Development and Application of Methods for the Synthesis of Lead-Like Scaffolds

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Submitted in accordance with the requirements for the degree of Doctor of Philosophy

The University of Leeds

School of Chemistry

July 2013

The candidate confirms that the work submitted is his own and that appropriate credit has been given where reference has been made to the work of others.

Acknowledgements

Firstly I would like to try and thank Adam, although the debt of gratitude I owe him I will probably be unable to convey in words. His mentorship was one of the major factors in not only joining his group as a potential MChem candidate, but why I stayed to embark on PhD studies. You have afforded me the freedom to follow my interests whilst helping me to work on weaknesses, ultimately making me more aware and rounded as a chemist. Thank you for everything.

Whilst on this project I have had the pleasure of working with two other exceptional people. I would like to thank Sri for his constant stream of ideas and support, especially when times were hard. I would like to thank Paul MacLellan for collaboration on this project. I think we made a pretty good team.

This project would not have been possible without funding and support from both the EPSRC and Astra Zeneca. I would also like to thank the technical support staff at Leeds, in particular Simon Barrett and Tanya Marinko-Covell. Special thanks also to Stuart Warriner for his support and enthusiasm right from my undergraduate days.

The Nelson group has changed significantly since I first joined. However, the enthusiasm and drive of the people who I have the pleasure to call colleagues has remained constant. I would like to thank Mark Dow in particular; not only for his constant encouragement in the laboratory, but for all times out of it as well. I would like to thank Richard Doveston, George Karageorgis, George Burslem and Giorgia Magnatti for making the working environment, and the pub, thoroughly stimulating and enjoyable.

Last, but by no means least, I would like to say thank you to my family and friends. Although they (mostly) have no idea what I do, they always offer me an alternative 'real world' perspective and have been an endless source of inspiration. I feel truly privileged to be surrounded by such a strong and supportive group of people.

Abstract

This thesis describes the development of novel methodology for the synthesis of diverse heterocycles with physicochemical properties desirable in early stage drug development. The methodology developed in this thesis aims to allow the systematic variation of molecular scaffold from readily available building blocks by using strategies utilising the chemoselective pairing of ambiphilic/ bifunctional building blocks.

Chapter 1 evaluates the requirement for lead-like compounds in early stages of drug development as well as summarising methods for the generation of diverse libraries of compounds. Chapter 2 describes the approaches taken towards the development of a modular approach to ketopiperazines, piperazines and related ring systems through the pairing of either amino acid or cyclic sulfamidate building blocks with amino alcohol derived building blocks. Key to this methodology was a 'hydroxy-activation' approach to induce cyclisation to generate heterocyclic scaffolds. Chapter 3 describes the synthesis of tetrahydropyrazine and related heterocycles through the pairing of cyclic sulfamidate and propargyl amine derived building blocks. Key to this approach was the transition metal–mediated cyclisation of unsaturated acyclic substrates to give unsaturated heterocycles. Furthermore, unsaturated heterocycles were used as substrates for further complexity–generating reactions to give saturated heterocycles. The potential ability of the methods described in both Chapter 2 and Chapter 3 to deliver lead-like heterocycles was illustrated by the *in silico* generation of virtual libraries of compounds from readily available materials and assessed according to calculated physicochemical properties.

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Abbreviations

°C	degrees Celsius
Å	Angstrom
Ac	acetyl
app.	apparent
Ar	aryl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Cbz	carboxybenzyl
cm	centimetre
COSY	correlation spectroscopy
Cp	cyclopentadienyl
Cp*	pentamethylcyclopentadienyl
d	doublet
dba	dibenzylideneacetone
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DCM	dichloromethane; CH_2Cl_2
dd	double doublet
ddd	double double doublet
DEAD	diethyl azodicarboxylate
DEPT	distortionless enhancement by polarization transfer
dioxane	1,4-dioxane
dm	decimeter
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-Dimethylformamide

DMSO	dimethylsulfoxide
DOS	diversity oriented synthesis
DPPA	diphenylphosphoryl azide
dr	diastereomeric ratio
E	*entgenen*; *trans*
ee	enantiomeric excess
eq.	equivalence
ESI	electrospray ionisation
Et	ethyl
et al.	*et alii*; and others
etc.	*et cetera*; and so forth
Ether	diethyl ether
FT	Fourier transform
g	grams
Ghosez's reagent	1-chloro-*N*,*N*-2-trimethyl-1-propenylamine
h	hour
HMBC	heteronuclear multiple bond correlation
HMQC	heteronuclear multiple quantum coherence
HRMS	high resolution mass spectrometry
HTS	high throughput screening
Hz	Hertz
in silico	performed by computer simulation
in situ	in place
in vacuo	in a vacuum

*i*Pr	*iso*-propyl
IPR	1,3-bis(2,6-diisopropylphenyl)-1,3-dihydro-2H-imidazol-2-ylidene
IR	Infrared
J	spin-spin coupling constant
LCMS	liquid chromatography mass spectrometry
LOS	lead oriented synthesis
m	multiple
mg	milligram
Me	methyl
MHz	megahertz
min	minute
mmol	milli mole
Ms	methylsulfonyl
*n*Bu	neobutyl
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
o-Ns	2-nitrobenzenesulfonyl
Petrol	petroleum ether
Ph	phenyl
PMB	4-methoxybenzyl
PMP	4-methoxyphenyl
p-Ns	4-nitrobenzenesulfonyl
ppm	parts per million
PTSA	4-toluene sulfonic acid

q	quartet
R_f	retention factor
RO5	Lipinski's rule of five
rt	room temperature
s	singlet
SCX	strong cation exchange
sept	septet
t	triplet
TBD	1,5,7-triazabicyclo[4.4.0]dec-5-ene
TBS	*tert*-butyldimethylsilyl
*t*Bu	*tert*-butyl
tert	tertiary
Tf	trifluoromethanesulfonyl
TFA	trifluoromethanesulfonic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TOF	time of flight
via	by way of
Z	*zusammen*, *cis*
d	chemical shift
ν	wavelength

Chapter 1: Introduction

The drug discovery process, and thus the pharmaceutical industry, remains hugely dependent upon the ability of synthetic organic chemistry to create new biologically active molecules. The evolution of synthetic chemistry over the past decades has facilitated the synthesis of molecules which were once considered to be an insurmountable challenge.[1] As such, it would be fair to expect that the advance in synthetic abilities would be mirrored by advancements in the productivity of the pharmaceutical industry. However, the number of new drugs reaching market has seen a dramatic decrease in the past five years.[2] Furthermore, it is estimated that 93-96% of potential clinical candidates fail to progress to market.[2] As such there is a huge demand for increasing the likelihood that a clinical candidate will progress to a marketable medicine during the drug discovery process.

1.1 Overview of the Drug Discovery Process

The process for the discovery of new biologically active molecules which aid in the treatment of clinical conditions (drugs) is interdisciplinary in nature. A summary of the key phases of the drug discovery process, highlighting the role of organic synthesis, is schematically shown in Figure **1**.[3] Chemical starting points in drug discovery are often found by screening compounds from small molecule libraries.[4] Compounds identified from initial screening approaches are commonly known as 'hit' compounds, which may be defined as compounds which have activity in both compound screening assays and more focussed assays.[3] The chemical libraries utilised in screening campaigns contain compounds from wide variety of sources, such as previous discovery campaigns, natural products, commercial libraries, etc.[5]

With initial hits identified from screening, a 'lead optimisation' process aims to improve the desirable characteristics of the hit compound to improve its drug-like profile.[6] This optimisation process is achieved by the synthesis of many analogues, typically to build up structure-activity relationships (SAR), to allow for a quantitative optimisation process.[7] Typically the methods used to generate the large numbers of analogues required, on limited time scales, are chemistries which have been proven to be robust and predictable. From the arrays of analogues, a single candidate molecule is eventually selected to be carried forward to the trial stages as a clinical candidate. The requirement for large, often multi-Kg, quantities of the clinical candidate molecule requires an optimised and robust synthetic route with the scope to deliver such quantities of product.

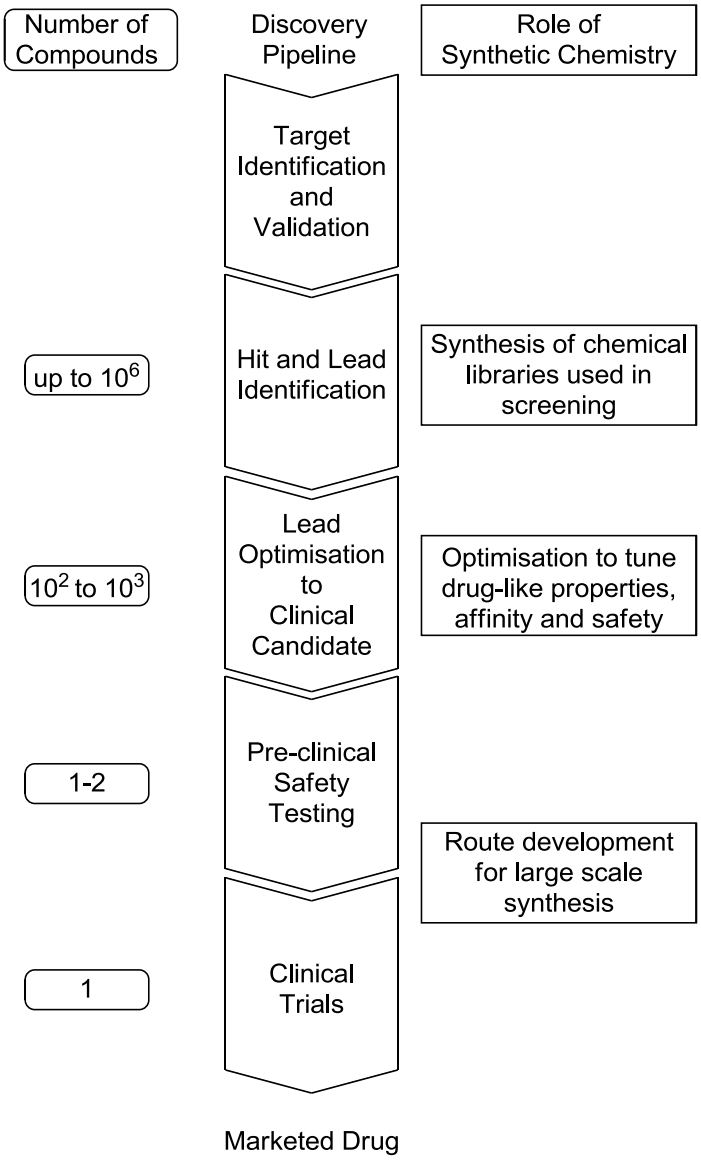
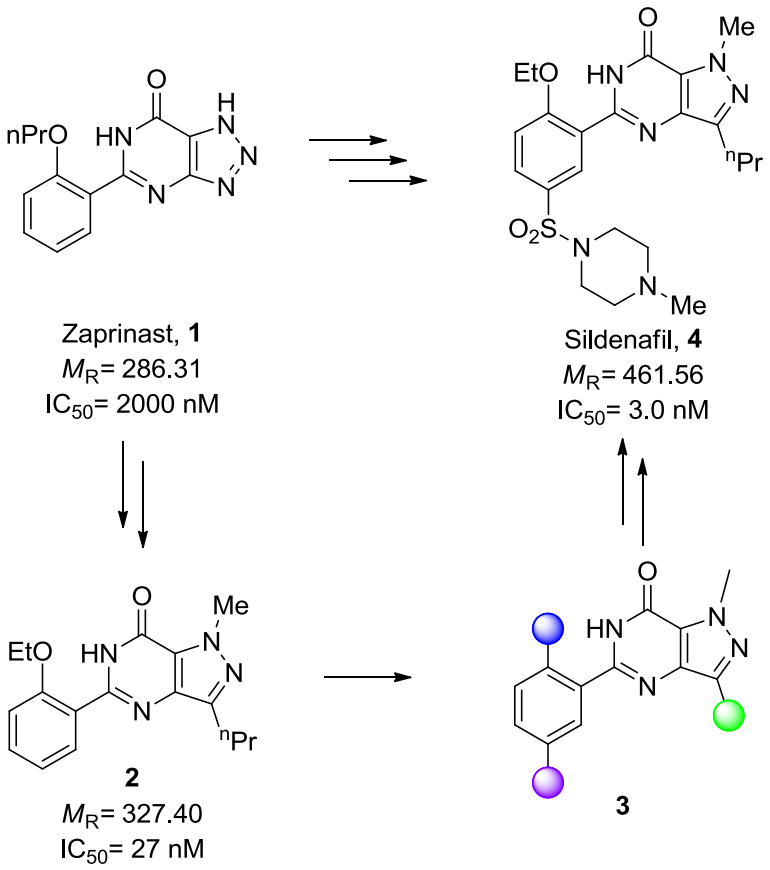


Figure **1**: The typical key phases of drug discovery. The requirements of the synthetic chemist (boxes) and typical numbers of compounds (rounded boxes) at each stages are shown.

An example of a classical discovery approach leading to the development of a blockbuster drug is illustrated by the Pfizer discovery of Sildenafil (Viagra) (Scheme **1**).[8] It was proposed that selective inhibition of phosphodiesterases (PDE) would be an attractive target for the Pfizer discovery group. It was suggested that a potent inhibitor of type 5 PDE would have therapeutic utility in the treatment of hypertension and angina. Prior to the Pfizer studies, Zaprinast (**1**), an anti-allergy agent, had been developed as a type-5 PDE inhibitor although it was only weakly active and a poorly selective compound. However, this compact, low molecular weight compound was taken as a start point (hit compound) for the development of novel type 5 PDE inhibitors. A wide range of 2-alkoxyphenyl-substituted heterocyclic systems were explored, leading to the identification of **2**, an active (IC_{50} 330 nM) PDE 5 inhibitor. Further scope for increasing both potency and selectivity

was explored by focussed structure–activity relationships (SAR) around the heterocyclic core (sites for intensive SAR activity shown as coloured balls in Scheme **1**, **3**). A key observation in these SAR studies was the requirement for co-planarity between the phenyl and heterocyclic systems, which was maintained by hydrogen bonding between the pyrimidinone NH and the 2-substituent on the phenyl group. *In silico* modelling approaches suggested that substituents positioned at the 5-position of the phenyl group would occupy the position normally occupied by phosphate residues of cGMP and as such, an array of bulky groups were screened. This optimisation led to the incorporation of the morpholine sulfonamide motif and subsequently the discovery of Sildenafil, **4**, a highly potent (IC_{50} 3.0 nM) and selective type-5 PDE inhibitor which remains as one of the top 50 highest selling drugs (sales of $1.93 billion in 2008).[9]



Scheme **1**: Summary of the development approach taken by Pfizer leading to the discovery of Sildenafil.

1.1.1 Identifying Hit and Lead Compounds

One of the most common approaches to the identification of hit compounds is that arising from high throughput screening (HTS).[4] Typically, large collections of compounds are screened against a biological target to identify small molecule ligands which are known as hit compounds. Thanks to huge advances in screening technology, HTS campaigns can

screen around 100 000 compounds per day, with total compound library sizes running into millions of compounds.[10] However, the question remains that although large numbers of compounds can be screened, are millions of compounds representative of drug–relevant chemical space?

Chemical space is the collection of all possible molecules.[11,12] The chemical space determined by molecules of molecular weight below 500 Da is populated by at least 10^{60} possible organic molecules. The combined efforts of synthetic chemistry over the last century has resulted in the production of over 60 million compounds (as collected by Chemical Abstracts Service),[13] a number that pales into insignificance when compared to chemical space relevant to drug discovery.

1.1.2 Screening Efficiency

It has been estimated that the addition of one extra heavy atom to an organic molecule leads to an increase in the number of potential structures by a factor of 10.[1] As such there are approximately 10^7 more molecules with a molecular weight of ≈400 than those with a molecular weight of ≈300. It thereby follows that a screening set of lower molecular weight compounds would cover a relatively greater proportion of chemical space, increasing the probability of identifying hit molecules.[14] This concept is easily illustrated by the comparison of carboxylic acid containing compounds held in GSK libraries with an estimation of the potential number of carboxylic acid–containing compounds (Chart **1**).[10]

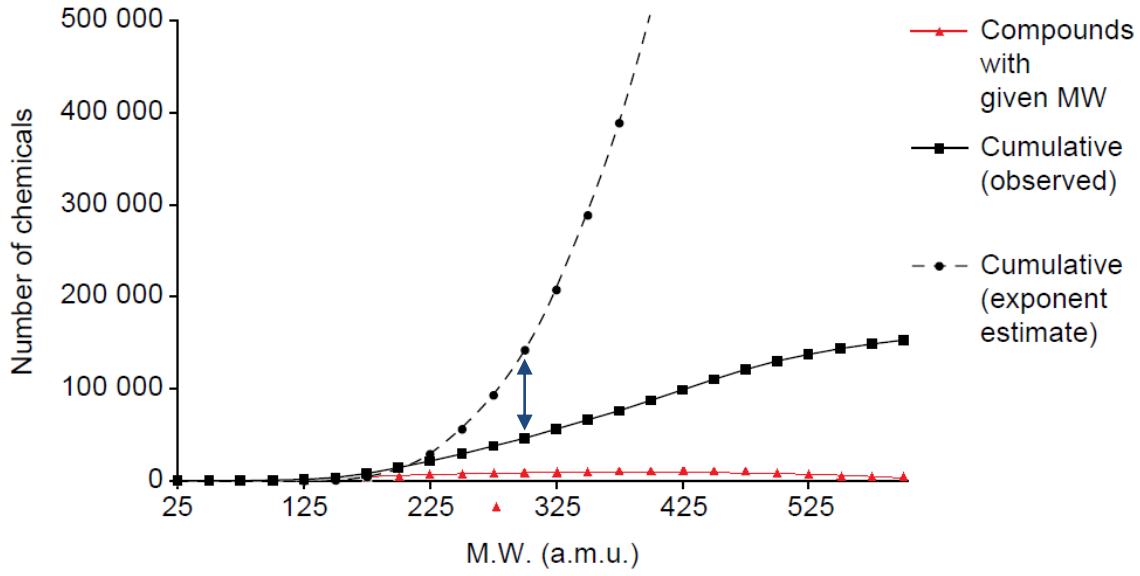


Chart **1**: Number of carboxylic acid–containing chemical entities plotted against molecular weight. The blue arrow shows increasing divergence between number of real compounds and exponential model above molecular weight~300. Plot adapted from Hann and Oprea.[10]

All carboxylic acid-containing compounds held in the GSK compound library were plotted against molecular weight (Chart 1, red triangles), as were the cumulative number of compounds (black squares). Also added was an exponential line as a model for the estimate of the total number of carboxylic acid–containing compounds as a function of molecular weight (black circles). The precise numbers are unknown but there may be 10^{10} carboxylic acid containing compounds with a molecular weight of less than 450 Da.[10] Comparing all three trends it is clear to see that at low molecular weights (MW < 225) both estimated and cumulative libraries have similar populations. However at increasing molecular weights (i.e. MW>225) there is an increasing disparity between observed library and estimated library population which dramatically diverges at MW~300 (blue arrow). This demonstrates that small compound libraries are much more representative of total possible compounds at low molecular weights and therefore screening of low molecular weight compounds is inherently more efficient and also, perhaps, more representative of chemical space as a whole.

The concept of screening low molecular weight entities has been pushed further in the area of fragment-based drug design.[15] This approach uses structure-guided rational design and sensitive biophysical techniques to identify and optimise small-molecules with molecular weight in the regions of 100-250 Da. With low molecular weight ligands as starting points further rational design approaches are employed to 'build up' the small molecule to increase binding affinity.

1.1.3 General Characteristics of Drugs and Lead-Like Compounds

There is a strong correlation between the molecular properties of clinical candidates and the likelihood of their successful progression through the development process to yield a marketed drug. [16,17,18,19] The link between physicochemical properties and drug-like characteristics has been known for some time. For example, Lipinski's description of orally available drug molecules suggests parameters that within which compounds are generally thought of as 'occupying drug-like chemical space'.[20] The Lipinski 'rule-of-five' (RO5) was devised by the analysis of physicochemical properties of over 2000 drugs and drug candidates in clinical trials. Analysis of these physicochemical properties revealed that a compound is more likely to be both membrane penetrable and readily adsorbed (key factors in oral bioavailability) if the properties match the preferred values outlined in Table **1**.

Drug-Likeness Guide	Preferred Values
Molecular weight	$M_R \leq 500$ Da.
Lipophilicity	log$P \leq 5$
No. H–Bond donors	≤5
No. H–Bond acceptors	≤10

Table **1**: Summary of Lipinski's description of orally available drug-like molecules.

Although these drug-like parameters are useful as general guidelines, the Lipinski RO5 is often taken out of context and there is no guarantee that a compound will be a successful drug if it passes the Lipinski criteria;[21] indeed Lipinski states that not all criteria need to be met for good penetration and adsorption.[20] Conversely, there are numerous compounds used in clinical environments which are not RO5–compliant. Typical examples include those which do not require oral dosing or target specific tissues within the body which have specialised membranes preventing free diffusion (such as central nervous system (CNS) drugs which have to cross the blood-brain barrier and antibacterials which have to cross bacterial membranes).

1.1.4 Evolution of Physicochemical Properties during Drug Discovery

One of the main challenges of drug discovery is to optimise both binding affinity and target selectivity whilst maintaining drug-like character (as defined by Lipinski's RO5). The comparison of the properties of marketed and late stage development compounds with the lead compounds from which they have evolved leads to clear trends indicating the increase of numerous properties,[22,23] including both molecular weight and log*P*.[24] The observed trend for the increase of these key properties may be rationalised by considering that the lead-to-drug development process requires optimisation of target-substrate binding which may, in some cases, exploit additional lipophilic interactions. Several analyses of these trends suggest that the progression from lead to drug compounds results in, typically, an increase of molecular weight of 100-200 Da and an increase of log*P* by 0.5-4 log units.[18,19]

1.1.5 Summary of Desirable Characteristics for Lead Compounds

Given the limits of drug-like chemical space, and the trend for the increase in value of key physicochemical properties in the process of lead-to-drug development, it is essential to

control the molecular properties of lead compounds. The concept of Lead-oriented Synthesis (LOS)[1] has been recently introduced to highlight specific challenges related to the generation of lead-like compounds. This concept has highlighted physicochemical properties which would be desirable in compounds which may form good starting points for lead optimisation. Preferred values for these properties are summarised in Table **2**.

Molecular Property	**Preferred Values**
Molecular Weight	M_R~ 200-350[a]
Lipophilicity	-1< clog*P* <3
Aromatic rings	*n*Ar ≤ 3
Shape	Favour high 3D [b]
Sub-structures	No chemically reactive, electrophilic or redox-active groups

Table **2**: Preferred values proposed for lead-like small molecules. [a] Equivalent to ~ 14-26 heavy atoms. [b] Fraction of sp^3 centres (Fsp^3) may be used to assess three dimensional shape.

Analysis of commercially available screening libraries against the parameters outlined above show that the vast majority of compounds (>99%) do not have lead-like properties.[1] Similarly, analysis of compounds reported in recent synthetic methodology literature showed that >98% do not lie within these lead-like parameters.[1] As such, the requirement for methodology which can generate diverse compounds with properties which lie within the parameters of lead-like chemical space may be of great significance to those involved in the early stages of drug development.

1.2 Existing Methods for Generation of Diverse Compound Libraries

Libraries of highly diverse small molecules are essential for enabling efficient screening of chemical space. Diversity-oriented synthesis (DOS) is an innovative field of chemistry which has evolved to address this demand for diverse small molecules.[25] Numerous approaches have been developed to generate substitutional or appendage diversity around a common molecular skeleton.[26] Furthermore, more challenging approaches which generate diverse molecular scaffolds have been developed. Approaches which allow the variation of molecular skeleton allow the generation of libraries which cover greater areas of chemical space and are thus deemed more powerful approaches to diverse libraries.

These approaches have been categorised into three conceptually different approaches; branching pathways, folding pathways and oligomer–based approaches (Figure **2**).

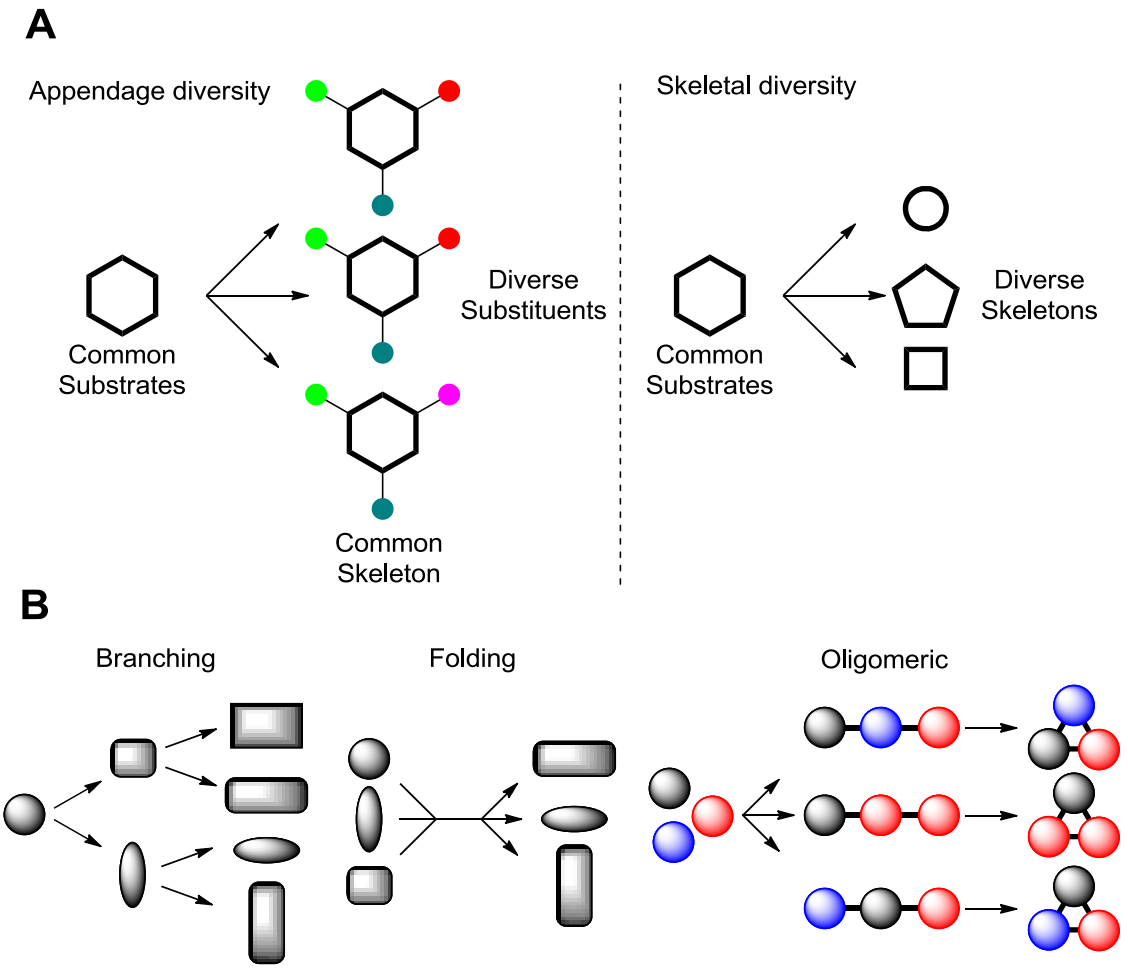
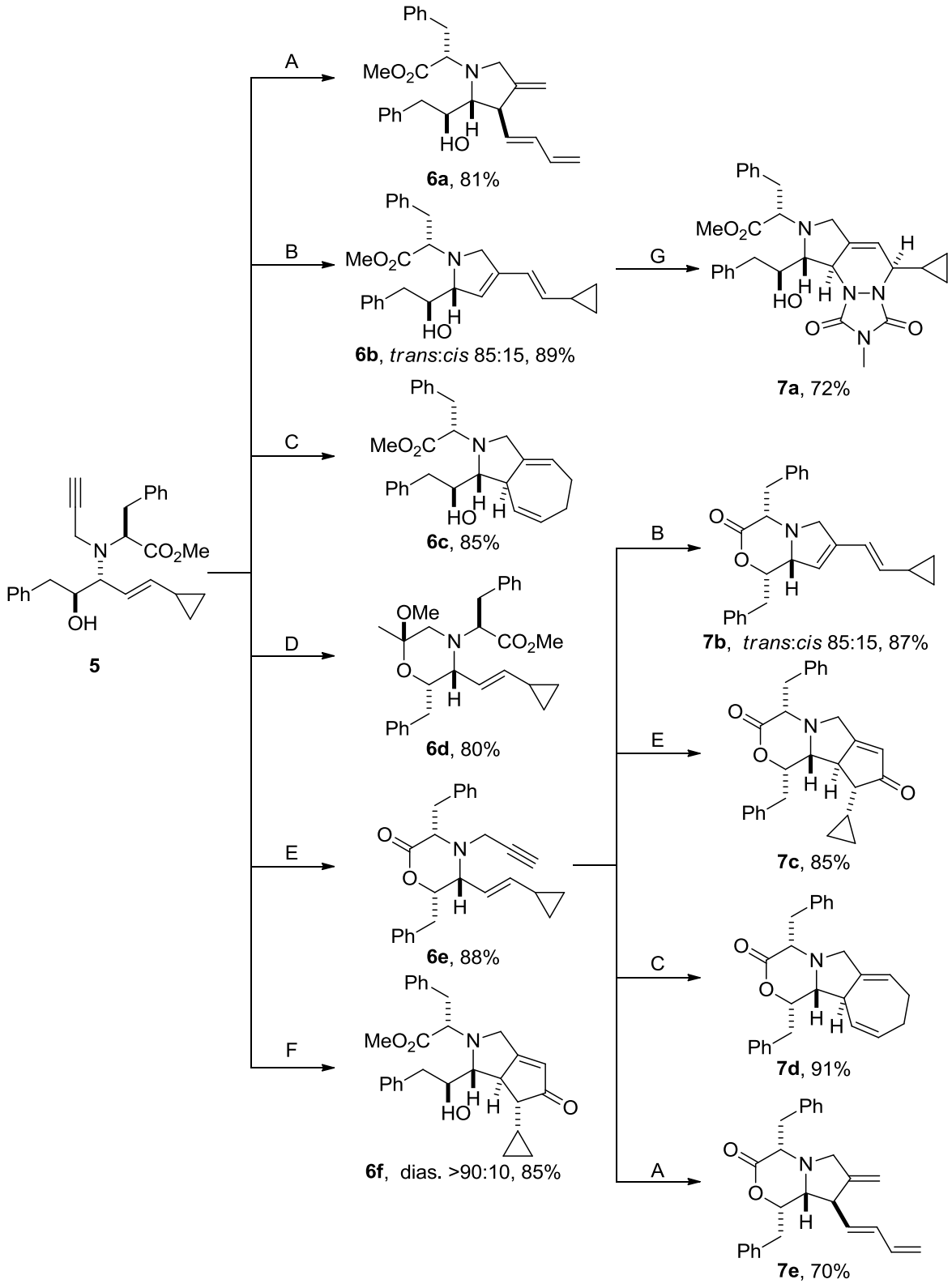


Figure **2**: Summary of common approaches utilised in diversity-oriented synthesis campaigns. Panel **A-** Appendage approaches generate one molecular skeleton (bold lines) but allows the introduction of diverse substituents (coloured shapes) although skeletal diversity approaches allow the generation of different molecular skeletons. Panel **B-** Skeletal diversity may be generated by using differing reagents from a common starting material (branching pathways), common conditions from differing starting materials (folding pathways) or coupling of common building blocks in different sequences followed by cyclisation (oligomer–based approaches).

1.2.1 Diverse Skeleton Generation through Branching Pathways

The branching approach to skeletal diversity involves sequences of divergent reactions which convert common reactants into a variety of distinct molecular skeletons. In order to facilitate this type of approach the initial reagents need to exhibit the versatility to undergo multiple transformations. An excellent example of the branching approach to skeletal diversity has been described by Schreiber and co-workers.[27] A four component Petasis reaction was used to generate common reagents (such as **5**) which contain

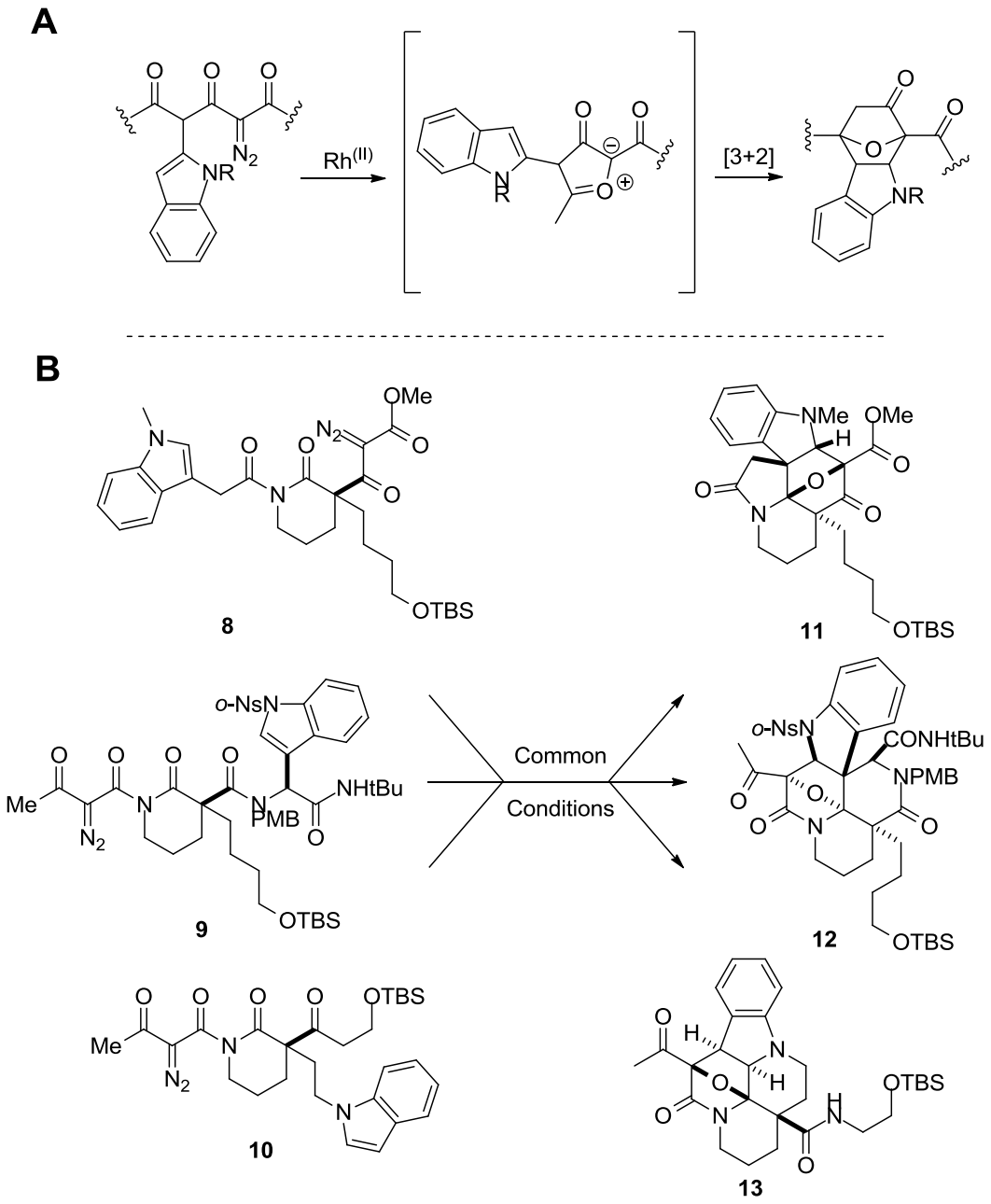
multiple sites for potential synthetic modification (Scheme **2**). Alternative cyclisation reactions were then used to transform **5** into a variety of molecules containing different scaffolds: Pd–mediated cyclisation (⟶ **6a**); Hoveyda–Grubbs mediated ene-yne metathesis (⟶ **6b**); ruthenium–mediated cycloheptadiene formation (⟶ **6c**); gold–catalysed acetal formation (⟶ **6d**); base–induced lactonisation (⟶ **6e**) and α,β-unsaturated ketone formation under Pauson–Khand conditions (⟶ **6f**). Some of these reaction conditions were used in a second round of diversity generation branching from **6e** to generate four further molecular scaffolds (**7b-e**). Furthermore, dienes (such as **6b**) were utilised as substrates for Diels–Alder reactions to give heterocycles such as **7a**. The key to this approach was the versatility of the initial branching reagent (such as **5**) to act as substrates for chemo- and diastereo-selective cyclisations to generate diverse skeletons. Numerous alternative branching pathways have been developed which have allowed the generation of diverse libraries of compounds containing a variety of bioactive molecules.



Scheme **2**: Branching approach to generate diverse molecular skeletons from a common intermediate by Schreiber *et al. Reagents and conditions*; A: 10 mol% $Pd(PPh_3)_2(OAc)_2$, benzene, 80 °C. B: 10 mol% Hoveyda–Grubbs 2nd gen. cat., CH_2Cl_2, Δ. C: 10 mol% $CpRu(MeCN)_3PF_6$, acetone, rt. D: 10 mol% $NaAuCl_4$, MeOH, rt. E: NaH, PhMe, rt. F: $Co_2(CO)_8$, Et_3NO, NH_4Cl, benzene, rt. G: 4-Methyl-1,2,4-triazoline-3,5-dione, CH_2Cl_2, rt.

1.2.2 Diverse Skeleton Generation through Folding Pathways

Complementary to branching approaches, folding pathways utilise a common set of reagents to induce formation of a variety of scaffolds from alternative substrates. An approach to alkaloid-like analogues using a folding approach was developed by Oguri and Schreiber (Scheme **3**).[28]



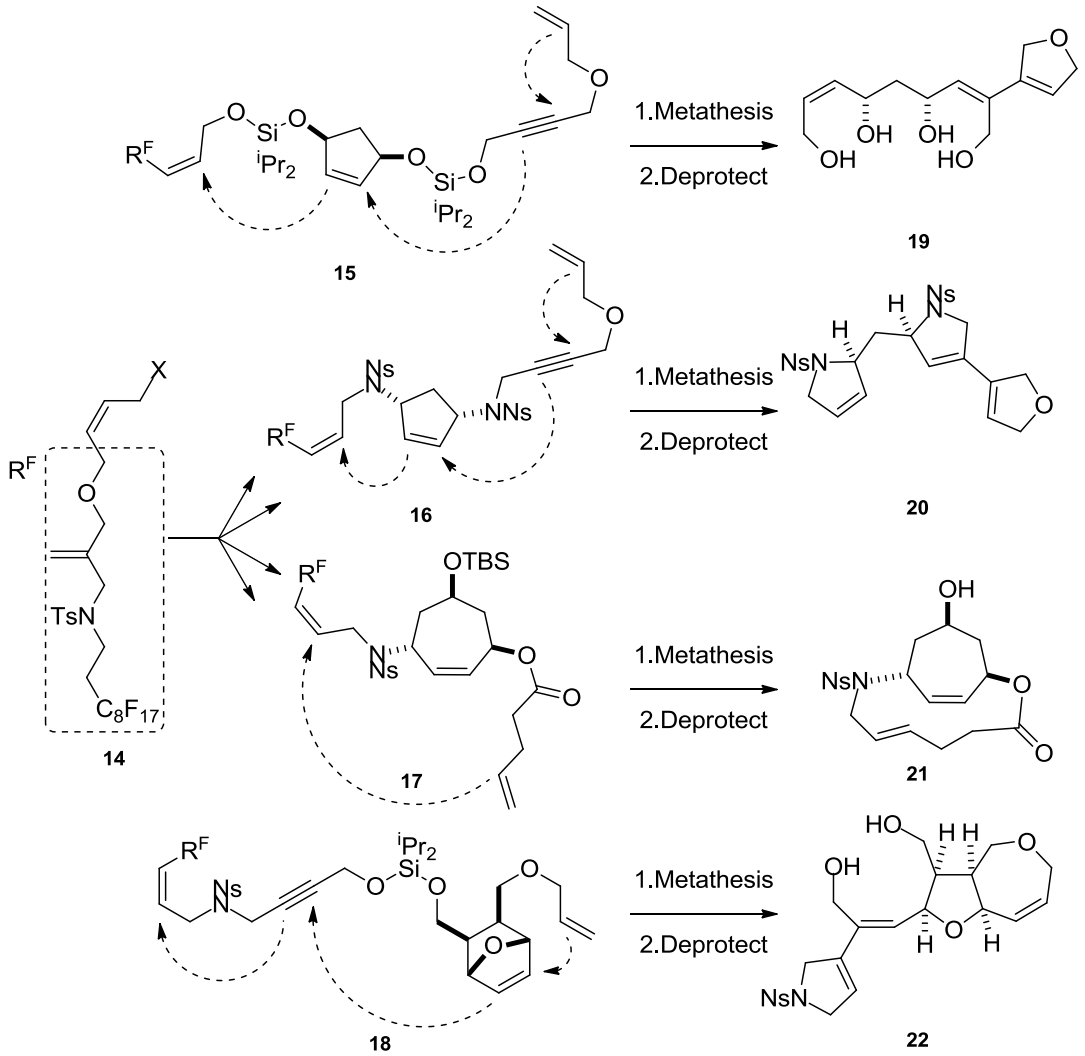
Scheme **3**: Folding approach to alkaloid-like skeletons by Oguri and Schreiber. Panel A- General mode of reactivity exploited in this folding approach. Panel B- Folding approach utilised to generate alkaloid-like polycycles. *Reagents and Conditions*: $Rh(O_2CC_7H_{15})_4$, benzene, 50 °C.

The folding approach outlined above (Scheme **3**) utilised the ruthenium–catalysed cyclisation-cycloadditon cascade developed by Padwa and co-workers.[29] The treatment of diazo–containing precursors with catalytic amounts of a $Rh^{(II)}$ catalyst induced selective

cyclisation-cycloaddition cascades to give a series of diverse alkaloid like skeletons. Key to this approach was the ability to generate different carbonyl ylides by the variation of the position at which both the σ,β-unsaturated diazo motif and the indole was positioned.

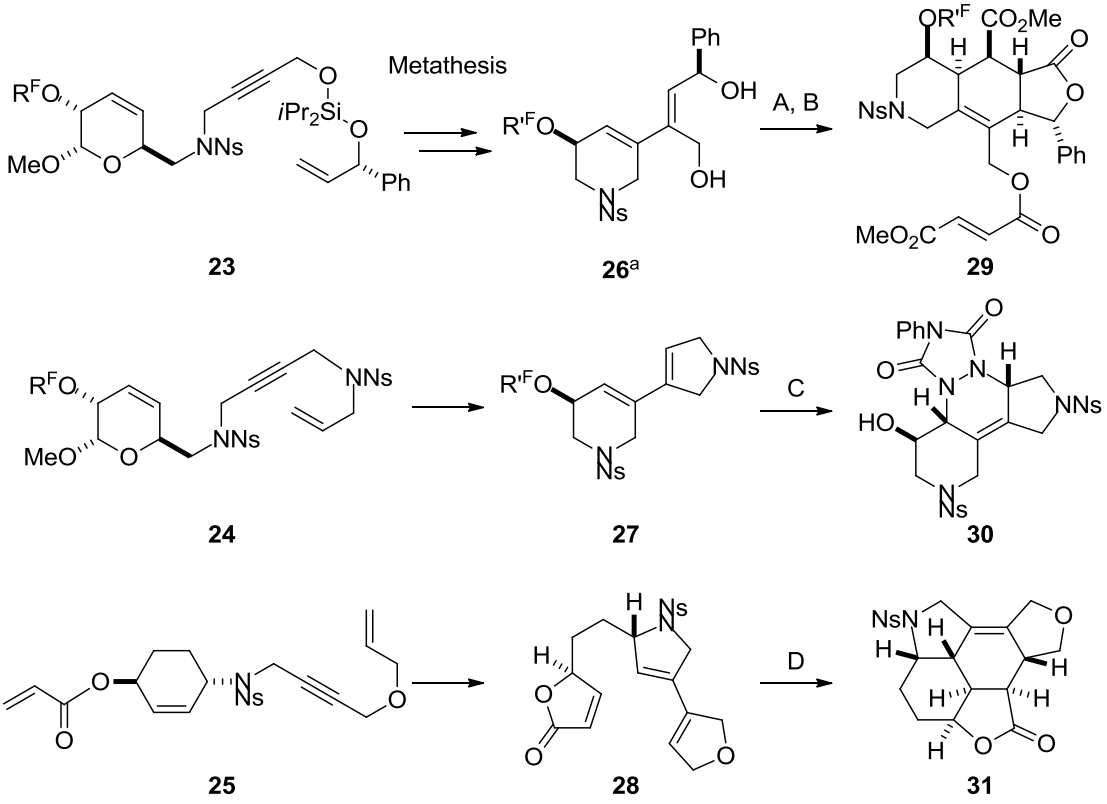
1.2.3 Diverse Skeleton Generation through Oligomer-Based Approaches

Oligomeric pathways utilise elements of both branching and folding pathways and can be an exceptionally powerful tool for the generation of diverse molecular skeletons. Approaches developed within the Nelson group have exploited oligomeric pathways which have resulted in the generation of libraries with unprecedented levels of skeletal diversity.[30] Their approaches utilised a common modular strategy which allowed the construction of cyclisation precursors through the coupling of unsaturated building blocks with either permanent or temporary tethers using a build/couple/pair strategy[30e] (Scheme **4**). This modular pairing approach required employment of only limited types of reaction: sulfonamide formation under Fukuyama–Mitsunobu conditions (to install permanent tethers), mixed silaketal formation and ester formation (to install temporary tethers). Subsequent skeletal reprogramming of these cyclisation-precursors, using cascade metathesis, generated different molecular skeletons dependent upon the position of unsaturation (alkene or alkyne) in the parent molecule. Finally, removal of temporary tethers and purification tags revealed a library of diverse compounds, based on over 80 different molecular scaffolds.



Scheme **4**: Oligomeric pathway developed by Nelson and co-workers which generated a library of compounds with unprecedented levels of molecular scaffold diversity.

This modular, oligomeric approach to generate diverse libraries was extended to incorporate further complexity generating reactions.[31] The selective incorporation of unsaturated groups at certain sites of the cyclisation precursor allows for the formation of 1,3 diene motifs to be generated in the cyclic products. These diene motifs were exploited as substrates for [4+2] cycloadditions in both an intra- and inter-molecular fashion to create more complex molecular skeletons (Scheme **5**). Intermolecular cycloaddition was achieved by treating the diene **27** with a hetero-dienophile to give the imide **30**. Intramolecular cycloaddition was achieved by appending dienophiles on the free hydroxy groups of the diol **26** to give an intermediate which underwent intramolecular cyclisation, under microwave irradiation, to give the ester **29**. An alternative approach was to generate the dienophile during the metathesis cascade. As such, the cyclisation substrate **25** was designed which gave the triene **28** after cyclisation under cascade metathesis conditions. Heating the triene **28** in *p*-xylene resulted in the intramolecular cycloaddition to give the lactam **31**.



Scheme **5**: Combining cascade metathesis with intra- and inter-molecular Diels–Alder reactions to generate compounds with diverse molecular skeletons. [a]Required cleavage of temporary silyl linkers post-metathesis cascade. *Reagents and conditions*: A- mono-Methyl fumarate, DCC, DMAP, THF. B- MeCN, MW irradiation. C- 4-Phenyl-[1,2,4]-triazole-3,5-dione, CH_2Cl_2. D-*p*-Xylene, reflux.

1.2.4 Analysis of DOS Libraries

In order to assess the ability of DOS approaches to deliver compounds with properties desirable for drug discovery programmes, a selection of over 6500 molecules from different DOS campaigns were analysed.[32] Analysis of key criteria (molecular weight and Log*P* as described in section **1.1.5**) allowed an assessment of the ability of DOS approaches to deliver compounds which may be described as lead-like. As such, each compound was given a numerical identifier which was plotted against both molecular weight (Chart **2**) and ALog*P* (Chart **3**).[33,34] Similarly, both molecular weight and ALog*P* for each individual compound was analysed as shown in Chart **4**.

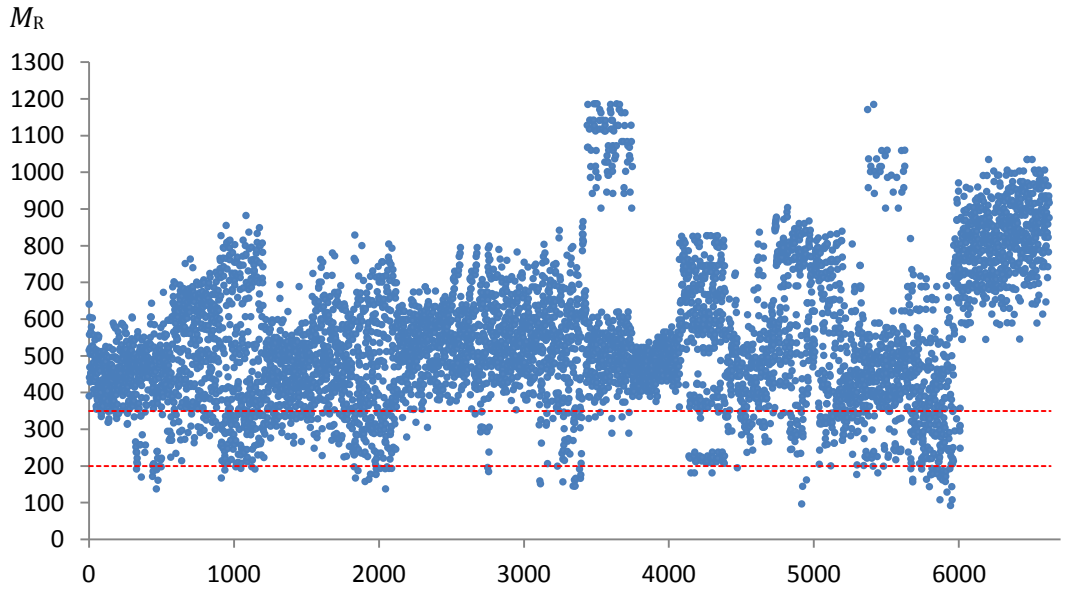


Chart **2**: Molecular weight analysis of compounds generated in DOS campaigns. Dashed red lines show molecular weight limits for lead-like compounds.

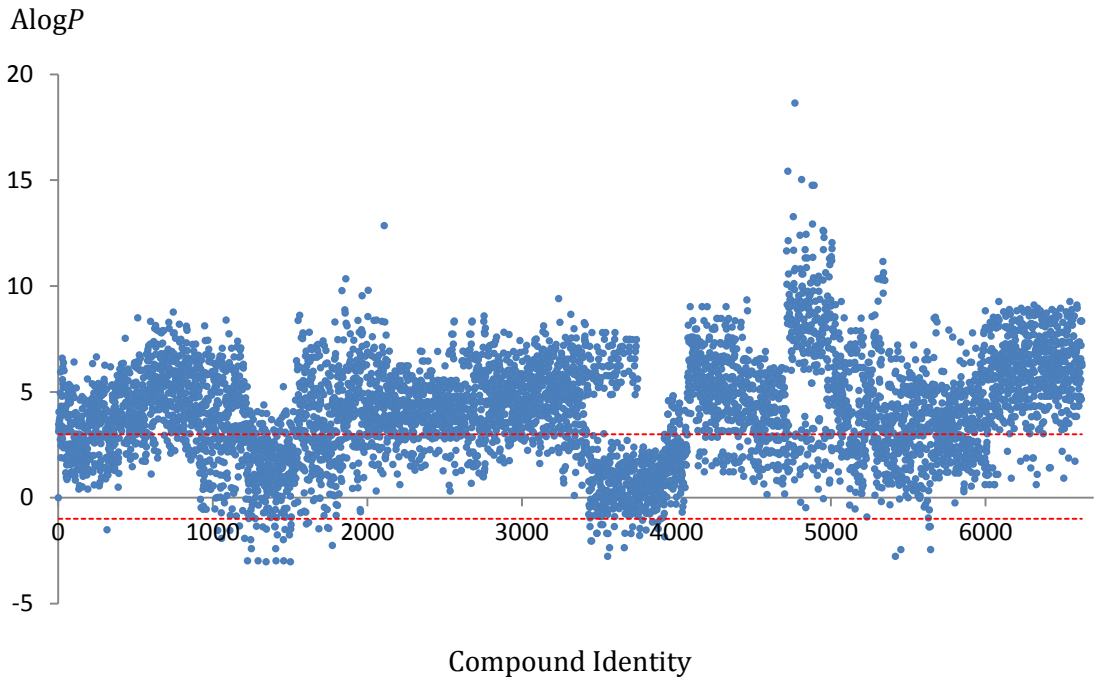


Chart **3**: ALog*P* analysis of compounds generated in DOS campaigns. Dashed red lines show AlogP limits for lead-like compounds.

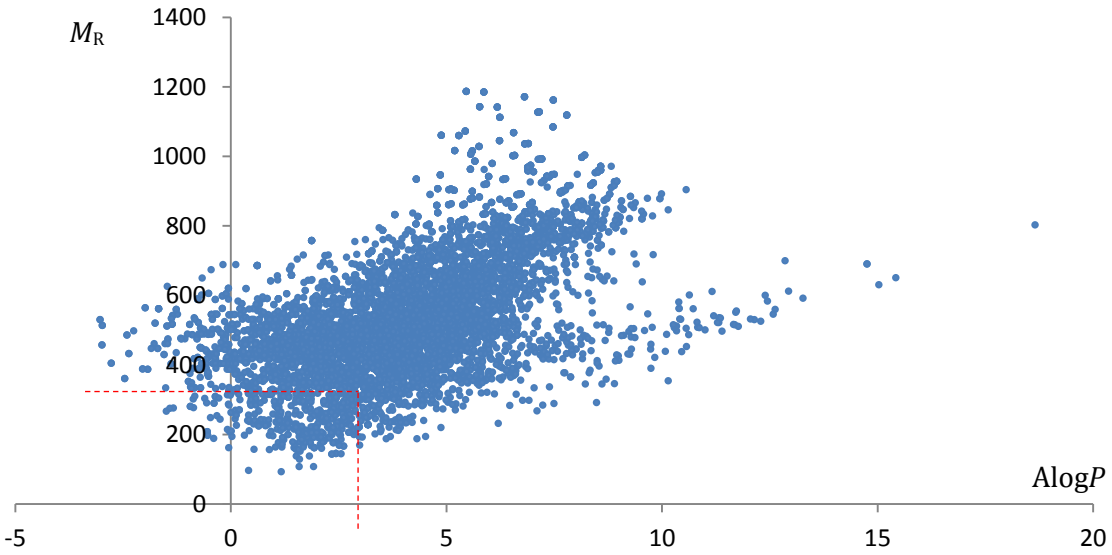


Chart **4**: ALog*P* Vs M_R analysis of compounds generated in DOS campaigns. Dashed red lines show limits of lead–like chemical space.

Molecular weight analysis of the DOS compound library (shown in Chart **2**) shows a wide variance (Min M_R= 93.1, Max M_R= 1187.1). However, only 11% of the compounds analysed would be described as lead-like as their molecular weights lay within the boundaries defining the perimeters of lead-like chemical space (red dashed lines on Chart **2**). Similarly, analysis of ALog*P* (Chart **3**) shows a wide variation (Min ALog*P*= −3.0, Max ALog*P*= 18.6) but with a low compound population which lie within lead-like parameters (30%). Furthermore, the population of compounds which would be deemed lead-like on the basis of both molecular weight and Alog*P* (Chart **4**) is only 4% (!). This analysis clearly shows that although DOS approaches are able to generate libraries of diverse compounds with wide variation of both molecular weight and ALog*P*, the compounds typically do not have the physicochemical properties which would be desirable for the early stages of drug development.

1.3 Strategies for the Synthesis of Diverse Lead-Like Compounds

A significant challenge for synthetic chemists is to develop synthetic methodologies that allow the variation of molecular lead-like skeletons. The origin of this challenge may be due to the need to employ low molecular weight, highly hydrophilic, molecules in order to maintain the required pharmacokinetic properties of the desired products. Many reactions are systematically less successful with polar building blocks, a phenomenon which results in the logP distribution of successful products being higher than that of the proposed library, known as Array logP Drift.[1] However, numerous approaches have recently emerged that allow (or have the potential to) the systematic variation of molecular skeleton whilst remaining within lead-like space.

Particularly valuable approaches to allowing systematic variation of molecular skeletons utilise methods whereby multiple bonds are formed to each of the new building blocks or the employment of multiple building blocks. Herein, examples of approaches which allow (or may allow) the generation of varied molecular skeletons whilst remaining within lead-like space are discussed.

1.3.1 Classification of Strategies

Approaches to generating compounds with varied molecular skeletons by the pairing of multiple building blocks bearing multiple reactive sites are very common. However, there are conceptual differences between different approaches utilising two building blocks which have been classified by a conceptual framework.[35] Examples of these concepts are represented in Figure **3**.

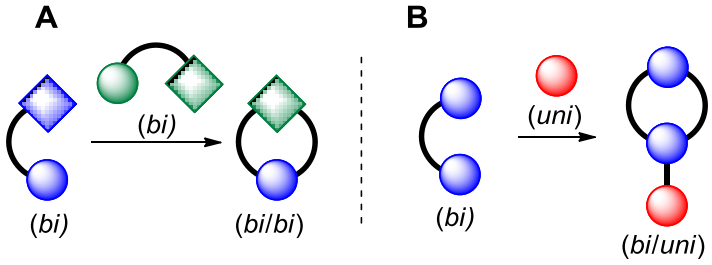


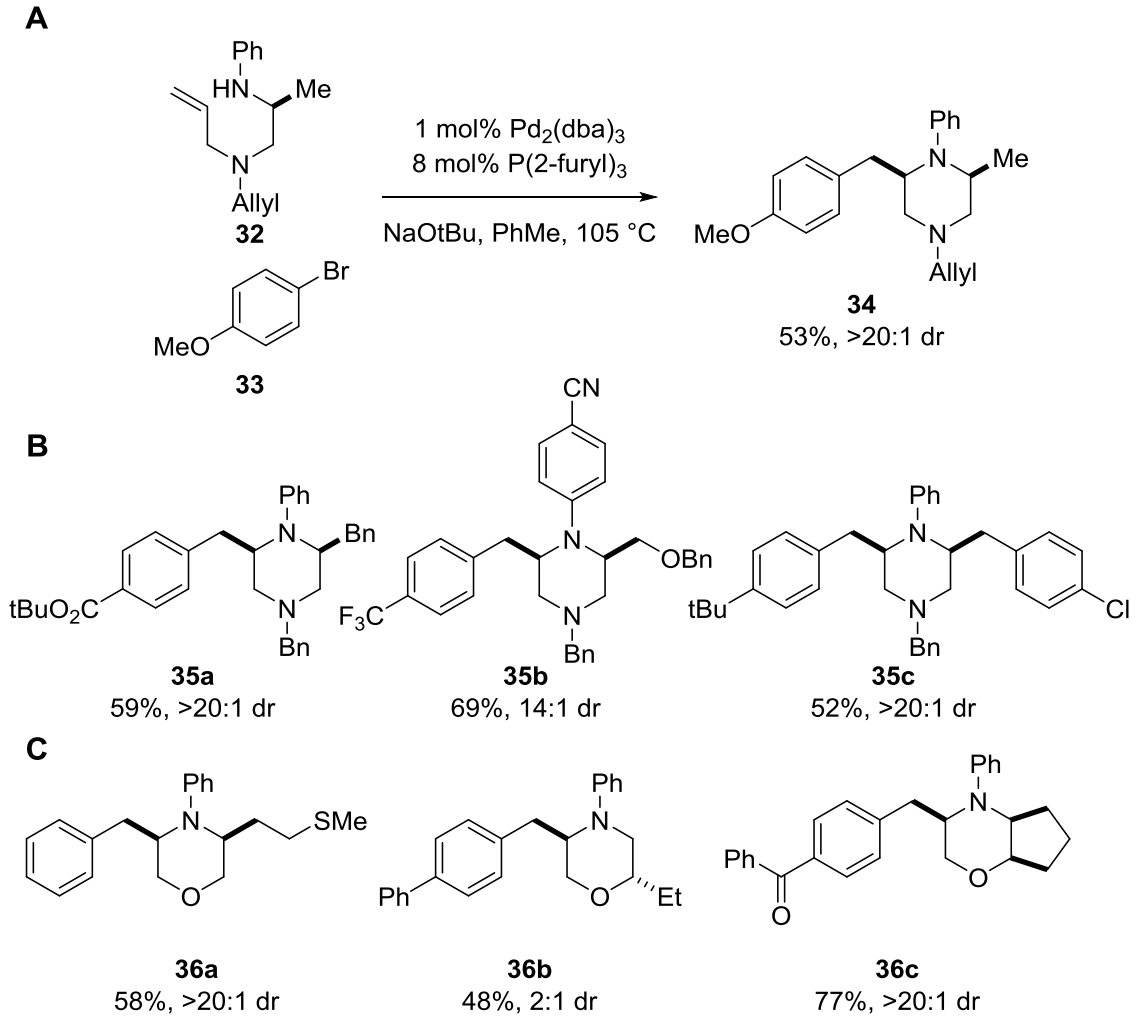
Figure **3**: Different concepts in the pairing of two building blocks. In this scheme different building blocks (represented by colours) are chemoselectively paired (represented by shapes) to give cyclic products.

The classification of these reactions are defined by the number of new bonds formed to each building block in the conversion to products, with new bonds between functional groups *within* building blocks being counted only once. As such building blocks which form one new bond are classified as *uni* building blocks, building blocks which make two new bonds are *bi*, etc. Overall, the process for molecular scaffold generation is classified by a compound naming of the building block functionality, such as (*bi*/*bi*) or (*bi*/*uni*) (Figure **3**, Panel **A** and **B** respectively).

1.3.2 Scaffold Generation Using *bi*/*uni* Approaches

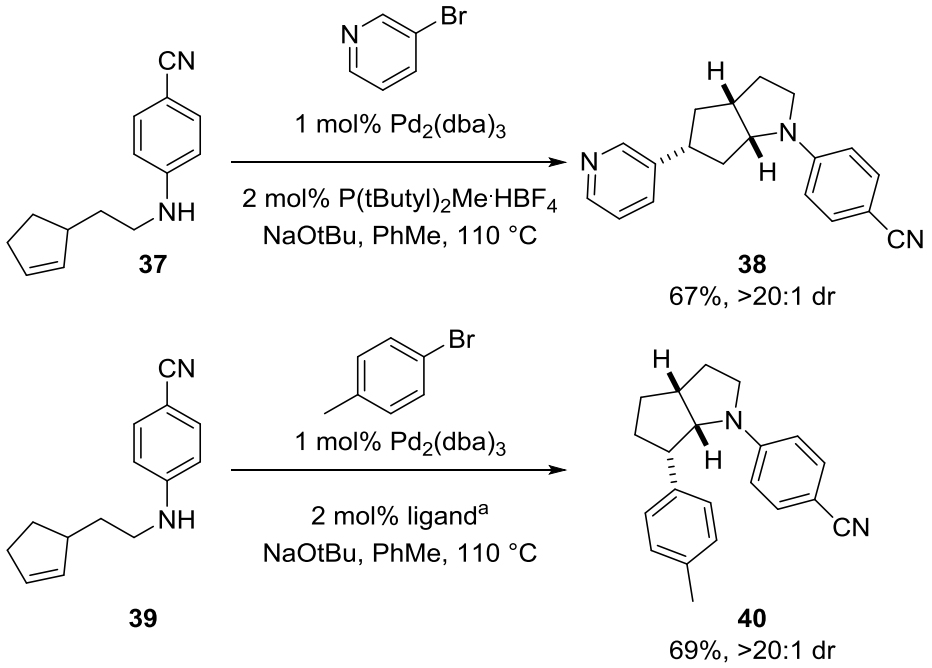
Aminoarylation approaches utilising a *bi*/*uni* strategy have been widely used to generate a wide range of (poly) heterocyclic scaffolds (Scheme **6**). The aminoarylation approach developed by Wolfe and co-workers exploited the palladium catalysed cyclisation of unsaturated amines (Scheme **6**, Panel **A**) such as **32** with an external aryl halide to generate heterocycles, such as **34**.[36] This approach yielded 2,6-disubstituted piperazines containing varied functional groups which may be used as handles for further chemistries

(Scheme **6**, Panel **B**). Under related conditions, the synthesis of substituted morpholines was achieved which allowed the authors to generate 3,5- and 3,6-disubstituted systems as well as polycyclic systems (Scheme **6**, Panel **C**).[37,38]



Scheme **6**- Aminoarylation approach to substituted heterocycles developed by Wolfe and co-workers. Panel **A**- Representative example of synthetic approach to piperazines by the synthesis of **34**. Panel **B**- Examples of 2,6-substituted piperazines synthesised from this work. Panel **C**- Illustrative examples of substituted morpholine scaffolds generated by Wolfe and co-workers.

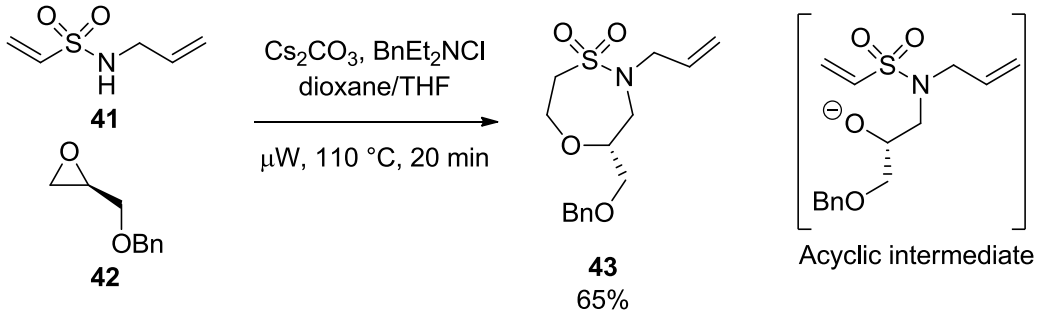
During efforts towards bicyclic pyrrolidines, the Wolfe group developed an approach which remarkably allowed regioselective aminoarylation of unsaturated amine substrates (Scheme **7**).[39] The selective approach to substituted pyrrolidine scaffolds was dependent upon the phosphine ligand with a variety of aryl groups giving reproducible regioselectivities. The authors propose that the ligands control relative rates of reductive amination or migration steps, leading to regioisomeric products under alternative conditions.



Scheme **7**- Regioselective aminoarylation approaches to the synthesis of polycyclic pyrrole scaffolds. [a] ligand= 2-diphenylphosphino-2'-(*N*,*N*-dimethylamino)biphenyl.

1.3.3 Scaffold Generation Using *bi*/*bi* Approaches

Pairing of bifunctional building blocks can be a particularly powerful approach to the synthesis of lead like compounds with diverse molecular scaffolds, especially if building blocks can be systematically varied. The pairing of some bifunctional building blocks has been dubbed ambiphile pairing due to the nucleophilic and electrophilic nature. An example of an ambiphilic approach to generate sultam scaffolds was developed by Hanson and co-workers (Scheme **8**).[40]



Scheme **8**- Synthesis of sultam scaffolds using an ambiphile pairing approach.

Treatment of the α,β-unsaturated sulfonamide **41** with the epoxide **42** led to the formation of the sultam **43**. Although the ambiphilic nature of the sulfonamide **41** is clear from the functionality in the reagent, the ambiphilic nature of the epoxide is only revealed once it has been opened to an acyclic intermediate as shown in Scheme **8**. The ambiphilic

nature of the α,β-unsaturated sulfonamide **41**, and substituted analogues thereof, has been utilised in further campaigns to generate a variety of different molecular scaffolds as illustrated in Figure **4**.[41,42]

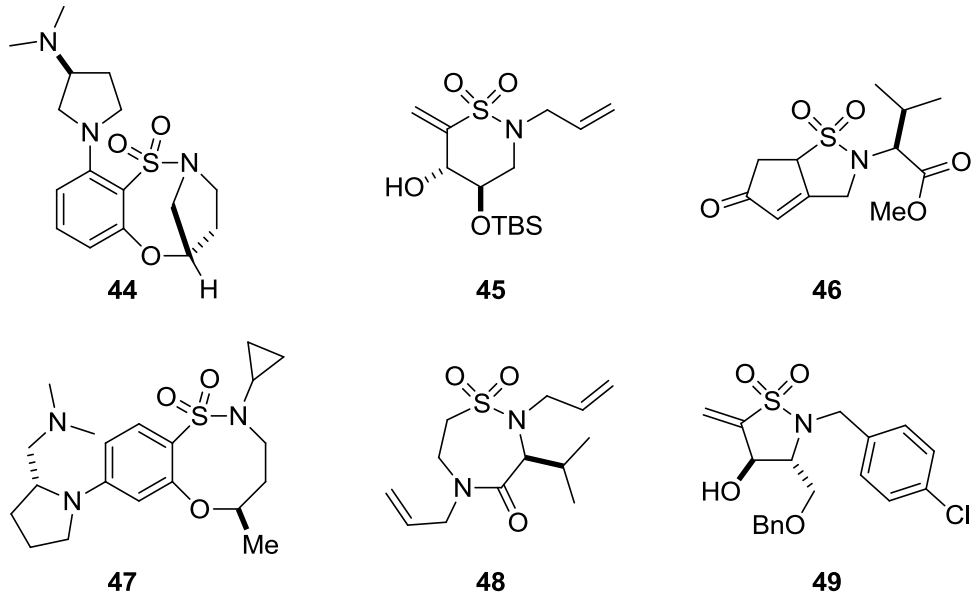
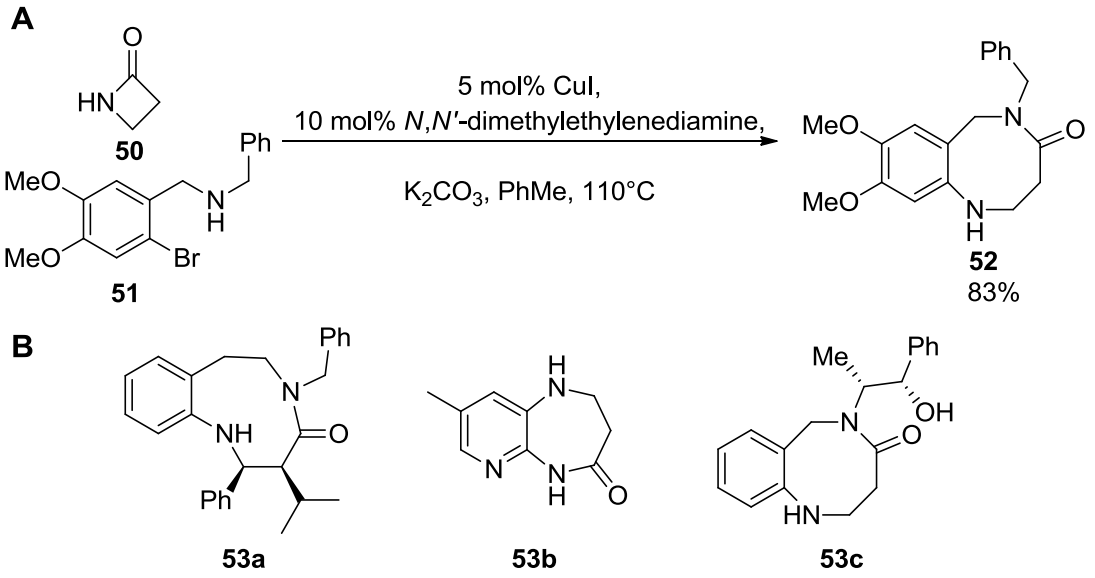


Figure **4**-Diverse molecular scaffolds generated by exploiting the ambiphilic nature of analogues of the sulfonamide **41**.

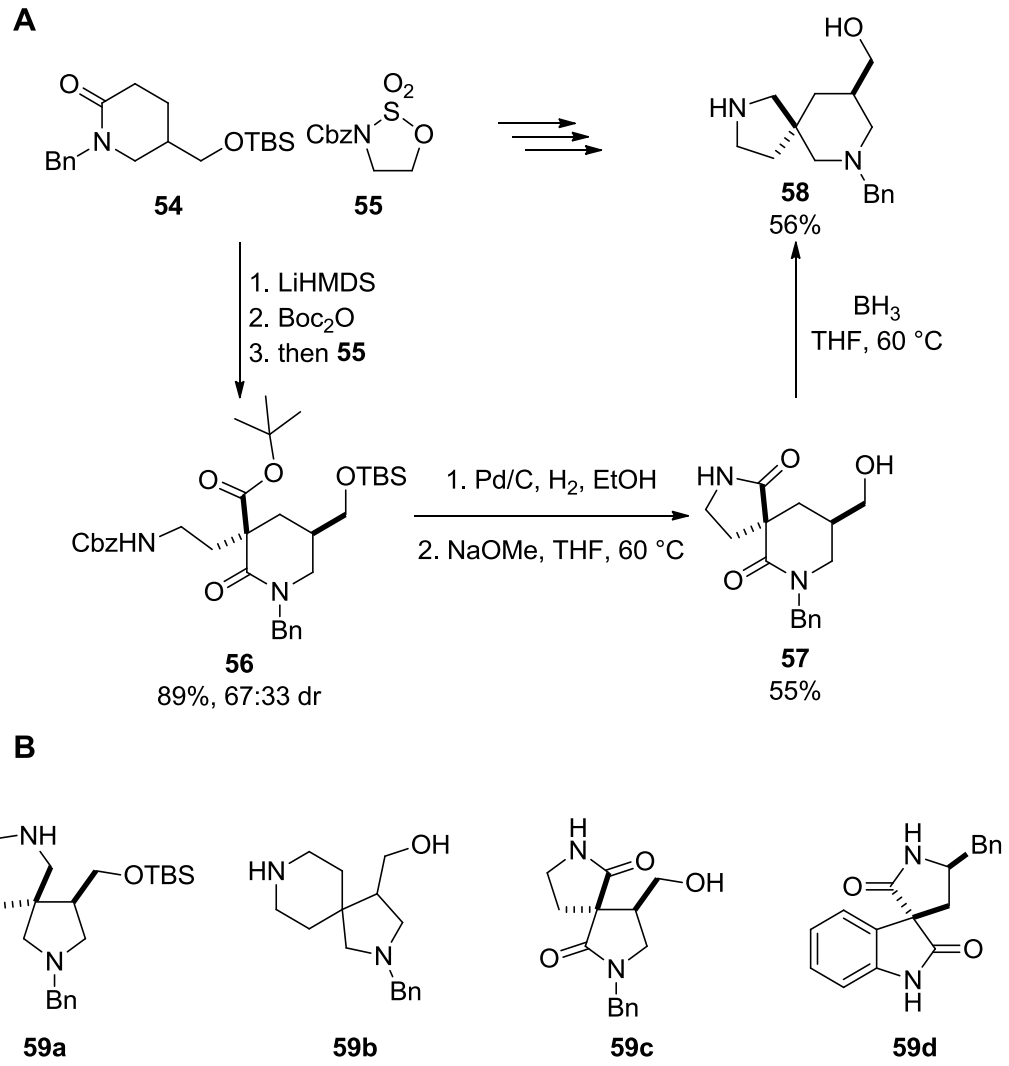
An alternative approach to the synthesis of medium ring heterocycles using an ambiphilic pairing pathway was developed by Buchwald and co-workers.[43] Their approach to medium ring nitrogen heterocycles was based on a tandem copper-catalysed *C—N* bond formation–ring-expansion cascade (Scheme **9**).



Scheme **9**- The Buchwald approach to the synthesis medium ring aza-cycles by way of a cross coupling–ring-expansion cascade. Panel **A**- Representative procedure for the synthesis of medium ring heterocycles. Panel **B**- Examples of alternative ring systems generated using this approach.

Treatment of β-lactam **40** and the aryl bromide **41** with 5 mol% CuI and 10 mol% *N*,*N*'-dimethylethylenediamine at 110 °C led to the formation of the lactam **52** in an 83% yield. This approach is thought to proceed *via* an *N*-arylation followed by an intramolecular acyl transfer to give the observed product. Analogously, the heterocycles **53a**, **53b** and **53c** (Scheme **9**, Panel **B**) were also generated. This approach clearly shows that the systematic variation of building blocks (in this case the aryl halides and β-lactams) in combination with a common reaction sequence can rapidly generate diverse molecular scaffolds to give novel heterocyclic ring systems.

A general approach to spirocyclic scaffolds was developed by Gallagher and co-workers by exploiting the ambiphilic nature of cyclic sulfamidate building blocks (Scheme **10**).[44] The approach relied upon the reactive nature of the cyclic sulfamidate **55**. The cyclic sulfamidate **55** was opened with an enolate derived from treating ketopiperadine **54** with LiHMDS and Boc_2O to give carbamate **56**. Hydrogenolysis of the Cbz group, followed by base mediated lactamisation and concomitant desilylation, gave **57** at which point diastereoisomers could be separated. Final borane–mediated reduction gave the spirocycle **58**. This approach proved itself to be highly flexible, enabling the synthesis of various spirocyclic motifs, including benzo-fused ring systems, shown in Panel **B**.

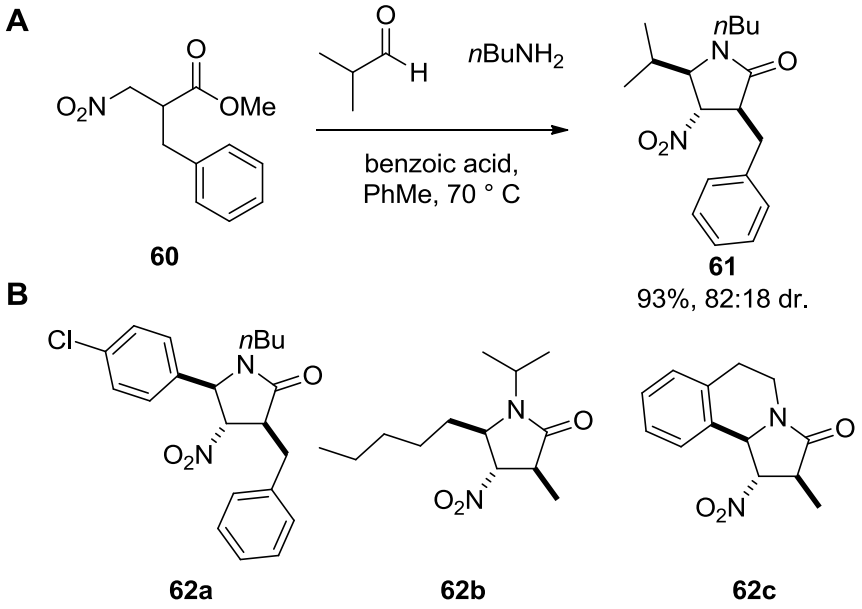


Scheme **10**: The approach developed by Gallagher and co-workers for the synthesis of compounds with diverse spirocyclic scaffolds. Panel **A**- Synthesis of piperadine **58** exploiting the ambiphilic nature of cyclic sulfamidate **55**. Panel **B**- Examples of diverse spirocyclic molecules generated from this campaign.

1.3.4 Multicomponent Approaches to Lead-Like Scaffolds

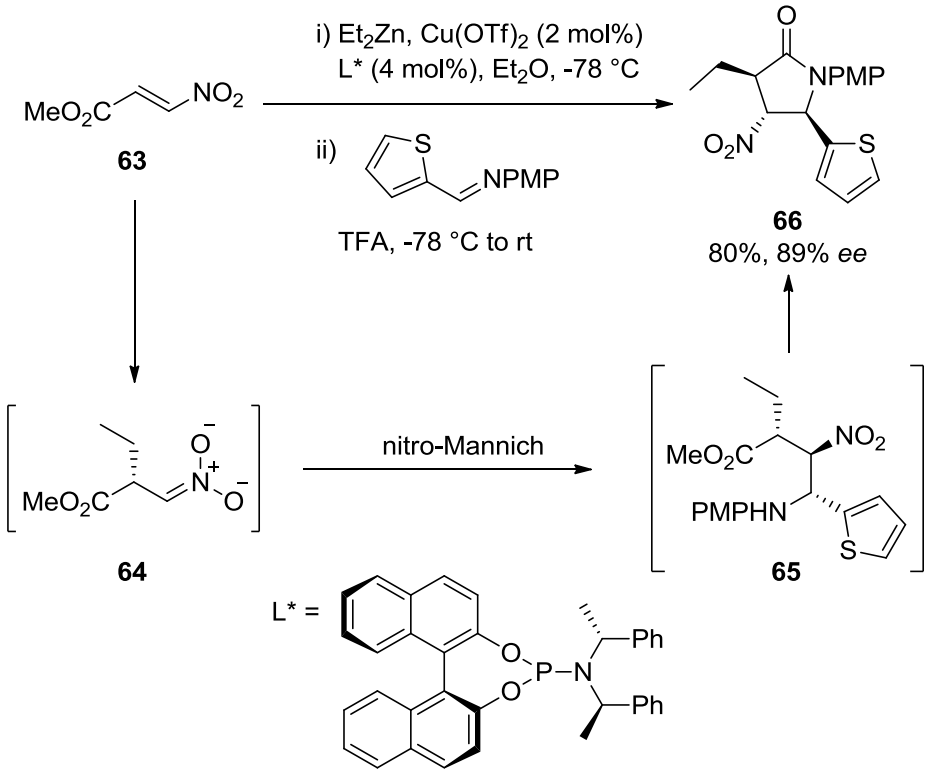
The ability of approaches to generate small molecule scaffolds is greatly enabled by the combination of more than two building blocks. Such multicomponent approaches may allow the variation and systematic combination of all components resulting in rapid access to diverse small molecules. A multicomponent approach to pyrrolidinones was developed by Dixon *et al.* employing a nitro-Mannich/lactamisation cascade (Scheme **11**).[45] Treatment of the ester **60** with the imine formed from the condensation isobutyraldehyde and butylamine led to the isolation of the pyrrolidone **61** in 93% as an 82:18 mixture of diastereoisomers. (Panel **A**). This approach showed wide building block tolerance allowing

variation in both amine, aldehyde and ester components allowing the synthesis of highly substituted scaffolds with moderate to high levels of diasterocontrol (Panel **B**).[46]



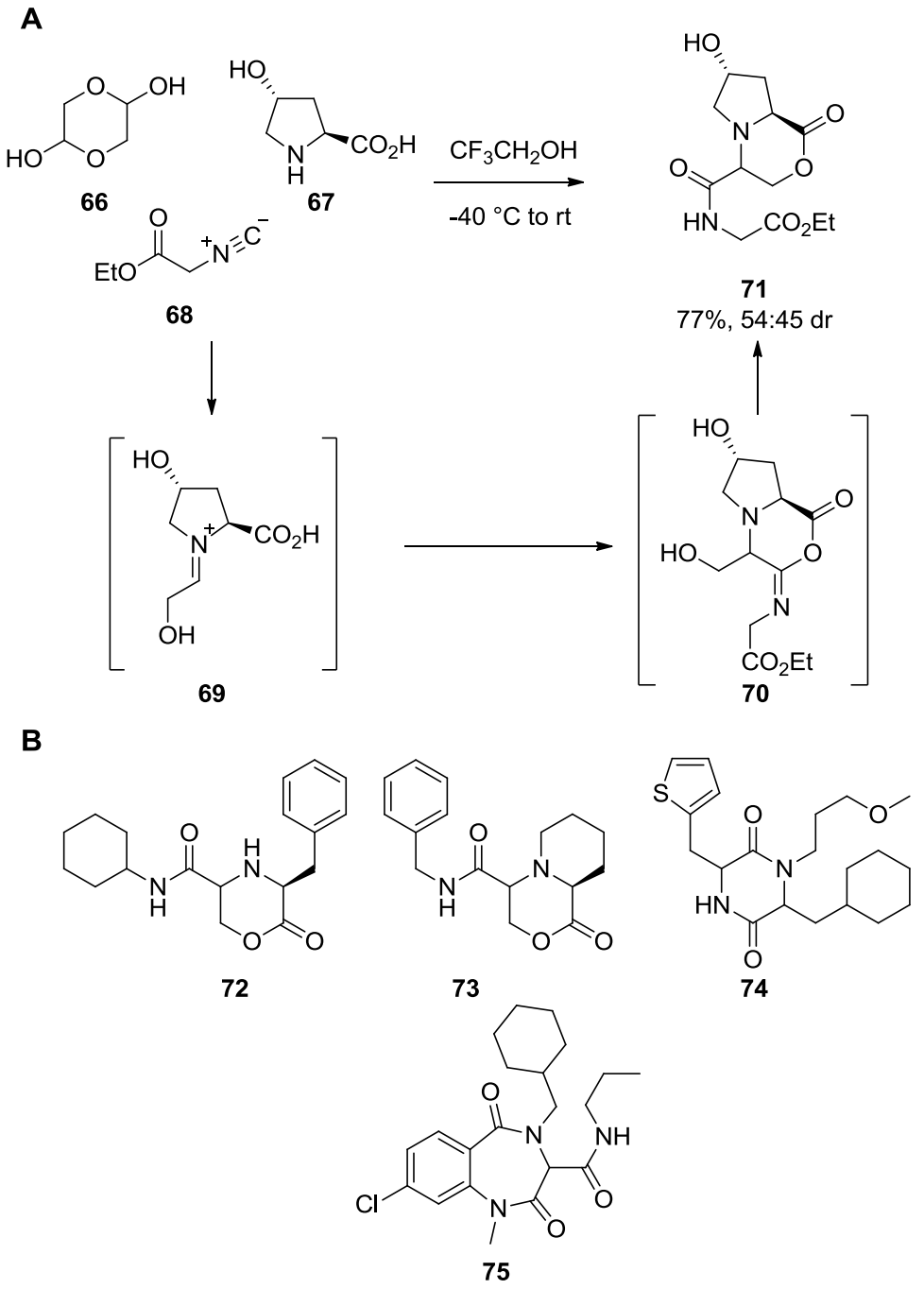
Scheme **11**: Dixon's multicomponent approach to the synthesis of pyrrolidones.

An alternative stereoselective multicomponent approach to similar pyrrolidones was developed using a conjugate addition/nitro-Mannich/Lactamisation strategy (Scheme **12**).[47] In this approach an asymmetric conjugate addition of dialkyl zinc reagents into nitro-olefins such as **63** gave an intermediate nitronate species (**64**) which, upon addition of an imine and warming to room temperature, underwent a nitro-Mannich addition. Subsequent lactamisation gave the *N*-protected heterocyclic scaffolds, such as **66**, with high levels of enantio- and diastereo-selectivity.



Scheme **12**: Enantioselective multicomponent approach to the synthesis of pyrrolidones.

An approach to the synthesis of morpholinone scaffolds was developed by Kim who made use of a variation of an Ugi multicomponent reaction (Scheme **13**).[48] An Ugi five-centre three-component reaction between aldehydes, amino acids and isonitriles led to the generation of diverse heterocyclic products based upon the identity of each of the three components. Condensation of the amine and aldehyde components led to iminium formation (⟶ **69**) which was trapped by the addition of the isonitrile to generate a nitrilium species. Subsequent intramolecular nitrilium trapping, with the carboxylic acid, led to a cyclic intermediate (⟶**70**). Intramolecular rearrangement, by virtue of an appended nucleophile, led to the formation of the morpholinone **71**. Systematic variation of amino acid building blocks, such as acyclic (⟶**72**) or homologated cyclic amino acids (⟶**73**), allowed variation of molecular scaffold. The generation of final heterocyclic scaffolds is dependent upon the nature of the tethered nucleophile; the alcohol motif from glycoaldehyde leads to morpholinone scaffolds. Variation of the tethered nucleophile to incorporate alternative nucleophiles, such as amines, using a similar multicomponent approach has led to the synthesis of various nitrogen based heterocycles (Panel **B**, **74** and **75**).[49] An obvious deficiency of this approach is the poor diastereoselectivity observed during the synthesis of the morpholinone **71**.

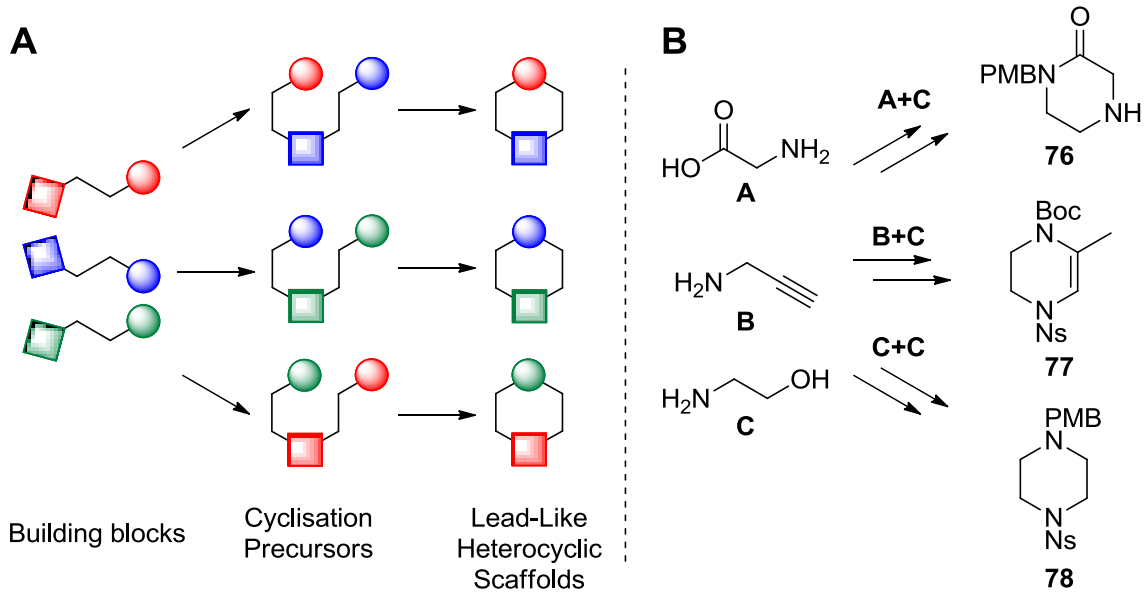


Scheme **13**: Multicomponent approach to morpholinone utilising an Ugi five-centre three-component approach. Panel **A**- Overview of the Ugi–based approach taken to the synthesis of heterocycles exemplified by the synthesis of **71**. Panel **B**- Examples of scaffolds generated by this approach (**72** and **73**) and through a similar multicomponent reaction approach (**74** and **75**).

1.4 Project Outline

This project is focused on the development of methodology for the facile generation of heterocyclic compounds, with desirable physicochemical properties for drug discovery, from readily available building blocks.

In order to generate diverse heterocycles from a limited number of building blocks a modular strategy, based upon selective coupling of bifunctional molecules, was devised and is summarised in Scheme **14**.



Scheme **14:** Summary of approaches taken to the generation of heterocycles with lead-like properties. Panel A- proposed strategy for the systematic pairing of bifunctional molecules may allow the generation of a variety of lead-like heterocyclic scaffolds. Panel **B**- Examples of building blocks used in these approaches and the heterocycles which may be generated.

The proposed strategy is based on a modular coupling approach in which bifunctional building blocks (those containing two electrophilic sites, two nucleophilic sites, or one nucleophilic and one electrophilic site) would be chemoselectively coupled to give cyclisation precursors (Scheme **14**, Panel **A**). The cyclisation precursors would then be chemoselectively cyclised to give heterocyclic scaffolds. The selection of both the building blocks and methods for coupling may allow the synthesis of diverse heterocyclic scaffolds which, after decoration with various capping groups, may lead to heterocycles with lead-like physicochemical properties.

The development of approaches to allow the generation of diverse heterocycles will focus on three readily available classes of building blocks: amino-acids, amino-alkynes and amino alcohols (Scheme **14**, Panel **B**). The methodology developed within these studies aims to allow the systematic combination of these classes of building blocks in both formal

hetero-coupling approaches (i.e. ⟶**76** and ⟶**77**) or a formal homo-coupling approach (⟶**78**). The key to these approaches is the ability to generate different ring sizes of heterocycle as well as the ability to selectively introduce substitution onto the carbon framework of the ring system. Furthermore, the ability to introduce orthogonally cleavable functional groups may allow further diversity generating reactions, giving more complex molecular skeletons. The development of these methods for the synthesis of heterocycles with lead-like physicochemical properties will be described in the following Chapters.

Chapter 2: Development of a Modular Approach to Piperazines, Diazepines and Related Ring Systems

This Chapter describes the development of approaches to the synthesis of diverse heterocyclic scaffolds. The approaches involve the pairing of bifunctional building blocks, with the reaction of an activated alcohol as the key step in heterocycle formation. A key challenge was to control the chemoselective condensation of the required ambiphilic building blocks. This Chapter focusses on the development, and subsequent exemplification, of methods for the ambiphilic pairing of amino acids with amino alcohols (Figure **5**, Panel **A**) and cyclic sulfamidates with amino alcohols (Figure **5**, Panel **B**)

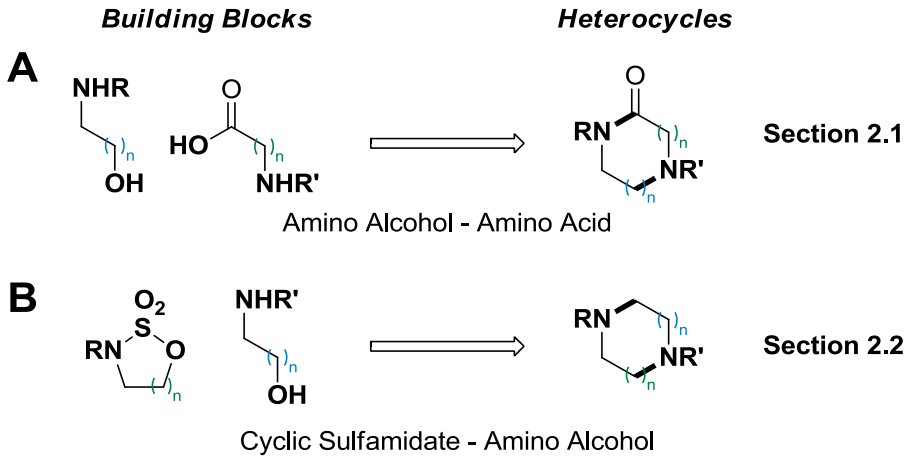


Figure **5**: Overview of approaches for the formation of heterocycles described in this Chapter. Bonds shown in bold are those made during the proposed heterocycle formation. Panel **A-** The bifunctional paring of amino acids and amino alcohols to give ketopiperazines and related ring systems. Panel **B-** The bifunctional pairing of cyclic sulfamidates and amino alcohols to give piperazines and related heterocycles.

2.1 Overview of Amino Acid – Amino Alcohol Pairing

This Section outlines the development of an approach to the synthesis of ketopiperazines and related heterocycles. An overview of the proposed approach is given in Figure **6**. The approach would involve the condensation of an amino acid derivative with an amino alcohol building block to give a heterocyclic ring.

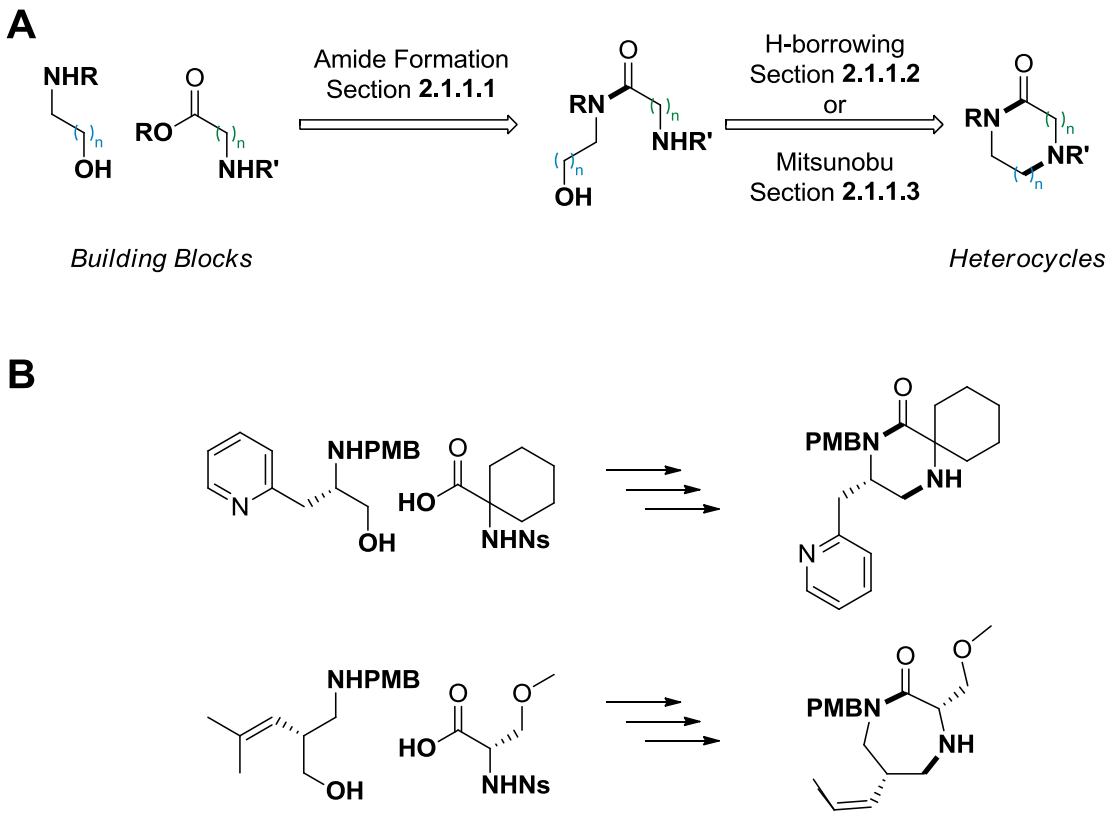


Figure **6**: Proposed approach to the synthesis of ketopiperazines and related ring systems. Panel **A**- Proposed general approach for the formation of ketopiperazines through the condensation of amino acid and amino alcohol derived building blocks. This approach would exploit sequential amide formation and intramolecular cyclisation to generate new heterocycles (new bonds formed are highlighted by broad bonds). Panel **B**- Examples of diverse ketopiperazine derived heterocycles which might be synthesised using this approach.

Initially, a pair of readily available building blocks – an amino acid derivative and an amino alcohol derivative – would be coupled by amide formation. Subsequently, it was proposed to form a new heterocyclic ring system, either using hydrogen-borrowing chemistry or a Mitsunobu reaction. The development of methods for these individual steps are outlined in Sections **2.1.1.2** and **2.1.1.3** respectively. Ideally, the methods developed to generate ketopiperazine–derived heterocycles would be performed using as few labour intensive purification steps as possible. As such, synthetic approaches have also taken into account the potential impurities for each coupling step. The scope and limitations of this approach were investigated by the synthesis (Section **2.1.2**) and subsequent coupling of varied amino acid and amino alcohol building blocks (Section **2.1.2.3**). The potential power of this approach was illustrated by the *in silico* generation of a diverse ketopiperazine based library from commercial amino alcohols and amino acids, guided by the results of the scope and limitation studies (Section **2.1.3**).

2.1.1 Reaction Development

This Section outlines the development of methodology for the efficient condensation of model amino acids and amino alcohols (Section **2.1.1.1**) and subsequent intramolecular cyclisation to give ketopiperazine ring systems (Section **2.1.1.2** and **2.1.1.3**).

2.1.1.1 Synthesis of Building Blocks for the Investigation of the Approach

In order to study the initial development of the method discussed in section **2.1** a small selection of commercially available amino acid and amino alcohol building blocks was required; these building blocks are shown in Figure **7**.

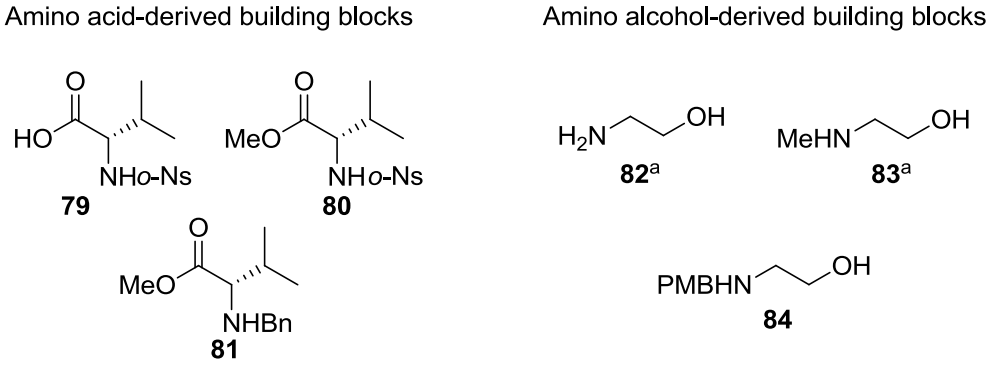
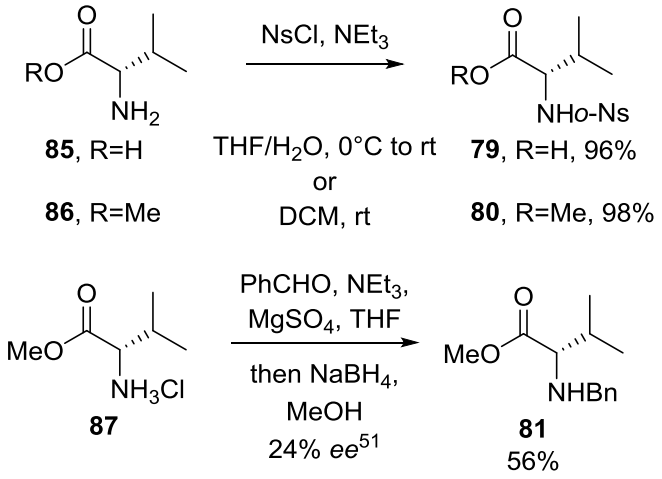


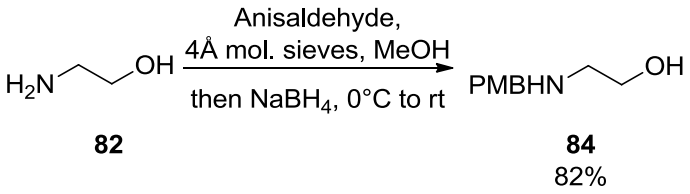
Figure **7**: Amino acid and amino alcohol building blocks required for the development of methodology. [a] Commercially available.

The synthesis of non-commercially available amino acid derived building blocks is outlined in Scheme **15**. The sulfonamides **79** and **80** were synthesised from the amino acid **85** and amino ester **86** respectively by treatment with 2-nitrobenzenesulfonyl chloride. [50] The amino ester **81** was obtained from the hydrochloride salt **87** by means of a two-step reductive amination sequence. [51]



Scheme **15**: Synthesis of valine-derived building blocks

The required amino alcohol building blocks were procured from commercial sources. However, the amino alcohol **84** was not readily available and was subsequently synthesised.[52] The amino alcohol **84** was synthesised from the amine **82** using a two-step reductive amination procedure as shown in Scheme **16**.

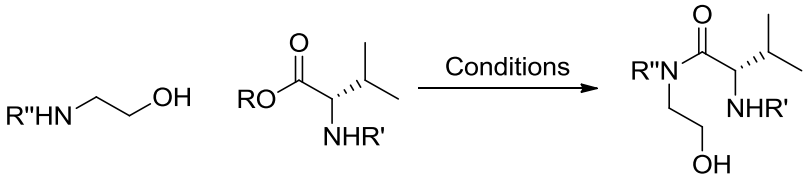


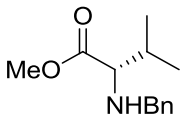
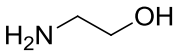
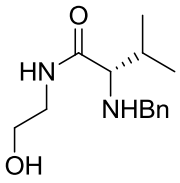
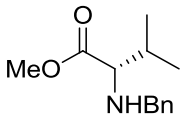
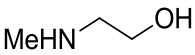
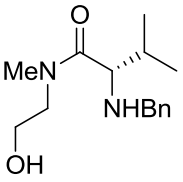
82 **84** 82%

Scheme **16**: Synthesis of **8** from **7** by reductive amination

2.1.1.2 Methods for Amide Formation

With a small selection of amino acid and amino alcohol derived building blocks in hand, the first step of the proposed bifunctional pairing approach was studied. The synthesis of cyclisation substrates through the amide coupling of amino alcohol building blocks and either amino acid- or amino ester- building blocks was studied and is outlined in Table **3.**



Entry	Amino Acid Derivative	Amino Alcohol	Conditions	Product	Yield (%)
1			A	 **88**	88
2			A	 **89**	91

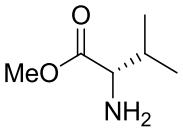
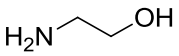
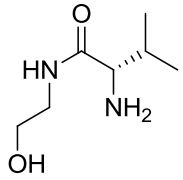
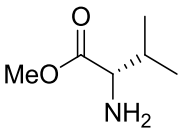
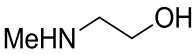
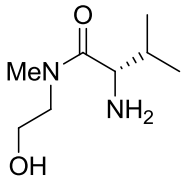
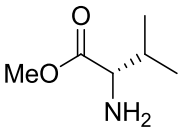
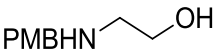
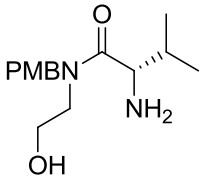
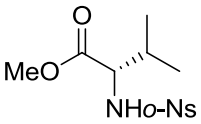
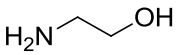
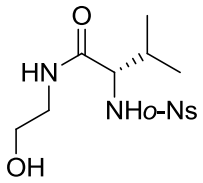
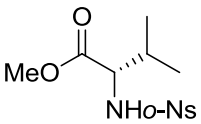
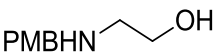
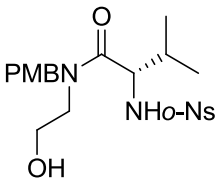
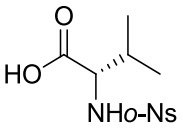
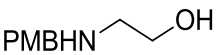
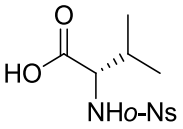
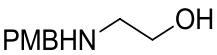
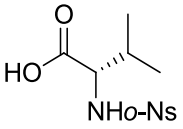
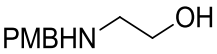
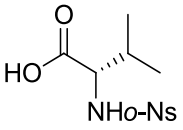
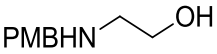
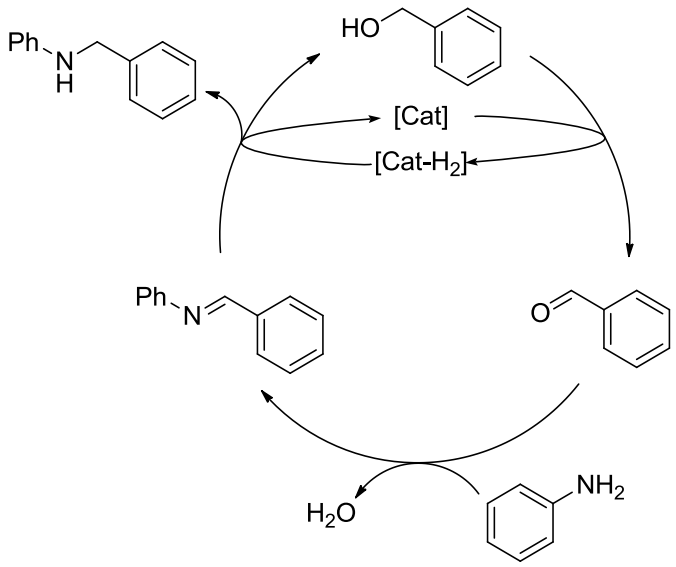
3			A	 **90**	75
4			B	 **91**	72
5			C	 **92**	56
6			A	 **93**	78
7			C	 **94**	18
8			D	**94**	No reaction[a]
9			E	**94**	38
10			F	**94**	No reaction[a]
11			G	**94**	70*

Table **3**: Investigation into the condensation of amino acid and amino alcohol derivatives. *Yield calculated by integration of the 500 MHz ^{1}H NMR- comparison of product to coupling agent by-product. [a] No product observed by TLC or LCMS analysis of crude reaction mixtures. Conditions: A: TBD (30 mol%), 70°C; B: 30 mol% TBD, NEt_3 , MeOH, 70°C; C: 30 mol% TBD, PhMe, 70°C; D: DCC; E: Acid, $SOCl_2$, DCM, then Amino alcohol, Na_2CO_3, DCM; F: PPh_3Cl_2, $CHCl_3$; G: Acid, Ghosez's reagent, DCM then Amino alcohol, K_2CO_3,

TBD-catalysed amide formation from methyl esters (Table **3**, entries 1-7) generally proceeded in high yield.[53] However, reactions between the amino esters **86** and **80** and the amino alcohol **84** (entries 5 and 7) were slow to progress, giving poor yields of expected product, and required dilution of the viscous reaction mixtures to allow the reaction to proceed. The condensation of the acid **79** with the amine **84** under a variety of conditions (entries 8-11) gave mixed results. The best results were achieved using Ghosez's reagent, to generate an acid chloride intermediate, (entry 11) which was significantly higher yielding than the TDB mediated method (entry 7).[54] As such, it was decided Ghosez's reagent would be exploited in an operationally simple approach to give model amides, with orthogonally cleavable nitrogen protecting groups, in good yields.

2.1.1.3 Heterocycle Formation under Hydrogen Borrowing Conditions

Hydrogen-borrowing approaches allow redox-neutral alkylation of nucleophiles through a reductive alkylation manifold.[55] The alkylation of amines with alcohols is proposed to proceed through a reductive amination process as illustrated in Scheme **3**.



Scheme **17**: Proposed[55,56] catalytic manifold for hydrogen borrowing alkylation of aniline with benzyl alcohol.

In order to investigate hydrogen borrowing as a route to intramolecular cyclisation towards heterocycles the commercially available $[Ir(Cp^*)Cl_2]_2$ complex was used to investigate substrate compatibility. A selection of amines were treated with an alcohol under conditions which have been demonstrated to induce hydrogen borrowing alkylation as outlined in Table **4**.[56]

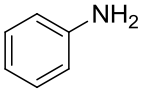
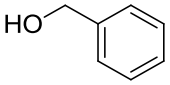
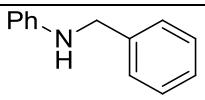
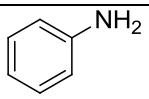
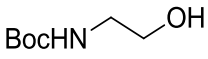
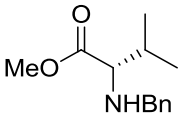
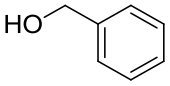
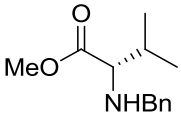
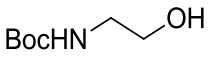
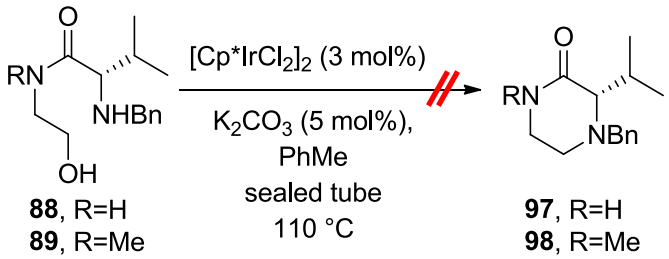
Entry	Amine	Alcohol	Product	Yield (%)
1			 **96**	75
2			—	0
3			—	0
4			—	0

Table **4**: Attempted amine alkylation under hydrogen borrowing conditions. Conditions- amine, alcohol, $[Cp^*IrCl_2]_2$ (3 mol%), K_2CO_3 (5 mol%), PhMe, 110°C, sealed tube.

Gratifyingly, repeating literature conditions (Table **4**, entry 1) led to the aniline **96** in a yield comparable to that reported.[56] However, variation of either amine or alcohol source led to a complete loss in reactivity in the intermolecular alkylation (entries 2-4).

It was hypothesised that an intramolecular hydrogen borrowing approach may allow an approach towards heterocycle formation. With amides **88** and **89** in hand, the intramolecular cyclisation under iridium catalysed conditions were studied as shown in Scheme **18**. Attempts to induce intramolecular cyclisation using the $[Ir(Cp^*)Cl_2]_2$ system reported by Fujita failed to give any desired material with significant quantities of starting material remaining even after extended reaction times (>48 h). A potential hypothesis for the failure of this approach is that the amide substrate may form a stable chelate with the iridium thus preventing any free catalyst from performing the desired transformation (Figure **8**). Due to this clear substrate incompatibility with iridium catalysed hydrogen borrowing methodology this route was abandoned.



88, R=H
89, R=Me

97, R=H
98, R=Me

Scheme **18**: Attempted iridium mediated intramolecular hydrogen borrowing to form keto-piperazines **97** and **98**.

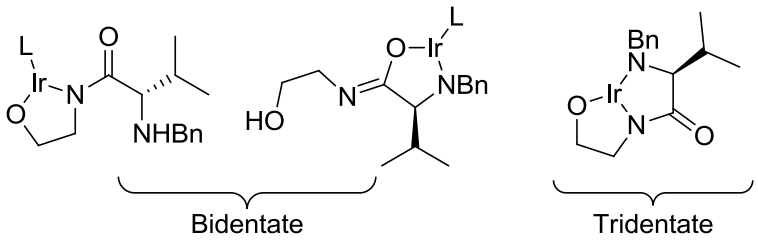
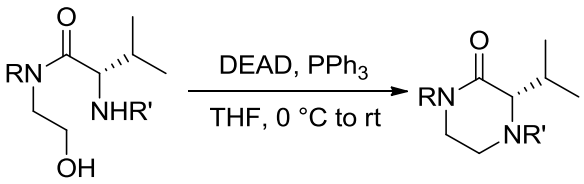


Figure **8**: Hypothesises substrate–catalyst coordination modes preventing catalysis.

Due to this clear substrate incompatibility with iridium catalysed hydrogen borrowing methodology this route was abandoned.

2.1.1.4 Heterocycle Formation under Mitsunobu Conditions

An alternative method for the *in situ* electrophilic hydroxyl group activation to give heterocycles is the Mitsunobu reaction.[47] Accordingly, the amide was treated with diethylazodicarboxylate (DEAD) and PPh_3 in cold (0°C) THF. This approach for intramolecular cyclisation was explored as outlined below (Table **5**).



Entry	R	R'	Yield (%)*	Product
1	H	H	No reaction	**99**
2	H	Ns	No reaction	**100**
3	Me	H	55	**101**
4	PMB	H	73	**102**
5	PMB	*o*-Ns	90	**103**

Table **5**: Cyclisation of keto-piperazine precursors under Mitsunobu conditions.* Isolated yields of purified product. Conditions; Amide (1.0 eq.), DEAD (1.4 eq.), PPh_3 (1.4 eq.), THF (0.05 M), rt.

Exposing amino alcohols **90** and **93** (which are secondary amides) to DEAD and triphenylphosphine in THF failed to give any identifiable cyclic material (Table **5**, entries 1 and 2). However, compounds containing tertiary amides (**91**, **92** and **94**) gave the cyclised products in good yields (entries 3, 4 and 5). 500 MHz ^{1}H NMR analysis of tertiary amides (entries 3, 4 and 5) shows the presence of two rotameric species, arising from slow rotation of the amide bond. It is proposed that a low population of the reactive conformation of the secondary amides, due to a preferred *Z* conformation minimising steric interactions, may be preventing the intramolecular cyclisation as outlined in Figure **9**.

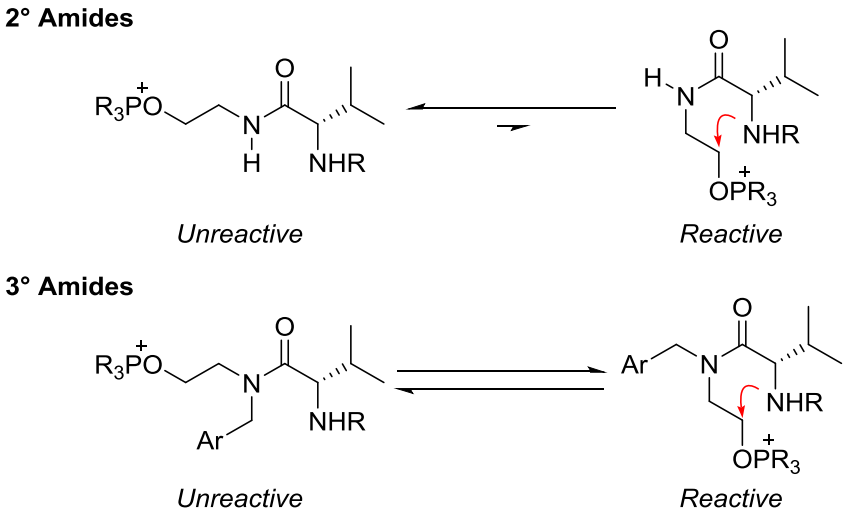


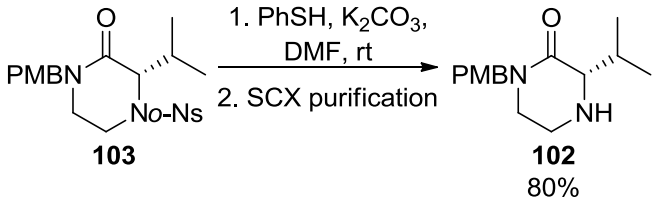
Figure **9**: Reactive and unreactive conformations of reactive intermediates. Conformations place nitrogen nucleophile in close proximity to the C-O σ* orbital allowing cyclisation to proceed. However, unreactive conformations place reactive groups remotely, preventing reaction progression.

Optimal cyclisation was achieved with sulfonamide **94** (Table **5**, Entry 5), presumably due to the increased acidity of the amine N-H (pKa approx. 10),[58] and subsequently the nitrobenzensulfonyl (Ns)[59] group was employed in further building blocks.

2.1.1.5 Ketopiperazine Deprotection

As incorporation of the nosyl group led to optimal yields of ketopiperazine **102** (Table **3**, Entry 5) it was deemed necessary to study the removal of the sulfonamide group in order to facilitate future scaffold elaboration. The cleavage of both 2- and 4- isomers of the nosyl group has been demonstrated with a variety of nucleophilic reagents (usually thiols). The

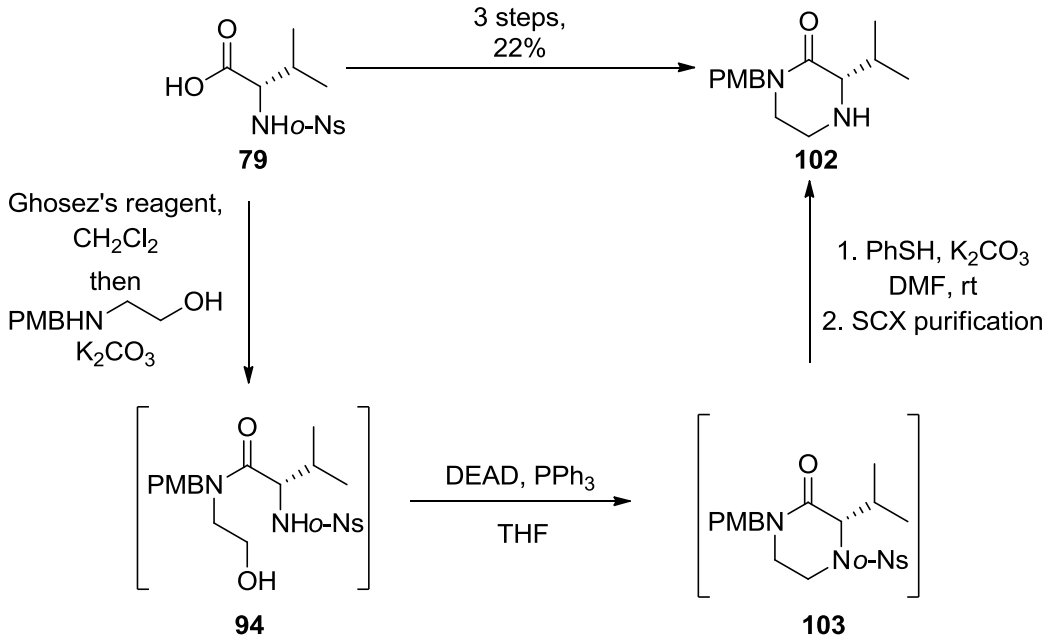
compatibility of this deprotection approach with ketopiperazines was investigated as shown in Scheme **19**. Treatment of the sulfonamide **103** with thiophenol and K_2CO_3 in DMF led to the clean isolation of **76** after isolation of the free base by ion exchange resin.



Scheme **19**: Nosyl group cleavage under nucleophilic conditions

2.1.1.6 Development of a 'One-Pot' Procedure

With a reliable method for the step-wise synthesis of ketopiperazine **76** from amino alcohol **84** and amino acid **79** in hand, efforts were focussed on the telescoping of the process. In order to develop a minimally labour-intensive approach, avoiding laborious purification steps such as column chromatography, a telescoped route for the synthesis of ketopiperazine **76** from amino acid **79** was investigated. The approach taken to the telescoping of the ketopiperazine formation process is outlined in Scheme **20**.



Scheme **20**: Telescoped route to the formation of ketopiperazine **76** using SCX as the only purification step. Compounds in square brackets were used as crude mixtures.

The treatment of the acid **79** with Ghosez's reagent, followed by amino alcohol **84** and K_2CO_3 in dichloromethane presumably gave the amide **94** as a crude reaction mixture after

aqueous work up. The crude mixture of **94** was then treated with diethylazodicarboxylate (DEAD) and triphenylphosphine which induced heterocycle formation. Finaly, cleavage of the 2-nitrophenylsulfonamide (*o*-Ns) group with thiophenol and K_2CO_3 in DMF, followed by purification with strong cation exchange resin (SCX), gave the ketopiperazine **102** in 22% yield over 3 synthetic steps. In comparison, the step-wise synthesis of the ketopiperazine **76** proceeded in an overall yield of 50%, requiring the purification of intermediates **94** and **102** by column chromatography. The lower yields presumably stems from unreacted starting materials or by-products reacting with required intermediates to give unwanted material. However, although the yields are diminished, this process demonstrated the viability of the ambiphile-pairing approach with minimal labour-intensive purification.

2.1.2 Scope and Limitation Studies

The scope and the limitations of this amino acid- amino alcohol pairing approach was investigated by the systematic variation of amino alcohol and amino acid building blocks bearing varied substitution on the carbon chains. The proposed building blocks were selected to include substitution on the amino alcohol chains (both α and β to OH), cyclic substituents (towards the incorporation of fused ring systems) and extended chain variants (1,2- and 1,3- amino alcohols towards variation of heterocycle size). The building blocks required for these scope and limitation studies are outlined in Figure **10**.

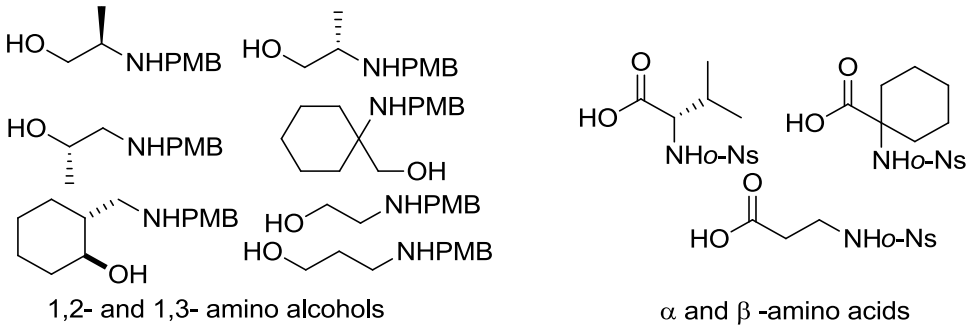


Figure **10**: Proposed building blocks for scope and limitation studies.

2.1.2.1 Synthesis of Amino Alcohol Building Blocks

The amino alcohol building blocks identified in Section **2.1.2** were synthesised from commercially available amino alcohols. In each case the primary amine was reductively aminated by treatment with anisaldehyde and an appropriate reducing agent (Table **6**).[60]

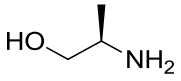
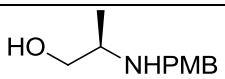
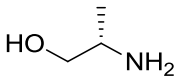
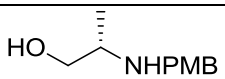
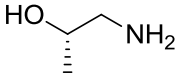
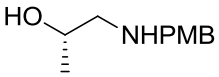
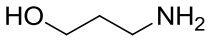
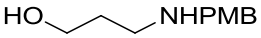
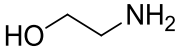
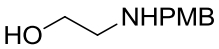
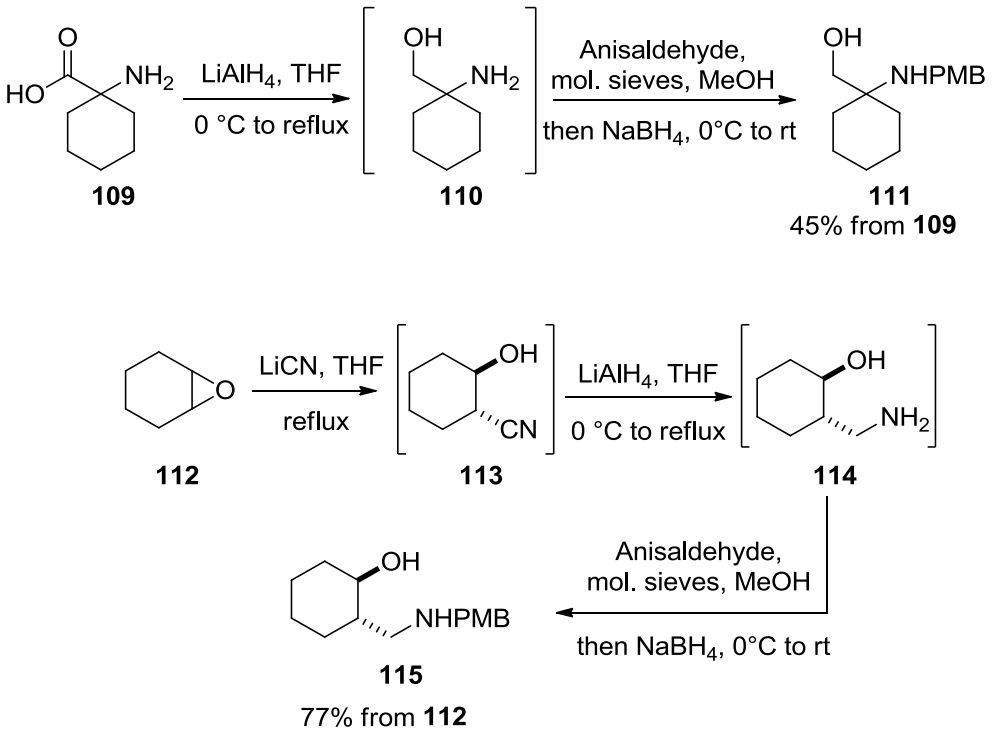
Entry	Primary amine	Conditions[a]	Product	Yield (%)[b]
1		A	 **105**	89
2		A	 **106**	80
3		A	 **107**	64
4		B	 **108**	80
5		A	 **84**	82

Table **6**: Synthesis of N-PMB amino alcohols by reductive amination. [a]Conditions; A- amino alcohol (1.0 eq.), anisaldehyde (1.2 eq.), 4 Å mol. sieves, MeOH (1 M), 50 °C then $NaBH_4$ (2.0 eq.), 0 °C to rt; B- anisaldehyde (1.0 eq.), amino alcohol (2.0 eq.), $Na(CN)BH_3$ (1.0 eq.) MeOH (0.1 M), rt. [b] Isolated yields.

A similar approach was employed to prepare the amino alcohols **111** and **115**. In these cases, the parent amino alcohol was synthesised and subsequently alkylated, without isolation, to give the required secondary amine. The synthese of the amino alcohols **111** and **115** are outlined in Scheme **21**.[61, 62]

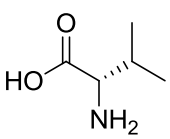
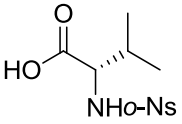


Scheme **21**: Multistep synthesis of the amino alcohols **111** and **115**.

Reduction of amino acid **109** with $LiAlH_4$ gave the intermediate amino alcohol **110** which was used as a crude mixture for the reductive alkylation with anisaldehyde to give amino alcohol **111** in 45% over two steps. The synthesis of amino alcohol **115** was achieved by the treatment of the epoxide **112** with LiCN to give the nitrile **113** which was reduced with $LiAlH_4$ to give the amino alcohol**114** as a crude product; which was then alkylated under reductive conditions to give the amino alcohol **115** in 77% yield over 3 steps.

2.1.2.2 Synthesis of Amino Acid Building Blocks

The sulfonamides identified in section 2.1.2 were synthesised from commercially available amino acids. Treatment of the commercially available amino acids with 2-nitrobenzenesulfonyl chloride under biphasic conditions gave the required sulfonamides **79** and **116** (Table **7**, entries 1 and 2). The preparation of the hindered amino acid **117** required the temporary protection of the acid group, giving **117** in 35% yield (entry 3).

Entry	Amino Acid	Conditions[a]	Product	Yield (%)[b]
1		A	 **79**	98

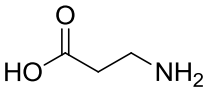
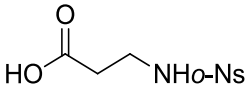
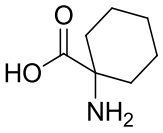
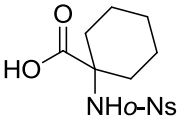
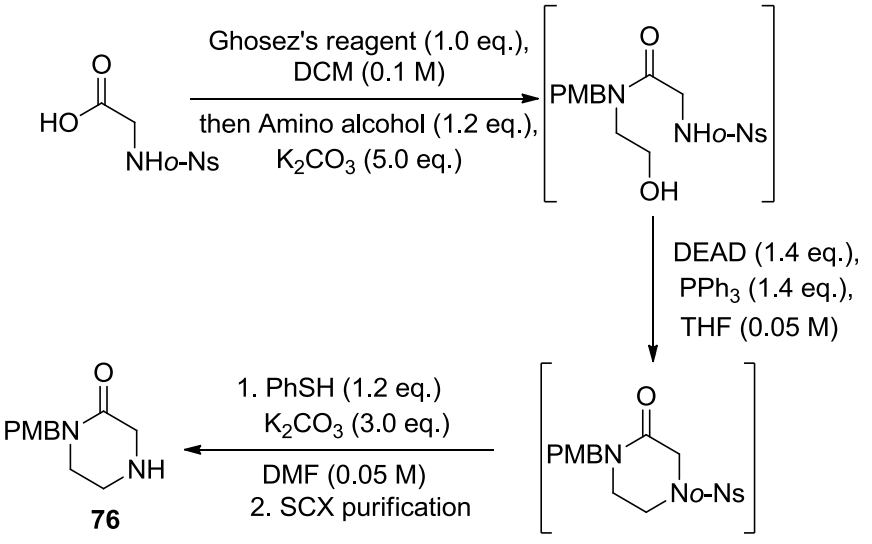
2		A	 **116**	46
3		A B C	 **117**	No isolated material No isolated material 35

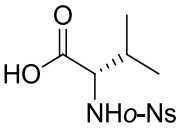
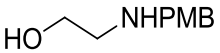
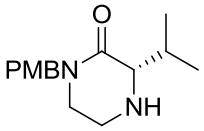
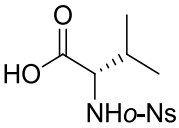
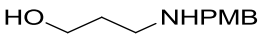
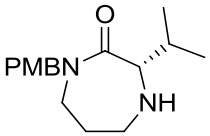
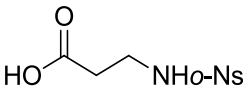
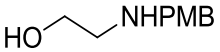
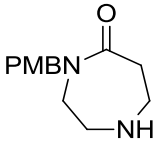
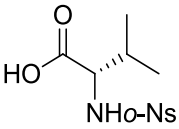
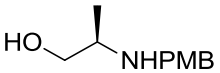
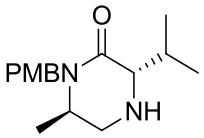
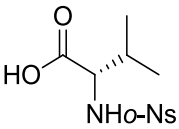
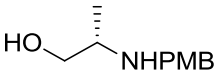
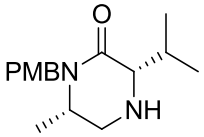
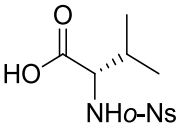
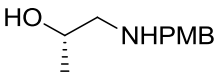
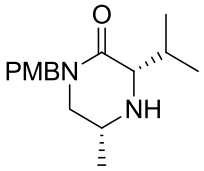
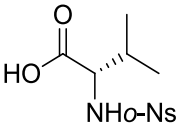
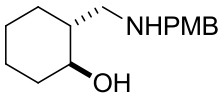
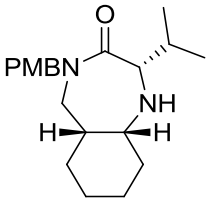
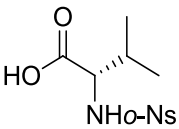
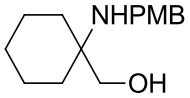
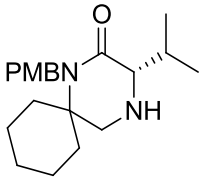
Table **7**: Synthesis of sulfonamides from amino acids. [a] Conditions; A- Amino acid (1.0 eq.), NsCl (1.3 eq.), THF/H_2O (1:3.5, 0.8 M); B- Amino acid (1.0 eq.), NsCl (1.5 eq.), $NaHCO_3$ (2.0 eq.), DMF/ H_2O (1:1, 0.2 M); C- Amino acid (1.0 eq.), *N*, *O*- Bistrimethylsilylacetamide (2.0 eq.), CH_2Cl_2 (0.2 M), then NsCl (1.1 eq.), then $NaHCO_3$ (5% w/w, 0.2M). [b] Isolated yields.

2.1.2.3 Scope and Limitation Studies- Building Block Pairing

With the required building blocks in hand investigations into the systematic coupling of building blocks were carried out using the general procedure shown in Scheme **8**. In each case, the acid building block was treated with Ghosez's reagent in dichloromethane, followed by addition of the appropriate amino alcohol and K_2CO_3 to give the amide intermediate which was not isolated. Amide intermediates were treated with DEAD and triphenylphosphine to give a crude heterocycle; subsequent exposure to thiophenol and K_2CO_3 gave the final deprotected heterocycle after purification with ion exchange resin. The results of this systematic building block coupling are shown in Table **8**.



Scheme **22**: General one pot approach to the formation of ketopiperazine like compounds by amino acid/ amino alcohol pairing illustrated by the synthesis of **76**.

Entry	Acid	Amino alcohol	Product	Yield (%)[a]
1			 **102**	22
2			 **118**	12
3			 **119**	9
4			 **120**	5
5			 **121**	18
6			 **122**	42
7			 **123**	-
8			 **124**	-

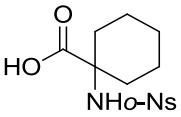
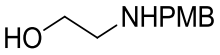
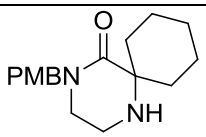
9			 **125**	15

Table **8**: Synthesis of ketopiperazine based ring systems for the determination of scope and limitations in the amino acid - amino alcohol pairing approach. [a] Isolated yields of compound over 3 step procedure outlined in Scheme **22**.

2.1.3 Summary Amino Acid – Amino Alcohol Pairing

Overall, these scope and limitation studies gave ketopiperazine and ketopiperazine derived heterocycles in generally disappointing yields, as outlined in Table **8**. However, it is clear that heterocycle size can be readily altered by the variation of either amino alcohol (entry 2) or amino acid (entry 3) when comparing with model ketopiperazine **76** (entry 1). Alkyl substituents are tolerated in the amino alcohol building blocks; either α- or β- to the hydroxy group (entries 4, 5 and 6) allowing substitution to be incorporated directly onto the heterocycle carbon framework. More complex substitution in amino alcohol building blocks are not well tolerated (entries 7 and 8) which may be due to steric factors affecting the amide formation step. However, spirocyclic substitution is well tolerated in the amino acid building blocks (entry 9). The achieved yields in this approach were often low and this may be indicative of significant undesired by-products. However, this approach clearly demonstrates the concept of bifunctional building block coupling through amino acid and amino alcohol pairing, thus acting as a 'proof of principle'.

2.2 Overview of Cyclic Sulfamidate – Hydroxy Sulfonamide Pairing

This Section describes the development of an approach for the synthesis of piperazines and related heterocycles. This approach involved the coupling of cyclic sulfamidate and amino alcohol building blocks, followed by an intramolecular cyclisation (Figure **11**). It was envisaged that variation of either, or both, building blocks would facilitate access to heterocycles of varied size and substitution patterns (Figure **11**, Panel **B**).

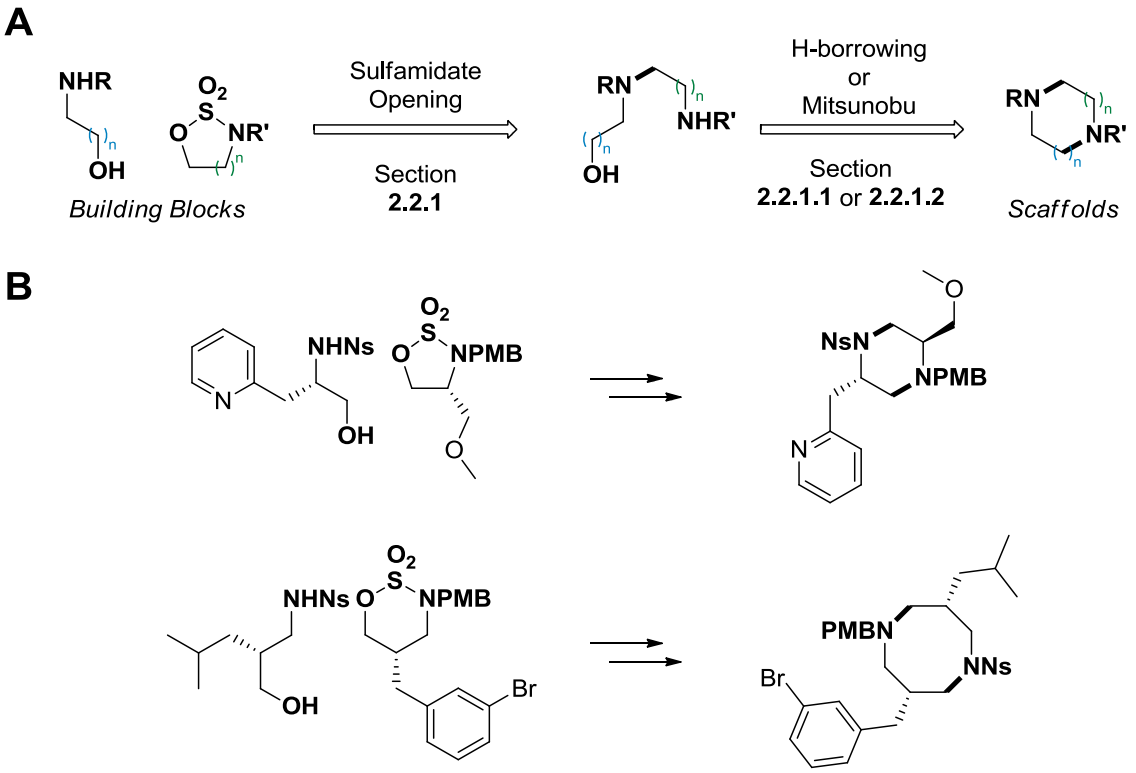


Figure 11: Panel **A-** General approach for the formation of piperazines through the fusion of amino alcohol building blocks. This approach would exploit sequential C-N bond forming steps (highlighted with bold bonds) to generate new heterocycles. Panel **B-** Examples of diverse piperazine-like heterocycles which might be synthesised using this approach.

Initially, pairs of readily available amino alcohol and cyclic sulfamidate building blocks would be chemoselectively paired using sequential C-N bond forming steps: cyclic sulfamidate opening and cyclisation using either hydrogen borrowing or Mitsunobu methods (Section **2.2.1**). The scope and limitations of this approach were investigated by systematically varying the combination of amino alcohol and cyclic sulfamidate building blocks and studying the subsequent pairing reactions (Section **2.2.2**). The potential power of this approach was further illustrated by the *in silico* enumeration of likely accessible diverse lead-like heterocycles from readily or commercially available building blocks (Section **2.2.3**) and exemplified by the synthesis of a small library of diverse heterocycles (Section **2.2.4**).

2.2.1 Reaction development

To investigate the feasibility of the proposed amino alcohol pairing approach a model system was devised. This model system was based on the pairing of the ethanolamine-derived cyclic sulfamidate **130** and the hydroxy sulfonamide **131** to give the piperazine **78** (Figure **12**).

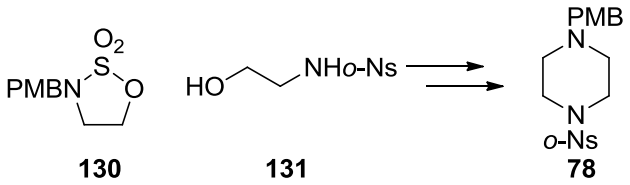


Figure **12**: Proposed model piperazine synthesis through formal dimerisation of ethanolamine.

In order to control selectivity (*i.e.* hetero-pairing of building blocks over homo-pairing) in the approach proposed above, consideration needs to be focussed on controlling the reactivity of functional groups in each reaction step. Cyclic sulfamidates behave as latent ambiphiles, *i.e.* their nucleophilic character is only revealed upon successful opening and subsequent sulfamic acid hydrolysis (Figure **13**).

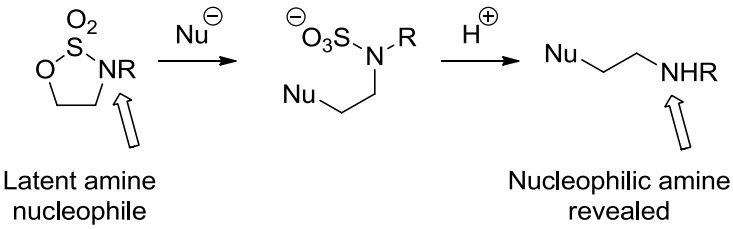
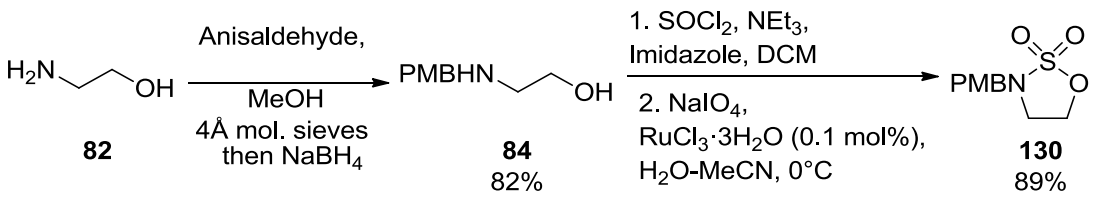


Figure **13**: General reactivity of cyclic sulfamidates allowing the selective unmasking of latent nucleophiles under protic conditions.

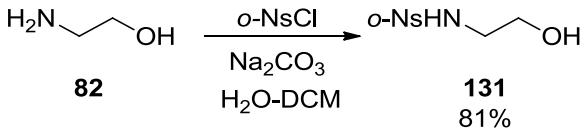
2.2.1.1 Synthesis of Building Blocks for the Investigation of the Approach

Ethanolamine-derived building blocks **84** and **131** were synthesised by employing literature methods (Scheme **23**). Reductive amination of the amine **82** with anisaldehyde gave the amino alcohol **84** which was subsequently converted into the cyclic sulfamidate **130** using the two-step cyclisation/ oxidation procedure developed by the Gallagher group.[64]



Scheme **23**: Synthesis of cyclic sulfamidate **130** from the amino alcohol **82**.

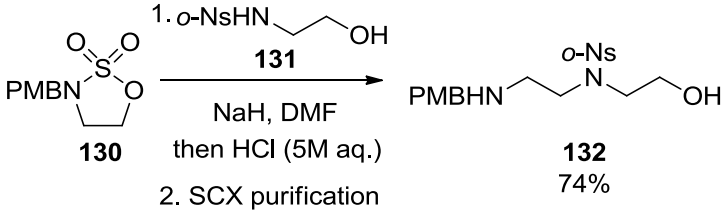
The sulfonamide **131** was synthesised by the treatment of ethanolamine **82** with 2-nitrobenzensulfonyl chloride under Schotten—Baumann conditions (Scheme **24**).



Scheme **24**: Synthesis of the sulfonamide **131** from the amino alcohol **82**.

2.2.1.2 Ring Opening of Cyclic Sulfamidates with Hydroxy Sulfonamides.

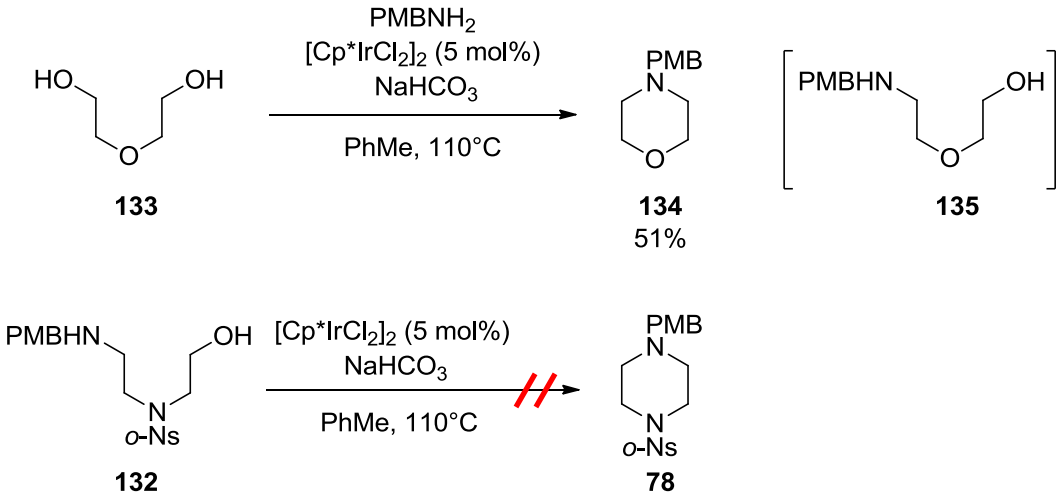
With both the cyclic sulfamidate **130** and the hydroxy sulfonamide **131** in hand the intermolecular pairing was investigated (Scheme **25**). Treatment of the sulfonamide **131** with sodium hydride in DMF followed by the addition of the cyclic sulfamidate **130** led to the isolation of the amine **132** after proteolytic work up.[65] In this case, facile purification by strong cation exchange (SCX) resin gave the expected material as pure product. This method of purification was deemed particularly powerful in this pairing step as only successful pairing of the building blocks **130** and **131** reveal the basic amine present in **132**, allowing for purification by SCX (no trace of **84** was observed through a potential acid mediated decomposition of cyclic sulfamidate **130**). Although the sulfonamide **131** could be seen as nucleophilic at both *N* and *O* termini; the only observed product was the amine **132** with no polymerisation or *O*-alkylation observed. This selectivity is believed to be due to the differences in pKa between the sulfonamide NH and alcohol OH (pKa approx. 10 and 15 respectively[58]) allowing selective deprotonation of the sulfonamide and facilitating *N*-alkylation.



Scheme **25**: Nucleophilic opening of cyclic sulfamidate **130** with sulfonamide **131** under basic conditions.

2.2.1.3 Heterocycle Formation under Hydrogen Borrowing Conditions

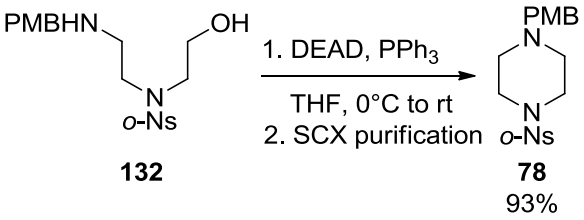
Having identified a facile method for the formation of the amine **132**, the subsequent intramolecular cyclisation was studied using hydrogen borrowing methodology (Scheme **26**). In a replication of literature method, the diol **133** was reacted with *p*-methoxybenzylamine by treatment with 5 mol% $[Cp^*IrCl_2]_2$ which led to the formation of the morpholine **134**.[66] Presumably, this method proceeds *via* an amino alcohol intermediate, such as **135**. Attempts to induce intramolecular cyclisation of **132** using 5 mol% $[Cp^*IrCl_2]_2$ resulted in recovered starting materials or traces of debenzylated starting material. This contrasting reactivity may stem from the potential for metal-substrate chelation resulting in the inactivation of the catalyst as previously discussed (Section **2.1.1.3**).



Scheme **26**: Attempted piperazine formation through intramolecular hydrogen borrowing approach from amino alcohols.

2.2.1.4 Heterocycle Formation under Mitsunobu Conditions

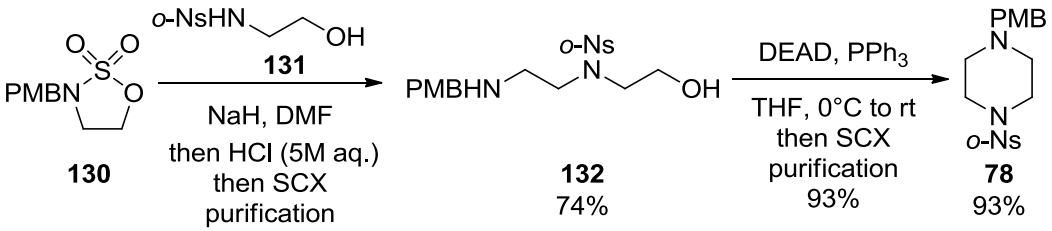
With the failure of hydrogen borrowing, attention was turned to an alternative method of activation of the hydroxyl group. The amine **132** was treated with diethylazodicarboxylate (DEAD) and triphenylphosphine: the piperazine **78** was obtained in a 93% yield after isolation with ion exchange resin (Scheme **27**).



Scheme **27**: Cyclisation of the amino alcohol **132** to the piperazine **78** under Mitsunobu conditions.

2.2.1.5 Summary of Cyclic Sulfamidate – Hydroxy Sulfonamide Paring Method

The combination of both anionic opening of cyclic sulfamidates with sulfonamides and cyclisation of the resulting acyclic intermediate, under Mitsunobu conditions, was thus validated as a process for the fusion of amino alcohol derived ambiphilic building blocks. Furthermore, the use of strong cation exchange resins as a facile purification method was also validated (Scheme **28**).



Scheme **28**: Validated approach for the synthesis of piperazines by ambiphilic paring of amino alcohols.

2.2.2 Scope and Limitation Studies

In order to determine the scope for the formation of heterocycles (Scheme **5**), a small selection of substrates was chosen. The factors which were studied were:

1. Ring Size- Potential for variation of the size of the heterocyclic ring system.
2. Substitutional Diversity- Potential to vary the pattern of substituents on carbon atoms in the heterocycle.
3. Matched and Mismatched effects- The potential to prepare either diastereoisomeric series of heterocycles with substitutions on the carbon atoms in the heterocycle.
4.

2.2.2.1 Synthesis of Cyclic Sulfamidate Building Blocks

The synthesis of a small array of cyclic sulfamidates was performed in order to determine scope and limitations of the approach. The required cyclic sulfamidate building blocks were synthesised from commercially-available amino alcohols (Table **9**).

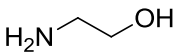
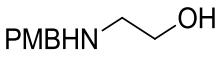
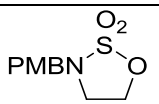
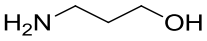
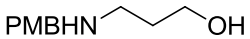
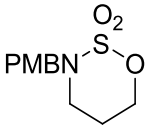
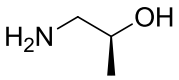
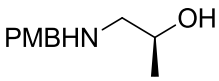
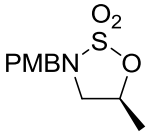
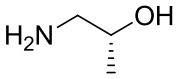
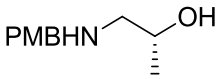
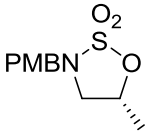
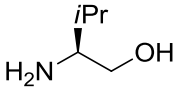
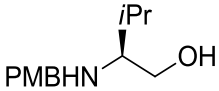
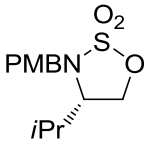
Entry	Amino alcohol	Secondary amine (Yield, %)	Yield (%)	Cyclic sulfamidate (Yield, %)	Yield (%)
1		 **84**	82	 **130**	89
2		 **108**	90	 **144**	83
3		 **107**	98	 **145**	95
4		 **140**	93	 **146**	88
5		 **141**	80	 **147**	89

Table **9**: Synthesis of cyclic sulfamidates. *Reagents and conditions*; 1. Anisaldehyde (1.2 eq,), MeOH (1.0 M) 4Å mol. sieves., 50 °C then $NaBH_4$ (2.0 eq.), 0 °C to rt. 2. $SOCl_2$ (1.1 eq.), imidazole (4 eq,), NEt_3 (2.2 eq.), CH_2Cl_2 (0.1 M), −60 °C to rt., 4. Cyclic sulfamidite (1.0 eq.), $NaIO_4$ (1.1 eq.), $RuCl_3{\cdot}3H_20$ (0.1 mol.%), MeCN (0.13 M), H_2O (0.13 M) 0 °C to rt.

The synthesis of cyclic sulfamidates from commercially available amino alcohols was performed using a two-step reductive amination procedure with anisaldehyde, giving amines **84**, **107**, **108**, **140** and **141** in good yields (Table **9**). Subsequent two-step cyclic sulfamidate formation was undertaken by treatment of the amino alcohol with thionyl chloride, to give the corresponding cyclic sulfamidite, followed by oxidation using $NaIO_4$ and catalytic amounts of $RuCl_3$ to the target materials **130**, **144–147**. In all cases, this approach proceeded in uniformly high yields for both reductive amination and subsequent cyclic sulfamidate formation steps.

2.2.2.2 Synthesis of Hydroxy Sulfonamide Building Blocks

The synthesis of required sulfonamides from commercially-available amino alcohols was performed by treatment with 2-nitrobenzenesulfonyl chloride under Schotten—Bauman conditions (Table **10**). In all cases, sulfonamide formation proceeded well, giving the target sulfonamides in >80% yield.

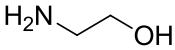
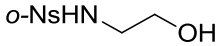
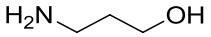
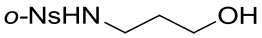
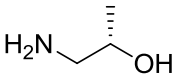
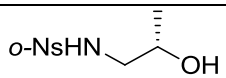
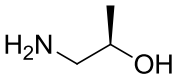
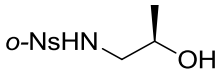
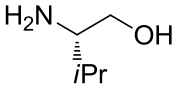
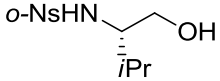
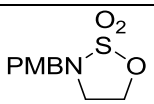
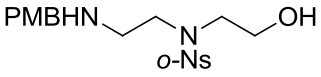
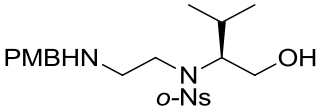
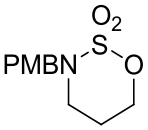
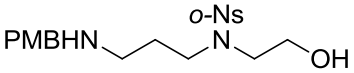
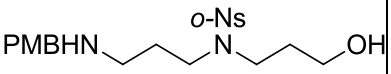
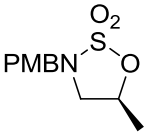
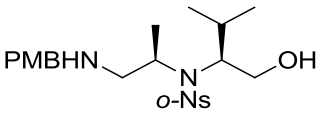
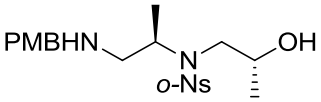
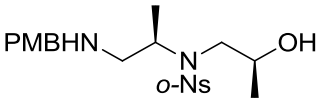
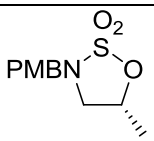
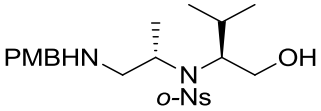
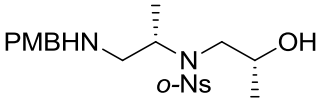
Entry	Amino Alcohol	Sulfonamide	Yield (%)
1		 **131**	84
2		 **151**	98
3		 **152**	94
4		 **153**	95
5		 **154**	88

Table **10**: Synthesis of hydroxysulfonamides. Reagents and conditions; Amino alcohol (1.05 eq.) 2-nitrobenzenesulfonyl chloride (1.0 eq.), Na_2CO_3 (1.05 eq.), CH_2Cl_2–H_2O (1:1, 0.8 M)

2.2.2.3 Scope and Limitation Studies- Building Block Pairing

Combinations of the amino alcohol and cyclic sulfamidate building blocks were systematically investigated. In each case the hydroxy sulfonamide building block was treated with NaH in DMF, followed by the addition of a cyclic sulfamidate building block. Upon completion of the reaction (as determined by TLC and LCMS analysis), the reaction mixture was treated with HCl to cleave residual sulfamic acid intermediates allowing the basic nature of the amine to be revealed. Purification of crude reaction mixtures by treatment with strong cation exchange resin gave cyclisation substrates (Table **11**).

Entry	Cyclic sulfamidate	Hydroxy Sulfonamide	Amino alcohol	Yield (%)
1	 **130**	**131**	 **132**	74
2	**130**	**154**	 **156**	72
3	 **144**	**131**	 **157**	49
4	**144**	**151**	 **158**	60
5	 **145**	**154**	 **159**	0[a]
6	**145**	**153**	 **160**	68
7	**145**	**152**	 **161**	71
8	 **146**	**154**	 **162**	0 [a]
9	**146**	**153**	 **163**	78

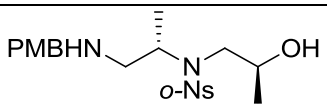
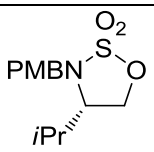
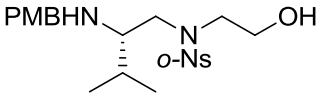
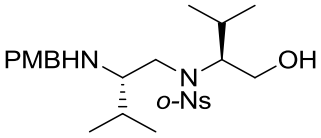
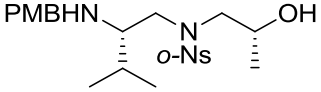
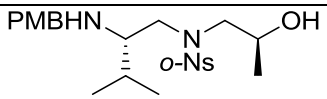
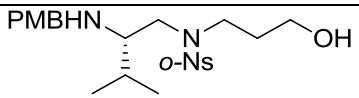
10	**146**	**152**	 **164**	74
11	 **147**	**131**	 **165**	75
12	**147**	**154**	 **166**	0 [a]
13	**147**	**153**	 **167**	87
14	**147**	**152**	 **168**	86
15	**147**	**151**	 **169**	78

Table **11**: Nucleophilic opening of cyclic sulfamidates. *Reagents and conditions*; sulfonamide (1.1 eq.), sulfamidate (1.0 eq.), NaH (1.1 eq.), DMF (1.0 M) then HCl (5.0 M, 1 mL). [a] Consumption of cyclic sulfamidate was not observed even after extended reaction times or reaction at elevated temperature (80°C).

Generally, nucleophilic opening of cyclic sulfamidates proceeded smoothly, tolerating variation in sulfamidate ring size and carbon centred substitution in both sulfamidate and sulfonamide building blocks. The combination of enantiomerically-pure building blocks resulted in similar yields of diasteroisomeric products (Table **11**, entries 6 and 7, 9 and 10, 13 and 14) which suggest that any matched/ mismatched effects have no detrimental outcome on the product yield.[67] One readily identifiable limitation is the combination of sulfonamides bearing substitution α- to the sulfonamide nitrogen with substituted sulfamidates (entries 5, 8 and 12) which did not react (even at elevated temperatures). The sulfonamide **147** has been shown to be a competent electrophile under these reaction conditions (entry 2) as have substituted cyclic sulfamidates (entries 6, 9 and 13). As such,

it is believed that the origin of the lack of reactivity arises from steric factors between substituents on both cyclic sulfamidates and sulfonamides (Figure **14**).

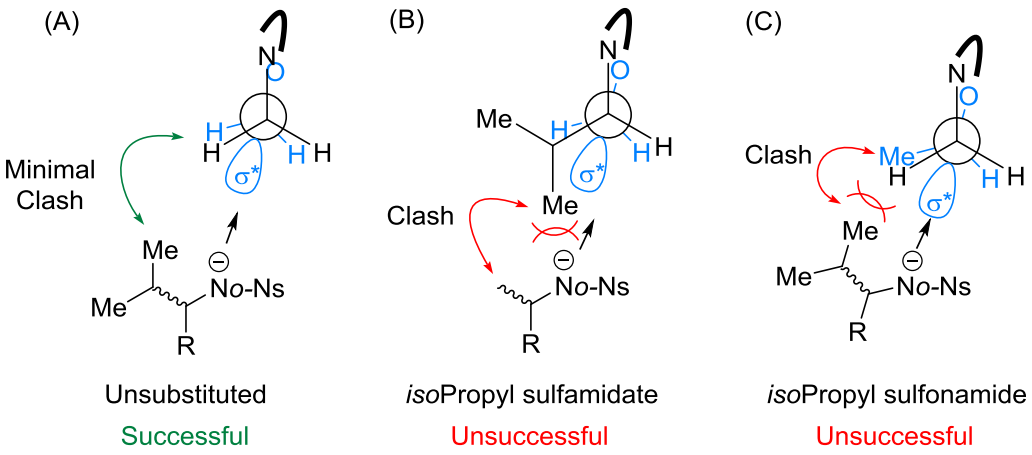
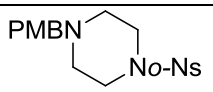
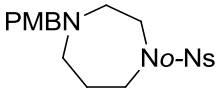
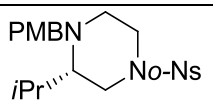
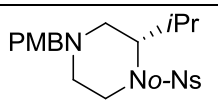


Figure **14**: Orientation of the nucleophile to maximise overlap with the carbon – oxygen σ*orbital (blue) may result in alkyl substituents being proximal to each other ((B) and (C), red arrows) which may hinder reactivity resulting in a lack of observable product when compared to situation (A) with minimal steric interactions (green arrows).

With the acyclic amino alcohols in hand, the ring-closures under Mitsunobu conditions were studied using conditions identified in section **2.2.1.2**. The acyclic amino alcohols were treated with DEAD and triphenylphosphine in THF, followed by purification by treatment with strong cation exchange resin to give the heterocyclic products (Table **12**).

Entry	Amino alcohol	Heterocycle	Yield (%)
1	**132**	 **78**	94
2	**137**	 **170**	80
3	**165**	 **171**	96
4	**156**	 **172**	95

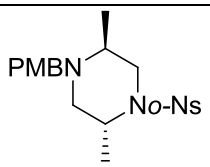
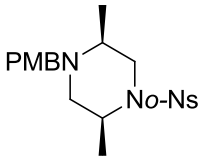
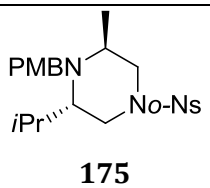
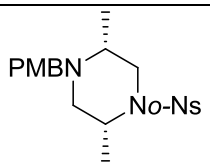
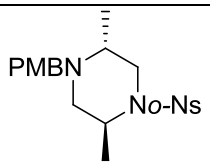
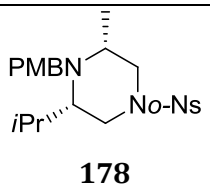
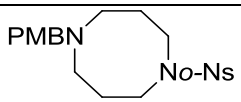
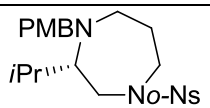
5	**160**	 **173**	48
6	**163**	 **174**	48
7	**167**	 **175**	46
8	**161**	 **176**	41
9	**152**	 **177**	55
10	**168**	 **178**	57
11	**158**	 **179**	95
12	**169**	 **180**	56

Table **12**: Intramolecular cyclisations under Mitsunobu conditions. *Reagents and conditions*; Amino–alcohol (1.00 eq.), DEAD (1.4 eq.), PPh_3 (1.4 eq.), THF (0.05M), 0 °C to rt.

Cyclisation under Mitsunobu conditions proceeded well in all examples. These conditions allow the variation of ring sizes in good to excellent yields (Table **12**). For example, this approach enabled the synthesis of unsubstituted 6- (entry 1), 7- (entry 2), and 8- (entry 11) membered rings. This methodology is tolerant of having single carbon- based substitutions on either the parent cyclic sulfamidate or amino alcohol building block (entries 3 and 4). Piperazines containing multiple carbon-based substitutions on the heterocycle skeleton are produced in a slightly diminished yield when compared to no substitutions (entries 5 to 10 compared to 1). However, the synthesis of all stereoisomers of **160** (entries 5, 6, 8 and 9) show that there are no significant matched or mismatched effects on the observed product yield, demonstrating the stereospecific nature of this process. Also the synthesis of diastereoisomers **175** and **178** (entries 7 and 10) again reinforce the lack of any significant matched/ mismatched effects.[67]

2.2.3 Diverse Piperazine Based Lead-Like Library

In order to illustrate the potential power of the synthetic approach in the generation of diverse molecules, with properties desired in lead like compounds, an *in silico* library of piperazine and piperazine-like compounds was enumerated.[33] A schematic outline of this *in silico* approach is shown in Figure **15.**

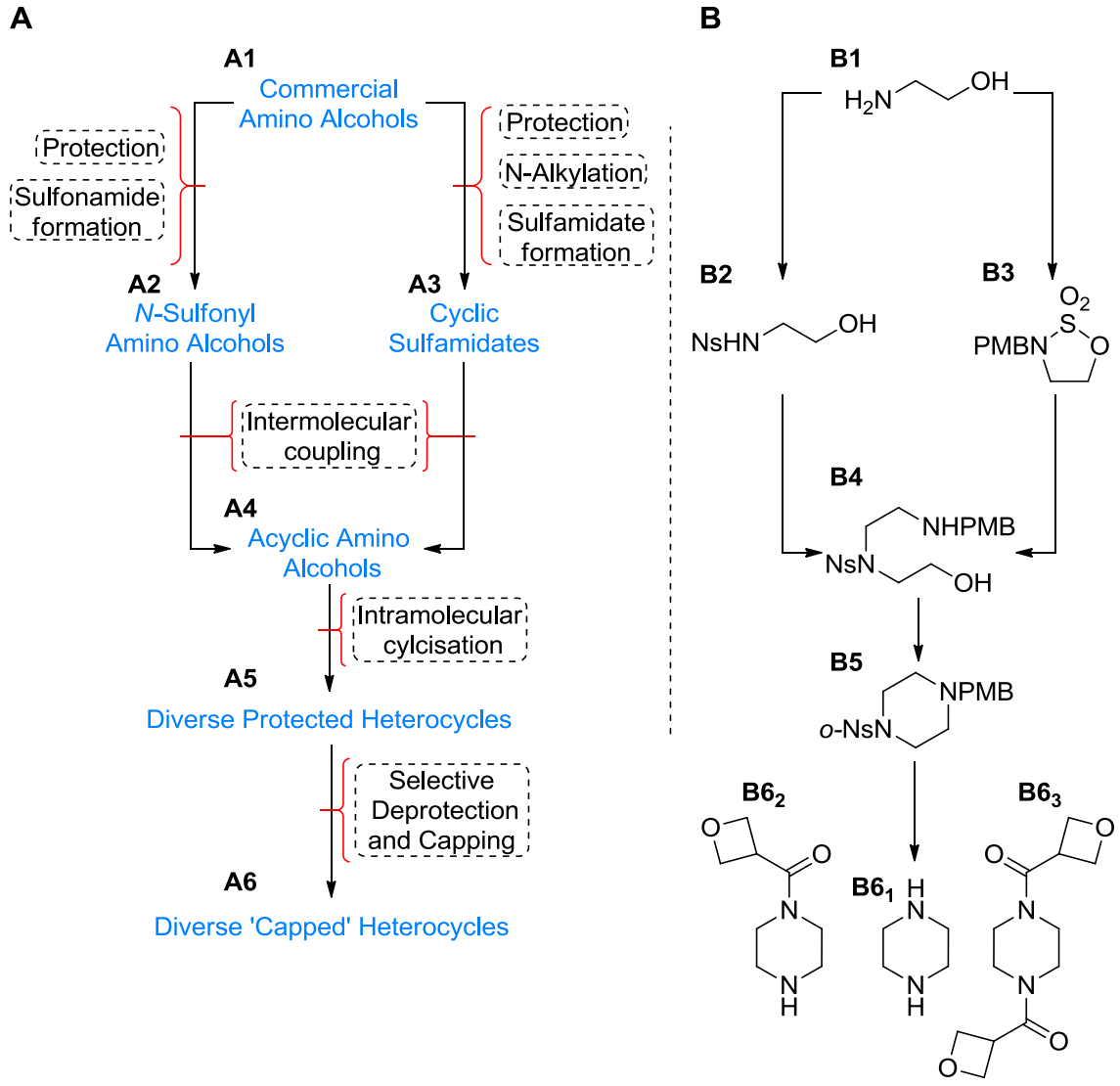


Figure **15**: A schematic outline to the *in silico* approach employed to illustrate the potential power of the amino alcohol and cyclic sulfamidate coupling approach to diverse heterocycles. Panel **A**- An overview of the *in silico* protocol utilised in this approach. Text in hashed boxes represents 'synthetic' transformations and text given in blue represents virtual libraries of compounds used/ generated in this approach. Panel **B**- An example of structures used in the *in silico* approach by demonstrating the synthesis of piperazine **B6$_1$** from ethanolamine **B1**.

The *in silico* approach used amino alcohols and amino acids from commercial sources (Figure **15**, **A1**), which were appropriately modified to include required functionalities

(i.e. *N*-Ns and *N*-PMB groups respectively) and protect any appended functionality, which would otherwise be incompatible with the proposed synthetic chemistry, to give virtual libraries of hydroxy sulfonamides (**A2**) and *N*-PMB cyclic sulfamidates (**A3**). These two virtual libraries were then systematically coupled to give a library of acyclic amines (**A4**). Cyclisation generated an array of diverse heterocycles (**A5**). Furthermore, as the enumerated heterocycles contain orthogonally cleavable protecting groups (*N*-PMB and *N*-Ns) and as such further diversity is introduced by means of capping the nitrogen atoms with commercially available reagents to give series of diverse 'capped' heterocycles (**A6**).[58,68] This *in silico* approach is exemplified by the synthesis of piperazine **B6$_1$** (Scheme **15**, Panel **B**) from amino alcohol **B1**. Further diversity may be introduced by a systematic capping strategy whereby heterocycles might contain no capping groups (⟶**B6$_1$**), one capping group on either heteroatom (⟶**B62**), from a selective capping approach, or two of the same capping groups (⟶**B6$_3$**) from a global capping approach.

The selections of amino alcohols from commercial sources were made by considering their compatibility with the reaction conditions and reactivity insights gleaned from scope and limitation studies. Furthermore, amino alcohols and capping groups were selected in such a way that the final *in silico* library may be biased toward the enumeration of compounds which might possess the physicochemical properties desirable in libraries of lead-like compounds (i.e. mol. weight < 350, -1<logP<3, etc.).

As such, a library of 10 cyclic sulfamidates and 10 hydroxy sulfonamides was selected and subjected to the *in silico* enumeration. This gave 14256 diverse piperazines and related ring systems which were analysed by considering their adherence to lead-like parameters (i.e. molecular weight between 200 and 350 and logP between -1 and 3). The variation of Alog*P* and molecular weight for the virtual library is shown in Chart **5**.

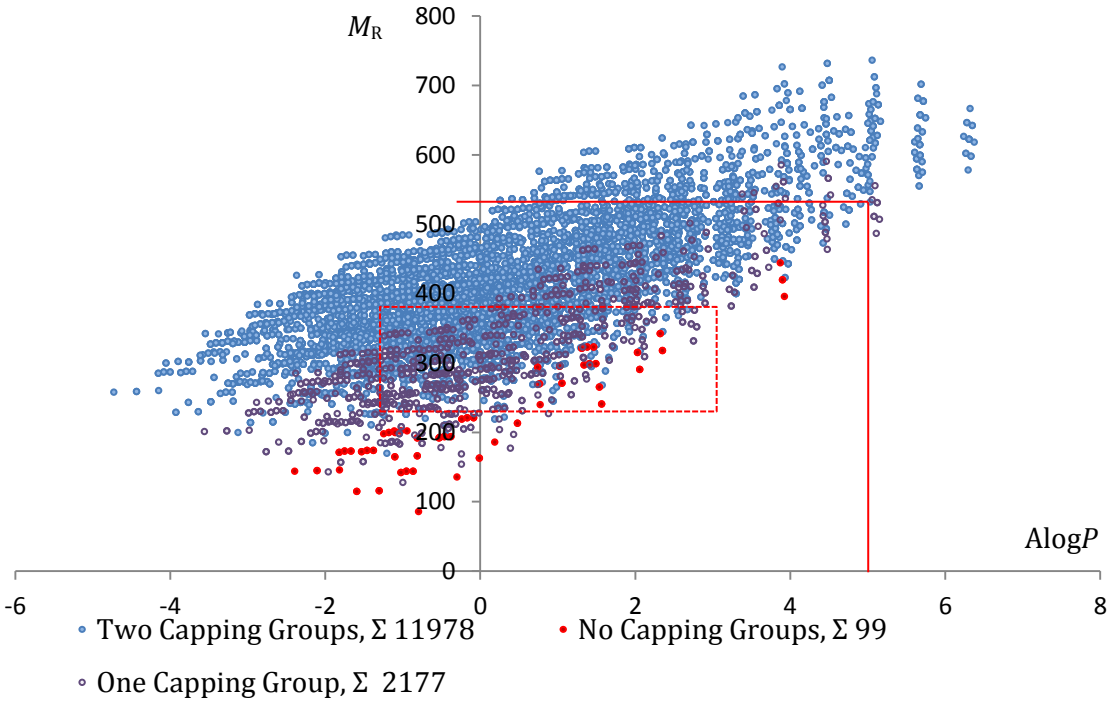


Chart **5**: Prediction of molecular weight and log*P* of the *in silico* generated piperazine and piperazine-like library. Red dashed lines represent the limits of lead-like chemical space whereas the solid red lines outline the limits of drug-like (Lipinski) chemical space. Building blocks used in this *in silico* approach are given in appendix **A**.

The systematic *in silico* pairing of a selection of 10 amino-alcohol building blocks and 12 capping groups (Appendix **A**) allowed the generation of a virtual library consisting of 14256 compounds. Of these compounds 99 were uncapped, core heterocycles, 2177 contained one capping group at either of the nitrogen centres within the ring skeleton and 11978 contained two capping groups. The uncapped compounds have average molecular weight (225.5 Da) and log*P* (0.05) within the limits of lead like chemical space. However, less than half (42%) the compound library lies within of the limits of lead-like chemical space due to having molecular weight and log*P* lower than the minimum values. This suggests that these uncapped cores are more fragment-like than lead-like.

The capped compounds have average calculated properties within lead like space (average molecular weight 321.0, average log*P* 0.22) however now over 62% of compounds lie within lead-like chemical space. This suggests that a library based on the selected building blocks bearing one capping group would have a high population of compounds which would be considered lead-like. Compounds bearing two capping groups tend to have properties outside of chemical space with only 13% of the compound population lying within lead-like chemical space. However, a significant proportion of compounds bearing two capping groups have properties within the boundaries of Lipinski chemical space suggesting that these compounds may be more suited to drug-like chemical space. Overall,

this *in silico* generated library contains a high proportion of compounds which would be deemed to be lead-like as they lie within the previously outlined parameters of lead-like chemical space. As such, it is believed that this computational approach has illustrated the potential power of the cyclic sulfamidate-amino alcohol pairing methodology for the generation of diverse, lead-like, compounds.

2.2.4 Exemplification of Methodology

In order to demonstrate the ability of the methodology developed in Section **2.2.1** to generate diverse lead like heterocycles a small number of commercially available amino alcohol building blocks were procured and subsequently used to synthesise a library of diverse heterocycles, as prepared by Dr Paul MacLellan.[69] Examples of heterocycles synthesised through this approach are shown in Figure **16**. Exemplification of this methodology clearly demonstrates the ability to vary ring size, heterocycle skeleton substitution and nitrogen substitution. Furthermore, it is also clear that handles for further chemistries may be incorporated into building blocks, such as aryl halides or amides.

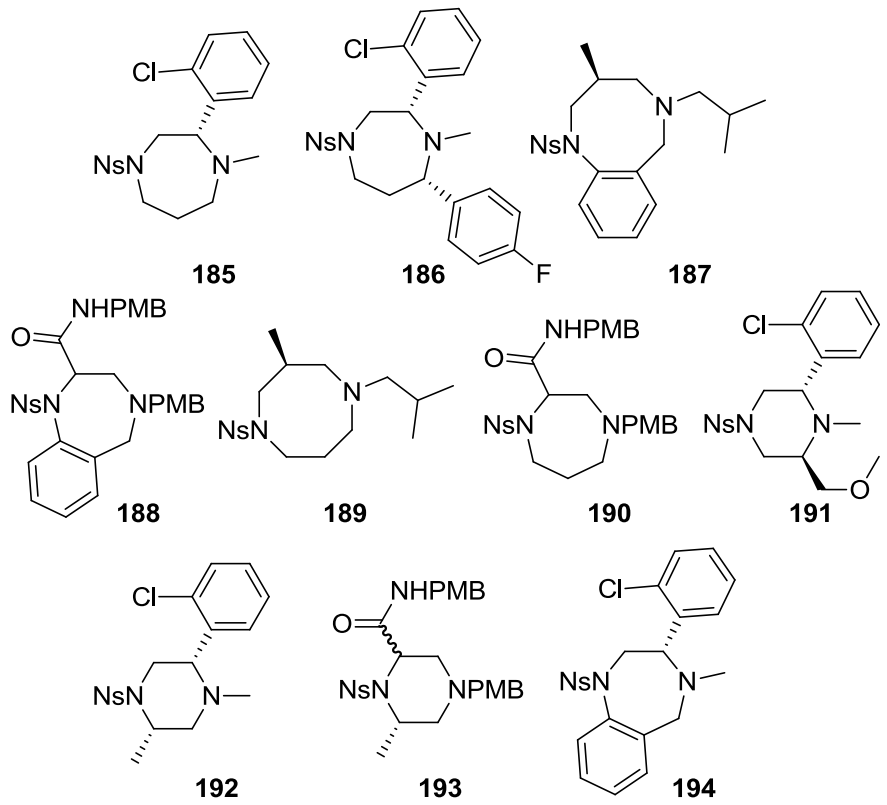


Figure **16**- Diverse heterocyclic compounds generated using the cyclic sulfamidate-amino alcohol pairing methodology.[69]

2.2.5 Summary of Cyclic Sulfamidate – Hydroxy Sulfonamide Pairing

This Chapter described the approaches taken towards the development of methods for the synthesis of piperazine and piperazine-like heterocycles by the pairing of cyclic sulfamidates and amino alcohols. The approach has developed methodology for the chemoselective opening of cyclic sulfamidates with amino alcohol derivatives and has allowed the systematic introduction of ring substituents and the variation of heterocycle size, allowing the synthesis of 6-, 7- and 8-membered systems. Furthermore, efficient methods were devised for the cyclisation of un-activated nitrogen nucleophiles to generate heterocycles under Mitsunobu conditions. A method for the facile purification of products from both building block pairing and cyclisation steps was developed which proved to be extremely valuable. The potential power of this approach has been illustrated by the generation of a virtual library of piperazine and piperazine-like compounds of which high proportions of compounds are deemed to have lead-like properties. Furthermore, the power of this approach has been demonstrated with the synthesis of a small library of diverse heterocycles, as prepared by Dr Paul MacLellan.

Chapter 3: Development of a Catalytic Approach to Piperazines and Related Ring Systems

This Chapter describes the development of an approach for the synthesis of diverse heterocyclic scaffolds utilising a transition metal–mediated process. The approach involved the pairing of bifunctional building blocks, followed by catalytic activation of an alkyne as the key step in heterocycle formation. The Chapter focusses on the development and subsequent exemplification of this approach (Figure **17**).

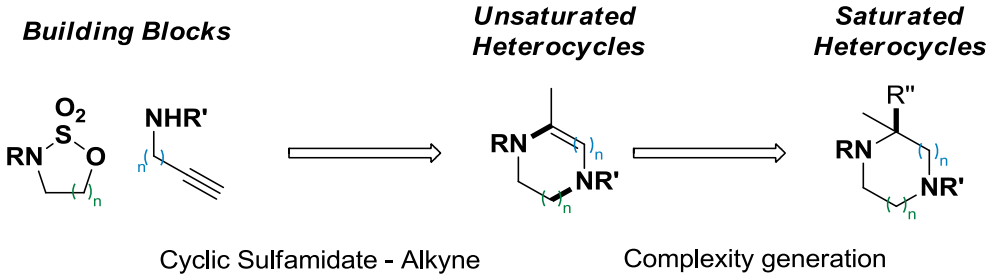


Figure **17**: Overview of the approach described in this Chapter. The pairing of cyclic sulfamidates and propargyl sulfonamides to give unsaturated heterocyclic ring systems which were then utilised as substrates for further complexity–generating transformations.

3.1 Overview of Cyclic Sulfaidate-Proprgyl Sulfonamide Pairing

This Section outlines the development of an approach to the synthesis of unsaturated piperazine heterocycles. An overview of the proposed approach is shown in Figure **18**. The approach would involve the coupling of a cyclic sulfamidate and an alkyne to give the cyclisation substrate. This reaction would then be followed by cyclisation, mediated by a transition metal, to give unsaturated heterocycles which may be utilised in further complexity generating reactions (Figure **18**).

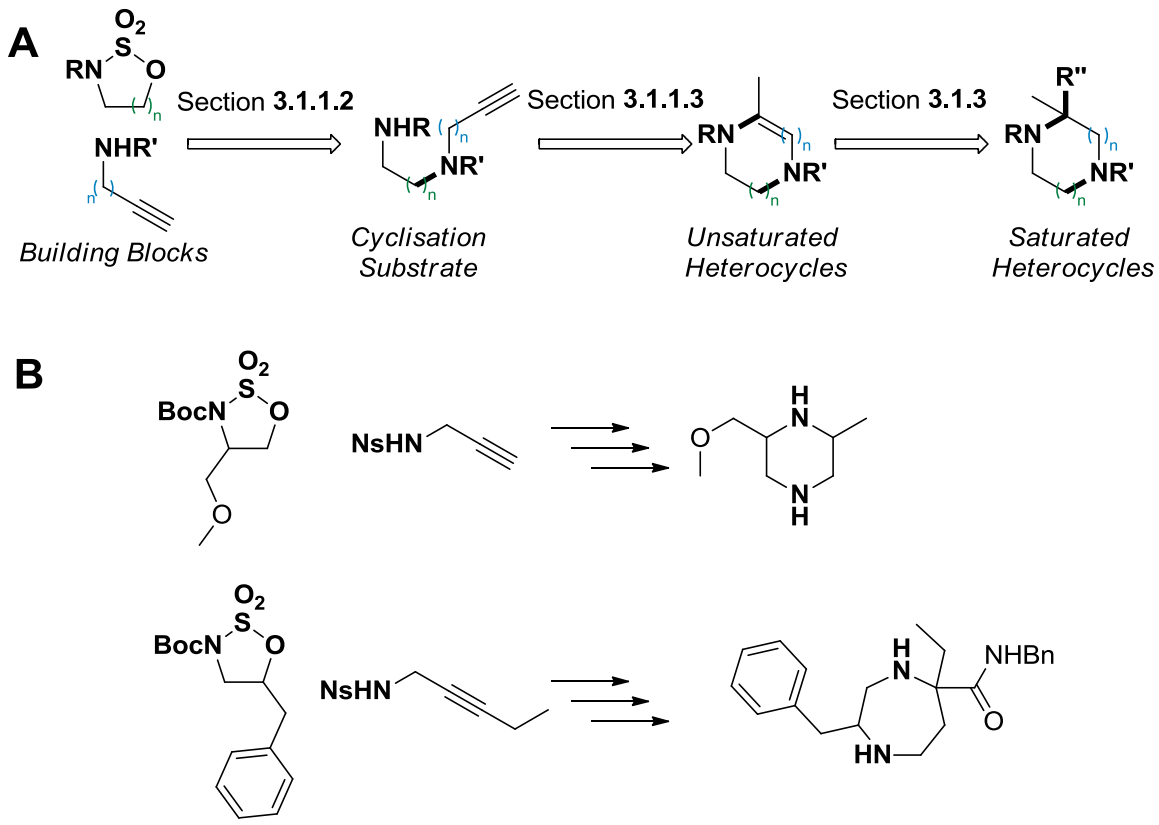


Figure **18**: Proposed approach to the synthesis of saturated piperazine and piperazine related ring systems (new bonds formed are highlighted by broad bonds). Panel **A**- Proposed general approach to the formation of piperazine ring systems through the coupling of cyclic sulfamidate and propargyl sulfonamide building blocks. This approach would utilise sequential nucleophilic sulfamidate opening and catalysed cyclisation. Finally, unsaturated heterocycles would be used as substrates for further diversity generating reactions. Panel **B**- Examples of heterocyclic systems which might be synthesised using this approach.

Initially, pairs of readily-available cyclic sulfamidate and alkyne building blocks would be chemoselectively coupled using sequential C-N bond forming steps: the opening of the cyclic sulfamidate, followed by the cyclisation under catalytic conditions (Section **3.1.1**). The scope and limitations of this approach were investigated by the systematic variation of the cyclic sulfamidate and alkyne building blocks and studying the subsequent cyclisation reactions (Section **3.1.2**). Increasing the diversity of groups appended to the heterocyclic skeleton might be achieved by utilising the unsaturation generated in the intramolecular cyclisation (Section **3.1.3**). The power of this approach was illustrated by the *in silico* enumeration of diverse lead-like heterocycles from readily available building blocks (Section **3.1.4**).

3.1.1 Reaction Development

This Section outlines the development of methodology for the efficient coupling of cyclic sulfamidate and alkyne building blocks (Section **3.1.1.1**) and the subsequent development of methods for the intramolecular cyclisation (Section **3.1.1.3**).

3.1.1.1 Design and Synthesis of Building blocks

To investigate the feasibility of the proposed approach, a number of cyclic sulfamidate and alkyne building blocks were required (Figure **19**). The building blocks selected were designed to probe the scope and limitations of both the nucleophilic opening of cyclic sulfamidates and the subsequent transition metal–mediated intramolecular cyclisation. The cyclic sulfamidate building blocks were selected to investigate if the nature of the nitrogen substituent played a significant role in the intramolecular cyclisation to give heterocycles. The nucleophile in the alkyne building blocks (X = OH or NHNs) was varied to allow investigation of the potential to prepare both morpholine- or piperazine-like heterocycles.

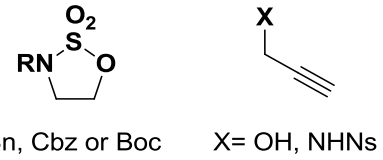
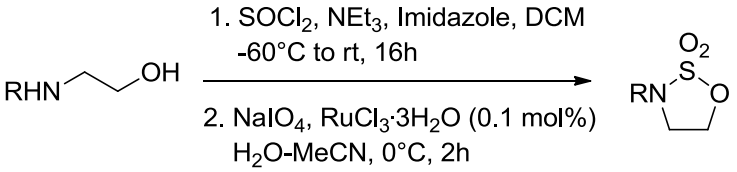


Figure **19**: Varied cyclic sulfamidate and alkyne building blocks required for initial reaction development.

The proposed cyclic sulfamidate building blocks were synthesised from commercially available amino alcohols. The *N*-protected amino alcohols were transformed into the required cyclic sulfamidates using a two-step procedure as shown below (Table **13**). Treatment of amino alcohol derived compounds with thionyl chloride under basic conditions at −60 °C gave the crude cyclic sulfamidite intermediates; ruthenium-catalysed oxidation of the cyclic sulfamidites, with $NaIO_4$ then gave the required cyclic sulfamidates in good yield.



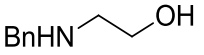
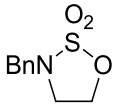
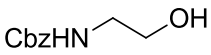
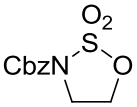
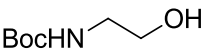
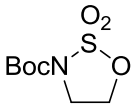
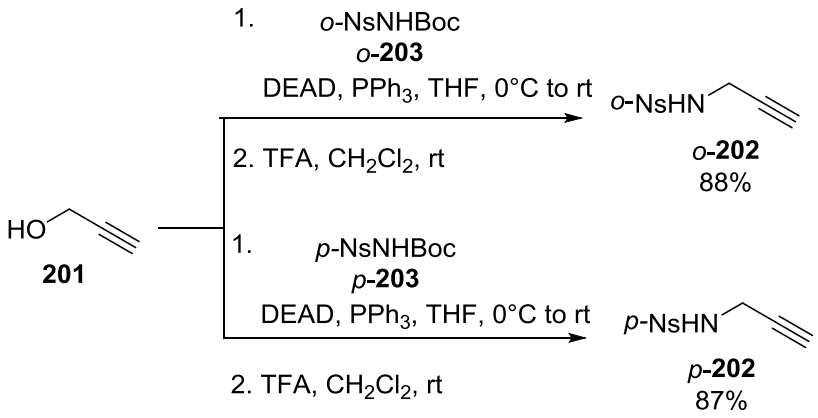
Entry	Amino Alcohol	Cyclic Sulfamidate	Yield (%)
1	 **195**	 **198**	66
2	 **196**	 **199**	87
3	 **197**	 **200**	86

Table **13**: Synthesis of cyclic sulfamidates required for initial reaction development.

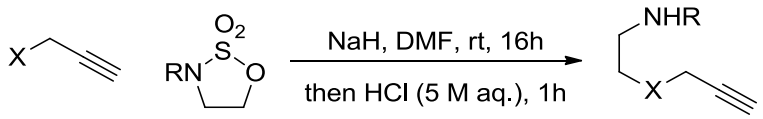
The required alkyne building blocks were either commercially available (i.e. propargyl alcohol **201**) or synthesised from propargyl alcohol using a two-step method. The required propargyl sulfonamides *o*-**202** and *p*-**202** were synthesised from propargyl alcohol by treatment with the *o*-**203** or *p*-**203**, DEAD and PPh_3 in THF followed by deprotection with TFA in CH_2Cl_2, respectively (Scheme **29**).



Scheme **29**: Synthesis of the propargyl sulfonamides *o*-**202** and *p*-**202**.

3.1.1.2 Cyclic Sulfamidate and Alkyne Building Block Coupling

With the cyclic sulfamidate and alkyne building blocks in hand (Section **3.1.1.1**), the pairing of building blocks was studied. The pairing of cyclic sulfamidates with sulfonamide nucleophiles under basic conditions has previously been developed (Section **2.2.1.2**) and thus these conditions were employed. Pairing of cyclic sulfamidate and alkyne building blocks is summarised in Table **14**.



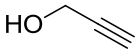
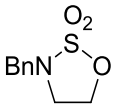
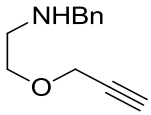
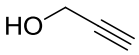
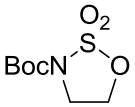
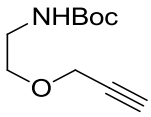
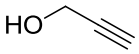
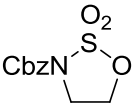
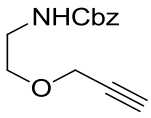
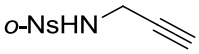
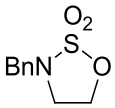
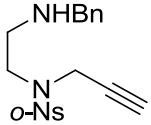
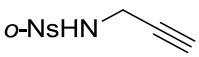
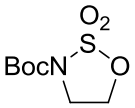
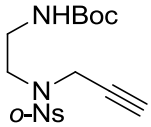
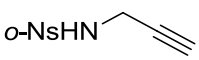
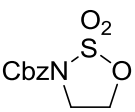
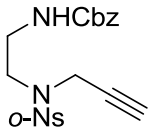
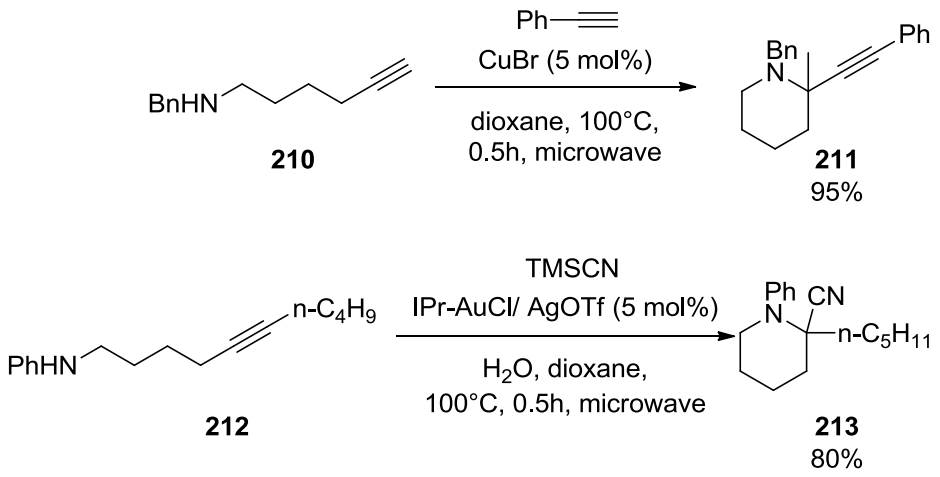
Entry	Alkyne	Cyclic Sulfamidate	Product	Yield (%)
1	 **201**	 **198**	 **204**	77
2	 **201**	 **200**	 **205**	77
3	 **201**	 **199**	 **206**	73
4	 **202**	 **198**	 **207**	27
5	 **202**	 **200**	 **208**	>98
6	 **202**	 **199**	 **209**	95

Table **14**: Ring opening of cyclic sulfamidates with propargyl nucleophiles.

The treatment of either alcohol **201** or sulfonamide **202** with NaH followed by the appropriate cyclic sulfamidate proceeded smoothly. This approach is tolerant of a range of sulfamidate *N*-protecting groups (Table **14**, entries 1, 2 and 3) and either *O*- or *N*-nucleophiles (compare entries 2 and 5). This pairing approach gave a range of substrates to allow the investigation into the cyclisation to yield heterocycles.

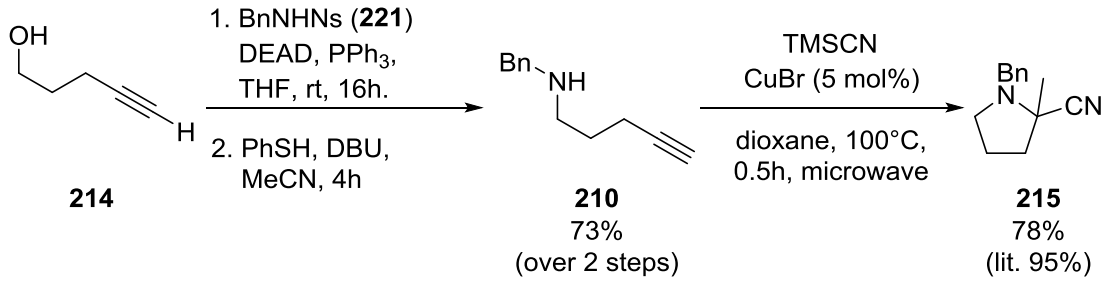
3.1.1.3 Development of Catalytic Methodology for Cyclisation

Alkyne activation with a variety of transition metals, such as copper,[70] gold,[71, 74, 75] silver [72]and palladium,[73] is well known. However, cyclisations of heteroatom-substituted alkyne substrates to give heterocycles have only recently been reported. Of particular interest were the reports from Hammond *et al.* which describes the tandem intramolecular cyclisation followed by iminium trapping (Scheme **30**). [76]



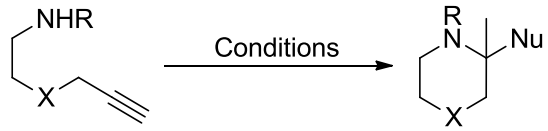
Scheme **30**: Reports by Hammond *et al.* into the tandem cyclisation/ trapping of alkyne-containing substrates.[76,78]

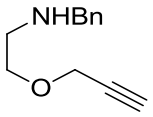
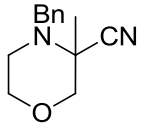
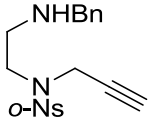
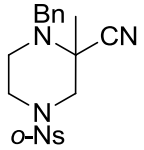
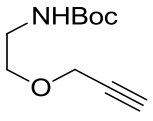
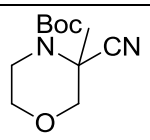
In order to validate the catalytic system developed by Hammond *et al*. as a key step for heterocycle formation a model reaction was performed (Scheme **31**).The commercially available alcohol **214** was transformed into the amine **210** using a Mitsunobu reaction with BnNHNs, [77] **221**, followed by de-sulfonylation with PhSH and DBU in acetonitrile. The amine **210**, a known substrate compatible with the copper cyclisation methodology,[78] was then exposed to the reported reaction conditions to give the pyrrolidine **215**. Although the yield of **215** was diminished compared to literature reports, the result validates the use of a copper–based catalytic system.



Scheme **31**: Confirmation of experimental procedure by the synthesis of **215** by catalytic intramolecular cyclisation.

It was demonstrated that numerous substrates can undergo cyclisation to give heterocycles containing one heteroatom. However there is only one example of cyclisation to give a morpholine scaffold.[78] These reports clearly demonstrate the requirement for different catalytic systems dependent upon the substitution of the nucleophilic nitrogen: a more π acidic metal (Au in the reported examples) is required for examples with delocalised lone pairs (such as N-carbamates). As such, a variety of conditions were selected, based upon the reports by Hammond *et al.,*[76, 78] and a selection of cyclisation substrates (synthesised in Section **3.1.1.2**) were exposed to these conditions, the results of which are summarised in Table **15**.



Entry	Substrate	Conditions	Anticipated Product
1	 **204**	A	 **216**
2	 **207**	A	 **217**
3	 **208**	B	 **218**

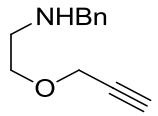
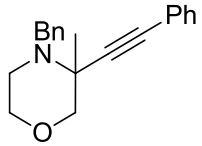
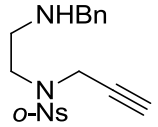
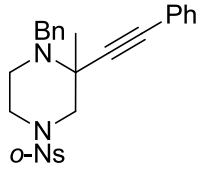
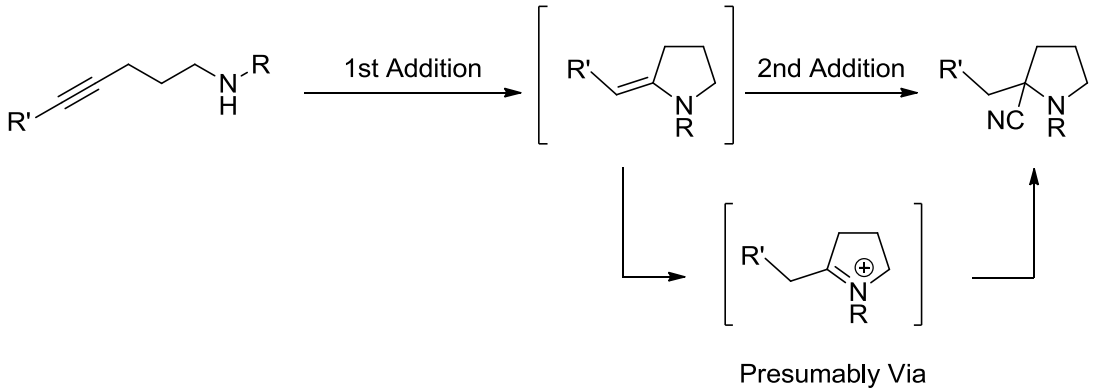
4	 **204**	C	 **219**
5	 **207**	C	 **220**

Table **15**: Summary of cyclisation conditions investigated. Conditions- A: TMSCN, CuBr (5 mol.%), dioxane, 100°C, 0.5h, microwave irradiation., B: TMSCN, IPr-AuCl (5 mol.%) AgOTf (5 mol.%), H_2O, Dioxane, 100°C, 0.5h, microwave irradiation C: Phenylacetylene, CuBr (5 mol.%), dioxane, 100°C, 0.5h, microwave irradiation.

The use of CuBr with either TMSCN or phenylacetylene has been shown to induce cyclisation of *N*-benzyl substrates. The replacement of $Cu^{(I)}$ with an $Au^{(I)}$ source has been shown to induce cyclisation of *N*-carbamate substrates.[77] However, exposing selected substrates from Section **3.1.1.2** to the cyclisation conditions above led, in all cases, to no identifiable product. In all cases, significant amounts of starting materials were observed by both LCMS and ^1H NMR analysis of crude reaction mixtures. These disappointing results clearly show substrate incompatibility, however the origin of the lack of reactivity is unknown.

The reports by Hammond *et al*. describe the tandem intramolecular cyclisation/ trapping as a dual addition to the alkyne and propose a mechanism outlined in Scheme **32**.



Scheme **32**: Proposed mechanism for the intramolecular amino alkyne cyclisation to give substituted pyrrolidines.

The proposed mechanism for formation of substituted pyrrolidines begins with a metal–mediated amine addition to the alkyne to give the proposed exocyclic enamine which is trapped with cyanide, presumably via tautomerisation to the iminium species. It was hypothesised that if the hydroamination product was stabilised in such a way that the olefin could be retained and isolated the overall 'dual addition' could be performed in a two-step process (Figure **20**). The *N*-carbamate was selected as the tautomerisation to an *N*-acyl iminium species (Figure **20**, panel **B**) may bias the formation of an unsaturated species.

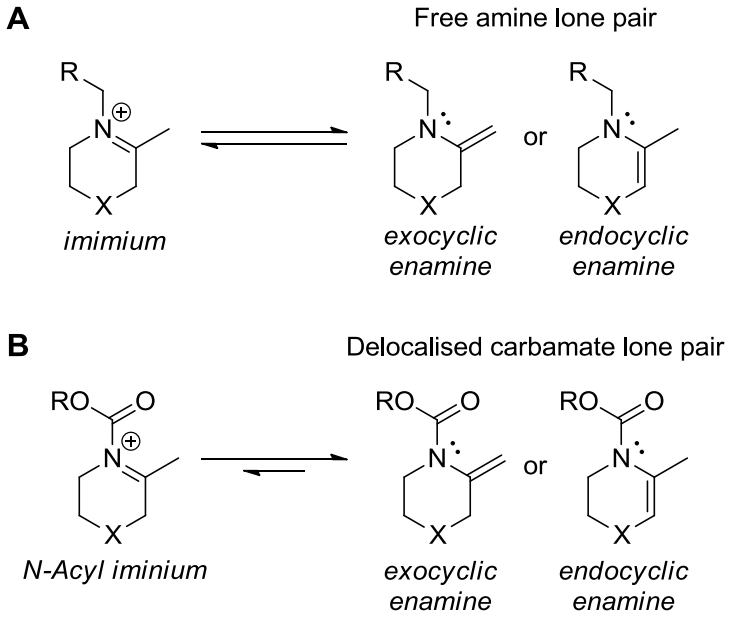
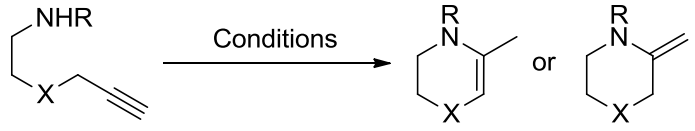
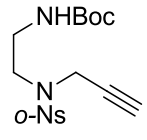
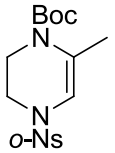


Figure **20**: Proposed rationale for the potential stabilisation of unsaturated intermediates by the delocalisation of amine lone pair.

It has been suggested that copper is a poor catalyst for inducing hydroamination with carbamate nucleophiles. [78] As such, the substrates synthesised in Section **3.1.1.2** were subjected to gold–mediated conditions which have been demonstrated to be competent in inducing carbamate addition to alkynes. These results are summarised in Table **16**.



Entry	Substrate	Product	Yield (%)
1	 **208**	 **77**	97%

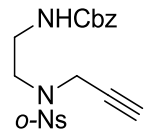
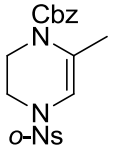
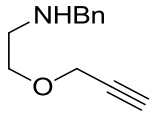
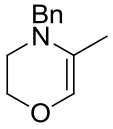
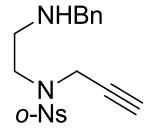
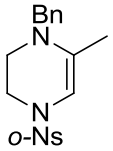
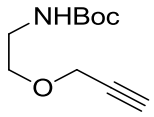
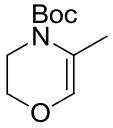
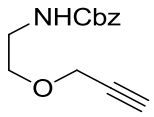
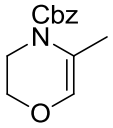
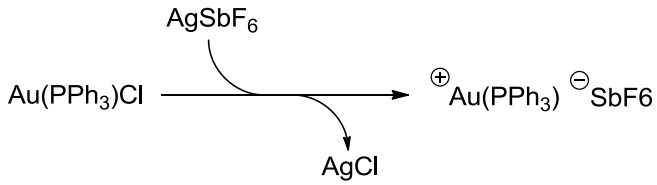
2	 **209**	 **222**	98%
3	 **204**	 **223**	–[a]
4	 **207**	 **224**	–[a]
5	 **205**	 **225**	–[b]
6	 **206**	 **226**	–[b]

Table **16**: Intramolecular cyclisation of alkynes under gold mediated hydroamination conditions. Conditions: $Au(PPh_3)Cl$ (5 mol%), $AgSbF_6$ (5 mol%), dioxane, 100°C, 10 min, microwave. [a] A complex material was obtained as determined by 500 MHz ^1H NMR and LCMS analysis of reaction mixtures. [b] Significant amounts of starting materials remained as determined by 500 MHz 1H NMR and LCMS analysis of reaction mixtures.

Pleasingly, subjecting the cyclisation substrates **208** and **209** to catalytic amounts of both $Au(PPh_3)Cl$ and $AgSbF_6$ (both 5 mol%) in dioxane at 100 °C under microwave irradiation, gave the tetrahydropyrazines **77** and **222** (Table **16**, entries 1 and 2) in near-quantitative yields, supporting the stabilisation hypothesis discussed previously (Figure **20**). *N*-Benzyl substrates (entries 3 and 4) gave complex mixtures of materials with no identifiable product by LCMS or NMR. Interestingly, etheric substrates **205** and **206** (entries 5 and 6) returned only starting materials, demonstrating the importance of a sulfonamide β- to the alkyne.

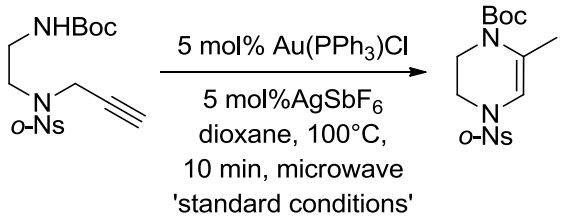
3.1.1.4 Investigations into Gold Catalysed Conditions

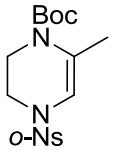
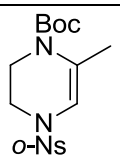
The use of of Au^{I} and Ag^{I} complexes in combination in catalytic transformations is well known.[79] Typically Ag^{I} complexes with weakly coordinating anions (such as SbF_6^-, OTf^- and NTf_2^-) are used to generate cationic Au^{I} complexes *in situ* by undergoing ligand exchange (Scheme **33**).

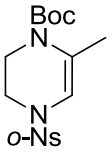
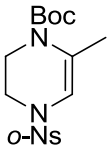


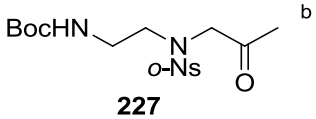
Scheme **33**: Typical use of Ag complexes with weakly coordinating ligands to generate cationic gold phosphine complexes.

However, there is an on-going debate as to whether silver plays an active role in catalysis.[79] In order to investigate the role of each component in the cyclising conditions identified in Section **3.1.1.3**, systematic variation of reaction conditions was undertaken (Table **17**).



Entry	Variation from standard conditions	Product	Yield (%)
1	None	 **77**	98
2	No $Au(PPh_3)Cl$	starting material only [c]	—
3	1 mol% Au(IPr)Cl[a] in place of $Au(PPh_3)Cl$ 1 mol% $AgSbF_6$	 **77**	97

4	No $AgSbF_6$	starting material only [c]	—
5	No Au or Ag complexes	starting material only [c]	—
6	MsOH (10 mol%) No $Au(PPh_3)Cl$ or $AgSbF_6$	starting material only [c]	—
7	Thermal heating (100 °C, 3h)	 **77**	95
8	CH_2Cl_2, rt 16h	 **77**	83 (15[b])



227

Table **17**: Systematic investigation into reaction conditions.[a] IPr= 1,3-Bis(2,6-diisopropylphenyl)-1,3-dihydro-2H-imidazol-2-ylidene. [b]Also isolated was the ketone **227**. Analysis of crude reaction mixtures showed a 5.5:1 mixture of **77** to **227**. [c] Starting material observed by 500 MHz ^{1}H NMR spectroscopic analysis of crude reaction mixtures.

When comparing the variations in reaction conditions to those previously established (Table **17**, entry 1) it is clear to see that removing the gold source, the silver source or both gold and silver (entries 2, 4 and 5 respectively), results in a complete lack of reaction. In each case, analysis of crude reaction mixtures by 500MHz ^{1}H NMR spectroscopy revealed only starting materials to be present. This is clear evidence that both gold and silver complexes are required for the generation of an active catalytic species. The cyclisation appears to be tolerant to variation of the source of gold (entry 3) with the NHC-gold complex readily catalysing the cyclisation even at lower catalyst loadings.[85] Replacing metal catalysts with methanesulfonic acid (entry 6) failed to give any observable product, suggesting the cyclisation is not due to trace amounts of strong acid. The mode of heating also appears to be well tolerated, with the reaction proceeding well with conventional oil bath heating (entry 7) or even at room temperature in DCM (entry 8) although here the

reaction time was significantly increased. A by-product isolated from the room temperature reaction (entry 8) was the ketone **227**. This by-product may have arisen due to moisture entering the reaction vessel over the extended period required for completion. Ideally the reactivity of the alkyne **208** would be studied in a silver free system, possibly by the use of $Au(PPh_3)SbF_6$,[79] or a suitable alternative, in the absence of any silver sources.[80]

3.1.1.5 Insights into the Mechanism of Tetrahydropyrazine Formation

The observation of the formation of the ketone **227** in dichloromethane at room temperature prompted investigation into plausible mechanisms for formation of tetrahydropyrazine **77**. Electrophilic activation of alkynes, and subsequent reactions with nucleophilic species (such as alcohols,[81, 82, 85] amines[83] and alkenes[84]), with gold complexes is well known. From these literature reports two mechanisms which may account for the formation of tetrahydropyrazine **77** from the carbamate **208**, and the potential formation of the ketone **227**, may be proposed (Figure **21**).

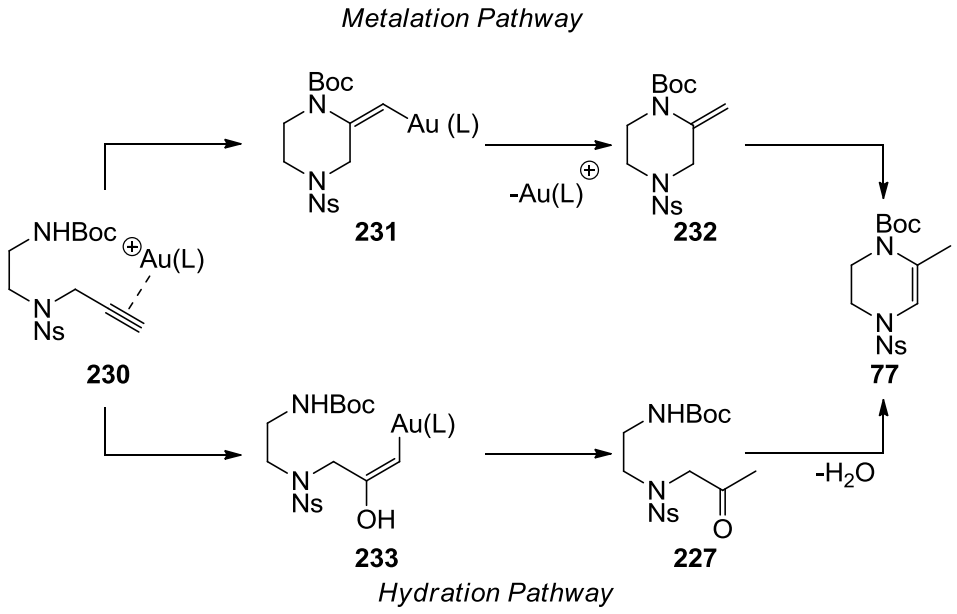
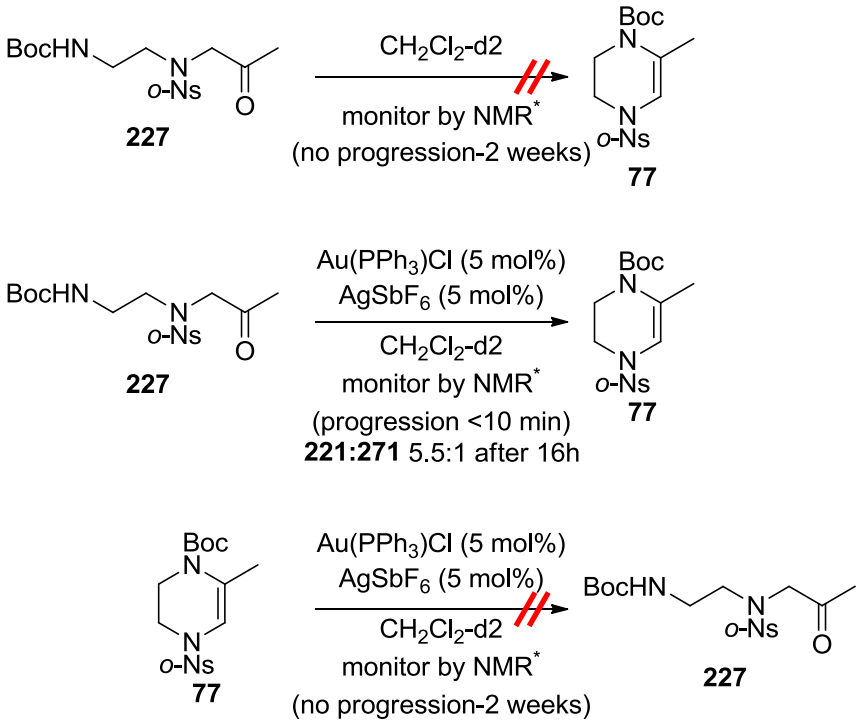


Figure **21**: Two possible mechanisms for the formation of **77** from **208** by either metalation or hydration pathways.

A possible mechanism follows a metalation pathway, *via* a formal 6-*exo*-dig cyclisation (⟶**231**). Subsequent protodeauration (⟶**232**) and tautomerisation to the observed product (⟶**77**) would account for the direct formation of tetrahydropyrazine **77**. An alternative approach may be a hydrative pathway, following a regioselective alkyne hydration (⟶**233**) and subsequent protodeauration-tautomerisation (⟶**227**) would account for the observation of the ketone **227** as observed in Table **17**. Finally, intramolecular enamine formation by dehydration would give the observed

tetrahydropyrazine **77**. In order to investigate these suggested mechanisms a small study was initiated. These studies aim to probe the feasibility of the hydrative route shown in Figure **21** by investigating the formation, and subsequent reactivity, of the ketone **227**.

With ketone **227** synthesised and isolated (Table **17**) the ability for dehydration to tetrahydropyrazine **77** was studied (Scheme **34**). The dehydration of the ketone **227** to the tetrahydropyrazine **77** was studied by 500 MHz ^{1}H NMR analysis of a solution of ketone **227** in DCM-d2, with and without catalysts, as a function of time. It was observed that the ketone **227** did not undergo dehydration to tetrahydropyrazine **77** without the addition of catalyst, even after extended period (>2 weeks). However, re-subjecting the ketone **227** to reaction conditions in DCM-d2 showed a rapid conversion to tetrahydropyrazine **77**; **77** was observed in < 10 min from addition of $Au(PPh_3)Cl$ and $AgSbF_6$ to **227** in CH_2Cl_2-d2, progressing to approximately 5.5:1 of **77**:**227** in 16h (Scheme **34**). However, re-exposing tetrahydropyrazine **77** to $Au(PPh_3)Cl$ and $AgSbF_6$ in CH_2Cl_2-d2, and subsequently monitoring the mixture by ^{1}H NMR spectroscopy failed to identify even trace formation of ketone **227**.

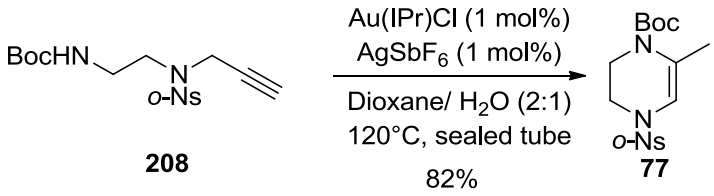


Scheme **34**: Investigation into the dehydration of the ketone **227** to give tetrahydropyrazine **77**. *500 MHz NMR analysis of ^{1}H signals in CH_2Cl_2-d2.

The results shown in Scheme **34** clearly suggest that ketone **227** is competent at forming tetrahydropyrazine **77** under the reaction conditions given in Table **17**. However, omitting the metal species from the reaction prevents formation of **77**. This may be due to either gold or silver complexes acting as Lewis acids, facilitating the dehydration of ketone **227**

to **77**. However, the lack of observed hydration of the tetrahydropyrazine **77**, to reform the ketone **227**, suggests that the tetrahydropyrazine **77** is the thermodynamic product of the reaction (with ketone **227** being the kinetic product).

An alternative approach to investigating the feasibility of a hydrative pathway in the formation of tetrahydropyrazine **77** was based on the hydration of carbamate **208**. Methods for the hydration of simple alkynes to give ketones have been developed using gold catalyst bearing *N*-heterocyclic carbene (NHC) ligands.[85] Carbamate **208** was subjected to these conditions that are known to induce alkyne hydration (Scheme **35**).



Scheme **35**: Reactivity of alkyne **208** under hydration conditions.

Subjecting carbamate **208** to 1 mol% Au(IPr)Cl and 1 mol% $AgSbF_6$ in a 2:1 mixture of dioxane and water at 120 °C gave the tetrahydropyrazine **77**. This result again suggests that although ketone **227** is being formed through alkyne hydration, the tetrahydropyrazine **77** is the thermodynamic product.

Overall, it is clear that the ketone **227** is indeed a competent intermediate on the route to the formation of the tetrahydropyrazine **77** from the carbamate **208** as summarised below (Figure **22**). However, these studies have not focussed on perturbing the hydroamination approach proposed in Figure **21** and thus parallel productive reaction pathways cannot be ruled out.

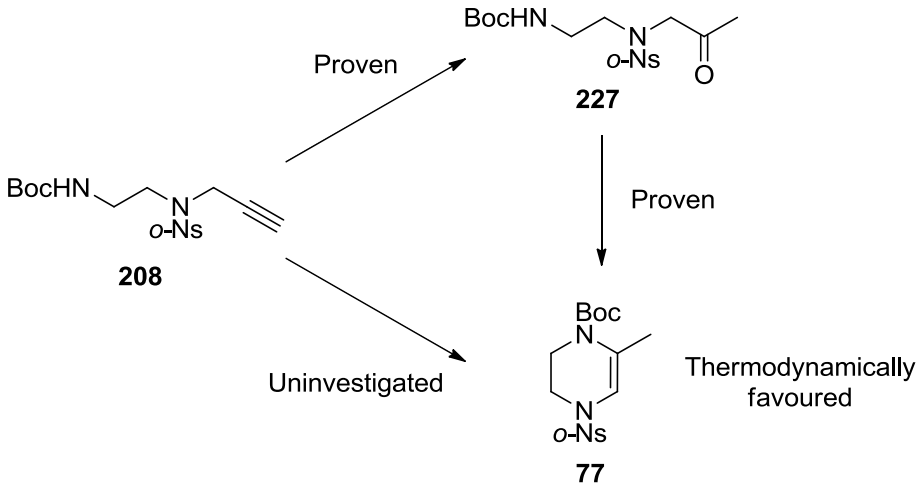


Figure **22**: Summary of findings from mechanistic investigations.

3.1.2 Scope and Limitation Studies

To allow a study into both the scope and limitations of the process, a systematic investigation into building block tolerance was undertaken. This study involved the synthesis (Section **3.1.2.1** and **3.1.2.2**), and subsequent pairing (Section **3.1.2.3**), of substituted building blocks. The proposed building blocks required for this study are outlined in Figure **23**.

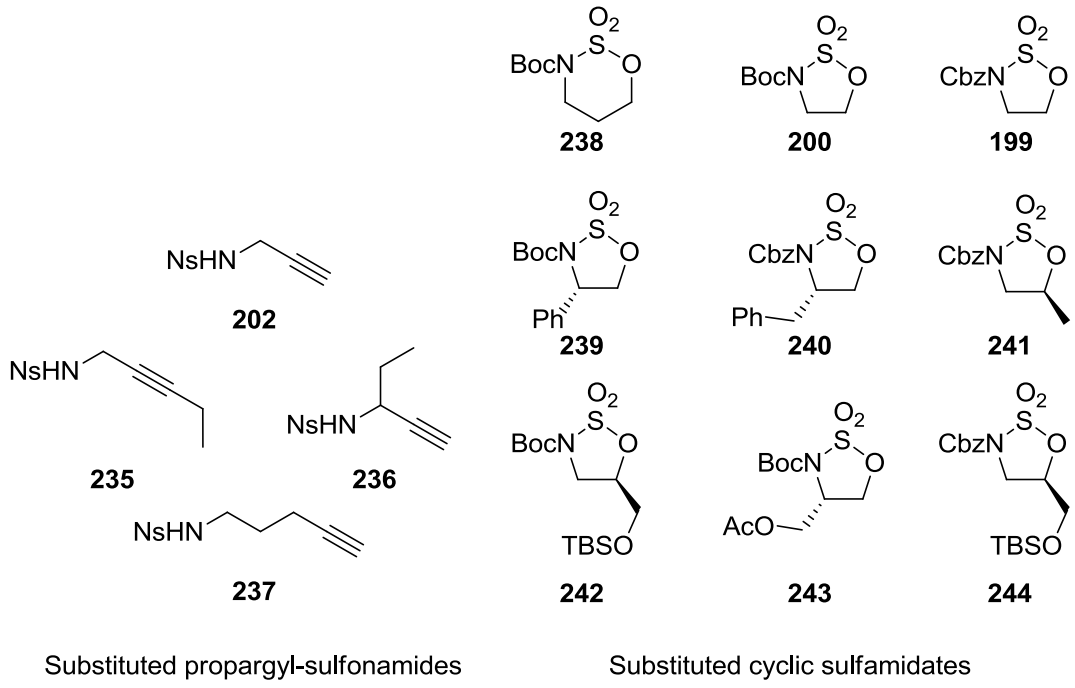
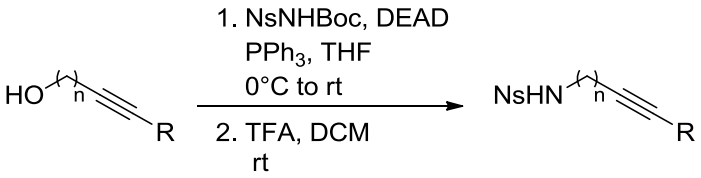


Figure **23**: Proposed building blocks required for scope and limitation studies.

The propargyl sulfonamide building blocks were selected to allow investigation of the effect of substituents both α- to nitrogen (**236**) and on the terminus of the alkyne (**235**). In addition, the sulfonamide **237** would allow the effect of chain length to be studied. The cyclic sulfamidate building blocks incorporate both *N*-Boc and *N*-Cbz protecting groups, both of which have been shown to be competent for cyclisation (Section **3.1.1.3**). The unsubstituted cyclic sulfamidates were selected to investigate the effect of chain length (**199**, **200** and **238**). The substituted cyclic sulfamidates would be derived from commercially-available enantiomerically pure β-amino alcohols and as such are all based on 5-membered ring systems. Substituents on the cyclic sulfamidates were selected to represent a variety substituents and substitution patterns. Building blocks containing common protecting groups (**242**, **243** and **244**) were included to investigate compatibility of chemically–sensitive groups.

3.1.2.1 Synthesis of Sulfonamide Building Blocks

The required propargyl sulfonamide building blocks outlined in Section **3.1.2** were synthesised from commercially-available materials. Sulfonamides **235**, **236** and **237** were synthesised from the commercially available alcohols using a two-step approach as outlined below (Table **18**). The commercially-available alcohols were treated with NsNHBoc, DEAD and PPh_3 in THF, followed by the removal of the Boc group with TFA in DCM to give the required sulfonamides. This approach allowed the synthesis of required building blocks on a multi-gram scale.



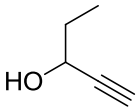
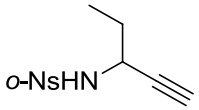
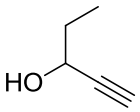
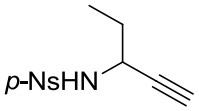
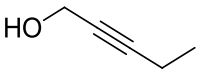
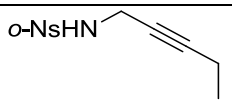
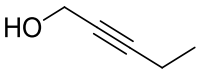
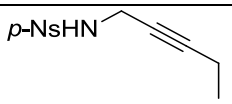
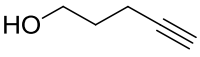
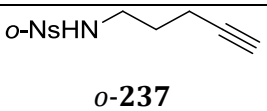
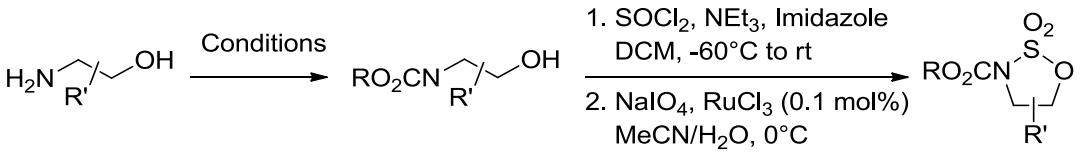
Entry	Alcohol	Product	Yield (%)
1		 *o*-**236**	81
1		 *p*-**236**	83
2		 *o*-**235**	82
2		 *p*-**235**	98
3		 *o*-**237**	84

Table **18**: Synthesis of sulfonamide building blocks.

3.1.2.2 Synthesis of Cyclic Sulfamidate Building Blocks

The required cyclic sulfamidates were synthesised, where possible, from the enantiomerically pure amino alcohol (Table **19**). The commercially-available amino alcohols were transformed into either the *N*-Boc or *N*-Cbz carbamates by treatment with either Boc_2O (entries 1 and 2), or Cbz-Cl (entries 3 and 4). Finally, the carbamates were transformed into the cyclic sulfamidates by treatment with $SOCl_2$ to give a crude cyclic sulfamidite and ruthenium-mediated oxidation to give the corresponding cyclic sulfamidates.



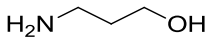
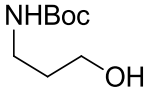
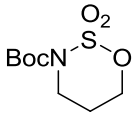
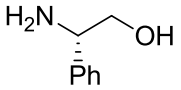
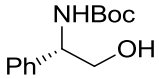
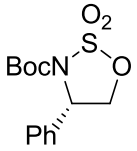
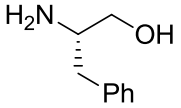
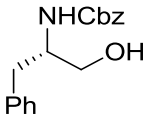
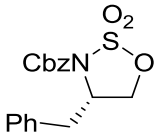
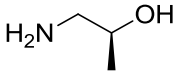
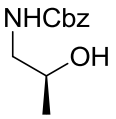
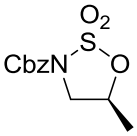
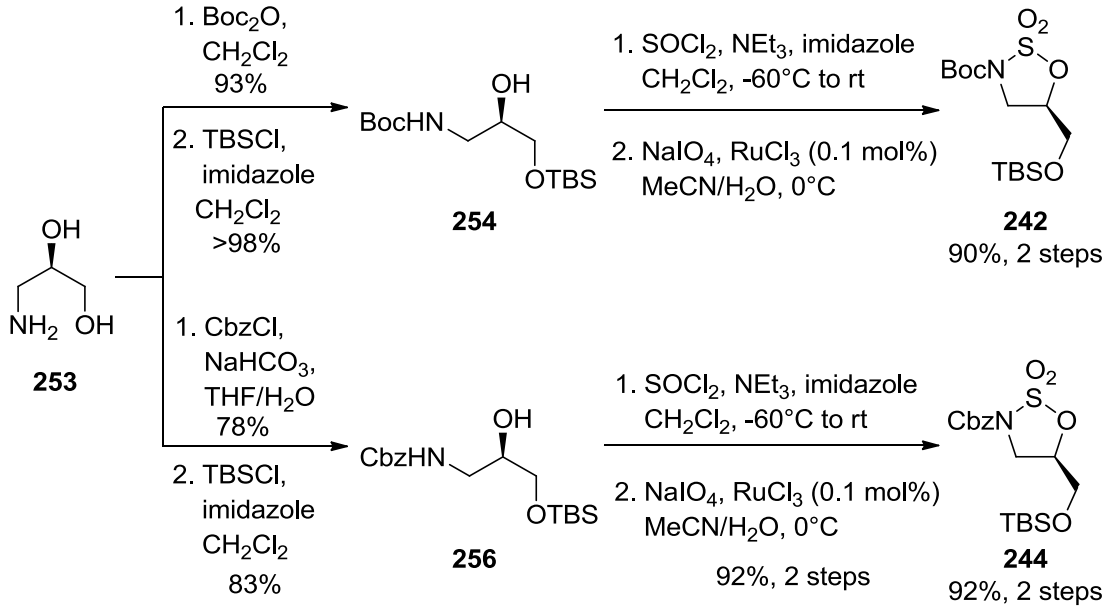
Entry	Amino alcohol	Conditions, Yield (%)	Carbamate	Cyclic Sulfamidate	Yield (%)
1		A, 97	 **245**	 **249**	82
2		A, 92	 **246**	 **250**	96
3		B, 93	 **247**	 **251**	93
4		B, 95	 **248**	 **252**	89

Table **19**: Synthesis of N-carbamate cyclic sulfamidates from commercially available amino alcohols. Conditions- A: Amino alcohol (1.0 eq.), Boc_2O (1.05 eq.), CH_2Cl_2 (0.3 M). B: Amino alcohol (1.0 eq.), CbzCl (1.05 eq.), $NaHCO_3$ (2.0 eq.) THF–H_2O (1:1, 0.15 M), 0 °C to rt.

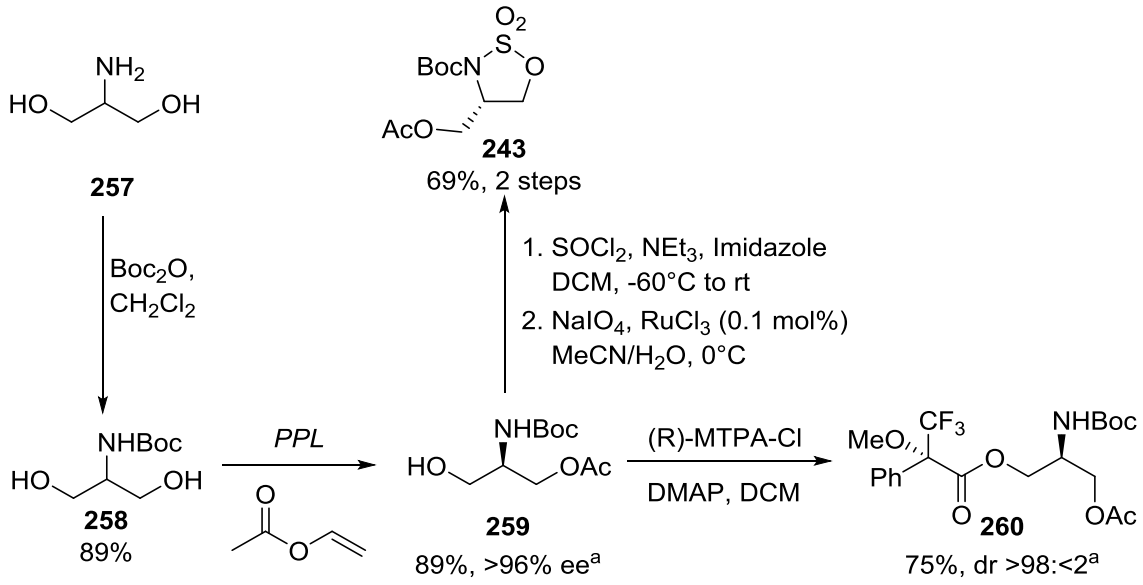
Efforts were then focused on the synthesis of non-commercially available building blocks. The synthesis of the cyclic sulfamidates **242** and **243** was achieved from the commercially available diol **253** (Scheme **36**).[86]



Scheme **36**: Synthesis of cyclic sulfamidates **242** and **244** from commercially amino alcohol **253**.

Synthesis of the carbamate **254** was achieved using a two-step protection procedure. *N*-protection was achieved by treatment of **253** with Boc_2O which was followed by treatment with TBSCl in CH_2Cl_2, to install the TBS group on the primary alcohol, to give **254**. Analogously, the carbamate **256** was synthesised by the installation of the Cbz group, by treatment with benzylchloroformate, followed by TBS protection with TBSCl in CH_2Cl_2. The carbamates **254** and **256** were transformed into the cyclic sulfamidates **242** and **244** respectively, by treatment with $SOCl_2$ in CH_2Cl_2 to give crude cyclic sulfamidites, followed by subsequent ruthenium–mediated oxidation.

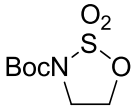
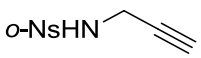
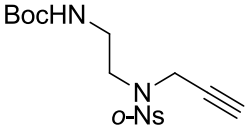
The cyclic sulfamidate **243** was synthesised from commercially available serinol following literature precedent[87] (Scheme **37**). Thus, serinol was treated with Boc_2O in CH_2Cl_2 to give the diol **259**. Enzymatic desymmetrisation of the diol **259** with *Porcine pancreatic lipase* (*PPL*) in vinyl acetate gave the acetate **260** in >96% ee (as determined by 500 MHz ^1H NMR spectroscopic analysis of the corresponding Mosher's esters **260**).[88] Finally, the carbamate **259** was converted into cyclic sulfamidate **243** by treatment with $SOCl_2$ in CH_2Cl_2 followed by ruthenium–mediated oxidation.

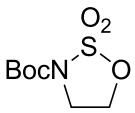
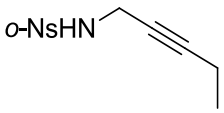
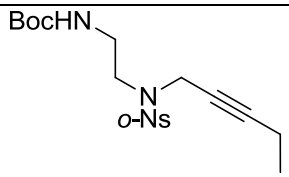
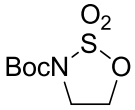
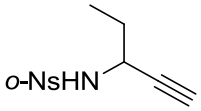
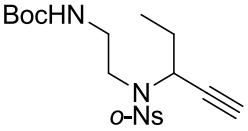
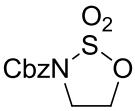
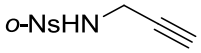
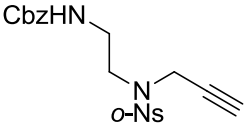
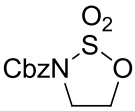
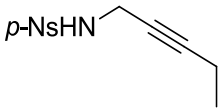
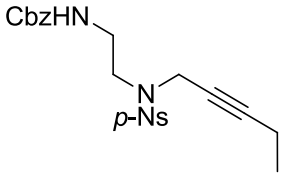
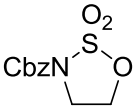
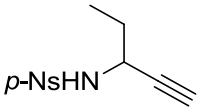
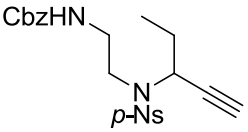
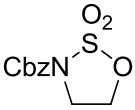
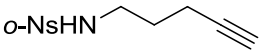
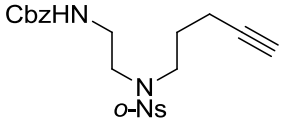
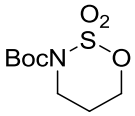
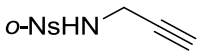
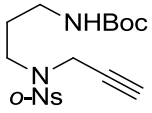
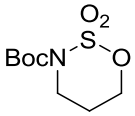
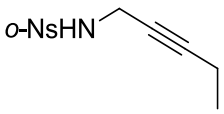
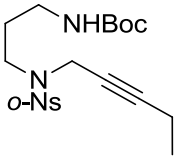


Scheme **37**: Synthesis of cyclic sulfamidate **243** from serinol. [a] The enantiomeric excess of the acetate **259** was determined by 500 MHz ^{1}H NMR spectroscopic analysis of the Mosher's ester **260**

3.1.2.3 Pairing of Cyclic Sulfamidate and Propargyl Sulfonamide Building Blocks

The cyclic sulfamidate and propargyl sulfonamide building blocks were paired using the conditions identified in Section **3.1.1.2**. The cyclisation precursors were synthesised by the treatment of a propargyl sulfonamide building block with NaH in DMF followed by the addition of a cyclic sulfamidate building block. The combinations of building blocks investigated is summarised in Table **20**

Entry	Cyclic sulfamidate	Propargyl sulfonamide	Carbamate	Yield (%)
1	 **200**	 *o*-**202**	 **208**	>98

2	 **200**	 ***o*-235**	 **261**	>98
3	 **200**	 ***o*-236**	 **262**	88
4	 **199**	 ***o*-202**	 **209**	95
5	 **199**	 ***p*-235**	 **263**	91
6	 **199**	 ***p*-236**	 **264**	90
7	 **199**	 ***o*-237**	 **265**	88
8	 **238**	 ***o*-202**	 **266**	86
9	 **238**	 ***o*-235**	 **267**	83

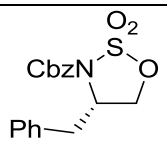
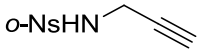
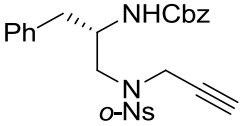
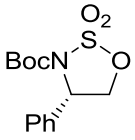
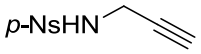
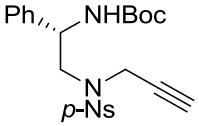
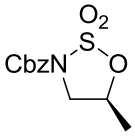
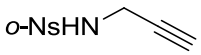
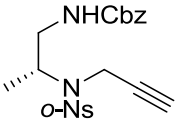
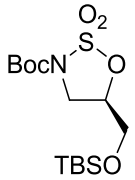
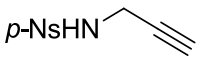
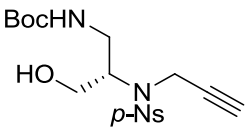
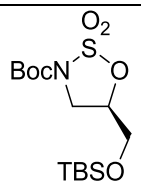
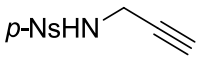
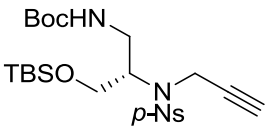
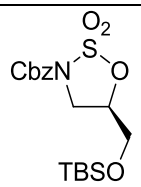
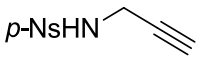
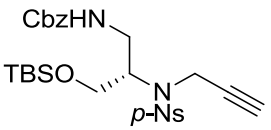
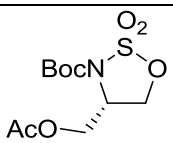
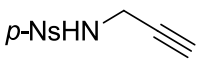
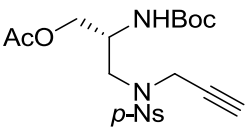
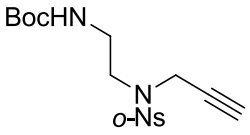
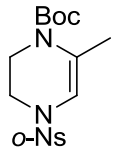
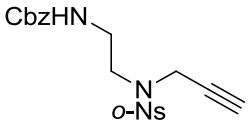
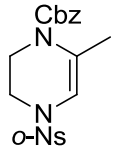
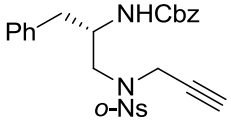
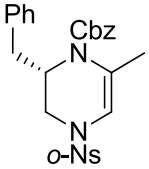
10	 **240**	 *o*-**202**	 **268**	72
11	 **239**	 *p*-**202**	 **269**	70
12	 **241**	 *o*-**202**	 **270**	94
13	 **242**	 *p*-**202**	 **271**	68
14	 **242**	 *p*-**202**	 **272**	74[a]
15	 **244**	 *p*-**202**	 **273**	67[a]
16	 **243**	 *p*-**202**	 **274**	89

Table **20**: Nucleophilic opening of cyclic sulfamidates with propargyl sulfonamide building blocks. *Reagents and conditions*- Propargyl sulfonamide (1.1 eq.), NaH (60% in oil, 1.1 eq.), DMF (0.2M), then cyclic sulfamidate (1.0 eq.), then HCl (5 eq., 5M aq. soln.). [a]Protolytic quench performed with citric acid (2 eq., 1M. aq. soln.).

Generally, the nucleophilic opening of cyclic sulfamidates proceeded smoothly, showing a wide tolerance in variation in sulfamidate ring size and appended substitution on both building blocks (Table **20**). The *N*-Boc and *N*-Cbz cyclic sulfamidates tended to give very similar yields of the acyclic carbamate products (e.g. compare entry 1 and entry 4). Substitution was well tolerated in propargyl sulfonamide derived building blocks. Both non-terminal alkynes (entries 2, 5 and 9) and sulfonamides bearing substitution α- to nitrogen (entries 3 and 6) were shown to be competent nucleophiles under these conditions. Cyclic sulfamidates containing ring substitution were treated with the sulfonamide **202** and in all cases gave good yields of the expected products (entries 10 to 16).

It was found that the silyl ether contained in cyclic sulfamidate **242** could either be removed (entry 13) or retained (entry 14) depending upon the protiolytic quench used upon the completion of ring opening.[89] Pleasingly, the acetate group contained in cyclic sulfamidate **243** (entry 16) was also retained during the ring opening reactions.

With the acyclic carbamates in hand (Table **20**), heterocycle formation under gold-catalysed conditions was studied. Initially, the acyclic carbamates derived from propargyl sulfonamide **202** and various 5-membered cyclic sulfamidates were investigated. The cyclisation reactions attempted are summarised in Table **21**.

Entry	Carbamate	Heterocycle	Yield
1	 **208**	 **77**	98
2	 **209**	 **222**	98
3	 **268**	 **275**	90

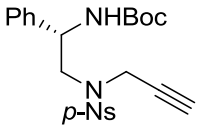
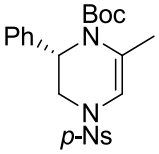
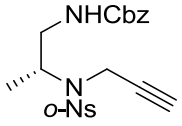
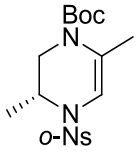
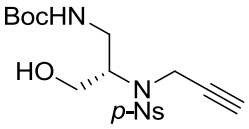
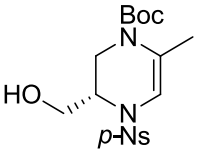
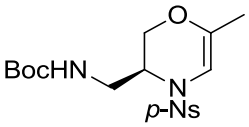
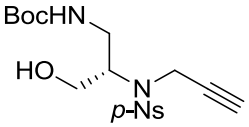
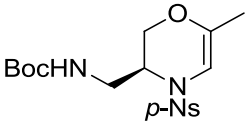
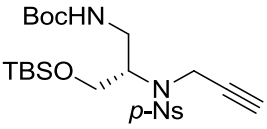
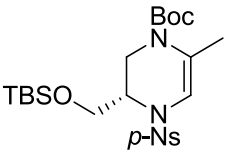
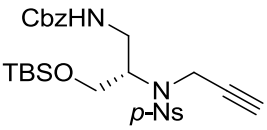
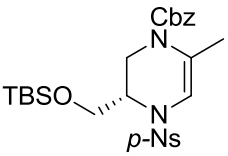
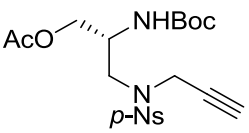
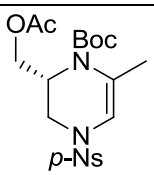
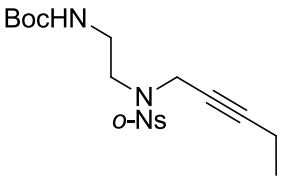
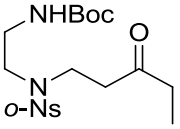
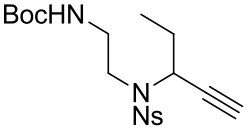
4	 **269**	 **276**	96
5	 **270**	 **277**	96
6	 **271**	 **278** And  **279**	36[a] 48
7	 **271**	 **279**	81[b]
8	 **272**	 **280**	79
9	 **273**	 **281**	85
10	 **274**	 **282**	92

Table **21**: Intramolecular cyclisation of acyclic carbamates to give tetrahydropyrazines. *Reagents and conditions*; A: $Au(PPh_3)Cl$ (5 mol%), $AgSbF_6$ (5 mol%), 1,4-dioxane, 100 °C. [a] Structure confirmed by desilylation of **280**, see Scheme **42**, Section **3.1.3**. [b] Cyclisation performed at room temperature in $CDCl_3$. Observed as the sole product by 500MHz ^1H NMR spectroscopy with complete consumption of starting material.

Treatment of the cyclisation substrates (Table **21**, entries 1–10) with 5 mol% $Au(PPh_3)Cl$ and 5 mol% $AgSbF_6$ in 1,4-dioxane at 100 °C led to the formation of heterocycles in good yield. This cyclisation methodology is clearly compatible with substitution either α- or β- to the carbamate nitrogen (entries 4 and 5 respectively). Both silyl ether (entries 8 and 9) and acetate (entry 10) protecting groups are well tolerated, enabling synthesis of the heterocycles **280**, **281** and **282**. Cyclisation of the alcohol **271** gave an approximately 1:1 mixture of **278** and **279** under these conditions. The structure of **278** was determined *via* an alternative synthesis of **278** by desilylation of **280** (Section **3.1.3**, Scheme **42**). However, modification of the reaction conditions (room temperature, $CDCl_3$) resulted in the formation of **279** as the sole product with complete consumption of the carbamate **271** suggesting that dihydrooxazine **279** is the kinetic product of the two possible heterocyclic compounds **278** and **279**.

In order to determine the scope of the cyclisation methodology, the gold-mediated cyclisation was applied to the remaining carbamates from Table **20**. It was found that heterocycle formation was incompatible with these substrates (Table **22**).

Entry	Carbamate	Conditions	Product	Yield (%)
1	 **261**	A	—[a]	
		B	 **285**	68
2	 **262**	A	—[a]	
		B	—[a]	

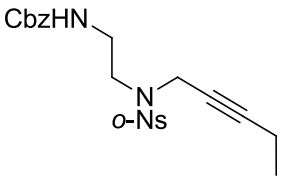
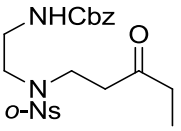
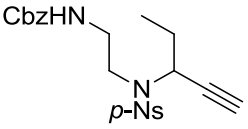
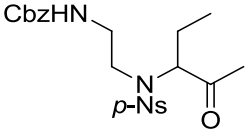
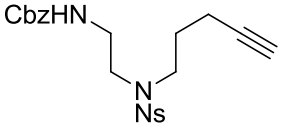
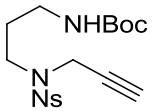
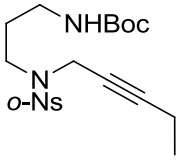
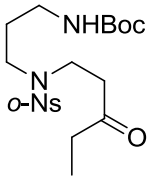
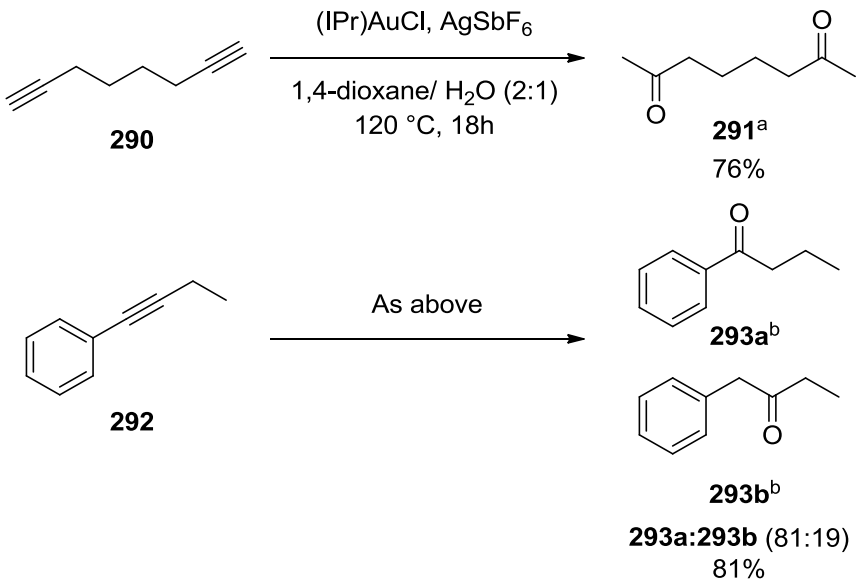
3	 **263**	A B	—[a]  **286**	85
4	 **264**	A B	—[a]  **287**	46
5	 **265**	A B	—[a] —[a]	
6	 **266**	A B	—[a] —[a]	
7	 **267**	A B	—[a]  **288**	61

Table **22**: Attempted cyclisation under gold-catalysed conditions. *Reagents and conditions*; A: $Au(PPh_3)Cl$ (5 mol%), $AgSbF_6$ (5 mol%), 1,4-dioxane, 100°C. B: Au(IPr)Cl (1 mol%), $AgSbF_6$ (1 mol%), 1,4-dioxane/ H_2O (2:1), 120°C, sealed tube. [a] Complex mixtures returned by analysis of crude reaction mixtures by LCMS and 500 MHz ^1H NMR spectroscopy.

Attempted cyclisation of the acyclic carbamates (Table **22**) using 5 mol% $Au(PPh_3)Cl$ and 5 mol% $AgSbF_6$ in 1,4-dioxane at 100 °C (Conditions A) failed to give any detectable heterocyclic products with complex reaction mixtures, containing starting material, returned. However, employing 1 mol% Au(IPr)Cl and 1 mol% $AgSbF_6$ in 2:1 1,4-dioxane–water at 120 °C (conditions B which were identified in Section **3.1.1.5**)[85] resulted, in some cases, in the hydration of the alkyne to a ketone. Hydration of carbamates with substitution on the propargylic position (entries 2 and 4) appears to be dependent upon the nature of the carbamate group (*N*-Boc or *N*-Cbz respectively). Attempted hydration of **262** resulted in consumption of starting materials but resulted in complex mixture of unidentifiable materials. Conversely, hydration of the benzyl carbamate **264** gave the ketone **287** in a good yield. These differing results may be due to the differing steric requirements of the carbamate groups to adopt conformations required for reaction progression. Elongation of the chain length between sulfonamide and alkyne (entry 5) also appears to have a detrimental effect on the outcome of the reaction with significant starting material remaining after elongated reaction times. Similarly, elongation of the chain length between sulfonamide and carbamate groups (entry 6) failed to give any identifiable materials. It is clear that non-terminal alkynes readily undergo regioselective hydration (entries 1 and 3). The hydration of non-terminal alkynes also tolerates elongated chain lengths between sulfonamide and carbamate groups (entry 7) giving ketone **288** in a good yield.

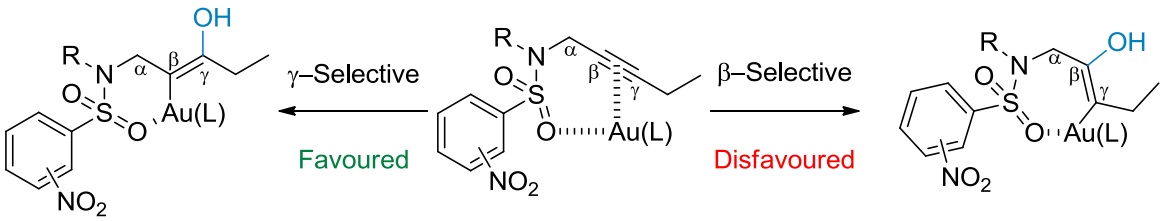
3.1.2.3.1 Regioselectivity of Alkyne Hydration

The hydration of alkynes using the Au(IPr)Cl/ $AgSbF_6$ system, as employed in Section **3.1.2.3**, has previously been shown to mediate the regioselective hydration of terminal alkynes and, to a lesser extent, some unsymmetrical alkynes (Scheme **38**).[85]



Scheme **38**: Selected alkyne hydration results as reported by Nolan *et al.* [a] Au catalyst loading at 100 ppm with Ag in excess. [b] Au catalyst loading at 1000 ppm.

The hydration of terminal alkynes reported by Nolan *et al.* (Scheme **38**)[85] showed double hydration of the diyne **290** to diketone **291** without observation of any aldehydes. This result suggests a substrate bias for ketone formation over aldehyde formation which is in agreement with the previously observed ketone formation of terminal alkynes (ketone **227**). Hydration of non-terminal alkynes, such as **292**, led to a mixture of regioisomeric products **293a** and **293b** showing that hydration at either position of the parent alkyne is feasible under these conditions. Presumably, the product bias towards the benzylic ketone **293a** arises from the formation of a lower energy conjugated product. However, successful hydration of substrates shown in Table **22** led, in all cases, to a single regioisomer (>98:<2 by 500MHz ^{1}H NMR spectroscopic analysis of crude reaction mixtures) of the ketone product being observed. The regioselective hydration may stem from coordination of the sulfonamide group to the Au$^{(I)}$ catalyst, biasing a regioselective γ-hydration *via* a 6-membered intermediate (Scheme **39**).[90]

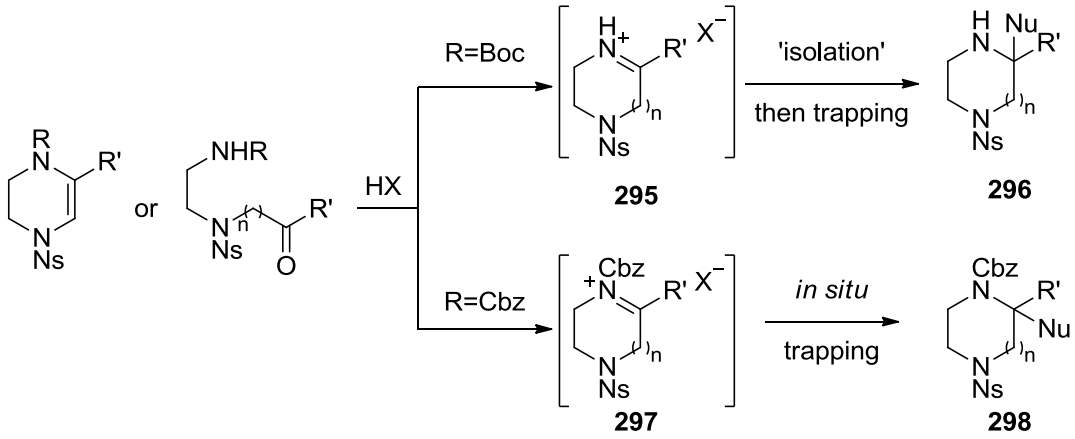


Scheme **39**: Proposed chelation model to explain the observed regioselective hydration of non-terminal alkynes such as **261** and **263**.

3.1.3 Reactivity of Products from Gold Mediated Transformations

It was envisaged that both the heterocyclic and hydrated products from the gold mediated transformations (Section **3.1.2**) could act as substrates for further complexity-generating reactions. This Section outlines the approaches undertaken in order to investigate the reactivity of both the hydrated and heterocyclic products.

It was hypothesised that both cyclic and hydrated products from Section **3.1.2** could undergo an iminium formation process which may allow further substitution to introduced on the heterocyclic scaffold (Scheme **40**).



Scheme **40**: Proposed general approach to the introduction of substitution onto heterocyclic scaffolds from both cyclic and acyclic substrates.

The envisaged approach towards saturated heterocycles (Scheme **40**) would be initiated by iminium ion formation (such as **295**), trapping with an appropriate nucleophile, leading to saturated heterocyclic systems **296**. It was hypothesised a *N*-Boc group may be removed under appropriate conditions, giving an iminium species which may allow isolation as a salt **295**. The removal of excess acid would then allow the use of acid-sensitive nucleophilic reagents, such as isonitriles. It was hypothesised that the more electrophilic *N*-acyl iminium **297** would not be isolatable and therefore more acid stable nucleophiles, such as silanes, would be required. Furthermore, it was hypothesised that the ene-diamine motif contained within tetrahydropyrazine compounds may be able to participate in cycloaddition reactions allowing the formation of polycyclic ring systems. Investigations undertaken to study the reactivity of the tetrahydropyrazine **77** are summarised in Table **23**.

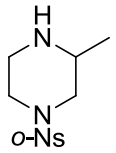
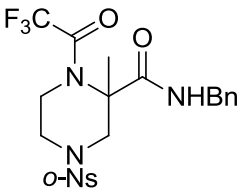
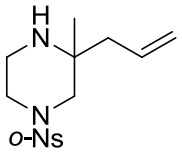
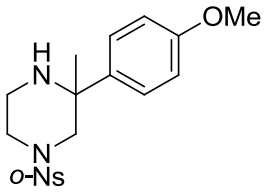
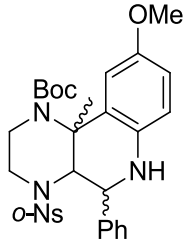
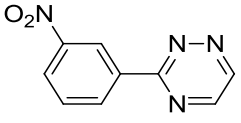
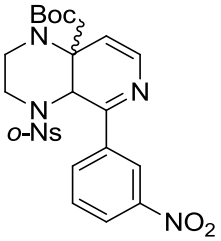
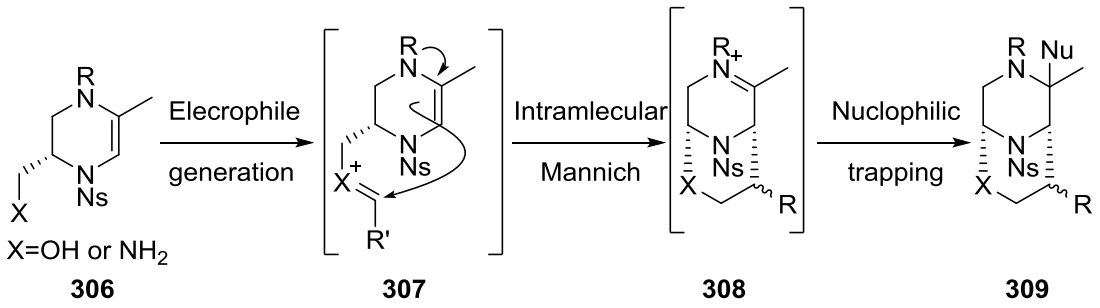
Entry	Conditions	Expected product	Yield (%)
1	Et_3SiH, TFA, CH_2Cl_2, 0 °C to rt	 **300**	76
2	TFA, CH_2Cl_2, then benzylisonitrile, EtOH, 0 °C to rt	 **301**	70
3	Allyl silane, TFA, CH_2Cl_2, 0 °C to rt	 **302**	— [1]
4	TFA, CH_2Cl_2, then 4-methoxyphenyl boronic acid, DCE, rt	 **303**	— [1]
5	4-Methoxyaniline, benzaldehyde, $Sc(OTf_3)$, PhMe, reflux	 **304**	— [2]
6	 PhMe, reflux	 **305**	— [2]

Table **23**: Screening or reactivity of **77** under varied of conditions. [1] Only removal of Boc group was observed by LCMS analysis of reaction mixtures. [2] Significant amounts of starting material

remained even after extended reaction times (up to 7 days) at elevated temperatures with no trace of expected products by LCMS.

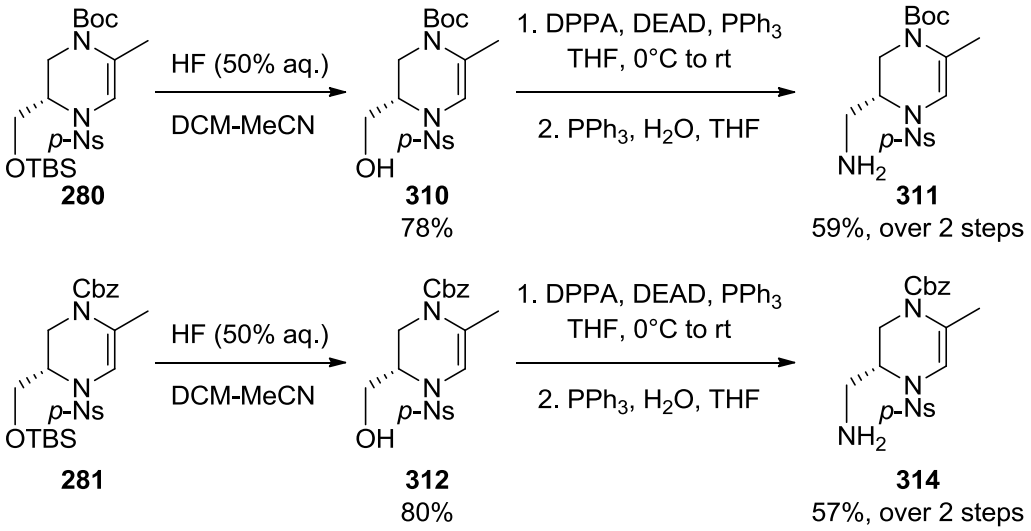
The reactions of the tetrahydropyrazine **77** were met with mixed success. Exposure to TFA and triethylsilane in CH_2Cl_2 (Table **23**, entry 1) led to the formation of piperazine **300**. Alternatively, subjecting the tetrahydropyrazine **77** to TFA in CH_2Cl_2, followed by treatment with benzylisonitrile, in ethanol, gave the piperazine **301** (entry 2). However, alternative approaches for the introduction of complexity were met with disappointment. Surprisingly, attempted addition of allyl silane, under conditions analogous to silane–mediated reduction (entry 3), failed to give any of the expected product with only *N*–Boc removal products observable by LCMS. Similarly, the attempted addition of electron rich aryl boronic acid (entry 4) failed to give detectable products; this result is perhaps not surprising as this reaction is formally a Petasis reaction, which typically require the presence of a proximal hydroxy group.[91] Two attempts to induce [4+2] cycloadditions were investigated (entries 6 and 7) although both approaches failed to give detectable products with significant quantities of the tetrahydropyrazine **77** remaining even after extended reaction times.

An alternative approach to investigate the reactivity of unsaturated heterocycles was an intramolecular complexity–generating reaction. This approach was based upon the generation of a tethered electrophile, which may allow an intramolecular Mannich reaction to give oxa- and aza-bispidines (Scheme **41**). An analogous approach towards oxygen–containing bridged heterocycles utilising an intramolecular Mannich approach has been reported.[92]



Scheme **41**: Proposed approach to polycyclic scaffolds *via* an intramolecular Mannich cyclisation.

In order to investigate the proposed intramolecular Mannich cyclisation, the synthesis of a series of building blocks was undertaken (Scheme **42**). The tetrahydropyrazines **280** and **281** were deprotected using aqueous HF in DCM–MeCN to give the alcohols **310** and **312**. The alcohols **310** and **312** were transformed into the amines **311** and **314** respectively by the treatment with DPPA, DEAD and PPh_3 in THF to give the corresponding azides, followed by reduction by treatment with PPh_3 and water in THF.



Scheme **42**: Synthesis of amines and alcohols for the investigations into intramolecular Mannich cyclisation.

With both the alcohols **310** and **312** and amines **311** and **314** in hand, the subsequent intramolecular cyclisations were studied. Cyclisation conditions were based upon both Lewis and Brønsted acid-mediated processes with benzylic aldehydes (Table **24**).[92]

Entry	Substrate	Conditions	Outcome
1	**310**	4-methoxybenzaldehyde, $BF_3{\cdot}OEt_2$, CH_2Cl_2	—[a]
2	**310**	4-methoxybenzaldehyde, Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2	—[a]
3	**310**	4-methoxybenzaldehyde dimethylacetal, PTSA or PPTS, MeOD-d4	—[b, c]
4	**311**	4-methoxybenzaldehyde, PTSA, MeOH	—[b]
5	**314**	4-methoxybenzaldehyde, PTSA, 4Å mol. sieves, MeOH	—[b, c, d]
6	**314**	4-bromobenzaldehyde, PTSA, MeOH	—[b]
7	**314**	4-methoxybenzaldehyde, $BF_3{\cdot}OEt_2$, CH_2Cl_2	—[b]

8	**314**	4-methoxybenzaldehyde, Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2	— [b]
9	**314**	4-methoxybenzaldehyde dimethylacetal, Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2	— [b]

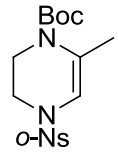
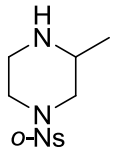
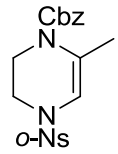
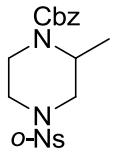
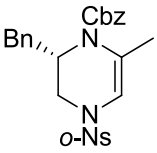
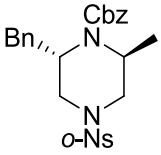
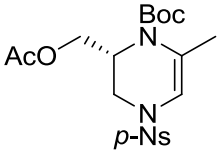
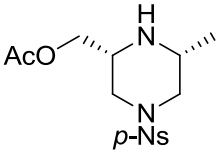
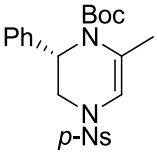
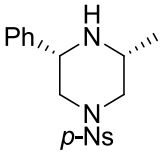
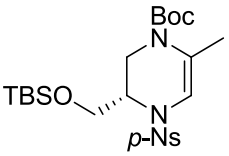
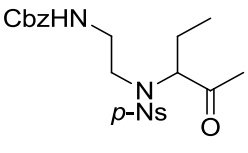
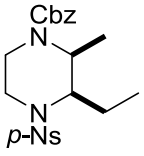
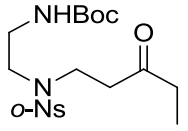
Table **24**: Attempted intramolecular Mannich approach toward polycyclic scaffolds. [a] Complex mixture of products by analysis by LCMS and 500 MHz ^{1}H NMR. [b] Significant amounts of starting material remained, even after extended durations (up to 7 days), as determined by LCMS and 500 MHz ^{1}H NMR analysis of crude reaction mixtures. [c] Reactions performed at 65°C. [d] Imine pre-formed by condensation of aldehyde and amine over molecular sieves, as confirmed by 500 MHz ^{1}H NMR, prior to addition of PTSA and heating.

A variety of alcohol and amine substrates (Table **24**), Lewis and Brønsted acids, aldehydes, additives and solvents were screened in order to identify conditions for an intramolecular Mannich type cyclisation. In each case, one substrate was treated with one aldehyde (or acetal) and one acid, whose selection was driven by the successful employment in literature reports.[92] In all cases the approaches summarised in Table **24** failed to give detectable products with either significant amounts of starting substrate remaining or complex mixtures being returned.

Throughout this section a variety of reaction conditions have been screened in order to probe potential inter- and intra-molecular complexity generating reactions towards saturated heterocycles. It is clear that both reduction and formal Ugi reactions (Table **23**, entries 1 and 2 respectively) were possible with the substrates derived from gold–mediated cyclisation of alkyne substrates.

3.1.3.1 Reactivity of Unsaturated Heterocycles and Ketones under Reductive Conditions

With conditions for the reduction of the tetrahydropyrazine **77** in hand, the scope and limitations of this approach to deliver saturated heterocycles were investigated. This approach employed both unsaturated heterocycles and ketones generated from gold–mediated cyclisation/ hydration of alkynes (Table **25**).

Entry	Substrate	Product	Yield, % (dr)[a]
1	 **77**	 **300**	76
2	 **222**	 **314**	72
3	 **275**	 **315**	68 (88:12)
4	 **282**	 **316**	76 (60:40)
5	 **276**	 **317**	71 (89:11)
6	 **280**	—[c]	
8	 **287**	 **318**	82[b]
7	 **285**	—[d]	

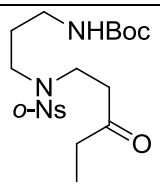
9	 **288**	—[d]	

Table **25**: Reduction of cyclic and acyclic substrates to give saturated heterocycles. *Reagents and conditions*: Substrate (1.0 eq.), TFA (10.0 eq.), Et_3SiH (6.0 eq.), CH_2Cl_2 (0.05 M), 0 °C to rt. [a] Major diastereoisomer shown. [b] Isolated as a single isomer as determined by 500 MHz ^1H NMR spectroscopy. [C] Complex mixtures of products were observed by analysis of crude reaction mixtures by LCMS and 500 MHz ^1H NMR spectroscopy. [d] No product formation observed with carbamate removal products observed by LCMS analysis of reaction mixtures.

Treatment of the tetrahydropyrazines **77**, **222**, **275**, **282** and **276** with Et_3SiH and TFA in CH_2Cl_2 led to good isolated yields of piperazines (Table **25**, entries 1–5). Modest diastereoselectivity (60:40 to 89:11) was observed when substrates already containing substitution on the heterocycle ring (entries 3–5). Subjecting the ketone **287** to Et_3SiH and TFA in CH_2Cl_2 led to the formation of the piperazine **318** with retention of the Cbz group. However, ketones **285** and **288** (entries 7 and 9 respectively), leading toward 7– and 8–membered heterocyclic systems, failed to give any detectable products with only *N*–deprotected material observed by LCMS analysis of reaction mixtures.

3.1.3.1.1 Determination of the Stereochemical Outcome of Reduction Reactions

The determination of the stereochemical outcome of the products shown in Table **25** was performed using ^1H NMR spectroscopy and investigating key nOe interactions. The determination of the configurations of the structures of **317** and **315** are summarised in Figure **24**.

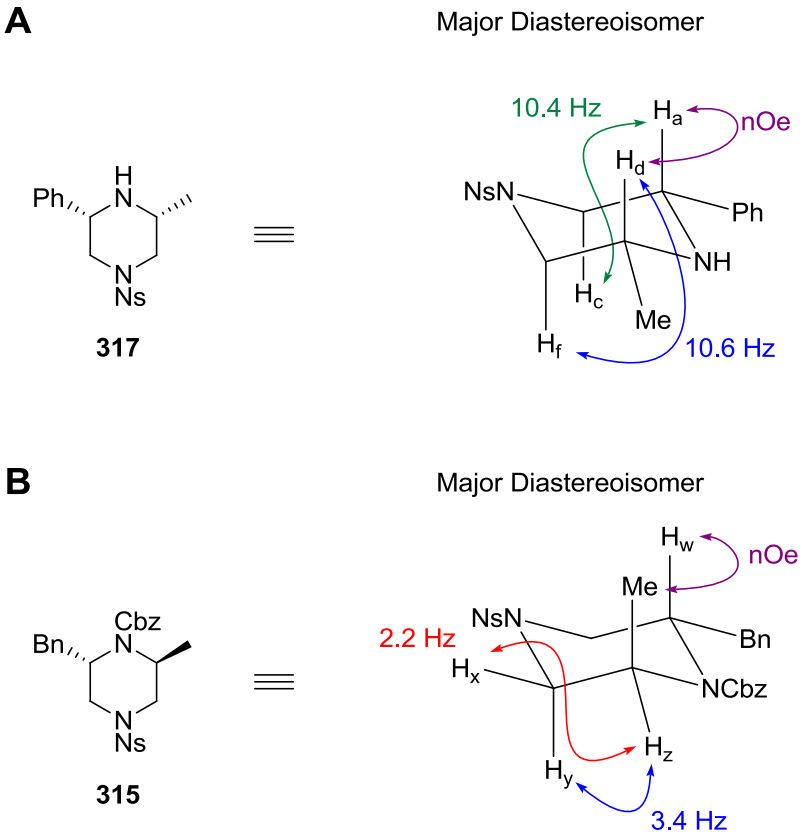


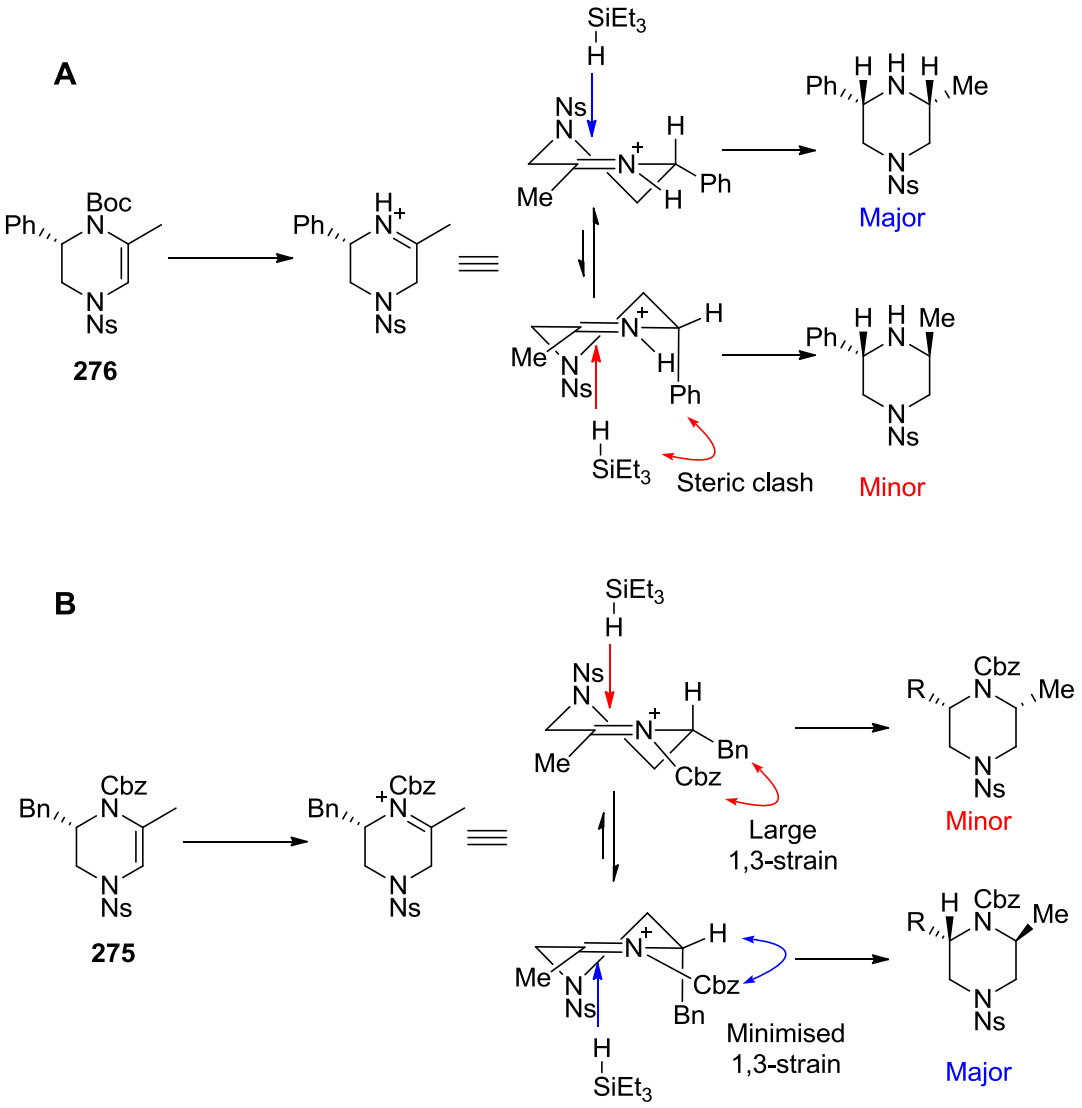
Figure **24**: Key coupling constants and observed nOe used in the structural determination of **317** and **315**. Panel **A**- Key coupling constants and observed nOe used in the structural determination of **317**. Panel **B**- Coupling constants and nOe used in the structural determination of **315**.

Analysis of the 500 MHz ^{1}H NMR spectrum of the piperazine **317** (Figure **24**, Panel **A**) showed H_f coupling to H_d with a coupling constant of 10.6 Hz, indicative of an axial–axial orientation. The coupling between H_c and H_a was observed 10.4 Hz, again indicative of an axial–axial orientation. Furthermore, a strong nOe was observed between H_d and H_a suggesting that these protons are positioned axially leading the structure to be assigned as the 2,6-*syn* product. Similarly, analysis of the ^{1}H NMR of **315** (Panel **B**) showed H_x coupling to H_z with a coupling constant of 2.2 Hz, indicative of equatorial–equatorial coupling. A strong nOe was observed between the methyl group and H_w leading the structure of **315** to be assigned as the 2,6-*anti* product. In both cases the key nOes observed for the major diastereoisomers were not observed for the minor diastereoisomers.

3.1.3.1.2 Rationalisation of Stereochemical Outcome of Reduction Reactions

As shown in Section **3.1.3.1.1** the stereochemical outcome of the reduction reactions appear to be dependent upon the *N*–protecting group. Reduction of the *N*-Boc substrates **276** and **282** resulted in 2,6-*syn* products as the major diastereoisomer, presumably via a transition state which proceeds by an axial approach of silane to the iminium with ring

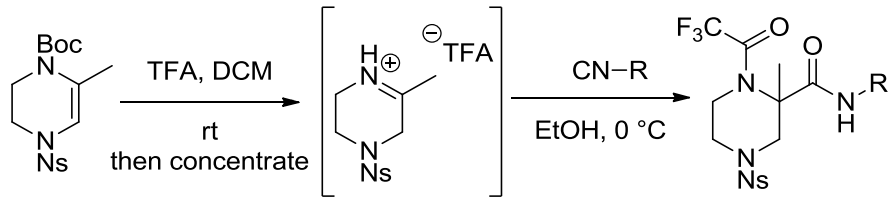
substitution placed in a pseudo-equatorial position (Scheme **43**, panel **A**).[93] Conversely, reduction of the *N*-Cbz substrate **275** resulted in the 2,6-*anti* substitution. This outcome may be rationalised by the potential for minimisation of 1,3-strain between *N*-Cbz and C-6 benzyl group by the placement of the benzyl group in an pseudo-axial position which allows axial silane addition to give the major diastereoisomer observed (Scheme **43**, panel **B**).

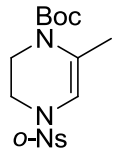
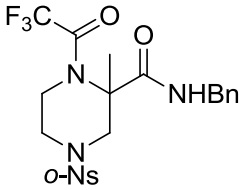
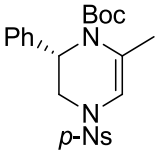
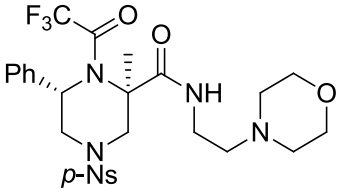
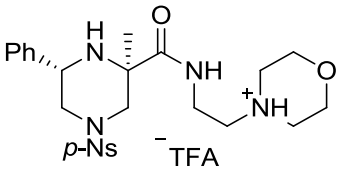
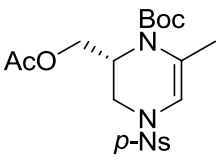
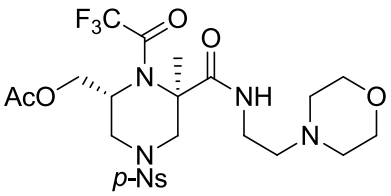


Scheme **43**: Rationalisation of stereochemical outcome for the reduction of substituted piperazines. Panel **A**- Reduction of *N*-Boc substrate **276**, *via* postulated iminium species, gives 2,6-*syn* product as major diastereoisomer. Panel **B-** Reduction of *N*-Cbz substrate **275**, *via* hypothesised *N*-acyl iminium species, to give the 2,6-*anti* substitution as the major diastereoisomer.

Z.1.3.2 Reactivity of Unsaturated Heterocycles and Ketones under Ugi–Type Conditions

With conditions identified for the formal Ugi[94, 95] reaction with iminium derived from the tetrahydropyrazine **77**, the scope and limitations of this approach to saturated heterocycles were studied. This study employed both the heterocycles and the acyclic ketones generated from the gold mediated cyclisation/ hydration studies and are summarised in Table **26**.



Entry	Substrate	Product	Yield, %
1	 **77**	 **301**	70[e]
2	 **276**	 **320**  **321**	28[d,f] 59[d,f]
3	 **282**	 **322**	65[d,f]

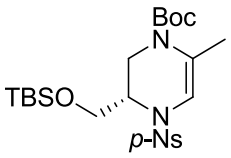
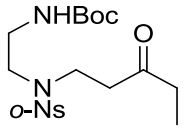
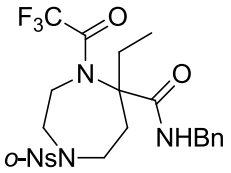
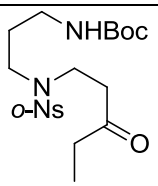
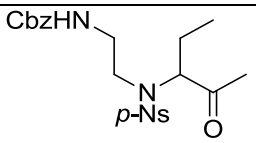
4	 **280**	—[a]	
5	 **285**	 **323**	71[e]
6	 **288**	—[c]	
7	 **287**	—[b]	

Table **26**: Formal Ugi approach to give saturated heterocycles.. [a] Complex mixtures of products observed by analysis of crude reaction mixtures by LCMS and 500 MHz ^{1}H NMR spectroscopy. [b] No iminium formation was observed by LCMS or 500 MHz ^{1}H NMR spectroscopy. [c] No isonitrile addition observed by LCMS analysis of crude reaction mixtures. [d] Single diastereoisomers observed by 500 MHz ^{1}H NMR analysis. [e] Obtained with benzylisonitirle. [f] Obtained with 4-(2-isocyanoethyl)morpholine.

Treatment of *N*-Boc heterocycles **77**, **276** and **282** (Table **26**, entries 1–3) with TFA in CH_2Cl_2 followed by treatment of the crude iminum salt with either benzylisonitrile (entry 1) or 2-morpholinoethyl isocyanide (entries 2 and 3) led to the formation of piperazines **301**, **322**, **320** and **321** (which was presumably formed from the decomposition of **320**) in >98:<2 diastereoselectivity. However, the tetrahydropyrazine **280** failed to give any detectable product with complex mixtures of products, including desilylated starting material, observed. Exposing the ketone **285** to these conditions (entry 5) led to the isolation of the amide **323** in a good yield showing that it is possible to form 7-membered heterocycles using this approach. However, attempts to generate the 8 membered analogue (entry 6) failed to give any detectable product. Similarly, the *N*-Cbz substrate (entry 7) failed to give any observable product.

3.1.3.2.1 Determination of the Stereochemical Outcome of Ugi–Type Reactions

The determination of the stereochemical configuration of the products shown in Table **26** was performed using both ^{1}H NMR spectroscopy and investigating key nOe interactions in a similar fashion to that described in Section **3.1.3.1.1**. The determination of the structures of **320** and **321** is summarised in Figure **25**.

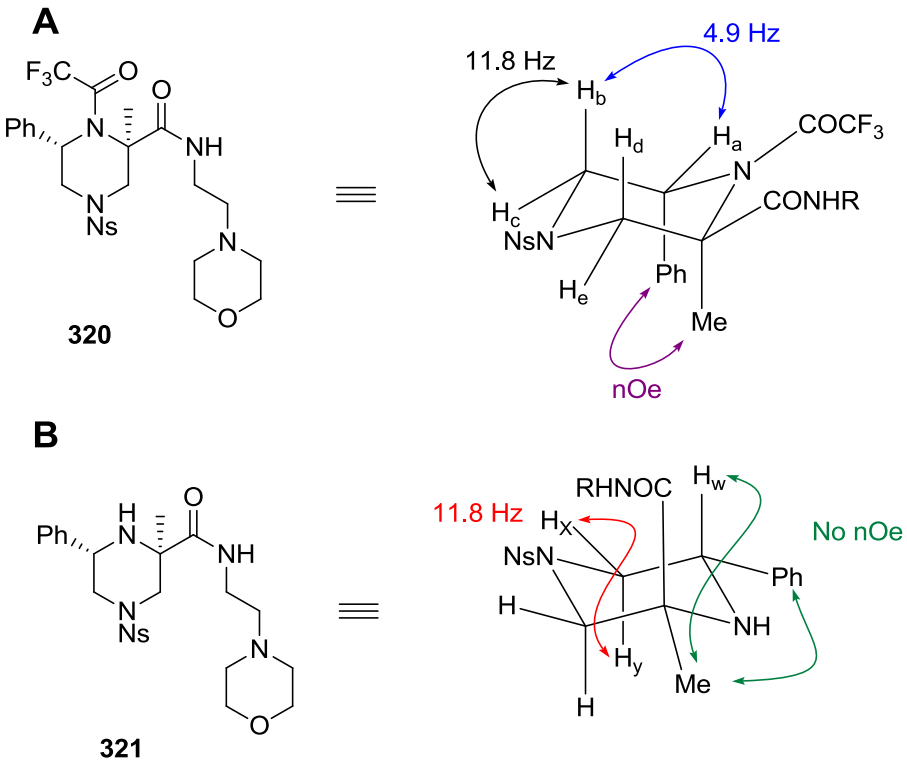


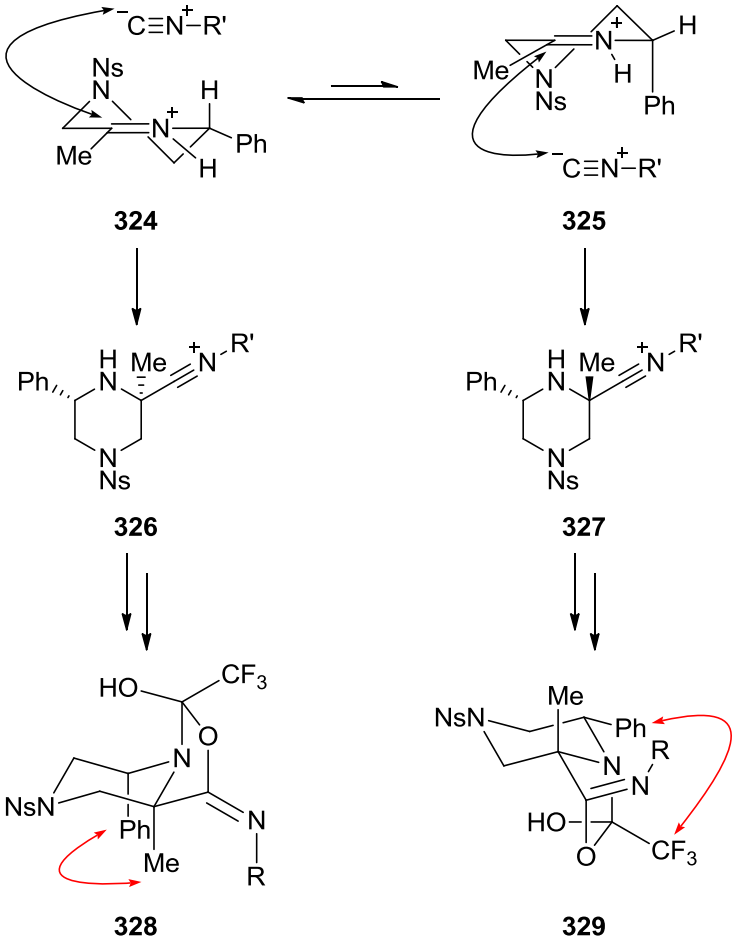
Figure **25**: Key coupling constants and observed nOe used in the structural determination of **320** and **321**. Panel **A**- Key coupling constants and observed nOe used in the structural determination of **320**. Panel **B**- Coupling constants and lack of nOe used in the structural determination of **321**.

The configuration of **320** was determined by using key coupling constants and observed nOe (Figure **25**, Panel **A**). H_a is observed as an apparent doublet with a coupling constant of 4.9 Hz, indicative of an axial–equatorial coupling. This could originate from either coupling between H_a and H_b in the conformation shown or if H_a was axially orientated. A strong nOe between the C-2 methyl group and the C-6 phenyl group is observed suggesting that these substituents are both axially orientated. These observations thus lead to the conclusion that the piperazine **320** is 2,6-*syn* substituted with both the methyl and phenyl groups occupying axial positions. The piperazine **321** showed similar ^{2}J coupling constants to that of the piperazine **320**. However, no nOe was observed between

the C-2 methyl group and either the C-6 phenyl group or H_w. This suggests the again 2,6-*syn* substitution but with both the amide and H_w axially oriented.

3.1.3.2.2 Rationalisation of Stereochemical Outcome of Ugi Reactions

The stereoselectivity of the Ugi reaction is often thought to be determined by the irreversible Mumm rearrangement.[95] However, there are selected reports that suggest that the stereoselectivity may arise, in some cases, from the isonitrile addition to an iminium species.[96] In order to rationalise the outcome of the Ugi reactions found in these studies both Mumm rearrangement and isonitrile addition were considered (Scheme **44**).



Scheme **44**: Rationalisation of observed diastereoselctivity for 'Ugi' reaction of tetrahydropyrazine **276**. Panel **A**- Proposed diastereoisomeric pathways of isonitrile addition to iminum species. Panel **B**- Proposed plausible intermediates in the Mumm rearrangement pathway.

Initial formation of iminium an species formed, by protolytic carbamate cleavage from **276**, is postulated to place the phenyl substituent in a pseudo-equatorial position which allows reversible isonitrile addition *via* an axial approach (Scheme **44**, **→326**).[93] Alternatively, the phenyl group may adopt an axial orientation which would generate

diastereoisomer **327**. In order to rationalise the diastereoselectivity of the Mumm rearrangement the hypothesised intermediates **328** and **329** were considered. It was hypothesised that during the Mumm rearrangement the breaking five-membered ring becomes flattened in order to accommodate the formation of numerous sp^2 centres. This flattening creates bowl shaped intermediates and as such the methyl groups, in both cases, were placed on the outside face of the bowl in order to minimise transannular interactions. Intermediate **328** shows destabilising 1,3-transannular interactions between the phenyl and methyl groups if placed in an axial orientation. Alternatively, placing the phenyl group in an equatorial orientation (**329**) increases the 1,3-strain between the phenyl group and the forming trifluoromethyl amide. Although it is not abundantly clear which of these intermediates is favourable, it is believed that **328** is favoured as this leads to the observed product.

3.2.4 Diverse Heterocyclic Lead-Like Library Design

In order to illustrate the potential power of the synthetic cyclic sulfamidate-propargyl sulfonamide pairing approach in the generation of diverse molecules, with properties desired in lead like compounds, an *in silico* library of piperazine and piperazine-like compounds was enumerated.[33] A schematic outline of this *in silico* approach is shown in Figure **26**. This *in silico* library generation utilised commercially available amino alcohol and alkyne building blocks (Panel **A**, **A1**), which were appropriately modified to incorporate appropriate protecting groups to prevent unwanted reactivity. These building blocks were then transformed into either cyclic sulfamidates (**A3**) or propargyl sulfonamides (**A2**). Pairs of functionalised building blocks were then systematically coupled to give a library of acyclic intermediates (**A4**). The acyclic intermediates, dependent upon their structure, were either cyclised to give unsaturated heterocycles (**B5**) or hydrated to give acyclic ketones. Subsequent reductions and/or Ugi reactions gave an array of heterocycles (**A7**) containing a variety of protecting groups on the nitrogen centres contained within the cyclic scaffold. Subsequent selective functionalization and/or deprotection at the nitrogen centres gave a library of capped diverse heterocycles (**A8**). The computational approach outlined in Panel **A** is exemplified by the synthesis of piperazines **B8** (Panel **B**) from ethanolamine and propargyl alcohol (**B1**).

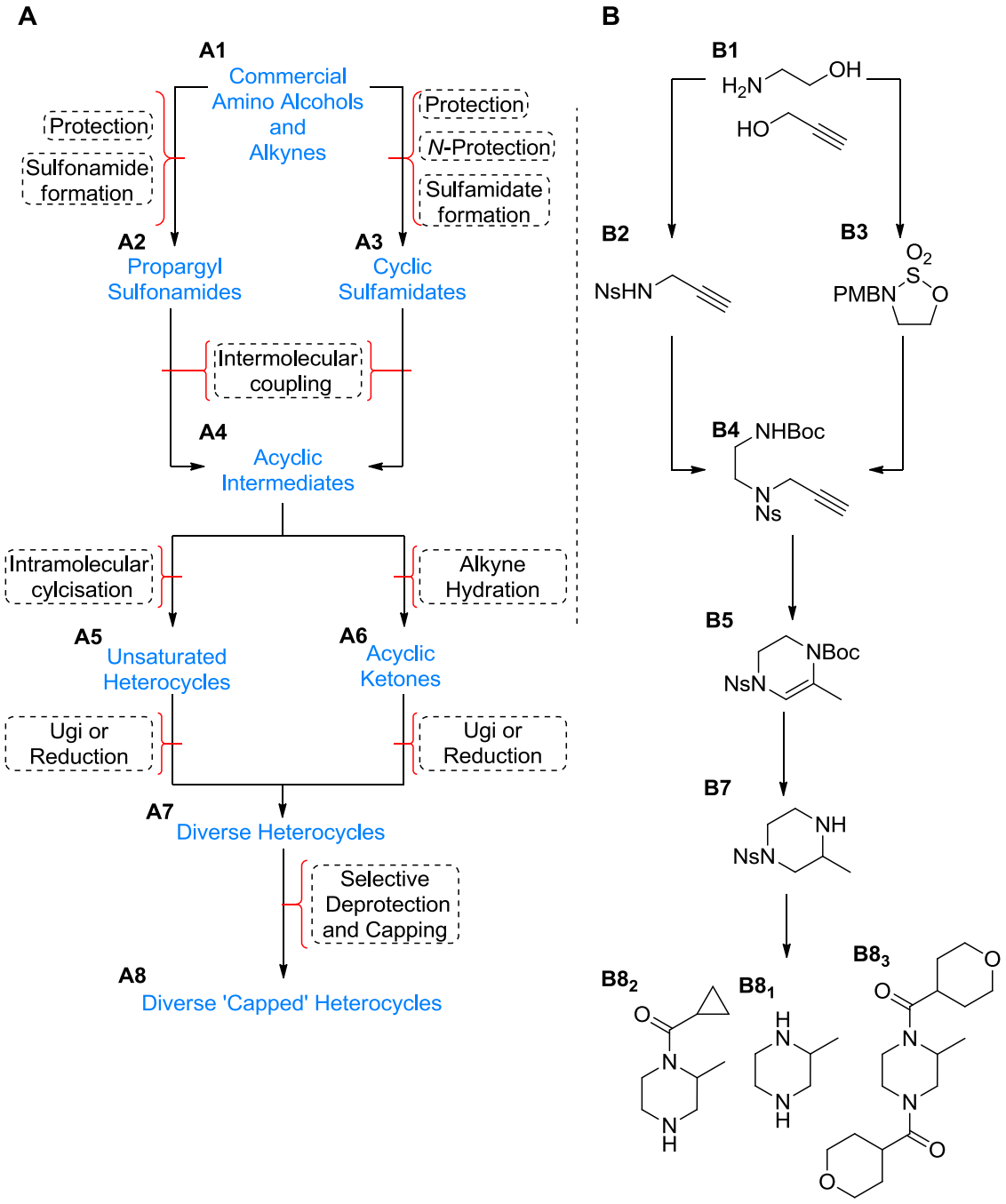


Figure **26**: An outline of the *in silico* approach employed to illustrate the potential power of the cyclic sulfamidate-propargyl sulfonamide pairing approach to diverse heterocycles. Panel **A**- An overview of the *in silico* protocol utilised in this approach. Text in hashed boxes represents 'synthetic' transformations and text given in blue represents virtual libraries of compounds used/ generated in this approach. Panel **B**- An example of structures used in the *in silico* approach by demonstrating the synthesis of piperazines **B8** from commercially available building blocks **B1**.

The selections of amino alcohols from commercial sources were made by considering their compatibility with the reaction conditions and reactivity insights gleaned from scope and limitation studies (Section **3.1.2**). Furthermore, building blocks and capping groups were selected in such a way that the final *in silico* library may be biased toward the enumeration

of compounds which might possess the physicochemical properties desirable in libraries of lead-like compounds (i.e. mol. weight <350, -1<logP<3, etc.). The variation of Alog*P* and molecular weight for the virtual library are shown in Chart **6**

.

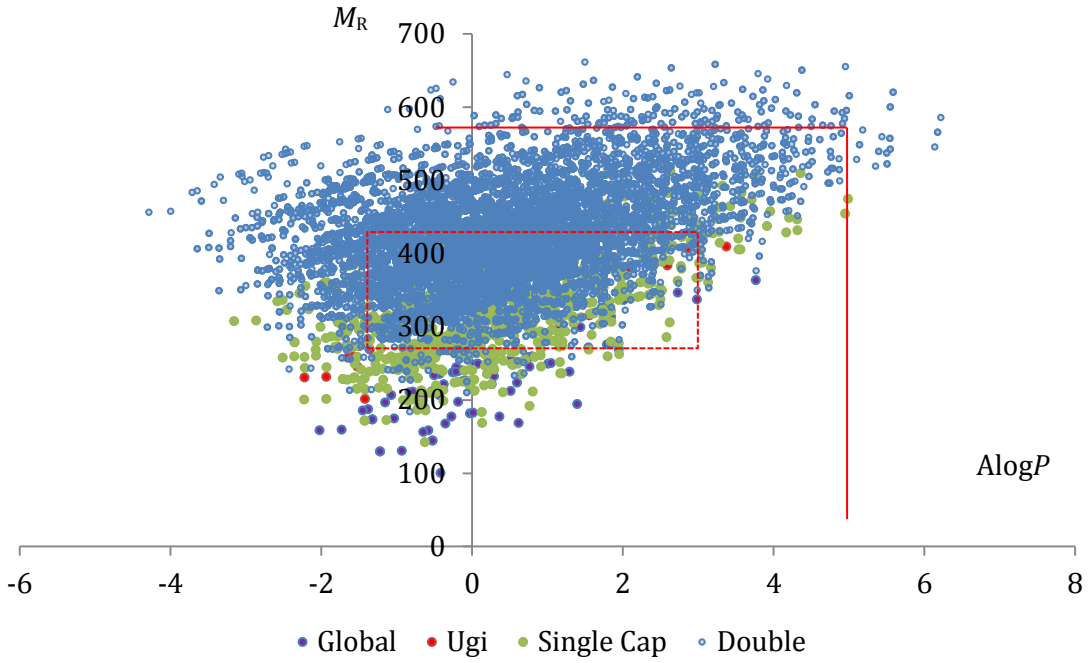


Chart **6**: Prediction of molecular weight and log*P* of the *in silico* generated library using the cyclic sulfamidate-propargyl sulfonamide pairing methodology. Red dashed lines represent the limits of lead-like chemical space whereas the solid red lines outline the limits of drug-like (Lipinski) chemical space. Building blocks used in this *in silico* approach are given in appendix **A**.

The systematic *in silico* pairing of a selection of 10 cyclic sulfamidates, 7 propargyl sulfonamides and 12 capping groups (Appendix **A**) allowed the generation of a virtual library of 11869 compounds. Of these 11869 compounds, 69 were uncapped, core heterocycles, 1678 contained one capping group at either of the nitrogen centres within the ring skeleton, 10079 contained two capping groups and 43 compounds contained the Ugi motif. The uncapped compounds have average molecular weight (232.1 Da) and log*P* (0.29) within the limits of lead like chemical space with 72 % of the population lying within this space. The capped compounds have average calculated molecular weight of 381.2, lying just outside lead-like space. However, this is believed to be due to the presence of a relatively small number of significantly heavier compounds (56 of 1678 compounds have molecular weight >350) rather than a general trend of the library. The average logP of the virtual library of capped compounds is -0.8 therefore lying within the parameters of lead like chemical space. Overall, 94% of the heterocycles generated bearing a single capping group would be described as lead-like when considering both molecular weight and logP. Compounds bearing two capping groups tend to have properties outside

of lead-like chemical space with only 15% of the compound population lying within lead-like chemical space generally by the virtue of having molecular weight greater than 350 Da. However, 85% of compounds bearing two capping groups have properties within the boundaries of Lipinski chemical space suggesting that these compounds may be more suited to drug-like chemical space.

Overall, this *in silico* generated library contains a high proportion of compounds which would be deemed to be lead-like as they lie within the previously outlined parameters of lead-like chemical space. As such, it is believed that this computational approach has illustrated the potential power of the cyclic sulfamidate-amino alcohol pairing methodology for the generation of diverse, lead-like, compounds.

3.1.5 Summary of Cyclic sulfamidate – Propargyl Sulfonamide Pairing

This Chapter has described an approach to the development of methods for the generation of diverse heterocycles from cyclic sulfamidate and propargyl sulfonamide building blocks. This approach has resulted in the development of methodology for the electrophilic activation of alkynes to give either tetrahydropyrazines or unsaturated ketones dependent upon the substrate. Regioselective hydration of non-terminal alkynes was observed to occur which is believed to be directed by the proximal sulfonamide group. The utility of both tetrahydropyrazines and acyclic ketones to generate saturated heterocycles has been demonstrated by the development of both reduction and Ugi methods which allow the formation of both 6- and 7-membered heterocycles. The potential power of this approach has been illustrated by the *in silico* generation of a library of heterocyclic compounds of which a large proportion lie within lead like space. Examples of the diverse heterocycles synthesised within this Chapter are summarised below (Figure **26**).

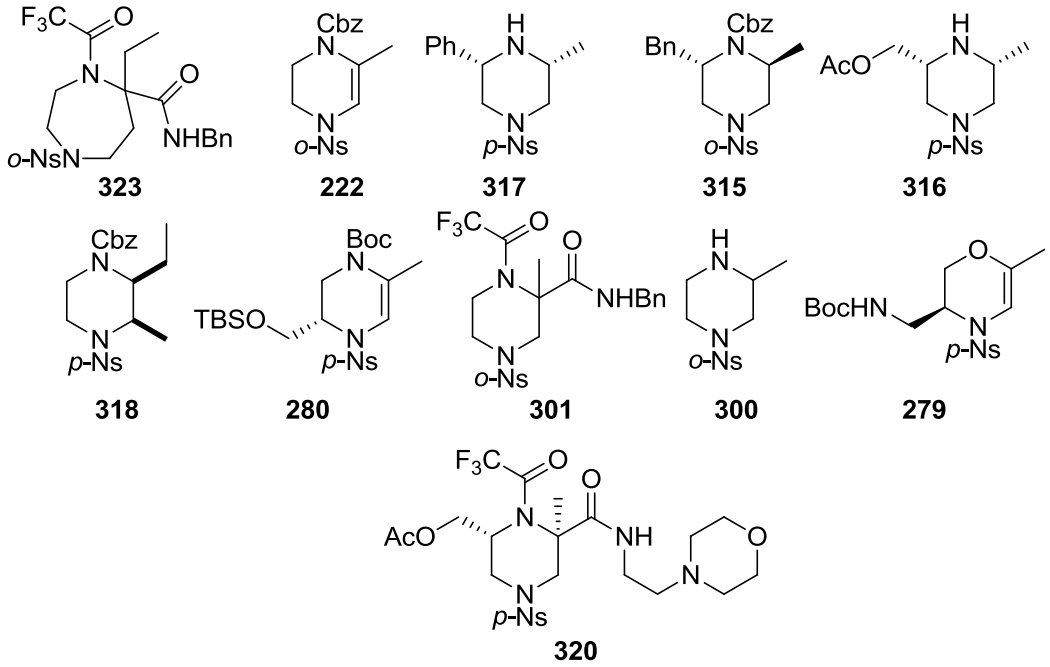


Figure **27**: Examples of some of the diverse heterocyclic structures synthesised in this Chapter.

Chapter 4: Conclusions and Outlook

In summary, this thesis reports studies into the development of methodologies for the robust and convenient synthesis of lead-like scaffolds. The three methods which have been described in this thesis have allowed for the synthesis of a small selection of diverse molecular scaffolds. Some examples of the differing heterocyclic compounds synthesised in each section are shown (Figure **28**).

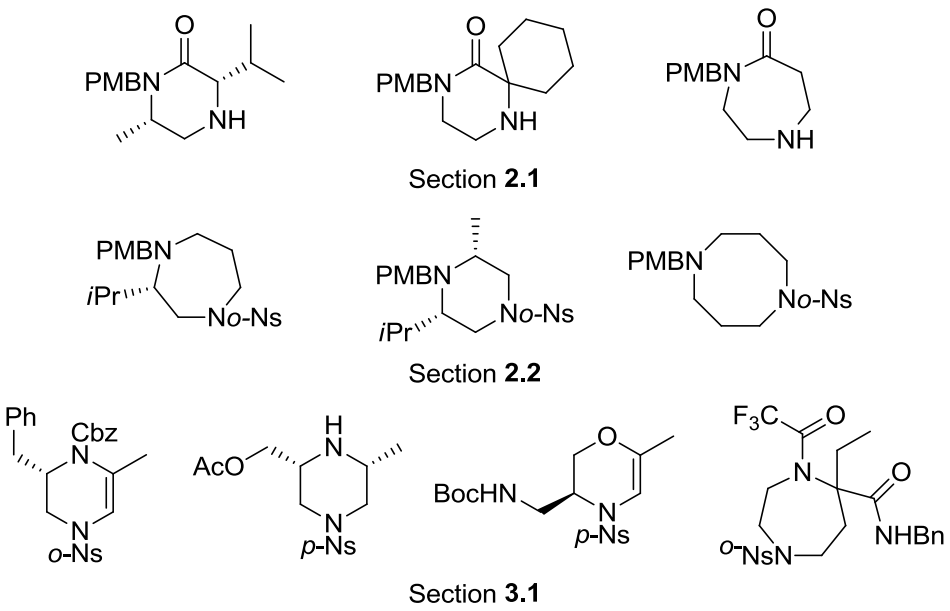


Figure **28**: Examples of some of the diverse heterocyclic scaffolds generated within this thesis.

These studies have resulted in the development of three approaches to the synthesis of nitrogen containing heterocycles; highlights and limitations of these approaches are summarised below:

The chemoselective pairing of amino acid and amino alcohol derived building blocks (Section **2.1**) has allowed the systematic synthesis of ketopiperazine and ketopiperazine-like heterocycles. Initial focus on a catalytic approach to heterocycle formation, using a hydrogen borrowing approach, failed to be productive. However, the Mitsunobu–based methodology developed in this study led to a non-labour intensive 'one pot' approach allowing the systematic variation of heterocycle size and substitution pattern on the carbon centres of the heterocyclic scaffold.

Pairing of amino alcohol derivatives was facilitated through the use of cyclic sulfamidate building blocks, allowing the chemoselective coupling of amino alcohol derived building blocks to give piperazine derived heterocycles (Section **2.2**). This approach again was non-compatible with a catalytic approach to cyclisation and the reactivity of building block pairing was limited by substrate substitution. However, the methodology developed in this

approach allowed the stereoselective synthesis of piperazine and piperazine-like compounds bearing substitution on the carbon centres of the ring system. The potential power of this approach to deliver diverse, lead-like, heterocycles was illustrated by an *in silico* generated virtual library of heterocycles, a high proportion of which were deemed to be lead-like in accordance with the properties suggested by Churcher *et al*.[1]

The approach developed towards a catalytic route to heterocycle formation again exploited the reactivity of cyclic sulfamidates to give unsaturated cyclisation precursors containing an alkyne motif (Section **3.1**). Methods for cyclisation under gold catalysed conditions were developed, to generate tetrahydropyrazine scaffolds. This approach was somewhat limited by the nature of the substrate, with substituted alkyne substrates not undergoing cyclisation. However, this issue was partially circumvented by the application of catalytic alkyne hydration to give ketone substrates. Both tetrahydropyrazines and ketones generated from the catalytic cyclisation/ hydration approaches were demonstrated to be suitable substrates for further complexity generation, through either reductive or Ugi-type pathways, generating saturated heterocyclic systems. Furthermore, illustrating the potential power of this approach by the generation of a virtual lead-like library, using *in silico* methods, resulted in a high proportion of the virtual library lying within lead-like chemical space.

Further to the exemplification of methodologies by the synthesis of diverse, lead-like compounds, future work will focus on the following areas:

- The development of catalytic methodology for the hydrogen borrowing approach to the formation of heterocycles, potentially using ruthenium based catalytic systems.[55]
- Investigation into newly developed gold catalysts for a milder, lower temperature approach to both tetrahydropyrazine formation and alkyne hydration.[84]
- Further studies into the origin of regioselective hydration of alkynes through potential directing groups at propargylic positions.
- Development of a catalyst–directed asymmetric approach to the reduction or Ugi-type reaction of tetrahydropyrazines.

It is hoped that the methods developed within this thesis will allow the synthesis of diverse libraries of heterocycle containing compounds with properties desirable in early stage drug development. As such, it is believed that these methods will be beneficial to the pharmaceutical industry.

Chapter 5 Experimental

5.1 General Experimental

All non-aqueous reactions were performed under an atmosphere of nitrogen unless otherwise stated. Water sensitive reactions were performed in oven dried glassware, cooled under nitrogen before use, or flame dried, and cooled, under vacuum if stated. Solvents were removed *in vacuo* using a Büchi rotary evaporator and a Vacuubrand PC2001 Vario diaphragm pump. Tetrahydrofuran, dichloromethane, toluene, ethanol and acetonitrile were dried and purified by means of a Pure Solv MD solvent purification system (Innovative Technology Inc.). Anhydrous *N*,*N*-dimethylformamide and 1,4-dioxane was obtained in Oxford sure/seal™ bottles from Sigma–Aldrich. All other solvents used were of chromatography or analytical grade. Ether refers to diethyl ether and petrol refers to petroleum spirit (b.p. 40-60 °C). Commercially available starting materials were obtained from Sigma–Aldrich, Fluka, Lancaster or Alfa Aesar.

Thin layer chromatography was carried out on aluminium backed silica (Merck silica gel 60 F_{254}) plates supplied by Merck. Visualisation of the plates was achieved using an ultraviolet lamp (λ_{max} = 254 nm), phosphomolybdic acid, $KMnO_4$ or anisaldehyde. Flash chromatography was carried out using silica gel 60 (35-70 μm particles).

All optical rotations were carried out on a Schmidt & Haensch H532 instrument with a path length of 1 dm; concentrations are g/100 mL, the optical rotations are given in 10^{-1} deg cm^2 g^{-1} and units are omitted for clarity. Infrared spectra were recorded on a Perkin-Elmer One FT-IR spectrometer.

Proton and carbon NMR data were collected on an Advance 500, Bruker DPX500 and DPX300 spectrometer. All shifts were recorded against and internal standard of tetramethylsilane. Solvents ($CDCl_3$, DMSO-*d*6 and MeOD-*d*4) used for NMR experiments were obtained from Sigma-Aldrich. Splitting patterns in this report have been recorded in an abbreviated manner; app. (apparent), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). NMR data was recorded in the following format; ppm (*number of protons, splitting pattern, coupling constant* (Hz), *proton ID*). Signal assignments were made with the aid of COSY, DEPT 90 and 135, HMQC and HMBC.

Low resolution mass spectra data were recorded on an Aligent 1200 series LC system comprising a Bruker HCT Ultra ion trap mass spectrometer, a high vacuum degasser, a binary pump, a high performance autosampler, an autosampler thermostat, a thermostated column compartment and a diode array detector. The system used two

solvent systems; MeCN/H_2O + 0.1% formic acid with a Phenomenex Luna C18 50 × 2 mm 5 micron column or MeCN/H_2O with a Phenomenex Luna C18 50 × 2 mm 5 micron column.

Nominal and high resolution mass spectrometry, using electrospray ionisation, was recorded by Mrs Tanya Marinko-Covell on a Micromass LCT-KA11 or a Bruker Daltronics micrOTOF spectrometer.

5.2 General Procedures

A. Reductive Amination

4-Methoxybenzaldehyde (1.2 eq.) was added to a suspension of amine (1.0 eq.) and molecular sieves (4Å) in methanol (1.0 M) and stirred at 50 °C until consumption of amine was complete (as indicated by TLC). The reaction mixture was filtered, cooled to 0 °C, $NaBH_4$ (2.0 eq.) added, and the reaction mixture warmed to rt and stirred until completion was observed. The reaction mixture was acidified (HCl, 5 M aq., to pH<2) concentrated to half volume *in vacuo* , extracted with EtOAc, and the aqueous phase basified (K_2CO_3, sat. aq. soln., to pH>12), extracted with EtOAc, and the resulting organic phase washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product.

B. TBD catalysed ester aminolysis

1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD, 0.3 eq.) was added to a stirred mixture of ester (1.0 eq.) and amine (1.2 eq.) in toluene (to 0.3 M) and heated at 75 °C until completion was indicated by TLC. The reaction mixture was concentrated *in vacuo* to give the crude product.

C. Cyclisation under Mitsunobu conditions

Diethylazodicarboxylate (1.3 eq.) was added dropwise to a solution of the alcohol (1.00 eq.) and PPh_3 (1.4 eq.) in THF (0.05 M) at 0 °C, the resulting solution was warmed to room temperature and stirred until completion was indicated by TLC (typically 16 h). The resulting reaction mixture was concentrated *in vacuo* to give the crude product.

D. 'One pot' ketopiperazine synthesis

•Ghosez's reagent (1-chloro-*N*,*N*-2-trimethyl-1-propenylamine, 1.0 eq.) was added to the desired acid (1.0 eq.) in CH_2Cl_2 (to 0.1 M) and the resulting suspension was stirred at rt for 1 h. Amine (1.2 eq.) and K_2CO_3 (5.0 eq.) were added and stirred until completion was indicated by TLC (typically 20 h). The reaction mixture was concentrated *in vacuo* , diluted with water, acidified (2 M HCl to pH<2) extracted with EtOAc, the combined organic phases washed with K_2CO_3 (sat. aq. soln.), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude amide which was carried forward without purification.

•Diethylazodicarboxylate (1.4 eq.) was added to a solution of crude sulfonamide (1.0 eq.) and triphenylphosphine (1.4 eq.) in THF (to 0.05 M) and stirred at rt until completion was indicated by TLC (typically 4 h). The reaction mixture was concentrated *in vacuo* to give the crude sulfonamide which was carried forward without purification.

•Thiophenol (1.2 eq.) was added to a suspension of crude sulfonamide (1.0 eq.) and K_2CO_3 (3.0 eq.) in DMF (0.05 M) and stirred at rt until completion was indicated by TLC (typically 5 h). The reaction mixture was concentrated *in vacuo* , diluted with EtOAc, extracted with HCl (2 M aq. to pH<2), basified with K_2CO_3 (sat. aq. soln., to pH>11), extracted with EtOAc, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product.

E. Hydroxy sulfonamide formation

2-Nitrobenzenesulfonyl chloride (1.0 eq.) was added to a vigorously stirred solution of amino alcohol (1.05 eq.), Na_2CO_3 (1.05 eq.) in CH_2Cl_2/ H_2O (1:1 mixture, 0.8 M solution) and the resulting mixture stirred at rt until completion was indicated by TLC (typically 24 h). The reaction mixture was acidified (HCl, 5 M aq., to pH<2), extracted with CH_2Cl_2, organic phase washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product.

F. Cyclic sulfamidate formation

Amino alcohol derivative (1.0 eq.) in CH_2Cl_2 (0.4 M) was added dropwise to a stirred solution of $SOCl_2$ (1.1 eq.), NEt_3 (2.2 eq.) and imidazole (4 eq.) in CH_2Cl_2 (0.1 M) at −60 °C (CO_2 and $CHCl_3$) and the resulting solution was stirred at −60 °C until completion was indicated by TLC (typically < 3 h). The reaction mixture was warmed to room temperature, quenched by addition of water, the phases separated and the organic phase washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude cyclic sulfamidite. The crude cyclic sulfamidite was dissolved in MeCN (0.13 M), cooled to 0 °C (ice water bath), $NaIO_4$ (1.1 eq) $RuCl_3 \cdot 3H_2O$ (0.1 mol%) and water (0.16 M) were added sequentially and the resulting solution was stirred until completion was indicated by TLC. The cold reaction mixture was diluted with water (equal volume to that used in reaction), warmed to room temperature, extracted with Et_2O, washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product.

G. Opening of cyclic sulfamidates with sulfonamides

NaH (60 % dispersion in oil, 1.1 eq.) was added to a solution of the sulfonamide (1.1 eq.) in DMF (0.2 M) and stirred for ten minutes, at which point the cyclic sulfamidate (1.0 eq.) was added and the resulting solution was stirred at room temperature (unless otherwise stated) until completion was indicated by TLC (typically 24 h). The reaction mixture was acidified (5 M HCl aq., 6 eq.), stirred for 1 h, basified (K_2CO_3 sat. aq. soln., to pH>12), extracted with EtOAc, washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product.

H. Cbz Protection of amino alcohols

Benzylchloroformate (1.05 eq,) was added drowpise to a suspension of amino alcohol (1.0 eq.) and $NaHCO_3$ (2.0 eq.) in THF–H_2O (1:1, 0.15 M) at 0 °C and the resulting solution warmed to rt and stirred for 1 h. The reaction mixture was acidified with HCl (1 M aq., to pH<2), extracted with EtOAc, organics washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give a crude product.

I. Boc Protection of amino alcohols

Di-*tert*-butyl dicarbonate (1.05 eq.) was slowly added to a solution of amino alcohol (1.0 eq.) in CH_2Cl_2 (0.3 M) at 0 °C and the resulting solution was warmed to rt and stirred until completion was indicated by TLC. The reaction mixture was diluted with H_2O acidified with HCl (1M aq, to pH<2), exctracted with CH_2Cl_2, organics washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give a crude product.

J. Propargyl sulfonamide formation

Diethyl azodicarboxylate (1.3 eq.) was added to a solution of alcohol (1.0 eq.), sulfonamide **203** (1.1 eq.) and PPh_3 (1.3 eq.) in THF (to 0.1 M) at 0 °C, the resulting solution warmed to rt and stirred until completion was observed by TLC and the reaction mixture was concentrated *in vacuo* to give the crude product. Filtration through a silica gel plug, eluting with Petrol–EtOAc, followed by concentration *in vacuo* gave the intermediate sulfonamide. TFA (10.0 eq.) was added to a solution of intermediate sulfonamide (1.0 eq.) in CH_2Cl_2 (0.1 M) at rt and stirred until completion was observed by TLC. The reaction mixture was quenched by addition of K_2CO_3 (sat. aq. soln., to pH>11), extracted with CH_2Cl_2, combined organic phases washed with brine, dried ($MgSO_4$) and concentrated *in vacco* to give the expected sulfonamide.

K. Gold mediated cyclisation

$Au(PPh_3)Cl$ (5 mol%), $AgSbF_6$ (5 mol%) and cyclisation substrate (1.0 eq.) were combined in 1,4-dioxane (0.2 M) and stirred at 100 °C until completion was observed by TLC. The reaction mixture was cooled to rt and concentrated *in vacuo* to give the crude product.

L. Gold mediated alkyne hydration

Au(IPr)Cl (1 mol%), $AgSbF_6$ (1 mol%) and hydration substrate (1.0 eq.) were combined in 1,4-dioxane (0.5 M), H_2O (0.8 M) added, and the resulting solution heated at 120 °C in a sealed tube until completion was observed by TLC. The reaction mixture was cooled to rt and concentrated *in vacuo* to give the crude product.

M. Triethylsilane mediated reduction

Triethylsilane (6.0 eq.) was added to a solution of substrate (1.0 eq.) and TFA (10 eq.) in CH_2Cl_2 (0.05 M) at 0 °C and slowly allowed to warm to rt until completion was observed by TLC. The reaction mixture was quenched with K_2CO_3 (sat. aq. soln., to pH>11), extracted with CH_2Cl_2, the combined organics washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give the crude product.

N. Ugi Reaction

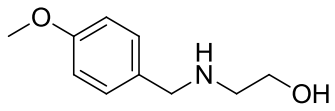
TFA (4 eq.) was added to a solution of substrate (1.0 eq.) in CH_2Cl_2 (0.1 M) at rt and stirred until completion was observed by TLC. The crude reaction mixture was concentrated *in vacuo* to give an intermediate TFA salt. Isonitrile (2.0 eq,) was added to a solution of the intermediate TFA salt (1.0 eq.) in EtOH (0.05 M) at 0 °C and stirred at rt until completion observed by TLC. The reaction mixture was concentrated *in vacuo* to give the crude product.

Purification by strong ion exchange (SCX) resin

Strong cation exchange resin (SCX, 5.0 g pre-packed cartridge, Supelco) was conditioned by washing with MeOH (>20 mL). The crude amine (<1 mmol) in MeOH (<5 mL) was added and non-basic compounds were eluted with MeOH. Basic compounds were eluted with NH_3 in MeOH (sat. soln.) and concentrated *in vacuo* to give the product. Resin was reconditioned by treatment with TfOH (1 M in MeOH, 20 mL) followed by washing with MeOH (10 mL).

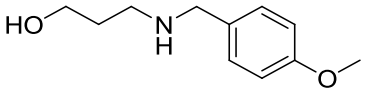
5.3 Experimental Procedures

2-(4-Methoxybenzylamino)ethanol, 84[97]



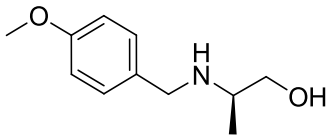
By general procedure **A**, 2-aminoethanol (4.10 g, 67.0 mmol) gave alcohol **84** (10.0 g, 55.3 mmol, 82%) as a light brown oil which required no further purification; R_f 0.32 (50:8:1 CH_2Cl_2–EtOH–NH_4OH); δ_H (500 MHz; $CDCl_3$) 7.25 (2H, d, *J* 8.7, Ar 2-H and Ar 6-H), 6.88 (2H, d, *J* 8.7, Ar 3-H and Ar 5-H), 3.8 (3H, s, OMe), 3.75 (2H, s, CH_2Ar), 3.65 (2H, t, *J* 5.2, 1-H), 2.79 (2H, t, *J* 5.1, 2-H), 2.24 (2H, s (broad), NH and OH); δ_C (75 MHz; $CDCl_3$) 159.1 (Ar 4-C), 132.6 (Ar 1-C), 129.7 (Ar 2-C and Ar 6-C), 114.2 (Ar 3-C and Ar 5-C), 61.3 (1-C), 55.7 (OMe), 53.3 (CH_2Ar), 50.8 (2-C); ν_{max}/cm^{-1} (film) 3307, 1612, 1514, 1248; *m*/*z* (*ESI*) 182.1 (100%, MH^+); HRMS found MH^+, 182.1176. $C_{10}H_{15}NO_2$ requires *MH,* 182.1176.

3-(4-Methoxybenzylamino)propan-1-ol, 108[97]



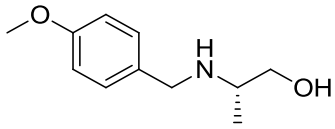
$Na(CN)BH_3$ (420 mg, 6.7 mmol) was added to a stirred solution of 3-aminopropanol (1.01 mL, 13.0 mmol) and 4-methoxybenzaldehyde (0.81 mL, 6.7 mmol) in methanol (50 mL) and stirred at rt for 16 h. Reaction was quenched by addition of HCl (5 M, to pH<2), concentrated *in vacuo* , taken up in water (20 mL) basified with K_2CO_3 (sat. aq. soln., to pH>11), extracted with CH_2Cl_2 (3 × 25 mL), dried ($MgSO_4$) and concentrated to give a crude product. Purification by column chromatography, eluting with 50:8:1 CH_2Cl_2–EtOH–NH_4OH, gave the amine **108** (1.04 g, 5.30 mmol, 80%) as a light brown oil; R_f 0.22 (50:8:1 CH_2Cl_2–EtOH–NH_4OH); δ_H (500 MHz; $CDCl_3$) 7.21 (2H, d, *J* 8.6, Ar 2-H and Ar 6-H), 6.86 (2H, d, *J* 8.6, Ar 3-H and Ar 5-H), 3.80 (5H, m, CH_2OH and OMe), 3.72 (2H, s, CH_2Ar), 3.05 (2H, s (broad), NH and OH), 2.88 (2H, t, *J* 5.7, CH_2NH), 1.71 (2H, pent, *J* 5.6, CH_2); δ_C (75 MHz; $CDCl_3$) 159.2 (Ar 4-C), 132.1 (Ar 1-C), 129.8 (Ar 2-C and Ar 6-C), 114.3 (Ar 3-C and Ar 5-C), 64.9 (CH_2OH), 55.7 (OMe), 53.8 (CH_2NH), 49.8 (CH_2Ar), 31.1 (CH_2); ν_{max} /cm^{-1} (film) 3295, 1613, 1514, 1248; *m*/*z* (*ESI*) 196.1 (100%, MH^+); HRMS found MH^+, 196.1340. $C_{11}H_{17}NO_2$ requires *MH,* 196.1332.

(*R*)-2-(4-Methoxybenzylamino)propan-1-ol, 105[60]



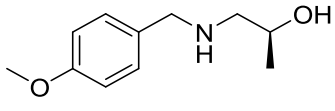
By general procedure **A**, followed by purification by column chromatography, eluting with 50:8:1 CH_2Cl_2–EtOH–NH_4OH, (2*R*)-2-aminopropanol (0.21 mL, 2.7 mmol) gave the amine **105** (464 mg, 2.4 mmol, 89%) as an amorphous solid; R_f 0.46 (50:8:1 CH_2Cl_2–EtOH–NH_4OH); $[\alpha]_D^{21}$: 45.0 (c. 0.8, MeOH); δ_H (300 MHz; $CDCl_3$) 7.23 (2H, d, *J* 8.6, Ar 2-H and Ar 6-H), 6.86 (2H, d, *J* 8.7, Ar 3-H and Ar 5-H), 3.81 (1H, d, *J* 12.7, CH_aAr), 3.79 (3H, s, OMe), 3.64 (1H, d, *J* 12.7, CH_bAr), 3.57 (1H, dd, *J* 10.6 and 4.0, 1-H_a), 3.26 (1H, dd, *J* 10.6, 7.1, 1-H_b), 2.81 (1H, m, 2-H), 2.32 (2H, s (broad), NH and OH), 1.07 (3H, d, *J* 6.5, 3-H); δ_C (75 MHz; $CDCl_3$) 159.1 (Ar 4-C), 132.7 (Ar 1-C), 129.7 (Ar 2-C and Ar 6-C), 114.2 (Ar 3-C and Ar 5-C), 65.9 (1-C), 55.7 (OMe), 54.1 (2-C), 50.9 (CH_2Ar), 17.5 (3-C); ν_{max} /cm^{-1} (film); 3390, 1652, 1514, 1248; *m/z* (*ESI*) 196.1 (100%, MH^+).

(*S*)-2-(4-Methoxybenzylamino)propan-1-ol, 106[60]



By general procedure **A**, followed by purification by column chromatography, eluting with 50:8:1 CH_2Cl_2–EtOH–NH_4OH, (2*S*)-2-aminopropanol (0.41 mL, 5.3 mmol) gave the amine **106** (819 mg, 4.2 mmol, 80%) as an amorphous solid; R_f 0.67 (50:8:1 CH_2Cl_2–EtOH–NH_4OH); $[\alpha]_D^{20}$: -48 (c. 1 $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 7.25 (2H, d, *J* 8.4, Ar 2-H and Ar 6-H), 6.88 (2H, d, *J* 8.6, Ar 3-H and Ar 4-H), 3.82 (1H, d, *J* 13.0, CH_aAr), 3.70 (1H, d, *J* 12.8, CH_bAr), 3.60 (1H, dd, *J* 10.6 and 4.6, 1-H_a), 3.27 (1H, dd, *J* 10.6 and 7.0, 1-H_b), 2.85 (1H, m, 2-H), 2.12 (2H, s (broad), NH and OH), 1.09 (3H, d, *J* 6. 4, 3-H); δ_C (75 MHz; $CDCl_3$) 129.8 (Ar 2-C and Ar 6-C), 114.3 (Ar-C3 and Ar-C5), 65.8 (1-C), 55.7 (OMe), 54.1 (2-C), 50.8 (CH_2Ar), 17.6 (3-C); ν_{max}/cm^{-1} (film) 3300, 2932, 1611, 1585, 1513, 1248, 1036; *m/z* (*ESI*) 196.1 (100%, MH^+); HRMS found MH^+, 196.1338. $C_{11}H_{17}NO_2$ requires *MH,* 196.1332.

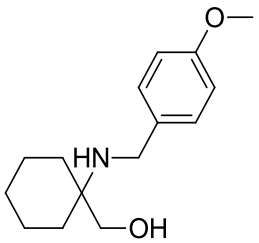
(*S*)-1-(4-Methoxybenzylamino)propan-2-ol, 107



By general procedure **A**, (*S*)-1-amino-2-propanol (1.00 g, 13.3 mmol) gave alcohol **107** (2.42 g, 12.4 mmol, 93%) as a light brown oil which required no further purification; R_f

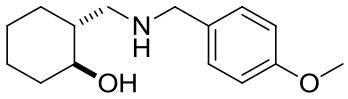
0.34 (9:1 CH_2Cl_2–MeOH); $[\alpha]_D^{26}$: 11.6 (c. 1.3, MeOH); δ_H (500 MHz; $CDCl_3$) 7.24 (2H, d, *J* 8.6, Ar 2-H and Ar 6-H), 6.87 (2H, d, *J* 8.7, Ar 3-H and Ar 5-H), 3.75 (5H, m, OMe, 2-H and benzyl CH_a), 3.72 (1H, d, *J* 12.8, benzyl CH_b), 2.73 (1H, dd, *J* 12.0, 3.0, 1-H_a), 2.43 (1H, dd, *J* 12.0, 9.5, 1-H_b), 2.28 (2H, s (broad), NH and OH), 1.15 (3H, d, *J* 6.2, 3-H); δ_C (75 MHz; $CDCl_3$) 129.3 (Ar 2-C and Ar 6-C), 113.9 (Ar 3-C and Ar 5-C), 65.6 (2-C), 56.1 (1-C), 55.3 (OMe), 53.0 (CH_2 benzyl), 20.4 (3-C) [Ar 1-C and 4-C were not observed]; ν_{max}/cm^{-1} (film) 3308, 2966, 1612, 1513; *m/z* (*ESI*) 196.1 (100%, MH^+); HRMS found MH^+, 196.1329. $C_{11}H_{17}NO_2$ requires *MH,* 196.1332.

(1-(4-Methoxybenzylamino)cyclohexyl)methanol, 111[61]



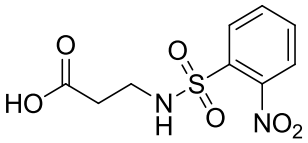
1-Amino cyclohexanecarboxylic acid (2.50 g, 17.5 mmol) was slowly added to a stirred suspension of $LiAlH_4$ (1.98 g, 52.5 mmol) in THF (175 mL) at 0 °C and the resulting suspension was stirred at reflux for 24 h. Reaction was quenched by slow addition of Na_2CO_3 (sat. aq. soln., to pH>11) filtered over celite, washing with EtOAc, the filtrate was concentrated *in vacuo,* extracted with *n*-butanol (3 × 50 mL), dried ($MgSO_4$) and concentrated to give a crude product. Purification by column chromatography, eluting with 50:8:1 CH_2Cl_2–EtOH–NH_4OH, gave the amine **110** (1.68 g) as a colourless oil which was alkylated using general procedure **A** and gave the amine **111** (425 mg, 1.7 mmol, 43% over two steps) as a colourless oil which required no further purification; R_f 0.31 (9:1 CH_2Cl_2–MeOH); δ_H (500 MHz; $CDCl_3$) 7.25 (2H, d, *J* 8.5, Ar 2-H and Ar-H6), 6.88 (2H, d, *J* 8.5, Ar 3-H and Ar 5-H), 3.81 (3H, s, OMe), 3.56 (2H, s, CH_2Ar), 3.37 (2H, s, CH_2OH), 1.64-1.35 (12H, m, c.Hex and NH and OH); δ_C (75 MHz; $CDCl_3$) 159.1 (Ar 4-C), 133.2 (Ar 1-C), 129.8 (Ar 2-C and Ar 6-C), 114.3 (Ar 3-C and Ar 5-C), 65.7 (CH_2OH), 55.7 (OMe), 55.6 (1-C), 44.8 (CH_2Ar), 33.1 (c.hex), 26.4 (c.hex), 22.1 (c.hex); ν_{max} /cm^{-1} (film) 2930, 1613, 1514, 1453, 1249; *m/z* (*ESI*) 250.2 (100%, MH^+); HRMS found MH^+, 250.1810. $C_{15}H_{23}NO_2$ requires *MH,* 250.1802.

(1,2-*trans*)-2-((4-Methoxybenzylamino)methyl)cyclohexanol, 112[62]



Cyclohexene oxide (1.11 mL, 11.0 mmol) was added to a solution of $LiCN{\cdot}(CH_3)_2CO$ (2.50 g, 27.5 mmol) in THF (40 mL) and heated at reflux for 1.5 h. Reaction was quenched with water (50 ml), extracted with diethylether (3 × 50 mL), dried ($MgSO_4$) and concentrated to give a crude product. Partial purification by column chromatography, eluting with 2:1 petrol–EtOAc, gave the nitrile **113** (1.28 g). $LiAlH_4$ (454 mg, 12.0 mmol) was added to a stirred solution of nitrile **113** (1.00 g) in THF (80 mL) and heated at reflux for 2.5h. Reaction was quenched with water (2 mL), diluted with EtOAc, filtered over celite, washing with EtOAc, and solvents removed *in vacuo* to give a crude product (1.01 g) which was used without further purification. Crude amine **114** (≈8.0 mmol) was alkylated using general method **A** to give amine **115** (1.54 g, 6.20 mmol, 77% from epoxide **112**) as a colourless oil; R_f 0.59 (9:1 CH_2Cl_2–MeOH); δ_H (300 MHz; $CDCl_3$) 7.22 (2H, d, *J* 8.6, Ar 2-H and Ar 6-H), 6.85 (2H, d, *J* 8.6, Ar 3-H and Ar 5-H), 3.81 (1H, d, *J* 12.8, CH_aAr), 3.80 (3H, s, OMe), 3.67 (1H, d, *J* 12.8, CH_bAr), 3.42 (1H, m, 1-H), 2.82 (1H, dd, *J* 11.9, 2.7, CH_aNH), 2.57 (1H, app. t, *J* 11.5, CH_bNH), 1.94 (1H, m, CH c.hex), 1.67 (2H, m, 2 × CH c.hex), 1.53 (1H, m, CH c.hex), 1.40 (1H, m, CH c.hex), 1.21 (3H, m, 3 × CH c.hex), 0.87 (1H, m, CH c.hex); δ_C (75 MHz; $CDCl_3$) 159.9 (Ar 4-C), 132.1 (Ar 1-C), 130.5 (Ar 2-C and Ar 6-C), 114.9 (Ar 3-C and Ar 5-C), 78.7 (1-C), 57.2 (CH_2NH), 56.3 (OMe), 54.3 (CH_2Ar), 44.4 (2-C), 35.7 (CH c.hex), 30.1 (CH c.hex), 26.6 (CH c.hex), 25.1 (CH c.hex); ν_{max} /cm^{-1} (film) 3293, 2928, 2159, 1612, 1513, 1449; *m/z* (*ESI*) 250.2 (100%, MH^+); HRMS found MH^+, 250.1881. $C_{15}H_{23}NO_2$ requires *MH,* 250.1802.

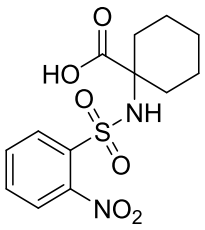
3-(2-Nitrophenylsulfonamido)propanoic acid, 116[99]



2-Nitrobenzenesulfonyl chloride (1.62 g, 7.30 mmol) was added to a solution of *β*-alanine (500 mg, 5.6 mmol) and triethylamine (2.40 mL, 16.8 mmol) in THF (2 mL) and water (6 mL) and stirred at rt for 19h. Reaction mixture was concentrated to half volume, acidified with HCl (2 M aq., to pH<2), extracted with EtOAc (3 × 30 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a crude product. Purification by column chromatography, eluting with 9:1 CH_2Cl_2–MeOH, gave the acid **116** (705 mg, 2.6 mmol, 46%) as a colourless solid; R_f 0.32 (9:1 CH_2Cl_2–MeOH); δ_H (300 MHz; DMSO-D_6) 8.15 (1H, t, *J* 5.6, NH), 8.00 (2H,

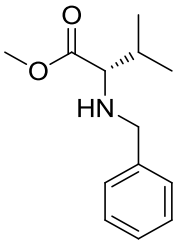
m, Ar), 7.88 (2H, m, Ar), 3.10 (2H, q, *J* 6.8, 3-H), 2.42 (2H, t, *J* 6.9, 2-H); δ_C (75 MHz; DMSO-D_6) 172.6 (C1), 148.1 (Ar 2-C), 134.5 (Ar 1-C), 133.1 (Ar), 132.8 (Ar), 129.8 (Ar), 124.8 (Ar), 40.5 (2-C), 34.4 (3-C); ν_{max} /cm^{-1} (solid) 1699, 1538, 1428, 1232; *m/z* (*ESI*) 297.0 (100%, MNa$^+$); HRMS found MH$^+$, 275.0334. $C_9H_{10}N_2O_6S$ requires *MH,* 275.0332.

1-(2-Nitrophenylsulfonamido)cyclohexanecarboxylic acid, 117[63]



N,*O*-Bistrimethylsilylacetamide (1.8 mL, 7.2 mmol) was added to 1-aminocyclohexanecarboxylic acid (500 mg, 3.5 mmol) in CH_2Cl_2 (15 mL) and stirred at rt for 1h. 2-Nitrobenzenesulfonyl chloride (840 mg, 3.8 mmol) in CH_2Cl_2 (10 mL) was added dropwise and the reaction mixture was stirred at rt for a further 16 h. The reaction mixture was concentrated *in vacuo* , treated with $NaHCO_3$ (5% w/w, 15 mL) for 30 min, washed with EtOAc (2 × 10 mL), acidified with HCl (2 M aq., to pH<2), extracted with EtOAc (3 × 30 mL), washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give acid **117** (400 mg, 1.2 mmol, 35%) as a colourless solid which was used without further purification; R_f 0.41 (9:1 CH_2Cl_2–MeOH); δ_H (500 MHz; $CDCl_3$) 8.06 (1H, m, Ar), 7.92 (1H, m, Ar), 7.83 (2H, m, Ar), 1.87 (2H, m, c.Hex), 1.70 (2H, m, c.Hex), 1.36-1.16 (6H, m, c.Hex); δ_C (75 MHz; $CDCl_3$) 174.9 (CO), 147.1 (Ar 2-C), 134.9 (Ar 1-C), 133.7 (Ar), 132.5 (Ar), 129.5 (Ar), 124.1 (Ar), 61.6 (1-C), 32.5 (2 × CH_2 c.Hex), 24.6 (c.Hex), 20.8 (2 × CH_2 c.Hex); ν_{max} /cm^{-1} (film); 2943, 1709, 1537, 1360; *m/z* (*ESI*) 346.3 (100%, MH_2O^+); HRMS found MNa$^+$, 351.0637. $C_{13}H_{16}N_2O_2S$ requires *MNa,* 351.0627.

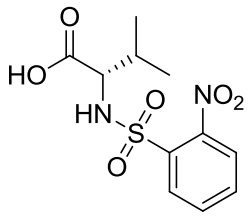
(*S*)-Methyl-2-(benzylamino)-3-methylbutanoate, 81[51]



Benzaldehyde (2.05 mL, 20.1 mmol) was added to a solution of *L*-valine methyl ester·HCl (1.70 g, 10.0 mmol), $MgSO_4$ (2.05 g, 17.1 mmol) and triethylamine (1.37 mL, 10.0 mmol) in THF (10 mL) at 0 °C and the mixture was stirred at rt for 4.5 h. The reaction mixture was

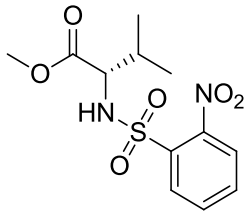
concentrated *in vacuo*, dissolved in MeOH (30 mL) at 0 °C, $NaBH_4$ (0.76 g, 20.1 mmol) added stirred for 45 min, quenched (NaOH 1 M aq., 20 mL), extracted (Et_2O, 2 × 100 mL), combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give a crude product. Purification by column chromatography, gradient elution 9:1→4:1 petrol–EtOAc, gave the amino ester **81** (1.25 g, 5.6 mmol, 56% yield) as colourless oil; R_f 0.38 (petrol–EtOAc 9:1); $[\alpha]_D^{26}$ -13 (c. 1.0 $CHCl_3$) [lit.[51] $[\alpha]_D^{27}$ -53.9 (c. 1.03 $CHCl_3$), 24% *ee*]; δ_H (500 MHz, $CDCl_3$); 7.40-7.35 (4H, m, Ar-H), 7.35 (1H, m, Ar 4-C), 3.90 (1H, d, *J* 13.1 CH_aAr), 3.77 (3H, s, OMe), 3.65 (1H, d, *J* 13.1 CH_bAr), 3.08 (1H, d, *J* 6.1, 2-H), 1.98 (1H, m, 3-H), 1.81 (1H, s (broad), NH), 1.01 (3H, d, *J* 6.8, 4-H), 0.99 (3H, d, *J* 6.8, CH_3); δ_C (75 MHz, $CDCl_3$); 176.4 (1-C), 140.6 (Ar 1-C), 128.9 (Ar 3-C and Ar 5-C), 128.8 (Ar 2-C and Ar 6-C), 127.5 (Ar 4-C) 67.1 (2-C) 53.1 (CH_2Ph), 52.0 (OMe), 32.3 (3-C), 19.9 (4-C), 19.2 (CH_3); ν_{max}/cm^{-1} (film); 3338, 2961, 1734 and 1454; *m/z* (*ESI*) 222.1 (100%, MNH_4^+); HRMS found MH^+, 222.1492. $C_{13}H_{19}NO_2$ requires *MH,* 222.1489.

(*S*)-3-Methyl-2-(2-nitrophenylsulfonamido)butanoic acid, 79



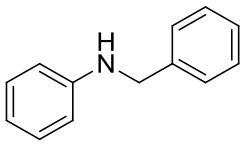
2-Nitrobenzenesulfonyl chloride (4.90 g, 22.0 mmol) was slowly added to a stirred solution of *L*-valine (2.00 g, 17.0 mmol) and triethylamine (7.1 mL, 51 mmol) in THF (5 mL) and water (17 mL) at 0 °C and the resulting mixture was stirred at rt for 22 h. Reaction mixture was concentrated to half volume, acidified (HCl, 2 M aq., to pH<2), extracted with EtOAc (3 × 50 mL), washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give acid **79** (5.07 g, 16.0 mmol, 98%) as a colourless amorphous solid; R_f 0.41 (9:1 CH_2Cl_2–MeOH); $[\alpha]_D^{21}$: -144.1 (c. 0.6, $CHCl_3$); δ_H (500 MHz; $CDCl_3$) 8.07 (1H, m, Ar), 7.93 (1H, m, Ar), 7.75 (2H, m, Ar), 7.53 (1H, s (broad), OH), 6.0 (1H, d, *J* 9.5, NH), 4.05 (1H, dd, *J* 9.5, 4.8, 2-H), 2.20 (1H, m, 3-H), 1.01 (3H, d, *J* 6.8, 4-H), 0.92 (3H, d, *J* 6.9, CH_3); δ_C (75 MHz; $CDCl_3$) 176.3 (1-C), 134.5 (Ar 1-C), 134.3 (Ar), 133.4 (Ar), 130.7 (Ar), 126.1 (Ar), 62.1 (2-C), 31.7 (3-C), 19.5 (4-C), 17.6 (CH_3) [Ar 2-C was not observed]; ν_{max}/cm^{-1} (solid) 3350, 2964, 2159, 1715, 1537; *m/z* (*ESI*) 320.1 (100%, MNH_4^+); HRMS found MNH_4^+, 320.0910. $C_{11}H_{14}N_2O_6S$ requires *MNH₄,* 320.0911.

(*S*)-Methyl-3-methyl-2-(2-nitrophenylsulfonamido)butanoate, 80[105]



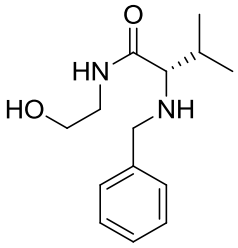
2-Nitrobenzenesulfonyl chloride (2.66 g, 12.0 mmol) was added to a stirred solution of *L*-valine methyl ester (2.00 g, 12.0 mmol) and triethylamine (3.85 mL, 27.0 mmol) in CH_2Cl_2 (75 mL) and stirred at rt for 22 h. Reaction was quenched with water (10 mL) dried ($MgSO_4$) and concentrated *in vacuo* to give a crude product. Purification by column chromatography, eluting with 1:1 petrol–EtOAc, gave the *sulfonamide* **80** (3.71 g, 11.7 mmol >98%) as a light yellow oil; R_f 0.30 (1:1 petrol–EtOAc); $[\alpha]_D^{21}$: −73.8 (c. 0.7, MeOH); δ_H (300 MHz; $CDCl_3$) 8.11-8.08 (1H, m, Ar), 7.99-7.95 (1H, m, Ar), 7.79-7.75 (2H, m, Ar), 6.09 (1H, d, *J* 9.8, NH), 4.05 (1H, dd, *J* 9.8, 5.2, 2-H), 3.47 (3H, s, OMe), 2.25-2.15 (1H, m, 3-H), 1.05 (3H, d, *J* 6.8, 4-H), 0.97 (3H, d, *J* 6.9, CH_3); δ_C (75 MHz; $CDCl_3$) 171.5 (C1), 134.1 (Ar), 133.3 (Ar), 130.8 (Ar), 126.1 (Ar), 62.55 (2-C), 52.6 (OMe), 32.0 (3-C), 19.4 (4-C), 17.9 (CH_3) [Ar C-1 and C-2 were not observed]; ν_{max}/cm^{-1} (film) 3321, 2967, 1741, 1542, 1422, 1360, 1174; *m*/*z* (*ESI*) 334.1 (100%, MNH_4^+); HRMS found MH^+, 317.0807. $C_{14}H_{23}N_2O_2$ requires *MH,* 317.0802.

***N*-Benzylaniline, 96**[56]



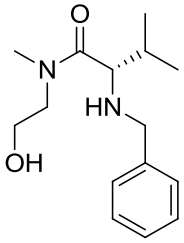
$[Cp^*IrCl_2]_2$ (20 mg, 0.03 mmol), aniline (0.09 mL, 1.0 mmol), benzylalcohol (0.10 mL, 1.0 mmol) and K_2CO_3 (7 mg, 0.05 mmol) were combined in toluene (0.5 mL) under an argon atmosphere and the mixture was heated at 110 °C for 24 h. The reaction mixture was concentrated *in vacuo*. Purification by column chromatography, eluting with 20:1 petrol–EtOAc, gave the aniline **96** (138 mg, 75%) as a light yellow oil; R_f 0.31 (20:1 petrol–EtOAc); δ_H (500 MHz; $CDCl_3$) 7.44-7.39 (4H, m, Ar), 7.35-7.32 (1H, m, Ar), 7.25-7.22 (2H, m, Ar), 6.78 (1H, t, *J* 7.3, Ar), 6.70 (2H, m, Ar), 4.39 (2H, s, CH_2Ph), 4.09 (1H, s (broad), NH); δ_C (75 MHz; $CDCl_3$) 139.8 (Bn 1-C), 129.7 (Ar 3-C and 5-C), 129.0 (Bn 3-C and 5-C), 127.9 (Bn 2-C and 6-C), 127.7 (Bn 4-C), 118.0 (Ar 4-C), 113.2 (Ar 2-C and 6-C), 48.7 (CH_2Ph) [Ar 1-C was not observed]; ν_{max}/cm^{-1} (film) 3419, 3052, 3026, 2849 1602, 1505; *m*/*z* (*ESI*) 184.0 (100%, MH^+).

(*S*)-2-(Benzylamino)-*N*-(2′-hydroxyethyl)-3-methylbutanamide, 88



Ethanolamine (0.72 mL, 1.2 mmol) was added to a mixture of ester **81** (221 mg, 1.0 mmol) and TBD (42 mg, 0.3 mmol) and the mixture heated at 68 °C for 18 h. The cooled reaction mixture was purified by column chromatography, eluting with 20:1 CH_2Cl_2–MeOH, to give the amide **88** (221 mg, 88%) as a colourless oil; R_f 0.51 (9:1 CH_2Cl_2–MeOH); δ_H (500 MHz; $CDCl_3$) 7.71 (1H, s (broad), NH), 7.41-7.31 (5H, m, Ar-H), 3.20 (1H, d, *J* 13.1 CH_aPh), 3.76 (2H, t, *J* 5.4, 2′-H), 3.72 (1H, d, *J* 13.1 CH_bPh), 3.48 (2H, *J* 5.4, 1-H′), 3.06 (1H, d, *J* 4.4, 2-H), 2.18 (1H, m, 3-H), 1.75 (1H, s (broad), OH), 1.02 (3H, d, *J* 7.0, 4-H), 0.96 (3H, d, *J* 7.0, CH_3); δ_C (75 MHz; $CDCl_3$) 175.7 (1-C), 140.0 (Ph 1-C), 129.1 (Ph 3-C and Ph 5-C), 128.7 (Ph 2-C and Ph 6-C), 127.9 (Ph 4-C), 68.4 (2-C), 63.5 (2-C′), 54.1 (CH_2Ph), 42.7 (1-C′), 31.8 (3-C), 20.1 (4-C), 18.2 (CH_3); ν_{max}/cm^{-1} (film) 3325, 2960, 1651, 1534, 1454, 1362, 1075; *m/z* (*ESI*) 251.2 (100%, MH^+); HRMS found MH^+, 251.1754. $C_{14}H_{22}N_2O_2$ requires *MH,* 251.1754.

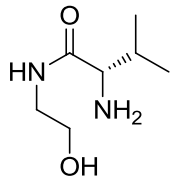
(*S*)-2-(Benzylamino)-*N*-(2′-hydroxyethyl)-*N*,3-dimethylbutanamide, 89



N-methylethanolamine (0.2 mL, 0.4 mmol) was added to a mixture of ester **81** (443 mg, 2.0 mmol) and TBD (84 mg, 0.3 mmol) and the mixture heated to 75 °C for 22 h. The cooled reaction mixture was purified by column chromatography, gradient elution 20:1→9:1 CH_2Cl_2–MeOH, to give the amide **89** (482 mg, 91%) as a colourless oil; R_f 0.43 (9:1 CH_2Cl_2–MeOH); δ_H (500 MHz; $CDCl_3$) (4.5:1 mixture of rotamers) 7.42-7.27 (10H, m, Ph_{rotA}+Ph_{rotB}), 3.87 (1H, d, *J* 13.4, CH_aPh_{rotA}), 3.84 (2H, t, *J* 5.1, 2′-H_{rotA}), 3.72 (4H, m, 2′-H_{rotB} and 1′-H_{rotA}) 3.64 (2H, m, 1′-H_{rotB}), 3.57 (1H, d, *J* 13.4, CH_aPh_{rotA}), 3.41 (1H, d, *J* 6.4, 2-H_{rotB}), 3.26 (1H, d, *J* 6.4, 2-H_{rotA}), 3.06 (3H, s, NMe_{rotB}), 2.97 (3H, s, NMe_{rotA}), 2.08 (1H, sept, 3-H_{rotB}) 1.86 (1H, sept, 6.9, 3-H_{rotA}), 1.05 (6H, d, *J* 6.5, 4-H_{rotA}+ 4-H_{rotB}), 0.99 (6H, d, *J* 0.67, CH_{3rotA}+ CH_{3rotB}); δ_C (75 MHz; $CDCl_3$) 177.8 (1-C), 128.7 (Ph), 127.3 (Ph), 62.6 (C), 62.2 (2'-C), 52.6 (CH_2Ph), 42.73 (1'-C), 32.1 (iPr), 20.1 (iPr), 18.7 (iPr); ν_{max}/cm^{-1} (film) 3401, 2959, 1621,

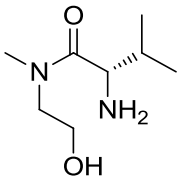
1469, 1404; *m/z* (*ESI*) 265.2 (100%, MH^+); HRMS found MH^+, 265.1928. $C_{15}H_{24}N_2O_2$ requires *MH,* 265.1928.

(*S*)-2-Amino-*N*-(2′-hydroxyethyl)-3-methylbutanamide, 90



TBD (317 mg, 2.3 mmol) was added to a stirred mixture of ester **86** (1.00 g, 7.6 mmol) and ethanolamine (0.55 mL, 9.13 mmol) and the resulting mixture was heated at 60 °C for 16 h. Reaction mixture was concentrated *in vacuo* to give a crude product. Purification by column chromatography, eluting with 50:8:1 CH_2Cl_2–EtOH–NH_4OH, gave the *amide* **90** (902 mg, 5.6 mmol, 74%) as a light yellow oil; R_f 0.22 (50:8:1 CH_2Cl_2–EtOH–NH_4OH); $[\alpha]_D^{21}$: 13.6 (c. 0.6, MeOH); δ_H (500 MHz; $CDCl_3$) 7.77 (1H, s (broad), OH), 3.75 (2H, t, *J* 4.9, 2′-H), 3.51-3.43 (2H, m, 1-H′), 3.29 (1H, d, *J* 3.8, 2-H), 2.37-2.26 (1H, m, 3-H), 2.20 (1H, s (broad), NH), 1.02 (3H, d, *J* 7.0, 4-H), 0.87 (3H, d, *J* 6.9, CH_3); δ_C (75 MHz; $CDCl_3$) 175.8 (1-C), 62.6 (1-C′), 60.1 (2-C′), 42.3 (2-C), 30.8 (3-C), 19.6 (4-C), 16.0 (CH_3); ν_{max}/cm^{-1} (film) 3294, 2964, 1650, 1465, 1069; *m/z* (*ESI*) 161.1 (100%, MH^+); HRMS found MH^+, 161.1285. $C_7H_{17}N_2O_2$ requires *MH,* 161.1282.

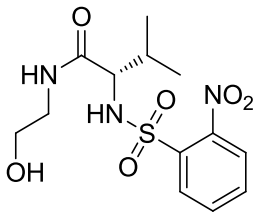
(*S*)-2-Amino-*N*-(2′-hydroxyethyl)-*N*-3-dimethylbutanamide, 91



TBD (230 mg, 1.7 mmol) was added to a mixture of *L*-valine methylester·HCl (924 mg, 5.5 mmol), *N*-methylethanolamine (1.33 mL, 16.5 mmol) and triethylamine(0.7 mL, 5.5 mmol) and the resulting solution was stirred at 75 °C for 24 h. Analysis (TLC) showed incomplete reaction. MeOH (1 mL) added and heated for a further 24 h. Reaction mixture was cooled and concentrated *in vacuo* to give a crude product. Purification by column chromatography, eluting with 50:8:1 CH_2Cl_2–EtOH–NH_4OH, gave the *amide* **91** (686 mg, 72%) as a light yellow oil; R_f 0.12 (9:1 CH_2Cl_2–MeOH); $[\alpha]_D^{21}$: 61.1 (c. 1.4, MeOH); δ_H (300 MHz; $CDCl_3$) (1:1 mixture of rotamers) 4.02-3.94 (1H, m, 2′-H_{rotA}), 3.89-3.80 (3H, m, 2′-H_{rotA} and 2′-H_{rotB}), 3.75-3.67 (1H, m), 3.62-3.58 (2H, m), 3.52 (1H, d, *J* 6.0, 2-H_{rotA}), 3.46 (1H, d, *J* 7.7, 2-H_{rotB}), 3.15 (3H, s, NMe_{rotA}), 3.01 (3H, s, NMe_{rotB}), 2.08-1.96 (1H, m, 3-H_{rotA}), 1.96-1.85 (1H, m, 3-H_{rotB}), 1.00 (6H, m, 4-H_{rotA} and CH_3), 0.94 (6H, m, 4-H_{rotB} and CH_3); δ_C (75

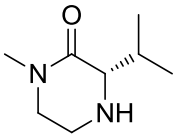
MHz; $CDCl_3$) 60.0 (2'-C_{rotA}), 58.2 (2'-C_{rotB}), 55.5 (2-C_{rotA}), 55.4 (2-C_{rotB}), 51.0 (1'-C_{rotA}), 50.4 (1'-C_{rotB}), 35.5 (MeN_{rotA}), 32.5 (MeN_{rotB}), 30.8 (3-C_{rotA}), 30.7 (3-C_{rotB}), 16.6 (4-C_{rotA} and $CH_{3\ rotA}$), 15.7 (4-C_{rotA} and $CH_{3\ rotA}$) [C-1_{rotA} and C-1_{rotB} were not observed]; ν_{max}/cm^{-1} (film) 3361, 2961, 1663, 1470, 1370; *m/z* (*ESI*) 197.1 (100%, MNa^+); HRMS found MNa^+, 197.1256. $C_8H_{18}N_2O_2$ requires *MNa,* 197.1260.

(*S*)-*N*-(2′-Hydroxyethyl)-3-methyl-2-(2-nitrophenylsulfonamido)butanamide, 93



Ethanolamine (0.34 mL, 5.7 mmol) was added to a solution of sulfonamide **80** (1.50 g, 4.70 mmol) and TBD (198 mg, 1.4 mmol) in MeOH (1 mL) and the resulting solution was stirred at 70 °C for 24 h. Incomplete reaction was observed. Ethanolamine (0.34 mL, 5.7 mmol) was added and stirred for a further 48 h. Reaction mixture was cooled and concentrated *in vacuo* to give a crude product. Purification by column chromatography, eluting with 9:1 CH_2Cl_2–MeOH, gave the *sulfonamide* **93** (1.26 g, 3.60 mmol, 78%) as a bright yellow oil; R_f 0.53 (9:1 CH_2Cl_2–MeOH); $[\alpha]_D^{21}$: −106.7 (c. 0.5, MeOH); δ_H (300 MHz; DMSO-D_6) 8.08-8.01 (2H, m, Ar), 7.84-7.82 (2H, m, Ar), 4.59 (1H, t, *J* 5.3, OH), 3.59 (1H, t, *J* 7.7, 2-H), 3.17 (2H, q, *J* 5.8, 2′-H), 3.00-2.85 (2H, m, 1-H′), 1.94-1.83 (1H, m, 3-H), 0.81 (6H, m, 4-H and CH_3); δ_C (75 MHz; MeOD) 173.0 (1-C), 135.4 (Ar), 134.0 (Ar), 131.9 (Ar), 126.5 (Ar), 64.6 (2-C), 61.5 (2'-C), 42.9 (1'-C), 33.0 (3-C), 19.9 (4-C), 18.8 (CH_3); ν_{max}/cm^{-1} (film) 3307, 2966, 1657, 1541, 1426, 1361, 1171; *m/z* (*ESI*) 346.1 (100%, MH^+); HRMS found MH^+, 346.1072. $C_{13}H_{19}N_3O_6S$ requires *MH,* 346.1067.

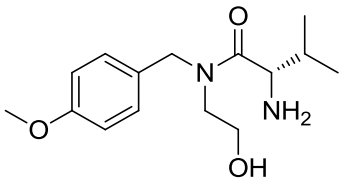
(*S*)-3-*iso*-Propyl-1-methylpiperazin-2-one, 101



Diethyl azodicarboxylate (0.9 mL, 5.0 mmol) was added to an ice cold solution of amine **91** (650 mg, 3.7 mmol) and triphenylphosphine (1.36 g, 5.20 mmol) in THF (30 mL) and the resulting solution was allowed to warm to rt and stirred for 16 h. Reaction mixture was concentrated *in vacuo* to give a crude product. Purification by column chromatography eluting with 20:1 CH_2Cl_2–MeOH, gave the *ketopiperazine* **101** (319 mg, 2.0 mmol, 55%) as a light yellow oil; R_f 0.42 (9:1 CH_2Cl_2–MeOH); $[\alpha]_D^{21}$: −127.8 (c. 0.7, MeOH); δ_H (300 MHz;

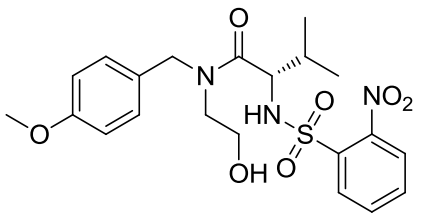
$CDCl_3$) 3.45-3.36 (1H, m, 6-H_a), 3.26 (1H, d, *J* 3.0, 3-H), 3.14-3.03 (2H, m, 5- H_a), 2.98-2.90 (1H, m, 6-H_b), 2.90 (3H, s, NMe), 2.47 (1H, d sept, *J* 3.1, 7.0, *i*Pr), 1.67 (1H, s (broad), NH), 0.94 (3H, d, *J* 7.1, *i*Pr), 0.80 (3H, d, *J* 6.8, *i*Pr); δ_C (75 MHz; $CDCl_3$) 170.5 (2-C), 64.7 (3-C), 50.6 (6-C), 42.8 (5-C), 35.1 (*i*Pr), 30.2 (NMe), 20.0 (*i*Pr), 17.1 (*i*Pr); ν_{max}/cm^{-1} (film) 3322, 2960, 2871, 1634, 1503, 1336; *m/z* (*ESI*) 157.1 (100%, MH^+); HRMS found MH^+, 157.1339. $C_8H_{16}N_2O$ requires *MH,* 157.1335.

(*S*)-2-Amino-*N*-(2′-hydroxyethyl)-*N*-(4-methoxybenzyl)-3-methylbutanamide, 92



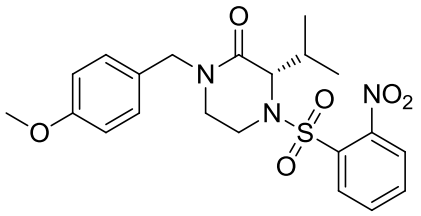
By general method **B**, the ester **86** (483 mg, 3.7 mmol) and amine **84** followed by purification by column chromatography, eluting with 9:1 CH_2Cl_2–MeOH, gave the amide **92** (573 mg, 2.0 mmol, 56%, 1:1 mixture of rotamers) as a light yellow oil; R_f 0.46 (50:8:1 CH_2Cl_2–EtOH–NH_4OH); $[\alpha]_D^{22}$: -22.2 (c. 0.9, $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 7.17 (2H, d, *J* 8.6, Ar 2 -H_{rotA} and Ar 6-H_{rotA}), 7.12 (2H, d, *J* 8.7, Ar 2-H $_{rotB}$ and Ar 6-H_{rotB}), 6.90 (2H, d, *J* 8.7, Ar 3-H_{rotA} and Ar 5-H_{rotA}), 6.86 (2H, d, *J* 8.6, Ar 3-H $_{rotB}$ and Ar 5-H_{rotB}), 5.26 (1H, d, *J* 14.6, CH_aAr_{rotA}), 4.71 (1H, d, *J* 16.6, CH_aAr_{rotB}), 4.46 (1H, d, *J* 16.6, CH_bAr_{rotB}), 4.00 (1H, d, *J* 14.6, CH_bAr_{rotA}), 3.79 (3H, s, OMe_{rotA}), 3.77-3.72 (3H, m, 2'-H_{rotA}+ 2'-$H_{a\ rotB}$), 3.68-3.61 (2H, m, 2'-$H_{b\ rotB}$), 3.47 (3H, s, OMe_{rotB}), 3.45-3.39 (1H, m, 1'-$H_{a\ rotB}$), 3.18-3.12 (1H, m, 1'-$H_{a\ rotB}$), 2.66 (6H, s (broad), NH_2+$OH_{rotB\ +rotA}$), 2.02 (1H, m, *i*Pr_{rotA}), 1.92 (1H, m, *i*Pr $_{rotB}$), 0.94 (12H, m, iPr $_{rotB\ +rotA}$); δ_C (75 MHz; $CDCl_3$) 129.5 (Ar), 127.9 (Ar), 114.5 (Ar), 114.1 (Ar), 61.9 (CH_2OH_{rotA}), 59.6 ($CH_2OH_{\ rotB}$), 57.1 (CHCO $_{rotA}$), 56.8 (CHCO $_{rotB}$), 55.4 (OMe $_{rotA}$), 55.4 (OMe $_{rotB}$), 51.9 ($NCH_{2\ rotA}$), 49.9 ($NCH_{2\ rotB}$), 49.0 (Bn $_{rotA}$), 47.7 (Bn $_{rotB}$), 32.5 (iPr $_{rotA}$), 32.1 (iPr $_{rotB}$), 20.2 (iPr $_{rotA}$), 20.0 (iPr $_{rotB}$), 17.8 (iPr $_{rotA}$), 17.2 (iPr $_{rotB}$) [Quaternary Ar-C, 1-C_{rotA} and 1-C_{rotB} were not observed]; ν_{max}/cm^{-1} (film) 3368, 1738, 1614, 1365; *m/z* (*ESI*) 281.2 (100%, MH^+); HRMS found MH^+, 281.1869. $C_{15}H_{24}N_2O_3$ requires *MH,* 281.1860.

(*S*)-*N*-(2′-Hydroxyethyl)-*N*-(4-methoxybenzyl)-3-methyl-2-(2-nitrophenylsulfonamido)butanamide, 94



By general method **B**, the ester **80** (1.16 g, 3.70 mmol) and the amine **84** followed by purification by column chromatography, eluting with 50:8:1 CH_2Cl_2–EtOH–NH_4OH, gave the amide **94** (300 mg, 0.6 mmol, 18%, 1:1 mixture of rotamers) as a light yellow oil; R_f 0.53 (9:1 CH_2Cl_2–MeOH); $[\alpha]_D^{21}$: -44.6 (c. 2.7, $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 8.08 (1H, m, Ns $_{rotA}$), 7.91 (3H, m, Ns $_{rotA+ rotB}$), 7.69 (4H, m, Ns $_{rotA+ rotB}$), 7.01 (2H, d, *J* 8.7, Ar_{rotA}), 6.97 (2H, d, *J* 8.7, Ar $_{rotB}$), 6.87 (2H, d, *J* 8.7, Ar_{rotA}), 6.76 (2H, d, *J* 8.7, Ar_{rotB}), 4.68 (1H, d, *J* 14.7, Bn_{rotA}), 4.56 (1H, d, *J* 16, Bn_{rotB}), 4.49 (1H, d, *J* 3.8, NH $_{rotA}$), 4.44 (1H, d, *J* 3.8, NH_{rotB}), 4.39 (1H, d, *J* 15.9, Bn_{rotB}), 4.03 (1H, d, *J* 14.7, Bn_{rotA}), 3.83 (3H, a, OMe_{rotA}), 3.80 (1H, m, CHCO $_{rotA}$), 3.77 (3H, s, OMe $_{rotB}$), 3.65 (2H, m, CH_2OH_{rotA}), 3.44 (4H, m, CH_2OH_{rotB} and CH_2NH_{rotA}), 3.34 (1H, m, $CHCO_{rotB}$), 3.21 (2H, m, CH_2NH_{rotA}), 2.01 (2H, m, *i*Pr $_{rotA+ rotB}$), 1.06 (7H, m, *i*Pr $_{rotA+ rotB}$), 0.91 (7H, m, *i*Pr $_{rotA+ rotB}$); δ_C (75 MHz; $CDCl_3$) 172.3 (CO_{rotA}), 171.2 (CO_{rotB}), 159.9 (*i*NO_2 $_{rotA}$), 159.4 (*i*NO_2 $_{rotB}$), 148.0 (iSO_2 $_{rotA+ rotB}$), 134.9 (*i*OMe $_{rotA}$), 134.0 (Ns), 133.8 (Ns), 133.2 (Ns), 133.1 (Ns), 130.8 (Ns), 130.4 (Ns), 129.7 (mOMe $_{rotA}$), 129.4 (iOMe), 128.9 (mOMe $_{rotB}$), 127.7 (*p*OMe), 126.2 (Ns), 125.9 (Ns), 114.8 (*o*OMe $_{rotA}$), 114.5 (*o*OMe $_{rotB}$), 61.6 (CH2OH $_{rotA}$), 59.9 (COCH $_{rotA}$), 59.8 (CH_2OH $_{rotB}$), 59.5 (COCH $_{rotB}$), 55.8 (OMe $_{rotA}$), 55.7 (OMe_{rotB}), 52.2 (CH_2H_{rotA}), 49.5 (CH_2N $_{rotA}$), 48.7 (Bn $_{rotA}$), 48.4 (Bn $_{rotA}$), 31.8 (*i*Pr $_{rotA}$), 31.6 (*i*Pr $_{rotA+ rotB}$), 20.3 (*i*Pr $_{rotA+ rotB}$), 16.6 (*i*Pr $_{rotA+ rotB}$); ν_{max}/cm^{-1} (film) 3304, 2967, 1634, 1541, 1513, 1464; *m*/*z* (*ESI*) 466.2 (100%, MH^+); HRMS found MNa^+, 466.1644. $C_{21}H_{27}N_3O_7S$ requires *MNa,* 466.1642.

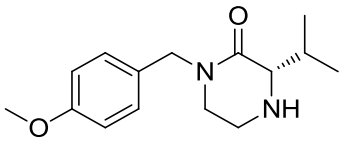
(*S*)-3-*iso*-Propyl-1-(4-methoxybenzyl)-4-(2-nitrophenylsulfonyl)piperazin-2-one, 103



By general procedure **C**, the alcohol **94** (200 mg, 0.4 mmol) gave a crude product. Purification by column chromatography, eluting with 1:1 petrol–EtOAc, gave sulfonamide

103 (173 mg, 0.4 mmol, 90%) as a light yellow gum; R_f 0.57 (50:8:1 CH_2Cl_2–MeOH–NH_4OH); $[\alpha]_D^{21}$: 102.7 (c. 1.1 $CHCl_3$); δ_H (500 MHz; $CDCl_3$) 7.98 (1H, m, Ns), 7.62 (3H, m, Ns), 7.04 (2H, d, *J* 8.6, Ar 2-H and Ar 6-H), 6.77 (2H, d, *J* 8.6, Ar 3-H and Ar 5-H), 4.48 (1H, d, *J* 14.4, CH_aAr), 4.35 (1H, d, *J* 14.4, CH_bAr), 4.22 (1H, d, *J* 7.4, 3-H), 3.99 (1H, dd, *J* 15.0, 5.4, CH), 3.79 (3H, s, OMe), 3.53 (1H, ddd, *J* 15.0, 11.1, 5.0, CH), 3.17 (1H, dd, *J* 12.5, 5.4, CH), 3.04 (1H, dd, *J* 12.5, 5.0, CH), 2.31 (1H, m, *i*Pr), 1.10 (3H, d, *J* 6.7, *i*Pr), 0.96 (3H, d, *J* 6.9, *i*Pr); δ_C (75 MHz; $CDCl_3$) 166.9 (1-C), 159.5 (Ar 4-C), 148.2 (Ns 2-C), 134.3 (Ns), 133.6 (Ns 1-C), 132.4 (Ns), 131.3 (Ns), 130.0 (Ar 2-C and Ar 6-C), 128.6 (Ar 1-C), 124.7 (Ns), 114.4 (Ar 3-C and Ar 5-C), 64.6 (3-C), 55.7 (OMe), 49.9 (CH_2Ar), 45.1 (CH_2), 40.1 (CH_2), 31.8 (*i*Pr), 20.5 (*i*Pr), 20.4 (*i*Pr); ν_{max}/cm^{-1} (film) 2966, 1711, 1650, 1544, 1513, 1370; *m/z* (*ESI*) 448.1 (100%, MH^+); HRMS found MNa^+, 470.1367. $C_{21}H_{25}N_3O_6S$ requires *MNa,* 470.1356.

(*S*)-3-*iso*-Propyl-1-(4-methoxybenzyl)piperazin-2-one, 102



Compound **102** was synthesised by the three methods outlined below.

1. General method **C**

By general method **C**, followed by purification by column chromatography, eluting with 8:1 EtOAc–MeOH, the alcohol **93** (540 mg, 1.9 mmol gave the *ketopiperazine* **102** (370 mg, 1.4 mmol, 73%) as a light yellow oil.

2. Deprotection of **103**

Thiophenol (0.03 mL, 0.3 mmol) was added to a solution of sulfonamide **103** (100 mg, 0.2 mmol) and K_2CO_3 (93 mg, 0.7 mmol) in DMF (4 mL) and stirred at rt for 1.5h. Reaction mixture was concentrated *in vacuo* , diluted with EtOAc (10 mL), washed with water (5 mL) and K_2CO_3 (aq. sat. soln. 5 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a crude product. Purification by ion exchange chromatography (Supelco DSC-SCX resin) gave *ketopiperazine* **102** (47 mg, 0.18 mmol, 80%) as a light yellow oil.

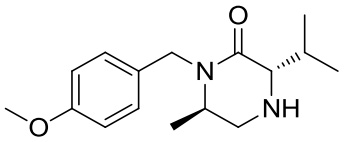
3. By general method **D**

By general procedure **D**, acid **79** (500 mg, 1.7 mmol) and amine **84** gave the *ketopiperazine* **102** (94 mg, 0.4 mmol, 22%) as a light yellow oil.

In all cases the resulting material was spectroscopically identical.

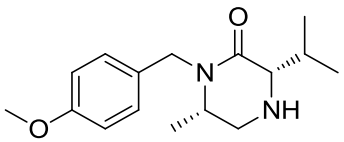
R_f 0.41 (9:1 CH_2Cl_2–MeOH); $[\alpha]_D^{22}$: -81.6 (c. 1 $CHCl_3$); δ_H (500 MHz; $CDCl_3$) 7.20 (2H, d, *J* 8.6, Ar 2-C and Ar 6-C), 6.85 (2H, d, *J* 8.6, Ar 3-C and Ar 5-C), 4.58 (1H, d, *J* 14.4, CH_aAr), 4.51 (1H, d, *J* 14.4, CH_bAr), 3.80 (3H, s, OMe), 3.42 (1H, d, *J* 3.0, 3-H), 3.31 (1H, dt, *J* 11.0, 5.0, 6-H_a), 3.10 (2H, m, 6-Hb and 5-H_a), 2.93 (1H, dt, *J* 12.1, 3.8, 5-H_a), 2.61 (1H, dsept, *J* 7.0, 3.1, *i*Pr), 1.64 (1H, s (broad), NH), 1.02 (3H, d, *J* 7.1, *i*Pr), 0.91 (3H, d, *J* 6.8, *i*Pr); δ_C (75 MHz; $CDCl_3$) 170.3 (2-C), 159.4 (Ar 4-C), 129.9 (Ar 2-C and Ar 6-C), 129.6 (Ar 4-C), 114.4 (Ar 3-C and Ar 5-C), 64.8 (3-C), 55.7 (OMe), 50.0 (CH_2Ar), 47.7 (6-C), 42.9 (5-C), 30.4 (*i*Pr), 20.0 (*i*Pr), 17.1 (*i*Pr); ν_{max}/cm^{-1} (film) 3436, 2961, 1631, 1513, 1247; *m/z* (*ESI*) 263.2 (100%, MH^+); HRMS found MH^+, 263.1756. $C_{15}H_{22}N_2O_2$ requires *MH,* 263.1754.

(3*S*,6*R*)-3-*iso*-Propyl-1-(4-methoxybenzyl)-6-methylpiperazin-2-one, 120



By general method **D**, acid **79** (387 mg, 1.3 mmol) and the amine **105** gave the ketopiperazine **120** (18 mg, 65 μmol, 5%) as a colourless oil; R_f 0.60 (9:1 CH_2Cl_2–MeOH); $[\alpha]_D^{21}$: -162.2 (c. 1.5, $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 7.21 (2H, d, *J* 8.6, Ar 2-H and Ar 6-H), 6.84 (2H, d, *J* 8.7, Ar 3-H and Ar 5-H), 5.23 (1H, d, *J* 14.7, CH_aAr), 3.85 (1H, d, *J* 14.7, CH_bAr), 3.79 (3H, s, OMe), 3.45 (1H, d, *J* 3.0, 3-H), 3.30 (1H, m, 6-H), 2.98 (1H, dd, *J* 12.4, 3.6, 5-H_a), 2.86 (1H, dd, *J* 12.3, 1.2, 5-H_b), 2.59 (1H, d sept, *J* 3.0, 7.0, *i*Pr), 1.76 (1H, s (broad), NH), 1.29 (3H, d, *J* 6.4, CH_3), 1.03 (3H, d, *J* 7.1, *i*Pr), 0.93 (3H, d, *J* 6.8, *i*Pr); δ_C (75 MHz; $CDCl_3$) 170.6 (2-C), 159.3 (Ar 4-C), 130.2 (Ar 1-C), 129.8 (Ar 2-C and Ar 6-C), 114.3 (Ar 3-C and Ar 5-C), 64.9 (3-C), 55.7 (OMe), 51.1 (6-C), 48.6 (CH_2Ar), 47.6 (5-C), 30.4 (*i*Pr), 19.9 (Me), 18.3 (*i*Pr), 17.0 (*i*Pr); ν_{max}/cm^{-1} (film) 2962, 1634, 1531, 1463, 1245, 1175; *m/z* (*ESI*) 277.2 (100%, MH^+); HRMS found MH^+, 277.1915. $C_{16}H_{24}N_2O_2$ requires *MH,* 277.1911.

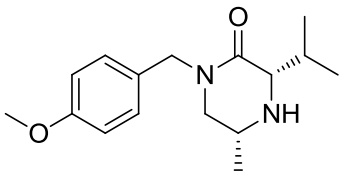
(3*S*,6*S*)-3-*iso*-Propyl-1-(4-methoxybenzyl)-6-methylpiperazin-2-one, 121



By general method **D**, acid **79** (200 mg, 0.7 mmol) and the amine **106** gave the ketopiperazine **121** (32 mg, 0.1 mmol, 18%) as a colourless oil; R_f 0.43 (50:1, EtOAc–petrol); $[\alpha]_D^{21}$: -151 (c. 3.1 $CHCl_3$); δ_H (300 MHZ; $CDCl_3$) 7.21 (2H, d, *J* 8.6, Ar 2-H and Ar 6-H), 6.85 (2H, d, *J* 8.6, Ar 3-H and Ar 5-H), 5.23 (1H, d, *J* 14.7, CH_aAr), 3.85 (1H, d, *J* 14.7, CH_bAr), 3.79 (3H, s, OMe), 3.45 (1H, d, *J* 3.4, 3-H), 3.30 (1H, m, 6-H), 2.98 (1H, dd, *J* 12.4, 3.6, 5-H_a), 2.86 (1H, d, *J* 11.7, 55-H_b), 2.59 (1H, d sept, *J* 3.0, 7.0, iPr), 1.66 (1H, s (broad),

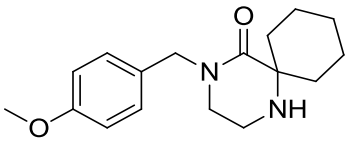
NH), 1.29 (3H, d, *J* 6.4, Me), 1.03 (3H, d, *J* 7.1, iPr), 0.93 (3H, d, *J* 6.8, iPr); δ_C (75 MHz; $CDCl_3$) 170.6 (2-C), 159.3 (Ar 4-C), 130.2 (Ar 1-C), 129.8 (Ar 2-C and 6-C), 114.3 (Ar 3-C and Ar 5-C), 64.9 (3-C), 55.7 (OMe), 51.1 (6-C), 48.7 (CH_2Ar), 47.6 (5-C), 30.4 (*i*Pr), 19.9 (Me), 18.3 (*i*Pr), 17.0 (*i*Pr), ; ν_{max}/cm^{-1} (film) 3337, 2965, 1633, 1513, 1246; *m*/*z* (*ESI*) 277.2 (100%, MH^+); HRMS found MH^+, 277.1901. $C_{16}H_{24}N_2O_2$ requires *MH,* 277.1911.

(3*S*,5*R*)-3-*iso*-Propyl-1-(4-methoxybenzyl)-5-methylpiperazin-2-one, 122



By general method **D**, acid **79** (250 mg, 0.8 mmol) and the amine **79** gave the ketopiperazine **122** (95 mg, 0.3 mmol, 42%) as a colourless oil; R_f 0.57 (9:1 CH_2Cl_2–MeOH); $[\alpha]_D^{21}$: -82.9 (c. 0.8, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 7.19 (2H, d, *J* 8.5, Ar 2-H and Ar 6-H), 6.85 (2H, d, *J* 8.6, Ar 3-H and Ar 5-H), 4.56 (1H, d, *J* 14.4, CH_aAr), 4.47 (1H, d, *J* 14.4, CH_bAr), 3.97 (3H, s, OMe), 3.48 (1H, d, *J* 2.8, 3-H), 3.05 (1H, m, 5-H), 2.98 (1H, dd, *J* 3.5, 11.3, 6-H_a), 2.91 (1H, m, 6-H_b), 2.67 (1H, d sept, *J* 7.0, 2.9, *i*Pr), 1.42 (1H, s (broad), NH), 1.09 (3H, d, *J* 6.2, Me), 1.01 (3H, d, *J* 7.2, *i*Pr), 0.91 (3H, d, *J* 6.8, *i*Pr); δ_C (75 MHz; $CDCl_3$) 170.2 (2-C), 129.9 (Ar 2-C and Ar 6-C), 129.6 (Ar 1-C), 114.3 (Ar 3-C and Ar 5-C), 64.7 (3-C), 55.7 (OMe), 54.2 (6-C), 50.0 (CH_2Ar), 48.3 (5-C), 30.6 (*i*Pr), 19.9 (CH_3), 19.7 (*i*Pr), 17.0 (*i*Pr) [Ar 4-C was not observed]; ν_{max}/cm^{-1} (film) 3436, 2965, 1709, 1630, 1513, 1247; *m*/*z* (*ESI*) 277.2 (100%, MH^+); HRMS found MH^+, 277.1919. $C_{16}H_{24}N_2O_2$ requires *MH,* 277.1911.

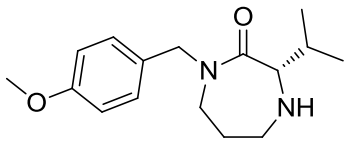
4-(4-Methoxybenzyl)-1,4-diazaspiro[5.5]undecan-5-one, 125



By general method **D**, acid **117** (200 mg, 0.6 mmol) and the amine **84** gave the ketopiperazine **125** (27 mg, 0.1 mmol, 15%) as a colourless oil; R_f 0.47 (100%, EtOAc); δ_H (500 MHz; $CDCl_3$) 7.16 (2H, d, *J* 8.5, Ar 2-H and Ar 6-H), 6.84 (2H, d, *J* 8.5, Ar 3-H and Ar 5-H), 4.51 (2H, s, CH_2Ar), 3.79 (3H, s, OMe), 3.19 (2H, t, *J* 5.5, 3-H), 3.00 (2H, t, *J* 5.5, 2-H), 2.00 (2H, dt, *J* 13.5, 3.9, 2 × CH c. hex), 1.92 (1H, s (broad), NH), 1.72 (2H, d, *J* 13.2, 2 × CH c. hex), 1.63 (2H, m, 2 × CH c. hex), 1.45 (2H, app. q, *J* 13.0, 2 × CH c. hex), 1.31 (2H, m, 2 × CH c. hex); δ_C (75 MHz; $CDCl_3$) 174.2 (5-C), 159.3 (Ar 4-C), 129.7 (Ar 2-C and Ar 6-C), 114.4 (Ar 3-C and Ar 5-C), 59.2 (6-C), 55.7 (OMe), 50.1 (CH_2Ar), 48.0 (2-C), 38.3 (3-C), 33.5 (2 × CH_2 c.hex), 25.7 (CH_2 c.hex), 21.1 (2 × CH_2 c.hex) [Ar 1-C was not observed]; ν_{max}/cm^{-1}

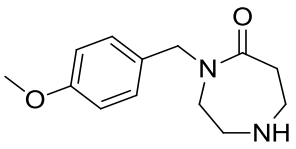
(film); 2929, 1736, 1629, 1513, 1248; *m*/*z* (*ESI*) 289.2 (100%, MH^+); HRMS found MH^+, 289.1920. $C_{17}H_{24}N_2O_2$ requires *MH,* 289.1911.

(*S*)-3-*iso*-Propyl-1-(4-methoxybenzyl)-1,4-diazepan-2-one, 118



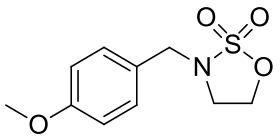
By general method **D**, acid **79** (1.00 g, 3.3 mmol) and the amine **84** gave the ketodiazepane **118** (111 mg, 0.4 mmol, 12%) as a colourless oil; R_f 0.53 (9:1 CH_2Cl_2–MeOH); $[\alpha]_D^{21}$: -28.6 (c. 0.8, $CHCl_3$); δ_H (500 MHz; $CDCl_3$) 7.21 (2H, d, *J* 8.7, Ar 2-H and Ar 6-H), 6.85 (2H, d, *J* 8.7, Ar 3-H and Ar 5-H), 4.63 (1H, d, *J* 14.4, CH_aAr), 4.42 (1H, d, *J* 14.4, CH_bAr), 3.80 (3H, s, OMe), 3.51 (1H, dd, *J* 15.5, 11.5, 7-H_a), 3.30 (2H, m, 5-H), 3.09 (1H, d, *J* 6.7, 3-H), 2.80 (1H, dd, *J* 11.0 and 3.7, 7-H_b), 2.21 (1H, m, *i*Pr), 1.68 (1H, s (broad), NH), 1.55 (1H, m, 6-H_a), 1.41 (1H, m, 6-H_b), 1.02 (6H, d, *J* 6.9, *i*Pr); δ_C (75 MHz; $CDCl_3$) 175.6 (2-C), 159.3 (Ar 4-C), 130.5 (Ar 1-C), 130.0 (Ar 2-C and Ar 6-C), 114.3 (Ar 3-C and Ar 5-C), 66.9 (3-C), 55.7 (OMe), 51.0 (CH_2Ar), 50.1 (7-C), 47.3 (5-C), 30.1 (6-C), 29.7 (*i*Pr), 21.1 (*i*Pr), 18.7 (*i*Pr); ν_{max}/cm^{-1} (film) 3444, 1707, 1634, 1513, 1365, 1244; *m*/*z* (*ESI*) 277.2 (100%, MH^+); HRMS found MH^+, 277.1919. $C_{16}H_{24}N_2O_2$ requires *MH,* 277.1911.

4-(4-Methoxybenzyl)-1,4-diazepan-5-one, 119



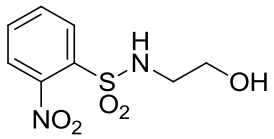
By general method **D**, acid **116** (260 mg, 0.9 mmol) and the amine **84** gave the ketodiazepane **119** (21 mg, 89 μmol, 9%) as a colourless oil R_f 0.25 (9:1 CH_2Cl_2–MeOH); δ_H (500 MHz; $CDCl_3$) 7.19 (2H, d, *J* 8.6, Ar 2-H and Ar 6-H), 6.85 (2H, d, *J* 8.6, Ar 3-H and Ar 5-H), 4.63 (2H, s, CH_2Ar), 3.80 (3H, s, OMe), 3.35 (2H, t, *J* 4.4, 6-H), 2.98 (2H, t, *J* 5.1, 3-H), 2.74 (2H, t, *J* 4.5, 7-H), 2.73 (2H, t, *J* 5.3, 2-H), 1.91 (1H, s (broad), NH); δ_C (75 MHz; $CDCl_3$) 175.5 (5-C), 159.4 (Ar 4-C), 130.0 (Ar 2-C and Ar 6-C), 114.4 (Ar 3-C and Ar 5-C), 55.7 (OMe), 51.3 (6-C), 51.2 (3-C), 49.4 (CH_2Ar), 44.5 (2-C), 41.4 (7-C) [Ar 1-C was not observed]; ν_{max}/cm^{-1} (film) 3444, 1738, 1626, 1513, 1217; *m*/*z* (*ESI*) 257.1 (100%, MNa^+); HRMS found MNa^+, 257.1206. $C_{13}H_{18}N_2O_2$ requires *MNa,* 257.1260.

3-[(4-Methoxyphenyl)methyl]-1,2,3- oxathiazolidine-2,2-dione, 130[64]



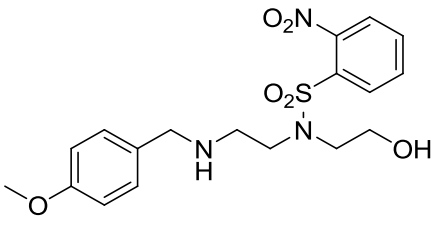
By general procedure **F**, the amino alcohol **130** (5.93 g, 33.0 mmol) gave cyclic sulfamidate **130** (7.09 g, 29.2 mmol, 89%) as a light brown oil which solidified upon standing; R_f 0.56 (1:1, petrol–EtOAc); δ_H (500 MHz; $CDCl_3$) 7.30 (2H, d, *J* 8.6, Ar 2-H and Ar 6-H), 8.90 (2H, d, *J* 8.6, Ar 3-H and Ar 4-H), 4.50 (2H, t, *J* 6.5, 5-H), 4.18 (2H, s, CH_2 benzyl), 3.81 (3H, s, OMe), 3.39 (2H, t, *J* 6.5, 4-H); δ_C (75 MHz; $CDCl_3$) 160.2 (Ar4-C), 136.0 (Ar 2-C and Ar 6-C), 126.6 (Ar6-C), 114.7 (Ar 3-C and Ar 5-C), 67.2 (5-C), 55.8 (OMe), 51.4 (CH_2 benzyl), 47.4 (4-C); ν_{max}/cm^{-1} (film) 2962, 1612, 1584, 1455, 1301; *m/z* (*ESI*) 266.0 (100%, MNa^+); HRMS found MNa^+, 266.0465. $C_{10}H_{13}NO_4S$ requires *MNa,* 266.0457.

***N*-(2-Hydroxyethyl)-2-nitrobenzenesulfonamide, 131**[106]



By general procedure **E**, 2-aminoethanol (1.22 g, 20.0 mmol) gave sulfonamide **131** (3.99 g, 16.2 mmol, 81%) as a light yellow oil which solidified upon standing; R_f 0.57 (50:5:1 CH_2Cl_2–EtOH–NH_4OH); δ_H (500 MHz; $CDCl_3$) 8.20 (1H, m, Ar 3-H), 7.93 (1H, m, Ar 6-H), 7.80 (2H, m, Ar 5-H and Ar 5-H), 5.81 (1H, t (broad), *J* 4.7, NH), 3.81 (2H, app. q, *J* 5.0, 2-H), 3.32 (2H, app. q, *J* 4.8, 1-H), 1.92 (1H, t, *J* 5.1, OH); δ_C (75 MHz; $CDCl_3$) 133.7 (Ar 3-C), 132.8 (Ar 6-C), 131.1 (Ar 4-C), 125.5 (Ar 5-C), 61.3 (2-C), 45.7 (1-C); ν_{max}/cm^{-1} (film) 3257, 1540, 1439, 1360; *m/z* (*ESI*) 269.0 (100%, MNa^+); HRMS found MNa^+, 269.0211. $C_8H_{10}N_2O_5S$ requires *MNa,* 269.0203.

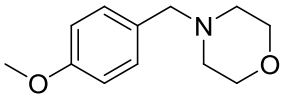
***N*-(2'-Hydroxyethyl)-*N*-(2-(4-methoxybenzylamino)ethyl)-2'-nitrobenzenesulfonamide, 132**



By general procedure **G**, the cyclic sulfamidate **130** (1.00 g, 4.1 mmol) and sulfonamide **131** gave sulfonamide **132** (1.25 g, 3.00 mmol, 74%) as a colourless oil; R_f 0.58 (1:1,

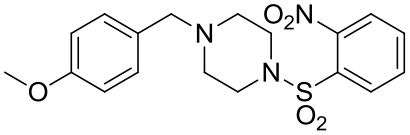
petrol–EtOAc); δ_H (500 MHz; $CDCl_3$) 8.00 (1H, m, Ar 3'-H), 7.74 (2H, m, Ar 5'-H and Ar H-'6), 7.65 (1H, m, Ar 4'-H), 7.26 (2H, d, *J* 8.6, Ar 2-H and Ar 6-H), 6.92 (2H, d, *J* 8.7, Ar 3-H and Ar 4-H), 3.87-3.85 (5H, m, OMe and 2-H), 3.80 (2H, s, CH_2 benzyl), 3.50 (2H, t, *J* 5.5, H1'), 3.47 (2H, t, *J* 4.7, 1-H), 2.99 (2H, t, *J* 6.5, 2'-H); δ_C (75 MHz; $CDCl_3$) 155.7 (Ar 4-C), 133.8 (Ar 4'-C), 131.7 (Ar 5'-C), 130.8 (Ar 6'-C), 129.9 (Ar 2-C and Ar 6-C), 124.2 (Ar 3'-C), 114.1 (Ar 3-C and Ar 5-C), 62.4 (2-C), 55.3 (1'-C), 54.0 (OMe), 52.7 (CH_2 benzyl), 49.7 (1-C), 47.5 (2'-C) [Ar 1-C, Ar 1'-C and Ar 2'-C were not observed]; ν_{max}/cm^{-1} (film) 3320, 1611, 1543, 1345, 1249; *m/z* (*ESI*) 410.1 (100%, MH^+).

4-(4-Methoxybenzyl)morpholine, 134[66]



The morpholine **134** was prepared as reported by Fujita and colleagues.[66] 4-Methoxybenzylamine (0.42 g, 3.0 mmol), diethylene glycol (0.21 g, 2.0 mmol), $[Cp^*IrCl_2]_2$ (40.0 mg, 50.0 μmol) and $NaHCO_3$ (1 mg, 1.0 μmol) were combined in toluene (1 mL), degassed (4 cycles of vacuum and argon, ending under positive pressure of argon), and heated at 100 °C for 24 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo* to give a crude product. Purification by column chromatography, gradient elution 100% CH_2Cl_2 to 20:1 CH_2Cl_2–MeOH, followed by a second column eluting with EtOAc–petrol 2:1, gave morpholine **134** (212 mg, 1.1 mmol, 51%) as a light yellow oil; δ_H (500 MHz; $CDCl_3$) 7.23 (2H, d, *J* 8.5, Ar 2-H and Ar 6-H), 6.85 (2H, d, *J* 8.6, Ar 3-H and Ar 5-H), 3.80 (3H, s, OMe), 3.70 (4H, t, *J* 4.7, 2-H and 6-H), 3.43 (2H, s, CH_2 benzyl), 2.42 (4H, t (broad), *J* 4.1, 3-H and 5-H); δ_C (75 MHz; $CDCl_3$) 158.8 (Ar 4-C), 130.4 (Ar 2-C and Ar 6-C), 113.6 (3-C and Ar 5-C), 67.0 (CH_2), 62.8 (CH_2), 55.3 (OMe), 53.5 (CH_2) [Ar 1-C was not observed]; *m/z* (*ESI*) 208.0 (100%, MH^+).

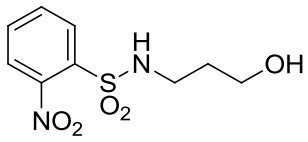
1-(4-Methoxybenzyl)-4-(2'-nitrophenylsulfonyl)piperazine, 78



By general procedure **C**, the sulfonamide **132** (0.40 g, 1.0 mmol), gave piperazine **78** (0.36 g, 0.90 mmol, 94%) as a light yellow oil; R_f 0.80 (9:1 CH_2Cl_2–MeOH); δ_H (500 MHz; $CDCl_3$) 7.94 (1H, dd, *J* 7.5, 1.6, Ar 3'-H), 7.68 (2H, m, Ar 5'-H and Ar 6'-H), 7.60 (1H, dd, *J* 7.5, 1.7, Ar 4'-H), 7.18 (2H, d, *J* 8.6, Ar 2-H and Ar 6-H), 6.84 (2H, d, *J* 8.6, Ar 3-H and Ar 5-H), 3.79 (3H, s, OMe), 3.45 (2H, s, CH_2 benzyl), 3.30 (4H, t (broad), *J* 4.6, 3-H and 5-H), 2.50 (4H, t (broad), *J* 4.8, 2-H and 6-H); δ_C (75 MHz; $CDCl_3$) 133.7 (Ar 5'-C), 131.4 (Ar 4'-C), 130.9 (Ar

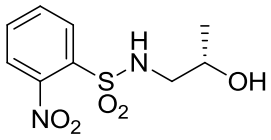
6'-C), 130.3 (Ar 2-C and Ar 6-C), 124.0 (Ar 4'-C), 113.7 (Ar 3-C and Ar 5-C), 62.0 (3-C and 5-C), 55.3 (OMe), 52.19 (CH_2 benzyl), 46.0 (2-C and 6-C) [quaternary Ar-C were not observed]; ν_{max}/cm^{-1} (film) 2937, 1612, 1546, 1513, 1373, 1249, 1174; *m/z* (*ESI*) 392.1 (100%, MH^+); HRMS found MH^+, 392.1285. $C_{18}N_{21}N_3O_5S$ requires *MH,* 392.1275.

_N_-(3-Hydroxypropyl)-2-nitrobenzenesulfonamide, 151[98]



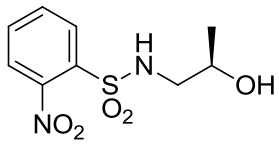
By general procedure **E**, 3-aminopropanol (1.58 g, 21.0 mmol) gave sulfonamide **151** (5.38 g, 20.7 mmol, 98%) as a light yellow semi solid which required no further purification; R_f 0.14 (1:1 petrol–EtOAc); δ_H (300 MHz, $CDCl_3$) 8.14 (1H, m, Ar 3-H), 7.56 (1H, m, Ar 6-H), 7.75 (2H, m, Ar 4-H and Ar 5-H), 5.87 (1H, s (broad), NH) 3.76 (2H, t, *J* 5.7, 3-H), 3.26 (2H, t, *J* 6.3, 1-H), 2.09 (1H, s (broad), OH), 1.78 (2H, app. pent., *J* 5.8, 2-H); δ_C (75 MHz; $CDCl_3$) 148.1 (Ar 2-C), 133.6 (Ar 5-C), 133.5 (Ar 1-C), 132.8 (Ar 4-C), 131.1 (Ar 6-C), 125.4 (Ar 3-C), 60.4 (3-C), 41.5 (1-C), 31.6 (2-C); ν_{max} /cm^{-1} (film) 3328, 2965, 1537, 1414, 1362; *m/z* (*ESI*) 283.0 (100%, MNa^+); HRMS found MNa^+, 283.0360. $C_9H_{12}N_2O_5S$ requires *MNa,* 283.0359.

(*S*)-*N*-(2-Hydroxypropyl)-2-nitrobenzenesulfonamide, 152



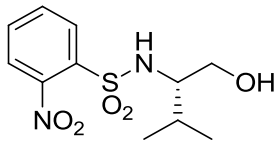
By general procedure **E**, (*S*)-1-amino-2-propanol (1.00 g, 13.3 mmol) gave sulfonamide **152** (3.29 g, 12.5 mmol, 94%) as a light yellow amorphous solid which required no further purification; R_f 0.73 (50:8:1 CH_2Cl_2–EtOH–NH_4OH); $[\alpha]_D^{26}$: -20.5 (c. 1.3, MeOH); δ_H (300 MHz; $CDCl_3$) 8.14 (1H, m, Ar 3-H), 7.88 (1H, m, Ar 6-H), 7.76 (2H, m, Ar 4-H and Ar 5-H), 5.78 (1H, t (broad), *J* 5.7, NH), 3.97 (1H, m, 2-H), 3.23 (1H, ddd, *J* 12.9, 7.1, 3.3, 1-H_a), 2.94 (1H, ddd, *J* 13.1, 8.0, 5.3, 1-H_b), 1.98 (1H, s (broad), OH), 1.20 (3H, d, *J* 6.3, 3-H); δ_C (75 MHz; $CDCl_3$) 134.1 (Ar 5-C), 133.3 (Ar 4-C), 131.5 (Ar 6-C), 125.9 (Ar 3-C), 66.9 (2-C), 50.9 (1-C), 21.1 (3-C) [Ar 1-C and Ar 2-C were not observed]; ν_{max}/cm^{-1} (film) 3340, 1538, 1361; *m/z* (*ESI*) 283.0 (100%, MNa^+); HRMS found MNa^+, 283.0346. $C_9H_{12}N_2O_5S$ requires *MNa,* 283.0359.

(*R*)-*N*-(2-Hydroxypropyl)-2-nitrobenzenesulfonamide, 153



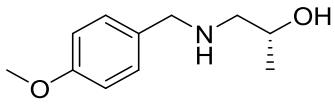
By general procedure **E**, (*R*)-1-amino-2-propanol (1.00 g, 13.3 mmol) gave sulfonamide **153** (3.30 g, 12.7 mmol, 95%) as a light yellow amorphous solid which required no further purification; R_f 0.65 (50:8:1 CH_2Cl_2–EtOH–NH_4OH); $[\alpha]_D^{26}$: 16.6 (c. 0.9, MeOH); δ_H (300 MHz; $CDCl_3$) 8.14 (1H, m, Ar 3-H), 7.88 (1H, m, Ar 6-H), 7.76 (2H, m, Ar 4-H and Ar 5-H), 5.77 (1H, t (broad), *J* 5.8, NH), 3.97 (1H, m (broad), 2-H), 3.22 (1H, ddd, *J* 13.0, 7.0, 3.2, 1-H_a), 2.94 (1H, ddd, *J* 13.1, 7.9, 5.2, 1-H_b), 1.95 (1H, d (broad), *J* 2.8, OH), 1.20 (3H, d, *J* 6.2, 3-H); δ_C (75 MHz; $CDCl_3$) 134.1 (Ar 5-C), 133.3 (Ar 4-C), 131.5 (Ar 6-C), 125.9 (Ar 3-C), 66.9 (2-C), 50.9 (1-C), 21.1 (3-C) [Ar 1-C and Ar 2-C were not observed]; ν_{max}/cm^{-1} (film) 3339, 1538, 1411, 1362; *m/z* (*ESI*) 283.0 (100%, MNa^+); HRMS found MNa^+, 283.0364. $C_9H_{12}N_2O_5S$ requires *MNa,* 283.0359.

(*S*)-*N*-(1-Hydroxy-3-methylbutan-2-yl)-2-nitrobenzenesulfonamide, 154



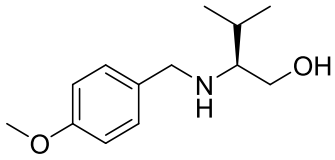
By general procedure **E**, (2*S*)-2-amino-3-methyl butanol (1.00 g, 9.7 mmol) gave sulfonamide **154** (2.47 g, 12.7 mmol, 88%) as a light yellow amorphous solid which required no further purification; R_f 0.39 (9:1 CH_2Cl_2–MeOH); $[\alpha]_D^{26}$: -29.6 (c. 1.1, MeOH); δ_H (300 MHz; $CDCl_3$) 8.14 (1H, m, Ar 3-H), 7.87 (1H, m, Ar 6-H), 7.72 (2H, m, Ar 4-H and Ar 5-H), 5.52 (1H, d (broad), *J* 8.24, NH), 3.62 (2H, m, 1-H), 3.30 (1H, m, 2-H), 1.89 (1H, app. oct, *J* 6.7, 3-H), 1.76 (1H, t, *J* 5.7, OH), 0.88 (6H, d, *J* 6.8, 4-H and Me); δ_C (75 MHz; $CDCl_3$) 134.9 (Ar 1-C), 133.4 (Ar 5-C), 132.9 (Ar 4-C), 130.6 (Ar 6-C), 125.3 (Ar 3-C), 63.3 (1-C), 62.3 (2-C), 29.5 (3-C), 19.3 (4-C), 18.3 (Me) [Ar 2-C was not observed]; ν_{max}/cm^{-1} (film) 3327, 2963, 1538, 1360; *m/z* (*ESI*) 311.1 (100%, MNa^+); HRMS found MNa^+, 311.0677. $C_{11}H_{16}N_2O_5S$ requires *MNa,* 311.0672.

(*R*)-1-(4-Methoxybenzylamino)propan-2-ol, 140



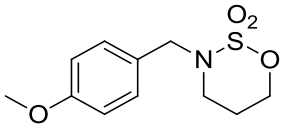
By general procedure **A**, (*R*)-1-amino-2-propanol (1.00 g, 13.3 mmol) gave alcohol **140** (2.57 g, 13.2 mmol, 98%) as a light brown oil which required no further purification; R_f 0.39 (9:1 CH_2Cl_2–MeOH); $[\alpha]_D^{26}$: -18.6 (c. 1.4, MeOH); δ_H (500 MHz; $CDCl_3$) 7.24 (2H, d, *J* 8.6, Ar 3-H and Ar 5-H), 6.87 (2H, d, *J* 8.7, Ar 2-H and Ar 6-H), 3.80 (5H, m, OMe, benzyl CH_a and 2-H), 3.73 (1H, d, *J* 13.0, benzyl CH_b), 2.73 (1H, dd, *J* 12.1, 3.0, 1-H_a), 2.43 (1H, dd, *J* 12.0, 9.5, 2-Hb), 2.38 (2H, s (broad), NH and OH), 1.15 (3H, d, *J* 6.2, 3-H); δ_C (75 MHz; $CDCl_3$) 129.3 (Ar 2-C and Ar 6-C), 113.9 (Ar 3-C and Ar 5-C), 65.5 (2-C), 56.1 (1-C), 55.3 (OMe), 53.0 (CH_2 benzyl), 20.4 (3-C) [Ar 1-C and Ar 4-C were not observed]; ν_{max}/cm^{-1} (film) 3392, 2968, 1613, 1514, 1249; *m*/*z* (*ESI*) 196.1 (100%, MH^+); HRMS found MH^+, 196.1324. $C_{11}H_{17}NO_2$ requires *MH,* 196.1332.

(*S*)-2-(4-Methoxybenzylamino)-3-methylbutan-1-ol, 141



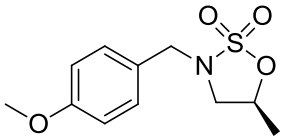
By general procedure **A**, (2*S*)-2-amino-3-methyl butanol (1.00 g, 6.1 mmol) gave the alcohol **141** (1.78 g, 8.00 mmol, 80%) as a light brown oil which required no further purification; R_f 0.39 (9:1 CH_2Cl_2–MeOH); $[\alpha]_D^{26}$: 0.5 (c. 1.1, MeOH); δ_H (500 MHz; $CDCl_3$) 7.25 (2H, d, *J* 8.6, Ar 2-H and Ar 6-H), 6.87 (2H, d, *J* 8.6, Ar 3-H and Ar 5-H), 3.80 (3H, s, OMe), 3.77 (1H, d, *J* 12.7, benzyl CH_a), 2.70 (1H, d, *J* 12.7, benzyl CH_b), 3.63 (1H, dd, *J* 10.5, 4.2, 1-H_a), 3.35 (1H, dd, *J* 15.6, 7.0, 1-H_b), 2.47 (1H, m, 2-H), 1.86 (1H, m, 3-H), 0.97 (3H, d, *J* 6.9, 4-H), 0.91 (3H, d, *J* 6.9, methyl); δ_C (75 MHz; $CDCl_3$) 129.9 (Ar 2-C and Ar 6-C), 114.0 (Ar 3-C and Ar 5-C), 63.8 (1-C), 60.1 (2-C), 55.3 (OMe), 50.6 (CH_2 benzyl), 28.6 (3-C), 19.6 (4-C), 18.4 (methyl) [Ar 1-C and Ar 4-C were not observed]; ν_{max}/cm^{-1} (film) 3367, 2957, 1612, 1513, 1248; *m*/*z* (*ESI*) 224.1 (100%, MH^+); HRMS found MH^+, 224.1645. $C_{13}H_{21}NO_2$ requires *MH,* 224.1645.

3-[(4-Methoxyphenyl)methyl]-1,2,3- oxathiazinane-2,2-dione, 144



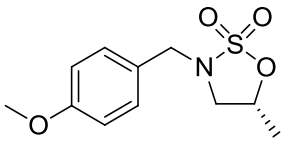
By general procedure **F**, alcohol **108** (1.00 g, 5.1 mmol) gave cyclic sulfamidate **144** (1.08 g, 4.20 mmol, 83%) as a light brow oil which solidified upon standing; R_f 0.67 (1:1, petrol–EtOAc); δ_H (500 MHz; $CDCl_3$) 7.26 (2H, d, *J* 8.6, Ar 2-H and Ar 6-H), 6.89 (2H, d, *J* 8.6, Ar3-H and Ar 5-H), 4.65 (2H, t, *J* 5.6, 6-H), 4.28 (2H, s, CH_2 benzyl), 3.81 (3H, s, OMe), 3.39 (2H, t, *J* 5.7, 4-H), 1.81 (2H, app. pent, *J* 5.7, 5-H); δ_C (75 MHz; $CDCl_3$) 159.6 (Ar 4-C), 130.1 (Ar 3-C and Ar 5-C), 126.8 (Ar 1-C), 114.2 (Ar 2-C and Ar 6-C), 73.2 (6-C), 55.3 (OMe), 51.8 (CH_2 benzyl), 46.7 (4-C), 20.2 (5-C); ν_{max}/cm^{-1} (film) 2963, 1614, 1514, 1300, 1243; *m/z* (*ESI*) 280.1 (100%, MNa^+); HRMS found MNa^+, 280.0630. $C_{11}H_{15}NO_4S$ requires *MNa,* 280.0614.

(5*S*)-3-[(4-Methoxyphenyl)methyl]-5-methyl- 1,2,3-oxathiazolidine-2,2-dione, 145



By general procedure **F**, alcohol **152** (1.00 g, 5.1 mmol) gave cyclic sulfamidate **145** (1.25 g, 4.80 mmol, 95%) as a light brow oil which solidified upon standing; R_f 0.69 (1:1, petrol–EtOAc); $[\alpha]_D^{26}$: -21.8 (c. 1.0, MeOH); δ_H (500 MHz; $CDCl_3$) 7.29 (2H, d, *J* 8.7, Ar 2-H and Ar 6-H), 6.90 (2H, d, *J* 8.7, Ar 3-H and Ar 5-H), 4.87 (1H, m, 5-H), 4.27 (1H, d, *J* 13.4, benzyl CH_a), 4.05 (1H, d, *J* 13.4, benzyl CH_b), 3.81 (3H, s, OMe), 3.40 (1H, dd, *J* 9.4, 6.1, 4-H_a), 3.03 (1H, dd, *J* 9.5, 8.0, 4-H_b), 1.49 (3H, d, *J* 6.3, CH_3); δ_C (75 MHz; $CDCl_3$) 159.7 (Ar 4-C), 130.1 (Ar 2-C and Ar 6-C), 126.3 (Ar 1-C), 114.2 (Ar 3-C and Ar 5-C), 76.6 (5-C), 55.3 (OMe), 53.6, 50.7, 19.4 (CH_3); ν_{max}/cm^{-1} (film) 2986, 1611, 1515, 1333, 1253; *m/z* (*ESI*) 280.1 (100%, MNa^+); HRMS found MNa^+, 280.0621. $C_{11}H_{15}NO_4S$ requires *MNa,* 280.0614.

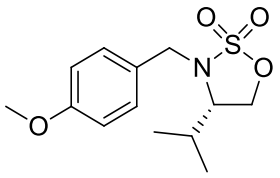
(5*R*)-3-[(4-Methoxyphenyl)methyl]-5-methyl- 1,2,3-oxathiazolidine-2,2-dione, 146



By general procedure **F**, alcohol **153** (1.00 g, 5.1 mmol) gave cyclic sulfamidate **146** (1.15 g, 4.50 mmol, 88%) as a light brow oil which solidified upon standing; R_f 0.72 (1:1, petrol–EtOAc); $[\alpha]_D^{26}$: 16.4 (c. 1.5, MeOH); δ_H (500 MHz; $CDCl_3$) 7.29 (2H, d, *J* 8.5, Ar 2-H and Ar 6-H), 6.90 (2H, d, *J* 8.7, Ar 3-H and Ar 5-H), 4.86 (1H, m, 5-H), 4.27 (1H, d, *J* 13.5, benzyl CH_a),

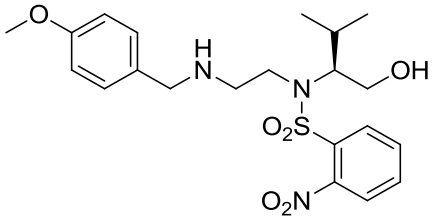
4.05 (1H, d, *J* 13.5, benzyl CH_b), 3.81 (3H, s, OMe), 3.40 (1H, dd, *J* 9.5, 6.1, 4-H_a), 3.02 (1H, dd, *J* 9.5, 8.0, 4-H_b), 1.49 (3H, d, *J* 6.3, CH_3); δ_C (75 MHz; $CDCl_3$) 130.1 (Ar 2-C and Ar 6-C), 126.4 (Ar 1-C), 114.3 (Ar 3-C and Ar 5-C), 76.8 (5-C), 55.3 (OMe), 53.6, 50.7, 19.4 (CH_3) [Ar 4-C was not observed]; ν_{max}/cm^{-1} (film) 2961, 1612, 1586, 1456, 1302; *m/z* (*ESI*) 280.1 (100%, MNa^+); HRMS found MNa^+, 280.0619. $C_{11}H_{15}NO_4S$ requires *MNa,* 280.0614.

(4*S*)-3-[(4-Methoxyphenyl)methyl]-4-(propan-2-yl)-1,2,3-oxathiazolidine-2,2-dione, 147



By general procedure **F**, alcohol **141** (1.60 g, 7.20 mmol) gave the cyclic sulfamidate **147** (1.81 g, 6.30 mmol, 89%) as a light brow oil which solidified upon standing; R_f 0.85 (9:1 CH_2Cl_2–MeOH); $[\alpha]_D^{26}$: -7.6 (c. 2.2, MeOH); δ_H (500 MHz; $CDCl_3$) 7.33 (2H, d, *J* 8.7, Ar 2-H and Ar 6-H), 6.89 (2H, d, *J* 8.7, Ar 3-H and Ar 5-H), 4.38 (1H, dd, *J* 8.9, 7.4, 5-H_a), 4.33 (1H, d, *J* 14.6, benzyl CH_a), 4.25 (1H, dd, *J* 8.9, 5.7, 5-H_b), 4.23 (1H, dd, *J* 14.6, benzyl CH_b), 3.81 (3H, s, OMe), 3.41 (1H, m, 4-H), 1.90 (1H, d sept., *J* 1.2, 5.6, propyl 2-H), 0.91 (3H, d, *J* 6.8, propyl 1-H), 0..87 (3H, d, *J* 7, propyl 3-H); δ_C (75 MHz; $CDCl_3$) 159.6 (Ar 4-C), 130.4 (Ar 2-C and Ar 6-C), 126.6 (Ar 1-C), 114.1 (Ar 3-C and Ar 5-C), 67.0 (5-C), 64.0 (4-C), 55.3 (OMe), 51.4 (CH_2 benzyl), 29.6 (2-C propyl), 18.2 (1-C propyl), 15.9 (3-C propyl); ν_{max}/cm^{-1} (film) 2965, 1613, 1515, 1346, 1185; *m/z* (*ESI*) 308.1 (100%, MNa^+); HRMS found MNa^+, 308.0932. $C_{13}H_{19}NO_4S$ requires *MNa,* 308.0927.

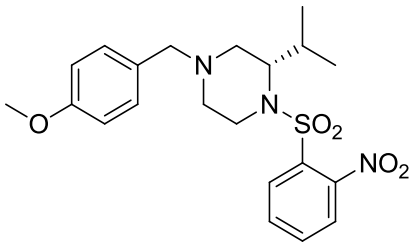
(2*S*)-1-Hydroxy-*N*-(2'-{[(4-methoxyphenyl)methyl]amino}ethyl)-3-methyl-*S*-(2'-nitrophenyl) butane-2-sulfonamide, 156



By general procedure **G**, cyclic sulfamidate 1**30** (219 mg, 0.9 mmol) and sulfonamide gave the sulfonamide **156** (294 mg, 0.7 mmol, 72%) as a light yellow oil; R_f 0.50 (9:1 CH_2Cl_2–MeOH); $[\alpha]_D^{24}$: 58.3 (c. 0.5, $CHCl_3$); δH (500 MHz; $CDCl_3$) 8.09 (1H, m, Ar 3'-H), 7.62 (2H, m, Ar 5'-H and Ar 6'-H), 7.47 (1H, m, Ar 4'-H), 7.14 (2H, d, *J* 8.5, Ar 2-H and Ar 6-H), 6.84 (2H, d, *J* 8.6, Ar 3-H and Ar 5-H), 3.91 (1H, m, 1-H_a), 3.84 (1H, m, 1-H_b), 3.80 (3H, s, OMe), 3.66-3.58 (4H, m, CH_2 benzyl and 1'-H), 3.26 (1H, ddd, *J* 15.8, 8.4, 4.4, 2-H), 3.03 (1H, ddd, *J* 13.2,

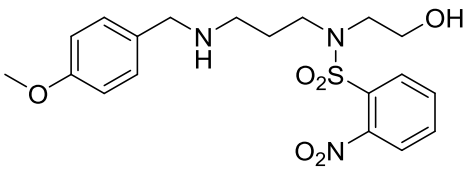
7.9, 4.0, 2'-H_a), 2.82 (1H, m, 2'-H_b), 1.93 (1H, m, 3-H), 1.64 (2H, s, NH and OH), 0.96 (3H, d, *J* 6.5, 4-H), 0.60 (3H, d, *J* 6.7, methyl); δ_C (75 MHz; $CDCl_3$) 133.4 (Ar 5-C′), 131.1 (Ar 4'-C), 129.7 (Ar 2-C and Ar 6-C), 124.2 (Ar 3'-C), 123.5 (Ar 6'-C), 114.1 (Ar 3-C and Ar 5-C), 61.5 (2-C), 55.3 (OMe), 54.2 (1-C), 52.7 (CH_2 benzyl), 52.0 (1'-C), 50.8 (2'-C), 27.2 (3-C), 20.1 (4-C), 19.9 (Me) [Quaternary Ar-C were not observed]; ν_{max}/cm^{-1}; 2964, 1611, 1544, 1513, 1344, 1249; *m/z* (*ESI*) 452.1 (100%, MH^+).

(*S*)-2-Isopropyl-4-(4-methoxybenzyl)-1-(2'-nitrophenylsulfonyl)piperazine, 172



By general procedure **C**, sulfonamide **156** (282 mg, 0.6 mmol) gave piperazine **172** (256 mg, 0.6 mmol, 95%) as a yellow oil; R_f 0.70 (1:1, petrol–EtOAc); $[\alpha]_D^{24}$: 13.8 (c. 0.6, $CHCl_3$); δ_H (500 MHz; $CDCl_3$) 8.03 (1H, m, Ar 3'-H), 7.66 (2H, m, Ar 5'-H and Ar 6'-H), 7.61 (1H, m, Ar 4'-H), 7.17 (2H, d, *J* 8.4, Ar 2-H and Ar 6-H), 6.83 (2H, d, *J* 8.5, Ar 3-H and Ar 5-H), 3.84 (1H, m, 2-H), 3.80 (3H, s, OMe), 3.44-3.40 (2H, m, benzyl CH_a and 6-H_a), 3.30 (1H, dt, *J* 15.5, 2.8, 6-H_b), 3.22 (1H, d, *J* 12.9, benzyl CH_b), 2.86 (1H, d, *J* 11.7, 3-H_a), 2.73 (1H, d, *J* 10.9, 5-H_a), 2.42 (1H, m, isopropyl CH), 2.00 (1H, dd, *J* 11.8, 3.4, 3-H_b), 1.95 (1H, dt, *J* 12.1, 3.3, 5-H_b), 0.76 (3H, d, *J* 6.5, methyl), 0.73 (3H, d, *J* 6.8, methyl); δ_C (75 MHz; $CDCl_3$) 158.8 (Ar 4-C), 147.6 (Ar 2-C′), 134.9 (Ar 1-C′), 133.2 9 (Ar 5-C′), 131.7 (Ar 6-C′), 130.0 (Ar 3-C and Ar 5-C), 124.1 (Ar 3-C′), 113.6 (Ar 2-C and Ar 6-C), 62.1, 61.4 (2-C), 55.3 (OMe), 53.2, 53.1, 42.1, 26.1 (isopropyl CH), 19.9 (Me), 19.5 (Me); ν_{max}/cm^{-1} (film) 2964, 1612, 1545, 1512, 1358, 1248; *m/z* (*ESI*) 434.2 (100%, MH^+); HRMS found MH^+, 434.1765. $C_{21}H_{27}N_3O_5S$ requires *MH,* 434.1765.

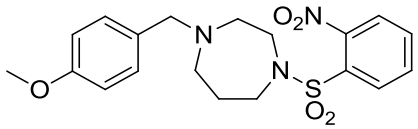
2-Hydroxy-*N*-(3'-{[(4-methoxyphenyl)methyl]amino}propyl)-*N*-(2'-nitrophenyl)ethane-1-sulfonamide, 157



By general procedure **G** (heating at 80 °C), cyclic sulfamidate **144** (206 mg, 0.8 mmol) and sulfonamide **131** gave **157** (165 mg, 0.4 mmol, 49%) as a light yellow oil; R_f 0.19 (9:1 CH_2Cl_2–MeOH); δ_H (500 MHz; $CDCl_3$) 7.96 (1H, dd, *J* 7.4, 1.4, Ar 3'-H), 7.68 (2H, m, Ar 5'-H

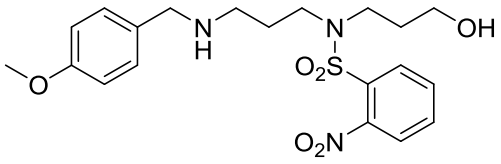
and Ar 6'-H), 7.60 (1H, dd, *J* 7.0, 1.8, Ar 4'-H), 7.22 (2H, d, *J* 8.7, Ar 2-H and Ar 6-H), 6.86 (2H, d, *J* 8.7, Ar 3-H and Ar 5-H), 3.79 (3H, s, OMe), 3.76 (2H, t, *J* 4.8, 2-H), 3.70 (2H, s, CH_2 benzyl), 3.43 (2H, t, *J* 6.6, 1'-H), 3.40 (2H, t, *J* 5.0, 1-H), 2.76 (2H, t, *J* 6.1, 3'-H), 1.88 (2H, pent, *J* 6.2, 2'-H); δ_C (75 MHz; $CDCl_3$) 158.8 (Ar 4-C), 148.4 (Ar 2'-C), 133.7 (Ar 1'-C), 132.0 (Ar 1-C), 131.6 (Ar 5'-C), 131.1 (Ar 4'-C), 130.8 (Ar 6'-C), 129.6 (Ar 2-C and Ar 6-C), 124.1 (Ar 3'-C), 113.9 (Ar 3-C and Ar 5-C), 61.5 (2-C), 55.3 (OMe), 53.4 (1-C), 52.6 (1'-C), 48.4 (CH_2 benzyl), 46.2 (3'-C), 28.5 (2'-C); ν_{max}/cm^{-1} (film) 2963, 1612, 1544, 1515, 1341, 1249; *m/z* (*ESI*) 424.1 (100%, MH^+).

1-(4-Methoxybenzyl)-4-(2'-nitrophenylsulfonyl)-1,4-diazepane, 170



By general procedure **C**, followed by purification by column chromatography, eluting with 50:1 CH_2Cl_2–MeOH, **157** (120 mg, 0.3 mmol) gave diazepane **170** (91 mg, 0.02 mmol, 80%) as a yellow oil; R_f 0.26 (1:1, petrol–EtOAc); δ_H (500 MHz; $CDCl_3$) 7.99 (1H, m, Ar H-'3), 7.67 (2H, m, Ar 5'-H and Ar 6-H), 7.60 (1H, m, Ar 4'-H), 7.22 (2H, d, *J* 8.6, Ar 2-H and Ar 6-H), 6.84 (2H, d, *J* 8.7, Ar 3-H and Ar 5-H), 3.80 (3H, s, OMe), 3.58 (2H, s, CH_2 benzyl), 3.49 (4H, m, 3-H and 5-H), 2.71 (4H, m, 2-H and 7-H), 1.89 (2H, m, 6-H); δ_C (75 MHz; $CDCl_3$) 133.3, 131.5, 130.8, 129.9 (Ar 2-C and Ar 6-C), 124.0, 113.7 (Ar 3-C and Ar 5-C), 61.5, 55.9, 55.3, 54.4, 47.2; ν_{max}/cm^{-1} (film); 3393, 1543, 1511, 1341, 1247, 1164; m/z (ES) 406.1 (MH^+); *m/z* (*ESI*) 406.1 (100%, MH^+); HRMS found MH^+, 406.1445. $C_{19}H_{23}N_3O_5S$ requires *MH,* 406.1431.

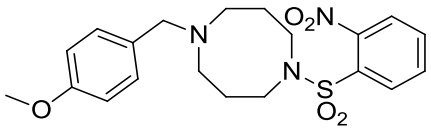
3-Hydroxy-*N*-(2'-{[(4-methoxyphenyl)methyl]amino}ethyl)-*N*-(2'-nitrophenyl)propane-1-sulfonamide, 158



By general procedure **G** (heating at 80 °C), cyclic sulfamidate **144** (206 mg, 0.8 mmol) and sulfonamide **151** gave **158** (209 mg, 0.5 mmol, 60%) as a light yellow oil; R_f 0.19 (9:1 CH_2Cl_2–MeOH); δ_H (500 MHz; $CDCl_3$) 7.98 (1H, dd, *J* 7.4, 2.0, Ar 3'-H), 7.66 (2H, m, Ar 5'-H and Ar H6'), 7.60 (1H, dd, *J* 7.7, 1.8, Ar 4'-H), 7.19 (2H, d, *J* 8.7, Ar 2-H and Ar 6-H), 6.85 (2H, d, *J* 8.7, Ar 3-H and Ar 6-H), 3.79 (3H, s, OMe), 3.65 (2H, s, CH_2 benzyl), 3.64 (2H, t, *J* 5.9, 3-H), 3.43 (2H, t, *J* 6.9, 1'-H), 3.38 (2H, t, *J* 7.4, 1'-H), 2.60 (2H, t, *J* 6.8, 3'-H), 2.12 (2H, s (broad), NH and OH), 1.76 (4H, m, H2 and H2'); δ_C (75 MHz; $CDCl_3$) 158.7 (Ar 4-C), 148.1

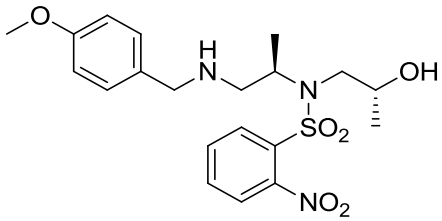
(Ar 2'-C), 133.5 (Ar 5'-C), 133.2 (Ar 1'-C), 131.9 (Ar 1'-C), 131.7 (Ar 4'-C), 130.6 (Ar 6'-C), 129.4 (Ar 2-C and Ar 6-C), 124.2 (Ar 3'-C), 113.8 (Ar 3-C and Ar 5-C), 58.9 (3-C), 55.3 (OMe), 53.3 (1'-C), 46.0 (CH_2 benzyl), 44.7 (1'-C), 31.0 (3'-C), 28.5 (2-C); ν_{max}/cm^{-1} (film) 2963, 1612, 1544, 1515, 1341, 1249; *m/z* (*ESI*) 438.2 (100%, MH^+).

1-(4-Methoxybenzyl)-5-(2'-nitrophenylsulfonyl)-1,5-diazocane, 179



By general procedure **C**, followed by purification by column chromatography, eluting with 50:1 CH_2Cl_2–MeOH, **158** (282 mg, 0.6 mmol) gave diazocane **179** (256 mg, 0.6 mmol, 95%) as a yellow oil; R_f 0.21 (1:1, petrol–EtOAc); δ_H (500 MHz; $CDCl_3$) 7.91 (1H, m, Ar 3'-H), 7.66 (2H, m, Ar 5'-H and Ar 6-H), 7.61 (1H, m, Ar 4'-H), 7.21 (2H, d, *J* 8.6, Ar 2-H and Ar 6-H), 6.84 (2H, d, *J* 8.6, Ar 3-H and Ar 5-H), 3.79 (3H, s, OMe), 3.60 (2H, s, CH_2 benzyl), 3.43 (4H, app. t, *J* 5.3), 2.66 (4H, t, *J* 6.3), 2.77 (4H, pent (broad), *J* 5.4); δ_C (75 MHz; $CDCl_3$) 158.6 (Ar 4-C), 113.1, 132.0, 131.4, 130.3, 130.1 (Ar 2-H and Ar 6-H), 124.1, 113.6 (Ar 3-H and Ar 5-H), 61.1 (OMe), 55.2 (CH_2 benzyl), 49.8, 49.5, 29.4; ν_{max}/cm^{-1} (film); 3399, 2933, 1611, 1543, 1371, 1246; *m/z* (*ESI*) 420.2 (100%, MH^+); HRMS found MH^+, 420.1602. $C_{20}H_{25}N_3O_5S$ requires *MH,* 420.1588.

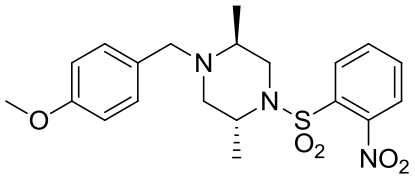
(2*R*)-2-Hydroxy-*N*-[(2'*R*)-1'-{[(4-methoxyphenyl)methyl]amino}propan-2-yl]-*S*-(2'-nitrophenyl) propane-1-sulfonamide, 160



By general procedure **G**, cyclic sulfamidate **145** (206 mg, 0.8 mmol) and sulfonamide **153** gave **160** (238 mg, 0.5 mmol, 68%) as a light yellow oil; R_f 0.45 (9:1 CH_2Cl_2–MeOH); $[\alpha]_D^{24}$: -48.5 (c. 3.1 $CHCl_3$); δ_H (500 MHz; $CDCl_3$) 8.02 (1H, m, Ar 3'-H), 7.65 (2H, m, Ar 5'-H and Ar 6'-H), 7.53 (1H, m, Ar 4'-H), 7.16 (2H, d, *J* 8.6, Ar 2-H and Ar 6-H), 6.86 (2H, d, *J* 8.7, Ar 3-H and Ar 5-H), 4.23 (1H, m, 2-H), 4.08 (1H, m, 2'-H), 3.80 (4H, m, OMe and 1-H_a), 3.75 (1H, d, *J* 13.0, benzyl CH_a), 3.57 (1H, d, *J* 13.0, benzyl CH_b), 3.55 (1H, dd, *J* 15.2, 1.7, 1-H_b), 2.76 (1H, dd, *J* 15.2, 9.9, 1'-H_a), 2.65 (2H, m, 1'-H_b and OH), 1.17 (3H, d, *J* 6.3, 3-H), 0.93 (3H, d, *J* 6.6, 3'-H); δ_C (75 MHz; $CDCl_3$) 158.9 (Ar 4-C), 133.7 (Ar 5'-C), 133.3 (Ar 2'-C), 131.6 (Ar 4'-C),

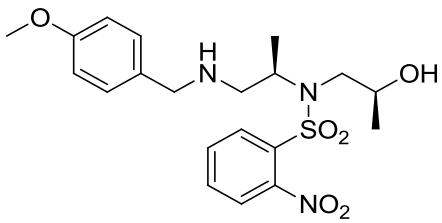
130.8 (Ar 6'-C), 130.5 (Ar 1'-C), 129.5 (Ar 2-C and Ar 6-C), 123.8 (Ar 3'-C), 114.0 (Ar 3-C and Ar 5-C), 66.9 (2-C), 55.3 (OMe), 52.8 (CH_2 benzyl), 52.0 (1-C), 51.7 (2-C), 51.3 (2'-C), 20.1 (3-C), 15.9 (3'-C) [Ar 1-C was not observed]; ν_{max}/cm^{-1} (film); 3313, 2973, 1612, 1545, 1347, 1249; *m/z* (*ESI*) 438.1 (100%, MH^+).

(2*S*,5*R*)-1-(4-Methoxybenzyl)-2,5-dimethyl-4-(2'-nitrophenylsulfonyl)piperazine, 173



By general procedure **C**, followed by purification by column chromatography, eluting with 50:1 CH_2Cl_2–MeOH, **160** (219 mg, 0.5 mmol) gave piperazine **173** (100 mg, 0.2 mmol, 48%) as a yellow oil; R_f 0.70 (1:1, petrol–EtOAc); $[\alpha]_D^{24}$: -82.7 (c. 1.9, $CHCl_3$); (500 MHz; $CDCl_3$) 8.03 (1H, m, Ar 3'-H), 7.69-7.62 (3H, m, Ar 4'-H, Ar 5'-H and Ar 6'-H), 7.23 (2H, d, *J* 8.4, Ar 2-H and Ar 6-H), 6.84 (2H, d, *J* 8.6, Ar 3-H and Ar 5-H), 4.05 (1H, s (broad), 5-H), 3.79 (3H, s, OMe), 3.60 (1H, d, *J* 13.1, 3-H_a), 3.52 (1H, d, *J* 13.3, benzyl CH_a), 3.43 (1H, d, *J* 13.2, benzyl CH_b), 3.37 (1H, d, *J* 13.4, 3-H_b), 2.96 (1H, s (broad), 2-H), 2.84 (1H, dd, *J* 11.8, 3.8, 6-H_a), 2.20 (1H, d, *J* 11.7, 6-H_b), 1.18 (3H, d, *J* 6.7, methyl 5-C), 0.91 (3H, d, *J* 6.4, methyl 2-C); δ_C (75 MHz; $CDCl_3$) 158.7 (Ar 4-C), 147.8 (Ar 2'-C), 134.2 (Ar 1'-C), 133.3 (Ar 5'-C), 132.0 (Ar 1-C), 131.6 (Ar 4'-C), 130.8 (Ar 6'-C), 129.6 (Ar 2-C and Ar 6-C), 124.2 (Ar 3'-C), 113.6 (Ar 3-C and Ar 4-C), 58.0 (3-C), 55.2 (5-C), 51.9 (OMe), 50.1 (6-C), 49.6 (CH_2 benzyl), 47.1 (C1), 15.9 (methyl), 7.5 (methyl); ν_{max}/cm^{-1} (film) 3383, 2974, 1612, 1544, 1372, 1248; *m/z* (*ESI*) 420.2 (100%, MH^+); HRMS found MH^+, 420.1601. $C_{20}H_{25}N_3O_5S$ requires *MH,* 420.1588.

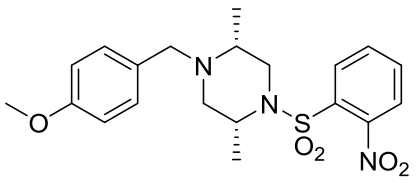
(2*S*)-2-Hydroxy-*N*-[(2'*R*)-1'-{[(4-methoxyphenyl)methyl]amino}propan-2-yl]-*S*-(2'-nitrophenyl) propane-1-sulfonamide, 161



By general procedure **G**, cyclic sulfamidate **145** (206 mg, 0.8 mmol) and sulfonamide **153** gave **161** (247 mg, 0.6 mmol, 71%) as a light yellow oil; R_f 0.50 (9:1 CH_2Cl_2–MeOH); $[\alpha]_D^{24}$: -11.5 (c. 3.2, $CHCl_3$); δ_H (500 MHz; $CDCl_3$) 8.02 (1H, m, Ar 3'-H), 7.65 (2H, m, Ar 5'-H and Ar 6'-H), 7.56 (1H, m, Ar 3'-H), 7.20 (2H, d, *J* 8.7, Ar 2-H and Ar 6-H), 6.85 (2H, d, *J* 8.7, Ar 3-H

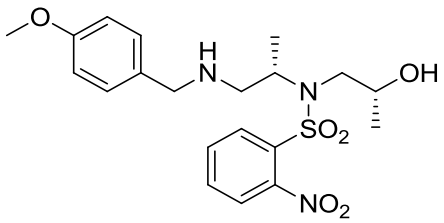
and Ar 5-H), 4.17 (1H, m, 2-H), 3.90 (1H, m, 2'-H), 3.81-3.75 (4H, m (broad), OMe, benzyl CH_a), 3.70 (1H, d, *J* 13.0, benzyl CH_b), 3.44 (1H, dd, *J* 14.8, 10.3, 1-H_a), 3.25 (1H, dd, *J* 14.8, 3.0, 1-H_b), 2.76 (1H, app. t, *J* 12.2, 1'-H_a), 2.68 (1H, dd, *J* 12.3, 5.9, 1'-H_b), 1.18 (3H, d, *J* 6.2, 3-H), 1.05 (3H, d, *J* 6.8, 3'-H); δ_C (75 MHz; $CDCl_3$) 158.9 (Ar 4-C), 134.1 (Ar 2'-C), 133.4 (Ar 5'-C), 131.5 (Ar 4'-C), 140.0 (Ar 6'-C), 130.7 (Ar 1'-C), 130.0 (Ar 1'-C), 129.5 (Ar 2-C and Ar 6-C), 124.0 (Ar 3'-C), 113.9 (Ar 3-C and Ar 5-C), 65.7 (2-C), 55.3 (OMe), 54.0 (CH_2 benzyl), 53.5 (1-C), 53.3 (1'-C), 52.8 (2'-C), 20.4 (3-C), 15.9 (3'-C); ν_{max}/cm^{-1} (film) 3316, 2935, 1611, 1544, 1249; *m/z* (*ESI*) 438.1 (100%, MH^+).

(2*R*,5*R*)-1-(4-Methoxybenzyl)-2,5-dimethyl-4-(2'-nitrophenylsulfonyl)piperazine, 176



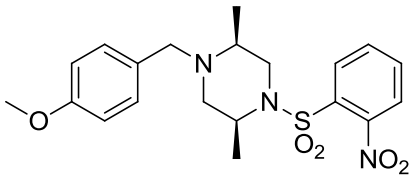
By general procedure **C**, followed by purification by column chromatography, eluting with 50:1 CH_2Cl_2–MeOH, **161** (208 mg, 0.5 mmol) gave piperazine **176** (82 mg, 0.2 mmol, 41%) as a yellow oil; R_f 0.78 (1:1, petrol–EtOAc); $[\alpha]_D^{24}$: -65.3 (c. 0.4, $CHCl_3$); δ_H (500 MHz; $CDCl_3$) 8.05 (1H, m, Ar 3'-H), 7.68-7.62 (3H, m, Ar 4'-H, Ar 5'-H and Ar 6'-H), 7.18 (2H, d, *J* 8.5, Ar 2-H and Ar 6-H), 6.83 (2H, d, *J* 8.7, Ar 3-H and Ar 5-H), 4.06 (1H, d, *J* 13.3, benzyl CH_a), 3.99 (1H, s (broad), 5-H), 3.79 (3H, s, OMe), 3.50 (1H, dd, *J* 12.3, 3.5, 3-H_a), 3.05 (1H, dd, *J* 13.3, 11.0, 3-H_b), 2.88 (1H, d, *J* 13.3, benzyl CH_b), 2.51 (1H, dd, *J* 11.7, 1.9, 6-H_a), 2.32 (1H, m, 2-H), 2.14 (1H, dd, *J* 11.6, 3.3, 6-H_b), 1.21 (3H, d, *J* 6.7, methyl), 1.16 (3H, d, *J* 6.1, methyl); δ_C (75 MHz; $CDCl_3$) 158.6 (Ar 4-C), 133.9 (Ar 2'-C), 133.3, 132.0, 131.7, 130.9, 130.8, 129.7 (Ar 2-C and Ar 6-C), 124.3, 113.7 (Ar 3-C and Ar 5-C), 56.4, 56.3, 56.2, 55.2, 50.2, 47.3, 17.5 (methyl), 15.8 (methyl); ν_{max}/cm^{-1} (film) 2937, 1611, 1544, 1512, 1373, 1249; *m/z* (*ESI*) 420.2 (100%, MH^+); HRMS found MH^+, 420.1607. $C_{20}H_{25}N_3O_5S$ requires *MH,* 420.1593.

(2*R*)-2-Hydroxy-*N*-[(2'*S*)-1'-{[(4-methoxyphenyl)methyl]amino}propan-2-yl]-*S*-(2'-nitrophenyl) propane-1-sulfonamide, 163



By general procedure **G**, cyclic sulfamidate **146** (206 mg, 0.8 mmol) and sulfonamide **153** gave **163** (265 mg, 0.6 mmol, 76%) as a light yellow oil; R_f 0.50 (9:1 CH_2Cl_2–MeOH); $[\alpha]_D^{24}$: 12.3 (c. 4.1 $CHCl_3$); δ_H (500 MHz; $CDCl_3$) 8.01 (1H, m, Ar 3'-H), 7.65 (2H, m, Ar 5'-H and Ar 6'-H), 7.55 (1H, m, Ar 4'-H), 7.20 (2H, d, *J* 8.7, Ar 2-H and Ar 6-H), 6.84 (2H, d, *J* 8.7, Ar 3-H and Ar 5-H), 4.17 (1H, m, 2-H), 3.90 (1H, m, 2'-H), 3.81-3.75 (4H, m (broad), OMe and benzyl CH_a), 3.70 (1H, d, *J* 13.0, benzyl CH_b), 3.44 (1H, dd, *J* 14.8, 10.3, 1-H_a), 3.25 (1H, dd, *J* 14.8, 3.0, 1-H_b), 2.76 (1H, app. t, *J* 12.3, 1'-H_a), 2.68 (1H, dd, *J* 12.3, 5.9, 1'-H_b), 1.18 (3H, d, *J* 6.2, 3-H), 1.05 (3H, d, *J* 6.9, 3'-H); δ_C (75 MHz; $CDCl_3$) 158.8 (Ar 4-C), 147.9 (Ar 2'-C), 134.1 (Ar 1'-C), 133.4 (Ar 5'-C), 131.6 (Ar 4'-C), 131.0 (Ar 4-C), 130.9 (Ar 6-C), 129.5 (Ar 2-C and Ar 6-C), 124.0 (Ar 3'-C), 113.9 (Ar 3-C and Ar 5-C), 65.7 (2-C), 55.3 (OMe), 53.9 (2'-C), 53.5 (CH_2 benzyl), 53.2 (1-C), 52.8 (1'-C), 20.3 (3-C), 15.9 (3'-C); ν_{max}/cm^{-1} (film) 3391, 2973, 1612, 1543, 1374, 1342, 1249; *m/z* (*ESI*) 438.2 (100%, MH^+).

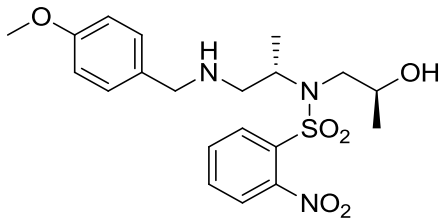
(2*S*,5*S*)-1-(4-Methoxybenzyl)-2,5-dimethyl-4-(2'-nitrophenylsulfonyl)piperazine, 174



By general procedure **C**, followed by purification by column chromatography, eluting with 50:1 CH_2Cl_2–MeOH, **163** (240 mg, 0.6 mmol) gave piperazine **174** (112 mg, 0.3 mmol, 48%) as a yellow oil; R_f 0.67 (1:1, petrol–EtOAc); $[\alpha]_D^{24}$: 64.8 (c. 0.3, $CHCl_3$); δ_H (500 MHz; $CDCl_3$) 8.04 (1H, m, Ar 3'-H), 7.70-7.62 (3H, m, Ar 4'-H, Ar 5'-H and Ar 6'-H), 7.18 (2H, d, *J* 8.5, Ar 2-H and Ar 6-H), 6.83 (2H, d, *J* 8.7, Ar 3-H and Ar 5-H), 4.05 (1H, d, *J* 13.2, benzyl CH_a), 3.99 (1H, m, 5-H), 3.79 (3H, s, OMe), 3.50 (1H, ddd, *J* 13.2, 3.4, 1.1, 3-H_a), 3.05 (1H, ddd, *J* 13.2, 10.9, 3-H_b), 2.88 (1H, d, *J* 13.2, benzyl CH_b), 2.51 (1H, dd, *J* 11.7, 1.9, 6-H_a), 2.32 (1H, m, 2-H), 2.14 (1H, dd, *J* 11.7, 3.6, 6-H_b), 1.21 (3H, d, *J* 6.7, methyl), 1.16 (3H, d, *J* 6.1, methyl); δ_C (75 MHz; $CDCl_3$) 158.6 (Ar 4-C), 133.9 (Ar 2'-C), 133.3, 132.0, 131.7, 130.8, 130.8, 129.7 (Ar 2-C and Ar 6-C), 124.3, 113.7 (Ar 3-C and Ar 5-C), 56.4, 56.3, 56.2, 55.2,

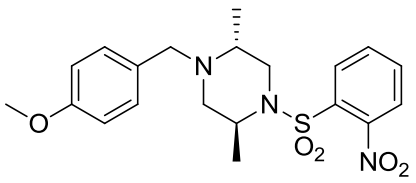
50.2, 47.3, 17.5 (methyl), 15.8 (methyl); ν_{max}/cm^{-1} (film) 2909, 2938, 1611, 1512, 1372, 1193; *m/z* (*ESI*) 420.2 (100%, MH^+); HRMS found MH^+, 420.1605. $C_{20}H_{25}N_3O_5S$ requires *MH,* 420.1588.

(2*S*)-2-Hydroxy-*N*-[(2'*S*)-1'-{[(4-methoxyphenyl)methyl]amino}propan-2-yl]-*S*-(2'-nitrophenyl) propane-1-sulfonamide, 164



By general procedure **G**, cyclic sulfamidate **148** (206 mg, 0.8 mmol) and sulfonamide **152** gave **164** (257 mg, 0.6 mmol, 74%) as a light yellow oil; R_f 0.63 (9:1 CH_2Cl_2–MeOH); $[\alpha]_D^{24}$: 47.6 (c. 4.1 $CHCl_3$); δ_H (500 MHz; $CDCl_3$) 8.01 (1H, m, Ar 3'-H), 7.64 (2H, m, Ar 5'-H and Ar 6'-H), 7.52 (1H, m, Ar 4'-H), 7.17 (2H, d, *J* 8.6, Ar 2-H and Ar 6-H), 6.86 (2H, d, *J* 8.7, Ar 3-H and Ar 6-H), 4.23 (1H, m, 2-H), 4.09 (1H, m, 2'-H), 3.80 (4H, m (broad), OMe and 1-H_a), 3.74 (1H, d, *J* 13.0, benzyl CH_a), 3.58 (1H, d, *J* 13.0, benzyl CH_b), 3.55 (1H, dd, *J* 15.4, 1.7, 1-H_b), 2.76 (1H, dd, *J* 15.2, 9.9, H1'-H_a), 2.65 (1H, m, 1'-H_b), 1.17 (3H, d, *J* 6.3, 3-H), 0.92 (3H, d, *J* 6.6, 3'-H); δ_C (75 MHz; $CDCl_3$) 158.9 (Ar 1-C), 148.2 (Ar 2'-C), 133.7 (Ar 5'-C), 133.3 (Ar 1'-C), 131.6 (Ar 6'-C), 130.8 (Ar 4'-C), 130.6 (Ar 1-C), 129.6 (Ar 2-C and Ar 6-C), 123.9 (Ar 3'-C), 114.0 (Ar 3-C and Ar 5-C), 66.9 (2-C), 55.3 (OMe), 52.8 (2'-C), 52.1 (CH_2 benzyl), 51.6 (1-C), 51.3 (C1-1'), 20.0 (3'-C), 15.9 (3'-C); ν_{max}/cm^{-1} (film) 2973, 1612, 1545, 1513, 1371, 1249; m/z (ES) 438.2 (MH^+).

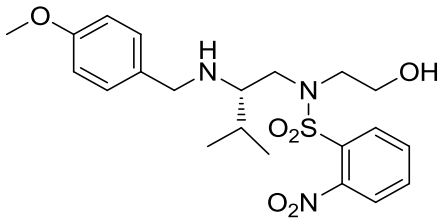
(2*R*,5*S*)-1-(4-Methoxybenzyl)-2,5-dimethyl-4-(2'-nitrophenylsulfonyl)piperazine, 177



By general procedure **C**, followed by purification by column chromatography, eluting with 50:1 CH_2Cl_2–MeOH, **164** (223 mg, 0.5 mmol) gave piperazine **177** (118 mg, 0.3 mmol, 55%) as a yellow oil; R_f 0.71 (1:1, petrol–EtOAc); $[\alpha]_D^{24}$: 94.9 (c. 0.4, $CHCl_3$); δ_H (500 MHz; $CDCl_3$) 8.03 (1H, m, Ar 3'-H), 7.69-7.62 (3H, m, Ar 4'-H, Ar 5'-H and Ar 6'-H), 7.23 (2H, d, *J* 8.4, Ar 2-H and Ar 6-H), 6.84 (2H, d, *J* 8.6, Ar 3-H and Ar 5-H), 4.05 (1H, m, 5-H), 3.79 (3H, s, OMe), 3.60 (1H, dd, *J* 12.9, 3.3, 3-H_a), 3.53 (1H, d, *J* 13.2, benzyl CH_a), 3.43 (1H, d, *J* 13.2, benzyl CH_b), 3.38 (1H, d, *J* 13.9, 3-H_b), 2.96 (1H, m, 2-H), 2.83 (1H, dd, *J* 11.8, 3.9, 6-H_a), 2.19

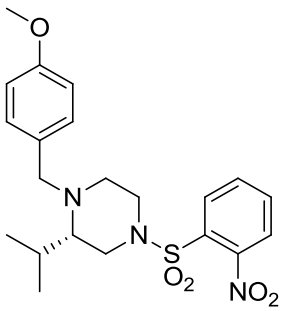
(1H, dd, *J* 11.8, 2.0, 6-H_b), 1.17 (3H, d, *J* 6.7, methyl), 0.91 (3H, d, *J* 6.6, methyl); δ_C (75 MHz; $CDCl_3$) 158.7 (Ar 4-C), 147.8 (Ar 2'-C), 134.2, 133.3, 132.0, 131.6, 130.7, 129.6 (Ar 2-C and Ar 6-C), 124.2, 113.7 (Ar 3-C and Ar 5-C), 57.9, 55.2, 51.9, 50.1, 49.6, 47.1, 15.9, 7.5; ν_{max}/cm^{-1} (film) 2973, 1544, 1512, 1372, 1248; *m/z* (*ESI*) 420.2 (100%, MH^+); HRMS found MH^+, 420.1588. $C_{20}H_{25}N_3O_5S$ requires *MH,* 420.1588.

2-Hydroxy-*N*-[(2'*S*)-2'-{[(4-methoxyphenyl)methyl]amino}-3-methylbutyl]-*S*-(2'-nitrophenyl) ethane-1-sulfonamide, 165



By general procedure **G**, cyclic sulfamidate **147** (257 mg, 0.9 mmol) and sulfonamide **131** gave **165** (306 mg, 0.7 mmol, 75%) as a light yellow oil; R_f 0.50 (9:1 CH_2Cl_2–MeOH); $[\alpha]_D^{24}$: 58.3 (c. 0.6, $CHCl_3$); δ_H (500 MHz; $CDCl_3$) 7.95 (1H, dd, *J* 7.2, 2.0, Ar 3'-H), 7.69 (2H, m, Ar 5'-H and Ar 6'-H), 7.60 (1H, dd, *J* 7.2, 1.7, Ar 4'-H), 7.27 (2H, d, *J* 8.5, Ar 2-H and Ar 6-H), 6.88 (2H, d, *J* 8.4, Ar 3-H and Ar 5-H), 3.90 (1H, ddd, *J* 12.4, 8.2, 2.4, 1-H_a), 3.86 (1H, d, *J* 12.4, benzyl CH_a), 3.83-3.80 (4H, m, OMe and benzyl CH_b), 3.74 (1H, ddd, *J* 12.6, 5.0, 2.4, 1-H_b), 3.67 (1H, ddd, *J* 14.4, 5.0, 2.4, 1'-H_a), 3.55 (1H, dd, *J* 14.1, 2.9, 1'-H_b), 3.16-3.10 (2H, m, 2-H), 3.07 (1H, m, 2'-H), 1.91 (1H, m, 3'-H), 1.60 (2H, s broad, NH and OH), 0.92 (3H, d, *J* 7, 4'-H), 0.89 (3H, d, *J* 6.9, methyl); δ_C (75 MHz; $CDCl_3$) 133.7 (Ar 5'-C), 131.6 (Ar 6'-C), 130.7 (Ar 4'-C), 129.9 (Ar 2-C and Ar 6-C), 124.2 (Ar 3'-C), 114.1 (Ar 3-C and Ar 5-C), 62.4 (2-C), 61.7 (3'-C), 55.3 (1-C), 54.8 (OMe), 52.7 (CH_2 benzyl), 52.0 (1'-C), 29.1 (3'-C), 18.5 (4'-C), 17.8 (methyl) [Quaternary Ar-C were not observed]; ν_{max}/cm^{-1} (film) 2965, 1606, 1543, 1513, 1346, 1250; m/z (ES) 452.1 (MH^+).

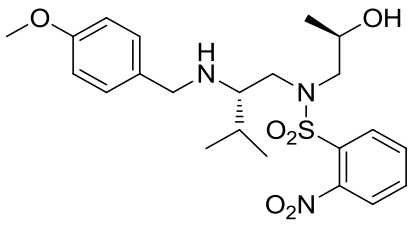
(*S*)-2-Isopropyl-1-(4-methoxybenzyl)-4-(2'-nitrophenylsulfonyl)piperazine, 171



By general procedure **C**, **165** (289 mg, 1.0 mmol) gave piperazine **171** (260 mg, 0.6 mmol, 96%) as a yellow oil; R_f 0.63 (1:1, petrol–EtOAc); $[\alpha]_D^{24}$: 19.2 (c. 0.4, $CHCl_3$); δ_H (500 MHz;

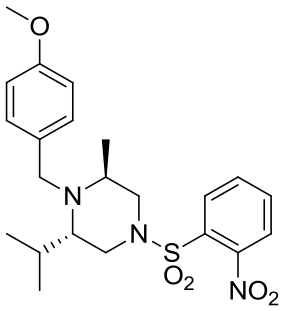
$CDCl_3$) 7.93 (1H, m, Ar 3'-H), 7.69 (2H, m, Ar 5'-H and Ar 6'-H), 7.61 (1H, m, Ar 4-H), 7.18 (2H, d, *J* 8.6, Ar 2-H and Ar 6-H), 6.83 (2H, d, *J* 8.6, Ar 3-H and Ar 5-H), 4.03 (1H, d, *J* 13.0, benzyl CH_a), 3.79 (3H, s, OMe), 3.61 (1H, dt, *J* 12.2, 2.7, 5-H_a), 3.47 (1H, m, 3-H_a), 3.06 (1H, d, *J* 13.0, benzyl CH_b), 2.86-2.79 (3H, m, 5-H_b, 3-H_b and 2-H), 2.36 (1H, m, isopropyl CH), 2.25-2.23 (1H, m, 6-H_a), 2.17 (1H, m, 6-H_b), 1.03 (3H, d, *J* 6.8, methyl), 0.95 (3H, d, *J* 6.8, methyl); δ_C (75 MHz, $CDCl_3$) 158.7 (Ar 4-C), 133.7 (Ar 5-C′), 131.4 (Ar 3-C′), 130.9 (Ar 6-C′), 129.9 (Ar 3-C and Ar 5-C), 124.0 (Ar 3-C′), 113.7 (Ar 2-C and Ar 6-C), 64.3 (2-C), 55.4, 55.3 (OMe), 49.7, 44.7, 44.4, 26.5 (isopropyl CH), 19.7 (Me), 16.2 (Me); ν_{max}/cm^{-1} (film) 2964, 1611, 1546, 1373, 1173 [Ar 1-C, Ar 1'-C and Ar 2'-C were not observed]; *m/z* (*ESI*) 434.2 (100%, MH^+); HRMS found MH^+, 434.1764. $C_{21}H_{27}N_3O_5S$ requires *MH,* 434.1744.

(2*R*)-2-Hydroxy-*N*-[(2'*S*)-2-{[(4-methoxyphenyl)methyl]amino}-3-methylbutyl]-*S*-(2'-nitrophenyl)propane-1-sulfonamide, 167



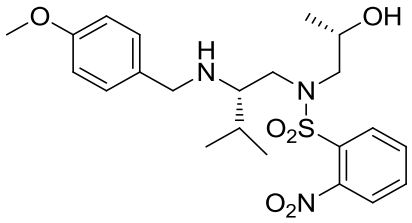
By general procedure **G**, cyclic sulfamidate **147** (228 mg, 0.8 mmol) and sulfonamide **153** gave **167** (323 mg, 0.7 mmol, 87%) as a light yellow oil; R_f 0.63 (9:1 CH_2Cl_2–MeOH); $[\alpha]_D^{24}$: 32.9 (c. 6.8, $CHCl_3$); δ_H (500 MHz; $CDCl_3$) 7.96 (1H, m, Ar 3'-H), 7.68 (2H, m, Ar 5'-H and Ar 6'-H), 7.56 (1H, m, Ar 4'-H), 7.25 (2H, d, *J* 8.7, Ar 2-H and Ar 6-H), 6.86 (2H, d, *J* 8.7, Ar 3-H and Ar 5-H), 4.04 (1H, m, 2-H), 3.79 (3H, s, OMe), 3.79 (1H, d, *J* 12.2, benzyl CH_a), 3.65 (1H, d, *J* 12.2, benzyl CH_b), 3.28-3.20 (3H, m, 1-H and 1'-H_a), 3.13 (1H, dd, *J* 14.3, 8.4, 1'-H_b), 2.96 (1H, m, 2'-H), 2.04 (1H, m, H3'), 1.18 (3H, d, *J* 6.3, 3-H), 0.95 (3H, d, *J* 7, 4'-H), 0.90 (3H, d, *J* 6.9, methyl); δ_C (75 MHz, $CDCl_3$) 158.8 (Ar 4-C), 148.6 (Ar 2'-C), 133.7 (Ar 5'-C), 131.6 (Ar 1'-C), 131.5 (Ar 1'-C), 131.4 (Ar 6'-C), 130.8 (Ar 4'-C), 129.7 (Ar 2-C and Ar 6-C), 124.0 (Ar 3'-C), 114.0 (Ar 3-C and Ar 5-C), 63.3 (2-C), 59.7 (2'-C), 57.8 (CH_2 benzyl), 55.3 (OMe), 50.4 (1-C), 50.1 (1'-C), 28.4 (3'-C), 20.1 (3-C), 19.0 (4'-C), 16.9 (methyl); ν_{max}/cm^{-1} (film) 2965, 1611, 1546, 1373, 1249; m/z (ES) 466.2 (MH^+).

(2*S*,6*S*)-2-*iso*Propyl-1-(4-methoxybenzyl)-6-methyl-4-(2'-nitrophenylsulfonyl)piperazine, 175



By general procedure **C**, followed by purification by column chromatography, eluting with 50:1 CH_2Cl_2–MeOH, **167** (280 mg, 0.6 mmol) gave piperazine **175** (123 mg, 0.3 mmol, 46%) as a yellow oil; R_f 0.78 (1:1, petrol–EtOAc); $[\alpha]_D^{24}$: -251.3 (c. 0.5, $CHCl_3$); δ_H (500 MHZ; $CDCl_3$) 7.93 (1H, m, Ar 3'-H), 7.70 (2H, m, Ar 5'-H and Ar 6'-H), 7.60 (1H, m, Ar 4'-H), 7.20 (2H, d, *J* 8.6, Ar 2-H and Ar 6-H), 6.83 (2H, d, *J* 8.7, Ar 3-H and Ar 5-H), 3.78 (3H, s, OMe), 3.67 (1H, d, *J* 13.6, benzyl CH_a), 3.53 (1H, d, *J* 13.6, benzyl CH_b), 3.44 (1H, dd, *J* 12.1, 3.0, 3-H_a), 3.14-3.05 (3H, m, 3-H_b and 5-H), 3.00 (1H, dd, *J* 12.0, 7.1, 2-H), 2.54 (1H, dt, *J* 7.2, 3.1, 6-H), 2.14 (1H, m, isopropyl CH), 1.07 (3H, d, *J* 6.6, Methyl), 0.95 (3H, d, *J* 6.8, Methyl), 0.87 (3H, d, *J* 6.7, Methyl); δ_C (75 MHz, $CDCl_3$) 158.6 (Ar 4-C), 148.5 (Ar 3'-C), 133.6, 133.6, 131.5, 131.2, 130.9, 129.4 (Ar 2-C and Ar 6-C), 124.0, 113.7 (Ar 3-C and Ar 5-C), 58.9, 55.3, 49.1, 48.3, 47.7, 42.3, 26.3, 19.8, 18.0, 13.2; ν_{max}/cm^{-1} (film) 2966, 1611, 1546, 1511, 1373, 1248; *m/z* (*ESI*) 448.1 (100%, MH^+); HRMS found MH^+, 448.1922. $C_{22}H_{29}N_3O_5S$ requires *MH,* 448.1901.

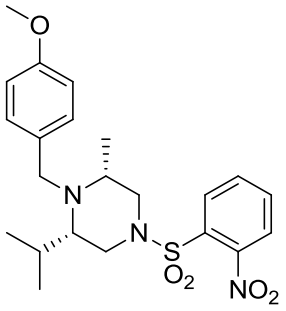
(2*S*)-2-Hydroxy-*N*-[(2'*S*)-2'-{[(4-methoxyphenyl)methyl]amino}-3-methylbutyl]-*S*-(2'-nitrophenyl)propane-1-sulfonamide, 168



By general procedure **G**, cyclic sulfamidate **147** (228 mg, 0.8 mmol) and sulfonamide **152** gave **168** (319 mg, 0.7 mmol, 86%) as a light yellow oil R_f 0.65 (9:1 CH_2Cl_2–MeOH); $[\alpha]_D^{24}$: 27.2 (c. 5.2, $CHCl_3$); δ_H (500 MHz; $CDCl_3$) 7.96 (1H, m, Ar 3'-H), 7.68 (2H, m, Ar 5'-H and Ar 6'-H), 7.56 (1H, m, Ar 4'-H), 7.25 (2H, d, *J* 8.7, Ar 2-H and Ar 6-H), 6.86 (2H, d, *J* 8.7, Ar 3-H and Ar 5-H), 4.04 (1H, m, 2-H), 3.79 (3H, s, OMe), 3.79 (1H, d, *J* 12.2, benzyl CH_a), 3.65 (1H, d, *J* 12.2, benzyl CH_b), 3.28-3.20 (3H, m, 1-H and 1'-H_a), 3.13 (1H, dd, *J* 14.3, 8.4, 1'-H_b), 2.96 (1H, m, 2'-H), 2.04 (1H, m, 3'-H), 1.18 (3H, d, *J* 6.3, 3-H), 0.95 (3H, d, *J* 7, 4'-H), 0.90 (3H, d, *J*

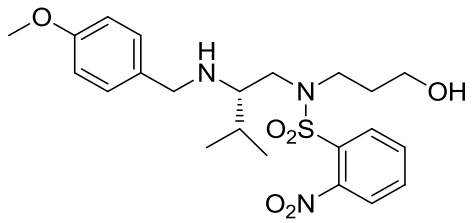
6.9, methyl); δ_C (75 MHz, $CDCl_3$) 158.8 (Ar 4-C), 148.6 (Ar 2'-C), 133.7 (Ar 5'-C), 131.6 (Ar 1'-C), 131.5 (Ar 1'-C), 131.4 (Ar 6'-C), 130.8 (Ar 4'-C), 129.7 (Ar 2-C and Ar 6-C), 124.0 (Ar 3'-C), 114.0 (Ar 3-C and Ar 5-C), 63.3 (2-C), 59.7 (2'-C), 57.8 (CH_2 benzyl), 55.3 (OMe), 50.4 (1-C), 50.1 (1'-C), 28.4 (3'-C), 20.1 (3-C), 19.0 (4'-C), 16.9 (methyl); ν_{max}/cm^{-1} (film) 3096, 2964, 1611, 1546, 1373, 1249; *m/z* (*ESI*) 466.2 (100%, MH^+).

(2*S*,6*R*)-2-*iso*Propyl-1-(4-methoxybenzyl)-6-methyl-4-(2'-nitrophenylsulfonyl)piperazine, 178



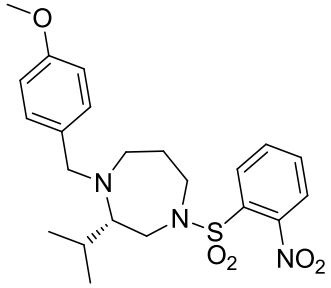
By general procedure **C**, followed by purification by column chromatography, eluting with 50:1 CH_2Cl_2–MeOH, **168** (280 mg, 0.6 mmol) gave piperazine **178** (126 mg, 0.3 mmol, 47%) as a yellow oil; R_f 0.72 (1:1, petrol–EtOAc); $[\alpha]_D^{24}$: 1.5 (c. 4, $CHCl_3$); δ_H (500 MHz; $CDCl_3$) 7.95 (1H, m, Ar 3-H), 7.70 (2H, m, Ar 4-H and Ar 6-H), 7.60 (1H, m, Ar 5-H), 7.20 (2H, d, *J* 8.6, Ar 2-H and Ar 6-H), 6.81 (2H, d, *J* 8.7 Ar 3-H and Ar 5-H), 3.78 (3H, s, OMe), 3.74 (1H, d, *J* 16.4 benzyl CH_a), 3.60 (1H, d, *J* 16.5, benzyl CH_b), 3.61 (1H, dt, *J* 11.9, 2.5, 5-H_a), 3.54 (1H, dt, *J* 11.9, 2.2, 3-H_a), 2.77 (1H, m, 6-H), 2.73 (1H, dd, *J* 12.0, 10.0, 5-H_b), 2.62 (1H, dd, *J* 12.0, 10.1, 3-H_b), 2.48 (1H, m, 1-H), 2.11 (1H, m, CH isopropyl), 1.10 (3H, d, *J* 6.3, Me), 0.94 (3H, d, *J* 6.9, Me (isopropyl)), 0.76 (3H, d, *J* 6.8, Me (isopropyl)); δ_C (75 MHz, $CDCl_3$) 158.3 (Ar 4-C), 148.6 (Ar 2'-C), 133.7, 132.3, 132.0, 131.5, 130.9, 128.9 (Ar 2-C and Ar 6-C), 124.0, 113.5 (Ar 3-C and Ar 5-C), 65.2, 55.4, 55.2, 52.7, 50.8, 44.8, 27.9 (CH isopropyl), 20.2 (Me), 19.0 (Me (isopropyl)), 16.6 (Me (isopropyl)); ν_{max}/cm^{-1} (film) 2965, 1610, 1546, 1511, 1373, 1246; *m/z* (*ESI*) 448.2 (100%, MH^+); HRMS found MH^+, 448.1922. $C_{22}H_{29}N_3O_5S$ requires *MH,* 448.1901.

3-Hydroxy-*N*-[(2'*S*)-2'-{[(4-methoxyphenyl)methyl]amino}-3-methylbutyl]-*S*-(2'-nitrophenyl) propane-1-sulfonamide, 169



By general procedure **G**, cyclic sulfamidate **147** (228 mg, 0.8 mmol) and sulfonamide **151** gave **169** (290 mg, 0.6 mmol, 78%) as a light yellow oil; R_f 0.50 (9:1 CH_2Cl_2–MeOH); $[\alpha]_D^{24}$: 10.4 (c. 0.3, $CHCl_3$); δ_H (500 MHz; $CDCl_3$) 8.02 (1H, m, Ar 3'-H), 7.62 (2H, m, Ar 5'-H and Ar 6'-H), 7.53 (1H, m, Ar 4'-H), 7.14 (2H, d, *J* 8.5, Ar 2-H and Ar 6-H), 6.82 (2H, d, *J* 8.6, Ar 3-H and Ar 5-H), 3.80 (3H, s, OMe), 3.71 (1H, d, *J* 12.7, benzyl CH_a), 3.63 (2H, app. t, *J* 5.8, 3-H), 3.57 (1H, d, *J* 12.8, benzyl CH_b), 3.55 (1H, m, 1-H_a), 3.34-3.26 (3H, m, 1-H_b and 1'-H), 2.66 (1H, m, 2'-H), 1.97 (1H, m, 3'-H), 1.72 (4H, m broad, 2-H, NH and OH), 0.90 (3H, d, *J* 4.1, 4-H), 0.89 (3H, d, *J* 4.1, methyl); δ_C (75 MHz, $CDCl_3$) 131.6 (Ar 4'-C), 131.0 (Ar 5'-C), 129.7 (Ar 2-C and Ar 6-C), 124.2 (Ar 3'-C), 113.8 (Ar 3-C and Ar 5-C), 59.2 (3-C), 55.3 (OMe), 48.5 (1-C), 30.7 (C1'), 27.9, 18.3 (4'-C), 17.1 (methyl) [Quaternary Ar-C were not observed]; ν_{max}/cm^{-1} (film) 3363, 2960, 1606, 1543, 1250; *m/z* (*ESI*) 466.2 (100%, MH^+).

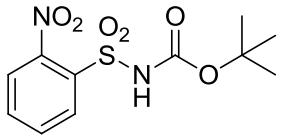
(*S*)-2-Isopropyl-1-(4-methoxybenzyl)-4-(2'-nitrophenylsulfonyl)-1,4-diazepane, 180



By general procedure **C**, followed by purification by column chromatography, eluting with 50:1 CH_2Cl_2–MeOH, **169** (270 mg, 0.6 mmol) gave the diazepane **180** (145 mg, 0.3 mmol, 56%) as a yellow oil; R_f 0.46 (1:1, petrol–EtOAc); $[\alpha]_D^{24}$: 15.4 (c. 1 $CHCl_3$); δ_H (500 MHz; $CDCl_3$) 7.99 (1H, m, Ar 2'-H), 7.69 (2H, m, Ar 5'-H and Ar 6-H), 7.62 (1H, m, Ar 4'-H), 7.27 (2H, d, *J* 8.6, Ar 2-H and Ar 6-H), 6.85 (2H, d, *J* 8.6, Ar 3-H and Ar 5-H), 3.93 (1H, d, *J* 13.8, benzyl CH_a), 3.80 (3H, s, OMe), 3.78 (1H, d, *J* 14.1 benzyl CH_b), 3.66 (1H, dd, *J* 14.3, 4.9, 3-H_a), 3.56 (1H, m, 5-H_a), 30 (1H, dd, *J* 14.2, 10.4, 3-H_b), 3.23 (1H, m, 5-H_b), 2.93 (1H, ddd, *J* 15.3, 8.7, 3.3, 7-H_a), 2.78 (1H, ddd, *J* 15.7, 7.9, 3.4, 7-H_b), 2.70 (1H, m, H2), 1.92 (1H, m, 6-H_a), 1.76 (1H, m, CH isopropyl), 1.65 (1H, m, 6-H_b), 1.02 (3H, d, *J* 6.7, methyl), 0.92 (3H, d, *J* 6.7, methyl); δ_C (75 MHz, $CDCl_3$) 133.3, 131.6, 130.6, 129.7 (Ar 2-C and Ar 6-C), 124.1,

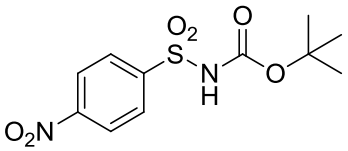
113.5 (Ar 3-C and Ar 5-C), 68.13, 55.3, 53.9, 51.6, 49.4, 47.6, 31.0, 26.2 (CH isopropyl), 20.5 (Me), 19.8 (Me) [Quaternary Ar-C were not observed]; ν_{max}/cm^{-1} (film) 3374, 2960, 1711, 1544, 1511, 1373, 1249; *m/z* (*ESI*) 448.2 (100%, MH^+); HRMS found MH^+, 448.1912. $C_{22}H_{29}N_3O_5S$ requires *MH,* 448.1901.

***tert*-Butyl-*N*-[(2-nitrobenzene)sulfonyl]carbamate, *o*-203**[100]



DMAP (10.0 mg, 0.08 mmol) was added to a stirred suspension of 2-nitrobenzenesulfonamide (5.00 g, 24.7 mmol) and Boc_2O (5.40 g, 24.7 mmol) and NEt_3 (5.00 mL, 35.9 mmol) in CH_2Cl_2 (25 mL) and the resulting solution stirred at rt for 16h. The reaction mixture was quenched with HCl (1 M aq. to pH<2), extracted with CH_2Cl_2 (2 × 20 mL), washed with brine (20 mL) dried ($MgSO_4$) and concentrated *in vacuo* . Purification by crystallisation, from toluene–EtOAc, gave the carbamate *o*-**203** (6.42 g, 21.3 mmol, 86%) as colourless plates; R_f 0.59 (1:1 petrol–EtOAc); δ_H (300 MHz, $CDCl_3$); 8.35 (1H, m, Ar 3-H), 7.87 (1H, m, Ar 6-H), 7.80 (2H, m, Ar 4-H and Ar 5-H), 1.43 (9H, s, *t*Bu); δ_C (75 MHz, $CDCl_3$); 134.7 (Ar 4-C), 133.3 (Ar 5-C), 132.5 (Ar 6-C), 125.1 (Ar 3-C), 84.9 (*t*Bu), 27.9 (*t*Bu); ν_{max}/cm^{-1} (solid); 3248, 2980, 1747, 1546, 1358, 1147; *m/z* (*ESI*) 325.0 (100%, MNa^+); HRMS found MNa^+, 325.0473. $C_{11}H_{14}N_2O_6S$ requires *MNa,* 325.0465.

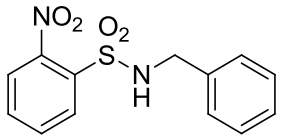
***tert*-Butyl-*N*-[(4-nitrobenzene)sulfonyl]carbamate, *p*-203**



DMAP (10.0 mg, 0.08 mmol) was added to a stirred suspension of 4-nitrobenzenesulfonamide (5.00 g, 24.7 mmol) and Boc_2O (5.40 g, 24.7 mmol) and NEt_3 (5.00 mL, 35.9 mmol) in CH_2Cl_2 (25 mL) and the resulting solution stirred at rt for 16h. The reaction mixture was quenched with HCl (1 M aq. to pH<2), extracted with CH_2Cl_2 (2 × 20 mL), washed with brine (20 mL) dried ($MgSO_4$) and concentrated *in vacuo* . Purification by crystallisation, from toluene–EtOAc, gave the carbamate *p*-**203** (5.68 g, 18.8 mmol, 76%) as colourless plates; R_f 0.68 (1:1 petrol–EtOAc); δ_H (300 MHz, $CDCl_3$); 8.41 (2H d, *J* 9.0, Ar 3-H and Ar 4-H), 8.25 (2H, d, *J* 9.0, Ar 2-H and Ar 6-H), 1.48 (9H, s, *t*Bu); δ_C (75 MHz, $CDCl_3$); 148.6 (Ar 4-C), 144.2 (Ar 1-C), 129.8 (Ar 2-C and Ar 6-C), 124.2 (Ar 3-C and Ar 5-

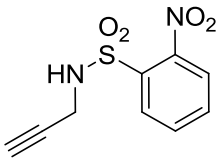
C), 85.2 (*t*Bu), 28.9 (*t*Bu); ν_{max}/cm^{-1} (film) 3253, 2982, 1748, 1545, 1361; *m*/*z* (*ESI*) 301.1 (100%, M^-).

_N_-Benzyl-2-nitrobenzene-1-sulfonamide, 221[107]



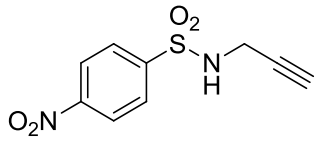
2-Nitrobenzenesulfonyl chloride (4.14 g, 18.7 mmol) was added to a stirred solution of benzylamine (2.04 mL, 18.7 mmol) and NEt_3 (7.80 mL, 56.0 mmol) in CH_2Cl_2 and the resulting solution was stirred at rt for 2 h. The reaxtion mixture was acidified with HCl (2M aq. soln, to pH<2), extracted with CH_2Cl_2 (3 × 20 mL), organics washed with brine and dried ($MgSO_4$) to give a crude product. Purification by column chromatography, gradient elution 9: to 1:1 petrol–EtOAc, gave the sulfonamide **221** (4.94 g, 16.9 mmol, 90%) as colourless oil which solidified upon standing; R_f 0.49 (1:1 petrol–EtOAc); δ_H (300 MHz, $CDCl_3$); 8.00 (1H, dd, *J* 7.3 and 1.9, Ar 3-H), 7.83 (1H, dd, *J* 7.5 and 1.7, Ar 6-H), 3.66 (2H, m, Ar 4-H and Ar 5-H), 7.22 (5H, m, Phenyl), 5.73 (1H, br t, *J* 6.9, NH), 4.32 (2H, d, *J* 6.3, CH_2); δ_C (75 MHz, $CDCl_3$); 135.6 (Ph 1-C), 134.0 (Ar-C), 133.4 (Ar 1-C), 132.8 (Ar 4-C), 131.1 (Ar 5-C), 128.7 (Ph 3-C and Ph 5-C), 128.1 (Ph 4-C), 127.9 (Ph 2-C and Ph 6-C), 125.3 (Ar 3-C), 47.9 (CH_2); ν_{max}/cm^{-1} (solid); 3031, 1539, 1362, 1219, 1167; *m*/*z* (*ESI*) 315.0 (100%, MNa^+); HRMS found MNa^+, 315.0422. $C_{13}H_{12}N_2O_4S$ requires *MNa,* 315.0410.

2-Nitro-_N_-(prop-2-yn-1-yl)benzene-1-sulfonamide, *o*-202[101]



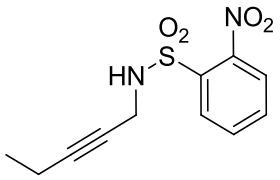
By general procedure **J**, propargyl alcohol (1.16 mL, 19.9 mmol) and sulfonamide *0*-**203** (6.63 g, 21.9 mmol) gave the sulfonamide *o*-**202** (4.21 g, 17.5 mmol, 88%) as a colourless solid; R_f 0.62 (1:1 petrol–EOAc); δ_H (300 MHz, $CDCl_3$); 8.26-8.16 (1H, m, Ar 3-H), 7.96-7.91 (1H, m, Ar 5-H), 7.81-7.73 (2H, m, Ar 4-H and 6-H), 5.71 (1H, br t, *J* 6.3, N-H), 4.03 (2H, dd, *J* 6.3 and 2.5, 1-H), 1.97 (1H, t, *J* 2.5, 3-H); δ_C (75 MHz, $CDCl_3$); 134.0 (Ar 1-C), 133.9 (Ar 4-C), 133.0 (Ar 5-C), 131.6 (Ar 6-C), 125.7 (Ar 3-C), 80.7 (2-C), 73.3 (3-C), 33.4 (1-C); ν_{max}/cm^{-1} (film); 3299, 2126, 1540, 1335; *m*/*z* (*ESI*) 241.8 (100%, MH^+).

4-Nitro-*N*-(prop-2-yn-1-yl)benzene-1-sulfonamide, *p*-202



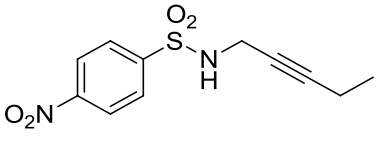
By general procedure **J**, propargyl alcohol (0.88 mL, 15.1 mmol) and sulfonamide *p*-**203** (5.00 g, 16.5 mmol) gave the sulfonamide *p*-**202** (3.16 g, 13.2 mmol, 87%) as a colourless solid; R_f 0.68 (1:1 petrol–EtOAc); δ_H (300 MHz, $CDCl_3$) 8.37 (2H, d, *J* 8.8, Ar 3-H and Ar 5-H), 8.10 (2H, d, *J* 8.8, Ar 2-H and Ar 6-H), 4.76 (1H, br s, N-H), 3.97 (2H, dd, *J* 7.2 and 2.5 , 1-H), 2.09 (1H, t, *J* 2.5, 3-H); δ_C (75 MHz, MeOD); 151.4 (Ar 4-C), 147.9 (Ar 1-C), 129.7 (Ar 2-C and 6), 125.1 (Ar 3-C and 5), 82.2 (3-C), 79.1 (2-C), 33.1 (1-C); ν_{max}/cm^{-1} (solid); 3275, 2978, 2121, 1607, 1537, 1350, 1069; *m/z* (*ESI*) 263.0 (100%, MNa^+); HRMS found MNa^+, 263.0105. $C_9H_8N_2O_4S$ requires *MNa,* 263.0097.

2-Nitro-*N*-(pent-2-yn-1-yl)benzene-1-sulfonamide, *o*-235



By general procedure **J**, 2-pentyn-1-ol (0.87 mL, 9.35 mmol) and sulfonamide *o*-**203** (4.26 g, 14.1 mmol) gave the sulfonamide *o*-**235** (2.17 g, 8.09 mmol, 82%) as a colourless solid; R_f 0.68 (1:1 petrol–EtOAc); δ_H (500 MHz, $CDCl_3$); 8.25-8.17 (1H, m, Ar 3-H), 7.94-7.89 (1H, m, 5-H), 7.80-7.72 (2H, m, Ar 4-H and 6-H), 5.61 (1H, br t, *J* 5.8, N-H), 3.97 (2H, dt, *J* 6.2 and 2.2, 1-H), 1.83 (2H, qt, *J* 7.5 and 2.2, 4-H), 0.82 (3H, t, *J* 7.5, 5-H), δ_C (75 MHz, $CDCl_3$); 147.9 (Ar 2-C), 134.3 (Ar 1-C), 133.6 (Ar 4-C), 132.9 (Ar 5-C), 131.7 (Ar 6-C), 125.4 (Ar 3-C), 87.3 (2-C), 72.9 (3-C), 34.0 (1-C), 13.4 (5-C), 12.0 (4-C), ν_{max}/cm^{-1} (film); 3347, 2979, 2238, 1542, 1362, 1168; *m/z* (*ESI*) 267.1 (100%, M^-).

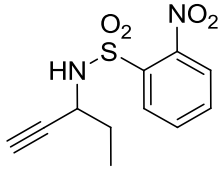
4-Nitro-*N*-(pent-2-yn-1-yl)benzene-1-sulfonamide, *p*-235



By general procedure **J**, 2-pentyn-1-ol (0.5 mL, 5.40 mmol) and sulfonamide *p*-**203** (1.80 g, 5.95 mmol) gave the sulfonamide *p*-**235** (1.42 g 5.31 mmol, 98%) as a colourless solid; R_f 0.73 (1:1 petrol–EtOAc); δ_H (300 MHz, $CDCl_3$); 8.38 (2H, d, *J* 9.0, Ar 3-H and Ar 5-H), 8.12 (2H, d, *J* 9.0, Ar 2-H and Ar 6-H), 4.85 (1H, t, *J* 6.0, NH), 3.92 (2H, dt, *J* 6.0 and 2.2, 1-H), 1.92

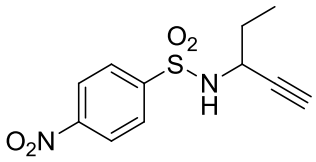
(2H, qt, *J* 7.5 and 2.3, 4-H), 0.91 (3H, t, *J* 7.5, 5-H); δ_C (75 MHz, $CDCl_3$); 150.1 (Ar 3-c), 146.0 (Ar 1-C), 128.8 (Ar 2-C and Ar 6-C), 124.2 (Ar 3-C and Ar 5-C), 87.5 (3-C), 72.9 (2-C), 33.5 (1-C), 13.4 (4-C), 12.1 (5-C); ν_{max}/cm^{-1} (film); 3255, 1605, 1531, 1348, 1160; *m*/*z* (*ESI*) 291.0 (100%, MNa^+); HRMS found MNa^+, 291.0410, $C_{11}H_{12}N_2O_4S$ requires *MNa*, 291.0410.

(±)-2-Nitro-*N*-(pent-1-yn-3-yl)benzene-1-sulfonamide, *o*-236



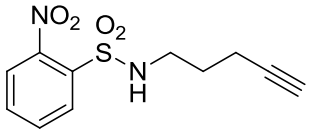
By general procedure **J**, 1-pentyn-3-ol (0.51 mL, 5.94 mmol) and sulfonamide *o*-**203** (2.70 g, 8.93 mmol) gave the sulfonamide *o*-**236** (1.29 g, 4.81 mmol, 81%) as a colourless solid; R_f 0.62 (1:1 petrol–EtOAc); δ_H (500 MHz, $CDCl_3$); 8.24-8.17 (1H, m, Ar 3-H), 7.95-7.89 (1H, m, Ar 5-H), 7.78-7.71 (2H, m, Ar 4-H and 6-H), 5.61 (1H, br d, *J* 9.5, N-H), 4.16 (1H, dtd, *J* 9.4, 6.9 and 2.2, 3-H), 1.96 (1H, d, *J* 2.2, 1-H), 1.86-1.72 (2H, m, 4-H), 1.05 (3H, t, *J* 7.4, 5-H); δ_C (75 MHz, $CDCl_3$); 133.7 (Ar 4-C), 132.9 (Ar 5-C), 131.6 (Ar 6-C), 125.5 (Ar 3-C), 80.7 (1-C), 73.0 (2-C), 47.5 (3-C), 29.6 (4-C), 9.8 (5-C) [Ar 1-C and Ar 2-C were not observed]; ν_{max}/cm^{-1} (film); 3292, 2122, 1541, 1354, 1172; *m*/*z* (*ESI*) 267.0 (100%, M^-).

(±)-4-Nitro-*N*-(pent-1-yn-3-yl)benzene-1-sulfonamide, *p*-236



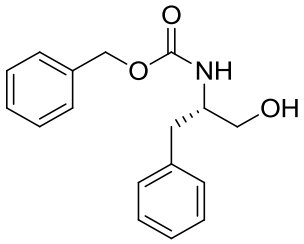
By general procedure **J**, 1-pentyn-3-ol (0.47 mL, 5.45 mmol) and sulfonamide *p*-**203** (1.80 g, 5.95 mmol) gave the sulfonamide *p*-**236** (1.21 g, 4.50 mmol, 83%) as a colourless solid; R_f 0.76 (1:1 petrol–EtOAc); δ_H (300 MHz, $CDCl_3$); 8.37 (2H, d, *J* 8.8, Ar 3-H and Ar 5-H), 8.10 (2H, d, *J* 8.8, Ar 2-H and Ar 6-H), 4.37 (1H, d, *J* 9.1, N-H), 4.10 (1H, m, 3-H), 2.08 (1H, d, *J* 2.3, 1-H), 1.36 (2H, m, 4-H), 1.03 (3H, t, *J* 7.4, 5-H); δ_C (75 MHz, $CDCl_3$); 128.7 (Ar 2-C and Ar 6-C), 124.2 (Ar 3-C and Ar 5-C), 80.92 (1-C), 41.2 (3-C), 29.9 (4-C), 9.8 (5-C) [Ar 1-C and Ar 4-C were not observed]; ν_{max}/cm^{-1} (solid); 3275, 2984, 2345, 1519, 1167; *m*/*z* (*ESI*) 291.0 (100%, MNa^+); (Found MNa^+, 291.0419. $C_{11}H_{12}N_2O_4S$ requires *MNa,* 291.0410).

2-Nitro-*N*-(pent-4-yn-1-yl)benzene-1-sulfonamide, *o*-237



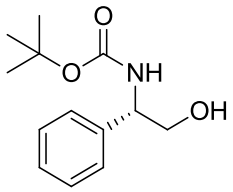
By general procedure **J**, 4-pentyn-1-ol (0.70 mL, 7.52 mmol) and sulfonamide *o*-**203** (3.39 g, 11.2 mmol) gave the sulfonamide o-**237** (1.70 g, 6.32 mmol, 84%) as a colourless oil; R_f 0.27 (7:3 petrol–EtOAc); δ_H (500 MHz, $CDCl_3$); 8.19-8.12 (1H, m, Ar 3-H), 7.91-7.83 (1H, m, Ar 6-H), 7.79-7.71 (2H, m, Ar 4-H and 5-H), 5.43 (1H, br t, *J* 5.5, N-H), 3.26 (2H, q, *J* 6.7, 1-H), 2.27 (2H, td, *J* 6.8 and 2.7, 3-H), 1.96 (1H, t, *J* 2.7, 5-H), 1.78 (2H, pentet, *J* 6.8, 2-H); δ_C (75 MHz, $CDCl_3$); 148.1 (Ar 2-C), 133.8 (Ar 1-C), 133.6 (Ar 4-C), 132.8 (Ar 5-C), 131.1 (Ar 6-C), 125.4 (Ar 1-C), 82.5 (4-C), 69.7 (5-C), 42.7 (1-C), 28.2 (2-C), 15.7 (3-C); ν_{max}/cm^{-1} (film) 3297, 2346, 1541, 1364, 1341, 1165; *m*/*z* (*ESI*) 291.3 (100%, MNa^+).

Benzyl *N*-[(2*S*)-1-hydroxy-3-phenylpropan-2-yl]carbamate, 247



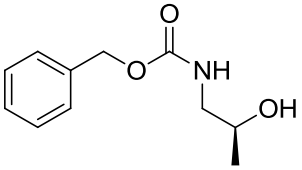
By general procedure **H**, (*S*)-2-amino-3-phenyl-1-propanol (1.0 g, 6.6 mmol), gave the carbamate **247** (1.7 g, 6.2 mmol, 93%) as a colourless oil which solidified on standing; R_f 0.44 (1:1 petrol–EtOAc); $[\alpha]_D^{19}$ −28.5 (c 1.0, $CHCl_3$); δ_H (500 MHz, $CHCl_3$); 7.35-7.18 (10H, m, Benzyl-H and Phenyl-H), 5.06 (3H, br s, N-H and Benzyl-H), 3.94 (1H, m, 2-H), 3.68 (1H, br m, 1-H_a), 3.57 (1H, br m, 1-H_b), 2.85 (2H, d, *J* 6.7, 3-H), 2.34 (1H, br s, O-H); δ_C (75 MHz, $CHCl_3$); 156.5 (Carbonyl-C), 137.7 (Phenyl 1-C), 136.3 (Benzyl 1-C), 129.3 (Phenyl 2-C and Phenyl 6-C), 128.6 (Phenyl 3-C and Phenyl 5-C), 128.6 (Benzyl Ar 2-C and Benzyl Ar 6-C), 128.2 (Benzyl Ar 3-C and Benzyl Ar 5-C), 128.1 (Benzyl Ar 4-C), 126.7 (Phenyl 4-C), 66.9 (Benzyl-C), 64.0 (1-C), 54.1 (2-C), 37.3 (3-C); ν_{max}/cm^{-1} (film); 3366, 2880, 1691, 1542, 1454, 1262, 1019; *m*/*z* (*ESI*) 308.1 (100%, MNa^+); HRMS found MNa^+, 308.1270. $C_{17}H_{19}NO_3$ requires *MNa,* 308.1257.

***tert*-Butyl-*N*-[(1*S*)-2-hydroxy-1-phenylethyl]carbamate, 246**



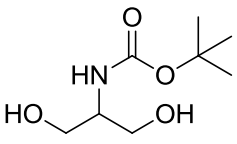
By general procedure **I**, (2*S*)-2-amino-2-phenylethanol (2.00 g, 14.6 mmol), gave the carbamate **246** (3.18 g, 13.4 mmol, 92%) as a colourless soild; R_f 0.50 (1:1 petrol–EtOAc); $[\alpha]_D^{19}$ +39.6 (c 0.5, $CHCl_3$); δ_H (300 MHz, $CDCl_3$); 7.39- 7.26 (5H, m, Ar-H), 5.19 (1H, br s, N-H), 4.77 (1H, br m, 1-H), 3.85 (2H, br m, 2-H), 2.25 (1H, br s, O-H), 1.43 (9H, s, *t*Bu-H); δ_C (75 MHz, $CDCl_3$); 128.8 (Ar 3-C and Ar 5-C), 127.8 (Ar 4-C), 126.6 (Ar 2-C and Ar 6-C), 80.1 (*t*Bu-C), 67.1 (2-C), 56.9 (1-C), 28.3 (*t*Bu-C) [Ar 1-C was not observed]; ν_{max}/cm^{-1} (solid); 3312, 3248, 2977, 1672, 1555, 1367, 1219; *m*/*z* (*ESI*) 260.1 (100%, MNa^+); HRMS found MNa^+, 260.1263. $C_{13}H_{19}NO_3$ requires *MNa,* 260.1257.

Benzyl-*N*-[(2*S*)-2-hydroxypropyl]carbamate, 248



By general procedure **H**, (2*S*)-1-amino-2-propanol (500 mg, 6.66 mmol), gave the carbamate **248** (1.32 g, 6.28 mmol, 95%) as a colourless oil; R_f 0.26 (1:1 petrol–EtOAc); $[\alpha]_D^{19}$ +21.5 (c 0.5, $CHCl_3$); δ_H (500 MHz, $CDCl_3$); 7.36-7.26 (5H, m, Benzyl Ar-H), 5.15 (1H, br s, N-H), 5.11 (2H, s, Benzyl-H), 3.93 (1H, m, 2-H), 3.36 (1H, m, 1-H_a), 3.07 (1H, dd, *J* 13.4 and 6.0 , 1-H_b), 2.10 (1H, s, O-H), 1.20 (3H, d, *J* 6.2, 3-H); δ_C (75 MHz, $CDCl_3$); 136.4 (benzyl Ar 1-C), 128.6 (benzyl Ar 3-C and benzyl Ar 5-C), 128.2 (benzyl Ar 2-C and benzyl Ar 6-C), 128.2 (benzyl Ar 4-C), 67.5 (2-C), 66.9 (benzyl-C), 48.3 (1-C), 20.7 (3-C); ν_{max}/cm^{-1} (film); 3308, 1681, 1526, 1261, 1150; *m*/*z* (*ESI*) 232.1 (100%, MNa^+); HRMS found MNa^+, 232.0946. $C_{11}H_{15}NO_3$ requires *MNa,* 232.0944).

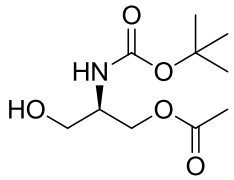
***tert*-Butyl-*N*-(1,3-dihydroxypropan-2-yl)carbamate, 258**[87]



By general procedure **I**, 2-amino-1,3-propanediol (4.00 g, 43.9 mmol), gave the carbamate **258** (7.46 g, 39.0 mmol, 89%) as a colourless solid; R_f 0.12 (1:1 petrol–EtOAc); δ_H (300

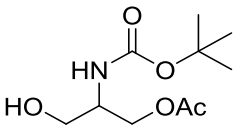
MHz, $CDCl_3$); 5.32 (1H, d, *J* 7.5, N-H), 3.85-3.65 (5H, m, 1-H, 2-H and 3-H), 2.97 (2H, br s, 2 × O-H), 1.45 (9H, s, *t*Bu-H); δ_C (75 MHz, $CDCl_3$); 154.0 (carbamate-C), 80.2 (*t*Bu-C), 63.5 (1-C and 3-C), 53.0 (2-C), 28.4 (*t*Bu-C); ν_{max}/cm^{-1} (film);3324, 2943, 1686, 1536, 1366, 1171; *m/z* (*ESI*) 214.1 (100%, MNa^+); HRMS found MNa^+, 214.1050. $C_8H_{17}NO_4$ requires *MNa,* 214.1050.

(2*R*)-2-{[(*tert*-Butoxy)carbonyl]amino}-3-hydroxypropyl acetate, 259[87]



Porcine pancreatic lipase (*PPL*, 2.93 g) was added to a solution of the carbamate **258** (4.00 g, 20.9 mmol) in vinyl acetate (100 mL) and the resulting suspension was stirred at rt for 2 h. The reaction mixture was filtered and the filtrate concentrated *in vacuo* to give a crude product. Purification by column chromatography, eluting with 1:1 petrol–EtOAc, gave the acetate **259** (4.80 g, 20.6 mmol, 98%) as a colourless oil; R_f 0.38 (1:1 petrol–EtOAc); $[\alpha]_D^{19}$ +4.8 (c 0.4, $CHCl_3$); δ_H (300 MHz, $CDCl_3$); 4.98 (1H, br d, *J* 7.8, N-H), 4.20 (2H, d, *J* 5.7, 1-H), 3.89 (1H, m, 2-H), 3.66 (2H, m, 3-H), 2.52 (1H, br s, O-H), 2.10 (3H, s, acetate-H), 1.45 (9H, s, *t*Bu-H); δ_C (75 MHz, $CDCl_3$); 171.5 (acetate), 80.2 (*t*Bu-C), 63.0 (1-C), 62.0 (3-C), 51.0 (2-C), 28.3 (*t*Bu-C), 20.9 (acetate-C); ν_{max}/cm^{-1} (film); 3374, 2979, 1693, 1525, 1376, 1244, 1170; *m/z* (*ESI*) 256.1 (100%, MNa^+); HRMS found MNa^+, 256.1165. $C_{10}H_{19}NO_5$ requires *MNa,* 256.1155.

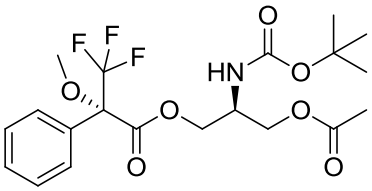
(±)-2-{[(*tert*-Butoxy)carbonyl]amino}-3-hydroxypropyl acetate, 259-rac



Acetic anhydride (0.11 mL, 1.16 mmol) was added dropwise to a solution of the carbamate **258** (191 mg, 1.00 mmol) and triethylamine (0.28 mL, 2.01 mmol) in CH_2Cl_2 (10 mL) at 0 °C and the resulting solution stirred for 2 h. The reaction mixture was warmed to rt, quenched by the addition of HCl (1 M aq., to pH <2), extracted with CH_2Cl_2 (3 × 10 mL), combined organics washed with brine (20 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give a crude product. Purification by column chromatography, elution with 6:4 petrol–EtOAc, gave the acetate **259**-rac (112 mg, 0.48 mmol, 48%) as a colourless oil; R_f 0.38 (1:1 petrol–EtOAc); δ_H (300 MHz, $CDCl_3$); 4.98 (1H, br d, *J* 7.8, N-H), 4.20 (2H, d, *J* 5.7, 1-H), 3.89 (1H, m, 2-H), 3.66 (2H, m, 3-H), 2.52 (1H, br s, O-H), 2.10 (3H, s, acetate-H), 1.45 (9H, s,

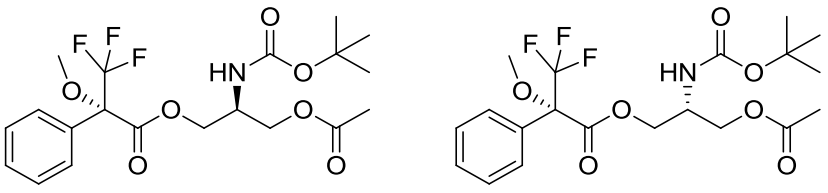
*t*Bu-H); δ_C (75 MHz, $CDCl_3$); 171.5 (acetate carbonyl-C), 80.2 (*t*Bu-C), 63.0 (1-C), 62.0 (3-C), 51.0 (2-C), 28.3 (*t*Bu-C), 20.9 (acetate-C); ν_{max}/cm^{-1} 3372, 2978, 1695, 1525, 1376, 1243, 1170; *m/z* (*ESI*) 256.1 (100%, MNa^+); HRMS found MNa^+, 256.1165. $C_{10}H_{19}NO_5$ requires *MNa,* 256.1155.

(2*S*)-3-(Acetyloxy)-2-{[(*tert*-butoxy)carbonyl]amino}propyl-(2'*S*)-3',3',3'-trifluoro-2'-methoxy-2'-phenylpropanoate, 260



(+)-MTPA chloride (37μL, 0.19 mmol) was added to a stirred solution of acetate **259** (23 mg, 0. 9 mmol), triethylamine (28 μL, 2.0 mmol) and DMAP (1.0 mg, 8.0 mmol) in CH_2Cl_2 (2 mL) at 0 °C and the resulting solution stirred for 1 h. The reaction mixture was concentrated *in vacuo* to give a crude product. Purification by column chromatography, eluting with 7:3 petrol–EtOAc, gave the ester **260** (33 mg, 0.7 mg, 75%) as a colorless oil; R_f 0.85 (1:1 petrol–EtOAc); δ_H (500 MHz, $CDCl_3$); 7.50-7.49 (2H, m, phenyl 3-H and phenyl 5-H), 7.43-7.40 (3H, m, phenyl 2-H, phenyl 4-H and phenyl 6-H), 7.60 (1H, br d, *J* 8.3, N-H), 4.39 (2H, d, *J* 5.1, 3-H), 4.20 (1H, m, 2-H), 4.10 (1H, dd, *J* 11.4 and 5.1, 1-H_a), 4.05 (1H, dd, *J* 11.4 and 5.5, 1-H_b), 3.54 (3H, s, OMe-H), 2.05 (3H, s, acetate-H), 1.43 (9H, s, *t*Bu -H); δ_C (75 MHz, $CDCl_3$); 170.6 (acetate carbonyl-C), 166.3 (1'-C), 154.9 (*t*Bu carbonyl-C), 131.9 (phenyl 1-C), 129.8 (ester-C), 128.6 (phenyl 2-C and phenyl 6-C), 127.2 (phenyl 3-C and phenyl 5-C), 125.1 (phenyl 4-C), 125.1 (q, $^1J_{C\text{-}F}$ 288, 3'-C), 80.3 (*t*Bu-C), 64.5 (1-C), 63.0 (3-C), 55.5 (OMe-C), 48.2 (2-C), 28.3 (*t*Bu-C), 20.7 (acetate-C); ν_{max}/cm^{-1} (film); 3363, 2979, 1751, 1717, 1513, 1237, 1169; *m/z* (*ESI*) 472.2 (100%, MNa); HRMS found MNa^+, 472.1569, $C_{20}H_{26}F_3NO_7$ requires *MNa*, 472.1554.

3-(Acetyloxy)-2-{[(*tert*-butoxy)carbonyl]amino}propyl(2'S)-3',3',3'-trifluoro-2'-methoxy-2'-phenylpropanoate, 260-rac

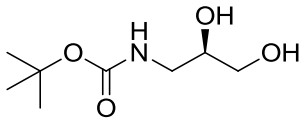


D1 D2

(+)-MTPA chloride (37μL, 0.19 mmol) was added to a stirred solution of acetate **259**-rac (23 mg, 0. 9 mmol), triethylamine (28 μL, 2.0 mmol) and DMAP (1.0 mg, 8.0 mmol) in

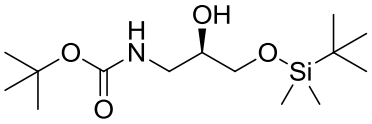
CH_2Cl_2 (2 mL) at 0 °C and the resulting solution stirred for 1 h. The reaction mixture was concentrated *in vacuo* to give a crude product. Purification by column chromatography, eluting with 7:3 petrol–EtOAc, gave the ester **260**-rac (33 mg, 0.7 mmol, 75%, 1:1 mixture of diasteroisomers) as a colorless oil; R_f 0.85 (1:1 petrol–EtOAc); δ_H (500 MHz, $CDCl_3$) 7.55-7.45 (4H, m, D1 and D2 Ar 2-H and 6), 7.46-7.36 (6H, m, D1 and D2 Ar 3-H, 4 and 5), 4.73 (1H, d, *J* 8.2, D2 NH), 4.69 (1H, d, *J* 8.5, D1 NH), 4.44 (1H, dd, *J* 11.2 and 5.0, D2 3-H_a), 4.38 (2H, app. d, *J* 5.1, D1 3-H), 4.33 (1H, dd, *J* 10.9 and 5.3, D2 3-H_b), 4.20-4.19 (2H, m, D1 and D2 2-H), 4.13-4.01 (4H, m, D1 and D2 1-H), 3.54 (3H, d, *J* 0.8, D1 OMe), 3.53 (3H, d, *J* 0.7, D2 OMe), 2.05 (6H, s, D1 and D2 OAc), 1.43 (18H, s, D1 and D2 *t*Bu); δ_C (75 MHz, $CDCl_3$) 170.6 (C-OAc), 166.3 (1'-C), 154.9 (carbamate), 131.9 (Ar 1-C), 129.8 (Ar 2-C and 6), 128.6 (Ar 3-C and 5), 127.3 (Ar C- 4), 123.2 (q, *J* 77.9, CF_3), 84.9 (C'-C), 80.3 (*t*Bu), 64.5 (1-C), 63.0 (3-C), 55.5 (OMe), 48.2 (2-C), 28.3 (*t*Bu-C), 20.7 (C-OAc); ν_{max}/cm^{-1} (film); 3364, 2980, 1750, 1717, 1516, 1368, 1236, 1169; *m/z* (*ESI*) 472.2 (100%, MNa); HRMS found MNa^+, 472.1568, $C_{20}H_{26}F_3NO_7$ requires *MNa*, 472.1559.

tert-Butyl-_N_-(1,3-dihydroxypropan-2-yl)carbamate, 254a



By general procedure **I**, (2*R*)-3-amino-1,2-propanediol (4.00 g, 43.9 mmol), gave the carbamate **254a** (7.79 g, 40.7 mmol, 93%) as colourless oil**;** R_f 0.10 (1:1 petrol–EtOAc); $[\alpha]_D^{19}$ −8.3 (c 1.4, $CHCl_3$); δ_H (300 MHz, $CDCl_3$); 5.10 (1H, br s, NH), 3.82-3.69 (1H, m, 2-H), 3.68-3.48 (2H, m, 3-H), 3.33-3.18 (4H, m, 1-H and 2 × OH), 1.45 (9H, s, tBu); δ_C (75 MHz, $CDCl_3$) 80.2 (C-tBu), 71.4 (2-C), 63.6 (3-C), 42.8 (1-C), 28.3 (C-tBu) [Carbonyl was not observed]; ν_{max}/cm^{-1} (film); 3357, 2978, 1689, 1528, 1367, 1172; *m/z* (*ESI*) 214.1 (100%, MNa^+); HRMS found MNa^+, 214.1052. $C_8H_{17}NO_4$ requires *MNa,* 214.1050.

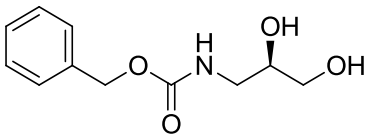
tert-Butyl-_N_-[(2_R_)-3-[(_tert_-butyldimethylsilyl)oxy]-2-hydroxypropyl]carbamate, 254



TBSCl (7.02 g, 46.6 mmol) was slowly added to a stirred solution of the carbamate **254a** (7.79 g, 40.7 mmol) and imidazole (4.50 g, 66.1 mmol) in CH_2Cl_2 (55 mL) at 0 °C and the resulting solution was stirred at rt for 2 h. The reaction was quenched with HCl (1 M, aq., to pH<2), extracted with CH_2Cl_2 (3 × 20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a crude product. Purification by column chromatography, gradient elution with 9:1 to

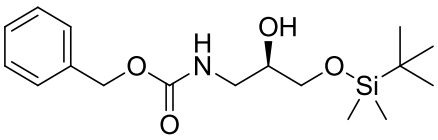
7:3 petrol–EtOAc, gave the carbamate **254** (12.4 g, 40.7 mmol, >98%.) as a colourless oil; R_f 0.77 (1:1 petrol–EtOAc); $[\alpha]_D^{19}$ +9.5 (c 0.9, $CHCl_3$); δ_H (500 MHz, $CDCl_3$); 4.88 (1H, br s, N-H), 3.66 (1H, m, 2-H), 3.57 (1H, dd, *J* 10.1 and 4.6, 3-H_a), 3.46 (1H, dd, *J* 10.1 and 6.2, 3-H_b), 3.27 (1H, m, 1-H_a), 3.06 (1H, ddd, *J* 12.0, 6.7 and 5.3, 1-H_b), 2.75 (1H, d, *J* 3.8, O-H), 1.37 (9H, s, *t*BuO-H), 0.84 (9H, s, *t*BuSi -H), 0.00 (6H, s, 2 × MeSi-H); δ_C (75 MHz, $CDCl_3$); 80.2 (*t*BuO -C), 71.2 (2-C), 64.8 (3-C), 43.3 (1-C), 28.4 (*t*BuO-C), 25.9 (*t*BuSi-C), 18.3 (*t*BuSi-C), -5.44 (2 × MeSi-C); ν_{max}/cm^{-1} (solid); 3375, 2930, 1694, 1515, 1253, 1173; *m/z* (*ESI*) 328.2 (100%, MNa^+); HRMS found MNa^+, 328.1917. $C_{14}H_{31}NO_4Si$ requires *MNa,* 328.1915.

Benzyl-*N*-[(2*R*)-2,3-dihydroxypropyl]carbamate, 256a



By general procedure **H**, (2*R*)-3-amino-1,2-propanediol (2.00 g, 22.0 mmol), gave the carbamate **256a** (3.84 g, 17.0 mmol, 78%) as colourless soild; R_f 0.08 (1:1 petrol–EtOAc); δ_H (500 MHz, $CDCl_3$) 7.39-7.27 (5H, m, Ar-H), 5.37 (1H, br s, N-H), 5.09 (2H, s, benzyl-H), 3.75 (1H, m, 2-H), 3.65-3.56 (1H, m, 3-H_a), 3.56-3.48 (1H, m, 3-H_b), 3.37-3.30 (1H, m, 1-H_a), 3.30-3.20 (2H, m, 3-H_b and OH), 3.07 (1H, s, OH); δ_C (75 MHz, $CDCl_3$) 157.7 (carbamate), 136.2 (Ar 1-C), 128.6 (Ar C), 128.3 (Ar C), 128.2 (Ar C), 71.2 (2-C), 67.2 (benzyl C), 63.7 (3-C), 43.2 (1-C); ν_{max}/cm^{-1} (solid); 3333, 2933, 1691, 1539, 1219; *m/z* (*ESI*) 248.1 (100%, MNa^+); HRMS found MNa^+, 248.0896. $C_{11}H_{15}NO_4$ requires *MNa,* 248.0893.

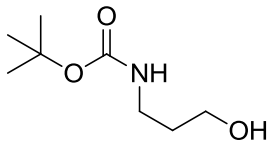
Benzyl-*N*-[(2*R*)-3-[(*tert*-butyldimethylsilyl)oxy]-2-hydroxypropyl]carbamate, 256



TBSCl (3.31 g, 22.0 mmol) was slowly added to a stirred solution of the carbamate **256a** (4.71 g, 20.9 mmol) and imidazole (2.14 g, 31.4 mmol) in CH_2Cl_2 (45 mL) at 0 °C and the resulting solution was stirred at rt for 2h. The reaction was quenched with HCl (1 M, aq., to pH<2), extracted with CH_2Cl_2 (3 × 20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a crude product. Purification by column chromatography, gradient elution with 9:1 to 7:3 petrol–EtOAc, gave the carbamate **256** (6.10 g, 18.0 mmol, 83%) as a colourless oil; R_f 0.64 (1:1 petrol–EtOAc); $[\alpha]_D^{19}$ +9.4 (c 1.5, $CHCl_3$); δ_H (300 MHz, $CDCl_3$); 7.28 (5H, m, benzyl Ar-H), 5.12 (1H, br s, N-H), 5.04 (2H, s, benzyl-H), 3.68 (1H, m, 2-H), 3.58 (1H, dd, *J* 10.1 and 4.4, 3-H_a), 3.46 (1H, dd, *J* 10.1 and 6.2, 3-H_b), 3.36 (1H, ddd, *J* 13.9, 6.7 and 3.67, 1-H_a), 3.12

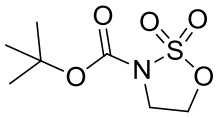
(1H, ddd, *J* 13.9, 6.9, 5.2, 1-H_b), 2.68 (1H, d, *J* 4.3, O-H), 0.83 (9H, s, *t*Bu-H), 0.00 (6H, s, 2 × MeSi-H); δ_C (75 MHz, $CDCl_3$); 136.5 (Ar 1-C), 128.5 (Ar 3-C and Ar 5-C), 128.1 (Ar 2-C and Ar-6C), 128.1 (Ar 5-C), 71.0 (2-C), 66.8 (benzyl-C), 64.7 (3-C), 43.7 (1-C), 25.8 (*t*Bu-C), 18.2 (*t*Bu-C), -5.5 (2 × MeSi-C); ν_{max}/cm^{-1} (solid) [carbonyl was not observed]; 3346, 2929, 1706, 1532, 1256; *m/z* (*ESI*) 362.2 (100%, MNa^+); HRMS found MNa^+, 362.1773. $C_{17}H_{29}NO_4Si$ requires *MNa,* 362.1758.

tert-Butyl-_N_-(3-hydroxypropyl)carbamate, 245[102]



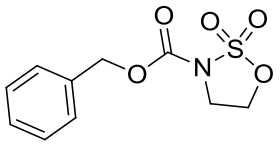
By general procedure **I**, 3-amino-1-propanol (756 mg, 10.0 mmol), gave the carbamate **245** (1.76 g, 9.54 mmol, 97%) as a colourless oil; R_f 0.36 (1:1 petrol–EtOAc); δ_H (300 MHz, $CDCl_3$); 4.78 (1H, br s, N-H), 3.67 (2H, br s, 3-H), 3.28 (2H, q, *J* 6.05, 1-H), 2.97 (1H, br s, O-H), 1.67 (2H, app. q, *J* 5.9, 2-H), 1.45 (9H, s, *t*Bu-H); δ_C (75 MHz, $CDCl_3$); 79.6 (*t*Bu-C), 59.2 (3-C), 36.9 (1-C), 32.9 (2-C), 28.4 (*t*Bu-C) ; ν_{max}/cm^{-1} (film); 3355, 2978, 1690, 1528, 1367, 1173; *m/z* (*ESI*) 198.1 (100%, MNa^+); HRMS found MNa^+, 198.1106. $C_8H_{17}NO_3$ requires *MNa,* 198.1101.

tert-Butyl-2,2-dioxo-1,2,3-oxathiazolidine-3-carboxylate, 200[103]



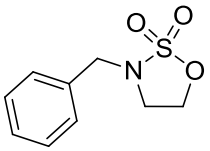
By general procedure **F**, the carbamate **197** (3.00 g, 18.6 mmol) gave the sulfamidate **200** (3.56 g, 15.9 mmol, 86%) as a colourless oil (solidified on standing) which required no further purification; R_f 0.74 (1:1 petrol–EtOAc); δ_H (300 MHz, $CDCl_3$); 4.62 (2H, t, *J* 6.4, 5-H), 4.05 (2H, t, *J* 6.4, 4-H), 1.56 (9H, s, *t*Bu-H); δ_C (75 MHz, $CDCl_3$); 148.6 (carbamate carbonyl-C), 85.6 (*t*Bu-C), 65.6 (5-C), 45.3 (4-C), 27.9 (*t*Bu-C); ν_{max}/cm^{-1} (film) 2989, 1719, 1477, 1373, 1156; *m/z* (*ESI*) 246.0 (100%, MNa^+); HRMS found MNa^+, 246.0411. $C_7H_{13}NO_5S$ requires *MNa,* 246.0407.

Benzyl-2,2-dioxo-1,2,3-oxathiazolidine-3-carboxylate, 199[103]



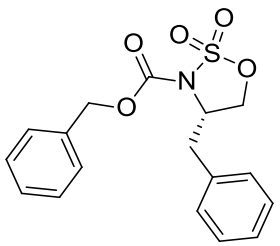
By general procedure **F**, the carbamate **196** (6.00 g, 30.7 mmol) gave the sulfamidate **199** (6.85 g, 26.6 mmol, 87%) as a colourless oil (solidified on standing) which required no further purification; R_f 0.72 (1:1 petrol–EtOAc); δ_H (500 MHz, $CDCl_3$); 7.42-7.34 (5H, m, Ar-H), 5.32 (2H, s, benzyl-H), 4.63 (2H, t, *J* 6.5, 5-H), 4.09 (2H, t, *J* 6.5, 4-H); δ_C (75 MHz, $CDCl_3$); 149.8 (carbamate carbonyl-C), 134.4 (Ar 1-C), 128.8 (Ar 3-C and Ar 5-C), 128.7 (Ar 2-C and Ar 6-C), 128.1 (Ar 4-C), 69.5 (benzyl-C), 66.0 (5-C), 45.6 (4-C); ν_{max}/cm^{-1} (film) 3035, 2983, 1732, 1454, 1323, 1144; *m/z* (*ESI*) 280.0 (100%, MNa); HRMS found MNa^+, 280.0257. $C_{10}H_{11}NO_5S$ requires *MNa,* 280.0250.

3-Benzyl-1,2,3-oxathiazolidine-2,2-dione, 198



By general procedure **F**, the amine **195** (3.00 g, 19.8 mmol) gave the sulfamidate **198** (2.62 g, 12.3 mmol, 66%) as a colourless oil (solidified on standing) which required no further purification; R_f 0.77 (1:1 petrol–EtOAc); δ_H (300 MHz, $CDCl_3$); 7.38 (5H, m, Ar-H), 4.52 (2H, t, *J* 6.5, 5-H), 4.24 (2H, s, X-H), 3.39 (2H, t, *J* 6.5, 4-H); δ_C (75 MHz, $CDCl_3$); 134.3 (Ar 1-C), 128.9 (Ar 3-C and Ar 5-C), 128.7 (Ar 2-C and Ar 6-C), 128.6 (Ar 4-C), 66.8 (5-C), 51.5 (benzyl), 47.2 (4-C); ν_{max}/cm^{-1} (film) 3034, 2914, 1456, 1331, 1214; *m/z* (*ESI*) 236.0 (100%, MNa^+); HRMS found MNa^+, 236.0352. $C_9H_{11}NO_3S$ requires *MNa,* 236.0352.

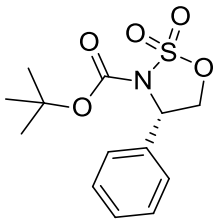
Benzyl(4*S*)-4-benzyl-2,2-dioxo-1,2,3- oxathiazolidine-3-carboxylate, 251



By general procedure **F**, the carbamate **247** (1.50 g**,** 5.26 mmol) gave the sulfamidate **251** (1.63 g, 4.90 mmol, 93%) as a colourless oil (solidified on standing) which required no further purification; R_f 0.67 (1:1 petrol–EtOAc); $[\alpha]_D^{22}$ -34.5 (c 1.7, MeOH); δ_H (500 MHz, $CDCl_3$); 7.45-7.24 (9H, m, 9 × Ph-H), 7.20 (1H, m, Ph-H), 5.33 (2H, s, Cbz benzyl-H), 4.50

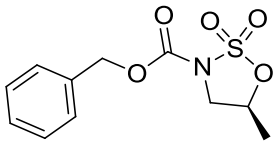
(1H, app. d, *J* 3.0, 4-H), 4.48 (1H, app. d, *J* 2.6, 5-H_a), 4.40-4.32 (1H, m, 5-H_b), 3.38 (1H, br d, *J* 13.7, benzyl-H_a), 2.94 (1H, dd, *J* 13.4 and 10.0, benzyl-H_a); δ_C (75 MHz, $CDCl_3$); 149.7 (Ar-C), 134.8 (Ar -C), 134.4 (Ar -C), 129.4 (Ar -C), 129.1 (Ar -C), 128.7 (Ar -C), 128.0 (Ar -C), 127.6 (Ar -C), 69.5 (Cbz benzyl-C), 69.0 (5C), 59.0 (4-C), 37.7 (benzyl-C); ν_{max}/cm^{-1} (film) 3032, 2928, 1740, 1383, 1308, 1193; *m/z* (*ESI*) 370.2 (100%, MNa^+).

tert-Butyl-2,2-dioxo-3-oxa-2-thia-1-azaspiro[5.5]nonane-1-carboxylate, 256



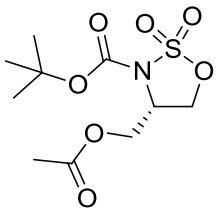
By general procedure **F**, the carbamate **246** (3.00 g, 12.6 mmol) gave the sulfamidate **256** (3.62 g, 12.1 mmol, 96%) as a colourless oil (solidified on standing) which required no further purification; R_f 0.87 (1:1 petrol–EtOAc); $[\alpha]_D^{19}$ +47.7 (c 0.5, $CHCl_3$); δ_H (300 MHz, $CDCl_3$); 7.42-7.39 (5H, m, phenyl-H), 5.28 (1H, dd, *J* 6.7 and 4.3, 4-H), 4.88 (1H, dd, *J* 6.7 and 9.2, 5-H_a), 4.41 (1H, dd, *J* 9.3 and 4.3, 5-H_b), 1.44 (9H, s, *t*Bu-H); δ_C (75 MHz, $CDCl_3$); 129.3 (Ar 3-C and Ar 5-C), 129.1 (Ar 4-C), 126.2 (Ar 2-C and Ar 6-C), 85.6 (*t*Bu-C), 71.8 (5-C), 60.8 (4-C), 27.8 (*t*Bu-C) [Ar 1-C was not observed]; ν_{max}/cm^{-1} (film) 2976, 1723, 1326, 1189, 1155; *m/z* (*ESI*) 322.1 (100%, MNa^+); HRMS found MNa^+, 322.0727. $C_{13}H_{17}NO_5S$ requires *MNa,* 322.0720.

Benzyl-(5*S*)-5-methyl-2,2-dioxo-1,2,3-oxathiazolidine-3-carboxylate, 252



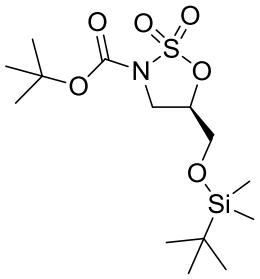
By general procedure **F**, the carbamate **248** (1.20 g, 5.74 mmol) gave the sulfamidate **252** (1.43 g, 5.28 mmol, 89%) as a colourless oil (solidified on standing) which required no further purification; R_f 0.72 (1:1 petrol–EtOAc); $[\alpha]_D^{19}$ −36.0 (c 0.5, $CHCl_3$); δ_H (300 MHz, $CDCl_3$); 7.43-7.34 (5H, m, Ar-H), 5.32 (2H, s, benzyl-H), 5.01 (1H, m, 5-H), 4.15 (1H, dd, *J* 5.6 and 10.0, 4-H_a), 3.7 (1H, app. t, *J* 9.8, 4-H_b), 1.60 (3H, d, *J* 6.2, Me-H); δ_C (75 MHz, $CDCl_3$); 128.7 (Ar 2-C, Ar 3-C, Ar 5-C and Ar 6-C), 128.1 (Ar 4-C), 80.3 (5-C), 69.4 (benzyl-C), 52.0 (4-C), 18.0 (Me-C) [Ar 1-C was not observed]; ν_{max}/cm^{-1} (film) 2926, 1743, 1403, 1323, 1196; *m/z* (*ESI*) 289.1 (100%, MNH_4^+); HRMS found MNH_4^+, 289.0861. $C_{11}H_{13}NO_5S$ requires *MNH_4,* 289.0853.

***tert*-Butyl-(4*S*)-4-[(acetyloxy)methyl]-2,2-dioxo-1,2,3-oxathiazolidine-3-carboxylate, 243**



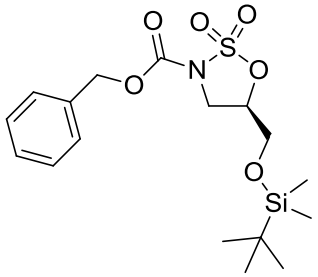
By general procedure **F**, the carbamate **259** (1.17 g**,** 5.02 mmol) gave the sulfamidate **242** (1.03 g, 3.49 mmol, 69%) as a colourless oil (solidified on standing) which required no further purification; R_f 0.69 (1:1 petrol–EtOAc); $[\alpha]_D^{19}$ 15.4 (c 0.6, MeOH); δ_H (300 MHz, $CDCl_3$); 4.68 (1H, dd, *J* 9.7 and 6.3, 5-H_a), 4.57-4.40 (3H, m, 5-H_b, 4-H and methylene-H_a), 4.30 (1H, dd, *J* 11.3 and 3.6, methylene-H_b), 2.12 (3H, s, acetyl-H), 1.57 (9H, s, *t*Bu-H); δ_C (75 MHz, $CDCl_3$); 170.6 (acetyl carbonyl-C), 148.3 (carbamate carbonyl-C), 86.1 (*t*Bu-C), 67.6 (5-C), 61.5 (methylene-C), 55.0 (4-C), 27.9 (*t*Bu-C), 20.7 (acetyl-C); ν_{max}/cm^{-1} (film) 2984, 1727, 1530, 1336, 1219; *m/z* (*ESI*) 318.1 (100%, MNa^+); HRMS found MNa^+, 318.0626. $C_{10}H_{17}NO_7S$ requires *MNa,* 318.0618.

***tert*-Butyl-(5*R*)-5-{[(*tert*-butyldimethylsilyl)oxy]methyl}-2,2-dioxo-1,2,3-oxathiazolidine-3-carboxylate, 242**



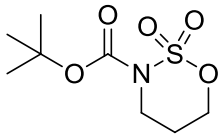
By general procedure **F**, the carbamate **256** (10.0 g**,** 32.7 mmol) gave the sulfamidate **242** (10.89 g, 29.6 mmol, 90%) as a colourless oil (solidified on standing) which required no further purification; R_f 0.95 (1:1 petrol–EtOAc); $[\alpha]_D^{19}$ +10.6 (c 0.6, $CHCl_3$); δ_H (500 MHz, $CDCl_3$); 4.71 (1H, m, 5-H), 3.90 (1H, dd, *J* 10.0, 6.4, methylene-H_a), 3.85-3.79 (3H, m, 4-H and methylene-H_b), 1.46 (9H, s, *t*BuO-H), 0.81 (9H, s, *t*BuSi-H), 0.00 (6H, s, 2 × CH_3Si-H); δ_C (75 MHz, $CDCl_3$); 85.5 (*t*BuO-C), 78.0 (5-C), 61.7 (methylene-C), 45.6 (4-C), 27.9 (*t*BuO-C), 25.7 (*t*BuSi-C), 18.2 (*t*BuSi-C), -5.45 (2 × CH_3Si -C); ν_{max}/cm^{-1} (film) 2932, 1747, 1475, 1397, 1261, 1105; *m/z* (*ESI*) 385.2 (100%, MNH_4^+); HRMS found MNH_4^+, 385.1843. $C_{14}H_{29}NO_6SSi$ requires *MNH₄,* 385.1823.

***tert*-Butyl-(5*R*)-5-{[(*tert*-butyldimethylsilyl)oxy]methyl}-2,2-dioxo-1,2,3-oxathiazolidine-3-carboxylate, 244**



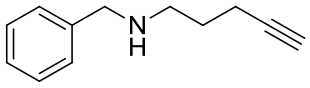
By general procedure **F**, the carbamate **256** (6.03 g**,** 17.7 mmol) gave the sulfamidate **244** (6.51 g, 16.2 mmol, 92%) as a colourless oil (solidified on standing) which required no further purification; R_f 0.92 (1:1 petrol–EtOAc); $[\alpha]_D^{22}$ 7.7 (c 1.3, $CHCl_3$); δ_H (500 MHz, $CDCl_3$); 7.39-7.19 (5H, m, Ar-H), 5.33 (1H, s, benzyl-H), 4.77 (1H, ddt, *J* 8.7, 6.3, 4.5, 5-H), 4.00-3.87 (2H, m, methylene-H), 3.87-3.78 (2H, m, 4-H), 0.81 (9H, s, *t*Bu-H), 03.00 (6H, s, 2 × CH_3Si-H); δ_C (75 MHz, $CDCl_3$); 148.8 (carbamate carbonyl-C), 133.3 (Ar 1-C), 127.8 (Ar 3-C and Ar 50C), 127.7 (Ar 2-C and Ar 6-C), 127.1 (Ar 4-C), 78.1 (5-C), 68.6 (benzyl-C), 60.0 (methylene-C), 45.2 (4-C), 24.7 (*t*Bu-C), -3.93 (2 × CH_3Si-C); ν_{max}/cm^{-1} (film) 3523, 2932, 1716, 1373, 1335, 1196; *m/z* (*ESI*) 424.1 (100%, MNa^+); HRMS found MNa^+, 424.1227. $C_{17}H_{27}NO_6S$ requires *MNa,* 424.1221.

tert-Butyl-2,2-dioxo-1,2,3-oxathiazinane-3-carboxylate, 249[103]



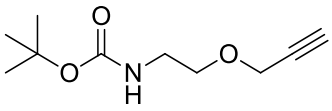
By general procedure **F**, the carbamate **245** (1.77 g, 10.1 mmol) gave the sulfamidate **249** (1.97 g, 8.32 mmol, 82%) as a colourless oil (solidified on standing) which required no further purification; R_f 0.74 (1:1 petrol–EtOAc); δ_H (500 MHz, $CDCl_3$); 4.67 (2H, t, *J* 6.0, 6-H), 4.03-3.98 (2H, m, 4-H), 2.12-2.06 (2H, m, 5-H), 1.53 (9H, s, tBu-H); δ_C (75 MHz, $CDCl_3$); 150.4 (carbonyl), 85.0 (tButyl-C), 73.2 (6-C), 45.9 (4-C), 27.9 (tBu-C), 23.7 (5-C); ν_{max}/cm^{-1} (film)2983, 1728, 1426, 13872, 1065; *m/z* (*ESI*) 260.1 (100%, MNa^+); HRMS found MNa^+, 260.0564. $C_8H_{15}NO_5S$ requires *MNa,* 260.0563.

Benzyl(pent-4-yn-1-yl)amine, 210[77]



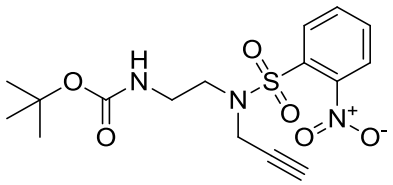
DEAD (3.67 mL, 23.2 mmol) was added dropwise to a solution of 4-pentyn-1-ol (2.16 mL, 23.2 mmol), the sulfonamide **221** (4.52 g, 15.5 mmol) and triphenylphosphine (6.08 g, 23.2 mmol) in THF (30 mL) at 0 °C and the resulting solution was warmed to rt and stirred for 6 h. Th reaction mixture was concentrated *in vacuo* to give a crude intermediate. Partial purification by filtration over SiO_2, eluting with CH_2Cl_2 gave an intermediate sulfonamide. PhSH (6.37 mL, 62.0 mmol) was added to a suspension of the sulfonamide intermediate and K_2CO_3 (8.60 g, 62.0 mmol) in MeCN (30 mL) and the resulting mixture was stirred for 24 h. The reaction mixture was acidified with HCl (2M aq. soln., to pH<2) extracted with EtOAc (3 × 20 mL), basified with K_2CO_3 (sat. aq. soln., to pH >12) extracted with CH_2Cl_2 (3 × 20 mL), washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give a crude product. Purification by column chromatography, gradient elution 100% CH_2Cl_2 to 10:1 CH_2Cl_2–MeOH, gave the amine **210** (1.95 g, 11.3 mmol, 73% over two steps) as a light brown oil: R_f 0.40 (EtOAc); δ_H (500 MHz, $CDCl_3$); 7.37-7.28 (4H, m, Ar 2-H, Ar 3-H, Ar 5-H and Ar 6-H), 7.28-7.20 (1H, m, 4-H), 3.80 (2H, s, benzyl-H), 2.75 (2H, t, *J* 7.0, 1-H), 2.27 (2H, td, *J* 7.1, 2.1, 3-H), 1.94 (1H, t, *J* 2.7, 5-H), 1.73 (2H, p, *J* 7.0, 2-H), 1.42 (1H, br s, N-H); δ_C (75 MHz, $CDCl_3$); δ 140.5 (Ar-C), 128.4 (Ar-C), 128.0(Ar-C), 126.9(Ar-C), 84.1(4-C), 68.5 (5-), 53.9 (benzyl), 48.2 (1-C), 28.7 (2-C), 16.3 (3-C); ν_{max}/cm^{-1} (film) 3300, 2938, 1648, 1495, 1453, 1217; *m/z* (*ESI*) 174.1 (100%, MH^+); HRMS found MH^+, 174.1278. $C_{12}H_{15}N$ requires *MH,* 174.1277.

***tert*-Butyl-*N*-[2-(prop-2'-yn-1'-yloxy)ethyl]carbamate, 205**



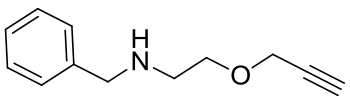
By general procedure **G**, the sulfamidate **200** (1.00 g, 4.50 mmol) and propargyl alcohol (0.4 mL mg, 6.7 mmol) gave a crude product. Purification by column chromatography, eluting with 7:3 petrol–EtOAc, gave the carbamate **205** (684 mg, 3.43 mmol, 77%) as a colourless oil; R_f 0.76 (1:1 petrol–EtOAc); δ_H (300 MHz, $CDCl_3$); 4.92 (1H, br s, N-H), 4.16 (2H, d, *J* 2.4, 1'-H), 3.59 (2H, t, *J* 5.1, 2-H), 3.34 (2H, dd, *J* 10.6, 5.3, 1-H), 2.45 (1H, t, *J* 2.4, 3'-H), 1.45 (9H, s, *t*Bu-H); δ_C (75 MHz, $CDCl_3$); 155.9 (carbamate-C), 79.4 (2'-C), 79.3 (*t*Bu-C), 74.6 (3'-C), 69.1 (2-C), 58.3 (1'-C), 40.3 (1-C), 28.4 (tBu-C); ν_{max}/cm^{-1} (film) 3357, 2933, 2116, 1708, 1514, 1366, 1215, 1173; *m/z* (*ESI*) 222.1 (100%, MNa^+); HRMS found MNa^+, 222.1099. $C_{10}H_{17}NO_3$ requires *MNa,* 222.1101.

***tert*-Butyl-*N*-{2-[*N*-(prop-2'-yn-1'-yl)(2-nitrobenzene)sulfonamido]ethyl}carbamate, 208**



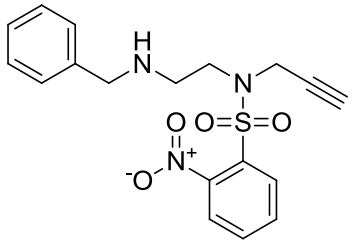
By general procedure **G**, the sulfamidate **200** (1.00 g, 4.48 mmol) and the sulfonamide *o*-**202** (1.61 g, 6.70 mmol) gave a crude product. Purification by column chromatography, eluting with 50:1 CH_2Cl_2–MeOH, gave the carbamate **208** (1.72 g, 4.49 mmol, >98%) as a light brown oil; R_f 0.52 (1:1 petrol–EtOAc); δ_H (300 MHz, $CDCl_3$); 8.11-8.00 (1H, m, Ar 3-H), 7.77-7.59 (3H, m, Ar 4-H, Ar 5-H and Ar 6-H), 4.80 (1H, br s, N-H), 4.26 (2H, d, *J* 2.3, 1'-H), 3.53 (2H, t, *J* 5.9, 2-H), 3.37 (2H, dd, *J* 11.4 and 5.6, 1-H), 2.20 (1H, t, *J* 2.20, 3'-H), 1.43 (9H, s, *t*Bu-H); δ_C (75 MHz, $CDCl_3$); 156.0 (carbamate-C), 148.2 (sulfonamide 2-C), 133.9 (sulfonamide 4-C), 132.5 (sulfonamide 1-C), 131.8 (sulfonamide 5-C), 131.0 (sulfonamide 6-C), 124.2 (sulfonamide 3-C), 79.7 (*t*Bu-C), 77.2 (2'-C), 74.2 (3'-C), 46.6 (2-C), 37.9 (1-C), 36.9 (1'-C), 28.3 (*t*Bu-C); ν_{max}/cm^{-1} (film) 3407, 3265, 2123, 1711, 1532, 1360, 1143; *m*/*z* (*ESI*) 406.1 (100%, MNa^+); HRMS found MNa^+, 406.1060. $C_{16}H_{21}N_3O_6S$ requires *MNa,* 406.1043.

Benzyl[2-(prop-2'-yn-1'-yloxy)ethyl]amine, 204



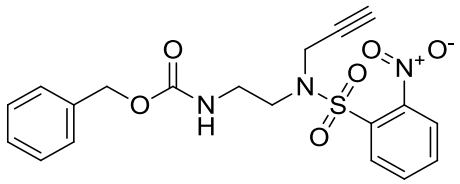
By general procedure **G**, the sulfamidate **198** (1.00 g, 4.48 mmol) and propargyl alohol (0.40 mL, 6.87 mmol) gave a crude product. Purification by SCX gave the amine **204** (684 mg, 3.43 mmol, 77%) as a colourless oil; R_f 0.1 (1:1 petrol–EtOAc); δ_H (500 MHz, $CDCl_3$); 7.38-7.29 (5H, m, Ar-H), 4.16 (2H, d, *J* 2.4, 1'-H), 3.87 (2H, s, benzyl-H), 3.67 (2H, app. t, *J* 5.2, 2-H), 2.88 (2H, app. t, *J* 5.1 1-H), 2.42 (1H, t, *J* 2.3, 3'-H); δ_C (75 MHz, $CDCl_3$); 138.8 (Ar 1-C), 128.5 (Ar 3-C and Ar 5-C), 128.5 (Ar 2-C and Ar 6-C), 127.3 (Ar4-C), 79.6 (2'-C), 74.5 (3'-C), 68.7 (2-C), 58.3 (1'-C), 53.4 (benzyl-C), 48.1 (1-C); ν_{max}/cm^{-1} (film)3288, 2924, 1605, 1454, 1103; *m*/*z* (*ESI*) 190.1 (100%, MH^+); HRMS found MH^+, 190.1235. $C_{12}H_{15}NO$ requires *MH,* 190.1226.

***N*-[2-(Benzylamino)ethyl]-2-nitro-*N*-(prop-2'-yn-1'-yl)benzene-1-sulfonamide, 207**



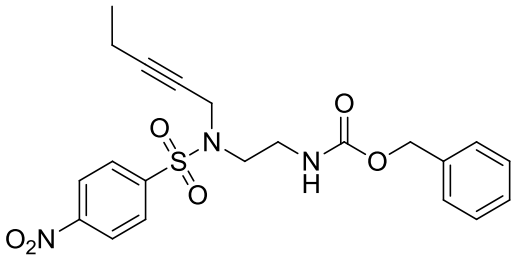
By general procedure **G**, the sulfamidate **198** (300 mg, 1.52 mmol) and sulfonamide *o*-**202** (731 mg, 3.04 mmol) gave a crude product. Purification by SCX gave the carbamate **207** (154 mg, 0.41 mmol, 27%) as a colourless oil; R_f 0.61 (1:1 petrol–EtOAc); δ_H (500 MHz, $CDCl_3$); 8.06 (1H, dd, *J* 7.0 and 2.1, Ar 3-H), 7.71-7.62 (2H, m, Ar 5-H and Ar-6H), 7.62-7.56 (1Hm, Ar 4-H), 7.35-7.21 (5H, m, Ph-H), 4.25 (2H, d, *J* 2.2, 1'-H), 3.77 (2H, s, benzyl-H), 3.56 (2H, t, *J* 6.1, 1-H), 2.87 (2H, t, *J* 6.1, 2-H), 2.16 (2H, t, *J* 2.2, 3'-H); δ_C (75 MHz, $CDCl_3$); 148.2 (sulfonamide 2-C),140.1 (Ph 1-C), 133.9 (sulfonamide 4-C), 132.4 (sulfonamide 1-C), 131.8 (sulfonamide 5-C), 131.0 (sulfonamide 6-C), 128.5 (Ph-C), 128.1 (Ph-C), 127.1 (Ph-C), 124.3 (sulfonamide 3-C), 76.8 (2'-C), 74.2 (3'-C), 61.0 (Bn-C), 50.5 (1-C), 46.6 (2-C); ν_{max}/cm^{-1} (film) 3294, 3106, 2125, 1538, 1366, 1163; *m/z* (*ESI*) 374.1 (100%, MH^+); (Found MH^+, 374.1166 $C_{18}H_{19}N_3O_4S$ requires *MH*, 374.1169).

Benzyl-*N*-{2-[*N*-(prop-2'-yn-1'-yl)(2-nitrobenzene)sulfonamido]ethyl}carbamate, 209



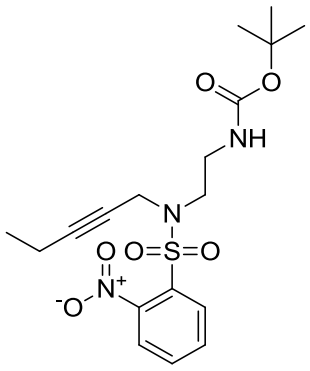
By general procedure **G**, the sulfamidate **199** (1.00 g, 3.90 mmol) and sulfonamide *o*-**202** (1.40 g, 5.83 mmol) gave a crude product. Purification by column chromatography, eluting with 7:3 petrol–EtOAc, gave the carbamate **209** (1.54 g, 3.69 mmol, 95%) as a colourless solid; R_f 0.39 (1:1 petrol–EtOAc); δ_H (300 MHz, $CDCl_3$); 8.03 (1H, m, Ar 3-H), 7.67-7.57 (3H, m, Ar 4-H, Ar 5-H and Ar 6-H), 7.42-7.27 (5H, m, benzyl-H), 5.05 (3H, br s, N-H and benzyl), 4.24 (2H, d, *J* 1.8, 1'-H), 3.62-3.49 (2H, m, 2-H), 3.44 (2H, m, 1-H), 2.20 (1H, br s, 3'-H); δ_C (75 MHz, $CDCl_3$); 156.5 (carbonyl-C), 148.2 (sulfonamide 2-C) 136.4 (benzyl 1-C), 133.9 (sulfonamide 4-C), 132.4 (sulfonamide 1-C), 131.8 (sulfonamide 5-C), 131.0 (sulfonamide 6-C), 128.5 (benzyl 3-C and benzyl 5-C), 128.1 (benzyl 2-C and benzyl 6-C), 128.0 (benzyl 4-C), 124.3 (sulfonamide 3-C), 76.8 (2'-C), 74.2 (3'-C), 66.8 (benzyl-C), 46.6 (2-C), 38.5 (1'-C), 37.0 (1-C); ν_{max}/cm^{-1} (film) 3418, 3298, 2122, 1713, 1544, 1359, 1167; *m/z* (*ESI*) 440.1 (100%, MNa^+); HRMS found MNa^+, 440.0903. $C_{19}H_{19}N_3O_6S$ requires *MNa,* 440.0887.

Benzyl-*N*-{2-[*N*-(pent-2'-yn-1'-yl)(4-nitrobenzene)sulfonamido]ethyl}carbamate, 263



By general procedure **G**, the sulfamidate **199** (600 mg, 2.33 mmol) and the sulfonamide *p*-**235** (750 mg, 2.80 mmol) gave a crude product. Purification by column chromatography, eluting with 7:3 petrol–EtOAc, gave the carbamate **263** (946 mg, 2.12 mmol, 91%) as a colourless solid; R_f 0.39 (1:1 petrol–EtOAc); δ_H (500 MHz, $CDCl_3$); 8.33 (2H, d, *J* 8.6, Ar 3-H and Ar 5-H), 8.04 (2H, d, *J* 8.6, Ar 2-H and Ar 6-H), 7.42-7.30 (5H, m, benzyl Ar-H), 5.12 (3H, br s, N-H and benzyl-H), 4.12 (2H, s, 1'-H), 3.43 (2H, dd, *J* 11.1, 5.5, 1-H), 3.35 (2H, t, *J* 5.4, 2-H), 1.92 (2H, q, *J* 7.4, 4'-H), 0.89 (2H, t, *J* 7.5, 5'-H); δ_C (75 MHz, $CDCl_3$); 129.0 (sulfonamide 2-C and 6-C), 128.6 (benzyl 3-C and 5-C), 128.2 (benzyl 2-C and 6-C), 128.1 (benzyl 4-C), 124.0 (sulfonamide 3-C and 5-C), 71.3 (2'-C), 66.9 (benzyl-C), 46.2 (2-C), 38.8 (1'-C), 37.8 (1-C), 13.4 (5'-C), 12.0 (4'-C); ν_{max}/cm^{-1} (film) 3406, 2978, 2228, 1720, 1531, 1351, 1167; *m*/*z* (*ESI*) 468.1 (100%, MNa^+); HRMS found MNa^+, 468.1206. $C_{21}H_{23}N_3O_6S$ requires *MNa,* 468.1200.

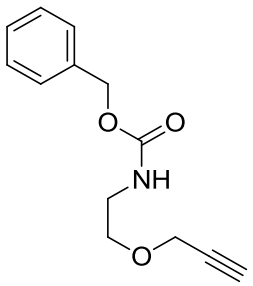
***tert*-Butyl-*N*-{2-[*N*-(pent-2'-yn-1'-yl)(2-nitrobenzene)sulfonamido]ethyl}carbamate, 261**



By general procedure **G**, the sulfamidate **200** (300 mg, 1.34 mmol) and the sulfonamide *o*-**236** (540 mg, 2.01 mmol) gave a crude product. Purification by column chromatography, eluting with 50:1 CH_2Cl_2–MeOH, gave the carbamate **261** (581 mg, 1.32 mmol, >98%) as a colourless oil; R_f 0.61 (1:1 petrol–EtOAc); δ_H (300 MHz, $CDCl_3$); 8.10-8.01 (1H, m, sulfonamide 3-H), 7.75-7.62 (3H, m, sulfonamide 4-H, 5-H and 6-H), 4.85 (2H, br s, N-H), 4.21 (2H, br s, 1'-H), 3.52 (2H, t, *J* 5.7, 2-H), 3.36 (2H, dt, *J* 11.3, 5.7, 1-H), 2.03 (2H, qt, *J* 7.5,

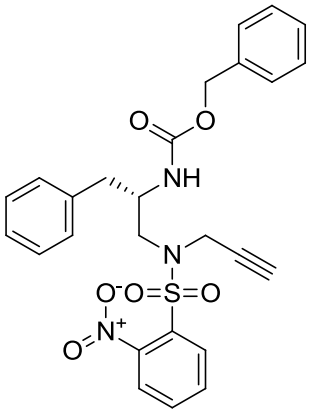
2.2, 4'-H), 1.43 (9H, s, *t*Bu-H), 0.98 (3H, t, *J* 7.5, 5'-H); δ_C (75 MHz, $CDCl_3$); 133.6 (sulfonamide 4-C), 132.7 (sulfonamide 1-C), 131.5 (sulfonamide 3-C), 131.0 (sulfonamide 6-C), 124.1 (sulfonamide 3-C), 88.1 (3'-C), 79.6 (*t*Bu-C), 72.1 (2'-C), 46.5 (2-C), 38.1 (1'-C), 37.4 (1-C), 28.4 (*t*Bu-C), 13.6 (5'-C), 12.2 (4'-C); ν_{max}/cm^{-1} (film) 3418, 2979, 2231, 1708, 1546, 1366, 1168; *m/z* (*ESI*) 434.1 (100%, MNa^+); HRMS found MNa^+, 434.1376. $C_{18}H_{25}N_3O_6S$ requires *MNa,* 434.1356.

Benzyl-*N*-[2-(prop-2'-yn-1'-yloxy)ethyl]carbamate, 206



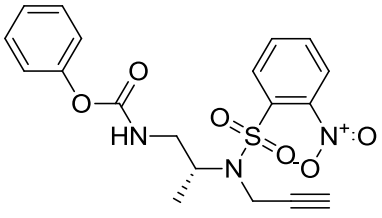
By general procedure **G**, the sulfamidate **199** (391 mg, 1.52 mmol) and propoargyl alcohol (0.180 mL, 3.04 mmol) gave a crude product. Purification by column chromatography, eluting with 7:3 petrol–EtOAc, gave the carbamate **206** (**4**63 mg, 1.12 mmol, 73%) as a colourless oil; R_f 0.55 (1:1 petrol–EtOAc); δ_H (500 MHz, $CDCl_3$); 7.41-7.29 (5H, m, benzyl Ar-H), 5.13 (1H, br s, N-H), 5.10 (2H, s, benzyl-H), 4.14 (2H, d, *J* 2.3, 1'-H), 3.60 (2H, t, *J* 5.0, 2-H), 3.42 (2H, m, 1-H), 2.43 (1H, t, *J* 2.4, 3'-H); δ_C (75 MHz, $CDCl_3$); 136.5 (benzyl 1-C), 125.5 (benzyl 3-C and 5C), 128.1 (benzyl 2-C, 4-C and 6-C), 79.3 (2'-C), 74.8 (3'-C), 68.9 (2-C), 66.7 (benzyl-C), 58.3 (1'-C), 40.8 (1-C); ν_{max}/cm^{-1} (film) 3294, 2940, 2116, 1712, 1528, 1257, 1102; *m/z* (*ESI*) 256.1 (100%, MNa^+); HRMS found MNa^+, 256.0947. $C_{13}H_{15}NO_3$ requires *MNa,* 256.0944.

Benzyl-*N*-[(2*S*)-1-phenyl-3-[*N*-(prop-2'-yn-1'-yl)(2-nitrobenzene)sulfonamido]propan-2-yl]carbamate, 268



By general procedure **G**, the sulfamidate **240** (348 mg, 1.04 mmol) and the sulfonamide *o*-**202** (376 mg, 1.57 mmol) gave a crude product. Purification by column chromatography, eluting with 7:3 petrol–EtOAc, gave the carbamate **268** (380 mg, 7.49 mmol, 72%) as a colourless soild; R_f 0.45 (1:1 petrol–EtOAc); $[\alpha]_D^{19}$ −47.1 (c 5.0, $CHCl_3$); δ_H (300 MHz, $CDCl_3$); 8.01-7.90 (1H, m, sulfonamide 3-H), 7.69-7.52 (3H, m, sulfonamide 4-H, 5-H and 6-H), 7.39-7.14 (10H, m, benzyl Ar and phenyl), 5.05 (1H, d, *J* 12.4, benzyl-H_a), 5.00 (1H, d, *J* 12.4, benzyl-H_b), 4.82 (1H, d, *J* 9, 2-H), 4.33 (1H, d, *J* 18.6, 1'-H_a), 4.16 (2H, m, 1'-H_b and N-H), 3.57 (1H, dd, *J* 14.5, 10.4, 3-H_a), 3.45 (1H, dd, *J* 14.5, 4.6, 3-H_b), 2.93-2.77 (2H, m, 1-H), 2.06 (1H, d, *J* 2.3, H-3'); δ_C (75 MHz, $CDCl_3$); 156.2 (sulfonamide-C), 148.1 (phenyl 1-C), 136.7 (sulfonamide 4-C), 136.4 (benzyl 1-C), 133.7 (phenyl 5-C), 132.7 (sulfonamide 1-C), 131.7, 130.9 , 129.2, 128.6 (benzyl 3-C and 5-C), 128.5 (benzyl 2-C and 6-C), 128.0 (benzyl 4-C), 127.9, 126.8, 124.3, 76.3 (2'-C), 74.3 (3'-C), 66.7 (benzyl-C), 49.7 (2-C), 49.4 (1-C), 39.0 (1'-C), 36.8 (3-C); ν_{max}/cm^{-1} (film) 3405, 3298, 2123, 1711, 1544, 1360, 1166; *m*/*z* (*ESI*) 530.1 (100%, MNa^+); HRMS found MNa^+, 530.1359. $C_{26}H_{25}N_3O_6S$ requires *MNa,* 530.1356.

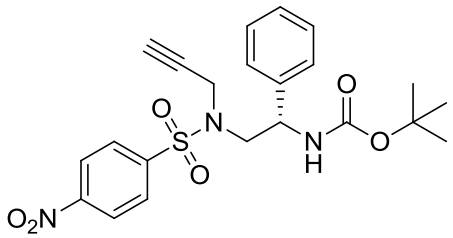
Benzyl-*N*-[(2*R*)-2-[*N*-(prop-2'-yn-1'-yl)(2-nitrobenzene)sulfonamido]propyl]carbamate, 270



By general procedure **G**, the sulfamidate **241** (271 mg, 1.00 mmol) and the sulfonamide *o*-**202** (360 mg, 1.50 mmol) gave a crude product. Purification by column chromatography, eluting with 6:4 petrol–EtOAc, gave the carbamate **270** (407 mg, 0.94 mmol, 94%) as a

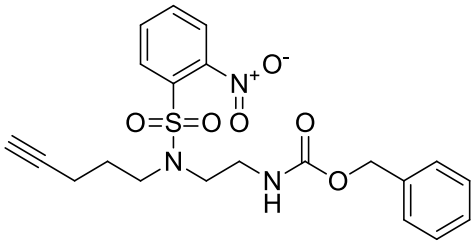
colourless solid; R_f 0.58 (1:1 petrol–EtOAc); $[\alpha]_D^{19}$ +20.5 (c 3.3, $CHCl_3$); δ_H (500 MHz, $CDCl_3$); 8.12 (1H, d, *J* 7.7, sulfonamide 3-H), 7.61 (2H, m, sulfonamide 6-H and 4-H), 7.53 (1H, m, sulfonamide 3-H), 7.42-7.28 (5H, m, benzyl Ar-H), 5.13 (1H, br s, N-H), 5.02 (1H, d, *J* 12.3, benzyl-H_a), 4.98 (1H, d, *J* 12.3, benzyl-H_b), 4.24-4.06 (3H, m, 1-H and 2-H), 3.40-3.28 (2H, m, 1'-H), 2.20 (1H, s, 3'-H), 1.24 (3H, d, *J* 6.8, 3-H); δ_C (75 MHz, $CDCl_3$); 156.3 (carbamate-C), 147.7 (sulfonamide 2-C), 136.4 (benzyl 1-C), 133.7 (sulfonamide 4-C), 133.3 (sulfonamide 5-C), 131.8 (sulfonamide 1-C), 131.6 (sulfonamide 6-C), 128.5 (benzyl 3-C and 5-C), 128.1 (benzyl 2-C and 6-C), 128.1 (benzyl 4-C), 124.3 (sulfonamide 3-C), 79.7 (2'-C), 72.8 (3'-C), 66.7 (benzyl-C), 54.1 (2-C), 43.6 (1-C), 31.9 (1'-C), 16.1 (3-C); ν_{max}/cm^{-1} (film) 3425, 3294, 2123, 1717, 1543, 1370, 1158; *m/z* (*ESI*) 454.1 (100%, MNa^+); HRMS found MNa^+, 454.1062. $C_{20}H_{21}N_3O_6S$ requires *MNa,* 454.1043.

tert-Butyl-*N*-[(1*S*)-1-phenyl-2-[*N*-(prop-2'-yn-1'-yl)(4-nitrobenzene)sulfonamido]ethyl]carbamate, 269



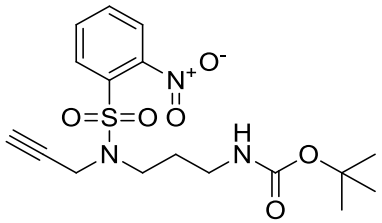
By general procedure **G**, the sulfamidate **239** (1.00 g, 3.34 mmol) and the sulfonamide *p*-**202** (963 mg, 4.01 mmol) gave a crude product. Purification by column chromatography, eluting with 7:3 petrol–EtOAc, gave the carbamate **269** (1.08 g, 2.34 mmol, 70%) as a colourless solid; R_f 0.84 (1:1 petrol–EtOAc); $[\alpha]_D^{19}$ –34.5 (c 1.7, MeOH); δ_H (500 MHz, $CDCl_3$); 8.32 (2H, d, *J* 8.8, sulfonamide 3-H and 5-H), 8.01 (2H, d, *J* 8.7, sulfonamide 2-H and 6-H), 7.43-7.34 (2H, m, phenyl 2 –H and 3-H), 7.32-7.30 (3H, m, phenyl 3-H, 4-H and 5-H), 5.30 (1H, br s, N-H), 4.94 (1H, br s, 1-H), 4.28 (1H, app. d, *J* 18.2, 1'-H_a), 4.19-4.06 (1H, m, 1'-H_b), 3.56 (1H, dd, *J* 14.3, 9.9, 2-H_a), 3.34 (1H, dd, *J* 14.3, 4.2, 2-H_b), 2.05 (1H, dd, *J* 5.3, 3.0, 3'-H), 1.48 (9H, s, *t*Bu-H); δ_C (75 MHz, $CDCl_3$); 155.5 (carbamate-C), 150.19 (sulfonamide 4-C), 144.5 (sulfonamide 1-C), 139.2 (phenyl 1-C), 129.0 (sulfonamide 2-C and 6-C), 128.9 (phenyl 3-C and 5-C), 128.1 (phenyl 4-C), 126.3 (sulfonamide 3-C and 5-C), 124.2 (phenyl 2-C and 6-C), 80.2 (*t*Bu-C), 75.5 (2,-C), 75.0 (3'-C), 52.0 (1-C), 51.3 (2-C), 36.8 (1'-C), 28.3 (*t*Bu-C); ν_{max}/cm^{-1} (film) 3406, 3294, 2979, 2122, 1706, 1531, 1351, 1167; *m/z* (*ESI*) 482.1 (100%, MNa^+); HRMS found MNa^+, 482.1365. $C_{22}H_{25}N_3O_6S$ requires *MNa,* 482.1356.

Benzyl-*N*-{2-[*N*-(pent-4'-yn-1'-yl)(2-nitrobenzene)sulfonamido]ethyl}carbamate, 265



By general procedure **G**, the sulfamidate **199** (200 mg, 0.77 mmol) and sulfonamide *o*-**237** (313 mg, 1.17 mmol) gave a crude product. Purification by column chromatography, eluting with 7:3 petrol–EtOAc, gave the carbamate **265** (305 mg, 0.68 mmol, 88%) as a colourless oil; R_f 0.47 (1:1 petrol–EtOAc); δ_H (300 MHz, $CDCl_3$); 8.10-7.95 (1H, m, sulfonamide 3 -H), 7.71-7.53 (3H, m, sulfonamide 4-H, 5-H and 6-H), 7.42-7.27 (5H, m, benzyl-H), 5.07 (1H, br s, N-H), 5.03 (2H, s, benzyl-H), 3.42 (6H, m, 1-H, 2-H and 1'H), 2.25-2.11 (2H, m, 3'-H), 1.93 (1H, t, *J* 2.5, 5'-H), 1.85-1.70 (2H, m, 2'-H); δ_C (75 MHz, $CDCl_3$); 156.3 (carbamate-C), 133.7 (sulfonamide 4-C), 132.9 (sulfonamide 1-C), 131.7 (sulfonamide 5-C), 131.1 (sulfonamide 6-C), 128.5 (benzyl 3-C and 5-C), 128.1 (benzyl 4-C), 128.0 (benzyl 2-C and 6-C), 124.3 (sulfonamide 3-C), 82.7 (4'-C), 69.4 (5'-C), 66.8 (benzyl-C), 46.8 (2-C), 46.8 (1'-C), 39.2 (1-C), 26.9 (2'-C), 15.7 (3'-C); ν_{max}/cm^{-1} (film) 3416, 3295, 2949, 2118, 1719, 1544, 1372, 1163; *m/z* (*ESI*) 468.1 (100%, MNa^+); HRMS found MNa^+, 468.1217. $C_{21}H_{23}N_3O_6S$ requires *MNa,* 468.1200.

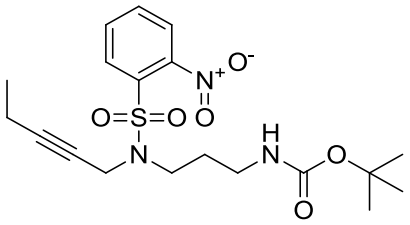
***tert*-Butyl-*N*-{3-[*N*-(prop-2-yn-1-yl)(2-nitrobenzene)sulfonamido]propyl}carbamate, 266**



By general procedure **G**, the sulfamidate **238** (500 mg, 2.11 mmol) and the sulfonamide *o*-**202** (760 mg, 3.16 mmol) gave a crude product. Purification by column chromatography, eluting with 100:1 CH_2Cl_2–MeOH, gave the carbamate **266** (722 mg, 1.82 mmol, 86%) as a colourless oil; R_f 0.47 (1:1 petrol–EtOAc); δ_H (300 MHz, $CDCl_3$); 8.08-7.99 (1H, m, sulfonamide 3-H), 7.77-7.61 (3H, m, sulfonamide 4-H, 5-H and 6-H), 4.84 (1H, br s, N-H), 4.20 (2H, d, *J* 2.4, 1'-H), 3.48 (2H, t, *J* 6.8, 3-H), 3.19 (2H, app. q, *J* 6.2, 1-H), 2.18 (1H, t, *J* 2.4, 3'-H), 1.80 (2H, app. p, *J* 6.7, 2-H), 1.44 (9H, s, *t*Bu-H); δ_C (75 MHz, $CDCl_3$); 156.0 (carbamate-C), 148.3 (sulfonamide 2-C), 133.8 (sulfonamide 4-C), 132.6 (sulfonamide 1-

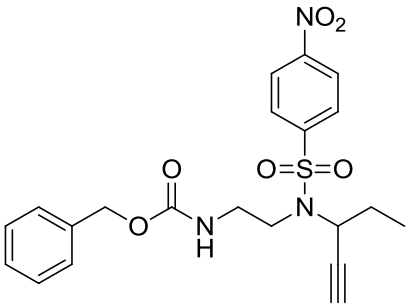
C), 131.7 (sulfonamide 5-C), 130.8 (sulfonamide 6-C), 124.3 (sulfonamide 3-C), 79.3 (*t*Bu-C), 77.2 (2'-C), 74.1 (3'-C), 44.3 (3-C), 37.2 (1'-C), 36.4 (1-C), 28.4 (*t*Bu-C), 27.6 (2-C); ν_{max}/cm^{-1} (film) 3294, 2978, 2122, 1703, 1546, 1367, 1167; *m/z* (*ESI*) 420.1 (100%, MNa^+); HRMS found MNa^+, 420.1217. $C_{17}H_{23}N_3O_6S$ requires *MNa,* 420.1200.

***tert*-Butyl-*N*-{3-[*N*-(pent-2'-yn-1'-yl)(2-nitrobenzene)sulfonamido]propyl}carbamate, 267**



By general procedure **G**, the sulfamidate **230** (300 mg, 1.26 mmol) and the sulfonamide *o*-**235** (510 mg, 1.90 mmol) gave a crude product. Purification by column chromatography, eluting with 7:3 petrol–EtOAc, gave the carbamate **267** (447 mg, 1.05 mmol, 83%) as a colourless oil; R_f 0.58 (1:1 petrol–EtOAc); δ_H (300 MHz, $CDCl_3$) 8.11–7.98 (1H, m, sulfonamide 3-H), 7.74–7.58 (3H, m, sulfonamide 4-H, 5-H and 6-H), 4.87 (1H, s, N-H), 4.15 (1H, t, *J* 2.2, 1'H), 3.46 (2H, t, *J* 6.7, 3-H), 3.19 (2H, m, 1H), 2.03 (2H, qt, *J* 7.5, 2.2, 4'-H), 1.78 (2H, m, 2-H), 1.44 (9H, s, *t*Bu-H), 0.98 (3H, t, *J* 7.5, 5'-H); δ_C (75 MHz, $CDCl_3$); 133.5 (sulfonamide 5-C), 131.4 (sulfonamide 4-C), 130.7 (sulfonamide 6-C), 124.1 (sulfonamide 3-C), 80.3 (*t*Bu-C), 71.9 (2'-C), 44.1 (3-C), 37.1 (1'-C), 36.8 (1-C), 28.4 (*t*Bu-C), 27.5 (2-C), 13.6 (5'-C), 12.2 (4'-C); ν_{max}/cm^{-1} (film) 3422, 2978, 1706, 1547, 1366, 1167; *m/z* (*ESI*) 448.2 (100%, MNa^+); HRMS found MNa^+, 448.1524. $C_{19}H_{27}N_3O_6S$ requires *MNa,* 448.1513.

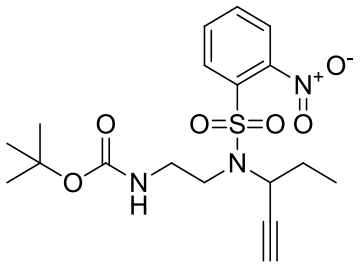
(±)-Benzyl-*N*-{2-[*N*-(pent-1'-yn-3'-yl)(4-nitrobenzene)sulfonamido]ethyl}carbamate, 263



By general procedure **G**, the sulfamidate **199** (600 mg, 2.33 mmol) and the sulfamidate *p*-**236** (750 mg, 2.80 mmol) gave a crude product. Purification by column chromatography, eluting with 7:3 petrol–EtOAc, gave the carbamate **263** (902 mg, 2.02 mmol, 90%) as a colourless solid; R_f 0.84 (1:1 petrol–EtOAc); δ_H (500 MHz, $CDCl_3$); 8.35 (2H, d, *J* 8.5,

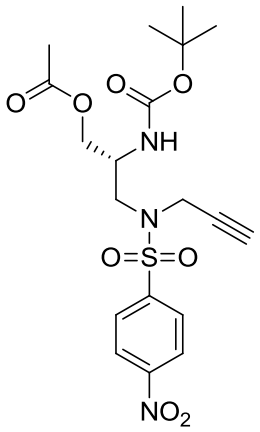
sulfonamide 3-H and 5-H), 8.03 (2H, d, *J* 8.4, sulfonamide 2-H and 6-H), 7.41-7.30 (5H, m, benzyl-H), 5.20 (1H, br s, N-H), 5.13 (1H, d, *J* 12.4, benzyl-H_a), 5.09 (1H, d, *J* 12.4, benzyl-H_b), 4.56 (1H, m, 3'-H), 3.54-3.43 (2H, m, 1-H), 3.38 (1H, dd, *J* 14.7, 6.7, 2-H_a), 3.16 (1H, m, 2-H_b), 2.09 (1H, s, 1'-H), 1.82-1.73 (2H, m, 4'-H), 1.03 (3H, t, *J* 7.1, 5'-H); δ_C (75 MHz, $CDCl_3$); 156.5 (carbamate-C), 150.2 (sulfonamide 4-C), 143.8 (sulfonamide 1-C), 136.3 (benzyl 1-C), 129.1 (sulfonamide 2-C and 6-C), 128.6 (benzyl 3-C and 5-C), 128.3 (benzyl 2-C and 6-C), 128.2 (benzyl 4-C), 124.2 (sulfonamide 3-C and 5-C), 79.35 (2'-C), 74.7 (1'-C), 66.9 (benzyl-C), 53.1 (3'-C), 44.6 (2-C), 41.6 (1-C), 28.8 (4'-C), 10.7 (5'-C); ν_{max}/cm^{-1} (film) 3279, 2973, 2110, 1692, 1531, 1347, 1168; *m/z* (*ESI*) 468.1 (100%, MNa^+); HRMS found MNa^+, 468.1214. $C_{21}H_{23}N_3O_6S$ requires *MNa,* 468.1200.

(±)-*tert*-Butyl-*N*-{2-[*N*-(pent-2'-yn-1'-yl)(2-nitrobenzene)sulfonamido]ethyl}carbamate, 262



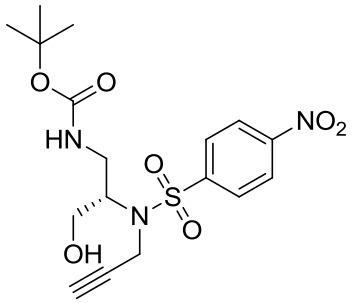
By general procedure **G**, the sulfamidate **200** (555 mg, 2.49 mmol) and the sulfonamide *o*-**236** (800 mg, 2.98 mmol) gave a crude product. Purification by column chromatography, eluting with 50:1 CH_2Cl_2–MeOH, gave the carbamate **262** (900 mg, 2.19 mmol, 88%) as a colourless oil; R_f 0.84 (1:1 petrol–EtOAc); δ_H (300 MHz, $CDCl_3$); 8.06-7.98 (1H, m, sulfonamide 3-H), 7.76-7.65 (2H, m, sulfonamide 5-H and 6-H), 7.64-7.58 (1H, m, sulfonamide 4-H), 4.95 (1H, br s, N-H), 4.60 (1H, td, *J* 7.8, 2.3, 3'-H), 3.59-3.45 (1H, m, 2-H_a), 3.43-3.36 (3H, m, 2-H_b, 1-H), 2.27 (1H, d, *J* 2.2, 1'-H), 1.89-1.75 (2H, m, 4'-H), 1.44 (9H, s, *t*Bu-H), 1.04 (3H, t, *J* 7.3, 5'-H); δ_C (75 MHz, $CDCl_3$); 155.9 (carbamate-C), 148.6 (sulfonamide 2-C), 133.8 (sulfonamide 4-C), 131.9 (sulfonamide 1-C), 131.5 (sulfonamide 5-C), 130.7 (sulfonamide 6-C), 124.1 (sulfonamide 3-C), 80.2 (*t*Bu-C), 79.5 (2'-C), 74.4 (1'-C), 52.9 (3'-C), 44.6 (2'-C), 40.8 (1-C), 28.8 (4'-C), 28.4 (*t*Bu-C), 10.7 (5'-C); ν_{max}/cm^{-1} (film) 3294, 2976, 2346, 1706, 1546, 1368, 1171; *m/z* (*ESI*) 434.1 (100%, MNa^+); HRMS found MNa^+, 434.1375. $C_{18}H_{25}N_3O_6S$ requires *MNa,* 434.1356.

(2*R*)-2-{[(*tert*-Butoxy)carbonyl]amino}-3-[*N*-(prop-2'-yn-1'-yl)(4-nitrobenzene)sulfonamido]propyl acetate, 274



By general procedure **G**, the sulfamidate **243** (100 mg, 0.349 mmol) and the sulfonamide *p*-**202** (98.0 mg, 0.410 mmol) gave a crude product. Purification by column chromatography, eluting with 7:3 petrol–EtOAc, gave the carbamate **274** (136 mg, 0.30 mmol, 89%) as a colourless soild; R_f 0.72 (1:1 petrol–EtOAc); $[\alpha]_D^{19}$ –19.9 (c 5.1 $CHCl_3$); δ_H (500 MHz, $CDCl_3$); 8.28 (2H, d, *J* 8.9, sulfonamide 3-H and 5-H), 3.97 (2H, d, *J* 8.9, sulfonamide 2-H and 6-H), 4.89 (1H, br d, *J* 8.3, N-H), 4.29 (1H, d, *J* 19, 1'-H_a), 4.17-4.06 (4H, m, 1'-H_b, 2-H and 1'-H), 3.36 (1H, dd, *J* 13.8 and 9.8, 3-H_a), 3.21 (1H, dd, *J* 13.9 and 4.5, 3-H_b), 2.03 (3H, s, acetate-H), 2.00 (1H, t, *J* 2.4, 3'-H), 1.38 (9H, s, *t*Bu-H); δ_C (75 MHz, $CDCl_3$); 170.7 (acetate-C), 155.6 (carbamate-C), 150.3 (sulfonamide 4-C), 144.5 (sulfonamide 1-C), 130 (sulfonamide 2-C and 4-C), 124.2 (sulfonamide 3-C and 5-C), 80.3 (*t*Bu-C), 75.6 (3'-C), 73.5 (2'-C), 63.9 (1-C), 47.3 (3-C), 47.1 (2-C), 37.1 (1'-C), 28.3 (*t*Bu-C), 20.8 (acetate-C); ν_{max}/cm^{-1} (film) 3276, 2979, 2121, 1740, 1709, 1532, 1352, 1167; *m/z* (*ESI*) 478.1 (100%, MNa^+); HRMS found MNa^+, 478.1272. $C_{19}H_{25}N_3O_8S$ requires *MNa,* 478.1255.

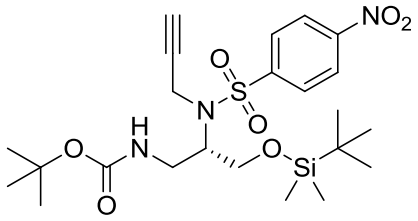
***tert*-Butyl-*N*-[(2*S*)-3-hydroxy-2-[*N*-(prop-2-yn-1-yl)(4-nitrobenzene)sulfonamido]propyl]carbamate, 271**



By general procedure **G**, the sulfamidate **242** (250 mg, 0.680 mmol) and the sulfonamide *p*-**202** (200 mg, 0.833 mmol) gave a crude product. Purification by column

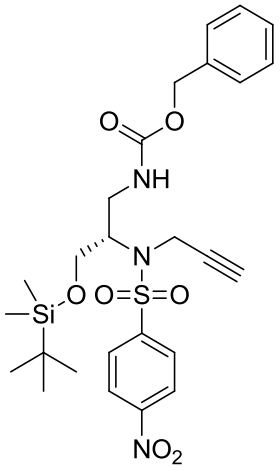
chromatography, gradient elution with 8:2 to 7:3 petrol–EtOAc, gave the carbamate **271** (184 mg, 0.445 mmol, 68%) as a colourless solid; R_f 0.59 (1:1 petrol–EtOAc); $[\alpha]_D^{22}$ –15.0 (c 0.5, MeOH); δ_H (500 MHz, $CDCl_3$); 8.34 (2H, d, *J* 8.9, sulfonamide 3-H and 5-H), 8.12 (2H, d, *J* 8.9, sulfonamide 2-H and 6-H), 4.80 (1H, br t, *J* 6.1, N-H), 4.43 (1H, dd, *J* 18.9 and 2.2, 1'-H_a), 4.32 (1H, dd, *J* 18.8 and 2.4, 1'-H_b), 4.01-3.91 (1H, m, 2-H), 3.77-3.63 (2H, m, 3-H), 3.47 (1H, dt, *J* 13.5 and 6.6, 1-H_a), 3.27 (1H, dt, *J* 14.2 and 6.9, 1-H_b), 2.74 (1H, t, *J* 6.5, O-H), 2.23 (1H, t, *J* 2.3, 3'-H), 1.43 (9H, s, *t*Bu-H); δ_C (75 MHz, $CDCl_3$); 150.1 (carbonyl-C), 128.9 (sulfonamide 2-C and 6-C), 124.1 (sulfonamide 3-C and 5-C), 80.5 (*t*Bu-C), 77.2 (2'-C), 73.3 (3'-C), 61.2 (3-C), 59.8 (2-C), 39.1 (1-C), 33.4 (1'-C), 28.3 (*t*Bu-C); ν_{max}/cm^{-1} (film) 3435, 2980, 1682, 15414, 1349, 1164; *m/z* (*ESI*) 136.2 (100%, MNa); HRMS Found MNa^+, 436.1166, $C_{17}H_{23}N_3O_7S$ requires *MNa*, 436.1149.

tert-Butyl-_N_-[(2_S_)-3-[(_tert_-butyldimethylsilyl)oxy]-2-[_N_-(prop-2'-yn-1'-yl)(4-nitrobenzene)sulfonamido]propyl]carbamate, 272



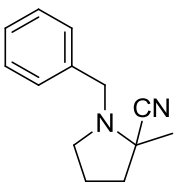
By general procedure **G**, the sulfamidate **242** (597 mg, 1.62 mmol) and the sulfonamide *p*-**202** (468 mg, 1.95 mmol) gave a crude product. Purification by column chromatography, eluting with 7:3 petrol–EtOAc, gave the carbamate **272** (638 mg, 1.21 mmol, 74%) as a colourless oil; R_f 0.82 (1:1 petrol–EtOAc); $[\alpha]_D^{19}$ –55.1 (c 3.4, $CHCl_3$); δ_H (500 MHz, $CDCl_3$); 8.32 (2H, d, *J* 8.7, sulfonamide 3-H and 5-H), 8.10 (2H, d, *J* 8.7, sulfonamide 2-H and 6-H), 4.65 (1H, t, *J* 5.5, N-H), 4.40 (1H, dd, *J* 19.8 and 1.8, 1'-H_a), 4.33 (1H, dd, *J* 18.9 and 1.9, 1'-H_b), 4.01 (1H, m, 2-H), 3.76 (2H, m, 3-H), 3.42 (1H, ddd, *J* 14.7, 6.7 and 5.1, 1-H_a), 3.33 (1H, dd, *J* 14.9, 9.1 and 5.1, 1-H_b), 2.19 (1H, t, *J* 2.1, 2'-H), 1.39 (9H, s, *t*BuO-H), 1.39 (9H, s, *t*BuSi-H), 0.02 (6H, s, 2 × SiMe-H); δ_C (75 MHz, $CDCl_3$); 155.8 (carbamate-C), 150.0 (sulfonamide 1-C), 128.8 (sulfonamide 2-C and 6-C), 124.1 (sulfonamide 3-C and 5-C), 79.7 (*t*BuO-C), 79.2 (2'-C), 73.2 (3'-C), 61.2 (3-C), 59.5 (2-C), 39.8 (1-C), 33.7 (1'-C), 28.3 (*t*BuO -C), 25.8 (*t*BuSi-C), 18.1 (*t*BuSi-C), -5.65 (2 × SiMe-C); ν_{max}/cm^{-1} (film) 3305, 2931, 2122, 1711, 1532, 1350, 1171; *m/z* (*ESI*) 550.2 (100%, MNa^+); HRMS found MNa^+, 550.2011. $C_{23}H_{37}N_3O_7SSi$ requires *MNa,* 550.2014.

Benzyl-*N*-[(2*S*)-3-[(*tert*-butyldimethylsilyl)oxy]-2-[*N*-(prop-2'-yn-1'-yl)(4-nitrobenzene)sulfonamido]propyl]carbamate, 273



By general procedure **G**, the sulfamidate **244** (2.9 g, 7.22 mmol) and the sulfonamide *p*-**202** (1.90 g, 7.91 mmol) gave a crude product. Purification by column chromatography, eluting with 7:3 petrol–EtOAc, gave the carbamate **273** (2.70 g, 4.81 mmol, 67%) as a colourless oil; R_f 0.49 (1:1 petrol–EtOAc); $[\alpha]_D^{19}$ +5.4 (c 1.8, $CHCl_3$); δ_H (500 MHz, $CDCl_3$); 8.21 (2H, d, *J* 8.7, sulfonamide 3-H and 5-H), 8.05 (2H, d, *J* 8.7, sulfonamide 2-H and 6-H), 7.39-7.28 (5H, m, benzyl Ar-H), 5.05 (1H, d, *J* 12.1, benzyl-H_a), 4.91 (1H, d, *J* 12.2, benzyl-H_b), 4.82 (1H, br s, N-H), 4.44 (1H, dd, *J* 18.8 and 2.3, 1'-H_a), 4.33 (1H, dd, *J* 18.9 and 2.1, 1'-H_b), 4.04 (1H, m, 2-H), 3.83-3.72 (2H, m, 3-H), 3.48 (1H, ddd, *J* 14.7, 6.6 and 4.8, 1-H_a), 3.37 (1H, ddd, *J* 15.1, 9.7 and 5.7, 1-H_b), 2.17 (1H, br t, *J* 2.18, 3'-H), 0.83 (9H, s, *t*BuSi-H), 0.00 (3H, s, SiMe-H), -0.01 (3H, s, SiMe-H); δ_C (75 MHz, $CDCl_3$); 156.9 (carbonyl-C), 150.1 (sulfonamide 4-C), 145.9 (sulfonamide 1-C), 136.0 (benzyl 1-C), 128.9 (sulfonamide 2-C and 6-C), 128.6 (benzyl 3-C and 5-C), 128.4 (benzyl 4-C), 128.2 (benzyl 2-C and 4-C), 124.1 (sulfonamide 3-C and 5-C), 77.2 (2'-C), 73.4 (3'-C), 67.3 (benzyl-C), 61.3 (3-C), 59.6 (2-C), 39.5 (1-C), 33.2 (1'-C), 25.7 (*t*Bu-C), 18.1 (*t*Bu-C), -2.95 (2 × SiMe-C); ν_{max}/cm^{-1} (film) 3418, 3293, 2955, 2122, 1708, 1530, 1350, 1166; *m*/*z* (*ESI*) 584.2 (100%, MNa); HRMS found MNa^+, 584.1852. $C_{26}H_{35}N_3O_7SSi$ requires *MNa,* 584.1857.

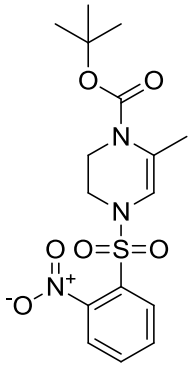
(±)-1-Benzyl-2-methylpyrrolidine-2-carbonitrile, 215[78]



The pyrrolidine **215** was prepared following the method of Hammond *et al.* TMSCN (0.25 mL, 2.0 mmol) was added to a suspension of the amine **210** (86.6 mg, 0.50 mmol) and

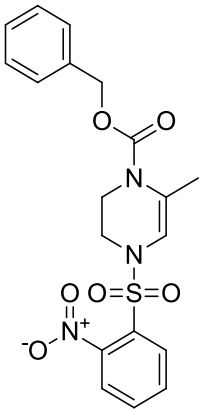
CuBr (3.6 mg, 25 μmol) in 1,4-dioxane (2 mL) and water (0.04 mL) in a microwave vial equipped with a magnetic stirrer. The vial was sealed, flushed with Ar and heated at 100 °C under microwave irradiation for 30 min. The reaction mixture was concentrated *in vacuo* to give a crude product. Purification by column chromatography, eluting with 4:1 hexane–Et_2O, gave the pyrrolidine **215** (78 mg, 0.4 mmol, 78%) as a light brown oil; δ_H (500 MHz, $CDCl_3$); 7.36-7.29 (4H, m, benzyl 2-H, 3-H, 5-H and 6-H), 7.29-7.24 (1H, m, benzyl 4-H), 4.01 (1H, d, *J* 13.0, benzyl-H_a), 3.35 (1H, d, *J* 13.0, benzyl-H_b), 2.99 (1H, td, *J* 9.4 and 3.4, 5-H_a), 2.41 (1H, td, *J* 9.4 and 7.9, 5-H_b), 2.36-2.31 (1H, m, 3-H_a), 1.95-1.72 (3H, m, 3-H_b, 4-H), 1.56 (3H, s, methyl-H); δ_C (75 MHz, $CDCl_3$); 138.5 (benzyl 1-C), 128.5 (benzyl 3-C and 5-C), 128.4 (benzyl 2-C and 6-C), 127.2 (benzyl 4-C), 120.0 (nitrile-C), 61.4 (2-C), 54.5 (benzyl-C), 51.6 (5-C), 38.9 (3-C), 23.7 (methyl-C), 20.0 (4-C); ν_{max}/cm^{-1} (film) 2949, 2210, 1450, 1156; *m*/*z* (*ESI*) 174.1 (100%, M^+-CN).

tert-Butyl-6-methyl-4-[(2-nitrobenzene)sulfonyl]-1,2,3,4-tetrahydropyrazine-1-carbamate, 77



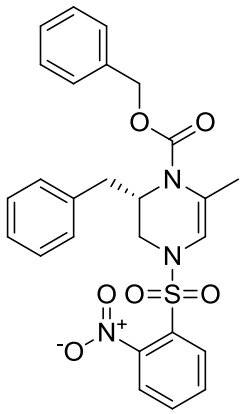
By general procedure **K**, the carbamate **208** (200 mg, 0.52 mmol) gave a crude product. Purification by column chromatography, eluting with 1:1 petrol–EtOAc, gave the carbamate **77** (194 mg, 0.51 mmol, 98%) as a bright yellow solid; R_f 0.33 (7:3 petrol–EtOAc); δ_H (500 MHz, $CDCl_3$); 7.96 (1H, dd, *J* 7.3 and 1.9, sulfonamide 3-H), 7.72 (2H, m, sulfonamide 5-H and 6-H), 7.63 (1H, m, sulfonamide 4-H), 5.98 (1H, s, 5-H), 3.67-3.61 (2H, m, 3-H), 3.61-3.57 (2H, m, 2-H), 2.07 (3H, s, methyl-H), 1.47 (9H, s, *t*Bu-H); δ_C (75 MHz, $CDCl_3$); 152.5 (sulfonamide 2-C), 134.0 (sulfonamide 4-C), 131.8 (sulfonamide 5-C), 131.3 (sulfonamide 1-C), 130.6 (sulfonamide 6-C), 124.2 (sulfonamide 3-C), 120.1 (6-C), 108.0 (5-C), 81.7 (*t*Bu-C), 44.6 (3-C), 41.6 (2-C), 28.3 (*t*Bu-C), 20.1 (methyl-C); ν_{max}/cm^{-1} (film) 2978, 1701, 1547, 1375, 1175; *m*/*z* (*ESI*) 406.1 (100%, MNa); HRMS found MNa^+, 406.1063, $C_{16}H_{21}N_3O_6S$ requires *MNa,* 406.1043.

Benzyl-6-methyl-4-[(2-nitrobenzene)sulfonyl]-1,2,3,4-tetrahydropyrazine-1-carbamate, 222



By general procedure **K**, the carbamate **209** (100 mg, 0.24 mmol) gave a crude product. Purification by column chromatography, eluting with 100% CH_2Cl_2, gave the carbamate **222** (98 mg, 0.23 mmol, 98%) as a bright yellow oil which solidified on standing; R_f 0.22 (7:3 petrol–EtOAc); δ_H (500 MHz, $CDCl_3$); 7.98-7.92 (1H, m, sulfonamide 3-H), 7.75-7.67 (2H, m, sulfonamide 5-H and 6-H), 7.65-7.61 (1H, m, 4-H), 7.39-7.30 (5H, m, benzyl Ar-H), 6.03 (1H, s, 5-H), 3.72-3.67 (4H, m, benzyl-H and 3-H), 3.67-3.62 (2H, m, 2-H), 2.08 (3H, s, methyl-H); δ_C (75 MHz, $CDCl_3$); 134.1 (sulfonamide 4-C), 131.8 (sulfonamide 5-C), 130.6 (sulfonamide 6-C), 128.6 (benzyl 3-C and 5-C), 128.4 (benzyl 4-C), 128.3 (benzyl 2-C and 6-C), 124.4 (6-C), 124.3 (sulfonamide 3-C), 108.8 (5-C), 68.0 (benzyl -C), 44.5 (3-C), 42.0 (2-C), 19.8 (methyl-C); ν_{max}/cm^{-1} (film) 3094, 2345, 1718, 1544, 1371, 1172; *m/z* (*ESI*) 440.1 (100%, MNa); HRMS found MNa^+, 440.0898, $C_{19}H_{19}N_3O_6S$ requires *MNa,* 440.0887.

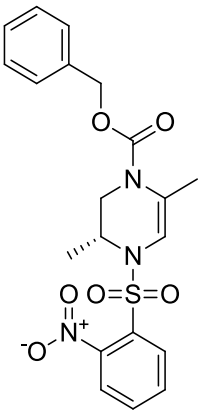
Benzyl-6-methyl-4-[(2-nitrobenzene)sulfonyl]-1,2,3,4-tetrahydropyrazine-1-carbamate, 275



By general procedure **K**, the carbamate **268** (200 mg, 0.39 mmol) gave a crude product. Purification by column chromatography, eluting with 1:1 petrol–EtOAc, gave the carbamate **275** (179 mg, 0.35 mmol, 90%) as a bright yellow solid; R_f 0.24 (7:3 petrol–

EtOAc); $[\alpha]_D^{19}$ −71.2 (c 1.3, $CHCl_3$); δ_H (500 MHz, $CDCl_3$); 7.94 (1H, d, *J* 7.9, sulfonamide 3-H), 7.76-7.60 (3H, m, sulfonamide 4-H, 5-H and 6-H), 7.38-7.29 (3H, m, benzyl 3-H, 4-H and 5-H), 7.25-7.17 (5H, m, benzyl 2-H and 6-H, phenyl 3-H, 4-H and 5-H), 7.08 (2H, m, phenyl 2-H and 6-H), 6.15 (1H, s, methly-H), 5.05 (1H, d, *J* 12.3, benzyl-H_a), 4.97 (1H, d, *J* 12.3, benzyl-H_b), 4.76 (1H, m, 2-H), 3.86 (1H, d, *J* 12.0, 3-H_a), 3.18 (1H, dd, *J* 11.9 and 3.3, 3-H_b), 2.72 (1H, dd, *J* 13.8 and 7.5, methylene-H_a), 2.70 (1H, dd, *J* 13.5 and 7.7, methylene-H_b) 2.10 (3H, s, methyl-H); δ_C (75 MHz, $CDCl_3$); 137.1 (phenyl 1-C), 135.7 (benzyl 1-C), 134.1 (sulfonamide 4-C), 131.8 (sulfonamide 5-C), 131.2 (sulfonamide 1-C), 130.6 (sulfonamide 6-C), 129.4, 128.6, 128.5, 128.3, 128.1, 126.7, 124.4 (sulfonamide 3-C), 108.8 (5-C), 67.8 (benzyl-C), 51.8 (2-C), 46.0 (3-C), 35.7 (methylene-C), 20.0 (methyl-C); ν_{max}/cm^{-1} (film) 3030, 2350, 1712, 1544, 1400, 1372, 1176; *m/z* (*ESI*) 530.1 (100%, MNa); HRMS found MNa^+, 530.1352, $C_{26}H_{25}N_3O_6S$ requires *MNa,* 530.1356.

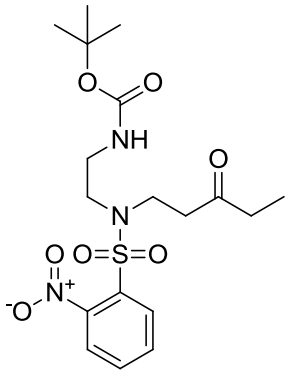
Benzyl-(3*R*)-3,6-dimethyl-4-[(2-nitrobenzene)sulfonyl]-1,2,3,4-tetrahydropyrazine-1- carbamate, 277



By general procedure **K**, the carbamate **270** (200 mg, 0.46 mmol) gave a crude product. Purification by column chromatography, eluting with 7:3 petrol–EtOAc, gave the carbamate **277** (192 mg, 0.45 mmol, 96%) as a bright yellow solid; R_f 0.38 (7:3 petrol–EtOAc); $[\alpha]_D^{19}$ −234.1 (c 2.4, $CHCl_3$); δ_H (500 MHz, $CDCl_3$); 8.01-7.94 (1H, m, sulfonamide 3-H), 7.73-7.67 (2H, m, sulfonamide 5-H and 6-H), 7.43-7.28 (1H, m, sulfonamide 4-H), 7.43-7.28 (5H, m, benzyl Ar-H), 5.94 (1H, s, 5-H), 5.20 (1H, d, *J* 12.2, benzyl-H_a), 5.12 (1H, d, *J* 12.2, benzyl-H_b), 4.35-4.26 (1H, m, 3-H), 4.21 (1H, d, *J* 13.2, 2-H_a), 2.66 (1H, dd, *J* 13.1 and 2.1, 2-H_b), 2.10 (3H, s, 6-methyl-H), 1.10 (3H, d, *J* 6.6, 3-methyl-H); δ_C (75 MHz, $CDCl_3$); 153.9 (carbamate-C), 148.2 (sulfonamide 2-C), 135.6 (benzyl 1-C), 134.0 (sulfonamide 4-C), 132.9 (sulfonamide 5-C), 131.6 (sulfonamide 6-C), 128.61 (benzyl 3-C and 5-C), 128.4 (benzyl 4-C), 128.2 (benzyl 2-C and 6-C), 124.1 (sulfonamide 3-C), 119.1 (5-C), 107.0 (4-C), 73.9 (benzyl-C), 49.5 (3-C), 46.5 (2-C), 19.7 (6-methyl-C), 17.1 (3-methyl-C), ν_{max}/cm^{-1}

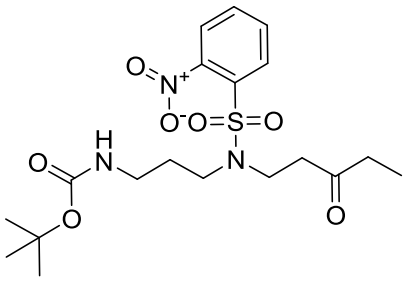
(film) 3094, 2933, 2341, 1712, 1544, 1402, 1244; *m*/*z* (*ESI*) 454.1 (100%, MNa); HRMS found MNa^+, 454.1061, $C_{20}H_{21}N_3O_6S$ requires *MNa,* 454.1043.

***tert*-Butyl-*N*-{2-[*N*-(3'-oxopentyl)(2-nitrobenzene)sulfonamido]ethyl}carbamate, 285**



By general procedure **L**, the carbamate **261** (150 mg, 0.36 mmol) gave a crude product. Purification by column chromatography, eluting with 1:1 petrol–EtOAc, gave the carbamate **285** (107 mg, 0.25 mmol, 68%) as a colourless oil; R_f 0.13 (7:3 petrol–EtOAc); δ_H (500 MHz, $CDCl_3$); 8.01 (1H, dd, *J* 7.4 and 1.7, sulfonamide 3-H), 7.76-7.67 (2H, m, sulfonamide 6-H and 5 -H), 7.67-7.60 (1H, m, sulfonamide 4-H), 4.90 (1H, br s, N-H), 3.56 (2H, t, *J* 7.2, 1'-H), 3.40 (2H, t, *J* 6.0, 2-H), 3.36-3.28 (2H, m, 1-H), 2.81 (2H, t, *J* 7.1, 2'-H), 2.44 (2H, q, *J* 7.3, 4'-H), 1.42 (9H, s, *t*Bu-H), 1.03 (3H, t, *J* 7.3, 5'-H); δ_C (75 MHz, $CDCl_3$); 209.2 (ketone-C), 155.9 (carbamate-C), 148.1 (sulfonamide 2-C), 133.8 (sulfonamide 4-C), 132.5 (sulfonamide 1-C), 131.9 (sulfonamide 5-C), 131.0 (sulfonamide 6-C), 124.3 (sulfonamide 3-C), 79.6 (*t*Bu-C), 48.3 (2-C), 43.3 (2'-C), 41.5 (1'C), 39.1 (1-C), 36.3 (4'-C), 28.4 (*t*Bu-C), 7.6 (5'-C); ν_{max}/cm^{-1} (film) 3414, 2979, 2391, 1710, 1590, 1545, 1367, 1164; *m*/*z* (*ESI*) 452.1 (100%, MNa); HRMS found MNa^+, 452.1475, $C_{18}H_{27}N_3O_7S$ requires *MNa,* 452.1462.

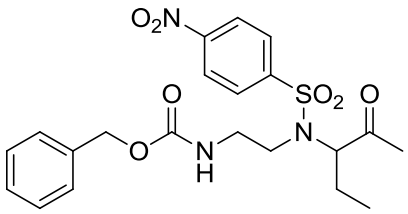
***tert*-Butyl-*N*-{3'-[*N*-(3-oxopentyl)(2-nitrobenzene)sulfonamido]propyl}carbamate, 288**



By general procedure **L**, the carbamate **267** (100 mg, 0.24 mmol) gave a crude product. Purification by column chromatography, eluting with 1:1 petrol–EtOAc, gave the

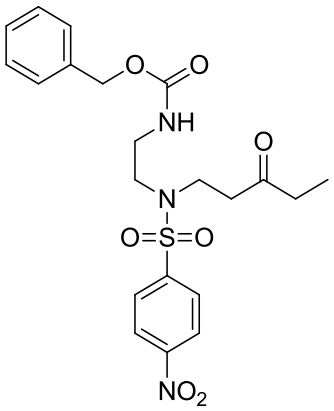
carbamate **288** (64 mg, 0.14 mmol, 61%) as a colourless oil**;** R_f 0.11 (7:3 petrol–EtOAc); δ_H (500 MHz, $CDCl_3$); 8.02-7.95 (1H, m, sulfonamide 3-H), 7.75-7.68 (2H, m, sulfonamide 5-H and 6-H), 7.65-7.63 (1H, m, sulfonamide 4-H), 4.85 (1H, br s, N-H), 3.54 (2H, t, *J* 7.2, 1'-H), 3.35 (2H, t, *J* 7.0, 3-H), 3.16 (2H, m, 1-H), 2.77 (2H, t, *J* 7.1, 2'-H), 2.43 (2H, q, *J* 7.3, 4'-H), 1.75 (2H, app. p, *J* 6.7, 2-H), 1.44 (9H, s, *t*Bu-H), 1.03 (3H, t, *J* 7.3, 5'-H); δ_C (75 MHz, $CDCl_3$); 209.1 (ketone-C), 156.0 (carbamate-C), 148.1 (sulfonamide 2-C), 133.7 (sulfonamide 4-C), 132.8 (sulfonamide 1-C), 131.8 (sulfonamide 5-C), 130.7 (sulfonamide 6-C), 124.3 (sulfonamide 3-C), 79.3 (*t*Bu-C), 46.5 (2-C), 42.6 (2'-C), 41.6 (1'-C), 37.4 (1-C), 36.3 (4'-C), 28.6 (2-C), 28.4 (*t*Bu-C), 7.6 (5'-C); ν_{max}/cm^{-1} (film) 3407, 2978, 1708, 1590, 1546, 1367, 1165; *m/z* (*ESI*) 466.2 (100%, MNa); HRMS found MNa^+, 466.1638, $C_{19}H_{29}N_3O_7S$ requires *MNa,* 466.1618.

(±)-Benzyl-*N*-{2-[*N*-(2'-oxopentan-3'-yl)(4-nitrobenzene)sulfonamido]ethyl}carbamate, 287



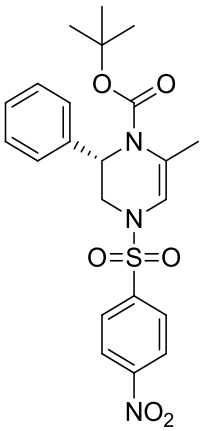
By general procedure **L**, the carbamate **264** (150 mg, 0.34 mmol) gave a crude product. Purification by column chromatography, eluting with 1:1 petrol–EtOAc, gave the carbamate **287** (72 mg, 0.16 mmol, 46%) as a colourless oil**;** R_f 0.16 (7:3 petrol–EtOAc); δ_H (500 MHz, $CDCl_3$); 8.32 (2H, d, *J* 8.6, sulfonamide 3-H and 5-H), 7.96 (2H, d, *J* 8.5, sulfonamide 2-H and 6-H), 7.40-7.29 (5H, m, phenyl-H), 5.29 (1H, br s, N-H), 5.07 (2H, s, benzyl-H), 4.36 (1H, dd, *J* 10.0 and 4.5, 3'-H), 3.46-3.38 (1H, m, 1-H_a), 3.37-3.23 (3H, m, 1-H_b and 2-H), 2.15 (3H, s, 1'-H), 2.07-1.98 (1H, m, 4'-H_a), 1.60-1.51 (1H, m, 4-H_b), 0.97 (3H, t, *J* 7.2, 5'-H); δ_C (75 MHz, $CDCl_3$); 206.2 (ketone), 150.1 (carbamate-C), 128.6 (sulfonamide 2-C and 6-C), 128.5 (benzyl-C), 128.3 (benzyl-C), 128.1 (benzyl-C), 124.3 (sulfonamide 3-C and 5-C), 68.8 (3'-C), 66.8 (benzyl-C), 45.2 (2-C), 41.1 (1-C), 27.8 (1'-C), 21.4 (4'-C), 11.7 (5'-C) [Sulfonamide 1-C and Ar 4-C were not observed]; ν_{max}/cm^{-1} (film) 3411, 2973, 2455, 1721, 1606, 1531, 1312, 1166; *m/z* (*ESI*) 486.1 (100%, MNa); (Found MNa^+, 486.1320, $C_{21}H_{25}N_3O_7S$ requires *MNa,* 486.1305).

Benzyl-*N*-{2-[*N*-(3'-oxopentyl)(4-nitrobenzene)sulfonamido]ethyl}carbamate, 286



By general procedure **L**, the carbamate **263** (200 mg, 0.45 mmol) gave a crude product. Purification by column chromatography, eluting with 1:1 petrol–EtOAc, gave the carbamate **286** (176 mg, 0.38 mmol, 85%) as a colourless oil; R_f 0.13 (7:3 petrol–EtOAc); δ_H (500 MHz, $CDCl_3$); 8.35 (2H, d, *J* 8.5, sulfonamide 3-H and 5-H), 7.98 (2H, d, *J* 8.5, sulfonamide 2-H and 6-H), 7.42-7.30 (5H, m, benzyl Ar-H), 5.14 (1H, br s, N-H), 5.10 (2H, s, benzyl-H), 3.42-3.38 (4H, m, 1-H and 1'), 3.27 (2H, t, *J* 5.9, 2-H), 2.82 (2H, t, *J* 7.0, 2'-H), 2.41 (2H, q, *J* 7.2, 4'-H), 1.01 (3H, t, *J* 7.3, 5'-H); δ_C (75 MHz, $CDCl_3$); 209.1 (ketone-C), 150.2 (sulfonamide 4-C), 144.4 (sulfonamide 2-C), 136.3 (benzyl 1-C), 128.6 (sulfonamide 2-C and 6-C), 128.5 (benzyl 3-C and 5-C), 128.3 (benzyl 4 -C), 128.1 (benzyl 2-C and 6-C), 124.5 (sulfonamide 3-C and 5-C), 66.9 (benzyl-C), 49.2 (2-C), 44.5 (2'-C), 42.1 (1'-C), 40.1 (1-C), 36.3 (4'-C), 7.6 (5'-C); ν_{max}/cm^{-1} (film) 3411, 2973, 1721, 1606, 1531, 1350, 1166; *m/z* (*ESI*) 486.1 (100%, MNa); HRMS found MNa^+, 486.1311, $C_{21}H_{25}N_3O_7S$ requires *MNa,* 486.1305.

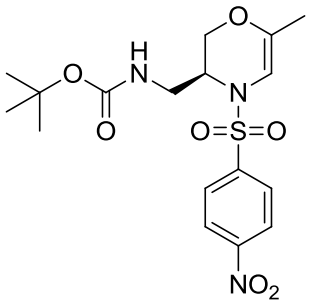
***tert*-Butyl-(2*S*)-6-methyl-4-[(4-nitrobenzene)sulfonyl]-2-phenyl-1,2,3,4-tetrahydropyrazine-1- carbamate, 276**



By general procedure **K**, the carbamate **269** (200 mg, 0.44 mmol) gave a crude product. Purification by column chromatography, eluting with 1:1 petrol–EtOAc, gave the

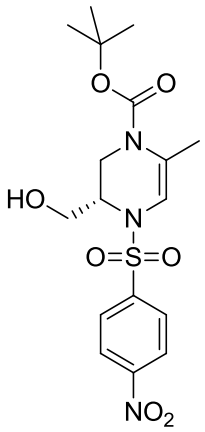
carbamate **276** (192 mg, 0.42 mmol, 96%) as a bright yellow solid; R_f 0.66 (7:3 petrol–EtOAc); $[\alpha]_D^{19}$ +23.0 (c 0.5, $CHCl_3$); δ_H (500 MHz, $CDCl_3$); 8.12 (2H, d, *J* 8.8, sulfonamide 3-H and 5-H), 7.67 (2H, d, *J* 8.8, sulfonamide 2-H and 6-H), 7.14-7.06 (3H, m, phenyl 3-H, 4-H and 5-H), 6.99 (2H, d, *J* 6.3, phenyl 2-H and 6-H), 6.00 (1H, s, 5-H), 5.60 (1H, app. s, 2-H), 4.33 (1H, d, *J* 12.7, 2-H_a), 3.44 (1H, dd, *J* 12.6 and 3.5, 2-H_b), 2.17 (3H, s, methyl-H), 1.43 (9H, s, *t*Bu-H); δ_C (75 MHz, $CDCl_3$); 152.6 (carbamate-C), 149.8 (sulfonamide 4-C), 143.7 (sulfonamide 1-C), 137.4 (phenyl 1-C), 128.5 (sulfonamide 2-C and 6-C), 127.8 (phenyl 3-C and 5-C), 127.3 (phenyl 4-C) 125.7 (phenyl 2-C and 6-C), 124.2 (sulfonamide 3-C and 5-C), 118.7 (6-C), 107.9 (5-C), 82.2 (*t*Bu-C), 53.2 (1-C), 47.7 (2-C), 28.2 (*t*Bu-C), 20.7 (methyl-C); ν_{max}/cm^{-1} (film) 2978, 1697, 1530, 1348, 1169; *m*/*z* (*ESI*) 482.1 (100%, MNa); HRMS found MNa^+, 482.1356, $C_{22}H_{25}N_3O_6S$ requires *MNa,* 482.1356.

tert-Butyl-*N*-{[(3*S*)-6-methyl-4-[(4-nitrobenzene)sulfonyl]-3,4-dihydro-2,1-H,4-oxazin-3-yl]methyl}carbamate, 279



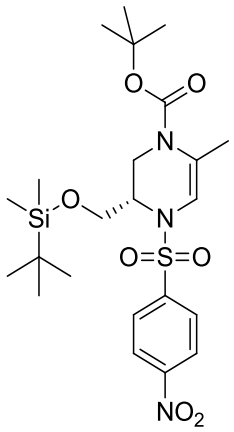
By general procedure **K**, the carbamate **271** (100 mg, 0.24 mmol) gave a mixture of crude products. Purification by column chromatography, eluting with 8:2 petrol–EtOAc, gave the carbamate **279** (48 mg, 0.12 mmol, 48%) as a bright yellow solid; R_f 0.50 (7:3 petrol–EtOAc); $[\alpha]_D^{19}$ +189.7 (c 0.3, $CHCl_3$); δ_H (500 MHz, $CDCl_3$); 8.38 (2H, d, *J* 8.7, sulfonamide 3-H and 5-H), 7.95 (2H, d, *J* 8.6, sulfonamide 2-H and 6-H), 5.81 (1H, s, 5-H), 4.94 (1H, br s, N-H), 4.05 (1H, br s, 3-H), 3.92 (2H, d, *J* 11.2, 2-H_a), 3.31-3.19 (1H, m, methylene-H_a), 3.17-3.02 (1H, m, methylene-H_b), 2.78 (2H, d, *J* 11.2, 2-H_b), 1.77 (3H, s, methyl-H), 1.46 (9H, s, *t*Bu-H); δ_C (75 MHz, $CDCl_3$); 156.2 (carbamate-C), 150.2 (sulfonamide 4-C), 142.5 (sulfonamide 2-C), 141.5 (6-C), 128.6 (sulfonamide 2-C and 6-C), 124.5 (sulfonamide 3-C and 5-C), 97.1 (5-C), 79.9 (*t*Bu-C), 63.7 (2-C), 51.3 (3-C), 40.1 (methylene-C), 28.4 (*t*Bu-C), 17.7 (methyl-C); ν_{max}/cm^{-1} (film) 3416, 2980, 1709, 1532, 1351, 1171; *m*/*z* (*ESI*) 436.1 (100%, MNa); HRMS found MNa^+, 136.1157, $C_{17}H_{23}N_3O_7S$ requires *MNa,* 436.1149. Also isolated was the carbamate **278** (36 mg, 0.09 mmol, 36%) as a bright yellow solid.

***tert*-Butyl(3*S*)-3-(hydroxymethyl)-6-methyl-4-[(4-nitrobenzene)sulfonyl]-1,2,3,4-tetrahydropyrazine-1-carbamate, 278**



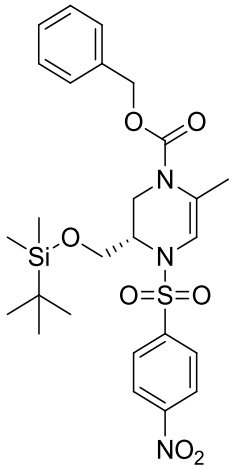
HF (50% in H_20, 0.40 mL, 9.47 mmol) was added to a solution of carbamate **280** (1.00 g, 1.89 mmol) in CH_2Cl_2 (20 mL) and MeCN (20 mL) and stirred at rt for 2h. Me_3SiOMe (1.40 ml, 10.2 mmol) was added to the reaction mixture and stirred for a further 30 min. The reaction mixture was concentrated *in vacuo* to give a crude product. Purification by column chromatography, eluting with 7:3 petrol–EtOAc, gave the carbamate **278** (611 mg, 1.48 mmol, 78%) as a yellow solid; R_f 0.34 (7:3 petrol–EtOAc); $[\alpha]_D^{19}$ −166.9 (c 1.3, $CHCl_3$); δ_H (500 MHz, $CDCl_3$); 8.39 (2H, d, *J* 8.4, sulfonamide 3-H and 5-H), 7.97 (2H, d, *J* 8.5, sulfonamide 2-H and 5-H), 6.06 (1H, s, 5-H), 4.36 (1H, d, *J* 13.6, 2-H_a), 4.01 (1H, br s, 3-H), 3.65 (1H, dd, *J* 11.6 and 6.1, methylene-H_a), 3.28 (1H, dd, *J* 11.5 and 8.9, methylene-H_b), 2.89 (1H, s, O-H), 2.05 (3H, s, methyl-H), 1.96 (1H, dd, *J* 13.6 and 2.5, 2-H_b), 1.47 (9H, s, *t*Bu-H); δ_C (75 MHz, $CDCl_3$); 150.3 (sulfonamide 4-C), 143.2 (sulfonamide 1-C), 128.3 (sulfonamide 2-C and 6-C), 124.6 (sulfonamide 3-C and 5-C), 120.8 (6-C), 107.7 (5-C), 82.6 (*t*Bu-C), 59.9 (methylene-C), 55.2 (2-C), 40.4 (1-C), 28.1 (*t*Bu-C), 20.0 (methyl-C); ν_{max}/cm^{-1} (film) 3416, 2977, 2932, 1701, 1532, 1367, 1176; *m/z* (*ESI*) 436.1 (100%, MNa); HRMS found MNa^+, 136.1158, $C_{17}H_{23}N_3O_7S$ requires *MNa,* 436.1149.

***tert*-Butyl-(3*S*)-3-{[(*tert*-butyldimethylsilyl)oxy]methyl}-6-methyl-4-[(4-nitrobenzene)sulfonyl]-1,2,3,4-tetrahydropyrazine-1- carbamate, 280**



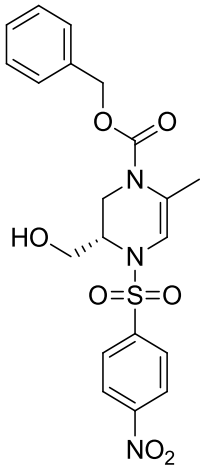
By general procedure **K**, the carbamate **272** (150 mg, 0.28 mmol) gave a crude product. Purification by column chromatography, eluting with 7:3 petrol–EtOAc, gave the carbamate **280** (119 mg, 0.23 mmol, 79%) as a bright yellow oil which solidified on standing; R_f 0.81 (7:3 petrol–EtOAc); $[\alpha]_D^{19}$ −331.3 (c 3.4, $CHCl_3$); δ_H (500 MHz, $CDCl_3$); 8.33 (2H, d, *J* 8.9, sulfonamide 3-H and 5-H), 7.91 (2H, d, *J* 8.9, sulfonamide 2-H and 6-H), 5.87 (1H, s, 5-H), 4.31 (1H, dd, *J* 13.1 and 1.9, 2-H_a), 3.82 (1H, br s, 2-H), 3.57 (1H, dd, *J* 9.9 and 4.9, methylene-H_a), 3.35 (1H, app. t, *J* 9.9, methlyene-H_b), 2.01 (3H, s, methyl-H), 1.92 (1H, dd, *J* 13.1 and 2.8, 2-H_b), 1.39 (9H, s, *t*BuO), 0.84 (9H, s, *t*BuSi), 0.02 (3H, s, MeSi), 0.00 (3H, s, MeSi -H); δ_C (75 MHz, $CDCl_3$); 152.3 (carbamate-C), 150.2 (sulfonamide 4-C), 143.0 (sulfonamide 1-C), 128.3 (sulfonamide 2-C and 6-C), 124.6 (sulfonamide 3-C and 5-C), 121.3 (6-C), 105.6 (5-C), 81.7 (*t*BuO-C), 60.7 (methylene-C), 54.9 (3-C), 40.0 (2-C), 27.9 (*t*BuO-C), 25.9 (*t*BuSi-C), 20.1 (*t*BuSi-C), 18.2 (methyl-C), -5.4 (MeSi-C), -5.5 (MeSi -C); ν_{max}/cm^{-1} (film) 2931, 1706, 1533, 1388, 1251, 1178; *m/z* (*ESI*) 550.2 (100%, MNa); HRMS found MNa^+, 550.2017, $C_{23}H_{37}N_3O_7SSi$ requires *MNa,* 550.2014.

Benzyl-(3*S*)-3-{[(tert-butyldimethylsilyl)oxy]methyl}-6-methyl-4-[(4-nitrobenzene)sulfonyl]-1,2,3,4-tetrahydropyrazine-1- carbamate, 281



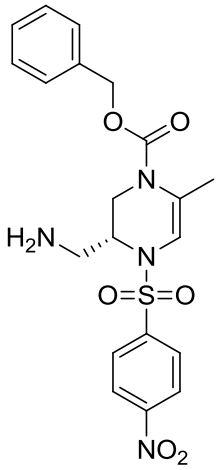
By general procedure **K**, the carbamate **273** (2.67 g, 4.80 mmol) gave a crude product. Purification by column chromatography, eluting with 8:2 petrol–EtOAc, gave the carbamate **281** (2.25 mg, 4.00 mmol, 85%) as a bright yellow solid; R_f 0.81 (7:3 petrol–EtOAc); $[\alpha]_D^{19}$ −270.5 (c 1.2, $CHCl_3$); δ_H (500 MHz, $CDCl_3$); 8.37 (2H, d, *J* 8.6, sulfonamide 3-H and 5-H), 7.94 (2H, d, *J* 8.6, sulfonamide 2-H and 6-H), 7.37-7.27 (5H, m, benzyl Ar-H), 5.96 (1H, s, 5-H), 5.15 (1H, d, *J* 12.2, benzyl-H_a), 5.03 (1H, d, *J* 12.2, benzyl-H_b), 4.43 (1H, dd, *J* 13.1 and 1.4, 2-H_a), 3.94-3.85 (1H, m, 3-H), 3.63 (1H, dd, *J* 9.9 and 5.0, methylene-H_a), 3.40 (1H, app. t, *J* 9.8, methylene-H_b), 2.10-2.01 (4H, m, benzyl-H and 2-H_b), 0.85 (9H, s, *t*Bu-H), 0.03 (3H, s, MeSi-H), 0.00 (3H, s, MeSi-H); δ_C (75 MHz, $CDCl_3$); 128.6 (sulfonamide 2-C and 6-C), 128.4 (benzyl 3-C and 5-C), 128.3 (benzyl 4-C), 128.2 (benzyl 2-C and 6-C), 124.6 (sulfonamide 3-C and 5-C), 106.2 (5-C), 68.0 (benzyl-C), 60.5 (methylene-C), 54.5 (3-C), 40.4 (2-C), 25.8 (*t*Bu-C), 19.8 (methyl-C), -5.6 (MeSi-C), -5.6 (MeSi-C) [Carbamate and quaternary Ar-C were not observed]; ν_{max}/cm^{-1} (film) 2954, 1717, 1532, 1401, 1349, 1252, 1178; *m/z* (*ESI*) 584.2 (100%, MNa); HRMS found MNa^+, 584.1875, $C_{26}H_{35}N_3O_7SSi$ requires *MNa,* 584.1857.

Benzyl(3*S*)-3-(hydroxymethyl)-6-methyl-4-[(4-nitrobenzene)sulfonyl]-1,2,3,4-tetrahydropyrazine-1- carbamate, 312



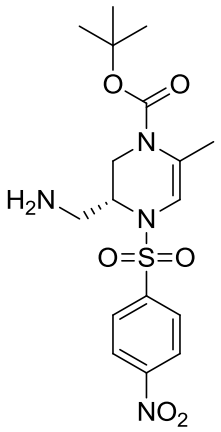
HF (50% in H_20, 0.72 mL, 19.7 mmol) was added to a solution of carbamate **281** (2.21 g, 3.94 mmol) in CH_2Cl_2 (30 mL) and MeCN (30 mL) and stirred at rt for 2h. Me_3SiOMe (2.7 ml, 19.7 mmol) was added to the reaction mixture and stirred for a further 30 min. The reaction mixture was concentrated *in vacuo* to give a crude product. Purification by column chromatography, eluting with 7:3 petrol–EtOAc, gave the carbamate **312** (1.41 g, 3.14 mmol, 80%) as a yellow oil which solidified on standing; R_f 0.28 (7:3 petrol–EtOAc); $[\alpha]_D^{19}$ −314.0 (c 0.8, $CHCl_3$); δ_H (500 MHz, $CDCl_3$); 8.38 (2H, d, *J* 8.6, sulfonamide 3-H and 5-H), 7.96 (2H, d, *J* 8.7, sulfonamide 2-H and 6-H), 7.40-7.29 (5H, m, benzyl-H), 6.07 (1H, s, 5-H), 5.19 (1H, d, *J* 12.1, benzyl-H_a), 5.11 (1H, d, *J* 12.1, benzyl-H_b), 4.41 (1H, dd, *J* 13.4 and 1.1, 2-H_a), 4.00 (1H, m, 3-H), 3.61 (1H, dd, *J* 10.9 and 5.9, methylene-H_a), 3.27 (1H, app. t, *J* 10.2, methylene-H_b), 2.09-2.04 (5H, m, 2-H_b, methyl-H and O-H); δ_C (75 MHz, $CDCl_3$); 143.1 (sulfonamide 1-C), 135.4 (benzyl 1-C), 128.7 (sulfonamide 2-C and 6-C), 128.6 (benzyl 3-C and 5-C), 128.3 (benzyl 4-C), 128.3 (benzyl 2-C and 6-C), 124.7 (sulfonamide 3-C and 5-C), 108.0 (5-C), 68.4 (benzyl-C), 60.0 (methylene-C), 55.0 (3-C), 40.9 (1-C), 19.8 (methyl-C) [Quaternary Ar-C were not observed]; ν_{max}/cm^{-1} (film) 3447, 2934, 1709, 1531, 1402, 1350, 1249, 1175; *m/z* (*ESI*) 470.1 (100%, MNa); HRMS found MNa^+, 470.1000, $C_{20}H_{21}N_3O_7S$ requires *MNa,* 470.0992.

Benzyl-(3*R*)-3-(aminomethyl)-6-methyl-4-[(4-nitrobenzene)sulfonyl]-1,2,3,4-tetrahydropyrazine-1- carbamate, 314



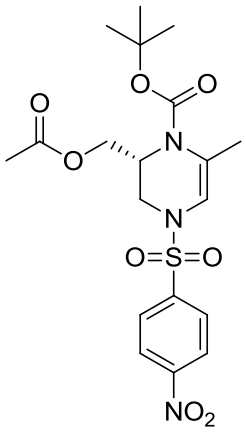
Diphenyl phosphoryl azide (0.96 mL, 4.45 mmol) was added dropwise to a solution of carbamate **312** (1.00 g, 2.23 mmol) and PPh_3 (1.17 g, 4.46 mmol) in THF (22 mL) at 0 °C and the resulting solution was stirred at rt for 4h. The reaction mixture was concentrated *in vacuo* to give a crude azide intermediate which was partially purified by cloumn chromatography, eluting with 8:2 petrol–EtOAc. H_20 (32 mL) was added to a solution of the azide intermediate and PPh_3 (645 mg, 2.45 mmol) in THF (10 mL) and the resulting solution was stirred at rt for 12h. The reaction mixture was concentrated *in vacuo* to give a crude product. Purification by SCX resin gave the carbamate **314** (572 mg, 1.28 mmol, 57% over 2 steps) as a yellow oil which solidified on standing; R_f 0.37 (9:1 CH_2Cl_2–MeOH; $[\alpha]_D^{19}$ −296.4 (c 0.6, $CHCl_3$); δ_H (500 MHz, $CDCl_3$); 8.37 (2H, d, *J* 8.8, sulfonamide 3-H and 5-H), 7.95 (2H, d, *J* 8.8, sulfonamide 2-H and 6-H), 7.40-7.28 (5H, m, benzyl Ar-H), 6.02 (1H, s, 5-H), 5.18 (1H, d, *J* 12.1, benzyl-H_a), 5.07 (1H, d, *J* 12.1, benzyl-H_b), 4.35 (1H, d, *J* 13.4, 2-H_a), 3.83 (1H, m, 3-H), 2.73 (1H, dd, *J* 13.3 and 6.6, methylene-H_a), 2.51 (1H, dd, *J* 13.3 and 7.9, methylene-H_b), 2.07 (3H, s, methyl-H), 1.97 (1H, dd, *J* 13.3 and 2.1, 2-H_b), 1.38 (2H, br s, N-H); δ_C (75 MHz, $CDCl_3$); 150.3 (sulfonamide 4-C), 142.9 (sulfonamide 1-C), 135.5 (benzyl 1-C), 128.7 (sulfonamide 2-C and 6-C), 128.6 (benzyl 3-C and 5-C), 128.4 (benzyl 4-C), 128.3 (benzyl 2-C and 6-C), 124.6 (sulfonamide 3-C and 5-C), 107.0 (5-C), 68.2 (benzyl-C), 55.9 (3-C), 41.4 (2-C), 41.3 (methylene-C), 19.8 (methyl-C); ν_{max}/cm^{-1} (film) 3384, 2977, 1531, 1401, 1349, 1243, 1178; *m/z* (*ESI*) 447.1 (100%, MH^+); HRMS found MH^+, 447.1354, $C_{20}H_{22}N_4O_6S$ requires *MH,* 447.1333.

***tert*-Butyl-(3*R*)-3-(aminomethyl)-6-methyl-4-[(4-nitrobenzene)sulfonyl]-1,2,3,4-tetrahydropyrazine-1-carbamate, 311**



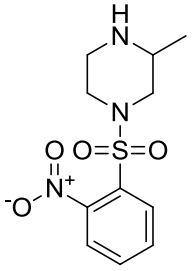
Diphenyl phosphoryl azide (0.96 mL, 4.43 mmol) was added dropwise to a solution of carbamate **278** (368 mg, 0.90 mmol) and PPh_3 (933 mg, 3.56 mmol) in THF (20 mL) at 0 °C and the resulting solution was stirred at rt for 4h. The reaction mixture was concentrated *in vacuo* to give a crude azide intermediate which was partially purified by cloumn chromatography, eluting with 8:2 petrol–EtOAc. H_20 (1 mL) was added to a solution of the azide intermediate and PPh_3 (260 mg, 1.00 mmol) in THF (20 mL) and the resulting solution was stirred at rt for 12h. The reaction mixture was concentrated *in vacuo* to give a crude product. Purification by SCX resin gave the carbamate **311** (216 mg, 0.52 mmol, 59% over 2 steps) as a yellow oil which solidified on standing; R_f 0.37 (9:1 CH_2Cl_2–MeOH); $[\alpha]_D^{19}$ −334.1 (c 0.6, $CHCl_3$); δ_H (500 MHz, $CDCl_3$); 8.39 (2H, d, *J* 8.8, sulfonamide 3-H and 5-H), 7.97 (2H, d, *J* 8.7, sulfonamide 2-H and 5-H), 6.00 (1H, s, 5-H), 4.31 (1H, d, *J* 13.3, 2-H_a), 3.85 (1H, br s, 3-H), 2.77 (1H, dd, *J* 13.4 and 6.7, methylene-H_a), 2.57 (1H, dd, *J* 13.4 and 7.8, methylene-H_b), 2.05 (3H, s, methyl-H), 1.88 (1H, dd, *J* 13.4 and 2.2, 2-H_b), 1.55 (2H, br s, N-H), 1.45 (9H, s, *t*Bu-H); δ_C (75 MHz, $CDCl_3$); 150.2 (sulfonamide 4-C), 143.0 (sulfonamide 1-C), 128.4 (sulfonamide 2 –C and 5-C), 124.6 (sulfonamide 3-C and 5-C), 121.2 (6-C), 106.5 (5-C), 82.1 (*t*Bu-C), 56.5 (3-C), 41.5 (2-C), 40.9 (methylene-C), 28.2 (*t*Bu-C), 20.1 (methyl-C) [Carbonyl was not observed]; ν_{max}/cm^{-1} (film) 3385, 3033, 1711, 1531, 1401, 1350, 1243; *m/z* (*ESI*) 413.1 (100%, MH^+); HRMS found MH^+, 413.1488, $C_{17}H_{24}N_4O_6S$ requires *MH,* 413.1489.

***tert*-Butyl(2*R*)-2-[(acetyloxy)methyl]-6-methyl-4-[(4-nitrobenzene)sulfonyl]-1,2,3,4-tetrahydropyrazine-1-carbamate, 282**



By general procedure **K**, the carbamate **274** (100 mg, 0.28 mmol) gave a crude product. Purification by column chromatography, eluting with 7:3 petrol–EtOAc, gave the carbamate **282** (92 mg, 0.20 mmol, 92%) as a bright yellow soild; R_f 0.73 (1:1 petrol–EtOAc); $[\alpha]_D^{19}$ −86.8 (c 1.7, $CHCl_3$); δ_H (500 MHz, $CDCl_3$); 8.38 (2H, d, *J* 8.7, sulfonamide 3-H and 5-H), 7.98 (2H, d, *J* 8.7, sulfonamide 2-H and 6-H), 6.00 (1H, s, 5-H), 4.80-4.70 (1H, br s, 2-H), 4.01 (1H, d, *J* 12.0, 3-H_a), 3.94 (1H, dd, *J* 11.1 and 7.5, methylene-H_a), 3.77 (1H, dd, *J* 11.1 and 7.2, methylene-H_b), 2.96 (1H, dd, *J* 12.0 and 3.5, 3-H_b), 2.04 (3H, s, acetyl-H), 1.44 (9H, s, *t*Bu-H); δ_C (75 MHz, $CDCl_3$); 170.3 (acetyl -C), 152.1 (carbamate-C), 150.3 (sulfonamide 4-C), 142.9 (sulfonamide 1-C), 128.3 (sulfonamide 2-C and 6-C), 124.6 (sulfonamide 3-C and 5-C), 124.4 (6-C), 107.0 (5-C), 82.2 (*t*Bu-C), 60.5 (methylene-C), 48.3 (2-C), 44.1 (3-C), 28.2 (*t*Bu-C), 20.7 (acetyl-C), 20.4 (methyl-C); ν_{max}/cm^{-1} (film) 3282, 2979, 1746, 1698, 1532, 1369; *m*/*z* (*ESI*) 478.1 (100%, MNa^+); HRMS found MNa^+, 478.1270, $C_{19}H_{25}N_3O_8S$ requires *MNa,* 478.1255.

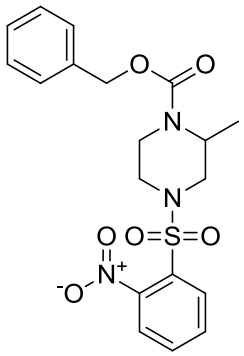
(±)-3-Methyl-1-[(2-nitrobenzene)sulfonyl]piperazine, 300[104]



By general procedure **M**, **77** (50.0 mg, 0.13 mmol) gave a crude product. Purification with SCX resin gave the piperazine **300** (28.0 mg, 0.01 mmol, 76%) as a colourless oil; R_f 0.67 (9:1 CH_2Cl_2–MeOH); δ_H (500 MHz, $CDCl_3$); 7.97 (1H, dd, *J* 7.3 and 1.8, sulfonamide 3-H), 7.71 (2H, m, sulfonamide 5-H and 6-H), 7.66-7.59 (1H, m, sulfonamide 4-H), 3.73 (2H, m, 2-

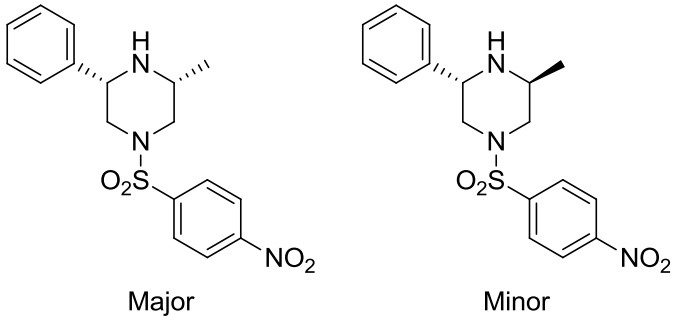
H_a and 6-H_a), 3.28 (1H, br s, N-H), 3.12 (1H, m, 6-H_b), 3.01-2.89 (3H, m, 3-H, 5-H_a and 5-H_b), 2.56 (1H, dd, *J* 12.1 and 10.4, 2-H_b), 1.16 (3H, d, *J* 6.4, methyl-H); δ_C (75 MHz, $CDCl_3$); 133.9 (Ar 4-C), 131.6 (Ar 5-C), 121.2 (Ar 1-C), 130.9 (Ar 6-C), 124.2 (Ar 3-C), 51.8 (2-C), 50.7 (3-C), 45.4 (6-C), 45.0 (5-C), 18.6 (methyl-C) [Ar 2-C was not observed]; ν_{max}/cm^{-1} (film) 2424, 2979, 1702, 1546, 1367, 1167; *m*/*z* (*ESI*) 286.3 (100%, MH^+).

(±)-Benzyl-2-methyl-4-[(2-nitrobenzene)sulfonyl]piperazine-1-carbamate, 314



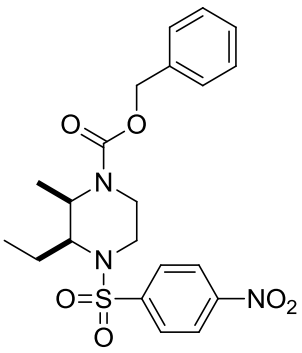
By general procedure **M**, **222** (50.0 mg, 0.12 mmol) gave a crude product. Purification by column chromatography, eluting with 6:4 petrol–EtOAc, gave the piperazine **314** (36.0 mg, 0.09 mmol, 72%) as a colourless oil; R_f 0.38 (1:1 petrol–EtOAc); δ_H (500 MHz, $CDCl_3$); 8.00-7.88 (1H, m, sulfonamide 3-H), 7.76-7.65 (2H, m, sulfonamide 5-H and 6-H), 7.64-7.57 (1H, m, sulfonamide 3-H), 7.40-7.28 (5H, m, phenyl-H), 5.13 (1H, d, *J* 12.5, benzyl-H_a), 5.11 (1H, d, *J* 12.5, benzyl-H_b), 4.46 (1H, br s, 2-H), 4.04 (1H, d, *J* 13.3, 6-H_a), 3.80 (1H, dd, *J* 12.4 and 1.6, 5-H_a), 3.61 (1H, dt, *J* 12.5 and 1.8, 3-H_a), 3.26 (1H, td, *J* 13.3 and 3.4, 6-H_b), 2.97 (1H, dd, *J* 12.4 and 3.7, 3-H_b), 2.77 (1H, td, *J* 12.3 and 3.5, 5-H_b), 1.24 (3H, d, *J* 7.0, methyl-H); δ_C (75 MHz, $CDCl_3$); 154.8 (carbonyl-C), 148.4 (sulfonamide 1-C), 136.3 (phenyl 1-C), 133.9 (sulfonamide 4-C), 131.9 (sulfonamide 5-C), 131.1 (sulfonamide 1-C), 130.94 (sulfonamide 6-C), 128.6 (phenyl 3-C and 5-C), 128.2 (phenyl 4-C), 128.0 (phenyl 2-C and 6-C), 124.2 (sulfonamide 3-C), 67.5 (benzyl-C), 50.1 (3-C), 46.7 (2-C), 45.8 (5-C), 38.5 (6-C), 15.0 (methyl-C); ν_{max}/cm^{-1} (film) 2923, 1699, 1545, 1374, 1172; *m*/*z* (*ESI*) 442.1 (100%, MNa^+); HRMS found MNa^+, 442.1065, $C_{19}H_{21}N_3O_6S$ requires *MNa,* 442.1043.

(3*R*, 5*S*)-3-Methyl-1-[(4-nitrobenzene)sulfonyl]-5-phenylpiperazine, 317



By general procedure **M**, the carbamate **276** (18.0 mg, 0.04 mmol) gave a crude product. Purification with SCX resin gave the piperazine **317** (10.0 mg, 0.03 mmol, 71%, 8:1 dr) as a colourless oil; R_f 0.79 (9:1 CH_2Cl_2–MeOH); $[\alpha]_D^{19}$ +114.7 (c 0.7, $CHCl_3$), δ_H (500 MHz, $CDCl_3$); Major 8.37 (2H, d, *J* 8.9, sulfonamide 3-H and 5-H), 7.91 (2H, d, *J* 8.9, sulfonamide 2-H and 6-H), 7.39-7.27 (5H, m, phenyl-H), 3.98 (1H, dd, *J* 10.4 and 3.0, 5-H), 3.79 (1H, ddd, *J* 11.0, 2.9 and 1.8, 2-H_a), 3.74 (1H, ddd, *J* 10.9, 2.7 and 1.8, 6-H_a), 3.16-3.09 (1H, m, 3-H), 2.18 (1H, app. t, *J* 10.7, 6-H_b), 2.04 (1H, app. t, *J* 10.6, 2-H_b), 1.11 (3H, d, *J* 6.3, methyl); Major δ_C (75 MHz, $CDCl_3$); 150.2 (sulfonamide 4-C), 142.0 (sulfonamide 1-C)128.8 (sulfonamide 2-C and 6-C), 128.7 (phenyl-C), 128.3 (phenyl -C), 127.0 (phenyl -C), 124.4 (sulfonamide 3-C and 5-C), 60.0 (5-C), 52.5 (2-C), 52.0 (6-C), 50.7 (3-C), 19.4 (methyl); Minor 8.37 (2H, d, *J* 8.9, sulfonamide 3-H and 5-H), 7.91 (2H, d, *J* 8.9, sulfonamide 2-H and 6-H), 7.39-7.27 (5H, m, phenyl-H), 4.30 (1H, dd, *J* 8.1, 3.4, 5-H), 3.56-3.51 (1H, m, 6-H_a), 3.37-3.32 (1H, m, 3-H), 3.20-3.16 (1H, m, 2-H_a), 3.03-3.00 (1H, m, 2-H_b), 2.83 (1H, m, 6-H_b), 1.33 (3H, d, *J* 6.6, methyl); ν_{max}/cm^{-1} (film) 3106, 2852, 1530, 1351, 1168; *m/z* (*ESI*) 362.1 (100%, MH^+); HRMS found MH^+, 362.1182, $C_{17}H_{20}N_3O_4S$ requires *MH,* 362.1169.

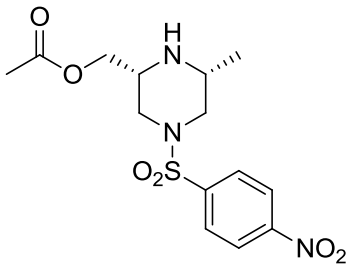
***rac*-(*cis*)Benzyl-3-ethyl-2-methyl-4-[(4-nitrobenzene)sulfonyl]piperazine-1-carbamate, 318**



By general procedure **M**, the carbamate **287** (50.0 mg, 0.11 mmol) gave a crude product. Purification by column chromatography, eluting with 8:2 petrol–EtOAc, gave the piperazine **318** (42.0 mg, 0.09 mmol, 82%) as a colourless oil; R_f 0.64 (1:1 petrol–EtOAc);

δ_H (500 MHz, $CDCl_3$); 8.24 (2H, d, *J* 8.8, sulfonamide 3-H and 5-H), 7.88 (2H, d, *J* 8.8, sulfonamide 2-H and 6-H), 7.33-7.24 (3H, m, benzyl 2-H, 4-H and 6-H), 7.21 (2H, m, benzyl 3-H and 5-H), 4.97 (1H, d, *J* 12.4, benzyl-H_a), 4.94 (1H, d, *J* 12.4, benzyl-H_b), 4.09-4.03 (1H, m, 2-H), 3.69-3.59 (2H, m, 6-H_a and 5-H_a), 3.41 (1H, td, *J* 7.7 and 4.7, 3-H), 3.34-3.19 (2H, m, 6-H_b and 5-H_b), 1.58 (2H, m, ethyl-H), 1.15 (3H, d, *J* 6.9, methyl-H), 0.84 (3H, t, *J* 7.4, ethyl-H); δ_C (75 MHz, $CDCl_3$); 154.8 (carbonyl-C), 149.9 (sulfonamide 4-C), 146.8 (sulfonamide 1-C), 136.2 (benzyl 1-C), 128.6 (sulfonamide 2-C and 6-C), 128.2 (benzyl 3-C and 5-C), 128.0 (benzyl 4-C), 127.8 (benzyl 2-C and 6-C), 124.5 (sulfonamide 3-C and 5-C), 67.3 (benzyl-C), 62.4 (3-C), 50.5 (2-C), 45.1 (5-C), 39.9 (6-C), 21.9 (ethyl CH_2-C), 13.2 (methyl-C), 11.0 (ethyl CH3-C); ν_{max}/cm^{-1} (film) 2973, 1699, 1530, 1350, 1163; *m/z* (*ESI*) 470.1 (100%, MNa^+); HRMS found MNa^+, 470.1371, $C_{21}H_{25}N_3O_6S$ requires *MNa,* 470.1356.

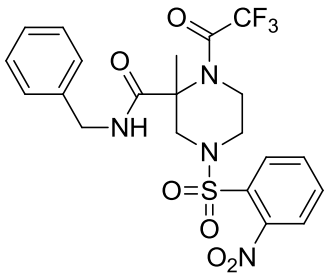
[(2*R*)-6-Methyl-4-[(4-nitrobenzene)sulfonyl]piperazin-2-yl]methyl acetate, 316



Major

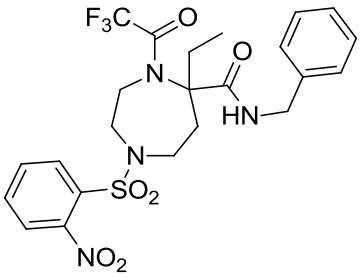
By general procedure **M**, the carbamate **282** (50.0 mg, 0.10 mmol) gave a crude product. Purification with SCX resin gave the piperazine **316** (30.0 mg, 0.08 mmol, 76%, 2:1 dr) as a colourless oil; R_f 0.52 (9:1 CH_2Cl_2–MeOH); $[\alpha]_D^{19}$ +17.5 (c 0.7, $CHCl_3$), δ_H (500 MHz, $CDCl_3$); 8.40 (2H, d, *J* 8.8, sulfonamide 3-H and 5-H), 7.95 (2H, d, *J* 8.8, sulfonamide 2-H and 6-H), 4.02 (1H, dd, *J* 11.2 and 5.1, 2-methyl-H_a), 3.92 (1H, dd, *J* 11.0 and 6.7, 2-methyl-H_b), 3.77 (1H, d, *J* 10.6, 3-H_a), 3.69 (1H, d, *J* 11.2, 5-H_a), 3.18 (1H, m, 2-H), 3.00 (1H, m, 6-H), 2.09-2.01 (4H, m, OAc and 3-H_b), 2.00-1.92 (1H, m, 5-H_b), 1.08 (3H, d, *J* 6.3, 6-methyl-H), δ_C (75 MHz, $CDCl_3$); 170.5 (OAc-C), 150.3 (sulfonamide 4-C), 141.9 (sulfonamide 1-C), 128.8 (sulfonamide 2-C and 6-C), 124.5 (sulfonamide 3-C and 5-C), 65.1 (2-methyl-C), 53.8 (5-C), 52.0 (2-C), 50.2 (4-C), 47.8 (6-C), 20.8 (OAc-C), 19.0 (6-methyl-C), ν_{max}/cm^{-1} (film) 2967, 1740, 1606, 1531, 1352, 1170; *m/z* (*ESI*) 358.1 (100%, MH^+); HRMS found MH^+, 358.1080, $C_{14}H_{19}N_3O_6S$ requires *MNa,* 358.1067.

(±)-*N*-Benzyl-2-methyl-4-[(2-nitrobenzene)sulfonyl]-1-(trifluoroacetyl)piperazine-2-carboxamide, 301



By general procedure **N**, the carbamate **77** (200 mg, 0.52 mmol) gave a crude product. Purification by column chromatography, eluting with 1:1 petrol–EtOAc, gave the piperazine **301** (187 mg, 0.36 mmol, 70%) as a colourless soild; R_f 0.33 (1:1 petrol–EtOAc); δ_H (500 MHz, $CDCl_3$); 7.98 (1H, d, *J* 7.7, sulfonamide 3-H), 7.77-7.67 (2H, m, sulfonamide 5-H and 6-H), 7.67-7.60 (1H, m, sulfonamide 4-H), 7.37-7.30 (2H, m, benzyl 2-H and 6-H), 7.30-7.22 (3H, m, benzyl 3-H, 4-H and 5-H), 6.26 (1H, d, *J* 5.2, N-H), 4.41 (1H, dd, *J* 14.9 and 5.4, benzyl CH_2-H_a), 4.36 (2H, dd, *J* 14.8 and 5.5, benzyl CH_2-H_b), 3.96-3.90 (1H, m, 5-H_a), 3.81-3.71 (3H, m, 5-H, 6-H_a and 3-H_b), 3.66 (1H, d, *J* 13.7, 3-H_b), 3.53-3.43 (1H, m, 6-H_b), 1.67 (3H, s, methyl-H); δ_C (75 MHz, $CDCl_3$); 169.2 (Amide-C), 134.3 (sulfonamide 4-C), 132.0 (sulfonamide 5-C), 131.2 (sulfonamide 6-C), 128.9 (Phenyl 3-C and 5-C), 127.9 (Phenyl 4-C), 127.8 (Phenyl 2-C and 6-C), 124.5 (sulfonamide 3-C), 80.3 (2-C), 64.2 (3-C), 51.8 (5-C), 44.3 (6-C), 44.2 (benzyl-C), 18.1 (methyl-C) [Quaternary Ar-C were not observed]; ν_{max}/cm^{-1} (film) 3385, 2927, 1703, 1674, 1544, 1372, 1159; *m/z* (*ESI*) 537.1 (100%, MNa^+); HRMS found MNa^+, 537.1038, $C_{21}H_{21}F_3N_4O_6S$ requires *MNa,* 537.1026.

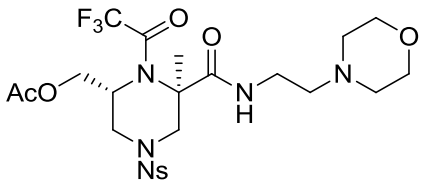
(±)-*N*-Benzyl-5-ethyl-1-[(2-nitrobenzene)sulfonyl]-4-(trifluoroacetyl)-1,4-diazepane-5-carboxamide, 323



By general procedure **N**, the carbamate **285** (50.0 mg, 0.10 mmol) gave a crude product**.** Purification by column chromatography, eluting with 7:3 petrol–EtOAc, gave the amide **323** (43.0 mg, 0.08 mmol, 71%) as a colourless solid; R_f 0.44 (1:1 petrol–EtOAc); δ_H (500 MHz, $CDCl_3$); 7.98-7.88 (1H, m, sulfonamide 3-H), 7.74-7.68 (2H, m, sulfonamide 5H and 6-

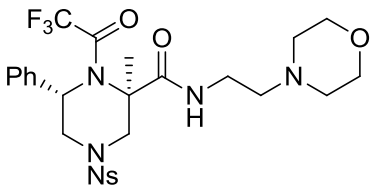
H), 7.65 (1H, m, sulfonamide 4-H), 7.37-7.31 (2H, m, benzyl 2-H and 6-H), 7.31-7.24 (3H, m, benzyl 3-H, 4-H and 5-H), 5.92 (1H, t, *J* 5.2, N-H), 4.47 (1H, dd, *J* 14.7 and 5.5, benzyl CH_2-H_a), 4.40 (1H, dd, *J* 14.7 and 5.4, benzyl CH_2-H_b), 4.21 (1H, dd, *J* 16.8 and 5.4, 3-H_a), 4.11-4.04 (1H, m, 2-H_a), 3.86 (1H, dd, *J* 14.6 and 6.7, 7-H_a), 3.60 (1H, dd, *J* 14.6 and 10.6, 7-H_b), 3.49 (1H, dd, *J* 16.8 and 9.0, 3-H_b), 3.36 (1H, dd, *J* 14.4 and 8.9, 2-H_b), 2.71-2.64 (1H, m, ethyl CH_2-H_a), 2.58 (1H, dd, *J* 16.3 and 10.7, 6-H_a), 1.91 (1H, dd, *J* 16.4 and 6.7, 6-H_b), 1.65-1.55 (1H, m, ethyl CH_2-H_b), 0.93 (3H, t, *J* 7.3, ethyl-H); δ_C (75 MHz, $CDCl_3$); 170.7 (amide-C), 148.0 (Ar-C), 137.8 (benzyl 1-C), 133.9 (Ar-C), 132.4 (Ar-C), 132.0 (Ar-C), 130.5 (Ar-C), 128.9 (Ar-C), 127.7 (Ar-C), 124.5 (sulfonamide 3-C), 114.4 (CF_3-C), 69.1 (5-C), 49.8 (2-C), 48.5 (3-C), 44.0 (benzyl-C), 43.9 (7-C), 37.4 (6-C), 26.8 (ethyl-C), 7.9 (ethyl-C); ν_{max}/cm^{-1} (film); 3424, 3026, 1698, 1670, 1545, 1372, 1207, 1155 *m/z* (*ESI*) 565.1 (100%, MNa^+); HRMS found MNa^+, 565.1336, $C_{23}H_{25}F_3N_4O_6S$ requires *MNa,* 565.1339.

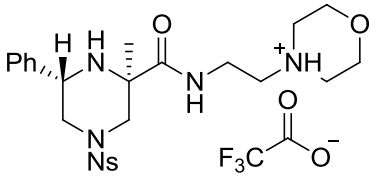
[(2*R*,6*R*)-6-Methyl-6-{[2'-(morpholin-4-yl)ethyl]carbamoyl}-4-[(4-nitrobenzene)sulfonyl]-1-(trifluoroacetyl)piperazin-2-yl]methyl acetate, 322



By general procedure **N**, the carbamate **282** (50.0 mg, 0.09 mmol) gave a crude product**.** Purification by column chromatography, eluting with 1:1 petrol–EtOAc, gave the amide **322** (38.0 mg, 0.06 mmol, 65%) as a colourless solid; R_f 0.25 (1:1 petrol–EtOAc); $[\alpha]_D^{19}$ +116.7 (c 0.4, $CHCl_3$); δ_H (500 MHz, $CDCl_3$); 11.0 (1H, br s, N-H), 8.39 (2H, d, *J* 8.7, sulfonamide 3-H and 5-H), 7.96 (2H, d, *J* 8.7, sulfonamide 2-H and 6-H), 4.16 (1H, app. q, *J* 10.4, CH_2-H_a), 4.09 (1H, dd, *J* 10.7, 5.8, CH_2-H_b), 4.01 (1H, d, *J* 15.6, 5-H_a), 3.96-3.88 (1H, m, 2-H), 3.66 (4H, br s, morpholine 2-H and 6-H), 3.48 (1H, d, *J* 11.6, 3-H_a), 3.36-3.27 (2H, m, 2'-H), 2.89 (1H, dd, *J* 11.5 and 5.3, 3-H_b), 2.53-2.50 (2H, m, 5-H_b and 1'-H_a), 2.44 (1H, d, *J* 13.6, 1'-H_b), 2.39 (4H, br s, morpholine 3-H and 5-H), 2.08 (3H, s, acetyl-H), 1.43 (3H, s, methyl-H); δ_C (125 MHz, $CDCl_3$); 170.4 (Acetate-C), 150.4 (sulfonamide 1-C), 142.5 (sulfonamide 4-C), 128.8 (sulfonamide 2-C and 6-C), 124.5 (sulfonamide 3-C and 5-C), 65.7 (AcetateCH_2-C), 63.7 (morpholine 2-C and 6-C), 59.3 (2'-C), 56.6 (morpholine 3-C and 5-C), 51.4 (5-C), 47.5 (2-C), 46.1 (3-C), 29.7 (1'-C), 23.8 (methyl-C), 20.8 (acetyl-C); δ_F (282 MHz, $CDCl_3$) -82.16; ν_{max}/cm^{-1} (film) 2924, 1724, 1533, 1353, 1167; *m/z* (*ESI*) 610.2 (100%, MH^+); HRMS found MH^+, 610.1789, $C_{23}H_{30}F_3N_5O_9S$ requires *MH*, 610.1789.

(2*R*,6*S*)-2-Methyl-*N*-[2'-(morpholin-4-yl)ethyl]-4-[(4-nitrobenzene)sulfonyl]-6-phenyl-1-(trifluoroacetyl)piperazine-2-carboxamide, 320, and **4-(2-{[(2*R*,6*S*)-2-Methyl-4-[(4-nitrobenzene)sulfonyl]-6-phenylpiperazin-2-yl]formamido}ethyl)morpholin-4-ium trifluoroacetate, 321**



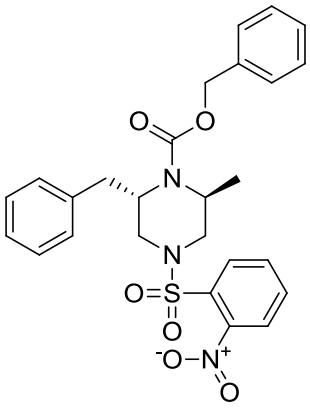


By general procedure **N**, the carbamate **276** (200 mg, 0.44 mmol) gave a crude product**.** Purification by column chromatography, gradient elution with 1:1 petrol–EtOAc to 100% EtOAc, gave the amide **320** (76.0 mg, 0.12 mmol, 28%) as a colourless soild; R_f 0.45 (1:1 petrol–EtOAc); δ_H (500 MHz, $CDCl_3$); 11.13 (1H, br s, N-H), 8.38 (2H, d, *J* 8.7, sulfonamide 3-H and 5-H), 7.96 (2H, d, *J* 8.7, sulfonamide 2-H and 6-H), 7.46 (2H, d, *J* 7.7, phenyl 2-H and 6-H), 7.32 (2H, t, *J* 7.5, phenyl 3-H and 5-H), 7.27-7.24 (1H, m, phenyl 4-H), 4.87 (1H, d, *J* 4.9, 6-H), 4.20 (1H, d, *J* 11.8, 5-H_a), 4.04 (1H, d, *J* 15.5, 1'-H_a), 3.70 (4H, br s, morpholine 2-H and 6-H), 3.45-3.33 (2H, m, 5-H_b and 1'-H_b), 3.15 (1H, d, *J* 11.6, 3-H_a), 2.67 (1H, d, *J* 11.6, 3-H_b), 2.56 (1H, app. t, *J* 11.6, 2'-Hb), 2.45 (1H, d, *J* 11.7, 2'-H), 2.34 (4H, br s, morpholine 3-H and 5-H), 0.96 (3H, s, Me-H); δ_C (75 MHz, $CDCl_3$); 174.0 (amide carbonyl-C), 150.3 (sulfonamide 4-C), 141.9 (phenyl 1-C), 139.9 (sulfonamide 1-C), 129.0 (sulfonamide-C), 128.3 (phenyl-C), 127.3 (sulfonamide-C), 124.3 (phenyl-C), 122.7 (q, $^1J_{C\text{-}F}$ 290, CF_3), 65.7 (morpholine 2-C), 60.6 (2-C), 56.4 (2'-C), 51.1 (morpholine 3-C), 50.6 (6-C), 46.1 (5-C), 37.2 (1'-C), 22.4 (methyl-C); δ_F (282 MHz, $CDCl_3$) -81.2 (s); ν_{max}/cm^{-1} (film) 3103, 2854, 2359, 1722, 1533, 1352, 1174; *m/z* (*ESI*) 614.2 (100%, MH^+); HRMS found MH^+, 614.1890. $C_{26}H_{30}F_3N_5O_7S$ requires *MH*, 614.1891.

Also isolated was and the amide **321** (162 mg, 0.26 mmol, 59%) as a colourless solid; R_f 0.14 (100% EtOAc); δ_H (500 MHz, $CDCl_3$); 8.39 (2H, d, *J* 8.8, sulfonamide 3-H and 5-H), 7.96 (2H, d, *J* 8.7, sulfonamide 2-H and 6-H), 7.39-7.29 (5H, m, phenyl-H), 7.17 (1H, br s, N-H), 4.30 (1H, d, *J* 11.8, 3-H_a), 4.00-3.94 (1H, m, 6-H), 3.86 (1H, d, *J* 11.0, 5-H_a), 3.75-3.65 (4H, m, morpholine 2-H and 6-H), 3.53-3.48 (1H, m, 2'-H_a), 3.48-3.39 (2H, m, 1'-H), 2.68 (1H, dd, *J* 8.8 and 4.1, 2'-H_b), 2.57-2.52 (4H, m, morpholine 3-H and 5-H), 2.30-2.18 (2H, m, 3-H_b and 5-H_a), 2.07 (1H, d, *J* 5.3, N-H), 1.28 (3H, s, methyl-H); δ_C (75 MHz, $CDCl_3$); 173.0 (carbonyl-C), 150.3 (sulfonamide 4-C), 141.9 (phenyl 1-C), 139.4 (sulfonamide 1-C), 128.8 (sulfonamide-C), 128.4 (phenyl-C), 128.3 (phenyl-C), 126.7 (sulfonamide-C), 124.5 (phenyl-C), 66.9 (morpholine 2-C and 6-C), 58.8 (2-C), 57.3 (2'-C), 55.8 (6-C), 53.4 (morpholine 3-C and 5-C), 51.4 (3-C), 51.3 (5-C) , 36.0 (1'-C), 25.9 (methyl-C); δ_F (282

MHz, $CDCl_3$) -82.2 (s); ν_{max}/cm^{-1} (film) 3351, 2818, 1659, 1525, 1349, 1165; *m/z* (*ESI*) 518.2 (100%, MH^+); HRMS found MH^+, 518.2090. $C_{24}H_{32}N_5O_6S$ requires *MH*, 518.2068.

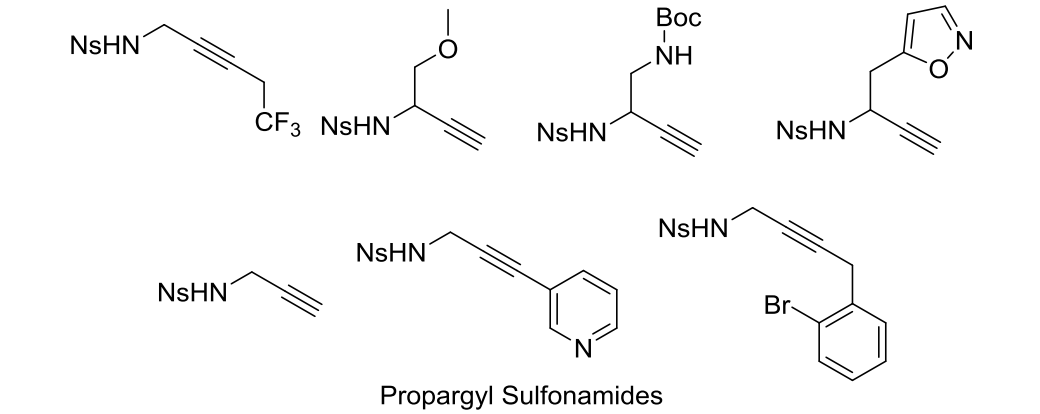
Benzyl-(2*S*,6*S*)-2-benzyl-6-methyl-4-[(2-nitrobenzene)sulfonyl]piperazine-1-carbamate, 315



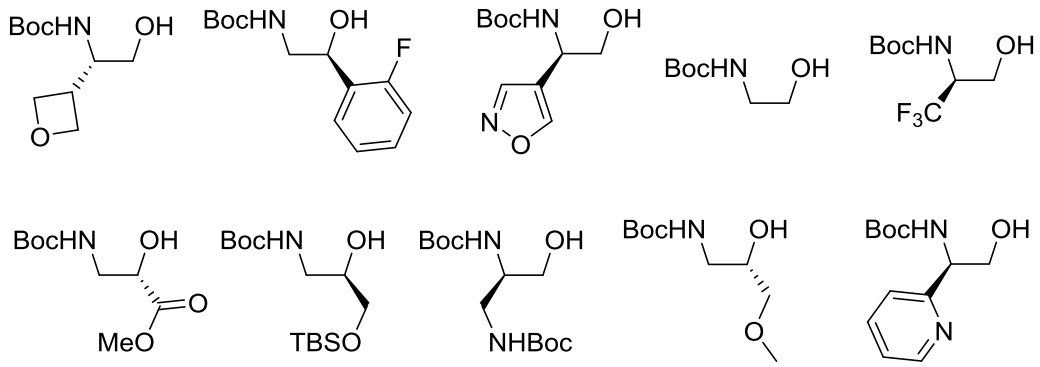
By general procedure **M**, **275** (100 mg, 0.20 mmol) gave a crude product. Purification by column chromatography, eluting with 7:3 petrol–EtOAc, gave the piperazine **315** (68.0 mg, 0.14 mmol, 68%, 7.7:1 dr) as a colourless oil; R_f 0.49 (1:1 petrol–EtOAc); $[\alpha]_D^{19}$ −177.2 (c 4.2, $CHCl_3$); δ_H (500 MHz, $CDCl_3$); 7.97 (1H, d, *J* 7.8, sulfonamide 3-H), 7.79-7.73 (1H, m, sulfonamide 6-H), 7.73-7.62 (2H, m, sulfonamide 4-H and 5-H), 7.41-7.37 (5H, m, carbamate Ar-H), 7.12 (3H, m, benzyl 2-H, 4-H and 6-H), 6.89 (2H, m, benzyl 3-H and 5-H), 5.22 (1H, d, *J* 12.1, carbamate CH_2-H_a), 5.14 (1H, d, *J* 12.1, carbamate CH_2-H_b), 4.25 (1H, m, 6-H), 4.14 (1H, br d, *J* 9.7, 2-H), 3.84 (1H, dd, *J* 12.9 and 3.4, 5-H_a), 3.68 (1H, dd, *J* 12.9 and 2.2, 5-H_b), 3.45 (1H, br d, *J* 11.8, CH_2-H_a), 3.39 (1H, dd, *J* 12.3 and 3.5, CH_2-H_b), 3.03 (1H, br d, *J* 12.6, 3-H_a), 2.68 (1H, app. t, *J* 11.7, 3-H_b), 1.24 (3H, d, *J* 6.6, methyl-H); δ_C (75 MHz, $CDCl_3$); 154.8 (carbonyl-C), 148.0 (sulfonamide 2-C), 137.5 (benzyl Ar 1-C), 137.0 (carbamate Ar 1-C), 133.8 (sulfonamide 4-C), 131.8 (sulfonamide 5-C), 131.4 (sulfonamide 1-C), 129.7 (benzyl 3-C and 5-C), 129.3 (benzyl 4-C), 128.7 (benzyl 2-C and 6-C), 128.4 (carbamate Ar 3-C and 5-C), 128.3 (carbamate Ar 4-C), 128.3 (carbamate Ar 2-and 6-C), 126.6 (sulfonamide 6-C), 124.41 (sulfonamide 3-C), 67.6 (carbamate CH_2-C), 54.7 (2-C), 48.4 (5-C), 48.0 (6-C), 42.9 (3-C), 40.2 (benzyl-C), 20.5 (methyl-C); ν_{max}/cm^{-1} (film) 3029, 1697, 1603, 1544, 1408, 1372, 1171; *m/z* (*ESI*) 532.2 (100%, MNa^+); HRMS found MNa^+, 532.1509. $C_{26}H_{27}N_3O_6S$ requires *MNa*, 532.1518.

5.4 Appendix

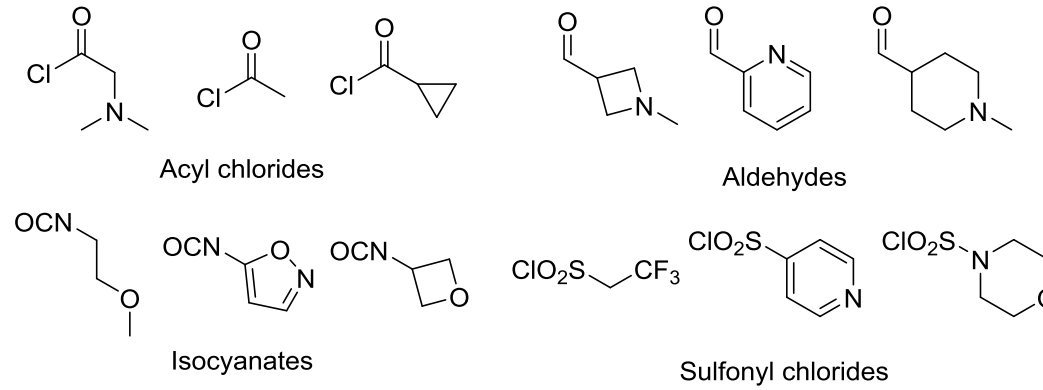
A. Building blocks used in the preparation of virtual libraries using *in silico* methods (Sections **2.2.3** and **3.1.4**).



Propargyl Sulfonamides



Amino Alcohols

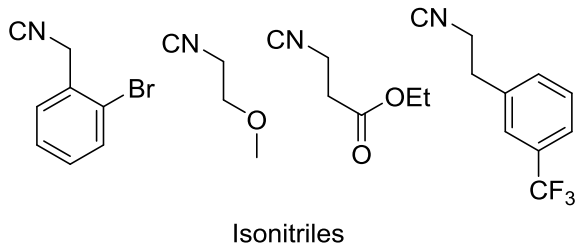


Acyl chlorides

Aldehydes

Isocyanates

Sulfonyl chlorides



Isonitriles

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