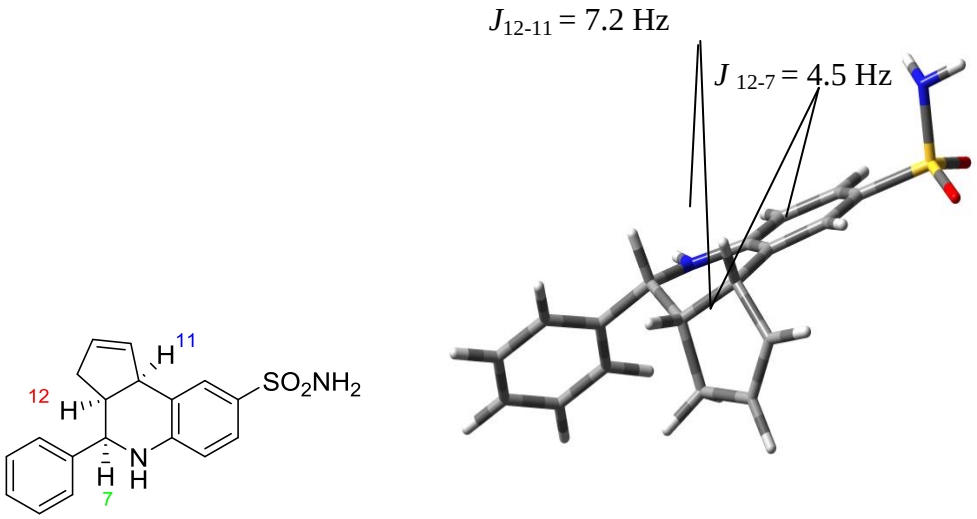


Figure 19. Calculated structure of compound **30b** determined by PC Model system v8.5 software.

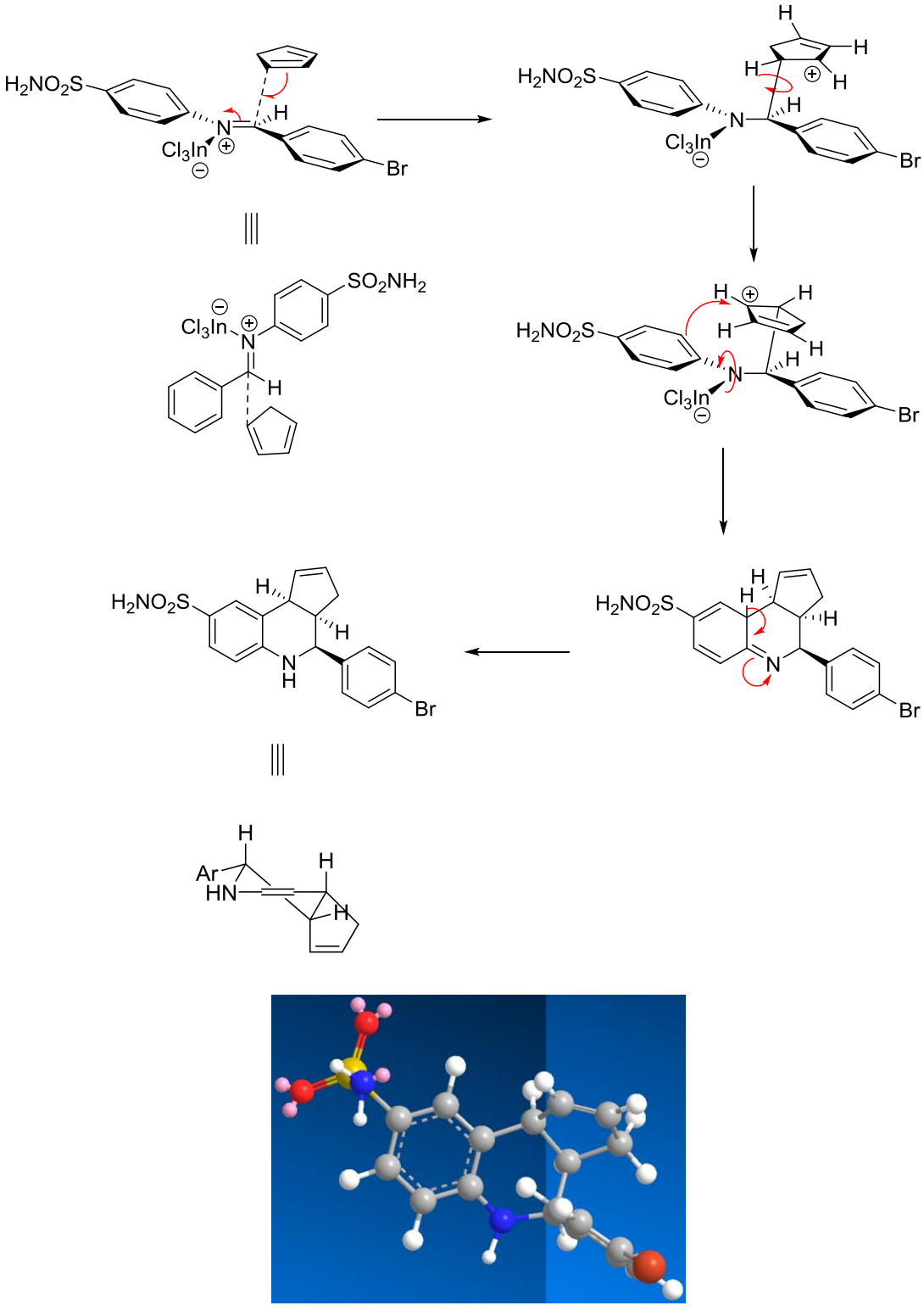
Similar coupling constants were measured for other cyclopentaquinoline compounds synthesised, further supporting the synthesis of all *cis: cis* diastereoisomer in each case. Calculated and measured coupling constants for compounds **22b-25b** and **30b-39b** are tabulated below **(Table 3)**.

R-1	Compound No.	$J_{12\text{-}11}$ measured (Hz) for 22b-25b to 30b-39b	$J_{12\text{-}11}$ calculated (Hz) for 22b-25to 30b-39b.	$J_{12\text{-}7}$ measured (Hz) for 22b-25b to 30b-39b.	$J_{12\text{-}7}$ calculated (Hz) for 22b-25b to 30b-39b
4-Br	**23b**	8.7	7.2	3.1	3.2
3-Br	**31b**	8.5	7.1	3.1	3.2
4-Cl	**32b**	9.0	7.1	3.1	3.2
4-OH	**33b**	8.1	7.1	3.1	3.2
4-F	**24b**	8.8	7.1	3.4	3.2
4-I	**34b**	8.7	7.1	3.3	3.2
3-I	**35b**	8.5	7.1	2.6	3.2
2-Napth	**25b**	8.4	7.1	2.7	3.2
4CF_3	**36b**	8.5	7.0	2.7	3.1

3,4-DiBr	**37b**	8.7	7.1	3.2	3.2
4-Me	**38b**	8.4	7.1	3.4	3.3
2-Br	**39b**	7.0	6.7	2.9	3.0
1Napth	**22b**	8.8	6.8	1.6	3.0

Table 3. Measured coupling constants (Hz) determined by ^{1}H NMR and measured coupling constants (Hz) determined by PC Model system v8.5 software.

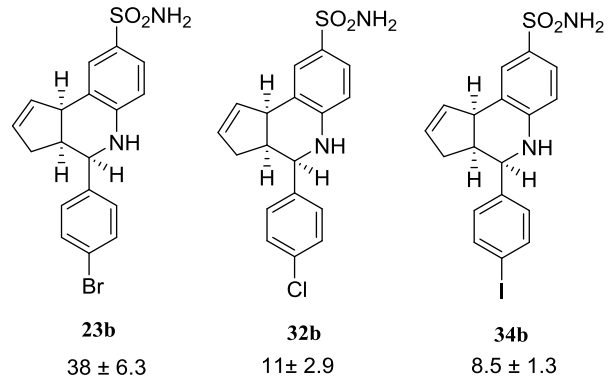
The mechanism for this multicomponent reaction is still under debate but has been proposed to occur *via* a stepwise mechanism as suggested by Whiting **(Scheme 12).**[70] The postulated mechanism is thought to occur by nucleophilic attack of the cyclopentadiene on the top face of the activated imine, since the imine is not electrophilic enough for a nucleophlilic attack, a suitable Lewis acid is used such as $InCl_3$. The new carbon-carbon bond formed rotates to enable nucleophilic attack by the aromatic ring on the carbocation. Re-aromatisation then drives the reaction to favour the observed *cis: cis* diastereoisomer.



Scheme 12. Proposed mechanism towards the *cis: cis* isomer, (below) 3D structure of **23b**.[70]

2.4 Biological testing results (work conducted by JasKiran Gill and Neil Millar, at UCL Pharmacology)

It was of interest to initially study the allosteric agonist response of the *para*-halogenated TQS compounds and to compare it with the agonist response of **23b**. As observed previously for **23b**, compounds containing either a chlorine or an iodine atom at the *para* position (**32b** and **34b**, respectively) were found to have potent agonist activity on α7 nAChRs **(Figure 18 and 19)**.



23b 38 ± 6.3 | **32b** 11± 2.9 | **34b** 8.5 ± 1.3

36b 0.9 ± 0.14 | **25b** 2.0 ± 0.4 | **38b** 9.3 ± 1.4

Figure 18. Compounds exhibiting allosteric agonist activity at the α7 nAChRs together with their potency values *I*max (fold > 3mM ACh).

However, replacement of the bromine atom at the para position for a fluorine atom (**24b**) led to a complete loss of agonist activity **(Figure 19)**. The half maximal agonist response (EC_{50}) values determined for **23b**, **32b**, and **34b** were not significantly different from one another. Interestingly, the agonist concentrations of these compounds causing half-maximal activation were significantly lower than that of acetylcholine (EC_{50} 128 ± 12 μM).

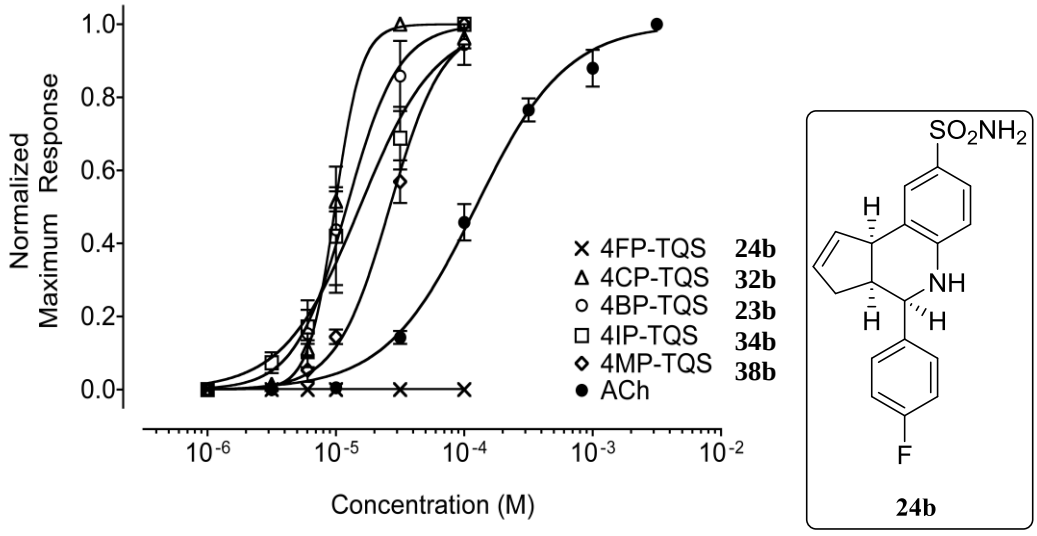


Figure 19. Dose response curve[71] and structure of **24b.**

Activation of α7 nAChRs by acetylcholine results in rapidly desensitising responses when ACh is applied for a long duration as previously reported by Couturier.[55] When α7 nAChR activation with *p*-halogenated TQS compounds was studied **(Table 4).**[72] A significant slowing in the rate of desensitisation was observed as the atomic radii of the halogen increased, with **23b** and **34b** showing largely non-desensitizing responses[54] when examined over a long timescale (**Figure 20)**.

Substituent	Van der Waals radii (Å)
H	1.20
F	1.47
Cl	1.77
Br	1.92
I	2.06
Me	2.0[(b)]
O of OH	1.52

Table 4. Showing the effective van der waals radii value of bound substituent on phenyl from liquid state calulations r_w, Å.[(b)] Van der Waals radii value of a free methyl group (Å). [73]

Interestingly, when a halogen at the *para* position was replaced with a methyl group, long applications resulted in a similar non-desensitizing response as observed with

23b and **34b**. This might be due to the similar atomic radii of the methyl group compared to bromo and iodo group **(Table 4).**

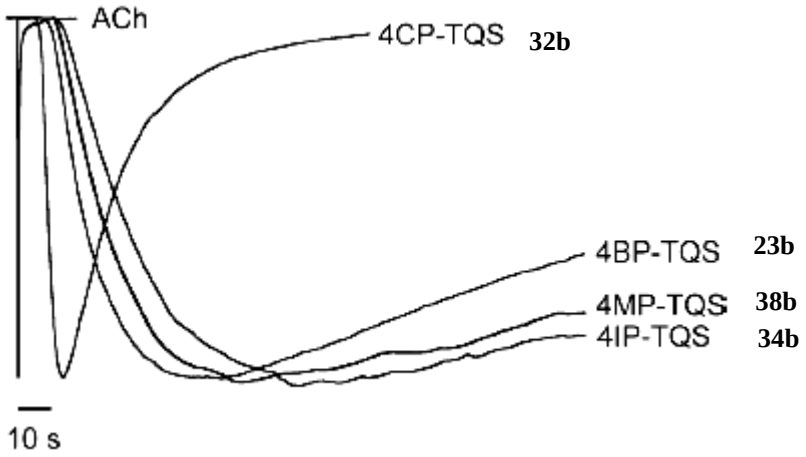


Figure 20. Graph illustrating the activation and desensitisaton rates upon continued exposure of maximum concentration of agonist on the α7 nAChR. [71]

In addition, the rate at which receptors return to their resting state after agonist activation differs between the three halogen-containing agonists **(Figure 20)**. Rates of desensitisation, rates of activation, and also rates of recovery after removal of agonist were found to increase as the size of the halogen atom decreased **(Figure 20).** However, introduction of the fluorine atom at this position (**24b**) resulted in a complete loss of agonist activity. A further difference in activation by acetylcholine and by **23b**, **32b** or **34b** is the slower activation rate that is observed with the latter compounds **(Figure 20)**. However, in all cases, levels of desensitization caused by these compounds were much slower than the very rapid desensitization that is characteristic of α7 nAChRs when activated by acetylcholine.[55]

The differences in activation rates of para-halogenated TQS compounds prompted our collaborators to examine the consequence of coapplication of acetylcholine with allosteric agonist **34b (Figure 21).** This was to see if allosteric agonists can potentiate/increase the ACh response at the α7 nAChRs when co-applied. Although this was not observed, interestingly, the response of receptor activation obtained can be explained by dividing the response into two components **(Figure 21)**. The initial response is the rapid activation and desensitisation, characteristic of ACh activation. This is followed by a secondary response, which is a slow but increased rate of activation and very slow desensitisation, characteristic of the **34b** response when applied on its own **(Figure 21)**. These two components of the agonist response are,

presumably, a consequence of the ability of acetylcholine to access its extracellular orthosteric binding site more rapidly than the allosteric agonists are able to access their binding sites.

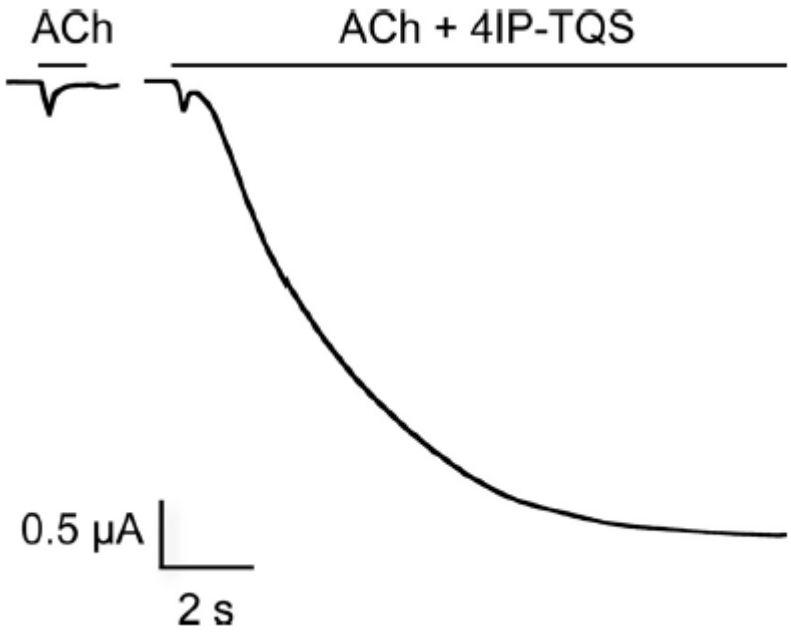


Figure 21. Profile showing activation of α7 nAChR by acetylcholine (3mM) (left), (right) profile showing activation upon coapplication of acetylcholine (3 mM) with 4IP-TQS **34b** (100 μM). [71]

This observation is further evidence for a difference in the mechanism of action of these two classes of agonist. In previous studies Millar and co-workers have demonstrated that the response to a submaximal concentration of **23b** is greatly potentiated by the subsequent coapplication of acetylcholine, indicating that **23b** may be more potent as a positive allosteric modulator than as an allosteric agonist.[54] Similar experiments conducted with other allosteric agonists described in the present study suggest that this is a common phenomenon for this series of compounds.

Interestingly, **35b** and **36b** also exhibited allosteric agonist responses at the α7 nAChR. However, their responses were much lower in comparison to the *para*-halogenated compound and **38b** with I_{max} values of 2.0 ± 0.4 and 0.94 ± 0.14, respectively **(Figure 22).**[71]

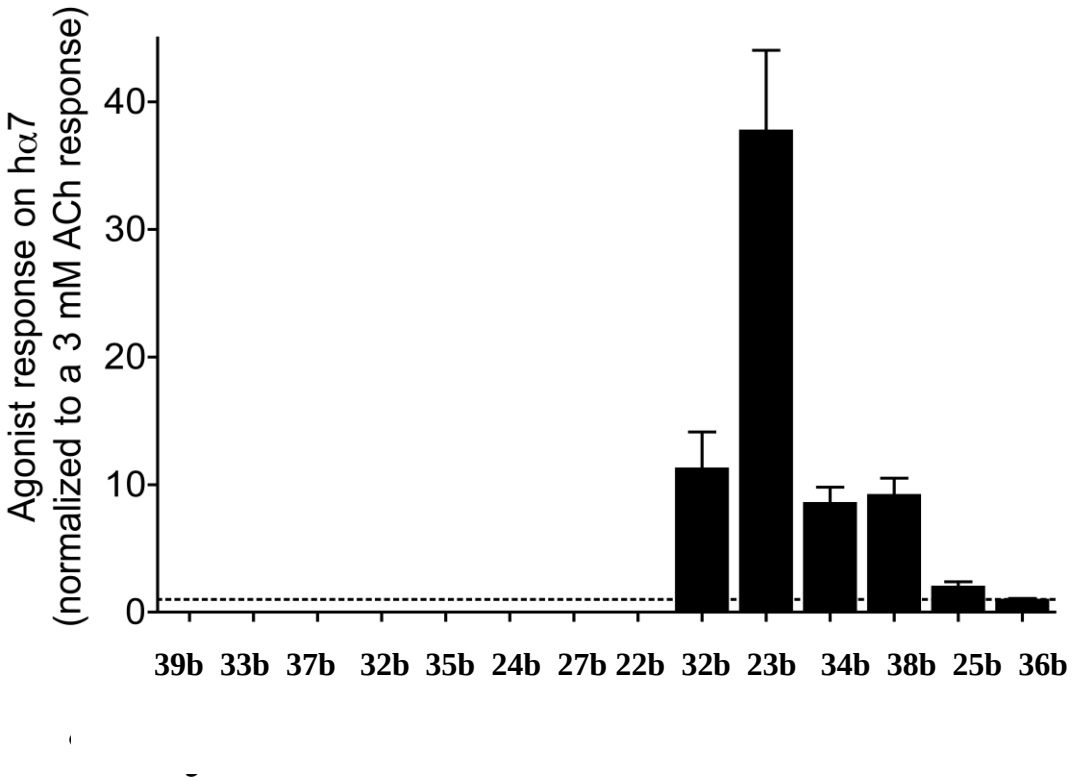


Figure 22. Bar graph of TQS compounds with allosteric agonist responses at the α7 nAChR.[71]

Of particular note, a much faster activation rate was observed with ACh than with any of the allosteric agonists examined.

2.4.1 PAM activity at the α7 nAChR

The pharmacological effect of the relative influence of the size and position of other groups attached to the phenyl ring were examined. Inclusion of a hydrogen atom or hydroxyl group at the para-position (**30b** and **33b**) resulted in complete loss of agonist activity **(Figure 22),** with atomic radii values of 1.20 and 1.54 Å **(Table 4)** respectively, which are significantly smaller in comparison to the atomic radii values of the halogens **(Table 4).** These findings support the conclusion that a relatively large group attached to the 4-position of the phenyl ring is required for agonist activity. In addition, **25b**, in which the naphthyl group is attached in an orientation different from that in TQS **22b (Figure 22)** displayed agonist activity in contrast to **22b**.[54] Taken together, these findings provide strong evidence that a relatively large group is required at the 4-position of the phenyl ring to confer agonist activity.

Despite the lack of agonist activity observed with **22b**, in all cases, PAM activity was retained **(Figure 23 and 24).** It seems, therefore, that relatively minor changes to the structure of these compounds can have a profound influence on their pharmacological properties. It is possible that these differences can be explained entirely by steric effects. For example, the slower activation rate observed with **34b** than with either **23b** or **32b** may be a consequence of reduced accessibility to its binding site.

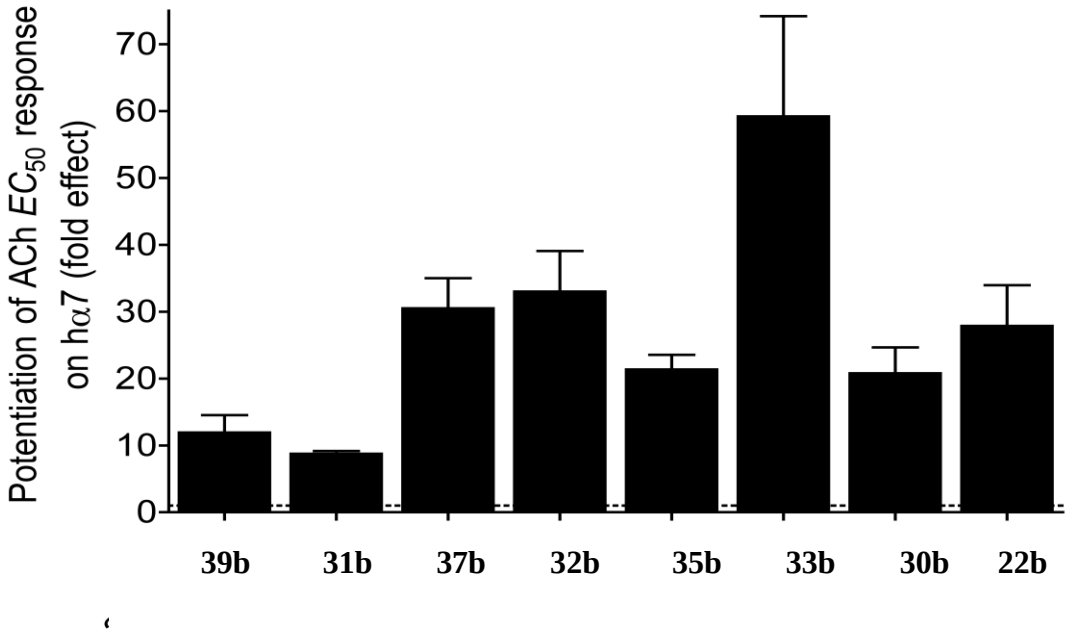


Figure 23 Bar graph of TQS compounds with type II PAM responses at the α7 nAChR [71]

Although it is possible that the differences in size between fluorine and the other three halogens could explain the differences in agonist activity observed, differences in chemical properties may also be significant. For example, halogens differ in their electrostatic surface potential and eletronegativities. Indeed, such differences have been suggested to be responsible for the ability of organic compounds containing chlorine, bromine, or iodine (but not those containing fluorine) to form halogen bonds.[74, 75] However, the fact that agonist activity was seen when the halogen atom was replaced by a methyl group **38b** or a trifluoromethyl group **36b** but not when it was replaced with a hydrogen atom **30b** or a hydroxyl group **33b** suggests that the sterics and not electronics of the group attached to the 4-position of the phenyl ring

may be more important than its electrostatic properties in determining allosteric agonist activity.

It is clear that alterations at the para-position of the phenyl ring have a dramatic effect on the agonist effects of this series of compounds. It is also of interest that the compounds lacking agonist activity (**39b**, **31b**, **35b**, **37b**, **24b**, **33b**, and **30b**), all increased acetylcholine-induced responses **(Figure 24)** when tested for PAM activity.[46, 54]

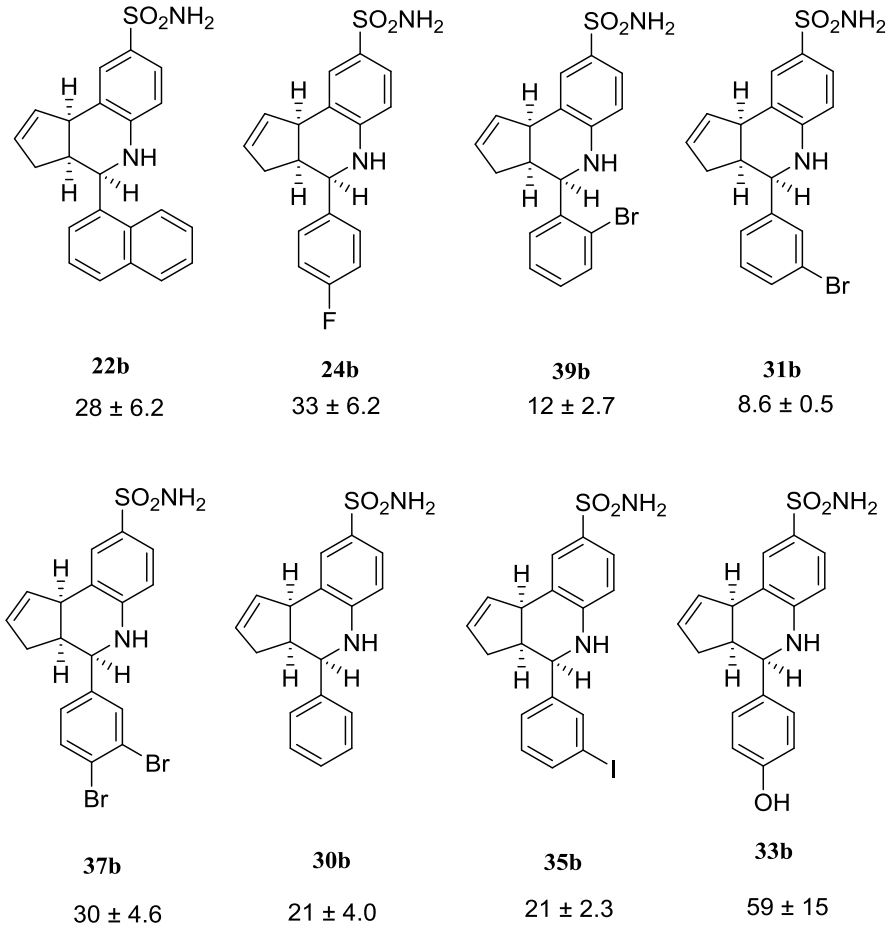


Figure 24. Compounds exhibiting positive allosteric agonist activity together with their potency values fold Potentiation values refers to sub maximal (EC_{50}) concentration of ACh (100 µM). *I*max Potency (fold > 100µM ACh).

Such effects are typical of a range of compounds that have been described as nAChR PAMs. Relatively small changes in chemical structure result in clear pharmacological differences. For example, as has been reported previously,[46, 54] minimal desensitization is observed with TQS **22b (Figure 25 A),** which acts as a

classic "type II" PAM, causing potentiation of acetylcholine evoked responses and a dramatic loss of receptor desensitization. In contrast, progressively faster rates of desensitization were observed with the other PAMs examined **(Figure 25 B).** The terms "type I" and "type II" have been used extensively to describe PAMs acting on α7 nAChRs that either have no effect on receptor desensitization (type I) or cause a loss of desensitization (type II). Just as differences were observed in the rates of desensitization of α7 nAChRs after activation by **23b**, **32b**, and **33b**, our collaborators JasKiran Gill and Neil Millar observed a marked difference in the rate of desensitization after potentiation of acetylcholine-evoked responses with different PAMs **(Figure 25)**.[71]

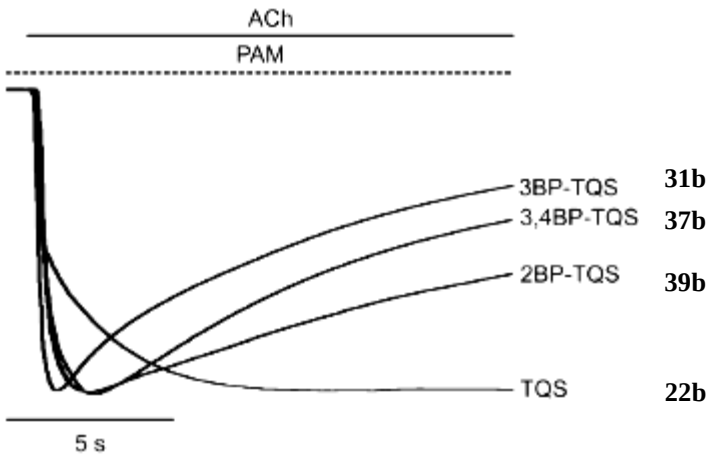


Figure 25A. Graph illustrating the differences in activation and desensitization rates for various PAMs. The PAM (100 μM) was preapplied for 5 s and then coapplied with a submaximal (EC_{50}) concentration of acetylcholine (100 μM).[71]

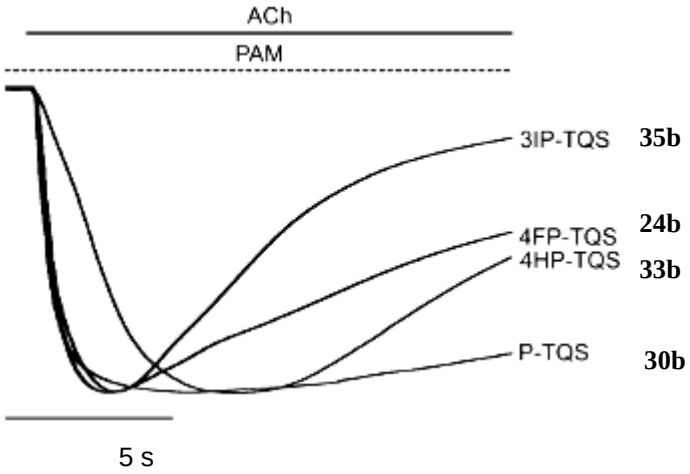


Figure 25B. Graph illustrating the differences in activation and desensitization rates for various PAMs. The PAM (100 μM) was preapplied for 5 s and then coapplied with a submaximal (EC_{50}) concentration of acetylcholine (100 μM) [71]

This study suggests that in addition to the size of the halogen atom being important in determining pharmacological properties, the position of the halogen is also critical. This was illustrated by the finding that changing the location of the bromine from the *para* position to either the *ortho* or *meta* position and changing the position of iodine from the *para* position to *meta* position resulted in loss of agonist activity (**39b**, **31b** and **35b**), respectively **(Figure 25A).** Likewise, no agonist activity was observed for **37b**, indicating that the allosteric agonist properties of **23b** can also be lost by the addition of a second halogen atom to the phenyl ring at the 3 position. Taken together, these results clearly show that the position, as well as the size, of groups attached to the phenyl ring is critical in determining agonist activity.

2.4.2 Antagonism by 4FP-TQS 24b of 4BP-TQS 28b Evoked Responses

As has been described above, the replacement of a single bromine atom with a fluorine atom converts the allosteric agonist **23b** into a PAM that lacks agonist activity **24b**. On the basis of previous studies with α7- selective allosteric modulators,[54 76] it seems reasonable to hypothesize that **23b** (an allosteric agonist) and **24b** (a type II PAM) might bind competitively at a common allosteric site. Hence, would be reasonable to predict that **24b** would act as an antagonist if coapplied with **23b,** if the hypothesis is correct. The hypothesis was tested by applying **23b** (10 μM) and then coapplying **23b** with a range of concentrations of **24b (Figure 26).** As predicted, the coapplication of **24b** resulted in a dose dependent inhibition of responses evoked by **23b**, with an IC_{50} concentration of 4.4 ±1.3 μM **(Figure 26).**

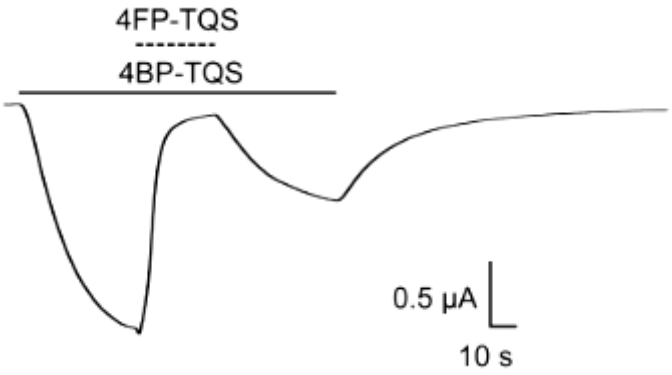


Figure 26. Antagonism by 4FP-TQS **24b** of 4BP-TQS **23b**-evoked responses on α7 nAChRs.Graph showing activation of wild-type α7 nAChRs by 4BP-TQS **23b** (10 µM) followed by the coapplication of 4FP-TQS **24b** (100 µM). [71]

In contrast, coapplication of 4FP-TQS **24b** with acetylcholine results in a dose-dependent potentiation of responses evoked by acetylcholine, with an EC_{50} concentration of 23 ± 8.1 µM **(Figure 27)** at the native α7 receptor. However, no potentiation of ACh by **24b** was observed at the mutant α7 receptor.

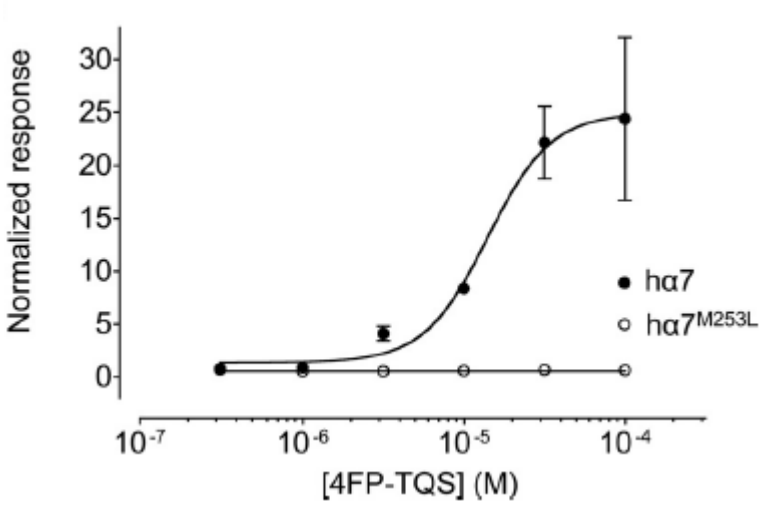


Figure 27. Dose-response data presented for a range of concentrations of 4FP-TQS on responses evoked by a submaximal (EC_{50}) concentration of ACh with either wild-type α7 nAChRs or α7 nAChRs containing the M253L mutation[71]

These findings suggest that **23b** and **24b** bind to a common site, which is distinct from that of acetylcholine. It was also demonstrated that α7 nAChR PAMs such as **24b** can act as antagonists of responses evoked by allosteric agonists such as **23b**. The simplest explanation for this observation is that these two chemically similar

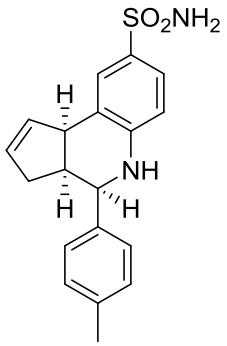
allosteric modulators interact at a common site. The binding of a PAM such as **24b** to its allosteric site can have two different effects: allosteric potentiation of responses to orthosteric agonists such as acetylcholine and antagonism of responses to allosteric agonists such as **24b**. The former is presumably a consequence of **24b** and acetylcholine binding to different sites, and the latter is a consequence of **24b** and **23b** binding competitively to a common site.

2.4.3 Influence of the Transmembrane M253L Mutation

It is well established that acetylcholine activates nAChRs by binding to an extracellular site. In contrast, recent studies have proposed that α7-selective PAMs such as **22b** and allosteric agonists such as **23b** act *via* a transmembrane binding site.[54, 76, 77] Evidence supporting this proposal is that potentiation by **22b** and agonist activation by **23b** are completely suppressed on α7 receptors containing the transmembrane mutation M253L.[54] In contrast, M253L has been shown to have no significant effect on activation by the conventional orthosteric agonist acetylcholine.[54] The effect of M253L on agonist activation by **32b**, **34b**, and **38b** were examined, and it was found to cause complete loss of agonist activation. In addition, the effect of M253L on allosteric potentiation by **30b, 31b**, **33b, 24b, 35b**, **37b**, and **39b** were examined, a complete loss of PAM activity of these compounds were observed. These findings support the conclusion that all of the TQS-related compounds examined in this study act by a similar mechanism of action. The simplest explanation is that they all act *via* a common allosteric binding site, as has been proposed previously for **22b** and **23b**.[54]

2.4.4 Conclusion

1) Allosteric agonists and PAMs of α7 nAChRs bind to a common transmembrane site.[54, 76, 77] This is supported by evidence that the effects of both allosteric agonists and PAMs can be blocked completely by a single point mutation (M253L) located in the transmembrane region: a mutation that has no significant effect on agonist activation by acetylcholine.[76]
2) As atomic radius of the halogen increases the rate of desensitisation is slowed significantly.
3) **38b** elicits allosteric agonist activity at the α7 nAChRs suggesting that sterics not electronics governs allosteric agonist activity **(Figure 28).**



38b

Figure 28. Structure of **38b.**

4) Both allosteric agonists and PAMs are presumably able to stabilise the open state of the receptor.
5) The difference between the two classes of allosteric modulator is that those compounds that lack agonist activity are able to stabilise the open conformation of the receptor efficiently only in the presence an orthosteric agonist, such as acetylcholine.

2.5 Synthesis of methylated TQS compounds

Having previously reported that **38b** elicits allosteric agonist activity at the α7 nAChR,[71] it was proposed that subtle changes to the TQS structure were made by varying the position of the methyl group, as well as the number of methyl groups attached to the phenyl group. This might result in differences in the chemical and pharmacological properties as was observed with the halogenated TQS compounds.

There are 19 different benzaldehydes incorporating only methyl substituents on the aromatic ring, of which 13 of these methyl benzaldehydes are commercially available. The other 6 methyl benzaldehydes are not commercially available and were synthesised **(Figure 29)**.

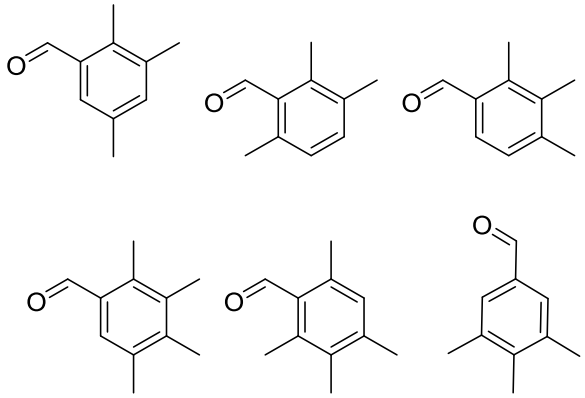
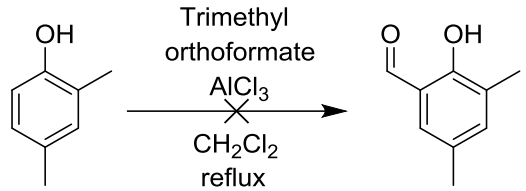


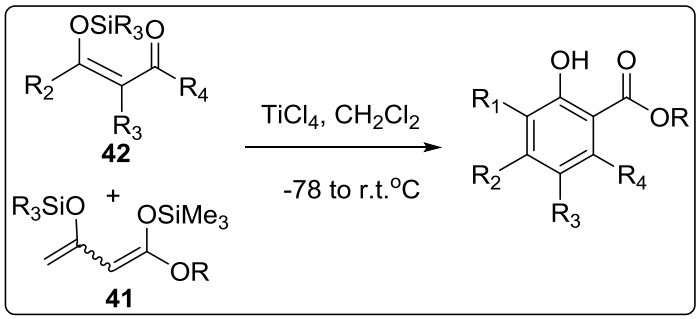
Figure 29. Structures of substituted methyl benzaldehydes that are not commercially available.

Literature surrounding the synthesis of the 6 non-commercial methyl benzaldehydes are limited, with use of reagents such as sulphuric acid,[78] potassium permanganate,[79] titanium tetrachloride,[80] carbon disulphide[81] and NaOH (16 M) in the Reimer Teimann reaction.[82] However, neither seemed promising as some conditions either require use of starting materials and reagents which are expensive, the reaction results in a mixture of products, requires harsh conditions or is laborious. Although a mild procedure using trimethyl- or triethyl- orthoformate seemed a promising approach to synthesise the corresponding benzaldehyde in one step,[83] no reaction occurred, affording just the starting material **(Scheme 13)**.



Scheme 13. Reaction of 2, 4-dimethyl phenol with trimethyl orthoformate and aluminium trichloride.

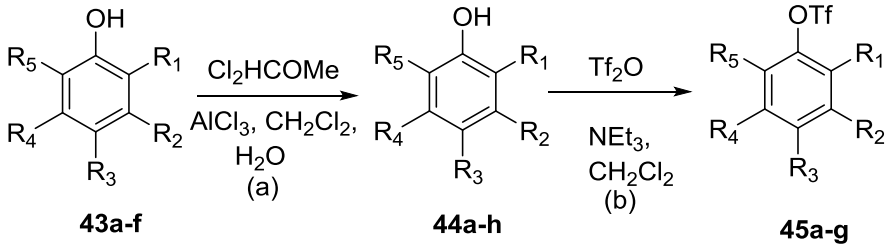
Some years ago Langer and co-workers demonstrated that salicylates can be formed by $TiCl_4$-mediated [3+3] cyclization of 1,3-bis (silyl enol ethers) **41** with 4-(silyloxy)pent3-en-2-ones **42** in moderate to good yields **(Scheme 14)**.[84] However, overall this method is laborious as the starting materials need to be synthesised, in addition triflation of the hydroxyl group and reduction to the corresponding aldehyde adds additional steps. An alternative approach was to synthesise these compounds from more readily available aryl precursors.

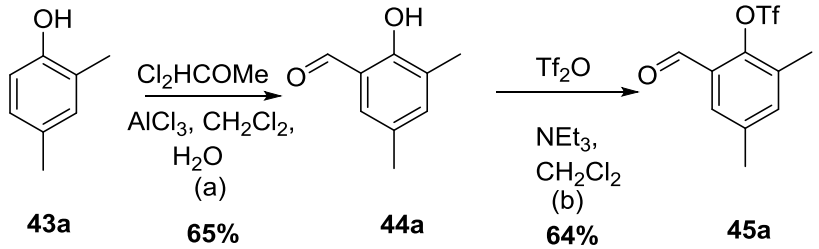


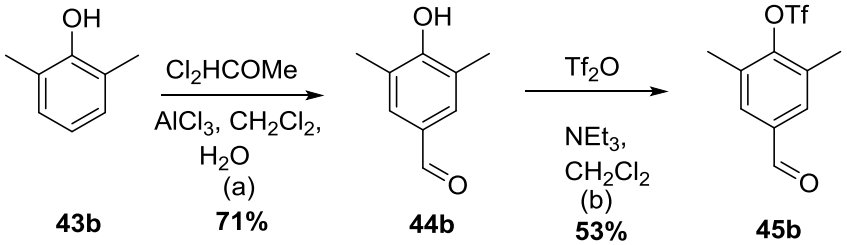
Scheme 14. General scheme for the synthesis of salicylates under Lindel's reaction conditions.[84]

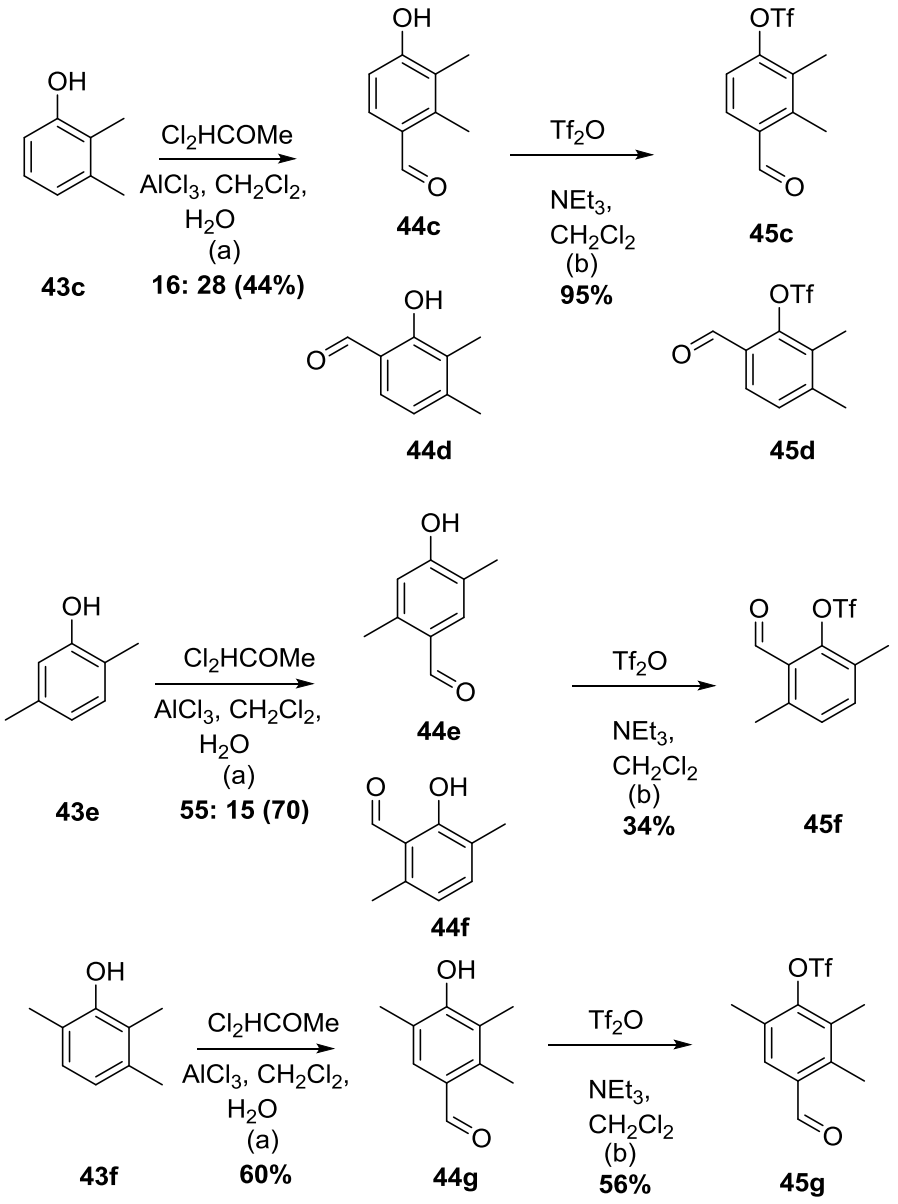
2.6.1 Synthetic route towards methyl substituted benzaldehydes.

Given that many poly-methylated phenols are cheap and commercially available, we envisaged that the desired methyl benzaldehydes could potentially be synthesised by formylation of the corresponding phenol in an electrophilic aromatic substitution reaction with dichloromethyl methyl ether in the presence of a Lewis acid,[85] followed by cross-coupling of the phenol-derived triflate[85] with methylboronic acid.[86]







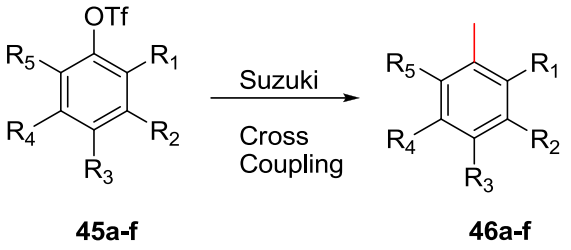


Scheme 14 (a) Product **44a-g**: $AlCl_3$ (1.2 eq), Cl_2HCOMe (1.2 eq), -10°C in CH_2Cl_2, -10°C, 2 hrs.[85] b) Product **45a-g** : NEt_3 (3eq), Tf_2O (1.1 eq), CH_2Cl_2, -78°C, 2.5 hrs.[85]

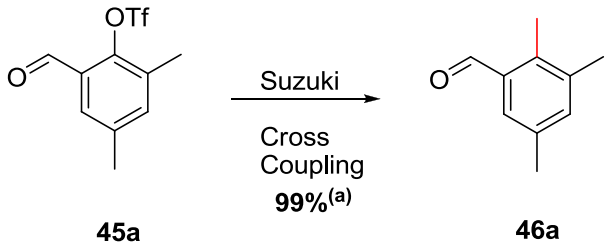
The phenols **43a-e** underwent formylation with dichloromethyl methyl ether and $AlCl_3$ in moderate to good yields to give aldehydes **44a-g**, which was converted into the corresponding trifluoromethanesulfonates **45a-f (Scheme 14)**. The formylation of phenols **43c** and **43d** gave a mixture of isomeric aldehydes where **43d** gave the major product as the undesired *para*-substitution product **44e**. The desired *ortho*-substitution product **44f** was therefore obtained selectively by column chromatography isolated in 15%. This was subsequently converted into aryl trifluoromethanesulfonate **45e (Scheme 14)**. The formylation of phenol **43c**, gave a mixture of isomeric aldehydes **44c** and **44d**, which were converted to a mixture of the two corresponding triflates **45c** and **45d**. This

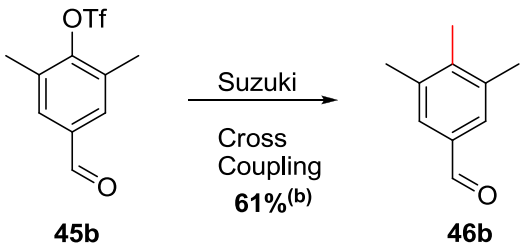
mixture of isomers is not problematic as both triflates **45c** and **45d** will be converted into aldehyde **46d** upon Suzuki coupling with methyl boronic acid.

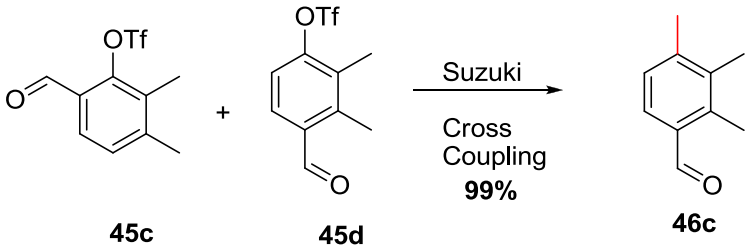
With the desired trifluoromethansulfonates in hand, we then turned our attention to the proposed Suzuki cross-coupling with methyl boronic acid **(Scheme 15 and 16(b)).** A procedure reported by Molander[86] involving use of (dppf)$PdCl_2$ as the catalyst for the cross-coupling of methyl boronic acid with aryl triflates proved successful, giving excellent conversion of the aryl trifluoromethanesulfonates **45a-f** to give the desired product **46a-f**.

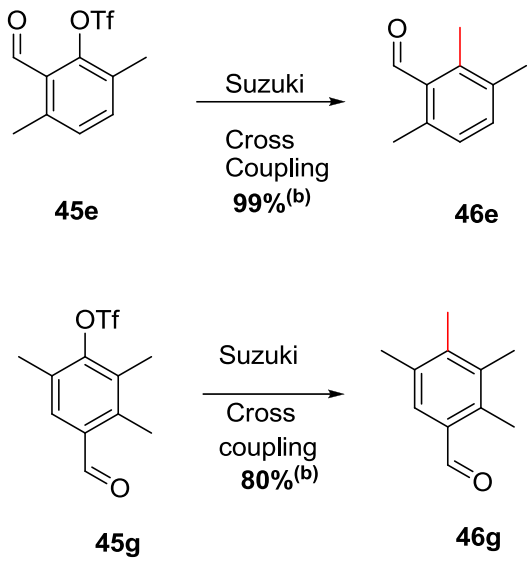


Scheme 14



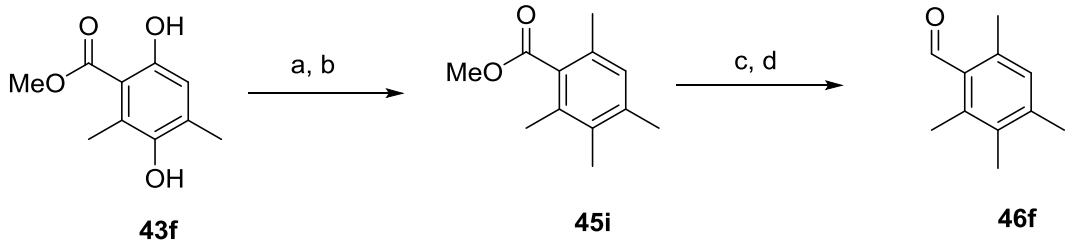






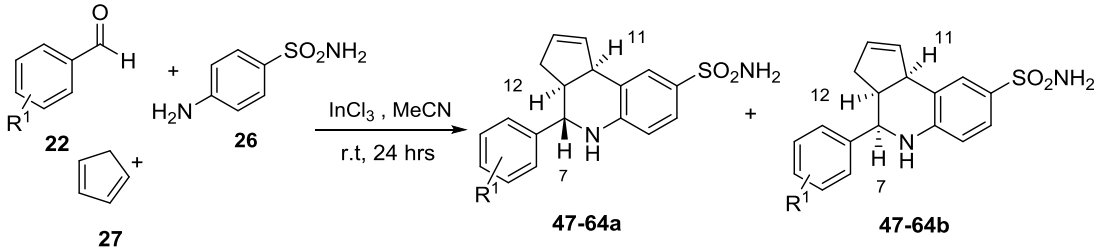
Scheme 15: (a) $PdCl_2dppf.CH_2Cl_2$ (10 mol%), K_2CO_3 (2 eq), $MeB(OH)_2$ (3 eq), THF : H_2O (20: 1), reflux, 24 hrs.[(b)] $PdCl_2dppf.CH_2Cl_2$ (15 mol%), K_2CO_3 (3eq), $MeB(OH)_2$ (5eq).[86]

The remaining aldehyde **46f** could be easily synthesized from commercially available diphenol **43f (Scheme 16)** via trifluoromethanesulfonate formation and cross-coupling followed by a reduction/oxidation sequence to convert the ester to the aldehyde **46f.**



Scheme 16. Conditions: (a) Tf_2O, Et_3N, CH_2Cl_2, 99%;[85] (b) $MeB(OH)_2$, K_2CO_3, $PdCl_2$.dppf, THF:H_2O, reflux, 87 %;[86] (c) DIBAL (1.5 eq), diethyl ether, -78°C, 4hrs, 63 %.[87] (d) Oxalyl chloride (1.1 eq), anhyd. DMSO (2 eq), CH_2Cl_2 (3 ml), methylbenzyl alcohol (1 eq) and NEt_3 (3 eq) at -78°C, 3 hrs, 18%. [88]

All possible combinations of mono-, di-, tri-, tetra-, and penta-methylated TQS compounds were synthesised. Under previous conditions reported by Becker,[26] the corresponding methylated TQS compounds were synthesised and isolated with yields ranging from 12 %-99 %, as shown **(Table 5)** below.



Entry	No.	Benz-aldehyde	dr 47b-64b: unknown[(a)]	dr unknown[(a)] :47a-64a	Yield (%)
1	**47b**	2-Me	93 :7	-	99
2	**48b**	3-Me	92 : 8	-	81
3	**49b**	2,4-DiMe	91 : 9	-	99
4	**50b**	3, 4-DiMeTQS	85 :15	-	17
5	**51a**	2, 3, 4, 5, 6-PentaMe	-	5: >95	10
6	**52b**	2, 4, 5-TriMe	>95: 5	-	32
7	**53b**	3, 5-DiMe	>95: 5	-	12
8	**54b**	2, 5-DiMe	92 : 8	-	56
9	**55a**	2, 6-DiMe	-	5: > 95	21
10	**56b**	2, 3-DiMe	87 : 13	-	33
11	**57a**	2, 3, 5, 6-TetraMe	-	5: >95	46
12	**58a**	2, 4, 6-TriMe	-	5: >95	35
13	**59b**	2,3,4-TriMe	89 : 11	-	66
14	**60b**	2,3,5-TriMe	86 : 14	-	36
15	**61a**	2,3,6-TriMe	-	5 : >95	35
16	**62b**	3,4,5-TriMe	76 : 24	-	59
17	**63b**	2,3,4,5-	89 : 11	-	56

		TetraMe			
18	**64a**	2,3,4,6-TetraMe	-	5 : >95	28

Table 5 [(a)] Configuration of the minor diastereoisomer not determined.

From the 18 methylated TQS compounds synthesised, compounds **51a**, **55a**, **57a**, **58a**, **61a** and **64a** were isolated as the single *trans: cis* isomer **(Table 5)**. Compounds **52b** and **53b** were isolated as the single *cis: cis* isomer **(Table 5)**. The other 10 methylated TQS compounds were isolated as a mixture of isomers, with the major isomer being the *cis: cis* isomer **(Table 5)** and the minor isomer not determined. The configuration of these compounds was further supported by PC model system software **(data shown in experimental section).** This stereochemistry measured is further supported by Perumal and co-workers, reporting coupling constant values of $J_{12\text{-}11}$ = 8.6 and $J_{12\text{-}7}$ = 2.9 Hz, respectively for the structure shown below **40b (Figure 18)**.[67]

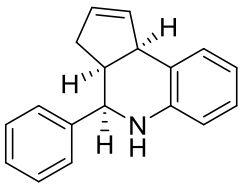


Figure 18. Stucture of **40b**

2.6.2 Biological test results of methylated TQS compounds (work conducted by JasKiran Gill and Neil Millar, UCL Pharmacology)

Given the interesting pharmacological response observed with **38b**, which behaved as a potent allosteric agonist at the α7 nAChRs,[71] it seemed reasonable to explore similar compounds by varying the position of the methyl group, and the number of methyl groups introduced on the phenyl ring. These modifications resulted in an array of pharmacological responses to be observed at the α7 nAChRs.

From the 19 compounds synthesised, compounds **38b**, **49b**, **50b**, **56b**, **59b**, **62b** and **63b** (shown below) exhibited allosteric agonist activity at the α7 nAChR **(Figure 30).**

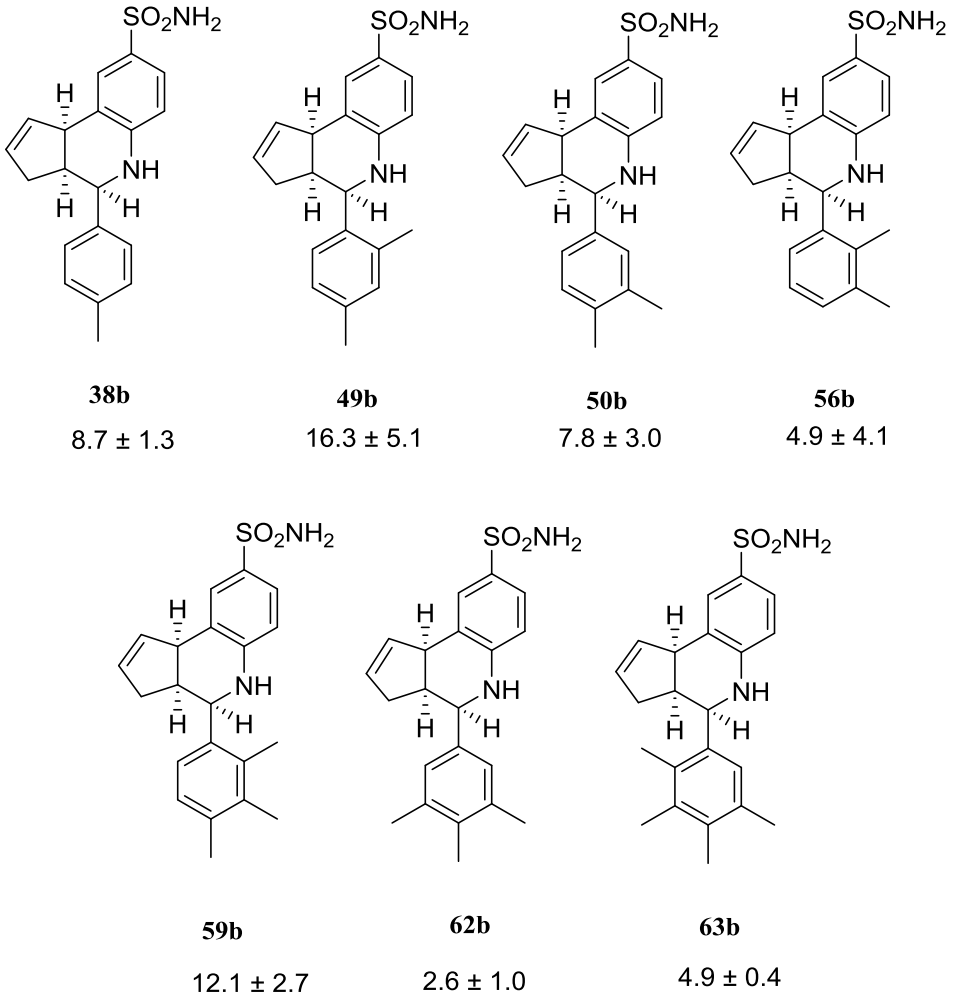
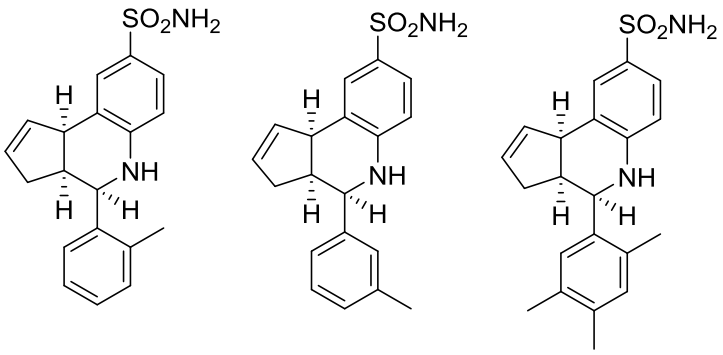


Figure 30. Allosteric agonists (a) *I*max at (fold > 3 mM ACh);

These compounds gave responses ranging from 2.6 to 16.3 fold, with **49b** exhibiting the greatest allosteric agonist response of 16.3 fold **(Figure 30).**

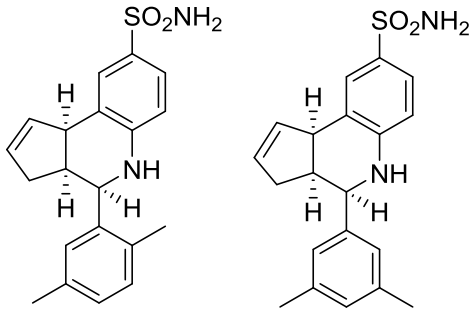
Compounds **47b**, **48b**, **52b**, **53b** and **54b** (shown below) exhibited type II positive allosteric agonist activity **(Figure 30).**



47b
40 ± 7.5

48b
22 ± 2.1

52b
11 ± 2.7



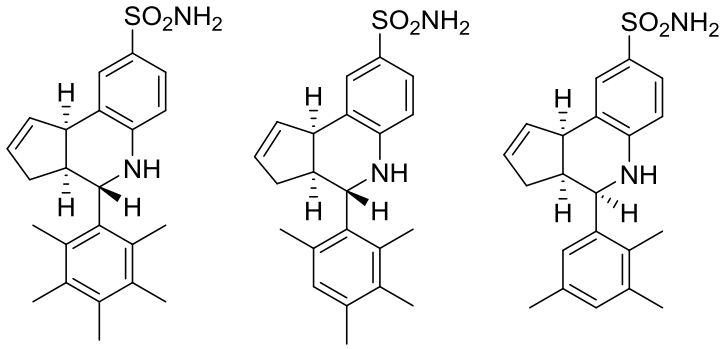
54b
2.1± 0.7

53b
33 ± 4.9

Figure 31. Type II PAMs *I*max (fold > 100 µM ACh).

The biological activity of these type II PAMs showed potentiation responses of ACh at the α7 receptor, ranging from 2.1 to 40 fold, with **47b** exhibiting the greatest potentiation of ACh with 40 fold **(Figure 31).**

Compounds **51a, 64a** and **60b** showed type I PAM activity **(Figure 32 below)**, with potentiation responses of ACh ranging from 2.4 to 5.3 fold. Compound **60b** showed the greatest potentiation of ACh response **(Figure 32).**

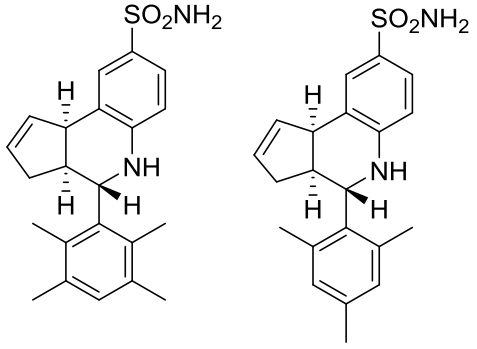


51a 2.4 ± 0.3 | **64a** 2.5 ± 0.3 | **60b** 5.3 ± 1.1

Figure 32.Type I PAM *I*max (fold > 100 µM ACh)

It is worth mentioning that **60b** exists as the *cis: cis* isomer whereas **51a** and **64a** are *trans: cis* isomers **(Figure 31).**

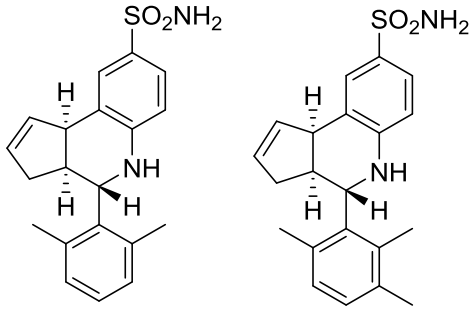
For compounds **57a** and **58a**, neither potentiated nor inhibited ACh-evoked responses were measured **(Figure 33).** This might be because the aromatic ring with the methyl groups are symmetrical, cancelling the overall response.



57a **58a**

Figure 33. No effect on ACh response

Compounds **55a** and **61a** behaved as antagonists for ACh with moderate inhibitory effects at the α7 receptor **(Table 6, Figure 34).**



55a **61a**

Figure 34. Antagonists for ACh

Compound	% inhibition of ACh of 100 mM	IC_{50} µM
55a	73.6 ± 4.2	43 ± 14
61a	68.2 ± 2.8	23 ± 2.8

Table 6.

Compound **61a** is more potent than **55a,** with IC_{50} values of 23 and 43 µM, respectively. However, **55a** showed greater % inhibition of ACh than **61a** with a inhibition value of 74 %.

It is worth mentioning that most of the methylated TQS compounds tested were isolated as a mixture of diastereoisomers, so there might be a major influence of the minor isomer on the overall pharmacological response of each methylated TQS compound. However, with methylated TQS compounds **51a**, **64a**, **57a**, **58a**, **55a** and **61a**, which were isolated as the single isomer in the *trans: cis* configuration with >95: 5 diastereoselectivity, we can be confident in concluding that *trans: cis* isomers exhibit either a type I PAM, antagonist of ACh or show no pharmacological effect. None of theses compounds were allosteric agonists or a type II PAM. Similarly, compounds **52b** and **53b** which have been isolated as the single isomer in the *cis: cis* configuration with >95: 5 diastereoselectivity, we can be confident in concluding that the pharmacological response observed is of a type II PAM and not of any other pharmacological effect that might be influenced by the minor diastereoisomer.

Given that most of the methylated TQS compounds were isolated as a mixture of diastereoisomers, these isomers could be separated by HPLC. If the minor isomer

isolated is determined to be the *trans: cis* isomer, the pharmacological trend between *trans: cis* isomers and with *cis: cis isomers* can be investigated.

Since methylated TQS compounds isolated as the *cis: cis* isomer showed either type II PAM or allosteric activity, differences in the pharmacological behaviour between *cis: cis* isomers were discussed. For example, a 3D structure for compound **38b** which is an allosteric agonist shows that the methyl group is pointing outwards whilst compound **47b** a type II PAM, the methyl group is pointing towards the heterocycle **(Figure 35).** Both **38b** and **47b** exist as the *cis: cis* isomer, so it might be that the orientation of the methyl group is what brings out the differences in the pharmacological responses observed. It could also be that rotation about the C-aryl bond axis shows no change in the position of the methyl group in **38b** whilst in **47b** the position of the methyl group relative to the axis of C-aryl bond significantly varies. However in **47b**, restricted rotation about the axial C-aryl bond could lock the phenyl ring into the conformation shown below **(Figure 35) 47b**, with the *ortho* methyl group pointing away from the cyclopentene ring.

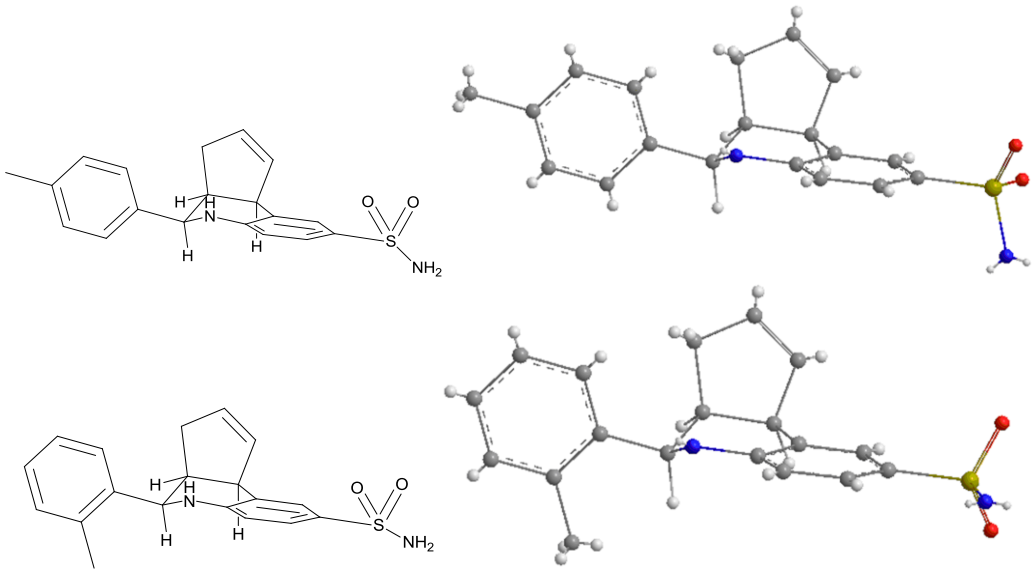


Figure 35. 3D models of *cis: cis* isomer of **38b (**above) and **47b** (below).

To explain the pharmacological differences observed between *cis: cis* and *trans: cis* isomers, a 3D structure of compound **49b** (which exists as the *cis: cis* isomer) and compound **58a** (a *trans: cis* isomer) were compared. Significant differences between the two 3D structures where observed **(Figure 36 and 37).** An energy minimized structure of **58a** shows that the phenyl group is slightly pointing in a pseudo-axial

position from the main structure **58a (Figure 37 far right).** As previously discussed, restricted rotation about the axial C-aryl bond could lock the phenyl ring into the conformation shown below **(Figure 36 and 37)**. If a *trans: cis* isomer of **49b** or a *cis: cis* isomer of **58a** was also subjected for pharmacological tests, key information would be obtained to explain the differences in pharmacological activity observed. This is due to be investigated.

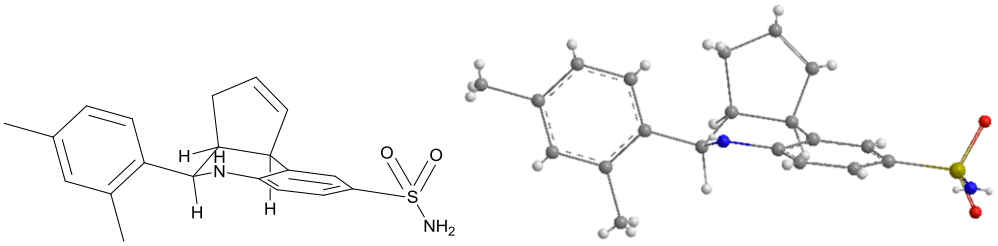


Figure. 36. 3D Structure and Model of **49b**

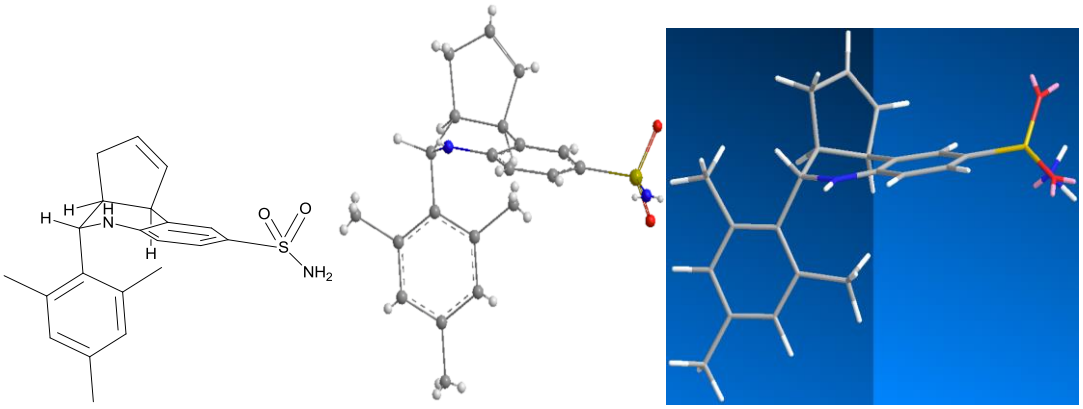
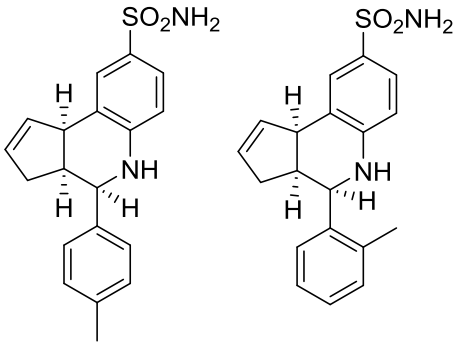


Figure 37. 3D structure of **58a** (far right) ball and stick 3D Model of **58a (**middle). Energy minimized 3D model of **58a (**far left).

2.6.3 Conclusion

1. Varying the position of the methyl group on the phenyl ring induces different pharmacological responses. For example, replacing a methyl group at the 4-position (in **38b**) with one at the 2- position (in **47b**) on the phenyl ring, changes the pharmacological response from an allosteric agonist to a type II PAM.



38b
allosteric agonist

47b
Type II PAM

2. The *cis: cis* substituted methylated TQS compounds show either an allosteric agonist or type II PAM response whereas *trans: cis* substituted methylated TQS compounds show either no effect on ACh, act as antagonists for ACh or give type I PAM responses.

3. Different levels in the potentiation of ACh responses for type II PAMs are observed, ranging from 2.1 to 40 fold.

4. Differences in agonist responses are observed for allosteric agonists, ranging from 2.6 to 16.3 fold.

5. Similarly, amongst the *trans: cis* substituted methylated compounds, differences in the potentiation of ACh and antagonist activity varies.

6. Interestingly, only **60b** of all the *cis: cis* isomers produced exhibits type I PAM activity.

7. The pharmacological response is likely to be a result of a combination of:

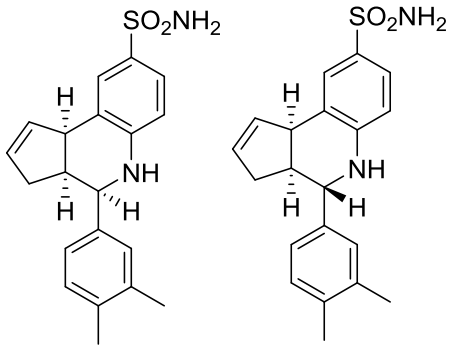
   a) The configuration of the compound,

b) The position of methyl group and/or

c) The number of methyl groups present.

2.6.4 Future Work

Given that many of the methylated TQS compounds were obtained as a mixture of diastereoisomers, a possibility could be to isolate each isomer by HPLC. If the minor isomer of **50b** isolated is a *trans*: *cis* isomer we could determine if there is a pharmacological trend observed. For example *a trans: cis* isomer of **50b** might result in either an antagonist or type I PAM pharmacological response **(Figure 38)**.



50b **50a**

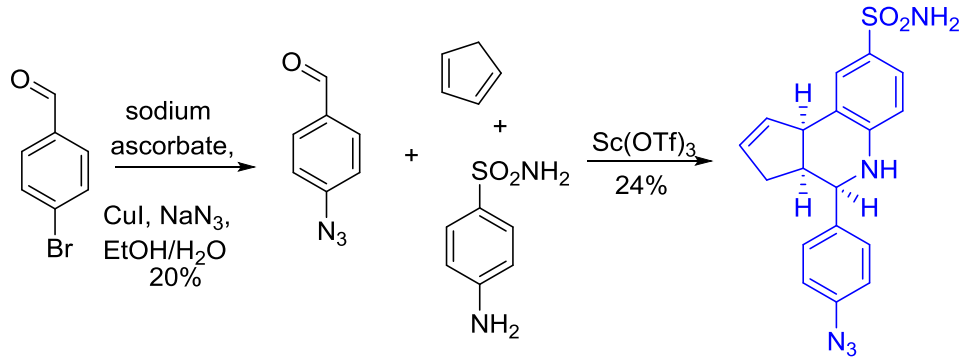
Figure 38

2.7 Additional examples of *p*-substituted TQS compounds

Additional examples by modification of the aldehyde component were made. It was of interest to study whether if replacing the methyl group, with other substituents e.g. a methoxy group at the para position **65b** would still maintain allosteric agonist activity. Another approach was to introduce a methyl sulphone group. Increasing the steric bulk at the *para* position by incorporating a *t*-butyl and an *i*-propyl group **68b** and **69b** would be an interesting pharmacological study to compare with **38b** and **23b**, since allosteric responses seem to be largely influenced by steric and not electronic effects influenced as previously reported.[71]

The effect of changing the hybridisation of the carbon substituted was then studied, with a *p*-vinyl group **70b**, which was introduced in **23b** *via* a Suzuki cross coupling reaction using a vinyl-BF_3K salt. In addition the effect of the presence of a cyano-group at the *para* position **66b** was also examined.

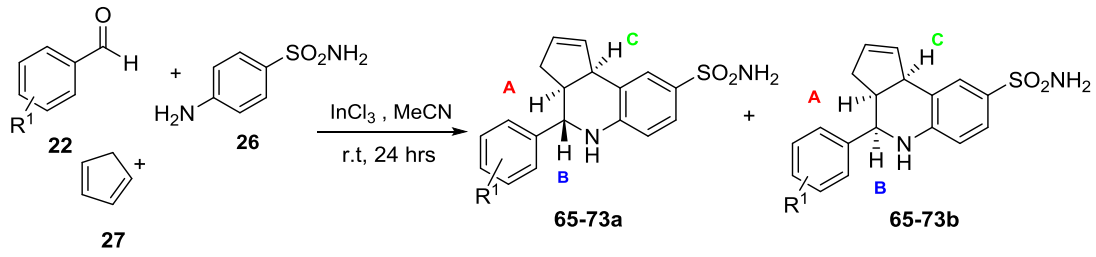
Introduction of an azide group was achieved by a copper catalysed reaction of bromobenzaldehyde. Evidence of azide attachment to the phenyl ring was determined by analysing the IR spectroscopy peak at 2100 cm^{-1} being present, which is characteristic for an azide group **(Scheme 17).**



Scheme 17. Synthesis of *p*-azido benzaldehyde[89] and *p*-azido TQS **71b**.

Under previous conditions reported by Becker,[26] the corresponding TQS compounds were synthesised and isolated with yields ranging from 3%-24% as shown in **Table 7.** $InCl_3$ proved to be ineffective to catalyse the reaction with *para*-azide benzaldehyde, however on employing $Sc(OTf)_3$ as the Lewis acid **71b** was isolated in

24% yield. All the compounds were isolated as *cis: cis* diastereoisomer as the major isomer.



Entry	No.	R^1	dr 65b-73b: unknown[(a)]	Yield (%)
1	**65b**	4-OMe	80 : 20	16
2	**66b**	4-CN	77 : 23	6
3	**67b**	4-SO_2Me	91 : 9	3
4	**68b**	4-*t*-butyl	95 :5	16
5	**69b**	4-*i*-propyl	83 : 17	19
6	**70b**	4-vinyl	91 : 9	14
7	**71b**	4-N_3	71 : 29	24[b]
8	**72b**	4-NO_2	95 : 5	21
9	**73b**	2,3,4-triOMe	91 : 9	10

Table 7 (a) Minor diastereoisomer not determined. (b) $Sc(OTf)_3$ used as the Lewis acid to catalyse the MCR.

2.7.1 Biological test results (conducted by JasKiran Gill and Neil Millar, UCL Pharmacology)

In comparison with **38b** (*para*-Me) and **59b** (2, 3, 4-TriMe), which exhibited allosteric agonist activity, **65b** (*para*-OMe) and **73b** (2, 3, 4-TriOMe) gratifyingly retained allosteric agonist activity at the α7 nAChR **(Figure 39).** However, compounds **65b** and **73b** showed potency values of 4.4 and 1.3 fold, respectively,

which were not as efficacious as their methylated equivalents with potency values of 8.7 and 12.1 fold, respectively **(Figure 39).**

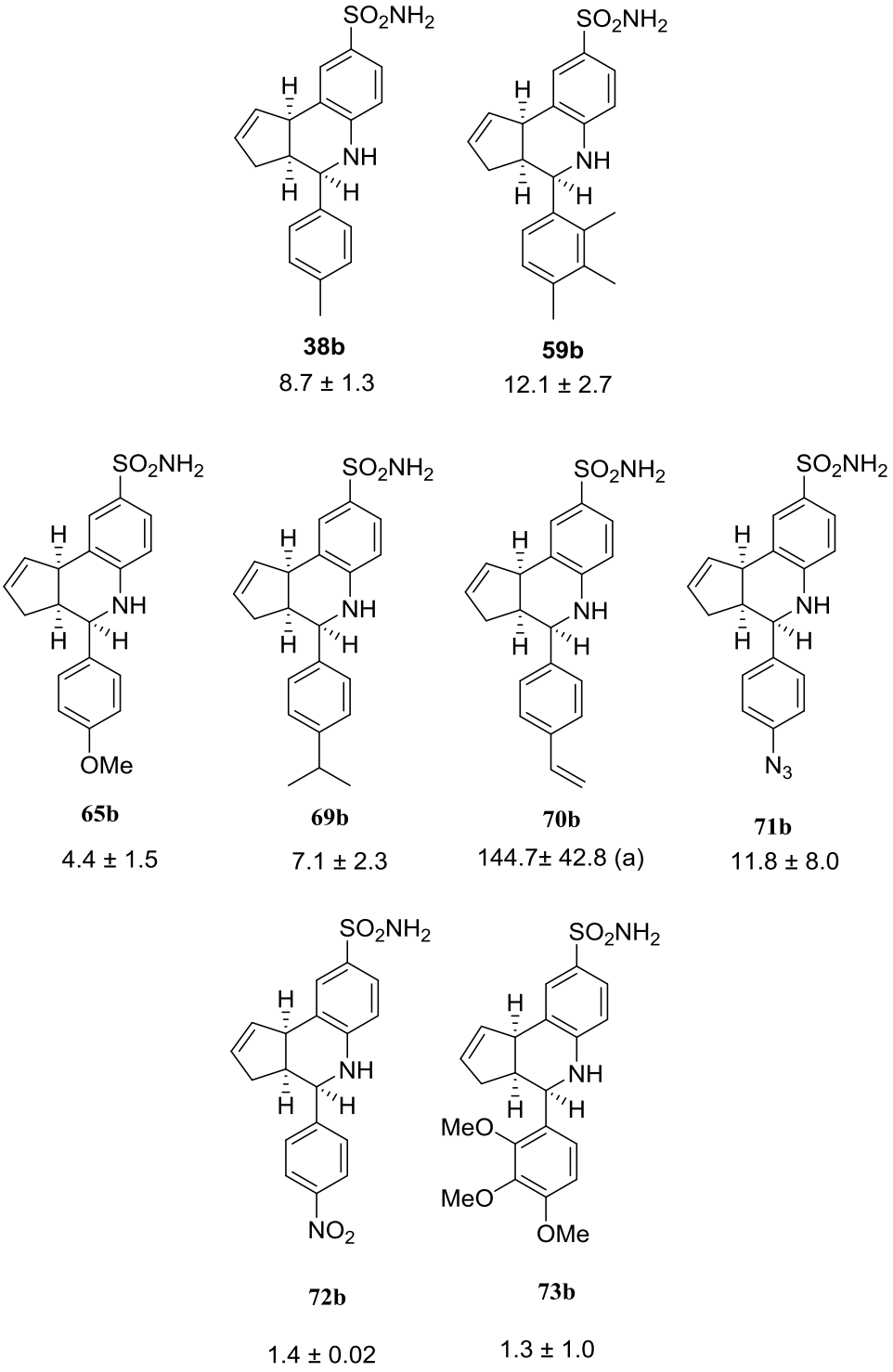


Figure 39. Allosteric agonists *I*max potency (fold > 3mM ACh).

Compounds **72b** and **71b** exhibited allosteric agonist activity with potency values of 1.4 and 11.8 fold, respectively **(Figure 39).** It seems that a relatively large group at

the para position on the phenyl ring is required to maintain allosteric agonist activity,[71] as incorporation of an isopropyl group as in **69b** gave a similar agonist response of 7.1 fold with respect to **38b**. Incorporation of a vinyl- group **70b** behaved as a potent allosteric agonist with an *I*max value of 144.7 ± 42.8 **(Figure 39).**

Compound **66b** behaved as a type II PAM with a potency value of 4.1 ± 0.5 fold **(Figure 40).** In addition, the *tert*-butyl group in **68b** seemed to be too large and bulky to retain allosteric agonist activity, behaving as a type II PAM with a 3.9 ± 0.5 efficacy **(Figure 40).** It seems that there is an atomic radius range for a substituent at the para position to elicit allosteric agonist activity.

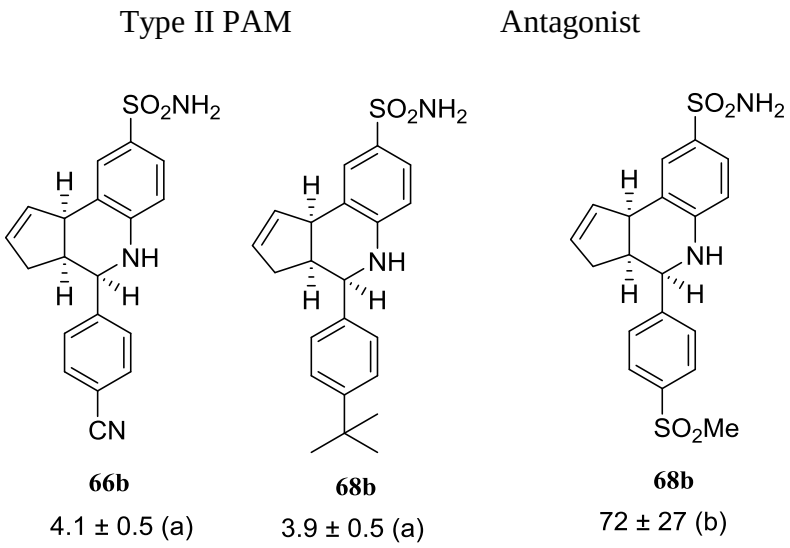


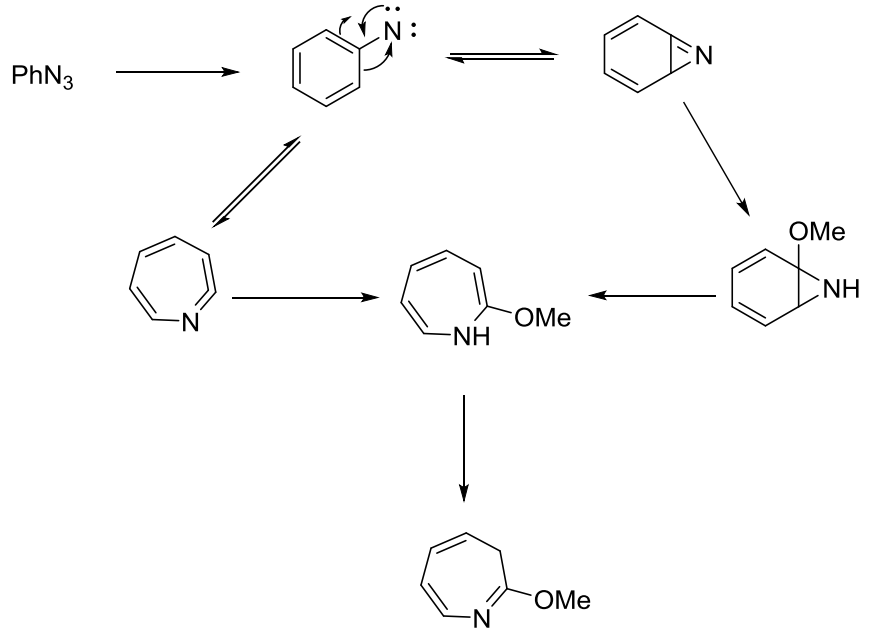
Figure 40. (a) Fold > 100μM ACh, (b) % inhibition of 100μM of ACh 72 ± 27.

Interestingly, when a methyl sulphone **67b** was present at the *para* position it acted as an inhibitor for ACh with a % inhibition of 72 **(Figure 40).**

2.7.2 Irradiation study

The rationale behind synthesising *p*-azide-TQS **71b** was to explore photochemical ligation of the compound to the receptor tested. This was to study where the compound binds to the α7 receptor. It has been known that aryl azides can rearrange and lose nitrogen to form nitrene derivatives when irradiated or thermally activated **(Scheme 18).**[90] As a result photochemistry of aryl azides has received considerable

attention due to the utility of these compounds in photo imaging and photo affinity labelling.[91-94]



Scheme 18.[91]

Irradiation of *p*–N_3TQS **71b** for 1 hr using a photochemical UV lamp turned the sample from a translucent orange solution to form an orange precipitate. Although the IR of the sample only showed a peak at 2100 cm^{-1} corresponding to an azide attachment, no peak at 1800 cm^{-1} corresponding to the azepine was observed. The ^{1}H NMR of the sample showed only the *p*-N_3TQS. On several attempts, **71b** did not show any photoactivity even after irradiation for several hours. As a result, this work was not progressed further.

All compounds synthesised were isolated as the *cis*-*cis* diastereoisomer which was further supported through the PC model software data in experimental section.

2.8 Heteroaromatic Benzaldehyde Analogues

The rationale behind the synthesis of TQS compounds using heteroaromatic benzaldehydes was to increase solubility, and to reduce complications experienced by the Millar group on constructing dose–response curves due to the compounds sticking to the tubing.[71] From a medicinal chemist's point of view it was of interest

to introduce nitrogen containing heteroaromatic benzaldehydes such as 2-pyridine and 2-pyrrole benzaldehyde, however, incorporation of such groups in the MCR reaction gave a complicated mixture which made it difficult to determine by ^{1}H NMR whether the product was formed. This led us to move to bioisosteres of the phenyl group, such as furan and to incorporate groups such as a bromine and methyl group which from our previous study were found to behave as allosteric agonists when present in 4BP- TQS and 4MP-TQS.[71] All four products were isolated in yields ranging from 8-32%, in a >95: 5 ratio with the *cis: cis* isomer **(Figure 41)** as the major isomer. The minor isomer was not determined.

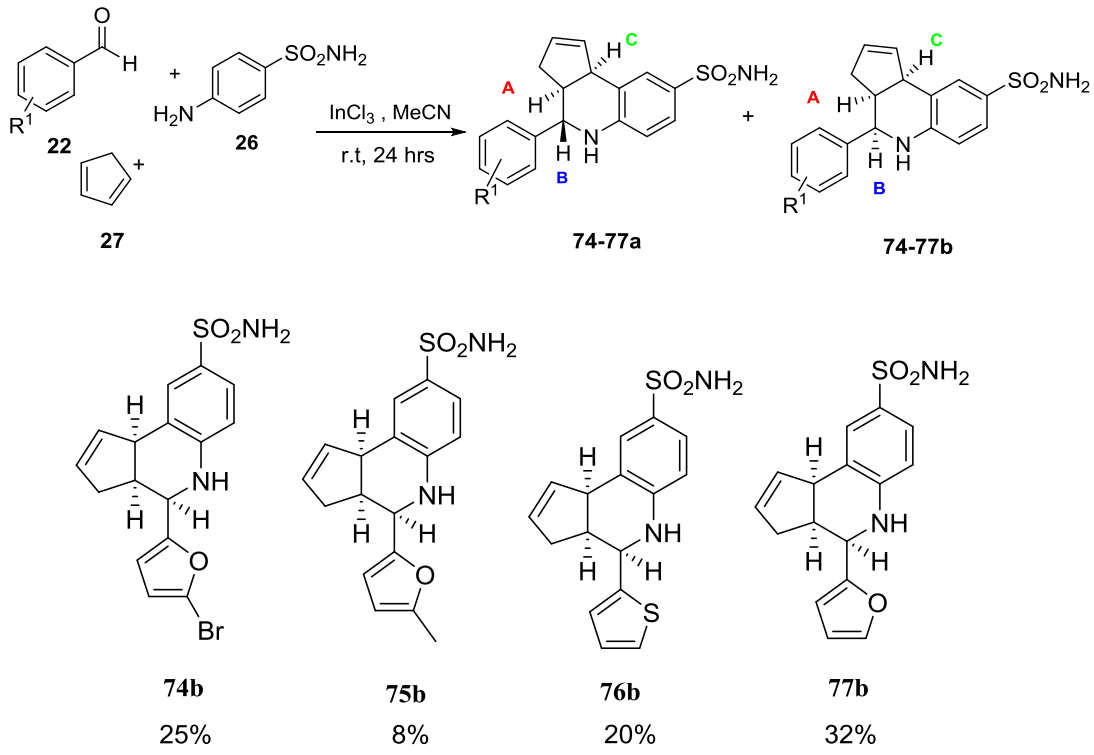


Figure 41. Structures of heteroaromatic TQS compounds.

Biological tests of the heteroaromatic TQS compounds are currently under investigation by our collaborators JasKiran Gill and Neil Millar.

2.8.1 Conclusion

For the additional TQS compounds synthesised by modification of the benzaldehyde component, all compounds were isolated as the *cis: cis* isomer. This is supported with the use of PC Model V8 software – a table showing the comparison of measured coupling constant values with the calculated coupling constant values is shown in the experimental chapter.

Although biological tests for the heteroaromatic TQS compounds are currently in the pipeline, the additional para substituted TQS compound **67b** behaved as an antagonist for ACh while compounds **66b** and **68b** acted as type II PAM **(Figure 42a).**

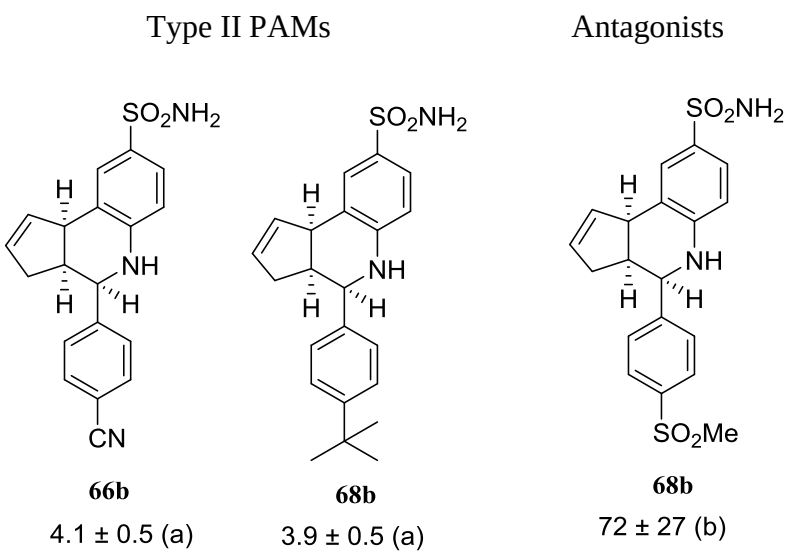


Figure 42a

Allosteric agonist activity was retained with **65b** and **73b**, although, the activity was significantly lower than **38b**[71] and **59b** (**Figure 42b**).

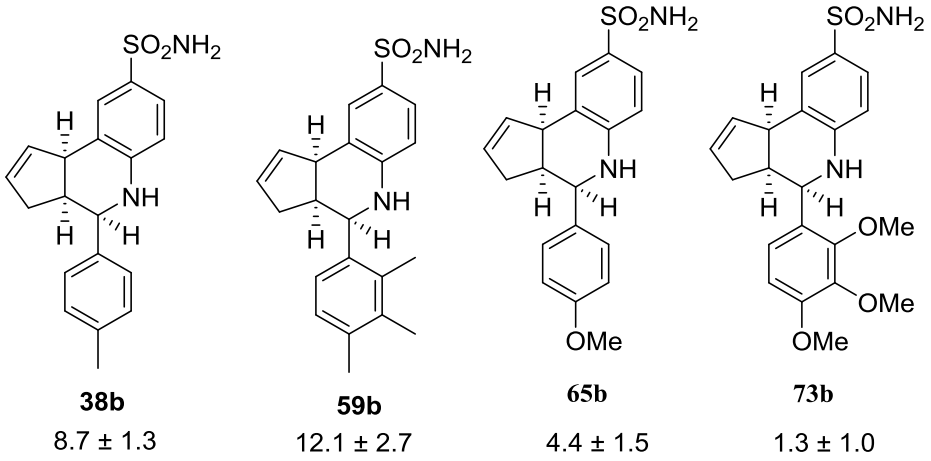
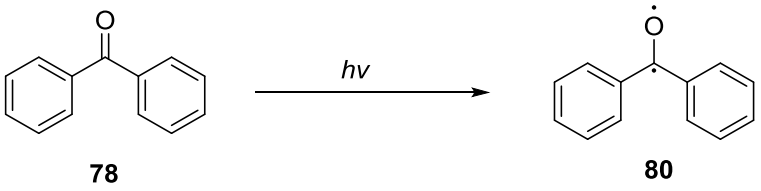
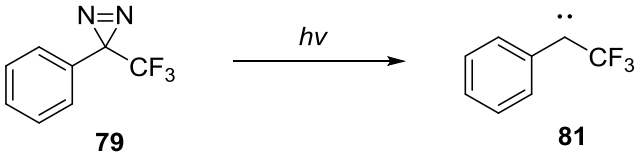


Figure 42b

Since the photochemical activation of the azide group proved unsuccessful in our study, other photoactive groups other than azide could be considered for photochemical ligation, such as, aryl ketones **78** or diazirines **79**, which form reactive diradicals **80** and carbenes **81**, respectively **(Scheme 19 and 20).**[95-97]

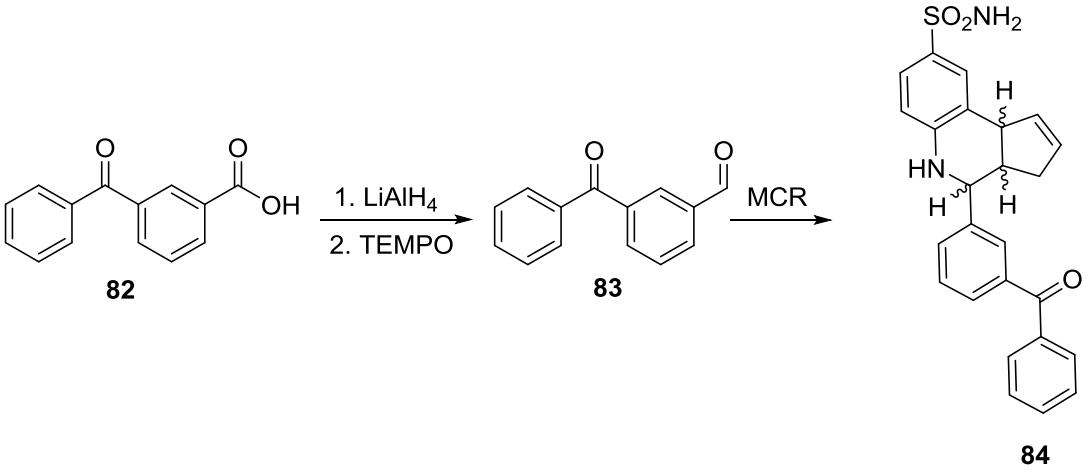


Scheme 19.



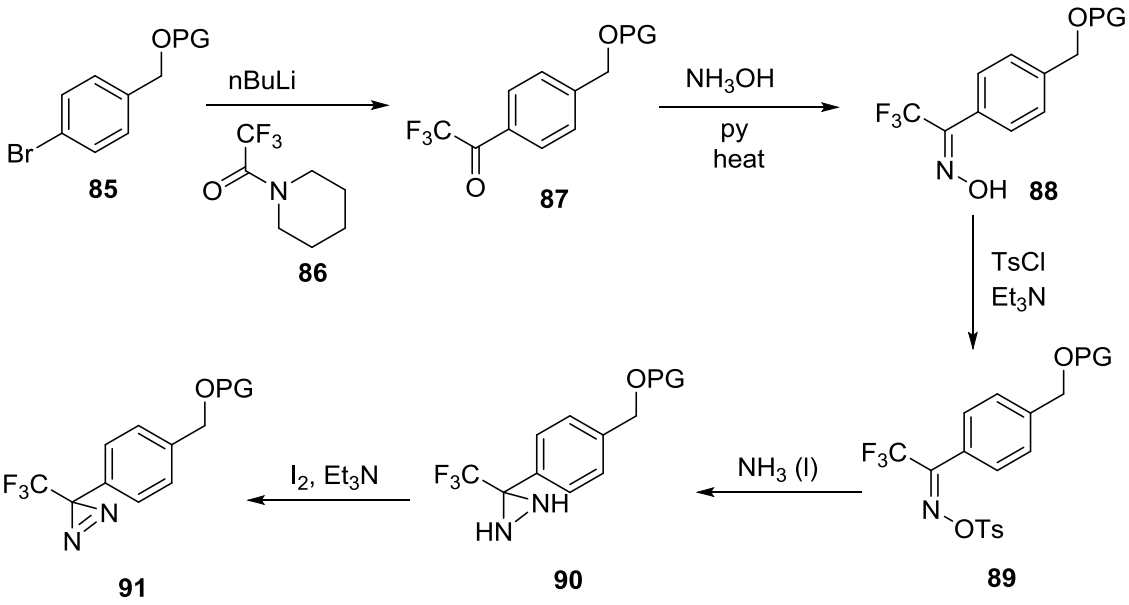
Scheme 20.

Introduction of an aryl ketone **78** could be achieved with commercially available 3-benzoylbenzoic acid **82**, which can be converted to a primary alcohol source upon reduction followed by oxidation to give the aldehyde substrate **83** for MCR **(Scheme 21)**.



Scheme 21

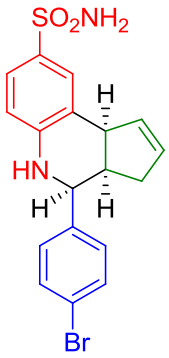
Introduction of a diaziridine group could be achieved from a protected bromo phenyl methanol **85** which reacts with N-(trifluoroacetyl)piperidine **86** to give **87**.The ketone could then be converted to the oxime **88**, followed by tosylation to give **89**. Reaction with liquid ammonia incorporates the diaziridine group **90**. Subsequent oxidation with iodine gives the diaziridine **91 (Scheme 22)**. This could then be converted to the aldehyde for the MCR with TEMPO.



Scheme 22

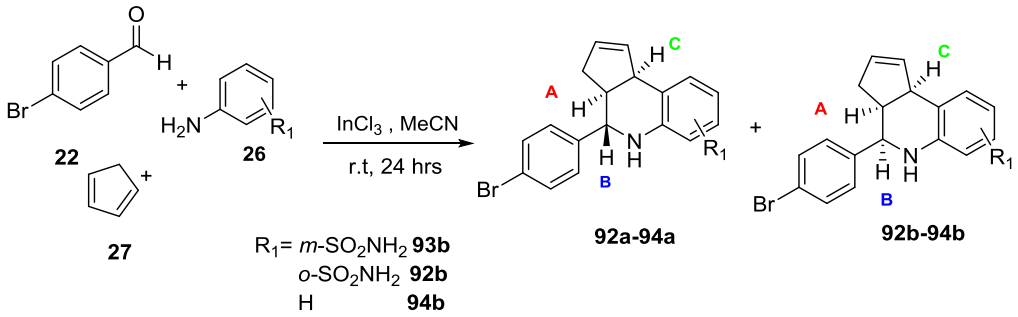
2.9 Modification of Sulphanilamide Component for the Synthesis of 4BP-TQS Analogues

On having synthesised several analogues of **23b** by varying the benzaldehyde component (in blue) figure, variation of the sulphanilamide component to study the pharmacological responses at the α7 nAChRs was then explored.

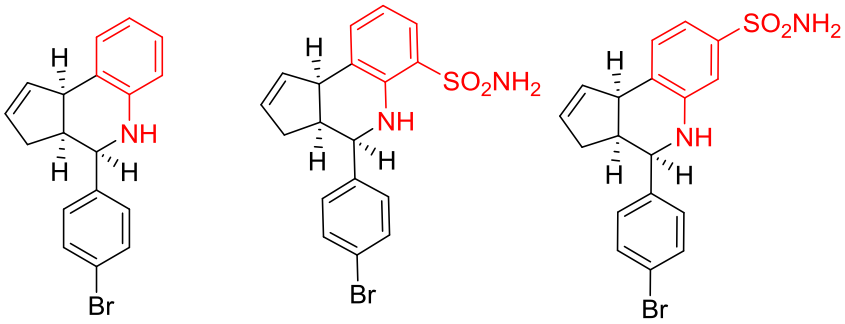


23b

It was of interest to study the pharmacological response by varying the position of the sulphonamide moiety from the *para*- position to the *ortho*- or *meta*- position, as well as examining compounds without the sulphonamide group. Since all the required sulphanilamide reagents were commercially available, subjecting them to the same protocol used earlier led to the synthesis of the corresponding compounds which were isolated as the *cis: cis* isomer as the major diastereoisomer **(Scheme 23)**, with the minor diastereoisomer not determined. Diastereoisomeric ratio of **92b** and **93b** were >95: 5 ratio of *cis: cis*: unknown isomer whilst **94b** in 91:9 *cis: cis*: unknown isomer ratio **(Figure 43).**



Scheme 23



94b 65%

92b 51%

93b 26%

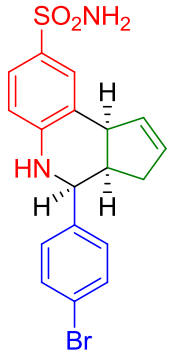
Figure 43. Structures of substituted sulphanilamide TQS compounds

Biological results for **92b** and **93b** are currently being investigated by Neil Millar and JasKiran Gill. However, **94b** was found to act as an antagonist of ACh, which suggests the sulphonamide group, is critical to maintain allosteric agonist activity and PAM activity at the α7 nAChR **(Table 8).**

Compound	% Inhibition of 100μM of ACh
94	70 ± 10

Table 8

2.10 Modification of the cyclopenta- ring component of 4BP-TQS



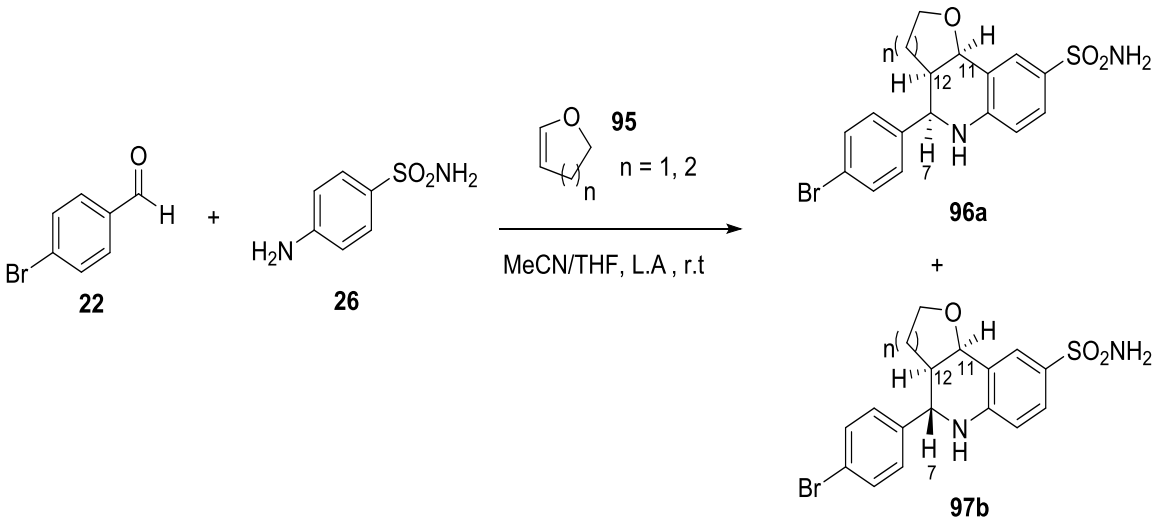
23b

Having synthesised a number of analogues of 4BP-TQS **23b** by varying the benzaldehyde (in blue) and aniline component (in red), variation of the cyclopentene- ring structure (in green) was also then considered.

2.10.1 Synthesis of furano- and pyrano- quinolines

Since the pioneering work by Pavarov,[98] the synthesis of furano- and pyrano-quinolines has been extensively studied with a number of Lewis acids $ZrCl_4$,[99] Bi(III)Cl_4,[100] $Mg(OCl)_4$,[68] TMSCl,[101] and lanthanide trichloride catalysts[102] with various substituted anilines and aldehydes.

We considered altering the cyclopentene ring structure in **23b** by using five and six membered cyclic enol ethers **95** for the synthesis of pyrano- and furanoquinoline analogues **96 (Table 9, Scheme 24)**.[102, 103]

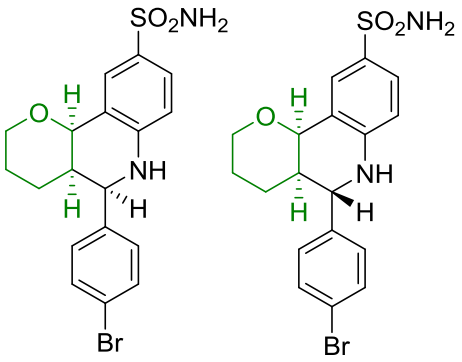


Scheme 24

Entry	R^2	R^1	Cyclic enol	Solvent	Lewis acid	Yield 96a: 96b
1	SO_2NH_2	Br	DHP	MeCN	$GdCl_3$	0.02% : 0.2%
2	SO_2NH_2	Br	DHF	MeCN	$GdCl_3$	(a)

Table 9. One pot synthesis of pyrano- and furano-quinolines; (a) Difficult to isolate, although peaks correspond to the product.

Despite the success with $InCl_3$ in the synthesis of 4BP-TQS analogues, no reaction with dihydropyran (DHP) or dihydrofuran (DHF) in the presence of $InCl_3$ occurred. However, $GdCl_3$ proved to be a useful Lewis acid to catalyse the MCR between 4-bromo benzaldehyde, DHP and sulphanilamide. ^{1}H NMR of the crude material showed desired peaks around 1.2-2 ppm, and the compounds were each successfully isolated despite the low yield (**Entry 1, Table 9**).



0.02%
96a

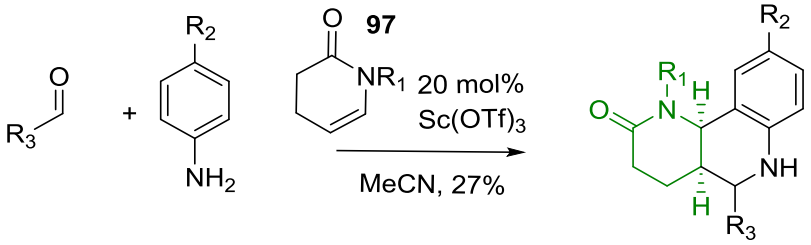
0.2%
96b

Figure 44

Similarly, reaction with DHF seemed to be successful from the ^{1}H NMR of the crude mixture. However, isolation of the furano-TQS compound proved unsuccessful **(Table 9)**.The structural assignment of **96a and 96b** was made on the basis of the coupling constants measured by ^{1}H NMR ($J_{12\text{-}11}$ = 5.4 Hz and $J_{12\text{-}7}$ = 2.5 Hz for **96a** and $J_{12\text{-}11}$ = 2.5 Hz and $J_{12\text{-}7}$ = 10.5 Hz) for **96b**. Further confirmation using the computer model system showed the coupling constant values were consistent with the cis configuration for **96a** with calculated values of $J_{12\text{-}11}$ = 6.5 Hz and $J_{12\text{-}7}$ = 3.1 Hz, respectively. Similarly, the stereochemistry was deduced through this method for **96b**. This suggests that $GdCl_3$ is a suitable Lewis acid to catalyse the three-component Diels-Alder reaction between sulphanilamide, 4-bromobenzaldehyde with cyclic enols 3,4-dihydropyran and 2,3-dihydrofuran **(Table 9)**, however, a low yield was obtained.

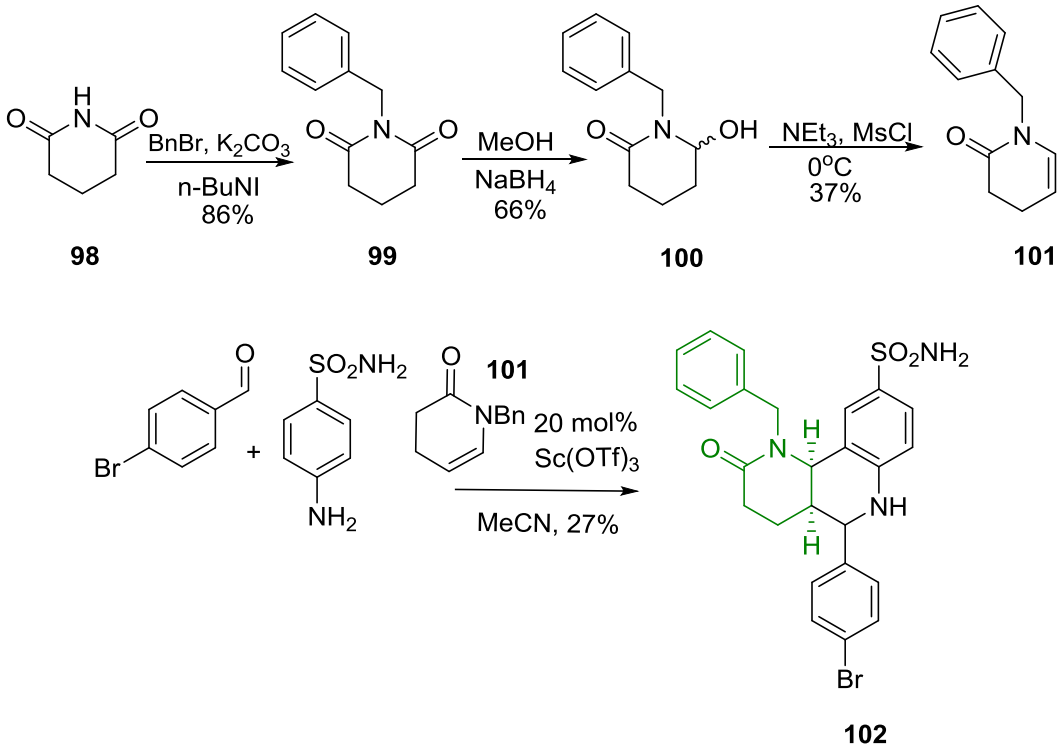
Optimisation of the pyrano-quinoline synthesis with various Lewis acids was explored with CAN, $FeCl_3$, $GdCl_3$, $ScOTf_3$, $BF_3.OEt_2$. However, none of the Lewis acids gave promising results. Given that the optimisation of the pyrano-quinoline synthesis was unsuccessful, this work was not further studied and the amount of pyrano-quinoline which was isolated was sufficient for biological studies.

A report by Lavilla and co-workers demonstrated that unsaturated lactams **97** can be employed in Pavarov–type multicomponent reactions, catalysed by $ScOTf_3$ to give the corresponding compound as the *cis: cis* isomer selectively **(Scheme 25)**.[104]



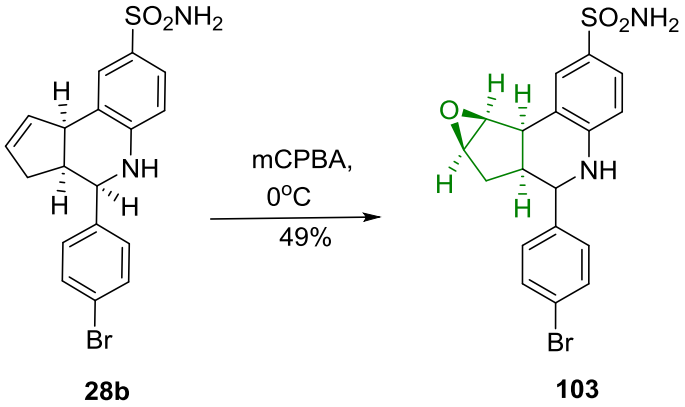
Scheme 25.[104]

Based on their study we decided to introduce a benzyl lactam in place of a small cyclopentene-ring. This was achieved by synthesising the enamine **101** from glutarimide **98**, which was benzylated **99**,[105, 106] reduced with $NaBH_4$ to give the amide alcohol **100**,[107] followed by mesylate formation[107] and to give the corresponding unsaturated benzylated lactam **101 (Scheme 26)**. This was subjected to the MCR with 4-bromobenzaldehyde and sulphanilamide to give **102** in 27% yield as the *cis: cis* isomer **(Scheme 26)**.



Scheme 26[106, 107]

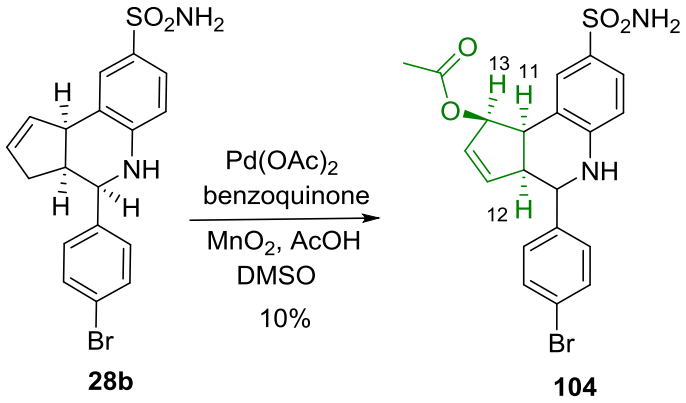
Additional modifications of the cyclopenta-ring involved introducing an epoxide with mCPBA, which gave the corresponding product **103 (Scheme 27)**.



28b **103**

Scheme 27.[108]

Subjecting **28b** to allylic oxidation conditions,[109] afforded **104 (Scheme 28)**. The stereochemistry was determined by NOE suggesting that H-11, H-12 and H-13 were all at the same face.



28b **104**

Scheme 28[109]

2.10.2 Biological test results (conducted by JasKiran Gill and Neil Millar, UCL Pharmacology).

Compounds **102**, **104** and **96a** behaved as antagonists for both ACh and **23b** whilst **96b** behaved as an antagonist for ACh only **(Figure 45** and **Table 10)**.

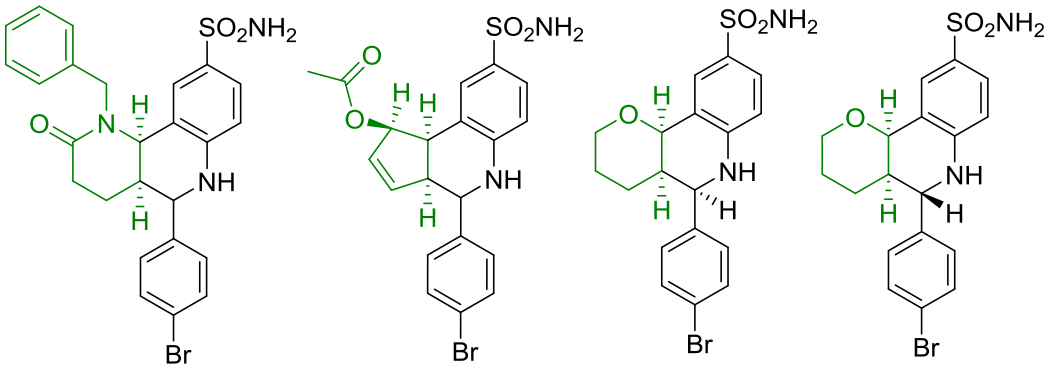


Figure 45. Antagonist response as a % inhibition of ACh 100 μM.

Compound **102** showed the greatest % inhibition of **23b** with 94% with respect to **104** and **96a (Table 10)**. This might be because of the relatively large benzyl group. **102** is a more potent inhibitor of ACh and **23b** than **96a** with % inhibition of ACh and **23b** value of 72% and 94%, 63% and 88%, respectively **(Table 10)**.

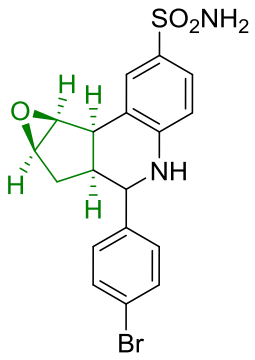
Compound	% Inhibition of 100 μM	
	ACh	**28b (**4BP-TQS)
96a	63 ± 14	88 ± 2.1
96b	22 ± 4.3	-
102	72 ± 4.5	94 ± 0.4
104	25 ± 3.0	42

Table 10

Interestingly, a significant difference in the % inhibition of ACh and **23b** between **96a** and **96b** were observed (**Table 10**), with **96a** showing 63 and 88% inhibition for

ACh and **28b**, while **96b** with 22% for ACh only, respectively. This difference between **96a** and **96b** might be a result of the configuration of both compounds.

Compound **103** exhibited allosteric agonist activity with an *I*max value of 6.4 fold **(Figure 46)**.



6.4 ± 3.1

103

Figure 46. Agonist response **103** *I*max/potency (fold when >3 mM ACh).

2.11 Conclusions/Future Work

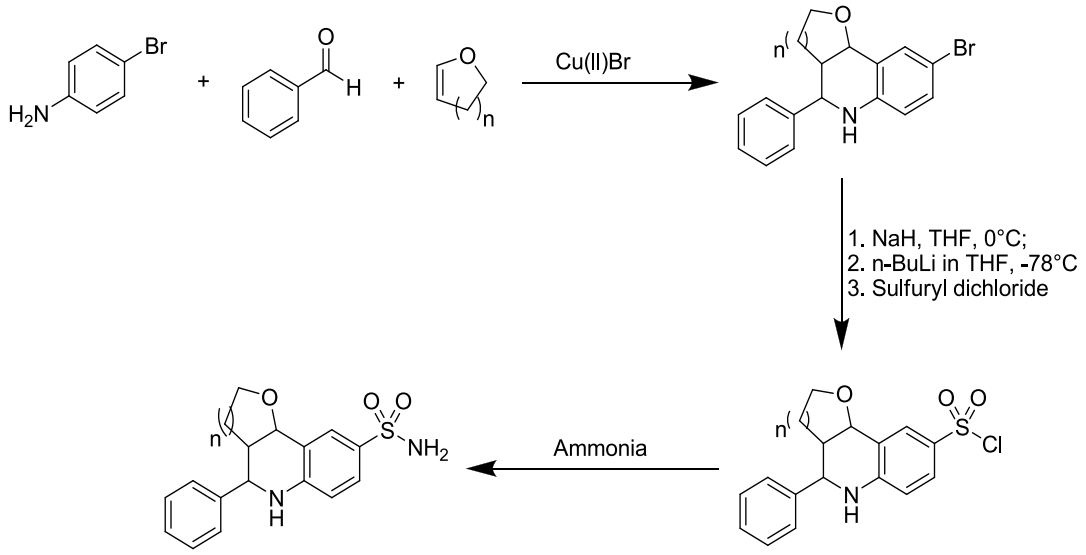
Various substituted benzaldehydes were used in the synthesis of cyclopentaquinoline analogues of **23b** under Becker's protocol.[26] On varying the benzaldehyde component a total of 45 TQS compounds were isolated in poor to excellent yields.

On varying the position of the sulphonamide group and with no sulphonamide group present, a total of three TQS compounds were synthesised in yields ranging from 26-65% yield.

Modifications of the cyclo-penta ring component gave 5 TQS compounds ranging from very poor to moderate yields.

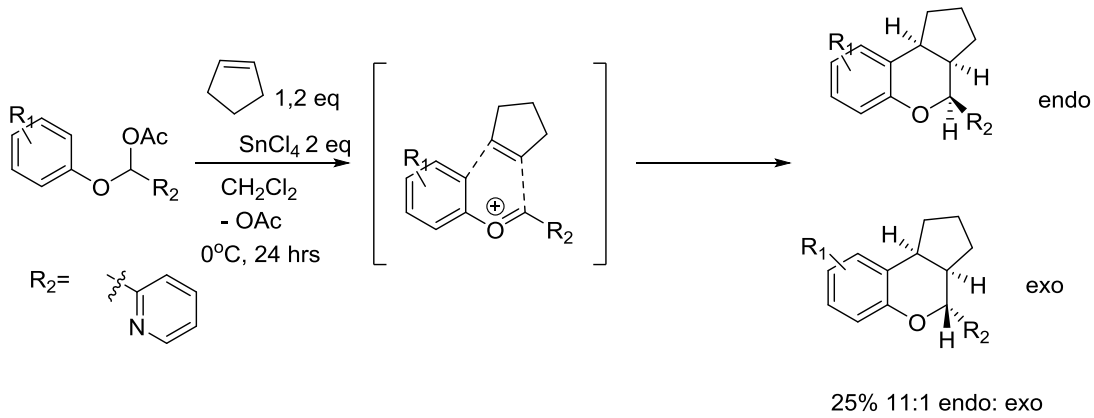
The use of $InCl_3$ led to selectivity towards for the *cis-cis* diastereoisomer as the major product using sterically unhindered benzaldehydes whereas the *trans: cis* isomer was favoured with sterically hindered benzaldehydes.

Gadolinium trichloride was an effective Lewis acid catalyst for the synthesis of pyrano-quinoline, though in low yield. Another method that could possibly be used for synthesising pyrano- and furano-quinolines is shown below **(Scheme 29)**.[110-112]



Scheme 29

On having varied the aniline, benzaldehyde and dienophile component, another area to introduce modification is at the secondary nitrogen, such as, by introducing an oxygen atom *via* a hetero Diels-Alder approach as demonstrated by Batey and co-workers in the synthesis of Chromans (3,4-Dihydrobenzopyrans) (**Scheme 30)**.[113]



Scheme 30 [113]

3 Ligands for α4β2 nAChRs

For α4β2 nAChRs there are two potential binding sites where agonists and antagonists bind. The ACh binding site resides at the interface of the α subunit and the neighbouring subunit. Nature has produced an array of potent and selective ligands such as epibatidine, cysteine and nicotine, which have provided a basis for drug design for nAChRs due to their therapeutic potential. A common feature of these ligands and their analogues is their low affinity for α7 relative to α4β2 nAChRs.

3.1 Agonists

Modifications of the linker between the pyridine and pyrrolidine rings in nicotine has resulted in several high-affinity and potent nAChRs.[36] The A-85380 compound **105** binds to the native α4β2 nAChRs with affinities comparable to that of (-)-epibatidine K_i 0.015 nM and 0.009 nM, respectively.[114-116] Its analog 5-Iodo-A85380 **109** showed extremely high affinity for the same receptor with K_i = 0.010 nM **(Figure 46)**. [117]

Cysteine is a potentially interesting lead for the development of subtype selective nAChR ligands due to its inherent preference for neuronal nAChRs over the muscle-type nAChRs in comparison to other ligands ACh, nicotine, or epibatidine. Bromination at the 3-position of the pyridone ring of cysteine resulted in a 10-fold increase in agonist potency **106** and efficacy on the α4β2 nAChR compared to that of (-)-cysteine (K_i = 0.16 nM) **(Figure 46)**.[10]

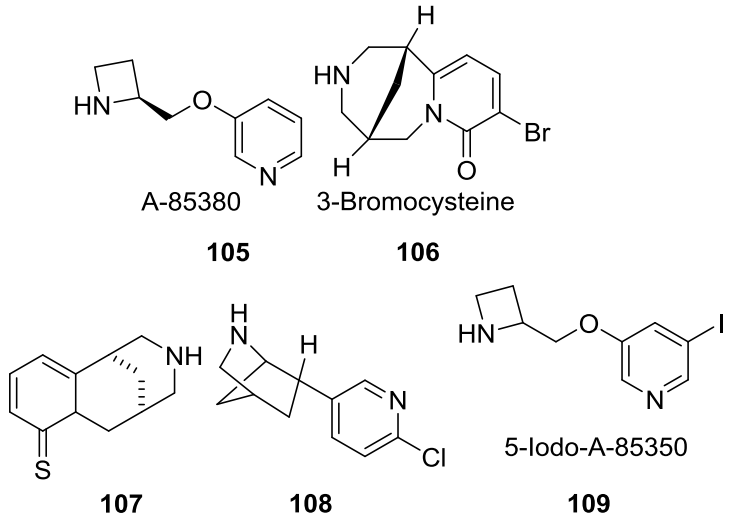


Figure 46

The replacement of oxygen for sulphur led to thiocysteine **107**, which was shown to bind with subnanomolar affinity at the α4β2 subtype, with improved selectivity to cysteine itself.[10, 118] Epibatidine analogues in which the basic nitrogen on the bicyclo[2.2.1]heptane nucleus has been moved from position 7 into position 2 have been shown to retain the high affinity of epibatidine **108** on the α4β2 subtype with K_i 0.056 nM **(Figure 46)**.[119]

3.1.1 Antagonists

Analogues of naturally existing antagonists have also shown selectivity for the α4β2 receptor.

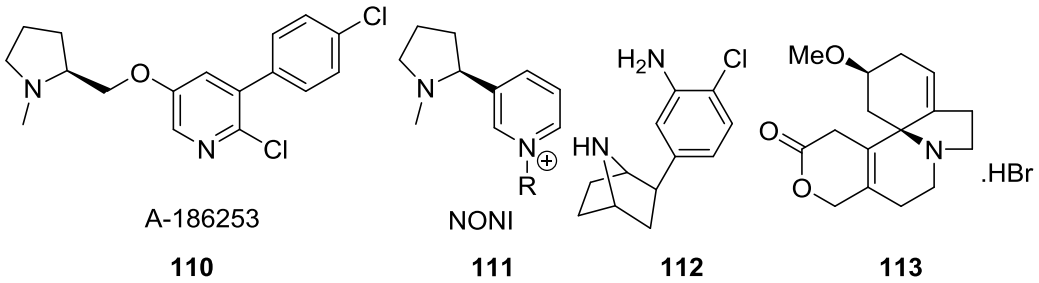


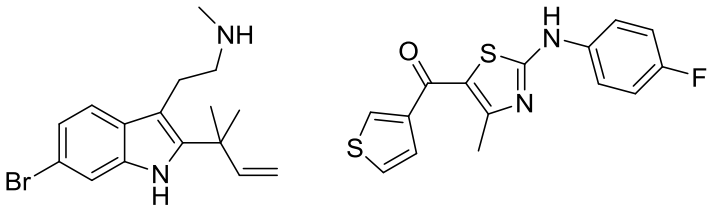
Figure 47

The introduction of *n* –alkyl groups ranging from methyl to dodecyl at the pyridine nitrogen of (*S*)-nicotine has produced compounds **111** displaying binding affinities

ranging from high-nano molar to mid-micromolar concentrations at the native α4β2 nAChRs. There is a clear correlation between the *n* –alkyl chain lengths of the compounds and binding affinities at α4β2, except for NONI **111**, which displayed weak binding to the receptor, but was a potent dopamine inhibitor.[120] The pyridyl ether A-186253 **110** displays high selectivity for α4β2 over the α3β4 and α7 receptors in binding assays.[121] The most potent competitive nAChR antagonists have come from epibatidine,[122-124] with a K_i value of 1 pM in the epibatidine binding assay on rat brain α4β2 nAChRs **112**, has the highest binding affinity reported to date.[123] A purely competitive nicotinic acetylcholine receptor antagonist is dihydro-beta-erythroidine (DhβE) **113**, an alkaloid originating from *Erythrina* seeds. Sub-micromolar concentrations of DhβE have been found to block both human and rat α4β2 nAChRs with moderate selectivity for the neuronal α4 receptor subunit (IC_{50} value 0.37 μM for α4β2 receptor) **(Figure 47)**.[125]

3.1.2 PAMs

Desformylflustrabromine **114** is a metabolite of the marine bryozoans *Flustra foliacea.*[126, 127] It is a derivative of tryptamine.[127, 128] When co-applied with ACh, dFBr was shown to selectively potentiate ACh-induced responses on α4β2 nAChRs in the nano- molar range (EC_{50} = 120 nM), with potent type II positive allosteric modulator selectivity for α4β2 nAChRs.[127, 129] When co-applied with ACh it causes an increase in the affinity and efficacy.[127, 129] This pharmacological response is similar to that observed with PNU-120596 which is a PAM on α7 nAChRs **(Figure 48)**.[127, 130, 131]



114 **115**

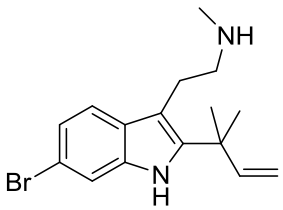
Figure 48

LY-2087101 **115** displays 14.7-fold selectivity for α4β2 over homomeric (α7) receptors.[132] The amplitudes of submaximal ACh-induced responses (100%) at α4β2

nAChRs were potentiated to 742 ± 63 fold, in the presence of 3 μM **115**.[132] Submaximal ACh-induced responses at α4β2 nAChRs were potentiated in a concentration-dependent manner by LY 2087101 **115** (between 30 nM and 30 μM), yielding EC_{50} values for potentiation of 0.99 and 1.1 μM at α4β2 nAChRs, respectively.[132] At concentrations required for potentiation LY-2087101 **115** did not displace [^{3}H]-epibatidine from the agonist binding site and potentiation was observed at all agonist concentrations, suggesting a competitive allosteric mechanism of action **(Figure 48)**. [127]

3.2 Synthesis of Desformylflustrabromine (DfBr) analogues for α4β2 nAChRs

Indoles and indole derived heterocycles are common structural precursors in alkaloid natural products, pharmaceuticals, medicinal products and organic materials,[133-139] such as, desformylflustrabromine **114 (Figure 49)**, a natural product which has been synthesised *via* a non-catalytic method as reported by Lindel *et al*.[126, 129] Compound **114** is reported to act as a selective PAM on the α4β2 receptor of nAChRs.[140, 141] Given the importance of indoles, much effort has been focused on the development of selective functionalisation of indoles at the N_1, C_2 and C_3 sites. Standard alkylation protocols necessitate the use of strong nucleophilic bases such as Grignard reagents which lead to a complicated mixture of C_1- and C_3-alkylated products.[142] Many groups have contributed towards solving the challenges associated with selective functionalization of substituted indoles through palladium catalysis.[143-153]

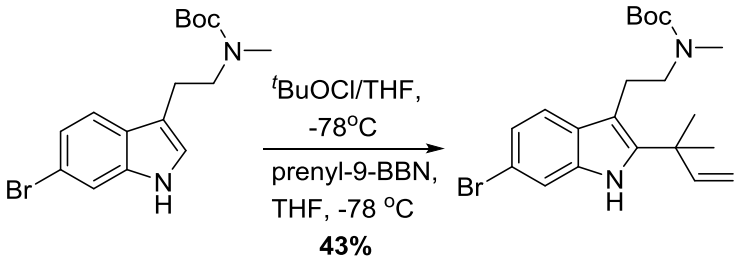


114

Figure 49. Structure of desformylflustrabromine **114**.[140]

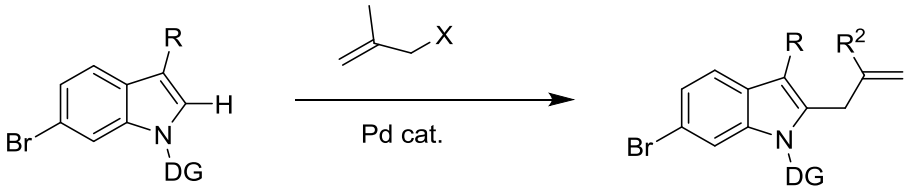
3.2.1 Aim

The prenyl functionality at the C-2 position present on the indole unit in desformylflustrabromine **114** was of interest. At present this prenyl moiety in **114** has been introduced *via* a classical boron-mediated prenylation method, which requires **(Scheme 31)** a large volume of 9-BBN to synthesise the starting material prenyl-9-BBN.[140, 141]



Scheme 31[129]

We were interested in exploring a catalytic approach to introduce an allyl functionality on indoles, by developing a direct Pd-catalysed allylation of indole **(Scheme 32)**.



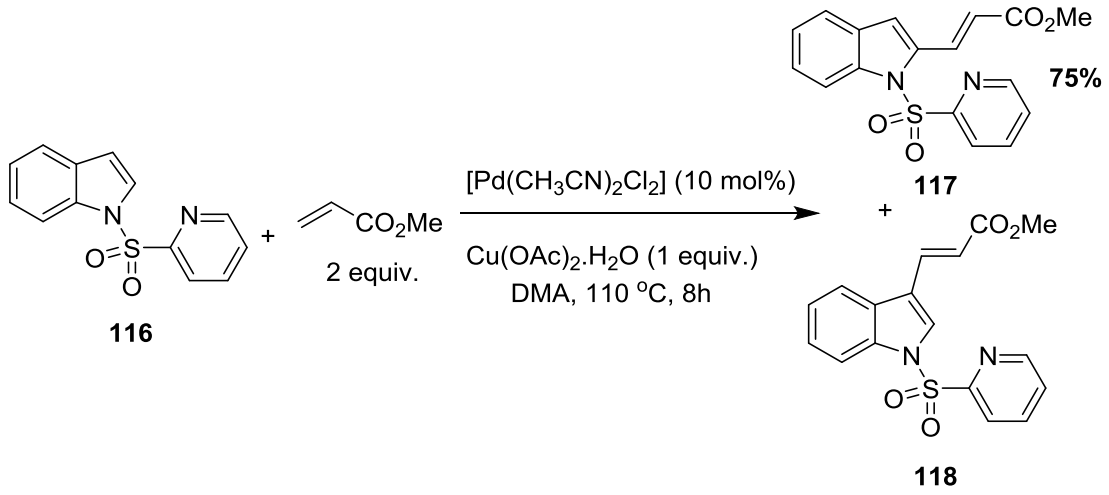
Scheme 32

This approach could potentially eliminate the use of moderately expensive (100 ml = £82) pyrogenic chemicals such as 9-BBN, which is used in stoichiometric amounts.[126] An extension of this methodology with introduction of substituted allylic electrophiles would be especially valuable, given the wide range of biologically active molecules containing prenylated indoles of this type. In addition, a catalytic version of the C-H activation would be highly desirable from an atom-economic and environmental perspective.

3.3 Results and Discussion

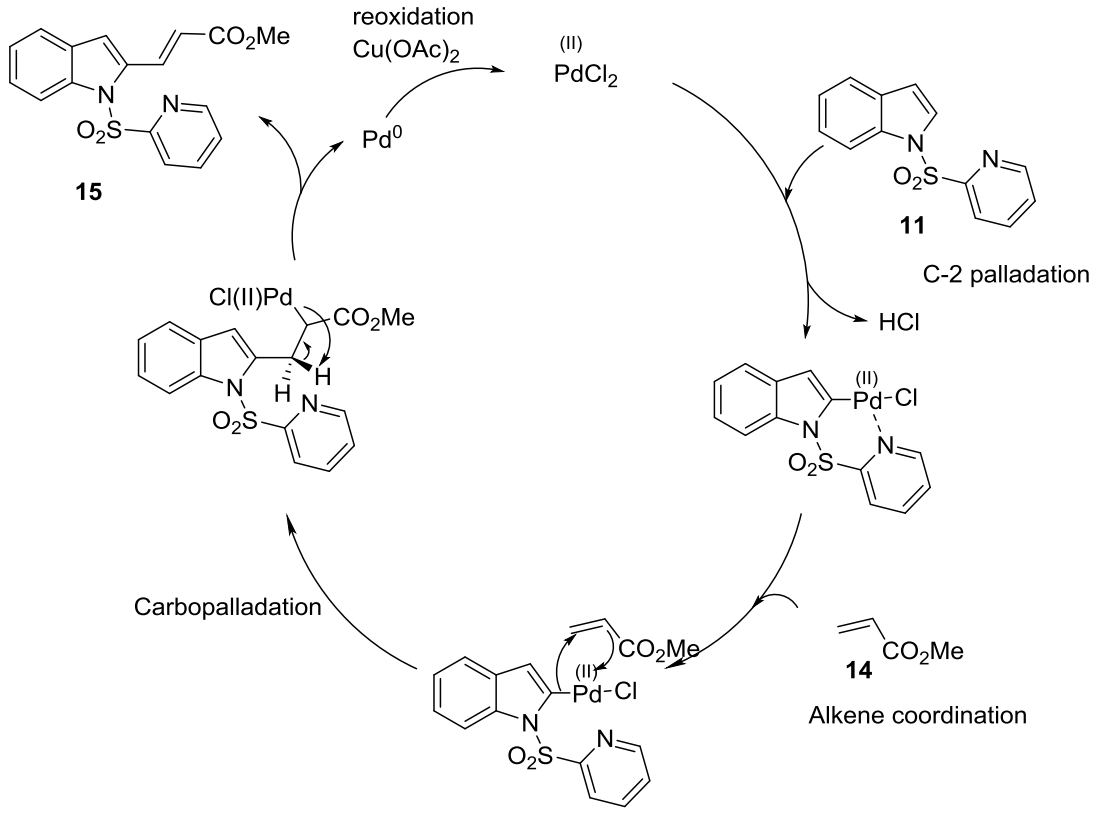
3.3.1 Directing group approach for regioselective C-2 allylation

A few groups have demonstrated regioselective alkylation of indoles with the use of directing groups such as *N* –pyrimidyl,[154-156] *N*-acetate,[157-159] *N*-pivalic acid.[158-160] Recently a paper by Garcia-Rubia and coworkers reported that C-2 alkenylation of indoles **117** could be regioselectively achieved over C-3 alkenylation **118** in a ratio of >98: <2, respectively in 75% isolated yield.[161] This was achieved using a 1-(2-pyridyl)sulfonyl moiety on the indole **116** as the directing and activating group as well as a readily removable protecting group on the indole nitrogen using the protocol shown (**Scheme 33**).[139, 161-165]

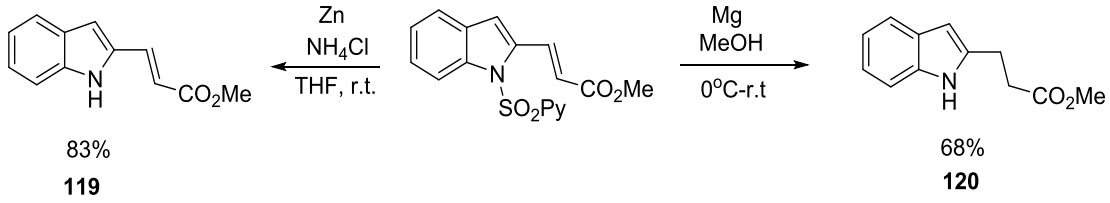


Scheme 33.

In addition, the reaction conditions were found to be compatible with a variety of substituted electron rich and electron poor alkenes as well as simple non-conjugated alkene such as 1-octene when using *N*-pyridylsulfonyl **(Scheme 33)** as the directing group. The reaction is suggested to proceed *via* a Heck mechanism to afford the product (**Scheme 34)**. Removal of the directing group under mild conditions in the presence of zinc or magnesium can also be achieved leading to direct formation of C2-alkenyl **119** or C2-alkyl **120** indoles[166] unlike the *N*-pyrimidyl directing group which requires harsh conditions to be removed **(Scheme 35)**. [154]



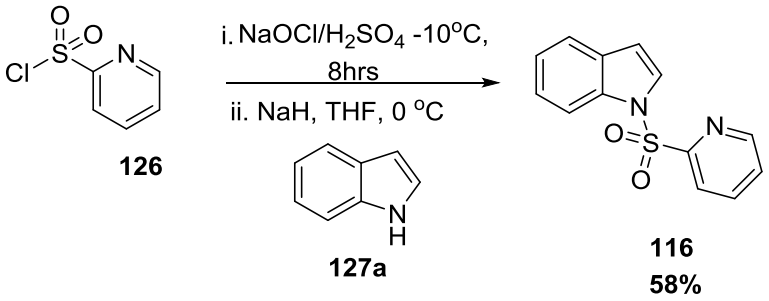
Scheme 34. Proposed mechanism



Scheme 35

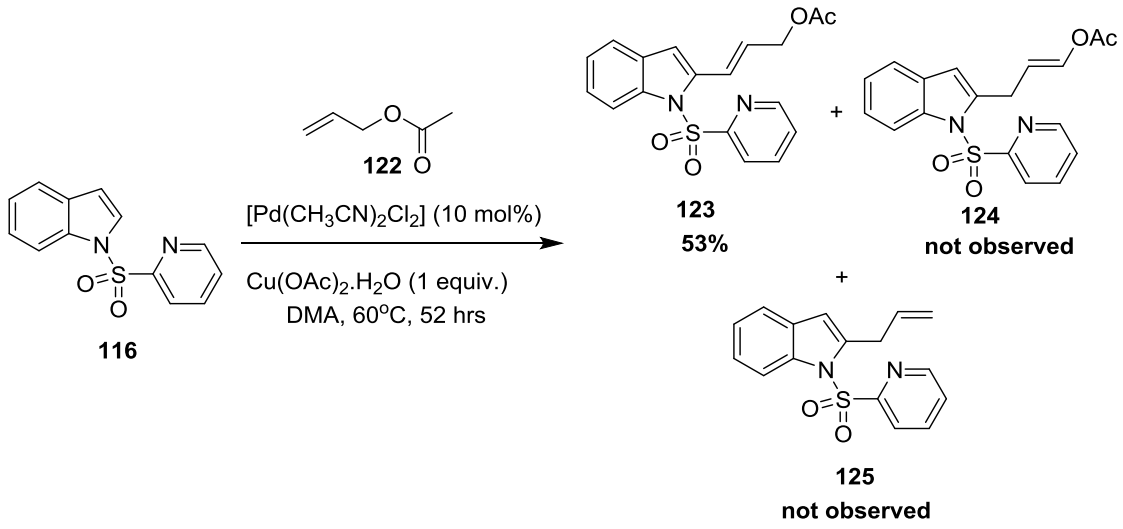
Although no precedent for regioselective C-2 allylation of indoles using a directing group has been reported to our knowledge, it was decided to explore the use of a 1-(2-pyridyl)sulfonyl moiety for the selective incorporation of an allyl moiety at the C-2 position of indole. It was proposed that using allyl acetate as the allyl precursor would result in acetate elimination and give Pd(II)$(OAc)_2$, which would be reused into the catalytic cycle without need of re-oxidation with Cu(II)$(OAc)_2$.

N–pyridylsulfonylindole **116** was synthesised by a two step procedure involving chlorination of 2-mercaptopyridine to give pyridine-2-sulfonyl chloride **126**.[167] Compund **126** was then subjected to nucleophilic attack by the indole nitrogen to afford **116** in 58% yield **(Scheme 36).**[161]



Scheme 36

The reaction was conducted in the absence of the $Cu(OAc)_2.H_2O$ oxidant under Garcia-Rubia's conditions, however, only the starting material **116** was observed with trace amounts of **123** in the crude mixture. This suggests that the oxidant is crucial for palladium coupling at the C-2 position of **116** and to reactivate the catalyst. Based on this result it was decided to repeat the reaction under Garcia-Rubia's protocol for C-2 coupling and to see if acetate elimination will be favoured over *β*-hydride elimination to give the C-2 allylated product **125 (Scheme 37)**. The reaction was conducted at a slightly lower temperature at 60 °C than reported by Garcia-Rubia to prevent any unwanted side reactions.



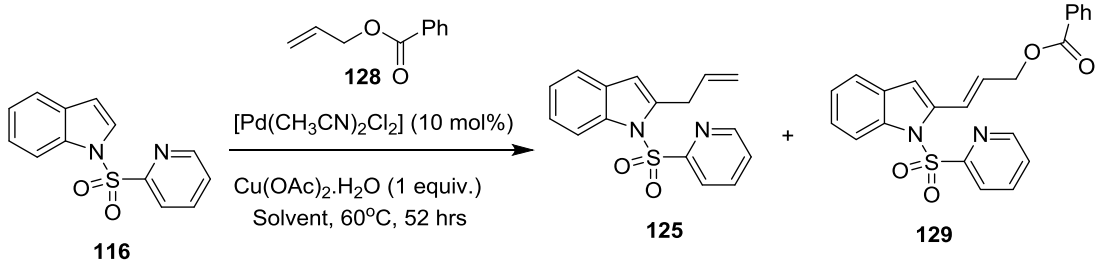
Scheme 37

Only the *β*-hydride elimination product **123** was observed in the reaction mixture, this compound was isolated in 53% yield **(Scheme 37).** The structure was assigned as **123** not **124** using HMBC spectroscopic data. The HMBC analysis showed a ^3J coupling between the carbonyl carbon signal at 170.9 ppm and $–CH_2$ at 4.77 ppm.

No acetate elimination product **125** was observed suggesting that β-hydride elimination is dominant under these conditions. The regioselectivity might be due to the greater acidity of the CH_2 protons near to the indole ring than the acidity of CH_2 protons near the acetate group, hence, elimination of the Pd-complex and the acidic proton near the indole ring is favoured.

The reaction between **116** and **128** was then explored, since it was considered that the benzoate group is a slightly better leaving group than the acetate group in allyl acetate, which might facilitate benzoate elimination over β-hydride elimination. The reaction was screened in a range of solvents as the nature of the solvent can control the regioselectivity of the reaction[168] and also might facilitate β-benzoate elimination. THF, DMA, toluene, DMF and DMSO were screened as the solvents, with 20 mol% of $Pd(MeCN)_2Cl_2$ as the catalyst and $Cu(OAc)_2.H_2O$ as the oxidant at 60 °C, with the reaction being monitored over a period of 52 hrs by TLC **(Table 11).** The reaction after 17 hrs showed no reaction in THF, DMA and toluene whereas an additional spot was observed which corresponded to **125** when the reaction was conducted in DMF or DMSO. On leaving the reaction for a further 35 hrs, a second spot was observed which corresponded to **129** in DMF and DMSO. Similarly, **129** was also observed in THF, DMA and toluene after 35 hrs. In addition, DMA showed a faint spot corresponding to compound **125** after 35 hrs.

Major products observed from crude ^1H NMR from these reactions are shown in **(Scheme 38**, **Table 11**).

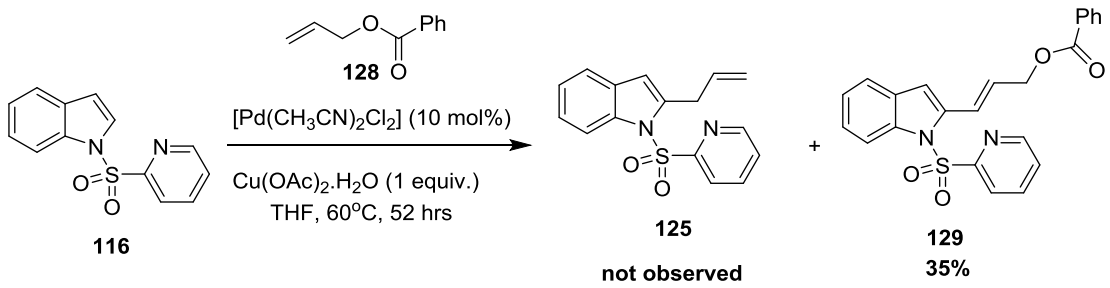


Scheme 38

Solvent	Time (hrs)	Major products
DMF	52	**125** and **129** (0.4 : 1)[a]
DMSO	52	**125** and **129** (1.8 : 1)[a]
THF	52	**129**
Toluene	52	**129**
DMA	52	**125** and **129** (0.5 : 1)[a]

Table 11. (a) Ratio of major isomers determined by ^{1}H NMR.

On repeating the reaction in THF on large scale, **129** was isolated in 35% yield **(Scheme 39)**



Scheme 39.

Analysis by ^{1}H NMR and HMBC showed that compound **129** was formed only, no presence of **125** was observed. This is supported by the HMBC spectrum, which shows the carbonyl carbon signal at 166.4 ppm (denoted as C-21 in **Figure 49**) having a ^{3}J coupling with the CH_2 at 5.03 ppm (denoted as H-19 in **Figure 49**).

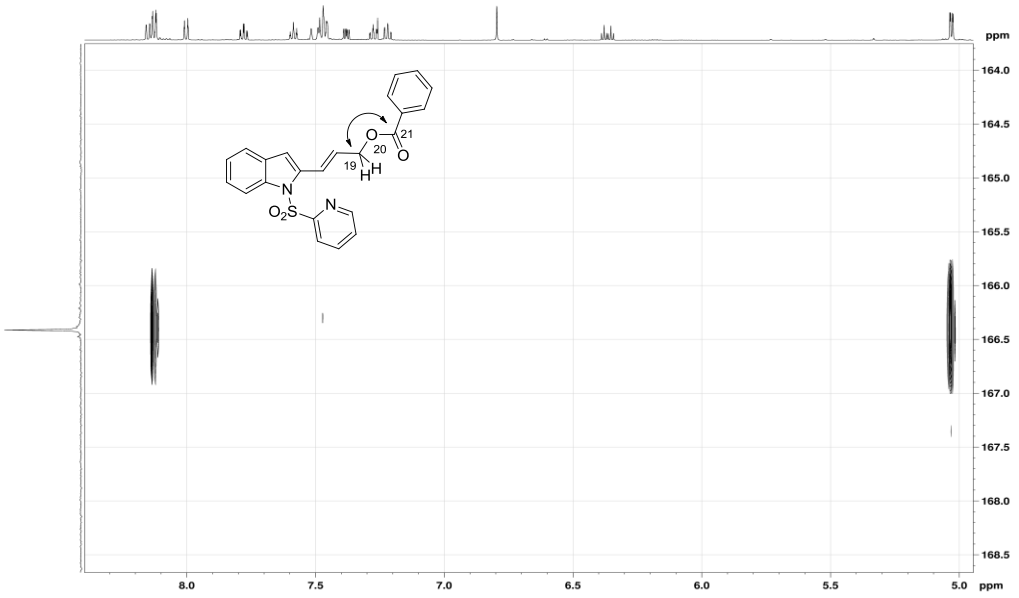
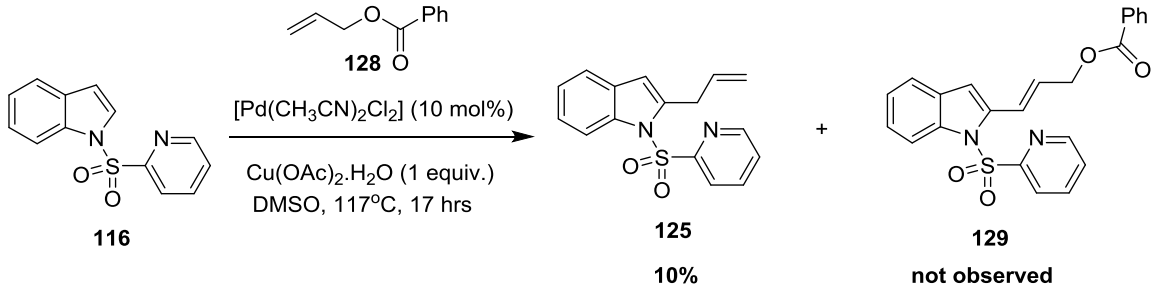


Figure 49

When the reaction was performed in DMSO on a large scale **(Scheme 40) 125** was isolated in 10% yield. Analysis by ^{1}H NMR and HMBC showed that C-9 at 109.1 ppm has ^{4}J coupling with H-17 at 3.97ppm **(Figure 50)**, which supports the formation of **125**.



Scheme 40

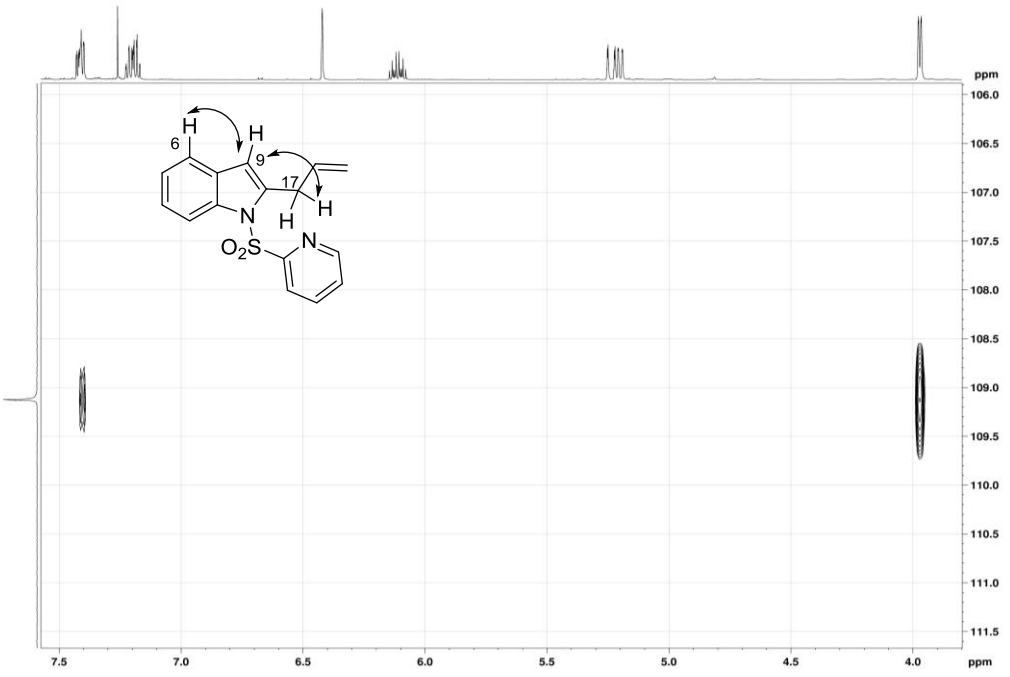


Figure 50.

The presence of **125** suggests that in polar aprotic solvents with large dielectric constants such as DMSO, DMF and DMA, elimination of the benzoate group can be favoured over β-hydride elimination. A possible explanation might be that polar, aprotic solvents such as DMSO, does not solvate the oxygen through hydrogen bonding. Hence, the lone pair on the carbonyl oxygen is less solvated, making it available to coordinate with the palladium intermediate complex in a syn conformation, enabling elimination of the benzoate leaving group **(Figure 51 (a))**. On the other hand non-polar and weakly polar aprotic solvents with small dielectric constants favour β-hydride elimination to give **129 (Figure 51 (b))** only.

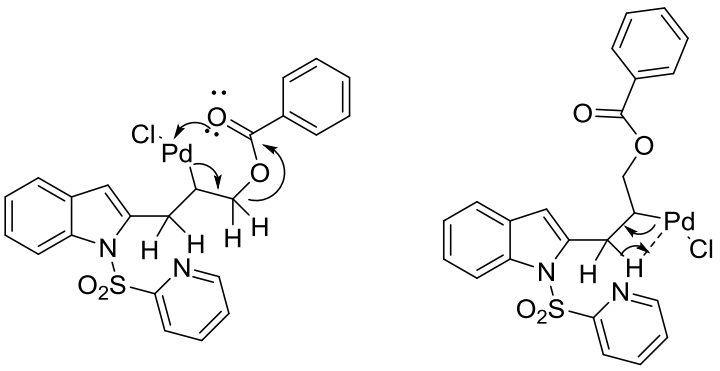
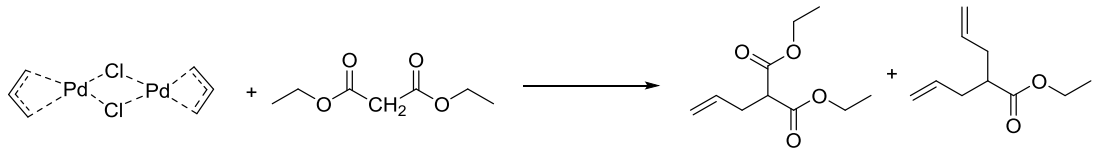


Figure 40 (a) and (b).

Although the directing group approach for regioselective C-2 allylation of indole afforded **125** in 10% yield, this synthetic approach was not promising enough to be investigated further.

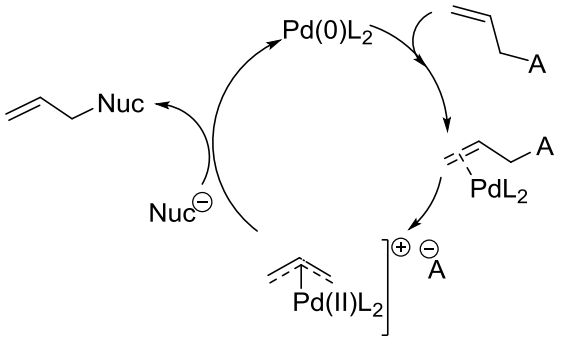
3.3.2 Non-directing group approach for regioselective allylation

Given the lack of success with the directing group approach for regioselective C-2 allylation, an alternative strategy was to focus on using indoles without directing groups, *via* the Tsuji-Trost allylation reaction. Tsuji and co-workers in 1965 were the first to report this reaction using a pre-formed π-allyl palladium complex with acetoacetate or ethyl malonate, which worked stoichiometrically **(Scheme 41)**.[169]



Scheme 41[169]

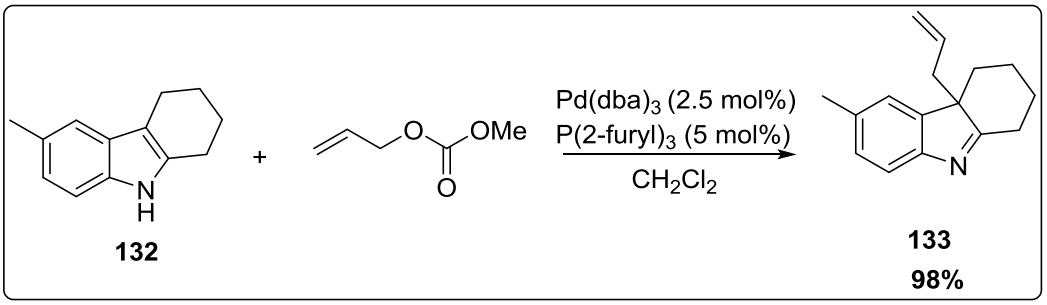
However, although organometallic reagents such as Grignard,[170, 171] act as nucleophiles, further independent studies by Trost and Tsuji building on previous work by Tsuji reported that π-allyl palladium complexes on the other hand were able to act as an electrophile towards C-nucleophiles such as malonates, acetoacetates, and enamines.[170-172] In addition, the Pd(0) regenerated after the reaction offered a catalytic process, which is now widely used in organic synthesis for the formation of C-C bonds **(Scheme 42)**.[170]



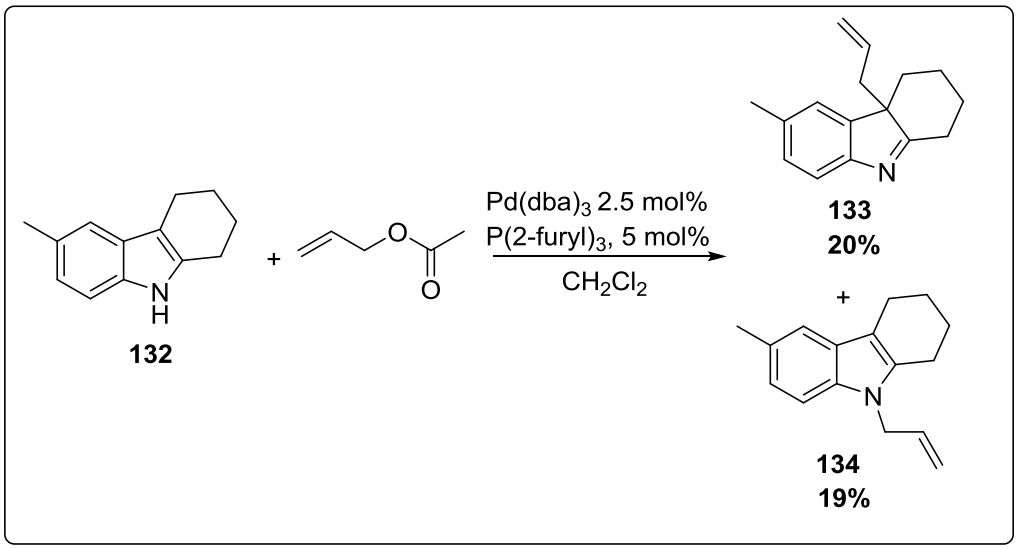
Scheme 42. General catalytic cycle of the Tsuji-Trost allylation.

As for allyl sources in the Tsuji-Trost reaction, a number of allylic precursors have been reported to be used for catalytic allylation reactions, with carbonate, acetates, and phosphonates being most widely used.[148, 152, 153, 170, 173, 174]

Regioselectivity for N1 or C3 alkylation has been achieved *via* Palladium catalysed allylation reaction using indole as the substrate by controlling the reaction conditions such as solvent, temperature, ligand and base. [134, 175] Recent reports such as by Rawal have explored a number of non-asymmetric approaches for C-3 allylation of indoles using allyl carbonate as the allyl source **(Scheme 43a).** [176 152, 173] However, the use of allyl acetate proved to be an ineffective allyl precursor under the conditions resulting in lower yield of the desired product **133** in 20% and the *N*-allylated product **134** was also obtained in 19% yield **(Scheme 43b).**[152]

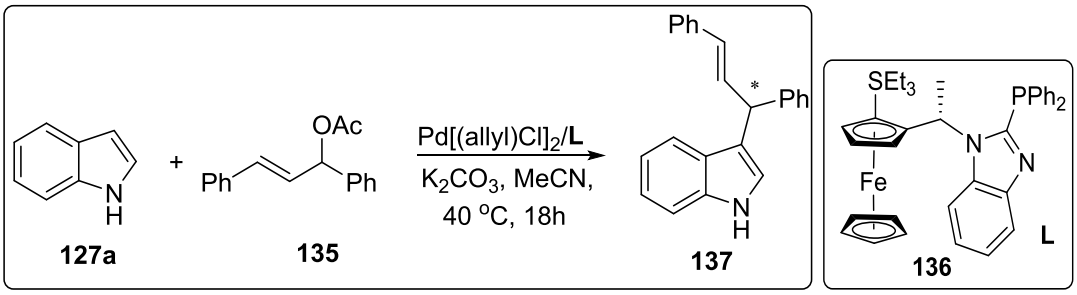


Scheme 43a[152]



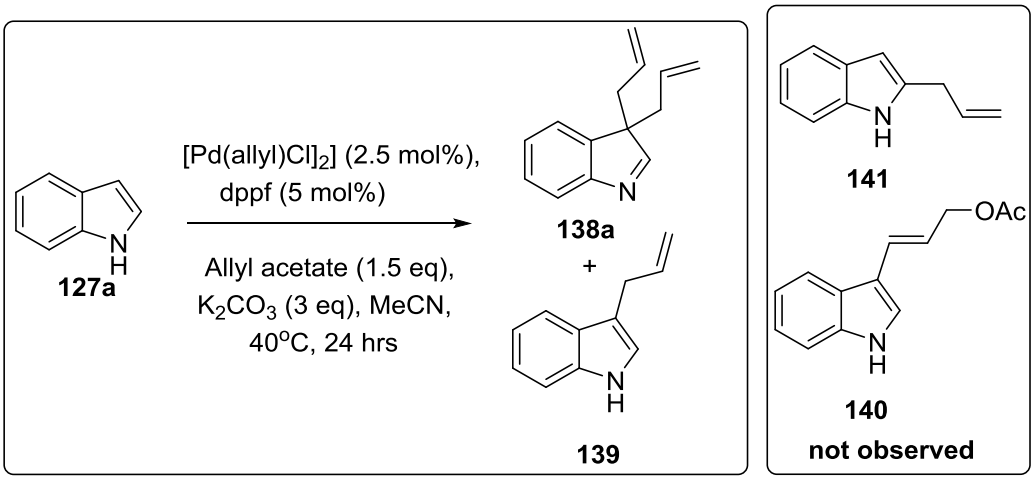
Scheme 43b[136]

Chan,[177] Liao[178] and You[179] however have demonstrated a catalytic and enantioselective approach for intra- or intermolecular versions using highly activated allylic acetates as the electrophiles with various Pd- and Ir- chiral complexes. For example, Chan has demonstrated that an asymmetric C-3 mono allylation of simple indoles **127a**, with 1,3-diphenyl allyl acetate **135** in the presence of a chiral ferrocene type ligand **136**, which gave the desired C-3 mono allylated product **137** in 74% yield and 95% *ee* **(Scheme 44)**.[177]



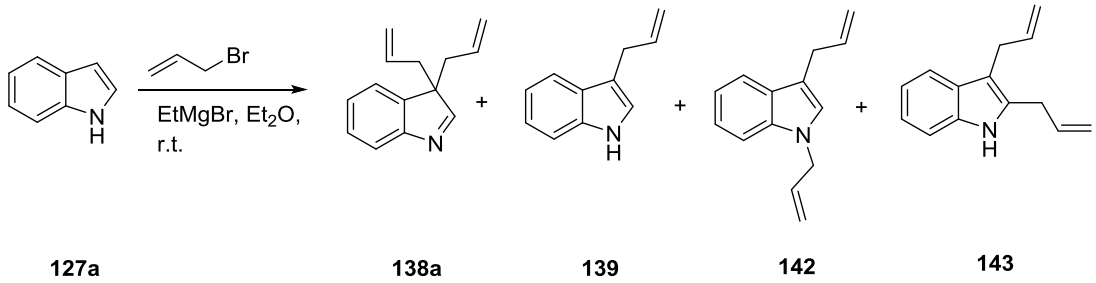
Scheme 44. Indole (0.3 mmol), $[Pd(C_3H_5)Cl]_2$ (2.5 mol %), ligand (5 mol %), 1,3-diphenyl-2-propenyl acetate (1.2 equiv), K_2CO_3 (2 equiv) in CH_3CN (2 mL).[177]

The aim of the project is to explore a regioselective C-2 direct Pd-catalysed allylation of indole using allyl acetate, in the absence of a directing group. The initial study was to determine the outcome of this reaction under the similar conditions reported by Chan, replacing the chiral ligand by a commercially available achiral diphosphine dppf ligand and allyl acetate. If the reaction works, it would be the first example to our knowledge of a regioselective C-2 allylation of indole using commerically available reagents in the absence of a directing group.To our surprise a mixture of **139** and **138a** in 2: 1 ratio was observed in the crude mixture. No β-H elimination product **140** or C-2 allyl indole **141** were observed.[180] The diallyl indolenine was isolated in 15% yield **(Scheme 45)**.



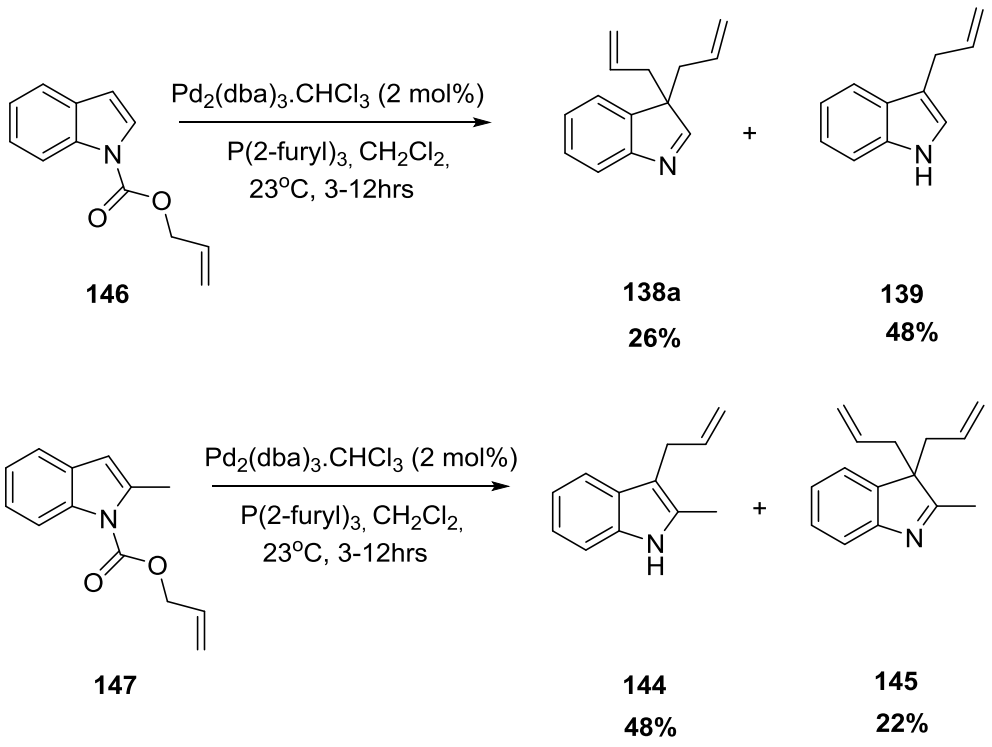
Scheme 45.

The earliest record of diallyl indolenine **138a** was by Pini in 1980 *via* a non-catalytic reaction between indole and allyl bromide in the presence of a Grignard reagent. In addition to diallylindolenine **138a**, byproducts **139**, **142** and **143** were identified **(Scheme 46).**[181]



Scheme 46[181]

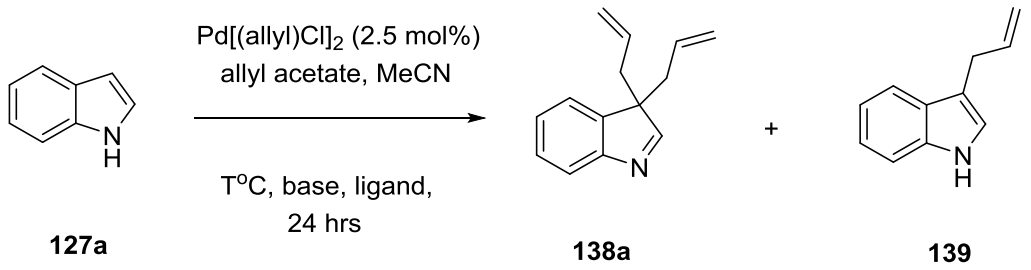
However, recently, Rawal reported a Pd catalysed approach towards diallyl indolenine **138a** which was isolated in 26% yield. In addition, 2-methyl indolenine **145** was also isolated in 22% yield. The compounds **138a** and **145** were formed using *N*-alloc indoles **146** and **147** where the allyl source is the more reactive carboxylate on the indole nitrogen (**Scheme 47)**.[182, 183]



Scheme 47

3.3.2.1 Optimisation of diallylindolenine formation

Although no C-2 allylation was observed, this reaction was interesting due to the use of allyl acetate and indole, both of which are cheap and commercially available. In addition, the isolation of compound **138a** could be potentially useful to create more complex structures with potential therapeutic properties. As a result of this interesting finding, a series of optimisation studies to favour **138a** commenced. Variation of the temperature, the type of bidentate ligand used, and the number of equivalents of potassium carbonate and allyl acetate were considered. The results are summarized in the **(Table 12)**.



127a **138a** **139**

Entry	K_2CO_3 (eq)	Allyl acetate (eq)	Ligand	T°C	Conversion %	Ratio of 139 :138a
1	2	1.5	Dppf	40	53 (15%)[a]	2 : 1[(a)]
2	2	2.2	Dppf	40	62	1 : 1[(b)]
3	2	7	Dppf	40	29	1: 0.2[(c)]
4	0	5	Dppf	40	-	No reaction
5	1	5	Dppf	23-80[(d)]	52	1: 0.4 [(c)]
6	3	5	Dppf	23-80[(d)]	91	0.8: 1.3 [(c)]
7	4	5	Dppf	23-80[(d)]	95	1 : 1 [(c)]
8	3	5	Dppf	r.t	97	1 : 2
9	3	5	Dppe	r.t	13	1 : 0
10	3	5	Rac-BINAP	r.t	63 (45%)[(e)]	1 : 1
11	3	5	DPEPHOS	r.t	>95% (82%)[(f)]	Trace: 1
12	3	5	Xantphos	r.t	76 (47%)[(g)]	0.6 : 1

Table12.[(a)] Diallylindolenine isolated in 15% yield. [(b)] Diallylindolenine isolated in 30% yield. [(c)] Reaction mixture observed by ^{1}H NMR resulted in unwanted side reactions making integration of products difficult, values are an estimate.[(d)] Temperature of reaction was conducted at 23°C for 4 hours then increased to 80°C overnight. [(e)] Diallylindolenine isolated in 45% yield. [(f)]Diallylindolenine isolated in 82% yield.[(g)] Diallylindolenine isolated in 47% yield.

Initially the effect of increasing the number of equivalents of allyl acetate in the reaction was studied. On increasing from 1.5 equivalents to 2.2 equivalents of allyl acetate the ratio of **139** to **138a** improved from 2: 1 to 1: 1 **(Entries 1 and 2)**.

However, on addition of 7 equivalents of allyl acetate, a complex mixture made it difficult to examine the ^{1}H NMR to integrate the ratio of **139** and **138a** accurately. It was deduced however from this reaction more **139** were formed upon increasing the equivalents of allyl acetate.Given that a complex mixture is formed with 7 equivalents of allyl acetate all further optimisation reactions were conducted using 5 eq of allyl acetate to prevent unwanted side reactions (as observed with 7 equivalents of allyl acetate, **(Entry 3).**

The effect of the base was then explored, when no base was present no reaction occurred **(Entry 4)** suggesting that the anion on nitrogen needs to be generated in order for the reaction to occur. On increasing the number of equivalents of base added to the reaction, formation of **138a** at room temperature was observed within a few hours when monitored by TLC **(Entries 6 and 7)** with 3 and 4 equivalents of K_2CO_3, but with 1 eq of K_2CO_3 only formation of **139** was observed **(Entry 5).** Furthermore, increasing the temperature of the same reaction **(Entry 5, 6** and **7)** from room temperature to 80°C resulted in a complicated mixture, despite complete consumption of the starting material **(Entries 5, 6** and **7)**. Based on the approximated ratio of **139: 138a (Entries 5, 6,** and **7)** the reaction with 3 equivalents of K_2CO_3 gave the best result of **139: 138a** with 0.8: 1.3 ratio, respectively. This reaction was repeated with 5 equivalents of allyl acetate and 3 equivalents of K_2CO_3 at room temperature, favouring the formation of **138a** over **139** in a ratio of 2: 1 **(Entry 8).** No reaction was observed with the use of a weak base such as KOAc.

Further, optimisation was achieved by screening various bidentate phosphine ligands.[145] We examined a panel of well-established commercially available phosphine ligands to see the effect of lower bite angle phosphine ligands such as BINAP and dppe **(Figure 41)**. The yield of **138a** was increased from 30% with dppf to 45% with BINAP. However, decreasing the bite angle of the phosphine ligand further to 86^{o} caused the reaction to become significantly slower even upon heating for several days, showing selectivity for **139** only. Recently, Rawal reported benzylation of indoles using DPEPhos as the ligand, with 15% of the dibenzylated indolenine as the side product.[173] Intrigued by his work we considered ligands with a larger bite angle such as DPEPhos (104^{o}). A substantial increase in the yield of **138a** from 30% with dppf to 82% with DPEPhos was observed **(Entries 10 and 11)**.

Increasing the bite angle further to 108^{o} with Xantphos resulted in the yield of **138a** being reduced to 47% **(Entry 12).**

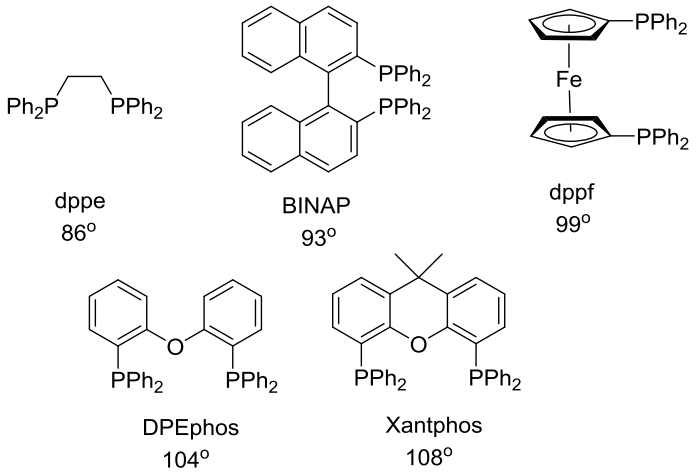
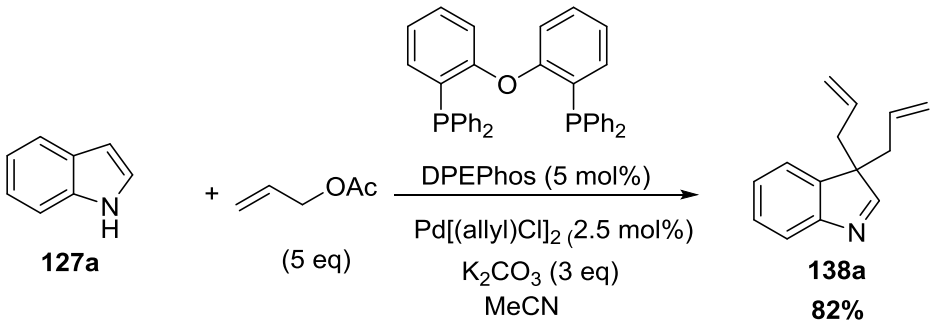


Figure 41. A few selected phosphine bidentate ligands and their bite angles.[184]

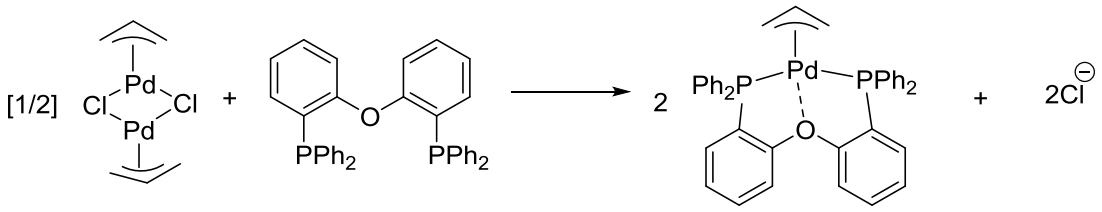
It can be concluded from this study that the bite angle is not of much importance in comparison to the backbone of the ligand. The presence of aflexible ether functionality between the phenyl groups as in DPEPhos seems to be preferable to the rigid ether functionality present in Xantphos. Furthermore, the oxygen in DPEPhos might also be assisting with coordination to the metal centre, further stabilizing the metal complex. The short functionalized saturated alkane backbone in dppe makes the reaction significantly slower.

Below is a summary of the optimised conditions for the synthesis of **138a (Scheme 48)**.



Scheme 48. Optimised conditions for the synthesis of **138a.**

3.4 Mechanism



Scheme 49. Showing ligand exchange and formation of the active species.

We propose that the reaction proceeds *via* the Tsuji-Trost allylation mechanism.The indole **127a** (pKa 16.7 (H_2O)) reacts *via* the nitrogen anion generated in the presence of the base, since the anion is more nucleophilic than the parent indole **127a**.[185] This is supported with our optimization result that when no base is present no reaction occurs **(Table 12, Entry 4).**

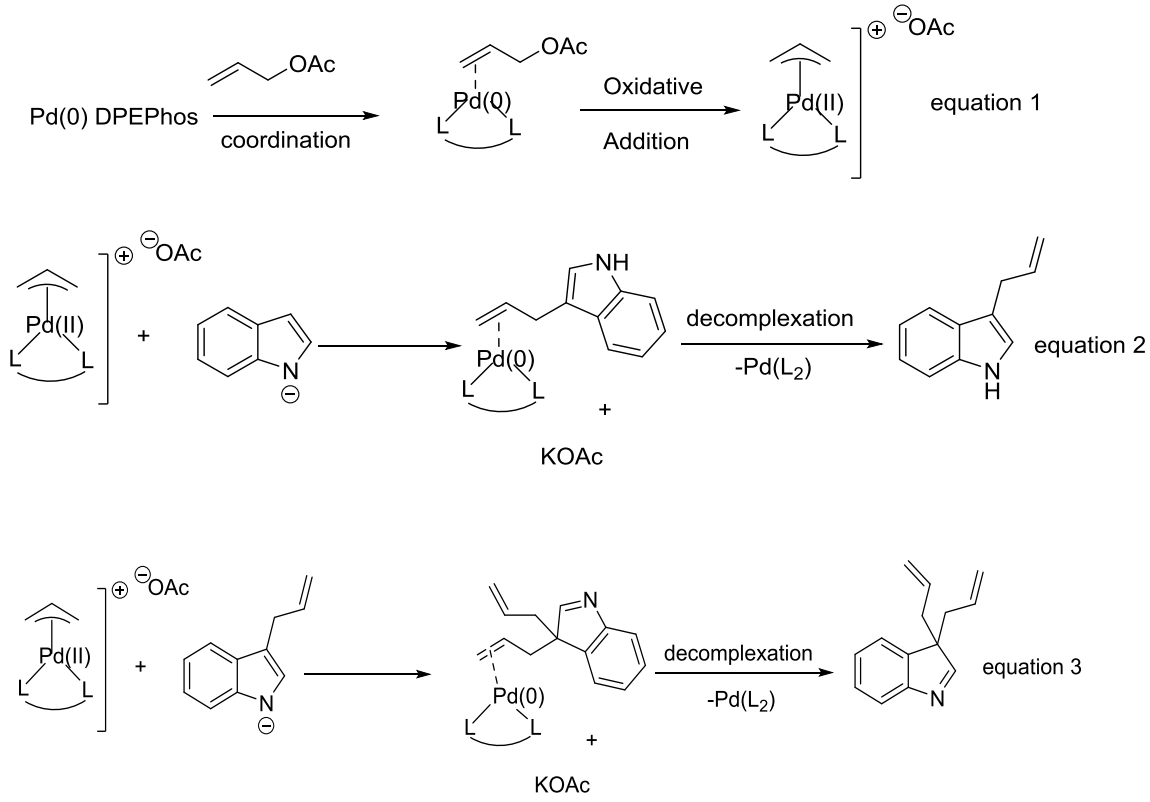
Equation 1: Illustrates the coordination of the active Pd(0)Ln species to allyl acetate anti to the leaving group, followed by oxidative addition to generate the π-allyl complex (**Scheme 50a).**

Equation 2: Illustrates depending on the strength of the nucleophile two pathways are possible:

a) Soft nucleophiles – direct addition to the allyl Pd complex.
b) Hard nucleophiles – attack at the Pd followed by reductive elimination.

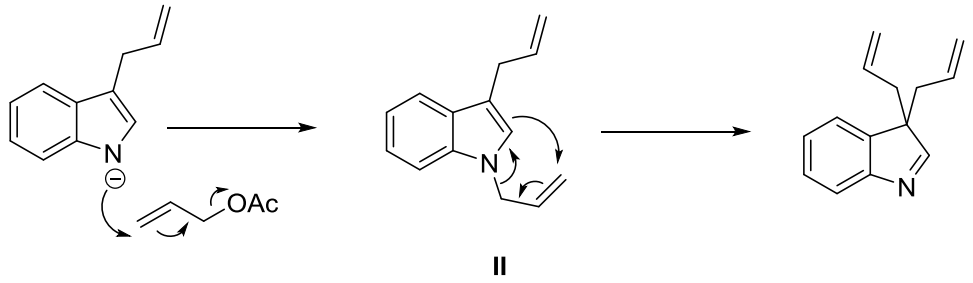
However, given the pK_a of indole is 16.7 (H_2O), which is less than pKa of <25 it is classified as a soft nucleophile.[134] Hence the reaction is followed by nucleophilic attack at the terminal η^3-allyl Pd (II) ionic complex anti to Pd(II)Ln (equation 2) this is known to occur *via* an outer sphere mechanism.[186-188]

Equation 3: Monoallylindole as the substrate to furnish a new allylation *via* equation 2 mechanism **(Scheme 50a).**



Scheme 50a. Proposed reaction mechanism *via* Tsuji–Trost allylation mechanism

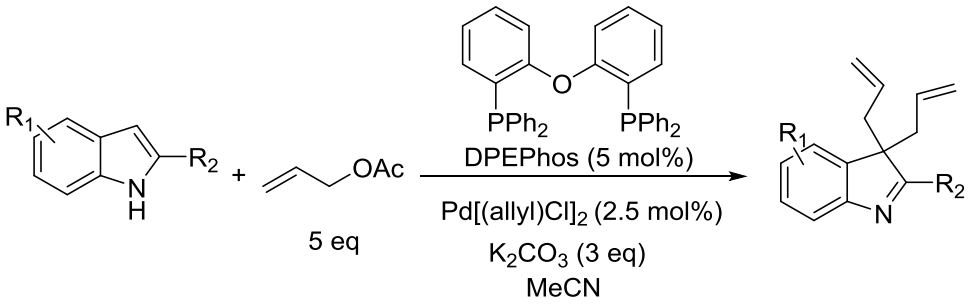
Another possible mechanism could be that upon formation of monoallyl indole *via* the Tsuji-Trost allylation mechanism, nucleophilic attack on allyl acetate by the nitrogen anion gives intermediate **II**, which upon [3+3] allyl shift rearrangement might give the corresponding diallylindolenine (**Scheme 50 b)**.

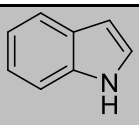
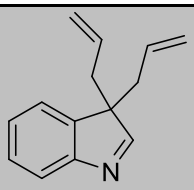
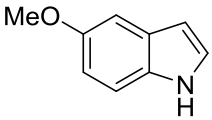
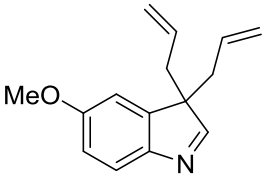
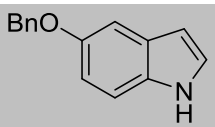
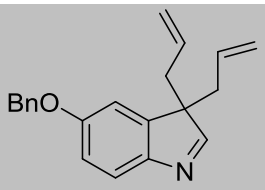


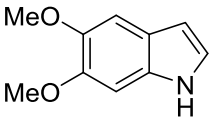
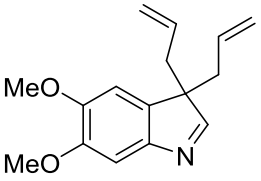
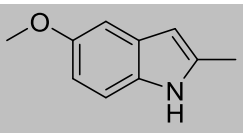
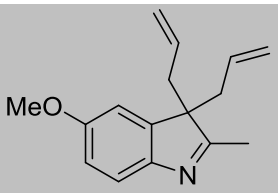
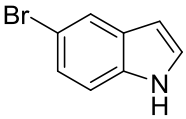
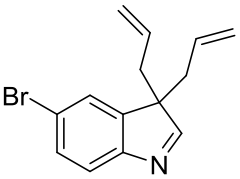
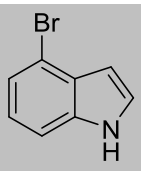
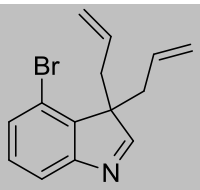
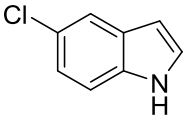
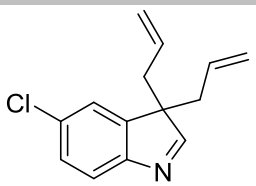
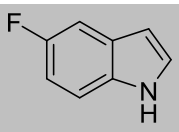
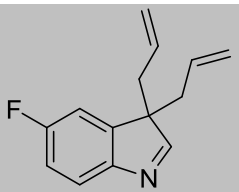
Scheme 50b. Another proposed mechanism towards diallylindolenine *via* [3+3] allyl shift of 1, 3–diallyl indole.

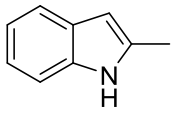
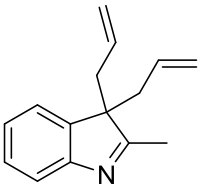
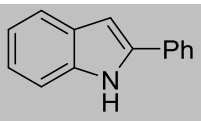
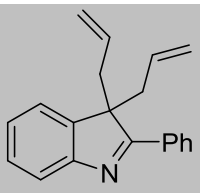
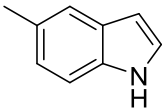
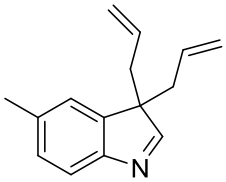
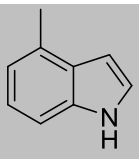
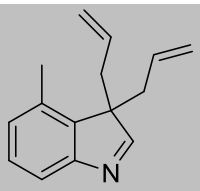
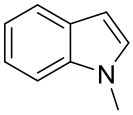
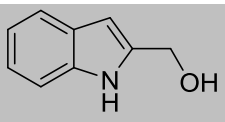
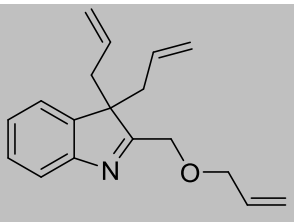
3.5 Substrate scope of diallylation (and monoallylation) of substituted indoles

With optimised conditions in hand, the scope of this double dearomatizing allylation reaction was explored. Pleasingly, a wide range of substituted indoles could undergo this reaction in good to excellent yields. The reaction was tolerant of a variety of substituents on the benzene ring and also at the C-2 position of the pyrrole unit. Gratifyingly, indoles bearing an electron-donating group **(Table 13, Entries 2-5)** gave the corresponding products **138b-138e** in excellent yields ranging from 88-76% **(Table 13)**.



Entry	Substrate	Product	Yield (%)
1	 **127a**	 **138a**	82
2	 **127b**	 **138b**	76
3	 **127c**	 **138c**	76

4	 **127d**	 **138d**	**88**
5	 **127e**	 **138e**	**80**
6	 **127f**	 **138f**	**58[a]**
7	 **127g**	 **138g**	**56 [a]**
8	 **127h**	 **138h**	**41[b]**
9	 **127i**	 **138i**	**32**

10	 **127j**	 **138j**	**98**
11	 **127k**	 **138k**	**74**
12	 **127l**	 **138l**	**66**
13	 **127m**	 **138m**	**57**
14	 **127n**	**N.R**	**N.R[c]**
15	 **127o**	 **148**	**30**

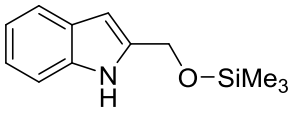
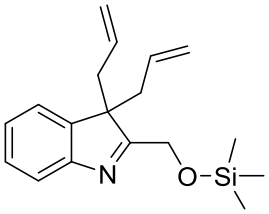
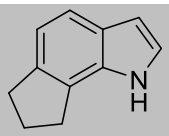
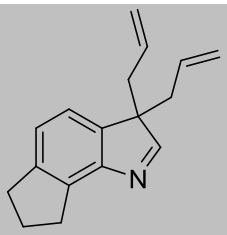
16	 **127p**	 **138n**	**66**
17	 **127q**	 **138o**	**50**

Table 13. All reactions were conducted at r.t. unless stated otherwise for 24 hrs. (a) Heated for 8 hrs at 50°C. (b) Heated for 3 hrs at 50 °C then left to stir for 21 hrs at r.t. (c) Left to stir for 48 hrs.

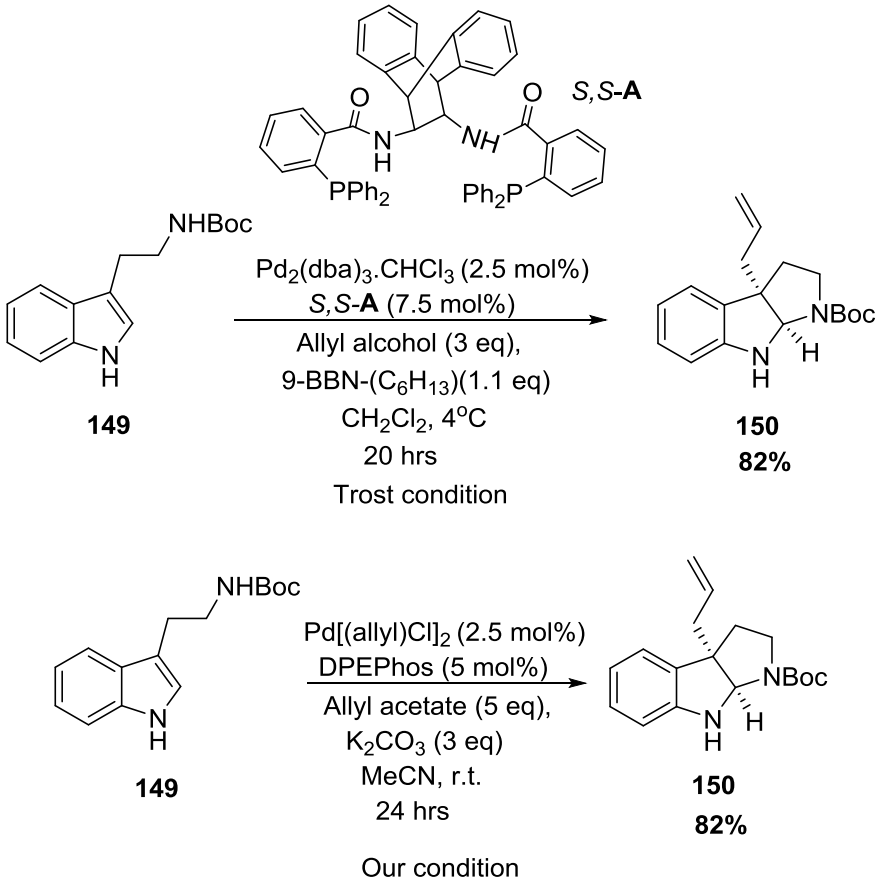
The halogenated indoles gave moderate yields of the desired product ranging from **32-58% (Entries 6-9)** under standard conditions. No reaction occurred with **127f** and **127g** at room temperature, however, when heated at 50 °C the reaction proceeded to give the diallyl indolenines **138f** and **138g** in moderate yields in 58% and 56%, respectively. This is behaviour observed with substituted bromo indoles might be due to poor overlap of the 4p orbital of bromine with the phenyl group, hence resulting in poor electron donating ability.[189] In the presence of an external energy in form of heat this might overcome the activation energy. This mismatch in orbital overlap decreases as you go from bromine to fluorine and hence, reaction proceeds to give the diallylated products without need of thermal energy. However, as electronegativity increases from bromine to fluorine the electron withdrawing ability by induction increases resulting in lower yield.[189]

The presence of a substituent at C-2 in **127j** and **127k** did not impair the reaction at all, despite the potential steric crowding around the reaction site, with **138j** affording the corresponding product in 98% yield **(Entry 10).** Based on this result, the effect of varying the position of the methyl group on the reaction was then explored. Both **127l** and **127m** gave the corresponding diallylated products in moderate yields in 66% and 57%, respectively **(Entry 12 and 13)**, much lower than when the methyl group was at the 2-position **(Entry 10)**.

It is worth nothing that when the methyl group is present on the nitrogen in **127n** no reaction occurred. This suggests that the reaction is affected by the electronic nature of the indole as well as the position of the functional group on the indole. In addition the proton on the nitrogen is necessary for the reaction to occur.

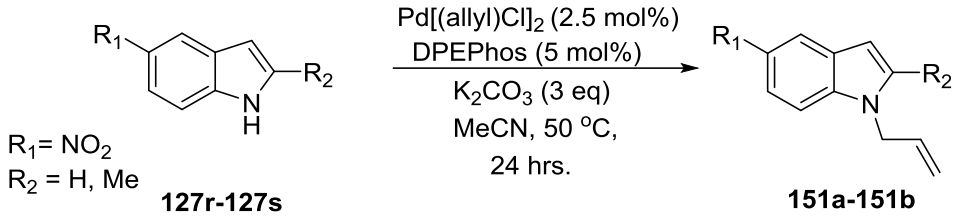
A reaction with a 5-hydroxyl indole resulted in a complex mixture which was difficult to examine by ^{1}H NMR. No diallylated product was present despite the electron donating ability of the hydroxy group. This observation was avoided by increasing the distance of the hydroxyl group from indole by an extra CH_2 group, to prevent direct influence of the OH group on the indole substrate. As expected the reaction worked giving the *tri*-allylated indolenine **148** in 30% yield **(Entry 15)**. It was interesting to see that under the reaction conditions, allylation on the oxygen was observed. It is possibsle that the yield of **148** could have been improved had the number of equivalents of allyl acetate added to the reaction been increased. After silyl protection of the hydroxyl group **138n** was obtained in good yield of 66% **(Entry 16)**. Furthermore the presence of a fused cyclopentane ring at the 6 and 7 position on the indole **127q** gave the corresponding **138o** product in modest yield of 50% **(Entry 17).**

A previous report by Trost had described the formation of a tricyclic alkaloid **150** by conducting a palladium catalysed allylation on Boc-protected tryptamine **149**, using trialkylborane and allyl alcohol **(Scheme 51).**[190] Application of our condition resulted in allylation of **149**, which gave **150** in excellent yield **(Scheme 44).**



Scheme 51. Showing Trost reaction condition for the synthesis of **150** (above); our optimised condition for the synthesis of **150** (below).

The presence of strongly electron-withdrawing groups on the indole **127r** and **127s** led to lower reactivity at room temperature. However, on heating at 50 °C only the *N*-allylated products were formed, which were isolated in excellent yields **(Table 14, Entries 18-19)**.



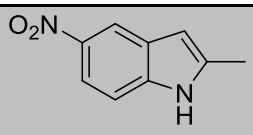
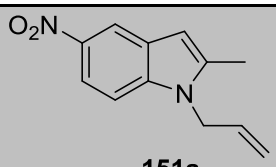
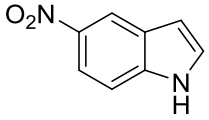
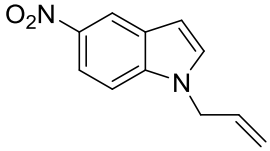
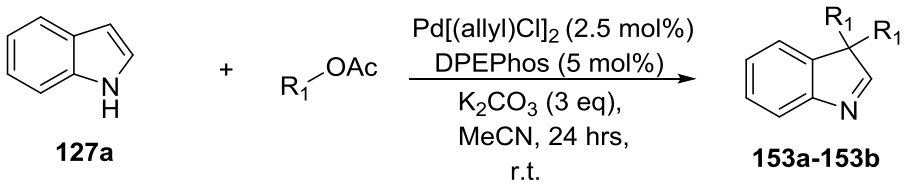
Entry	Substrate	Product	Yield (%)
18	 127r	 151a	86
19	 127s	 151b	79

Table 14.

The reaction scope with various substituted allyl acetates was also studied but this resulted in no reaction, giving just the starting materials under the protocol conditions. However when crotyl acetate **152** was employed as the allyl precursor the branched mono allyl indole **153a** product was observed and was isolated in 43% yield **(Table 15).** This was interesting as it is known that reactions involving unsymmetrically substituted allyl substrates often give a substrate-dependent product distribution.[33-36] For example with allylation using (*E*)-substrates with Pd-complexes having bidentate phosphine ligands usually results in formation of the linear (*E*)-product.[28]



127a 153a-153b

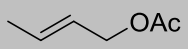
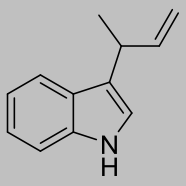
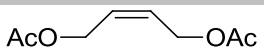
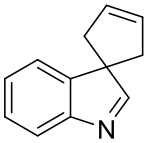
Entry	Substrate	Product	Yield%
1	 152	 153a	43%[(a)]
2		 153b	Trace[(b)]

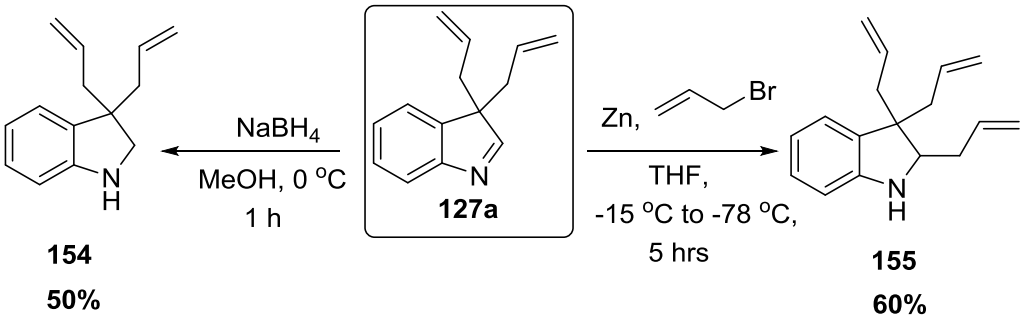
Table 15. [(a)] Reaction conducted at 40°C. [(b)] Trace amounts of cyclopenta-indolenine not isolated.

With (Z)-but-2-ene-1,4-diyl diacetate as the allyl precursor, trace amounts of the cyclopenta indolenine **153b** was observed in the ^{1}H NMR, but this was not isolated.

3.6 Reactions of substituted diallyl indolenine

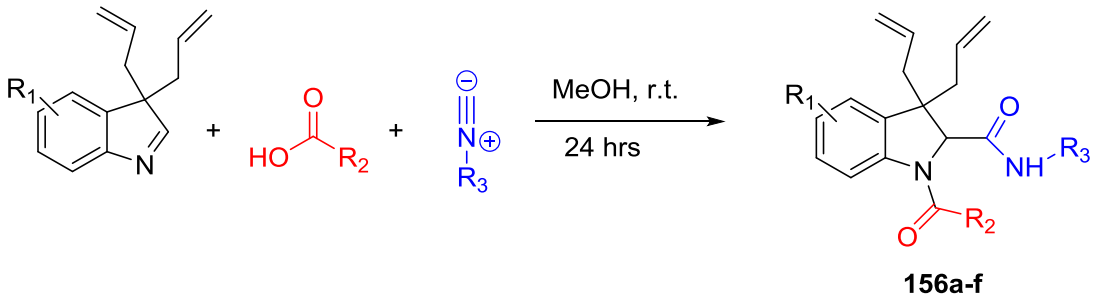
Having explored the substrate scope of the protocol with various substituted indoles **127a-127q**, the reactivity of the substituted diallyl products was then studied to create simple and complex molecules that could be interesting from a synthetic and pharmaceutical perspective.

On reduction of **127a** using $NaBH_4$ and allylation under Luche allylation conditions[191, 192] the corresponding products **154** and **155** were obtained in moderate yields of 50% and 60%, respectively (**Scheme 52)**.

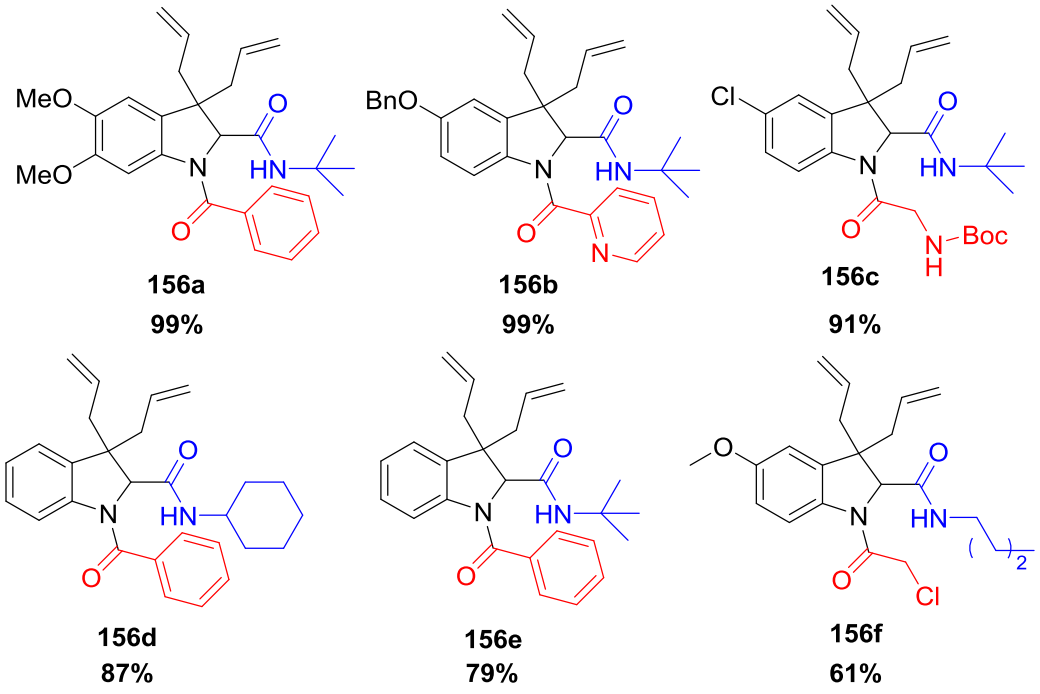


Scheme 52

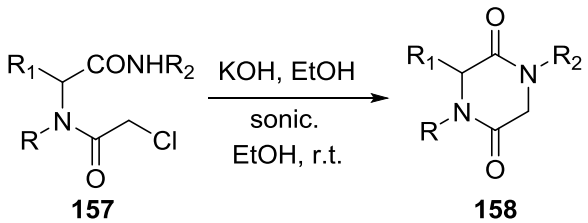
We thought it would be of interest to explore the reactivity of substituted diallyl indolenines under Ugi conditions as it would lead to an efficient route to complex molecules with potential drug like characteristics in two synthetic steps.[193] Gratifyingly, the reaction worked efficiently when using heteroaromatic and aliphatic carboxylic acids with sterically hindered isocyanides giving the corresponding Ugi products in excellent yields **(Scheme 53).**



Scheme 53



These Ugi products isolated could undergo further modification, particularly compound **156f**, which would be a suitable substrate to afford a cyclic product with potentially interesting biological activity. For example, compound **157** has been reported to undergo cyclisation to give the piperizinedione structure **158 (Scheme 54).**[194]



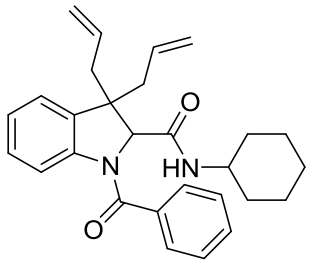
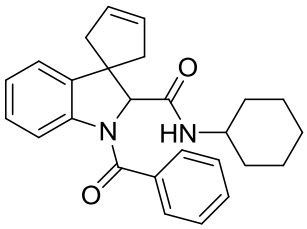
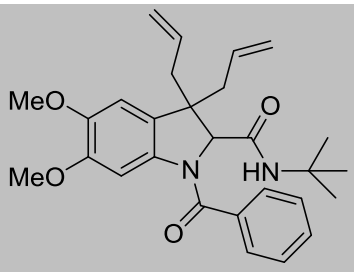
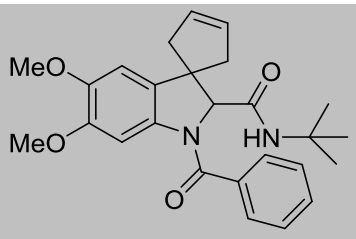
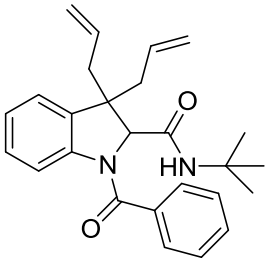
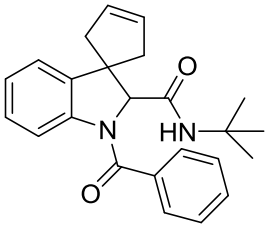
R = *o*-C_6H_{11}, R_1=4-BrC_6H_4, R_3= $C_6H_5CH_2$

Scheme 54

Several attempts were made to conduct ring closing metathesis of the diallyl functionality present in the indolenine compounds **138a** and **138k**, however, all proved unsuccessful with Grubbs 1st generation, 2nd generation and Grubbs-Hoveyda catalysts. This might be due to the imine nitrogen's ability to coordinate to the metal catalyst as a good ligand, hence, leading to the deactivation of the catalyst. However, on subjecting the products isolated from the Ugi reaction to the Grubbs 1st

generation catalyst, the reaction provided the desired spirocyclic indoline compounds in excellent yields **(Table 16)**.

159a-d

Entry	Substrate	Product	Yield %
1	 **156d**	 **159a**	**98**
2	 **156a**	 **159b**	**89**
3	 **156e**	 **159c**	**96**

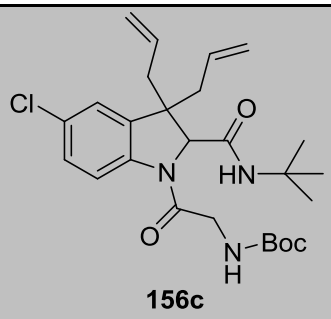
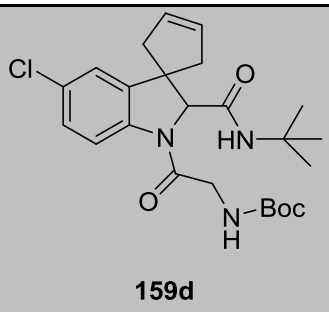
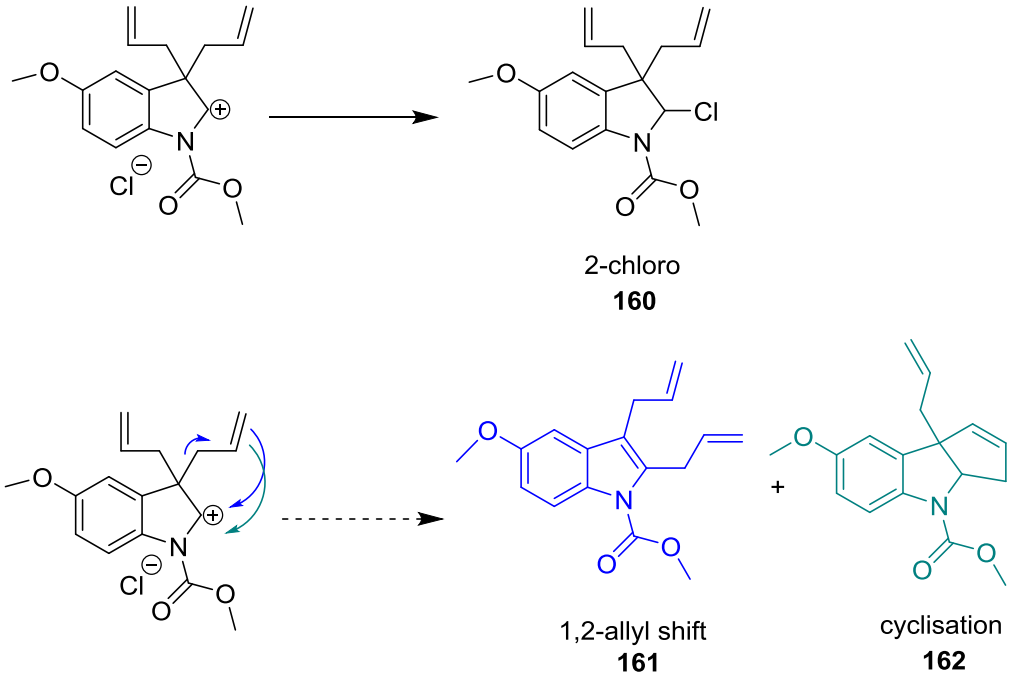
4		77
	 156c	 159d

Table 16

3.6.1 Reaction with Methyl Chloroformate

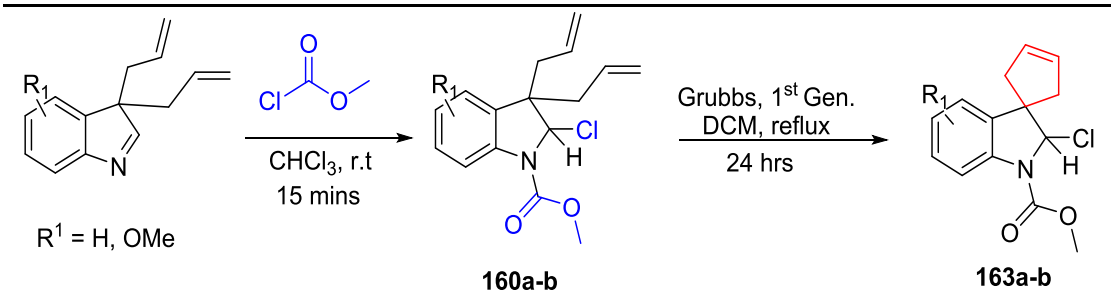
An alternative strategy for functionalization of the imine was devised *via* reaction with methyl chloroformate, which gave diallyl 2-chloroindolines **160a** and **160b** rather than the 1, 2-allyl shift **161** or cyclisation **162** of the allyl functionality **(Scheme 55)** proposed.



Scheme 55. Above: Structure of product **160** observed from the reaction; Below: Showing the possible products formed from the reaction between 5-methoxy diallyl indolenine and methyl chloroformate.

Nevertheless, these substrates readily underwent ring-closing metathesis to generate the corresponding spirocycles **163a-b (Table 17).** With room for further

functionalization at the chloride atom such as in situ metallation *via* Grignard formation in the presence of an aldehyde for example, butrylaldehyde.[195]



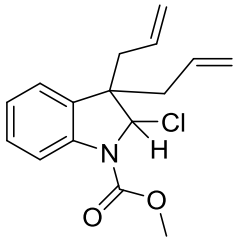
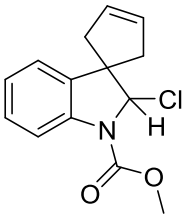
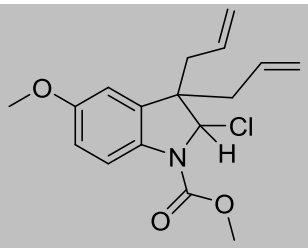
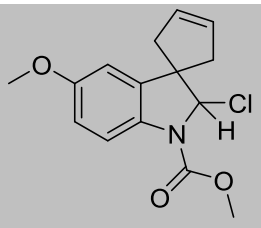
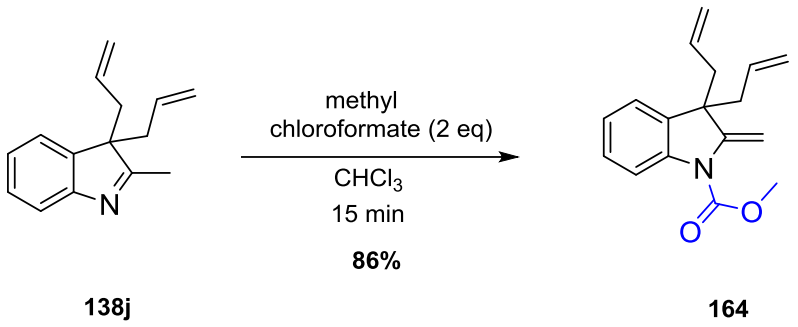
Product	Yield%	Product	Yield%
 160a	88	 163a	78
 160b	83	 163b	66

Table 17

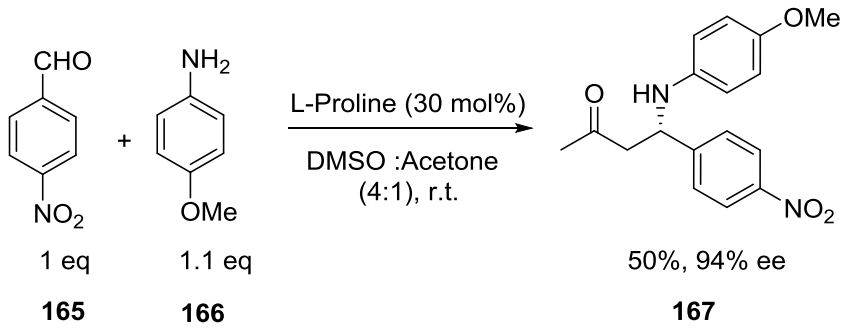
Interestingly, when 2-Me diallylindolenine **138j** was subjected under the same reaction conditions, **164** was obtained in 86% yield **(Scheme 56).**



Scheme 56. Structure of product **156** formed upon subjecting **138j** to methyl choroformate.

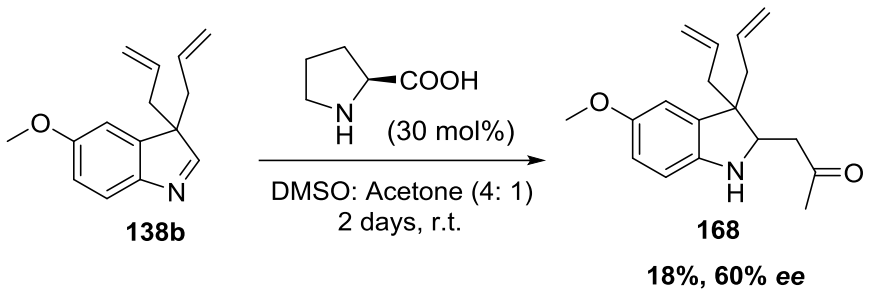
3.6.2 Asymmetric Proline Catalysed Mannich Reaction

A strategy for conducting an enantioselective catalytic addition of a carbon nucleophile to the imine group present in diallylindoline was envisaged. List has demonstrated that amino ketones **167** can be formed in moderate yield and excellent *ee* using an asymmetric L-proline catalysed Mannich reaction between aldehydes or ketones with amines. One such example is a proline catalysed Mannich reaction with acetone, *p*–nitro benzaldehyde **165** and *p*-methoxy aniline **166 (Scheme 57).**[196]



Scheme 57. [196]

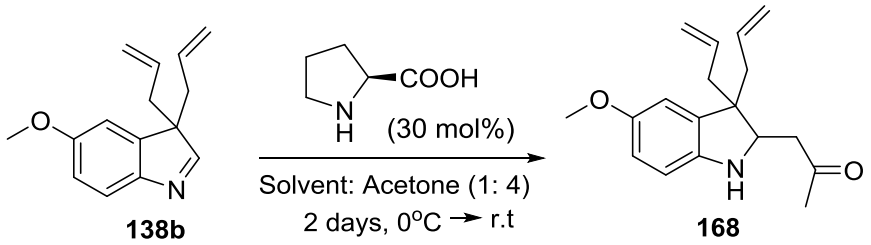
On subjecting our pre-formed imine **138b** under the procedure reported by List as previously mentioned above **(Scheme 57)**, the reaction worked to give the Mannich product **168 (Scheme 58)**, however the reaction did not go to completion. In addition, extracting the Mannich product from DMSO proved to be very difficult. Nevertheless, the Mannich product was isolated in 18% yield with a moderate 60% *ee* **(Scheme 58)**.



Scheme 58

Based on this interesting result the reaction was optimised by screening a range of solvents using an excess of acetone in a minimum amount of solvent. A ratio of 1: 4 solvent: acetone ratio at 0 °C to r.t. over a period of 2 days was decided.

3.6.2.1 Optimisation



Solvent	Conversion of S.M %[(a)]	e.r.
DMSO	95	99 : 1
$CHCl_3$	95	99 : 1
MeCN	69	>99: 1
MeOH	95	55: 45
DMF	63	99 : 1

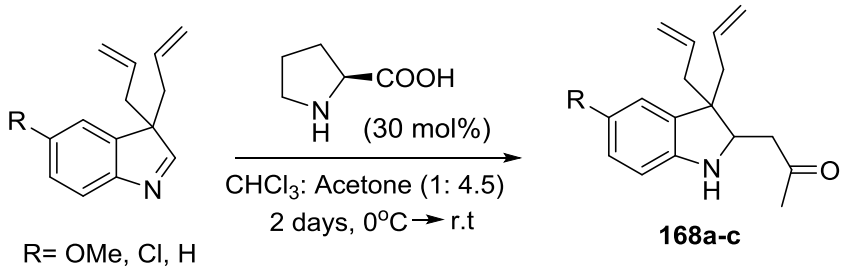
Table 18. (a) Conversion of starting material **138b** (%) from crude mixture determined by ^{1}H NMR (not isolated).

Excluding the reaction in methanol, which resulted in the racemisation of the Mannich product, the reactions conducted in other solvents gave excellent enantiomeric ratios of the Mannich product formed **(Table 18)**. Considering factors

such as complete conversion of the reaction, ease of extraction of product from the solvent and excellent e.r, the reaction condition involving use of chloroform as the solvent was selected to study the reaction scope with a few substituted diallylindolenines.

3.6.2.2 Proline catalysed asymmetric Mannich reaction

The solvent ratio of chloroform: acetone was increased to 1: 4.5 to ensure there was sufficient excess of acetone for the reaction to go to completion. Gratifyingly, L-proline was able to catalyse the Mannich reaction of acetone with substituted diallyl indolenines **138a, 138b, 138h** to give the corresponding 3-aminoketones **168a-c** in good yield and with very high enantioselectivity **(Table 19).**



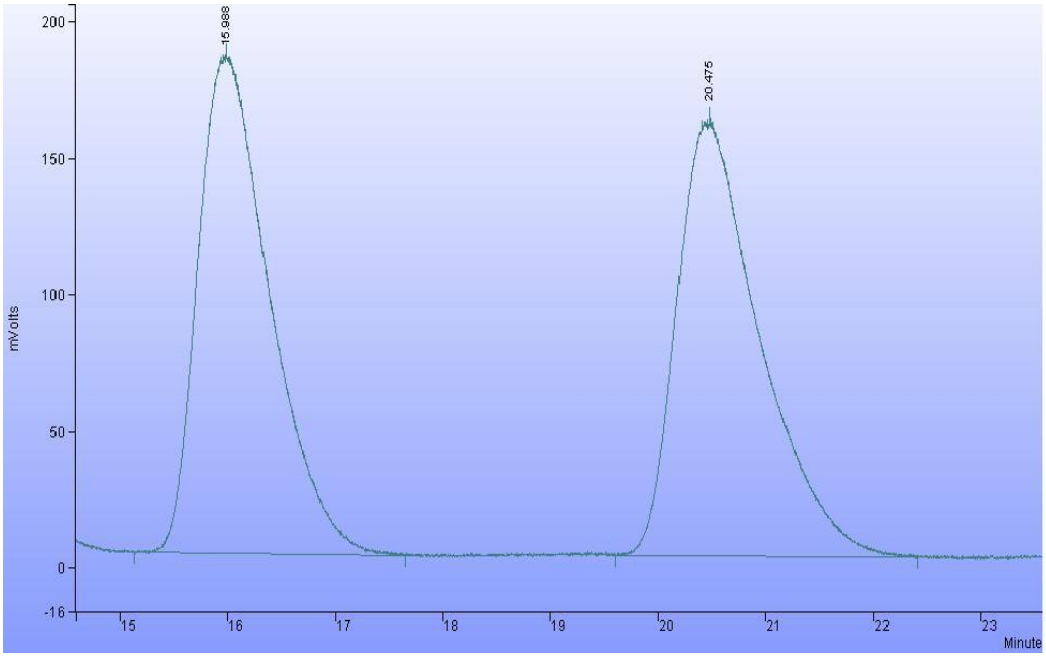
Substrate	e.r. (Major : Minor)	Yield%
138a	99: 1	**168a 81**
138b	99 : 1	**168b 96**
138h	99: 1	**168c 64**[(a)]

Table 19. [(a)] 30 mol% L-proline in DMSO: Acetone (1: 4) 2 days 0 °C→ r.t.

The diallyl indolenine **138a** and 5-methoxy diallylindolenine **138b** underwent the Mannich reaction in good-excellent yields to give **168a** and **168b**, respectively. Despite the reaction with 5-chloro diallylindolenine **138h** not going to completion in $CHCl_3$: acetone, the reaction worked very well in DMSO: acetone (1: 4), and the product **168c** was isolated in moderate yield. These highly enantioenriched compounds could then be converted into the spirocyclic indolines in good yield by Boc protection of the amine followed by RCM.

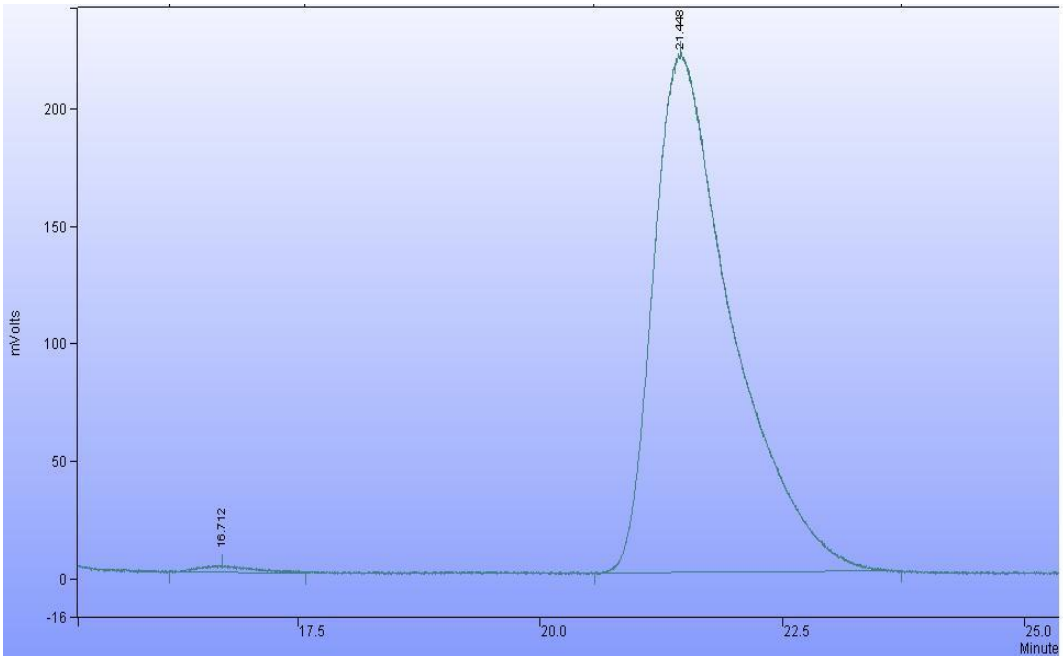
Below showing HPLC traces of racemic and enantioenriched product **168a**.

168a : racemic.



Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)
1		49.7419	15.988	0.000	8422639
2		50.2581	20.475	0.000	8510034
	Totals:	100.0000		0.000	16932673

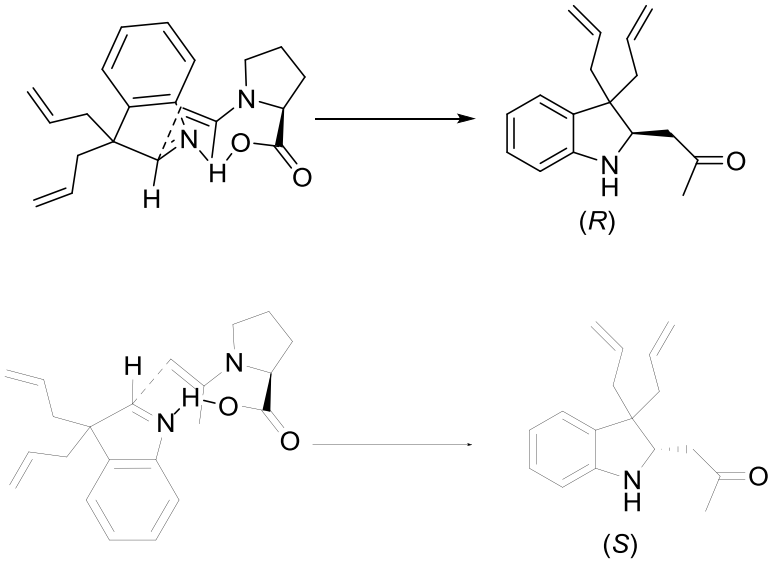
168a : enantioenriched.



Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)
1		0.7257	16.712	0.000	91246
2		99.2743	21.448	0.000	12482930
	Totals:	100.0000		0.000	12574176

3.6.2.3 Reaction mechanism

The reaction occurs *via* the asymmetric proline catalysed Mannich reaction, with nucleophilic attack on the imine occurring *via* the enamine.[197] The major isomer of the Mannich product is yet to be determined, however, it is proposed that the reaction proceeds *via* a 6-membered transition state. The (*R*)-isomer is proposed to form when the imine proton is facing downwards in the axial position in the chair-like transition state, this transition state has also been suggested by Tian and co-workers[198] further supporting our study whereas the (*S*)-isomer is thought to form when the imine proton faces upwards in the axial position in the boat-like transition state. It is likely that the (*R*)-isomer is favored over the (*S*)-isomer.

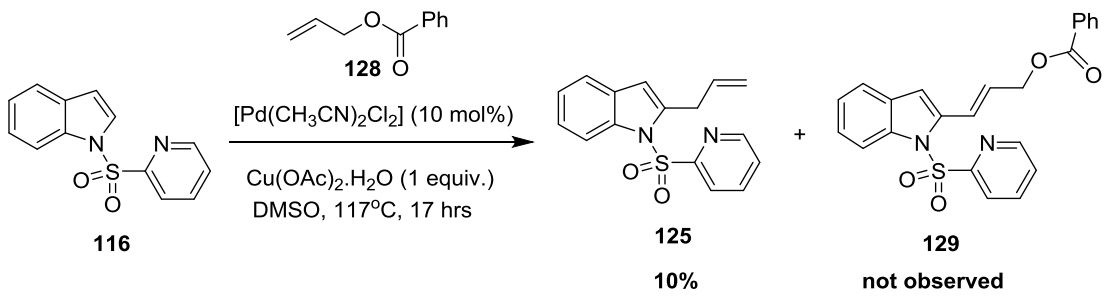


Scheme 59

Although we have demonstrated an efficient route for the asymmetric L-proline catalysed Mannich reaction with a few substituted diallyl indolenines, which furnished the Mannich products isolated in excellent yields and enantiomeric ratio, towards the end of this work similar chemistry was recently published by Tian and co-workers.[198]

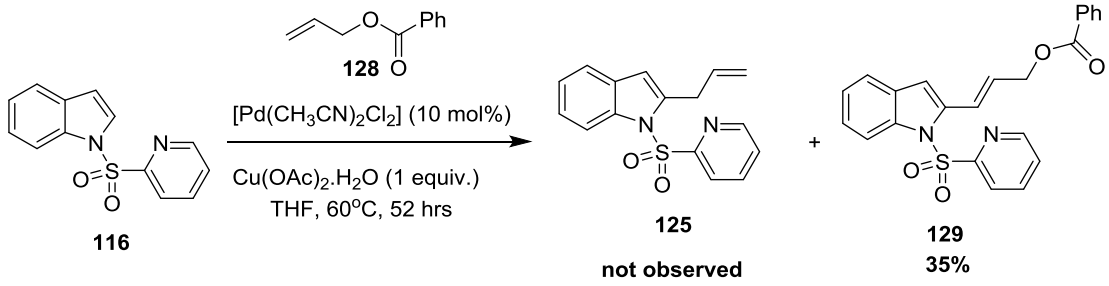
3.7 Conclusion/Future Work

Although the directing group approach did not prove successful enough for further study, we were able to carry out C-2 allylation using polar aprotic solvents with larger dielectric constants to give **125** in 10% yield **(Scheme 60)**.



Scheme 60

By varying the type of solvent such as using weakly polar aprotic solvents/non polar solvents with smaller dielectric constants the conditions favoured **129** with E-configuration of the alkene, which was isolated in 35% yield **(Scheme 61).**



Scheme 61

Although in both cases complete conversion was not observed, optimisation of reaction conditions towards the synthesis of **125** by varying the temperature or screening with a range of palladium catalysts could be investigated.

To favour elimination of the leaving group over beta-hydride elimination, use of a sterically hindered allyl precursor such as methyl or dimethyl allyl acetate could be investigated **(Figure 42)** to enable formation of **125** with additional methyl groups.

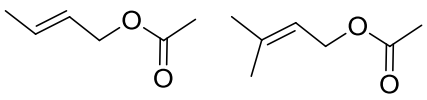
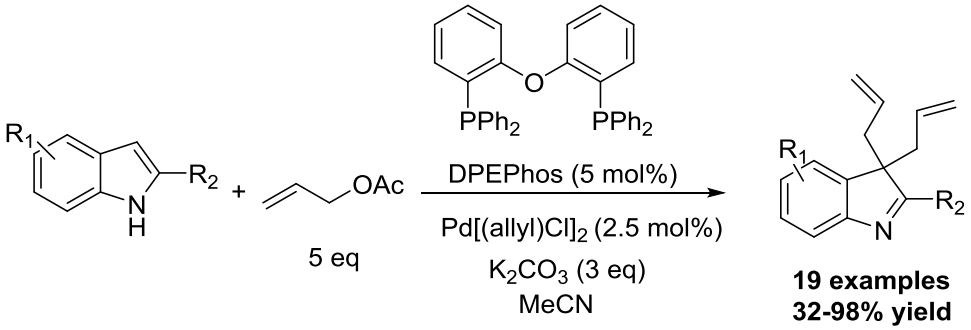


Figure 42. Structures of substituted allyl acetates which might favour acetate elimination over β-hydride elimination when subjected under the reaction condition.

In order for the reaction to be an efficient catalytic process, various Pd(II) catalysts such as $Pd(OAc)_2$ and $Pd_2(dba)_3$ could be examined.

A novel mild and efficient method has been developed for regioselective C-3 diallylation which can be performed with substituted indoles using allyl acetate **(Scheme 62)**.



Scheme 62. Protocol for the synthesis of substituted diallyl indolenines

It has been demonstrated that these diallylated products are versatile substrates when subjected to further elaboration to give the corresponding spirocyclic products in excellent yields in two steps. We have also demonstrated that asymmetric Mannich reactions can be performed easily giving enantioenriched products **(Figure 43)**.

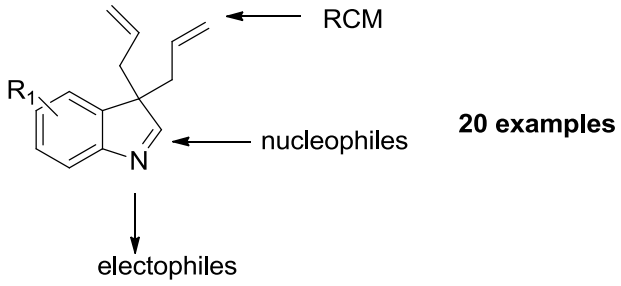
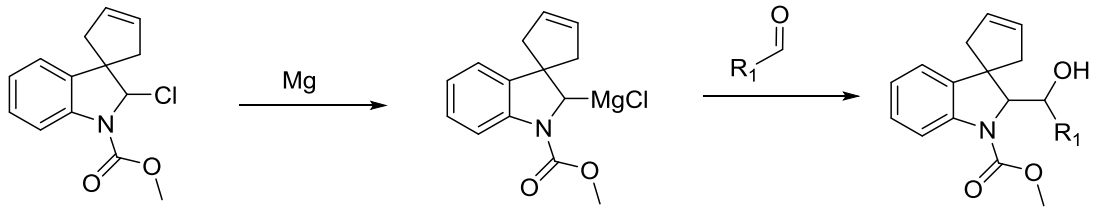


Figure 43. Regions of further elaboration introduced on substituted diallylindolenines.

Given the success with the synthesis of spiro-indolines, it would be reasonable to explore the synthetic scope of the spiro-indoline carbamates by functionalisation at the chloride atom, such as formation of a Grignard and reaction with an aldehyde

(Scheme 63). This would give rise to additional interesting examples of biological interest.



Scheme 63

Biological tests of these alkaloid compounds synthesised on the α4β2 nAChR would give us information about any compounds with interesting pharmacological properties.

4 Experimental

4.1 General Methods and Experimentation

General Information

Chemicals:

All chemicals were purchased from Sigma-Aldrich, Acros, Alfa Aesar, Santa Cruz Biotechnology and used without further purification unless otherwise stated.

Solvents:

Anhydrous tetrahydrofuran, dichloromethane and toluene were collected under argon from an LC Technologies solvent purification system, having passed through two columns packed with molecular sieves. Acetonitrile (MeCN) were dried over 3 Å molecular sieves. 3Å Molecular sieves were freshly dried at 240°C and allowed to cool to room temperature under positive argon pressure before use. All other solvents used as received unless otherwise stated. Petrol refers to petroleum ether (b.p. 40-60°C).

Method:

All reactions were conducted with continuous magnetic stirring using either a round bottom flask or a carousel tube screw cap lid, under ambient conditions unless otherwise stated.

Chromatography/Purification:

All reactions were monitored by thin-layer chromatography (TLC) on pre-coated silica gel 60 F_{254} on aluminium plates (Merck KGaA). Silica gel plates were examined under UV light at 254 nm.

Flash column chromatography was carried out using normal phase silica gel (33-70 μm) supplied by VWR and sand (VWR).

Chiral High Performance Liquid Chromatography (HPLC) was measured using a Varian prostar and prepstar, with a UV detector system at 254 nm. The enantiomeric

excess was determined using a CHIRALPAK-AD column (Daicel; Chemical Industries, LTD) 25 × 0.46 cm.

Characterization:

Mass spectra were obtained at UCL on either a VG70-SE (FAB), Thermo Finnigan MAT900Xp (EI and CI) or Waters LCT Premier XE (ES) mass spectrometer. ^{1}H NMR spectra were recorded at 400 or 600 MHz on a Bruker AMX400 and AMX600 spectrometer using the residual protic solvent $CDCl_3$ (δ = 7.26 ppm, s), DMSO-d_6 (δ = 2.50, qn) or MeOD-d_4 (δ = 3.31, qn) as the internal standard. Chemical shifts are quoted in ppm using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; qn, quintet; sext, sextet; dd (doublet of doublets), dt (doublet of triplets), m, multiplet defined as all multipeak signals where overlap or complex coupling of signals makes definitive descriptions of peaks difficult. The coupling constants ~~(*J*)~~ are measured in Hertz. ^{13}C NMR spectra were recorded at 100 or 150 MHz on a Bruker AMX400 and AMX600 at 25°C in $CDCl_3$ as described below. All chemical shifts were referenced with $CDCl_3$ solvent (δ = 77.0 ppm, t), DMSO-d_6 (δ = 39.5, septet) or MeOD-d_4 (δ = 49.2, septet) as the internal standard. Chemical shifts are reported to the nearest 0.1 ppm. Coupling constants are defined as *J* and quoted in Hz to one decimal place. In the case of a mixture of diastereoisomers, only the major diastereoisomer was assigned, the minor disatereoisomer was not determined. Infrared spectra were obtained on a Perkin Elmer Spectrum 100 FT-IR Spectrometer operating in ATR mode. Melting points were measured with a Gallenkamp apparatus and are uncorrected. Room temperature is defined as between 19-22ºC. Optical rotation$[\alpha]^{D}$ values are given in 10^{-1}deg cm^2 g^{-1} at 20.0 ^{o}C, concentration (c) in g per 100 mL measured on a Perkin-Elmer 343 polarimeter (sodium $_{D\text{-line}}$, 589 nm).

Experimental

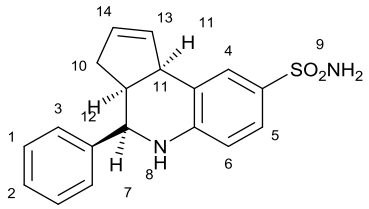
General procedure for the synthesis of cyclopentaquinolines

General method A: Indium trichloride (0.2 mmol) was added to a solution of aldehyde (1 mmol), sulphanilamide (1 mmol), and cyclopentadiene (3 mmol) in acetonitrile (0.1 M). The reaction mixture was stirred for 24 hrs at room temperature. To the reaction mixture EtOAc (3 ml) was added and washed with aqueous (0.08 M) Na_2CO_3 (3 ml), brine (10 mL) and water (10 ml), dried over $MgSO_4$, and concentrated under reduced pressure.

General method B: Indium trichloride (0.2 mmol) was added to a solution of the corresponding imine (1 mmol), and cyclopentadiene (3 mmol) in acetonitrile (0.08 M). The reaction mixture was stirred for 24 hrs at room temperature. To the reaction mixture EtOAc (3 ml) was added and washed with aqueous (0.08 M) Na_2CO_3 (3 ml), brine (10 mL) and water (10 ml), dried over $MgSO_4$, and concentrated under reduced pressure.

4-Phenyl-3a, 4, 5, 9b-tetrahydro-3H-cyclopenta[c]quinoline-8-sulfonamide (30b) [71]

Method A: Purified by recrystallisation from isopropanol: petrol to give afforded the title compound as a pale orange solid (169 mg, 51%).



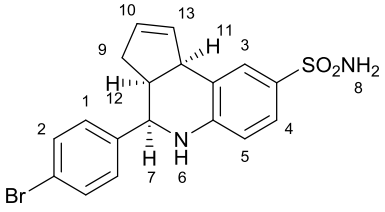
27b

m.p. 142-144 °C; R_f = 0.45 (3 : 2 EtOAc : petrol); IRυ_{max} 3343 (C-H), 3062 (C-H), 2967 (N-H), 1598 (aromatic), 1313 (SO_2-N), 1301 (S=O), 1147-1124 (S=O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) 7.59 (d, 1H, *J* = 1.9 Hz, H-4), 7.52 (dd, 1H, *J* = 8.5, 1.9 Hz, H-5), 7.41 (br s, 2H, H-3), 7.38 (d, 2H, *J* = 7.4 Hz, H-1), 7.32 (m, 1H, H-2), 6.66 (d, 1H, *J* = 8.5 Hz, H-6), 5.90-5.88 (m, 1H, H-13), 5.70-5.67 (m, 1H, H-14), 4.72 (br d, 1H, *J* = 3.1 Hz, H-7), 4.64 (s, 2H, NH_2), 4.24 (br s, 1H, NH), 4.12 (br d,

1H, *J* = 8.7 Hz, H-11), 3.03 (dtd, 1H, *J* = 9.2, 8.7, 3.1 Hz, H-12), 2.56 (ddd, 1H, *J* = 16.4, 9.2, 3.1 Hz, H-10), 1.83 (br dd, 1H, *J* = 16.4, 8.7 Hz, H-10); δ ^{13}C NMR (150 MHz, $CDCl_3$) 149.8 (C_q), 141.7 (C_q), 133.4 (CH), 131.2 (CH), 130.8 (C_q), 128.8 (2 × CH), 128.2 (CH), 127.8 (CH), 126.4 (2 × CH), 125.9 (C_q), 125.5 (CH), 115.6 (CH), 57.5 (CH), 45.9 (CH), 45.8 (CH), 31.6 (CH_2). HRMS (EI) calcd. for $C_{18}H_{18}O_2N_2S$ 326.10889, found 326.10929.

4-(4-Bromophenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-sulfonamide (23b).[71]

Method B: Purified by recrystallisation from isopropanol: petrol to give the title compound as cream coloured solid (151 mg, 37%).

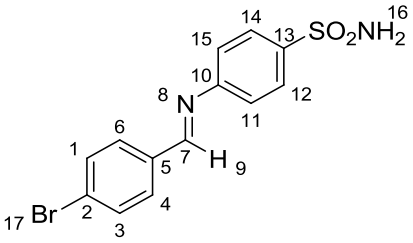


23b

m.p. 192-194 ˚C; R_f = 0.4 (3 : 2 EtOAc : petrol); IRυ$_{max}$ 3326 (C-H), 3261 (C-H), 1598 (aromatic), 1316 (SO_2-N), 1184 (S=O), 1149-1125 (SO_2-N), 1086 (S=O), 722 (C-Br) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) 7.59 (d, 1H, *J* = 2.0 Hz, H-3), 7.53 (d, 1H, *J* = 2.0 Hz, H-4), 7.52 (d, 2H, *J* = 8.1 Hz, H-2), 7.29 (d, 2H, *J* = 8.1 Hz, H-1), 6.67 (d, 1H, *J* = 8.4 Hz, H-5), 5.90-5.88 (m, 1H, H-13), 5.69-5.68 (m, 1H, H-10), 4.68 (d, 1H, *J* = 3.1 Hz, H-7), 4.62 (s, 2H, NH_2), 4.17 (br s, 1H, NH), 4.06 (d, 1H, *J* = 8.5 Hz, H-11), 2.98 (dtd, 1H, *J* = 9.7, 8.5, 3.1 Hz, H-12), 2.51 (ddd, 1H, *J* = 16.5, 9.7, 2.4 Hz, H-9), 1.82 (br dd, 1H, *J* = 16.5, 8.5 Hz, H-9); δ ^{13}C NMR (150 MHz, $CDCl_3$) 149.4 (C_q), 140.8 (C_q), 133.4 (CH), 132.0 (2 × CH), 131.9 (CH), 131.1 (C_q), 131.0 (CH), 128.2 (2 × CH), 125.8 (C_q), 125.5 (CH), 121.6 (C_q), 115.8 (CH), 57.0 (CH), 45.73 (CH), 45.70 (CH), 31.5 (CH_2); HRMS (EI) calcd. for $C_{18}H_{18}O_2N_2SBr$ 405.02724, found 405.02674.

(E)-4-(4-Bromobenzylideneamino)benzenesulfonamide (29)[199, 200]

To refluxed ethanol (absolute ethanol, 31 ml), sulphanilamide (3.45g, 20 mmol) was added and left to stir to form a white suspension. Addition of 4-bromobenzaldehyde (3.75 g, 20 mmol) was followed and refluxed for approximate 3 hrs. Reaction mixture was cooled to r.t. On evaporated of a small volume of ethanol the reaction mixture was cooled further to 0°C, filtered under gravity and dried to give the title compound as a white powder (5.72 g, 84%).

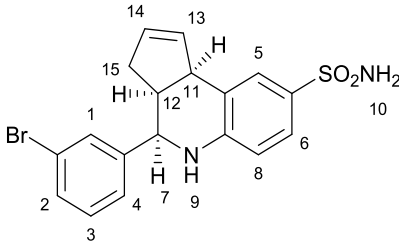


40

m.p. 195-196 ˚C; IRυ_{max} 3284 (N-H), 2977.5 (=C-H),1619.9(C=N), 1580 (aromatic), 1562 (N-H bend), 1498 (aromatic), 1333 (SO_2-N), 1152 (O=S=O), 732 (CH=CH bend) cm^{-1}; δ ^{1}H NMR (600 MHz, DMSO) 8.66 (s, 1H, H-9), 7.90(d, 2H, *J* = 8.3 Hz, H-4, 6), 7. 86 (d, 2 H, *J* = 8.4 Hz, H-11,15), 7.76 (d, 2H, *J* = 8.3 Hz, H-1,3), 7.41 (d, 2H, *J* = 8.4 Hz, H-12,14), 7.38 (s, 2H, NH_2); ^{13}C NMR (150 MHz, DMSO) 161.8 (CH), 154.1 (C_q), 141.4 (C_q), 134.8 (C_q), 132.1 (2 × CH), 130.8 (2 × CH), 127.4 (2 × CH), 125.7 (C_q), 121.4 (2 × CH).

4-(3-Bromophenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-sulfonamide (31b).[71]

A: Purified by recrystallisation from isopropanol: petrol to give title compound as a dark greenish gold coloured solid (178 mg, 49%).

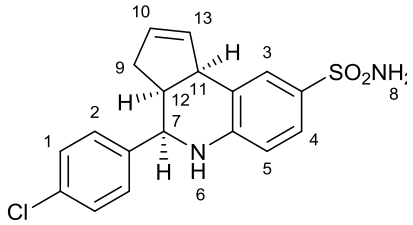


29b

mp 139-142 °C; R_f = 0.44 (3 : 2 EtOAc : petrol); IRυ_{max} 3260-3252 (C-H), 2921-2900 (C-H), 1597 (aromatic), 1307 (SO_2-N), 1187 (S=O), 1151-1128 (SO_2-N), 1090 (S=O) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.60 (d, 1H, *J* = 2.0 Hz, H-5), 7.57 (t, 1H, *J* =1.6 Hz, H-1), 7.53 (dd, 1H, *J* = 8.5, 2.0 Hz, H-6), 7.45 (br d, 1H, *J* = 7.7 Hz, H-2), 7.34 (br d, 1H, *J* = 7.7 Hz, H-4), 7.26 (t, 1H, *J* = 7.7 Hz, H-3), 6.67 (d, 1H, *J* = 8.5 Hz, H-8), 5.90-5.88 (m, 1H, H-13), 5.69-5.68 (m, 1H, H-14), 4.70 (s, 2H, NH_2), 4.68 (d, 1H, *J* = 3.1 Hz, H-7), 4.19 (br s, 1H, -NH), 4.10 (d, 1H, *J* = 8.1 Hz, H-11), 3.01 (dtd, 1H, *J* = 9.4, 8.1, 3.1 Hz, H-12), 2.52 (ddd, 1H, *J* = 16.3, 9.4, 2.3 Hz, H-15), 1.83 (br dd, 1H, *J* = 16.3, 8.1 Hz, H-15); δ ^{13}C NMR (150 MHz, $CDCl_3$) 149.3 (C_q), 144.1 (C_q), 133.4 (CH), 131.1 (C_q), 131.0 (CH), 130.9 (CH), 130.4 (CH), 129.5 (CH), 128.2 (CH), 125.8 (C_q), 125.5 (CH), 125.2 (CH), 123.0 (C_q), 115.8 (CH), 57.0 (CH), 45.72 (CH), 45.71 (CH), 31.5 (CH_2); HRMS (EI) calcd. for $C_{18}H_{18}O_2N_2SBr$ 405.02724, found 405.02674.

4-(4-Chlorophenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-sulfonamide (32b).[71]

A: Purified by flash column chromatography using gradient method 10-30% EtOAc: petrol to give the title compound as a light pink foam (230 mg, 63%).



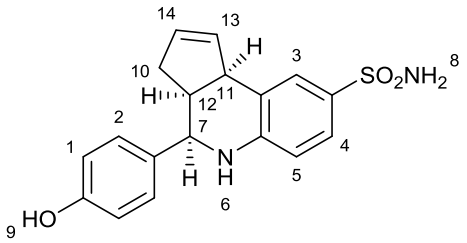
30b

R_f = 0.43 (3 : 2 EtOAc : Petrol); IRυ_{max} 3342 (C-H), 3271 (C-H), 2923 (N-H), 1597 (aromatic), 1313 (SO_2-N), 1088 (S=O) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.60 (d, 1 H, *J* = 1.8 Hz, H-3), 7.52 (dd, 1 H, *J* = 8.4, 1.8 Hz, H-4), 7.37 (d, 2 H, *J* = 8.6 Hz, H-1), 7.35 (d, 2 H, *J* = 8.6 Hz, H-2), 6.67 (d, 1H, *J* = 8.4 Hz, H-5), 5.90-5.88 (m, 1H, H-13), 5.70-5.67 (m, 1H, H-10), 4.70 (d, 1H, *J* = 3.4 Hz, H-7), 4.63 (s, 2H, NH_2), 4.17 (br s, 1H, NH), 4.11 (br d, 1H, *J* = 8.7 Hz, H-11), 2.99 (dtd, 1H, *J* = 9.5, 8.7, 3.4 Hz, H-12), 2.52 (ddd, 1H, *J* = 16.1, 9.5, 2.2 Hz, H-9), 1.82 (br dd, 1H, *J* = 16.1, 8.7 Hz, H-9); δ ^{13}C NMR (150 MHz, $CDCl_3$) 149.3 (C_q), 140.1 (C_q), 133.4 (C_q), 133.3 (CH), 131.0 (C_q), 130.9 (CH) 128.9 (2 × CH), 128.1 (CH), 127.7 (2 ×

CH), 125.7 (C_q), 125.4 (CH), 115.6 (CH), 56.9 (CH), 45.7 (CH), 45.6 (CH), 31.3 (CH_2). HRMS (EI) calcd. for $C_{18}H_{17}O_2N_2SCl$ $[M]^+$ 359.0612, found 359.0627.

4-(4-Hydroxyphenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-sulfonamide (33b). [71]

A: Purified by flash column chromatography using a gradient elution of 40-60% EtOAc: petrol to give the title compound as an pink foam (110 mg, 32%).

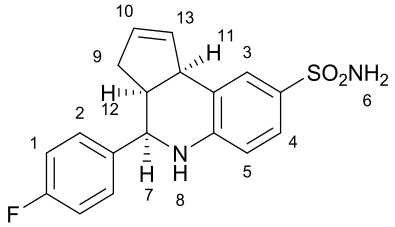


31b

m.p. 213-215˚C; R_f = 0.31 (3 : 2 EtOAc: petrol); IRυ_{max} 3389 (C-H), 2923 (C-H), 1501 (aromatic), 1307 (SO_2-N, S=O), 1287 (O-H), 1149 (SO_2-N) cm^{-1}; δ^1H NMR (600 MHz, MeOD) 7.52 (d, 1H, *J* = 1.8 Hz, H-3), 7.42 (dd, 1H, *J* = 8.5, 1.8 Hz, H-4), 7.26 (d, 2H, *J* = 8.5 Hz, H-1), 6.79 (d, 2H, *J* = 8.5 Hz, H-2), 6.75 (d, 1H, 8.5 Hz, H-5), 5.90-5.89 (m, 1H, H-13), 5.64-5.63 (m, 1H, H-14), 4.57 (d, 1H, *J* = 3.4 Hz, H-7), 4.06 (d, 1H, *J* = 8.8 Hz, H-11), 2.95 (dtd, 1H, *J* = 9.6, 8.8, 3.4 Hz, H-12), 2.51 (ddd, 1H, *J* = 16.2, 9.6, 2 Hz, H-10) 1.77 (br dd, 1H, *J* = 15.7, 8.8, H-10); δ ^{13}C NMR (150 MHz, MeOD) 157.7 (C_q), 151.7 (C_q), 135.0 (CH), 134.4 (C_q), 132.6 (C_q), 131.4 (CH), 130.6 (CH), 128.7 (2 × CH), 128.5 (CH), 126.4 (C_q), 125.6 (CH), 116.2 (2 × CH), 57.8 (CH), 47.9 (CH), 47.7 (CH), 32.6 (CH_2). HRMS (ES-) calcd. for $C_{18}H_{17}N_2O_3$ $[M -H]^-$ 341.0952, found 341.0960.

4-(4-Fluorophenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-sulfonamide (24b).[26, 71]

A: Purified by flash chromatography (0-30% EtOAc: petrol) and recrystallisation from isopropanol: toluene: petrol to give title compound as a dark green amorphous solid (6 mg, 2%).

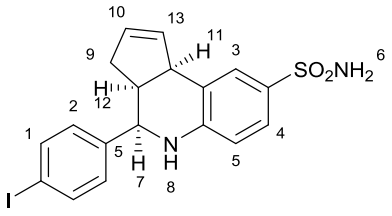


32b

m.p. 52-54 ˚C; R_f = 0.34 (3 : 2 EtOAc : petrol); IR υ_{max} 3352 (C-H), 3226 (C-H), 2921 (N-H), 2851 (N-H), 1600 (aromatic), 1221.7 (C-F), 1309 (SO_2-N), 1188 (S=O), 1150-1128 (SO_2-N) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.60 (br d, 1H, *J* = 2.0 Hz, H-3), 7.55 (dd, 1H, *J* = 8.4, 2.0 Hz, H-4), 7.38 (m, 2H, H-2), 7.08 (m, 2H, H-1), 6.66 (d, 1H, *J* = 8.4 Hz, H-5), 5.91-5.88 (m, 1H, H-13), 5.70-5.66 (m, 1H, H-10), 4.70 (d, 1H, *J* = 3.2 Hz, H-7), 4.63 (s, 2H, NH_2), 4.18 (br s, 1H, NH), 4.11 (d, 1H, *J* = 8.7 Hz, H-11), 2.98 (dtd, 1H, *J* = 10.1, 8.7, 3.2 Hz, H-12), 2.54 (ddd, 1H, *J* = 15.8, 10.1, 2.3 Hz, H-9), 1.82 (br dd, 1H, *J* = 15.8, 8.7 Hz, H-9); δ ^{13}C NMR (150 MHz, $CDCl_3$) 162.3 (d, *J* = 246.5 Hz, C_q), 149.6 (C_q), 137.5 (C_q), 133.5 (CH), 131.1 (CH), 131.0 (C_q), 128.2 (CH), 128.0 (d, *J* = 7.7 Hz, 2 × CH), 125.8 (C_q), 125.5 (CH), 115.7 (d, 11.0 Hz, 2 × CH), 115.6 (CH), 56.9 (CH), 45.9 (CH), 45.7 (CH), 31.5 (CH_2). HRMS (EI) calcd. for $C_{18}H_{17}O_2N_2SF$ $[M]^+$ 344.0989, found 344.0996.

4-(4-Iodophenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-sulfonamide (34b).[71]

A: Purified by recrystallisation from isopropanol: toluene: petrol to give title compound as a brownish grey powder (68 mg, 15%).



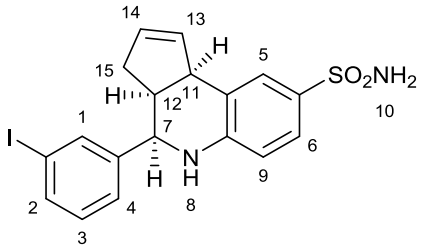
33b

m.p. 220-222 ˚C; R_f = 0.34 (3: 2 EtOAc : petrol); IRυ_{max} 3327 (C-H), 2936 (N-H), 1598 (aromatic), 1149 (SO_2-N) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.72 (d, 2H, *J* =

8.5 Hz, H-1), 7.59 (br s, 1H, H-3), 7.52 (dd, 1H, *J* = 8.4, 1.8 Hz, H-4), 7.16 (d, 2H, *J* = 8.5 Hz, H-2), 6.65 (d, 1H, *J* = 8.4 Hz, H-5), 5.90-5.87 (m, 1H, H-13), 5.70-5.67 (m, 1H, H-10), 4.66 (m, 3H, NH_2, H-7), 4.16 (br s, NH), 4.10 (d, 1H, *J* = 8.1 Hz, H-11), 2.98 (dtd, 1H, *J* = 9.1, 8.1, 2.9 Hz, H-12), 2.51 (ddd, 1H, *J* = 15.7, 9.1, 1.5 Hz, H-9), 1.82 (br dd, 1H, *J* = 15.7, 8.1 Hz, H-9); δ ^{13}C NMR (150 MHz, $CDCl_3$) 149.4 (C_q), 141.5 (C_q), 137.9 (2 × CH), 133.4 (CH), 131.1 (C_q), 131.0 (CH), 128.4 (2 × CH), 128.2 (CH), 125.8 (C_q), 125.5 (CH), 115.8 (CH), 93.1 (C_q), 57.1 (CH), 45.72 (CH), 45.71 (CH), 31.5 (CH_2). HRMS (EI), cald. for $C_{18}H_{17}O_2N_2SI$ $[M]^+$ 452.00499, found 452.00563.

4-(3-Iodophenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-sulfonamide (35b).[71]

A: Purified by recrystallisation from isopropanol: petrol to give title compound as pale brown powder (34 mg, 8%).



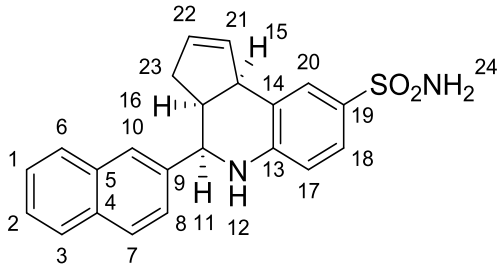
34b

R_f 0.34 (3 : 2 EtOAc: petrol); mp 177-179 °C; IR υ_{max} 3338 (C-H), 3258 (C-H), 2911 (N-H), 2901 (N-H), 1600 (aromatic), 1308 (SO_2-N), 1191 (S=O), 1170 (SO_2-N), 1092 (S=O) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.77 (br t, 1H, *J* = 1.4 Hz, H-1), 7.66 (br dt, 1H, *J* = 7.9, 1.7 Hz, H-2), 7.60 (br d, 1H, *J* = 1.7 Hz, H-5), 7.53 (dd, 1H, *J* = 8.5, 1.7 Hz, H-6), 7.37 (br d, 1H, *J* = 7.8 Hz, H-4), 7.13 (t, 1H, *J* = 7.8 Hz, H-3), 6.67 (d, 1H, *J* = 8.5 Hz, H-9), 5.90-5.88 (m, 1H, H-13), 5.70-5.67 (m, 1H, H-14), 4.65 (d, 1H, *J* = 3.2, H-7), 4.63 (s, 2H, NH_2), 4.17 (br s, 1H, -NH), 4.10 (d, 1H, *J* = 8.3 Hz, H-11), 3.00 (dtd, 1H, *J* = 9.4, 8.3, 3.2 Hz, H-12), 2.52 (ddd, 1H, *J* = 16.3, 9.4, 2.3 Hz, H-15), 1.84 (br dd, 1H, *J* = 16.3, 8.3, Hz, H-15); δ ^{13}C NMR (150 MHz, $CDCl_3$) 149.4 (C_q), 144.2 (C_q), 136.9 (CH), 135.4 (CH), 133.4 (CH), 131.1 (C_q), 131.0 (CH), 130.6 (CH), 128.2 (CH), 125.8 (CH), 125.7 (C_q), 125.5 (CH),

115.8 (CH), 94.9 (C_q), 56.9 (CH), 45.7 (2 × CH), 31.5 (CH_2); HRMS (EI) calcd. for $C_{18}H_{17}O_2N_2SI$ $[M]^+$ 452.00499, found 452.00563.

4-(Naphthalen-2-yl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-sulfonamide (25b).[26, 71]

A: Purified by recrystallisation from isopropanol: petrol to give title compound as a pale orange powder (35 mg, 9%).

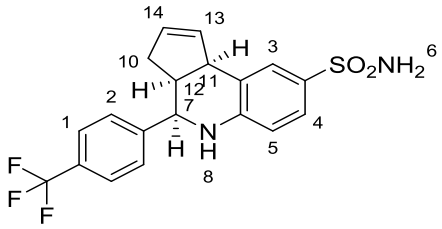


35b

m.p. 180-182 ˚C; R_f = 0.34 (3 : 2 EtOAc : petrol); IRυ $_{max}$ 3347 (C-H), 2727 (N-H), 1598 (aromatic), 1314 (SO_2-N), 1154 (S=O) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.88-7.85 (m, 4H, H-10, 7, 6, 3), 7.63 (d, 1H, *J* = 1.6 Hz, H-20), 7.56-7.48 (m, 4H, H-18,1,2,8), 6.72 (d, 1H, *J* = 8.5 Hz, H-17), 5.91-5.89 (m, 1H, H-21), 5.69-5.67 (m, 1H, H-22), 4.88 (d, 1H, *J* = 3.1 Hz, H-11), 4.66 (s, 2H, NH_2), 4.37 (br s, 1H, NH), 4.17 (d, 1H, *J* = 8.5, H-15), 3.14 (dtd, 1H, *J* = 9.4, 8.5, 3.1 Hz, H-16), 2.62 (ddd, 1H, *J* = 16.4, 9.4, 2.4 Hz, H-23), 1.80 (ddd, 1H, *J* = 16.4, 8.5, 1.4 Hz, H-23); δ ^{13}C NMR (150 MHz, $CDCl_3$) 149.8 (C_q), 139.2 (C_q), 133.5 (C_q), 133.4 (CH), 133.0 (C_q), 131.2 (CH), 130.9 (C_q), 128.6 (CH), 128.2 (CH), 127.9 (CH), 127.8 (CH), 126.5 (CH), 126.2 (CH), 126.0 (C_q), 125.5 (CH), 124.8 (CH), 124.7 (CH), 115.7 (CH), 57.6 (CH), 45.9 (CH), 45.7 (CH), 31.7 (CH_2).

(3a*S*,4*R*,9b*R*)-4-(4-(Trifluoromethyl)phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-sulfonamide (36b)[71]

A: Under the same protocol conditions above with exception to sulphanilamide (2 eq) and $InCl_3$ (10 mol %) were considered. No purification required (941 mg, 72%).

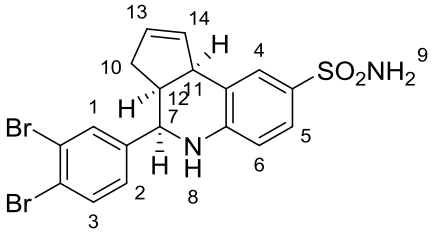


36b

m.p. 112-115 ˚C; R_f = 0.42 (1: 1 EtOAc : petrol); IRυ $_{max}$ 3359 (C-H), 2569 (N-H), 1499 (aromatic), 1300 (-CF_3), 1313 (SO_2-N), 1153 (O=S=O) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.70 (d, 2H, *J* = 8.0 Hz, H-1), 7.6 (d, 1H, *J* = 1.5 Hz, H-3), 7.54 (br d, 3H, *J* = 8.0 Hz, H-4, 2), 6.69 (d, 1H, *J* = 8.6 Hz, H-5), 5.91-5.89 (m, 1H, H-13), 5.68 (br d, 1H, *J* = 4.6 Hz, H-14), 4.78 (d, 1H, *J* = 2.7 Hz, H-7), 4.76 (s, 2H, NH_2), 4.13 (d, 1H, *J* = 8.5 Hz, H-11), 3.03 (dtd, 1H, *J* = 9.4, 8.5, 2.7 Hz, H-12), 2.53 (dtd, 1H, 16.1, 9.4, 2.7 Hz, H-10), 1.79 (br dd, 1H, *J* = 16.1, 8.5 Hz, H-10); δ ^{13}C NMR (150 MHz, $CDCl_3$) 149.3 (C_q), 145.8 (C_q), 133.4 (CH), 131.3 (C_q), 130.9 (CH), 130.1 (q, *J* = 32.8 Hz, C_q), 128.2 (CH), 126.8 (3 × CH), 125.8 (q, *J* = 3.7 Hz, 2 × CH), 125.7 (C_q), 124.1 (q, *J* = 271.7 Hz, C_q), 115.9 (CH), 57.3 (CH), 45.7 (CH), 45.4 (CH), 31.5 (CH_2); HRMS (EI) calcd. for $C_{19}H_{17}F_3N_2O_2S$ $[M]^+$ 394.0963, found 394.0963.

4-(3,4-Dibromophenyl)-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[c]quinoline-8-sulfonamide (37b)[71]

A: Purified from hot isopropanol: petrol to give title compound as a light brown powder (180 mg, 37%).



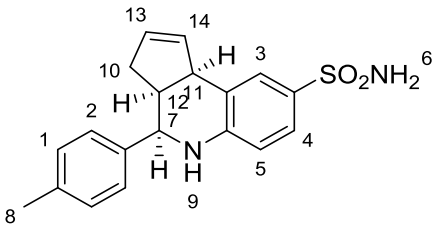
37b

m. p. 143-145 ˚C; R_f = 0.45 (1 : 1 EtOAc : petrol); IRυ$_{max}$ 3361 (C-H), 3255 (C-H), 2929 (N-H), 1598 (aromatic), 1495 (aromatic), 1313 (SO_2-N), 1307-1289 (O=S=O), 1151-1127 (O=S=O), 1019.8 (S=O) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.69 (d, 1H, *J* = 1.7 Hz, H-1), 7.63 (d, 1H, *J* = 8.2 Hz, H-3), 7.60 (d, 1H, *J* = 1.6 Hz, H-4), 7.53

(dd, 1H, *J* = 8.5, 1.6 Hz, H-5), 7.22 (dd, 1H, *J* = 8.2, 1.7 Hz, H-2), 6.68 (d, 1H, *J* = 8.5 Hz, H-6), 5.90-5.88 (m, 1H, H-14), 5.69 (br d, 1H, *J* = 4.8 Hz, H-13), 4.67 (d, 1H, *J* = 5.4 Hz, H-7), 4.66 (s, 2H, NH_2), 4.14 (br s, 1H, NH), 4.10 (br d, 1H, *J* = 8.7 Hz, H-11), 2.98 (m, 1H, H-12), 2.50 (m, 1H, H-10), 1.83 (m, 1H, H-10); ^{13}C NMR (150 MHz, $CDCl_3$) 149.1 (C_q), 142.9 (C_q), 134.1 (CH), 133.4 (CH), 131.6 (CH), 131.5 (C_q), 131.0 (CH), 128.2 (CH), 126.7 (CH), 125.7 (C_q), 125.5 (CH), 125.3 (C_q), 123.9 (C_q), 115.9 (CH), 56.6 (CH), 45.6 (CH), 45.5 (CH), 31.5 (CH_2); HRMS (EI) calcd. for $C_{18}H_{16}O_2N_2SBr_2$ $[M]^+$ 481.9299, found 481.9300.

4-*p*-Tolyl-3a,4,5,9b-tetrahydro-1*H*-cyclopenta[c]quinoline-8-sulfonamide (38b)[26, 71]

A: Under the same protocol conditions as above with sulfanilamide (1.5 eq) and $InCl_3$ (0.2 mmol).Purification by flash chromatography dry load gradient method using 20-30% EtOAc: petrol gave the title compound as yellow crystals (374 mg, 44%).

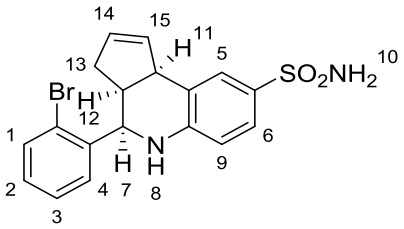


38b

m.p. 88-90 ˚C; R_f = 0.63 (1:1 EtOAc : petrol); IRυ_{max} 3320 (C-H), 2924 (C-H), 2862 (N-H), 1500 (aromatic), 1324.8 (SO_2-N), 1163.7 (S=O) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.59 (d, 1H, *J* = 1.8 Hz, H-3), 7.51 (dd, 1H, *J* = 8.5, 1.8 Hz, H-4), 7.28 (d, 2H, *J* = 8.0 Hz, H-2), 7.19 (d, 2H, *J* = 8.0 Hz, H-1), 6.64 (d, 1H, *J* = 8.5 Hz, H-5), 5.89-5.87 (m, 1H, H-14), 5.69-5.67 (m, 1H, H-13), 4.67 (d, 1H, *J* = 2.9 Hz, H-7), 4.66 (s, 2H, NH_2), 4.21 (br s, 1H, NH), 4.10 (d, 1H, *J* = 8.6 Hz, H-11), 3.00 (dtd, 1H, *J* = 12.1, 9.1, 2.9 Hz, H-12), 2.55 (dtd, 1H, *J* = 16.4, 9.1, 2.9 Hz, H-10), 2.36 (s, 3H, H-8), 1.84 (dd, 1H, *J* = 16.4, 8.6 Hz, H-10); δ ^{13}C NMR (150 MHz, $CDCl_3$) 149.9 (C_q), 139.3 (C_q), 137.5 (C_q), 133.4 (CH), 131.2 (CH), 130.7 (C_q), 129.5 (2 × CH), 128.2 (CH), 126.4 (2 × CH), 125.9 (C_q), 125.4 (CH), 115.6 (CH), 57.3 (CH), 46.0 (CH), 45.9 (CH), 31.6 (CH_2), 21.2 (CH_3); HRMS (EI) calcd. for $C_{19}H_{20}O_2N_2S$ $[M]^+$ 340.1246, found 340.1244.

4-(-2-Bromophenyl)-3a,4,5,9b-tetrahydro-3*H*-cyclopena[c]quinoline-8-sulfonamide (39b)[71]

A: Purified by recrystallisation from hot isopropanol: petrol gave the title compound as pale yellow powder (523 mg, 60%).

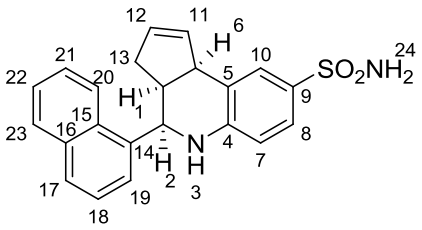


39b

m.p. 204-206 °C; R_f = 0.41 (1 : 1 EtOAc : petrol), IR υ_{max} 3396 (C-H), 3354 (C-H), 3259 (N-H), 2927 (N-H), 1588 (aromatic), 1316 (SO_2-N), 1157 (S=O), 1090, 665 cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.62 (d, 1H, *J* = 1.3 Hz, H-5), 7.59 (dd, 1H, *J* = 8.0, 1.3 Hz, H-1), 7.57 (dd, 1H, *J* = 8.0, 1.1 Hz, H-4), 7.53 (dd, 1H, *J* = 8.0, 1.3 Hz, H-6), 7.37 (td, 1H, *J* = 8.0, 1.1 Hz, H-2), 7.18 (td, 1H, *J* = 8.0, 1.3 Hz, H-3), 6.67 (d, 1H, *J* = 8.0 Hz, H-9), 5.91-5.89 (m, 1H, H-15), 5.69-5.67 (m, 1H, H-14), 5.06 (d, 1H, *J* = 2.9 Hz, H-7), 4.76 (s, 2H, NH_2), 4.14 (d, 1H, *J* = 7.0 Hz, H-11), 4.10 (s, 1H, NH), 3.29 (dtd, 1H, *J* = 9.9, 7.0, 2.9 Hz, H-12), 2.53 (dtd, 1H, *J* = 16.1, 9.9, 2.9 Hz, H-13), 1.75 (br dd, 1H, *J* = 16.1, 7.0 Hz, H-13); δ ^{13}C NMR (150 MHz, $CDCl_3$) 149.7 (C_q), 140.2 (C_q), 133.5 (CH), 133.3 (CH), 131.2 (C_q), 131.0 (CH), 129.2 (CH), 128.2(CH), 127.9 (CH), 127.8 (CH), 126.1 (C_q), 125.4 (CH), 123.1 (C_q), 115.9 (CH), 56.5 (CH), 45.6 (CH), 41.9 (CH), 31.5 (CH_2); HRMS (EI) calcd. for $C_{18}H_{18}O_2N_2SBr$ 405.02724, found 405.02674.

TQS-4-(naphthalen-1-yl)-3a, 4, 5, 9b-tetrahydro-1*H*-cyclopenta[c]quinoline-8-sulfonamide (22b)[71]

A: Purified by recrystallisation from isopropanol: petrol gave the title compound as a pale yellow solid (216 mg, 22%).



22b

mp 203-205 °C; R_f = 0.35 (3 : 2 EtOAc : petrol), IRυ_{max} 3344 (C-H), 3268 (C-H), 2930 (N-H), 1496 (aromatic), 1321 (SO_2-N), 1197 (S=O), 1127 (SO_2–N), 1091 cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 8.09 (d, 1H, *J* = 8.2 Hz, H-20), 7.92 (d, 1H, *J* = 8.2 Hz, H-23), 7.84 (d, 1H, *J* = 7.5 Hz, H-17), 7.73 (d, 1H, *J* = 7.5 Hz, H-19), 7.66 (d, 1H, *J* = 1.9 Hz, H-10), 7.58-7.51 (m, 4H, H-22, 21, 18, 8), 6.73 (d, 1H, *J* = 8.1 Hz, H-7), 5.90-5.88 (m, 1H, H-11), 5.67-5.64 (m, 1H, H-12), 5.52 (d, 1H, *J* = 1.56 Hz, H-2), 4.66 (s, 2H, N*H*$_2$), 4.25 (d, 1H, *J* = 8.83 Hz, H-6), 4.22 (s, 1H, N*H*), 3.34 (dtd, 1H, *J* = 9.4, 7.3, 3.3 Hz, H-12), 2.58 (ddd, 1H, *J* = 16.7, 9.6, 2.4 Hz, H-15), 1.65 (br dd, 1H, *J* = 16.2, 5.1 Hz, H-15); δ ^{13}C NMR (150 MHz, $CDCl_3$) 150.3 (C_q), 137.2 (C_q), 133.9 (C_q), 133.4 (CH), 131.2 (CH), 130.9 (C_q), 130.4 (C_q), 129.3 (CH), 128.2 (d, 5.4 Hz, CH), 126.5 (CH), 126.3 (C_q), 122.7 (CH), 122.3 (CH), 115.9 (CH), 53.3 (CH), 45.9 (CH), 43.7 (CH), 32.0 (CH_2).

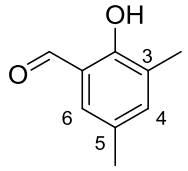
Formylation of phenols

General procedure C:

To a solution of phenol (4 ml, 33 mmol) in CH_2Cl_2 (anhydrous) (50 ml) stirred at -10°C under dry argon conditions was added $AlCl_3$ (4.82 g, 36 mmol, 1.2 eq) and stirred for an additional 10 minutes. Dichloromethyl methyl ether (3.3 ml, 36 mmol, 1.2 eq) was added dropwise via a syringe pump for 18 minutes at 7.7 ml/hr. The reaction was left to stir for a further 10 minutes before cold water (200 ml) was added slowly. The reaction was left to stir for 10 minutes. Extracted organic layer

with CH_2Cl_2 and washed with brine (100 ml) and water (150 ml), dried with $MgSO_4$, filtered and evaporated.

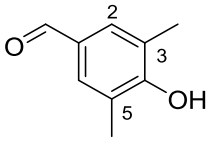
2-Hydroxy-3,5-dimethylbenzaldehyde (44a)



44a

Purification by column chromatography with 100% petrol; brown viscous oil (3.2 g, 65%); R_f = 0.97 (1 : 1 EtOAc : petrol); IRυ_{max} 3201 (O-H), 2921 (C-H), 1646 (C=O), 1467 (aromatic), 1260 (C-O) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 11.09 (s, 1H, -OH), 9.81 (s, 1H, CHO), 7.20 (br s, 1H, 4-H), 7.15 (s, 1H, 6-H), 2.29 (s, 3H, 5-Me), 2.23 (s, 3H, 3-Me); δ ^{13}C NMR (150 MHz, $CDCl_3$) 196.8 (CHO), 158.0 (C_q), 139.1 (CH), 131.0 (CH), 128.6 (C_q), 126.6 (C_q), 119.9 (C_q), 20.3 (CH_3), 15.1 (CH_3); HRMS (EI) calcd. for $C_9H_{10}O_2$ $[M]^+$ 150.0680, found 150.0681.

4-Hydroxy-3,5-dimethylbenzaldehyde (44b)[201]

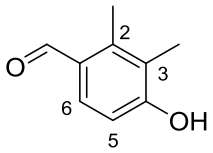


44b

Compound used directly without purification; purple-pink powder (3.5 g, 71%). M.p. 92-95˚C [lit. 111-113°C]; R_f = 0.73 (1 : 1 EtOAc : petrol); IRυ_{max} 3248 (O-H), 2915 (C-H), 1664 (C=O), 1591 (aromatic), 1488 (aromatic), 1200 (C-O) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 9.81 (s, 1H, CHO), 7.54 (s, 2H, 2-H), 5.38 (s, 1H, OH), 2.31 (s, 6H, 3-Me); δ ^{13}C NMR (150 MHz, $CDCl_3$) 191.6 (CHO), 158.1 (C_q), 131.1 (2 × CH), 129.5 (C_q), 123.8 (2 × C_q), 15.9 (2 × CH_3); HRMS (EI) calcd. for $C_9H_{10}O_2$ $[M]^+$150.0680, found 150.0673.

4-Hydroxy-2, 3-dimethylbenzaldehyde (44c)[202]

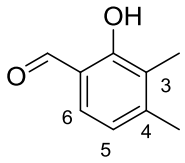
A mixture of 1: 0.4 ratio of **44c**: **44d** was observed in the crude material, each of which were isolated by purification by dry load flash column under gradient method 0-30% EtOAc: petrol to isolate first **44c** first then **44d.**



44c

Isolated as white crystals (1.36g, 28%); m.p 155-157 °C [lit. 160-171 °C]; R_f = 0.51 (1: 1 EtOAc: petrol); IRυ $_{max}$ 3251 (O-H), 2953 (C-H), 1651 (C=O), 1580 (aromatic), 1251 (C-O) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 10.2 (s, 1H, CHO), 7.54 (d, 1H, *J* = 8.5 Hz, 6-H), 6.76 (d, 1H, *J* = 8.5 Hz, 5-H), 5.62 (s, 1H, OH), 2.61 (s, 3H, 2-Me), 2.22 (s, 3H, 3-Me); δ ^{13}C NMR (150 MHz, $CDCl_3$) 192.0 (CHO), 158.5 (C_q), 142.3 (C_q), 131.1 (CH), 128.3 (C_q), 124.1 (C_q), 113.1 (CH), 14.9 (CH_3), 11.4 (CH_3); HRMS (CI) calcd. for $C_9H_{11}O_2$ $[M+H]^+$ 151.0680, found 151.0753.

2-Hydroxy-3,4-dimethylbenzaldehyde (44d)[203]



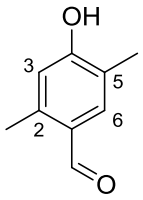
44d

Isolated as a yellow powder (750 mg, 16%); m.p. 43-45 °C; R_f = 0.91 (1: 1 EtOAc : petrol); IRυ $_{max}$ 3200 (O-H), 2839 (C-H), 1645 (C=O), 1620 (aromatic), 1499 (aromatic), 1230 (C-O) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 11.37 (s, 1H, OH), 9.81 (s, 1H, CHO), 7.29 (d, 1H, *J* = 7.9 Hz, 6-H), 6.83 (d, 1H, *J* = 7.9 Hz, 5-H), 2.33 (s, 3H, 4-Me), 2.17 (s, 3H, 3-Me); δ ^{13}C NMR (150 MHz, $CDCl_3$) 196.1 (CHO), 159.9 (C_q), 147.3 (C_q), 130.9 (CH), 125.0 (C_q), 121.6 (CH), 118.6 (C_q), 21.1 (CH_3), 10.8 (CH_3); HRMS (CI) calcd. for $C_9H_{11}O_2$ $[M+H]^+$ 151.0680, found 151.0752.

4-Hydroxy-2,5-dimethylbenzaldehyde (44e)[85]

General procedure C: Using dichloromethyl methyl ether (1.1 eq) and $AlCl_3$ (1.1 eq) with respect to the phenol. A crude mixture of **44e** and **44f** were present in a ratio of 1: 0.4. Purification by dry load flash column gradient method 0-40% EtOAc: petrol enabled separation of isomers which gave:

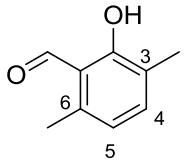
a) Orange yellow solid (3.5 g, 55%).



44e

m.p. 107-111˚C [lit. 130°C]; R_f = 0.63 (1 : 1 EtOAc : petrol); IRυ_{max} 3236 (O-H), 2927 (C-H), 1662 (C=O), 1579 (aromatic), 1269 (C-O) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) para dimethylphenolbenzaldehyde: 10.1 (s, 1H, CHO), 7.60 (s, 1H, H-6), 6.65 (s, 1H, H-3), 5.77 (s, 1H, OH), 2.59 (s, 3H, 5-Me), 2.27 (s, 3H, 2-Me); δ ^{13}C NMR (150 MHz, $CDCl_3$) 191.6 (CHO), 158.1 (C_q), 141.5 (C_q), 135.7 (CH), 127.8 (C_q), 122.1 (C_q), 118.0 (CH), 19.3 (CH_3), 15.3 (CH_3); HRMS (CI) calcd. for $C_9H_{11}O_2$ $[M + H]^+$ 151.0680, found 151.0743.

2-Hydroxy-3,6-dimethylbenzaldehyde (44f)[85]



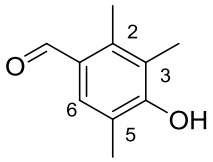
44f

Purification by dry load flash column gradient method 0-40% EtOAc: petrol isolated minor isomer as a pale green oil (720 mg, 15%); R_f = 0.87 (1 : 1 EtOAc : petrol); IRυ_{max} 2926 (C-H), 1633 (C=O), 1458 (aromatic), 1424 (aromatic), 1232 (C-O) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 12.1 (s, 1H, OH), 10.3 (s, 1H, CHO), 7.24 (d, 1H, *J* = 7.4 Hz, 4-H), 6.62 (d, 1H, *J* = 7.4 Hz, 5-H), 2.57 (s, 3H, 6-Me), 2.21 (s, 3H, 3-Me); δ ^{13}C NMR (150 MHz, $CDCl_3$) 195.8 (CHO), 161.7 (C_q), 139.5 (C_q), 138.4

(CH), 125.1 (C_q), 121.3 (CH), 118.1 (C_q), 18.1 (CH_3), 15.1 (CH_3); HRMS (EI) calcd. for $C_9H_{10}O_2$ $[M]^+$ 150.0680, found 150.0669.

4-Hydroxy-2,3,5-trimethylbenzaldehyde (44g)[204]

Using dichloromethyl methyl ether (1.1 eq) and $AlCl_3$ (1.1 eq) with respect to phenol.



44g

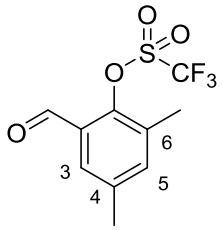
Isolated as a yellow viscous oil (2.9 g, 60%); m.p. 123-125 °C; R_f = 0.91 (1 : 1 EtOAc : petrol); IRυ_{max} 3356 (O-H), 2926 (C-H), 1657 (C=O), 1570 (aromatic), 1290 (C-O) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 10.1 (s, 1H, CHO), 7.49 (s, 2H, 6-H), 5.31 (d, 1H, *J* = 6.1 Hz, OH), 2.57 (s, 3H, 2-Me), 2.28 (s, 3H, 5-Me), 2.21 (s, 3H, 3-Me); δ ^{13}C NMR (150 MHz, $CDCl_3$) 192.1 (CHO), 157.1 (C_q), 139.7 (C_q), 132.6 (CH), 127.8 (C_q), 123.2 (C_q), 120.5 (C_q), 15.7 (CH_3), 14.7 (CH_3), 11.7 (CH_3); HRMS (CI) calcd. for $C_{10}H_{13}O_2$ $[M + H]^+$ 165.0837, found 165.0906.

Preparation of trifluoromethanesulfonate from phenols (44a-44g)

General Procedure D:

To a solution of phenol (2 g, 13 mmol) in CH_2Cl_2 (anhydrous) (13 ml) at -78°C under dry argon conditions was added triethylamine (4.04 g, 40 mmol, 3 eq) and stirred for 30 minutes. Trifluoromethylsulfonate anhydride (2.5 ml, 15 mmol, 1.1 eq) was added dropwise via a syringe pump for 18 minutes at 7.7 ml/hr. Reaction was left to stir for a further 2 hrs. Diluted in CH_2Cl_2 (15 ml), and washed with saturated solution of $NaHCO_3$ (20 ml), brine (20 ml) and water (20 ml). Dried with $MgSO_4$, filtered and concentrated to give the corresponding aryl triflates.

2-Formyl-4,6-dimethylphenyl trifluoromethanesulfonate (45a)

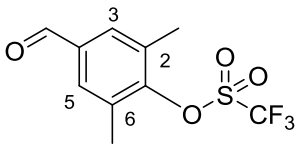


45a

Purified by column chromatography (0-40% EtOAc in petrol); Yellow viscous oil (2.4 g, 64%). R_f = 0.91 (1: 1 EtOAc : petrol); IRυ_{max} 2883 (C-H), 1701 (C=O), 1598 (aromatic), 1407 (O=S=O), 1207 (C-O), 1136 (C-F) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 10.19 (s, 1H, CHO), 7.62 (d, 1H, *J* = 2.0 Hz, 3-H), 7.38 (d, 1H, *J* = 2.0 Hz 5-H), 2.42 (s, 3H, 6-Me), 2.40 (s, 3H, 4-Me); δ ^{13}C NMR (150 MHz, $CDCl_3$) 187.4 (CHO), 145.9 (C_q), 139.1 (C_q), 138.8 (CH), 132.5 (C_q), 129.2 (C_q), 128.5 (CH), 118.4 (q, *J* = 321 Hz, C_q), 20.9 (CH_3), 16.5 (CH_3); HRMS (EI) calcd. for $C_{10}H_9F_3O_4S$ $[M]^+$ 282.0174, found 282.0174.

4-Formyl-2, 6-dimethylphenyl trifluoromethanesulfonate (45b)

Method D: Using **44b** (94 mg, 0.63 mmol), trifluoromethylsulfonate anhydride (0.20 ml, 1.1 mmol, 1.9 eq) and NEt_3 (0.28 ml, 0.2 mmol, 3.2 eq).



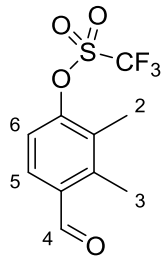
45b

Purified by column chromatography (0-20% EtOAc in petrol); yellow oil (88 mg, 53%); R_f = 0.89 (1:1 EtOAc: petrol); IRυ_{max} 2922-2864 (ald C-H), 1701 (ald C=O), 1604 (aromatic), 1290 (O=S=O), 1212 (C-O), 1132 (C-F) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 9.96 (s, 1H, CHO), 7.66 (br s, 2H, H-3, 5), 2.47 (s, 6H, 6-Me and 2-Me); δ ^{13}C NMR (150 MHz, $CDCl_3$) 191.1 (CHO), 150.8 (C_q), 135.4 (C_q) , 133.1 (2 × C_q), 131.2 (2 × CH), 118.7 (q, *J* = 321 Hz, C_q), 17.5 (2 × CH_3); HRMS (CI) calcd. for $C_{10}H_{10}F_3O_4S$ $[M + H]^+$ 283.0174, found 283.0237.

4-Formyl-2,3-dimethylphenyl trifluoromethanesulfonate (45c)[202] and 6-formyl-2,3-dimethylphenyl trifluoromethanesulfonate (45d)[203]

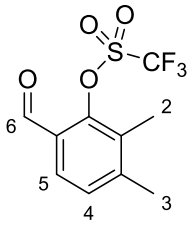
Method D: Using methyl phenol benzaldehyde (1 g) and trifluoromethylsulfonate anhydride (1.2 eq).

Purification by dry load flash column chromatography gradient method in 0-20% EtOAc: petrol to give title compound as a mixture of isomers as a yellow oil (1.8 g, 95%).



45c

45c: R_f = 0.92 (1 : 1 EtOAc : petrol); IRυ_{max} 2881 (C-H ald), 1695 (C=O ald), 1423 (aromatic), 1390 (O=S=O), 1213 (C-O), 1137 (C-F) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 10.2 (s, 1H, CHO), 7.75 (d, 1H, *J* = 7.8 Hz, 5-H), 7.34 (d, 1H, *J* = 7.8 Hz 6-H), 2.41 (s, 3H, 2-Me), 2.34 (s, 3H, 3-Me); δ ^{13}C NMR (150 MHz, $CDCl_3$) 187.1 (CHO), 147.7 (C_q), 147.4 (C_q), 131.5 (C_q), 130.2 (CH), 127.8 (CH), 127.5 (C_q), 118.7 (q, *J* = 320 Hz, C_q), 21.1 (CH_3), 13.4 (CH_3).



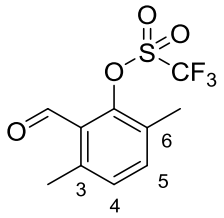
45d

45d: 10.23 (s, 1H, CHO), 7.76 (d, 1H, *J* = 9.0 Hz, 5-H), 7.28 (d, 1H, *J* = 9.0 Hz 4-H), 2.66 (s, 3H, 3-Me), 2.35 (s, 3H, 2-Me); δ ^{13}C NMR (150 MHz, $CDCl_3$) 191.5 (CHO), 151.4 (C_q), 142.9 (C_q), 134.0 (C_q), 131.6 (C_q), 130.8 (CH), 119.4 (CH), 118.

7 (q, J = 290 Hz, C_q), 15.3 (CH_3), 13.1 (CH_3); HRMS (CI) calcd. for $C_{10}H_{10}F_3O_4S$ $[M + H]^+$ 283.0174, found 283.024837.

2-Formyl-3,6-dimethylphenyl trifluoromethanesulfonate (45f)

Method D: Prepared according to the general procedure using 2.2 eq. of trifluoromethanesulfonic anhydride and 3.2 eq triethylamine.

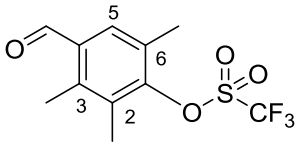


45f

Purified column chromatography (0-20% EtOAc in petrol); red-brown oil (925 mg, 34%). R_f = 0.72 (1 : 1 EtOAc : petrol); IRυ_{max} 2981 (C-H ald), 1612 (C=O ald), 1455 (aromatic), 1350 (O=S=O), 1207 (C-O), 1132 (C-F)cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 10.4 (s, 1H, H-CHO), 7.41 (d, 1H, J = 8.0 Hz, 4-H), 7.21 (d, 1H, J = 8.0 Hz, 5-H), 2.60 (s, 3H, 6-Me), 2.42 (s, 3H, 3-Me); δ ^{13}C NMR (150 MHz, $CDCl_3$) 189.9 (CHO), 148.9 (C_q), 140.8 (C_q), 136.7 (CH), 132.0 (CH), 130.2 (C_q), 128.0 (C_q), 121.4 (q, J = 299.3 Hz, C_q), 20.8 (CH_3), 16.5 (CH_3); HRMS (CI) calcd. for $C_{10}H_9F_3O_4S$ $[M]^+$ 282.0174, found 282.0110.

4-Formyl-2, 3, 6-trimethylphenyl trifluoromethanesulfonate (45g)

Method D: Using **44g** (300 mg, 1.8 mmol), trifluoromethylsulfonate anhydride (0.5 ml, 1.7 eq) and NEt_3 (0.80 ml, 5.8 mmol, 3.2 eq).



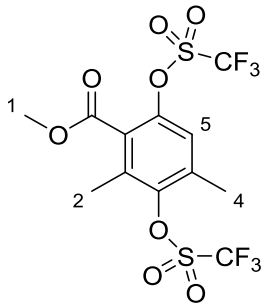
45g

Purified by column chromatography (0-10% EtOAc in petrol); yellow oil (250 mg, 46%). R_f = 0.93 (1:1 EtOAc: petrol); IRυ_{max} 2956 (ald C-H), 1699 (ald C=O), 1407

(aromatic), 1209 (O=S=O), 1136 (C-O), 1040 (C-F) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 10.30 (s, 1H, H-CHO), 7.61 (s, 1H, 5-H), 2.60 (s, 3H, 2-Me), 2.43 (s, 3H, 6-Me), 2.34 (s, 3H, 3-Me); δ ^{13}C NMR (150 MHz, $CDCl_3$) 191.9 (CHO), 150.2 (C_q), 139.9 (C_q), 133.6 (C_q), 132.6 (CH), 132.3 (C_q), 129.6 (C_q), 118.6 (q, J = 319.4 Hz, C_q), 17.2 (CH_3), 14.7 (CH_3), 14.0 (CH_3); HRMS (EI) calcd. for $C_{11}H_{11}F_3O_4S$ $[M]^+$ 296.0330, found 296.0324.

Methyl-2,4-dimethyl-3,6-bis(trifluoromethyl)sulfonyl)oxy)benzoate (45h)

Under the same conditions mentioned above with methyl phenol benzaldehyde (1.35 g) and trifluoromethylsulfonate anhydride (2.2 eq).



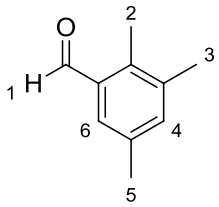
45h

Purification by dry load flash column chromatography gradient method in 20% EtOAc: petrol to give the title compound as a yellow viscous oil (3.0 g, 98%). R_f = 0.68 (1 : 1 EtOAc : petrol); IRυ $_{max}$ 1740 (C=O), 1420 (aromatic), 1399 (O=S=O), 1206 (C-O), 1130 (C-F) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.22 (s, 1H, H-5), 3.94 (s, 3H, H-1), 2.45 (s, 3H, H-4), 2.37 (s, 3H, H-2); δ ^{13}C NMR (150 MHz, $CDCl_3$) 164.6 (C_q), 148.9 (C_q), 145.2 (C_q), 138.6 (C_q), 127.9 (C_q), 124.3 (C_q), 123.6 (CH), 118.6 (q, J = 320.6 Hz, C_q), 118.4 (q, J = 320.6 Hz, C_q), 53.1 (CH_3), 20.5 (CH_3), 11.1 (CH_3); HRMS (CI) calcd. for $C_{12}H_{11}$ $F_6O_8S_2$ $[M + H]^+$ 460.9721, found 460.9785.

Suzuki cross coupling reaction between aryl triflate and methylboronic acid

General procedure E: Under flame dry argon conditions, to a solution of aryl triflate (400 mg, 1mmol, 1eq) in THF (0.04 M), was added $PdCl_2$(dppf).dcm (116 mg, 10 mol%) and K_2CO_3 (397 mg, 3 mmol, 2 eq) which was left to stir for 5 minutes. Water (0.8 M) (HPLC grade) was added followed by addition of methyl boronic acid (255 mg, 4 mmol, 3 eq). Ratio of THF: H_2O (20: 1). Reaction was left to reflux overnight. After adding EtOAc (7 ml) to the reaction mixture, the organic layer was washed with water (2 × 10 ml), dried with $MgSO_4$, filtered and concentrated.

2,3,5-Trimethylbenzaldehyde (46a)

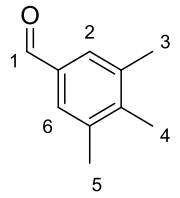


46a

Dry load flash column 30% EtOAc: petrol to give the title compound as a brown oil (208 mg, 99%); R_f = 0.82 (1 : 1 EtOAc: petrol); IRυ_{max} 2923 (C-H ald), 1692 (C=O ald), 1478 (aromatic) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 10.28 (s, 1H, CHO), 7.46 (s, 1H, H-6), 7.20 (s, 1H, H-4), 2.52 (s, 3H, H-2), 2.33 (s, 3H, H-5), 2.30 (s, 3H, H-3); δ ^{13}C NMR (150 MHz, $CDCl_3$) 193.5 (CHO), 138.3 (C_q), 136.4 (CH), 136.3 (C_q), 135.4 (C_q), 134.3 (C_q), 130.1 (CH), 21.2 (CH_3), 20.2 (CH_3), 14.3 (CH_3); HRMS (EI) calcd. for $C_{10}H_{12}O$ $[M]^+$ 148.0888, found 148.0876.

3,4,5-Trimethylbenzaldehyde (46b)

Under the same conditions as above using aryl triflate (500 mg), methyl boronic acid (5 eq), K_2CO_3 (3 eq) and $PdCl_2$(dppf).dcm (15 mol%).

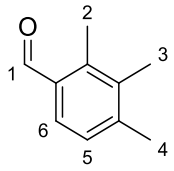


46b

Purification by dry load flash column in 0-10% EtOAc: petrol to give the title compound as a yellow oil (159 mg, 61%). R_f = 0.93 (1 : 1 EtOAc : petrol); IRυ $_{max}$ 2929 (C-H ald), 1694 (C=O ald), 1406 (aromatic) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 9.90 (s, 1H, H-1), 7.51 (s, 2H, H-2, 6), 2.36 (s, 6H, H-3, 5), 2.25 (s, 3H, H-4); δ ^{13}C NMR (150 MHz, $CDCl_3$) 192.7 (CHO), 143.2 (C_q), 137.5 (2 × C_q), 133.9 (C_q), 129.0 (2 × CH), 20.7 (2 × CH_3), 16.2 (CH_3); HRMS (EI) calcd. for $C_{10}H_{12}O$ $[M]^+$ 148.0888, found 148.0878.

2, 3, 4-Trimethylbenzaldehyde (46c)

Under the same conditions as above using aryl triflate (500 mg), methyl boronic acid (3 eq), K_2CO_3 (2 eq) and $PdCl_2$(dppf).dcm (10 mol%).

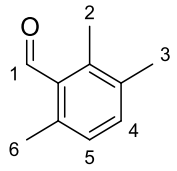


46c

Purification by dry load flash column in 0-40% EtOAc: petrol to give the title compound as a yellow oil (255 mg, 97%). R_f = 0.89 (1: 1 EtOAc : petrol); IRυ $_{max}$ 2935 (C-H ald), 1693 (C=O ald), 1680 (aromatic), 1593 (aromatic) $cm^{-1;}$ δ ^{1}H NMR (600 MHz, $CDCl_3$) 10.3 (s, 1H, CHO), 7.56 (d, 1H, *J* = 7.7 Hz, H-6), 7.16 (d, 1H, *J* = 7.7 Hz, H-5), 2.60 (s, 3H, H-3), 2.36 (s, 3H, H-4), 2.24 (s, 3H, H-2); δ ^{13}C NMR (150 MHz, $CDCl_3$) 193.2 (CHO), 143.5 (C_q), 139.2 (C_q), 137.0 (C_q), 132.8 (C_q), 129.7 (CH), 127.8 (CH), 21.7 (CH_3), 15.4 (CH_3), 14.9 (CH_3); HRMS (CI) calcd. for $C_{10}H_{13}O$ $[M + H]^+$ 149.0888, found 149.0959.

2,3,6-Trimethylbenzaldehyde (46e)

Under the same conditions as above using aryl triflate (400 mg), methyl boronic acid (3 eq), K_2CO_3 (2 eq) and $PdCl_2$(dppf).dcm (10 mol%).

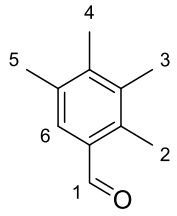


46e

Purification by dry load flash column in 0-10% EtOAc: petrol to give the title compound as an orange yellow oil (209 mg, 99%). R_f = 0.91 (1:1 EtOAc : petrol); IRυ $_{max}$ 2930 (C-H ald), 1687 (C=O ald), 1461 (aromatic) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 10.6 (s, 1H, CHO), 7.22 (d, 1H, *J*= 7.7 Hz, H-4), 6.98 (d, 1H, *J* = 7.7 H-5), 2.52 (s, 3H, H-6), 2.48 (s, 3H, H-2), 2.29 (s, 3H, H-3); δ ^{13}C NMR (150 MHz, $CDCl_3$) 194.9 (CHO), 139.1 (C_q), 138.2 (C_q), 135.7 (C_q), 134.5 (CH), 133.3 (C_q), 129.1 (CH), 20.5 (CH_3), 20.2 (CH_3), 15.6 (CH_3); HRMS (EI) calcd. for $C_{10}H_{12}O$ $[M]^+$ 148.0888, found 148.0873.

2,3,4,5-Tetramethylbenzaldehyde (45g)

Under the same conditions as above using **45g** (800 mg), methyl boronic acid (5 eq), K_2CO_3 (3 eq) and $PdCl_2$(dppf).dcm (15 mol%).



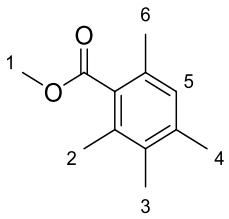
46g

Purification by dry load flash column in 0-10% EtOAc: petrol to give the title compound as a yellow oil (438 mg, 80%). R_f = 0.93 (1 : 1 EtOAc : petrol); IRυ $_{max}$ 2931 (C-H ald), 1688 (C=O), 1600 (aromatic) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$)

10.25 (s, 1H, H-CHO), 7.46 (s, 1H, H-6), 2.58 (s, 3H, H-4), 2.33 (s, 3H, H-5), 2.27 (s, 3H, H-2), 2.25(s, 3H, H-3); δ ^{13}C NMR (150 MHz, $CDCl_3$) 193.5 (CHO), 142.2 (C_q), 136.8 (CH), 136.7 (C_q), 134.3 (C_q), 132.3 (C_q), 130.8 (CH), 21.8 (CH_3), 17.0 (CH_3), 15.9 (CH_3), 14.8 (CH_3); HRMS (EI) calcd. for $C_{11}H_{14}O$ $[M]^+$ 162.1045, found 162.1035.

Methyl-2, 3, 4, 6-tetramethylbenzoate (45h)

Under the same conditions as above using **45h** (1 g), boronic acid (10 eq), K_2CO_3 (3 eq) and $PdCl_2$(dppf).dcm (15 mol%).

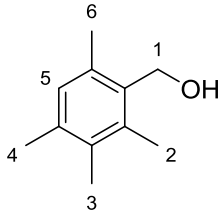


45i

Purification by dry load flash column in 0-10% EtOAc: petrol to give the title compound as an orange yellow oil (447 mg, 87%). R_f = 0.68 (1:4 EtOAc : petrol); IRυ $_{max}$ 2949 (C-H), 1730 (C=O), 1435 (aromatic), 1268 (C-O) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 6.86 (s, 1H, H-5), 3.90 (s, 3H, H-1), 2.25 (s, 3H, H-6), 2.22 (s, 3H, H-4), 2.20(s, 3H, H-3), 2.15 (s, 3H, H-2); δ ^{13}C NMR (150 MHz, $CDCl_3$) 171.5 (C_q), 137.7 (C_q), 132.9 (C_q), 132.8 (C_q), 132.5 (C_q), 131.3 (C_q), 129.3 (CH), 52.0 (CH_3), 20.9 (CH_3), 19.3 (CH_3), 17.6 (CH_3), 15.3 (CH_3); HRMS (EI) calcd. for $C_{12}H_{16}O_2$ $[M]^+$ 192.1150, found 192.1153.

2, 3, 4, 6-Tetramethylphenyl)methanol (45j)

To a flame dried flask under an atmosphere of argon containing a solution of tetramethylbenzoate (50 mg, 0.26 mmol, 1 eq) in toluene (3 ml), were added DIBAL (39 μl, 5 mmol, 1.5 eq) in a solution of diethyl ether dropwise at -78°C. The reaction was stirred for 4 hrs at the same -78°C. Added CH_2Cl_2 (5 ml) to the reaction mixture and washed with brine (5 ml) and water (2 × 10 ml), dried with $MgSO_4$, filtered and evaporated. Purification by dry load flash column in 20% EtOAc: petrol to give the title compound as a white oil (27 mg, 63%).

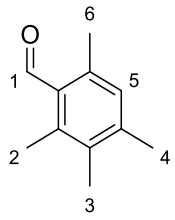


45j

R_f = 0.81 (1 : 1 EtOAc : petrol); $IR_{\upsilon\ max}$ 3383 (O-H), 2921 (C-H), 1443 (aromatic), 1265 (C-O) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 6.88 (s, 1H, H-5), 4.74 (s, 2H, H-1), 2.37 (s, 3H, H-6), 2.35 (s, 3H, H-2), 2.26 (s, 3H, H-4), 2.18 (s, 3H, H-3); δ ^{13}C NMR (150 MHz, $CDCl_3$) 136.5 (C_q), 136.2 (C_q), 134.4 (C_q), 134.1 (C_q), 133.5 (C_q), 129.8 (CH), 59.9 (CH_2), 20.9 (CH_3), 19.5 (CH_3), 15.91 (CH_3), 15.88 (CH_3); HRMS (EI) calcd. for $C_{11}H_{16}O$ $[M]^+$ 164.1201, found 164.1195.

2, 3, 4, 6-Tetramethylbenzaldehyde (46f)

To a flame dried flask under an atmosphere of argon were added oxalyl chloride (0.3 ml, 0.6 mmol, 2M, 1.1 eq) and anhydrous DMSO (78 µl, 1 mmol, 2 eq) to DCM (3 ml) at -78°C. After stirring for 15 minutes methylbenzyl alcohol (90 mg, 0.55 mmol, 1 eq) and NEt_3 (2.29 ml, 2 mmol, 3 eq) was added and the reaction was left to stir for 3 hrs. Added CH_2Cl_2 (5 ml) to the reaction mixture and washed with aqueous saturated sodium carbonate (15 ml), followed by brine (15 ml) and water (15 ml). Dried with $MgSO_4$, filtered and evaporated. Purification by dry load flash column in 20% EtOAc: petrol to give the title compound as a yellow oil (17 mg, 18%).



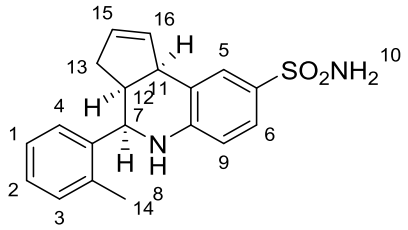
46f

R_f = 0.89 (1 : 1 EtOAc: petrol); IRυ $_{max}$ 2924 (C-H), 1690 (C=O), 1596 (aromatic) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 10.6 (s, 1H, H-CHO), 6.90 (s, 1H, H-5), 2.52 (s, 3H, H-5), 2.51 (s, 3H, H-6), 2.30 (s, 3H, H-3), 2.19 (s, 3H, H-2); δ ^{13}C NMR (150 MHz, $CDCl_3$) 194.5 (CHO), 142.2 (C_q), 139.2 (C_q), 137.9 (C_q), 134.3 (C_q), 131.5

(C_q), 131.2 (CH), 21.5 (CH_3), 20.5 (CH_3), 15.9 (CH_3), 15.3 (CH_3); HRMS (EI) calcd. for $C_{11}H_{14}O$ $[M]^+$ 162.1045, found 162.1031.

(3a*S*,4*R*,9b*R*)-4-o-Tolyl-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[c]quinoline-8-sulfonamide (47b)

A: Under the same protocol conditions as above with exception to sulphanilamide (2 eq) added to the reaction. Purification by flash chromatography dry load method using 50% EtOAc: petrol gave the title compound as an off-white amorphous solid (850 mg, 99%). Isolated as a mixture of two diastereoisomers in 93: 7 ratio.

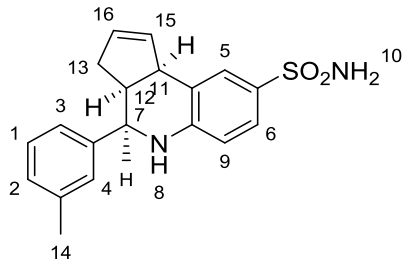


47b

M.p. 75-78 ˚C; R_f = 0.35 (1 : 1 EtOAc : petrol); IRυ $_{max}$ 3360 (C-H), 3263 (C-H), 2931 (N-H), 1494 (aromatic), 1461 (SO_2-N), 1308 (SO_2-N), 1290 (O=S=O), 1153 (O=S=O) cm^{-1}; Major diastereoisomer: δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.62 (d, 1H, *J* = 1.6 Hz, H-5), 7.53 (m, 2H, H-6, 4), 7.26 (td, 1H, *J* = 7.1, 1.5 Hz, H-1), 7.22 (td, 1H, *J* = 7.1, 1.0 Hz, H-2), 7.20 (d, 1H, *J* = 7.1 Hz, H-3), 6.64 (d, 1H, *J* = 8.5 Hz, H-9), 5.89-5.87 (m, 1H, H-16), 5.69-5.68 (m, 1H, H-15), 4.91 (d, 1H, *J* = 2.8 Hz, H-7), 4.84 (s, 2H, NH_2), 4.13 (d, 1H, *J* = 8.7 Hz, H-11), 3.09 (dtd, 1H, *J* = 10.8, 8.7, 2.8 Hz, H-12), 2.61 (dtd, 1H, *J* = 16.4, 10.8, 2.8 Hz, H-13), 2.39 (s, 3H, H-14), 1.79 (br dd, 1H, *J* = 16.4, 8.7 Hz, H-13); δ ^{13}C NMR (150 MHz, $CDCl_3$) 150.3 (C_q), 139.6 (C_q), 135.1 (C_q), 133.5 (CH), 131.2 (CH), 130.79 (CH), 130.75 (C_q), 128.2 (CH), 127.4 (CH), 126.5 (CH), 125.9 (C_q), 125.7 (CH), 125.4 (CH), 114.2 (CH), 53.7 (CH), 46.0 (CH), 42.8 (CH), 31.7 (CH_2), 19.3 (CH_3); HRMS (EI) calcd. for $C_{19}H_{21}O_2N_2S$ $[M + H]^+$ 341.1312, found 341.1342.

(3a*S*,4*R*,9b*R*)-4-m-Tolyl-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[c]quinoline-8-sulfonamide (48b)

A: Under the same protocol conditions above with exception to sulphanilamide (2 eq) added to the reaction. Purification by flash chromatography dry load method using 50% EtOAc: petrol to afford the title compound as a pale amorphous crystals (685 mg, 81%). Isolated as a mixture of two diastereoisomers in 92: 8 ratio.

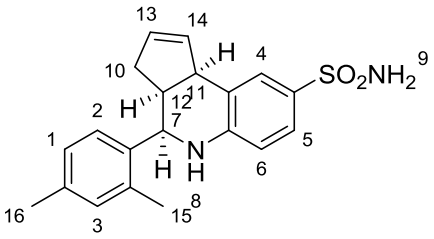


48b

m.p. 78 ˚C; R_f = 0.55 (1 : 1 EtOAc : petrol); IRυ $_{max}$ 3300 (C-H), 3252 (C-H), 2279 (N-H), 1494 (aromatic), 1314 (SO_2-N), 1152 (O=S=O) cm^{-1}; Major diastereoisomer: δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.60 (d, 1H, *J* = 1.8 Hz, H-5), 7.51 (dd, 1H, *J* = 8.2, 1.8 Hz, H-6), 7.27 (t, 1H, *J* = 7.7 Hz, H-1), 7.19 (m, 2H, H-4, 3), 7.12 (d, 1H, *J* = 7.7 Hz, H-2), 6.64 (d, 1H, *J* = 8.2 Hz, H-9), 5.89-5.87 (m, 1H, H-16), 5.67-5.66 (m, 1H, H-15), 4.83 (s, 2H, NH_2), 4.66 (d, 1H, *J* = 2.9 Hz, H-7), 4.24 (s, 1H, NH), 4.10 (d, 1H, *J* = 8.7 Hz, H-11), 3.01 (dtd, 1H, *J* = 10.8, 8.7, 2.9 Hz, H-12, 2.56 (dtd, 1H, *J* = 16.3, 10.8 , 2.9 Hz, H-13), 2.38 (s, 3H, H-14), 1.83 (br dd, 1H, *J* = 16.3, 8.7 Hz, H-13); δ ^{13}C NMR (150 MHz, $CDCl_3$) 149.9 (C_q), 141.7 (C_q), 138.5 (C_q), 133.5 (CH), 131.2 (CH), 130.8 (C_q), 128.7 (CH), 128.5 (CH), 128.2 (CH), 127.2 (CH), 125.9 (C_q), 125.4 (CH), 123.5 (CH), 115.6 (CH), 57.5 (CH), 45.91 (CH), 45.90 (CH), 31.6 (CH_2), 21.7 (CH_3); HRMS (EI) calcd. for $C_{19}H_{21}O_2N_2S$ $[M+H]^+$ 341.1324, found 341.1324.

(3a*S*,4*R*,9b*R*)-4-(2,4-Dimethylphenyl)-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[c]quinoline-8-sulfonamide (49b)

A: Purification by flash chromatography dry load gradient method 30-40% EtOAc: petrol gave the title compound as a pale orange crystals (835 mg, 99%). Isolated as a mixture of two diastereoisomers in 91: 9 ratio.

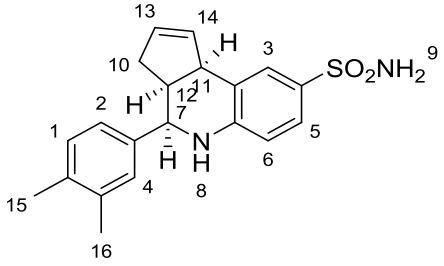


49b

m.p. 125-128 ˚C; R_f = 0.42 (1:1 EtOAc : petrol); IRυ $_{max}$ 3359 (C-H), 3264 (C-H), 2923 (N-H), 1498 (aromatic), 1310 (SO_2-N), 1290 (O=S=O), 1152 (O=S=O) cm^{-1}; Major diastereoisomer: δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.61 (d, 1H, *J* = 1.7, Hz, H-4), 7.51 (dd, 1H, *J* = 8.4, 1.7 Hz, H-5), 7.40 (d, 1H, *J* = 8.4 Hz, H-2), 7.06 (br d, 1H, *J* = 8.4 Hz, H-1), 7.02 (br s, 1H, H-3), 6.64 (d, 1H, *J* = 8.4 Hz, H-6), 5.89-5.86 (m, 1H, H-14), 5.70-5.68 (m, 1H, H-13), 4.87 (d, 1H, *J* = 3.2 Hz, H-7), 4.76 (s, 2H, NH_2), 4.11 (d, 1H, *J* = 8.3 Hz, H-11), 3.06 (dtd, 1H, *J* = 9.4, 8.3, 3.2 Hz, H-12), 2.61 (dtd, 1H, *J* = 16.3, 9.4, 3.2 Hz, H-1), 2.35 (s, 3H, H-15), 2.33 (s, 3H, H-16), 1.80 (ddd, 1H, *J* = 16.3, 8.3, 3.2 Hz, H-10); ^{13}C NMR (150 MHz, $CDCl_3$) 150.4 (C_q), 137.0 (C_q), 136.6 (C_q), 135.0 (C_q), 133.5 (CH), 131.6 (CH), 131.3 (CH), 130.6 (C_q), 128.2 (CH), 127.1 (CH), 125.9 (C_q), 125.6 (CH), 125.4 (CH), 115.6 (CH), 53.5 (CH), 46.0 (CH), 43.0 (CH), 31.6 (CH_2), 21.1 (CH_3), 19.2 (CH_3); HRMS (EI) calcd. for $C_{20}H_{23}O_2N_2S$ $[M+H]^+$ 355.1402, found 355.14769.

(3a*S*,4*R*,9b*R*)-4-(3,4-Dimethylphenyl)-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[c]quinoline-8-sulfonamide (50b)

A: Purification by flash chromatography dry load gradient method in 30-60% EtOAc: petrol gave the title compound as red yellow crystals (179 mg, 17%). Isolated as a mixture of two diastereoisomers in 85: 15 ratio.

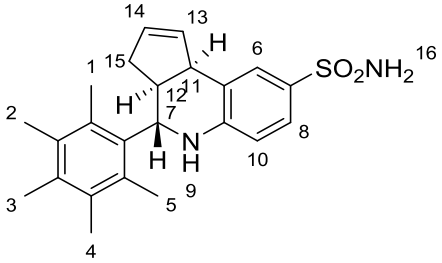


50b

m.p. 110-111 ˚C; R_f = 0.42 (1 : 1 EtOAc : petrol); IRυ_{max} 3362 (C-H), 3269 (C-H), 2921 (N-H), 1499 (aromatic), 1328 (SO_2-N), 1158-1130 (O=S=O) cm^{-1}; Major diastereoisomer: δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.59 (dd, 1H, *J* = 2.0, 0.7 Hz, H-3), 7.50 (dd, 1H, *J* = 8.4, 2.0 Hz, H-5), 7.15 (br s, 1H, H-4), 7.14 (brs, 1H, H-1), 7.12 (dd, 1H, *J* = 7.7, 1.6 Hz, H-2), 6.65 (d, 1H, *J* = 8.4 Hz, H-6), 5.89-5.86 (m, 1H, H-14), 5.69-5.67 (m, 1H, H-13), 4.64 (d, 1H, *J* = 3.3 Hz, H-7), 4.62 (s, 2H, NH_2), 4.20 (s, 1H, NH), 4.10 (d, 1H, *J* = 8.8 Hz, H-11), 3.00 (dtd, 1H, *J* = 9.3, 8.8, 3.3 Hz, H-12), 2.56 (dtd, 1H, *J* = 16.5, 8.8, 3.3 Hz, H-10), 2.29 (s, 3H, H-15), 2.27 (s, 3H, H-16), 1.86 (ddd, 1H, *J* = 16.5, 9.3, 3.3 Hz, H-10); ^{13}C NMR (150 MHz, $CDCl_3$) 150.4 (C_q), 139.2 (C_q), 137.1 (C_q), 136.1 (C_q), 133.5 (CH), 131.3 (CH), 130.5 (C_q), 130.0 (CH), 128.2 (CH), 127.7 (CH), 125.9 (C_q), 125.4 (CH), 123.7 (CH), 115.6 (CH), 57.3 (CH), 46.0 (CH), 45.9 (CH), 31.7 (CH_2), 20.1 (CH_3), 19.6 (CH_3); HRMS (EI) calcd. for $C_{20}H_{23}O_2N_2S$ $[M+H]^+$ 355.1402, found 355.14770.

4-(2,3,4,5,6-Pentamethylphenyl)-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[c]quinoline-8-sulfonamide (51a)

Method B: Hydrolysis of imine: 0.1M of HCl (20 ml) in water and EtOAc (1.5 ml). The reaction mixture was stirred for 1 hr. Purification by dry load flash column chromatography in 40% EtOAc: petrol gave the title compound as a white film (50 mg, 34%). Isolated as a mixture of two diastereoisomers in >95: 5 ratio.



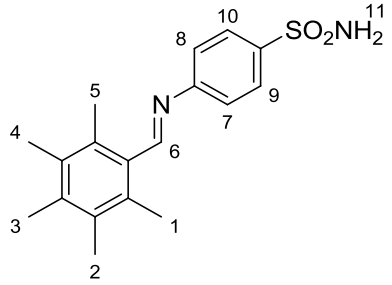
51a

m.p. 132-135˚C; R_f = 0.42 (1 : 1 EtOAc : petrol); IRυ_{max} 3365 (C-H), 3260 (C-H), 2926 (N-H), 1505 (aromatic), 1321 (SO_2-N), 1153 (O=S=O) cm^{-1}; Major diastereoisomer: δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.81 (d, 1H, *J* = 2.2 Hz, H-6), 7.53 (dd, 1H, *J* = 8.5, 2.2 Hz, H-8), 6.52 (d, 1H, *J* = 8.5 Hz, H-10), 5.95-5.93 (m, 1H, H-13), 5.75-5.73 (m, 1H, H-14), 4.51 (s, 2H, NH_2), 4.51 (d, 1H, *J* = 10.9 Hz, H-7), NH missing, 4.02 (br s, 1H, H-11), 3.09 (dt, 1H, *J* = 10.7, 6.8 Hz, H-13), 2.45 (m, 4H, H-

15 and 5, 4, 3, 2 or 1), 2.28 (s, 3H, H-5, 4, 3, 2 or 1), 2.26 (br s, 3H, H – 5, 4, 3, 2 or 1), 1.90 (br d, 1H, *J* = 16.8 Hz, H-15); δ ^{13}C NMR (150 MHz, $CDCl_3$) 149.4 (C_q), 140.2 (C_q), 138.6 (C_q), 136.8 (CH), 135.1 (C_q), 134.9 (C_q), 133.7 (C_q), 133.6 (C_q), 132.4 (C_q), 128.9 (CH), 128.7 (CH), 125.7 (CH), 122.6 (C_q), 113.9 (CH), 52.4 (CH), 47.4 (CH), 38.9 (CH), 36.2 (CH_2), 18.2 (CH_3), 17.6 (CH_3), 17.5 (CH_3), 17.4 (2 × CH_3); HRMS (ES) calcd. for $C_{23}H_{27}O_2N_2S$ $[M-H]^-$ 395.1871, found 395.1793.

(E)-4-((2,3,4,5,6-Pentamethylbenzylidene)amino)benzenesulfonamide (51)[200]

To a flame dried flask under an atmosphere of argon was added aniline (1.95 g, 11 mmol, 1 eq) and refluxed for 20 mins in ethanol. This was followed by addition of aldehyde (2 g, 11 mmol). The reaction was left to stir for a further 2.5 hrs. Reaction was cooled and ethanol was evaported to give the title compound as a pale yellow powder (3.3 g, 88%)

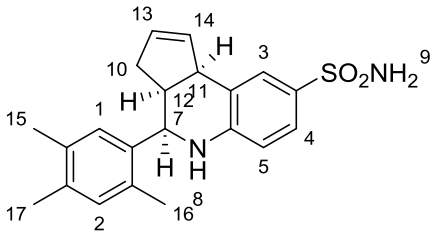


51

M.p. 207-210 ˚C; IRυ $_{max}$ 3342 (C-H), 3253 (C-H), 1634 (C=N), 1589 (aromatic), 1327 (SO_2-N), 1157 (O=S=O) cm^{-1} ;. δ ^{1}H NMR (600 MHz, $CDCl_3$) 8.96 (s, 1H, H-6), 7.86 (d, 2H, *J* = 8.5 Hz, H-7, 8), 7.38 (s, 2H, NH_2), 7.34 (d, 2H, J = 8.5 Hz, H-9, 10), 2.28 (s , 6H, H-CH_3), 2.23 (s, 3H, H-CH_3), 2.19 (s, 6H, H-CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) 166.2 (CH), 155.1 (C_q), 141.0 (C_q), 136.3 (C_q), 132.5 (2 × C_q), 132.3 (C_q), 131.1 (2 × C_q), 26.9 (2 × CH), 121.0 (2 × CH), 16.9 (3 × CH_3), 16.1 (2 × CH_3); HRMS (CI) calcd. for $C_{18}H_{22}O_2N_2S$ $[M + H]^+$ 331.1402, found 331.1484.

(3a*S*,4*R*,9b*R*)-4-(2,4,5-Trimethylphenyl)-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[c]quinoline-8-sulfonamide (52b)

A: Purification by flash chromatography dry load method in 40% EtOAc: petrol gave the title compound (below) as a yellow green powder (320 mg, 32%). Isolated a mixture of two diastereoisomers in >95: 5 ratio.

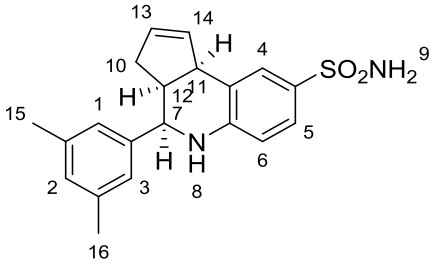


52b

m.p. 210 ˚C; R_f = 0.42 (1: 1 EtOAc: petrol); IRυ $_{max}$ 3360 (C-H), 3266 (C-H), 2922 (N-H), 1500 (aromatic), 1326 (SO_2-N), 1290 (O=S=O), 1155 (O=S=O) cm^{-1}; Major diastereoisomer: δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.60 (d, 1H, *J* = 1.6 Hz, H-3), 7.52 (dd, 1H, *J* = 8.7, 1.6 Hz, H-4), 7.25 (s, 1H, H-1), 6.96 (s, 1H, H-2), 6.65 (d, 1H, *J* = 8.7 Hz, H-5), 5.89-5.86 (m, 1H, H-14), 5.70-5.69 (m, 1H, H-13), 4.84 (d, 1H, *J* = 2.6 Hz, H-7), 4.62 (s, 2H, NH_2), 4.11 (d, 1H, *J* = 9.0 Hz, H-11), 3.04 (dtd, 1H, *J* = 9.2, 9.0, 2.6 Hz, H-12), 2.62 (dtd, 1H, *J* = 16.7, 9.2, 2.6 Hz, H-10), 2.30 (s, 3H, H-17), 2.26 (s, 3H, H-15), 2.23 (s, 3H, H-16), 1.82 (ddd, 1H, *J* = 16.7, 9.0, 2.6 Hz, H-10); δ ^{13}C NMR (150 MHz, $CDCl_3$) 150.5 (C_q), 136.7 (C_q), 135.5 (C_q), 134.4 (C_q), 133.5 (CH), 132.2 (C_q), 132.1 (CH), 131.5 (CH), 130.5 (C_q), 128.2 (CH), 126.9 (CH), 126.0 (C_q), 125.5 (CH), 115.5 (CH), 53.6 (CH), 46.1 (CH), 42.9 (CH), 31.7 (CH_2), 19.7 (CH_3), 19.4 (CH_3), 18.6 (CH_3); HRMS (EI) calcd. for $C_{21}H_{25}O_2N_2S$ $[M+H]^+$ 369.1559, found 363.1629.

(3a*S*,4*R*,9b*R*)-4-(3,5-Dimethylphenyl)-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[c]quinoline-8-sulfonamide (53b)

A: Purified compound by flash chromatography dry load gradient method 30-40% EtOAc: petrol gave the titled compound as a yellow powder (126 mg, 12%). Isolated a mixture of two diastereoisomers in >95: 5.

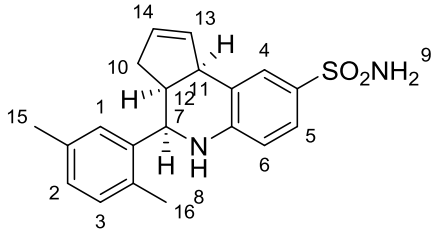


53b

m.p. 194-196 ˚C; R_f = 0.42 (1 : 1 EtOAc : petrol); IRυ $_{max}$ 3363 (C-H), 3268 (C-H), 2921 (N-H), 1494 (aromatic), 1327 (SO_2-N), 1152-1129 (O=S=O) cm^{-1}; Major diastereoisomer: δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.59 (dd, 1H, *J* = 2.2, 0.6 Hz, H-4), 7.51 (dd, 1H, *J* = 8.5, 2.2 Hz, H-5), 7.00 (s, 2H, H-1, 3), 6.95 (brs, 1H, H-2), 6.65 (d, 1H, *J* = 8.5 Hz, H-6), 5.88-5.86 (m, 1H, H-14), 5.69-5.67 (m, 1H, H-13), 4.63 (d, 1H, *J* = 3.0 Hz, H-7), 4.61 (s, 2H, NH_2), 4.12 (d, 1H, *J* = 8.6 Hz, H-11), 3.01 (dtd, 1H, *J* = 9.6, 8.6, 3.0 Hz, H-12), 2.55 (dtd, 1H, *J* = 16.6, 9.6, 3.0 Hz, H-10), 2.34 (s, 6H, H-16, 15), 1.86 (ddd, 1H, *J* = 16.6, 8.6, 3.0 Hz, H-10); δ ^{13}C NMR (150 MHz, $CDCl_3$) 150.0 (C_q), 141.7 (C_q), 138.4 (2 × C_q), 133.4 (CH), 131.2 (CH), 130.6 (C_q), 129.3 (CH), 128.2 (CH), 125.9 (C_q), 125.4 (CH), 124.2 (2 × CH), 115.5 (CH), 57.5 (CH), 45.9 (CH), 45.9 (CH), 31.4 (CH_2), 21.6 (2 × CH_3); HRMS (EI) calcd. for $C_{20}H_{23}O_2N_2S$ $[M+H]^+$ 355.1402, found 355.14839.

(3a*S*,4*R*,9b*R*)-4-(2,5-Dimethylphenyl)-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[c]quinoline-8-sulfonamide (54b)

A: Purification by flash chromatography dry load method in 50% EtOAc: petrol gave the title compound as a pale yellow powder (591 mg, 56%). Isolated a mixture of two diastereoisomers in 92: 8 ratio.

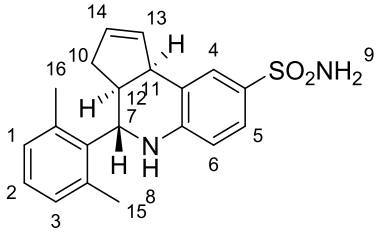


54b

m.p. 193-195 ˚C; R_f = 0.42 (1 : 1 EtOAc : petrol); IRυ $_{max}$ 3360 (C-H), 3265 (C-H), 2256 (N-H), 1598 (aromatic), 1307 (SO_2-N), 1288 (O=S=O), 1153 (O=S=O), 1124 (O=S=O) cm^{-1}; Major diastereoisomer : δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.62 (dd, 1H, *J* = 2.2, 0.8 Hz, H-4), 7.53 (dd, 1H, *J* = 8.6, 2.2 Hz, H-5), 7.33 (d, 1H, *J* = 0.9 Hz, H-1), 7.08 (d, 1H, *J* = 7.8 Hz, H-3), 7.03 (dd, 1H, *J* = 7.8, 0.9 Hz, H-2), 6.66 (d, 1H, *J* = 8.6 Hz, H-6), 5.89-5.87 (m, 1H, H-13), 5.70-5.68 (m, 1H, H-14), 4.87 (d, 1H, *J* = 3.2 Hz, H-7), 4.84 (s, 2H, NH_2), 4.13 (br s, 1H, NH), 4.11 (d, 1H, *J* = 8.6 Hz, H-11), 3.06 (dtd, 1H, *J* = 9.5, 8.6, 3.2 Hz, H-12), 2.61 (dtd, 1H, *J* = 16.5, 9.5, 3.2 Hz, H-10), 2.36 (s, 3H, H-15), 2.33 (s, 3H, H-16), 1.81 (ddd, 1H, *J* = 16.5, 8.6, 3.2 Hz, H-10); δ ^{13}C NMR (150 MHz, $CDCl_3$) 150.4 (C_q), 139.4 (C_q), 135.9 (C_q), 133.5 (CH), 131.9 (C_q), 131.2 (CH), 130.7 (CH, C_q), 128.2 (CH), 128.0 (CH), 126.3 (CH), 126.0 (C_q), 125.4 (CH), 115.6 (CH), 53.8 (CH), 46.1 (CH), 42.8 (CH), 31.8 (CH_2), 21.4 (CH_3), 18.8 (CH_3); HRMS (EI) calcd. for $C_{20}H_{23}O_2N_2S$ $[M+H]^+$ 355.1402, found 355.14794.

4-(2,6-Dimethylphenyl)-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[c]quinoline-8-sulfonamide (55a)

A: Purification by flash chromatography dry load gradient method using 0-40% EtOAc: petrol gave title compound as a dark green solid (111 mg, 21%). Isolated a mixture of two diastereoisomers in >95: 5 ratio.

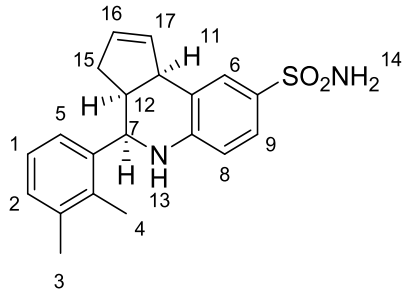


55a

m.p. 142-144 ˚C; R_f = 0.45 (3 : 2 EtOAc : petrol); IRυ $_{max}$ 3343 (C-H), 3062 (C-H), 2967 (N-H), 1494 (aromatic), 1313 (SO_2-N), 1301 (O=S=O), 1147-1124 (O=S=O) cm^{-1}; Major diastereoisomer : δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.82 (d, 1H, *J* = 1.9 Hz, H-4), 7.55 (dd, 1H, *J* = 8.4, 1.9 Hz, H-5), 7.13 (t, 1H, *J* = 7.6 Hz, H-2), 7.08-7.02 (br s, 2H, H-1,3), 6.58 (d, 1H, *J* = 8.5 Hz, H-6), 5.96-5.94 (m, 1H, H-13), 5.77-5.75 (m, 1H, H-14), 4.81 (s, 2H, NH_2), 4.36 (d, 2H, *J* = 10.8, H-7 and NH), 4.02 (br s, 1H, H-11), 3.09 (dt, 1H, *J* = 10.8, 5.4 Hz, H-12), 2.56 (br s, 3H, H-16 or 15), 2.46 (m, 1H,

H-10), 2.28 (br s, 1H, H-16 or 15), 1.92 (br d, 1H, *J* = 16.8 Hz, H-10); δ ^{13}C NMR (150 MHz, $CDCl_3$) 149.6 (C_q), 138.5 (C_q), 136.7 (CH), 137.9 (C_q), 136.3 (C_q), 131.1 (CH), 129.2 (C_q), 128.9 (CH), 128.6 (2 × CH), 127.9 (CH), 125.7 (CH), 122.9 (C_q), 114.2 (CH), 52.1 (CH), 47.3 (CH), 38.3 (CH), 35.9 (CH_2), 21.8 (CH_3), 20.9 (CH_3); HRMS (EI) calcd. for $C_{20}H_{22}O_2N_2S$ $[M]^+$ 354.1402, found 354.1403.

(3a*S*,4*R*,9b*R*)-4-(2,3-Dimethylphenyl)-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[c]quinoline-8-sulfonamide (56b)



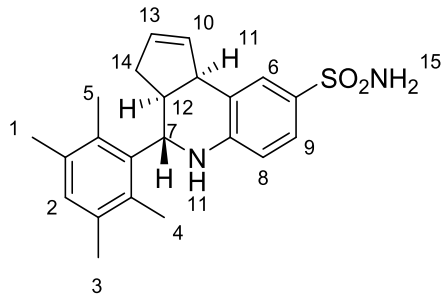
56b

A: Purification by dry load flash column chromatography 30-40% EtOAc: petrol gave the title compound as a pale yellow white powder (528 mg, 33%). Isolated as a mixture of two diastereoisomers in 87: 13 ratio.

mp. 202-205˚C; R_f = 0.35 (1 : 1 EtOAc : petrol); IRυ $_{max}$ 3350 (C-H), 3263 (C-H), 2925 (N-H), 2848 (N-H), 1495 (aromatic), 1455 (SO_2-N), 1337 (SO_2-N), 1155 (O=S=O) cm^{-1}; Major diastereoisomer : δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.61 (d, 1H, *J* = 1.7 Hz, H-6), 7.52 (dd, 1H, *J* = 8.4, 1.7 Hz, H-9), 7.39 (d, 1H, *J* = 7.7 Hz, H-5), 7.15 (br dt, 2H, *J* = 17.8, 7.2 Hz, H-1, 2), 6.65 (d, 1H, *J* = 8.4 Hz, H-8), 5.89-5.87 (m, 1H, H-17), 5.70-5.67 (m, 1H, H-16), 4.97 (d, 1H, *J* = 3.0 Hz, H-7), 4.69 (s, 2H, NH_2), 4.13 (d, 1H, 6.3 Hz, H-11), 3.07 (dtd, 1H, *J* = 9.5, 6.3, 3.0 Hz, H-12), 2.59 (dtd, 1H, *J* = 16.4, 9.5, 3.0 Hz, H-15), 2.32 (s, 3H, H-4), 2.27 (s, 3H, H-3), 1.77 (dr dd, 1H, *J* = 16.4, 6.3 Hz, H-15); δ ^{13}C NMR (150 MHz, $CDCl_3$) 150.4 (C_q), 139.3 (C_q), 137.4 (C_q), 133.6 (C_q), 133.4 (CH), 131.3 (CH), 130.6 (C_q), 129.2 (CH), 128.2 (CH), 126.0 (CH), 125.4 (CH), 123.4 (CH) , 115.7 (CH), 54.1 (CH), 46.0 (CH), 43.1 (CH), 31.7 (CH_2), 21.0 (CH_3), 14.7 (CH_3); HRMS (CI) calcd. for $C_{20}H_{23}O_2N_2S$ $[M+H]^+$ 355.1402, found 355.1477.

(3a*S*,4*R*,9b*R*)-4-(2,3,5,6-Tetramethylphenyl)-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[c]quinoline-8-sulfonamide (57b)

B: Purification by dry load flash column gradient method 0-10% EtOAc: petrol gave the title compound as a pale orange powder (221 mg, 46%). Isolated as a mixture of two diastereoisomers in >95: 5 ratio.



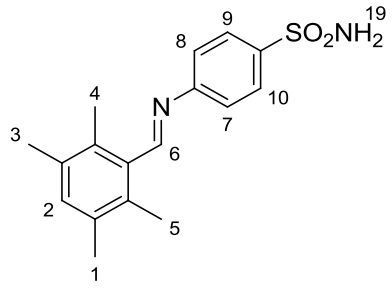
57a

m.p. 212-215 ˚C; R_f = 0.97 (1: 1 EtOAc: petrol); IRυ $_{max}$ 3320 (C-H), 2927 (N-H), 1498 (aromatic), 1470 (SO_2-N), 1285 (SO_2-N), 1140 (O=S=O) cm^{-1}; Major diastereoisomer: δ ^{1}H NMR (600 MHz, DMSO-d_6) 7.61 (d, 1H, *J* = 2.1 Hz, H-6), 7.33 (dd, 1H, *J* = 8.0, 2.1 Hz, H-9), 6.97 (br s, 1H, H-2), 6.93 (s, 2H, NH_2), 6.67 (d, 1H, *J* = 8.0 Hz, H-8), 6.65 (s, 1H, NH), 5.92-5.90 (m, 1H, H-10), 5.77-5.75 (m, 1H, H-13), 4.26 (d, 1H, *J* = 10.7 Hz, H-7), 3.95 (br s, 1H, H-11), 3.36 (s, 1H, NH), 2.94 (dt, 1H, *J* = 10.8, 6.9 Hz, H-12), 2.35 (s, 3H, H-5 or 4), 2.36 (m, 1H, H-14), 2.22 (s, 3H, H-1 or 3), 2.17 (s, 3H, H-1 or 3), 2.11 (s, 3H, H-5 or 4), 1.74 (br d, 1H, *J* = 15.6 Hz, H-14); δ ^{13}C NMR (150 MHz, DMSO–d_6) 149.0 (C_q), 137.0 (CH), 136.6 (C_q), 135.0 (C_q), 133.6 (C_q), 133.4 (C_q), 133.0 (C_q), 132.8 (CH), 130.9 (CH), 130.4 (C_q), 127.6 (CH), 124.4 (CH), 120.7 (C_q), 113.4 (CH), 51.3 (CH), 46.7 (CH), 38.0 (CH), 35.6 (CH_2), 21.0 (CH_3), 20.2 (CH_3), 16.7 (CH_3), 16.2 (CH_3); HRMS (EI) calcd. for $C_{22}H_{26}O_2N_2S$ $[M]^+$ 382.1715, found 382.1712.

(*E*)-4-((2, 3, 5, 6-Tetramethylbenzylidene)amino)benzenesulfonamide (57)

To a flame dried flask under an atmosphere of argon was added aniline (531 mg, 3 mmol, 1 eq) and refluxed for 20 mins in ethanol (15 ml). This was followed by

addition of aldehyde (0.486 ml, 3 mmol) and stir for a further 1 hr. The reaction mixture was cooled and ethanol was evaporated to give the title compound as a white powder (966 mg, 99%)

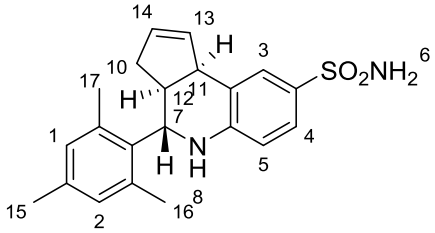


57

M.p. 203-206 ˚C; IRυ $_{max}$ 3330 (C-H)), 3072 (C-H), 2926 (N-H), 1624 (C=N), 1586 (aromatic), 1336 (SO_2-N), 1154 (O=S=O) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 8.85 (s, 1H, H-6), 7.86 (d, 2H, *J* = 8.4 Hz, H-7, 8), 7.38 (s, 2H, NH_2), 7.35 (d, 2H, J = 8.4 Hz, H-9, 10), 7.10 (s, 1H, H-2), 2.27 (s, 6H, H-4,5), 2.22 (s, 6H, H-1,3); ^{13}C NMR (150 MHz, $CDCl_3$) 165.5 (CH), 155.0 (C_q), 141.1 (C_q), 134.3 (C_q), 133.7 (3 × C_q), 133.0 (CH), 132.4 (C_q), 127.1 (2 × CH), 121.0 (2 × CH), 19.7 (2 × CH_3), 15.9 (2 × CH_3); HRMS (CI) calcd. for $C_{17}H_{21}O_2N_2S$ $[M+H]^+$ 317.12455, found 317.13264.

(3a*S*,4*R*,9b*R*)-4-Mesityl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-sulfonamide (58a)

Method A: Purification by flash chromatography dry load gradient method using 10-30% EtOAc: petrol gave the title compound as a pale orange oil (130 mg, 35%). Isolated as a mixture of two diastereoisomers in >95: 5 ratio.



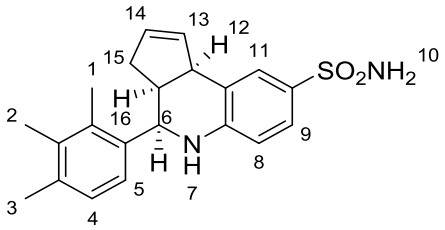
58a

R_f = 0.45 (1: 1 EtOAc : petrol); IRυ $_{max}$ 3364 (C-H), 3264 (C-H), 2918 (N-H) 2851 (N-H), 1600 (aromatic), 1502 (aromatic), 1328 (SO_2-N), 1154 (O=S=O) cm^{-1}; Major

diastereoisomer: : δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.81 (d, 1H, *J* = 2.1 Hz, H-3), 7.54 (dd, 1H, *J* = 8.6, 2.1 Hz, H-4), 6.88 (m, 2H, H-1, 2), 6.55 (d, 1H, *J* = 8.6 Hz, H-5), 5.95-5.92 (m, 1H, H-13), 5.76-5.74 (m, 1H, H-14), 4.70 (s, 2H, NH_2), 4.31 (d, 1H, *J* = 11.0 Hz, H-7), 4.01 (br s, 1H, H-11), 3.10 (dt, 1H, *J* = 10.9, 6.8 Hz, H-12), 2.52 (br s, 3 H, H-17or 16), 2.50 (br d, 1H, *J* = 17.7 Hz, H-10), 2.24 (br s, 3H, H-17 or 16), 1.92 (br d, 1H, *J* = 17.7, H-10), 1.59 (br s, 3H, H-25); δ ^{13}C NMR (150 MHz, $CDCl_3$) 149.7 (C_q), 138.3 (C_q), 137.7 (C_q), 137.5 (C_q), 136.7 (CH), 133.3 (C_q), 131.8 (CH), 129.4 (CH), 129.1 (C_q), 128.9 (CH), 128.6 (CH), 125.7 (CH), 122.9 (C_q), 114.4 (CH), 52.0 (CH), 47.3 (CH), 38.5 (CH), 36.0 (CH_2), 20.9 (2 × CH_3), 21.4 (CH_3); HRMS (ES) calcd. for $C_{21}H_{23}O_2N_2S$ $[M-H]^-$ 367.1559, found 367.1480.

(3a*S*,4*R*,9b*R*)-4-(2,3,4-Trimethylphenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-sulfonamide (59b)

Purification by dry load flash column chromatography gradient method 0-50% EtOAc: petrol gave the title compound as a yellow white powder (622 mg, 66%). Isolated as a mixture of two diastereoisomers in 89: 11 ratio.



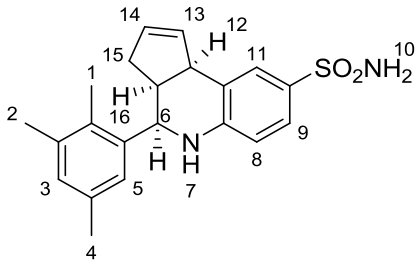
59b

m.p. 210-213 ˚C; R_f = 0.53 (1 : 1 EtOAc : petrol); IRυ $_{max}$ 3360 (C-H), 3267 (C-H), 2931 (N-H), 2843 (N-H), 1598 (aromatic), 1307 (SO_2-N), 1152 (O=S=O) cm^{-1}; Major diastereoisomer: δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.61 (d, 1H, *J* = 1.4 Hz, H-11), 7.51 (dd, 1H, *J* = 8.5, 1.4 Hz, H-9), 7.28 (d, 1H, *J* = 7.9 Hz, H-5), 7.07 (d, 1H, *J* = 7.9 Hz, H-4), 6.64 (d, 1H, *J* = 8.5 Hz, H-8), 5.88-5.86 (m, 1H, H-14), 5.68 (br d, 1H, *J* = 5.4 Hz, H-13), 4.94 (d, 1H, *J* = 2.8 Hz, H-6), 4.70 (s, 2H, NH_2), 4.11 (d, 1H, *J* = 9.4 Hz, H-12), 4.08 (br s, 1H, NH), 3.06 (dtd, 1H, *J* = 9.4, 8.9, 2.8 Hz, H-16), 2.58 (ddd, 1H, *J* = 16.5, 9.4, 2.8 Hz, H-15), 2.31 (s, 3H, H-3), 2.28 (s, 3H, H-2), 2.22 (s, 3H, H-1), 1.78 (br dd, 1H, *J* = 16.5, 8.9 Hz, H-15); δ ^{13}C NMR (150 MHz,

$CDCl_3$) 150.5 (C_q), 137.0 (C_q), 135.8 (C_q), 135.7 (C_q), 133.44 (C_q), 133.43 (CH), 131.4 (CH), 130.5 (C_q), 128.2 (CH), 127.6 (CH), 126.0 (C_q), 125.4 (CH),122.8 (CH), 115.6 (CH), 54.2 (CH), 46.0 (CH), 43.2 (CH), 31.7 (CH_2), 21.0 (CH_3), 16.2 (CH_3), 15.1 (CH_3); HRMS (ES) calcd. for $C_{21}H_{25}O_2N_2S$ $[M + H]^+$ 369.1559, found 369.1637.

(3a*S*,4*R*,9b*R*)-4-(2,3,5-Trimethylphenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-sulfonamide (60b)

Purfication by dry load flash column chromatography gradient method 0-50% EtOAc: petrol gave the title compound as a pale yellow powder (181 mg, 36%). Isolated as a mixture of two diastereoisomers in 86: 14 ratio.

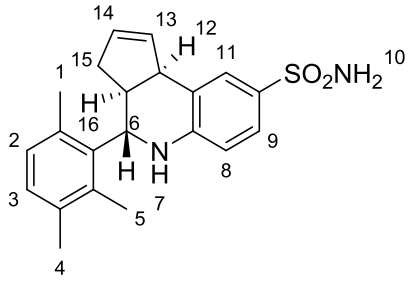


60b

m.p. 235-238 ˚C; R_f = 0.55 (1 : 1 EtOAc : petrol); IRυ $_{max}$ 3360 (C-H), 3267 (C-H), 2931 (N-H), 2843 (N-H), 1598 (aromatic), 1307 (SO_2-N), 1152 (O=S=O) cm^{-1}; Major diastereoisomer: δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.61 (d, 1H, *J* = 1.8 Hz, H-11), 7.52 (dd, 1H, *J* = 8.5, 1.8 Hz, H-9), 7.19 (br s, 1H, H-5), 6.96 (br s, 1H, H-3), 6.66 (d, 1H, *J* = 8.5 Hz, H-8), 5.88-5.86 (m, 1H, H-14), 5.69 (br d, 1H, *J* = 5.2 Hz, H-13), 4.93 (d, 1H, *J* = 2.8 Hz, H-6), 4.62 (s, 2H, NH_2), 4.12 (d, 1H, *J* = 8.5 Hz, H-12), 3.06 (dtd, 1H, *J* = 9.5, 8.5, 2.8 Hz, H-16), 2.58 (ddd, 1H, *J* = 16.4, 9.5, 2.8 Hz, H-15), 2.32 (s, 3H, H-4), 2.28 (s, 3H, H-2), 2.22 (s, 3H, H-1), 1.79 (br dd, 1H, *J* = 16.4, 8.5 Hz, H-15); δ ^{13}C NMR (150 MHz, $CDCl_3$) 150.6 (C_q), 139.2 (C_q), 135.2 (C_q), 133.4 (CH), 131.3 (CH), 130.5 (C_q), 130.4 (C_q), 130.0 (CH), 128.2 (CH), 125.7 (C_q), 125.4 (CH), 123.9 (CH), 115.6 (CH), 54.0 (CH), 46.1 (CH), 43.1 (CH), 31.7 (CH_2), 21.4 (CH_3), 20.9 (CH_3), 14.3 (CH_3); quaternary carbon overlapping with another peak; HRMS (ES) calcd. for $C_{21}H_{25}O_2N_2S$ $[M + H]^+$ 369.1635, found 369.1637.

(3a*S*,4*R*,9b*R*)-4-(2,3,6-Trimethylphenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-sulfonamide (61a)

Purification by dry load flash column chromatography gradient method 20-45% EtOAc: petrol gave the title compound as an orange yellow solid (373 mg, 82%). Isolated as a mixture of two diastereoisomers in >95: 5 ratio.

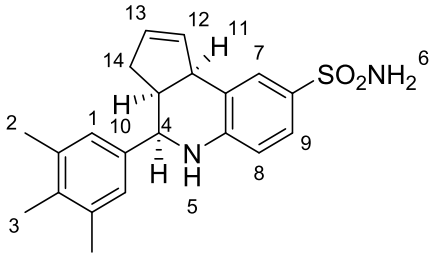


61a

m.p. 125-128˚C; R_f = 0.51 (1:1 EtOAc : petrol); IRυ $_{max}$ 3365 (C-H), 3266 (C-H), 2925 (C-H), 2811 (N-H), 1503 (aromatic), 1327 (SO_2-N), 1175 (O=S=O) cm^{-1}; Major diastereisomer δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.82 (d, 1H, *J* = 1.7 Hz, H-11), 7.55 (dd, 1H, *J* = 8.8, 1.7 Hz, H-9), 7.34 (d, 2H, *J* = 7.8 Hz, H-2), 7.05 (d, 1H, *J* = 7.8 Hz, H-3), 6.95 (d, 1H, *J* = 8.8 Hz, H-8), 5.94 (br s, 1H, H-14), 5.77-5.75 (m, 1H, H-13), 4.73 (s, 2H, NH_2), 4.39 (s, 1H, NH), 4.36 (d, 1H, *J* = 8.8 Hz, H-6), 4.02 (br s, 1H, H-12), 3.09 (dtd, 1H, *J* = 10.8, 8.8, 2.8 Hz, H-16), 2.46-2.44 (m, 4H, H-15, 5), 2.25 (s, 6H, H-1, 4), 1.90 (br dd, 1H, *J* = 15.7, 8.8 Hz, H-15); δ ^{13}C NMR (150 MHz, $CDCl_3$) 149.4 (C_q), 137.1 (C_q), 136.7 (CH), 136.6 (C_q), 136.1 (C_q), 136.0 (C_q), 129.6 (CH), 129.0 (C_q), 128.9 (CH), 128.6 (CH), 128.1 (CH), 122.8 (C_q), 114.1 (CH), 52.4 (CH), 47.4 (CH), 47.0 (CH), 36.0 (CH_2), 21.8 (CH_3), 20.8 (CH_3), 17.3 (CH_3); HRMS (ES) calcd. for $C_{21}H_{25}O_2N_2S$ $[M + H]^+$ 369.1621, found 369.1637.

(3aS,4R,9bR)-4-(3,4,5-trimethylphenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-sulfonamide (62b)

Purification by dry load flash column 0-50% EtOAc: petrol gave the title compound as a yellow oil (308 mg, 59%). Isolated as a mixture of two diastereoisomers in 76: 24 ratio.

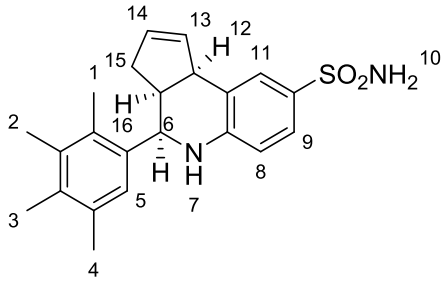


62b

R_f = 0.51 (1: 1 EtOAc : petrol); $IR_{\upsilon\ max}$ 3358 (C-H), 3264 (C-H), 2930 (N-H), 1496 (aromatic), 1329 (SO_2-N), 1158 (O=S=O) cm^{-1}; Major diastereoisomer: δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.59 (d, 1H, *J* = 2.0 Hz, H-7), 7.51 (dd, 1H, *J* = 8.5, 2.0 Hz, H-9), 7.02 (s, 2H, H-1), 6.63 (d, 1H, *J* = 8.5 Hz, H-8), 5.88-5.86 (m, 1H, H-13), 5.69-5.68 (m, 1H, H-12), 4.71 (s, 2H, NH_2), 4.60 (d, 1H, *J* = 2.9 Hz, H-4), 4.19 (s, 1H, NH), 4.08 (d, 1H, *J* = 8.6 Hz, H-11), 3.00 (dtd, 1H, *J* = 9.5, 8.6, 2.9 Hz, H-10), 2.57 (ddd, 1H, *J* = 16.4, 9.5, 2.9 Hz, H-14), 2.31 (s, 6H, H-2), 2.18 (s, 3H, H-3), 1.88 (ddd, 1H, *J* = 16.4, 8.6, 2.9 Hz, H-14); δ ^{13}C NMR (150 MHz, $CDCl_3$) 150.1 (C_q), 138.5 (C_q), 136.9 (2 × C_q), 134.5 (C_q), 133.6 (CH), 131.3 (CH), 130.5 (C_q), 128.2 (CH), 125. 9 (C_q), 125.6 (2 × CH), 125.4 (CH), 115.5 (CH) 57.2 (CH), 46.0 (CH), 45.9 (CH), 31.8 (CH_2), 20.9 (2 × CH_3), 15.4 (CH_3); HRMS (ES) calcd. for $C_{21}H_{25}O_2N_2S$ $[M-H]^-$ 367.1470, found 367.1480.

(3a*S*,4*R*,9b*R*)-4-(2,3,4,5-Tetramethylphenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-sulfonamide (63b)

Purification by dry load flash column chromatography gradient method 0-50% EtOAc: petrol gave the title compound as a pale yellow powder (181 mg, 56%). Isolated as a mixture of two diastereoisomers in 89: 11 ratio.

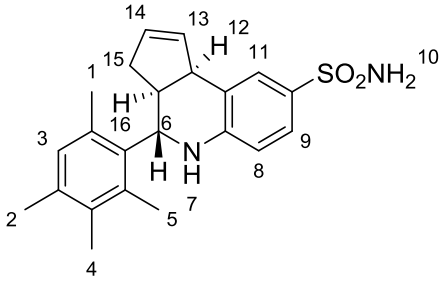


63b

R_f = 0.49 (1: 1 EtOAc : petrol); IRυ_{max} 3354-3261 (C-H), 2927 (N-H), 1487 (aromatic), 1309 (SO_2-N), 1151 (O=S=O) cm^{-1}; Major diastereoisomer: δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.52 (dd, 1H, *J* = 8.6, 1.6 Hz, H-9), 7.50 (d, 1H, *J* = 1.6 Hz, H-11), 7.18 (s, 1H, H-5), 6.65 (d, 1H, *J* = 8.6 Hz, H-8), 5.88-5.86 (m, 1H, H-14), 5.69 (br d, 1H, *J* = 4.8Hz, H-13), 4.92 (d, 1H, *J* = 2.8 Hz, H-6), 4.76 (s, 2H, NH_2), 4.11 (d, 1H, *J* = 8.7 Hz, H-12), 4.10 (s, 1H, NH), 3.05 (dtd, 1H, *J* = 10.7, 8.7, 2.8 Hz, H-16), 2.59 (ddd, 1H, *J* = 16.2, 10.7, 2.8 Hz, H-15), 2.32 (s, 3H, H-4), 2.26 (s, 3H, H-2), 2.24 (s, 3H, H-1), 2.23 (s, 3H, H-3), 1.81 (br dd, 1H, *J* = 16.2, 8.7 Hz, H-15); δ ^{13}C NMR (150 MHz, $CDCl_3$) 150.6 (C_q), 136.2 (C_q), 135.8 (C_q), 134.2 (C_q), 134.0 (C_q), 133.5 (CH), 131.3 (CH), 130.9 (C_q), 130.5 (C_q), 128.2 (CH), 126.1 (C_q), 125.4 (CH), 124.6 (CH), 115.6 (CH), 54.1 (CH), 46.1 (CH), 43.2 (CH), 31.7 (CH_2), 21.2 (CH_3), 16.6 (CH_3), 16.2 (CH_3), 15.2 (CH_3); HRMS (ES) calcd. for $C_{22}H_{25}O_2N_2S$ $[M-H]^-$ 381.1715, found 381.1637.

(3a*S*, 4*R*, 9b*R*)-4-(2,3,4,6-Tetramethylphenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-sulfonamide (64a)

Purification by dry load flash column chromatography gradient method 0-40% EtOAc: petrol to give the title compound as a colourless oil (20 mg, 28%). Isolated as a mixture of two diastereoisomers in >95: 5 ratio.



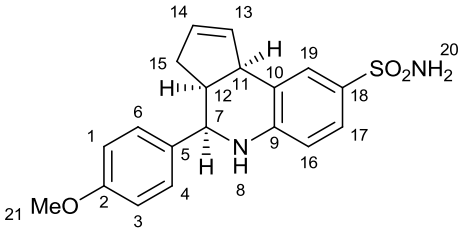
64a

R_f = 0.59 (1 : 1 EtOAc : petrol); IR$_{\upsilon\ max}$ 3356 (C-H), 3259 (C-H), 2923 (N-H), 1503 (aromatic), 1327 (SO_2-N), 1145 (O=S), 1139 (O=S=O) cm^{-1}; Major diastereoisomer: δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.81 (d, 1H, *J* = 1.5 Hz, H-11), 7.54 (dd, 1H, *J* = 8.5, 1.5 Hz, H-9), 6.88 (s, 1H, H-3), 6.54 (d, 1H, *J* = 8.5 Hz, H-8), 5.95-5.93 (br s, 1H, H-14), 5.76-5.74 (br s, 1H, H-13), 4.72 (s, 2H, NH_2), 4.37 (s, 1H, NH), 4.33 (d, 1H, *J* = 7.9 Hz, H-6), 4.02 (br d, 1H, *J* = 10.0 Hz, H-12), 3.08 (dtd, 1H, *J* = 10.0, 7.9, 2.9 Hz, H-16), 2.45 (m, 4H, H-15, 5), 2.28 (s, 3H, H-2), 2.17 (s, 3H, H-4), 2.15 (s,

3H, H-1), 1.90 (d, 1H, *J* = 16.3 Hz, H-15); δ ^{13}C NMR (150 MHz, $CDCl_3$) 149.5 (C_q), 136.7 (CH), 136.5 (C_q), 136.2 (2 × C_q), 135.5 (C_q), 135.3 (C_q), 133.8 (C_q), 130.1 (CH), 128.9 (CH), 128.6 (CH), 125.7 (CH), 122.7 (C_q), 114.1 (CH), 52.2 (CH), 47.4 (CH), 47.0 (CH), 36.1 (CH_2), 21.6 (CH_3), 20.8 (CH_3),17.7 (CH_3), 15.8 (CH_3); HRMS (ES) calcd. for $C_{22}H_{25}O_2N_2S$ $[M–H]^-$ 381.1637, found 381.1637.

4-(4-Methoxyphenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-sulfonamide (65b).

Method A: Purified by flash column chromatography using a gradient elution of 10-50 % EtOAc: petrol gave the title compound as an orange foam (228 mg, 16%). Isolated as a mixture of two diastereoisomers in 80: 20 ratio.

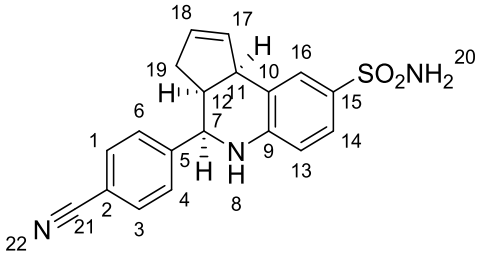


65b

R_f = 0.33 (1:1 EtOAc : petrol); IR υ $_{max}$ 3358 (C-H), 3054 (C-H), 2932- 2839 (N-H), 1512 (aromatic), 1304 (SO_2-N), 1244 (S=O), 1128 (SO_2-N), 1090 (S=O) cm^{-1}; Major diastereoisomer: δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.54 (d, 1H, *J* = 2.0 Hz, H-19), 7.42 (dd, 1H, *J* = 8.5, 2.0 Hz, H-17), 7.31 (d, 2H, *J* = 8.6, H-1,3), 6.89 (d, 2H, *J* = 8.6 Hz, H-4,6), 6.75 (d, 1H, *J* = 8.5 Hz, H-16), 5.87-5.85 (m, 1H, H-13), 5.60-5.57 (m, 1H, H-14), 4.56 (d, 1H, *J* = 3.3 Hz, H-7), 4.03 (br d, 1H, *J* = 8.7 Hz, H-11), 3.75 (s, 3H, H-21), 2.91 (dtd, 1H, *J* = 9.5, 8.7, 3.3 Hz, H-12), 2.48 (ddd, 1H, *J* = 16.3, 9.5, 2.3 Hz, H-15), 1.70 (br dd, 1H, *J* = 16.3, 8.7 Hz, H-15); δ ^{13}C NMR (600 MHz, $CDCl_3$) 160.3 (C_q), 151.6 (C_q), 135.6 (C_q), 135.1 (CH), 132.6 (C_q), 131.4 (CH), 128.7 (2 × CH), 128.4 (CH), 126.5 (C_q), 125.7 (CH), 116.5 (CH), 114.9 (2 × CH), 57.8 (CH), 55.8 (CH_3), 47.6 (CH), 47.1 (CH), 32.7 (CH_2); HRMS (ES-) calcd. for $C_{18}H_{17}N_2O_3$ $[M - CH_3]^-$ 341.0952, found 341.0960.

(3a*S*,4*R*,9b*R*)-4-(4-Cyanophenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-sulfonamide (66b)

Method A: Purification by dry load flash chromatography gradient method 70-50% EtOAc: petrol gave title compound as brown solid (69 mg, 6%). Isolated as a mixture of two diastereoisomers in 77: 23 ratio.

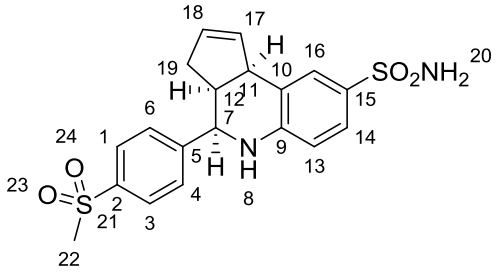


66b

m.p. 210-212˚C; R_f = 0.14 (1 :1 EtOAc : petrol); IRυ $_{max}$ 3354 (C-H), 3269 (C-H), 2930 (N-H), 2229 (nitrile), 1501 (aromatic), 1328 (SO_2-N), 1158 (O=S=O) cm^{-1}; Major diastereoisomer: δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.70 (br d, 2H, *J* = 8.0 Hz, H-1, 3), 7.61 (d, 1H, *J* = 1.5 Hz, H-16), 7.54 (m, 3H, H-14, 6, 4), 6.69 (d, 1H, *J* = 8.3 Hz, H-13), 5.91-5.89 (m, 1H, H-17), 5.68-5.67 (m, 1H, H-18), 4.78 (d, 1H, *J* = 2.6 Hz, H-7), 4.66 (s, 2H, NH_2), 4.19 (s, 1H, NH), 4.13 (d, 1H, *J* = 8.5 Hz, H-11), 3.00 (dtd, 1H, *J* = 9.5, 8.5, 2.6 Hz, H-12), 2.50 (dtd, 1H, *J* = 16.1, 9.5, 2.6 Hz, H-19), 1.77 (ddd, 1H, *J* = 16.1, 8.5, 2.6 Hz, H-19); δ ^{13}C NMR (150 MHz, $CDCl_3$) 148.9 (C_q), 147.2 (C_q), 133.4 (CH), 132.7 (2 × CH), 131.6 (C_q), 130.9 (CH), 129.2 (C_q), 128.2 (CH), 127.3 (2 × CH), 125.7 (C_q), 125.6 (CH), 115.9 (CH), 111.7 (-CN), 57.3 (CH), 45.7 (CH), 45.5 (CH), 31.4 (CH_2); HRMS (EI) calcd. for $C_{19}H_{18}O_2N_3S$ $[M+H]^+$ 352.1042, found 352.1118.

(3a*S*,4*R*,9b*R*)-4-(4-(Methylsulfonyl)phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-sulfonamide (67b)

Method A: Using sulphanilamide (2 eq) and $InCl_3$ (9 mol %). Purification by dry load flash chromatography method 10% MeOH: DCM gave the title compound as a brown powder (51 mg, 3%). Isolated as a mixture of two diastereoisomers in 91: 9 ratio.

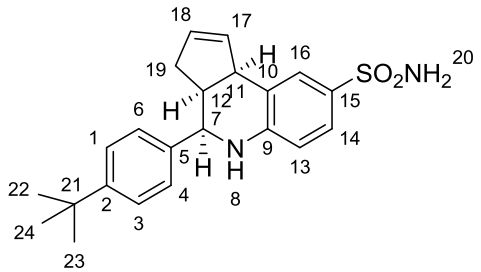


67b

m.p. 182-185˚C; R_f = 0.7 (1 : 9 MeOH : DCM); IRυ $_{max}$ 3353 (C-H), 3264 (C-H), 2925 (N-H), 2853 (N-H), 1598 (aromatic C=C), 1303 (SO_2-N), 1147 (O=S=O) cm^{-1}; Major diastereoisomer: δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.98 (d, 2H, *J* = 8.3 Hz, H-1, 3), 7.64 (d, 2H, *J* = 8.3 Hz, H-4, 6), 7.62 (d, 1H, *J* = 1.9 Hz, H-16), 7.55 (dd, 1H, *J* = 8.5, 1.9 Hz, H-14), 6.71 (d, 1H, *J* = 8.5 Hz, H-13), 5.92-5.90 (m, 1H, H-17), 5.69-5.67 (m, 1H, H-18), 4.82 (d, 1H, *J* = 3.6 Hz, H-7), 4.67 (s, 2H, NH_2), 4.22 (1H, s, NH), 4.12 (d, 1H, *J* = 8.5 Hz, H-11), 3.09 (s, 3H, H-22), 3.04 (dtd, 1H, *J* = 9.4, 8.5, 3.6 Hz, H-12), 2.52 (dtd, 1H, *J* = 16.3, 9.4, 3.6 Hz, H-19), 1.78 (ddd, 1H, *J* = 16.3, 8.5, 3.6 Hz, H-19); ^{13}C NMR (150 MHz, $CDCl_3$) 148.9 (C_q), 148.2 (C_q), 139.9 (C_q), 133.4 (CH), 131.6 (C_q), 130.9 (CH), 128.2 (CH), 128.0 (2 × CH), 127.5 (2 × CH), 125.8 (C_q), 125.6 (CH), 116.0 (CH), 57.3 (CH), 45.7 (CH), 45.6 (CH), 44.6 (CH_3), 31.4 (CH_2); HRMS (EI) calcd. for $C_{19}H_{20}O_4N_2S_2$ $[M]^+$ 404.0869, found 404.0868.

(3a*S*,4*R*,9b*R*)-4-(4-Tert-butylphenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-sulfonamide (68b)

Method A: Using sulphanilamide (2 eq) and $InCl_3$ (11 mol %). Purification by dry load flash chromatography method 50% EtOAc: petrol to afford the title compound as a orange yellow solid (112 mg, 16%). Isolated as a mixture of two diastereoisomers in 95: 5 ratio.

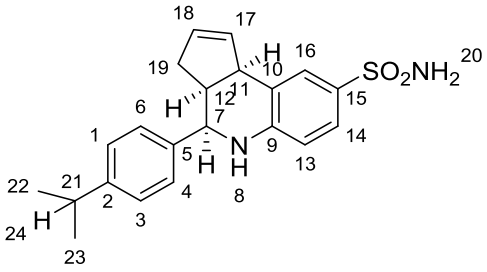


68b

m.p. 215˚C; R_f = 0.66 (1: 1 EtOAc : petrol); IRυ $_{max}$ 3362 (C-H), 3062 (C-H), 2962 (N-H), 1498 (aromatic), 1328 (SO_2-N), 1297 (O=S=O), 1147-1124 (O=S=O) cm^{-1}; Major diastereoisomer: δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.59 (d, 1H, *J* = 2.2 Hz, H-16), 7.51 (dd, 1H, *J* = 8.6, 2.2 Hz, H-14), 7.41 (d, 2H, *J* = 8.6 Hz, H-4,6), 7.33 (d, 2H, *J* = 8.6 Hz, H-1,3), 6.63 (d, 1H, *J* = 8.6 Hz, H-13), 5.89-5.87 (m, 1H, H-17), 5.70-5.68 (m, 1H, H-18), 4.68 (d, 1H, *J* = 2.8 Hz, H-7), 4.65 (s, 2H, NH_2), 4.22 (brs, 1H, NH), 4.10 (d, 1H, *J* = 8.6 Hz, H-11), 3.00(1H, dtd, *J* = 9.2, 8.6, 2.8 Hz, H-12), 2.58 (dtd, 1H, *J* = 16.6, 9.2, 2.8 Hz, H-19), 1.87 (br dd, 1H, *J* = 16.6, 8.6 Hz, H-19), 1.33 (s, 9H, H-22, 23, 24); ^{13}C NMR (150 MHz, $CDCl_3$) 150.8 (C_q), 150.0 (C_q), 138.7 (C_q), 133.4 (CH), 131.2 (CH), 130.6 (C_q), 128.2 (CH), 126.2 (2 × CH), 125.9 (C_q), 125.72 (C_q), 125.7 (2 × CH), 125.4 (CH), 115.5 (CH), 57.3 (CH), 45.9 (CH), 45.90 (CH), 34.2 (C_q), 31.6 (CH_2), 31.4 (-$C(CH_3)_3$); HRMS (EI) calcd. for $C_{22}H_{26}O_2N_2S$ $[M]^+$ 382.17150, found 382.17123.

(3a*S*,4*R*,9b*R*)-4-(4-Isopropylphenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-sulfonamide (69b)

Method A: Under the same protocol conditions above with exception to sulphanilamide (2 eq) and $InCl_3$ (9 mol%) were considered. Purification by dry load flash chromatography method 50% EtOAc: petrol gave the title compound as a dark green amorphous solid (957 mg, 19%). Isolated as a mixture of two diastereoisomers in 83: 17 ratio.



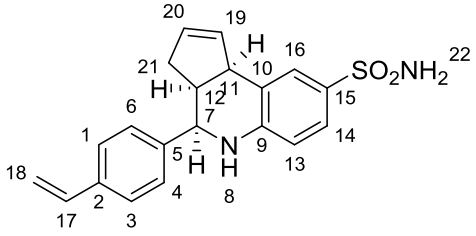
69b

m.p. 203 ˚C; R_f = 0.64 (1 :1 EtOAc : petrol); IRυ $_{max}$ 3363 (C-H), 3257 (C-H), 2960 (N-H), 2955 (N-H), 1498 (aromatic), 1332 (SO_2-N), 1155-1129 (S=O) cm^{-1}; Major diastereoisomer: δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.59 (d, 1H, *J* = 1.9 Hz, H-16), 7.51 (dd, 1H, *J* = 8.5, 1.9 Hz, H-14), 7.33 (d, 2H, *J* = 7.9 Hz, H-4, 6), 7.25 (d, 2H, *J* = 7.9 Hz, H-1, 3), 6.63 (d, 1H, *J* = 8.5 Hz, H-13), 5.89-5.87 (m, 1H, H-17), 5.69-5.67 (m,

1H, H-18), 4.68 (d, 1H, *J* = 2.9 Hz, H-7), 4.65 (br s, 2H, NH_2), 4.22 (brs, 1H, NH), 4.10 (d, 1H, *J* = 9.8 Hz, H-11), 3.00 (1H, dtd, *J* = 11.4, 9.8, 2.9 Hz, H-12), 2.92 (septet, 1H, *J* = 7.1 Hz, H-24), 2.57 (dtd, 1H, *J* = 16.3, 11.4, 2.9 Hz, H-19), 1.87 (br dd, 1H, *J* = 16.3, 9.8 Hz, H-19), 1.26 (d, 6 H, *J* = 7.1 Hz, H-22, 23); ^{13}C NMR (150 MHz, $CDCl_3$) 150.0 (C_q), 148.6 (C_q), 139.1 (C_q), 133.5 (CH), 131.2 (CH), 130.6 (C_q), 128.2 (CH), 126.8 (2 × CH), 126.5 (2 × CH), 125.9 (C_q), 125.4 (CH), 115.6 (CH), 57.4 (CH), 46.0 (CH), 45.9 (CH), 34.0 (C**H**$(CH_3)_2$, 31.6 (CH_2), 24.1 (2 × CH_3); HRMS (EI) calcd. for $C_{21}H_{25}O_2N_2S$ $[M+H]^+$ 369.15585, found 369.1637.

(3a*S*,4*R*,9b*R*)-4-(4-Vinylphenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-sulfonamide (70b)

Potassium carbonate (409 mg, 2.96 mmol, 3 eq), potassium tetraflourovinylborate (334 mg, 2.49 mmol, 2.5 eq), $Pd(PPh_3)_2$ (5 mol%, 57 mg), **28b** (400 mg, 0.99 mmol, 1 eq) was refluxed in toluene/EtOH/H_2O (5.8: 1.6: 0.8) for 48 hrs at 80°C. To the reaction mixture EtOAc (6 ml) was added and washed with water (12 ml), dried with $MgSO_4$ and concentrated. Purification by flash chromatography dry load method using 30% EtOAc: petrol gave the title compound as brown amorphous solid (49 mg, 14%).



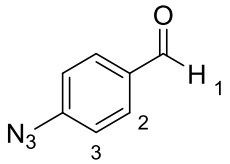
70b

m.p. 88-90 ˚C; R_f = 0.42 (1 : 1 EtOAc : Petrol) IRυ $_{max}$ 3360 (C-H), 2263 (N-H), 1494 (aromatic), 1320 (SO_2-N), 1154-1129 (O=S=O) cm^{-1}; Major diastereoisomer: δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.59 (s, 1H, H-16), 7.52 (dd, 1H, *J* = 8.8, 2.6 Hz, H-14), 7.43 (d, 2H, *J* = 7.9 Hz, H-1,3), 7.36 (d, 2H, *J* = 7.9 Hz, H-6,4), 6.73 (dd, 1H, *J* = 11.0, 17.6 Hz, H-17), 6.66 (d, 1H, *J* = 8.8 Hz, H-13), 5.88 (br s, 1H, H-19), 5.77 (d, 1H, *J* = 17.6 Hz, H-18), 5.67 (br d, 1H, *J* = 4.4 Hz, H-20), 5.27 (d, 1H, *J* = 11.0 Hz, H-18), 4.71 (s, 3H, NH_2, H-7), 4.23 (s, 1H, NH), 4.10 (d, 1H, *J* = 7.0 Hz, H-11), 3.01 (dtd, 1H, *J* = 9.5, 7.0, 2.5 Hz, H-12), 2.52 (dtd, 1H, 16.3, 9.5, 2.5 Hz, H-21),

1.84 (ddd, 1H, *J* = 16.3, 7.0, 1.4 Hz, H-21); δ ^{13}C NMR (150 MHz, $CDCl_3$) 150.0 (C_q), 141.3 (C_q), 137.2 (C_q), 136.4 (CH), 133.5 (CH), 132.0 (CH), 131.3 (CH), 130.8 (C_q), 128.2 (CH), 128.2 (C_q), 126.6 (4 × CH), 115.6 (CH), 114.3 (CH_2), 57.3 (CH), 45.9 (CH), 45.8 (CH), 31.7 (CH_2); HRMS (EI) for $C_{20}H_{20}O_2N_2S$ $[M]^+$ 352.1245, found 352.1261.

4-Azidobenzaldehyde (70)[205]

To a flame dried flask under an atmosphere of argon was added 4-bromobenzaldehyde (2.7 mmol, 1 eq, 500 mg), sodium ascorbate (27 mg, 0.27 mmol), Cu(I)I (5 mg, 0.54 mmol), and sodium azide (350 mg, 10.8 mmol) was refluxed in EtOH/H_2O (3.5 ml/1.5 ml). *N, N* dimethylethylenediamine (0.5 ml) was then added and left to reflux for 2 hrs. On having cooled the reaction mixture CH_2Cl_2 (10 ml) was added and was washed with water (15 ml), dried with $MgSO_4$, filtered and evaporated. Purification by dry load flash chromatography 10% EtOAc: petrol to give product as yellow viscous oil (80 mg, 20%).



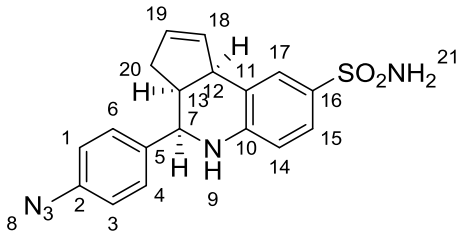
70

R_f = 0.73 (1: 1 EtOAc : petrol); IRυ_{max} 2837 (C-H of CHO), 2773 (C-H), 2095.0 (N_3), 1694 (C=O), 1506 (aromatic), 1284.9 (C-N) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 9.94 (s, 1H, H-1), 7.88 (d, 2H, *J* = 9.1 Hz, H-2), 7.16 (d, 2H, *J* = 9.1 Hz, H-3); δ ^{13}C NMR (150 MHz) 190.5 (CHO), 146.7 (C_q), 133.4 (2 × CH), 132.1 (2 × CH), 120.0 (C_q).

4-(4-Azidophenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-sulfonamide (71b)

Dissolved 4-azidobenzaldehyde (0.55 mmol, 80 mg), sulphanilamide (120 mg), and $Sc(OTf)_3$ (20 mol%) in MeCN. Cyclopentadiene (3 eq, 0.14 ml) was added to the reaction mixture and left to stir overnight. Extracted from EtOAc and washed with (0.1M) $NaHCO_3$ solution (10 ml), brine (10 ml) and water (10 ml). The organic layer was dried with $MgSO_4$, filtered and concentrated. Purification by flash

chromatography dry load gradient method 0-35% EtOAc: petrol gave the title compound as an orange-pink viscous oil (12 mg, 24%). Isolated as a mixture of two diastereoisomers in 71: 29 ratio.

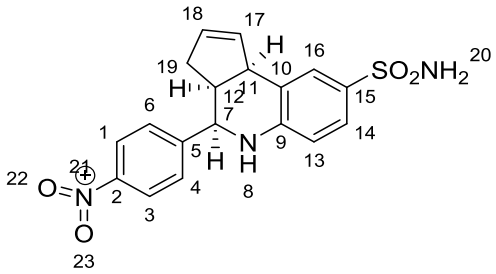


71b

R_f = 0.45 (1: 1 EtOAc : petrol); IRυ $_{max}$ 3233 (C-H), 2995 (C-H), 2790 (N-H) 2254 (N_3), 1599 (aromatic), 1471 (SO_2-N), 1382 (O=S=O), 1160 (O=S=O) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.60 (d, 1H, *J* = 1.5 Hz, H-17), 7.52 (m, 3H, H-1,3, and 15), 7.29 (d, 2H, *J* = 8.5 Hz, H-4,6), 6.69 (d, 1H, *J* = 8.6 Hz, H-14), 5.90-5.87 (m, 1H, H-18), 5.70-5.66 (m, 1H, H-19), 4.78 (s, 2H, NH_2), 4.67 (d, 1H, *J* = 2.9 Hz, H-7), 4.19 (s, 1H, N*H*), 4.10 (d, 1H, *J* = 8.5 Hz, H-12), 2.98 (dtd, 1H, *J* = 9.8, 8.5, 2.9 Hz, H-13), 2.51 (dtd, 1H, *J* = 16.3, 9.8, 2.9 Hz, H-20), 1.81 (dd, 1H, *J* = 16.3, 8.5 Hz, H-20); ^{13}C NMR (150 MHz, $CDCl_3$) 149.9 (C_q), 140.8 (C_q), 133.5 (CH), 132.0 (2 × CH), 131.2 (C_q), 131.0 (CH), 128.2 (3 × CH), 125.8 (C_q), 125.4 (CH), 121.5 (C_q), 115.8 (CH), 57.0 (CH), 45.73 (CH), 45.71 (CH), 31.2 (CH_2); HRMS (EI) calcd. for $C_{18}H_{17}O_2N_5S$ $[M]^+$ 367.4270, found 367.4267.

(3a*S*,4*R*,9b*R*)-4-(4-Nitrophenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-sulfonamide (72b)[26]

Method A: Under the same protocol conditions above with exception to sulphanilamide (2 eq) and $InCl_3$ (10 mol%) were considered. Purification by recrystallisation in DCM: EtOAc gave the title compound as a yellow powder (157 mg, 21%). Isolated as a mixture of two diastereoisomers in 95: 5 ratio.

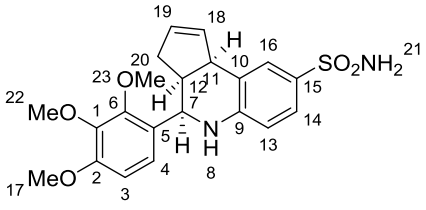


72b

m.p. 125˚C; R_f = 0.37 (1: 1 EtOAc : petrol); IRυ $_{max}$ 3360 (C-H), 3258 (C-H), 1599 (aromatic), 1504 (N-O), 1346 (N-O), 1313 (SO_2-N), 1166 (O=S=O) cm^{-1}; Major diastereoisomer: δ ^{1}H NMR (600 MHz, DMSO-d_6) 8.27 (d, 2H, 8.7 Hz, H-1, 3), 7.74 (d, 2H, *J* = 8.6 Hz, H-4, 6), 7.46 (d, 1H, *J* = 1.7 Hz, H-16), 7.36 (dd, 1H, *J* = 8.3, 1.7 Hz, H-14), 7.00 (s, 2H, NH_2), 6.82 (d, 1H, *J* = 8.4 Hz, H-13), 6.54 (s, 1H, NH), 5.92-5.89 (m, 1H, H-17), 5.69-5.67 (br d, 1H, *J* = 4.4 Hz, H-18), 4.80 (d, 1H, *J* = 2.6 Hz, H-7), 4.10 (d, 1H, *J* = 8.5 Hz, H-11), 3.00 (dtd, 1H, *J* = 9.3, 8.5, 2.6 Hz, H-12), 2.32 (dtd, 1H, *J* = 16.0, 9.3, 2.6 Hz, H-19), 1.60 (ddd, 1H, *J* = 16.0, 8.5, 2.6 Hz, H-19); ^{13}C NMR (150 MHz, DMSO-d_6) 150.1 (C_q), 148.9 (C_q), 146.5 (C_q), 134.2 (CH), 132.7 (C_q), 129.9 (CH), 127.9 (2 × CH), 126.8 (CH), 124.1 (CH), 124.0 (C_q), 123.5 (2 × CH), 115.2 (CH), 55.6 (CH), 45.0 (CH), 44.7 (CH), 31.7 (CH_2).

4-(2,3,4-Trimethoxyphenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-sulfonamide (73b)

Method A: Purified by flash chromatography dry load gradient method 40-50% EtOAc: petrol gave the title compound as an orange viscous oil (42 mg, 10%). Isolated as a mixture of two diastereoisomers in 91: 9 ratio.



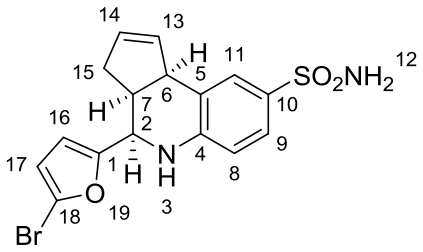
73b

R_f = 0.26 (1 :1 EtOAc : Petrol); IRυ $_{max}$ 3354 (C-H), 3257 (C-H), 2936 (N-H), 2848 (N-H), 1494 (aromatic), 1464 (C-O), 1330 (SO_2-N), 1296 (O=S=O), 1153 (O=S=O), 1090 (C-O) cm^{-1}; Major diastereoiomser: δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.60 (d, 1H,

J = 1.8 Hz, H-16), 7.50 (dd, 1H, *J* = 8.4, 1.8 Hz, H-14), 7.14 (d, 1H, *J* = 8.7 Hz, H-4), 6.69 (d, 1H, *J* = 8.6 Hz, H-3), 6.63 (d, 1H, *J* = 8.4, H-13), 5.87-5.85 (m, 1H, H-18), 5.69-5.66 (m, 1H, H-19), 4.94 (br d, 1H, *J* = 2.7 Hz, H-7), 4.86 (s, 2H, NH_2), 4.11 (br d, 1H, *J* = 8.8 Hz, H-11), 4.05 (br s, 1H, N*H*), 3.92 (br s, 3H, H-22), 3.88 (br s, 6H, H-17, 23), 3.09 (dtd, 1H, *J* = 10.5, 8.8, 2.7 Hz, H-12), 2.50 (ddd, 1H, *J* = 16.3, 8.8, 2.7 Hz, H-15), 1.84 (ddd, 1H, *J* = 16.3, 10.5 Hz, H-15); δ ^{13}C NMR (150 MHz, $CDCl_3$) 153.2 (C_q), 151.2 (C_q), 150.4 (C_q), 142.1 (C_q), 133.7 (CH), 131.1 (CH), 130.6 (C_q), 128.2 (CH), 127.5 (C_q), 126.1 (C_q), 125.3 (CH), 120.7 (CH), 115.6 (CH), 107.1 (CH), 61.3 (CH_3), 60.9 (CH_3), 56.2 (CH_3), 51.2 (CH), 45.9 (CH), 43.7 (CH), 31.9 (CH_2); HRMS (EI) calcd. for $C_{21}H_{24}O_5N_2S$ $[M]^+$ 416.14004, found 416.14087.

4-(5-Bromofuran-2-yl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-sulfonamide (74b)

Method A: Purification by dry load flash chromatography gradient method 50-40% EtOAc: petrol gave the title compound as a dark green powder (172 mg, 25%). Isolated as a mixture of two diastereoisomers in >95: 5 ratio.



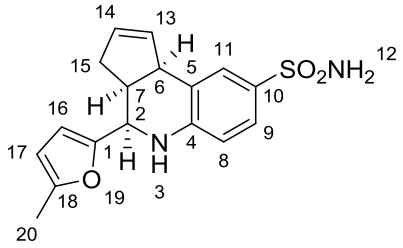
74b

m.p. 168-169˚C; R_f = 0.53 (1 :1 EtOAc : petrol); IRυ $_{max}$ 3362 (C-H), 3263 (C-H), 2936 (N-H), 1499 (aromatic), 1315 (SO_2-N), 1153 (O=S=O), 1127 (C-O-C), 1090 (C-O) cm^{-1}; Major diastereoiomser: δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.59 (d, 1H, *J* = 1.9 Hz, H-11), 7.52 (dd, 2H, *J* = 8.6, 1.9 Hz, H-9), 6.67 (d, 1H, *J* = 8.6 Hz, H-8), 6.29 (d, 1H, *J* = 3.4 Hz, H-17), 6.25 (d, 1H, 3.4 Hz, H-16), 5.85-5.82 (m, 1H, H-13), 5.72-5.69 (m, 1H, H-14), 4.62 (s, 3H, H-2, NH_2), 4.27 (1H, s, NH), 4.09 (d, 1H, *J* = 8.9 Hz, H-6), 3.18 (dtd, 1H, *J* = 9.1, 8.9, 2.8, H-7), 2.58 (dtd, 1H, *J* = 16.5, 9.1, 2.8 Hz, H-15), 2.24 (br dd, 1H, *J* = 16.5, 8.9 Hz, H- 15); ^{13}C NMR (150 MHz, $CDCl_3$) 156.5 (C_q), 148.7 (C_q), 133.4 (CH), 131.4 (C_q), 131.0 (CH), 128.1 (CH), 126.0 (C_q), 125.5 (CH), 121.2 (C_q), 115.7 (CH), 112.1 (CH), 108.9 (CH), 52.0 (CH), 45.5 (CH),

42.3 (CH), 32.6 (CH_2); HRMS (CI) calcd. for $C_{16}H_{15}O_3N_2SBr$ $[M]^+$ 395.2710, found 395.0069.

4-(5-Methylfuran-2-yl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-sulfonamide (75b)

Method A: Purification by dry load flash chromatography gradient method 30-50% EtOAc: petrol gave the title compound as a pale yellow orange viscous oil (69 mg, 8%). Isolated as a mixture of two diastereoisomers in >95: 5 ratio.

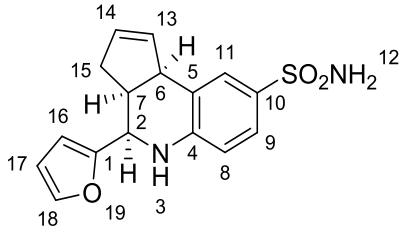


75b

R_f = 0.27 (1: 1 EtOAc : petrol); IRυ $_{max}$ 3361 (C-H), 3268 (C-H), 2923 (N-H), 1499 (aromatic), 1319 (SO_2-N), 1292 (C-O), 1154 (O=S=O), 1130.2 (C-O-C) cm^{-1}; Major diastereoiomser: δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.58 (d, 1H, *J* = 1.9 Hz, H-11), 7.51 (dd, 1H, *J* = 8.6, 1.9 Hz, H-9), 6.64 (d, 1H, *J* = 8.6 Hz, H-8), 6.12 (d, 1H, *J* = 3.0 Hz, H-16), 5.94 (d, 1H, 3.0, 1.1 Hz, H-17), 5.84-5.81 (m, 1H, H-13), 5.72-5.69 (m, 1H, H-14), 4.70 (s, 2H, NH_2), 4.64 (d, 1H, *J* = 3.0 Hz, H-2), 4.31 (s, 1H, NH), 4.08 (d, 1H, *J* = 8.9 Hz, H-6), 3.18 (dtd, 1H, *J* = 9.1, 8.9, 3.0 Hz, H-7), 2.60 (dddd, 1H, *J* = 16.6, 9.1, 3.0 Hz, H-15), 2.30 (s, 3H, CH_3), 2.23 (br dd, 1H, *J* = 16.6, 8.9 Hz, H-15); ^{13}C NMR (150 MHz, $CDCl_3$) 152.6 (C_q), 151.7 (C_q), 149.3 (C_q), 133.5 (CH), 131.2 (CH), 131.0 (C_q), 128.1 (CH), 126.1 (C_q), 125.4 (CH), 115.7 (CH), 106.7 (CH), 106.2 (CH), 52.0 (CH), 45.8 (CH), 42.5 (CH), 32.7 (CH_2), 13.8 (CH_3); HRMS (CI) calcd. for $C_{17}H_{19}O_3N_2S$ 331.4020 $[M + H]^+$ found 331.1119.

4-(Furan-2-yl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-sulfonamide (76b)

Method A: Purification by dry load flash chromatography gradient method 30-40% EtOAc: petrol gave the title compound as a pale yellow powder (319 mg, 32%). Isolated as a mixture of two diastereoisomers in >95: 5 ratio.

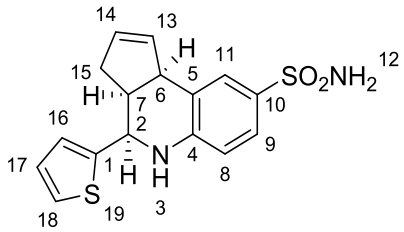


76b

m.p. 182-184 ˚C; R_f = 5.57 (1: 1 EtOAc : petrol); IRυ $_{max}$ 3361 (C-H), 3200 (C-H), 2940 (N-H), 1497 (aromatic), 1322 (SO_2-N), 1147 (O=S=O), 1127 (C-O-C), 912 (C-O) cm^{-1}; Major diastereoiomser: δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.59 (d, 1H, *J* = 1.9 Hz, H-11), 7.52 (dd, 1H, *J* = 8.6, 1.9 Hz, H-9), 7.40 (dd, 1H, *J* = 3.1, 0.8 Hz, H-18), 6.66 (d, 1H, *J* = 8.6 Hz, H-8), 6.38 (dd, 1H, 3.1, 2.0 Hz, H-17), 6.26 (dt, 1H, *J* = 3.1, 0.8 Hz, H-16), 5.85-5.82 (m, 1H, H-13), 5.72-5.69 (m, 1H, H-14), 4.71 (d, 1H, *J* = 2.8 Hz, H-2), 4.63 (s, 2H, NH_2), 4.33 (s, 1H, NH), 4.10 (d, 1H, *J* = 8.7 Hz, H-6), 3.04 (dtd, 1H, *J* = 9.0, 8.7, 2.8 Hz, H-7), 2.59 (dtd, 1H, *J* = 16.7, 9.0, 2.8 Hz, H-15), 2.21 (ddd, 1H, *J* = 16.7, 8.7, 2.8 Hz, H-15); δ ^{13}C NMR (150 MHz, $CDCl_3$) 154.4 (C_q), 149.1 (C_q), 142.0 (CH), 133.4 (CH), 131.1 (CH), 131.1 (C_q), 128.1 (CH), 126.1 (C_q), 125.4 (CH), 115.7 (CH), 110.5 (CH), 106.0 (CH), 52.0 (CH), 45.7 (CH), 42.5 (CH), 32.7 (CH_2); HRMS (CI) calcd. for $C_{16}H_{17}O_3N_2S$ $[M + H]^+$ 317.0882 found, 317.0965.

4-(Thiophen-2-yl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-sulfonamide (77b)

Method A: Purification by dry load flash chromatography gradient method 30-40% EtOAc: petrol gave the title compound as a pale yellow powder (185 mg, 20%). Isolated a mixture of two diastereoisomers in >95: 5 ratio.

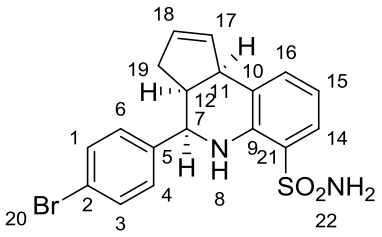


77b

m.p. 174-177 ˚C; R_f = 0.57 (1 :1 EtOAc : petrol); IRυ $_{max}$ 3355 (C-H), 3261 (C-H), 2911 (N-H), 1494 (aromatic), 1329 (SO_2-N), 1155 (O=S=O) cm^{-1}; Major diastereoiomser: δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.59 (d, 1H, *J* = 2.1 Hz, H-11), 7.52 (dd, 1H, *J* = 8.5, 2.1 Hz, H-9), 7.27 (dd, 1H, *J* = 5.1, 0.8 Hz, H-18), 7.10 (br d, 1H, *J* = 3.5 Hz, H-16), 7.02 (dd, 1H, 5.1, 3.5 Hz, H-17), 6.64 (d, 1H, *J* = 8.5 Hz, H-8), 5.89-5.86 (m, 1H, H-13), 5.73-5.70 (m, 1H, H-14), 4.99 (d, 1H, *J* = 2.8 Hz, H-2), 4.71 (s, 2H, NH_2), 4.30 (1H, s, NH), 4.11 (d, 1H, *J* = 8.4 Hz, H-6), 3.06 (dtd, 1H, *J* = 9.6, 8.4, 2.8 Hz, H-7), 2.67 (ddd, 1H, *J* = 16.4, 9.6, 2.8 Hz, H-15), 2.10 (dddd, 1H, *J* = 16.4, 8.4, 2.8 Hz, H- 15); ^{13}C NMR (150 MHz, $CDCl_3$) 149.1 (C_q), 144.9 (C_q), 133.4 (CH), 131.3 (C_q), 131.2 (CH), 128.2 (CH), 126.9 (CH), 126.0 (C_q), 125.4 (CH), 124.6 (CH), 124.3 (CH), 115.7 (CH), 54.1 (CH), 46.1 (CH), 45.8 (CH), 32.4 (CH_2); HRMS (CI) calcd. for $C_{16}H_{17}O_2N_2S_2$ $[M + H]^+$ 333.0653 found, 333.0729.

4-(4-Bromophenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-6-sulfonamide (92b)

Method A: Purification by dry load flash chromatography dry load gradient method 0-50% EtOAc: petrol to afford title compound as a white foam (339 mg, 51%). Isolated as a mixture of two diastereoisomers in >95:5 ratio.



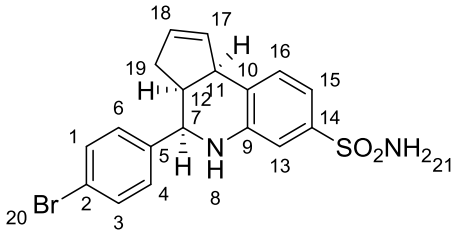
92b

m.p. 95-97 ˚C; R_f = 0.58 (1: 1 EtOAc : petrol); IRυ $_{max}$ 3359 (C-H), 3274 (C-H), 2927 (N-H), 2848 (N-H), 1487 (aromatic), 1450 (SO_2-N), 1327 (SO_2-N), 1163 (O=S=O) cm^{-1}; Major diastereoisomer: δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.65 (d, 1H, *J* = 7.8 Hz, H-14), 7.51 (d, 2H, *J* = 8.5 Hz, H-1, 3), 7.29 (d, 2H, *J* = 8.5 Hz, H-4, 6), 7.25 (br d, 1H, *J* = 7.8 Hz, H-16), 6.81 (t, 1H, *J* = 7.8 Hz, H-15), 6.02(s, 1H, NH), 5.84-5.82 (m, 1H, H-17), 5.68-5.66 (m, 1H, H-18), 4.83 (s, 2H, NH_2), 4.63 (d, 1H, *J* = 2.9 Hz, H-7), 4.16 (d, 1H, *J* = 8.5 Hz, H-11), 3.02 (dtd, 1H, *J* = 9.5, 8.5, 2.9 Hz, H-12), 2.51 (dtd, 1H, *J* = 16.4, 9.5, 2.9 Hz, H-19), 1.86 (ddd, 1H, *J* = 16.4, 8.5, 2.9 Hz, H-19); ^{13}C NMR (150 MHz, $CDCl_3$) 143.3 (C_q), 140.7 (C_q), 134.4 (CH), 133.8

(CH), 132.0 (2 × CH), 131.1 (CH), 128.05 (2 × CH), 128.10 (C_q), 126.5 (CH), 124.9 (C_q), 121.5 (C_q), 118.3 (CH), 56.6 (CH), 46.0 (CH), 44.9 (CH), 31.5 (CH_2); HRMS (ES) calcd. for $C_{18}H_{17}O_2N_2SBr$ $[M-H]^-$ 403.0194, found 403.0116.

4-(4-Bromophenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-7-sulfonamide (93b)

Purification by flash chromatography dry load method 1: 1 EtOAc: petrol to afford title compound as a green crystalline foam (173 mg, 26%). Isolated as a mixture of two diastereoisomers in >95: 5 ratio as a percentage.

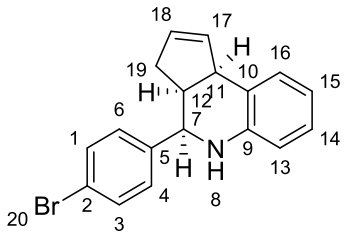


93b

m.p. 112-115˚C; R_f = 0.28 (1:1 EtOAc : petrol); IRυ $_{max}$ 3361 (C-H), 3267 (C-H), 2926 (N-H), 2849 (N-H), 1474 (aromatic), 1320 (SO_2-N), 1159 (O=S=O) cm^{-1}; Major diastereoisomer: δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.51 (m, 3H, H-13, 1, 3), 7.28 (d, 2H, *J* = 8.4 Hz, H-4, 6), 7.25 (dd, 1H, *J* = 7.2, 1.6 Hz, H-15), 7.17 (d, 1H, *J* = 1.6 Hz, H-13), 7.15 (d, 1H, *J* = 7.2 Hz, H-16), 5.82-5.80 (m, 1H, H-17), 5.69-5.67 (m, 1H, H-18), 4.77 (s, 2H, NH_2), 4.62 (d, 1H, *J* = 3.0 Hz, H-7), 4.11 (d, 1H, *J* = 8.1 Hz, H-11), 2.99 (dtd, 1H, *J* = 9.1, 8.1, 3.0 Hz, H-12), 2.53 (dtd, 1H, *J* = 16.4, 9.1, 3.0 Hz, H-19), 1.81 (br dd, 1H, *J* = 16.4, 8.1 Hz, H-19); ^{13}C NMR (150 MHz, $CDCl_3$) 146.0 (C_q), 141.0 (C_q), 139.8 (C_q), 133.1 (CH), 131.9 (2 × CH), 131.3 (CH), 131.0 (C_q), 130.0 (CH), 128.2 (2 × CH), 121.4 (C_q), 116.7 (CH), 113.7 (CH), 57.3 (CH), 46.2 (CH), 45.7 (CH), 31.8 (CH_2); HRMS (ES) calcd. for $C_{18}H_{17}O_2N_2SBr$ $[M-H]^-$ 403.0195, found 403.0116.

4-(4-Bromophenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolone (94b)[26]

Purification by dry load flash chromatography gradient method using 0-50% EtOAc: petrol gave the title compound as an orange white solid (213 mg, 65%). Isolated as a mixture of two diastereoisomers in 91: 9 ratio.



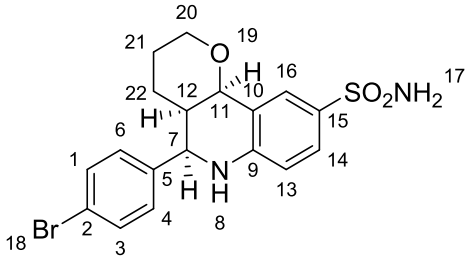
94b

mp 148-149 °C; R_f = 0.76 (1:1 EtOAc: petrol), IRυ_{max} 2928 (C-H), 2846 (N-H), 1472 (aromatic) cm^{-1}; Major diastereoisomer: δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.49 (d, 2H, *J* = 8.4 Hz, H-1, 3), 7.32 (d, 2H, *J* = 8.4 Hz, H-4, 6), 7.06 (br d, 1H, *J* = 7.7 Hz, H-16), 6.99 (td, 1H, *J* = 7.7, 1.5 Hz, H-14), 6.77 (td, 1H, *J* = 7.7, 1.2 Hz, H-15), 6.63 (dd, 1H, *J* = 7.7, 1.2 Hz, H-13), 5.85-5.83 (m, 1H, H-17), 5.65-5.63 (m, 1H, H-18), 4.60 (d, 1H, *J* = 2.9 Hz, H-7), 4.11 (d, 1H, *J* = 8.6 Hz, H-11), 3.70 (br s, 1H, N*H*), 2.97 (dtd, 1H, *J* = 9.3, 8.6, 2.9 Hz, H-12), 2.58 (ddd, 1H, *J* = 16.4, 9.3, 2.9 Hz, H-19), 1.79 (ddd, 1H, *J* = 16.4, 8.6, 2.9 Hz, H-19); δ ^{13}C NMR (150 MHz, $CDCl_3$) 145.3 (C_q), 142.1 (C_q), 134.1 (CH), 131.7 (2 × CH), 130.4 (CH), 129.1 (CH), 128.3 (2 × CH), 126.5 (CH), 126.1 (C_q), 121.1 (C_q), 119.5 (CH), 116.1 (CH), 57.7 (CH), 46.4 (CH), 46.0 (CH), 31.5 (CH_2).

5-(4-bromophenyl)-3,4,4a,5,6,10b-hexahydro-2H-pyrano[3,2-c]quinoline-9-sulfonamide (96a)

To a dry flask under an atmosphere of argon were added **28b** (5.00 mmol, 925 mg), sulphanilamide (5.49 mmol, 945 mg, 1.4 eq), 3, 4-dihydropyran (7 mmol, 0.6 ml, 1.4 eq) and MeCN (5 ml). This was followed by addition of $GdCl_3$ (20 mol%, 265 mg) and reaction was stirred overnight at r.t. Purification by dry load flash column chromatography 0-50%. Isolated two spots which were each further purified by

recrystallisation from isopropanol: petrol: toluene, which gave the title compound as a white powder (0.4 mg, 0.02%).

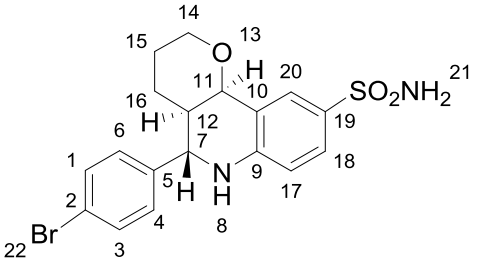


96a

R_f = 0.32 (3 : 2 EtOAc/petrol); mp 192-194 °C; IRυ $_{max}$ 3344 (N-H), 2933 (N-H), 1489 (aromatic), 1332 (SO_2-N), 1191 (S=O), 1170 (N-SO_2) ,1132 (N-SO_2), 1092 (S=O) cm^{-1}; δ ^{1} H NMR (600 MHz, $CDCl_3$) 7.98 (br s, 1H, H-16), 7.62 (d, 1H, *J* = 8.5 Hz, H-14), 7.52 (d, 2H, *J* = 8.4 Hz, H-1, 3), 7.25 (d, 2H, *J* = 8.4 Hz, H-4, 6), 6.63 (d, 1H, *J* = 8.5 Hz, H-13), 5.27 (d, 1H, *J* = 5.4 Hz, H-11), 4.73 (d, 1H, *J* = 2.5 Hz, H-7), 4.70 (s, 2H, NH_2), 4.32 (br s, 1H, -NH), 3.64 (dd, 1H, *J* = 11.8, 4.5 Hz, H-20), 3.40 (td, 1H, *J* = 11.8, 2.5 Hz, H-20), 2.19-2.14 (m, 1H, H-12), 1.56-1.50 (m, 1H, H-21), 1.49-1.45 (m, 1H, H-21), 1.42-1.35 (m, 1H, H-22), 1.32-1.27 (m, 1H, H-22); δ ^{13}C NMR (150 MHz, $CDCl_3$) 148.7 (C_q), 138.9 (C_q), 131.9 (2 × CH), 130.7 (C_q), 128.5 (2 × CH), 127.3 (CH), 127.0 (CH), 121.8 (C_q), 119.8 (C_q), 114.1 (CH), 72.0 (CH), 61.0 (CH_2), 58.8 (CH), 38.2 (CH), 25.3 (CH_2), 18.3 (CH_2); HRMS (EI) $C_{18}H_{19}BrO_3N_2S$ $[M]^+$ 422.0311, found 422.0294.

***Trans:cis* isomer isolated from above reaction (96b):**

Purified by recrystallisation from isopropanol: petrol: toluene gave title compound as a brown viscous oil (4.0 mg, 0.2%).

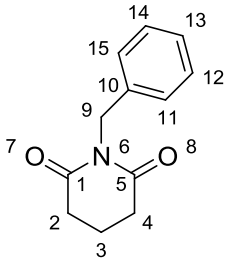


96b

R_f 0.23 (3 : 2 EtOAc/petrol); IRυ_{max} 3370 (C-H), 3321(C-H), 2936 (N-H), 2871 (N-H), 1474 (aromatic), 1332 (-SO_2-N), 1195 (-SO_2-N), 1150 (-SO_2-) cm^{-1}; (600 MHz, $CDCl_3$) δ 7.80 (d, 1H, *J* = 2.2 Hz, H-20), 7.61 (dd, 1H, *J* = 8.7, 2.2 Hz, H-18), 7.53 (d, 2H, *J* = 8.4 Hz, H-1,3), 7.27 (d, 2H, *J* = 8.4 Hz, H-4,6), 6.56 (d, 1H, *J* = 8.7 Hz, H-17), 4.72 (d, 1H, *J* = 10.3 Hz, H-7), 4.65 (s, 2H, NH_2), 4.52 (br s, 1H, -NH), 4.40 (d, 1H, *J* = 2.5 Hz, H-11), 4.09 (br d, 1H, *J* = 11.4 Hz, H-14), 3.72 (td, 1H, 11.4, 2.5 Hz, H-14), 2.02 (m, 1H, H-12), 1.81 (qt, 1H, *J* = 12.8, 4.4 Hz, H-15), 1.70 (tt, 1H, *J* = 14.7, 4.4 Hz, H-16), 1.47 (m, 1H, H-16), 1.40 (m, 1H, H-15); δ ^{13}C NMR (600 MHz, $CDCl_3$) 148.1 (C_q), 140.3 (C_q), 132.2 (2 × CH), 130.4 (CH), 129.5 (2 × CH), 129.2 (C_q), 128.4 (CH), 122.3 (C_q), 120.0 (C_q), 114.0 (CH), 73.8 (CH), 68.5 (CH_2), 54.3 (CH), 38.4 (CH), 23.8 (CH_2), 21.9 (CH_2); (EI) $C_{18}H_{19}BrO_3N_2S$ $[M]^+$ 422.0311, found 422.0294.

1-benzylpiperidine-2,6-dione (99)[105]

Purification by dry load flash column chromatography gradient method 10-20-60% EtOAc: petrol gave title compound as a colourless oil (1.5 g, 86%).

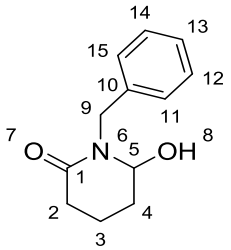


99

R_f = 0.45 (3 : 2 EtOAc : petrol); IRυ_{max} 3032 (C-H), 1722 (C=O), 1663 (aromatic), 1344 (CH_2), 1167 (C-N), 1136 (OC-N), 1013 (C-N) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.36 (t, 2H, *J* = 7.4 Hz, H-14, 12), 7.28 (t, 2H, *J* = 7.4 Hz, H-15, 11), 7.23 (t, 1H, *J* = 7.4 Hz, H-13), 4.94 (s, 2H, H-9), 2.67 (t, 4H, *J* = 6.6 Hz, H-4, 2), 1.93 (qn, 2H, *J* = 6.6 Hz, H-3); δ ^{13}C NMR (150 MHz, $CDCl_3$) 172.6 (2 × C_q), 137.4 (C_q), 128.9 (2 × CH), 128.5 (2 × CH), 127.5 (CH), 43.0 (CH_2), 32.9 (2 × CH_2), 17.4 (CH_2).

1-benzyl-6-hydroxypiperidin-2-one (100)[206]

In a flame dried flask under an atmosphere of argon was added **99** (1.00 g, 4.93 mmol) dissolved in MeOH (10 ml). Sodium borohydride (946 mg, 24.0 mmol, 5 eq) was added portionwise to the reaction mixture at 0°C and was stirred for 2 hrs. The reaction mixture was dissolved in CH_2Cl_2 (10 ml) then washed with water (2 × 60 ml), dried with $MgSO_4$, filtered and concentrated to give the title compound as a white oil (666 mg, 66%).

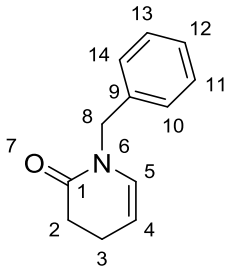


100

R_f = 0.12 (1 : 1 EtOAc : petrol); IRυ $_{max}$ 3347 (O-H), 1737 (C=O), 1624 (aromatic), 1373 (OC-N), 1230 (C-O), 1045 (C-O) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.29 (m, 5H, H-11, 12, 13, 14, 15), 5.06 (d, 1H, *J* = 15.0 Hz, H-9), 4.93 (m, 1H, H-5), 4.38 (d, 1H, *J* = 15.0 Hz, H-9), 2.55 (m,1H, H-3), 2.42 (m, 1H, H-3), 2.09 (m, 1H, H-4), 1.82 (m, 2H, H-2), 1.77-1.71 (m, 1H, H-4); ^{13}C NMR (150 MHz, $CDCl_3$) 170.5 (C_q), 137.7 (C_q), 128.9 (2 × CH), 128.2 (2 × CH), 127.6 (CH), 78.9 (CH), 47.2 (CH_2), 32.6 (CH_2), 31.0 (CH_2), 15.9 (CH_2); HRMS (EI) cald. for $C_{12}H_{15}NO_2$ $[M]^+$ 205.1102, required 205.1104.

1-benzyl-3,4-dihydropyridin-2(1H)-one (101)[105]

Under argon conditions **100** (300mg, 1.46 mmol, 1eq) was dissolved in CH_2Cl_2 at 0°C. Triethylamine (0.6 ml) was added dropwise followed by MsCl (0.2 ml) dropwise. The reaction mixture was stirred for 3 hrs at r.t. The reaction mixture was washed with aq. sat. $NaHCO_3$ (2 × 25 ml), brine (50 ml) and water (50 ml). The organic layer was dried with $MgSO_4$, filtered and evaporated to give the crude product. Purification by dry load flash chromatography 30% EtOAc: petrol gave the title compound as a pale yellow oil (101 mg, 37%).

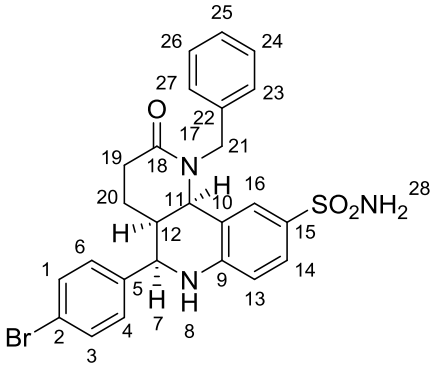


101

R_f = 0.48 (1 : 1 EtOAc : petrol); IRυ $_{max}$ 2990 (=C-H), 2845 (C-H),1655 (C=O, C=C alkene), 1590 (aromatic), 1403 (OC-N), 1391 (C-N) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.32 (t, 2H, *J* = 7.5 Hz, H-13,11), 7.26 (t, 1H, *J* = 7.5 Hz, H-12), 7.23 (d, 2H, *J* = 7.5 Hz, H-14, 10), 6.01 (dt, 1H, *J* = 7.8, 1.6 Hz, H-5), 5.13 (dt, 1H, *J* = 7.8, 4.4 Hz, H-4), 4.69 (s, 2H, H-8), 2.59 (t, 2H, *J* = 9.9 Hz, H-2), 2.34 (tdd, 1H, *J* = 9.9, 4.4, 1.6 Hz, H-3); ^{13}C NMR (150 MHz, $CDCl_3$) 169.6 (C_q), 137.1 (C_q), 129.6 (CH), 128.9 (2 × CH), 127.7 (2 × CH), 127.6 (CH), 106.7 (CH), 49.1 (CH_2), 31.4 (CH_2), 20.7 (CH_2); HRMS (EI) calcd. for $C_{12}H_{13}ON$ $[M]^+$ 187.0997, found 187.0993.

1-benzyl-5-(4-bromophenyl)-2-oxo-1,2,3,4,4a,5,6,10b-octahydrobenzo[h][1,6]naphthyridine-9-sulfonamide (102)

Under dry argon conditions, sulphanilamide (78 mg, 045 mmol, 1 eq), 4-bromobenzaldehyde (80 mg, 0.43 mmol, 1 eq) and $Sc(OTf)_3$ (20 mol%, 4 mg) were dissolved in dry MeCN (3 ml). After stirring for 5 minutes, *N*-benzyl lactam (80 mg, 0.43 mmol, 1eq) was added to reaction mixture and left to stir for 24 hrs at room temperature under argon. The reaction mixture was diluted with EtOAc (5 ml) and washed with aq. sat. $NaHCO_3$ (10 ml). The organic extract was washed with brine (10 ml) and water (10 ml), dried with $MgSO_4$, filtered and concentrated. Purification by dry load flash chromatography gradient method 50-100% EtOAc: petrol gave the product as an off white amorphous solid (62 mg, 27%).

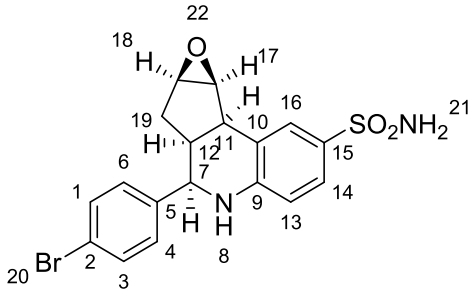


102

m.p. 143-145 °C, R_f = 0.23 (3 : 2 EtOAc : petrol); IRυ $_{max}$ 3343 (C-H), 3062 (C-H), 2967 (N-H), 1598 (C=O), 1494 (aromatic), 1391 (C-N), 1319 (SO_2-N), 1301 (O=S=O), 1147 (O=S=O) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$)7.65 (d, 1H, *J* = 8.4 Hz, H-14), 7.51 (s, 1H, H-16), 7.38 (d, 2H, *J* = 7.8 Hz, H-3,1), 7.18 (t, 1H, *J* = 7.4 Hz, H-25), 7.15 (t, 2H, *J* = 7.4 Hz, H-26, 24), 6.99 (d, 2H, *J* = 7.4 Hz, H-27, 23), 6.97 (d, 2H, *J* = 7.8 Hz, H-6, 4), 6.59 (d, 1H, *J* = 8.4 Hz, H-13), 5.41 (d, 1H, *J* = 14.5 Hz, H-21), 4.73 (s,1H, NH), 4.64 (s, 2H, NH_2), 4.34 (d, 1H, *J* = 4.2 Hz, H-7), 4.21 (d, 1H, *J* = 3.4 Hz, H-11), 4.06 (d, 1H, *J* = 14.5 Hz, H-21), 2.58-2.44 (m, 2H, H-19), 2.09-2.05 (m, 1H, H-12), 1.98-1.92; 1.69-1.62 (m, 2H, H-20); ^{13}C NMR (150 MHz, $CDCl_3$) 171.3 (C_q), 146.9 (C_q), 141.5(C_q), 136.4 (C_q), 132.1 (2 × CH), 129.7 (C_q), 128.7 (2 × CH), 128.1 (2 × CH), 128.0 (3 × CH), 127.6 (2 × CH), 127.5 (C_q), 122.0 (C_q), 113.1 (CH), 56.9 (CH), 52.8 (CH), 49.8 (CH_2), 38.2 (CH), 29.8 (CH_2), 22.2 (CH_2); HRMS (EI) calcd. for $C_{25}H_{24}BrN_3O_3S$ $[M-H]^-$ 524.0722, found 524.0643.

(7aR,8aS)-6-(4-bromophenyl)-6,6a,7,7a,8a,8b-hexahydro-5H-oxireno[2',3':3,4]cyclopenta[1,2-c]quinoline-2-sulfonamide (103)

28b (2.60 mmol, 1.06 g) was dissolved in CH_2Cl_2 (2 ml) at 0°C. MCPBA (10.4 mmol, 4 eq, 1.80 g) was added and left to stir overnight. The reaction mixture was diluted with EtOAc (5 ml) and washed with saturated solution of $NaHCO_3$ (10 ml) followed by brine (10 ml) and water (10 ml). Dried with $MgSO_4$, filtered and evaporated. Purification by dry load flash chromatography gradient method in 20-60% EtOAc: petrol gave a pale brown amorphous solid (541 mg, 49%).

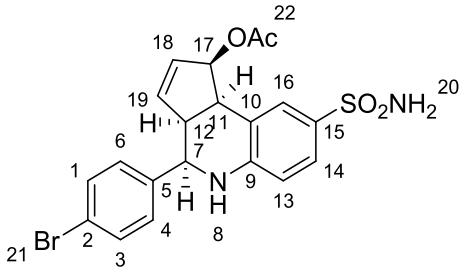


103

m.p. 154-155˚C; R_f = 0.29 (1: 1 EtOAc : petrol); IRυ $_{max}$ 3361 (C-H), 2219 (N-H), 1488 (aromatic), 1314 (SO_2-N), 1147 (O=S=O), 1130 (C-O) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.78 (d, 1H, *J* = 1.8 Hz, H-16), 7.58 (dd, 1H, *J* = 8.5, 1.8 Hz, H-14), 7.50 (d, 2H, *J* = 8.4 Hz, H-1,3), 7.23 (d, 2H, 8.4 Hz, H-4,6), 6.70 (d, 1H, *J* = 8.5 Hz, H-13), 4.84 (s, 2H, NH_2), 4.52 (d, 1H, *J* =4.5 Hz, H-7), 4.33 (br s, 1H, NH), 3,67 (d, 1H, 7.5 Hz,H-11), 3.66 (d, 1H, 2.4 Hz, H-18), 3.40 (d, 1H, 2.4 Hz, H- 17), 2.43 (m,1H, H-12), 1.75 (dd, 1H, *J* = 14.2, 10.2, H-19), 1.58 (dd, 1H, *J* = 14.2, 7.5 Hz, H-19); ^{13}C NMR (150 MHz, $CDCl_3$) 149.1 (C_q), 140.0 (C_q), 132.0 (2 × CH), 131.1 (C_q), 128.6 (CH), 128.0 (2 × CH), 126.3 (CH), 121.8 (C_q), 119.4 (C_q), 115.6 (CH), 61.3 (CH), 56.6 (CH), 55.4 (CH), 40.5 (CH), 39.4 (CH), 26.2 (CH_2); HRMS (EI) cald. for $C_{18}H_{18}BrN_2O_3S$ $[M+H]^+$ 421.3190, found 422.0299.

4-(4-Bromophenyl)-8-sulfamoyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-1-yl acetate (104)

A solution of **28b** (100 mg, 0.25 mmol), $Pd(OAc)_2$ (5.7 mg, 15mol%), benzoquinone (10.7 mg, 0.099 mmol), MnO_2 (15.6 mg, 0.22 mmol), acetic acid (42 µl, 0.0000734 mmol), and anhydrous DMSO (1.5 ml) was stirred under argon at 80 °C for 48 hrs. To the reaction mixture diethyl ether (5 ml) was added and washed with brine (10 ml) and water (6 ml). Dried with $MgSO_4$, filtered and concentrated. Purification by dry load flash chromatography gradient method 50-40% EtOAc: petrol gave the title compound as a light brown viscous oil (18 mg, 10%).

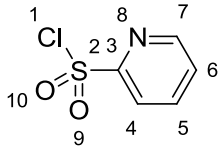


104

R_f = 0.35 (1: 1 EtOAc : petrol); IRυ $_{max}$ 3333 (C-H), 3262 (C-H), 2924 (N-H), 2852 (N-H), 1714 (C=O), 1498 (aromatic), 1327 (SO_2-N), 1250 (C-O), 1301(O=S=O) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 8.14 (d, 1H, *J* = 1.6 Hz, H-16), 7.57 (dd, 1H, *J* = 7.8, 1.6 Hz, H-14), 7.56 (d, 2H, *J* = 8.4 Hz, H-1,3), 7.32 (d, 2H, *J* = 8.4 Hz, H-4,6), 6.64 (d, 1H, *J* = 7.8 Hz, H-13), 5.92 (dd, 1H, *J* = 5.8, 1.4 Hz, H-19), 5.90-5.88 (m, 1H, H-18), 5.49 (br s, 1H, H-17), 4.90 (s, 2H, NH_2), 4.51 (d, 1H, *J* = 3.2 Hz, H-7), 4.19 (br s, 1H, NH), 3.70 (d, 1H, *J* = 6.8 Hz, H-11), 3.57 (br s, 1H, H-12), 2.08 (s, 3H, H-22); δ ^{13}C NMR (150 MHz, $CDCl_3$) 171.4 (C_q), 149.4 (C_q), 140.0 (C_q), 132.4 (C_q), 132.2 (2 × CH), 131.9 (CH), 131.0 (CH), 129.7 (CH), 128.4 (2 × CH), 126.1 (CH), 122.5 (C_q), 121.9 (C_q), 115.6 (CH), 87.6 (CH), 57.3 (CH), 51.2 (CH), 45.8 (CH), 21.4 (CH_3); HRMS (EI) calcd. for $C_{20}H_{19}BrO_4N_2S$ $[M]^+$ 462.0249, found 462.0246.

Pyridine-2-sulfonyl chloride (126)[167]

2-mercaptopyridine (5.0 g, 4.5 mol) was dissolved in concentrated sulfuric acid (125 ml) at -10°C. Sodium hypochlorite solution (chlorine content 5%, 315 ml) was added dropwise for 8 hrs. The mixture was stirred for an additional 30 min at the same temperature. The reaction mixture was diluted with water (100 ml), and extracted with CH_2Cl_2 (100 ml). The extract was washed with sat. solution of $NaHCO_3$ (500 ml), saturated brine (500 ml) and water (500 ml), dried over $MgSO_4$ and concentrated under reduced pressure to give the title compound as colourless oil (2.5 g, 77%).

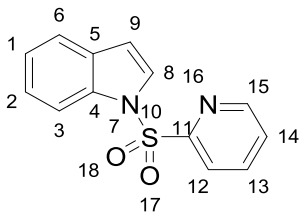


126

IRυ_{max} 3113 (C-H), 3087 (C-H), 1578 (aromatic), 1360 (SO_2-N), 1180 (S=O), 1149 (SO_2-N), 1086 (S=O) cm^{-1} ; δ ^{1}H NMR (600 MHz, $CDCl_3$) 8.83 (1H, ddd, *J* = 4.7, 1.4, 0.8 Hz, H-7), 8.12 (1H, dt, *J* = 7.7, 0.8 Hz, H-4), 8.06 (td, 1H, *J* = 7.7, 1.4 Hz, H-5), 7.70 (ddd, 1H, *J* = 7.7, 4.7, 1.1 Hz, H-6); δ ^{13}C NMR (150 MHz, $CDCl_3$) 159.3 (C_q), 150.8 (CH), 139.2 (CH), 129.2 (CH), 122.1 (CH).

1-(Pyridin-2-ylsulfonyl)-1H-indole (116)[166]

To a flame dried flask under an atmosphere of argon were added indole (840 mg, 7.2 mmol) and sodium hydride (240 mg, 10.0 mmol) dissolved in dry THF (10 ml) for 30 min at 0°C. The resulting solution was added dropwise to 2-pyridylsulfonylchloride (1.9 g, 10.7 mmol) at 0 °C and stirred at r.t. overnight under argon. The reaction mixture was quenched with sat aq. NH_4Cl solution (5 ml) and extracted with EtOAc (2 × 10 ml). The combined organic phases was dried with $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (0-30% EtOAc: petrol) to afford **1** (1.09 g, 58%) as a brown solid.

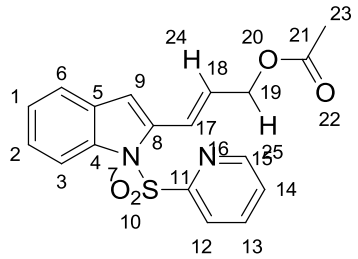


116

m.p. 55-57 °C; R_f = (3 : 2 EtOAc : petrol); IR υ_{max} 3113 (C-H), 3087 (C-H), 1578 (aromatic), 1368 (SO_2-N), 1180 (S=O), 1149 (SO_2-N), 1086 (S=O) cm^{-1}; δ ^{1}H NMR 8.59 (ddd, 1H, *J* = 4.7, 1.7, 1.0 Hz, H-15), 8.12 (dt, 1H, *J* = 7.8, 1.0 Hz, H-12), 8.00 (dd, 1H, *J* = 7.9, 1.5 Hz, H-3), 7.88 (td, 1H, *J* = 7.8, 1.7 Hz, H-13), 7.67 (d, 1H, 3.7 Hz, H-8), 7.54 (ddd, 1H, *J* = 7.8, 1.3, 0.8 Hz, H-6), 7.44 (ddd, 1H, *J* = 7.8, 4.7, 1.1 Hz, H-14), 7.29 (td, 1H, *J* = 7.9, 1.3 Hz, H-2), 7.23 (td, 1H, *J* = 7.9, 1.5 Hz, H-1), 6.68 (dd, 1H, *J* = 3.7, 0.8 Hz H-9); δ ^{13}C NMR (150 MHz, $CDCl_3$) 155.5 (C_q), 150.6 (CH), 138.3 (CH), 135.0 (C_q), 130.9 (C_q), 127.7 (CH), 127.5 (CH), 124.6 (CH), 123.6 (CH), 122.5 (CH), 121.5 (CH), 113.8 (CH), 109.0 (CH).

(*E*)-3-(1-(Pyridin-2-ylsulfonyl)-1H-indol-2-yl)allyl acetate (123)

To an oven dried carosuel tube under an atmosphere of argon, *N*-(2-pyridyl)sulfonylindole (0.39 mmol, 100 mg), $PdCl_2(CH_3CN)_2$ (10 mol%, 10 mg) and $Cu(OAc)_2.H_2O$ (0.6 mmol, 120 mg) dissolved in DMA (4 ml) with allyl acetate (0.73 mmol, 83 µl, 2 eq.) was stirred at 60°C for 17 hrs. The reaction mixture was dissolved with EtOAc (5ml) and washed with water (2 × 10 ml), dried with $MgSO_4$, filtered and concentrated to give a brown oil (120 mg). Purification by flash chromatography gradient method (20-40% EtOAc: petrol) gave a pale yellow viscous oil (72 mg, 53%).

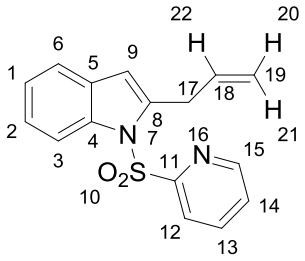


123

R_f = 0.34 (1 :1 EtOAc : petrol); IR υ_{max} 3020 (aromatic), 2253 (C-H), 1736 (C=O), 1712 (C=O), 1449 (aromatic), 1378 (SO_2-N), 1183 (S=O), 1151 (SO_2-N), 1126 (S=O), 1023 (C-O) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 8.54 (ddd, 1H, *J* = 4.7, 1.7, 0.9 Hz, H-15), 8.12 (dd, 1H, *J* = 7.6, 0.9 Hz, H-3), 8.01 (dt, 1H, *J* = 7.8, 0.9 Hz, H-12), 7.85 (td, 1H, *J* = 7.8, 1.7 Hz, H-13), 7.45 (ddd, 1H, *J* = 7.6, 1.4, 0.7 Hz, H-6), 7.42 (ddd, 1H, *J* = 7.8, 4.7, 1.1 Hz, H-14), 7.38 (dtd, 1H, *J* = 15.8, 1.6, 1.0 Hz, H-17), 7.27 (td, 1H, *J* = 7.6, 1.4 Hz, H-2), 7.21 (td, 1H, *J* = 7.6, 0.9 Hz, H-1), 6.78 (s, 1H, H-9), 6.24 (dt, 1H, *J* = 15.8, 6.1 Hz, H-18), 4.77 (dd, 2H, *J* = 6.1, 1.6 Hz, H-19), 2.13 (s, 3H, H-23); ^{13}C NMR (150 MHz, $CDCl_3$) 170.9 (C_q), 155.8 (C_q), 150.5 (CH), 138.9 (C_q), 138.1 (CH), 137.4 (C_q), 129.6 (C_q), 127.7 (CH), 127.3 (CH), 124.9 (CH), 124.1 (CH), 124.0 (CH), 122.3 (CH), 120.8 (CH), 115.0 (CH), 108.8 (CH), 64.7 (CH_2), 21.1 (CH_3); HRMS (CI) $C_{18}H_{17}N_2O_4S$ $[M+H]^+$ 357.08308 found, 357.09117.

2-Allyl-1-(pyridin-2-ylsulfonyl)-1H-indole (125)

Under dry argon conditions N-(2-pyridyl)sulfonylindole (0.77 mmols, 199.6 mg) together with $Cu(OAc)_2 .H_2O$ (20 mmol, 312 mg) and $PdCl_2(CH_3CN)_2$ (20 mmol%, 40.5 mg) were dissolved in anhydrous DMSO (7 ml). Allyl benzoate (2.1 mmol, 0.22 ml, 2 eq) was then added to the reaction mixture which was stirred at 117 °C for 17 hrs. The crude mixture was extracted with EtOAc and washed three times with water, dried, filtered and concentrated to give a brown oil. Purification by flash chromatography using a gradient method (0-20% EtOAc: petrol) gave the title compound as a yellow-brown viscous oil (23 mg, 10%)

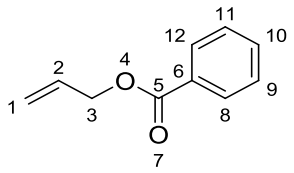


125

R_f = 0.6 (1: 1 EtOAc : petrol); IR υ_{max} 3398 (C-H), 3079 (C-H), 1579 (aromatic), 1376 (SO_2-N), 1181 (S=O), 1146 (SO_2–N), 1053 (S=O) cm^{-1};δ ^{1}H NMR (600 MHz, $CDCl_3$) 8.57 (ddd, 1H, *J* = 4.7, 1.8, 0.9 Hz, H-15), 8.07 (dq, 1H, *J* = 7.7, 0.9 Hz, H-3), 8.04 (dt, 1H, *J* = 7.8, 0.9 Hz, H-12), 7.84 (td, 1H, *J* = 7.8, 1.8 Hz, H-13), 7.42 (m, 1H, H-14), 7.40 (m, 1H, H-6), 7.21 (td, 1H, *J* = 7.7, 1.3 Hz, H-2), 7.18 (td, 1H, *J* = 7.7, 0.9 Hz, H-1), 6.4 (s, 1H, H-9), 6.11 (ddt, 1H, *J* = 17.0, 10.1, 6.7 Hz, H-22), 5.23 (dq, 1H, *J* = 17.0, 1.5 Hz, H-21), 5.20 (dq, 1H, *J* = 10.1, 1.5 Hz, H-20), 3.97 (dd, 2H, *J* = 6.7, 1.1 Hz, H-17); δ ^{13}C NMR (150 MHz, $CDCl_3$) 156.0 (C_q), 150.5 (CH), 141.8 (C_q), 138.1 (CH), 137.0 (C_q), 134.5 (CH), 129.9 (C_q), 127.6 (CH), 123.9 (CH), 123.7 (CH), 122.1 (CH), 120.3 (CH), 117.8 (CH_2), 114.6 (CH), 109.1 (CH), 33.5 (CH_2); HRMS (CI) $C_{16}H_{14}N_2O_2S$ $[M]^+$ 298.07705 found, 298.07763.

Allyl benzoate (128)[52]

To a solution of benzoyl chloride (3.77 mmol, 0.4 ml) and CH_2Cl_2 (1 ml) at 0 °C, were added allyl alcohol (3.36 mmol, 0.4 ml), pyridine (6.21 mmol, 0.5 ml) and was stirred at r.t. overnight. Added EtOAc (10 ml) and washed with $NaHCO_3$ 1M (2 × 5 ml), HCl 1M (2 × 5 ml), brine (10 ml) and H_2O (2 × 50 ml), gave the title compound as a colourless oil (0.5 ml, 92%).

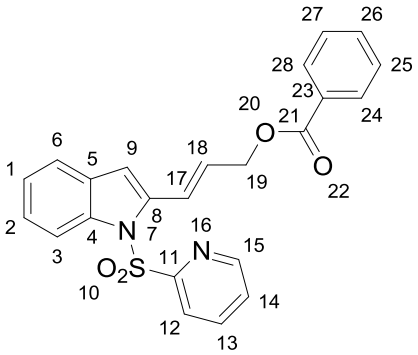


128

R_f = 0.5 (2: 3 EtOAc : petrol); IRυ_{max} 3072 (aromatic), 1721 (C=O), 1583 (aromatic), 1451 (aromatic), 1360 (C-O), 1250 (C-O), 1111 (C-O) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 8.06 (d, 2H, *J* = 7.5 Hz, H-8, 12), 7.55 (br t, 1H, *J* = 7.5 Hz, H-10), 7.43 (br t, 2H, *J* = 7.5 Hz, H-9, 11), 6.04 (ddt, 1H, *J* = 17.2, 10.6, 5.6 Hz, H-2), 5.41 (dd, 1H, *J* = 17.2, 1.2 Hz, H-1), 5.28 (dd, 1H, *J* =10.6, 1.2 Hz, H-1), 4.82 (d, 2H, *J* = 5.6 Hz, H-3); ^{13}C NMR (150 MHz, $CDCl_3$) 166.4 (C=O), 133.1 (CH), 132.4 (CH), 130.2 (C_q), 129.7 (2 × CH), 128.5 (2 × CH), 118.3 (CH_2), 65.7 (CH_2).

(*E*)-3-(1-(Pyridin-2-ylsulfonyl)-1H-indol-2-yl)allyl benzoate (129)

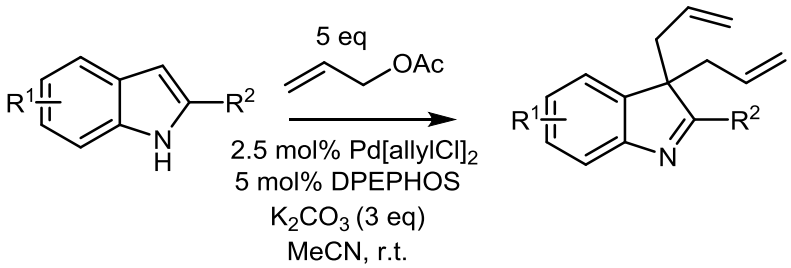
To an oven dried carosuel tube under an atmosphere of argon *N*-(2-pyridyl)sulfonylindole (0.39 mmol, 100 mg), $PdCl_2(CH_3CN)_2$ (20 mol%, 21 mg) and $Cu(OAc)_2.H_2O$ (0.78 mmol, 168 mg) was added in dry THF (4 ml) with allyl benzoate (1.12 mmol, 0.12 ml, 2 eq.), To the reaction mixture at 60°C for 52 hrs. Product was extracted from EtOAc and washed with water twice, dried, filtered and concentrated to give a yellow brown oil (154 mg). Crude mixture was purified by flash chromatography (0-50% EtOAc: petrol) to give a pale yellow viscous oil (57 mg, 35%).



129

R_f = 0.34 (1 :1 EtOAc : petrol); IRυ $_{max}$ 3407 (aromatic), 2254 (C-H), 1602 (C=O), 1450 (aromatic), 1378 (SO_2-N), 1181 (S=O), 1151 (SO_2–N), 1124 (S=O), 1070 (C-O) cm^{-1} ; δ ^{1}H NMR (600 MHz, $CDCl_3$) 8.50 (ddd, 1H, *J* = 4.6, 1.7, 1.0 Hz, H-15), 8.15 (dq, 1H, *J* = 8.2, 1.0, H-3), 8.13 (m, 2H, H-24, 28), 8.00 (dt, 1H, *J* = 7.8, 1.0 Hz, H-12), 7.78 (td, 1H, *J* = 7.8, 1.7 Hz, H-13), 7.59 (tt, 1H, *J* = 7.4, 1.4 Hz, H-26), 7.50 (dtd, 1H, *J* = 15.9, 1.4, 0.8 Hz, H-17), 7.47 (m, 3H, H-6, 25, 27), 7.38 (ddd, 1H, *J* = 7.8, 4.6, 1.1 Hz, H-14), 7.28 (td, 1H, *J* = 8.2, 1.4 Hz, H-2), 7.22 (ddd, 1H, *J* = 8.2, 7.3, 1.0 Hz, H-1), 6.80 (s, 1H, H-9), 6.37 (dt, 1H, *J* = 15.9, 6.1 Hz, H-18), 5.03 (dd, 2H, *J* = 6.1, 1.4 Hz, H-19); δ ^{13}C NMR (150 MHz, $CDCl_3$) 166.4 (C_q), 155.8 (C_q), 150.5 (CH), 138.8 (C_q), 138.1 (CH), 137.4 (C_q), 133.3 (CH), 130.2 (C_q), 129.8 (2 × CH), 129.6 (C_q), 128.6 (2 × CH), 127.7 (CH), 127.4 (CH), 125.0 (CH), 124.1 (d, *J* = 6.5 Hz, CH), 122.3 (CH), 120.9 (CH), 115.0 (CH), 108.8 (CH), 65.1 (CH_2); HRMS (CI) $C_{23}H_{19}N_2O_4S$ $[M+H]^+$ 419.09873 found, 419.10532.

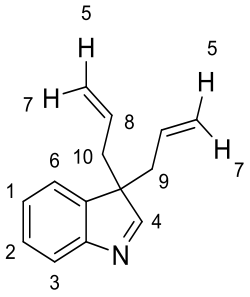
Synthesis of substituted 3,3-diallyl-3*H*-indole



General procedure F: To an oven dried carousel tube under an atmosphere of argon were added $[Pd(allylCl)_2]_2$ (2.5 mol%) and DPEPhos (5 mol%) in MeCN (0.025M) at r.t. After stirring for 15 mintues, allyl acetate (5 eq) was added to the reaction.

Potassium carbonate (3 eq), the substituted indole (1 eq) were added 5 minutes later. The reaction mixture was degassed and stirred overnight under argon. Then diethyl ether was added to the reaction mixture (7 ml) and washed with water (10 ml), dried with $MgSO_4$, filtered and concentrated. Purification by dry load flash chromatography gave the corresponding substituted 3,3-diallyl-3*H*-indole compound.

3,3-Diallyl-3*H*-indole (138a)[182]

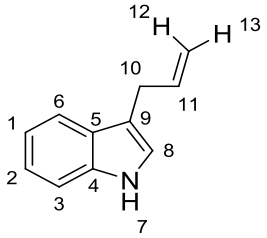


138a

The crude material was purified by gradient method 10% EtOAc: PE to give the title compound as a brown oil (70 mg, 82%). R_f = 0.64 (1:1 EtOAc : PE); IRυ $_{max}$ 3074 (=C-H), 2978 (C-H), 1600 (N=CH), 1559 (aromatic), 1475 (aromatic) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 8.05 (brs, 1H, H-4), 7.62 (d, 1H, *J* = 7.1 Hz, H-3), 7.35 (td, 1H, *J* = 7.1, 1.1 Hz, H-2), 7.31 (brd, 1H, *J* = 7.1 Hz, H-6), 7.26 (br t, 1H, *J* = 7.1 Hz, H-1), 5.44 (ddt, 2H, *J* = 17.1, 10.1, 7.3 Hz, H-8), 5.01 (dd, 2H, *J* = 17.1, 1.1 Hz, H-7), 4.95 (dd, 2H, *J* = 10.1, 1.1 Hz, H-5), 2.57 (dd, 2H, *J* = 13.9, 7.3 Hz, H-10 and 9), 2.52 (dd, 2H, *J* = 13.9, 7.3 Hz, H-10 and 9); δ ^{13}C NMR (150 MHz, $CDCl_3$) 177.9 (CH), 155.6 (C_q), 141.4 (C_q), 132.5 (2 × CH), 128.0 (CH), 126.1 (CH), 122.4 (CH), 121.3 (CH), 118.8 (2 × $=CH_2$), 60.9 (C_q), 38.6 (2 × CH_2); HRMS (CI) cald. for $C_{14}H_{15}N$ $[M]^+$ 197.12045, found 197.11946.

3-Allyl-1*H*-indole (139) [207, 208]

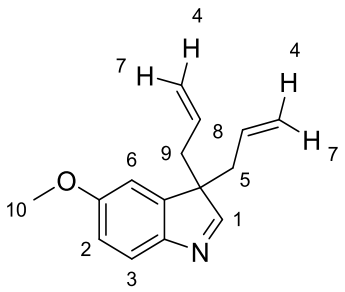
Method F: Using dppf (5 mol%) instead of DPEPhos. Purification by dry load flash chromatography method 10% EtOAc: Petrol to give the title compound as a brown oil (20 mg, 30%).



139

R_f = 0.74 (3 : 7 EtOAc : Petrol); IRυ $_{max}$ 3056 (=C-H), 2980 (C-H), 2895 (N-H), 1628 (C=C), 1488 (aromatic), 1345 (CH_2), 1253 (N-C), 1052 (N-C) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.61 (d, 1H, *J* = 7.7 Hz, H-6), 7.36 (d, 1H, *J* = 7.7 Hz, H-3), 7.20 (td, 1H, *J* = 7.7, 0.8 Hz, H-2), 7.12 (td, 1H, *J* = 7.7, 0.8 Hz, H-1), 6.99 (br s, 1H, H-8), 5.17 (ddt, 1H, *J* = 17.1, 10.1, 6.8 Hz, H-11), 5.17 (dq, 1H, *J* = 17.1, 1.7 Hz, H-12), 5.08 (dq, 1H, *J* = 10.1, 1.7 Hz, H-13), 3.53 (dq, 2H, *J* = 6.8, 1.2 Hz, H-10); δ ^{13}C NMR (150 MHz, $CDCl_3$) 137.5 (CH), 136.5 (C_q), 127.6 (C_q), 121.8 (CH), 119.4 (CH), 119.2 (CH), 114.7 (C_q), 111.2 (CH), 115.2 (=CH_2), 30.0 (CH_2).

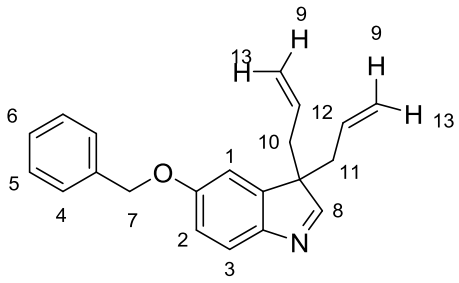
3,3-Diallyl-5-methoxy-3*H*-indole (138b)



138b

The crude material was purified by gradient method 0-20% EtOAc: PE which gave the title compound as a yellow oil (233 mg, 76%). R_f = 0.22 (1 : 4 EtOAc : PE); IRυ $_{max}$ 3074 (=C-H), 2921 (C-H), 1591 (N=C), 1500 (aromatic), 1437 (aromatic), 1264 (C-O) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.91 (s, 1H, H-1), 7.51 (d, 1H, *J* = 8.3 Hz, H-3), 6.86 (dd, 1H, *J* = 8.3, 2.2 Hz, H-2), 6.84 (d, 1H, *J* = 2.2 Hz, H-6), 5.45 (ddt, 2H, *J* = 17.0, 10.1, 7.2 Hz, H-8), 5.02 (dq, 2H, *J* = 17.0, 1.1 Hz, H-7), 4.96 (dd, 2H, *J* = 10.1, 1.1 Hz, H-4), 3.84 (s, 3H, H-10), 2.54 (ddt, 2H, *J* = 13.9, 7.2, 1.1 Hz, H-9 and 5), 2.49 (ddt, 2H, *J* = 13.9, 7.2, 1.1 Hz, H-9 and 5); δ ^{13}C NMR (150 MHz, $CDCl_3$) 175.8 (CH), 158.6 (C_q), 149.4 (C_q), 143.2 (C_q), 132.5 (2 × CH), 121.6 (CH), 118.8 (2 × $=CH_2$), 112.4 (CH), 109.2 (CH), 61.0 (C_q), 55.9 (CH_3), 38.8 (2 × CH_2); HRMS (EI) cald. for $C_{15}H_{17}NO$ $[M]^+$ 227.13101, found 227.130326.

3,3-Diallyl-5-benzyloxy-3*H*-indole (138c)

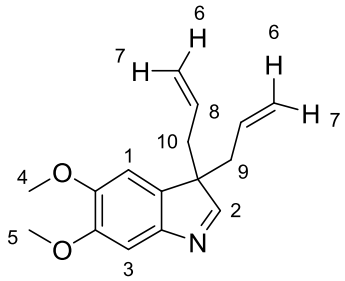


138c

Purification of crude mixture by gradient method 0-30% EtOAc: PE which gave the title compound as a purple oil (196 mg, 76%). R_f = 0.29 (1:4 EtOAc : PE); IRυ $_{max}$ 3076 (=C-H), 2910 (C-H), 1590 (N=C), 1580 (aromatic), 1575 (aromatic), 1181 (C-O), 1022 (C-O) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.92 (s, 1H, H-8), 7.52 (d, 1H, *J* = 8.4 Hz, H-3), 7.45 (br d, 2H, *J* = 7.3 Hz, H-4), 7.40 (t, 2H, *J* = 7.3 Hz, H-5), 7.34 (td, 1H, *J* = 7.3, 1.4 Hz, H-6), 6.95 (dd, 1H, *J* = 8.4, 2.5 Hz, H-2), 6.92 (d, 1H, *J* = 2.5 Hz, H-1), 5.43 (ddt, 2H, *J* = 17.1, 10.5, 7.4 Hz, H-12), 5.08 (s, 2H, H-7), 5.00 (dq, 2H, *J* = 17.1, 1.4 Hz, H-13), 4.96 (br d, 2H, *J* = 10.5 Hz, H-9), 2.53 (dd, 2H, *J* = 14.1, 7.4 Hz, H-10 and 11), 2.48 (dd, 2H, 14.1, 7.4 Hz, H-10 and 11); δ ^{13}C NMR (150 MHz, $CDCl_3$) 175.9 (CH), 157.7 (C_q), 149.5 (C_q), 143.2 (C_q), 137.0 (C_q), 132.4 (2 × CH), 128.7 (2 × CH), 128.2 (CH), 127.7 (2 × CH), 121.6 (CH), 118.9 (2 ×

=CH_2), 113.6 (CH), 110.2 (CH), 70.7 (CH_2), 61.1 (C_q), 38.8 (2 × CH_2); HRMS (EI) cald. for $C_{21}H_{21}NO$ $[M]^+$ 303.1623 found, 303.1612.

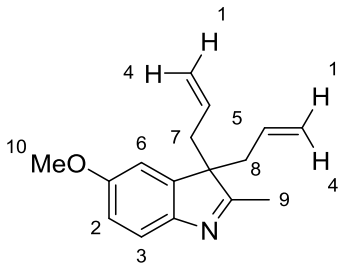
3,3-Diallyl-5,6-dimethoxy-3*H*-indole (138d)



138d

Purification of crude mixture by gradient method 0-20% EtOAc: PE which gave the title compound as a yellow oil (169 mg, 88%). R_f = 0.44 (1: 4 EtOAc : PE); IRυ $_{max}$ 3075 (=C-H), 2938 (C-H), 1600 (N=C), 1465 (aromatic), 1442 (aromatic), 1305 (C-O), 1214 (C-O) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.94 (s, 1H, H-8), 7.20 (s, 1H, H-3), 6.81 (s, 1H, H-1), 5.42 (ddt, 2H, *J* = 17.0, 10.2, 7.3 Hz, H-8), 5.00 (dq, 2H, *J* = 17.0, 1.1 Hz, H-7), 4.95 (dq, 2H, *J* = 10.2, 1.1 Hz, H-6), 3.92 (s, 3H, H-5), 3.90 (s, 3H, H-4), 2.53 (ddt, 2H, *J* = 13.9, 7.3, 1.1 Hz, H-10 and 9), 2.48 (dtd, 2H, *J* = 13.9, 7.3, 1.1 Hz, H-10 and 9); δ ^{13}C NMR (150 MHz, $CDCl_3$) 176.8 (CH), 149. 1 (C_q), 148.8 (C_q), 148.0 (C_q), 133.3 (C_q), 132.6 (2 × CH), 118.7 (2 × =CH_2), 105.6 (CH), 104.9 (CH), 61.3 (C_q), 56.5 (CH_3), 56.2 (CH_3), 38.8 (2 × CH_2); HRMS (CI) cald. for $C_{16}H_{20}NO_2$ $[M + H]^+$ 258.1415, found 258.1484.

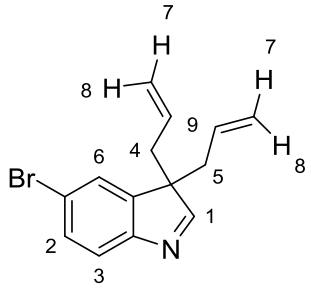
3,3-Diallyl-5-methoxy-2-methyl-3*H*-indole (138e)



138d

Purification of crude mixture by gradient method 0-10% EtOAc: PE which gave the title compound as a yellow oil (173 mg, 80%). R_f = 0.33 (3: 7 EtOAc: PE); IRυ $_{max}$ 2919 (C-H), 1581 (N=C), 1471 (aromatic), 1266 (C-O) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.40 (dd, 1H, *J* = 7.2, 1.8 Hz, H-3), 6.83 (dd, 1H, *J* = 7.2, 2.5 Hz, H-2), 6.82 (s, 1H, H-6), 5.12 (ddt, 2H, *J* = 16.9, 10.1, 7.0 Hz, H-5), 4.96 (dq, 2H, *J* = 16.9, 1.4 Hz, H-4), 4.85 (dq, 2H, *J* = 10.1, 1.2 Hz, H-1), 3.83 (s, 3H, H-10), 2.64 (ddt, 2H, *J* = 13.9, 7.0 Hz, H-8 and 7), 2.44 (ddt, 2H, *J* = 13.9, 7.0 Hz, H-8 and 7), 2.21 (s, 3H, H-9); δ ^{13}C NMR (150 MHz, $CDCl_3$) 183.0 (C_q), 157.9 (C_q), 148.8 (C_q), 143.0 (C_q), 132.3 (2 × CH), 120.1 (CH), 118.2 (2 × $=CH_2$), 112.2 (CH), 109.2 (CH), 61.9 (C_q), 55.8 (CH_3), 40.5 (2 × CH_2), 16.6 (CH_3); HRMS (ES) cald. for $C_{16}H_{18}NO$ $[M - H]^-$ 240.1388, found 240.1376.

3,3-Diallyl-5-bromo-3*H*-indole (138f)

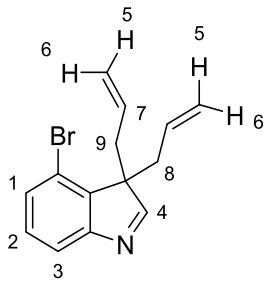


138f

Reaction conducted at 50 °C for 8 hrs. The crude mixture was purified by gradient method 0-20% EtOAc: PE which gave the title compound as a brown oil (123 mg, 58%). R_f = 0.36 (3 : 7 EtOAc : PE); IRυ $_{max}$ 3076 (=C-H), 2911 (C-H), 1719 (N=C),

1596 (aromatic), 1435 (aromatic) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 8.02 (s, 1H, H-1), 7.48 (s, 2H, H-3, 2), 7.44 (s, 1H, H-6), 5.43 (ddt, 2H, *J* = 17.2, 10.1, 7.3 Hz, H-9), 5.03 (dq, 2H, *J* = 17.2, 1.5 Hz, H-8), 4.99 (dq, 2H, *J* = 10.1, 1.5 Hz, H-7), 2.55 (dd, 2H, *J* = 14.1, 7.3 Hz, H-5 and 4), 2.50 (dd, 2H, *J* = 14.1, 7.3 Hz, H-5 and 4); δ ^{13}C NMR (150 MHz, $CDCl_3$) 178.4 (CH), 154.7 (C_q), 143.7 (C_q), 131.9 (2 × CH), 131.2 (CH), 125.8 (CH), 122.7 (CH), 120.2 (C_q), 119.4 (2 × $=CH_2$), 61.5 (C_q), 38.4 (2 × CH_2); HRMS (ES) Cald. for $C_{14}H_{13}NBr$ $[M-H]^-$ 274.0232, found 274.0231.

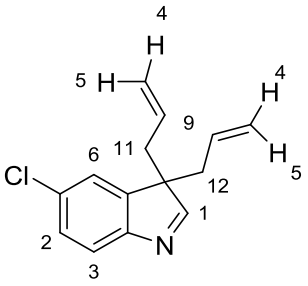
3,3-Diallyl-4-bromo-3*H*-indole (138g)



138g

Reaction conducted at 50 °C for 24 hrs. The crude mixture was purified by gradient method 0-10% EtOAc: PE which gave the title compound as a light purple oil (159 mg, 56%) from 4-bromo indole (200 mg). R_f = 0.41 (1:4 EtOAc : PE); IRυ $_{max}$ 3077 (=C-H), 2979 (C-H), 1641 (N=C), 1574 (aromatic), 719 cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 8.02 (s, 1H, H-4), 7.53 (d, 1H, *J* =7.7 Hz, H-3 or 1), 7.36 (d, 1H, *J* = 7.7 Hz, H-3 or 1), 7.21 (t, 1H, *J* = 7.7 Hz, H-2), 5.24 (ddt, 2H, *J* = 16.9, 10.2, 7.7 Hz, H-7), 5.02 (d, 2H, *J* = 16.9 Hz, H-6), 4.85 (d, 2H, *J* = 10.2 Hz, H-5), 2.99 (dd, 2H, *J* = 13.9, 7.7 Hz, H-9 and 8), 2.78 (dd, 2H, *J* = 13.9, 7.7 Hz, H-9 and 8); δ ^{13}C NMR (150 MHz, $CDCl_3$) 178.7 (CH), 157.8 (C_q), 138.9 (C_q), 131.8 (2 × CH), 130.2 (CH), 129.8 (CH), 120.4 (CH), 118.6 (2 × $=CH_2$), 118.0 (C_q), 64.7 (C_q), 36.2 (2 × CH_2); HRMS (EI) cald. for $C_{14}H_{14}NBr$ $[M]^+$ 275.0309, found 275.0302.

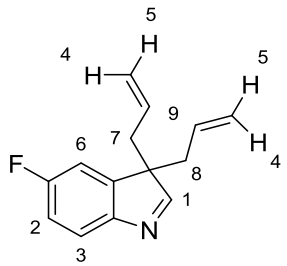
3,3-Diallyl-5-chloro-3*H*-indole (138h)



138h

Purification of crude mixture by gradient method 0-10% EtOAc : PE to give the title compound as a pale yellow oil (126 mg, 41%). R_f = 0.21 (1: 4 EtOAc : PE); IRυ $_{max}$ 3055 (=C-H), 2954 (C-H), 1640 (N=C), 1555 (aromatic), 1447 cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 8.03 (s, 1H, H-1), 7.53 (d, 1H, *J* = 8.3 Hz, H-3), 7.32 (dd, 1H, *J* = 8.3, 2.1 Hz, H-2), 7.28 (d, 1H, *J* = 2.1 Hz, H-6), 5.43 (ddt, 2H, *J* = 17.0, 10.1, 7.2 Hz, H-9), 5.03 (dq, 2H, *J* = 17.0, 1.0 Hz, H-5), 5.00 (br dd, 2H, *J* = 10.1, 1.0 Hz, H-4), 2.56 (dd, 2H, *J* = 13.7, 7.2 Hz, H-12 and 11), 2.51 (dd, 2H, *J* = 13.7, 7.2 Hz, H-11 and 12); δ ^{13}C NMR(150 MHz, $CDCl_3$) 178.2 (CH), 154.2 (C_q), 143.3 (C_q), 132.1 (C_q), 131.9 (CH), 128.3 (CH), 122.9 (CH), 122.2 (CH), 119.3 (2 × $=CH_2$), 61.5 (C_q), 38.2 (2 × CH_2); HRMS (CI) cald. for $C_{14}H_{15}ClN$ $[M+H]^+$ 232.0815, found 232.0877.

3,3-Diallyl-5-flouro-3*H*-indole (138i)

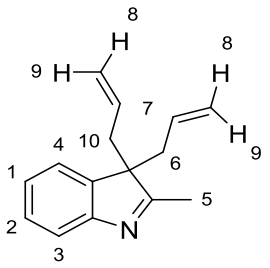


138i

Purification of crude mixture by gradient method 0-20% EtOAc: PE to give the title compound as a red-brown oil (101 mg, 32%). R_f = 0.4 (3 : 7 EtOAc : PE); IRυ $_{max}$ 3010 (=C-H), 2928 (C-H), 1597 (N=C), 1460 (aromatic), 1165 cm^{-1}; δ ^{1}H NMR (600

MHz, $CDCl_3$) δ 7.99 (s, 1H, H-1), 7.53 (dd, 1H, *J* = 8.4, 4.6 Hz, H-3), 7.02 (dd, 1H, *J* = 8.4, 2.8 Hz, H-2), 6.99 (dd, 1H, *J* = 8.0, 2.8 Hz, H-6), 5.41 (dtd, 2H, *J* = 17.1, 10.0, 7.5 Hz, H-9), 5.00 (dd, 2H, *J* = 17.1, 1.3 Hz, H-4), 4.96 (br d, 2H, *J* = 10.0 Hz, H-5), 2.53 (dd, 2H, *J* = 14.0, 7.5 Hz, H- 8 and 7), 2.48 (dd, 2H, *J* = 14.0, 7.5 Hz, H-8 and 7); δ ^{13}C NMR (150 MHz, $CDCl_3$) 177.7 (CH), 161.7 (d, J_{C-F} = 245.8 Hz, C_q), 151.5 (d, J_{C-F} = 2.1 Hz, C_q), 143.6 (d, J_{C-F} = 8.7 Hz, C_q), 132.0 (2 × CH), 122.0 (d, J_{C-F} = 9.1 Hz, CH), 119.2 (2 × $=CH_2$), 114.7 (d, J_{C-F} = 23.7 Hz, CH), 110.2 (d, J_{C-F} = 24.6 Hz, CH), 61.6 (C_q), 38.5 (2 × CH_2); HRMS (CI) cald. for ($C_{14}H_{15}NF$) $[M+H]^+$ 216.1189, found 216.1187.

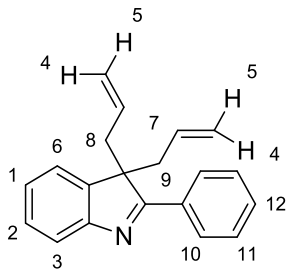
3,3-Diallyl-2-methyl-3*H*-indole (138j)[182]



138j

Crude mixture was purified by flash column chromatography 20% EtOAc: PE which gave the title compound as a yellow oil (290 mg, 98%). R_f = 0.60 (3: 7 EtOAc: PE); IRυ $_{max}$ 3077 (=C-H), 2916 (C-H), 1640 (N=C), 1457 (aromatic) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.51 (d, 1H, *J* = 7.4 Hz, H-3), 7.31 (t, 1H, *J* = 7.4 Hz, H-2), 7.26 (d, 1H, *J* = 7.4 Hz, H-4), 7.19 (t, 1H, *J* = 7.4 Hz, H-1), 5.10 (ddt, 2H, *J* = 16.7, 9.9, 7.1 Hz, H-7), 4.95 (br d, 2H, *J* = 16.7 Hz, H-9), 4.84 (br d, 2H, *J* = 9.9 Hz, H-8), 2.68 (dd, 2H, *J* = 14.0, 7.1 Hz, H-10 and 6), 2.45 (dd, 2H, *J* = 14.0, 7.1 Hz, H-10 and 6), 2.25 (s, 3H, H-5); δ ^{13}C NMR (150 MHz, $CDCl_3$) 185.2 (C_q), 155.2(C_q), 141.2 (C_q), 132.2 (2 × CH), 128.0 (CH), 125.1 (CH), 122.3 (CH), 120.0 (CH), 118.2 (2 × $=CH_2$), 61.9 (C_q), 40.5 (2 × CH_2), 16.7 (CH_3); HRMS (ES) cald. for $C_{15}H_{16}N$ $[M-H]^-$ 210.1282, found 210.1273.

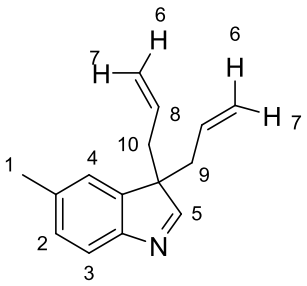
3,3-Diallyl-2-phenyl-3*H*-indole (138k)



138j

Crude mixture was purified by gradient method 0-20% EtOAc: PE which gave the title compound as a colourless oil (232 mg, 74%). R_f = 0.63 (1 : 4 EtOAc : PE); IRυ $_{max}$ 3075 (=C-H), 2924 (C-H), 1640 (N=C), 1522 (aromatic), 1443 (aromatic) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.11 (m, 2H, H-10), 7.66 (d, 1H, *J* = 7.5 Hz, H-3), 7.48 (m, 3H, H-12, 11), 7.37 (td, 1H, *J* = 7.5, 1.0 Hz, H-2), 7.34 (d, 1H, *J* = 7.5 Hz, H-6), 7.28 (d, 1H, *J* = 7.5 Hz, H-1), 5.11 (ddt, 2H, 17.2, 9.8, 7.2 Hz, H-7), 4.76 (br d, 2H, *J* = 17.2 Hz, H-4), 4.72 (br d, 2H, *J* = 9.8 Hz, H-5), 2.92 (dd, 2H, *J* = 14.1, 7.2 Hz, H-9 and 8), 2.88 (dd, 2H, *J* = 14.1, 7.2 Hz, H-9 and 8); δ ^{13}C NMR (150 MHz, $CDCl_3$) 180.4 (C_q), 154.6 (C_q), 143.1 (C_q), 134.1 (C_q), 132.0 (2 × $=CH_2$), 130.7 (CH), 128.7 (2 × CH), 128.2 (2 × CH), 128.1 (CH), 125.8 (CH), 121.8 (CH), 120.9 (CH), 118.3 (2 × CH), 62.5 (C_q), 42.0 (2 × CH_2); HRMS (CI) cald. for $C_{20}H_{20}N$ [M + H]$^+$ 274.1599, found 274.1571.

3, 3-Diallyl-5-methyl-3*H*-indole (138l)

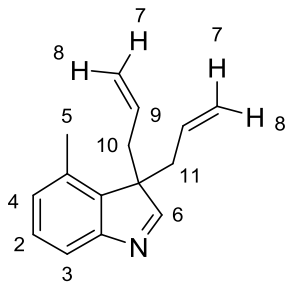


138l

Purification of crude mixture by gradient method 0-10% EtOAc: PE which gave the title compound as a brown oil (212 mg, 66%). R_f = 0.49 (1 : 4 EtOAc : PE); IRυ $_{max}$

3077 (=C-H), 2921 (C-H), 1640 (N=C), 1556 (aromatic), 1465 (aromatic) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.97 (s, 1H, H-5), 7.49 (d, 1H, *J* = 7.9 Hz, H-3), 7.14 (dd, 1H, *J* = 7.9, 1.3 Hz, H-2), 7.11 (d, 1H, *J* = 1.3 Hz, H-4), 5.44 (ddt, 2H, *J* = 17.1, 10.2, 7.3 Hz, H-8), 5.01 (dq, 2H, *J* = 17.1, 1.4 Hz, H-7), 4.96 (dd, 2H, *J* = 10.2, 1.4 Hz, H-6), 2.54 (ddt, 2H, *J* = 14.0, 7.3, 1.4 Hz, H-10 and 9), 2.49 (ddt, 2H, *J* = 14.0, 7.3, 1.4 Hz, H-10 and 9), 2.41 (s, 3H, H-1); δ ^{13}C NMR (150 MHz, $CDCl_3$) 176.9 (CH), 153.5 (C_q), 141.7 (C_q), 136.0 (C_q), 132.6 (2 × CH), 128.7 (CH), 123.1 (CH), 120.8 (CH), 118.7 (2 × $=CH_2$), 60.9 (C_q), 38.8 (2 × CH_2), 21.2 (CH_3); HRMS (EI) $C_{15}H_{17}N$ $[M]^+$ 211.1355, found 211.1349.

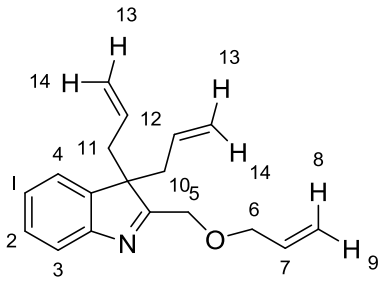
3,3-Diallyl-4-methyl-3*H*-indole (138m)



138m

Purification of crude mixture by gradient method 30% EtOAc: PE which gave the title compound as a purple oil (185 mg, 57%). R_f = 0.47 (1: 4 EtOAc : PE); IRυ $_{max}$ 3076 (=C-H), 2921 (C-H), 1640 (N=C), 1558 (aromatic), 1439 (aromatic) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 8.04 (s, 1H, H-6), 7.16 (m, 2H, H-4, 3), 7.12 (m, 1H, H-2), 5.45 (ddt, 2H, *J* = 17.2, 10.0, 7.3 Hz, H-9), 5.01 (dq, 2H, *J* = 17.2, 1.4 Hz, H-8), 4.96 (dq, 2H, *J* = 10.0, 1.4 Hz, H-7), 2.59 (s, 3H, H-5), 2.55 (ddt, 2H, *J* = 14.0, 7.3, 1.4 Hz, H-10 and 11), 2.49 (ddt, 2H, *J* = 14.0, 7.3, 1.4 Hz, H-10 and 11); δ ^{13}C NMR (150 MHz, $CDCl_3$) 176.7 (CH), 154.1 (C_q), 141.4 (C_q), 132.7 (2 × CH), 130.9 (C_q), 129.4 (CH), 126.1 (CH), 119.8 (CH), 118.7 (2 × $=CH_2$), 61.1 (C_q), 38.7 (2 × CH_2), 17.0 (CH_3); HRMS (CI) cald. for $C_{15}H_{18}N$ $[M + H]^+$ 212.1361, found 212.1446.

3,3-diallyl-2-((allyloxy)methyl)-3H-indole (140)

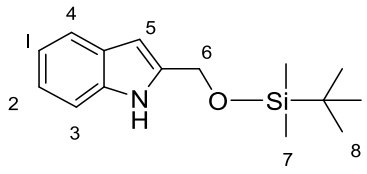


148

Purification by dry load flash chromatography gradient method 0-30% EtOAc: Petrol gave the title compound as an orange yellow oil (108 mg, 30%) from 2-methanol indole (200 mg). R_f = 0.23 (3 : 7 EtOAc : Petrol); IRυ $_{max}$ 3070 (C-H), 2913 (C-H), 1714 (N=C), 1469 (aromatic), 1276 (C-O) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.59 (d, 1H, *J* = 7.3 Hz, H-3), 7.32 (td, 1H, *J* = 7.3, 0.9 Hz, H-2), 7.27 (d, 1H, *J* = 7.3 Hz, H-4), 7.23 (td, 1H, *J* = 7.3, 0.9 Hz, H-1), 5.98 (dtd, 1H, *J* = 16.8, 10.4, 5.7 Hz, H-7), 5.34 (dq, 1H, *J* = 16.8, 1.7 Hz, H-8), 5.25 (dq, 1H, *J* = 10.4, 1.7 Hz, H-9), 5.17 (dtd, 2H, *J* = 17.0, 9.9, 7.4 Hz, H-12), 4.94 (dq, 2H, *J* = 17.0, 1.3 Hz, H-14), 4.84 (br d, 2H, *J* = 9.9 Hz, H-13), 4.51 (s, 2H, H-5), 4.16 (dt, 2H, *J* = 5.7, 1.5 Hz, H-6), 2.70 (dd, 2H, *J* = 14.0, 7.4 Hz, H-11 or 10), 2.64 (dd, 2H, *J* = 14.0, 7.4 Hz, H-11 or 10); δ ^{13}C NMR (150 MHz, $CDCl_3$) 183.4 (C_q), 154.7 (C_q), 141.9 (C_q), 134.4 (CH), 132.4 (2 × CH), 128.0 (CH), 125.7 (CH), 122.1 (CH), 120.8 (CH), 118.3 (2 × $=CH_2$), 117.8 ($=CH_2$), 72.6 (CH_2), 68.5 (CH_2), 62.0 (C_q), 40.5 (2 × CH_2); HRMS (CI) cald. for $C_{12}H_{13}NO$ $[M + Na]^+$ 198.2420, found 198.1274.

2-(((*tert*-butyldimethylsilyl)oxy)methyl)-1*H*-indole (127p)[209]

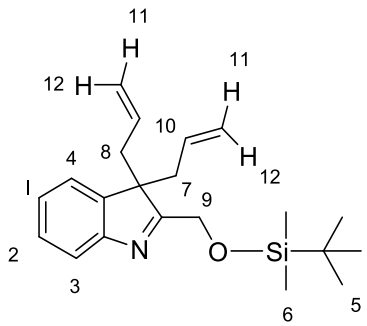
To an oven dry flask purged with argon, were added indole-2-methanol (250 mg, 1.7 mmol), NEt_3 (0.71 ml, 5.1 mmol, 3 eq) and TBSCl (384 mg, 2.5 mmol, 1.5 eq) in CH_2Cl_2 (2 ml). The reaction mixture was stirred for 4 hrs at r.t. Organic layer was washed with saturated solution of sodium hydrogen carbonate (2 × 20 ml), water (15 ml) and brine (15 ml).



127p

Flash chromatography gradient method 0-10% EtOAc: PE gave the title compound as orange brown oil (254 mg, 57%). R_f = 0.63 (1 : 4 EtOAc: PE); IRυ $_{max}$ 3015 (C-H), 2928 (C-H), 2857 (N-H), 1457 (aromatic), 1255, 1074 cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 8.29 (s, 1H, NH), 7.56 (d, 1H, *J* = 7.8 Hz, H-3), 7.37 (d, 1H, *J* = 7.8 Hz, H-4), 7.16 (td, 1H, *J* = 7.8, 1.1 Hz, H-1), 7.08 (td, 1H, *J* = 7.8, 1.1 Hz, H-2), 6.31 (s, 1H, H-5), 4.87 (s, 2H, H-6), 0.93 (s, 9H, H-8), 0.12 (s, 6H, H-7); δ ^{13}C NMR (150 MHz, $CDCl_3$) 138.3 (C_q), 136.0 (C_q), 128.5 (C_q), 121.7 (CH), 120.5 (CH), 119.8 (CH), 110.9 (CH), 98.9 (CH), 59.4 (CH_2), 26.0 (-$C(CH_3)_3$), 18.5 (C_q), -5.17 (-$Si(CH_3)_2$).

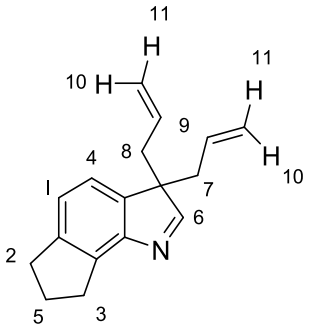
3,3-Diallyl-2-(((tert-butyldimethylsilyl)oxy)methyl)-3*H*-indole (138n)



138n

Purification of crude mixture by gradient method 0-10% EtOAc: PE which gave the title compound as an orange yellow oil (172 mg, 66%). R_f = 0.80 (1: 4 EtOAc : PE); IRυ $_{max}$ 3015 (=C-H), 2929 (C-H), 1693 (N=C), 1501 (aromatic), 1490 (aromatic), 1254, 1090 cm^{-1}; δ ^{1}H (600 MHz, $CDCl_3$) 7.52 (d, 1H, *J* = 7.5 Hz, H-3), 7.25 (td, 1H, *J* = 7.5, 1.3 Hz, H-2), 7.25 (d, 1H, *J* = 7.5 Hz, H-4), 7.21 (td, 1H, *J* = 7.5, 1.3 Hz, H-1), 5.18 (ddt, 2H, *J* = 17.0, 9.9, 7.2 Hz, H-10), 4.91 (dq, 2H, *J* = 17.0, 1.9 Hz, H-12), 4.80 (dq, 2H, *J* = 9.9, 1.9 Hz, H-11), 4.77 (s, 2H, H-9), 2.84 (ddt, 2H, *J* = 13.5, 7.2, 1.1 Hz, H-8 and 7), 2.71 (ddt, 2H, *J* = 13.6, 7.2, 1.1 Hz, H-8 and 7), 0.97 (s, 9H, H-5), 0.17 (s, 6H, H-6); δ ^{13}C (150 MHz, $CDCl_3$) 185.5 (C_q), 154.5 (C_q), 142.3 (C_q), 132.9 (2 × CH), 127.9 (CH), 125.6 (CH), 122.1 (CH), 120.5 (CH), 117.9 (2× =CH_2), 64.3 (CH_2), 62.7 (C_q), 40.4 (2 × CH_2), 26.4 (-$C(CH_3)_3$), 18.6 (C_q), -5.6 (-$Si(CH_3)_2$); HRMS (CI) cald. for ($C_{15}H_{16}NO$) [M-SiC_7H_{16}]$^-$ 226.3070, found 226.1226.

3,3-Diallyl-3,6,7,8-tetrahydrocyclopenta-indole (138o)



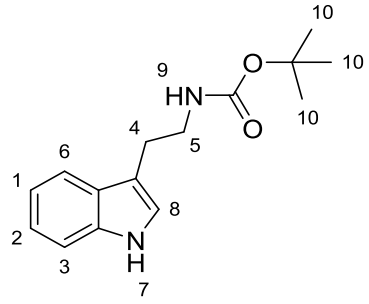
138o

Purification of crude mixture by gradient method 0-20% EtOAc: PE which gave a yellow oil (152 mg, 50%); R_f = 0.31 (1:4 EtOAc: PE); IRυ $_{max}$ 3078 (C-H), 2951 (C-H), 1639 (N=C), 1553 (aromatic), 1438 (aromatic) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 8.03 (br s, 1H, H-6), 7.12 (d, 1H, *J* = 7.5 Hz, H-4), 7.08 (d, 1H, *J* = 7.5 Hz, H-1), 5.47 (ddt, 2H, *J* = 17.1, 10.0, 7.2 Hz, H-9), 5.02 (dd, 2H, *J* = 17.1, 1.2 Hz, H-10), 4.96 (d, 2H, *J* = 10.0 Hz, H-11), 3.19 (t, 2H, *J* = 7.5 Hz, H-3), 2.96 (t, 2H, *J* = 7.5 Hz, H-2), 2.70 (dd, 2H, *J* = 13.4, 7.2 Hz, H-8 and 7), 2.49 (dd, 2H, *J* = 13.8, 7.2 Hz, H-8 and 7), 2.16 (quintet, 2H, *J* = 7.2 Hz, H-5); δ ^{13}C NMR (150 MHz, $CDCl_3$) 177.8 (CH), 151.4 (C_q), 145.4 (C_q), 139.4 (C_q), 136.6 (C_q), 132.8 (2 × CH), 122.7

(CH), 120.1 (CH), 118.6 (2 × $=CH_2$), 60.6 (C_q), 38.9 (2 × CH_2), 33.0 (CH_2), 30.0 (CH_2), 25.7 (CH_2); HRMS (CI) $C_{17}H_{20}N$ $[M+H]^+$ 238.1595, found 238.1590.

Tert-butyl (2-(1H-indol-3-yl)ethyl)carbamate (149)[190, 210]

To a solution of tryptamine (200 mg, 1.24 mmol) in $CHCl_3$ (2 ml) and a saturated aqueous solution of sodium carbonate (5 ml) in an ice bath, was added acid anhydride (0.14 ml, 1.49 mmol, 1.2 eq) dissolved in chloroform (1 ml) and was left to stir for 2 hrs. Organic layer was washed with 10% HCl (15 ml), water (15 ml) and brine (15 ml) and dried with $MgSO_4$, filtered and evaporated. Purification by dry load flash column in a light brown oil (251 mg, 78%).

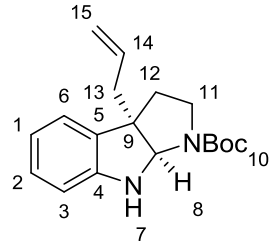


149

R_f = 0.41 (2: 3 EtOAc: Petrol); IRυ $_{max}$ 3405 (C-H), 3336 (C-H), 2977 (N-H), 2934 (N-H), 1700 (C=O), 1513 (aromatic), 1169 cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 8.43 (br s, 1H, NH), 7.62 (d, 1H, *J* = 7.7 Hz, H-3), 7.36 (d, 1H, *J* = 7.7 Hz, H-6), 7.21 (td, 1H, *J* = 7.7, 1.1 Hz, H-2), 7.14 (td, 1H, *J* = 7.7 Hz, 0.7, H-1), 6.99 (s, 1H, H-8), 4.72 (brs, 1H, $NHCO_2C(CH_3)_3$), 3.49 (q, 2H, *J* = 7.1 Hz, H-5), 2.97 (t, 2H, *J* = 7.1 Hz, H-4), 1.47 (s, 9H, $-C(CH_3)_3$); δ ^{13}C NMR (150 MHz, $CDCl_3$) 156.3 (C_q), 137.5 (C_q), 122.4 (C_q), 122.3 (CH), 122.1 (CH), 119.4 (CH), 118.4 (CH), 113.2 (C_q), 111.4 (CH), 79.4 (C_q), 41.2 (CH_2), 28.7 (($CH_3)_3$), 26.0 (CH_2); HRMS (EI) calcd. for $C_{15}H_{20}N_2O_2$ $[M]^+$ 260.15248, found 260.15237.

Tert-butyl3a-allyl-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate (150)[190]

Under previous conditions as before for the synthesis of substituted 3, 3-diallyl-3*H*-indole.

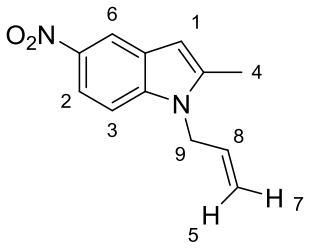


150

Purification by dry load flash chromatography method 0-20% EtOAc: petrol gave the title compound as a pale yellow oil (180 mg, 82%). R_f = 0.66 (2 : 8 EtOAc : Petrol); IRυ_{max} 2976 (C-H), 2929 (N-H), 1691 (C=O), 1488 (aromatic), 1393 (C-O), 1155 (N-C) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.06 (tt, 1H, *J* = 7.1, 1.2 Hz, H-2), 7.05 (d, 1H, *J* = 7.1 Hz, H-6), 6.77-6.72 (m, 1H, H-1), 6.61 (d, 1H, *J* = 7.1 Hz, H-3), 5.75 (m, 1H, H-14), 5.12-5.01 (m, 3H, Boc cis/trans isomerization, H-15, 8), 3.69; 3.53 (m, 1H, H-11), 3.04-2.98 (m, 1H, H-11), 2.46 (dd, 1H, *J* = 15.0, 6.6 Hz, H-13), 2.42 (dd, 1H, *J* = 15.0, 6.6 Hz, H-13), 2.17-2.06 (m, 2H, H-12), 1.52 + 1.44 (2s, Boc cis/trans isomerization, 9H, H-10); δ ^{13}C NMR (150 MHz, $CDCl_3$) 154.5 (C_q), 153.3 (C_q), 149.3 (C_q), 149.0 (C_q), 133.9 (C_q), 131.9 (CH), 131.8 (CH), 128.5 (CH), 128.4 (CH), 123.40 (CH), 123.36 (CH), 119.2 (CH), 118.7 (CH), 118.4 (=CH_2), 118.4 (=CH_2), 109.4 (CH), 109.3 (CH), 80.1 (CH), 79.8 (C_q), 79.6 (C_q), 57.4 (C_q), 56.4 (C_q), 45.9 (CH_2), 45.5 (CH_2), 35.1 (CH_2), 34.9 (CH_2), 28.8 (-$C(CH_3)_3$), 28.6 (-$C(CH_3)_3$).

1-Allyl-2-methyl-5-nitro-1H-indole, nobelium salt (151a)

Reaction mixture was heated at 50°C overnight under the same conditions as before.



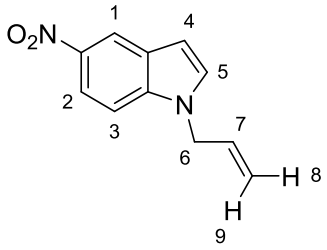
143a

Purification by dry load flash chromatography gradient method 0-20% EtOAc: Petrol to give the title compound as a red-yellow oil (234 mg, 86%). R_f = 0.56 (1: 4 EtOAc : Petrol); IRυ_{max} 2923 (C-H), 1513 (N=C), 1476 (aromatic), 1350 (O=N=O),

1071 cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 8.48 (d, 1H, *J* = 1.9 Hz, H-6), 8.04 (dd, 1H, *J* = 8.9, 1.9 Hz, H-2), 7.22 (d, 1H, *J* = 8.9 Hz, H-3), 6.45 (s, 1H, H-1), 5.94 (dtd, 1H, *J* = 17.2, 9.7, 5.5 Hz, H-8), 5.16 (d, 1H, *J* = 9.7 Hz, H-7), 4.77 (d, 2H, *J* = 17.2 Hz, H-5), 4.23 (dd, 2H, *J* = 5.5, 2.8 Hz, H-9), 2.42 (s, 3H, H-4); δ ^{13}C NMR (150 MHz, $CDCl_3$) 141.7 (C_q), 140.4 (C_q), 139.9 (C_q), 132.4 (CH), 127.4 (C_q), 116.9 ($=CH_2$), 108.9 (CH), 102.7 (CH), 45.7 (CH_2), 12.8 (CH_3); HRMS (ES) cald. for $C_{12}H_{12}N_2O_2$ $[M]^+$ 216.24000, found 216.24300.

1-allyl-5-nitro-1H-indole (151b)[211]

Reaction mixture was heated at 50°C overnight under the same conditions as before.



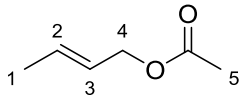
151b

Purification by dry load flash chromatography method 20% EtOAc: Petrol to give the title compound as a yellow oil (177 mg, 79%). R_f = 0.88 (3: 7 EtOAc: Petrol); IRυ_{max} 2923 (C-H), 2924 (C-H), 1509 (aromatic), 1478 (aromatic), 1340 (O=N=O), 1069 cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 8.60 (d, 1H, *J* = 2.4 Hz, H-1), 8.11 (dd, 1H, *J* = 9.2, 2.4 Hz, H-2), 7.34 (d, 1H, *J* = 9.2 Hz, H-3), 7.25 (d, 1H, *J* = 3.3 Hz, H-5), 6.70 (dd, 1H, *J* = 3.3, 0.7 Hz, H-4), 6.00 (ddt, 1H, *J* = 17.1, 10.1, 7.8 Hz, H-7), 5.26 (dq, 1H, *J* = 10.1, 1.3 Hz, H-8), 5.08 (dq, 1H, *J* = 17.1, 1.3 Hz, H-9), 4.79 (dt, 2H, *J* = 5.3, 1.3 Hz, H-6); δ ^{13}C NMR (150 MHz, $CDCl_3$) 141.8 (C_q), 139.0 (C_q), 132.4 (CH), 131.2 (CH), 127.9 (C_q), 118.4 (CH), 118.2 ($=CH_2$), 117.4 (CH), 109.6 (CH), 104.3 (CH), 49.4 (CH_2); HRMS (ES) cald. for $C_{11}H_{11}N_2O_2$ $[M + H]^+$ 203.2130, found 203.0666.

(*E*)-But-2-en-1-yl acetate(152)[212]

Under dry argon conditions was added acetyl chloride (21.7 ml, 0.31 mmol, 1.1 eq) in CH_2Cl_2 (20 ml) at 0°C. The (*E*)-but-2-en-1-ol (23 ml, 0.27 mmol) and pyridine (39.2 ml, 0.49 mmol, 1.8 eq) was added dropwise with vigorous stirring at 0°C for 2

hrs. The reaction was left to stir for a further 10 minutes. To the reaction mixture CH_2Cl_2 (50 ml) was added to the reaction mixture. The organic layer was then washed with a solution of HCl (1M) (3 × 100 ml), sodium carbonate (1 M) (3 × 100 ml), water (3 × 100 ml) and brine (3 × 100 ml), dried with $MgSO_4$, filtered and concentrated to give a yellow oil (1.5 g, 43%).

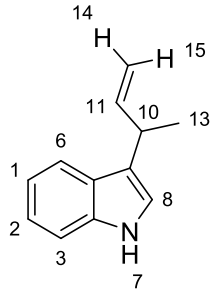


152

IRυ $_{max}$ 2924 (C-H), 1620 (C=O), 1340, 1069 cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 5.80 (m, 1H, H-3), 5.77 (m, 1H, H-2), 4.80 (d, 1H, *J* = 6.2 Hz, H-4), 2.05 (s, 3H, H-5), 1.73 (m, 3H, H-1); δ ^{13}C NMR (150 MHz, $CDCl_3$) 172.1 (C_q), 135.0 (CH), 124.4 (CH), 66.8 (CH_2), 20.1 (CH_3), 17.2 (CH_3).

3-(but-3-en-2-yl)-1H-indole (153a)[213]

To a stirred solution of $[Pd(allylCl)_2]_2$ (2.5 mol%) and DPEPhos (5 mol%) in MeCN (0.025M) was added (E)-but-2-en-2-yl acetate (5 eq) after stirring for 15 mins at rt. After stirring for a further 5 mins potassium carbonate (3 eq), the substituted indole (1 eq) were added. The reaction mixture was degassed and left to stir overnight under argon at 40°C. Then diethyl ether was added to the reaction mixture (7 ml) and washed with water (10 ml), dried with $MgSO_4$, filtered and concentrated. Purification by dry load flash chromatography gave the corresponding substituted 3,3-diallyl-3*H*-indole compound.

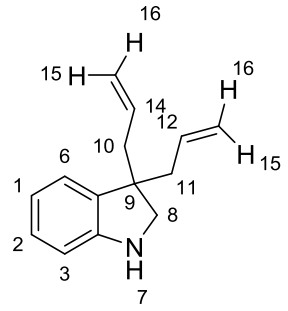


145a

Reaction mixture was heated at 50°C overnight. Purification by dry load flash chromatography method 0-20% EtOAc: petrol to give the title compound as a red brown oil (89 mg, 43%); R_f = 0.45 (3 : 7 EtOAc : petrol); IRυ_{max} 3405 (C-H), 2970 (N-H), 1457 (aromatic), 1295 cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.93 (br s, 1H, NH), 7.66 (d, 1H, *J* = 7.8 Hz, H-6), 7.36 (d, 1H, *J* = 8.2 Hz, H-3), 7.19 (t, 2H, *J* = 7.5 Hz, H-2), 7.11 (t, 1H, *J* = 7.3 Hz, H-1), 6.98 (d, 2H, *J* = 1.7 Hz, H-8), 6.08 (ddd, 1H, *J* = 17.0, 10.0, 6.7 Hz, H-11), 5.14 (dt, 1H, *J* = 17.2, 1.5 Hz, H-15), 5.04 (dt, 1H, *J* = 10.2, 1.5 Hz, H-14), 3.77 (m, 1H, H-10), 1.49 (s, 3H, H-13); δ ^{13}C NMR (150 MHz, $CDCl_3$) 143.8 (CH), 136.7 (C_q), 126.9 (C_q), 123.2 (CH), 122.1 (CH), 119.7 (CH), 119.3 (CH), 112.9 (=CH_2), 110.5 (C_q), 110.2 (CH), 35.2 (CH), 20.3 (CH_3).

3,3-diallylindoline (154)

Under dry argon conditions was added 3, 3-diallyl-3*H*-indole (150 mg, 0.76 mmol) in MeOH (2 ml).This was followed by addition of $NaBH_4$ (116 mg, 3 mmol, 4 eq) at 0°C, and left to stir for 2 hrs at 0°C. Added diethyl ether (5 ml) to the reaction mixture and washed with water (10 ml), dried with $MgSO_4$, filtered and concentrated.



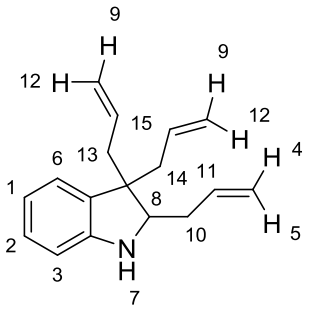
154

Purification by dry load flash chromatography method 0-10% EtOAc : petrol to give the title compound as a pale yellow oil (77 mg, 51%); R_f = 0.63 (1 : 4 EtOAc : petrol); IRυ_{max} 3072 (C-H), 3074 (C-H), 2919 (N-H), 1487 (aromatic), 1462 (aromatic) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.05 (td, 1H, *J* = 7.5, 1.0 Hz, H-1), 7.02 (d, 1H, *J* = 7.5 Hz, H-6), 6.74 (t, 1H, *J* = 7.5 Hz, H-2), 6.64 (d, 1H, *J* = 7.5 Hz, H-3), 5.72 (ddt, 2H, *J* = 17.2, 9.7, 7.4 Hz, H-14, 12), 5.07-5.04 (m, 4H, H-15, 16), 3.37 (s, 2H, H-8), 2.42 (dd, 2H, *J* = 14.0, 7.4, H-10 or 11), 2.40 (dd, 2H, *J* = 14.0, 7.4 Hz, H-10 and 11); δ ^{13}C NMR (150 MHz, $CDCl_3$) 151.3 (C_q), 134.8 (2 × CH),

134.7 (C_q), 127.7 (CH), 123.6 (CH), 118.6 (CH), 117.9 (2 × $=CH_2$), 109.8 (CH), 56.4 (CH_2), 48.5 (C_q), 43.0 (2 × CH_2); HRMS (CI) cald. for $C_{14}H_{17}N$ $[M + H]^+$ 200.14392, found 200.14292.

2,3,3-triallylindoline (155)

Under dry argon conditions at -15°C was added zinc (84 mg, 1.28 mmol, 1.59 eq) and allyl bromide (0.11 ml, 1.28 mmol, 1.59 eq) in dry THF (2 ml) for 3 hrs. This was followed by dropwise addition of 3,3-diallyl-3*H*-indole (159 mg, 0.81 mmol) in dry THF (2 ml) at -78°C, and was left to stir for 4 hrs under argon. The reaction mixture was quenched with saturated aqueous NH_4Cl (10 ml). The mixture was partitioned with diethyl ether (5 ml). Organic layer was washed with water (10 ml), dried with $MgSO_4$, filtered and concentrated.

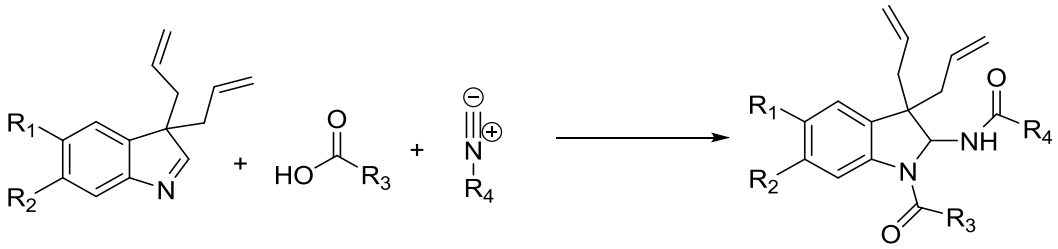


155

Purification by dry load flash chromatography method 0-10% EtOAc: petrol to give the title compound as a yellow oil (114 mg, 60%). R_f = 0.64 (1 : 1 EtOAc : petrol); IRυ_{max} 3350 (C-H), 3075 (C-H), 2922 (N-H), 1607 (aromatic), 1483 (aromatic) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 7.03 (td, 1H, *J* = 7.4, 1.0 Hz, H-2), 7.00 (dd, 1H, *J* = 7.4, 1.0 Hz, H-6), 6.72 (td, 1H, *J* = 7.4, 0.9 Hz, H-1), 6.62 (dd, 1H, *J* = 7.4, 0.9 Hz, H-3), 5.82 (dtd, 1H, *J* = 16.1, 9.7, 7.2 Hz, H-11), 5.74 (dtd, 2H, *J* = 16.9, 9.9, 7.6 Hz, H-15), 5.16 (dq, 1H, *J* = 17.3, 1.9 Hz, H-5), 5.12 (br d, 1H, *J* = 9.7 Hz, H-4), 5.07-4.99 (m, 4H, H-12, 9), 4.00 (br s, 1H, NH), 3.64 (dd, 1H, *J* = 10.7, 3.0 Hz, H-8), 2.55 (ddt, 1H, *J* = 14.4, 6.8, 1.4 Hz, H-14 or 13), 2.47-2.39 (m, 3H, H-14, 13 and 10), 2.29-2.24 (m, 1H, H-10), 2.18 (ddt, 1H, *J* = 13.9, 7.7, 1.1, H-14 or 13); δ ^{13}C NMR (150 MHz, $CDCl_3$) 149.7 (C_q), 136.3 (CH), 135.0 (CH), 134.9 (CH), 134.3 (C_q), 127.6 (CH), 124.3 (CH), 118.4 (CH), 117.9 ($=CH_2$), 117.7 ($=CH_2$), 117.6

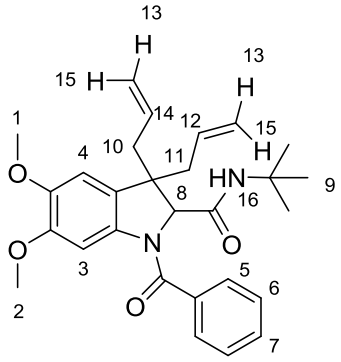
(=CH_2), 109.6 (CH), 66.1 (CH), 49.3 (C_q), 40.7 (CH_2), 37.9 (CH_2), 34.6 (CH_2); HRMS (ES) cald. for $C_{17}H_{21}N$ $[M]^+$ 239.36200, found 238.1593.

Reactivity of substituted 3,3-diallyl-3*H*-indole compounds UGI reaction



General procedure G: To a solution of 3,3-diallyl-3*H*-indole(1eq) in MeOH (0.07 M) were added the carboxylic acid (1eq) and isocyanide (1eq). Reaction mixture was left to stir overnight at r.t. Added diethyl ether (3 ml) washed with water (5 ml), dried with $MgSO_4$, and evaporated solvent.

3,3-Diallyl-1-benzoyl-*N*-(*tert*-butyl)-5,6-dimethoxyindoline-2-carboxamide (156a)

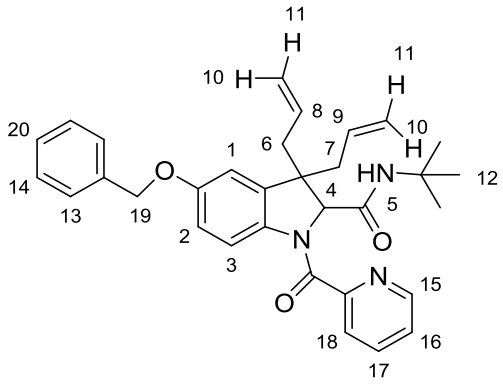


156a

Evaporation of solvent gave the title compound as a yellow brown oil (249 mg, 99%). R_f = 0.15 (1 : 4 EtOAc : Petrol); IRυ $_{max}$ 3342 (N-H), 2966 (C-H), 2936 (C-H), 1682 (C=C alkene), 1623 (C=O), 1501 (aromatic), 1448 (OC-N), 1214 (C-O) cm^{-1}; δ ^{1}H NMR (400 MHz, $CDCl_3$, 55°C) 7.53 (d, 2H, *J* = 8.2 Hz, H-5), 7.46 (t, 3H, *J* = 8.2 Hz, H-6, 7), 6.88 (br s, 1H, H-3), 6.76 (s, 1H, H-4), 6.04 (ddt, 1H, *J* = 17.4, 10.6, 7.1 Hz, H-14 or 12), 5.61 (ddt, 1H, *J* = 17.4, 10.6, 7.1 Hz, H-14 or 12), 5.18-5.05 (m, 4H, H-15, 13), 5.52 (br s, 1H, NH), 4.52 (s, 1H, H-8), 3.84 (s, 3H, H-1), 3.67 (s, 3H,

H-2), 2.64 (dd, 1H, *J* = 14.6, 7.1 Hz, H-11 or 10), 2.59 (dd, 1H, *J* = 14.6, 7.1 Hz, H-11 or 10), 2.46 (dd, 1H, *J* = 13.9, 7.1 Hz, H-11 or 10), 2.40 (dd, 1H, *J* = 13.7, 7.1 Hz, H-11 or 10), 1.30 (s, 9H, H-9); δ ^{13}C NMR (150 MHz, $CDCl_3$, r.t.) 168.9 (C_q), 167.8 (C_q), 148.4 (C_q), 145.9 (C_q), 136.2 (C_q), 135.3 (C_q), 134.3 (CH), 133.6 (CH), 130.8 (CH), 128.8 (2 × CH), 128.4 (C_q), 127.4 (2 × CH), 119.4 (=CH_2), 119.1 (=CH_2), 107.4 (CH), 101.0 (C_q), 73.9 (CH), 56.6 (CH_3), 55.8 (CH_3), 51.8 (C_q), 45.2 (CH_2), 39.1 (CH_2), 28.7 (-$C(CH_3)_3$); carbon of H-3 and 2 not observed by ^{13}C NMR; HRMS (EI) cald. for $C_{28}H_{34}N_2O_4$ $[M]^+$ 462.2519, found 462.2524.

3,3-Diallyl-5-(benzyloxy)-*N*-(*tert*-butyl)-1-picolinoylindoline-2-carboxamide (156b)

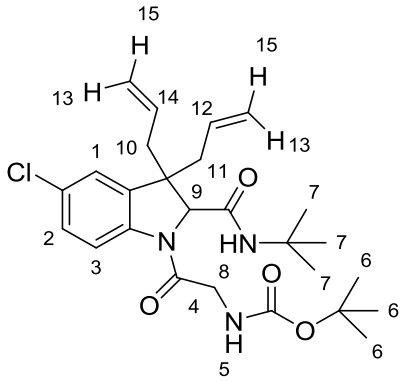


156b

Evaporation of solvent gave the title compound as a yellow brown oil (286 mg, 99%); R_f = 0.15 (1 : 4 EtOAc : petrol); IRυ $_{max}$ 3342 (N-H), 2965 (C-H), 2933 (C-H), 1683 (C=C alkene), 1630 (C=O), 1501 (aromatic), 1446 (OC-N), 1214 (C-O) cm^{-1}; δ ^{1}H NMR (400 MHz, $CDCl_3$, 55°C) 8.56 (d, 1H, *J* = 4.7 Hz, H-15), 8.12-8.00 (br s, 1H, H-3), 7.88 (d, 1H, *J* = 7.6 Hz, H-18), 7.81 (td, 1H, *J* = 7.6, 1.4 Hz, H-17), 7.44 (d, 2H, *J* = 7.4 Hz, H-13), 7.40 (t, 2H, *J* = 7.4 Hz, H-14), 7.36 (ddd, 1H, *J* = 7.6, 4.7, 1.4 Hz, H-16), 7.33 (tt, 1H, *J* = 7.4, 1.3 Hz, H-20), 6.89 (br s, 1H, H-2), 6.86 (br s, 1H, H-1), 6.03 (ddt, 1H, *J* = 16.8, 10.7, 7.4 Hz, H-8 or 9), 5.51 (ddt, 2H, *J* = 16.8, 10.7, 7.4 Hz, H-8 or 9 and NH), 5.10 (dd, 2H, *J* = 16.8, 10.7 Hz, H-11 and 10), 5.06 (s, 2H, H-19), 5.00 (d, 2H, *J* = 10.7 Hz, H-11 and 10), 4.92 (s, 1H, H-4), 2.58 (m, 2H, H-6 or 7), 2.34 (br d, 2H, ,*J* = 7.4 Hz, H-6 or 7), 1.21 (s, 9H, H-12); δ ^{13}C NMR (150 MHz, $CDCl_3$, r.t.) 168.6 (C_q), 166.3 (C_q), 156.3 (C_q), 153.5 (C_q), 147.9 (CH), 138.9 (C_q), 137.4 (CH), 137.0 (C_q), 136.1 (C_q), 134.4 (CH), 133.5 (CH), 128.7

(2 × CH), 128.2 (CH), 127. 2 (2 × CH), 125.2 (CH), 124.4 (CH), 119.1 (=CH_2), 118.8 (=CH_2), 118.5 (C_q), 113.7 (CH), 111.6 (CH), 74.1 (CH), 70.7 (CH_2), 51.4 (C_q), 50.9 (C_q), 45.5 (CH_2), 39.0 (CH_2), 28.6 (CH_3); carbon of H-3 not observed by ^{13}C NMR; HRMS (CI) cald. for $C_{32}H_{36}N_3O_3$ $[M+H]^+$ 510.2757, found 510.2729.

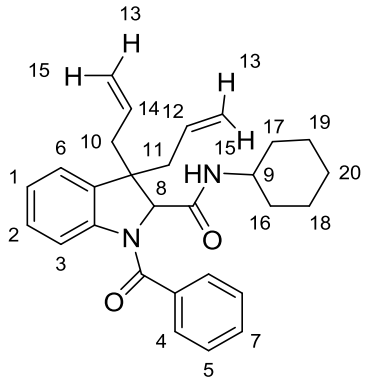
Tert-butyl(2-(3,3-diallyl-2-(*tert*-butylcarbamoyl)-5-chloroindolin-1-yl)-2-oxoethyl)carbamate (156c)



156c

After evaporation of volatiles, purification by dry load column chromatography by gradient method 0-20% EtOAc: petrol, gave the title compound as a colourless oil (106 mg, 91%). R_f = 0.64 (1 : 4 EtOAc : petrol); IRυ $_{max}$ 3455 (C-H), 3348 (C-H), 2977 (N-H), 2940 (N-H), 1667 (C=O), 1476 (aromatic), 1394 (aromatic), 1366 (OC-N), 1251 (C-O) cm^{-1}; δ ^1H NMR (400 MHz, $CDCl_3$, 55°C) 7.89 (br s, 1H, H-3), 7.24 (dd, 1H, *J* = 8.5, 1.8 Hz, H-2), 7.19 (d, 1H, *J* = 1.8 Hz, H-1), 6.00 (ddt, 1H, *J* = 16.8, 8.3, 7.3 Hz, H-14 or 12), 5.51 (br s, 1H, NH), 5.50 (ddt, 1H, *J* = 16.8, 8.3, 7.3 Hz, H-14 or 12), 5.31 (br s, 1H, NH), 5.23-5.07 (m, 4H, H-15, 13), 4.45 (br s, 1H, H-9), 4.09 (dd, 1H, *J* = 16.8, 15.4 Hz, H-4), 3.93 (br d, 1H, *J* = 15.4 Hz, H-4), 2.67 (dd, 1H, *J* = 15.4, 7.3 Hz, H-11 or 10), 4.49 (dd, 1H, *J* = 15.4, 7.3 Hz, H-11 or 10), 2.41 (dd, 1H, *J* = 15.4, 7.3 Hz, H-11 or 10), 2.34 (dd, 1H, *J* = 15.4, 7.3 Hz, H-11 or 10), 1.48 (s, 9H, H-7 or 6), 1.33 (s, 9H, H-7 or 6); δ ^{13}C NMR (150 MHz, $CDCl_3$, r.t.) 167.5 (C_q), 167.1 (C_q), 155.8 (C_q), 140.3 (C_q), 138.2 (C_q), 133.3 (CH), 132.5 (CH), 129.7 (C_q), 128.5 (CH), 124.4 (CH), 120.1 (=CH_2), 119.9 (=CH_2), 80.2 (C_q), 71.1 (CH), 52.3 (C_q), 50.8 (C_q), 45.8 (CH_2), 44.1 (CH_2), 38.2 (CH_2), 28.6 (-$C(CH_3)_3$), 28.4 (-$C(CH_3)_3$); carbon of H-3 not observed by ^{13}C NMR; HRMS (CI) cald. for $C_{26}H_{37}N_3O_4Cl$ $[M + H]^+$ 490.2473, found 490.2457.

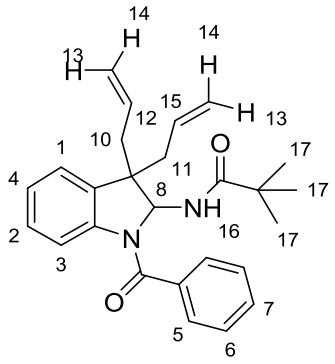
3,3-Diallyl-1-benzoyl-*N*-cyclohexylindoline-2-carboxamide (156d)



156d

After evaporation of the volatiles, purification by dry load flash column chromatography 30% EtOAc: petrol gave the title compound as a pale yellow oil (174 mg, 87%). R_f = 0.30 (1 : 4 EtOAc : petrol); IRυ $_{max}$ 3314 (C-H), 2930 (C-H), 2855 (N-H), 1638 (C=O), 1594 (N=CH), 1559 (aromatic), 1470 (OC-N) cm^{-1}; δ ^{1}H NMR (400 MHz, $CDCl_3$, 55°C) 7.54-7.47 (m, 3H, H-7, 4), 7.42 (t, 2H, *J* = 7.9 Hz, H-5), 7.20 (d, 1H, *J* = 7.5 Hz, H-6), 7.15 (br s, 1H, H-3), 7.11 (t, 1H, *J* = 7.8 Hz, H-2), 7.05 (td, 1H, *J* = 7.1, 1.4 Hz, H-1), 6.00 (ddt, 1H, *J* = 17.0, 9.9, 7.5 Hz, H-14 or 12), 5.62 (ddt, 2H, *J* = 17.0, 9.9, 7.5 Hz, H-14 or 12, NH), 5.14-5.03 (m, 4H, H-15, 13), 4.60 (s, 1H, H-8), 3.75 (m, 1H, H-9), 2.63 (dd, 2H, *J* = 14.3, 7.5 Hz, H-10 or 11), 2.47 (dt, 2H, *J* = 14.3, 7.5 Hz, H-11 or 10), 1.95 (dd, 1H, *J* = 11.7, 2.8 Hz, H-17 or 16), 1.81-1.73 (m, 1H, H-17 or 16), 1.69-1.64 (m, 1H, H-19, 18), 1.62-1.54 (m, 2H, H-20 eq, 19 or 18), 1.44-1.28 (m, 2H, H-(19 and 18) or (20 and 18)), 1.23-1.12 (qd, 2H, *J* = 12.0, 4.0 Hz, H-20 ax, 17 or 16), 1.07 (qd, 1H, *J* = 11.3, 3.4 Hz, H-17 or 16 ax); δ ^{13}C NMR (150 MHz, $CDCl_3$, r.t.) 169.5 (C_q), 167.6 (C_q), 141.8 (C_q), 137.2 (C_q), 136.0 (C_q), 133.9 (CH), 133.5 (CH), 131.0 (CH), 128.8 (2 × CH), 128.0 (CH), 127.4 (2 × CH), 124.3 (2 × CH), 119.5 (=CH_2), 119.0 (=CH_2), 73.0 (CH), 50.0 (C_q), 48.2 (CH), 45.1 (CH_2), 38.8 (CH_2), 32.9 (CH_2), 32.8 (CH_2), 25.5 (CH_2), 24.8 (CH_2), 24.7 (CH_2); carbon of H-3 not seen by ^{13}C NMR; HRMS (CI) cald. for $C_{28}H_{32}N_2O_2$ $[M]^+$ 428.2463, found 428.2460.

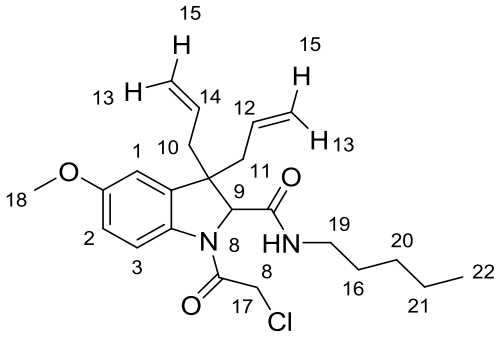
N-(3,3-Diallyl-1-benzoylindolin-2-yl)pivalamide (156e)



156e

Evaporation of solvent gave the title compound as a pale yellow solid (81 mg, 79%). m.p. 137-138 °C; R_f = 0.37 (1: 4 EtOAc : petrol); IRυ $_{max}$ 3347 (C-H), 2970 (C-H), 2925 (N-H), 1685 (C=O), 1624 (C=O), 1501 (aromatic), 1393 (OC-N), 1393 (C-O) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$, r.t.) 7.53 (d, 2H, *J* = 7.4 Hz, H-5), 7.50 (t, 1H, *J* = 7.4 Hz, H-7), 7.43 (t, 2H, *J* = 7.4 Hz, H-6), 7.17 (d, 1H, J = 7.5 Hz, H-1), 7.06 (br s, 1H, H-2), 7.02 (t, 1H, *J* = 7.5 Hz, H-4), 6.00 (ddt, 1H, *J* = 16.5, 9.2, 7.2 Hz, H-15 or 12), 5.58 (ddt, 1H, *J* = 16.5, 9.2, 7.2 Hz, H-15 or 12), 5.49 (br s, 1H, NH), 5.15-5.05 (m, 4H, H-14, 13), 4.48 (s, 1H, H-8), 2.62; 2.55 (dd, 1H, *J* = 14.7, 7.2 Hz, H-11 or 10) (dd, 1H, *J* = 14.7, 7.2 Hz, H-11 or 10)), 2.42 (m, 2H, H-11 or 10), 1.30 (s, 9H, H-17); missing H-3 peak present at baseline around 7.06 ppm; δ ^{13}C NMR (150 MHz, $CDCl_3$, r.t) 169.5 (C_q), 167.6 (C_q), 142.0 (C_q), 137.1 (C_q), 136.1 (C_q), 134.0 (CH), 133.6 (CH), 131.1 (CH), 128.9 (2 × CH), 128.1 (CH), 127.6 (2 × CH), 124.2 (CH), 124.0 (CH), 119.4 (=CH_2), 119.2 (=CH_2), 73.1 (CH), 51.9 (C_q), 49.8 (C_q), 44.7 (CH), 38.9 (CH_2), 28.6 (-$C(CH_3)_3$); carbon of H-3 not observed by ^{13}C NMR); HRMS (CI) cald. for $C_{26}H_{31}N_2O_2$ $[M+H]^+$ 403.2386, found 403.2353.

3,3-Diallyl-1-(2-chloroacetyl)-5-methoxy-*N*-pentylindoline-2-carboxamide (156f)



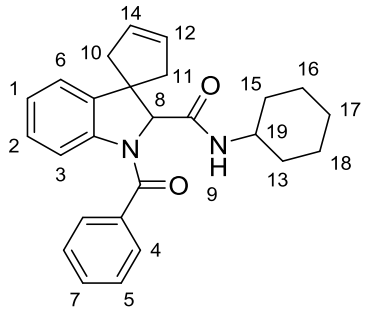
156f

After evaporation of volatiles, purification by dry load column chromatography by gradient method 0-20% EtOAc: petrol, gave the title compound as a yellow oil (67 mg, 61%). R_f = 0.27 (1 : 4 EtOAc : petrol); IRυ $_{max}$ 3010 (C-H), 2930 (N-H), 1648 (C=O), 1488 (aromatic), 1398 (OC-N), 1246 (C-O-C), 1204 (C-N), 1156 (C-O), 1033 (C-O-C), 811 (C-Cl) cm^{-1}; δ ^{1}H NMR (400 MHz, $CDCl_3$, 55°C) 8.00 (br s, 1H, H-3), 6.83 (dd, 1H, *J* = 8.0, 2.5 Hz, H-2), 6.80 (d, 1H, *J* = 2.5 Hz, H-1), 5.94 (ddt, 1H, J = 16.4, 9.5, 7.4 Hz, H-14 or 12), 5.62 (br s, 1H, NH), 5.53 (ddt, 1H, *J* = 16.4, 9.5, 7.4 Hz, H-14 or 12), 5.20-5.05 (m, 4H, H-15, 13), 4.66 (s, 3H, H-9), 4.15 (d, 1H, *J* = 13.0 Hz, H-17), 4.08 (d, 1H, *J* = 13.0 Hz, H-17), 3.81 (s, 3H, H-18), 3.21 (sextet, 1H, *J* = 13.3, 7.1, 6.1 Hz, H-19), 3.10 (sext, 1H, *J* = 13.3, 7.1, 6.1 Hz, H-19), 2.64 (d, 2H, *J* = 7.4 Hz, H-11 or 10), 2.44 (ddt, 1H, *J* = 13.9, 7.4, 1.0 Hz, H-11 or 10), 2.39 (ddt, 1H, *J* = 13.9, 7.4, 1.0 Hz, H-11 or 10), 1.42 (qn, 2H, *J* = 14.7, 7.1 Hz, H-16), 1.27 (m, 2H, H-21), 1.18 (m, 2H, H-20), 0.86 (t, 3H, *J* = 6.7 Hz, H-22); δ ^{13}C NMR (150 MHz, $CDCl_3$, r.t.) 168.5 (C_q), 164.1 (C_q), 157.5 (C_q), 137.9 (C_q), 134.8 (C_q), 133.3 (CH), 132.5 (CH), 120.1 (=CH_2), 119.1 (=CH_2), 118.2 (CH), 112.9 (CH), 110.7 (CH), 71.7 (CH), 55.8 (CH_3), 51.2 (C_q), 46.6 (CH_2), 42.7 (CH_2), 39.6 (CH_2), 38.3 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 22.3 (CH_2), 14.0 (CH_3); HRMS (CI) cald. for $C_{23}H_{32}ClN_2O_3$ $[M + H]^+$ 419.2101, found 419.2074.

Grubbs metathesis for ring closing metathesis:

General procedure H: To a degassed solution of the corresponding UGI substrate (1eq) in CH_2Cl_2 (0.06 M) at 45°C was added Grubbs 1st generation catalyst (15 mol%). The reaction mixture was refluxed overnight under argon. Workup with diethyl ether (5 ml) and washed with water (10 ml), dried with $MgSO_4$, filtered and evaporated.

1'-Benzoyl-*N*-cyclohexylspiro[cyclopentane-1,3'-indolin]-3-ene-2'-carboxamide (159a)

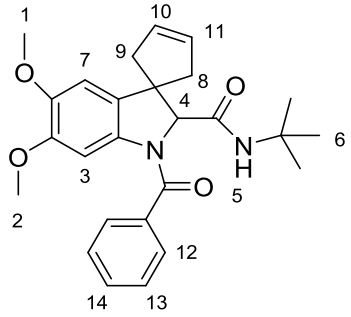


159a

After evaporation of volatiles, purification by dry load column chromatography at 40% EtOAc: petrol gave the title compound as a grey black oil (60 mg, 98%). R_f = 0.25 (1 : 4 EtOAc : petrol); IRυ $_{max}$ 3314 (C-H), 2930 (C-H), 2854 (N-H), 1634 (C=O), 1479 (aromatic), 1374 (OC-N) cm^{-1}; δ ^{1}H NMR (400 MHz, $CDCl_3$, 55°C) 7.53 (d, 2H, *J* = 7.6 Hz, H-4), 7.48 (t, 1H, *J* = 6.9 Hz, H-5), 7.44 (t, 2H, *J* = 7.2 Hz, H-7), 7.21 (d, 1H, *J* = 7.3 Hz, H-6), 7.15 (br s, 1H, H-3), 7.08 (t, 1H, *J* = 7.1 Hz, H-2), 7.01 (t, 1H, *J* = 7.4 Hz, H-1), 5.89 (m, 1H, H-14 or 12), 5.69 (m, 1H, H-14 or 12), 5.52 (d, 1H, *J* = 6.5 Hz, NH), 4.64 (s, 1H, H-8), 3.76 (m, 1H, H-19), 2.87 (dd, 1H, *J* = 17.1, 1.5 Hz, H-11 or 10), 2.81 (d, 1H, *J* = 16.4 Hz, H-11 or 10), 2.68 (d, 1H, *J* = 16.9 Hz, H-11 or 10), 2.62 (d, 1H, *J* = 15.9 Hz, H-11 or 10), 2.81 (d, 1H, *J* = 16.4 Hz, H-11 or 10), 2.68 (d, 1H, *J* = 16.9 Hz, H-11 or 10), 2.62 (d, 1H, *J* = 15.9 Hz, H-11 or 10), 1.88 (d, 1H, *J* = 10.4 Hz, H-15 or 13), 1.77 (m, 1H, H-15 or 13), 1.64 (m, 1H, H-18 or 16), 1.56 (br d, 1H, *J*= 12.6 Hz, 18 or 16), 1.39 (m, 3H, H-(18 and 16) or (18 and 17)), 1.16 (q, 2H, H-17 ax and 15 or 12), 1.04 (q, 1H, *J* = 10.9 Hz, H-15 or 13 ax); δ ^{13}C NMR (150 MHz, $CDCl_3$, 55°C) 169.5 (C_q), 168.1 (C_q), 141.2 (C_q),

140.3 (C_q), 136.0 (C_q), 130.7 (CH), 130.7 (2 × CH), 128.8 (2 × CH), 127.9 (2 × CH), 127.4 (2 × CH), 124.7 (CH), 122.3 (CH), 75.7 (CH), 53.8 (C_q), 50.2 (CH_2), 48.2 (CH), 40.2 (CH_2), 32.9 (CH_2), 32.8 (CH_2), 25.5 (CH_2), 24.7 (CH_2), 24.6 (CH_2); carbon of H-3 was not observed by ^{13}C NMR; HRMS (CI) cald. for $C_{26}H_{28}N_2O_2$ $[M]^+$ 400.2150, found 400.2146.

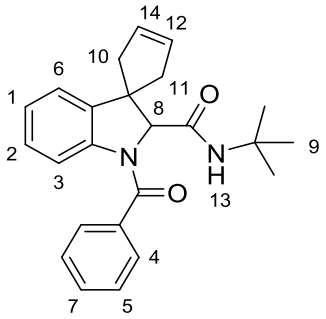
1'-Benzoyl-*N*-(*tert*-butyl)-5',6'-dimethoxyspiro[cyclopentane-1,3'-indolin]-3-ene-2'-carboxamide (159b)



159b

After evaporation of volatiles, purification by dry load column chromatography by gradient method 30-40% EtOAc: petrol gave the title compound as a grey black oil (50 mg, 89%). R_f = 0.15 (1 : 4 EtOAc : petrol); IRυ $_{max}$ 3342 (C-H), 3061 (C-H), 2965 (N-H), 1686 (C=O), 1634 (C=O), 1500 (aromatic), 1447 (aromatic), 1398 (C-O), 1215 (C-O) cm^{-1}; δ ^1H NMR (400 MHz, $CDCl_3$, 55°C) 7.77-7.45 (m, 5H, H-14, 13, 12), 6.76 (s, 1H, H-7), 5.91 (td, 1H, *J* = 5.7, 2.1 Hz, H-11 or 10), 5.72 (td, 1H, *J* = 5.7, 2.1 Hz, H-11 or 10), 5.36 (br s, 1H, NH), 4.51 (s, 1H, H-4), 3.84 (s, 3H, H-1), 3.69 (s, 3H, H-2), 2.87 (ddt, 1H, *J* = 17.1, 5.7, 2.1 Hz, H-9 or 8), 2.76 (ddt, 1H, *J* = 16.3, 5.7, 2.1 Hz, H-9 or 8), 2.67 (ddt, 1H, *J* = 17.1, 5.7, 2.1 Hz, H-9 or 8), 2.60 (ddt, 1H, *J* = 16.3, 5.7, 2.1 Hz, H-9 or 8), 1.31 (s, 9H, H-6); δ ^{13}C NMR (150 MHz, $CDCl_3$, r.t) 169.3 (C_q), 168.3 (C_q), 148.8 (C_q), 146.3 (C_q), 136.4 (C_q), 134.6 (C_q), 130.7 (CH), 131.1 (C_q), 130.5 (CH), 128.5 (2 × CH), 128.4 (CH), 127.4 (2 × CH), 105.6 (CH), 66.0 (CH), 56.4 (CH_3), 55.9 (CH_3), 54.1 (C_q), 51.8 (C_q), 50.1 (CH_2), 39.8 (CH_2), 28.7 (-$C(CH_3)_3$); carbon of H-3 not observed in ^{13}C NMR; HRMS (CI) cald. for $C_{26}H_{30}N_2O_4$ $[M]^+$ 434.2205, found 434.2202.

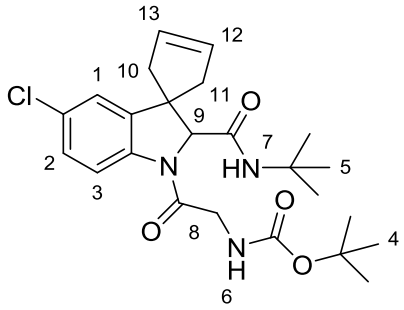
1'-Benzoyl-*N*-(*tert*-butyl)spiro[cyclopentane-1,3'-indolin]-3-ene-2'-carboxamide (159c)



159c

After evaporation of volatiles, purification by dry load column chromatography at 40% EtOAc: Petrol gave the title compound as a grey black oil (56 mg, 96%). R_f = 0.44 (1 : 4 EtOAc : Petrol); IRυ $_{max}$ 3339 (C-H), 2967 (C-H), 2925 (N-H), 1679 (C=O), 1630 (C=O), 1479 (aromatic), 1390 (OC-N) cm^{-1}; δ ^{1}H NMR (400 MHz, $CDCl_3$, 55°C) 7.54 (d, 2H, *J* = 7.4 Hz, H-4), 7.49 (t, 1H, *J* = 7.4 Hz, H-7), 7.44 (t, 2H, *J* = 7.4 Hz, H-5), 7.22 (d, 1H, *J* = 7.6 Hz, H-6), 7.13 (br s, 1H, H-3), 7.08 (t, 1H, *J* = 7.6 Hz, H-2), 7.01 (t, 1H, *J* = 7.6 Hz, H-1), 5.91 (dt, 1H, *J* = 5.4, 2.1 Hz, H-14 or 12), 5.71 (dt, 1H, *J* = 5.4, 2.1 Hz, H-12 or 14), 5.39 (br s, 1H, NH), 4.50 (s, 1H, H-8), 2.90 (ddt, 1H, *J* = 17.0, 5.4, 2.1 Hz, H-11 or 10), 2.79 (ddt, 1H, *J* = 16.2, 5.4, 2.1 Hz, H-11 or 10), 2.72 (ddt, 1H, *J* = 17.0, 5.4, 2.1 Hz, H-11 or 10), 2.62 (ddt, 1H, *J* = 16.2, 5.4, 2.1 Hz, H-11 or 10), 1.27 (s, 9H, H-9); δ ^{13}C NMR (150 MHz, $CDCl_3$, r.t) 169.3 (C_q), 168.3 (C_q), 141.4 (C_q), 140.1 (C_q), 136.2 (C_q), 130.81 (CH), 130.76 (CH), 128.9 (2 × CH), 128.1 (CH), 127.8 (CH), 127.5 (2 × CH), 124.5 (CH), 122.3 (CH), 116.1 (CH), 76.0 (CH), 53.8 (C_q), 51.7 (C_q), 50.4 (CH_2), 39.9 (CH_2), 28.6 (-$C(CH_3)_3$); HRMS (CI) cald. for $C_{24}H_{27}N_2O_2$ $[M + 1]^+$ 375.2075, found 375.2057.

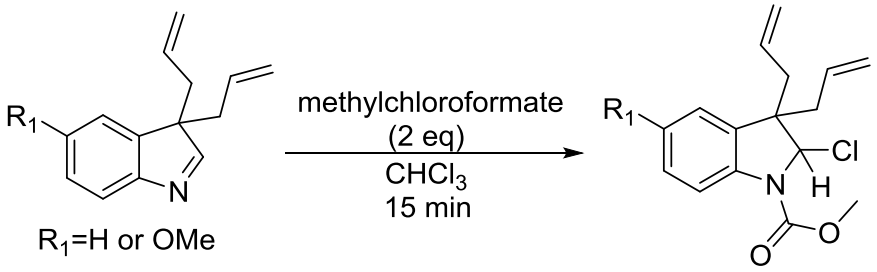
Tert-Butyl (2-(2'-(*tert*-butylcarbamoyl)-5'-chlorospiro[cyclopentane-1,3'-indolin]-3-en-1'-yl)-2-oxoethyl)carbamate (159d)



159d

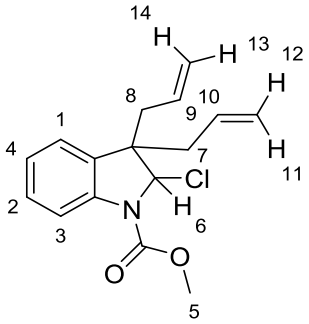
After evaporation of volatiles, purification by dry load column chromatography by gradient method 0-40% EtOAc: petrol gave the title compound as a pale yellow oil (78 mg, 77%). R_f = 0.35 (2 : 3 EtOAc : petrol); IRυ $_{max}$ 3450 (C-H), 3423 (C-H), 2957 (N-H), 1662 (C=O), 1476 (aromatic), 1366 (OC-N), 1253 (C-O), 821 cm^{-1}; δ ^{1}H NMR (400 MHz, $CDCl_3$, 55°C) 7.94 (brs, 1H, H-3), 7.21 (dd, 1H, *J* = 8.8, 2.0 Hz, H-2), 7.19 (s, 1H, H-1), 5.93 (m, 1H, H-13 or 12), 5.73 (m, 1H, H-13 or 12), 5.54 (br s, 1H, NH), 5.41 (br s, 1H, NH), 4.53 (s, 1H, H-9), 4.20 (dd, 1H, *J* = 16.7, 4.9 Hz, H-8), 3.91 (br s, 1H, H-8), 2.89 (d, 1H, *J* = 16.6 Hz, H-11 or 10), 2.74 (d, 1H, *J* = 17.6 Hz, H-11 or 10), 2.69 (d, 1H, *J* = 17.6 Hz, H-11 or 10), 2.56 (d, 1H, *J* = 16.6 Hz, H-11 or 10), 1.48 (s, 9H, H-4), 1.33 (s, 9H, H-5); δ ^{13}C NMR (150 MHz, $CDCl_3$, r.t.) 167.4 (C_q), 155.9 ($C_{q)}$, 140.5 (C_q), 140.0 (C_q), 138.6 (C_q), 130.7 (CH), 129.9 (C_q), 128.4 (CH), 128.2 (CH), 122.5 (CH), 117.6 (CH), 80.2 (C_q), 73.8 (CH), 55.0 (C_q), 52.2 (C_q), 51.0 (CH_2), 43.8 (CH_2), 40.1 (CH_2), 28.6 (-$C(CH_3)_3$, 28.4 (-$C(CH_3)_3$); HRMS (CI) $C_{24}H_{33}ClN_3O_4$ $[M+H]^+$ 462.9870, found 462.2150.

Synthesis of substituted methyl-3,3-Diallyl-2-chloroindoline-1-carboxylate



General procedure I: To a solution of 3,3-diallyl-*3H*-indole in $CHCl_3$ (0.07 M) under argon conditions was added methyl chloroformate (2 eq) and left to stir for 15 minutes at r.t. before a saturated solution of sodium bicarbonate was added (2 × 10 ml). After extraction of reaction mixture with chloroform, the combined organic layers were washed with water (10 ml) and brine (10 ml), dried over $MgSO_4$ and filtered. Evaporation of solvent under vacuum gave the desired compound.

Methyl 3,3-diallyl-2-chloroindoline-1-carboxylate (160a)

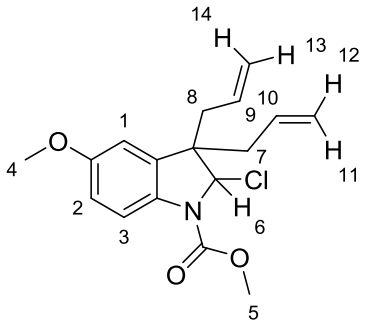


160a

Brown oil (78 mg, 88%); R_f = 0.47 (1 : 4 EtOAc : Petrol); IRυ_{max} 3055 (C-H), 2938 (C-H), 1699 (C=O), 1484 (aromatic), 1445, 1385 (OC-N) cm^{-1}; δ ^{1}H NMR (400 MHz, $CDCl_3$, 60°C) 7.65 (br s, 1H, H-3), 7.23 (td, 1H, *J* = 7.4, 1.2 Hz, H-2), 7.12 (d, 1H, *J* = 7.4 Hz, H-1), 7.03 (td, 1H *J* = 7.4, 1.2 Hz, H-4), 5.99 (dtd, 1H, *J* = 17.8, 10.7, 7.3 Hz, H-10 or 9), 5.61 (s, 1H, H-6), 5.56 (dtd, 1H, *J* = 17.8, 10.7, 7.3 Hz, H-10 or 9), 5.14 (tdd, 2H, *J* = 17.8, 10.7, 1.6 Hz, H-14 and 13 or 12 and 11), 5.03 (tdd, 2H, *J* = 17.8, 10.7, 1.6 Hz, H-14 and 13 or 12), 3.93 (s, 3H, H-5), 2.65 (d, 2H, *J* =

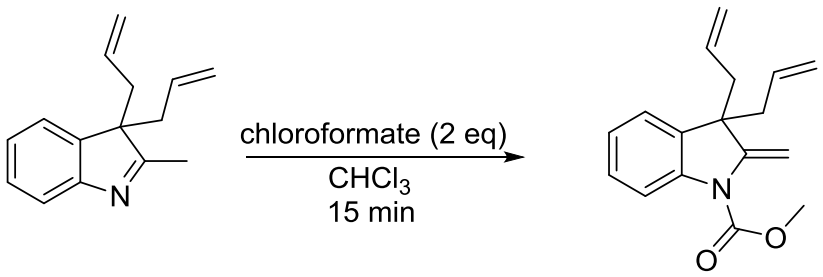
7.2 Hz, H-8 or 7), 2.39 (dd, 1H, *J* = 13.9, 7.2 Hz, H-8 or 7), 2.32 (dd, 1H, *J* = 14.1, 7.7 Hz, H-8 or 7); δ ^{13}C NMR (100 MHz, $CDCl_3$, 60°C) 139.8 (C_q), 135.1 (CH), 132.9 (CH), 129.6 (C_q), 128.0 (CH), 123.8 (CH), 122.8 (CH), 118.5 ($=CH_2$), 117.9 ($=CH_2$), 114.5 (CH), 89.8 (CH), 52.7 (CH_3), 50.0 (C_q), 42.8 (CH_2), 36.9 (CH_2); carbamate quaternary carbon not observed by ^{13}C NMR; HRMS (CI) $C_{16}H_{18}NO_2$ $[M\text{-}Cl]^+$ 256.1332, found 256.1333.

Methyl 3,3-diallyl-2-chloro-5-methoxyindoline-1-carboxylate (160b)



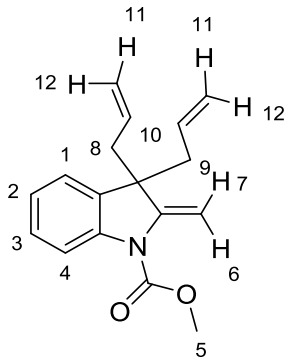
160b

Red brown oil (91 mg, 91%); R_f = 0.44 (1 : 4 EtOAc : petrol); IRυ $_{max}$ 3075 (C-H), 2938 (C-H), 1689 (C=O), 1490 (aromatic), 1459 (aromatic), 1320 (OC-N), 1271 (C-O) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$, 55°C) 7.54 (br s, 1H, H-3), 6.78 (dd, 1H, *J* = 9.0, 2.7 Hz, H-2), 6.71 (d, 1H, *J* = 2.7 Hz, H-1), 6.00 (ddt, 1H, *J* = 17.0, 10.2, 7.5 Hz, H-10 or 9), 5.57 (ddt, 2H, J = 17.0, 10.2, 7.5 Hz, H-10 or 9 and 6), 5.17-5.02 (m, 4H, 14, 13, 12, 11), 3.91 (s, 3H, H-5), 3.79 (s, 3H, H-4), 2.65 (dd, 1H, *J* = 14.3, 7.5 Hz, H-8 and 7), 2.60 (dd, 1H, *J* = 14.3, 7.5 Hz, H-8 and 7), 2.38 (dd, 1H, J = 14.0, 7.5 Hz, H-8 and 7), 2.31 (dd, 1H, *J* = 13.7, 7.5 Hz, H-8 and 7); δ ^{13}C NMR (150 MHz, $CDCl_3$, r.t) 156.0 (C_q), 137.1 (C_q), 136.5 (C_q), 135.5 (CH), 133.9 (C_q), 132.9 (CH), 119.0 ($=CH_2$), 118.5 ($=CH_2$), 115.8 (CH), 112.5 (CH), 110.8 (CH), 90.4 (CH), 55.7 (CH_3), 54.6 (C_q), 52.5 (CH_3), 47.6 (CH_2), 37.3 (CH_2); HRMS (CI) $C_{17}H_{20}NO_3$ $[M\text{-}Cl]^+$ 286.1437, found 286.1439.



To a solution of substituted 3,3-diallyl-*3H*-indole in $CHCl_3$ (0.13 M) under argon conditions was added methyl chloroformate (2 eq) and left to stir for 15 minutes at r.t. before a saturated solution of sodium bicarbonate was added (2 × 10 ml). After extraction of reaction mixture with chloroform, the combined organic layers were washed with water (10 ml) and brine (10 ml), dried over $MgSO_4$ and filtered. Evaporation of solvent under vacuum gave the desired compound as an oil.

Methyl 3,3-diallyl-2-methyleneindoline-1-carboxylate (164)

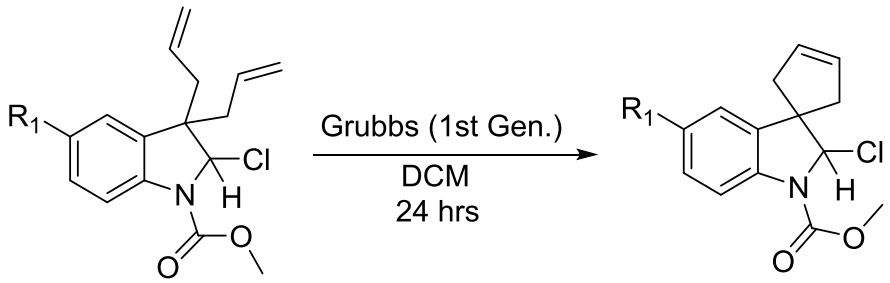


164

Gave the title compound as a dark purple oil (280 mg, 86%). R_f = 0.58 (1 : 4 EtOAc : petrol); IRυ $_{max}$ 3020 (C-H), 2938 (C-H), 1714 (C=O), 1481 (aromatic), 1354 (C-O), 1237 (C-N), 1094 (C-O) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$, r.t) 7.76 (d, 1H, *J* = 7.6 Hz, H-4), 7.20 (td, 1H, *J* = 7.6, 1.5 Hz, H-3), 7.13 (dd, 1H, *J* = 7.6, 0.9 Hz, H-1), 7.07 (td, 1H, *J* = 7.6, 0.9 Hz, H-2), 5.82 (s, 1H, H-7 or 6), 5.43 (ddt, 2H, *J* = 17.2, 10.2, 7.2 Hz, H-10), 4.93-4.87 (m, 4H, H-12, 11), 4.62 (d, 1H, *J* = 1.5 Hz, H-7 or 6), 3.95 (s, 3H, H-5), 2.56 (dd, 2H, *J* = 13.8, 7.2 Hz, H-9 and 8), 2.43 (dd, 2H, *J* = 13.8, 7.2 Hz, H-9 and 8); δ ^{13}C NMR (100 MHz, $CDCl_3$, 55°C) 153.5 (C_q), 150.2 (C_q), 141.7 (C_q), 133.8 (C_q), 133.2 (2 × CH), 127.9 (CH), 123.5 (CH), 123.2 (CH), 118.4

(2 × =CH_2), 94.3 (=CH_2), 53.0 (CH_3), 52.2 (C_q), 46.6 (2 × CH_2); HRMS (CI) $C_{17}H_{20}NO_2$ $[M + H]^+$ 270.1942 found, 270.14815.

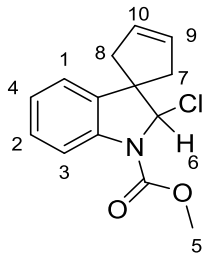
Synthesis of spiro-indolin carboxylates by ring closing metathesis



R_1=H or OMe

General procedure J: To a refluxed solution of Grubbs 1st generation catalyst (15 mol%) in CH_2Cl_2 (0.04 M) was added the corresponding substituted methyl-3,3-Diallyl-2-chloroindoline-1-carboxylate compound under argon. The reaction was refluxed for 24 hrs under argon. After extraction with diethyl ether (3 ml), the combined organic layers were washed with water (10 ml), dried over $MgSO_4$, filtered and evaporated under *vacuo*. The crude material was purified by dry load flash chromatography which gave the desired product.

Methyl 2'-chlorospiro[cyclopentane-1,3'-indolin]-3-ene-1'-carboxylate (164a)

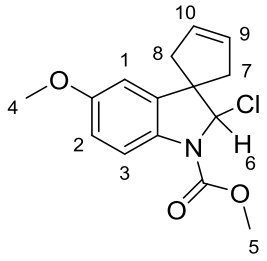


163a

Purification by dry load flash chromatography gradient method 0-20% EtOAc: petrol which gave the title compound as a dark green oil (59 mg, 78%). R_f = 0.20 (1 : 4 EtOAc : petrol); IRυ $_{max}$ 3020 (C-H), 2938 (C-H), 1687 (C=O), 1481 (aromatic),

1381 (C-O), 1135 (C-N), 690 cm^{-1}; δ ^{1}H NMR (400 MHz, $CDCl_3$, 55°C) 7.64 (br s, 1H, H-3), 7.28-7.20 (m, 2H, H-4, 1), 7.02 (t, 1H, *J* = 7.1 Hz, H-2), 5.90 (s, 1H, H-10, 9), 5.71 (s, 1H, H-10, 9), 5.59 (s, 1H, H-6), 3.94 (s, 3H, H-5), 3.26 (dd, 1H, *J* = 16.9 Hz, H-8 or 7), 2.66 (t, 2H, *J* = 16.9 Hz, H-8 or 7), 2.41 (d, 1H, *J* = 16.9 Hz, H-8 or 7); δ ^{13}C NMR (100 MHz, $CDCl_3$, 60°C) 139.9 (C_q), 138.1 (C_q), 130.5 (CH), 127.8 (CH), 127.5 (CH), 123.4 (CH), 122.2 (CH), 114.5 (CH), 91.3 (CH), 55.0 (C_q), 52.7 (CH_3), 47.7 (CH_2), 37.3 (CH_2); carbamate carbon not observed by ^{13}C NMR at 60°C; HRMS (CI) cald. for $C_{14}H_{14}NO_2$ $[M\text{-}Cl\text{-}H]^+$ 228.1019, found 228.1018.

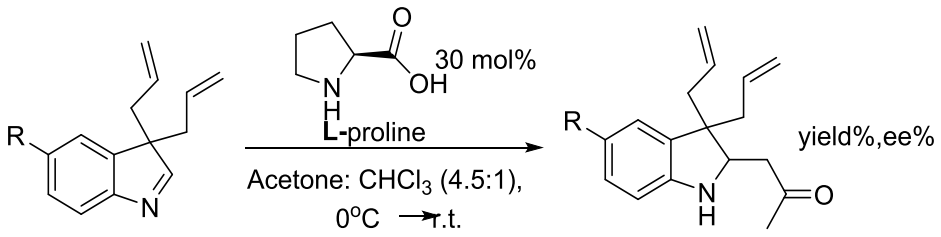
Methyl 2'-chloro-5'-methoxyspiro[cyclopentane-1,3'-indolin]-3-ene-1'-carboxylate (163b)



163b

Purification by dry load flash chromatography gradient method 0-30% EtOAc: petrol which gave the title compound as a dark green oil (59 mg, 70%). R_f = 0.29 (3 : 7 EtOAc : petrol); IRυ $_{max}$ 3075 (C-H), 2890 (C-H), 1692 (C=O), 1490 (aromatic), 1272 (C-O), 1135 (C-N), 1032, 694 cm^{-1}; δ ^{1}H NMR (400 MHz, $CDCl_3$, 60°C) 7.53 (br s, 1H, H-3), 6.81 (d, 1H, *J* = 2.6 Hz, H-1), 6.75 (dd, 1H, *J* = 8.5, 2.6 Hz, H-2), 5.90 (dtd, 1H, *J* = 6.4, 4.5, 2.3 Hz, H-10 or 9), 5.70 (dtd, 1H, *J* = 6.4, 4.5, 2.3 Hz, H-10 or 9), 5.57 (br s, 1H, H-6), 3.91 (s, 3H, H-5), 3.79 (s, 3H, H-4), 3.24 (d, 1H, *J* = 17.3 Hz, H-8 or 7), 2.67 (d, 1H, *J* = 16.5 Hz, H-8 or 7), 2.61 (d, 1H, *J* = 17.3 Hz, H-8 or 7), 2.40 (d, 1H, *J* = 16.5 Hz, H-8 or 7); δ ^{13}C NMR (150 MHz, $CDCl_3$, 60°C) 156.6 (C_q), 140.0 (C_q), 132.7 (C_q), 130.4 (CH), 127.5 (CH), 125.8 (C_q), 115.1 (CH), 112.7 (CH), 108.9 (CH), 91.5 (CH), 55.7 (CH_3), 54.6 (C_q), 52.6 (CH_3), 47.5 (CH_2), 37.3 (CH_2); HRMS (CI) cald. for $C_{15}H_{16}NO_3$ $[M\text{-}Cl\text{-}H]^+$ 258.1125, found 258.1127.

(L)-Proline catalysed asymmetric Mannich reaction



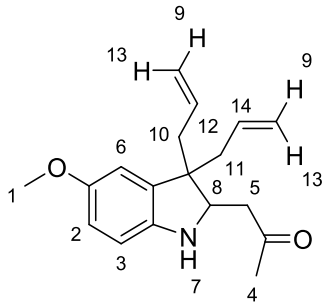
R = H, Cl, OMe

General Procedure for asymmetric Mannich reaction:

Method K: To the substituted 3,3-diallyl-3*H*-indole (1 eq) were added (1 : 4.5) $CHCl_3$: acetone (0.022 M) and 30 mol% of L-proline at 0°C and left to stir for 2 days allowing the reaction temperature to rise to r.t. Evaporation of solvent and purification of dry load flash column chromatography gave the desired product.

Method L: To the substituted 3,3-diallyl-3*H*-indole (1 eq) were added (1 : 4.0) DMSO: acetone (0.016 M) and 30 mol% of L-proline at 0°C and left to stir for 2 days allowing the reaction temperature to rise to r.t. The reaction mixture was diluted with diethyl ether (5ml) and washed with saturated solution of sodium bicarbonate (5 ml), water (10 ml), and brine (5 ml), dried with $MgSO_4$, filtered and concentrated to give the crude oil. Purification by dry load flash column chromatography gave the desired product.

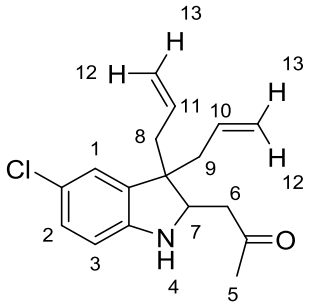
1-(3,3-Diallyl-5-methoxyindolin-2-yl)propan-2-one (168a)



168a

Using method A: Purification by dry load flash chromatography gradient method 0-5% Et_2O: CH_2Cl_2 which gave the title compound as a yellow oil (60 mg, 96%); R_f = 0.50 (9.5 : 0.5 CH_2Cl_2 : Et_2O); IRυ_{max} 3367 (C-H), 2977 (N-H), 1713 (C=O), 1500 (aromatic), 1434, 1220 (C-O), 1168 (C-N) cm^{-1}; δ ^{1}H NMR (600 MHz, $CDCl_3$) 6.61 (dd, 1H, *J* = 8.3, 2.4 Hz, H-2), 6.59 (d, 1H, *J* = 2.4 Hz, H-6), 6.56 (d, 1H, *J* = 8.3 Hz, H-3), 5.74 (dtd, 1H, *J* = 16.3, 9.2, 7.3 Hz, H-14 or 12), 5.67(dtd, 1H, *J* = 16.3, 9.2, 7.3 Hz, H-14 or 12), 5.06-5.00 (m, 4H, H-13, 9), 3.99 (dd, 1H, *J* = 10.5, 2.4 Hz, H-8), 3.74 (s, 3H, H-1), 2.81 (m, 2H, H-5), 2.51; 2.39 ((dd, 1H, *J* = 14.3, 7.3 Hz, H-11 or 10) (dd, 1H, *J* = 14.3, 7.3 Hz, H-11 or 10)), 2.36; 2.12 ((dd, 1H, *J* = 14.3, 7.3 Hz, H-11 or 10) (dd, 1H, *J* = 14.3, 7.3 Hz, H-11 or 10), 2.20 (s, 3H, H-4); δ ^{13}C NMR (150 MHz, $CDCl_3$) 208.9 (C_q), 154.3 (C_q), 143.8 (C_q), 135.5 (C_q), 134.7 (CH), 134.3 (CH), 118.3 (=CH_2), 118.1 (=CH_2), 112.4 (CH), 111.4 (CH), 110.1 (CH), 62.6 (CH), 56.1 (CH_3), 49.3 (C_q), 44.3 (CH_2), 40.9 (CH_2), 38.4 (CH_2), 30.8 (CH_3); HRMS (CI) cald. for $C_{18}H_{24}NO_2$ $[M+H]^+$ 286.18070, found 286.17948. Enantiomeric ratio 98.8: 1.2 (major: minor) by chiral HPLC (Chiralpak Diacel AD, 75:25 hexane: *i*PrOH, 0.5 mL/min, 15.12 min (minor), 16.70 min (major). $[\alpha]_D^{20}$ = + 0.100 (c = 1.01 mg/mL, $CHCl_3$).

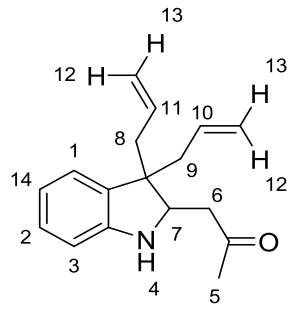
1-(3,3-Diallyl-5-chloroindolin-2-yl)propan-2-one (168b)



168b

Using method B: Purification by dry load flash chromatography gradient method 0-20% EtOAc: Petrol which gave the title compound as a yellow oil (28 mg, 64%). R_f = 0.50 (9.5 : 0.5 CH_2Cl_2 : Et_2O); IRυ_{max} 3010 (=C-H), 2918 (N-H), 1713 (C=O), 1479 (aromatic), 1427, 1169 (C-N) cm^{-1}; δ ^{1}H (600 MHz, $CDCl_3$) 6.98 (dd, 1H, *J* = 8.3, 2.3 Hz, H-2), 6.90 (d, 1H, *J* = 2.3 Hz, H-1), 6.53 (d, 1H, *J* = 8.3 Hz, H-3), 5.71 (dtd, 1H, *J* = 17.0, 9.8, 7.0 Hz, H-11or 10), 5.65 (dtd, 1H, *J* = 17.0, 9.8, 7.0 Hz, H-11 or 10), 5.09-5.00 (m, 4H, H-13, 12), 4.55 (br s, 1H, NH), 4.01 (dd, 1H, *J* = 8.4, 4.8 Hz, H-7), 2.79 (m, 2H, H-6), 2.48; 2.39 ((dd, 1H, *J* = 13.8, 7.0 Hz, H-9 or 8) (dd, 1H, *J* = 13.8, 7.0 Hz, H-9 or 8), 2.35; 2.12 (dd, 1H, *J* = 13.8, 7.0 Hz, H-9 or 8) (dd, 1H, *J* = 13.8, 7.0 Hz, H-9 or 8)), 2.20 (s, 3H, H-5); δ ^{13}C (150 MHz, $CDCl_3$) 208.3 (C_q), 148.4 (C_q), 135.9 (C_q), 134.1 (CH), 134.0 (CH), 127.7 (CH), 124.3 (CH), 123.2 (C_q), 118.6 (=CH_2), 118.5 (=CH_2), 110.8 (CH), 63.1 (CH), 49.2 (C_q), 43.8 (CH_2), 40.7 (CH_2), 38.2 (CH_2), 30.7 (CH_3); HRMS (CI) cald. for $C_{17}H_{21}NO$ $[M+H]^+$ 290. 8030, found 290.1311. Enantiomeric ratio 99.0: 1.0 (major: minor) by chiral HPLC (Chiralpak Diacel AD, 75:25 hexane : *i*PrOH, 0.5 mL/min, 11.56 min minor, 13.14 min major). $[\alpha]_D^{20}$ = + 0.360 (c = 1.36 mg/mL, $CHCl_3$).

1-(3,3-Diallylindolin-2-yl)propan-2-one (168c)



168c

Using method A: (61 mg, 81% pale yellow oil); R_f = 0.50 (9.5 : 0.5 CH_2Cl_2 : Et_2O); $IR_{\upsilon\ max}$ 3010 (=C-H), 2929 (N-H), 1693 (C=O), 1505 (aromatic), 1253 cm^{-1}; δ ^1H (600 MHz, $CDCl_3$) 7.04 (td, 1H, *J* = 7.4, 1.0 Hz, H- 2), 6.97 (d, 1H, *J* = 7.4 Hz, H-1), 6.73 (td, 1H, *J* = 7.4, 1.0 Hz, H-14), 6.63 (d, 1H, *J* = 7.4 Hz, H-3), 5.75 (dtd, 1H, *J* = 17.1, 9.7, 7.3 Hz, H-11 or 10), 5.68 (dtd, 1H, *J* = 17.1, 9.7, 7.3 Hz, H-11 or 10), 5.07-5.00 (m, 4H, H-13, 12), 4.53 (br s, 1H, NH), 4.00 (dd, 1H, *J* = 8.5, 4.6 Hz, H-7), 2.80 (m, 2H, H-6), 2.52; 2.38 ((dd, 1H, *J* = 14.1, 7.3 Hz, H-9 or 8) (dd, 1H, *J* = 14.1, 7.3 Hz, H-9 or 8)), 2.43; 2.10 ((dd, 1H, J = 14.1, 7.3 Hz, H-9 or 8) (dd, 1H, *J* = 14.1, 7.3 Hz, H-9 or 8), 2.20 (s, 3H, H-5); δ ^{13}C (150 MHz, $CDCl_3$) 208.6 (C_q), 150.0 (C_q), 143.8 (CH), 134.4 (CH), 133.8 (C_q), 127.8 (CH), 124.1 (CH), 118.6 (CH), 118.2 (=CH_2), 118.0 (=CH_2), 109.9 (CH), 62.1 (CH), 49.0 (C_q), 44.0 (CH_2), 41.0 (CH_2), 38.5 (CH_2), 30.7 (CH_3); HRMS (CI) cald. for $C_{17}H_{22}NO$ $[M+H]^+$ 256.17012, found 256.16980. Enantiomeric ratio 99.3: 0.7 (major: minor) by chiral HPLC (Chiralpak Diacel AD, 95:5 hexane : *i*PrOH, 0.5 mL/min, 16.71 min minor, 21.45 min major). $[\alpha]_D^{20}$ = + 0.111 (c = 1.01 mg/mL, $CHCl_3$).

Experimental for Molecular Modelling:

Molecular modelling was carried out using PCModel software and MMX force field.[214] Vicinal $^{3}J_{HH}$ couplings were calculated using empirically parameterized Karplus equations of Haasnoot *et al.*[215] These equations contain terms accounting for the differences in electronegativities of α- and β-substituents, and hence are better suited for the analysis of the $^{3}J_{HH}$ couplings than the original Karplus equation.[216, 217] The precision of equations proposed by Haasnoot *et al.* is estimated to be <0.6 Hz (expressed as the rms deviation) using a set of 100 experimental $^{3}J_{HH}$ couplings.[217]

Experimental data of TQS compounds showing tables of measured coupling constant values determined by ^{1}H NMR and calculated coupling constants determined by PC Model V8 software for:

Methylated TQS compounds isolated as cis: cis isomers

Entry	*J* value (Hz) for A-C determined by ^{1}H NMR	*J* value (Hz) for A-B determined by ^{1}H NMR	Entry	Energy minimized *J* value (Hz) for A- C determined by PC Model	Energy minimized *J* value (Hz) for A-B determined by PC Model
47b	8.7	2.8	**47b**	6.8	3.3
48b	8.7	2.9	**48b**	7.0	3.1
49b	8.3	3.2	**49b**	6.8	3.3
50b	8.8	3.3	**50b**	8.8	2.5
52b	9.0	2.6	**52b**	9.0	2.8
53b	8.6	3.0	**53b**	8.6	3.1
54b	8.6	3.2	**54b**	8.6	2.1
56b	6.3	3.0	**56b**	6.3	3.2
59b	9.4	2.8	**59b**	9.4	2.7
60b	8.5	2.8	**60b**	8.5	2.7
62b	8.6	2.9	**62b**	8.6	3.1
63b	8.7	2.8	**63b**	8.7	2.7

Methylated TQS compounds isolated as trans: cis isomers

Entry	*J* value (Hz) for A-C determined by ^{1}H NMR	*J* value (Hz) for A-B determined by ^{1}H NMR	Entry	Energy minimized *J* value (Hz) for A-C determined by PC Model	Energy minimized *J* value (Hz) for A-B determined by PC Model
50a	**6.8**	**10.9**	**50a**	**6.8**	**11.1**
55a	**5.4**	**10.8**	**55a**	**5.4**	**11.2**
57a	**6.9**	**10.7**	**57a**	**6.9**	**11.2**
58a	**6.8**	**11.0**	**58a**	**6.8**	**11.2**
61a	**8.8**	**9.8**	**61a**	**8.8**	**11.2**
64a	**7.9**	**10.0**	**64b**	**6.9**	**11.2**

Additional para- substituted TQS compounds isolated as cis: cis isomers

Entry	*J* value (Hz) for A-C determined by ^{1}H NMR	*J* value (Hz) for A-B determined by ^{1}H NMR	Entry	Energy minimized *J* value (Hz) for A-C determined by PC Model	Energy minimized *J* value (Hz) for A-B determined by PC Model
65b	8.7	3.3	**65b**	7.0	3.1
66b	8.5	2.6	**66b**	7.0	3.1
67b	8.5	3.6	**67b**	7.0	3.1
68b	8.6	2.8	**68b**	7.0	3.1
69b	9.8	2.9	**69b**	7.0	3.1
70b	7.0	2.5	**70b**	7.0	3.1

71b	8.5	2.9	**71b**	7.0	3.1
72b	8.5	2.7	**72b**	7.0	3.1
73b	8.8	2.7	**73b**	7.1	2.9

Heteroaromatic TQS compounds

Entry	***J* value (Hz) for A-C determined by ^{1}H NMR**	***J* value (Hz) for A-B determined by ^{1}H NMR**	**Entry**	**Energy minimized *J* value (Hz) for A-C determined by PC Model**	**Energy minimized *J* value (Hz) for A-B determined by PC Model**
74b	8.9	2.8	**74b**	7.1	3.0
75b	8.9	3.0	**75b**	7.1	3.1
76b	8.4	2.8	**76b**	7.0	2.7
77b	8.6	7.0	**77b**	2.8	3.1

Substituted Sulfanilamide TQS compounds

Entry	***J* value (Hz) for A-C determined by ^{1}H NMR**	***J* value (Hz) for A-B determined by ^{1}H NMR**	**Entry**	**Energy minimized *J* value (Hz) for A-C determined by PC Model**	**Energy minimized *J* value (Hz) for A-B determined by PC Model**
94b	8.6	2.9	**94b**	7.0	3.1
92b	8.5	2.9	**92b**	7.0	3.1
93b	8.1	3.0	**93b**	7.0	3.1

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