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

Joan Mayol Llinàs

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

The University of Leeds

School of Chemistry

March 2018
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:

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:

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.

This copy has been supplied on the understanding that it is copyright material and that no quotation from the thesis may be published without proper acknowledgement.

© 2018 The University of Leeds and Joan Mayol Llinàs.

The right of Joan Mayol Llinàs to be identified as Author of this work has been asserted by him in accordance with the Copyright, Designs and Patents Act 1988.
Acknowledgements

I am really glad to have arrived to this stage of my life, but I am also sad to be leaving behind a fantastic group that I will always remember. Studying a PhD and living abroad is not always easy. However, my time in Leeds has been great. I have improved myself in so many aspects, as a scientist and as a person. I have learned a lot about organic chemistry and chemical biology and I have made great friends in and outside of the laboratory.

Firstly, I would really like to thank my supervisor Prof. Adam Nelson for accepting me as a PhD student in his group. Thanks to him all of this has been possible. He gave me the project I was looking for, which combines synthetic chemistry with computational chemistry. Consequently, I have been very motivated during my PhD trying to do my best. In addition, he has always been happy to help at any time and he has always been trying to encourage me to attend national and international conferences and to publish my work in high-quality journals. I really appreciate all his efforts during the last years. I have been very lucky to do my PhD in his group. I would also like to thank my second supervisor William Farnaby. He has been a great industrial supervisor. He has always been involved in the project since the beginning until the end. He has always been willing to help and I really appreciate all his efforts and time invested in my project. I also thank you the University of Leeds and Takeda Cambridge for funding my PhD.

Secondly, a big thank you to all the great postdocs who have been in the group during my PhD. In my first years I would especially like to thank Richard Doveston, James Firth and Phil Craven. Richard Doveston introduced me to the laboratory and helped me to start my project. James Firth and Phil Craven deserve a huge thank you for all their support. They helped me a lot with my project and taught me a lot of chemistry with the “Big School Board”. Thanks to them my project has been possible. I will always remember the good times in the lab (9-BBN, the tale of the turtle, the emails, change of backgrounds…) and the less good ones (NaH). Thank you very much also to the postdocs who joined the group during my last years, especially to Shiao Chow and Tom James. Thanks to Shiao I learned from the best how to perform biological assays. Thanks to Tom I have learned some high-level chemistry with his great
problem sessions.

Also thank you very much to all the other PhD students who have shared their time with me, starting with Steven Kane and Rong Zhang. Thanks Steven for all the help during my first year and all the great moments playing squash and in the pub. Thanks Rong for all these day trips around the north of England and the fantastic cakes. Thanks of course to the ADS duo Jacob Masters (Masters chef) and Sam Liver (Sal). Sorry for confusing your names and calling you “Jasal”. However, it was great sharing our lives for few years. The lab without you two would not have been the same. You two are great guys! Thanks as well to the other PhD students Adam Green and Chloe Townley. Adam for being able to sit next to me for all these years and his great suggestions during my assays. Chloe for proofreading this thesis, sharing great moments in the lab with the “Foo Fighters” and being always positive. She is TBGE! Also, thank you to the fresher PhD students Luke Trask (nice gin and tonic with orange mate) Chris Arter (your freak videos are very interesting), Scott Rice (great secret santa) and Abbie Leggott (great conversations). Also, to Ravi Singh, a guy who has always made me laugh with his great Spanish and pK_a knowledge. Outside the lab, I would like to thank Anjo Lapitan and Maria Kwan for all the great dinners, and Charlene Jordan for always keeping in touch. Also, thank you very much to Catherine Gu for all the great times.

Finalment, m’agradaria agraïr a la meva família per tot l’esforç gastat amb la meva educació. Sempre m’han donat suport i gràcies a ells he pogut arribar fins aquí. Al principi no ho veia clar i anava equivocat però gràcies a tots els seus consells he elegit el camí correcte. No m’en penedeixo i n’estic ben content! Estic molt orgullós dels pares que tinc.

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

Declaration iii  
Acknowledgements v  
Abstract vii  
Contents viii  
Abbreviations & Symbols xi  

### Chapter 1: Importance of Molecular Properties in CNS Drug Discovery  

1.1. Introduction 1  
1.2. The Drug Discovery Process 1  
1.3. The Productivity Decline in Pharmaceutical R&D 3  
1.4. Physicochemical Properties of Drugs 6  
  1.4.1. Physicochemical Properties in the Design of Oral Drugs 7  
  1.4.2. Physicochemical Properties in the Design of CNS-Drugs 9  
1.5. Diversity- and Lead-Oriented Synthesis 15  
1.6. Molecular Scaffolds for the Design of Lead-like Molecules 19  
  1.6.1. CNS Relevant Molecular Scaffolds 20  
1.7. Conclusions 21  
1.8. Project Outline 21  

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

2.1. Development of the Computational Tool 24  
  2.1.1. Enumeration of Virtual Libraries 25  
  2.1.2. Filtering of the Virtual Libraries 26  
  2.1.3. Calculation of the Physicochemical Properties and Scoring 28  
  2.1.4. Novelty Assessment 30  
  2.1.5. Summary of Results 31  
2.2. Validation of the Computational Tool 31  
2.3. Exemplification of the Computational Tool 36  
  2.3.1. Identification of a Lead-Oriented Synthesis Approach Based on an Ir-catalysed Connective Reaction 37  
  2.3.2. Application of the Computational Tool 38  
  2.3.3. Preparation of Scaffolds 42  
    2.3.3.1. Synthesis of Cyclisation Precursors 42
2.3.3.1. Preparation of Building Blocks 42
2.3.3.1.2. Connective Reactions 44
  2.3.3.1.2.1. Ir-catalysed Asymmetric Allylic Substitution 44
2.3.3.2. Cyclisation Reactions 47
  2.3.3.2.1. Pd-catalysed Aminoarylation 47
2.3.4. Experimental Determination of Permeability 49
2.4. Summary and Conclusions 50

Chapter 3: Development of a Modular Approach for the Synthesis of Scaffolds Relevant to CNS Drug Discovery 52
3.1. Identification of a Lead-Oriented Synthesis Approach Based on a Mannich/Alkylation and a Pd-catalysed Connective Reactions 52
3.2. Synthesis of Cyclisation Precursors 53
  3.2.1. Preparation of Building Blocks 53
  3.2.2. Connective Reactions 56
    3.2.2.1. Mannich/Alkylation Reaction 56
    3.2.2.2. Pd-catalysed Decarboxylative Allylic Alkylation 58
  3.2.3. Summary and Conclusions 60
3.3. Investigation of the Scope of the Cyclisation Reactions and Synthesis of Scaffolds 60
  3.3.1. Cyclisation Reactions Between the Ketone and the Alkene 61
  3.3.2. Cyclisation Reactions Between the Ketone and the NHBoc 73
  3.3.3. Cyclisation Reactions Between the Alkene and the NHBoc 75
  3.3.4. Cyclisation Reactions Between the NHBoc and the \( \alpha \)-position of the Ketone 87
  3.3.5. Summary of Results 88
3.4. Application of the Computational Tool 93
3.5. Conclusions 95

Chapter 4: Realising the Biological Relevance of the Developed Scaffolds for CNS Drug Discovery 97
4.1. Ligand Discovery Against BACE1 97
4.2. Decoration of the Scaffolds 99
4.3. Evaluation of the Biological Activity 104
4.4. Conclusions and Future Perspectives 108

Chapter 5: Methods & Materials 111
5.1. Design of the Computational Tool
5.2. Synthesis and Decoration of the Scaffolds
   5.2.1. General Experimental
   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
      5.2.2.2. Connective Reactions
      5.2.2.3. Cyclisation Reactions
   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
      5.2.3.2. Connective Reactions
      5.2.3.3. Cyclisation Reactions
   5.2.4. Experimental for the Decoration of the Scaffolds
      5.2.4.1. Preparation of the BACE1 Capping Group
      5.2.4.2. Decoration of the Scaffolds
   5.3. Experimental for the Determination of the Biological Activity
Appendix
Library of Virtual Medicinal Chemistry Capping Groups
X-Ray Structure Data
NOESY Spectra
References
## Abbreviations & Symbols

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$[\alpha_0]$</td>
<td>Optical rotation</td>
</tr>
<tr>
<td>9-BBN</td>
<td>9-Borabicyclo[3.3.1]nonane</td>
</tr>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>ADMET</td>
<td>Absorption, distribution, metabolism, elimination, toxicity</td>
</tr>
<tr>
<td>app</td>
<td>Apparent</td>
</tr>
<tr>
<td>APP</td>
<td>Amyloid precursor protein</td>
</tr>
<tr>
<td>Aq</td>
<td>Aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>Aromatic</td>
</tr>
<tr>
<td>Asp</td>
<td>Aspartic acid</td>
</tr>
<tr>
<td>b.p.</td>
<td>Boiling point</td>
</tr>
<tr>
<td>BACE1</td>
<td>$\beta$-Site amyloid precursor protein cleaving enzyme 1</td>
</tr>
<tr>
<td>BBB</td>
<td>Blood-brain barrier</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-Butyloxycarbonyl</td>
</tr>
<tr>
<td>br</td>
<td>Broad</td>
</tr>
<tr>
<td>Bu</td>
<td>Butyl</td>
</tr>
<tr>
<td>Bz</td>
<td>Benzoyl</td>
</tr>
<tr>
<td>c</td>
<td>Concentration</td>
</tr>
<tr>
<td>cat</td>
<td>Catalysed, catalytic</td>
</tr>
<tr>
<td>Cbz</td>
<td>Carboxybenzyl</td>
</tr>
<tr>
<td>CCDC</td>
<td>Cambridge crystallographic data centre</td>
</tr>
<tr>
<td>CDI</td>
<td>Carbonyldiimidazole</td>
</tr>
<tr>
<td>clogD</td>
<td>Calculated logarithm of the coefficient of partition octanol:water of a molecule at specific pH</td>
</tr>
<tr>
<td>clogD$_{7.4}$</td>
<td>Calculated logarithm of the coefficient of partition octanol:water of a molecule at pH 7.4</td>
</tr>
<tr>
<td>clogP</td>
<td>Calculated logarithm of the coefficient of partition octanol:water of a neutral molecule</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>cod</td>
<td>1,5-Cyclooctadiene</td>
</tr>
<tr>
<td>COSY</td>
<td>Correlation spectroscopy</td>
</tr>
<tr>
<td>d</td>
<td>Doublet</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>dba</td>
<td>Dibenzylideneacetone</td>
</tr>
<tr>
<td>dbcot</td>
<td>Dibenzo[a,e]cyclooctatriene</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-Diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>DEAD</td>
<td>Diethyl azodicarboxylate</td>
</tr>
<tr>
<td>DEPT</td>
<td>Distortionless enhancement of polarisation transfer</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>Diisobutylaluminium hydride</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-Dimethylamino pyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>Dimethylformamide</td>
</tr>
<tr>
<td>DMS</td>
<td>Dimethyl sulfide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide</td>
</tr>
<tr>
<td>DOS</td>
<td>Diversity-oriented synthesis</td>
</tr>
<tr>
<td>DPE-Phos</td>
<td>Bis-[2-(diphenylphosphino)phenyl]ether</td>
</tr>
<tr>
<td>dr</td>
<td>Diastereomeric ratio</td>
</tr>
<tr>
<td>ee</td>
<td>Enantiomeric excess</td>
</tr>
<tr>
<td>em</td>
<td>Emission</td>
</tr>
<tr>
<td>eq</td>
<td>Equivalents</td>
</tr>
<tr>
<td>ES</td>
<td>Electrospray</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>ex</td>
<td>Excitation</td>
</tr>
<tr>
<td>Exp</td>
<td>Experimental</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and drug administration</td>
</tr>
<tr>
<td>Gly</td>
<td>Glycine</td>
</tr>
<tr>
<td>HBA</td>
<td>Hydrogen bond acceptors</td>
</tr>
<tr>
<td>HBD</td>
<td>Hydrogen bond donors</td>
</tr>
<tr>
<td>hERG</td>
<td>Human ether-a-go-go-related gene</td>
</tr>
<tr>
<td>HMQC</td>
<td>Heteronuclear multiple quantum coherence</td>
</tr>
<tr>
<td>HPLC</td>
<td>High-pressure liquid chromatography</td>
</tr>
<tr>
<td>HRMS</td>
<td>High-resolution mass spectrometry</td>
</tr>
<tr>
<td>HTS</td>
<td>High throughput screening</td>
</tr>
<tr>
<td>IC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>Concentration of ligand to achieve 50% inhibition</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared</td>
</tr>
<tr>
<td>J</td>
<td>Coupling constant</td>
</tr>
<tr>
<td>K&lt;sub&gt;d&lt;/sub&gt;</td>
<td>Dissociation constant</td>
</tr>
<tr>
<td>LC-MS</td>
<td>Liquid chromatography-mass spectrometry</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>LDA</td>
<td>Lithium diisopropylamide</td>
</tr>
<tr>
<td>LiHMDS</td>
<td>Lithium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>LLAMA</td>
<td>Lead-likeness and molecular analysis</td>
</tr>
<tr>
<td>LogBBB</td>
<td>Logarithm of the coefficient of partition brain: blood of a molecule</td>
</tr>
<tr>
<td>LOS</td>
<td>Lead-oriented synthesis</td>
</tr>
<tr>
<td>m</td>
<td>multiplet</td>
</tr>
<tr>
<td>m.p.</td>
<td>Melting point</td>
</tr>
<tr>
<td>m/z</td>
<td>Mass to charge ratio</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
</tr>
<tr>
<td>MPO</td>
<td>Multi-parameter optimisation</td>
</tr>
<tr>
<td>Ms</td>
<td>Methanesulfonyl</td>
</tr>
<tr>
<td>MTPA-Cl</td>
<td>3,3,3-Trifluoro-2-methoxy-2-phenylpropanoyl chloride, Mosher’s acid chloride</td>
</tr>
<tr>
<td>MW</td>
<td>Molecular weight</td>
</tr>
<tr>
<td>NBS</td>
<td>N-Bromosuccinimide</td>
</tr>
<tr>
<td>NME</td>
<td>New molecular entity</td>
</tr>
<tr>
<td>NMO</td>
<td>N-Methylmorpholine-N-oxide</td>
</tr>
<tr>
<td>NMP</td>
<td>N-Methyl-2-pyrrolidone</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>nOe</td>
<td>Nuclear overhauser effect</td>
</tr>
<tr>
<td>NOESY</td>
<td>Nuclear overhauser effect spectroscopy</td>
</tr>
<tr>
<td>NR</td>
<td>No referred</td>
</tr>
<tr>
<td>Ns</td>
<td>4-Nitrobenzenesulfonyl</td>
</tr>
<tr>
<td>Nu</td>
<td>Nucleophile</td>
</tr>
<tr>
<td>ORTEP</td>
<td>Oak ridge thermal-ellipsoid plot program</td>
</tr>
<tr>
<td>P-gp</td>
<td>P-Glycoprotein</td>
</tr>
<tr>
<td>PAMPA</td>
<td>Parallel artificial membrane permeability assay</td>
</tr>
<tr>
<td>( P_{\text{app}} )</td>
<td>Apparent permeability coefficient</td>
</tr>
<tr>
<td>PDB</td>
<td>Protein data bank</td>
</tr>
<tr>
<td>PDC</td>
<td>Pyridinium dichromate</td>
</tr>
<tr>
<td>Petrol</td>
<td>Petroleum spirit (boiling point 40–60 °C)</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>pH</td>
<td>Potential of hydrogen</td>
</tr>
<tr>
<td>( pK_a )</td>
<td>Logarithm of the acid dissociation constant</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>PMB</td>
<td>4-Methoxybenzyl ether</td>
</tr>
<tr>
<td>PS</td>
<td>Permeability surface–area product</td>
</tr>
<tr>
<td>PSA</td>
<td>Polar surface area</td>
</tr>
<tr>
<td>Pyr</td>
<td>Pyridine</td>
</tr>
<tr>
<td>q</td>
<td>quartet</td>
</tr>
<tr>
<td>R&amp;D</td>
<td>Research and development</td>
</tr>
<tr>
<td>RB</td>
<td>Rotatable bonds</td>
</tr>
<tr>
<td>Ref</td>
<td>Reference</td>
</tr>
<tr>
<td>$R_f$</td>
<td>Retention factor</td>
</tr>
<tr>
<td>rt</td>
<td>Room temperature</td>
</tr>
<tr>
<td>s</td>
<td>Singlet</td>
</tr>
<tr>
<td>SCX</td>
<td>Strong cation exchange</td>
</tr>
<tr>
<td>SEM</td>
<td>Standard error mean</td>
</tr>
<tr>
<td>$S_N$</td>
<td>Nucleophilic substitution</td>
</tr>
<tr>
<td>SPE</td>
<td>Solid phase extraction</td>
</tr>
<tr>
<td>t</td>
<td>Triplet</td>
</tr>
<tr>
<td>$T:I$</td>
<td>Ratio terminal alkene:internal alkene</td>
</tr>
<tr>
<td>TBA</td>
<td>Tetrabutylammonium</td>
</tr>
<tr>
<td>TBD</td>
<td>1,5,7-Triazabicyclo[4.4.0]dec-5-ene</td>
</tr>
<tr>
<td>TBDPS</td>
<td>tert-Butyldiphenylsilyl</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-Butyldimethylsilyl</td>
</tr>
<tr>
<td>^{t}Bu</td>
<td>tert-Butyl</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>Thr</td>
<td>Threonine</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethylsilane</td>
</tr>
<tr>
<td>TPAP</td>
<td>Tetrapropylammonium perruthenate</td>
</tr>
<tr>
<td>Ts</td>
<td>$p$-toluenesulfonyl</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>$\delta$</td>
<td>Chemical shift</td>
</tr>
<tr>
<td>$\lambda$</td>
<td>Wavelength</td>
</tr>
<tr>
<td>$\mu$W</td>
<td>Microwave</td>
</tr>
<tr>
<td>v</td>
<td>Wavenumber</td>
</tr>
</tbody>
</table>


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.\textsuperscript{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.\textsuperscript{8} One of the reasons is that drug candidates have poor ADMET (absorption, distribution, metabolism, excretion and toxicity) properties.\textsuperscript{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.\textsuperscript{8,10} Different \textit{in silico} methodologies have been developed to control the physicochemical properties during the lead optimisation stage.\textsuperscript{9,11,12}

However, there is a low success in the development of drugs for diseases of the central nervous system (CNS).\textsuperscript{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. \textit{In silico} MPO (multi-parameter optimisation) systems\textsuperscript{15,16} and synthetic methodologies like lead-oriented synthesis (LOS)\textsuperscript{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).\textsuperscript{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.\textsuperscript{19–21} The biological targets include enzymes, receptors, ion channels and nucleic acids.\textsuperscript{22,23} Once the target is
identified, it is validated to prove that its modulation can give the desired response.\textsuperscript{19–21} Subsequently, research for small molecules that are able to modulate its activity starts.

![Diagram of the drug discovery process](image)

**Figure 1:** Stages of the drug discovery process. Adapted from references.\textsuperscript{11,18}

Small bioactive molecules are usually identified via high throughput screening (HTS).\textsuperscript{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,\textsuperscript{26} which can be developed to generate leads.\textsuperscript{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.\textsuperscript{23} For this reason, when a lead is generated, different studies \textit{in silico} and \textit{in vitro} are performed to optimise its potency and safety profile.\textsuperscript{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).\textsuperscript{8,11}

![Diagram of the lead optimisation process](image)

**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 \textit{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{1,2,5–8,10,23,28–31}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{Total number of drugs approved per year by the FDA since 1950.\textsuperscript{6,30}}
\end{figure}

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.\textsuperscript{1,10,32} This fact can be explained by the patent cliff and by the low success in the drug discovery process.\textsuperscript{1,8} A high investment in time and costs is necessary to undertake every one of the drug discovery stages.\textsuperscript{33} The drug discovery process usually takes between 12–15 years and it can cost more than $1 billion.\textsuperscript{18} During the years 2009–2014, many patents of
current blockbuster drugs expired.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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).\textsuperscript{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.\textsuperscript{6}](image)

Increasing R&D efficiency in the drug discovery process is a difficult challenge.\textsuperscript{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\%.\textsuperscript{8,10} In addition, they are the longest stages.
Most drug candidates fail during clinical trials (66% of compounds fail in Phase II), when a high amount of time and cost has already been spent.

Failure in the last stages should be reduced. Drug candidates can fail during clinical trials due to different reasons such as lack of efficacy, lack of improvement and poor/unexpected ADMET profile. 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). 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).

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. Therefore, more effective research should be done during the early stages, especially during lead generation because this stage is much cheaper and shorter. 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. In the past, attention was not paid to the ADMET profile because the main objective was to increase the potency and selectivity of leads, as achieving nanomolar activity was the main goal. Consequently, many candidates passed the first stages but they failed during clinical trials. 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. 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. As a result, this selection of better leads could increase R&D efficiency. 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. 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. 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. 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. 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. There are different in silico models available. 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. clogP is a property that defines the lipophilicity of the molecule. 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 pKₐ. 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. Nevertheless, it has been said that clogP and clogD (lipophilicity) are the most important properties. The reason is because lipophilicity influences drug potency and the ADMET profile. Normally, a drug needs a balanced lipophilicity, if the lipophilicity is too high or too low the molecule will have a poor ADMET profile.

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. 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. These are PSA, which should
not be greater than 140 Å²; the number of rotatable bonds (RB), which should not be greater than 10;\textsuperscript{41} the clogD\textsubscript{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.\textsuperscript{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).\textsuperscript{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. Panel B: Example of some leads (left) and corresponding drugs (right). 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).](image)

Due to the increase in MW and clogP during the lead optimisation, leads should have more restricted molecular properties than their derived oral drugs.\textsuperscript{46,47} There are guidelines that suggest the preferred properties for leads.\textsuperscript{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 recommendations have been included, suggesting that leads should have fewer sp² carbons. Consequently, they should not have more than 3 aromatic rings.

In silico approaches have been widely used to control the physicochemical properties of leads during the lead generation stage. These approaches can help to identify leads with the desired efficacy and ADMET properties. The final ADMET profile of a molecule depends on the combination of all its physicochemical properties. The different physicochemical properties have to be optimised at the same time. Therefore, in silico multi-parameter optimisation (MPO) methodologies are used. The first models of these methodologies were usually pass/fail filters. 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. 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. 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. Currently, there is a low clinical success (8%) in the CNS drug discovery area compared with other therapeutic areas (Figure 7).
This low clinical success is due to the fact that the causes of CNS diseases are poorly understood.\textsuperscript{53} It is difficult to study drug candidates for CNS disorders due to lack of predictable animal disease models.\textsuperscript{8,13,28} Consequently, there are high fail rates in clinical trials due to lack of efficacy.\textsuperscript{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).

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. Consequently, most of molecules must pass through transcellular passive diffusion through cells, which are rich in enzymes that metabolise them. 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. 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. 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). 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. 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. 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. 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, classification trees 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).

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 Å², the number of RB should be not greater than 8 and the pK_a should be lower than 10.5. However, other publications\textsuperscript{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 Å³. In addition, it has been suggested that some substructures can negatively affect brain penetration.\textsuperscript{62} Substructures identified as undesired for brain penetration are
sulfonamides, sulfones, tetrazoles, amine N-oxides and carboxylic acids. 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. A library of desired substructures with an occurrence in CNS-drugs higher than 5% has been reported. 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. Therefore, many CNS-drugs are basic molecules. The rule-of-four guideline suggests the properties that CNS-drugs should have to avoid interaction with the P-gp. This guideline states that molecules should have MW lower than 400, number of N + O atoms lower than 4 and the most basic pKₐ should be lower than 8. In addition, it has also been suggested that to avoid P-gp recognition PSA should be lower than 60 Å². 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. Highly lipophilic drugs often produce liver toxicity due to interaction with the cytochrome P450 and cardiovascular toxicity due to inhibition of the hERG channel. 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. There are different softwares available that predict the likelihood of a molecule entering the CNS. 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), logPS (permeability surface-area product) and the affinity for the P-gp. Recently, in silico MPO methodologies have also been applied to the selection of CNS-drugs. One example is the CNS MPO scoring system developed by Pfizer. In this method, six physicochemical properties (MW, clogP, clogD₇.₄, pKₐ, 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).\textsuperscript{67} Monotonic decreasing function is used for MW, clogP, clogD\textsubscript{7,4}, pK\textsubscript{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).

![Monotonic decreasing function and Hump function](image)

**Figure 10:** General examples of desirability functions used in the CNS MPO scoring system.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\(^73,75,76\)

![Chemical space diagram](image)

**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.\textsuperscript{82,83} For this reason, the chemical space occupied by the current small molecules is not necessarily valid for the discovery of new drugs.\textsuperscript{77} New “druggable” chemical space should be explored. Consequently, lead optimisation can still occur outside the drug-like chemical space known so far.\textsuperscript{84} Therefore, synthesis of new lead-like molecules is necessary to further investigate new drug-like chemical space.\textsuperscript{77} The use of libraries of molecular scaffolds for the search of NMEs has increased.\textsuperscript{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.\textsuperscript{78} Molecular scaffolds able to yield molecules that reside in new lead-like chemical space are of vital importance.\textsuperscript{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.\textsuperscript{86} Traditionally, combinatorial chemistry was used for the preparation of HTS libraries.\textsuperscript{87} However, it yields molecules with similar structures. Conversely, DOS yields molecules with very different structures,\textsuperscript{86,88} which allows a better exploration of chemical space (Figure 12).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure12.jpg}
\caption{Chemical space explored by combinatorial chemistry and by diversity-oriented synthesis. Adapted from a reference.\textsuperscript{88}}
\end{figure}

DOS allows chemical space to be explored.\textsuperscript{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.\textsuperscript{86,88,90} There are two key strategies to achieve this molecular diversity.\textsuperscript{91} These approaches are the branching pathway (reagent-based
approach) and the folding pathway (substrate-based approach). 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. **Panel B:** Example of folding pathway. Method: A: NH$_3$, NaBH$_4$, 250 mol% Ti(OEt)$_4$, EtOH, then AcOH; B: NH$_2$OH•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. 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. In this stage...
different intramolecular reactions are performed through the functional groups to yield the final scaffolds (Scheme 2).  

**Scheme 2**: Example of the build/couple/pair (build/connect/cyclisation) strategy used in DOS for the synthesis of diverse scaffolds.  

When more connective points (coloured blobs) present in the cyclisation precursor, more diversity can be obtained. **Method**: A: 10 mol% modified cinchona alkaloid catalyst,  

-20 °C or -40 °C, THF; B: Grubbs 1st generation 10 mol%, ethylene, µW, 150 W, 60 °C, DCM; C: PhNCO, Et₃N, toluene, rt; D: Zn, AcOH/THF, rt, then Na₂CO₃ (aq).

A high structural diversity of sp³-rich molecular scaffolds with different physicochemical properties has been obtained from DOS. Therefore, this strategy can be very useful to identify biologically active compounds. In addition, DOS can be focused to obtain molecules within the lead-like chemical space. It has been used to synthesise molecular scaffolds able to yield lead-like compounds. There is a methodology called lead-oriented synthesis (LOS), which allows achieving structurally-diverse sp³-rich scaffolds able to yield different molecules within the lead-like chemical space. 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 sp³-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.⁴⁸,¹⁰⁸–¹¹⁸

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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{106}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{scaffold.pdf}
\caption{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.\textsuperscript{106}}
\end{figure}

\textit{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.\textsuperscript{106} In addition, subsequent \textit{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).
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. 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).

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.](image)

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 softwares 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

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

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.

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.
- It has a number of basic amines higher than one.
- 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, clogD$_{7.4}$, $pK_a$, HBD and PSA) that Pfizer calculates in its CNS MPO scoring system. The reason is that these properties are usually used to address ADMET issues. 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, 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, clogD$_{7.4}$, $pK_a$, HBD, and a model of a hump function is used for PSA (Figure 18). These models were adapted from Pfizer’s functions. 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.
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. 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). 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 \( \alpha \)-atoms (only ring systems) and with their \( \alpha \)-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: Murcko fragment without and with \( \alpha \)-atoms does not show any hit. Consequently the scaffold is novel. Scaffold 54: Murcko fragment without \( \alpha \)-atoms shows 275 hits. However, when the \( \alpha \)-atoms are considered, there is not any hit. As a result, the substitution pattern of the scaffold is novel.](image-url)
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 $\geq$4.00) and if the scaffold has a novel structure (number of hits without or with $\alpha$-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. 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. 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.
Table 1: Results obtained for the 29 literature-related scaffolds using the computational tool. 

Scaffolds derived from bioactive molecules (70 (sumanireole), 76 (rupatadine), 77 (mizolastine), 78 (azelastine), 79 (olopatadine)). 

<table>
<thead>
<tr>
<th>Scaffold number and ref.</th>
<th>Mean Pfizer’s CNS MPO score</th>
<th>Mean CNS Lead MPO score</th>
<th>Number of derived compounds</th>
<th>Hits without α-atoms</th>
<th>Novelties</th>
</tr>
</thead>
<tbody>
<tr>
<td>5510</td>
<td>4.97</td>
<td>4.47</td>
<td>3038</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>56107</td>
<td>4.92</td>
<td>4.52</td>
<td>384</td>
<td>53</td>
<td>0</td>
</tr>
<tr>
<td>57120</td>
<td>4.37</td>
<td>3.96</td>
<td>1140</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>58106</td>
<td>5.09</td>
<td>4.59</td>
<td>3038</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>59126</td>
<td>5.84</td>
<td>4.86</td>
<td>696</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>60127</td>
<td>5.75</td>
<td>5.49</td>
<td>1522</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>61108</td>
<td>5.66</td>
<td>4.99</td>
<td>114</td>
<td>2924</td>
<td>585</td>
</tr>
<tr>
<td>62113</td>
<td>4.73</td>
<td>4.08</td>
<td>114</td>
<td>275</td>
<td>0</td>
</tr>
<tr>
<td>63118</td>
<td>4.69</td>
<td>4.22</td>
<td>3038</td>
<td>154</td>
<td>4</td>
</tr>
<tr>
<td>64106</td>
<td>4.13</td>
<td>3.89</td>
<td>795</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>65106</td>
<td>4.87</td>
<td>4.43</td>
<td>3038</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>66122</td>
<td>5.45</td>
<td>4.86</td>
<td>2204</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>67121</td>
<td>3.55</td>
<td>3.02</td>
<td>3038</td>
<td>104</td>
<td>0</td>
</tr>
<tr>
<td>68128</td>
<td>5.48</td>
<td>4.93</td>
<td>551</td>
<td>1850</td>
<td>1</td>
</tr>
<tr>
<td>69129</td>
<td>4.98</td>
<td>4.60</td>
<td>464</td>
<td>28392</td>
<td>3</td>
</tr>
<tr>
<td>7010</td>
<td>4.81</td>
<td>4.31</td>
<td>986</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>71130</td>
<td>4.34</td>
<td>3.69</td>
<td>3038</td>
<td>557</td>
<td>110</td>
</tr>
<tr>
<td>72122</td>
<td>3.87</td>
<td>2.83</td>
<td>551</td>
<td>27526</td>
<td>8608</td>
</tr>
<tr>
<td>73131</td>
<td>5.33</td>
<td>4.38</td>
<td>651</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>74132</td>
<td>3.94</td>
<td>3.48</td>
<td>360</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>75110</td>
<td>4.00</td>
<td>3.64</td>
<td>3038</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7610</td>
<td>3.18</td>
<td>2.99</td>
<td>1140</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7710</td>
<td>3.03</td>
<td>2.81</td>
<td>1140</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>7810</td>
<td>3.29</td>
<td>2.88</td>
<td>1140</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7910</td>
<td>3.27</td>
<td>2.97</td>
<td>551</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>80113</td>
<td>3.42</td>
<td>2.70</td>
<td>285</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>81110</td>
<td>4.61</td>
<td>4.07</td>
<td>3038</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>82113</td>
<td>4.20</td>
<td>3.88</td>
<td>795</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>83107</td>
<td>2.76</td>
<td>2.52</td>
<td>814</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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 clogD7.4. 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 clogD7.4 too high to be able to cross the BBB.
Mean CNS Lead MPO score = 5.49
Mean CNS Lead MPO score = 3.02
Mean CNS Lead MPO score = 4.86
Mean CNS Lead MPO score = 2.81

**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.

![Chemical structures of compounds 84, 85, 86, and 87](image)

### 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.

<table>
<thead>
<tr>
<th>Derived compound:</th>
<th>84</th>
<th>85</th>
<th>86</th>
<th>87</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer’s CNS MPO score:</td>
<td>5.21</td>
<td>6.00</td>
<td>5.57</td>
<td>5.22</td>
</tr>
<tr>
<td>CNS Lead MPO score:</td>
<td>5.21</td>
<td>6.00</td>
<td>3.86</td>
<td>3.36</td>
</tr>
<tr>
<td>MW:</td>
<td>256</td>
<td>275</td>
<td>399</td>
<td>391</td>
</tr>
<tr>
<td>PSA (Å³):</td>
<td>23.5</td>
<td>47.5</td>
<td>83.8</td>
<td>88.0</td>
</tr>
</tbody>
</table>

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. Consequently, using these two reactions with an allylic carbonate building block, different amines and different electron deficient het(aryl) bromide groups, a library of pyrroolidine-derived scaffolds for CNS drug discovery could be prepared (Scheme 6). 

**Scheme 6:** Connective reaction involving iridium chemistry and subsequent cyclisation reaction involving palladium chemistry. Different pyrroolidine-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). 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.
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.
Table 3: Results obtained for the 25 virtual scaffolds using the computational protocol. Only the amines were used as point of decoration. aMean of all the CNS Lead MPO scores of the derived compounds per scaffold. bBased on Murcko fragments against a random 2% of the ZINC database.

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

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).
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.

![Virtual pyrrolidine-derived scaffolds selected for synthesis.](image)

**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. *Lower yield compared to the other steps due to the formation of the isomer Z (detected by 1H-NMR spectroscopy of the crude product mixture).

The synthesis started with the Boc protection of the nitrogen of the amino alcohol 119 using Boc₂O to give the carbamate 120 with a quantitative yield. Successively, Parkih–Doering oxidation was applied to the carbamate 120 followed by a Wittig reaction 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). These compounds were prepared following literature procedures. The synthesis of the catalyst 92 is necessary because the dbcot ligand makes the catalyst more stable to oxygen. In addition, it increases the regioselectivity of the reaction for the desired product.
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 nBuNH₂ 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.
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 Et3N and the (S)-Mosher’s acid chloride ((S)-MTPA-Cl) 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 TBDPSCI in the presence of Et$_3$N and DMAP to give the silyl derivatives 128. Subsequently, these two enantiomers were independently treated with benzoyl chloride and Et$_3$N 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 Bu₄N-HSO₄ 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. *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 Cs₂CO₃ 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.

\[
\begin{align*}
\text{BocHN} & \quad \text{N} \quad \text{R}^1 \\
\text{N} & \quad \text{R}^2 \\
\end{align*}
\]

Cyclisation precursor

\[
\begin{align*}
\text{ArBr} & \quad 5 \text{ mol\% Pd(OAc)}_2 \\
10 \text{ mol\% 93} & \quad \text{Cs}_2\text{CO}_3 \\
1,4\text{-Dioxane} & \quad 105^\circ\text{C}, 18 \text{ h} \\
\end{align*}
\]

1.4-Dioxane

Entry | Cyclisation precursor | Het(aryl)bromide | Scaffold | Crude dr \(^a\) | Yield and dr \(^b\)
--- | --- | --- | --- | --- | ---
1 | Bo\(\text{cHN}\) | \(\text{N} \quad \text{R}^1\) | \(\text{N} \quad \text{R}^2\) | >95:<5 | 66% >95:<5
2 | Bo\(\text{cHN}\) | \(\text{N} \quad \text{R}^1\) | \(\text{N} \quad \text{R}^2\) | >95:<5 | 61% >95:<5
3 | Bo\(\text{cHN}\) | \(\text{N} \quad \text{R}^1\) | \(\text{N} \quad \text{R}^2\) | >95:<5 | 38% >95:<5
4 | Bo\(\text{cHN}\) | \(\text{N} \quad \text{R}^1\) | \(\text{N} \quad \text{R}^2\) | 83:17 | 42% >95:<5
5 | Bo\(\text{cHN}\) | \(\text{N} \quad \text{R}^1\) | \(\text{N} \quad \text{R}^2\) | 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.\(^{a}\)\(^{a}\) Determined by \(^1\text{H}-\text{NMR}\) spectroscopy (500 MHz) of the crude product mixture. \(^b\)Yield and dr (\(^1\text{H}-\text{NMR}, 500 \text{ MHz}\) 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. As a result, the *in vitro* permeability of these derived compounds for passive transport was evaluated using PAMPA (Parallel Artificial Membrane Permeability Assay). 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 ($P_{\text{app}}$ (apparent permeability coefficient) >$10^{-5}$ cm/s) (Table 6). Consequently, they could also be BBB penetrant.

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

Table 6: CNS Lead MPO scores, experimental logD$_{7.4}$ and $P_{\text{app}}$ 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). This connective reaction starts with an allyl ester building block and involves a Mannich/alkylation reaction followed by a palladium-catalysed decarboxylative allylic alkylation. The cyclisation precursor obtained could undertake different cyclisation reactions that could yield different novel, sp³-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, sp³-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). 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$_2$CO$_3$, 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, 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. 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).
Table 7: Optimisation and synthesis of the allyl ester building blocks 146. *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, Et₂O, rt, then allyl acrylate, DMSO, 0 ºC to rt. *Observed as a mixture of 24:76 keto-enol tautomers (¹H-NMR, CDCl₃, 500 MHz). *Only enol tautomers observed (¹H-NMR, CDCl₃, 400 MHz). *O-Acylation ratio determined by ¹H-NMR spectroscopy (300–500 MHz) of the crude product mixture. *No reaction observed by TLC and ¹H-NMR spectroscopy of the crude product mixture. *Decomposition observed by TLC and ¹H-NMR spectroscopy of the crude product mixture. *Not applicable. *Yield of the purified building block. *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). The synthesis of the ketone-derived allyl esters 146b-d needed non-polar solvents to proceed 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, 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. The use of other strategies such as the transesterification reaction did not work (Table 7, entries 5c–d).

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 Cs₂CO₃ and the carbamate 153 at rt. 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 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 K₂CO₃ and two different aryl bromides. 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 reactions. However, the yield of 147g was much lower. This lower yield could be related with the nucleophilicity and higher polarity of 3-(bromomethyl)pyridine.

![Chemical structure](image)

**Table 8:** Mannich/alkylation reactions of the different allyl ester building blocks 146 to form the quaternary allyl esters 147.\textsuperscript{a}Yield of the purified quaternary allyl ester. \textsuperscript{b}No product observed by \textsuperscript{1}H-NMR spectroscopy (400 MHz) of the crude product mixture due to the formation of compound 157 (Scheme 13). \textsuperscript{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 Cs₂CO₃.

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. 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 PPh₃ as ligand. Therefore, the different quaternary allyl esters 147 were treated with 5 mol% Pd(OAc)₂ and 20 mol% PPh₃ in THF at 70 °C for 1h. 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).
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\textsuperscript{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 $\alpha$-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.
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 NaBO₃ and H₂O.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 diastereomeric diols \textbf{160} (Table 10, entries 1a–c).\textsuperscript{159} This mixture of diols \textbf{160} was never observed when using disiamylborane.
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 \textbf{159} were dissolved in DCM, combined with Et$_3$SiH 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 \textbf{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 $\geq 91:9$. The six-membered ring hemiacetals \textbf{159a-b} and \textbf{159e-f} were treated with TFA. However, the use of TFA did not work with the five-membered ring hemiacetal \textbf{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, \textbf{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$_3$,\textsuperscript{162,163} AcOH or other reducing agents like NaBH(OAc)$_3$ only showed traces or no formation of product (Table 11, entries 1b–d).
Once these scaffolds 149 were obtained in good yields, it was decided to determine their relative configurations. \(^1\)H-NMR spectroscopy (400–500 MHz)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Hemiacetal</th>
<th>Method(^a)</th>
<th>Scaffold</th>
<th>Crude dr</th>
<th>Yield and dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>159a</td>
<td>A</td>
<td>149a</td>
<td>&gt;95:5(^b)</td>
<td>31(^h), &gt;95:5(^i)</td>
</tr>
<tr>
<td>b</td>
<td></td>
<td>B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c</td>
<td></td>
<td>C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d</td>
<td></td>
<td>D</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e</td>
<td></td>
<td>E</td>
<td></td>
<td></td>
<td>99(^%), &gt;95:5(^i)</td>
</tr>
<tr>
<td>2</td>
<td>159b</td>
<td>E</td>
<td>149b</td>
<td>&gt;95:5(^f)</td>
<td>51(^%), &gt;95:5(^i)</td>
</tr>
<tr>
<td>3</td>
<td>159c</td>
<td>F</td>
<td>149c</td>
<td>&gt;95:5(^g)</td>
<td>65(^%), &gt;95:5(^i)</td>
</tr>
<tr>
<td>a</td>
<td></td>
<td>E</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b</td>
<td></td>
<td>G</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c</td>
<td></td>
<td>F</td>
<td></td>
<td></td>
<td>43(^%), &gt;95:5(^i)</td>
</tr>
<tr>
<td>5</td>
<td>159e</td>
<td>H</td>
<td>149e</td>
<td>93:7(^f)</td>
<td>63(^%), &gt;95:5(^i)</td>
</tr>
<tr>
<td>6</td>
<td>159f</td>
<td>H</td>
<td>149f</td>
<td>91:9(^f)</td>
<td>88(^%), 91:9(^j)</td>
</tr>
</tbody>
</table>

Table 11: Optimisation and utilisation of the hemiacetal reduction to obtain different tetrahydropyran-derived scaffolds. \(^a\)Method: A: Et\(_3\)SiH, BF\(_3\)•Et\(_2\)O, DCM, –78 °C to rt; B: Et\(_3\)SiH, FeCl\(_3\), CH\(_3\)NO\(_2\), rt; C: Et\(_3\)SiH, AcOH, rt; D: NaBH(OAc)\(_3\), AcOH, rt; E: Et\(_3\)SiH, TFA, DCM, rt, then Boc\(_2\)O, Et\(_3\)N, DCM, rt; F: Et\(_3\)SiH, BF\(_3\)•Et\(_2\)O, DCM, –78 °C to rt, then Boc\(_2\)O, Et\(_3\)N, DCM, rt; G: Et\(_3\)SiH, TFA, DCM, 40 °C, then Boc\(_2\)O, Et\(_3\)N, DCM, rt; H: Et\(_3\)SiH, 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.
showed that all the protons in the tertiary carbon had a singlet or small doublet of $J \leq 4.0$ 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).

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, with Grignard reagents like PhMgBr and with organocopper reagents made in situ from CuBr and PhMgBr. However, the arylation reaction was not successful (Table 12). For this reason, the arylation of the hemiacetals was not continued.

![Figure 30: X-ray structure of the scaffold 149a confirming the cis ring fusion.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents &amp; conditions</th>
<th>Ar</th>
<th>Yield 162</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BF₃•Et₂O, anisole</td>
<td>4-methoxyphenyl</td>
<td>–d</td>
</tr>
<tr>
<td>2</td>
<td>BF₃•Et₂O, DCM, –20 °C, then PhMgBr, DCM, –20 °C</td>
<td>Ph</td>
<td>–d</td>
</tr>
<tr>
<td>3</td>
<td>Me₂S•CuBr and PhMgBr, then Et₂O•BF₃, THF</td>
<td>Ph</td>
<td>–e</td>
</tr>
</tbody>
</table>

Table 12: Transformation of the hemiacetal 159a into the acetal 161 and attempts for its arylation. The relative configuration of 161 could not be resolved by NOESY. Determined by ¹H-NMR spectroscopy (400 MHz) of the purified product. The procedure followed uses Et₂O as solvent. However, 161 was not soluble in Et₂O and for this reason the solvent was changed to THF. No reaction observed by LC-MS of the crude product mixture. Degradation observed by ¹H-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 O₃ 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, reducing agent or amine 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.

![Chemical structure](image)

Table 13: Ozonolysis of the alkene 148i to give the hemiaminals 163 and optimisation of the following double reductive amination. a Determined by ¹H-NMR spectroscopy (400 MHz) of the purified hemiaminals. b Method: A: BnNH₂, AcOH, NaBH(OAc)₃, DCM, rt; B: BnNH₂, AcOH, NaBH(OAc)₃, DCM, 0 °C to rt; C: BnNH₂, AcOH, NaBH(OAc)₃, THF, rt; D: BnNH₂, NaCNBH₃, THF, rt; E: BnNH₂, AcOH, NaCNBH₃, MeOH, –78 °C to rt; F: Ph₂CHNH₂, NaBH(OAc)₃, AcOH, DCM, rt; G: Ph₂CHNH₂, NaCNBH₃, AcOH, MeOH, –78 °C to rt; H: NH₂OAc, NaBH₃CN, 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 ¹H-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.](image)

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.
Table 14: Optimisation and utilisation of the diastereoselective ketone reduction.  
*aMethod: 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: NaBH₄ 2.00 eq, MeOH, 0 °C; E: DIBAL-H 1.10 eq, DCM, −100 °C.  
bDetermined by ¹H-NMR spectroscopy (400 MHz) of the crude product mixture.  
cCbz cleavage observed by TLC and ¹H-NMR spectroscopy (500 MHz) of the crude product mixture.  
dDetermined by ¹H-NMR spectroscopy (500 MHz) of the crude product mixture.  
eYield and dr (¹H-NMR, 400 MHz) of the purified alcohol.  
fNot purified.  
gYield and dr (¹H-NMR, 500 MHz) of the purified alcohol.  

The relative configuration of the alcohols 167a-b was determined by analogy with the carbocyclic analogue, by ¹H-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 (1H-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. 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 complicated mixture was observed by TLC of the crude product mixture. Finally, it was decided to try an iodocyclisation reaction as another method to cyclise between the alcohol and the alkene. Therefore, the alcohol 167a was dissolved in acetonitrile and combined with I₂ and NaHCO₃. 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. \(^{\text{a}}\)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.

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'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'Bu only deprotonates the alcohol, where NaH also deprotonates the NHBoc.
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.
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 O₃ 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.

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$_2$O and pyridine$^{142}$ (Table 16). The reaction worked very well and the corresponding esters 171 were obtained in $\geq$95% yield.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alcohol</th>
<th>Ester</th>
<th>Yield$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>167a</td>
<td>171a</td>
<td>95%</td>
</tr>
<tr>
<td>2</td>
<td>167b</td>
<td>171b</td>
<td>95%</td>
</tr>
<tr>
<td>3</td>
<td>167c</td>
<td>171c</td>
<td>99%</td>
</tr>
<tr>
<td>4</td>
<td>167d</td>
<td>171d</td>
<td>95%</td>
</tr>
</tbody>
</table>

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)$_3$. 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.

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. 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 and the use of TPAP/NMO only gave traces of product after one week (Table 18, entries 1a–b).

Once the previous spirocyclic compounds were obtained, it was investigated 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. Consequently, the aminals 175 were treated with DMS•CuBr, PhMgBr and BF₃ in Et₂O. 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 ¹H-NMR spectroscopy (500 MHz).](image)

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 NaBO₃•4H₂O. 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).
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 Et₃N 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. 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 reprotction, 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\textsuperscript{142} were not successful either with six- or five-membered rings (Table 20, entries 1a and 4c).

![Chemical structure](image)

**Table 20:** Optimisation and utilisation of an intramolecular S\textsubscript{N}2 cyclisation reaction to yield different piperidine-derived scaffolds. \textsuperscript{a}The mesylated alcohols 178 were always formed (observed by TLC and LC-MS of the crude product mixture after the first step). \textsuperscript{b}Method: A: NaH, THF, 65 ºC; B: TFA, DCM, rt, then Et\textsubscript{3}N, DCM, rt, then Boc\textsubscript{2}O, DCM, rt; C: TFA, (Bu)\textsubscript{4}NI, DCM, 40 ºC, then Et\textsubscript{3}N, DCM, rt, then Boc\textsubscript{2}O, DCM, rt. \textsuperscript{c}Yield of the purified scaffold. \textsuperscript{d}Decomposition observed by TLC and \textsuperscript{1}H-NMR spectroscopy of the crude product mixture. \textsuperscript{e}No cyclisation observed by TLC and \textsuperscript{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. *Observed by LC-MS of the crude product mixture.*](image)

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. 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). If other bases like KOtBu were used, the reaction did not work well (Table 21, entry 2). The reason is that once the alcohol of **167a** is deprotonated by KOtBu, it rapidly reacts with the NHBoc group to form the six-membered ring carbamate **150a** previously synthesised (Table 15).
With compound 182 in hand, it was used as substrate for a Pd-catalysed aminoarylation reaction,\textsuperscript{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)\textsubscript{2} and Cs\textsubscript{2}CO\textsubscript{3} in 1,4-dioxane for 18 h at 105 °C. 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).\textsuperscript{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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Procedure</th>
<th>Yield\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaH</td>
<td>Addition of BnBr as the last reagent</td>
<td>52%</td>
</tr>
<tr>
<td>2</td>
<td>KO\textsubscript{t}Bu</td>
<td>Addition of BnBr as the last reagent</td>
<td>–\textsuperscript{b}</td>
</tr>
<tr>
<td>3</td>
<td>NaH</td>
<td>Addition of NaH as the last reagent</td>
<td>86%</td>
</tr>
</tbody>
</table>

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

---

**Table 22**: Optimisation of the Pd-catalysed aminoarylation reaction to obtain pyrrolidine-derived scaffolds.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting material</th>
<th>Scaffold</th>
<th>Crude dr</th>
<th>Yield &amp; dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Starting material" /></td>
<td><img src="image2" alt="Scaffold" /></td>
<td>65:35</td>
<td>34%, 69:31</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Starting material" /></td>
<td><img src="image4" alt="Scaffold" /></td>
<td>–b</td>
<td>–b</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Starting material" /></td>
<td><img src="image6" alt="Scaffold" /></td>
<td><strong>67:33</strong></td>
<td><strong>31%, &gt;95:&lt;5</strong></td>
</tr>
</tbody>
</table>

*Determined by \(^1\)H-NMR spectroscopy (500 MHz) of the crude product mixture.

*Complicated mixture observed by TLC and \(^1\)H-NMR spectroscopy of the crude product mixture.

\(^1\)Yield and dr \((^1\)H-NMR, 500 MHz) of the purified product.
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$_A$.

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

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. 

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.

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).

![Chemical Structure]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid</th>
<th>Aldehyde</th>
<th>Scaffold</th>
<th>Crude dr&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield and dr&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 a</td>
<td>AcOH</td>
<td>(CHO)&lt;sub&gt;n&lt;/sub&gt;</td>
<td>152</td>
<td>_</td>
<td>30%, _</td>
</tr>
<tr>
<td>1 b</td>
<td>TFA</td>
<td>(CHO)&lt;sub&gt;n&lt;/sub&gt;</td>
<td></td>
<td>_</td>
<td>33%, &gt;95:&lt;5</td>
</tr>
<tr>
<td>2</td>
<td>TFA</td>
<td>Benzaldehyde</td>
<td>188</td>
<td>&gt;95:&lt;5</td>
<td>33%, &gt;95:&lt;5</td>
</tr>
</tbody>
</table>

Table 23: Optimisation of the intramolecular Mannich reaction to give bridged bicyclic scaffolds.

<sup>a</sup>Determined by <sup>1</sup>H-NMR spectroscopy (500 MHz) of the crude product mixture.
<sup>b</sup>No cyclisation observed by TLC and <sup>1</sup>H-NMR spectroscopy of the crude product mixture.
<sup>c</sup>Not applicable.
<sup>d</sup>Yield and dr (<sup>1</sup>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<sub>A</sub>. In addition, proton 6-H also showed two nOe signals; one with the proton 5-H and one with the proton 8-H<sub>B</sub>. 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\textsubscript{B}, and between the protons 4-H\textsubscript{A} and 6-H.

![Figure 37](image)

**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\textsuperscript{3}-rich ring systems was achieved.
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-Kishner reaction.\(^{183}\)
<table>
<thead>
<tr>
<th>Entry</th>
<th>Scaffold</th>
<th>Number of steps from the cyclisation precursor 148i and average yield</th>
<th>dr After purification</th>
<th>Prioritised for the synthesis of other scaffolds</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Scaffold 1" /></td>
<td>Two steps, 75%</td>
<td>&gt;95:&lt;5</td>
<td>✔</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Scaffold 2" /></td>
<td>Two steps, 23%</td>
<td>83:17</td>
<td>✗</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3.png" alt="Scaffold 3" /></td>
<td>Two steps, 89%</td>
<td>86:14</td>
<td>✔</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4.png" alt="Scaffold 4" /></td>
<td>Four steps, 52%</td>
<td>&gt;95:&lt;5</td>
<td>✔</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5.png" alt="Scaffold 5" /></td>
<td>Four steps, 42%</td>
<td>&gt;95:&lt;5</td>
<td>✔</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6.png" alt="Scaffold 6" /></td>
<td>Five steps, 44%</td>
<td>57:43</td>
<td>✗</td>
</tr>
<tr>
<td>7</td>
<td><img src="image7.png" alt="Scaffold 7" /></td>
<td>Four steps, 37%</td>
<td>&gt;95:&lt;5</td>
<td>✔</td>
</tr>
<tr>
<td>8</td>
<td><img src="image8.png" alt="Scaffold 8" /></td>
<td>Three steps, 25%</td>
<td>&gt;95:&lt;5</td>
<td>✗</td>
</tr>
<tr>
<td>a</td>
<td><img src="image9.png" alt="Scaffold 9" /></td>
<td>Three steps, 24%</td>
<td>77:23</td>
<td>✗</td>
</tr>
<tr>
<td>9</td>
<td><img src="image10.png" alt="Scaffold 10" /></td>
<td>Three steps, 6%</td>
<td>&gt;95:&lt;5</td>
<td>✗</td>
</tr>
<tr>
<td>b</td>
<td><img src="image11.png" alt="Scaffold 11" /></td>
<td>Three steps, 6%</td>
<td>&gt;95:&lt;5</td>
<td>✗</td>
</tr>
<tr>
<td>10</td>
<td><img src="image12.png" alt="Scaffold 12" /></td>
<td>Two steps, 36%</td>
<td>&gt;95:&lt;5</td>
<td>✗</td>
</tr>
</tbody>
</table>
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).
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).

![Chemical structures](image)

**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).
Table 26: Results obtained for the 23 virtual scaffolds using the computational protocol. aMean of all the CNS Lead MPO scores of the derived compounds per scaffold. bBased on Murcko fragments against a random 2% of the ZINC database.

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

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 pKa. 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 pKa. 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. Consequently, they would also be likely to yield lead-like molecules for CNS drug discovery.
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.\textsuperscript{184,185} It is predominantly found in the neurons of the CNS.\textsuperscript{186} The inhibition of this protease has been of great interest for the treatment of Alzheimer’s disease.\textsuperscript{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.\textsuperscript{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).\textsuperscript{188}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{amyloid_beta.png}
\caption{Amyloid β formation initiated by BACE1 in Alzheimer’s disease. Adapted from a reference.\textsuperscript{188}}
\end{figure}

Consequently, inhibition of BACE1 has become of interest to stop the progression of the disease.\textsuperscript{189} Different inhibitors have been designed, which involve peptidomimetics, pseudo-peptidomimetics and non-peptidomimetics.\textsuperscript{190} However, the problem of the peptidomimetics is that they do not have the desired properties to cross the BBB.\textsuperscript{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
Different small molecule inhibitors have already been designed and reached clinical trials. 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. For this reason, more studies are required to understand the physiological and pathological role of BACE1 and if its inhibition will significantly improve cognitive functions.

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

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

This initial hit was developed into the compound (Figure 43, panel A). Consequently, the fragment was grown in opposite vectors to increase the number of interaction in the binding site. During this process, different intermediate compounds like were prepared and tested against BACE1.
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). 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.
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.
<table>
<thead>
<tr>
<th>Virtual derived compound</th>
<th>CNS Lead MPO score</th>
</tr>
</thead>
<tbody>
<tr>
<td>214</td>
<td>3.71</td>
</tr>
<tr>
<td>215</td>
<td>3.62</td>
</tr>
<tr>
<td>216</td>
<td>3.74</td>
</tr>
<tr>
<td>217</td>
<td>3.85</td>
</tr>
<tr>
<td>218</td>
<td>3.05</td>
</tr>
<tr>
<td>219</td>
<td>3.63</td>
</tr>
<tr>
<td>220</td>
<td>3.74</td>
</tr>
<tr>
<td>221</td>
<td>2.93</td>
</tr>
<tr>
<td>222</td>
<td>3.45</td>
</tr>
<tr>
<td>223</td>
<td>4.31</td>
</tr>
<tr>
<td>224</td>
<td>5.32</td>
</tr>
<tr>
<td>225</td>
<td>3.40</td>
</tr>
<tr>
<td>226</td>
<td>4.20</td>
</tr>
</tbody>
</table>

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). The first step involved the nucleophilic aromatic substitution of the commercially available chloro-derivative 228 with tBuNH₂ 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 H₂ 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.](image_url)

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. 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 Et₃N (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 = 'Bu). The second step involved the removal of the '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.

![Chemical Structures](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Scaffold</th>
<th>Method</th>
<th>Intermediate, R = 'Bu</th>
<th>Derived compound, R = H</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Step 1</td>
<td>Step 2</td>
<td></td>
<td>Step 1</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>A</td>
<td></td>
<td>231a</td>
<td>215, 21%</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>A</td>
<td></td>
<td>231b</td>
<td>216, 60%</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>A</td>
<td></td>
<td>231c</td>
<td>217, 72%</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>A</td>
<td></td>
<td>231d</td>
<td>218, 75%</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>B</td>
<td></td>
<td>231e</td>
<td>219, 28%</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>B</td>
<td></td>
<td>231f</td>
<td>220, 31%</td>
</tr>
</tbody>
</table>
Table 28: Decoration of the scaffolds to yield the final derived compounds where R = H.

Method: A: NaOMe, MeOH, rt, then TFA, DCM, rt, then 227, TBD, Et3N, toluene, 75 °C; B: TFA, DCM, rt, then 227, TBD, Et3N, toluene, 75 °C; C: H2, Pd/C, MeOH, rt, then 227, TBD, toluene, 75 °C; D: 227, TBD, toluene, 75 °C; E: 227, TBD, Et3N, 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. This assay exploited a peptide substrate containing in its termini a red-shifted fluorescent donor ($\lambda_{\text{excitation}} = 530$ nm, $\lambda_{\text{emission}} = 595$ 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 suppresses 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 fluorescence-quenching assay used to evaluate the biological activity of the 13 derived compounds. Under light excitation, the quencher suppresses 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-EVNLLDAEFK-quencher; peptide sequence after cleavage, rhodamine-EVNL + DAEGK-quencher.

The fluorescence-quenching assay was firstly performed using the 13 derived compounds at 100 µM. Consequently, inhibitors could be 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\textsubscript{50} for each of these compounds could be determined. The IC\textsubscript{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.

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.\textsuperscript{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.

\textbf{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).\textsuperscript{192} Consequently, the methylation of the amide on this class of compounds has previously shown a 70-fold lost in potency.\textsuperscript{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).

![Figure 48: General idea of tertiary amides that could be developed for BACE1 inhibition.](image)

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.
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. 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 ($\lambda_{\text{max}} = 254$ 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 Supelco. Optical rotation measurements were performed at the sodium D-line (589 nm) on a Schmidt and Haensch H532. They are given in $10^{-1} \text{ deg cm}^2\text{g}^{-1}$. 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$_2$O + 0.1% formic acid or MeCN/H$_2$O. 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 K$_{\alpha}$ radiation ($\lambda = 1.54184 \text{ Å}$) 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 ($^1$H) 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 ($\delta$) 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**

According to an existing procedure, 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 (MgSO₄), filtered and concentrated under reduced pressure to give the carbamate derivative 120 (24.3 g, >99%) as a colourless oil, \( R_f 0.31 \) (30:70 petrol–EtOAc); \( \nu_{\text{max}}/\text{cm}^{-1} \) 3339, 2975, 2932, 2874, 1681, 1515, 1365, 1274, 1250, 1165; \( \delta_H \) (500 MHz, CDCl₃) 4.78 (1H, br. s, NH), 3.65 (2H, t, \( J 5.7 \), 3-H₂), 3.27 (2H, t, \( J 6.2 \), 1-H₂), 2.70 (1H, br. s, OH), 1.66 (2H, app. p, \( J 5.9 \) 2-H₂), 1.44 (9H, s, \textsuperscript{t}Bu); \( m/z \) (ES) 198.0 (100%, MNa⁺).

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

According to an existing procedure, triethylamine (116 mL, 830 mmol), DMSO (108 mL, 1.52 mol) and SO₃•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 NaHCO₃ (100 ml) and with water (100 ml). The organic layer was dried (MgSO₄), 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 121¹³⁴ (21.0 g, 62%) as a yellow oil, Rf 0.57 (60:40 petrol–EtOAc); νmax/cm⁻¹ 3367, 2977, 2933, 1691, 1654, 1516, 1365, 1248, 1165; δH (500 MHz, CDCl₃) 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-H₂), 3.37–3.15 (2H, m, 5-H₂), 2.40 (2H, app. q, J 6.6, 4-H₂), 1.43 (9H, s, tBu), 1.28 (3H, t, J 7.1, ethyl 2-H₃); m/z (ES) 266.0 (100%, MNa⁺).

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

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 NH₄Cl (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 (MgSO₄), filtered and concentrated under reduced pressure to give the alcohol 122¹³⁴ (16.6 g, 96%) as a yellow oil, Rf 0.18 (60:40 petrol–EtOAc); νmax/cm⁻¹ 3328, 2975, 2930, 2868, 1684, 1518, 1391, 1364, 1249, 1165; δH (500 MHz, CDCl₃) 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-H₂), 3.21–3.14 (2H, m, 1-H₂), 2.23 (2H, app. q, J 6.5, 2-H₂), 1.66 (1H, br. s, OH) 1.43 (9H, s, tBu); m/z (ES) 224.3 (100%, MNa⁺).
According to an existing procedure,\textsuperscript{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 \(\text{NH}_4\text{Cl} \) (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\textsuperscript{134} (18.4 g, 86%) as a colourless oil, \(R_f\) 0.36 (80:20 petrol–EtOAc); \(\nu_{\text{max}}/\text{cm}^{-1}\) 3366, 2975, 1746, 1692, 1513, 1442, 1365, 1249, 1165; \(\delta_H\) (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

According to an existing procedure,\textsuperscript{134} a solution of \(\text{dbcot} \) (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\textsuperscript{200} (0.46 g, 61%) as a bright yellow solid, \(\delta_H\)
(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,$^{116}$ nBuNH$_2$ (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 existing procedure,$^{139}$ (2S)-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, 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 (MgSO₄), filtered and concentrated under reduced pressure to give a crude material.

General Procedure E
According to an existing procedure, 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 NH₄Cl (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 (MgSO₄), filtered and concentrated under reduced pressure to give a crude material.

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

According to General Procedure A, the allylic carbonate 88 (2.50 g, 9.64 mmol), (S,S,aS)-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 ¹H-NMR) was purified by flash column chromatography, eluting with 92.4:6.8:0.8 DCM–EtOH–NH₄OH to give the alkene 89a (1.45 g, 59%, 67% ee) as a yellow oil, Rᵣ 0.13 (92.4:6.8:0.8 DCM–EtOH–NH₄OH); [α]D²⁶ −3.00 (c 1.00, CHCl₃);
According to General Procedure A, the allylic carbonate 88 (0.25 g, 0.96 mmol), (R,R,aR)-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 1H-NMR) was purified by flash column chromatography, eluting with 92.4:6.8:0.8 DCM-EtOH-NH4OH to give the alkene 89a (90.0 mg, 37%, 67% ee) as a yellow oil, [αD]24 +1.25 (c 1.20, CHCl3); spectroscopically identical to the enantiomer previously prepared. The absolute configuration was determined by comparison with analogues.116

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

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−NH₄OH); \([\alpha]_{D}^{23} +0.94 \ (c \ 0.73, \text{MeOH})\); \( \nu_{\max }/\text{cm}^{-1} \) 3397, 2965, 1666, 1426, 1175, 1124; \( \delta_H \) (500 MHz, CD₃OD) 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\(_{\text{cis}}\)), 5.64 (1H, dd, \( J \) 17.0 and 0.8, 5-H\(_{\text{trans}}\)), 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\(_4\)); \( \delta_C \) (125 MHz, CD₃OD) 162.9 (app. m, TFA C=O), 131.3 (C-4), 126.8 (C-5), 118.2 (app d, \( J \) 300.0, TFA CF₃), 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\(_9\)H\(_{18}\)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. \( \delta_H \) (500 MHz, C\(_6\)D\(_6\)) 4.87 (major) and 4.80 (minor).

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

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, \([\alpha]_{D}^{24} -0.06 \ (c \ 0.70, \text{MeOH})\); 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. \( \delta_H \) (500 MHz, C\(_6\)D\(_6\)) 4.89 (minor) and 4.83 (major).
tert-Butyl N-[(3S)-3-(morpholin-4-yl)pent-4-en-1-yl]carbamate

According to General Procedure A, the allylic carbonate 88 (2.72 g, 10.5 mmol), (R,R,aR)-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); \([\alpha]_D^{23}\) +16.0 (c 1.00, CHCl\(_3\)); \(\nu_{\text{max}}/\text{cm}^{-1}\) 3343, 2972, 2930, 2853, 2813, 1693, 1514, 1167, 1114; \(\delta_H\) (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\(_{\text{cis}}\)), 5.08 (1H, dd, \(J = 17.1\) and 1.5, 5-H\(_{\text{trans}}\)), 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); \(\delta_C\) (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\(_2\)O\(_3\) 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-[(3R)-3-(morpholin-4-yl)pent-4-en-1-yl]carbamate

According to General Procedure A, the allylic carbonate 88 (0.25 g, 0.96 mmol), (S,S,aS)-91 (20.0 mg, 37.0 \(\mu\)mol) 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, [αD]24 −14.0 (c 1.00, CHCl3); 
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; t1 = 8.79 
min (major), t2 = 9.65 min (minor). The absolute configuration was determined 
by comparison with analogues.\textsuperscript{116}

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

According to General Procedure A, the allylic carbonate 88 (0.88 g, 3.40 mmol), 
(R,R,aR)-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 1H-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, Rf 0.28 (30:70 EtOAc−petrol); [αD]23 +9.80 (c 1.00, CHCl3); νmax/cm\(^{-1}\) 
3340, 2973, 2949, 2811, 1693, 1512, 1167; δ\(_H\) (500 MHz, CDCl3) 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, tBu); δ\(_C\) (75 MHz, CDCl3) 156.1 
(C=O), 136.2 (C-4), 117.8 (C-5), 78.9 (tBu 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 (tBu C\(_3\)), 27.0 (bicyclooctanyl C\(_2\)-6,7); HRMS found MH\(^+\), 
297.2178. C\(_{16}\)H\(_{28}\)N\(_2\)O\(_3\) requires MH, 297.2172. The absolute configuration was 
determined by comparison with analogues.\textsuperscript{116}
tert-Butyl N-[(3R)-3-{8-oxa-3-azabicyclo[3.2.1]octan-3-yl}pent-4-en-1-yl] carbamate

According to General Procedure A, the allylic carbonate 88 (0.25 g, 0.96 mmol), (S,S,aS)-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 1H-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]D24 −8.30 (c 1.00, CHCl3); spectroscopically identical to the enantiomer previously prepared. The absolute configuration was determined by comparison with analogues.116

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

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, Rf 0.13 (84.7:13.6:1.7 DCM–EtOH–NH4OH); [αD23] −0.92 (c 0.52, MeOH); νmax/cm−1 3392, 2971, 1666, 1426, 1176, 1124; δH (500 MHz, CD3OD) 5.85 (1H, app. dt, J16.9 and 10.0, 4-H), 5.71 (1H, dd, J 10.3 and 1.2, 5-Hcis), 5.62 (1H, dd, J 16.9 and 1.2, 5-Htrans), 4.53 (2H, app. s, bicyclooctanyl 1,5-H2), 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-HA), 3.34 (1H, app. d, J 12.6, bicyclooctanyl 2,4-HB), 3.23 (1H, dd, J 12.4 and 2.9, bicyclooctanyl 2,4-HC), 3.14 (1H, dd, J 12.4 and 2.9, bicyclooctanyl 2,4-HD), 2.95-2.83 (2H, m, 1-H2), 2.45-2.28 (1H, m, 2-HA), 2.17-1.99 (5H, m, 2-HB and bicyclooctanyl 6,7-H4); δH (125 MHz, CD3OD) 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 CF3), 116.8 (q, J 289.3, TFA CF3), 73.9 (bicyclooctanyl C2-1,5), 69.6 (C-3), 56.4 (bicyclooctanyl C4A-2.4), 55.0 (bicyclooctanyl C5B-2.4), 37.7 (C-1), 27.9 (C-2), 27.5 (bicyclooctanyl C6A-6,7),
27.4 (bicyclooctanyl C₆-6,7); HRMS found MH⁺, 197.1642. C₁₁H₂₀N₂O 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, C₆D₆) 7.73 (major) and 7.70 (minor).

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

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, C₆D₆) 7.73 (minor) and 7.70 (major).

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

According to General Procedure A, the allylic carbonate 88 (3.00 g, 11.6 mmol), (S,S,aS)-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 ^1H-NMR) was purified by flash column chromatography, eluting with 90.8:8.2:1.0 DCM–EtOH–NH₄OH to give the alkene 89d (1.70 g, 60%, 85% ee) as an amorphous white solid, R_t 0.18 (90.8:8.2:1.0 DCM–EtOH–NH₄OH); [α_D]_26 −8.40 (c 1.00, CHCl₃); ν_max/cm⁻¹ 3368, 3267, 3071, 3014, 2975, 2933, 2840, 1681, 1523, 1366, 1165, 1053; δ_H (500 MHz, CDCl₃) 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, tBu); δ C (75 MHz, CDCl 3 ) 156.2 (C=O), 140.2 (C-4), 116.5 (C-5), 79.2 (tBu 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 (tBu C 3 ); HRMS found MH + , 245.1862. C 12 H 24 N 2 O 3 requires MH + , 245.1859. The absolute configuration was determined by comparison with analogues. 116

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

According to General Procedure A, the allylic carbonate 88 (0.25 g, 0.96 mmol), (R,R,aR)-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 1H-NMR) was purified by flash column chromatography, eluting with 90.8:8.2:1.0 DCM-EtOH-NH 4 OH to give the alkene 89d (90.0 mg, 38%, 85% ee) as an amorphous white solid, [α] 24 D +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-[(3R)-3-[(2-[(tert-butyldiphenylsilyl)oxy]ethyl)amino]pent-4-en-1-yl]carbamate

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); \([\alpha_D]^{23}\) -3.40 (c 1.00, CHCl\(\text{3}\)); \(\nu_{\text{max}}/\text{cm}^{-1}\) 3346, 3071, 2856, 1703, 1589, 1427, 1364, 1248, 1169, 1109; \(\delta_H\) (300 MHz, CDCl\(\text{3}\)) 7.71-7.63 (4H, m, phenyl 2,6-\(\text{H}\)), 7.50-7.30 (6H, m, phenyl 3,4,5-\(\text{H}\)), 5.61 (1H, ddd, \(J\) 16.7, 9.8 and 7.9, 4-\(\text{H}\)), 5.12 (1H, dd, \(J\) 9.8 and 1.0, 5-\(\text{H}_{\text{cis}}\)), 5.10 (1H, app. d, \(J\) 18.0, 5-\(\text{H}_{\text{trans}}\)), 4.73 (1H, br. s, NH), 3.87-3.63 (2H, m, ethyl 2-\(\text{H}\)), 3.34-3.12 (2H, m, 1-\(\text{H}\)), 3.07 (1H, app. q, \(J\) 6.9, 3-\(\text{H}\)), 2.78 (1H, app. dt, \(J\) 11.6 and 5.3, ethyl 1-\(\text{H}\)), 2.61 (1H, app. dt, \(J\) 12.0 and 5.1, ethyl 1-\(\text{H}\)), 1.63 (2H, app. q, \(J\) 6.7, 2-\(\text{H}\)), 1.43 (9H, s, Boc \(\text{tBu}\)), 1.06 (9H, s, TBDPS \(\text{tBu}\)); \(\delta_C\) (75 MHz, CDCl\(\text{3}\)) 156.1 (C=O), 140.5 (C-4), 135.6 (phenyl C\(\text{4-2,6}\)), 133.7 (phenyl C\(\text{2-1}\)), 129.8 (phenyl C\(\text{2-4}\)), 127.8 (phenyl C\(\text{4-3,5}\)), 116.3 (C-5), 79.1 (Boc \(\text{tBu}\) C\(\text{1}\)), 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 \(\text{tBu}\) C\(\text{3}\)), 27.0 (TBDPS \(\text{tBu}\) C\(\text{3}\)), 19.3 (TBDPS \(\text{tBu}\) C\(\text{1}\)); HRMS found MH\(^{+}\), 483.3048. C\(\text{28}\)H\(\text{42}\)N\(\text{2}\)O\(\text{3}\)Si requires MH, 483.3037.

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

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, \([\alpha_D]^{21}\) +4.10 (c 1.00, CHCl\(\text{3}\)); spectroscopically identical to the enantiomer previously prepared.
**tert-Butyl N-[[3R]-3-(N-{2-[[tert-butyldiphenylsilyloxy]ethyl]-1-phenylformimidopent-4-en-1-yl}carbamate**

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); \([\alpha]_D^{24}\) +19.6 (c 1.00, CHCl\(_3\)); \(v_{\text{max}}/\text{cm}^{-1}\) 3344, 3070, 2961, 2930, 2857, 1709, 1624, 1507, 1426, 1410, 1364, 1248, 1168, 1106; \(\delta_H\) (500 MHz, CD\(_3\)OD, 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); \(\delta_C\) (125 MHz, CD\(_3\)OD, 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\(_{48}\)N\(_2\)O\(_4\)Si 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-[(3S)-3-(N-2-[(tert-butyldiphenylsilyl)oxy]ethyl]-1-phenylformimidopent-4-en-1-yl]carbamate**

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 (0.12 g, 90%) as a colourless oil, [α]D$_{25}^2$ -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-[(3R)-3-[[2R]-1-hydroxypropan-2-yl]amino]pent-4-en-1-yl]carbamate**

According to General Procedure A, the allylic carbonate 88 (2.00 g, 7.70 mmol), (S,S,aS)-91 (0.17 g, 0.31 mmol) and (2R)-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$_4$OH to give the alkene 89e (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$_4$OH); [α]D$_{25}^2$ -10.6 (c 1.00, MeOH); $\nu$$_{max}$/cm$^{-1}$ 3369, 3254, 3074, 2969, 2934, 2893, 2831, 1682, 1524, 1365, 1250, 1219, 1166, 1039; δ$_H$ (500 MHz, CD$_3$OD) 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-[(3R)-3-(2-oxo-1,3-oxazolidin-3-yl)pent-4-en-1-yl]carbamate

![](image)

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); [α]_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\textsubscript{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-[(3R)-3-[(3R)-3-methyl-5-oxomorpholin-4-yl]pent-4-en-1-yl] carbamate**

![Chemical Structure](89g)

By modification of an existing procedure,\textsuperscript{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\textsubscript{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\textsuperscript{116} (0.65 g, 49%) as a yellow oil, \(R_t\) 0.28 (60:40 EtOAc–petrol; \([\alpha]D^{24}\) +49.0 (c 1.00, CHCl\textsubscript{3}); \(\nu_{\text{max}}/\text{cm}^{-1}\) 3327, 2974, 2930, 2872, 1705, 1636, 1518, 1364, 1270, 1248, 1166, 1150; \(\delta_H\) (500 MHz, CDCl\textsubscript{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-\(H_\Lambda\)), 4.13 (1H, d, J 16.8, morpholinyl 6-\(H_\beta\)), 3.75 (1H, dd, J 11.6 and 2.7, morpholinyl 2-\(H_\Lambda\)), 3.66 (1H, dd, J 11.6 and 2.0, morpholinyl 2-\(H_\beta\)), 3.54-3.47 (1H, m, morpholinyl 3-H), 3.33-3.22 (1H, m, 1-\(H_\Lambda\)), 3.06-2.95 (1H, m, 1-\(H_\beta\)), 2.03-1.96 (1H, m, 2-\(H_\Lambda\)), 1.95-1.87 (1H, m, 2-\(H_\beta\)), 1.43 (9H, s, \({^3}\text{Bu}) 1.31 (3H, d, J 6.5, methylmorpholinyl 1-\(H_3\)); \(m/z\) (ES) 321.1 (100%, Mn\textsuperscript{+})).
5.2.2.3. Cyclisation Reactions

General Procedure F

According to an existing procedure, 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$_2$CO$_3$ (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

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$_4$OH 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$_4$OH); $[\alpha]_D^{27} +14.5$ (c 1.00, CHCl$_3$); $\nu_{\text{max}}/\text{cm}^{-1}$ 2968, 2796, 1686, 1559, 1391, 1364, 1166, 1110; $\delta$H (500 MHz, CD$_3$OD, 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, tBu); $\delta$C (125 MHz, CD$_3$OD) 158.9 (pyrimidinyl C$_2$-4,6), 157.5 (pyrimidinyl C-2), 156.1 (pyrimidinyl C-5), 134.1 (C=O), 81.3 (tBu 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 (tBu C$_3$), 28.1 (C-4'), 24.2 (C$_2$-3,4); HRMS found MH$^+$, 333.2288. C$_{18}$H$_{28}$N$_4$O$_2$ requires MH, 333.2285. The absolute configuration was determined by comparison with analogues.
tert-Butyl (2R,3S)-3-(morpholin-4-yl)-2-[(pyrimidin-5-yl)methyl]pyrrolidine-1-carboxylate

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$_4$OH 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$_4$OH); $[\alpha]D^{23}$ $-$13.0 (c 1.00, CHCl$_3$); $\nu_{\text{max}}$/cm$^{-1}$ 2970, 2856, 2831, 1684, 1390, 1164, 1112; $\delta$H (500 MHz, CD$_3$OD, 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, tBu); $\delta$C (125 MHz, CD$_3$OD, 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 (tBu 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 (tBu C$_3$), 25.8 (C-4); HRMS found MH$^+$, 349.2241. C$_{18}$H$_{28}$N$_4$O$_3$ requires MH, 349.2234. The absolute configuration was determined by comparison with analogues.$^{116}$

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

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); $[\alpha]_D^{23}$ $-6.60$ (c 1.00, CHCl$_3$); $\nu_{\text{max}}$/cm$^{-1}$ 2949, 2809, 1685, 1389, 1363, 1162, 1111; $\delta_H$ (500 MHz, CD$_3$OD, 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, tBu); $\delta_C$ (125 MHz, CD$_3$OD, 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 (tBu C$_1$), 76.2 (bicyclooctanyl C$_A$-1,5), 76.1 (bicyclooctanyl C$_B$-1,5), 69.1 (pyrrolinylmethyl C-1), 61.6 (C-2), 56.7 (bicyclooctanyl C$_A$-2,4), 55.5 (bicyclooctanyl C$_B$-2,4), 46.3 (C-5), 37.0 (C-3), 29.0 (bicyclooctanyl C$_A$-6,7), 29.2 (bicyclooctanyl C$_B$-6,7), 28.8 (tBu C$_3$), 25.8 (C-4); HRMS found MH$^+$, 374.2445. C$_{21}$H$_{31}$N$_3$O$_3$ requires MH, 374.2438. The absolute configuration was determined by comparison with analogues.$^{116}$

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

![Structure of 90m](image)

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$_4$OH 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$_4$OH); $[\alpha]_D^{25}$ $+16.2$ (c 1.00, MeOH); $\nu_{\text{max}}$/cm$^{-1}$ 2975, 2930, 1742, 1683, 1479, 1389, 1165, 1115; $\delta_H$ (500 MHz, CD$_3$OD, 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-H₂), 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-Hₐ), 3.55 (1H, ddd, J 9.1, 8.3 and 7.1, oxazolidinyl 4-Hₐ), 3.46 (1H, app. td, J 8.7 and 6.6, oxazolidinyl 4-Hₐ), 3.23-3.13 (1H, m, 5-Hₐ), 3.00 (2H, app. d, J 5.7, pyridinylmethyl 1-H₂), 2.14-2.04 (1H, m, 4-Hₐ), 2.04-1.95 (1H, m, 4-Hₐ), 1.44 (9H, s, tBu); δC (125 MHz, CD₃OD, 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 (tBu C₁), 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 (tBu C₃), 27.9 (C-4); HRMS found MH⁺, 348.1917. The absolute configuration was determined by comparison with analogues.¹¹⁶

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

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 ¹H-NMR) was purified by flash column chromatography, eluting with 96.9:2.8:0.3 DCM–EtOH–NH₄OH to give the pyrrolidine derivative 90n (0.50 g, 61%, dr >95:<5 by ¹H-NMR) as a yellow oil, Rᵣ 0.15 (96.9:2.8:0.3 DCM–EtOH–NH₄OH); [α]²³ +35.4 (c 1.00, CHCl₃); ν_max/cm⁻¹ 2974, 2930, 2872, 1685, 1645, 1392, 1149, 1119; δH (500 MHz, CD₃OD, 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-Hₐ), 3.98 (1H, d, J 16.9, morpholinyl 6-Hₐ), 3.80-3.70 (1H, m, 5-Hₐ), 3.65 (1H, dd, J 11.6 and 1.6, morpholinyl 2-Hₐ), 3.54 (1H, dd, J 11.6 and 2.4, morpholinyl 2-Hₐ), 3.47-3.41 (1H, m, morpholinyl 3-H), 3.10-3.03 (1H, m, 5-Hₐ), 3.02 (2H, app. d, J 5.5, pyridinylmethyl 1-H₂), 2.07-2.01 (2H, m, 4-H₂), 1.44
(9H, s, tBu), 1.23 (3H, d, J 6.5, methylmorpholinyl 1-H3); m/z (ES) 376.1 (100%, MH+).

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

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, Rf 0.10 (84.7:13.6:1.7 DCM–EtOH–NH4OH); [αD]24 -18.0 (c 1.00, MeOH); νmax/cm⁻¹ 2969, 2487, 1663, 1560, 1412, 1194, 1170, 1117; δH (500 MHz, CD3OD) 9.16 (1H, s, pyrimidinyl 2-H), 8.88 (2H, s, pyrimidinyl 4,6-H2), 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'-H2 and 2,5-H4), 3.44 (1H, dd, J 15.2 and 5.8, pyrimidinylmethyl 1-HA), 3.19 (1H, dd, J 15.2 and 9.8, pyrimidinylmethyl 1-HB), 2.78-2.64 (1H, m, 4'-HA), 2.57-2.45 (1H, m, 4'-HB), 2.16-2.08 (4H, m, 3,4-H4); δc (125 MHz, CD3OD) 162.2 (q, J 36.8, TFA C=O), 159.1 (pyrimidinyl C2=4,6), 158.7 (pyrimidinyl C-2), 117.5 (q, J 289.8, TFA CF3), 116.0 (q, J 284.4, TFA CF3), 68.1 (C-3'), 62.6 (C-2'), 45.3 (C-5' and C2=2,5), 32.8 (pyrimidinylmethyl C-1), 28.5 (C-4'), 23.9 (C2=3,4); HRMS found MH+, 233.1759. C13H21N4 requires MH+ 233.1760.

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

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, Rf 0.11 (84.7:13.6:1.7 DCM–EtOH–NH4OH); [αD]25 +15.4 (c 1.00, MeOH); νmax/cm⁻¹ 2979, 2482, 1664,
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, Rf 0.15 (84.7:13.6:1.7 DCM−EtOH−NH₄OH); [α]D₂⁵ +16.4 (c 1.00, MeOH); νmax/cm⁻¹ 2978, 2638, 1662, 1434, 1172, 1126; δH (500 MHz, CD₃OD) 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-HA), 4.28−4.23 (1H, m, bicyclooctanyl 1,5-HB), 4.03−3.96 (1H, m-under residual solvent peak, 2-H), 3.48−3.34 (5H, m, 3-H, 5-H₂ and pyridinylmethyl 1-H₂), 2.75−2.54 (4H, m, bicyclooctanyl 2,4-H₄), 2.26−2.12 (2H, m, 4-H₂), 1.85−1.79 (2H, m, bicyclooctanyl 6-H₄ and bicyclooctanyl 7-H₄), 1.68 (2H, app. d, J 6.6, bicyclooctanyl 6-H₄ and bicyclooctanyl 7-H₄); δC (125 MHz, CD₃OD) 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 CF₃), 116.0 (q, J 284.4, TFA CF₃), 75.6
(bicyclooctanyl C<sub>A-1,5</sub>), 75.3 (bicyclooctanyl C<sub>B-1,5</sub>), 69.7 (C-3), 60.3 (C-2), 58.6 (bicyclooctanyl C<sub>A-2,4</sub>), 53.2 (bicyclooctanyl C<sub>B-2,4</sub>), 45.3 (C-5), 35.2 (pyridinylmethyl C-1), 28.8 (bicyclooctanyl C<sub>2-6,7</sub>), 23.7 (C-4); HRMS found MH<sup>+</sup>, 274.1908. C<sub>16</sub>H<sub>23</sub>N<sub>3</sub>O requires MH<sup>+</sup>, 274.1913.

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

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<sub>f</sub> 0.11 (84.7:13.6:1.7 DCM−EtOH−NH₄OH); [α]<sub>D</sub><sup>23</sup> −11.0 (c 1.00, MeOH); ν<sub>max</sub>/cm⁻¹ 2961, 2687, 2521, 1725, 1659, 1439, 1170, 1125; δ<sub>H</sub> (500 MHz, CD₃OD) 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<sub>A</sub>), 4.18 (1H, app. td, J 8.8 and 7.4, oxazolidinyl 5-H<sub>B</sub>), 4.08 (1H, app. q, J 7.7, 2-H), 3.60-3.51 (2H, m, oxazolidinyl 4-H<sub>2</sub>), 3.52-3.45 (2H, m, 5-H<sub>2</sub>), 3.27 (2H, dd, J 7.5 and 2.9, pyridinylmethyl 1-H<sub>2</sub>), 2.38-2.29 (1H, m, 4-H<sub>A</sub>), 2.29-2.21 (1H, m, 4-H<sub>B</sub>); δ<sub>C</sub> (75 MHz, CD₃OD) 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 CF₃), 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<sup>+</sup>, 248.1387. C<sub>13</sub>H<sub>17</sub>N<sub>3</sub>O<sub>2</sub> requires MH<sup>+</sup>, 248.1393.
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$_4$OH); [α$_D$]$_{23}^2$ −28.8 (c 1.00, MeOH); $\nu_{\text{max}}$/cm$^{-1}$ 2982, 2677, 1663, 1662, 1172, 1122; $\delta_H$ (500 MHz, CD$_3$OD) 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), 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$_3$); $\delta_C$ (125 MHz, CD$_3$OD) 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$_3$O$_2$ 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, 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 NH₄Cl (5 mL per 1.00 mmol of the carbonyl derivative) was added. The phases were separated and the aqueous phase was extracted with Et₂O or EtOAc (3 × (2 mL per 1.00 mmol of the carbonyl derivative)). Finally, the organic phases were combined, dried (MgSO₄), filtered and concentrated under reduced pressure to give a crude material.

**General Procedure H**

By modification of an existing procedure, 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 NH₄Cl (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 (MgSO₄), filtered and concentrated under reduced pressure to give a crude material.

**4-Benzoylmorpholin-3-one**

![Structure of 4-Benzoylmorpholin-3-one](image)

By modification of an existing procedure, 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 Et₂O (125 mL), cooled to 0 °C and the solvent was removed by filtration. The precipitate was washed with cold Et₂O (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 (MgSO₄), filtered and concentrated under reduced pressure to yield the benzoyl derivative 154a (20.7 g, 78%) as white crystals, m.p. (Et₂O) 61–64 °C; Rᵋ 0.50 (50:50 petrol–EtOAc); νmax/cm⁻¹ 2944, 2893, 2866, 1702, 1672, 1462, 1450, 1375, 1347, 1302, 1278, 1216, 1138; δH (500 MHz, CDCl₃) 7.59–7.56 (2H, m, phenyl 2,6-H₂), 7.50 (1H, tt, J 6.9 and 1.2, phenyl 4-H), 7.43–7.37 (2H, m, phenyl 3,5-H₂), 4.27 (1H, s, 2-H₂), 4.02 (2H, dd, J 6.0 and 4.4, 6-H₂), 3.93 (2H, dd, J 6.0 and 4.4, 5-H₂); δC (125 MHz, CDCl₃) 172.8 (C-3), 169.0 (benzoyl C=O), 135.4 (phenyl C-1), 132.0 (phenyl C-4), 128.2 (phenyl C₄-2,3,5,6), 68.8 (C-2), 64.1 (C-6), 44.7 (C-5); HRMS found MH⁺, 206.0811. C₁₁H₁₁NO₃ requires MH⁻, 206.0811.

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

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 (10.6 g, >99%) as a colourless oil, Rᵋ 0.38 (50:50 petrol–EtOAc); νmax/cm⁻¹ 3131, 2952, 1755, 1471, 1391, 1314, 1278, 1237, 1171, 1094; δH (500 MHz, CDCl₃) 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-Htrans), 5.36 (1H, dq, J 10.4 and 1.2, propenyl 3-Hcis), 4.87 (2H, dt, J 6.0 and 1.2, propenyl 1-H₂); δC (125 MHz, CDCl₃) 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. C₇H₈N₂O₂ requires MH⁻, 153.0658.
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$_2$O 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); $\nu_{\text{max}}$/cm$^{-1}$ 2950, 2893, 1745, 1685, 1449, 1373, 1274, 1227, 1155, 1139; $\delta$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$_{\text{trans}}$), 5.30 (1H, app. dq, J 10.5 and 1.3, propenyl 3-H$_{\text{cis}}$), 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$_A$); $\delta$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.

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 \textit{allyl ester derivative} 146b (3.48 g, 45%, \textit{keto:enol} 24:76 by $^1$H-NMR in CDCl$_3$) as a colourless oil, $R_t$ 0.72 (50:50 petrol–EtOAc); $\nu_{\text{max}}$/cm$^{-1}$ 2968, 2856, 1741, 1718, 1663, 1624, 1395, 1305, 1216, 1101, 1047; $\delta_H$ (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$_{\text{trans}}$\textit{keto}), 5.31 (1H, app. dq, $J$ 17.3 and 1.5, propenyl 3-H$_{\text{trans}}$\textit{enol}), 5.26 (1H, app. dd, $J$ 10.5 and 1.2, propenyl 3-H$_{\text{cis}}$\textit{keto}), 5.25 (1H, app. dq, $J$ 10.5 and 1.5, propenyl 3-H$_{\text{cis}}$\textit{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$_2$\textit{enol}), 4.23 (1H, dd, $J$ 11.6 and 7.1, 2-H$_A$\textit{keto}), 4.11 (1H, ddd, $J$ 11.6, 5.1 and 0.9, 2-H$_B$\textit{keto}), 4.05-3.93 (2H, m, 6-H$_2$\textit{enol}), 3.84 (2H, t, $J$ 5.7, 6-H$_2$\textit{enol}), 3.50 (1H, app. ddd, $J$ 6.8, 5.1 and 1.3, 3-H$_B$\textit{keto}), 2.67 (1H, ddd, $J$ 14.5, 6.2 and 5.1, 5-H$_A$\textit{keto}), 2.55 (1H, dddd, $J$ 14.5, 7.1, 5.5 and 1.3, 5-H$_B$\textit{keto}), 2.39 (2H, tt, $J$ 5.7 and 1.7, 5-H$_2$\textit{enol}); $\delta_C$ (75 MHz, CDCl$_3$) 201.2 (C-4\textit{keto}), 169.7 (carboxylate C=O\textit{enol}), 169.3 (C-4\textit{enol}), 167.5 (carboxylate C=O\textit{keto}), 131.9 (propenyl C-2\textit{enol}), 131.5 (propenyl C-2\textit{keto}), 118.8 (propenyl C-3\textit{keto}), 118.3 (propenyl C-3\textit{enol}), 97.3 (C-3\textit{enol}), 69.6 (C-2\textit{keto}), 68.2 (C-6\textit{keto}), 66.0 (propenyl C-1\textit{keto}), 64.8 (propenyl C-1\textit{enol}), 63.9 (C-6\textit{enol}), 63.0 (C-2\textit{enol}), 57.8 (C-3\textit{keto}), 42.0 (C-5\textit{keto}), 28.8 (C-5\textit{enol}); HRMS found MNa$^+$, 207.0627. C$_9$H$_{12}$O$_4$ requires MNa, 207.0627. Compound 146b existed as a mixture of keto and enol tautomers.

\textbf{1-Benzy 3-prop-2-en-1-yl 4-hydroxy-1,2,5,6-tetrahydropyridine-1,3-dicarboxylate}

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 \textit{allyl ester derivative} 146c (5.77 g, 40%, >98% \textit{enol} by $^1$H-NMR in CDCl$_3$) as a colourless oil, $R_t$ 0.60 (70:30 petrol–EtOAc); $\nu_{\text{max}}$/cm$^{-1}$ 3032, 2945, 1697, 1662, 1620, 1422, 1305, 1227, 1193, 1111, 1056; $\delta_H$ (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$_{\text{trans}}$), 5.26 (1H, app. dq, $J$ 10.5 and 1.4, propenyl 3-H$_{\text{cis}}$), 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$_2$); $\delta$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-1H-indene-2-carboxylate

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 (5.23 g, 47%) as a brown oil, $R_f$ 0.56 (70:30 petrol–EtOAc); $\nu_{\text{max}}$/cm$^{-1}$ 2940, 2837, 1736, 1704, 1571, 1491, 1432, 1317, 1296, 1273, 1204, 1184, 1148, 1024; $\delta$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$_{\text{trans}}$), 5.26 (1H, app. dq, J 10.5 and 1.4, propenyl 3-H$_{\text{cis}}$), 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$_B$); $\delta$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

According to an existing procedure, 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 Et₂O (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 Et₂O (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 Et₂O (4 × 100 mL). The organic phases were combined, washed with brine (300 mL), dried (MgSO₄), 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, Rᵣ 0.43 (70:30 petrol–EtOAc); ν<sub>max</sub>/cm⁻¹ 2951, 2883, 1770, 1725; δ<sub>H</sub> (400 MHz, CDCl₃) 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<sub>trans</sub>), 5.26 (1H, dd, J 10.3 and 1.4, propenyl 3-H<sub>cis</sub>), 4.71-4.60 (2H, m, propenyl 1-H₂), 4.49 (1H, dd, J 9.7 and 8.3, 2-H<sub>α</sub>), 4.44 (1H, dd, J 9.7 and 8.3, 2-H<sub>β</sub>), 4.02 (1H, d, J 17.1, 5-H<sub>α</sub>), 3.94 (1H, d, J 17.1, 5-H<sub>β</sub>), 3.53 (1H, t, J 8.3, 3-H); δ<sub>C</sub> (100 MHz, CDCl₃) 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. C₈H₁₀O₄ requires MNa, 193.0471.

5.2.3.2. Connective Reactions

General Procedure I

According to an existing procedure, 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, Cs₂CO₃ (2.50 eq) was added and the reaction was stirred for the specified time at rt. Subsequently, a saturated
aqueous solution of NH₄Cl (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 (MgSO₄), filtered and concentrated under reduced pressure to give a crude material.

**General Procedure J**

By modification of an existing procedure, the specified amount of K₂CO₃ 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 NH₄Cl (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 (MgSO₄), filtered and concentrated under reduced pressure to give a crude material.

**General Procedure K**

According to an existing procedure, PPh₃ (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**

![tert-Butyl N-[(benzenesulfonyl)methyl]carbamate](image)

According to an existing procedure, 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 Et₂O (100 mL). Subsequently, the precipitate was dissolved in DCM (500 mL), dried (MgSO₄), filtered and concentrated under reduced pressure to afford the carbamate derivative 153 (37.9 g, 65%) as a crystalline white powder, m.p. (DCM) 155−160 °C; Rf 0.63 (50:50 petrol−EtOAc); νmax/cm⁻¹ 3352, 3011, 2980, 2934, 1699, 1475, 1358, 1288, 1135, 1087, 1007; δH (400 MHz, CDCl₃) 7.92 (2H, d, J 7.5, phenyl 2,6-H₂), 7.65 (1H, t, J 7.5, phenyl 4-H), 7.54 (2H, t, J 7.5, phenyl 3,5-H₂), 5.47 (1H, t, J 6.9, NH), 4.53 (2H, d, J 6.9, 1-H₂), 1.25 (9H, s, tBu); δC (100 MHz, CDCl₃) 153.9 (C=O), 137.0 (phenyl C-1), 134.1 (phenyl C-4), 129.3 (phenyl C-3,5), 129.1 (phenyl C-2,6), 81.1 (tBu C₁), 62.2 (C-1), 28.1 (tBu C₃); HRMS found MH⁺, 272.0946. C₁₂H₁₇NO₄S requires MH⁺, 272.0951.

Prop-2-ene-1-yl-4-benzoyl-2-((tert-butoxycarbonyl)amino)methyl)-3-oxomorpholine-2-carboxylate

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 (6.00 g, 83%) as a colourless oil, Rf 0.70 (50:50 petrol−EtOAc); νmax/cm⁻¹ 3390, 2977, 1687, 1504, 1366, 1275, 1228, 1143, 1064; δH (500 MHz, CDCl₃) 7.69-7.62 (2H, m, phenyl 2,6-H₂), 7.52 (1H, tt, J 7.1 and 1.2, phenyl 4-H), 7.42-7.37 (2H, m, phenyl 3,5-H₂), 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-Htrans), 5.32 (1H, app. dq, J 10.4 and 1.3, propenyl 3-Hcis), 5.00 (1H, br. s, NH), 4.74 (2H, app. d, J 5.8, propenyl 1-H₂), 4.30-4.23 (1H, m, 6-HA), 4.19 (1H, dt, J 12.3 and 4.0, 6-HB), 4.00 (1H, ddd, J 13.4, 9.3 and 4.0, 5-HA), 3.92 (1H, dt, J 13.4 and 3.6, 5-HB), 3.82 (1H, dd, J 14.3 and 7.4, methylcarbamate 1-HA), 3.74 (1H, dd, J 14.3 and 5.8, methylcarbamate 1-HB),
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, Rf 0.67 (50:50 petrol–EtOAc); νmax/cm−1 3403, 2976, 2934, 2868, 1709, 1501, 1366, 1249, 1225, 1212, 1163, 1135, 1112; δH (400 MHz, CDCl3) 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-Htrans), 5.24 (1H, app. dq, J 10.4 and 1.4, propenyl 3-Hcis), 5.09 (1H, app. t, J 5.6, NH), 4.65 (1H, app. t, J 1.4, propenyl 1-Ha), 4.64 (1H, app. t, J 1.4, propenyl 1-Hb), 4.44 (1H, d, J 11.8, 2-Ha), 4.14-4.05 (1H, m, 6-Ha), 3.87-3.76 (1H, m, 6-Hb), 3.60 (1H, dd, J 14.1 and 6.8, methylcarbamate 1-Ha), 3.58 (1H, d, J 11.8, 2-Hb), 3.50 (1H, dd, J 14.1 and 6.8, methylcarbamate 1-Hb), 2.76 (1H, ddd, J 15.4, 9.3 and 6.4, 5-Ha), 2.59 (1H, app. dt, J 14.9 and 4.4, 5-Hb), 1.38 (9H, s, 1Bu); δC (100 MHz, CDCl3) 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 (1Bu C1), 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 (1Bu C3); HRMS found MH+, 314.1601. C15H23NO6 requires MH, 314.1598.
1-Benzyl 3-prop-2-en-1-yl 3-(((tert-butoxy)carbonyl]amino)methyl)-4-oxopiperidine-1,3-dicarboxylate

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, Rf 0.63 (50:50 petrol–EtOAc); νmax/cm^-1 3398, 2977, 1697, 1499, 1423, 1365, 1234, 1138; δH (500 MHz, CD3OD, 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-Htrans), 5.19 (1H, app. dq, J 10.5 and 1.4, propenyl 3-Hcis), 5.16 (1H, app. s, phenylmethyl 1-HA), 5.15 (1H, app. s, phenylmethyl 1-HB), 4.61 (1H, d, J 13.9, 2-HA), 4.57-4.52 (2H, m, propenyl 1-H2), 4.18-4.09 (1H, m, 6-HA), 3.61 (1H, d, J 14.4, methylcarbamate 1-HA), 3.46 (1H, d, J 14.4, methylcarbamate 1-HB), 3.46-3.39 (1H, m, 6-HB), 3.35 (1H, d, J 13.9, 2-HB), 2.68 (1H, ddd, J 15.2, 9.9 and 6.5, 5-HA), 2.53 (1H, app. dt, J 15.2 and 4.7, 5-HB), 1.41 (9H, s, ‘Bu); δC (125 MHz, CD3OD, 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 C2-3,5), 129.2 (phenyl C-4), 129.0 (phenyl C2-2,6), 119.3 (propenyl C-3), 80.7 (‘Bu C1), 68.9 (phenethylmethyl 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 (‘Bu C3); HRMS found MNa+, 469.1936. C23H30N2O7 requires MNa, 469.1945.
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); \( \nu_{\text{max}}/\text{cm}^{-1} \) 3377, 2974, 2940, 1727, 1697, 1514, 1492, 1280, 1241, 1189, 1161, 1134; \( \delta \) (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\(_{\text{trans}}\)), 5.18 (1H, br. s, NH), 5.17 (1H, dd, \( J = 10.6 \) and 1.3, propenyl 3-H\(_{\text{cis}}\)), 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, \( ^{\text{T}}\)Bu); \( \delta \) (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 (\( ^{\text{T}}\)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 (\( ^{\text{T}}\)Bu, C\(_3\)); HRMS found \( M\text{Na}^+ \), 398.1572. C\(_{20}\)H\(_{25}\)NO\(_6\) requires \( M\text{Na}^+ \), 398.1574.

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

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, $R_t$ 0.41 (70:30 petrol–EtOAc); $\nu_{\text{max}}/\text{cm}^{-1}$ 3367, 2978, 1770, 1710, 1504, 1366; $\delta_H$ (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$_{\text{trans}}$), 5.25 (1H, app. t, $J$ 1.4, propenyl 1-H$_A$), 4.65 (1H, app. t, $J$ 1.4, propenyl 1-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, tert-Bu); $\delta_C$ (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**

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

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 *$\alpha,\beta$-unsaturated ester* 157 (0.39 g, 67%) as a light-yellow oil, $R_t$ 0.54 (70:30 petrol–EtOAc); $\nu_{\text{max}}/\text{cm}^{-1}$ 3366, 2978, 2933, 1702, 1509, 1365, 1249, 1154; $\delta_H$ (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$_{\text{trans}}$), 5.23 (1H, app. dq, $J$ 10.4 and 1.4, propenyl 3-H$_{\text{cis}}$), 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, tert-Bu); $\delta_C$ (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.
According to General Procedure J, the allyl ester derivative \textbf{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 \textit{quaternary allyl ester derivative} \textbf{147f} (0.86 g, 89\%) as a colourless oil, \(R_f\) 0.38 (70:30 petrol–\(EtOAc\)); \(\nu_{\text{max}}/\text{cm}^{-1}\) 3063, 3030, 2936, 1698, 1427, 1266, 1239, 1217, 1178, 1121; \(\delta_H\) (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\textsubscript{trans}), 5.21 (1H, app. dq, \(J\) 10.7 and 1.3, propenyl 3-H\textsubscript{cis}), 5.17 (1H, app. s, Cbz phenylmethyl 1-H\textsubscript{A}), 5.16 (1H, app. s, Cbz phenylmethyl 1-H\textsubscript{B}), 4.72 (1H, dd, \(J\) 13.8 and 2.1, 2-H\textsubscript{A}), 4.50 (2H, d, \(J\) 5.6, propenyl 1-H\textsubscript{2}), 4.25 (1H, app. br. s, 6-H\textsubscript{A}), 3.31 (1H, d, \(J\) 13.9, phenylmethyl 1-H\textsubscript{A}), 3.31-3.25 (1H, m, 6-H\textsubscript{B}), 3.17 (1H, d, \(J\) 13.9, phenylmethyl 1-H\textsubscript{B}), 3.14 (1H, d, \(J\) 13.8, 2-H\textsubscript{B}), 2.75 (1H, ddd, \(J\) 14.9, 10.4 and 6.6, 5-H\textsubscript{A}), 2.49 (1H, app. dt, \(J\) 14.9 and 4.4, 5-H\textsubscript{B}); \(\delta_C\) (125 MHz, \(CDCl_3\), 323 K) 203.5 (C=O), 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\textsubscript{2}-2,6), 128.6 (Cbz phenyl C\textsubscript{2}-3,5), 128.5 (phenyl C\textsubscript{2}-3,5), 128.2 (Cbz phenyl C\textsubscript{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 \(M\text{Na}^+\), 430.1624. \(C_{24}H_{25}NO_5\) requires \(M\text{Na}\), 430.1630.
1-Benzyl 3-prop-2-en-1-yl 4-oxo-3-[(pyridin-3-yl)methyl]piperidine-1,3-dicarboxylate

According to General Procedure J, the allyl ester derivative 146c (1.00 g, 3.15 mmol), K$_2$CO$_3$ (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); $\nu_{\text{max}}$/cm$^{-1}$ 3031, 2946, 1697, 1423, 1235, 1215, 1177, 1125; $\delta_H$ (500 MHz, CD$_3$OD, 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 $J_{6.0}$, propenyl 2-$H$), 4.05 (1H, dd, $J_{16.9}$ and 1.4, propenyl 3-$H_{\text{trans}}$), 4.01 (1H, dd, $J_{10.1}$ and 1.4, propenyl 3-$H_{\text{cis}}$), 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-$H_B$); $\delta_C$ (125 MHz, CD$_3$OD, 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$_2$O$_5$ requires MH, 409.1763.
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 (4.30 g, 80%) as a brown oil, Rf 0.65 (50:50 petrol–EtOAc); νmax/cm⁻¹ 3379, 2977, 2933, 1682, 1505, 1366, 1277, 1246, 1221, 1140, 1116, 1087; δH (400 MHz, CDCl₃) 7.55 (2H, d, J 7.6, phenyl 2,6-H₂), 7.50 (1H, t, J 7.6, phenyl 4-H), 7.39 (2H, t, J 7.6, phenyl 3,5-H₂), 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-H₂), 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, tBu); δC (100 MHz, CDCl₃) 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 C₂-3,5), 128.0 (phenyl C₂-2,6), 119.8 (propenyl C-3), 82.1 (C-2), 79.7 (tBu C₁), 60.4 (C-6), 45.7 (methylcarbamate C-1), 45.4 (C-5), 39.7 (propenyl C-1), 28.4 (tBu C₃); HRMS found MH⁺, 375.1919. C₂₀H₂₆N₂O₅ requires MH, 375.1914

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

By modification of an existing procedure, toluene (8.00 mL) was added to a mixture of PPh₃ (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, Rf 0.52 (50:50 petrol–EtOAc); νmax/cm⁻¹ 3369, 2976, 2930, 1682, 1507, 1366, 1275, 1226, 1158, 1136; δH (400 MHz, CDCl₃) 7.57-7.54 (2H, m, phenyl 2,6-H₂), 7.51 (1H, tt, J 7.5 and 1.3, phenyl 4-H), 7.41 (2H, app. t, J 7.5, phenyl 3,5-H₂), 4.94 (1H, br., NH), 4.26-4.21 (2H, m, 2-H and 6-Hₐ), 4.02-3.95 (1H, m, 5-Hₐ), 3.68-3.53 (2H, m, methylcarbamate 1-H₂), 1.45 (9H, s, tBu); δC (100 MHz, CDCl₃) 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 C₂-3,5), 128.1 (phenyl C₂-2,6), 79.8 (tBu C₇), 77.5 (C-2), 63.4 (C-6), 45.1 (C-5), 41.9 (methylcarbamate C-1), 28.5 (tBu C₃); HRMS found MNa⁺, 357.1431. C₁₇H₂₂N₂O₅ requires MNa, 357.1426.

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

![Structure of tert-Butyl N-[[4-oxo-3-(prop-2-en-1-yl)oxan-3-yl]methyl]carbamate](image)

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, Rf 0.39 (70:30 petrol–EtOAc); νmax/cm⁻¹ 3351, 2975, 2932, 2861, 1702, 1504, 1365, 1246, 1214, 1163, 1115; δH (400 MHz, CDCl₃) 5.66 (1H, app. dq, J 16.8 and 7.5, propenyl 2-H), 5.15-5.10 (2H, m, propenyl 3-H₂), 4.83 (1H, br. s, NH), 4.14-4.07 (1H, m, 6-Hₐ), 3.83 (1H, d, J 11.8, 2-Hₐ), 3.80-3.77 (1H, m, 6-Hₐ), 3.59 (1H, d, J 11.8, 2-Hₐ), 3.35 (1H, dd, J 14.3 and 7.9, methylcarbamate 1-Hₐ), 3.26 (1H, dd, J 14.3 and 5.5, methylcarbamate 1-Hₐ), 2.65 (1H, ddd, J 15.1, 9.8 and 6.5, 5-Hₐ), 2.53 (1H, dd, J 14.3 and 7.5, propenyl 1-Hₐ), 2.47 (1H, app. dt, J 15.1 and 4.1, 5-Hₐ), 2.34 (1H, dd, J 14.3 and 7.5, propenyl 1-Hₐ), 1.41 (9H, s, tBu); δC (100 MHz, CDCl₃) 210.1 (C-4), 156.0 (Boc C=O), 131.9 (propenyl C-2), 119.3 (propenyl C-3), 79.4 (tBu C₇), 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 (tBu C₃); HRMS found MH⁺, 270.1701. C₁₄H₂₃NO₄ requires MH, 270.1699.

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

![Chemical Structure](image)

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, Rᵣ 0.74 (50:50 petrol–EtOAc); v_max/cm⁻¹ 3366, 2976, 2931, 1689, 1429, 1365, 1273, 1157; δ_H (500 MHz, CD₃OD, 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-H₂), 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), 3.57 (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, tBu); δ_C (125 MHz, CD₃OD) 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 (tBu C₁), 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 (tBu C₃); HRMS found MNa⁺, 425.2043. C₂₂H₃₀N₂O₅ requires MNa, 425.2046.
tert-Butyl N-[[6-methoxy-1-oxo-2-(prop-2-en-1-yl)-2,3-dihydro-1H-inden-2-yl]methyl] carbamate

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); $\nu_{\max }$/cm$^{-1}$ 3359, 2975, 2928, 1694, 1490, 1274, 1245, 1161; $\delta_H$ (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-$H_{\text{trans}}$), 5.00 (1H, dd, $J$ 10.1 and 1.9, propenyl 3-$H_{\text{cis}}$), 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); $\delta_C$ (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

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); $\nu_{\max }$/cm$^{-1}$ 3357, 2977, 2933, 1697, 1515, 1392, 1366, 1248,
156

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, Rf 0.45 (70:30
petrol–EtOAc); νmax/cm⁻¹ 3063, 3029, 2916, 1694, 1430, 1231; δH (500 MHz,
CD3OD, 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-H₂), 5.05 (1H, app. d, J 10.4,
propenyl 3-Hcis), 5.03 (1H, app. d, J 17.6, propenyl 3-Htrans), 3.77 (1H, app. dt, J
13.0 and 6.5, 6-H₆), 3.68 (1H, d, J 13.8, 2-H₆), 3.58 (1H, d, J 13.8, 2-H₈), 3.56-
3.51 (1H, m, 6-H₆), 2.93 (1H, d, J 13.9, phenylmethyl 1-H₆), 2.80 (1H, d, J 13.9,
phenylmethyl 1-H₈), 2.55-2.40 (2H, m, 5-H₂), 2.31 (1H, dd, J 14.3 and 6.8,
propenyl 1-H₆), 2.16 (1H, dd, J 14.3 and 7.8, propenyl 1-H₈); δC (125 MHz,
CD3OD, 333 K) 212.0 (C₄), 157.2 (Cbz C=O), 137.9 (Cbz phenyl C-1), 137.8
(phenyl C-1), 134.0 (propenyl C-2), 131.5 (phenyl C₂-3,5), 129.5 (Cbz phenyl
C₂-3,5), 129.2 (phenyl C₂-2,6 and Cbz phenyl C₂-2,6), 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

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

```
```

1158, 1059; δH (400 MHz, CDCl₃) 5.70 (1H, ddt, J 16.6, 10.5 and 7.4, propenyl
2-H), 5.14–5.10 (1H, m, propenyl 3-Htrans), 5.12–5.08 (1H, m, propenyl 3-Hcis),
4.84 (1H, app. t, J 5.3, NH), 4.10 (1H, d, J 9.9, 2-H₆b), 3.99 (1H, d, J 9.9, 2-H₆b),
3.94 (2H, app. s, 5-H₂), 3.31 (1H, app. s, methylcarbamate 1-H₆a), 3.29 (1H,
app. s, methylcarbamate 1-H₆b), 2.27 (1H, app. d, J 1.2, propenyl 1-H₆a), 2.25
(1H, app. d, J 1.2, propenyl 1-H₆b), 1.40 (9H, s, tBu); δC (100 MHz, CDCl₃) 217.6
(C-4), 156.2 (Boc C=O), 131.9 (propenyl C-2), 119.8 (propenyl C-3), 79.9 (tBu
C₁), 73.8 (C-2), 71.5 (C-5), 52.5 (C-3), 42.4 (methylcarbamate C-1), 36.3
(propenyl C-1), 28.4 (tBu C₃); HRMS found MNa⁺, 278.1362. C₁₃H₂₁NO₄
requires MNa, 278.1362.
(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**

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); \nu_{\text{max}}/\text{cm}^{-1} 3030, 2915, 1693, 1422, 1230; \delta_{H} (500 MHz, CD_{3}OD, 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), 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}); \delta_{C} (125 MHz, CD_{3}OD, 333 K) 211.3 (C-4), 157.2 (C_{Bz} 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_{2}O_{3} requires MH, 365.1865.
5.2.3.3. Cyclisation Reactions

General Procedure L

By modification of an existing procedure,\textsuperscript{158} 2-methyl-2-butene (7.50 eq) was added dropwise to BH\textsubscript{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\textsubscript{3}•4H\textsubscript{2}O (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\textsubscript{4}), filtered and concentrated under reduced pressure to give a crude material.

General Procedure M

TFA (20.0 eq) and Et\textsubscript{3}SiH (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\textsubscript{3}N (10.0 eq) and Boc\textsubscript{2}O (1.20 eq) were added. After stirring the reaction mixture for 18 h at rt, a saturated aqueous solution of NaHCO\textsubscript{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\textsubscript{4}), filtered and concentrated under reduced pressure to give a crude material.

General Procedure N

By modification of an existing procedure,\textsuperscript{161} Et\textsubscript{3}SiH (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\textsubscript{3}•Et\textsubscript{2}O (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\textsubscript{3}N (5.00 eq) and Boc\textsubscript{2}O (1.20 eq) were added and the reaction mixture was stirred overnight at rt. A saturated aqueous solution of NH\textsubscript{4}Cl (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 (MgSO₄), filtered and concentrated under reduced pressure to give a crude material.

**General Procedure O**

TFA (20.0 eq) and Et₃SiH (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 NaHCO₃ (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 (MgSO₄), filtered and concentrated under reduced pressure to give a crude material.

**General Procedure P**

TsOH•H₂O (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, 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 (MgSO₄), filtered and concentrated under reduced pressure to give a crude material.

General Procedure S
According to an existing procedure,¹¹⁹ NaHCO₃ (2.00 eq) and I₂ (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 Na₂S₂O₃ (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 (MgSO₄), filtered and concentrated under reduced pressure to give a crude material.

General Procedure T
¹'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 NH₄Cl (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 (MgSO₄), 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 Ac₂O (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% CuSO₄ (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 (MgSO₄), 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 NaHCO₃ (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 (MgSO₄), 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, 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\(_2\)O (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**

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); \(\nu_{\text{max}}/\text{cm}^{-1}\) 3301, 2960, 2880, 1692, 1594, 1365, 1283, 1273, 1254, 1170, 1109, 1068; \(\delta_{\text{H}}\) (400 MHz, CD\(_3\)OD) 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\textsubscript{A}), 3.80 (1H, app. tt, J 5.5 and 1.2, 7-H\textsubscript{A}), 3.69-3.60 (2H, m, 2-H\textsubscript{B} and 7-H\textsubscript{B}), 3.44 (1H, d, J 11.6, 5-H\textsubscript{B}), 3.40-3.32 (3H, m, OH and methylcarbamate 1-H\textsubscript{2}), 2.02 (1H, td, J 13.1 and 5.5, 8-H\textsubscript{A}), 1.92 (1H, app. td, J 13.3 and 4.9, 3-H\textsubscript{A}), 1.79 (1H, app. qt, J 13.3 and 4.6, 3-H\textsubscript{B}), 1.57 (1H, app. d, J 13.5, 8-H\textsubscript{B}), 1.47 (9H, s, \textsuperscript{t}Bu), 1.46-1.39 (1H, m, 4-H\textsubscript{A}), 1.25 (1H, app. d, J 13.7, 4-H\textsubscript{B}); \(\delta\)\textsubscript{C} (100 MHz, CD\textsubscript{3}OD) 158.7 (Boc C=O), 96.0 (C-8a), 79.8 (\textsuperscript{t}Bu C\textsubscript{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 (\textsuperscript{t}Bu C\textsubscript{3}), 24.6 (C-4), 22.3 (C-3); HRMS found MNa\textsuperscript{+}, 310.1628.

**C\textsubscript{14}H\textsubscript{25}NO\textsubscript{5}** requires MNa, 310.1624.

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

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 \textsuperscript{1}H-NMR) as an amorphous colourless solid, \(R_f\) 0.37 (50:50 petrol–EtOAc); \(\nu\textsubscript{max}/cm\textsuperscript{-1}\) 3317, 2957, 2889, 2472, 1672, 1432, 1363, 1250, 1164, 1142, 1089, 1065; \(\delta\text{H} (500 MHz, CD\textsubscript{3}OD, 333 K)\) \(7.42-7.26 (5H, m, phenyl), 5.14 (1H, d, J 12.4, phenethyl 1-H\textsubscript{A}), 5.11 (1H, d, J 12.4, phenethyl 1-H\textsubscript{B}), 4.02 (1H, td, J 11.9 and 3.2, 2-H\textsubscript{A}), 3.95 (1H, app. dt, J 13.1 and 2.6, 7-H\textsubscript{A}), 3.66-3.57 (2H, m, 2-H\textsubscript{B} and 5-H\textsubscript{A}), 3.40-3.33 (3H, m, 5-H\textsubscript{B} and methylcarbamate 1-H\textsubscript{2}), 3.08 (1H, td, J 13.1 and 3.4, 7-H\textsubscript{B}), 2.93 (1H, br. s, OH), 1.95 (1H, td, J 13.5 and 5.0, 4-H\textsubscript{A}), 1.83-1.71 (2H, m, 8-H\textsubscript{A} and 3-H\textsubscript{A}), 1.65-1.51 (1H, m, 8-H\textsubscript{B}), 1.42 (10H, s, \textsuperscript{t}Bu and 3-H\textsubscript{B}), 1.30 (1H, app. d, J 13.5, 4-H\textsubscript{B}); \(\delta\text{C} (125 MHz, CD\textsubscript{3}OD, 333 K)\) 158.4 (Boc C=O), 157.3 (Cbz C=O), 138.1 (phenyl C-1), 129.6 (phenyl C\textsubscript{2-3,5}), 129.1 (phenyl C\textsubscript{2-2,6}), 129.0 (phenyl C-4), 96.6 (C-8a), 80.1 (\textsuperscript{t}Bu C\textsubscript{1}), 68.6 (phenethyl 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 (\textsuperscript{t}Bu C\textsubscript{3}),
25.8 (C-4), 22.1 (C-3); HRMS found MNa+, 443.2147. C_{22}H_{32}N_{2}O_{6} requires MNa, 443.2152.

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

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); $\nu_{\text{max}}$ cm$^{-1}$ 3368, 2931, 2870, 1687, 1490, 1365, 1274, 1245, 1161, 1054, 1024; $\delta_H$ (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$_B$); $\delta_C$ (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.
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, $R_t$ 0.19 (50:50 petrol–EtOAc; $\nu_{\text{max}}$ cm$^{-1}$ 3342, 2936, 2881, 1688, 1510, 1365, 1248, 1164, 1049, 1008; $\delta$$_H$ (400 MHz, CDCl$_3$) 5.30 (1H, s, NH$_{\text{alcohol}}$), 4.94 (1H, app. t, $J$ 6.6, NH$_{\text{hemiacetal}}$), 4.05 (1H, d, $J$ 8.7, 5-$H_A$$_{\text{alcohol}}$), 3.89–3.80 (2H, m, 2-$H_A$$_{\text{hemiacetal}}$ and hydroxypropyl 3-$H_A$$_{\text{alcohol}}$), 3.79–3.73 (4H, m, 2-$H_2$$_{\text{alcohol}}$, 5-$H_2$$_{\text{hemiacetal}}$), 3.73–3.66 (2H, m, 2-$H_B$$_{\text{hemiacetal}}$ and hydroxypropyl 3-$H_B$$_{\text{alcohol}}$), 3.61–3.57 (2H, m, 7-$H_2$$_{\text{hemiacetal}}$), 3.30 (1H, d, $J$ 8.7, 5-$H_B$$_{\text{alcohol}}$), 3.37–3.25 (3H, m, methylcarbamate 1-$H_2$$_{\text{alcohol}}$ and methylcarbamate 1-$H_A$$_{\text{hemiacetal}}$), 3.30 (1H, dd, J 14.4 and 4.5, methylcarbamate 1-$H_B$$_{\text{hemiacetal}}$), 1.85–1.67 (2H, m, 3-$H_A$$_{\text{hemiacetal}}$ and hydroxypropyl 2-$H_A$$_{\text{alcohol}}$), 1.66–1.57 (2H, m, 4-$H_A$$_{\text{hemiacetal}}$ and hydroxypropyl 1-$H_A$$_{\text{alcohol}}$), 1.54–1.45 (2H, m, 3-$H_B$$_{\text{hemiacetal}}$ and hydroxypropyl 2-$H_B$$_{\text{alcohol}}$), 1.46–1.36 (20H, m, 4-$H_B$$_{\text{hemiacetal}}$, hydroxypropyl 1-$H_B$$_{\text{alcohol}}$, 'Bu$_{\text{hemiacetal}}$ and 'Bu$_{\text{alcohol}}$); $\delta$$_C$ (100 MHz, CDCl$_3$) 218.1 (C-4$_{\text{alcohol}}$), 157.0 (Boc C=O$_{\text{hemiacetal}}$), 156.4 (Boc C=O$_{\text{alcohol}}$), 103.4 (C-7a$_{\text{hemiacetal}}$), 80.0 (t'Bu C$_1$$_{\text{alcohol}}$), 79.7 (t'Bu C$_1$$_{\text{hemiacetal}}$), 77.2 (C-5$_{\text{hemiacetal}}$), 74.5 (C-2$_{\text{alcohol}}$), 73.9 (C-7$_{\text{hemiacetal}}$), 71.5 (C-5$_{\text{alcohol}}$), 62.5 (hydroxypropyl C-3$_{\text{alcohol}}$), 61.2 (C-2$_{\text{hemiacetal}}$), 52.2 (C-3$_{\text{alcohol}}$), 46.3 (methylcarbamate C-1$_{\text{hemiacetal}}$), 44.9 (C-4a$_{\text{hemiacetal}}$), 42.3 (methylcarbamate C-1$_{\text{alcohol}}$), 28.5 (t'Bu C$_3$$_{\text{alcohol}}$), 28.4 (t'Bu C$_3$$_{\text{hemiacetal}}$), 28.1 (hydroxypropyl C-1$_{\text{alcohol}}$), 27.1 (hydroxypropyl C-2$_{\text{alcohol}}$), 22.5 (C-4$_{\text{hemiacetal}}$), 21.1 (C-3$_{\text{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-2H-pyrano[3,2-c]pyridine-6-carboxylate

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 1H-NMR in CD$_3$OD) as colourless oil, $R_f$ 0.39 (50:50 petrol–EtOAc); $\nu_{\text{max}}$/cm$^{-1}$ 3399, 2943, 2877, 2523, 2068, 1672, 1431, 1269, 1248, 1138, 1071; $\delta_H$ (500 MHz, CD$_3$OD, 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$_B$); $\delta_C$ (125 MHz, CD$_3$OD, 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-2H-pyrano[3,2-c]pyridine-6-carboxylate

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 1H-NMR in CD3OD) as a colourless oil, Rf 0.26 (EtOAc); νmax/cm−1 3339, 2943, 2877, 2519, 2065, 1692, 1426, 1351, 1270, 1247, 1138, 1072, 1024; δH (500 MHz, CD3OD, 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-H2), 4.15-3.98 (2H, m, 7-HA and 2-HA), 3.60 (1H, ddd, J 11.3, 5.4 and 1.6, 2-HB), 3.55 (1H, d, J 13.5, 5-HA), 3.31 (1H, d, J 13.5, 5-HB), 3.13 (1H, td, J 12.9 and 3.3, 7-HB), 2.85 (1H, d, J 13.7, pyridinylmethyl 1-HA), 2.80 (1H, d, J 13.7, pyridinylmethyl 1-HB), 1.98 (1H, td, J 13.3 and 5.4, 8-HA), 1.85 (1H, td, J 13.4 and 4.9, 4-HA), 1.77-1.67 (1H, m, 3-HA), 1.64 (1H, app. d, J 14.1, 8-HB), 1.34 (1H, app. d, J 13.7, 3-HB), 0.77 (1H, app. d, J 13.4, 4-HB); δC (125 MHz, CD3OD, 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 C2-3,5), 129.2 (phenyl C2-2,6), 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. C22H26N2O4 requires MH+, 383.1965. Compound 159f existed >90% as a single hemiacetal.

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

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 1H-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 1H-NMR) as colourless blocks, (CHCl3/Et2O), 98–102 °C; Rf 0.50 (50:50 petrol–EtOAc); νmax/cm−1 3318, 2959, 2932, 2873, 2858, 2824, 1710, 1546, 1365, 1249, 1169, 1094, 1073, 1057; δH (400 MHz, CDCl3) 4.73 (1H, br. s, NH), 3.97 (1H, app. dd, J 11.6 and 4.9, 2-HA), 3.85 (1H, d, J 11.6, 5-HA), 3.72-3.64 (2H, m, 7-H2), 3.42 (1H, app. t, J 3.8, 8a-H), 3.37 (1H, td, J 11.6 and 2.3, 2-HB),
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, tBu); δ_C (100 MHz, CDCl_3) 156.4 (Boc C=O), 79.4 (tBu 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 (tBu 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 8a-H, 8a-H and 8a-H, 8a-H and NH.

Benzyl (4aR^*,8aR^*)-4a-(((tert-butoxy)carbonyl)amino)methyl)-octahydro-2H-pyran[ 3,2-c]pyridine-6-carboxylate

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 ^1H-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 ^1H-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, tBu 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 (tBu 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 (tBu C_3), 28.3 (C-8), 23.1 (C-3); HRMS found
MNa\(^+\), 427.2202. C\(_{22}\)H\(_{32}\)N\(_2\)O\(_5\) requires MNa, 427.2203. The relative configuration was determined using NOESY (500 MHz, CD\(_3\)OD, 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-\{[(4aR\(^*\),9bS\(^*\))-8-methoxy-2H,3H,4H,4aH,5H,9bH-indeno[1,2-b]pyran-4a-yl]methyl\}carbamate

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); \(\nu_{\text{max}}/\text{cm}^{-1}\) 3336, 2929, 2856, 1696, 1513, 1488, 1451, 1364, 1275, 1264, 1244, 1166, 1152, 1079, 1029; \(\delta_{\text{H}}\) (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, \(^1\)Bu and 3-H\(_B\)); \(\delta_{\text{C}}\) (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 (\(^1\)Bu C\(_1\)), 63.1 (C-2), 55.5 (methoxy), 46.2 (methylcarbamate C-1), 39.0 (C-5), 28.5 (\(^1\)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\(_3\)OD), nOe observed between 9b-H and methylcarbamate 1-H\(_A\), 9b-H and methylcarbamate 1-H\(_B\).
tert-Butyl N-([(4aR*,7aS*)-hexahydro-2H-furo[3,4-b]pyran-4a-yl]methyl)carbamate

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 ¹H-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 ¹H-NMR) as colourless oil, R_f 0.35 (50:50 petrol–EtOAc); νmax/cm⁻¹ 3318, 2949, 2928, 2875, 2855, 1677, 1540, 1365, 1276, 1250, 1160, 1135, 1093, 1081, 1059, 1034; δH (500 MHz, CDCl₃) 4.76 (1H, app. t, J 5.1, NH), 4.11 (1H, dd, J 10.1 and 4.0, 7-Hₐ), 3.92-3.86 (1H, m, 2-Hₐ), 3.87 (1H, d, J 8.4, 5-Hₐ), 3.79 (1H, app. d, J 7.1, 7-Hₐ), 3.73 (1H, app. d, J 4.0, 7a-H), 3.51 (1H, d, J 8.4, 5-Hₐ), 3.31 (1H, app. d, J 7.1, 7-Hₐ), 3.15 (1H, dd, J 14.1 and 6.8, methylcarbamate 1-Hₐ), 2.98 (1H, dd, J 14.1 and 6.5, methylcarbamate 1-Hₐ), 1.80-1.69 (1H, m, 3-Hₐ), 1.69-1.64 (2H, m, 4-H₂), 1.53-1.46 (1H, m, 3-Hₐ), 1.43 (9H, s, ³Bu); δC (100 MHz, CDCl₃) 156.5 (Boc C=O), 80.3 (C-7a), 79.7 (³Bu C₁), 74.2 (C-7), 71.2 (C-5), 66.2 (C-2), 46.5 (methylcarbamate C-1), 45.9 (C-4a), 28.5 (³Bu C₃), 24.3 (C-4), 21.7 (C-3); HRMS found MNa⁺, 280.1517. C₁₃H₂₃NO₄ requires MNa, 280.1519. The relative configuration was determined using NOESY (500 MHz, CDCl₃), nOe observed between 7a-H and methylcarbamate 1-Hₐ, 7a-H and methylcarbamate 1-Hₐ, 7a-H and NH.

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

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 ¹H-NMR) was purified by flash column chromatography, eluting with 10:90 EtOAc–hexane to
yield the ether derivative 149e (0.27 g, 63%, \( \text{dr} >95:<5 \) by \(^1\text{H}-\text{NMR} \)) as colourless oil, \( R_f 0.40 \) (70:30 petrol–EtOAc); \( \nu_{\text{max}}/\text{cm}^{-1} 3061, 3028, 2932, 2851, 1692, 1427, 1265, 1243, 1210, 1129, 1086, 1074, 1025; \( \delta_H \) (500 MHz, CD\(_3\)OD, 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\(_B\)), 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\(_B\)); \( \delta_C \) (125 MHz, CD\(_3\)OD, 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\(_3\)OD, 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-2H-pyrano[3,2-c]pyridine-6-carboxylate

According to General Procedure O, the hemiacetal derivative 159f (0.13 g, 0.34 mmol) gave a crude material. The crude material (\( \text{dr} 91:9 \) by \(^1\text{H}-\text{NMR} \)) was purified by flash column chromatography, eluting with 70:30 EtOAc–hexane to yield the ether derivative 149f (0.11 g, 88%, \( \text{dr} 91:9 \) by \(^1\text{H}-\text{NMR} \)) as colourless oil, \( R_f 0.32 \) (EtOAc); \( \nu_{\text{max}}/\text{cm}^{-1} 3030, 2934, 2851, 1690, 1424, 1266, 1243, 1207, 1130, 1085, 1025; \( \delta_H \) (500 MHz, CD\(_3\)OD, 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-H2), 3.99 (1H, ddd, J 13.0, 3.0 and 1.3, 7-HA), 3.96-3.91 (1H, m, 2-HA), 3.14 (1H, td, J 13.0 and 3.3, 7-HB), 2.81 (1H, d, J 13.5, pyridinylmethyl 1-HA), 2.40 (1H, d, J 13.5, pyridinylmethyl 1-HB), 2.13-2.02 (1H, m, 8-HA), 1.74-1.68 (1H, m, 8-HB), 1.68-1.63 (1H, m, 3-HA), 1.45 (1H, td, J 13.4 and 3.0, 4-HA), 1.41-1.36 (1H, m, 3-HB), 1.07 (1H, app. d, J 13.4, 4-HB); δC (125 MHz, CD3OD, 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 C2-3,5), 129.1 (phenyl C2-2,6), 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. C22H26N2O3 requires MH+, 367.2021. The relative configuration was determined using NOESY (500 MHz, CD3OD, 333 K), nOe observed between 8a-H and pyridinylmethyl 1-HB, 8a-H and 8-HA, 8a-H and 8-HB.

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

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 1H-NMR) as an amorphous white solid, Rf 0.59 (50:50 petrol–EtOAc); νmax/cm−1 3325, 3068, 2971, 2949, 2876, 1714, 1546, 1363, 1267, 1248, 1165, 1140, 1125, 1115, 1098, 1076, 1064, 1021; δH (400 MHz, CDCl3) 5.03 (1H, br. s, NH), 3.91-3.84 (1H, m, 7-HA), 3.85 (1H, d, J 11.7, 5-HA), 3.67-3.60 (2H, m, 2-H2), 3.55 (1H, app. td, J 12.9 and 2.8, 7-HB), 3.37 (1H, d, J 11.7, 5-HB), 3.33-3.27 (2H, m, methylcarbamate 1-H2), 3.18 (3H, s, methoxy 1-H3), 1.93 (1H, td, J 13.8 and 5.0, 4-HA), 1.83 (1H, app. td, J 13.1 and 5.7, 8-HA), 1.77-1.71 (1H, m, 3-HA), 1.67 (1H, app. d, J 13.1, 8-HB), 1.42 (9H, s, 'Bu), 1.39-1.32 (1H, m, 3-HB), 1.10 (1H, app. d, J 13.6, 4-HB);
\[ \delta_C \text{ (100 MHz, CDCl}_3\text{)} = 156.4 \text{ (C=O), 98.5 (C-8a), 78.9 (}^t\text{Bu C}_1\text{), 70.9 (C-5), 65.8 (C-7), 60.3 (C-2), 46.7 \text{ (methoxy C-1), 44.9 (methylcarbamate C-1), 40.7 (C-4a), 31.0 (C-8), 28.5 (}^t\text{Bu C}_3\text{), 23.3 (C-4), 21.1 (C-3). HRMS found MNa}^+, 324.1789. \]

\[ C_{15}H_{27}NO_5 \text{ requires } MNa^+, 324.1781. \]

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

\[
\text{According to General Procedure Q, the alkene derivative 148i (0.25 g, 0.93 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 50:50 EtOAc–hexane to yield the hemiaminals 163 (0.19 g, 75\%, } dr 66:34 \text{ by } ^1H-\text{NMR) as an amorphous colourless solid, } R_f 0.23 \text{ and 0.34 (50:50 petrol–EtOAc); } v_{\text{max}}/\text{cm}^{-1} 3432, 2956, 2923, 2852, 1697, 1382, 1365, 1255, 1223, 1169, 1149, 1115, 1097; \delta_H \text{ (400 MHz, CDCl}_3\text{)} 5.53 \text{ (1H, app. d, } J 6.5, 3-H_{\text{major}}\text{), 2.46 (1H, app. d, } J 4.9 3-H_{\text{minor}}\text{), 4.11 (4H, app. d, } J 11.6, 8-H_A \text{ and 6-H}_A\text{), 3.89 (2H, ddd, } J 11.6, 8.8 \text{ and 4.5, 8-H}_B\text{), 3.76 (1H, br s, OH}_{\text{minor}}\text{), 2.93 (1H, br. s, OH}_{\text{minor}}\text{), 2.70-2.43 (6H, m, 9-H}_2 \text{ and 4-H}_A\text{), 1.75 (2H, app. d, } J 14.1, 4-H_B\text{), 1.64 (1H, br. s, OH}_{\text{major}}\text{), 1.48 (18H, s, } ^t\text{Bu); } \delta_C \text{ (100 MHz, CDCl}_3\text{)} 206.2 \text{ (C}_2-10\text{), 154.8 (Boc 2C=O), 81.7 (C}_2-3\text{), 80.9 (}^t\text{Bu 2C}_1\text{), 75.5 (C}_2-6\text{), 68.5 (C}_2-8\text{), 56.6 (C-5}_{\text{major}}\text{), 55.8 (C-5}_{\text{minor}}\text{), 51.1 (C-1}_{\text{minor}}\text{), 50.9 (C-4}_{\text{major}}\text{), 40.9 (C}_2-9\text{), 36.6 (C-4}_{\text{minor}}\text{), 36.0 (C-4}_{\text{major}}\text{), 28.5 (}^t\text{Bu 2C}_3\text{); HRMS found MNa}^+, 294.1314. \]

\[ C_{13}H_{21}NO_5 \text{ requires MNa, 294.1311.} \]

**tert-Butyl N-[[3aR,7aS]-1-benzyl-octahydropyrano[4,3-b]pyrrol-3a-yl] methyl]carbamate**

\[
\text{Benzylamine (12.9 } \mu\text{L, 117 } \mu\text{mol), acetic acid (12.2 } \mu\text{L, 214 } \mu\text{mol) and NaBH(OAc)}_3\text{ (56.7 mg, 267 } \mu\text{mol) were added to a solution of the hemiaminals} \]

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 NaHCO₃ (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 (MgSO₄), 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 ¹H-NMR) as an amorphous colourless solid, Rₜ 0.53 (50:50 petrol–EtOAc); νₘₐₓ/cm⁻¹ 3323, 2965, 2924, 2792, 1712, 1537, 1452, 1388, 1268, 1247, 1165, 1131, 1085; δₜ (400 MHz, CDCl₃) 7.35–7.21 (5H, m, phenyl), 5.22 (1H, br. s, NH), 3.96 (1H, d, J 13.3, phenylmethyl 1-Hₐ), 3.80 (1H, td, J 10.9 and 3.1, 6-Hₐ), 3.66–3.61 (1H, m, 6-Hₐ), 3.59 (1H, d, J 11.8, 4-Hₐ), 3.45 (1H, d, J 11.8, 4-Hₐ), 3.39–3.30 (1H, m, methylcarbamate 1-Hₐ), 3.29–3.20 (2H, m, phenylmethyl 1-Hₐ and methylcarbamate 1-Hₐ), 2.92 (1H, td, J 9.4 and 4.5, 2-Hₐ), 2.50 (1H, app. s, 7a-H), 2.39–2.27 (1H, m, 2-Hₐ), 1.91–1.78 (1H, m, 7-Hₐ), 1.70 (1H, app. dq, J 14.6 and 3.6, 7-Hₐ), 1.63–1.51 (1H, m, 3-Hₐ), 1.45 (9H, s, ’Bu), 1.39–1.28 (1H, m, 3-Hₐ); δₜ (100 MHz, CDCl₃) 156.5 (C=O), 139.7 (phenyl C-1), 128.5 (phenyl C₂-3,5), 128.3 (phenyl C₂-2,6), 127.0 (phenyl C-4), 79.2 (’Bu C₁), 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 (’Bu C₃), 24.0 (C-7); HRMS found MH⁺, 347.2337. C₂₀H₃₀N₂O₃ requires MH⁺, 347.2329. The relative configuration was determined using NOESY (500 MHz, CDCl₃), nOe observed between 7a-H and methylcarbamate 1-Hₐ, 7a-H and methylcarbamate 1-Hₐ, 7a-H and 7-Hₐ, 7a-H and 7-Hₐ.

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

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
175

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%, \(d_r\) 86:14 by \(^1\)H-NMR) as a yellow oil, \(R_t\) 0.31 (70:30 petrol–EtOAc); \(\nu_{\text{max}}/\text{cm}^{-1}\) 3340, 2975, 2932, 2856, 1682, 1512, 1365, 1274, 1248, 1163, 1083; \(\delta_H\) (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\(_{\text{trans}}\)), 5.10 (1H, app. d, \(J\) 9.5, propenyl 3-H\(_{\text{cis}}\)), 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, \(^1\)Bu); \(\delta_C\) (100 MHz, CDCl\(_3\)) 157.8 (Boc C=O), 134.0 (propenyl C-2), 118.6 (propenyl C-3), 80.3 (\(^1\)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 (\(^1\)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 (3R\(^*\),4R\(^*\))-3-\{[(tert-butoxy)carbonylamino)methyl]-4-hydroxy-3-(prop-2-en-1-yl)piperidine-1-carboxylate**

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 (\(d_r\) >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%, \(d_r\) >95:<5 by \(^1\)H-NMR) as a colourless oil, \(R_t\) 0.55 (50:50 petrol–EtOAc); \(\nu_{\text{max}}/\text{cm}^{-1}\) 3367, 2975, 2935, 2870, 2492, 1672, 1428, 1364, 1234, 1155, 1079; \(\delta_H\) (500 MHz, CD\(_3\)OD, 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-H₂), 5.03 (1H, app. d, J 17.0 propenyl 3-Htrans), 5.00 (1H, app. d, J 10.2, propenyl 3-Hcis), 3.95 (1H, app. d, J 13.3, 6-HA), 3.72 (1H, d, J 13.7, 2-HA), 3.63 (1H, dd, J 9.7 and 4.4, 4-H), 3.15 (1H, d, J 14.3, methylcarbamate 1-HA), 3.06 (1H, app. br. s, 6-HB), 2.95 (1H, d, J 14.3, methylcarbamate 1-HB), 2.78 (1H, d, J 13.7, 2-HB), 2.18 (1H, dd, J 14.2 and 7.9, propenyl 1-HA), 2.09 (1H, dd, J 14.2 and 7.0, propenyl 1-HB), 1.78-1.71 (1H, m, 5-HA), 1.70-1.60 (1H, m, 5-HB), 1.43 (9H, s, 'Bu); δC (125 MHz, CD3OD, 333 K) 158.9 (Boc C=O), 157.3 (Cbz C=O), 138.1 (phenyl C1), 135.2 (propenyl C-2), 129.5 (phenyl C2-3,5), 129.1 (phenyl C2-2,6), 129.0 (phenyl C-4), 118.6 (propenyl C-3), 80.5 ('Bu C1), 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 ('Bu C3); HRMS found MNa+, 427.2205. C22H32N2O5 requires MNa+, 427.2203. The relative configuration was determined by analogy with the carbocyclic analogue142 and using NOESY (500 MHz, CD3OD), nOe observed between 4-H and methylcarbamate 1-HA, 4-H and methylcarbamate 1-HB.

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

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 1H-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 1H-NMR) as a yellow oil, Rf 0.37 (70:30 petrol–EtOAc); νmax/cm⁻¹ 3368, 2976, 2931, 2835, 1685, 1512, 1490, 1435, 1365, 1272, 1245, 1159, 1029; δH (400 MHz, CDCl3) 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-Htrans), 5.04 (1H, app. d, J 11.7, propenyl 3-Hcis), 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-HA), 3.20 (1H, dd, J 14.2 and 5.8, methylcarbamate 1-HB),
2.73 (1H, d, J 15.4, 3-H₆), 2.51 (1H, d, J 15.4, 3-H₆), 2.34 (1H, dd, J 14.2 and 7.4, propenyl 1-H₆), 2.05 (1H, dd, J 14.2 and 7.3, propenyl 1-H₆), 1.44 (9H, s, tBu); δC (100 MHz, CDCl₃) 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 (tBu C₁), 55.6 (methoxy), 52.7 (C-2), 46.5 (methylcarbamate C-1), 36.8 (C-2), 34.6 (propenyl C-1), 28.5 (tBu C₃); HRMS found MNa⁺, 356.1838. C₁₉H₂₇NO₄ requires MNa, 356.1832. The relative configuration was determined from compound 150c.

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

![Chemical Structure](image)

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 ¹H-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 ¹H-NMR) as a light-yellow oil, Rₜ 0.29 (50:50 petrol–EtOAc); νmax/cm⁻¹ 3341, 2976, 2930, 2872, 1686, 1516, 1365, 1272, 1248, 1162, 1068, 1046; δH (400 MHz, CDCl₃) 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-Htrans), 5.12 (1H, dd, J 10.1 and 1.8, propenyl 3-Hcis), 4.84 (1H, app. t, J 5.0, NH), 4.24–4.10 (2H, m, 5-H₆ and 4-H), 3.71–3.67 (1H, m, 5-H₆), 3.66 (1H, d, J 8.9, 2-H₆), 3.54 (1H, d, J 8.9, 2-H₆), 3.17–3.02 (2H, m, methylcarbamate, 1-H₂), 2.60 (1H, br. s, OH), 2.33 (1H, dd, J 14.3 and 7.7, propenyl 1-H₆), 2.26 (1H, dd, J 14.3 and 7.1, propenyl 1-H₆), 1.43 (9H, s, tBu); δC (100 MHz, CDCl₃) 156.9 (Boc C=O), 134.7 (propenyl C-2), 118.5 (propenyl C-3), 79.9 (tBu C₁), 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 (tBu C₃); HRMS found MNa⁺, 280.1514. C₁₃H₂₃NO₄ requires MNa, 280.1519. The relative configuration was determined from compound 150d.
tert-Butyl N-\{[(2R*,3aR*,7aR*)-2-(iodomethyl)-hexahydro-2H-furo[3,2-c]pyran-3a-yl]methyl\}carbamate

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); $\nu_{\text{max}}$/cm$^{-1}$ 3323, 2975, 2950, 2923, 2895, 2868, 2848, 1703, 1547, 1349, 1273, 1252, 1235, 1164, 1139, 1069; $\delta_\text{H}$ (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, $^3$Bu), 1.29 (1H, dd, $J$ 13.4 and 6.9, 3-H$_B$); $\delta_\text{C}$ (125 MHz, CDCl$_3$) 156.3 (C=O), 79.5 ($^3$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 ($^3$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.
(4aR*, 8aR*)-4a-(Prop-2-en-1-yl)-octahydropyran[3,4-e][1,3]oxazin-2-one

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, Rf 0.20 (EtOAc); νmax/cm⁻¹ 3277, 2964, 2922, 2852, 1707, 1660, 1471, 1442, 1366, 1312, 1256, 1179, 1101, 1081, 1059; δH (400 MHz, CDCl₃) 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-Hₐ), 4.11 (1H, app. dd, J 12.1 and 5.3, 7-Hₐ), 3.88 (1H, dd, J 11.6 and 1.2, 5-Hₐ), 3.46 (1H, td, J 12.1 and 2.7, 7-Hₐ), 3.14 (1H, dd, J 11.3 and 4.4, 4-Hₐ), 2.94 (1H, dd, J 11.6 and 1.7, 5-Hₐ), 2.81 (1H, dd, J 11.3 and 1.4, 4-Hₐ), 2.61 (1H, dd, J 13.9 and 6.7, propenyl 1-Hₐ), 2.18 (1H, dd, J 13.9 and 8.2, propenyl 1-Hₐ), 2.03 (1H, app. d, J 12.6 and 5.3, 8-Hₐ), 1.87-1.77 (1H, m, 8-Hₐ); δC (100 MHz, CDCl₃) 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. C₁₀H₁₅NO₃ requires MH⁺, 198.1124.

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

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, Rf 0.42 (10:90 MeOH–EtOAc); νmax/cm⁻¹ 3480, 3376, 3215, 3133, 2938, 2874, 1671,
180

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_8), 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_{2}O_{4} requires MNa^+, 353.1477.

(4aR^*,9bS^*)-8-Methoxy-4a-(prop-2-en-1-yl)-2H,3H,4H,4aH,5H,9bH-indeno[2,1-e][1,3]oxazin-2-one

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.

\((4aR^*,7aS^*)\)-4a-(Prop-2-en-1-yl)-hexahydro-2\(H\)-furo[3,4-e][1,3]oxazin-2-one

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); \(\nu_{\text{max}}/\text{cm}^{-1}\) 3254, 3132, 2979, 2950, 2929, 2895, 1700, 1384, 1301, 1257, 1132, 1076, 1014; \(\delta_H\) (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\(_B\)), 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\(_2\)); \(\delta_C\) (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\(_9\)H\(_{13}\)NO\(_3\) requires \(MH\), 184.0968. The relative configuration was determined using X-ray crystallography.

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

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); \(\nu_{\text{max}}/\text{cm}^{-1}\) 3355, 2973, 2933, 2859, 1739, 1714, 1508,
1365, 1236, 1164, 1089; δ_H (400 MHz, CDCl₃) 5.88-5.73 (1H, m, propenyl 2-H), 5.11 (1H, app. s, propenyl 3-Htrans), 5.08 (1H, app. d, J 2.5, propenyl 3-Hcis), 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-HA), 3.68 (1H, d, J 12.0, 2-HA), 3.55-3.46 (1H, m, 6-HA), 3.28 (1H, dd, J 14.6 and 8.2, methylcarbamate 1-HA), 3.18 (1H, d, J 12.0, 2-HA), 2.87 (1H, dd, J 14.6 and 5.5, methylcarbamate 1-HA), 2.35 (1H, dd, J 14.1 and 7.5, propenyl 1-HA), 2.13-2.04 (1H, m, propenyl 1-HB), 2.08 (3H, s, acetyl), 1.87-1.79 (2H, m, 5-H), 1.41 (9H, s, tBu); δ_C (100 MHz, CDCl₃) 170.9 (acetyl C=O), 156.2 (Boc C=O), 133.1 (propenyl C-2), 118.8 (propenyl C-3), 79.4 (tBu C1), 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 (tBu C3), 27.6 (C-5), 21.2 (acetyl CH3). HRMS found MNa⁺, 336.1791. C₁₆H₂₇NO₅ requires MNa⁺, 336.1786.

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

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, Rf 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, CD₃OD, 333 K) 7.38-7.26 (5H, m, phenyl), 5.93-5.78 (1H, m, propenyl 2-H), 5.12 (2H, s, phenylmethyl 1-H2), 5.05 (1H, app. d, J 10.2, propenyl 3-Hcis), 5.04 (1H, app. d, J 17.2, propenyl 3-Htrans), 4.85 (1H, dd, J 8.3 and 4.0, 4-H), 3.71 (1H, app. br. s, 6-HA), 3.57 (1H, d, J 13.9, 2-HA), 3.35 (1H, app. br. s, 6-HB), 3.16 (1H, d, J 13.9, 2-HB), 3.13 (1H, d, J 15.1, methylcarbamate 1-HA), 3.03 (1H, d, J 15.1, methylcarbamate 1-HB), 2.22-2.08 (2H, m, propenyl 1-H2), 2.05 (3H, s, acetyl), 1.96-1.86 (1H, m, 5-H), 1.75-1.66 (1H, m, 5-H), 1.42 (9H, s, tBu); δ_C (125 MHz, CD₃OD, 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 C₂-3,5), 129.1 (phenyl C₂-2,6), 129.0 (phenyl C-4), 118.8 (propenyl C-3), 80.3 (tBu C1), 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
(tBu C₃), 27.1 (C-5), 21.0 (acetyl CH₃); HRMS found MNa⁺, 469.2304. C₂₄H₃₄N₂O₆ requires MNa, 469.2309.

\((1R^*,2S^*)\)-2-(((tert-Butoxy)carbonyl)amino)methyl)-6-methoxy-2-(prop-2-en-1-yl)-2,3-dihydro-1H-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); \(v_{	ext{max}}/\text{cm}^{-1}\) 3376, 2976, 2930, 1712, 1493, 1366, 1233, 1163, 1029; \(\delta_H\) (400 MHz, CDCl₃) 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\text{_{trans}}), 5.05 (1H, d, \(J\) 10.4, propenyl 3-H\text{_{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\text{_{A}}), 3.11 (1H, dd, \(J\) 14.2 and 6.2, methylcarbamate 1-H\text{_{B}}), 2.86 (1H, d, \(J\) 15.9, 3-H\text{_{A}}), 2.67 (1H, d, \(J\) 15.9, 3-H\text{_{B}}), 2.21 (2H, app. d, \(J\) 7.4, propenyl 1-H\text{_{A}}), 2.13 (3H, s, acetyl), 1.42 (9H, s, tBu); \(\delta_C\) (100 MHz, CDCl₃) 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 (tBu C₁), 55.6 (methoxy), 51.8 (C-2), 45.5 (methylcarbamate C-1), 38.2 (C-3), 36.5 (propenyl C-1), 28.5 (tBu C₃), 21.2 (acetyl CH₃); HRMS found MNa⁺, 398.1934. C₂₁H₂₉NO₅ requires MNa, 398.1937.

\((3R^*,4S^*)\)-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
tert-Butyl (5R*,10R*)-10-(acetyloxy)-3-hydroxy-7-oxa-2-azaspiro[4.5]decan-2-carboxylate

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 1H-NMR) as an amorphous colourless solid, Rf 0.53 and 0.33 (50:50 EtOAc−petrol); νmax/cm⁻¹ 3451, 2973, 2861, 1739, 1694, 1389, 1365, 1233, 1160; δH (500 MHz, CD3OD, 333 K) 5.08-4.99 (1H, m, 3-Hmajor), 4.95-4.86 (1H, m, 3-Hminor) 4.79-4.68 (2H, m, 10-H), 3.81-3.63 (2H, m, 8-HA), 3.54-3.36 (6H, m, 8-HB, 6-HA and 1-HA), 3.30-3.09 (4H, m, 6-HB and 1-HB), 2.02-1.91 (8H, m, acetyl and 4-HA), 1.83-1.68 (4H, m, 4-HB and 9-HA), 1.64-1.54 (2H, m, 9-HB), 1.38 (18H, s, tBu); δC (125 MHz, CD3OD, 333 K) 171.9 (acetyl 2C=O), 156.0 (Boc C=Omajor), 155.7 (Boc C=Ominor), 90.5 (C-3major), 89.8 (C-3minor), 81.8 (tBu C1major), 81.7 (tBu C1minor), 74.5 (C-10major), 73.4 (C-8major), 72.9 (C-10minor), 72.4 (C-8minor) 65.4 (C-6major), 64.7 (C-6minor) 52.3 (C-1major), 50.6 (C-1minor), 46.1 (C2-5), 39.0 (C-4minor), 37.4 (C-4major), 30.1 (C-9major), 29.5 (C-9minor), 28.6 (tBu 2C3), 20.8 (acetyl 2CH3); HRMS found MNa⁺, 338.1575. C15H25NO5 requires MNa, 338.1579.
**tert-Butyl (5R*, 10R*)-10-(acetyloxy)-7-oxa-2-azaspiro[4.5]decane-2-carboxylate**

![Chemical Structure](image)

By modification of an existing procedure, \(^{175}\) NaBH(OAc)\(_3\) (93.0 mg, 441 \(\mu\)mol) was added to a solution of the hemiaminals \(172\)a (20.0 mg, 63.4 \(\mu\)mol) 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 \(\times\) 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 \(173\)a (15.0 mg, 79%) as a colourless oil, \(R_f\) 0.47 (50:50 petrol–EtOAc); \(\nu_{\text{max}}/\text{cm}^{-1}\) 2971, 2863, 1738, 1691, 1398, 1364, 1234, 1172, 1145, 1103, 1090, 1071; \(\delta_H\) (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); \(\delta_C\) (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-Benzy1 2-tert-butyl (5R*,10S*)-10-(acetyloxy)-2,7-diaza-spiro[4.5]decane-2,7-dicarboxylate**

![Chemical Structure](image)

According to General Procedure V, the alkene derivative \(171\)b (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); \( \nu_{\max}/\text{cm}^{-1} \) 2974, 2876, 1737, 1688, 1430, 1398, 1364, 1233, 1211, 1145, 1101, 1059, 1041; \( \delta_H \) (500 MHz, CD3OD, 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, d, \( J \) 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\(_B\)), 3.22 (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, tBu); \( \delta_C \) (125 MHz, CD3OD, 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-2,6), 81.1 (tBu C\(_I\)), 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 (tBu C\(_3\)), 20.8 (acetyl CH3); HRMS found MNa\(^+\), 455.2152. C\(_{23}\)H\(_{32}\)N\(_2\)O\(_6\) requires MNa\(^+\), 455.2152.

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

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); \( \nu_{\max}/\text{cm}^{-1} \) 2974, 2933, 1733, 1689, 1492, 1395, 1365, 1227, 1163, 1144, 1118, 1100, 1020; \( \delta_H \) (500 MHz, CD3OD, 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, tBu); \( \delta_C \) (100 MHz, CD3OD, 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 (tBu 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 (tBu C_3), 20.8 (acetyl CH_3); HRMS found M\text{Na}^+, 384.1779. C_{20}H_{27}NO_5 requires M\text{Na}, 384.1781.

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

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_{\text{max}}/\text{cm}^{-1} 2975, 2934, 2873, 1738, 1693, 1400, 1366, 1236, 1161, 1122; δ_\text{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, 6-H_A), 3.34-3.28 (1H, m, 8-H_A), 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, tBu); δ_\text{C} (125 MHz, CD_3OD, 333 K) 172.1 (acetyl C=O), 156.3 (Boc C=O), 81.1 (tBu 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 tBu C_3), 20.6 (acetyl CH_3); HRMS found M\text{Na}^+, 308.1465. C_{14}H_{23}NO_5 requires M\text{Na}, 308.1468.

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

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; \( \nu_{\text{max}}/\text{cm}^{-1} \): 2974, 2888, 1682, 1394, 1366, 1313, 1279, 1234, 1172, 1132, 1100, 1082; \( \delta_H \) (500 MHz, CD3OD, 333 K): 7.57-7.53 (2H, m, phenyl 2,6-H2), 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-H2), 4.14-4.01 (2H, m, 7-H2), 3.99-3.86 (2H, m, 8-H2), 3.69 (2H, app. s, 1-H2), 3.54 (1H, ddd, J 10.5, 8.5 and 3.5, 3-Ha), 3.47 (1H, ddd, J 10.5, 8.9 and 7.5, 3-Hb), 2.43-2.35 (1H, m, 4-Ha), 2.35-2.26 (1H, m, 4-Hb), 1.46 (9H, s, \(^t^6\)Bu); \( \delta_C \) (125 MHz, CD3OD, 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 C2-3,5), 129.0 (phenyl C2-2,6), 81.3 (C-5), 81.1 (\(^t^6\)Bu C1), 61.4 (C-7), 56.6 (C-1), 46.8 (C-8), 45.9 (C-3), 36.6 (C-4), 28.8 (\(^t^6\)Bu C3); HRMS found MNa+, 383.1575. C19H24N2O5 requires MNa+, 383.1577.

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

[Diagram]

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 \(\mu\)mol) 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); \( \nu_{\text{max}}/\text{cm}^{-1} \): 2975, 2933, 2857, 1785, 1738, 1711, 1367, 1310, 1230, 1147, 1093, 1044, 1025; \( \delta_H \) (500 MHz, CDCl3) 4.90 (1H, dd, J 8.8 and 4.2, 10-H), 3.88 (1H, app. dt, J 12.0 and 4.7, 8-Ha), 3.70 (1H, d, J 11.6, 6-Ha), 3.57 (1H, ddd, J 12.0, 9.0 and 3.3, 8-Hb), 3.49 (2H, app. s, 1-H2), 3.36 (1H, d, J 11.6, 6-Hb), 2.68 (1H, d, J 17.9, 4-Ha), 2.49 (1H, d, J 17.9, 4-Hb), 2.09 (3H, s, acetyl), 1.90 (1H, app. dq, J 13.0 and 4.0, 9-Ha), 1.68 (1H, app dtd, J 13.9, 9.3 and 4.5, 9-Hb), 1.52 (9H, s, \(^t^6\)Bu); \( \delta_C \) (125 MHz, CDCl3): 171.9 (C-3), 170.3 (acetyl C=O), 149.9 (Boc C=O), 83.5 (\(^t^6\)Bu C1), 72.3 (C2-6,10), 65.3 (C-8), 51.0 (C-1), 38.6 (C-5), 37.9 (C-4), 28.7 (C-9), 28.1 (\(^t^6\)Bu C3), 21.1 (acetyl CH3); HRMS found MH+, 314.1598. C15H23NO6 requires MH, 314.1598.
7-Benzyl 2-tert-butyl (5R*,10S*)-10-(acetyloxy)-3-oxo-2,7-diazaspiro[4.5]decane-2,7-dicarboxylate

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); \( \nu \text{max}/\text{cm}^{-1} \: 2978, 1785, 1738, 1696, 1432, 1367, 1315, 1229, 1148, 1104, 1041; \( \delta_H \) (500 MHz, CD\(_3\)OD, 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, ddd, J 14.0, 8.4 and 4.4, 9-H\(_B\)), 1.49 (9H, s, \(^t^Bu\)); \( \delta_C \) (125 MHz, CD\(_3\)OD, 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\(_2\)O\(_7\) requires MNa\(^+\), 469.1945.

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

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); $\nu_{\text{max}}/\text{cm}^{-1}$ 2978, 2934, 1784, 1737, 1715, 1492, 1367, 1310, 1224, 1150, 1022; $\delta_H$ (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, tBu); $\delta_C$ (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 (tBu 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 (tBu C$_3$), 20.9 (acetyl CH$_3$); HRMS found MNa$^+$, 398.1583. C$_{20}$H$_{25}$NO$_6$ requires MNa, 398.1574.

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

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); $\nu_{\text{max}}/\text{cm}^{-1}$ 2977, 2933, 2873, 1786, 1737, 1699, 1389, 1366, 1311, 1230, 1151, 1104, 1062, 1047, 1023; $\delta_H$ (500 MHz, CD$_3$OD, 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, tBu); $\delta_C$ (125 MHz, CD$_3$OD, 333 K) 174.1 (C-8), 172.0 (acetyl C=O), 151.3 (Boc C=O), 84.5 (tBu 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 (tBu C$_3$), 20.6 (acetyl CH$_3$); HRMS found MNa$^+$, 322.1257. C$_{14}$H$_{21}$NO$_6$ requires MNa, 322.1261.
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 1H-NMR) as a colourless oil, Rf 0.33 (50:50 petrol–EtOAc); ν_max/cm⁻¹ 2973, 2934, 2859, 1740, 1697, 1390, 1366, 1234, 1164, 1068; δ_H (500 MHz, CD₃OD, 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_B), 2.08 (3H, s, acetyl 1-H₃_minor), 2.05 (3H, s, acetyl 1-H₃_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, CD₃OD, 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 2C₁), 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 (C₂-1), 46.3 (C₂-5), 37.3 (C₂-4), 30.1 (C-g_major), 29.5 (C-g_minor), 28.6 (t-Bu 2C₃), 20.8 (acetyl 2CH₃); HRMS found MNa⁺, 352.1740. C₁₆H₂₇NO₆ requires MNa, 352.1730.

According to an existing procedure, PhMgBr (0.75 mL, 0.75 mmol of a 1.0 M solution in THF) was added dropwise to a suspension of CuBr•Me₂S (0.15 g,
0.75 mmol) in Et₂O (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, Et₂O•BF₃ (92.6 µL, 0.75 mmol) and a solution of the aminals 175 (0.10 g, 0.30 mmol) in Et₂O (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 NH₄Cl (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 (MgSO₄), filtered and concentrated under reduced pressure to give a crude product. The crude product (dr 50:50 by ¹H-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 ¹H-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, CD₃OD, 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_major), 4.87–4.78 (1H, m, 10-H_minor), 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-HA), 3.60 (2H, d, J 11.5, 6-HA), 3.56 (2H, ddd, J 11.3, 6.7 and 4.1, 8-HB), 3.45 (2H, d, J 12.0, 1-HA), 3.35 (2H, d, J 12.0, 1-HB), 3.29 (2H, J 11.5, 6-HB), 2.46 (1H, app. dd, J 13.5 and 8.5, 4-HA_minor), 2.28 (1H, ddd, J 13.5, 8.0 and 1.3, 4-HA_major), 2.00 (3H, s, acetyl_minor), 1.91 (3H, s, acetyl_major), 1.86–1.79 (1H, m, 9-HA_minor), 1.79–1.71 (2H, m, 4-HB_major and 9-HA_major), 1.70–1.62 (2H, m, 4-HB_minor and 9-HB_minor), 1.58 (1H, app. ddd, J 13.8, 6.7 and 3.7, 9-HB_major); δ_C (125 MHz, CD₃OD, 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 C₂-4), 127.8 (phenyl C₂-3,5_major), 127.7 (phenyl C₂-3,5_minor), 126.6 (phenyl C₂-2,6_minor), 126.5 (phenyl C₂-2,6_major), 73.5 (C-6_minor), 73.1 (C₂-10), 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 CH₃_minor), 20.7 (acetyl CH₃_major); HRMS found MH⁺, 276.1594. C₁₆H₂₁NO₃ requires MH, 276.1594.
(3R*,4R*)-3-(((tert-Butoxy)carbonyl)amino)methyl)-3-(3-hydroxypropyl)oxan-4-yl acetate

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); $\nu_{\text{max}}$/cm$^{-1}$ 3364, 2960, 2865, 1712, 1514, 1365, 1237, 1165, 1083, 1048, 1027; $\delta_H$ (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); $\delta_C$ (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 $M^+$, 332.2072. C$_{16}$H$_{29}$NO$_6$ requires $M^+$, 332.2067.

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

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); $\nu_{\text{max}}$/cm$^{-1}$ 3400, 2937, 2872, 2508, 1681, 1433, 1365, 1235, 1157, 1035; $\delta_H$ (500
MHz, CD$_3$OD, 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$_A$), 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, 'Bu), 1.40-1.32 (1H, m, hydroxypropyl 1-H$_B$); $\delta$C (125 MHz, CD$_3$OD, 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 ('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 ('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$_2$O$_7$ requires MNa, 487.2420.

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

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); $\nu_{\text{max}}$/cm$^{-1}$ 3376, 3270, 3145, 2937, 2873, 1705, 1493, 1394, 1368, 1234, 1167, 1144, 1121, 1008; $\delta_H$ (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$_A$), 1.41 (9H, s, 'Bu); $\delta_C$ (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 ('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 ('Bu C₃), 27.6 (hydroxypropyl C-1), 27.3 (hydroxypropyl C-2), 21.3 (acetyl CH₃); HRMS found MNa⁺, 416.2049. C₂₁H₃₁NO₆ requires MNa⁺, 416.2043.

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

![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); \(\nu_{\text{max}}/\text{cm}^{-1}\) 3365, 2972, 2932, 2873, 1712, 1689, 1526, 1365, 1242, 1164, 1035, 1004; \(\delta_H\) (400 MHz, CDCl₃) 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, \('\text{Bu}\)); \(\delta_C\) (100 MHz, CDCl₃) 171.3 (acetyl C=O), 156.7 (Boc C=O), 79.9 ('Bu C₁), 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 ('Bu C₃), 24.5 (hydroxypropyl C-2), 23.9 (hydroxypropyl C-1), 21.1 (acetyl CH₃); HRMS found MNa⁺, 340.1727. C₁₅H₂₇NO₆ requires MNa⁺, 340.1730.

\textit{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); \( \nu_{\text{max}}/\text{cm}^{-1} \) 3307, 2974, 2932, 2876, 1696, 1660, 1509, 1484, 1365, 1340, 1269, 1248, 1163, 1124, 1063; \( \delta_h \) (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, \( \text{t-Bu} \)); \( \delta_c \) (100 MHz, CDCl\(_3\)) 172.8 (C-3), 156.2 (Boc C=O), 80.9 (\( \text{t-Bu} \) 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 (\( \text{t-Bu} \) C\(_3\)), 26.6 (hydroxypropyl C-1); HRMS found MNa\(^+\), 311.1574. \( \text{C}_{13}\text{H}_{24}\text{N}_2\text{O}_5 \) requires MNa\(^+\), 311.1577.

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

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); \( \nu_{\text{max}}/\text{cm}^{-1} \) 2936, 2857, 1737, 1687, 1423, 1365, 1274, 1234, 1160, 1141, 1090, 1040; \( \delta_h \) (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, \( \text{t-Bu} \)), 1.42-1.38 (1H, m, 11-H\(_B\)); \( \delta_c \) (125 MHz, CDCl\(_3\), 323 K) 170.1 (acetyl C=O), 154.9 (Boc C=O), 79.7 (\( \text{t-Bu} \) 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 (\( \text{t-Bu} \) C\(_3\)), 27.4 (C-4), 26.6 (C-10), 21.0 (acetyl CH\(_3\)), 20.5 (C-11); HRMS found MNa\(^+\), 336.1789. \( \text{C}_{16}\text{H}_{27}\text{NO}_5 \) requires MNa, 336.1786.
2-Benzyl 8-tert-butyl (5R*,6S*)-5-(acetyloxy)-2,8-diazaspiro[5.5]undecane-2,8-dicarboxylate

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, Rf 0.60 (50:50 petrol–EtOAc); vmax/cm–1 2936, 2866, 1737, 1686, 1425, 1364, 1273, 1232, 1205, 1154, 1108, 1038; δH (500 MHz, CD3OD, 333 K) 7.37–7.27 (5H, m, phenyl), 5.14 (1H, d, J 12.4, phenylmethyl 1H), 5.11 (1H, d, J 12.4, phenylmethyl 1H), 4.89 (1H, dd, J 6.8 and 3.6, 5H), 3.63–3.44 (3H, m, 3H and 1H), 3.44–3.33 (4H, m, 9H2 and 7H), 3.19 (1H, d, J 12.9, 7H), 2.06 (3H, s, acetyl), 1.99-1.90 (1H, m, 4H), 1.74-1.65 (1H, m, 4H), 1.64-1.58 (1H, m, 11H), 1.57-1.47 (2H, m, 10H), 1.43 (9H, s, τBu), 1.41-1.36 (1H, m, 11H), 1.26 (15H, s, tert-butyl); δC (125 MHz, CD3OD, 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 C2-3, 5), 129.1 (phenyl C2-3, 5), 129.0 (phenyl C-4), 81.3 (τBu C1), 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 (τBu C3), 28.0 (C-10), 27.2 (C-4), 21.7 (C-11), 20.8 (acetyl CH3); HRMS found MNa+, 469.2306. C24H34N2O6 requires MNa+, 469.2314.

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

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, Rf 0.50 (70:30
tert-Butyl 5-oxo-1-oxa-4,8-diazaspiro[5.5]undecane-8-carboxylate

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); $\nu_{\text{max}}$/cm$^{-1}$ 3192, 3071, 2954, 2925, 1687, 1667, 1421, 1364, 1335, 1276, 1243, 1175, 1150, 1107, 1086; $\delta$ (500 MHz, CD$_3$OD, 333 K) 4.37 (1H, br. s, 4-H$_A$), 4.16 (1H, d, $J$ 13.9, 7-H$_A$), 3.79 (1H, d, $J$ 12.1, 8.5 and 3.5, 2-H$_A$), 3.72 (1H, app. br. s, 2-H$_B$), 3.32 (1H, d, $J$ 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); $\delta_C$ (125 MHz, CD$_3$OD, 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$_2$O$_4$ requires MNa, 293.1471.
**tert-Butyl N-[(3R*,4R*)-4-(benzyloxy)-3-(prop-2-en-1-yl)oxan-3-yl]methyl} carbamate**

By modification of an existing procedure, 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 NaHCO₃ (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 (MgSO₄), 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, R₉ 0.75 (50:50 petrol-EtOAc); νmax/cm⁻¹ 3426, 3344, 2973, 2930, 2859, 1712, 1504, 1453, 1365, 1243, 1165, 1088; δH (400 MHz, CDCl₃) 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), 4.87 (1H, app. t, J 4.8, NH), 4.66 (1H, d, J 11.6, phenylmethyl 1-Hₐ), 4.39 (1H, d, J 11.6, phenylmethyl 1-Hₐ), 4.05-3.90 (1H, m, 6-Hₐ), 3.67 (1H, d, J 11.8, 2-Hₐ), 3.48 (1H, app. td, J 7.9 and 3.8, 4-H), 3.45-3.38 (1H, m, 6-Hₐ), 3.18-3.09 (1H, m, methylcarbamate 1-Hₐ), 3.01 (1H, d, J 11.8, 2-Hₐ), 3.00 (1H, d, J 13.5, methylcarbamate 1-Hₐ), 2.33 (2H, app. d, J 7.6, propenyl 1-H₂), 2.00-1.90 (1H, m, 5-Hₐ), 1.78 (1H, app. dtd, J 13.7, 9.5 and 4.5, 5-Hₐ), 1.41 (9H, s, ¹Bu); δC (100 MHz, CDCl₃) 156.1 (C=O), 138.4 (phenyl C-1), 133.8 (propenyl C-2), 128.6 (phenyl C₂-3,5), 127.8 (phenyl C₂-2,6), 126.2 (phenyl C-4), 118.6 (propenyl C-3), 81.3 (¹Bu C₁), 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 (¹Bu C₃), 26.3 (C-5); HRMS found MH⁺, 362.2328. C₂₁H₃₁NO₄ requires MH, 362.2325.
**tert-Butyl 10-oxo-3-(pyridin-3-ylmethyl)-7-oxa-2-azaspiro[4.5]decane-2-carboxylate**

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–NH₄OH 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); $\nu_{\text{max}}$/cm$^{-1}$ 2971, 2930, 2861, 1709, 1685, 1391, 1364, 1222, 1147, 1111, 1094, 1027; $\delta_H$ (500 MHz, CD$_3$OD, 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-$H_B$); $\delta_C$ (125 MHz, CD$_3$OD, 333 K) 208.9 (C-10 minor), 208.8 (C-10 major), 156.2 (Boc C=O major), 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 ($^6$Bu C$^1$ minor), 81.5 ($^6$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 minor), 58.7 (C-3 major), 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 ($^6$Bu 2C$_3$); HRMS found MH$^+$, 347.1975. C$_{19}$H$_{26}$N$_2$O$_4$ requires MH, 347.1970.
**tert-Butyl (3R*,5S*,10S*)-10-(benzyloxy)-3-[(pyridin-3-yl)methyl]-7-oxa-2-azaspiro[4.5]decane-2-carboxylate**

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); $\nu_{\text{max}}$/cm$^{-1}$ 2928, 2858, 1685, 1393, 1364, 1155, 1085; $\delta$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); $\delta$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 $M^+$, 439.2604. $C_{28}H_{34}N_2O_4$ requires $M^+$, 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 (5R*,10R*)-10-(benzyloxy)-3-(iodomethyl)-7-oxa-2-azaspiro[4.5]decan-2-carboxylate (186)**


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 ¹H-NMR) as a yellow oil,  

$$R_f 0.63 \text{ (50:50 petrol–EtOAc); } \nu_{max}/\text{cm}^-1 2928, 2857, 1687, 1391, 1364, 1157, 1087; \delta_H (500 MHz, CDCl}_3, 323 K) 7.37-7.26 (10H, m, phenyl), 4.67 (1H, d, J 11.8, phenylmethyl 1-\text{H}_A^{\text{major}}), 4.64 (1H, d, J 11.9, phenylmethyl 1-\text{H}_A^{\text{minor}}), 4.45 (1H, d, J 11.8, phenylmethyl 1-\text{H}_B^{\text{major}}), 4.42 (1H, d, J 11.9, phenylmethyl 1-\text{H}_B^{\text{minor}}), 3.92-3.82 (2H, m, 8-\text{H}_A^{\text{major}}), 3.79-3.75 (2H, m, 3-\text{H}) 3.73 (2H, d, J 11.1, 6-\text{H}_A), 3.61 (2H, d, J 11.3, 1-\text{H}_A), 3.58-3.49 (4H, m, 8-\text{H}_B and iodomethyl 1-\text{H}_A), 3.44-3.40 (4H, m, 10-\text{H} and iodomethyl 1-\text{H}_B), 3.33 (2H, d, J 11.1, 6-H), 3.21 (2H, d, J 11.3, 1-H), 2.20-2.08 (2H, m, 9-H), 1.93-1.65 (6H, m, 9-H and 4-H), 1.47 (9H, s, 'Bu^{\text{major}}), 1.45 (9H, s, 'Bu^{\text{minor}}); \delta_C (125 MHz, CDCl}_3, 323 K) 154.3 (2C=O), 138.5 (phenyl C-1^{\text{major}}), 138.4 (phenyl C-1^{\text{minor}}), 128.6 (phenyl C-2,3-5^{\text{minor}}), 128.5 (phenyl C-2,3,5^{\text{major}}), 127.8 (phenyl C-4^{\text{minor}}), 127.7 (phenyl C-4^{\text{major}}), 127.6 (phenyl C-4=-2,6), 80.1 ('Bu C_1^{\text{minor}}), 80.0 ('Bu C_1^{\text{major}}), 78.0 (C-10^{\text{minor}}), 77.1 (C-10^{\text{major}}), 73.0 (C-2-6), 71.1 (phenylmethyl C-1^{\text{minor}}), 70.9 (phenylmethyl C-1^{\text{major}}), 64.9 (C-8^{\text{major}}), 63.2 (C-8^{\text{minor}}), 56.3 (C-3^{\text{major}}), 55.2 (C-3^{\text{minor}}), 52.3 (C-1^{\text{minor}}), 51.6 (C-1^{\text{major}}), 46.3 (C-5^{\text{major}}), 45.8 (C-5^{\text{minor}}), 36.6 (C-2-4), 28.6 ('Bu 2C_2), 27.4 (C-9^{\text{major}}), 26.3 (C-9^{\text{minor}}), 13.7 (iodomethyl C-1^{\text{major}}), 12.9 (iodomethyl C-1^{\text{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 ¹H-NMR) as an amorphous colourless solid,  

$$R_f 0.73 \text{ (50:50 petrol–EtOAc); } \nu_{max}/\text{cm}^-1 2979, 2955, 2928, 2854, 1683, 1604, 1477, 1453, 1402, 1361, 1249, 1165, 1137, 1091, 1066, 1020; \delta_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 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, 12-H$_B$), 1.31 (1H, dd, J 13.6 and 6.9, 12-H$_B$); $\delta$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$_{22}$lNO$_4$ 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

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$_4$OH to yield the bridged bicyclic derivative 152 (20.0 mg, 30%) as a yellow oil, $R$$_f$ 0.40 (92.4:6.8:0.8 DCM–EtOH–NH$_4$OH); $\nu$$_{\text{max}}$/cm$^{-1}$ 3362, 3074, 2848, 1709, 1674, 1638, 1455, 1435, 1375, 1234, 1211, 1082; $\delta$H (400 MHz, CD$_3$OD) 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$_{\text{cis}}$), 5.08 (1H, dd, J 16.7 and 1.5, propenyl 3-H$_{\text{trans}}$), 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$_2$); $\delta$C (100 MHz, CD$_3$OD) 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. \(\text{C}_{16}\text{H}_{15}\text{NO}_2\) requires \(\text{MH}\), 182.1175.

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

![Chemical Structure](image)

According to General Procedure Y, benzaldehyde (57.6 \(\mu\)L, 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\(_4\)OH 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); \(\nu_{\text{max}}/\text{cm}^{-1}\) 3337, 3059, 3030, 2921, 2851, 1708, 1470, 1372, 1225, 1210, 1088; \(\delta_H\) (500 MHz, CDCl\(_3\)) 7.34–7.18 (5H, m, phenyl), 5.75 (1H, dtt, \(J = 17.3, 10.0\) and 7.5, propenyl 2-\(H\)), 5.03 (1H, dd, \(J = 10.0\) and 1.9, propenyl 3-\(H\)_\text{cis}), 5.00 (1H, dd, \(J = 17.3\) and 1.9, propenyl 3-\(H\)_\text{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\(_B\)), \(\delta_C\) (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. \(\text{C}_{16}\text{H}_{15}\text{NO}_2\) requires \(\text{MH}\), 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

By modification of an existing procedure,\textsuperscript{192} tert-butylamine (27.4 mL, 261 mmol) was added to a solution of the chloroquinoline derivative \textbf{228} (5.00 g, 26.1 mmol) in \textit{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\textsubscript{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 \textit{amine derivative} \textbf{229} (3.10 g, 52%) as a bright yellow amorphous solid, \textit{R}\textsubscript{f} 0.57 (80:20 petrol–EtOAc); \textit{\nu}\textsubscript{max}/cm\textsuperscript{-1} 3335, 2961, 2839, 2725, 1670, 1620, 1573, 1535, 1400, 1356, 1219; \delta\textsubscript{H} (400 MHz, CDCl\textsubscript{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\textsubscript{3}), 7.21-7.15 (1H, m, 6-H), 1.60 (9H, s, \textit{t}Bu); \delta\textsubscript{C} (100 MHz, CDCl\textsubscript{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 (\textit{t}Bu C\textsubscript{1}), 29.1 (\textit{t}Bu C\textsubscript{3}); HRMS found MH\textsuperscript{+}, 229.1336. C\textsubscript{14}H\textsubscript{16}N\textsubscript{2}O requires MH, 229.1340.
Ethyl (2E)-3-[2-(tert-butylamino)quinolin-3-yl]prop-2-enoate

By modification of an existing procedure,\textsuperscript{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 \textbf{229} (2.00 g, 8.76 mmol), triethyl phosphononoacetate (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\textsubscript{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\textsubscript{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 \textit{alkene derivative} \textbf{230} (2.58 g, 99%) as a yellow oil, \textit{R}\textsubscript{f} 0.27 (96:4 petrol–EtOAc); \textit{v}\textsubscript{max}/cm\textsuperscript{-1} 3402, 3054, 2960, 1706, 1613, 1600, 1511, 1410, 1301, 1173, 1162; \textit{δ}\textsubscript{H} (400 MHz, CDCl\textsubscript{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\textsubscript{2}), 1.60 (9H, s, \textsuperscript{t}Bu), 1.37 (3H, t, J 7.1. ethyl 2-H\textsubscript{3}); \textit{δ}\textsubscript{C} (100 MHz, CDCl\textsubscript{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 (\textsuperscript{t}Bu C\textsubscript{1}), 29.3 (\textsuperscript{t}Bu C\textsubscript{3}), 14.4 (ethyl C-2); HRMS found MH\textsuperscript{+}, 299.1751. C\textsubscript{18}H\textsubscript{22}N\textsubscript{2}O\textsubscript{2} requires MH, 299.1759.
Ethyl 3-[2-(tert-butylamino)quinolin-3-yl]propanoate

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, Rf 0.39 (90:10 petrol–EtOAc); νmax/cm⁻¹ 3468, 2962, 2911, 2868, 1720, 1626, 1521, 1421, 1359, 1261, 1228, 1212, 1038; δH (300 MHz, CDCl₃) 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-H₂), 2.89-2.80 (2H, m, propanoate 3-H₂), 2.74-2.66 (2H, m, propanoate 2-H₂), 1.61 (9H, s, t-Bu), 1.28 (3H, t, J = 7.1, ethyl 2-H₃); δC (75 MHz, CDCl₃) 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 C₁), 33.0 (propanoate C-2), 29.4 (t-Bu C₃), 26.2 (propanoate C-3), 14.3 (ethyl C-2); HRMS found MH⁺, 301.1907. C₁₈H₂₄N₂O₂ 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 Et₃N 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, 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 Et₃N, 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, 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, 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, Et₃N (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 NH₃ in MeOH. The fraction containing the saturated solution of NH₃ 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-[(5R*,6R*)-5-hydroxy-2-oxa-8-azaspiro[5.5]undecan-8-yl]propan-1-one

According to General Procedure Z, the acetate derivative 179a (50.0 mg, 0.16 mmol), TBD (62.3 mg, 0.45 mmol) and Et₃N (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 ¹H-NMR) as a colourless oil, Rᵣ 0.48 (EtOAc); νₓmax/cm⁻¹ 3385, 2954, 2927, 2857, 1621, 1517, 1470, 1446, 1415, 1355, 1260, 1213, 1085; δₓ (400 MHz, CDCl₃) 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-Hₐₐmajor), 3.87-3.72 (2H, m, 3-Hₐ), 3.63-3.51 (6H, m, 1-Hₐ, 3-Hₐ and 7-Hₐ), 3.49 (2H, dd, J 7.6 and 3.9, 5-H), 3.42-3.29 (1H, m, 9-Hₐₐminor), 3.28-3.22 (1H, m, 9-Hₐmajor), 3.15 (2H, d, J 13.6, 1-Hₐ), 3.10 (2H, d, J 11.9, 7-Hₐ), 2.99-2.81 (5H, m, propanone 3-H₂ and 9-Hₐₐminor), 2.79-2.56 (4H, m, propanone 2-H₂), 2.00-1.89 (2H, m, 4-Hₐ), 1.82 (2H, app. ddt, J 13.5, 8.6 and 4.0, 10-Hₐ), 1.71-1.61 (2H, m, 4-Hₐ), 1.58 (18H, s, †Bu), 1.55-1.38 (6H, m, 10-Hₐ and 11-H₂); δₐ (100 MHz, CDCl₃) 171.3 (propanone C-1ₐminor), 171.1 (propanone C-1ₐmajor), 155.0 (quinolinyl C₂-2), 147.0 (quinolinyl C₂-8a), 134.7 (quinolinyl C₄₆major), 134.6 (quinolinyl C₄₆minor), 128.5 (quinolinyl C-7ₐmajor), 128.4 (quinolinyl C-7ₐminor), 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<sup>major</sup>), 121.6 (quinolinyl C-6<sup>minor</sup>), 70.7 (C-1<sup>major</sup>), 69.9 (C-2-5), 68.6 (C-1<sup>minor</sup>), 65.2 (C-3<sup>major</sup>), 64.3 (C-3<sup>minor</sup>), 51.9 ('Bu C-2), 50.3 (C-7<sup>minor</sup>), 47.5 (C-7<sup>major</sup>), 46.6 (C-9<sup>major</sup>), 42.9 (C-9<sup>minor</sup>), 38.9 (C-2-6), 32.0 (propanone C-2<sup>minor</sup>), 31.7 (propanone C-2<sup>major</sup>), 30.7 (C-2-4), 29.4 ('Bu C-6), 26.9 (propanone C-3<sup>major</sup>), 26.8 (propanone C-3<sup>minor</sup>), 21.3 (C-2-10), 20.4 (C-2-11); HRMS found MH<sup>+</sup>, 426.2748. C<sub>28</sub>H<sub>35</sub>N<sub>3</sub>O<sub>3</sub> requires MH, 426.2756.

3-[2-(tert-Butylamino)quinolin-3-yl]-1-[(5R<sup>*</sup>,10R<sup>*</sup>)-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<sub>3</sub>N (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 EtOAc–hexane to yield the amide derivative 231b (34.0 mg, 60%, rotamers >95:<5 by <sup>1</sup>H-NMR) as a colourless oil, R<sub>f</sub> 0.31 (EtOAc); <sup>v</sup><sub>max</sub>/cm<sup>-1</sup> 3360, 2954, 2862, 1621, 1518, 1447, 1416, 1355, 1213, 1082; δ<sub>n</sub> (400 MHz, CDCl<sub>3</sub>) 7.67 (2H, d, <i>J</i> 8.3, quinolinyl 8-H), 7.52 (2H, app. d, <i>J</i> 5.9, quinolinyl 4-H), 7.49 (2H, dd, <i>J</i> 7.9 and 1.6, quinolinyl 5-H), 7.45 (2H, ddd, <i>J</i> 8.3, 6.9 and 1.6, quinolinyl 7-H), 7.14 (2H, app. t, <i>J</i> 7.4, quinolinyl 6-H), 5.10 (2H, br. s, NH), 3.91-3.78 (2H, m, 8-H<sub>A</sub>), 3.72-3.52 (4H, m, 6-H<sub>A</sub> and 10-H), 3.53-3.32 (6H, m, 1-H<sub>A</sub>, 3-H<sub>A</sub> and 8-H<sub>B</sub>), 3.31-3.18 (4H, m, 1-H<sub>B</sub> and 3-H<sub>B</sub>), 3.11 (2H, d, <i>J</i> 11.5, 6-H<sub>B</sub>), 2.87 (4H, t, <i>J</i> 7.4, propanone 3-H<sub>B</sub>), 2.63-2.53 (4H, m, propanone 2-H<sub>B</sub>), 2.12-2.00 (2H, m, 4-H<sub>A</sub>), 1.93-1.82 (2H, m, 4-H<sub>B</sub>), 1.82-1.72 (2H, m, 9-H<sub>A</sub>), 1.70-1.58 (2H, m, 9-H<sub>B</sub>), 1.57 (18H, s, 'Bu); δ<sub>c</sub> (100 MHz, CDCl<sub>3</sub>) 171.1 (propanone C-2-1), 154.8 (quinolinyl C-2-2), 146.9 (quinolinyl C-2-8a), 134.5 (quinolinyl C-4<sup>minor</sup>), 134.4 (quinolinyl C-4<sup>major</sup>), 128.5 (quinolinyl C-2<sup>7</sup>-7), 126.7 (quinolinyl C-2<sup>5</sup>-5), 126.4 (quinolinyl C-2<sup>8</sup>-8), 123.7 (quinolinyl C-2<sup>3</sup>-3), 123.0 (quinolinyl C-2-4a), 121.7 (quinolinyl C-2-6), 71.3 (C-6<sup>major</sup>), 70.4 (C-6<sup>minor</sup>), 69.7 (C-10<sup>major</sup>), 69.5 (C-10<sup>minor</sup>), 65.6 (C-8<sup>major</sup>), 64.8 (C-8<sup>minor</sup>), 51.8 (C-3<sup>minor</sup>), 50.9 (C-3<sup>major</sup>), 48.2 ('Bu C-2), 46.5 (C-2-5), 45.5 (C-1<sup>major</sup>),
44.5 (C-1\text{minor}), 33.7 (propanone C-2), 33.3 (C-2), 32.3 (C-4\text{major}), 32.1 (C-4\text{minor}), 29.4 ('Bu C-6), 26.4 (propanone C-3\text{minor}), 26.3 (propanone C-3\text{major}); HRMS found MH\textsuperscript{+}, 412.2598. C\textsubscript{24}H\textsubscript{33}N\textsubscript{3}O\textsubscript{3} requires MH\textsuperscript{+}, 412.2600.

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

![Chemical Structure](image)

According to General Procedure Z, the acetate derivative 173d (0.10 g, 0.35 mmol), TBD (0.12 mg, 0.87 mmol) and Et\textsubscript{3}N (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 \textsuperscript{1}H-NMR) as a colourless amorphous solid, R\textsubscript{f} 0.34 (EtOAc); ν\textsubscript{max}/cm\textsuperscript{-1} 3278, 2950, 2914, 2866, 1625, 1517, 1453, 1418, 1353, 1216, 1054; δ\textsubscript{H} (400 MHz, DMSO–d\textsubscript{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\text{minor}), 5.82 (1H, br. s, NH\text{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\textsubscript{6}), 3.24 (2H, app. s, 6-H\textsubscript{A}), 3.19 (2H, app. s, 6-H\textsubscript{B}), 2.84 (4H, td, J 6.9 and 4.0, propanone 3-H\textsubscript{2}), 2.59 (4H, app. q, J 6.4, propanone 2-H\textsubscript{2}), 2.15 (1H, ddd, J 12.7, 7.9 and 6.3, 9-H\textsubscript{A}\text{minor}), 2.05 (1H, ddd, J 13.0, 7.7 and 5.9, 9-H\textsubscript{A}\text{major}), 1.75-1.65 (1H, m, 9-H\textsubscript{B}\text{minor}), 1.59 (1H, app. dt, J 13.0 and 7.7, 9-H\textsubscript{B}\text{major}), 1.53 (18H, s, 'Bu); δ\textsubscript{C} (100 MHz, DMSO–d\textsubscript{6}) 170.2 (propanone C-1\text{minor}), 170.1 (propanone C-1\text{major}), 155.0 (quinolinyl C-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\text{minor}), 74.4 (C-3\text{major}), 73.8 (C-4\text{major}), 73.7 (C-1\text{major}), 73.6 (C-4\text{minor}), 73.5 (C-1\text{minor}), 54.2 (C-6\text{minor}), 54.1 (C-5\text{major}), 53.6 (C-6\text{major}), 52.2 (C-5\text{minor}), 51.1 ('Bu C-2), 45.1 (C-8\text{minor}), 44.6 (C-8\text{major}), 32.9 (propanone C-2\text{major}), 32.6 (propanone C-2\text{minor}), 28.9 ('Bu C-6), 27.5 (C-9\text{minor}), 25.7 (C-9\text{major}),
25.3 (propanone C-3_minor), 25.1 (propanone C-3_major); HRMS found MH+, 398.2435. C_{23}H_{31}N_{3}O_{3} requires MH, 398.2443.

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

According to General Procedure Z, the acetate derivative 173c (50.0 mg, 0.14 mmol), TBD (73.0 mg, 0.52 mmol) and Et₃N (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 ¹H-NMR) as a colourless oil, Rf 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, CDCl₃) 7.69 (2H, app. t, J 9.3, quinolinyl 8-H), 7.57-7.41 (6H, m, quinolinyl 4,5,7-H), 7.21-7.09 (2H, m, quinolyl 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-H2), 2.83-2.74 (2H, m, 1-H_A), 2.65-2.55 (4H, m, propanone 2-H2), 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, tBu_major), 1.57 (9H, s, tBu_minor); δ_C (100 MHz, CDCl₃) 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),
213

115.0 (C-6major), 110.0 (C-4minor), 109.7 (C-4major), 79.3 (C-3minor), 79.1 (C-3major), 56.7 (C-2major), 55.6 (methoxy), 55.4 (C-2minor), 54.0 (C2-2), 53.9 (tBu C2), 46.1 (C-5minor), 45.3 (C-5major), 40.3 (C-1major), 40.0 (C-1minor), 35.7 (C-2-4'), 34.3 (propanone C-2major), 33.6 (propanone C-2minor), 29.4 (tBu C6), 26.6 (propanone C-3major), 26.4 (propanone C-3minor); HRMS found MH+, 474.2757. C29H35N3O3 requires MH, 474.2756.

N-[[4aR*,8aR*]-Octahydropyrano[4,3-b]pyran-4a-yl]methyl]-3-[2-(tert-butyl amino) quinolin-3-yl]propanamide

According to General Procedure AA, the carbamate derivative 149a (50.0 mg, 0.18 mmol), TBD (76.5 mg, 0.55 mmol) and Et3N (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, Rf 0.50 (EtOAc); νmax/cm⁻¹ 3314, 2952, 2926, 2859, 1648, 1623, 1516, 1486, 1447, 1415, 1355, 1274, 1259, 1214, 1098, 1080, 1024; δH (400 MHz, CDCl3) 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, tBu 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-H2), 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-H2), 2.54 (2H, td, J 7.1 and 1.8, propanamide 2-H2), 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, tBu), 1.48-1.38 (1H, m, 8-H_B), 1.31-1.15 (3H, m, 3-H_B and 4-H2); δC (100 MHz, CDCl3) 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 (tBu C1), 45.2
(methylpropanamide C-1), 36.2 (C-4a), 35.7 (propanamide C-2), 29.4 (tBu 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_{3}O_{3} requires MH, 426.2756.

**N-[(4aR⁺,7aS⁺)-Hexahydro-2H-furo[3,4-b]pyran-4a-yl]methyl)-3-[2-(tert-butylamino)quinolin-3-yl]propanamide**

According to General Procedure AA, the carbamate derivative **149d** (0.10 g, 0.39 mmol), TBD (0.13 g, 0.93 mmol) and Et₃N (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, Rᵣ 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, CDCl₃) 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, tBu NH), 4.02 (1H, dd, J 10.1 and 4.1, 7-Hₐ), 3.84-3.77 (1H, m, 2-Hₐ), 3.81 (1H, d, J 8.6, 5-Hₐ), 3.74 (1H, d, J 10.1, 7-Hₘ), 3.61 (1H, d, J 4.1, 7a-H), 3.46 (1H, d, J 8.6, 5-Hₘ), 3.27 (1H, dd, J 14.0 and 6.3, methylpropanamide 1-Hₐ), 3.15 (1H, app. td, J 11.5 and 2.4, 2-Hₘ), 3.11 (1H, dd, J 14.0 and 6.3, methylpropanamide 1-Hₐ), 2.90 (2H, t, J 7.0, propanamide 3-H₂), 2.56 (2H, t, J 7.0, propanamide 2-H₂), 1.58 (9H, s, tBu), 1.49 (1H, app. dd, J 11.2 and 4.3, 3,4-Hₐ), 1.48-1.46 (1H, m, 3,4-Hₘ), 1.39-1.30 (1H, m, 3,4-Hₐ), 1.28-1.21 (1H, m, 3,4-Hₐ); δ(C) (100 MHz, CDCl₃) 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 C₂-4a,6), 80.3 (C-7a), 74.2 (C-7), 71.1 (C-5), 66.0 (C-2), 51.9 (tBu C₁), 45.5 (C-4a), 45.4 (methylpropanamide C-1), 35.6 (propanamide C-2), 29.4 (tBu C₃), 26.8 (propanamide C-3), 24.4 (C-4), 21.5 (C-3); HRMS found MH⁺, 412.2594. C_{24}H_{33}N_{3}O_{3} requires MH, 412.2600.
1-[(4aR*,8aR*)-4a-Benzyl-octahydro-2H-pyran-3,2-c]pyridinyl-6-yl]-3-[2-(tert-butyramino)quinolin-3-yl]propan-1-one

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 1H-NMR) as a colourless oil, Rf 0.44 (50:50 EtOAc-petrol); νmax/cm⁻¹ 3305, 2951, 2925, 2868, 1634, 1622, 1582, 1543, 1447, 1419, 1352, 1272, 1227, 1212, 1116, 1090; δH (400 MHz, CDCl₃) 7.68 (2H, d, J 8.6, quinolinyl 8-H), 7.58 (2H, s, quinolinyl 4-H), 7.47-7.40 (2H, m, quinolinyl 5,7-H₂), 7.31-7.15 (8H, m, phenyl 2,6-H₂major and phenyl 3,4,5-H₃), 7.12 (2H, app. q, J 6.9, quinolinyl 6-H), 7.07-7.00 (2H, m, phenyl 2,6-H₂minor), 5.14 (2H, br. s, NH), 4.42 (1H, app. d, J 13.1, 7-H₁Amajor), 4.18 (1H, d, J 13.2, 5-H₃Amajor), 3.95-3.81 (2H, m, 2-H₂), 3.70-3.61 (1H, m, 7-H₂Amajor), 3.46 (1H, d, J 13.2, 5-H₃Amminor), 3.40-3.20 (5H, m, 2-H₂B, 7-H₃Bmajor and 8a-H), 3.14 (1H, d, J 13.2, 5-H₃Bmajor), 3.07 (1H, d, J 13.2, 5-H₃Bminor), 3.00-2.89 (5H, m, 7-H₃Bminor and propanone 3-H₂), 2.86-2.71 (5H, m, phenylmethyl 1-H₃Amminor and propanone 2-H₂), 2.63 (1H, d, J 13.4, phenylmethyl 1-H₃Bmajor), 2.47 (1H, d, J 13.4, phenylmethyl 1-H₃Bminor), 2.25 (1H, d, J 13.4, phenylmethyl 1-H₃Bmajor), 2.17-2.07 (1H, m, 8-H₂Amminor), 1.94-1.81 (1H, m, 8-H₂Ammajor), 1.78-1.61 (4H, m, 3-H₃A and 8-H₃A), 1.60 (9H, s, 8-Bumajor), 1.56 (9H, s, 8-Buminor), 1.59-1.52 (2H, m, 3-H₃B), 1.45-1.31 (2H, m, 4-H₃A), 1.17-1.05 (2H, m, 4-H₃B); δC (100 MHz, CDCl₃) 171.8 (propanone C-1aminor). 171.2 (propanone C-1major), 154.9 (quinolinyl C₃-2), 147.0 (quinolinyl C₂-8a), 136.8 (phenyl C₂-1), 134.6 (quinolinyl C₄aminor), 134.5 (quinolinyl C₄amajor), 131.0 (phenyl C₂-2,6aminor), 130.7 (phenyl C₂-2,6amajor), 128.4 (quinolinyl C₇amajor), 128.3 (quinolinyl C₇aminor), 128.1 (phenyl C₄-3,5), 126.7 (quinolinyl C₂-5), 126.5 (quinolinyl C₂-8), 126.4 (phenyl C₂-4), 123.6 (quinolinyl C₂-3), 123.1 (quinolinyl C₂-4a), 121.7 (quinolinyl C₂-6), 77.1 (C-8aminor), 75.4 (C-8amajor), 67.8 (C-2aminor), 67.2 (C-2amajor), 51.9 (8-Bumajor), 51.8 (8-Buminor), 48.7 (C-5aminor), 43.6 (C-5amajor), 41.4 (phenylmethyl C₂-1), 41.0 (C-7aminor), 37.4 (C-4aminor), 37.3 (C-4amajor), 36.5 (C-7aminor), 32.1
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, $R_t$ 0.17 (EtOAc); $\nu_{\text{max}}$/cm$^{-1}$ 3312, 2926, 2852, 1622, 1518, 1474, 1447, 1415, 1354, 1272, 1213, 1118, 1091; $\delta_H$ (400 MHz, CDCl$_3$) 8.46 (2H, br. s, pyridinyl 6-H), 8.33 (1H, br. s, pyridinyl 2-H$_{\text{major}}$), 8.26 (1H, br. s, pyridinyl 2-H$_{\text{minor}}$), 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$_{\text{minor}}$), 5.05 (1H, br. s, NH$_{\text{major}}$), 4.43 (1H, app. d, $J$ 13.0, 7-H$_{\text{A minor}}$), 4.13 (1H, d, $J$ 13.3, 5-H$_{\text{A major}}$), 3.91 (2H, dd, $J$ 11.4 and 4.5, 2-H$_{\text{A}}$), 3.72-3.61 (1H, m, 7-H$_{\text{A major}}$), 3.48 (1H, d, $J$ 13.3, 5-H$_{\text{A minor}}$), 3.37-3.27 (3H, m, 2-H$_{\text{B}}$ and 7-H$_{\text{B major}}$), 3.25 (2H, s, 8a-H), 3.10 (2H, d, $J$ 13.3, 5-H$_{\text{B}}$), 3.04-2.82 (5H, m, 7-H$_{\text{B minor}}$ 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$_{\text{A minor}}$), 2.52 (1H, d, $J$ 13.6, pyridinylmethyl 1-H$_{\text{A major}}$), 2.27 (1H, d, $J$ 13.8 pyridinylmethyl 1-H$_{\text{B minor}}$), 2.09 (1H, d, $J$ 13.6, pyridinylmethyl 1-H$_{\text{B major}}$), 2.05-1.97 (1H, m, 8-H$_{\text{A minor}}$), 1.80-1.70 (1H, m, 8-H$_{\text{A major}}$), 1.69-1.60 (2H, m, 8-H$_{\text{B}}$), 1.59 (9H, s, $t$Bu$_{\text{major}}$), 1.54 (9H, s, $t$Bu$_{\text{minor}}$), 1.55-1.50 (2H, m, 3-H$_{\text{A}}$), 1.39-1.32 (2H, m, 3-H$_{\text{B}}$), 1.30-1.23 (2H, m, 4-H$_{\text{A}}$), 1.10-1.00 (2H, m, 4-H$_{\text{B}}$); $\delta_C$ (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\text{major}), 74.8 (C-8a\text{minor}), 67.9 (C_2-2), 51.9 (t-Bu C_1), 43.1 (C_2-5), 41.0 (C_2-7), 38.2 (t-Bu C_3\text{major}), 29.3 (t-Bu C_3\text{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

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 231\text{ii}^{192} (0.30 g, 98%) as a colourless amorphous solid, R_f 0.47 (60:40 petrol–EtOAc); \nu_{\text{max}}/\text{cm}^{-1} 3423, 3252, 3083, 2948, 2923, 2850, 1621, 1524, 1449, 1413, 1352, 1271, 1222; \delta_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), 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), 2.87 (2H, t, J 7.1, propanamide 3-H), 2.48 (2H, t, J 7.1, propanamide 3-H), 1.81-1.61 (4H, m, 2-H_2A, 6-H_2A 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_3), 0.92-0.79 (2H, m, 2-H_2 and 6-H_2); \delta_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.
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); $v_{max}$/cm$^{-1}$ 3307, 2959, 2928, 2866, 1644, 1623, 1485, 1448, 1414, 1355, 1273, 1212; $\delta_H$ (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, tBu 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, tBu), 1.54-1.41 (1H, m, 4-H$_B$); $\delta_C$ (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 (tBu C$_1$), 42.6 (methylpropanamide C-1), 39.0 (C-3), 35.6 (propanamide C-2), 29.8 (C-4), 29.3 (tBu C$_3$), 26.7 (propanamide C-3); HRMS found MH$^+$, 356.2334. C$_{21}$H$_{29}$N$_3$O$_2$ requires MH, 356.2338.
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); \( \nu_{\text{max}}/\text{cm}^{-1} \) 3452, 3391, 2954, 2915, 2860, 2242, 1639, 1624, 1515, 1419, 1354, 1216, 1116; \( \delta_H \) (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); \( \delta_C \) (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), 125.3 (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. \( C_{20}H_{27}N_{3}O_{2} \) requires MH\(^+\), 342.2181.

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

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 \textbf{231I} (50.0 mg, 37%, rotamers 51:49 by \textsuperscript{1}H-NMR) as a colourless oil, \(R_t\) 0.37 (70:30 petrol–EtOAc); \(\nu_{\text{max}}/\text{cm}^{-1}\) 3455, 2942, 2923, 2869, 2848, 1645, 1623, 1517, 1489, 1449, 1437, 1420, 1353, 1278, 1215, 1194, 1175; \(\delta_H\) (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\textsubscript{minor}), 5.17 (1H, br. s, NH\textsubscript{major}), 4.55 (1H, ddt, \(J\) 12.9, 3.8 and 1.7, phenylmethyl 1-H\textsubscript{A}\textsubscript{minor}), 4.44 (1H, app. dt, \(J\) 12.9 and 3.8, phenylmethyl 1-H\textsubscript{A}\textsubscript{major}), 3.74 (1H, app. dt, \(J\) 12.4 and 4.2, phenylmethyl 1-H\textsubscript{B}\textsubscript{minor}), 3.66-3.59 (1H, m, phenylmethyl 1-H\textsubscript{B}\textsubscript{major}), 2.97 (2H, app. dd, \(J\) 12.0 and 2.8, 6-H\textsubscript{2}\textsubscript{major}), 2.93 (2H, t, \(J\) 7.2, propanone 3-H\textsubscript{2}\textsubscript{minor}), 2.84 (2H, t, \(J\) 7.2, propanone 3-H\textsubscript{2}\textsubscript{major}), 2.78-2.70 (2H, m, 6-H\textsubscript{2}\textsubscript{minor}), 2.69-2.62 (4H, m, 2-H\textsubscript{2}\textsubscript{major} and propanone 2-H\textsubscript{2}\textsubscript{minor}), 2.55-2.48 (2H, m, propanone 2-H\textsubscript{2}\textsubscript{major}), 2.47-2.38 (2H, m, 2-H\textsubscript{2}\textsubscript{minor}, 1.86-1.62 (6H, m, 3-H, 4-H\textsubscript{A} and 5-H\textsubscript{A}), 1.60 (18H, s, \textsuperscript{t}Bu), 1.49-1.07 (4H, m, 4-H\textsubscript{B} and 5-H\textsubscript{B}); \(\delta_C\) (100 MHz, CDCl\(_3\)) 170.5 (propanone C-1\textsubscript{minor}), 170.4 (propanone C-1\textsubscript{major}), 154.9 (quinolinyl C-2-2), 147.0 (quinolinyl C-2-8a), 139.5 (phenyl C-1\textsubscript{minor}), 139.3 (phenyl C-1\textsubscript{major}), 134.5 (quinolinyl C-4\textsubscript{major}), 134.3 (quinolinyl C-4\textsubscript{minor}), 129.1 (phenyl C-2-2,6\textsubscript{major}), 128.8 (phenyl C-2-2,6\textsubscript{minor}), 128.6 (quinolinyl C-2-7), 128.4 (phenyl C-2-3,5\textsubscript{major}), 128.3 (phenyl C-2-3,5\textsubscript{minor}), 126.6 (quinolinyl C-2-5), 126.4 (quinolinyl C-2-8), 126.1 (phenyl C-2-4), 124.0 (quinolinyl C-3\textsubscript{major}), 123.8 (quinolinyl C-3\textsubscript{minor}), 123.1 (quinolinyl C-2-4a), 121.6 (quinolinyl C-2-6), 51.8 (\textsuperscript{t}Bu C-2), 51.3 (C-2\textsubscript{major}), 48.0 (C-2\textsubscript{minor}), 46.4 (phenylmethyl C-1\textsubscript{minor}), 42.9 (phenylmethyl C-1\textsubscript{major}), 40.3 (C-6\textsubscript{minor}), 40.0 (C-6\textsubscript{major}), 38.8 (phenylmethyl C-3\textsubscript{major}), 37.8 (phenylmethyl C-3\textsubscript{minor}), 32.2 (propanone C-2\textsubscript{minor}), 31.9 (propanone C-2\textsubscript{major}), 30.9 (C-4\textsubscript{major}), 30.8 (C-4\textsubscript{minor}), 29.4 (\textsuperscript{t}Bu C-6), 26.7 (propanone C-3\textsubscript{minor}), 26.5 (propanone C-3\textsubscript{major}), 25.8 (C-5\textsubscript{minor}), 24.7 (C-5\textsubscript{major}); HRMS found MH\textsuperscript{+}, 430.2858. C\textsubscript{28}H\textsubscript{35}N\textsubscript{3}O requires MH, 430.2858.
According to General Procedure AC, the amine hydrochloride derivative \textbf{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 \textit{amide derivative} \textbf{231m} (50.0 mg, 43%) as a colourless oil, \(R_f\) 0.45 (30:70 petrol–EtOAc); \(\nu_{\text{max}}/\text{cm}^{-1}\) 3429, 3294, 3089, 2953, 2920, 2843, 1641, 1622, 1557, 1518, 1448, 1413, 1354, 1212, 1089; \(\delta_H\) (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, \(t^\text{Bu}\) 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, \(t^\text{Bu}\)), 1.55-1.45 (2H, m, 5-H\(_2\)), 1.16 (1H, app. dtd, \(J\) 13.7, 10.5 and 4.6, 4-H\(_B\)); \(\delta_C\) (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 (\(t^\text{Bu}\) C\(_1\)), 41.7 (methylpropanamide C-1), 36.3 (C-3), 35.5 (propanamide C-2), 29.3 (\(t^\text{Bu}\) C\(_3\)), 27.3 (C-4), 26.7 (propanamide C-3), 25.0 (C-5); HRMS found \textit{MH}^+, 370.2488. \(C_{22}H_{31}N_3O_2\) requires \textit{MH}, 370.2494.
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–NH₄OH to yield the amine derivative 215 (9.80 mg, >99% rotamers 78:22 by ¹H-NMR) as a pale yellow oil, Rᵣ 0.68 (84.7:13.6:1.70 DCM–EtOH–NH₄OH); νₓ/cm⁻¹ 3337, 3200, 2929, 2854, 1617, 1498, 1468, 1432, 1260, 1233, 1132, 1083, 1002; δₓ (400 MHz, CDCl₃) 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, NH₂minor), 5.37 (2H, br. s, NH₂major), 4.27 (1H, app. d, J 13.1, 9-Hₐminor), 3.85-3.75 (2H, m, 3-Hₐ), 3.74-3.62 (2H, m, 3-Hₐ), 3.60 (2H, d, J 11.9, 1-Hₐ), 3.56-3.50 (4H, m, 5-H and 7-Hₐ), 3.46-3.36 (1H, m, 9-Hₐmajor), 3.35-3.25 (1H, m, 9-Hₐmajor), 3.10 (2H, d, J 12.6, 7-Hₐ), 3.05-2.75 (7H, m, 1-Hₐ, 9-Hₐminor and propanone 3-H₂), 2.74-2.55 (4H, m, propanone 2-H₂), 2.12-1.81 (2H, m, 4-Hₐ), 1.75-1.65 (2H, m, 10-Hₐ), 1.64-1.44 (8H, m, 4-Hₐ, 10-Hₐ and 11-H₂); δₓ (100 MHz, CDCl₃) 171.3 (propanone C-1minor), 171.1 (propanone C-1major), 156.7 (quinolinyl C₂-2), 146.7 (quinolinyl C₂-8a), 136.7 (quinolinyl C₂-4), 129.2 (quinolinyl C₂-7), 127.0 (quinolinyl C₂-5), 125.5 (quinolinyl C₂-8), 124.3 (quinolinyl C₂-3), 123.5 (quinolinyl C₂-4a), 122.7 (quinolinyl C-6major), 122.6 (quinolinyl C-6minor), 70.6 (C-1major), 69.8 (C-5major), 69.7 (C-5minor), 68.4 (C-1minor), 65.3 (C-3minor), 64.2 (C-3major), 50.3 (C-7minor), 47.6 (C-7major), 46.6 (C-9major), 42.9 (C-9minor), 39.0 (C-6major), 38.9 (C-6minor), 32.4 (propanone C-2major), 32.3 (propanone C-2minor), 30.7 (C₂-4), 26.9 (propanone C-3minor), 26.6 (propanone C-3major), 21.3 (C₂-10), 20.5 (C₂-11); HRMS found MH⁺, 370.2123. C₂₁H₂₇N₅O₃ requires MH, 370.2130.
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, $R_t$ 0.63 (84.7:13.6:1.70 DCM−EtOH−NH$_4$OH); $v_{\text{max}}$/cm$^{-1}$ 3410, 3324, 3149, 2941, 2878, 2850, 1655, 1624, 1473, 1438, 1340, 1328, 1134, 1108, 1086, 1068; $\delta$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$^{\text{major}}$), 5.70 (2H, br. s, NH$^{\text{minor}}$), 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$_{\alpha}$), 1.98−1.86 (2H, m, 4$^-$H$_{\beta}$), 1.85−1.75 (2H, m, 9$^-$H$_{\alpha}$), 1.69−1.55 (2H, m, 9$^-$H$_{\beta}$); $\delta$C (100 MHz, CDCl$_3$) 171.2 (propanone C$^-$1$^\text{major}$), 171.1 (propanone C$^-$1$^\text{minor}$), 156.7 (quinolinyl C$_2^-$2), 146.0 (quinolinyl C$^-$8$^a$$^\text{major}$), 145.8 (quinolinyl C$^-$8$^a$$^\text{minor}$), 137.0 (quinolinyl C$_2^-$4), 129.4 (quinolinyl C$_2^-$7), 127.0 (quinolinyl C$_2^-$5), 124.9 (quinolinyl C$^-$8$^m$$^\text{major}$), 124.1 (quinolinyl C$^-$3$^m$$^\text{minor}$), 124.0 (quinolinyl C$^-$3$^m$$^\text{major}$), 123.8 (quinolinyl C$^-$4$^a$$^\text{major}$), 123.7 (quinolinyl C$^-$4$^a$$^\text{minor}$), 122.8 (quinolinyl C$_2^-$6), 71.4 (C$^-$6$^m$$^\text{major}$), 70.6 (C$^-$6$^m$$^\text{minor}$), 69.8 (C$^-10$$^m$$^\text{major}$), 69.5 (C$^-10$$^m$$^\text{minor}$), 65.7 (C$^-8$$^m$$^\text{major}$), 65.0 (C$^-8$$^m$$^\text{minor}$), 51.8 (C$^-3$$^m$$^\text{minor}$), 51.1 (C$^-3$$^m$$^\text{major}$), 48.5 (C$^-5$$^m$$^\text{minor}$), 46.5 (C$^-5$$^m$$^\text{major}$), 45.6 (C$^-1$$^m$$^\text{major}$), 44.7 (C$^-1$$^m$$^\text{minor}$), 34.1 (propanone C$_2^-$2), 33.9 (C$_2^-$9), 32.4 (C$^-4$$^m$$^\text{major}$), 32.3 (C$^-4$$^m$$^\text{minor}$), 26.1 (propanone C$^-$3$^m$$^\text{minor}$), 26.0 (propanone C$^-$3$^m$$^\text{major}$); HRMS found MH$^+$, 356.1971. C$_{20}$H$_{25}$N$_3$O$_3$ requires MH, 356.1974.
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, $R_t$ 0.51 (84.7:13.6:1.70 DCM−EtOH−NH$_4$OH); $\nu_{\text{max}}$/cm$^{-1}$ 3326, 3148, 2919, 2872, 1625, 1567, 1471, 1431, 1362, 1216, 1124, 1054; $\delta_H$ (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$_A^{\text{major}}$), 2.22 (1H, ddd, $J$ 13.2, 7.6 and 5.8, 9-H$_A^{\text{minor}}$), 1.80 (1H, app. dt, $J$ 12.9 and 7.6, 9-H$_B^{\text{major}}$), 1.71 (1H, app. dt, $J$ 13.0 and 7.8, 9-H$_B^{\text{minor}}$); $\delta_C$ (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$_4^{\text{minor}}$), 137.0 (quinolinyl C$_4^{\text{major}}$), 129.5 (quinolinyl C$_7^{\text{minor}}$), 129.4 (quinolinyl C$_7^{\text{major}}$), 127.1 (quinolinyl C$_2$-5), 125.0 (quinolinyl C$_8^{\text{major}}$), 124.9 (quinolinyl C$_8^{\text{minor}}$), 124.1 (quinolinyl C$_3^{\text{major}}$), 124.0 (quinolinyl C$_3^{\text{minor}}$), 123.5 (quinolinyl C$_2$-4a), 122.9 (quinolinyl C$_6^{\text{minor}}$), 122.8 (quinolinyl C$_6^{\text{major}}$), 75.3 (C$_2$-1), 74.9 (C$_2$-4), 74.4 (C$_2$-3), 55.5 (C$_6^{\text{minor}}$), 54.7 (C$_5^{\text{minor}}$), 54.4 (C$_6^{\text{major}}$), 52.7 (C$_5^{\text{major}}$), 46.1 (C$_8^{\text{major}}$), 45.3 (C$_8^{\text{minor}}$), 34.3 (propanone C$_2^{\text{minor}}$), 33.7 (propanone C$_2^{\text{major}}$), 28.3 (C$_2$-9), 26.3 (propanone C$_3^{\text{major}}$), 26.2 (propanone C$_3^{\text{minor}}$); HRMS found MH$^+$, 342.1807. C$_{19}$H$_{23}$N$_3$O$_3$ requires MH, 342.1817.
3-(2-Aminoquinolin-3-yl)-1-[(2R*,3R*)-3-hydroxy-5-methoxy-1,3-dihydros\npiro[indene-2,3'-pyrrolidin]-1'-yl]propan-1-one

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–NH₄OH to yield the amine derivative 218 (5.00 mg, 32%, rotamers 53:47 by ¹H-NMR) as a colourless oil, Rᵣ 0.27 (92:4.6:76:0.84 DCM–EtOH–NH₄OH); νmax/cm⁻¹ 3341, 3214, 3057, 2960, 2921, 1613, 1490, 1432, 1259, 1095, 1019; δH (400 MHz, CDCl₃) 7.75-7.45 (8H, m, quinolinyl 4,5,7,8-H₄), 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, NHₗₗₗ), 5.47 (2H, br. s, NHₗₗ), 4.64 (1H, s, 3-Hₗₗₗ), 4.50 (1H, s, 3-\nHₗₗ), 3.78 (3H, methoxyₗ), 3.77 (3H, methoxyₗₗ), 3.75-3.63 (2H, m, 5'-\nHₐ), 3.61-3.49 (2H, m, 5'-Hₐ), 3.42-3.23 (2H, m, 2'-Hₐ), 3.22-3.11 (2H, m, 2'-\nHₐ), 3.10-2.95 (4H, m, propanone 3-H₂), 2.94-2.81 (2H, m, 1-Hₐ), 2.73-2.61 (4H, m, propanone 2-H₂), 2.60-2.49 (2H, m, 1-Hₐ), 2.37-2.28 (1H, m, 4'-\nHₐₗ), 2.27-2.18 (1H, m, 4'-\nHₐₗₗₗ), 1.96-1.84 (1H, m, 4'-\nHₐₗₗ), 1.83-1.65 (1H, m, 4'-\nHₐₗₗₗ); δC (100 MHz, CDCl₃) 171.3 (propanone C-1ₗₗₗ), 171.2 (propanone C-
1ₗ), 159.4 (C-5ₗₗₗ), 159.3 (C-5ₗ), 156.8 (quinolinyl C₂-2), 146.7 (quinolinyl 
C-8ₗₗₗ), 146.6 (quinolinyl C-8ₗₗ), 145.0 (C-3ₗₗₗ), 144.9 (C-3ₗ), 136.8 (quinolinyl 
C-4ₗₗₗ), 136.7 (quinolinyl C-4ₗ), 133.1 (C-7ₗₗₗ), 132.9 (C-7ₗ), 129.3 (quinolinyl 
C₇ₗₗₗ), 129.2 (quinolinyl C₇ₗ), 127.0 (quinolinyl 
C₂₅), 126.0 (C-7ₗₗₗ), 125.8 (C-7ₗ), 125.5 (quinolinyl C₈ₗₗₗ), 125.3 (quinolinyl 
C₈ₗₗ), 124.3 (quinolinyl C₂₃), 123.6 (quinolinyl C₈₄ₗ), 122.7 (quinolinyl 
C₆ₗₗₗ), 122.6 (quinolinyl C₆ₗ), 115.2 (C₆ₗₗₗ), 115.1 (C₆ₗ), 109.8 (C-₄ₗₗₗ), 109.7 (C-₄ₗₗ), 80.0 (C-₃ₗₗₗ), 79.4 (C-₃ₗ), 56.7 (C₂-2'), 55.6 (methoxy), 54.1 (C-₂ₗₗₗ), 53.9 (C-₂ₗₗ), 46.3 (C-₅ₗₗₗ), 45.3 (C-₅ₗ), 40.3 (C-₁ₗₗₗ), 40.0 (C-₁ₗₗ), 36.0 (C₂₄'), 34.4 (propanone C-₂ₐₗₗ), 33.9 (propanone C-₂ₐₗ), 26.4 (propanone C-₃ₐₗₗ), 26.2 (propanone C-₃ₐₗ); HRMS found MH⁺, 418.2125. C₂₅H₂₇N₃O₃ requires MH⁺, 418.2130.
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, Rf 0.43 (92.4:6.76:0.84 DCM–EtOH–NH₄OH); νmax/cm⁻¹ 3316, 3209, 3058, 2930, 2859, 1632, 1555, 1498, 1433, 1258, 1235, 1097, 1078, 1024; δH (400 MHz, CDCl₃) 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, NH₂), 3.92-3.84 (1H, m, 2-HA), 3.80 (1H, d, J 11.7, 5-HA), 3.66-3.59 (2H, m, 7-H₂), 3.37 (1H, dd, J 13.9 and 6.7, methylpropanamide 1-Hₐ), 3.32-3.24 (2H, m, 8a-H and methylpropanamide 1-Hₐ), 3.23-3.15 (1H, m, 2-Hₐ), 3.21 (1H, d, J 11.7, 5-Hₐ), 2.99 (2H, t, J 7.1, propanamide 3-H₂), 2.58 (2H, t, J 7.1, propanamide 2-H₂), 2.03-1.88 (1H, m, 8-Hₐ), 1.62-1.49 (1H, m, 3-Hₐ), 1.48-1.40 (1H, m, 8-Hₐ), 1.31-1.12 (3H, m, 3-Hₐ and 4-H₂); δC (100 MHz, CDCl₃) 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. C₂₁H₂₇N₃O₃ requires MH, 370.2130.
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, Rf 0.65 (84.7:13.6:1.70 DCM–EtOH–NH4OH); νmax/cm⁻¹ 3322, 3206, 3055, 2927, 2876, 1632, 1550, 1498, 1472, 1433, 1262, 1097, 1082, 1055; δH (400 MHz, CDCl3) 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, NH2), 4.00 (1H, dd, J 10.1 and 4.1, 7-HA), 3.78 (1H, d, J 8.5, 5-HA), 3.82-3.75 (1H, m, 2-HA), 3.71 (1H, d, J 10.1, 7-HB), 3.60 (1H, d, J 4.0, 7a-H), 3.46 (1H, d, J 8.5, 5-HB), 3.24 (1H, dd, J 13.9 and 6.2, methylpropanamide 1-Ha), 3.17-3.05 (2H, m, 2-HB and methylpropanamide 1-Hb), 3.00 (2H, t, J 7.0, propanamide 3-H2), 2.59 (2H, t, J 7.0, propanamide 2-H2), 1.65-1.52 (1H, m, 3-HA), 1.51-1.44 (2H, m, 4-H2), 1.36-1.27 (1H, m, 3-HB); δC (100 MHz, CDCl3) 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. C20H25N3O3 requires MH, 356.1974.
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); $v_{\text{max}}$/cm$^{-1}$ 3329, 3177, 3052, 2932, 2852, 1620, 1497, 1470, 1431, 1264, 1118, 1091, 1075; $\delta_H$ (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$_B$ 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, phenethyl 1-H$_A$ minor and propanone 2-H$_2$), 2.64 (1H, d, J 13.4, phenethyl 1-H$_A$ major), 2.48 (1H, d, J 13.4, phenethyl 1-H$_B$ minor), 2.26 (1H, d, J 13.4, phenethyl 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$_B$); $\delta_C$ (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-4 a minor), 123.5 (quinolinyl C-4 a major), 122.7 (quinolinyl C$_2$-6), 77.2 (C-8 a major), 75.4 (C-8 a minor), 67.9 (C$_2$-2), 48.7 (C-5 minor), 43.6 (C-5 major), 41.4 (phenethyl 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$_3$O$_2$ requires MH, 430.2494.
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 ¹H-NMR) as a colourless amorphous solid, Rf 0.43 (92.4:6.76:0.84 DCMP–EtOH–NH₄OH); νmax/cm⁻¹ 3332, 3173, 3048, 2929, 2852, 1619, 1471, 1432, 1272, 1259, 1118, 1089; δH (400 MHz, CDCl₃) 8.46 (2H, dd, J 4.8 and 1.7, pyridinyl 6-H), 8.33 (1H, d, J 2.3, pyridinyl 2-Hmajor), 8.30 (1H, d, J 2.3, pyridinyl 2-Hmin), 7.72 (1H, s, quinolinyl 4-Hmajor), 7.70 (1H, s, quinolinyl 4-Hmin), 7.64-7.57 (4H, m, pyridinyl 4-H and quinolinyl 8-H), 7.53-7.40 (4H, m, quinolinyl 5,7-H₂), 7.25-7.11 (4H, m, quinolinyl 6-H and pyridinyl 5-H), 5.46 (4H, br. s, NH₂), 4.39 (1H, app. d, J 13.2, 7-Hₐminor), 4.13 (1H, d, J 13.2, 5-Hₐmajor), 2.93 (2H, app. dd, J 11.3 and 4.7, 2-Hₐ), 3.67 (1H, ddd, J 11.0, 5.0 and 2.6, 7-Hₐmajor), 3.56 (1H, d, J 13.3, 5-Hₐmin), 3.37-3.29 (3H, m, 2-Hₜ and 7-Hₜmajor), 3.28 (2H, s, 8a-H), 3.10 (2H, d, J 13.2, 5-Hₜ), 3.07-2.98 (5H, m, 7-Hₜmin and propanone 3-H₂), 2.96-2.71 (4H, m, propanone 2-H₂), 2.70 (1H, d, J 13.6, pyridinylmethyl 1-Hₐmin), 2.55 (1H, d, J 13.6, pyridinylmethyl 1-Hₐmajor), 2.37 (1H, d, J 13.6, pyridinylmethyl 1-Hₜmin), 2.13 (1H, d, J 13.6, pyridinylmethyl 1-Hₜmajor), 2.10-2.00 (1H, m, 8-Hₐmin), 1.85 (1H, app. tdd, J 13.2, 5.0 and 2.9, 8-Hₐmajor), 1.74-1.59 (4H, m, 3-Hₜ and 8-Hₜ), 1.43-1.27 (4H, m, 3-Hₜ and 4-Hₐ), 1.10-1.00 (2H, m, 4-Hₜ); δC (100 MHz, CDCl₃) 171.2 (propanone C₂-1), 156.5 (quinolinyl C₂-2), 151.6 (pyridinyl C₂-2), 147.9 (pyridinyl C₂-6 and quinolinyl C₂-8a), 138.2 (pyridinyl C₂-4), 136.8 (quinolinyl C₂-4), 132.3 (pyridinyl C₂-3), 129.3 (quinolinyl C₂-7), 126.9 (quinolinyl C₂-5), 125.4 (quinolinyl C₂-8), 124.2 (quinolinyl C₂-3), 123.4 (quinolinyl C₂-4a), 123.3 (pyridinyl C₂-5), 122.7 (quinolinyl C₂-6), 77.3 (C-8ₐmajor), 74.9 (C-8ₐmin), 68.0 (C₂-2), 43.1 (C₂-5), 41.0 (C₂-7), 38.3 (pyridinylmethyl C₂-1), 36.5 (C₂-4a), 32.5 (propanone C₂-2), 30.8 (C₂-4), 28.1 (C₂-8), 26.7 (propanone C₂-3), 22.2 (C₂-3); HRMS found MH⁺, 431.2438. C₂₆H₃₀N₄O₂ requires MH⁺, 431.2447.
3-(2-Aminoquinolin-3-yl)-N-(cyclohexylmethyl)propanamide

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 (70.0 mg, 83%) as a colourless amorphous solid, Rf 0.37 (92.4:6.76:0.84 DCM−EtOH−NH₄OH); νmax/cm⁻¹ 3461, 3314, 3059, 2915, 2843, 1640, 1539, 1500, 1437; δH (400 MHz, DMSO-d₆) 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-H₂), 7.14 (1H, ddd, J 8.0, 6.4 and 1.6, quinolinyl 6-H), 6.40 (2H, br. s, NH₂), 2.88 (2H, app. t, J 6.3, methylpropanamide 1-H₂), 2.81 (2H, t, J 7.2, propanamide 3-H₂), 2.46 (2H, t, J 7.2, propanamide 2-H₂), 1.65-1.45 (4H, m, 2-Hₐ, 6-Hₐ and 3,4,5-H₂), 1.35-1.20 (1H, m, 1-H), 1.14-0.95 (4H, m, 3,4,5-H₄), 0.86-0.66 (2H, m, 2-Hₐ and 6-Hₐ); δC (100 MHz, DMSO-d₆) 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 (C₂-2,6), 26.3 (propanamide C-3), 26.0 (C-4), 25.3 (C₂-3,5); HRMS found MH⁺, 312.2068. C₁₉H₂₅N₃O requires MH⁺, 312.2075.

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

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−NH₄OH to yield the amine derivative 223 (40.0 mg, 47%) as a colourless amorphous solid, Rf 0.61
(84.7:13.6:1.70 DCM–EtOH–NH₄OH); ν_max/cm⁻¹ 3476, 3329, 3083, 2965, 2924, 2840, 1637, 1618, 1529, 1501, 1477, 1438, 1260, 1069; δ_H (400 MHz, CDCl₃) 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, NH₂), 3.71 (1H, app. td, J 8.3 and 5.3, 5-Hₐ), 3.64–3.50 (2H, m, 2-Hₐ and 5-Hₜ), 3.38 (1H, dd, J 8.8 and 5.3, 5-Hₐ), 3.25–3.08 (2H, m, methylpropanamide 1-H₂), 2.89 (2H, t, J 7.1, propanamide 3-H₂), 2.47 (2H, t, J 7.1, propanamide 2-H₂), 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-Hₐ), 1.42 (1H, ddd, J 12.6, 8.0, 7.1 and 5.7, 4-Hₜ); δ_C (100 MHz, CDCl₃) 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), 125.3 (quinolinyl C-5), 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. C₁₇H₂₁N₃O₂ requires MH⁺, 300.1712.

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

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–NH₄OH to yield the amine derivative 224 (93.0 mg, 93%) as colourless crystals, m.p. (DCM), 183–193 °C; Rᵣ 0.31 (92.4:6.76:0.84 DCM–EtOH–NH₄OH); ν_max/cm⁻¹ 3315, 3133, 2965, 2899, 2853, 1628, 1614, 1461, 1428, 1408, 1240, 1228, 1108; δ_H (400 MHz, DMSO-d₆) 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-H₂), 7.12 (1H, t, J 7.2, quinolinyl 6-H), 6.29 (2H, br. s, NH₂), 3.51-3.45 (4H, m, 2,6-H₄), 3.45-3.39 (4H, m, 3,5-H₄), 2.82 (2H, t, J 7.4, propanone 3-H₂), 2.67 (2H, t, J 7.4, propanone 2-H₂); δ_C (75 MHz, DMSO-d₆) 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 (C₂-2,6), 41.5 (C₂-3,5), 30.7 (propanone C-2), 25.9 (propanone C-3); HRMS found MH⁺, 286.1550. C₁₆H₁₉N₃O₂ requires MH, 286.1555.

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

According to General Procedure AD, TFA (0.50 mL) and the amide derivative 231I (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 ¹H-NMR) as a colourless amorphous solid, Rf 0.45 (92.4:6.76:0.84 DCM–EtOH–NH₄OH); v_max/cm⁻¹ 3369, 3338, 3128, 2942, 2917, 2865, 2847, 1665, 1499, 1476, 1452, 1434, 1330, 1218, 1143, 1111; δ_H (400 MHz, CDCl₃) 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), 7.13 (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, phenethyl 1-H_A_major), 4.42 (1H, app. dt, J 13.3 and 4.2, phenethyl 1-H_A_minor), 3.72 (1H, app. dt, J 13.5 and 4.1, phenethyl 1-H_B_major), 3.63 (1H, ddt, J 13.3, 3.7 and 1.6, phenethyl 1-H_B_minor), 3.02 (4H, t, J 7.0, 6-H₂_major and propanone 3-H₂_major), 2.93 (2H, t, J 7.0, propanone 3-H₂_minor), 2.72 (2H, t, J 7.0, propanone 2-H₂_major), 2.70-2.63 (4H, m, 2-H₂_minor and 6-H₂_minor), 2.55 (2H, t, J 7.0, propanone 2-H₂_major), 2.48-2.34 (2H, m, 2-H₂_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, CDCl₃) 170.6 (propanone C-1_major), 170.5 (propanone C-1_minor), 156.6 (quinolinyl C₂-2), 146.7 (quinolinyl C₂-8a), 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 C₂-2,6_major), 129.1 (phenyl C₂-2,6minor), 128.9 (quinolinyl C₂-7), 128.6 (phenyl C₂-3,5_major), 128.4 (phenyl C₂-3,5_minor), 127.0 (quinolinyl C₂-5), 126.4 (quinolinyl C₂-8), 125.6 (phenyl C-4_major), 125.5 (phenyl C-4_minor), 124.3 (quinolinyl C₂-3), 123.6
(quinolinyl C-4\text{a}_{\text{minor}}), 123.5 (quinolinyl C-4\text{a}_{\text{major}}), 122.6 (quinolinyl C-2-6), 51.4 (C-2\text{major}), 48.1 (C-2\text{minor}), 46.4 (phenylmethyl C-1\text{minor}), 43.0 (phenylmethyl C-1\text{major}), 40.4 (quinolinyl C-6\text{minor}), 40.1 (quinolinyl C-6\text{major}), 38.8 (quinolinyl C-3\text{major}), 37.7 (quinolinyl C-3\text{minor}), 32.7 (propanone C-2\text{minor}), 32.4 (propanone C-2\text{major}), 31.0 (C-4\text{major}), 30.4 (C-4\text{minor}), 26.6 (propanone C-2), 25.7 (C-5\text{minor}), 24.7 (C-5\text{major}); HRMS found MH\textsuperscript{+}, 374.2233. C\textsubscript{24}H\textsubscript{27}N\textsubscript{3}O requires MH\textsuperscript{+}, 374.2232.

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

According to General Procedure AD, TFA (0.50 mL) and the amide derivative \textbf{231m} (11.0 mg, 29.7 µmol) were stirred for 3 h to give the amine derivative \textbf{226} (9.30 mg, >99%) as a colourless oil, R\textsubscript{f} 0.28 (92.4:6.76:0.84 DCM–EtOH–NH\textsubscript{4}OH); \(\nu_{\text{max}}/\text{cm}^{-1}\) 3397, 3277, 3148, 3083, 2948, 2930, 2916, 2850, 1654, 1627, 1565, 1501, 1477, 1154; \(\delta\text{H} (400 MHz, CDCl\textsubscript{3})\) 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\textsubscript{2}), 3.83-3.61 (2H, m, 2-H\textsubscript{A} and 6-H\textsubscript{A}), 3.35 (1H, ddd, J 11.2, 9.6 and 3.3, 6-H\textsubscript{B}), 3.14-3.06 (1H, m, 2-H\textsubscript{A}), 3.11 (2H, t, J 6.5, methylpropanamide 1-H\textsubscript{2}), 2.97 (2H, t, J 7.0, propanamide 3-H\textsubscript{2}), 2.54 (2H, t, J 7.0, propanamide 2-H\textsubscript{2}), 1.78-1.62 (2H, m, 3-H and 4-H\textsubscript{B}), 1.60-1.40 (2H, m, 5-H\textsubscript{2}), 1.15 (1H, app. dtd, J 12.7, 10.1, 9.6 and 4.6, 4-H\textsubscript{B}); \(\delta\text{C} (100 MHz, CDCl\textsubscript{3})\) 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\textsuperscript{+}, 314.1867. C\textsubscript{18}H\textsubscript{23}N\textsubscript{3}O\textsubscript{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). The kit was composed of a “Swedish” mutant APP peptide tagged with a rhodamine derivative (fluorescence donor) and a proprietary 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. 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, $\lambda_{\text{excitation}} = 531$ nm and $\lambda_{\text{emission}} = 595$ nm. The measurements were taken every minute over 2 h.
### A

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
<th>16</th>
<th>17</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>+</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The 13 derived compounds in concentrations of 100 µM in triplicate (each compound in a different column)

### B

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
<th>16</th>
<th>17</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>+</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Derived compound 214, 218, 219 or 221 in concentrations from up to 0.67 mM to 1 µM in triplicate (each concentration in a different column)

---

**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).

\[
\text{Equation 1: Calculation of the } \% \text{ of inhibition from the slopes.}
\]
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.

<table>
<thead>
<tr>
<th>Derived compound</th>
<th>LogIC$_{50}$ ± SEM</th>
<th>IC$_{50}$</th>
<th>Hill slope</th>
</tr>
</thead>
<tbody>
<tr>
<td>214</td>
<td>-4.508 ± 0.06</td>
<td>31.0 μM</td>
<td>-1.55</td>
</tr>
<tr>
<td>218</td>
<td>-4.257 ± 0.01</td>
<td>55.3 μM</td>
<td>-3.27</td>
</tr>
<tr>
<td>219</td>
<td>-4.542 ± 0.02</td>
<td>28.7 μM</td>
<td>-2.54</td>
</tr>
<tr>
<td>221</td>
<td>-4.074 ± 0.02</td>
<td>84.2 μM</td>
<td>-3.80</td>
</tr>
</tbody>
</table>

*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.
Library of Virtual Medicinal Chemistry Capping Groups

The next reagents were used to decorate the scaffolds with the computational tool:
<table>
<thead>
<tr>
<th>Type</th>
<th>Number</th>
<th>Mean MW</th>
<th>Range MW</th>
<th>Mean clogP</th>
<th>Range clogP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboxylic acids</td>
<td>20</td>
<td>118.6</td>
<td>60.0 – 156.6</td>
<td>0.71</td>
<td>-0.49 – 2.12</td>
</tr>
<tr>
<td>Sulfonyl chlorides</td>
<td>15</td>
<td>173.2</td>
<td>114.5 – 211.1</td>
<td>1.24</td>
<td>0.00 – 2.40</td>
</tr>
<tr>
<td>Halides</td>
<td>30</td>
<td>163.3</td>
<td>94.9 – 205.5</td>
<td>1.88</td>
<td>0.68 – 3.24</td>
</tr>
<tr>
<td>Ketones</td>
<td>3</td>
<td>76.7</td>
<td>58.1 – 100.1</td>
<td>-0.32</td>
<td>-0.68 – -0.10</td>
</tr>
<tr>
<td>Aldehydes</td>
<td>15</td>
<td>102.4</td>
<td>44.0 – 140.6</td>
<td>0.93</td>
<td>-0.44 – 2.25</td>
</tr>
<tr>
<td>Isocyanates</td>
<td>15</td>
<td>119.9</td>
<td>71.1 – 167.6</td>
<td>1.01</td>
<td>-0.05 – 2.36</td>
</tr>
<tr>
<td>Amines</td>
<td>20</td>
<td>96.6</td>
<td>31.1 – 141.6</td>
<td>0.25</td>
<td>-0.92 – 1.64</td>
</tr>
<tr>
<td>Boronic acids</td>
<td>15</td>
<td>121.6</td>
<td>59.8 – 157.3</td>
<td>0.90</td>
<td>-0.49 – 2.16</td>
</tr>
</tbody>
</table>

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)**

<table>
<thead>
<tr>
<th>Crystal data and structure refinement for 149a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
</tr>
<tr>
<td>Formula weight</td>
</tr>
<tr>
<td>Temperature/K</td>
</tr>
<tr>
<td>Crystal system</td>
</tr>
<tr>
<td>Space group</td>
</tr>
<tr>
<td>a/Å</td>
</tr>
<tr>
<td>b/Å</td>
</tr>
<tr>
<td>c/Å</td>
</tr>
<tr>
<td>α/°</td>
</tr>
<tr>
<td>β/°</td>
</tr>
<tr>
<td>γ/°</td>
</tr>
<tr>
<td>Volume/Å^3</td>
</tr>
<tr>
<td>Z</td>
</tr>
<tr>
<td>ρ_{calc} g/cm^3</td>
</tr>
<tr>
<td>μ/mm^{-1}</td>
</tr>
<tr>
<td>F(000)</td>
</tr>
<tr>
<td>Crystal size/mm^3</td>
</tr>
<tr>
<td>Radiation</td>
</tr>
<tr>
<td>2θ range for data collection/°</td>
</tr>
<tr>
<td>Index ranges</td>
</tr>
<tr>
<td>Reflections collected</td>
</tr>
<tr>
<td>Independent reflections</td>
</tr>
<tr>
<td>Data/restraints/parameters</td>
</tr>
<tr>
<td>Goodness-of-fit on F^2</td>
</tr>
<tr>
<td>Final R indexes [I&gt;2σ(I)]</td>
</tr>
<tr>
<td>Final R indexes [all data]</td>
</tr>
<tr>
<td>Largest diff. peak/hole / e Å^{-3}</td>
</tr>
</tbody>
</table>
**ORTEP diagram of 150c (CCDC 1566499)**

![ORTEP diagram of 150c](image)

**Crystal data and structure refinement for 150c**

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C\textsubscript{15}H\textsubscript{17}NO\textsubscript{3}</td>
</tr>
<tr>
<td>Formula weight</td>
<td>259.29</td>
</tr>
<tr>
<td>Temperature/K</td>
<td>119.97(16)</td>
</tr>
<tr>
<td>Crystal system</td>
<td>triclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P-1</td>
</tr>
<tr>
<td>a/Å</td>
<td>6.7483(5)</td>
</tr>
<tr>
<td>b/Å</td>
<td>9.9314(7)</td>
</tr>
<tr>
<td>c/Å</td>
<td>11.0967(8)</td>
</tr>
<tr>
<td>α/°</td>
<td>63.764(7)</td>
</tr>
<tr>
<td>β/°</td>
<td>79.148(6)</td>
</tr>
<tr>
<td>γ/°</td>
<td>74.800(6)</td>
</tr>
<tr>
<td>Volume/Å\textsuperscript{3}</td>
<td>641.49(9)</td>
</tr>
<tr>
<td>Z</td>
<td>2</td>
</tr>
<tr>
<td>ρ\textsubscript{calc}/g/cm\textsuperscript{3}</td>
<td>1.342</td>
</tr>
<tr>
<td>μ/mm\textsuperscript{-1}</td>
<td>0.762</td>
</tr>
<tr>
<td>F(000)</td>
<td>276.0</td>
</tr>
<tr>
<td>Crystal size/mm\textsuperscript{3}</td>
<td>0.15 × 0.08 × 0.06</td>
</tr>
<tr>
<td>Radiation</td>
<td>CuKα (λ = 1.54184)</td>
</tr>
<tr>
<td>2θ range for data collection/°</td>
<td>8.916 to 147.94</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-8 ≤ h ≤ 7, -12 ≤ k ≤ 10, -13 ≤ l ≤ 12</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>4223</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>2397 [R\textsubscript{int} = 0.0277, R\textsubscript{sigma} = 0.0391]</td>
</tr>
<tr>
<td>Data/restraints/parameters</td>
<td>2397/0/173</td>
</tr>
<tr>
<td>Goodness-of-fit on F\textsuperscript{2}</td>
<td>1.028</td>
</tr>
<tr>
<td>Final R indexes [I&gt;=2σ (I)]</td>
<td>R\textsubscript{1} = 0.0379, wR\textsubscript{2} = 0.0941</td>
</tr>
<tr>
<td>Final R indexes [all data]</td>
<td>R\textsubscript{1} = 0.0450, wR\textsubscript{2} = 0.0996</td>
</tr>
<tr>
<td>Largest diff. peak/hole / e Å\textsuperscript{-3}</td>
<td>0.35/-0.22</td>
</tr>
</tbody>
</table>
ORTEP diagram of 150d (CCDC 1566498)

<table>
<thead>
<tr>
<th>Crystal data and structure refinement for 150d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
</tr>
<tr>
<td>Formula weight</td>
</tr>
<tr>
<td>Temperature/K</td>
</tr>
<tr>
<td>Crystal system</td>
</tr>
<tr>
<td>Space group</td>
</tr>
<tr>
<td>a/Å</td>
</tr>
<tr>
<td>b/Å</td>
</tr>
<tr>
<td>c/Å</td>
</tr>
<tr>
<td>α/°</td>
</tr>
<tr>
<td>β/°</td>
</tr>
<tr>
<td>γ/°</td>
</tr>
<tr>
<td>Volume/Å³</td>
</tr>
<tr>
<td>Z</td>
</tr>
<tr>
<td>ρcalc g/cm³</td>
</tr>
<tr>
<td>μ/mm⁻¹</td>
</tr>
<tr>
<td>F(000)</td>
</tr>
<tr>
<td>Crystal size/mm³</td>
</tr>
<tr>
<td>Radiation</td>
</tr>
<tr>
<td>2θ range for data collection/°</td>
</tr>
<tr>
<td>Index ranges</td>
</tr>
<tr>
<td>Reflections collected</td>
</tr>
<tr>
<td>Independent reflections</td>
</tr>
<tr>
<td>Data/restraints/parameters</td>
</tr>
<tr>
<td>Goodness-of-fit on F²</td>
</tr>
<tr>
<td>Final R indexes [I&gt;2σ (I)]</td>
</tr>
<tr>
<td>Final R indexes [all data]</td>
</tr>
<tr>
<td>Largest diff. peak/hole / e Å⁻³</td>
</tr>
</tbody>
</table>
NOESY Spectra

NOESY Spectra with the nOe enhancements:

[Diagram of NOESY Spectra with annotations for 149a and 149b]
References


2016.


60 V. L. Nienaber, in *Library Design, Search Methods, and Applications of Fragment-Based Drug Design*, ed. R. Bienstock, American Chemical


82. T. J. Ritchie and S. J. F. Macdonald, *Drug Discovery Today*, 2009, **14**, ...
254

1011–1020.


17125.


