Realising Lead-Oriented Synthesis-
A 'Top-Down' Approach to Synthesising Lead-Like Scaffolds

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Declaration

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Abstract

This report focusses on the concept of lead-oriented synthesis in an attempt to synthesise diverse small molecule scaffolds that target lead-like chemical space. The 'top-down' approach was taken, which is a method used within the Marsden and Nelson group where polycyclic assemblies are prepared and then deconstructed to give a library of diverse lead-like molecules. Each lead-like scaffold was synthesised with good stereo/regio control, on a large scale from cheap starting materials, with appropriate molecular properties. Each compound was then investigated for its diversification at points of the scaffold, in the possibility of providing access to a variety of novel-like, sp^3-riched compounds suitable for screening. The computational software LLAMA was used throughout the project to help analyse properties and guide the development of three-dimensional compounds.

Chapter 1 discusses the overview of the drug discovery process, detailing the problems faced in the pharmaceutical industry, highlighting the high failure rates for drug candidates possessing certain molecular properties. The ideal molecular properties for drug, leads and fragment compounds is discussed, with the modern synthetic approaches to prepare such lead diverse screening compounds in an efficient manner.

Chapter 2 – 4 details the synthesis of diverse novel scaffolds prepared from robust synthetic methodologies to access a library of compounds with appropriate molecular properties for biological screening. In total 14 scaffolds were synthesised from 28 synthetic operations and 52 novel compounds from a total of 73 synthetic operations. Here the method has produced a library of complex and highly three-dimensional compounds with attention paid to physicochemical and functional group properties, whilst maintaining synthetic efficiency. The library was sent for biological evaluation against five different targets, of which 15 hits were observed. A follow-up library was then produced where 13 compounds were sent for a second round of biological evaluation against the *Plasmodium falciparum* cells.

List of abbreviations

δ - chemical shift

μ – mean

λ – wavelength

3D – three dimensional

Ac – acetate

ADME – absorption, distribution, metabolism and excretion

ADMET– absorption, distribution, metabolism, excretion, and toxicity

AlogP – logarithm of the partition coefficient (atom–based prediction)

ATAD2 – ATPase Family AAA Domain Containing 2

B/C/P – build/couple/pair

CAM – cerium ammonium nitrate

CAS – chemical abstracts service

Cbz – carboxybenzyl

clogP – logarithm of the partition coefficient (fragment–based prediction)

cod – 1,5–cyclooctadiene

COSY – correlation spectroscopy

Cy – cyclohexyl

d – doublet

Da – Daltons

DABCO – (1,4–diazabicyclo[2.2.2]octane)

DCM – dichloromethane

dd – doublet of doublets

ddd – double doublet of doublets

DDQ – 2,3–dichloro–5,6–dicyano–1,4–benzoquinone

DEPT – distortionless enhancement through polarisation transfer

DIBAL – diisobutylaluminium hydride

DIPEA – N,N–diisopropylethylamine

DMAP – 4–dimethylaminopyridine

DMF – N,N–dimethylformamide

DMSO – dimethylsulfoxide

DNA – deoxyribonucleic nucleic acid

DOS – diversity oriented synthesis

dr – diastereomeric ratio

ee – enantiomeric excess

e.g. – exempli gratia

EDCI – 1–ethyl–3–(3–dimethylaminopropyl)carbodiimide

eq. – equivalents

er – enantiomeric ratio

ESI – electrospray ionisation

FBDD – fragment based drug discovery

FDA – Food and Drug Administration

FID – Fluorescent intercalator displacement

Fsp3 – fraction of sp3 hybridized carbons

FT–IR – Fourier Transform Infrared Spectroscopy

GSK – GlaxoSmithKline

HAC – heavy atom count

HMBC – Heteronuclear Multiple Bond Correlation

HMQC – Heteronuclear Multiple Quantum Coherence

HPLC – high performance liquid chromatography

HRMS – high resolution mass spectrometry

HTS – High–Throughput Screening

J – coupling constant

JMJD2D – jumonji–domain–containing–2d–gene

LA – Lewis acid

LC–MS – Liquid Chromatography–Mass Spectrometry

LiHMDS – Lithium bis(trimethylsilyl)amide

LLAMA – Lead–Likeness and Molecular Analysis

LOS – lead–oriented synthesis

MDAP – mass directed automated purification

MHz – megahertz

MOM – methoxymethyl

M.p – melting point

MPI – Max Planck Institute of Molecular Physiology

MS – molecular sieves

nAr – number of aromatic rings

NBS – N-bromosuccinimide

NCS – N-chlorosuccinimide

NIS – N-iodosuccinimide

nOe – nuclear Overhauser effect

NOESY – nuclear Overhauser effect spectroscopy

Nu – nucleophile

[o] – oxidation

P. falciparum – *Plasmodium falciparum*

PG – protecting group

PMB – para-methoxybenzyl

PMI – principal moment of inertia

PSA – polar surface area

Py – pyridine, pyridyl

q – quartet

qn – quintet

QSARs – Quantitative structure–activity realtionships

Rf – retention factor

RO5 – rule of five

rt – room temperature

s – singlet

SAR – structure–activity relationship

SCX – strong cation exchange

SN – nucleophilic substitution

T – temperature

TBS – tert-butyldimethylsilyl

TBDPS – tert-butyldiphenylsilyl

TBS – tert-butyldimethylsilyl

TEMP – 2,2,6,6-tetramethylpiperidine

Tf – trifluoromethanesulfonyl

THF – tetrahydrofuran

TLC – thin layer chromatography

TosMIC – tosylmethyl isocyanide

Ts – p-toluenesulfonyl

TSA – toluenesulfonic acid

Table of contents

1.0 Introduction

1.1 An overview of the drug discovery and development process

The drug discovery process is a highly complex and multidisciplinary process which arises from the requirement for medicinal products for the treatment of a disease or clinical condition.[1] In very early development stages, a biological target can be found which causes or leads to a disease.[2] A hypothesis is proposed that states inhibition or activation of the protein or pathway will result in a therapeutic effect in a disease state.[1,3] Chemical or biological compounds are screened and tested against the target to find *lead* candidates for further investigation.[4] Active compounds are usually identified through the widely available technology known as high throughput screening, whereby a *hit* is found from screening the compounds against the given biological target. A *hit* is a primary active compound with biological relevance and is a small molecule with non-promiscuous binding behaviour, exceeding a certain threshold value in a given assay.[5] Once a high quality hit has been identified it is then further validated and developed into a *lead*, this process is known as *hit-to-lead* and is an early stage in drug development (as seen in **Figure 1**).[5] The next step is *lead optimisation*, which involves the lead compound being improved for downstream development ADMET (absorption, distribution, metabolism, excretion, and toxicity) testing can be carried out to understand and optimise a candidate's biological properties.[6] Here *in vivo* and *in vitro* cell based studies are used to characterise the biological mechanism of action.[7] Toxicological data is produced, which allows the lead compound to be developed into a safe and effective drug, with good affinity and selectivity.[1,8] The development drug candidate will then progress through into pre-clinical/clinical trials and ultimately become a marketed medicine.[5,9] An alternative method for small molecule drug discovery is fragment based drug discovery (FBBD),[10] which involves screening fragments; this technique is further elaborated in **Section 1.6**.

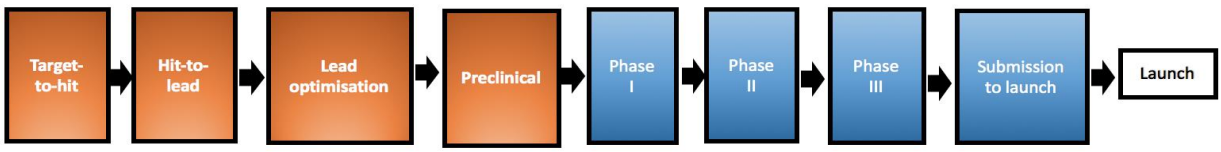


Figure 1. A schematic to outline the process by which drug discovery is undertaken. Adapted from ref.[5]

1.2 Problems in the pharmaceutical industry

High attrition rates have been identified in clinical drug development and this has been an ongoing problem in the pharmaceutical industry.[11] Monitoring the physicochemical properties of candidates in early phases of discovery may reduce the number of efficacy and safety related failures that the industry suffers, and may be beneficial in identifying compounds of candidate drug quality.[12]

Drug candidates fail in clinical trials because of a variety of complications;[13] often difficulties arise due to toxicological problems and poor bioavailability and pharmacokinetic properties.[1,14] Phase II/III attrition rates are increasing and evidence has demonstrated that improving research and development (R&D) efficiently and productively will help this. Overall attrition rates of 93-96% have been identified in clinical drug development,[11] with 66% of compounds that enter phase II failing prior to phase III and a further 30% of candidates that enter phase III failing prior to the *submission to launch* phase.[15] Efforts have been made to reduce failure rate and advances in cheminformatics reveal a clear link between drug candidate success and physicochemical properties relevant in small-molecule drug discovery.[12] With judicious selection of lead compounds and constant monitoring of physical properties during optimisation, a medicinal chemist can be in control of the compound's physicochemical properties and this hopefully will increase the success rate of drug candidates. An attrition percentage that decreases by 5% can in turn lead to an improvement of up to double the amount of new medicines brought to market.[16] Recent studies have shown that lead-oriented synthesis (LOS) can increase the range and quality of molecules used to develop medicines, in the hope of reducing attrition in the drug discovery process.[17,18,19]

The cost of drug discovery and developing new drugs has increased rapidly each year.[20] The estimated cost of a new drug is ~ £1 billion (this also includes cost of failed campaigns) with a timescale of approximately 12-15 years for the drug to reach the marketplace.[21,22] Due to these remarkably high numbers, it is becoming an important problem which needs addressing. A number of challenges face the pharmaceutical industry such as the loss of capital from expiring patents and the low number of new chemical entities[11,23]

Reducing attrition rates of drug candidates during the early stages of drug discovery and development is critical in order to help solve these ongoing problems in the pharmaceutical industry.[21] There are now numerous pieces of evidence to support the theory that the chance of a small molecule drug candidate being successful is highest when its physicochemical

properties lie within a certain range.[24] Some of these properties, such as molecular weight and lipophilicity, have a significant effect on the drug's ability to succeed. These desired properties can be targeted from an early stage by the use of a suitable synthetic strategy so that a *lead* compound can be developed without problematic characteristics and occupying the conceptual area known as *lead-like space*.[25]

1.3 Drug likeness - properties of successful hits and drugs

As described above, there is an apparent link between physicochemical properties and drug-like properties for a drug candidate. An attempt to characterise these links was introduced by Lipinski and co-workers in 1997,[26] who analysed the physicochemical properties of a large number of orally bioavailable drugs and concluded that a compound is more likely to be membrane permeable and easily absorbed by the body if it matches the following criteria (**Table 1**).[27] These observations are referred to as the *Lipinski rule of 5*.

Physicochemical Properties	Ideal value
Molecular Weight (Daltons)	≤500
Hydrogen bond acceptors	≤10
Hydrogen bond donors	≤5
clog*P*	≤5

Table 1. Outline of the 'Lipinski rule of 5', which predicts that poor absorption or permeation is more likely when these rules are breached. [26,27]

The majority of compounds which are orally bioavailable conform to these rules and Lipinski advises that an ideal drug will have a higher chance of being successful if it possess such characteristics. [26,28] (N.B. there are numerous successful drugs with characteristics that lie outside this range). Ideally these should be a small molecule that is no larger than 500 Daltons, with a log*P* being no greater than 5. The property log*P* is the log of the ratio of concentrations of a solute between immiscible phases, water and octanol (**Equation 1**).[27,31] The compound should also possess no more than 5 groups that can donate hydrogen bonds and no more than 10 groups that can accept hydrogen bonds. These criteria have been widely applied by medicinal chemists to predict the overall drug-likeness of a molecule. However, recent studies have shown that compounds with significantly lower molecular weight and log*P* values are now being favoured, because compounds that are close to the Lipinski limits have a lower probability of success.[24,29,30]

$$\log P_{\,oct/wat} = log \left(\frac{[\text{solute}]_{\,octanol}}{[\text{solute}]_{\,un\text{-}ionized\ water}} \right)$$

Equation 1. Equation showing the calculation of logP.[31]

Recent studies have highlighted the detrimental effect of excessive lipophilicity for numerous reasons.[16,30] In order to deliver a drug molecule to its given target, the drug must be polar enough to be soluble in aqueous media (such as the blood) and yet lipophilic enough to pass through the lipid membrane to get into the cell without binding to unwanted proteins upon entry. If a drug is too lipophilic it may have undesirable absorption, distribution, metabolism and excretion (ADME) properties,[32] as well as having issues with binding to serum proteins in the blood, thus leaving a low level of the unbound drug free to bind to the desired target. Lastly, it may have off-target effects.[33] However, although lowering lipophilicity is important, if the log*P* value is below 1 this has been shown to increase problems with metabolic clearance, aqueous solubility and the drug may have difficulty in crossing cellular membranes.[34,35,36]

During the lead optimisation process, the candidate molecule generally increases in molecular weight and lipophilicity downstream from the initial lead compound, as substituents are added to the molecule in order to enhance binding to and selectivity for the target.[24,37] Therefore the lead molecule will ideally have a preferred set of physicochemical properties, which allow for further optimisation. This smaller area of physicochemical space is known as *lead-like* space and controlling the molecular properties of a lead molecule is crucial if the final compound is to remain in optimal drug-like space (**Figure 2**). [17,24,38]

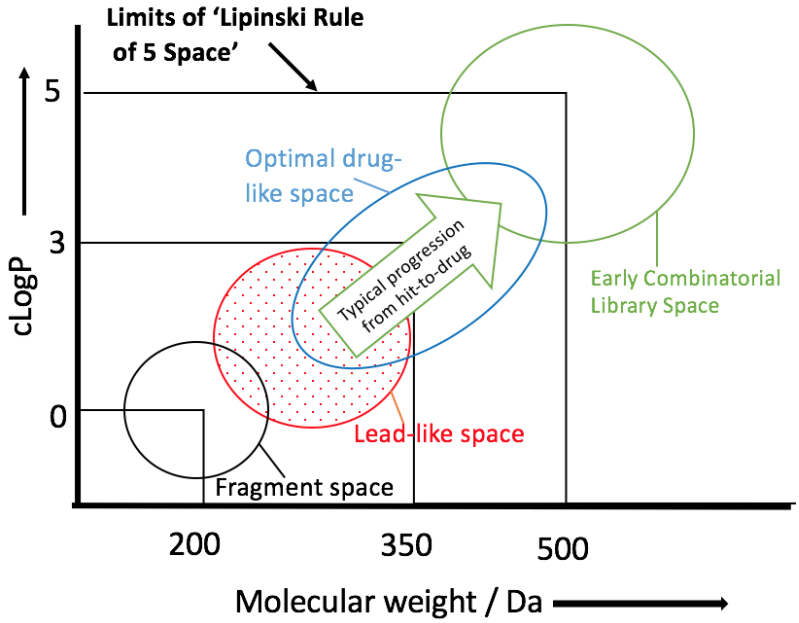


Figure 2. A graph demonstrating areas of chemical space. Fragment-like space (black circle), lead-like space (red-circle) optimal drug-like space (blue oval) and early combinatorial library space (green circle). It also indicates the molecular weight and clogP for each chemical space. Adapted from source.[24]

1.4 Lead-likeness

A molecule that has properties outside the lead-like parameters before optimisation will have a much reduced chance of succeeding at later stages in drug development and discovery.[24] As stated in the previous section, optimisation will generally increase lipophilicity and log*P*, therefore possibly leading to off-target activity. A range of parameters for lead-likeness have been developed and are summarised below (**Table 2**).

Physicochemical Properties	**Ideal Value**
Molecular Weight (Daltons)	200 – 350
Heavy atoms (C, O, N, S etc.)	14 – 26
Lipophilicity	-1 ≤ clog*P* ≤ 3
Shape	More 3D shape
Number of aromatic rings (*nAr*)	1 - 3
Undesired sub-substructure filters	Remove moieties containing chemically reactive, electrophilic or redox active groups

Table 2. Outline of the preferred molecular properties and features for lead-like small molecules. [19,24]

Although there has been extensive research into the influence of lipophilicity and molecular weight on drug candidate success rates, there has now been increased interest in the degree of three-dimensional (3D) shape and aromatic character of the lead compound.[39,40] Increasing the complexity of a drug candidate by varying its chirality and shape has a good correlation with the success of a compound's transition from discovery, through clinical testing, to market.[39] Compared with unsaturated molecules, saturated molecules have been shown to have higher aqueous solubility and lower lipophilicity, both of which are important physical properties for success in the drug discovery setting.[39] One way of assessing the complexity and saturation of a 3D molecule is to look at the fraction of sp^3 hybridized carbons (Fsp^3), with highly complex 3D molecules having a higher Fsp^3 count; the Fsp^3 count is calculated below (Equation 2). Furthermore, studies have suggested that complex 3D shapes have desirable aqueous solubility because of increased solvation and poorer solid state crystal lattice packing.[39,41,42] In addition, more than three aromatic rings in a molecule correlates with poorer developability and decreased aqueous solubility, therefore increasing the risk of attrition in early drug development.[40]

$$\text{Fraction } sp^3 \ (Fsp^3) = \left(\frac{\text{Number of } sp^3 \text{ hybridized carbons}}{\text{Total carbon count}} \right)$$

Equation 2. Equation showing how to calculate the degree of saturation of a compound.[39]

Due to the industry's focus on specific reaction types and the synthetic accessibility of molecules with high sp^2 character (through e.g. biaryl couplings and amide bond formation), there is a large proportion of screening compounds that are relatively two-dimensional.[43] The complexity of synthesising sp^3 hybridised carbon centres has led to limited availability of complex chiral structures.[44] As an illustration of the traditional focus on these molecules, one can examine their 3D structure by using a normalized principal moment of inertia (PMI) plot.

PMI plots represent the three-dimensional shape of a molecule on a two-dimensional ternary plot. The vertices of the plot portray the three extremes of molecular geometry.[45] The left-hand vertex represents the *rod-like* molecular shape which is symbolised by an sp-hybridised 2,4,6-octatriyne. The right-hand vertex represents the *sphere-like* molecular shape which is symbolised by an sp^3 hybridised adamantane. The bottom vertex represents the *disk-like* molecular shape which is symbolised by an sp^2 hybridised benzene molecule. Compounds are

plotted between the three vertices and assessed on their three-dimensional shape.

A PMI plot was produced for a random 1% (90911 compounds) of compounds from the ZINC database, showing the molecular shape of the compounds (**Figure 3**).[46] The ZINC database consists of commercially available compounds for virtual screening, where over 35 million compounds can be purchased.[47] It provides evidence of the lack of 3D shape of available compounds, and thus giving increased importance to produce molecular scaffolds with 3D shape and chirality.

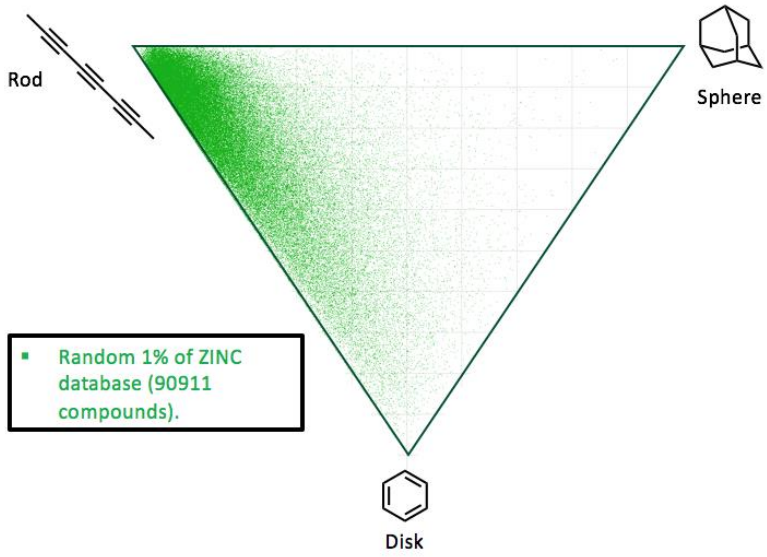


Figure 3. A PMI plot of 90911 virtual compounds from a random 1% the ZINC database of commercially available compounds. The compounds (green dots) are plotted based on their rod-like properties, disk-like properties and sphere-like properties.[46]

A study by Shivanyuk and co- workers in 2010 performed an analysis of the lead-likeness of a library of 7.9×10^6 compounds, using a more relaxed early definition of lead like properties.* The study consisted of assembling and analysing 7.9×10^6 commercially available compounds from 29 suppliers, within which 5.2×10^6 structures were identified as unique. These compounds were then subjected to assessments of their physical and biological properties. A broader set of parameters* to **Table 2** were applied to the compounds which revealed only 16% of them had potential to be leads.[48]

* The corresponding values used to select lead-like compounds were taken from a paper by Hann and Oprea[38]: 200 < molecular weight (Da) < 460, -4 < log*P* < 4.2, rotating bonds ≤ 10, polar surface area ≤ 170.

However, a more recent study reviewed 4.9×10^6 commercially available compounds from 104 different sources, with the aim of finding the percentage of lead-like compounds. A much lower percentage of compounds were of lead-likeness. Using the GlaxoSmithKline (GSK) lead-likeness guide, featured in **Table 2**, the compounds were then analysed for molecular weight, lipophilicity and undesired features. The results showed that 70% of compounds fell outside 'lead-like' space because of their molecular weight and the remaining half then failed because of lipophilicity issues. The remaining compounds had undesired functional groups, leaving only 2.6% compounds (1.2×10^4 compounds) that had desirable lead-like properties.[24]

A good starting point for a drug discovery programme is to follow simple molecular property guidelines. These guidelines in **Table 2** broadly describe lead-like space and provide simple parameters to follow in order to increase chances of the derived drug candidate being successful; also with the help of readily available computational tools, synthetic approaches can be evaluated and prioritised to ensure the compounds stay in lead-like space. Software tools such as LLAMA can be freely accessed and used to monitor lead-like synthesis of compounds.[45]

1.5 Diversity-oriented synthesis (DOS)

Diversity-oriented synthesis, first introduced by Schreiber,[49] aimed to scope chemical space by preparing a large number of skeletally diverse compounds for use in high-throughput screening, in the hope of finding hits with biological targets. This method aims to efficiently produce a collection of diverse complex molecules with a wide range of desirable physical and biological properties.[50] This strategy has major advantages with its exploration of wider chemical space and its use as a tool for the discovery of novel biologically active molecules.[51,52] However, this method has been criticised for its lack of consideration of molecular properties.[51]

A successful DOS strategy termed *build/couple/pair* (B/C/P) was described by Nielsen and Schreiber.[53] A generation of stereochemically diverse compounds were prepared, from chiral building blocks containing orthogonal sets of functionality suitable for subsequent coupling. The B/C/P strategy involves the asymmetric syntheses of these chiral building blocks, that when coupled provides the basis for large stereochemical diversity (**Figure 4a**). The *Couple* phase (**Figure 4b**) involves intermolecular coupling reactions that join the building blocks,

with the aim of complete control of all possible stereochemical outcomes (or without stereochemical consequences). Finally, the *Pair* phase involves functional group pairing reactions, which involves intramolecular coupling reactions that provide the basis for skeletal diversity (**Figure 4c**).

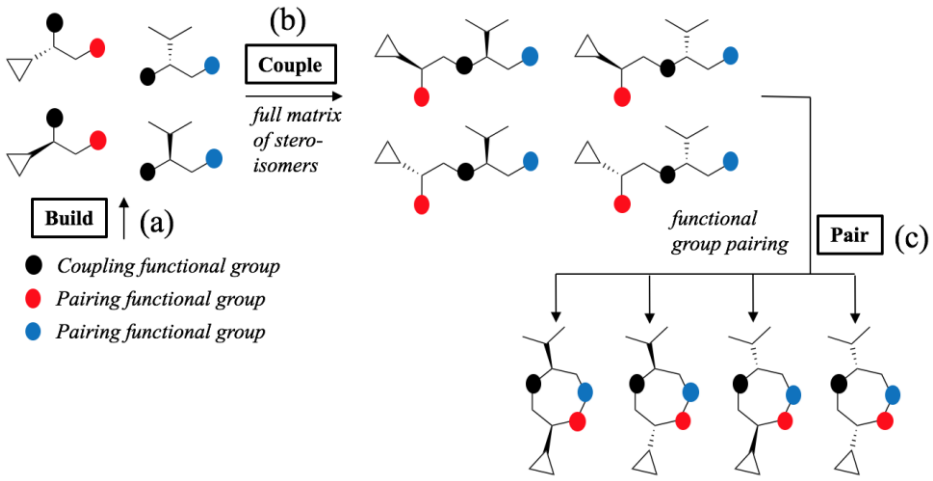


Figure 4. A general example of the B/C/P strategy in action. Step (a) showing the 'build' phase with the black dot representing coupling functional groups, the red dot and blue dot representing a pairing functional group. Step (b) represents the coupling phase and step (c) represents the pair stage.

1.6 Fragment based drug discovery (FBDD)

Fragment-based lead discovery is a discovery approach that involves the screening of smaller, lower molecular weight (140–230 Da) compounds, called fragments.[54] Compared with HTS hits, these fragments-based hits are typically weak inhibitors (100 μM–mM) of the biological target. Fragment-based compounds are much simpler, less functionalized compounds that have a lower affinity than typical commercially available compounds used in a HTS.[55]

One of the earliest approaches to describe the building of fragment libraries, was the *rule-of-three* guidelines which was first reported by Jhoti *et al*. in 2003.[56] However, since the strategy has been more developed over the years, a more strict set of guidelines can be used for the construction of fragment libraries.[54] Rees and Murray of Astex Pharmaceuticals have reported a more detailed set of properties, which is shown below (**Table 3**).

Property	**Guideline**
Molecular recognition	Diverse, usually polar groups for binding to a protein (a single pharmacophore)
Synthetic vectors	Multiple synthetically accessible vectors for fragment growth (allows access to a variety of new binding interactions in 3D space)
Physicochemical properties	Molecular weight: 140 – 230 (Daltons) Heavy atoms: 10 – 16 Lipophilicity: $0 \leq \text{clog}P \leq 2$ Stability: >24 h in solution Number of rotatable bonds: 0 – 3 Undesired sub-structure filters: Remove moieties known to be associated with high reactivity, aggregation in solution or false positives.[57] Properties commensurate with biophysical screening at high concentrations, e.g., aqueous solubility (preferably ≥ 5 mm in 5% DMSO, or other screening co-solvents);
Synthetic tractability	~ 50 – 100 mg and ≤ 4 steps from commercially available reagents
Shape	Variety of 3-dimensional shapes for each scaffold and pharmacophore; Number of chiral centres: 0 – 1, sometimes 2

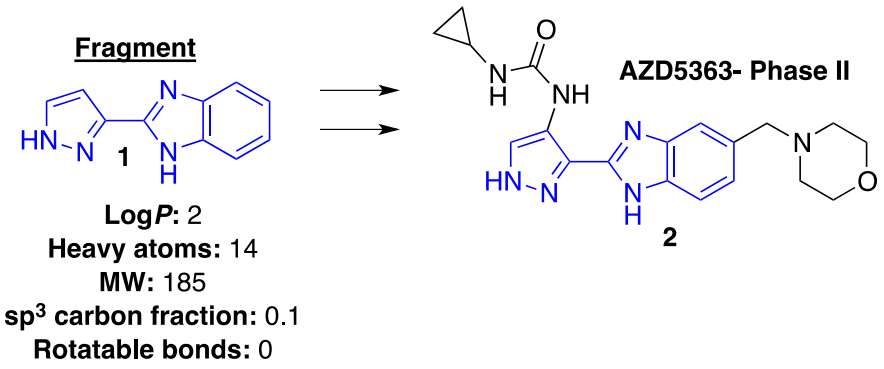
Table 3- Outline of the Astex guidelines for fragment-like molecules.[54]

The principal disadvantage of FBDD is that because of the small nature of the fragment molecules, there are fewer protein-ligand interactions when compared with drug-like/lead-like compound that are more complex and hence binding affinities are much lower, meaning direct assay of bioactivity is not possible in many cases.[58] The process requires sensitive biophysical detection techniques such as protein crystallography or NMR spectroscopy as the primary screening techniques, and preferably requires high quality structural data in-order to determine the binding of the fragment to a target.[10]

Where structural information exists fragments can be grown to form new interactions using structure-based drug design, to form high affinity leads. These low potency fragments have high-quality interactions that can be readily optimized into potent lead molecules through linking similar proximal binding fragments of a protein site.[59]

A typical fragment library can consist of 1,000 – 5,000 compounds, to provide a reasonable number of hits.[60,61] An example of a fragment compound is shown below, where a large

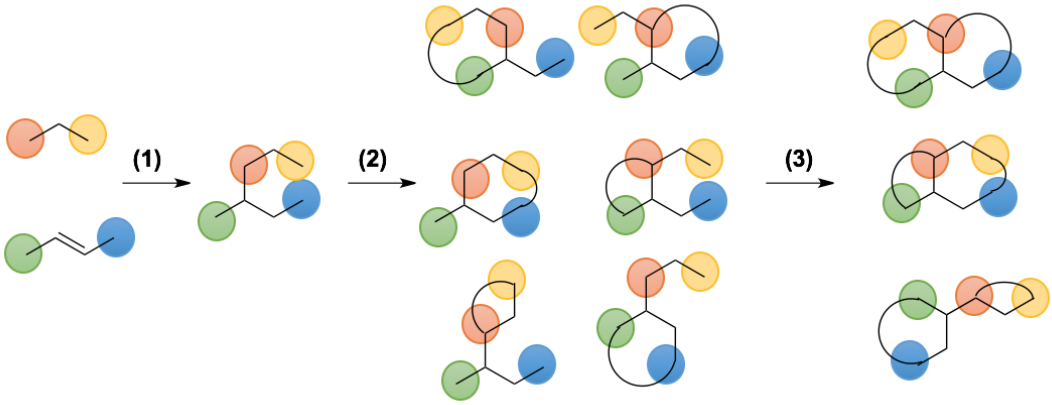
number of drugs derived from this widely practised strategy have entered clinical trials (**Scheme 1**).[61]



Scheme 1 An example of a fragment which follows the guidelines in Table 3 and its corresponding drug candidate

1.7 Lead-oriented synthesis (LOS)

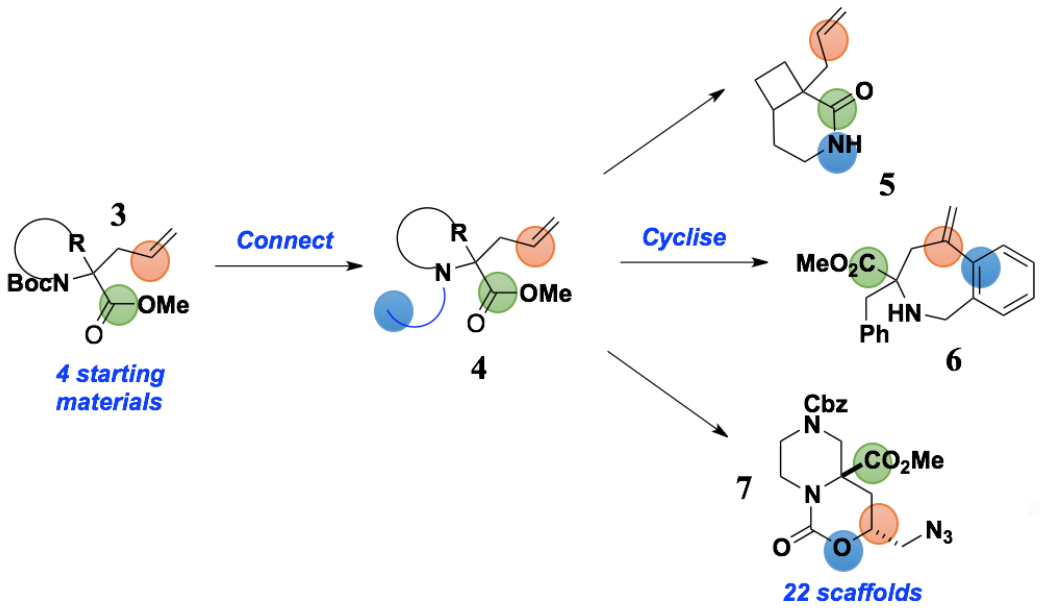
The objective of lead-oriented synthesis is to prepare diverse novel compounds that target lead-like chemical space. Its major challenge is to identify and demonstrate the use of new synthetic methodologies to achieve these goals. Although very similar to DOS, LOS focuses on the physicochemical nature of the product molecules, rather than solely their skeletal diversity.[25] Another key aim is to be able to produce a wide range of lead-like chemical structures that are not susceptible to excessive Log*P* drift and also, can be synthesised in an efficient way with the use of cheap reagents and conditions.[62] Syntheses must be tolerant to a wide range of polar functional groups, with the scaffolds also having no residual electrophilic or reactive centres. In order for a lead-like molecule to be successful it must be able to efficiently and effectively interact with biological systems.[24] Scaffolds which are primarily synthesised are susceptible to further diversification and decoration to create a library of lead-like compounds for biological screening.



Scheme 2. A general schematic for 'bottom-up' approach. Step 1- functional group-tolerant bimolecular coupling, step 2 monocyclisation to pairwaise coupling and step 3 bicyclisation by pairwaise coupling

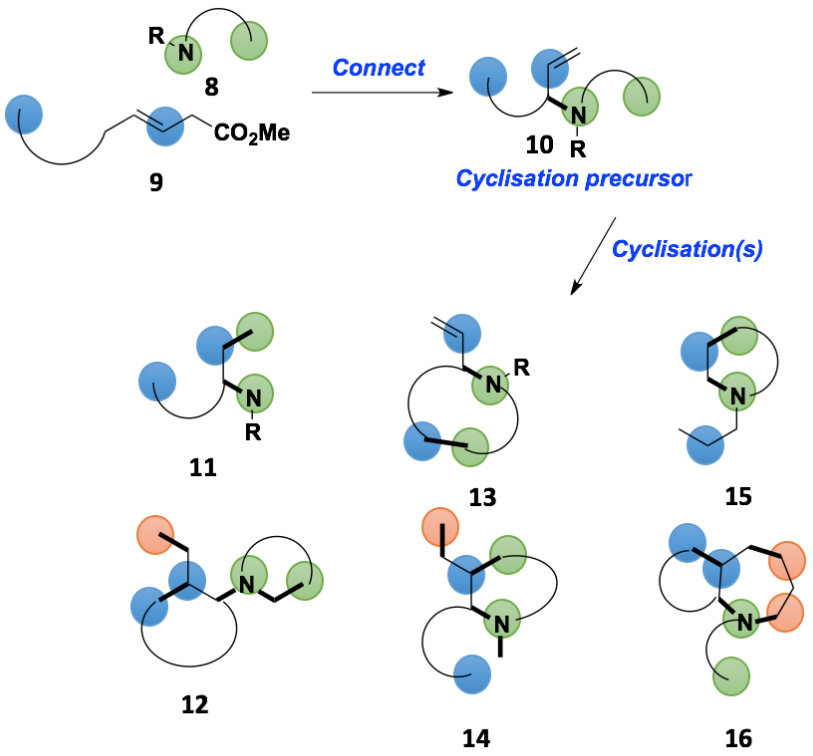
1.7.1 *Bottom-up* approach to lead-oriented synthesis

The *bottom-up* approach is used within the Marsden and Nelson group, which involves the preparation of small polyfunctionalised precursors to synthesise diverse lead scaffolds;[46] the approach shows similarities to Schreiber's BCP approach. An example of this method in action was performed by Marsden, Nelson and co-workers.[17] It involved a strategy for the efficient lead-oriented synthesis, by the preparation of twenty-two novel lead-like scaffolds from four α-amino acid-derived building blocks and six connective reactions. The small building blocks contained multiple chemically-orthogonal functional groups, which were then coupled using a minimal toolkit of reactions. To then confirm the validity of the library analysis, exemplar decoration was performed. The compounds were then evaluated for lead-like assessment, finding the library targeted the broad regions of lead-like chemical space and followed the rules for lead-likeness (c.f. **Table 2**). Their novelty and diversity assessment found that the twenty-two scaffolds synthesised were both novel and skeletally diverse. An example is shown below showing a few examples of successfully synthesised lead-like scaffolds (**Scheme 3**).



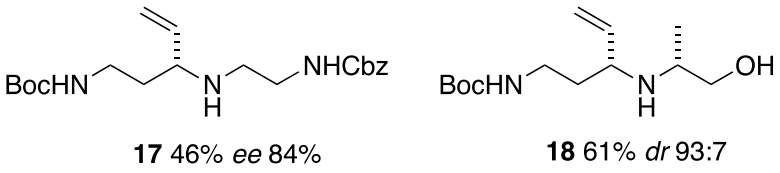
Scheme 3. A general example of a 'bottom-up' approach, where four starting material compounds produce twenty-two scaffolds.

Previous work has been carried out within the group by Marsden, Nelson and co-workers in 2015, where 52 diverse lead-like molecular scaffolds were synthesized from a set of 13 precursors, which targeted lead-like chemical space.[18] They exploited a suite of robust, functional group-tolerant transformations, from commercially available compounds and synthesised cyclisation precursors from allylic carbonates and amines (**Scheme 4**). From there, a range of scaffolds were produced from cyclisation or functionalization (filled circles), with third building blocks labelled in red and new bonds marked bold, yielding a large number of novel compounds with lead-like molecular properties.[18]



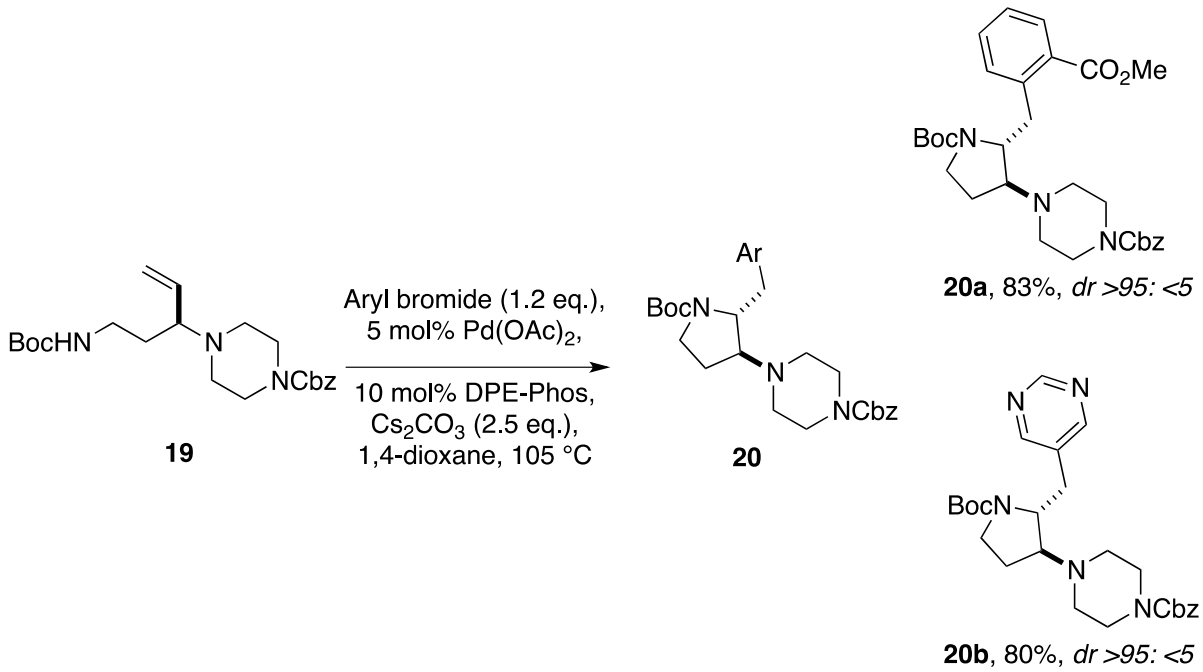
Scheme 4. A general outline of the formation of lead-like scaffolds from cyclisation precursors. Filled circles represent cyclisation functional groups and bold lines represent new bonds.

With the use of ten amine substrates and an allylic carbonate (two alternatives), thirteen cyclisation precursors were successfully prepared via iridium catalysis in excellent yields (46-82%) and with high enantio- or diastereoselectivity. A few examples are shown below. (**Scheme 5**).



Scheme 5. Two examples of cyclisation precursors.

Lead-like molecules were then synthesised from the thirteen cyclisation precursors, using a robust cyclisation toolkit. The toolkit consisted of six cyclisation methods that were exploited to convert the precursors into novel scaffolds. An example of such is below (**Scheme 6**), showing a Pd-catalysed aminoarylation which enabled conversion of the cyclisation precursor **19**, into the pyrrolidines **20a** and **20b**. Each of the reactions proceeded efficiently and with high diastereoselectivity.



*Scheme 6. A scheme showing the synthesis of two lead-like scaffolds **20a** and **20b** from a cyclisation precursor **19**.*

The 52 scaffolds were assessed for their novelty, diversity and their Fsp^3 character. They elaborated a virtual library based on these scaffolds and compared the properties of these to a selection of the ZINC database. The compounds were successively filtered by molecular size ($14 \leq$ number of heavy atoms (nHA) ≤ 26), lipophilicity ($-1 \leq$ Alog*P* ≤ 3) and undesirable structural features, with the result it was found each one of the 52 scaffolds allow significant regions within lead-like chemical space to be targeted (**Table 4**).

Filter	**Random 1% of ZINC Database (90911)**	**Virtual Library (19530)**
Fail 14 ≤ nHA ≤ 26	43971 (**48%**)	5104 (**26%**)
Fail -1 ≤ Alog*P* ≤ 3	17828 (**20%**)	2905 (**14.8%**)
Fail Structural	8180 (**9%**)	53 (**0.2%**)
Pass All	20932 (**23%**)	11468 (**59%**)

Table 4. Lead-like assessment data of the a random 1% of the ZINC database and the virtual library.

The compounds were compared with the ZINC database and CAS registry for novelty and were assessed using a hierarchical analysis for diversity (**Table 4**).[63,64] Then finally, the fraction of sp^3 was analysed by comparing to a random sample of compounds from the ZINC database, which showed on average the 52 scaffolds had significantly greater sp^3 character than most

commercially available compounds (**Figure 5**). This shows that the unified lead-oriented synthetic approach yielded novel, diverse and lead-like molecular scaffolds.[18,19]

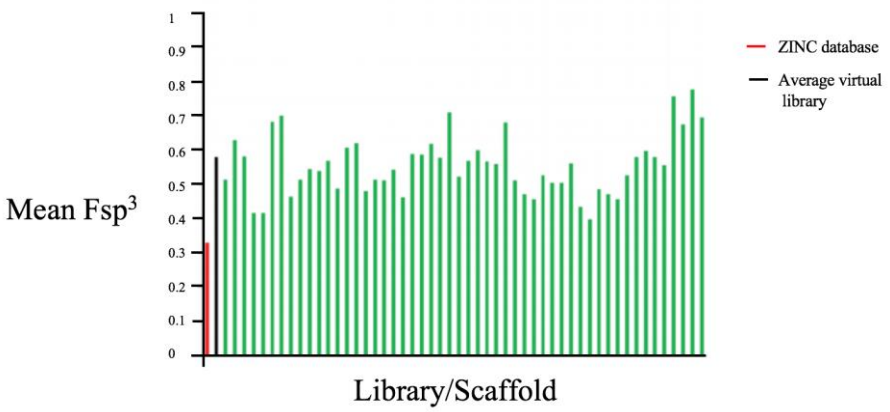


Figure 5. A graph comparing the fraction of sp^3 hybridized carbons from the ZINC database (red) and the 52 scaffolds (average in black and individual in green).

1.7.2 *Top-down* approach to lead-oriented synthesis

The *top-down* approach is a new method used within the Marsden and Nelson groups whereby complex polycycles are prepared and are then deconstructed by selectively cleaving and modifying chemical bonds to give a library of diverse lead-like molecules.[46] A range of chemical methodologies are used to break apart the assemblies and generate lead compounds. The *bottom-up* approach differs from the *top-down* approach, in that complexity is added sequentially leading to a final complex molecule. However, each of the approaches have the same intention of synthesising lead-like molecules.

This strategy requires a complex molecule that is capable of subsequent synthetic elaboration to further produce a library that possess the characteristics of lead-like molecules. Compound **21** below (**Figure 6**) shows an example of such, were the molecule is susceptible to ring addition, expansion and cleavage.

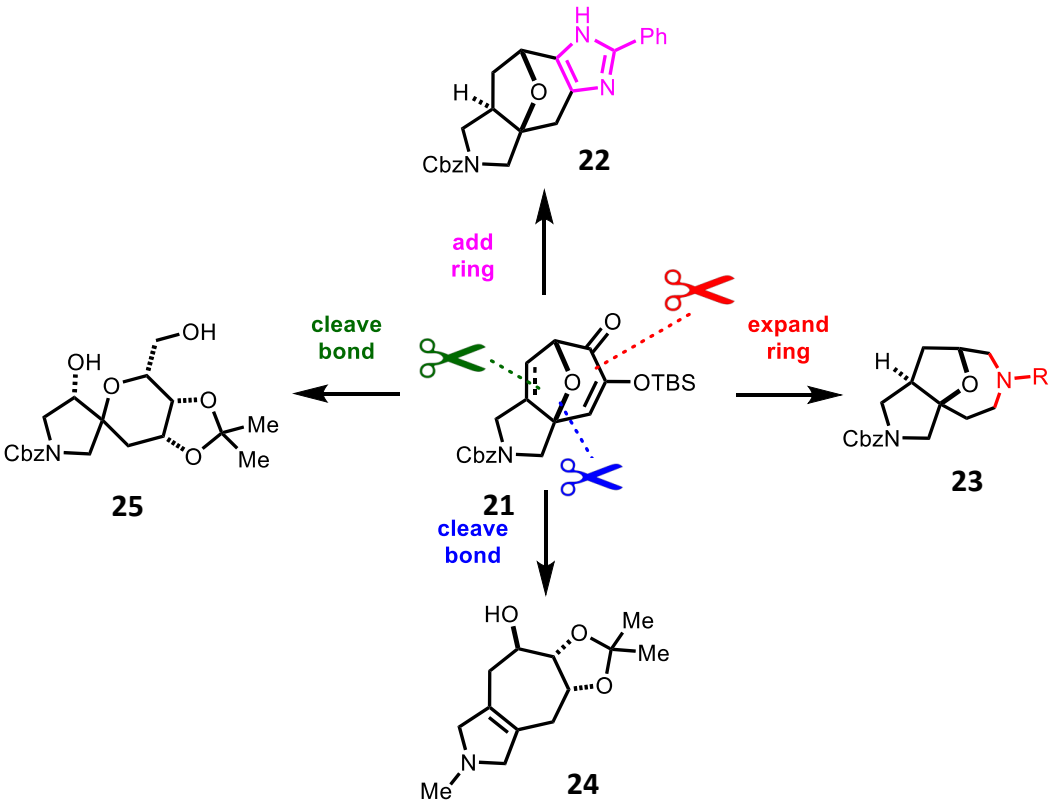


Figure 6. An example of 'top-down' approach, where compound ***21*** *is susceptible to ring expansion and bond cleavage, to synthesise lead-like molecules.*

Previous work has been carried out within the group using the *top-down* approach. Here, intramolecular [5+2] cycloadditions yielded four complex parent scaffolds, where the scaffolds were diversified at various points to synthesise a fragment library with controlled molecular properties. Each cycloadduct followed the *top-down* strategy, following the criteria of a short synthetic sequence (≤5 steps), scalable and synthetically tractable (**Figure 7**).[46] Each cycloadduct was then investigated for its diversification at points of the scaffold, in the possibility of providing access to a variety of novel-like, natural product-like scaffolds for its use in the LOS/FOS programme.[46] The scaffolds had a focus of natural product likeness, as it was important to synthesise a library of sp^3-riched fragments.[65]

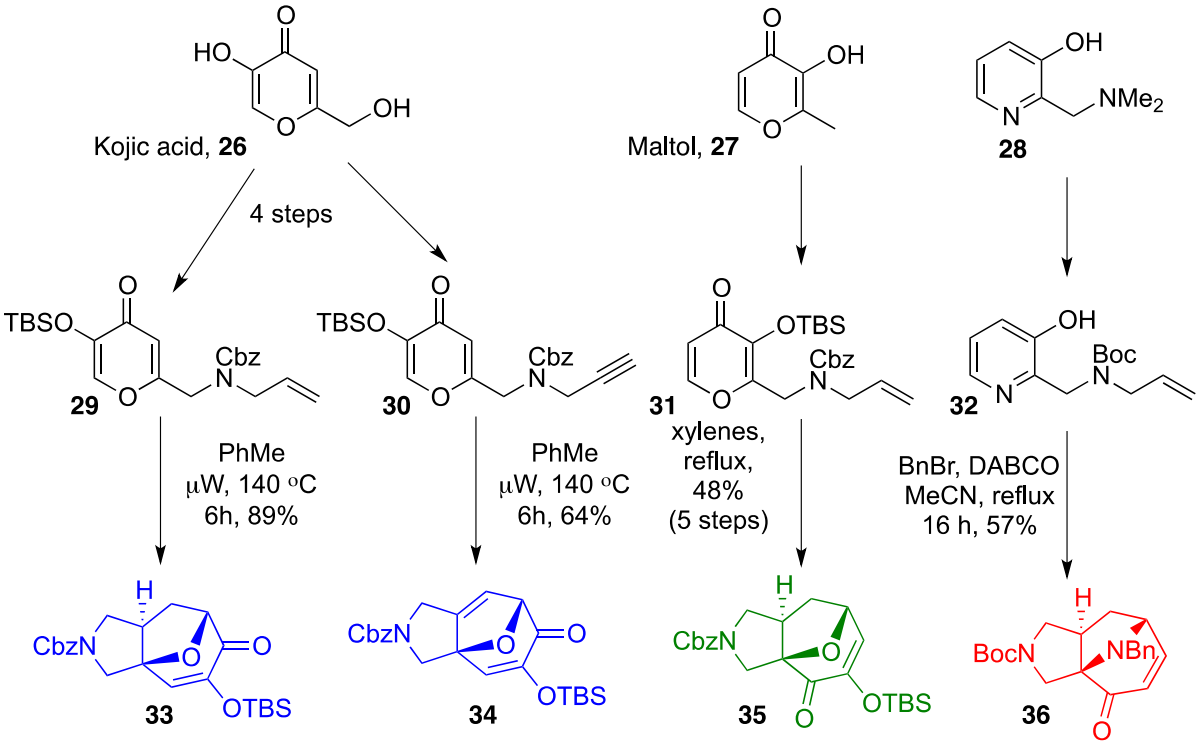


Figure 7. An example of four compounds following the 'top-down' strategy.

Once the cycloadducts had been synthesised, the scaffolds were then subjected to scaffold manipulation at various points of the scaffolds (**Figure 8**). A toolkit of chemical methodologies was applied to either generate a ring expanded product or used to break apart the assemblies to generate ring-cleaved compounds. Some examples are shown below (**Figure 8**), where the products were deprotected and in some cases, decorated with medicinally relevant capping groups.

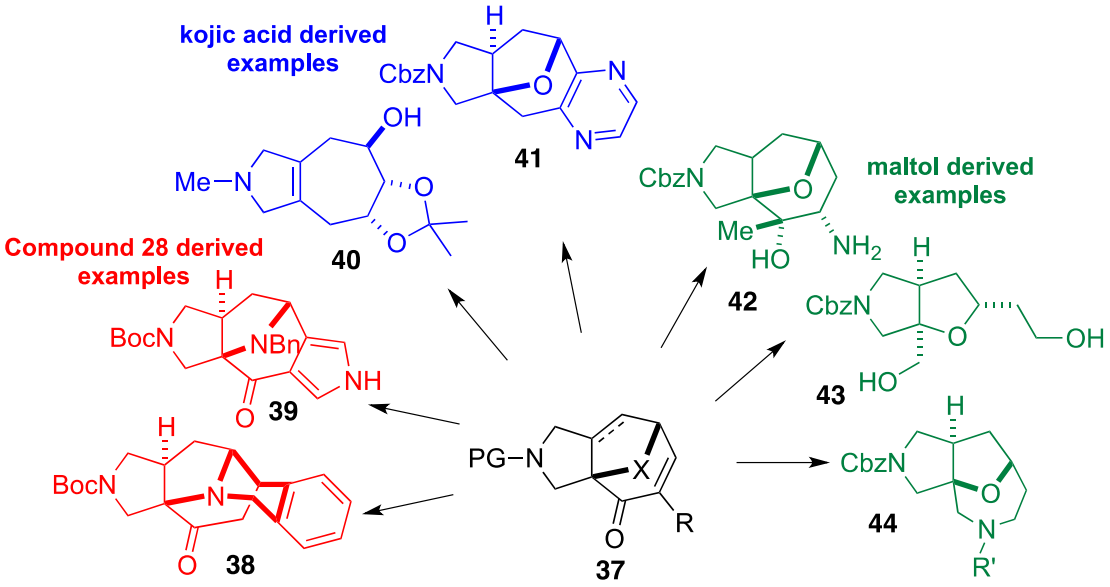


*Figure 8. Some examples of manipulated compounds derived from the maltol **27**, Kojic acid **26** and compound **28**.*

From the 4 complex bridged parent scaffolds, the unified-approach led to the synthesis of 26 diverse sp^3-rich scaffolds, from a total of 64 synthetic operations[†]. Each scaffold was produced with high step efficiency and with high 'natural product likeness' (**Figure 9,** Panel A). A set of 52 racemic fragments were then prepared, and all designed to have high shape diversity and controlled molecular properties (HAC: 13-19, AlogP 1.5<clogP<3). The library was identified as more 3D and natural product-like (**Figure 9**, Panel B), than commercially available fragments.

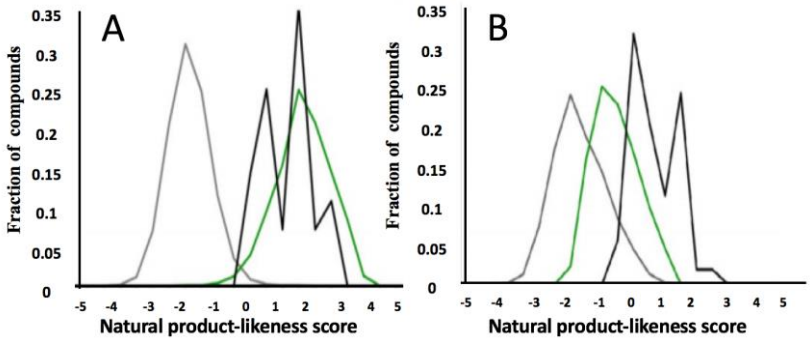


Figure 9. The natural product-likeness assessment of (A) 26 scaffolds (black), 4,460 natural products (green) and acommercial screening collection (278,365 largely synthetic compounds, grey). (B) Naturalproduct likeness scores for the 52 fragments prepared (black), 1,236 commercially-available fragments(grey) and 128 natural product-inspired fragments (green).

To assess the compound's shape diversity and the relationship between the scaffolds, the frameworks were assessed using Waldmann's hierarchical tree analysis.[66] The comparison of the compounds framework was done by removal of rings until a parent monocyclic ring system was achieved. The 26 scaffolds were simplified to obtain nine parent monocycles (**Figure 11**), thus concluding this approach led to significant diversity.

[†] Processes conducted in a single reaction vessel

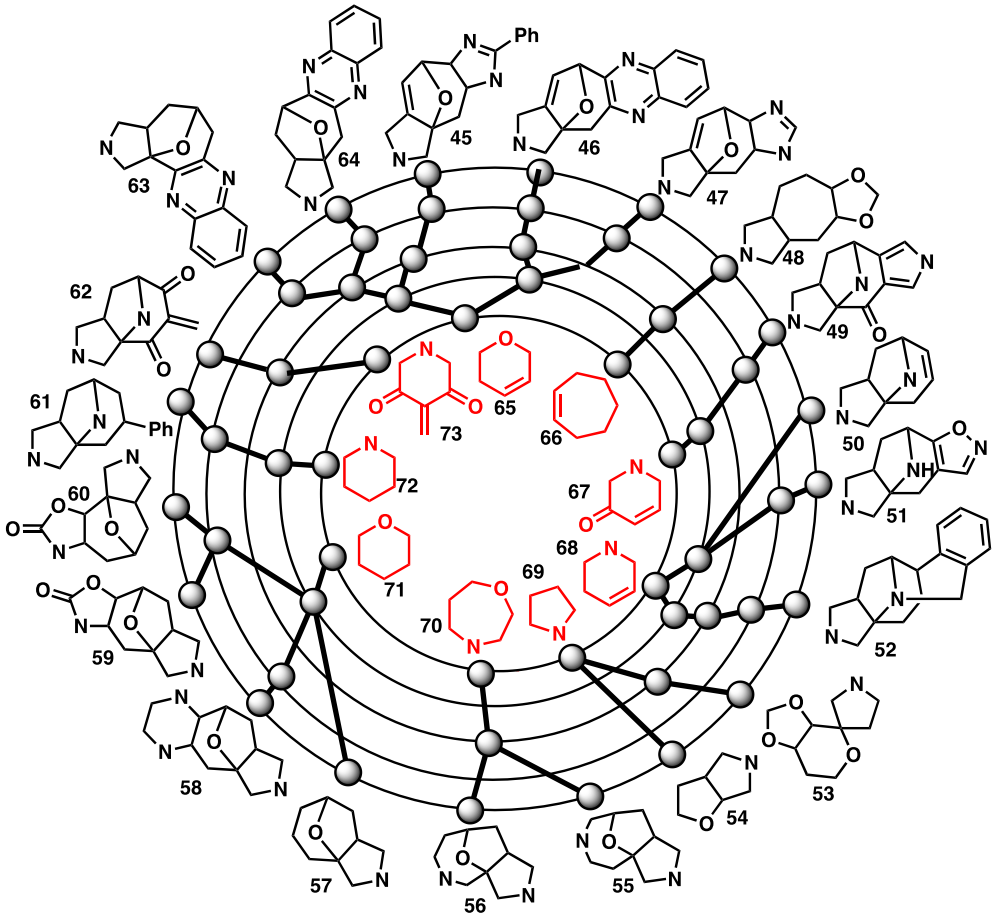


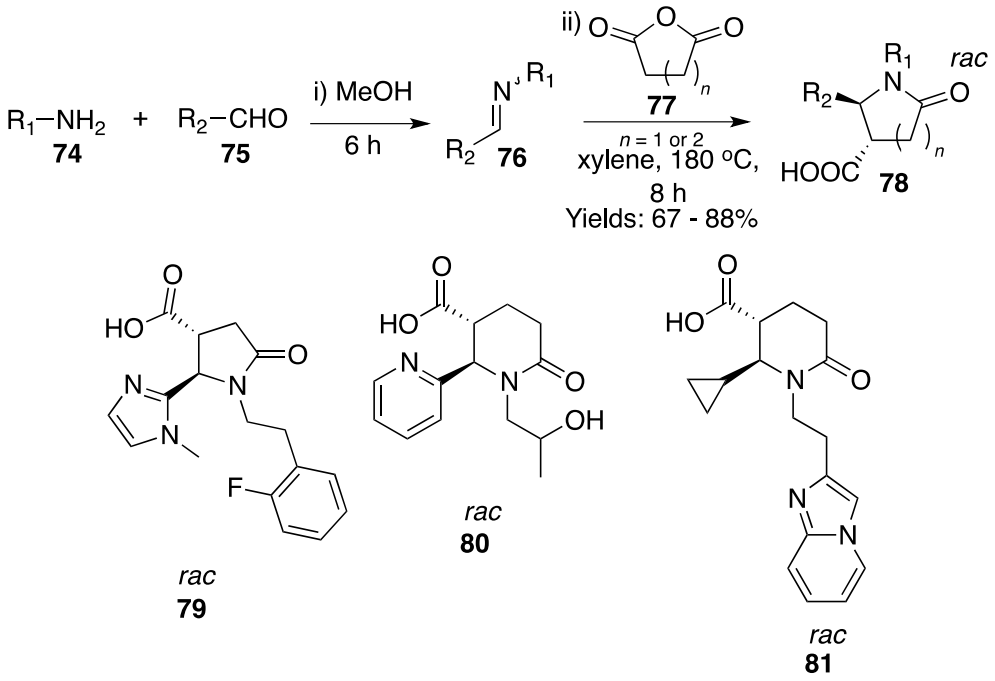
Figure 10 Waldmanns' hierarchical tree analysis for the 26 fragment scaffolds

Each fragment was then screened against the protein targets, with the use of high-throughput crystallographic screens. The proteins were soaked with fragments and then subjected to automated X-ray diffraction. In total, the screening resulted in seven hits for the ATAD2 bromodomain, eight hits for the BRD1 bromodomain and two hits for the JMJD2D. The approach hoped to serve as distinctive starting points for drug discovery, with the possibility of fragment growth to improve potency.

1.7.3 Other studies

When searching the literature, no study of the *top-down* approach to LOS has been conducted outside the group. However, a study of the *bottom-up* approach to LOS was performed by Ryabukhin and co-workers in 2014.[67] They developed a method which fitted well in the concept of lead-oriented synthesis using the *bottom-up* approach, where they synthesised 132 lead-like compounds from a one-pot variation of a Castagnoli condensation reaction, in high yields and diastereoselectivities. The one-pot multicomponent reaction involved aldehydes **75**, alicyclic primary amines **74**, and anhydrides **76**, obtaining a range of 1,2-disubstituted 5-

oxopyrrolidines (example **79)** and 6-oxopiperidine-3-carboxylic acids (example **80** and **81)** (**Scheme 7**).



Scheme 7. A one-pot variation of a Castagnoli condensation reaction, showing three lead-like compounds, as an example of lead-oriented synthesis.

The predicted physicochemical property values of the library were summarised and they conformed to the GSK lead-like guide.[24] The calculated log*P* range of the scaffolds fell slightly outside the range of the desirable parameters, but the average was within range (log*P* average = 1.29). The multicomponent library showed 3D characteristics, with the Fsp^3 count ranging from 0.25 − 0.82 (average Fsp^3 = 0.51). According to the GSK guidelines this is seen as a positive because it defines a more 3D shape.

Physicochemical property	**Lead-like library (132 compounds)**	**GSK lead-like guide**
Molecular Weight (Daltons)	265 – 349	200 – 350
Lipophilicity	1.25 – 3.32	-1 ≤ clog*P* ≤ 3
Number of aromatic rings (*nAr*)	1 – 3	1 – 3

Table 5. A comparison of their lead-like library with the GSK lead-like guide.

By applying the multicomponent Castagnoli condensation reaction, 132 lead-like compounds were synthesised in two synthetic steps. Despite the high number of scaffolds produced using

this method no novelty or diversity assessment was applied, so the validity of this approach cannot be confirmed. If a Waldmann hierarchical tree analysis was performed on the library,[66] only two parent monocycles (**83, 84**) would be obtained (**Figure 11**). Therefore, it can be concluded that this approach lacks skeletal diversity.

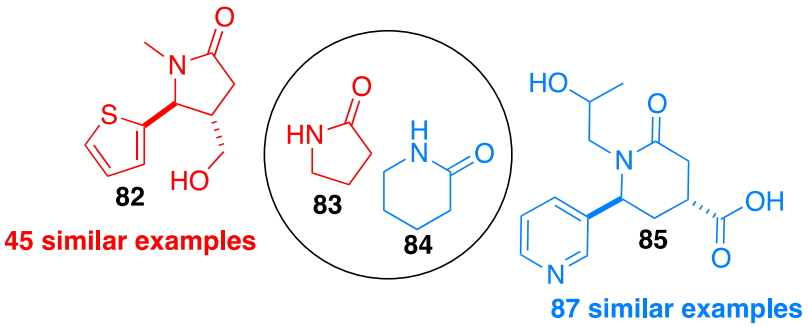


Figure 11. Waldmanns' hierarchical tree analysis for the multicomponent Castagnoli series.

When comparing this study to previous *bottom-up* approaches, this particular library requires the synthesis of a new set of starting material for each lead-like compound. This is a major disadvantage for its efficiency of producing a large library, as only a small number of compounds can be produced from each starting material. With the absence of cyclising and coupling functional groups, like those seen in previous *bottom-up* approaches, the diversity of the overall compounds is limited to two similar core structures, therefore limiting its exploration of chemical space.

1.7.4 Summary of LOS

For drug discovery to increase its productivity, new methodologies are needed to help prepare bioactive molecules to improve human health, with clear guidelines of what molecules that will have the biggest impact on the search for new medicines. New methods such as LOS, which is described above, will hopefully help solve these significant challenges in drug discovery.[24]

1.8 Aims and objectives

1.8.1 General aims and objectives

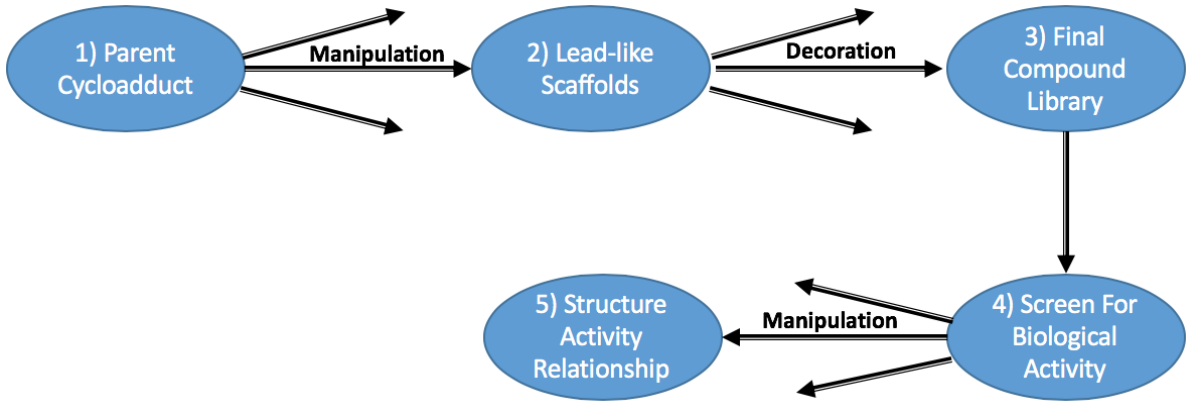


Figure 12. The general aims of the project, starting from the synthesis of a starting material scaffold, then decorating, screening for biological activity and performing structure-activity relationship.

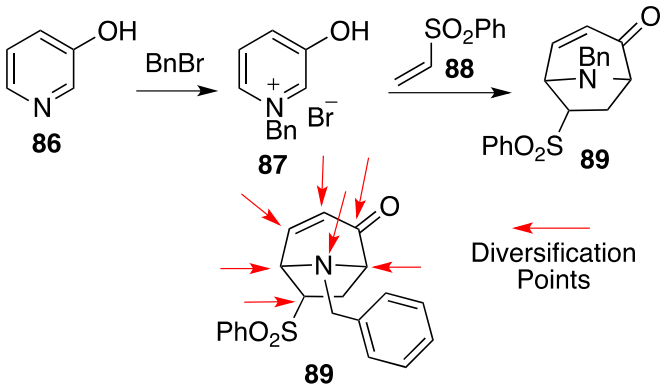
To address the ongoing issues in the drug discovery process, as described in **Section 1.2**, it was therefore proposed to synthesise a library of compounds with specific molecular properties (described in **Section 1.3 & 1.4**) that would be a good starting point in drug discovery. Thus, the overall aims of the project were to: (1) prepare a parent cycloadduct in an efficient and concise manner, from readily available starting materials, which can be diversified at each point of the scaffold; (2) manipulate the parent cycloadduct to prepare a variety of novel and diverse molecular scaffolds; (3) decorate scaffolds to create a library that covers broad regions of lead-like chemical space; (4) test these libraries against a range of biological targets; (5) perform structure-activity relationship (SAR) on active compounds, if any hits are observed.

The synthesis of this lead-like library will hopefully expand the relevant chemical space accessible to drug discovery programmes. This further exploration of space may help address the challenges of increased productivity in the drug discovery industry. [18,68]

1.8.2 Objective 1 – parent cycloadduct synthesis

The project will follow the *top-down* approach, where first the synthesis of a small, 3D, highly-functionalised parent cycloadduct is required, which has different regions of the molecule that are open to manipulation. The rigid bicyclic system **89** was initially identified as possessing

numerous functional handles that are capable of subsequent synthetic elaboration and therefore being suitable for the *top-down* approach. (**Scheme 8**).



*Scheme 8. A scheme for the synthesis of compound **100** and its diversification points.*

1.8.3 Objective 2 – lead-like scaffold synthesis

Once a parent cycloadduct has been successfully synthesised, the next objective is to prove the chosen scaffold can be diversified at a variety of positions of the scaffold. Using known chemistry within the Marsden and Nelson group, the chosen scaffold will undergo annulation (**Figure 13**, example 1), bond cleavage (**Figure 13**, example 2), group addition (**Figure 13**, example 3) and ring expansion (**Figure 13**, example 4) to produce a variety of diverse molecular scaffolds.

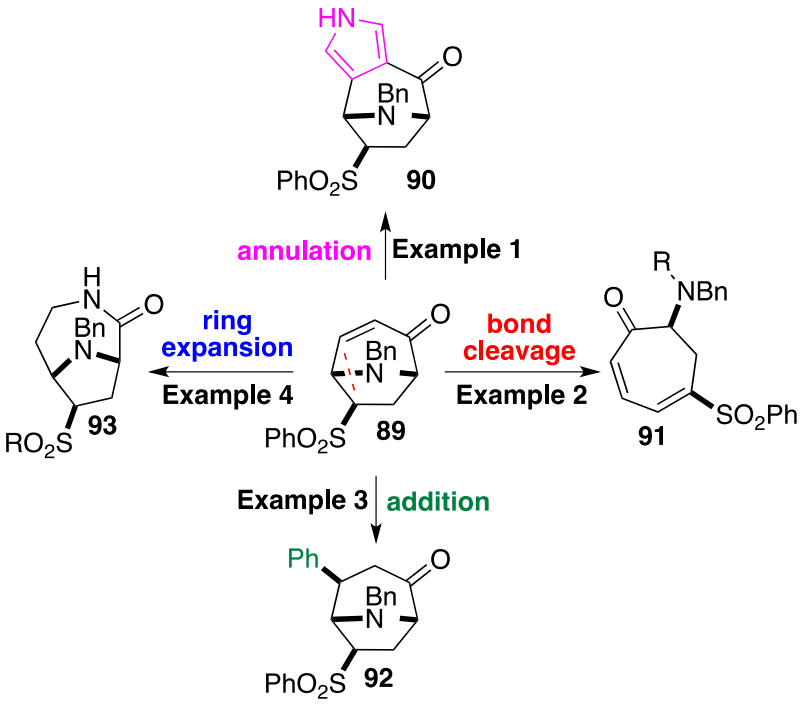


*Figure 13. Manipulation reactions planned for the parent cycloadduct **89**.*.

1.8.4 Objective 3 – final compound synthesis

Once objective 2 is achieved and a range of lead-like scaffolds have been synthesised, the next step is to select appropriate scaffolds for decoration to produce a final compound library for biological screening. The selected scaffolds will undergo various decoration reactions from a known organic toolkit, which involves well known reactions such as amide coupling, reductive amination and alcohol alkylation. The ability of a scaffold to access lead-like space will be assessed by creation of a virtual library using computational software such as LLAMA or PipelinePilot.[45] Once a set of scaffolds (around 10) has been selected, these will be decorated with medicinally-relevant capping groups to yield the compound library.

1.8.5 Objective 4 – biological evaluation

Once the compound library is complete, it will be screened against a range of biological assays. Suitable biological targets will be selected upon completion of the compound library, and will be screened in Leeds or with collaborators at other universities which have specified screening facilities.

1.8.6 Objective 5 – structure-activity relationship

If any of the compounds result in positive biological data, the next objective will be to perform structure-activity relationship. The analysis of SAR enables the identification and determination of important chemical motifs that are responsible for activity. Each position of the scaffold will be examined by changing functional groups independently and identifying the important active chemical groups of the compounds. Observing and analysing the difference in potencies will gain a better understanding of which chemical groups are responsible for evoking a target biological effect in the organism.[69]

2.0 Results and discussion 1: Lead-like scaffold synthesis

The *top-down* strategy for lead-oriented synthesis depended upon a complex molecule that was capable of subsequent synthetic elaboration to further produce a library that was both diverse and novel. To explore objectives 1 and 2 it was therefore proposed to prepare a library of diverse tropane-related scaffolds that were to be formed by addition of substituents to, cyclisation reactions of, and fusion of additional ring(s) to the key bicyclic intermediates. These key indeterminates would obtain various functional groups able to be decorated with medicinal relevant capping groups for screening.

2.1 Development of potential parent scaffolds

Tropane containing skeleton **94** was chosen as the parent scaffold due to the multitude of different functionalities present, as well as the potential for manipulation at multiple diversification points (**Figure 14a**). The scaffold's diverse functionality could be exploited to form lead-like scaffolds and would be ideal for a 'top-down' approach. Embedded in this scaffold is the well-known, often medicinally active, [3.2.1]-bridged bicyclic tropane core. The tropane moiety is a frequently observed bicyclic nitrogen containing heterocycle among U.S. FDA approved drugs and natural products (**Figure 14b)**.[70]

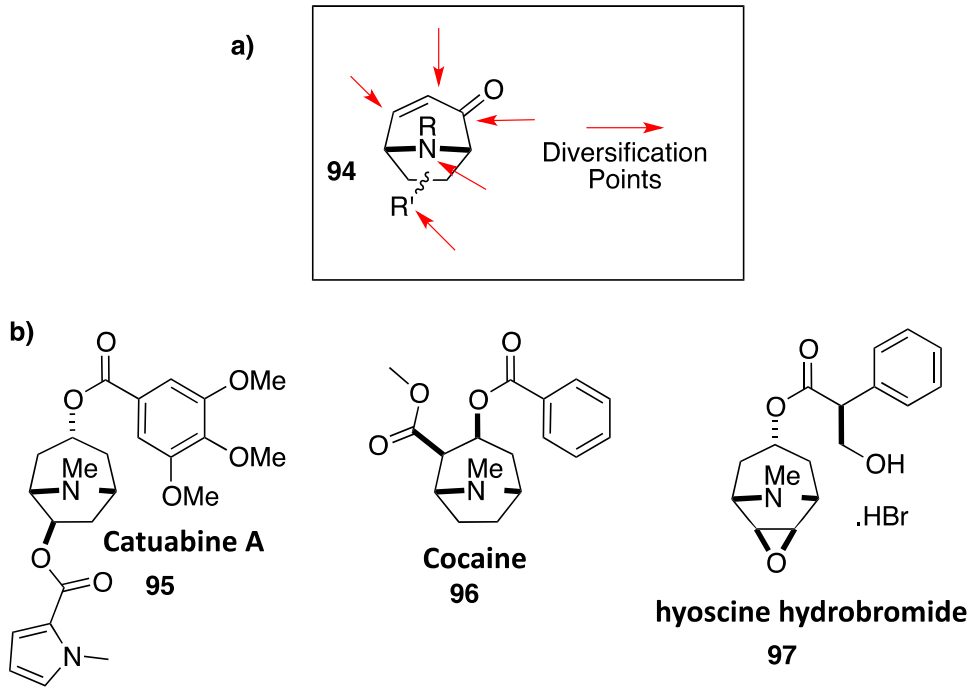
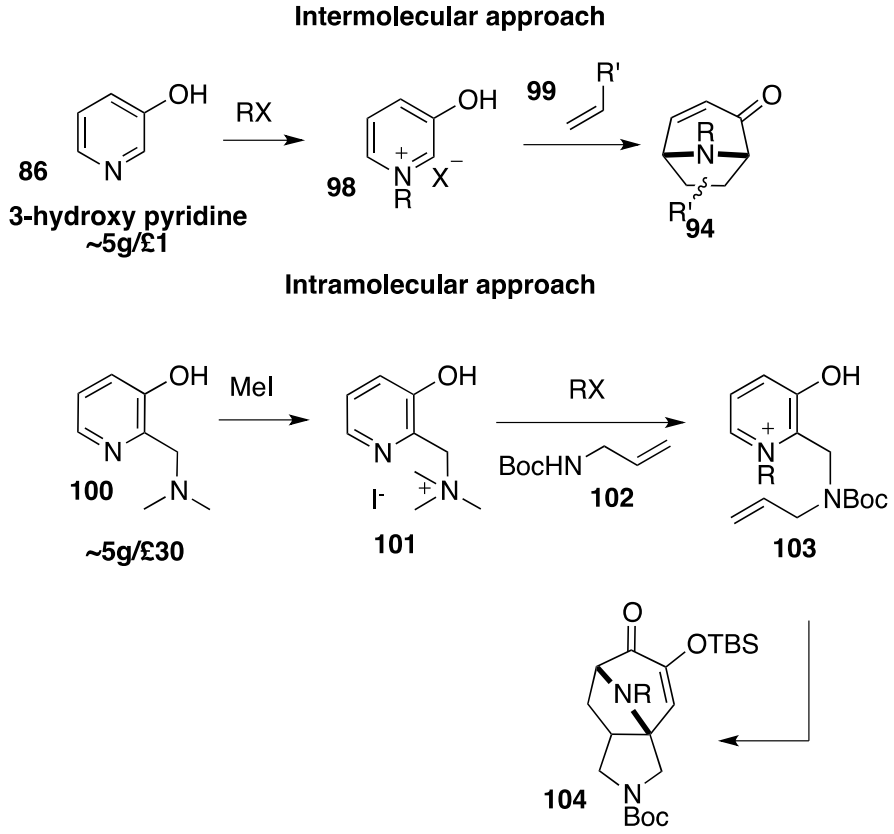


Figure 14a). The parent scaffold chosen for the 'top-down' approach strategy and the diversification points. b) An example of three [3.2.1]-bridged bicyclic compounds ***95-97****.*

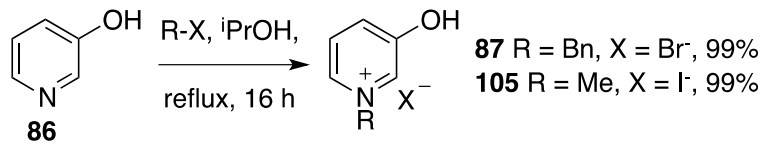
The proposed route to the desired framework was centred around a one-pot two-step intermolecular [5+2] cycloaddition between an oxopyridinium salt **98** and a dipolarophile **99 (Scheme 9**). The advantage to this approach is that a variety of dipolarophiles could be utilised for the cycloaddition. This approach followed a similar synthetic route to a parent scaffold which was synthesised in the Marsden and Nelson group,[65] where the scaffold formed contains a bridged heteroatom and an enone functional group. However, the below intramolecular approach required more steps for the synthesis and it lacked diversity. Each parent scaffold contains a fused pyrrolidine and no other functional group can be introduced easily.



Scheme 9. An example of both the intramolecular and intermolecular approach for the 'top-down' approach strategy.

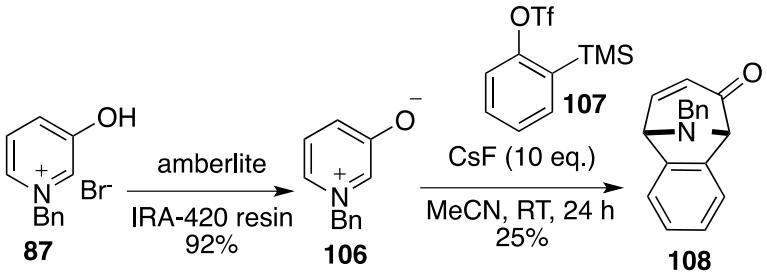
2.2 [5+2] Cycloaddition chemistry to synthesise parent scaffolds

In order to synthesise the chosen scaffold for the *top-down* approach, the *N*-substituted hydroxypyridinium salts (**87** and **105**) were obtained by *N*-alkylation of 3-hydroxypyridine **86** with an appropriate alkyl halide (BnBr and MeI) (**Scheme 10**). This gave the pyridinium precursors required for the [5+2] cycloadditions in near quantitative yields, where no purification was required.[71]



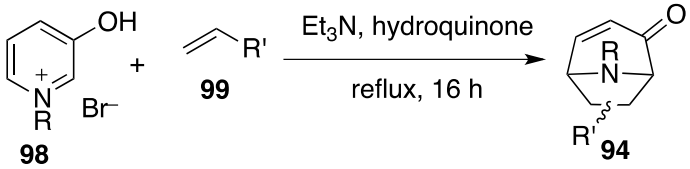
*Scheme 10. Formation of the benzyl and methyl substituted hydroxypyridinium salt **2.13** and **2.14**.*

With the *N*-substituted pyridinium salts in hand, attention was focused on synthesising the potential parent scaffold **108**. Initial efforts involved the [5+2] cycloaddition with benzyne as the dipolarophile. The scaffold was synthesised following a modified procedure by Shi *et al.*[71] which required pre-formation of the oxidopyridinium ylide **106**. This was achieved by the deprotonation of pyridinium salt **87** using Amberlite IRA- 420 resin giving ylide **106** in a 92% yield (**Scheme 11**). Subsequent [5+2] cycloaddition between ylide **106** and benzyne, which was generated *in situ* from precursor **107** and a fluoride anion, gave the desired cycloadduct **108** in a low 25% yield. However, despite success in the synthesis of cycloadduct **108**, it was discontinued due to the expensive benzyne precursor starting material **107** and its overall poor yield of the product. Also, more functionalised reagents were more expensive and may have produced a mixture of regioisomers.



*Scheme 11. Scheme for formation of cycloadduct **108**, from salt **87** and benzyne precursor **107**.*

The pyridinium salt was then subjected to cycloaddition reactions with a range of dipolarophile alkenes via the *in-situ* generation of the ylide, a summary of which is shown below (**Table 6**).



Entry	R	R'	Solvent	No. of isomers	Ratio of isomers ⊕	Combined yield
1	Bn	CN	Neat	4	4:4:2:1	**109,** 45%
2	Bn	SO_2Ph	THF	1	100:0:0:0	**89,** 70%

⊕ The ratio isomers were determined using integration of distinct peaks of the crude ^{1}H NMR

3	Bn	CO_2Me	Neat	4	6:4:1:2	**110,** 92%
4	Bn	SOPh	THF	4	8:5:3:1	**111,** 24%
5	Bn	$CO_2{}^tBu$	1,4-dioxane	4	8:3:3:2	**112,** 65%

*Table 6. Outcome of cycloaddition reactions involving pyridinium salt **98** and dipolarophile **99**.*

Moderate to good yields were observed in the cycloaddition reactions, however, in most cases an inseparable mixture of diastereomers and regioisomers was obtained. These were seen by the ^{1}H NMR of the crude mixture and isolated compounds. Interestingly, when phenyl vinyl sulfone was used as the dipolarophile a single isomer was formed in a good 70% yield (**Table 6**, entry 2). The conditions were adapted from those detailed by Ducrot and Lallemand.[72,73] The stereochemistry and regioselectivity of cycloadduct **89** were assigned according to the ^{1}H NMR spectra data, where the key proton H_β coupling was predicted to show only coupling to proton H_γ.[+‡] The predicted coupling constants matched those of the ^{1}H NMR data as shown in (**Figure 15**) and the interpretation of data supports the literature precedent.

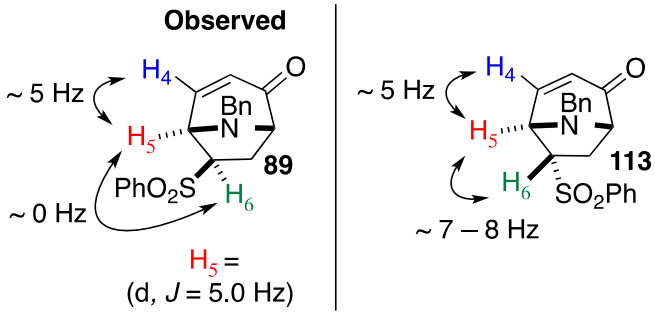
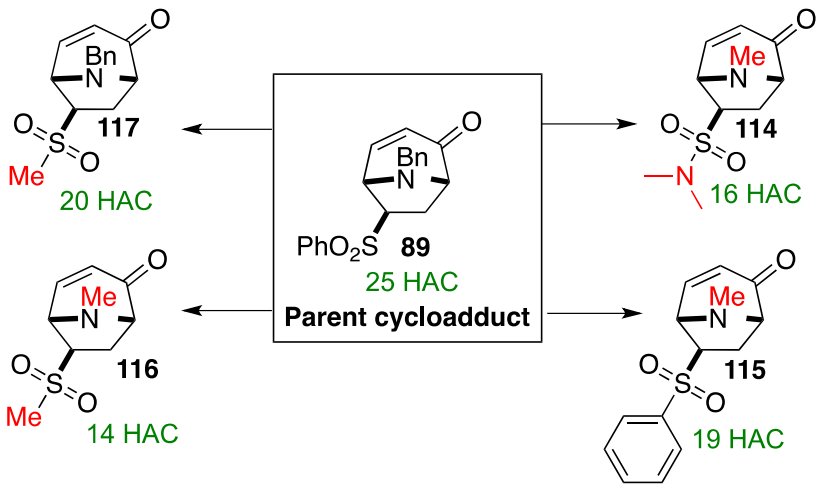


*Figure 15. The stereochemistry assignment for the parent cycloadduct **89,** including its predicted coupling constants for the endo/exo isomer.*

Due to the high molecular weight of the phenyl sulfonyl substituent on the parent cycloadduct **89**, derivatisations were planned that would incorporate smaller or more chemically diverse sulfonyl substituents. These derivatives would allow for the synthesis of new scaffolds via ring addition reactions and for the addition of larger capping groups in the library synthesis, whilst remaining in lead-like space. The smaller scaffolds would also allow access to a larger fragment library. In the cases where removing the benzyl group was not feasible, smaller nitrogen substituents were introduced. The planned parent scaffold derivatives are shown below (**Scheme 12**).

[+‡] H_β of compound **89** had coupling at ~ 5 Hz and no coupling constant with H_α. The coupling constants were predicted using the software chem3D.



Scheme 12. A proposed set of sulfonyl derivatives to be synthesised using the [5+2] cycloaddition chemistry.

It was envisioned that five vinyl sulfonyl derivatives would be used for the synthesis of the parent scaffold series (**Figure 16**). Methyl vinyl sulfone **118** was commercially available and the vinyl sulfonyl pyridine **122** was synthesised using chemistry reported by Carretero *et al.*[74] A vinyl sulfonamide/sulfonate series (**118** – **122**) was also synthesised using a modified synthesis by Caddick *et al.*[75]

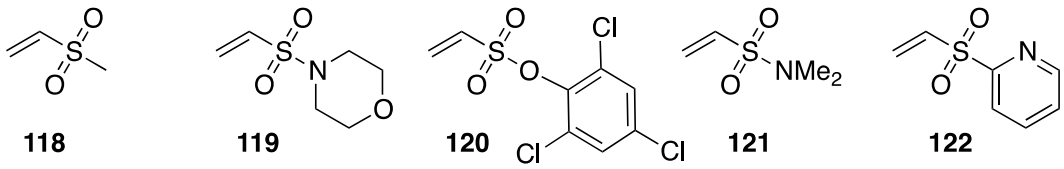
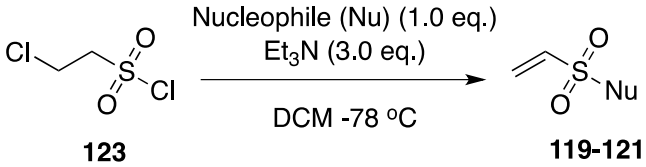


Figure 16. The five vinyl sulfonyl derivatives planned for parent scaffold derivative synthesis.

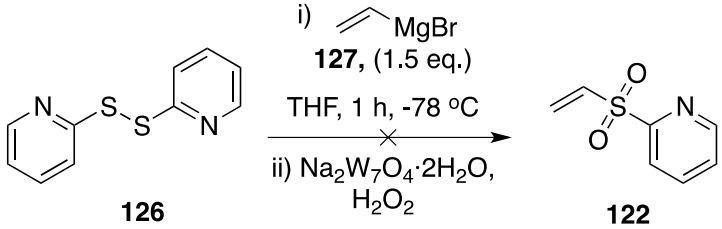
Three vinyl sulfonyl derivatives **119** – **121** were obtained, using the conditions detailed by Caddick *et al* in 2009.[75] Moderate to good yields were observed when a range of nucleophiles were added to compound **123** at -78 ^{o}C, as shown below (**Table 2**).



Entry	Nucleophile (Nu)	Product	Yield
1	$HNMe_2$	**121**	50%
2	**124**	**119**	33%
3	**125**	**120**	80%

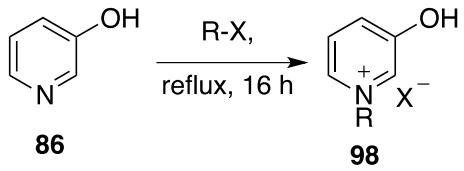
Table 7. Outcome of vinyl sulfonyl derivative reactions.

A procedure by Carretero *et al.*[74] was used for the synthesis of compound **122**. Disulfide **126** was subjected to a Grignard substitution with vinylmagnesium bromide followed by an oxidation with $NaW_7O_4.2H_2O/H_2O_2$. However, no formation of compound **122** was observed, and only starting material **126** was recovered (**Scheme 5).** The route was discontinued as the four sulfonyl derivatives (**118 – 121**) were considered enough to bring diversity at this stage.



*Scheme 13. The proposed synthetic route to compound **122** via i) Grignard addition and ii) oxidation.*

In order to synthesise the cycloadducts, a range of *N*-substituted hydroxypyridinium salts were obtained by *N*-alkylation of 3-hydroxypyridine **85**. Different alkyl halides were chosen and in each case the salts were obtained in near quantitative yields on a 12 – 24 mmol scale.[76,77,78]



86 **98**

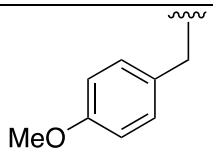
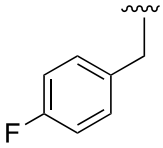
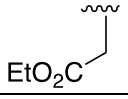
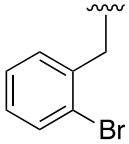
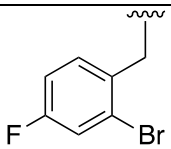
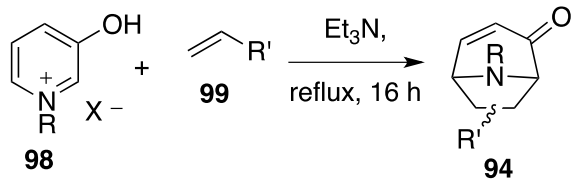
Conditions	X	R	Outcome
PhMe (0.5M)	Cl		**128,** 99%
THF (0.5 M)	Br		**129,** 99%
MeCN (0.5 M)	Br		**130,** 99%
THF (0.5 M)	Br		**131,** 99%
THF (0.5 M)	Br		**132,** 99%

*Table 8 Outcome of alyklation reactions involving 3-hydroxypyridine **86** and a range of electrophiles.*

With a new panel of compounds in hand, the newly synthesised pyridinium salts and vinyl sulfonyl derivatives were subjected to the [5+2] cycloaddition procedure.[73] The results are shown below, where a range of cycloadducts were synthesised in poor to excellent yield (20-89%) (**Table 9**).



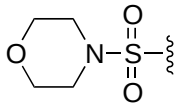
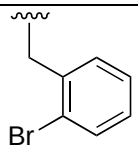
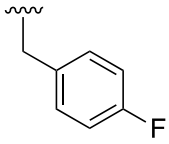
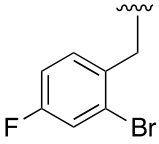
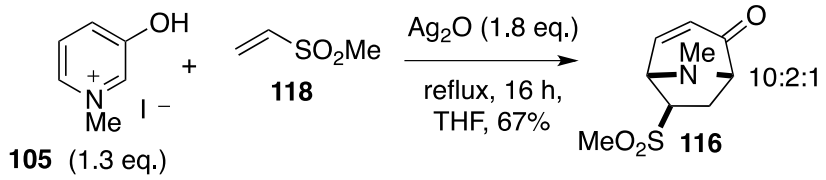
Entry	R	R'	HAC	No. of isomers	Ratio of isomers ▽	Major product yield (%)§
1	Bn	SO_2Me	20	2	10:1	**117,** 57%
2	Bn		25	3	20:2:1	**133,** 36 %
3	PMB	SO_2Me	22	2	10:1	**134,** 52 %
4		SO_2Ph	26	2	10:1	**135,** 41%
5	Me	SO_2Me	14	3	10:2:1	**116,** 20%
6	Me	SO_2NMe_2	16	3	20:4:1	**114,** 54%
7		SO_2Me	26	2	10:1	**136,** 50 %
8	Me	SO_2Ph	19	2	7:1	**115**, 20 %
9		SO_2Me	27	1	100:0	**137,** 89%

Table 9. Outcome of cycloaddition reactions involving N-substituted hydroxypyridinium salts and vinyl sulfonyl derivatives.

It was noticed that the yields were particularly low when the cycloaddition involved the methyl pyridinium salt **105** (**Table 9**, entry 5), with large quantities of the unreacted dipolarophile seen but no residual pyridinium salt observed. It was proposed that the iodide counterion could be interfering with the reaction by dealkylating the methylhydroxy pyridinium salt. The base was therefore changed to silver oxide, where the silver can act as an iodide scavenger and this increased the yield dramatically. Consequently, new conditions were identified and applied to the synthesis of cycloadduct **116** (**Scheme 14**).

▽ The ratio isomers were determined using integration of distinct peaks of the crude ^{1}H NMR field.
§ Major isomer isolated as a single isomer. The yield recorded for the major isomer only.

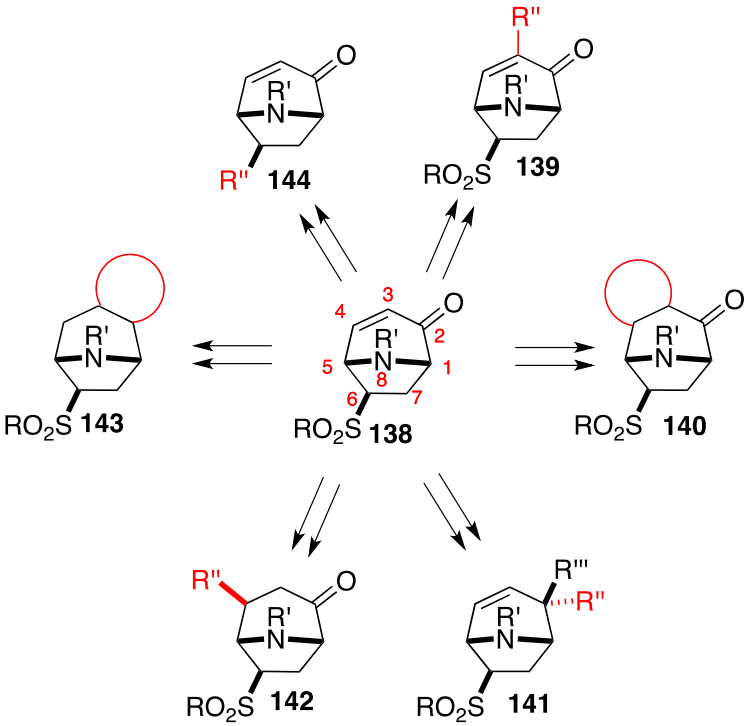


*Scheme 14. The formation of cycloadduct **116** using the alternative base silver oxide.*

In total 10 parent scaffolds were synthesised with different sulfonyl and nitrogen-bridged substituents. Each parent scaffold was synthesised with good stereo/regio control, on a large scale from cheap starting materials, therefore following the 'top-down' approach strategy rules. Objective one, a synthesis of a highly functionalised parent cycloadduct, was successfully achieved, therefore attention was turned to the exploitation of the present functionality to synthesise a range of lead-like scaffolds.

2.3 Development of methods to enable exploration of each vector of the parent scaffold

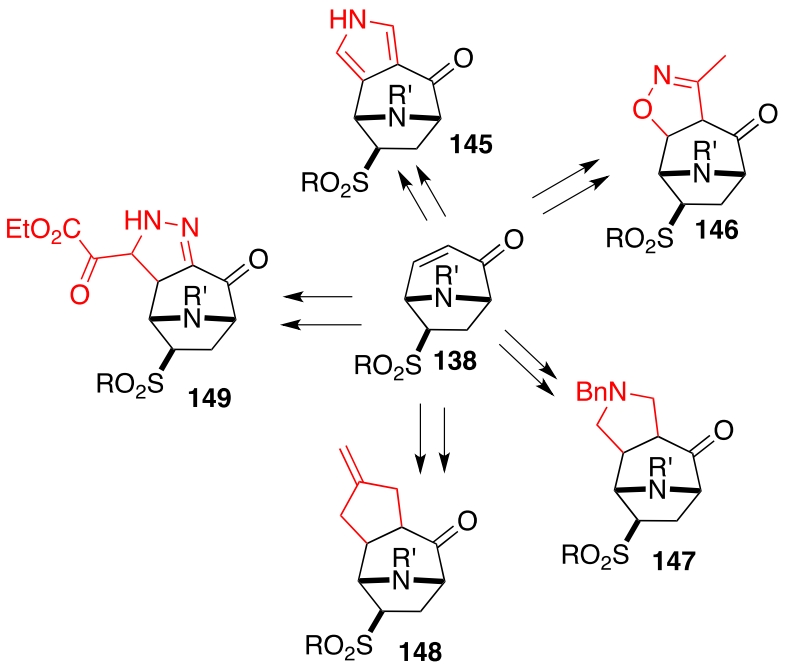
With a range of parent scaffolds in hand, the next step was to investigate the reactivity of functionality at the different positions of the scaffold (**Scheme 15**). Exploring each growth vector is necessary to prove the parent scaffold is worthy of the 'top-down' approach strategy. Therefore, a variety of molecular scaffolds were proposed, applying a toolkit of chemical methodologies to produce a library of novel and diverse lead-like scaffolds.



*Scheme 15. A proposed set of manipulation reactions of the parent cycloadduct **2.46** at different points of the scaffold.*

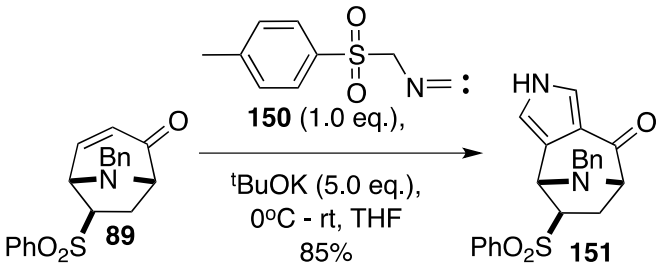
2.3.1 Development of methods to enable exploration of growth vectors at the 3- and 4- positions

The first vector of interest was the electron-deficient alkene of the enone. Similar enone containing scaffolds had been made previously in the Marsden and Nelson group,[46] and success had occurred when producing lead-like compounds from ring and functional group addition strategies. Therefore, a range of annulation reactions were investigated at this position, as shown below (**Scheme 16**).



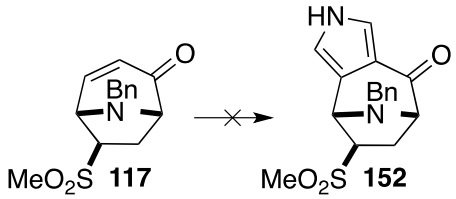
*Scheme 16. A variety of annulation reactions at the 3- and 4-position of the parent cycloadduct **138**.*

With the primary aim of synthesising medicinally relevant heterocycles at the 3- and 4-positions, the first reaction attempted was the formation of pyrrole **151**. The pyrrole was obtained using chemistry first introduced by van Leusen,[79] using toluenesulfonylmethyl isocyanide (TosMIC) **150** and potassium *tert*-butoxide. This afforded the product in an 85% yield, introducing another point of diversification at the pyrrole nitrogen (**Scheme 17**).



*Scheme 17. Formation of pyrrole containing scaffold **151** using van Leusen chemistry.*

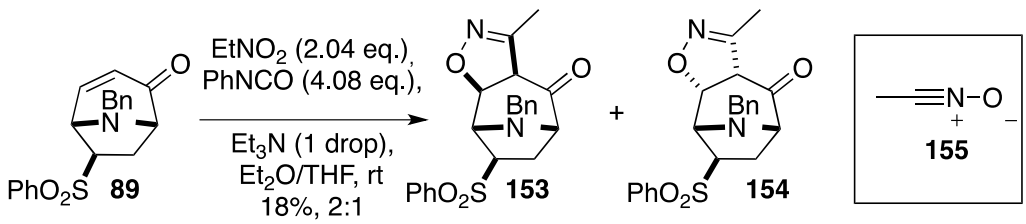
Interestingly when using the methyl sulfonyl derivative **117**, the cyclocondensation reaction was unsuccessful. Several conditions were used in the attempt to synthesise the pyrrole **152** (**Table 10**). It was proposed that the deprotonation of the methyl sulfone was competing with the TosMIC deprotonation; consequently TosMIC was first deprotonated and a solution of the scaffold was subsequently cannulated into the deprotonated TosMIC solution. However, still no product was obtained after purification and other routes involving stronger bases were also unsuccessful (**Table 10**).



Entry	Conditions	Outcome
1	TosMIC (1.0 eq.), ^{t}BuOK (5.0 eq.), 0^{o}C - rt, THF	Starting material **117**
2	TosMIC (3.0 eq.), ^{t}BuOK (10.0 eq.), slow addition of compound **117**	LCMS analysis showed traces of product (**152**) but no material obtained from purification
3	TosMIC (1.0 eq.), LiHMDS (5.0 eq.), slow addition of compound **117**	Complex mixture of products, no observation of **152**

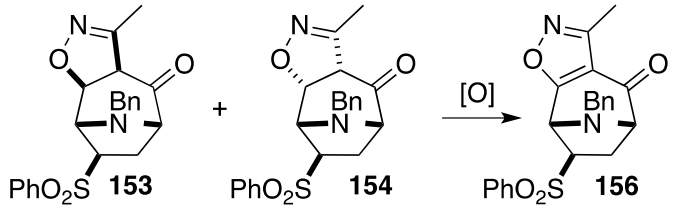
*Table 10. Outline of conditions used in an attempt to synthesise pyrrole scaffold **152**.*

The next scaffold of interest was the dihydroisoxazole **153 – 154**. The reaction conditions selected for this synthesis were adapted from the chemistry performed by Mukaiyama and Hoshino.[80] The procedure involved the reaction of phenyl isocyanate and nitroethane to generate a nitrile oxide **155** *in situ*, with the subsequent 1,3-dipolar cycloaddition affording the dihydroisoxazole scaffold **153 – 154** in 18% yield (**Scheme 18**), as a 2:1 mixture of cis-isoxazolines with endo and exo stereochemistry. Due to the next synthetic step being an oxidation reaction, both stereoisomers would afford the same product, therefore no separation of compounds **153 – 154** was necessary.



*Scheme 18. A general scheme for the synthesis of the fused dihydroisoxazole compound **153** and **154**.*

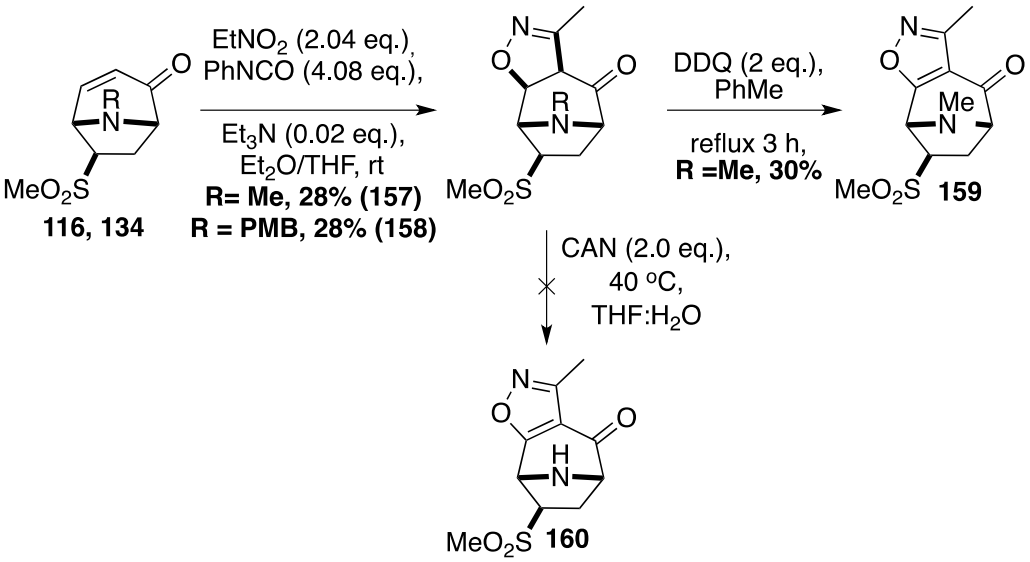
With the substrate **153 – 154** now in hand, oxidation was attempted to form isoxazole **156**. Several attempts were made and success occurred when using the oxidation reagent DDQ in toluene for 2 hours in a low yield of 12%; the conditions are shown below (**Table 11**).



Entry	Conditions	Outcome
1	DBU (4 eq.), I_2 (1.2 eq), THF, reflux, 16 h.	Starting material
2	DDQ (1.2 eq.), PhMe, reflux, 16 h.	Complex mixture
3	*p*-chloranil (1.04 eq.), *o*-xylene reflux, 16 h.	Complex mixture
4	DDQ (2.0 eq.), PhMe, reflux, 2 h.	**156,** 12%

*Table 11. Outcome of oxidation reactions of dihydroisoxazole **153– 154** to form isoxazole compound **156**.*

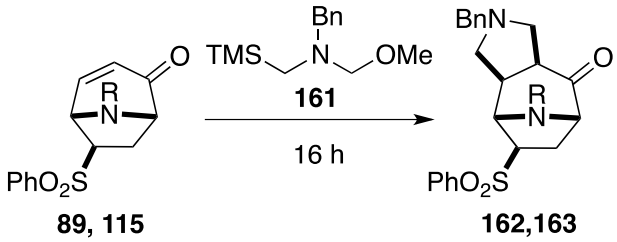
The same reaction conditions (**Scheme 18**) that were used to synthesise compounds **153 – 154** (**Scheme 19**) were then repeated on substrates **116** and **134**, with varying *N*-substituents. Dihydroisoxazole **157** was then oxidised to form the isoxazole fused scaffold **159** albeit in poor yield (**Scheme 19**). It was also envisaged that when compound **158** was exposed to cerium ammonium nitrate (CAN), the *para*-methoxybenzyl (PMB) group might be removed alongside the scaffold undergoing oxidation giving rise to the unprotected isoxazole **160**. However, a complex mixture of products was observed and this route was deprioritised (**Scheme 19**).



*Scheme 19. A scheme to show the synthesis of scaffolds **157, 158** and **159** .*

Synthetic efforts were next focused on the pyrrolidine-fused compound **162** and **163**, formed via an azomethine ylide [3+2] cycloaddition, where the best conditions found were those described by Fray *et al* (**Table 12**, entry 2 and 3).[81] When acidic conditions for the ylide

generation were applied, the desired product was not obtained (**Table 12**, entry 1), presumably because of problems with the presence of a basic nitrogen. Consequently, basic conditions were used to successfully synthesise compound **162** and **163** in good yields.



Entry	R	Conditions	Outcome
1	Bn	Ylide precursor **161** (1.7 eq.), TFA (2.6 eq.), DCM, 0°C - rt	Starting material
2	Bn	Ylide precursor **161** (1.1 eq.), LiF (1.2 eq.), MeCN, rt	**162,** 63%
3	Me	Ylide precursor **161** (1.1 eq.), LiF (1.2 eq.), MeCN, rt	**163,** 67%

*Table 12. Outcome of cycloaddition reactions involving enone **89**, **115** and ylide **161** to form compound **162** and **163**.*

The stereochemistry was assigned according to the ^{1}H NMR spectra and NOESY data (**Figure 17**). The predicted coupling constants of H_β matched those of the ^{1}H NMR data, and the key NOESY interactions helped confirm the structures configuration. The key proton H_β was predicted to show no coupling with protons H_α and H_γ, and this was confirmed with a singlet present in the NMR data. The structure hypothesis was later confirmed by the acquisition of a crystal structure of a decorated analogue from this substrate **(Section 2.5.2**).

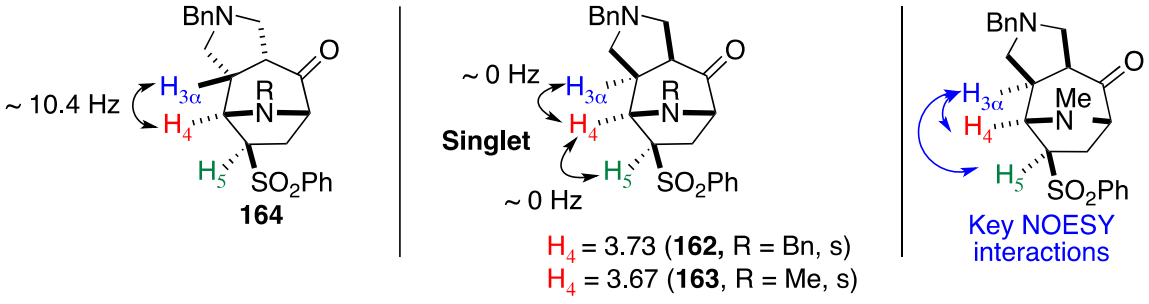
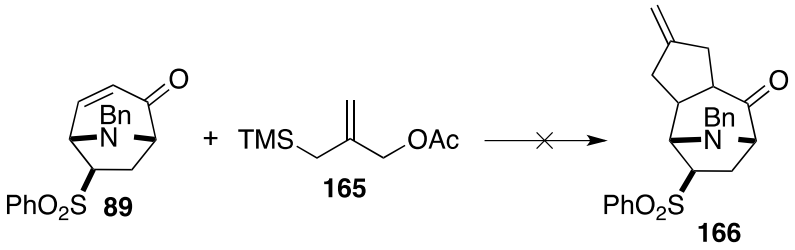


*Figure 17. Stereochemistry assignment of compound **162 – 163.** with measured J* values..

The next substrate explored was compound **166**, which involved the use of a trimethylenemethane ylide using conditions highlighted by Trost and Chan,[82] however, the desired [3+2] cycloaddition was unsuccessful in both attempts, using the conditions

summarised below (**Table 13**). Only the Arbuzov product **167** was observed (with unknown stereochemistry), when $P(OEt)_3$ was used as the ligand (**Table 13**, entry 1). When the active palladium source was changed, no reaction was observed and only starting material was recovered. Consequently, efforts towards this target were discontinued.



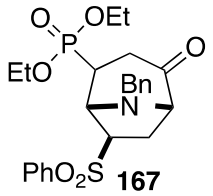
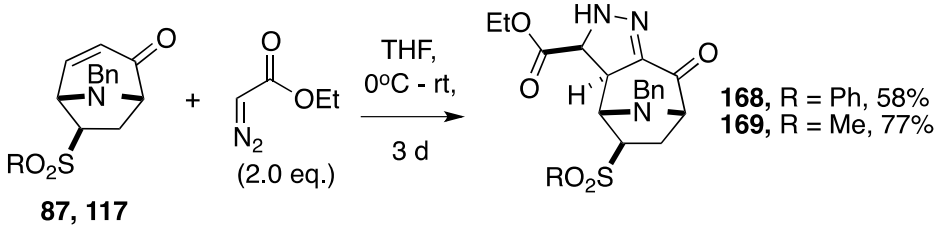
Entry	Conditions	Outcome
1	Enone **89** (1.0 eq.), $Pd(OAc)_2$ (20 mol%), $P(OEt)_3$ (1.1 eq.), ylide (1.86 eq.), THF reflux	 **167**
2	Enone **89** (1.0 eq.), $Pd(PPh_3)_4$ (4 mol%), dppe (1.5 mol%), ylide (1.0 eq.), THF reflux	Starting material, **89**

*Table 13. Conditions used in attempt to synthesise compound **166**.*

The final compounds targeted at this vector were the fused dihydropyrazole scaffolds **168 - 169**. The conditions were adapted from those detailed by Shi *et al.* [71] The [3+2] cycloaddition of ethyl diazoacetate followed by a tautomerisation gave the desired compounds in moderate to high yields (58 - 77%) (**Scheme 20**).



*Scheme 20. The synthesis of pyrazole **168** and **169** from a [3+2] cycloaddition reaction.*

The stereochemistry of the compound was determined by the comparison with a similar compound reported by Shi *et al.*[71] The NOESY data was used to confirm the stereochemistry of the dihydropyrazole scaffold **168**, with the key interactions shown on the cycloadduct

compound (**Figure 18**). To further verify the stereochemistry, a comparison of key interactions was undertaken with a similar literature compound.[71]

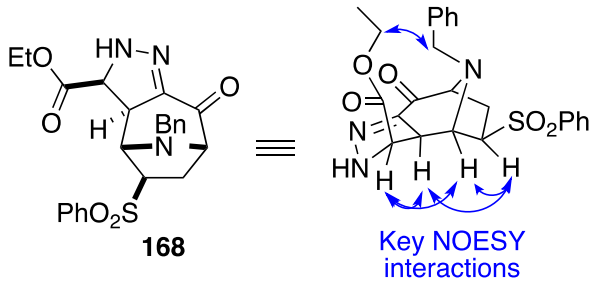
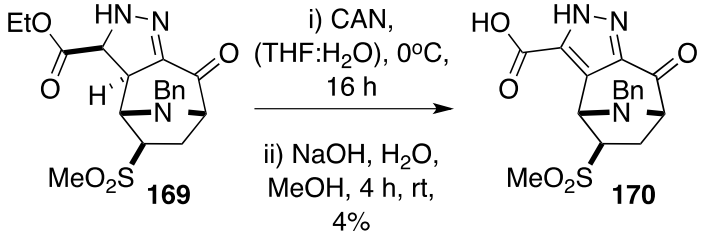


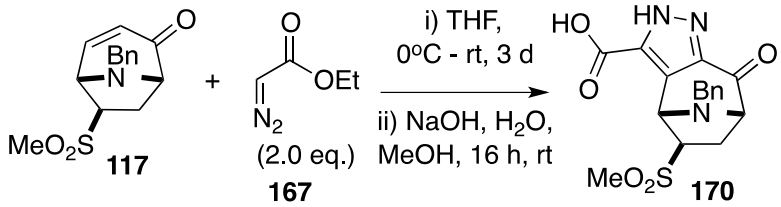
*Figure 18. Stereochemistry assignment for pyrazole **2.76**.*

The dihydropyrazole compound **169** was then aromatised by an oxidation with CAN at 0 °C for 4 hours (**Scheme 21**). However, due to difficulties in the purification, the crude material was subsequently hydrolysed to form the pyrazole carboxylate **170** in an overall yield of 4%. It was concluded that a new route should be devised to the desired compound because of the extremely low yield.



*Scheme 21. The new synthetic route towards the synthesis of pyrazole carboxylate **2.78**.*

An alternate route was attempted using a one-pot procedure method, where both the aromatisation and hydrolysis occurred in one step **(Scheme 22)**. This route involved aromatisation (presumably by an aerobic oxidation) to synthesise the desired scaffold **170**. Unfortunately, the reaction also proceeded in a low yield 14%.

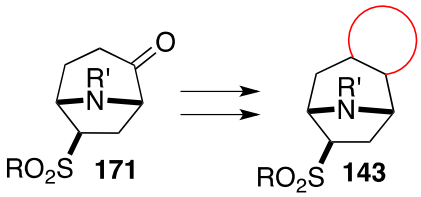


*Scheme 22. The new synthetic route for pyrazole carboxylate **170.***

In total for the exploration of growth vectors at the 3- and 4- positions, 10 scaffolds were synthesised from 4 core scaffolds. The results provided evidence that the parent scaffolds showed promising reactivity at the enone position, where the scaffolds were synthesised with

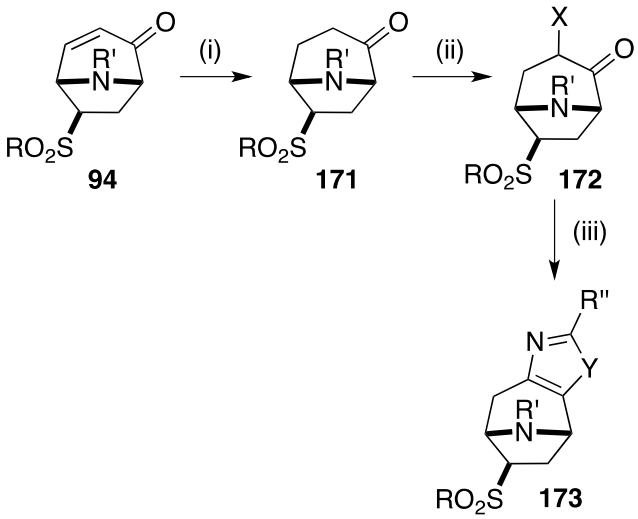
good stereo/regio control. Further exploitation of the present functionality was to be explored to synthesise a library of diverse scaffolds for biological testing.

2.3.2 Development of methods to enable exploration of growth vectors at the 2- and 3-positions



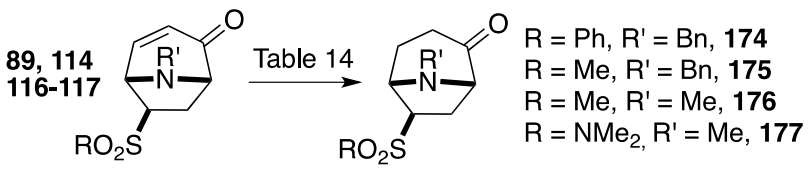
Scheme 23. A general scheme depicting an annulation reaction at the 2- and 3-position

Having achieved success with the functionalisation at the 3- and 4- positions, which in turn gave rise to a diverse set of scaffolds, the next vectors to be explored were at the 2- and 3-positions. A simple two-step route to an α-halogenated substrate **172** was suggested, using readily available starting materials. It was envisioned that the α-halogenated ketone **172** could be converted to a range of heterocycles **173** by applying Hantzsch-type syntheses (**Scheme 24**).[83]



Scheme 24. Step (i) palladium on carbon reduction, step (ii) alpha halogenation and step (iii) hantzsch synthesis.

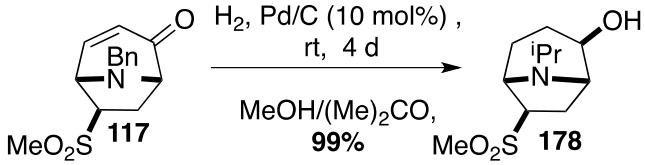
To enable α-halogenation, reduction of the olefin was required which was achieved by following hydrogenation conditions detailed in the literature,[73] shown below (**Table 14**). The reactions proceeded overnight at room temperature, giving the reduced tropanones in excellent yields of 89 - 99%.



Starting material	R	R'	Conditions	Outcome
89	Ph	Bn	H_2, Pd/C 10mol%, rt, 16 h MeOH/$(Me)_2CO$	**174,** 97%
117	Me	Bn	H_2, Pd/C 10mol%, rt, 16 h MeOH	**175,** 96%
116	Me	Me	H_2, Pd/C 10mol%, rt, 16 h MeOH/$(Me)_2CO$	**176,** 96%
114	NMe_2	Me	H_2, Pd/C 10mol%, rt, 16 h MeOH/$(Me)_2CO$	**177,** 89%

Table 14 Outcome of reductions reactions involving palladium on carbon and hydrogen with the sulfonyl derivatives.

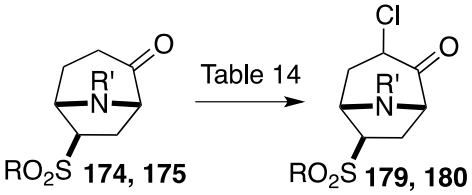
However, when synthesising compound **175** on a larger scale, the reaction was left for 4 days and as a result underwent secondary reactions to produce alcohol **178** in quantitative yield. The expected compound was not present in the ^1H NMR with evidence suggesting no benzyl group was present. The HRMS matched the proposed structure, where the benzyl-protected nitrogen had been deprotected and a reductive amination occurred with acetone. The observed compound was produced on a large scale with a free OH available for decoration and final library synthesis. It should be noted that the benzyl group remained intact in some cases, which can be deemed an issue when the free nitrogen is required for decoration.



*Scheme 25. A scheme for the formation of the unexpected compound **178**.*

With step (i) achieved in high yields, α-halogenation was attempted using a wide range of procedures. The conditions attempted are highlighted below, where the conditions used by a modified procedure from Jørgensen *et al* in 2004,[84] gave the only route to the compound of interest (**Table 15**, entry 4 and 5). No attempt to assign stereochemistry was made and only a

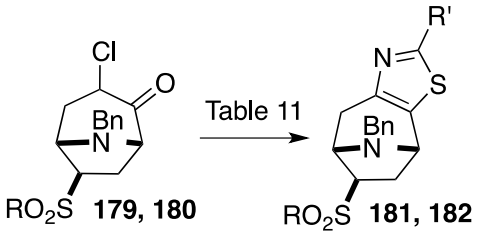
single isomer was observed from inspection of ^{1}H NMR spectra. When the nitrogen substituent was a methyl group, the same conditions were repeated but only a complex mixture was observed. No product was seen in the LCMS and it was suggested that the nitrogen may be reacting with the α-chloro substituent, resulting in a tricyclo-quaternary nitrogen, although no evidence for this was observed.



Entry	SO_2R	NR'	Conditions	Outcome
1	SO_2Ph	NBn	*p*-TsOH (0.1 eq), NBS (1.2 eq.), DCM, 0 °C – 40 °C	Complex mixture
2	SO_2Ph	NBn	Amberlyst - 15, NBS (1.1 eq.), EtOAc, 0 °C – rt stir	Starting material **174**
3	SO_2Ph	NBn	Trichloroiscyanuric acid (1.0 eq.), MeOH (2.0 eq.), DCM	Starting material **174**
4	SO_2Ph	NBn	Proline (30 mol%), NCS (2.0 eq.), DCM	**179**, 40%
5	SO_2Me	NBn	Proline (1.0 eq.), NCS (1.3 eq.), DCM	**180,** 57%
6	SO_2Me	NMe	Proline (1.0 eq.), NCS (1.3 eq.), DCM	Complex mixture

*Table 15 Outcome of α-halogenation reactions involving tropanone **174 - 175**.*

Upon synthesising α-chloro compounds **179** and **180**, a range of heterocyclic fused scaffolds were then planned, which would exploit the α-haloketone functionality. Firstly, a Hantzsch thiazole synthesis was carried out using the conditions reported by Donohoe *et al.* in 2012 and the results are shown below (**Table 16**).[83]



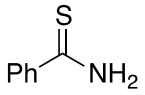
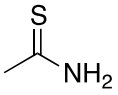
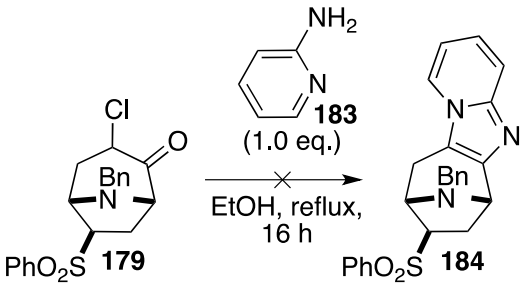
Entry	Starting material	R	Conditions	R'	Outcome
1	**179**	Ph	 (3.0 eq.) DMF (0.15 M)	Ph	**181,** 20%
2	**180**	Me	 (4.0 eq.), DMF (0.15 M)	Me	**182**, 3%

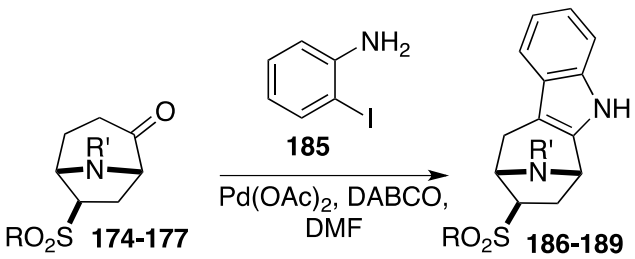
*Table 16. Outcome of Hantzsch thiazole synthesis reactions involving α-chloro compounds **181** sand **182***

α-Haloketone **179** was treated with 2-aminopyridine **183** using the procedure of Chen *et al.*[85] in an attempt to prepare the annulation product aza-indole **184**. Unfortunately, the desired product was not obtained and only starting material was observed (**Scheme 26**). Due to difficulties synthesising azaindole **184**, this scaffold was deprioritised.



*Scheme 26. Scheme for the attempted annulation reaction to form azaindole **184.***

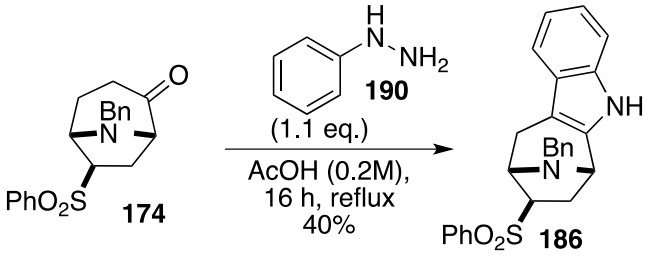
Tropanone compounds **174-177** were subjected to indole synthesis using conditions detailed by Chen *et al*.[86] The conditions involved the reaction of the ketone with an *o*-iodoaniline under palladium catalysis. A series of indole annulated analogues were synthesised with different sulfonyl groups and nitrogen substituents, all in moderate to poor yields (**Table 17**).



Entry	Starting material	R	R'	Conditions	Outcome
1	**174**	Ph	Bn	Ketone (1.0 eq.), *o*-iodoaniline (1.2 eq.), DABCO (1.0 eq.), $Pd(OAc)_2$ (10 mol%), DMF, 105 ^oC	**186,** 40 %
2	**177**	NMe_2	Me	Ketone (1.0 eq.), *o*-iodoaniline (3.0 eq.), DABCO (3.0 eq.), $Pd(OAc)_2$ (10 mol%), DMF, 105 ^oC	**187,** 29%
3	**175**	Me	Bn	Ketone (1.0 eq.), *o*-iodoaniline(3.0 eq.), DABCO (3.0 eq.), $Pd(OAc)_2$ (10 mol%), DMF, 120 ^oC	**188,** 20%
4	**176**	Me	Me	Ketone (1.0 eq.), *o*-iodoaniline(3.0 eq.), DABCO (3.0 eq.), $Pd(OAc)_2$ (10 mol%), DMF, 120 ^oC	**189,** 17%

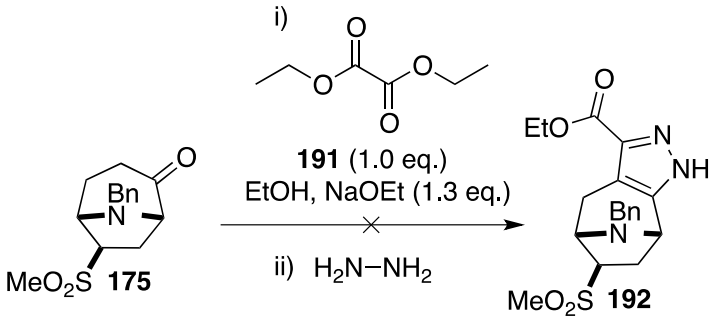
*Table 17. Outcome of indole synthesis reactions involving tropanone **174 – 177**.*

The classical Fischer indole synthesis was also used to synthesise the indole scaffold **186** in a 40% yield and can be used as an alternative approach to synthesise the fused heterocycle (**Scheme 27**).[87, 88,89]



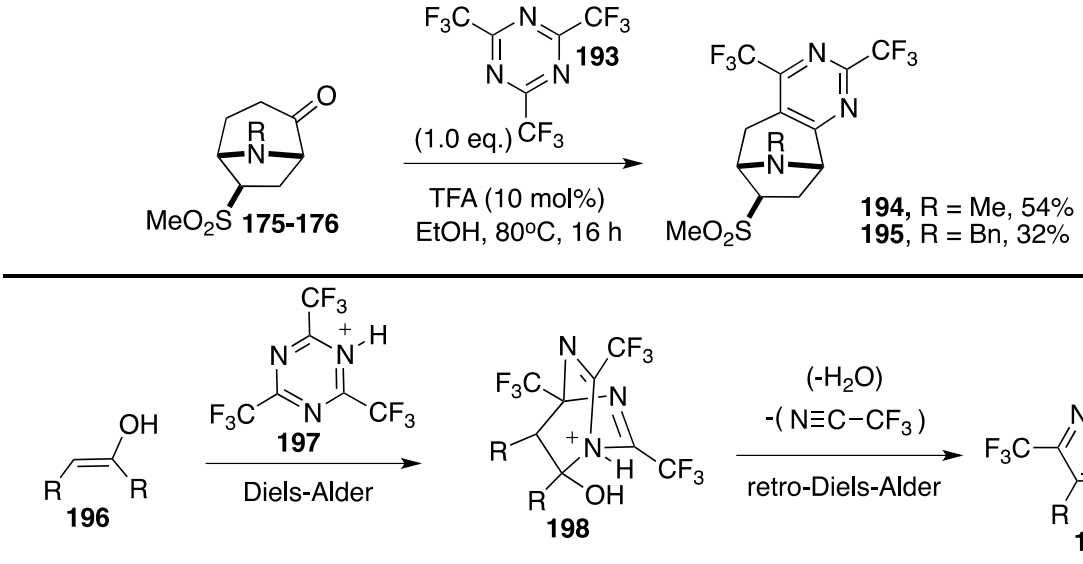
*Scheme 27. Fischer indole conditions used to synthesise compound **186.***

Another annulation reaction was investigated based on conditions detailed by Wu *et al.* in 2001,[69] with the hope of producing a fused pyrazole scaffold **192** (**Scheme 28**). However, when the tropanone **175** was treated with diethyl oxalate **191** and sodium ethoxide, only starting material was recovered. Consequently, the scaffold was deprioritised.



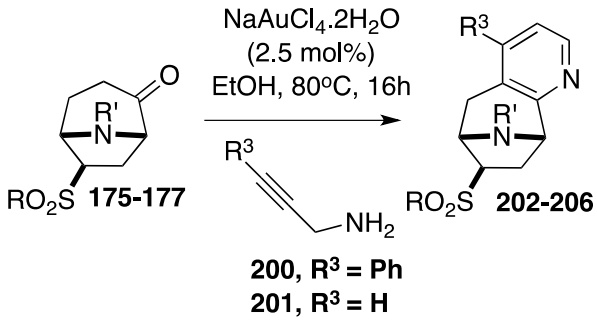
*Scheme 28. The attempted annulation reaction to synthesise scaffold **192** .*

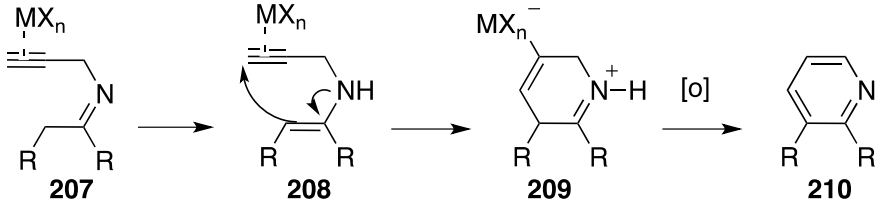
To further explore the vectors about the ketone, a procedure by Bai *et al* in 2017 was executed for the synthesis of the fused pyrimidine compounds **194** and **195** (**Scheme 29a**). [23] Under these reaction conditions, the core scaffold underwent an enolisation, followed by an acid mediated Diels-Alder and retro-Diels-Alder sequence. The reaction resulted in a loss of water and trifluoroacetonitrile, affording the desired pyrimidines in low to moderate yields. The key intermediates are shown below (**Scheme 29b**).



*Scheme 29a) The scheme for the formation of pyrimidine **194** and **195**. b) key intermediates in the formation.*

Synthetic efforts were then focused on the pyridine-fused scaffolds **202 - 206**. By using the conditions detailed by Rossi *et al* in 2003, the pyridine core was synthesised by a one-pot gold catalysed process. This proceeded through the sequential amination of the carbonyl compounds **175 – 177** followed by a regioselective cyclisation of the *N*-propargylenamine intermediate and aromatisation. The mechanism is shown below (**Table 18**) where the desired compounds were formed in low to good yields (20-63%).

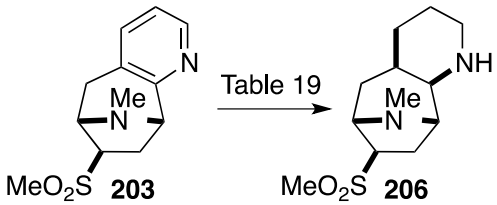




Entry	Starting material	R	R'	R^3	Outcome
1	**175**	Me	Bn	H	**202**, 63%
2	**176**	Me	Me	H	**203,** 43%
3	**177**	NMe_2	Me	H	**204**, 40%
4	**176**	Me	Me	Ph	**205**, 20%

Table 18. Outcome of synthesis of pyridine scaffold derivatives. Above shows the key mechanistic steps and scheme.

It was envisaged that by applying metal-catalysed reduction conditions to the pyridine scaffold **203**, another point of diversification would be introduced at the free NH of the piperidine **206**. However, when attempting to isolate the piperidine **206**, no product was obtained and only a complex mixture was observed. An alternative set of conditions were applied using a different catalyst, high pressure and temperature, and even these harsh conditions only resulted in starting material (**Table 19**).



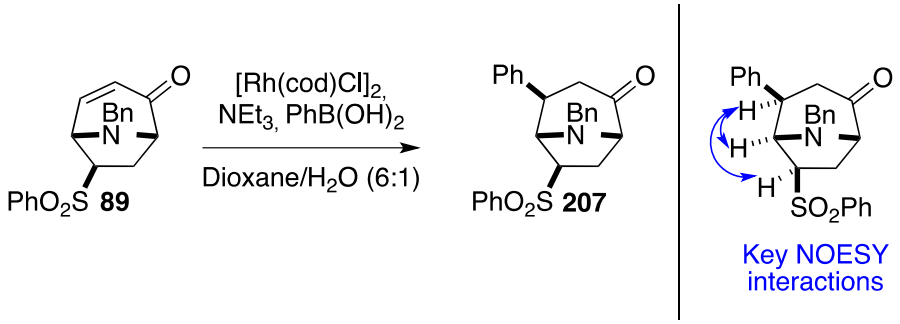
Entry	Conditions	Outcome
1	PtO_2 (20 mol%), H_2, AcOH, 16 h	Complex mixture

2	Pd/C, 10 bar, 50 °C, H_2, 16 h	Starting material **203** recovered

*Table 19. Outcome of the conditions used in attempt to synthesise piperidine **206.***

2.3.3 Development of methods to enable exploration of growth vectors at the 4-position

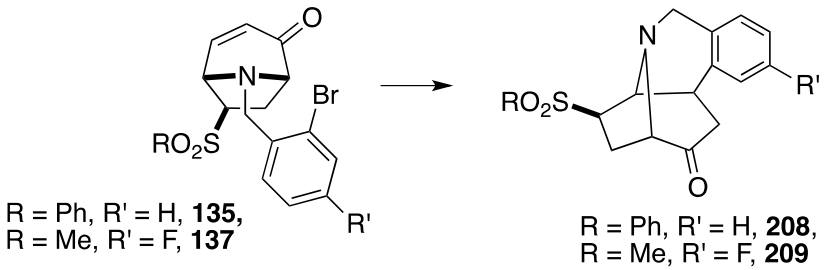
Positon 4 was the next position of investigation, where known chemistry within the Marsden and Nelson group was used to introduce diversity to another point of the sulfone cycloadduct. A Rh(I)-catalysed conjugate addition of phenylboronic acid was used to add a phenyl group to the 4-position, by using conditions adapted from those detailed by Miyaura *et al*.[90] The conditions were optimised upon scale up, however, modest yields were still observed as shown below (**Table 20**). Nevertheless, this would allow the 4-position to be diversified with a range of arylboronic acids.



Entry	mmol	[Rh] eq.	NEt_3 eq.	$PhB(OH)_2$ eq.	Temp. (°C)	Time	Yield
1	0.57	1 mol%	1.0	1.5	50	16 h	38%
2	1.41	1 mol%	1.0	3.0	90	3 d	40%
3	4.10	1 mol%	1.0	3.0	90	16 h	28%

*Table 20. Outcome of 1,4-addition reactions involving parent scaffold **89***

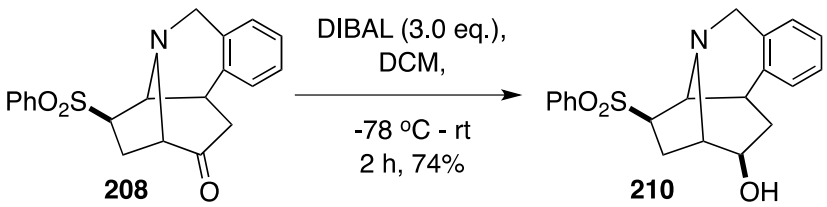
The last scaffold to be synthesised in this vector series was the tetracyclic scaffold **208** and **209**. Exposing the aryl bromide **135** and **137** to a range of Heck conditions, the novel compounds **208** and **209** were ultimately synthesised in poor yields (12- 24%) by following a literature procedure by Grigg *et al* (**Table 21**).[91]



Entry	R	R'	Conditions	Outcome
1	Ph	H	$Pd(OAc)_2$ (20 mol%), PPh_3 (20 mol%), NEt_3 (2.0 eq.), THF, reflux	Starting material **135**
2	Ph	H	$Pd(PPh_3)_4$ (20 mol%), NEt_3 (2.0 eq.), THF, reflux	Starting material **135**
3	Ph	H	$Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), HCOONa (1.5 eq.), $ZnCl_2$ (1.0 eq.), PhMe, reflux	**208,** 24%
4	Me	F	$Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), HCOONa (1.5 eq.), $ZnCl_2$ (1.0 eq.), PhMe, reflux	**209,** 12%

Table 21. Outcome of intramolecular 1,4-addition reactions involving parent scaffold derivatives 135 and 137.

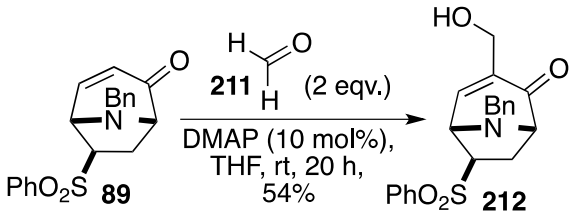
To further elaborate the library, the carbonyl was reduced to the alcohol using DIBAL at -78 ^{o}C, yielding only one diastereoisomer as observed via ^{1}H NMR (**Scheme 30**). The desired scaffold **210** now had a free hydroxyl group for decoration, where a range of medicinally-relevant capping groups could potentially be reacted to produce an array of screening compounds. The relative stereochemistry was predicted by analogy with to similar compounds synthesised (Comparison to a crystal structure **(Section 2.5.2**)).



*Scheme 30. The formation of alcohol **210** derived from tetracyclic scaffold **208**.*

2.3.4 Development of methods to enable exploration of growth vectors at the 3-position

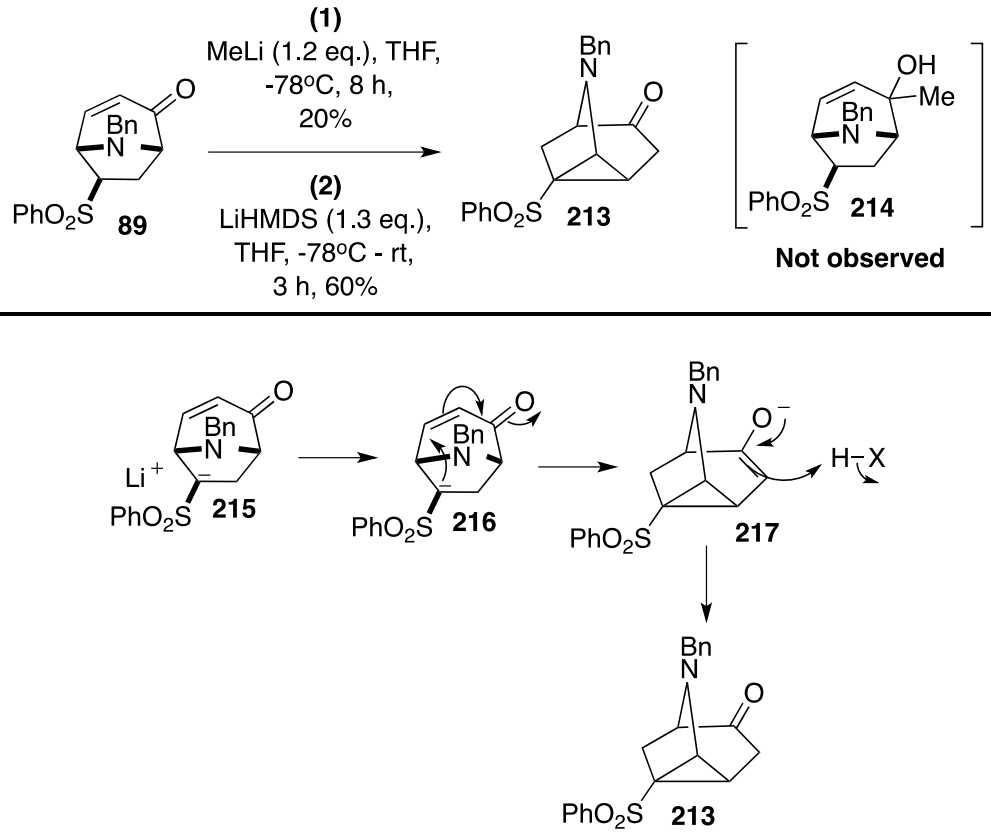
Diversification at the 3-position was investigated by using the conditions detailed by Shi *et al*. in 2012, proceeding through a Baylis-Hillman reaction (**Scheme 31**).[71] The reaction gave rise to primary alcohol **212** in moderate yield, with the alkene left available for further scaffold synthesis (e.g. annulation) and a primary alcohol to diversify.



*Scheme 31. The conditions used for the Baylis-Hillman reaction to synthesise compound **212**.*

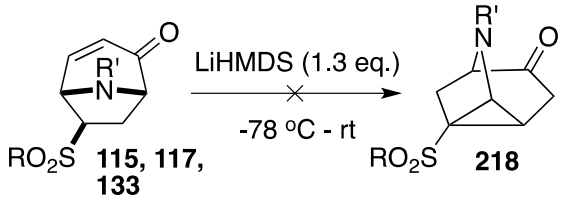
2.3.5 Development of methods to enable exploration of growth vectors at the 2-position

In an attempt to introduce diversity at the 2-position of cycloadduct **89**, nucleophilic addition of a methyl group to the ketone was attempted (**Scheme 32)**. The conditions using methyllithium were taken from within the group due to success with similar tropane scaffolds, however, the desired addition into the carbonyl at C-2 did not occur. Instead, the methyllithium apparently acted as a base, effecting deprotonation alpha to the sulfone followed by an intramolecular Michael addition into the enone afforded the cyclopropane exclusively in 20% yield. Analysis by LC-MS showed the correct mass, with the ^{1}H-NMR spectrum showing the absence of the starting material alkene protons. The proposed mechanism is shown below (**Scheme 32**).



*Scheme 32. The general scheme of the synthesis of cyclopropane **213** and its mechanism of formation.*

This unexpected reaction was intriguing and it also gave rise to a novel scaffold with potential points for further diversity. It was found that switching the base to the non-nucleophilic LiHMDS gave a higher selectivity for the cyclopropane **213**, affording the desired compound in a 60% yield. However, when changing the R group of the sulfone, no analogous compounds were synthesised. The summary is shown below (**Table 22**). It was proposed that for entry 1, the deprotonation of the methyl sulfone was competing with the deprotonation of the proton adjacent to the sulfone, and a complex mixture was observed. When the reaction in entry 2 was attempted, a side product **219** occurred from dimerization of the starting material, which was confirmed by ^{1}H-NMR and LCMS analysis**.** In an attempt to solve this problem, a lower concentration of solvent was used to decrease the reaction rate (**Table 22**, entry 3), however, only starting material was observed. To our surprise, when the nitrogen substituent was changed to a methyl, no reaction occurred and only starting material was recovered.



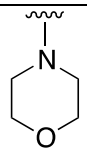
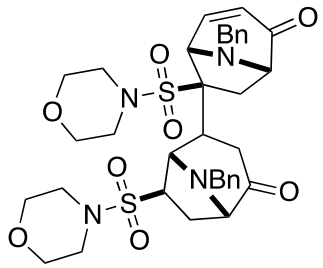
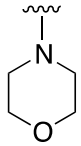
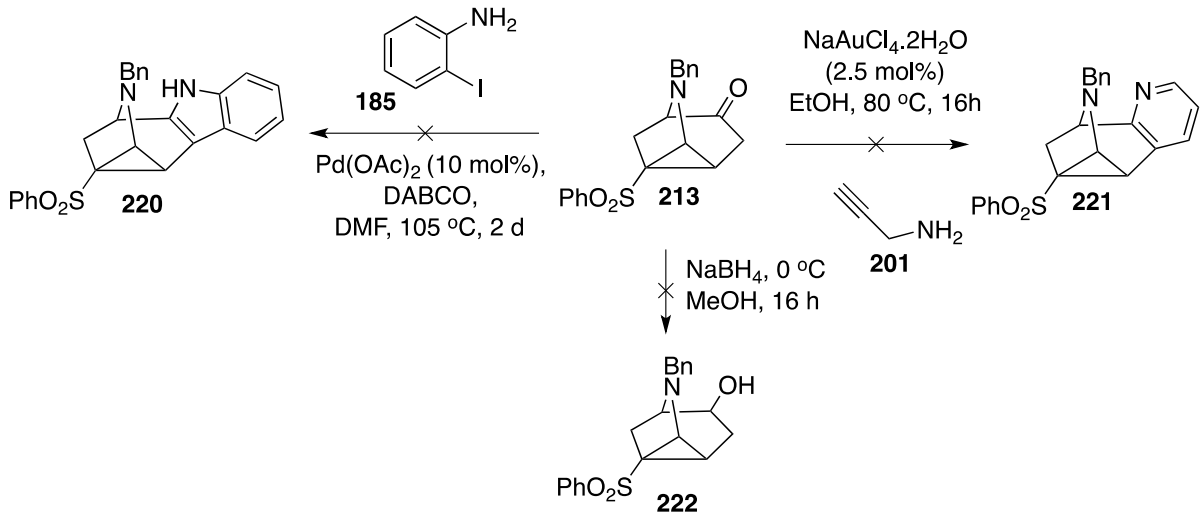
Entry	Starting material	NR'	R	Conditions	Outcome
1	**117**	NBn	SO_2Me	THF (0.02M), 3 h	Complex mixture
2	**133**	NBn		THF (0.2M), 3 h	 **219**
3	**133**	NBn		THF (0.02M), 3 h dropwise addition of **133**	Starting material **133**
4	**115**	NMe	SO_2Ph	THF (0.02M), 3 h dropwise addition of **115**	Starting material **115**

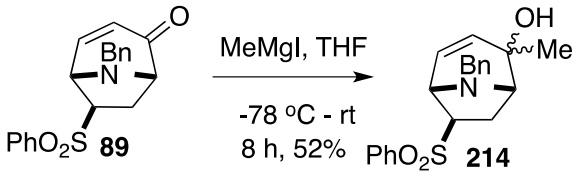
Table 22. Outcome of the attempted conditions to synthesise cyclopropane derivatives.

It was proposed that cyclopropane **213** was potentially unstable due to its ability to undergo a retro-Michael reaction. Three compounds were therefore proposed that eradicated the ketone functionality to remove this possibility (**Scheme 33**). The three reactions followed previous procedures but unfortunately were all unsuccessful, rendering this compound problematic and therefore it was to be deprioritised as a screening library set.



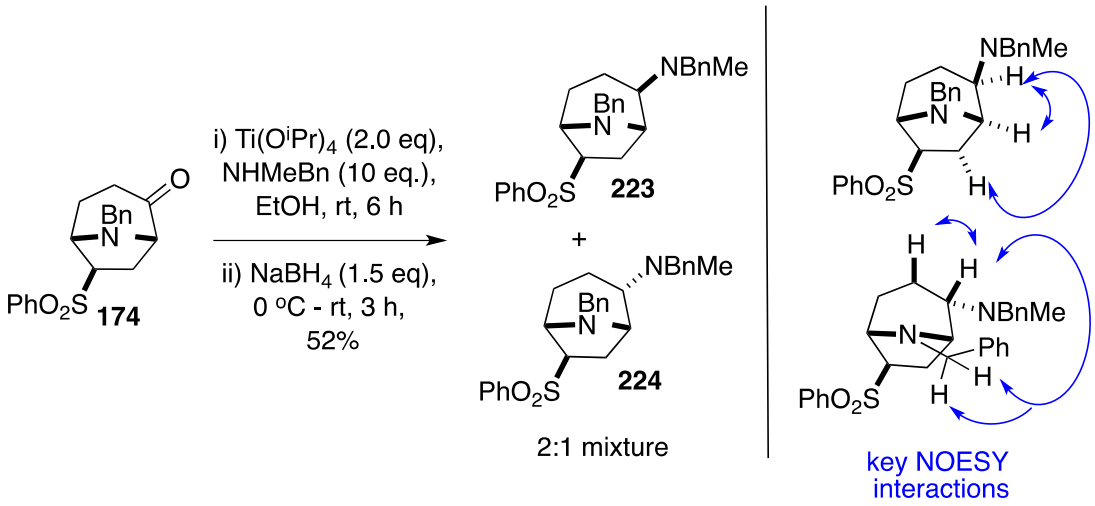
Scheme 33. A scheme showing the routes to three compounds using previously described procedures.

To accomplish the desired methyl addition at the 2-position, an alternative approach was undertaken using methylmagnesium iodide. Due to the less basic nature of the Grignard reagent the decorated product was obtained in a 52% yield with no trace of the cyclopropane-containing compound. A mixture of diastereoisomers were obtained in a 3:2 ratio, however no attempt was made to isolate the isomers. The relative stereochemistry of the major diastereomer was not determined due to the complexity of the crude ^{1}H-NMR (**Scheme 34**).



*Scheme 34. A general scheme for the formation of compound **2.126** from a Grignard addition.*

Subsequent efforts to introduce different groups at the 2-position included a reductive amination, using the conditions detailed by Bhattacharyya *et al.*[92] Compound **174** was susceptible to 1,4 addition, so the partially reduced substrate was used instead. The tropanone **174** was treated with *N*-methylbenzylamine and titanium isopropoxide in ethanol at room temperature for 6 hours, then cooled to 0 °C and reduced via sodium borohydride. The reaction produced a separable 2:1 mixture of diastereomers, which was assigned according to the crude ^{1}H NMR in 52% yield. The stereochemistry of the two isomers was assigned according to key NOESY interactions (**Scheme 35**).



*Scheme 35. A scheme for the synthesis of compound **223** and **224**, with their stereochemistry assignment.*

2.3.6 Development of methods to enable exploration of growth vectors at the 6-position

2.3.6.1 Oxidative desulfonylation

Two methods were proposed to lower the heavy atom count of the parent cycloadduct **89**. The first was to change the sulfonyl substituent, which could be achieved by using smaller sulfonyl substituents on the dipolarophile in the cycloaddition (see **Table 8, Section 2.2.2**). However, a more challenging approach would be to change the functional group entirely, thereby also increasing the diversity. The proposed functional group interconversion was from a sulfone to a ketone, which in turn would also offer an extra vector to explore. This change would help further demonstrate the scaffold's potential to be diversified at numerous positions, and would dramatically decrease the heavy atom count from 25 to 10 (**Figure 19a**, compounds **89** and **225**). This would allow the pursuit of a potential fragment library for testing. Also, the desired compound **89** would possess a similar core to the known natural products alstoniaphylline A and B (**Figure 19b,** compounds **226 - 227**).

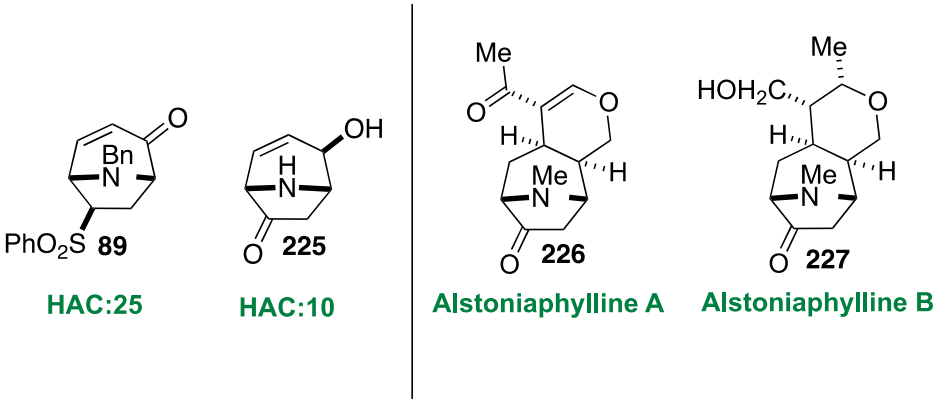
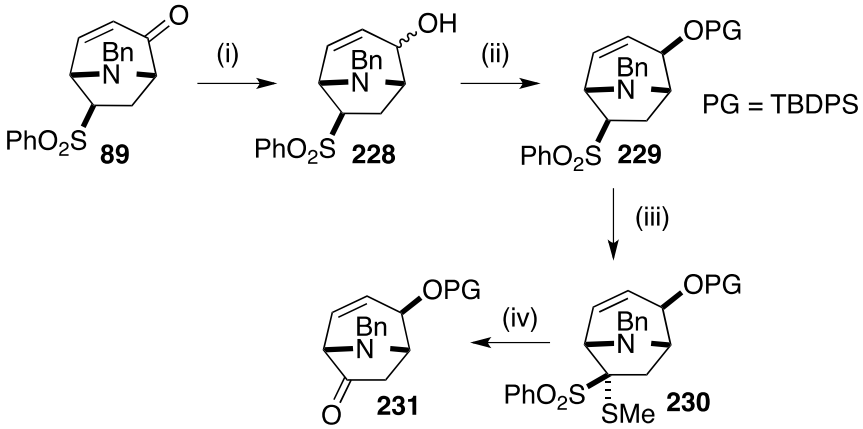


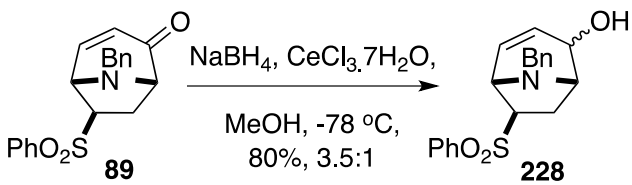
*Figure 19a). The parent scaffold **89** and the planned smaller derivative compound **225**. b) Two natural products **226 – 227** which share similar framework to compound **89**..*

To further functionalise at the 6-position it was proposed that the functional group interconversion would occur through an oxidative desulfonylation.[93-94] The suggested route was a four-step, three-pot synthesis involving a Luche reduction and an alcohol protecting step, therefore avoiding the complications from the reactive enone functionality. The final step involved the key oxidative desulfonylation step (**Scheme 36**).[95]



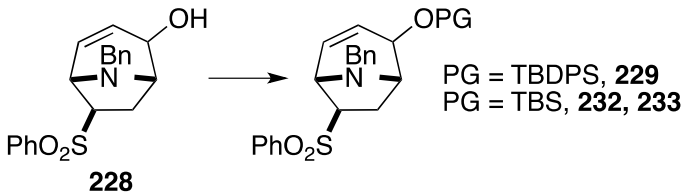
Scheme 36 Step (i) Luche reduction, step (ii) alcohol protection and step (iii & iv) oxidative desulfonylation.

A Luche reduction[96] using cerium (III) chloride, sodium borohydride and methanol at -78 °C, with the parent cycloadduct **89** proceeded in an 80% yield and afforded the desired alcohol **228** as an inseparable 3.5:1 mixture of stereoisomers. The major isomer was assigned according to key NOESY interactions (**Scheme 37**)



*Scheme 37. The Luche reduction conditions and the stereochemistry assignment of compound **228**.*

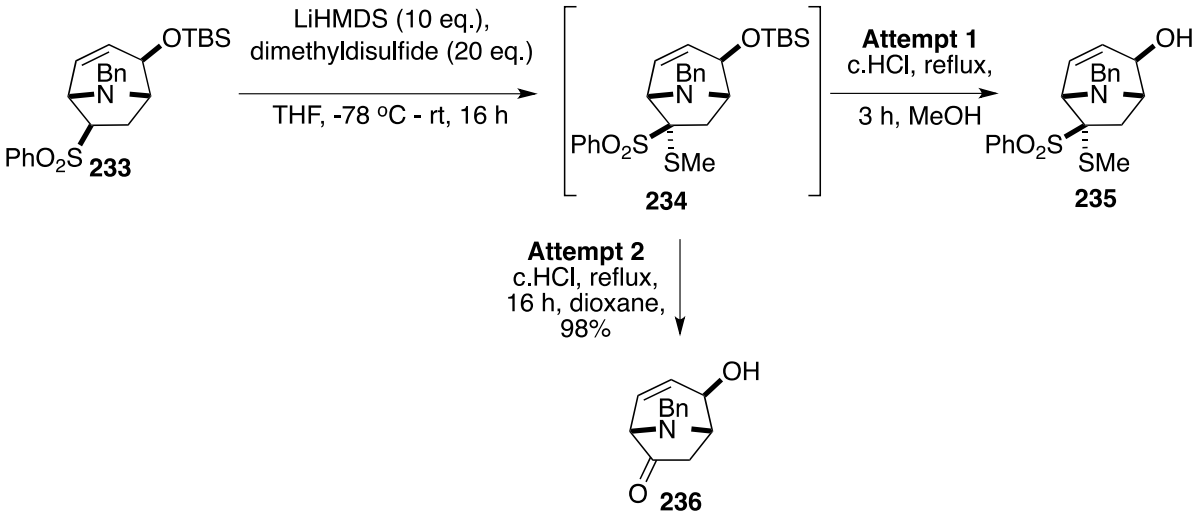
Attempts were then made to protect the alcohol. First, *tert*-butyldiphenylsilyl (TBDPS) protection was trialled, however no desired product was obtained after two conditions were applied. It was proposed that this was due to steric interactions between the bulky OTBDPS group and the *N*-benzyl group, or the reactivity of the silyl electrophile. A third attempt involved *tert*-butyldimethylsilyl (TBS) protection via the silyl triflate, and silyl ether **232 – 233** was obtained in a high 82% yield (**Table 23**).



Entry	Conditions	Outcome (product)
1	TBDPS-Cl (1.1 eq.), imdiazole (2.2 eq.), DMF (0.4 M), rt, 6h	Starting material, **228**
2	TBDPS-Cl (1.1 eq.), imdiazole (2.2 eq.), DMF (4 M), rt, 6h	Starting material, **228**
3	TBS-OTf (1.1 eq.), imidazole (2.0 eq.), DMF (0.7 M), 0 ^{o}C – rt, 6h	82% (**232, 233)** (3.5:1 mixture of isomers)

*Table 23. Outcome of the conditions used to synthesise a protected alcohol **232** and **233.***

The next aim was to successfully remove the phenylsulfonyl functional group using a method described by Tsuchihashi *et al.*[94,95] The method involves a formal oxidation of the sulfone-bearing carbon by lithiation and electrophilic sulfenylation then hydrolysis of the sulfenylsulfone. The intermediate α-sulfenylsulfone **234** was observed by LC-MS analysis, but not isolated and the intermediate was subjected to two sets of conditions (**Scheme 38**). On first attempt, the crude product was refluxed in acid with Methanol and the only product observed by LC-MS analysis was the deprotected intermediate **235**. Step (iv) was reattempted with dioxane as solvent, giving the desulfonylated compound **236** in a 98% yield (over two steps). The reaction mixture was able to be heated at reflux at high temperatures which not only enabled the desulfonylation, but also removal of the TBS group to afford the keto alcohol **236** (**Scheme 38**).



Scheme 38. A scheme showing the two attempts of the oxidative desulfonylation step. Attempt 1 was unsuccessful and attempt 2 was successful.

The stereochemistry of compound **236** was assigned according to the ^{1}H NMR spectra data, using the software Avogadro (**Figure 20**). The key proton H_{β} was predicted to show only coupling to proton H_{γ}, where a doublet was observed. No coupling interaction was seen between H_{α} and H_{β}.

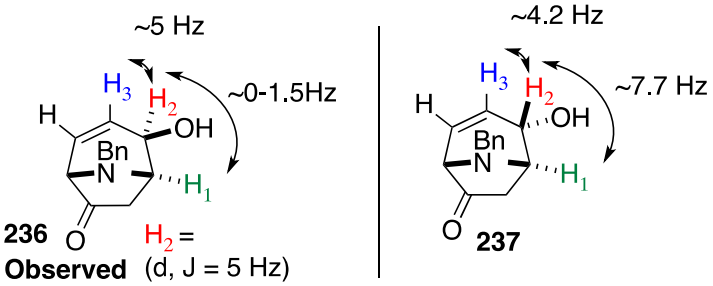
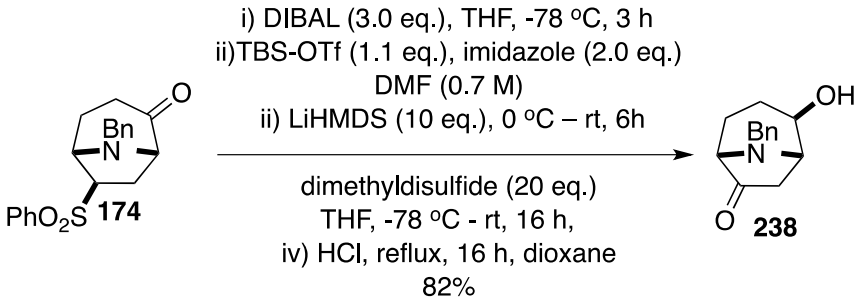


Figure 20. The predicted coupling constants for both possible isomers of the desulfonylation product 2.141.

An alternative route was suggested to a different desulfonylation product. It was proposed this route would avoid the product loss through the mixtures of diastereomers, which occurred using the route above (**Table 23)**. It was envisaged that when reducing the ketone in the absence of the double bond, a single diastereomer would be produced, as this is a known product in the literature.[97] When tropanone **174** was subjected to the reduction using DIBAL, the intermediate product was formed as a single diastereomer. The crude alcohol was protected with a silyl ether TBS protecting group and the desulfonylation conditions were applied. The desired product was achieved in an 82% yield. When comparing to the previous route, product **238** was obtained in a 76% yield over three steps, therefore the new route was more efficient and higher yielding. The alcohol stereochemistry was already determined in the first step by comparison

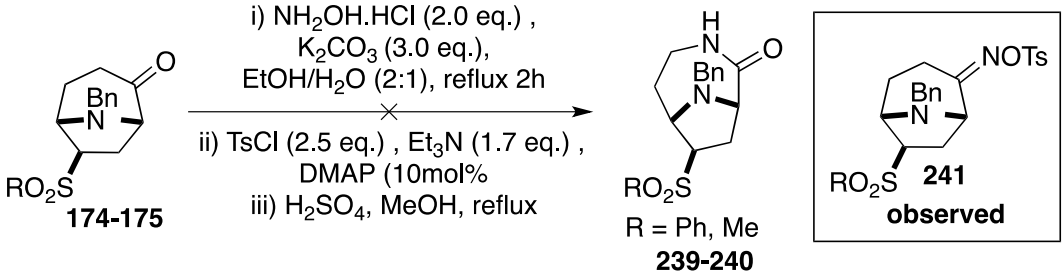
to known compounds and similar compounds in the literature.[98,99] The major isomer is predominantly syn stereochemistry to the bridgehead nitrogen.



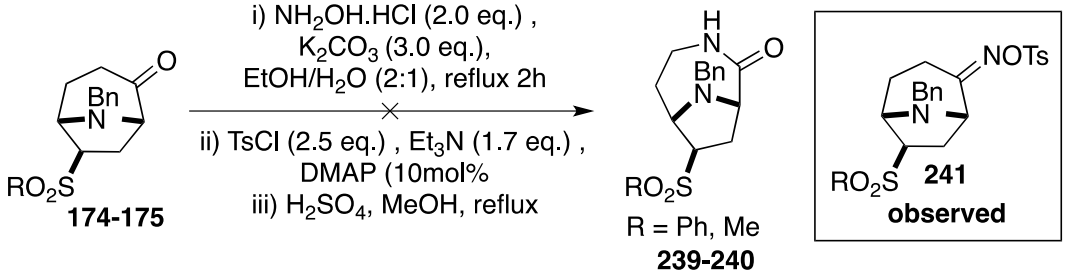
*Scheme 39. A scheme showing the new efficient route to a desulfonylated compound **238**.*

2.3.7 Ring expansion

To introduce more diversity to the lead-like scaffold set, ring expansion reactions were to be undertaken to synthesise 8-membered rings. The Beckman rearrangement was first investigated, where conditions to synthesise the desired scaffolds are shown below (



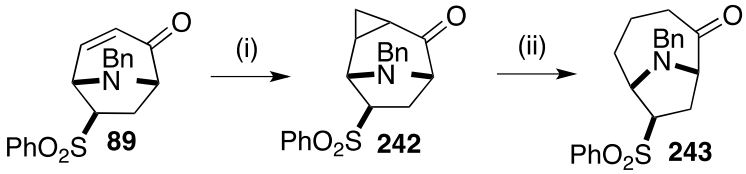
Scheme 40). Tropanone compounds **174 – 175** was first subjected to hydroxylamine to synthesise the oxime, which was then treated with tosyl chloride. In both cases the intermediate *O*-sulfonyl oxime **241** was observed by the LCMS. When acid was added the reaction was not successful. There were no traces detected by LCMS analysis, nor any product isolated upon purification. Due to time constraints, this scaffold was discontinued.



*Scheme 40. The attempted Beckman rearrangement on scaffolds **174** and **175**.*

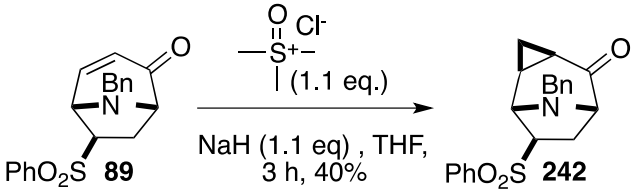
Having achieved no success with the above ring expansion, an alternative 8-membered scaffold was suggested. A two-step route via a fused cyclopropane **242** was proposed, using readily available starting materials. It was envisioned that the strained cyclopropane system would be

a pivotal intermediate that guides the ensuing reaction towards ring expansion.[100] With the aid of palladium on carbon under a hydrogen atmosphere, a larger ring structure could be obtained.



Scheme 41. The new proposed route to a novel ring expanded scaffold. Step (i) cyclopropanation and step(ii) reduction.

A Corey-Chaykovsky reaction was carried out in an attempt to synthesise the desired scaffold **242**, with the reaction conditions shown below (**Scheme 42**).[101,102] First a sulfur ylide is synthesised in-situ, following a 1,4-addition reaction and subsequent ring closure to produce the scaffold **242** as a single diastereomer.



*Scheme 42. The conditions used to synthesise the fused cyclopropane scaffold **242**.*

The stereochemical assignment is shown below (**Figure 21**): proton H_b has no coupling between adjacent protons, therefore a singlet is only observed in the ^1H NMR spectra.

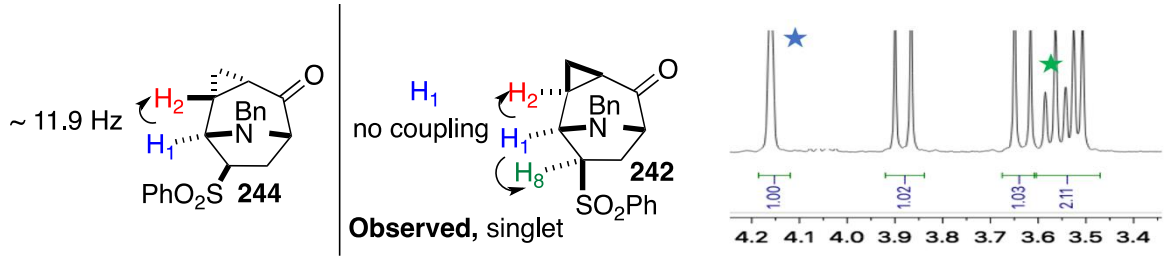
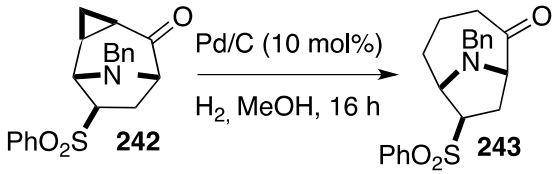


Figure 21. Shows the predicted coupling constants for each isomer and the proton NMR spectra

With step (i) achieved in a moderate yield, the next step was to expand the ring system. When using palladium on carbon under hydrogen, no product was observed and, only the starting material was detected via LCMS analysis and this scaffold was deprioritised. Alternative routes would consist of SmI_2-induced ring expansion reactions and radical expansion using AIBN and tributyltin hydride.[103,104]



*Scheme 43. The reaction conditions attempted to break open the fused cyclopropane **242**.*

2.4 Summary of lead-like scaffold synthesis

In summary, 14 lead-like scaffolds were synthesised in a total of 24 steps from a single parent core scaffold **89**. This efficient process has demonstrated the feasibility of the top-down approach to LOS, where the chosen parent scaffold **89** was ideal for this approach. It should be noted that the sulfonyl group was initially chosen as a substituent that may be removed from the scaffolds. Even though this has proven possible with the oxidative desulfonylation reaction (**Scheme 39**), it suffered from a long synthetic sequence and this would be a synthetic challenge to undertake for every scaffold. Therefore, it was decided in the interests of efficiency that this substituent will remain in most lead-like and final compounds. Other sulfonyl groups were chosen to introduce diversity to the scaffold set, however again because of the lengthy process it was only attempted in a small number of compounds. Due to time constraints, the ring expansion chemistry was not explored thoroughly and there remain several reactivity pathways which could still be investigated to prepare new scaffolds. Nevertheless, the 14 lead-like scaffolds that were prepared were enough to complete the first objective.

A summary of each scaffold is shown below (**Figure 22)**. As explained previously (**Section 1.4**), it was important that these scaffolds possessed certain properties in order to be good starting points in drug discovery. Prior to any laboratory work each scaffold was analysed for their molecular properties and a selection of particular scaffolds was done following a set of key criteria (c.f. **Table 2**). However, it was still necessary to analyse and compare each successfully synthesised scaffold using computationally analysis.

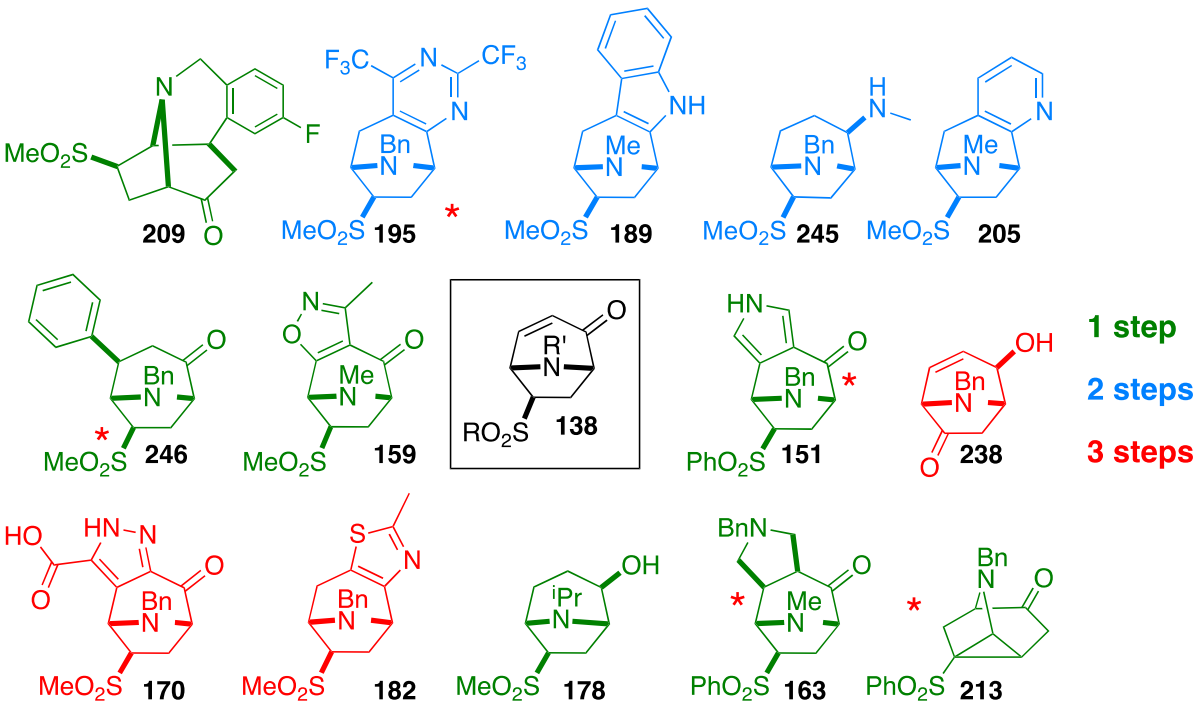


*Figure 22. The collection of novel lead-like scaffolds produced from parent scaffold core **138**. (colour coded according to step count)*

2.5 Computational assessment of the of lead-like scaffolds prepared

2.5.1 Lead-likeness assessment of lead-like scaffolds

To assess the scaffolds' molecular weight and lipophilicity, the in-house open-access tool LLAMA was used.[45] The properties of the 14 lead-like scaffolds were calculated and plotted on a scatter graph (**Figure 23**). In some cases,[**] the benzyl group was removed to minimalize molecular weight. Each compound was plotted against lipophilicity (AlogP) and molecular weight (mw), leading to 93% of the compounds occupying lead-like chemical space. Compound **248** fell just outside lead-like space, due to its larger molecular weight. To avoid this and reduce molecular weight, different dipolarophiles could be used in the cycloaddition, which could access the pyrimidine scaffold with a lower molecular weight or alternatively the sulfone could be removed. Compound **178** had a lead-like penalty of 2 because of the absence of aromatic groups, where the other compounds all had a penalty of 0. The penalty is a measure of how far outside lead-like space a compound lies and the properties of which they are assessed against are shown in **Table 2** in **Section 1.4**. The properties include heavy atom count, AlogP, number of aromatic rings and undesirable functional group filter, where the score is obtained from a sum of each penalty incurred.

[**] Compounds marked with a '*' in **Figure 22**.

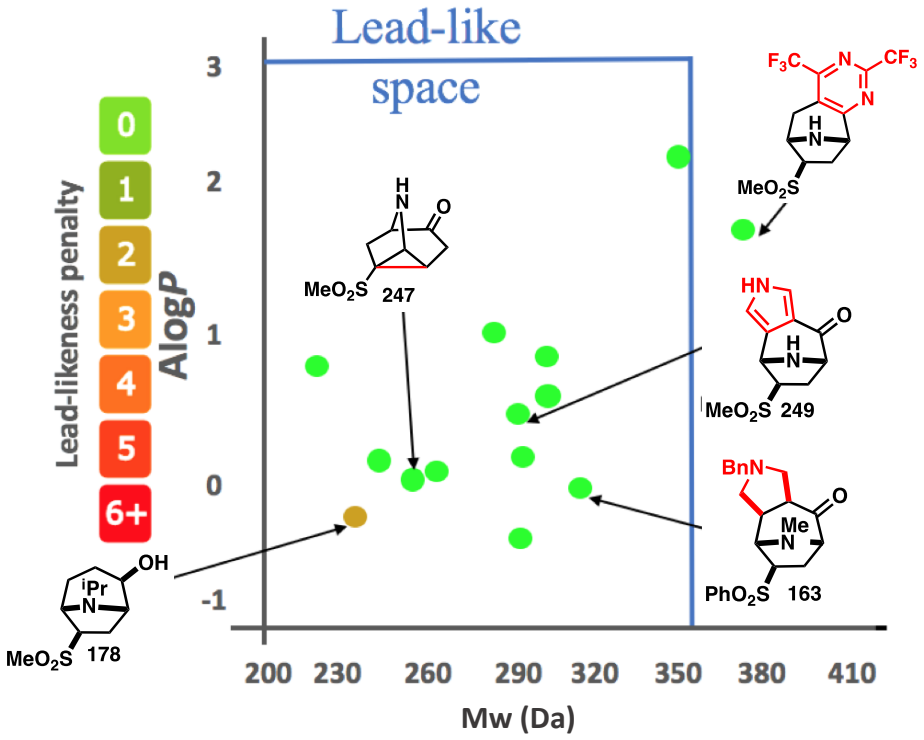


Figure 23. The lipophilic and molecular weight assessment of the 14 lead-like scaffolds. Coloured according to lead-like penalty

2.5.2 Fraction of sp^3 hybridised carbon assessment of lead-like scaffolds

As discussed in **Section 1.4**, studies have found that compounds with a higher Fsp^3 value (and presence of chiral centres) have a better chance of succeeding through subsequent stages of drug discovery.[24] To assess each scaffolds' fraction of sp^3 hybridised carbons, the software LLAMA was used to calculate each value and the results are plotted below (**Figure 24**).[45] Each scaffolds value was analysed and compared with a random 1% of the ZINC database. The analysis of lead-like scaffolds showed that 93% of the library have a larger Fsp^3 value, therefore achieving one of the objectives proposed. Compound **178** has a high Fsp^3 score due to the compound consisting of only sp^3 carbons. However, compound **249** has a low score, as it contains very few sp3 carbons and contains 'flat' sp^2–rich groups, such as a fused pyrrole and a phenyl substituent. The four acyclic precursors used to synthesise the parent scaffolds have an average Fsp^3 value of 0.14, showing a 4-fold increase when compared to the average scaffold value. It should also be noted that each compound has the presence of at least three chiral centres.

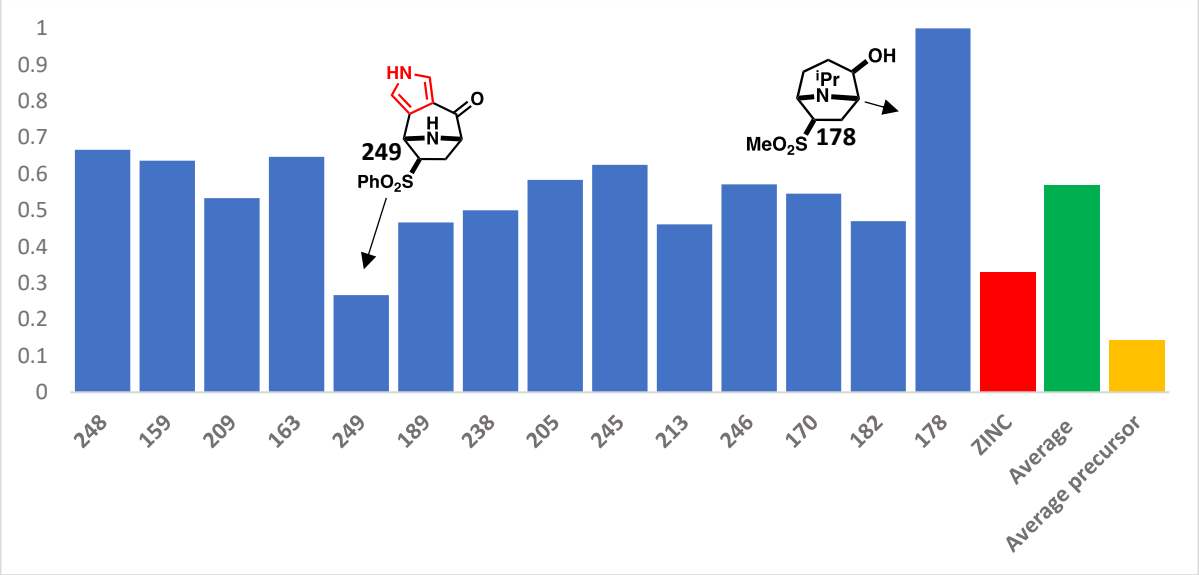


Figure 24. A Fsp3 value comparison of lead-like scaffolds (average in green), average ZINC database(in red) and average acyclic precursor (in yellow).

2.5.3 Three-dimensionality assessment of lead-like scaffolds

To assess the lead-like scaffolds' three-dimensional shape, each compound was plotted on a PMI plot using LLAMA (**Figure 25**).[45] The lowest energy conformer for each compound was generated computationally and the system calculates the moments of inertia in the x, y and z axes. The system then calculates two plot coordinates (I1 and I2) by dividing inertia (x) and inertia (y) by inertia (z). Each two coordinates are plotted on a triangular scatter diagram to assess three-dimensionality, where each of the three vertices of the triangular plot represent the extremes of molecular geometry, as discussed in **Section 1.4** (**Figure 3**). For comparison, a random 1% of the ZINC database was also plotted. As seen below, the scaffolds are now starting to move away from the heavily located area of chemical space (the 'rod-like' / 'disc-like' area), and starting to populate the more unexplored area 'sphere-like' chemical space. Compound **239** (**Figure 25**, A) was located in the heavily explored region of chemical space due to the presence of the benzyl protecting group. However, due to the small nature of this compound the unprotected scaffold would lie outside lead-like chemical space, therefore this group was not removed. Nevertheless, if the methylated analogue was synthesised this would locate the compound in a more 'sphere-like' area of space (**Figure 25**, G)

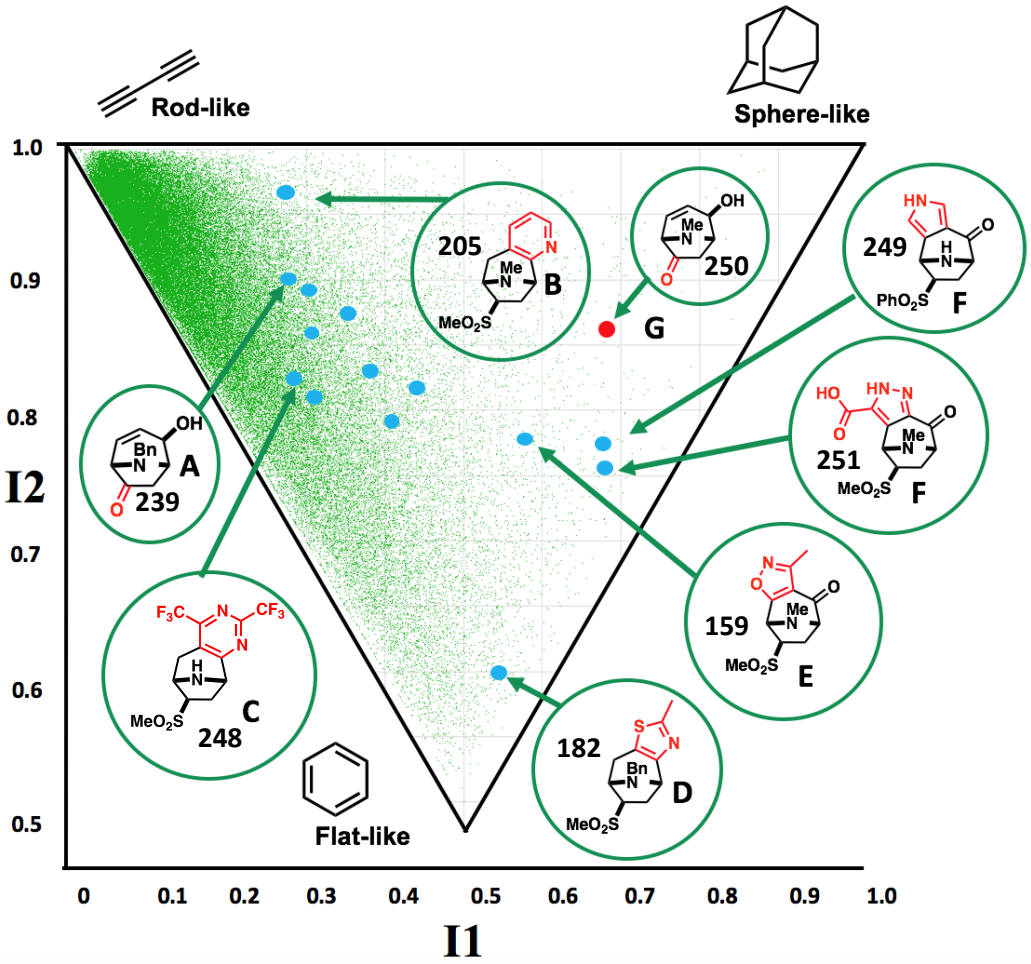


Figure 25. PMI plot of lead-like scaffolds plotted in blue and random 1% of ZINC database compounds plotted in green.

2.5.4 Diversity assessment of lead-like scaffolds

To assess the diversity of the library, each compound's framework was analysed. The method used was inspired by Waldmann's 'scaffold tree' hierarchical analysis technique.[66] The process involved 'stripping' away substituents, leaving the core-framework. Each core-framework was then analysed against a random 2% of the ZINC database using LLAMA. Frameworks **257** and **254** had structures which were embedded as a substructure; this was expected for compound **257** as the tropane-like moiety is frequently observed in many natural products. Framework **254** only compared to 4 compounds in a possible ~180,000 compounds in the database. Therefore, in conclusion, these lead-like scaffolds possessed novel frameworks and experienced a diverse nature (which this strategy hoped to achieve). It should also be noted that a structure search in the literature was also performed for each scaffold to confirm their novelty.

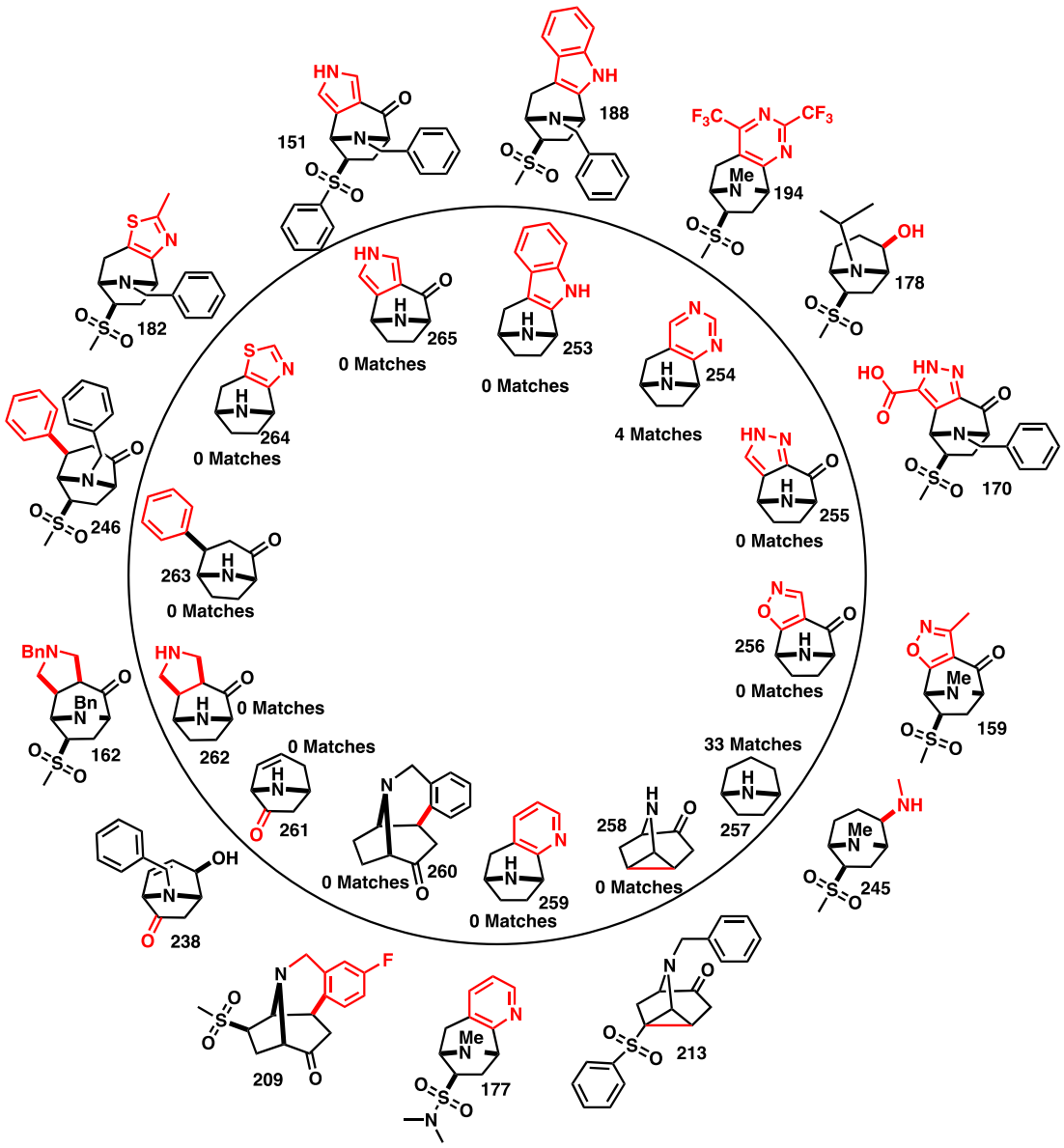


Figure 26. Skeletal diversity assessment of lead-like scaffolds. The outer circle signifies synthesised scaffolds, where the inside circle displays the core-frameworks analysed against the ZINC database.

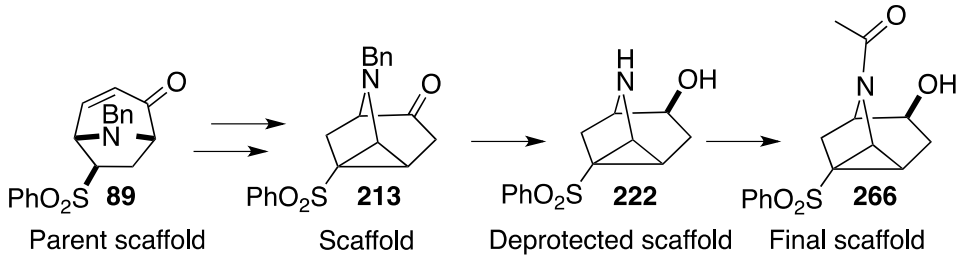
With a total of 14 novel diverse lead-like scaffolds synthesised from one parent core scaffold, the second objective was now complete. These results set up the third objective well, where compounds which had been synthesised on a large scale can be decorated with medically relevant capping groups. A final library could be assembled for screening against a wide range of biological targets.

3.0 Results and discussion 2: decorating lead-like scaffolds for final library synthesis

With a variety of scaffolds synthesised our third objective was to synthesise a compound library from each scaffold. This involved firstly synthesising each scaffold on a large scale in good yield, then changing functionality and finally decorating with medicinally relevant capping groups.

In each case a change of functionality may occur:

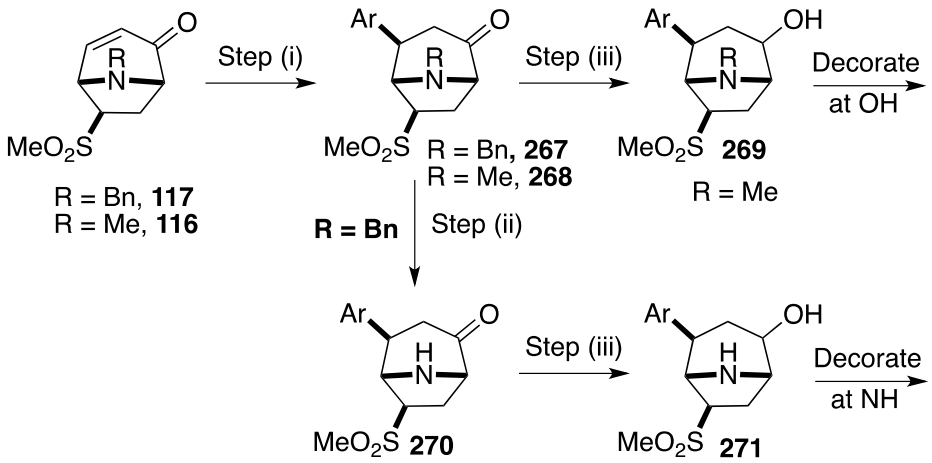
- If a carbonyl is present - reduce to a single diastereoisomer of the corresponding alcohol
- If a protecting group is present - deprotect
- If undesirable functionality is present - change functional group (e.g. ester to amide)



*Scheme 44 An example synthesis of a final decorated compound from parent scaffold **89.***

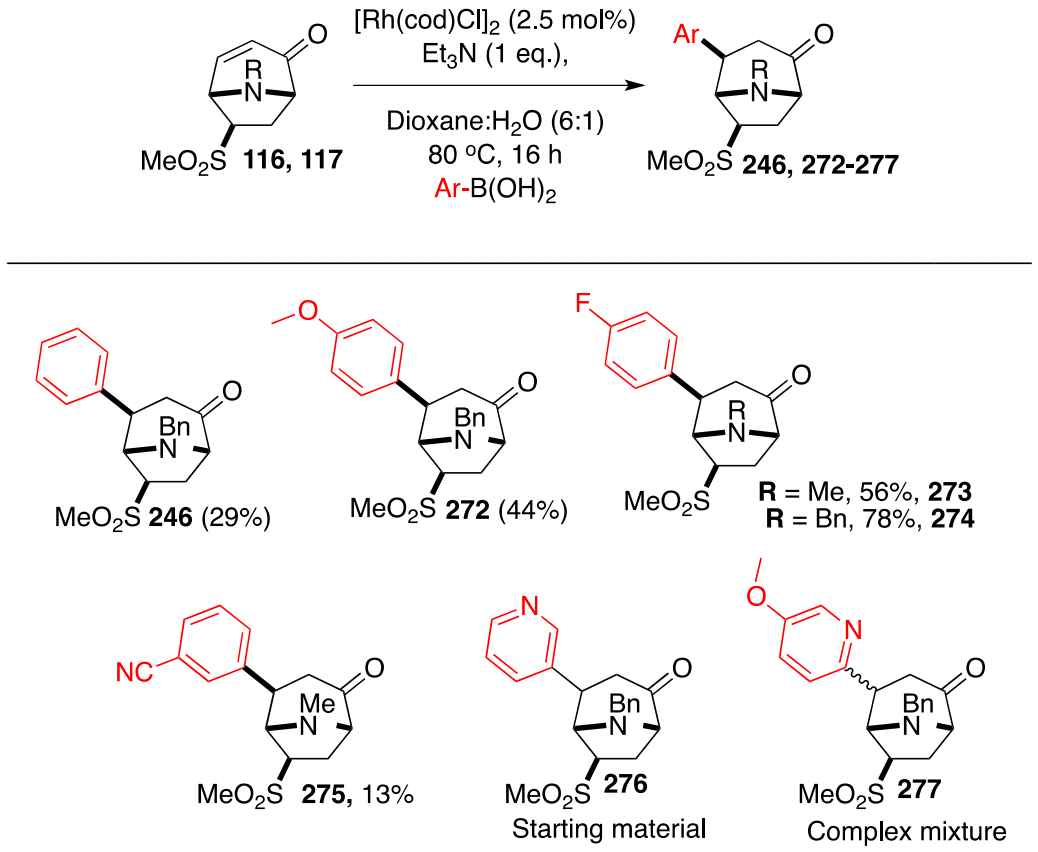
3.1.1. Manipulation of different scaffolds by a 1,4-addition

The first scaffold selected for the library synthesis was the scaffold **207** that was produced from a 1,4-addition of an aryl boronic acid. A simple route was proposed involving the scaffold synthesis (step i), a deprotection if required (step ii) and finally a diastereoselective ketone reduction (step iii) (**Scheme 45**).



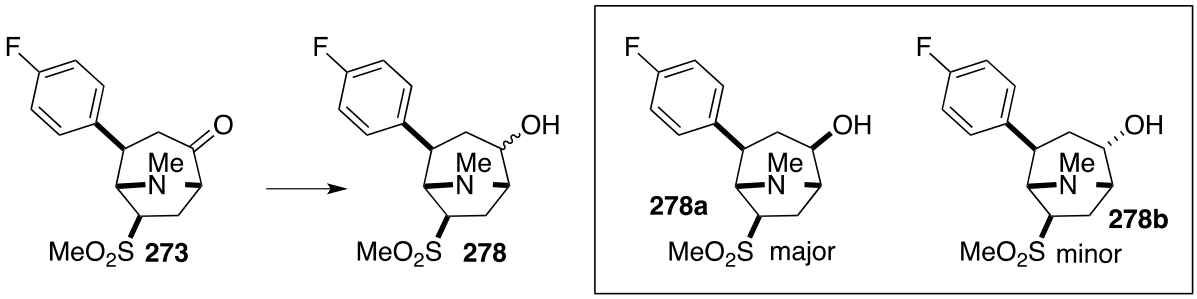
Scheme 45. Step (i) scaffold synthesis, step (ii) reduction, step (iii) deprotection, step (iv) reduction.

The initial step of the proposed route was a rhodium catalysed 1,4-conjugate addition with a range of arylboronic acids. In order to synthesise a diverse range of compounds for screening, the arylboronic acids selected ranged from electron-poor to electron-rich. The results are shown below (**Scheme 46**). Unfortunately, the more polar heterocyclic boronic acids (compounds **277** and **278**) were not successful, as no product was observed. While reactions with aryl and alkenylboronic acids are well-documented, there are few examples of heteroaryl residues.[105] The addition of the 4-fluorophenyl group however looked promising and the products **274** and **275** were synthesised on a large scale (11.7 – 13.4 mmol).



*Scheme 46. A scheme showing the general route to scaffolds **246, 262-277** and the derivatives synthesised.*

The next step in the synthesis was the diastereoselective reduction of the ketone. When compound **273** was reduced with sodium borohydride at 0 °C, an inseparable 1:1 mixture of diastereomers was obtained. Even upon decoration, in most cases the compounds remained a mixture of inseparable diastereoisomers after purification. To alleviate this problem compound **273** was screened with a range of reducing agents in attempt to improve the diastereomeric ratio (d/r). The summary is shown below (**Table 24**). The conditions that generated the best selectivity were DIBAL at -78 °C in DCM. The diastereomeric ratio obtained was 3:1, which was determined by distinct proton integration ratios in the ^{1}H NMR spectrum.



Entry	Conditions	Temp	d/r
1	$NaBH_4$ (2.0 eq.), MeOH	0 °C	1:1
2	DIBAL (1M in cyclohexane) (3.0 eq.), DCM (**278a,** 71%)∅	-78 °C	3:1
3	DIBAL (1M in cyclohexane) (3.0 eq.), THF	-78 °C	3:2
4	L-selectride (3.0 eq.), THF	-78 °C	3:1
5	$LiAlH(O^tBu)_3$ (3.0 eq.), THF	-78 °C	5:2

*Table 24. Outcome of reduction reactions involving the 1,4-addition product **273**..*

The major isomer **278a** was isolated via crystallisation from ethanol. A crystal structure was obtained to confirm the relative stereochemistry, where the alcohol and the *para*-fluorophenyl group display a *syn*-relationship to the sulfone and bridged nitrogen (**Figure 27**).

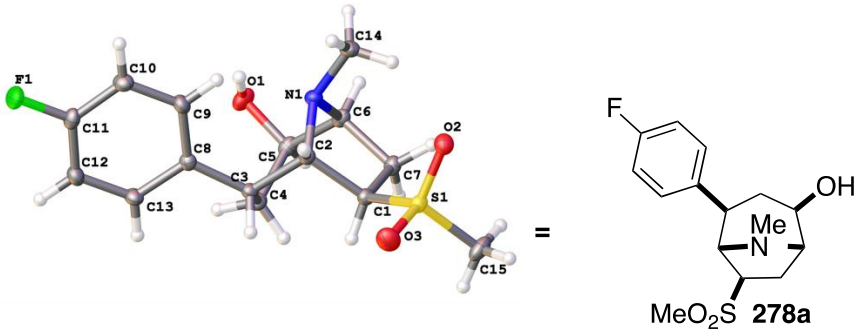
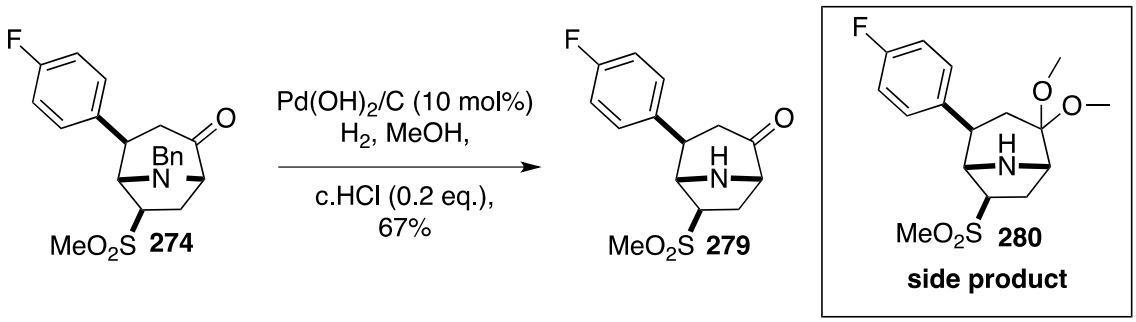


*Figure 27. Left - A crystal structure of compound **278a** and right – compound **278a** structure.*

In cases where the benzyl group was present, a deprotection was performed before the reduction step. The conditions used were those detailed below using palladium hydroxide on carbon as catalyst and pleasingly the desired product **279** was obtained in 67% yield. However,

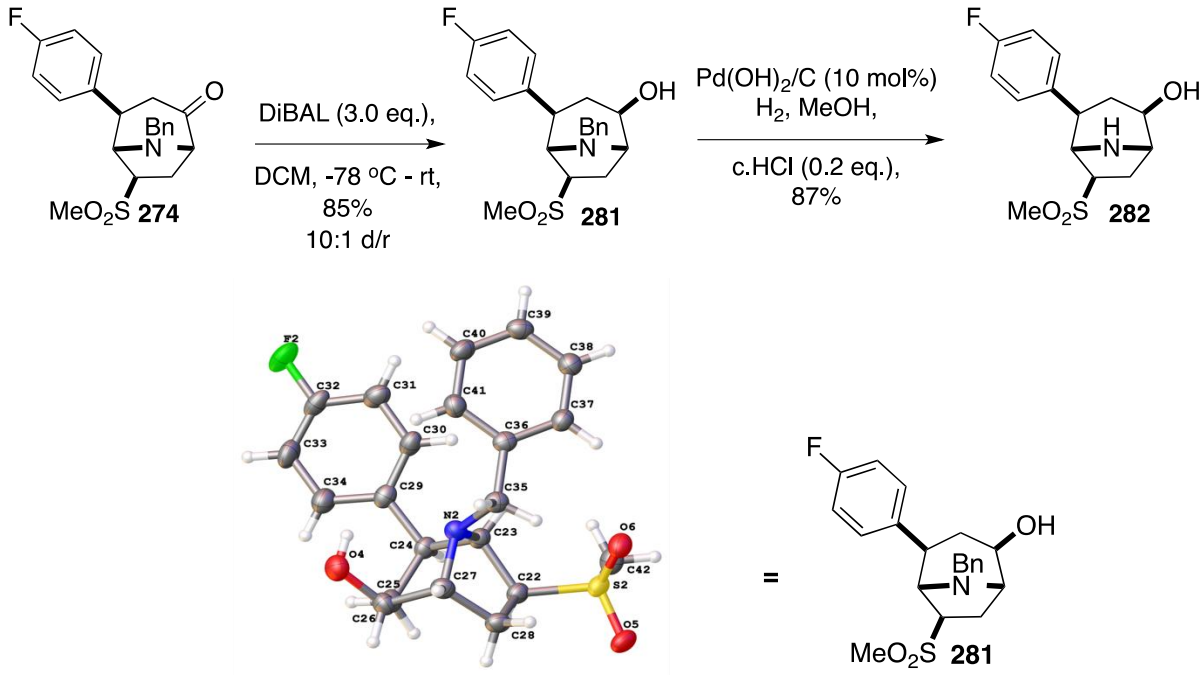
∅ Yield for the isolated major isomer.

a side product, dimethyl acetal **280**, was also formed by a competing acid catalysed acetalisation reaction (**Scheme 47**).



*Scheme 47. A scheme showing the synthesis of deprotected **279** and side product **280.***

To alleviate this problem an alternative route was suggested. Instead, the compound was reduced prior to deprotection using the optimised reduction conditions. The major isomer **281** of the alcohol was synthesised in an excellent yield of 85%. The deprotection of the benzyl group afforded the desired compound **282** in an 87% yield (**Scheme 48**). The acquired X-ray crystal structure revealed the same relative stereochemistry as for the *N*-methyl derivative.



*Scheme 48. A general scheme to compound **281** and the crystal structure of **281** with its structure.*

The *para*-fluorophenyl compounds **279a** and **282** were then decorated with a range of medicinally-relevant capping groups and purified using a mass directed automated purification (MDAP) system. All the successful products were obtained in poor yields due to either problems with the MDAP system or due to issues with separating the diastereoisomers. The

results are shown below where 9 diverse novel compounds were synthesised ready for biological screening (**Figure 28)**. All successful and failed reaction conditions can be seen in **Appendix 6.1.1**.

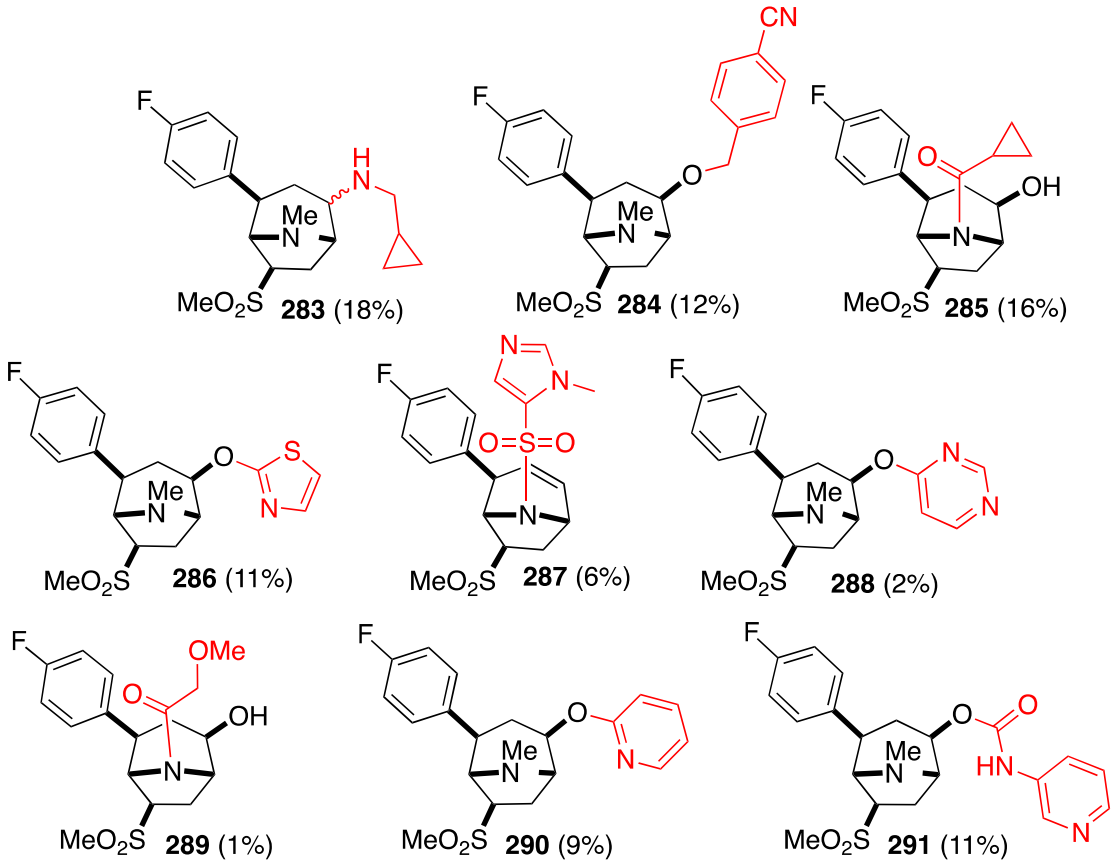
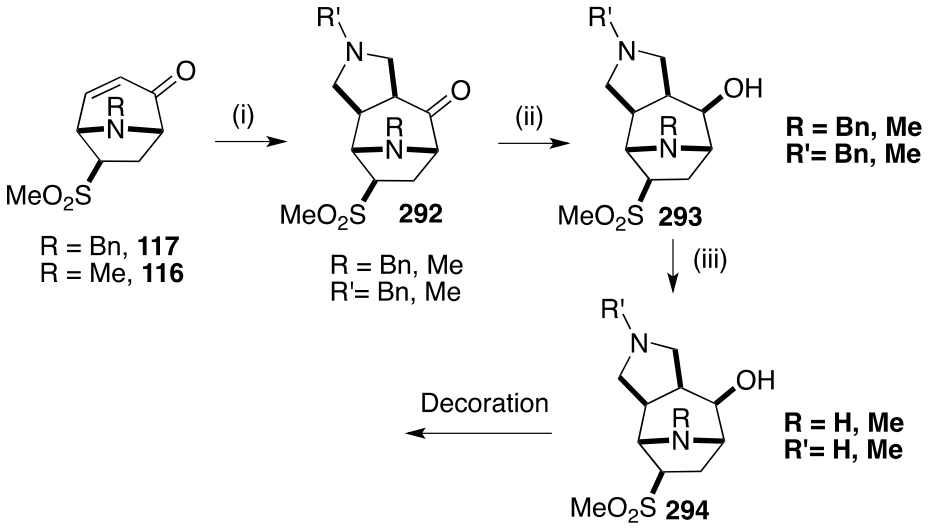


Figure 28. A figure showing the 1,4-addition series of final compounds for screening.

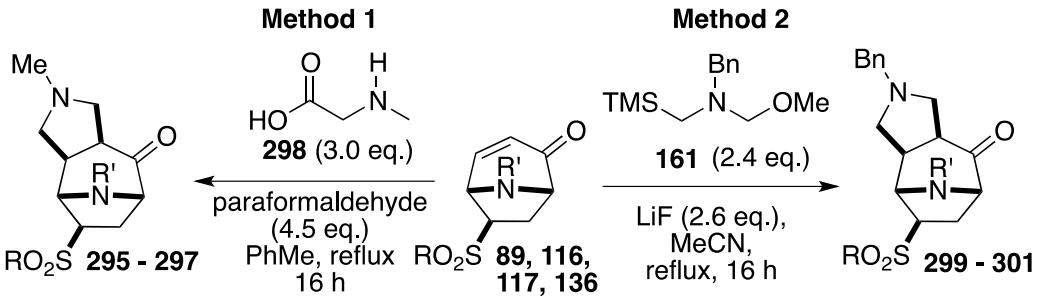
3.1.2 Manipulation of the pyrrolidine scaffold

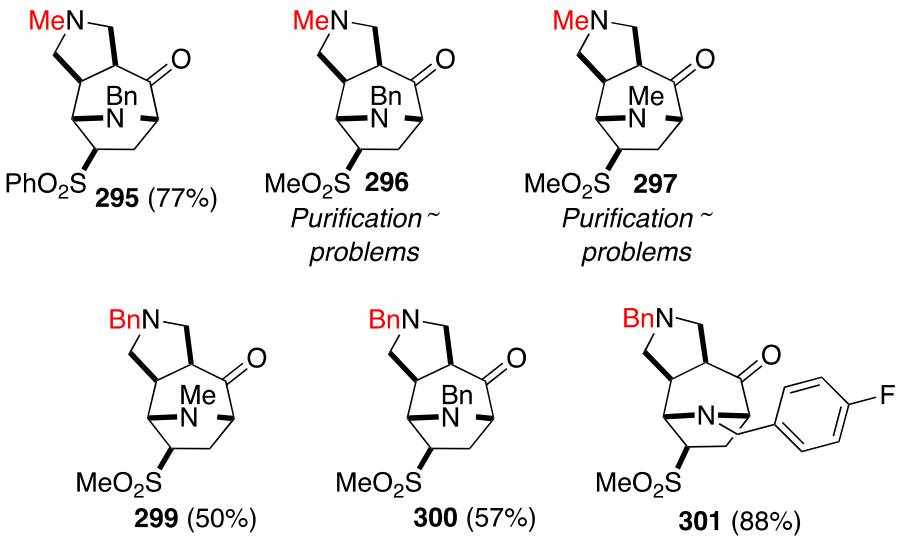
The next scaffold selected for library synthesis was the pyrrolidine series. The proposed route was a three-step synthesis involving preparation of the pyrrolidine scaffold (step i), a diastereoselective ketone reduction (step ii) and deprotection of the benzyl group (step iii). It was envisioned that once deprotected, the free NH could be decorated with a range of capping groups (**Scheme 49**).



Scheme 49. Step (i) Pyrollidine synthesis, (ii) Steroselective reduction of the ketone, (iii) Debenzlyation, then decoration with capping groups

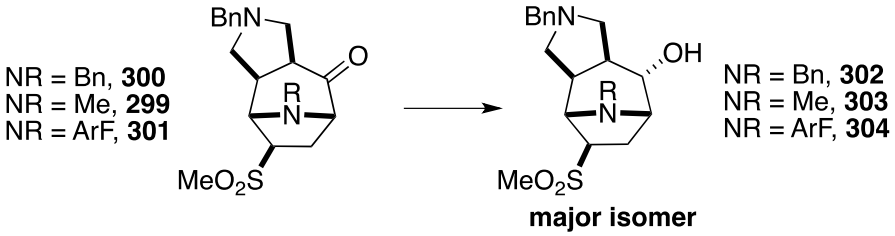
The first step of the proposed route was the synthesis of the pyrrolidine. It was hypothesised that this core scaffold could be synthesised by two sets of conditions, resulting in the nitrogen substituent being either a methyl or a benzyl group. The core scaffold could then contain either a fixed *N*-methyl group or a 'removable' group which could unmask a decoration position. Both conditions form an azomethine ylide *in situ* and the pyrrolidine is formed via a subsequent [3+2] cycloaddition. Method 1 forms an azomethine ylide by decarboxylative condensation of paraformaldehyde and sarcosine **298** and method 2 forms the ylide via compound **161** and LiF (**Scheme 50**).[81,106] However, due to the polar nature of the compounds there was issues with the purification. Therefore, the *N*-methyl pyrrolidine scaffold was deprioritised and a range of *N*-benzyl substituted derivatives were synthesised on a large scale in good to excellent yields.





*Scheme 50. a) The two routes to synthesise the fused pyrroldiine scaffolds **295 – 297**, **288 – 301**. b) The results.*

With the pyrrolidine derivatives in hand, diastereoselective reduction using a range of reducing agents and conditions was attempted (**Table 25**). The d/r was determined by ratios of distinct protons in the ^{1}H NMR spectrum and the best d/r was obtained when using the reducing agent DIBAL in THF at -78 ^{o}C. The best d/r's were obtained from bulkier reducing agents and when the R group of the nitrogen bridgehead was a benzyl group (**Table 25**, entry 1, 3-4). The stereochemistry was later confirmed by the acquisition of a crystal structure of the decorated analogue **310** (**Figure 29**).



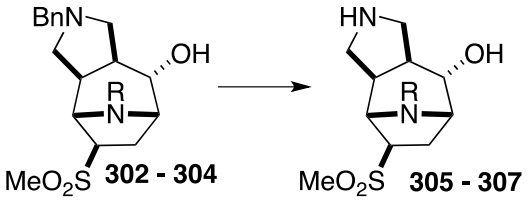
Entry	Conditions	R	Outcome
1	DIBAL (1M cyclohexane), DCM (0.08M), -78 ^{o}C - rt, 16h	Bn	d/r -3:1, Single isomer isolated after purification, **302,** 57%$^{\oplus}$
2	DIBAL (1M cyclohexane), THF (0.08M), -78 ^{o}C - rt, 16h	Me	d/r - 3:2, Inseparable isomers **303** (not isolated)
3	DIBAL (1M cyclohexane), (3.0 eq.),	*para*-fluorobenzyl	d/r – 3:1

$^{\oplus}$ Yield for the isolated major isomer.

	DCM (0.08M), -78 ^{o}C- rt, 16 h		**304,** 50%$^{\oplus}$
4	DIBAL (1M cyclohexane), THF (0.08M), -78 ^{o}C- rt, 16 h	*para*-fluorobenzyl	d/r – 4:1, Single isomer obtained **304**
5	$NaBH_4$, -78 ^{o}C - rt, MeOH, 16 h	*para*-fluorobenzyl	d/r – 1:1 Inseparable isomers **304**
6	$CeCl_3.7H_2O$, $NaBH_4$, MeOH -78 ^{o}C –rt, 16 h	*para*-fluorobenzyl	d/r – 1:1 Inseparable isomers **304**

*Table 25. Outcome of reduction reactions involving of the pyrollidine scaffolds **299 – 301.***

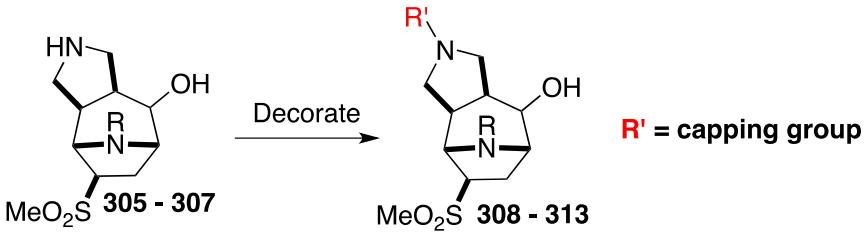
With step 2 of the synthesis complete, the debenzylation of both the bridged nitrogen and the pyrrolidine nitrogen was attempted. It was found that the bridged nitrogen could not to be deprotected with the conditions used and therefore the scaffold could not be decorated with capping groups at this position. However, the benzyl group on the pyrrolidine was removed using palladium(II) hydroxide in MeOH under hydrogen, affording a position for decoration (**Table 26**). Again, due to issues with polarity, (entry 3, **Table 26**), compound **307** was not isolated and instead telescoped through to the next step.

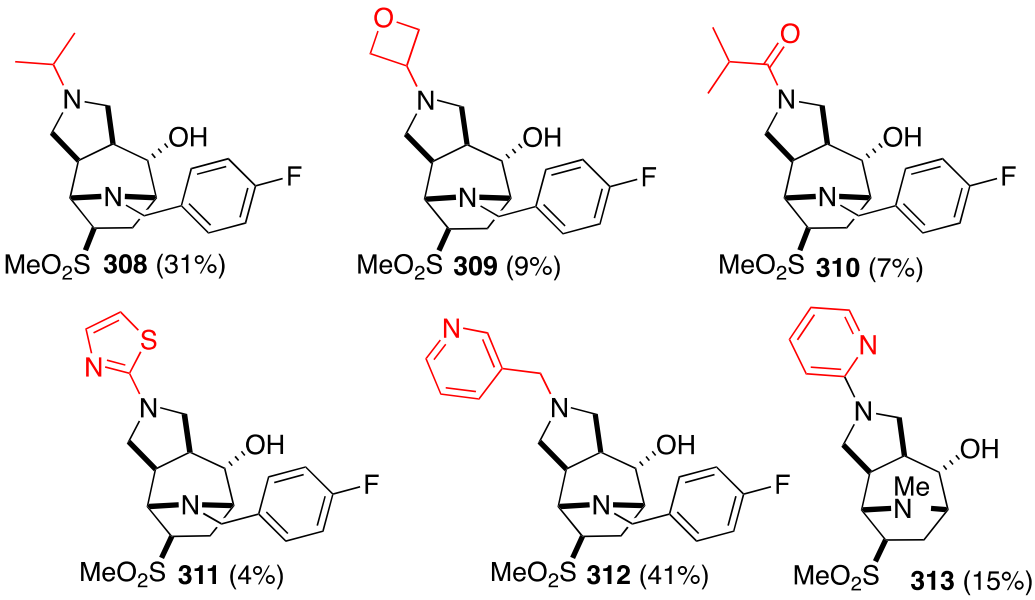


Entry	Conditions	NR	Outcome
1	$Pd(OH)_2$/C, H_2, MeOH, conc.HCl (0.02 eq.)	Bn	**305** (92%)
2	$Pd(OH)_2$/C, H_2, MeOH,	*para*-fluorobenzyl	**306** (92%)
3	$Pd(OH)_2$/C, H_2, MeOH,	Me	**307,** Not isolated

*Table 26. Outcome of deprotection conditions involving scaffolds **302 – 304**.*

With the third step of the scaffold synthesis achieved, the next aim was to decorate at the nitrogen of the pyrrolidine with a range of capping groups. The results are shown below where five diverse, novel compounds were synthesised (**Scheme 51**). A range of chemical reactions were performed at the free nitrogen, including amide synthesis, sulfonamide synthesis, reductive amination and urea formation All successful and failed reaction conditions can be seen in **Appendix 6.1.2**.





Scheme 51. A general scheme for decoration and the resulting screening compounds.

To confirm the stereochemistry of this series of compounds, a crystal structure was obtained of the decorated final compound **310** (**Figure 29A**). To our surprise, the alcohol substituent had the opposite configuration to the predicted structure, as the bulky reducing agent was expected to attack on the opposite face to the pyrrolidine ring. It was therefore postulated that there was a coordination between the pyrrolidine nitrogen atom and the aluminium, consequently delivering the hydride to the more hindered face (**Figure 29B**).

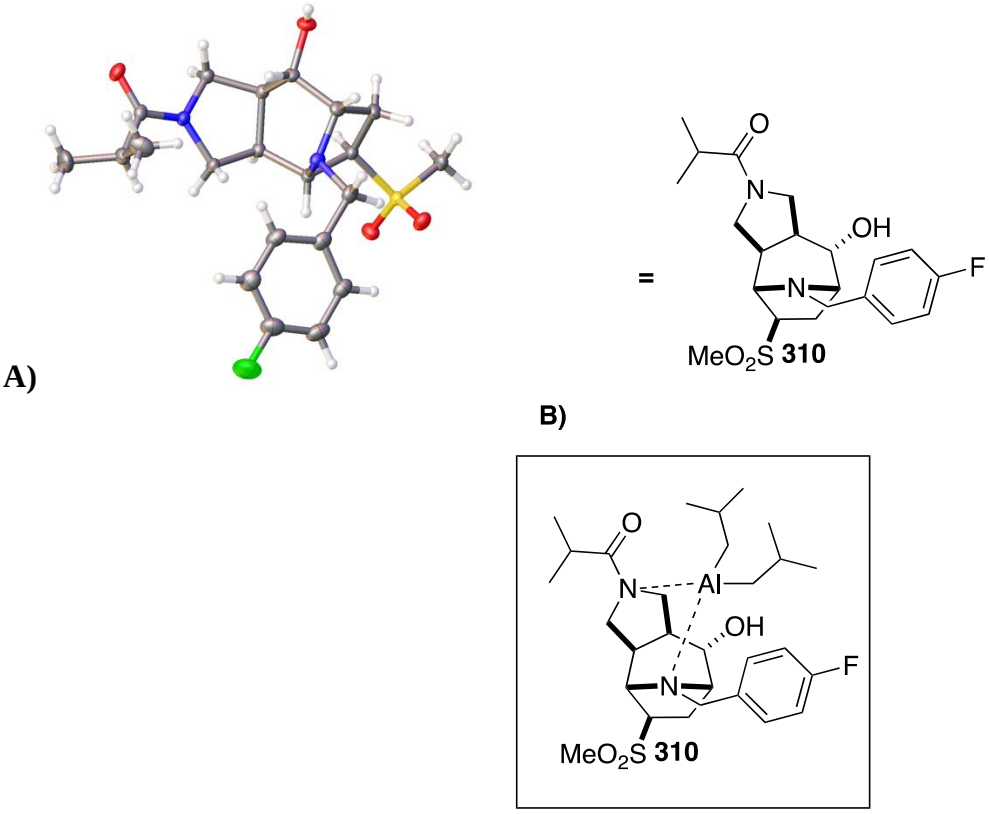
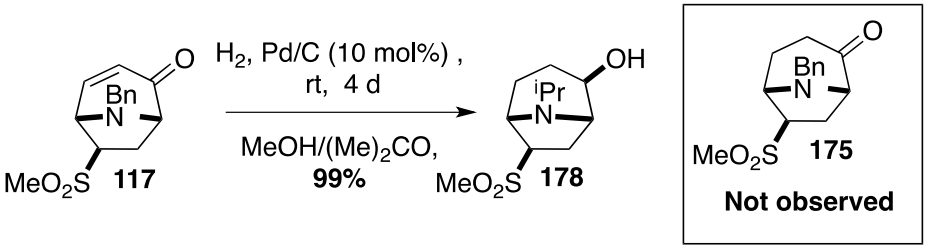
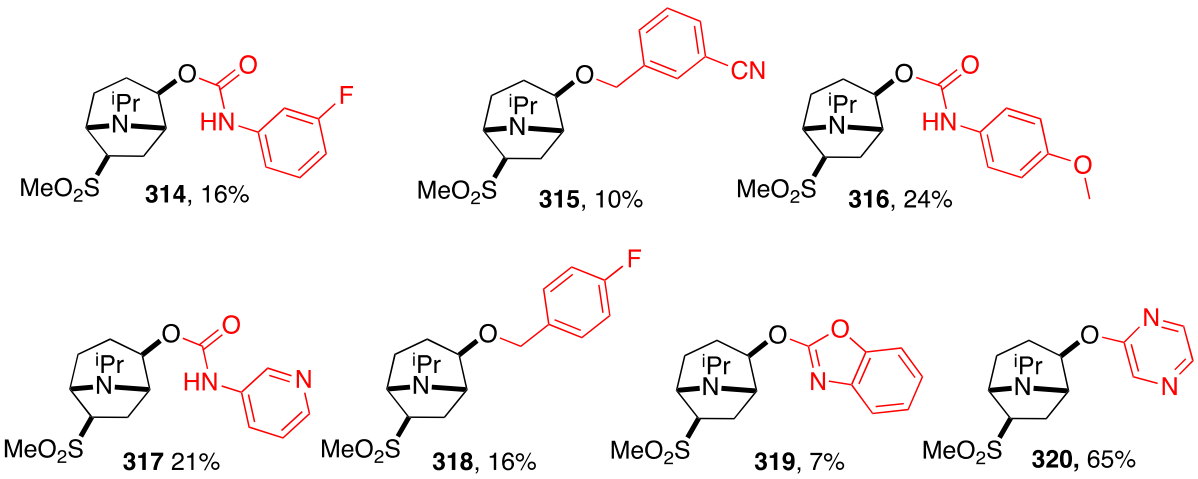


*Figure 29.A) A figure showing the crystal structure and its related compound **2.187.** B) The proposed coordination of DIBAL and compound **2.187**.*

3.1.3 Manipulation of the alcohol scaffold 178

As described in **Section 2.3.2**, when attempting to reduce the double bond of the enone, alcohol **179** was synthesised in quantitative yield on a large scale. With the free hydroxyl group being available for decoration, the key scaffold was subjected to a range of medicinally relevent capping groups. Seven final compounds were obtained from the decoration process, with each compound shown below (**Scheme 52**). The conditions for each reaction are shown in the **Appendix 6.1.3**.

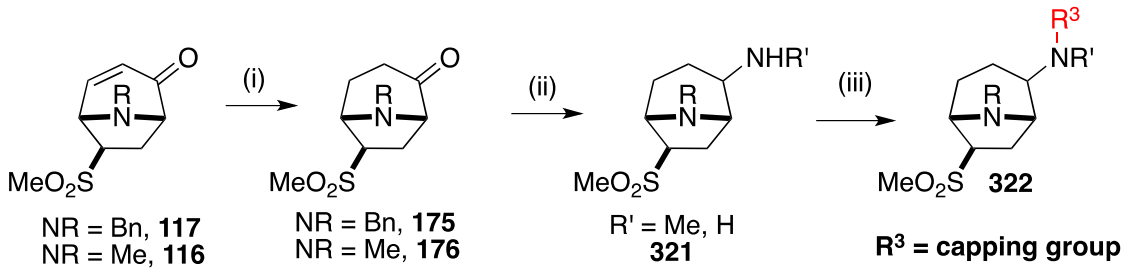




*Scheme 52. A scheme showing the seven final screening compounds synthesised from decoration of alcohol **178**.*

3.1.4 Manipulation of secondary amine 324

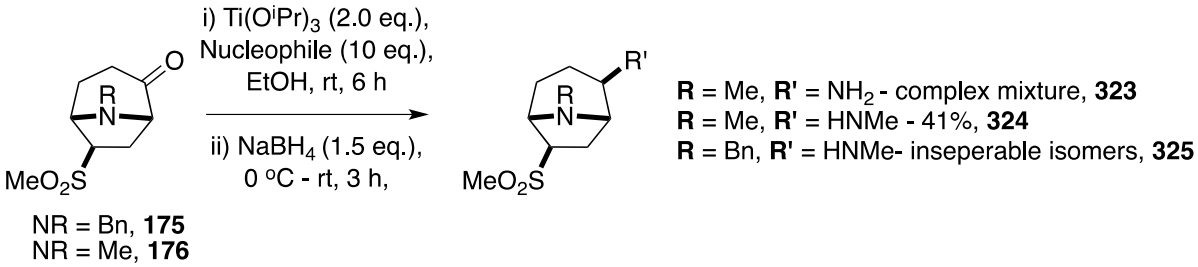
The next scaffold selected for library synthesis was the tertiary amine series. The proposed route was a three-step synthesis: (step i) reduction, (step ii) diastereoselective reductive amination and (step iii) decoration (**Scheme 53**).



Scheme 53. A general scheme to synthesise some decorated screening compounds. Step(i) enone reduction, step(ii) reductive amination, step (iii) decoration.

The initial step was performed in quantitative yield as explained previously in **Section 2.3.2 (Table 14)**. The scaffold-synthesising step was performed using conditions detailed earlier (**Section 2.3.5**), where the nucleophile methylamine was used. The reductive amination with methylamine was successful where compound **324** was synthesised with high levels of selectivity, with only one isomer being produced in a 41% yield. This afforded a point of diversification at the NH for library synthesis. Due to the difficulties with ammonia causing a complex mixture, this nucleophile was deprioritised. The stereochemistry was determined by comparison with similar compounds in the literature, where the amine shows a *syn*-relationship

to the bridged nitrogen and the sulfone group.[107] When the nitrogen substituent was benzyl protected, a mix of inseparable isomers was formed, so compound **325** was discontinued.



*Scheme 54 A scheme for the synthesis of a secondary amine **324**, and conditions in attempt to make compound **323** and **325**.*

With compound **324** obtained in moderate yield on a large scale (4.46 mmol), a range of final compounds were obtained from the subsequent decoration reactions (**Figure 30**). The conditions are shown in **Appendix 6.1.4**. In total four of the five reactions obtained final compounds for screening, each with a diverse range of functional groups attained from decoration.

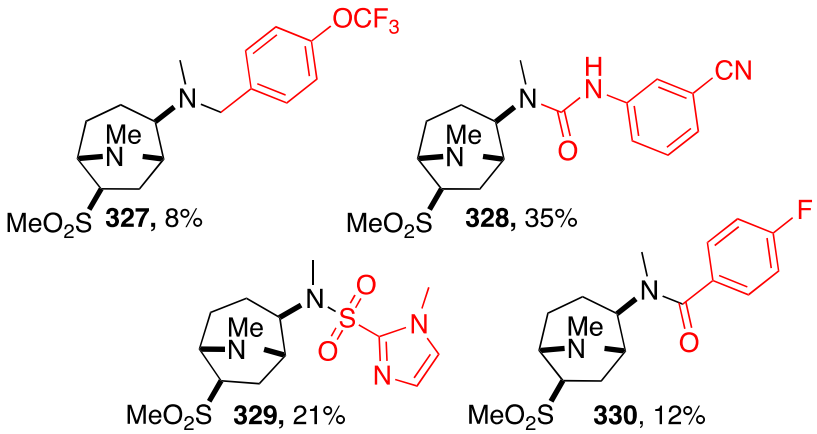
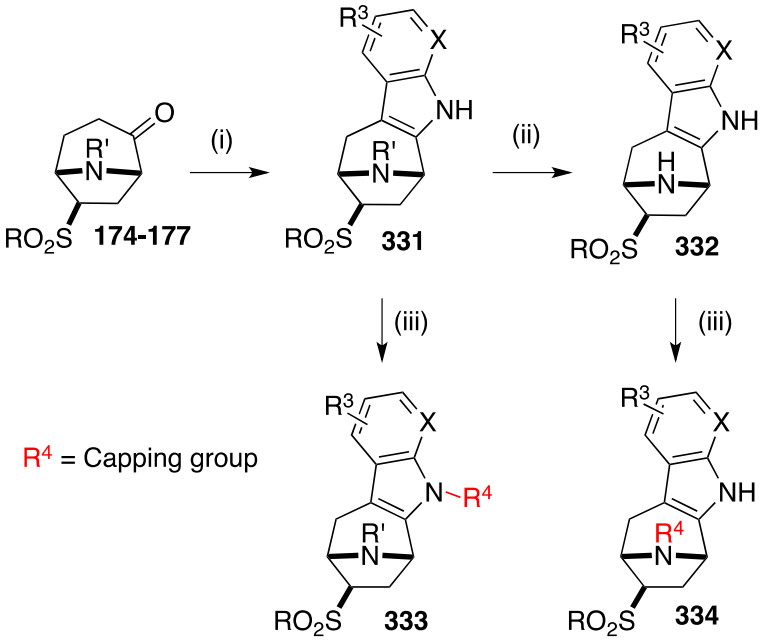


*Figure 30. Four decorated tertiary amines synthesised from compound **324**.*

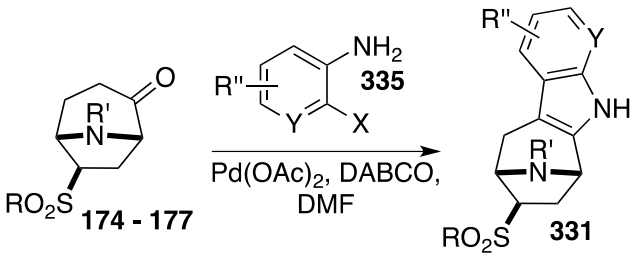
3.1.5 Manipulation of the indole scaffold

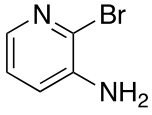
The last of the series to undergo final compound synthesis were the indole fused scaffolds. The planned synthetic route required a scaffold synthesis step (step i), deprotection (step ii) and a decoration with capping groups at either the free NH of the indole or the bridge head nitrogen (**Scheme 55**).



Scheme 55. Step(i) scaffold synthesis, step(ii) deprotection, step(iii) decoration

Due to difficulties with the Fischer indole conditions, the initial proposed step was to be undertaken using the palladium-mediated process (**Table 17, Section 2.3.2)**. Different indole derivatives were planned which required a range of alternative halogenated-aniline reagents, which were purchased from readily available suppliers. The proposed substituted indole and azaindole compounds however were not obtained due to isolation issues: where some products were seen on the LCMS/^{1}H NMR, but no compound was recovered after purification (**Table 27**).



Entry	R	NR'	X,Y, R''	Conditions	Outcome
1	Ph	NBn	Br, N, H	 (1.2 eq.), Ketone (1.0 eq.), DABCO (1.0 eq.), $Pd(OAc)_2$ (10 mol%), DMF, 105 ^{o}C, 2d	Starting material (**174**)

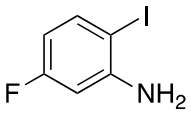
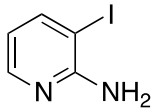
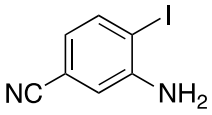
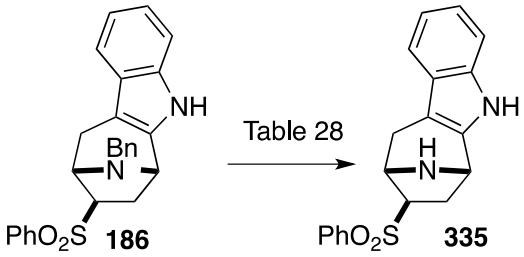
2	Me	NMe	I, C, F	 (3.0 eq.) Ketone (1.0 eq.), DABCO (3.0 eq.), $Pd(OAc)_2$ (15 mol%), DMF, 120 °C, 2 d	Complex mixture
3	Me	NMe	I,N,H	 (3.0 eq.) Ketone (1.0 eq.), DABCO (3.0 eq.), $Pd(OAc)_2$ (15 mol%), DMF, 120 °C, 2 d	Complex mixture
4	NMe_2	NMe	I,C,CN	 (3.0 eq.) Ketone (1.0 eq.), DABCO (3.0 eq.), $Pd(OAc)_2$ (15 mol%), DMF, 120 °C, 2 d	Complex mixture

Table 27. Outcome of conditions used in attempt to synthesise azaindole and indole derivative.

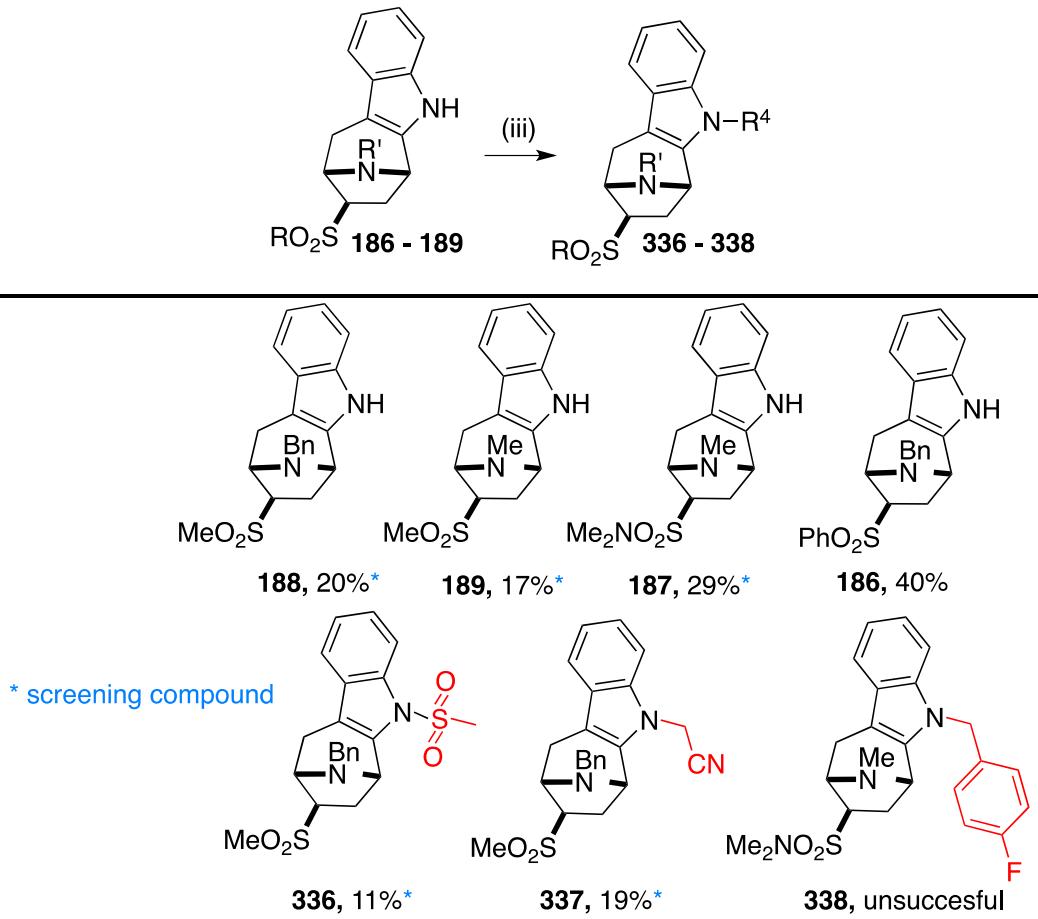
As discussed previously, four compounds had been successfully synthesised using this palladium method, compound **2.96** – **2.99** (**Table 17**). With these compounds in hand, our next proposed route involved the deprotection of the benzyl group on the nitrogen. However, after screening several sets of conditions, only starting material was observed (**Table 28**).



Entry	Conditions	Outcome
1	$Pd(OH)_2/C$, H_2, 16h, MeOH	Starting material, **186**
2	$Pd(OH)_2/C$, H_2, 16h, MeOH, c. HCl	Starting material, **186**
3	Pd/C, H_2, 16h, MeOH	Starting material, **186**
4	Pd/C, ammonium formate, 16h, MeOH	Starting material, **186**

*Table 28. Outcome of the conditions used in an attempted to deprotect compound **335**.*

Due to the synthetic difficulties of removing the protecting group we endeavoured to decorate with medicinal capping groups at the free nitrogen of the indole. Three reactions took place to bring diversity at this point and the conditions are detailed in **Appendix 6.1.5**. The five screening compounds from this series are shown below (**Scheme 56**), where only two final compounds were achieved after decoration.



*Scheme 56. The indole precursors **186 - 189** and decorated indoles **336 - 338**. The compounds chosen for the screening collection marked with *.*

3.2 Computational assessment of 52 screening compounds

Now a library of screening compounds had been synthesised, the compound properties such as lipophilicity and molecular weight were analysed. As discussed previously, lipophilicity is an important factor to monitor when a compound goes through the different stages of drug discovery, because if a compound is too lipophilic it may experience off-target biological activity. The ideal lipophilic values for optimal drug space are -1 – 5 AlogP. Each compound fell in optimal drug like space, where the heavily decorated compounds **195** and **181** exceeded lead-like space. However, removal of protecting groups or the use of smaller substituents such as methyl groups could be used to alleviate this problem.

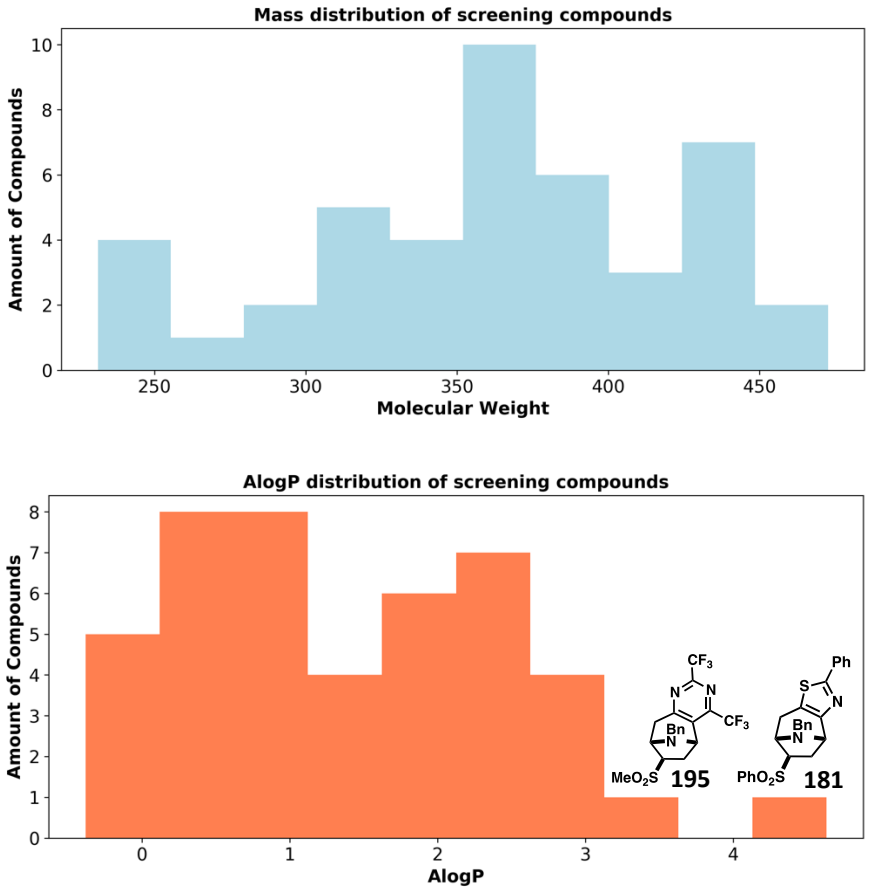


Figure 31. A) Mass distribution of screening compounds B) AlogP distribution of screening compounds with the two examples outside of lead-like space.

3.2.1 Three-dimensionality assessment of screening compounds

As stated previously, more three-dimensional compounds typically have lower attrition rates in drug discovery,[39] therefore it was necessary to assess the 54 compounds on their three-dimensionality. Each compound was plotted on a PMI plot using LLAMA (**Figure 32**). Evidence below suggests the compounds are moving away from the heavily populated region and now venturing into the more unpopulated 'sphere-like' region of chemical space. A random library was downloaded from the ZINC database consisting of 90,911 molecules and an average value was plotted (in yellow) for comparison. Examples D and E shown on the plot exhibit more 3D characteristics, whereas examples A an F are below the average value and populate the more explored area of chemical space. It is understandable that these are below the average value as they contain substituents of a 'rod-like' nature, whereas the better performers are smaller and have less linear characteristics. Comparing the mean PMI coordinates below, it was clear that these compounds were more 3D then the random ZINC database library. It was therefore concluded that the objective of synthesising more 3D screening compounds was successfully achieved.

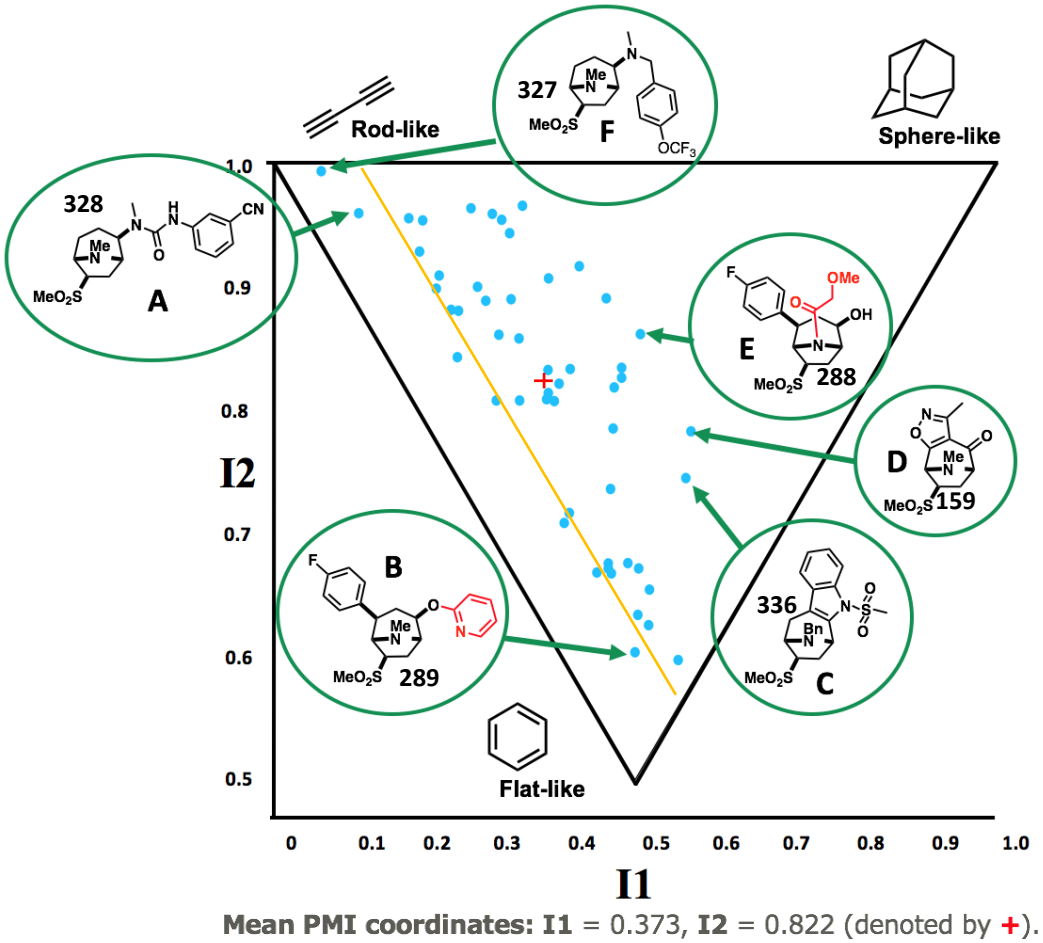


Figure 32. A PMI plot showing the three-dimensionality of the screening compounds, with particular examples highlighted. The average value for the random ZINC library is shown in yellow and, the average coordinates for this library is shown by a red cross.

3.2.2 Fsp^3 value assessment of screening compounds

Another objective of this project was to synthesise compounds that have a higher fraction of sp^3 hybridised carbons. Each compound was again analysed in LLAMA and the Fsp^3 value was calculated for the 52 screening compounds (**Figure 33**). A comparison to a random 1% of the ZINC database was shown, where it was clear the screening set experienced a higher Fsp^3 nature. As seen from the graph only two compounds (**151**, **337**) (4%) have a lower value than the ZINC database score, where the average value has increased by 70%.

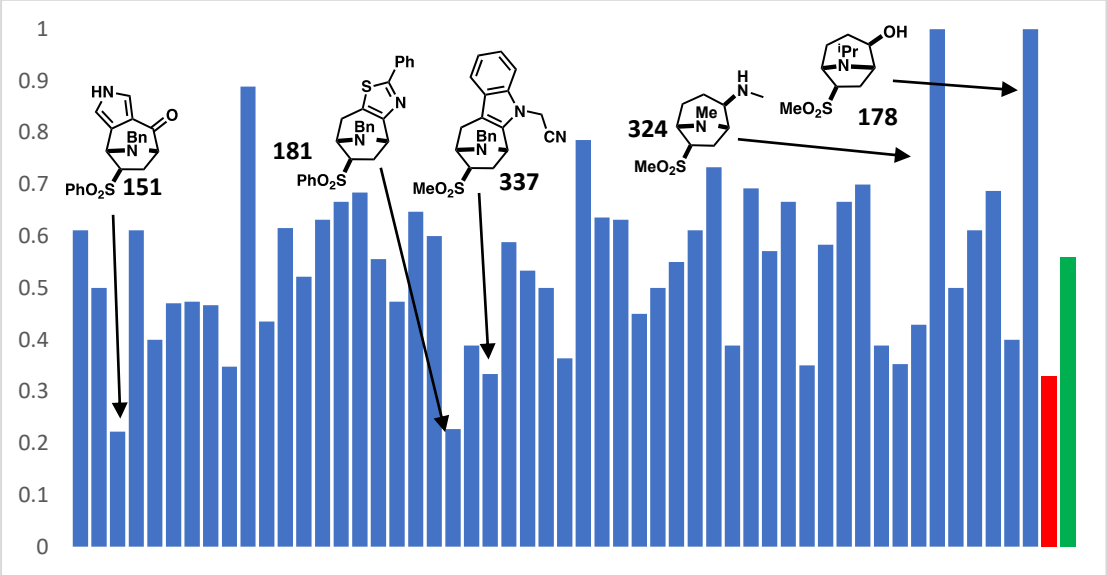


Figure 33. A Fsp3 value comparison of the screening compounds. The average value 0.56 (in green) is also compared with the average ZINC database value 0.33 (in red).

3.2.3 Conclusion and summary of screening compounds

In summary, the careful selection of capping groups has facilitated the creation of a diverse and novel screening library for biological testing. The compounds have the correct molecular properties and all compounds fall in optimal drug-like space, with a heavy proportion still in lead-like chemical space. When compared to readily available screening compounds, this library has a larger average value of Fsp^3 carbons and has a greater 3D nature.

It should be noted that the removal of the benzyl protecting group posed a significant problem when synthesising final screening compounds. In many cases the deprotection step was essential as the free nitrogen was required for decoration with capping groups. A range of conditions were used in attempts to remove the protection group. In some cases the deprotection was achieved, which led to the conclusion that the correct conditions were scaffold dependent. Due to these issues, the benzyl group was present in some final compounds and resulted in a lower number of screening compounds than anticipated.

Due to careful planning and searching of the literature, an ideal parent scaffold was selected that had a multitude of different functionalities present with various potential growth vectors available. This would be advantageous if any positive biological data was received, as there would be various vectors to explore when carrying out SAR. The parent scaffold was initially selected with the intension to remove the sulfone group or to use a variety of different sulfonyl

derivatives. However, due to problems with synthetic tractability 85% compounds contained the methyl sulfone group. Nevertheless, when comparing to previous ‘top-down’ approach strategies, this intermolecular approach is advantageous as the functionality can be changed prior to the cycloaddition. This allows for a diverse follow series to be synthesised rapidly and efficiently.

Although each compound was novel and diverse, there are still issues with skeletal diversity. When assessing the relationship between the skeletal systems, using the ‘scaffold tree’ hierarchical analysis,[66] it was found that the scaffolds were ultimately related to five similar parental frameworks. The analysis works by deconstruction of the scaffolds by iterative removal of rings, until a final parental core scaffold is observed. At each iteration step a ring is removed, retaining the central and complex rings (**Figure 34**). Due to the lack of ring expansion executed, 94% of compounds featured a [3.2.1]-bridged bicyclic core, explaining the reason for similar parental frameworks.

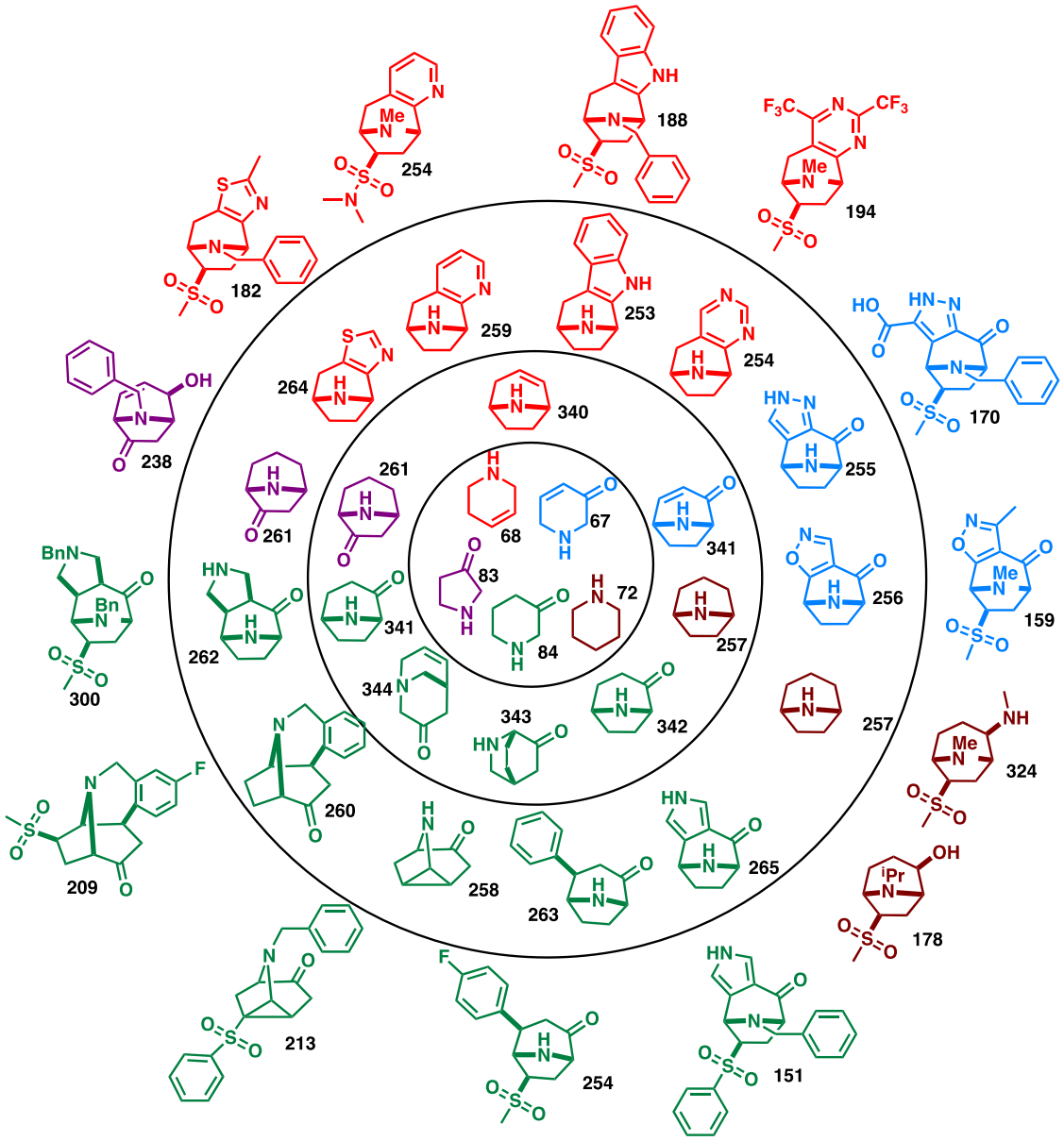


Figure 34. A waldmann 'scaffold tree' hierarchical analysis of the lead-like scaffolds. Compounds in blue are the five parental core frameworks found from ring deconstruction.

As stated earlier, during discovery drug candidates tend to experience a shift in lipophilicity, known as 'AlogP drift'. The graph below supports this theory and a comparison of four libraries is shown (**Figure 35**). The four libraries consist of:

1) **Lead-like scaffold library:** initial scaffold library where no decoration has been undertaken.

2) **Screening library**: 52 final compounds produced from the lead-like scaffold set.

3) **Virtual library:** produced using LLAMA, where lead-like scaffolds were decorated using common medicinally relevant capping groups.

4) **Failed library:** the compounds which failed when synthesising the screening library (these compounds can be seen in the appendix)

When comparing the first three libraries, there is a clear indication that the percentage of compounds in the more lipophilic regions is increasing. When comparing the lead-like library to the screening library, there is a 28% increase of compounds in the 2 – 5 regions of lipophilicity, and a decrease of 12% in the region of -1. When comparing to the virtual library it clearly shows without careful selection of capping groups it would be easy to synthesise compounds with a more lipophilic nature (AlogP = 3 – 5). It is also interesting to see the failed compound library heavily situates in the more polar areas of AlogP. This also supports the research carried out by Churcher *et al*, where a study found final compound libraries were often found to have a higher AlogP than intended. The reasoning behind this is due to the poor tolerance towards the polar functionalities, thereby, less polar compounds being isolated easier.

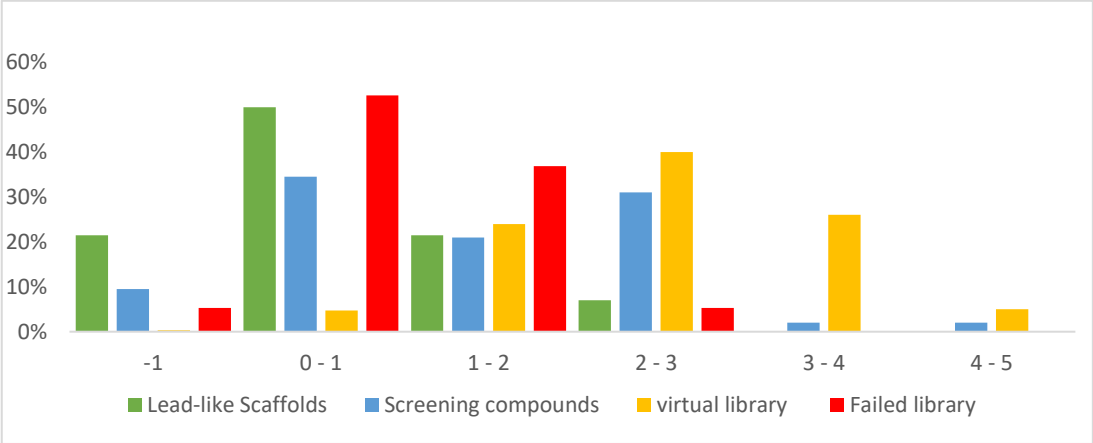


Figure 35. Percentage of compounds y-axis. A comparison of lipophilic values from four different libraries. 1) lead-like scaffolds in green, 2) 52 screening compounds (in blue), 3) virtual library (in yellow) and 4) the failed library unsuccessfully synthesised (in red).

4.0 Biological evaluation of the 52 Screening compounds and SAR of active compounds

4.1 Biological evaluation of the 52 screening compounds

With a library of 52 screening compounds having been synthesised, and their molecular properties analysed, the next objective was to send each compound for biological evaluation against a wide range of biological targets. The compounds were screened against four different targets, at three different facilities (**Table 29**). A more detailed description of each assay and target will be given below.

Entry	Facility	Target	Assay type	Number of compounds
1	MPI Dortmund	Autophagy	phenotypic assay	52
2	MPI Dortmund	Hedgehog osteogenesis	phenotypic assay	52
3	University of East Anglia	DNA i-motif binding	phenotypic assay	52
4	University of Cape Town	*Plasmodium falciparum*	phenotypic assay	52

Table 29. A table showing each target the 52 screening compounds were tested against.

4.1.1 Autophagy target; screening for autophagy modulators

Autophagy is a highly conserved catabolic process that is regularly used by the cell as a mechanism for quality control and survival under nutrient stress conditions.[108,109] It becomes activated under various conditions of cellular stress such as amino acid starvation and cytosolic Ca^{2+} upload.[110] Autophagy modulation by targeting the pathway in cancer and neurodegenerative diseases has a considerable potential as a therapeutic approach,[108] therefore the compound collection was sent to MPI Dortmund, where they were screened for autophagy modulators. Each compound was tested for the ability to inhibit autophagy induced by amino acid starvation. Autophagy is required for removal of damaged proteins and clearance of pathogens.[110,111] In cancer, it can promote tumour growth and there is a requirement for small molecules with a novel mode of action.[111]

The phenotypic assay for autophagy inhibition works by the process of MCF7 cells expressing eGFP-conjugated LC3 (MCF7-LC3 cells) that are treated under starved conditions using EarleQs balanced salt solution (EBSS), which induces the autophagy.[111] If the compounds induce autophagy, LC3-I is lipidated with phosphatidylethanolamine to form LC3-II, which localizes to the autophagosomal membrane. Chloroquine inhibits autophagosome–lysosome fusion, of which will cause an accumulation of LC3-II. This will be visible as green puncta when tagged with eGFP. Autophagy inhibitors will reverse this accumulation (**Figure 36**).[111] A description of the assay can be found in **Appendix 6.2.1** However, the 52 compounds unfortunately showed no activity.

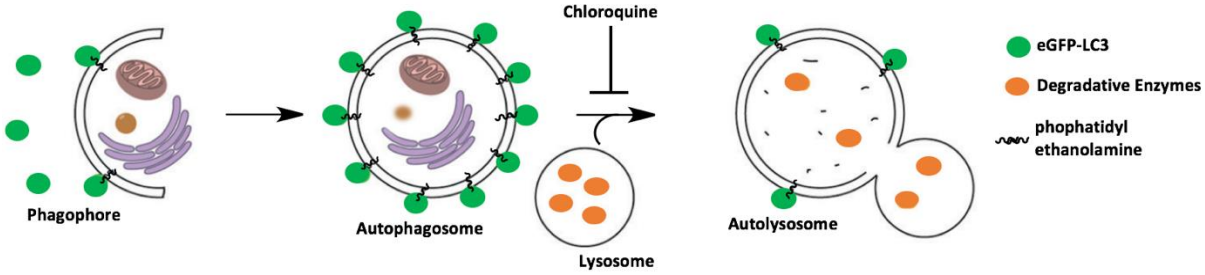
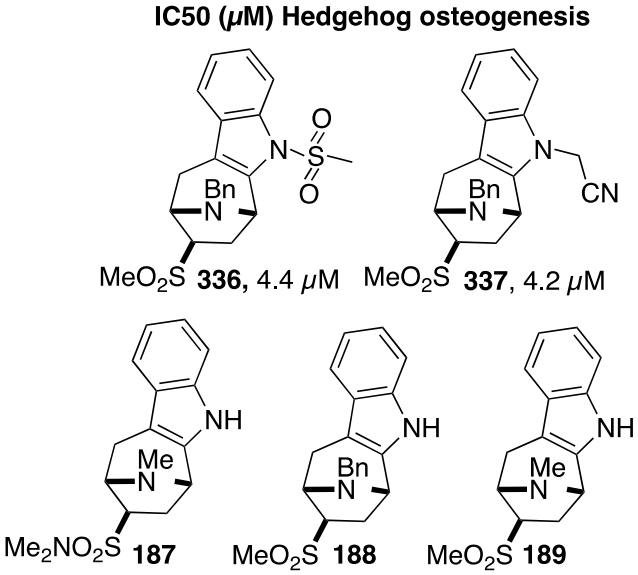


Figure 36. Outline of autophagy and the assay principle.

4.1.2 Hedgehog Osteogenesis target; screening for inhibitors of the hedgehog signalling pathway

To identify inhibitors of hedgehog signalling, an osteoblast differentiation assay was carried out on the 52 screening compounds.[112] The hedgehog signalling pathway is essential for normal embryonic development and plays a critical role in tissue maintenance and regeneration.[113,112] The signalling pathway has been linked to cancers such as basal cell carcinoma and medulloblastoma.[112,114] A transmembrane protein Smoothened (SMO) agonist called purmorphamine, was used to activate the signalling, where the pathway activity induces osteoblast differentiation. This leads to the expression of alkaline phosphatase enzyme that can serve as an indirect measure for hedgehog pathway induction.[115] The screening for small molecule inhibitors of the hedgehog pathway was carried out by MPI Dortmund, where the compound collection was analysed for direct interaction with SMO. The compounds were analysed by monitoring the displacement of the BODIPY-labelled SMO antagonist cyclopamine. Cyclopamine binds to the heptahelical bundle of SMO,[116] and treatment of these cells with BODIPY-labelled cyclopamine led to cellular fluorescence, thus an indication of the binding to SMO.[117] Of the 52 compounds screened, only two showed any activity. A detailed description of the assay can be found in **Appendix 6.2.2**.

The results of the two active compounds can be seen below, where the EC50 values were determined in dose-dependent mode (4.2 – 4.4 μM) **(Scheme 57**). It was interesting to see that while the *N*-substituted indole derivatives showed activity and undecorated indole derivatives **187 – 189** showed no activity. This SAR may suggest that the activity is induced by growing substituents from the free NH of the indole. However, the activity was deemed too weak to warrant follow-up with such limited time.



*Scheme 57. Active compounds **336** and **377**, with inactive derivative **187 – 189.***

4.1.3 DNA binding motif; TO displacement

I-motifs are four-stranded quadruplex DNA structures formed by sequences of cytosine-rich DNA, with building blocks consisting of cytosine–cytosine+ base pairs.[118,119,120] These sequences may play a role in gene transcription, where targeting the structures with compounds may provide a way to target genetic diseases.[119] A fluorescent intercalator displacement (FID)-based method was used to screen the compounds against DNA secondary structures; here the screening compounds were monitored for binding with the i-motif DNA. This FID-based ligand screening uses thiazole orange (TO) against the i-motif forming sequence from the human telomere, to reveal new i-motif binding compounds.[119] The 52 screening compounds were sent for screening to the University of East Anglia, where the compounds were examined

for change in fluorescence upon binding. The details of the assay can be found in **Appendix 6.2.3.**

The results are shown below, where the top 8 ligands showing ≥ 15% TO displacement (within error) are plotted (**Figure 37**). It should be noted that compound **170** with KCl shows enhanced displacement of TO from DAP over G4 or DS, but not when DAP is tested without KCl. Due to the nature of the project, structurally similar compounds are tested upon initial screening, therefore providing a clearer direction for performing structure activity relationship on the follow-up series. Compounds **314, 316** and **378** all share structural similarities, where aryl carbamates are observed at the 2-hydroxyl position. Compounds **314, 316** and **318** share the same structural 'core', as they were synthesised from the same precursor, compound **178**. The results were interesting as the majority (though not all) of compounds which interact with i-motifs are flat aromatics, which can intercalate the DNA base pair stacks.[121],[122],[123] and the following examples below are highly 3D lead-like compounds.

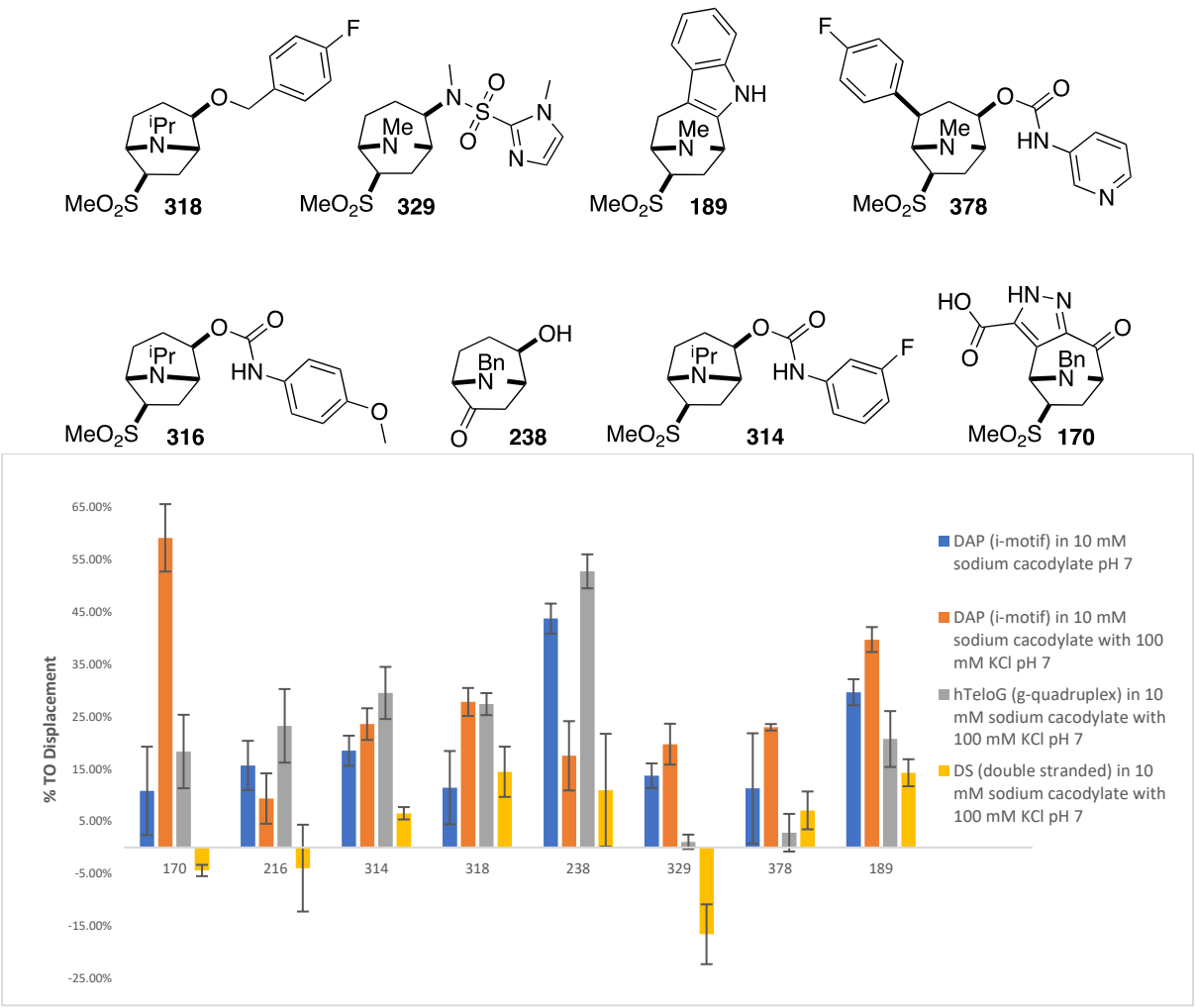


Figure 37a) The top 8 TO displacement ligands for the DNA binding motif series, b) The results from the four screening conditions tested against from the 8 ligands. 1) DAP in sodium cacodylate, 2) DAP in sodium cacodylate in KCl, 3) h TeloG in sodium cacodylate in KCl and 4) DS in sodium cacodylate with KCl

4.1.4 *Plasmodium falciparum*

Malaria is the most common parasitic disease worldwide, where in 2017 it was reported that 445,000 deaths occur annually.[124] There are no specific symptoms for *P. falciparum* malaria infection, however illness with malaria occurs through complex interaction between the parasite, environment and human host.[125,126,127] A recent challenge in the fight against malaria is that the species is affected by resistance to antimalarial drugs, therefore new drugs are required. [125, 128,129]

The 52 compounds were tested against the drug-sensitive strain of *P. falciparum.* The assay was carried out using activity of the parasite lactate dehydrogenase enzyme as a marker for parasite activity and thus survival.[130] The compounds were biologically evaluated by testing the inhibition of the enzyme at various concentrations, where active compounds would inhibit

the enzyme activity. The assay details are provided in the **Appendix 6.2.4**. Of the 52 compounds tested, none showed significant activity against the human malaria parasite *in vitro*. For 48 of the compounds, no growth inhibition was observed at the highest starting concentration of 6µM. The remaining 4 compounds (were weakly active, with mean IC50 values from the two occasions of between 5µM and 6µM (highlighted in **Figure 38**). A follow-up series was planned where each position of the scaffold was to be examined by changing functional groups independently and identifying the important active chemical groups of the compounds.

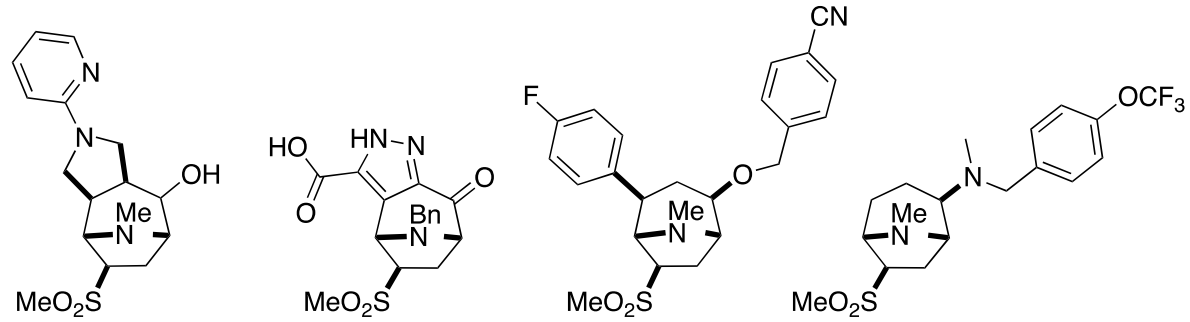


Figure 38. The four active compounds against the target Plasmodium falciparum, with the data averages shown for each.

In total, the 52 screening compounds were sent for biological evaluation against four targets at three different screening facilities. Weak activity was observed at most targets and there was potential to follow-up on each hit. Due to the time constraints, the promising compounds observing activity against *P.falciparum* was chosen to perform the synthesis of derivatives by exploration of structure activity relationship.

4.2 SAR library of the active Cape Town compounds

Most objectives of the project have been successfully achieved with 15 compounds showing promising activity in four different assays. The final objective was to carry out SAR and synthesise a new library based on the active compounds. This unified approach allowed for a fast follow-up series to be synthesised in an efficient manner. The synthetic efficiency is demonstrated below (**Figure 39**), where each scaffold can be synthesised in three or fewer steps. A range of derivatives of the active compounds were then synthesised in an attempt to improve the potency. The active compounds are shown below, four hits from the *Plasmodium falciparum* series (in blue), and two from the hedgehog osteogenesis series (in red).

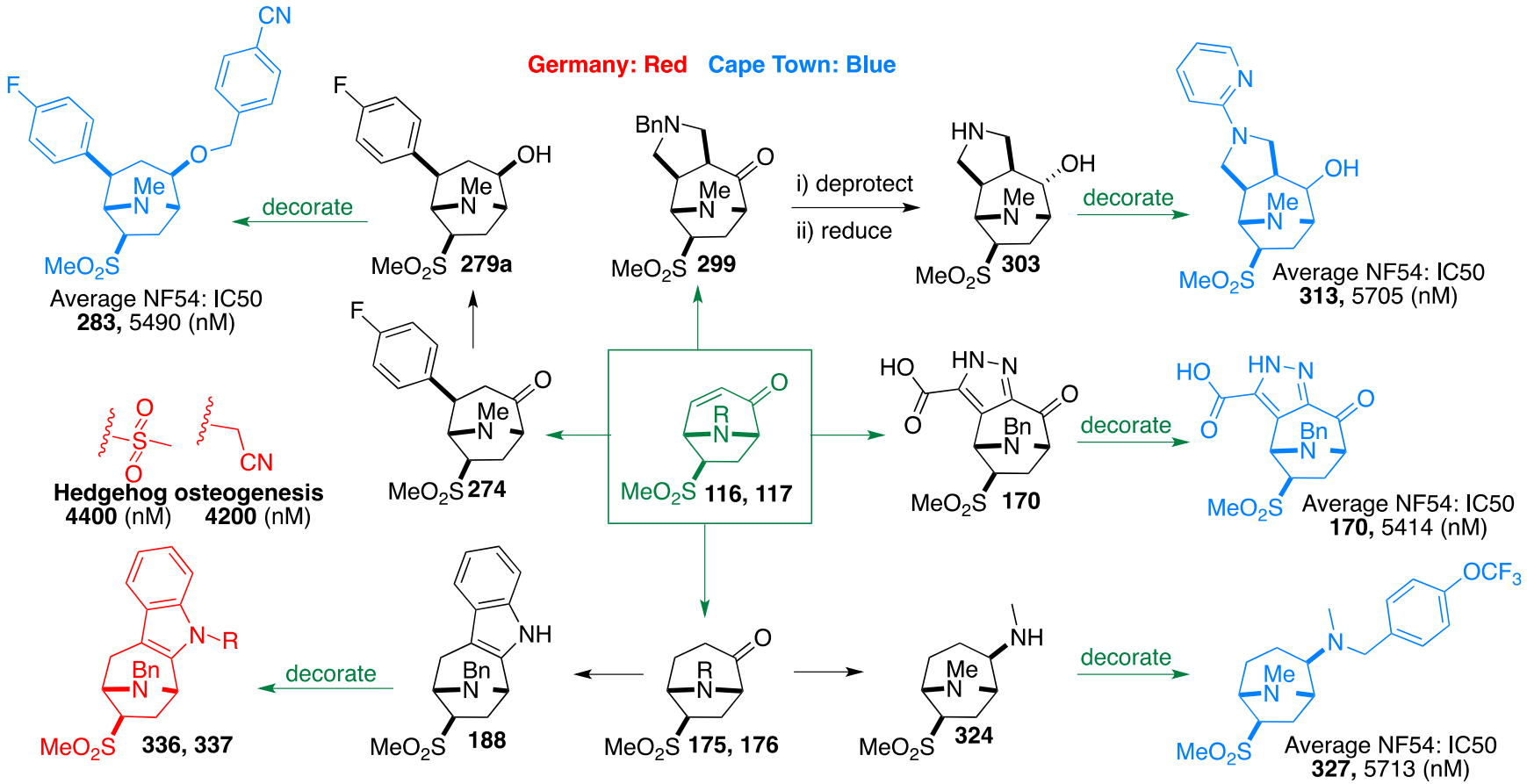


Figure 39. An overview of the synthetic route to the active compounds, Cape Town compounds in blue and Germany in red.

Owing to time constraints, the four hits produced from the *Plasmodium falciparum* series were selected as the scaffolds to pursue (**Figure 39,** in blue). The idea of this final series was to identify a chemical motif that possessed activity, with the primary aim to further increase the potency of the active compounds. Each position of the scaffold was to be examined by changing functional groups independently and identifying the groups within the compounds responsible for the activity. The library can then be analysed by observing the difference in potencies. A general plan for the follow-up SAR library is highlighted below (**Figure 40**). Methods for the scaffold elaboration involve the manipulation of the ketone (**Figure 40**, Method A and B), the amine (**Figure 40**, Method C), the sulfone (**Figure 40**, Method D) and the fused ring substituents (**Figure 40**, Method E). Each method will provide an insight into the important chemical groups responsible for the biological activity.

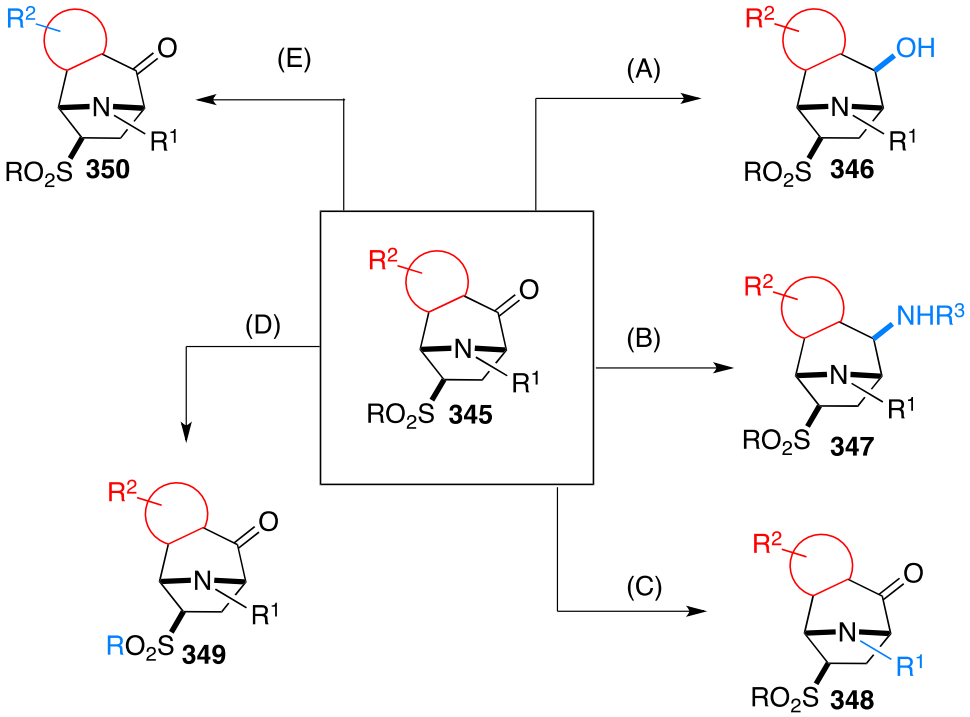
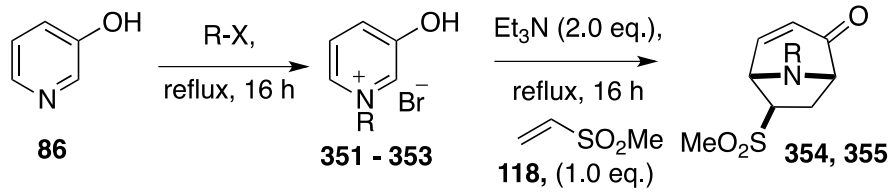


Figure 40. A range of scaffold elaboration methods for the potential follow-up SAR library

A range of novel cycloadducts were proposed, featuring different substituents at the bridged nitrogen. Applying the same conditions first described in **Section 2.2** (**Table 6**), three novel cycloaddition precursors (**351 - 353**) were synthesised in near quantitative yields (**Table 30**). Each precursor was then subjected to the established cycloaddition conditions; however, only two were successful giving the desired compounds in low yields (**Table 30**, entry 2 and 3). The stereochemistry and regioselectivity of cycloadducts were assigned according to the ^{1}H NMR

spectral data.[††] It was envisaged that the ester group at the bridged nitrogen would feature as a synthetic handle for decoration, however, the cycloadduct was not observed in the crude LCMS and the scaffold was deprioritised (**Table 30**, entry 1).



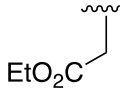
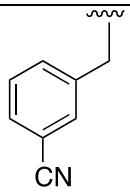
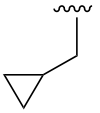
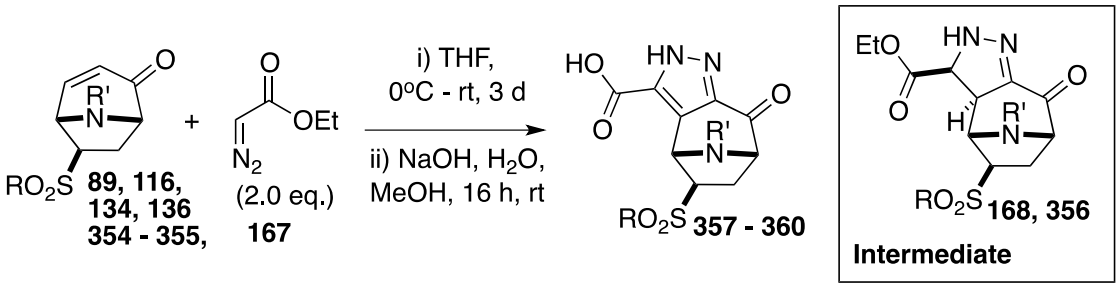
Entry	R	Conditions for salt formation	Outcome for cycloaddition[‡‡]
1		MeCN (0.5 M), 16h, **351,** 99%	No reaction
2		IPA (0.5 M), 16 h, **352,** 99%	**354**, 29%
3		IPA (0.5 M), 16 h, **353,** 99%	**355**, 22%

*Table 30. Outcome of cycloaddition conditions involving three salts **351 – 353**, and with dipolarphile **118**.*

4.3 Manipulation of the active pyrazole scaffold 170

A collection of cycloadducts containing different nitrogen substituents were subjected to a [3+2] cycloaddition with ethyl diazoacetate (method first detailed in **section 2.3.1**). It was determined previously that the procedure to prepare the fused pyrazoles could be done via telescoping the dihydropyrazole intermediates, so no isolation was necessary. However, due to polarity issues, the isolation of each product was found challenging and the overall yields for this compound series was poor (**Table 31**).

[††] The coupling constants matched the predicted coupling and the data was validated by comparison to previously synthesised cycloadducts.
[‡‡] Yield for the major isomer only, only this isomer was isolated.



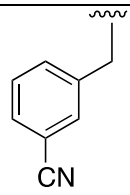
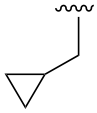
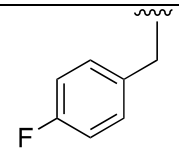
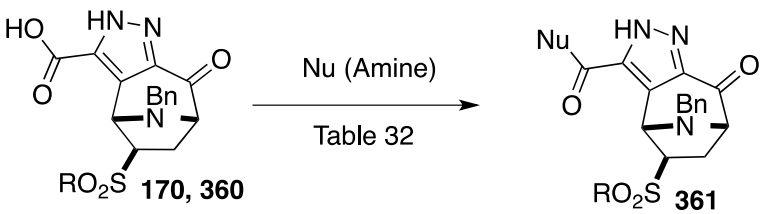
Entry	R	R'	Intermediate yield	Product Outcome
1	Me	Me	**356**, 84%	**357**, 3%
2	Me		**358**, 62%	Complex mixture (isolation issues)
3	Me		N/A	Complex mixture (stability issues)
4	Me	PMB	N/A	**134**, Starting material
5	Me		N/A	**359**, 8%
6	Ph	Bn	**168**, 58%	**360**, 11%

*Table 31. Outcome of the synthesis of pyrazole compounds **357 – 360** involving ethyl diazoacetate and subsequent aerobic oxidation.*

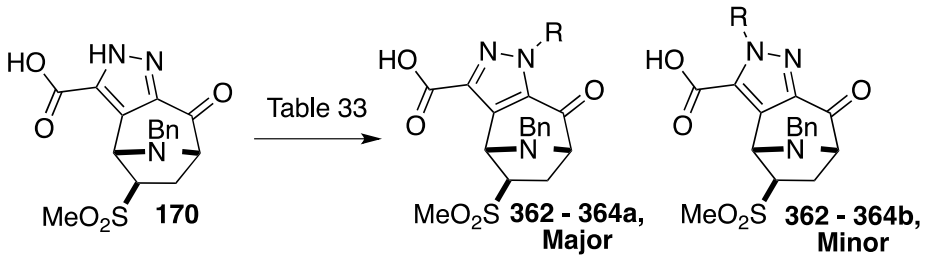
The next transformation of interest was a series of amide coupling reactions at the free carboxylic acid (**Table 32**). It was envisaged that a range of amides could be introduced as a point of diversification, which would be ideal for this SAR library. However, when changing the amines, conditions and starting materials, no desired product was observed or isolated in all cases. Consequently this route was discontinued as only the acid was recovered.

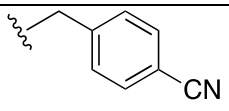


Entry	R	Nu (Amine)	Conditions	Outcome
1 2 3	Me	1) Methylamine 2) Morpholine 3) Dimethylamime	DIPEA (2.5 eq.), amine (1.5 eq.), DMA, TBTU (1.6 eq.)	Starting material **360**
4 5 6	Me	4) Methylamine 5) Morpholine 6) Dimethylamime	EDC (2.0 eq.), DMAP (10 mol%), DMF	Starting material **360**
7	Ph	Morpholine	EDC (2.0 eq.), DMAP (10 mol%), DMF	Starting material **360**

*Table 32. Outcome of amide formation conditions used in attempt to synthesise a range of amide derivatives of the pyrazole scaffold **170** and **360**.*

Synthetic efforts were then focused on a range of alkylation reactions that would deliver diverse capping groups at the free nitrogen of the pyrazole. With the pyrazole unprotected, there was a possibility of forming regioisomers. This was exemplified in the cases of alkylated pyrazoles **362** – **364** (**Table 33**, entry 1 and 2) where regioisomers were formed in a 3:2 mixture.[§§] Unfortunately, the regioisomers were inseparable by column chromatography and the alkylated pyrazoles were all isolated in moderate yields (33 – 52%) (**Table 33**). It was unclear on the clarification of the major regioisomer, however, literature precedence for pyrazole alkylation mainly reported observation of pyrazole type **362 – 264a** as the major product. [131,132]



Entry	Conditions	R	Outcome
1	KOH (2.3 eq.), MeI (1.3 eq.), DMF	Me	**362**, 52% 3:2 Mixture of regioisomers
2	KOH (2.3 eq.), DMF, 4-(bromomethyl) benzonitrile		**363**, 41%

[§§] The isomeric ratios were determined by ratios of distinct protons in the ^{1}H NMR spectrum.

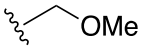
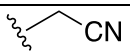
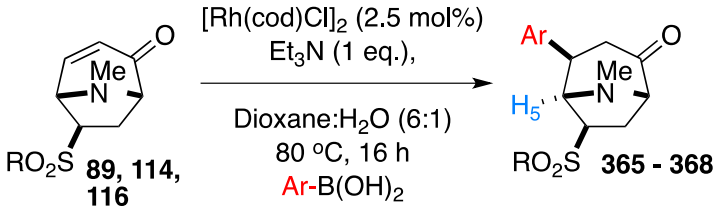
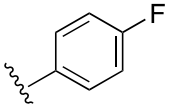
	(1.3 eq.)		3:2 Mixture of regioisomers
3	KOH (2.3 eq.), MOM-Cl (3.0 eq.), DMF		**364a**, 33% major only
4	KOH (2.3 eq.), $NCCH_2Br$ (3.0 eq.), DMF		**170**, Starting material

*Table 33. Outcome of alkylation reactions involving the free NH of pyrazole scaffold **170** and a range of alkyl electrophiles.*

4.4 Manipulation of the active compound 283 via 1,4-addition and decoration

To fully investigate the important features of the active compound **283**, it was proposed that a range of different boronic acids could be used to synthesise a diverse second round of screening compounds via the 1,4 addition to the enone. The 1,4-additions were performed on cycloadducts with varying sulfones, using conditions previously described (**Table 20, section 2.3.3**). As predicted, boronic acids substituted at the *para* and *meta* positions furnished the desired 1,4 adducts in good to high yields (**Table 34**, entries 1-3, 5). However, when the boronic acid was *ortho* substituted, no desired 1,4-adduct was formed (**Table 34**, entry 4). It was believed that this was due to increased steric interactions, hindering the addition to the enone. The stereochemistry of each was assigned according to the ^{1}H NMR spectra data and comparison to the active compound **283**. In each case, a singlet or doublet of a low coupling constant was observed for proton H_5 (as opposed to the opposite stereochemistry being a large coupling constant of 11 Hz).



Entry	Ar	SO_2R	Outcome
1		Ph	**365**, Telescoped***

*** The product was not isolated and telescoped through to the next step.

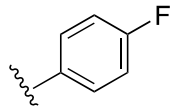
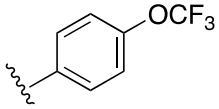
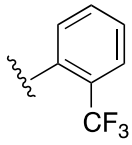
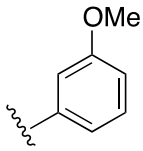
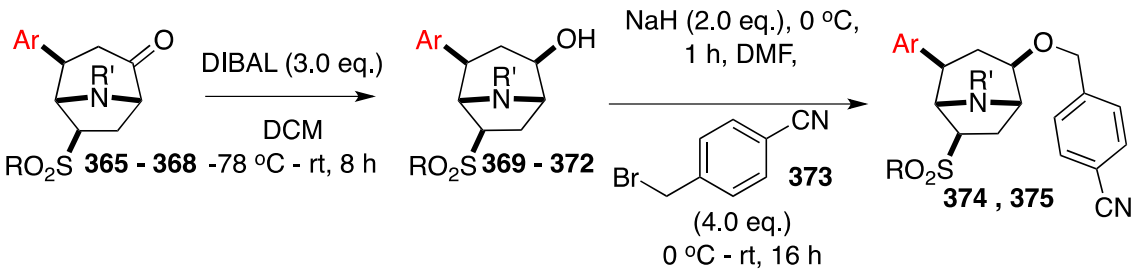
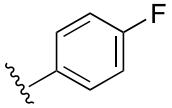
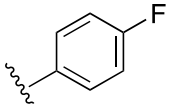
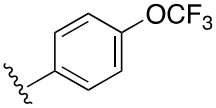
2		NMe_2	**366**, Telescoped
3		Me	**367**, 94%
4		Me	**116**, Starting material only
5		Me	**368**, 73%

Table 34. Outcome of a series of 1,4 addition reactions with a range of aryl boronic acids.

A series of alcohol intermediates were synthesised by applying the established conditions used to synthesise the hit compound precursor **278a** (**Table 35**). In each case, the alcohol was not purified but rather the crude material was decorated directly with 4-(bromomethyl)benzonitrile **373**. Compounds **374** and **375** were isolated in moderate yields of 33% and 29% respectively (**Table 35**, entry 1 and 4). The stereochemistry of each stereocentre was determined by comparison of ^{1}H NMR data with the active compound. However, there was purification problems and no product was isolated (**Table 35**, entry 2, 3 and 5).



Entry	Ar	SO_2R	NR'	Outcome
1		Ph	Me	**374**, 33%
2		NMe_2	Me	Purification problems
3		Me	Me	Purification problems

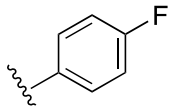
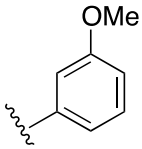
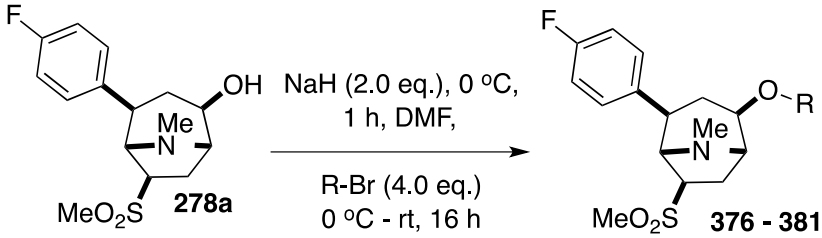
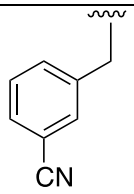
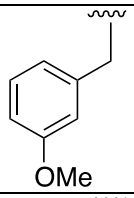
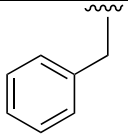
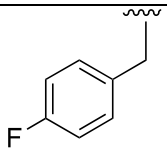
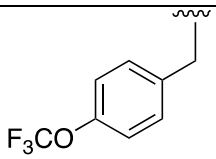
4		Me	Bn	**375**, 29%
5		Me	Me	Purification problems

*Table 35. Outcome of a series of reduction and decoration with compound **373** involving scaffolds **365 - 368**.*

For this SAR follow-up library, it was proposed to synthesise a range of substituted benzyl derivatives at the alcohol with *para*, *meta* and *ortho* substituted aromatics. Using conditions previously identified, ethers **376 – 381** were isolated in moderate yields (**Table 36**, entry 1-6). For entry 7, only starting material was observed by LCMS analysis and this compound was discontinued.



Entry	R	Outcome
1		**376**, 19%
2		**377**, 21%
3		**378**, 37%
4		**379**, 32%
5		**380**, 24%

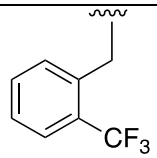
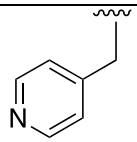
6		**381**, 25%
7		**278a**, starting material

*Table 36. Outcome of a series of alkylation reactions involving scaffold **278a** and a range of aryl derivatives.*

4.5 Manipulation of the active compound 327 via reductive amination and decoration

The last compounds to be synthesised for the SAR follow-up series were tertiary amine compounds produced from the key reductive amination reaction. Synthetic efforts were focused on three routes to produce a diverse library. Route one involved the synthesis of the secondary amine **327** (**Figure 41**, route 1). The idea was to decorate amine **327** with a range of capping groups to produce compounds with different functional groups. The second route featured the synthesis of the tertiary amine **382**, with a different sulfone substituent or the bridged nitrogen substituent (**Figure 41**, route 2). Finally, in route 3 the amine **383** was to be decorated with a range of different benzyl derivatives (**Figure 41**, route 3).

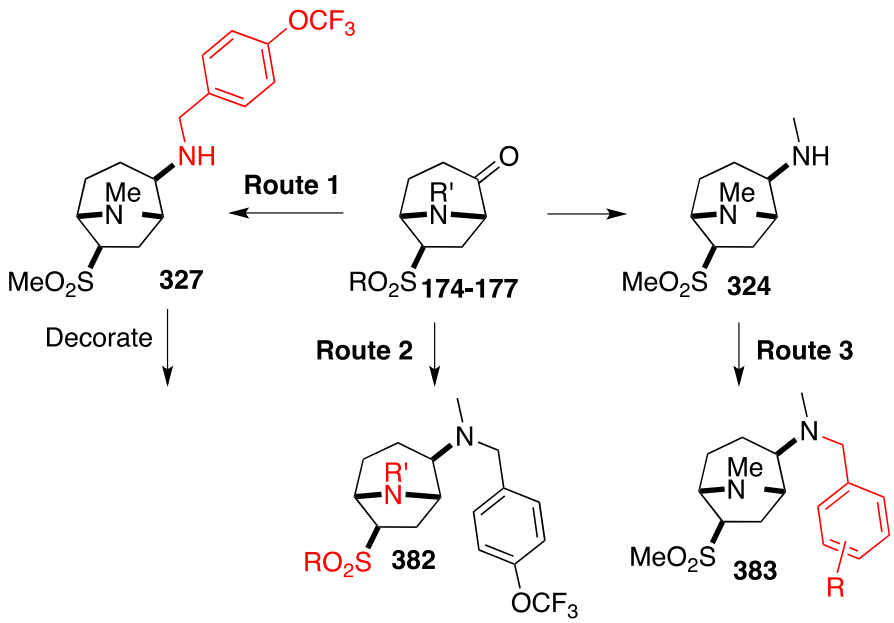
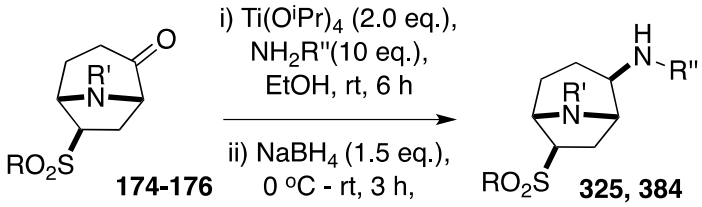


Figure 41. The planned SAR route for the tertiary amine compounds produced from a reductive amination.

The amine containing scaffold **325** and **384** were produced using the reductive amination conditions discussed previously by Bhattacharyya *et al.*[92] The summary is shown below, where each compound was synthesised with high levels of selectivity, with only one isomer being

produced in both cases (**Table 37**). The stereochemistry was determined by 1H-NMR comparison to the minor and major compounds in **Section 2.3.5** (**Scheme 35**).



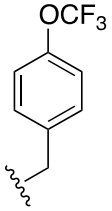
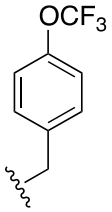
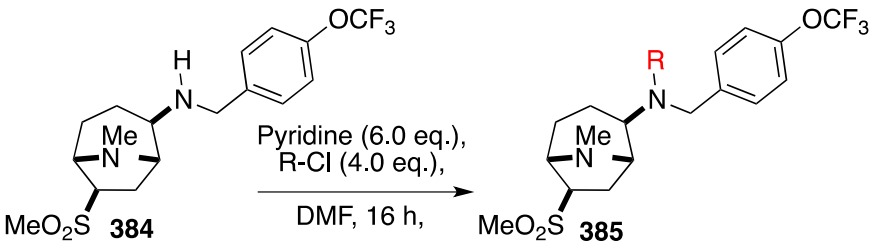
Entry	R	R'	R''	Outcome
1	Me	Me		**384**, 11%
2	Ph	Me		Starting material
3	Me	Bn	Me	**325**, 94%
4	Ph	Me	Me	Starting material

*Table 37. Outline of reductive amination reactions involving tropanone **174-176** and a range of amine nucleophiles.*

With compound **384** in hand, it was proposed to decorate the free amine with a range of capping groups. However, due to problems with synthetic tractability and poor yielding reactions, only two reactions were carried out (**Table 38**). The reactions were unsuccessful due to problems with isolation and purification. Consequently, this route to the follow-up compounds this way was deprioritised because of difficulty synthesising the starting material in large quantities.



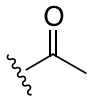
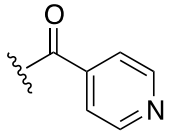
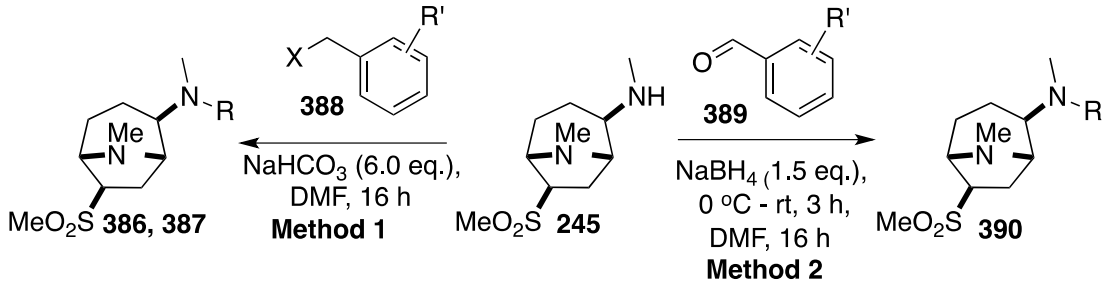
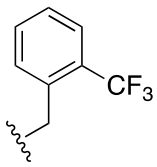
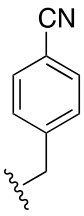
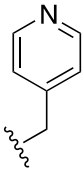
Entry	R	Outcome
1		Complex mixture
2		Complex mixture

*Table 38. Outcome of amide formation reactions involving free amine scaffold **384**.*

It was envisaged that the follow-up series would include a range of different benzyl derivatives of the active compound **327**. Therefore, compound **245** was subjected to two different sets of conditions; a reductive amination or an alkylation reaction. The alkylation reactions gave some success, where two compounds with different aromatic substituents were synthesised in low yields (**Table 39**, entry 1 and 2). Unfortunately, none of the reductive amination reactions were successful due to failure to isolate pure. (**Table 39**, entry 3 - 6)



Entry	Method	R	Outcome
1	1		**386**, 9%
2	1		**387**, 20%
3	2		Failed to isolate

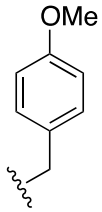
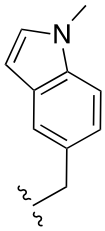
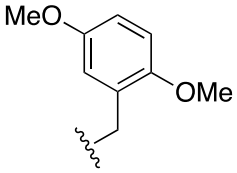
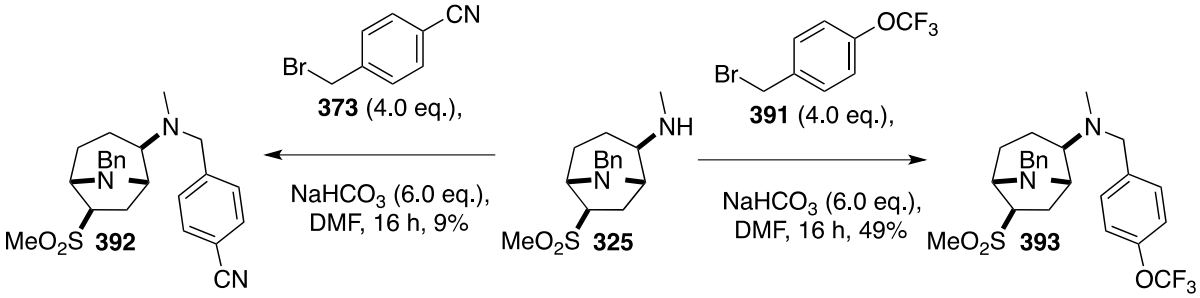
4	2		Failed to isolate
5	2		Failed to isolate
6	2		Failed to isolate

*Table 39. Outcome of alkylation or reductive amination reactions involving of amine **245** to produce a library of benzyl derivatives*

The last route to be investigated involved synthesising variants of the active compound **327** with different sulfonyl or nitrogen bridgehead substituents. Since the reductive amination reaction was unsuccessful with the different sulfonyl groups (**Table 37**, entry 4), the only modification of the chemical motif was the bridgehead nitrogen substituent. Amine **325**, was consequently subjected to alkylation reactions, where compounds **392** and **393** were synthesised in low to moderate yields (9 - 49%) (**Scheme 58**).



*Scheme 58. Outcome of alkylation reactions involving amine **325** and two aryl electrophiles **373** and **391**.*

4.6 Computational assessment of the SAR scaffold series

In total, 22 final compounds were synthesised in 36 synthetic operations from 5 scaffolds. The chemical structure of the active scaffolds were modified by either the addition of different chemical groups, or the synthesis of different derivatives; all with the aim to increase potency and explore SAR. Since only one position was changed for each compound, the follow-up data should indicate the most important features.

To assess the molecular properties, the follow-up series were plotted on a scatter graph to analyse their molecular weight and AlogP properties (**Figure 42**). It should be noted that the compounds are now drifting into more lipophilic and high molecular weight areas of chemical space. When comparing to the previous screening library, there is a decrease of 20% of compounds in the polar regions of 0 – 1 AlogP, and a 19% increase of compounds in the more lipophilic areas of chemical space (3 – 5 AlogP). Therefore, this evidence further supports the hypothesis that compounds AlogP tends to increase through the discovery process.[24]

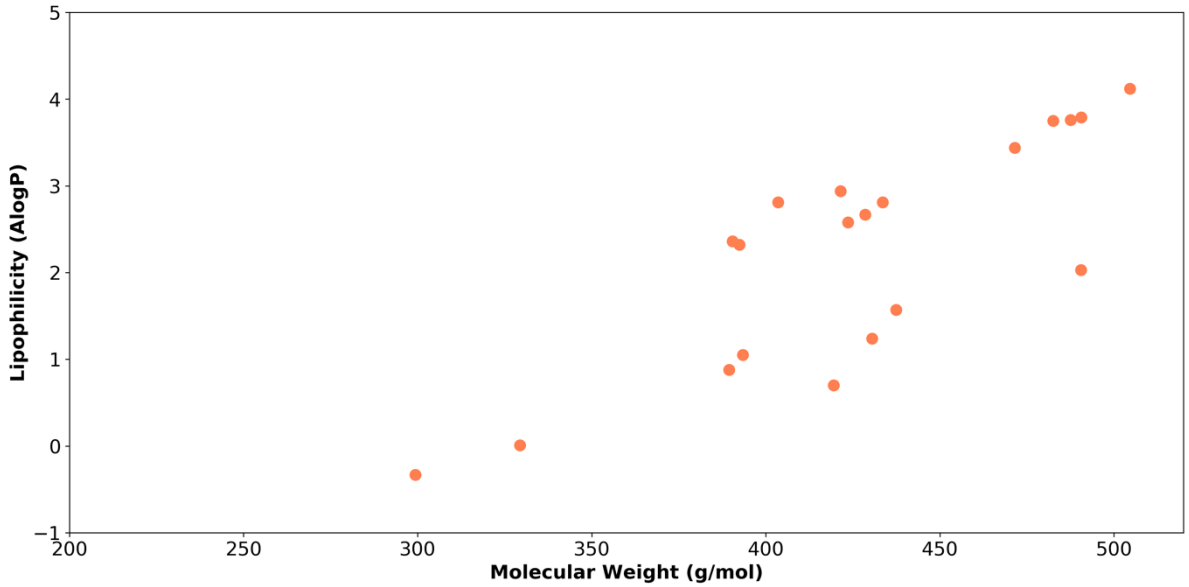


Figure 42. A graph showing the relationship between lipophilicity and molecular weight of each screening compound.

It is also important to monitor the relative three-dimensionality and diversity of the SAR library, so the compounds were plotted on a PMI plot using LLAMA.[45] The plot can be seen below (**Figure 43**), where the library still shows a high level of diversity and three-dimensionality. Compound **375** showed higher levels of three-dimensionality as it explored the more unpopulated region of chemical space. However, compounds **393** and **384** are situated in the more populated area of chemical space; the 'rod-like' region of chemical space. This is understandable as the negative impact of the 'OCF_3' substituent deems the compounds as 'rod-like'. In conclusion, when comparing to the random 1% of ZINC database (90,911 compounds), it is clear from the plot hat this objective has successfully been achieved.

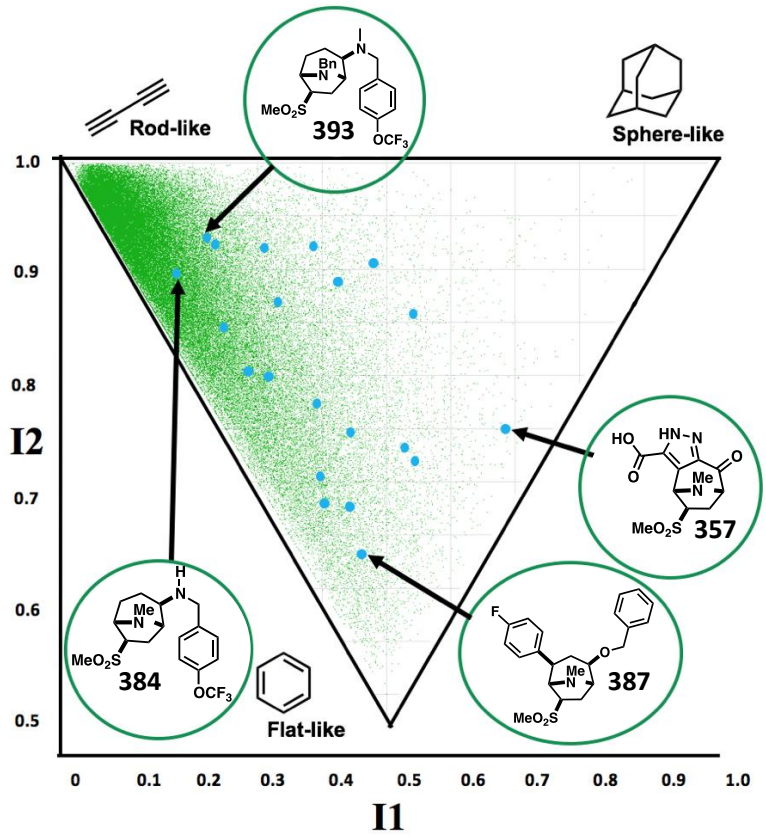


Figure 43 A PMI plot showing the three-dimensionality of the screening compounds, with particular examples highlighted

Each compound was then analysed for their fraction of sp^3 hybridised carbons (**Figure 44**). It was found that 14% of the compounds experienced a lower Fsp^3 value than a random 1% of the ZINC database. It was concluded that the compounds experienced high Fsp^3 character and were therefore still to be considered as 'complex'. Again, an original aim of the project was successfully achieved.

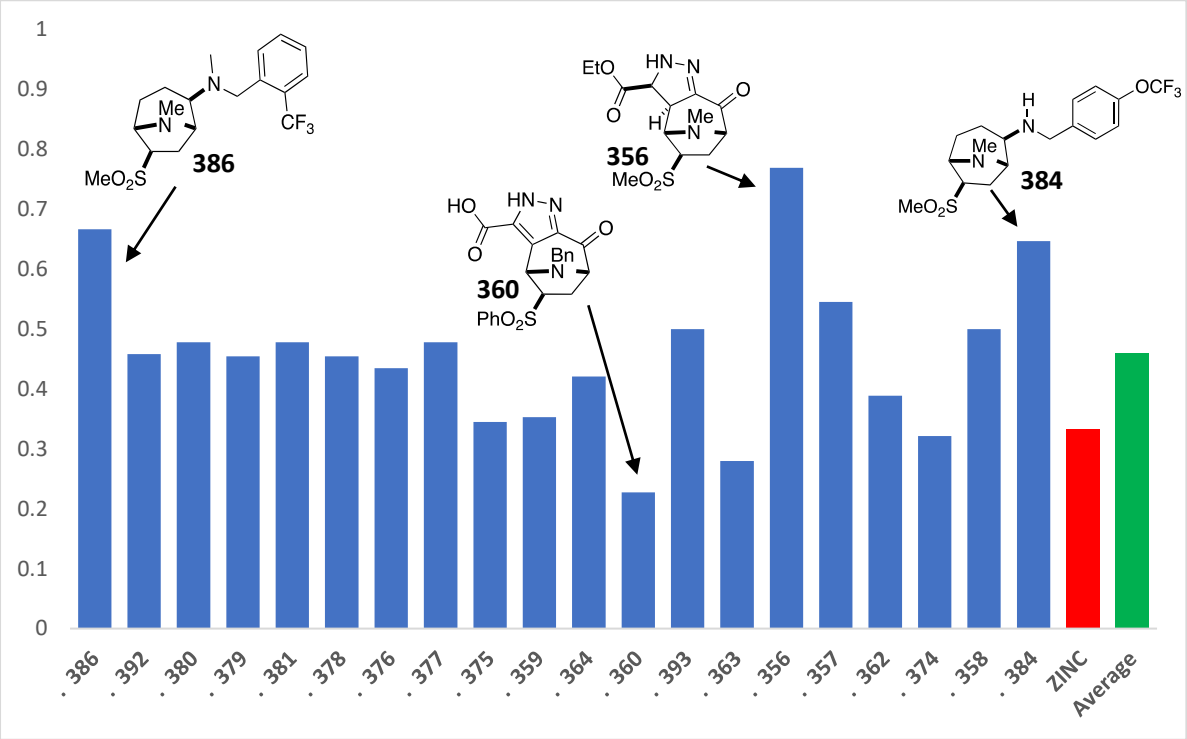


Figure 44. A Fsp3 value comparison of the screening compounds. The average value (in green) is also compared with the average ZINC database value (in red).

In total, 13 compounds were sent for biological evaluation against the *Plasmodium falciparum* cells. Due to problems with stability and synthetic tractability, several compounds were not sent for screening. Because of time constraints, the remaining compounds were therefore not re-synthesised. However, this follow-up library was synthesised in a rapid and efficient manner (in under 2 months), using minimal steps. Again, because of time restrictions, SAR for the other active compounds were not carried out and there remains several follow-up compounds to be investigated.

5.0 Conclusions and future work

5.1 Summary and conclusions

In the search for clinical candidates, thousands of compounds are synthesised and screened for biological activity. SAR must then be carried out and the candidate produced on a multi-kg scale. Therefore, the candidate must be scalable and produced from readily available starting materials. When carrying out SAR, various accessible points of the compound must be available for modification. The advantage of the LOS method in general is its ability to produce a large number of small, diverse molecules in an efficient manner. In doing so this method produced 14 lead-like scaffolds from 28 synthetic operations and 52 novel compounds from a total of 73 synthetic operations. Each had the potential to be produced on a large scale, with various accessible points available for SAR.

In comparison to other methods such as combinatorial synthesis, this method relies on capping groups to bring diversity to the library set and often results in synthesising compounds outside of lead-like space.[24] With efforts to increase the library size, multiple points available on the molecules are subjected to a wide range of capping groups, therefore producing compounds with no focus on molecular properties. A comparison of the method vs LOS is shown below (**Figure 45**). A combinatorial approach aims at similar structures, therefore lacking in diversity. The LOS approach has diverse target structures and produces a library of complex diverse compounds, with a focus on molecular properties.

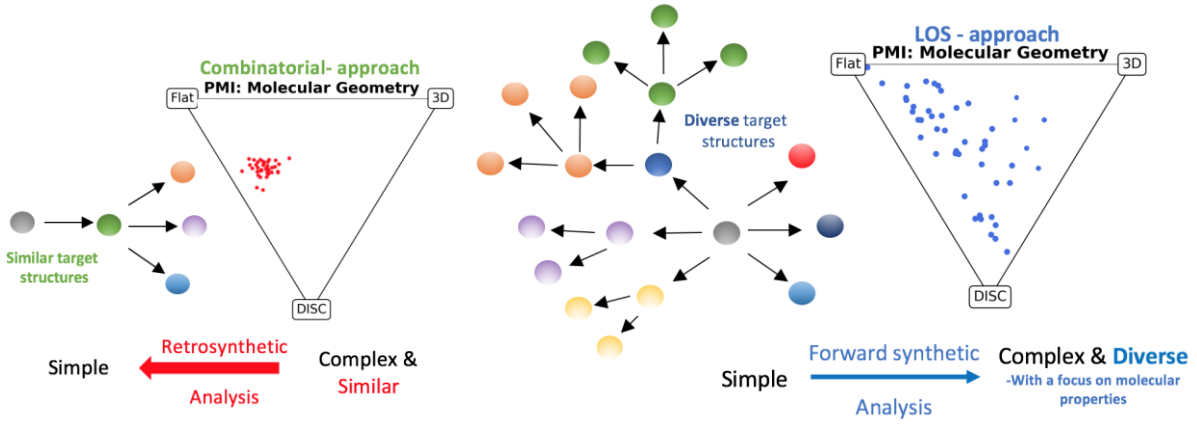


Figure 45. A) an example of a combinatorial library approach to synthesising screening compounds vs B) a LOS approach to synthesising screening compounds

Other methods such as DOS, also have issues with molecular properties as many libraries are often produced using cascades, with a heavy focus on producing a diverse library. When comparing to a DOS library by Spring *et al* in 2015,[133] only 4 novel scaffolds were synthesised from 22 synthetic operations, and with no focus on molecular properties. In comparison to the LOS library, the DOS library is averaging 1 scaffold per 5.5 steps, whereas the LOS library is averaging 1 scaffold per 2 steps, showing a greater efficiency. When comparing another a DOS library, this time within the group,[134] 96 molecules were synthesised (from no more than five discrete steps). The library however, only produced 65% novel compounds and again with no focus on molecular properties. Comparatively, the LOS library produced only novel compounds with controlled molecular and the compounds were sent for biological evaluation.

Here our method has produced a library of diverse novel compounds with attention paid to physicochemical and functional group properties, whilst maintaining synthetic efficiency. This method is advantageous as it is a combination of each method described. The drug discovery process seeks to identify molecules able that efficiently interact with biological systems, therefore the library has specifically been designed to contain various groups that do interact. Interactions with biological systems frequently occur through polar or hydrogen bonding interactions, normally from acidic groups, Brønsted bases and heterocycles.[24] With this in mind, strategic planning enabled the synthesis of each final compound possessing these characteristics. It should be noted that the presence of such groups is known to be troublesome in synthetic operations, therefore making this a challenging task. However, each final compound has various relevant functional groups available for interactions and these compounds were sent for biological evaluation against a wide range of biological targets.

From 5 different assay targets, 15 number of compounds showed promising activity, where SAR was performed on 3 compounds of the Cape Town malaria series. In total 13 compounds were sent for a second round of biological evaluation against the *Plasmodium falciparum* cells, where unfortunately no activity was observed. Due to time constraints no further synthesis was carried out.

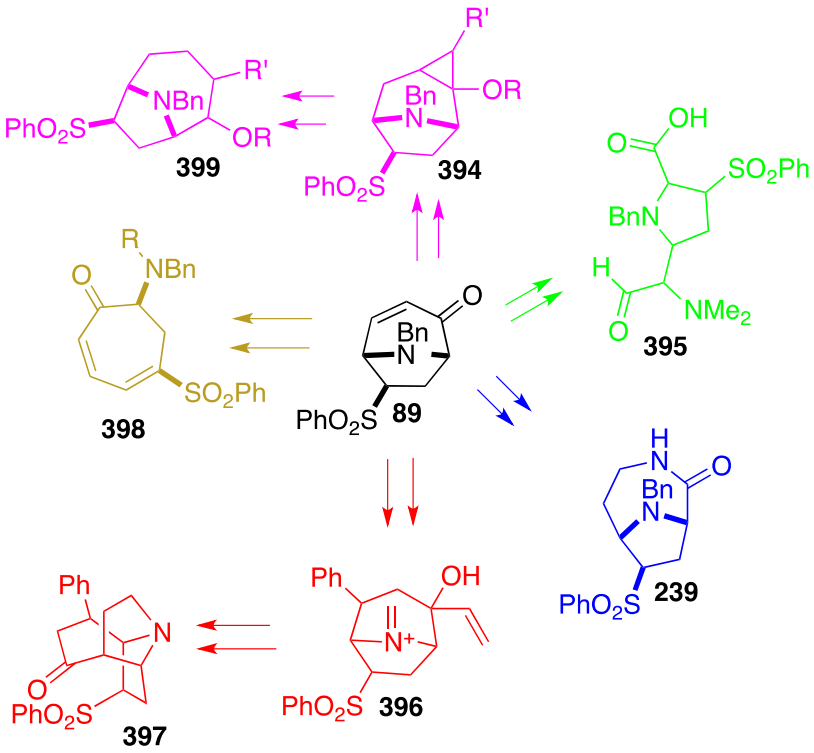
Overall, the method has demonstrated a successful LOS strategy, where a large number of scaffolds were produced in an efficient and rapid manner. The novel and diverse compound set experienced high levels of three-dimensionality and complexity. A number of hits from different targets was observed with each compound possessing the correct physicochemical

properties for screening. However, the method cannot be truly verified as no evidence can be provided for the reducing of attrition rates in drug discovery.

5.2 Future work

5.2.1 Synthesising a more diverse set of scaffolds for screening

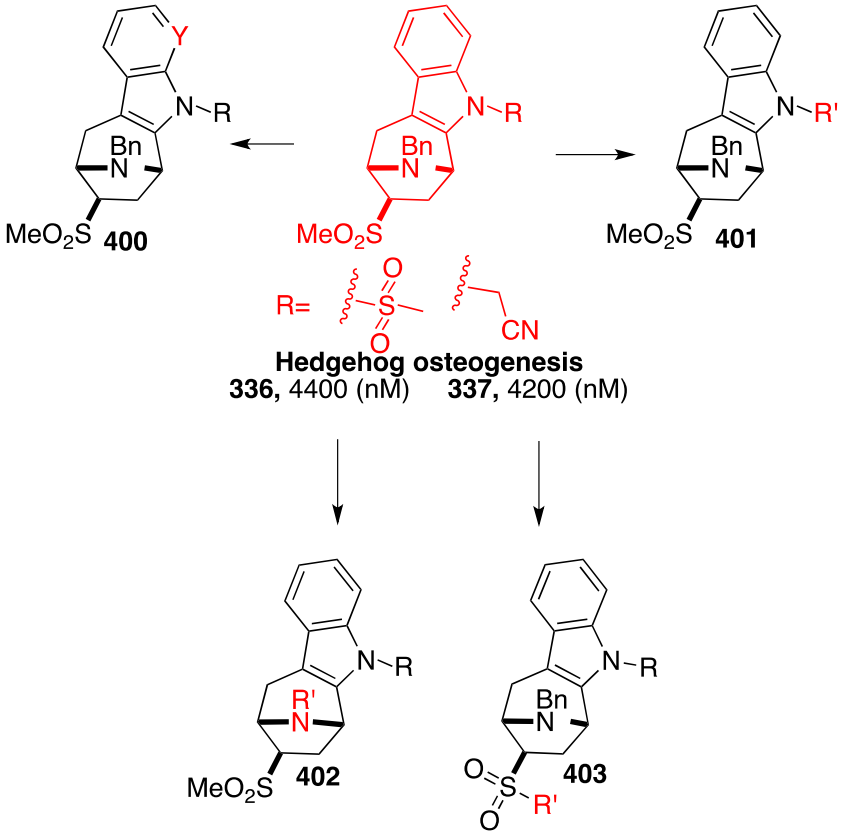
As briefly discussed, 85% of the screening compounds contained the methyl sulfone group. In order for a more diverse set of compounds a focus should have been on producing compounds with different functionality. However, this would have consequently led to a lower number of compounds for the screening library. Also, there remains several reactive pathways available for ring expansion, that would synthesise a more structurally diverse set of scaffolds for screening. With only the decoration of the [3.2.1] cycloadduct being explored, the core diversity is limited. In future, a focus should be to try to manipulate the chosen scaffold by a range of cleaving and ring expansion reactions to produce a more skeletally diverse library, thus, so that the scaffolds are not simple derivatives of each other. Below shows a range of ideas to produce a skeletally diverse collection of future lead-like and screening compounds **(Scheme 59**).



Scheme 59. A proposed route to five new molecular scaffolds with different core structures.

5.2.2 SAR with indole compounds 336 – 337

Due to time constraints, there remain a number of compounds to synthesise for a follow-up SAR library. In particular the compounds from the hedgehog osteogenesis assay from Dortmund, Germany. An example of a few synthetic strategies for an SAR library are shown below (**Scheme 60**). More work could have been undertaken in an attempt to increase the potency of such compounds.



Scheme 60. Suggested SAR library follow up series for the Hedgehog osteogenesis target

5.3 Using machine learning to predict biological activity

Machine learning is currently one of the most discussed and rapidly evolving topics in drug discovery.[135,136,137,138] Owing to the high demand of exploring and analysing big data, this has encouraged the use of machine learning algorithms to predict biological effect of chemical compounds based on mathematical and statistical relations.[138] Quantitative structure-activity realtionships (QSARs) are predictive statistical models that correlate big data and analyse the response, chemical data and their relationship. It is therefore proposed that computational future work could be undertaken that would involve machine learning algorithms comparing the 52 screening compounds with known active compounds in the literature. This strategy would compare the structures to a large data set of known compounds with activity and would

indicate certain compounds that may show activity. This process would have huge advantages such as prevention of material loss, increasing the chances of hits and less manual labour. Also, less money would be spent on screening and re-synthesising screening compounds. In terms of SAR, machine learning programs could be used to accurately predict *in silico* how structure modifications influence biological behaviour.[139] To conclude, these suggestions with the use of machine learning could potentially increase activity and efficiency, there it could play crucial part in future LOS strategies.

6.0 Experimental

6.1 General experimental

All reactions were carried out under an atmosphere of nitrogen. Solvents were removed under reduced pressure using a Büchi rotary evaporator and a Vacuubrand PC2001 Vario diaphragm pump.

All other solvents and reagents were of analytical grade and dried using a solvent Pure Solv MD solvent purification system (Innovative Technology Inc.) Commercially available starting materials were obtained from Sigma–Aldrich, Fluorochem Ltd and Alfa Aesar.

Flash column chromatography was carried out using silica (35-70 μm particles). Thin layer chromatography was carried out on commercially available pre-coated glass or aluminium plates (Merck silica 2 8 8 0 Kieselgel 60F254).

Analytical LC-MS was performed using a system comprising of a Bruker HCT Ultra ion trap mass spectrometer equipped with electrospray ionization and an Agilent 1200 series LC made up of, a high vacuum degasser, a binary pump, a high performance autosampler, an autosampler thermostat, a thermostated column compartment and diode array detector.

Proton and carbon NMR spectra were recorded on a Bruker Avance DPX 300, Avance 500, AV-3 400 or DRX 500 or JEOL ECA600II spectrometer using an internal deuterium lock. Carbon NMR spectra were recorded with composite pulse decoupling using the watts 16 pulse sequence. DEPT, COSY, HMQC and HMBC pulse sequences were routinely used to aid the assignment of spectra. Chemical shifts are quoted in parts per million downfield of tetramethylsilane, and coupling constants (J) are given in Hz. NMR spectra were recorded at 300 K unless otherwise stated.

Melting points were determined on a Reichert hot stage microscope and are uncorrected.

Infrared spectra were recorded on a Bruker alpha FT-IR spectrometer using a “platinum ATR” accessory and are reported in wavenumbers (cm^{-1}).

High resolution mass spectrometry was routinely performed on a Bruker HCT Ultra spectrometer using electrospray (+) ionization. Nominal and accurate mass spectrometry using electrospray ionisation was carried in the School of Chemistry at the University of Leeds, using a Bruker MaXis Impact spectrometer.

6.2 General procedures

General Procedure A: 3-Hydroxypyridinium salt

To a solution of 3-hydroxypyridine (1.0 eq.) in solvent (0.2-1.8M) at rt was added alkyl halide (1.0 eq.). The reaction mixture was heated at reflux for 16 h, then cooled and concentrated *in vacuo*.

General Procedure B: Cycloaddition with pyridinium salt

To a solution of compound salt **87** (1.3 eq.) in anhydrous THF (0.2 M) at rt was added vinylsulfone (1.0 eq.) and triethylamine (2.0 eq.). The reaction mixture was heated at reflux for 16 h – 2.5 d then cooled to rt and filtered. The crude mixture was taken up in water, and the aqueous phase was extracted with EtOAc (× 3) and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*.

General Procedure C: Cycloaddition with methylhydroxypyridinium salt

To a solution of compound methyl salt **105** (1.3 eq.) in anhydrous THF (0.2 M) at rt was added vinyl compound (1.0 eq.), and silver oxide (1.8 eq.). The reaction mixture was covered from light and heated at reflux for 16 h - 2.5 d. The reaction was then cooled to rt and silver iodide was filtered off. The crude mixture was taken up in water, and the aqueous phase was extracted with EtOAc (× 3) and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*.

General procedure D: Vinyl sulfonyl derivatives

To a stirred solution of amine (1.0 eq.) and NEt_3 (2.2 eq.) in DCM (0.2M) at –78 °C was added dropwise of 2-chloroethanesulfonyl chloride **123** (1.1 eq.) in DCM (0.2M) over 4 h. The mixture was allowed to warm to rt. The crude mixture was taken up in water, and the aqueous

phase was extracted with DCM (× 3) and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*.

General procedure E: Strong cation exchange solid phase extraction (SCX SPE)

TfOH (0.5 M in MeOH, 10 mL / 5 g SCX SPE) was dripped through the SCX SPE cartridge prior to use. MeOH (20 mL) was then flushed through using pressurised air. The crude residue was loaded (3.5 mmol / 5 g SCX SPE silica) in the minimum amount of MeOH. The cartridge was flushed with MeOH and the fractions were collected and monitored by TLC. The cartridge was then flushed with sat. NH_3/MeOH and the fractions were collected and monitored by TLC. Fractions containing product were combined and concentrated.

General Procedure F: Hydrogenation using Pd/C or Pd(OH$_2$)/C

The substrate (1.0 eq.) was dissolved in MeOH or EtOH (~20 mL g^{-1}) and added *via* syringe to a round-bottomed flask containing 10 wt% Pd/C (% w/w as specified) or 20 wt% $Pd(OH)_2$/C (% w/w as specified) submerged in minimal solvent (MeOH or EtOH) under N_2. If required, conc. HCl (~12 M) was added as specified. The head space of the flask was exposed to a sequence of vacuum/H_2 flushes (×3), then exposed to an atmosphere of H_2 (balloon). The reaction was monitored by TLC until complete. At this point the balloon was removed and the reaction mixture was purged with a vacuum then with N_2 (with a gas outlet) for 5 minutes. The reaction mixture was filtered through Celite eluting with MeOH, then concentrated *in vacuo*. The product was typically used in the next step without further purification.

General procedure G: Alcohol TBS protection

To a stirred solution of alcohol (1.0 eq.) in anhydrous DMF (0.5M) at 0 ^oC, was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.1 eq.), imidazole (2.0 eq.). The reaction mixture was left to stir for 16 h at rt. The crude mixture was taken up in water, and the aqueous phase was extracted with EtOAc (3 ×) and the combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*.

General procedure H: Oxidative desulfonylation

To a stirred solution of protected alcohol (1.0 eq.) in THF (0.2 M) at −78 °C was added LiHMDS (1 M solution in THF, 10 eq.) dropwise. After 10 min, dimethyl disulfide (20 eq.) was added and stirred for 16 h at rt. The crude mixture was taken up in water, and the aqueous phase was extracted with DCM (3 ×) and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The reaction mixture was taken up in 1,4-dioxane (0.2M) and followed by an addition of conc.HCl (60 eq.). The reaction mixture was heated at reflux for 16 h, cooled to rt and concentrated *in vacuo*

General Procedure I: DIBAL reduction

To a solution of ketone (1.0 eq.) in anhydrous solvent (0.08 M) at -78 ^oC was added DIBAL (1M cyclohexane) (3.0 eq.) dropwise over 0.5 h. The reaction mixture was stirred for 4 h at -78 ^oC and then allowed to warm to rt. The residue was taken up in saturated potassium sodium tartrate tetrahydrate solution and stirred for 1 h. The aqueous phase was extracted with DCM (×3) and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*.

General procedure J: thiazole Thiazole formation

To a stirred solution of alpha-chlorinated ketone (1.0 eq.) in DMF (0.15 M) at rt was added thiobenzamide (4.5 eq.). The reaction mixture was heated at reflux for 16h, then cooled and concentrated *in vacuo*.

General procedure K: Pyrimidine formation

To a solution of ketone (1.0 eq.) in EtOH (0.5 M) at rt was added 2,4,6-tris(trifluoromethyl)-1,3,5-triazine (2.0 eq.) and TFA (10 mol%). The reaction mixture was heated at reflux for 16 h, quenched with $NaHCO_3$. The crude mixture was was taken up in EtOAc, and aqueous phase was extracted with EtOAC (3 ×) and the combined organic extracts were washed with water (3 ×), dried over $MgSO_4$ and concentrated *in vacuo*.

General procedure L: Isoxazole formation

To a solution of enone (1.0 eq.) in THF/Et_2O (1:1) (0.1M) at 0 ^oC was added nitroethane (2.0 eq.), phenylisocyanate (4.1 eq.) and triethylamine (0.08 eq.). The reaction was left to stir for 16 h at room temperature and then filtered. The crude mixture was taken up in water, and the

aqueous phase was extracted with Et_2O (3 ×) and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*.

General procedure M: Dihydropyrazole formation

To a solution of enone (1.0 eq.) in anhydrous THF (0.2M) at 0 ^oC was added ethyl diazoacetate (contains ≥13 wt. % dichloromethane) (2.0 eq.). The reaction mixture was stirred for 3 d at rt. The crude mixture was taken up in water, and the aqueous phase was extracted with EtOAc (3 ×) and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*.

General procedure N: Pyrazole formation

To a solution of dihydropyrazole (1.0 eq.) in MeOH (0.2M), was added NaOH (2M, 10 eq.). The reaction was stirred at rt and monitored by LC-MS, where more NaOH (2M) was added until the reaction went to completion. The crude mixture was neutralised to pH 7 and taken up in DCM, and the aqueous phase was extracted with DCM. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*.

General procedure O: Pyridine formation

To a solution of ketone (1.0 eq.) in EtOH (0.2 M) at rt was added propylamine (2.0 eq.) and sodium tetrachloroaurate(III) dihydrate (2.5 mol%). The reaction mixture was heated at 80 ^oC for 16 h. The crude mixture was concentrated *in vacuo*.

General procedure P: Indole synthesis

To a solution of ketone (1.0 eq.) in anhydrous DMF (0.2M) at rt was added 2-iodoaniline (1.2 eq.), $Pd(OAc)_2$ (10 mol%) and DABCO (1.0 eq.). The reaction was stirred for 48 h at 105 ^oC and then cooled to rt. The crude mixture was taken up in water, and the aqueous phase was extracted with EtOAc (3 ×) and the combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*.

General procedure Q: Sulfonamide formation

To a stirred solution of nucleophile (1.0 eq.) in anhydrous DMF (0.2M) at rt was added base (4 eq.) and sulfonyl chloride (8.0 eq.). The reaction was left to stir for 16 h at rt. If the reaction had not gone to completion, then heated until completion. The reaction mixture was concentrated *in vacuo*.

General procedure R: S_NAr/Alkylation formation

To a stirred solution of nucleophile (1.0 eq.) in anhydrous DMF (0.2M) at rt was added base (1.5 eq.). The reaction was left to stir for 0.5 h at 0 ^oC, then electrophile (3.0 eq.) was added and the reaction left to stir for 16 h at rt. If the reaction had not gone to completion, then heat at 80 ^oC until completion.

General procedure S: Intramolecular Heck reactions

To a stirred solution of enone (1.0 eq.) in PhMe (0.2 M) at rt was added sodium formate (1.5 eq.), $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%) and $ZnCl_2$ (1.0 eq.). The reaction mixture was heated at reflux for 16h, then cooled and concentrated *in vacuo*.

General Procedure T: 1,4-addition series

To a solution of enone (1.0 eq.) in degassed dioxane:H_2O (6:1) (0.3 M) at rt was added boronic acid (4 eq.), chloro(1,5-cyclooctadiene)rhodium(I) dimer (2.5 mol%) and triethylamine (1.0 eq.). The reaction mixture was left to stir for 16 h at 80 ^oC. Once cooled to rt the crude mixture was concentrated *in vacuo*.

General procedure U: Pyrrolidine formation

To a solution of enone (1.0 eq.) in anhydrous MeCN (0.2M) at rt was added *N*-(Methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine (2.2 eq.) and lithium fluoride (2.5 eq.). The reaction mixture was heated at reflux for 16 h. The crude mixture was concentrated *in vacuo*.

General procedure V: Amide formation

To a solution of amine or amine hydrochloride salt (1.0 eq.) in anhydrous DCM (3 mL) at rt was added acid chloride (8.0 eq.) and pyridine (4.0 eq.). The reaction was left to stir for 16 h at room temperature, then NaOH (5.0 eq.) in MeOH/water (1:1) was added and stirred at rt for 16 hours. The crude mixture was neutralised to pH 7 and taken up in DCM, and the aqueous phase was extracted with DCM. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*.

General procedure W: Reductive amination decoration with amine-containing scaffold

To a solution of amine or amine hydrochloride salt (1.0 eq.) in anhydrous DMF (0.2M) in 4A MS at rt was added aldehyde/ketone (5.0 eq.). The reaction was left to stir for 16 h at rt, then the reaction mixture was cooled to 0 ^{o}C and $NaBH_4$ (3.0 eq.) was added and the reaction left to stir for 3 h at rt. If the reaction had not gone to completion, then heat at 80 ^{o}C until completion. The reaction mixture is concentrated *in vacuo*.

General procedure X: Reductive amination with ketone –containing scaffold

To a stirred solution of ketone (1.0 eq.) in MeOH (0.2 M) at rt was added amine (10 eq.) and $Ti(O^{i}Pr)_4$ (2.0 eq.). After 6 h the reaction mixture was cooled to 0 ^{o}C and $NaBH_4$ (1.5 eq.) was added portionwise. The reaction mixture was warmed to rt, stirred for 3 h, then concentrated *in vacuo*. The residue was taken up in EtOAc and ammonium hydroxide (2 M, 6.0 eq.) was added. The resulting mixture was dried over $MgSO_4$, and then filtered through celite. The resulting solution was concentrated *in vacuo*.

General procedure Y: Urea/carbamate synthesis

To a solution of alcohol (1.0 eq.) in anhydrous DMF (0.2 M) at rt was added base (6.0 eq.). The reaction mixture was stirred for 30 min and isocyanate (2.5 eq.) was added and the reaction was stirred overnight. Water was added and the reaction was stirred for 2 h, then the crude mixture was taken up in EtOAc, and aqueous phase was extracted with EtOAC (3 ×) and the combined organic extracts were washed with water (5 ×), dried over $MgSO_4$ and concentrated *in vacuo*.

General procedure Z: Amine alkylation

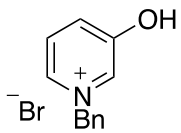
To a stirred solution of nucleophile (1.0 eq.) in anhydrous DMF (0.2M) at rt was added $NaHCO_3$ (6.0 eq.) and electrophile (4.0 eq.) was added and the reaction left to stir for 16 h at rt. If the reaction had not gone to completion, it was heated at 80 ^{o}C until completion.

General procedure α: Pyrazole alkylation

To a stirred solution of pyrazole (1.0 eq.) in anhydrous DMF (0.2M) at rt was added KOH (2.3 eq.) and electrophile (3.0 eq.), then the reaction left to stir for 16 h. The reaction mixture was concentrated *in vacuo*.

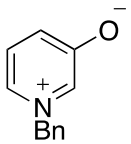
6.3 Experimental

1-Benzyl-3-hydroxypyridin-1-ium bromide (**87**)[98]



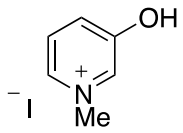
General procedure **A** was followed using 3-hydroxypyridine (3.00 g, 32.0 mmol, 1.0 eq.), benzyl bromide (3.80 mL, 32.0 mmol, 1.0 eq.) and 2-propanol (20 mL). *Title compound* **87** (8.43 g, 32.0 mmol, 99%) was isolated as a yellow solid. The NMR data is in accordance with the literature.[98] **^{1}H NMR** (400 MHz, DMSO-d_6): δ 11.97 (1H, s, O*H*), 8.81 – 8.66 (2H, m, Ar*H*), 8.01 – 7.93 (2H, m, Ar*H*), 7.59 – 7.52 (2H, m, Ar*H*), 7.52 – 7.38 (3H, m, Ar*H*), 5.80 (2H, s, NCH_2). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 157.6 (*Ar*), 136.2 (*Ar*H), 134.8 (*Ar*), 133.1 (*Ar*H), 132.3 (*Ar*H), 129.8 (*Ar*H), 129.7 (*Ar*H), 129.4 (*Ar*H), 129.2 (*Ar*H), 63.6 (*C*H_2). **IR** ν_{max} (neat)/cm^{-1}: 3339 (OH), 3031, 2991 (C-H), 2867, 2736, 2632, 1494, 1454 (C=C); **HRMS** (ESI): $C_{12}H_{11}NO$ [M-H]: calculated 186.0913, found 186.0913.

N-Benzyl-3-oxypyridinium betaine (**106**)[71]



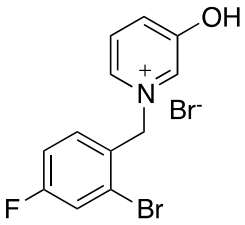
A solution of pyridinium salt **87** (8.43 g, 32.0 mmol, 1.0 eq.) was taken up in 3:1 THF/water and Amberlite IRA-420 resin was added. The reaction was stirred for 0.5 h, then the reaction mixture was filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel, eluting with 10% MeOH in DCM with 1 vol% NH_4OH afforded the title compound **106** (5.39 g, 29.1 mmol, 92%) as a yellow solid; $\boldsymbol{R_f}$ = 0.30, (10% MeOH in DCM 1 vol% NH_4OH). The NMR Data is in accordance with the literature.[71] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.59 (1H, s, Ar*H*), 7.90 (1H, d, *J* 5.8, Ar*H*), 7.77 (1H, dd, *J* 8.8, 2.3, Ar*H*), 7.54 (1H, dd, *J* 8.8, 5.8, Ar*H*), 7.45 – 7.37 (5H, m, Ar*H*), 5.70 (2H, s, NCH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.9 (*Ar*), 133.8 (*Ar*H), 133.2 (*Ar*), 132.4 (*Ar*H), 130.0 (*Ar*H), 129.7 (*Ar*H), 129.5(*Ar*H), 129.0 (*Ar*H), 127.7 (*Ar*H), 64.9 (N*C*H_2). **IR** ν_{max} (neat)/cm^{-1}: 3339 (O-H), 3035, 2992, 2864, 2751, 1495, 1454 (C=C), 1412; **HRMS** (ESI): $C_{12}H_{11}NO$ [M^+]: calculated 186.0913, found 186.0916.

3-Hydroxy-1-methylpyridin-1-ium iodide (**105**)[140]



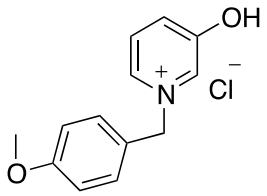
General procedure **A** was followed using 3-hydroxypyridine (3.00 g, 32 mmol, 1.0 eq.), iodomethane (2.00 mL, 32 mmol, 1.0 eq.) in 2-propanol (20 mL). *Title compound* **105** (7.50 g, 31.6 mmol, 99%) as an orange solid. The NMR data is in accordance with the literature.[140] **^{1}H NMR** (400 MHz, DMSO-d_6): 11.83 (1H, s, O*H*), 8.52 – 8.43 (2H, m, Ar*H*), 7.97 – 7.87 (2H, m, Ar*H*), 4.28 (3H, s, CH_3); **^{13}C NMR** (126 MHz, DMSO-d_6): 157.2 (*Ar*), 136.8 (*Ar*H), 134.2 (*Ar*H), 131.3 (*Ar*H), 128.7 (*Ar*H), 26.0 (*C*H_3); **IR** ν_{max} (neat)/cm^{-1}: 3023, 2967 (C-H), 1789, 1720 (C=O), 1635, 1553, 1510, 1495 (C=C); **HRMS** (ESI): C_6H_7NO [M-H]: calculated 110.0597, found 110.0600.

1-(2-Bromo-4-fluorobenzyl)-3-hydroxypyridin-1-ium bromide (**132**)



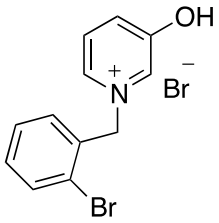
General procedure **A** was followed using 3-hydroxypyridine (1.50 g, 15.75 mmol) and 2-bromo-4-fluorobenzyl bromide (4.23 g, 15.75 mmol) in THF (25 mL). *Title compound* ***132*** (5.28 g, 14.5 mmol, 99%) as a colourless solid; **δ_H (400 MHz, DMSO-d_6)**: 11.98 (1H, s, O*H*), 8.61 – 8.56 (2H, m, Ar*H*), 8.08 – 7.98 (2H, m, Ar*H*), 7.78 (1H, dd, *J* 8.5, 2.7, Ar*H*), 7.58 (1H, dd, *J* 8.7, 5.9, Ar*H*), 7.42 (1H, td, *J* 8.5, 2.7, Ar*H*), 5.93 (2H, s, NCH_2); **δ_C (101 MHz, DMSO-d_6)**: 162.8 (d, *J* 251.2, *Ar*-F), 157.5 (*Ar*), 136.5 (*Ar*H), 133.9 (d, *J* 9.0, *Ar*H), 133.3 (*Ar*H), 132.8 (*Ar*H), 129.9 (d, *J* 3.1, *Ar*), 129.3 (*Ar*H), 124.9 (d, *J* 10.2, *Ar*), 121.2 (d, *J* 25.2, *Ar*H), 116.2 (d, *J* 21.3, *Ar*H), 62.9 (*C*H_2); **IR** ν_{max} (neat)/cm^{-1}: 3024 (CH), 2915, 2826, 2749, 1558 (C=C), 1479, 1456, 1433; **HRMS** (ESI): $C_{12}H_{10}Br^{79}FNO$ [M-H]: calculated 282.9997, found 282.9954

3-Hydroxy-1-(4-methoxybenzyl)pyridin-1-ium chloride (**128**)



General procedure **A** was followed using 3-hydroxypyridine (2.00 g, 21.0 mmol) and 4-methoxybenzyl chloride (2.80 mL, 21.0 mmol) in toluene (10 mL). *Title compound **128*** (5.21 g, 20.7 mmol, 99%) as a colourless solid. The NMR data is in accordance with the literature. [76] **δ_H(400 MHz, DMSO-*d*$_6$);** 8.78 (1H, m, Ar*H*), 8.68 (1H, m, Ar*H*), 8.12 – 8.02 (1H, m, Ar*H*), 7.94 (1H, m, Ar*H*), 7.64 – 7.45 (2H, m, Ar*H*), 7.04 – 6.97 (2H, m, Ar*H*), 5.71 (2H, s, C*H*$_2$), 3.76 (3H, s, O*Me*); **δ_C(101 MHz, DMSO-*d*$_6$);** 160.5 (*Ar*), 157.8 (*Ar*), 135.6 (*Ar*H), 132.9 (*Ar*H), 131.1 (*Ar*H), 129.4 (*Ar*H), 129.2 (*Ar*H), 126.7 (*Ar*), 115.0 (*Ar*H), 63.3 (*C*H$_2$), 55.7 (O*Me*); **IR** ν_{max} (neat)/cm^{-1}: 3040, 2992, 2904 (CH), 2446, 1571 (C=C), 1504, 1546, 1438; **HRMS** (ESI): $C_{13}H_{13}NO_2$ [M-H]: calculated 216.1019, found 216.1011.

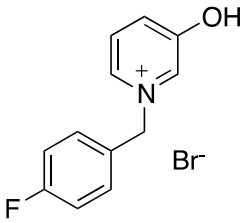
1-(2-Bromobenzyl)-3-hydroxypyridin-1-ium bromide (**131**)



General procedure **A** was followed using 3-hydroxypyridine (1.15 g, 12.0 mmol) and 2-bromobenzyl bromide (3.00 g, 12.0 mmol) in THF (19 mL). *Title compound* **131** (4.10 g, 11.9 mmol, 99%) as a colourless solid. The NMR data is in accordance with the literature.[141] **δ_H(400 MHz, DMSO-*d*$_6$);** 12.03 (1H, s, O*H*), 8.83 – 8.41 (2H, m, Ar*H*), 8.13 – 7.91 (2H, m, Ar*H*), 7.78 (1H, d, *J* 8.0, 1.2, Ar*H*), 7.54 – 7.46 (1H, m, Ar*H*), 7.43 (1H, td, *J* 7.7, 1.8, Ar*H*), 7.35 (1H, dd, *J* 7.6, 1.7, Ar*H*), 5.91 (2H, s, C*H*$_2$); **δ_C(101 MHz, DMSO-*d*$_6$);** 157.6 (*Ar*), 136.7 (*Ar*H), 133.9 (*Ar*H), 133.5 (*Ar*), 133.5 (*Ar*H), 132.8 (*Ar*H), 131.9 (*Ar*H), 131.7 (*Ar*H), 129.4 (*Ar*H), 129.2 (*Ar*H), 123.9 (*Ar*), 63.7 (*C*H$_2$); **IR** ν_{max} (neat)/cm^{-1}: 3404 (OH), 3008 (CH), 2993,

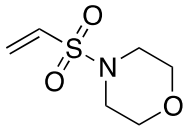
2947, 1584, 1508 (C=C), 1459, 1416; **HRMS** (ESI): $C_{12}H_{10}Br^{79}NO$ [M-H]: calculated 264.0019, found. 263.7976.

1-(4-Fluorobenzyl)-3-hydroxypyridin-1-ium bromide (**129**)



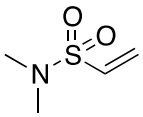
General procedure **A** was followed using 3-hydroxypyridine (2.28 mL, 24.1 mmol) and 4-fluorobenzyl bromide (3.00 mL, 24.1 mmol) in THF (14 mL). *Title compound **129*** (6.80 g, 23.9 mmol, 99%) as a white solid; **δ_H(400 MHz, DMSO-*d*$_6$)**; 11.97 (1H, s, O*H*), 8.92 – 8.59 (2H, m, Ar*H*), 8.26 – 7.90 (2H, m, Ar*H*), 7.82 – 7.54 (2H, m, Ar*H*), 7.43 – 7.05 (2H, m, Ar*H*), 5.81 (2H, s, CH_2); **δ_C(101 MHz, DMSO-*d*$_6$);** 163.0 (d, *J* 246.2, *Ar*F), 157.6 (*Ar*), 136.1 (*Ar*H), 133.1 (*Ar*H), 132.3 (*Ar*H), 131.9 (d, *J* 8.7, *Ar*H), 131.1 (d, *J* 3.1, *Ar*), 129.4 (*Ar*H), 116.6 (d, *J* 21.7, *Ar*H), 62.7 (*C*H_2); **IR** ν_{max} (neat)/cm^{-1}: 3061, 2872, 2830 (CH), 2510, 1604, 1578 (C=C), 1506, 1487; **HRMS** (ESI): $C_{12}H_{10}FNO$ [M-H]: calculated 204.0819, found 204.0816.

4-(Vinylsulfonyl)morpholine (**119**)



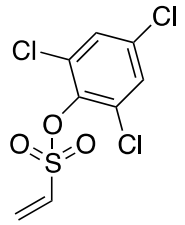
General procedure **C** was followed using morpholine (1.75 mL, 20.1 mmol), 2-chloroethanesulfonyl chloride **30** (1.9 mL, 18.4 mmol), and NEt_3 (2.90 mL, 20.1 mmol) in DCM (40 mL). Purification by flash chromatography on silica gel, eluting with a gradient of 70% EtOAc in hexane afforded the *title compound **119*** (1.00 g, 5.64 mmol, 31%) as a colourless oil; ***R*$_f$** = 0.28, (40% EtOAc in hexane); **δ_H(400 MHz, Chloroform-*d*):** 6.44 (1H, dd, *J* 16.6, 9.9, C*H*), 6.26 (1H, d, *J* 16.6, CH_2), 6.10 (1H, d, *J* 9.9, CH_2), 3.81 – 3.72 (4H, m, OCH_2CH_2), 3.18 – 3.09 (4H, m, NCH_2CH_2); **δ_C(101 MHz, Chloroform-*d*):** 131.8 (*C*H), 129.5 (*C*H_2), 66.2 (OCH_2CH_2), 45.6 (NCH_2CH_2); **IR** ν_{max} (neat)/cm^{-1}: 3105 (CH), 3057, 2972, 2899, 1610 (C=C), 1455, 1343 (S=O); **HRMS** (ESI): $C_6H_{12}NO_3S$ [M+H$^+$]: calculated 178.0532, found 178.0530.

N,*N*-Dimethylethenesulfonamide (**121**)



General procedure **C** was followed using dimethylamine (2M in THF) (24.0 mL, 48.0 mmol), 2-chloroethanesulfonyl chloride (3.00 mL, 28.7 mmol), NEt_3 (6.00 mL, 43.0 mmol) in DCM (90 mL). Purification by flash chromatography on silica gel, eluting with a gradient of 70% EtOAc in hexane afforded the *title compound **121*** (2.59 g, 19.1 mmol, 67%) as a yellow oil; $\boldsymbol{R_f}$ 0.57, (70% EtOAc in hexane); **δ_H(300 MHz, Chloroform-*d*):** 6.45 (1H, dd, *J* 16.6, 9.9, C*H*), 6.25 (1H, d, *J* 16.6, CH_2), 6.06 (1H, d, *J* 9.9, CH_2), 2.80 (6H, s, N*Me*$_2$); **δ_C(101 MHz, Chloroform-*d*):** 131.4 (*C*H), 128.6 (*C*H_2), 37.5 (N*Me*$_2$); **IR** ν_{max} (neat)/cm^{-1}: 3105, 3058 (C-H), 3019, 2967, 2885, 2813, 1461 (C=C), 1333 (S=O); **HRMS** (ESI): $C_4H_{10}NO_2S$ [$M+H^+$]: calculated 136.0427, found 136.0635;

2,4,6-Trichlorophenyl ethenesulfonate (**120**)[75]

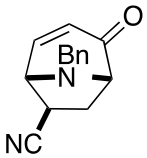


General procedure **C** was followed using 2,4,6-trichlorophenol (1.99 g, 10.0 mmol, 1.0 eq.), NEt_3 (31 mL, 22 mmol, 2.2 eq.), and 2-chloroethanesulfonyl chloride (11.5 mL, 11.0 mmol, 1.1 eq.) in DCM (250 mL). Purification through a plug of 10% K_2CO_3/silica with DCM (250 mL). *Title compound **120*** (7.70 g, 21.8 mmol, 70%) as a colourless solid; $\boldsymbol{R_f}$ = 0.40, (30% EtOAc in hexane). The data is in accordance with the literature.[75] **^{1}H NMR** (400 MHz, $CDCl_3$) 7.40 (2H, s, Ar*H*), 6.94 (1H, dd, *J* 16.5, 9.9, C*H*), 6.56 (1H, dd, *J* 16.5, 0.9, CH_2), 6.26 (1H, dd, *J* 9.9, 0.9, CH_2). **^{13}C NMR** (101 MHz, $CDCl_3$): 142.0 (*Ar*), 133.9 (*Ar*H), 133.1 (2-*C*H), 131.3 (*Ar*), 130.8 (*Ar*), 129.2 (1-*C*H_2); **IR** ν_{max} (neat)/cm^{-1}: 3114, 3073, 2980 (C-H), 2498 (C=C), 1613, 1561, 1441 (C=C), 1374 (S=O); **HRMS** (ESI): $C_8H_6Cl_3O_3S$ [$M+H^+$]: calculated 285.9025, found 285.9025.

8-Benzyl-2-oxo-8-azabicyclo[3.2.1]oct-3-ene-6-carbonitrile and
8-Benzyl-2-oxo-8-azabicyclo[3.2.1]oct-3-ene-7-carbonitrile (**109)**

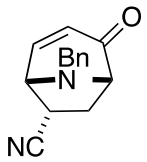
To a solution of compound **87** (1.00 g, 3.76 mmol, 1.0 eq.) was added acrylonitrile (7.30 mL, 113 mmol, 30 eq.), hydroquinone (10 mg, 0.08 mmol, 0.02 eq.) and triethylamine (1.05 mL, 7.52 mmol, 2.0 eq.). The reaction mixture was heated at reflux for 16 h, cooled to rt and concentrated *in vacuo*. Purification by flash chromatography on silica gel, eluting with 40% EtOAc in hexane, to give in order of elution, *compound **109a*** (242 mg, 1.02 mmol, 27%) as a brown oil; $\boldsymbol{R_f}$ = 0.28 (40% EtOAc in hexane), followed by *compound **109b*** (161 mg, 0.68 mmol, 18%) as a brown oil; $\boldsymbol{R_f}$ = 0.29 (40% EtOAc in hexane). The product was a mix of inseparable isomers and the major diagnostic peaks were used to report the ratio of isomers, 4:4:2:1. The NMR data is in accordance with the literature[142] and the major peaks are reported:

(1*S**,5*S**,6*R**)-8-Benzyl-2-oxo-8-azabicyclo[3.2.1]oct-3-ene-6-carbonitrile (**109a)**



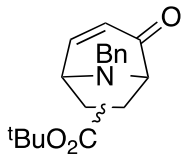
^{1}H NMR (400 MHz, $CDCl_3$): 7.40 – 7.20 (5H, m, Ar*H*), 6.91 (1H, dd, *J* 9.8, 5.0, 4-C*H*), 6.15 (1H, dd, *J* 9.8, 1.6, 3-C*H*), 4.02 (1H, d, *J* 5.0, 5-C*H*), 3.92 (1H, d, *J* 13.3, N*C*H_2), 3.81 (1H, d, *J* 13.3, N*C*H_2), 3.78 – 3.70 (1H, m, 1-C*H*), 2.99 (1H, dd, *J* 9.3, 3.4, 6-C*H*), 2.76 (1H, ddd, *J* 14.0, 7.9, 3.4, 7-CH_2), 2.15 (1H, ddd, *J* 14.0, 9.3, 0.9, 7-CH_2). **^{13}C NMR** (101 MHz, $CDCl_3$): 194.6 (*C*=O), 150.1 (4-*C*H), 136.8 (*Ar*), 129.0 (3-*C*H), 128.7 (*Ar*H), 128.6 (*Ar*H), 127.8 (*Ar*H), 119.1 (*C*N), 71.4 (1-*C*H), 57.4 (5-*C*H), 53.4 (NC$H_{2)}$, 34.3 (6-*C*H), 26.3 (7-*C*H_2); **IR** ν_{max} (neat)/cm^{-1}: 3027, 2953 (C-H), 2843, 1733 (C=O), 1683, 1495, 1454 (C=C), 1435; **HRMS** (ESI): $C_{15}H_{15}N_2O$ [M+H^+]: calculated 239.1180, found 239.1179.

(1*S**,5*S**,6*S**)-8-Benzyl-2-oxo-8-azabicyclo[3.2.1]oct-3-ene-6-carbonitrile (**109b**)



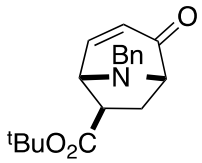
^{1}H NMR (501 MHz, $CDCl_3$): 7.41 – 7.18 (5H, m, Ar*H*), 7.07 (1H, dd, *J* 9.9, 5.0, 4-C*H*), 6.33 (1H, dd, *J* 9.9, 1.5, 3-C*H*), 3.99 – 3.96 (1H, m, 5-C*H*), 3.73 (1H, d, *J* 13.0, N*C*H_2), 3.70 (1H, d, *J* 13.0, N*C*H_2), 3.65 (1H, ddt, *J* 7.9, 1.9, 1.0, 1-C*H*), 3.38 (1H, dt, *J* 10.4, 6.0, 6-C*H*), 2.86 (1H, ddd, *J* 13.9, 10.4, 7.9, 7-C*H*$_2$), 1.96 (1H, ddd, *J* 13.9, 6.0, 1.1, 7-C*H*$_2$); **^{13}C NMR** (126 MHz, $CDCl_3$): 197.2 (*C*=O), 145.7 (4-*C*H), 136.8 (*Ar*), 130.0 (3-*C*H), 128.7 (*Ar*H), 128.6 (*Ar*H), 127.9 (*Ar*H), 119.4 (*C*N), 68.2 (1-*C*H), 58.9 (5-*C*H), 53.1 (NC*H*$_2$), 30.8 (6-*C*H), 30.1 (7-*C*H_2); **IR** ν_{max} (neat)/cm^{-1}: 3063, 3030, 2958 (C-H), 2844, 1759, 1683 (C=O), 1495, 1435 (C=C); **HRMS** (ESI): $C_{15}H_{15}N_2O$ [M+H$^+$]: calculated 239.1180, found 239.1179.

tert-Butyl 8-benzyl-2-oxo-8-azabicyclo[3.2.1]oct-3-ene-6-carboxylate and
tert-Butyl 8-benzyl-2-oxo-8-azabicyclo[3.2.1]oct-3-ene-7-carboxylate (**112**)[97]



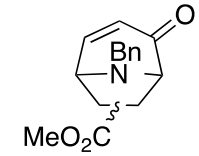
To a solution of compound **87** (250 mg, 1.35 mmol, 1.2 eq.) in anhydrous 1,4-dioxane (3 mL) was added *tert*-butyl acrylate (0.46 mL, 3.13 mmol, 1.0 eq.) and triethylamine (1.30 mL, 9.40 mmol, 3.0 eq.). The reaction mixture was heated at reflux for 16 h, cooled to rt and concentrated *in vacuo*. Purification by flash chromatography on silica gel, eluting with 30% EtOAc in hexane to give *compound **112a*** (640 mg, 2.04 mmol, 65%) as a brown oil; $\boldsymbol{R_f}$ = 0.50, (30% EtOAc in hexane). The product was a mix of inseparable isomers and the major diagnostic peaks were used to report the ratio of isomers, 8:3:3:2. Data for the major isomer is reported:

(1*S**,5*S**,6*R**)-*tert*-Butyl 8-benzyl-2-oxo-8-azabicyclo[3.2.1]oct-3-ene-6-carboxylate (**112a**)[97]



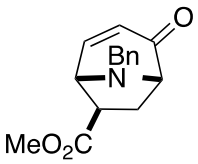
^{1}H NMR (501 MHz, $CDCl_3$): 7.36 – 7.21 (5H, m, Ar*H*), 6.95 (1H, dd, *J* 9.8, 5.0, 4-C*H*), 6.08 (1H, dd, *J* 9.8, 1.6, 3-C*H*), 3.97 (1H, d, *J* 5.0, 5-C*H*), 3.85 (1H, d, *J* 13.4, N*C*H$_2$), 3.73 – 3.65 (1H, m, N*C*H$_2$), 3.47 (1H, dt, *J* 10.3, 6.1, 6-C*H*), 2.91 (1H, ddd, *J* 13.8, 8.0, 3.5, 7-C*H*), 2.84 (1H, dd, *J* 9.2, 3.4, 1-C*H*$_2$), 1.84 (1H, ddd, *J* 13.8, 9.2, 0.9, 7-C*H*$_2$), 1.44 (9H, s, ^{t}Bu); **^{13}C NMR** (126 MHz, $CDCl_3$): 199.3 (*C*=O), 171.7 (*C*=O), 147.7 (4-*C*H), 138.2 (*Ar*), 128.4 (*Ar*H), 128.4 (*Ar*H), 128.3 (*Ar*H), 128.3 (3-*C*H), 81.2 (*C*), 69.0 (1-*C*H), 60.1 (5-*C*H), 51.9 (N*C*H$_2$), 48.2 (6-*C*H), 28.1 (*^{t}Bu*), 27.5 (7-*C*H$_2$); **IR** ν_{max} (neat)/cm^{-1}: 3029, 2976 (C-H), 1722 (C=O), 1682, 1604, 1585, 1495, 1453 (C=C); **HRMS** (ESI): $C_{19}H_{23}NNaO_3$ [M+Na]: calculated 336.1571, found 336.1570.

Methyl 8-benzyl-2-oxo-8-azabicyclo[3.2.1]oct-3-ene-6-carboxylate and
Methyl 8-benzyl-2-oxo-8-azabicyclo[3.2.1]oct-3-ene-7-carboxylate(**110**)[73]



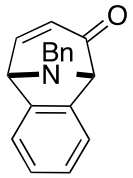
To a solution of compound **87** (1.00 g, 3.76 mmol, 1.0 eq.) was added methyl acrylate (3.30 mL, 37.6 mmol, 10 eq.), hydroquinone (10 mg, 0.07 mmol, 0.02 eq.) and triethylamine (1.05 mL, 7.52 mmol, 2.0 eq.). The reaction mixture was heated neat at reflux for 16 h, cooled to rt and concentrated *in vacuo*. Purification by flash chromatography on silica gel, eluting with 20% EtOAc in hexane to give *compound **110*** (939 mg, 3.46 mmol, 92%) as a brown oil; $\boldsymbol{R_f}$ = 0.16, (20% EtOAc in hexane). The product was a mix of inseparable stereo/regioisomers and the major diagnostic peaks were used to report the ratio of isomers, 6:4:1:2. Only major listed, ^{1}H NMR data was in accordance with the literature:[73]

(1*S**,5*S**,6*R**)-Methyl 8-benzyl-2-oxo-8-azabicyclo[3.2.1]oct-3-ene-6-carboxylate (**110a**)[73]



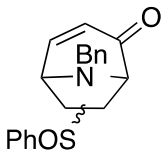
^{1}H NMR (400 MHz, $CDCl_3$): 7.40 – 7.19 (5H, m, Ar*H*), 6.98 (1H, dd, *J* 9.8, 5.0, 4-C*H*), 6.15 – 6.08 (1H, m, 3-C*H*), 4.08 (1H, d, *J* 5.0, 5-C*H*), 3.84 (1H, d, *J* 13.5, N*C*H$_2$), 3.79 – 3.51 (5H, m, N*C*H$_2$, O*C*H$_3$, 1-C*H*), 3.01 – 2.88 (2H, m, 6-C*H*, 7-C*H*$_2$), 1.98 – 1.90 (1H, m, 7-C*H*$_2$). **^{13}C NMR** (101 MHz, $CDCl_3$) 198.8 (*C*=O), 173.1 (*C*=O), 147.5 (4-*C*H), 137.9 (*Ar*), 128.6 (*Ar*H), 128.6 (*Ar*H), 128.5 (3-CH), 128.4 (*Ar*H), 68.5 (1-*C*H), 60.0 (5-*C*H), 52.3 (O*C*H$_3$), 52.0 (N*C*H$_2$), 47.0 (6-*C*H), 27.9 (7-*C*H$_2$). **IR** ν_{max} (neat)/cm^{-1}: 3029, 2976 (C-H), 1722, 1683 (C=O), 1604, 1585, 1495, 1454 (C=C); **HRMS** (ESI): $C_{16}H_{18}NO_3$ [M+H$^+$]: calculated 272.1289, found 272.1289.

(5*S**,9*S**)-Dihydro-10-(phenylmethyl)-6*H*-benzocycloheptene-5,9-imin-6-one (**108**) [71]



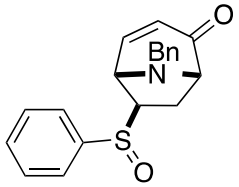
To a stirred solution of compound **106** (478 mg, 3.35 mmol, 1.0 eq.), in anhydrous MeCN (13 mL) was added 2-(trimethylsilyl)phenyltrifluoromethanesulfonate (1.00 g, 3.35 mmol, 1.3 eq.) and caesium fluoride (3.90 g, 8.56 mmol, 9.9 eq.). The reaction mixture was stirred for 24 h, then concentrated *in vacuo.* The resulting mixture was diluted with water (10 mL) and EtOAc (10 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography on silica gel, eluting with 20% EtOAc in hexane afforded the title *compound **108*** (17 mg, 0.07 mmol, 20%) as a yellow oil; $\boldsymbol{R_f}$ = 0.33, (10% EtOAc in hexane). NMR Data is in accordance with the literature.[71] **^{1}H NMR** (400 MHz, $CDCl_3$): 7.69 – 6.94 (10H, m, Ar*H*, 8-C*H*), 5.58 (1H, dd, *J* 9.7, 1.4, 7-C*H*), 4.46 (1H, s, 5-C*H*), 4.45 (1H, d, *J* 5.5, 9-C*H*), 3.78 (2H, s, N*C*H$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) 194.6 (*C*=O), 151.1(8-*C*H), 145.9 (*C*), 138.6 (*C*), 137.4 (*C*), 129.1 (*Ar*H), 128.6 (*Ar*H), 127.7 (*Ar*H), 127.6 (*Ar*H), 127.3 (*Ar*H), 126.0 (*Ar*H), 123.1 (7-*C*H), 123.0 (*Ar*H), 76.8 (5-*C*H), 64.7 (9-*C*H), 56.1 (N*C*H$_2$); **IR** ν_{max} (neat)/cm^{-1}: 3063, 3028, 2965 (C-H), 2836, 1756, 1681 (C=O), 1495, 1454 (C=C); **HRMS** (ESI): $C_{18}H_{16}NO$ [M+H$^+$]: calculated 261.1154, found 262.1241.

8-Benzyl-6-(phenylsulfinyl)-8-azabicyclo[3.2.1]oct-3-en-2-one and
8-benzyl-7-(phenylsulfinyl)-8-azabicyclo[3.2.1]oct-3-en-2-one (**111**)[72]



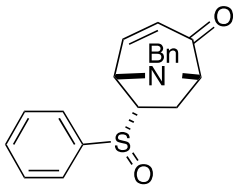
To a solution of compound **87** (250 mg, 1.35 mmol, 1.0 eq.) in anhydrous THF (4 mL) was added phenylvinylsulfoxide (0.18 mL, 1.35 mmol, 1.0 eq.), hydroquinone (3.00 mg, 0.03 mmol, 0.02 eq.) and triethylamine (0.34 mL, 2.70 mmol, 2.0 eq.). The reaction mixture was heated at reflux for 4 d, cooled to rt and concentrated *in vacuo*. Purification by flash chromatography on silica gel, eluting with 20 % EtOAc in hexane. To give in order of elution, *compound **108a*** (81 mg, 0.24 mmol, 18%) as a yellow solid; $\boldsymbol{R_f}$ = 0.40 (20% EtOAc in Hexane), followed by *compound **108b*** (25 mg, 0.07 mmol, 6%) as a yellow solid; $\boldsymbol{R_f}$ = 0.45 (20% EtOAc in Hexane). The product was a mix of inseparable stereo/regioisomers and the major diagnostic peaks were used to report the data and the ratio of isomers, 8:5:3:1:

(1*S**,5*S**,6*R**)-8-Benzyl-6-phenylsulfinyl)-8-azabicyclo[3.2.1]oct-3-en-2-one (**108**) [72]



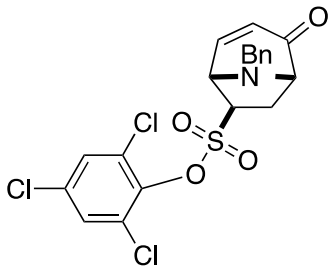
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.73 (1H, m, Ar*H*), 7.65 – 7.39 (4H, m, Ar*H*), 7.40 – 7.22 (5H, m, Ar*H*), 6.98 (1H, dd, *J* 9.8, 5.0, 4-C*H*), 6.15 (1H, dd, *J* 9.8, 1.5, 3-C*H*) ,4.39 (1H, d, *J* 5.0, 5-C*H*), 3.96 – 3.83 (1H, m, N*C*H_2), 3.81 – 3.65 (1H, m, N*C*H_2), 3.61 (1H, d, *J* 7.5, 6-C*H*), 3.25 (1H, dd, *J* 8.5, 3.2, 1-C*H*), 2.12 (1H, ddd, *J* 14.6, 7.5, 3.2, 7-CH_2), 1.58 (1H, dd, *J* 14.6, 8.5, 7-CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) 198.0 (*C*=O), 145.9 (4-*C*H), 143.0 (*C*), 137.6 (*C*), 132.0 (3-*C*H), 129.5 (*Ar*H), 128.6 (*Ar*H), 128.5 (*Ar*H), 127.6 (*Ar*H), 125.4 (*Ar*H), 124.7 (*Ar*H), 69.1 (6-*C*H), 67.6 (5-*C*H), 57.7 (1-*C*H), 51.7 (N*C*H_2), 26.3 (7-*C*H_2). **IR** ν_{max} (neat)/cm^{-1}: 3065, 2981 (C-H), 2954, 2926, 1682 (C=O), 1605, 1465 (C=C), 1380 (S=O).

(1*S**,5*S**,6*S**)-8-Benzyl-6-phenylsulfinyl)-8-azabicyclo[3.2.1]oct-3-en-2-one (**108b**) [72]



^{1}H NMR (400 MHz, $CDCl_3$) 7.75 – 7.66 (2H, m, Ar*H*), 7.70 – 7.43 (3H, m, Ar*H*), 7.39 – 7.16 (6H, m, Ar*H*, 4-C*H*), 6.41 (1H, dd, *J* 9.8, 1.5, 3-C*H*), 4.27 – 4.12 (1H, m, 5-C*H*), 3.93 – 3.66 (3H, m, N*C*H_2, 6-C*H*, 1-C*H*), 3.59 (1H, dd, *J* 8.0, 1.4, N*C*H_2), 2.17 (1H, ddd, *J* 14.2, 9.8, 7.7, 7-C*H*$_2$), 1.53 – 1.40 (1H, m, 7-C*H*$_2$). **^{13}C NMR** (101 MHz, $CDCl_3$) 197.9 (C=O), 146.6 (4-*C*H), 143.0 (*C*), 137.1 (*C*), 130.5 (3-*C*H), 129.6 (*Ar*H), 129.4 (*Ar*H), 128.6 (*Ar*H), 127.7 (*Ar*H), 125.1 (*Ar*H), 124.8 (*Ar*H), 69.7 (6-*C*H), 68.7 (5-*C*H), 59.5 (1-*C*H), 52.9 (N*C*H_2), 25.7 (7-*C*H_2). **IR** ν_{max} (neat)/cm^{-1}: 3065, 2981 (C-H), 2954, 2926, 1682 (C=O), 1605, 1465 (C=C), 1380 (S=O).

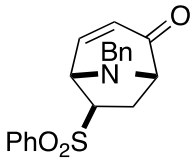
(1*S**,5*S**,6*R**)-2,4,6-Trichlorophenyl-8-benzyl-2-oxo-8-azabicyclo[3.2.1]oct-3-ene-6-sulfonate (**138**)



To a solution of compound **87** (250 mg, 1.35 mmol, 1.0 eq.) in anhydrous THF (4 mL) was added 2,4,6-trichlorophenyl ethenesulfonate (227 mg, 1.35 mmol, 1.0 eq.), hydroquinone (3 mg, 0.03 mmol, 0.02 eq.) and triethylamine (0.34 mL, 2.70 mmol, 2.0 eq.). The reaction mixture was heated at reflux for 16 h then cooled to rt and concentrated *in vacuo*. Purification by flash chromatography on silica gel, eluting with 5% EtOAc in hexane. Crystallization from EtOAc afforded the *title compound **138*** (207 mg, 0.59 mmol, 43%) as a yellow solid; $\mathbf{R_f}$ = 0.40 (20% EtOAc in hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) 7.41 (2H, s, Ar*H*), 7.37 – 7.23 (5H, m, Ar*H*), 6.98 (1H, dd, *J* 9.8, 5.0, 4-C*H*), 6.23 (1H, dd, *J* 9.8, 1.5, 3-C*H*), 4.40 (1H, d, *J* 5.0, 5-C*H*), 4.16 (1H, dd, *J* 9.1, 4.6, 6-C*H*), 3.95 (1H, d, *J* 13.5, NC*H*$_2$), 3.84 (1H, d, *J* 13.5, NC*H*$_2$), 3.81 (1H, d, *J* 7.6, 1-C*H*), 3.13 (1H, ddd, *J* 14.6, 7.6, 4.2, 7-C*H*$_2$), 2.31 (1H, dd, *J* 14.6, 9.1, 7-C*H*$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) 197.5 (*C*=O), 144.5 (4-*C*H), 141.8 (*Ar*), 137.0 (*Ar*), 133.2 (*Ar*), 130.5 (*Ar*), 129.6 (3-*C*H), 129.3 (*Ar*H), 128.6 (*Ar*H), 128.3 (*Ar*H), 127.6 (*Ar*H), 67.8 (1-

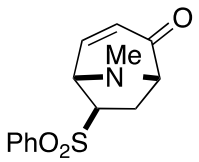
*C*H), 66.0 (6-*C*H), 58.6 (5-*C*H), 51.5 (N*C*H$_2$), 28.5 (7-*C*H$_2$); **IR** ν_{max} (neat)/cm^{-1}: 3087, 3032, 2945 (CH), 2890, 2833, 1688 (C=O), 1441 (C=C) 1323 (S=O); **HRMS** (ESI): $C_{20}H_{16}{}^{35}Cl_3NO_4S$ [M+]: calculated 471.9944, found 471.9938.

(1*S**,5*S**,6*R**)-8-Benzyl-6-(phenylsulfonyl)-8-azabicyclo[3.2.1]oct-3-en-2-one (**89**)[73]



General procedure **B** was followed using compound **87** (8.30 g, 31.2 mmol, 1.0 eq.), phenyl vinyl sulfone (5.24 g, 31.2 mmol, 1.0 eq.), hydroquinone (0.07 g, 0.62 mmol, 0.02 eq.) and triethylamine (8.60 mL, 62.3 mmol, 2.0 eq.) in anhydrous THF (154 mL). Crystallization from EtOAc twice afforded the *title compound **89*** (7.70 g, 21.8 mmol, 70%) as a yellow solid; $\boldsymbol{R_f}$ = 0.40 (30% EtOAc in hexane). The NMR data is in accordance with the literature.[73] **^{1}H NMR** (400 MHz, $CDCl_3$) 7.91 – 7.83 (2H, m, Ar*H*), 7.73 – 7.64 (1H, m, Ar*H*), 7.61 – 7.51 (2H, m, Ar*H*), 7.33 – 7.21 (3H, m, Ar*H*), 7.11 – 7.04 (2H, m, Ar*H*), 6.92 (1H, dd, *J* 9.8, 5.0, 4-C*H*), 6.13 (1H, dd, *J* 9.8, 1.5, 3-C*H*), 4.17 (1H, d, *J* 5.0, 5-C*H*), 3.79 (1H, d, *J* 13.2, N*C*H$_2$), 3.68 (1H, d, *J*13.2, N*C*H$_2$), 3.64 – 3.55 (2H, m, 6-C*H*, 1-C*H*), 2.80 (1H, ddd, *J* 14.4, 7.7, 4.6, 7-C*H*$_2$), 2.01 (1H, dd, *J* 14.4, 9.3, 7-C*H*$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$): 197.6 (*C*=O), 145.6 *(C*), 138.1 (*C*), 137.0 (4-*C*H), 133.9 (*Ar*H), 129.4 (*Ar*H), 129.0 (3-*C*H), 129.0 (*Ar*H), 128.5 (*Ar*H), 128.5 (*Ar*H), 127.5 (*Ar*H), 77.2 (6-*C*H), 68.0 (5-*C*H), 58.1 (1-*C*H), 51.6 (N*C*H$_2$), 27.3 (7-*C*H$_2$); **IR** ν_{max} (neat)/cm^{-1}: 3169, 3036, 2967 (C=H), 2927, 1672 (C=O), 1477, 1448 (C=C), 1315 (S=O); **HRMS** (ESI): $C_{20}H_{20}NO_3S$ [M+H$^+$]: calculated 354.1155, found 354.1158.

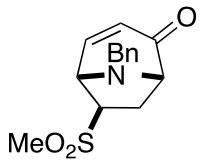
(1*S**,5*S**,6*R**)-8-Methyl-6-(phenylsulfonyl)-8-azabicyclo[3.2.1]oct-3-en-2-one (**115**)



General procedure **B** was followed using compound **105** (780 mg, 5.94 mmol, 1.0 eq.), phenyl vinyl sulfone (1.00 g, 5.95 mmol, 1.0 eq.), hydroquinone (10 mg, 0.62 mmol, 0.02 eq.) and triethylamine (1.70 mL, 11.9 mmol, 2.0 eq.) in anhydrous THF (2.3 mL). Purification by flash chromatography on silica gel, eluting with 30% EtOAc in hexane. Crystallization from EtOAc afforded the *title compound **115*** (330 mg, 1.19 mmol, 20%) as a yellow solid; $\boldsymbol{R_f}$ = 0.40, (30% EtOAc in hexane.). The NMR data is in accordance with the literature. [73,143] **^{1}H NMR** (400

MHz, $CDCl_3$) 7.88 – 7.81 (2H, m, Ar*H*), 7.65 – 7.56 (1H, m, Ar*H*), 7.56 – 7.46 (2H, m, Ar*H*), 6.86 (1H, dd, *J* 9.8, 5.0, 4-C*H*), 5.99 (1H, dd, *J* 9.8, 1.5, 3-C*H*), 4.16 (1H, d, *J* 4.9, 5-C*H*), 3.54 – 3.43 (2H, m, 6-C*H*, 1-C*H*), 2.70 (1H, ddd, *J* 14.3, 7.7, 4.4, 7-CH_2), 2.31 (3H, s, CH_3), 1.85 (1H, dd, *J* 14.3, 9.1, 7-CH_2). **^{13}C NMR** (101 MHz, $CDCl_3$): 197.7 (*C*=O), 145.4 (4-*C*H), 138.2 (*Ar*), 134.0 (*Ar*), 129.3 (*Ar*), 128.7 (*Ar*), 128.5 (3-*C*H), 69.9 (6-*C*H), 67.7 (1-*C*H), 60.2 (5-*C*H), 34.5 (N*Me*), 27.8 (7-*C*H_2). **IR** ν_{max} (neat)/cm^{-1}: 3060, 3029, 2945 (C-H), 2899, 1721 (C=O), 1496, 1448 (C=C), 1369 (S=O); **HRMS** (ESI): $C_{14}H_{16}NO_3S$ [M+H^+]: calculated 278.0845, found 278.0845.

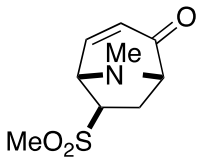
(1*S**,5*S**,6*R**)-8-Benzyl-6-(methylsulfonyl)-8-azabicyclo[3.2.1]oct-3-en-2-one (**117**)



General procedure **B** was followed using methyl vinyl sulfone (3.4 mL, 38.8 mmol) and benzyl salt **87** (14.0 g, 52.4 mmol), triethylamine (11 mL, 77.6 mmol). Purification by crystallization from EtOAc afforded the *title compound **117*** (6.40 g, 22.0 mmol, 57%) as a yellow solid; ***R*$_f$** = 0.57, (100% EtOAc in hexane); **M.Pt.** 132.1 – 133.0 ^oC; **δ_H(400 MHz, Chloroform-*d*)** 7.36 – 7.20 (3H, m, Ar*H*), 7.12 (2H, dd, *J* 7.6, 1.8, Ar*H*), 6.93 (1H, dd, *J* 9.8, 5.0, 4-C*H*), 6.16 (1H, dd, *J* 9.8, 1.5, 3-C*H*), 4.02 (1H, d, *J* 5.0, 5-C*H*), 3.77 (1H, d, *J* 12.7, N*Bn*), 3.71 (1H, d, *J* 12.7, N*Bn*), 3.65 (1H, d, *J* 7.9, 6-C*H*), 3.34 (1H, dd, *J* 9.5, 4.1, 1-C*H*), 2.80 (3H, s, *Me*), 2.63 (1H, ddd, *J* 15.0, 7.9, 4.1, 7-CH_2), 2.16 (1H, dd, *J* 15.0, 9.5, 7-CH_2); **δ_C(75 MHz, Chloroform-*d*):** 197.0 (*C*=O), 144.7 (4-*C*), 136.7 (*Ar*), 129.1 (*Ar*H), 128.8 (*Ar*H), 128.7 (*Ar*H), 128.0 (3-*C*), 67.7 (1-*C*), 66.5 (1-*C*), 58.0 (5-*C*), 51.7 (N*Bn*), 38.1 (*Me*), 27.8 (7-*C*H_2); **IR** ν_{max} (neat)/cm^{-1}: 3032, 3003 (CH), 2934, 2847, 1675 (C=O), 1497 (C=C), 1451, 1292 (S=O); **HRMS** (ESI): $C_{15}H_{18}NO_3S$ [M+H^+]: calculated 292.1002, found 292.1003.

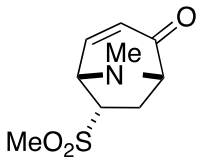
(1*S**,5*S**,6*R**)-8-Methyl-6-(methylsulfonyl)-8-azabicyclo[3.2.1]oct-3-en-2-one (**116a**)

.



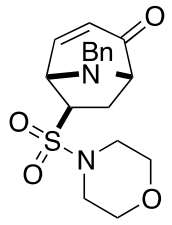
General procedure **C** was followed using methyl vinyl sulfone (4.2 mL, 47.6 mmol) and salt **105** (14.7 g, 61.9 mmol), silver oxide (20 g, 85.7 mmol). Purification by flash chromatography on silica gel, eluting with a gradient of 60 - 100% EtOAc in hexane afforded the major *title compound **20a*** (6.40 g, 29.7 mmol, 67%) as a yellow solid; $\boldsymbol{R_f}$ = 0.22, (60% EtOAc in hexane). Recrystallisation from EtOAc afforded the *title compound **116***; **M.Pt.** 110.0 – 111.7 ºC; **δ_H(400 MHz, Methanol-*d*$_4$): δ** 6.98 (1H, dd, *J* 9.8, 5.0, 4-C*H*), 5.98 (1H, dd, *J* 9.8, 1.6, 3-C*H*), 4.10 (1H, d, *J* 5.0, 5-C*H*), 3.54 (1H, dd, *J* 9.3, 4.1, 6-C*H*), 3.48 (1H, d, *J* 7.7, 1-C*H*), 2.89 (3H, s, N*Me*), 2.68 (1H, ddd, *J* 14.7, 7.7, 4.1, 7-C*H*), 2.37 (3H, s, *Me*), 2.03 (1H, d, *J* 14.7, 9.3, 7-C*H*); **δ_C(101 MHz, Methanol-*d*$_4$): δ** 197.3 (*C*=O), 146.0 (4-*C*H), 127.4 (3-*C*H), 69.5 (6-*C*H), 66.0 (1-*C*H), 60.3 (5-*C*H), 37.4 (*Me*), 33.1 (N*Me*), 27.2 (7-*C*H$_2$); **IR** ν_{max} (neat)/cm^{-1}: 3052, 2980 (C-H), 2919, 2847, 1681 (C=O), 1468 (C=C), 1453, 1291 (S=O); **HRMS** (ESI): $C_9H_{14}NO_3S$ [M+H$^+$]: calculated 216.0689, found 216.0692.

(1*S**,5*S**,6*S**)-8-Methyl-6-(methylsulfonyl)-8-azabicyclo[3.2.1]oct-3-en-2-one (**116b)**



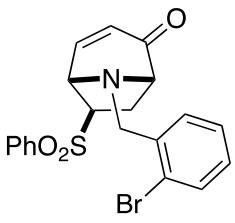
Purification by flash chromatography on silica gel, eluting with a gradient of 60 - 100% EtOAc in hexane afforded the minor *title compound **20b*** (500 mg, 2.32 mmol, 67%) as a yellow solid; $\boldsymbol{R_f}$ = 0.14, (60% EtOAc in hexane); **δ_H(400 MHz, Chloroform-*d*):** 6.97 (1H, dd, *J* 9.5, 5.0, 4-C*H*), 5.98 (1H, dd, *J* 9.9, 1.5, 3-C*H*), 3.82 (1H, t, *J* 5.0, 5-C*H*), 3.77 (1H, d, *J* 1.5, 6-C*H*), 3.25 (1H, *J* 8.0, at, 1-C*H*), 2.92 (3H, s, N*Me*), 2.58 (1H, dt, *J* 13.0, 6.3, 7-C*H*$_2$), 2.44 (3H, s, *Me*), 2.23 (1H, dd, *J* 13.0, 9.5, 7-C*H*$_2$). **δ_C(101 MHz, Chloroform-*d*):** 194.5 (*C*=O), 149.1 (4-*C*H), 126.8 (3-*C*H), 71.6 (6-*C*H), 63.0 (1-*C*H), 59.8 (5-*C*H), 39.4 (*Me*), 35.5 (N*Me*), 31.2 (7-*C*H$_2$); **IR** ν_{max} (neat)/cm^{-1}: 3023, 2958 (C-H), 2939, 2895, 1679 (C=O), 1453 (C=C), 1408, 1321 (S=O); **HRMS** (ESI): $C_9H_{14}NO_3S$ [M+H$^+$]: calculated 216.0689, found 216.0691.

(1*S**,5*S**,6*R**)-8-Benzyl-6-(morpholinosulfonyl)-8-azabicyclo[3.2.1]oct-3-en-2-one (**133**)



General procedure **B** was followed using sulfone **119** (999 mg, 5.64 mmol) and benzylpyridinium salt **87** (1.95 g, 7.33 mmol), trimethylamine (2.00 mL, 11.3 mmol). Purification by flash chromatography on silica gel, eluting with a gradient of 30% EtOAc in hexane afforded the *title compound **133*** (700 mg, 1.93 mmol, 57%) as a yellow solid; $\boldsymbol{R_f}$ = 0.16, (40% EtOAc in hexane); **δ_H(400 MHz, Chloroform-*d*):** 7.32 – 7.16 (5H, m, Ar*H*), 6.93 (1H, dd, *J* 9.8, 5.0, 4-C*H*), 6.12 (1H, dd, *J* 9.8, 1.5, 3-C*H*), 4.08 (1H, d, *J* 5.0, 5-C*H*), 3.81 (1H, d, *J* 13.0, N*Bn*), 3.74 (1H, d, *J* 13.0, N*Bn*), 3.69 – 3.58 (5H, m, OCH_2CH_2, 6-C*H*), 3.48 (1H, dd, *J* 9.3, 4.5, 1-C*H*), 3.27 – 3.20 (4H, m, NCH_2CH_2), 2.67 (1H, ddd, *J* 14.3, 7.7, 4.5, 7-C*H*), 2.00 (1H, dd, *J* 14.3, 9.3, 7-C*H*); **δ_C(101 MHz, Chloroform-*d*):** 197.5 (*C*=O), 145.7 (4-*C*H), 137.0 (*Ar*), 129.0 (3-*C*H), 128.9 (*Ar*H), 128.7 (*Ar*H), 127.7 (*Ar*H), 68.3 (6-*C*H), 66.9 (O*C*H_2*C*H_2), 63.9 (1-*C*H), 58.5 (5-*C*H), 51.9 (N*Bn*), 46.4 (NCH_2*C*H_2), 27.6 (7-*C*H_2); **IR** ν_{max} (neat)/cm^{-1}: 3035, 2972 (C-H), 2919, 2864, 1682 (C=O), 1495 (C=C), 1451, 1367 (S=O); **HRMS** (ESI): $C_{18}H_{23}N_2O_4S$ [M+H$^+$]: calculated 363.1373, found 363.1382.

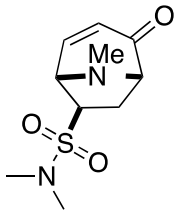
(1*S**,5*S**,6*R**)-8-(2-Bromobenzyl)-6-(phenylsulfonyl)-8-azabicyclo[3.2.1]oct-3-en-2-one (**131**)



General procedure **B** was followed using phenyl vinyl sulfone (1.21 g, 7.20 mmol) and bromo salt **131** (1.91 g, 7.20 mmol) and triethylamine (2.00 mL, 14.4 mmol). Purification by flash chromatography on silica gel, eluting with a gradient of 30% EtOAc in hexane. Crystallization

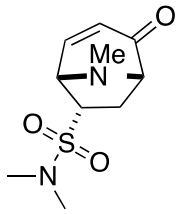
from EtOAc afforded the *title compound* ***131*** (1.26 g, 2.91 mmol, 41%) as a green solid; $\boldsymbol{R_f}$ = 0.25, (30% EtOAc in hexane); **δ_H(400 MHz, Chloroform-*d*):** 7.87 – 7.71 (2H, m, Ar*H*), 7.67 – 7.55 (1H, m, Ar*H*), 7.53 – 7.40 (3H, m, Ar*H*), 7.31 – 7.13 (2H, m, Ar*H*), 7.13 – 7.01 (1H, m, Ar*H*), 6.94 (1H, dd, *J* 9.8, 5.0, 4-C*H*), 6.09 (1H, dd, *J* 9.8, 1.5, 3-C*H*), 4.19 (1H, d, *J* 5.0, 5-C*H*), 3.83 (1H, d, *J* 14.8, NCH_2), 3.78 (1H, d, *J* 14.8, NCH_2), 3.64 (1H, d, *J* 7.7, 6-C*H*), 3.55 (1H, dd, *J* 9.5, 4.6, 1-C*H*), 2.77 (1H, ddd, *J* 14.5, 7.7, 4.6, 7-CH_2), 1.94 (1H, dd, *J* 14.5, 9.5, 7-CH_2); **δ_C(101 MHz, Chloroform-*d*):** 197.2 (*C*=O), 146.4 (4-*C*), 138.1 (*Ar*), 136.5 (*Ar*), 134.1 (*Ar*H), 134.0 (*Ar*H), 132.7 (*Ar*H), 130.2 (3-*C*), 129.5 (*Ar*H), 128.8 (*Ar*H), 128.6 (*Ar*H), 127.6 (*Ar*H), 123.8 (*Ar*), 68.6 (6-*C*), 67.5 (1-*C*), 58.3 (5-*C*), 51.1 (N-*C*), 27.3 (7-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3062 (C-H), 3020, 2955, 2868, 1684 (C=O), 1479 (C=C), 1446, 1304 (S=O); **HRMS** (ESI): $C_{20}H_{19}{}^{79}BrNO_3S$ [M+H^+]: calculated 434.0244, found 434.0258.

(1*S**,5*S**,6*R**)-*N*,*N*,8-Trimethyl-2-oxo-8-azabicyclo[3.2.1]oct-3-ene-6-sulfonamide (**114a**)



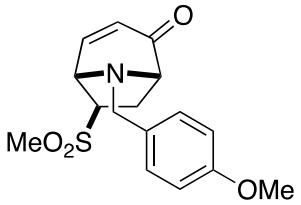
General procedure **B2** was followed using sulfone compound **121** (581 mg, 4.30 mmol) and salt **105** (1.20 g, 6.45 mmol), triethylamine (1.2 mL, 8.6 mmol). Purification by flash chromatography on silica gel, eluting with a gradient of 50% EtOAc in hexane afforded the major *title compound* **114a** (494 mg, 2.02 mmol, 54%) as a yellow solid; $\boldsymbol{R_f}$ = 0.31, (60% EtOAc in hexane); **δ_H(400 MHz, Chloroform-*d*):** 6.90 (1H, dd, *J* 9.8, 5.0, 4-C*H*), 6.03 (1H, dd, *J* 9.8, 1.5, 3-C*H*), 4.08 (1H, d, *J* 5.0, 5-C*H*), 3.58 (1H, d, *J* 8.0, 6-C*H*), 3.50 (1H, dd, *J* 9.3, 4.2, 1-C*H*), 2.89 (6H, s, NMe_2), 2.71 (1H, ddd, *J* 14.4, 8.0, 4.2, 7-CH_2), 2.45 (3H, s, N*Me*), 1.96 (1H, dd, *J* 14.4, 9.3, 7-CH_2). **δ_C(101 MHz, Chloroform-*d*):** 197.8 (*C*=O), 45.4 (4-*C*H), 128.2 (3-*C*H), 70.0 (6-*C*H), 64.2 (1-*C*H), 61.0 (5-*C*H), 38.2 (NMe_2), 34.7 (N*Me*), 27.8 (7-CH_2); **IR** ν_{max} (neat)/cm^{-1}: 3019, 2960 (CH), 2914, 2878, 2805, 1674 (C=O), 1487 (C=C), 1319 (S=O); **HRMS** (ESI): $C_{10}H_{17}N_2O_3S$ [M+H^+]: calculated 245.0954, found 245.0961.

Minor (1S*,5S*,6S*)-*N*,*N*,8-trimethyl-2-oxo-8-azabicyclo[3.2.1]oct-3-ene-6-sulfonamide (**114b**)



Purification by flash chromatography on silica gel, eluting with a gradient of 50% EtOAc in hexane afforded the minor *title compound **114b*** (71 mg, 0.29 mmol, 54%) as a yellow solid; R_f = 0.16, (60% EtOAc in hexane); **δ_H(400 MHz, Chloroform-*d*):** 7.04 (1H, dd, *J* 9.9, 5.3, 4-C*H*), 6.02 (1H, dd, *J* 9.9, 1.5, 3-C*H*), 3.88 (1H, at, *J* 5.3, 5-C*H*), 3.82 (1H, as, 1-C*H*), 3.40 (1H, t, *J* 6.9, 6-C*H*), 2.96 (6H, s, N*Me*$_2$), 2.69 (1H, dt, *J* 12.7, 6.9, 7-CH_2), 2.52 (3H, s, N*Me*), 2.21 (1H, dd, *J* 12.7, 8.9, 7-CH_2); **δ_C(101 MHz, Chloroform-*d*):** 195.5 (*C*=O), 149.6 (4-*C*H), 126.7 (3-*C*H), 72.1 (6-*C*H), 60.2 (1-*C*H), 59.2 (5-*C*H), 38.0 (N*Me*$_2$), 36.3 (N*Me*), 31.6 (7-*C*H_2); **IR** ν_{max} (neat)/cm^{-1}: 3009 (CH), 2959, 2928, 2893, 2809, 1603 (C=O), 1454, 1294 (S=O); **HRMS** (ESI): $C_{10}H_{17}N_2O_3S$ [M+H$^+$]: calculated 245.0954, found 245.0961.

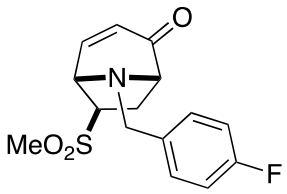
(1*S**,5*S**,6*R**)-8-(4-Methoxybenzyl)-6-(methylsulfonyl)-8-azabicyclo[3.2.1]oct-3-en-2-one (**134**)



General procedure **B** was followed using methyl vinyl sulfone (500 µl, 5.65 mmol) and salt **128** (2.14 g, 8.48 mmol), triethylamine (1.60 mL, 11.3 mmol). Recrystallisation from EtOAc afforded the *title compound **134*** (700 mg, 1.93 mmol, 52%) as a green solid, **Mpt** 139.9 – 140.8 ^oC; **δ_H (400 MHz, Chloroform-*d*)**: 7.03 (2H, d, *J* 8.5, Ar*H*), 6.91 (1H, dd, *J* 9.8, 4.9, 4-C*H*), 6.78 (2H, d, *J* 8.5, Ar*H*), 6.15 (1H, dd, *J* 9.8, 1.5, 3-C*H*), 4.00 (1H, d, *J* 4.9, 5-C*H*), 3.75 – 3.69 (4H, m, O*Me*, NCH_2), 3.67 – 3.62 (2H, m, 6-C*H*, NCH_2), 3.33 (1H, dd, *J* 9.6, 4.1, 1-C*H*), 2.79 (3H, s, SO_2*Me*), 2.62 (1H, ddd, *J* 15.0, 7.8, 4.1, 7-CH_2), 2.15 (1H, dd, *J* 15.0, 9.6, 7-CH_2); **δ_C(101 MHz, Chloroform-*d*):** 197.2 (*C*=O), 159.3 (*Ar*), 144.6 (4-*C*), 130.0 (*Ar*), 129.1

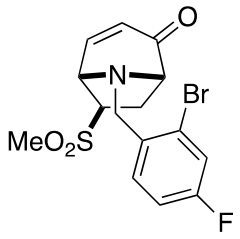
(*Ar*H), 128.8 (3-*C*), 114.2 (*Ar*H), 67.6 (6-*C*), 66.5 (1-*C*), 57.8 (5-*C*), 55.3 (O*Me*), 51.0 (N*C*H_2), 38.0 (SO_2*Me*), 27.8 (7-*C*H_2); **IR** ν_{max} (neat)/cm^{-1}: 3025 (OH), 3023, 2993 (CH), 2947, 2893, 1730 (C=O), 1512 (C=C), 1459, 1296 (S=O); **HRMS** (ESI): $C_{16}H_{20}NO_4S$ [M+H^+]: calculated 322.1108, found 322.1035

(1*S**,5*S**,6*R**)-8-(4-Fluorobenzyl)-6-(methylsulfonyl)-8-azabicyclo[3.2.1]oct-3-en-2-one (**136**)



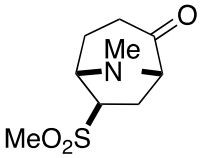
General procedure **B** was followed using methyl vinyl sulfone (2.0 mL, 22.7 mmol) and salt **129** (5.52 g, 27.2 mmol, 1.2 eq.), triethylamine (6.3 mL, 45.3 mmol). Purification by crystallization from EtOAc afforded the *title compound **136*** (3.26 g, 10.5 mmol, 46%) as a yellow solid; R_f = 0.57, (100% EtOAc in hexane). **M.Pt.** 142.1 – 143.0 °C; **δ_H(400 MHz, Chloroform-*d*):** 7.23 – 7.15 (2H, m, Ar*H*), 7.07 – 6.99 (3H, m, Ar*H*, 4-C*H*), 6.24 (1H, dd, *J* 9.8, 1.5, 3-C*H*), 4.14 (1H, d, *J* 4.9, 5-C*H*), 3.83 (1H, d, *J* 12.9, NCH_2), 3.78 (1H, d, *J* 12.9, NCH_2), 3.72 (1H, d, *J* 6.5, 6-C*H*), 3.45 (1H, dd, *J* 9.5, 4.1, 1-C*H*), 2.90 (3H, s, SO_2Me), 2.73 (1H, ddd, *J* 14.9, 7.7, 4.1, 7-CH_2), 2.24 (1H, dd, *J* 14.9, 9.5, 7-CH_2); **δ_C(101 MHz, Chloroform-*d*):** 196.9 (*C*=O), 162.4 (d, *J* 246.8, *Ar*-F), 144.7 (4-*C*), 132.5 (d, *J* 3.3, *Ar*), 130.4 (d, *J* 8.1, *Ar*H), 129.1 (3-*C*), 115.7 (d, *J* 21.5, *Ar*H), 67.6 (6-*C*), 66.4 (1-*C*), 58.0 (5-*C*), 51.0 (N*C*H_2), 38.3 (SO_2*Me*), 27.7 (7-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3021 (C-H), 2992, 2947, 2903, 1690 (C=O), 1508 (C=C), 1462, 1317 (S=O); **HRMS** (ESI): $C_{15}H_{17}FNO_3S$ [M+H^+]: calculated 310.0908, found 310.0916.

(1*S**,5*S**,6*R**)-8-(2-Bromo-4-fluorobenzyl)-6-(methylsulfonyl)-8-azabicyclo[3.2.1]oct-3-en-2-one (**137**)



General procedure **B** was followed using methyl vinyl sulfone (1 mL, 11.2 mmol) and methyl salt **132** (5.28 g, 14.54 mmol, 1.3 eq.), triethylamine (3.2 mL, 22.4 mmol) in THF (56 mL). Purification by crystallization from EtOAc afforded the *title compound **137*** (3.89 g, 10.0 mmol, 89%) as a yellow solid; **M.Pt.** 132.1 – 133.0 °C; **δ_H (400 MHz, Chloroform-*d*):** 7.33 (1H, dd, *J* 8.2, 2.6, Ar*H*), 7.24 (1H, dd, *J* 8.5, 5.9, Ar*H*), 7.10 (1H, dd, *J* 9.8, 4.9, 4-C*H*), 7.04 (1H, td, *J* 8.2, 2.6, Ar*H*), 6.25 (1H, dd, *J* 9.8, 1.4, 3-C*H*), 4.16 (1H, d, *J* 4.9, 5-C*H*), 3.94 (1H, d, *J* 13.3, N*Bn*), 3.86 (1H, d, *J* 13.3, N*Bn*), 3.77 (1H, d, *J* 8.0, 6-C*H*), 3.44 (1H, dd, *J* 9.6, 4.1, 1-C*H*), 2.85 (3H, s, *Me*), 2.70 (1H, ddd, *J* 14.9, 8.0, 4.1, 7-CH_2), 2.24 (1H, dd, *J* 14.9, 9.6, 7-CH_2); **δ_C (101 MHz, Chloroform-*d*):** 196.7 (*C*=O), 161.9 (d, *J* 251.8, *Ar*-F), 132.3 (d, *J* 3.6, *Ar*), 132.0 (d, *J* 8.4, *Ar*H), 124.8 (d, *J* 9.5, *Ar*), 120.6 (d, *J* 24.3, *Ar*H), 115.0 (d, *J* 21.1, *Ar*H), 68.0 (1-*C*), 66.5 (1-*C*), 58.2 (5-*C*), 50.7 (N*Bn*), 38.1 (*Me*), 27.7 (7-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3065 (CH), 3031, 2994, 2944, 1677 (C=O), 1465 (C=C), 1453, 1227 (S=O); **HRMS** (ESI): $C_{15}H_{16}{}^{79}BrFNO_3S$ [M+H$^+$]: calculated 388.0013, found 388.0009.

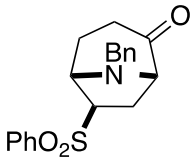
(1*S**,5*S**,6*R**)-8-Methyl-6-(methylsulfonyl)-8-azabicyclo[3.2.1]octan-2-one (**176**)



General procedure **F** was followed using compound **116** (6.40 g, 29.45 mmol) in MeOH/Acetone (60 mL) was added 10% Pd/C (600 mg, 10% weight) at rt. *Title compound **176*** (6.27 g, 28.89 mmol, 98%) as a colourless solid; **δ_H (400 MHz, DMSO-d_6)** 3.91 (1H, dd, *J* 9.5, 6.4, 1-C*H*), 3.68 (1H, s, 5-C*H*), 3.24 (1H, d, *J* 7.0, 6-C*H*), 2.97 (3H, s, SO_2*Me*), 2.64 – 2.51 (1H, m, 3-CH_2), 2.41 (1H, dt, *J* 14.0, 6.4, 7-CH_2), 2.36 (3H, s, N*Me*), 2.30 (1H, ddd, *J* 13.4, 7.2, 3.6, 4-CH_2), 2.23 (1H, dd, *J* 14.0, 9.5, 7-CH_2), 2.13 (1H, dd, *J* 16.7, 7.2, 3-CH_2), 1.85 (1H, dd, *J* 13.4, 8.7, 4-CH_2); **δ_C (101 MHz, DMSO-d_6)** 210.0 (*C*=O), 70.7 (1-*C*), 65.5 (6-*C*),

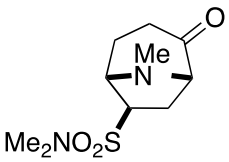
59.2 (5-*C*), 38.6 (*Me*), 35.5 (N*Me*), 33.2 (3-*C*), 29.4 (7-*C*), 27.5 (4-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3004 (CH), 2965, 2923, 2879, 2853, 1707 (C=O), 1274 (S=O), 1157; **HRMS** (ESI): $C_9H_{16}NO_3S$ [M+H^+]: calculated 218.0845, found 218.0845.

(1*S**,5*S**,6*R**)-8-Benzyl-6-(phenylsulfonyl)-8-azabicyclo[3.2.1]octan-2-one (**174**)



General procedure **F** was followed using compound **89** (1.10 g, 3.11 mmol, 1.0 eq.) in MeOH/Acetone (20 mL) was added 10% Pd/C (100 mg, 10% weight) at rt. *Title compound **174*** (1.07 g, 3.01 mmol, 97%) as a colourless solid, $\boldsymbol{R_f}$ = 0.40 (30% EtOAc in hexane); **^{1}H NMR** (400 MHz, $CDCl_3$) 7.89 – 7.80 (2H, m, Ar*H*), 7.68 – 7.56 (1H, m, Ar*H*), 7.60 – 7.45 (2H, m, Ar*H*), 7.28 – 7.13 (3H, m, Ar*H*), 7.16 – 7.06 (2H, m, Ar*H*), 3.82 (1H, br s, 5-C*H*), 3.79 (1H, d, *J* 13.5, NCH_2), 3.65 (1H, d, *J* 13.5, NCH_2), 3.59 (1H, dd, *J* 9.3, 6.7, 6-C*H*), 3.37 (1H, d, *J* 7.1, 1-C*H*), 2.59 (1H, dt, *J* 14.1, 7.1, 7-CH_2), 2.44 – 2.15 (3H, m, 4-C*H*, 3-CH_2), 2.04 (1H, dd, *J* 14.1, 9.3, 7-CH_2), 1.78 – 1.64 (1H, m, 4-C*H*). **^{13}C NMR** (101 MHz, $CDCl_3$): 207.9 (*C*=O), 138.3 (*Ar*), 137.4 (*Ar*), 133.9 (*Ar*), 129.4 (*Ar*), 128.8 (*Ar*), 128.5 (*Ar*), 128.4 (*Ar*), 127.4 (*Ar*), 67.8 (6-*C*H), 60.4 (1-*C*H), 58.0 (5-*C*H), 53.0 (N*C*H_2), 33.1 (7-*C*H_2), 30.0 (4-*C*H_2), 28.8 (3-*C*H_2); **IR** ν_{max} (neat)/cm^{-1}: 2948 (C-H), 2927, 2839, 2811, 1772 (C=O), 1582, 1448 (C=C), 1316 (S=O); **HRMS** (ESI): $C_{20}H_{22}NO_3S$ [M+H^+]: calculated 356.1315, found. 356.1313

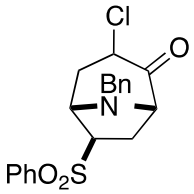
(1*S**,5*S**,6*R**)-*N*,*N*,8-Trimethyl-2-oxo-8-azabicyclo[3.2.1]octane-6-sulfonamide (**177)**



General procedure **F** was followed using compound **114** (1.30 g, 5.32 mmol) in MeOH/Acetone (20 mL) was added 10% Pd/C (60 mg, 10% weight) at rt. Purification by flash chromatography on silica gel, eluting with a gradient of 60% EtOAc in hexane afforded the *title compound **177*** (1.17 g, 4.75 mmol, 89%) as a colourless solid; $\boldsymbol{R_f}$ = 0.10, (60% EtOAc); **δ_H(400 MHz, Chloroform-*d*):** 3.74 (1H, s, 5-C*H*), 3.56 (1H, dd, *J* 9.1, 6.2, 6-C*H*), 3.37 (1H, d, *J* 7.0, 1-C*H*), 2.89 (6H, s, SO_2N*Me*$_2$), 2.56 (1H, dt, *J* 14.1, 7.0, 7-CH_2), 2.45 (3H, s, N*Me*), 2.39 – 2.26 (3H, m, 4-CH_2, 3-CH_2), 2.09 (1H, dd, *J* 14.1, 9.1, 7-CH_2), 1.93 – 1.79 (1H, m, 4-CH_2); **δ_C(101 MHz, Chloroform-*d*):** 209.1 (*C*=O), 71.1 (1-*C*), 64.0 (6-*C*), 60.3 (5-*C*), 38.2

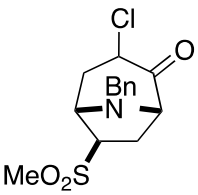
(N*Me*$_2$), 36.1 (N*Me*), 32.8 (3-*C*), 30.3 (7-*C*), 27.7 (4-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3189, 3001, 2935 (CH), 2879, 2818, 1644 (C=O), 1296 (S=O), 1157; **HRMS** (ESI): $C_{10}H_{18}N_2O_3S$ [M+H$^+$]: calculated 247.1111, found 249.1265.

(1*S**,5*S**,6*R**)-8-Benzyl-3-chloro-6-(phenylsulfonyl)-8-azabicyclo[3.2.1]octan-2-one (**179**)



To a solution of ketone **174** (200 mg, 0.56 mmol, 1.0 eq.) in DCM (4 mL) at rt was added NCS (150 mg, 1.13 mmol, 2.0 eq.) and L-proline (21 mg, 0.34 mmol, 30 mol%). The reaction was stirred for 16 h at rt. The crude mixture was taken up in water (10 mL), and the aqueous phase was extracted with DCM (3 × 10 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gel, eluting with a gradient of 20% EtOAc in hexane. Crystallisation from EtOAc afforded the *title compound **179*** (88 mg, 0.23 mmol, 40%) as a white solid as a single isomer of undetermined stereochemistry; $\boldsymbol{R_f}$ = 0.16 (30% EtOAc in hexane); **δ_H(300 MHz, Chloroform-*d*):** 7.97 – 7.83 (2H, m, Ar*H*), 7.77 – 7.64 (1H, m, Ar*H*), 7.65 – 7.53 (2H, m, Ar*H*), 7.36 – 7.23 (3H, m, Ar*H*), 7.19 – 7.08 (2H, m, Ar*H*), 4.53 (1H, t, *J* 9.8, 3-C*H*), 3.91 (1H, s, 5-C*H*), 3.82 – 3.61 (4H, m, NCH_2, 6-C*H*, 1-C*H*), 2.70 (1H, dt, *J* 14.8, 6.7, 7-CH_2), 2.58 (2H, dd, *J* 9.8, 3.0, 4-CH_2), 2.22 (1H, dd, *J* 14.8, 9.4, 7-CH_2); **δ_C(101 MHz, Chloroform-*d*):** 199.3 (*C*=O), 137.7 (*Ar*), 136.5 (*Ar)*, 134.1 (*Ar*H), 129.5 (*Ar*H), 128.9 (*Ar*H), 128.5 (*Ar*H), 128.5 (*Ar*H), 127.6 (*Ar*H), 68.2 (6-*C*H), 66.7 (1-*C*H), 58.4 (3-*C*H), 57.2 (5-*C*H), 52.0 (2-*C*H$_2$), 42.3 (4-*C*H$_2$), 29.1 (7-*C*H$_2$); **IR** ν_{max} (neat)/cm^{-1}: 3061, 3030, 3005 (CH), 2964, 2927, 1730 (C=O), 1602 (C=C), 1291 (S=O); **HRMS** (ESI): $C_{20}H_{21}{}^{35}ClNO_3S$ [M+H$^+$]: calculated 390.0925, found 390.1668.

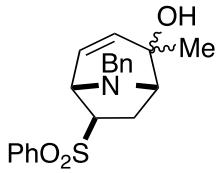
(1*S**,5*S**,6*R**)-8-Benzyl-3-chloro-6-(methylsulfonyl)-8-azabicyclo[3.2.1]octan-2-one (**180**)



To a solution of ketone **175** (200 mg, 0.68 mmol, 1.0 eq.) in DCM (6 mL) at rt was added NCS (119 mg, 0.88 mmol, 1.3 eq.) and L-proline (50 mg, 0.68 mmol, 1.0 eq.). The reaction was

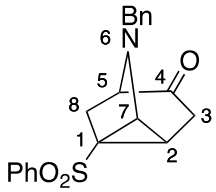
stirred for 16 h at rt. The crude mixture was taken up in water (10 mL), and the aqueous phase was extracted with DCM (3 × 10 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gel, eluting with a gradient of 20% EtOAc in hexane. Crystallisation from EtOAc afforded the *title compound* ***180*** (88 mg, 0.23 mmol, 57%) as a white solid a single isomer of undetermined stereochemistry; $\boldsymbol{R_f}$ = 0.17 (40% EtOAc in hexane); **δ_H(400 MHz, DMSO-*d*$_6$)** 7.42 – 7.16 (5H, m, Ar*H*), 5.25 (1H, dd, *J* 11.3, 8.2, 3-C*H*), 4.06 – 3.99 (1H, m, 6-C*H*), 3.87 (1H, d, *J* 13.7, N*Bn*), 3.83 (1H, s, 5-C*H*), 3.59 (1H, d, *J* 13.7 N*Bn*), 3.50 (1H, d, *J* 6.0, 1-*C*H), 2.98 (3H, s, *Me*), 2.76 – 2.65 (1H, m, 7-CH_2), 2.60 – 2.38 (2H, m, 4-CH_2), 2.41 – 2.26 (1H, m, 7-CH_2); **IR** ν_{max} (neat)/cm^{-1}: 3054, 3020, 3005 (CH), 2960, 2900, 1720 (C=O), 1658 (C=C), 1298 (S=O); **HRMS** (ESI): $C_{15}H_{19}{}^{35}ClNO_3S$ [M+H$^+$]: calculated 328.0769, found 328.1376.

(1*S**,5*S**,6*R**)-8-Benzyl-2-methyl-6-(phenylsulfonyl)-8-azabicyclo[3.2.1]oct-3-en-2-ol (**214**)



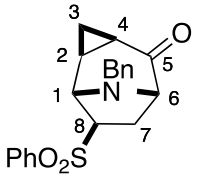
To a stirred solution of enone **89** (100 mg, 0.28 mmol, 1.0 eq.) in THF (1.4 mL) at −78 °C was added methylmagnesium iodide (3 M solution in THF) (0.12 mL, 0.37 mmol, 1.3 eq.) dropwise. The reaction mixture was stirred for 1 h, then warmed up to rt and stirred for 16 h. The crude mixture was taken up in water (5 mL), and the aqueous phase was extracted with EtOAc (3 × 5 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to afford *compound* ***214*** as a 3:2 mixture of diastereoisomers. Purification by flash chromatography on silica gel, eluting with a gradient of 30% EtOAc in hexane afforded only the major isomer, *title compound* **214** (54 mg, 0.15 mmol, 52%) as a colourless oil; $\boldsymbol{R_f}$ = 0.33, (30% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) 7.82 – 7.77 (2H, m, Ar*H*), 7.62 – 7.42 (4H, m, Ar*H*), 7.41 – 7.30 (2H, m, Ar*H*), 7.27 (1H, s, OH), 7.26 – 7.13 (2H, m, Ar*H*), 5.93 (1H, dd, *J* 9.5, 5.9, 4-C*H*), 5.26 (1H, d, *J* 9.4, 3-C*H*), 3.98 – 3.87 (2H, m, NCH_2, 5-C*H*), 3.74 (1H, d, *J* 13.7, NCH_2), 3.61 (1H, dd, *J* 9.2, 6.5, 6-C*H*), 3.22 (1H, d, *J* 6.6, 1-C*H*), 2.51 (1H, dd, *J* 13.8, 9.2, 7-C*H*), 2.34 (1H, dt, *J* 13.8, 6.6, 7-C*H*), 1.37 (3H, s, Me); **^{13}C NMR** (101 MHz, $CDCl_3$): 138.9 (*Ar*), 138.2 (*Ar*), 133.5 (*Ar*H), 132.5 (*Ar*H), 129.4 (*Ar*H), 129.3 (*Ar*H), 129.2 (4-*C*H), 128.2 (3-*C*H), 128.1 (*Ar*H), 128.1 (*Ar*H), 71.4 (1-*C*H), 70.4 (6-*C*H), 69.6 (*C*), 59.0 (5-*C*H), 55.9 (N*C*H_2), 27.8 (*Me*), 24.2 (7-*C*H_2); **IR** ν_{max} (neat)/cm^{-1}: ; **HRMS** (ESI): $C_{21}H_{24}NO_3S$ [M+H$^+$]: calculated 370.1465, found 370.1571.

6-Benzyl-1-(phenylsulfonyl)-6-azatricyclo[3.2.1.$0^{2,7}$]octan-4-one (**213**)



To a stirred solution of enone **89** (100 mg, 0.28 mmol, 1.0 eq.) in THF (1.4 mL) at −78 °C was added LiHMDS (1 M solution in THF, 0.34 mL, 0.34 mmol, 1.2 eq.) dropwise. The reaction was stirred for 16 h at rt. The crude mixture was taken up in water (5 mL), and the aqueous phase was extracted with EtOAc (3 × 5 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gel, eluting with a gradient of 30% EtOAc in hexane afforded the *title compound **213*** (170 mg, 0.17 mmol, 60%) as a colourless oil; $\boldsymbol{R_f}$ = 0.48 (30% EtOAc in hexane). **^{1}H NMR** (300 MHz, $CDCl_3$) 7.95 – 7.84 (2H, m, Ar*H*), 7.76 – 7.53 (3H, m, Ar*H*), 7.40 – 7.21 (5H, m, Ar*H*), 3.72 – 3.63 (2H, m, NCH_2), 3.61 (1H, dd, *J* 7.1, 0.9, 7-C*H*), 3.38 (1H, d, *J* 5.9, 5-C*H*), 2.76 – 2.53 (3H, m, 8-CH_2, 3-CH_2), 2.36 (1H, dt, *J* 7.1, 2.1, 2-C*H*), 1.85 (1H, d, *J* 12.7, 8-CH_2). **^{13}C NMR** (101 MHz, $CDCl_3$): 202.2 (*C*=O), 139.2 (*Ar*), 136.5 (*Ar*), 133.8 (*Ar*H), 129.4 (*Ar*H), 128.7 (*Ar*H), 128.6 (*Ar*H), 127.9 (*Ar*H), 127.8 (*Ar*H), 68.4 (5-*C*H), 56.4 (N*C*H_2), 47.9 (7-*C*H), 46.3 (1-*C*), 32.1 (3-*C*H_2), 26.8 (8-*C*H_2), 19.8 (2-*C*H); **IR** ν_{max} (neat)/cm^{-1}: 3028, 2927 (CH), 2897, 1730 (C=O), 1684, 1638, 1445 (C=C), 1379 (S=O); **LCMS** (ESI): $C_{20}H_{20}O_3S$ [M+H^+]: calculated 354.1158, found 354.20

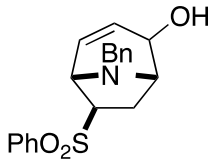
(1*S**,2*S**,4*R**,6*S**,8*R**)-9-Benzyl-8-(phenylsulfonyl)-9-azatricyclo[4.2.1.$0^{2,4}$]nonan-5-one (**242**)



To a stirred solution of trimethylsulfoxonium chloride (60 mg, 0.46 mmol, 1.1 eq.) in anhydrous THF (3 mL) was added sodium hydride (in 60% mineral oil) (19 mg, 0.46 mmol, 1.1 eq.) at 0 ^{o}C and the mixture left to stir at rt for 1h. Enone **89** (150 mg, 0.42 mmol, 1.0 eq.) was added to the reaction mixture and stirred for 3 h. The resulting mixture was diluted with water (10 mL) and DCM (10 mL). The phases were separated and the aqueous phase was extracted with DCM (2 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography on silica gel, eluting with 40%

EtOAc in hexane afforded the title *compound **242*** (56 mg, 0.15 mmol, 36%) as a brown oil; ***R*f** = 0.28, (40% EtOAc in hexane). **δH (400 MHz, Chloroform-*d*):** 7.90 – 7.84 (2H, m, Ar*H*), 7.63 – 7.58 (1H, m, Ar*H*), 7.56 – 7.49 (2H, m, Ar*H*), 7.33 – 7.17 (5H, m, Ar*H*), 4.16 (1H, s, 1-C*H*), 3.88 (1H, d, *J* 13.4, N*Bn*), 3.63 (1H, d, *J* 13.4, N*Bn*), 3.56 (1H, t, *J* 8.6, 1.3, 8-C*H*), 3.52 (1H, d, *J* 7.3, 6-C*H*), 2.56 (1H, dt, *J* 13.8, 7.8, 7-CH_2), 1.98 – 1.93 (1H, m, *cyp*), 1.86 (1H, dd, *J* 13.8, 8.9, 7-CH_2), 1.51 – 1.39 (2H, m, *cyp*), 1.01 (1H, ddd, *J* 10.9, 7.1, 4.2, *cyp*); **δc (126 MHz, Chloroform-*d*):** 204.5 (*C*=O), 139.4 (*Ar*), 138.2 (*Ar*), 133.9 (*Ar*H), 129.6 (*Ar*H), 129.2 (*Ar*H), 128.5 (*Ar*H), 128.1 (*Ar*H), 127.4 (*Ar*H), 71.7 (6-*C*), 71.3 (5-*C*H), 60.3 (1-*C*), 55.8 (N*Bn*), 31.2 (*cyp*), 23.4 (*cyp*), 22.2 (7-*C*), 13.2 (*cyp*); **IR** ν_{max} (neat)/cm^{-1}: 3018, 2943, 2880 (CH), 2806, 1709 (C=O), 1515 (C=C), 1496, 1291 (S=O); **LCMS** (ESI): $C_{21}H_{22}NO_3S$ [M+H$^+$]: calculated 368.1315, found 368.10.

(1*S**,5*S**,6*R**)-8-Benzyl-6-(phenylsulfonyl)-8-azabicyclo[3.2.1]oct-3-en-2-ol (**228**)



3.5:1

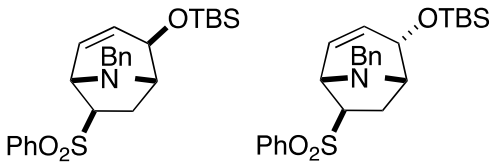
To a solution of enone **89** (2.40 g, 6.98 mmol, 1.0 eq.) in MeOH (70 mL) at rt was added $CeCl_3.7H_2O$ (5.20 g, 14.0 mmol, 2.0 eq.) and the mixture stirred for 10 min. The reaction mixture was cooled to 0 ^oC followed by a portionwise addition of $NaBH_4$ (370 mg, 9.77 mmol, 1.4 eq.). The reaction mixture was stirred for 16 h at rt and concentrated *in vacuo.* The crude mixture was taken up in water (10 mL) and DMF (5 mL), and the aqueous phase was extracted with Et_2O (3 × 10 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gel, eluting with a gradient of 40% EtOAc in hexane afforded a 1:3.5 mixture of inseparable diastereoisomers. Major isomer reported: *Compound **228*** (1.92 g, 5.42 mmol, 80%) as a colourless solid; ***R*f** = 0.15 (40% EtOAc in Hexane). **^{1}H NMR** (501 MHz, $CDCl_3$): 7.94 – 7.76 (2H, m, Ar*H*), 7.73 – 7.61 (1H, m, Ar*H*), 7.59 – 7.48 (2H, m, Ar*H*), 7.36 – 7.21 (3H, m, Ar*H*), 7.19 – 7.06 (2H, m, Ar*H*), 5.88 (1H, ddd, *J* 9.7, 4.8, 1.6, 4-C*H*), 5.71 (1H, ddd, *J* 9.7, 2.3, 1.7, 3-C*H*), 4.69 – 4.50 (1H, m, 2-C*H*), 3.88 (1H, d, *J* 13.4, NCH_2), 3.78 (1H, d, *J* 13.4, NCH_2), 3.75 (1H, d, *J* 4.8, 5-C*H*), 3.59 (1H, dd, *J* 9.4, 4.1, 1-C*H*) 3.36 (1H, t, *J* 6.2, 6-C*H*), 2.65 – 2.56 (1H, m, 7-CH_2), 2.40 (1H, dd, *J* 7.2, 4.1, 7-CH_2). **^{13}C NMR** (101 MHz, DMSO-d_6) 139.2 (*Ar*), 139.0 (*Ar*), 134.1

(*Ar*H), 131.3 (4-*C*H), 129.7 (*Ar*H), 129.1 (*Ar*H), 128.5 (*Ar*H), 128.5 (3-*C*H), 128.4 (*Ar*H), 127.2 (*Ar*H), 69.4 (1-*C*H), 63.4 (5-*C*H), 59.9 (6-*C*H), 57.2 (2-*C*H), 50.8 (N*C*H$_2$), 24.9 (7-*C*H$_2$); **IR** ν_{max} (neat)/cm^{-1}: 3537 (OH), 3055, 3028, 3002, 2934 (CH), 2885, 1445 (C=C), 1312 (S=O); **HRMS** (ESI): $C_{20}H_{22}NO_3S$ [M+H$^+$]: calculated, 356.1319 found 356.1313.

(1*S**,2*S**,5*S**,6*R**)-8-Benzyl-2-((*tert*-butyldimethylsilyl)oxy)-6-(phenylsulfonyl)-8-azabicyclo[3.2.1]oct-3-ene (**232 Major**).

(1*S**,2*R**,5*S**,6*R**)-8-Benzyl-2-((*tert*-butyldimethylsilyl)oxy)-6-(phenylsulfonyl)-8-azabicyclo[3.2.1]oct-3-ene (**233 Minor**).

Major **Minor**



General procedure **G** was followed using alcohol **228** (890 mg, 2.51 mmol, 1.0 eq.), *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.64 mL, 2.76 mmol, 1.1 eq.), imidazole (341 mg, 5.01 mmol, 2.0 eq.) in anhydrous DMF (4 mL). Purification by flash chromatography on silica gel, eluting with a gradient of 5% EtOAc in hexane afforded the *title compound* ***130a*** (585 mg, 1.25 mmol, 50%) as a colourless oil; $\boldsymbol{R_f}$ = 0.16, (5% EtOAc in hexane), followed by the *title compound* ***130b*** (350 mg, 0.75 mmol, 30%) as a colourless oil; $\mathbf{R_f}$ = 0.20 (5% EtOAc in hexane).

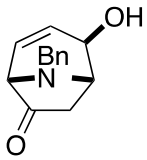
Compound **232**:

^{1}H NMR (400 MHz, $CDCl_3$) 7.94 – 7.84 (2H, m, Ar*H*), 7.70 – 7.60 (1H, m, Ar*H*), 7.60 – 7.49 (2H, m, Ar*H*), 7.36 – 7.20 (3H, m, Ar*H*), 7.19 – 7.09 (2H, m, Ar*H*), 5.81 (1H, ddd, *J* 9.8, 4.6, 1.5, 3-CH), 5.65 (1H, dt, *J* 9.8, 2.1, 4-CH), 4.50 (1H, s, 5-CH), 3.89 (1H, d, *J* 13.1, NC*H*$_2$), 3.79 (1H, d, *J* 13.1, NC*H*$_2$), 3.74 (1H, d, *J* 4.6, 2-CH), 3.63 (1H, dd, *J* 9.5, 3.8, 1-CH), 3.20 (1H, t, *J* 7.0, 6-CH), 2.73 (1H, dd, *J* 14.4, 9.5, 7-CH$_2$), 2.35 (1H, ddd, *J* 14.4, 7.0, 3.8, 7-CH$_2$), 0.86 (9H, s, ^{t}Bu), 0.00 (3H, s, SiMe), – 0.05 (3H, s, SiMe). **^{13}C NMR** (101 MHz, $CDCl_3$): 138.9 (*Ar*), 138.4 (*Ar*), 133.3 (*Ar*H), 130.8 (4-*C*H), 129.1 (*Ar*H), 128.9 (*Ar*H), 128.6 (3-*C*H), 128.5 (*Ar*H), 128.2 (*Ar*H), 127.1 (*Ar*H), 70.0 (2-*C*H), 65.5 (5-*C*H), 60.4 (6-*C*H), 57.4 (1-*C*H), 51.4 (N*C*H$_2$), 25.8 (SiC(*C*H$_3$)$_3$), 24.9 (7-*C*H$_2$), 18.1 (*C*), – 4.7 (Si(*C*H$_3$)$_2$); **IR** ν_{max} (neat)/cm^{-1}: 3086, 3019, 2985 (C-H), 2905, 1706 (C=O), 1493, 1445 (C=C), 1310 (S=O); **HRMS** (ESI): $C_{26}H_{36}NO_3SSi$ [M+H$^+$]: calculated 470.2180, found 470.2208.

Compound **233**:

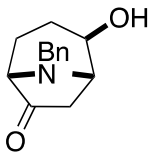
^{1}H NMR (400 MHz, $CDCl_3$) 7.88 – 7.78 (2H, m, Ar*H*), 7.67 – 7.58 (1H, m, Ar*H*), 7.57 – 7.43 (2H, m, Ar*H*), 7.40 – 7.17 (3H, m, Ar*H*), 7.19 – 7.11 (2H, m, ArH), 5.83 (1H, s, 3-C*H*), 5.82 (1H, s, 4-C*H*), 3.99 (1H, d, *J* 14.0, NCH_2), 3.83 – 3.73 (2H, m, NCH_2, *5*-C*H*), 3.52 (1H, s, 2-C*H*), 3.45 (1H, d, *J* 7.7, 1-C*H*), 3.41 (1H, dd, *J* 9.3, 4.4, 6-C*H*), 2.60 (1H, ddd, *J* 14.0, 7.7, 4.4, 7-C*H*), 1.77 (1H, dd, *J* 14.0, 9.3, 7-C*H*), 0.85 (9H, s, ^{t}*Bu*), 0.05 (3H, s, Si*Me*), 0.00 (3H, s, Si*Me*). **^{13}C NMR** (101 MHz, $CDCl_3$): 139.3 (*Ar*), 138.4 (*Ar*), 133.4 (*Ar*H), 129.1 (*Ar*H), 129.0 (*Ar*H), 128.9 (*Ar*H), 128.5 (4-*C*H), 128.0 (3-*C*H), 127.9 (*Ar*H), 126.6 (*Ar*H), 69.3 (6-*C*H), 67.6 (2-*C*H), 61.8 (1-*C*H), 56.2 (5-*C*H), 51.5 (NCH_2), 28.8 (7-*C*H_2), 25.8 (SiC(*C*H_3)$_3$), 18.0 (*C*), – 4.7 (Si*C*H_3), – 4.9 (Si*C*H_3); **IR** ν_{max} (neat)/cm^{-1}: 3086, 3019, 2985 (C-H), 2905, 1706 (C=O), 1493, 1445 (C=C), 1310 (S=O); **HRMS** (ESI): $C_{26}H_{36}NO_3SSi$ [M+H$^+$]: calculated 470.2180, found 470.2208.

(1*S**,2*R**,5*S**)-8-Benzyl-2-hydroxy-8-azabicyclo[3.2.1]oct-3-en-6-one (**236**)



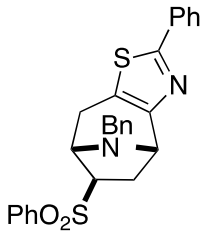
General procedure **H** was followed using protected alcohol **232** (357 mg, 0.76 mmol, 1.0 eq.), LiHMDS (1 M solution in THF, 7.6 mL, 7.6 mmol, 10 eq.), dimethyl disulfide (1.4 mL, 15 mmol, 20 eq.) anhydrous THF (4 mL). The reaction mixture was taken up in 1,4-dioxane (3.5 mL), conc.HCl (1.4 mL, 46 mmol, 60 eq.) and heated at reflux for 2 h. Purification by flash chromatography on silica gel, eluting with a gradient of 30% EtOAc in hexane afforded the *title compound* ***236*** (170 mg, 0.74 mmol, 98%) as a brown oil; $\boldsymbol{R_f}$ = 0.10, (40% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) 7.33 – 7.15 (5H, m, Ar*H*), 5.87 – 5.73 (2H, m, 3-C*H*, 4-C*H*), 4.63 (1H, d, *J* 5.0, 2-C*H*), 3.70 (2H, s, NCH_2), 3.62 – 3.55 (2H, m, O*H*, 1-C*H*), 3.31 – 3.24 (1H, m, 5-C*H*), 2.81 (1H, dt, *J* 18.7, 1.0, 7-CH_2), 2.35 (1H, ddd, *J* 18.7, 7.4, 1.2, 7-CH_2). **^{13}C NMR** (101 MHz, $CDCl_3$): 210.3 (*C*=O), 137.5 (*Ar*), 132.4 (4-*C*H), 128.7 (*Ar*H), 128.5 (*Ar*H), 127.5 (*Ar*H), 125.7 (3-*C*H), 66.1 (2-*C*H), 65.0 (5-*C*H), 59.5 (1-*C*H), 55.4 (NCH_2), 32.8 (7-*C*H_2); **IR** ν_{max} (neat)/cm^{-1}: 3399 (OH), 3031, 2930 (CH), 2870, 1742 (C=O), 1495, 1454 (C=C) 1360 (S=O); **HRMS** (ESI): $C_{14}H_{16}NO_2$ [M+H$^+$]: calculated 230.1178, found 230.1176.

(1*S**,2*R**,5*S**)-8-Benzyl-2-hydroxy-8-azabicyclo[3.2.1]octan-6-one (**238**)



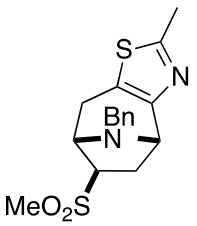
General procedure **I** was followed using ketone **174** (1.00 g, 2.81 mmol), DIBAL (1M cyclohexane) (8.4 mL,8.4 mmol) in anhydrous DCM (35 mL) to give crude *compound* as a colourless oil. General procedure **G** was followed using alcohol (1.00 g, 2.81 mmol), *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.9 mL, 8.43 mmol, 3.0 eq.), imidazole (600 mg, 8.43 mmol, 3.0 eq.) in anhydrous DMF (4 mL); the compound was taken through crude to the next step. General procedure **H** was followed using crude protected alcohol (161 mg, 0.34 mmol, 1.0 eq.), LiHMDS (1 M solution in THF, 7.6 mL, 7.6 mmol, 10 eq.), dimethyl disulfide (1 mL, 6.82 mmol, 20 eq.) in THF (2 mL). The reaction mixture was taken up in 1,4-dioxane (2.0 mL), conc.HCl (0.7 mL, 23 mmol, 60 eq.) and heated at reflux for 2 h. Purification by reverse phase biotage MeCN/H_2O 1% formic acid gave *title compound **238*** (64 mg, 0.28 mmol, 82%); **δ_H (400 MHz, Methanol-*d*$_4$):** 7.33 – 7.29 (2H, m, Ar*H*), 7.25 – 7.19 (2H, m, Ar*H*), 7.18 – 7.12 (1H, m, Ar*H*), 3.63 – 3.58 (2H, m, N*Bn*, 2-C*H*), 3.55 (1H, d, *J* 13.1, N*Bn*), 3.47 – 3.37 (1H, m, 1-C*H*), 2.84 – 2.77 (1H, m, 5-C*H*), 2.57 (1H, ddd, *J* 19.0, 7.8, 1.4, 7-CH_2), 2.01 – 1.92 (1H, m, 4-CH_2), 1.89 (1H, d, *J* 19.0, 7-CH_2), 1.73 – 1.43 (3H, m, 4-CH_2, 3-CH_2); **δ_C (126 MHz, Methanol-*d*$_4$):** 220.3 (*C*=O), 138.2 (*Ar*), 128.6 (*Ar*H), 128.1 (*Ar*H), 127.0 (*Ar*H), 68.0 (2-*C*), 66.8 (5-*C*), 62.0 (1-*C*), 57.5 (N*Bn*), 35.8 (7-*C*), 24.5 (3-*C*), 24.4 (4-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3420 (OH), 3061, 3029 (CH), 2945, 2853, 1742 (C=O), 1455 (C=C), 1438; **HRMS** (ESI): $C_{14}H_{18}NO_2$ [M+H^+]: calculated 232.1332, found 232.1334.

(4*S**,6*R**,7*S**)-9-Benzyl-2-phenyl-6-(phenylsulfonyl)-5,6,7,8-tetrahydro-4*H*-4,7-epiminocyclohepta[*d*]thiazole (**181**)



General procedure **J** was followed using chloroketone **179** (60 mg, 0.15 mmol) and thiobenzamide (94 mg, 0.69 mmol). Purification by flash chromatography on silica gel, eluting with a gradient of 40% EtOAc in hexane afforded the *title compound **181*** (20 mg, 0.04 mmol, 30%) as a colourless oil; $\boldsymbol{R_f}$ = 0.56, (40% EtOAc); **δ_H (400 MHz, Chloroform-*d*):** 7.99 – 7.69 (5H, m, Ar*H*), 7.54 – 7.40 (2H, m, Ar*H*), 7.38 – 7.31 (3H, m, Ar*H*), 7.25 – 7.11 (5H, m, Ar*H*), 4.24 (1H, d, *J* 6.0, 6-C*H*), 4.04 (1H, d, *J* 4.4, 7-C*H*), 3.72 (1H, d, *J* 13.6, NBn), 3.57 (1H, d, *J* 13.6, NBn), 3.47 (1H, t, *J* 8.3, 4-C*H*), 3.21 (1H, dd, *J* 16.9, 4.4, 8-CH_2), 2.58 (1H, dt, *J* 12.7, 6.0, 5-CH_2), 2.47 (1H, d, *J* 16.9, 8-CH_2), 2.23 (1H, dd, *J* 12.7, 8.3, 5-CH_2); **δ_C (151 MHz, DMSO-d_6):** 165.7 (*Ar*), 153.9 (*Ar*), 138 .9 (*Ar*), 138.6 (*Ar*), 133.7 (*Ar*), 134.4 (*Ar*H), 133.7 (*Ar*), 130.5 (*Ar*H), 129.9 (*Ar*H), 129.8 (*Ar*H), 129.0 (*Ar*H), 128.7 (*Ar*H), 128.6 (*Ar*H), 127.4 (*Ar*H), 126.3 (*Ar*H), 67.7 (6-*C*), 59.3 (7-*C*), 56.9 (4-*C*), 51.1 (N*Bn*), 37.0 (8-*C*), 27.8 (5-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3010, 2967 (CH), 2918, 2880, 2848, 1597 (C=C), 1436, 1237 (S=O); **HRMS (ESI)**: [M+H$^+$]: $C_{27}H_{25}N_2O_2S_2$ calculated 473.1352, found 473.1345

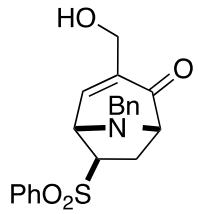
(4*S**,6*R**,7*S**)-9-Benzyl-2-methyl-6-(methylsulfonyl)-5,6,7,8-tetrahydro-4*H*-4,7-epiminocyclohepta[*d*]thiazole (**182**)



General procedure **J** was followed using chloroketone **180** (164 mg, 0.50 mmol) and thioacetamide (150 mg, 2.00 mmol) in DMF (2.5 mL). Purification by reverse phase biotage MeCN/H_2O 1% formic acid gave *title compound **182*** (6 mg, 0,02 mmol, 3%) as a colourless

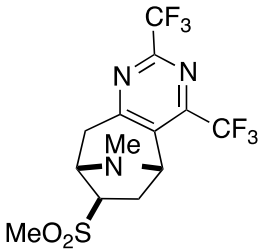
oil; **δ_H (600 MHz, DMSO-*d*$_6$)**: 7.33 – 7.17 (5H, m, Ar*H*), 4.24 (1H, d, *J* 5.6, 4-C*H*), 3.83 (1H, d, *J* 4.6, 7-C*H*), 3.63 (1H, d, *J* 13.8, N*Bn*), 3.58 (1H, t, *J* 8.0, 6-C*H*), 3.52 (1H, d, *J* 13.8, N*Bn*), 3.09 (1H, dd, *J* 16.9, 4.7, 8-CH_2), 2.91 (3H, s, *Me*), 2.58 (3H, s, *Me*), 2.53 – 2.45 (1H, m, 8-CH_2) 2.43 – 2.33 (1H, m, 5-CH_2), 2.20 (1H, dd, *J* 12.4, 9.0, 5-CH_2); **δ_C (**151 MHz, **DMSO-*d*$_6$)**: 163.2(*Ar*), 145.5(*Ar*), 139.1(*Ar*), 130.3 (*Ar*), 128.8 (*Ar*H), 128.8 (*Ar*H), 127.5 (*Ar*H), 66.7 (6-*C*), 56.5 (7-*C*), 56.1 (4-*C*), 50.7 (N*Bn*), 38.5 (*Me*), 38.4 (8-*C*), 30.7 (5-*C*), 19.4 (*Me*); **IR** ν_{max} (neat)/cm^{-1}: 3026, 3012 (CH), 2980, 2922, 1594, 1521 (C=C), 1304, 1122 (S=O); **HRMS** (ESI): $C_{17}H_{21}N_2O_2S_2$ [M+H$^+$]: calculated 349.1039, found 349.1053.

(1*S**,5*S**,6*R**)-8-Benzyl-3-(hydroxymethyl)-6-(phenylsulfonyl)-8-azabicyclo[3.2.1]oct-3-en-2-one (**212**)



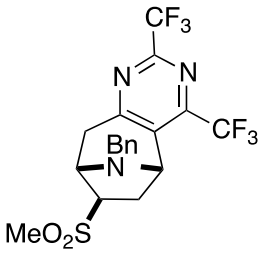
To a solution of enone **89** (70 mg, 0.20 mmol, 1.0 eq.) in anhydrous THF (1.0 mL) was added formaldehyde (36% in water) (0.03 mL, 0.4 mmol 2.0 eq.) and DMAP (2.5 mg, 10 mol%). The reaction was stirred for 16 h at rt and the reaction mixture was acidified with the addition of one drop of HCl (2M), and aqueous phase was extracted with DCM (3 x 5 mL). The combined organic extracts were washed with $NaHCO_3$ (5 mL) and brine (5 mL), dried over $MgSO_4$ and concentrated *in vacuo.* Purification by flash chromatography on silica gel, eluting with a gradient of 30% EtOAc in hexane afforded the *title compound **212*** (41 mg, 0.12 mmol, 54%) as a yellow oil; ***R*$_f$** = 0.10, (30% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) 7.90 – 7.82 (2H, m, Ar*H*), 7.72 – 7.62 (1H, m, Ar*H*), 7.60 – 7.50 (2H, m, Ar*H*), 7.33 – 7.22 (2H, m, Ar*H*), 7.26 (1H, s, Ar*H*), 7.09 (2H, dd, *J* 7.5, 2.0, Ar*H*), 6.85 (1H, dt, *J* 5.2, 1.5, 4-C*H*), 4.36 – 4.23 (2H, m, CH_2-OH), 4.22 (1H, d, *J* 5.2, 5-C*H*), 3.78 (1H, d, *J* 13.3, NCH_2), 3.69 (1H, d, *J* 13.3, NCH_2), 3.64 – 3.57 (2H, m, 6-C*H*, 1-C*H*), 2.80 (1H, ddd, *J* 14.3, 7.7, 4.5, 7-CH_2), 2.34 (1H, s, O*H*), 1.97 (1H, dd, *J* 14.3, 9.2, 7-CH_2). **^{13}C NMR** (101 MHz, $CDCl_3$): 198.5 (C=O), 140.3 (4-C*H*), 138.4 (*Ar*), 138.2 (*C*), 137.0 (*Ar*), 133.9 (*Ar*H), 129.4 (*Ar*H), 128.8 (*Ar*H), 128.5 (*Ar*H), 127.5 (*Ar*H), 127.5 (*Ar*H), 67.7 (6-*C*H), 67.3 (5-*C*H), 59.6 (*C*H$_2$-OH), 58.3 (1-*C*H), 51.6 (NCH$_2$), 27.1 (7-*C*H$_2$); **IR** ν_{max} (neat)/cm^{-1}: 3492 (OH), 3062, 3028, 2949 (CH), 2843, 1677 (C=O), 1446 (C=C), 1367 (S=O); **HRMS** (ESI): $C_{21}H_{22}NO_4S$ [M+H$^+$]: calculated 384.1271, found 384.1276.

(5*S**,7*R**,8*S**)-10-Methyl-7-(methylsulfonyl)-2,4-bis(trifluoromethyl)-6,7,8,9-tetrahydro-5*H*-5,8-epiminocyclohepta[*d*]pyrimidine (**194**)



General procedure **K** was followed using ketone **176** (250 mg, 1.15 mmol), 2,4,6-tris(trifluoromethyl)-1,3,5-triazine (0.2 mL, 2.29 mmol, 2.0 eq.) and TFA (9 μL, 10 mol%) in EtOH (2.5 mL). Purification by flash chromatography on silica gel, eluting with a gradient of 100% EtOAc in hexane afforded the *title compound **194*** (171 mg, 0,44 mmol, 54%) as a brown oil; **δ_H (400 MHz, DMSO-*d*$_6$)**: 4.30 (1H, d, *J* 6.9, 6-C*H*), 4.03 (1H, d, *J* 5.0, 5-C*H*), 3.78 (1H, t, *J* 8.6, 1-C*H*), 3.43 (1H, dd, *J* 18.4, 5.0, 4-CH_2), 3.01 (3H, s, *Me*), 2.86 (1H, d, *J* 18.4, 4-CH_2), 2.62 (1H, dt, *J* 13.4, 6.9, 7-CH_2), 2.38 (3H, s, *Me*), 2.32 (1H, dd, *J* 13.4, 8.6, 7-CH_2); **δ_c (101 MHz, DMSO):** 172.7 (*Ar*), 153.0 (q, *J* 37.0, *Ar*), 152.8 (q, *J* 35.0, *Ar*), 128.6 (*Ar*), 121.1 (q, *J* 277.1, *C*F$_3$), 119.6 (q, *J* 275.3, *C*F$_3$), 66.3 (1-*C*), 65.5 (6-*C*), 58.2 (5-*C*), 39.2 (*Me*), 35.7 (*Me*), 27.7 (4-*C*), 27.7 (7-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3023, 2953(CH), 2882, 2807, 1569 (C=C), 1419, 1202 (S=O) 1123; **HRMS** (ESI): $C_{13}H_{14}F_6N_3O_2S$ [M+H$^+$]: calculated 390.0705, found 390.0707.

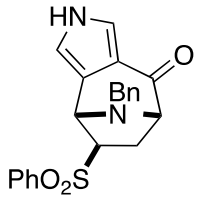
(5*S**,7*R**,8*S**)-10-Benzyl-7-(methylsulfonyl)-2,4-bis(trifluoromethyl)-6,7,8,9-tetrahydro-5*H*-5,8-epiminocyclohepta[*d*]pyrimidine (**195**)



General procedure **K** was followed using ketone **175** (200 mg, 0.68 mmol), 2,4,6-Tris(trifluoromethyl)-1,3,5-triazine (0.25 mL, 1.36 mmol, 2.0 eq.) and TFA (6 μL, 10 mol%) in EtOH (6 mL). Purification by flash chromatography on silica gel, eluting with a gradient of

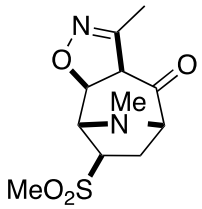
100% EtOAc in hexane afforded the *title compound **195*** (45.4 mg, 0,43 mmol, 32%) as a brown oil; **δ_H (400 MHz, DMSO-d_6):** 7.36 – 6.92 (5H, m, Ar*H*), 4.23 (1H, d, *J* 6.7, 6-C*H*), 3.95 (1H, d, *J* 5.0, 5-C*H*), 3.80 – 3.72 (2H, m, 1-C*H*, N*Bn*), 3.68 (1H, d, *J* 13.7, N*Bn*), 3.36 – 3.26 (1H, m, 4-CH_2), 2.93 (3H, s, *Me*), 2.83 (1H, d, *J* 18.4, 4-CH_2), 2.61 (1H, dt, *J* 13.5, 6.7, 7-CH_2), 2.28 (1H, dd, *J* 13.5, 9.2, 7-CH_2); **δ_C (101 MHz, DMSO-d_6)**: 172.6 (*Ar*), 172.6 (*Ar*), 153.1 (q, *J* 36.8, *Ar*), 152.9 (q, *J* 35.8, *Ar*), 138.6 (*Ar*H) , 128.8 (*Ar*H), 128.8 (*Ar*H), 127.6 (*Ar*), 121.1 (q, *J* 277.1, *C*F_3), 119.6 (q, *J* 275.3, *C*F_3), 66.1 (1-*C*), 63.8 (6-*C*), 56.7 (5-*C*), 51.8 (N*Bn*), 39.1 (*Me*), 35.5 (4-*C*), 28.5 (7-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3000 (CH), 2951, 2916, 2847, 1589, 1530 (C=C), 1454, 1290 (S=O); **HRMS** (ESI): $C_{19}H_{18}F_6N_3O_2S$ [M+H$^+$]: calculated 466.1018, found 446.1021.

(4*S**,5*R**,7*S**)-9-Benzyl-5-(phenylsulfonyl)-4,5,6,7-tetrahydro-4,7-epiminocyclohepta[*c*]pyrrol-8(2*H*)-one (**151)**



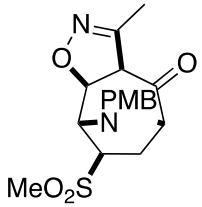
To a solution of enone **89** (100 mg, 0.29 mmol, 1.0 eq.) in anhydrous THF (1.5 mL) at 0 ^oC was added *t*-BuOK (159 mg, 1.42 mmol, 5.0 eq.) and TosMIC (55 mg, 0.29 mmol, 1.0 eq.). The reaction mixture was stirred for 16 h at room temperature. The crude mixture was taken up in water (5 mL), and the aqueous phase was extracted with DCM (3 × 5 mL) and dried over $MgSO_4$ and concentrated *in vacuo.* Crystallization from EtOAc afforded the *title compound **151*** (94 mg, 0.24 mmol, 85%) as a colourless solid; **^{1}H NMR** (400 MHz, DMSO-d_6) 11.63 (1H, s, N*H*), 7.93 (2H, d, *J* 7.8, Ar*H*), 7.78 (1H, t, *J* 7.8, Ar*H*), 7.65 (2H, t, *J* 7.8, Ar*H*), 7.43 (1H, s, 1-C*H*), 7.29 – 7.16 (3H, m, Ar*H*), 6.92 (2H, d, *J* 6.0, Ar*H*), 6.67 (1H, s, 3-C*H*), 4.53 (1H, s, 4-C*H*), 3.74 (1H, dd, *J* 9.4, 4.6, 7-C*H*), 3.48 (1H, d, *J* 15.0, NCH_2), 3.47 (1H, d, *J* 15.0, NCH_2), 3.30 – 3.28 (1H, m, 5-C*H*), 2.62 (1H, ddd, *J* 13.4, 8.0, 4.6, 6-CH_2), 2.04 – 1.93 (1H, m, 6-CH_2); **^{13}C NMR** (101 MHz, DMSO-d_6) 194.2 (*C*=O), 138.7 (*Ar*H), 138.5 (*Ar*H), 134.3 (*Ar*H), 129.9 (*Ar*H), 129.1 (*Ar*H), 128.5 (*Ar*H), 128.4 (*Ar*H), 127.3 (*Ar*H), 123.8 (1-*C*H), 121.0 (3-*C*H), 117.4 (8a-*C*), 114.3 (3a-*C*), 69.7 (5-*C*H), 67.3 (7-*C*H), 56.7 (4-*C*H), 51.3 (N*C*H_2), 28.4 (6-*C*H_2); **IR** ν_{max} (neat)/cm^{-1}: 3172, 3122, 2896 (C-H), 1658 (C=O), 1494, 1460 (C=C), 1445, 1324 (S=O); **HRMS** (ESI): $C_{22}H_{21}N_2O_3S$ [M+H$^+$]: calculated 393.1267, found 393.1267.

(3a*R**,5*S**,7*R**,8*S**,8a*S**)-3,9-Dimethyl-7-(methylsulfonyl)-6,7,8,8a-tetrahydro-3a*H*-5,8-epiminocyclohepta[*d*]isoxazol-4(5*H*)-one **(157)**



General procedure **L** was followed using cycloadduct **116** (1.00 g, 4.65 mmol), nitroethane (0.67 mL, 9.29 mmol), phenylisocyanate (2.20 mL, 18.6 mmol) and triethylamine (33 μL, 0.23 mmol). Purification by flash chromatography on silica gel, eluting with a gradient of 40 - 100% EtOAc in hexane afforded the *title compound **157*** (358 mg, 1.31 mmol, 28%) as a colourless solid; $\boldsymbol{R_f}$ = 0.09, (100% in EtOAc); **δ_H(400 MHz, DMSO-*d*$_6$):** 4.61 (1H, dd, *J* 10.5, 1.6, 8a-C*H*), 4.05 (1H, d, *J* 10.5, 3a-C*H*), 3.93 – 3.81 (2H, m, 8-C*H*, 7-C*H*), 3.62 (1H, d, *J* 7.5, 5-C*H*), 3.07 (3H, s, N*Me*), 2.50 – 2.44 (1H, m, 6-CH_2), 2.37 (3H, s, SO_2*Me*), 2.14 (1H, dd, *J* 13.9, 9.1, 6-CH_2), 1.92 (3H, s, *Me*); **δ_C(101 MHz, DMSO-*d*$_6$):** 201.5 (*C*=O), 152.0 (3-*C*), 81.4 (8a-*C*), 71.7 (5-*C*), 64.3 (8-*C*), 63.4 (7-*C*), 58.8 (3a-*C*), 40.2 (SO_2*Me*) 39.1 (N*Me*), 28.3 (6-*C*H_2), 12.7 (*Me*); **IR** ν_{max} (neat)/cm^{-1}: 3025, 2985 (CH), 2944, 2918, 1715 (C=O), 1459 (C=C), 1432, 1272 (S=O); **HRMS** (ESI): [M+H$^+$]: $C_{11}H_{17}N_2O_4S$ calculated 273.0904, found 273.0566.

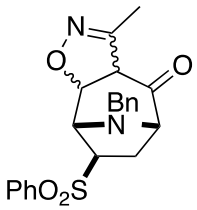
(3a*R**,5*S**,7*R**,8*S**,8a*S**)-9-(4-Methoxybenzyl)-3-methyl-7-(methylsulfonyl)-6,7,8,8a-tetrahydro-3a*H*-5,8-epiminocyclohepta[*d*]isoxazol-4(5*H*)-one **(158)**



General procedure **L** was followed using cycloadduct **134** (391 mg, 1.22 mmol), nitroethane (0.22 mL, 3.04 mmol), phenylisocyanate (0.6 mL, 5.49 mmol) and triethylamine (15 μL, 0.10 mmol). Purification by flash chromatography on silica gel, eluting with a gradient of 40 - 100% EtOAc in hexane afforded the *title compound **158*** (130 mg, 0.34 mmol, 28%) as a colourless solid; $\boldsymbol{R_f}$ = 0.14, (60% EtOAc in hexane); **δ_H (400 MHz, Chloroform-*d*):** 7.15 (2H, d, *J* 8.7, Ar*H*), 6.77 (2H, d, *J* 8.7, Ar*H*), 4.57 (1H, dd, *J* 10.5, 1.7, 8a-C*H*), 4.08 (1H, s, 8-C*H*), 3.83 – 3.68 (3H, m, NCH_2, 3a-C*H*), 3.63 (1H, d, *J* 7.6, 5-C*H*), 3.26 (1H, t, 7-C*H*), 2.87 (3H, s, O*Me*), 2.59 (1H, dt, *J* 14.5, 7.6, 6-CH_2), 2.54 (3H, s, SO_2*Me*), 2.16 (1H, dd, *J* 14.5, 9.2, 6-CH_2), 1.97

(3H, s, *Me*); **δc(101 MHz, Chloroform-*d*):** 200.4 (*C*=O), 159.1 (*Ar*), 151.3 (3-*C*), 130.1 (*Ar*H), 129.3 (*Ar*H), 113.8 (*Ar*), 81.5 (8a-*C*), 69.5 (5-*C*), 64.2 (8-*C*), 62.6 (7-*C*), 60.0 (3a-*C*), 55.2 (O*Me*), 54.3 (N*C*H_2), 39.9 (SO_2*Me*), 29.6 (6-*C*H_2), 12.3 (*Me*); **IR** ν_{max} (neat)/cm^{-1}: 3034 (CH), 3008, 2951, 2932, 1716 (C=O), 1510 (C=C), 1455, 1316 (S=O); **LCMS:** $C_{18}H_{23}N_2O_5S$ [M+H^+]: calculated 379.1322, found 379.35.

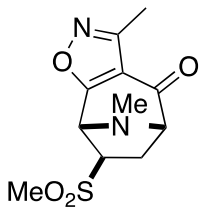
(5*S**,7*R**,8*S**)-9-benzyl-3-methyl-7-(phenylsulfonyl)-6,7,8,8a-tetrahydro-3a*H*-5,8-epiminocyclohepta[*d*]isoxazol-4(5*H*)-one (**152 – 153**)



2:1

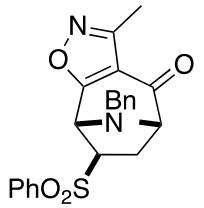
General procedure **L** was followed using cycloadduct **87** (600 mg, 0.29 mmol, 1.0 eq.), nitroethane (0.3 mL, 3.4 mmol, 2.0 eq.), phenylisocyanate (0.8 mL, 6.93 mmol, 4.1 eq.), triethylamine (6 drops) in THF/Et_2O (1:1) (8 mL). Purification by flash chromatography on silica gel, eluting with a gradient of 25% EtOAc in hexane afforded the *title compound* **152 – 153** (142 mg, 0.35 mmol, 18%) as yellow solid; $\boldsymbol{R_f}$ = 0.15, (25% EtOAc in hexane). Major isomer was determined by protons on the crude 1H-NMR spectra. **^{1}H NMR** (400 MHz, $CDCl_3$) 8.01 – 7.14 (10H, m Ar*H*), 4.51 (1H, d, *J* 10.9, 8-C*H*), 4.02 (1H, d, *J* 1.5, 3a-C*H*) 3.95 (1H, d, *J* 12.7, NCH_2), 3.83 – 3.78 (1H, m, 7-C*H*), 3.64 (1H, d, *J* 12.7, NCH_2), 3.44 (1H, td, *J* 8.7, 2.0, 5-C*H*), 3.23 (1H, dt, *J* 10.9, 1.5, 8a-C*H*), 2.70 – 2.55 (1H, m, 6-C*H*), 1.97 – 1.83 (1H, m, 6-C*H*), 1.28 (3H, s, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): 199.4 (*C*=O), 138.5 (*Ar*), 137.3 (*Ar*), 134.4 (*Ar*H), 129.8 (*Ar*H), 129.8 (*Ar*H), 128.6 (*Ar*H), 128.1 (*Ar*H), 127.8 (*Ar*H), 79.1(8-*C*H), 71.6 (7-*C*H), 69.5 (5-*C*H), 59.1 (8a-*C*H), 59.0 (3a-*C*H), 55.5 (N*C*H_2) 30.7 (6-*C*H_2), 10.5 (*C*H_3); **IR** ν_{max} (neat)/cm^{-1}: 3096, 3019, 2995 (C-H), 2906, 1706 (C=O), 1470, 1445 (C=C), 1310 (S=O); **HRMS** (ESI): $C_{22}H_{23}N_2O_4S$ [M+H^+]: calculated 411.1373, found 411.1377.

(5*S**,7*R**,8*S**)-3,9-Dimethyl-7-(methylsulfonyl)-5,6,7,8-tetrahydro-4*H*-5,8-epiminocyclohepta[*d*]isoxazol-4-one (**159**)



To a stirred solution of dihydroisoxazole **157** (255 mg, 0.83 mmol) in PhMe (4 mL) was added DDQ (258 mg, 1.25 mmol, 1.5 eq.) and the mixture refluxed for 2h. The cooled crude mixture was concentrated *in vacuo.* Purification by reverse phase biotage MeCN/H_2O 1% formic acid gave *title compound* **159** *(*36 mg, 0.13 mmol, 16%) as a white solid; **δ_H (300 MHz, DMSO-*d*$_6$)** 5.08 (1H, s, 8-C*H*), 3.96 (1H, dd, *J* 9.4, 4.2, 7-C*H*), 3.65 (1H, d, *J* 7.8, 5-C*H*), 3.06 (3H, s, *Me*), 2.71 (1H, ddd, *J* 14.5, 7.8, 4.3, 6-CH_2), 2.40 (3H, s, *Me*), 2.32 (3H, s, *Me*), 2.04 (1H, dd, *J* 14.5, 9.4, 6-CH_2); δ_C (75 MHz, DMSO): 217.0 (*C*=O), 197.3 (*Ar*), 174.3 (*Ar*), 123.0 (*Ar*), 75.0 (5-*C*), 70.9 (8-*C*), 64.4 (7-*C*), 41.0 (*Me*), 35.6 (*Me*), 28.5 (6-*C*), 9.0 (*Me*); **IR** ν_{max} (neat)/cm^{-1}: 3015, 3006 (CH), 2984, 2908, 1720 (C=O), 1469 (C=C), 1432, 1271 (S=O); **HRMS** (ESI): [M+H$^+$]: $C_{11}H_{15}N_2O_4S$ calculated 271.0747, found 271.0747.

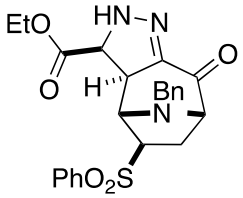
(5*S**,7*R**,8*S8*)-9-Benzyl-3-methyl-7-(phenylsulfonyl)-5,6,7,8-tetrahydro-4*H*-5,8-epiminocyclohepta[*d*]isoxazol-4-one (**156**)



To a stirred solution of dihydroisoxazole **152 – 153** (2.00 g, 4.88 mmol) in PhMe (24 mL) was added DDQ (2.76 g, 7.32 mmol, 1.5 eq.) and the mixture refluxed for 2h. The cooled crude mixture was concentrated *in vacuo.* Purification by reverse phase biotage MeCN/H_2O 1% formic acid gave *title compound* **156** *(*125 mg, 0.31 mmol, 6%); **δ_H (400 MHz, Chloroform-*d*)** 7.80 – 7.75 (2H, m, Ar*H*), 7.62 (1H, ddt, *J* 8.7, 7.0, 1.2, Ar*H*), 7.52 – 7.46 (2H, m, Ar*H*), 7.24 – 7.20 (3H, m, Ar*H*), 7.02 (2H, dd, *J* 7.3, 2.2, Ar*H*), 4.72 (1H, s, 8-C*H*), 3.73 – 3.63 (2H, m, 5-C*H*, NB*n*), 3.56 (1H, dd, *J* 9.2, 4.4, 7-C*H*), 3.49 (1H, d, *J* 13.3, NB*n*), 2.84 (1H, ddd, *J* 14.6, 7.9, 4.4, 6-CH_2), 2.40 (3H, s, *Me*), 2.01 – 1.93 (1H, m, 6-CH_2); **δ_C** (101 MHz, **Chloroform-*d*)** 193.7 (*C*=O), 176.5 (*Ar*), 157.2 (*Ar*), 136.0 (*Ar*), 134.3 (*Ar*), 129.6 (*Ar*H),

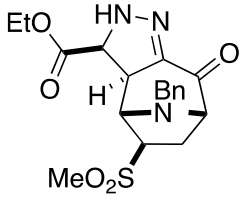
128.8 (*Ar*H), 128.7 (*Ar*H), 128.5 (*Ar*H), 127.9 (*Ar*H), 119.2 (*Ar*H), 112.1 (*Ar*), 67.6 (8-*C*H), 66.8 (6-*C*H), 58.0 (7-*C*H), 51.7 (N*C*H_2), 27.7 (6-*C*H_2), 10.6 (*Me*); **IR** ν_{max} (neat)/cm^{-1}: 3025, 2982 (CH), 2957, 2937, 1697 (C=O), 1494 (C=C), 1457, 1150 (S=O); **HRMS** (ESI): $C_{22}H_{21}N_2O_4S$ [$M+H^+$]: calculated 409.1217, found 409.1218.

(3*S**,3a*S**,4*S**,5*R**,7*S**)-Ethyl-9-benzyl-8-oxo-5-(phenylsulfonyl)-2,3,3a,4,5,6,7,8-octahydro-4,7-epiminocyclohepta[*c*]pyrazole-3-carboxylate (**168)**



General procedure **M** was followed using cycloadduct **89** (200 mg, 0.56 mmol, 1.0 eq.), and ethyl diazoacetate (0.90 mL, 1.12 mmol, 2.0 eq.) in anhydrous THF (1.4 mL). Purification by flash chromatography on silica gel, eluting with a gradient of 50% EtOAc in hexane afforded the *title compound **168*** (150 mg, 0.32 mmol, 58%) as yellow oil; $\boldsymbol{R_f}$ = 0.79 (40% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) 8.01 – 7.94 (2H, m, Ar*H*), 7.75 – 7.64 (1H, m, Ar*H*), 7.61 (2H, dd, *J* 8.3, 7.0, Ar*H*), 7.36 – 7.22 (5H, m, Ar*H*), 6.74 (1H, s, N*H*), 4.74 (1H, s, 4-C*H*), 4.18 – 3.86 (4H, m, 3-C*H*, NCH_2, OCH_2), 3.77 (1H, d, *J* 13.3, NCH_2), 3.72 (1H, d, *J* 7.5, 5-C*H*), 3.66 (1H, t, *J* 7.6, 7-C*H*), 3.36 (1H, dd, *J* 11.3, 1.9, 3a-C*H*), 2.83 (1H, dt, *J* 14.5, 7.6, 6-CH_2), 2.16 (1H, dd, *J* 14.5, 9.2, 6-CH_2), 1.19 (3H, t, *J* 7.6, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): 201.7 (*C*=O), 161.1 (*C*=O), 142.6 (*Ar*), 138.8 (*Ar*), 137.6 (8a-*C*), 134.2 (*Ar*H), 129.7 (*Ar*H), 129.0 (*Ar*H), 128.4 (*Ar*H), 128.3 (*Ar*H), 127.4 (*Ar*H), 69.7 (7-*C*H), 69.7 (3-*C*H), 63.6 (5-*C*H), 61.1 (*C*H_2), 60.3 (4-*C*H), 55.5 (N*C*H_2), 53.2 (3a-*C*H), 28.6 (6-*C*H_2), 14.0 (*C*H_3); **IR** ν_{max} (neat)/cm^{-1}:3067, 2903 (C-H), 2870, 1715 (C=O), 1627, 1494, 1445 (C=C), 1331 (S=O); **HRMS** (ESI): $C_{24}H_{26}N_3O_5S$ [M+H$^+$]: calculated 468.1588, found 468.1578.

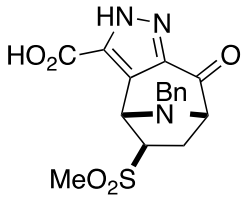
(3*S**,3a*S**,4*S**,5*R**,7*S**)-Ethyl 9-benzyl-5-(methylsulfonyl)-8-oxo-2,3,3a,4,5,6,7,8-octahydro-4,7-epiminocyclohepta[*c*]pyrazole-3-carboxylate (**169**)



General procedure **M** was followed using cycloadduct **117** (3.19 g, 10.94 mmol) and ethyl diazoacetate (2.3 mL, 21.9 mmol) in anhydrous THF (54 mL). Purification by flash chromatography on silica gel, eluting with a gradient of 80 - 100% EtOAc in hexane afforded the *title compound **169*** (3.44 g, 8.52 mmol, 78%) as a colourless solid; $\boldsymbol{R_f}$ = 0.38, (100% EtOAc); **δ_H (400 MHz, Chloroform-*d*):** 7.33 – 7.20 (5H, m, Ar*H*), 6.85 (1H, s, N*H*), 4.72 (1H, s, 4-C*H*), 4.27 (1H, d, *J* 11.6, 3-C*H*), 4.06 – 4.02 (2H, m, OCH_2), 3.94 (1H, d, *J* 13.2, N*Bn*),

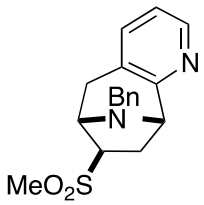
3.80 – 3.72 (2H, m, N*Bn*, 5-C*H*), 3.68 – 3.57 (2H, m, 7-C*H*, 3a-C*H*), 3.04 (3H, s, SO_2*Me*), 2.80 (1H, dt, *J* 14.6, 7.4, 6-CH_2), 2.37 (1H, dd, *J* 14.6, 9.3, 6-CH_2), 1.24 (3H, t, *J* 7.1, CH_3); **δC(101 MHz, Chloroform-*d*):** 201.8 (*C*=O), 161.4 (*C*=O), 142.4 (*Ar*), 137.3 (*C*), 129.0 (*Ar*H), 128.5 (*Ar*H), 127.5 (*Ar*H), 69.3 (5-*C*), 67.9 (7-*C*), 63.7 (3-*C*), 61.3 (OCH_2), 60.0 (4-*C*), 55.0 (NCH_2), 53.1 (3a-*C*), 40.3 (SO_2*Me*), 28.2 (6-CH_2), 14.0 (CH_3); **IR** ν_{max} (neat)/cm^{-1}: 3286 (NH), 3003 (CH), 2981, 2931, 1716 (C=O), 1565 (C=C), 1494, 1292 (S=O); **HRMS** (ESI): $C_{19}H_{24}N_3O_5S$ [M+H^+]: calculated 406.1431, found 406.1427.

(4*S**,5*R**,7*S**)-9-Benzyl-5-(methylsulfonyl)-8-oxo-2,4,5,6,7,8-hexahydro-4,7-epiminocyclohepta[*c*]pyrazole-3-carboxylic acid (**170**)



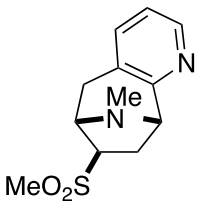
General procedure **M** was followed using cycloadduct **19** (3.19 g, 10.94 mmol) and ethyl diazoacetate (contains ≥ 13 wt. % DCM) (2.3 mL, 21.9 mmol) in THF (55 mL). The reaction mixture was filtered through silica. General procedure **N** was followed using compound **169**, NaOH (4M) (20 mL) and MeOH (15 mL). The reaction mixture was concentrated *in vacuo* and purification by reverse phase biotage MeCN/H_2O 1% formic acid gave the *title compound* **170** (322 mg, 0.86 mmol, 8%) as a colourless oil; **δH (300 MHz, DMSO-*d*6):** 7.34 – 7.16 (5H, m, Ar*H*), 5.00 (1H, s, 4-C*H*), 3.75 – 3.62 (4H, m NBn, 5-C*H*, 7-C*H*), 2.99 (3H, s, *Me*), 2.83 – 2.71 (1H, m, 6-CH_2), 2.09 (1H, dd, *J* 14.9, 9.6, 6-CH_2); **δc (126 MHz, DMSO):** 190.0 (*C*=O), 172.5 (*C*=O), 163.6 (*Ar*), 162.8 (*Ar*), 162.7 (*Ar*), 137.3(*Ar*), 128.5 (*Ar*H), 128.1 (ArH), 127.2 (*Ar*), 67.6 (7-*C*), 66.8(5-*C*), 56.5 (4-*C*), 51.3, (N*Bn*), 39.0 (*Me*), 26.5. (6-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3466 (OH), 3047, 3023, 2995 (CH), 1699 (C=O), 1557 (C=C), 1455, 1296 (S=O); **HRMS** (ESI): $C_{17}H_{18}N_3O_5S$ [M+H^+]: calculated 376.0962, found 376.0971.

(6S*,7R*,9S*)-10-Benzyl-7-(methylsulfonyl)-6,7,8,9-tetrahydro-5H-6,9-epiminocyclohepta[b]pyridine (**202**)



General procedure **O** was followed using compound **175** (111 mg, 0.38 mmol), propylamine (50 μl, 0.76 mmol) and sodium tetrachloroaurate(III) dihydrate (4 mg, 2.5 mol%) in EtOH (1.9 mL). Purification by flash chromatography on silica gel, eluting with a gradient of 100% EtOAc in hexane afforded the *title compound **202*** (79 mg, 0,24 mmol, 63%) as a brown oil; $\boldsymbol{R_f}$ = 0.44 (1% MeOH in DCM); **δ_H (300 MHz, Chloroform-*d*):** 8.32 (1H, dd, *J* 4.8, 1.5, Ar*H*), 7.37 (1H, d, *J* 7.7, Ar*H*), 7.30 – 7.16 (5H, m, Ar*H*), 7.10 (1H, dd, *J* 7.7, 4.8, Ar*H*), 4.18 (1H, d, *J* 6.2, 6-C*H*) 3.82 (1H, d, *J* 5.0, 5-C*H*), 3.71 (1H, d, *J* 13.1, N*Bn*), 3.57 (1H, d, *J* 13.1, N*Bn*), 3.37 – 3.18 (2H, m, 1-C*H*, 4-CH_2), 2.81 (3H, s, *Me*), 2.65 – 2.43 (2H, m, 7-CH_2, 4-CH_2), 2.33 (1H, dd, *J* 13.3, 9.2, 7-CH_2); **^{13}C NMR (75 MHz, Chloroform-*d*):** 157.7 (*Ar*), 147.9 (*Ar*H), 137.9 (*Ar*H), 137.2 (*Ar*H), 128.7 (*Ar*H), 128.5 (*Ar*H), 127.5 (*Ar*), 126.8 (*Ar*H), 122.8 (*Ar*H), 68.1 (6-*C*), 64.2 (1-*C*), 56.7 (5-*C*), 52.2 (N*Bn*), 37.4 (*Me*), 36.9 (4-*C*), 30.7 (7-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3061, 3028 (CH), 3007, 2928, 2845, 1495 (C=C), 1444, 1292 (S=O); **HRMS** (ESI): $C_{18}H_{21}N_2O_2S$ [M+H$^+$]: calculated 329.1318, found 329.1324.

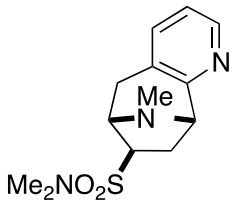
(6*S**,7*R**,9*S**)-10-Methyl-7-(methylsulfonyl)-6,7,8,9-tetrahydro-5*H*-6,9-epiminocyclohepta[*b*]pyridine (**205**)



General procedure **O** was followed using compound **176** (1.00 g, 4.60 mmol), propylamine (2.1 mL, 9.2 mmol) and sodium tetrachloroaurate(III) dihydrate (37 mg, 2.5 mol%) in EtOH (23 mL). Purification by reverse phase biotage MeCN/H_2O 1% formic acid gave *title compound* **205** (500 mg, 1.98 mmol, 43%) as a brown oil; **δ_H (400 MHz, DMSO-d_6):** 8.31 (1H, dd, *J* 4.9, 1.5, Ar*H*), 7.52 (1H, dd, *J* 7.7, 1.5, Ar*H*), 7.21 (1H, dd, *J* 7.7, 4.9, Ar*H*), 3.99 (1H, d, *J* 6.1, 6-C*H*), 3.87 – 3.82 (1H, m, 5-C*H*), 3.60 (1H, t, *J* 8.2, 1-C*H*), 3.29 – 3.15 (1H, m,

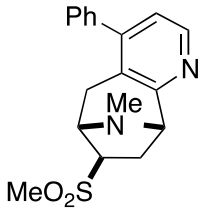
4-CH_2), 2.97 (3H, s, *Me*), 2.61 – 2.39 (2H, m, 4-CH_2, 7-CH_2), 2.31 (3H, s, *Me*), 2.11 (1H, dd, *J* 12.8, 9.1, 7-CH_2); **δ_C (101 MHz, DMSO-d_6)**: 158.3 (*Ar*), 147.5 (*Ar*H), 137.4 (*Ar*H), 127.7 (*Ar*), 122.9 (*Ar*H), 66.8 (1-*C*), 65.9 (6-*C*), 58.9 (5-*C*), 39.0 (*Me*), 36.1 (4-*C*), 35.9 (*Me*), 30.9 (7-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3050, 3026 (CH), 2967, 2880, 1558, 1540 (C=C), 1430, 1202 (S=O); **HRMS** (ESI): $C_{12}H_{17}N_2O_2S$ [M+H$^+$]: calculated 253.1005, found 253.1002.

(6*S**,7*R**,9*S**)-*N*,*N*,10-Trimethyl-6,7,8,9-tetrahydro-5*H*-6,9-epiminocyclohepta[*b*]pyridine-7-sulfonamide (**204**)



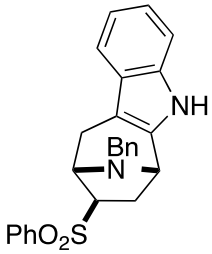
General procedure **O** was followed using compound **177** (89 mg, 0.36 mmol), propylamine (47 µl, 0.72) and sodium tetrachloroaurate(III) dihydrate (4 mg, 2.5 mol%) in EtOH (1.8 mL). Purification by reverse phase biotage MeCN/H_2O 1% formic acid gave *title compound* **204** (40.1 mg, 0.14 mmol, 40%) as a brown oil; **δ_H (400 MHz, Chloroform-*d*):** 8.40 (1H, d, *J* 4.5, Ar*H*), 7.45 (1H, dd, *J* 7.9, 1.5, Ar*H*), 7.18 (1H, dd, *J* 7.9, 4.5, Ar*H*), 4.21 (1H, d, *J* 6.2, 6-C*H*), 4.04 – 3.95 (1H, m, 5-C*H*), 3.45 – 3.31 (2H, m, 1-CH_2, 4-CH_2), 2.92 (6H, s, NMe_2), 2.72 (1H, ddd, *J* 12.7, 7.8, 6.2, 7-CH_2), 2.58 (1H, d, *J* 17.1, 4-CH_2), 2.52 (3H, s, *Me*), 2.29 (1H, dd, *J* 12.7, 8.8, 7-CH_2); **δ_C** (101 MHz, **Chloroform-*d*):** 158.0 (*Ar*), 147.2 (*Ar*H), 137.5 (*Ar*H), 127.1 (*Ar*), 122.7 (*Ar*H), 66.2 (6-*C*), 64.6(1-*C*), 60.5 (5-*C*), 38.0 (*Me*), 36.7 (*Me*), 36.5 (4-*C*), 32.2 (7-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3062 (CH), 2994, 2849, 2801, 1577 (C=C), 1446, 1429, 1280 (S=O); **HRMS** (ESI): $C_{13}H_{20}N_3O_2S$ [M+H$^+$]: calculated 282.1271, found 282.1278.

(6*S**,7*R**,9*S**)-10-Methyl-7-(methylsulfonyl)-4-phenyl-6,7,8,9-tetrahydro-5*H*-6,9-epiminocyclohepta[*b*]pyridine (**205**)



General procedure **O** was followed using compound **176** (250 mg, 1.15 mmol), 3-Phenyl-2-propyn-1-ol (386 mg, 2.30 mmol) and sodium tetrachloroaurate(III) dihydrate (10 mg, 2.5 mol%). in EtOH (6 mL). Purification by reverse phase biotage MeCN/H_2O 1% formic acid gave *title compound* afforded the *title compound* **205** (75 mg, 0,23 mmol, 20%) as a brown oil; **δ_H (400 MHz, Chloroform-*d*)**: 8.37 (1H, d, *J* 5.0, Ar*H*), 7.49 – 7.28 (3H, m, Ar*H*), 7.23 – 7.18 (2H, m, Ar*H*), 7.02 (1H, d, *J* 5.0, Ar*H*), 4.19 (1H, d, *J* 6.1, 6-C*H*), 3.85 (1H, dd, *J* 5.2, 1.3, 5-C*H*), 3.22 – 3.11 (2H, m, 1-C*H*, 4-CH_2), 2.84 (3H, s, *Me*), 2.59 (1H, ddd, *J* 13.2, 7.2, 6.2, 7-CH_2), 2.46 – 2.31 (5H, m, *Me*, 7-CH_2, 4-CH_2); **δ_C** (101 MHz, **Chloroform-*d*)**: 157.7 (Ar), 150.4 (Ar), 147.8 (Ar*H*), 137.9 (Ar), 128.7 (Ar*H*), 128.4 (Ar*H*), 128.1 (Ar*H*), 124.2 (*Ar*), 123.6 (Ar*H*), 68.1 (1-*C*), 66.4 (6-*C*), 59.4 (5-*C*), 38.1 (*Me*), 36.8 (4-*C*), 35.8 (*Me*), 30.1 (7-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3024 (CH), 2953, 2883, 2855, 1508 (C=C), 1420, 1270 (S=O), 1123; **HRMS** (ESI): $C_{18}H_{21}N_2O_2S$ [M+H^+]: calculated 329.1318, found 329.1313.

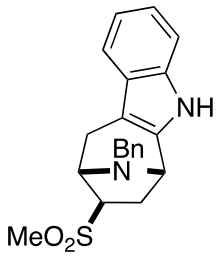
(6*S**,8*R**,9*S**)-11-Benzyl-8-(phenylsulfonyl)-5,6,7,8,9,10-hexahydro-6,9-epiminocyclohepta[*b*]indole (**186**)



General procedure **P** was followed using ketone **174** (100 mg, 0.29 mmol, 1.0 eq.), 2-iodoaniline (74 mg, 0.34 mmol, 1.2 eq.), $Pd(OAc)_2$ (4 mg, 10 mol%) and DABCO (32 mg, 0.34 mmol, 1.0 eq.) in anhydrous DMF (0.3 mL). Purification by flash chromatography on silica gel, eluting with a gradient of 60% EtOAc in hexane. Crystallization from EtOAc afforded the *title compound **186*** (48 mg, 0.11 mmol, 40%) as a brown solid; $\boldsymbol{R_f}$ = 0.80, (60% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) 8.00 – 7.86 (2H, m, Ar*H*), 7.79 (1H, s, NH),

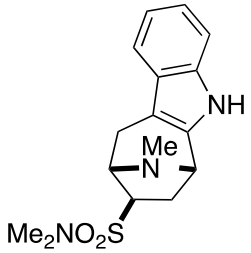
7.74 – 7.59 (1H, m, Ar*H*), 7.66 – 7.47 (2H, m, Ar*H*), 7.52 – 7.37 (1H, m, Ar*H*), 7.35 – 7.21 (4H, m, Ar*H*), 7.27 – 7.02 (4H, m, Ar*H*), 4.10 (1H, s, 9-C*H*), 3.98 (1H, d, *J* 5.5, 8-C*H*), 3.70 (1H, d, *J* 13.6, NCH_2), 3.64 (1H, d, *J* 13.6, NCH_2), 3.55 (1H, t, *J* 7.8, 6-C*H*), 3.18 (1H, dd, *J* 16.2, 4.4, 10-CH_2), 2.63 (1H, ddd, *J* 12.4, 7.4, 5.6, 7-CH_2), 2.40 (1H, dd, *J* 16.2, 1.2, 10-CH_2), 2.24 (1H, dd, *J* 12.4, 8.7, 7-CH_2). **^{13}C NMR** (101 MHz, $CDCl_3$): 138.5 (*Ar*), 138.4 (*Ar*), 135.5 (*Ar*H), 135.3 (*Ar*), 133.6 (*Ar*H), 129.2 (*Ar*H), 128.9 (*Ar*H), 128.9 (*Ar*), 128.4 (*Ar*H), 128.3 (*Ar*H), 127.0 (*Ar*), 121.8 (*Ar*H), 119.9 (*Ar*H), 118.2 (*Ar*H), 111.2 (*Ar*H), 103.7 (*Ar*), 69.4 (8-*C*H), 57.1 (9-*C*H), 56.2 (6-*C*H), 51.2 (NCH_2), 37.9 (7-*C*H_2), 25.7 (10-*C*H_2); **IR** ν_{max} (neat)/cm^{-1}: 3381, 3026 (C-H), 2800, 2685, 2615, 1495 (C=C), 1445, 1337 (S=O); **HRMS** (ESI): $C_{26}H_{25}N_2O_2S$ [M+H$^+$]: calculated 429.1631, found 429.1650.

(6*S**,8*R**,9*S**)-11-Benzyl-8-(methylsulfonyl)-5,6,7,8,9,10-hexahydro-6,9-epiminocyclohepta[*b*]indole (**186**)



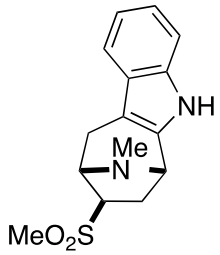
General procedure **P** was followed using ketone **175** (100 mg, 0.34 mmol), 2-iodoaniline (150 mg, 0.68 mmol), $Pd(OAc)_2$ (6 mg, 10 mol%) and DABCO (77 mg, 0.68 mmol). Purification by flash chromatography on silica gel, eluting with a gradient of 50% EtOAc in hexane afforded the *title compound* **186** (25 mg, 0.07 mmol, 20%) as a colourless solid; $\boldsymbol{R_f}$ = 0.23, (50% EtOAc); **δ_H(400 MHz, Chloroform-*d*):** 7.92 (1H, s, N*H*), 7.53 – 7.37 (3H, m, Ar*H*), 7.34 – 6.95 (6H, m, Ar*H*), 4.05 (1H, d, *J* 5.4, 9-C*H*), 3.90 (1H, d, *J* 4.6, 8-C*H*), 3.67 (1H, d, *J* 13.2 N*Bn*), 3.62 (1H, d, *J* 13.2, N*Bn*), 3.32 – 3.19 (2H, m, 6-C*H*, 10-CH_2), 2.85 (3H, s, N*Me*), 2.54 – 2.33 (3H, m, 10-CH_2, 7-CH_2); **δ_C(101 MHz, Chloroform-*d*):** 138.4 (*Ar*), 135.6 (*Ar*), 134.9 (*Ar*), 129.8 (*Ar*H), 128.6 (*Ar*H), 127.2 (*Ar*), 121.9 (*Ar*H), 120.0 (*Ar*H), 118.9 (*Ar*H), 118.3 (*Ar*H), 111.3 (*Ar*H), 103.3 (*Ar*), 68.5 (8-*C*), 57.3 (9-*C*), 56.2 (6-*C*), 51.2 (N*Bn*), 38.4 (*Me*), 37.0 (7-*C*), 25.1(10-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3285 (NH), 3003 (CH), 2995, 2922, 2876, 1510 (C=C), 1498, 1298 (S=O); **HRMS** (ESI): [M+H$^+$]: $C_{21}H_{23}N_2O_2S$ calculated 367.1475, found 367.2178.

(6S*,8R*,9S*)-N,N,11-Trimethyl-5,6,7,8,9,10-hexahydro-6,9-epiminocyclohepta[b]indole-8-sulfonamide (**187**)



General procedure **P** was followed using compound **177** (105 g, 0.43 mmol) and 2-iodoaniline (280 mg, 1.29 mmol), $Pd(OAc)_2$ (20 mg, 15 mol%) and DABCO (143 mg, 1.29 mmol) in DMF (1 mL). Purification by flash chromatography on silica gel, eluting with a gradient of 90% EtOAc in hexane affording the *title compound* **187** (40 mg, 0.12 mmol, 29%) as a colourless solid; $\boldsymbol{R_f}$ = 0.34, (90% EtOAc in hexane); **δ_H (400 MHz, Chloroform-*d*):** 8.13 (1H, s, N*H*), 7.43 – 7.35 (1H, m, Ar*H*), 7.27 (1H, dd, *J* 7.8, 1.2, Ar*H*), 7.13 – 6.97 (2H, m, Ar*H*), 4.04 (1H, d, *J* 5.3, 8-C*H*), 3.94 (1H, d, *J* 4.1, 9-C*H*), 3.47 – 3.33 (1H, m, 6-C*H*), 3.17 (1H, dd, *J* 16.0, 4.3, 10-CH_2), 2.82 (6H, s, NMe_2), 2.58 (1H, ddd, *J* 12.3, 7.6, 5.5, 7-CH_2), 2.43 (1H, dd, *J* 16.0, 1.2, 10-CH_2), 2.37 (3H, s, *Me*), 2.22 (1H, dd, *J* 12.3, 8.7, 7-CH_2); **δ_C (101 MHz, Chloroform-*d*):** 135.7 (*Ar*), 135.2 (*Ar*), 127.2 (*Ar*), 121.7 (*Ar*H), 119.8 (*Ar*H), 118.1 (*Ar*H), 111.3 (*Ar*H) 103.2 (*Ar*), 64.8 (6-*C*), 59.6 (9-*C*), 58.8 (8-*C*), 38.4 (N*Me*), 38.0 (7-*C*), 34.8 (Me), 25.5 (10-C);**IR νmax (neat)/cm-1:** 3385(NH), 3102 (CH), 3058, 2943, 2849, 1541 (C=C), 1453, 1291 (S=O); **HRMS (ESI):** $C_{16}H_{22}N_3O_2S$ [M+H+]: calculated 320.1427, found 320.1428.

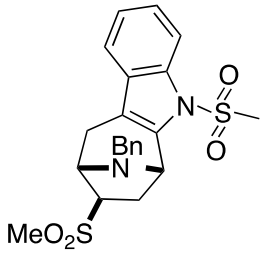
(6*S**,8*R**,9*S**)-11-Methyl-8-(methylsulfonyl)-5,6,7,8,9,10-hexahydro-6,9-epiminocyclohepta[*b*]indole (**189**)



General procedure **P** was followed using compound **176** (200 mg, 0.92 mmol) and 2-iodoaniline (633 mg, 2.76 mmol), $Pd(OAc)_2$ (31 mg, 15 mol%) and DABCO (310 mg, 2.76 mmol) in DMF (4.6 mL) at 120 ^oC for 2 d. Purification by reverse phase biotage MeCN/H_2O 1% formic acid gave *title compound **189*** (45 mg, 0,16 mmol, 17%) as a brown oil; **δ_H (400 MHz, DMSO-d_6):** 10.83 (1H, s, N*H*), 7.36 (1H, d, *J* 8.0, Ar*H*), 7.30 (1H, d, *J* 8.0, Ar*H*), 7.03

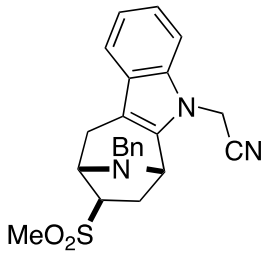
(1H, t, *J* 7.4, Ar*H*), 6.96 (1H, t, *J* 7.4, Ar*H*), 4.08 (1H, d, *J* 5.4, 8-CH_2), 3.86 (1H, d, *J* 4.2, 9-CH_2), 3.50 (1H, t, *J* 8.0, 6-CH_2), 3.16 – 3.04 (1H, m, 10-CH_2), 2.97 (3H, s, *Me*), 2.28 (3H, s, *Me*), 2.54 – 2.39 (2H, m, 10-CH_2, 7-CH_2) 2.24 (1H, dd, *J* 12.0, 8.9, 7-CH_2); **δ_C (101 MHz, DMSO-d_6):** 136.4 (*Ar*), 136.0 (*Ar*), 127.4 (*Ar*), 120.8 (*Ar*H), 119.0 (*Ar*H), 118.1 (*Ar*H), 111.7 (*Ar*H), 101.9 (*Ar*), 67.5 (6-*C*), 58.4 (8-*C*), 58.4 (9-*C*), 38.6 (*Me*), 37.7 (7-*C*), 34.4 (*Me*), 25.0 (10-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3216 (NH), 3100, 2990 (CH), 2923, 2877, 1507 (C=C), 1418, 1285 (S=O); **HRMS** (ESI): $C_{15}H_{19}N_2O_2S$ [M+H$^+$]: calculated 291.1162, found 291.1158.

(6*S**,8*R**,9*S**)-11-Benzyl-5,8-bis(methylsulfonyl)-5,6,7,8,9,10-hexahydro-6,9-epiminocyclohepta[*b*]indole (**336**)



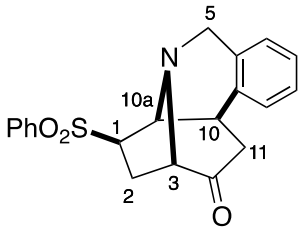
General procedure **Q** was followed using compound **188** (71 mg, 0.19 mmol) in DMF (0.4 mL), NaH (12 mg, 0.29 mmol, 1.5 eq.) and methanesulfonyl chloride (90 μL, 1.14 mmol, 6.0 eq.) at 60 °C for 3 d. The reaction mixture was concentrated *in vacuo* and purification by reverse phase biotage MeCN/H_2O 1% formic acid gave the *title compound **336*** (9.6 mg, 0.02 mmol, 11%) as a brown oil; **δ_H (400 MHz, Methanol-d_4)** 7.98 – 7.92 (1H, m, Ar*H*), 7.63 – 7.51 (1H, m, Ar*H*), 7.45 – 7.23 (7H, m, Ar*H*), 4.75 (1H, d, *J* 5.4, 9-C*H*), 4.06 (1H, s, 8-C*H*), 3.86 (1H, d, *J* 13.3, N*Bn*), 3.75 (1H, d, *J* 13.3, N*Bn*), 3.62 (1H, t, *J* 8.2, 6-C*H*), 3.42 – 3.27 (1H, m, 7-CH_2) 3.06 (3H, s, *Me*), 3.01 (3H, s, *Me*), 2.76 – 2.48 (3H, m, 7-CH_2, 10-CH_2); **δ_C (101 MHz, Methanol-d_4)** 135.9 (*Ar*), 135.9 (*Ar*), 129.3 (*Ar*), 128.4 (*Ar*H), 128.2 (*Ar*H), 128.2 (*Ar*H), 127.1 (*Ar*), 124.3, (*Ar*H) 123.4 (*Ar*H), 118.5 (*Ar*H), 113.4 (*Ar*H), 112.4 (*Ar*), 67.4 (6-*C*), 56.5 (8-*C*), 56.5 (9-*C*), 50.9 (N*Bn*), 39.6 (*Me*), 37.4 (7-*C*), 36.7 (*Me*), 24.7 (10-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3062 (CH), 3026, 2928, 2848, 1605, 1584, 1541 (C=C),1300 (S=O); **HRMS** (ESI): $C_{22}H_{25}N_2O_4S_2$ [M+H$^+$]: calculated 445.1250, found 445.1244.

2-((6*S**,8*R**,9*S**)-11-Benzyl-8-(methylsulfonyl)-7,8,9,10-tetrahydro-6,9-epiminocyclohepta[*b*]indol-5(6*H*)-yl)acetonitrile (**337**)



General procedure **R** was followed using compound **188** (71 mg, 0.19 mmol) in DMF (0.4 mL), NaH (12 mg, 0.29 mmol, 1.5 eq.), bromoacetonitrile (93 μL, 1.33 mmol, 7.0 eq.) at 90 ^{o}C for 3 d. The reaction mixture was concentrated *in vacuo* and purification by reverse phase biotage MeCN/H_2O 1% formic acid gave the *title compound **337*** (15 mg, 0.04 mmol, 19%) as a brown oil; **δ_H (400 MHz, Methanol-*d*$_4$)** 7.56 – 7.45 (6H, m, Ar*H*), 7.42 – 7.22 (7H, m, Ar*H*), 7.18 (1H, td, *J* 7.5, 1.0, Ar*H*), 5.30 (1H, d, *J* 18.5, NCH_2), 5.22 (1H, d, *J* 18.5, NCH_2), 4.43 (1H, d, *J* 5.5, 9-C*H*), 4.05 (1H, d, *J* 4.0, 8-C*H*), 3.81 (1H, d, *J* 13.2, N*Bn*), 3.73 (1H, d, *J* 13.2, N*Bn*), 3.56 (1H, t, *J* 8.0, 6-C*H*), 3.36 – 3.22 (1H, m, 7-CH_2) 3.00 (3H, s, *Me*), 2.75 – 2.43 (3H, m, 7-CH_2, 10-CH_2); **δ_C (101 MHz, Methanol-*d*$_4$)** 136.4 (*Ar*), 135.8 (*Ar*), 128.6 (*Ar*H), 128.4 (*Ar*) 128.1 (*Ar*H), 127.6 (*Ar*), 127.0 (*Ar*H), 122.0 (*Ar*H), 120.3 (*Ar*H), 118.2 (*Ar*H), 115.2 (*Ar*), 108.9 (*Ar*H), 105.3 (CN), 67.6 (6-*C*), 56.9 (8-*C*), 54.6 (9-*C*), 51.0 (N*Bn*), 37.3(7-*C*), 36.7 (*Me*), 30.1 (N-*C*), 24.5 (10-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3034 (CH), 2963, 2873, 2828, 2106 (CN), 1557 (C=C), 1459, 1300 (S=O); **HRMS** (ESI): $C_{23}H_{24}N_3O_2S$ [M+H$^+$]: calculated 406.1584, found 406.1578.

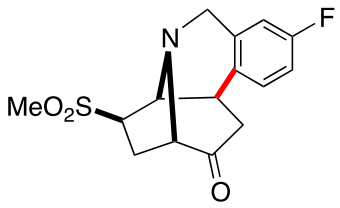
(1*R**,3*R**,4*R**,10*R**,10a*S**)-1-(Phenylsulfonyl)-1,2,3,5,10,10a-hexahydro-3,10-ethanopyrrolo[1,2-*b*]isoquinolin-12-one (**208**)



General procedure **S** was followed using enone **135** (105 mg, 0.25 mmol), sodium formate (19 mg, 0.28 mmol), $Pd(OAc)_2$ (6 mg), PPh_3 (14 mg) and $ZnCl_2$ (34 mg, 0.25 mmol) in anhydrous THF (1.2 mL). Purification by flash chromatography on silica gel, eluting with a gradient of 30% EtOAc in hexane afforded the *title compound **208*** (21 mg, 0.06 mmol, 24%) as a colourless solid; ***R*$_f$** = 0.19, (30% EtOAc), **δ_H(400 MHz, Chloroform-*d*):** 8.00 – 7.83 (2H,

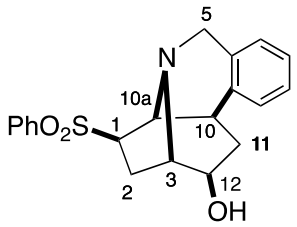
m, Ar*H*), 7.72 – 7.57 (1H, m, Ar*H*), 7.57 – 7.49 (2H, m, Ar*H*), 7.16 – 7.04 (2H, m, Ar*H*), 6.96 – 6.82 (2H, m, Ar*H*), 4.28 (1H, d, *J* 18.0, 5-CH_2), 4.02 – 3.93 (2H, m, 5-CH_2, 10a-C*H*), 3.87 (1H, dd, *J* 9.3, 6.1, 3-C*H*), 3.49 (1H, dd, *J* 7.0, 1.9, 1-C*H*), 3.25 (1H, d, *J* 6.6. 10-C*H*), 2.76 – 2.60 (2H, m, 2-CH_2, 11-CH_2), 2.17 (1H, dd, *J* 15.8, 1.8, 11-CH_2), 2.07 (1H, dd, *J* 14.3, 9.3, 2-CH_2); **δC(101 MHz, Chloroform-*d*):** 209.4 (*C*=O), 137.7 (*Ar*), 137.3 (*Ar*), 134.1 (*Ar*H), 131.8 (*Ar*), 129.4 (*Ar*H), 128.9 (*Ar*H), 128.0 (*Ar*H), 127.8 (*Ar*H), 127.0 (*Ar*H), 125.9 (*Ar*H), 71.4 (10a-*C*), 66.0 (3-*C*), 56.5 (1-*C*), 48.4 (5-*C*), 42.7 (11-*C*), 42.4 (10-*C*), 29.8 (2-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3104, 3060 (CH), 3024, 2928, 1603 (C=O), 1510 (C=C), 1478, 1316 (S=O); **HRMS** (ESI): [M+H$^+$]: $C_{20}H_{20}NO_3S$ calculated 354.1158, found 354.1150.

(1*R**,3*R**,4*R**,10*R**,10a*S**)-7-Fluoro-1-(methylsulfonyl)-1,2,3,5,10,10a-hexahydro-3,10-ethanopyrrolo[1,2-*b*]isoquinolin-12-one (**209**)



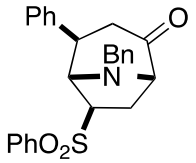
General procedure **S** was followed using enone **137** (50 mg, 0.13 mmol), sodium formate (13 mg, 0.19 mmol), $Pd(OAc)_2$ (1 mg, 15 mol%), PPh_3 (7 mg, 0.05 mmol) and $ZnCl_2$ (18 mg, 0.19 mmol). Purification by reverse phase biotage MeCN/H_2O 1% formic acid gave *title compound **209*** (4.9 mg, 0.16 mmol, 12 %) as a colourless solid. **δH (400 MHz, DMSO-*d*6):** 7.23 – 7.15 (1H, m, Ar*H*), 7.10 – 7.04 (2H, m, Ar*H*), 4.59 (1H, d, *J* 18.4, 5-CH_2), 4.41 (1H, d, *J* 18.4, 5-CH_2), 4.00 (1H, d, *J* 8.6, 5-CH_2), 3.85 (1H, d, *J* 8.1, 10a-C*H*), 3.61 (1H, dd, *J* 9.4, 5.9, 3-C*H*), 3.50 (1H, d, *J* 7.5, 1-C*H*), 2.94 (3H, s, *Me*), 2.24 (1H, dd, *J* 14.3, 7.7, 2-CH_2), 2.09 (1H, dd, *J* 13.6, 9.4, 2-CH_2); **δC(101 MHz, DMSO-*d*6):** 208.3 (*C*=O), 160.1 (d, *J* 252.5, *Ar*F), 139.2 (d, *J* 7.1, *Ar*), 130.0 (d, *J* 8.3, *Ar*), 129.3 (d, *J* 34.1, *Ar*H), 115.2 (d, *J* 21.5, *Ar*H), 114.7 (d, *J* 20.9, *Ar*H), 68.4 (10a-*C*), 67.0 (3-*C*), 56.0 (1-*C*), 51.6 (5-*C*), 51.4 (11-*C*), 38.1 (*Me*), 36.4 (10-*C*), 30.8 (2-*C*), **IR** ν_{max} (neat)/cm^{-1}: 3062, 3013, 2929 (CH), 2881, 1722 (C=O), 1543 (C=C), 1499, 1297 (S=O); **HRMS** (ESI): $C_{15}H_{17}FNO_3S$ [M+H$^+$]: calculated 310.0908, found 310.0904.

(1*R**,3*R**,4*R**,10*R**,10a*S**,12*R**)-1-(Phenylsulfonyl)-1,2,3,5,10,10a-hexahydro-3,10-ethanopyrrolo[1,2-*b*]isoquinolin-12-ol (**210**)



General procedure **I** was followed using ketone **208** (10 mg, 0.03 mmol) and DIBAL (1M cyclohexane) (0.1 mL, 0.1 mmol) in anhydrous DCM (1 mL). Purification by flash chromatography on silica gel, eluting with a gradient of 35-60% EtOAc in hexane afforded the *title compound **210*** (7.4 mg, 0,02 mmol, 74%) as a colourless oil; **δ_H (400 MHz, Methanol-*d*$_4$)**: 7.87 – 7.80 (2H, m, Ar*H*), 7.67 – 7.60 (1H, m, Ar*H*), 7.57 – 7.50 (2H, m, Ar*H*), 7.03 – 6.80 (5H, m, Ar*H*), 4.35 (1H, d, *J* 17.8, N*Bn*), 4.05 (1H, d, *J* 17.8, N*Bn*), 3.86 (1H, dd, *J* 9.3, 6.0, 3-C*H*), 3.52 (1H, s, 10a-C*H*), 3.48 – 3.34 (2H, m, 12-C*H*, 1-C*H*), 2.44 – 2.38 (1H, m, 10-CH_2), 2.37 – 2.25 (1H, m, 2-CH_2), 2.16 (1H, dt, *J* 15.2, 5.2, 11-CH_2), 1.80 (1H, dd, *J* 13.6, 9.3, 2-CH_2), 1.56 (1H, dt, *J* 15.2, 1.7, 11-CH_2); **δ_C** (101 MHz, **Methanol-*d*$_4$)**: 139.8 (*Ar*), 138.1 (*Ar*), 136.3 (*Ar*H), 133.6 (*Ar*), 129.0 (*Ar*H), 128.5 (*Ar*H), 128.5 (*Ar*H), 127.5 (*Ar*H), 125.9 (*Ar*H), 124.2 (*Ar*H), 67.6 (12), 64.9 (10), 63.9 (10a), 56.8 (NBn), 48.8 (Me), 34.2 (1-C), 31.8 (2-C), 28.9 (11-C); **IR** ν_{max} (neat)/cm^{-1}: 3368 (OH), 3061 (CH), 3002, 2922, 2872, 1490 (C=C), 1445, 1290 (S=O); **HRMS** (ESI): $C_{20}H_{22}NO_3S$ [M+H$^+$]: calculated 356.1315, found 356.1323

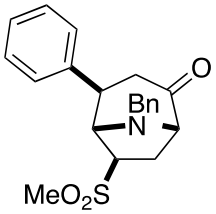
(1*S**,4*R**,5*S**,6*R**)-8-Benzyl-4-phenyl-6-(phenylsulfonyl)-8-azabicyclo[3.2.1]octan-2-one (**207**)



General procedure **T** was followed using cycloadduct **89** (200 mg, 0.57 mmol, 1.0 eq.), phenylboronic acid (104 mg, 0.85 mmol, 1.5 eq.), chloro(1,5-cyclooctadiene)rhodium(I) dimer (3 mg, 2.5 mol%) and triethylamine (0.08 mL, 0.6 mmol, 1.0 eq.) in degassed dioxane:H_2O (6:1) (2 mL). Purification by flash chromatography on silica gel, eluting with a gradient of 30% EtOAc in hexane gave title compoound. Crystallization from EtOAc–afforded the *title compound **207*** (244 mg, 0.577 mmol, 40%) as a colourless solid; ***R*$_f$** = 0.30, (30% EtOAc in hexane). **M.Pt.** **^{1}H NMR** (400 MHz, $CDCl_3$) 8.00 – 7.88 (2H, m, Ar*H*), 7.79 – 7.63 (1H, m,

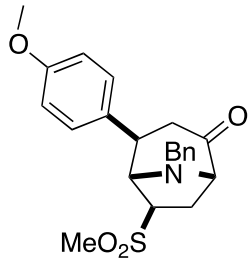
Ar*H*), 7.66 – 7.55 (2H, m, Ar*H*), 7.34 – 7.21 (3H, m, Ar*H*), 7.19 – 6.98 (7H, m, Ar*H*), 3.93 (1H, s, 5-C*H*), 3.87 (1H, d, *J* 13.3, NCH_2), 3.76 – 3.66 (3H, m, NCH_2, 1-C*H*, 6-C*H*), 3.05 (1H, dt, *J* 8.6, 2.5, 4-C*H*), 2.83 – 2.65 (2H, m, 7-CH_2, 3-CH_2), 2.55 (1H, dd, *J* 17.6, 8.5, 3-CH_2), 2.11 (1H, dd, *J* 13.9, 8.9, 7-CH_2). **^{13}C NMR** (101 MHz, $CDCl_3$): 205.6 (*C*=O), 143.0 (*C*), 139.2 (*C*), 137.6 (*C*), 134.0 (*Ar*H), 129.6 (*Ar*H), 128.9 (*Ar*H), 128.3 (*Ar*H), 128.2 (*Ar*H), 128.1 (*Ar*H), 127.8 (*Ar*H), 127.0 (*Ar*H), 126.8 (*Ar*H), 72.2 (1-*C*H), 70.4 (5-*C*H), 67.6 (6-*C*H), 56.2 (NCH_2), 47.4 (4-*C*), 39.0 (3-CH_2), 29.9 (7-CH_2). **IR** ν_{max} (neat)/cm^{-1}: 2977 (CH), 2966, 2965, 2890, 1718 (C=O), 1496 (C=C), 1444, 1331 (S=O); **HRMS** (ESI): $C_{26}H_{26}NO_3S$ [M+H$^+$]: calculated 432.1628 found 432.1628.

(1*S**,4*R**,5*S**,6*R**)-8-Benzyl-6-(methylsulfonyl)-4-phenyl-8-azabicyclo[3.2.1]octan-2-one (**246**)



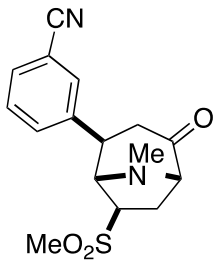
General procedure **T** was followed using cycloadduct **116** (1.5 g, 5.2 mmol), phenylboronic acid (2.4 g, 15.6 mmol) chloro(1,5-cyclooctadiene)rhodium(I) dimer (30 mg, 2.5 mol%) and triethylamine (0.80 mL, 6.0 mmol, 1.0 eq.) in degassed dioxane:H_2O (6:1) (20 mL). Purification by flash chromatography on silica gel, eluting with a gradient of 50 - 100% EtOAc in hexane affording the *title compound* **246** (542 mg, 1.47 mmol, 29%) as a colourless solid; $\boldsymbol{R_f}$ = 0.14, (100% EtOAc in hexane); **δ_H(400 MHz, DMSO-*d*$_6$):** 7.47 – 7.19 (3H, m, Ar*H*), 7.20 – 6.97 (5H, m, Ar*H*), 6.87 – 6.77 (2H, m, Ar*H*), 4.30 (1H, t, *J* 8.5, 6-C*H*), 3.71 – 3.61 (3H, m, 1-C*H*, N*Bn*, 5-C*H*), 3.56 (1H, d, *J* 13.8, N*Bn*), 3.32 (1H, s, 4-C*H*), 3.13 (3H, s, SO_2*Me*), 3.05 – 2.87 (1H, m, 3-CH_2), 2.60 (1H, dt, *J* 14.3, 7.2, 7-CH_2), 2.51 – 2.34 (2H, m, 3-CH_2, 7-CH_2); **δ_C(101 MHz, DMSO-*d*$_6$):** 205.4 (*C*=O), 144.2 (*Ar*), 138.7 (*Ar*), 134.5 (*Ar*H), 130.4 (*Ar*), 128.8 (*Ar*H), 128.4 (*Ar*H), 128.3 (*Ar*H), 127.0 (*Ar*H), 126.8 (*Ar*H), 72.8 (1-*C*), 66.9 (5-*C*), 66.7 (6-*C*), 55.7 (N*Bn*), 46.8 (4-*C*), 40.9 (*Me*), 38.8 (3-*C*), 29.2 (7-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3027, 2985, 2955 (CH), 2902, 1716 (C=O), 1459 (C=C), 1432, 1292 (S=O); **HRMS** (ESI): $C_{21}H_{24}NO_3S$ [M+H$^+$]: calculated 369.1399, found 369.1396.

(1*S**,4*R**,5*S**,6*R**)-8-Benzyl-4-(4-methoxyphenyl)-6-(methylsulfonyl)-8-azabicyclo[3.2.1]octan-2-one (**272**)



General procedure **T** was followed using cycloadduct **116** (150 mg, 0.52 mmol) and 4-methoxyphenylboronic acid (240 mg, 1.54 mmol), chloro(1,5-cyclooctadiene)rhodium(I) dimer (3 mg, 2.5 mol%) and triethylamine (0.08 mL, 6.0 mmol, 1.0 eq.) in degassed dioxane:H_2O (6:1) (4 mL). Purification by flash chromatography on silica gel, eluting with a gradient of 40% EtOAc in hexane-afforded the *title compound **272*** (92 mg, 0.23 mmol, 44%) as a colourless solid; $\boldsymbol{R_f}$ = 0.25, (40% EtOAc in hexane); **δ_H(400 MHz, Chloroform-*d*):** 7.26 – 7.18 (1H, m, Ar*H*), 7.11 – 7.00 (4H, m, Ar*H*), 6.98 – 6.91 (2H, m, Ar*H*), 6.77 – 6.70 (2H, m, Ar*H*), 3.88 (1H, s, 5-C*H*), 3.78 – 3.64 (5H, m, O*Me*, N*Bn*, 6-C*H*), 3.62 – 3.54 (2H, m, N*Bn*, 1-C*H*), 3.11 (1H, dt, *J* 8.4, 2.5, 4-C*H*), 2.93 (3H, s, SO_2*Me*), 2.76 – 2.52 (3H, m, 3-CH_2, 7-CH_2), 2.28 (1H, dd, *J* 13.7, 8.9, 7-CH_2). **δ_C(101 MHz, Chloroform-*d*):** 205.2 (*C*=O), 163.0 (*Ar*), 160.6 (*Ar*), 138.7 (*Ar*), 129.0 (*Ar*H), 128.8 (*Ar*H), 128.1 (*Ar*H), 127.1 (*Ar*H), 113.7 (*Ar*H), 77.2 (6-*C*), 72.5 (1-*C*), 68.3 (5-*C*), 66.4 (O*Me*), 55.9 (N*Bn*), 46.7 (4-*C*), 40.7 (3-*C*), 39.3 (SO_2*Me*), 30.2 (7-*C*); **IR ν_{max} (neat)/cm^{-1}:** 3062 (CH), 3029, 2955, 29255, 1716 (C=O), 1495 (C=C), 1454, 1336 (S=O); **HRMS** (ESI): $C_{22}H_{26}NO_4S$ [M+H$^+$]: calculated 400.1504, found 400.2338.

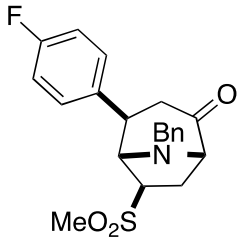
3-((1*S**,2*R**,5*S**,7*R**)-8-Methyl-7-(methylsulfonyl)-4-oxo-8-azabicyclo[3.2.1]octan-2-yl)benzonitrile (**275**)



General procedure **T** was followed using cycloadduct **117** (3.70 g, 17.2 mmol), 3-cyanophenylboronic acid (7.58 g, 51.6 mmol), chloro(1,5-cyclooctadiene)rhodium(I) dimer (60 mg, 2.5 mol%) and triethylamine (1.60 mL, 12.0 mmol, 1.0 eq.) in degassed dioxane:H_2O

(6:1) (40 mL). Purification by flash chromatography on silica gel, eluting with a gradient of 80 - 100% EtOAc in hexane afforded the *title compound **275*** (1.00 g, 3.14 mmol, 18%) as a yellow oil; $\boldsymbol{R_f}$ = 0.33, (100% EtOAc in hexane); **δ_H(400 MHz, Chloroform-*d*):** 7.93 – 7.84 (1H, m, Ar*H*), 7.73 – 7.58 (1H, m, Ar*H*), 7.58 – 7.42 (2H, m, Ar*H*), 4.13 (1H, t, *J* 8.5, 6-C*H*), 3.79 (1H, s, 5-*C*H), 3.69 (1H, d, *J* 6.9, 1-*C*H), 3.67 – 3.56 (1H, m, 4-C*H*), 3.33 (3H, s, SO_2*Me*), 2.88(1H, dd, *J* 17.9, 8.8, 3-CH_2), 2.68 (1H, dt, *J* 14.5, 7.4, 7-CH_2), 2.55 – 2.44 (1H, m, 3-CH_2), 2.43 – 2.27 (4H, m N*Me*, 7-CH_2); **δ_C(101 MHz, Chloroform-*d*):** 209.4 (*C*=O), 149.9 (*Ar*), 136.5 (*Ar*H), 135.2 (*Ar*H), 134.1 (*Ar*H), 133.0 (*Ar*H), 122.3 (*C*N), 115.8 (*Ar*), 78.2 (1-CH), 72.5 (5-*C*), 71.3 (6-*C*), 50.3 (SO_2*Me*), 43.6 (4-*C*), 43.4 (N*Me*), 42.4 (3-*C*) 32.8 (7-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3097 (CH), 2959, 2872, 2830, 2509 (CN) 1631 (C=O), 1578 (C=C), 1305 (S=O); **HRMS** (ESI): [M+H$^+$]: $C_{16}H_{19}N_2O_3S$ calculated 319.1111, found 319.0338.

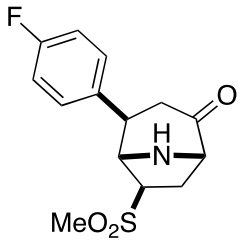
(1*S**,4*R**,5*S**,6*R**)-8-Benzyl-4-(4-fluorophenyl)-6-(methylsulfonyl)-8-azabicyclo[3.2.1]octan-2-one (**274**)



General procedure **T** was followed using cycloadduct **116** (5.00 g, 17.2 mmol) and 4-fluorophenylboronic acid (7.2 g, 51.6 mmol, 3.0 eq.) chloro(1,5-cyclooctadiene)rhodium(I) dimer (250 mg, 2.5 mol%) and triethylamine (17 mL, 17.2 mmol, 1.0 eq.) in degassed dioxane:H_2O (6:1) (57 mL). Purification was by flash chromatography on silica gel, eluting with a gradient of 80 - 100% EtOAc in hexane. Crystallization of the resulting material from EtOAc afforded the *title compound **274*** (5.20 g, 13.4 mmol, 78%) as a colourless solid; $\boldsymbol{R_f}$ = 0.50, (100% EtOAc in hexane). **M.Pt.:**152.4 – 153.1 ^oC; **δ_H(400 MHz, Chloroform-*d*):** 7.10 – 6.99 (5H, m, Ar*H*), 6.99 – 6.90 (2H, m, Ar*H*), 6.87 – 6.79 (2H, m, Ar*H*), 3.91 – 3.77 (1H, s, 5-C*H*), 3.71 (1H, dd, *J* 6.7, 1.6, 6-C*H*), 3.67 (1H, d, *J* 13.1, N*Bn*), 3.64 – 3.56 (1H, m, 1-C*H*), 3.53 (1H, d, *J* 13.1, N*Bn*), 3.13 (1H, dt, *J* 8.4, 2.6, 4-C*H*), 2.93 (3H, s, SO_2*Me*), 2.71 – 2.51 (3H, m 3-CH_2, 7-CH_2), 2.29 (1H, dd, *J* 13.8, 9.0, 7-CH_2). **δ_C(101 MHz, Chloroform-*d*)** 205.2 (*C*=O), 161.8 (d, *J* 245.1, *Ar*-F), 138.7 (d, *J* 3.5, *Ar*), 137.3 (*Ar*), 129.4 (d, *J* 8.0, *Ar*H), 129.0 (*Ar*H), 128.1 (*Ar*H), 127.2 (*Ar*H), 115.1 (d, *J* 21.3, *Ar*H), 72.5 (6-*C*H), 68.3 (1-*C*H), 66.4 (5-*C*H), 55.9 (N*Bn*), 46.7 (4-*C*H), 40.7 (SO_2*Me*), 39.3 (3-*C*H_2), 30.2 (7-*C*H_2). **IR** ν_{max} (neat)/cm^{-}

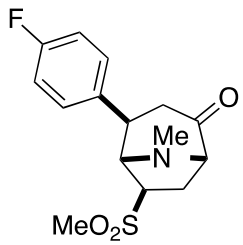
[1]: 3003 (CH), 2926, 2897, 2885, 1717 (C=O), 1510 (C=C), 1430, 1330 (S=O); **HRMS** (ESI): $C_{21}H_{23}FNO_3S$ [M+H$^+$]: calculated 388.1304, found 388.0436.

(1*S**,4*R**,5*S**,6*R**)-4-(4-Fluorophenyl)-6-(methylsulfonyl)-8-azabicyclo[3.2.1]octan-2-one (**279**)



General procedure **F** was followed using ketone **274** (160 mg, 0.41 mmol), $Pd(OH)_2/C$ (6 mg, 10 w/w%) and conc. HCl (0.1 mL) in MeOH (10 mL) over 18 h. Purification by flash chromatography on silica gel, eluting with a gradient of 70% EtOAc in hexane afforded the *title compound **279*** (82 mg, 0.27 mmol, 67%) as a colourless oil; $\boldsymbol{R_f}$ = 0.16, (50% EtOAc in hexane); **δ_H(400 MHz, Chloroform-*d*):** 7.31 – 7.18 (2H, m, Ar*H*), 7.14 – 6.99 (2H, m, Ar*H*), 4.06 (1H, s, 5-C*H*), 3.93 (1H, d, *J* 6.8 6-C*H*), 3.66 (1H, dd, *J* 8.7, 5.9, 1-C*H*), 3.36 (1H, d, *J* 7.5, 4-C*H*), 2.95 (3H, s, SO_2*Me*), 2.77 – 2.60 (2H, m, 3-CH_2), 2.58 – 2.36 (2H, m. 7-CH_2); **δ_C(101 MHz, Chloroform-*d*):** 206.5 (*C*=O), 162.0 (d, *J* 246.3, *Ar*F), 138.4 (d, *J* 3.1, *Ar*), 129.1 (d, *J* 7.9, *Ar*H), 115.7 (d, *J* 21.3, *Ar*H), 66.5 (6-*C*H), 66.2 (1-*C*H), 62.2 (5-*C*H), 46.5 (4-*C*H), 39.1 (3-*C*H_2), 38.7 (SO_2*Me*), 31.7 (7-*C*H_2); **IR** ν_{max} (neat)/cm^{-1}: 3054, 2997 (CH), 2981, 2950, 1716 (C=O), 1510 (C=C), 1456, 1314 (S=O); **LCMS**: $C_{14}H_{17}FNO_3S$ [M+H$^+$]: calculated 298.0908, found 298.14.

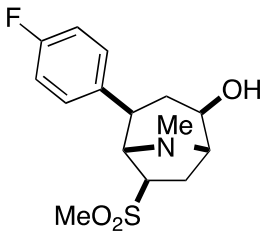
(1*S**,4*R**,5*S**,6*R**)-4-(4-Fluorophenyl)-8-methyl-6-(methylsulfonyl)-8-azabicyclo[3.2.1]octan-2-one (**273**)



General procedure **T** was followed using cycloadduct **117** (4.40 g, 20.4 mmol) and 4-fluorophenylboronic acid (8.5 g, 61.2 mmol, 3.0 eq.) chloro(1,5-cyclooctadiene)rhodium(I) dimer (300 mg, 2.5 mol%) and triethylamine (20 mL, 20.4 mmol, 1.0 eq.) in degassed

dioxane:H_2O (6:1) (68 mL). Purification by flash chromatography on silica gel, eluting with a gradient of 60 - 100% EtOAc in hexane afforded the *title compound* ***273*** (3.65 g, 11.7 mmol, 57%) as a colourless solid; $\boldsymbol{R_f}$ = 0.05, (60% EtOAc in hexane). **M.Pt.** 141.9 – 142.7 °C; **δ_H(400 MHz, Chloroform-*d*):** 7.35 – 7.19 (2H, m), 7.05 – 6.81 (2H, m), 3.81 (1H, s, 5-C*H*), 3.62 (1H, d, *J* 6.6, 1.6, 6-C*H*), 3.47 (1H, td, *J* 8.7, 1.8, 1-C*H*), 3.05 (1H, dd, *J* 8.3, 4.0, 4-C*H*), 2.92 (3H, s, SO_2*Me*), 2.67 – 2.51 (3H, m, 3-CH_2 7-CH_2), 2.32 (3H, s, N*Me*), 2.23 (1H, dd, *J* 13.6, 8.7, 7-CH_2). **δ_C(101 MHz, Chloroform-*d*):** 206.3 (*C*=O), 161.9 (d, *J* 245.7, *Ar*F), 139.5 (d, *J* 3.1, *Ar*), 129.1 (d, *J* 8.0, *Ar*H), 115.3 (d, *J* 21.2, *Ar*H), 74.0 (6-*C*), 68.9 (1-*C*), 68.7 (5-*C*), 46.7 (4-*C*), 40.6 (N*Me*), 40.2 (SO_2*Me*), 40.0 (3-*C*), 30.0 (7-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3075, 2998 (CH), 2939, 2897, 1716 (C=O), 1510 (C=C), 1455, 1222 (S=O); **HRMS** (ESI): $C_{15}H_{19}FNO_3S$ [M+H^+]: calculated 312.1064, found 312.1656.

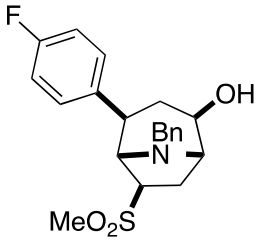
(1*S**,2*R**,4*R**,5*S**,6*R**)-4-(4-Fluorophenyl)-8-methyl-6-(methylsulfonyl)-8-azabicyclo[3.2.1]octan-2-ol (**278a**)



General procedure **I** was followed using ketone **273** (1.96 g, 6.30 mmol) DIBAL (1M cyclohexane, 12.0 mL, 12.0 mmol) in anhydrous DCM (50 mL) to give a crude mixture of diastereomers 5:1. Crystallization from ethanol gave the major *title compound* **278a** (1.40 g, 4.47 mmol, 71%) as a colourless solid;

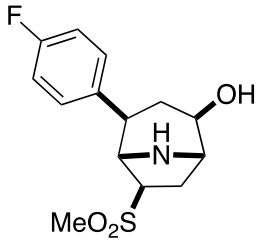
M.Pt. 162.8 – 163.4 °C; **δ_H(400 MHz, Chloroform-*d*):** 7.47 – 7.32 (2H, m, Ar*H*), 6.98 – 6.87 (2H, m, Ar*H*), 4.09 (1H, s, 5-C*H*), 3.62 – 3.54 (1H, m, 2-C*H*), 3.52 (1H, at, *J* 7.1, 6-C*H*), 3.31 – 3.26 (1H, m, 1-C*H*), 2.91 (3H, s, SO_2*Me*), 2.84 (1H, d, *J* 7.8, 4-C*H*), 2.66 (1H, d, *J* 11.5, O*H*), 2.50 (1H, dt, *J* 14.1, 7.1, 7-CH_2), 2.42 (3H, s, N*Me*), 2.13 – 1.96 (2H, m, 7-CH_2, 3-CH_2), 1.88 (1H, ddd, *J* 15.7, 7.8, 4.2, 3-CH_2); **δC(101 MHz, Chloroform-*d*):** 162.4 (d, *J* 241.0, *Ar*-F), 139.3 (*Ar*), 129.0 (d, *J* 7.8, *Ar*-H), 115.1 (d, *J* 21.1, *Ar*-H), 69.7 (1-*C*), 69.0 (2-*C*), 68.6 (6-*C*), 67.1 (5-*C*), 44.1 (4-*C*), 42.1 (N*Me*), 40.8 (SO_2*Me*), 29.9 (3-*C*), 28.1 (7-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3497 (O-H), 3043, 3001 (C-H), 2998, 2937, 2943, 1509 (C=C), 1295 (S=O); **HRMS** (ESI): [M+H^+]: $C_{15}H_{21}FNO_3S$ calculated 314.1221, found 314.1815.

(1*S**,2*R**,4*R**,5*S**,6*R**)-8-Benzyl-4-(4-fluorophenyl)-6-(methylsulfonyl)-8-azabicyclo[3.2.1]octan-2-ol (**281**)



General procedure **I** was followed using ketone **274** (1.50 g, 3.95 mmol), DIBAL (1M cyclohexane, 12.0 mL, 12.0 mmol) in anhydrous DCM (50 mL) to give a crude mixture of diastereomers 10:1. Crystallization from ethanol gave the major *title compound **281*** (1.30 g, 3.34 mmol, 85%) as a colourless solid; **M.pt.** 139.9 – 140.8 ^{o}C; **δ_H(400 MHz, DMSO-*d*$_6$):** 7.73 – 7.59 (2H, m, Ar*H*), 7.18 – 6.91 (7H, m, Ar*H*), 4.51 (1H, d, *J* 4.8, 5-C*H*), 4.03 (1H, at, *J* 8.4, 6-C*H*), 3.67 – 3.57 (2H, m, 4-C*H*, N*Bn*), 3.55 – 3.46 (2H, m, 2-C*H*, N*Bn*), 3.34 (1H, s, 1-C*H*), 3.06 (3H, s, SO_2*Me*), 2.91 (1H, d, *J* 8.0, O*H*), 2.36 (1H, dt, *J* 14.1, 7.2, 7-CH_2), 2.25 – 2.01 (2H, m. 3-CH_2, 7-CH_2), 1.72 (1H, d, *J* 15.7, 3-CH_2); **δ_C(101 MHz, DMSO-*d*$_6$):** 161.1 (d, *J* 241.0, *Ar*-F), 141.6 (d, *J* 2.9, *Ar*), 139.8 (*Ar*), 131.4 (d, *J* 7.7, *Ar*H), 128.9 (*Ar*H), 128.0 (*Ar*H), 126.8 (*Ar*H), 114.3 (d, *J* 20.6, *Ar*H), 68.4 (2-*C*), 68.4 (6-*C*), 67.4 (5-*C*), 66.3 (1-*C*), 56.9 (N*Bn*), 46.3 (4-*C*), 40.8 (*Me*), 29.4 (7-*C*), 28.4 (3-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3473 (OH), 3002 (CH), 2960, 2930, 2885, 1512 (C=C), 1431, 1326 (S=O); **HRMS** (ESI): $C_{21}H_{25}FNO_3S$ [M+H$^+$]: calculated 390.1534, found 390.1537.

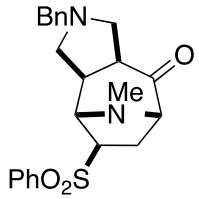
(1*S**,2*R**,4*R**,5*S**,6*R**)-4-(4-Fluorophenyl)-6-(methylsulfonyl)-8-azabicyclo[3.2.1]octan-2-ol (**282**)



General procedure **F** was followed using alcohol **281** (300 mg, 0.77 mmol), Pd(OH)2/C (15 mg, 10 w/w%) and conc. HCl (0.2 mL) in MeOH (10 mL) over 18 h. Purification by general procedure **D** (SCX SPE) afforded the *title compound **282*** (200 mg, 0.67 mmol, 87%) as a

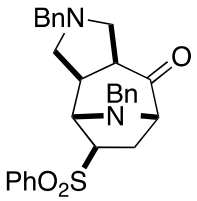
colourless oil; **δ_H(400 MHz, Methanol-*d*$_4$):** 7.80 – 7.61 (2H, m, Ar*H*), 7.20 – 6.88 (2H, m, Ar*H*), 4.00 (1H, s, 5-C*H*), 3.86 (1H, dd, *J* 9.0, 5.5, 6-C*H*), 3.80 – 3.67 (1H, m, 2-CH), 3.63 – 3.49 (1H, m, 1-C*H*), 3.03 (3H, s, SO_2Me), 2.98 (1H, d, *J* 8.2, 4-CH), 2.41 – 2.11 (3H, m, 7-CH_2, 3-CH_2), 1.97 (1H, d, *J* 15.8, 3-CH_2); **δ_C (101 MHz, Methanol-*d*$_4$):** 161.4 (d, *J* 243.2, *Ar*F), 139.6 (d, *J* 3.1, *Ar*), 130.1 (d, *J* 7.7, *Ar*H), 114.4 (d, *J* 21.1, *Ar*H), 67.0 (2-*C*), 65.6 (6-*C*), 61.3 (5-*C*), 60.7 (1-*C*), 42.6 (4-*C*), 37.7 (*Me*), 28.8 (7-*C*), 27.8 (3-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3499 (O-H), 3319 (N-H), 3059, 3004 (C-H), 3028, 2937, 1508 (C=C), 1288 (S=O); **HRMS** (ESI): $C_{14}H_{19}FNO_3S$ [M+H$^+$]: calculated 300.1064, found 300.1071.

(3a*R**,4*S**,5*R**,7*S**,8a*S**)-2-Benzyl-9-methyl-5-(phenylsulfonyl)-octahydro-4,7-epiminocyclohepta[*c*]pyrrol-8(2*H*)-one (**162)**



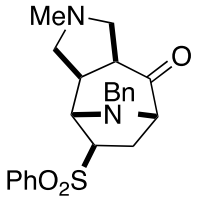
General procedure **U** was followed using enone **89** (162 mg, 0.58 mmol, 1.0 eq.), *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine (0.16 mL, 0.64 mmol, 1.1 eq.) and lithium fluoride (18 mg, 0.70 mmol, 1.2 eq.) in anhydrous MeCN (1.2 mL). Purification by flash chromatography on silica gel, eluting with a gradient of 40% EtOAc in hexane. Crystallization from EtOAc afforded the *title compound **162*** (158 mg, 0.38 mmol, 67%) as a white solid; R_f = 0.20 (40% EtOAc in hexane); **^{1}H NMR** (400 MHz, $CDCl_3$) 7.87 – 7.79 (2H, m, Ar*H*), 7.64 – 7.53 (1H, m, Ar*H*), 7.55 – 7.45 (2H, m, Ar*H*), 7.29 – 7.12 (5H, m, Ar*H*), 3.67 (1H, s, 4-CH), 3.51 (2H, s, NCH_2), 3.49 (1H, s, 7-C*H*), 3.34 (1H, td, *J* 8.8, 1.9, 5-C*H*), 3.00 – 2.92 (2H, m, 1-CH_2), 2.65 (1H, q, *J* 8.7, 8a-C*H*), 2.55 (1H, dt, *J* 14.0, 7.9, 6-CH_2), 2.46 (3H, s, N*Me*), 2.41 (2H, dt, *J* 17.5, 8.8, 3-CH_2), 2.36 – 2.23 (1H, m, 3a-C*H*), 1.81 (1H, dd, *J* 13.9, 8.8, 6-CH_2). **^{13}C NMR** (101 MHz, $CDCl_3$): 207.6 (C=O), 139.2 (*Ar*), 138.5 (*Ar*), 133.9 (*Ar*H), 129.5 (*Ar*H), 128.7 (*Ar*H), 128.3 (*Ar*H), 128.1 (*Ar*H), 127.1(*Ar*H), 73.4 (5-*C*H), 70.2 (7-*C*H), 65.3 (4-*C*H), 59.8 (N*C*H$_2$), 58.5 (1-*C*H$_2$), 57.4 (3-*C*H$_2$), 45.9 (8a-*C*H), 45.2 (3a-*C*H), 40.5 (N*Me*), 29.7 (6-*C*H$_2$); **IR** ν_{max} (neat)/cm^{-1}: 3062, 3026, 2939 (CH), 2795, 1711 (C=O), 1585, 1446 (C=C), 1319 (S=O); **HRMS** (ESI): $C_{23}H_{27}N_2O_3S$ [M+H$^+$]: calculated 411.1737, found 411.1765.

(3a*R**,4*S**,5*R**,7*S**,8a*S**)-2,9-Dibenzyl-5-(phenylsulfonyl)octahydro-4,7-epiminocyclohepta[*c*]pyrrol-8(2*H*)-one (**163**)



General procedure **U** was followed using enone **115** (100 mg, 0.29 mmol, 1.0 eq.), *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine (80 μL, 0.31 mmol, 1.1 eq.) and lithium fluoride (9.00 mg, 0.34 mmol, 1.2 eq.) in anhydrous MeCN (0.6 mL). Purification by flash chromatography on silica gel, eluting with a gradient of 80% EtOAc in hexane afforded the *title compound* **163** (88 mg, 0.18 mmol, 63%) as a yellow oil; $\boldsymbol{R_f}$ = 0.10 (60% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) 7.89 – 7.76 (2H, m, Ar*H*), 7.63 – 7.54 (1H, m, Ar*H*), 7.54 – 7.43 (2H, m, Ar*H*), 7.37 – 7.29 (2H, m, Ar*H*), 7.32 – 7.10 (8H, m, Ar*H*), 3.91 (1H, d, *J* 13.2, 9-NCH_2), 3.73 (1H, s, 4-C*H*), 3.70 (1H, d, *J* 13.2, 9-NCH_2), 3.62 (1H, dd, *J* 7.1, 1.5, 5-C*H*), 3.54 (1H, d, *J* 12.7, 2-NCH_2), 3.47 (1H, d, *J* 12.7, 2-NCH_2), 3.41 (1H, td, *J* 8.8, 1.8, 7-C*H*), 3.00 – 2.85 (1H, m, 1-CH_2), 2.74 – 2.51 (4H, m, 6-CH_2, 8a-C*H*, 1-CH_2, 3-CH_2), 2.41 – 2.28 (1H, m, 3-CH_2), 2.25 (1H, dtd, *J* 9.4, 7.7, 1.6, 3a-C*H*), 1.88 (1H, dd, *J* 13.8, 8.8, 6-CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): 207.5 (*C*=O), 139.1 (*Ar*), 138.3 (*Ar*), 138.2 (*Ar*), 134.0 (*Ar*H), 129.6 (*Ar*H), 129.4 (*Ar*H), 128.9 (*Ar*H), 128.9 (*Ar*H), 128.4 (*Ar*H), 128.1 (*Ar*H), 127.4 (*Ar*H), 127.2 (*Ar*H), 71.7 (5-*C*H), 70.1 (7-*C*H), 63.0 (4-*C*H), 59.8 (2-N*C*H_2), 58.0 (9-N*C*H_2), 57.6 (3-*C*H_2), 55.9 (1-*C*H_2), 46.4 (8a-*C*H), 44.9 (3a-*C*H), 30.3 (6-*C*H_2); **IR** ν_{max} (neat)/cm^{-1}: 3061, 3028, 2940, 2795 (C-H), 1714 (C=O), 1672, 1446 (C=C), 1321 (S=O); **HRMS** (ESI): $C_{29}H_{31}N_2O_3S$ [M+H$^+$]: calculated 487.2050, found 487.2073.

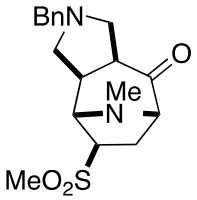
(3a*R**,4*S**,5*R**,7*S**,8a*S**)-9-Benzyl-2-methyl-5-(phenylsulfonyl)octahydro-4,7-epiminocyclohepta[*c*]pyrrol-8(2*H*)-one **(295**)



To a solution of enone **89** (100 mg, 0.28 mmol, 1.0 eq.) in anhydrous PhMe (3 mL) at rt was added paraformaldehyde (86 mg, 1.8 mmol, 10 eq.) and sarcosine (100 mg, 1.12 mmol, 4 eq.).

The reaction was refluxed for 16 h. The crude mixture was cooled to rt and concentrated *in vacuo*. Purification by flash chromatography on silica gel, eluting with a gradient of 60 - 100% EtOAc in hexane afforded the *title compound* ***295*** (83 mg, 0.20 mmol, 72%) as a white solid; **δ_H(400 MHz, Chloroform-*d*):** 7.91 – 7.80 (2H, m, Ar*H*), 7.65 – 7.56 (1H, m, Ar*H*), 7.56 – 7.45 (3H, m, Ar*H*), 7.41 – 7.34 (2H, m, Ar*H*), 7.32 – 7.17 (2H, m, Ar*H*), 3.92 (1H, d, *J* 13.0, NCH_2), 3.77 (1H, s, 4-C*H*), 3.73 – 3.61 (2H, m, NCH_2, 5-C*H*), 3.46 – 3.36 (1H, m, 7-C*H*), 2.97 (1H, t, *J* 8.7, 1-CH_2), 2.81 – 2.67 (2H, m, 3-CH_2, 8a-C*H*), 2.66 – 2.54 (1H, m, 6-CH_2), 2.54 – 2.41 (2H, m, 3-CH_2,1-CH_2), 2.37 – 2.17 (4H, m, NMe, 3a-C*H*), 1.86 (1H, dd, *J* 13.8, 8.9, 6-CH_2); **δ_C(101 MHz, Chloroform-*d*)**: 207.3 (*C*=O), 139.1 (*Ar*), 138.0 (*Ar*), 134.0 (*Ar*H), 129.6 (*Ar*H), 129.3 (*Ar*H), 128.4 (*Ar*H), 128.1 (*Ar*H), 127.5 (*Ar*H), 71.9 (5-*C*), 70.0 (7-*C*), 62.5 (4-*C*), 60.3 (1-*C*H_2), 59.6 (3-*C*H_2), 56.0 (N*C*H_2), 47.0 (8a-*C*), 45.4 (3a-*C*), 41.7 (N*C*H_3), 30.6 (6-*C*H_2); **IR** ν_{max} (neat)/cm^{-1}: 3029, 2939 (CH), 2844, 2787, 1715 (C=O), 1476 (C=C), 1446, 1381 (S=O); **HRMS** (ESI): $C_{23}H_{27}N_2O_3S$ [$M+H^+$]: calculated 411.1737, found 411.2529.

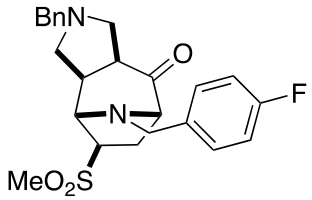
(3a*R**,4*S**,5*R**,7*S**,8a*S**)-2-Benzyl-9-methyl-5-(methylsulfonyl)octahydro-4,7-epiminocyclohepta[*c*]pyrrol-8(2*H*)-one (**299**)



General procedure **U** was followed using cycloadduct **117** (3.60 g, 16.7 mmol), *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine (8.9 mL, 36.8 mmol) and lithium fluoride (1.10 g, 41.8 mmol). Purification was by flash chromatography on silica gel, eluting with a gradient of 80 - 100% EtOAc in hexane. Crystallization from ethanol afforded the *title compound* ***299*** (2.85 g, 8.19 mmol, 49%) as a colourless solid; $\boldsymbol{R_f}$ = 0.11, (100% EtOAc); **δ_H (400 MHz, DMSO-d_6)** 7.36 – 7.19 (5H, m, Ar*H*), 3.87 (1H, t, *J* 8.9, 5-C*H*), 3.62 (1H, s, 4-C*H*), 3.56 (1H, d, *J* 13.0, N*Bn*), 3.53 – 3.47 (2H, m, N*Bn*, 7-C*H*), 3.03 (3H, s, SO_2*Me*), 2.84 – 2.71 (2H, m, 3-CH_2, 1-CH_2), 2.58 – 2.52 (4H, m, 3-CH_2, 1-CH_2, 8a-C*H*, 3a-C*H*), 2.44 (1H, dd, *J* 14.4, 7.2, 6-CH_2,), 2.38 (3H, s, N*Me*), 2.11 (1H, dd, *J* 13.9, 9.2, 6-CH_2); **δ_C(101 MHz, DMSO) δ** 207.6 (*C*=O), 139.4 (*Ar*), 128.9 (*Ar*H), 128.6 (*Ar*H), 127.3 (*Ar*H), 72.9 (7-*C*), 67.3 (5-*C*), 64.4 (4-*C*), 59.5 (N*Bn*), 57.8 (3-*C*H_2), 56.7 (1-*C*H_2), 45.5 (SO_2*Me*), 45.0 (*Me*), 40.5 (8a-*C*), 39.9 (3a-*C*), 28.2 (6-*C*H_2); **IR** ν_{max} (neat)/cm^{-1}: 3084, 3030 (CH), 2951, 2907, 1659 (C=O),

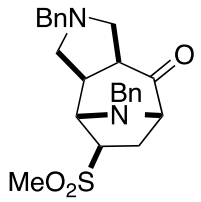
1510 (C=C), 1440, 1275 (S=O); **HRMS** (ESI): $C_{18}H_{25}N_2O_3S$ [M+H$^+$]: calculated 349.1580, found 349.1599.

(3a*R**,4*S**,5*R**,7*S**,8a*S**)-2-Benzyl-9-(4-fluorobenzyl)-5-(methylsulfonyl)octahydro-4,7-epiminocyclohepta[*c*]pyrrol-8(2*H*)-one (**301**)



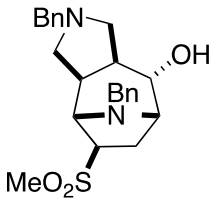
General procedure **U** was followed using cycloadduct **136** (2.50 g, 8.08 mmol), *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine (4.5 mL, 17.3 mmol) and lithium fluoride (525 mg, 20.2 mmol). Purification by flash chromatography on silica gel, eluting with a gradient of 70 - 100% EtOAc in hexane. Crystallization from ethanol afforded the *title compound **301*** (6.31 g, 14.3 mmol, 88%) as a colourless solid; $\boldsymbol{R_f}$ = 0.14, (100% EtOAc). **δ_H(400 MHz, DMSO-*d*$_6$):** 7.42 – 7.23 (7H, m, Ar*H*), 7.08 (2H, t, *J* 8.9, Ar*H*), 3.95 (1H, t, *J* 8.9, 5-C*H*), 3.76 (1H, d, *J* 13.4, N*Bn*), 3.7 (1H, d, *J* 13.4, N*Bn*), 3.63 – 3.56 (3H, m, N*Bn*, 4-C*H*, 7-C*H*), 3.45 (1H, d, *J* 12.8, N*Bn*), 3.05 (3H, s, SO_2*Me*), 2.83 (1H, td, *J* 7.7, 5.0, 8a-C*H*), 2.75 (1H, dd, *J* 8.5, 5.0, 1-CH_2), 2.66 (1H, t, *J* 8.5, 1-CH_2), 2.58 – 2.44 (3H, m, 6-CH_2, 3-CH_2, 3a-C*H*), 2.37 (1H, dd, *J* 7.5, 5.6, 3-CH_2), 2.17 (1H, dd, *J* 13.9, 9.2, 6-CH_2); **δ_C(101 MHz, DMSO-*d*$_6$):** 207.3 (*C*=O), 161.7 (d, *J* 242.4, *Ar*F), 139.3 (*Ar*), 135.6 (*Ar*), 131.2 (d, *J* 8.1, *Ar*H), 129.0 (*Ar*H), 128.6 (*Ar*H), 127.3 (*Ar*H), 115.3 (d, *J* 21.1, *Ar*H), 71.4 (7-*C*), 67.0 (5-*C*), 62.5 (4-*C*), 59.6 (N*C*H$_2$), 57.4 (3-*C*H$_2$), 57.1 (1-*C*H$_2$), 54.2 (N*C*H$_2$), 46.0 (8a-*C*), 44.7 (3a-*C*), 40.5 (SO_2*Me*), 28.9 (6-*C*H$_2$); **IR** ν_{max} (neat)/cm^{-1}: 3000 (CH), 2936, 2906, 2863, 1705 (C=O), 1505 (C=C), 1474, 1288 (S=O); **HRMS** (ESI): [M+H$^+$]: $C_{24}H_{28}FN_2O_3S$ calculated 443.1799, found 442.8340.

(3a*R**,4*S**,5*R**,7*S**,8a*S**)-2,9-Dibenzyl-5-(methylsulfonyl)octahydro-4,7-epiminocyclohepta[*c*]pyrrol-8(2*H*)-one (**300**)



General procedure **U** was followed using cycloadduct **116** (1.05 g, 3.60 mmol), *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine (<80% purity) (1.6 mL, 6.40 mmol) and lithium fluoride (226 mg, 8.71 mmol). Purification by flash chromatography on silica gel, eluting with a gradient of 70 - 100% EtOAc in hexane afforded the *title compound **300*** (863 mg, 2.03 mmol, 57%) as a colourless solid; $\boldsymbol{R_f}$ = 0.14, (100% EtOAc); Compound had impurities so was telescoped to subsequent reactions without full characterisation.

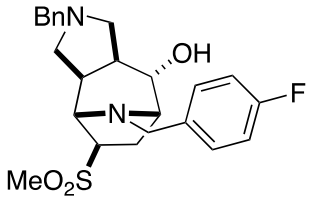
(3a*R**,4*S**,5*R**,7*S**,8*S**,8a*S**)-2,9-Dibenzyl-5-(methylsulfonyl)decahydro-4,7-epiminocyclohepta[*c*]pyrrol-8-ol (**302**)



General procedure **I** was followed using impure compound **300** (863 mg, 2.04 mmol) in DCM (25 mL) and DIBAL (6.10 mL, 6.10 mmol). Crystallization from ethanol afforded the *title compound **302*** (500 mg, 1.17 mmol, 57%) as a colourless solid; **M.Pt.** 175.8 – 176.8 °C; **δ_H (400 MHz, Chloroform-*d*):** 7.47 – 7.22 (8H, m, Ar*H*), 7.11 – 6.99 (2H, m, Ar*H*), 3.86 – 3.70 (2H, m, N*Bn*, N*Bn*), 3.62 – 3.47 (2H, m, N*Bn*, 4-C*H*), 3.46 – 3.38 (2H, m, 5-C*H*, 8-C*H*), 3.36 – 3.24 (2H, m, 7-*C*H, N*Bn*), 3.05 (1H, d, *J* 8.7, 3-C*H*), 2.83 (3H, s, *Me*), 2.58 (1H, dd, *J* 9.4, 3.7, 1-CH_2), 2.41 (1H, dt, *J* 13.3, 7.4, 6-CH_2), 2.25 – 2.10 (3H, m, 3a-C*H*, 3-CH_2, 8a-C*H*), 2.05 – 1.92 (2H, m, 1-CH_2, 6-CH_2); **δ_C(101 MHz, Chloroform-*d*):** 139.3 (*Ar*), 138.3 (*Ar*), 129.5 (*Ar*H), 128.6 (*Ar*H), 128.5 (*Ar*H), 128.0 (*Ar*H), 127.3 (*Ar*H), 126.8 (*Ar*H), 70.1 (4-*C*), 69.8 (7-*C*), 68.7 (5-*C*), 61.2 (8-*C*), 59.6 (N*C*H$_2$), 56.9 (3-*C*), 56.7 (N*C*H$_2$), 54.6 (1-*C*), 46.4 (8a-*C*), 40.5

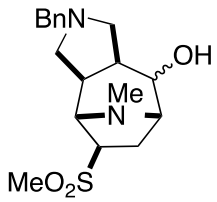
(*Me*), 34.6 (3a-*C*), 27.9 (6-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3349 (OH), 3028, 2928 (CH), 2868, 2870, 1494 (C=C), 1472, 1288 (S=O); **HRMS** (ESI): [M+H^+]: $C_{24}H_{31}N_2O_3S$ calculated 427.2050, found 427.2074.

(3a*R**,4*S**,5*R**,7*S**,S*R**,8a*S**)-2-Benzyl-9-(4-fluorobenzyl)-5-(methylsulfonyl)decahydro-4,7-epiminocyclohepta[*c*]pyrrol-8-ol **(304)**



General procedure **I** was followed using compound **301** (2.70 g, 6.10 mmol) in THF (80 mL) and DIBAL (18.3 mL, 18.3 mmol). Recrystallization from ethanol afforded the *title compound **304*** (1.24 g, 2.79 mmol, 50%) as a colourless solid; **M.Pt.** 173.2 – 174.0 ^oC; **δ_H(400 MHz, DMSO-d_6):** 7.45 – 7.20 (7H, m, Ar*H*), 7.15 – 7.03 (2H, m, Ar*H*), 4.80 (1H, d, *J* 4.6, OH), 3.79 (1H, d, *J* 13.3, NBn), 3.73 (1H, t, *J* 8.3, 7-CH), 3.70 – 3.58 (3H, m, 4-C*H*, NBn), 3.47 (1H, d, *J* 13.3, NBn), 3.41 (1H, s, 8-CH), 3.13 (1H, t, *J* 5.8, 5-CH), 3.00 (3H, s, Me), 2.75 (1H, d, *J* 8.7, 3-CH), 2.70 (1H, dd, *J* 8.2, 5.7, 1-CH), 2.38 (1H, dd, *J* 8.7, 4.7, 3-C*H*), 2.31 – 2.23 (1H, m, 6-C*H*), 2.23 – 2.16 (1H, m, 8a-C*H*), 2.17 – 2.03 (2H, m, 1-C*H*, 6-C*H*), 1.78 (1H, td, *J* 7.7, 4.7, 3a-C*H*). **δ_C(101 MHz, DMSO-d_6) δ** 161.5 (d, *J* 242.0, *Ar*F), 140.4 (*Ar*), 137.1 (d, *J* 2.9, *Ar*), 130.6 (d, *J* 8.0, *Ar*H), 128.6 (*Ar*H), 128.6 (*Ar*H), 127.1 (*Ar*H), 115.1 (d, *J* 20.9, *Ar*H), 71.9 (4-*C*), 68.2 (7-*C*), 66.0 (5-*C*), 62.4 (8-*C*), 59.7 (N*C*H_2), 58.8 (3-*C*H_2), 55.8 (N*C*H_2), 55.1 (1-*C*H_2), 46.2 (8a-*C*), 41.3 (*Me*), 40.4 (3a-*C*), 24.0 (6-*C*H_2); **IR** ν_{max} (neat)/cm^{-1}: 3119 (OH), 2968 (CH), 2927, 2882, 1506, 1482 (C=C), 1445, 1321 (S=O); **HRMS** (ESI): $C_{24}H_{30}FN_2O_3S$ [M+H^+]: calculated 445.1956, found 445.1960.

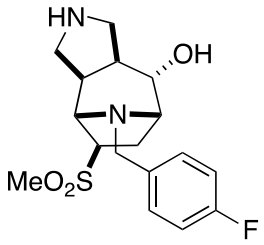
(3a*R**,4*S**,5*R**,7*S**,8*R**,8a*S**)-2-Benzyl-9-methyl-5-(methylsulfonyl)decahydro-4,7-epiminocyclohepta[*c*]pyrrol-8-ol (**303a)**
(3a*R**,4*S**,5*R**,7*S**,8*S**,8a*S**)-2-Benzyl-9-methyl-5-(methylsulfonyl)decahydro-4,7-epiminocyclohepta[*c*]pyrrol-8-ol (**303b**)



3:2 Mixture of diasteroisomers

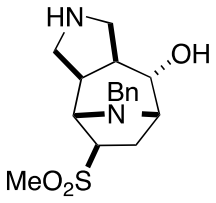
General procedure **I** was followed using compound **299** (2.60 g, 7.46 mmol) in THF (94 mL) and DIBAL (22 mL, 22.4 mmol). *Title compound **303*** (1.20 g, 3.43 mmol, 46%) as a colourless solid; **^{1}H NMR (400 MHz, DMSO-*d*$_6$):** 7.40 – 7.18 (10H, m, Ar*H*), 4.78 (1H, d, *J* 4.7, O*H*), 3.78 (1H, t, *J* 8.3, 7-C*H*), 3.70 – 3.65 (1H, m, 7-C*H* minor), 3.66 – 3.50 (4H, m, 4-C*H* minor N*Bn*, N*Bn* minor), 3.39 – 3.35 (2H, m, 4-C*H*, 8-C*H*, 8-C*H* minor), 3.10 – 3.04 (2H, m, 5-C*H*, 5-C*H* Minor), 2.98 (3H, s, *Me*), 2.97 (3H, s, *Me* Minor) 2.87 – 2.73 (4H, m, 1-C*H*$_2$ minor, 3-C*H*$_2$, 1-C*H*$_2$), 2.68 (1H, d, *J* 8.7, 3-C*H*$_2$ minor), 2.40 – 2.31 (3H, m, 3-C*H*$_2$, 1-C*H*$_2$, 3-C*H*$_2$ minor,), 2.29 (3H, s, N*Me*), 2.26 (3H, s, N*Me*), 2.25 – 2.12 (5H, m, 8a-C*H*, 6-C*H*$_2$, 3a-C*H*, 8a-C*H* minor, 6-C*H*$_2$ minor), 2.01 (1H, dt, *J* 13.6, 6.8, 6-C*H*$_2$ minor), 1.90 (1H, dd, *J* 13.7, 9.3, 6-C*H*$_2$), 1.72 (1H, td, *J* 7.9, 4.8, 3a-C*H*minor); **δC(101 MHz, DMSO-*d*$_6$):** 140.1 (*Ar* minor), 138.9 (*Ar*), 129.0 (*Ar*H), 128.8 (*Ar*H minor),128.8 (*Ar*H), 128.6 (*Ar*H minor), 127.5 (*Ar*H), 127.1 (*Ar*H minor), 71.5 (4-*C* minor), 70.5 (4-*C*), 69.6 (7-*C*), 68.4 (7-*C* minor), 68.1 (5-*C* minor), 67.6 (5-*C*), 64.2 (8-*C* minor), 64.1 (8-*C*), 60.1 (N*C*H$_2$ minor), 59.5 (N*C*H$_2$), 58.3 (3-*C*H$_2$ minor), 56.1 (3-*C*H$_2$), 55.4 (1-*C*H$_2$), 55.3 (1-*C*H$_2$ minor), 46.2 (8a-*C* minor), 45.8 (8a-*C*), 41.5 (*Me* minor), 41.0 (3a-*C* minor), 40.8 (*Me*), 40.7 (*Me* minor), 40.5 (3a-*C*), 34.1 (*Me*), 26.2 (6-*C*H$_2$) 23.5 (6-*C*H$_2$ minor); **IR** ν_{max} (neat)/cm^{-1}: 3283 (OH), 3026 (CH), 2976, 2938, 2896, 2972, 1444 (C=C), 1329 (S=O); **HRMS** (ESI): $C_{18}H_{27}N_2O_3S$ [M+H$^+$]: calculated 351.1737, found 351.1736.

(3a*R**,4*S**,5*R**,7*S**,8*S**,8a*S**)-9-(4-Fluorobenzyl)-5-(methylsulfonyl)decahydro-4,7-epiminocyclohepta[*c*]pyrrol-8-ol (**306)**



General procedure **F** was followed using compound **304** (1.2 g, 6.10 mmol) in MeOH (20 mL) and $Pd(OH)_2$ (120 mg, 20% w/w) at rt. The *title compound **306*** (880 mg, 2.48 mmol, 92%) as a colourless solid; **M.Pt.** 167.1 – 168.0 ^oC; **δ_H(400 MHz, Chloroform-*d*)** 7.27 (2H, dd, *J* 8.5, 5.6, Ar*H*), 6.91 (2H, t, *J* 8.5, Ar*H*), 3.70 (1H, d, *J* 13.4, N*Bn*), 3.64 (1H, s, 8-CH), 3.59 (1H, d, *J* 13.4, N*Bn*), 3.51 (1H, dd, *J* 8.6, 4.5, 4-C*H*), 3.40 (1H, t, *J* 8.4, 7-C*H*), 3.26 (1H, t, *J* 5.7, 5-C*H*), 2.97 – 2.85 (5H, m, 1-CH_2, 3-CH_2, *Me*), 2.83 – 2.75 (2H, m, 3-CH_2, 1-CH_2), 2.39 (1H, dd, *J* 13.7, 9.2, 6-CH_2), 2.24 (1H, dt, *J* 13.7, 6.8, 6-CH_2), 2.18 – 2.09 (1H, m, 8a-C*H*), 1.76 (1H, td, *J* 7.9, 5.1, 3a-C*H*); **δ_C (101 MHz, Chloroform-*d*)** 162.0 (d, *J* 244.9, *Ar*F), 135.2 (*Ar*), 130.6 (d, *J* 7.9, *Ar*H), 115.1 (d, *J* 21.1, *Ar*H), 71.6 (4-*C*), 69.9 (7-*C*), 66.7 (5-*C*), 61.4 (8-*C*), 56.2 (N-*C*H_2), 51.4 (3-*C*H_2), 48.8 (8a-*C*), 48.2 (1-*C*H_2), 42.7 (3a-*C*), 40.5 (*Me*), 24.6 (6-*C*H_2); **IR** ν_{max} (neat)/cm^{-1}: 3340 (OH), 3006 (CH), 2993, 2895, 1632 (C=O), 1508 (C=C), 1459, 1270 (S=O); **HRMS** (ESI): $C_{17}H_{24}FN_2O_3S$ [$M+H^+$]: calculated 355.1486, found 355.1488.

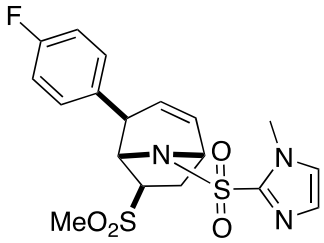
(3a*R**,4*S**,5*R**,7*S**,8*S**,8a*S**)-9-Benzyl-5-(methylsulfonyl)decahydro-4,7-epiminocyclohepta[*c*]pyrrol-8-ol **(305)**



General procedure **F** was followed using compound **302** (205 mg, 0.48 mmol) in MeOH (10 mL), 10% $Pd(OH)_2$/C (20 mg, 20% w/w) and conc. HCl (0.1 mL) at rt. Purification by SCX SPE (strong cation exchange solid phase extraction) afforded the *title compound **305*** (150 mg, 0.45 mmol, 92%) as a colourless oil; **δ_H(501 MHz, Methanol-d_4):** 7.35 – 7.12 (5H, m), 3.83

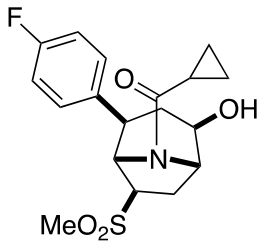
(1H, d, *J* 12.8, N*Bn*), 3.72 (1H, d, *J* 12.8, N*Bn*), 3.70 (1H, s, 4-C*H*), 3.58 (1H, dd, *J* 9.1, 4.9, 5-C*H*), 3.49 – 3.45 (1H, m, 8-C*H*), 3.42 (1H, dd, *J* 7.8, 3.3, 7-C*H*), 3.09 (1H, dd, *J* 9.9, 6.4, 1-CH_2), 2.94 (1H, d, *J* 9.9, 1-CH_2), 2.89 (3H, s, SO_2*Me*), 2.64 (1H, t, *J* 9.9, 3-CH_2), 2.55 (1H, dd, *J* 9.9, 4.5, 3-CH_2), 2.36 – 2.22 (2H, m, 3a-C*H*, 8a-C*H*), 2.15 (1H, ddd, *J* 14.5, 7.8, 4.9, 6-CH_2), 2.02 (1H, ddd, *J* 14.5, 9.1, 1.1, 6-CH_2); **δ_C(126 MHz, Methanol-*d*$_4$) δ** 137.7 (*Ar*), 130.2 (*Ar*H), 129.7 (*Ar*H), 128.9 (*Ar*H), 69.5 (4-*C*), 67.0 (7-*C*), 62.1 (8-*C*), 60.2 (N*Bn*), 57.9 (8-*C*), 56.9 (3-*C*), 55.7 (1-*C*), 43.2 (8a-*C*), 39.0 (*Me*), 35.5 (3a-*C*), 28.6 (6-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3376 (O-H), 3330 (N-H), 3027, 2928 (C-H), 2825, 1550 (C=C), 1453, 1286(S=O); **HRMS** (ESI): [M+H$^+$]: $C_{17}H_{25}N_2O_3S$ calculated 337.1580, found 337.1584.

(1*S**,2*R**,5*S**,7*R**)-2-(4-Fluorophenyl)-8-((1-methyl-1*H*-imidazol-2-yl)sulfonyl)-7-(methylsulfonyl)-8-azabicyclo[3.2.1]oct-3-ene (**287**)



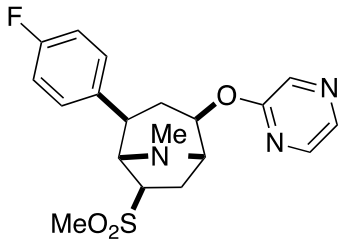
General procedure **Q** was followed using amine **282** (125 mg, 0,37 mmol), 1-methylimidazole-2- sulfonyl chloride (330 mg, 5.0 eq.) and pyridine (120 μL, 1.49 mmol). Purification by MDAP afforded *title compound* **287** (6 mg, 0.14 mmol, 4%) as a colourless oil; **δ_H (400 MHz, Methanol-*d*$_4$)** 7.65 – 7.49 (1H, m, Ar*H*), 7.26 – 7.09 (2H, m, Ar*H*), 7.11 – 6.97 (3H, m, Ar*H*), 6.35 (1H, ddd, *J* 9.7, 5.5, 1.7, 2-C*H*), 5.68 (1H, ddd, *J* 9.7, 4.3, 1.5, 3-C*H*), 4.95 (1H, td, *J* 5.6, 1.5, 1-C*H*), 4.77 (1H, q, *J* 1.7, 5-C*H*), 4.02 (1H, td, *J* 8.1, 1.8, 6-C*H*), 3.68 – 3.63 (1H, m, 4-C*H*), 3.50 (3H, s, SO_2Me), 3.01 (3H, s, N*Me*), 2.59 – 2.50 (1H, m, 7-CH_2), 2.29 (1H, ddd, *J* 12.1, 8.1, 5.6, 7-CH_2); **δ_C (101 MHz, Methanol-*d*$_4$)** 162.2 (d, *J* 244.4, *Ar*-F), 135.5 (*Ar*), 135.5 (d, *J* 3.2 *Ar*), 131.1 (4-*C*H), 130.1 (d, *J* 8.2, *Ar*H), 127.4 (*Ar*H), 125.8 (3-*C*H), 125.3 (*Ar*H), 114.7 (d, *J* 21.7, *Ar*H), 66.3 (6-*C*), 63.2 (5-*C*), 57.6 (1-*C*), 50.4 (4-*C*), 38.6 (*Me*), 37.5 (7-*C*H_2), 34.5 (SO_2*Me*); **IR** ν_{max} (neat)/cm^{-1}: 3063 (CH), 3033, 2975, 2922, 2821, 1604, 1540 (C=C), 1509; **HRMS** (ESI): [M+H$^+$]: $C_{18}H_{21}FN_3O_4S_2$ calculated 426.0952, found 426.1082.

Cyclopropyl((1*S**,2*R**,4*R**,5*S**,6*R**)-4-(4-fluorophenyl)-2-hydroxy-6-(methylsulfonyl)-8-azabicyclo[3.2.1]octan-8-yl)methanone (**285**)



General procedure **V** was followed using amine **282** (127 mg, 0.38 mmol) and cyclopropanecarbonyl chloride (350 µl, 3.80 mmol, 10.0 eq.) and pyridine (125 µl, 1.52 mmol, 4.0 eq.). Purification by MDAP gave *title compound* **285** (22 mg, 0.06 mmol, 16%) as a colourless oil with 1:1 ratio of rotamers; **δ_H(501 MHz, DMSO-*d*$_6$):** 7.90 – 7.72 (2H, m, Ar*H*), 7.73 – 7.52 (2H, m, Ar*H*), 7.07 (2H, t, *J* 8.9, Ar*H*), 6.99 (2H, t, *J* 8.9, Ar*H*), 5.35 (1H, s, O*H*), 5.20 (1H, s, O*H*), 4.88 (1H, s, 5-C*H*), 4.72 (1H, s, 2-C*H*), 4.67 (1H, s, 5-C*H*), 4.62 (1H, d, *J* 6.3, 2-C*H*), 4.08 (1H, t, *J* 7.5, 6-C*H*), 3.91 (1H, dd, *J* 9.4, 5.3, 6-C*H*), 3.82 (1H, s, 1-C*H*), 3.78 (1H, s, 1-C*H*), 3.20 (1H, d, *J* 6.2, 4-C*H*), 3.10 – 2.99 (4H, m, SO_2*Me*, 4-C*H*), 2.79 (3H, s, SO_2*Me*), 2.40 – 2.28 (3H, m, 7-CH_2, 7-CH_2), 2.24 (1H, dd, *J* 14.2, 9.4, 3-CH_2), 2.15 – 2.05 (2H, m, 7-CH_2, 3-CH_2), 1.99 – 1.84 (1H, m, *cyp*.), 1.68 (1H, d, *J* 16.0, 3-CH_2), 1.62 (1H, d, *J* 15.9, 3-CH_2), 0.86 – 0.78 (1H, m, *cyp*.), 0.64 – 0.57 (3H, m, *cyp*), 0.50 – 0.42 (2H, m, *cyp*, *cyp*), 0.41 – 0.34 (1H, m, *cyp*.), 0.34 – 0.26 (1H, m, *cyp*.), 0.06 – -0.09 (1H, m, *cyp*.) **δ_C (126 MHz, DMSO-*d*$_6$):** 170.0 (*C*=O), 169.6 (*C*=O), 161.0 (d, *J* 241.8, *Ar*F), 160.7 (d, *J* 241.2, *Ar*F), 139.7 (d, *J* 3.1, *Ar*), 139.2 (d, *J* 3.1, *Ar*), 131.4 (d, *J* 7.8, *Ar*H), 130.7 (d, *J* 7.8, *Ar*H), 114.4 (d, *J* 20.7, *Ar*H), 114.1 (d, *J* 20.7, *Ar*H), 67.1 (1-*C*), 67.0 (1-*C*), 64.2 (6-*C*), 64.2 (6-*C*), 60.6 (2-*C*), 59.9 (2-*C*), 57.2 (5-*C*), 57.2 (5-*C*), 44.6 (4-*C*), 44.1 (4-*C*), 38.6 (SO_2*Me*), 36.7 (SO_2*Me*), 28.6 (3-*C*), 28.4 (7-*C*), 27.8 (3-*C*), 26.6 (7-*C*) , 11.0 (*cyp*), 10.7 (*cyp*), 6.6 (*cyp*), 6.5 (*cyp*), 6.4 (*cyp*), 6.2 (*cyp*); **IR** ν_{max} (neat)/cm^{-1}: 3369 (OH), 3009 (CH), 2928, 2893, 1603 (C=O), 1510 (C=C), 1439, 1296 (S=O); **HRMS** (ESI): [M+H$^+$]: $C_{18}H_{23}FNO_4S$ calculated 368.1326, found 368.2022.

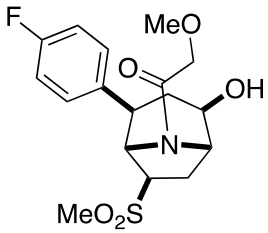
(1*S**,2*R**,4*R**,5*S**,6*R**)-4-(4-Fluorophenyl)-8-methyl-6-(methylsulfonyl)-2-(pyrazin-2-yloxy)-8-azabicyclo[3.2.1]octane (**288**)



General procedure **R** was followed using alcohol **279a** (147 mg, 0.47 mmol), NaH (17 mg, 0.71 mmol) and 2-chloropyrazine (85 µL, 0.94 mmol, 2.0 eq.). Purification by MDAP afforded *title compound* **288** (2.4 mg, 0.01 mmol, 2%) as a colourless oil.

δ_H(400 MHz, Chloroform-*d*): 8.11 (1H, d, *J* 1.5, Ar*H*), 8.06 (1H, d, *J* 2.8, Ar*H*), 8.01 (1H, dd, *J* 2.8, 1.5, Ar*H*), 7.42 – 7.32 (2H, m, Ar*H*), 7.05 – 6.85 (2H, m, Ar*H*), 5.55 – 5.30 (1H, m, 2-C*H*), 3.82 (1H, s, 5-C*H*), 3.65 (1H, t, *J* 5.5, 1-C*H*), 3.52 (1H, t, *J* 8.2, 6-C*H*), 3.05 – 2.96 (1H, m, 4-C*H*), 2.92 (3H, s, SO_2*Me*), 2.53 – 2.36 (1H, m, 7-CH_2), 2.38 – 2.16 (5H, m, N*Me*, 3-CH_2, 7-CH_2), 1.74 (1H, ddd, *J* 14.7, 11.0, 7.8, 3-CH_2); **δ_C(101 MHz, Chloroform-*d*):** 161.4 (d, *J* 242.9, *Ar*F), 159.2 (Ar), 140.6 (*Py*-H), 139.1 (d, *J* 3.0, *Ar*), 137.0 (*Py*-H), 136.0 (*Py*-H), 129.7 (d, *J* 7.8, *Ar*H), 115.0 (d, *J* 21.0, *Ar*H), 70.6 (2-*C*), 69.2 (6-*C*), 67.9 (5-*C*), 65.7 (1-*C*), 46.4 (4-*C*), 41.5 (N*Me*), 40.6 (SO_2*Me*), 28.0 (3-*C*), 25.7 (7-*C*); **IR** ν_{max} (neat)/cm^{-1}: 2952 (CH), 2926, 2876, 2867, 1510 (C=C), 1457, 1409, 1298 (S=O); **HRMS** (ESI): [M+H$^+$]: $C_{19}H_{23}FN_3O_3S$ calculated 392.1439, found 392.1435.

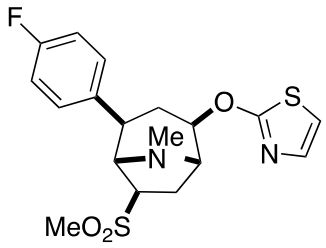
1-((1*S**,2*R**,4*R**,5*S**,6*R**)-4-(4-Fluorophenyl)-2-hydroxy-6-(methylsulfonyl)-8-azabicyclo[3.2.1]octan-8-yl)-2-methoxyethanone (**289**)



General procedure **V** was followed using amine hydrochloride **282** (127 mg, 0.38 mmol) and methoxyacetyl chloride (0.2 mL, 2.9 mmol) and pyridine (250 µl, 3.04 mmol). Purification by MDAP afforded *title compound* **289** (2 mg, 0.57 µmol, 1%) as a colourless oil with a ratio of 1:1 rotamers; **δ_H(400 MHz, Methanol-d_4):** 7.96 – 7.80 (2H, m, Ar*H*), 7.78 – 7.63 (2H, m, Ar*H*), 7.15 – 7.00 (2H, m, Ar*H*), 7.02 – 6.87 (2H, m, Ar*H*), 5.12 (1H, s, 5-C*H*), 4.93 (1H, d, *J* 7.5, 2-C*H*), 4.50 (1H, s, 5-C*H*), 4.48 – 4.43 (1H, m, 2-C*H*), 4.24 (1H, d, *J* 14.7, CH_2OMe),

4.15 (1H, d, *J* 14.7, C*H*$_2$OMe), 4.07 (1H, dd, *J* 9.1, 5.6, 1-C*H*), 3.98 (1H, dd, *J* 5.0, 2.6, 2-C*H*), 3.97 – 3.89 (2H, m, 2-C*H*, 1-C*H*,), 3.72 (1H, d, *J* 15.0, C*H*$_2$OMe), 3.33 (3H, s, *Me*), 3.28 – 3.20 (2H, m, 4-C*H*, 4-C*H*), 3.07 (3H, s, *Me*), 3.05 (3H, s, *Me*), 2.95 (3H, s, *Me*), 2.83 (1H, d, *J* 15.0, C*H*$_2$OMe), 2.59 – 2.12 (6H, m, 7-C*H*$_2$, 7-C*H*$_2$, 3-C*H*$_2$, 3-C*H*$_2$), 1.96 – 1.91 (1H, m, 3-C*H*$_2$), 1.91 – 1.86 (1H, m, 3-C*H*$_2$); **δc (101 MHz, Methanol-*d*$_4$)**: 168.4 (*C*=O), 167.8 (*C*=O), 165.8 (d, *J* 242.4, *Ar*F), 165.4 (d, *J* 242.4, *Ar*F), 138.9 (d, *J* 3.0 *Ar*), 138.7 (d, *J* 3.0, *Ar*), 131.1 (d, *J* 7.8, *Ar*H), 130.5 (d, *J* 7.8, *Ar*H), 114.6 (d, *J* 21.3, *Ar*H), 114.1 (d, *J* 21.2, *Ar*H), 69.7 (1-*C*), 69.0 (1-*C*), 67.9 (6-*C*), 67.8 (6-*C*), 64.2 (2-*C*), 63.9 (2-*C*), 60.2 (*C*H$_2$), 59.6 (*C*H$_2$), 58.3 (5-*C*), 58.0 (5-*C*), 57.8 (O*Me*), 57. 8 (O*Me*), 45.3 (4-*C*), 44.9 (4-*C*), 37.7 (SO$_2$*Me*), 36.5 (SO$_2$*Me*), 27.9 (3-*C*), 27.9 (3-*C*), 27.1 (7-*C*), 26.5 (7-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3429 (OH), 2994 (CH), 2955, 2929, 1684 (C=O), 1511 (C=C), 1457, 1329 (S=O); **LCMS**: [M+H$^+$]: $C_{17}H_{23}FNO_5$ calculated 372.1275, found 372.40.

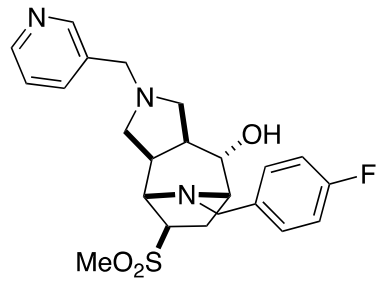
2-(((1*S**,2*R**,4*R**,5*S**,6*R**)-4-(4-Fluorophenyl)-8-methyl-6-(methylsulfonyl)-8-azabicyclo[3.2.1]octan-2-yl)oxy)thiazole **(286)**



General procedure **R** was followed using alcohol **279a** (147 mg, 0.47 mmol), NaH (17 mg, 0.71 mmol) and 2-bromothiazole (85 μL, 0.94 mmol, 2.0 eq.). Purification by MDAP afforded *title compound* **286** (19 mg, 0.05 mmol, 11%) as a brown oil.

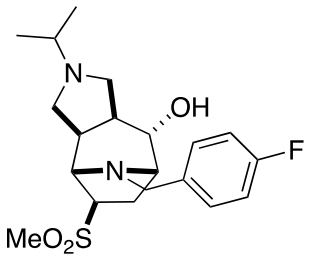
δH(400 MHz, Chloroform-*d*): 7.45 – 7.33 (2H, m, Ar*H*), 7.07 – 6.93 (2H, m, Ar*H*), 6.60 (1H, d, *J* 5.2, Ar*H*), 6.17 (1H, d, *J* 5.2, Ar*H*), 4.27 – 4.14 (1H, m, 2-C*H*), 3.85 (1H, s, 5-C*H*), 3.51 (1H, t, *J* 8.0, 6-C*H*), 3.39 (1H, t, *J* 5.4, 1-C*H*), 2.99 (3H, s, SO$_2$*Me*), 3.14 – 2.86 (1H, m, 4-C*H*), 2.57 – 2.21 (5H, m, 7-C*H*$_2$, N*Me*), 2.15 (1H, dd, *J* 14.5, 6.5, 3-C*H*$_2$), 1.61 (1H, ddd, *J* 14.5, 10.7, 7.7, 3-C*H*$_2$). **δC(101 MHz, Chloroform-*d*):** 175.8 (*Ar*), 161.4 (d, *J* 244.7, *Ar*F), 139.4 (d, *J* 3.3, *Ar*), 129.6 (d, *J* 7.6, *Ar*H), 114.9 (d, *J* 21.0, *Ar*), 120.6 (*Ar*-H), 103.8 (*Ar*-H), 69.3 (6-*C*), 68.9 (1-*C*), 67.3 (5-*C*), 66.9 (2-*C*), 46.1 (4-*C*), 41.5 (N*Me*), 40.6 (SO$_2$*Me*), 31.3 (3-*C*), 24.6 (7-*C*); **IR** ν_{max} (neat)/cm^{-1}: 2975 (C-H), 2938, 2908, 2877, 1656, 1510 (C=C), 1459, 1224 (S=O); **HRMS** (ESI): [M+H$^+$]: $C_{18}H_{22}FN_2O_3S_2$ calculated 397.1050, found 397.1082.

(3a*R**,4*S**,5*R**,7*S**,8*S**,8a*S**)-9-(4-Fluorobenzyl)-5-(methylsulfonyl)-2-(pyridin-3-ylmethyl)decahydro-4,7-epiminocyclohepta[*c*]pyrrol-8-ol (**312**)



General procedure **W** was followed using amine hydrochloride **306** (140 mg, 0.36 mmol) and isonicotinaldehyde (170 μL, 1.8 mmol), $NaBH_4$ (40 mg, 3.0 eq.). Purification by automated reversed-phase flash chromatography eluting with MeCN/H_2O/1% formic acid gave *title compound* **312** (66 mg, 0.15 mmol, 41%) as a colourless oil; **δ_H (400 MHz, Methanol-*d*$_4$)** 8.72 (1H, s, Ar*H*), 8.63 (1H, d, *J* 4.9, Ar*H*), 8.08 – 7.97 (1H, m, Ar*H*), 7.55 (1H, dd, *J* 7.9, 4.8, Ar*H*), 7.42 – 7.37 (2H, m, Ar*H*), 7.05 – 6.98 (2H, m, Ar*H*), 4.36 (2H, s, NCH_2), 3.88 – 3.78 (3H, m, N-CH_2, 7-C*H*), 3.78 – 3.71 (1H, m, 4-C*H*), 3.71 – 3.64 (2H, m, 8-C*H*, N-CH_2), 3.50 – 3.34 (3H, m, 1-CH_2, 5-C*H*, 3-CH_2), 3.10 (1H, dd, *J* 10.8, 8.6, 1-CH_2), 3.04 (3H, s, *Me*), 2.63 – 2.50 (1H, m, 8a-C*H*), 2.46 (1H, dd, *J* 13.8, 9.9, 6-CH_2), 2.33 (1H, dt, *J* 13.8, 6.9, 6-CH_2), 2.22 – 2.12 (1H, m, 3a-C*H*); **δ_C(101 MHz, Methanol-*d*$_4$) δ** 167.0 (*Ar*H), 162.1 (d, *J* 243.7, *Ar*-F), 150.4 (*Ar*H), 138.8 (*Ar*H), 135.4 (d, *J* 3.0, *Ar*), 130.6 (d, *J* 7.9, *Ar*H), 129.3 (*Ar*), 124.1 (*Ar*H), 114.5 (d, *J* 21.4, *Ar*H), 70.8 (4-*C*), 68.3 (7-*C*), 66.7 (5-*C*), 59.7 (8-*C*), 57.6 (N-*C*H_2), 56.3 (N-*C*H_2), 55.4 (3-*C*H_2), 54.6 (1-*C*H_2), 45.5 (8a-*C*), 40.8 (3a-*C*), 39.2 (*Me*), 23.8 (6-*C*H_2); **IR** ν_{max} (neat)/cm^{-1}: 3203 (OH), 3015 (CH), 2943, 2922, 1577, 1508 (C=C), 1421, 1297 (S=O); **HRMS** (ESI): $C_{23}H_{29}FN_3O_3S$ [M+H^+]: calculated 446.1908, found 446.1908.

(3a*R**,4*S**,5*R**,7*S**,8*S**,8a*S**)-9-(4-Fluorobenzyl)-2-isopropyl-5-(methylsulfonyl)decahydro-4,7-epiminocyclohepta[*c*]pyrrol-8-ol (**308**)

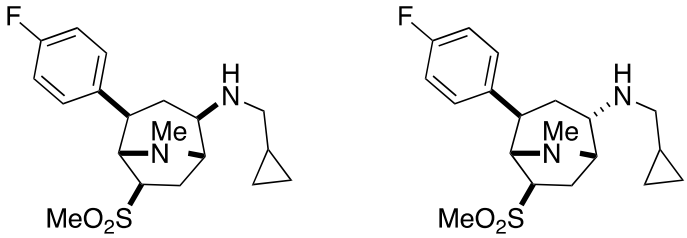


General procedure **W** was followed using amine hydrochloride **306** (140 mg, 0.36 mmol) and acetone (300 μL, 3.6 mmol, 10 eq.) $NaBH_4$ (40 mg, 3.0 eq.).. Purification by automated reversed-phase flash chromatography eluting with MeCN/H_2O 1% formic acid gave *title*

compound **308** (44 mg, 0.11 mmol, 31%) as a colourless oil; **δ_H (400 MHz, DMSO-*d*$_6$)**: 7.45 – 7.30 (2H, m, Ar*H*), 7.22 – 7.04 (2H, m, Ar*H*), 3.85 (1H, t, *J* 8.2, 7-C*H*), 3.69 – 3.60 (2H, m, N*Bn*), 3.60 – 3.50 (2H, m, 8-C*H*, 4-C*H*), 3.24 – 3.04 (4H, m, 1-CH_2, 3-CH_2, C*H*(Me)$_2$, 5-C*H*), 3.03 (3H, s, SO_2*Me*), 2.99 – 2.89 (2H, m, 1-CH_2, 3-CH_2), 2.36 – 2.21 (2H, m, 8a-C*H*, 6-CH_2), 2.11 (1H, dt, *J* 13.6, 6.9, 6-CH_2), 1.94 (1H, q, *J* 7.6, 3a-CH_2), 1.19 – 1.14 (6H, m, *Me*, *Me*); **δ_C (101 MHz, DMSO-*d*$_6$):** 161.7 (d, *J* 242.1, *Ar*-F), 136.6 (d, *J* 2.9, *Ar*), 130.8 (d, *J* 8.0, *Ar*H), 115.3 (d, *J* 21.0, *Ar*H), 70.6 (4-*C*), 68.2 (7-*C*), 66.4 (5-*C*), 60.8 (8-*C*), 55.8 (*C*H(Me)$_2$), 55.8 (N-*C*H_2), 54.6 (3-*C*H_2), 52.1 (1-*C*H_2), 45.6 (8a-*C*), 40.8 (3a-*C*), 40.5 (SO_2*Me*), 23.9 (6-*C*H_2), 19.5 (*Me*), 19.5 (*Me*); **IR** ν_{max} (neat)/cm^{-1}: 3454 (OH), 3009 (CH), 2929, 2898, 1602, 1510 (C=C), 1440, 1294 (S=O); **HRMS** (ESI): $C_{20}H_{30}FN_2O_3S$ [M+H$^+$]: calculated 397.1956, found 397.1956.

(1*S*,2*R*,4*R*,5*S*,6*R*)-*N*-(Cyclopropylmethyl)-4-(4-fluorophenyl)-8-methyl-6-(methylsulfonyl)-8-azabicyclo[3.2.1]octan-2-amine (**283 major)**

(1*S**,2*S** 4*R**,5*S**,6*R**)-*N*-(cyclopropylmethyl)-4-(4-fluorophenyl)-8-methyl-6-(methylsulfonyl)-8-azabicyclo[3.2.1]octan-2-amine (**283 minor)**

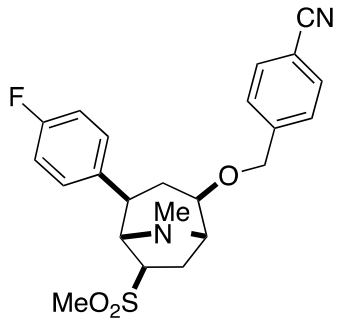


3:2 mixture of diastereosiomers

General procedure **X** was followed using ketone **273** (174 mg, 0.56 mmol), titanium isopropoxide (0.4 mL, 1.4 mmol), cyclopropanemethylamine (0.5 mL, 5.6 mmol) and $NaBH_4$ (42 mg, 1.12 mmol). Purification by automated reversed-phase flash chromatography eluting with MeCN/H_2O 1% formic acid gave *title compound* **283** (37 mg, 0.10 mmol, 18%) as a brown oil as an inseparable 3:2 mixture of diastereomers; **δ_H (400 MHz, Chloroform-*d*)** 7.27 – 7.21 (2H, m, Ar*H*), 7.21 – 7.16 (2H, m Ar*H* minor), 6.86 (2H, t, *J* 8.5, Ar*H*), 6.78 (2H, t, *J* 8.5, Ar*H* minor), 4.03 (1H, s, 5-C*H*), 3.65 (1H, s, 5-C*H*minor), 3.56 – 3.49 (2H, m, 6-C*H*, 1-C*H*), 3.44 – 3.30 (2H, m, 6-C*H* minor, 1-C*H* minor), 3.15 (1H, s, 2-C*H* minor), 2.97 (1H, s, 2-C*H*), 2.78 (4H, s, SO_2*Me*, 4-C*H* minor), 2.76 (3H, s, SO_2*Me* minor), 2.73 – 2.64 (1H, m, 4-C*H*), 2.53 – 2.29 (12H, m, N*Me* minor, N*Me*, NCH_2, NCH_2 minor, 7-CH_2, 7-CH_2 minor), 2.14 – 2.05 (1H, m, 7-CH_2 minor),

2.05 – 1.94 (1H, m, 7-CH_2), 1.93 – 1.77 (3H, m, 3-CH_2, 3-CH_2 minor), 1.71 (1H, d, *J* 8.3, NCH_2 minor), 1.68 (1H, d, *J* 8.3, NCH_2), 1.65 – 1.50 (1H, m, 3-CH_2 minor), 0.79 (1H, s, C*H* minor), 0.54 (1H, dq, *J* 14.4, 6.0, 5.1, C*H*), 0.36 (1H, d, *J* 7.2, CH_2 minor), 0.25 – 0.16 (2H, m, CH_2, CH_2 minor), 0.14 – 0.05 (2H, m, CH_2, CH_2 minor), 0.03 – -0.04 (1H, m, CH_2), -0.27 (1H, dq, *J* 9.9, 5.0, CH_2), -0.81 (1H, dq, *J* 10.0, 5.0, CH_2); **δc (101 MHz, Chloroform-*d*)** 161.5 (d, *J* 247.0, *Ar*F), 161.4 (d, *J* 244.8, *Ar*F), 139.4 (d, *J* 3.1, *Ar*), 138.8 (d, *J* 3.3, *Ar*), 129.6 (d, *J* 7.7, *Ar*H), 129.1 (d, *J* 7.7, *Ar*H), 115.7 (d, *J* 21.1, *Ar*H), 114.9 (d, *J* 20.9, *Ar*H), 69.2 (6-*C*), 69.1 (6-*C*), 67.3 (5-*C*), 65.8 (1-*C*), 65.7 (5-*C*), 65.4 (1-*C*), 56.0 (2-*C*), 54.8 (2-*C*), 51.2 (NCH_2), 50.0 (NCH_2), 45.4 (4-*C*), 42.8 (4-*C*H), 41.7 (*Me*), 41.6 (*Me*), 40.9 (N*Me*), 40.7 (N*Me*), 28.9 (3-*C*H_2), 28.4 (3-*C*H_2), 25.2 (7-*C*H_2), 25.0 (7-*C*H_2), 9.6 (*C*H), 8.4 (*C*H), 3.8 (*C*H_2), 4.1 (*C*H_2), 3.8 (*C*H_2), 3.3 (*C*H_2); **IR** ν_{max} (neat)/cm^{-1}: 3404 (NH), 3079 (CH), 3007, 2937, 2847, 1508 (C=C), 1463, 1293 (S=O); **HRMS**: $C_{19}H_{28}FN_2O_2S$ [M+H$^+$]: calculated 367.1850, found 367.1858.

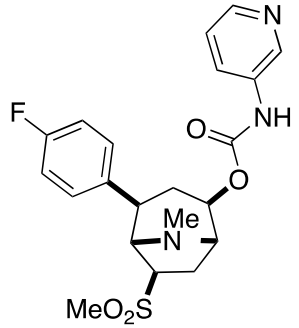
4-((((1*S**,2*R**,4*R**,5*S**,6*R**)-4-(4-Fluorophenyl)-8-methyl-6-(methylsulfonyl)-8-azabicyclo[3.2.1]octan-2-yl)oxy)methyl)benzonitrile (**284**)



General procedure **R** was followed using alcohol **278a** (140 mg, 0.48 mmol), NaH (30 mg, 0.72 mmol) and 4-(bromomethyl)benzonitrile (188 mg, 0.96 mmol, 2.0 eq.). Purification by MDAP afforded *title compound* **284** (24 mg, 0.06 mmol, 12%) as a colourless oil; **δH (400 MHz, DMSO-*d*6)** 7.90 – 7.79 (2H, m, Ar*H*), 7.76 – 7.61 (2H, m, Ar*H*), 7.49 (2H, d, *J* 8.5, Ar*H*), 7.04 (2H, t, *J* 8.5, Ar*H*), 4.77 (1H, s, 2-CH), 4.63 (1H, d, *J* 13.7, NCH_2), 4.57 (1H, d, *J* 13.7, NCH_2), 4.00 (1H, t, *J* 8.4, 6-C*H*), 3.51 (1H, s, 5-C*H*), 3.50 – 3.42 (1H, m, 1-C*H*), 3.06 (3H, s, *Me*), 2.95 – 2.85 (1H, m, 4-C*H*), 2.31 (1H, dq, *J* 13.7, 6.9, 7-CH_2), 2.25 – 2.11 (4H, m, N*Me*, 3-CH_2), 2.03 (1H, dd, *J* 13.7, 9.1, 7-CH_2), 1.79 (1H, d, *J* 16.0, 3-CH_2); [1] **δC(101 MHz, DMSO-*d*6):** 161.1 (d, *J* 241.4, *Ar*-F), 145.6 (*Ar*), 144.0 (*Ar*), 141.9 (d, *J* 3.0, *Ar*), 132.6 (*Ar*H), 131.2 (d, *J* 7.6, *Ar*H), 130.7 (*Ar*H), 128.1 (CN), 114.5 (d, *J* 20.5, *Ar*H), 69.1 (2-*C*), 68.4 (5-*C*), 67.8 (6-C), 66.1 (1-*C*), 45.5 (4-*C*), 42.1 (O-*C*), 40.9 (N*Me*), 33.1 (SO_2*Me*), 27.8 (7-*C*), 26.9 (3-

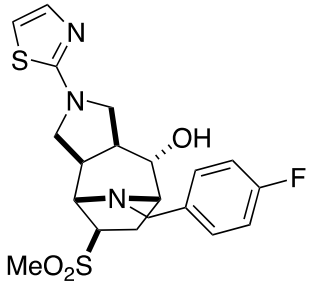
C); **IR** ν_{max} (neat)/cm^{-1}: 3037 (CH), 3014, 2951, 2894, 2228 (CN), 1506 (C=C), 1418, 1288 (S=O); **HRMS** (ESI): $[M+H^+]$: $C_{23}H_{26}FN_2O_3S_2$ calculated 429.1643, found 429.1643.

(1*S**,2*R**,4*R**,5*S**,6*R**)-4-(4-Fluorophenyl)-8-methyl-6-(methylsulfonyl)-8-azabicyclo[3.2.1]octan-2-yl pyridin-3-ylcarbamate (**291**)



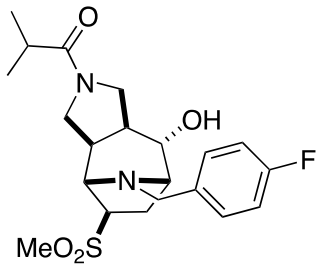
General procedure **Y** was followed using alcohol **278a** (150 mg, 0.48 mmol), $NaHCO_3$ (242 mg, 2.88 mmol) and 3-pyridyl isocyanate (144 mg, 1.20 mmol). Purification by MDAP afforded *title compound* **291** (23 mg, 0.05 mmol, 11%) as a colourless oil; **δ_H(400 MHz, Methanol-*d*$_4$):** 8.62 (1H, s, Ar*H*), 8.27 – 8.11 (1H, m, Ar*H*), 8.01 (1H, s, Ar*H*), 7.71 – 7.56 (2H, m, Ar*H*), 7.50 – 7.27 (1H, m, Ar*H*), 7.13 – 6.85 (2H, m, Ar*H*), 4.79 (1H, ad, J 8.3, 2-C*H*), 4.01 (1H, t, *J* 8.0, 6-C*H*), 3.76 (1H, s, 5-C*H*), 3.57 (1H, d, *J* 8.6, 1-C*H*), 3.11 – 3.03 (3H, m, SO_2*Me*), 3.02 – 2.91 (1H, m, 4-C*H*), 2.53 (1H, ddd, *J* 16.4, 9.0, 8.2, 7-CH_2), 2.44 – 2.18 (5H, m, 3-CH_2, 7-CH_2, N*Me*), 2.03 – 1.94 (1H, m, 3-CH_2); **δ_C(101 MHz, Methanol-*d*$_4$) δ** 162.7 (*Ar*-F), 160.3 (*Ar*-F), 153.9 (*Ar*), 142.7 (*Ar*H), 140.9 (*Ar*H), 130.2 (*Ar*H), 129.5 (*Ar*), 126.4 (*Ar*H), 123.9 (*Ar*H), 114.1 (*Ar*H), 72.7 (2-*C*), 68.0 (5-*C*), 67.8 (6-*C*), 67.1 (1-*C*), 45.6 (4-*C*), 40.9 (N*Me*), 39.5 (SO_2*Me*), 27.7 (7-*C*), 26.5 (3-*C*); **HRMS** (ESI): $C_{21}H_{25}FN_3O_4S$ $[M+H^+]$: calculated 434.1544, found 434.1546.

(3a*R**,4*S**,5*R**,7*S**,8*S**,8a*S**)-9-(4-Fluorobenzyl)-5-(methylsulfonyl)-2-(thiazol-2-yl)decahydro-4,7-epiminocyclohepta[*c*]pyrrol-8-ol (**311**)



General procedure **R** was followed using amine hydrochloride **306** (140 mg, 0.36 mmol), DIPEA (95 μL, 0.54 mmol) and 2-bromothiazole (50 μL, 0.54 mmol). Purification by automated reversed-phase flash chromatography eluting with MeCN/H_2O 1% formic acid gave *title compound* **311** (7 mg, 0.02 mmol, 4%) as a colourless oil; **^{1}H NMR (400 MHz, Methanol-*d*$_4$):** 7.41 (2H, dd, *J* 8.5, 5.6, *Ar*H), 7.14 (1H, d, *J* 3.7, *Ar*H), 7.04 (2H, t, *J* 8.8, *Ar*H), 6.65 (1H, d, *J* 3.7, *Ar*H), 3.91 (1H, t, *J* 8.2, 7-C*H*), 3.84 (1H, d, *J* 13.3, N*Bn*), 3.77 (1H, s, 8-C*H*), 3.75 – 3.67 (2H, m, N*Bn*, 1-CH_2), 3.62 (1H, d, *J* 10.3, 3-CH_2), 3.54 – 3.46 (2H, m, 4-C*H*, 3-CH_2), 3.44 – 3.34 (2H, m, 1-CH_2, 5-C*H*), 3.06 (4H, s, *Me*), 2.67 – 2.57 (1H, m, 8a-C*H*), 2.47 (1H, dd, *J* 13.8, 9.3, 6-CH_2), 2.36 (1H, dt, *J* 13.8, 6.9, 6-CH_2), 2.15 (1H, dt, *J* 9.2, 6.3, 3a-C*H*); **δC(101 MHz, Methanol-*d*$_4$):** 169.0 (*Ar*), 162.0 (d, *J* 243.4, *Ar*F), 138.4 (*Ar*H), 135.6 (*Ar*), 130.5 (d, *J* 8.0, *Ar*H), 114.5 (d, *J* 21.4, *Ar*H), 105.9 (*Ar*H), 71.3 (4-*C*), 68.4 (7-*C*), 66.8 (5-*C*), 60.6 (8-*C*), 55.7 (N-*C*H_2), 53.4 (3-*C*H_2), 50.9 (1-*C*H_2), 46.1 (8a-*C*), 41.3 (3a-*C*), 39.3 (*Me*), 23.8 (6-*C*H_2); **HRMS** (ESI): [M+H^+]: $C_{20}H_{25}FN_3O_3S_2$ calculated 438.1316, found 438.1311.

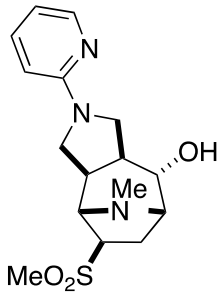
1-((3a*R**,4*S**,5*R**,7*S**,8*S**,8a*S**)-9-(4-Fluorobenzyl)-8-hydroxy-5-(methylsulfonyl)octahydro-4,7-epiminocyclohepta[*c*]pyrrol-2(1*H*)-yl)-2-methylpropan-1-one (**310)**



General procedure **V** was followed using amine **306** (120 mg, 0.363mmol) and isobutyryl chloride (300 μl, 2.64 mmol) and pyridine (120 μl, 1.32 mmol). Purification by automated reversed-phase flash chromatography eluting with MeCN/H_2O 1% formic acid. Crystallisation from ethanol gave *title compound* **310** (10 mg, 0.02 mmol, 7%) as a colourless solid as a 1:1 ratio of rotamers; **M.pt.** 223.8 – 224.8 °C; **^{1}H NMR (501 MHz, Methanol-*d*$_4$, 333K):** 7.33 – 7.17 (4H, m, Ar*H*, Ar*H*), 7.02 – 6.79 (4H, m, Ar*H*, Ar*H*), 3.96 – 3.60 (10H, m, 1-CH_2, 8-C*H*, 8-C*H*, NCH_2, NCH_2, 7-C*H*, 7-C*H*), 3.60 – 3.51 (2H, m, 1-CH_2), 3.48 – 3.33 (6H, m, 3-CH_2, 5-C*H*, 5-C*H*, 4-*C*H, 4-C*H*), 3.24 (2H, t, *J* 5.8, 3-CH_2), 2.92 (3H, s, SO_2*Me*), 2.92 (3H, s, SO_2*Me*), 2.71 – 2.55 (2H, m, C*H*(Me)$_2$, C*H*(Me)$_2$), 2.44 – 2.37 (1H, m, 8a-C*H*), 2.37 – 2.28 (3H, m, 6-CH_2, 6-CH_2), 2.28 – 2.20 (2H, m, 6-CH_2, 8a-C*H*), 1.98 – 1.91 (1H, m 3a-C*H*), 1.90 – 1.85 (1H, m, 3a-C*H*), 1.05 (3H, d, *J* 6.7, *Me*), 1.03 (3H, d, *J* 6.7, *Me*), 1.00 (3H, d, *J* 4.6, *Me*), 0.99 (3H,

d, *J* 4.6, *Me*); **δC(101 MHz, Methanol-*d*4):** 177.3 (*C*=O), 177.1 (*C*=O), 162.1 (d, *J* 243.0, *Ar*F), 162.1 (d, *J* 243.0, *Ar*F), 135.7 (d, *J* 3.0, *Ar*), 135.6 (d, *J* 3.0, *Ar*), 130.5 (d, *J* 7.9, *Ar*H), 130.5 (d, *J* 7.9, *Ar*H), 114.5 (d, *J* 21.4, *Ar*H), 114.5 (d, *J* 21.4, *Ar*H), 71.0 (4-*C*), 70.7 (4-*C*), 68.5 (7-*C*), 68.3 (7-*C*), 66.8 (5-*C*), 66.7 (5-*C*), 60.6 (8-*C*), 60.5 (8-*C*), 55.7 (N-*C*H_2), 55.7 (N-*C*H_2), 50.0 (3-*C*H_2), 49.3 (3-*C*H_2), 47.6 (1-*C*H_2), 47.2 (1-*C*H_2), 46.1 (8a-*C*), 44.5 (8a-*C*), 41.3 (3a-*C*), 39.5 (3a-*C*), 39.3 (SO_2*Me*), 39.2 (SO_2*Me*), 32.1 (*C*H(Me)$_2$), 31.8 (*C*H(Me)$_2$), 23.9 (6-*C*H_2), 23.7 (6-*C*H_2), 18.1 (*Me*), 18.1 (*Me*), 17.7 (*Me*), 17.6 (*Me*); **IR** ν_{max} (neat)/cm^{-1}: 3433 (OH), 2961 (CH), 2936, 2919, 2886, 1620 (C=O), 1509 (C=C), 1328 (S=O); **HRMS** (ESI): $C_{21}H_{30}FN_2O_4S$ [M+H$^+$]: calculated 425.1905, found 425.1902.

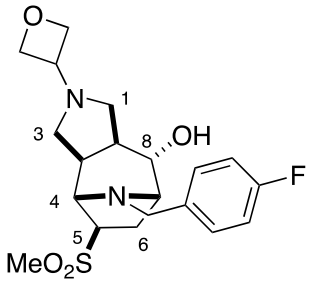
(3a*R**,4*S**,5*R**,7*S**,8*S**,8a*S**)-9-Methyl-5-(methylsulfonyl)-2-(pyridin-2-yl)decahydro-4,7-epiminocyclohepta[*c*]pyrrol-8-ol (**313**)



General procedure **R** was followed using free amine **307** (120 mg, 0.46 mmol), DIPEA (121 μL, 0.69 mmol, 1.5 eq.) and 2-fluoropyridine (60 μL, 0.69 mmol, 1.5 eq.) in DMF (2.3 mL). Purification by automated reversed-phase flash chromatography eluting with MeCN/H_2O/1% formic acid gave *title compound* **313** (24 mg, 0.07 mmol, 15%) as a brown solid as a ratio of 1:6 isomers. Only the major isomer was assigned.

δH (400 MHz, Chloroform-*d*): 8.10 (1H, dd, *J* 7.0, 1.8, Ar*H*), 7.63 (1H, ddd, *J* 8.8, 7.0, 1.8, Ar*H*), 6.68 (1H, t, *J* 7.0, Ar*H*), 6.57 (1H, d, *J* 8.8, Ar*H*), 4.00 (1H, s, O*H*), 3.82 – 3.74 (2H, m, 7-C*H*, 1-CH_2), 3.65 – 3.59 (2H, m, 3-CH_2, 4-C*H*), 3.56 – 3.40 (3H, m 3-CH_2,1-CH_2, 8-C*H*), 3.33 (1H, t, *J* 5.6, 5-C*H*), 3.00 – 2.96 (3H, m, SO_2*Me*), 2.61 – 2.51 (1H, m, 8a-C*H*), 2.52 – 2.38 (4H, m, N*Me*, 6-CH_2), 2.37 – 2.26 (1H, m, 6-CH_2), 2.14 – 2.05 (1H, m, 3a-CH_2); **δC NMR (101 MHz, Chloroform-*d*):** 165.5 (*Ar*H), 142.9(*Ar*), 140.0(*Ar*H), 111.5(*Ar*H), 109.3 (*Ar*H), 70.9 (7-*C*), 69.3 (5-*C*), 68.9 (4-*C*), 63.1 (3-*C*), 51.5 (1-*C*), 49.3 (SO_2*Me*), 46.0 9 (*Me*), 41.6 (8-*C*), 41.1 (8a-*C*), 40.7 (3a-*C*), 24.5 (6-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3387 (OH), 3013, 2940 (CH), 2894, 2824, 1556 (C=C), 1475, 1285 (S=O); **HRMS** (ESI): $C_{16}H_{24}N_3O_3S$ [M+H$^+$]: calculated 338.1533, found 338.1530.

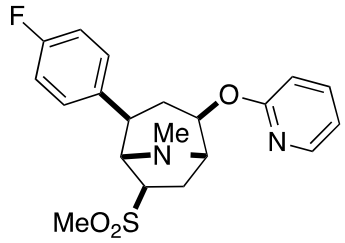
(3a*R**,4*S**,5*R**,7*S**,8*S**,8a*S**)-9-(4-Fluorobenzyl)-5-(methylsulfonyl)-2-(oxetan-3-yl)decahydro-4,7-epiminocyclohepta[*c*]pyrrol-8-ol (**309**)



General procedure **W** was followed using amine hydrochloride **306** (140 mg, 0.36 mmol) and cyclobutanone (113 μL, 1.8 mmol), $NaBH_4$ (40 mg, 3.0 eq.). Purification by automated reversed-phase flash chromatography eluting with MeCN/H_2O/1% formic acid gave *title compound* **309** (14 mg, 0.03 mmol, 9%) as a brown oil.

δ_H (400 MHz, DMSO-*d*$_6$): 7.38 (2H, dt, *J* 8.5, 6.2, Ar*H*), 7.18 – 7.09 (2H, m, Ar*H*), 4.60 – 4.54 (2H, m, C*H*$_2$), 4.48 – 4.41 (2H, m, C*H*$_2$), 3.77 (1H, t, *J* 8.5, 7-C*H*), 3.74 – 3.68 (1H, m, 3-C*H*), 3.65 (1H, d, *J* 13.3, N*Bn*), 3.61 – 3.52 (1H, m, 3-C*H*), 3.47 (1H, s, 4-C*H*), 3.44 – 3.36 (1H, m, N*Bn*), 3.33 (1H, t, *J* 5.5, 1-C*H*), 3.20 – 3.12 (1H, m, 5-C*H*), 3.01 (3H, s, *Me*), 2.75 (1H, t, *J* 7.8, 1-C*H*), 2.69 – 2.63 (1H, m, 8-C*H*), 2.39 – 2.05 (4H, m, 6-C*H*$_2$, 8a-C*H*, C*H*), 1.83 – 1.75 (1H, m, 3a-C*H*); **δ_C (101 MHz, DMSO-*d*$_6$):** 163.9 (d, *J* 242.1, *Ar*-F), 136.9 (d, *J* 3.3, *Ar*), 130.8 (d, *J* 8.0, *Ar*H), 115.3 (d, *J* 21.0, *Ar*H), 75.5 (*C*H$_2$), 75.2 (*C*H$_2$), 71.7 (4-*C*), 66.3 (7-*C*), 61.9 (5-*C*), 57.4 (8-*C*), 55.8 (N*Bn*), 54.7 (3-*C*), 51.3 (1-*C*), 46.2 (8a-*C*), 42.4 (3a-*C*), 41.1 (*Me*), 24.0 (6-*C*). **IR** ν_{max} (neat)/cm^{-1}: 3364 (OH), 3011 (CH), 2923, 2874, 1602, 1507 (C=C), 1417, 1284 (S=O); **HRMS** (ESI): $C_{20}H_{28}FN_2O_4S$ [M+H$^+$]: calculated 411.1748, found 411.1746.

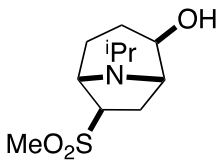
(1*S**,2*R**,4*R**,5*S**,6*R**)-4-(4-Fluorophenyl)-8-methyl-6-(methylsulfonyl)-2-(pyridin-2-yloxy)-8-azabicyclo[3.2.1]octane (**290**)



General procedure **R** was followed using alcohol **278a** (147 mg, 0.47 mmol), NaH (17 mg, 0.71 mmol) and 2-fluoropyridine (81 μL, 0.94 mmol, 2.0 eq.). Purification by MDAP afforded *title compound* **290** (16 mg, 0.04 mmol, 9%) as a brown oil;

δ_H(501 MHz, Methanol-*d*$_4$): 8.02 (1H, ddd, *J* 5.1, 2.0, 0.9, Pyr-*H*), 7.55 (1H, ddd, *J* 8.3, 7.1, 2.0, Pyr-*H*), 7.47 – 7.39 (2H, m, Ar*H*), 7.01 – 6.89 (2H, m, Ar*H*), 6.82 (1H, ddd, *J* 7.1, 5.1, 1.0, Pyr-*H*), 6.65 (1H, dt, *J* 8.3, 0.9, Pyr-*H*), 5.36 (1H, ddd, *J* 10.9, 6.6, 4.2, 2-C*H*), 3.89 (1H, t, *J* 8.2, 5-C*H*), 3.68 – 3.65 (1H, m, 6-C*H*), 3.27 – 3.18 (1H, m, 4-C*H*), 3.06 – 2.90 (3H, m, SO_2*Me*), 2.43 (1H, dd, *J* 13.7, 9.3, 7-CH_2), 2.31 – 2.11 (5H, m, N*Me*, 3-CH_2, 7-CH_2), 1.82 (1H, ddd, *J* 14.5, 10.9, 7.7, 3-CH_2); **δ_C (126 MHz, Methanol-*d*$_4$):** 162.7 (*Ar*), 161.2 (d, *J* 242.9, *Ar*F), 146.4 (*Ar*H), 139.7 (d, *J* 3.1, *Ar*), 138.8 (*Ar*H), 129.5 (d, *J* 7.6, *Ar*H), 116.7 (*Ar*H), 114.0 (d, *J* 21.0, *Ar*H), 110.9 (*Ar*H), 69.9 (2-*C*), 68.1 (6-*C*), 68.1 (5-*C*), 65.8 (1-*C*), 45.9 (4-*C*), 40.5 (N*Me*), 39.2 (SO_2*Me*), 27.3 (3-*C*), 24.5 (7-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3063, 3013 (CH), 2948, 2898, 1595, 1510 (C=C), 1433, 1288 (S=O); **HRMS** (ESI): [M+H$^+$]: $C_{20}H_{24}FN_2O_3S$ calculated 391.1486, found 391.2219.

(1*S**,2*R**,5*S**,6*R**)-8-Isopropyl-6-(methylsulfonyl)-8-azabicyclo[3.2.1]octan-2-ol (**178**)

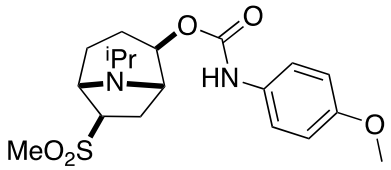


General procedure **F** was followed using compound **117** (1.50 g, 5.15 mmol) and 10% Pd/C (250 mg, 10% weight) in MeOH/Acetone (30 mL) at rt. The *title compound **178*** (1.25 g, 5.05 mmol, 99%) as a yellow oil;

δ_H (400 MHz, Chloroform-*d*): 3.94 (1H, ddd, *J* 10.1, 5.7, 3.4, 5-C*H*), 3.78 (1H, d, *J* 3.0, 2-C*H*), 3.47 (1H, dd, *J* 7.0, 3.5, 6-C*H*), 3.15 (1H, dd, *J* 9.8, 5.5, 1-C*H*), 3.05 (1H, p, *J* 6.1, 8-C*H*),

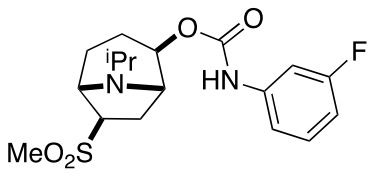
2.82 (3H, s, Me), 2.35 (1H, dd, *J* 14.5, 9.8, 7-C*H*$_2$), 2.06 – 1.97 (1H, m, 7-C*H*$_2$), 1.95 – 1.81 (2H, m, 3-C*H*$_2$, 4-C*H*$_2$), 1.39 (1H, ddd, *J* 14.2, 6.1, 2.5, 3-C*H*$_2$), 1.32 – 1.14 (1H, m, 4-C*H*$_2$), 1.05 (3H, d, *J* 6.1, *Me*), 0.98 (3H, d, *J* 6.1, *Me*). **δ_C (101 MHz, Chloroform-*d*):** 67.1 (1-*C*), 63.1 (5-*C*), 59.7 (6-*C*), 55.3 (2-*C*), 44.1 (*Me*), 37.5 (8-*C*), 26.8 (7-*C*), 26.4 (3-*C*), 24.0 (4-*C*), 21.9 (*Me*), 21.9 (*Me*); **IR** ν_{max} (neat)/cm^{-1}: 3473 (OH), 3120, 3102 (CH), 3047, 2967, 2944, 2874, 1288 (S=O); **HRMS** (ESI): $C_{11}H_{22}NO_3S$ [M+H$^+$]: calculated 248.1315, found 248.1314.

(1*S**,2*R**,5*S**,6*R**)-8-isopropyl-6-(methylsulfonyl)-8-azabicyclo[3.2.1]octan-2-yl (4-methoxyphenyl)carbamate) (**317**)



General procedure **Y** was followed using compound **178** (100 mg, 0.4 mmol) in DMF (1mL), NaH (65 mg, 1.62 mmol, 4.0 eq.) and 4-methoxyphenylisocyanate (0.2 mL, 1.62 mmol, 4.0 eq.). The reaction mixture was concentrated *in vacuo* and purification by automated reversed-phase flash chromatography eluting with eluting with MeCN/H_2O/1% formic acid gave the *title compound* **317** (37.6 mg, 0.09 mmol, 24 %) as a brown oil; **δ_H(400 MHz, Chloroform-*d*)** 7.35 (2H, d, *J* 8.7, Ar*H*), 6.85 (2H, d, *J* 8.7 , Ar*H*), 4.89 – 4.77 (1H, m, 5-C*H*), 3.73 (1H, s, 2-C*H*), 3.70 (3H, s, Me), 3.67 – 3.60 (2H, m, 1-C*H*, 6-C*H*), 3.11 (1H, q, *J* 6.0, 8-C*H*), 2.90 (3H, s, Me), 2.19 (1H, dd, *J* 14.0, 9.5, 7-C*H*$_2$), 2.08 (1H, dd, *J* 14.0, 6.2, 7-C*H*$_2$), 1.95 – 1.84 (2H, m, 4-C*H*$_2$, 3-C*H*$_2$), 1.57 (1H, qd, *J* 14.2, 12.3, 7.6, 4-C*H*$_2$), 1.42 (1H, dt, *J* 14.2, 4.3, 3-C*H*$_2$), 1.11 (3H, d, *J* 6.0, *Me*), 1.00 (3H, d, *J* 6.0, *Me*);**δ_C (101 MHz, Chloroform-*d*)** 155.2 (*Ar*), 153.5 (*C*=O), 132.5 (*Ar*), 120.3 (*Ar*-H), 114.4 (*Ar*-H), 67.1 (5-*C*), 65.8 (6-*C*), 57.5 (2-*C*), 55.6 (*Me*), 55.3 (1-*C*), 44.3 (8-*C*), 38.3(*Me*), 26.6 (7-*C*), 24.6 (3-*C*), 23.3 (4-*C*), 22.2 (*Me*), 22.1 (*Me*); **IR** ν_{max} (neat)/cm^{-1}: 3372 (NH), 3047 (CH), 2953 2851, 1684 (C=O), 1656, 1515 (C=C), 1222 (S=O); **HRMS** (ESI): $C_{19}H_{29}N_2O_5S$ [M+H$^+$]: calculated 397.1792, found 397.1786.

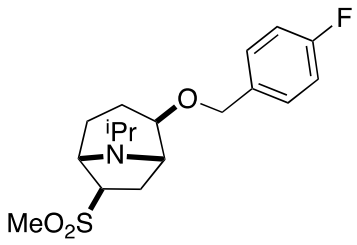
(1*S**,2*R**,5*S**,6*R**)-8-Isopropyl-6-(methylsulfonyl)-8-azabicyclo[3.2.1]octan-2-yl (4-fluorophenyl)carbamate (**314**)



General procedure **Y** was followed using compound **178** (100 mg, 0.4 mmol) in DMF (1mL), NaH (65 mg, 1.62 mmol, 4.0 eq.), and 3-fluorophenylisocyanate (0.2 mL, 1.62 mmol, 4.0 eq.). The reaction mixture was concentrated *in vacuo* and purification by automated reversed-phase flash chromatography eluting with MeCN/H_2O/1% formic acid gave the *title compound* **314** (22.6 mg, 0.06 mmol, 16%) as a colourless solid;

δ_H(400 MHz, Chloroform-*d*) 7.30 – 7.15 (1H, m, Ar*H*), 6.98 – 6.90 (1H, m, Ar*H*), 6.70 (1H, tdd, *J* 8.3, 2.5, 0.9, Ar*H*), 6.61 (1H, s, Ar*H*), 5.00 (1H, ddd, *J* 9.8, 5.9, 3.3, 5-C*H*), 3.79 (1H, s, 1-C*H*), 3.67 (1H, dd, *J* 6.9, 3.3, 6-C*H*), 3.22 – 3.09 (2H, m, 8-C*H*, 2-C*H*), 2.82 (3H, s, *Me*), 2.32 (1H, dd, *J* 14.6, 9.8, 3-CH_2), 2.13 – 1.96 (3H, m, 3-CH_2, 7-CH_2, 4-CH_2), 1.54 – 1.37 (2H, m, 4-CH_2, 7-CH_2), 1.14 (3H, d, *J* 6.1, *Me*), 1.01 (3H, d, *J* 6.0, *Me*); **δ_C (101 MHz, Chloroform-*d*)** 163.2 (d, *J* 245.0, *Ar*), 152.4 (*C*=O), 139.2 (d, *J* 10.8, *Ar*H), 130.2 (d, *J* 9.5, *Ar*H), 113.9 (*Ar*H), 110.3 (d, *J* 21.4, *Ar*H), 106.1 (d, *J* 28.6, *Ar*), 67.0 (5-*C*), 66.7 (2-*C*), 56.7 (6-*C*), 55.3 (1-*C*), 44.0 (8-*C*), 37.1 (*Me*), 27.3 (3-*C*), 23.4 (7-*C*), 23.1 (4-*C*), 21.9 (*Me*), 21.8 (*Me*); **IR** νmax (neat)/cm-1: 3317 (NH), 3090 (CH), 3011, 2847, 1659 (C=O), 1542 (C=C), 1470, 1292 (S=O); **HRMS** (ESI): $C_{18}H_{26}FN_2O_4S$ [$M+H^+$]: calculated 385.1592, found 385.1599.

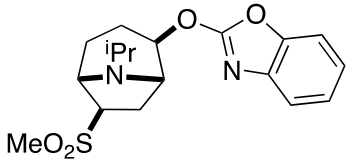
(1*S**,2*R**,5*S**,6*R**)-2-((4-Fluorobenzyl)oxy)-8-isopropyl-6-(methylsulfonyl)-8-azabicyclo[3.2.1]octane (**318**)



General procedure **R** was followed using compound **178** (100 mg, 0.4 mmol) in DMF (1mL), NaH (65 mg, 1.62 mmol, 4.0 eq.) and 4-fluorobenzyl bromide (0.2 mL, 1.62 mmol, 4.0 eq.). The reaction mixture was concentrated *in vacuo* and purification by automated reversed-phase flash chromatography eluting with MeCN/H_2O/1% formic acid gave the *title compound* **318** (22.6 mg, 0.06 mmol, 16%) as a colourless oil;

δ_H (400 MHz, Methanol-*d*$_4$) 7.38 (2H, dd, *J* 8.5, 5.6, Ar*H*), 7.09 (2H, t, *J* 8.8, Ar*H*), 4.57 (1H, d, *J* 11.9, NC*H*$_2$), 4.53 (1H, d, *J* 11.8, NC*H*$_2$), 3.99 (1H, s, 2-C*H*), 3.85 – 3.68 (2H, m, 5-C*H*, 6-C*H*), 3.59 (1H, dd, *J* 9.9, 5.8, 1-C*H*), 3.18 (1H, p, *J* 6.1, 8-C*H*), 2.96 (3H, s, *Me*), 2.44 (1H, dd, *J* 14.2, 9.8, 7-C*H*$_2$), 2.21 – 2.11 (1H, m, 7-C*H*$_2$), 2.11 – 2.02 (1H, m, 4-C*H*$_2$), 2.03 – 1.88 (1H, m, 3-C*H*$_2$), 1.64 – 1.38 (2H, m, 4-C*H*$_2$, 3-C*H*$_2$), 1.11 (6H, at, *J* 5.8, *Me*); **δ_C (101 MHz, Methanol-*d*$_4$)** 162.36 (d, *J* 244.2, *Ar*-F), 134.7 (d, *J* 3.1, *Ar*), 129.4 (d, *J* 8.2, *Ar*H), 114.6 (d, *J* 21.7, *Ar*H), 71.0 (5-*C*), 69.2 (N-*C*), 65.8 (1-*C*), 58.5 (6-*C*), 56.4 (2-*C*), 45.7 (*Me*), 37.5 (8-*C*), 25.6 (7-*C*), 25.0 (3-*C*), 23.6 (4-*C*), 20.3 (*Me*); **IR** ν_{max} (neat)/cm^{-1}: 2964 (CH), 2944, 2928, 1769 (C=O), 1656, 1459 (C=C), 1410, 1293 (S=O); **HRMS** (ESI): $C_{18}H_{27}FNO_3S$ [M+H$^+$]: calculated 356.1690, found 356.1689.

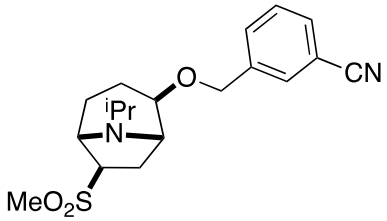
2-(((1*S**,2*R**,5*S**,6*R**)-8-Isopropyl-6-(methylsulfonyl)-8-azabicyclo[3.2.1]octan-2-yl)oxy)benzo[*d*]oxazole (**319**)



General procedure **R** was followed using compound **178** (100 mg, 0.4 mmol) in DMF (1mL), NaH (65 mg, 1.62 mmol, 4.0 eq.) and 2-chlorobenzoxazole (250 mg, 1.62 mmol, 4.0 eq.). The reaction mixture was concentrated *in vacuo* and purification by automated reversed-phase flash chromatography eluting with MeCN/H_2O/1% formic acid gave the *title compound* **319** (9.7 mg, 0.03 mmol, 7%) as a brown oil;

δ_H (400 MHz, DMSO-*d*$_6$) 7.49 (1H, dd, *J* 8.0, 1.1, Ar*H*), 7.35 (1H, dd, *J* 8.0, 1.1, Ar*H*), 7.24 (1H, td, *J* 8.0, 1.1, Ar*H*), 7.15 (1H, td, *J* 8.0, 1.1, Ar*H*), 4.45 (1H, ddd, *J* 12.8, 5.4, 2.7, 5-C*H*), 3.88 (1H, dd, *J* 9.5, 5.9, 2-C*H*), 3.82 (1H, s, 1-C*H*), 3.68 (1H, d, *J* 6.5, 2.4, 6-C*H*), 3.24 (1H, p, *J* 6.1, 8-C*H*), 2.91 (3H, s, *Me*), 2.81 (1H, qd, *J* 12.4, 5.7, 4-C*H*$_2$), 2.44 (1H, dd, *J* 14.1, 9.5, 3-C*H*$_2$), 2.16 – 2.08 (1H, m, 3-C*H*$_2$), 2.06 – 1.87 (2H, m, 4-C*H*$_2$, 7-C*H*$_2$), 1.60 – 1.50 (1H, m, 7-C*H*$_2$), 1.13 (3H, d, *J* 6.0, *Me*), 1.05 (3H, d, *J* 6.0, *Me*); **δ_C (101 MHz, DMSO-*d*$_6$)** 154.0 (*Ar*), 142.4 (*Ar*), 131.5 (*Ar*), 124.3 (*Ar*H), 122.6 (*Ar*H), 110.3 (*Ar*H), 110.3 (*Ar*H), 65.5 (2-*C*), 58.7 (6-*C*), 55.5 (1-*C*), 51.0 (5-*C*), 44.3 (8-*C*), 38.4 (*Me*), 28.4 (3-*C*), 25.0 (7-*C*), 22.2 (4-*C*), 19.6 (*Me*); **IR** ν_{max} (neat)/cm^{-1}: 3014 (CH), 2997, 2878, 2807, 1591 (C=C), 1512, 1445, 1229 (S=O); **HRMS** (ESI): $C_{18}H_{25}N_2O_4S$ [M+H$^+$]: calculated 365.1530, found 365.1527.

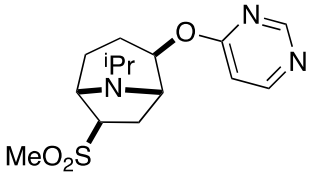
3-((((1*S**,2*R**,5*S**,6*R**)-8-Isopropyl-6-(methylsulfonyl)-8-azabicyclo[3.2.1]octan-2-yl)oxy)methyl)benzonitrile (**315**)



General procedure **R** was followed using compound **178** (100 mg, 0.4 mmol) in DMF (1mL), NaH (65 mg, 1.62 mmol, 4.0 eq.), and 3-(bromomethyl)benzonitrile (317 mg, 1.62 mmol, 4.0 eq.). The reaction mixture was concentrated *in vacuo* and purification by automated reversed-phase flash chromatography eluting with MeCN/H_2O/1% formic acid gave the *title compound* **315** (14.2 mg, 0.04 mmol, 10%) as a colourless solid;

δ_H (400 MHz, DMSO-*d*$_6$) 7.79 – 7.72 (2H, m, Ar*H*, Ar*H*), 7.68 (1H, dd, *J* 8.0, 1.6, Ar*H*), 7.58 (1H, t, *J* 7.7, Ar*H*), 4.56 (2H, s, NCH_2), 3.72 (1H, s, 2-C*H*), 3.65 – 3.58 (2H, m, 5-C*H*, *6*-C*H*), 3.55 (1H, dd, *J* 9.7, 5.8, 1-C*H*), 3.00 – 2.94 (1H, m, 8-C*H*), 2.90 (3H, s, *Me*), 2.21 (1H, dd, *J* 13.9, 9.7, 7-CH_2), 2.03 – 1.88 (2H, m, 7-CH_2, 4-CH_2), 1.86 – 1.69 (1H, m, 3-CH_2), 1.45 – 1.28 (2H, m, 3-CH_2, 4-CH_2), 0.97 (6H, at, *J* 6.5, *Me*); **δ_C (101 MHz, DMSO-*d*$_6$)** 141.3 (*Ar*), 132.6 (*Ar*H), 131.6 (*Ar*H), 131.1 (*Ar*H), 130.0 (*Ar*H), 119.3 (*C*N), 111.7 (*Ar*), 71.8 (5-*C*), 68.4 (N-*C*), 66.1 (1-*C*), 58.0 (6-*C*), 55.7 (2-*C*), 44.7 (8-*C*), 38.7 (*Me*), 26.4 (2-*C*), 25.7 (3-*C*), 24.2 (4-*C*), 22.3 (*Me*), 22.2 (*Me*);**IR** ν_{max} (neat)/cm^{-1}: 3022 (CH), 2963, 2944, 2257 (CN), 1595 (C=C), 1409, 1330, 1289 (S=O); **HRMS** (ESI): $C_{19}H_{27}N_2O_3S$ [M+H$^+$]: calculated 363.1737, found 363.1732.

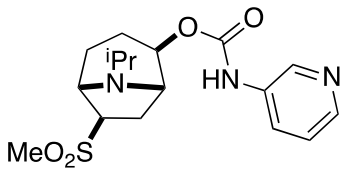
(1*S**,2*R**,5*S**,6*R**)-8-Isopropyl-6-(methylsulfonyl)-2-(pyrimidin-4-yloxy)-8-azabicyclo[3.2.1]octane (**320**)



General procedure **R** was followed using compound **178** (100 mg, 0.4 mmol) in DMF (1mL), NaH (65 mg, 1.62 mmol, 4.0 eq.) and 2-chloropyrazine (186 mg, 1.62 mmol, 4.0 eq.). The reaction mixture was concentrated *in vacuo* and purification by automated reversed-phase flash chromatography eluting with MeCN/H_2O/1% formic acid gave the *title compound* **315** (85.1 mg, 0.26 mmol, 65%) as a brown solid;

δ_H (300 MHz, Methanol-*d*$_4$) 8.15 – 7.91 (3H, m, Ar*H*), 5.35 – 5.24 (1H, m, 5-C*H*), 3.90 (1H, s, 1-C*H*), 3.86 (1H, dd, *J* 6.7, 3.4, 6-C*H*), 3.55 (1H, dd, *J* 9.8, 5.7, 2-C*H*), 3.28 – 3.08 (1H, m, 8-C*H*), 2.87 (3H, s, *Me*), 2.41 (1H, dd, *J* 14.3, 9.8, 3-CH_2), 2.23 – 1.97 (3H, m, 3-CH_2, 7-CH_2), 1.73 – 1.62 (1H, m, 4-CH_2), 1.59 – 1.43 (1H, m, 4-CH_2), 1.17 (3H, d, *J* 6.1, *Me*), 1.04 (3H, d, *J* 6.1, *Me*); **δ_C (101 MHz, Methanol-*d*$_4$)** 159.7 (*Ar*), 140.9 (*Ar*H), 136.1 (*Ar*H), 135.4 (*Ar*H), 68.3 (5-*C*), 66.0 (2-*C*) , 57.2 (6-*C*), 55.9 (1-*C*), 45.1 (8-*C*), 37.2 (*Me*), 26.0 (3-*C*H_2), 24.3 (7-*C*H_2), 22.7 (4-*C*H_2), 20.6 (*Me*); **IR** ν_{max} (neat)/cm^{-1}: 3011 (CH), 2942, 2879, 1650 (C=C), 1600, 1530, 1472 1285 (S=O); **HRMS** (ESI): $C_{15}H_{24}N_3O_3S$ [M+H$^+$]: calculated 326.1533, found 326.1529.

(1*S**,2*R**,5*S**,6*R**)-8-Isopropyl-6-(methylsulfonyl)-8-azabicyclo[3.2.1]octan-2-yl pyridin-3-ylcarbamate (**317**)

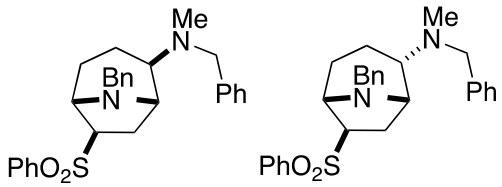


General procedure **Y** was followed using compound **178** (100 mg, 0.4 mmol) in DMF (1mL), NaH (65 mg, 1.62 mmol, 4.0 eq.) and 3-pyridineisocynate (200 mg, 1.62 mmol, 4.0 eq.). The reaction mixture was concentrated *in vacuo* and purification by automated reversed-phase flash chromatography eluting with MeCN/H_2O/1% formic acid gave the *title compound* **317** (30.9 mg, 0.08 mmol, 21%) as a colourless solid;

δ_H (400 MHz, DMSO-*d*$_6$) 9.86 (1H, s, N*H*), 8.63 (1H, s, Ar*H*), 8.22 – 8.18 (1H, m, *ArH*), 8.17 (1H, s, Ar*H*), 7.48 – 7.22 (1H, m, Ar*H*), 4.90 (1H, ddd, *J* 11.4, 5.7, 3.3, 5-C*H*), 3.74 (1H, d, *J* 3.0, 1-C*H*), 3.70 – 3.62 (2H, m, 2-C*H*, 8-C*H*), 3.11 (1H, dq, *J* 10.0, 5.0, 4.0, 8-C*H*), 2.91 (3H, s, *Me*), 2.20 (1H, dd, *J* 13.8, 9.6, 3-CH_2), 2.10 (1H, dt, *J* 13.8, 6.1, 3-CH_2), 2.00 – 1.87 (2H, m, 4-CH_2, 7-CH_2), 1.70 – 1.51 (1H, m, 4-CH_2), 1.43 (1H, ddd, *J* 12.7, 6.3, 2.3, 7-CH_2), 1.11 (3H, d, *J* 6.0, *Me*), 1.01 (3H, d, *J* 6.0, *Me*); **δ_C (101 MHz, DMSO-*d*$_6$)** 153.5 (*C*=O), 143.6 (*Ar*H), 140.7 (*Ar*H), 136.7 (*Ar*), 125.9 (*Ar*H), 124.1 (*Ar*H), 67.9 (5-*C*), 65.8 (2-*C*), 57.4 (6-*C*), 55.3(1-*C*), 44.3(8-*C*), 38.3 (*Me*), 26.6 (3-*C*), 24.6 (7-*C*), 23.3 (4-*C*), 22.2 (*Me*), 22.1 (*Me*); **IR** ν_{max} (neat)/cm^{-1}: 3384 (NH), 3011 (CH), 2942, 2879, 1650(C=O), 1531 (C=C), 1472, 1285 (S=O); **HRMS** (ESI): $C_{17}H_{26}N_3O_4S$ [M+H$^+$]: calculated 368.1639, found 368.1638.

(1*S**,2*R**,5*S**,6*R**)-*N*,8-dibenzyl-*N*-methyl-6-(phenylsulfonyl)-8-azabicyclo[3.2.1]octan-2-amine (**223**)

(1*S**,2*S**,5*S**,6*R**)-*N*,8-dibenzyl-*N*-methyl-6-(phenylsulfonyl)-8-azabicyclo[3.2.1]octan-2-amine (**224**)



2:1 regioisomers

General procedure **X** was followed using ketone **174** (100 mg, 0.28 mmol, 1.0 eq.), *N*-benzylmethylamine (0.37 mL, 2.81 mmol, 10 eq.), $Ti(O^iPr)_4$ (0.17 mL, 0.36 mmol, 2.0 eq.) in MeOH (100 mL) and $NaBH_4$ (16 mg, 0.42 mmol, 1.5 eq.). Purification by flash chromatography on silica gel, eluting with a gradient of 20% EtOAc in hexane afforded a 1:2 mixture of the amine diastereoisomers: **223** (35 mg, 0.08 mmol, 27%) as a colourless oil; $\mathbf{R_f}$ = 0.06 (30% EtOAc in hexane) and **224** (33 mg, 0.07 mmol, 26%) as a colourless oil; $\mathbf{R_f}$ = 0.66 (30% EtOAc in hexane).

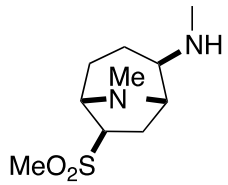
Compound **223**:

^{1}H NMR (400 MHz, $CDCl_3$) 7.98 – 7.87 (2H, m, Ar*H*), 7.69 – 7.58 (1H, m, Ar*H*), 7.63 – 7.49 (2H, m, Ar*H*), 7.38 – 7.09 (10H, m, Ar*H*), 3.99 (1H, d, *J* 14.0, 8-NCH_2), 3.86 – 3.77 (2H, m, 8-NCH_2, 2-CH), 3.56 (1H, d, *J* 3.5, 6-C*H*), 3.48 (1H, t, *J* 8.0, 1-C*H*), 3.40 (2H, s, NMeCH_2), 2.53 (1H, ddd, *J* 11.3, 5.2, 3.2, 5-C*H*), 2.38 – 2.20 (2H, m, 7-CH_2), 1.99 (3H, s, Me), 2.00 – 1.84 (2H, m, 4- CH_2, 3-CH_2), 1.51 – 1.36 (1H, m, 3- CH_2), 1.33 – 1.13 (1H, m, 4- CH_2). **^{13}C NMR** (101 MHz, $CDCl_3$): 139.7 (*Ar*), 139.6 (*Ar*), 193.4 (*Ar*), 133.4 (*Ar*H), 129.3 (*Ar*H), 128.7 (*Ar*H), 128.5 (*Ar*H), 128.4 (*Ar*H), 128.2 (*Ar*H), 128.2 (*Ar*H), 126.8 (*Ar*H), 126.8 (*Ar*H), 69.2 (1-*C*H), 61.8 (6-*C*H), 60.3 (2-*C*H), 60.2 (5-*C*H), 58.2 (NMe*C*H_2), 55.5 (N*C*H_2), 38.8 (*C*H_3), 29.6 (3-*C*H_2), 26.6 (7-*C*H_2), 23.6 (4-*C*H_2). **IR** ν_{max} (neat)/cm^{-1}: 3061, 3027, 2943 (CH), 2863, 2785, 1814, 1446 (C=C), 1325 (S=O); **HRMS** (ESI): $C_{28}H_{33}N_2O_2S$ [M+H$^+$]: calculated 461.2267, found 461.2257.

Compound **224**:

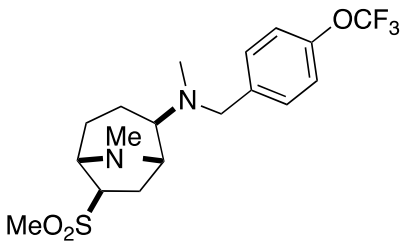
^{1}H NMR (400 MHz, $CDCl_3$) 7.94 – 7.85 (2H, m, Ar*H*), 7.67 – 7.57 (1H, m, Ar*H*), 7.59 – 7.48 (2H, m, Ar*H*), 7.48 – 7.40 (2H, m, Ar*H*), 7.35 – 7.15 (8H, m, Ar*H*), 4.03 (1H, d, *J* 13.3, 8-NC*H*$_2$), 3.89 (1H, d, *J* 13.3, NMe*C*H$_2$), 3.80 (1H, dt, *J* 3.5, 1.9, 2-C*H*), 3.77 – 3.68 (2H, m, 8-NC*H*$_2$, 1-C*H*), 3.61 – 3.48 (2H, m, NMeC*H*$_2$, 6-C*H*), 2.61 (1H, dt, *J* 13.6, 7.4, 7-CH), 2.41 (1H, d, *J* 7.3, 5-C*H*), 2.26 (3H, s, *Me*), 2.12 – 1.98 (1H, m, 3-C*H*$_2$), 1.88 – 1.77 (1H, m, 4-C*H*$_2$), 1.74 (1H, dd, *J* 13.6, 9.0, 7- C*H*$_2$), 1.55 (1H, ddt, *J* 15.1, 12.0, 7.3, 4-C*H*$_2$), 1.43 – 1.32 (1H, m, 3-C*H*$_2$). **^{13}C NMR** (101 MHz, $CDCl_3$): 140.4, (*C*), 140.1, (*C*), 139.6 (*C*), 133.4 (*Ar*H), 129.5 (*Ar*H), 129.3 (*Ar*H), 128.6 (*Ar*H), 128.2 (*Ar*H), 128.2 (*Ar*H), 128.0 (*Ar*H), 126.9 (*Ar*H), 126.7 (*Ar*H), 69.5 (6-*C*H), 65.0 (1-*C*H), 61.9 (5-*C*H), 60.9 (2-*C*H), 58.9 (NMe*C*H$_2$), 57.3 (8-N*C*H$_2$), 39.8 (*C*H$_3$), 32.0 (3-*C*H$_2$), 31.2 (7-*C*H$_2$), 18.7 (4-*C*H$_2$); **IR** ν_{max} (neat)/cm^{-1}: 3061, 3027, 2947 (CH), 2847, 2787, 1813, 1446 (C=C), 1367 (S=O); **HRMS** (ESI): $C_{28}H_{33}N_2O_2S$ [M+H$^+$]: calculated 461.2267, found 461.2279.

(1*S**,2*R**,5*S**,6*R**)-*N*,8-Dimethyl-6-(methylsulfonyl)-8-azabicyclo[3.2.1]octan-2-amine (**324**)



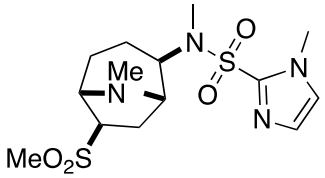
General procedure **X** was followed using compound **176** (1.00 g, 4.60 mmol, 1.0 eq.), methylamine (2M MeOH) (23 mL, 2.5 eq.), Ti(O^{i}Pr)$_4$ (2.8 mL, 9.2 mmol, 2.0 eq.), $NaBH_4$ (262 mg, 6.9 mmol, 1.5 eq.). Purification by SCX SPE (strong cation exchange solid phase extraction) afforded the *title compound* **324** (595 mg, 2.56 mmol, 41%) as a yellow oil; **δ_H (400 MHz, Chloroform-*d*):** 3.97 (1H, t, 8.3, 6-C*H*), 3.78 (1H, dt, *J* 3.7, 1.9, 5-C*H*), 3.56 – 3.50 (1H, m, 1-C*H*), 3.14 (3H, s, *Me*), 2.84 (3H, s, *Me*), 2.66 – 2.56 (2H, m, 7-C*H*$_2$), 2.20 (1H, dd, *J* 13.8, 9.3, 7-C*H*$_2$), 2.17 (1H, m, 2-C*H*), 2.06 (3H, s, *Me*), 1.83 – 1.72 (2H, m, 3-C*H*$_2$), 1.66 – 1.55 (2H, m, 4-C*H*$_2$); **δ_C (101 MHz, Chloroform-*d*):** 70.2 (6-*C*), 70.0 (1-*C*), 67.3 (2-*C*), 61.7 (5-*C*), 45.5(*Me*), 43.7 (*Me*), 35.7 (*Me*), 33.1 (7-*C*), 32.3 (3-*C*), 23.4 (4-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3336 (NH), 3229, 3100 (CH), 3049, 2941, 1471, 1286 (S=O), 1127; **HRMS** (ESI): $C_{10}H_{21}N_2O_2S$ [M+H$^+$]: calculated 233.1318, found 233.1324.

(1*S**,2*R**,5*S**,6*R**)-*N*,8-Dimethyl-6-(methylsulfonyl)-*N*-(4-(trifluoromethoxy)benzyl)-8-azabicyclo[3.2.1]octan-2-amine (**327**)



General procedure **W** was followed using compound **324** (99 mg, 0.43 mmol) in DMF (2.2 mL), 4-(trifluoromethoxy)benzaldehyde (0.3 mL, 2.15 mmol, 5.0 eq.) $NaBH_4$ (49 mg, 1.29 mmol, 3.0 eq.) at 60 ^oC for 16 h. The reaction mixture was cooled and concentrated *in vacuo*, then purification by automated reversed-phase flash chromatography eluting with $MeCN/H_2O$/1% formic acid gave the *title compound* **327** (13.6 mg, 0.03 mmol, 8%) as a colourless solid; **δ_H(400 MHz, Chloroform-*d*)** 7.31 (2H, d, *J* 8.6, Ar*H*), 7.15 – 7.05 (2H, m, Ar*H*), 3.99 (1H, d, *J* 13.6, NCH_2), 3.78 – 3.71 (1H, m, 5-C*H*), 3.61 (1H, d, *J* 7.3, 6-C*H*), 3.57 (1H, d, *J* 13.6, NCH_2), 3.40 (1H, t, *J* 8.2, 1-C*H*), 2.90 – 2.77 (3H, m, *Me*), 2.52 – 2.41 (2H, m, 7-CH_2, 2-C*H*), 2.40 (3H, s, *Me*), 2.32 (3H, s, *Me*), 2.19 – 2.07 (1H, m, 4-CH_2), 1.91 – 1.83 (2H, m, 3-CH_2, 7-CH_2), 1.62 – 1.43 (2H, m, 3-CH_2, 4-CH_2); **δ_C (101 MHz, Chloroform-*d*)** ; 148.4 (*Ar*), 136.9 (*Ar*), 131.3 (OC_3)130.4 (*Ar*H), 120.9 (*Ar*H), 67.5 (1-*C*), 65.3 (6-*C*), 63.0 (5-*C*), 61.5 (2-*C*), 58.3 (N-*C*), 41.1 (*Me*), 40.4 (*Me*), 39.3 (*Me*), 30.4 (7-*C*), 30.3 (3-*C*), 18.2 (4-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3077, 2956 (CH), 2866, 2827, 2787, 1593 (C=C), 1507, 1259 (S=O); **HRMS** (ESI): $C_{18}H_{26}F_3N_2O_3S$ [$M+H^+$]: calculated 407.1611, found 407.1606.

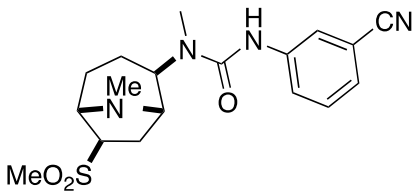
((1*S**,2*R**,5*S**,6*R**)-*N*,1-Dimethyl-*N*8-methyl-6-(methylsulfonyl)-8-azabicyclo[3.2.1]octan-2-yl)-1*H*-imidazole-2-sulfonamide (**329**)



General procedure **Q** was followed using compound **324** (99 mg, 0.43 mmol) in DMF (2.2 mL), $NaHCO_3$ (217 mg, 2.88 mmol, 6.0 eq.) and 1-methylimidazole-2-sulfonyl chloride (311 mg, 1.72 mmol, 4.0 eq.). The reaction mixture was concentrated *in vacuo* and purification by automated reversed-phase flash chromatography eluting with $MeCN/H_2O$/1% formic acid gave the *title compound* **329** (32.6 mg, 0.09 mmol, 21%) as a colourless solid;

δ_H (400 MHz, DMSO-*d*$_6$) 7.43 (1H, d, *J* 1.0, Ar*H*), 7.06 (1H, d, *J* 1.0, Ar*H*), 3.84 (3H, s, *Me*), 3.79 (1H, t, *J* 8.4, 1-C*H*), 3.72 – 3.66 (1H, m, 5-C*H*), 3.62 (1H, s, 2-C*H*), 3.35 (1H, d, *J* 7.1, 6-C*H*), 3.22 (3H, s, *Me*), 2.99 (3H, s, *Me*), 2.34 – 2.26 (1H, m, 7-CH_2), 2.24 (3H, s, *Me*), 2.05 – 1.96 (2H, m, 7-CH_2, 3-CH_2), 1.90 – 1.77 (1H, m, 4-CH_2), 1.71 (1H, dd, *J* 16.0, 6.5, 4-CH_2), 1.48 (1H, ddd, *J* 12.9, 6.2, 2.8, 3-CH_2); **δ_C (101 MHz, DMSO-*d*$_6$)** 142.9 (*Ar*), 128.0 (*Ar*H), 126.4 (*Ar*H), 70.1 (6-*C*), 66.3 (1-*C*), 62.8 (2-*C*), 55.9 (5-*C*), 41.9 (*Me*), 40.8 (*Me*), 34.9 (*Me*), 33.4 (*Me*), 31.3 (3-*C*), 28.9 (7-*C*), 18.9 (4-*C*); **IR ν_{max} (neat)/cm^{-1}:** 3488, 3112 (CH), 2993, 2941, 1651(C=C), 1458, 1288 (S=O), 1132; **HRMS (ESI):** $C_{14}H_{25}N_4O_4S_2$ [M+H$^+$]: calculated 377.1312, found 377.1308.

((1*S**, 2*R**, 5*S**, 6*R**)-3-(3-Cyanophenyl)-1-methyl-18-methyl-6-(methylsulfonyl)-8-azabicyclo[3.2.1]octan-2-yl)urea (**328**)

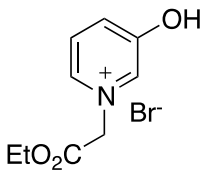


General procedure **Y** was followed using compound **324** (99 mg, 0.43 mmol) in DMF (2.2 mL), 3-isocyanatobenzonitrile (151 mg, 1.08 mmol) and $NaHCO_3$ (216 mg, 2.58 mml). The reaction mixture was concentrated *in vacuo* and purification by automated reversed-phase flash chromatography eluting with MeCN/H_2O/1% formic acid gave the *title compound* **328** (57 mg, 0.15 mmol, 35%) as a colourless solid;

δ_H (400 MHz, Methanol-*d*$_4$) 8.30 (1H, s, N*H*), 7.93 (1H, t, *J* 1.9, Ar*H*), 7.65 (1H, ddd, *J* 8.0, 2.3, 1.1, Ar*H*), 7.46 (1H, t, *J* 8.0, Ar*H*), 7.37 (1H, dt, *J* 8.0, 1.3, Ar*H*), 4.08 (1H, s, 2-C*H*), 4.02 (1H, t, *J* 8.5, 1-C*H*), 3.82 (1H, d, *J* 7.3, 5-C*H*), 3.77 (1H, d, *J* 7.3, 6-C*H*), 3.23 (3H, s, *Me*), 3.07 (3H, s, *Me*), 2.79 – 2.57 (4H, m, 4-CH_2, *Me*), 2.51 – 2.41 (1H, m, 3-CH_2), 2.36 (1H, dd, *J* 14.2, 9.4, 7-CH_2), 2.29 – 2.17 (1H, m, 4-CH_2), 1.87 – 1.71 (2H, m, 4-CH_2, 3-CH_2); **δ_C (101 MHz, Methanol-*d*$_4$)** 157.5 (*C*=O), 140.8 (*Ar*), 129.5 (*Ar*H), 125.8 (*Ar*H), 124.5 (*Ar*H), 123.2 (*Ar*H), 118.4 (*C*N), 112.1 (*Ar*), 68.8 (6-*C*), 64.9 (1-*C*), 63.0 (2-*C*), 58.1 (5-*C*), 39.9 (*Me*), 39.3 (*Me*), 34.7 (*Me*), 30.1 (3-*C*), 28.8 (7-*C*), 19.6 (4-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3385 (NH), 2896 (CH), 2786, 2257 (CN), 1653 (C=O), 1456 (C=C), 1386, 1295 (S=O); **HRMS** (ESI): $C_{18}H_{25}N_4O_3S$ [M+H$^+$]: calculated 377.1642, found 377.1641.

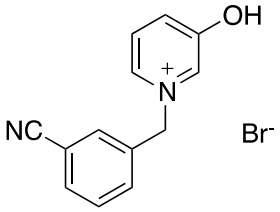
6.3.1 Chapter 2 compounds

1-(2-Ethoxy-2-oxoethyl)-3-hydroxypyridin-1-ium bromide (**351**)



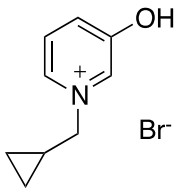
General procedure **A** was followed using 3-hydroxypyridine **86** (1.00 g, 10.52 mmol) and ethyl bromoacetate (1.30 mL, 11.57 mmol) in MeCN (22 mL). *Title compound **351*** (2.7 g, 10.3 mmol, 98%) was obtained as a colourless solid; **δ_H (300 MHz, DMSO-*d*$_6$):** 8.68 – 8.63 (1H, m, Ar*H*), 8.59 (1H, dt, *J* 5.7, 1.3, Ar*H*), 8.13 – 8.07 (1H, m, Ar*H*), 8.04 (1H, dd, *J* 8.7, 5.6, Ar*H*), 5.66 (2H, s, CH_2), 4.23 (2H, q, *J* 7.1, OCH_2), 1.25 (3H, t, *J* 7.1, CH_2); **δ_C (75 MHz, DMSO *d*$_6$):** 166.3 (*C*=O), 156.5 (*Ar*H), 137.2 (*Ar*H), 134.3 (*Ar*), 132.5 (*Ar*H), 128.3 (*Ar*H), 62.2 (*C*H_2) , 60.2 (*C*H_2) , 13.9 (*Me*); **IR** ν_{max} (neat)/cm^{-1}: 3045, 2880, (CH), 2852, 1707 (C=O), 1456 (C=C), 1401, 1360, 1216, **HRMS** (ESI): $C_9H_{12}NO_3$ [M-H]: calculated 182.0812, found 182.0811.

1-(3-Cyanobenzyl)-3-hydroxypyridin-1-ium bromide (**352**)



General procedure **A** was followed using 3-hydroxypyridine **86** (2.50 g, 26.3 mmol) and 3-(bromomethyl)benzonitrile (2.55 mL, 26.3 mmol) in IPA (50 mL). *Title compound **352*** (7.65g, 23.4 mmol, 99%) was obtained as a colourless solid; **δ_H (600 MHz, DMSO-*d*$_6$):** 8.76 – 8.69 (2H, m, Ar*H*), 8.07 (1H, s, Ar*H*), 8.00 – 7.92 (2H, m, Ar*H*), 7.91 – 7.85 (2H, m, Ar*H*), 7.61 (1H, d, *J* 8.4, Ar*H*), 5.86 (2H, s, NCH_2); **δ_c (151 MHz, DMSO-*D*$_6$):** 157.7 (*Ar*), 136.4 (*Ar*), 136.2 (*Ar*H), 134.3 (*Ar*H), 133.5 (*Ar*H), 133.2 (*Ar*H), 132.5 (*Ar*H), 130.9 (*Ar*H), 129.5 (*Ar*H), 118.8 (*Ar*), 112.4 (*C*N), 62.5 (*C*H_2); **IR** ν_{max} (neat)/cm^{-1}: 3341 (OH), 3003 (CH), 2980, 2853, 2212 (CN), 1585 (C=C), 1488, 1452; **HRMS** (ESI): $C_{13}H_{10}N_2O$ [M-H]: calculated 211.2387, found 211.0879.

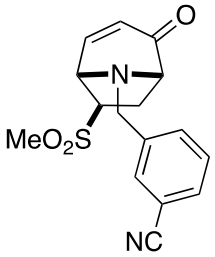
1-(Cyclopropylmethyl)-3-hydroxypyridin-1-ium bromide (**353**)



General procedure **A** was followed using 3-hydroxypyridine **86** (2.30 g, 26.3 mmol) and (bromomethyl)cyclopropane (2.55 mL, 26.3 mmol) in IPA (50 mL). *Title compound* **353** (6.00g, 26.1 mmol, 99%) was obtained as a colourless solid.

δ_H (600 MHz, DMSO-*d*$_6$): 8.68 (1H, s, Ar*H*), 8.66 – 8.63 (1H, m, Ar*H*), 7.98 (1H, d, *J* 8.9, Ar*H*), 7.96 – 7.90 (1H, m, Ar*H*), 4.45 (2H, d, *J* 7.6, CH_2), 1.43 – 1.32 (1H, m, *cyp*), 1.02 – 0.94 (1H, m, *cyp*), 0.67 – 0.44 (3H, m, *cyp*); **δ_c** (151 MHz, **DMSO-*d*$_6$):** 157.3 (*Ar*), 136.0 (*Ar*H), 133.1 (*Ar*H), 131.9 (*Ar*H), 129.1 (*Ar*H), 65.0 (*C*H_2), 25.9 (*cyp*), 12.6 (*cyp*), 4.4 (*C*H). **IR** ν_{max} (neat)/cm^{-1}: 3341 (OH), 3002 (CH), 2980, 2950, 2729, 1584 (C=C), 1556, 1489; **HRMS** (ESI): $C_9H_{11}NO$ [M-H]: calculated 150.0913, found 150.0909.

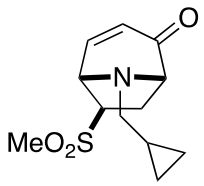
3-(((1*S**,5*S**,6*R**)-6-(Methylsulfonyl)-2-oxo-8-azabicyclo[3.2.1]oct-3-en-8-yl)methyl)benzonitrile (**354**)



General procedure **B** was followed using methyl vinyl sulfone (1.8 mL, 20.2 mmol) and benzyl salt **352** (7.65.0 g, 26.3 mmol), triethylamine (5.6 mL, 40.4 mmol). Purification by flash chromatography on silica gel, eluting with a gradient of 60-100% EtOAc in hexane afforded the major *title compound* ***354*** (1.89 g, 5.98 mmol, 29%) as a yellow solid; ***R*$_f$** = 0.47, (100% EtOAc in hexane); **δ_H (400 MHz, Chloroform-*d*):** 7.61 (1H, dt, *J* 7.4, 1.6, Ar*H*), 7.54 (2H, d, *J* 11.6, Ar*H*), 7.48 (1H, t, *J* 7.6, Ar*H*), 7.06 (1H, dd, *J* 9.8, 5.0, 4-C*H*), 6.25 (1H, dd, *J* 9.8, 1.5, 3-C*H*), 4.20 (1H, d, *J* 5.0, 5-C*H*), 3.88 (2H, s, N*Bn*), 3.72 (1H, d, *J* 7.7, 6-C*H*), 3.49 (1H, dd, *J* 9.4, 4.2, 1-C*H*), 2.93 (3H, s), 2.78 (1H, ddd, *J* 14.7, 7.7, 4.2, 7-CH_2), 2.24 (1H, dd, *J* 14.7, 9.4, 7-CH_2); **δ_c (126 MHz, Chloroform-*d*):** 196.6 (*C*=O), 145.1 (4-*C*), 138.5 (*Ar*), 133.1 (*Ar*H), 132.0 (*Ar*H), 131.7 (*Ar*H), 129.7 (*Ar*H), 129.2 (3-*C*), 118.5 (*Ar*), 112.9 (*C*N), 67.8 (6-*C*), 66.2 (1-*C*), 58.2 (5-*C*), 51.2 (N*Bn*), 38.8 (*Me*), 27.5 (7-*C*H_2); **IR** ν_{max} (neat)/cm^{-1}: 3058, 3010, 2924

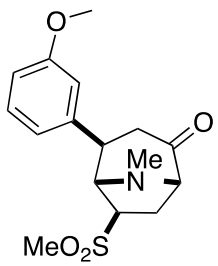
(CH), 2229 (CN), 1684 (C=O), 1573 (C=C), 1476, 1276 (S=O); **HRMS** (ESI): $C_{16}H_{17}N_2O_3S$ [M+H$^+$]: calculated 317.0954, found 317.0960.

(1*S**,5*S**,6*R**)-8-(Cyclopropylmethyl)-6-(methylsulfonyl)-8-azabicyclo[3.2.1]oct-3-en-2-one (**355**)



General procedure **B** was followed using methyl vinyl sulfone (2.55 mL, 20.2 mmol) and salt **353** (6.0 g, 26.3 mmol), triethylamine (5.6 mL, 40.4 mmol). Purification by flash chromatography on silica gel, eluting with a gradient of 60-100% EtOAc in hexane afforded the major *title compound* **355** (1.13 g, 4.41 mmol, 22%) as a yellow solid; $\boldsymbol{R_f}$ = 0.32, (60% EtOAc in hexane); **δ_H (400 MHz, Chloroform-*d*):** 6.88 (1H, dd, *J* 9.8, 4.9, 4-C*H*), 6.02 (1H, dd, *J* 9.8, 1.5, 3-C*H*), 4.33 (1H, d, *J* 4.9, 5-C*H*), 3.73 (1H, dd, *J* 7.8, 1.5, 6-C*H*), 3.34 (1H, dd, *J* 9.5, 3.9, 1-C*H*), 2.63 (1H, ddd, *J* 15.0, 7.8, 3.9, 7-CH_2), 2.52 (1H, dd, *J* 12.5, 6.5, CH_2), 2.46 (3H, s, SO_2*Me*), 2.39 (1H, dd, *J* 12.5, 7.0, CH_2), 2.14 (1H, dd, *J* 15.0, 9.5, 7-CH_2), 0.80 – 0.68 (1H, m, *cyp*), 0.52 – 0.40 (2H, m, *cyp*), 0.05 – -0.06 (2H, m, *cyp*); **δ_C (126 MHz, Chloroform-*d*):** 197.4 (*C*=O), 144.5 (4-*C*), 128.9 (3-*C*), 67.8 (6-*C*), 66.5 (1-*C*), 58.1 (5-*C*), 51.9 (*C*H_2), 38.1 (*Me*), 27.7 (7-*C*), 9.8 (*cyp)*, 3.9 (*cyp)*, 3.4 (*cyp)*; **IR** ν_{max} (neat)/cm^{-1}: 3075, 3005 (CH), 2949, 2828, 1682 (C=O), 1458 (C=C), 1402, 1272 (S=O); **HRMS** (ESI): $C_{12}H_{18}NO_3S$ [M+H$^+$]: calculated 256.1002, found 256.1000.

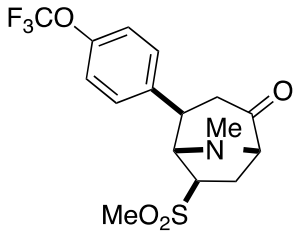
(1*S**,4*R**,5*S**,6*R**)-4-(3-Methoxyphenyl)-8-methyl-6-(methylsulfonyl)-8-azabicyclo[3.2.1]octan-2-one (**368**)



General procedure **T** was followed using cycloadduct **116** (1 g, 4.65 mmol), 3-methoxyphenylboronic acid (2.12 g, 14.0 mmol, 3.0 eq.), chloro(1,5-cyclooctadiene)rhodium(I) dimer (57 mg, 10 mol%), dioxane:H_2O (6:1) (16 mL) and

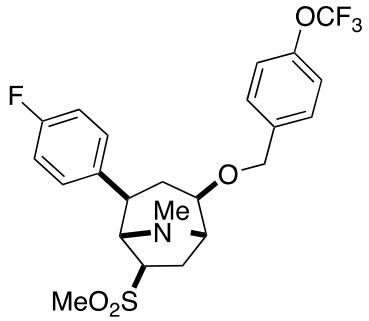
triethylamine (0.7 mL, 4.65 mmol, 1.0 eq). Purification by flash chromatography on silica gel, eluting with a gradient of 50-100% EtOAc in hexane-afforded the *title compound **368*** (1.1 g, 3.40 mmol , 73%) as a colourless solid; $\boldsymbol{R_f}$ = 0.54, (100% EtOAc in hexane); **δ_H (501 MHz, Chloroform-*d*)**: 7.14 (1H, t, *J* 8.0, Ar*H*), 6.87 – 6.80 (2H, m, Ar*H*), 6.71 (1H, ddd, *J* 8.0, 2.6, 1.0, Ar*H*), 3.83 (1H, d, *J* 1.9, 5-C*H*), 3.71 (3H, s, O*Me*), 3.57 (1H, d, *J* 6.7, 6-C*H*), 3.51 (1H, t, *J* 7.6, 1-C*H*), 3.03 – 2.96 (1H, m, 4-C*H*), 2.88 (3H, s, SO_2*Me*), 2.63 (1H, dd, *J* 13.5, 6.7, 7-CH_2), 2.57 – 2.47 (2H, m, 3-CH_2), 2.32 (3H, s, N*Me*), 2.21 (1H, dd, *J* 13.5, 8.9, 7-CH_2); **δ_C** (126 MHz, **Chloroform-*d*)**: 207.1 (*C*=O), 159.7 (*Ar*), 145.7 (*Ar*), 129.5 (*Ar*H), 119.9 (*Ar*H), 113.4 (*Ar*H), 112.1 (*Ar*H), 73.8 (6-*C*), 69.0 (1-*C*), 68.6 (5-*C*), 55.2 (OMe), 47.2 (4-*C*), 40.5 (N*Me*), 40.1 (SO_2*Me*), 40.1 (3-*C*), 29.8 (7-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3015, 2940 (CH), 2895, 2873, 1603 (C=O), 1507 (C=C), 1462, 1267 (S=O); **LCMS** (ESI): $C_{16}H_{22}NO_4S$ [M+H^+]: calculated 324.1264, found 324.11.

(1*S**,4*R**,5*S**,6*R**)-8-Methyl-6-(methylsulfonyl)-4-(4-(trifluoromethoxy)phenyl)-8-azabicyclo[3.2.1]octan-2-one (**367**)



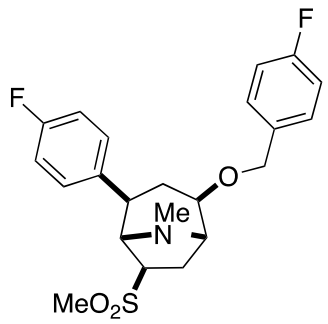
General procedure **T** was followed using cycloadduct **116** (1 g, 4.65 mmol) and 4-trifluoromethoxyphenyl boronic acid (2.87 g, 14.0 mmol, 3.0 eq.), chloro(1,5-cyclooctadiene)rhodium(I) dimer (57 mg, 10 mol%), dioxane:H_2O (6:1) (16 mL) and triethylamine (0.7 mL, 4.65 mmol, 1.0 eq). Purification by flash chromatography on silica gel, eluting with a gradient of 50-100% EtOAc in hexane-afforded the *title compound* **367** (1.65g, 4.38 mmol ,94%) as a colourless solid; $\boldsymbol{R_f}$ = 0.57, (100% EtOAc in hexane); **δ_H (501 MHz, Chloroform-*d*)** 7.29 (2H, d, *J* 8.0), 7.07 (2H, d, *J* 8.0), 3.78 (1H, d, *J* 1.8, 5-C*H*), 3.62 – 3.52 (2H, m, 6-C*H*, 1-C*H*), 3.08 (1H, ddd, *J* 7.9, 4.4, 1.6, 4-C*H*), 2.90 (3H, s, SO_2*Me*), 2.59 – 2.49 (3H, m, 3-CH_2 7-CH_2), 2.30 (3H, s, N*Me*), 2.23 (1H, dd, *J* 13.6, 8.9, 7-CH_2); **δ_C (126 MHz, Chloroform-*d*):** 204.3 (*C*=O), 146.4 (*Ar*), 146.4 (O*C*F_3), 140.9 (*Ar*), 127.3 (*Ar*H), 119.2 (*Ar*H), 72.3 (6-*C*), 66.9 (1-*C*), 66.8 (5-*C*), 44.8 (4-*C*), 38.8 (N*Me*), 38.5 (SO_2*Me*), 38.0 (3-*C*), 28.1 (7-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3059 (OH), 3009 (CH), 2972, 2946, 1682 (C=O), 1461 (C=C), 1452, 1288 (S=O); **LCMS** (ESI): $C_{16}H_{19}F_3NO_4S$ [M+H^+]: calculated 378.0981, found 378.15.

(1*S**,2*R**,4*R**,5*S**,6*R**)-4-(4-Fluorophenyl)-8-methyl-6-(methylsulfonyl)-2-((4-(trifluoromethoxy)benzyl)oxy)-8-azabicyclo[3.2.1]octane (**380**)



General procedure **R** was followed using compound **278a** (74 mg, 0.24 mmol) in DMF (1 mL), 4-(trifluoromethoxy)benzyl bromide (100 μL, 0.96 mmol, 4.0 eq.) and sodium hydride (20 mg, 0.48 mmol, 2.0 eq.) at rt. Purification by automated reversed-phase flash chromatography eluting with MeCN/H_2O/1%Formic acid gave *title compound* **380** (28 mg, 0.06 mmol, 24%) as a colourless oil; **δ_H (600 MHz, DMSO-*d*$_6$):** 7.64 (2H, dd, *J* 8.7, 5.8, Ar*H*), 7.36 (2H, d, *J* 8.4, Ar*H*), 7.31 – 7.25 (2H, m, Ar*H*), 6.99 (2H, t, *J* 8.9, Ar*H*), 4.50 (1H, d, *J* 12.4, O-CH_2), 4.45 (1H, d, *J* 12.4, O-CH_2), 3.97 – 3.87 (1H, m, 6-C*H*), 3.48 – 3.42 (2H, m, 1-C*H*, 5-C*H*), 3.41 – 3.39 (1H, m, 2-C*H*), 3.00 (3H, s, *Me*), 2.86 – 2.84 (1H, m, 4-C*H*), 2.27 (1H, dt, *J* 13.6, 7.4, 7-CH_2), 2.14 (3H, s, *Me*), 2.10 (1H, ddd, *J* 15.8, 8.3, 6.0, 3-CH_2), 1.98 (1H, dd, *J* 13.5, 9.2, 7-CH_2), 1.74 (1H, dt, *J* 15.8, 1.4, 3-CH_2); **δ_C (151 MHz, DMSO-*d*$_6$):** 164.1 (*Ar*), 162.0 (d, *J* 242.7, *Ar*-F), 147.9 (d, *J* 2.9, *Ar*), 139.3 (*Ar*), 135.9 (O-*C*F_3) 131.26 (d, *J* 7.9, *Ar*H), 129.5 (*Ar*H), 121.3 (*Ar*H), 114.5 (d, *J* 20.8, *Ar*H), 77.0 (2-*C*), 69.1 (O-*C*), 68.4 (1-*C*), 67.9 (6-*C*), 66.3 (5-*C*), 45.7 (4-*C*), 42.1 (*Me*), 41.0 (*Me*), 27.9 (7-*C*), 26.9 (3-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3080, 3042, 3008 (CH), 2944, 2869, 1600, 1509 (C=C), 1220 (S=O); **HRMS** (ESI): $C_{23}H_{26}F_4NO_4S$ [M+H$^+$]: calculated 488.1513, found 488.1540.

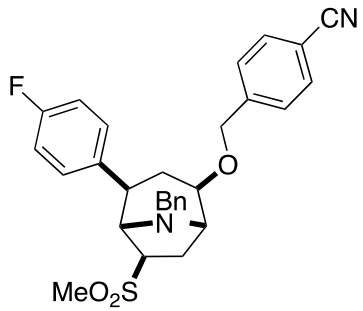
(1*S**,2*R**,4*R**,5*S**,6*R**)-2-((4-Fluorobenzyl)oxy)-4-(4-fluorophenyl)-8-methyl-6-(methylsulfonyl)-8-azabicyclo[3.2.1]octane (**379**)



General procedure **R** was followed using compound **278a** (74 mg, 0.24 mmol) in DMF (1 mL), 4-fluorophenylmethyl bromide (130 μL, 0.96 mmol, 4.0 eq.) and sodium hydride (20 mg, 0.48 mmol, 2.0 eq.) at rt. Purification by automated reversed-phase flash chromatography eluting with MeCN/H_2O/1% formic acid gave *title compound* **379** (32 mg, 0.08 mmol, 32%) as a colourless oil;

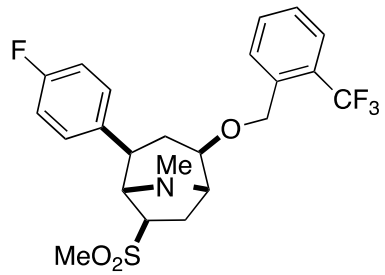
δ_H (600 MHz, DMSO-*d*$_6$): 7.64 (2H, dd, *J* 8.7, 5.8, Ar*H*), 7.33 – 7.22 (2H, m, Ar*H*), 7.12 (2H, t, *J* 8.9), 6.98 (2H, t, *J* 8.9, Ar*H*), 4.45 (1H, d, *J* 11.6, OCH_2), 4.41 (1H, d, *J* 11.6, OCH_2), 3.99 – 3.88 (1H, m, 6-C*H*), 3.48 – 3.39 (2H, m, 1-C*H*, 5-C*H*), 3.38 (1H, dt, *J* 5.7, 1.9, 2-C*H*), 3.00 (3H, s, *Me*), 2.85 (1H, d, *J* 9.1, 4-C*H*), 2.32 – 2.21 (1H, m, 7-CH_2), 2.14 (3H, s, *Me*), 2.14 – 2.02 (1H, m, 3-CH_2), 1.97 (1H, dd, *J* 13.5, 9.2, 7-CH_2), 1.73 (1H, d, *J* 16.0, 3-CH_2); **δ_C (151 MHz, DMSO-*d*$_6$):** 161.9 (d, *J* 242.7, *Ar*-F), 161.2 (d, *J* 241.7, *Ar*-F), 142.1 (d, *J* 2.9, *Ar*), 135.7 (d, *J* 2.9, *Ar*), 131.3 (d, *J* 7.3, *Ar*H), 129.8 (d, *J* 8.0, *Ar*H), 115.5 (d, *J* 21.0, *Ar*H), 114.5 (d, *J* 20.2, *Ar*H), 76.8 (2-*C*), 69.2 (O-*C*), 68.5 (1-*C*), 67.9 (6-*C*), 66.4 (5-*C*), 45.8 (4-*C*), 42.1 (N*Me*), 41.0 (SO2M*e*), 27.9 (7-*C*), 26.8 (3-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3064, 2961 (CH), 2921, 2880, 1624 (C=C), 1497, 1418, 1240 (S=O); **HRMS** (ESI): $C_{22}H_{26}F_2NO_3S$ [M+H$^+$]: calculated 422.1596, found 422.1616.

4-((((1*S**,2*R**,4*R**,5*S**,6*R**)-8-Benzyl-4-(4-fluorophenyl)-6-(methylsulfonyl)-8-azabicyclo[3.2.1]octan-2-yl)oxy)methyl)benzonitrile (**375**)



General procedure **R** was followed using compound **281** (265 mg, 0.67 mmol) in DMF (3 mL), 4-(bromomethyl)benzonitrile (450 mg, 2.35 mmol, 3.5 eq.) and sodium hydride (67 mg, 1.68 mmol, 2.5 eq.) at rt. Purification by automated reversed-phase flash chromatography eluting with MeCN/H_2O/1% formic acid gave *title compound* **379** (97mg, 0.19 mmol, 29%) as a colourless solid; **δ_H (501 MHz, Chloroform-*d*):** 7.60 – 7.56 (2H, m, Ar*H*), 7.56 – 7.51 (2H, m, Ar*H*), 7.23 – 7.18 (2H, m, Ar*H*), 7.15 – 7.11 (2H, m, Ar*H*), 7.08 – 6.99 (3H, m, Ar*H*), 6.88 – 6.82 (2H, m, Ar*H*), 4.31 (1H, d, *J* 13.0, N*Bn*), 4.23 (1H, d, *J* 13.0, N*Bn*), 3.87 (1H, s, 5-C*H*), 3.65 – 3.50 (3H, m, OCH_2, 6-C*H*) 3.38 – 3.33 (1H, m, 1-C*H*), 2.97 – 2.87 (5H, m, *Me*, 2-C*H*), 2.52 (1H, dt, *J* 14.6, 7.4, 7-CH_2), 2.11 – 1.96 (3H, m, 7-CH_2, 3-CH_2); **δ_C (126 MHz, Chloroform-*d*):** 161.6 (d, *J* 244.4, *Ar*F), 144.1 (*Ar*), 139.8 (d, *J* 3.2, *Ar*), 139.3 (*Ar*), 132.1 (*Ar*H), 130.8 (d, *J* 7.6, *Ar*H), 129.0 (*Ar*H), 127.9 (*Ar*H), 127.2 (*Ar*H), 126.8 (*Ar*H), 118.9 (*Ar*), 114.4 (d, *J* 20.8, *Ar*H), 111.1 (*C*N), 76.9 (2-*C*), 69.2 (O-*C*), 69.0 (1-*C*), 67.6 (6-*C*), 62.8 (5-*C*), 57.5 (N*Bn*), 46.8 (4-*C*), 40.6 (*Me*), 28.4 (7-*C*), 27.4 (3-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3061, 3008 (CH), 2947, 2927, 2231 (CN), 1496 (C=C), 1455, 1290 (S=O); **HRMS** (ESI): $C_{29}H_{30}FN_2O_3S$ [$M+H^+$]: calculated 505.1956, found 505.1962.

(1*S**,2*R**,4*R**,5*S**,6*R**)-4-(4-Fluorophenyl)-8-methyl-6-(methylsulfonyl)-2-((2-(trifluoromethyl)benzyl)oxy)-8-azabicyclo[3.2.1]octane (**381**)

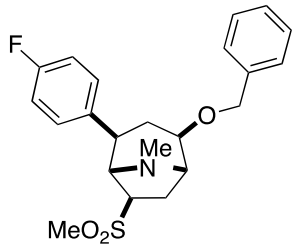


General procedure **R** was followed using compound **278a** (124 mg, 0.40 mmol) in DMF (2 mL), 2-(trifluoromethyl)phenyl bromide (380 mg, 1.6 mmol, 4.0 eq.) and sodium hydride (31 mg, 0.8 mmol, 2.0 eq.) at rt. Purification by automated reversed-phase flash chromatography eluting with MeCN/H_2O/1% formic acid gave *title compound* **381** (47 mg, 0.1 mmol, 25%) as a colourless oil;

δ_H (600 MHz, DMSO-*d*$_6$) 7.70 – 7.58 (4H, m, Ar*H*), 7.48 – 7.43 (2H, m, Ar*H*), 7.00 – 6.94 (2H, m, Ar*H*). 4.63 (1H, d, *J* 13.1, OCH_2), 4.57 (1H, d, *J* 13.1, OCH_2), 3.94 (1H, t, *J* 8.4, 6-C*H*), 3.49 (1H, s, 5-C*H*), 3.47 – 3.44 (2H, m, 2-C*H*, 1-C*H*), 3.01 (3H, s, *Me*), 2.86 (1H, d, *J* 8.5, 4-C*H*), 2.29 (1H, dt, *J* 14.0, 7.2, 7-CH_2), 2.18 – 2.09 (4H, m, *Me*, 3-CH_2), 2.00 (1H, dd, *J* 13.6, 9.2, 7-CH_2), 1.75 (1H, d, *J* 15.9, 3-CH_2); **δ_C (151 MHz, DMSO-*d*$_6$)** 161.1 (d, *J* 241.0, *Ar*-F), 142.0 (d, *J* 2.9, *Ar*), 137.9 (*Ar*), 133.1 (*Ar*H), 131.2 (d, *J* 7.9, *Ar*H), 129.9 (*Ar*H), 128.3 (*Ar*H), 126.8 (CF_3), 126.1 (*Ar*H), 124.2 (*Ar*), 114.5 (d, *J* 20.8, *Ar*H), 77.5 (2-*C*), 68.3 (1-*C*), 67.9 (6-*C*), 66.5(O-*C*), 66.2 (5-*C*), 45.5 (4-*C*), 42.1 (Me), 41.0 (Me), 27.9 (7-*C*), 27.1 (3-*C*).

IR ν_{max} (neat)/cm^{-1}: 3080, 3013 (CH), 2945, 2874, 1509 (C=C), 1457, 1313, 1219 (S=O); **HRMS** (ESI): $C_{23}H_{26}F_4NO_3S$ [M+H$^+$]: calculated 472.1564, found 472.1579.

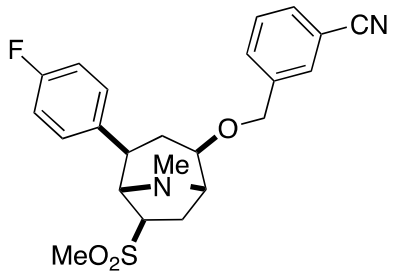
(1*S**,2*R**,4*R**,5*S**,6*R**)-2-(Benzyloxy)-4-(4-fluorophenyl)-8-methyl-6-(methylsulfonyl)-8-azabicyclo[3.2.1]octane (**378**)



General procedure **R** was followed using compound **278a** (124 mg, 0.40 mmol) in DMF (2 mL), benzyl bromide (190 μL, 1.6 mmol, 4.0 eq.) and sodium hydride (31 mg, 0.8 mmol, 2.0 eq.) at rt. Purification by automated reversed-phase flash chromatography eluting with MeCN/H_2O/1% formic acid gave *title compound* **378** (60 mg, 0.15 mmol , 37%) as a colourless oil;

δ_H (600 MHz, DMSO-*d*$_6$): 7.66 (2H, dd, *J* 8.4, 5.7, Ar*H*), 7.30 (2H, t, *J* 7.7, Ar*H*), 7.27 – 7.21 (3H, m, Ar*H*), 7.00 – 6.95 (2H, m, Ar*H*), 4.47 (1H, d, *J* 12.2, O-CH_2), 4.43 (1H, d, *J* 12.2, O-CH_2), 3.93 (1H, t, *J* 8.3, 6-C*H*), 3.48 – 3.41 (2H, m, 1-C*H*, 5-C*H*), 3.38 (1H, d, *J* 6.0, 2-C*H*), 3.00 (3H, s, *Me*), 2.85 (1H, d, *J* 8.0, 4-C*H*), 2.27 (1H, dt, *J* 14.1, 7.3, 7-CH_2), 2.14 (3H, s, *Me*), 2.15 – 2.01 (1H, m, 3-CH_2), 1.97 (1H, dd, *J* 13.5, 9.1, 7-CH_2), 1.74 (1H, dt, *J* 15.8, 1.4, 3-CH_2); **δ_C (151 MHz, DMSO-*d*$_6$):** 161.2 (d,; *J* 241.3, *Ar*-F), 142.1 (d, *J* 2.9, *Ar*), 139.5 (*Ar*) 131.3 (d, *J* 7.9, *Ar*H), 128.7 (*Ar*H), 127.8 (*Ar*H), 127.7 (*Ar*H), 114.5 (d, *J* 20.4, *Ar*H), 76.8 (2-*C*), 70.0 (O-*C*), 68.5 (1-*C*), 68.0 (6-*C*), 66.4 (5-*C*), 45.8 (4-*C*), 42.1(*Me*), 41.0 (*Me*), 28.0 (7-*C*), 26.8 (3-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3064, 3030 (CH), 2943, 2867, 1509 (C=C), 1491, 1456, 1267 (S=O); **HRMS** (ESI): $C_{22}H_{27}FNO_3S$ [M+H$^+$]: calculated 404.1690, found 404.1712.

3-((((1*S**,2*R**,4*R**,5*S**,6*R**)-4-(4-Fluorophenyl)-8-methyl-6-(methylsulfonyl)-8-azabicyclo[3.2.1]octan-2-yl)oxy)methyl)benzonitrile (**376**)

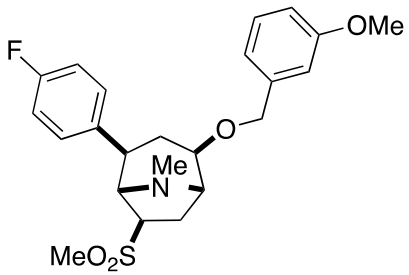


General procedure **R** was followed using compound **278a** (124 mg, 0.40 mmol) in DMF (2 mL), 3-(bromomethyl)benzonitrile bromide (313 mg, 1.6 mmol, 4.0 eq.) and sodium hydride

(31 mg, 0.8 mmol, 2.0 eq.) at rt. Purification by automated reversed-phase flash chromatography eluting with MeCN/H_2O/1% formic acid gave *title compound* **376** (32 mg, 0.07 mmol , 19%) as a colourless oil;

δ_H (600 MHz, DMSO-*d*$_6$): 7.70 – 7.68 (1H, m), 7.67 – 7.62 (3H, m), 7.58 – 7.55 (1H, m), 7.51 (1H, t, *J* 7.6), 7.01 – 6.96 (2H, m), 4.53 (1H, d, *J* 12.8, OC*H*$_2$), 4.48 (1H, d, *J* 12.8, OC*H*$_2$), 3.99 – 3.90 (1H, m, 6-CH), 3.50 (1H, d, *J* 2.1, 5-CH), 3.45 (1H, d, *J* 7.4, 2-CH), 3.42 – 3.41 (1H, m, 1-CH), 3.01 (3H, s, *Me*), 2.89 – 2.84 (1H, m, 4-C*H*), 2.28 (1H, dt, *J* 14.1, 7.3, 7-C*H*$_2$), 2.16 – 2.07 (4H, m, 3-C*H*$_2$), 1.99 (1H, dd, *J* 13.5, 9.2, 7-C*H*$_2$), 1.76 (1H, d, *J* 16.0, 3-C*H*$_2$); **δ_C (151 MHz, DMSO-*d*$_6$):** 161.1 (d, *J* 241.9, *Ar*-F), 142.0 (d, *J* 3.0, Ar), 141.4 (*Ar*), 132.3 (*Ar*H), 131.4 (*Ar*H), 131.2 (d, *J* 7.3, *Ar*H), 131.0 (*Ar*H), 129.9 (*Ar*H), 119.3 (*Ar*), 114.5 (d, *J* 20.2, *Ar*H), 111.8 (*C*N), 77.1 (2-*C*), 68.8 (O-*C*), 68.3 (1-*C*), 67.9 (6-*C*), 66.1(5-*C*), 45.5 (4-*C*), 42.0 (Me), 41.0 (Me), 27.9 (7-*C*), 27.1 (3-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3078, 3013 (CH), 2944, 2870, 2229 (CN), 1509 (C=C), 1484, 1293 (S=O); **HRMS** (ESI): $C_{23}H_{26}FN_2O_3S$ [M+H$^+$]: calculated 429.1643, found 429.1657.

(1*S**,2*R**,4*R**,5*S**,6*R**)-4-(4-Fluorophenyl)-2-((3-methoxybenzyl)oxy)-8-methyl-6-(methylsulfonyl)-8-azabicyclo[3.2.1]octane (**377**)

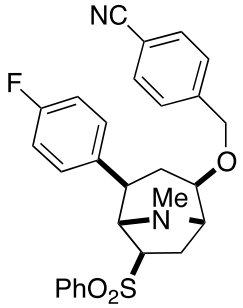


General procedure **R** was followed using compound **278a** (124 mg, 0.40 mmol) in DMF (2 mL), 3-methoxybenzyl bromide (220 μL, 1.6 mmol, 4.0 eq.) and sodium hydride (31 mg, 0.8 mmol, 2.0 eq.) at rt. Purification by automated reversed-phase flash chromatography eluting with MeCN/H_2O/1% formic acid gave *title compound* **377 (**37 mg, 0.09 mmol , 21%) as a colourless oil;

δ_H (400 MHz, DMSO-*d*$_6$) 7.81 – 7.64 (2H, m, Ar*H*), 7.26 (1H, t, *J* 7.8, Ar*H*), 7.11 – 6.96 (2H, m, Ar*H*), 6.93 – 6.82 (3H, m, Ar*H*), 4.52 – 4.40 (2H, m, OC*H*$_2$), 3.99 (1H, t, *J* 8.3, 6-C*H*), 3.73 (3H, s, *Me*), 3.51 – 3.44 (2H, m, 1-C*H*, 5-C*H*), 3.42 (1H, dd, *J* 5.0, 3.0, 2-C*H*), 3.06 (3H, s, *Me*), 2.94 – 2.85 (1H, m, 4-C*H*), 2.31 (1H, dt, *J* 14.0, 7.3, 7-C*H*$_2$), 2.18 (4H, s, *Me*, 3-C*H*$_2$), 2.01 (1H, dd, *J* 14.0, 9.2, 7-C*H*$_2$), 1.78 (1H, d, *J* 16.0, 3-C*H*$_2$); **^{13}C NMR (151 MHz, DMSO-**

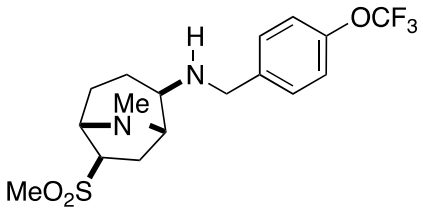
***D*$_6$) δ** 161.2 (d, *J* 241.3), 159.8 (*Ar*), 142.1 (d, *J* 2.9, *Ar*), 141.2 (Ar), 131.3 (d, *J* 7.3), 129.8 (*Ar*H), 119.9 (*Ar*H), 114.5 (d, *J* 20.9), 113.2 (*Ar*H), 76.9 (2-*C*), 69.9 (O-*C*)), 68.5 (1-*C*), 68.0 (6-*C*), 66.3 (5-*C*), 55.5 (*Me*), 45.8 (4-*C*), 42.1 (*Me*), 41.0 (*Me*), 27.9 (7-*C*), 26.9 (3-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3077, 3008 (CH), 2943, 2869, 1586, 1509 (C=C), 1490, 1265 (S=O); **HRMS** (ESI): $C_{23}H_{29}FNO_4S$ [M+H$^+$]: calculated 434.1796, found 434.1809.

4-((((1*S**,2*R**,4*R**,5*S**,6*R**)-4-(4-Fluorophenyl)-8-methyl-6-(phenylsulfonyl)-8-azabicyclo[3.2.1]octan-2-yl)oxy)methyl)benzonitrile (**374**)



General procedure **R** was followed using alcohol **369** (203 mg, 0.54 mmol), NaH (54 mg, 1.35 mmol) and 4-(bromomethyl)benzonitrile (370 mg, 1.89 mmol, 3.5 eq.) in DMF (3 mL). Purification by flash chromatography on silica gel, eluting with a gradient of 10 - 40% EtOAc in hexane afforded the *title compound* **374** (68 mg, 0.14 mmol, 33%) as a colourless solid; R_f = 0.18, (30% in EtOAc); **δ$_H$ (600 MHz, DMSO-*d*$_6$)** 7.98 – 7.90 (1H, m, Ar*H*), 7.85 – 7.70 (4H, m, Ar*H*), 7.65 (2H, t, *J* 8.1, Ar*H*), 7.48 (2H, dd, *J* 6.1, 2.60, Ar*H*), 7.43 (2H, d, *J* 7.2, Ar*H*), 6.96 (2H, t, *J* 8.9, Ar*H*), 4.55 (1H, d, *J* 13.5, OC*H*$_2$), 4.50 (1H, d, *J* 13.5, OC*H*$_2$), 4.04 (1H, t, *J* 7.6, 6-C*H*), 3.45 (1H, d, *J* 6.6, 2-C*H*), 3.39 (1H, s, 5-C*H*), 3.38 – 3.29 (1H, m, 1-C*H*), 3.26 (3H, s, *Me*), 2.71 (1H, d, *J* 4.9, 4-C*H*), 2.30 (1H, dt, *J* 13.4, 7.4, 7-C*H*$_2$), 2.17 – 2.06 (1H, m, 3-C*H*$_2$), 1.79 (1H, dd, *J* 13.4, 9.0, 7-C*H*$_2$), 1.65 (1H, d, *J* 16.0, 3-C*H*$_2$); **δ$_C$ NMR (151 MHz, DMSO-*d*$_6$)** 161.2 (d, *J* 241.3, *Ar*-F), 145.6 (Ar), 142.0 (d, *J* 3.0, *Ar*), 140.1 (*Ar*), 134.3 (*Ar*H), 133.2 (*Ar*H), 132.7 (*Ar*H), 131.0 (d, *J* 8.1, *Ar*H), 130.0 (*Ar*H), 128.4 (*Ar*H), 128.1 (*C*N), 114.7 (d, *J* 20.3, *Ar*H), 110.3 (Ar), 77.1 (2-*C*), 69.5 (5-*C*), 69.5 (6-*C*), 69.2 (1-*C*), 66.4 (4-*C*), 45.8 (O-*C*), 42.3 (N*Me*), 28.0 (7-*C*), 26.9 (3-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3018, 2967 (CH), 2940, 2896, 2227 (CN), 1507 (C=C), 1462, 1268 (S=O); **HRMS** (ESI): $C_{28}H_{28}FN_2O_3S$ [M+H$^+$]: calculated 491.1799, found 491.1798.

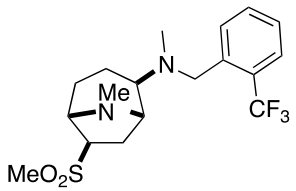
(1*S**,2*R**,5*S**,6*R**)-8-Methyl-6-(methylsulfonyl)-*N*-(4-(trifluoromethoxy)benzyl)-8-azabicyclo[3.2.1]octan-2-amine (**384**)



General procedure **W** was followed using ketone **176** (1.03 g, 4.74 mmol), titanium isopropoxide (1.4 mL, 9.48 mmol), (3-(trifluoromethoxy)phenyl)methanamine (3 mL, 19.0 mmol) and sodium borohydride (270 mg, 7.11 mmol, 1.5 eq.). Purification by automated reversed-phase flash chromatography eluting with MeCN/H_2O/1% formic acid gave *title compound* **384** (212 mg, 0.54 mmol, 11%) as a brown oil;

δ_H (600 MHz, DMSO-*d*$_6$): 7.60 – 7.56 (2H, m, Ar*H*), 7.29 (2H, d, *J* 8.3, Ar*H*), 4.01 (1H, d, *J* 13.9, NCH_2), 3.97 (1H, d, *J* 13.7, NCH_2), 3.82 (1H, t, *J* 8.2, 6-C*H*), 3.57 (1H, s, 5-C*H*), 3.48 – 3.43 (1H, m, 1-C*H*), 2.96 (3H, s, *Me*), 2.80 (1H, s, 2-C*H*), 2.33 – 2.23 (4H, m, *Me*, 7-CH_2) 2.00 – 1.93 (2H, m, 4-CH_2, 7-CH_2), 1.68 – 1.54 (2H, m, 3-CH_2), 1.36 (1H, d, *J* 12.9, 3.7, 4-CH_2); **δ_C (151 MHz, DMSO-*d*$_6$):** 165.9 (*Ar*), 148.5 (*Ar*), 131.7 (*Ar*H), 129.6 (O-*C*), 121.3 (*Ar*H), 66.1 (1-*C*), 65.1 (6-*C*), 63.4 (5-*C*), 56.0 (2-*C*), 48.4 (N-*C*), 41.9 (*Me*), 40.9 (*Me*), 28.9 (7-*C*), 28.4 (3-*C*), 19.3 (4-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3287 (NH), 3006 (CH), 2840, 2787, 1557 (C=C), 1510, 1343, 1149 (S=O); **HRMS** (ESI): $C_{17}H_{24}F_3N_2O_3$ [M+H$^+$]: calculated 393.1454, found 383.1462.

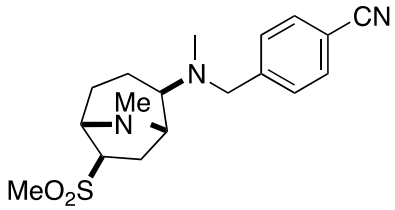
(1*S**,2*R**,5*S**,6*R**)-*N*,8-Dimethyl-6-(methylsulfonyl)-*N*-(2-(trifluoromethyl)benzyl)-8-azabicyclo[3.2.1]octan-2-amine (**386**)



General procedure **Z** was followed using compound **324** (142 mg, 0.7 mmol) in DMF (1.6 mL), $NaHCO_3$ (302 mg, 3.62 mmol, 6.0 eq.) and 2-(trifluoromethyl)benzyl bromide (574 mg, 2.4 mmol, 4.0 eq.). The reaction mixture was concentrated *in vacuo* and purification by automated reversed-phase flash chromatography eluting with MeCN/H_2O 1% formic acid

gave the *title compound* **386** (25 mg, 0.06 mmol, 9%) as a brown solid; **δ_H (300 MHz, DMSO-*d*$_6$):** 7.87 (1H, d, *J* 8.1, Ar*H*), 7.66 (2H, td, *J* 5.9, 2.9, Ar*H*), 7.42 (1H, t, *J* 7.6, Ar*H*), 4.12 (1H, d, *J* 15.1, NCH_2), 3.82 (1H, t, *J* 8.3, 6-C*H*), 3.67 (1H, d, *J* 15.1, NCH_2), 3.58 (1H, s, 5-C*H*), 3.48 (1H, d, *J* 7.1, 1-C*H*), 2.98 (3H, s, *Me*), 2.41 (1H, t, *J* 2.4, 2-C*H*), 2.34 (1H, dd, *J* 13.8, 7.0, 7-CH_2), 2.26 (3H, s, *Me*), 2.22 (3H, s, *Me*), 1.88 (1H, dd, *J* 13.6, 9.2, 7-CH_2), 1.69 – 1.59 (2H, m, 3-CH_2), 1.51 – 1.41 (2H, m, 4-CH_2); **δ_C (126 MHz, Methanol-*d*$_4$):** 139.7 (*Ar*H), 131.8 (*Ar*H), 130.1 (*Ar*H), 127.9 (*Ar*), 127.8 (*Ar*), 126.4 (*Ar*H), 125.0 (d, *J* 5.9, CF_3), 66.2 (6-*C*), 63.1 (1-*C*), 62.6 (5-*C*), 40.5 (*Me*), 39.4 (*Me*), 39.1 (*Me*), 30.3 (7-*C*), 29.4 (3-*C*), 18.0 (4-*C*); **IR** ν_{max} (neat)/cm^{-1}: 2999(CH), 2939, 2909, 1559, 1497 (C=C), 1464, 1214 (S=O), 1154; **HRMS** (ESI): $C_{18}H_{26}F_3N_2O_2S$ [M+H$^+$]: calculated 391.1662, found 391.1671.

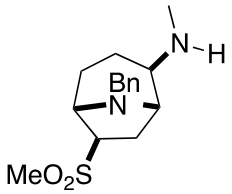
4-((methyl((1*S**,2*R**,5*S**,6*R**)-8-Methyl-6-(methylsulfonyl)-8-azabicyclo[3.2.1]octan-2-yl)amino)methyl)benzonitrile (**387**)



General procedure Z was followed using compound **324** (76 mg, 0.33 mmol) in DMF (1.6 mL), $NaHCO_3$ (165 mg, 1.98 mmol, 6.0 eq.), and 4-(bromomethyl)benzonitrile (258 mg, 1.32 mmol, 4.0 eq.). The reaction mixture was concentrated *in vacuo* and purification by automated reversed-phase flash chromatography eluting with MeCN/H_2O 1% formic acid gave the *title compound* **387** (52 mg, 0.15 mmol, 20%) as a brown solid.

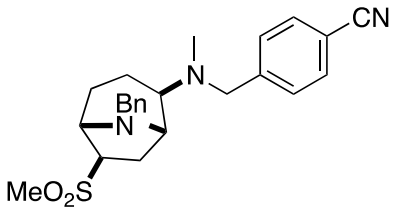
δ_H (501 MHz, DMSO-*d*$_6$): 7.77 (2H, d, *J* 8.2, Ar*H*), 7.52 (2H, d, *J* 8.2, Ar*H*), 4.05 (1H, d, *J* 14.6, NCH_2), 3.82 (1H, t, *J* 8.3, 6-C*H*), 3.61 – 3.55 (2H, m, NCH_2, 5-C*H*), 3.48 (1H, d, *J* 7.2, 1-C*H*), 2.99 (3H, s, *Me*), 2.40 – 2.36 (1H, m, 2-C*H*), 2.36 – 2.29 (1H, m, 7-CH_2), 2.27 (3H, s, *Me*), 2.19 (3H, s, *Me*), 2.03 – 1.93 (1H, m, 4-CH_2), 1.88 (1H, dd, *J* 13.5, 9.2, 7-CH_2), 1.70 – 1.61 (2H, m, 3-CH_2), 1.48 – 1.42 (1H, m, 4-CH_2); **δ_C (126 MHz, DMSO-*d*$_6$):** 147.7 (*Ar*), 132.6 (*Ar*H), 129.5 (*Ar*H), 119.5 (*Ar*), 109.7 (*C*N), 66.6 (6-*C*), 66.3 (1-*C*), 62.8 (2-*C*), 61.9 (5-*C*), 58.7 (*Me*), 41.5 (*Me*), 40.7 (*Me*), 40.7 (*C*H_2), 30.9 (7-*C*), 29.8 (3-*C*), 18.4 (4-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3097 (CH), 3006, 2975, 2932, 2889, 2280 (CN), 1558 (C=C), 1308 (S=O); **HRMS** (ESI): $C_{18}H_{26}N_3O_2S$ [M+H$^+$]: calculated 348.1740, found 348.1784.

(1*S**,2*R**,5*S**,6*R**)-8-Benzyl-*N*-methyl-6-(methylsulfonyl)-8-azabicyclo[3.2.1]octan-2-amine (**325)**



General procedure **W** was followed using ketone **175** (383 mg, 1.3 mmol), titanium isopropoxide (373 μL, 2.6 mmol, 2.0 eq.), methylamine (2M in MeOH) (20 mL, 20 mmol) and sodium borohydride (99 mg, 2.6 mmol, 2.0 eq.). Purification by automated reversed-phase flash chromatography eluting with MeCN/H_2O/1% formic acid gave *title compound* **325** (375 mg, 1.22 mmol , 94%) as a brown oil; **δ_H (400 MHz, Chloroform-*d*):** 7.30 – 7.25 (2H, m, Ar*H*), 7.24 – 7.18 (2H, m, Ar*H*), 7.16 – 7.10 (1H, m, Ar*H*), 3.75 – 3.69 (2H, m, N*Bn*, 5-C*H*), 3.54 – 3.45 (2H, m, N*Bn*, 6-C*H*), 3.40 – 3.36 (1H, m, 1-C*H*), 2.45 (1H, dt, *J* 13.8, 7.0, 7-CH_2), 2.29 – 2.17 (1H, m, 2-C*H*), 2.03 (3H, s, *Me*), 1.98 – 1.88 (1H, m, 7-CH_2), 1.88 – 1.79 (1H, m, 4-CH_2), 1.59 (1H, dd, *J* 14.9, 5.5, 3-CH_2), 1.49 – 1.39 (1H, m, 3-CH_2), 1.37 – 1.28 (1H, m, 4-CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** 139.8 (*Ar*), 129.1 (*Ar*H), 128.2 (*Ar*H), 126.9 (*Ar*H), 66.9 (6-*C*), 63.5 (1-*C*), 61.4 (2-*C*), 58.0 (5-*C*), 57.4 (N-*C*), 40.5 (*Me*), 33.2 (*Me*), 29.8 (7-*C*), 29.5 (3-*C*), 21.7 (4-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3369 (NH), 3062, 3023 (CH), 2947, 2861, 1585 (C=C), 1453, 1290 (S=O); **HRMS** (ESI): $C_{16}H_{25}N_2O_2S$ [M+H$^+$]: calculated 309.1631, found 309.1634.

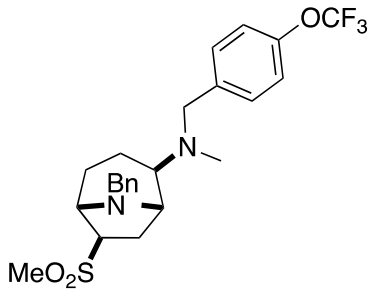
4-((((1*S**,2*R**,5*S**,6*R**)-8-Benzyl-6-(methylsulfonyl)-8-azabicyclo[3.2.1]octan-2-yl)(methyl)amino)methyl)benzonitrile (**392**)



General procedure **Z** was followed using compound **325** (125 mg, 0.41 mmol) in DMF (2 mL), $NaHCO_3$ (200 mg, 2.46 mmol, 6.0 eq.) and 4-(bromomethyl)benzonitrile (318 mg, 1.64 mmol, 4.0 eq.). The reaction mixture was concentrated *in vacuo* and purification by automated reversed-phase flash chromatography eluting with MeCN/H_2O/1% formic acid gave the *title compound* **392** (15 mg, 0.04 mmol, 9%) as a brown solid; **δ_H (400 MHz, DMSO-d_6):** 7.75 (2H, d, *J* 8.0, Ar*H*), 7.42 (2H, d, *J* 8.0, Ar*H*), 7.32 – 7.14 (5H, m, Ar*H*), 4.08 (1H, d, *J* 14.4, NCH_2),

3.88 (1H, t, *J* 8.4, 6-C*H*), 3.76 (1H, d, *J* 13.3, NCH_2), 3.66 (1H, d, *J* 7.0, 1-C*H*), 3.63 – 3.53 (3H, m, 5-C*H*, NCH_2, NCH_2), 3.00 (3H, s, *Me*), 2.48 – 2.44 (1H, m, 2-C*H*), 2.40 (1H, dd, *J* 13.9, 7.1, 7-CH_2), 2.14 (3H, s, *Me*), 2.03 – 1.87 (2H, m, 7-CH_2, 3-CH_2), 1.78 – 1.66 (2H, m, 3-CH_2, 4-CH_2), 1.52 – 1.41 (1H, m, 4-CH_2); **δ_C (126 MHz, MeOD):** 146.5 (*Ar*), 139.6 (*Ar*), 132.5 (*Ar*H), 129.5 (*Ar*H), 129.4 (*Ar*H), 128.5 (*Ar*H), 127.1 (*Ar*H), 118.5 (*C*N), 110.0 (*Ar*), 66.4 (6-*C*), 65.1 (1-*C*), 62.0 (2-*C*), 60.3 (5-*C*), 40.9 (*Me*), 40.7 (*Me*), 58.2 (N-*C*), 57.0 (N-*C*), 31.4 (7-*C*), 30.6 (3-*C*), 18.5 (4-C); **IR** ν_{max} (neat)/cm^{-1}: 3060, 3025, 2941 (CH), 2862, 2225 (CN) 1507 (C=C), 1472, 1290 (S=O); **HRMS** (ESI): $C_{24}H_{30}N_3O_2S$ [M+H$^+$]: calculated 424.2053, found 424.2061

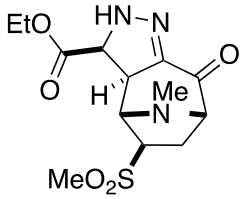
(1*S**,2*R**,5*S**,6*R**)-8-Benzyl-*N*-methyl-6-(methylsulfonyl)-*N*-(4-(trifluoromethoxy)benzyl)-8-azabicyclo[3.2.1]octan-2-amine (**393**)



General procedure **Z** was followed using compound **325** (125 mg, 0.41 mmol) in DMF (2 mL), $NaHCO_3$ (200 mg, 2.46 mmol, 6.0 eq.) and 4-(trifluoromethoxy)benzyl bromide (204 mg, 1.64 mmol, 4.0 eq.). The reaction mixture was concentrated *in vacuo* and purification by automated reversed-phase flash chromatography eluting with MeCN/H_2O/1% formic acid gave the *title compound* **393** (97 mg, 0.20 mmol, 49%) as a colourless solid.

δ_H (501 MHz, Chloroform-*d*) 7.40 – 7.37 (2H, m, Ar*H*), 7.35 – 7.27 (5H, m, Ar*H*), 7.17 (2H, d, *J* 8.1, Ar*H*), 4.03 (1H, d, *J* 13.4, NCH_2), 3.94 – 3.85 (3H, m, NCH_2, 5-C*H*, 6-C*H*), 3.73 (1H, d, *J* 13.1, NCH_2), 3.63 (1H, d, *J* 13.4, NCH_2), 3.55 (1H, t, *J* 8.3, 6-C*H*), 2.94 (3H, s, *Me*), 2.75 (1H, d, *J* 7.0, 5-C*H*), 2.68 – 2.60 (1H, m, 1-C*H*), 2.35 (3H, s, *Me*), 2.21 – 2.11 (1H, m, 4-CH_2), 2.11 – 2.00 (2H, m, 3-CH_2, 7-CH_2), 1.87 – 1.72 (1H, m, 3-CH_2), 1.68 – 1.57 (1H, m, 4-CH_2); **δ_C (126 MHz, Chloroform-*d*)** ; 148.6 (*Ar*), 148.6 (*Ar*), 139.1 (*Ar*), 135.9 (O-*C*), 130.6 (*Ar*H), 129.6 (*Ar*H), 128.4 (*Ar*H), 127.3 (*Ar*H), 120.9 (*Ar*H), 67.4 (1-*C*), 63.1 (6-*C*), 61.6 (5-*C*), 60.8 (2-*C*), 57.4 (N-*C*), 57.3 (N-*C*), 40.6 (*Me*), 39.0 (*Me*), 31.2 (7-*C*), 30.8 (3-*C*), 18.5 (4-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3012, 2999 (CH), 2965, 2891, 2201 (CN), 1558 (C=C), 1447, 1281 (S=O); **HRMS** (ESI): $C_{24}H_{30}F_3N_2O_3S$ [M+H$^+$]: calculated 483.1924, found 483.1948

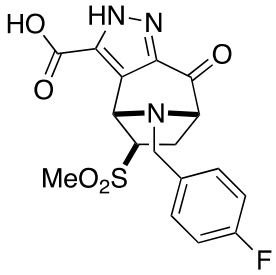
(3*S**,3a*S**,4*S**,5*R**,7*S**)-Ethyl 9-methyl-5-(methylsulfonyl)-8-oxo-2,3,3a,4,5,6,7,8-octahydro-4,7-epiminocyclohepta[*c*]pyrazole-3-carboxylate (**356**)



General procedure **M** was followed using cycloadduct **116** (1.35 g, 6.27 mmol) and ethyl diazoacetate (contains ≥ 13 wt. % DCM) (1.8 mL, 15.68 mmol, 2.5 eq.) in THF (30 mL). The reaction mixture was concentrated *in vacuo* and purification by automated reversed-phase flash chromatography eluting with MeCN/H_2O/1% formic acid gave the *title compound* **356** (1.74 g, 5.29 mmol, 84%) as a colourless oil;

δ_H (501 MHz, Chloroform-*d*): 6.81 (1H, s, N*H*), 4.73 (1H, s, 4-C*H*), 4.32 – 4.23 (2H, m, O*Et*), 4.12 (1H, d, *J* 11.3, 3-C*H*), 3.59 (1H, d, *J* 11.5, 5-C*H*), 3.54 – 3.45 (2H, m, 7-C*H*, 3a-C*H*), 2.93 (3H, s, *Me*), 2.67 (1H, dt, *J* 14.7, 7.1, 6-CH_2), 2.43 (3H, s, *Me*), 2.26 (1H, dd, *J* 14.7, 9.4, 6-CH_2), 1.31 (3H, t, *J* 7.1, O*Et*); **δ_c** (126 MHz, **Chloroform-*d*)**: 203.1 (*C*=O), 161.9 (*C*=O), 142.7 (*C*), 70.0 (5-*C*), 67.9 (7-*C*), 63.4 (3-*C*), 61.6 (OCH_2), 61.1 (4-*C*), 53.4 (3a-*C*), 39.7 (*Me*), 38.4 (SO_2*Me*), 27.8 (6-*C*H_2), 14.2(*C*H_3); **IR** ν_{max} (neat)/cm^{-1}: 3329 (NH), 3010 (CH), 2982, 2940, 1684 (C=O), 1497 (C=C), 1436, 1272 (S=O); **HRMS** (ESI): $C_{13}H_{20}N_3O_5S$ [M+H^+]: calculated 330.1118, found 330.1122.

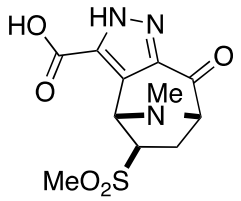
(4*S**,5*R**,7*S**)-9-(4-Fluorobenzyl)-5-(methylsulfonyl)-8-oxo-2,4,5,6,7,8-hexahydro-4,7-epiminocyclohepta[*c*]pyrazole-3-carboxylic acid (**359**)



General procedure **M** was followed using cycloadduct **136** (200 mg, 0.64 mmol) and ethyl diazoacetate (contains ≥ 13 wt. % DCM) (185 μL, 1.6 mmol, 2.5 eq.) in THF (3.2 mL). The reaction mixture was filtered through silica and the crude material taken to the next step.

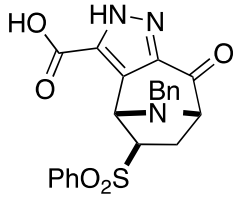
General procedure **N** was then followed using compound x, NaOH (2M) (10 mL) and MeOH (5 mL). The reaction mixture was concentrated *in vacuo* and purification by automated reversed-phase flash chromatography eluting with MeCN/H_2O/1% formic acid gave the *title compound* **359** (21 mg, 0.05 mmol, 8%) as a brown solid; **δ_H (400 MHz, DMSO-*d*$_6$):** 7.33 – 7.17 (2H, m, Ar*H*), 7.14 – 7.08 (2H, m, Ar*H*), 4.98 (1H, s, 4-C*H*), 3.74 – 3.60 (4H, m, 7-C*H*, 5-C*H*, N*Bn*), 3.00 (3H, s, *Me*), 2.76 (1H, ddd, *J* 14.6, 8.1, 4.2, 6-CH_2), 2.09 (1H, dd, *J* 14.6, 9.7, 6-CH_2); **δ_C (101 MHz, DMSO-*d*$_6$):** 163.5 (*C*=O), 161.8 (d, *J* 242.5, *Ar*F), 134.4 (d, *J* 2.9, *Ar*), 130.7 (d, *J* 7.9, *Ar*), 115.5 (d, *J* 21.2, *Ar*), 67.6 (5-*C*), 66.6 (7-*C*), 56.6 (4-*C*), 50.4 (N*Bn*), 40.9 (*Me*), 26.9 (6-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3322 (NH), 3011 (CH), 2983, 2955, 1717 (C=O), 1616 (C=C), 1457, 1297 (S=O); **HRMS** (ESI): $C_{17}H_{17}FN_3O_5S$ [M+H$^+$]: calculated 394.0867, found 394.0869.

(4*S**,5*R**,7*S**)-9-Methyl-5-(methylsulfonyl)-8-oxo-2,4,5,6,7,8-hexahydro-4,7-epiminocyclohepta[*c*]pyrazole-3-carboxylic acid (**357**)



General procedure **M** was followed using cycloadduct **116** (1.35 g, 6.27 mmol) and ethyl diazoacetate (contains ≥ 13 wt. % DCM) (1.8 mL, 15.68 mmol, 2.5 eq.) in THF (30 mL). The reaction mixture was filtered through silica and the crude material taken to the next step. General procedure **N** was followed using intermediate compound, NaOH (4M) (15 mL) and MeOH (10 mL). The reaction mixture was concentrated *in vacuo* and purification by automated reversed-phase flash chromatography eluting with MeCN/H_2O/1% formic acid gave the *title compound* **357** (64 mg, 0.21 mmol, 3%) as a colourless oil; **δ_H (400 MHz**, **Chloroform-*d*)**: 8.13 (1H, O*H*), 5.38 (1H, s, 4-C*H*), 4.12 – 4.03 (2H, m, 5-C*H*, 7-C*H*), 3.44 (3H, s, *Me*), 3.14 (1H, ddd, *J* 14.7, 8.1, 4.3, 6-CH_2), 2.70 (3H, s, *Me*), 2.46 (1H, dd, *J* 14.7, 9.6, 6-CH_2); **δ_c (101 MHz, Chloroform-*d*):** 163.5 (*C*=O), 69.4 (5-*C*), 67.1 (7-*C*), 58.7 (4-*C*), 39.4 (*Me*), 34.5 (*Me*), 27.2 (6-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3293 (NH), 3003 (CH), 2919, 2845, 1698 (C=O), 1521, 1489 (C=C), 1297 (S=O); **LCMS** (ESI): $C_{11}H_{14}N_3O_5S$ [M+H$^+$]: calculated 300.0649, found 299.97.

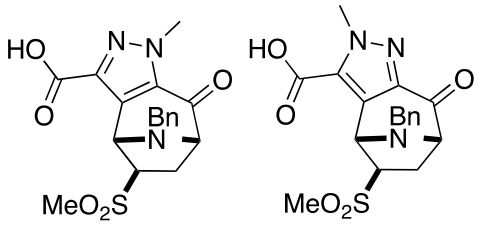
(4*S**,5*R**,7*S**)-9-Benzyl-8-oxo-5-(phenylsulfonyl)-2,4,5,6,7,8-hexahydro-4,7-epiminocyclohepta[*c*]pyrazole-3-carboxylic acid (**360**)



General procedure **M** was followed using cycloadduct **89** (3.14 g, 8.87 mmol) and ethyl diazoacetate (contains ≥ 13 wt. % DCM) (2.5 mL, 22.2 mmol, 2.5 eq.) in THF (45 mL). The reaction mixture was filtered through silica and the crude material taken to the next step. General procedure **N** was followed using intermediate compound, NaOH (8M) (20 mL) and MeOH (20 mL). The reaction mixture was concentrated *in vacuo* and purification by automated reversed-phase flash chromatography eluting with MeCN/H_2O/1% formic acid gave the *title compound* **360** (426 mg, 0.97 mmol, 11%) as a brown solid;

δ_H (400 MHz, DMSO-*d*$_6$): 7.88 (2H, d, *J* 7.7, Ar*H*), 7.75 (1H, t, *J* 7.7, Ar*H*), 7.62 (2H, t, *J* 7.7, Ar*H*), 7.31 – 7.16 (3H, m, Ar*H*), 7.06 – 6.99 (2H, m, Ar*H*), 4.94 (1H, s, 4-C*H*), 3.97 (1H, dd, *J* 9.3, 4.2, 7-C*H*), 3.66 – 3.57 (2H, m, N*Bn*, 5-C*H*), 3.49 (1H, d, *J* 13.8, N*Bn*), 2.79 (1H, ddd, *J* 14.5, 8.2, 4.2, 6-CH_2), 2.13 – 2.02 (1H, m, 6-CH_2), **δ_C (101 MHz, DMSO-*d*$_6$):** 161.4 (*C*=O), 161.4 (*C*=O), 136.5 (*Ar*), 135.8 (*Ar*), 132.3 (*Ar*H), 127.7 (*Ar*H), 126.8 (*Ar*H), 126.5 (*Ar*H), 126.4 (*Ar*), 126.4 (*Ar*H), 125.4 (*Ar*H), 116.3 (*Ar*), 65.6 (5-*C*), 65.6 (7-*C*), 54.4 (4-*C*), 49.0 (N*Bn*), 24.9 (6-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3448 (NH), 3063 (CH), 3004, 2949, 2845, 1700 (C=O), 1582 (C=C), 1304 (S=O); **HRMS** (ESI): $C_{22}H_{20}N_3O_5S$ [M+H$^+$]: calculated 438.1118, found 438.1135.

(4*S**,5*R**,7*S**)-9-Benzyl-1-methyl-5-(methylsulfonyl)-8-oxo-1,4,5,6,7,8-hexahydro-4,7-epiminocyclohepta[*c*]pyrazole-3-carboxylic acid (**362a**)
(4*S**,5*R**,7*S**)-9-Benzyl-2-methyl-5-(methylsulfonyl)-8-oxo-2,4,5,6,7,8-hexahydro-4,7-epiminocyclohepta[*c*]pyrazole-3-carboxylic acid (**362b)**



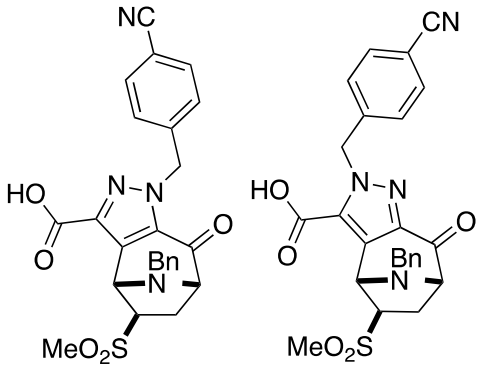
3:2 mixture of regioisomers

General procedure α was followed using pyrazole **170** (60 mg, 0.16 mmol), KOH (20 mg, 0.37 mmol, 2.3 eq.), MeI (13 μL, 0.21 mmol, 1.3 eq.) and DMF (0.8 mL). The reaction mixture was heated at 60 ^{o}C for 16 h. Purification by automated reversed-phase flash chromatography eluting with MeCN/H_2O/1% formic acid gave *title compound* **362** (52 mg, 0.13 mmol, 52%) as a colourless oil as a 3:2 mixture of reogioisomers.

δ_H (400 MHz, DMSO-*d*$_6$): 7.39 – 7.18 (10H, m, Ar*H*, Ar*H*$_{min}$), 5.02 (1H, s, 4-C*H*), 4.99 (1H, s, 4-C*H*$_{min}$), 4.21 (3H, s, *Me*$_{min}$), 4.14 (3H, s, *Me*), 3.74 – 3.61 (8H, m, NBn, 5-C*H*, 7-C*H*-, NBn$_{minor}$, 5-C*H*$_{minor}$, 7-C*H*$_{minor}$), 3.00 (3H, s, *Me*), 2.98 (3H, s, *Me*$_{min}$), 2.82 – 2.71 (2H, m, 6-C*H*$_{2}$-, 6-C*H*$_{2minor}$), 2.16 – 2.04 (2H, m, 6-C*H*$_2$, 6-C*H*$_{2minor}$); **δ_C** (101 MHz, **DMSO-*d*$_6$):** 193.1 (*C*=O-), 190.4 (*C*=O$_{minor}$), 162.6 (*C*=O-), 160.5 (*C*=O$_{minor}$), 142.2 (*Ar*$_{minor}$), 138.4 (*Ar*-), 138.1 (*Ar*$_{minor}$), 138.1 (*Ar*-), 134.1 (*Ar*-), 130.5 (*Ar*$_{minor}$), 129.2 (*Ar*$_{-\text{ and min}}$), 128.9 (*Ar*H$_{-\text{ and min}}$), 128.8 (*Ar*H$_{-\text{ and min}}$), 127.7 (*Ar*H$_{-\text{ and min}}$), 67.7 (7-*C*$_{min}$), 67.5 (7-*C*), 66.8 (5-*C*$_{min}$), 66.5 (5-*C*), 57.2 (4-*C*), 57.1 (4-*C*$_{min}$), 51.3 (N*Bn*$_{min}$), 51.1 (N*Bn*), 41.1 (*Me*$_{min}$), 40.9 (*Me*), 39.3 (*Me*), 39.2 (*Me*$_{min}$), 27.1 (6-*C*$_{min}$), 26.9 (6-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3032 (CH), 2978, 2904, 1639 (C=O), 1482 (C=C), 1420, 1270 (S=O), 1024; **HRMS** (ESI): $C_{18}H_{20}N_3O_5S$ [M+H$^+$]: calculated 390.1118, found 390.1135.

(4*S**,5*R**,7*S**)-9-Benzyl-1-(4-cyanobenzyl)-5-(methylsulfonyl)-8-oxo-1,4,5,6,7,8-hexahydro-4,7-epiminocyclohepta[*c*]pyrazole-3-carboxylic acid (**363a**)

(4*S**,5*R**,7*S**)-9-Benzyl-2-(4-cyanobenzyl)-5-(methylsulfonyl)-8-oxo-2,4,5,6,7,8-hexahydro-4,7-epiminocyclohepta[*c*]pyrazole-3-carboxylic acid (**363b**)



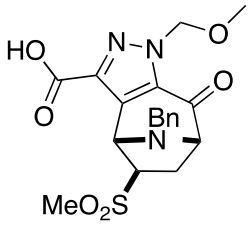
3:2 mixture of regioisomers

General procedure α was followed using pyrazole **170** (60 mg, 0.16 mmol), KOH (20 mg,0.37 mmol, 2.3 eq.), 4-(bromomethyl)benzonitrile (41 mg, 0.21 mmol, 1.3 eq.) and DMF (0.8 mL). Purification by automated reversed-phase flash chromatography eluting with MeCN/H_2O/1% formic acid gave *title compound* **363** (66 mg, 0.15 mmol, 41%) as a colourless oil as a 3:2 mixture of regioisomers.

δ_H (501 MHz, Chloroform-*d*): 7.57 (2H, d, *J* 8.2, Ar*H*), 7.53 (2H, d, *J* 8.2, ArH_{min}), 7.44 (2H, d, *J* 8.2, ArH_{min}), 7.39 (2H, d, *J* 8.1, Ar*H*), 7.24 – 7.13 (6H, m, Ar$H_{\text{and min}}$), 7.04 (2H, dd, *J* 6.8, 1.7, ArH_{min}), 7.02 – 6.95 (2H, m, Ar*H*), 5.92 – 5.80 (2H, m, NCH_{2minor}), 5.76 – 5.60 (2H, m, NC$H_{2\text{-}}$), 5.12 (2H, s, 4-C$H_{\text{and min}}$), 3.76 (1H, d, *J* 8.1, 5-CH_{min}), 3.69 (1H, d, *J* 8.0, 5-C*H*), 3.66 – 3.58 (2H, m, NBn_{minor}), 3.59 (1H, d, *J* 13.0, N$Bn_{\text{-}}$), 3.50 (1H, d, *J* 13.0, N$Bn_{\text{-}}$), 3.45 – 3.40 (1H, m, 7-CH), 3.37 (1H, dd, *J* 9.5, 3.8, 7-CH_{min}), 2.84 (3H, s, $Me_{\text{-}}$), 2.82 (3H, s, Me_{minor}), 2.74 – 2.66 (1H, m, 6-$CH_{2\text{-}}$), 2.66 – 2.60 (1H, m, 6-CH_{2minor}), 2.18 (1H, dd, *J* 15.4, 9.7, 6-CH_{2minor}), 2.10 – 2.00 (1H, m, 6-$CH_{2\text{-}}$); **δ_C (126 MHz, Chloroform-*d*)**: 192.5 (C=O), 189.4 (C=O $_{min}$), 163.2 (C=O), 163.1 (C=O $_{min}$), 143.0 (*Ar*), 140.7 (Ar_{min}), 139.9 (*Ar*), 136.6 (Ar_{min}), 136.2 (*Ar*), 133.6 (Ar_{min}), 132.8 (*Ar*H), 132.6 (*Ar*), 132.6 (*Ar*H$_{min}$), 131.2 (Ar_{min}),129.8 (*Ar*), 129.2 (*Ar*H$_{min}$), 129.1 (Ar_{min}), 128.9 (*Ar*H), 128.8 (*Ar*H$_{min}$), 128.8 (*Ar*H), 128.8 (*Ar*H$_{min}$), 128.7 (*Ar*H), 128.1 (*Ar*), 127.9 (Ar_{min}), 118.5 (Ar_{min}), 118.2 (*Ar*), 112.8 (*C*N$_{min}$), 112.2 (*C*N$_{min}$), 67.9 (7-C_{min}), 67.2 (7-C_{min}), 67.1 (5-*C*), 67.0 (5-*C*), 57.6 (4-C_{min}), 57.5 (4-*C*), 55.6 (NBn$_{min}$), 55.5 (NBn), 52.1 (NBn$_{min}$), 52.0 (NBn), 38.5 (Me-*C*), 38.2 (Me-C_{min}), 28.0 (6-C_{min}), 27.5 (6-*C*). **IR**

ν_{max} (neat)/cm^{-1}: 3061, 3029, 3019 (CH), 2945, 2361 (CN), 1761 (C=O), 1558 (C=C), 1257 (S=O); **HRMS** (ESI): $C_{25}H_{23}N_4O_5S$ [M+H$^+$]: calculated 491.1384, found 491.1390.

(4*S**,5*R**,7*S**)-9-Benzyl-1-(methoxymethyl)-5-(methylsulfonyl)-8-oxo-1,4,5,6,7,8-hexahydro-4,7-epiminocyclohepta[*c*]pyrazole-3-carboxylic acid (**364a**)

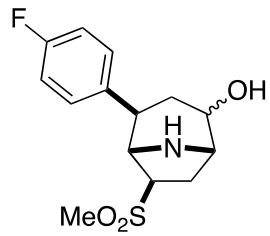
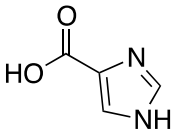
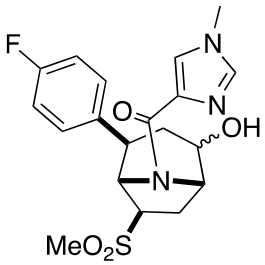
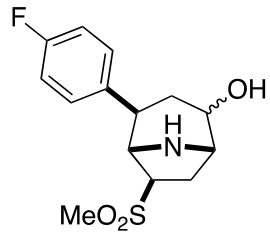
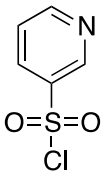
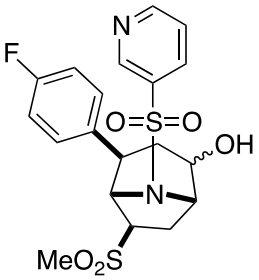
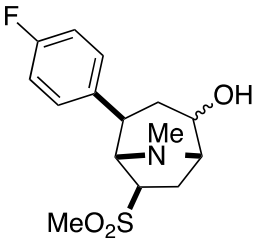
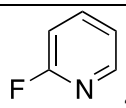
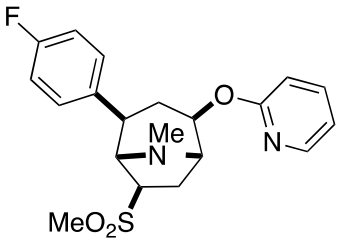
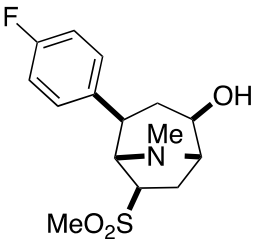
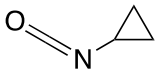
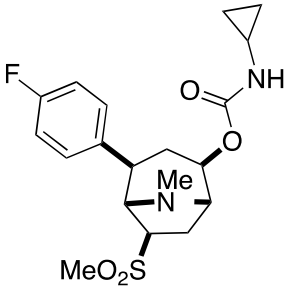


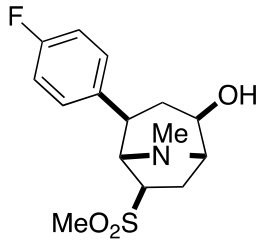
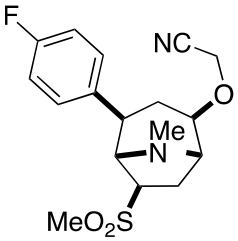
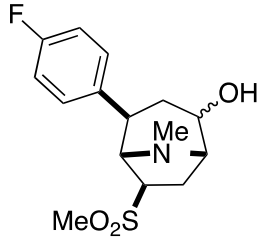
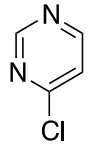
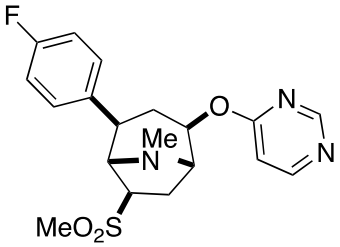
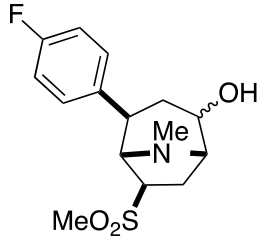
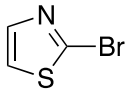
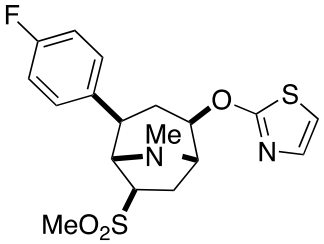
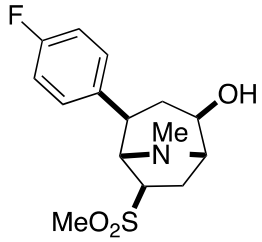
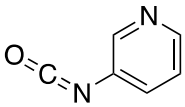
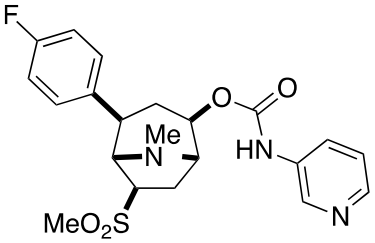
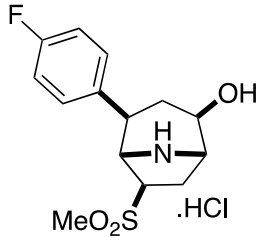
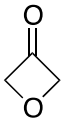
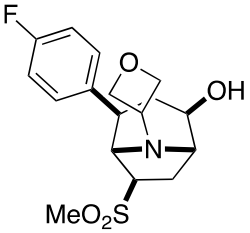
General procedure α was followed using pyrazole **170** (62 mg, 0.16 mmol), KOH (19 mg,0.37 mmol, 2.3 eq.), MOM-Cl (45 μL, 0.47 mmol, 3.0 eq.) and DMF (0.8 mL). Purification by automated reversed-phase flash chromatography eluting with MeCN/H_2O/1% formic acid gave *title compound* **364a** (22 mg, 0.05 mmol, 33%) as a colourless oil; **δ_H (501 MHz, Methanol-*d*$_4$):** 7.23 – 7.08 (5H, m, Ar*H*), 5.69 (1H, d, *J* 10.4, OC*H*$_2$), 5.63 (1H, d, *J* 10.4, OC*H*$_2$), 5.05 (1H, s, 4-C*H*), 3.74 – 3.66 (2H, m, N*Bn*, 5-C*H*), 3.64 – 3.58 (2H, m, 7-C*H*, N*Bn*), 3.30 (3H, s, *Me*), 2.95 – 2.90 (3H, m, *Me*), 2.78 (1H, ddd, *J* 14.9, 8.2, 4.3, 6-C*H*$_2$), 2.12 – 2.04 (1H, m, 6-C*H*$_2$); **δ_c (126 MHz, Methanol-*d*$_4$):** 189.7 (*C*=O), 163.0 (*C*=O), 140.7 (*Ar*), 137.2 (*Ar*), 129.3 (*Ar*), 128.5 (*Ar*H), 128.1 (*Ar*H), 127.2 (*Ar*H), 81.2 (*Me*), 67.6 (7-*C*), 66.3 (5-*C*), 57.1 (4-*C*), 56.2 (O*Bn*), 51.2 (N*Bn*), 38.3 (*Me*), 26.2 (6-*C*); **IR** ν_{max} (neat)/cm^{-1}: 3028, 3007 (CH), 2935, 2839, 1697 (C=O), 1508 (C=C), 1496, 1246 (S=O); **HRMS** (ESI): $C_{19}H_{22}N_3O_6S$ [M+H$^+$]: calculated 420.1224, found 420.1251.

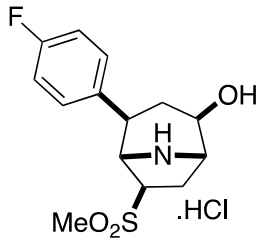
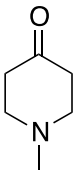
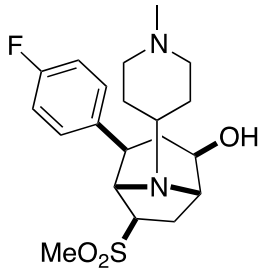
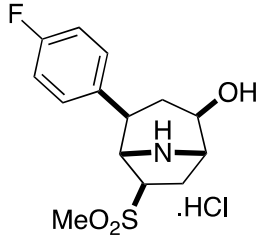
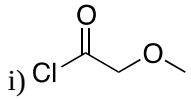
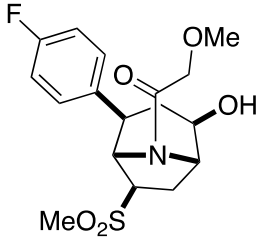
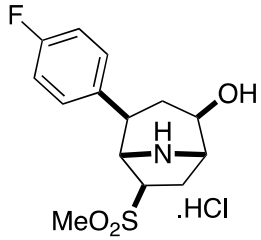
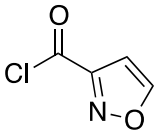
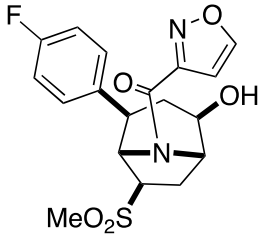
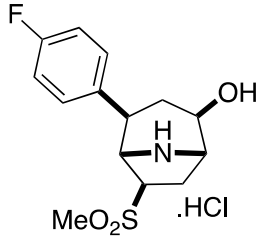
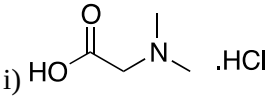
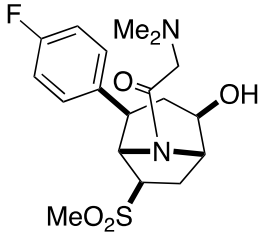
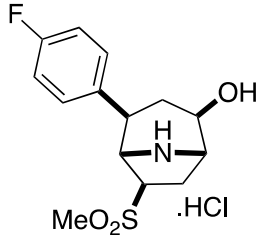
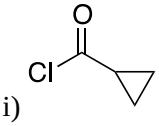
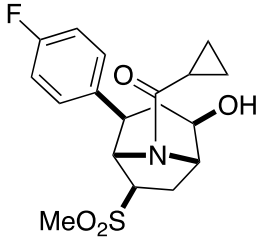
7.0 Appendix

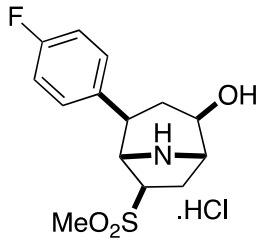
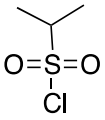
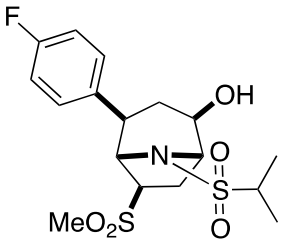
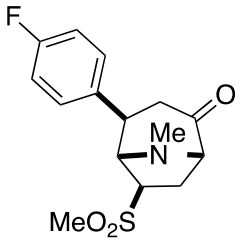
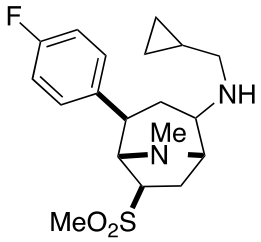
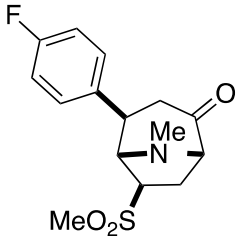
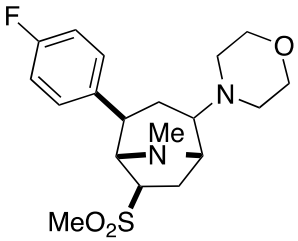
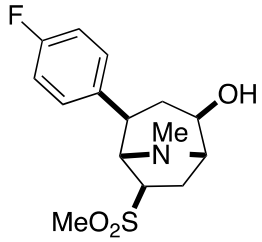
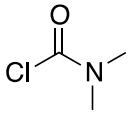
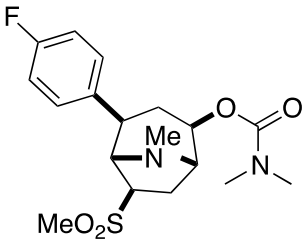
7.1 Listed decoration reactions

7.1.1 Listed decoration reactions for section 3.1.1

Starting material	Conditions	Product	Outcome
 **278**	 **404,** (2.0 eq.) TBTU (2.0 eq.) DIPEA (4.0 eq.) DMA, rt, 36h	 **405**	Complex mixture
 **282**	 **406,** (3.0 eq.) DMA (0.2M), $NaHCO_3$ (6 eq.) 16 h, 80 ^oC	 **407**	Complex mixture
 **278**	 **408** (2.0 eq.) NaH (1.5 eq.), DMF (0.5M), 0 ^oC - rt, 16 h	 **290**	Yield: **9%** Only major isolated
 **278a**	DMA (0.2M), $NaHCO_3$ (6 eq.) 16 h, rt  **409** (2.5 eq.)	 **410**	Trouble purifying

 **278a**	 **411** (3.0 eq.) NaH (1.5 eq.), DMF (0.5M), 0 - 50 °C , 16 h	 **412**	Complex mixture
 **278a**	 **413,** (2.0 eq.) NaH (1.5 eq.), DMF (0.5M), 0 °C - rt, 16 h	 **288**	Yield: **2%** Only major isolated
 **278a**	 **414** (2.0 eq.) NaH (1.5 eq.), DMF (0.5M), 0 °C - rt, 16 h	 **286**	Yield: **11%** Only major isolated
 **278a**	 **415** (2.5 eq.) DMA (0.2M), $NaHCO_3$ (6 eq.) 16 h, rt	 **291**	11%
 **282b**	 **416** (3 eq.) STAB (2 eq.) DMA (1.13M), 80 °C, 16 h	 **417**	Starting material

 **282b**	 **418** (3 eq.) Stab (2 eq.) DMA (1.13M), 80 °C, 16 h	 **419**	Purification problems
 **282b**	 **420** 6.0 eq.) DMA (0.15M) Pyridine (8.0 eq.), 16 h, rt ii) NaOH, H_2O, MeOH, 16 h, rt	 **289**	Yield: **1%**
 **282b**	 **421** (3.0 eq.) Pyiridne (4.0 eq.) DMA (0.15M), 16 h, rt	 **422**	Complex mixture
 **282b**	 **423** (3.0 eq.) DIPEA (6.0 eq.) TBTU (6.0 eq.) DMA (0.15M), 16 h, rt ii) NaOH, H_2O, MeOH, 16 h, rt	 **424**	Trouble purifying
 **282b**	 **425** (6 eq.) pyridine (4.0 eq.) DMA (0.15M), 16 h, rt ii) NaOH, H_2O, MeOH, 16 h, rt	 **285**	Yield: **16%**

 **282b**	 **426** (5.0 eq.) DMA (0.2M), DIPEA (5eq.) 80 °C, 16 h	 **427**	Complex mixture
 **273**	Cyclopropanemethyl amine $Ti(O^iPr)_4$ (2.0 eq.) MeOH (0.2M), 8 h, rt, 4Å MS (ii) $NaBH_4$ (1.5 eq.), 0 °C - rt, 4h	 **283**	2:1 mixture 18%
 **273**	1i) Morpholine (20 eq.), 4Å MS, AcOH (0.2 eq.), 16 h, rt ii) STAB (3 eq.), 0 °C - rt, 16 h 2i) Morpholine (20 eq.) $Ti(O^iPr)_4$ (2.0 eq.) MeOH (0.2M), 8 h (ii) $NaBH_4$ (1.5 eq.), 0 °C - rt, 4 h	 **428**	1) Starting material 2) Starting material and reduced alcohol compound
 **278a**	$NaHCO_3$ (6.0 eq.)  **429 ,** (8.0 eq.) Heat 80°C, 16 h	 **430**	Complex mixture

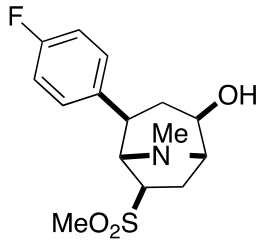
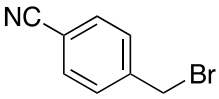
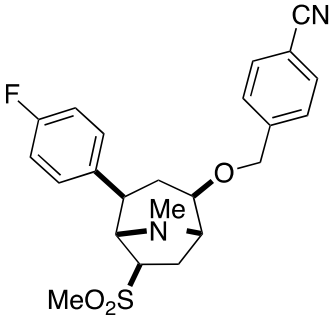
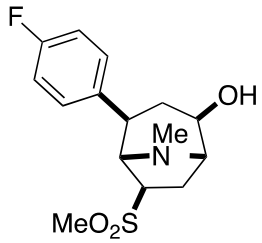
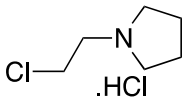
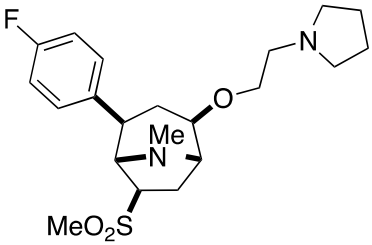
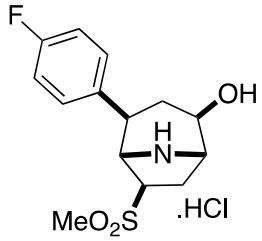
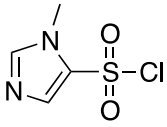
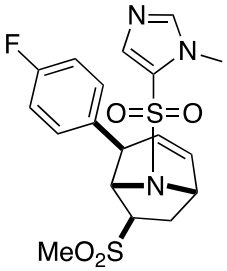
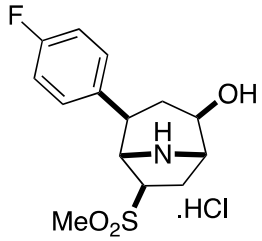
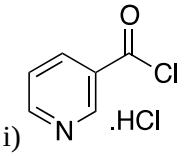
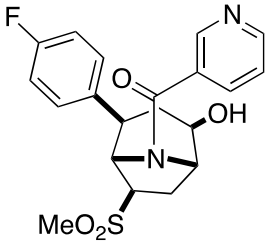
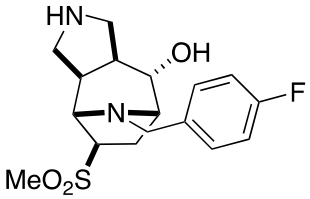
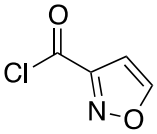
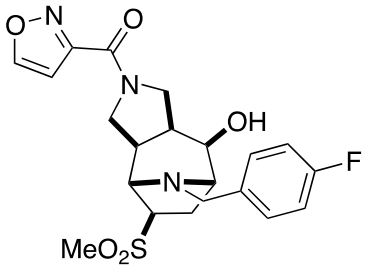
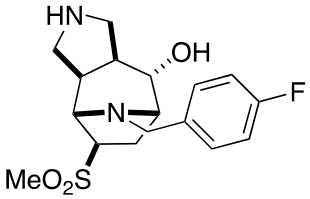
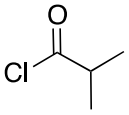
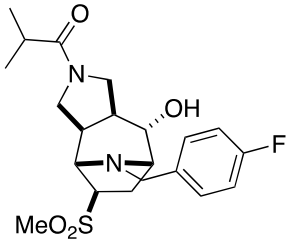
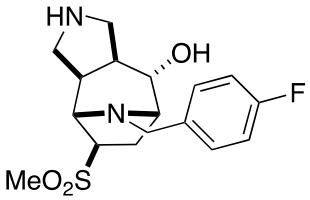
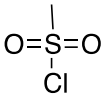
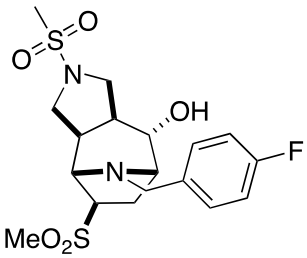
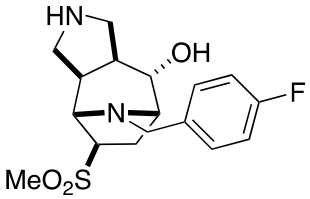
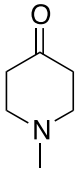
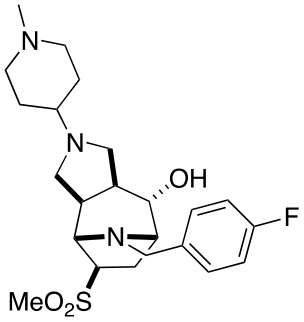
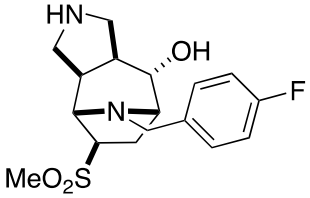
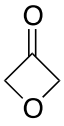
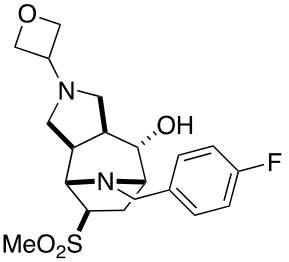
 **278a**	NaH (1.5 eq.) DMF (0.5 M), 0 °C  **373** (2.0 eq.), 16 h, rt	 **284**	12%
 **278a**	NaH (1.5 eq.)  **431** (2.0 eq.), 16 h, rt	 **432**	Complex mixture
 **282b**	 **433** (3.0 eq.) DMA (0.2M), pyridine (4 eq.) 16 h, 80°C	 **287**	6%
 **282b**	 i) **434** (10 eq.) Pyridine (4 eq.) DMA (0.15M), 16 h, rt ii) NaOH, H_2O, MeOH, 16 h, rt	 **435**	**Human error**

Table 40. A table showing the decoration reactions for the 1,4 addition series of compounds.

7.1.2 Listed decoration reactions for section 3.1.2

Starting material	Conditions	Product	Outcome

 **306**	 **421** (8.0 eq.) Pyiridne (4.0 eq.) DCM (0.2M), 16 h, rt ii) NaOH, H_2O, MeOH, 16 h, rt	 **436**	Complex mixture
 **306**	 i) **437** (8 eq.) Pyridine (4.0 eq.) DCM (0.2M), 16 h, rt ii) NaOH, H_2O, MeOH, 16 h, rt	 **310**	7%
 **306**	 **437** (8.0 eq.) DMA (0.2M), pyridine (4 eq.) 16 h, 80 °C	 **438**	Complex mixture
 **306**	 i) **418** (5 eq.) 4Å MS, DMF (1.15M), 16 h ii) $NaBH_4$ (3 eq.) 0 - 80 °C, 16 h	 **439**	Complex mixture
 **306**	 i) **416** (5 eq.) 4Å MS, DMF (1.15M), 16 h, rt ii) $NaBH_4$ (3 eq.) 0 - 80 °C, 16 h	 **309**	9%

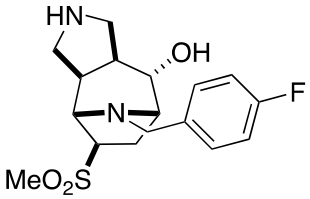
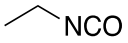
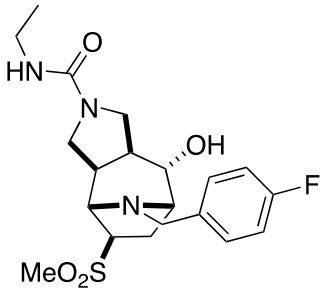
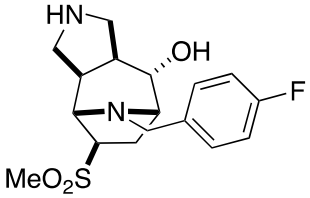
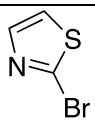
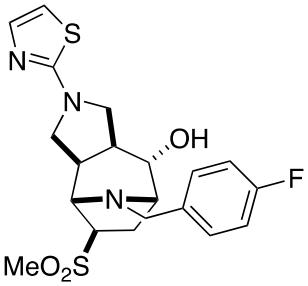
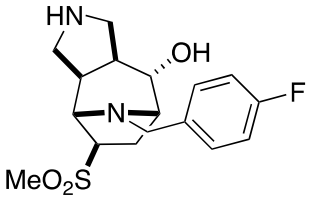
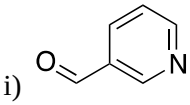
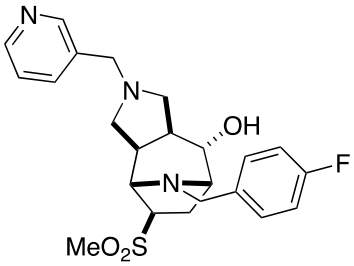
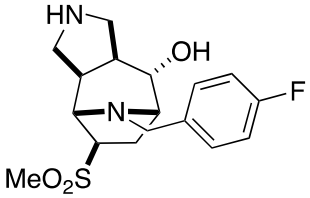
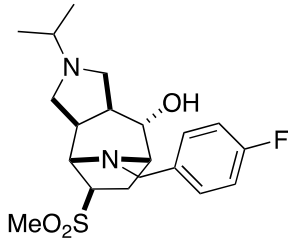
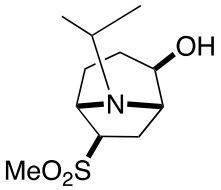
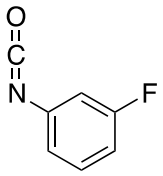
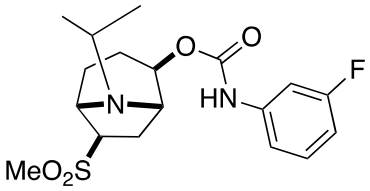
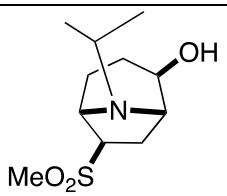
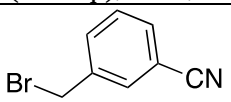
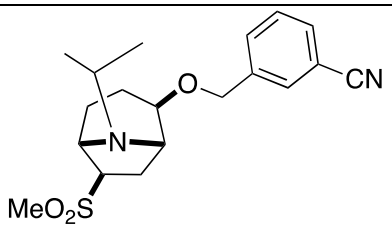
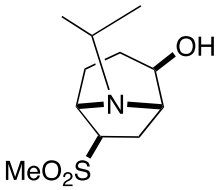
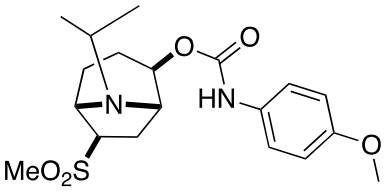
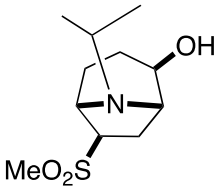
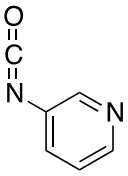
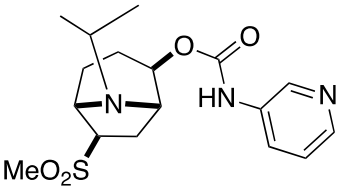
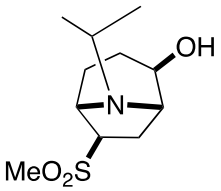
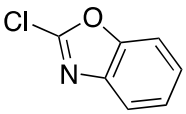
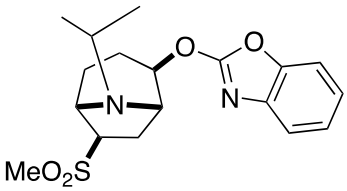
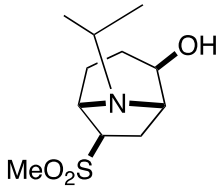
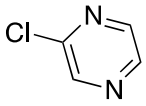
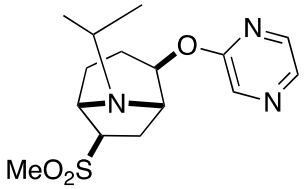
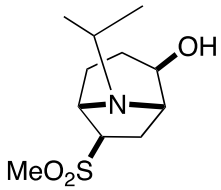
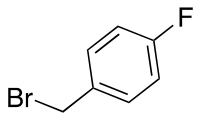
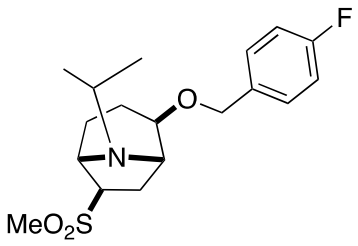
 **306**	 **440** (8.0 eq.) DMF (0.2M), DIPEA (4 eq.) 16 h, rt	 **441**	Complex mixture
 **306**	 **442** (1.5 eq.) at 0°C DMF (0.2M), DIPEA (1.5 eq.) 16 h, rt	 **311**	4%
 **306**	 i) **443** (5 eq.) 4Å MS, DMF (1.15M), ii) $NaBH_4$ (3 eq.) 0 - 80 °C, 16 h	 **312**	41%
 **306**	 **444** (10 eq.), 4Å MS, DMF (1.15M), ii) $NaBH_4$ (3 eq.) 0 - 80 °C, 16 h	 **308**	31%

Table 41. A table showing the decoration reactions for the pyrrolidine series of compounds

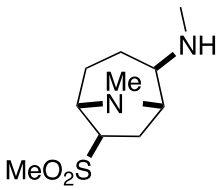
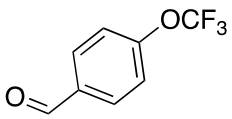
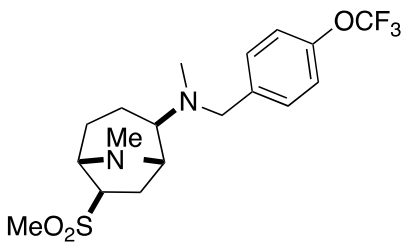
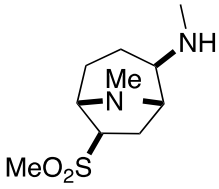
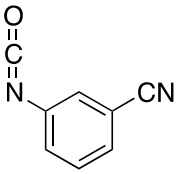
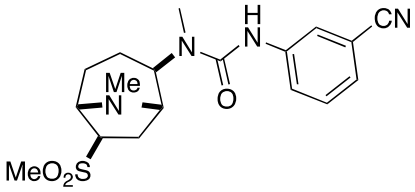
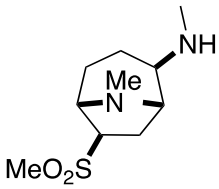
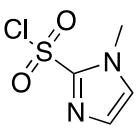
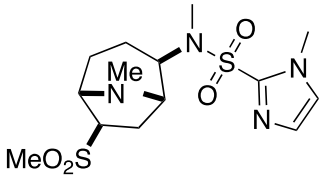
7.1.3 Listed decoration reactions for section 3.1.3

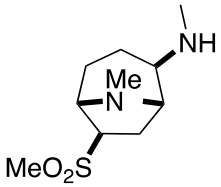
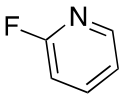
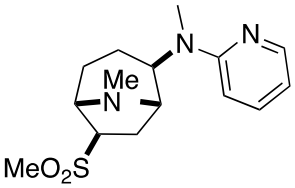
Starting material	Conditions	Product	Outcome

 **178**	 **445** (4.0 eq.) DMF (0.5M), NaH (4.0 eq.), 16 h, rt	 **314**	16%
 **178**	 **446** (4.0 eq.) DMF (0.5M), NaH (4.0 eq.), 16 h, rt	 **315**	10%
 **178**	 **447** (4.0 eq.) DMF (0.5M), NaH (4.0 eq.), 16 h, rt	 **316**	24%
 **178**	 **448** (4.0 eq.) DMF (0.5M), NaH (4.0 eq.)	 **317**	21%
 **178**	 **449** (4.0 eq.) DMF (0.5M), NaH (4.0 eq.), 16 h, rt	 **319**	7%

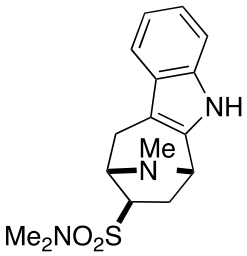
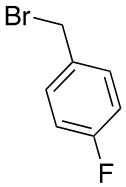
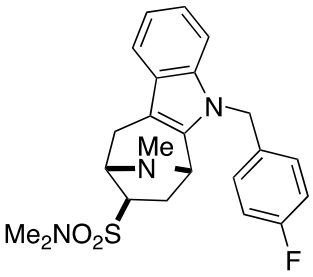
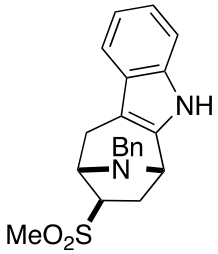
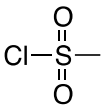
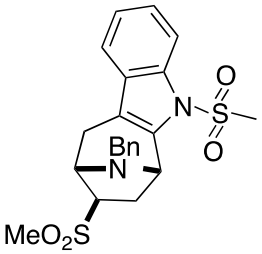
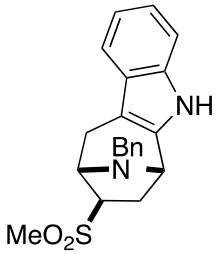
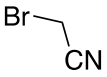
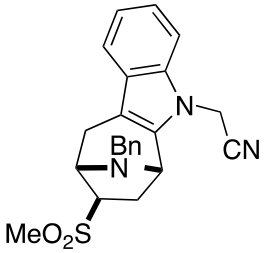
 **178**	 **450** (4.0 eq.) DMF (0.5M), NaH (4.0 eq.), 16 h, rt	 **320**	65%
 **178**	 **451** (4.0 eq.) DMF (0.5M), NaH (4.0 eq.), 16 h, rt	 **318**	16%

7.1.4 Listed decoration reactions for section 3.1.4

Starting material	Conditions	Product	Outcome
 **327**	 **452** (5.0 eq.) DMF (0.5M), $NaBH_4$ (3.0 eq.) 60 ^oC for 16 h		8%
 **327**	 **453** (4.0 eq.) DMF (0.5M), $NaHCO_3$ (6.0 eq.), 16 h	 **328**	35%
 **327**	 **433** (4.0 eq.), $NaHCO_3$ (6.0 eq.), DMF (0.5M), 16h	 **329**	21%

 **327**	 **408** (4.0 eq.), NaH (4.0 eq.) DMF (0.5M), 0 °C - rt	 **454**	Complex mixture

7.1.5 Listed decoration reactions for section 3.1.5

Starting material	Conditions	Product	Outcome
 **189**	 **451** (4.0 eq), NaH (1.5 eq.), DMF (0.5M), 0-60 °C, 16 h	 **455**	Complex mixture
 **188**	 **437** (6.0 eq), NaH (1.5 eq.), DMF (0.5M), 0-60 °C, 3 d	 **336**	11%
 **188**	 **411** (7.0 eq), NaH (1.5 eq.), DMF (0.5M), 0-90 °C, 3 d	 **337**	19%

7.2 Assay descriptions

7.2.1 Autophagy modulator assay description

MCF7-LC3 (4000 cells/ well) cells were seeded in 384 well plates (Greiner). The next day cells were washed three times with 1x PBS using plate washer ELX405 (Biotek). After that, 10 µM of compound was added using Echo dispenser (Labcyte) along with EBSS (starvation medium) and Chloroquine (50 µM) or Rapamycin (100 nM) and Chloroquine (50 µM). Three hours after incubation at 37°C cells were fixed by addition of 25 µl formaldehyde in 1 x PBS (4.6% final concentration) and simultaneously staining the nucleus with 1:500 Hoechst (Stock 1 mg/ml) for 20 min at RT. Fixed cells were washed thrice with 1x PBS using plate washer ELX405 (Biotek). For visualization 4 pictures/well were acquired using ImageXpress Micro XL (Molecular Devices) at 20x and analysed with the granularity algorithm of MetaXpress Software (Molecular Devices).

Dose-response analysis was carried out starting from 10 µM using a three-fold dilution curve over eight steps. IC50 calculations were done using Quattro Workflow software (Quattro Research GmbH).

7.2.2 Hedgehog pathway assay description

For assaying signal transduction through the Hh pathway, mouse embryonic mesoderm fibroblast C3H10T1/2 cells were used. These multipotent mesenchymal progenitor cells differentiate into osteoblasts upon treatment with the SMO agonist Purmorphamine. During differentiation osteoblast specific genes such as alkaline phosphatase (ALK), which plays an essential role in bone formation, are highly expressed. Activity of ALK can directly be monitored by following substrate hydrolysis yielding a highly luminescent product. Inhibition of the pathway results in reduction of luminescence.

The screening for small molecule inhibitors of the Hh pathway was carried out in 384 well format. Shortly, 800 cells per well were seeded and allowed to grow overnight. The next day, compounds were added to a final concentration of 10 µM using the acoustic nanoliter dispenser ECHO 520. After one hour, Purmorphamine was added to a final concentration of 1.5 µM; control cells did not receive Purmorphamine. After four days, the cell culture medium was aspirated and a commercial luminogenic ALK substrate (CDP-Star, Roche) was added. After one hour, luminescence was read. To identify and exclude toxic compounds that also lead to a reduction in the luminescent signal, cell viability measurements were carried out in parallel. The cell viability assay followed the same workflow as the HH assay, except that only 200

cells per well were seeded. Cell culture medium alone served as control for the cell viability assay. For the measurement of cell viability, Cell Titer Glo reagent (Promega) which determines the cellular ATP content was used. Hits were scored as showing at least a 50% reduction in the luminescent signal in the HH assay, and a minimum of 80% cell viability. Dose-response analysis for hit compounds was done using a three-fold dilution curve starting from 10 µM. IC_{50} values were calculated using the Quattro software suite (Quattro Research GmbH).

7.2.3 DNA binding motif assay description

The initial screen was done using 2 µM TO, 1 µM DAP and 250 µM fragment, in 10 mM sodium cacodylate at pH 7 (without KCl). Follow up screen was performed on the top 10 ligands (roughly ≥15% displacement within error), each screened hTeloG and DS: 2 µM TO, 1 µM DNA and 250 µM fragment in 10 mM sodium cacodylate with 100 mM KCl at pH 7. The repeated screen of the top 10 against DAP in 10 mM sodium cacodylate with 100 mM KCl at pH 7. Some of the fragments' interactions with the DAP i-motif were dramatically affected by the addition of the KCl.

FID ASSAY TO was diluted to 2 µM in buffer at pH 5.5 and hTeloC i-motif was diluted to 50 µM. The tested ligands were diluted to 50 µM in buffer at pH 5.5. 196 µL of the TO solution was excited at 430 nm and the background fluorescence recorded from 450 to 650 nm. The background fluorescence emission intensity at 450 nm was normalised as 0%. Then 4 µL of hTeloC was added, mixed, allowed to equilibrate for 5 minutes and a second background fluorescence spectrum was taken when the sample was excited at 430 nm. The fluorescence emission intensity at 450 nm was normalized as 100% fluorescence. Then 1 µL aliquots of ligand were titrated into the sample and a spectrum measured. TO displacement was calculated using Equation S1 and plotted against concentration to calculate the DC50.

Equation S1 $Dx = 1 - Fx\ F0 = 1 - Fread - Fc0\ Frefereence - Fc0$

The IM-FID assay was conducted using 384-well microplates (Corning® Low Volume 384 well Black Flat Bottom Polystryrene NBS TM Microplate) at 25°C. Microplate wells were

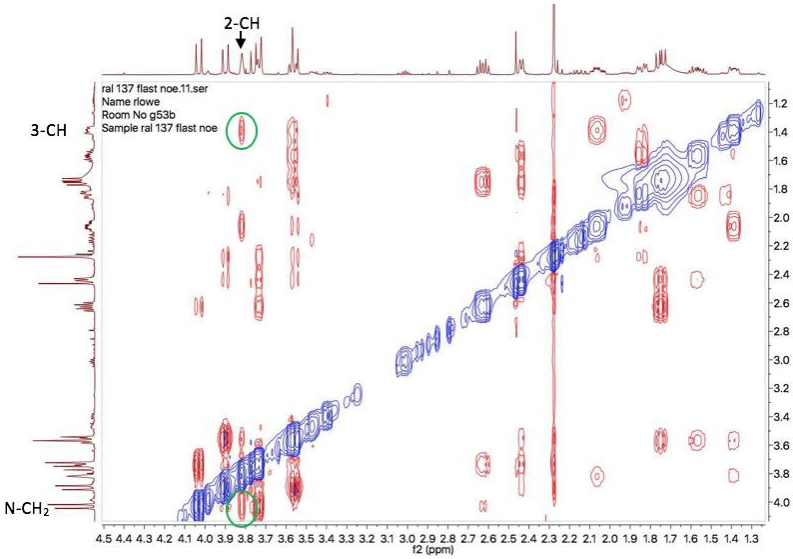
filled with 40 μL of a testing solution consisting of hTeloC (0.5 μM) and TO (1.0 μM) in buffer at pH 5.5. Then 0.5 μL of library compound solution (1 mM in DMSO) was added into each well. Each plate had three control wells of DNA in buffer and another three reference wells of DNA and TO in buffer without ligand. After mixing, plates were read on a BMG CLARIOstar using an excitation filter from 400 to 430 nm and an emission filter from 460 to 480 nm. Each scan was performed three times. The basal fluorescence signal (Fc0) were assigned as the average fluorescence intensity read from the control wells. The 100% fluorescence intensity read (Freference) was assigned as the average fluorescence intensity read from reference wells. The DC50 for each compound was calculated using the average of three reads (Fread) using Equation 1. Hit compounds were ranked according to DC50 (Supporting information).

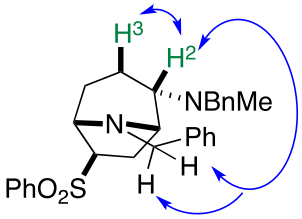
7.2.4 *Plasmodium falciparum* NF54 assay description

The compounds were tested in triplicate on two separate occasions against the drug-sensitive strain of *P. falciparum.* The assay was carried out using activity of the parasite lactate dehydrogenase enzyme as a marker for parasite activity and thus survival.[130] Compounds were tested at 10 different concentrations from a starting concentration of 6000nM down to approximately 12nM.[144] Conditions of the assay were 2% parasitized erythrocytes at a 1% overall haematocrit in a total volume of 200μL. Cells were incubated in a specialised gaseous environment for 72h at 37°C.[145] Three controls, comprising of compounds with known and significant anitplasmodial activity, were used to validate the experiment. The IC50-values were obtained using regression analysis of a non-linear dose-response curve fitted using GraphPad Prism v.4.0 software.

Of the 52 compounds tested, none showed significant activity against the human malaria parasite *in vitro*. For 48 of the compounds, no growth inhibition was observed at the highest starting concentration of 6000nM. The remaining 4 compounds were weakly active, with mean IC50 values from the two occasions of between 5μM and 6μM (highlighted in accompanying chart). In contrast, the reference compounds chloroquine, artesunate, and H3D-4060, all showed antiplasmodial activity between 5 and 35nM as expected.

7.3 Key NOESY interactions





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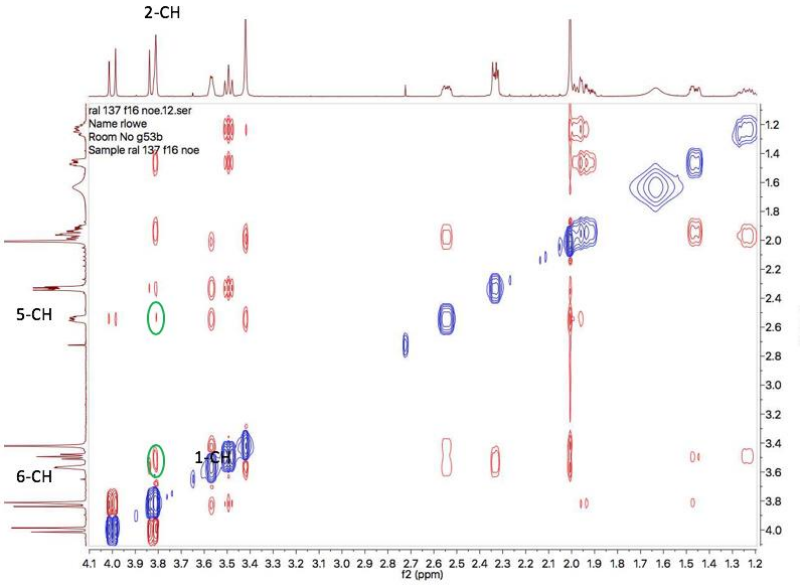

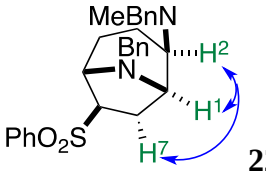

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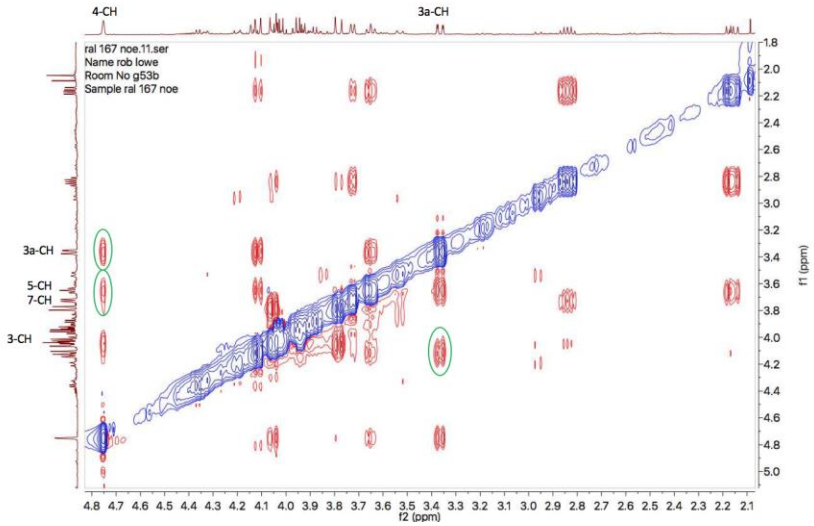
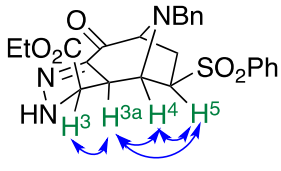
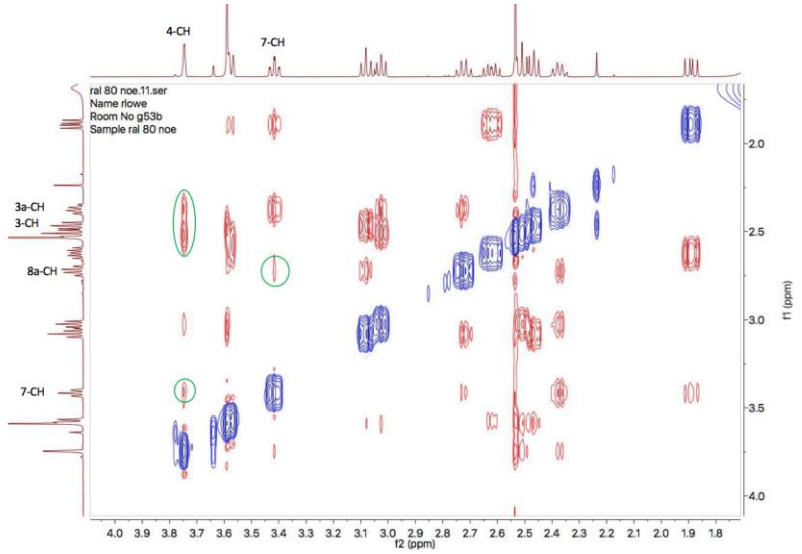




168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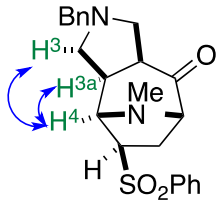
7-CH
ral 80 noe.11.ser
Name rlowe
Room No g53b
Sample ral 80 noe
3a-CH
3-CH
8a-CH
7-CH
f2 (ppm)
f1 (ppm)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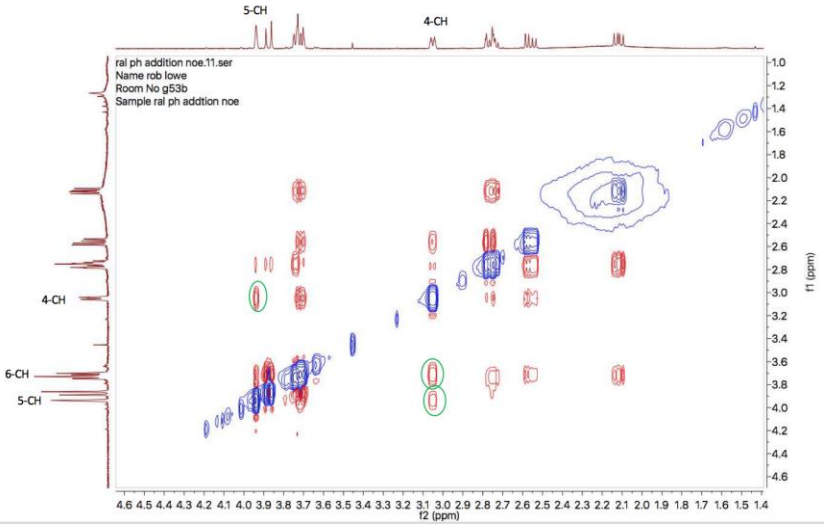
H3
O
H3a
Me
H4
N
H
SO2Ph

163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4-CH
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Sample ral ph addtion noe
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6-CH
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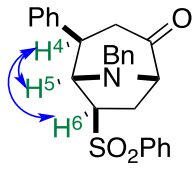
f2 (ppm)
f1 (ppm)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Bn
H5
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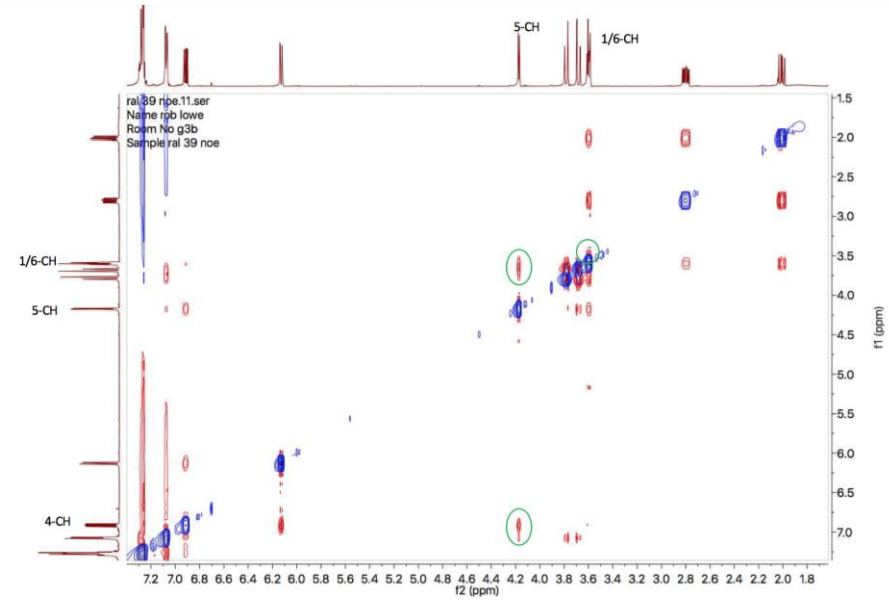
H6
SO2Ph

207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1/6-CH
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Sample ral 39 noe
1/6-CH
5-CH
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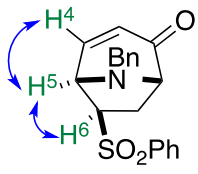
f2 (ppm)
f1 (ppm)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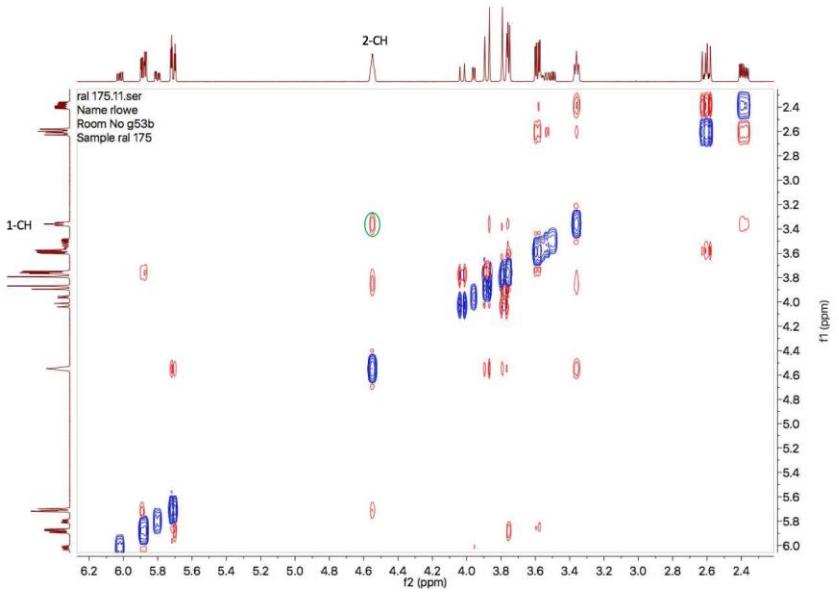
Bn
H5
N
H6
SO2Ph

89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1-CH
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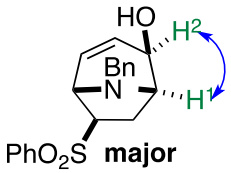
Name rlowe
Room No g53b
Sample ral 175
f1 (ppm)
f2 (ppm)


HO
H2
Bn
N
H1
PhO2S
major

228

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