Realisation of CNS-relevant Molecular Scaffolds Using an Integrated Computational and Synthetic Approach

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Declaration

The candidate confirms that all the work submitted is his own, except where work which has formed part of jointly authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

The work in Chapter 2 has appeared in the following publication:
"Assessing molecular scaffolds for CNS drug discovery", J. Mayol-Llinàs, A. Nelson, W. Farnaby and A. Ayscough, *Drug Discovery Today,* 2017, **22**, 965–969.

From the work contained in this publication, the candidate designed the computational tool to identify CNS scaffolds and prepared the five scaffolds to exemplify the value of the tool. Contributions from other authors involve the preparation of the sixteen lead-like compounds from the five scaffolds, the determination of their experimental logD, the PAMPA absorption and the calculated logBBB. This appears in **Section 2.3.4** of this thesis and was performed by William Farnaby in collaboration with Takeda Cambridge. The research project was supervised by Adam Nelson, and conceived by Adam Nelson and Andrew Ayscough.

The work in Chapter 3 has appeared in the following publication:
"Modular synthesis of thirty lead-like scaffolds suitable for CNS drug discovery", J. Mayol-Llinàs, W. Farnaby and A. Nelson, *Chem. Commun*., 2017, **53**, 12345–12348.

From the work contained in this publication the candidate designed the toolkit of cyclisation reactions, prepared the thirty scaffolds and assessed them for CNS suitability. The research project was supervised by William Farnaby and Adam Nelson, and conceived by Adam Nelson.

Other contributions:

The desirability functions of the CNS Lead MPO scoring system and the medicinal chemistry capping groups to decorate the scaffolds with the computational tool were developed by Takeda Cambridge. Richard Doveston prepared the ligands **91** and *dbcot*. Chiral HPLC was performed by Martin Huscroft. X-ray crystallography experiments were performed by Christopher Pask.

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Aquesta tesis està dedicada al meu padrí Joan Mayol Bennàsar i al meu avi José Llinàs Amengual.

Abstract

The physicochemical properties of leads are of vital importance to obtain drugs with the desired therapeutic effect. In central nervous system (CNS) drug discovery, the properties of CNS-leads are even more restricted due to the fact that the resulting drugs must cross the blood-brain barrier (BBB). This thesis is focused on the development of computational and synthetic approaches that can assist the identification of molecular scaffolds that, after decoration, can yield high-quality lead-like molecules for CNS drug discovery.

Chapter 1 describes the drug discovery process and its productivity decline. It discusses the importance of physicochemical properties in the early stages, particularly for CNS-drugs. It describes the current computational methodologies and synthetic approaches used to obtain high-quality lead-like molecules.

Chapter 2 features the development and validation of a novel computational tool to assist the identification of scaffolds likely to yield high-quality lead-like molecules for CNS drug discovery. Successively, it describes the exemplification of this tool using a Lead-Oriented Synthesis (LOS) approach.

Chapter 3 details the elaboration of a novel LOS approach for the synthesis of diverse scaffolds able to yield lead-like molecules with the desired properties for CNS. This approach involves the preparation of highly functionalised cyclisation precursors. Subsequently, different cyclisation reactions are investigated and optimised to yield a library of different scaffolds. The previously developed computational tool is used to assess the value of the scaffolds for CNS.

Chapter 4 shows the decoration of some of the prior scaffolds to produce diverse derived molecules, which are used for ligand discovery against the CNS-target BACE1 (β-site amyloid precursor protein cleaving enzyme 1).

Chapter 5 describes the methods and materials for the preparation of the computational tool, for the synthesis of all the scaffolds and derived compounds and for the assessment of the biological activity.

Contents

Abbreviations & Symbols

$[\alpha_D]$	Optical rotation
9-BBN	9-Borabicyclo[3.3.1]nonane
Ac	Acetyl
ADMET	Absorption, distribution, metabolism, elimination, toxicity
app	Apparent
APP	Amyloid precursor protein
Aq	Aqueous
Ar	Aromatic
Asp	Aspartic acid
b.p.	Boiling point
BACE1	β-Site amyloid precursor protein cleaving enzyme 1
BBB	Blood-brain barrier
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
br	Broad
Bu	Butyl
Bz	Benzoyl
c	Concentration
cat	Catalysed, catalytic
Cbz	Carboxybenzyl
CCDC	Cambridge crystallographic data centre
CDI	Carbonyldiimidazole
clogD	Calculated logarithm of the coefficient of partition octanol:water of a molecule at specific pH
$clogD_{7.4}$	Calculated logarithm of the coefficient of partition octanol:water of a molecule at pH 7.4
clogP	Calculated logarithm of the coefficient of partition octanol:water of a neutral molecule
CNS	Central nervous system
cod	1,5-Cyclooctadiene
COSY	Correlation spectroscopy
d	Doublet

dba	Dibenzylideneacetone
dbcot	Dibenzo[a,e]cyclooctatriene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DEPT	Distortionless enhancement of polarisation transfer
DIBAL-H	Diisobutylaluminium hydride
DMAP	4-Dimethylamino pyridine
DMF	Dimethylformamide
DMS	Dimethyl sulfide
DMSO	Dimethyl sulfoxide
DOS	Diversity-oriented synthesis
DPE-Phos	Bis-[2-(diphenylphosphino)phenyl]ether
dr	Diastereomeric ratio
ee	Enantiomeric excess
em	Emission
eq	Equivalents
ES	Electrospray
Et	Ethyl
ex	Excitation
Exp	Experimental
FDA	Food and drug administration
Gly	Glycine
HBA	Hydrogen bond acceptors
HBD	Hydrogen bond donors
hERG	Human ether-a-go-go-related gene
HMQC	Heteronuclear multiple quantum coherence
HPLC	High-pressure liquid chromatography
HRMS	High-resolution mass spectrometry
HTS	High throughput screening
IC_{50}	Concentration of ligand to achieve 50% inhibition
IR	Infrared
J	Coupling constant
K_d	Dissociation constant
LC-MS	Liquid chromatography-mass spectrometry

LDA	Lithium diisopropylamide
LiHMDS	Lithium bis(trimethylsilyl)amide
LLAMA	Lead-likeness and molecular analysis
LogBBB	Logarithm of the coefficient of partition brain:blood of a molecule
LOS	Lead-oriented synthesis
m	multiplet
m.p.	Melting point
m/z	Mass to charge ratio
Me	Methyl
MPO	Multi-parameter optimisation
Ms	Methanesulfonyl
MTPA-Cl	3,3,3-Trifluoro-2-methoxy-2-phenylpropanoyl chloride, Mosher's acid chloride
MW	Molecular weight
NBS	*N*-Bromosuccinimide
NME	New molecular entity
NMO	*N*-Methylmorpholine-*N*-oxide
NMP	*N*-Methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
nOe	Nuclear overhauser effect
NOESY	Nuclear overhauser effect spectroscopy
NR	No referred
Ns	4-Nitrobenzenesulfonyl
Nu	Nucleophile
ORTEP	Oak ridge thermal-ellipsoid plot program
P-gp	P-Glycoprotein
PAMPA	Parallel artificial membrane permeability assay
P_{app}	Apparent permeability coefficient
PDB	Protein data bank
PDC	Pyridinium dichromate
Petrol	Petroleum spirit (boiling point 40–60 °C)
Ph	Phenyl
pH	Potential of hydrogen
pK_a	Logarithm of the acid dissociation constant

PMB	4-Methoxybenzyl ether
PS	Permeability surface–area product
PSA	Polar surface area
Pyr	Pyridine
q	quartet
R&D	Research and development
RB	Rotatable bonds
Ref	Reference
R_f	Retention factor
rt	Room temperature
s	Singlet
SCX	Strong cation exchange
SEM	Standard error mean
S_N	Nucleophilic substitution
SPE	Solid phase extraction
t	Triplet
T:*I*	Ratio terminal alkene:internal alkene
TBA	Tetrabutylammonium
TBD	1,5,7-Triazabicyclo[4.4.0]dec-5-ene
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
^{t}Bu	*tert*-Butyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
Thr	Threonine
TLC	Thin layer chromatography
TMS	Trimethylsilane
TPAP	Tetrapropylammonium perruthenate
Ts	*p*-toluenesulfonyl
US	United States
δ	Chemical shift
λ	Wavelength
μW	Microwave
v	Wavenumber

Chapter 1: Importance of Molecular Properties in CNS Drug Discovery

1.1. Introduction

Despite the recent improvements in the fields of life science and technology, the pharmaceutical industry has experienced a decrease in its R&D productivity.[1–7] Most of the drug candidates fail during the last stages of the drug discovery process, when a large amount of time and cost has already been spent.[8] One of the reasons is that drug candidates have poor ADMET (absorption, distribution, metabolism, excretion and toxicity) properties.[8,9] Consequently, improving the quality of leads in the early stages of the drug discovery process can help to increase the later clinical success.[8,10] Different *in silico* methodologies have been developed to control the physicochemical properties during the lead optimisation stage.[9,11,12]

However, there is a low success in the development of drugs for diseases of the central nervous system (CNS).[13,14] This low success is due to the presence of the blood-brain barrier (BBB), which limits the penetration of drugs to the CNS. CNS-drugs must have special physicochemical properties to be able to cross this barrier. As a result, the identification of CNS-leads is difficult. *In silico* MPO (multi-parameter optimisation) systems[15,16] and synthetic methodologies like lead-oriented synthesis (LOS)[17] are approaches that can help in the development of a variety of molecular scaffolds with suitable properties. These scaffolds could be decorated to yield high-quality CNS-leads that would yield CNS-drugs more likely to cross the BBB.

1.2. The Drug Discovery Process

The drug discovery process starts when there is an unmet medical need or when the current treatment for a disease could be improved. The main objective of pharmaceutical companies is to discover suitable new drugs, which are effective and safe. The drug discovery process is very complex and it can be divided into different stages (Figure 1).[11,18] In the initial stages, research is done to identify a “druggable” biological target, whose modulation can give a therapeutic response to the unmet disease.[19–21] The biological targets include enzymes, receptors, ion channels and nucleic acids.[22,23] Once the target is

identified, it is validated to prove that its modulation can give the desired response.[19–21] Subsequently, research for small molecules that are able to modulate its activity starts.

Figure 1: Stages of the drug discovery process. Adapted from references.[11,18]

Small bioactive molecules are usually identified via high throughput screening (HTS).[24,25] In this approach, large libraries of compounds are tested against the biological target to identify if some of them can bind to it and modulate its activity. As a result, molecules that are able to bind weakly to the desired target can be identified. These molecules are initially called hits,[26] which can be developed to generate leads.[26] Leads are molecules that display activity and selectivity in a particular pharmacological or biochemically relevant screen and form the basis for identifying new drug candidates.[23] For this reason, when a lead is generated, different studies *in silico* and *in vitro* are performed to optimise its potency and safety profile.[23,27] During the lead optimisation stage, the chemical structure of the lead is modified. When a lead is modified and its profile is improved, the new molecule can become a drug candidate, also known as a new molecular entity (NME) (Figure 2).[8,11]

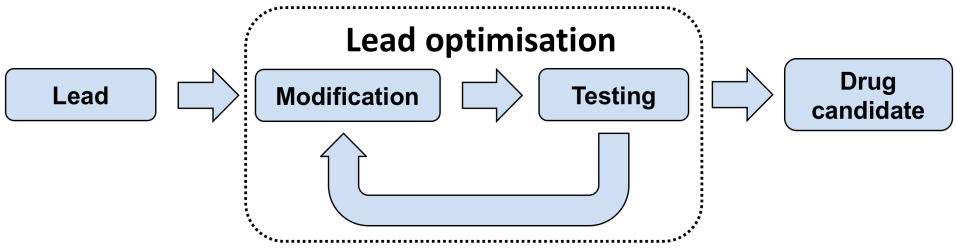


Figure 2: The lead optimisation process. A lead is modified and tested to improve its potency and safety. If the potency and safety increases, it can become a drug candidate. If its profile is not optimised, the lead is modified again until there is improvement.

Once a drug candidate is identified, the preclinical development starts. During this stage, the drug candidate is tested *in vivo* to check its efficacy and its safety profile in animal models. If the drug candidate is successful, it is submitted to clinical trials to study the effect in humans. Clinical trials are divided into three phases (Phase I, Phase II and Phase III) and they are the longest and the most

expensive stages of the drug discovery process.[8] If the drug candidate is successful in all of these phases, it is approved and it is brought to the market. As a result, the process finishes with the launch of a final effective and safe product to the market.

1.3. The Productivity Decline in Pharmaceutical R&D

In the last few decades, many successful drugs have succeeded through all the stages of the drug discovery process and they have been released to the market.[1] The success was especially high during the year 1996, when 56 drugs were approved by the Food and Drug Administration (FDA) in the US.[1] Some of these drugs became blockbuster drugs, giving high sales to pharmaceutical companies. In addition, techniques in molecular biology, computational drug design, HTS and combinatorial chemistry have also improved, allowing widespread identification of targets and screening of compounds.[2,6,28] However, despite all these advances and the high investment in research and development, there has not been the corresponding increase in the number of approved drugs in the last few decades by the FDA (Figure 3).[1,2,5–8,10,23,28–31]

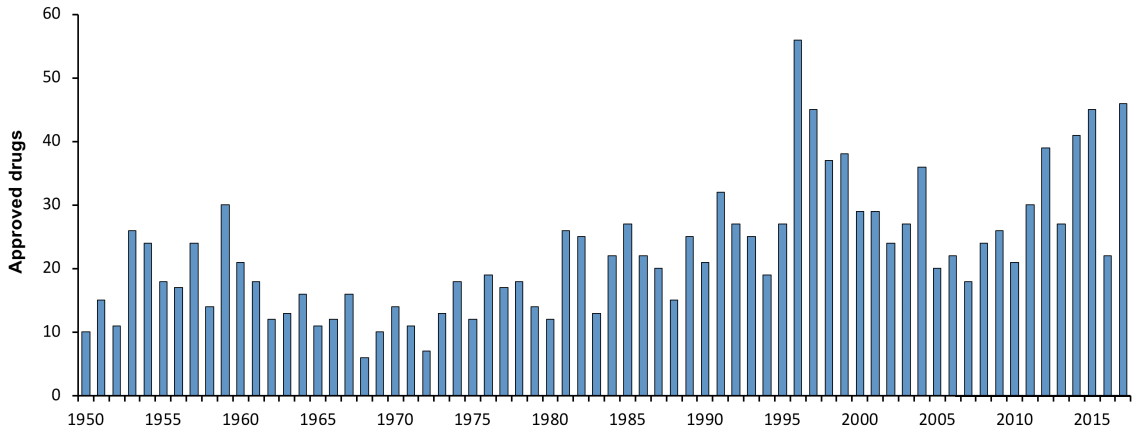


Figure 3: Total number of drugs approved per year by the FDA since 1950.[6,30]

There has not been a very high increase in the number of approved drugs per year in the last few decades in part due to a decline in the R&D productivity of pharmaceutical companies.[1,10,32] This fact can be explained by the patent cliff and by the low success in the drug discovery process.[1,8] A high investment in time and costs is necessary to undertake every one of the drug discovery stages.[33] The drug discovery process usually takes between 12–15 years and it can cost more than $1 billion.[18] During the years 2009–2014, many patents of

current blockbuster drugs expired.[1,8] This fact has decreased the number of sales (around $100 billion) due to the increase of generic drugs, which now represent around 70% of total prescriptions in the US.[1,3,8] Consequently, pharmaceutical companies are less likely to develop new drugs. In addition, at the end of every stage of the drug discovery process, many efficacy and safety requirements need to be satisfied for every molecule in order to proceed to the next stage. Recently, these safety requirements have become stricter, decreasing the success rate.[3] Furthermore, more complicated "druggable" targets are currently being investigated. To be able to increase R&D productivity, companies should increase their efficiency (drugs brought to the market per billion dollars of R&D spending).[6] As a result, they would increase their success and they would be able to counteract their current loss of sales. However, due to the recent high investments and high fails, R&D efficiency has decreased during the last decades (Figure 4).[1–3,5,6,8]

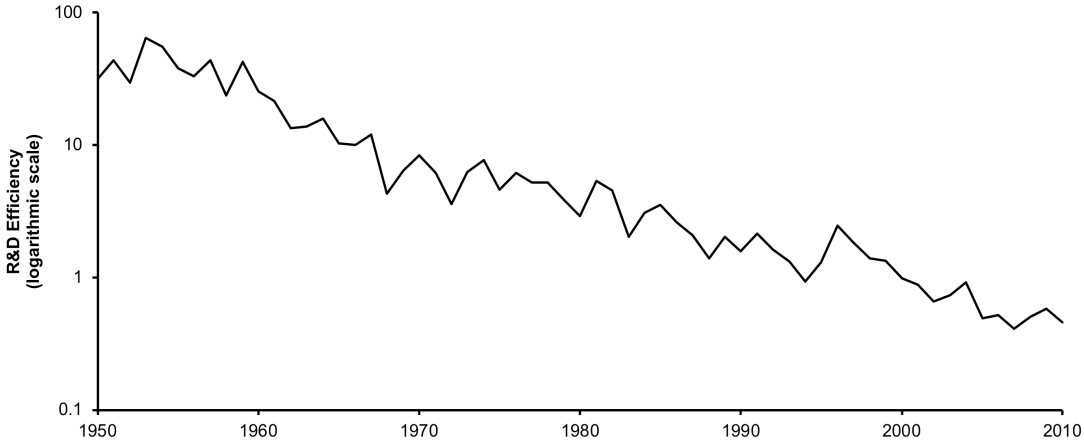


Figure 4: Decreasing in the R&D efficiency of pharmaceutical companies during the last decades. R&D efficiency as drugs brought to the market per billion dollars of R&D spending (inflation-adjusted). Adapted from a reference.[6]

Increasing R&D efficiency in the drug discovery process is a difficult challenge.[2] The process normally starts with thousands of promising compounds, but normally most of them are unsuccessful. Occasionally only one arrives to the market as a new drug (Figure 5). In addition, every stage has different costs and duration. The first stages of the drug discovery program (target identification, lead generation and lead optimisation) are the ones with lowest cost and with the shortest time. However, for every successful drug into the market, preclinical costs comprises approximately 32% of the total costs and clinical costs approximately 63%.[8,10] In addition, they are the longest stages.

Most drug candidates fail during clinical trials (66% of compounds fail in Phase II),[8] when a high amount of time and cost has already been spent.

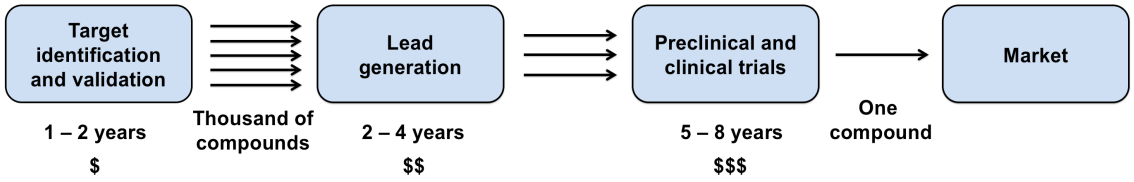


Figure 5: Overview of the time, cost and success of developing a new drug. Adapted from references.[18,23]

Failure in the last stages should be reduced.[10] Drug candidates can fail during clinical trials due to different reasons such as lack of efficacy, lack of improvement and poor/unexpected ADMET profile.[6,8,23,34–36] The lack of efficacy/improvement can be due to the fact that the wrong target was selected or its biological role in the disease is poorly understood. This can lead to failures at the last stages of the clinical trials (Phases II and III).[8,35] A poor ADMET profile can make that candidates that are active against the target cannot reach it or they give toxicity. As a result, they are not successful. It has been observed that an improvement in the ADMET profile leads to an increased clinical success in the early stages of the clinical trials (Phase I).[8,35]

The ADMET properties of the drug candidates that arrive to the clinical phases are related with the ADMET properties of their previous leads. Few alterations can usually be made to the structural core of the molecule during the lead optimisation process.[37] Therefore, more effective research should be done during the early stages,[4,33] especially during lead generation[4,23] because this stage is much cheaper and shorter.[37] A better lead generation with an improved ADMET profile removes molecules likely to fail later in the early stages of clinical trials, saving more costs and more time.[4,23] In the past, attention was not paid to the ADMET profile because the main objective was to increase the potency and selectivity of leads,[29] as achieving nanomolar activity was the main goal. Consequently, many candidates passed the first stages but they failed during clinical trials.[23] Therefore, libraries of better leads with a controlled ADMET profile should be used before the lead optimisation process. Leads with undesired ADMET profile should be identified and removed from the library.[6,8,38] Consequently, the lead optimisation would yield drug candidates with the

desired ADMET profile and they would be less likely to fail in the clinical stages.[8] As a result, this selection of better leads could increase R&D efficiency.[10,28] Accordingly, R&D productivity could also increase and the number of drugs launched to the market would be higher.

1.4. Physicochemical Properties of Drugs

A successful drug must have a balance of biological and physicochemical properties.[15] The ADMET profile is directly related to the physicochemical properties of the molecule. To be able to achieve therapeutic concentrations at the site of action, drugs must pass through biological membranes. To be able to pass through these membranes drugs must have determined physicochemical properties. If they do not satisfy these properties, they cannot reach the site of action with enough concentration to produce the desired effect.

Experimental pharmacokinetic and pharmacodynamic studies are performed during the early stages of the drug discovery process to identify molecules with the desired ADMET profile and to discard the others.[28,34,38] These studies can involve different evaluations such as the determination of bioavailability (% of drug dose in blood plasma), the fraction of drug in blood plasma bound to proteins, the volume of distribution of the drug in the organism, the rate of clearance (elimination) of the drug from the blood plasma, the metabolic stability of the drug, the toxicity (off-target effects) and the minimum effective dose. However, when large libraries of compounds need to be tested, these experimental studies can take a long time and they can have high costs. Therefore, *in silico* ADMET studies have also been implemented.[9,34] They are much faster, cheaper and they can be applied to large libraries of compounds. These studies have an accuracy of 60–90% with respect to the experimental studies.[34] Therefore, they are used as a filter to discard compounds likely to fail in the future *in vitro*/*in vivo* studies. As a result, fewer compounds need to be synthesised and tested experimentally.[34] There are different *in silico* models available.[34] All of them are based on the physicochemical properties of the molecules. They calculate the value of each property for a selected molecule and they predict its ADMET profile. These methods allow control of the physicochemical properties during the early stages of a drug discovery program, when a large library of compounds is being investigated.

A molecule is defined by several physicochemical properties. The main ones are molecular weight (MW), clogP, clogD, net charge, number of atoms that can produce hydrogen bonds and polar surface area (PSA). MW refers to the size of the molecule and it is quantified as the sum of the masses of all its atoms (in daltons) or as the number of its heavy atoms.[39] clogP is a property that defines the lipohilicity of the molecule.[39,40] It is the calculated logarithm of the coefficient of partition between octanol:water of the neutral molecule. Lipophilic molecules will have high values of clogP. clogD is a property related to clogP, the difference is that clogD is the calculated logarithm of the coefficient of partition octanol:water of the molecule at a specific pH. It also takes an account the net charge of the molecule, which is a property that is influenced by the pK_a. The number of atoms that can make hydrogen bonds is related with the polarity of the molecule and its ability to be solvated by water. It can be described by the number of hydrogen bond donors (HBD) and the number of hydrogen bond acceptors (HBA). Another property related with the polarity of the molecule is the PSA, which is defined as the surface area occupied by the nitrogen and oxygen atoms and by the polar hydrogen atoms bound to them.[39,41] Nevertheless, it has been said that clogP and clogD (lipophilicity) are the most important properties.[41] The reason is because lipophilicity influences drug potency and the ADMET profile.[39,40] Normally, a drug needs a balanced lipophilicity, if the lipophilicity is too high or too low the molecule will have a poor ADMET profile.[40]

1.4.1. Physicochemical Properties in the Design of Oral Drugs

The physicochemical properties have to be carefully controlled in the design of new drugs. They are particularly important in the case of oral drugs. Oral drugs have to be absorbed into the bloodstream from the gastrointestinal tract. Therefore, they must have a balance between lipophilicity and hydrophilicity. There are some rules that can be used as guidelines for the design of oral drugs. Lipinski's guidelines, also called rule-of-five, state the preferred properties for absorption of oral drugs.[42–44] These guidelines state that a molecule should have a MW below or equal to 500, the clogP should be below or equal to 5, the maximum number of HBD should be 5 and the maximum number of HBA should be 10. Only one violation of these rules is allowed. Recently, more properties have been added.[42,43] These are PSA, which should

not be greater than 140 Å^2; the number of rotatable bonds (RB), which should not be greater than 10;[41] the clogD$_{7.4}$, which should not be greater than 3; the net charge, which should range from -2 to +2; and the molar refractivity, which should be between 40–130. In a first instance, most oral drugs satisfy these rules. However, there are some exceptions for drugs that are absorbed to the bloodstream through active transport. For this reason, these guidelines only apply for oral drugs absorbed by simple passive diffusion.

In the past, the majority of oral drug candidates that showed desirable ADMET profile, satisfied most of the previous requirements.[42] Therefore, the properties of new oral drugs should be controlled during the lead generation and optimisation stages. During the lead optimisation stage, there is generally an increase in complexity, lipophilicity and molecular size (Figure 6).[17,29,45,46] Consequently, the library of compounds for screening should have determined physicochemical properties. Therefore, if a lead is identified, it can be optimised to a final candidate that will satisfy Lipinski's guidelines. In this manner, an increased rate of success can be expected after the lead optimisation process.

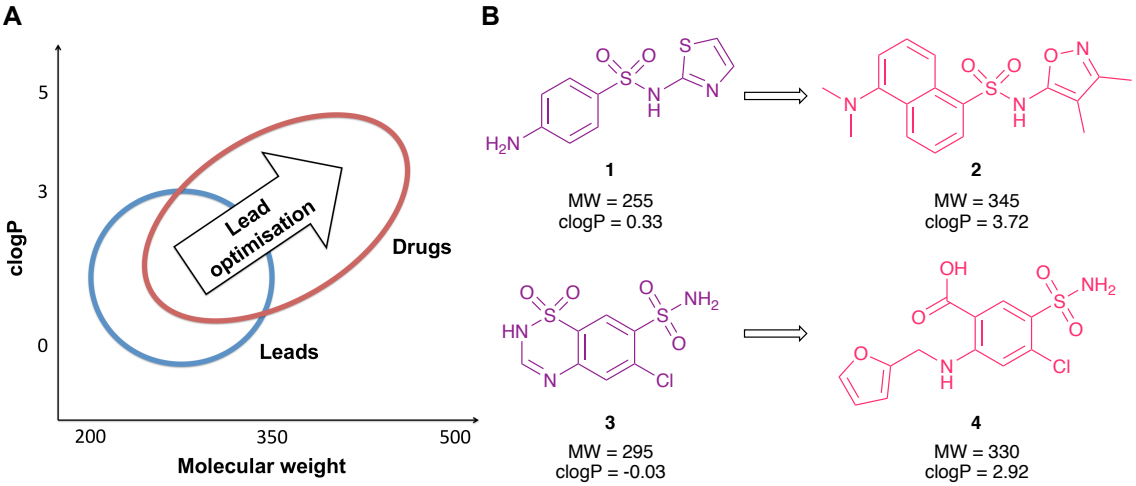


Figure 6: Increase of the lipophilicity and the size of the molecules during the lead optimisation stage. **Panel A**: Diagram showing the difference in lipophilicity and size of leads and drugs. Adapted from a reference.[17] **Panel B**: Example of some leads (left) and corresponding drugs (right).[46] Compound **1** is also known as sulfathiazole, which is optimised to **2** (BMS-182874). Compound **3** is also known as chlorotiazide, which is optimised to **4** (furosemide).

Due to the increase in MW and clogP during the lead optimisation, leads should have more restricted molecular properties than their derived oral drugs.[46,47] There are guidelines that suggest the preferred properties for leads.[17,48] They suggest that the MW should be between 200–350 and the clogP should be

between -1 and 3. In addition, some other recomendations have been included, suggesting that leads should have fewer sp^2 carbons.[17,48] Consequently, they should not have more than 3 aromatic rings.[17,48]

In silico approaches have been widely used to control the physicochemical properties of leads during the lead generation stage.[11,12] These approaches can help to identify leads with the desired efficacy and ADMET properties.[49] The final ADMET profile of a molecule depends on the combination of all its physiochemical properties. The different physicochemical properties have to be optimised at the same time. Therefore, *in silico* multi-parameter optimisation (MPO) methodologies are used.[15,16,36,50,51] The first models of these methodologies were usually pass/fail filters.[15,16] Only molecules that satisfy the specified rules will be accepted. However, it was observed that these models could be too strict. Consequently, a lead compound that has a property narrowly outside the desired range is rejected. However it could still be a good lead for the design of oral drugs if the other properties are optimal. Consequently, models involving desirability functions are now used.[15,16,51] These models assign a total desirability score for each molecule depending on all its physicochemical properties. The score is an indicator of the lead-likeness of the molecule. This approach employs a single value that defines all properties. Consequently, it allows more flexibility, a better balance of the properties and avoids a straight cut off for compounds with some properties out of the optimal range.

1.4.2. Physicochemical Properties in the Design of CNS-Drugs

More than one billion people are affected by central nervous system (CNS) disorders worldwide.[52] It is predicted that CNS disorders like Alzheimer's disease, Parkinson's disease, stroke and brain cancers will be the major cause of health expenses by 2040.[14,41] Currently, there is a low clinical success (8%) in the CNS drug discovery area compared with other therapeutic areas (Figure 7).[13,14]

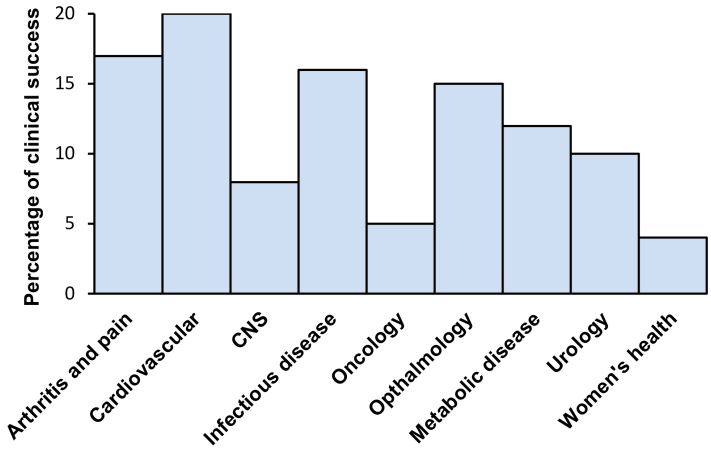


Figure 7: Percentage of clinical success of the drug discovery process in different therapeutic areas. Adapted from a reference.[13]

This low clinical success is due to the fact that the causes of CNS diseases are poorly understood.[53] It is difficult to study drug candidates for CNS disorders due to lack of predictable animal disease models.[8,13,28] Consequently, there are high fail rates in clinical trials due to lack of efficacy.[13] In addition to the gastrointestinal membrane, which separates the gastrointestinal tract from the bloodstream, there is also another biological membrane that separates the bloodstream from the CNS. This membrane is called the blood-brain barrier (BBB) (Figure 8).

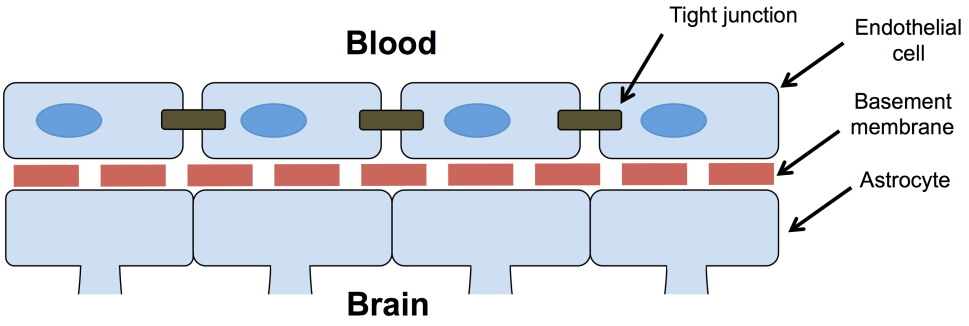


Figure 8: Diagram of the blood-brain barrier. Adapted from a reference.[54]

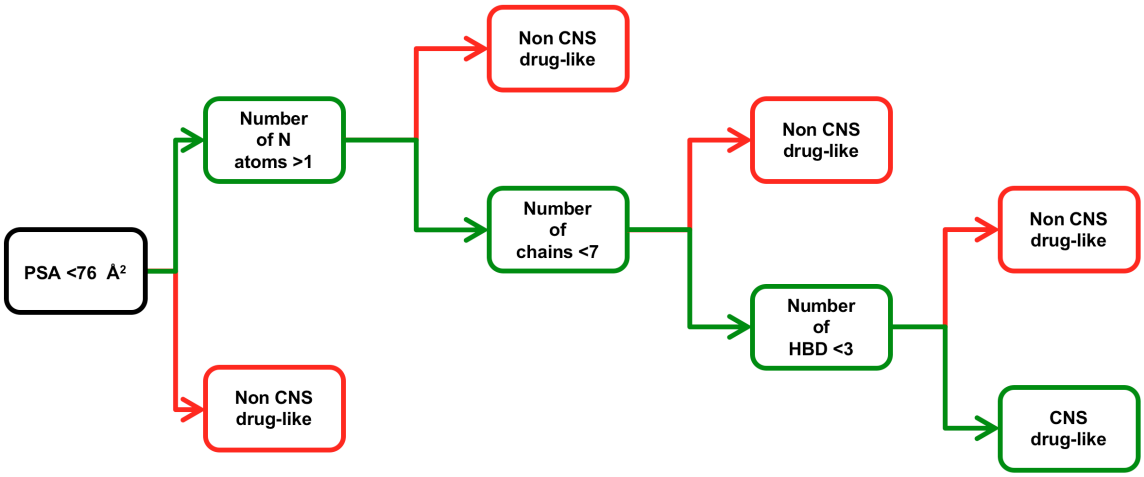
The BBB is formed by endothelial cells that have very tight junctions (areas of two cells whose membranes join together creating an impermeable barrier to fluids) compared to the endothelial cells that separate the bloodstream from others parts of the body. These tight junctions allow the passage of nutrients and hormones but they protect the CNS from the passage of many other molecules through paracellular diffusion. In addition, these cells do not have many fenestrations (small pores in the cellular membrane) and they do not undergo pinocytosis (invagination of small particles through the cellular

membrane) frequently.[55] Consequently, most of molecules must pass through transcellular passive diffusion through cells, which are rich in enzymes that metabolise them.[55] In addition, the lipid bilayer of the cells of the BBB has an heterogeneous organisation of phospholipids with highly limited mobility and charged head moieties that interact with water molecules in the interface.[55] This makes the process of passive diffusion difficult due to the fact that molecules must displace the water bound to the membrane and separate the tightly bounded phospholipids. Finally, another feature of the BBB is the presence of a transmembrane protein called P-glycoprotein (P-gp) in the endothelial cells.[56] P-gp makes an active efflux of small molecules, which have entered the cytoplasm of the cells of the BBB, back to the bloodstream. Due to these features, the BBB is more selective than the gastrointestinal membrane. The BBB is an effective membrane that protects the CNS from xenobiotics. Therefore, the BBB is very selective to the passage of most drugs (98% of drugs do not cross this membrane).[14] This makes the discovery of drugs with CNS exposure difficult.

To be able to treat CNS disorders, CNS-drugs must cross the BBB. Therefore, they must have different physicochemical properties to non CNS-drugs. It has been observed that like for gastrointestinal absorption; molecular weight, lipophilicity and hydrogen bonding are also very important for brain penetration.[55] However, due to the characteristics of the BBB, these properties are more restricted than for gastrointestinal absorption. Consequently, CNS-drugs must have more restricted physicochemical properties than non CNS-drugs.[28,41] CNS-drugs should be polar enough to be able to dissolve in the extracellular fluid and displace the waters bound to the phospholipids of the BBB; small and rigid enough to be able to afford the entropic cost of desolvation and membrane disruption; and have a balance of lipophilicity to cross the cellular membrane of the BBB. It has been suggested that CNS-drugs should have lower molecular weight, less HBD and HBA, less charge, smaller PSA and more limited flexibility than non CNS-drugs.[14,41,55] For this reason, the Lipinski's rule-of-five cannot be applied for the design of CNS-drugs. The differences between the physicochemical properties of CNS-drugs and non CNS-drugs have been studied. As a result, radar charts,[14] classification trees[14,57] and different physicochemical properties for CNS-drugs have been proposed to be

able to discriminate between CNS drug-like molecules and non CNS drug-like molecules (Figure 9).

A



B

	Value / Range						
Ref.	Pfizer[58]	Cephalon[14]	Neuromed Technologies[55]	Amgen[59]	Pfizer[60]	Gedeon Richter and Argenta Discovery[60,61]	AstraZeneca[39,60]
MW	305.3	140–450	<450	<500	<400	<450	310
clogP	2.8	-0.66–6.1	<5	2–5	<5	1–3	2.5
PSA (Å^2)	44.8	<76	<60–70	<90	NR	<60–70	NR
HBD	1	<3	<3	<3	<3	NR	1.5
pK_a	8.4	6–10.5	7.5–10.5	NR	NR	NR	NR
clogD$_{7.4}$	1.7	-0.55–5.5	NR	2–5	NR	NR	NR
RB	NR	≤8	<8	NR	NR	NR	4.7
HBA	NR	NR	<7	NR	<7	<6	2.1

Figure 9: Guidelines for the physicochemical properties of CNS-drugs. **Panel A:** Classification tree to differentiate between CNS drug-like molecules and non CNS drug-like molecules.[14] Arrows in green mean that the property is satisfied. Arrows in red mean that the property is not satisfied. **Panel B:** Opinions on the desired physicochemical properties of CNS-drugs. NR (no referred).

From the values in Figure 9, it could be suggested that generally CNS-drugs should have a MW not greater than 450, a clogP and a clogD$_{7.4}$ not more than 5, the number of HBD should not be greater than 3, the number of HBA should not be greater than 7, the PSA should be <90 Å^2, the number of RB should be not greater than 8 and the pK_a should be lower than 10.5. However, other publications[14,45,60] suggest that the clogP - (number of N + O atoms) should be greater than 0, the number of linear chains (unbranched chains outside rings) should be less than 7, the sum of O and N atoms should be between 1–7 and the volume of the molecule should be between 460–1250 Å^3. In addition, it has been suggested that some substructures can negatively affect brain penetration.[62] Substructures identified as undesired for brain penetration are

sulfonamides, sulfones, tetrazoles, amine *N*-oxides and carboxylic acids.[62] Therefore, these substructures should be avoided in the design of CNS-drugs. However, there are some substructures that are preferred in CNS-drugs because they can help to cross the BBB and they can avoid P-gp transport.[60,63] A library of desired substructures with an occurrence in CNS-drugs higher than 5% has been reported.[14] Some of these substructures contain one tertiary nitrogen with a positive charge or/and one aromatic group. It has been observed that tertiary basic amines give resistance to P-gp transport.[60] Therefore, many CNS-drugs are basic molecules.[41,60] The rule-of-four guideline suggests the properties that CNS-drugs should have to avoid interaction with the P-gp.[41] This guideline states that molecules should have MW lower than 400, number of N + O atoms lower than 4 and the most basic pK_a should be lower than 8. In addition, it has also been suggested that to avoid P-gp recognition PSA should be lower than 60 Å^2.[41] However, P-gp recognition is not the only problem of CNS-drugs. Because CNS-drugs can sometimes be more lipophilic (clogP >3), they can present high levels of protein binding in blood plasma (which will decrease brain penetration) and can give toxic effects easily by interaction with other hydrophobic targets.[55] Highly lipophilic drugs often produce liver toxicity due to interaction with the cytochrome P450 and cardiovascular toxicity due to inhibition of the hERG channel.[28,39,55,58] As a result, CNS-drugs must have a delicate balance of properties to be able to cross the BBB, to avoid high levels of protein binding in blood plasma, to avoid the P-gp efflux and to avoid off-target effects.

Therefore, *in silico* techniques have also been developed to help in the design of CNS-drugs.[56,59,64,65] There are different softwares available that predict the likelihood of a molecule entering the CNS.[14,64,65] These softwares calculate the physicochemical properties of the molecules and study how desirable they are for CNS penetration. In addition, they also predict the permeability for the BBB through the determination of the logBBB (logarithm of the brain-blood partition coefficient),[64–66] logPS (permeability surface-area product)[65] and the affinity for the P-gp.[56] Recently, *in silico* MPO methodologies have also been applied to the selection of CNS-drugs.[67–71] One example is the CNS MPO scoring system developed by Pfizer.[67] In this method, six physicochemical properties (MW, clogP, clog$D_{7.4}$, pK_a, PSA and HBD) are calculated and scored by desirability

functions to identify CNS drug-like molecules. These functions can be a monotonic decreasing function or a hump function (Figure 10).[67] Monotonic decreasing function is used for MW, clogP, clog$D_{7.4}$, pK_a and HBD. Hump function is used for PSA. A score between 0.00 and 1.00 is assigned to every value of the property depending on the CNS desirability (from 0.00 if the value of the property is completely undesired for brain penetration to 1.00 if it is completely desired).

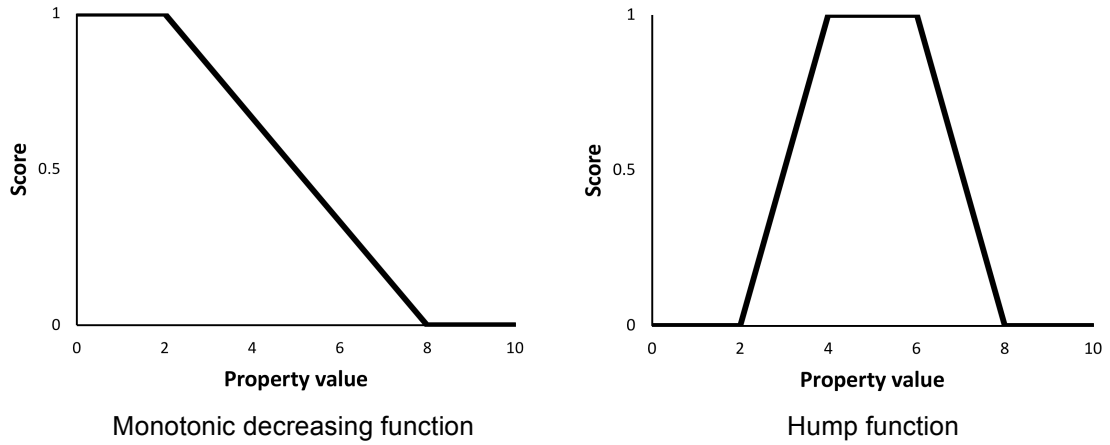


Figure 10: General examples of desirability functions used in the CNS MPO scoring system.[67]

All six properties are balanced equally. As a sum of each score of every one of the six properties, a final score (CNS MPO score) between 0.00 and 6.00 is obtained for each molecule.[67] Better CNS drug-like and safety profiles are achieved for molecules that have this score close to six. Therefore, molecules with CNS MPO score equal or higher than 4.00 are identified as molecules with desired CNS drug-like and safety properties. They should have high permeability through the BBB and poor P-gp binding. The CNS MPO score has already shown utility for a CNS-target where the scores obtained correlated with the experimental results.[72]

These *in silico* approaches used to identify molecules with CNS-drug like properties could be used to identify molecules with CNS-lead like properties. Consequently, CNS-lead like molecules could be identified before the lead optimisation process. This could allow achieving the right ADMET profile for CNS-drugs candidates. As in the case of oral drugs, better CNS lead-like molecules would improve the success of CNS-drug candidates in clinical trials. However, CNS lead-like molecules should have even more restricted properties

than CNS-drugs. CNS-leads should have lower MW and lower lipophilicity. Consequently, after lead optimisation these leads could become CNS-drugs with the desired properties. Unlike the leads for the design of oral drugs, there is not any accepted rule (or guideline) to define the physicochemical properties of CNS-leads yet. Therefore, the design of CNS lead-like molecules is not easy. It is necessary to have access to molecules with different physicochemical properties to be able to identify CNS-leads with the *in silico* techniques.

1.5. Diversity- and Lead-Oriented Synthesis

Chemical space is the region defined by physicochemical properties that contains all the small organic molecules that could theoretically exist.[73,74] The chemical space defined by molecules with MW lower than 500 is very large. It could contain from 10^{23} to 10^{60} organic compounds that could be of interest for drug discovery (Figure 11).[73,75,76]

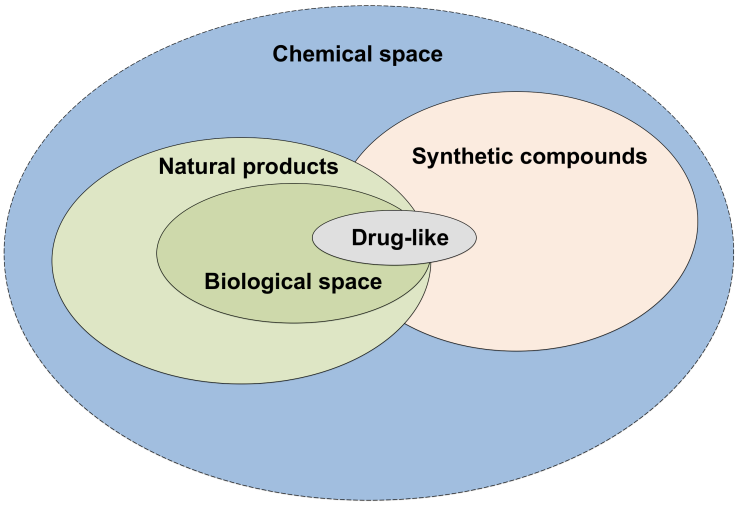


Figure 11: Explored chemical space. Adapted from a reference.[77]

Drugs are placed in a region of chemical space called drug-like chemical space. Only a small portion of the total drug-like chemical space is known, and it has allowed the discovery of different drugs. Drug-like chemical space overlaps with biological space, which is the part of the chemical space where biologically active molecules are found.[74] It has been proposed that more biologically-relevant chemical space should be explored to be able to increase productivity in drug discovery.[77] Currently, there is a limited diversity in the explored drug-like chemical space.[78–81] Most drugs have similar molecular frameworks and are sp^2-rich. Consequently, compounds with new molecular frameworks and more

sp^3-rich character could be of interest.[82,83] For this reason, the chemical space occupied by the current small molecules is not necessarily valid for the discovery of new drugs.[77] New “druggable” chemical space should be explored. Consequently, lead optimisation can still occur outside the drug-like chemical space known so far.[84] Therefore, synthesis of new lead-like molecules is necessary to further investigate new drug-like chemical space.[77] The use of libraries of molecular scaffolds for the search of NMEs has increased.[74] Molecular scaffolds are small synthetically accessible core structures that can be derivatised (decorated), using well-known reactions, to create libraries of molecules. Different definitions have been described.[78] Molecular scaffolds able to yield molecules that reside in new lead-like chemical space are of vital importance.[74,85]

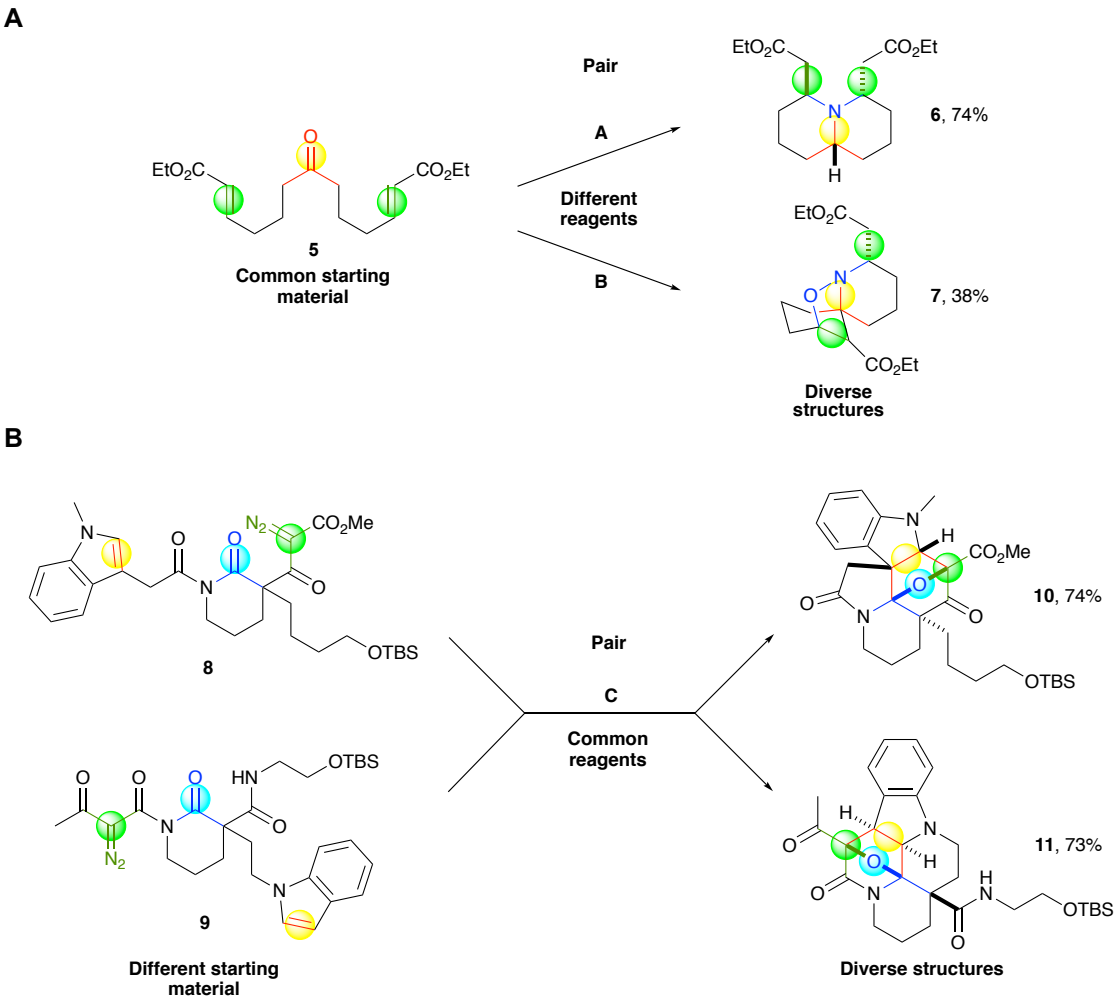
To access molecules in new chemical space, new synthetic approaches are required. Diversity-oriented synthesis (DOS) is a methodology that allows the synthesis of different molecular scaffolds.[86] Traditionally, combinatorial chemistry was used for the preparation of HTS libraries.[87] However, it yields molecules with similar structures. Conversely, DOS yields molecules with very different structures,[86,88] which allows a better exploration of chemical space (Figure 12).

Combinatorial chemistry **DOS**

Figure 12: Chemical space explored by combinatorial chemistry and by diversity-oriented synthesis. Adapted from a reference.[88]

DOS allows chemical space to be explored.[89] It allows access to complex scaffolds with high diversity in physicochemical properties and tri-dimensional shape using complex reactions with common and simple starting materials.[86,88,90] There are two key strategies to achieve this molecular diversity.[91] These approaches are the branching pathway (reagent-based

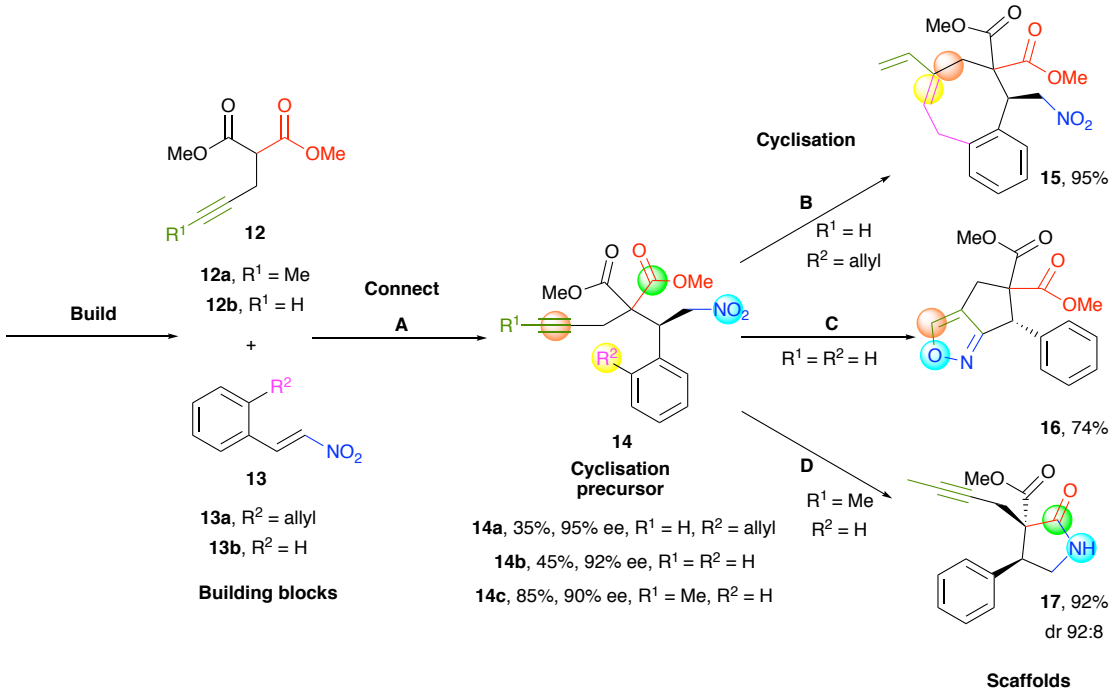
approach) and the folding pathway (substrate-based approach).[88,90–92] In the branching pathway, common starting materials are transformed to different scaffolds using different reagents and reactions. In the folding pathway, different starting materials react under common reaction conditions to yield different scaffolds (Scheme 1).



Scheme 1: Two key approaches used in DOS. **Panel A:** Example of branching pathway. The starting material **5** can give up to 12 different scaffolds.[93–95] **Panel B:** Example of folding pathway.[94,96–98] **Method: A:** NH_3, $NaBH_4$, 250 mol% $Ti(OEt)_4$, EtOH, then AcOH; **B:** NH_2OH•HCl, NaOAc, MeCN, then toluene, μW, 140 °C; **C:** 1 mol% $Rh_2(OAc)_4$, benzene, 50 °C.

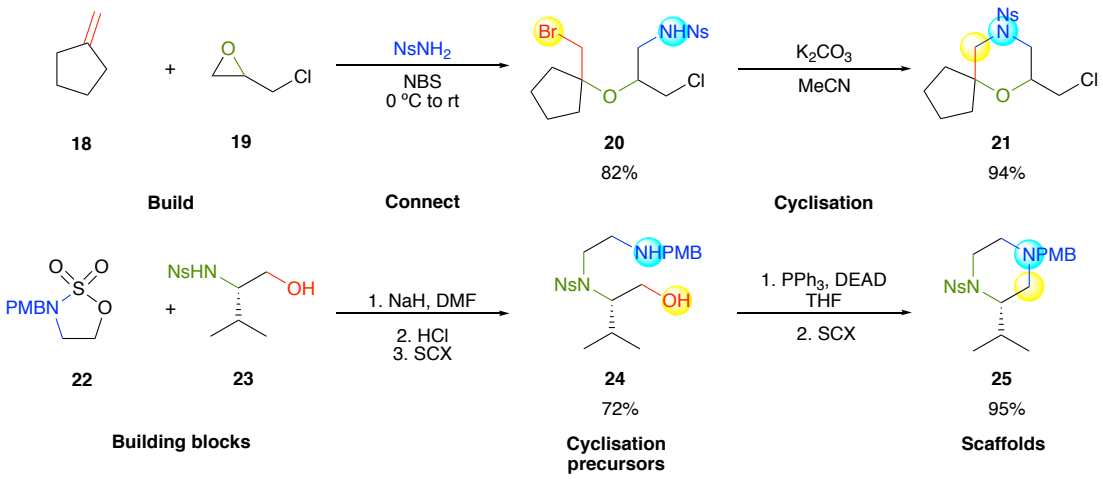
The branching pathway and the folding pathway represent the pair stage (cyclisation stage) of an approach called the build/couple/pair (build/connect/cyclisation) strategy.[86,99] The build stage consists in the synthesis of the starting materials, containing different sets of functionalities suitable for the next two steps. In the couple (connect) stage, the starting materials are coupled together to achieve highly functionalized molecules. Finally, diversity is generated in the pair (cyclisation) stage.[99] In this stage

different intramolecular reactions are performed through the functional groups to yield the final scaffolds (Scheme 2).[86]



Scheme 2: Example of the build/couple/pair (build/connect/cyclisation) strategy used in DOS for the synthesis of diverse scaffolds.[91,100] When more connective points (coloured blobs) present in the cyclisation precursor, more diversity can be obtained. **Method: A:** 10 mol% modified cinchona alkaloid catalyst,[100] –20 °C or –40 °C, THF; **B:** Grubbs 1st generation 10 mol%, ethylene, μW, 150 W, 60 °C, DCM; **C:** PhNCO, Et_3N, toluene, rt; **D:** Zn, AcOH/THF, rt, then Na_2CO_3 (aq).

A high structural diversity of sp^3-rich molecular scaffolds with different physicochemical properties has been obtained from DOS.[101–103] Therefore, this strategy can be very useful to identify biologically active compounds.[88,104,105] In addition, DOS can be focused to obtain molecules within the lead-like chemical space.[94] It has been used to synthesise molecular scaffolds able to yield lead-like compounds.[106,107] There is a methodology called lead-oriented synthesis (LOS), which allows achieving structurally-diverse sp^3-rich scaffolds able to yield different molecules within the lead-like chemical space.[17] In LOS, synthetic approaches similar to the DOS (build/connect/cyclisation) strategies are used to achieve these molecular scaffolds (Scheme 3).



Scheme 3: Examples of the lead-oriented synthesis approach for the synthesis of different sp^3-rich scaffolds.[48,108] These scaffolds could be decorated to yield different molecules with lead-like physicochemical properties.

1.6. Molecular Scaffolds for the Design of Lead-like Molecules

Molecular scaffolds can be used to achieve high-quality lead-like molecules for drug discovery programs.[48,94] Different molecular scaffolds have been synthesised so far, using LOS methodologies (Figure 13).[94,108–117]

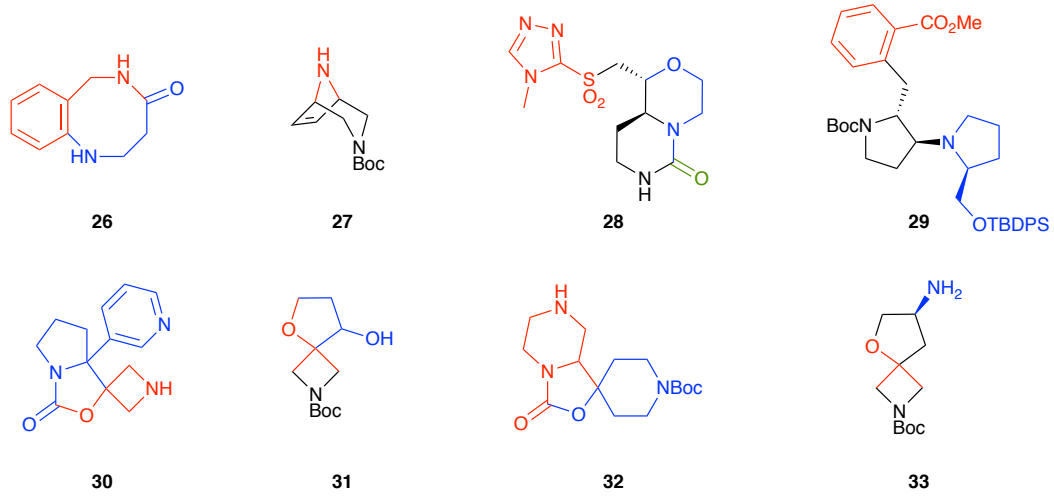


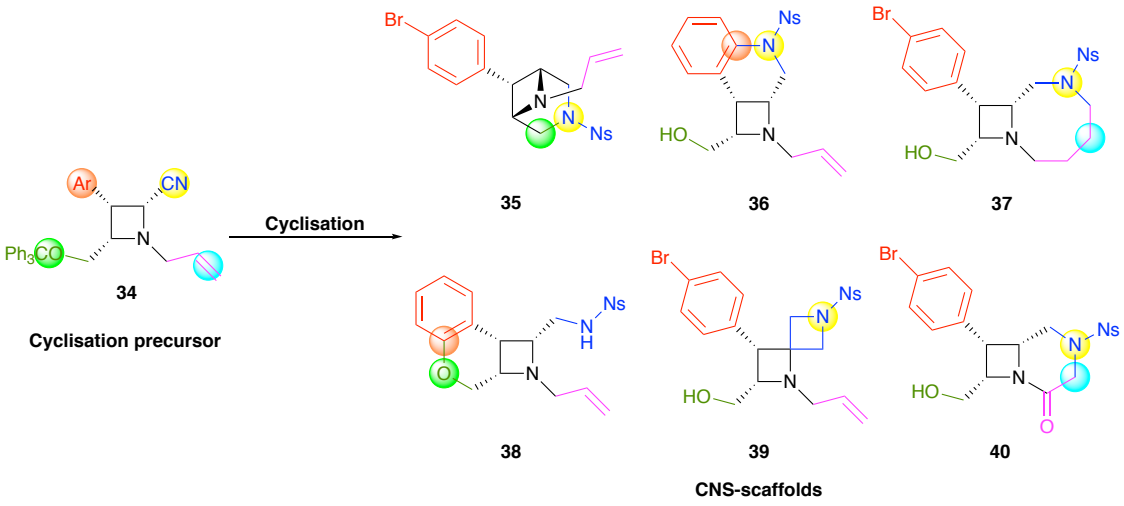
Figure 13: Examples of scaffolds obtained using LOS methodologies. *In silico* calculations have predicted that these scaffolds are likely to yield molecules with desirable lead-like physicochemical properties for the development of oral drugs.[48,94,116–118]

In silico calculations demonstrated that these scaffolds can be decorated with medicinal chemistry capping groups to achieve molecules with desirable lead-like physicochemical properties for the development of oral drugs.[48,94,117] Therefore, these derived molecules would have the desired properties and they could be tested in HTS to identify active molecules for a determined target. As a result, if an active molecule is found, it would be less likely to fail in the following

stages due to an undesired ADMET profile. Consequently, high-quality leads could be obtained from these molecular scaffolds. Due to the popularity of this approach, an open access tool called LLAMA (lead-likeness and molecular analysis) has been recently developed.[119] Using this tool, one can rapidly know if a scaffold is likely to be decorated to yield many lead-like molecules.

1.6.1. CNS Relevant Molecular Scaffolds

Due to the different physicochemical properties of CNS-drugs, they occupy a more restricted region than other drugs in the chemical space. The chemical space of CNS-drugs has already been studied.[28,58] Through the use of LOS, different scaffolds could be synthesised as precursors of lead-like molecules to identify CNS-drugs. This methodology has already been applied in CNS drug discovery. Few scaffolds stated to yield lead-like molecules with CNS molecular properties have been synthesised so far using LOS methodologies (Scheme 4).[106]



Scheme 4: Example of a LOS approach to obtain azetidine-based scaffolds. These scaffolds have been designed to yield lead-like molecules with CNS molecular properties.[106]

In silico approaches, like the Pfizer's CNS MPO scoring system, showed that most of the physicochemical properties of the derived compounds from these scaffolds were in the desired range for brain penetration.[106] In addition, subsequent *in vitro* assays also demonstrated good permeability. Consequently, these scaffolds were decorated to produce a derived library of lead-like molecules. As a result, this derived library could be used as screening library against CNS-targets. However, the CNS MPO scoring system has been

developed to identify CNS-drugs, not CNS-leads. Consequently, if a lead-like compound derived from the previous scaffolds is optimised to a drug-like compound, it could lose brain penetration. For this reason, new MPO scoring systems focused on CNS-leads would be of interest to be able to keep good brain penetration even when the leads are optimised to drug-like compounds.

1.7. Conclusions

High-quality leads are required to be able to increase the current R&D productivity of pharmaceutical companies. *In silico* MPO methodologies and synthetic methodologies based on LOS have been developed to obtain molecular scaffolds that are likely to yield lead-like molecules with the desired properties to become oral drugs. However, in the case of CNS-drugs this process is more difficult due to the existence of the BBB. Identifying molecular scaffolds for the development of high-quality leads for CNS drug discovery is a new challenge. Therefore, new *in silico* MPO methodologies and new LOS approaches are of interest to identify scaffolds able to yield molecules with CNS lead-like molecular properties.

1.8. Project Outline

The main goal of this project is to facilitate the identification of high-quality leads for drug discovery programs in the CNS area. To achieve this goal, this project will combine computational and synthetic methodologies. Through these two methodologies, molecular scaffolds able to yield molecules with CNS lead-like physicochemical properties are going to be identified. This project has five objectives:

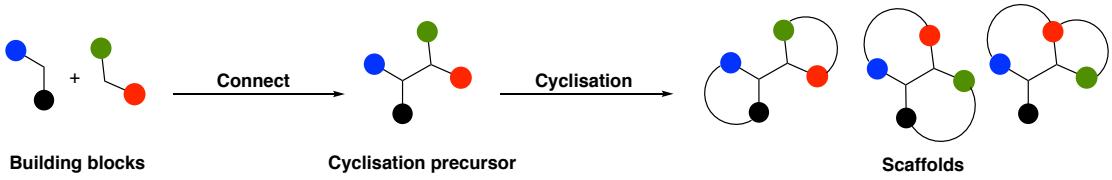
1) Develop and validate a computational tool that allows the identification of novel scaffolds for exploitation in CNS drug discovery **(Chapter 2, Sections 2.1–2.2)**. This computational protocol must identify novel scaffolds able to yield molecules with CNS lead-like molecular properties (Figure 14).

Figure 14: General idea of the computational protocol.

To be able to achieve this objective, this computational methodology is going to use a new MPO scoring system called CNS Lead MPO system. This scoring system is a modification of the CNS MPO scoring system developed by Pfizer.[67] The difference is that the CNS Lead MPO system gives scores with more CNS lead-like character instead of CNS drug-like character.

2) Exemplify the value of the computational tool using a set of molecular scaffolds that could be scored and easily synthesised using a known LOS approach. Consequently, these scaffolds could be decorated to experimentally test the permeability of the resulting lead-like molecules. As a result, the predictability of the computational tool could be validated experimentally **(Chapter 2, Section 2.3)**.

3) Develop a new LOS approach (build/connect/cyclisation approach) for the synthesis of novel scaffolds **(Chapter 3, Sections 3.1–3.3)**. For this reason, connective reactions involving highly functionalised building blocks are going to be selected. These connective reactions need to yield cyclisation precursors that can undertake different cyclisation reactions to yield different scaffolds (Scheme 5).



Scheme 5: General idea of connective reactions to yield cyclisation precursors, which can cyclise to afford different scaffolds. The coloured blobs correspond to different functional groups.

4) Prioritise key cyclisation reactions from the developed LOS approach and exemplify the synthetic methodology through the synthesis of the novel scaffolds **(Chapter 3, Section 3.3)**. Use the computational tool to demonstrate

the value of the scaffolds prepared for CNS drug discovery **(Chapter 3, Section 3.4)**.

5) Realise the biological relevance of the prepared scaffolds. Consequently, some of the scaffolds are going to be decorated using a medicinal chemistry capping group to produce a library of derived molecules **(Chapter 4, Section 4.2)**. Subsequently, the biological activity of these derived molecules is going to be assessed against the CNS-target BACE 1 to allow ligand discovery **(Chapter 4, Section 4.3)**.

Chapter 2: Development of a Computational Tool to Assess Scaffolds for CNS Drug Discovery

2.1. Development of the Computational Tool

The design of new *in silico* MPO methodologies to identify molecular scaffolds for exploitation in CNS drug discovery is of interest. Consequently, it was decided to develop a computational tool to allow different scaffolds to be prioritised on the basis to yield lead-like molecules to support CNS drug discovery. The design of the computational tool would involve different steps (Figure 15).

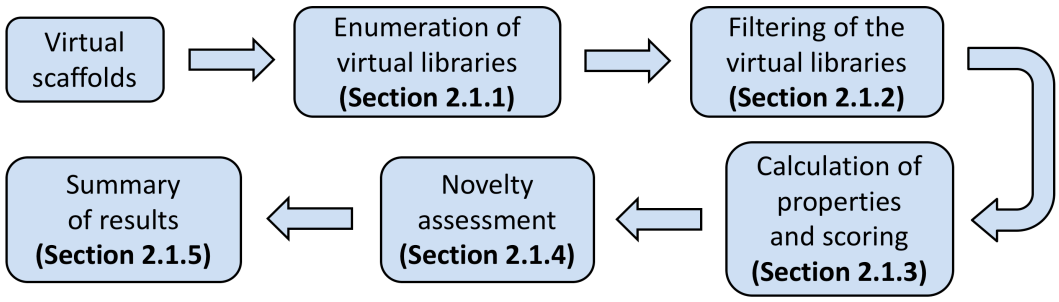


Figure 15: Overview of the *in silico* protocol for the identification of scaffolds for exploitation in CNS drug discovery.

The computational protocol would start when a virtual library of molecular scaffolds is loaded into it. Subsequently, each scaffold would be decorated with different virtual medicinal chemistry capping groups. The resulting library of derived compounds would be then filtered to remove compounds with toxicophores and undesired substructures for brain penetration. Once molecules with undesired substructures have been removed, the physicochemical properties of the derived compounds that passed the filter would be calculated. Successively, each derived compound would be scored depending on its physicochemical properties. Subsequently, the mean score for each scaffold would be calculated from the scores of all of its derived compounds. This score would reflect the likelihood of the scaffold to give lead-like compounds for CNS drug discovery. In addition, the novelty of each scaffold would also be assessed. Finally, this protocol would give three results for each scaffold. These results would be the mean score of its derived virtual compounds, the number of derived virtual compounds generated and the novelty.

To be able to generate every step of this computational protocol, two different sofwares will be used. These two softwares are Accelrys Pipeline Pilot and ChemAxon (see Section 5.1). These softwares are available under an academic licence and they are used to create, modify or analyse chemical databases.

2.1.1. Enumeration of Virtual Libraries

The scaffolds of interest need to be scored depending on their ability to yield lead-like molecules for CNS drug discovery. For this reason, the first step of the computational tool to be developed was the enumeration of virtual libraries. In this stage, each scaffold is decorated with a selected library of virtual medicinal chemistry capping groups (see Appendix). It was decided to decorate the scaffolds one or two times, depending on the points of decoration. The scaffolds were not decorated more than two times to avoid a high increase in MW. Well-known decoration reactions were used to create the library of derived compounds (Figure 16).

A

Type of decoration reaction	Functionality in the scaffold	Functionality in the reagent
Amidation	Acid chlorides	Amines
Amidation	Amines	Carboxylic acid
Amidation	Carboxylic acids	Amines
Sulfonylation	Sulfonyl chlorides	Amines
Sulfonylation	Amines	Sulfonyl chlorides
O-alkylation/arylation	Alcohols, carboxylic acids	Halides
N-alkylation/arylation	Amines, amides, sulfonamides	Halides
C-alkylation/arylation	Halides	Boronic acids
Reductive amination	Amines	Ketones, aldehydes
Reductive amination	Ketones, aldehydes	Amines
Urea formation	Amines	Isocyanates

B

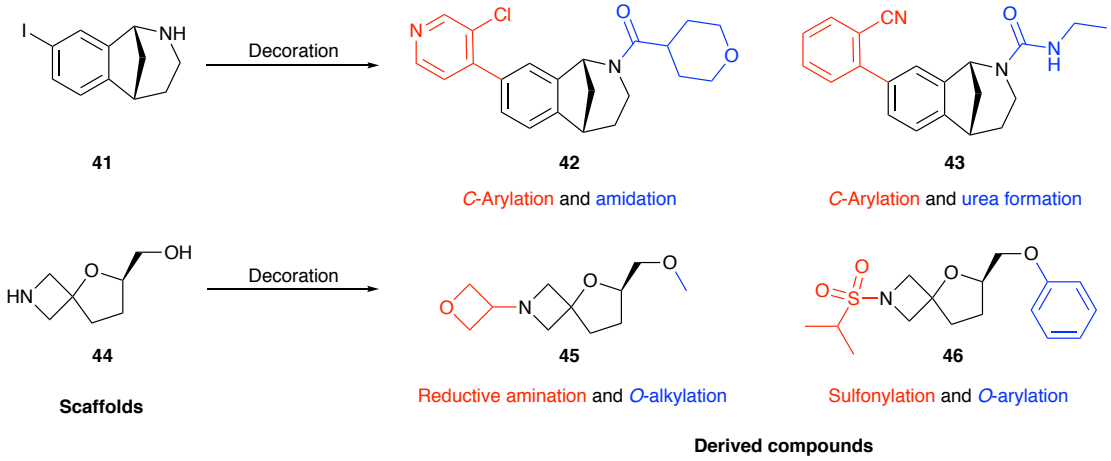


Figure 16: Generation of virtual libraries from scaffolds. **Panel A:** Reactions used for the decoration of the virtual scaffolds. **Panel B:** Example of derived compounds from scaffolds.[112,120]

The medicinal chemistry capping groups were chosen depending on their commercial availability, their presence in drug molecules and their physicochemical properties. Capping groups with a specific range of MW and clogP were selected (see Appendix). Consequently, the different types of capping groups should all, on average, induce a similar change of properties to the scaffolds.

2.1.2. Filtering of the Virtual Libraries

The library of derived compounds created can contain compounds with toxicophores and undesired substructures for brain penetration. These compounds should not be included because they are not attractive molecules

for CNS. Consequently, a filter to remove these compounds was implemented before the scoring (Figure 17). Derived compounds that pass the filter go to the next step of the computational protocol. However, derived compounds that do not pass the filter are removed and they do not go to the next step.

A

A derived compound does not pass the filter if:	It has a number of amides + sulfonamides + sulfamides + carbamates + ureas higher than one. or It has a number of basic amines higher than one. or It has carboxylic acids, esters, ketones, aldehydes, alkyl halides, electrophilic aryl halides, epoxides, aziridines, furans, pyrroles, thiophenes, aminothiazoles, indoles, anilines, silicon groups, thioethers or acetals.

B

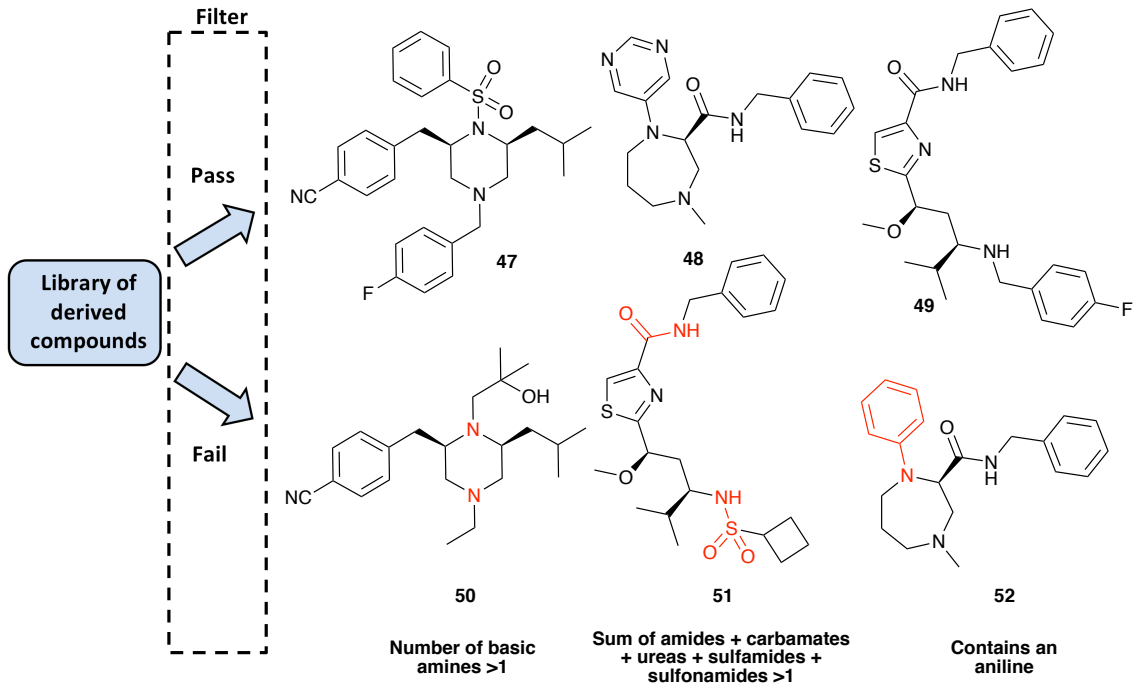


Figure 17: Filtering of derived compounds. **Panel A:** Filtering rules for derived compounds. **Panel B:** Example of derived compounds that pass the filter and example of derived compounds that do not pass the filter.[108,121,122]

It is important to indicate that due to the use of collections of capping groups with similar physicochemical properties, removing some derived molecules before scoring should not affect the final scaffold score. It should only affect the number of derived compounds that will be scored. As a result, this computational tool should penalise more the original scaffold rather than the capping groups used.

2.1.3. Calculation of Physicochemical Properties and Scoring

The next step of the computational protocol is the calculation of the physicochemical properties of the filtered library of the derived compounds. It was decided to calculate the same six fundamental physicochemical properties (MW, clogP, clog$D_{7.4}$, pK_a, HBD and PSA) that Pfizer calculates in its CNS MPO scoring system.[67] The reason is that these properties are usually used to address ADMET issues.[67] Once these six physicochemical properties have been calculated, the scoring system is applied. The scoring system used is a modification of the Pfizer's CNS MPO scoring system,[67] which has been adapted for CNS-leads rather than CNS-drugs. Therefore, it was designated the name of CNS Lead MPO scoring system.

The CNS Lead MPO scoring system scores using desirability functions focused on the desired physicochemical properties of CNS lead-like molecules. A model of a monotonic decreasing function and a model of a hump function were implemented to transform each physicochemical value in a score. A model of a monotonic decreasing function is used for MW, clogP, clog$D_{7.4}$, pK_a, HBD, and a model of a hump function is used for PSA (Figure 18). These models were adapted from Pfizer's functions.[67] Pfizer decided to use these functions of desirable, less desirable and undesirable ranges based on its medicinal chemistry experiences. However, in the CNS Lead MPO scoring system, the boundaries for optimal scores were reduced for MW, HBD and PSA to leave scope for subsequent lead optimisation. In addition, Pfizer's CNS MPO scoring system scores from 0.00 (very undesirable property) to 1.00 (very desirable property). However, it was decided to score from 0.05 to 1.00 to give slightly higher score to undesired properties, making less strict the penalty. Consequently, properties with a value totally undesirable obtain a score of 0.05 and properties with a value totally desirable obtain a score of 1.00. Accordingly, properties partially desirable/undesirable will obtain a score between 0.05 and 1.00.

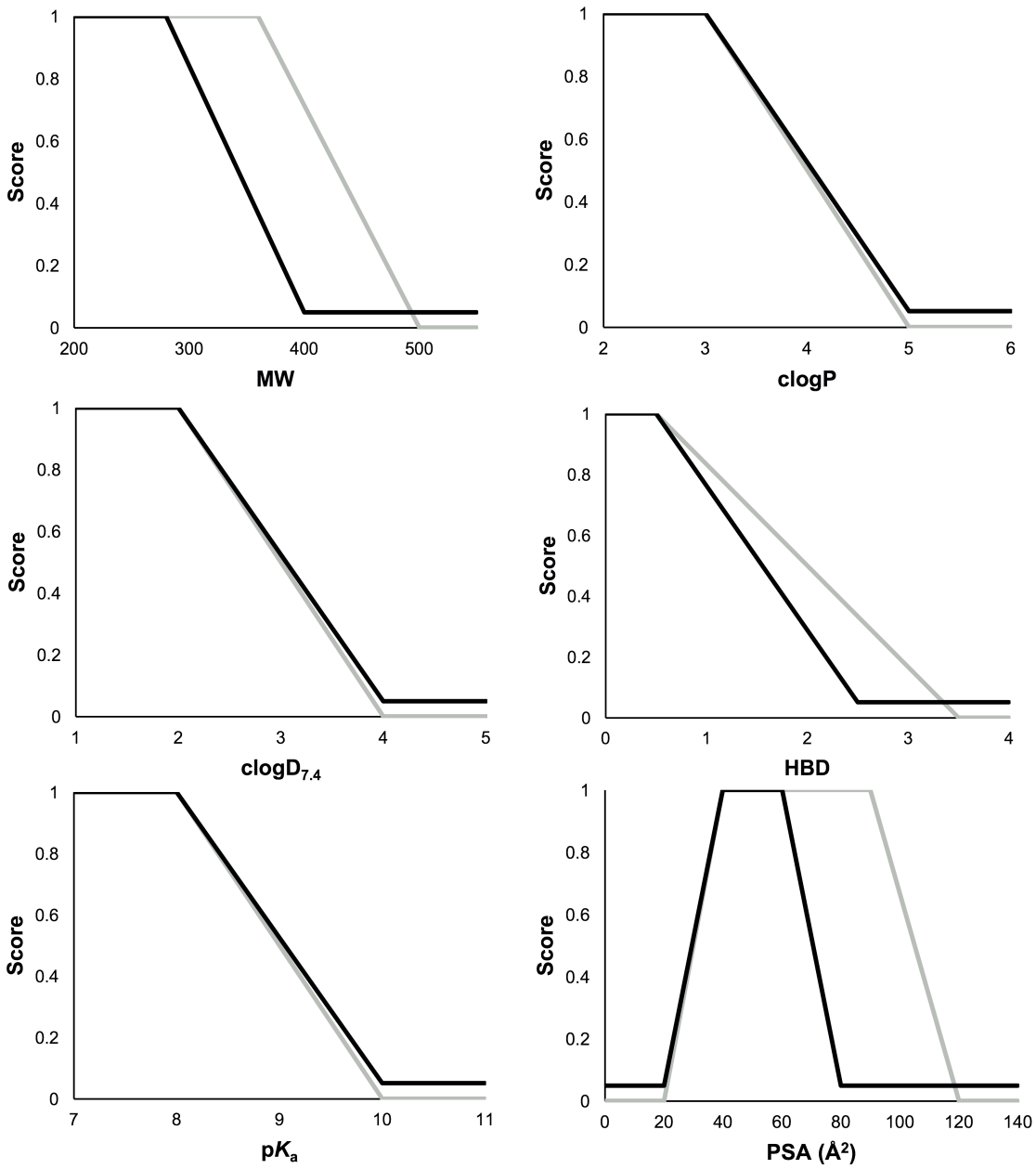


Figure 18: Desirability functions used in the scoring system. In black the developed CNS Lead MPO score. In grey the Pfizer's CNS MPO score.

As a result, six scores between 0.05 and 1.00 are obtained for each derived compound. Subsequently, these six scores are summed to achieve the final CNS Lead MPO score for each derived compound. This score ranges from 0.30 to 6.00. The lowest score of 0.30 indicates a molecule with totally undesirable properties whereas the highest score of 6.00 shows the molecule has perfect properties. All other scores between 0.03 and 6.00 indicate that the compound will have a mixture of both desirable and undesirable properties. It was decided to give to all six properties the same weight, as Pfizer also did. The reason is that Pfizer observed that weighting all six properties equally gives the best predictions.[67] Finally, the mean of all the CNS Lead MPO scores of all the

derived compounds that come from the same scaffold is calculated to obtain the mean CNS Lead MPO score per scaffold. The same scale from 0.30 to 6.00 is used to indicate the desirability of the parent scaffolds. Consequently, it was agreed that scaffolds with a mean CNS Lead MPO score close or >4.00 are going to be scaffolds with a good score and likely to yield molecules with lead-like properties for CNS drug discovery.

2.1.4. Novelty Assessment

The value of the mean CNS Lead MPO score per scaffold is the main result. However, novel scaffolds are preferred. Therefore, a novelty assessment for the scaffolds was implemented in the protocol. This assessment is achieved comparing Murcko fragments from the scaffolds with Murcko fragments from a random 2% of the ZINC database (database of commercially available compounds).[123,124] A Murcko fragment is generated when only the rings and the chains between the rings of a molecule (ring systems) are maintained. These Murcko fragments are compared without their α-atoms (only ring systems) and with their α-atoms (ring systems with the atoms attached directly to the rings) (Figure 19). The results are shown as the number of times (number of hits) that these two kinds of Murcko fragments have been found in the database.

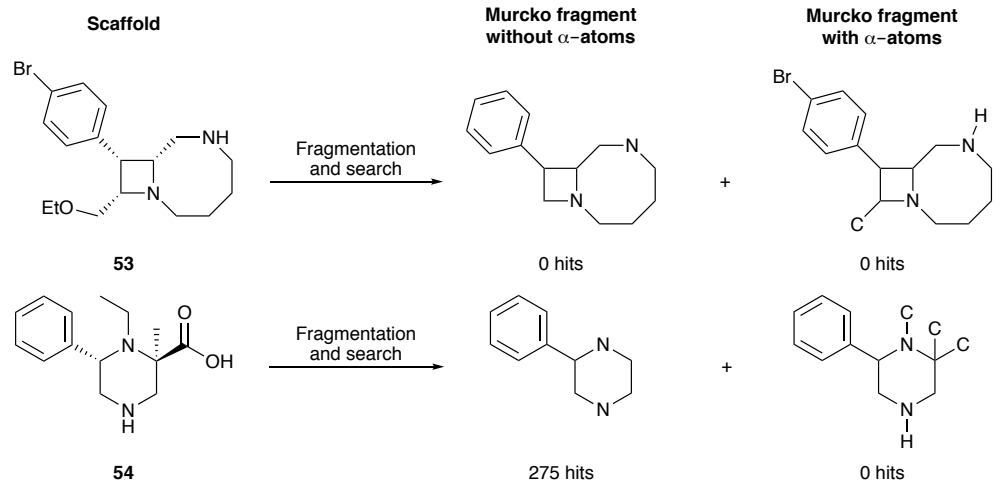


Figure 19: Example of generation of Murcko fragments from two scaffolds and their hits (number of times found) in a random 2% of the ZINC database. It was observed that comparing 2% or the entire database give the same results. **Scaffold 53:**[106] Murcko fragment without and with α-atoms does not show any hit. Consequently the scaffold is novel. **Scaffold 54:**[113] Murcko fragment without α-atoms shows 275 hits. However, when the α-atoms are considered, there is not any hit. As a result, the substitution pattern of the scaffold is novel.

2.1.5. Summary of Results

Once the mean CNS Lead MPO score has been calculated and the novelty assessment has been performed, the computational tool gives the final results. The final results for each scaffold are the mean CNS Lead MPO score, the number of derived compounds generated and the novelty. Consequently, after using this computational tool, one could know how likely is a molecular scaffold to give lead-like molecules for CNS drug discovery programs (mean CNS Lead MPO score ~>4.00) and if the scaffold has a novel structure (number of hits without or with α-atoms = 0).

2.2. Validation of the Computational Tool

After developing the computational protocol, it was validated to know if each decision taken during the development (selection of capping groups, filtration rules, properties scored and scoring functions) was appropriate. For the validation, 29 different literature-related molecular scaffolds were scored (**55**–**83**) (Figure 20). Literature-related scaffolds with two points of decoration, and with desirable and undesirable physicochemical properties to cross the BBB were selected. Consequently, they should give a library of derived compounds with both good and poor CNS Lead MPO scores. For example, scaffolds **64** and **65** should give good mean CNS Lead MPO scores (>4.00) because they have already been reported as CNS relevant scaffolds.[106] In contrast, scaffolds **77** and **78** should give poor mean CNS Lead MPO scores (<4.00) due to the fact that they are scaffolds found in drugs that belong to the second generation of H_1-antihistamines, which cross the BBB poorly.[125] Finally, the Pfizer's mean CNS MPO score was also calculated for each scaffold to be able to compare it to the mean CNS Lead MPO score.

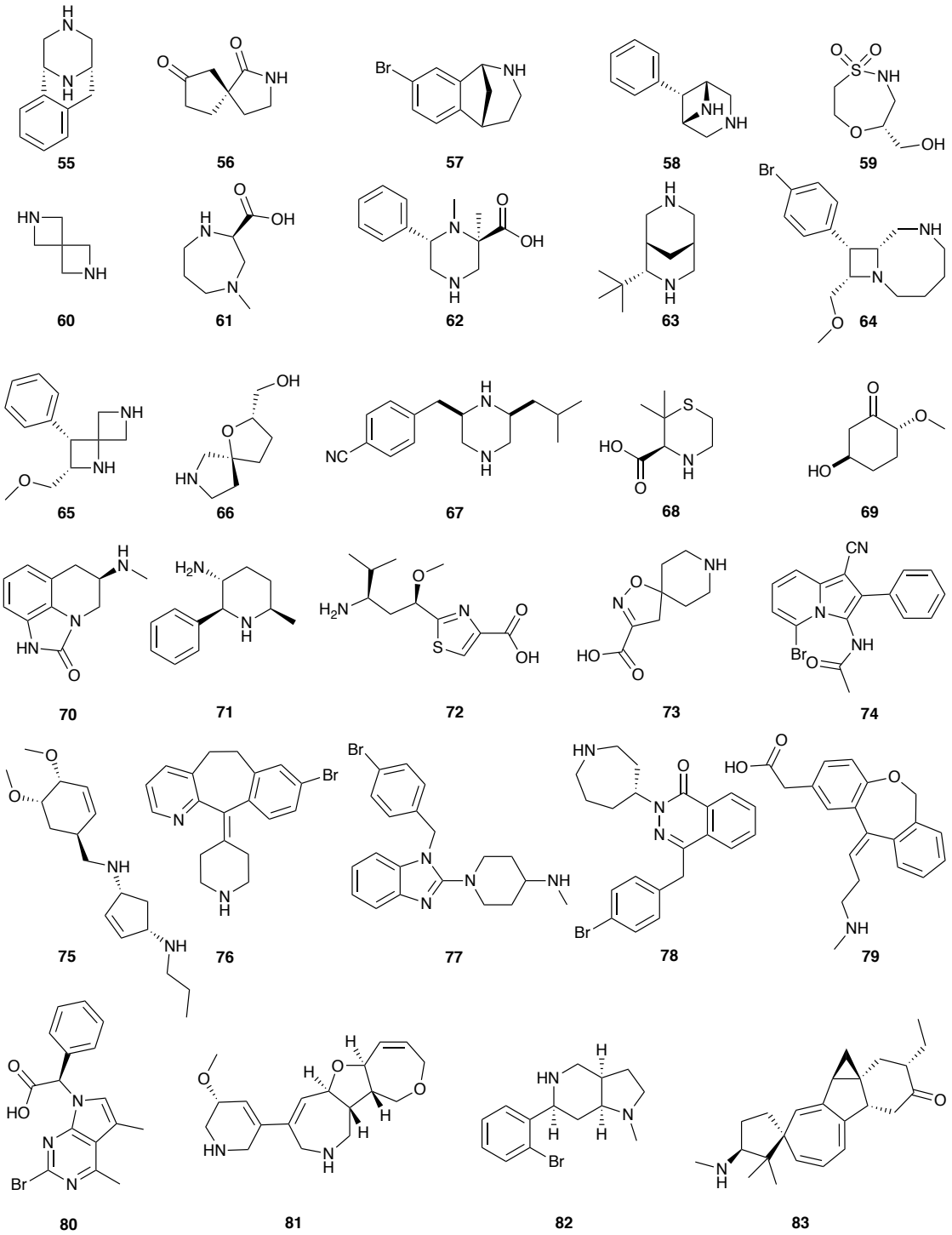


Figure 20: Literature-related scaffolds selected for the validation of the computational protocol (references in Table 1). Scaffolds that should give a low mean CNS Lead MPO score and scaffolds that should give a high mean CNS Lead MPO score were selected.

After applying the computational protocol, it was observed that the mean CNS Lead MPO score was always lower than the Pfizer's mean CNS MPO score (Table 1). This is due to the fact that the CNS Lead MPO score penalises heavily for high MW, PSA and HBD. Some of these scaffolds have a good mean CNS Lead MPO score (>4.00) and others have a poor mean CNS Lead MPO score (<4.00). Consequently, some scaffolds are considered more likely

than others to yield lead-like molecules for CNS drug discovery. As expected, scaffolds **64** and **65** gave mean CNS Lead MPO scores closer or higher than 4.00 and scaffolds **77** and **78** gave mean CNS Lead MPO scores much lower than 4.00. This shows that the selection of capping groups, the scoring functions and the equal weighting of the properties was appropriate. In addition, it can also be observed that some scaffolds like **61** and **62** score well but they give a smaller number of derived compounds than other scaffolds. The reason is that these scaffolds contain functionalities that will make most of the derived library fail during the filtration step. Consequently, these scaffolds would deliver a lower number of useful lead-like molecules than others and therefore they would be less interesting than other scaffolds with similar score but higher number of scored derived compounds. This shows that it was important to implement the filtration step. By scoring the derived compounds without the filtration step, it was observed that a very similar score was obtained for every scaffold. Consequently, the filtration step does not affect the final scaffold score, it only affects the number of useful derived compounds that could be prepared. This shows again that the selection of capping groups was appropriate because the derived compounds were penalised more by the original scaffold rather than by the capping groups. Finally, some of these scaffolds are novel due to the fact that they are not commercially available.

Scaffold number and ref.	Mean Pfizer's CNS MPO score[b]	Mean CNS Lead MPO score[c]	Number of derived compounds	Novelty[d] Hits without α-atoms	Novelty[d] Hits with α-atoms
55[115]	4.97	4.47	3038	0	0
56[107]	4.92	4.52	384	53	0
57[120]	4.37	3.96	1140	0	0
58[106]	5.09	4.59	3038	0	0
59[126]	5.84	4.86	696	0	0
60[127]	5.75	5.49	1522	1	1
61[108]	5.66	4.99	114	2924	585
62[113]	4.73	4.08	114	275	0
63[48]	4.69	4.22	3038	154	4
64[106]	4.13	3.89	795	0	0
65[106]	4.87	4.43	3038	0	0
66[112]	5.45	4.86	2204	1	0
67[121]	3.55	3.02	3038	104	0
68[128]	5.48	4.93	551	1850	1
69[129]	4.98	4.60	464	28392	3
70[a]	4.81	4.31	986	0	0
71[130]	4.34	3.69	3038	557	110
72[122]	3.87	2.83	551	27526	8608
73[131]	5.33	4.38	551	0	0
74[132]	3.94	3.48	360	7	0
75[110]	4.00	3.64	3038	0	0
76[a]	3.18	2.99	1140	0	0
77[a]	3.03	2.81	1140	17	0
78[a]	3.29	2.88	1140	0	0
79[a]	3.27	2.97	551	3	0
80[133]	3.42	2.70	285	1	0
81[110]	4.61	4.07	3038	0	0
82[133]	4.20	3.88	795	0	0
83[107]	2.76	2.52	848	0	0

Table 1: Results obtained for the 29 literature-related scaffolds using the computational tool. [a]Scaffolds derived from bioactive molecules (**70** (sumanirole), **76** (rupatadine), **77** (mizolastine), **78** (azelastine), **79** (olopatadine)). [b]Mean of all the Pfizer's CNS MPO scores of the derived compounds per scaffold. [c]Mean of all the CNS Lead MPO scores of the derived compounds per scaffold. [d]Based on Murcko fragments against a random 2% of the ZINC database.

To understand these scores, some scaffolds with good mean CNS Lead MPO scores and some scaffolds with poor mean CNS Lead MPO scores were selected and analysed (Figure 21). It was observed that some scaffolds like **60** and **66** present good mean CNS Lead MPO scores because most of their derived compounds score values close to 6.00. This means that scaffolds **60** and **66** are likely to yield lead-like molecules, which once optimised to drugs, will have the desired physicochemical properties to cross the BBB. However, scaffolds **67** and **77** present a poor mean CNS Lead MPO score. This poor score is due to the fact that most of their derived compounds only score 0.05 for MW, clogP and $clogD_{7.4}$. These results mean that scaffolds **67** and **77** would be predicted to yield lead-like molecules, which once optimised to drugs, would have values for MW, clogP and $clogD_{7.4}$ too high to be able to cross the BBB.

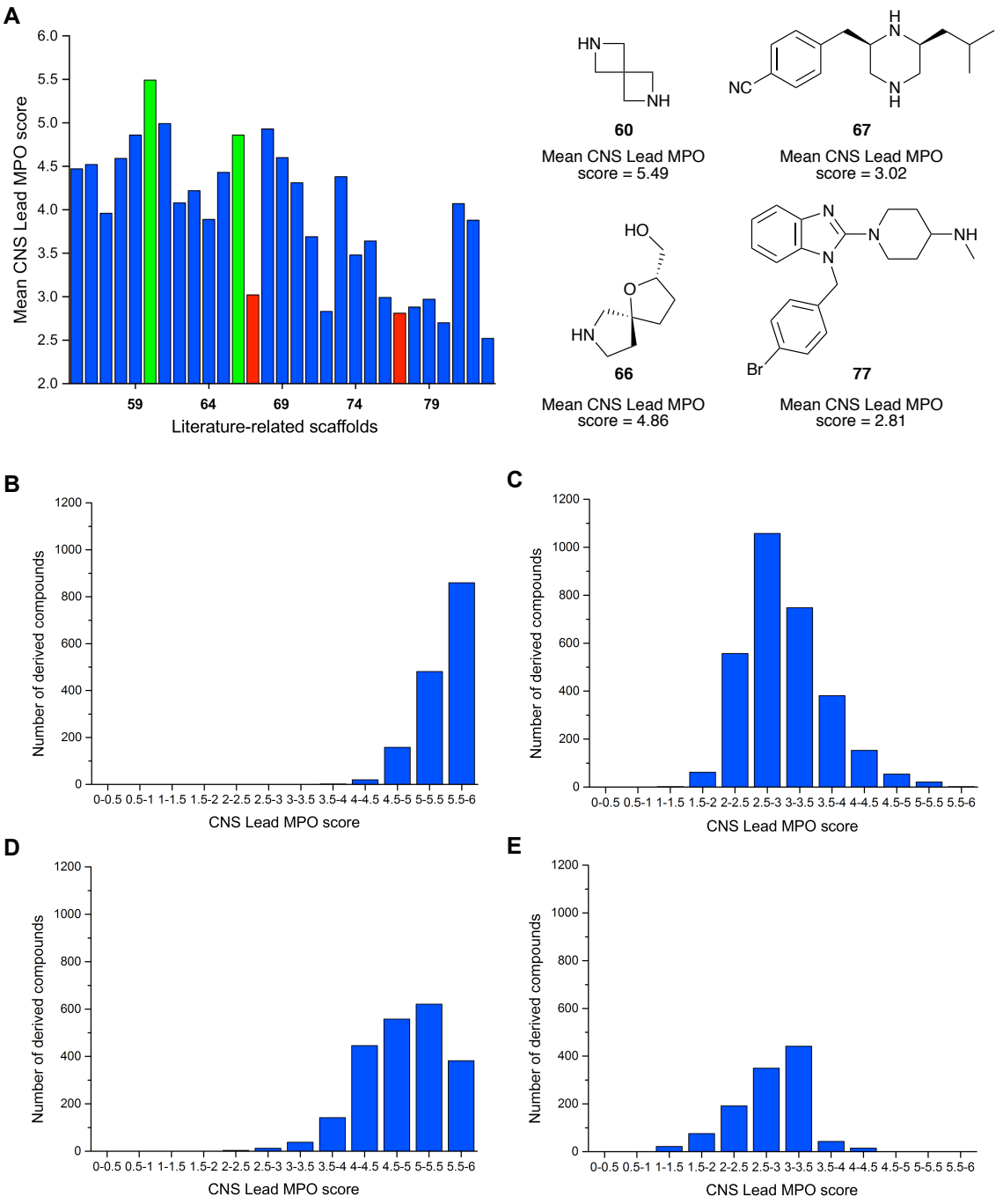
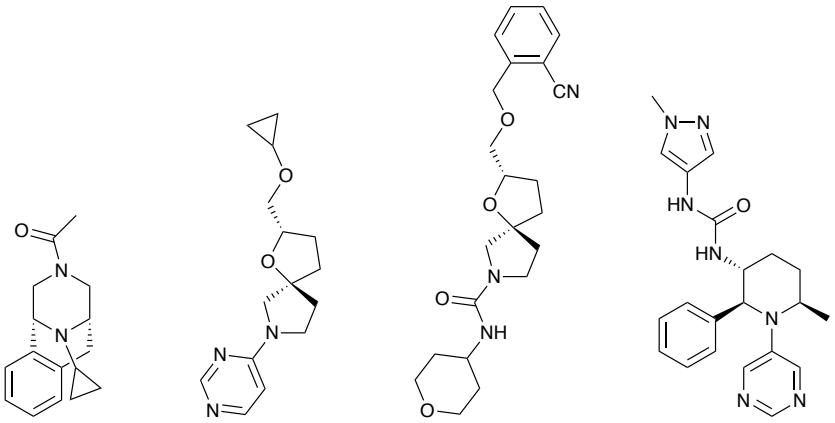


Figure 21: Panel A: Analysis of the mean CNS Lead MPO scores of the derived compounds for each literature-related scaffold. In green, examples of scaffolds with good scores (**60** and **66**) (score >4.00). In red, examples of scaffolds with poor scores (**67** and **77**) (score <4.00). **Panels B, C, D, E:** Distribution of the CNS Lead MPO scores of the derived compounds of the scaffolds **60**, **67**, **66** and **77**, respectively.

To finish with the validation, some derived compounds from the scaffolds **55**, **66** and **71** were selected and their Pfizer's CNS MPO scores were compared with their CNS Lead MPO scores (Table 2). It can be seen that all these derived compounds (**84**–**87**) have a high score using the Pfizer's CNS MPO scoring system. Consequently, these four compounds would have the desired physicochemical properties to be drug-like molecules able to cross the BBB.

However, derived compounds **86** and **87** have a lower CNS Lead MPO score than derived compounds **84** and **85**, due to higher MW and higher PSA. Consequently, if these compounds are used as lead-like molecules and undertake a lead optimisation process, they would increase their MW and PSA to yield drug-like molecules too large and too polar for brain penetration. Due to the fact that compounds **84** and **85** have a higher CNS Lead MPO score, there is more scope for lead optimisation and they could deliver drug-like molecules with the desired properties for brain penetration. For this reason, using the CNS Lead MPO score, one can distinguish that compounds **84** and **85** would be better lead-like molecules for CNS drug discovery than compounds **86** and **87**.



Derived compound:	**84**	**85**	**86**	**87**
Pfizer's CNS MPO score:	5.21	6.00	5.57	5.22
CNS Lead MPO score:	5.21	6.00	3.86	3.36
MW:	256	275	399	391
PSA (Å^2):	23.5	47.5	83.8	88.0

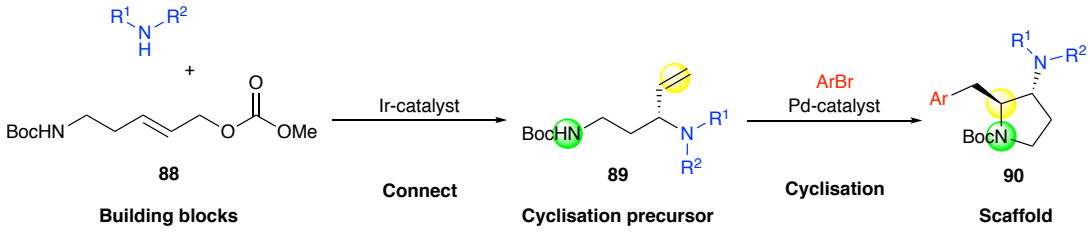
Table 2: Comparison of the Pfizer's CNS MPO score and the CNS Lead MPO score of some derived compounds from scaffolds **55**, **66** and **71**.

2.3. Exemplification of the Computational Tool

After developing and validating the computational tool, it was used to assess a library of molecular scaffolds for CNS drug discovery. For this assessment, novel scaffolds that could be scored and quickly synthesised using a known LOS approach (build, connect and cyclise) were of interest. Consequently, these scaffolds could be decorated, and the resulting lead-like compounds could be experimentally assessed for permeability. As a result, it could be observed if the predictions of the computational tool are in accordance with the experimental results of permeability.

2.3.1. Identification of a Lead-Oriented Synthesis Approach Based on an Ir-catalysed Connective Reaction

A LOS approach involving an Ir-catalysed connective reaction followed by a Pd-catalysed cyclisation reaction was identified.[116] Consequently, using these two reactions with an allylic carbonate building block, different amines and different electron deficient het(aryl) bromide groups, a library of pyrrolidine-derived scaffolds for CNS drug discovery could be prepared (Scheme 6).[116,134,135]



Scheme 6: Connective reaction involving iridium chemistry and subsequent cyclisation reaction involving palladium chemistry. Different pyrrolidine-derived scaffolds can be accessed by using different amines and different electron deficient (het)aryl bromide groups. Finally, the Boc group can be removed to allow one point of decoration.

These two reactions were selected because their potential to yield different novel molecular scaffolds for the synthesis of lead-like molecules has already been investigated (Figure 22).[116,135] Therefore, this connective reaction and the subsequent cyclisation reaction have already been optimised and their scopes are known. As a result, this would allow a quick access to a wide number of different potential scaffolds. These scaffolds could be scored with the computational tool, synthesised and decorated to yield lead-like molecules, which could be experimentally assessed for permeability.

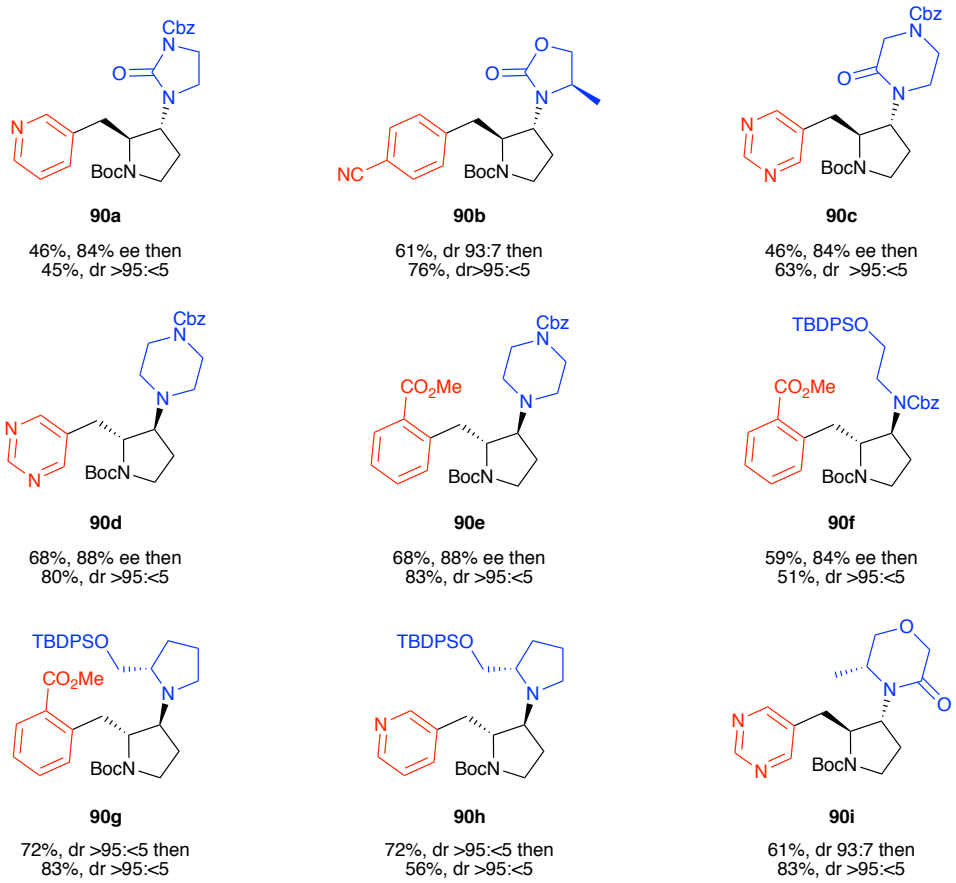


Figure 22: Precedent showing the scope for the synthesis of pyrrolidine-derived scaffolds using different amines (in blue) and different aromatic groups (in red).[116] First yields and ee/dr correspond to the Ir-catalysed asymmetric allylic substitution (amine, 4 mol% **91**, 2 mol% **92**, *n*BuNH$_2$, DMSO, 55 °C), second yields and dr correspond to the Pd-catalysed aminoarylation reaction (ArBr, 5 mol% Pd(OAc)$_2$, 10 mol% **93**, Cs$_2$CO$_3$, 1,4-dioxane, 105 °C).

2.3.2. Application of the Computational Tool

The Ir-catalysed connective reaction and the Pd-catalysed cyclisation reaction were identified as a pathway for the preparation of different pyrrolidine-derived scaffolds. Consequently, a virtual library of 25 different scaffolds (**94**–**118**), which could be prepared using these reactions with different amines and different aromatic groups, was designed (Figure 23). The amine and aromatic substituents were selected depending on their structural diversity and availability/synthetic accessibility. However, the aromatic groups were required to have electron deficient bromide groups for the Pd-catalysed reaction to work.

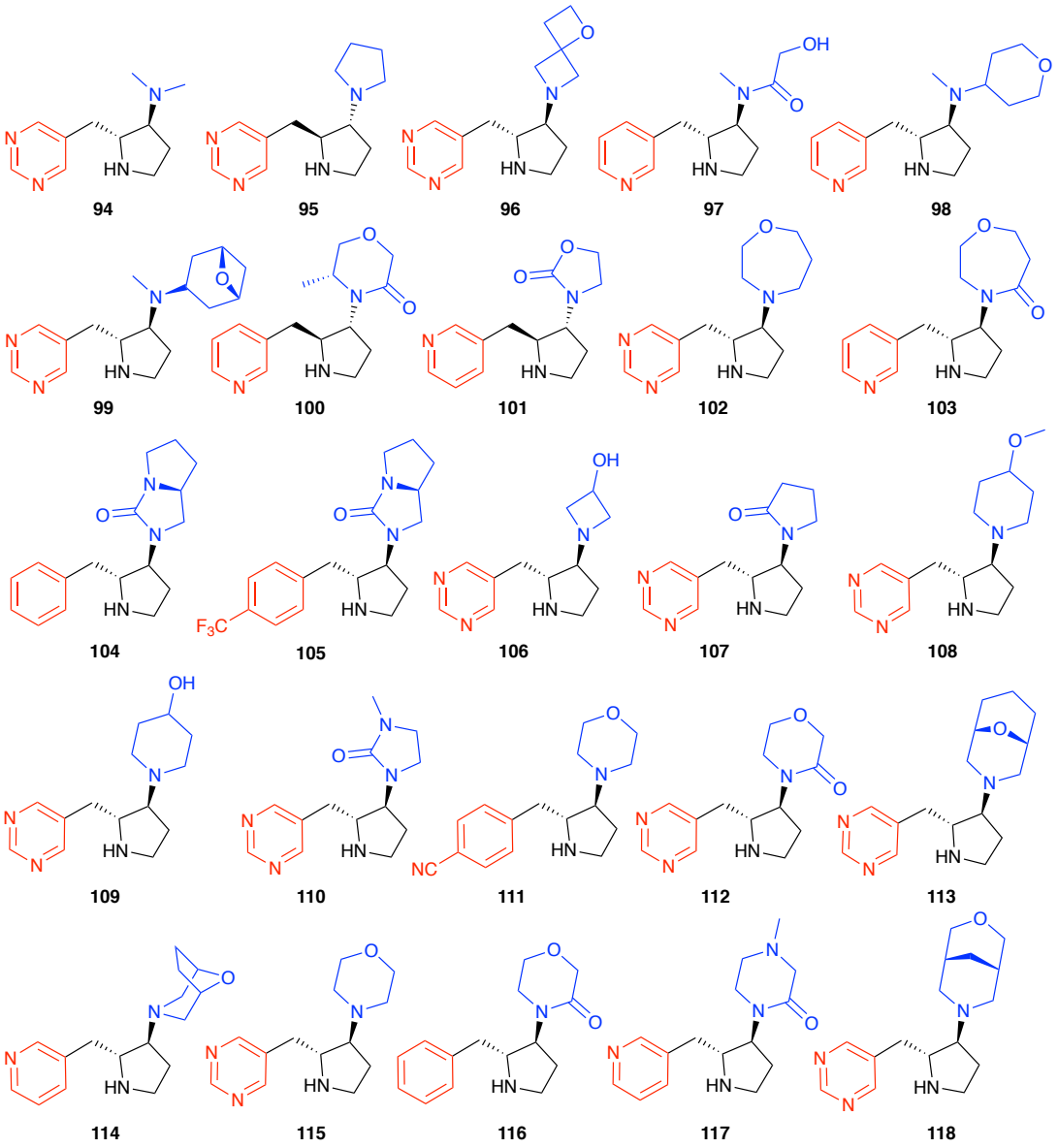


Figure 23: Virtual library of 25 different pyrrolidine-derived scaffolds that could potentially be synthesised using the Ir- and Pd-catalysed reactions with different amines (in blue) and different aromatic groups (in red).

Due to the synthetic accessibility of these 25 virtual scaffolds, they were scored with the computational protocol, using the secondary amine as the only point of decoration (Table 3). Consequently, it would be possible to identify which scaffolds are novel and more likely to yield molecules with CNS lead-like molecular properties.

Scaffold number	Mean CNS Lead MPO score[a]	Number of derived compounds	Novelty[b]	
			Hits without α-atoms	Hits with α-atoms
94	5.03	53	0	0
95	4.91	53	0	0
96	4.67	53	0	0
97	4.88	29	1	0
98	4.27	53	0	0
99	3.91	53	0	0
100	5.12	29	0	0
101	5.35	29	0	0
102	4.64	53	0	0
103	5.15	29	0	0
104	4.52	29	0	0
105	3.85	29	0	0
106	4.27	53	0	0
107	5.35	29	0	0
108	4.45	53	0	0
109	4.05	53	0	0
110	5.18	29	0	0
111	4.48	53	0	0
112	5.05	29	0	0
113	4.51	53	0	0
114	4.90	53	0	0
115	4.75	53	0	0
116	5.05	29	0	0
117	5.29	6	0	0
118	4.21	53	0	0

Table 3: Results obtained for the 25 virtual scaffolds using the computational protocol. Only the amines were used as point of decoration. [a]Mean of all the CNS Lead MPO scores of the derived compounds per scaffold. [b]Based on Murcko fragments against a random 2% of the ZINC database.

The results indicated that all of these scaffolds are novel (one of the scaffolds was found once without its α-atoms in the ZINC database; even here, it is novel when α-atoms are considered). In addition, most scaffolds have a score very close or higher than 4.00. Therefore, it suggests that most of them could yield lead-like molecules for CNS drug discovery. To understand these scores, some scaffolds with high mean CNS Lead MPO scores and some scaffolds with low mean CNS Lead MPO scores were selected and analysed (Figure 24).

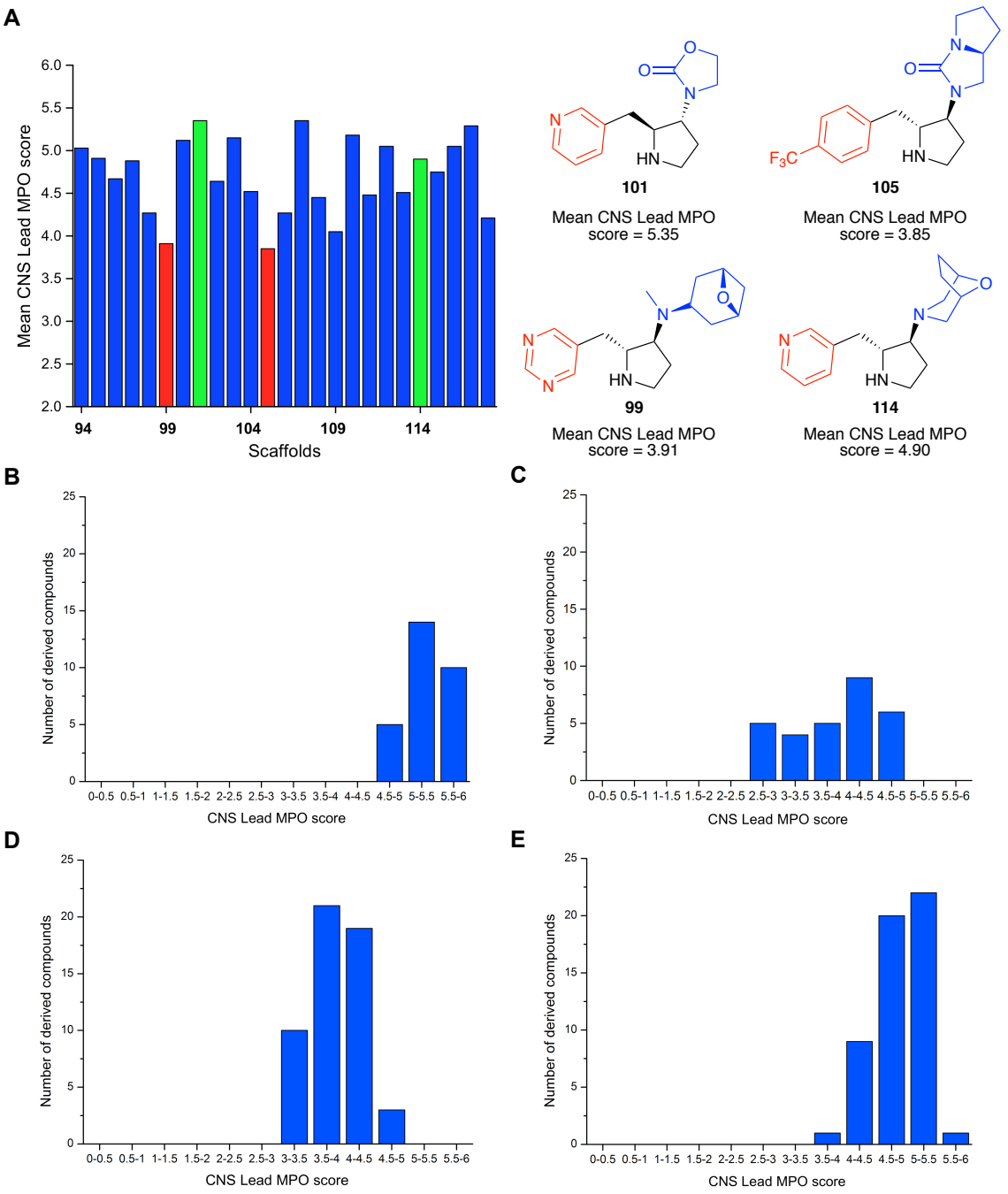


Figure 24: Panel A: Analysis of the mean CNS Lead MPO scores of derived compounds for each of the 25 virtual scaffolds. In green, examples of scaffolds with good scores (**101** and **114**). In red, examples of scaffolds with lower scores (**99** and **105**). **Panels B, C, D, E:** Distribution of the CNS Lead MPO scores of the derived compounds of the scaffolds **101**, **105**, **99** and **114**, respectively.

It was observed that some scaffolds like **101** and **114** present a good mean score because all of their derived compounds score values close to 6.00. This means that scaffolds **101** and **114** are likely to yield molecules with the desired physicochemical properties to be CNS lead-like compounds. However, scaffolds **99** and **105** present lower score. This lower score is because their derived library of compounds score only 0.05 for MW. These results mean that scaffolds

99 and **105** would yield molecules that could have values for MW too high to be CNS lead-like compounds.

With the results obtained, the virtual scaffolds **95, 100**, **101**, **114** and **115** were selected for synthesis (Figure 25). They were selected because they are novel, they have a good mean CNS Lead MPO score (>4.00) and they are readily synthetically accessible.

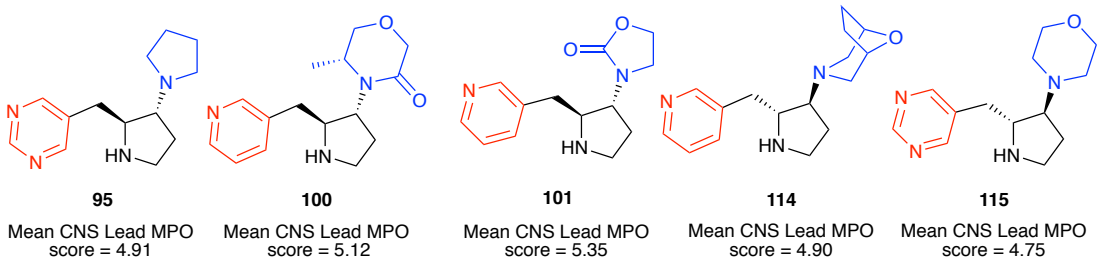


Figure 25: Virtual pyrrolidine-derived scaffolds selected for synthesis.

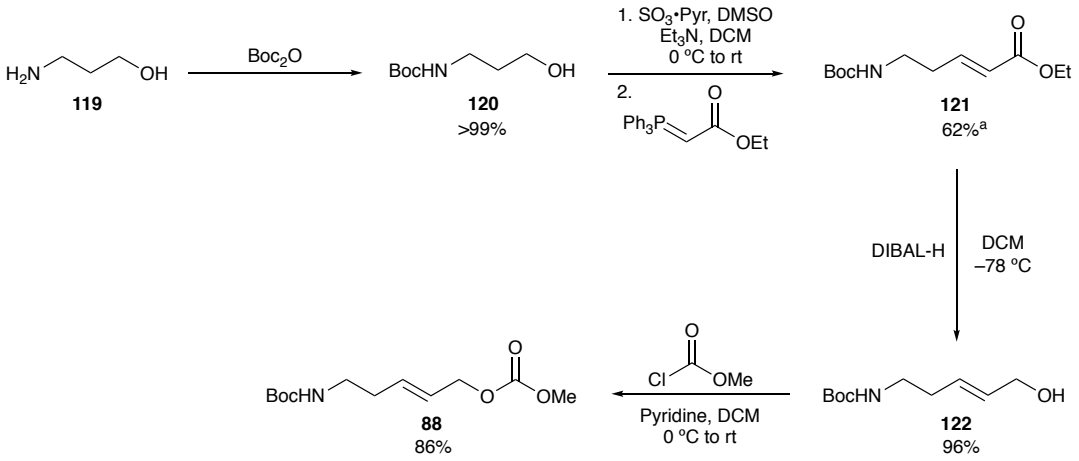
2.3.3. Preparation of Scaffolds

The pyrrolidine-derived scaffolds **95**, **100**, **101**, **114** and **115** were identified through the computational protocol as novel scaffolds likely to yield lead-like molecules for CNS drug discovery. Consequently, they were selected for the exemplification of the computational tool.

2.3.3.1. Synthesis of Cyclisation Precursors

2.3.3.1.1. Preparation of Building Blocks

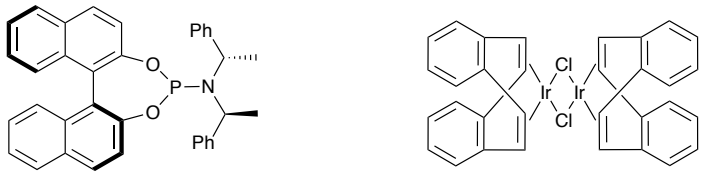
To be able to obtain the selected pyrrolidine-derived scaffolds, the synthesis of different cyclisation precursors is required. In addition, the synthesis of the cyclisation precursors requires the allylic carbonate building block **88**. The synthesis of this building block is known[116] and it was prepared in four steps (Scheme 7).



Scheme 7: Synthesis of the allylic carbonate building block **88**. [a]Lower yield compared to the other steps due to the formation of the isomer *Z* (detected by ^{1}H-NMR spectroscopy of the crude product mixture).

The synthesis started with the Boc protection of the nitrogen of the amino alcohol **119** using Boc_2O to give the carbamate **120** with a quantitative yield. Successively, Parkih−Doering oxidation[136] was applied to the carbamate **120** followed by a Wittig reaction[137] using carbethoxymethylene triphenylphosphorane to provide the α,β-unsaturated ester **121** in 62% yield. This ester was then reduced with DIBAL-H to give the allylic alcohol **122** in 96% yield. Finally, treatment of the allylic alcohol **122** with methyl chloroformate yielded the allylic carbonate building block **88** in 86% yield. The second step, which involved the Parkih−Doering reaction followed by the Wittig reaction, gave the lowest yield. The reason is that during this transformation, the undesired *Z* isomer of the ester **121** is also formed. Since the allylic carbonate **88** was necessary for the synthesis of five cyclisation precursors, it was prepared on a multi-gram scale.

In addition to this building block, the synthesis of the cyclisation precursors also needs the chiral phosphoramidite ligand **91** and the Ir-catalyst **92** (Figure 26).[116] These compounds were prepared following literature procedures.[134,138] The synthesis of the catalyst **92** is necessary because the *dbcot* ligand makes the catalyst more stable to oxygen.[134] In addition, it increases the regioselectivity of the reaction for the desired product.



(*S*,*S*,a*S*)-**91** **92**

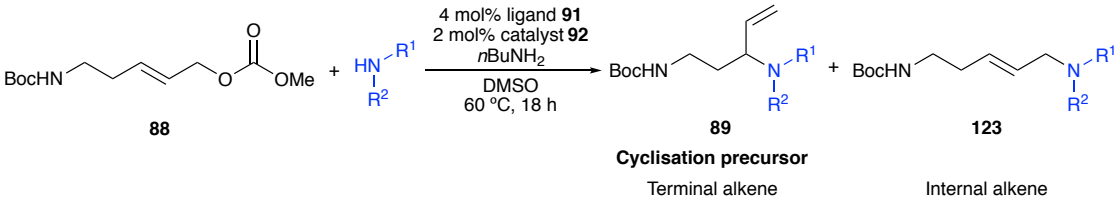
Figure 26: Structure of the ligand **91** and the Ir-catalyst **92**.

Once the allylic carbonate building block **88**, the ligand **91** and the Ir-catalyst **92** were available, the syntheses of the cyclisation precursors **89** started. The next step involved the Ir-catalysed asymmetric allylic substitution.

2.3.3.1.2. Connective Reactions

2.3.3.1.2.1. Ir-catalysed Asymmetric Allylic Substitution

The Ir-catalysed connective reactions were performed combining the allylic carbonate **88** with different amines in the presence of 2 mol% of the catalyst **92**, 4 mol% of the chiral phosphoramidite ligand **91** and *n*$BuNH_2$ in DMSO at 60 °C. The reactions were highly reproducible with the different amines, providing after 18 h the cyclisation precursors **89a**-**e** (Table 4). The different cyclisation precursors were obtained in similar yields from 58% to 63% and usually with a good ee from 83% to 86%, excluding the cyclisation precursor **89a**, which was obtained in 67% ee (see below for methods for ee determination). In addition, the diastereselectivity for the synthesis of the alkene **89e** was also high, with a crude dr 94:6. In some cases, an undesired regioisomer **123** was observed. This is due to the fact that this reaction is not completely selective for the formation of the cyclisation precursor, which has an alkene in the terminal position. This reaction can also yield small amounts of an undesirable regioisomer with the alkene in the internal position. This undesirable internal alkene **123** was obtained in higher amounts in the syntheses of the cyclisation precursors **89a**-**c** (ratios terminal alkene:internal alkene (*T*:*I*) 85:15, 83:17 and 71:29, respectively) than in the syntheses of the alkenes **89d**-**e** (ratio *T*:*I* >95:<5). For the preparation of the alkenes **89a**-**c**, a secondary amine was used as reagent. For the preparation of the alkenes **89d**-**e**, primary amines were used instead. Consequently, the use of primary amines or secondary amines could affect the regioselectivity of this reaction.



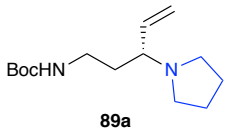
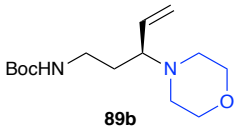
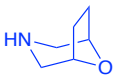
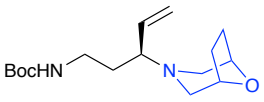
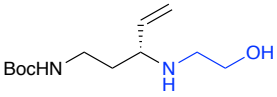
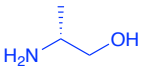
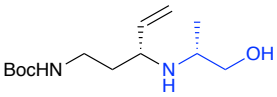
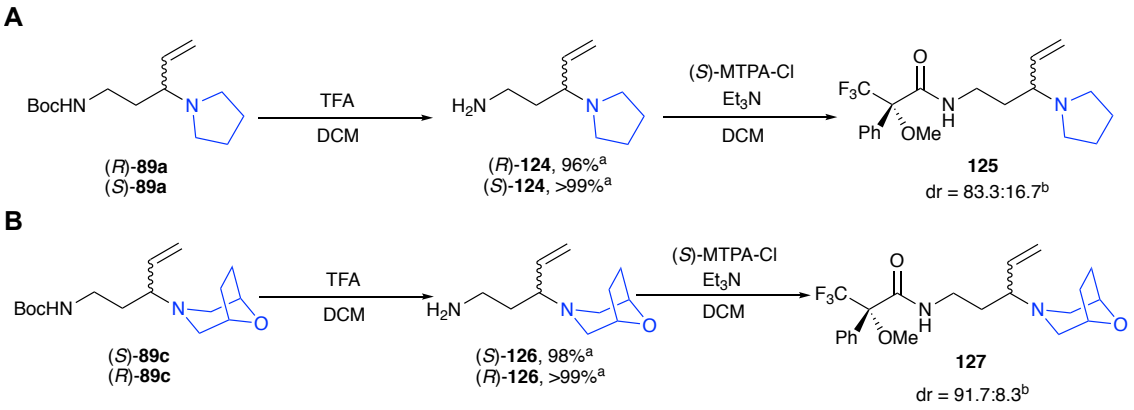
Entry	Amine	Ligand	Cyclisation precursor	*T*:*I* [a]	Yield[d]	ee
1		(*S*,*S*,a*S*)-**91**	 **89a**	85:15[b]	59%	67%[e]
2		(*R*,*R*,a*R*)-**91**	 **89b**	83:17[b]	63%	86%[f]
3		(*R*,*R*,a*R*)-**91**	 **89c**	71:29[c]	63%	83%[e]
4		(*S*,*S*,a*S*)-**91**	 **89d**	>95:<5[b]	60%	85%[g]
5		(*S*,*S*,a*S*)-**91**	 **89e**	>95:<5[b]	58%	–[h]

Table 4: Ir-catalysed connective reaction of the allylic carbonate **88** with different amines to yield diverse cyclisation precursors. The absolute stereochemistry was determined by comparison to analogues.[116] [a]Ratio between the terminal:internal alkenes. [b]Determined by ^{1}H-NMR spectroscopy (500 MHz) of the crude product mixture. [c]Determined by ^{1}H-NMR spectroscopy (300 MHz) of the crude product mixture. [d]Yield of the purified cyclisation precursor. [e]Determined by derivatisation to yield diastereomers (Scheme 8). [f]Determined by chiral HPLC. [g]Determined by derivatisation to yield benzoyl derivatives and chiral HPLC (Scheme 9). [h]This reaction gave a pair of diastereomers due to the use of an enantiopure chiral amine. The crude dr of this reaction was 94:6 and it was determined by ^{1}H-NMR spectroscopy (500 MHz) of the crude product mixture. The product **89e** was isolated with dr >95:<5, which was determined by ^{1}H-NMR spectroscopy (500 MHz) of the purified product.

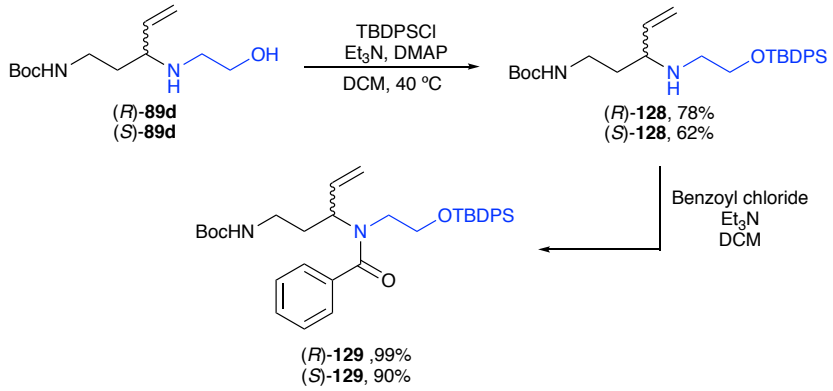
To be able to determine the ee of the Ir-catalysed reactions, the enantiomers of the cyclisation precursors **89a-d** were prepared using the opposite chiral phosphoramidite ligand **91**. Only the pair of enantiomers **89b** were successfully separated by chiral HPLC to give an ee value of 86%. Consequently, other procedures were investigated for the determination of the ee of the other pair of enantiomers. The ee of the enantiomers **89a** was determined by chiral derivatisation through two steps (Scheme 8, panel A). In the first step, each of the enantiomers of **89a** was treated with TFA to remove the Boc group. Subsequently, the resulting amine salts **124** were individually treated with Et_3N and the (*S*)-Mosher's acid chloride ((*S*)-MTPA-Cl)[139] to give **125** as a mixture of

two diastereomers. The same procedure was used to determine the ee of the enantiomers **89c** (Scheme 8, panel B). Analysis of the crude product mixture of diastereomers by ^{1}H-NMR spectroscopy (500 MHz) allowed the determination of the dr. From this result, the ee of the Ir-catalysed reaction for the cyclisation precursor **89a** and **89c** were determined, which were 67% and 83% respectively.



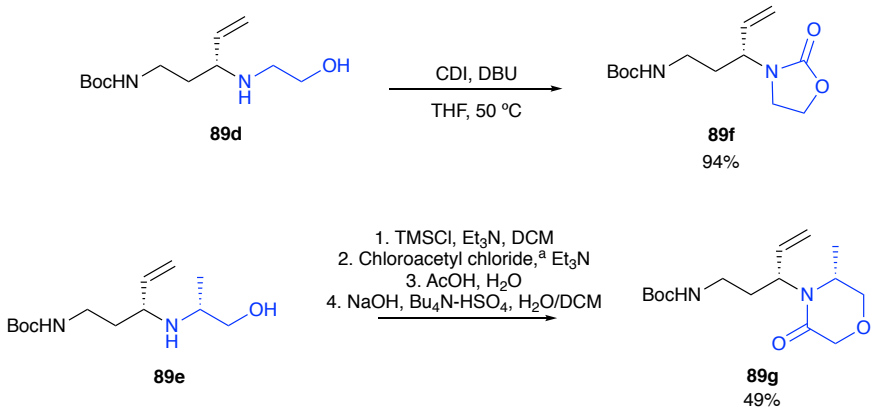
Scheme 8: Derivatisation of the pair of enantiomers **89a** (**Panel A**) and **89c** (**Panel B**) to diastereomers using the (*S*)-Mosher's acid chloride. [a]Isolated and characterised as TFA salts. [b]Determined by ^{1}H-NMR spectroscopy (500 MHz) of the crude product mixture.

The pair of enantiomers **89d** could not be separated by chiral HPLC either. However, these enantiomers were already known. Consequently, there is an established procedure to determine the ee.[116] Following this procedure, each enantiomer of **89d** was treated with TBDPSCl in the presence of Et_3N and DMAP to give the silyl derivatives **128**. Subsequently, these two enantiomers were independently treated with benzoyl chloride and Et_3N to yield the benzoyl derivatives **129**, which can be separated by chiral HPLC (Scheme 9). An ee of 85% was determined for this Ir-catalysed reaction.



Scheme 9: Synthesis of the enantiomers **129**, which can be separated by chiral HPLC.

Before moving to the Pd-catalysed cyclisation reaction, an extra transformation was required for the cyclisation precursors **89d**-**e** (Scheme 10). The alkene **89d** was reacted with CDI in the presence of DBU to provide the oxazolidinone **89f** in 94% yield. The alkene **89e** undertook four reactions in one pot. The first reaction was the protection of the hydroxyl group by TMS using trimethylsilyl chloride. Successively, the amine underwent a nucleophilic addition-elimination reaction with chloroacetyl chloride. After this reaction, the TMS protecting group was removed using acetic acid. Finally, the free hydroxyl group was treated with NaOH and Bu_4N-HSO_4 to undertake an intramolecular S_N2 reaction to afford the morpholine derivative **89g** in 49% yield. Once the alkenes **89f**-**g** were obtained, they were used in the Pd-catalysed cyclisation reaction, conjointly with the cyclisation precursors **89a**-**c**.



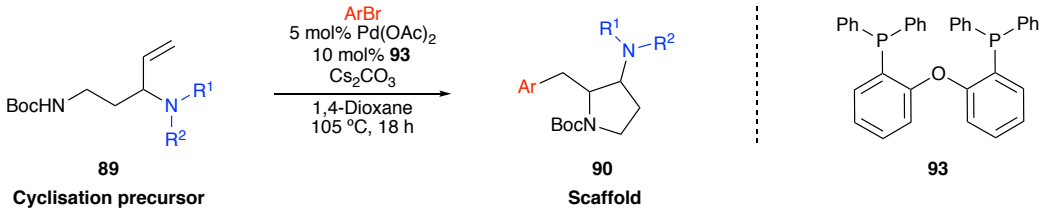
Scheme 10: Extra transformation required for the cyclisation precursors **89d**-**e** before undertaking the Pd-catalysed cyclisation reaction. [a]Bromoacetyl bromide was firstly used instead of chloroacetyl chloride, but analysis of the crude product mixture by TLC (thin layer chromatography) did not show consumption of the starting material.

2.3.3.2. Cyclisation Reactions

2.3.3.2.1. Pd-catalysed Aminoarylation

The Pd-catalysed cyclisation reactions were accomplished by combining the cyclisation precursors **89** with different het(aryl)bromide groups in the presence of 5 mol% of $Pd(OAc)_2$, 10 mol% of the ligand **93** (DPE-Phos), and the base Cs_2CO_3 in 1,4-dioxane at 105 °C (Table 5). The reactions were highly reproducible with the different substrates, providing after 18 h of reaction the pyrrolidine-derived scaffolds **90j**-**n** in yields ranging from 38% to 66% and crude dr varying from 83:17 to >95:<5. It was observed that the synthesis of the scaffolds **90j**-**l** gave higher dr (crude dr >95:<5) than the synthesis of the scaffolds **90m**-**n** (crude dr 83:17 and 89:11, respectively). Scaffolds **90j**-**l** have a

basic aliphatic amine. Scaffolds **90m-n** do not have a basic aliphatic amine. Consequently, this could affect the dr of the reaction. However, all the scaffolds were purified as single diastereomers.



89 **Cyclisation precursor** | **90** **Scaffold** | **93**

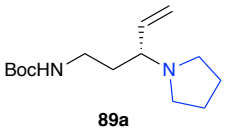
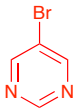
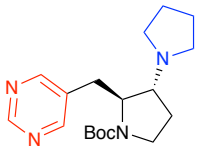
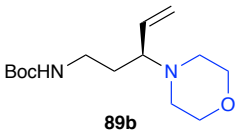
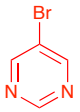
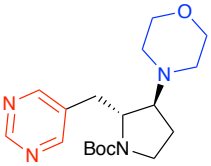
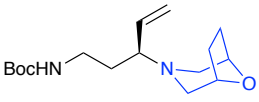
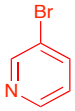
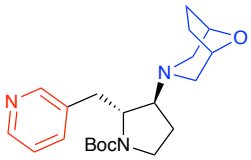
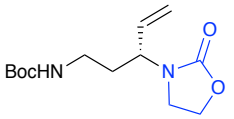
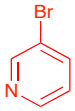
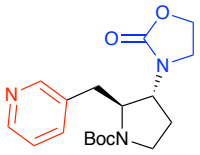
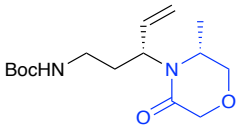
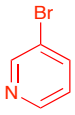
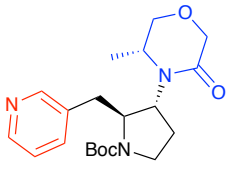
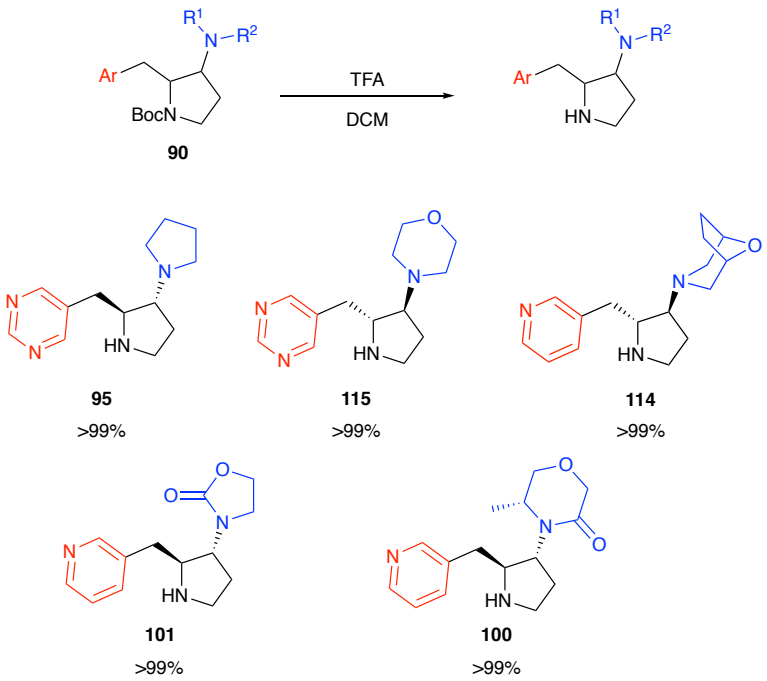
Entry	Cyclisation precursor	Het(aryl)bromide	Scaffold	Crude dr[a]	Yield and dr[b]
1	 **89a**		 **90j**	>95:<5	66% >95:<5
2	 **89b**		 **90k**	>95:<5	61% >95:<5
3	 **89c**		 **90l**	>95:<5	38% >95:<5
4	 **89f**		 **90m**	83:17	42% >95:<5
5	 **89g**		 **90n**	89:11	61% >95:<5

Table 5: Pd-catalysed cyclisation reaction of the different cyclisation precursors with different het(aryl)bromide groups to yield the diverse pyrrolidine-derived scaffolds. The absolute stereochemistry was determined by comparison to analogues.[116] [a]Determined by ^{1}H-NMR spectroscopy (500 MHz) of the crude product mixture. [b]Yield and dr (^{1}H-NMR, 500 MHz) of the purified scaffold.

Once the pyrrolidine-derived scaffolds **90j-n** were obtained, they were treated with TFA to yield the final deprotected scaffolds **95**, **115**, **114**, **101** and **100** (Scheme 11). All the Boc deprotections worked well with quantitative yields.

These scaffolds were prepared in enough amounts to allow the subsequent decorations.



Scheme 11: Boc deprotection of the pyrrolidine-derived scaffolds. All the scaffolds were isolated and characterised as TFA salts.

2.3.4. Experimental Determination of Permeability *(This section was performed by William Farnaby in collaboration with Takeda Cambridge)*

Once the five pyrrolidine-derived scaffolds **95**, **100**, **101**, **114** and **115** were prepared, they were decorated at the free amine with different medicinal chemistry capping groups. This gave a library of sixteen lead-like compounds (**130**–**145**), whose chemical structure is not shown due to a confidentiality agreement with Takeda Cambridge. The aqueous solubility of these derived compounds was assessed using a kinetic solubility assay. This demonstrated that these compounds have high solubility, ranging from 79 µg/mL to 108 µg/mL.

Once the aqueous solubility was measured, the *in vitro* permeability of these lead-like compounds was assessed. *In vitro* assays to determine BBB permeability are expensive and time consuming.[140] As a result, the *in vitro* permeability of these derived compounds for passive transport was evaluated using PAMPA (Parallel Artificial Membrane Permeability Assay).[141] PAMPA does not correlate with BBB permeability, but it was used as an inexpensive

and quick filter for BBB permeability. If a compound is not permeable in a PAMPA, it is not going to be BBB penetrant. PAMPA demonstrated that fourteen out of the sixteen derived compounds were highly permeable (P_{app} (apparent permeability coefficient) $>10^{-5}$ cm/s) (Table 6).[72] Consequently, they could also be BBB penetrant.

Lead-like compound	CNS Lead MPO score	Exp. $logD_{7.4}$	P_{app} (10^{-6} cm/s)
130	4.82	1.92	132.4
131	5.13	1.27	70.8
132	4.81	1.79	138.3
133	4.60	1.05	34.4
134	5.34	1.13	17.1
135	5.37	1.89	116.8
136	4.48	1.35	38.6
137	5.49	1.41	55.5
138	4.86	0.90	10.6
139	5.00	1.03	6.0
140	4.60	0.57	7.4
141	5.24	1.90	71.3
142	5.26	0.85	40.2
143	4.73	2.17	186.3
144	5.05	1.37	118.6
145	5.00	2.02	125.5

Table 6: CNS Lead MPO scores, experimental $logD_{7.4}$ and Papp from the PAMPA of the sixteen lead-like compounds prepared from the previous pyrrolidine-derived scaffolds.

In addition, a computational model that predicts brain penetration[66] suggested that most of these lead-like compounds (fourteen out of sixteen) would have a logBBB >0.5. As a result, if these compounds were optimised to drug-like molecules, they should be likely to cross the BBB.

2.4. Summary and Conclusions

A computational tool for the identification of novel CNS molecular scaffolds was successfully developed. Subsequently, it was validated using a library of different literature-related scaffolds, which included CNS scaffolds and non-CNS scaffolds. The validation showed that CNS scaffolds obtained higher CNS Lead MPO scores than non-CNS scaffolds. In addition, it showed that the CNS Lead MPO score could effectively identify more accurately CNS lead-like molecules than the Pfizer's CNS MPO score. Successively, the value of the computational tool was exemplified using a library of pyrrolidine-based scaffolds. A virtual library of these scaffolds was scored. Consequently, five of these virtual scaffolds were selected for synthesis because they were novel, they obtained a good mean CNS Lead MPO score and they were readily

synthetically accessible. These five scaffolds were successfully synthesised using an Ir- and Pd-catalysed reactions, which were highly reproducible with the different substrates and usually gave high yields and high ee/dr. Subsequently, these scaffolds were decorated to obtain a library of lead-like compounds. These lead-like compounds were experimentally assessed and they showed high aqueous solubility and high permeability through a lipidic artificial membrane, indicating that these compounds could also be brain penetrant. Therefore, it can be suggested that the computational tool could correctly identify scaffolds that could be useful for CNS drug discovery programs.

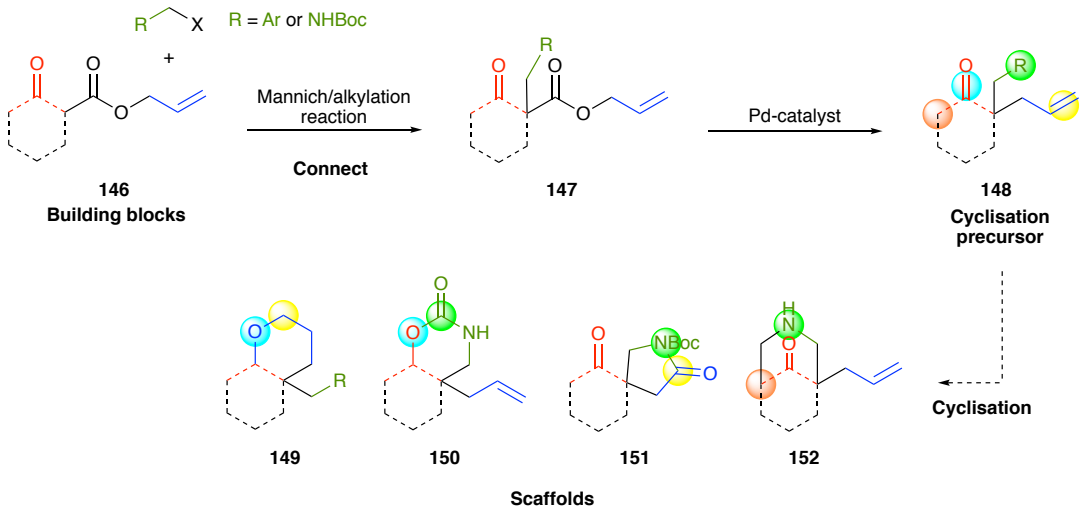
In conclusion, this computational tool could be very useful as a quick and inexpensive filter to improve the quality of lead-like molecules used in HTS libraries for CNS-targets. If a lead-like molecule from these improved screening libraries shows activity for a CNS-target, its potency could be improved to yield a CNS-drug that could cross the BBB. Consequently, less time, costs and efforts would be spent in unsuccessful lead-like compounds. This *in silico* tool could be another valuable predictor that could be added to the collection of predictors that are currently used in the early stages of CNS drug discovery. It could help to decrease the amount of experimental work and improve the clinical success in the later stages of CNS drug discovery programs, improving the current productivity.

Chapter 3: Development of a Modular Approach for the Synthesis of Scaffolds Relevant to CNS Drug Discovery

3.1. Identification of a Lead-Oriented Synthesis Approach Based on a Mannich/Alkylation and a Pd-catalysed Connective Reactions

The development of a new LOS approach is essential for the identification of novel scaffolds for CNS drug discovery. Consequently, connective reactions that yield highly functionalised cyclisation precursors were of interest. Ideally, the connective reaction should have easily accessible building blocks and provide a rapid route to cyclisation precursors. In addition, the cyclisation precursors should allow many alternative possible cyclisation reactions. They should be able to give scaffolds that can be decorated to yield compounds within the lead-like chemical space relevant to CNS drug discovery.

As a result, a new attractive connective reaction to yield cyclisation precursors was identified (Scheme 12).[142,143] This connective reaction starts with an allyl ester building block and involves a Mannich[144]/alkylation reaction followed by a palladium-catalysed decarboxylative allylic alkylation.[145] The cyclisation precursor obtained could undertake different cyclisation reactions that could yield different novel, sp^3-rich and structurally-diverse scaffolds.



Scheme 12: Mannich/alkylation reaction followed by a palladium-catalysed decarboxylative allylic alkylation as source of cyclisation precursors, which could yield novel, sp^3-rich and structurally-diverse scaffolds.

It has been previously demonstrated that this connective reaction works with building blocks containing different ring sizes and different heteroatoms (Figure 27).[142,143] Consequently, it suggests how the scope for the synthesis of the cyclisation precursors might be extended.

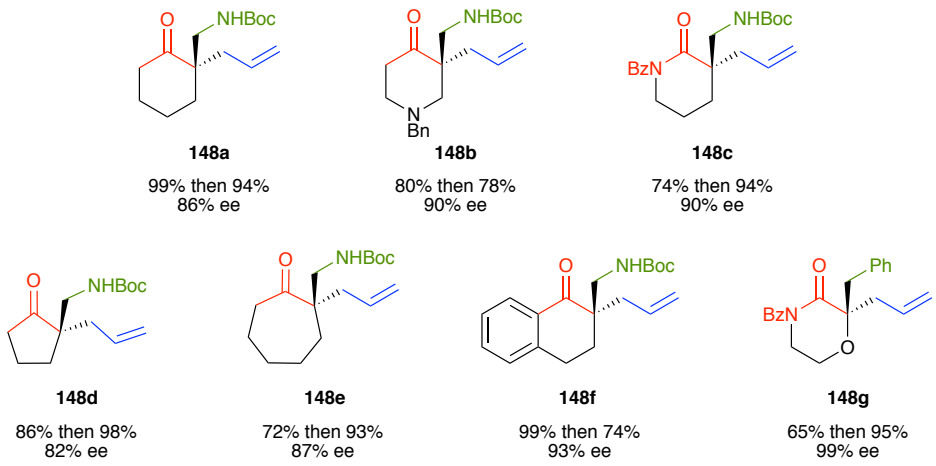


Figure 27: Precedent that suggests how the scope for the synthesis of the cyclisation precursors might be extended. First yields correspond to the Mannich reaction (Cs_2CO_3, **153**, DCM, rt) and to the alkylation reaction for the bottom-right compound (NaH, BnBr, THF, rt). Second yields and ee correspond to the palladium-catalysed asymmetric decarboxylative allylic alkylation (5 mol% $Pd_2(dba)_3$, 12.5 mol% PHOX ligand,[142] toluene, rt).

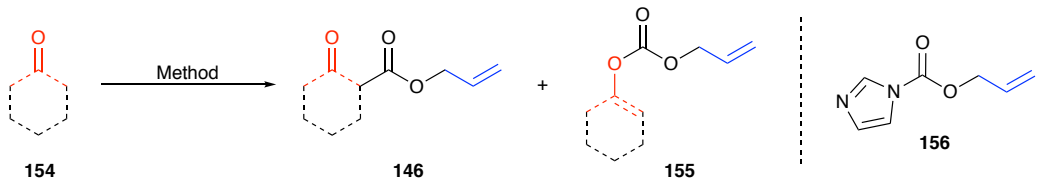
For this reason, this reaction would allow the use of different building blocks with different ring sizes and different heteroatoms. As a result, this could allow the synthesis of a wide number of different cyclisation precursors. Subsequently, these cyclisation precursors could undertake different cyclisation reactions to yield different potential novel scaffolds for CNS drug discovery.

3.2. Synthesis of Cyclisation Precursors

3.2.1. Preparation of Building Blocks

To be able to study the value of the Mannich/alkylation reaction and the Pd-catalysed decarboxylative allylic alkylation as a pathway to yield different novel, structurally-diverse and sp^3-rich scaffolds; the synthesis of different cyclisation precursors was investigated. For this reason, the synthesis of different allyl esters building blocks **146** was firstly studied. The preparation of some of these building blocks is known in the literature.[143,146] However, the procedure was not reproducible; or cyanoformate derivatives, which can give highly toxic by-products, are used in the synthesis. Consequently, an alternative preparation of the allyl esters **146** was investigated.

During the investigation, it was shown that the synthesis of this type of compound was very irreproducible when using different carbonyl derivatives **154**. The use of specific electrophiles, bases and solvents was essential. Consequently, the carbonyl-derived starting materials **154** were usually treated under different optimised conditions (Table 7). Eventually, the different allyl ester building blocks **146** were successfully obtained. Compounds **146a**-**d** were obtained in yields between 40%–47% and compound **146e** in 29% yield (Table 7, entries 1f, 2e, 3b, 4b and 5e).



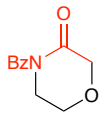
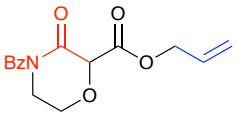
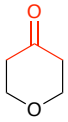
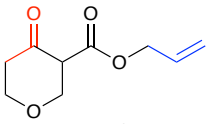
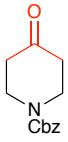
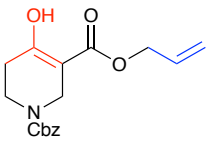
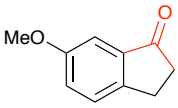
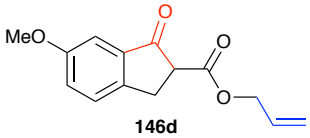
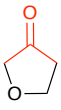
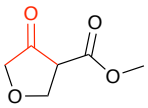
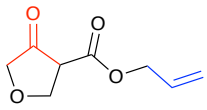
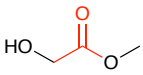
Entry		Carbonyl derivative	Method[a]	Building block	C-:O-Acylation[d]	Yield[h]
1	a	 154a	A	 146a	32:68	6%
	b		B		–[e]	
	c		C		<5:>95	–[i]
	d		D		80:20	43%
	e		E		75:25	–[i]
	f		**F**		**>95:<5**	**41%**
2	a	 154b	F	 146b[b]	>95:<5	27%
	b		G		>95:<5	5%
	c		E		>95:<5	36%
	d		H		>95:<5	8%
	e		**I**		**>95:<5**	**45%**
3	a	 154c	I	 146c[c]	>95:<5	20%
	b		**E**		**>95:<5**	**40%**
4	a	 154d	G	 146d	–[f]	
	b		**E**		**>95:<5**	**47%**
5	a	 154e	I		–[f]	
	b		E		–[f]	
	c	 154f	J	 146e	–[f]	
	d		K		–[f]	
	e	 154g	**L**		**–[g]**	**29%**

Table 7: Optimisation and synthesis of the allyl ester building blocks **146**. [a]**Method: A:** LiHMDS, allyl chloroformate, THF, –78 ºC; **B:** LiHMDS, diallyl carbonate, THF, –78 ºC; **C:** LDA, allyl chloroformate, THF:toluene, –78 ºC; **D:** LiHMDS, allyl chloroformate, toluene –78 ºC; **E:** LiHMDS, allyl chloroformate, toluene, 0 ºC to rt; **F:** LiHMDS, **156**, toluene:THF, –78 ºC; **G:** NaH, diallyl carbonate, THF, rt; **H:** LiHMDS, **156**, THF, –78 ºC; **I:** LiHMDS, **156**, toluene, –78 ºC; **J:** Allyl alcohol, Zn(0), toluene, reflux; **K:** Allyl alcohol, DMAP, molecular sieves 3 Å, toluene, reflux; **L:** NaH, Et_2O, rt, then allyl acrylate, DMSO, 0 ºC to rt. [b]Observed as a mixture of 24:76 *keto-enol* tautomers (^{1}H-NMR, $CDCl_3$, 500 MHz). [c]Only *enol* tautomer observed (^{1}H-NMR, $CDCl_3$, 400 MHz) [d]*C*-:*O*-Acylation ratio determined by ^{1}H-NMR spectroscopy (300–500 MHz) of the crude product mixture. [e]No reaction observed by TLC and ^{1}H-NMR spectroscopy of the crude product mixture. [f]Decomposition observed by TLC and ^{1}H-NMR spectroscopy of the crude product mixture. [g]Not applicable. [h]Yield of the purified building block. [i]Yield not determined.

The preparation of the lactam-derived allyl ester **146a** gave some problems because *O*-acylation was also possible when using allyl chloroformate.

Consequently, the use of the soft electrophile **156** was necessary (Table 7, entry 1).[147] The synthesis of the ketone-derived allyl esters **146b**-**d** needed non-polar solvents to proceed[148,149] and *O*-acylation was never observed (Table 7, entries 2–4). The preferred base for all of these previous reactions was always LiHMDS. The use of alternative bases such as LDA or NaH,[150] or the use of different electrophiles such as diallyl carbonate resulted in a decreased yield (Table 7, entries 1b–c, 2b and 4a). Finally, the synthesis of the tetrahydrofuran-derived allyl ester **146e** was not successful using the optimised conditions used for the synthesis of the other allyl esters (Table 7, entries 5a–b). Consequently, a completely different pathway using the carbonyl derivative **154g** and allyl acrylate as electrophile was used. This reaction involved a Michael addition and a subsequent intramolecular Dieckmann condensation.[151] The use of other strategies such as the transesterification reaction did not work (Table 7, entries 5c–d).[152–154]

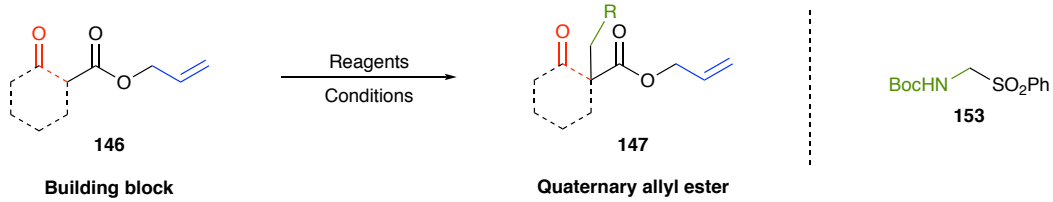
3.2.2. Connective Reactions

3.2.2.1. Mannich/Alkylation Reaction

Once the allyl ester building blocks **146** were obtained, they were taken into the next step, which involves the Mannich/alkylation connective reaction to form the quaternary centre. To perform the Mannich reactions, the allyl esters **146** were dissolved in DCM and treated with Cs_2CO_3 and the carbamate **153** at rt.[155] Consequently, the corresponding quaternary allyl esters **147a**-**e** were obtained in yields ranging from 83% to >99% (Table 8, entries 1–4 and 5c). The reaction time for compounds **146a**-**d** was of 18 h. However, the reaction time for the tetrahydrofuran derivative **146e** was only of 3 h. The reason is that after 18 h, the desired product **147e** was not observed. Instead, the product decomposed through a retro-Dieckmann reaction followed by a retro-Michael reaction[156] to give the α,β-unsaturated ester **157** (Table 8, entry 5a and Scheme 13). Furthermore, the Mannich reaction did not work at 0 ºC (Table 8, entry 5b).

After completing the Mannich reactions, the allyl ester building block **146c** was also used as substrate for the alkylation reactions. Therefore, it was dissolved in acetone and combined with K_2CO_3 and two different aryl bromides.[157] After 2 h at 70 ºC, these alkylations yielded the quaternary allyl esters **147f**-**g** in 89% and 49% yield, respectively (Table 8, entries 6–7). The yield of **147f** was similar to

the yield of the previous Mannich rections. However, the yield of **147g** was much lower. This lower yield could be related with the nucleophilicity and higher polarity of 3-(bromomethyl)pyridine.



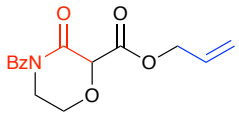
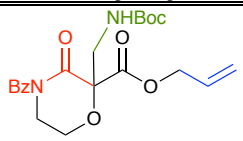
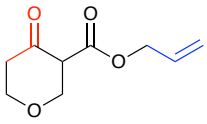
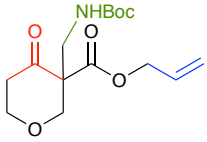
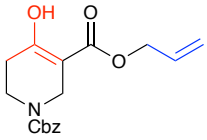
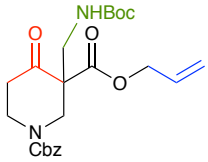
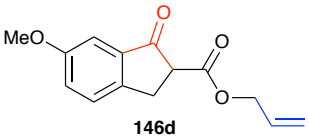
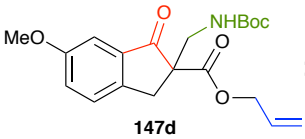
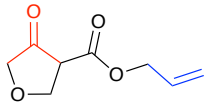
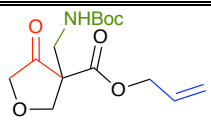
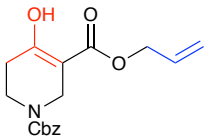
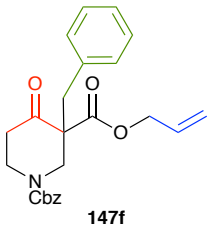
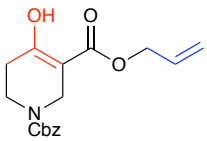
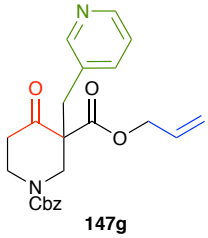
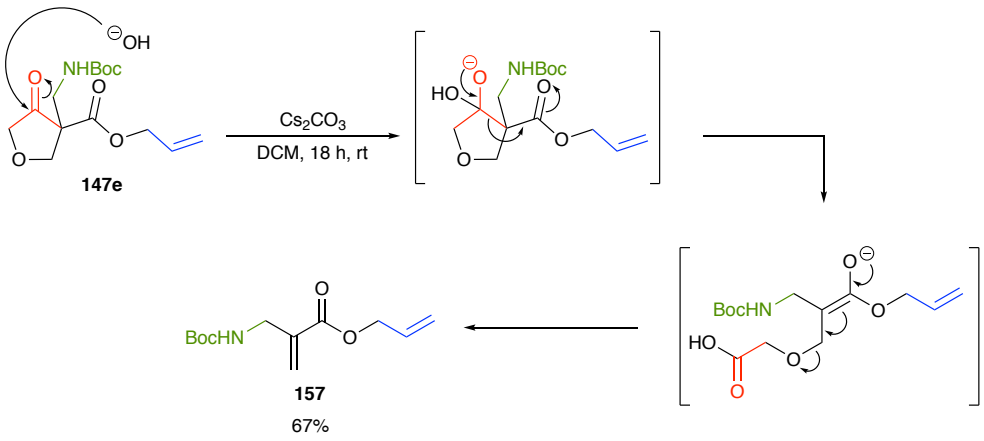
Entry	Building block	Reagents & Conditions	Quaternary allyl ester	Yield[a]
1	 146a	**153, Cs_2CO_3, DCM, 18 h, rt**	 147a	**83%**
2	 146b	**153, Cs_2CO_3, DCM, 18 h, rt**	 147b	**85%**
3	 146c	**153, Cs_2CO_3, DCM, 18 h, rt**	 147c	**84%**
4	 146d	**153, Cs_2CO_3, DCM, 18 h, rt**	 147d	**>99%**
a	 146e	**153**, Cs_2CO_3, DCM, 18 h, rt	 147e	–[b]
5 b		**153**, Cs_2CO_3, DCM, 3 h, 0 °C		–[c]
c		**153, Cs_2CO_3, DCM, 3 h, rt**		**87%**
6	 146c	**Benzyl bromide, K_2CO_3, acetone, 2 h, 70 °C**	 147f	**89%**
7	 146c	**3-(Bromomethyl)pyridine hydrobromide, K_2CO_3, acetone, 2 h, 70 °C**	 147g	**49%**

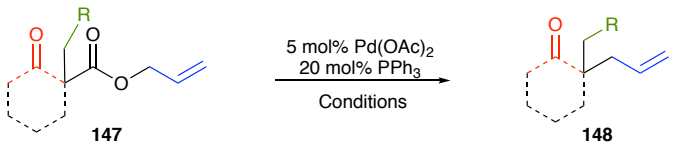
Table 8: Mannich/alkylation reactions of the different allyl ester building blocks **146** to form the quaternary allyl esters **147**. [a]Yield of the purified quaternary allyl ester. [b]No product observed by ^{1}H-NMR spectroscopy (400 MHz) of the crude product mixture due to the formation of compound **157** (Scheme 13). [c]No reaction observed by TLC of the crude product mixture.



Scheme 13: Proposed mechanism for the decomposition of the quaternary allyl ester **147e** to give the α,β-unsaturated ester **157**. This decomposition was observed in the Mannich reaction of **146e** after 18 h of reaction at rt (Table 8, entry 5a). The hydroxide nucleophile that starts this reaction could come from residual water in the Cs_2CO_3.

3.2.2.2. Pd-catalysed Decarboxylative Allylic Alkylation

With the quaternary allyl esters **147** in hand, the Pd-catalysed decarboxylative allylic alkylation was the last step to the cyclisation precursors. To be able to perform this reaction with high enantioselectivity, a chiral PHOX ligand is required.[142,143] However, this ligand is very expensive because it comes from an unnatural aminoacid. For this reason, it was decided to prepare the cyclisation precursors as racemates using PPh_3 as ligand. Therefore, the different quaternary allyl esters **147** were treated with 5 mol% $Pd(OAc)_2$ and 20 mol% PPh_3 in THF at 70 °C for 1h.[145] The reaction was highly reproducible with the different substrates and the corresponding cyclisation precursors **148** were obtained in yields ranging from 76% to 89% (Table 9, entries 1b and 2–7).



Quaternary allyl ester — Cyclisation precursor

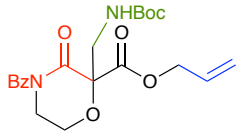
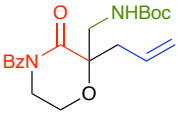
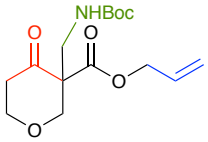
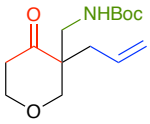
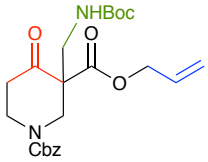
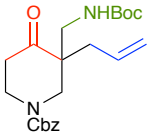
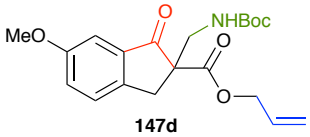
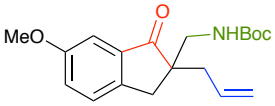
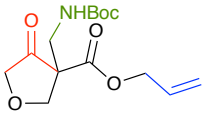
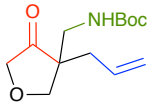
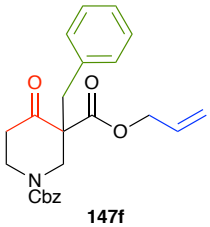
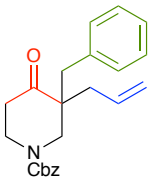
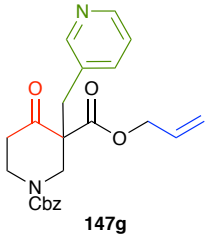
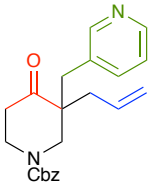
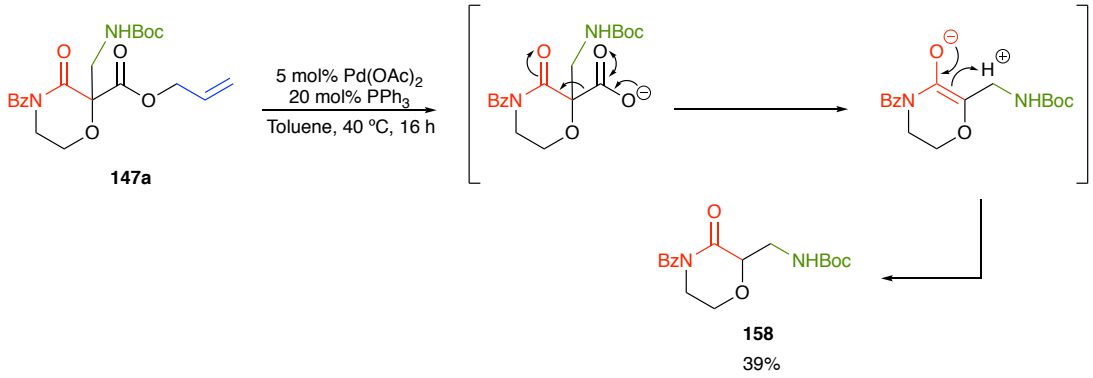
Entry	Quaternary allyl ester	Conditions	Cyclisation precursor	Yield[a]
1a	 **147a**	Toluene, 40 °C, 16 h	 **148h**	28%[b]
1b		**THF, 70 °C, 1 h**		**80%**
2	 **147b**	**THF, 70 °C, 1 h**	 **148i**	**76%**
3	 **147c**	**THF, 70 °C, 1 h**	 **148j**	**87%**
4	 **147d**	**THF, 70 °C, 1 h**	 **148k**	**81%**
5	 **147e**	**THF, 70 °C, 1 h**	 **148l**	**88%**
6	 **147f**	**THF, 70 °C, 1 h**	 **148m**	**89%**
7	 **147g**	**THF, 70 °C, 1 h**	 **148n**	**80%**

Table 9: Pd-catalysed decarboxylative allylic alkylation of the quaternary allyl esters **147** to yield the corresponding cyclisation precursors **148**. [a]Yield of the purified cyclisation precursor. [b]Lower yield due to the formation of product **158** (Scheme 14).

The polarity of the solvent and the temperature were important in this reaction. Consequently, the reaction of the quaternary allyl ester **147a** in toluene at 40°C[142] gave the cyclisation precursor **148h** in a lower yield because an undesired major product **158** was obtained (Table 9, entry 1a and Scheme 14).



Scheme 14: Proposed mechanism for the formation of the undesired compound **158** obtained from the quaternary allyl ester **147a** using the Pd-catalysed decarboxylative allylic alkylation in toluene at 40 °C (Table 9, Entry 1a).

3.2.3. Summary and Conclusions

The synthesis of the cyclisation precursors **148h-n** was successfully accomplished after three steps. The most challenging step for the synthesis was the preparation of the allyl ester building blocks, which was very irreproducible when using different substrates and it gave lower yields. Consequently, different optimisations were required. However, the connective Mannich/alkylation step and the Pd-catalysed reaction were highly reproducible with all the substrates and high yields were obtained. For this reason, few optimisations were required. In addition, the Pd-catalysed reaction could be performed using a chiral PHOX ligand instead of PPh_3, which would allow the synthesis of enantioenriched cyclisation precursors.[142,143]

3.3. Investigation of the Scope of the Cyclisation Reactions and Synthesis of Scaffolds

Once the synthesis of the cyclisation precursors was completed, the investigation of the scope of the cyclisation reactions started. The different cyclisation precursors previously prepared could undertake a different number of cyclisation reactions (Figure 28). The lactam-derived cyclisation precursor **148h** could undertake cyclisation reactions between the NHBoc and the terminal alkene. The ketone-derived cyclisation precursors **148i-j** and **148l** could undertake cyclisation reactions between the terminal alkene, the NHBoc, the ketone and the α-position of the ketone. The ketone-derivative **148k** could undertake cyclisation reactions between the terminal alkene, the NHBoc and the ketone. Finally, the ketone-derived cyclisation precursors **148m-n** could undertake cyclisation reactions between the ketone and the alkene.

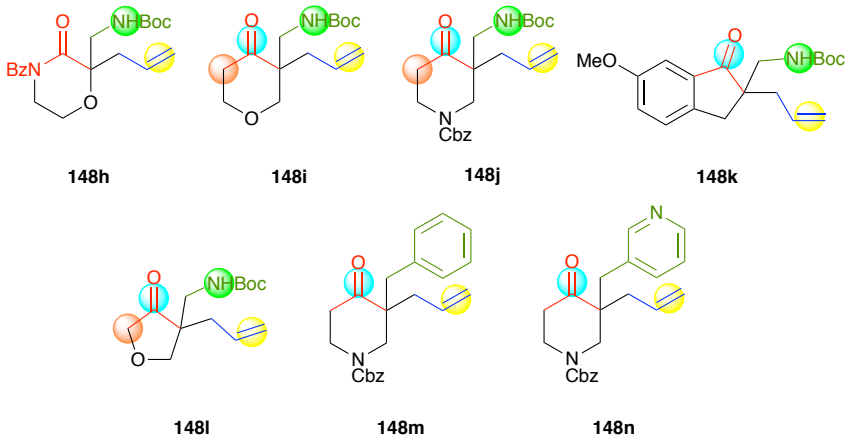


Figure 28: Functional groups present in the cyclisation precursors that could allow different cyclisation reactions.

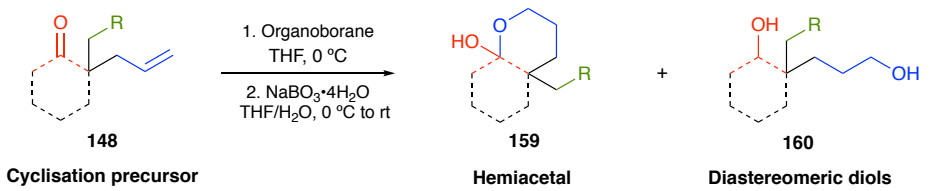
These cyclisation precursors have closely related structures. Consequently, depending on the functional groups, each cyclisation precursor could undertake the same cyclisations under the same or similar reaction conditions. For this reason, it was decided to use the cyclisation precursor **148i** to investigate and optimise the scope of the cyclisation reactions. Subsequently, the successful optimised cyclisations with **148i** are going to be performed with the other cyclisation precursors.

3.3.1. Cyclisation Reactions Between the Ketone and the Alkene

It was decided to use the cyclisation precursor **148i** to investigate and optimise the scope of the cyclisation reactions. Compound **148i** could undertake cyclisation reactions between the terminal alkene, the NHBoc, the ketone and the α-position of the ketone. The first cyclisation reactions to be investigated were reactions involving the ketone and the terminal alkene.

The first transformation studied was the hydroboration of the alkene to give a terminal alcohol. As a result, the terminal alcohol could react with the ketone to give a hemiacetal. Consequently, the cyclisation precursors **148i-n** were treated with disiamylborane in THF followed by $NaBO_3$ and H_2O.[158] The reaction was highly reproducible with the different substrates, giving the corresponding products **159** in yields from 58% to 83% (Table 10, entries 1d and 2–6). All the hemiacetals were obtained as single diastereomers. However, the relative configuration could not be determined. It was observed that the organoborane used in this reaction was crucial to get high yields of the desired hemiacetal. If

other organoborane reagents like 9-BBN, dicyclohexylborane or borane were used, the yield of the desired product was lower due to the fact that the cyclic ketone was reduced to the alcohol, giving a mixture of diastereoromeric diols **160** (Table 10, entries 1a–c).[159] This mixture of diols **160** was never observed when using disiamylborane.



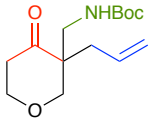
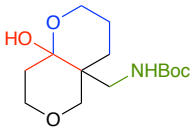
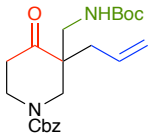
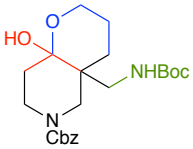
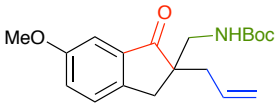
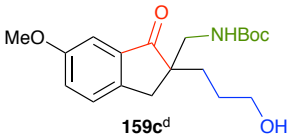
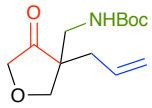
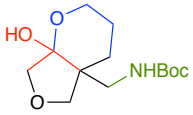
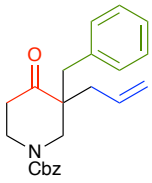
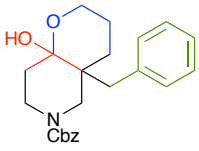
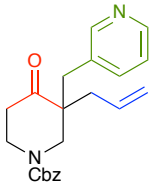
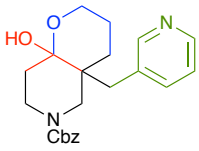
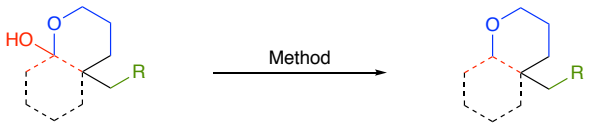
Entry	Cyclisation precursor	Organoborane	Hemiacetal[a]	Yield[g]
1 a	 148i	9-BBN	 159a[b]	35%[h]
1 b		BH_3		–[i]
1 c		Dicyclohexylborane		–[j]
1 d		**Disiamylborane**		**76%**
2	 148j	**Disiamylborane**	 159b[c]	**58%**
3	 148k	**Disiamylborane**	 159c[d]	**61%**
4	 148l	**Disiamylborane**	 159d[e]	**73%**
5	 148m	**Disiamylborane**	 159e[f]	**83%**
6	 148n	**Disiamylborane**	 159f[f]	**70%**

Table 10: Optimisation and utilisation of the hydroboration reaction for the synthesis of the hemiacetals **159**. [a]The relative configuration of the hemiacetals could not be determined by NOESY (500 MHz). [b]Observed as a single diastereomer (CD_3OD, ^{1}H-NMR, 400 MHz). [c]Observed as a single diastereomer (CD_3OD, ^{1}H-NMR, 500 MHz). [d]Observed as the primary alcohol ($CDCl_3$, ^{1}H-NMR, 400 MHz; $CDCl_3$, ^{13}C-NMR, 100 MHz). [e]Observed as a 67:33 mixture of a hemicetal as a single diastereomer and primary alcohol ($CDCl_3$, ^{1}H-NMR, 400 MHz; $CDCl_3$, ^{13}C-NMR, 100 MHz). [f]Observed >90% as a single hemiacetal (CD_3OD, ^{1}H-NMR, 500 MHz; CD_3OD, ^{13}C-NMR, 125 MHz). [g]Yields of the purified hemiacetals. [h]Lower yield due to the partial reduction of the cyclic ketone to give the diols **160**, observed by LC-MS, TLC and ^{1}H-NMR spectroscopy (400 MHz) of the crude product mixture. [i]Desired hemiacetal not observed by LC-MS and TLC of the crude product mixture due to completely reduction of the cyclic ketone to the diols **160**. [j]Decomposition observed by TLC and ^{1}H-NMR spectroscopy of the crude product mixture.

After optimising the hydroboration reaction and obtaining the different hemiacetals **159**, the next step was their reduction to form the first scaffolds. In

this reduction, it was observed that the selection of the acid depended on the structure of the starting material. Consequently, the corresponding hemiacetals **159** were dissolved in DCM, combined with Et_3SiH and treated with different acids. It was shown that some of the products were very polar due to removal of the Boc group. Consequently, the Boc group was reintroduced. After reprotection (when required), these reactions gave the desired scaffolds **149** in yields ranging from 43% to 99% (Table 11, entries 1e, 2–3, 4c and 5–6). In addition, the diastereoselectivity of all of these reactions was always very high, obtaining the scaffolds with crude dr ≥91:≤9. The six-membered ring hemiacetals **159a**-**b** and **159e**-**f** were treated with TFA. However, the use of TFA did not work with the five-membered ring hemiacetal **159d** (Table 11, entries 4a–b). This could be due to the fact that the rigidity of the five-membered ring does not allow the formation of the intermediate oxocarbenium ion. Consequently, **159c**-**d** were treated with the stronger Lewis-acid BF_3 instead of TFA.[160,161] The use of BF_3 in the six-membered rings gave lower yields due to decomposition (Table 11, entry 1a). Milder acids as $FeCl_3$,[162,163] AcOH or other reducing agents like $NaBH(OAc)_3$ only showed traces or no formation of product (Table 11, entries 1b–d).



159
Hemiacetal

149
Scaffold

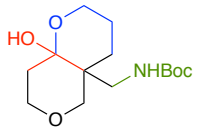
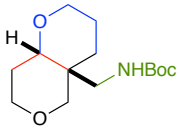
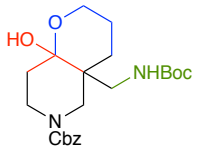
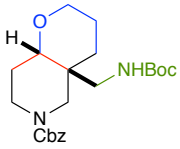
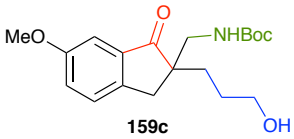
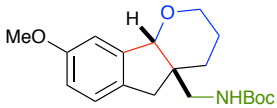
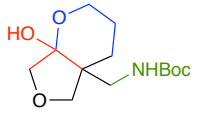
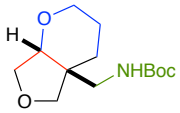
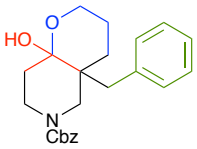
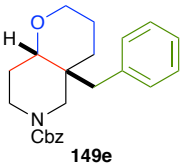
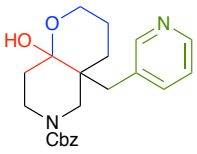
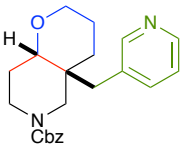
Entry		Hemiacetal	Method[a]	Scaffold	Crude dr	Yield and dr
1	a	 **159a**	A	 **149a**	>95:<5[b]	31%[h], >95:<5[i]
	b		B			–[c]
	c		C			–[d]
	d		D			–[e]
	e		**E**		**>95:<5[b]**	**99%, >95:<5[j]**
2		 **159b**	**E**	 **149b**	**>95:<5[f]**	**51%, >95:<5[j]**
3		 **159c**	**F**	 **149c**	**>95:<5[g]**	**65%, >95:<5[j]**
4	a	 **159d**	E	 **149d**		–[d]
	b		G			–[c]
	c		**F**		**>95:<5[g]**	**43%, >95:<5[j]**
5		 **159e**	**H**	 **149e**	**93:7[f]**	**63%, >95:<5[j]**
6		 **159f**	**H**	 **149f**	**91:9[f]**	**88%, 91:9[j]**

Table 11: Optimisation and utilisation of the hemiacetal reduction to obtain different tetrahydropyran-derived scaffolds. [a]**Method: A:** Et_3SiH, BF_3•Et_2O, DCM, –78 °C to rt; **B:** Et_3SiH, $FeCl_3$, CH_3NO_2, rt; **C:** Et_3SiH, AcOH, rt; **D:** $NaBH(OAc)_3$, AcOH, rt; **E:** Et_3SiH, TFA, DCM, rt, then Boc_2O, Et_3N, DCM, rt; **F:** Et_3SiH, BF_3•Et_2O, DCM, –78 °C to rt, then Boc_2O, Et_3N, DCM, rt; **G:** Et_3SiH, TFA, DCM, 40 °C, then Boc_2O, Et_3N, DCM, rt; **H:** Et_3SiH, TFA, DCM, rt. [b]Determined by ^{1}H-NMR spectroscopy (400 MHz) of the crude product mixture. [c]Decomposition detected by TLC of the crude product mixture. [d]No reaction detected by TLC of the crude product mixture. [e]Traces of product detected by LC-MS of the crude product mixture. [f]Determined by ^{1}H-NMR spectroscopy (500 MHz) of the crude product mixture. [g]Determined by ^{1}H-NMR spectroscopy (300 MHz) of the crude product mixture. [h]Lower yield due to Boc removal and subsequent decomposition observed by TLC, LC-MS and ^{1}H-NMR spectroscopy of the crude product mixture. [i]Yield and dr (^{1}H-NMR, 400 MHz) of purified scaffold. [j]Yield and dr (^{1}H-NMR, 500 MHz) of purified scaffold.

Once these scaffolds **149** were obtained in good yields, it was decided to determine their relative configurations. ^{1}H-NMR spectroscopy (400–500 MHz)

showed that all the protons in the tertiary carbon had a singlet or small doublet of *J* ≤4.0 Hz. Consequently, there should not be a vicinal proton in a *trans* position with respect to these protons because a much larger value of *J* would be expected. Therefore, these scaffolds should have a *cis* ring fusion. This was supported by NOESY (500 MHz), where different nOe enhancements were observed between the proton of the tertiary carbon, the protons next to the tertiary carbon and the protons in the adjacent chain (Figure 29, Panel A). If the scaffolds had a *trans* ring fusion, nOe enhancements between the proton of the tertiary carbon and the adjacent chain would not be observed. In addition, the *cis* ring fusion would be expected because when the intermediate six-membered ring oxocarbenium ion is formed, only the observed product or a twisted boat, which is not stable, can be formed (Figure 29, Panel B).

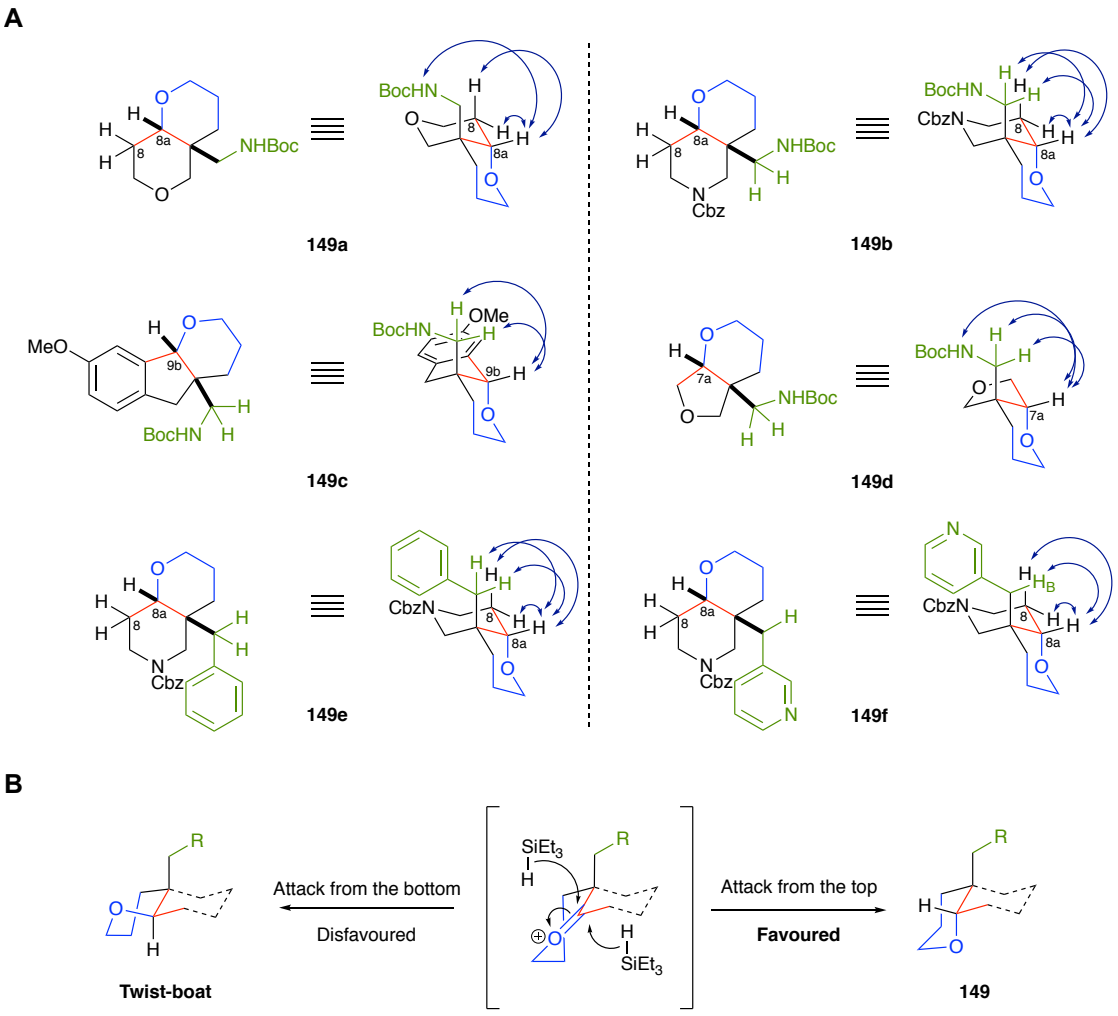


Figure 29: Determination of the relative configuration of the scaffolds **149**. **Panel A:** Key nOe enhancements of the NOESY (500 MHz). **Panel B:** Proposed rationale for the formation of the observed stereochemistry.

The scaffold **149a** was the only one that crystallised. For this reason, it was analysed by X-ray crystallography. The X-ray structure also confirmed that scaffold **149a** adopts a *cis* ring fusion (Figure 30).

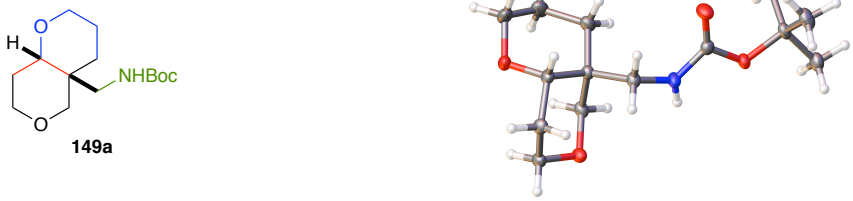
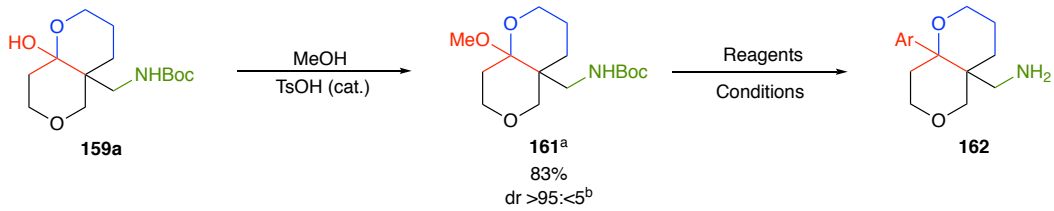


Figure 30: X-ray structure of the scaffold **149a** confirming the *cis* ring fusion.

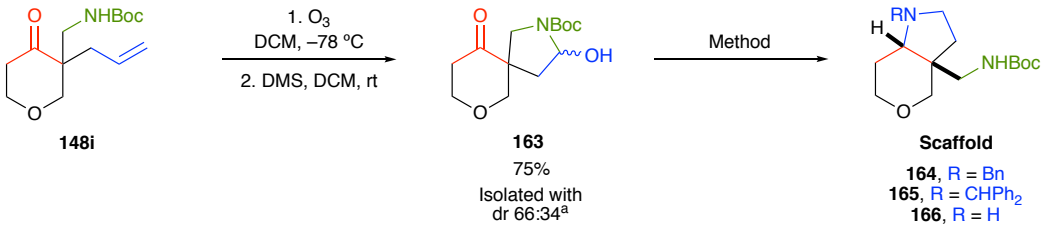
Before moving to the next cyclisation reaction, it was decided to investigate if the intermediate oxocarbenium ion (formed from the hemiacetals in the presence of an acid) could also be arylated. However, before doing this transformation, the hemiacetal needed to be converted to an acetal. This transformation was required to avoid the deprotonation of the hemiacetal by the reagents used in the arylation reaction. As a result, after treating the hemiacetal **159a** with catalytic amounts of TsOH in MeOH, compound **161** was purified in 83% yield and dr >95:<5 (Table 12). Successively, the acetal **161** was combined with electron rich aromatic groups like anisole,[164] with Grignard reagents like PhMgBr[165] and with organocopper reagents made *in situ* from CuBr and PhMgBr.[166] However, the arylation reaction was not successful (Table 12). For this reason, the arylation of the hemiacetals was not continued.



Entry	Reagents & conditions	Ar	Yield 162
1	BF_3•Et_2O, anisole	4-methoxyphenyl	–[d]
2	BF_3•Et_2O, DCM, –20 °C, then PhMgBr, DCM, –20 °C	Ph	–[d]
3	Me_2S•CuBr and PhMgBr, then Et_2O•BF_3, THF[c]	Ph	–[e]

Table 12: Transformation of the hemiacetal **159a** into the acetal **161** and attempts for its arylation. [a]The relative configuration of **161** could not be resolved by NOESY. [b]Determined by ^{1}H-NMR spectroscopy (400 MHz) of the purified product. [c]The procedure followed uses Et_2O as solvent. However, **161** was not soluble in Et_2O and for this reason the solvent was changed to THF. [d]No reaction observed by LC-MS of the crude product mixture. [e]Degradation observed by ^{1}H-NMR spectroscopy of the crude product mixture.

Due to the attempted arylation of the acetal **161** failing, a second cyclisation reaction between the ketone and the alkene was investigated. In this second transformation, the alkene of the cyclisation precursor **148** would be converted into an aldehyde to be able to perform a double reductive amination between the ketone and the resulting aldehyde. For this reason, compound **148i** was treated with O_3 gas followed by a reductive work-up with DMS. Consequently, compound **163** was obtained as a mixture of two hemiaminals in 75% yield (Table 13). The hemiaminal mixture **163** should interconvert with its aldehyde form. Consequently, a double reductive amination, involving the aldehyde and the ketone, could be possible starting from the hemiaminal mixture **163** and a primary amine. For this reason, the hemiaminal mixture **163** was treated with benzylamine in DCM followed by $NaBH(OAc)_3$ and AcOH at rt. After purification, the corresponding amine **164** was isolated in 30% yield and dr 83:17 (Table 13, Entry 1). It was observed that this transformation was very particular. Changes in the temperature, solvent,[167,168] reducing agent [169] or amine[170–173] always gave lower yields and lower dr (Table 13, entries 2–8). Consequently, the reaction could not be improved. For this reason, it was decided not to try this cyclisation with the other cyclisation precursors.



148i

163
75%
Isolated with
dr 66:34[a]

Scaffold
164, R = Bn
165, R = $CHPh_2$
166, R = H

Entry	Method[b]	Time	Yield scaffold[c]	dr[f]
1	**A**	**18 h**	**30% of 164**	**83:17**
2	B	18 h	16% of **164**	66:33
3	C	72 h	19% of **164**	53:47
4	D	72 h	Traces of product **164**[d]	
5	E	18 h	Only imine formation[d]	
6	F	24 h	Traces of product **165**[d]	
7	G	18 h	–[e]	
8	H	24 h	–[e]	

Table 13: Ozonolysis of the alkene **148i** to give the hemiaminals **163** and optimisation of the following double reductive amination. [a]Determined by ^{1}H-NMR spectroscopy (400 MHz) of the purified hemiaminals. [b]**Method: A:** $BnNH_2$, AcOH, $NaBH(OAc)_3$, DCM, rt; **B:** $BnNH_2$, AcOH, $NaBH(OAc)_3$, DCM, 0 °C to rt; **C:** $BnNH_2$, AcOH, $NaBH(OAc)_3$, THF, rt; **D:** $BnNH_2$, $NaCNBH_3$, THF, rt; **E:** $BnNH_2$, AcOH, $NaCNBH_3$, MeOH, –78 °C to rt; **F:** Ph_2CHNH_2, $NaBH(OAc)_3$, AcOH, DCM, rt; **G:** Ph_2CHNH_2, $NaCNBH_3$, AcOH, MeOH, –78 °C to rt; **H:** NH_4OAc, $NaBH_3CN$, AcOH, EtOH, rt. [c]Yield of purified scaffold. [d]Detected by LC-MS of the crude product mixture. [e]Degredation detected by TLC of the crude product mixture. [f]Determined by ^{1}H-NMR spectroscopy (400 MHz) of the purified product.

The relative configuration of the major diastereomer of the amine-derived scaffold **164** was determined by ^{1}H-NMR spectroscopy and NOESY. ^{1}H-NMR spectroscopy (400 MHz) showed that proton 7a-H appears as an apparent singlet, suggesting that there is not a vicinal proton in *trans* respect 7a-H. NOESY (500 MHz) showed four nOe enhancements. Two between the protons of the methylcarbamate chain and the proton 7a-H, and two between the protons 7-H_2 and 7a-H (Figure 31). For this reason, compound **164** should adopt a *cis* ring fusion. If **164** had a *trans* ring fusion, the nOe signals between 7a-H and the methylcarbamate chain woud not be observed and nOe signals between 7a-H and the axial proton from the carbon at position six would be expected.

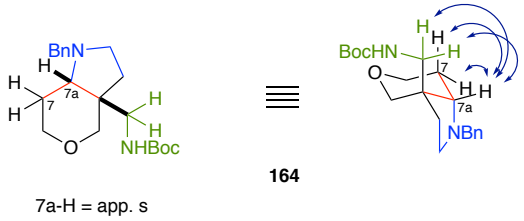
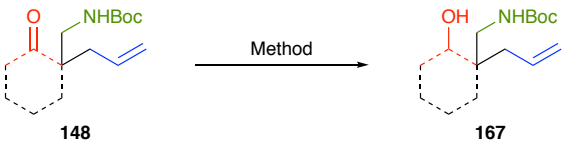


Figure 31: Multiplicity (^{1}H-NMR, 400 MHz) and key nOe enhancements (NOESY, 500 MHz) to resolve the relative configuration of the major diastereomer of the amine **164**.

Due to the low success of the double reductive amination, more intramolecular reactions starting with the alkene and the ketone were investigated. The ketone could be reduced to a secondary alcohol. For this reason, the cyclisation precursors **148i-l** were treated with DIBAL-H for 1 h.[142] This gave the corresponding secondary alcohols **167** from 63% to 93% yield and with high diastereoselectivities (crude dr ≥86:≤14) (Table 14, entries 1a, 2c and 3–4). For most of the reductions, 2.20 eq of DIBAL-H was used. However, only 1.10 eq was used for the reduction of **148j**. The reason is that DIBAL-H can cleave the Cbz group (Table 14, entry 2a). It was seen that DIBAL-H was essential to obtain these high dr. The use of other reducing agents always gave lower diastereoselectivity (Table 14, entries 1c-d and 2b). Therefore, it was suggested that DIBAL-H gave the best dr because it could coordinate to the NHBoc group.



148 Cyclisation precursor — 167 Alcohol

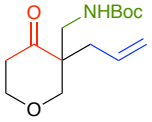
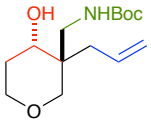
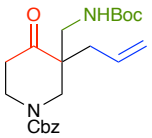
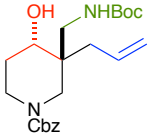
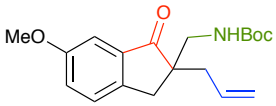
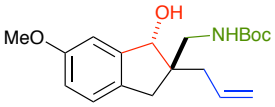
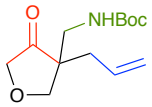
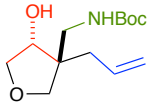
Entry		Cyclisation precursor	Method[a]	Alcohol	Crude dr	Yield and dr
1	a	 148i	**A**	 167a	**86:14**[b]	**93%, 86:14**[e]
	b		B		86:14[b]	–[f]
	c		C		28:72[b]	–[f]
	d		D		56:44[b]	–[f]
2	a	 148j	A	 167b		–[c]
	b		C		45:55[d]	–[f]
	c		**E**		**>95:<5**[d]	**78%, >95:<5**[g]
3		 148k	**A**	 167c	**90:10**[b]	**63%, >95:<5**[e]
4		 148l	**A**	 167d	**>95:<5**[b]	**92%, >95:<5**[g]

Table 14: Optimisation and utilisation of the diastereoselective ketone reduction. [a]**Method: A**: DIBAL-H 2.20 eq, DCM, –78 °C; **B:** DIBAL-H 2.20 eq, DCM, –100 °C; **C:** *L*-Selectride 2.20 eq, THF, –78 °C; **D:** $NaBH_4$ 2.00 eq, MeOH, 0 °C; **E:** DIBAL-H 1.10 eq, DCM, –100 °C. [b]Determined by ^{1}H-NMR spectroscopy (400 MHz) of the crude product mixture. [c]Cbz cleavage observed by TLC and ^{1}H-NMR spectroscopy (500 MHz) of the crude product mixture. [d]Determined by ^{1}H-NMR spectroscopy (500 MHz) of the crude product mixture. [e]Yield and dr (^{1}H-NMR, 400 MHz) of the purified alcohol. [f]Not purified. [g]Yield and dr (^{1}H-NMR, 500 MHz) of the purified alcohol.

The relative configuration of the alcohols **167a**-**b** was determined by analogy with the carbocyclic analogue,[142] by ^{1}H-NMR spectroscopy (400 MHz–500 MHz) and NOESY (500 MHz). A high *J* value of 11.1 Hz and 9.7 Hz was observed for the proton 4-H in **167a**-**b**, respectively. Consequently, proton 4-H must have a vicinal proton in a *trans* position. Different nOe interactions were observed between the proton 4-H and the protons in the methylcarbamate chain (Figure 32, Panel A). Consequently, the alcohol has a *trans* position compared with the methylcarbamate chain. If the relative configuration was *cis*, the nOe signal between 4-H and the methylcarbamate chain would not be detected or a smaller *J* value would be observed for 4-H because it would not have a vicinal proton in *trans*. In addition, DIBAL-H could coordinate to the NHBoc group. Therefore, it would deliver the hydride from the same face of the NHBoc chain, providing the expected stereochemistry (Figure 32, Panel B). The relative configuration of the five-membered ring alcohols **167c**-**d** could not be

determined by NOESY and it was determined later using compounds **150c-d** (Figure 34).

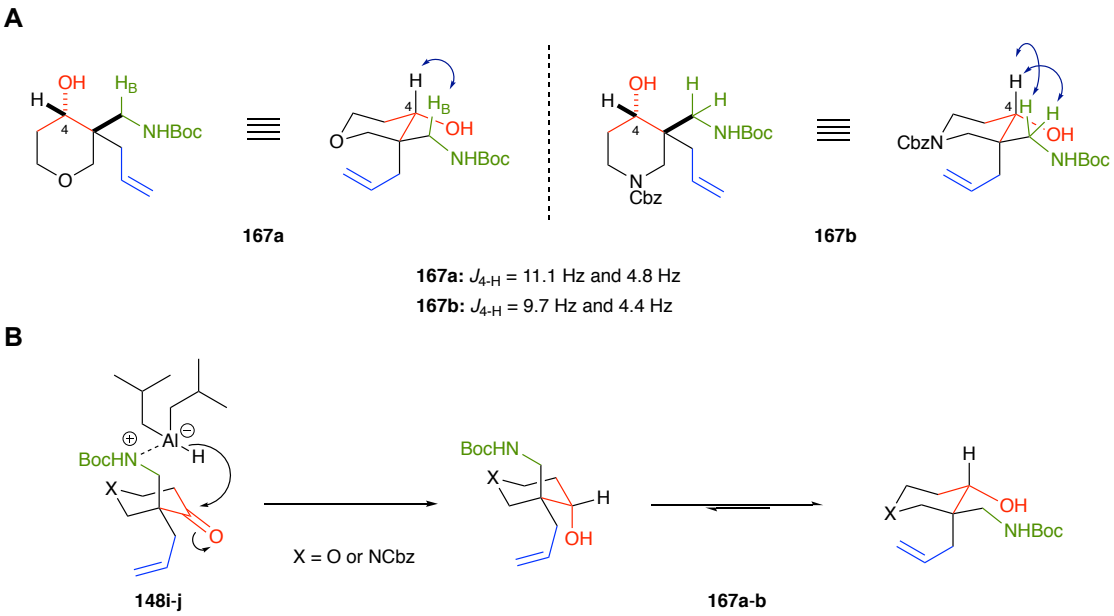
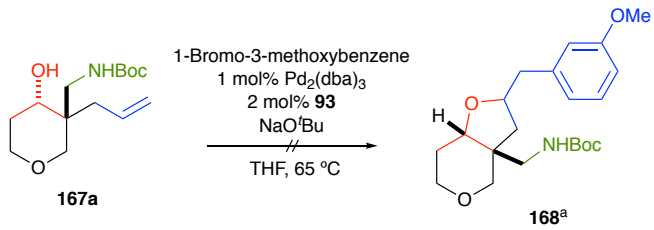


Figure 32: Determination of the relative stereochemistry of compounds **167a-b. Panel A:** Key nOe enhancements of the NOESY (500 MHz) and key *J* couplings (^{1}H-NMR (400–500 MHz)). **Panel B:** Proposed rationale for the formation of the observed stereochemistry.

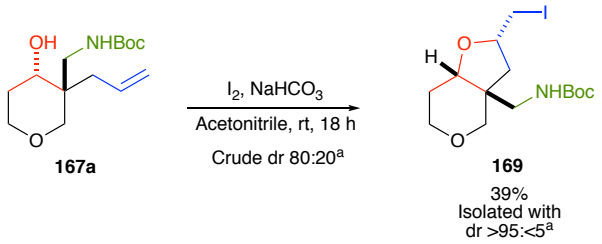
Once the secondary alcohols were obtained, they were used for cyclisation reactions with the alkene. It has been stated that alcohols can be involved in intramolecular carboetherification reactions with alkenes.[174] Consequently, it was decided to use compound **167a** with the preferred conditions for this transformation to take place (Scheme 15). However, the reaction was not successful. This result could be due to the fact that the NHBoc could also react under these conditions.



Scheme 15: Attempted carboetherification reaction of the alcohol **167a**. [a]A complicated mixture was observed by TLC of the crude product mixture.

Finally, it was decided to try an iodocyclisation reaction[119] as another method to cyclise between the alcohol and the alkene. Therefore, the alcohol **167a** was dissolved in acetonitrile and combined with I_2 and $NaHCO_3$. The reaction was

moderately diastereoselective and after purification, the scaffold **169** was obtained as a single diastereomer in 39% yield (Scheme 16).



Scheme 16: Iodocyclisation reaction of the alcohol **167a** to give the tetrahydrofuran-derived scaffold **169**. [a]Determined by ^{1}H-NMR spectroscopy (500 MHz).

Since compound **169** was isolated as a single diastereomer, the relative stereochemistry was investigated. ^{1}H-NMR spectroscopy (500 MHz) showed a *J* value of 3.8 Hz for the proton 7a-H. Consequently, it should not have a vicinal proton in a *trans* position. NOESY (500 MHz) showed that compound **169** has two nOe signals between the proton 2-H from the tetrahydrofuran ring and the two protons from the methylcarbamate chain, and another nOe signal between 2-H and 7a-H. Consequently, the new chiral centre formed in compound **169** should adopt the same relative configuration than the other two chiral centres (Figure 33). If the relative configuration of the new chiral centre was the opposite, the previous nOe interactions could not be observed and nOe interactions would be observed between 2-H and 7-H_2.

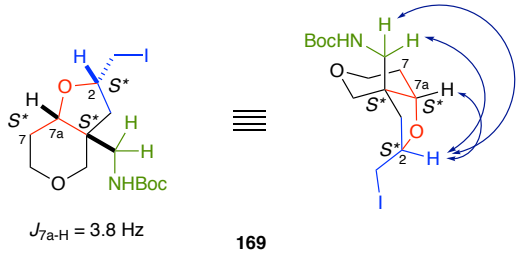


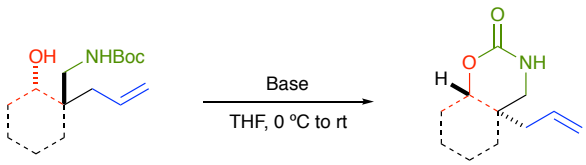
Figure 33: Key nOe enhancements observed by NOESY (500 MHz) for the resolution of the relative stereochemistry of compound **169**.

In conclusion, three successful cyclisation reactions were performed starting from the ketone and the alkene functionalities. One cyclisation reaction involved the formation of a hemiacetal. The other cyclisation reaction involved the formation of a hemiaminal. The last one involved an alcohol intermediate. The hemiacetal, the hemiaminal and the alcohol intermediates allowed the formation of *cis* fused-ring systems through an etherification reaction, a double reductive

amination and an iodocyclisation reaction, respectively. The cyclisation reaction involving the hemiacetals gave the best results. Consequently, it was successfully performed with the other cyclisation precursors.

3.3.2. Cyclisation Reactions Between the Ketone and the NHBoc

After investigating cyclisation reactions between the ketone and the alkene, cyclisation reactions between the ketone and the NHBoc were studied. The cyclisation precursors were previously reduced to the corresponding secondary alcohols in high yields and high dr. Consequently, these alcohols were used for the following cyclisation reactions. Treatment of the alcohols **167** with KO^{t}Bu gave the derived carbamates **150** in yields from 58% to 96% (Table 15, entries 1b and 2–4). It was observed that the reaction time was different depending on the structure of the alcohol. Six-membered ring alcohols gave the corresponding carbamates in only 1 h. However, five-membered ring alcohols needed more than 1 h to give the corresponding carbamates. The reaction with the five-membered ring substrate could be slower because of the rigidity of the five-membered ring. In addition, during the optimisation it was shown that the use of other bases like NaH decreased the reaction time and the yield (Table 15, entry 1a). Two explanations for this result could be that the potassium alkoxide intermediate has a harder character than the sodium alkoxide, and that KO^{t}Bu only deprotonates the alcohol, where NaH also deprotonates the NHBoc.



167
Alcohol

150
Scaffold

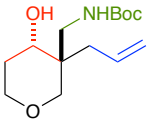
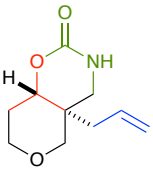
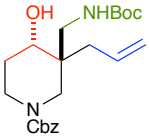
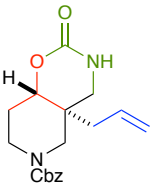
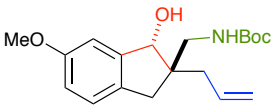
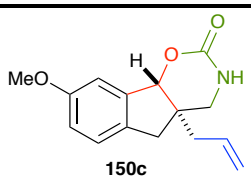
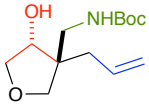
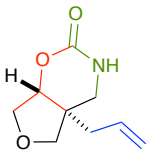
Entry	Alcohol	Base	Reaction time	Scaffold	Yield[a]
1 a	 **167a**	NaH	18 h	 **150a**	22%
1 b		**KO^{t}Bu**	**1 h**		**96%**
2	 **167b**	**KO^{t}Bu**	**1 h**	 **150b**	**63%**
3	 **167c**	**KO^{t}Bu**	**18 h**	 **150c**	**58%**
4	 **167d**	**KO^{t}Bu**	**18 h**	 **150d**	**65%**

Table 15: Optimisation and utilisation of an intramolecular carbamate formation for the synthesis of carbamate-derived scaffolds. [a]Yield of purified scaffold.

The carbamates **150c**-**d** were obtained as crystalline solids and they were analysed by X-ray crystallography to be able to corroborate the relative stereochemistry of the preceding alcohols **167c**-**d**. The X-ray structures of **150c**-**d** demonstrated that they have a *trans* fused-ring system (Figure 34). Consequently, the relative stereochemistry of the five-membered ring secondary alcohols **167c**-**d** is the same than the six-membered ring secondary alcohols **167a**-**b**.

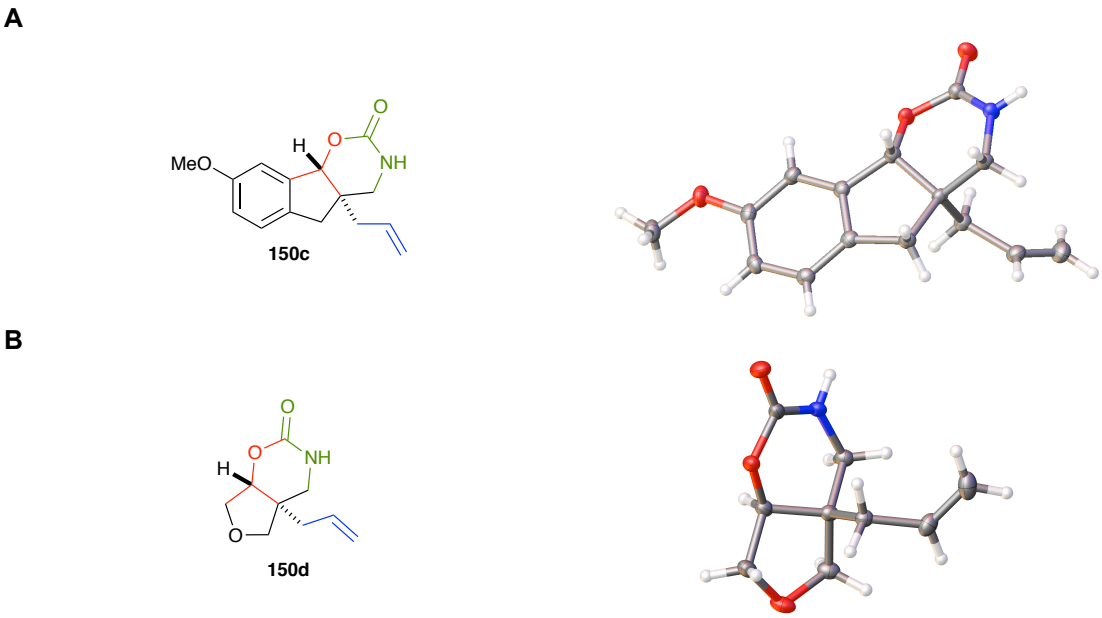


Figure 34: Determination of the relative stereochemistry of the carbamates **150c**-**d**. **Panel A:** X-ray crystal structure of the carbamate-derived scaffold **150c** confirming the *trans* relative configuration. **Panel B:** X-ray crystal structure of the carbamate-derived scaffold **150d** confirming the *trans* relative configuration

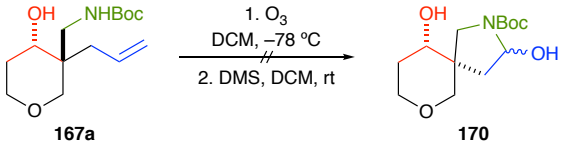
In conclusion, only one cyclisation reaction was achieved starting from the ketone and the NHBoc of the cyclisation precursors. This reaction involved an intermediate alcohol. However, the reaction worked very well. Therefore it was used with the different cyclisation precursors to obtain different *trans* fused-ring systems.

3.3.3. Cyclisation Reactions Between the Alkene and the NHBoc

Cyclisation reactions between the alkene and the NHBoc were the next ones to be investigated. The secondary alcohols **167** can be obtained in a good dr. For this reason, they were used as starting points for cyclisation reactions between the NHBoc and the alkene. As a result, it would allow access to diverse spirocyclic compounds. The use of compounds **148** was avoided because the reduction of their ketone in the subsequent spirocyclic products could give a poor dr.

Therefore, the alcohol **167a** was used as substrate in the ozonolysis reaction. Consequently, it was treated with O_3 gas followed by DMS to give the intermediate aldehyde, which should give hemiaminals as a mixture of diastereomers. However, this reaction gave a complicated mixture of

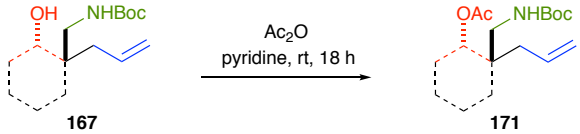
compounds (Scheme 17). One explanation could be that the free alcohol of the aldehyde intermediate also reacts with the aldehyde to form hemiacetals.



167a **170**

Scheme 17: Ozonolysis of the alcohol **167a**. As both the alcohol and the NHBoc could react with the aldehyde of the resulting product, a complicated mixture of compounds was observed by ^{1}H-NMR spectroscopy of the crude product mixture.

Consequently, it was decided to protect the secondary alcohols to avoid side-reactions. Consequently, the secondary alcohols **167** were treated with Ac_2O and pyridine[142] (Table 16). The reaction worked very well and the corresponding esters **171** were obtained in ≥95% yield.



167 **171**

Alcohol **Ester**

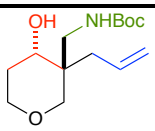
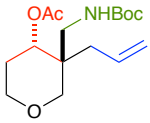
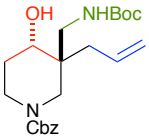
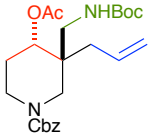
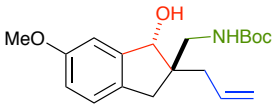
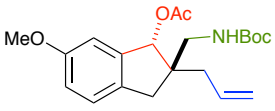
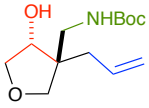
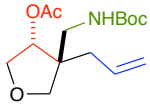
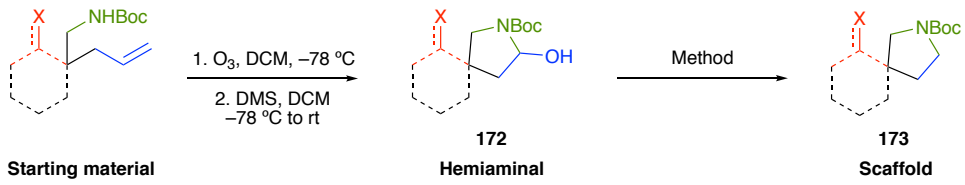
Entry	Alcohol	Ester	Yield[a]
1	 **167a**	 **171a**	**95%**
2	 **167b**	 **171b**	**95%**
3	 **167c**	 **171c**	**99%**
4	 **167d**	 **171d**	**95%**

Table 16: Protection of the secondary alcohols with an acetyl group to form esters. [a]Yield of purified ester.

Once the esters **171** were obtained, they were used as substrates, conjointly with the cyclisation precursor **148h**, in the ozonolysis reaction. Consequently, they were treated with O_3 gas followed by the reductive work-up with DMS. This

yielded a mixture of diastereomeric hemiaminals. Successively, the hemiaminals were dissolved in AcOH and reduced with $NaBH(OAc)_3$.[175] The reaction was very reproducible with all the substrates and it gave the corresponding pyrrolidine-derived scaffolds **173** in yields ranging from 49% to 76% (Table 17, entries 1b and 2–5). It was important to use a mild acid to form the cyclic *N*-acyliminium ion intermediate. Removal of the Boc group was observed if TFA was used as acid, making the deprotected product too polar and difficult to handle (Table 17, entry 1a). In addition, the use of TFA also produced decomposition of the resulting imine.



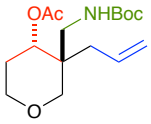
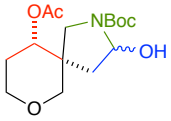
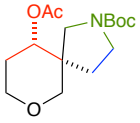
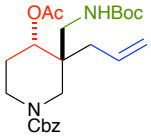
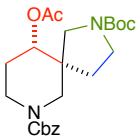
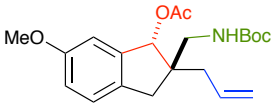
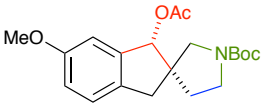
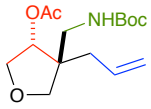
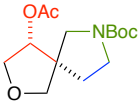
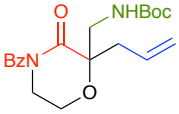
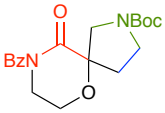
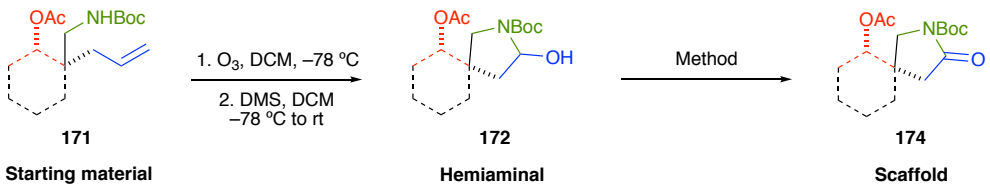
Entry	Starting material	Hemiaminal	Yield & dr[a]	Method[c]	Scaffold	Yield
1a	 171a	 172a	74%, 58:42	A	 173a	–[d]
1b				B		58%[e]
2	 171b	–[b]		B	 173b	61%[f]
3	 171c	–[b]		B	 173c	51%[f]
4	 171d	–[b]		B	 173d	76%[f]
5	 148h	–[b]		B	 173e	49%[f]

Table 17: Optmisation and utilisation of the hemiaminal reduction to yield different pyrrolidine-derived scaffolds. [a]Yield and dr (^{1}H-NMR, 500 MHz) of the purified hemiaminal. [b]Hemiaminal not isolated. [c]**Method: A:** TFA, DCM, rt, then $NaBH(OAc)_3$, DCM, rt; **B:** $NaBH(OAc)_3$, AcOH, rt. [d]Removal of the Boc group and subsequent decomposition observed by TLC, LC-MS and ^{1}H-NMR spectroscopy of the crude product mixture. [e]Yield of the purified scaffold after the two steps, the yield of the second step was 79%. [f]Yield of the purified scaffold after the two steps.

In addition to the reduction of the hemiaminals **172**, their oxidations were also investigated to obtain lactam-derived scaffolds. Consequently, the preceding

hemiaminals **172** were dissolved in DCM and treated with PDC at rt.[176] This reaction was also highly reproducible with the different substrates and it gave the desired lactam-derived scaffolds **174** from 37% to 76% yield (Table 18, entries 1c and 2–4). Nevertheless, these reactions with PDC were very slow and all needed one week to be completed. It was observed that this oxidation was very particular. The use of other oxidative conditions like the Parikh–Doering oxidation[136] and the use of TPAP/NMO[177] only gave traces of product after one week (Table 18, entries 1a–b).



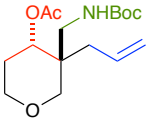
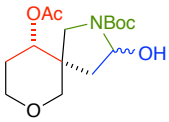
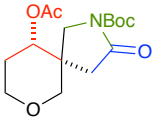
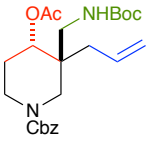
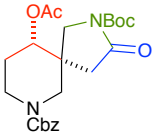
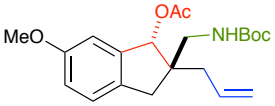
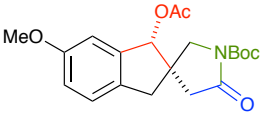
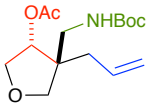
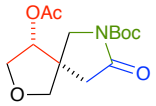
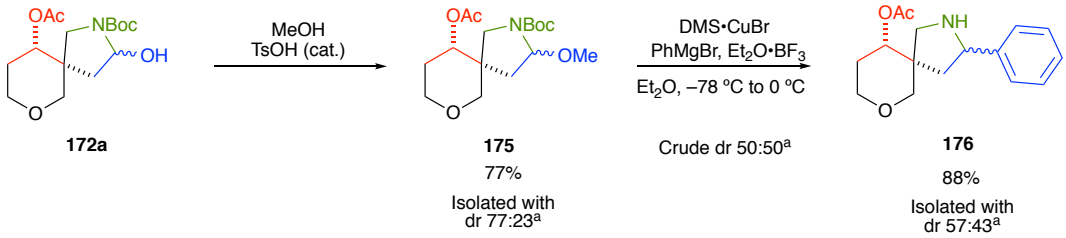
Entry	Starting material	Hemiaminal	Method[b]	Scaffold	Yield
1 a			A		–[c]
1 b			B		–[c]
1 c	171a	172a	C	174a	48%[d]
2		–[a]	C		60%[e]
	171b			174b	
3		–[a]	C		37%[e]
	171c			174c	
4		–[a]	C		76%[e]
	171d			174d	

Table 18: Optimisation and utilization of the hemiaminal oxidation to form different lactam-derived scaffolds. [a]Hemiaminal not isolated. [b]**Method: A:** SO_3•Pyr, DMSO, Et_3N, DCM, 0 °C to rt, 1 week; **B:** TPAP, NMO, molecular sieves 4 Å, DCM, rt, 1 week; **C:** PDC, celite, DCM, rt, 1 week. [c]Traces of product detected by LC-MS of the crude product mixture. [d]Yield of the purified scaffold after the two steps, the yield of the second step was 65%. [e]Yield of the purified scaffold after the two steps.

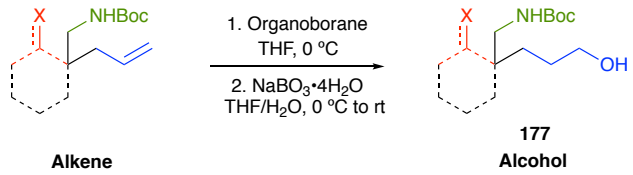
Once the previous spirocyclic compounds were obtained, it was invesitgated if the *N*-acyliminium ion, formed from the hemiaminals under acidic conditions, could be arylated to obtain spirocycles with aromatic rings. As a result, it was decided to treat the hemiaminals **172a** with MeOH and catalytic amounts of TsOH to achieve the aminals **175** in 77% yield and dr 77:23 (Scheme 18). Once the aminals **175** were obtained, their arylation using an organocopper reagent

(previously unsuccessful with the acetal **161**) was attempted.[166] Consequently, the aminals **175** were treated with DMS•CuBr, PhMgBr and BF_3 in Et_2O. This time the reaction worked, and the phenyl-derived scaffold **176** was isolated in 88% yield with dr 57:43 (Scheme 18). The yield was high, but there was poor diastereoselectivity (crude dr 50:50). For this reason it was decided not to repeat this reaction with the other substrates.



Scheme 18: Synthesis and arylation of the aminals **175** to form the scaffold **176**. [a]Determined by ^{1}H-NMR spectroscopy (500 MHz).

After completing the synthesis of the previous spirocycles, another pathway for the synthesis of more spirocyclic compounds was investigated. Disiamylborane previously showed good results for the hydroboration of terminal alkenes in the synthesis of the previous hemiacetal derivatives (Table 10). For this reason, the alkenes **171** and **148h** were also treated with disiamylborane followed by $NaBO_3$•$4H_2O$. This reaction gave the terminal alcohols **177** in yields ranging from 41% to 86% (Table 19, entries 1b, 2–4 and 5a). The lower yield for the alcohol **177d** was due to the fact that its acetyl group was partially removed. This undesired reaction was not observed with the other substrates when using disamylborane. However, the change of disiamylborane for 9-BBN completely hydrolysed the acetyl group of the product, or did not give the desired product when the substrate used contained a lactam (Table 19, entries 1a and 5b).



Alkene **177** **Alcohol**

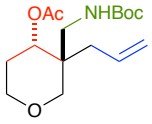
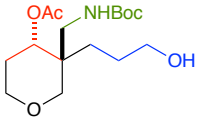
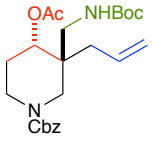
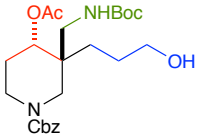
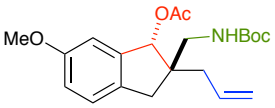
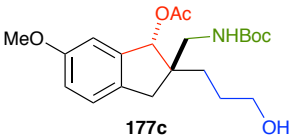
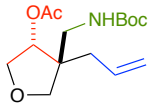
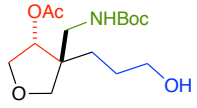
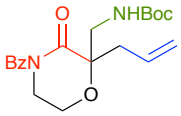
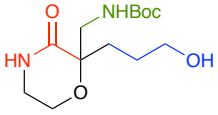
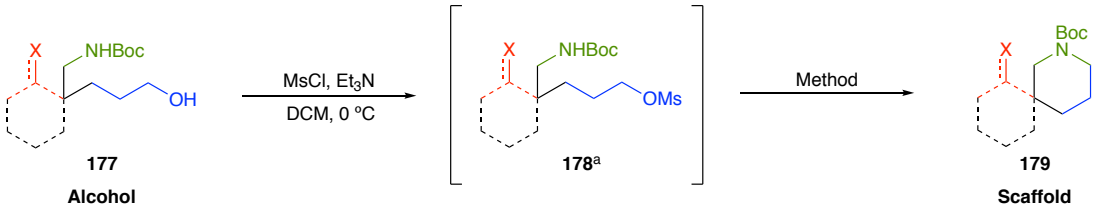
Entry		Alkene	Organoborane	Alcohol	Yield[a]
1	a	 **171a**	9-BBN	 **177a**	–[b]
	b		**Disiamylborane**		**73%**
2		 **171b**	**Disiamylborane**	 **177b**	**86%**
3		 **171c**	**Disiamylborane**	 **177c**	**83%**
4		 **171d**	**Disiamylborane**	 **177d**	**41%**[c]
5	a	 **148h**	**Disiamylborane**	 **177e**	**71%**
	b		9-BBN		–[d]

Table 19: Hydroboration reaction to yield terminal alcohols. [a]Yield of the purified alcohol. [b]Desired product not observed by ^{1}H-NMR spectroscopy and LC-MS of the crude product mixture due to the fact that the acetyl group was completely removed. [c]A lower yield was obtained for this reaction due to the fact that it was observed by ^{1}H-NMR spectroscopy and LC-MS of the crude product mixture that the acetyl group was partially removed. [d]No hydroboration reaction observed by TLC and ^{1}H-NMR spectroscopy of the crude product mixture, only the cleavage of the benzoyl group by $NaBO_3$•$4H_2O$ was observed.

Once the alcohol derivatives **177** were obtained, their cyclisations were attempted to be able to form piperidine-derived scaffold. Consequently, the different primary alcohols were dissolved in DCM and treated with MsCl and Et_3N to successfully form all the mesylated intermediates **178**. Successively, they were treated with TFA to remove the Boc group. Once the Boc group was removed the resulting free amines should displace the mesylated alcohol to form the new piperidine ring.[178] Due to the fact that a basic amine could be difficult to handle, the Boc group was always reintroduced once the cyclisation was completed. After reprotection, this cyclisation reaction gave different yields depending of the structure of the staring material. The reaction worked well for the six-membered rings **177a**-**b** and **177e**, giving the desired piperidine-derived

scaffolds in yields ranging from 40% to 57% (Table 20, entries 1b, 2 and 5). However, this reaction gave a lower yield of 13% and no product for the five-membered rings **177c-d**, respectively (Table 20, entries 3 and 4a–b). Consequently, the yield of this reaction could be affected by the rigidity of the ring in the starting material. In addition, other cyclisation conditions involving the use of NaH[142] were not successful either with six- or five-membered rings (Table 20, entries 1a and 4c).



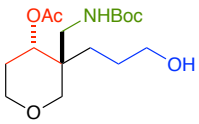
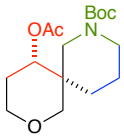
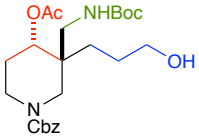
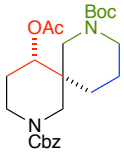
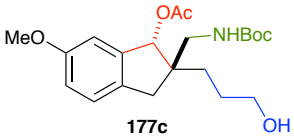
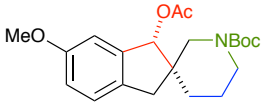
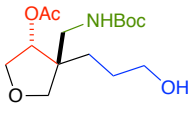
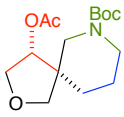
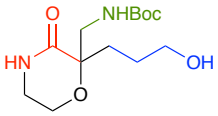
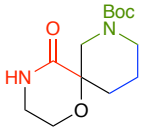
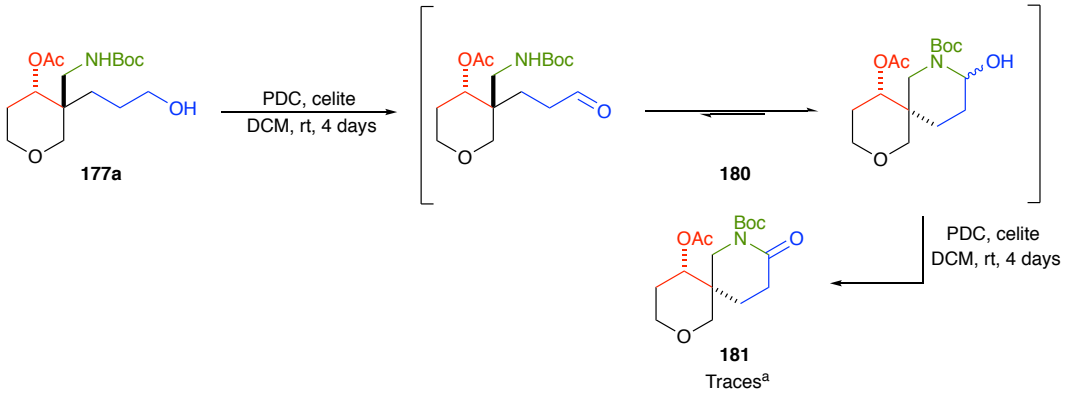
Entry		Alcohol	Method[b]	Scaffold	Yield[c]
1	a	 177a	A	 179a	–[d]
	b		B		57%
2		 177b	B	 179b	40%
3		 177c	B	 179c	13%
4	a	 177d	B	 179d	–[e]
	b		C		–[e]
	c		A		–[d]
5		 177e	B	 179e	57%

Table 20: Optimisation and utilisation of an intramolecular S_N2 cyclisation reaction to yield different piperidine-derived scaffolds. [a]The mesylated alcohols **178** were always formed (observed by TLC and LC-MS of the crude product mixture after the first step). [b]**Method: A:** NaH, THF, 65 °C; **B:** TFA, DCM, rt, then Et_3N, DCM, rt, then Boc_2O, DCM, rt; **C:** TFA, $(Bu)_4NI$, DCM, 40 °C, then Et_3N, DCM, rt, then Boc_2O, DCM, rt. [c]Yield of the purified scaffold. [d]Decomposition observed by TLC and ^{1}H-NMR spectroscopy of the crude product mixture. [e]No cyclisation observed by TLC and ^{1}H-NMR spectroscopy of the crude product mixture.

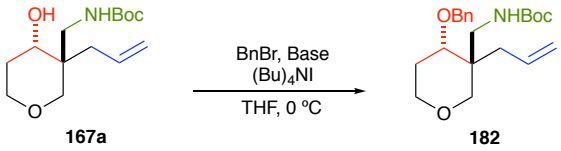
After the formation of the piperidine-derived scaffolds **179** was achieved, the synthesis of their oxidised versions was also attempted. For this reason, the

alcohol derivative **177a** was treated with PDC in DCM. PDC should oxidise the alcohol **177a** to the aldehyde, which would cyclise to form the hemiaminal intermediates **180**. These hemiaminals would be oxidised again to form the scaffold **181**. The use of PDC as oxidising agent worked well for the oxidation of the previous hemiaminals (Table 18). However, it did not work for the formation of compound **181** from **177a** and only traces of product were observed after 4 days of reaction (Scheme 19).



Scheme 19: Failed attempt of a double oxidation reaction to form compound **181** from the alcohol **177a**. [a]Observed by LC-MS of the crude product mixture.

After obtaining the previous two-ring system spirocycles, the synthesis of more complex spirocyclic ring systems was investigated. However, due to the basic conditions of the following cyclisation reactions it was decided to change the acetyl protective group of compound **171a** for a base-stable protecting group. Therefore, the protection of the alcohol **167a** with a benzyl group was attempted. For this reason, the secondary alcohol **167a**, BnBr and catalytic amounts of $(Bu)_4NI$ were dissolved in THF. Successively, NaH was added to the reaction mixture.[179] This gave the benzylated product **182** in 86% yield (Table 21, entry 3). It was observed that the order of addition and the base used were important in this reaction. If NaH was added to the reaction mixture before BnBr, the yield decreased (Table 21, entry 1).[179] If other bases like KO^{t}Bu were used, the reaction did not work well (Table 21, entry 2). The reason is that once the alcohol of **167a** is deprotonated by KO^{t}Bu, it rapidly reacts with the NHBoc group to form the six-membered ring carbamate **150a** previously synthesised (Table 15).

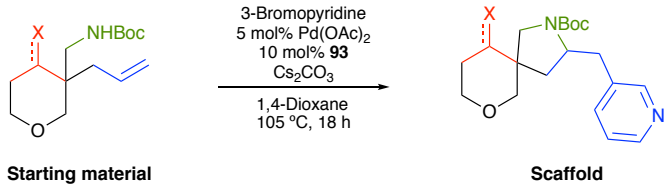


167a 182

Entry	Base	Procedure	Yield[a]
1	NaH	Addition of BnBr as the last reagent	52%
2	KO^{t}Bu	Addition of BnBr as the last reagent	–[b]
3	**NaH**	**Addition of NaH as the last reagent**	**86%**

Table 21: Optimisation of the benzyl protection of the alcohol **167a** to form compound **182**. [a]Yield of purified product. [b]Not isolated, it was observed by ^{1}H-NMR spectroscopy of the crude product mixture that most of the product is the carbamate **150a**.

With compound **182** in hand, it was used as substrate for a Pd-catalysed aminoarylation reaction,[116] conjointly with the free alcohol **167a** (to know if the reaction requires a protected alcohol) and the ketone **148i**. The use of the cyclisation precursor **148i** has been previously avoided for the synthesis of spirocycles because the reduction of the ketone in the resulting spirocyclic products could give a poor dr. Nevertheless, it was of interest to try the aminoarylation on the ketone **148i** because the resulting spirocyclic product would have an additional chiral centre and consequently it could undertake a diastereoselective ketone reduction. Consequently, compounds **148i**, **167a** and **182** were treated with 3-bromopyridine in the presence of 10 mol% of the ligand **93**, 5 mol% of $Pd(OAc)_2$ and Cs_2CO_3 in 1,4-dioxane for 18 h at 105 ºC. As expected, the reaction did not work for the alcohol **167a** due to the fact that the free alcohol could also react under this kind of conditions through a carboetherification reaction (Table 22, entry 2).[174,180,181] However, the reaction worked for the ketone **148i** and the protected alcohol **182**, yielding the pyrrolidine-derived products **183** and **185** in 34% and 31% yield, respectively (Table 22, entries 1 and 3). Nevertheless, the reaction was not very diastereoselective, giving a crude dr 65:35 and 67:33, respectively. Only product **185** was purified as a single diastereomer. Consequently, the best substrate for the aminoarylation reaction was the protected alcohol **182**.



Starting material **Scaffold**

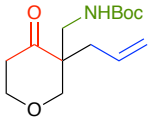
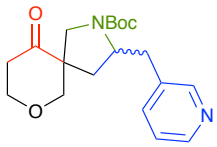
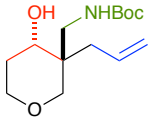
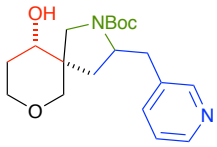
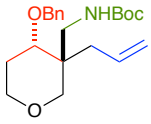
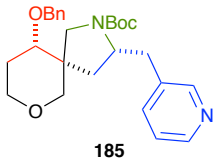
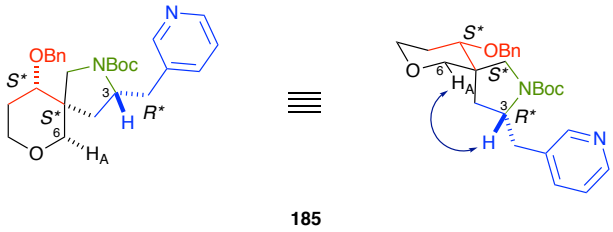
Entry	Starting material	Scaffold	Crude dr[a]	Yield & dr[c]
1	 **148i**	 **183**	65:35	34%, 69:31
2	 **167a**	 **184**	–[b]	
3	 **182**	 **185**	**67:33**	**31%, >95:<5**

Table 22: Optimisation of the Pd-catalysed aminoarylation reaction to obtain pyrrolidine-derived scaffolds. [a]Determined by ^{1}H-NMR spectroscopy (500 MHz) of the crude product mixture. [b]Complicated mixture observed by TLC and ^{1}H-NMR spectroscopy of the crude product mixture. [c]Yield and dr (^{1}H-NMR, 500 MHz) of the purified product.

It was thought that changing the benzyl protecting group for a larger protecting group could improve the diastereoselectivity of the aminoarylation reaction. Consequently, a larger protecting group could give better selectivity for one diastereomer. Therefore, the TBDPS group was selected due to the fact that it has a larger size and because it has been used to protect similar alcohols.[182] However, the protection of the alcohol **167a** with TBDPS did not work, even with the use of imidazole or DMAP. This result could be because the alcohol could be too hindered to react with TBDPS. Due to the fact that the aminoarylation reaction could not be improved, it was not attempted with other cyclisation precursors.

Due to the fact that the pyrrolidine-derived scaffold **185** was isolated as a single diastereomer, the relative configuration of the new chiral centre was investigated by NOESY (500 MHz) analysis (Figure 35). One nOe interaction was observed between the proton 6-H_A and the proton 3-H. Consequently, the new chiral centre at C-3 should have the opposite relative configuration respect the other chiral centres. If the relative configuration of the new chiral centre was

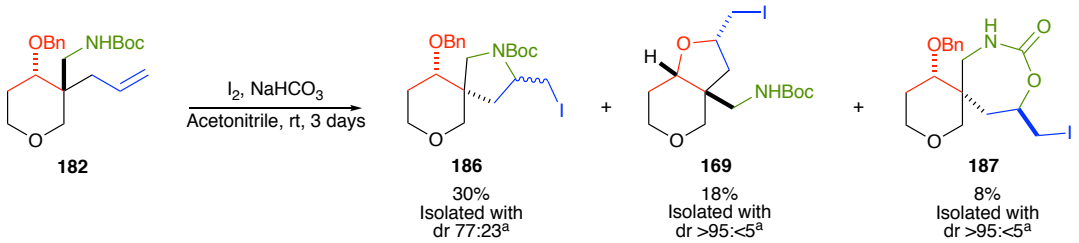
the same than the other chiral centres, this nOe signal would not be observed and nOe signals would be observed between the pyridinylmethyl chain and 6-H_A.



185

Figure 35: Key nOe enhancement of the NOESY (500 MHz) analysis for the determination of the relative stereochemistry of the scaffold **185**.

Due to the poor yield and dr of the aminoarylation reaction, the iodocyclisation reaction was investigated again as an alternative source of other complex spirocyclic compounds. It was assessed with the benzylated derivative **182** because it gave the best result in the aminoarylation reaction. For this reason, compound **182** was dissolved in acetonitrile and combined with I_2 and $NaHCO_3$. After the reaction was completed, the expected product **186** was only obtained in 30% yield as a mixture of two inseparable diastereomers (dr 77:23) (Scheme 20). This yield was low because two other products were also obtained in this reaction. One of these side-products is the iodo-derivative **169**, which has been previously prepared (Scheme 16). The second side-product is the seven-membered ring **187**, which would be a new scaffold. Both of these two side-products were isolated as single diastereomers, in 18% and 8% yield, respectively. Product **169** was obtained because iodide can remove the protecting Bn group, releasing a free alkoxide, which can react instead of the NH group. Product **187** was obtained due to the fact that the iodocyclisation reaction can also give a side-reaction where the Boc group reacts instead of the NH group. Since the reaction gave different products, the mixture was complicated and the crude dr could not be determined. Due to the low yield and dr of **186**, this reaction was not tried with the other cyclisation precursors.



Scheme 20: Iodocyclisation reaction of the benzyl derivative **182** to form the expected product **186** and two other unexpected products, the known scaffold **169** and the new scaffold **187**. [a]Determined by ^{1}H-NMR spectroscopy (500 MHz) of the isolated product.

Since the scaffold **187** was isolated as a single diastereomer, the relative stereochemistry was investigated by NOESY (500 MHz). One nOe signal was observed between 5-H and 11-H. Consequently, the new chiral centre formed in compound **187** should have the opposite relative configuration than the other two chiral centres (Figure 36). If the new chiral centre had the same relative configuration than the other chiral centres, this nOe interaction could not be observed and nOe interactions would be observed between 5-H and the iodomethyl chain.

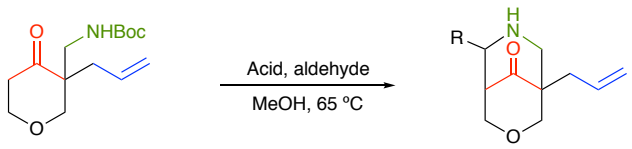
187

Figure 36: Key nOe enhancement for the resolution of the relative stereochemistry of compound **187** by NOESY (500 MHz).

In conclusion, different spirocyclic compounds were successfully prepared using cyclisation reactions between the alkene and the NHBoc. The ketone of compounds **148** can be reduced with a good dr to the corresponding alcohols. For this reason, the alcohols were usually used as starting points for cyclisation reactions between the NHBoc and the alkene. Protection of the alcohols was important before performing the cyclisation reactions. Some cyclisation reactions gave poor yields and/or poor dr. However, some others worked very well and they were used with the other cyclisation precursors.

3.3.4. Cyclisation Reactions Between the NHBoc and the α-position of the Ketone

After investigating different cyclisation reactions between the main functionalities of the cyclisation precursors, a final cyclisation reaction was investigated. This cyclisation reaction could be an intramolecular Mannich reaction, involving the α-carbon of the ketone and the NHBoc. For this reason, it was decided to dissolve the cyclisation precursor **148i** in MeOH and treat it with TFA and different aldehydes at 65 ºC. The reaction worked, giving the bridged bicyclic scaffolds **152** and **188** in 30% and 33% yield, respectively (Table 23, entries 1b and 2). In addition, compound **188** was obtained as a single diastereomer. Removal of the Boc group was necessary for this cyclisation to proceed. It was observed that when changing TFA for a milder acid as AcOH, there was no cyclisation (Table 23, entry 1a).



148i **Scaffold**

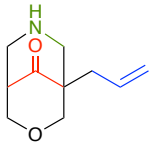
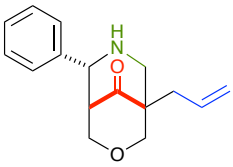
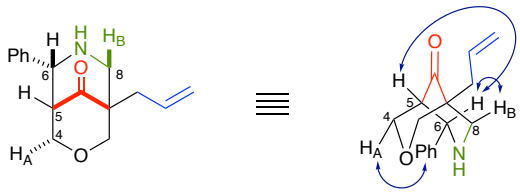
Entry	Acid	Aldehyde	Scaffold	Crude dr[a]	Yield and dr[d]
1 a	AcOH	$(CHO)_n$		–[b]	
1 b	**TFA**	**$(CHO)_n$**	**152**	**–[c]**	**30%, –[c]**
2	**TFA**	**Benzaldehyde**	 **188**	**>95:<5**	**33%, >95:<5**

Table 23: Optimisation of the intramolecular Mannich reaction to give bridged bicyclic scaffolds. [a]Determined by ^{1}H-NMR spectroscopy (500 MHz) of the crude product mixture. [b]No cyclisation observed by TLC and ^{1}H-NMR spectroscopy of the crude product mixture. [c]Not applicable. [d]Yield and dr (^{1}H-NMR, 500 MHz) of purified scaffold.

The relative configuration of the scaffold **188** was confirmed by NOESY (500 MHz). Protons from the aromatic ring showed nOe enhancements with the proton 4-H_A. In addition, proton 6-H also showed two nOe signals; one with the proton 5-H and one with the proton 8-H_B. These signals suggested that the phenyl ring should be situated in an equatorial position (Figure 37). If the phenyl

ring was situated in an axial position, these nOe interactions would not be observed and nOe interactions would be observed between the phenyl ring and the proton 8-H_B, and between the protons 4-H_A and 6-H.



188

Figure 37: Key nOe enhancements of the NOESY (500 MHz) analysis to resolve the relative configuration of compound **188**.

In conclusion, two other cyclisation reactions were performed from the cyclisation precursor **148i** using an intramolecular Mannich reaction. This transformation afforded bridged bicyclic scaffolds. This result was interesting because these scaffolds have very different ring systems and tri-dimensional conformations compared to the scaffolds obtained from previous cyclisation reactions. However, these cyclisation reactions were not attempted with the other cyclisation precursors due to the challenging diastereoselective reduction of the resulting ketone.

3.3.5. Summary of Results

The cyclisation precursor **148i** was used to investigate the scope of the different possible cyclisation reactions. As a result, thirteen different cyclisation reactions were accomplished with this cyclisation precursor as starting point and thirteen scaffolds were obtained (Figure 38). The scaffolds include fused-rings, spirocyclic rings and bridged bicyclic rings. Consequently, a high structural diversity of sp^3-rich ring systems was achieved.

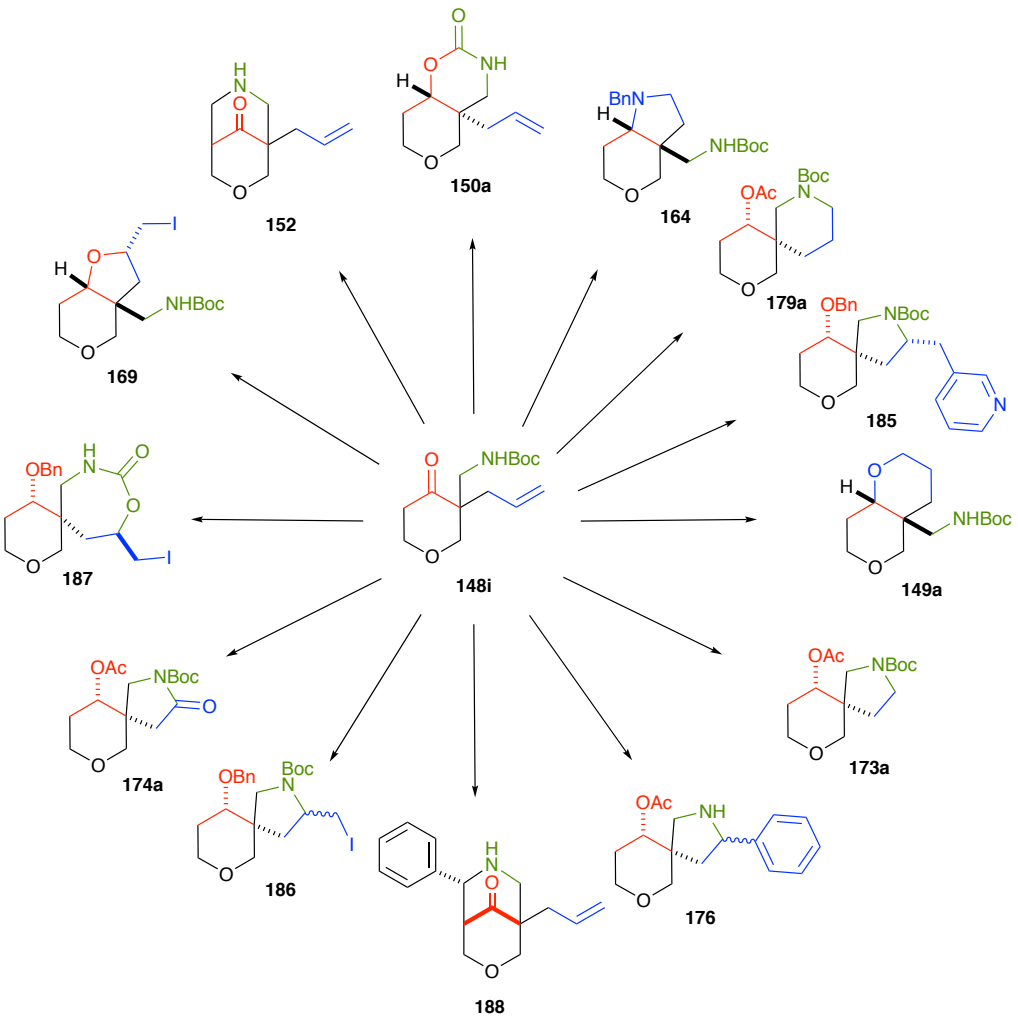
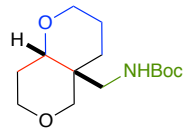
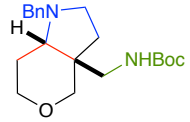
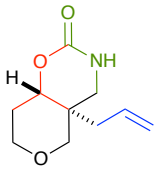
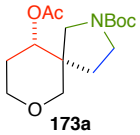
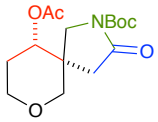
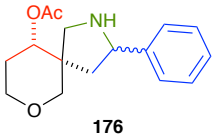
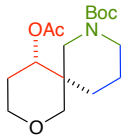
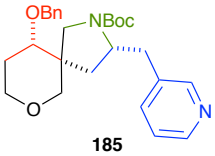
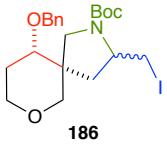
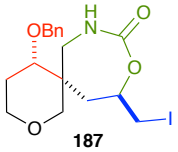
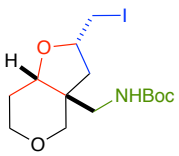


Figure 38: Summary of all the scaffolds obtained from cyclisation reactions of the cyclisation precursor **148i**.

Despite a large number of scaffolds being obtained from the cyclisation precursor **148i**, not all the cyclisation reactions were successfully optimised to give good average yields (≥30%) and high diastereoselectivities (dr ≥80:≤20). For this reason, the cyclisation reactions that yielded these scaffolds in low average yields and low dr were not used for the synthesis of other scaffolds (Table 24). Consequently, scaffolds **164**, **176**, **185**, **186** and **187** were not prioritised. In addition, compound **169** was also not prioritised because the main possible change of the iodine group would have been to form a primary amine, making the resulting compound too polar for CNS. However, if a less polar transformation was going to be used to displace the iodide, this compound could also be prioritised. Finally, scaffolds **152** and **188** were also not selected. The reason is that they have a bridgehead ketone, which would be difficult to reduce to a single diastereomer. However, these two scaffolds could also be prioritised if the ketone was removed using the Wolff-Kisher reaction.[183]

Entry	Scaffold	Number of steps from the cyclisation precursor 148i and average yield	dr After purification	Prioritised for the synthesis of other scaffolds
1	 **149a**	Two steps, 75%	>95:<5	✓
2	 **164**	Two steps, 23%	83:17	✘
3	 **150a**	Two steps, 89%	86:14	✓
4	 **173a**	Four steps, 52%	>95:<5	✓
5	 **174a**	Four steps, 42%	>95:<5	✓
6	 **176**	Five steps, 44%	57:43	✘
7	 **179a**	Four steps, 37%	>95:<5	✓
8	 **185**	Three steps, 25%	>95:<5	✘
9a	 **186**	Three steps, 24%	77:23	✘
9b	 **187**	Three steps, 6%	>95:<5	✘
10	 **169**	Two steps, 36%	>95:<5	✘

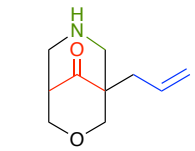
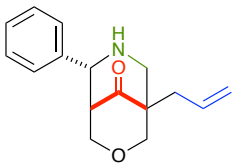
11	 **152**	One step, 30%	>95:<5	✘
12	 **188**	One step, 33%	>95:<5	✘

Table 24: Summary of the average yields and dr of all the scaffolds obtained from the cyclisation precursor **148i**. Scaffolds prioritised depending on average yield, dr and functional groups. Scaffolds **186** and **187** (Entry 9) were obtained from the same reaction.

As a result, the five cyclisation reactions that yielded the prioritised scaffolds were used with the other cyclisation precursors. The cyclisation reactions were highly reproducible with the different precursors, only in few instances the optimised cyclisation reaction had to be slightly modified. Consequently, 18 additional scaffolds were obtained using the other six cyclisation precursors (Table 25).

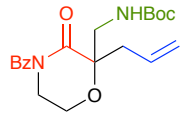
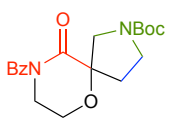
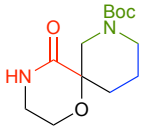
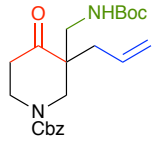
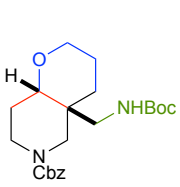
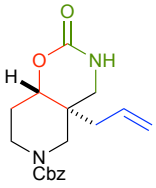
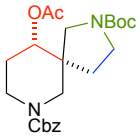
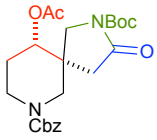
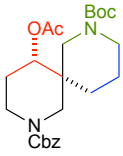
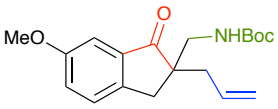
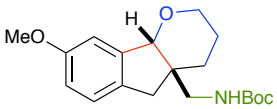
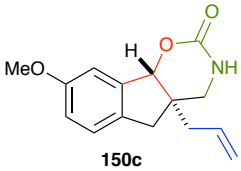
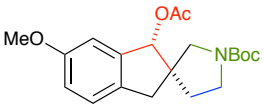
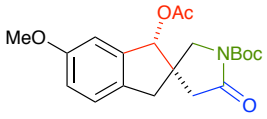
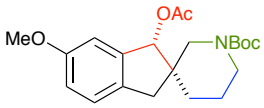
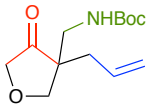
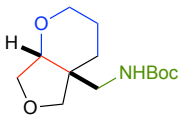
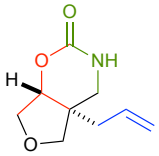
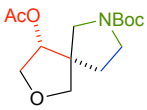
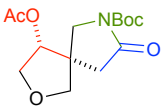
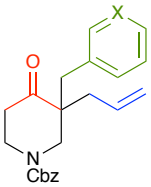
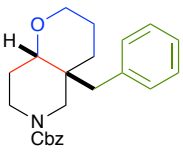
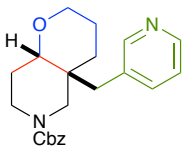
Cyclisation precursor	Additional scaffolds obtained using the prioritised cyclisation reactions
 **148h**	 **173e**  **179e**
 **148j**	 **149b**  **150b**  **173b**  **174b**  **179b**
 **148k**	 **149c**  **150c**  **173c**  **174c**  **179c**
 **148l**	 **149d**  **150d**  **173d**  **174d**
 **148m**, X = CH **148n**, X = N	 **149e**  **149f**

Table 25: Additional scaffolds obtained from the cyclisation precursors **148h** and **148j-n** using the prioritised cyclisation reactions.

Consequently, a total of 23 scaffolds were prepared from the seven cyclisation precursors using the prioritised cyclisation reactions. The reactions were very efficient, delivering the 23 scaffolds in 42 steps (steps counted as isolated and characterised compounds) from the seven cyclisation precursors. Due to the fact that these scaffolds can be prepared in good average yields and good dr, some of them were prepared on a larger scale to allow subsequent decoration to lead-like molecules.

3.4. Application of the Computational Tool

After completing the synthesis of the 23 scaffolds using the prioritised cyclisation reactions, the value of these scaffolds for CNS drug discovery was assessed. Consequently, a virtual library of the unprotected/decorable versions of these scaffolds was prepared (Figure 39).

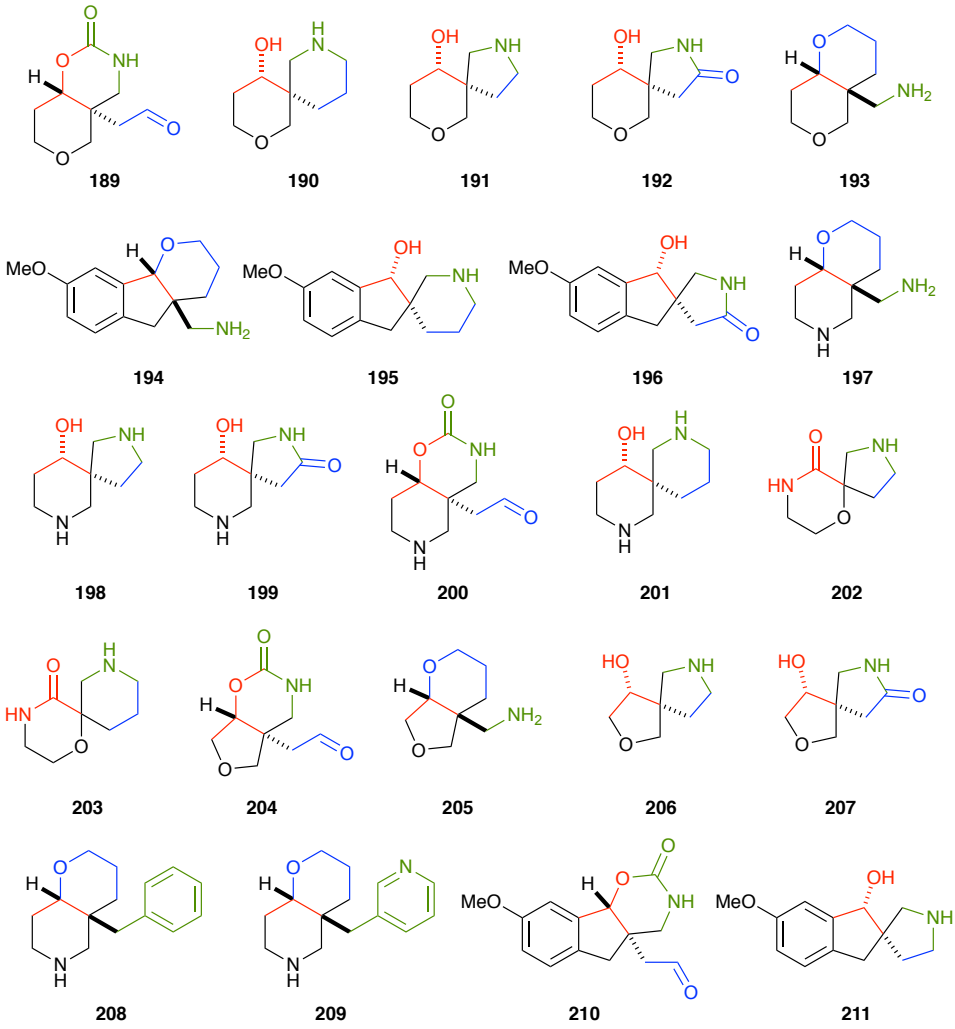


Figure 39: Virtual library of scaffolds assessed using the computational tool. Scaffolds with one point of decoration were decorated once. Scaffolds with two or more points of decoration were decorated twice. Primary amines served as two points of decoration. Terminal alkenes were converted into aldehydes, which were converted to alcohols before decoration or were decorated with a reductive amination reaction. As the deprotections, it is assumed that these transformations could be synthetically accessible.

Successively, this virtual library of 23 scaffolds was decorated once or twice (depending of the points of decoration) and scored with the computational tool. It was observed that all the scaffolds were novel and most of them obtained a good mean CNS Lead MPO score ~>4.00 (Table 26).

Scaffold number	Mean CNS Lead MPO score[a]	Number of derived compounds	Novelty[b]	
			Hits without α-atoms	Hits with α-atoms
189	4.54	1080	0	0
190	4.75	2204	0	0
191	4.91	2204	0	0
192	5.30	696	0	0
193	4.84	1798	0	0
194	3.83	1798	0	0
195	3.67	2204	0	0
196	4.42	696	23	0
197	4.14	7598	26	0
198	4.15	6112	241	0
199	4.62	2233	241	0
200	4.18	2329	0	0
201	4.07	6112	122	0
202	5.30	696	0	0
203	5.17	696	0	0
204	4.65	1080	0	0
205	4.94	1798	2	0
206	5.01	2204	40	0
207	5.40	696	40	0
208	4.46	76	0	0
209	5.05	76	0	0
210	3.65	1080	0	0
211	3.94	2204	23	0

Table 26: Results obtained for the 23 virtual scaffolds using the computational protocol. [a]Mean of all the CNS Lead MPO scores of the derived compounds per scaffold. [b]Based on Murcko fragments against a random 2% of the ZINC database.

Once the results of the computational tool were obtained, the scores of some scaffolds were further analysed (Figure 40). It was observed that some scaffolds like **199** and **206** present a high score because all of their derived compounds have the desired physicochemical properties. Consequently, scaffolds **199** and **206** are likely to yield lead-like molecules, which once optimised, would have the desired physicochemical properties to cross the BBB. Scaffold **194** presents a lower score because its derived compounds usually have too high MW due to the presence of the aromatic ring. Finally, scaffold **201** also presents a lower score. This is due to the fact that its derived compounds usually have too high pK_a. The reason is that this scaffold has two basic amines and one alcohol as points of decoration. All the scaffolds are not decorated more than twice. Consequently, some of the derived compounds of the scaffold **201** will always have a basic amine with a high pK_a. However, due to the fact that the CNS Lead MPO score takes into account six different properties, scaffolds **194** and **201** do not score very low because the other properties have the desirable values. Consquently, they would also be likely to yield lead-like molecules for CNS drug discovery.

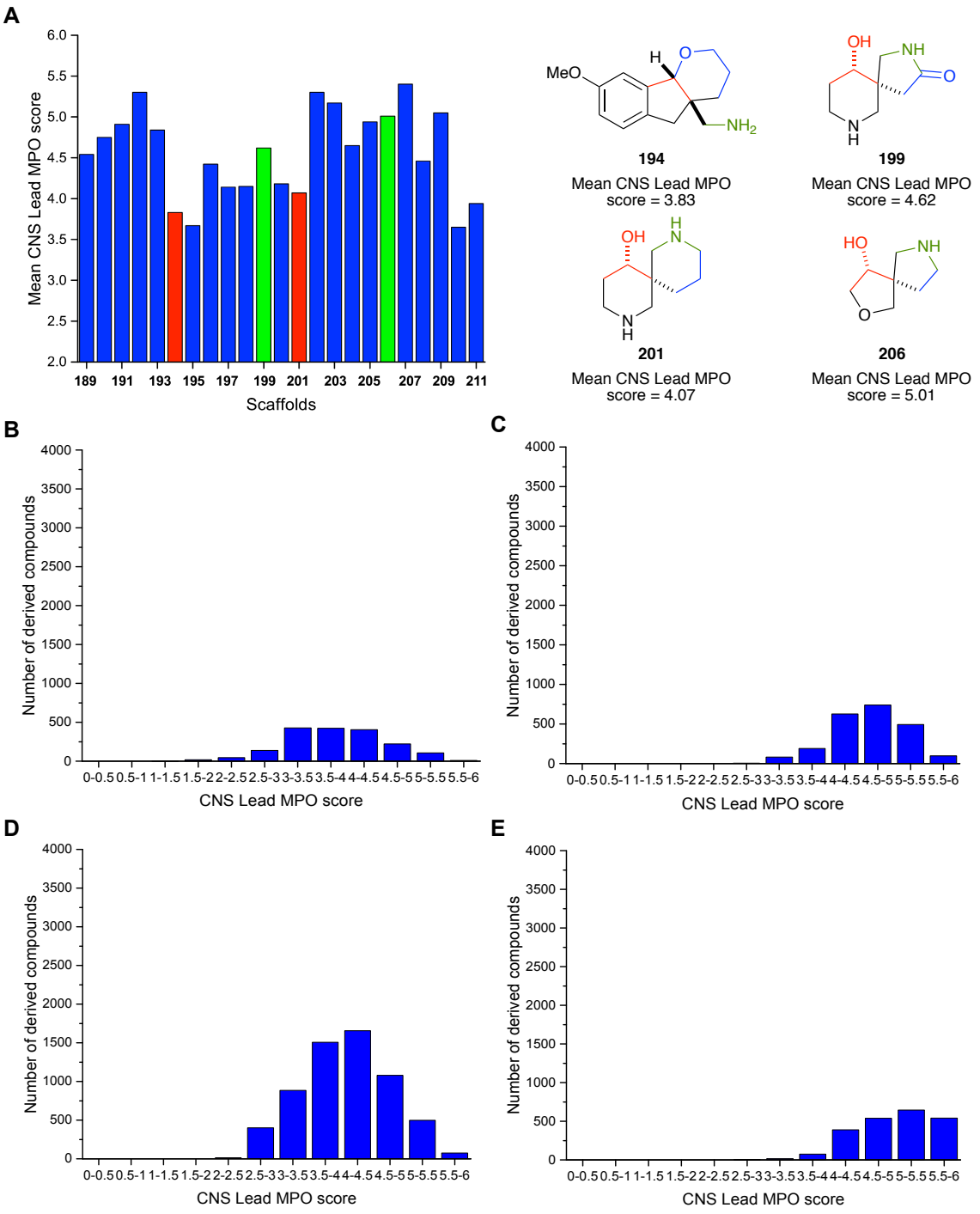


Figure 40: Panel A: Analysis of the mean CNS Lead MPO scores of the derived compounds for each of the 23 virtual scaffolds. In red, examples of scaffolds with lower scores (**194** and **201**). In green, examples of scaffolds with higher scores (**199** and **206**). **Panels B, C, D, E:** Distribution of the CNS Lead MPO scores of the derived compounds of the scaffolds **194**, **199**, **201** and **206**, respectively.

3.5. Conclusions

In conclusion, a highly modular and efficient toolkit of cyclisation reactions was developed and used to prepare a library of 23 structurally-diverse and sp^3-rich scaffolds. This library of scaffolds was subsequently assessed with the computational tool. It was observed that all the scaffolds were novel and they

had good mean CNS Lead MPO scores. Consequently, lead-like molecules derived from these scaffolds would allow to further study the CNS lead-like chemical space. The value of these scaffolds would be highlighted in the design of high-quality HTS libraries for CNS-targets. These scaffolds could be used as starting points for the synthesis of novel and high-quality lead-like molecules for CNS drug discovery programs. These lead-like molecules could be added to the current collection of compounds used for HTS in CNS drug discovery. If some of these molecules are active, their potency could be improved to deliver a drug-like molecule with the desired properties for crossing the BBB. This would improve the success in the later stages of the drug discovery programme.

Chapter 4: Realising the Biological Relevance of the Developed Scaffolds for CNS Drug Discovery

4.1. Ligand Discovery Against BACE1

β-Site amyloid precursor protein cleaving enzyme 1 (BACE1), also known as β-secretase 1, Asp2 or memapsin 2, is a transmembrane aspartic protease that belongs to the pepsin family.[184,185] It is predominantly found in the neurons of the CNS.[186] The inhibition of this protease has been of great interest for the treatment of Alzheimer's disease.[187] Alzheimer's disease is a CNS disorder characterised by the loss of neurones due to the extracellular accumulation of an hydrophobic peptide called amyloid β.[186] The formation of amyloid β is initiated by the proteolytic activity of BACE1. This enzyme cleaves a peptide called APP (amyloid precursor protein), which is subsequently cleaved by another secretase to form amyloid β (Figure 41).[188]

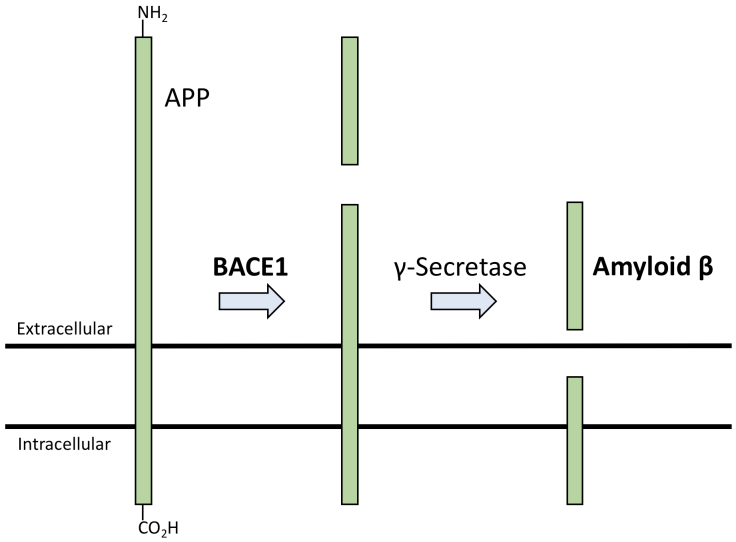


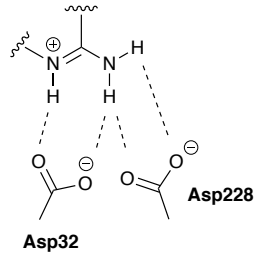
Figure 41: Amyloid β formation initiated by BACE1 in Alzheimer's disease. Adapted from a reference.[188]

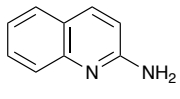
Consequently, inhibition of BACE1 has become of interest to stop the progression of the disease.[189] Different inhibitors have been designed, which involve peptidomimetics, pseudo-peptidomimetics and non-peptidomimetics.[190] However, the problem of the peptidomimetics is that they do not have the desired properties to cross the BBB.[190] Consequently, non-peptidomimetics inhibitors have attracted more attention due to the fact that they are smaller molecules. For this reason, they have better BBB penetration and lower P-gp

efflux.[190] Different small molecule inhibitors have already been designed and reached clinical trials.[190] However, some have recently been withdrawn after being successful in Phase I. One example is the drug candidate verubecestat, a BACE1 inhibitor developed by Merck. This candidate was removed in the last stages of clinical trials because it did not improve the cognitive function and showed side effects.[189,191] For this reason, more studies are required to understand the physiological and pathological role of BACE1 and if its inhibition will significally improve cognitive funtions.

To be able to continue studying BACE1 as target to treat Alzheimer's disease, the screening of new small molecules is of interest.[190] Recently, a fragment-based HTS allowed the identification of an amidine-like hit **212** (Figure 42).[192] It is known that amidine-like groups form interactions with the two catalytic aspartates in the active site of BACE1.[192]

A **B**



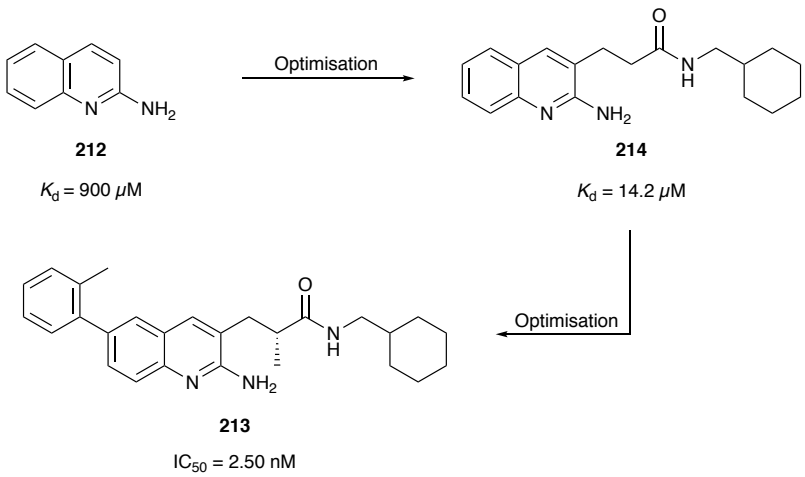


212

Figure 42: Panel A: Binding mode of amidine-like groups in the active site of BACE1.[192] **Panel B:** BACE1 hit identified by fragment-based HTS.[192]

This initial hit was developed into the compound **213** (Figure 43, panel A).[192] Consequently, the fragment **212** was grown in opposite vectors to increase the number of interaction in the binding site. During this process, different intermediate compounds like **214** were prepared and tested against BACE1.

A



B

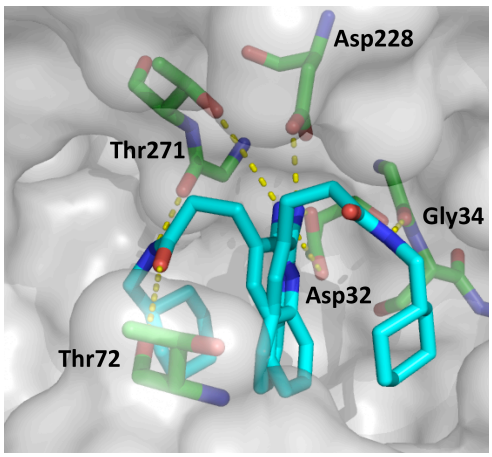


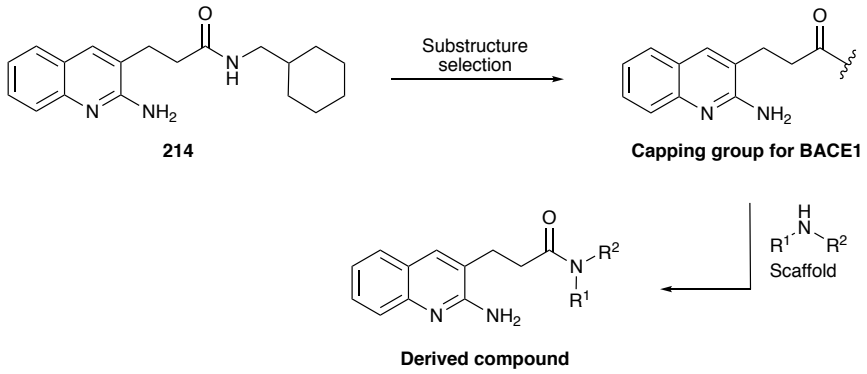
Figure 43: Panel A: Optimisation of the aminoquinoline fragment **212** to obtain the compound **213**. **Panel B:** Co-crystal structure of the intermediate **214** in the active site of BACE1 (PDB: 3RU1).[193] Compound **214** can adopt two binding conformations. Key interactions are shown in yellow dashes.

It was observed by looking at the co-crystal structure of BACE1 with **214** that alternative optimisations could be possible if the cyclohexylmethyl ring of **214** was changed for more interesting ring systems, due to the fact that the active site is quite large and the new ring system could fill it (Figure 43, panel B). For this reason, this cyclohexylmethyl ring could be changed for some of the scaffolds previously prepared using the Mannich/alkylation and palladium connective reactions. Using this approach, it could be possible to assess the biological value of the developed scaffolds for CNS drug discovery.

4.2. Decoration of the Scaffolds

The substructure of compound **214** without the cyclohexylmethyl group was identified as a potential medicinal chemistry capping group for BACE1. For this reason, it was decided to use this capping group to decorate some of the

scaffolds previously prepared (Scheme 21). Consequently, a library of derived compounds could be obtained. It was decided to use the amines of the scaffolds as point of decoration. Consequently, the substructure of **214** could be added to the amine through an amide bond.



Scheme 21: Overview of the selected approach for the design of different derived compounds from the substructure of compound **214** and different scaffolds.

For this reason, 13 different virtual derived compounds were designed from the substructure of compound **214** coupled to different scaffolds (Figure 44). It was decided to generate eight derived compounds from the designed scaffolds and five from simpler commercially available scaffolds, including the already known compound **214**. The designed scaffolds were selected on the basis of their suitability for the decoration, the CNS Lead MPO score of the corresponding derived molecule and their structural diversity. The commercially available scaffolds were selected as simpler substructures of the designed scaffolds. Consequently, it could be observed if the designed scaffolds have a higher value for the inhibition of BACE1 than the respective and simpler commercial scaffolds. Compound **214** was selected as a future reference compound.

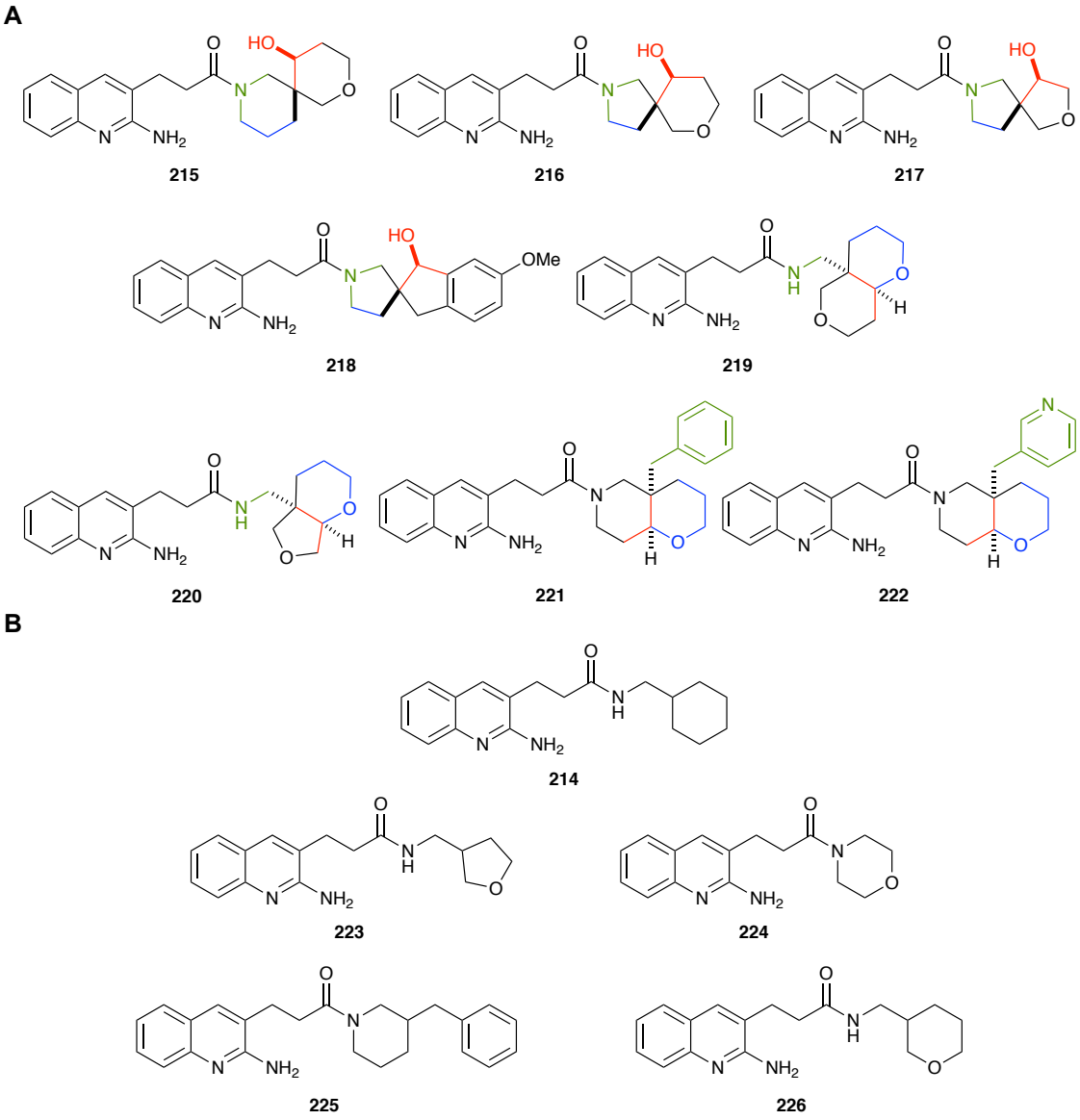


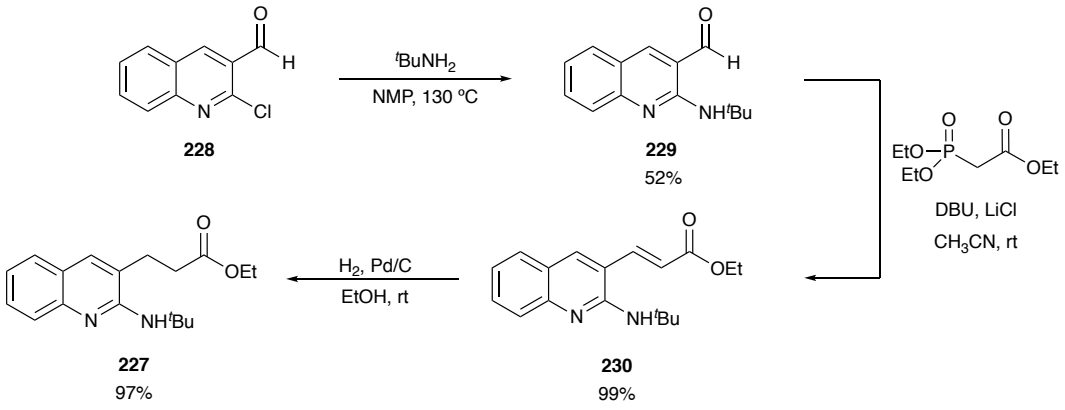
Figure 44: Virtual derived compounds generated from coupling the BACE1 capping group with different scaffolds. **Panel A:** Derived molecules from the designed virtual scaffolds **190**, **191**, **206**, **211**, **193**, **205**, **208** and **209**; respectively. **Panel B:** Compound **214** and derived molecules from commercially available scaffolds.

Successively, these derived molecules were scored with the computational tool (Table 27). It was observed that all of them have CNS Lead MPO ~>3.00. The reason the scores are below four is mainly due to the high MW of the decorating group. However, the MW of this capping group cannot be reduced because it would reduce the affinity for BACE1. For this reason, these scores were accepted as good. Consequently, if any of these derived compounds is active, it could be optimised to a compound that could be CNS-compliant.

Virtual derived compound	CNS Lead MPO score
214	3.71
215	3.62
216	3.74
217	3.85
218	3.05
219	3.63
220	3.74
221	2.93
222	3.45
223	4.31
224	5.32
225	3.40
226	4.20

Table 27: CNS Lead MPO scores of the generated virtual derived compounds.

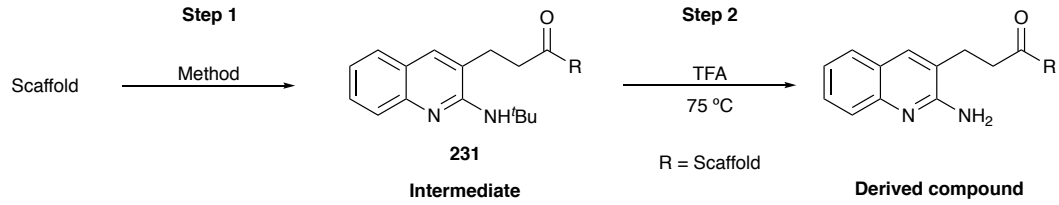
Consequently, these 13 derived molecules were selected for synthesis. To be able to prepare these compounds, the synthesis of the capping group **227** is necessary. Compound **227** was prepared in three steps (Scheme 22).[192] The first step involved the nucleophilic aromatic substitution of the commercially available chloro-derivative **228** with $^{t}BuNH_2$ to yield the amine derivative **229** in 52% yield. Successively, a Wittig reaction was performed on **229** to give the alkene derivative **230** in a quantitative yield. Finally, the alkene **230** was dissolved in EtOH and treated with H_2 gas in the presence of 10 mol% Pd/C. This yielded the capping group **227** in 97% yield.

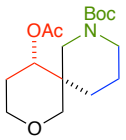
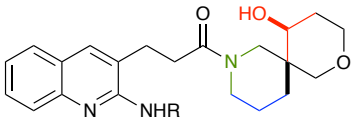
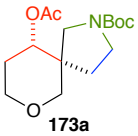
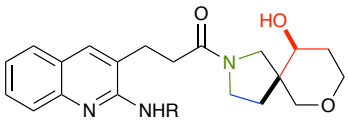
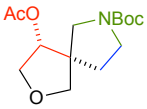
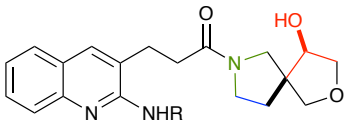
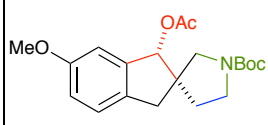
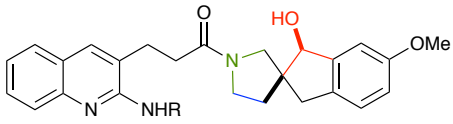
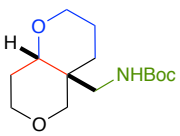
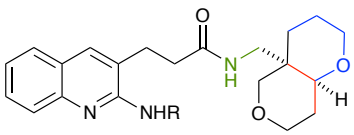
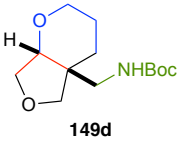
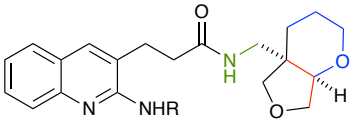


Scheme 22: Synthesis of the capping group **227**, necessary for the decoration of the scaffolds.

Once the ester **227** was prepared, it was used for the decoration of the scaffolds. The decoration of the scaffolds to prepare the derived molecules involved two steps. The first step was the coupling reaction between each scaffold and the ester **227** using an aminolysis reaction.[194] This step was always performed in one pot. Firstly, the scaffolds were fully deprotected (if required) and dissolved in toluene. Subsequently, they were combined with

1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) and Et_3N (if required) and heated to 75 °C. After purification, the corresponding intermediate amide-derived products **231** were obtained in yields ranging from 20% to 98% (Table 28, where R = ^{t}Bu). The second step involved the removal of the ^{t}Bu group by treating the intermediates **231** with TFA at 75 °C.[192] This yielded the final compounds (Table 28, where R = H). The yields of the deprotection were usually very high (≥83%), despite compounds **231d** and **231j**, which gave a yield of 32% and 47%, respectively, due to decomposition.



Entry	Scaffold	Method[a]	Intermediate, R = ^{t}Bu Derived compound, R = H	Yield[b] Step 1 R = ^{t}Bu	 Step 2 R = H
1	 179a	A		231a, 21%	215, >99%
2	 173a	A		231b, 60%	216, 93%
3	 173d	A		231c, 72%	217, >99%
4	 173c	A		231d, 75%	218, 32%[c]
5	 149a	B		231e, 28%	219, 98%
6	 149d	B		231f, 31%	220, >99%

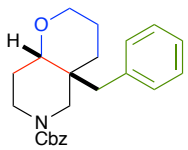
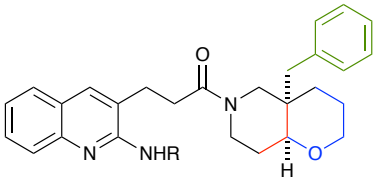
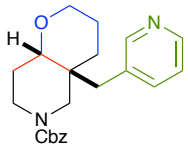
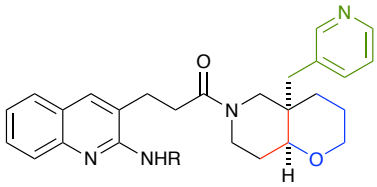
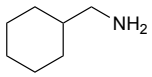
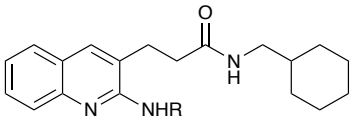
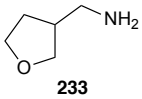
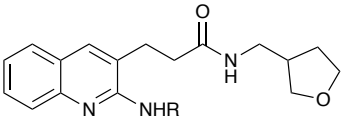
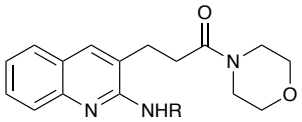
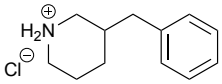
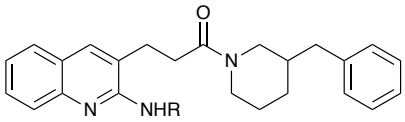
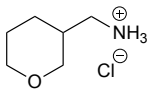
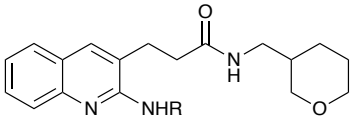
7	 **149e**	**C**		**231g, 23%**	**221, >99%**
8	 **149f**	**C**		**231h, 20%**	**222, 99%**
9	 **232**	**D**		**231i, 98%**	**214, 83%**
10	 **233**	**D**		**231j, 90%**	**223, 47%[c]**
11	 **234**	**D**		**231k, 56%**	**224, 93%**
12	 **235**	**E**		**231l, 37%**	**225, >99%**
13	 **236**	**E**		**231m, 43%**	**226, >99%**

Table 28: Decoration of the scaffolds to yield the final derived compounds where R = H. [a]**Method: A:** NaOMe, MeOH, rt, then TFA, DCM, rt, then **227**, TBD, Et_3N, toluene, 75 °C; **B:** TFA, DCM, rt, then **227**, TBD, Et_3N, toluene, 75 °C; **C:** H_2, Pd/C, MeOH, rt, then **227**, TBD, toluene, 75 °C; **D: 227**, TBD, toluene, 75 °C; **E: 227**, TBD, Et_3N, toluene, 75 °C. [b]Yield of purified product. [c]Lower yield due to decomposition (observed by TLC of the crude product mixture).

4.3. Evaluation of the Biological Activity

The biological activity of the library of 13 derived compounds was evaluated using a fluorescence-quenching assay.[195] This assay exploited a peptide substrate containing in its termini a red-shifted fluorescent donor ($\lambda_{excitation}$ = 530 nm, $\lambda_{emission}$ = 595 nm) and a fluorescence quencher. The specific substrate used was important because of the intrinsic fluorescence of the compounds screened. Under light excitation, the quencher supresses the fluorescence of the fluorescent donor and low fluorescence is detected. However, BACE1-catalysed cleavage of the peptide separates the donor and the quencher,

leading to an increase in fluorescence (Figure 45). Consequently, this assay enables potential BACE1 inhibitors to be screened.

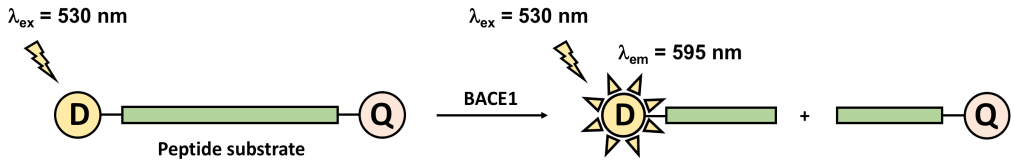


Figure 45: Principle of the flurorescence-quenching assay used to evaluate the biological activity of the 13 derived compounds. Under light excitation, the quencher supresses the fluorescence of the donor and low fluorescence is detected. However, after BACE1 cleaves the peptide and separates the quencher from the donor, an increase in fluorescence is observed. D, fluorescence donor (rhodamine derivative); Q, fluorescence quencher. Peptide sequence before cleavage, rhodamine-EVNLDAEFK-quencher; peptide sequence after cleavage, rhodamine-EVNL + DAEFK-quencher.

The fluorescence-quenching assay was firstly performed using the 13 derived compounds at 100 µM. Consequently, inhibitors could be first identified. After the assay, it was observed that none of the molecules derived from the commercially available scaffolds (**223**–**226**) was an inhibitor at 100 µM. However, reference compound **214** and three molecules derived from the designed scaffolds (**218**, **219** and **221**) showed inhibition of BACE1 at 100 µM (Figure 46).

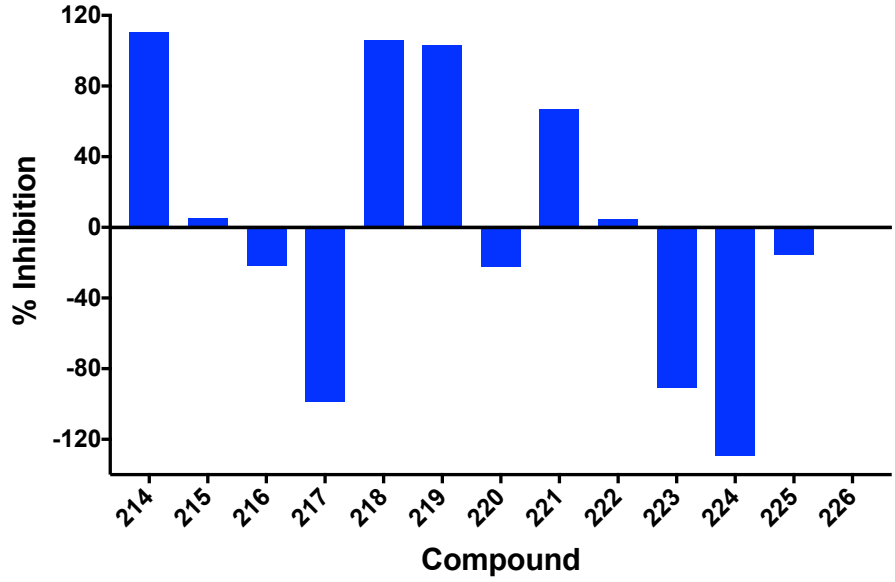


Figure 46: Determination of BACE1 inhibition of the 13 derived molecules using a red-shifted fluorescence-quenching assay. Normalised to negative and positive controls. Compounds were pre-incubated for 20 min with BACE1. Assay conditions were [BACE1] = 0.34 unit/mL; [Substrate] = 250 nM; [Compounds] = 100 µM; 0.50 mM sodium acetate buffer, pH 4.5, 25 °C. The above values were calculated from at three independent experiments. Some compounds showed enhanced BACE1 activity. This observation could be due to the aggregation of the compounds.

Some of the non-inhibitory compounds, in particular **217**, **223** and **224**, showed enhanced BACE1 activity at 100 µM (Figure 46). This observation could suggest that these compounds activate the enzyme. However, this could be due to the fact that these compounds could form aggregates at 100 µM. Consequently, the use of detergents could be investigated.

Due to the fact that compounds **218**, **219**, **221** and **214** were inhibitors, their sigmoidal dose-response models were obtained using the same fluorescence-quenching assay in concentrations between 0.67 mM and 1.00 µM (Figure 47). Consequently, the IC_{50} for each of these compounds could be determined. The IC_{50} of each compound was compared with the CNS Lead MPO score. It was observed that only compound **219** had similar potency and similar CNS Lead MPO score to the reference compound **214**. The other two compounds had lower potency and lower score.

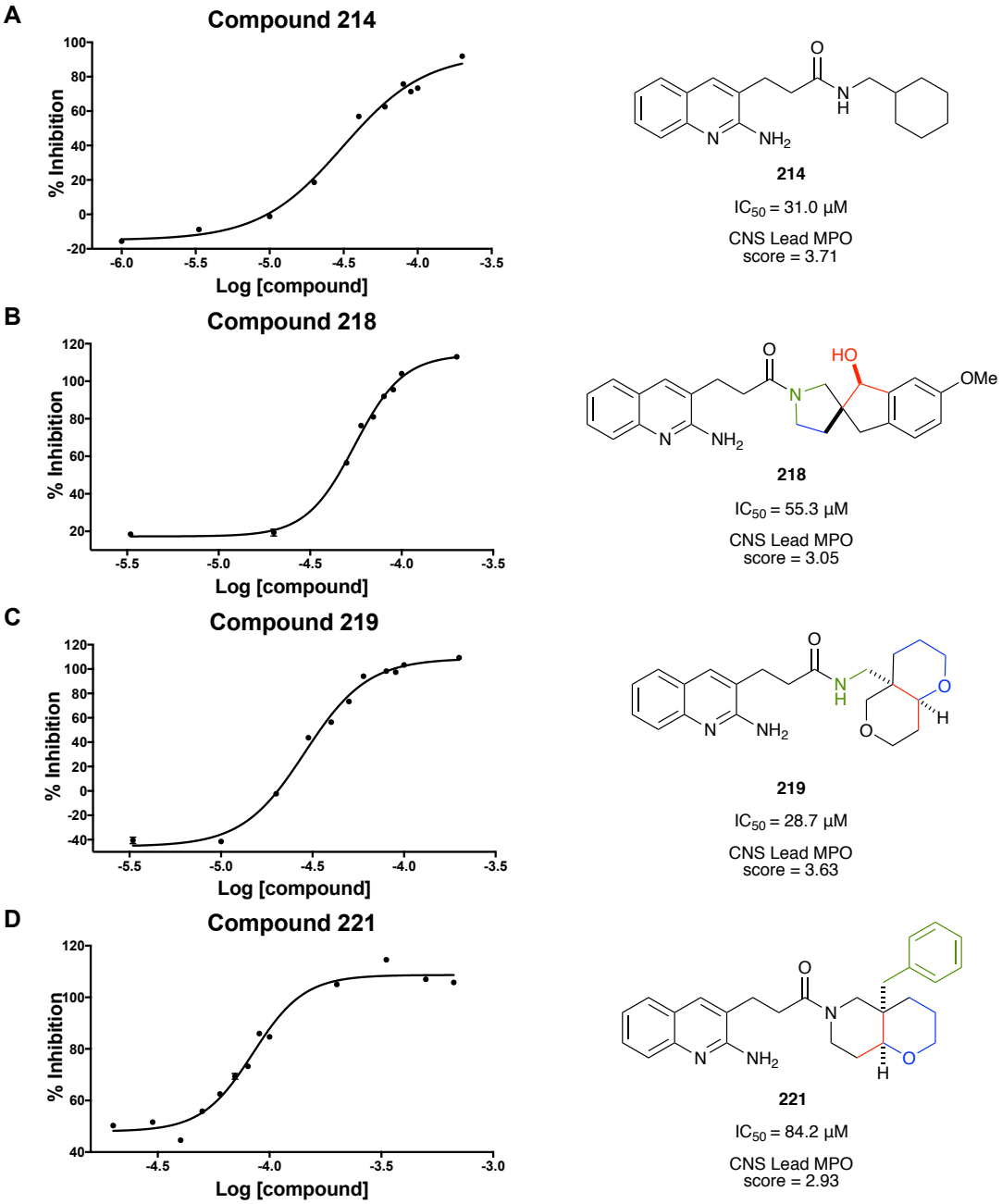


Figure 47: Panels A–D: Sigmoidal dose-response models, IC_{50} and CNS Lead MPO scores for the inhibitors **214** (reference), **218**, **219** and **221**, respectively. Dose-response models and IC_{50} determined using a red-shifted fluorescence-quenching assay and normalised to negative and positive controls. Compounds were pre-incubated for 20 min with BACE1. Assay conditions were [BACE1] = 0.34 unit/mL; [Substrate] = 250 nM; [Compounds] from 0.67 mM to 1.00 µM; 0.50 mM sodium acetate buffer, pH 4.5, 25 °C. The inhibition values were calculated from three independent experiments. Compound **214** is a compound known in the literature and it was used as reference compound. However, its IC_{50} was not reported before.[192]

It was observed that some of the sigmoidal dose-response models do not start at zero % of inhibition and some start even below (Figure 47). This observation could be due to problems with the assay such as plate layout or edge effects, or because of aggregation of the compounds. For this reason, as mentioned previously, the addition of detergents could be investigated. In addition, the

slopes of the dose-response model curves are above one for all the compounds. This observation could be due to the fact that BACE1 can form dimers.[196] Consequently, once the inhibitor has been bound to one monomer, it could modulate the binding of another molecule of inhibitor to the other monomer.

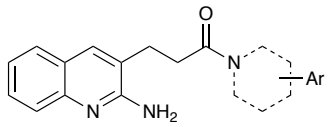
4.4. Conclusions and Future Perspectives

In conclusion, a library of 13 derived molecules was prepared from different scaffolds and successfully assessed for BACE1 ligand discovery. It was observed that none the molecules derived from commercially available scaffolds were inhibitors of BACE1 (despite the known reference compound **214**). However, three of the molecules derived from the designed scaffolds showed BACE1 inhibition. Consequently, the designed scaffolds could be more biologically relevant than the simpler commercially available scaffolds.

It was expected that derived compounds containing structurally-related scaffolds would have similar biological activities against BACE1. However, the inhibitors **214**, **218**, **219** and **221** contain very structurally-diverse scaffolds, and the non-inhibitors **226**, **217**, **220** and **222** have very similar structures to the inhibitors, respectively. Consequently, it can be stated that there was not any structure-activity relationship observed.

It was observed that compounds **218** and **221** were less potent than the reference compound **214**. It has been previously reported that in these type of compounds, secondary amides can be more potent than tertiary amides due to an extra hydrogen bond donor interaction in the active site of BACE1 (Figure 43, panel B).[192] Consequently, the methylation of the amide on this class of compounds has previously shown a 70-fold lost in potency.[192] However, the tertiary amides **218** and **221** do not show such a high decrease in potency compared to the reference compound **214**. This could be because they might have different additional interactions in the active site of BACE1 with their aromatic rings. Therefore, compound **217**, which is almost an analogue of **218** without the aromatic ring, did not show inhibition at high concentrations (Figure 46). In addition, compounds **218** and **221** also have lower CNS Lead MPO score than the control **214**. Due to the lack in improved potency and lower CNS

Lead MPO score, compounds **218** and **221** would not be better starting points for optimisation than the reference **214**. Nevertheless, other tertiary amides containing aromatic rings could be developed as another class of BACE1 inhibitors (Figure 48).

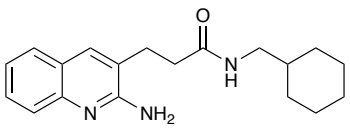


237

Figure 48: General idea of tertiary amides that could be developed for BACE1 inhibition.

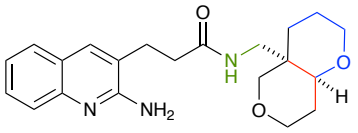
However, compound **219** has similar potency and similar CNS Lead MPO score than the reported compound **214**. Consequently, the highly lipophilic cyclohexyl ring of compound **214** could be changed for a more polar heterocyclic system, keeping the potency and the CNS-compliance. This would allow the active lead **219** to be further developed to improve the potency as it was done with compound **214** (Figure 43, panel A). The comparison of the Pfizer's CNS MPO scores of the possible optimisation products of **214** (**213**, **238** and **239**) and **219** (**240**, **241** and **242**) shows that both can yield compounds that could have desirable properties for brain penetration (Pfizer's CNS MPO scores ≥3.00) (Figure 49). However, the optimisation products from compound **219** could be more promising because they do not contain a highly lipophilic moiety.

A



214

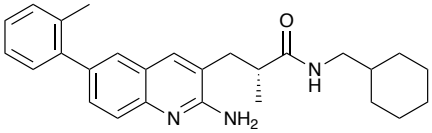
CNS Lead MPO
score = 3.71



219

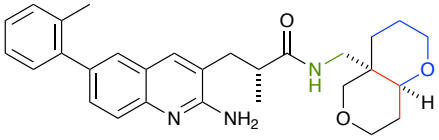
CNS Lead MPO
score = 3.63

B



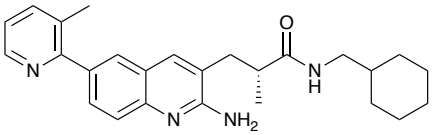
213

Pfizer's CNS MPO
score = 3.10



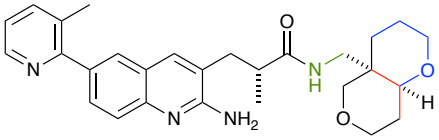
240

Pfizer's CNS
MPO score = 3.00



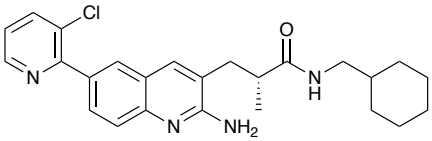
238

Pfizer's CNS
MPO score = 3.10



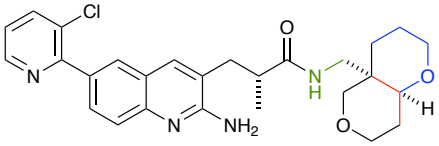
241

Pfizer's CNS
MPO score = 3.34



239

Pfizer's CNS
MPO score = 2.95



242

Pfizer's CNS
MPO score = 3.10

Figure 49: Panel A: Structures of the BACE1 inhibitors **214** and **219** and their CNS Lead MPO scores. **Panel B:** Possible future optimisations of the lead molecules **214** and **219** to give optimised compounds, which could have higher potency and be CNS-compliant. Compound **213** has been already reported (Figure 43, panel A). The idea for these optimisations has been obtained from a reference.[192]

Chapter 5: Methods & Materials

5.1. Design of the Computational Tool

Two different softwares were used to build the computational tool. These softwares were Accelrys Pipeline Pilot version 8.5 (Pipeline Pilot v8.5.0.200, Accelrys® Software Inc., 2011) and ChemAxon version 15.3.30.0. Pipeline Pilot was used to create a workflow to decorate each virtual scaffold in a derived library of compounds, to filter the derived library, to score the derived compounds using the CNS Lead MPO or Pfizer's CNS MPO scoring systems, to calculate the mean CNS Lead MPO score per scaffold, and to assess the novelty of the scaffolds. ChemAxon was used to calculate the six physicochemical properties of the derived library of compounds. In addition, two other different softwares were used to analyse the data and to plot the results. These softwares were Dotmatics Vortex (Vortex v2013.12.25046) and OriginPro 9.1.0.

5.2. Synthesis and Decoration of the Scaffolds

5.2.1. General Experimental

Commercially available starting materials were obtained from Sigma−Aldrich, Acros, Fluorochem and Alfa Aesar. Ligands **91** and *dbcot* were synthesised according to literature procedures.[138,197] All non-aqueous reactions were performed under nitrogen atmosphere unless otherwise stated. Water-sensitive reactions were performed in anhydrous solvents in oven-dried glassware cooled under nitrogen before use. Anhydrous dichloromethane, anhydrous tetrahydrofuran, anhydrous toluene, anhydrous diethyl ether, anhydrous ethanol, anhydrous methanol and anhydrous acetonitrile were obtained from a PureSolv MD5 Purification System. Anhydrous dimethyl sulfoxide and anhydrous 1,4-dioxane were obtained from SureSeal bottles from Sigma−Aldrich. All other solvents used were of chromatography or analytical grade. Petrol refers to petroleum spirit (b.p. 40–60 °C). An IKA RV 10 rotary evaporator was used to remove the solvents under reduced pressure.

Thin layer chromatography was performed using aluminium backed silica (Merck silica gel 60 F254) plates obtained from Merck. Ultraviolet lamp (λ_{max} = 254 nm) and $KMnO_4$ were used for visualization. Flash column chromatography

was performed using silica gel 60 (35–70 μm particles) supplied by Merck. Strong cation exchange solid phase extraction (SCX-SPE) was performed using pre-packed Discovery DSC-SCX cartridges supplied by Supleco. Optical rotation measurements were performed at the sodium D-line (589 nm) on a Schmidt and Haensch H532. They are given in 10^{-1} deg cm^2g^{-1}. Chiral HPLC was performed on an Agilent Infinity 1290 series HPLC system. Racemic standards were prepared by obtaining samples of both enantiomers and combining them in an approximated 50:50 ratio. Perkin-Elmer One FT-IR spectrometer was used to analyse the infrared spectra. Absorptions are reported in wavenumbers (cm^{-1}). Melting points (m.p.) were determined using Stuart melting point apparatus SMP3.

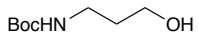
An Agilent 1200 series liquid chromatography system comprising a Bruker HCT Ultra ion trap mass spectrometer, a high vacuum degasser, a binary pump, a high performance autosampler and a micro well plate autosampler, an autosampler thermostat, a thermostated column compartment and a diode array detector was used for low-resolution mass spectrometry. The system used a Phenomenex Luna C18 50 x 2 mm 5 micron column with two solvent systems: MeCN/H_2O + 0.1% formic acid or MeCN/H_2O. A Bruker Daltonics micrOTOF spectrometer with electrospray (ES) ionisation source was used for high-resolution mass spectrometry (HRMS). X-ray measurements were carried out at 120 K on an Agilent SuperNova diffractometer equipped with an Atlas CCD detector and connected to an Oxford Cryostream low temperature device using mirror monochromated Cu Kα radiation (λ = 1.54184 Å) from a Microfocus X-ray source. The structure was solved by intrinsic phasing using SHELXT[198] and refined by a full matrix least squares technique based on F^2 using SHELXL2014.[199]

Proton (^1H) and carbon (^{13}C) NMR data was collected on a Bruker 300, 400 or 500 MHz spectrometer. Data was collected at 300 K unless otherwise stated. Chemical shifts (δ) are given in parts per million (ppm) and they are referenced to the residual solvent peak. Coupling constants (*J*) are reported in Hertz (Hz) and splitting patterns are reported in an abbreviated manner: app. (apparent), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). Assignments were made using COSY, DEPT, HMQC and NOESY experiments.

5.2.2. Experimental for the Lead-Oriented Synthesis Approach Based on an Ir-catalysed Connective Reaction

5.2.2.1. Preparation of Building Blocks

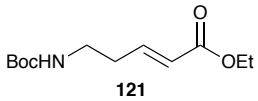
tert-Butyl *N*-(3-hydroxypropyl)carbamate



120

According to an existing procedure,[134] the amine derivative **119** (10.3 g, 137 mmol) was added dropwise to di-*tert*-butyl dicarbonate (29.8 g, 137 mmol) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 21 h. Water (50 mL) and EtOAc (50 mL) were added and the aqueous layer was extracted with EtOAc (3 × 50 mL). The organic layers were combined, washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the carbamate derivative **120**[134] (24.3 g, >99%) as a colourless oil, R_f 0.31 (30:70 petrol−EtOAc); ν_{max}/cm^{-1} 3339, 2975, 2932, 2874, 1681, 1515, 1365, 1274, 1250, 1165; δ_H (500 MHz, $CDCl_3$) 4.78 (1H, br. s, NH), 3.65 (2H, t, *J* 5.7, 3-H_2), 3.27 (2H, t, *J* 6.2, 1-H_2), 2.70 (1H, br. s, OH), 1.66 (2H, app. p, *J* 5.9 2-H_2), 1.44 (9H, s, ^{t}Bu); *m/z* (ES) 198.0 (100%, MNa^+).

Ethyl (2*E*)-5-{[(*tert*-butoxy)carbonyl]amino}pent-2-enoate

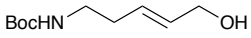


121

According to an existing procedure,[134] triethylamine (116 mL, 830 mmol), DMSO (108 mL, 1.52 mol) and SO_3•Pyr (66.1 g, 415 mmol) were added to a solution of the carbamate **120** (24.3 g, 138 mmol) in DCM (300 mL) at 0 °C. The mixture was stirred for 10 min, warmed to room temperature and stirred for 1 h. Subsequently, the mixture was cooled to 0 °C and carbethoxymethylene triphenylphosphorane (72.3 g, 208 mmol) was added. The reaction mixture was stirred for 20 min, allowed to warm to room temperature, stirred overnight, cooled to 0 °C and acidified to pH 3 by addition of an aqueous solution of 3.0 M HCl (300 mL). The organic layer was separated and the aqueous layer was extracted with DCM (2 × 100 ml). The organic layers were combined and

washed with an aqueous solution of 1.0 M HCl (100 mL), with a saturated aqueous solution of $NaHCO_3$ (100 ml) and with water (100 ml). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude product, which was purified by flash column chromatography, eluting with 80:20 petrol−EtOAc to give the α,β-unsaturated ester **121**[134] (21.0 g, 62%) as a yellow oil, R_f 0.57 (60:40 petrol−EtOAc); ν_{max}/cm^{-1} 3367, 2977, 2933, 1691, 1654, 1516, 1365, 1267, 1248, 1165; δ_H (500 MHz, $CDCl_3$) 6.89 (1H, dt, *J* 15.7 and 7.1, 3-H), 5.87 (1H, dt, *J* 15.7 and 1.5, 2-H), 4.58 (1H, br. s, NH), 4.19 (2H, q, *J* 7.1, ethyl 1-H_2), 3.37-3.15 (2H, m, 5-H_2), 2.40 (2H, app. q, *J* 6.6, 4-H_2), 1.43 (9H, s, ^{t}Bu), 1.28 (3H, t, *J* 7.1, ethyl 2-H_3); *m/z* (ES) 266.0 (100%, MNa^+).

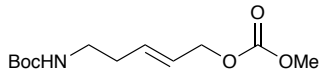
***tert*-Butyl *N*-[(3*E*)-5-hydroxypent-3-en-1-yl]carbamate**



122

According to an existing procedure,[134] diisobutylaluminium hydride (259 mL, 259 mmol of a 1.0 M solution in hexane) was added dropwise to a solution of the ester **121** (21.0 g, 86.3 mmol) in DCM (200 mL) cooled to −78 °C. The reaction mixture was stirred at −78 °C for 2 h. Subsequently, it was quenched by addition of a saturated aqueous solution of NH_4Cl (150 mL) dropwise, warmed to room temperature and stirred for 18 h. The solution was filtered through a celite pad and concentrated under reduced pressure to give a crude product. The crude product was dissolved in DCM (200 mL), washed with brine (200 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the alcohol **122**[134] (16.6 g, 96%) as a yellow oil, R_f 0.18 (60:40 petrol-EtOAc); ν_{max}/cm^{-1} 3328, 2975, 2930, 2868, 1684, 1518, 1391, 1364, 1249, 1165; δ_H (500 MHz, $CDCl_3$) 5.71 (1H, dt, *J* 15.4 and 5.6, 4-H), 5.64 (1H, dt, *J* 15.4 and 5.6, 3-H), 4.58 (1H, br. s, NH), 4.10 (2H, dd, *J* 5.4 and 1.1, 5-H_2), 3.21-3.14 (2H, m, 1-H_2), 2.23 (2H, app. q, *J* 6.5, 2-H_2), 1.66 (1H, br. s, OH) 1.43 (9H, s, ^{t}Bu); *m/z* (ES) 224.3 (100%, MNa^+).

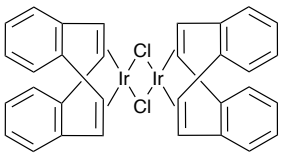
2-({[(3*E*)-5-[(Methoxycarbonyl)oxy]pent-3-en-1-yl]carbamoyl}oxy)-2-methyl propane



88

According to an existing procedure,[134] pyridine (7.32 mL, 90.5 mmol) and methyl chloroformate (7.00 mL, 90.5 mmol) were added to a solution of the alcohol **122** (16.6 g, 82.3 mmol) in DCM (165 mL) cooled to 0 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight. Afterwards, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (150 mL). The aqueous layer was separated and washed with DCM (2 × 100 mL). The organic layers were combined, washed with water (100 mL), washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography, eluting with 80:20 petrol−EtOAc to give the allylic carbonate **88**[134] (18.4 g, 86%) as a colourless oil, R_f 0.36 (80:20 petrol−EtOAc); ν_{max}/cm^{-1} 3366, 2975, 1746, 1692, 1513, 1442, 1365, 1249, 1165; δ_H (500 MHz, $CDCl_3$) 5.75 (1H, dt, *J* 15.4 and 6.5, 4-H), 5.65 (1H, dtt, *J* 15.4, 6.5 and 1.1, 3-H), 4.57 (2H, dd, *J* 6.5 and 1.1, 5-H_2), 4.55 (1H, br. s, NH), 3.77 (3H, s, OMe 1-H_3), 3.21-3.14 (2H, m, 1-H_2), 2.24 (2H, app. q, *J* 6.7, 2-H_2), 1.43 (9H, s, ^{t}Bu); *m/z* (ES) 282.0 (100%, MNa^+).

Chloro(dibenzo[a,e]cyclooctatetraene)iridium(I) dimer



92

According to an existing procedure,[134] a solution of *dbcot* (0.35 g, 1.72 mmol) in DCM (10.0 mL) was added dropwise over 40 min to a solution of bis(1,5-cyclooctadiene)diiridium(I)dichloride (0.59 g, 0.88 mmol) in DCM (10.0 mL). The reaction mixture was stirred for 20 min, cooled to 0 °C and filtered. The precipitate was washed with cold cyclohexane and dried under reduced pressure to give the Ir-catalyst **92**[200] (0.46 g, 61%) as a bright yellow solid, δ_H

(500 MHz, $CDCl_3$) 6.99 (8H, dd, *J* 5.7 and 3.2, dbcot 1,4,7,10-H_8), 6.85 (8H, dd, *J* 5.7 and 3.2, dbcot 2,3,8,9-H_8), 5.33 (8H, s, dbcot 5,6,11,12-H_8).

5.2.2.2. Connective Reactions

General Procedure A

According to an existing procedure,[116] *n*$BuNH_2$ (0.04 eq) was added to a solution of the Ir-catalyst **92** (0.02 eq) and the chiral phosphoramidite **91** (0.04 eq) in DMSO (concentration of **92** 20.0 mM). The mixture was stirred and heated to 60 °C for 30 min (the mixture changes in colour from orange to yellow). A solution of the allylic carbonate **88** (1.00 eq) and the desired amine (1.30 eq) in DMSO (concentration of **88** 2.00 M) was added and the resulting reaction mixture was stirred for 18 h at 60 °C. Afterwards, it was loaded into a SCX pad, eluting with MeOH and with a solution of saturated NH_3 in MeOH. The fraction containing the saturated solution of NH_3 in MeOH was collected and concentrated under reduced pressure to yield a crude material.

General Procedure B

The specified amount of TFA was added dropwise to a solution of the protected amine (1.00 eq) in DCM (0.10 M) under air atmosphere. The mixture was stirred at room temperature for 18 h. Subsequently, the solvent and TFA were removed under reduced pressure to give a TFA salt.

General Procedure C

According to an exissting procedure,[139] (2*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl chloride (1.90 eq) was added to a solution of triethylamine (5.00 eq) and the selected amine as TFA salt (1.00 eq) in DCM (concentration of the selected amine 55.0 mM) at 0 °C. The reaction mixture was stirred for 4 h at room temperature. Subsequently, DCM (53 mL for each 1.00 mmol of the amine) and water (18 mL for each 1.00 mmol of the amine) were added. The organic layer was separated and the aqueous layer was washed with DCM (3 × (53 mL for each 1.00 mmol of the amine)). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a mixture of two diastereomers.

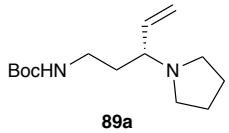
General Procedure D

According to an existing procedure,[201] triethylamine (1.20 eq), DMAP (0.60 eq) and *tert*-butyl(chloro)diphenylsilane (1.20 eq) were added to a solution of the alkene derivative (1.00 eq) in DCM (51.2 mM). The reaction mixture was stirred for 18 h at 40 °C. Subsequently, the reaction was allowed to cool to room temperature and water (7 mL for each 1.00 mmol of the alkene) and ether (22 mL for each 1.00 mmol of the alkene) were added. The organic phase was separated and washed with water (7 mL for each 1.00 mmol of the alkene) and brine (7 mL for each 1.00 mmol of the alkene). Afterwards, it was dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material.

General Procedure E

According to an existing procedure,[116] triethylamine (2.00 eq) and benzoyl chloride (1.30 eq) were added to a solution of the silyl derivative (1.00 eq) in DCM (0.10 M) at 0 °C. The reaction mixture was allowed to warm to room temperature and it was stirred for 18 h. Afterwards, it was quenched with a saturated aqueous solution of NH_4Cl (16 mL for each 1.00 mmol of silyl). The organic phase was separated and the aqueous phase was extracted with DCM (3 × (16 mL for each 1.00 mmol of silyl)). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material.

***tert*-Butyl *N*-[(3*R*)-3-(pyrrolidin-1-yl)pent-4-en-1-yl]carbamate**

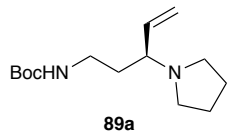


89a

According to General Procedure A, the allylic carbonate **88** (2.50 g, 9.64 mmol), (*S,S,*a*S*)-**91** (0.21 g, 0.39 mmol) and pyrrolidine (1.04 mL, 12.53 mmol) gave a crude material. The crude material (*terminal*:*internal alkenes* 85:15 by ^{1}H-NMR) was purified by flash column chromatography, eluting with 92.4:6.8:0.8 DCM−EtOH−NH_4OH to give the *alkene* ***89a*** (1.45 g, 59%, 67% *ee*) as a yellow oil, R_f 0.13 (92.4:6.8:0.8 DCM−EtOH−NH_4OH); [α_D^{26}] −3.00 (*c* 1.00, $CHCl_3$);

ν_{max}/cm^{-1} 3349, 2966, 2930, 2874, 2788, 1691, 1513, 1364, 1247, 1169; δ_H (500 MHz, $CDCl_3$) 5.75 (1H, ddd, *J* 16.7, 10.7 and 9.0, 4-H), 5.14 (1H, dd *J* 10.7 and 1.7, 5-H_{cis}), 5.13 (1H, dd, *J* 16.7 and 1.7, 5-H_{trans}), 5.01 (1H br. NH), 3.25-3.15 (1H, m, 1-H_A), 3.15-3.07 (1H, m, 1-H_B), 2.77 (1H, app. td, *J* 8.6 and 4.6, 3-H), 2.61-2.49 (4H, m, pyrrolidinyl 2,5-H_4), 1.91-1.81 (1H, m, 2-H_A), 1.78-1.73 (4H, m, pyrrolidinyl 3,4-H_4), 1.65 (1H, app. td, *J* 14.0 and 7.2, 2-H_B), 1.43 (9H, s, ^{t}Bu); δ_C (75 MHz, $CDCl_3$) 156.1 (C=O), 138.7 (C-4), 117.3 (C-5), 79.1 (^{t}Bu C_1), 66.7 (C-3), 51.4 (pyrrolidinyl C_2-2,5), 38.2 (C-1), 33.7 (C-2), 28.6 (^{t}Bu C_3), 23.4 (pyrrolidinyl C_2-3,4); HRMS found MH^+, 255.2075. $C_{14}H_{26}N_2O_2$ requires *MH*, 255.2067. The absolute configuration was determined by comparison with analogues.[116]

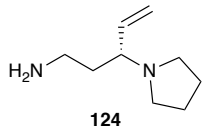
tert-Butyl _N_-[(3_S_)-3-(pyrrolidin-1-yl)pent-4-en-1-yl]carbamate



89a

According to General Procedure A, the allylic carbonate **88** (0.25 g, 0.96 mmol), (*R,R,*a*R*)-**91** (20.0 mg, 38.0 μmol) and pyrrolidine (0.10 mL, 1.25 mmol) gave a crude material. The crude material (*terminal*:*internal alkenes* 85:15 by ^{1}H-NMR) was purified by flash column chromatography, eluting with 92.4:6.8:0.8 DCM−EtOH−NH_4OH to give the *alkene* ***89a*** (90.0 mg, 37%, 67% *ee*) as a yellow oil, [α_D^{24}] +1.25 (*c* 1.20, $CHCl_3$); spectroscopically identical to the enantiomer previously prepared. The absolute configuration was determined by comparison with analogues.[116]

(3_R_)-3-(Pyrrolidin-1-yl)pent-4-en-1-amine



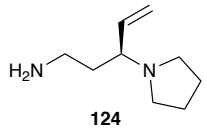
124

According to General Procedure B, TFA (0.50 mL, 6.53 mmol) and the protected amine **89a** (15.0 mg, 58.0 μmol) gave the TFA salt of the *amine* ***124***

(21.8 mg, 96%) as an amorphous brown solid, R_f 0.34 (65.0:30.0:5.0 DCM−EtOH−NH_4OH); [α_D^{23}] +0.94 (*c* 0.73, MeOH); ν_{max}/cm^{-1} 3397, 2965, 1666, 1426, 1175, 1124; δ_H (500 MHz, CD_3OD) 5.86 (1H, ddd, *J* 17.0, 10.3 and 9.4, 4-H), 5.66 (1H, dd, *J* 10.3 and 0.8, 5-H_{cis}), 5.64 (1H, dd, *J* 17.0 and 0.8, 5-H_{trans}), 3.85 (1H, ddd, *J* 11.1, 9.4 and 3.5, 3-H), 3.72-3.62 (1H, m, pyrrolidinyl 2-H_A), 3.56-3.45 (1H, m, pyrrolidinyl 5-H_A), 3.26-3.03 (2H, m, pyrrolidinyl 2-H_B and pyrrolidinyl 5-H_B), 2.94 (2H, app. t, *J* 8.0, 1-H_2), 2.35-2.26 (1H, m, 2-H_A), 2.16-2.00 (5H, m, 2-H_B and pyrrolidinyl 3,4-H_4); δ_C (125 MHz, CD_3OD) 162.9 (app. m, TFA C=O), 131.3 (C-4), 126.8 (C-5), 118.2 (app d, *J* 300.0, TFA CF_3,), 66.6 (C-3), 53.1 (pyrrolidinyl C_2-2,5), 37.4 (C-1), 29.8 (C-2), 24.0 (pyrrolidinyl C_2-3,4); HRMS found MH^+, 155.1538. $C_9H_{18}N_2$ requires *MH*, 155.1542.

Determination of the ee: According to General Procedure C, the TFA salt of the amine **124** (19.0 mg, 49.7 μmol) gave a mixture of two diastereomers in a 83.3:16.7 ratio. δ_H (500 MHz, C_6D_6) 4.87 (major) and 4.80 (minor).

(3*S*)-3-(Pyrrolidin-1-yl)pent-4-en-1-amine

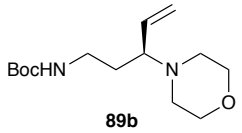


124

According to General Procedure B, TFA (0.50 mL, 6.53 mmol) and the protected amine **89a** (15.0 mg, 60.0 μmol) gave the TFA salt of the *amine **124*** (22.5 mg, >99%) as an amorphous brown solid, [α_D^{24}] −0.06 (*c* 0.70, MeOH); spectroscopically identical to the enantiomer previously prepared.

Determination of the ee: According to General Procedure C, the TFA salt of the amine **124** (22.5 mg, 59.0 μmol) gave a mixture of two diastereomers in a 83.3:16.7 ratio. δ_H (500 MHz, C_6D_6) 4.89 (minor) and 4.83 (major).

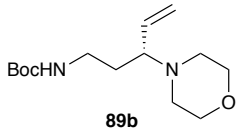
***tert*-Butyl *N*-[(3*S*)-3-(morpholin-4-yl)pent-4-en-1-yl]carbamate**



89b

According to General Procedure A, the allylic carbonate **88** (2.72 g, 10.5 mmol), (*R,R,a*R)-**91** (0.23 g, 0.42 mmol) and morpholine (1.20 mL, 13.7 mmol) gave a crude material. The crude material (*terminal*:*internal alkenes* 83:17 by ^{1}H-NMR) was purified by flash column chromatography, eluting with EtOAc to give the *alkene **89b*** (1.80 g, 63%, 86% *ee*) as a brown oil, R_f 0.28 (EtOAc); [α_D^{23}] +16.0 (*c* 1.00, $CHCl_3$); ν_{max}/cm^{-1} 3343, 2972, 2930, 2853, 2813, 1693, 1514, 1167, 1114; δ_H (300 MHz, $CDCl_3$) 5.69 (1H, ddd, *J* 17.1, 10.3 and 8.8, 4-H), 5.31 (1H, br. s, NH), 5.18 (1H, dd, *J* 10.3 and 1.5, 5-H_{cis}), 5.08 (1H, dd, *J* 17.1 and 1.5, 5-H_{trans}), 3.71-3.61 (4H, m, morpholinyl 2,6-H_4), 3.22 (1H, app. td, *J* 11.7 and 6.1, 1-H_A), 3.08 (1H, app. td, *J* 13.3 and 6.8, 1-H_B), 2.82 (1H, app. q, *J* 6.9, 3-H), 2.55 (2H, app. dt, *J* 11.2 and 4.7, morpholinyl 3-H_A and morpholinyl 5-H_A), 2.40 (2H, app. dt, *J* 11.2 and 4.7, morpholinyl 3-H_B and morpholinyl 5-H_B), 1.89-1.70 (1H, m, 2-H_A), 1.66-1.50 (1H, m, 2-H_B), 1.40 (9H, s, ^{t}Bu); δ_C (75 MHz, $CDCl_3$) 156.0 (C=O), 136.2 (C-4), 118.3 (C-5), 78.9 (^{t}Bu C_1), 67.4 (C-3), 67.3 (morpholinyl C_2-2,6), 50.0 (morpholinyl C_2-3,5), 38.6 (C-1), 31.0 (C-2), 28.5 (^{t}Bu C_3); HRMS found MH$^+$, 271.2019. $C_{14}H_{26}N_2O_3$ requires *MH*, 271.2016; chiral HPLC: OD-H, 5.0:95.0 isopropyl alcohol–hexane over 60 min, 1.0 mL/min; t_1 = 8.81 min (minor), t_2 = 9.56 min (major). The absolute configuration was determined by comparison with analogues.[116]

***tert*-Butyl *N*-[(3*R*)-3-(morpholin-4-yl)pent-4-en-1-yl]carbamate**

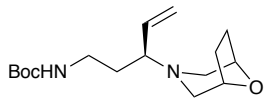


89b

According to General Procedure A, the allylic carbonate **88** (0.25 g, 0.96 mmol), (*S,S,a*S)-**91** (20.0 mg, 37.0 μmol) and morpholine (0.11 mL, 1.25 mmol) gave a crude material. The crude material (*terminal*:*internal alkenes* 83:17 by ^{1}H-NMR)

was purified by flash column chromatography, eluting with EtOAc to give the *alkene* ***89b*** (0.15 g, 57%, 86% *ee*) as a brown oil, [α_D^{24}] −14.0 (*c* 1.00, $CHCl_3$); spectroscopically identical to the enantiomer previously prepared; chiral HPLC: OD-H, 5.0:95.0 isopropyl alcohol–hexane over 60 min, 1.0 mL/min; t_1 = 8.79 min (major), t_2 = 9.65 min (minor). The absolute configuration was determined by comparison with analogues.[116]

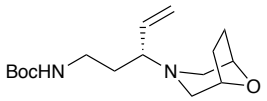
tert-Butyl _N_-[(3_S_)-3-{8-oxa-3-azabicyclo[3.2.1]octan-3-yl}pent-4-en-1-yl] carbamate



89c

According to General Procedure A, the allylic carbonate **88** (0.88 g, 3.40 mmol), (*R,R,*a*R*)-**91** (73.4 mg, 136 μmol) and 8-oxa-3-azabicyclo[3.2.1]octane (0.50 g, 4.42 mmol) gave a crude material. The crude material (*terminal*:*internal alkenes* 71:29 by ^{1}H-NMR) was purified by flash column chromatography, eluting with 30:70 EtOAc−petrol to give the *alkene* ***89c*** (0.63 g, 63%, 83% *ee*) as a yellow-brown oil, R_f 0.28 (30:70 EtOAc−petrol); [α_D^{23}] +9.80 (*c* 1.00, $CHCl_3$); ν_{max}/cm^{-1} 3340, 2973, 2949, 2811, 1693, 1512, 1167; δ_H (500 MHz, $CDCl_3$) 5.73 (1H, app. dt, *J* 18.0 and 9.5, 4-H), 5.64 (1H, br. s, NH), 5.17 (1H, dd, *J* 10.3 and 0.9, 5-H_{cis}), 5.07 (1H, app. d, *J* 17.3, 5-H_{trans}), 4.28 (2H, app. br. s, bicyclooctanyl 1,5-H_2), 3.32-3.22 (1H, m, 1-H_A), 3.16 (1H, app. td, *J* 12.9 and 6.9, 1-H_B), 2.82 (1H, app. td, *J* 8.0 and 5.9, 3-H), 2.61 (1H, dd, *J* 10.9 and 0.9, bicyclooctanyl 2,4-H_A), 2.56 (1H, app. d, *J* 10.9, bicyclooctanyl 2,4-H_B), 2.45 (1H, dd, *J* 10.9 and 0.4, bicyclooctanyl 2,4-H_C), 2.40 (1H, dd, *J* 10.9 and 1.2, bicyclooctanyl 2,4-H_D), 2.00-1.90 (2H, m, bicyclooctanyl 6-H_A and bicyclooctanyl 7-H_A), 1.90-1.80 (2H, m, bicyclooctanyl 6-H_B and bicyclooctanyl 7-H_B), 1.75 (1H, app. td, *J* 14.4 and 7.4, 2-H_A), 1.60-1.54 (1H, m, 2-H_B), 1.44 (9H, s, ^{t}Bu); δ_C (75 MHz, $CDCl_3$) 156.1 (C=O), 136.2 (C-4), 117.8 (C-5), 78.9 (^{t}Bu C_1), 74.8 (bicyclooctanyl C_2-1,5), 66.5 (C-3), 56.9 (bicyclooctanyl C_A-2,4), 52.2 (bicyclooctanyl C_B-2,4), 38.9 (C-1), 30.2 (C-2), 28.5 (^{t}Bu C_3), 27.0 (bicyclooctanyl C_2-6,7); HRMS found MH$^+$, 297.2178. $C_{16}H_{28}N_2O_3$ requires *MH*, 297.2172. The absolute configuration was determined by comparison with analogues.[116]

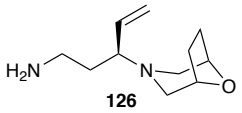
***tert*-Butyl *N*-[(3*R*)-3-{8-oxa-3-azabicyclo[3.2.1]octan-3-yl}pent-4-en-1-yl] carbamate**



89c

According to General Procedure A, the allylic carbonate **88** (0.25 g, 0.96 mmol), (*S,S,*a*S*)-**91** (20.0 g, 37.0 μmol) and 8-oxa-3-azabicyclo[3.2.1]octane (0.14 g, 1.25 mmol) gave a crude material. The crude material (*terminal*:*internal alkenes* 71:29 by ^{1}H-NMR) was purified by flash column chromatography, eluting with 30:70 EtOAc−petrol to give the *alkene **89c*** (0.19 g, 66%, 83% *ee*) as a yellow-brown oil, [α_D^{24}] −8.30 (*c* 1.00, $CHCl_3$); spectroscopically identical to the enantiomer previously prepared. The absolute configuration was determined by comparison with analogues.[116]

(3*S*)-3-{8-Oxa-3-azabicyclo[3.2.1]octan-3-yl}pent-4-en-1-amine



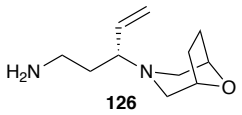
126

According to General Procedure B, TFA (0.50 mL, 6.53 mmol) and the protected amine **89c** (15.0 mg, 50.6 μmol) gave the TFA salt of the *amine **126*** (21.0 mg, 98%) as an amorphous brown solid, R_f 0.13 (84.7:13.6:1.7 DCM−EtOH−NH_4OH); [α_D^{23}] −0.92 (*c* 0.52, MeOH); ν_{max}/cm^{-1} 3392, 2971, 1666, 1426, 1176, 1124; δ_H (500 MHz, CD_3OD) 5.85 (1H, app. dt, *J* 16.9 and 10.0, 4-H), 5.71 (1H, dd, *J* 10.3 and 1.2, 5-H_{cis}), 5.62 (1H, dd, *J* 16.9 and 1.2, 5-H_{trans}), 4.53 (2H, app. s, bicyclooctanyl 1,5-H_2), 3.78 (1H, ddd, *J* 11.3, 9.6 and 3.3, 3-H), 3.42 (1H, app. d, *J* 12.3, bicyclooctanyl 2,4-H_A), 3.34 (1H, app. d, *J* 12.6, bicyclooctanyl 2,4-H_B), 3.23 (1H, dd, *J* 12.4 and 2.9, bicyclooctanyl 2,4-H_C), 3.14 (1H, dd, *J* 12.4 and 2.9, bicyclooctanyl 2,4-H_D), 2.95-2.83 (2H, m, 1-H_2), 2.45-2.28 (1H, m, 2-H_A), 2.17-1.99 (5H, m, 2-H_B and bicyclooctanyl 6,7-H_4); δ_H (125 MHz, CD_3OD) 163.2-161.6 (app m, TFA C=O,), 130.6 (C-4), 127.5 (C-5), 118.0 (app d, *J* 293.5, TFA CF_3), 116.8 (q, *J* 289.3, TFA CF_3), 73.9 (bicyclooctanyl C_2-1,5), 69.6 (C-3), 56.4 (bicyclooctanyl C_A-2,4), 55.0 (bicyclooctanyl C_B-2,4), 37.7 (C-1), 27.9 (C-2), 27.5 (bicyclooctanyl C_A-6,7),

27.4 (bicyclooctanyl C_B-6,7); HRMS found MH^+, 197.1642. $C_{11}H_{20}N_2O$ requires *MH*, 197.1648.

Determination of the ee: According to General Procedure C, the TFA salt of the amine **126** (23.1 mg, 54.5 μmol) gave a mixture of two diastereomers in a 91.7:8.3 ratio. δ_H (500 MHz, C_6D_6) 7.73 (major) and 7.70 (minor).

(3*R*)-3-{8-Oxa-3-azabicyclo[3.2.1]octan-3-yl}pent-4-en-1-amine

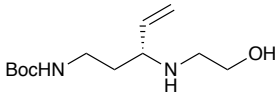


126

According to General Procedure B, TFA (0.50 mL, 6.53 mmol) and the protected amine **89c** (15.0 mg, 50.6 μmol) gave the TFA salt of the *amine **126*** (22.2 mg, >99%) as an amorphous brown solid, [α_D^{23}] +2.22 (*c* 0.81, MeOH); spectroscopically identical to the enantiomer previously prepared.

Determination of the ee: According to General Procedure C, the TFA salt of the amine **126** (22.0 mg, 51.8 μmol) gave a mixture of two diastereomers in a 91.7:8.3 ratio. δ_H (500 MHz, C_6D_6) 7.73 (minor) and 7.70 (major).

***tert*-Butyl *N*-[(3*R*)-3-[(2-hydroxyethyl)amino]pent-4-en-1-yl]carbamate**

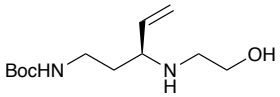


89d

According to General Procedure A, the allylic carbonate **88** (3.00 g, 11.6 mmol), (*S,S,*a*S*)-**91** (0.25 g, 0.46 mmol) and 2-aminoethan-1-ol (0.91 mL, 15.0 mmol) gave a crude material. The crude material (*terminal*:*internal alkenes* >95:<5 by ^{1}H-NMR) was purified by flash column chromatography, eluting with 90.8:8.2:1.0 DCM−EtOH−NH_4OH to give the *alkene **89d*** (1.70 g, 60%, 85% *ee*) as an amorphous white solid, R_f 0.18 (90.8:8.2:1.0 DCM−EtOH−NH_4OH); [α_D^{26}] −8.40 (*c* 1.00, $CHCl_3$); ν_{max}/cm^{-1} 3368, 3267, 3071, 3014, 2975, 2933, 2840, 1681, 1523, 1366, 1165, 1053; δ_H (500 MHz, $CDCl_3$) 5.61 (1H, ddd, *J* 17.0, 10.0

and 8.1, 4-H), 5.14 (1H, dd, *J* 10.0 and 1.3, 5-H_{cis}), 5.12 (1H, dd, *J* 17.0 and 1.3, 5-H_{trans}), 4.90 (1H, br. s, NH), 3.65 (1H, ddd, *J* 10.8, 7.1 and 3.6, hydroxyethyl 2-H_A), 3.59 (1H, ddd, *J* 10.8, 6.0 and 3.8, hydroxyethyl 2-H_B), 3.38-3.23 (1H, m, 1-H_A), 3.15 (1H, m, 1-H_B), 3.09 (1H, app. q, *J* 7.1, 3-H), 2.82 (1H, ddd, *J* 12.5, 7.1 and 3.8, hydroxyethyl 1-H_A), 2.65 (1H, ddd, *J* 12.5, 6.0 and 3.6, hydroxyethyl 1-H_B), 2.01 (1H, br. s, OH), 1.64 (2H, app. ddt, *J* 16.0, 13.7 and 6.9, 2-H_2), 1.44 (9H, s, ^{t}Bu); δ_C (75 MHz, $CDCl_3$) 156.2 (C=O), 140.2 (C-4), 116.5 (C-5), 79.2 (^{t}Bu C_1), 60.8 (hydroxyethyl C-2), 59.3 (C-3), 48.7 (hydroxyethyl C-1), 37.6 (C-1), 35.6 (C-2), 28.4 (^{t}Bu C_3); HRMS found MH^+, 245.1862. $C_{12}H_{24}N_2O_3$ requires *MH*, 245.1859. The absolute configuration was determined by comparison with analogues.[116]

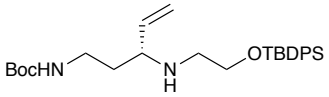
tert-Butyl _N_-[(3_S_)-3-[(2-hydroxyethyl)amino]pent-4-en-1-yl]carbamate



89d

According to General Procedure A, the allylic carbonate **88** (0.25 g, 0.96 mmol), (*R,R,*a*R*)-**91** (20.0 mg, 37.0 μmol) and 2-aminoethan-1-ol (75.6 μL, 1.25 mmol) gave a crude material. The crude material (*terminal*:*internal alkenes* >95:<5 by ^{1}H-NMR) was purified by flash column chromatography, eluting with 90.8:8.2:1.0 DCM−EtOH−NH_4OH to give the *alkene* ***89d*** (90.0 mg, 38%, 85% *ee*) as an amorphous white solid, [α_D^{24}] +9.65 (*c* 0.64, $CHCl_3$); spectroscopically identical to the enantiomer previously prepared. The absolute configuration was determined by comparison with analogues.[116]

tert-Butyl _N_-[(3_R_)-3-({2-[(_tert_-butyldiphenylsilyl)oxy]ethyl}amino)pent-4-en-1-yl]carbamate

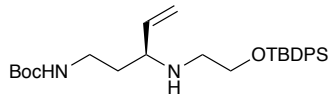


128

According to General Procedure D, the alkene **89d** (0.11 g, 0.45 mmol) gave a crude material. The crude material was purified by flash column

chromatography, eluting with 30:70 EtOAc−petrol to give the silyl derivative **128**[116] (0.17 g, 78%) as a yellow oil, R_f 0.19 (50:50 EtOAc−petrol); [α_D^{23}] −3.40 (*c* 1.00, $CHCl_3$); ν_{max}/cm^{-1} 3346, 3071, 2929, 2856, 1703, 1589, 1427, 1364, 1248, 1169, 1109; δ_H (300 MHz, $CDCl_3$) 7.71-7.63 (4H, m, phenyl 2,6-H_4), 7.50-7.30 (6H, m, phenyl 3,4,5-H_6), 5.61 (1H, ddd, *J* 16.7, 9.8 and 7.9, 4-H), 5.12 (1H, dd, *J* 9.8 and 1.0, 5-H_{cis}), 5.10 (1H, app. d, *J* 18.0, 5-H_{trans}), 4.73 (1H, br. s, NH), 3.87-3.63 (2H, m, ethyl 2-H_2), 3.34-3.12 (2H, m, 1-H_2), 3.07 (1H, app. q, *J* 6.9, 3-H), 2.78 (1H, app. dt, *J* 11.6 and 5.3, ethyl 1-H_A), 2.61 (1H, app. dt, *J* 12.0 and 5.1, ethyl 1-H_B), 1.63 (2H, app. q, *J* 6.7, 2-H_2), 1.43 (9H, s, Boc ^{t}Bu), 1.06 (9H, s, TBDPS ^{t}Bu); δ_C (75 MHz, $CDCl_3$) 156.1 (C=O), 140.5 (C-4), 135.6 (phenyl C_4-2,6), 133.7 (phenyl C_2-1), 129.8 (phenyl C_2-4), 127.8 (phenyl C_4-3,5), 116.3 (C-5), 79.1 (Boc ^{t}Bu C_1), 63.4 (ethyl C-2), 60.1 (C-3), 48.9 (ethyl C-1), 38.1 (C-1), 35.4 (C-2), 28.6 (Boc ^{t}Bu C_3), 27.0 (TBDPS ^{t}Bu C_3), 19.3 (TBDPS ^{t}Bu C_1); HRMS found MH^+, 483.3048. $C_{28}H_{42}N_2O_3Si$ requires *MH*, 483.3037.

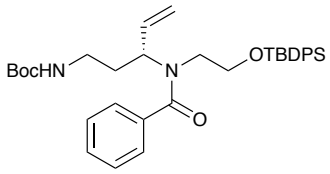
tert-Butyl *N*-[(3*S*)-3-({2-[(*tert*-butyldiphenylsilyl)oxy]ethyl}amino)pent-4-en-1-yl]carbamate



128

According to General Procedure D, the alkene **89d** (90.4 mg, 0.37 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 30:70 EtOAc−petrol to give the silyl derivative **128**[116] (0.11 g, 62%) as a yellow oil, [α_D^{21}] +4.10 (*c* 1.00, $CHCl_3$); spectroscopically identical to the enantiomer previously prepared.

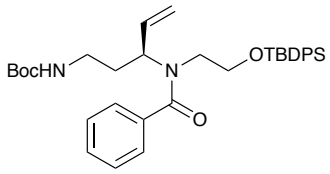
***tert*-Butyl *N*-[(3*R*)-3-(*N*-{2-[(*tert*-butyldiphenylsilyl)oxy]ethyl}-1-phenylformamido)pent-4-en-1-yl]carbamate**



129

According to General Procedure E, the silyl derivative **128** (0.15 g, 0.31 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 80:20 petrol−EtOAc to give the benzoyl derivative **129**[116] (0.18 g, 99%) as a colourless oil, R_f 0.28 (75:25 petrol−EtOAc); [α_D^{24}] +19.6 (*c* 1.00, $CHCl_3$); ν_{max}/cm^{-1} 3344, 3070, 2961, 2930, 2857, 1709, 1624, 1507, 1426, 1410, 1364, 1248, 1168, 1106; δ_H (500 MHz, CD_3OD, 333 K) 7.73-7.50 (5H, m, benzoyl-H_5), 7.47-7.27 (10H, m, TBDPS Ar-H_{10}), 6.04-5.67 (1H, m, 4-H_1), 5.14 (2H, app. dt, *J* 10.6 and 1.3, 5-H_2), 5.09 (1H, br. s, NH), 4.43-4.24 (1H, m, 3-H_1), 3.96-3.62 (2H, m, ethyl 2-H_2), 3.51 (2H, app. br. s, 1-H_2), 3.08-2.79 (2H, m, ethyl 1-H_2), 1.87-1.71 (2H, m, 2-H_2), 1.40 (9H, s, Boc ^{t}Bu), 1.04 (9H, s, TBDPS ^{t}Bu); δ_C (125 MHz, CD_3OD, 333 K) 174.8 (benzoyl C=O), 158.1 (Boc C=O), 137.7 (benzoyl C-1), 136.6 (C-4), 134.7 (TBDPS phenyl C_2-1), 130.9 (TBDPS phenyl C_2-4), 130.7 (benzoyl C-4), 129.7 (TBDPS phenyl C_4-3,5), 128.9 (benzoyl C_2-3,5), 128.8 (TBDPS phenyl C_4-2,6), 127.6 (benzoyl C_2-2,6), 118.0 (C-5), 80.2 (Boc ^{t}Bu C_1), 62.8 (ethyl C-2), 62.7 (C-3), 38.6 (C-1), 33.3 (C-2), 28.8 (Boc ^{t}Bu C_3), 27.4 (TBDPS ^{t}Bu C_3), 19.9 (TBDPS ^{t}Bu C_1), ethyl C-1 no observed; HRMS found MH^+, 587.3312. $C_{35}H_{46}N_2O_4Si$ requires *MH*, 587.3299; chiral HPLC: OD-H, 5.0:95.0 isopropyl alcohol–hexane over 60 min, 0.3 mL/min; t_1 = 32.49 min (major), t_2 = 35.96 min (minor).

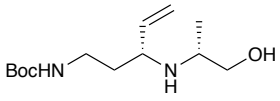
***tert*-Butyl *N*-[(3*S*)-3-(*N*-{2-[(*tert*-butyldiphenylsilyl)oxy]ethyl}-1-phenylformamido)pent-4-en-1-yl]carbamate**



129

According to General Procedure E, the silyl derivative **128** (0.11 g, 0.23 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 80:20 petrol−EtOAc to give the benzoyl derivative **129**[116] (0.12 g, 90%) as a colourless oil, [α_D^{25}] −18.7 (*c* 1.00, $CHCl_3$); spectroscopically identical to the enantiomer previously prepared; chiral HPLC: OD-H, 5.0:95.0 isopropyl alcohol–hexane over 60 min, 0.3 mL/min; t_1 = 32.71 min (minor), t_2 = 36.05 min (major).

***tert*-Butyl *N*-[(3*R*)-3-{[(2*R*)-1-hydroxypropan-2-yl]amino}pent-4-en-1-yl] carbamate**

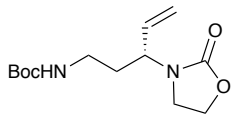


89e

According to General Procedure A, the allylic carbonate **88** (2.00 g, 7.70 mmol), (*S,S,*a*S*)-**91** (0.17 g, 0.31 mmol) and (2*R*)-2-amino-1-propanol (0.78 mL, 10.0 mmol) gave a crude material. The crude material (*terminal*:*internal alkenes* >95:<5 and *dr* 94:6 by ^{1}H-NMR) was purified by flash column chromatography, eluting with 90.8:8.2:1.0 DCM−EtOH−NH_4OH to give the alkene **89e**[116] (1.15 g, 58%, *dr* >95:<5 by ^{1}H-NMR) as an amorphous white solid, R_f 0.28 (90.8:8.2:1.0 DCM−EtOH−NH_4OH); [α_D^{25}] −10.6 (*c* 1.00, MeOH); ν_{max}/cm^{-1} 3369, 3254, 3074, 2969, 2934, 2893, 2831, 1682, 1524, 1365, 1250, 1219, 1166, 1039; δ_H (500 MHz, CD_3OD) 5.62 (1H, ddd, *J* 17.3, 10.2 and 8.6, 4-H), 5.20-5.10 (2H, m, 5-H_2), 3.47 (1H, dd, *J* 10.9 and 5.1, hydroxypropyl 1-H_A), 3.41 (1H, dd, *J* 10.9 and 5.1, hydroxypropyl 1-H_B), 3.20 (1H, app. td, *J* 8.3 and 5.5, 3-H), 3.11 (1H, app. dt, *J* 13.5 and 6.8, 1-H_A), 3.02 (1H, app. dt, *J* 13.9 and 7.2, 1-H_B), 2.83-2.76 (1H, m, hydroxypropyl 2-H), 1.68 (1H, app. td, *J* 13.1 and 7.1, 2-H_A), 1.58-1.47

(1H, m, 2-H_B), 1.43 (9H, s, ^{t}Bu), 1.05 (3H, d, *J* 6.6, hydroxypropyl 3-H_3); *m/z* (ES) 259.1 (100%, MH^+).

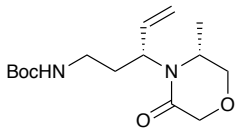
tert-Butyl _N_-[(3_R_)-3-(2-oxo-1,3-oxazolidin-3-yl)pent-4-en-1-yl]carbamate



89f

By modification of an existing procedure,[116] CDI (1.70 g, 10.4 mmol) and DBU (2.60 mL, 17.4 mmol) were added to a solution of the alkene **89d** (1.70 g, 6.95 mmol) in THF (35.0 mL). The mixture was stirred at 50 °C for 18 h and concentrated under reduced pressure. Afterwards, DCM (30 mL) and a saturated aqueous solution of NH_4Cl (30 mL) were added and the aqueous layer was extracted with DCM (3 × 30 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography, eluting with EtOAc to give the *oxazolidinone derivative* ***89f*** (1.77 g, 94%) as a yellow oil, R_f 0.48 (EtOAc); $[\alpha_D^{26}]$ +19.8 (*c* 1.00, MeOH); ν_{max}/cm^{-1} 3337, 2976, 2930, 1735, 1703, 1514, 1422, 1365, 1249, 1166; δ_H (500 MHz, $CDCl_3$) 5.79 (1H, ddd, *J* 17.0, 10.7 and 5.8, 4-H), 5.30-5.22 (2H, m, 5-H_2), 4.98 (1H, br. s, NH), 4.41 (1H, app. dt, *J* 11.0 and 5.6, 3-H), 4.38-4.30 (2H, m, oxazolidinyl 5-H_2), 3.50-3.46 (2H, m, oxazolidinyl 4-H_2), 3.40-3.29 (1H, m, 1-H_A), 2.96-2.89 (1H, m, 1-H_B), 1.92-1.73 (2H, m, 2-H_2), 1.43 (9H, s, ^{t}Bu); δ_C (125 MHz, CD_3OD) 160.6 (Boc C=O), 158.3 (oxazolidinyl C=O), 136.2 (C-4), 117.9 (C-5), 80.0 (^{t}Bu C_1), 64.0 (oxazolidinyl C-5), 54.5 (C-3), 41.7 (oxazolidinyl C-3), 38.2 (C-1), 32.2 (C-2), 28.8 (^{t}Bu C_3); HRMS found MH^+, 271.1653. $C_{13}H_{22}N_2O_4$ requires *MH*, 271.1652.

***tert*-Butyl *N*-[(3*R*)-3-[(3*R*)-3-methyl-5-oxomorpholin-4-yl]pent-4-en-1-yl] carbamate**



89g

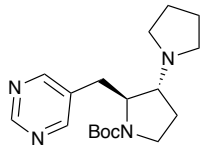
By modification of an existing procedure,[116] triethylamine (3.06 mL, 21.9 mmol) and trimethylsilyl chloride (1.89 mL, 14.9 mmol) were added to a solution of the alkene **89e** (1.15 g, 4.45 mmol) in DCM (23.0 mL) at rt. The reaction mixture was stirred for 18 h at room temperature. Afterwards, triethylamine (3.06 mL, 21.9 mmol) was added and the mixture was cooled to 0 °C. Chloroacetyl chloride (0.53 mL, 6.68 mmol) was added and the mixture was stirred at 0 °C for 15 min. Afterwards, it was allowed to warm to room temperature and stirred for 3 h. Acetic acid (2.54 mL, 44.5 mmol) and water (2.54 mL) were added and the solution was stirred for 18 h. The solvent was removed under reduced pressure. DCM (12 mL) was added and the solution was cooled to 0 °C. Subsequently, tetrabutylammonium hydrogensulfate (0.76 g, 2.23 mmol) and an aqueous solution of 35% NaOH (12 mL) were added and the solution was stirred for 3 h at room temperature. Afterwards, water (24 mL) and DCM (48 mL) were added and the aqueous layer was extracted with DCM (3 × 35 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography, eluting with 60:40 EtOAc−petrol to give the ketomorpholine derivative **89g**[116] (0.65 g, 49%) as a yellow oil, R_f 0.28 (60:40 EtOAc−petrol); $[\alpha_D^{24}]$ +49.0 (*c* 1.00, $CHCl_3$); ν_{max}/cm^{-1} 3327, 2974, 2930, 2872, 1705, 1636, 1518, 1364, 1270, 1248, 1166, 1150; δ_H (500 MHz, $CDCl_3$) 5.98 (1H, ddd, *J* 17.1, 10.5 and 6.5, 4-H), 5.32-5.23 (2H, m, 5-H_2), 5.15 (1H, br. s, NH), 4.61-4.52 (1H, m, 3-H), 4.21 (1H, d, *J* 16.8, morpholinyl 6-H_A), 4.13 (1H, d, *J* 16.8, morpholinyl 6-H_B), 3.75 (1H, dd, *J* 11.6 and 2.7, morpholinyl 2-H_A), 3.66 (1H, dd, *J* 11.6 and 2.0, morpholinyl 2-H_B), 3.54-3.47 (1H, m, morpholinyl 3-H), 3.33-3.22 (1H, m, 1-H_A), 3.06-2.95 (1H, m, 1-H_B), 2.03-1.96 (1H, m, 2-H_A), 1.95-1.87 (1H, m, 2-H_B), 1.43 (9H, s, ^{t}Bu), 1.31 (3H, d, *J* 6.5, methylmorpholinyl 1-H_3); *m/z* (ES) 321.1 (100%, MNa^+).

5.2.2.3. Cyclisation Reactions

General Procedure F

According to an existing procedure,[116] a solution of the respective alkene (1.00 eq) and the respective (het)aryl bromide (1.20 eq) in 1,4-dioxane (concentration of alkene 0.17 M) was added to a mixture of $Pd(OAc)_2$ (0.05 eq), the ligand **93** (0.10 eq) and Cs_2CO_3 (2.50 eq). The reaction mixture was stirred vigorously for 18 h at 105 °C. Subsequently, it was filtered through celite and concentrated under reduced pressure to give a crude material.

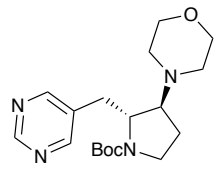
***tert*-Butyl (2'*S*,3'*R*)-2'-[(pyrimidin-5-yl)methyl]-[1,3'-bipyrrolidine]-1'-carboxylate**



90j

According to General Procedure F, the alkene **89a** (1.45 g, 5.70 mmol) and 5-bromopyrimidine (1.10 g, 6.84 mmol) gave a crude material. The crude material (*dr* >95:<5 by ^{1}H-NMR) was purified by flash column chromatography, eluting with 95.4:4.1:0.5 DCM−EtOH−NH_4OH to give the *pyrrolidine derivative* ***90j*** (1.25 g, 66%, *dr* >95:<5 by ^{1}H-NMR) as a brown oil, R_f 0.06 (95.4:4.1:0.5 DCM−EtOH−NH_4OH); [α_D^{27}] +14.5 (*c* 1.00, $CHCl_3$); ν_{max}/cm^{-1} 2968, 2796, 1686, 1559, 1391, 1364, 1166, 1110; δ_H (500 MHz, CD_3OD, 333 K) 9.01 (1H, s, pyrimidinyl 2-H), 8.66 (2H, s, pyrimidinyl 4,6-H_2), 4.13 (1H, app. t, *J* 6.8, 2'-H), 3.58 (1H, m, 5'-H_A), 3.27 (1H, app. dt, *J* 10.9 and 6.4, 5'-H_B), 2.89 (2H, app. d, *J* 6.8, pyrimidinylmethyl 1-H_2), 2.86-2.77 (1H, m, 3'-H), 2.59-2.52 (2H, m, 2-H_A and 5-H_A), 2.51-2.44 (2H, m, 2-H_B and 5-H_B), 2.12-1.96 (2H, m, 4'-H_2), 1.76 (4H, app. td, *J* 6.4 and 3.7, 3,4-H_4), 1.38 (9H, s, ^{t}Bu); δ_C (125 MHz, CD_3OD) 158.9 (pyrimidinyl C_2-4,6), 157.5 (pyrimidinyl C-2), 156.1 (pyrimidinyl C-5), 134.1 (C=O), 81.3 (^{t}Bu C_1), 69.3 (C-3'), 63.4 (C-2'), 52.8 (C_2-2,5), 45.9 (C-5'), 35.2 (pyrimidinylmethyl C-1), 28.7 (^{t}Bu C_3), 28.1 (C-4'), 24.2 (C_2-3,4); HRMS found MH^+, 333.2288. $C_{18}H_{28}N_4O_2$ requires *MH*, 333.2285. The absolute configuration was determined by comparison with analogues.[116]

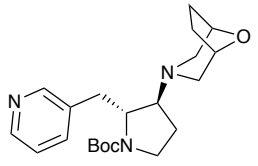
***tert*-Butyl (2*R*,3*S*)-3-(morpholin-4-yl)-2-[(pyrimidin-5-yl)methyl]pyrrolidine-1-carboxylate**



90k

According to General Procedure F, the alkene **89b** (1.80 g, 6.66 mmol) and 5-bromopyrimidine (1.27 g, 8.00 mmol) gave a crude material. The crude material (*dr* >95:<5 by ^{1}H-NMR) was purified by flash column chromatography, eluting with 95.4:4.1:0.5 DCM−EtOH−NH_4OH to give the *pyrrolidine derivative* ***90k*** (1.42 g, 61%, *dr* >95:<5 by ^{1}H-NMR) as a yellow-orange oil, R_f 0.06 (95.4:4.1:0.5 DCM−EtOH−NH_4OH); [α_D^{23}] −13.0 (*c* 1.00, $CHCl_3$); ν_{max}/cm^{-1} 2970, 2856, 2831, 1684, 1390, 1164, 1112; δ_H (500 MHz, CD_3OD, 333 K) 9.01 (1H, s, pyrimidinyl 2-H), 8.65 (2H, s, pyrimidinyl 4,6-H_2), 4.10 (1H, app. td, *J* 6.6 and 2.6, 2-H), 3.66-3.54 (5H, m, 5-H_A and morpholinyl 2,6-H_4), 3.22 (1H, app. dt, *J* 11.0 and 7.1, 5-H_B), 2.97-2.85 (3H, m, 3-H and pyrimidinylmethyl 1-H_2), 2.47-2.37 (4H, m, morpholinyl 3,5-H_4), 2.07-1.94 (2H, m, 4-H_2), 1.38 (9H, s, ^{t}Bu); δ_C (125 MHz, CD_3OD, 333 K) 158.8 (pyrimidinyl C_2-4,6), 157.4 (pyrimidinyl C-2), 155.9 (C=O), 134.1 (pyrimidinyl C-5), 81.3 (^{t}Bu C_1), 70.7 (C-3), 67.9 (morpholinyl C_2-2,6), 60.9 (C-2), 51.4 (morpholinyl C_2-3,5), 46.2 (C-5), 35.4 (pyrimidinylmethyl C-1), 28.7 (^{t}Bu C_3), 25.8 (C-4); HRMS found MH^+, 349.2241. $C_{18}H_{28}N_4O_3$ requires *MH*, 349.2234. The absolute configuration was determined by comparison with analogues.[116]

***tert*-Butyl (2*R*, 3*S*)-3-{8-oxa-3-azabicyclo[3.2.1]octan-3-yl}-2-[(pyridin-3-yl) methyl] pyrrolidine-1-carboxylate**

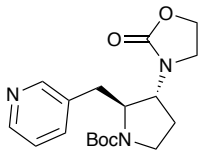


90l

According to General Procedure F, the alkene **89c** (0.60 g, 2.02 mmol) and 3-bromopyridine (0.23 mL, 2.43 mmol) gave a crude material. The crude material

(*dr* >95:<5 by ^{1}H-NMR) was purified by flash column chromatography, eluting with EtOAc to give the *pyrrolidine derivative* ***90l*** (0.29 g, 38%, *dr* >95:<5 by ^{1}H-NMR) as a light-brown oil, R_f 0.11 (EtOAc); [α_D^{23}] −6.60 (*c* 1.00, $CHCl_3$); ν_{max}/cm^{-1} 2949, 2809, 1685, 1389, 1363, 1162, 1111; δ_H (500 MHz, CD_3OD, 333 K) 8.40 (2H, d, *J* 2.4, pyridinyl 2,6-H_2), 7.69 (1H, d, *J* 5.9, pyridinyl 4-H), 7.36 (1H, dd, *J* 7.8 and 4.9, pyridinyl 5-H), 4.22-4.15 (2H, m, bicyclooctanyl 1,5-H_2), 4.03 (1H, ddd, *J* 7.6, 5.4 and 2.3, 2-H), 3.50 (1H, app. td, *J* 17.4 and 8.0, 5-H_A), 3.23-3.11 (1H, m, 5-H_B), 2.99-2.87 (1H, m, 3-H), 2.87-2.78 (2H, m, pyridinylmethyl 1-H_2), 2.43 (2H, dd, *J* 17.9 and 10.8, bicyclooctanyl 2-H_A and bicyclooctanyl 4-H_A), 2.29 (2H, app. td, *J* 11.5 and 2.0, bicyclooctanyl 2-H_B and bicyclooctanyl 4-H_B), 2.00-1.84 (2H, m, 4-H_2), 1.80-1.70 (4H, m, bicyclooctanyl 6,7-H_4), 1.42 (9H, s, ^{t}Bu); δ_C (125 MHz, CD_3OD, 333 K) 156.1 (C=O), 151.0 (pyridinyl C_A-2,6), 148.1 (pyridinyl C_B-2,6), 139.2 (pyridinyl C-4), 136.3 (pyridinyl C-3), 125.0 (pyridinyl C-5), 81.1 (^{t}Bu C_1), 76.2 (bicyclooctanyl C_A-1,5), 76.1 (bicyclooctanyl C_B-1,5), 69.1 (pyridinylmethyl C-1), 61.6 (C-2), 56.7 (bicyclooctanyl C_A-2,4), 55.5 (bicyclooctanyl C_B-2,4), 46.3 (C-5), 37.6 (C-3), 29.3 (bicyclooctanyl C_A-6,7), 29.2 (bicyclooctanyl C_B-6,7), 28.8 (^{t}Bu C_3), 25.8 (C-4); HRMS found MH^+, 374.2445. $C_{21}H_{31}N_3O_3$ requires *MH*, 374.2438. The absolute configuration was determined by comparison with analogues.[116]

tert-Butyl (2*S*, 3*R*)-3-(2-oxo-1,3-oxazolidin-3-yl)-2-[(pyridin-3-yl)methyl] pyrrolidine-1-carboxylate

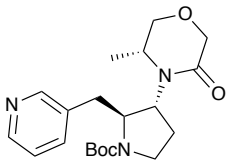


90m

According to General Procedure F, the alkene **89f** (1.14 g, 4.22 mmol) and 3-bromopyridine (0.49 mL, 5.06 mmol) gave a crude material. The crude material (*dr* 83:17 by ^{1}H-NMR) was purified by flash column chromatography, eluting with 95.4:4.1:0.5 DCM−EtOH−NH_4OH to give the *pyrrolidine derivative* ***90m*** (0.62 g, 42%, *dr* >95:<5 by ^{1}H-NMR) as a yellow oil, R_f 0.20 (95.4:4.1:0.5 DCM−EtOH−NH_4OH); [α_D^{25}] +16.2 (*c* 1.00, MeOH); ν_{max}/cm^{-1} 2975, 2930, 1742, 1683, 1479, 1389, 1165, 1115; δ_H (500 MHz, CD_3OD, 333 K) 8.44 (1H, d, *J* 1.6, pyridinyl 2-H), 8.41 (1H, dd, *J* 4.9 and 1.6, pyridinyl 6-H), 7.74 (1H, d, *J* 7.7,

pyridinyl 4-H), 7.35 (1H, ddd, *J* 7.7, 4.9 and 0.6, pyridinyl 5-H), 4.31-4.18 (3H, m, 3-H and oxazolidinyl 5-H_2), 4.11 (1H, app. td, *J* 6.1 and 4.0, 2-H), 3.65 (1H, app. dt, *J* 11.1 and 7.7, 5-H_A), 3.55 (1H, ddd, *J* 9.1, 8.3 and 7.1, oxazolidinyl 4-H_A), 3.46 (1H, app. td, *J* 8.7 and 6.6, oxazolidinyl 4-H_B), 3.23-3.13 (1H, m, 5-H_B), 3.00 (2H, app. d, *J* 5.7, pyridinylmethyl 1-H_2), 2.14-2.04 (1H, m, 4-H_A), 2.04-1.95 (1H, m, 4-H_B), 1.44 (9H, s, ^{t}Bu); δ_C (125 MHz, CD_3OD, 333 K) 160.0 (oxazolidinyl C=O), 155.9 (Boc C=O), 151.2 (pyridinyl C-2), 148.3 (pyridinyl C-6), 139.3 (pyridinyl C-4), 135.3 (pyridinyl C-3), 125.0 (pyridinyl C-5), 81.6 (^{t}Bu C_1), 63.8 (oxazolidinyl C-5), 62.4 (C-2), 58.7 (C-3), 46.0 (C-5), 42.9 (oxazolidinyl C-4), 36.6 (pyridinylmethyl C-1), 28.7 (^{t}Bu C_3), 27.9 (C-4); HRMS found MH^+, 348.1927. $C_{18}H_{25}N_3O_4$ requires *MH*, 348.1917. The absolute configuration was determined by comparison with analogues.[116]

tert-Butyl (2*S*, 3*R*)-3-[(3*R*)-3-methyl-5-oxomorpholin-4-yl]-2-[(pyridin-3-yl) methyl] pyrrolidine-1-carboxylate

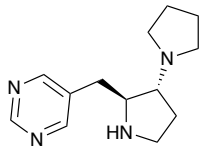


90n

According to General Procedure F, the alkene **89g** (0.65 g, 2.17 mmol) and 3-bromopyridine (0.25 mL, 2.61 mmol) gave a crude material. The crude material (*dr* 89:11 by ^{1}H-NMR) was purified by flash column chromatography, eluting with 96.9:2.8:0.3 DCM−EtOH−NH_4OH to give the pyrrolidine derivative **90n**[116] (0.50 g, 61%, *dr* >95:<5 by ^{1}H-NMR) as a yellow oil, R_f 0.15 (96.9:2.8:0.3 DCM−EtOH−NH_4OH); [α_D^{23}] +35.4 (*c* 1.00, $CHCl_3$); ν_{max}/cm^{-1} 2974, 2930, 2872, 1685, 1645, 1392, 1149, 1119; δ_H (500 MHz, CD_3OD, 333 K) 8.45 (1H, d, *J* 2.0, pyridinyl 2-H), 8.40 (1H, dd, *J* 4.9 and 1.3, pyridinyl 6-H), 7.76 (1H, d, *J* 8.0, pyridinyl 4-H), 7.35 (1H, dd, *J* 8.0 and 4.9, pyridinyl 5-H), 4.47 (1H, br. s, under signal for residual water, 3-H), 4.18 (1H, app. q, *J* 5.1, 2-H), 4.11 (1H, d, *J* 16.9, morpholinyl 6-H_A), 3.98 (1H, d, *J* 16.9, morpholinyl 6-H_B), 3.80-3.70 (1H, m, 5-H_A), 3.65 (1H, dd, *J* 11.6 and 1.6, morpholinyl 2-H_A), 3.54 (1H, dd, *J* 11.6 and 2.4, morpholinyl 2-H_B), 3.47-3.41 (1H, m, morpholinyl 3-H), 3.10-3.03 (1H, m, 5-H_B), 3.02 (2H, app. d, *J* 5.5, pyridinylmethyl 1-H_2), 2.07-2.01 (2H, m, 4-H_2), 1.44

(9H, s, ^{t}Bu), 1.23 (3H, d, *J* 6.5, methylmorpholinyl 1-H_3); *m/z* (ES) 376.1 (100%, MH^+).

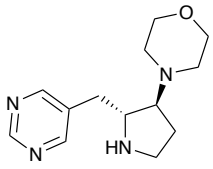
(2'*S*,3'*R*)-2'-[(Pyrimidin-5-yl)methyl]-1,3'-bipyrrolidine



95

According to General Procedure B, TFA (4.00 mL, 52.0 mmol) and the protected amine **90j** (1.20 g, 3.61 mmol) gave the TFA salt of the *amine **95*** (1.68 g, >99%) as an amorphous dark brown solid, R_f 0.10 (84.7:13.6:1.7 DCM−EtOH−NH_4OH); [α_D^{24}] −18.0 (*c* 1.00, MeOH); ν_{max}/cm^{-1} 2969, 2487, 1663, 1560, 1412, 1194, 1170, 1117; δ_H (500 MHz, CD_3OD) 9.16 (1H, s, pyrimidinyl 2-H), 8.88 (2H, s, pyrimidinyl 4,6-H_2), 4.48 (1H, app. p, *J* 5.2, 2'-H), 4.06 (1H, app. dt, *J* 9.0 and 4.5, 3'-H), 3.62-3.50 (6H, m, 5'-H_2 and 2,5-H_4), 3.44 (1H, dd, *J* 15.2 and 5.8, pyrimidinylmethyl 1-H_A), 3.19 (1H, dd, *J* 15.2 and 9.8, pyrimidinylmethyl 1-H_B), 2.78-2.64 (1H, m, 4'-H_A), 2.57-2.45 (1H, m, 4'-H_B), 2.16-2.08 (4H, m, 3,4-H_4); δ_c (125 MHz, CD_3OD) 162.2 (q, *J* 36.8, TFA C=O), 159.1 (pyrimidinyl C_2-4,6), 158.7 (pyrimidinyl C-2), 117.5 (q, *J* 289.8, TFA CF_3), 116.0 (q, *J* 284.4, TFA CF_3), 68.1 (C-3'), 62.6 (C-2'), 45.3 (C-5' and C_2-2,5), 32.8 (pyrimidinylmethyl C-1), 28.5 (C-4'), 23.9 (C_2-3,4); HRMS found MH^+, 233.1759. $C_{13}H_{21}N_4$ requires *MH*, 233.1760.

4-[(2*R*,3*S*)-2-[(Pyrimidin-5-yl)methyl]pyrrolidin-3-yl]morpholine

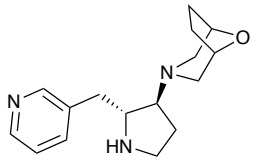


115

According to General Procedure B, TFA (4.00 mL, 52.0 mmol) and the protected amine **90k** (1.42 g, 4.07 mmol) gave the TFA salt of the *amine **115*** (1.80 g, >99%) as an amorphous orange solid, R_f 0.11 (84.7:13.6:1.7 DCM−EtOH−NH_4OH); [α_D^{25}] +15.4 (*c* 1.00, MeOH); ν_{max}/cm^{-1} 2979, 2482, 1664,

1415, 1175, 1124; δ_H (500 MHz, CD_3OD) 9.12 (1H, s, pyrimidinyl 2-H), 8.82 (2H, s, pyrimidinyl 4,6-H_2), 3.98 (1H, app. q, *J* 7.3, 2-H), 3.67-3.62 (2H, m, morpholinyl 2-H_A and morpholinyl 6-H_A), 3.62-3.56 (2H, m, morpholinyl 2-H_B and morpholinyl 6-H_B), 3.48-3.40 (1H, m, 3-H), 3.40-3.34 (2H, m, 5-H_2), 3.25 (1H, dd, *J* 14.7 and 7.0, pyrimidinylmethyl 1-H_A), 3.17 (1H, dd, *J* 14.7 and 8.1, pyrimidinylmethyl 1-H_B), 2.73-2.68 (2H, m, morpholinyl 3-H_A and morpholinyl 5-H_A), 2.68-2.63 (2H, m, morpholinyl 3-H_B and morpholinyl 5-H_B), 2.31-2.18 (2H, m, 4-H_2); δ_C (125 MHz, CD_3OD) 162.1 (q, *J* 34.8, TFA C=O), 158.9 (pyrimidinyl C_2-4,6), 158.4 (pyrimidinyl C-2), 131.4 (pyrimidinyl C-5), 117.6 (q, *J* 290.1, TFA CF_3), 115.8 (q, *J* 289.9, TFA CF_3), 70.2 (C-3), 66.4 (morpholinyl C_2-2,6), 60.6 (C-2), 51.6 (C-5), 45.3 (morpholinyl C_2-3,5), 33.1 (pyrimidinylmethyl C-1), 24.8 (C-4); HRMS found MH^+, 249.1703. $C_{13}H_{20}N_4O$ requires *MH*, 249.1709.

3-[(2*R*,3*S*)-2-[(Pyridin-3-yl)methyl]pyrrolidin-3-yl]-8-oxa-3-azabicyclo[3.2.1] octane

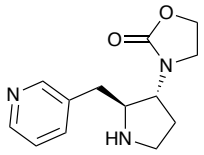


114

According to General Procedure B, TFA (1.00 mL, 13.1 mmol) and the protected amine **90l** (0.29 g, 0.77 mmol) gave the TFA salt of the *amine **114*** (0.42 g, >99%) as an amorphous red-brown solid, R_f 0.15 (84.7:13.6:1.7 DCM−EtOH−NH_4OH); [α_D^{25}] +16.4 (*c* 1.00, MeOH); v_{max}/cm^{-1} 2978, 2638, 1662, 1434, 1172, 1126; δ_H (500 MHz, CD_3OD) 8.88 (1H, d, *J* 1.2, pyridinyl 2-H), 8.79 (1H, d, *J* 5.3, pyridinyl 6-H), 8.52 (1H, app. dt, *J* 8.2 and 1.8, pyridinyl 4-H), 8.00 (1H, dd, *J* 8.0 and 5.3, pyridinyl 5-H), 4.34-4.29 (1H, m, bicyclooctanyl 1,5-H_A), 4.28-4.23 (1H, m, bicyclooctanyl 1,5-H_B), 4.03-3.96 (1H, m-under residual solvent peak, 2-H), 3.48-3.34 (5H, m, 3-H, 5-H_2 and piridinylmethyl 1-H_2), 2.75-2.54 (4H, m, bicyclooctanyl 2,4-H_4), 2.26-2.12 (2H, m, 4-H_2), 1.85-1.79 (2H, m, bicyclooctanyl 6-H_A and bicyclooctanyl 7-H_A), 1.68 (2H, app. d, *J* 6.6, bicyclooctanyl 6-H_B and bicyclooctanyl 7-H_B); δ_C (125 MHz, CD_3OD) 161.9 (app. d, *J* 35.8, TFA C=O), 159.0 (app. d, *J* 42.2, TFA C=O), 147.3 (pyridinyl C-4), 144.3 (pyridinyl C-2), 142.8 (pyridinyl C-6), 138.0 (pyridinyl C-3), 128.3 (pyridinyl C-5), 117.6 (q, *J* 289.0, TFA CF_3), 116.0 (q, *J* 284.4, TFA CF_3), 75.6

(bicyclooctanyl C_A-1,5), 75.3 (bicyclooctanyl C_B-1,5), 69.7 (C-3), 60.3 (C-2), 58.6 (bicyclooctanyl C_A-2,4), 53.2 (bicyclooctanyl C_B-2,4), 45.3 (C-5), 35.2 (pyridinylmethyl C-1), 28.8 (bicyclooctanyl C_2-6,7), 23.7 (C-4); HRMS found MH^+, 274.1908. $C_{16}H_{23}N_3O$ requires *MH*, 274.1913.

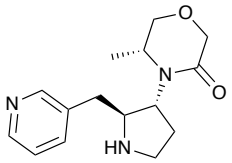
3-[(2*S*,3*R*)-2-[(Pyridin-3-yl)methyl]pyrrolidin-3-yl]-1,3-oxazolidin-2-one



101

According to General Procedure B, TFA (2.00 mL, 26.0 mmol) and the protected amine **90m** (0.60 g, 1.72 mmol) gave the TFA salt of the *amine **101*** (0.78 g, >99%) as an amorphous light brown solid, R_f 0.11 (84.7:13.6:1.7 DCM−EtOH−NH_4OH); [α_D^{23}] −11.0 (*c* 1.00, MeOH); ν_{max}/cm^{-1} 2961, 2687, 2521, 1725, 1659, 1439, 1170, 1125; δ_H (500 MHz, CD_3OD) 8.70 (1H, d, *J* 1.7, pyridinyl 2-H), 8.63 (1H, d, *J* 4.8, pyridinyl 6-H), 8.18 (1H, app. dt, *J* 8.1 and 1.7, pyridinyl 4-H), 7.71 (1H, dd, *J* 7.9 and 4.8, pyridinyl 5-H), 4.37-4.26 (2H, m, 3-H and oxazolidinyl 5-H_A), 4.18 (1H, app. td, *J* 8.8 and 7.4, oxazolidinyl 5-H_B), 4.08 (1H, app. q, *J* 7.7, 2-H), 3.60-3.51 (2H, m, oxazolidinyl 4-H_2), 3.52-3.45 (2H, m, 5-H_2), 3.27 (2H, dd, *J* 7.5 and 2.9, pyridinylmethyl 1-H_2), 2.38-2.29 (1H, m, 4-H_A), 2.29-2.21 (1H, m, 4-H_B); δ_C (75 MHz, CD_3OD) 162.4 (app d, *J* 36.1, TFA C=O), 159.9 (oxazolidinyl C=O), 147.9 (pyridinyl C-4), 144.0 (pyridinyl C-2), 142.5 (pyridinyl C-6), 137.7 (pyridinyl C-3), 128.3 (pyridinyl C-5), 117.8 (q, *J* 288.2, TFA CF_3), 64.12 (oxazolidinyl C-5), 60.5 (C-2), 58.1 (C-3), 44.6 (C-5), 42.3 (oxazolidinyl C-4), 34.0 (pyridinylmethyl C-1), 26.4 (C-4); HRMS found MH^+, 248.1387. $C_{13}H_{17}N_3O_2$ requires *MH*, 248.1393.

(5*R*)-5-Methyl-4-[(2*S*,3*R*)-2-[(pyridin-3-yl)methyl]pyrrolidin-3-yl]morpholin-3-one



100

According to General Procedure B, TFA (1.50 mL, 19.6 mmol) and the protected amine **90n** (0.50 g, 1.33 mmol) gave the TFA salt of the *amine **100*** (0.50 g, >99%) as an amorphous light yellow solid, R_f 0.12 (84.7:13.6:1.7 DCM−EtOH−NH_4OH); $[\alpha_D^{23}]$ −28.8 (*c* 1.00, MeOH); v_{max}/cm^{-1} 2982, 2677, 1663, 1662, 1172, 1122; δ_H (500 MHz, CD_3OD) 8.72 (1H, s, pyridinyl 2-H), 8.65 (1H, d, *J* 4.8, pyridinyl 6-H), 8.18 (1H, d, *J* 7.9, pyridinyl 4-H), 7.73 (1H, dd, *J* 7.9 and 4.8, pyridinyl 5-H), 4.51 (1H, app. td, *J* 7.9 and 5.5, 2-H), 4.15 (1H, d, *J* 16.9, morpholinyl 2-H_A), 4.03 (1H, d, *J* 16.9, morpholinyl 2-H_B), 3.91 (1H, app. dt, *J* 8.9 and 5.7, 3-H), 3.75-3.63 (3H, m, 5-H_2 and morpholinyl 6-H_A), 3.50-3.42 (2H, m, morpholinyl 6-H_B and morpholinyl 5-H), 3.21 (2H, app. d, *J* 7.9, pyridinylmethyl 1-H_2), 2.65-2.55 (1H, m, 4-H_A), 2.39-2.26 (1H, m, 4-H_B), 0.97 (3H, d, *J* 6.5, methylmorpholinyl 1-H_3); δ_C (125 MHz, CD_3OD) 170.7 (morpholinyl C=O), 162.5 (q, *J* 36.4, TFA C=O), 146.7 (pyridinyl C-2), 145.1 (pyridinyl C-4), 144.7 (pyridinyl C-6), 136.4 (pyridinyl C-3), 127.4 (pyridinyl C-5), 117.9 (q, *J* 290.1, TFA CF_3), 70.8 (morpholinyl C-6), 68.9 (morpholinyl C-2), 63.1 (C-2), 62.5 (C-3), 54.7 (morpholinyl C-5), 45.5 (C-5), 34.3 (pyridinylmethyl C-1), 28.6 (C-4), 18.5 (methylmorpholinyl C-1); HRMS found MH^+, 276.1704. $C_{15}H_{21}N_3O_2$ requires *MH*, 276.1706.

5.2.3. Experimental for the Lead-Oriented Synthesis Approach Based on a Mannich/Alkylation and a Pd-catalysed Connective Reactions

5.2.3.1. Preparation of Building Blocks

General Procedure G

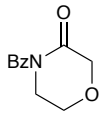
By modification of an existing procedure,[143] LiHMDS (2.20 eq of a 1.0 M solution in toluene or THF) was added to a solution of the carbonyl derivative (1.00 eq) in toluene (0.17 M) at −78 °C. After stirring the mixture for 1.5 h at −78 °C, a solution of the imidazole derivative **156** (1.20 eq) in toluene (2.50 M) was added dropwise and the reaction mixture was stirred at −78 °C for 3 h.

Subsequently, the reaction was allowed to warm to rt and a saturated aqueous solution of NH_4Cl (5 mL per 1.00 mmol of the carbonyl derivative) was added. The phases were separated and the aqueous phase was extracted with Et_2O or EtOAc (3 × (2 mL per 1.00 mmol of the carbonyl derivative)). Finally, the organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material.

General Procedure H

By modification of an existing procedure,[149] LiHMDS (2.20 eq of a 1.0 M solution in toluene) was added to a solution of the carbonyl derivative (1.00 eq) in the specified amount of toluene at 0 °C. After stirring for 15 min, allyl chloroformate (1.20 eq) was added and the reaction mixture was allowed to warm to rt and stirred for 1 h. Subsequently, a saturated aqueous solution of NH_4Cl (3 mL per 1.00 mmol of the carbonyl derivative) was added, the mixture was stirred for 15 min, the phases were separated and the aqueous phase was extracted with EtOAc (3 × (1 mL per 1.00 mmol of the carbonyl derivative)). The organic phases were combined, washed with brine (2 mL per 1.00 mmol of the carbonyl derivative), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material.

4-Benzoylmorpholin-3-one

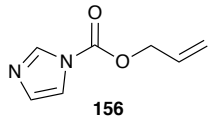


154a

By modification of an existing procedure,[202] triethylamine (19.9 mL, 143 mmol) was added to a suspension of 3-oxomorpholine (13.1 g, 130 mmol) in toluene (42.0 mL). After warming the reaction mixture to 90 °C, benzoyl chloride (15.0 mL, 130 mmol) was added dropwise and the reaction mixture was stirred for 18 h at 90 °C. Subsequently, the solution was allowed to cool to rt, toluene (125 mL) was added and the solution was cooled to 0 °C. The precipitate was removed by filtration and the solvent was concentrated under reduced pressure to give a crude material. Afterwards, the crude material was dissolved in Et_2O (125 mL), cooled to 0 °C and the solvent was removed by filtration. The precipitate was washed with cold Et_2O (2 × 125 mL) and it was dissolved in

DCM (250 mL). Water (250 mL) was added, the phases were separated and the aqueous phase was extracted with DCM (3 × 250 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield the benzoyl derivative **154a**[202] (20.7 g, 78%) as white crystals, m.p. (Et_2O) 61−64 °C; R_f 0.50 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 2944, 2893, 2866, 1702, 1672, 1462, 1450, 1375, 1347, 1302, 1278, 1216, 1138; δ_H (500 MHz, $CDCl_3$) 7.59-7.56 (2H, m, phenyl 2,6-H_2), 7.50 (1H, tt, *J* 6.9 and 1.2, phenyl 4-H), 7.43-7.37 (2H, m, phenyl 3,5-H_2), 4.27 (1H, s, 2-H_2), 4.02 (2H, dd, *J* 6.0 and 4.4, 6-H_2), 3.93 (2H, dd, *J* 6.0 and 4.4, 5-H_2); δ_C (125 MHz, $CDCl_3$) 172.8 (C-3), 169.0 (benzoyl C=O), 135.4 (phenyl C-1), 132.0 (phenyl C-4), 128.2 (phenyl C_4-2,3,5,6), 68.8 (C-2), 64.1 (C-6), 44.7 (C-5); HRMS found MH^+, 206.0810. $C_{11}H_{11}NO_3$ requires *MH*, 206.0811.

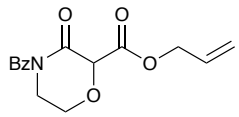
Prop-2-en-1-yl 1*H*-imidazole-1-carboxylate



156

According to an existing procedure,[147] a solution of allyl alcohol (4.47 mL, 65.8 mmol) in DCM (123 mL) was added dropwise to a solution of CDI (16.0 g, 98.7 mmol) in THF (515 mL) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C. Subsequently, the solvent was removed under reduced pressure to give a crude product. The crude product was purified by flash column chromatography, eluting with 40:60 EtOAc–hexane to yield the imidazole derivative **156**[147] (10.6 g, >99%) as a colourless oil, R_f 0.38 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3131, 2952, 1755, 1471, 1391, 1314, 1278, 1237, 1171, 1094; δ_H (500 MHz, $CDCl_3$) 8.13 (1H, s, 2-H), 7.42 (1H, app. t, *J* 1.5, 5-H), 7.05 (1H, dd, *J* 1.5 and 0.9, 4-H), 5.99 (1H, ddt, *J* 17.3, 10.4 and 6.0, propenyl 2-H), 5.44 (1H, dq, *J* 17.3 and 1.2, propenyl 3-H_{trans}), 5.36 (1H, dq, *J* 10.4 and 1.2, propenyl 3-H_{cis}), 4.87 (2H, dt, *J* 6.0 and 1.2, propenyl 1-H_2); δ_C (125 MHz, $CDCl_3$) 148.5 (C=O), 137.2 (C-2), 130.7 (propenyl C-2), 130.5 (C-4), 120.5 (propenyl C-3), 117.2 (C-5), 68.7 (propenyl C-1); HRMS found MH^+, 153.0659. $C_7H_8N_2O_2$ requires *MH*, 153.0658.

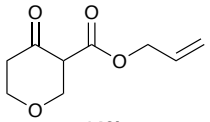
Prop-2-en-1-yl-4-benzoyl-3-oxomorpholine-2-carboxylate



146a

According to General Procedure G, the carbonyl derivative **154a** (9.32 g, 45.4 mmol) and LiHMDS (100 mL, 100 mmol of a 1.0 M solution in THF) gave a crude material. The crude material (*C-acylated:O-acylated* >95:<5 by ^{1}H-NMR) was extracted with Et_2O and purified by flash column chromatography eluting with DCM to yield the allyl ester derivative **146a**[143] (5.00 g, 41%) as a light yellow oil, R_f 0.62 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 2950, 2893, 1745, 1685, 1449, 1373, 1274, 1227, 1155, 1139; δ_H (500 MHz, $CDCl_3$) 7.65-7.61 (2H, m, phenyl 2,6-H_2), 7.51 (1H, tt, *J* 7.1 and 1.2, phenyl 4-H), 7.42-7.36 (2H, m, phenyl 3,5-H_2), 5.94 (1H, ddt, *J* 17.3, 10.5 and 5.9, propenyl 2-H), 5.38 (1H, app. dq, *J* 17.3 and 1.3, propenyl 3-H_{trans}), 5.30 (1H, app. dq, *J* 10.5 and 1.3, propenyl 3-H_{cis}), 4.83 (1H, s, 2-H), 4.74 (2H, app. dt, *J* 5.9 and 1.3, propenyl 1-H_2), 4.35 (1H, ddd, *J* 12.0, 7.9 and 3.7, 6-H_A), 4.07 (1H, ddd, *J* 12.0, 5.4 and 3.8, 6-H_B), 4.00 (1H, ddd, *J* 13.3, 7.9 and 3.8, 5-H_B), 3.93 (1H, ddd, *J* 13.3, 5.4 and 3.7, 5-H_A); δ_C (125 MHz, $CDCl_3$) 172.6 (C-3), 166.5 (benzoyl C=O), 165.6 (carboxylate C=O), 134.6 (phenyl C-1), 132.4 (phenyl C-4), 131.0 (propenyl C-2), 128.5 (phenyl C_2-2,6), 128.2 (phenyl C_2-3,5), 119.7 (propenyl C-3), 77.1 (under signal for residual solvent, C-2), 66.9 (propenyl C-1), 62.4 (C-6), 44.7 (C-5); HRMS found MH^+, 290.1024. $C_{15}H_{15}NO_5$ requires *MH*, 290.1022.

Prop-2-en-1-yl 4-oxooxane-3-carboxylate

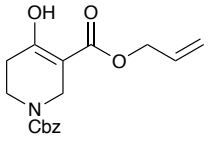


146b

According to General Procedure G, the carbonyl derivative **154b** (3.84 mL, 41.6 mmol) and LiHMDS (91.6 mL, 91.6 mmol of a 1.0 M solution in toluene) gave a crude material. The crude material (*C-acylated:O-acylated* >95:<5 by ^{1}H-NMR) was extracted with EtOAc and purified by flash column chromatography eluting

with 5:95 EtOAc−hexane to yield the *allyl ester derivative* ***146b*** (3.48 g, 45%, *keto:enol* 24:76 by ^{1}H-NMR in $CDCl_3$) as a colourless oil, R_f 0.72 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 2968, 2856, 1741, 1718, 1663, 1624, 1395, 1305, 1216, 1101, 1047; δ_H (500 MHz, $CDCl_3$) 5.92 (2H, ddt, *J* 17.3, 10.5 and 5.6, propenyl 2-H), 5.34 (1H, app. q, *J* 1.5, 3-H_{trans}^{keto}), 5.31 (1H, app. dq, *J* 17.3 and 1.5, propenyl 3-H_{trans}^{enol}), 5.26 (1H, app. dd, *J* 10.5 and 1.2, propenyl 3-H_{cis}^{keto}), 5.25 (1H, app. dq, *J* 10.5 and 1.5, propenyl 3-H_{cis}^{enol}), 4.65 (4H, dt, *J* 5.6 and 1.5, propenyl 1-H_2), 4.29 (2H, app. t, *J* 1.7, 2-H_2^{enol}), 4.23 (1H, dd, *J* 11.6 and 7.1, 2-H_A^{keto}), 4.11 (1H, ddd, *J* 11.6, 5.1 and 0.9, 2-H_B^{keto}), 4.05-3.93 (2H, m, 6-H_2^{keto}), 3.84 (2H, t, *J* 5.7, 6-H_2^{enol}), 3.50 (1H, app. ddd, *J* 6.8, 5.1 and 1.3, 3-H^{keto}), 2.67 (1H, ddd, *J* 14.5, 6.2 and 5.1, 5-H_A^{keto}), 2.55 (1H, dddd, *J* 14.5, 7.1, 5.5 and 1.3, 5-H_B^{keto}), 2.39 (2H, tt, *J* 5.7 and 1.7, 5-H_2^{enol}); δ_C (75 MHz, $CDCl_3$) 201.2 (C-4^{keto}), 169.7 (carboxylate C=O^{enol}), 169.3 (C-4^{enol}), 167.5 (carboxylate C=O^{keto}), 131.9 (propenyl C-2^{enol}), 131.5 (propenyl C-2^{keto}), 118.8 (propenyl C-3^{keto}), 118.3 (propenyl C-3^{enol}), 97.3 (C-3^{enol}), 69.6 (C-2^{keto}), 68.2 (C-6^{keto}), 66.0 (propenyl C-1^{keto}), 64.8 (propenyl C-1^{enol}), 63.9 (C-6^{enol}), 63.0 (C-2^{enol}), 57.8 (C-3^{keto}), 42.0 (C-5^{keto}), 28.8 (C-5^{enol}); HRMS found MNa^+, 207.0627. $C_9H_{12}O_4$ requires *MNa*, 207.0627. Compound **146b** existed as a mixture of keto and enol tautomers.

1-Benzyl 3-prop-2-en-1-yl 4-hydroxy-1,2,5,6-tetrahydropyridine-1,3-dicarboxylate

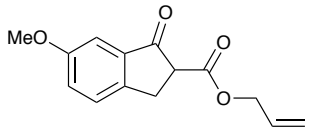


146c

According to General Procedure H, the carbonyl derivative **154c** (10.6 g, 45.45 mmol) in toluene (68.0 mL) gave a crude material. The crude material (*C-acylated:O-acylated* >95:<5 by ^{1}H-NMR) was purified by flash column chromatography, eluting with 10:90 EtOAc−hexane to yield the *allyl ester derivative* ***146c*** (5.77 g, 40%, >98% *enol* by ^{1}H-NMR in $CDCl_3$) as a colourless oil, R_f 0.60 (70:30 petrol−EtOAc); ν_{max}/cm^{-1} 3032, 2945, 1697, 1662, 1620, 1422, 1305, 1227, 1193, 1111, 1056; δ_H (400 MHz, $CDCl_3$) 7.39-7.31 (5H, m, phenyl), 5.94 (1H, ddt, *J* 17.2, 10.5 and 5.6, propenyl 2-H), 5.34 (1H, dd, *J* 17.2 and 1.4, propenyl 3-H_{trans}), 5.26 (1H, app. dq, *J* 10.5 and 1.4, propenyl 3-H_{cis}), 5.17 (2H,

s, phenylmethyl 1-H_2), 4.69 (2H, app. dt, *J* 5.6 and 1.4, propenyl 1-H_2), 4.18 (2H, s, 2-H_2), 3.65 (2H, t, *J* 5.9, 6-H_2), 2.40 (2H, app. br. s, 5-H_2); δ_C (100 MHz, $CDCl_3$) 170.6 (carboxylate C=O), 170.3 (C-4), 155.3 (Cbz C=O), 136.7 (phenyl C-1), 131.8 (propenyl C-2), 128.6 (phenyl C_2-3,5), 128.2 (phenyl C_2-2,6), 128.1 (phenyl C-4), 118.6 (propenyl C-3), 95.8 (C-3), 67.4 (phenylmethyl C-1), 65.2 (propenyl C-1), 40.6 (C-2), 40.0 (C-6), 28.8 (C-5); HRMS found MH^+, 318.1330. $C_{17}H_{19}NO_5$ requires *MH*, 318.1335. Compound **146c** existed as the enol tautomer.

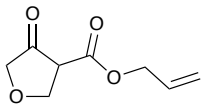
Prop-2-en-1-yl 6-methoxy-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate



146d

According to General Procedure H, the carbonyl derivative **154d** (7.37 g, 45.4 mmol) in toluene (100 mL) gave a crude material. The crude material (*C-acylated:O-acylated* >95:<5 by ^{1}H-NMR) was purified by flash column chromatography, eluting with 10:90 EtOAc−hexane to yield the allyl ester derivative **146d**[146] (5.23 g, 47%) as a brown oil, R_f 0.56 (70:30 petrol−EtOAc); ν_{max}/cm^{-1} 2940, 2837, 1736, 1704, 1571, 1491, 1432, 1317, 1296, 1273, 1204, 1184, 1148, 1024; δ_H (400 MHz, $CDCl_3$) 7.39 (1H, dd, *J* 8.3 and 0.8, 4-H), 7.22 (1H, dd, *J* 8.3 and 2.5, 5-H), 7.19 (1H, d, *J* 2.5, 7-H), 5.94 (1H, ddt, *J* 17.2, 10.5 and 5.7, propenyl 2-H), 5.37 (1H, app. dq, *J* 17.2 and 1.4, propenyl 3-H_{trans}), 5.26 (1H, app. dq, *J* 10.5 and 1.4, propenyl 3-H_{cis}), 4.69 (2H, app. tt, *J* 5.7 and 1.4, propenyl 1-H_2), 3.83 (3H, s, methoxy), 3.78 (1H, dd, *J* 8.1 and 3.9, 2-H), 3.47 (1H, dd, *J* 16.9 and 3.9, 3-H_A), 3.32 (1H, dd, *J* 16.9 and 8.1, 3-H_B); δ_C (100 MHz, $CDCl_3$) 199.3 (C-1), 168.9 (carboxylate C=O), 159.8 (C-6), 146.5 (C-3a), 136.5 (C-7a), 131.7 (propenyl C-2), 127.2 (C-4), 125.0 (C-5), 118.6 (propenyl C-3), 105.7 (C-7), 66.2 (propenyl C-1), 55.7 (methoxy), 54.0 (C-2), 29.7 (C-3); HRMS found MNa^+, 269.0782. $C_{14}H_{14}O_4$ requires *MNa*, 269.0784.

Prop-2-en-1-yl 4-oxooxolane-3-carboxylate



146e

According to an existing procedure,[151] the carbonyl derivative **154g** (8.57 mL, 111 mmol) was added dropwise to a suspension of NaH (4.88 g, 122 mmol of a 60% dispersion in mineral oil) in Et_2O (370 mL). After stirring for 4 h, the solvent was removed under reduced pressure and the crude material was dissolved in DMSO (222 mL). The solution was cooled to 0 °C and allyl acrylate (16.3 mL, 122 mmol) was added dropwise. The reaction mixture was allowed to warm to rt and stirred overnight. An aqueous solution of 10% HCl (70 mL) and Et_2O (200 mL) were added and the mixture was stirred for 30 min. Water (70 mL) was added, the phases were separated and the aqueous phase was extracted with Et_2O (4 × 100 mL). The organic phases were combined, washed with brine (300 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material. The crude material was purified by flash column chromatography, eluting with 10:90→20:80 EtOAc−hexane to yield the *allyl ester derivative* ***146e*** (5.45 g, 29%) as a pink oil, R_f 0.43 (70:30 petrol−EtOAc); ν_{max}/cm^{-1} 2951, 2883, 1770, 1725; δ_H (400 MHz, $CDCl_3$) 5.90 (1H, ddt, *J* 17.2, 10.3 and 5.7, propenyl 2-H), 5.34 (1H, dd, *J* 17.2 and 1.4, propenyl 3-H_{trans}), 5.26 (1H, dd, *J* 10.3 and 1.4, propenyl 3-H_{cis}), 4.71-4.60 (2H, m, propenyl 1-H_2), 4.49 (1H, dd, *J* 9.7 and 8.3, 2-H_A), 4.44 (1H, dd, *J* 9.7 and 8.3, 2-H_B), 4.02 (1H, d, *J* 17.1, 5-H_A), 3.94 (1H, d, *J* 17.1, 5-H_B), 3.53 (1H, t, *J* 8.3, 3-H); δ_C (100 MHz, $CDCl_3$) 207.3 (C-4), 166.3 (carboxylate C=O), 131.4 (propenyl C-2), 119.1 (propenyl C-3), 70.8 (C-5), 69.5 (C-2), 66.5 (propenyl C-1), 53.4 (C-3); HRMS found MNa^+, 193.0467. $C_8H_{10}O_4$ requires *MNa*, 193.0471.

5.2.3.2. Connective Reactions

General Procedure I

According to an existing procedure,[142] the sulfone derivative **153** (1.20 eq) was added to a solution of the allyl ester derivative (1.00 eq) in DCM (0.10 M) at rt. After stirring the mixture for 5 min, Cs_2CO_3 (2.50 eq) was added and the reaction was stirred for the specified time at rt. Subsequently, a saturated

aqueous solution of NH_4Cl (10 mL per 1.00 mmol of the allyl ester derivative) was added and the mixture was stirred for 30 min at rt. The phases were separated and the organic phase was extracted with DCM (3 × (5 mL per 1.00 mmol of the allyl ester derivative)). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material.

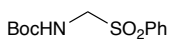
General Procedure J

By modification of an existing procedure,[157] the specified amount of K_2CO_3 was added to a solution of the allyl ester derivative **146c** (1.00 eq) in acetone (0.26 M). After stirring for 15 min at rt, the specified amount of the arylmethyl bromide derivative was added dropwise and the reaction mixture was stirred at 70 °C for 2 h. Subsequently, the mixture was allowed to cool to rt, a saturated aqueous solution of NH_4Cl (9 mL per 1.00 mmol of the allyl ester derivative **146c**) was added and the mixture was stirred for 30 min. Afterwards, EtOAc (6 mL per 1.00 mmol of the allyl ester derivative **146c**) was added, the phases were separated and the aqueous phase was extracted with EtOAc (3 × (5 mL per 1.00 mmol of the allyl ester derivative **146c**)). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material.

General Procedure K

According to an existing procedure,[145] PPh_3 (0.20 eq) and $Pd(OAc)_2$ (0.05 eq) were added to a solution of the quaternary allyl ester derivative (1.00 eq) in THF (0.10 M) and the reaction mixture was stirred for 1 h at 70 °C. Subsequently, the solution was allowed to cool to rt, filtered through celite and concentrated under reduced pressure to give a crude material.

***tert*-Butyl *N*-[(benzenesulfonyl)methyl]carbamate**

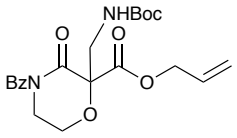


153

According to an existing procedure,[155] a 37% aqueous solution of formaldehyde (43.0 mL, 432 mmol) and formic acid (25.3 mL) were added to a suspension of

tert-butyl carbamate (25.3 g, 216 mmol) and benzenesulfinic acid sodium salt (70.9 g, 432 mmol) in methanol (253 mL) and water (506 mL). After stirring the reaction mixture for 3 days at rt, the solvent was removed by filtration and the precipitate was washed with water (100 mL) and Et_2O (100 mL). Subsequently, the precipitate was dissolved in DCM (500 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the carbamate derivative **153**[155] (37.9 g, 65%) as a crystalline white powder, m.p. (DCM) 155−160 °C; R_f 0.63 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3352, 3011, 2980, 2934, 1699, 1475, 1358, 1288, 1135, 1087, 1007; δ_H (400 MHz, $CDCl_3$) 7.92 (2H, d, *J* 7.5, phenyl 2,6-H_2), 7.65 (1H, t, *J* 7.5, phenyl 4-H), 7.54 (2H, t, *J* 7.5, phenyl 3,5-H_2), 5.47 (1H, t, *J* 6.9, NH), 4.53 (2H, d, *J* 6.9, 1-H_2), 1.25 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 153.9 (C=O), 137.0 (phenyl C-1), 134.1 (phenyl C-4), 129.3 (phenyl C_2-3,5), 129.1 (phenyl C_2-2,6), 81.1 (^{t}Bu C_1), 62.2 (C-1), 28.1 (^{t}Bu C_3); HRMS found MH^+, 272.0946. $C_{12}H_{17}NO_4S$ requires *MH*, 272.0951.

Prop-2-ene-1-yl-4-benzoyl-2-({[(*tert*-butoxy)carbonyl]amino}methyl)-3-oxomorpholine-2-carboxylate

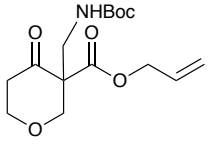


147a

According to General Procedure I, the allyl ester derivative **146a** (5.00 g, 17.3 mmol) was stirred for 18 h to give a crude material. The crude material was purified by flash column chromatography, eluting with 20:80 EtOAc−hexane to yield the quaternary allyl ester derivative **147a**[142] (6.00 g, 83%) as a colourless oil, R_f 0.70 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3390, 2977, 1687, 1504, 1366, 1275, 1228, 1143, 1064; δ_H (500 MHz, $CDCl_3$) 7.69-7.62 (2H, m, phenyl 2,6-H_2), 7.52 (1H, tt, *J* 7.1 and 1.2, phenyl 4-H), 7.42-7.37 (2H, m, phenyl 3,5-H_2), 5.96 (1H, ddt, *J* 17.2, 10.4 and 5.8, propenyl 2-H), 5.40 (1H, app. dq, *J* 17.2 and 1.3, propenyl 3-H_{trans}), 5.32 (1H, app. dq, *J* 10.4 and 1.3, propenyl 3-H_{cis}), 5.00 (1H, br. s, NH), 4.74 (2H, app. d, *J* 5.8, propenyl 1-H_2), 4.30-4.23 (1H, m, 6-H_A), 4.19 (1H, dt, *J* 12.3 and 4.0, 6-H_B), 4.00 (1H, ddd, *J* 13.4, 9.3 and 4.0, 5-H_A), 3.92 (1H, dt, *J* 13.4 and 3.6, 5-H_B), 3.82 (1H, dd, *J* 14.3 and 7.4, methylcarbamate 1-H_A), 3.74 (1H, dd, *J* 14.3 and 5.8, methylcarbamate 1-H_B),

1.42 (9H, s, ^{t}Bu); δ_C (125 MHz, $CDCl_3$) 172.7 (C-3), 167.7 (benzoyl C=O), 167.5 (carboxylate C=O), 155.7 (Boc C=O), 134.7 (phenyl C-1), 134.4 (phenyl C-4), 131.0 (propenyl C-3), 128.5 (phenyl C_2-2,6), 128.3 (phenyl C_2-3,5), 119.9 (propenyl C-2), 83.0 (C-2), 79.8 (^{t}Bu C_1), 67.1 (propenyl C-1), 62.1 (C-6), 44.9 (C-5), 44.7 (methylcarbamate C-1), 28.4 (^{t}Bu C_3); HRMS found MH^+, 419.1814. $C_{21}H_{26}N_2O_7$ requires *MH*, 419.1812.

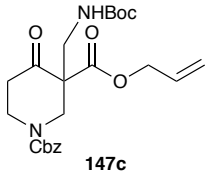
Prop-2-en-1-yl 3-({[(*tert*-butoxy)carbonyl]amino}methyl)-4-oxooxane-3-carboxylate



147b

According to General Procedure I, the allyl ester derivative **146b** (7.00 g, 38.0 mmol) was stirred for 18 h to give a crude material. The crude material was purified by flash column chromatography, eluting with 20:80 EtOAc−hexane to yield the *quaternary allyl ester derivative **147b*** (10.1 g, 85%) as a colourless oil, R_f 0.67 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3403, 2976, 2934, 2868, 1709, 1501, 1366, 1249, 1225, 1212, 1163, 1135, 1112; δ_H (400 MHz, $CDCl_3$) 5.88 (1H, ddt, *J* 17.3, 10.4 and 5.8, propenyl 2-H), 5.31 (1H, app. dq, *J* 17.3 and 1.4, propenyl 3-H_{trans}), 5.24 (1H, app. dq, *J* 10.4 and 1.4, propenyl 3-H_{cis}), 5.09 (1H, app. t, *J* 5.6, NH), 4.65 (1H, app. t, *J* 1.4, propenyl 1-H_A), 4.64 (1H, app. t, *J* 1.4, propenyl 1-H_B), 4.44 (1H, d, *J* 11.8, 2-H_A), 4.14-4.05 (1H, m, 6-H_A), 3.87-3.76 (1H, m, 6-H_B), 3.60 (1H, dd, *J* 14.1 and 6.8, methylcarbamate 1-H_A), 3.58 (1H, d, *J* 11.8, 2-H_B), 3.50 (1H, dd, *J* 14.1 and 6.8, methylcarbamate 1-H_B), 2.76 (1H, ddd, *J* 15.4, 9.3 and 6.4, 5-H_A), 2.59 (1H, app. dt, *J* 14.9 and 4.4, 5-H_B), 1.38 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 204.1 (C-4), 169.4 (carboxylate C=O), 155.8 (Boc C=O), 131.3 (propenyl C-2), 119.2 (propenyl C-3), 79.7 (^{t}Bu C_1), 72.3 (C-2), 68.4 (C-6), 66.5 (propenyl C-1), 64.0 (C-3), 41.0 (C-5 and methylcarbamate C-1), 28.3 (^{t}Bu C_3); HRMS found MH^+, 314.1601. $C_{15}H_{23}NO_6$ requires *MH*, 314.1598.

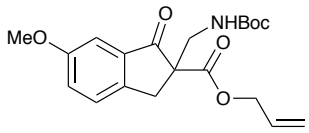
1-Benzyl 3-prop-2-en-1-yl 3-({[(*tert*-butoxy)carbonyl]amino}methyl)-4-oxopiperidine-1,3-dicarboxylate



147c

According to General Procedure I, the allyl ester derivative **146c** (6.47 g, 20.4 mmol) was stirred for 18 h to give a crude material. The crude material was purified by flash column chromatography, eluting with 20:80 EtOAc−hexane to yield the *quaternary allyl ester derivative* ***147c*** (7.69 g, 84%) as a colourless oil, R_f 0.63 (50:50 petrol−EtOAc); v_{max}/cm^{-1} 3398, 2977, 1697, 1499, 1423, 1365, 1234, 1138; δ_H (500 MHz, CD_3OD, 333 K) 7.42-7.28 (5H, m, phenyl), 5.86 (1H, ddt, *J* 17.3, 10.5 and 5.8, propenyl 2-H), 5.28 (1H, app. dq, *J* 17.3 and 1.4, propenyl 3-H_{trans}), 5.19 (1H, app. dq, *J* 10.5 and 1.4, propenyl 3-H_{cis}), 5.16 (1H, app. s, phenylmethyl 1-H_A), 5.15 (1H, app. s, phenylmethyl 1-H_B), 4.61 (1H, d, *J* 13.9, 2-H_A), 4.57-4.52 (2H, m, propenyl 1-H_2), 4.18-4.09 (1H, m, 6-H_A), 3.61 (1H, d, *J* 14.4, methylcarbamate 1-H_A), 3.46 (1H, d, *J* 14.4, methylcarbamate 1-H_B), 3.46-3.39 (1H, m, 6-H_B), 3.35 (1H, d, *J* 13.9, 2-H_B), 2.68 (1H, ddd, *J* 15.2, 9.9 and 6.5, 5-H_A), 2.53 (1H, app. dt, *J* 15.2 and 4.7, 5-H_B), 1.41 (9H, s, ^{t}Bu); δ_C (125 MHz, CD_3OD, 333 K) 205.1 (C-4), 170.3 (carboxylate C=O), 157.9 (Boc C=O), 156.8 (Cbz C=O), 137.9 (phenyl C-1), 132.8 (propenyl C-2), 129.5 (phenyl C_2-3,5), 129.2 (phenyl C-4), 129.0 (phenyl C_2-2,6), 119.3 (propenyl C-3), 80.7 (^{t}Bu C_1), 68.9 (phenylmethyl C-1), 67.6 (propenyl C-1), 63.2 (C-3), 49.5 (C-2), 44.2 (C-6), 42.9 (methylcarbamate C-1), 40.4 (C-5), 28.7 (^{t}Bu C_3); HRMS found MNa^+, 469.1936. $C_{23}H_{30}N_2O_7$ requires *MNa*, 469.1945.

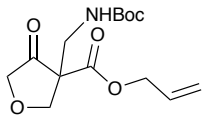
Prop-2-en-1-yl 2-({[(*tert*-butoxy)carbonyl]amino}methyl)-6-methoxy-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate



147d

According to General Procedure I, the allyl ester derivative **146d** (5.12 g, 20.8 mmol) was stirred for 18 h to give a crude material. The crude material was purified by flash column chromatography, eluting with 15:85 EtOAc−hexane to yield the *quaternary allyl ester derivative* ***147d*** (7.80 g, >99%) as an amorphous colourless solid, R_f 0.50 (70:30 petrol−EtOAc); ν_{max}/cm^{-1} 3377, 2974, 2940, 1727, 1697, 1514, 1492, 1280, 1241, 1189, 1161, 1134; δ_H (300 MHz, $CDCl_3$) 7.37 (1H, d, *J* 8.3, 4-H), 7.21 (1H, dd, *J* 8.3 and 2.6, 5-H), 7.17 (1H, d, *J* 2.6, 7-H), 5.81 (1H, ddt, *J* 17.2, 10.6 and 5.6, propenyl 2-H), 5.20 (1H, dd, *J* 17.2 and 1.3, propenyl 3-H_{trans}), 5.18 (1H, br. s, NH), 5.17 (1H, dd, *J* 10.6 and 1.3, propenyl 3-H_{cis}), 4.59 (2H, app. dt, *J* 5.6 and 1.5, propenyl 1-H_2), 3.82 (3H, s, methoxy), 3.67 (1H, d, *J* 6.6, methylcarbamate 1-H_A), 3.65 (1H, d, *J* 6.6, methylcarbamate 1-H_B), 3.45 (1H, d, *J* 17.2, 3-H_A), 3.24 (1H, d, *J* 17.2, 3-H_B), 1.40 (9H, s, ^{t}Bu); δ_C (75 MHz, $CDCl_3$) 201.0 (C-1), 170.8 (carboxylate C=O), 159.9 (C-6), 156.4 (Boc C=O), 146.4 (C-3a), 136.2 (C-7a), 131.5 (propenyl C-2), 127.4 (C-4), 125.3 (C-5), 118.6 (propenyl C-3), 105.9 (C-7), 79.7 (^{t}Bu C_1), 66.2 (propenyl C-1), 62.4 (C-2), 55.7 (methoxy), 44.0 (methylcarbamate C-1), 35.0 (C-3), 28.4 (^{t}Bu, C_3); HRMS found MNa^+, 398.1572. $C_{20}H_{25}NO_6$ requires *MNa*, 398.1574.

Prop-2-en-1-yl 3-({[(*tert*-butoxy)carbonyl]amino}methyl)-4-oxooxolane-3-carboxylate

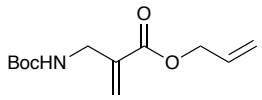


147e

According to General Procedure I, the allyl ester derivative **146e** (9.60 g, 56.4 mmol) was stirred for 3 h to give a crude material. The crude material was purified by flash column chromatography, eluting with 10:90→15:85

EtOAc−petrol to yield the *quaternary allyl ester derivative* ***147e*** (14.7 g, 87%) as a colourless oil, R_f 0.41 (70:30 petrol−EtOAc); ν_{max}/cm^{-1} 3367, 2978, 1770, 1710, 1504, 1366; δ_H (400 MHz, $CDCl_3$) 5.86 (1H, ddt, *J* 17.2, 10.5 and 5.7, propenyl 2-H), 5.30 (1H, app. dq, *J* 17.2 and 1.3, propenyl 3-H_{trans}), 5.25 (1H, app. dq, *J* 10.5 and 1.3, propenyl 3-H_{cis}), 5.11 (1H, app. t, *J* 5.3, NH), 4.65 (1H, app. t, *J* 1.4, propenyl 1-H_A), 4.64 (1H, app. t, *J* 1.4, propenyl 1-H_B), 4.49 (1H, d, *J* 9.9, 2-H_A), 4.21 (1H, d, *J* 9.9, 2-H_B), 4.11 (1H, d, *J* 17.2, 5-H_A), 4.05 (1H, d, *J* 17.2, 5-H_B), 3.72-3.55 (2H, m, methylcarbamate 1-H_2), 1.40 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 208.8 (C-4), 168.6 (carboxylate C=O), 156.2 (Boc C=O), 131.1 (propenyl C-2), 119.2 (propenyl C-3), 80.1 (^{t}Bu C_1), 73.3 (C-2), 71.2 (C-5), 66.7 (propenyl C-1), 61.0 (C-3), 41.4 (methylcarbamate C-1), 28.4 (^{t}Bu C_3); HRMS found MNa^+, 322.1256. $C_{14}H_{21}NO_6$ requires *MNa*, 322.1261.

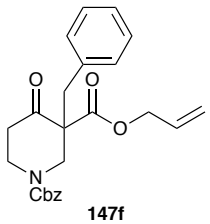
Prop-2-en-1-yl 2-({[(*tert*-butoxy)carbonyl]amino}methyl)prop-2-enoate



157

According to General Procedure I, the allyl ester derivative **146e** (0.41 g, 2.41 mmol) was stirred for 18 h to give a crude material. The crude material was purified by flash column chromatography, eluting with 10:90 EtOAc−hexane to yield the *α,β-unsaturated ester* ***157*** (0.39 g, 67%) as a light-yellow oil, R_f 0.54 (70:30 petrol−EtOAc); ν_{max}/cm^{-1} 3366, 2978, 2933, 1702, 1509, 1365, 1249, 1154; δ_H (400 MHz, $CDCl_3$) 6.26 (1H, s, 3-H_A), 5.93 (1H, ddt, *J* 17.1, 10.4 and 5.6, propenyl 2-H), 5.78 (1H, s, 3-H_B), 5.32 (1H, app. dq, *J* 17.1 and 1.4, propenyl 3-H_{trans}), 5.23 (1H, app. dq, *J* 10.4 and 1.4, propenyl 3-H_{cis}), 4.99 (1H, br. s, NH), 4.65 (2H, dt, *J* 5.6 and 1.4, propenyl 1-H_2), 3.94 (2H, d, *J* 6.0, methylcarbamate 1-H_2), 1.42 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 165.9 (C-1), 155.7 (Boc C=O), 137.3 (C-2), 132.0 (propenyl C-2), 126.6 (C-3), 118.4 (propenyl C-3), 79.6 (^{t}Bu C_1), 65.5 (propenyl C-1), 41.7 (methylcarbamate C-1), 28.5 (^{t}Bu C_3); HRMS found MNa^+, 264.1205. $C_{12}H_{19}NO_4$ requires *MNa*, 264.1206.

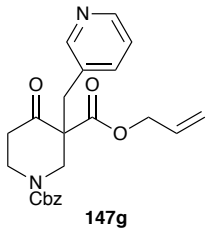
1-Benzyl 3-prop-2-en-1-yl 3-benzyl-4-oxopiperidine-1,3-dicarboxylate



147f

According to General Procedure J, the allyl ester derivative **146c** (0.75 g. 2.36 mmol), K_2CO_3 (1.30 g, 9.44 mmol) and (bromomethyl)benzene (0.56 mL, 4.72 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 20:80 EtOAc−hexane to yield the *quaternary allyl ester derivative* ***147f*** (0.86 g, 89%) as a colourless oil, R_f 0.38 (70:30 petrol−EtOAc); v_{max}/cm^{-1} 3063, 3030, 2936, 1698, 1427, 1266, 1239, 1217, 1178, 1121; δ_H (500 MHz, $CDCl_3$, 323 K) 7.41-7.15 (10H, phenyl), 5.77 (1H, ddt, *J* 16.9, 10.7 and 5.6, propenyl 2-H), 5.26 (1H, dd, *J* 16.9 and 1.3, propenyl 3-H_{trans}), 5.21 (1H, app. dq, *J* 10.7 and 1.3, propenyl 3-H_{cis}), 5.17 (1H, app. s, Cbz phenylmethyl 1-H_A), 5.16 (1H, app. s, Cbz phenylmethyl 1-H_B), 4.72 (1H, dd, *J* 13.8 and 2.1, 2-H_A), 4.50 (2H, d, *J* 5.6, propenyl 1-H_2), 4.25 (1H, app. br. s, 6-H_A), 3.31 (1H, d, *J* 13.9, phenylmethyl 1-H_A), 3.31-3.25 (1H, m, 6-H_B), 3.17 (1H, d, *J* 13.9, phenylmethyl 1-H_B), 3.14 (1H, d, *J* 13.8, 2-H_B), 2.75 (1H, ddd, *J* 14.9, 10.4 and 6.6, 5-H_A), 2.49 (1H, app. dt, *J* 14.9 and 4.4, 5-H_B); δ_C (125 MHz, $CDCl_3$, 323 K) 203.5 (C-4), 169.5 (carboxylate C=O), 155.2 (Cbz C=O), 136.6 (Cbz phenyl C-1), 135.6 (phenyl C-1), 131.4 (propenyl C-2), 130.6 (phenyl C_2-2,6), 128.6 (Cbz phenyl C_2-3,5), 128.5 (phenyl C_2-3,5), 128.2 (Cbz phenyl C_2-2,6), 128.0 (Cbz phenyl C-4), 127.2 (phenyl C-4), 119.3 (propenyl C-3), 67.7 (Cbz phenylmethyl C-1), 66.4 (propenyl C-1), 62.3 (C-3), 50.1 (C-2), 43.5 (C-6), 40.0 (C-5), 37.6 (phenylmethyl C-1); HRMS found MNa^+, 430.1624. $C_{24}H_{25}NO_5$ requires *MNa*, 430.1630.

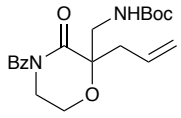
1-Benzyl 3-prop-2-en-1-yl 4-oxo-3-[(pyridin-3-yl)methyl]piperidine-1,3-dicarboxylate



147g

According to General Procedure J, the allyl ester derivative **146c** (1.00 g. 3.15 mmol), K_2CO_3 (2.17 g, 15.7 mmol) and 3-(bromomethyl)pyridine hydrobromide (1.03 g, 4.10 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 60:40 EtOAc−hexane to yield the *quaternary allyl ester derivative* ***147g*** (0.63 g, 49%) as a yellow oil, R_f 0.50 (EtOAc); v_{max}/cm^{-1} 3031, 2946, 1697, 1423, 1235, 1215, 1177, 1125; δ_H (500 MHz, CD_3OD, 333 K) 7.23 (2H, d, *J* 6.3, pyridinyl 2,6-H_2), 6.51 (1H, d, *J* 7.9, pyridinyl 4-H), 6.20-6.14 (5H, m, phenyl), 6.14-6.11 (1H, m, pyridinyl 5-H), 4.58 (1H, ddt, *J* 16.9, 10.1 and 6.0, propenyl 2-H), 4.05 (1H, dd, *J* 16.9 and 1.4, propenyl 3-H_{trans}), 4.01 (1H, dd, *J* 10.1 and 1.4, propenyl 3-H_{cis}), 3.97 (1H, app. s, phenylmethyl 1-H_A), 3.96 (1H, app. s, phenylmethyl 1-H_B), 3.50 (1H, dd, *J* 13.6 and 2.2, 2-H_A), 3.30-3.27 (1H, m, propenyl 1-H_A), 3.10-3.04 (1H, m, 6-H_A), 2.18 (1H, d, *J* 14.3, pyridinylmethyl, 1-H_A), 2.18-2.15 (2H, m, 6-H_B and propenyl 1-H_B), 2.12 (1H, d, *J* 13.6, 2-H_B), 1.82 (1H, d, *J* 14.3, pyridinylmethyl 1-H_B), 1.63-1.52 (1H, m, 5-H_A), 1.35 (1H, app. dt, *J* 14.9 and 4.1, 5-H_B); δ_C (125 MHz, CD_3OD, 333 K) 204.6 (C-4), 170.5 (carboxylate C=O), 156.6 (Cbz C=O), 151.9 (pyridinyl 2-C), 148.7 (pyridinyl C-6), 140.1 (pyridinyl C-4), 137.8 (phenyl C-1), 133.8 (pyridinyl C-3), 132.5 (propenyl C-2), 129.5 (phenyl C_2-3,5), 129.1 (phenyl C-4), 128.9 (phenyl C_2-2,6), 124.7 (pyridinyl C-5), 119.8 (propenyl C-3), 68.8 (phenylmethyl C-1), 67.5 (propenyl C-1), 63.3 (C-3), 51.2 (C-2), 44.5 (C-6), 40.6 (C-5), 35.4 (pyridinylmethyl C-1); HRMS found MH^+, 409.1755. $C_{23}H_{24}N_2O_5$ requires *MH*, 409.1763.

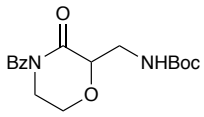
***tert*-Butyl *N*-{[4-benzoyl-3-oxo-2-(prop-2-en-1-yl)morpholin-2-yl]methyl} carbamate**



148h

According to General Procedure K, the quaternary allyl ester derivative **147a** (6.00 g, 14.3 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 20:80 EtOAc−hexane to yield the lactam derivative **148h**[142] (4.30 g, 80%) as a brown oil, R_f 0.65 (50:50 petrol−EtOAc); v_{max}/cm^{-1} 3379, 2977, 2933, 1682, 1505, 1366, 1277, 1246, 1221, 1140, 1116, 1087; δ_H (400 MHz, $CDCl_3$) 7.55 (2H, d, *J* 7.6, phenyl 2,6-H_2), 7.50 (1H, t, *J* 7.6, phenyl 4-H), 7.39 (2H, t, *J* 7.6, phenyl 3,5-H_2), 5.88 (1H, ddt, *J* 16.0, 11.1 and 7.3, propenyl 2-H), 5.20 (1H, app. d, *J* 10.5, propenyl 3-H_{cis}), 5.19 (1H, app. d, *J* 16.8, propenyl 3-H_{trans}), 4.90 (1H, br. s, NH), 4.10-4.04 (2H, m, 6-H_2), 3.98 (1H, app. dt, *J* 9.9 and 4.8, 5-H_A), 3.90 (1H, app. dt, *J* 13.1 and 4.8, 5-H_B), 3,62 (1H, dd, *J* 14.0 and 7.1, methylcarbamate 1-H_A), 3.39 (1H, dd, *J* 14.0 and 5.6, methylcarbamate 1-H_B), 2.67 (1H, dd, *J* 14.3 and 7.3, propenyl 1-H_A), 2.51 (1H, dd, *J* 14.3 and 7.0, propenyl 1-H_B), 1.43 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 172.9 (C-3), 172.6 (benzoyl C=O), 155.8 (Boc C=O), 135.4 (phenyl C-1), 132.0 (phenyl C-4), 131.6 (propenyl C-2), 128.2 (phenyl C_2-3,5), 128.0 (phenyl C_2-2,6), 119.8 (propenyl C-3), 82.1 (C-2), 79.7 (^{t}Bu C_1), 60.4 (C-6), 45.7 (methylcarbamate C-1), 45.4 (C-5), 39.7 (propenyl C-1), 28.4 (^{t}Bu C_3); HRMS found MH^+, 375.1919. $C_{20}H_{26}N_2O_5$ requires *MH*, 375.1914

***tert*-Butyl *N*-[(4-benzoyl-3-oxomorpholin-2-yl)methyl]carbamate**

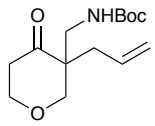


158

By modification of an existing procedure,[142] toluene (8.00 mL) was added to a mixture of PPh_3 (20.0 mg, 76.2 μmol) and $Pd(OAc)_2$ (4.26 mg, 18.9 μmol). After stirring the mixture for 30 min at rt, a solution of the quaternary allyl ester derivative **147a** (0.16 g, 0.28 mmol) in toluene (4.00 mL) was added and the

reaction mixture was stirred for 16 h at 40 °C. Subsequently, the solution was allowed to cool to rt, filtered through celite and concentrated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography, eluting with 20:80 EtOAc−hexane to yield the *lactam derivative* ***158*** (50.0 mg, 39%) as a colourless oil, R_f 0.52 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3369, 2976, 2930, 1682, 1507, 1366, 1275, 1226, 1158, 1136; δ_H (400 MHz, $CDCl_3$) 7.57-7.54 (2H, m, phenyl 2,6-H_2), 7.51 (1H, tt, *J* 7.5 and 1.3, phenyl 4-H), 7.41 (2H, app. t, *J* 7.5, phenyl 3,5-H_2), 4.94 (1H, br., NH), 4.26-4.21 (2H, m, 2-H and 6-H_A), 4.02-3.95 (1H, m, 5-H_A), 3.95-3.88 (2H, m, 6-H_B and 5-H_B), 3.68-3.53 (2H, m, methylcarbamate 1-H_2), 1.45 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 173.0 (C-3 and benzoyl C=O), 155.7 (Boc C=O), 135.3 (phenyl C-1), 132.2 (phenyl C-4), 128.3 (phenyl C_2-3,5), 128.1 (phenyl C_2-2,6), 79.8 (^{t}Bu C_1), 77.5 (C-2), 63.4 (C-6), 45.1 (C-5), 41.9 (methylcarbamate C-1), 28.5 (^{t}Bu C_3); HRMS found MNa^+, 357.1431. $C_{17}H_{22}N_2O_5$ requires *MNa*, 357.1426.

tert-Butyl _N_-{[4-oxo-3-(prop-2-en-1-yl)oxan-3-yl]methyl}carbamate

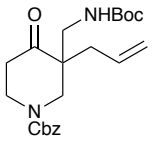


148i

According to General Procedure K, the quaternary allyl ester derivative **147b** (10.1 g, 32.2 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 10:90 EtOAc−hexane to yield the *ketone derivative* ***148i*** (6.60 g, 76%) as a brown oil, R_f 0.39 (70:30 petrol−EtOAc); ν_{max}/cm^{-1} 3351, 2975, 2932, 2861, 1702, 1504, 1365, 1246, 1214, 1163, 1115; δ_H (400 MHz, $CDCl_3$) 5.66 (1H, app. dq, *J* 16.8 and 7.5, propenyl 2-H), 5.15-5.10 (2H, m, propenyl 3-H_2), 4.83 (1H, br. s, NH), 4.14-4.07 (1H, m, 6-H_A), 3.83 (1H, d, *J* 11.8, 2-H_A), 3.80-3.77 (1H, m, 6-H_B), 3.59 (1H, d, *J* 11.8, 2-H_B), 3.35 (1H, dd, *J* 14.3 and 7.9, methylcarbamate 1-H_A), 3.26 (1H, dd, *J* 14.3 and 5.5, methylcarbamate 1-H_B), 2.65 (1H, ddd, *J* 15.1, 9.8 and 6.5, 5-H_A), 2.53 (1H, dd, *J* 14.3 and 7.5, propenyl 1-H_A), 2.47 (1H, app. dt, *J* 15.1 and 4.1, 5-H_B), 2.34 (1H, dd, *J* 14.3 and 7.5, propenyl 1-H_B), 1.41 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 210.1 (C-4), 156.0 (Boc C=O), 131.9 (propenyl C-2), 119.3 (propenyl C-3), 79.4 (^{t}Bu C_1), 73.1 (C-2), 68.2 (C-6), 55.1 (C-3), 42.0

(methylcarbamate C-1), 40.1 (C-5), 36.9 (propenyl C-1), 28.3 (^{t}Bu C_3); HRMS found MH^+, 270.1701. $C_{14}H_{23}NO_4$ requires *MH*, 270.1699.

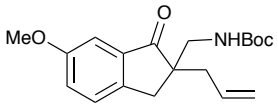
Benzyl 3-({[(*tert*-butoxy)carbonyl]amino}methyl)-4-oxo-3-(prop-2-en-1-yl) piperidine-1-carboxylate



148j

According to General Procedure K, the quaternary allyl ester derivative **147c** (7.56 g, 16.9 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 20:80 EtOAc−hexane to yield the *ketone derivative* ***148j*** (5.93 g, 87%) as a yellow oil, R_f 0.74 (50:50 petrol−EtOAc); v_{max}/cm^{-1} 3366, 2976, 2931, 1689, 1429, 1365, 1273, 1157; δ_H (500 MHz, CD_3OD, 333 K) 7.42-7.27 (5H, m, phenyl), 5.67 (1H, app. dq, *J* 16.9 and 8.0, propenyl 2-H), 5.18 (2H, s, phenylmethyl 1-H_2), 5.06 (1H, app. d, *J* 10.8, propenyl 3-H_{cis}), 5.05 (1H, app. d, *J* 18.8, propenyl 3-H_{trans}), 3.93-3.83 (1H, m, 6-H_A), 3.75 (1H, d, *J* 14.0, 2-H_A), 3.67 (1H, app. br. s, 6-H_B), 3.52 (1H, d, *J* 14.0, 2-H_B), 3.37 (1H, d, *J* 14.7, methylcarbamate 1-H_A), 3.15 (1H, d, *J* 14.7, methylcarbamate 1-H_B), 2.63-2.53 (1H, m, 5-H_A), 2.53-2.45 (1H, m, 5-H_B), 2.34 (1H, dd, *J* 14.2 and 7.0, propenyl 1-H_A), 2.24 (1H, dd, *J* 14.2 and 8.0, propenyl 1-H_B), 1.41 (9H, s, ^{t}Bu); δ_C (125 MHz, CD_3OD) 211.1 (4-C), 158.2 (Boc C=O), 157.2 (Cbz C=O), 137.9 (phenyl C-1), 133.6 (propenyl C-2), 129.6 (phenyl C_2-3,5), 129.2 (phenyl C_2-2,6), 129.0 (phenyl C-4), 119.4 (propenyl C-3), 80.5 (^{t}Bu C_1), 68.8 (phenylmethyl C-1), 55.2 (C-3), 50.3 (C-2), 44.2 (C-6 and methylcarbamate C-1), 39.6 (C-5), 37.7 (propenyl C-1), 28.7 (^{t}Bu C_3); HRMS found MNa^+, 425.2043. $C_{22}H_{30}N_2O_5$ requires *MNa*, 425.2046.

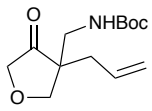
***tert*-Butyl *N*-{[6-methoxy-1-oxo-2-(prop-2-en-1-yl)-2,3-dihydro-1*H*-inden-2-yl]methyl} carbamate**



148k

According to General Procedure K, the quaternary allyl ester derivative **147d** (7.80 g, 20.8 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 10:90 EtOAc−hexane to yield the *ketone derivative* ***148k*** (5.58 g, 81%) as an amorphous brown solid, R_f 0.57 (70:30 petrol−EtOAc); ν_{max}/cm^{-1} 3359, 2975, 2928, 1694, 1490, 1274, 1245, 1161; δ_H (400 MHz, $CDCl_3$) 7.31 (1H, d, *J* 8.4, 4-H), 7.18 (1H, dd, *J* 8.4 and 2.6, 5-H), 7.13 (1H, d, *J* 2.6, 7-H), 5.60 (1H, ddt, *J* 17.0, 10.1 and 7.4, propenyl 2-H), 5.07 (1H, dd, *J* 17.0 and 1.9, propenyl 3-H_{trans}), 5.00 (1H, dd, *J* 10.1 and 1.9, propenyl 3-H_{cis}), 4.90 (1H, app. t, *J* 5.4, NH), 3.80 (3H, s, methoxy), 3.46 (1H, dd, *J* 13.7 and 6.6, methylcarbamate 1-H_A), 3.29 (1H, dd, *J* 13.7 and 6.1, methylcarbamate 1-H_B), 3.00 (1H, d, *J* 17.2, 3-H_A), 2.93 (1H, d, *J* 17.2, 3-H_B), 2.45-2.27 (2H, m, propenyl 1-H_2), 1.38 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 209.9 (C-1), 159.6 (C-6), 156.4 (Boc C=O), 146.5 (C-3a), 137.4 (C-7a), 132.9 (propenyl C-2), 127.4 (C-4), 124.8 (C-5), 119.1 (propenyl C-3), 105.2 (C-7), 79.5 (Boc C_1), 55.7 (methoxy), 54.0 (C-2), 45.7 (methylcarbamate C-1), 39.4 (propenyl C-1), 34.9 (C-3), 28.4 (Boc C_3); HRMS found MNa^+, 354.1679. $C_{19}H_{25}NO_4$ requires *MNa*, 354.1675.

***tert*-Butyl *N*-{[4-oxo-3-(prop-2-en-1-yl)oxolan-3-yl]methyl}carbamate**

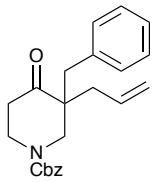


148l

According to General Procedure K, the quaternary allyl ester derivative **147e** (14.7 g, 49.1 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 20:80 EtOAc−hexane to yield the *ketone derivative* ***148l*** (11.0 g, 88%) as a light-brown oil, R_f 0.42 (85:15 petrol−EtOAc); ν_{max}/cm^{-1} 3357, 2977, 2933, 1697, 1515, 1392, 1366, 1248,

1158, 1059; δ_H (400 MHz, $CDCl_3$) 5.70 (1H, ddt, *J* 16.6, 10.5 and 7.4, propenyl 2-H), 5.14-5.10 (1H, m, propenyl 3-H_{trans}), 5.12-5.08 (1H, m, propenyl 3-H_{cis}), 4.84 (1H, app. t, *J* 5.3, NH), 4.10 (1H, d, *J* 9.9, 2-H_A), 3.99 (1H, d, *J* 9.9, 2-H_B), 3.94 (2H, app. s, 5-H_2), 3.31 (1H, app. s, methylcarbamate 1-H_A), 3.29 (1H, app. s, methylcarbamate 1-H_B), 2.27 (1H, app. d, *J* 1.2, propenyl 1-H_A), 2.25 (1H, app. d, *J* 1.2, propenyl 1-H_B), 1.40 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 217.6 (C-4), 156.2 (Boc C=O), 131.9 (propenyl C-2), 119.8 (propenyl C-3), 79.9 (^{t}Bu C_1), 73.8 (C-2), 71.5 (C-5), 52.5 (C-3), 42.4 (methylcarbamate C-1), 36.3 (propenyl C-1), 28.4 (^{t}Bu C_3); HRMS found MNa^+, 278.1363. $C_{13}H_{21}NO_4$ requires *MNa*, 278.1362.

Benzyl 3-benzyl-4-oxo-3-(prop-2-en-1-yl)piperidine-1-carboxylate

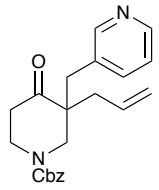


148m

According to General Procedure K, the quaternary allyl ester derivative **147f** (0.83 g, 2.03 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 20:80 EtOAc−hexane to yield the *ketone derivative* ***148m*** (0.66 g, 89%) as a brown oil, R_f 0.45 (70:30 petrol−EtOAc); ν_{max}/cm^{-1} 3063, 3029, 2916, 1694, 1430, 1231; δ_H (500 MHz, CD_3OD, 333 K) 7.36-7.04 (10H, m, phenyl), 5.70 (1H, ddt, *J* 17.6, 10.4 and 7.3, propenyl 2-H), 5.13 (2H, s, Cbz phenylmethyl 1-H_2), 5.05 (1H, app. d, *J* 10.4, propenyl 3-H_{cis}), 5.03 (1H, app. d, *J* 17.6, propenyl 3-H_{trans}), 3.77 (1H, app. dt, *J* 13.0 and 6.5, 6-H_A), 3.68 (1H, d, *J* 13.8, 2-H_A), 3.58 (1H, d, *J* 13.8, 2-H_B), 3.56-3.51 (1H, m, 6-H_B), 2.93 (1H, d, *J* 13.9, phenylmethyl 1-H_A), 2.80 (1H, d, *J* 13.9, phenylmethyl 1-H_B), 2.55-2.40 (2H, m, 5-H_2), 2.31 (1H, dd, *J* 14.3 and 6.8, propenyl 1-H_A), 2.16 (1H, dd, *J* 14.3 and 7.8, propenyl 1-H_B); δ_C (125 MHz, CD_3OD, 333 K) 212.0 (C-4), 157.2 (Cbz C=O), 137.9 (Cbz phenyl C-1), 137.8 (phenyl C-1), 134.0 (propenyl C-2), 131.5 (phenyl C_2-3,5), 129.5 (Cbz phenyl C_2-3,5), 129.2 (phenyl C_2-2,6 and Cbz phenyl C_2-2,6), 129.0 (Cbz phenyl C-4), 127.7 (phenyl C-4), 119.3 (propenyl C-3), 68.7 (Cbz phenylmethyl C-1), 54.6 (C-3), 51.0 (C-2), 43.8 (C-6), 40.7 (phenylmethyl C-1), 39.7 (C-5), 39.6

(propenyl C-1); HRMS found MNa^+, 386.1717. $C_{23}H_{25}NO_3$ requires *MNa*, 386.1732.

Benzyl 4-oxo-3-(prop-2-en-1-yl)-3-[(pyridin-3-yl)methyl]piperidine-1-carboxylate



148n

According to General Procedure K, the quaternary allyl ester derivative **147g** (0.60 g, 1.47 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 60:40 EtOAc−hexane to yield the *ketone derivative **148n*** (0.43 g, 80%) as a yellow oil, R_f 0.48 (EtOAc); ν_{max}/cm^{-1} 3030, 2915, 1693, 1422, 1230; δ_H (500 MHz, CD_3OD, 333 K) 8.37 (1H, dd, *J* 4.9 and 1.7, pyridinyl 6-H), 8.32 (1H, d, *J* 2.3, pyridinyl 2-H), 7.58 (1H, d, *J* 7.9, pyridinyl 4-H), 7.37-7.24 (6H, m, phenyl and pyridinyl 5-H), 5.69 (1H, ddt, *J* 17.1, 10.3 and 7.3, propenyl 2-H), 5.15 (2H, s, phenylmethyl 1-H_2), 5.09 (1H, app. dt, *J* 10.3 and 1.6, propenyl 3-H_{cis}), 5.05 (1H, dd, *J* 17.1 and 1.6, propenyl 3-H_{trans}), 3.87-3.81 (1H, m, 6-H_A), 3.74 (1H, dd, *J* 13.8 and 1.2, 2-H_A), 3.57 (1H, d, *J* 13.8, 2-H_B), 3.56-3.51 (1H, m, 6-H_B), 2.98 (1H, d, *J* 14.2, pyridinylmethyl 1-H_A), 2.84 (1H, d, *J* 14.2, pyridinylmethyl 1-H_B), 2.56 (1H, ddd, *J* 15.6, 8.3 and 6.1, 5-H_A), 2.48 (1H, app. dt, *J* 15.6 and 6.1, 5-H_B), 2.29 (1H, dd, *J* 14.6 and 6.8, propenyl 1-H_A), 2.20 (1H, dd, *J* 14.6 and 7.7, propenyl 1-H_B); δ_C (125 MHz, CD_3OD, 333 K) 211.3 (C-4), 157.2 (Cbz C=O), 151.8 (pyridinyl C-2), 148.4 (pyridinyl C-6), 140.0 (pyridinyl C-4), 137.9 (phenyl C-1), 134.5 (pyridinyl C-3), 133.5 (propenyl C-2), 129.5 (phenyl C_2-3,5), 129.2 (phenyl C_2-2,6), 129.1 (phenyl C-4), 124.7 (pyridinyl C-5), 119.7 (propenyl C-3), 68.7 (phenylmethyl C-1), 54.5 (C-3), 51.0 (C-2), 43.9 (C-6), 39.6 (propenyl C-1), 39.5 (C-5), 37.5 (pyridinylmethyl C-1); HRMS found MH^+, 365.1862. $C_{22}H_{24}N_2O_3$ requires *MH*, 365.1865.

5.2.3.3. Cyclisation Reactions

General Procedure L

By modification of an existing procedure,[158] 2-methyl-2-butene (7.50 eq) was added dropwise to BH_3•THF (3.50 eq of a 1.0 M solution in THF) at 0 °C. The mixture was stirred for 2 h at 0 °C. Subsequently, a solution of the alkene derivative (1.00 eq) in THF (0.35 M) at 0 °C was added dropwise. The reaction mixture was stirred for 45 min at 0 °C and for 1 h at rt. Afterwards, $NaBO_3$•$4H_2O$ (7.50 eq) and water (3 mL per 1.00 mmol of the alkene derivative) were added. After stirring the mixture vigorously for 18 h at rt, EtOAc (3 mL per 1.00 mmol of the alkene derivative) was added, the phases were separated and the aqueous phase was extracted with EtOAc (4 × (3 mL per 1.00 mmol of the alkene derivative)). Subsequently, the organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material.

General Procedure M

TFA (20.0 eq) and Et_3SiH (1.50 eq) were added to a solution of the hemiacetal derivative (1.00 eq) in DCM (0.10 M) at rt. The reaction mixture was stirred for 18 h at rt. After removing the solvent and TFA under reduced pressure, the crude material was dissolved in DCM (0.10 M), and Et_3N (10.0 eq) and Boc_2O (1.20 eq) were added. After stirring the reaction mixture for 18 h at rt, a saturated aqueous solution of $NaHCO_3$ (10 mL per 1.00 mmol of the hemiacetal derivative) was added, the phases were separated and the aqueous phase was extracted with DCM (3 × (4 mL per 1.00 mmol of the hemiacetal derivative)). Subsequnetly, the organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material.

General Procedure N

By modification of an existing procedure,[161] Et_3SiH (16.0 eq) was added dropwise to a solution of the hemiacetal derivative (1.00 eq) in DCM (16.0 mM) at rt. The mixture was cooled to –78 °C and BF_3•Et_2O (4.00 eq) was added dropwise. After stirring the reaction mixture at –78 °C for 2 h, it was allowed to warm to rt and stirred overnight. The solvent was removed under reduced pressure and the crude material was dissolved in DCM (0.10 M). Subsequently, Et_3N (5.00 eq) and Boc_2O (1.20 eq) were added and the reaction mixture was stirred overnight at rt. A saturated aqueous solution of NH_4Cl (10 mL per 1.00

mmol of the hemiacetal derivative) was added, the phases were separated and the aqueous phase was extracted with DCM (3 × (3 mL per 1.00 mmol of the hemiacetal derivative)). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material.

General Procedure O

TFA (20.0 eq) and Et_3SiH (1.50 eq) were added to a solution of the hemiacetal derivative (1.00 eq) in DCM (0.10 M) at rt. The reaction mixture was stirred for 18 h at rt. A saturated aqueous solution of $NaHCO_3$ (10 mL per 1.00 mmol of the hemiacetal derivative) was added, the phases were separated and the aqueous phase was extracted with DCM (3 × (4 mL per 1.00 mmol of the hemiacetal derivative)). Subsequently, the organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material.

General Procedure P

$TsOH•H_2O$ (0.03 eq) was added to a solution of the hemiacetal or hemiaminal derivative in MeOH (0.30 M) at rt. The reaction mixture was stirred for 18 h at rt. Subsequently, the solvent was removed under reduced pressure to give a crude material.

General Procedure Q

Ozonized oxygen gas was passed through a solution of the alkene derivative (1.00 eq) in DCM (0.10 M) at −78 °C until the solution became blue in colour. Subsequently, the solution was purged with oxygen gas until the blue colour disappeared and dimethyl sulfide (20.0 eq) was added dropwise. After stirring the reaction mixture for 30 min at −78 °C, it was allowed to warm to rt. Finally, it was stirred at rt for 18 h and the solvent was removed under reduced pressure to yield a crude material.

General Procedure R

According to an existing procedure,[142] the specified amount of a solution of diisobutylaluminium hydride 1.0 M in DCM was added dropwise to a solution of the ketone derivative (1.00 eq) in DCM (0.18 M) at the specified temperature. After stirring the reaction mixture for 1 h at the same temperature, the mixture

was allowed to warm to rt and a saturated aqueous solution of potassium sodium tartrate tetrahydrate (5 mL per 1.00 mmol of the ketone derivative) was added dropwise. Subsequently, the mixture was stirred for 18 h at rt, the phases were separated and the aqueous phase was extracted with DCM (5 × (3 mL per 1.00 mmol of the ketone derivative). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material.

General Procedure S

According to an existing procedure,[119] $NaHCO_3$ (2.00 eq) and I_2 (1.10 eq) were added to a solution of the alkene derivative (1.00 eq) in acetonitrile (0.10 M) at 0 °C. The reaction mixture was stirred at rt for the specified time. Subsequently, a saturated aqueous solution of $Na_2S_2O_3$ (7 mL per 1.00 mmol of the alkene derivative) was added, the phases were separated and the aqueous phase was extracted with EtOAc (3 × (7 mL per 1.00 mmol of the alkene derivative)). The organic phases were combined, washed with brine (3 mL per 1.00 mmol of the alkene derivative), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material.

General Procedure T

^{t}BuOK (3.00 eq) was added to a solution of the alcohol derivative (1.00 eq) in THF (75.0 mM) at 0 °C. After stirring the reaction mixture for the specified time at rt, a saturated aqueous solution of NH_4Cl (10 mL per 1.00 mmol of the alcohol derivative) and EtOAc (10 mL per 1.00 mmol of the alcohol derivative) were added. The phases were separated and the aqueous phase was extracted with EtOAc (4 × (5 mL per 1.00 mmol of the alcohol derivative)). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield a crude material.

General Procedure U

By modification of an existing procedure,[142] pyridine (31.0 eq) was added to a solution of the alcohol derivative (1.00 eq) in Ac_2O (26.4 eq) at rt. Subsequently, the reaction mixture was stirred for 18 h at rt and the solvent was removed under reduced pressure. The crude material was dissolved in DCM (3 mL per 1.00 mmol of the alcohol derivative) and an aqueous solution of 10% $CuSO_4$ (3

mL per 1.00 mmol of the alcohol derivative) was added. After stirring the mixture for 5 min at rt, the phases were separated and the aqueous phase was extracted with DCM (3 × (2 mL per 1.00 mmol of the alcohol derivative)). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield the specified acetate derivative.

General Procedure V

Ozonized oxygen gas was passed through a solution of the alkene derivative (1.00 eq) in DCM (0.10 M) at −78 °C until the solution became blue in colour. Subsequently, the solution was purged with oxygen gas until the blue colour disappeared and dimethyl sulfide (20.0 eq) was added dropwise. After stirring the reaction mixture for 30 min at −78 °C, it was allowed to warm to rt. Afterwards, it was stirred at rt for 18 h and the solvent was removed under reduced pressure. The crude material was dissolved in acetic acid (0.20 M) and $NaBH(OAc)_3$ (7.00 eq) was added. The reaction mixture was stirred for 2 h at rt. Subsequently, a saturated aqueous solution of $NaHCO_3$ (50 mL per 1.00 mmol of the alkene) and DCM (20 mL per 1.00 mmol of the alkene) were added. The mixture was stirred for 1 h at rt, the phases were separated and the aqueous phase was extracted with DCM (4 × (10 mL per 1.00 mmol of the alkene)). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material.

General Procedure W

Ozonized oxygen gas was passed through a solution of the alkene derivative (1.00 eq) in DCM (0.10 M) at −78 °C until the solution became blue in colour. Subsequently, the solution was purged with oxygen gas until the blue colour disappeared and dimethyl sulfide (20.0 eq) was added dropwise. After stirring the reaction mixture for 30 min at −78 °C, it was allowed to warm to rt. Afterwards, it was stirred at rt for 18 h and the solvent was removed under reduced pressure. The crude material was dissolved in DCM (0.10 M) and pyridinium dichromate (2.00 eq) and celite (0.4 g per 1.00 mmol of the alkene derivative) were added. The reaction mixture was stirred for 1 week at rt. Subsequently, the mixture was filtered through celite and concentrated under reduced pressure to give a crude material.

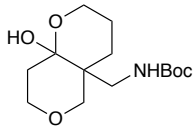
General Procedure X

By modification of an existing procedure,[178] triethylamine (2.00 eq) and methanesulfonyl chloride (1.20 eq) were added to a solution of the alcohol derivative (1.00 eq) in DCM (0.20 M) at 0 °C. The reaction mixture was stirred for 2 h at rt. Subsequently, TFA (65.0 eq) was added dropwise and the mixture was stirred for a further 5 h at rt. Afterwards, the solvent and TFA were removed under reduced pressure. After dissolving the crude product in DCM (0.20 M), triethylamine (35.0 eq) was added and the resulting mixture was stirred for 18 h at rt. Subsequently, Boc_2O (1.20 eq) was added and the reaction was stirred for a further 18 h at rt. A saturated aqueous solution of $NaHCO_3$ (5 mL per 1.00 mmol of the alcohol derivative) was added, the phases were separated and the aqueous phase was extracted with DCM (3 × (3 mL per 1.00 mmol of the alcohol derivative)). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material.

General Procedure Y

The respective aldehyde (1.50 eq) and TFA (35.0 eq) were added dropwise to a solution of the ketone derivative (1.00 eq) in MeOH (0.18 M). The reaction mixture was stirred at 65 °C for 4 days. Subsequently, the mixture was allowed to cool to rt and the solvent and TFA were removed under reduced pressure to give a crude material.

***tert*-Butyl *N*-({8a-hydroxy-octahydropyrano[4,3-*b*]pyran-4a-yl}methyl) carbamate**

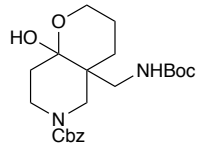


159a

According to General Procedure L, the alkene derivative **148i** (0.50 g, 1.85 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 50:50 EtOAc−hexane to yield the *hemiacetal derivative* ***159a*** (0.41 g, 76%, *dr* >95:<5 by ^{1}H-NMR) as an amorphous colourless solid, R_f 0.25 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3301, 2960, 2880, 1692, 1594, 1365, 1283, 1273, 1254, 1170, 1109, 1068; δ_H (400 MHz, CD_3OD) 6.32 (1H, app.t, *J* 5.1, NH), 4.06 (1H, ddd, *J* 12.4, 11.2 and 3.0, 2-H_A), 3.85 (1H,

d, *J* 11.6, 5-H_A), 3.80 (1H, app. tt, *J* 5.5 and 1.2, 7-H_A), 3.69-3.60 (2H, m, 2-H_B and 7-H_B), 3.44 (1H, d, *J* 11.6, 5-H_B), 3.40-3.32 (3H, m, OH and methylcarbamate 1-H_2), 2.02 (1H, td, *J* 13.1 and 5.5, 8-H_A), 1.92 (1H, app. td, *J* 13.3 and 4.9, 3-H_A), 1.79 (1H, app. qt, *J* 13.3 and 4.6, 3-H_B), 1.57 (1H, app. d, *J* 13.5, 8-H_B), 1.47 (9H, s, ^{t}Bu), 1.46-1.39 (1H, m, 4-H_A), 1.25 (1H, app. d, *J* 13.7, 4-H_B); δ_C (100 MHz, CD_3OD) 158.7 (Boc C=O), 96.0 (C-8a), 79.8 (^{t}Bu C_1), 70.5 (C-5), 66.7 (C-7), 60.8 (C-2), 45.0 (methylcarbamate C-1), 41.9 (C-4a), 36.9 (C-8), 28.7 (^{t}Bu C_3), 24.6 (C-4), 22.3 (C-3); HRMS found MNa^+, 310.1628. $C_{14}H_{25}NO_5$ requires *MNa*, 310.1624.

Benzyl 4a-({[(*tert*-butoxy)carbonyl]amino}methyl)-8a-hydroxy-octahydro-2*H*-pyrano[3,2-*c*]pyridine-6-carboxylate

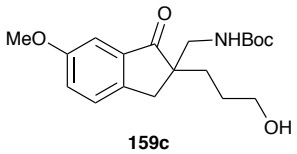


159b

According to General Procedure L, the alkene derivative **148j** (0.20 g, 0.49 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 30:70 EtOAc−hexane to yield the *hemiacetal derivative* ***159b*** (0.12 g, 58%, *dr* >95:<5 by ^{1}H-NMR) as an amorphous colourless solid, R_f 0.37 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3317, 2957, 2889, 2472, 1672, 1432, 1363, 1250, 1164, 1142, 1089, 1065; δ_H (500 MHz, CD_3OD, 333 K) 7.42-7.26 (5H, m, phenyl), 5.14 (1H, d, *J* 12.4, phenylmethyl 1-H_A), 5.11 (1H, d, *J* 12.4, phenylmethyl 1-H_B), 4.02 (1H, td, *J* 11.9 and 3.2, 2-H_A), 3.95 (1H, app. dt, *J* 13.1 and 2.6, 7-H_A), 3.66-3.57 (2H, m, 2-H_B and 5-H_A), 3.40-3.33 (3H, m, 5-H_B and methylcarbamate 1-H_2), 3.08 (1H, td, *J* 13.1 and 3.4, 7-H_B), 2.93 (1H, br. s, OH), 1.95 (1H, td, *J* 13.5 and 5.0, 4-H_A), 1.83-1.71 (2H, m, 8-H_A and 3-H_A), 1.65-1.51 (1H, m, 8-H_B), 1.42 (10H, s, ^{t}Bu and 3-H_B), 1.30 (1H, app. d, *J* 13.5, 4-H_B); δ_C (125 MHz, CD_3OD, 333 K) 158.4 (Boc C=O), 157.3 (Cbz C=O), 138.1 (phenyl C-1), 129.6 (phenyl C_2-3,5), 129.1 (phenyl C_2-2,6), 129.0 (phenyl C-4), 96.6 (C-8a), 80.1 (^{t}Bu C_1), 68.6 (phenylmethyl C-1), 61.0 (C-2), 49.0 (C-5), 47.3 (C-4a), 44.6 (methylcarbamate C-1), 42.9 (C-7), 35.7 (C-8), 28.8 (^{t}Bu C_3),

25.8 (C-4), 22.1 (C-3); HRMS found MNa^+, 443.2147. $C_{22}H_{32}N_2O_6$ requires *MNa*, 443.2152.

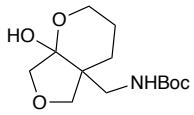
***tert*-Butyl *N*-{[2-(3-hydroxypropyl)-6-methoxy-1-oxo-2,3-dihydro-1*H*-inden-2-yl]methyl} carbamate**



159c

According to General Procedure L, the alkene derivative **148k** (0.50 g, 1.50 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 50:50 EtOAc−hexane to yield the *alcohol derivative* ***159c*** (0.32 g, 61%, >98% *as primary alcohol* by ^{1}H-NMR in $CDCl_3$) as a pale-yellow oil, R_f 0.40 (30:70 petrol−EtOAc); ν_{max}/cm^{-1} 3368, 2931, 2870, 1687, 1490, 1365, 1274, 1245, 1161, 1054, 1024; δ_H (400 MHz, $CDCl_3$) 7.32 (1H, d, *J* 8.4, 4-H), 7.18 (1H, dd, *J* 8.4 and 2.6, 5-H), 7.13 (1H, d, *J* 2.6, 7-H), 4.95 (1H, app. t, *J* 5.0, NH), 3.82 (3H, s, methoxy), 3.54 (2H, t, *J* 6.3, hydroxypropyl 3-H_2), 3.45 (1H, dd, *J* 13.5 and 7.0, methylcarbamate 1-H_A), 3.25 (1H, dd, *J* 13.5 and 5.9, methylcarbamate 1-H_B), 2.98 (1H, d, *J* 17.1, 3-H_A), 2.93 (1H, d, *J* 17.1, 3-H_B), 1.81 (1H, br. s, OH), 1.74-1.64 (2H, m, hydroxypropyl 1-H_2), 1.56-1.44 (1H, m, hydroxypropyl 2-H_A), 1.37 (9H, s, ^{t}Bu), 1.36-1.28 (1H, m, hydroxypropyl 2-H_B); δ_C (100 MHz, $CDCl_3$) 210.5 (C-1), 159.6 (C-6), 156.5 (Boc C=O), 146.5 (C-3a), 137.5 (C-7a), 127.4 (C-4), 124.9 (C-5), 105.2 (C-7), 79.6 (Boc C_1), 62.8 (hydroxypropyl C-3), 55.7 (methoxy), 54.0 (C-2), 45.8 (methylcarbamate C-1), 35.6 (C-3), 31.0 (hydroxypropyl C-1), 28.4 (^{t}Bu C_3), 27.5 (hydroxypropyl C-2); HRMS found MNa^+, 372.1784. $C_{19}H_{27}NO_5$ requires *MNa*, 372.1781. Compound **159c** existed as the primary alcohol.

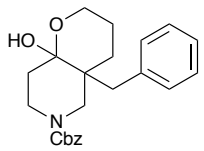
tert-Butyl _N_-({7a-hydroxy-hexahydro-2_H_-furo[3,4-b]pyran-4a-yl}methyl) carbamate



159d

According to General Procedure L, the alkene derivative **148l** (1.00 g, 3.91 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 40:60 EtOAc−hexane to yield the *hemiacetal derivative* ***159d*** (0.78 g, 73%, *hemiacetal:primary alcohol* 67:33 by ^{1}H-NMR in $CDCl_3$, *dr* >95:<5 by ^{1}H-NMR) as a colourless oil, R_f 0.19 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3342, 2936, 2881, 1688, 1510,1365, 1248, 1164, 1049, 1008; δ_H (400 MHz, $CDCl_3$) 5.30 (1H, s, $NH^{alcohol}$), 4.94 (1H, app. t, *J* 6.6, $NH^{hemiacetal}$), 4.05 (1H, d, *J* 8.7, 5-$H_A^{alcohol}$), 3.89-3.80 (2H, m, 2-$H_A^{hemiacetal}$ and hydroxypropyl 3-$H_A^{alcohol}$), 3.79-3.73 (4H, m, 2-$H_2^{alcohol}$, 5-$H_2^{hemiacetal}$), 3.73-3.66 (2H, m, 2-$H_B^{hemiacetal}$ and hydroxypropyl 3-$H_B^{alcohol}$), 3.63 (1H, d *J* 8.7, 5-$H_B^{alcohol}$), 3.61-3.57 (2H, m, 7-$H_2^{hemiacetal}$), 3.37-3.25 (3H, m, methylcarbamate 1-$H_2^{alcohol}$ and methylcarbamate 1-$H_A^{hemiacetal}$), 3.30 (1H, dd, *J* 14.4 and 4.5, methylcarbamate 1-$H_B^{hemiacetal}$), 1.85-1.67 (2H, m, 3-$H_A^{hemiacetal}$ and hydroxypropyl 2-$H_A^{alcohol}$), 1.66-1.57 (2H, m, 4-$H_A^{hemiacetal}$ and hydroxypropyl 1-$H_A^{alcohol}$), 1.54-1.45 (2H, m, 3-$H_B^{hemiacetal}$ and hydroxypropyl 2-$H_B^{alcohol}$), 1.46-1.36 (20H, m, 4-$H_B^{hemiacetal}$, hydroxypropyl 1-$H_B^{alcohol}$, ^{t}Bu^{hemiacetal} and ^{t}Bu^{alcohol}); δ_C (100 MHz, $CDCl_3$) 218.1 (C-4^{alcohol}), 157.0 (Boc C=O^{hemiacetal}), 156.4 (Boc C=O^{alcohol}), 103.4 (C-7a^{hemiacetal}), 80.0 (^{t}Bu $C_1^{alcohol}$), 79.7 (^{t}Bu $C_1^{hemiacetal}$), 77.2 (C-5^{hemiacetal}), 74.5 (C-2^{alcohol}), 73.9 (C-7^{hemiacetal}), 71.5 (C-5^{alcohol}), 62.5 (hydroxypropyl C-3^{alcohol}), 61.2 (C-2^{hemiacetal}), 52.2 (C-3^{alcohol}), 46.3 (methylcarbamate C-1^{hemiacetal}), 44.9 (C-4a^{hemiacetal}), 42.3 (methylcarbamate C-1^{alcohol}), 28.5 (^{t}Bu $C_3^{hemiacetal}$), 28.4 (^{t}Bu $C_3^{alcohol}$), 28.1 (hydroxypropyl C-1^{alcohol}), 27.1 (hydroxypropyl C-2^{alcohol}), 22.5 (C-4^{hemiacetal}), 21.1 (C-3^{hemiacetal}); HRMS found MNa^+, 296.1463. $C_{13}H_{23}NO_5$ requires *MNa*, 296.1468. Compound **159d** existed as a mixture of the hemiacetal and primary alcohol.

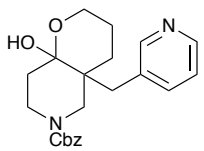
Benzyl 4a-benzyl-8a-hydroxy-octahydro-2*H*-pyrano[3,2-*c*]pyridine-6-carboxylate



159e

According to General Procedure L, the alkene derivative **148m** (0.60 g, 1.65 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 30:70 EtOAc−hexane to yield the *hemiacetal derivative* ***159e*** (0.52 g, 83%, >90% *as single hemiacetal* by ^{1}H-NMR in CD_3OD) as colourless oil, R_f 0.39 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3399, 2943, 2877, 2523, 2068, 1672, 1431, 1269, 1248, 1138, 1071; δ_H (500 MHz, CD_3OD, 333 K) 7.44-7.25 (5H, m, Cbz phenyl), 7.17-7.06 (5H, m, phenyl), 5.16 (2H, s, Cbz phenylmethyl 1-H_2), 4.12-3.95 (2H, m, 2-H_A and 7-H_A), 3.64-3.59 (1H, m, 5-H_A), 3.59-3.56 (1H, m, 2-H_B), 3.27 (1H, d, *J* 13.3, 5-H_B), 3.14 (1H, t, *J* 12.9, 7-H_B), 2.79 (2H, s, phenylmethyl 1-H_2), 1.97 (1H, td, *J* 13.1 and 5.2, 8-H_A), 1.82 (1H, td, *J* 13.5 and 5.0, 4-H_A), 1.74-1.66 (1H, m, 3-H_A), 1.66-1.60 (1H, m, 8-H_B), 1.37-1.24 (1H, m, 3-H_B), 0.77 (1H, app. d, *J* 13.5, 4-H_B); δ_C (125 MHz, CD_3OD, 333 K) 157.7 (Cbz C=O), 138.9 (Cbz phenyl C-1 and phenyl C-1), 132.2 (phenyl C_2-3,5), 129.5 (Cbz phenyl C_2-3,5), 129.1 (phenyl C_2-2,6 and Cbz phenyl C_2-2,6), 128.7 (Cbz phenyl C-4), 126.9 (phenyl C-4), 96.9 (C-8a), 68.5 (Cbz phenylmethyl C-1), 60.7 (C-2), 46.9 (C-5), 42.7 (C-7), 41.5 (C-4a), 39.1 (phenylmethyl C-1), 35.1 (C-8), 27.3 (C-4), 22.2 (C-3); HRMS found MNa^+, 404.1830. $C_{23}H_{27}NO_4$ requires *MNa*, 404.1837. Compound **159e** existed >90% as a single hemiacetal.

Benzyl 8a-hydroxy-4a-[(pyridin-3-yl)methyl]-octahydro-2*H*-pyrano[3,2-*c*] pyridine-6-carboxylate

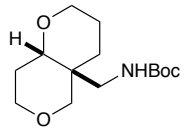


159f

According to General Procedure L, the alkene derivative **148n** (0.20 g, 0.55 mmol) gave a crude material. The crude material was purified by flash column

chromatography, eluting with 80:20→100:0 EtOAc−hexane to yield the *hemiacetal derivative* ***159f*** (0.15 g, 70%, >90% *as single hemiacetal* by ^{1}H-NMR in CD_3OD) as a colourless oil, R_f 0.26 (EtOAc); ν_{max}/cm^{-1} 3339, 2943, 2877, 2519, 2065, 1692, 1426, 1351, 1270, 1247, 1212, 1138, 1072, 1024; δ_H (500 MHz, CD_3OD, 333 K) 8.37 (1H, app. s, pyridinyl 6-H), 8.31 (1H, d, *J* 4.9, pyridinyl 2-H), 7.70-7.57 (1H, m, pyridinyl 4-H), 7.51-7.23 (5H, m, phenyl), 7.15 (1H, br. s, pyridinyl 5-H), 5.18 (2H, s, phenylmethyl 1-H_2), 4.15-3.98 (2H, m, 7-H_A and 2-H_A), 3.60 (1H, ddd, *J* 11.3, 5.4 and 1.6, 2-H_B), 3.55 (1H, d, *J* 13.5, 5-H_A), 3.31 (1H, d, *J* 13.5, 5-H_B), 3.13 (1H, td, *J* 12.9 and 3.3, 7-H_B), 2.85 (1H, d, *J* 13.7, pyridinylmethyl 1-H_A), 2.80 (1H, d, *J* 13.7, pyridinylmethyl 1-H_B), 1.98 (1H, td, *J* 13.3 and 5.4, 8-H_A), 1.85 (1H, td, *J* 13.4 and 4.9, 4-H_A), 1.77-1.67 (1H, m, 3-H_A), 1.64 (1H, app. d, *J* 14.1, 8-H_B), 1.34 (1H, app. d, *J* 13.7, 3-H_B), 0.77 (1H, app. d, *J* 13.4, 4-H_B); δ_C (125 MHz, CD_3OD, 333 K) 157.5 (Cbz C=O), 152.3 (pyridinyl C-2), 147.7 (pyridinyl C-6), 140.6 (pyridinyl C-4), 138.1 (phenyl C-1), 135.5 (pyridinyl C-3), 129.6 (phenyl C_2-3,5), 129.2 (phenyl C_2-2,6), 129.0 (phenyl C-4), 124.4 (pyridinyl C-5), 96.7 (C-8a), 68.6 (phenylmethyl C-1), 60.6 (C-2), 46.9 (C-5), 42.7 (C-7), 41.6 (C-4a), 36.5 (pyridinylmethyl C-1), 35.3 (C-8), 27.4 (C-4), 22.1 (C-3); HRMS found MH^+, 383.1961. $C_{22}H_{26}N_2O_4$ requires *MH*, 383.1965. Compound **159f** existed >90% as a single hemiacetal.

tert-Butyl *N*-{[(4a*R**,8a*R**)-octahydropyrano[4,3-*b*]pyran-4a-yl]methyl} carbamate

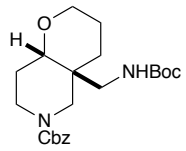


149a

According to General Procedure M, the hemiacetal derivative **159a** (0.16 g, 0.55 mmol) gave a crude material. The crude material (*dr* >95:<5 by ^{1}H-NMR) was purified by flash column chromatography, eluting with 30:70 EtOAc−hexane to yield the *ether derivative* ***149a*** (0.15 g, 99%, *dr* >95:<5 by ^{1}H-NMR) as colourless blocks, ($CHCl_3/Et_2O$), 98–102 °C; R_f 0.50 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3318, 2959, 2932, 2873, 2858, 2824, 1710, 1546, 1365, 1249, 1169, 1094, 1073, 1057; δ_H (400 MHz, $CDCl_3$) 4.73 (1H, br. s, NH), 3.97 (1H, app. dd, *J* 11.6 and 4.9, 2-H_A), 3.85 (1H, d, *J* 11.6, 5-H_A), 3.72-3.64 (2H, m, 7-H_2), 3.42 (1H, app. t, *J* 3.8, 8a-H), 3.37 (1H, td, *J* 11.6 and 2.3, 2-H_B),

3.30-3.23 (3H, m, 5-H_B and methylcarbamate 1-H_2), 2.08 (1H, dddd, *J* 14.4, 10.6, 7.2 and 3.3, 8-H_A), 1.78-1.64 (1H, m, 3-H_A), 1.54 (1H, app. dd, *J* 14.4 and 2.8, 8-H_B), 1.48-1.37 (3H, m, 3-H_B and 4-H_2), 1.43 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 156.4 (Boc C=O), 79.4 (^{t}Bu C_1), 74.6 (C-8a), 67.9 (C-5), 67.7 (C-2), 63.4 (C-7), 45.7 (methylcarbamate C-1), 36.8 (C-4a), 28.6 (C-4), 28.5 (^{t}Bu C_3), 28.3 (C-8), 22.3 (C-3); HRMS found MH^+, 272.1856. $C_{14}H_{25}NO_4$ requires *MH*, 272.1856. The relative configuration was determined using X-ray crystallography and NOESY (500 MHz, $CDCl_3$), nOe observed between 8a-H and 8-H_A, 8a-H and 8-H_B, 8a-H and NH.

Benzyl (4a*R,8a*R**)-4a-({[(*tert*-butoxy)carbonyl]amino}methyl)-octahydro-2*H*-pyrano[3,2-*c*]pyridine-6-carboxylate**

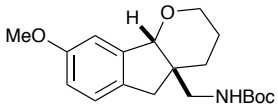


149b

According to General Procedure M, the hemiacetal derivative **159b** (0.10 g, 0.24 mmol) gave a crude material. The crude material (*dr* >95:<5 by ^{1}H-NMR) was purified by flash column chromatography, eluting with 20:80 EtOAc−hexane to yield the *ether derivative **149b*** (49.0 mg, 51%, *dr* >95:<5 by ^{1}H-NMR) as colourless oil, R_f 0.45 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3320, 2925, 2874, 2851, 1711, 1672, 1534, 1445, 1432, 1360, 1281, 1246, 1220, 1163, 1149, 1131, 1086; δ_H (500 MHz, CD_3OD, 333 K) 7.40-7.25 (5H, m, phenyl), 5.12 (2H, s, phenylmethyl 1-H_2), 3.94 (1H, app. dt, *J* 11.1 and 2.4, 2-H_A), 3.87 (1H, app. dt, *J* 13.1 and 3.0, 7-H_A), 3.51 (1H, d, *J* 13.5, 5-H_A), 3.42-3.33 (3H, m, 2-H_B, 5-H_B and 8a-H), 3.16 (1H, d, *J* 14.3, methylcarbamate 1-H_A), 3.12 (1H, app. dt, *J* 13.1 and 3.3, 7-H_B), 2.84 (1H, d, *J* 14.3, methylcarbamate 1-H_B), 2.01-1.91 (1H, m, 8-H_A), 1.82-1.69 (1H, m, 3-H_A), 1.63-1.52 (2H, m, 8-H_B and 4-H_A), 1.50-1.44 (1H, m, 3-H_B), 1.43 (10H, s, ^{t}Bu and 4-H_B); δ_C (125 MHz, CD_3OD, 333 K) 158.5 (Boc C=O), 157.5 (Cbz C=O), 138.2 (phenyl C-1), 129.5 (phenyl C_2-3,5), 129.1 (phenyl C_2-2,6), 128.9 (phenyl C-4), 80.3 (^{t}Bu C_1), 76.2 (C-8a), 68.6 (C-2), 68.4 (phenylmethyl C-1), 46.1 (C-5), 45.9 (methylcarbamate C-1), 40.5 (C-7), 38.8 (C-4a), 30.0 (C-4), 28.8 (^{t}Bu C_3), 28.3 (C-8), 23.1 (C-3); HRMS found

MNa^+, 427.2202. $C_{22}H_{32}N_2O_5$ requires *MNa*, 427.2203. The relative configuration was determined using NOESY (500 MHz, CD_3OD, 333 K), nOe observed between 8a-H and 8-H_A, 8a-H and 8-H_B, 8a-H and methylcarbamate 1-H_A, 8a-H and methylcarbamate 1-H_B.

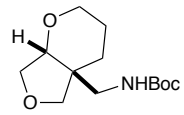
tert-Butyl _N_-{[(4a_R_*,9b_S_*)-8-methoxy-2_H_,3_H_,4_H_,4a_H_,5_H_,9b_H_-indeno[1,2-_b_]pyran-4a-yl]methyl}carbamate



149c

According to General Procedure N, the alcohol derivative **159c** (0.10 g, 0.28 mmol) gave a crude material. The crude material (*dr* >95:<5 by ^{1}H-NMR) was purified by flash column chromatography, eluting with 20:80 EtOAc−hexane to yield the *ether derivative* ***149c*** (62.0 mg, 65%, *dr* >95:<5 by ^{1}H-NMR) as a colourless oil, R_f 0.48 (60:40 petrol−EtOAc); ν_{max}/cm^{-1} 3336, 2929, 2856, 1696, 1513, 1488, 1451, 1364, 1275, 1264, 1244, 1166, 1152, 1079, 1029; δ_H (400 MHz, $CDCl_3$) 7.09 (1H, d, *J* 8.2, 6-H), 6.89 (1H, d, *J* 2.4, 9-H), 6.77 (1H, dd, *J* 8.2 and 2.4, 7-H), 4.76 (1H, app. t, *J* 6.3, NH), 4.74 (1H, s, 9b-H), 3.78 (3H, s, methoxy), 3.60 (2H, app. t, *J* 4.3, 2-H_2), 3.37 (1H, dd, *J* 14.0 and 6.9, methylcarbamate 1-H_A), 3.25 (1H, dd, *J* 14.0 and 6.3, methylcarbamate 1-H_B), 2.60 (2H, app. s, 5-H_2), 1.79-1.67 (1H, m, 3-H_A), 1.67-1.58 (1H, m, 4-H_A), 1.57-1.47 (1H, m, 4-H_B), 1.43 (10H, s, ^{t}Bu and 3-H_B); δ_C (100 MHz, $CDCl_3$) 159.1 (C-8), 156.3 (Boc C=O), 143.0 (C-9a), 133.1 (C-5a), 126.4 (C-6), 114.6 (C-7), 109.5 (C-9), 82.8 (C-9b), 79.3 (^{t}Bu C_1), 63.1 (C-2), 55.5 (methoxy), 46.2 (methylcarbamate C-1), 39.0 (C-5), 28.5 (^{t}Bu C_3), 28.0 (C-4), 22.0 (C-3); HRMS found MNa^+, 356.1838. $C_{19}H_{27}NO_4$ requires *MNa*, 356.1832. The relative configuration was determined using NOESY (500 MHz, CD_3OD), nOe observed between 9b-H and methylcarbamate 1-H_A, 9b-H and methylcarbamate 1-H_B.

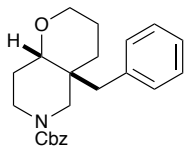
tert-Butyl _N_-{[(4a_R_*,7a_S_*)-hexahydro-2_H_-furo[3,4-_b_]pyran-4a-yl]methyl} carbamate



149d

According to General Procedure N, the hemiacetal derivative **159d** (0.74 g, 2.70 mmol) gave a crude material. The crude material (*dr* >95:<5 by ^{1}H-NMR) was purified by flash column chromatography, eluting with 20:80 EtOAc−hexane to yield the *ether derivative* ***149d*** (0.30 g, 43%, *dr* >95:<5 by ^{1}H-NMR) as colourless oil, R_f 0.35 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3318, 2949, 2928, 2875, 2855, 1677, 1540, 1365, 1276, 1250, 1160, 1135, 1093, 1081, 1059, 1034; δ_H (500 MHz, $CDCl_3$) 4.76 (1H, app. t, *J* 5.1, NH), 4.11 (1H, dd, *J* 10.1 and 4.0, 7-H_A), 3.92-3.86 (1H, m, 2-H_A), 3.87 (1H, d, *J* 8.4, 5-H_A), 3.79 (1H, app. d, *J* 10.1, 7-H_B), 3.73 (1H, app. d, *J* 4.0, 7a-H), 3.51 (1H, d, *J* 8.4, 5-H_B), 3.31 (1H, td, *J* 11.4 and 2.3, 2-H_B), 3.15 (1H, dd, *J* 14.1 and 6.8, methylcarbamate 1-H_A), 2.98 (1H, dd, *J* 14.1 and 6.5, methylcarbamate 1-H_B), 1.80-1.69 (1H, m, 3-H_A), 1.69-1.64 (2H, m, 4-H_2), 1.53-1.46 (1H, m, 3-H_B), 1.43 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 156.5 (Boc C=O), 80.3 (C-7a), 79.7 (^{t}Bu C_1), 74.2 (C-7), 71.2 (C-5), 66.2 (C-2), 46.5 (methylcarbamate C-1), 45.9 (C-4a), 28.5 (^{t}Bu C_3), 24.3 (C-4), 21.7 (C-3); HRMS found MNa^+, 280.1517. $C_{13}H_{23}NO_4$ requires *MNa*, 280.1519. The relative configuration was determined using NOESY (500 MHz, $CDCl_3$), nOe observed between 7a-H and methylcarbamate 1-H_A, 7a-H and methylcarbamate 1-H_B, 7a-H and NH.

Benzyl (4a_R_*,8a_R_*)-4a-benzyl-octahydro-2_H_-pyrano[3,2-_c_]pyridine-6-carboxylate

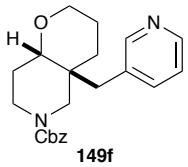


149e

According to General Procedure O, the hemiacetal derivative **159e** (0.45 g, 1.18 mmol) gave a crude material. The crude material (*dr* 93:7 by ^{1}H-NMR) was purified by flash column chromatography, eluting with 10:90 EtOAc−hexane to

yield the *ether derivative* ***149e*** (0.27 g, 63%, *dr* >95:<5 by ^{1}H-NMR) as colourless oil, R_f 0.40 (70:30 petrol−EtOAc); ν_{max}/cm^{-1} 3061, 3028, 2932, 2851, 1692, 1427, 1265, 1243, 1210, 1129, 1086, 1074, 1025; δ_H (500 MHz, CD_3OD, 333 K) 7.35-7.25 (5H, m, Cbz phenyl), 7.15 (5H, app. br. s, phenyl), 5.19 (1H, d, *J* 12.4, Cbz phenylmethyl 1-H_A), 5.15 (1H, d, *J* 12.4, Cbz phenylmethyl 1-H_B), 3.97 (1H, app. ddt, *J* 13.0, 5.5 and 2.0, 7-H_A), 3.92 (1H, app. ddt, *J* 11.3, 4.7 and 1.8, 2-H_A), 3.60 (1H, d, *J* 13.3, 5-H_A), 3.38-3.29 (3H, m, 5-H_B, 8a-H and 2-H_B), 3.15 (1H, td, *J* 13.0 and 3.2, 7-H_B), 2.75 (1H, d, *J* 13.4, phenylmethyl 1-H_A), 2.40 (1H, d, *J* 13.4, phenylmethyl 1-H_B), 2.10 (1H, dddd, *J* 14.4, 13.0, 5.5 and 3.2, 8-H_A), 1.76-1.69 (1H, m, 3-H_A), 1.69-1.63 (1H, m, 8-H_B), 1.48 (1H, td, *J* 13.8 and 4.7, 4-H_A), 1.37 (1H, app. ddt, *J* 13.2, 4.7 and 2.4, 3-H_B), 1.10 (1H, app. dt, *J* 13.8 and 3.6, 4-H_B); δ_C (125 MHz, CD_3OD, 333 K) 157.7 (Cbz C=O), 138.2 (phenyl C-1 and Cbz phenyl C-1), 131.9 (phenyl C_2-3,5), 129.5 (Cbz phenyl C_2-3,5), 129.1 (phenyl C_2-2,6 and Cbz phenyl C_2-2,6), 128.9 (Cbz phenyl C-4), 127.2 (phenyl C-4), 78.7 (C-8a), 68.7 (Cbz phenylmethyl C-1), 68.5 (C-2), 46.4 (C-5), 42.3 (phenylmethyl C-1), 40.2 (C-7), 37.7 (C-4a), 31.7 (C-4), 28.0 (C-8), 23.3 (C-3); HRMS found MNa^+, 388.1880. $C_{23}H_{27}NO_3$ requires *MNa*, 388.1888. The relative configuration was determined using NOESY (500 MHz, CD_3OD, 333 K), nOe observed between 8a-H and phenylmethyl 1-H_A, 8a-H and phenylmethyl 1-H_B, 8a-H and 8-H_A, 8a-H and 8-H_B.

Benzyl (4a*R,8a*R**)-4a-[(pyridin-3-yl)methyl]-octahydro-2*H*-pyrano[3,2-*c*] pyridine-6-carboxylate**

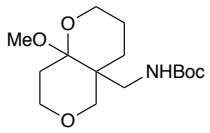


149f

According to General Procedure O, the hemiacetal derivative **159f** (0.13 g, 0.34 mmol) gave a crude material. The crude material (*dr* 91:9 by ^{1}H-NMR) was purified by flash column chromatography, eluting with 70:30 EtOAc−hexane to yield the *ether derivative* ***149f*** (0.11 g, 88%, *dr* 91:9 by ^{1}H-NMR) as colourless oil, R_f 0.32 (EtOAc); ν_{max}/cm^{-1} 3030, 2934, 2851, 1690, 1424, 1266, 1243, 1207, 1130, 1085, 1025; δ_H (500 MHz, CD_3OD, 333 K) 8.36 (1H, d, *J* 6.8, pyridinyl 6-H), 8.35 (1H, s, pyridinyl 2-H), 7.76-7.57 (1H, m, pyridinyl 4-H), 7.39 (2H, d, *J* 7.9, phenyl 2,6-H_2), 7.34 (2H, t, *J* 7.9, phenyl 3,5-H_2), 7.28 (1H, t, *J* 7.9, phenyl

4-H), 7.20 (1H, app. br. s, pyridinyl 5-H), 5.18 (2H, s, phenylmethyl, 1-H_2), 3.99 (1H, ddd, *J* 13.0, 3.0 and 1.3, 7-H_A), 3.96-3.91 (1H, m, 2-H_A), 3.55 (1H, d, *J* 13.4, 5-H_A), 3.40-3.33 (3H, m, 5-H_B, 8a-H and 2-H_B), 3.14 (1H, td, *J* 13.0 and 3.3, 7-H_B), 2.81 (1H, d, *J* 13.5, pyridinylmethyl 1-H_A), 2.40 (1H, d, *J* 13.5, pyridinylmethyl 1-H_B), 2.13-2.02 (1H, m, 8-H_A), 1.74-1.68 (1H, m, 8-H_B), 1.68-1.63 (1H, m, 3-H_A), 1.45 (1H, td, *J* 13.4 and 3.0, 4-H_A), 1.41-1.36 (1H, m, 3-H_B), 1.07 (1H, app. d, *J* 13.4, 4-H_B); δ_C (125 MHz, CD_3OD, 333 K) 157.6 (Cbz C=O), 152.0 (pyridinyl C-2), 148.0 (pyridinyl C-6), 140.3 (pyridinyl C-4), 138.2 (phenyl C-1), 134.7 (pyridinyl C-3), 129.6 (phenyl C_2-3,5), 129.1 (phenyl C_2-2,6), 129.0 (phenyl C-4), 124.5 (pyridinyl C-5), 78.7 (C-8a), 68.7 (phenylmethyl C-1), 68.5 (C-2), 45.8 (C-5), 40.2 (C-7), 39.1 (pyridinylmethyl C-1), 37.6 (C-4a), 31.7 (C-4), 28.0 (C-8), 23.2 (C-3); HRMS found MH^+, 367.2015. $C_{22}H_{26}N_2O_3$ requires *MH*, 367.2021. The relative configuration was determined using NOESY (500 MHz, CD_3OD, 333 K), nOe observed between 8a-H and pyridinylmethyl 1-H_B, 8a-H and 8-H_A, 8a-H and 8-H_B.

tert-Butyl *N*-({8a-methoxy-octahydropyrano[4,3-*b*]pyran-4a-yl}methyl) carbamate

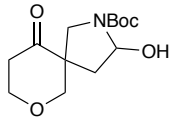


161

According to General Procedure P, the hemiacetal derivative **159a** (0.23 g, 0.80 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 20:80 EtOAc−petrol to yield the *acetal derivative* ***161*** (0.20 g, 83%, *dr* >95:<5 by ^{1}H-NMR) as an amorphous white solid, R_f 0.59 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3325, 3068, 2971, 2949, 2929, 2876, 1714, 1546, 1363, 1267, 1248, 1224, 1165, 1140, 1125, 1115, 1098, 1076, 1064, 1021; δ_H (400 MHz, $CDCl_3$) 5.03 (1H, br. s, NH), 3,91-3.84 (1H, m, 7-H_A), 3.85 (1H, d, *J* 11.7, 5-H_A), 3.67-3.60 (2H, m, 2-H_2), 3.55 (1H, app. td, *J* 12.9 and 2.8, 7-H_B), 3.37 (1H, d, *J* 11.7, 5-H_B), 3.33-3.27 (2H, m, methylcarbamate 1-H_2), 3.18 (3H, s, methoxy 1-H_3), 1.93 (1H, td, *J* 13.8 and 5.0, 4-H_A), 1.83 (1H, app. td, *J* 13.1 and 5.7, 8-H_A), 1.77-1.71 (1H, m, 3-H_A), 1.67 (1H, app. d, *J* 13.1, 8-H_B), 1.42 (9H, s, ^{t}Bu), 1.39-1.32 (1H, m, 3-H_B), 1.10 (1H, app. d, *J* 13.6, 4-H_B);

δ_C (100 MHz, $CDCl_3$) 156.4 (C=O), 98.5 (C-8a), 78.9 (^{t}Bu C_1), 70.9 (C-5), 65.8 (C-7), 60.3 (C-2), 46.7 (methoxy C-1), 44.9 (methylcarbamate C-1), 40.7 (C-4a), 31.0 (C-8), 28.5 (^{t}Bu C_3), 23.3 (C-4), 21.1 (C-3). HRMS found MNa^+, 324.1789. $C_{15}H_{27}NO_5$ requires *MNa*, 324.1781.

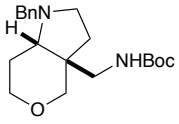
tert-Butyl 3-hydroxy-10-oxo-7-oxa-2-azaspiro[4.5]decane-2-carboxylate



163

According to General Procedure Q, the alkene derivative **148i** (0.25 g, 0.93 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 50:50 EtOAc−hexane to yield the *hemiaminals* ***163*** (0.19 g, 75%, *dr* 66:34 by ^{1}H-NMR) as an amorphous colourless solid, R_f 0.23 and 0.34 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3432, 2956, 2923, 2852, 1697, 1382, 1365, 1255, 1223, 1169, 1149, 1115, 1097; δ_H (400 MHz, $CDCl_3$) 5.53 (1H, app. d, *J* 6.5, 3-H^{major}), 2.46 (1H, app. d, *J* 4.9 3-H^{minor}), 4.11 (4H, app. d, *J* 11.6, 8-H_A and 6-H_A), 3.89 (2H, ddd, *J* 11.6, 8.8 and 4.5, 8-H_B), 3.76 (1H, d, *J* 11.6, 6-H_B^{major}), 3.72-3.60 (4H, m, 6-H_B^{minor}, 1-H_A and 1H_B^{minor}), 3.50 (1H, d, *J* 11.2, 1-H_B^{major}), 2.93 (1H, br. s, OH^{minor}), 2.70-2.43 (6H, m, 9-H_2 and 4-H_A), 1.75 (2H, app. d, *J* 14.1, 4-H_B), 1.64 (1H, br. s, OH^{major}), 1.48 (18H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 206.2 (C_2-10), 154.8 (Boc 2C=O), 81.7 (C_2-3), 80.9 (^{t}Bu 2C_1), 75.5 (C_2-6), 68.5 (C_2-8), 56.6 (C-5^{major}), 55.8 (C-5^{minor}), 51.1 (C-1^{minor}), 50.9 (C-1^{major}), 40.9 (C_2-9), 36.6 (C-4^{minor}), 36.0 (C-4^{major}), 28.5 (^{t}Bu 2C_3); HRMS found MNa^+, 294.1314. $C_{13}H_{21}NO_5$ requires *MNa*, 294.1311.

tert-Butyl _N_-{[(3a_R_,7a_S_)-1-benzyl-octahydropyrano[4,3-_b_]pyrrol-3a-yl] methyl}carbamate

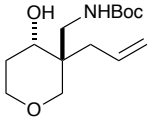


164

Benzylamine (12.9 μL, 117 μmol), acetic acid (12.2 μL, 214 μmol) and $NaBH(OAc)_3$ (56.7 mg, 267 μmol) were added to a solution of the hemiaminals

163 (29.0 mg, 107 μmol) in DCM (1.00 mL) at rt. The reaction mixture was stirred for 18 h at rt. Subsequently, a saturated aqueous solution of $NaHCO_3$ (1 mL) was added and the solution was stirred for 5 min. The phases were separated and the aqueous phase was extracted with DCM (3 × 1 mL). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography, eluting with 20:80 EtOAc−hexane to yield the *amine derivative* ***164*** (11.0 mg, 30%, *dr* 83:17 by ^{1}H-NMR) as an amorphous colourless solid, R_f 0.53 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3323, 2965, 2924, 2792, 1712, 1537, 1452, 1388, 1268, 1247, 1165, 1131, 1085; δ_H (400 MHz, $CDCl_3$) 7.35-7.21 (5H, m, phenyl), 5.22 (1H, br. s, NH), 3.96 (1H, d, *J* 13.3, phenylmethyl 1-H_A), 3.80 (1H, td, *J* 10.9 and 3.1, 6-H_A), 3.66-3.61 (1H, m, 6-H_B), 3.59 (1H, d, *J* 11.8, 4-H_A), 3.45 (1H, d, *J* 11.8, 4-H_B), 3.39-3.30 (1H, m, methylcarbamate 1-H_A), 3.29-3.20 (2H, m, phenylmethyl 1-H_B and methylcarbamate 1-H_B), 2.92 (1H, td, *J* 9.4 and 4.5, 2-H_A), 2.50 (1H, app. s, 7a-H), 2.39-2.27 (1H, m, 2-H_B), 1.91-1.78 (1H, m, 7-H_A), 1.70 (1H, app. dq, *J* 14.6 and 3.6, 7-H_B), 1.63-1.51 (1H, m, 3-H_A), 1.45 (9H, s, ^{t}Bu), 1.39-1.28 (1H, m, 3-H_B); δ_C (100 MHz, $CDCl_3$) 156.5 (C=O), 139.7 (phenyl C-1), 128.5 (phenyl C_2-3,5), 128.3 (phenyl C_2-2,6), 127.0 (phenyl C-4), 79.2 (^{t}Bu C_1), 71.2 (C-4), 64.0 (C-6), 63.0 (C-7a), 57.1 (phenylmethyl C-1), 51.2 (C-2), 46.3 (methylcarbamate C-1), 44.1 (C-3a), 29.4 (C-3), 28.5 (^{t}Bu C_3), 24.0 (C-7); HRMS found MH$^+$, 347.2337. $C_{20}H_{30}N_2O_3$ requires *MH*, 347.2329. The relative configuration was determined using NOESY (500 MHz, $CDCl_3$), nOe observed between 7a-H and methylcarbamate 1-H_A, 7a-H and methylcarbamate 1-H_B, 7a-H and 7-H_A, 7a-H and 7-H_B.

***tert*-Butyl *N*-{[(3*R**, 4*R**)-4-hydroxy-3-(prop-2-en-1-yl)oxan-3-yl]methyl} carbamate**

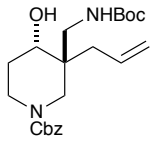


167a

According to General Procedure R, the ketone derivative **148i** (0.50 g, 1.85 mmol) and diisobutylaluminium hydride (4.08 mL, 4.08 mmol of a 1.0 M solution in DCM) were stirred at –78 °C to give a crude material. The crude material (*dr*

86:14 by ^{1}H-NMR) was purified by flash column chromatography, eluting with 50:50 EtOAc−hexane to yield the *alcohol derivative* ***167a*** (0.47 g, 93%, *dr* 86:14 by ^{1}H-NMR) as a yellow oil, R_f 0.31 (70:30 petrol−EtOAc); ν_{max}/cm^{-1} 3340, 2975, 2932, 2856, 1682, 1512, 1365, 1274, 1248, 1163, 1083; δ_H (400 MHz, $CDCl_3$) 5.83 (1H, ddt, *J* 15.3, 9.5 and 7.7, propenyl 2-H), 5.13 (1H, app. d, *J* 15.3, propenyl 3-H_{trans}), 5.10 (1H, app. d, *J* 9.5, propenyl 3-H_{cis}), 4.80 (1H, app. t, *J* 7.0, NH), 3.97 (1H, app. dd, *J* 11.6 and 4.0, 6-H_A), 3.68 (1H, dd, *J* 11.1 and 4.8, 4-H), 3.61 (1H, d, *J* 11.4, 2-H_A), 3.39 (1H, td, *J* 11.6 and 2.9, 6-H_B), 3.35-3.33 (1H, app. d, *J* 8.0, methylcarbamate 1-H_A), 2.98 (1H, d, *J* 11.4, 2-H_B), 2.70 (1H, dd, *J* 14.9 and 5.4, methylcarbamate 1-H_B), 2.43 (1H, dd, *J* 14.0 and 7.2, propenyl 1-H_A), 2.26 (1H, dd, *J* 14.0 and 8.1, propenyl 1-H_B), 1.85 (1H, app. qd, *J* 11.9 and 4.8, 5-H_A), 1.70 (1H, app. dt, *J* 13.1 and 1.84, 5-H_B), 1.45 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 157.8 (Boc C=O), 134.0 (propenyl C-2), 118.6 (propenyl C-3), 80.3 (^{t}Bu C_1), 70.3 (C-2), 70.1 (C-4), 67.2 (C-6), 43.7 (methylcarbamate C-1), 42.9 (C-3), 31.6 (propenyl C-1), 29.5 (C-5), 28.4 (^{t}Bu C_3); HRMS found MH^+, 272.1855. $C_{14}H_{25}NO_4$ requires *MH*, 272.1856. The relative configuration was determined by comparison with the carbocyclic analogue[142] and using NOESY (500 MHz, $CDCl_3$), nOe observed between 4-H and methylcarbamate 1-H_B.

Benzyl (3*R,4*R**)-3-({[(*tert*-butoxy)carbonyl]amino}methyl)-4-hydroxy-3-(prop-2-en-1-yl)piperidine-1-carboxylate**

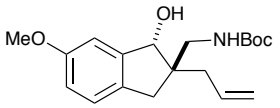


167b

According to General Procedure R, the ketone derivative **148j** (0.50 g, 1.24 mmol) and diisobutylaluminium hydride (1.36 mL, 1.36 mmol of a 1.0 M solution in DCM) were stirred at –100 °C to give a crude material. The crude material (*dr* >95:<5 by ^{1}H-NMR) was purified by flash column chromatography, eluting with 30:70 EtOAc−hexane to yield the *alcohol derivative* ***167b*** (0.39 g, 78%, *dr* >95:<5 by ^{1}H-NMR) as a colourless oil, R_f 0.55 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3367, 2975, 2935, 2870, 2492, 1672, 1428, 1364, 1234, 1155, 1079; δ_H (500 MHz, CD_3OD, 333 K) 7.37-7.27 (5H, m, phenyl), 5.87 (1H, app. dd, *J* 13.3 and

7.0, propenyl 2-H), 5.11 (2H, s, phenylmethyl 1-H_2), 5.03 (1H, app. d, *J* 17.0 propenyl 3-H_{trans}), 5.00 (1H, app. d, *J* 10.2, propenyl 3-H_{cis}), 3.95 (1H, app. d, *J* 13.3, 6-H_A), 3.72 (1H, d, *J* 13.7, 2-H_A), 3.63 (1H, dd, *J* 9.7 and 4.4, 4-H), 3.15 (1H, d, *J* 14.3, methylcarbamate 1-H_A), 3.06 (1H, app. br. s, 6-H_B), 2.95 (1H, d, *J* 14.3, methylcarbamate 1-H_B), 2.78 (1H, d, *J* 13.7, 2-H_B), 2.18 (1H, dd, *J* 14.2 and 7.9, propenyl 1-H_A), 2.09 (1H, dd, *J* 14.2 and 7.0, propenyl 1-H_B), 1.78-1.71 (1H, m, 5-H_A), 1.70-1.60 (1H, m, 5-H_B), 1.43 (9H, s, ^{t}Bu); δ_C (125 MHz, CD_3OD, 333 K) 158.9 (Boc C=O), 157.3 (Cbz C=O), 138.1 (phenyl C-1), 135.2 (propenyl C-2), 129.5 (phenyl C_2-3,5), 129.1 (phenyl C_2-2,6), 129.0 (phenyl C-4), 118.6 (propenyl C-3), 80.5 (^{t}Bu C_1), 71.8 (C-4), 68.5 (phenylmethyl C-1), 48.3 (C-2), 45.0 (methylcarbamate C-1), 43.6 (C-3), 43.0 (C-6), 33.3 (propenyl C-1), 29.8 (C-5), 28.8 (^{t}Bu C_3); HRMS found MNa^+, 427.2205. $C_{22}H_{32}N_2O_5$ requires *MNa*, 427.2203. The relative configuration was determined by analogy with the carbocyclic analogue[142] and using NOESY (500 MHz, CD_3OD), nOe observed between 4-H and methylcarbamate 1-H_A, 4-H and methylcarbamate 1-H_B.

tert-Butyl *N*-{[(1*R**,2*S**)-1-hydroxy-6-methoxy-2-(prop-2-en-1-yl)-2,3-dihydro-1*H*-inden -2-yl]methyl}carbamate

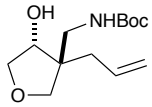


167c

According to General Procedure R, the ketone derivative **148k** (1.00 g, 3.01 mmol) and diisobutylaluminium hydride (6.63 mL, 6.63 mmol of a 1.0 M solution in DCM) were stirred at –78 °C to give a crude material. The crude material (*dr* 90:10 by ^{1}H-NMR) was purified by flash column chromatography, eluting with 20:80 EtOAc−hexane to yield the *alcohol derivative* ***167c*** (0.63 g, 63%, *dr* >95:<5 by ^{1}H-NMR) as a yellow oil, R_f 0.37 (70:30 petrol−EtOAc); ν_{max}/cm^{-1} 3368, 2976, 2931, 2835, 1685, 1512, 1490, 1435, 1365, 1272, 1245, 1159, 1029; δ_H (400 MHz, $CDCl_3$) 7.03 (1H, d, *J* 8.2, 4-H), 6.91 (1H, d, *J* 2.4, 7-H), 6.75 (1H, dd, *J* 8.2 and 2.4, 5-H), 5.85-5.68 (1H, m, propenyl 2-H), 5.03 (1H, app. d, *J* 19.7, propenyl 3-H_{trans}), 5.04 (1H, app. d, *J* 11.7, propenyl 3-H_{cis}), 4.94 (1H, app. t, *J* 6.3, NH), 3.79 (3H, s, methoxy), 3.29 (1H, dd, *J* 14.2 and 6.9, methylcarbamate 1-H_A), 3.20 (1H, dd, *J* 14.2 and 5.8, methylcarbamate 1-H_B),

2.73 (1H, d, *J* 15.4, 3-H_A), 2.51 (1H, d, *J* 15.4, 3-H_B), 2.34 (1H, dd, *J* 14.2 and 7.4, propenyl 1-H_A), 2.05 (1H, dd, *J* 14.2 and 7.3, propenyl 1-H_B), 1.44 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 159.2 (C-6), 157.1 (Boc C=O), 145.5 (C-7a), 135.2 (propenyl C-2), 131.4 (C-3a), 125.6 (C-4), 118.0 (propenyl C-3), 114.5 (C-5), 108.9 (C-7), 80.7 (C-1), 79.8 (^{t}Bu C_1), 55.6 (methoxy), 52.7 (C-2), 46.5 (methylcarbamate C-1), 36.8 (C-3), 34.6 (propenyl C-1), 28.5 (^{t}Bu C_3); HRMS found MNa^+, 356.1838. $C_{19}H_{27}NO_4$ requires *MNa*, 356.1832. The relative configuration was determined from compound **150c**.

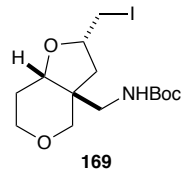
tert-Butyl *N*-{[(3*R**,4*S**)-4-hydroxy-3-(prop-2-en-1-yl)oxolan-3-yl]methyl} carbamate



167d

According to General Procedure R, the ketone derivative **148l** (2.00 g, 7.83 mmol) and diisobutylaluminium hydride (17.2 mL, 17.2 mmol of a 1.0 M solution in DCM) were stirred at –78 °C to give a crude material. The crude material (*dr* >95:<5 by ^{1}H-NMR) was purified by flash column chromatography, eluting with 20:80→40:60 EtOAc−hexane to yield the *alcohol derivative* ***167d*** (1.85 g, 92%, *dr* >95:<5 by ^{1}H-NMR) as a light-yellow oil, R_f 0.29 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3341, 2976, 2930, 2872, 1686, 1516, 1365, 1272, 1248, 1162, 1068, 1046; δ_H (400 MHz, $CDCl_3$) 5.83 (1H, ddt, *J* 17.2, 10.1 and 7.5, propenyl 2-H), 5.17 (1H, dd, *J* 17.2 and 1.8, propenyl 3-H_{trans}), 5.12 (1H, dd, *J* 10.1 and 1.8, propenyl 3-H_{cis}), 4.84 (1H, app. t, *J* 5.0, NH), 4.24-4.10 (2H, m, 5-H_A and 4-H), 3.71-3.67 (1H, m, 5-H_B), 3.66 (1H, d, *J* 8.9, 2-H_A), 3.54 (1H, d, *J* 8.9, 2-H_B), 3.17-3.02 (2H, m, methylcarbamate, 1-H_2), 2.60 (1H, br. s, OH), 2.33 (1H, dd, *J* 14.3 and 7.7, propenyl 1-H_A), 2.26 (1H, dd, *J* 14.3 and 7.1, propenyl 1-H_B), 1.43 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 156.9 (Boc C=O), 134.7 (propenyl C-2), 118.5 (propenyl C-3), 79.9 (^{t}Bu C_1), 75.6 (C-4), 74.3 (C-5), 73.9 (C-2), 50.2 (C-3), 44.1 (methylcarbamate C-1), 33.5 (propenyl C-1), 28.5 (^{t}Bu C_3); HRMS found MNa^+, 280.1514. $C_{13}H_{23}NO_4$ requires *MNa*, 280.1519. The relative configuration was determined from compound **150d**.

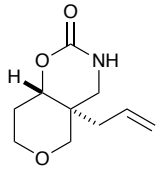
***tert*-Butyl *N*-{[(2*R**,3a*R**,7a*R**)-2-(iodomethyl)-hexahydro-2*H*-furo[3,2-*c*]pyran-3a-yl]methyl}carbamate**



169

According General Procedure S, the alkene derivative **167a** (0.10 g, 0.37 mmol) was stirred for 18 h to give a crude material. The crude material (*dr* 80:20 by ^{1}H-NMR) was purified by flash column chromatography, eluting with 15:85 EtOAc−hexane to yield the *tetrahydrofuran derivative* ***169*** (57.0 mg, 39%, *dr* >95:<5 by ^{1}H-NMR) as an amorphous colourless solid, R_f 0.50 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3323, 2975, 2950, 2923, 2895, 2868, 2848, 1703, 1547, 1349, 1273, 1252, 1235, 1164, 1139, 1069; δ_H (500 MHz, $CDCl_3$, 323 K) 4.85 (1H, br. s, NH), 4.06 (1H, app. dtd, *J* 8.5, 6.9 and 5.3, 2-H), 3.78 (1H, app. t, *J* 3.8, 7a-H), 3.71 (1H, ddd, *J* 11.4, 5.7 and 2.7, 6-H_A), 3.63 (1H, td, *J* 11.4 and 3.1, 6-H_B), 3.56 (1H, d, *J* 11.9, 4-H_A), 3.48 (1H, d, *J* 11,9, 4-H_B), 3.35-3.29 (3H, m, methylcarbamate 1-H_2 and iodomethyl 1-H_A), 3.24 (1H, dd, *J* 10.0 and 6.9, iodomethyl 1-H_B), 1.98 (1H, dd, *J* 13.4 and 8.5, 3-H_A), 1.95-1.91 (1H, m, 7-H_A), 1.82 (1H, app. dq, *J* 14.9 and 3.0, 7-H_B), 1.45 (9H, s, ^{t}Bu), 1.29 (1H, dd, *J* 13.4 and 6.9, 3-H_B); δ_C (125 MHz, $CDCl_3$) 156.3 (C=O), 79.5 (^{t}Bu C_1), 77.9 (C-7a), 77.0 (C-2), 71.0 (C-4), 64.0 (C-6), 44.8 (methylcarbamate C-1), 44.6 (C-3a), 38.9 (C-3), 28.5 (^{t}Bu C_3), 26.9 (C-7), 9.43 (iodomethyl C-1); HRMS found MH^+, 398.0823. $C_{14}H_{24}INO_4$ requires *MH*, 398.0822. The relative configuration was determined by NOESY (500 MHz, $CDCl_3$) nOe observed between methylcarbamate 1-H_A and 2-H, methylcarbamate 1-H_B and 2-H, 2-H and 7a-H.

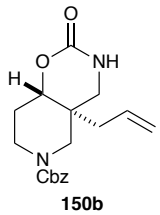
(4a*R, 8a*R**)-4a-(Prop-2-en-1-yl)-octahydropyrano[3,4-e][1,3]oxazin-2-one**



150a

According to General Procedure T, the alcohol derivative **167a** (20.0 mg, 73.7 μmol) was stirred for 1 h to yield the crude *carbamate derivative **150a*** (14.0 mg, 96%) as an amorphous colourless solid, R_f 0.20 (EtOAc); ν_{max}/cm^{-1} 3277, 2964, 2922, 2852, 1707, 1660, 1471, 1442, 1366, 1312, 1256, 1179, 1101, 1081, 1059; δ_H (400 MHz, $CDCl_3$) 5.91 (1H, br. s, NH), 5.87-5.72 (1H, m, propenyl 2-H), 5.22 (1H, app. d, *J* 2.5, propenyl 3-H_A), 5.18 (1H, app. s, propenyl 3-H_B), 4.25 (1H, dd, *J* 12.0 and 4.9, 8a-H), 4.11 (1H, app. dd, *J* 12.1 and 5.3, 7-H_A), 3.88 (1H, dd, *J* 11.6 and 1.2, 5-H_A), 3.46 (1H, td, *J* 12.1 and 2.7, 7-H_B), 3.14 (1H, dd, *J* 11.3 and 4.4, 4-H_A), 2.94 (1H, dd, *J* 11.6 and 1.7, 5-H_B), 2.81 (1H, dd, *J* 11.3 and 1.4, 4-H_B), 2.61 (1H, dd, *J* 13.9 and 6.7, propenyl 1-H_A), 2.18 (1H, dd, *J* 13.9 and 8.2, propenyl 1-H_B), 2.03 (1H, app. qd, *J* 12.6 and 5.3, 8-H_A), 1.87-1.77 (1H, m, 8-H_B); δ_C (100 MHz, $CDCl_3$) 154.0 (C-2), 132.1 (propenyl C-2), 120.3 (propenyl C-3), 78.9 (C-8a), 70.4 (C-5), 66.7 (C-7), 45.2 (C-4), 35.5 (C-4a), 28.6 (propenyl C-1), 26.8 (C-8); HRMS found MH^+, 198.1124. $C_{10}H_{15}NO_3$ requires *MH*, 198.1124.

Benzyl (4a*R,8a*R**)-2-oxo-4a-(prop-2-en-1-yl)-octahydro-2*H*-pyrido[3,4-e][1,3]oxazine-6-carboxylate**

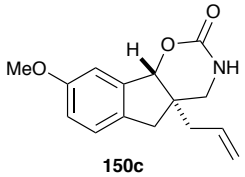


150b

According to General Procedure T, the alcohol derivative **167b** (0.12 g, 0.30 mmol) was stirred for 1 h to yield a crude material. The crude material was purified by flash column chromatography, eluting with 80:20 EtOAc−hexane to yield the *carbamate derivative **150b*** (62.0 mg, 63%) as a colourless oil, R_f 0.42 (10:90 MeOH−EtOAc); ν_{max}/cm^{-1} 3480, 3376, 3215, 3133, 2938, 2874, 1671,

1437, 1311, 1267, 1236, 1215, 1157, 1112, 1086, 1054; δ_H (500 MHz, CD_3OD, 333 K) 7.38-7.25 (5H, m, phenyl), 5.81 (1H, app. br. s, propenyl 2-H), 5.13 (2H, s, phenylmethyl 1-H_2), 5.12-5.04 (2H, m, propenyl 3-H_2), 4.34 (1H, app. dt, *J* 13.0 and 2.1, 7-H_A), 4.28 (1H, dd, *J* 10.0 and 6.8, 8a-H), 4.20 (1H, d, *J* 13.7, 5-H_A), 3.15 (1H, d, *J* 11.7, 4-H_A), 2.96-2.90 (1H, m, 7-H_B), 2.87 (1H, d, *J* 11.7, 4-H_B), 2.51 (1H, d, *J* 13.7, 5-H_B), 2.20 (1H, dd, *J* 14.3 and 6.4, propenyl 1-H_A), 2.03 (1H, dd, *J* 14.3 and 8.6, propenyl 1-H_B), 1.86-1.75 (2H, m, 8-H_2); δ_C (125 MHz, CD_3OD, 333 K) 157.0 (C-2), 156.3 (Cbz C=O), 137.9 (phenyl C-1), 133.6 (propenyl C-2), 129.5 (phenyl C_2-3,5), 129.2 (phenyl C_2-2,6), 129.1 (phenyl C-4), 120.2 (propenyl C-3), 81.0 (C-8a), 68.7 (phenylmethyl C-1), 48.6 (C-5), 46.6 (C-4), 43.2 (C-7), 36.1 (C-4a), 29.8 (propenyl C-1), 26.6 (C-8); HRMS found MNa^+, 353.1473. $C_{18}H_{22}N_2O_4$ requires *MNa*, 353.1477.

(4a*R,9b*S**)-8-Methoxy-4a-(prop-2-en-1-yl)-2*H*,3*H*,4*H*,4a*H*,5*H*,9b*H*-indeno [2,1-*e*][1,3] oxazin-2-one**

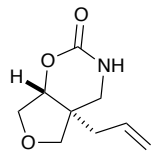


150c

According to General Procedure T, the alcohol derivative **167c** (20.0 mg, 60.0 µmol) was stirred for 18 h to yield a crude material. The crude material was purified by flash column chromatography, eluting with 70:30 EtOAc−hexane to yield the *carbamate derivative* ***150c*** (9.00 mg, 58%) as colourless blocks, m.p. ($CHCl_3$/pentane), 180–185 °C; R_f 0.46 (EtOAc); ν_{max}/cm^{-1} 3231, 3122, 2935, 2354, 1691, 1481, 1434, 1295, 1242, 1081; δ_H (400 MHz, $CDCl_3$) 7.13 (1H, d, *J* 8.2, 6-H), 7.00 (1H, d, *J* 2.5, 9-H), 6.79 (1H, dd, *J* 8.2 and 2.5, 7-H), 5.84 (1H, br. s, NH), 5.72 (1H, ddt, *J* 17.0, 10.1 and 7.5, propenyl 2-H), 5.39 (1H, s, 9b-H), 5.12 (1H, ddt, *J* 10.1, 1.7 and 0.9, propenyl 3-H_{cis}), 5.03 (1H, app. dq, *J* 17.0 and 1.7, propenyl 3-H_{trans}), 3.80 (3H, s, methoxy), 3.54-3.41 (2H, m, 4-H_2), 2.95 (1H, d, *J* 14.7, 5-H_A), 2.45 (1H, d, *J* 14.7, 5-H_B), 2.20 (1H, dd, *J* 14.5 and 7.5, propenyl 1-H_A), 1.84 (1H, dd, *J* 14.5 and 7.0, propenyl 1-H_B); δ_C (100 MHz, $CDCl_3$) 159.4 (C-8), 155.1 (C-2), 139.6 (C-9a), 133.1 (propenyl C-2), 131.3 (C-5b), 126.5 (C-6), 119.6 (propenyl C-3), 114.5 (C-7), 108.2 (C-9), 85.8 (C-9b), 55.6 (methoxy), 49.0 (C-4), 45.3 (C-4a), 35.6 (C-5), 31.2 (propenyl C-1); HRMS

found MH^+, 260.1275. $C_{15}H_{17}NO_3$ requires *MH*, 260.1281. The relative configuration was determined using X-ray crystallography.

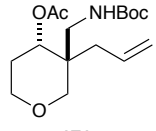
(4a*R,7a*S**)-4a-(Prop-2-en-1-yl)-hexahydro-2*H*-furo[3,4-*e*][1,3]oxazin-2-one**



150d

According to General Procedure T, the alcohol derivative **167d** (0.56 g, 2.17 mmol) was stirred for 18 h to yield a crude material. The crude material was purified by flash column chromatography, eluting with EtOAc to yield the *carbamate derivative **150d*** (0.26 g, 65%) as colourless blocks, m.p. (DCM), 138–142 °C; R_f 0.20 (EtOAc); ν_{max}/cm^{-1} 3254, 3132, 2979, 2950, 2929, 2895, 1700, 1384, 1301, 1257, 1132, 1104, 1076, 1014; δ_H (400 MHz, $CDCl_3$) 6.57 (1H, br. s, NH), 5.78 (1H, ddt, *J* 17.1, 9.8 and 7.4, propenyl 2-H), 5.27-5.12 (2H, m, propenyl 3-H_2), 4.58 (1H, dd, *J* 10.1 and 8.0, 7a-H), 4.05 (1H, dd, *J* 10.1 and 8.0, 7-H_A), 4.01 (1H, d, *J* 8.6, 5-H_A), 3.70 (1H, dd, *J* 10.1 and 8.0, 7-H_B), 3.46 (1H, d, *J* 8.6, 5-H_B), 3.38 (1H, dd, *J* 11.1 and 4.3, 4-H_A), 3.18 (1H, d, *J* 11.1, 4-H_B), 2.34-2.17 (2H, m, propenyl 1-H_2); δ_C (100 MHz, $CDCl_3$) 154.9 (C-2), 132.0 (propenyl C-2), 120.4 (propenyl C-3), 80.5 (C-7a), 71.7 (C-5), 64.9 (C-7), 46.7 (C-4), 40.5 (C-4a), 29.9 (propenyl C-1); HRMS found MH^+, 184.0964. $C_9H_{13}NO_3$ requires *MH*, 184.0968. The relative configuration was determined using X-ray crystallography.

(3*R, 4*R**)-3-({[(*tert*-Butoxy)carbonyl]amino}methyl)-3-(prop-2-en-1-yl)oxan-4-yl acetate**

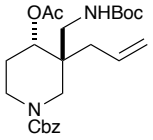


171a

According to General Procedure U, the alcohol derivative **167a** (0.36 g, 1.35 mmol) gave the *acetyl derivative **171a*** (0.40 g, 95%) as a yellow oil, R_f 0.71 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3355, 2973, 2933, 2859, 1739, 1714, 1508,

1365, 1236, 1164, 1089; δ_H (400 MHz, $CDCl_3$) 5.88-5.73 (1H, m, propenyl 2-H), 5.11 (1H, app. s, propenyl 3-H_{trans}), 5.08 (1H, app. d, *J* 2.5, propenyl 3-H_{cis}), 5.00 (1H, app. t, *J* 6.9, 4-H), 4.95 (1H, br. s, NH), 3.86 (1H, app. dt, *J* 11.6 and 4.6, 6-H_A), 3.68 (1H, d, *J* 12.0, 2-H_A), 3.55-3.46 (1H, m, 6-H_B), 3.28 (1H, dd, *J* 14.6 and 8.2, methylcarbamate 1-H_A), 3.18 (1H, d, *J* 12.0, 2-H_B), 2.87 (1H, dd, *J* 14.6 and 5.5, methylcarbamate 1-H_B), 2.35 (1H, dd, *J* 14.1 and 7.5, propenyl 1-H_A), 2.13-2.04 (1H, m, propenyl 1-H_B), 2.08 (3H, s, acetyl), 1.87-1.79 (2H, m, 5-H_2), 1.41 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 170.9 (acetyl C=O), 156.2 (Boc C=O), 133.1 (propenyl C-2), 118.8 (propenyl C-3), 79.4 (^{t}Bu C_1), 71.5 (C-4), 70.4 (C-2), 65.8 (C-6), 42.3 (methylcarbamate C-1), 42.0 (C-3), 33.5 (propenyl C-1), 28.4 (^{t}Bu C_3), 27.6 (C-5), 21.2 (acetyl CH_3). HRMS found MNa^+, 336.1791. $C_{16}H_{27}NO_5$ requires *MNa*, 336.1786.

Benzyl (3*R,4*R**)-4-(acetyloxy)-3-({[(*tert*-butoxy)carbonyl]amino}methyl)-3-(prop-2-en-1-yl)piperidine-1-carboxylate**

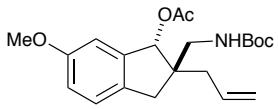


171b

According to General Procedure U, the alcohol derivative **167b** (0.34 g, 0.84 mmol) gave the *acetyl derivative **171b*** (0.36 g, 95%) as a colourless oil, R_f 0.70 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3367, 2976, 2936, 1738, 1697, 1510, 1434, 1365, 1232, 1160, 1036; δ_H (500 MHz, CD_3OD, 333 K) 7.38-7.26 (5H, m, phenyl), 5.93-5.78 (1H, m, propenyl 2-H), 5.12 (2H, s, phenylmethyl 1-H_2), 5.05 (1H, app. d, *J* 10.2, propenyl 3-H_{cis}), 5.04 (1H, app. d, *J* 17.2, propenyl 3-H_{trans}), 4.85 (1H, dd, *J* 8.3 and 4.0, 4-H), 3.71 (1H, app. br. s, 6-H_A), 3.57 (1H, d, *J* 13.9, 2-H_A), 3.35 (1H, app. br. s, 6-H_B), 3.16 (1H, d, *J* 13.9, 2-H_B), 3.13 (1H, d, *J* 15.1, methylcarbamate 1-H_A), 3.03 (1H, d, *J* 15.1, methylcarbamate 1-H_B), 2.22-2.08 (2H, m, propenyl 1-H_2), 2.05 (3H, s, acetyl), 1.96-1.86 (1H, m, 5-H_A), 1.75-1.66 (1H, m, 5-H_B), 1.42 (9H, s, ^{t}Bu); δ_C (125 MHz, CD_3OD, 333 K) 172.1 (acetyl C=O), 158.2 (Boc C=O), 157.2 (Cbz C=O), 138.0 (phenyl C-1), 134.5 (propenyl C-2), 129.5 (phenyl C_2-3,5), 129.1 (phenyl C_2-2,6), 129.0 (phenyl C-4), 118.8 (propenyl C-3), 80.3 (^{t}Bu C_1), 73.2 (C-4), 68.6 (phenylmethyl C-1), 48.6 (C-2), 43.6 (C-6), 42.9 (C-3), 42.2 (methylcarbamate C-1), 35.3 (propenyl C-1), 28.8

(^{t}Bu C_3), 27.1 (C-5), 21.0 (acetyl CH_3); HRMS found MNa^+, 469.2304. $C_{24}H_{34}N_2O_6$ requires *MNa*, 469.2309.

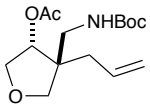
(1*R,2*S**)-2-({[(*tert*-Butoxy)carbonyl]amino}methyl)-6-methoxy-2-(prop-2-en-1-yl)-2,3-dihydro-1*H*-inden-1-yl acetate**



171c

According to General Procedure U, the alcohol derivative **167c** (0.63 g, 1.89 mmol) gave the *acetyl derivative* ***171c*** (0.70 g, 99%) as a pale-yellow oil, R_f 0.50 (70:30 petrol−EtOAc); ν_{max}/cm^{-1} 3376, 2976, 2930, 1712, 1493, 1366, 1233, 1163, 1029; δ_H (400 MHz, $CDCl_3$) 7.08 (1H, d, *J* 8.9, 4-H), 6.81 (2H, app. d, *J* 6.3, 5-H and 7-H), 6.04 (1H, s, 1-H), 5.86 (1H, ddt, *J* 16.6, 10.4 and 7.4, propenyl 2-H), 5.06 (1H, d, *J* 16.6, propenyl 3-H_{trans}), 5.05 (1H, d, *J* 10.4, propenyl 3-H_{cis}), 4.96 (1H, app. t, *J* 7.5, NH), 3.78 (3H, s, methoxy), 3.27 (1H, dd, *J* 14.2 and 6.9, methylcarbamate 1-H_A), 3.11 (1H, dd, *J* 14.2 and 6.2, methylcarbamate 1-H_B), 2.86 (1H, d, *J* 15.9, 3-H_A), 2.67 (1H, d, *J* 15.9, 3-H_B), 2.21 (2H, app. d, *J* 7.4, propenyl 1-H_2), 2.13 (3H, s, acetyl), 1.42 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 171.4 (acetyl C=O), 159.1 (C-6), 156.3 (Boc C=O), 141.5 (C-7a), 134.4 (propenyl C-2), 133.5 (C-3a), 125.7 (C-4), 118.2 (propenyl C-3), 115.5 (C-5), 110.1 (C-7), 80.5 (C-1), 79.4 (^{t}Bu C_1), 55.6 (methoxy), 51.8 (C-2), 45.5 (methylcarbamate C-1), 38.2 (C-3), 36.5 (propenyl C-1), 28.5 (^{t}Bu C_3), 21.2 (acetyl CH_3); HRMS found MNa^+, 398.1934. $C_{21}H_{29}NO_5$ requires *MNa*, 398.1937.

(3*R,4*S**)-4-({[(*tert*-Butoxy)carbonyl]amino}methyl)-4-(prop-2-en-1-yl) oxolan-3-yl acetate**

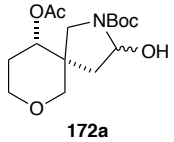


171d

According to General Procedure U, the alcohol derivative **167d** (1.76 g, 6.83 mmol) gave the *acetyl derivative* ***171d*** (1.95 g, 95%) as a yellow oil, R_f 0.52

(50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3254, 3139, 2974, 2938, 2874, 1737, 1704, 1449, 1395, 1366, 1352, 1249, 1233, 1223, 1162, 1131, 1082, 1020; δ_H (400 MHz, $CDCl_3$) 5.72 (1H, ddt, *J* 17.3, 10.0 and 7.4, propenyl 2-H), 5.18-5.04 (3H, m, 3-H and propenyl 3-H_2), 4.91 (1H, app. t, *J* 5.0, NH), 4.25 (1H, dd, *J* 10.6 and 5.6, 2-H_A), 3.71 (1H, dd, *J* 10.6 and 2.9, 2-H_B), 3.68 (1H, d, *J* 9.0, 5-H_A), 3.61 (1H, d, *J* 9.0, 5-H_B), 3.21 (1H, dd, *J* 14.2 and 6.4, methylcarbamate 1-H_A), 3.13 (1H, dd, *J* 14.2 and 6.4, methylcarbamate 1-H_B), 2.30-2.14 (2H, m, propenyl 1-H_2), 2.08 (3H, s, acetyl), 1.43 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 170.7 (acetyl C=O), 156.4 (Boc C=O), 133.9 (propenyl C-2), 118.7 (propenyl C-3), 79.7 (^{t}Bu C_1), 77.2 (C-3), 74.7 (C-5), 73.4 (C-2), 50.1 (C-4), 43.9 (methylcarbamate C-1), 34.0 (propenyl C-1), 28.5 (^{t}Bu C_3), 21.0 (acetyl CH_3); HRMS found MNa^+, 322.1621. $C_{15}H_{25}NO_5$ requires *MNa*, 322.1624.

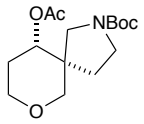
tert-Butyl (5*R,10*R**)-10-(acetyloxy)-3-hydroxy-7-oxa-2-azaspiro[4.5]decane -2-carboxylate**



172a

According to General Procedure Q, the alkene derivative **171a** (69.0 mg, 0.22 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 30:70→50:50 EtOAc−hexane to yield *hemiaminals* ***172a*** (51.0 mg, 74%, *dr* 58:42 by ^{1}H-NMR) as an amorphous colourless solid, R_f 0.53 and 0.33 (50:50 EtOAc−petrol); ν_{max}/cm^{-1} 3451, 2973, 2861, 1739, 1694, 1389, 1365, 1233, 1160; δ_H (500 MHz, CD_3OD, 333 K) 5.08-4.99 (1H, m, 3-H^{major}), 4.95-4.86 (1H, m, 3-H^{minor}) 4.79-4.68 (2H, m, 10-H), 3.81-3.63 (2H, m, 8-H_A), 3.54-3.36 (6H, m, 8-H_B, 6-H_A and 1-H_A), 3.30-3.09 (4H, m, 6-H_B and 1-H_B), 2.02-1.91 (8H, m, acetyl and 4-H_A), 1.83-1.68 (4H, m, 4-H_B and 9-H_A), 1.64-1.54 (2H, m, 9-H_B), 1.38 (18H, s, ^{t}Bu); δ_C (125 MHz, CD_3OD, 333 K) 171.9 (acetyl 2C=O), 156.0 (Boc C=O^{major}), 155.7 (Boc C=O^{minor}), 90.5 (C-3^{major}), 89.8 (C-3^{minor}), 81.8 (^{t}Bu $C_1{}^{major}$), 81.7 (^{t}Bu $C_1{}^{minor}$), 74.5 (C-10^{major}), 73.4 (C-8^{major}), 72.9 (C-10^{minor}), 72.4 (C-8^{minor}) 65.4 (C-6^{major}), 64.7 (C-6^{minor}) 52.3 (C-1^{major}), 50.6 (C-1^{minor}), 46.1 (C_2-5), 39.0 (C-4^{minor}), 37.4 (C-4^{major}), 30.1 (C-9^{major}), 29.5 (C-9^{minor}), 28.6 (^{t}Bu $2C_3$), 20.8 (acetyl $2CH_3$); HRMS found MNa^+, 338.1575. $C_{15}H_{25}NO_6$ requires *MNa*, 338.1579.

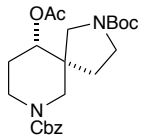
***tert*-Butyl (5*R**, 10*R**)-10-(acetyloxy)-7-oxa-2-azaspiro[4.5]decane-2-carboxylate**



173a

By modification of an existing procedure,[175] $NaBH(OAc)_3$ (93.0 mg, 441 μmol) was added to a solution of the hemiaminals **172a** (20.0 mg, 63.4 μmol) in AcOH (0.30 mL) at rt. The reaction mixture was stirred for 3 h at rt. Subsequently, a saturated aqueous solution of $NaHCO_3$ (1 mL) and DCM (1 mL) were added. The phases were separated and the aqueous phase was extracted with DCM (4 × 1 mL). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography, eluting with 25:75 EtOAc−hexane to yield the *pyrrolidine derivative* ***173a*** (15.0 mg, 79%) as a colourless oil, R_f 0.47 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 2971, 2863, 1738, 1691, 1398, 1364, 1234, 1172, 1145, 1103, 1090, 1071; δ_H (500 MHz, $CDCl_3$, 323 K) 4.91 (1H, dd, *J* 7.5 and 3.8, 10-H), 3.81 (1H, ddd, *J* 11.2, 7.0 and 3.9, 8-H_A), 3.65 (1H, d, *J* 11.5, 6-H_A), 3.61 (1H, ddd, *J* 11.2, 7.4 and 3.7, 8-H_B), 3.48-3.45 (1H, m, 3-H_A), 3.37-3.26 (1H, m, 3-H_B), 3.34 (1H, d, *J* 11.5, 6-H_B), 3.29 (1H, d, *J* 11.3, 1-H_A), 3.16 (1H, m, 1-H_B), 2.08 (3H, s, acetyl), 1.94-1.86 (2H, m, 9-H_A and 4-H_A), 1.84-1.78 (1H, m, 4-H_B), 1.75-1.67 (1H, m, 9-H_B), 1.46 (9H, s, ^{t}Bu); δ_C (125 MHz, $CDCl_3$, 323 K) 170.3 (acetyl C=O), 154.6 (Boc C=O), 79.6 (^{t}Bu C_1), 72.2 (C-10), 71.4 (C-6), 65.0 (C-8), 51.3 (C-1), 44.4 (C_2-3,5), 29.2 (C-9), 28.7 (C-4 and ^{t}Bu C_3), 21.1 (acetyl CH_3); HRMS found MH^+, 300.1805. $C_{15}H_{25}NO_5$ requires *MH*, 300.1805.

7-Benzyl 2-*tert*-butyl (5*R,10*S**)-10-(acetyloxy)-2,7-diazaspiro[4.5]decane-2,7-dicarboxylate**

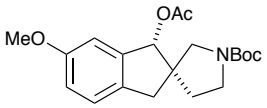


173b

According to General Procedure V, the alkene derivative **171b** (0.10 g, 0.23 mmol) gave a crude material. The crude material was purified by flash column

chromatography, eluting with 30:70 EtOAc−hexane to yield the *pyrrolidine derivative* ***173b*** (61.0 mg, 61%) as a colourless oil, R_f 0.41 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 2974, 2876, 1737, 1688, 1430, 1398, 1364, 1233, 1211, 1145, 1101, 1059, 1041; δ_H (500 MHz, CD_3OD, 333 K) 7.38-7.26 (5H, m, phenyl), 5.16 (1H, d, *J* 12.4, phenylmethyl 1-H_A), 5.09 (1H, d, *J* 12.4, phenylmethyl 1-H_B), 4.90 (1H, dd, *J* 7.1 and 3.7, 10-H), 3.61 (1H, ddd, *J* 12.5, 7.7 and 4.2, 8-H_A), 3.53 (1H, d, *J* 13.4, 6-H_A), 3.52-3.47 (1H, m, 8-H_B), 3.45-3.40 (1H, m, 3-H_A), 3.38 (1H, d, *J* 13.4, 6-H_B), 3.35-3.27 (1H, m, 3-H_B), 3.22 (1H, d, *J* 11.2, 1-H_A), 3.12 (1H, d, *J* 11.2, 1-H_B), 2.06 (3H, s, acetyl), 1.93-1.84 (1H, m, 4-H_A), 1.82-1.74 (1H, m, 9-H_A), 1.73-1.63 (2H, m, 4-H_B and 9-H_B), 1.43 (9H, s, ^{t}Bu); δ_C (125 MHz, CD_3OD, 333 K) 171.9 (acetyl C=O), 157.1 (Boc C=O), 156.3 (Cbz C=O), 138.0 (phenyl C-1), 129.6 (phenyl C_2-3,5), 129.1 (phenyl C-4), 128.9 (phenyl C_2-2,6), 81.1 (^{t}Bu C_1), 73.9 (C-10), 68.6 (phenylmethyl C-1), 52.6 (C-1), 49.2 (C-6), 47.5 (C-5), 45.4 (C-3), 41.6 (C-8), 30.2 (C-4), 28.9 (C-9), 28.8 (^{t}Bu C_3), 20.8 (acetyl CH_3); HRMS found MNa^+, 455.2147. $C_{23}H_{32}N_2O_6$ requires *MNa*, 455.2152.

***tert*-Butyl (2*R**,3*R**)-3-(acetyloxy)-5-methoxy-1,3-dihydrospiro[indene-2,3'-pyrrolidine]-1'-carboxylate**

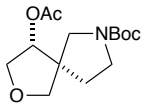


173c

According to General Procedure V, the alkene derivative **171c** (0.10 g, 0.26 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 20:80 EtOAc−hexane to yield the *pyrrolidine derivative* ***173c*** (49.0 mg, 51%) as a colourless oil, R_f 0.38 (70:30 petrol−EtOAc); ν_{max}/cm^{-1} 2974, 2933, 1733, 1689, 1492, 1395, 1365, 1227, 1163, 1144, 1118, 1100, 1020; δ_H (500 MHz, CD_3OD, 333 K) 7.14 (1H, d, *J* 8.3, 7-H), 6.92 (1H, d, *J* 2.5, 4-H), 6.86 (1H, dd, *J* 8.3 and 2.5, 6-H), 5.92 (1H, s, 3-H), 3.76 (3H, s, methoxy), 3.50-3.37 (2H, m, 5'-H_2), 3.33 (1H, d, *J* 11.0, 2'-H_A), 3.16 (1H, d, *J* 11.0, 2'-H_B), 3.01 (1H, d, *J* 15.3, 1-H_A), 2.77 (1H, d, *J* 15.3, 1-H_B), 2.15 (1H, app. dt, *J* 13.0 and 7.4, 4'-H_A), 2.06 (3H, s, acetyl), 1.89 (1H, app. dt, *J* 13.0 and 6.8, 4'-H_B), 1.44 (9H, s, ^{t}Bu); δ_C (100 MHz, CD_3OD, 333 K) 172.5 (acetyl C=O), 160.7 (C-5), 156.5 (Boc C=O), 142.9 (C-3a), 136.1 (C-7a), 126.6

(C-7), 116.9 (C-6), 112.2 (C-4), 82.1 (C-3), 81.0 (^{t}Bu C_1), 57.2 (C-2'), 56.0 (methoxy), 55.0 (C-2), 46.3 (C-5'), 41.5 (C-1), 32.1 (C-4'), 28.8 (^{t}Bu C_3), 20.8 (acetyl CH_3); HRMS found MNa^+, 384.1779. $C_{20}H_{27}NO_5$ requires *MNa*, 384.1781.

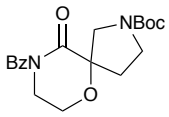
tert-Butyl (4*R,5*S**)-4-(acetyloxy)-2-oxa-7-azaspiro[4.4]nonane-7-carboxylate**



173d

According to General Procedure V, the alkene derivative **171d** (0.25 g, 0.83 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 30:70 EtOAc−hexane to yield the *pyrrolidine derivative* ***173d*** (0.18 g, 76%) as a colourless oil, R_f 0.42 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 2975, 2934, 2873, 1738, 1693, 1400, 1366, 1236, 1161, 1122; δ_H (500 MHz, CD_3OD, 333 K) 5.04 (1H, dd, *J* 4.9 and 2.1, 4-H), 4.09 (1H, dd, *J* 10.7 and 4.9, 3-H_A), 3.71 (1H, dd, *J* 10.7 and 2.1, 3-H_B), 3.70 (1H, d, *J* 8.6, 1-H_A), 3.67 (1H, d, *J* 8.6, 1-H_B), 3.40-3.34 (1H, m, 8-H_A), 3.34-3.28 (1H, m, 8-H_B), 3.28-3.22 (2H, m, 6-H_2), 2.04 (3H, s, acetyl), 2.03-2.01 (1H, m, 9-H_A), 1.81 (1H, ddd, *J* 13.6, 8.0 and 6.1, 9-H_B), 1.42 (9H, s, ^{t}Bu); δ_C (125 MHz, CD_3OD, 333 K) 172.1 (acetyl C=O), 156.3 (Boc C=O), 81.1 (^{t}Bu C_1), 78.9 (C-4), 75.9 (C-1), 74.2 (C-3), 55.5 (C-6), 54.0 (C-5), 46.1 (C-8), 28.8 (C-9 and ^{t}Bu C_3), 20.6 (acetyl CH_3); HRMS found MNa^+, 308.1465. $C_{14}H_{23}NO_5$ requires *MNa*, 308.1468.

tert-Butyl 9-benzoyl-10-oxo-6-oxa-2,9-diazaspiro[4.5]decane-2-carboxylate

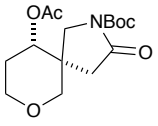


173e

According to General Procedure V, the alkene derivative **148h** (0.20 g, 0.53 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 20:80 EtOAc−hexane to yield the *pyrrolidine derivative* ***173e*** (94.0 mg, 49%) as a colourless oil, R_f 0.63 (50:50

petrol−EtOAc); ν_{max}/cm^{-1} 2974, 2888, 1682, 1394, 1366, 1313, 1279, 1234, 1172, 1132, 1100, 1082; δ_H (500 MHz, CD_3OD, 333 K) 7.57-7.53 (2H, m, phenyl 2,6-H_2), 7.50 (1H, tt, *J* 7.2 and 1.6, phenyl 4-H), 7.41 (2H, td, *J* 7.2 and 1.6, phenyl 3,5-H_2), 4.13-4.01 (2H, m, 7-H_2), 3.99-3.86 (2H, m, 8-H_2), 3.69 (2H, app. s, 1-H_2), 3.54 (1H, ddd, *J* 10.5, 8.5 and 3.5, 3-H_A), 3.47 (1H, ddd, *J* 10.5, 8.9 and 7.5, 3-H_B), 2.43-2.35 (1H, m, 4-H_A), 2.35-2.26 (1H, m, 4-H_B), 1.46 (9H, s, ^{t}Bu); δ_C (125 MHz, CD_3OD, 333 K) 174.6 (C-10), 173.3 (benzoyl C=O), 156.2 (Boc C=O), 136.9 (phenyl C-1), 132.9 (phenyl C-4), 129.3 (phenyl C_2-3,5), 129.0 (phenyl C_2-2,6), 81.3 (C-5), 81.1 (^{t}Bu C_1), 61.4 (C-7), 56.6 (C-1), 46.8 (C-8), 45.9 (C-3), 36.6 (C-4), 28.8 (^{t}Bu C_3); HRMS found MNa^+, 383.1575. $C_{19}H_{24}N_2O_5$ requires *MNa*, 383.1577.

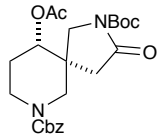
tert-Butyl (5*R, 10*R**)-10-(acetyloxy)-3-oxo-7-oxa-2-azaspiro[4.5]decane-2-carboxylate**



174a

Pyridinium dichromate (47.4 mg, 0.126 mmol) and celite (20 mg) were added to a solution of the hemiaminals **172a** (20.0 mg, 63.4 μmol) in DCM (1.00 mL) at rt. The reaction mixture was stirred for 1 week at rt. Subsequently, the mixture was filtered through celite and concentrated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography, eluting with 40:60 EtOAc−hexane to yield the *pyrrolidine derivative* ***174a*** (13.0 mg, 65%) as a colourless oil, R_f 0.30 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 2975, 2933, 2857, 1785, 1738, 1711, 1367, 1310, 1230, 1147, 1093, 1044, 1025; δ_H (500 MHz, $CDCl_3$) 4.90 (1H, dd, *J* 8.8 and 4.2, 10-H), 3.88 (1H, app. dt, *J* 12.0 and 4.7, 8-H_A), 3.70 (1H, d, *J* 11.6, 6-H_A), 3.57 (1H, ddd, *J* 12.0, 9.0 and 3.3, 8-H_B), 3.49 (2H, app. s, 1-H_2), 3.36 (1H, d, *J* 11.6, 6-H_B), 2.68 (1H, d, *J* 17.9, 4-H_A), 2.49 (1H, d, *J* 17.9, 4-H_B), 2.09 (3H, s, acetyl), 1.90 (1H, app. dq, *J* 13.0 and 4.0, 9-H_A), 1.68 (1H, app dtd, *J* 13.9, 9.3 and 4.5, 9-H_B), 1.52 (9H, s, ^{t}Bu); δ_C (125 MHz, $CDCl_3$) 171.9 (C-3), 170.3 (acetyl C=O), 149.9 (Boc C=O), 83.5 (^{t}Bu C_1), 72.3 (C_2-6,10), 65.3 (C-8), 51.0 (C-1), 38.6 (C-5), 37.9 (C-4), 28.7 (C-9), 28.1 (^{t}Bu C_3), 21.1 (acetyl CH_3); HRMS found MH^+, 314.1598. $C_{15}H_{23}NO_6$ requires *MH*, 314.1598.

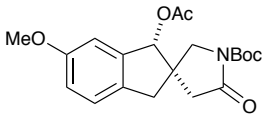
7-Benzyl 2-*tert*-butyl (5*R,10*S**)-10-(acetyloxy)-3-oxo-2,7-diazaspiro[4.5] decane-2,7-dicarboxylate**



174b

According to General Procedure W, the alkene derivative **171b** (0.20 g, 0.45 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 35:65 EtOAc−hexane to yield the *pyrrolidine derivative* ***174b*** (0.12 g, 60%) as a colourless oil, R_f 0.42 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 2978, 1785, 1738, 1696, 1432, 1367, 1315, 1229, 1148, 1104, 1041; δ_H (500 MHz, CD_3OD, 333 K) 7.37-7.27 (5H, m, phenyl), 5.15 (1H, d, *J* 12.3, phenylmethyl 1-H_A), 5.12 (1H, d, *J* 12.3, phenylmethyl 1-H_B), 4.97 (1H, dd, *J* 8.4 and 3.9, 10-H), 3.80-3.75 (1H, m, 8-H_A), 3.73 (1H, dd, *J* 13.6 and 1.5, 6-H_A), 3.58 (1H, d, *J* 11.2, 1-H_A), 3.53 (1H, d, *J* 11.2, 1-H_B), 3.39-3.34 (1H, m, 8-H_B), 3.32 (1H, d, *J* 13.6, 6-H_B), 2.63 (1H, d, *J* 17.7, 4-H_A), 2.33 (1H, d, *J* 17.7, 4-H_B), 2.04 (3H, s, acetyl), 1.83 (1H, app. ddt, *J* 14.0, 6.4 and 3.9, 9-H_A), 1.67 (1H, dtd, *J* 14.0, 8.4 and 4.4, 9-H_B), 1.49 (9H, s, ^{t}Bu); δ_C (125 MHz, CD_3OD, 333 K) 174.1 (C-3), 171.7 (acetyl C=O), 157.1 (Boc C=O), 151.3 (Cbz C=O), 137.9 (phenyl C-1), 129.6 (phenyl C_2-3,5), 129.2 (phenyl C-4), 128.9 (phenyl C_2-2,6), 84.5 (^{t}Bu C_1), 74.7 (C-10), 68.7 (phenylmethyl C-1), 53.3 (C-1), 50.2 (C-6), 41.9 (C-8), 40.3 (C-5), 39.4 (C-4), 28.3 (C-9), 28.2 (^{t}Bu C_3) 20.7 (acetyl CH_3); HRMS found MNa^+, 469.1942. $C_{23}H_{30}N_2O_7$ requires *MNa*, 469.1945.

***tert*-Butyl (2*R**,3*R**)-3-(acetyloxy)-5-methoxy-5'-oxo-1,3-dihydrospiro [indene-2,3'-pyrrolidine]-1'-carboxylate**

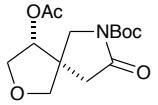


174c

According to General Procedure W, the alkene derivative **171c** (0.10 g, 0.26 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 25:75 EtOAc−hexane to yield the *pyrrolidine*

derivative ***174c*** (37.0 mg, 37%) as a colourless oil, R_f 0.48 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 2978, 2934, 1784, 1737, 1715, 1492, 1367, 1310, 1224, 1150, 1022; δ_H (400 MHz, $CDCl_3$, 323 K) 7.13 (1H, d, *J* 8.3, 7-H), 6.91 (1H, d, *J* 2.6, 4-H), 6.85 (1H, dd, *J* 8.3 and 2.6, 6-H), 6.00 (1H, s, 3-H), 3.78 (3H, s, methoxy), 3.76 (1H, d, *J* 11.0, 2'-H_A), 3.57 (1H, d, *J* 11.0, 2'-H_B), 3.06 (1H, d, *J* 15.3, 1-H_A), 2.90 (1H, d, *J* 15.3, 1-H_B), 2.83 (1H, d, *J* 17.4, 4'-H_A), 2.44 (1H, d, *J* 17.4, 4'-H_B), 2.08 (3H, s, acetyl), 1.51 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$, 323 K) 172.1 (C-5'), 170.7 (acetyl C=O), 159.7 (C-5), 150.0 (Boc C=O), 141.1 (C-3a), 133.1 (C-7a), 125.9 (C-7), 116.2 (C-6), 111.1 (C-4), 83.2 (^{t}Bu C_1), 81.1 (C-3), 56.2 (C-2'), 55.7 (methoxy), 47.5 (C-2), 41.8 (C-1), 40.4 (C-4'), 28.2 (^{t}Bu C_3), 20.9 (acetyl CH_3); HRMS found MNa^+, 398.1583. $C_{20}H_{25}NO_6$ requires *MNa*, 398.1574.

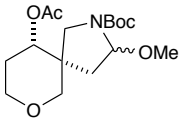
tert-Butyl (4*R,5*S**)-4-(acetyloxy)-8-oxo-2-oxa-7-azaspiro[4.4]nonane-7-carboxylate**



174d

According to General Procedure W, the alkene derivative **171d** (0.25 g, 0.83 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 40:60→60:40 EtOAc−hexane to yield the *pyrrolidine derivative* ***174d*** (0.19 g, 76%) as a yellow oil, R_f 0.34 (40:60 petrol−EtOAc); ν_{max}/cm^{-1} 2977, 2933, 2873, 1786, 1737, 1699, 1389, 1366, 1311, 1230, 1151, 1104, 1062, 1047, 1023; δ_H (500 MHz, CD_3OD, 333 K) 5.15 (1H, dd, *J* 5.3 and 2.7, 4-H), 4.20 (1H, dd, *J* 10.8 and 5.3, 3-H_A), 3.86 (1H, d, *J* 8.7, 1-H_A), 3.75 (1H, dd, *J* 10.8 and 2.7, 3-H_B), 3.73 (1H, d, *J* 11.0, 6-H_A), 3.72 (1H, d, *J* 8.7, 1-H_B), 3.68 (1H, d, *J* 11.0, 6-H_B), 2.78 (1H, d, *J* 17.8, 9-H_A), 2.48 (1H, d, *J* 17.8, 9-H_B), 2.08 (3H, s, acetyl), 1.52 (9H, s, ^{t}Bu); δ_C (125 MHz, CD_3OD, 333 K) 174.1 (C-8), 172.0 (acetyl C=O), 151.3 (Boc C=O), 84.5 (^{t}Bu C_1), 79.4 (C-4), 76.2 (C-1), 73.7 (C-3), 55.7 (C-6), 46.7 (C-5), 37.2 (C-9), 28.3 (^{t}Bu C_3), 20.6 (acetyl CH_3); HRMS found MNa^+, 322.1257. $C_{14}H_{21}NO_6$ requires *MNa*, 322.1261.

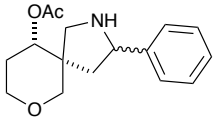
***tert*-Butyl (5*R**,10*R**)-10-(acetyloxy)-3-methoxy-7-oxa-2-azaspiro[4.5] decane-2-carboxylate**



175

According to General Procedure P, the hemiaminals **172a** (0.15 g, 0.48 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 20:80 EtOAc−hexane to yield the *aminals* ***175*** (0.12 g, 77%, *dr* 77:23 by ^{1}H-NMR) as a colourless oil, R_f 0.33 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 2973, 2934, 2859, 1740, 1697, 1390, 1366, 1234, 1164, 1068; δ_H (500 MHz, CD_3OD, 333 K) 5.16 (1H, app. d, *J* 6.3, 3-H^{minor}), 5.13 (1H, app. d, *J* 5.7, 3-H^{major}), 4.99 (1H, dd, *J* 5.5 and 3.5, 10-H^{minor}), 4.85 (1H, dd, *J* 7.6 and 3.8, 10-H^{major}), 3.94 (1H, d, *J* 11.5, 6-H$_A$^{minor}) 3.83 (1H, d, *J* 11.5, 6-H$_A$^{major}), 3.79 (2H, ddd, *J* 11.2, 7.0 and 3.9, 8-H$_A$), 3.62-3.59 (2H, m, 8-H$_B$), 3.57 (1H, d, *J* 11.5, 6-H$_B$^{major}), 3.54 (2H, d, *J* 11.6, 1-H$_A$), 3.47 (1H, d, *J* 11.5, 6-H$_B$^{minor}), 3.33-3.27 (8H, m, 1-H$_B$ and methoxy 1-H$_3$), 2.08 (3H, s, acetyl 1-H$_3$^{minor}), 2.05 (3H, s, acetyl 1-H$_3$^{major}), 2.00 (2H, dd, *J* 13.8 and 5.7, 4-H$_A$), 1.91 (2H, app. d, *J* 13.8, 4-H$_B$), 1.86-1.80 (2H, m, 9-H$_A$), 1.73-1.64 (2H, m, 9-H$_B$), 1.49 (9H, s, ^{t}Bu^{minor}), 1.48 (9H, s, ^{t}Bu^{major}); δ_C (125 MHz, CD_3OD, 333 K) 172.0 (acetyl C=O^{major}), 171.9 (acetyl C=O^{minor}) 156.0 (Boc 2C=O), 90.7 (C-3^{major}), 89.9 (C-3^{minor}), 81.8 (^{t}Bu 2C$_1$), 74.5 (C-10^{major}), 73.4 (C-6^{major}), 72.9 (C-10^{minor}), 72.4 (C-6^{minor}), 65.4 (C-8^{major}), 64.6 (C-8^{minor}), 56.0 (methoxy C-1^{major}), 55.7 (methoxy C-1^{minor}), 52.4 (C$_2$-1), 46.3 (C$_2$-5), 37.3 (C$_2$-4), 30.1 (C-9^{major}), 29.5 (C-9^{minor}), 28.6 (^{t}Bu 2C$_3$), 20.8 (acetyl 2CH$_3$); HRMS found MNa^{+}, 352.1740. $C_{16}H_{27}NO_6$ requires *MNa*, 352.1730.

***tert*-Butyl (5*R**,10*R**)-10-(acetyloxy)-3-phenyl-7-oxa-2-azaspiro[4.5]decane-2-carboxylate**

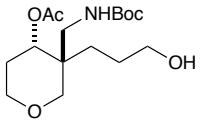


176

According to an existing procedure,[166] PhMgBr (0.75 mL, 0.75 mmol of a 1.0 M solution in THF) was added dropwise to a suspension of CuBr•Me_2S (0.15 g,

0.75 mmol) in Et_2O (1.50 mL) at –40 °C. The suspension was stirred at –40 °C for 1 h and Subsequently it was cooled to –78 °C. Subsequently, $Et_2O•BF_3$ (92.6 μL, 0.75 mmol) and a solution of the aminals **175** (0.10 g, 0,30 mmol) in Et_2O (0.50 mL) were added and the reaction mixture was warmed to 0 °C. The reaction was stirred at 0 °C for 18 h. Subsequently, it was warmed to rt, a saturated aqueous solution of NH_4Cl (2 mL) and EtOAc (2 mL) were added, the phases were separated and the aqueous phase was extracted with EtOAc (4 × 2 mL). The organic phases were combined, washed with brine (4 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude product. The crude product (*dr* 50:50 by ^{1}H-NMR) was purified by flash column chromatography, eluting with 20:80 EtOAc−hexane to yield the *phenyl derivative* ***176*** (0.10 g, 88%, *dr* 57:43 by ^{1}H-NMR) as a colourless oil, R_f 0.56 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3504, 2972, 2930, 2859, 1738, 1688, 1392, 1363, 1234, 1159, 1090, 1070; δ_H (500 MHz, CD_3OD, 333 K) 7.24-7.16 (5H, m, phenyl^{minor}), 7.14-7.05 (5H, m phenyl^{major}), 4.91 (1H, dd, *J* 7.4 and 3.9, 10-H^{minor}), 4.87-4.78 (1H, m, 10-H^{major}), 4.80-4.73 (1H, m, 3-H^{minor}) 4.66 (1H, app. t, *J* 8.4, 3-H^{major}), 3.70 (2H, ddd, *J* 11.3, 7.5 and 3.7, 8-H_A), 3.60 (2H, d, *J* 11.5, 6-H_A), 3.56 (2H, ddd, *J* 11.3, 6.7 and 4.1, 8-H_B), 3.45 (2H, d, *J* 12.0, 1-H_A), 3.35 (2H, d, *J* 12.0, 1-H_B), 3.29 (2H, *J* 11.5, 6-H_B), 2.46 (1H, app. dd, *J* 13.5 and 8.5, 4-H_A^{minor}), 2.28 (1H, ddd, *J* 13.5, 8.0 and 1.3, 4-H_A^{major}), 2.00 (3H, s, acetyl^{minor}), 1.91 (3H, s, acetyl^{major}), 1.86-1.79 (1H, m, 9-H_A^{minor}), 1.79-1.71 (2H, m, 4-H_B^{major} and 9-H_A^{major}), 1.70-1.62 (2H, m, 4-H_B^{minor} and 9-H_B^{minor}), 1.58 (1H, app. dtd, *J* 13.8, 6.7 and 3.7, 9-H_B^{major}); δ_C (125 MHz, CD_3OD, 333 K) 172.0 (C=O^{minor}), 171.8 (C=O^{major}), 156.3 (phenyl C-1^{major}), 156.1 (phenyl C-1^{minor}), 129.4 (phenyl C_2-4), 127.8 (phenyl C_2-3,5^{major}), 127.7 (phenyl C_2-3,5^{minor}), 126.6 (phenyl C_2-2,6^{minor}), 126.5 (phenyl C_2-2,6^{major}), 73.5 (C-6^{minor}), 73.1 (C_2-10), 71.4 (C-6^{major}), 65.7 (C-8^{minor}), 65.5 (C-8^{major}), 62.4 (C-3^{major}), 61.6 (C-3^{minor}), 55.3 (C-1^{major}), 53.1 (C-10^{minor}), 46.9 (C-5^{major}), 46.6 (C-5^{minor}), 41.4 (C-4^{major}), 41.2 (C-4^{minor}), 30.2 (C-9^{major}), 29.7 (C-9^{minor}), 20.9 (acetyl CH_3^{minor}) 20.7 (acetyl CH_3^{major}); HRMS found MH^+, 276.1594. $C_{16}H_{21}NO_3$ requires *MH*, 276.1594.

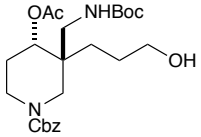
(3*R,4*R**)-3-({[(*tert*-Butoxy)carbonyl]amino}methyl)-3-(3-hydroxypropyl) oxan-4-yl acetate**



177a

According to General Procedure L, the alkene derivative **171a** (0.22 g, 0.69 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 60:40 EtOAc−hexane to yield the *alcohol derivative* ***177a*** (0.17 g, 73%) as a light-yellow oil, R_f 0.13 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3364, 2960, 2865, 1712, 1514, 1365, 1237, 1165, 1083, 1048, 1027; δ_H (400 MHz, $CDCl_3$) 5.05 (1H, app. t, *J* 6.9, NH), 4.95 (1H, app. t, *J* 6.4, 4-H), 3.81 (1H, app. dt, *J* 10.7 and 5.0, 6-H_A), 3.67-3.58 (3H, m, 2-H_A and hydroxypropyl 3-H_2), 3.54 (1H, app. dt, *J* 12.0 and 6.3, 6-H_B), 3.28 (1H, dd, *J* 14.4 and 7.9, methylcarbamate 1-H_A), 3.21 (1H, d, *J* 12.0, 2-H_B), 2.94 (1H, dd, *J* 14.4 and 5.6, methylcarbamate 1-H_B), 2.07 (3H, s, acetyl), 1.98 (1H, br. s, OH), 1.82 (2H, app. q, *J* 5.9, 5-H_2), 1.65-1.32 (4H, m, hydroxypropyl 1,2-H_4), 1.41 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 170.9 (acetyl C=O), 156.5 (Boc C=O), 79.5 (^{t}Bu C_1), 71.5 (C-4), 70.1 (C-2), 65.4 (C-6), 62.9 (hydroxypropyl C-3), 41.7 (methylcarbamate C-1), 41.3 (C-3), 28.4 (^{t}Bu C_3), 27.4 (C-5), 25.7 (hydroxypropyl C-2), 24.6 (hydroxypropyl C-1), 21.2 (acetyl CH_3); HRMS found MH^+, 332.2072. $C_{16}H_{29}NO_6$ requires *MH*, 332.2067.

Benzyl (3*R,4*R**)-4-(acetyloxy)-3-({[(*tert*-butoxy)carbonyl]amino}methyl)-3-(3-hydroxypropyl)piperidine-1-carboxylate**

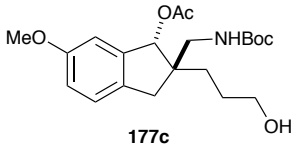


177b

According to General Procedure L, the alkene derivative **171b** (0.25 g, 0.55 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 60:40 EtOAc−hexane to yield the *alcohol derivative* ***177b*** (0.22 g, 86%) as a colourless oil, R_f 0.38 (20:80 petrol−EtOAc); ν_{max}/cm^{-1} 3400, 2937, 2872, 2508, 1681, 1433, 1365, 1235, 1157, 1035; δ_H (500

MHz, CD_3OD, 333 K) 7.38-7.28 (5H, m, phenyl), 5.12 (2H, s, phenylmethyl 1-H_2), 4.87 (1H, dd, *J* 8.1 and 3.8, 4-H), 3.68 (1H, app. br. s, 6-H_A), 3.53 (1H, app. br. s, 2-H_A), 3.53-3.40 (2H, m, hydroxypropyl 3-H_2), 3.38 (1H, app. br. s, 6-H_B), 3.18 (2H, d, *J* 14.7, 2-H_B and methylcarbamate 1-H_A), 3.03 (1H, d, *J* 14.7, methylcarbamate 1-H_B), 2.05 (3H, s, acetyl), 1.95-1.86 (1H, m, 5-H_A), 1.76-1.63 (1H, m, 5-H_B), 1.61-1.53 (1H, m, hydroxypropyl 2-H_A), 1.53-1.44 (2H, m, hydroxypropyl 2-H_B and hydroxypropyl 1-H_A), 1.42 (9H, s, ^{t}Bu), 1.40-1.32 (1H, m, hydroxypropyl 1-H_B); δ_C (125 MHz, CD_3OD, 333 K) 172.2 (acetyl C=O), 158.3 (Boc C=O), 157.2 (Cbz C=O), 138.1 (phenyl C-1), 129.5 (phenyl C_2-3,5), 129.1 (phenyl C_2-2,6), 129.0 (phenyl C-4), 80.3 (^{t}Bu C_1), 73.5 (C-4), 68.5 (phenylmethyl C-1), 63.6 (hydroxypropyl C-3), 48.7 (C-2), 43.1 (methylcarbamate C-1), 42.5 (C-6), 42.2 (C-3), 28.8 (^{t}Bu C_3), 27.2 (hydroxypropyl C-1), 27.0 (hydroxypropyl C-2), 21.0 (acetyl CH_3); HRMS found MNa^+, 487.2411. $C_{24}H_{36}N_2O_7$ requires *MNa*, 487.2420.

(1*R,2*S**)-2-({[(*tert*-Butoxy)carbonyl]amino}methyl)-2-(3-hydroxypropyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-yl acetate**

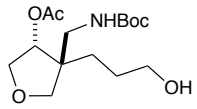


177c

According to General Procedure L, the alkene derivative **171c** (0.20 g, 0.53 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 50:50 EtOAc−hexane to yield the *alcohol derivative* ***177c*** (0.17 g, 83%) as a colourless oil, R_f 0.36 (30:70 petrol−EtOAc); ν_{max}/cm^{-1} 3376, 3270, 3145, 2937, 2873, 1705, 1493, 1394, 1368, 1234, 1167, 1144, 1121, 1008; δ_H (400 MHz, $CDCl_3$) 7.08 (1H, d, *J* 8.1, 4-H), 6.81 (2H, app. d, *J* 7.6, 5-H and 7-H), 5.97 (1H, s, 1-H), 5.06 (1H, app. t, *J* 7.0, NH), 3.77 (3H, s, methoxy), 3.67-3.51 (2H, m, hydroxypropyl 3-H_2), 3.24-3.04 (2H, m, methylcarbamate 1-H_2), 2.83 (1H, d, *J* 15.8, 3-H_A), 2.65 (1H, d, *J* 15.8, 3-H_B), 2.11 (3H, s, acetyl), 1.87 (1H, br. s, OH), 1.63-1.49 (4H, m, hydroxypropyl 1,2-H_4), 1.41 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 171.5 (acetyl C=O), 159.1 (C-6), 156.7 (Boc C=O), 141.6 (C-7a), 133.7 (C-3a), 125.7 (C-4), 115.6 (C-5), 110.3 (C-7), 80.6 (C-1), 79.6 (^{t}Bu C_1), 63.2 (hydroxypropyl C-3), 55.6 (methoxy), 51.7

(C-2), 45.0 (methylcarbamate C-1), 38.7 (C-3), 28.5 (^{t}Bu C_3), 27.6 (hydroxypropyl C-1), 27.3 (hydroxypropyl C-2), 21.3 (acetyl CH_3); HRMS found MNa^+, 416.2049. $C_{21}H_{31}NO_6$ requires *MNa*, 416.2043.

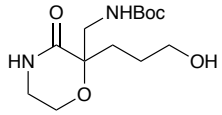
(*3R,*4S**)-4-({[(*tert*-Butoxy)carbonyl]amino}methyl)-4-(3-hydroxypropyl) oxolan-3-yl acetate**



177d

According to General Procedure L, the alkene derivative **171d** (0.25 g, 0.83 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 60:40 EtOAc−hexane to yield the *alcohol derivative **177d*** (0.11 g, 41%) as a colourless oil, R_f 0.52 (EtOAc); ν_{max}/cm^{-1} 3365, 2972, 2932, 2873, 1712, 1689, 1526, 1365, 1242, 1164, 1035, 1004; δ_H (400 MHz, $CDCl_3$) 4.86 (1H, br. s, NH), 4.15 (1H, dd, *J* 9.5 and 5.7, 2-H_A), 4.12-4.02 (3H, m, 2-H_B and hydroxypropyl 3-H_2), 3.65 (1H, dd, *J* 9.5 and 3.6, 3-H), 3.61 (1H, d, *J* 8.9, 5-H_A), 3.56 (1H, d, *J* 8.9, 5-H_B), 3.10 (2H, app. d, *J* 6.5, methylcarbamate 1-H_2), 2.56 (1H, br. s, OH), 2.04 (3H, s, acetyl), 1.77-1.47 (4H, m, hydroxypropyl 1-H_2 and hydroxypropyl 2-H_2), 1.42 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 171.3 (acetyl C=O), 156.7 (Boc C=O), 79.9 (^{t}Bu C_1), 75.5 (C-3), 74.7 (C-2), 74.1 (C-5), 65.0 (hydroxypropyl C-3), 50.1 (C-4), 43.5 (methylcarbamate C-1), 28.5 (^{t}Bu C_3), 24.5 (hydroxypropyl C-2), 23.9 (hydroxypropyl C-1), 21.1 (acetyl CH_3); HRMS found MNa^+, 340.1727. $C_{15}H_{27}NO_6$ requires *MNa*, 340.1730.

***tert*-Butyl *N*-{[2-(3-hydroxypropyl)-3-oxomorpholin-2-yl]methyl}carbamate**

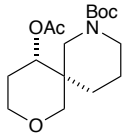


177e

According to General Procedure L, the alkene derivative **148h** (0.20 g, 0.53 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with EtOAc to yield the *alcohol derivative **177e*** (0.11 g,

71%) as a pale oil, R_f 0.20 (10:90 MeOH−EtOAc); ν_{max}/cm^{-1} 3307, 2974, 2932, 2876, 1696, 1660, 1509, 1484, 1365, 1340, 1269, 1248, 1163, 1124, 1063; δ_H (400 MHz, $CDCl_3$) 7.20 (1H, br. s, 4-H), 5.12 (1H, app. t, *J* 5.0, methylcarbamate NH), 3.96-3.78 (2H, m, 6-H_2), 3.65-3.49 (3H, m, hydroxypropyl 3-H_2 and methylcarbamate 1-H_A), 3.49-3.40 (1H, m, 5-H_A), 3.40-3.28 (2H, m, 5-H_B and methylcarbamate 1-H_B), 2.54 (1H, br. s, OH), 2.00-1.85 (1H, m, hydroxypropyl 1-H_A), 1.79-1.64 (2H, m, hydroxypropyl 1-H_B and hydroxypropyl 2-H_A), 1.63-1.51 (1H, m, hydroxypropyl 2-H_B), 1.42 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 172.8 (C-3), 156.2 (Boc C=O), 80.9 (^{t}Bu C_1), 79.5 (C-2), 62.5 (hydroxypropyl C-3), 59.5 (C-6), 44.9 (C-5), 42.2 (methylcarbamate C-1), 31.3 (hydroxypropyl C-2), 28.5 (^{t}Bu C_3), 26.6 (hydroxypropyl C-1); HRMS found MNa^+, 311.1574. $C_{13}H_{24}N_2O_5$ requires *MNa*, 311.1577.

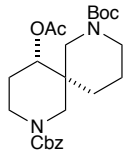
tert-Butyl (5*R, 6*R**)-5-(acetyloxy)-2-oxa-8-azaspiro[5.5]undecane-8-carboxylate**



179a

According to General Procedure X, the alcohol derivative **177a** (0.10 g, 0.30 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 20:80 EtOAc−hexane to yield the *piperidine derivative* ***179a*** (54.0 mg, 57%) as a colourless oil, R_f 0.59 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 2936, 2857, 1737, 1687, 1423, 1365, 1274, 1234, 1160, 1141, 1090, 1040; δ_H (500 MHz, $CDCl_3$, 323 K) 4.89 (1H, dd, *J* 6.2 and 3.7, 5-H), 3.71 (1H, ddd, *J* 12.1, 8.7 and 3.6, 3-H_A), 3.65 (1H, app. t, *J* 5.1, 3-H_B), 3.62 (1H, d, *J* 12.0, 1-H_A), 3.50 (1H, d, *J* 13.7, 7-H_A), 3.42-3.34 (1H, m, 9-H_A), 3.32-3.28 (1H, m, 9-H_B), 3.25 (1H, d, *J* 12.0, 1-H_B), 3.24 (1H, d, *J* 13.7, 7-H_B), 2.05 (3H, s, acetyl), 2.03-1.98 (1H, m, 4-H_A), 1.69-1.60 (1H, m, 4-H_B), 1.53-1.48 (3H, m, 10-H_2 and 11-H_A), 1.43 (9H, s, ^{t}Bu), 1.42-1.38 (1H, m, 11-H_B); δ_C (125 MHz, $CDCl_3$, 323 K) 170.1 (acetyl C=O), 154.9 (Boc C=O), 79.7 (^{t}Bu C_1), 71.1 (C-5), 70.8 (C-1), 64.7 (C-3), 49.4 (C-7), 44.5 (C-9), 37.5 (C-6), 28.5 (^{t}Bu C_3), 27.4 (C-4), 26.6 (C-10), 21.0 (acetyl CH_3), 20.5 (C-11); HRMS found MNa^+, 336.1789. $C_{16}H_{27}NO_5$ requires *MNa*, 336.1786.

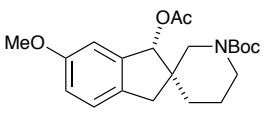
2-Benzyl 8-*tert*-butyl (5*R,6*S**)-5-(acetyloxy)-2,8-diazaspiro[5.5]undecane-2,8-dicarboxylate**



179b

According to General Procedure X, the alcohol derivative **177b** (50.0 mg, 0.12 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 30:70 EtOAc−hexane to yield the *piperidine derivative* ***179b*** (19.0 mg, 40%) as a colourless oil, R_f 0.60 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 2936, 2866, 1737, 1686, 1425, 1364, 1273, 1232, 1205, 1154, 1108, 1038; δ_H (500 MHz, CD_3OD, 333 K) 7.37-7.27 (5H, m, phenyl), 5.14 (1H, d, *J* 12.4, phenylmethyl 1-H_A), 5.11 (1H, d, *J* 12.4, phenylmethyl 1-H_B), 4.89 (1H, dd, *J* 6.8 and 3.6, 5-H), 3.63-3.44 (3H, m, 3-H_2 and 1-H_A), 3.44-3.33 (4H, m, 9-H_2, 1-H_B and 7-H_A), 3.19 (1H, d, *J* 12.9, 7-H_B), 2.06 (3H, s, acetyl), 1.99-1.90 (1H, m, 4-H_A), 1.74-1.65 (1H, m, 4-H_B), 1.64-1.58 (1H, m, 11-H_A), 1.57-1.47 (2H, m, 10-H_2), 1.43 (9H, s, ^{t}Bu), 1.41-1.36 (1H, m, 11-H_B); δ_C (125 MHz, CD_3OD, 333 K) 171.9 (acetyl C=O), 157.1 (Boc C=O), 156.5 (Cbz C=O), 138.1 (phenyl C-1), 129.5 (phenyl C_2-3,5), 129.1 (phenyl C_2-2,6), 129.0 (phenyl C-4), 81.3 (^{t}Bu C_1), 72.7 (C-5), 68.5 (phenylmethyl C-1), 50.2 (C-7), 49.0 (C-1), 45.5 (C-9), 41.7 (C-3), 39.3 (C-6), 28.7 (^{t}Bu C_3), 28.0 (C-10), 27.2 (C-4), 21.7 (C-11), 20.8 (acetyl CH_3); HRMS found MNa^+, 469.2306. $C_{24}H_{34}N_2O_6$ requires *MNa*, 469.2314.

***tert*-Butyl (2*R**,3*S**)-3-(acetyloxy)-5-methoxy-1,3-dihydrospiro[indene-2,3'-piperidine]-1'-carboxylate**

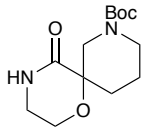


179c

According to General Procedure X, the alcohol derivative **177c** (50.0 mg, 0.13 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 10:90 EtOAc−hexane to yield the *piperidine derivative* ***179c*** (6.00 mg, 13%) as a colourless oil, R_f 0.50 (70:30

petrol−EtOAc); ν_{max}/cm^{-1} 2928, 2851, 1732, 1689, 1493, 1426, 1365, 1285, 1234, 1152, 1018; δ_H (500 MHz, $CDCl_3$, 323 K) 7.10 (1H, d, *J* 8.3, 7-H), 6.98 (1H, d, *J* 2.5, 4-H), 6.84 (1H, dd, *J* 8.3 and 2.5, 6-H), 5.83 (1H, s, 3-H), 3.78 (3H, s, methoxy), 3.60-3.48 (1H, m, 6'-H_A), 3.32 (1H, ddd, *J* 12.8, 7.0 and 5.1, 6'-H_B), 3.25 (1H, d, *J* 13.2, 2'-H_A), 3.15 (1H, d, *J* 13.2, 2'-H_B), 2.81 (1H, d, *J* 15.6, 1-H_A), 2.66 (1H, d, *J* 15.6, 1-H_B), 2.04 (3H, s, acetyl), 1.87-1.78 (1H, m, 4'-H_A), 1.69 (1H, app. dt, *J* 13.0 and 5.6, 4'-H_B), 1.61-1.54 (2H, m, 5'-H_2), 1.40 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$, 323 K) 170.8 (acetyl C=O), 159.3 (C-5), 155.0 (Boc C=O), 141.7 (C-3a), 135.2 (C-7a), 125.9 (C-7), 116.3 (C-6), 111.7 (C-4), 80.6 (C-3), 79.7 (^{t}Bu C_1), 55.7 (methoxy), 51.8 (C-2'), 47.4 (C-2), 44.3 (C-6'), 39.8 (C-1), 30.4 (C-4'), 28.6 (^{t}Bu C_3), 22.9 (C-5'), 21.2 (acetyl CH_3); HRMS found MNa^+, 398.1935. $C_{21}H_{29}NO_5$ requires *MNa*, 398.1937.

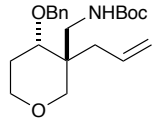
tert-Butyl 5-oxo-1-oxa-4,8-diazaspiro[5.5]undecane-8-carboxylate



179e

According to General Procedure X, the alcohol derivative **177e** (78.0 mg, 0.27 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 60:40 EtOAc−hexane to yield the *piperidine derivative* ***179e*** (42.0 mg, 57%) as a colourless oil, R_f 0.44 (EtOAc); ν_{max}/cm^{-1} 3192, 3071, 2954, 2925, 1687, 1667, 1421, 1364, 1335, 1276, 1243, 1175, 1150, 1107, 1086; δ_H (500 MHz, CD_3OD, 333 K) 4.37 (1H, br. s, 4-H), 4.16 (1H, d, *J* 13.9, 7-H_A), 3.95 (1H, app. d, *J* 12.3, 9-H_A), 3.79 (1H, ddd, *J* 12.1, 8.5 and 3.5, 2-H_A), 3.72 (1H, app. br. s, 2-H_B), 3.32 (1H, ddd, *J* 12.5, 8.5 and 4.2, 3-H_A), 3.26-3.15 (1H, m, 3-H_B), 3.00 (1H, app. br. s, 7-H_B), 2.69 (1H, app. br. s, 9-H_B), 1.93 (1H, app. td, *J* 13.5 and 4.5, 10-H_A), 1.86-1.76 (1H, m, 10-H_B), 1.75-1.62 (1H, m, 11-H_A), 1.36 (10H, s, 11-H_B and ^{t}Bu); δ_C (125 MHz, CD_3OD, 333 K) 173.9 (C-5), 157.1 (Boc C=O), 81.1 (^{t}Bu C_1), 77.6 (C-6), 60.1 (C-2), 45.0 (C-7), 43.1 (C-9), 43.0 (C-3), 32.8 (C-10), 28.7 (^{t}Bu C_3), 20.6 (C-11); HRMS found MNa^+, 293.1466. $C_{13}H_{22}N_2O_4$ requires *MNa*, 293.1471.

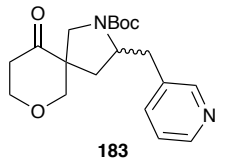
tert-Butyl _N_-{[(3_R_*,4_R_*)-4-(benzyloxy)-3-(prop-2-en-1-yl)oxan-3-yl]methyl} carbamate



182

By modification of an existing procedure,[179] NaH (37.0 mg, 0.92 mmol of a 60% dispersion in mineral oil) was added to a mixture of the alcohol derivative **167a** (0.23 g, 0.84 mmol), benzyl bromide (0.12 mL, 1.00 mmol) and tetrabutylammonium iodide (62.0 mg, 0.17 mmol) in THF (5.00 mL) at 0 °C. The reaction mixture was stirred for 18 h at rt. Subsequently, a saturated aqueous solution of $NaHCO_3$ (5 mL) was added, the phases were separated and the aqueous phase was extracted with EtOAc (4 × 5 mL). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography, eluting with 10:90 EtOAc−hexane to yield the *benzyl derivative **182*** (0.26 g, 86%) as a colourless oil, R_f 0.75 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3426, 3344, 2973, 2930, 2859, 1712, 1504, 1453, 1365, 1243, 1165, 1088; δ_H (400 MHz, $CDCl_3$) 7.40-7.27 (5H, m, phenyl), 5.81 (1H, ddt, *J* 15.2, 10.1 and 7.5, propenyl 2-H), 5.17-5.01 (2H, m, propenyl 3-H_2), 4.87 (1H, app. t, *J* 4.8, NH), 4.66 (1H, d, *J* 11.6, phenylmethyl 1-H_A), 4.39 (1H, d, *J* 11.6, phenylmethyl 1-H_B), 4.05-3.90 (1H, m, 6-H_A), 3.67 (1H, d, *J* 11.8, 2-H_A), 3.48 (1H, app. td, *J* 7.9 and 3.8, 4-H), 3.45-3.38 (1H, m, 6-H_B), 3.18-3.09 (1H, m, methylcarbamate 1-H_A), 3.01 (1H, d, *J* 11.8, 2-H_B), 3.00 (1H, d, *J* 13.5, methylcarbamate 1-H_B), 2.33 (2H, app. d, *J* 7.6, propenyl 1-H_2), 2.00-1.90 (1H, m, 5-H_A), 1.78 (1H, app. dtd, *J* 13.7, 9.5 and 4.5, 5-H_B), 1.41 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 156.1 (C=O), 138.4 (phenyl C-1), 133.8 (propenyl C-2), 128.6 (phenyl C_2-3,5), 127.8 (phenyl C_2-2,6), 126.2 (phenyl C-4), 118.6 (propenyl C-3), 81.3 (^{t}Bu C_1), 78.9 (C-4), 70.6 (C-2), 70.3 (phenylmethyl C-1), 66.0 (C-6), 44.3 (methylcarbamate C-1), 42.1 (C-3), 32.1 (propenyl C-1), 28.5 (^{t}Bu C_3), 26.3 (C-5); HRMS found MH^+, 362.2328. $C_{21}H_{31}NO_4$ requires *MH*, 362.2325.

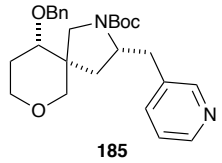
***tert*-Butyl 10-oxo-3-(pyridin-3-ylmethyl)-7-oxa-2-azaspiro[4.5]decane-2-carboxylate**



183

According to General Procedure F, the alkene derivative **148i** (0.18 g, 0.67 mmol) and 3-bromopyridine (77.1 μL, 0.80 mmol) were combined to give a crude product. The crude product (*dr* 65:35 by ^{1}H-NMR) was purified by flash column chromatography, eluting with 97.0:2.7:0.3 DCM−EtOH−NH_4OH to yield the *pyrrolidine derivative **183*** (80.0 mg, 34%, *dr* 69:31 by ^{1}H-NMR) as a yellow oil, R_f 0.40 (EtOAc); ν_{max}/cm^{-1} 2971, 2930, 2861, 1709, 1685, 1391, 1364, 1222, 1147, 1111, 1094, 1027; δ_H (500 MHz, CD_3OD, 333 K) 8.41-8.40 (2H, m, pyridine 2,6-H_2^{minor}), 8.39 (2H, app. d, *J* 3.4, pyridine 2,6-H_2^{major}), 7.70-7.65 (2H, m, pyridine 4-H), 7.35 (2H, app. dtd, *J* 8.0, 5.0 and 0.8, pyridine 5-H), 4.17-4.09 (2H, m, 3-H), 4.06 (1H, d, *J* 11.9, 1-H_A^{major}), 4.03-3.97 (2H, m, 8-H_A), 3.94-3.80 (2H, m, 8-H_B), 3.72 (2H, d, *J* 11.5, 6-H_A), 3.65 (2H, d, *J* 11.5, 6-H_B), 3.54 (1H, d, *J* 11.5, 1-H_A^{minor}), 3.33 (1H, d, *J* 11.5, 1-H_B^{minor}), 3.11 (1H, dd, *J* 13.5 and 4.6, pyridinylmethyl 1-H_A^{major}), 3.04 (1H, dd, *J* 13.5 and 4.0, pyridinylmethyl 1-H_A^{minor}), 2.97 (1H, d, *J* 11.9, 1-H_B^{major}), 2.82 (1H, dd, *J* 13.5 and 8.0, pyridinylmethyl 1-H_B^{major}), 2.78 (1H, dd, *J* 13.5 and 8.4, pyridinylmethyl 1-H_B^{minor}) 2.67-2.59 (2H, m, 9-H_A), 2.54-2.44 (2H, m, 9-H_B), 2.37 (1H, ddd, *J* 13.4, 8.0 and 1.2, 4-H_A^{major}), 2.17 (1H, app. dd, *J* 13.4 and 5.4, 4-H_A^{minor}), 1.85 (1H, app. dd, *J* 13.4 and 8.1, 4-H_B^{minor}), 1.54-1.38 (19H, m, ^{t}Bu and 4-H_B^{major}); δ_C (125 MHz, CD_3OD, 333 K) 208.9 (C-10^{minor}), 208.8 (C-10^{major}), 156.2 (Boc C=O^{major}), 156.0 (Boc C=O^{minor}), 151.1 (pyridine C_A-2,6^{minor}), 151.0 (pyridine C_A-2,6^{major}), 148.3 (pyridine C_B-2,6^{major}), 148.2 (pyridine C_B-2,6^{minor}) 139.1 (pyridine C_2-4), 135.9 (pyridine C_2-3), 125.0 (pyridine C_2-5), 81.6 (^{t}Bu C_1^{minor}), 81.5 (^{t}Bu C_1^{major}), 76.1 (C-6^{major}), 75.8 (C-6^{minor}), 69.4 (C-8^{minor}), 69.3 (C-8^{major}), 59.2 (C-3^{major}), 58.7 (C-3^{minor}), 57.8 (C-5^{minor}), 57.6 (C-5^{major}), 53.7 (C-1^{major}), 53.6 (C-1^{minor}), 41.7 (pyridinylmethyl C_2-1), 40.0 (C_2-9), 36.8 (C_2-4), 28.7 (^{t}Bu $2C_3$); HRMS found MH^+, 347.1975. $C_{19}H_{26}N_2O_4$ requires *MH*, 347.1970.

***tert*-Butyl (3*R**,5*S**,10*S**)-10-(benzyloxy)-3-[(pyridin-3-yl)methyl]-7-oxa-2-azaspiro[4.5] decane-2-carboxylate**

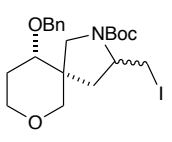


185

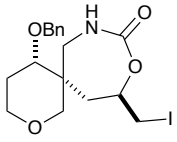
According to General Procedure F, the alkene **182** (0.10 g, 0.28 mmol) and 3-bromopyridine (31.8 μL, 0.33 mmol) gave a crude material. The crude material (*dr* 67:33 by ^{1}H-NMR) was purified by flash column chromatography, eluting with 70:30→50:50 hexane−EtOAc to yield the *pyrrolidine derivative* ***185*** (38.0 mg, 31%, *dr* >95:<5 by ^{1}H-NMR) as a grey oil, R_f 0.56 (EtOAc); ν_{max}/cm^{-1} 2928, 2858, 1685, 1393, 1364, 1155, 1085; δ_H (500 MHz, $CDCl_3$, 323 K) 8.44 (1H, d, *J* 1.7, pyridinyl 2-H), 8.40 (1H, app. s, pyridinyl 6-H), 7.43 (1H, d, *J* 4.5, pyridinyl 4-H), 7.38-7.25 (5H, m, phenyl), 7.13 (1H, dd, *J* 7.7 and 4.5, pyridinyl 5-H), 4.61 (1H, d, *J* 11.7, phenylmethyl 1-H_A), 4.36 (1H, d, *J* 11.7, phenylmethyl 1-H_B), 4.04 (1H, app. br. s, 3-H), 3.83 (1H, m, 8-H_A), 3.54 (1H, d, *J* 11.4, 6-H_A), 3.50-3.43 (2H, m, 1-H_A and 8-H_B), 3.26 (1H, app. br. s, 10-H), 3.15 (1H, d, *J* 11.4, 6-H_B), 3.13-2.87 (2H, m, 1-H_B and pyridinylmethyl 1-H_A), 2.72 (1H, app. br. s, pyridinylmethyl 1-H_B), 1.99 (1H, dd, *J* 13.6 and 8.0, 4-H_A), 1.78-1.71 (2H, m, 4-H_B and 9-H_A), 1.66-1.56 (1H, m, 9-H_B), 1.48 (9H, s, ^{t}Bu); δ_C (125 MHz, $CDCl_3$, 323 K) 154.7 (C=O), 151.0 (pyridinyl C-2), 147.8 (pyridinyl C-6), 138.5 (pyridinyl C-3), 137.0 (pyridinyl C-4), 134.0 (phenyl C-1), 128.5 (phenyl C_2-3,5), 127.8 (phenyl C-4), 127.7 (phenyl C_2-2,6), 123.2 (pyridinyl C-5), 79.7 (^{t}Bu C_1), 76.7 (C-10), 71.7 (C-6), 70.7 (phenylmethyl C-1), 64.9 (C-8), 57.1 (C-3), 51.1 (C-1), 46.5 (C-5), 37.7 (C-4), 34.1 (pyridinylmethyl C-1), 28.6 (C-9 and ^{t}Bu C_3); HRMS found MH^+, 439.2604. $C_{26}H_{34}N_2O_4$ requires *MH*, 439.2596. The relative stereochemistry was determined using NOESY (500 MHz, $CDCl_3$, 323 K) nOe observed between 3-H and 6-H_A.

***tert*-Butyl (5*R**,10*R**)-10-(benzyloxy)-3-(iodomethyl)-7-oxa-2-azaspiro[4.5] decane-2-carboxylate (186)**

(5*R,6*R**,11*S**)-5-(Benzyloxy)-11-(iodomethyl)-2,10-dioxa-8-azaspiro[5.6] dodecan-9-one (187)**



186



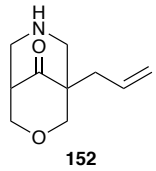
187

According General Procedure S, the alkene derivative **182** (0.10 g, 0.28 mmol) was stirred for 3 days to give a crude material. The crude material was purified by flash column chromatography, eluting with 15:85 EtOAc−hexane to yield the *pyrrolidine derivative **186*** (41.0 mg, 30%, *dr* 77:23 by ^{1}H-NMR) as a yellow oil, R_f 0.63 (50:50 petrol−EtOAc); v_{max}/cm^{-1} 2928, 2857, 1687, 1391, 1364, 1157, 1087; δ_H (500 MHz, $CDCl_3$, 323 K) 7.37-7.26 (10H, m, phenyl), 4.67 (1H, d, *J* 11.8, phenylmethyl 1-H_A^{major}), 4.64 (1H, d, *J* 11.9, phenylmethyl 1-H_A^{minor}), 4.45 (1H, d, *J* 11.8, phenylmethyl 1-H_B^{major}), 4.42 (1H, d, *J* 11.9, phenylmethyl 1-H_B^{minor}), 3.92-3.82 (2H, m, 8-H_A), 3.79-3.75 (2H, m, 3-H) 3.73 (2H, d, *J* 11.1, 6-H_A), 3.61 (2H, d, *J* 11,3, 1-H_A), 3.58-3.49 (4H, m, 8-H_B and iodomethyl 1-H_A), 3.44-3.40 (4H, m, 10-H and iodomethyl 1-H_B), 3.33 (2H, d, *J* 11.1, 6-H_B), 3.21 (2H, d, *J* 11.3, 1-H_B), 2.20-2.08 (2H, m, 9-H_A), 1.93-1.65 (6H, m, 9-H_B and 4-H_2), 1.47 (9H, s, ^{t}Bu^{major}), 1.45 (9H, s, ^{t}Bu^{minor}); δ_C (125 MHz, $CDCl_3$, 323 K) 154.3 (2C=O), 138.5 (phenyl C-1^{major}), 138.4 (phenyl C-1^{minor}), 128.6 (phenyl C_2-3,5^{minor}), 128.5 (phenyl C_2-3,5^{major}), 127.8 (phenyl C-4^{minor}), 127.7 (phenyl C-4^{major}), 127.6 (phenyl C_4-2,6), 80.1 (^{t}Bu C_1^{minor}), 80.0 (^{t}Bu C_1^{major}), 78.0 (C-10^{minor}), 77.1 (C-10^{major}), 73.0 (C_2-6), 71.1 (phenylmethyl C-1^{minor}), 70.9 (phenylmethyl C-1^{major}), 64.9 (C-8^{major}), 63.2 (C-8^{minor}), 56.3 (C-3^{major}), 55.2 (C-3^{minor}), 52.3 (C-1^{minor}), 51.6 (C-1^{major}), 46.3 (C-5^{major}), 45.8 (C-5^{minor}), 36.6 (C_2-4), 28.6 (^{t}Bu 2C_3), 27.4 (C-9^{major}), 26.3 (C-9^{minor}), 13.7 (iodomethyl C-1^{major}), 12.9 (iodomethyl C-1^{minor}); HRMS found MH^{+}, 488.1295. $C_{21}H_{30}INO_4$ requires *MH*, 488.1292.

Also obtained was the *carbamate derivative **187*** (10.0 mg, 8%, *dr* >95:<5 by ^{1}H-NMR) as an amorphous colourless solid, R_f 0.73 (50:50 petrol−EtOAc); v_{max}/cm^{-1} 2979, 2955, 2928, 2854, 1683, 1604, 1477, 1453, 1402, 1361, 1249, 1165, 1137, 1091, 1066, 1020; δ_H (500 MHz, $CDCl_3$, 323 K) 7.35-7.29 (2H, m, phenyl

3,5-H_2), 7.28-7.24 (1H, m, phenyl 4-H), 7.19 (2H, d, *J* 7.5 phenyl 2,6-H_2), 4.60 (1H, d, *J* 15.8, phenylmethyl 1-H_A), 4.45 (1H, d, *J* 15.8, phenylmethyl 1-H_B), 4.08 (1H, app. dtd, *J* 8.6, 6.9 and 5.6, 11-H), 3.80 (1H, app. t, *J* 3.7, 5-H), 3.71-3.64 (2H, m, 3-H_2), 3.59 (1H, d, *J* 11.9, 1-H_A), 3.45 (1H, d, *J* 11.9, 1-H_B), 3.37-3.30 (2H, m, 7-H_2 and iodomethyl 1-H_A), 3.24 (1H, dd, *J* 9.9 and 6.9, iodomethyl 1-H_B), 2.26 (1H, app. t, *J* 11.0, 12-H_A), 1.97-1.86 (1H, m, 4-H_A), 1.80 (1H, app. dq, *J* 14.8 and 3.2, 4-H_B), 1.31 (1H, dd, *J* 13.6 and 6.9, 12-H_B); δ_C (125 MHz, $CDCl_3$) 156.7 (C-9), 138.5 (phenyl C-1), 128.6 (phenyl C_2-3,5), 127.3 (phenyl C-4), 126.9 (phenyl C_2-2,6), 77.8 (C-5), 77.3 (C-11), 70.7 (C-1), 64.1 (C-3), 53.2 (phenylmethyl C-1), 50.4 (C-7), 46.4 (C-6), 39.0 (C-12), 26.7 (C-4), 9.6 (iodomethyl C-1); HRMS found MH^+, 432.0671. $C_{17}H_{22}INO_4$ requires *MH*, 432.0671. The relative configuration was determined using NOESY (500 MHz, $CDCl_3$, 323 K) nOe observed between 5-H and 11-H.

(1*R, 5*S**)-1-(Prop-2-en-1-yl)-3-oxa-7-azabicyclo[3.3.1]nonan-9-one**

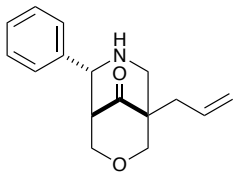


152

According to General Procedure Y, paraformaldehyde (16.8 mg, 0.56 mmol) and the ketone derivative **148i** (0.10 g, 0.37 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 95.4:4.1:0.5 DCM−EtOH−NH_4OH to yield the *bridged bicyclic derivative* ***152*** (20.0 mg, 30%) as a yellow oil, R_f 0.40 (92.4:6.8:0.8 DCM−EtOH−NH_4OH); ν_{max}/cm^{-1} 3362, 3074, 2922, 2848, 1709, 1674, 1638, 1455, 1435, 1375, 1234, 1211, 1082; δ_H (400 MHz, CD_3OD) 5.86 (1H, ddt, *J* 15.4, 11.0 and 7.5, propenyl 2-H), 5.09 (1H, dd, *J* 10.5 and 1.5, propenyl 3-H_{cis}), 5.08 (1H, dd, *J* 16.7 and 1.5, propenyl 3-H_{trans}), 4.43 (1H, app. dt, *J* 11.3 and 1.6, 4-H_A), 4.26 (1H, dd, *J* 11.3 and 1.6, 2-H_A), 3.97 (1H, app. dt, *J* 11.3 and 2.5, 4-H_B), 3.73 (1H, dd, *J* 11.3 and 3.1, 2-H_B), 3.63 (1H, app. dt, *J* 13.8 and 2.2, 6-H_A), 3.49 (1H, dd, *J* 13.7 and 2.4, 8-H_A), 3.13 (1H, app. dt, *J* 13.8 and 2.9, 6-H_B), 2.89 (1H, dd, *J* 13.7 and 3.1, 8-H_B), 2.37 (1H, app. s, 5-H), 2.15 (2H, app. d, *J* 7.5, propenyl 1-H_2); δ_C (100 MHz, CD_3OD) 213.7 (C-9), 134.0 (propenyl C-2), 118.7 (propenyl C-3), 79.3 (C-2), 75.9 (C-4), 60.3 (C-8), 55.8 (C-6), 53.9 (C-1), 52.7 (C-5), 35.3

(propenyl C-1). HRMS found MH^+, 182.1179. $C_{10}H_{15}NO_2$ requires *MH*, 182.1175.

(1*R,5*S**,6*R**)-6-phenyl-1-(prop-2-en-1-yl)-3-oxa-7-azabicyclo[3.3.1]nonan-9-one**



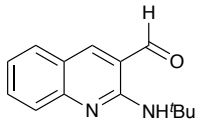
188

According to General Procedure Y, benzaldehyde (57.6 μL, 0.56 mmol) and the ketone derivative **148i** (0.10 g, 0.37 mmol) gave a crude material. The crude material (*dr* >95:<5 by ^{1}H-NMR) was purified by flash column chromatography, eluting with 97:2.7:0.3 DCM−EtOH−NH_4OH to yield the *bridged bicyclic derivative **188*** (32.0 mg, 33%, *dr* >95:<5 by ^{1}H-NMR) as an amorphous yellow solid, R_f 0.40 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3337, 3059, 3030, 2921, 2851, 1708, 1470, 1372, 1225, 1210, 1088; δ_H (500 MHz, $CDCl_3$) 7.34-7.18 (5H, m, phenyl), 5.75 (1H, ddt, *J* 17.3, 10.0 and 7.5, propenyl 2-H), 5.03 (1H, dd, *J* 10.0 and 1.9, propenyl 3-H_{cis}), 5.00 (1H, dd, *J* 17.3 and 1.9, propenyl 3-H_{trans}), 4.27 (1H, app. s, 6-H), 4.16 (1H, dd, *J* 11.4 and 1.6, 2-H_A), 4.06 (1H, app. d, *J* 11.7, 4-H_A), 3.69 (1H, dd, *J* 11.4 and 3.1, 2-H_B), 3.61 (1H, app. dt, *J* 11.7 and 2.1, 4-H_B), 3.54 (1H, d, *J* 13.8, 8-H_A), 2.97 (1H, dd, *J* 13.8 and 3.2, 8-H_B), 2.82 (1H, br. s, NH), 2.51 (1H, app. s, 5-H), 2.18 (1H, dd, *J* 14.4 and 7.3, propenyl 1-H_A), 2.11 (1H, dd, *J* 14.4 and 7.7, propenyl 1-H_B); δ_C (125 MHz, $CDCl_3$) 212.0 (C-9), 139.1 (phenyl C-1), 132.4 (propenyl C-2), 128.8 (phenyl C_2-3,5), 127.6 (phenyl C-4), 126.2 (phenyl C_2-2,6), 118.7 (propenyl C-3), 78.4 (C-2), 70.1 (C-4), 66.9 (C-6), 58.8 (C-8), 56.6 (C-5), 52.2 (C-1), 34.3 (propenyl C-1); HRMS found MH^+, 258.1491. $C_{16}H_{19}NO_2$ requires *MH*, 258.1488. The relative configuration was determined using NOESY (500 MHz, $CDCl_3$), nOe observed between phenyl and 4-H_A, 6-H and 8-H_B, 5-H and 6-H.

5.2.4. Experimental for the Decoration of the Scaffolds

5.2.4.1. Preparation of the BACE1 Capping Group

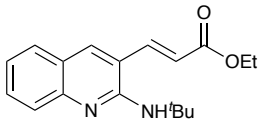
2-(*tert*-Butylamino)quinoline-3-carbaldehyde



229

By modification of an existing procedure,[192] *tert*-butylamine (27.4 mL, 261 mmol) was added to a solution of the chloroquinoline derivative **228** (5.00 g, 26.1 mmol) in *N*-methyl-2-pyrrolidone (141 mL) at rt. After stirring for 3 days at 130 °C, the mixture was allowed to cool to rt and an aqueous solution of 1.0 M HCl (210 mL) was added. The mixture was stirred for 1.5 h and the resulting precipitate was removed by filtration. Subsequently, toluene (150 mL) and water (150 mL) were added. The phases were separated and the aqueous phase was extracted with toluene (10 × 100 mL). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield a crude material. The crude material was purified by flash column chromatography eluting with 5:95 EtOAc−hexane to yield the *amine derivative* ***229*** (3.10 g, 52%) as a bright yellow amorphous solid, R_f 0.57 (80:20 petrol−EtOAc); ν_{max}/cm^{-1} 3335, 2961, 2839, 2725, 1670, 1620, 1573, 1535, 1400, 1356, 1219; δ_H (400 MHz, $CDCl_3$) 9.93 (1H, s, CHO), 8.16 (1H, s, 4-H), 8.04 (1H, br. s, NH), 7.69-7.52 (3H, m, 5,7,8-H_3), 7.21-7.15 (1H, m, 6-H), 1.60 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 193.4 (CHO), 154.2 (C-2), 150.9 (C-8a), 148.7 (C-4), 133.3 (C-7), 129.2 (C-5), 126.9 (C-8), 122.2 (C-6), 121.5 (C-3), 117.8 (C-4a), 51.7 (^{t}Bu C_1), 29.1 (^{t}Bu C_3); HRMS found MH^+, 229.1336. $C_{14}H_{16}N_2O$ requires *MH*, 229.1340.

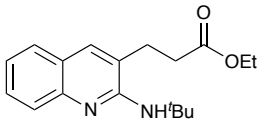
Ethyl (2*E*)-3-[2-(*tert*-butylamino)quinolin-3-yl]prop-2-enoate



230

By modification of an existing procedure,[192] LiCl (0.81 g, 19.3 mmol) was added to acetonitrile (82.0 mL) and the resulting suspension was stirred overnight at rt. Subsequently, the aldehyde derivative **229** (2.00 g, 8.76 mmol), triethyl phosphonoacetate (2.43 mL, 12.3 mmol) and DBU (1.60 mL, 10.7 mmol) were added. After stirring the reaction mixture for 4 h at rt, a saturated aqueous solution of $NaHCO_3$ (80 mL) and EtOAc (40 mL) were added. The phases were separated and the aqueous phase was extracted with EtOAc (3 × 20 mL). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield a crude material. The crude material was purified by flash column chromatography eluting with 4:96 EtOAc−hexane to yield the *alkene derivative **230*** (2.58 g, 99%) as a yellow oil, R_f 0.27 (96:4 petrol−EtOAc); ν_{max}/cm^{-1} 3402, 3054, 2960, 1706, 1613, 1600, 1511, 1410, 1301, 1173, 1162; δ_H (400 MHz, $CDCl_3$) 7.88 (1H, s, 4-H), 7.72 (1H, d, *J* 15.9, propenoate 3-H), 7.68 (1H, d, *J* 8.3. 8-H), 7.56 (1H, dd, *J* 8.0 and 1.5, 5-H), 7.53 (1H, ddd, *J* 8.3, 6.9 and 1.5. 7-H), 7.19 (1H, ddd, *J* 8.0, 6.9 and 1.2, 6-H), 6.46 (1H, d, *J* 15.9, propenoate 2-H), 4.60 (1H, br.s, NH), 4.31 (2H, q, *J* 7.1, ethyl 1-H_2), 1.60 (9H, s, ^{t}Bu), 1.37 (3H, t, *J* 7.1. ethyl 2-H_3); δ_C (100 MHz, $CDCl_3$) 166.6 (propenoate C-1), 153.5 (C-2), 148.6 (C-8a), 139.7 (propenoate C-3), 135.6 (C-4), 130.2 (C-7), 127.8 (C-5), 126.7 (C-8), 122.6 (C-3), 122.4 (C-6), 121.9 (propenoate C-2), 119.2 (C-4a), 60.8 (ethyl C-1), 52.3 (^{t}Bu C_1), 29.3 (^{t}Bu C_3), 14.4 (ethyl C-2); HRMS found MH^+, 299.1751. $C_{18}H_{22}N_2O_2$ requires *MH*, 299.1759.

Ethyl 3-[2-(*tert*-butylamino)quinolin-3-yl]propanoate



227

Hydrogen gas was passed through a mixture of the alkene derivative **230** (2.58 g, 8.64 mmol) and Pd (0.46 g, 0.43 mmol of a 10% Pd/C) in EtOH (173 mL) for 30 min. Subsequently, the suspension was filtered through a pad of celite and the filtrate was concentrated under reduced pressure to yield a crude material. The crude material was purified by flash column chromatography eluting with 4:96 EtOAc−hexane to yield the *ester derivative* ***227*** (2.53 g, 97%) as a light yellow amorphous solid, R_f 0.39 (90:10 petrol−EtOAc); ν_{max}/cm^{-1} 3468, 2962, 2911, 2868, 1720, 1626, 1521, 1421, 1359, 1261, 1228, 1212, 1038; δ_H (300 MHz, $CDCl_3$) 7.71 (1H, d, *J* 8.3, 8-H), 7.55 (1H, s, 4-H), 7.53 (1H, dd, *J* 8.1 and 1.3, 5-H), 7.48 (1H, ddd, *J* 8.3, 7.3 and 1.3, 7-H), 7.18 (1H, ddd, *J* 8.1, 7.3 and 1.2, 6-H), 4.71 (1H, br. s, NH), 4.19 (1H, q, *J* 7.1, ethyl 1-H_2), 2.89-2.80 (2H, m, propanoate 3-H_2), 2.74-2.66 (2H, m, propanoate 2-H_2), 1.61 (9H, s, ^{t}Bu), 1.28 (3H, t, *J* 7.1, ethyl 2-H_3); δ_C (75 MHz, $CDCl_3$) 173.1 (propanoate C-1), 154.6 (C-2), 146.9 (C-8a), 134.2 (C-4), 128.5 (C-7), 126.8 (C-5), 126.5 (C-8), 123.1 (C-3), 122.6 (C-4a), 121.8 (C-6), 60.9 (ethyl C-1), 51.9 (^{t}Bu C_1), 33.0 (propanoate C-2), 29.4 (^{t}Bu C_3), 26.2 (propanoate C-3), 14.3 (ethyl C-2); HRMS found MH^+, 301.1907. $C_{18}H_{24}N_2O_2$ requires *MH*, 301.1916.

5.2.4.2. Decoration of the Scaffolds

General Procedure Z

By modification of an existing procedure,[194,203] NaOMe (0.10 eq of a 0.5 M solution in MeOH) was added to a solution of the respective acetate derivative (1.00 eq) in MeOH (10.0 mL for each 1.00 mmol of the acetate derivative). After stirring for 45 min at rt, the solvent was removed under reduced pressure. Subsequently, DCM (10.0 mL for each 1.00 mmol of the acetate derivative) and TFA (18.0 eq) were added, the mixture was stirred at rt for 1 h and it was concentrated under reduced pressure. Afterwards, toluene (6.00 mL for each 1.00 mmol of the acetate derivative) and the ester derivative **227** (1.05 eq) were added. Subsequently, the specified amount of Et_3N and the specified amount of

TBD were added and the reaction mixture was stirred for the indicated time at 75 °C. Finally, the solvent was removed under reduced pressure to yield a crude material.

General Procedure AA

By modification of an existing procedure,[194] TFA (17.0 eq) was added to a solution of the respective carbamate derivative (1.00 eq) in DCM (9.00 mL for each 1.00 mmol of the carbamate derivative). The mixture was stirred at rt for 1 h and it was concentrated under reduced pressure. Afterwards, toluene (5.00 mL for each 1.00 mmol of the carbamate derivative), the specified amount of Et_3N, the specified amount of TBD and the ester derivative **227** (1.05 eq) were added and the reaction mixture was stirred for 4 days at 75 °C. Finally, the solvent was removed under reduced pressure to yield a crude material.

General Procedure AB

By modification of an existing procedure,[194] hydrogen gas was passed through a mixture of the respective carbamate derivative (1.00 eq) and Pd (0.03 eq of a 10% Pd/C) in MeOH (7.30 mL for each 1.00 mmol of the carbamate derivative) for 1 h at rt. Subsequently, the suspension was filtered through a pad of celite and the solvent was removed under reduced pressure. Toluene (7.30 mL for each 1.00 mmol of the carbamate derivative), the ester derivative **227** (1.05 eq) and the specified amount of TBD were added and the reaction mixture was stirred for 2 days at 75 °C. Finally, the solvent was removed under reduced pressure to yield a crude material.

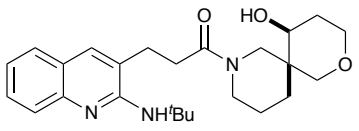
General Procedure AC

By modification of an existing procedure,[194] the respective amine (1.00 eq) and the specified amount of TBD were added to a solution of the ester derivative **227** (1.05 eq) in the specified amount of toluene. If an amine hydrochloride salt was used, Et_3N (17.0 eq) was also added. The reaction mixture was stirred for the specified time at 75 °C. Subsequently, the solvent was removed under reduced pressure to yield a crude material.

General Procedure AD

The specified amount of TFA was added to the respective amide derivative (1.00 eq) and the reaction was stirred for the specified time at 75 °C under air atmosphere. Subsequently, the mixture was concentrated under reduced pressure and it was loaded into a SCX pad, which was eluted with MeOH and with a solution of saturated NH_3 in MeOH. The fraction containing the saturated solution of NH_3 in MeOH was collected and concentrated under reduced pressure to yield a crude material or the respective amine derivative.

3-[2-(*tert*-Butylamino)quinolin-3-yl]-1-[(5*R,6*R**)-5-hydroxy-2-oxa-8-azaspiro[5.5] undecan-8-yl]propan-1-one**

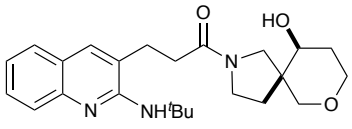


231a

According to General Procedure Z, the acetate derivative **179a** (50.0 mg, 0.16 mmol), TBD (62.3 mg, 0.45 mmol) and Et_3N (0.75 mL, 5.40 mmol) were stirred for 5 days to yield a crude material. The crude material was purified by flash column chromatography eluting with 60:40→100:0 EtOAc−hexane to yield the *amide derivative* ***231a*** (14.0 mg, 21%, *rotamers* 78:22 by ^{1}H-NMR) as a colourless oil, R_f 0.48 (EtOAc); ν_{max}/cm^{-1} 3385, 2954, 2927, 2857, 1621, 1517, 1470, 1446, 1415, 1355, 1260, 1213, 1085; δ_H (400 MHz, $CDCl_3$) 7.68 (2H, dd, *J* 8.5 and 2.6, quinolinyl 8-H), 7.54 (2H, s, quinolinyl 4-H), 7.50 (2H, dd, *J* 7.9 and 1.6, quinolinyl 5-H), 7.46 (2H, ddd, *J* 8.5, 7.0 and 1.6, quinolinyl 7-H), 7.15 (2H, app. td, *J* 7.4 and 3.3, quinolinyl 6-H), 5.07 (2H, br. s, NH), 4.29-4.19 (1H, m, 9-H_A^{minor}), 3.87-3.72 (2H, m, 3-H_A), 3.63-3.51 (6H, m, 1-H_A, 3-H_B and 7-H_A), 3.49 (2H, dd, *J* 7.6 and 3.9, 5-H), 3.42-3.29 (1H, m, 9-H_A^{major}), 3.28-3.22 (1H, m, 9-H_B^{major}), 3.15 (2H, d, *J* 13.6, 1-H_B), 3.10 (2H, d, *J* 11.9, 7-H_B), 2.99-2.81 (5H, m, propanone 3-H_2 and 9-H_B^{minor}), 2.79-2.56 (4H, m, propanone 2-H_2), 2.00-1.89 (2H, m, 4-H_A), 1.82 (2H, app. ddt, *J* 13.5, 8.6 and 4.0, 10-H_A), 1.71-1.61 (2H, m, 4-H_B), 1.58 (18H, s, ^{t}Bu), 1.55-1.38 (6H, m, 10-H_B and 11-H_2); δ_C (100 MHz, $CDCl_3$) 171.3 (propanone C-1^{minor}), 171.1 (propanone C-1^{major}), 155.0 (quinolinyl C_2-2), 147.0 (quinolinyl C_2-8a), 134.7 (quinolinyl C-4^{major}), 134.6 (quinolinyl C-4^{minor}), 128.5 (quinolinyl C-7^{major}), 128.4 (quinolinyl C-7^{minor}), 126.7

(quinolinyl C_2-5), 126.5 (quinolinyl C_2-8), 123.6 (quinolinyl C_2-3), 123.1 (quinolinyl C_2-4a), 121.7 (quinolinyl C-6^{major}), 121.6 (quinolinyl C-6^{minor}), 70.7 (C-1^{major}), 69.9 (C_2-5), 68.6 (C-1^{minor}), 65.2 (C-3^{major}), 64.3 (C-3^{minor}), 51.9 (^{t}Bu C_2), 50.3 (C-7^{minor}), 47.5 (C-7^{major}), 46.6 (C-9^{major}), 42.9 (C-9^{minor}), 38.9 (C_2-6), 32.0 (propanone C-2^{minor}), 31.7 (propanone C-2^{major}), 30.7 (C_2-4), 29.4 (^{t}Bu C_6), 26.9 (propanone C-3^{major}), 26.8 (propanone C-3^{minor}), 21.3 (C_2-10), 20.4 (C_2-11); HRMS found MH^+, 426.2748. $C_{25}H_{35}N_3O_3$ requires *MH*, 426.2756.

3-[2-(*tert*-Butylamino)quinolin-3-yl]-1-[(5*R,10*R**)-10-hydroxy-7-oxa-2-azaspiro[4.5] decan-2-yl]propan-1-one**

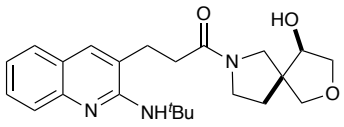


231b

According to General Procedure Z, the acetate derivative **173a** (41.3 mg, 0.14 mmol), TBD (73.0 mg, 0.52 mmol) and Et_3N (0.75 mL, 5.40 mmol) were stirred for 4 days to yield a crude material. The crude material was purified by flash column chromatography eluting with 90:10→100:0 EtOAc−hexane to yield the *amide derivative* ***231b*** (34.0 mg, 60%, *rotamers* >95:<5 by ^{1}H-NMR) as a colourless oil, R_f 0.31 (EtOAc); ν_{max}/cm^{-1} 3360, 2954, 2862, 1621, 1518, 1447, 1416, 1355, 1213, 1082; δ_H (400 MHz, $CDCl_3$) 7.67 (2H, d, *J* 8.3, quinolinyl 8-H), 7.52 (2H, app. d, *J* 5.9, quinolinyl 4-H), 7.49 (2H, dd, *J* 7.9 and 1.6, quinolinyl 5-H), 7.45 (2H, ddd, *J* 8.3, 6.9 and 1.6, quinolinyl 7-H), 7.14 (2H, app. t, *J* 7.4, quinolinyl 6-H), 5.10 (2H, br. s, NH), 3.91-3.78 (2H, m, 8-H_A), 3.72-3.52 (4H, m, 6-H_A and 10-H), 3.53-3.32 (6H, m, 1-H_A, 3-H_A and 8-H_B), 3.31-3.18 (4H, m, 1-H_B and 3-H_B), 3.11 (2H, d, *J* 11.5, 6-H_B), 2.87 (4H, t, *J* 7.4, propanone 3-H_2), 2.63-2.53 (4H, m, propanone 2-H_2), 2.12-2.00 (2H, m, 4-H_A), 1.93-1.82 (2H, m, 4-H_B), 1.82-1.72 (2H, m, 9-H_A), 1.70-1.58 (2H, m, 9-H_B), 1.57 (18H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 171.1 (propanone C_2-1), 154.8 (quinolinyl C_2-2), 146.9 (quinolinyl C_2-8a), 134.5 (quinolinyl C-4^{minor}), 134.4 (quinolinyl C-4^{major}), 128.5 (quinolinyl C_2-7), 126.7 (quinolinyl C_2-5), 126.4 (quinolinyl C_2-8), 123.7 (quinolinyl C_2-3), 123.0 (quinolinyl C_2-4a), 121.7 (quinolinyl C_2-6), 71.3 (C-6^{major}), 70.4 (C-6^{minor}), 69.7 (C-10^{major}), 69.5 (C-10^{minor}), 65.6 (C-8^{major}), 64.8 (C-8^{minor}), 51.8 (C-3^{minor}), 50.9 (C-3^{major}), 48.2 (^{t}Bu C_2), 46.5 (C_2-5), 45.5 (C-1^{major}),

44.5 (C-1^{minor}), 33.7 (propanone C_2-2), 33.3 (C_2-9), 32.3 (C-4^{major}), 32.1 (C-4^{minor}), 29.4 (^{t}Bu C_6), 26.4 (propanone C-3^{minor}), 26.3 (propanone C-3^{major}); HRMS found MH^+, 412.2598. $C_{24}H_{33}N_3O_3$ requires *MH*, 412.2600.

3-[2-(*tert*-Butylamino)quinolin-3-yl]-1-[(4*R,5*S**)-4-hydroxy-2-oxa-7-azaspiro[4.4]nonan-7-yl]propan-1-one**

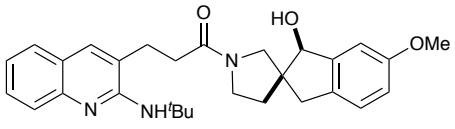


231c

According to General Procedure Z, the acetate derivative **173d** (0.10 g, 0.35 mmol), TBD (0.12 mg, 0.87 mmol) and Et_3N (0.50 mL, 3.60 mmol) were stirred for 2 days to yield a crude material. The crude material was purified by flash column chromatography eluting with 80:20→100:0 EtOAc−hexane to yield the *amide derivative* ***231c*** (0.10 g, 72%, *rotamers* 53:47 by ^{1}H-NMR) as a colourless amorphous solid, R_f 0.34 (EtOAc); ν_{max}/cm^{-1} 3278, 2950, 2914, 2866, 1625, 1517, 1453, 1418, 1353, 1216, 1054; δ_H (400 MHz, DMSO-d_6) 7.66 (2H, s, quinolinyl 4-H), 7.56 (2H, dd, *J* 8.0 and 1.5, quinolinyl 5-H), 7.50 (2H, d, *J* 8.4, quinolinyl 8-H), 7.42 (2H, ddd, *J* 8.4, 6.8 and 1.5, quinolinyl 7-H), 7.13 (2H, ddd, *J* 8.0, 6.8 and 1.3, quinolinyl 6-H), 5.88 (1H, br. s, NH^{minor}), 5.82 (1H, br. s, NH^{major}), 5.18 (2H, app. t, *J* 4.1, OH), 3.95-3.81 (2H, m, 4-H), 3.59-3.35 (12H, m, 1,3,8-H_6), 3.24 (2H, app. s, 6-H_A), 3.19 (2H, app. s, 6-H_B), 2.84 (4H, td, *J* 6.9 and 4.0, propanone 3-H_2), 2.59 (4H, app. q, *J* 6.4, propanone 2-H_2), 2.15 (1H, ddd, *J* 12.7, 7.9 and 6.3, 9-H_A^{minor}), 2.05 (1H, ddd, *J* 13.0, 7.7 and 5.9, 9-H_A^{major}), 1.75-1.65 (1H, m, 9-H_B^{minor}), 1.59 (1H, app. dt, *J* 13.0 and 7.7, 9-H_B^{major}), 1.53 (18H, s, ^{t}Bu); δ_C (100 MHz, DMSO-d_6) 170.2 (propanone C-1^{minor}), 170.1 (propanone C-1^{major}), 155.0 (quinolinyl C_2-2), 146.1 (quinolinyl C_2-8a), 134.2 (quinolinyl C_2-4), 128.1 (quinolinyl C_2-7), 126.7 (quinolinyl C_2-5), 125.5 (quinolinyl C_2-8), 125.0 (quinolinyl C_2-3), 124.8 (quinolinyl C_2-4a), 121.2 (quinolinyl C_2-6), 74.5 (C-3^{minor}), 74.4 (C-3^{major}), 73.8 (C-4^{major}), 73.7 (C-1^{major}), 73.6 (C-4^{minor}), 73.5 (C-1^{minor}), 54.2 (C-6^{minor}), 54.1 (C-5^{majoror}), 53.6 (C-6^{major}), 52.2 (C-5^{minor}), 51.1 (^{t}Bu C_2), 45.1 (C-8^{minor}), 44.6 (C-8^{major}), 32.9 (propanone C-2^{major}), 32.6 (propanone C-2^{minor}), 28.9 (^{t}Bu C_6), 27.5 (C-9^{minor}), 25.7 (C-9^{major}),

25.3 (propanone C-3^{minor}), 25.1 (propanone C-3^{major}); HRMS found MH^+, 398.2435. $C_{23}H_{31}N_3O_3$ requires *MH*, 398.2443.

3-[2-(*tert*-Butylamino)quinolin-3-yl]-1-[(2*R,3*R**)-3-hydroxy-5-methoxy-1,3-dihydrospiro[indene-2,3'-pyrrolidin]-1'-yl]propan-1-one**

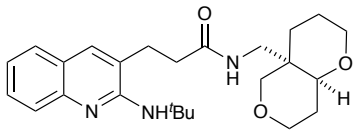


231d

According to General Procedure Z, the acetate derivative **173c** (50.0 mg, 0.14 mmol), TBD (73.0 mg, 0.52 mmol) and Et_3N (0.75 mL, 5.40 mmol) were stirred for 4 days to yield a crude material. The crude material was purified by flash column chromatography eluting with 70:30→100:0 EtOAc−hexane to yield the *amide derivative* ***231d*** (49.0 mg, 75%, *rotamers* 53:47 by ^{1}H-NMR) as a colourless oil, R_f 0.56 (EtOAc); ν_{max}/cm^{-1} 3338, 2956, 1619, 1517, 1487, 1445, 1414, 1387, 1354, 1270, 1248, 1213, 1147, 1028; δ_H (400 MHz, $CDCl_3$) 7.69 (2H, app. t, *J* 9.3, quinolinyl 8-H), 7.57-7.41 (6H, m, quinolinyl 4,5,7-H$_3$), 7.21-7.09 (2H, m, quinolinyl 6-H), 7.04-6.97 (2H, m, 7-H), 6.92-6.83 (2H, m, 4-H), 6.78 (2H, app. dt, *J* 8.3 and 2.4, 6-H), 5.14 (2H, br. s, NH), 4.61 (1H, s, 3-H^{minor}), 4.58 (1H, d, *J* 2.5, 3-H^{major}), 3.77 (3H, s, methoxy^{major}), 3.76 (3H, s, methoxy^{minor}), 3.71-3.59 (2H, m, 5'-H$_A$), 3.56-3.43 (2H, m, 5'-H$_B$), 3.35-3.23 (2H, m, 2'-H$_A$), 3.14 (2H, app. t, *J* 9.7, 2'-H$_B$), 2.96-2.84 (4H, m, propanone 3-H$_2$), 2.83-2.74 (2H, m, 1-H$_A$), 2.65-2.55 (4H, m, propanone 2-H$_2$), 2.54-2.46 (2H, m, 1-H$_B$), 2.29 (1H, app. dt, *J* 12.4 and 7.4, 4'-H$_A^{major}$), 2.18 (1H, app. dt, *J* 12.6 and 7.7, 4'-H$_A^{minor}$), 1.97-1.80 (1H, m, 4'-H$_B^{major}$), 1.79-1.61 (1H, m, 4'-H$_B^{minor}$), 1.58 (9H, s, ^{t}Bu^{major}), 1.57 (9H, s, ^{t}Bu^{minor}); δ_C (100 MHz, $CDCl_3$) 171.2 (propanone C-1^{major}), 171.1 (propanone C-1^{minor}), 159.3 (C-5^{major}), 159.2 (C-5^{minor}), 155.0 (quinolinyl C-2^{major}), 154.9 (quinolinyl C-2^{minor}), 147.0 (quinolinyl C-8a^{major}), 146.9 (quinolinyl C-8a^{minor}), 145.0 (C-3a^{major}), 144.9 (C-3a^{minor}), 134.7 (quinolinyl C-4^{major}), 134.5 (quinolinyl C-4^{minor}), 133.0 (C-7a^{minor}), 132.8 (C-7a^{major}), 128.5 (quinolinyl C-7^{major}), 128.4 (quinolinyl C-7^{minor}), 126.7 (quinolinyl C_2-5), 126.4 (quinolinyl C_2-8), 125.9 (C-7^{major}), 125.7 (C-7^{minor}), 123.7 (quinolinyl C-3^{major}), 123.6 (quinolinyl C-3^{minor}), 123.0 (quinolinyl C-4a^{major}), 122.9 (quinolinyl C-4a^{minor}), 121.7 (quinolinyl C-6^{major}), 121.6 (quinolinyl C-6^{minor}), 115.1 (C-6^{minor}),

115.0 (C-6^{major}), 110.0 (C-4^{minor}), 109.7 (C-4^{major}), 79.3 (C-3^{minor}), 79.1 (C-3^{major}), 56.7 (C-2'^{major}), 55.6 (methoxy), 55.4 (C-2'^{minor}), 54.0 (C_2-2), 53.9 (^{t}Bu C_2), 46.1 (C-5'^{minor}), 45.3 (C-5'^{major}), 40.3 (C-1^{major}), 40.0 (C-1^{minor}), 35.7 (C_2-4'), 34.3 (propanone C-2^{major}), 33.6 (propanone C-2^{minor}), 29.4 (^{t}Bu C_6), 26.6 (propanone C-3^{major}), 26.4 (propanone C-3^{minor}); HRMS found MH^+, 474.2757. $C_{29}H_{35}N_3O_3$ requires *MH*, 474.2756.

_N_-{[(4a*R,8a*R**)-Octahydropyrano[4,3-*b*]pyran-4a-yl]methyl}-3-[2-(*tert*-butyl amino) quinolin-3-yl]propanamide**

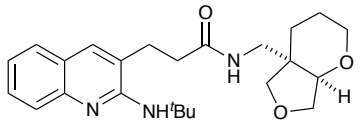


231e

According to General Procedure AA, the carbamate derivative **149a** (50.0 mg, 0.18 mmol), TBD (76.5 mg, 0.55 mmol) and Et_3N (0.55 mL, 3.94 mmol) gave a crude material. The crude material was purified by flash column chromatography eluting with 60:40→100:0 EtOAc−hexane to yield the *amide derivative* ***231e*** (22.0 mg, 28%) as a colourless oil, R_f 0.50 (EtOAc); ν_{max}/cm^{-1} 3314, 2952, 2926, 2859, 1648, 1623, 1516, 1486, 1447, 1415, 1355, 1274, 1259, 1214, 1098, 1080, 1024; δ_H (400 MHz, $CDCl_3$) 7.66 (1H, dd, *J* 8.3 and 1.2, quinolinyl 8-H), 7.53 (1H, s, quinolinyl 4-H), 7.48 (1H, dd, *J* 8.0 and 1.5, quinolinyl 5-H), 7.44 (1H, ddd, *J* 8.3, 6.9 and 1.5, quinolinyl 7-H), 7.14 (1H, ddd, *J* 8.0, 6.9 and 1.2, quinolinyl 6-H), 5.92 (1H, t, *J* 6.4, amide NH), 4.96 (1H, br. s, ^{t}Bu NH), 3.93-3.86 (1H, m, 2-H_A), 3.82 (1H, d, *J* 11.7, 5-H_A), 3.64 (2H, app. dd, *J* 9.3 and 2.2, 7-H_2), 3.40 (1H, dd, *J* 13.9 and 6.4, methylpropanamide 1-H_A), 3.30 (1H, app. s, 8a-H), 3.28-3.24 (1H, m, 2-H_B), 3.24-3.19 (1H, m, methylpropanamide 1-H_B), 3.22 (1H, dd, *J* 11.7 and 1.7, 5-H_B), 2.89 (2H, t, *J* 7.1, propanamide 3-H_2), 2.54 (2H, td, *J* 7.1 and 1.8, propanamide 2-H_2), 1.95 (1H, app. dtd, *J* 14.8, 9.1 and 3.2, 8-H_A), 1.59-1.50 (1H, m, 3-H_A), 1.58 (9H, s, ^{t}Bu), 1.48-1.38 (1H, m, 8-H_B), 1.31-1.15 (3H, m, 3-H_B and 4-H_2); δ_C (100 MHz, $CDCl_3$) 172.3 (propanamide C-1), 154.7 (quinolinyl C-2), 147.0 (quinolinyl C-8a), 134.7 (quinolinyl C-4), 128.5 (quinolinyl C-7), 126.7 (quinolinyl C-5), 126.5 (quinolinyl C-8), 123.1 (quinolinyl C-3), 123.0 (quinolinyl C-4a), 121.7 (quinolinyl C-6), 74.8 (C-8a), 68.0 (C-5), 67.6 (C-2), 63.4 (C-7), 51.9 (^{t}Bu C_1), 45.2

(methylpropanamide C-1), 36.2 (C-4a), 35.7 (propanamide C-2), 29.4 (^{t}Bu C_3), 28.8 (C-4), 28.7 (C-8), 26.8 (propanamide C-3), 22.1 (C-3); HRMS found MH^+, 426.2753. $C_{25}H_{35}N_3O_3$ requires *MH*, 426.2756.

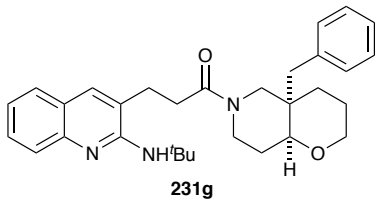
_N_-{[(4a*R,7a*S**)-Hexahydro-2*H*-furo[3,4-*b*]pyran-4a-yl]methyl}-3-[2-(*tert*-butylamino)quinolin-3-yl]propanamide**



231f

According to General Procedure AA, the carbamate derivative **149d** (0.10 g, 0.39 mmol), TBD (0.13 g, 0.93 mmol) and Et_3N (0.50 mL, 3.58 mmol) gave a crude material. The crude material was purified by flash column chromatography eluting with 70:30→100:0 EtOAc−hexane to yield the *amide derivative* ***231f*** (50.0 mg, 31%) as a colourless amorphous solid, R_f 0.53 (EtOAc); ν_{max}/cm^{-1} 3410, 3336, 2959, 2943, 2908, 2875, 1653, 1621, 1549, 1520, 1488, 1450, 1417, 1355, 1277, 1263, 1214, 1189; δ_H (400 MHz, $CDCl_3$) 7.67 (1H, app. d, *J* 8.3, quinolinyl 8-H), 7.54 (1H, s, quinolinyl 4-H), 7.49 (1H, dd, *J* 8.0 and 1.4, quinolinyl 5-H), 7.47-7.42 (1H, m, quinolinyl 7-H), 7.15 (1H, ddd, *J* 8.0, 6.9 and 1.2, quinolinyl 6-H), 5.66 (1H, t, *J* 6.3, amide NH), 4.94 (1H, br. s, ^{t}Bu NH), 4.02 (1H, dd, *J* 10.1 and 4.1, 7-H_A), 3.84-3.77 (1H, m, 2-H_A), 3.81 (1H, d, *J* 8.6, 5-H_A), 3.74 (1H, d, *J* 10.1, 7-H_B), 3.61 (1H, d, *J* 4.1, 7a-H), 3.46 (1H, d, *J* 8.6, 5-H_B), 3.27 (1H, dd, *J* 14.0 and 6.3, methylpropanamide 1-H_A), 3.15 (1H, app. td, *J* 11.5 and 2.4, 2-H_B), 3.11 (1H, dd, *J* 14.0 and 6.3, methylpropanamide 1-H_B), 2.90 (2H, t, *J* 7.0, propanamide 3-H_2), 2.56 (2H, t, *J* 7.0, propanamide 2-H_2), 1.58 (9H, s, ^{t}Bu), 1.49 (1H, app. dd, *J* 11.2 and 4.3, 3,4-H_A), 1.48-1.46 (1H, m, 3,4-H_B), 1.39-1.30 (1H, m, 3,4-H_C), 1.28-1.21 (1H, m, 3,4-H_D); δ_C (100 MHz, $CDCl_3$) 172.5 (propanamide C-1), 154.7 (quinolinyl C-2), 147.0 (quinolinyl C-8a), 134.7 (quinolinyl C-4), 128.6 (quinolinyl C-7), 126.7 (quinolinyl C-5), 126.5 (quinolinyl C-8), 123.0 (quinolinyl C-3), 121.8 (quinolinyl C_2-4a,6), 80.3 (C-7a), 74.2 (C-7), 71.1 (C-5), 66.0 (C-2), 51.9 (^{t}Bu C_1), 45.5 (C-4a), 45.4 (methylpropanamide C-1), 35.6 (propanamide C-2), 29.4 (^{t}Bu C_3), 26.8 (propanamide C-3), 24.4 (C-4), 21.5 (C-3); HRMS found MH^+, 412.2594. $C_{24}H_{33}N_3O_3$ requires *MH*, 412.2600.

1-[(4a*R,8a*R**)-4a-Benzyl-octahydro-2*H*-pyrano[3,2-*c*]pyridin-6-yl]-3-[2-(*tert*-butylamino)quinolin-3-yl]propan-1-one**

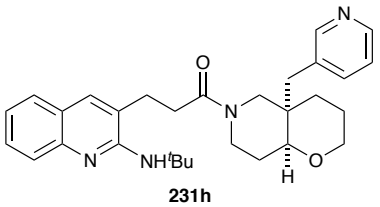


231g

According to General Procedure AB, the carbamate derivative **149e** (50.0 mg, 0.14 mmol) and TBD (29.5 mg, 0.21 mmol) gave a crude material. The crude material was purified by flash column chromatography eluting with 30:70 EtOAc−hexane to yield the *amide derivative **231g*** (15.0 mg, 23%, *rotamers* 65:35 by ^{1}H-NMR) as a colourless oil, R_f 0.44 (50:50 EtOAc−petrol); ν_{max}/cm^{-1} 3305, 2951, 2925, 2868, 1634, 1622, 1582, 1543, 1447, 1419, 1352, 1272, 1227, 1212, 1116, 1090; δ_H (400 MHz, $CDCl_3$) 7.68 (2H, d, *J* 8.6, quinolinyl 8-H), 7.58 (2H, s, quinolinyl 4-H), 7.47-7.40 (4H, m, quinolinyl 5,7-H$_2$), 7.31-7.15 (8H, m, phenyl 2,6-H$_2^{major}$ and phenyl 3,4,5-H$_3$), 7.12 (2H, app. q, *J* 6.9, quinolinyl 6-H), 7.07-7.00 (2H, m, phenyl 2,6-H$_2^{minor}$), 5.14 (2H, br. s, NH), 4.42 (1H, app. d, *J* 13.1, 7-H$_A^{minor}$), 4.18 (1H, d, *J* 13.2, 5-H$_A^{major}$), 3.95-3.81 (2H, m, 2-H$_A$), 3.70-3.61 (1H, m, 7-H$_A^{major}$), 3.46 (1H, d, *J* 13.2, 5-H$_A^{minor}$), 3.40-3.20 (5H, m, 2-H$_B$, 7-H$_B^{major}$ and 8a-H), 3.14 (1H, d, *J* 13.2, 5-H$_B^{major}$), 3.07 (1H, d, *J* 13.2, 5-H$_B^{minor}$), 3.00-2.89 (5H, m, 7-H$_B^{minor}$ and propanone 3-H$_2$), 2.86-2.71 (5H, m, phenylmethyl 1-H$_A^{minor}$ and propanone 2-H$_2$), 2.63 (1H, d, *J* 13.4, phenylmethyl 1-H$_A^{major}$), 2.47 (1H, d, *J* 13.4, phenylmethyl 1-H$_B^{minor}$), 2.25 (1H, d, *J* 13.4, phenylmethyl 1-H$_B^{major}$), 2.17-2.07 (1H, m, 8-H$_A^{minor}$), 1.94-1.81 (1H, m, 8-H$_A^{major}$), 1.78-1.61 (4H, m, 3-H$_A$ and 8-H$_B$), 1.60 (9H, s, ^{t}Bu^{major}), 1.56 (9H, s, ^{t}Bu^{minor}), 1.59-1.52 (2H, m, 3-H$_B$), 1.45-1.31 (2H, m, 4-H$_A$), 1.17-1.05 (2H, m, 4-H$_B$); δ_C (100 MHz, $CDCl_3$) 171.8 (propanone C-1^{minor}). 171.2 (propanone C-1^{major}), 154.9 (quinolinyl C$_2$-2), 147.0 (quinolinyl C$_2$-8a), 136.8 (phenyl C$_2$-1), 134.6 (quinolinyl C-4^{major}), 134.5 (quinolinyl C-4^{minor}), 131.0 (phenyl C$_2$-2,6^{major}), 130.7 (phenyl C$_2$-2,6^{minor}), 128.4 (quinolinyl C-7^{major}), 128.3 (quinolinyl C-7^{minor}), 128.1 (phenyl C$_4$-3,5), 126.7 (quinolinyl C$_2$-5), 126.5 (quinolinyl C$_2$-8), 126.4 (phenyl C$_2$-4), 123.6 (quinolinyl C$_2$-3), 123.1 (quinolinyl C$_2$-4a), 121.7 (quinolinyl C$_2$-6), 77.1 (C-8a^{major}), 75.4 (C-8a^{minor}), 67.8 (C-2^{major}), 67.2 (C-2^{minor}), 51.9 (^{t}Bu C$_1^{major}$), 51.8 (^{t}Bu C$_1^{minor}$), 48.7 (C-5^{minor}), 43.6 (C-5^{major}), 41.4 (phenylmethyl C$_2$-1), 41.0 (C-7^{major}), 37.4 (C-4a^{minor}), 37.3 (C-4a^{major}), 36.5 (C-7^{minor}), 32.1

(propanone C_2-2), 30.6 (C_2-4), 29.4 (^{t}Bu C_3^{major}), 29.3 (^{t}Bu C_3^{minor}), 28.0 (C_2-8), 27.0 (propanone C_2-3), 22.3 (C-3^{major}), 22.2 (C-3^{minor}); HRMS found MH^+, 486.3116. $C_{31}H_{39}N_3O_2$ requires *MH*, 486.3120.

1-[(4a*R,8a*R**)-4a-[(Pyridin-3-yl)methyl]-octahydro-2*H*-pyrano[3,2-*c*]pyridin-6-yl]-3-[2-(*tert*-butylamino)quinolin-3-yl]propan-1-one**

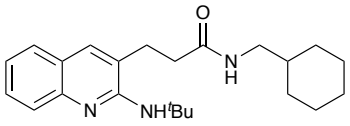


231h

According to General Procedure AB, the carbamate derivative **149f** (50.0 mg, 0.14 mmol) and TBD (43.4 mg, 0.31 mmol) gave a crude material. The crude material was purified by flash column chromatography eluting with 90:10→100:0 EtOAc−hexane to yield the *amide derivative* ***231h*** (13.0 mg, 20%, *rotamers* 80:20 by ^{1}H-NMR) as a colourless oil, R_f 0.17 (EtOAc); ν_{max}/cm^{-1} 3312, 2926, 2852, 1622, 1518, 1474, 1447, 1415, 1354, 1272, 1213, 1118, 1091; δ_H (400 MHz, $CDCl_3$) 8.46 (2H, br. s, pyridinyl 6-H), 8.33 (1H, br. s, pyridinyl 2-H^{major}), 8.26 (1H, br. s, pyridinyl 2-H^{minor}), 7.71-7.61 (4H, m, pyridinyl 4-H and quinolinyl 8-H), 7.56 (2H, s, quinolinyl 4-H), 7.42 (2H, ddd, *J* 8.4, 6.9 and 1.5, quinolinyl 7-H), 7.38 (2H, dd, *J* 8.1 and 1.5, quinolinyl 5-H), 7.25-7.19 (2H, m, pyridinyl 5-H), 7.07 (2H, ddd, *J* 8.1, 6.9 and 1.2, quinolinyl 6-H), 5.16 (1H, br. s, NH^{minor}), 5.05 (1H, br. s, NH^{major}), 4.43 (1H, app. d, *J* 13.0, 7-H_A^{minor}), 4.13 (1H, d, *J* 13.3, 5-H_A^{major}), 3.91 (2H, dd, *J* 11.4 and 4.5, 2-H_A), 3.72-3.61 (1H, m, 7-H_A^{major}), 3.48 (1H, d, *J* 13.3, 5-H_A^{minor}), 3.37-3.27 (3H, m, 2-H_B and 7-H_B^{major}), 3.25 (2H, s, 8a-H), 3.10 (2H, d, *J* 13.3, 5-H_B), 3.04-2.82 (5H, m, 7-H_B^{minor} and propanone 3-H_2), 2.78-2.68 (4H, m, propanone 2-H_2), 2.64 (1H, d, *J* 13.8 pyridinylmethyl 1-H_A^{minor}), 2.52 (1H, d, *J* 13.6, pyridinylmethyl 1-H_A^{major}), 2.27 (1H, d, *J* 13.8 pyridinylmethyl 1-H_B^{minor}), 2.09 (1H, d, *J* 13.6, pyridinylmethyl 1-H_B^{major}), 2.05-1.97 (1H, m, 8-H_A^{minor}), 1.80-1.70 (1H, m, 8-H_A^{major}), 1.69-1.60 (2H, m, 8-H_B), 1.59 (9H, s, ^{t}Bu^{major}), 1.54 (9H, s, ^{t}Bu^{minor}), 1.55-1.50 (2H, m, 3-H_A), 1.39-1.32 (2H, m, 3-H_B), 1.30-1.23 (2H, m, 4-H_A), 1.10-1.00 (2H, m, 4-H_B); δ_C (100 MHz, $CDCl_3$) 171.2 (propanone C_2-1), 154.8 (quinolinyl C_2-2), 151.6 (pyridinyl C_2-2), 147.7 (quinolinyl C_2-8a), 147.0 (pyridinyl C_2-6), 138.3 (pyridinyl

C_2-4), 134.9 (quinolinyl C_2-4), 132.4 (pyridinyl C_2-3), 128.5 (quinolinyl C_2-7), 126.7 (quinolinyl C_2-5), 126.5 (quinolinyl C_2-8), 123.4 (quinolinyl C_2-3), 123.0 (quinolinyl C_2-4a), 121.8 (quinolinyl C_2-6), 121.7 (pyridinyl C_2-5), 77.2 (C-8a^{major}), 74.8 (C-8a^{minor}), 67.9 (C_2-2), 51.9 (^{t}Bu C_2), 43.1 (C_2-5), 41.0 (C_2-7), 38.2 (pyridinylmethyl C_2-1), 36.4 (C_2-4a), 31.8 (propanone C_2-2), 30.8 (C_2-4), 29.4 (^{t}Bu C_3^{major}), 29.3 (^{t}Bu C_3^{minor}), 28.1 (C_2-8), 27.1 (propanone C_2-3), 22.1 (C_2-3); HRMS found MH^+, 487.3071. $C_{30}H_{38}N_4O_2$ requires *MH*, 487.3073.

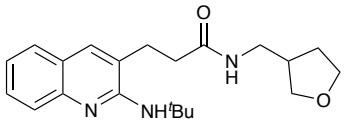
3-[2-(*tert*-Butylamino)quinolin-3-yl]-*N*-(cyclohexylmethyl)propanamide



231i

According to General Procedure AC, the amine derivative **232** (0.11 mL, 0.88 mmol), TBD (61.2 mg, 0.44 mmol) and toluene (1.00 mL) were stirred overnight to give a crude material. The crude material was purified by flash column chromatography eluting with 20:80 EtOAc−hexane to yield the amide derivative **231i**[192] (0.30 g, 98%) as a colourless amorphous solid, R_f 0.47 (60:40 petrol−EtOAc); ν_{max}/cm^{-1} 3423, 3252, 3083, 2948, 2923, 2850, 1621, 1524, 1449, 1413, 1352, 1271, 1222; δ_H (400 MHz, $CDCl_3$) 7.68 (1H, d, *J* 8.2, quinolinyl 8-H), 7.50 (1H, s, quinolinyl 4-H), 7.49-7.40 (2H, m, quinolinyl 5,7-H_2), 7.15 (1H, ddd, *J* 7.9, 6.9 and 1.1, quinolinyl 6-H), 5.50 (1H, t, *J* 5.9, amide NH), 5.03 (1H, br. s, ^{t}Bu NH), 3.07 (2H, t, *J* 6.4, methylpropanamide 1-H_2), 2.87 (2H, t, *J* 7.1, propanamide 3-H_2), 2.48 (2H, t, *J* 7.1, propanamide 2-H_2), 1.81-1.61 (4H, m, 2-H_A, 6-H_A and 3,4,5-H_2), 1.58 (9H, s, ^{t}Bu), 1.36 (1H, app. dtp, *J* 14.1, 6.6 and 3.5, 1-H), 1.22-1.02 (4H, m, 3,4,5-H_4), 0.92-0.79 (2H, m, 2-H_B and 6-H_B); δ_C (100 MHz, $CDCl_3$) 172.0 (propanamide C-1), 154.8 (quinolinyl C-2), 147.0 (quinolinyl C-8a), 134.5 (quinolinyl C-4), 128.4 (quinolinyl C-7), 126.7 (quinolinyl C-5), 126.4 (quinolinyl C-8), 123.4 (quinolinyl C-3), 123.0 (quinolinyl C-4a), 121.6 (quinolinyl C-6), 51.8 (^{t}Bu C_1), 46.0 (methylpropanamide C-1), 37.9 (C-1), 35.7 (propanamide C-2), 30.9 (C_2-2,6), 29.3 (^{t}Bu C_3), 26.8 (propanamide C-3), 26.4 (C-4), 25.8 (C_2-3,5); HRMS found MH^+, 368.2695. $C_{23}H_{33}N_3O$ requires *MH*, 368.2701.

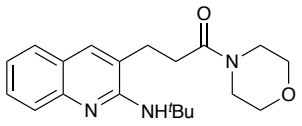
3-[2-(*tert*-Butylamino)quinolin-3-yl]-*N*-[(oxolan-3-yl)methyl]propanamide



231j

According to General Procedure AC, the amine derivative **233** (0.10 g, 0.98 mmol), TBD (68.2 mg, 0.49 mmol) and toluene (1.00 mL) were stirred overnight to give a crude material. The crude material was purified by flash column chromatography eluting with 50:50→100:0 EtOAc−hexane to yield the *amide derivative* ***231j*** (0.32 g, 90%) as a yellow oil, R_f 0.45 (EtOAc); ν_{max}/cm^{-1} 3307, 2959, 2928, 2866, 1644, 1623, 1516, 1485, 1448, 1414, 1355, 1273, 1212; δ_H (400 MHz, $CDCl_3$) 7.69 (1H, d, *J* 8.3, quinolinyl 8-H), 7.51 (1H, s, quinolinyl 4-H), 7.49-7.42 (2H, m, quinolinyl 5,7-H_2), 7.16 (1H, t, *J* 7.4, quinolinyl 6-H), 5.71 (1H, t, *J* 6.1, amide NH), 5.01 (1H, br. s, ^{t}Bu NH), 3.79 (1H, app. td, *J* 8.3 and 5.3, 5-H_A), 3.74-3.60 (2H, m, 2-H_A and 5-H_B), 3.45 (1H, dd, *J* 8.8 and 5.1, 2-H_B), 3.23 (2H, t, *J* 6.4, methylpropanamide 1-H_2), 2.87 (2H, t, *J* 7.1, propanamide 3-H_2), 2.49 (2H, t, *J* 7.1, propanamide 2-H_2), 2.37 (1H, app. hept, *J* 6.6, 3-H), 1.98-1.84 (1H, m, 4-H_A), 1.59 (9H, s, ^{t}Bu), 1.54-1.41 (1H, m, 4-H_B); δ_C (100 MHz, $CDCl_3$) 172.3 (propanamide C-1), 154.7 (quinolinyl C-2), 147.0 (quinolinyl C-8a), 134.5 (quinolinyl C-4), 128.5 (quinolinyl C-7), 126.7 (quinolinyl C-5), 126.4 (quinolinyl C-8), 123.2 (quinolinyl C-3), 123.0 (quinolinyl C-4a), 121.7 (quinolinyl C-6), 71.3 (C-2), 67.7 (C-5), 51.9 (^{t}Bu C_1), 42.6 (methylpropanamide C-1), 39.0 (C-3), 35.6 (propanamide C-2), 29.8 (C-4), 29.3 (^{t}Bu C_3), 26.7 (propanamide C-3); HRMS found MH^+, 356.2334. $C_{21}H_{29}N_3O_2$ requires *MH*, 356.2338.

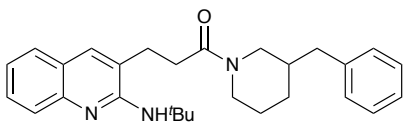
3-[2-(*tert*-Butylamino)quinolin-3-yl]-1-(morpholin-4-yl)propan-1-one



231k

According to General Procedure AC, the amine derivative **234** (71.6 μL, 0.83 mmol), TBD (57.7 mg, 0.41 mmol) and toluene (1.00 mL) were stirred for 4 days to give a crude material. The crude material was purified by flash column chromatography eluting with 50:50 EtOAc−hexane to yield the *amide derivative* ***231k*** (0.16 g, 56%) as a pale yellow oil, R_f 0.36 (40:60 petrol−EtOAc); ν_{max}/cm^{-1} 3452, 3391, 2954, 2915, 2860, 2242, 1639, 1624, 1515, 1419, 1354, 1272, 1216, 1116; δ_H (400 MHz, $CDCl_3$) 7.68 (1H, d, *J* 8.3, quinolinyl 8-H), 7.52 (1H, s, quinolinyl 4-H), 7.50 (1H, dd, *J* 8.0 and 1.5, quinolinyl 5-H), 7.46 (1H, ddd, *J* 8.3, 7.0 and 1.5, quinolinyl 7-H), 7.16 (1H, ddd, *J* 8.0, 7.0 and 1.2, quinolinyl 6-H), 5.09 (1H, br. s, NH), 3.63 (4H, app. s, 2-H_A, 3-H_A, 5-H_A and 6-H_A), 3.55-3.49 (2H, m, 2-H_B and 6-H_B), 3.42-3.36 (2H, m, 3-H_B and 5-H_B), 2.92 (2H, t, *J* 7.1, propanone 3-H_2), 2.65 (2H, t, *J* 7.1, propanone 2-H_2), 1.58 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 170.8 (propanone C-1), 154.8 (quinolinyl C-2), 147.0 (quinolinyl C-8a), 134.6 (quinolinyl C-4), 128.5 (quinolinyl C-7), 126.6 (quinolinyl C-5), 126.5 (quinolinyl C-8), 123.5 (quinolinyl C-3), 123.0 (quinolinyl C-4a), 121.7 (quinolinyl C-6), 66.9 (C_A-2,6), 66.5 (C_B-2,6), 51.8 (^{t}Bu C_1), 46.0 (C_A-3,5), 42.2 (C_B-3,5), 31.8 (propanone C-2), 29.3 (^{t}Bu C_3), 26.6 (propanone C-3); HRMS found MH^+, 342.2179. $C_{20}H_{27}N_3O_2$ requires *MH*, 342.2181.

1-(3-Benzylpiperidin-1-yl)-3-[2-(*tert*-butylamino)quinolin-3-yl]propan-1-one

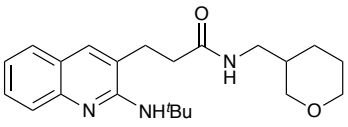


231l

According to General Procedure AC, the amine hydrochloride derivative **235** (67.1 mg, 0.32 mmol), TBD (0.10 g, 0.72 mmol) and toluene (2.00 mL) were stirred for 2 days to give a crude material. The crude material was purified by

flash column chromatography eluting with 20:80 EtOAc−hexane to yield the *amide derivative* ***231l*** (50.0 mg, 37%, *rotamers* 51:49 by ^{1}H-NMR) as a colourless oil, R_f 0.37 (70:30 petrol−EtOAc); ν_{max}/cm^{-1} 3455, 2942, 2923, 2869, 2848, 1645, 1623, 1517, 1489, 1449, 1437, 1420, 1353, 1278, 1215, 1194, 1175; δ_H (400 MHz, $CDCl_3$) 7.71 (2H, dd, *J* 8.3 and 3.7, quinolinyl 8-H), 7.57-7.38 (6H, m, quinolinyl 4,5,7-H_3), 7.33-7.06 (12H, phenyl and quinolinyl 6-H), 5.19 (1H, br. s, NH^{minor}), 5.17 (1H, br. s, NH^{major}), 4.55 (1H, ddt, *J* 12.9, 3.8 and 1.7, phenylmethyl 1-H_A^{minor}), 4.44 (1H, app. dt, *J* 12.9 and 3.8, phenylmethyl 1-H_A^{major}), 3.74 (1H, app. dt, *J* 12.4 and 4.2, phenylmethyl 1-H_B^{minor}), 3.66-3.59 (1H, m, phenylmethyl 1-H_B^{major}), 2.97 (2H, app. dd, *J* 12.0 and 2.8, 6-H_2^{major}), 2.93 (2H, t, *J* 7.2, propanone 3-H_2^{minor}), 2.84 (2H, t, *J* 7.2, propanone 3-H_2^{major}), 2.78-2.70 (2H, m, 6-H_2^{minor}), 2.69-2.62 (4H, m, 2-H_2^{major} and propanone 2-H_2^{minor}), 2.55-2.48 (2H, m, propanone 2-H_2^{major}), 2.47-2.38 (2H, m, 2-H_2^{minor}), 1.86-1.62 (6H, m, 3-H, 4-H_A and 5-H_A), 1.60 (18H, s, ^{t}Bu), 1.49-1.07 (4H, m, 4-H_B and 5-H_B); δ_C (100 MHz, $CDCl_3$) 170.5 (propanone C-1^{minor}), 170.4 (propanone C-1^{major}), 154.9 (quinolinyl C_2-2), 147.0 (quinolinyl C_2-8a), 139.5 (phenyl C-1^{minor}), 139.3 (phenyl C-1^{major}), 134.5 (quinolinyl C-4^{major}), 134.3 (quinolinyl C-4^{minor}), 129.1 (phenyl C_2-2,6^{minor}), 128.8 (phenyl C_2-2,6^{major}), 128.6 (quinolinyl C_2-7), 128.4 (phenyl C_2-3,5^{major}), 128.3 (phenyl C_2-3,5^{minor}), 126.6 (quinolinyl C_2-5), 126.4 (quinolinyl C_2-8), 126.1 (phenyl C_2-4), 124.0 (quinolinyl C-3^{major}), 123.8 (quinolinyl C-3^{minor}), 123.1 (quinolinyl C_2-4a), 121.6 (quinolinyl C_2-6), 51.8 (^{t}Bu C_2), 51.3 (C-2^{major}), 48.0 (C-2^{minor}), 46.4 (phenylmethyl C-1^{minor}), 42.9 (phenylmethyl C-1^{major}), 40.3 (C-6^{minor}), 40.0 (C-6^{major}), 38.8 (phenylmethyl C-3^{major}), 37.8 (phenylmethyl C-3^{minor}), 32.2 (propanone C-2^{minor}), 31.9 (propanone C-2^{major}), 30.9 (C-4^{major}), 30.8 (C-4^{minor}), 29.4 (^{t}Bu C_6), 26.7 (propanone C-3^{minor}), 26.5 (propanone C-3^{major}), 25.8 (C-5^{minor}), 24.7 (C-5^{major}); HRMS found MH^+, 430.2858. $C_{28}H_{35}N_3O$ requires *MH*, 430.2858.

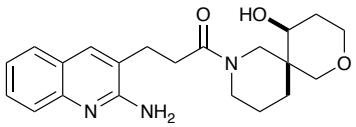
3-[2-(*tert*-Butylamino)quinolin-3-yl]-*N*-[(oxan-3-yl)methyl]propanamide



231m

According to General Procedure AC, the amine hydrochloride derivative **236** (48.1 mg, 0.32 mmol), TBD (0.10 g, 0.72 mmol) and toluene (2.00 mL) were stirred for 2 days to give a crude material. The crude material was purified by flash column chromatography eluting with 60:40 EtOAc−hexane to yield the *amide derivative* ***231m*** (50.0 mg, 43%) as a colourless oil, R_f 0.45 (30:70 petrol−EtOAc); ν_{max}/cm^{-1} 3429, 3294, 3089, 2953, 2920, 2843, 1641, 1622, 1557, 1518, 1448, 1413, 1354, 1212, 1089; δ_H (400 MHz, $CDCl_3$) 7.67 (1H, dd, *J* 8.4 and 1.2, quinolinyl 8-H), 7.49 (1H, s, quinolinyl 4-H), 7.48-7.42 (2H, m, quinolinyl 5,7-H_2), 7.14 (1H, ddd, *J* 8.0, 7.0 and 1.2, quinolinyl 6-H), 5.61 (1H, t, *J* 6.2, amide NH), 5.00 (1H, br. s, ^{t}Bu NH), 3.81-3.72 (2H, m, 2-H_A and 6-H_A), 3.35 (1H, ddd, *J* 11.2, 9.7 and 3.3, 6-H_B), 3.14-3.11 (1H, m, 2-H_B), 3.10 (2H, t, *J* 6.2, methylpropanamide 1-H_2), 2.85 (2H, t, *J* 7.1, propanamide 3-H_2), 2.47 (2H, t, *J* 7.1, propanamide 2-H_2), 1.76-1.63 (2H, m, 3-H and 4-H_A), 1.58 (9H, s, ^{t}Bu), 1.55-1.45 (2H, m, 5-H_2), 1.16 (1H, app. dtd, *J* 13.7, 10.5 and 4.6, 4-H_B); δ_C (100 MHz, $CDCl_3$) 172.2 (propanamide C-1), 154.7 (quinolinyl C-2), 147.0 (quinolinyl C-8a), 134.5 (quinolinyl C-4), 128.5 (quinolinyl C-7), 126.7 (quinolinyl C-5), 126.4 (quinolinyl C-8), 123.3 (quinolinyl C-3), 123.0 (quinolinyl C-4a), 121.7 (quinolinyl C-6), 71.1 (C-2), 68.5 (C-6), 51.9 (^{t}Bu C_1), 41.7 (methylpropanamide C-1), 36.3 (C-3), 35.5 (propanamide C-2), 29.3 (^{t}Bu C_3), 27.3 (C-4), 26.7 (propanamide C-3), 25.0 (C-5); HRMS found MH^+, 370.2488. $C_{22}H_{31}N_3O_2$ requires *MH*, 370.2494.

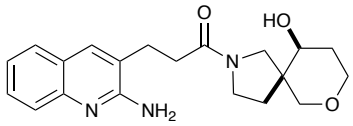
3-(2-Aminoquinolin-3-yl)-1-[(5*R,6*R**)-5-hydroxy-2-oxa-8-azaspiro[5.5]undecan-8-yl]propan-1-one**



215

According to General Procedure AD, TFA (0.50 mL) and the amide derivative **231a** (11.3 mg, 26.5 μmol) were stirred for 3 h to give a crude material. The crude material was purified by flash column chromatography eluting with 93.9:5.42:0.68 DCM−EtOH−NH_4OH to yield the *amine derivative* ***215*** (9.80 mg, >99%, *rotamers* 78:22 by ^{1}H-NMR) as a pale yellow oil, R_f 0.68 (84.7:13.6:1.70 DCM−EtOH−NH_4OH); ν_{max}/cm^{-1} 3337, 3200, 2929, 2854, 1617, 1498, 1468, 1432, 1260, 1233, 1132, 1083, 1002; δ_H (400 MHz, $CDCl_3$) 7.70 (2H, app. d, *J* 10.1, quinolinyl 4-H), 7.63 (2H, d, *J* 8.4, quinolinyl 8-H), 7.57 (2H, dd, *J* 8.0 and 1.6, quinolinyl 5-H), 7.50 (2H, ddd, *J* 8.4, 6.9 and 1.6, quinolinyl 7-H), 7.23 (2H, app. tt, *J* 8.0 and 1.3, quinolinyl 6-H), 5.39 (2H, br. s, NH_2^{minor}), 5.37 (2H, br. s, NH_2^{major}), 4.27 (1H, app. d, *J* 13.1, 9-H_A^{minor}), 3.85-3.75 (2H, m, 3-H_A), 3.74-3.62 (2H, m, 3-H_B), 3.60 (2H, d, *J* 11.9, 1-H_A), 3.56-3.50 (4H, m, 5-H and 7-H_A), 3.46-3.36 (1H, m, 9-H_A^{major}), 3.35-3.25 (1H, m, 9-H_B^{major}), 3.10 (2H, d, *J* 12.6, 7-H_B), 3.05-2.75 (7H, m, 1-H_B, 9-H_B^{minor} and propanone 3-H_2), 2.74-2.55 (4H, m, propanone 2-H_2), 2.12-1.81 (2H, m, 4-H_A), 1.75-1.65 (2H, m, 10-H_A), 1.64-1.44 (8H, m, 4-H_B, 10-H_B and 11-H_2); δ_C (100 MHz, $CDCl_3$) 171.3 (propanone C-1^{minor}), 171.1 (propanone C-1^{major}), 156.7 (quinolinyl C_2-2), 146.7 (quinolinyl C_2-8a), 136.7 (quinolinyl C_2-4), 129.2 (quinolinyl C_2-7), 127.0 (quinolinyl C_2-5), 125.5 (quinolinyl C_2-8), 124.3 (quinolinyl C_2-3), 123.5 (quinolinyl C_2-4a), 122.7 (quinolinyl C-6^{major}), 122.6 (quinolinyl C-6^{minor}), 70.6 (C-1^{major}), 69.8 (C-5^{major}), 69.7 (C-5^{minor}), 68.4 (C-1^{minor}), 65.3 (C-3^{minor}), 64.2 (C-3^{major}), 50.3 (C-7^{minor}), 47.6 (C-7^{major}), 46.6 (C-9^{major}), 42.9 (C-9^{minor}), 39.0 (C-6^{major}), 38.9 (C-6^{minor}), 32.4 (propanone C-2^{major}), 32.3 (propanone C-2^{minor}), 30.7 (C_2-4), 26.9 (propanone C-3^{minor}), 26.6 (propanone C-3^{major}), 21.3 (C_2-10), 20.5 (C_2-11); HRMS found MH^+, 370.2123. $C_{21}H_{27}N_3O_3$ requires *MH*, 370.2130.

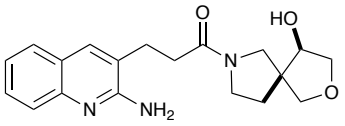
3-(2-Aminoquinolin-3-yl)-1-[(5*R,10*R**)-10-hydroxy-7-oxa-2-azaspiro[4.5]decan-2-yl]propan-1-one**



216

According to General Procedure AD, TFA (0.50 mL) and the amide derivative **231b** (10.0 mg, 24.3 μmol) were stirred for 3 h to give the *amine derivative **216*** (8.00 mg, 93%, *rotamers* >95:<5 by ^{1}H-NMR) as a colourless oil, R_f 0.63 (84.7:13.6:1.70 DCM−EtOH−NH_4OH); v_{max}/cm^{-1} 3410, 3324, 3149, 2941, 2878, 2850, 1655, 1624, 1473, 1438, 1340, 1328, 1134, 1108, 1086, 1068; δ_H (400 MHz, $CDCl_3$) 7.67 (2H, d, *J* 5.3, quinolinyl 4-H), 7.62 (2H, d, *J* 8.4, quinolinyl 8-H), 7.55 (2H, d, *J* 8.0, quinolinyl 5-H), 7.50 (2H, ddd, *J* 8.4, 6.8 and 1.5, quinolinyl 7-H), 7.22 (2H, app. t, *J* 7.4, quinolinyl 6-H), 5.76 (2H, br. s, NH^{major}), 5.70 (2H, br. s, NH^{minor}), 3.93-3.81 (2H, m, 8-H_A), 3.74-3.65 (2H, m, 10-H), 3.63 (2H, d, *J* 12.5, 6-H_A), 3.56-3.45 (4H, m, 3-H_A and 8-H_B), 3.44-3.33 (4H, m, 1-H_A and 3-H_B), 3.32-3.24 (2H, m, 1-H_B), 3.19-3.10 (2H, app. dd, *J* 11.6 and 2.4, 6-H_B), 2.98 (4H, t, *J* 6.8, propanone 3-H_2), 2.62 (4H, t, *J* 6.8, propanone 2-H_2), 2.08 (2H, app. dt, *J* 12.9 and 9.1, 4-H_A), 1.98-1.86 (2H, m, 4-H_B), 1.85-1.75 (2H, m, 9-H_A), 1.69-1.55 (2H, m, 9-H_B); δ_C (100 MHz, $CDCl_3$) 171.2 (propanone C-1^{major}), 171.1 (propanone C-1^{minor}), 156.7 (quinolinyl C_2-2), 146.0 (quinolinyl C-$8a^{minor}$), 145.8 (quinolinyl C-$8a^{major}$), 137.0 (quinolinyl C_2-4), 129.4 (quinolinyl C_2-7), 127.0 (quinolinyl C_2-5), 124.9 (quinolinyl C-8^{minor}), 124.8 (quinolinyl C-8^{major}), 124.1 (quinolinyl C-3^{minor}), 124.0 (quinolinyl C-3^{major}), 123.8 (quinolinyl C-$4a^{major}$), 123.7 (quinolinyl C-$4a^{minor}$), 122.8 (quinolinyl C_2-6), 71.4 (C-6^{major}), 70.6 (C-6^{minor}), 69.8 (C-10^{major}), 69.5 (C-10^{minor}), 65.7 (C-8^{major}), 65.0 (C-8^{minor}), 51.8 (C-3^{minor}), 51.1 (C-3^{major}), 48.5 (C-5^{minor}), 46.5 (C-5^{major}), 45.6 (C-1^{major}), 44.7 (C-1^{minor}), 34.1 (propanone C_2-2), 33.9 (C_2-9), 32.4 (C-4^{major}), 32.3 (C-4^{minor}), 26.1 (propanone C-3^{minor}), 26.0 (propanone C-3^{major}); HRMS found MH^+, 356.1971. $C_{20}H_{25}N_3O_3$ requires *MH*, 356.1974.

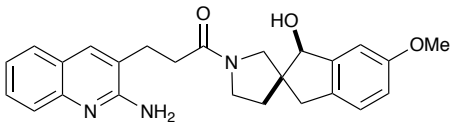
3-(2-Aminoquinolin-3-yl)-1-[(4*R,5*S**)-4-hydroxy-2-oxa-7-azaspiro[4.4]nona n-7-yl]propan-1-one**



217

According to General Procedure AD, TFA (0.50 mL) and the amide derivative **231c** (20.0 mg, 50.3 μmol) were stirred for 3 h to give the *amine derivative **217*** (17.1 mg, >99%, *rotamers* 53:47 by ^{1}H-NMR) as a colourless oil, R_f 0.51 (84.7:13.6:1.70 DCM−EtOH−NH_4OH); v_{max}/cm^{-1} 3326, 3148, 2919, 2872, 1625, 1567, 1471, 1431, 1362, 1327, 1216, 1124, 1054; δ_H (400 MHz, $CDCl_3$) 7.66 (2H, s, quinolinyl 4-H), 7.59 (2H, dd, *J* 8.4 and 5.2, quinolinyl 8-H), 7.55 (2H, d, *J* 8.0, quinolinyl 5-H), 7.49 (2H, app. ddt, *J* 8.4, 6.8 and 1.6, quinolinyl 7-H), 7.21 (2H, ddd, *J* 8.0, 6.8 and 1.2, quinolinyl 6-H), 5.61 (4H, br. s, NH_2), 4.01-3.87 (2H, m, 4-H), 3.81-3.69 (6H, m, 1-H_2 and 3-H_A), 3.68-3.55 (2H, m, 3-H_B), 3.54-3.44 (2H, m, 8-H_A), 3.43-3.38 (2H, m, 8-H_B), 3.21 (2H, d, *J* 10.3, 6-H_A), 3.08 (2H, d, *J* 10.3, 6-H_B), 3.05-2.86 (4H, m, propanone 3-H_2), 2.66-2.50 (4H, m, propanone 2-H_2), 2.31 (1H, ddd, *J* 13.2, 7.8 and 5.7, 9-H_A^{major}), 2.22 (1H, ddd, *J* 13.2, 7.6 and 5.8, 9-H_A^{minor}), 1.80 (1H, app. dt, *J* 12.9 and 7.6, 9-H_B^{major}), 1.71 (1H, app. dt, *J* 13.0 and 7.8, 9-H_B^{minor}); δ_C (100 MHz, $CDCl_3$) 171.2 (propanone C_2-1), 156.7 (quinolinyl C_2-2), 146.2 (quinolinyl C_2-8a), 137.1 (quinolinyl C-4^{minor}), 137.0 (quinolinyl C-4^{major}), 129.5 (quinolinyl C-7^{minor}), 129.4 (quinolinyl C-7^{major}), 127.1 (quinolinyl C_2-5), 125.0 (quinolinyl C-8^{major}), 124.9 (quinolinyl C-8^{minor}), 124.1 (quinolinyl C-3^{major}), 124.0 (quinolinyl C-3^{minor}), 123.5 (quinolinyl C_2-4a), 122.9 (quinolinyl C-6^{minor}), 122.8 (quinolinyl C-6^{major}), 75.3 (C_2-1), 74.9 (C_2-4), 74.4 (C_2-3), 55.5 (C-6^{minor}), 54.7 (C-5^{minor}), 54.4 (C-6^{major}), 52.7 (C-5^{major}), 46.1 (C-8^{major}), 45.3 (C-8^{minor}), 34.3 (propanone C-2^{minor}), 33.7 (propanone C-2^{major}), 28.3 (C_2-9), 26.3 (propanone C-3^{major}), 26.2 (propanone C-3^{minor}); HRMS found MH^+, 342.1807. $C_{19}H_{23}N_3O_3$ requires *MH*, 342.1817.

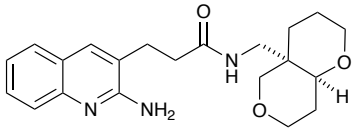
3-(2-Aminoquinolin-3-yl)-1-[(2*R,3*R**)-3-hydroxy-5-methoxy-1,3-dihydros piro[indene-2,3'-pyrrolidin]-1'-yl]propan-1-one**



218

According to General Procedure AD, TFA (0.50 mL) and the amide derivative **231d** (18.0 mg, 38.0 μmol) were stirred for 3 h to give a crude material. The crude material was purified by flash column chromatography eluting with 95.4:4.08:0.52 DCM−EtOH−NH_4OH to yield the *amine derivative **218*** (5.00 mg, 32%, *rotamers* 53:47 by ^{1}H-NMR) as a colourless oil, R_f 0.27 (92.4:6.76:0.84 DCM−EtOH−NH_4OH); v_{max}/cm^{-1} 3341, 3214, 3057, 2960, 2921, 1613, 1490, 1432, 1259, 1095, 1019; δ_H (400 MHz, $CDCl_3$) 7.75-7.45 (8H, m, quinolinyl 4,5,7,8-H_4), 7.23-7.15 (2H, m, quinolinyl 6-H), 7.07-7.00 (2H, m, 7-H), 6.88 (2H, app. ddd, *J* 9.4, 7.2 and 2.5, 4-H), 6.79 (2H, dd, *J* 8.3 and 2.6, 6-H), 5.51 (2H, br. s, NH^{minor}), 5.47 (2H, br. s, NH^{major}), 4.64 (1H, s, 3-H^{major}), 4.50 (1H, s, 3-H^{minor}), 3.78 (3H, methoxy^{minor}), 3.77 (3H, methoxy^{major}), 3.75-3.63 (2H, m, 5'-H_A), 3.61-3.49 (2H, m, 5'-H_B), 3.42-3.23 (2H, m, 2'-H_A), 3.22-3.11 (2H, m, 2'-H_B), 3.10-2.95 (4H, m, propanone 3-H_2), 2.94-2.81 (2H, m, 1-H_A), 2.73-2.61 (4H, m, propanone 2-H_2), 2.60-2.49 (2H, m, 1-H_B), 2.37-2.28 (1H, m, 4'-H_A^{minor}), 2.27-2.18 (1H, m, 4'-H_A^{major}), 1.96-1.84 (1H, m, 4'-H_B^{minor}), 1.83-1.65 (1H, m, 4'-H_B^{major}); δ_C (100 MHz, $CDCl_3$) 171.3 (propanone C-1^{major}), 171.2 (propanone C-1^{minor}), 159.4 (C-5^{major}), 159.3 (C-5^{minor}), 156.8 (quinolinyl C_2-2), 146.7 (quinolinyl C-8a^{minor}), 146.6 (quinolinyl C-8a^{major}), 145.0 (C-3a^{major}), 144.9 (C-3a^{minor}), 136.8 (quinolinyl C-4^{major}), 136.7 (quinolinyl C-4^{minor}), 133.1 (C-7a^{minor}), 132.9 (C-7a^{major}), 129.3 (quinolinyl C-7^{major}), 129.2 (quinolinyl C-7^{minor}), 127.0 (quinolinyl C_2-5), 126.0 (C-7^{minor}), 125.8 (C-7^{major}), 125.5 (quinolinyl C-8^{major}), 125.3 (quinolinyl C-8^{minor}), 124.3 (quinolinyl C_2-3), 123.6 (quinolinyl C_2-4a), 122.7 (quinolinyl C-6^{minor}), 122.6 (quinolinyl C-6^{major}), 115.2 (C-6^{minor}), 115.1 (C-6^{major}), 109.8 (C-4^{major}), 109.7 (C-4^{minor}), 80.0 (C-3^{major}), 79.4 (C-3^{minor}), 56.7 (C_2-2'), 55.6 (methoxy), 54.1 (C-2^{major}), 53.9 (C-2^{minor}), 46.3 (C-5'^{major}), 45.3 (C-5'^{minor}), 40.3 (C-1^{minor}), 40.0 (C-1^{major}), 36.0 (C_2-4'), 34.4 (propanone C-2^{major}), 33.9 (propanone C-2^{minor}), 26.4 (propanone C-3^{minor}), 26.2 (propanone C-3^{major}); HRMS found MH$^+$, 418.2125. $C_{25}H_{27}N_3O_3$ requires *MH*, 418.2130.

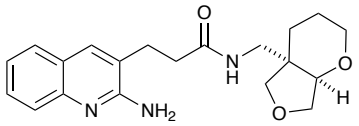
***N*-{[(4a*R**,8a*R**)-Octahydropyrano[4,3-*b*]pyran-4a-yl]methyl}-3-(2-aminoquinolin-3-yl)propanamide**



219

According to General Procedure AD, TFA (0.50 mL) and the amide derivative **231e** (11.7 mg, 27.5 μmol) were stirred for 3 h to give the *amine derivative **219*** (10.0 mg, 98%) as a colourless oil, R_f 0.43 (92.4:6.76:0.84 DCM−EtOH−NH_4OH); ν_{max}/cm^{-1} 3316, 3209, 3058, 2930, 2859, 1632, 1555, 1498, 1433, 1258, 1235, 1097, 1078, 1024; δ_H (400 MHz, $CDCl_3$) 7.67 (1H, s, quinolinyl 4-H), 7.62 (1H, dd, *J* 8.3 and 1.2, quinolinyl 8-H), 7.55 (1H, dd, *J* 8.1 and 1.5, quinolinyl 5-H), 7.50 (1H, ddd, *J* 8.3, 6.9 and 1.5, quinolinyl 7-H), 7.22 (1H, ddd, *J* 8.1, 6.9 and 1.2, quinolinyl 6-H), 6.03 (1H, t, *J* 6.3, amide NH), 5.29 (2H, br. s, NH_2), 3.92-3.84 (1H, m, 2-H_A), 3.80 (1H, d, *J* 11.7, 5-H_A), 3.66-3.59 (2H, m, 7-H_2), 3.37 (1H, dd, *J* 13.9 and 6.7, methylpropanamide 1-H_A), 3.32-3.24 (2H, m, 8a-H and methylpropanamide 1-H_B), 3.23-3.15 (1H, m, 2-H_B), 3.21 (1H, d, *J* 11.7, 5-H_B), 2.99 (2H, t, *J* 7.1, propanamide 3-H_2), 2.58 (2H, t, *J* 7.1, propanamide 2-H_2), 2.03-1.88 (1H, m, 8-H_A), 1.62-1.49 (1H, m, 3-H_A), 1.48-1.40 (1H, m, 8-H_B), 1.31-1.12 (3H, m, 3-H_B and 4-H_2); δ_C (100 MHz, $CDCl_3$) 172.5 (propanamide C-1), 156.4 (quinolinyl C-2), 146.6 (quinolinyl C-8a), 136.8 (quinolinyl C-4), 129.3 (quinolinyl C-7), 127.0 (quinolinyl C-5), 125.5 (quinolinyl C-8), 124.3 (quinolinyl C-3), 122.8 (quinolinyl C-6), 122.7 (quinolinyl C-4a), 74.7 (C-8a), 67.8 (C-5), 67.6 (C-2), 63.4 (C-7), 45.1 (methylpropanamide C-1), 36.3 (C-4a), 36.0 (propanamide C-2), 28.7 (C-4), 28.6 (C-8), 26.9 (propanamide C-3), 22.1 (C-3); HRMS found MH^+, 370.2120. $C_{21}H_{27}N_3O_3$ requires *MH*, 370.2130.

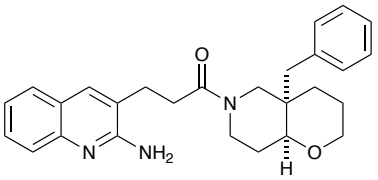
***N*-{[(4a*R**,7a*S**)-Hexahydro-2*H*-furo[3,4-*b*]pyran-4a-yl]methyl}-3-(2-aminoquinolin-3-yl)propanamide**



220

According to General Procedure AD, TFA (0.50 mL) and the amide derivative **231f** (11.0 mg, 26.7 μmol) were stirred for 3 h to give the *amine derivative* ***220*** (10.0 mg, >99%) as a pale yellow oil, R_f 0.65 (84.7:13.6:1.70 DCM−EtOH−NH_4OH); v_{max}/cm^{-1} 3322, 3206, 3055, 2927, 2876, 1632, 1550, 1498, 1472, 1433, 1262, 1097, 1082, 1055; δ_H (400 MHz, $CDCl_3$) 7.69 (1H, s, quinolinyl 4-H), 7.62 (1H, d, *J* 8.4, quinolinyl 8-H), 7.55 (1H, dd, *J* 8.0 and 1.5, quinolinyl 5-H), 7.50 (1H, ddd, *J* 8.4, 6.9 and 1.5, quinolinyl 7-H), 7.23 (1H, ddd, *J* 8.0, 6.9 and 0.9, quinolinyl 6-H), 6.12 (1H, t, *J* 5.3, amide NH), 5.51 (2H, br. s, NH_2), 4.00 (1H, dd, *J* 10.1 and 4.1, 7-H_A), 3.78 (1H, d, *J* 8.5, 5-H_A), 3.82-3.75 (1H, m, 2-H_A), 3.71 (1H, d, *J* 10.1, 7-H_B), 3.60 (1H, d, *J* 4.0, 7a-H), 3.46 (1H, d, *J* 8.5, 5-H_B), 3.24 (1H, dd, *J* 13.9 and 6.2, methylpropanamide 1-H_A), 3.17-3.05 (2H, m, 2-H_B and methylpropanamide 1-H_B), 3.00 (2H, t, *J* 7.0, propanamide 3-H_2), 2.59 (2H, t, *J* 7.0, propanamide 2-H_2), 1.65-1.52 (1H, m, 3-H_A), 1.51-1.44 (2H, m, 4-H_2), 1.36-1.27 (1H, m, 3-H_B); δ_C (100 MHz, $CDCl_3$) 172.7 (propanamide C-1), 156.2 (quinolinyl C-2), 145.9 (quinolinyl C-8a), 137.2 (quinolinyl C-4), 129.6 (quinolinyl C-7), 127.1 (quinolinyl C-5), 125.0 (quinolinyl C-8), 124.1 (quinolinyl C-3), 123.0 (quinolinyl C-6), 122.7 (quinolinyl C-4a), 80.3 (C-7a), 74.2 (C-7), 71.1 (C-5), 66.1 (C-2), 53.5 (C-4a), 45.5 (methylpropanamide C-1), 35.8 (propanamide C-2), 24.9 (propanamide C-3), 24.5 (C-4), 21.5 (C-3); HRMS found MH^+, 356.1968. $C_{20}H_{25}N_3O_3$ requires *MH*, 356.1974.

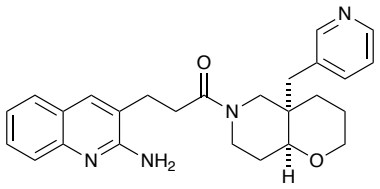
1-[(4a*R,8a*R**)-4a-benzyl-octahydro-2*H*-pyrano[3,2-*c*]pyridin-6-yl]-3-(2-amin oquinolin-3-yl)propan-1-one**



221

According to General Procedure AD, TFA (0.50 mL) and the amide derivative **231g** (10.5 mg, 21.6 μmol) were stirred for 3 h to give the *amine derivative **221*** (9.20 mg, >99%, *rotamers* 69:31 by ^{1}H-NMR) as a pale yellow oil, R_f 0.27 (EtOAc); ν_{max}/cm^{-1} 3329, 3177, 3052, 3026, 2932, 2852, 1620, 1497, 1470, 1431, 1264, 1118, 1091, 1075; δ_H (400 MHz, $CDCl_3$) 7.73 (2H, s, quinolinyl 4-H), 7.63 (2H, d, *J* 8.4, quinolinyl 8-H), 7.54 (2H, dd, *J* 8.2 and 1.4, quinolinyl 5-H), 7.49 (2H, ddd, *J* 8.4, 6.9 and 1.4, quinolinyl 7-H), 7.31-7.19 (8H, m, phenyl 3,4,5-H_3 and quinolinyl 6-H), 7.18-7.13 (2H, m, phenyl 2,6-H_2^{major}), 7.07-7.01 (2H, m, phenyl 2,6-H_2^{minor}), 5.43 (4H, br. s, NH_2), 4.17 (1H, d, *J* 13.2, 5-H_A^{major}), 4.39 (1H, app. d, *J* 13.3, 7-H_A^{minor}), 3.96-3.82 (2H, m, 2-H_A), 3.71-3.60 (1H, m, 7-H_A^{major}), 3.54 (1H, d, *J* 13.2, 5-H_A^{minor}), 3.40-3.21 (5H, m, 2-H_B, 7-H_B^{major} and 8a-H), 3.13 (2H, d, *J* 13.2, 5-H_B), 3.10-2.97 (5H, m, 7-H_B^{minor} and propanone 3-H_2), 2.94-2.71 (5H, m, phenylmethyl 1-H_A^{minor} and propanone 2-H_2), 2.64 (1H, d, *J* 13.4, phenylmethyl 1-H_A^{major}), 2.48 (1H, d, *J* 13.4, phenylmethyl 1-H_B^{minor}), 2.26 (1H, d, *J* 13.4, phenylmethyl 1-H_B^{major}), 2.15-2.06 (1H, m, 8-H_A^{minor}), 2.00-1.85 (1H, m, 8-H_A^{major}), 1.80-1.53 (4H, m, 3-H_A and 8-H_B), 1.49-1.31 (4H, m, 3-H_B and 4-H_A), 1.18-1.05 (2H, m, 4-H_B); δ_C (100 MHz, $CDCl_3$) 171.2 (propanone C_2-1), 156.6 (quinolinyl C_2-2), 146.6 (quinolinyl C_2-8a), 136.7 (phenyl C_2-1), 136.6 (quinolinyl C_2-4), 130.9 (phenyl C_2-2,6^{major}), 130.7 (phenyl C_2-2,6^{minor}) 129.2 (quinolinyl C_2-7), 128.3 (phenyl C_2-3,5^{minor}), 128.1 (phenyl C_2-3,5^{major}), 127.0 (quinolinyl C_2-5), 126.4 (quinolinyl C_2-8), 125.5 (phenyl C_2-4), 124.3 (quinolinyl C_2-3), 123.6 (quinolinyl C-4a^{minor}), 123.5 (quinolinyl C-4a^{major}), 122.7 (quinolinyl C_2-6), 77.2 (C-8a^{major}), 75.4 (C-8a^{minor}), 67.9 (C_2-2), 48.7 (C-5^{minor}), 43.6 (C-5^{major}), 41.4 (phenylmethyl C_2-1), 40.9 (C-7^{major}), 37.3 (C-7^{minor}), 36.6 (C_2-4a), 32.7 (propanone C_2-2), 30.7 (C_2-4), 28.0 (C_2-8), 26.7 (propanone C_2-3), 22.3 (C_2-3); HRMS found MH^+, 430.2488. $C_{27}H_{31}N_3O_2$ requires *MH*, 430.2494.

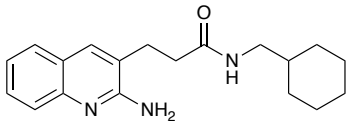
1-[(4a*R,8a*R**)-4a-[(Pyridin-3-yl)methyl]-octahydro-2*H*-pyrano[3,2-*c*]pyridin-6-yl]-3-(2-aminoquinolin-3-yl)propan-1-one**



222

According to General Procedure AD, TFA (0.50 mL) and the amide derivative **231h** (10.3 mg, 21.2 μmol) were stirred for 3 h to give the *amine derivative* ***222*** (9.00 mg, 99%, *rotamers* 80:20 by ^{1}H-NMR) as a colourless amorphous solid, R_f 0.43 (92.4:6.76:0.84 DCM−EtOH−NH_4OH); ν_{max}/cm^{-1} 3332, 3173, 3048, 2929, 2852, 1619, 1471, 1432, 1272, 1259, 1118, 1089; δ_H (400 MHz, $CDCl_3$) 8.46 (2H, dd, *J* 4.8 and 1.7, pyridinyl 6-H), 8.33 (1H, d, *J* 2.3, pyridinyl 2-H^{major}), 8.30 (1H, d, *J* 2.3, pyridinyl 2-H^{minor}), 7.72 (1H, s, quinolinyl 4-H^{major}), 7.70 (1H, s, quinolinyl 4-H^{minor}), 7.64-7.57 (4H, m, pyridinyl 4-H and quinolinyl 8-H), 7.53-7.40 (4H, m, quinolinyl 5,7-H_2), 7.25-7.11 (4H, m, quinolinyl 6-H and pyridinyl 5-H), 5.46 (4H, br. s, NH_2), 4.39 (1H, app. d, *J* 13.2, 7-H_A^{minor}), 4.13 (1H, d, *J* 13.2, 5-H_A^{major}), 2.93 (2H, app. dd, *J* 11.3 and 4.7, 2-H_A), 3.67 (1H, ddd, *J* 11.0, 5.0 and 2.6, 7-H_A^{major}), 3.56 (1H, d, *J* 13.3, 5-H_A^{minor}), 3.37-3.29 (3H, m, 2-H_B and 7-H_B^{major}), 3.28 (2H, s, 8a-H), 3.10 (2H, d, *J* 13.2, 5-H_B), 3.07-2.98 (5H, m, 7-H_B^{minor} and propanone 3-H_2), 2.96-2.71 (4H, m, propanone 2-H_2), 2.70 (1H, d, *J* 13.6, pyridinylmethyl 1-H_A^{minor}), 2.55 (1H, d, *J* 13.6, pyridinylmethyl 1-H_A^{major}), 2.37 (1H, d, *J* 13.6, pyridinylmethyl 1-H_B^{minor}), 2.13 (1H, d, *J* 13.6, pyridinylmethyl 1-H_B^{major}), 2.10-2.00 (1H, m, 8-H_A^{minor}), 1.85 (1H, app. tdd, *J* 13.2, 5.0 and 2.9, 8-H_A^{major}), 1.74-1.59 (4H, m, 3-H_A and 8-H_B), 1.43-1.27 (4H, m, 3-H_B and 4-H_A), 1.10-1.00 (2H, m, 4-H_B); δ_C (100 MHz, $CDCl_3$) 171.2 (propanone C_2-1), 156.5 (quinolinyl C_2-2), 151.6 (pyridinyl C_2-2), 147.9 (pyridinyl C_2-6 and quinolinyl C_2-8a), 138.2 (pyridinyl C_2-4), 136.8 (quinolinyl C_2-4), 132.3 (pyridinyl C_2-3), 129.3 (quinolinyl C_2-7), 126.9 (quinolinyl C_2-5), 125.4 (quinolinyl C_2-8), 124.2 (quinolinyl C_2-3), 123.4 (quinolinyl C_2-4a), 123.3 (pyridinyl C_2-5), 122.7 (quinolinyl C_2-6), 77.3 (C-8a^{major}), 74.9 (C-8a^{minor}), 68.0 (C_2-2), 43.1 (C_2-5), 41.0 (C_2-7), 38.3 (pyridinylmethyl C_2-1), 36.5 (C_2-4a), 32.5 (propanone C_2-2), 30.8 (C_2-4), 28.1 (C_2-8), 26.7 (propanone C_2-3), 22.2 (C_2-3); HRMS found MH^+, 431.2438. $C_{26}H_{30}N_4O_2$ requires *MH*, 431.2447.

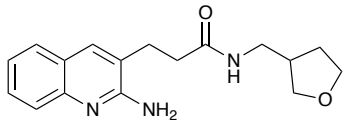
3-(2-Aminoquinolin-3-yl)-*N*-(cyclohexylmethyl)propanamide



214

According to General Procedure AD, TFA (2.00 mL) and the amide derivative **231i** (0.10 g, 0.27 mmol) were stirred for 1.5 h to give the amine derivative **214**[192] (70.0 mg, 83%) as a colourless amorphous solid, R_f 0.37 (92.4:6.76:0.84 DCM−EtOH−NH_4OH); ν_{max}/cm^{-1} 3461, 3314, 3059, 2915, 2843, 1640, 1539, 1500, 1437; δ_H (400 MHz, DMSO-d_6) 7.86 (1H, t, *J* 5.9, NH), 7.69 (1H, s, quinolinyl 4-H), 7.56 (1H, d, *J* 8.0, quinolinyl 5-H), 7.50-7.36 (2H, m, quinolinyl 7,8-H_2), 7.14 (1H, ddd, *J* 8.0, 6.4 and 1.6, quinolinyl 6-H), 6.40 (2H, br. s, NH_2), 2.88 (2H, app. t, *J* 6.3, methylpropanamide 1-H_2), 2.81 (2H, t, *J* 7.2, propanamide 3-H_2), 2.46 (2H, t, *J* 7.2, propanamide 2-H_2), 1.65-1.45 (4H, m, 2-H_A, 6-H_A and 3,4,5-H_2), 1.35-1.20 (1H, m, 1-H), 1.14-0.95 (4H, m, 3,4,5-H_4), 0.86-0.66 (2H, m, 2-H_B and 6-H_B); δ_C (100 MHz, DMSO-d_6) 171.2 (propanamide C-1), 156.9 (quinolinyl C-2), 146.1 (quinolinyl C-8a), 134.7 (quinolinyl C-4), 128.3 (quinolinyl C-7), 126.8 (quinolinyl C-8), 124.3 (quinolinyl C-5), 123.3 (quinolinyl C-4a), 123.2 (quinolinyl C-3), 121.2 (quinolinyl C-6), 44.8 (methylpropanamide C-1), 37.4 (C-1), 33.9 (propanamide C-2), 30.3 (C_2-2,6), 26.3 (propanamide C-3), 26.0 (C-4), 25.3 (C_2-3,5); HRMS found MH^+, 312.2068. $C_{19}H_{25}N_3O$ requires *MH*, 312.2075.

3-(2-Aminoquinolin-3-yl)-*N*-[(oxolan-3-yl)methyl]propanamide

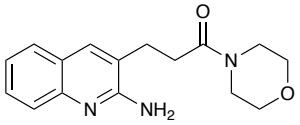


223

According to General Procedure AD, TFA (2.00 mL) and the amide derivative **231j** (0.10 g, 0.28 mmol) were stirred for 1.5 h to give a crude material. The crude material was purified by flash column chromatography eluting with 92.4:6.76:0.84→84.7:13.6:1.70 DCM−EtOH−NH_4OH to yield the *amine derivative* ***223*** (40.0 mg, 47%) as a colourless amorphous solid, R_f 0.61

(84.7:13.6:1.70 DCM−EtOH−NH_4OH); ν_{max}/cm^{-1} 3476, 3329, 3083, 2965, 2924, 2840, 1637, 1618, 1529, 1501, 1477, 1438, 1260, 1069; δ_H (400 MHz, $CDCl_3$) 7.57 (1H, app. d, *J* 7.9, quinolinyl 8-H), 7.56 (1H, s, quinolinyl 4-H), 7.50 (1H, dd, *J* 8.1 and 1.5, quinolinyl 5-H), 7.45 (1H, ddd, *J* 8.4, 6.9 and 1.5, quinolinyl 7-H), 7.18 (1H, ddd, *J* 8.1, 6.9 and 1.2, quinolinyl 6-H), 6.32 (1H, t, *J* 6.0, amide NH), 5.36 (2H, br. s, NH_2), 3.71 (1H, app. td, *J* 8.3 and 5.3, 5-H_A), 3.64-3.50 (2H, m, 2-H_A and 5-H_B), 3.38 (1H, dd, *J* 8.8 and 5.1, 2-H_B), 3.25-3.08 (2H, m, methylpropanamide 1-H_2), 2.89 (2H, t, *J* 7.1, propanamide 3-H_2), 2.47 (2H, t, *J* 7.1, propanamide 2-H_2), 2.31 (1H, app. ddt, *J* 8.3, 6.9 and 5.3, 3-H), 1.83 (1H, app. dtd, *J* 13.2, 8.1 and 5.3, 4-H_A), 1.42 (1H, dddd, *J* 12.6, 8.0, 7.1 and 5.7, 4-H_B); δ_C (100 MHz, $CDCl_3$) 172.5 (propanamide C-1), 156.5 (quinolinyl C-2), 146.6 (quinolinyl C-8a), 136.4 (quinolinyl C-4), 129.2 (quinolinyl C-7), 127.0 (quinolinyl C-5), 125.3 (quinolinyl C-8), 124.2 (quinolinyl C-3), 122.7 (quinolinyl C-4a), 122.6 (quinolinyl C-6), 71.1 (C-2), 67.7 (C-5), 42.5 (methylpropanamide C-1), 39.0 (C-3), 35.5 (propanamide C-2), 29.8 (C-4), 26.8 (propanamide C-3); HRMS found MH^+, 300.1703. $C_{17}H_{21}N_3O_2$ requires *MH*, 300.1712.

3-(2-Aminoquinolin-3-yl)-1-(morpholin-4-yl)propan-1-one

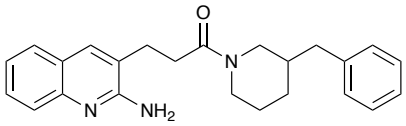


224

According to General Procedure AD, TFA (8.00 mL) and the amide derivative **231k** (0.12 g, 0.35 mmol) were stirred for 2 h to give a crude material. The crude material was purified by flash column chromatography eluting with 95.4:4.08:0.52 DCM−EtOH−NH_4OH to yield the *amine derivative* ***224*** (93.0 mg, 93%) as colourless crystals, m.p. (DCM), 183–193 °C; R_f 0.31 (92.4:6.76:0.84 DCM−EtOH−NH_4OH); ν_{max}/cm^{-1} 3315, 3133, 2965, 2899, 2853, 1628, 1614, 1461, 1428, 1408, 1240, 1228, 1108; δ_H (400 MHz, DMSO-d_6) 7.71 (1H, s, quinolinyl 4-H), 7.58 (1H, d, *J* 7.9, quinolinyl 8-H), 7.48-7.35 (2H, m, quinolinyl 5,7-H_2), 7.12 (1H, t, *J* 7.2, quinolinyl 6-H), 6.29 (2H, br. s, NH_2), 3.51-3.45 (4H, m, 2,6-H_4), 3.45-3.39 (4H, m, 3,5-H_4), 2.82 (2H, t, *J* 7.4, propanone 3-H_2), 2.67 (2H, t, *J* 7.4, propanone 2-H_2); δ_C (75 MHz, DMSO-d_6) 170.2 (propanone C-1), 157.1 (quinolinyl C-2), 146.6 (quinolinyl C-8a), 134.8 (quinolinyl C-4), 128.2

(quinolinyl C-7), 126.8 (quinolinyl C-8), 124.7 (quinolinyl C-5), 123.4 (quinolinyl C-3), 123.3 (quinolinyl C-4a), 121.2 (quinolinyl C-6), 45.3 (C_2-2,6), 41.5 (C_2-3,5), 30.7 (propanone C-2), 25.9 (propanone C-3); HRMS found MH^+, 286.1550. $C_{16}H_{19}N_3O_2$ requires *MH*, 286.1555.

3-(2-Aminoquinolin-3-yl)-1-(3-benzylpiperidin-1-yl)propan-1-one

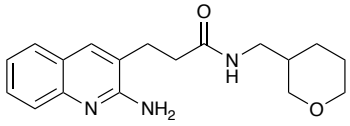


225

According to General Procedure AD, TFA (0.50 mL) and the amide derivative **231l** (13.0 mg, 30.3 μmol) were stirred for 3 h to give the *amine derivative **225*** (11.3 mg, >99%, *rotamers* 51:49 by ^{1}H-NMR) as a colourless amorphous solid, R_f 0.45 (92.4:6.76:0.84 DCM−EtOH−NH_4OH); v_{max}/cm^{-1} 3369, 3338, 3128, 2942, 2917, 2865, 2847, 1665, 1619, 1499, 1476, 1452, 1434, 1330, 1279, 1218, 1143, 1111; δ_H (400 MHz, $CDCl_3$) 7.69 (1H, s, quinolinyl 4-H^{minor}), 7.65 (2H, dd, *J* 8.4 and 2.6, quinolinyl 8-H), 7.59 (2H, dd, *J* 8.0 and 1.6, quinolinyl 5-H), 7.57 (1H, s, quinolinyl 4-H^{major}), 7.53-7.46 (2H, m, quinolinyl 7-H), 7.33-7.23 (6H, m, phenyl 3,4,5-H_3), 7.24-7.17 (2H, m, quinolinyl 6-H), 7.13 (2H, d, *J* 7.1, phenyl 2,6-H_A), 7.07 (2H, d, *J* 7.1, phenyl 2,6-H_B), 5.41 (2H, br. s, NH^{minor}), 5.35 (2H, br. s, NH^{major}), 4.50 (1H, ddt, *J* 12.9, 3.8 and 1.7, phenylmethyl 1-H_A^{minor}), 4.42 (1H, app. dt, *J* 13.3 and 4.2, phenylmethyl 1-H_A^{major}), 3.72 (1H, app. dt, *J* 13.5 and 4.1, phenylmethyl 1-H_B^{minor}), 3.63 (1H, ddt, *J* 13.3, 3.7 and 1.6, phenylmethyl 1-H_B^{major}), 3.02 (4H, t, *J* 7.0, 6-H_2^{major} and propanone 3-H_2^{major}), 2.93 (2H, t, *J* 7.0, propanone 3-H_2^{minor}), 2.72 (2H, t, *J* 7.0, propanone 2-H_2^{major}), 2.70-2.63 (4H, m, 2-H_2^{minor} and 6-H_2^{minor}), 2.55 (2H, t, *J* 7.0, propanone 2-H_2^{minor}), 2.48-2.34 (2H, m, 2-H_2^{major}), 1.85-1.73 (2H, m, 4-H_A), 1.75-1.59 (4H, m, 3-H and 5-H_A), 1.48-1.33 (2H, m, 5-H_B), 1.29-1.04 (2H, m, 4-H_B); δ_C (100 MHz, $CDCl_3$) 170.6 (propanone C-1^{major}), 170.5 (propanone C-1^{minor}), 156.6 (quinolinyl C_2-2), 146.7 (quinolinyl C_2-8a), 139.5 (phenyl C-1^{minor}), 139.3 (phenyl C-1^{major}), 136.5 (quinolinyl C-4^{minor}), 136.4 (quinolinyl C-4^{major}), 129.2 (phenyl C_2-2,6^{major}), 129.1 (phenyl C_2-2,6^{minor}), 128.9 (quinolinyl C_2-7), 128.6 (phenyl C_2-3,5^{major}), 128.4 (phenyl C_2-3,5^{minor}), 127.0 (quinolinyl C_2-5), 126.4 (quinolinyl C_2-8), 125.6 (phenyl C-4^{major}), 125.5 (phenyl C-4^{minor}), 124.3 (quinolinyl C_2-3), 123.6

(quinolinyl C-4a^{minor}), 123.5 (quinolinyl C-4a^{major}), 122.6 (quinolinyl C_2-6), 51.4 (C-2^{major}), 48.1 (C-2^{minor}), 46.4 (phenylmethyl C-1^{minor}), 43.0 (phenylmethyl C-1^{major}), 40.4 (quinolinyl C-6^{minor}), 40.1 (quinolinyl C-6^{major}), 38.8 (quinolinyl C-3^{major}), 37.7 (quinolinyl C-3^{minor}), 32.7 (propanone C-2^{minor}), 32.4 (propanone C-2^{major}), 31.0 (C-4^{major}), 30.4 (C-4^{minor}), 26.6 (propanone C_2-3), 25.7 (C-5^{minor}), 24.7 (C-5^{major}); HRMS found MH^+, 374.2233. $C_{24}H_{27}N_3O$ requires *MH*, 374.2232.

3-(2-Aminoquinolin-3-yl)-*N*-[(oxan-3-yl)methyl]propanamide



226

According to General Procedure AD, TFA (0.50 mL) and the amide derivative **231m** (11.0 mg, 29.7 μmol) were stirred for 3 h to give the *amine derivative **226*** (9.30 mg, >99%) as a colourless oil, R_f 0.28 (92.4:6.76:0.84 DCM−EtOH−NH_4OH); v_{max}/cm^{-1} 3397, 3277, 3148, 3083, 2948, 2930, 2916, 2850, 1654, 1627, 1565, 1501, 1477, 1154; δ_H (400 MHz, $CDCl_3$) 7.66 (1H, s, quinolinyl 4-H), 7.63 (1H, dd, *J* 8.5 and 1.2, quinolinyl 8-H), 7.53 (1H, dd, *J* 8.1 and 1.5, quinolinyl 5-H), 7.50 (1H, ddd, *J* 8.5, 6.9 and 1.5, quinolinyl 7-H), 7.23 (1H, ddd, *J* 8.1, 6.9 and 1.2, quinolinyl 6-H), 5.81 (1H, *t*, *J* 5.2, amide NH), 5.35 (2H, s, NH_2), 3.83-3.61 (2H, m, 2-H_A and 6-H_A), 3.35 (1H, ddd, *J* 11.2, 9.6 and 3.3, 6-H_B), 3.14-3.06 (1H, m, 2-H_A), 3.11 (2H, t, *J* 6.5, methylpropanamide 1-H_2), 2.97 (2H, t, *J* 7.0, propanamide 3-H_2), 2.54 (2H, t, *J* 7.0, propanamide 2-H_2), 1.78-1.62 (2H, m, 3-H and 4-H_A), 1.60-1.40 (2H, m, 5-H_2), 1.15 (1H, app. dtd, *J* 12.7, 10.1, 9.6 and 4.6, 4-H_B); δ_C (100 MHz, $CDCl_3$) 172.4 (propanamide C-1), 156.4 (quinolinyl C-2), 146.4 (quinolinyl C-8a), 136.8 (quinolinyl C-4), 129.3 (quinolinyl C-7), 127.0 (quinolinyl C-5), 125.3 (quinolinyl C-8), 124.2 (quinolinyl C-3), 122.9 (quinolinyl C-4a), 122.8 (quinolinyl C-6), 71.0 (C-2), 68.5 (C-6), 41.7 (methylpropanamide C-1), 36.2 (C-3), 35.8 (propanamide C-2), 27.3 (C-4), 26.9 (propanamide C-3), 24.9 (C-5); HRMS found MH^+, 314.1867. $C_{18}H_{23}N_3O_2$ requires *MH*, 314.1868.

5.3. Experimental for the Determination of the Biological Activity

The derived compounds were assessed using a BACE1 red-shifted fluorescence-quenching assay kit supplied from ThermoFisher Scientific (PanVera®, Part Number P2985).[204] The kit was composed of a "Swedish" mutant APP peptide tagged with a rhodamine derivative (fluorescence donor) and a propietary quenching acceptor (rhodamine-EVNLDAEFK-quencher) in a 75 µM aqueous solution of 50 mM ammonium bicarbonate (PanVera®, Part Number P2986); purified baculovirus-expressed BACE1 in a 50 mM aqueous solution of tris(hydroxymethyl) aminomethane (pH 7.5) with 10% glycerol (PanVera®, Part Number P2947); and an assay buffer of 50 mM aqueous solution of sodium acetate (pH 4.5) (PanVera®, Part Number P2948). The assay was performed using black 384 round-bottom well plates (Corning®, Part number 4514).

The assay procedure was adapted from an existing protocol.[204] The BACE1 solution and the substrate solution provided were diluted in assay buffer to obtain 1 protein unit/mL and a 750 nM solution, respectively, as working solutions. The corresponding derived molecules were dissolved in DMSO (supplied by Sigma–Aldrich) to obtain a 200 mM or 100 mM solution. Lower concentrations of the derived compounds were achieved by serial dilution in DMSO in 10–12 steps to obtain different concentrations until 0.30 mM. Finally, each concentration in DMSO was diluted 100-fold with assay buffer to obtain the working solutions. For determination of inhibition activity, 5 µL of each of the working solutions (compound, BACE1 and substrate) was added to each well to obtain a total volume of 15 µL/well. For the positive control, a 1% DMSO solution in assay buffer was used instead of the working solution of the compounds. For the negative control, 1% DMSO solution in assay buffer and assay buffer were used instead of the working solutions of the compounds and BACE1. The compounds were added to the wells first, followed by the protein and 20 min later by the substrate. Each well was repeated in triplicate (Figure 50). The enzyme inhibition was measured at 25 °C by quantifying the fluorescence released using an Envision™ 2013 multilabel plate reader (PerkinElmer), with BODIPY TMR mirror, $\lambda_{excitation}$ = 531 nm and $\lambda_{emission}$ = 595 nm. The measurements were taken every minute over 2 h.

A

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	24
A	The 13 derived compounds in																	
B	concentrations of 100 µM in triplicate																	
C	(each compound in a different column)																	
D																		
E	+	–																
F																		
G																		
P																		

B

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	24
A	Derived compound **214**, **218**, **219** or **221**																	
B	in concentrations from up to 0.67 mM to 1 µM in triplicate																	
C	(each concentration in a different column)																	
D																		
E	+	–																
F																		
G																		
P																		

Figure 50: Well plate layout to assess BACE1 inhibition. The + and – means positive and negative control, respectively. Positive control does not contain compounds and negative control does not contain protein nor compounds. **Panel A:** First fluorescence-quenching assay to identify if some of the 13 derived compounds were inhibitors at 100 µM. **Panel B:** Successive fluorescence-quenching assays to determine the IC_{50} of the inhibitors **214**, **218**, **219** and **221** identified in the previous assay in panel A.

All the data was processed using Graphpad Prism V.6 (Graphpad Software Inc. CA). To process the data the average value of fluorescence unit for each compound at the specific concentration, for the negative control and for the positive control was plotted against the time. A linear fit was applied, the slopes were obtained and the % of inhibition was determined (Equation 1).

$$\frac{\text{Compound slope–Positive control slope}}{\text{Negative control slope–Positive control slope}} \times 100$$

Equation 1: Calculation of the % of inhibition from the slopes.

The % of inhibition was reported as mean of the triplicate ± SEM. The dose-response data, expressed as % of inhibition *vs* log[compound] was represented with a sigmoidal dose-response model. This sigmoidal dose-response model allowed the determination of the IC_{50} (Table 29). The values were calculated from three independent experiments.

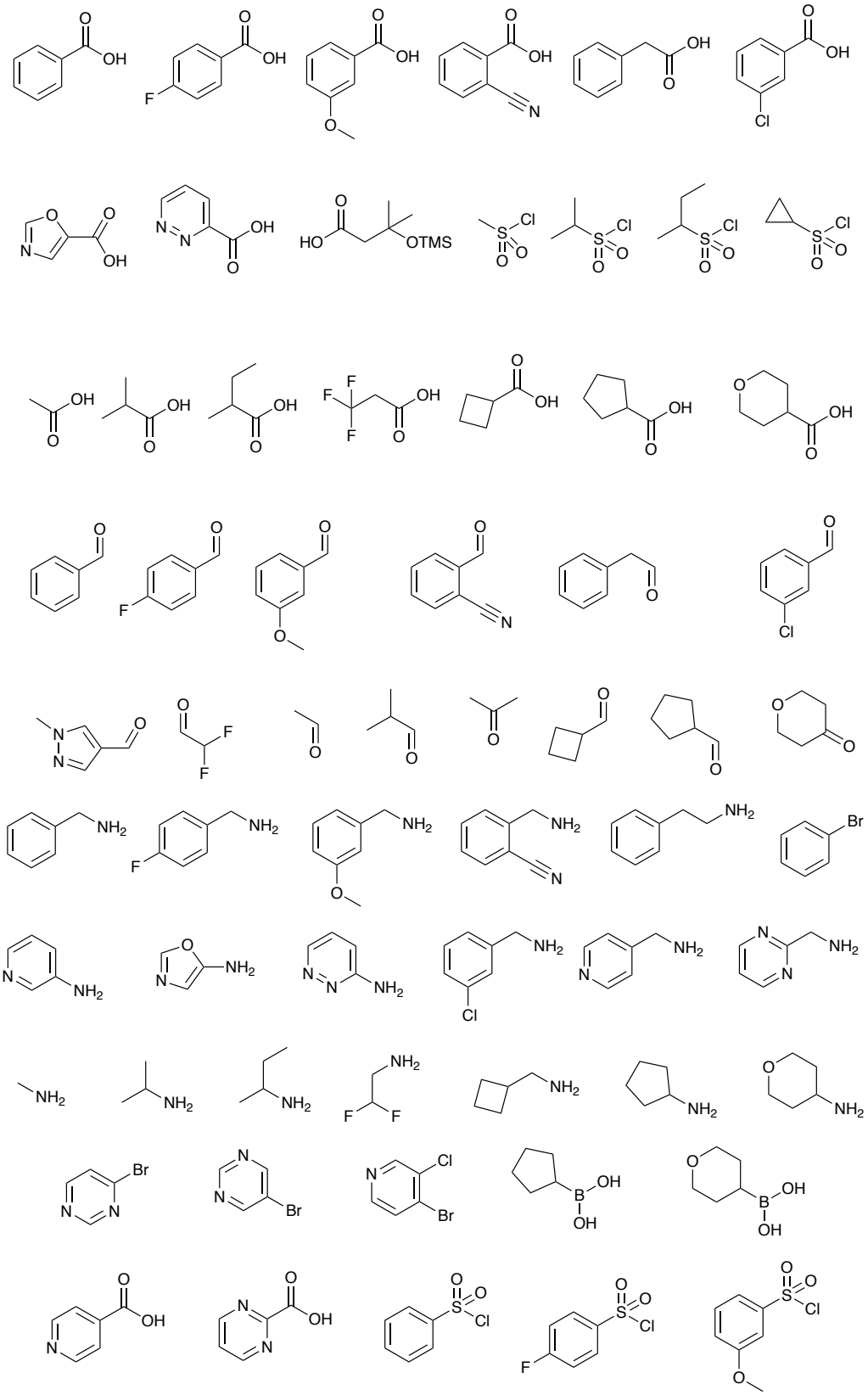
Derived compound	LogIC_{50} ± SEM	IC_{50}	Hill slope
214	-4.508 ± 0.06	31.0 µM	-1.55
218	-4.257 ± 0.01	55.3 µM	-3.27
219	-4.542 ± 0.02	28.7 µM	-2.54
221	-4.074 ± 0.02	84.2 µM	-3.80

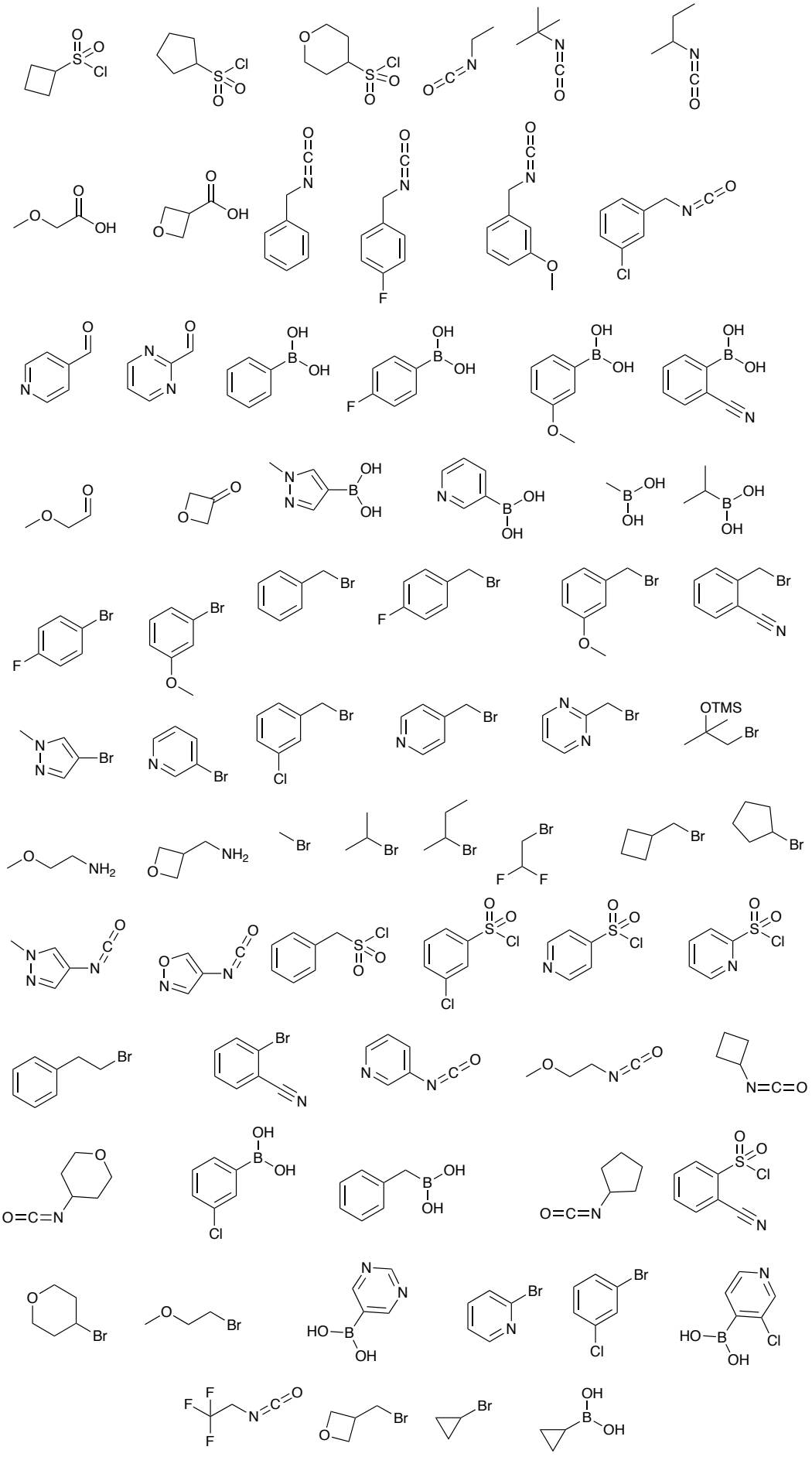
Table 29: IC_{50} values for compounds **214**, **218**, **219** and **221** obtained from the sigmoidal dose-response models. Normalised to negative and positive controls.

Appendix

Library of Virtual Medicinal Chemistry Capping Groups

The next reagents were used to decorate the scaffolds with the computational tool:



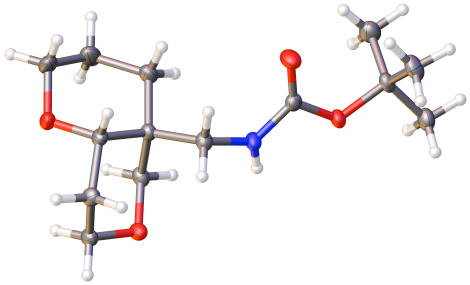


Type	Number	Mean MW	Range MW	Mean clogP	Range clogP
Carboxylic acids	20	118.6	60.0 – 156.6	0.71	-0.49 – 2.12
Sulfonyl chlorides	15	173.2	114.5 – 211.1	1.24	0.00 – 2.40
Halides	30	163.3	94.9 – 205.5	1.88	0.68 – 3.24
Ketones	3	76.7	58.1 – 100.1	-0.32	-0.68 – -0.10
Aldehydes	15	102.4	44.0 – 140.6	0.93	-0.44 – 2.25
Isocyanates	15	119.9	71.1 – 167.6	1.01	-0.05 – 2.36
Amines	20	96.6	31.1 – 141.6	0.25	-0.92 – 1.64
Boronic acids	15	121.6	59.8 – 157.3	0.90	-0.49 – 2.16

Properties of the previous medicinal chemistry capping groups used for the derivatisation of the virtual scaffolds. These properties are based on the capping group itself.

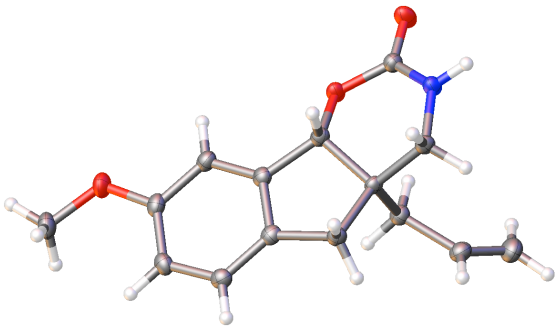
X-Ray Structure Data

ORTEP diagram of 149a (CCDC 1566497)



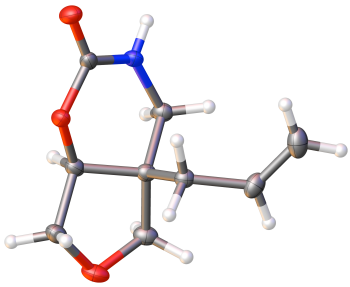
Crystal data and structure refinement for 149a	
Empirical formula	$C_{14}H_{25}NO_4$
Formula weight	271.35
Temperature/K	120.01(19)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	11.04739(18)
b/Å	12.2038(2)
c/Å	10.96322(18)
α/°	90.00
β/°	91.7913(16)
γ/°	90.00
Volume/Å^3	1477.35(4)
Z	4
ρ_{calc}g/cm^3	1.220
μ/mm^{-1}	0.721
F(000)	592.0
Crystal size/mm^3	0.21 × 0.12 × 0.09
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	8 to 147.5
Index ranges	-9 ≤ h ≤ 13, -14 ≤ k ≤ 14, -13 ≤ l ≤ 13
Reflections collected	6401
Independent reflections	2882 [R_{int} = 0.0214, R_{sigma} = 0.0256]
Data/restraints/parameters	2882/0/175
Goodness-of-fit on F^2	1.052
Final R indexes [I>=2σ (I)]	R_1 = 0.0374, wR_2 = 0.0880
Final R indexes [all data]	R_1 = 0.0435, wR_2 = 0.0918
Largest diff. peak/hole / e Å^{-3}	0.29/-0.19

ORTEP diagram of 150c (CCDC 1566499)



Crystal data and structure refinement for 150c	
Empirical formula	$C_{15}H_{17}NO_3$
Formula weight	259.29
Temperature/K	119.97(16)
Crystal system	triclinic
Space group	P-1
a/Å	6.7483(5)
b/Å	9.9314(7)
c/Å	11.0967(8)
α/°	63.764(7)
β/°	79.148(6)
γ/°	74.800(6)
Volume/Å^3	641.49(9)
Z	2
ρ_{calc}g/cm^3	1.342
μ/mm^{-1}	0.762
F(000)	276.0
Crystal size/mm^3	0.15 × 0.08 × 0.06
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	8.916 to 147.94
Index ranges	-8 ≤ h ≤ 7, -12 ≤ k ≤ 10, -13 ≤ l ≤ 12
Reflections collected	4223
Independent reflections	2397 [R_{int} = 0.0277, R_{sigma} = 0.0391]
Data/restraints/parameters	2397/0/173
Goodness-of-fit on F^2	1.028
Final R indexes [I>=2σ (I)]	R_1 = 0.0379, wR_2 = 0.0941
Final R indexes [all data]	R_1 = 0.0450, wR_2 = 0.0996
Largest diff. peak/hole / e Å^{-3}	0.35/-0.22

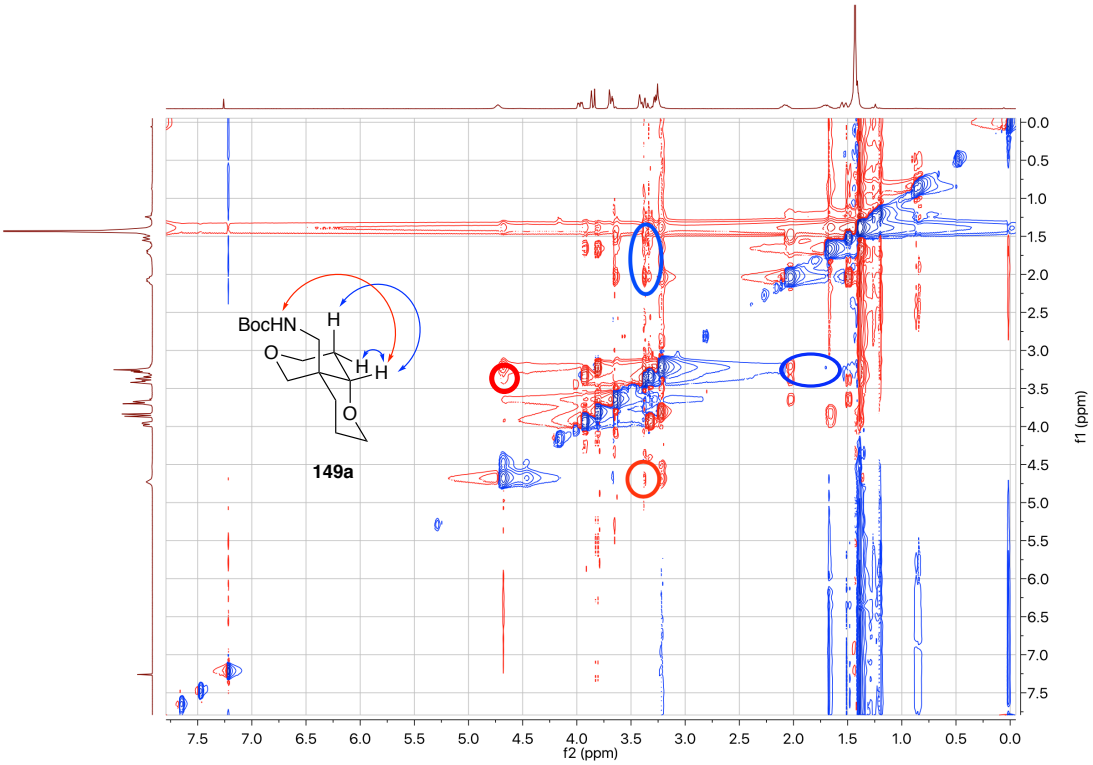
ORTEP diagram of 150d (CCDC 1566498)

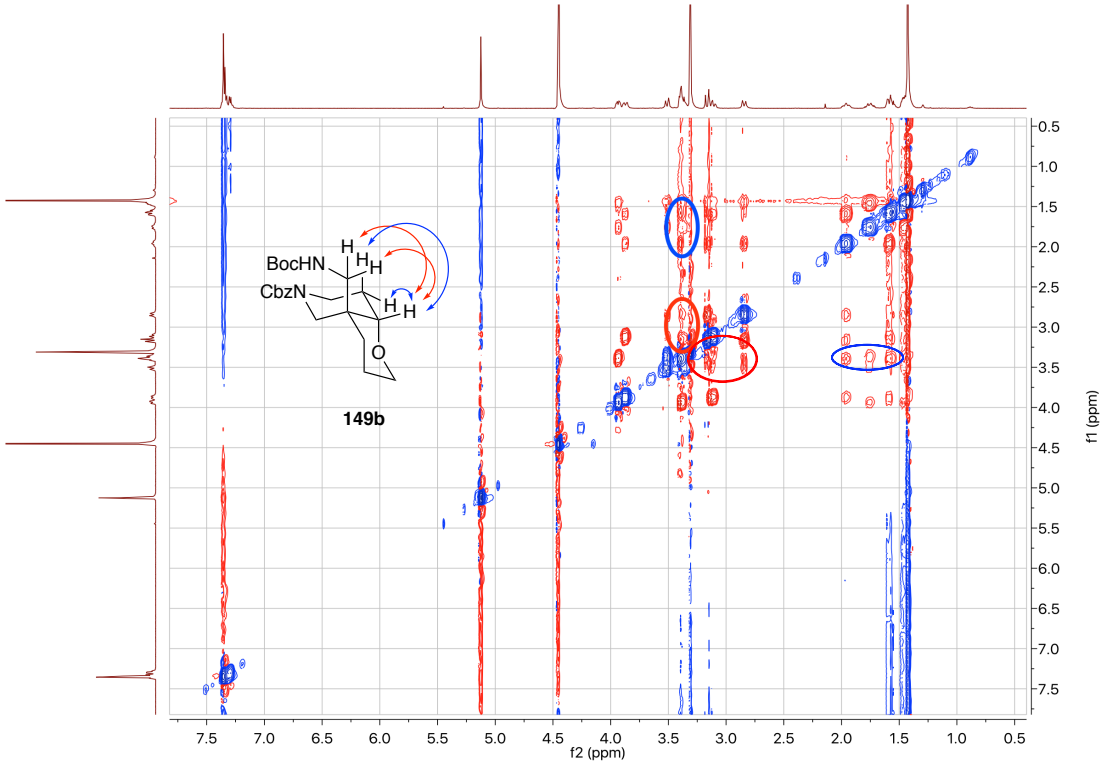


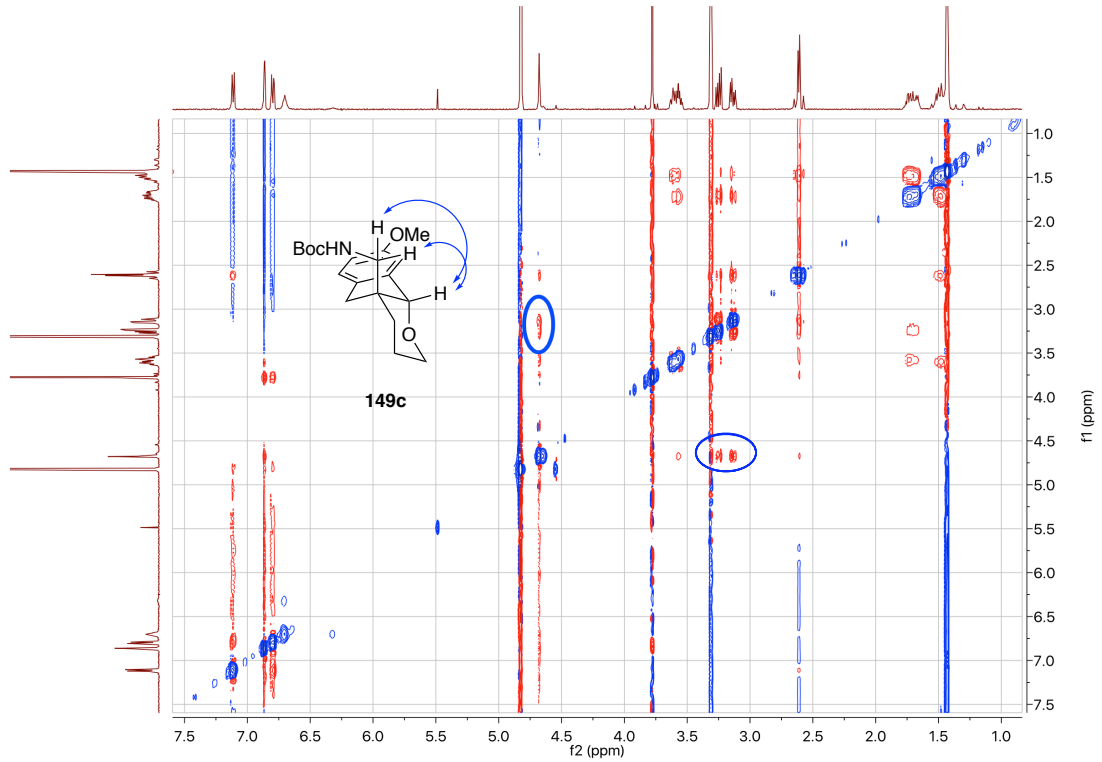
Crystal data and structure refinement for 150d	
Empirical formula	$C_9H_{13}NO_3$
Formula weight	183.20
Temperature/K	120.01(10)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	7.65800(10)
b/Å	9.53160(10)
c/Å	12.1849(2)
α/°	90
β/°	94.8050(10)
γ/°	90
Volume/Å^3	886.29(2)
Z	4
ρ_{calc}g/cm^3	1.373
μ/mm^{-1}	0.859
F(000)	444.0
Crystal size/mm^3	0.48 × 0.28 × 0.26
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	11.596 to 147.354
Index ranges	-8 ≤ h ≤ 9, -8 ≤ k ≤ 11, -14 ≤ l ≤ 15
Reflections collected	4943
Independent reflections	1726 [R_{int} = 0.0130, R_{sigma} = 0.0130]
Data/restraints/parameters	1726/0/118
Goodness-of-fit on F^2	1.072
Final R indexes [I>=2σ (I)]	R_1 = 0.0315, wR_2 = 0.0799
Final R indexes [all data]	R_1 = 0.0339, wR_2 = 0.0817
Largest diff. peak/hole / e Å^{-3}	0.31/-0.19

NOESY Spectra

NOESY Spectra with the nOe enhancements:



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H
H
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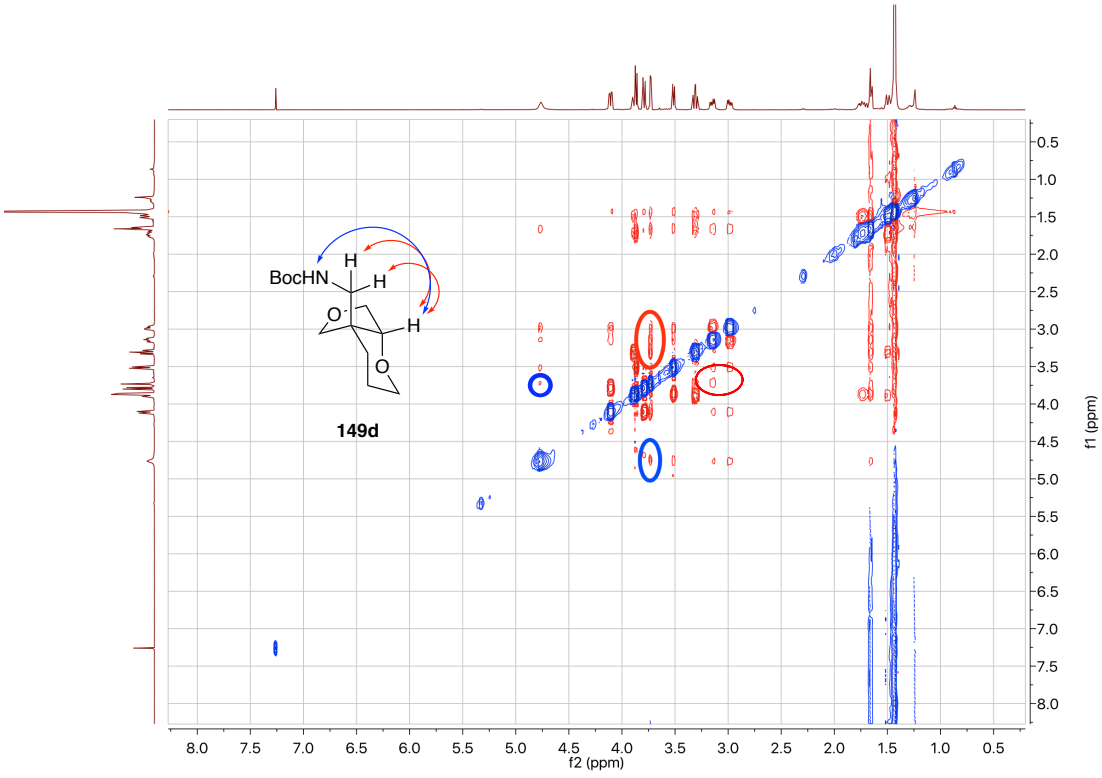
f1 (ppm)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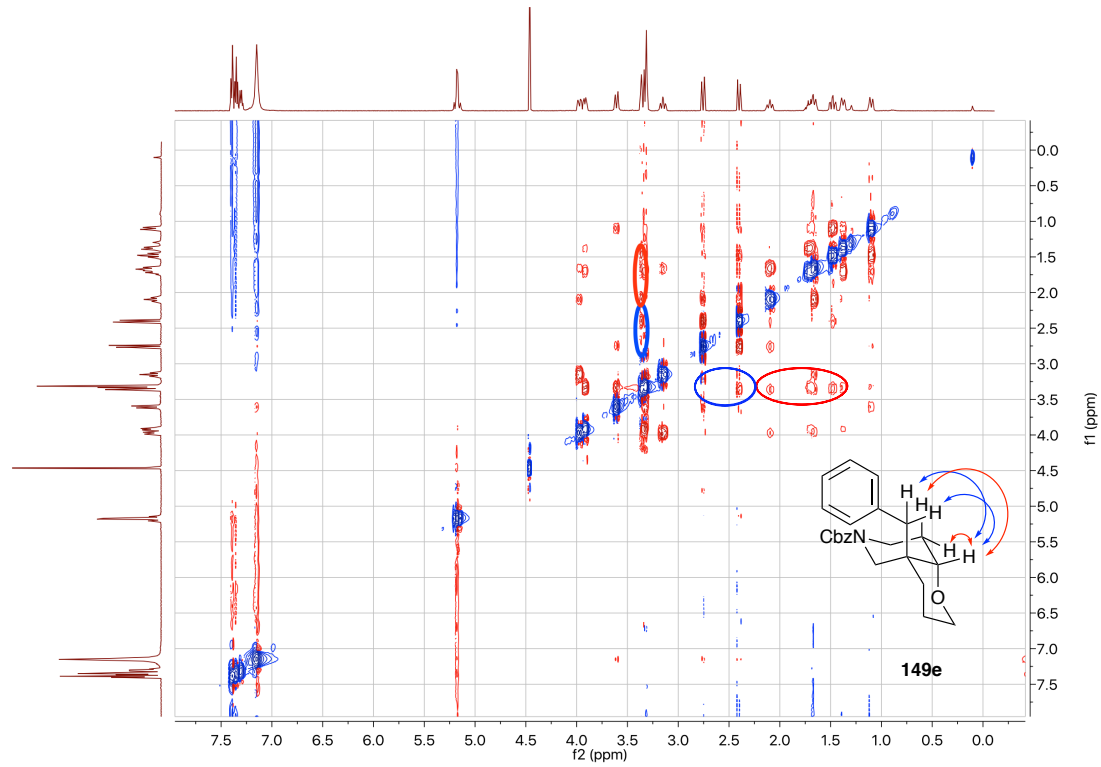
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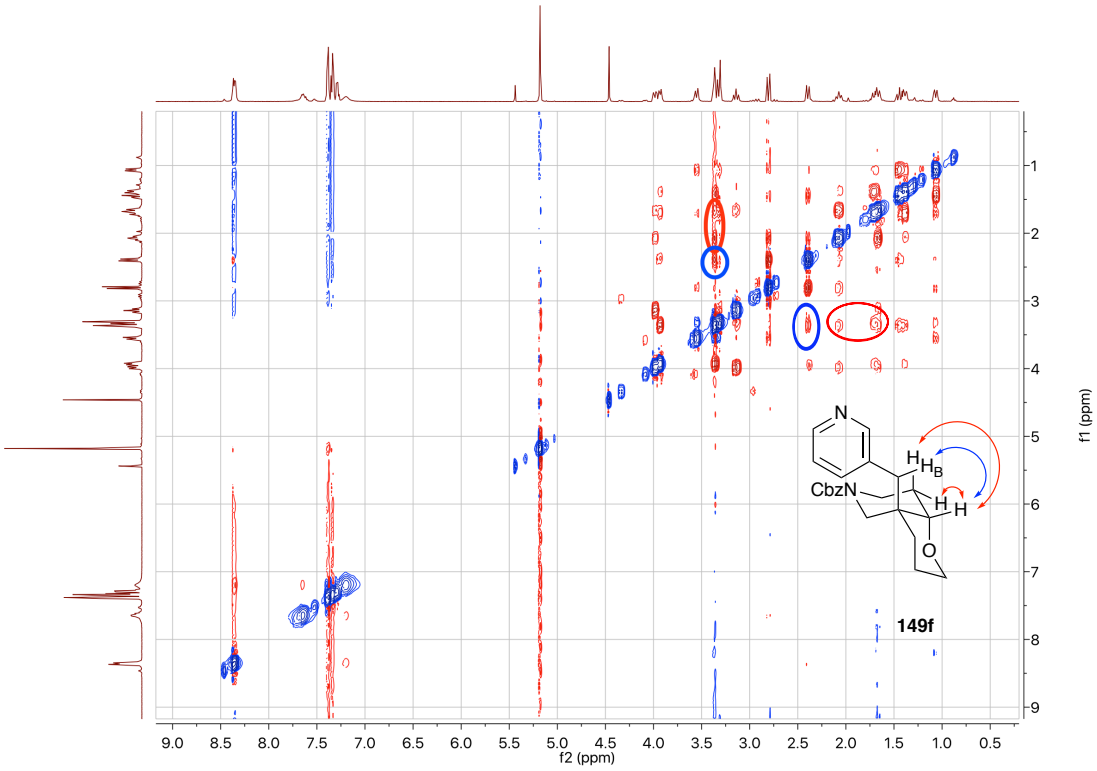
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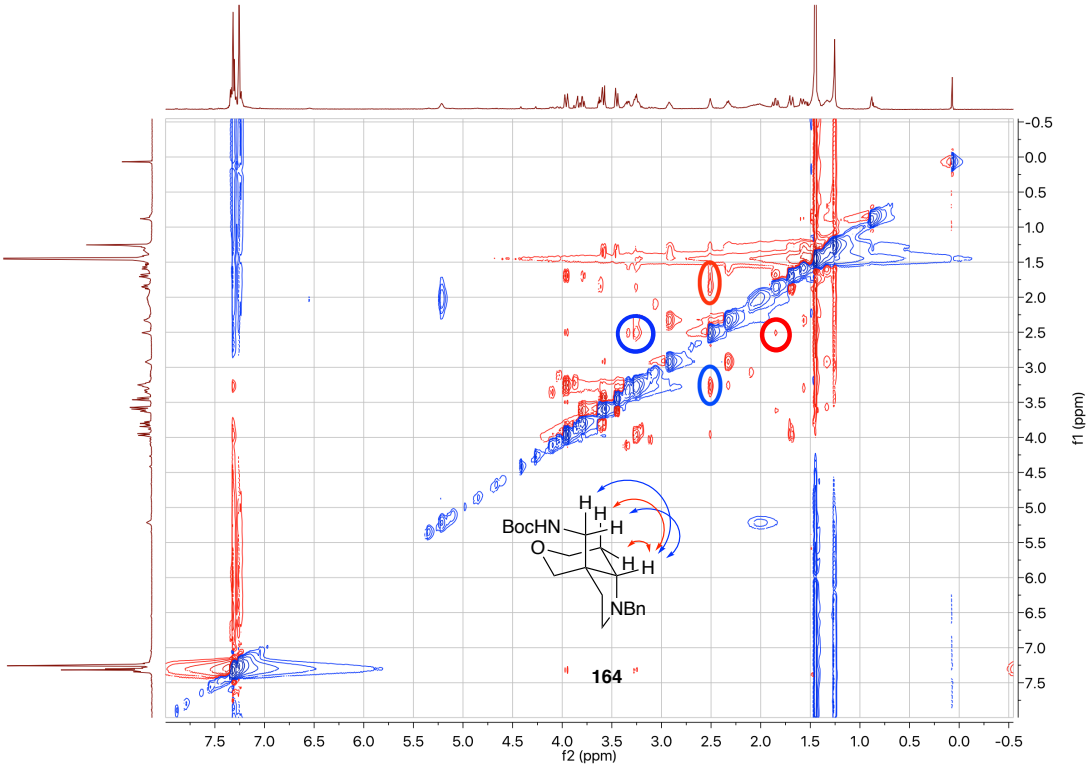
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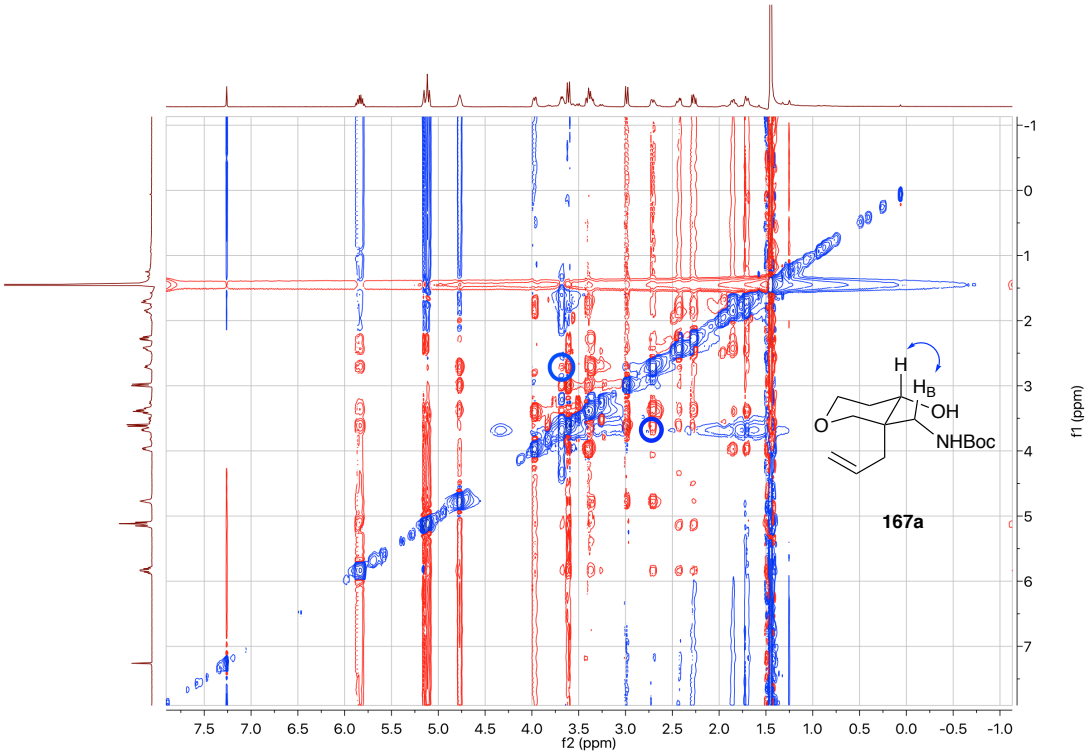
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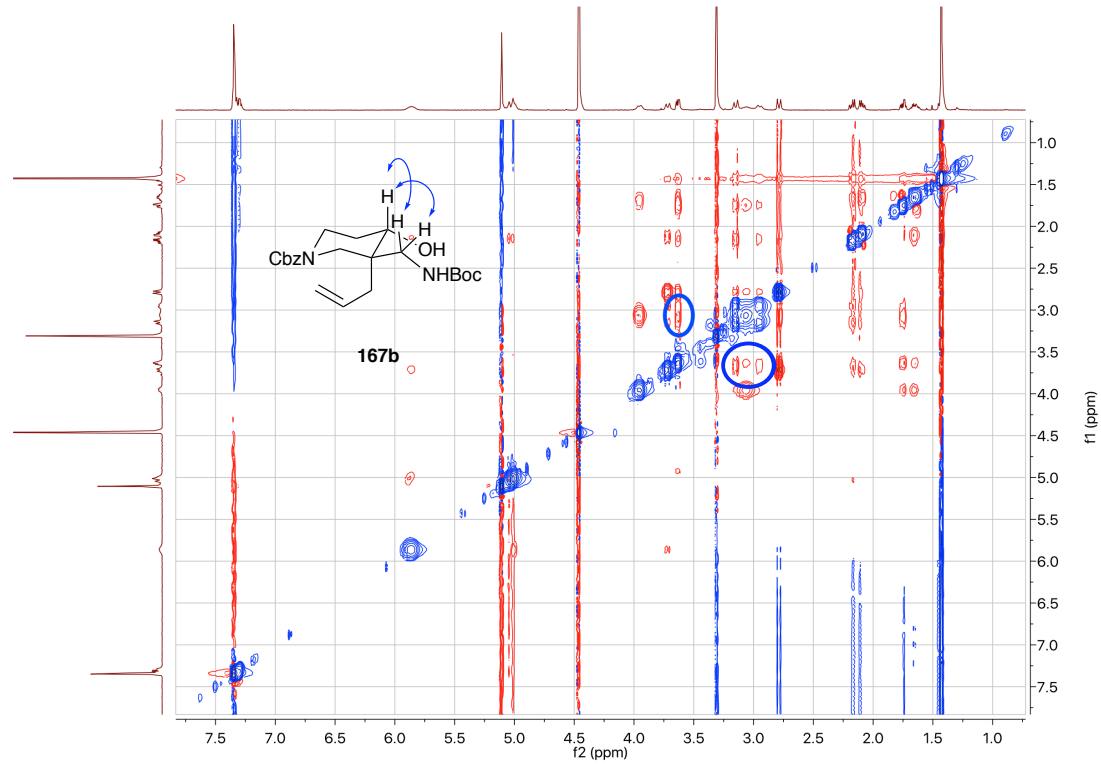
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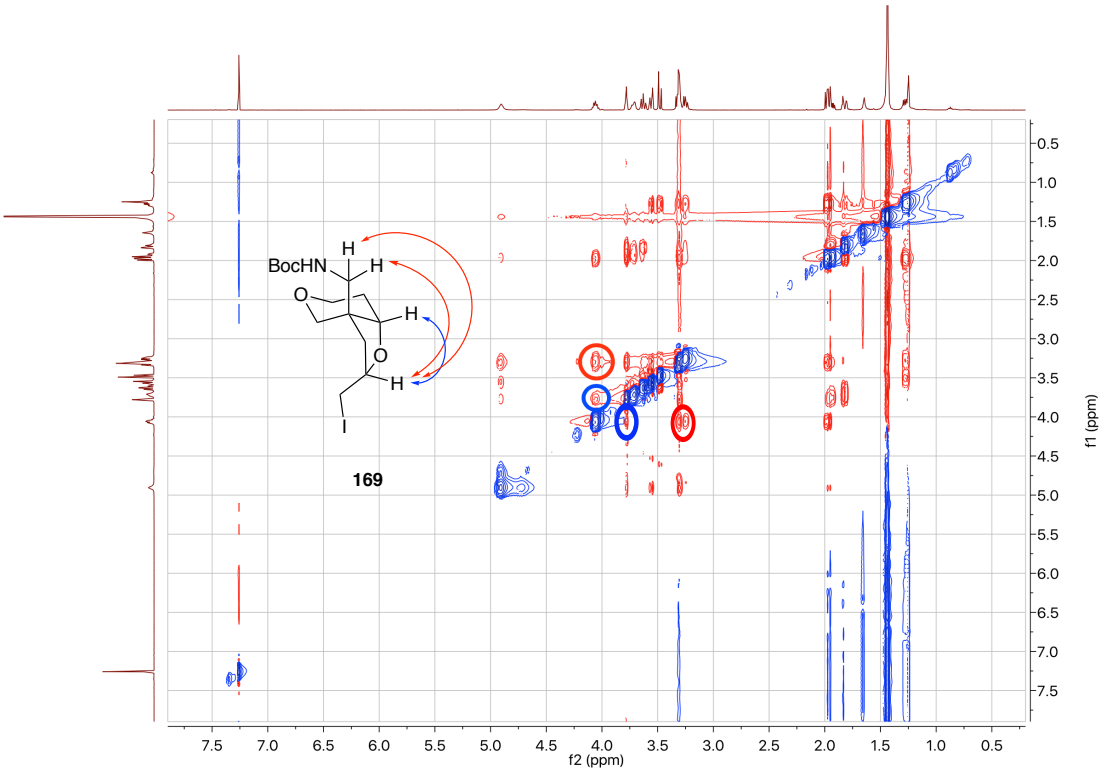
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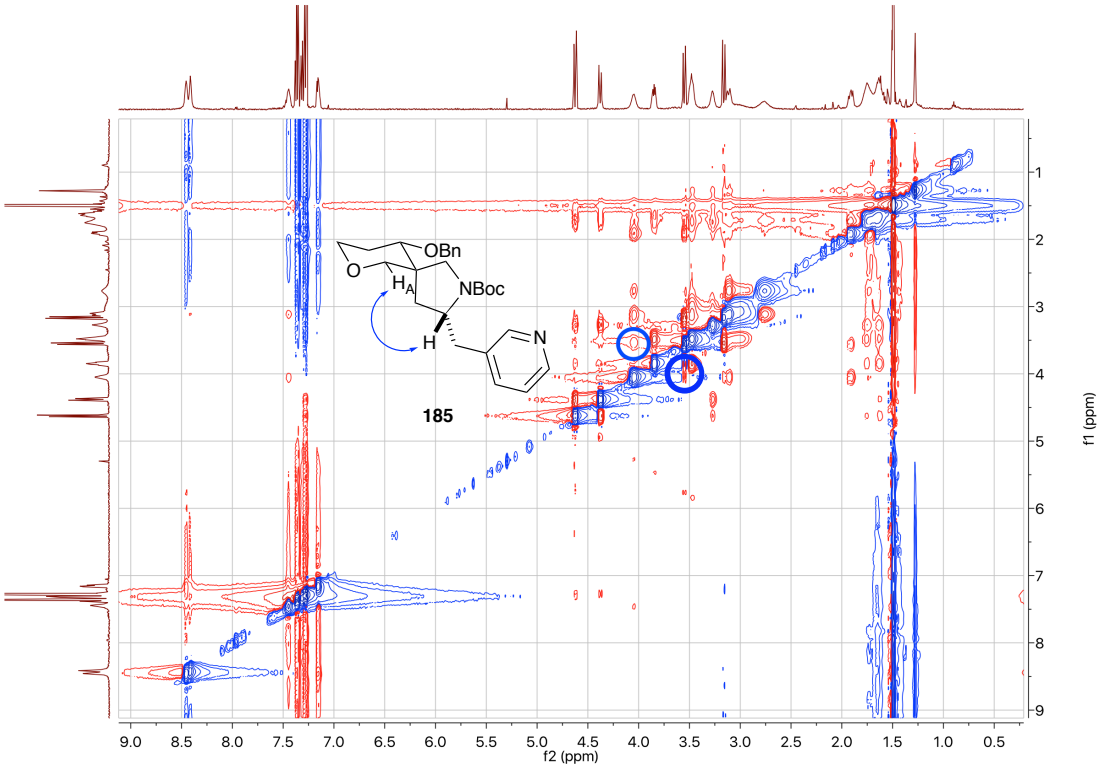
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N
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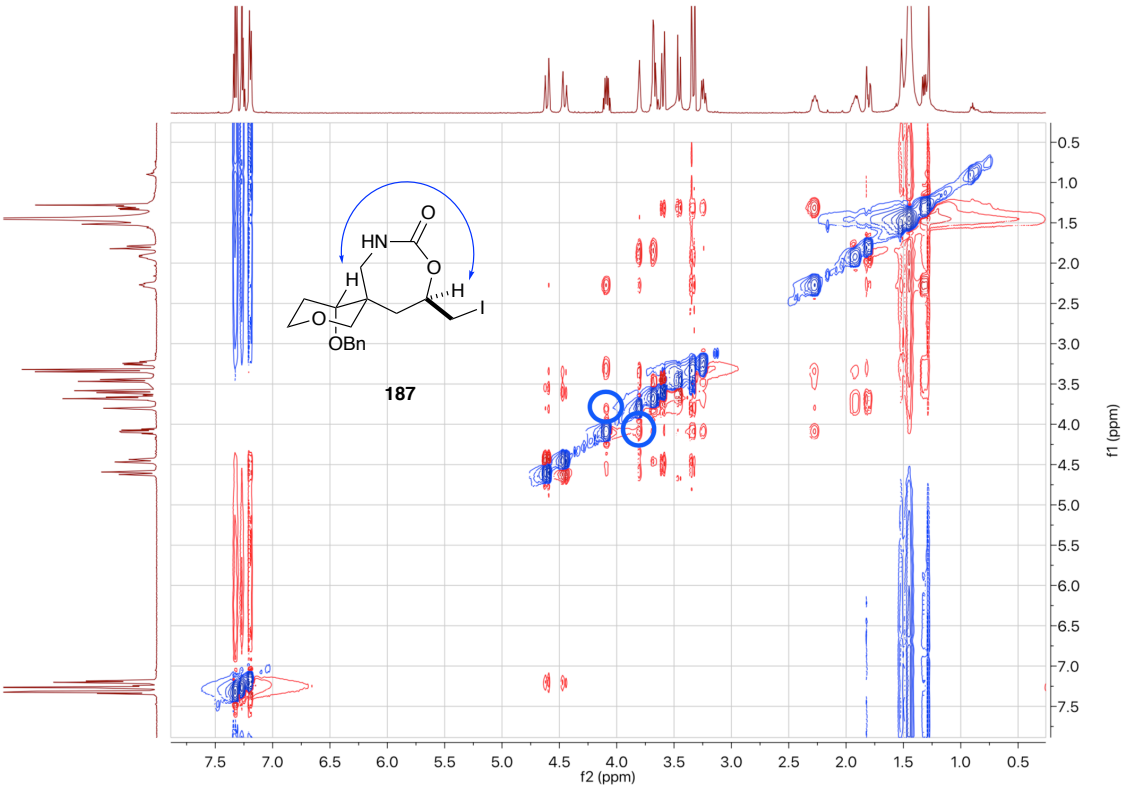
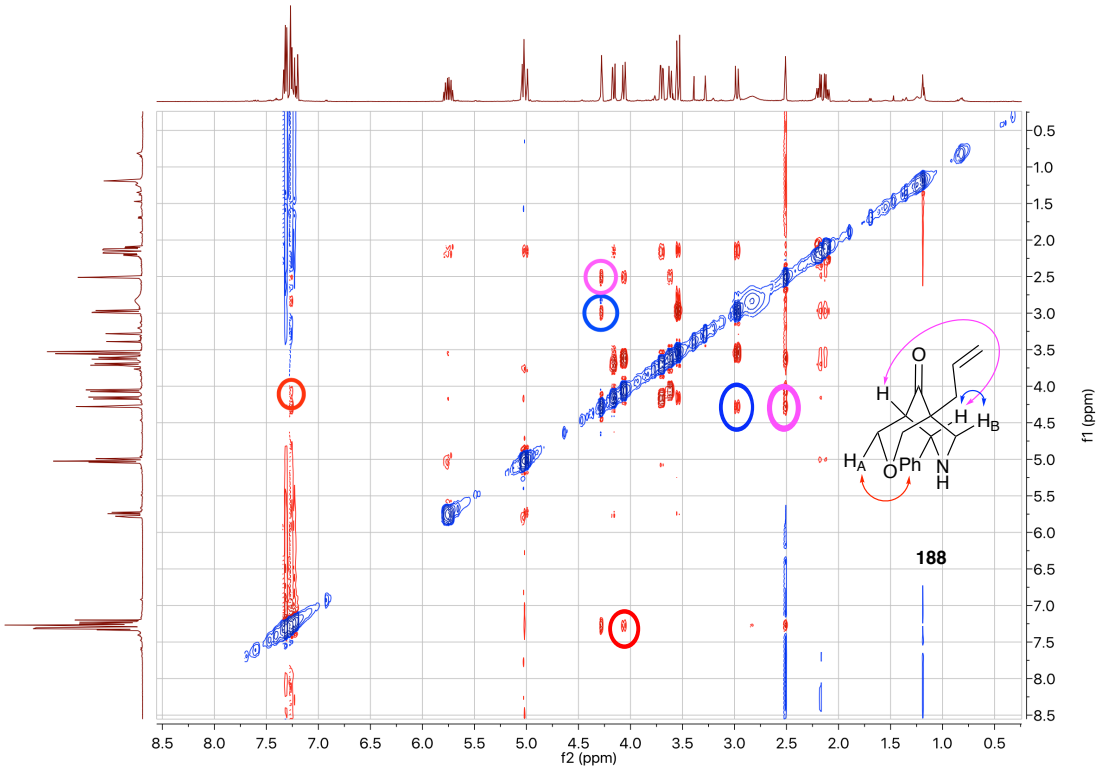
f2 (ppm)
f1 (ppm)


HN
O
O
H
H
O
I
OBn
187
f2 (ppm)
f1 (ppm)


f2 (ppm)
f1 (ppm)
188
O
H
H
H
H
H
A
B
O
Ph
N
H

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