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Synthesis and Applications of Pluripotent Frameworks for Drug Discovery

by

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Abstract

This thesis describes the exploration of epoxy-bridged fused polycycles as starting frameworks for the synthesis of pharmaceutically relevant nitrogen containing polycycles and the generation of a compound library for early-stage drug discovery.

Exploiting a gold-catalysed double annulation process, a range of epoxy-bridged fused polycycles were synthesised and the reactivity of the embedded amidine functionality was investigated to generate a diverse set of sp^3-rich nitrogen containing polycyclic architectures. Following the Diversity Oriented Synthesis principle (DOS), five different scaffolds were generated from a single pluripotent framework based on the deachydro-1,6-napthyridine core. Further three other scaffolds were generated starting from an octahydro-pyranopyridine framework, for a total of nine scaffolds investigated during these studies. The synthesis scale-up and reactivity of the final architectures was studied to assess their suitability as starting points for a compound library generation.

Chemoinformatic analysis was performed using Knime and Datawarrior, and three different libraries were designed and synthesised based on the newly synthesised scaffolds to deliver a set of 103 compounds, all compliant with the recent medicinal chemistry trends. Chemical space coverage of the newly synthesised compounds was performed *via* principal component comparing the library compounds with a set of marketed drugs and molecules undergoing clinical trials.

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Abbreviations

ADME	absorption, distribution metabolism, excretion
Ar	aryl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
C	Celsius
Calcd	calculated
Cbz	carboxybenzyl
COSY	correlation spectroscopy
d.r.	diastereomeric ratio
DCB	dichlorobenzene
DCE	1,2-dichloroethane
DIAD	diisopropyl azodicarboxylate
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
eq	equivalent(s)
ELSD	evaporative light scattering
ES	electrospray
Et	ethyl
EWG	electron-withdrawing group
g	gram(s)
GPCR	G protein coupled receptor
h	hour(s)
hit(s)	compound with the desired activity in a screen
HMBC	heteronuclear multiple bond correlation
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
HTS	high-throughput screening
IR	infrared
J	coupling constant
K	Kelvin
L	litre
LA	Lewis acid
LG	leaving group
M	molar
m/z	mass/charge
Me	methyl
min	minutes
mol	moles
mp	melting point
Ms	methanesulfonyl
MS	molecular sieves
MW	molecular weight
NBS	*N*-bromosuccinimmide
NMR	nuclear magnetic resonance
Ph	phenyl
Pic	pyridinecarboxylato
PMB	para-methoxybenzyl

ppm	parts per million
r.t.	room temperature
RO5	rule of 5
RoB	rotatable bonds
Tf	trifluoromethansulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TOF	time of flight
TPSA	topological polar surface area
Ts	4-methylbenzenesulfonyl
ν	wavenumber

1. Chapter 1: A brief history of drug discovery

1.1. Drug discovery: metrics and bias

Since the early 1990s, high throughput screening (HTS) and combinatorial chemistry have had a great impact on the drug discovery process, and millions of compounds have been synthesised and screened across both industrial and academic laboratories.[1] The immense output of synthesised molecules however, did not translate as efficiently as expected into the discovery of novel hits.[2] It became clear that achieving novel bioactive molecules cannot be reduced to a simple numbers game and library design had to be taken into account to deliver better compounds. With a focus on improving the physicochemical properties of the molecules, several ideologies were published from both academic and industry perspectives to enhance the efficiency and success of the next generations of screening libraries.

Perhaps the most widespread of these was that conceived by Lipinski, based upon the many drug candidates that failed as a result of poor bioavailability under physiological conditions.[1] Lipinski investigated a list of FDA approved drugs and identified 4 key characteristics that could help predict the oral bioavailability of novel drug candidates. “Lipinski’s rule” or “rule of 5” (Ro5) were defined by the following: molecular weight <500, hydrogen bond donors ≤5, hydrogen bond acceptors ≤10 and LogP ≤5. Whilst Lipinski initially intended these parameters as guidelines, their strict application heavily influenced drug design. Many authors argued that Lipinski’s rules have been over emphasized, some limitations of the Ro5 predictivity have been brought to light, such as the equal weight given to each of the rules and their application as sharp property thresholds.[3-5] Several drug candidates falling outside the sharp thresholds of

Lipinski's rule have reached the market, showing that there is scope for discovery beyond the Ro5.[4, 6]

Further parameters were introduced to aid the design of screening libraries with suitable ADME profiles for bioavailability under physiological conditions. Topological Polar Surface Area (TPSA) and rotatable bonds count became useful predictive tools for bioavailability.[7,8] TPSA is a fragment based approach to calculate the molecular polar surface area and offers an estimation on molecular transport properties.[7] The suggested limits vary within the targeted body compartment.[7, 8] For optimal intestinal absorption TPSA should be <140 $Å^2$,[9] while lower values are suggested for blood brain barrier permeation <90 $Å^2$,[10] and central nervous system <70 $Å^2$.[11]

Rotatable bond counts, defined as any single bond, not in a ring, bound to an internal heavy atom, provides a good estimation of molecular rigidity. The suggested threshold for a target compound is to contain ≤10 rotatable bonds.[8] Further studies elucidated that an increase in rigidity and low polar surface areas would improve bioavailability and that poor bioavailability of high molecular weight drug targets could be linked to increased molecular flexibility and TPSA.[8]

Lowering identified two novel metrics for the measure of molecular complexity, the fraction of sp^3-carbons (Fsp^3, Eq.1) and the number of stereogenic centres.[12] The authors exploited this new tool to examine the relationship between planarity, physical properties, and clinical success. From the analysis of small molecule data across the drug development process (phase 1 to approval) a clear trend was observed: mean molecular weights saw a clear decrease, whilst the degree of saturation, expressed as Fsp^3, and number of stereogenic centres experienced a constant increase when moving from discovery to marketed drugs. In contrast, large and flat

compounds had a greater chance of attrition during the drug development process.[12] Further studies revealed how higher Fsp^3 values were linked to an increased selectivity and reduced toxicity due to off target effects.[13] Overall, the drug discovery process tends to favour compounds with a high level of saturation and complexity, due to their fewer chances of attrition during the transition from discovery through clinical trials to drugs.

$$\boldsymbol{Eq.\,1}: Fsp^3 = \frac{N°\ of\ sp^3 hybridised\ carbons}{total\ carbon\ count}$$

Other methods to quantify "flatness" were also postulated, either based on a count of the number of aromatic rings in a molecule,[14] or via the "aromatic balance" (Eq. 2).[15] These independent studies came to the similar conclusion that flat molecules have a significantly higher probability of attrition during clinical trials. However, combinatorial libraries are still dominated by flat sp^2-rich molecules,[16] highlighting the need for compound collections that contain saturated, highly complex structures to increase the opportunity of discovering hits with better chances of success in biological screenings.

$$\boldsymbol{Eq.\,2}: aromatic\ balance = N°\ aromatic\ atoms\ - N°\ sp^3\ carbon\ atoms$$

These predictive tools of molecular properties allow analysis of potential target libraries and help to prioritise sets of molecules during the drug discovery process. However, ligand-receptor binding is a complex 3-dimensional event. This set of parameters, solely based on a few physicochemical properties, were aimed at improving bioavailability and are not sufficient to discriminate between the immense set of compounds generated in medicinal chemistry. Therefore, novel approaches and concepts that consider the diversity and chemical space coverage of the synthesised compound collections were conceived to improve the drug discovery process. These new concepts would not replace the previous set of rules, but add to

them, providing medicinal chemists with a new set of tools to help their decision making in library design.

1.2. Introduction to Chemical space and its exploration

Despite the introduction of predictive metrics and the advancements in synthetic chemistry, the pharmaceutical industry is still suffering from a lack of productivity in terms of new approved molecules.[17, 18] HTS proved a useful, productive source of leads for only a handful of target classes, including, kinases, GPCRs, ion channels and hormone receptors, however its success rate remained low for many novel targets.[19] Further studies exposed the bias of classical screening libraries towards a limited structural diversity with the emphasis put on varying single scaffolds with a large number of substituents.[19,20]

The topic was not new to medicinal chemistry. In 1996 Murcko reported that half of the 5120 molecules included in the Comprehensive Medicinal Chemistry database, could be described with only 32 of the most recurring molecular frameworks[a] and that the top 20 side chains[b] represent 73% of the total used in marketed drugs.[21, 22] Very similar results were found when the analysis was repeated in 2010 by Whang and Hou, with the top 50 frameworks were still making up half of all the approved drugs.[23] Furthermore, less than 2% of the available combinations of known ring systems are contained in combinatorial screening libraries.[24] Overall, it was possible to conclude that medicinal chemistry focused on a limited set of

a: molecular framework: defined as the union of ring systems and linkers in a molecule;

b: side chain: acyclic arrays of atom attached to a framework.

possibilities and "exhausted" its comfort zone targets, exploring only a limited portion of the available chemical space.[25]

It was estimated that chemical space, or the number of all the possible molecules with drug-like properties, exceed 10^{60} units.[26] By contrast, the bioactive space is far more limited, considering that only the 10% of human genes are associated with diseases.[27] The challenge for every drug discovery program is uniting the synthetically accessible chemical space with the disease-relevant biological space. Thus far only a small portion of the bioactive space has been successfully "drugged" and approximately only 200 protein targets out of 5000 estimated disease related proteins have been paired with a small molecule ligand.[27-29] Many areas of this overlapping chemical and biological space have not yet been explored due to the limitations in modern day design and synthesis techniques.[25] The claim is corroborated by the high scaffold redundancy and the employment of a limited array of reactions in medicinal chemistry programs.[20,25]

Chemoinformatics provides the means to navigate chemical space and to visualise the molecules based on their molecular properties.[30,31] Dimensionality reduction techniques, such as principal component analysis (PCA), have been used to visualise the chemical space explored by potential libraries.[32] PCA combines a set of correlated variables (MW, Fsp^3, logP, etc) to produce a set of variables in a lower-dimensional space (principal components) while keeping the characteristics that contribute most to the variance of the data. Often the first components (PC1, PC2, PC3) of a PCA cover much of the variability, as multi-dimensional data are often highly correlated (e.g.: carbon atom count, ring count and heteroatom count are all correlated with molecular weight). The first two or three dimensions taken from a PCA can be used to position the objects on a plane or in space such that clusters of similar objects can easily be

recognised in the view. This allows for redundant variation of the compounds to be removed and focus placed on synthesising diverse libraries.[32]

Chemical space and PCA analyses have been performed for drug molecules, chemical libraries, and natural products to study the different coverage of these three classes of molecules.[16] Two approaches were exploited to visualise the different coverage in chemical space: one based on the physicochemical properties,[16] and the other on chemical structure,[33, 34] with both yielding the conclusion that the three classes of molecules have different properties and occupy different portions of the chemical space. Moreover, natural products covered greater portions of chemical space when compared to the other two classes, presenting distinct structural features and physicochemical profiles. It has been suggested by several authors that, owing to the different properties of natural products and their derivatives, they could be exploited to investigate uncharted portions of chemical space and find hits against novel targets.[35, 36]

Integrating the classical drug discovery metrics (Ro5, TPSA, RoB) with the cheminformatic analysis of chemical space coverage provided the conclusion that classical combinatorial libraries were structurally similar and highlighted the need for the development of novel synthetic strategies providing more diverse ranges of screening libraries.[25] These new synthetic approaches should target the synthesis of underexplored structures that identify gaps in the chemical space coverage, increasing the chances of finding hits against novel biological targets.

1.3. Natural product-inspired libraries, BIOS and DOS

Natural products (NPs) have always played a pivotal role in drug discovery and have found applications in many therapeutics areas, including cancer, infectious and cardiovascular diseases.[37]

Owing to their complex architectures, NPs usually present higher molecular weights, lower logP and higher Fsp^3 than synthetic compounds. They also present higher number of stereogenic centres and fused rings, resulting in a greater molecular rigidity when compared to the structures generated from classical combinatorial methods.[16] Additionally NPs are recognised as "privileged structures" as they co-evolved with proteins and, therefore, are biologically validated.[38] Nevertheless, NPs also present some challenges for the drug discovery process. Their isolation from natural sources remains challenging and their synthesis is often complex and unsuitable for the generation of structural analogues in a combinatorial library setting.[39]

NPs represent a relevant fraction of the bioactive chemical space and their implementation in the drug discovery process is important to avoid missing out on important compound classes. To overcome these limitations, NP-like scaffolds are often targeted as starting points for the synthesis of NP-inspired libraries and many strategies have been conceived to accomplish this task.[40]

Biology-oriented synthesis (BIOS) relies on the structural classification of NPs in a "scaffold tree" in which the scaffolds of the NPs rather than the molecule itself are organised hierarchically. Following a set of rules, a branch is generated from deconstruction of each scaffold, from larger, more complex architectures, towards smaller and less-complex structures (one ring).[41] This approach has been used effectively, such as the pentacyclic scaffold of yohimbine which was deconstructed into tetra-, tri- and bicyclic scaffolds. Compounds collections based on these systems yielded several phosphatase inhibitors for cancer and diabetes treatment (Figure 1).[41]

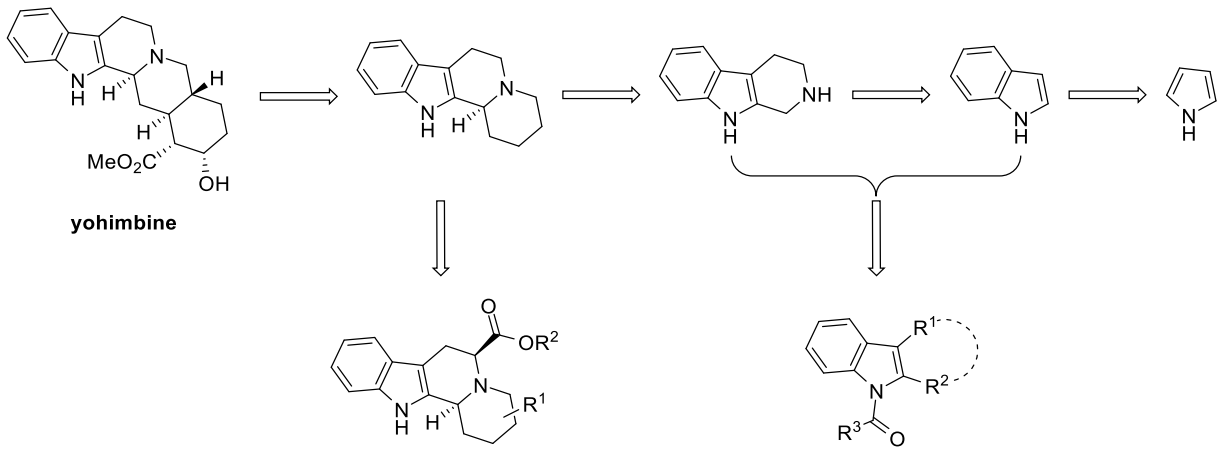


Figure 1: Deconstruction of the yohimbine scaffold into different branches.

Diversity oriented synthesis (DOS) aims at the synthesis of highly diverse scaffolds collections that mimic the structural complexity of NPs. Building on the concept that classical parallel chemistry libraries contain a multitude of very similar molecules mostly synthesised around one core structure, DOS instead suggests that focus should be aimed towards the generation of small molecule collections with a high degree of structural diversity that would therefore explore large areas of chemical space. There have been different definitions of "diversity" for a library collection, but broadly they could be summarised into four main concepts: appendage diversity, functional group diversity, stereochemical diversity and, skeletal diversity.[42]

Arguably skeletal diversity is the main parameter to address when a DOS is planned. It is worth reiterating that the ligand-receptor interaction is a 3-dimensional event and biological macromolecules will interact only with ligands with complementary 3D binding shape.[43] It has been demonstrated that the binding surface depends mainly on the 3D scaffold structure rather than the substituents attached to it, therefore skeletal diversity has the main role in defining the overall shape diversity of the generated small molecule library.[42] Indeed, in terms of biorelevant diversity, small multiple scaffolds libraries are superior to large single-scaffold libraries, thus increasing the possibility of finding hits against novel targets.[42]

A powerful approach towards the generation of structurally diverse collections involve the exploitation of a pluripotent functional group that can undergo different types of transformations.[44] An example of this strategy is the one that lead to the synthesis of five different NP-like scaffolds based on alkaloids motifs from a common interemediate (Figure 2).[45]

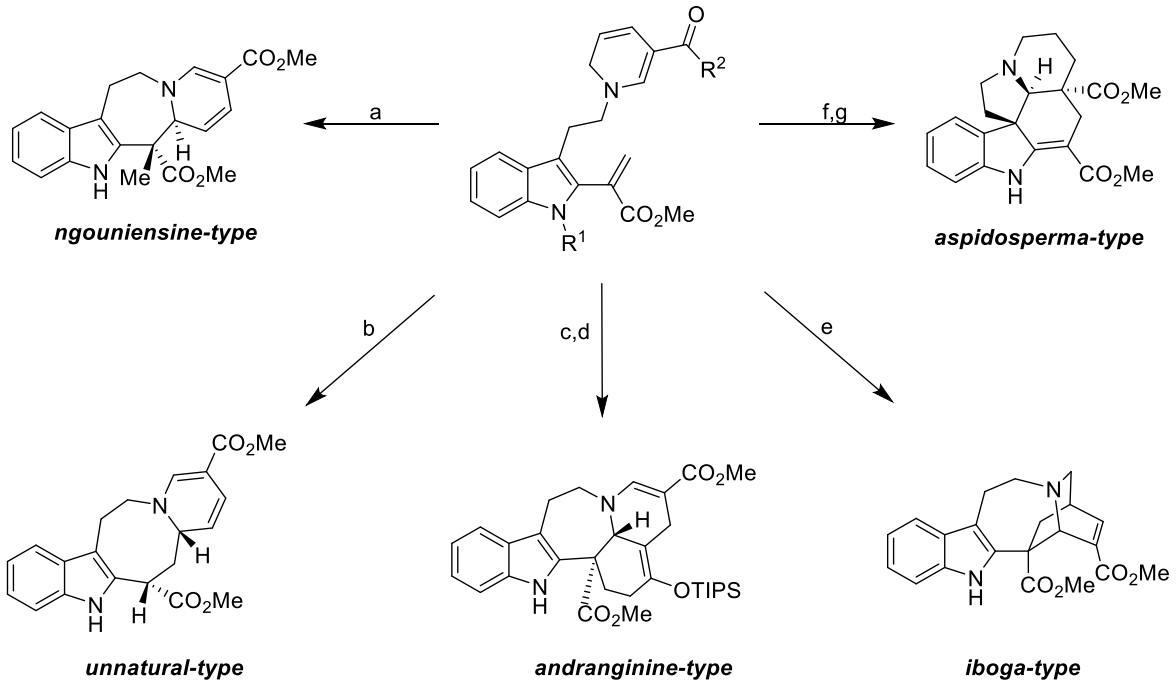


Figure 2: DOS of 5 alkaloid scaffolds from a common intermediate. a $ClCH_2CH_2Cl$, 120 °C. b $[Ru(bpy)_3](BF_4)_2$, $CH_2Cl_2/MeNO_2$, r.t. c TBAF, THF, r.t. d TIPSOTf, iPr_2NEt, $ClCH_2CH_2Cl$, r.t. e $ClCH_2CH_2Cl$, 60 °C. f Pd/C, H_2, MeOH. g hydroquinone, Et_3N, PhMe/ClCH2CH2Cl, 180 °C.

By carefully planning diversity-oriented synthesis, medicinal chemists can access previously underrepresented scaffolds inspired by NPs, from which they could generate highly diverse small molecule collections to investigate uncharted portions of chemical space. However, the judicious selection of the NP from which to take inspiration is critical to avoid scaffold redundancy and low diversity from overrepresented frameworks found in existing libraries.

2. Chapter 2: Fused piperidines for drug discovery

2.1. Synthesis of Piperidines and Fused piperidines

Piperidines are a very common motif in drug discovery, with a prevalence amongst all other nitrogen-containing saturated heterocycles. It is the third most frequent ring system found from an analysis of the FDA approved drugs, with benzene and pyridine being first and second respectively.[46] Various strategies have been developed to prepare functionalised piperidines. Hydrogenations of pyridines under various transition metal catalysts,[47-51] intramolecular Michael addition,[52, 53] aza-Diels-Alder reaction with nitrogen installed either on the diene[54] or dienophile,[55] ring-closing metathesis strategies,[56] and intramolecular substitution reactions of amine nucleophiles tethered with a suitable placed leaving group (Figure 3).[57, 58]

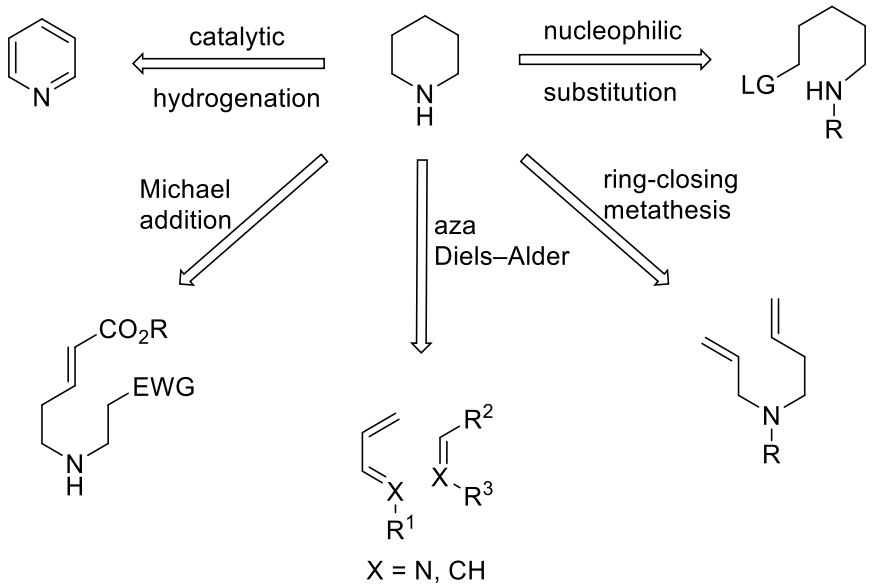


Figure 3: Overview of common strategies to prepare piperidines

The vast biological activity of piperidines has been exploited in various marketed drugs, however only a limited variety of piperidine-based structures have been incorporated in this class of molecules. [59, 60] Aside from functionalised piperidine motifs, polycyclic piperidines are

typically fused with aromatic systems, with the 1,2,3,4-tetrahydroquinoline motif the most frequent bicyclic system involving a piperidine found from an analysis of marketed drugs in 2014.[59, 60]

Additionally, fused piperidines are commonly found in nature, in particular across a range of alkaloid structures, bearing a broad range of connectivity and potent bioactivity (Figure 4), one of which being the decahydro-naphthyridine motif.

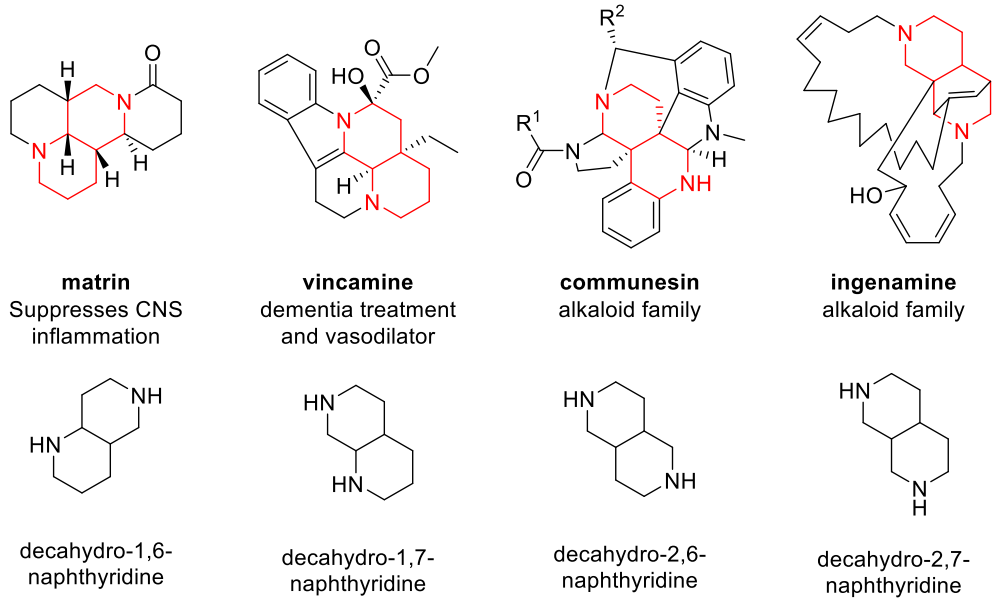
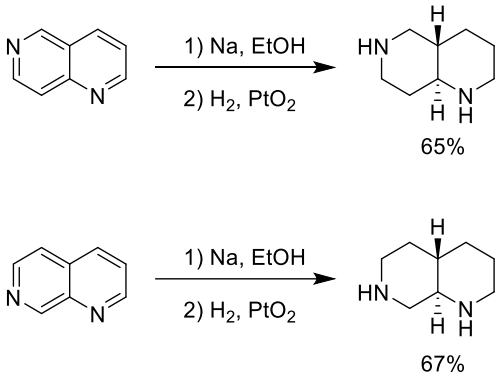


Figure 4: Natural products bearing the decahydro-naphthyridine core

The decahydro-naphthyridine motif would represent an optimal NP-inspired scaffold given its presence amongst many alkaloid structures and underrepresentation in mainstream drug discovery programs.[60] Moreover the conformationally restricted shape of these bicyclic-diamines might be beneficial to achieve efficient and selective binding to biological targets.[61] The exceptional structural diversity of decahydro-naphthyridines frameworks is exemplified by the nitrogens relative disposition across the carbon skeleton that would allow for the synthesis of compound libraries with a very diverse disposition of the sidechains participating in the biologically relevant interactions, probing the 3-dimensional space around the molecule.[61]

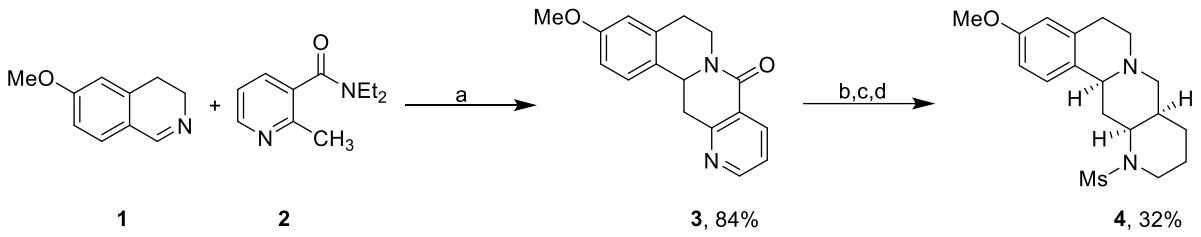
While the methods available for the preparations of functionalised piperidines vary, the methodologies available for the synthesis of decahydro-naphthyridines are limited, and generally revolve around the reduction of the desired naphthyridine core in Na/EtOH and H_2/PtO_2 (Scheme 1).[61] Despite possibly representing the fastest methodology to access these structures, the presence of the two unprotected nitrogen atoms could result in a difficult selective functionalisation across the scaffold.



Scheme 1: Reduction of naphthyridines.

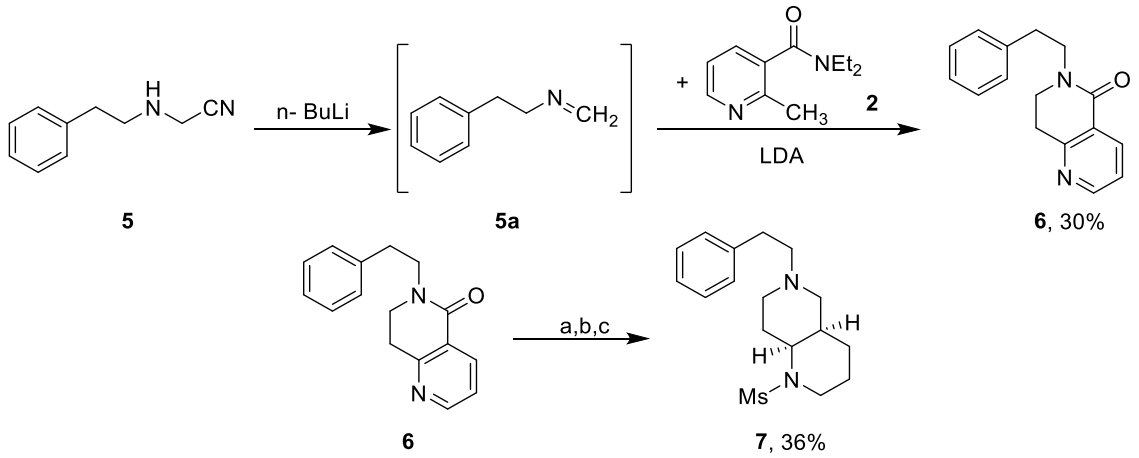
Most commonly functionalised piperidines have been synthesised as part of synthetic efforts towards the generation of NP-analogues to investigate their biological activities.

As part of their investigation towards the synthesis of effective α2-adrenoceptor antagonists, Clark et al. developed a concise 4-step synthesis into various rauwolscine analogues (Scheme 2).[62] The condensation between 3,4-dihydroisoquinoline **1** and nicotinamide **2** in the presence of lithium diisopropylamide provided the tetracyclic pyridine amide core **3**. Catalytic hydrogenation of **3**, followed by reduction of the carbonyl moiety with $LiAlH_4$ and protection of the amine with mesyl chloride afforded tetracycle **4** in 32% yield over the last three steps.



Scheme 2: Synthesis of the decahydro-naphthyridine core Rauwolscine analogues. [a]: LDA, THF, -40 °C. [b]: H_2, HOAc, Rh-Al_2O_3. [c]: $LiAlH_4$, THF. [d]: MsCl, Et_3N, CH_2Cl_2.

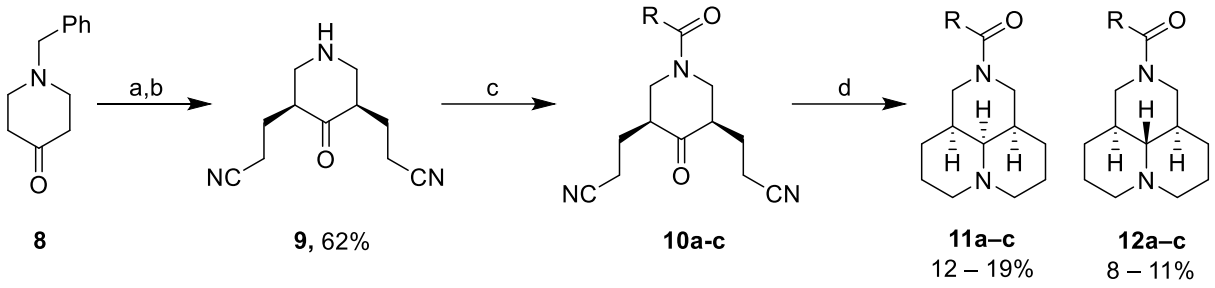
In the same paper the authors proposed an alternative synthesis for the generation of the decahydro-1,6-naphthyirdine bicyclic core (Scheme 3) in which cyanomethylamine **5** was treated with *n*-BuLi to generate the corresponding formaldimine **5a**. A solution of the lithio derivative of **2** was then added affording bicyclic amide **6** in low yield. Compound **6** was then treated as its tetracyclic analogue affording the desired final scaffold **7** in 36% yield over the last three steps.



Scheme 3: Clark's synthesis of the decahydro-1,6-naphthyridine core. [a]: H_2, HOAc, Rh-Al_2O_3. [b]: $LiAlH_4$, THF. [c]: MsCl, Et_3N, CH_2Cl_2.

Matrine-type alkaloids also possess a decahydro-naphthyridine core, and their synthesis has been attempted during the investigations of the structure-activity relation of allomatrine analogues toward *κ*-opiod receptors.[63] 1-Benzyl-4-piperidone **8** was bisalkylated with acrylonitrile *via* Stork enamine synthesis, and successfully hydrogenated to the corresponding amine **9**. The amine was then acylated with acetic anhydride (**10a**), pentanoyl chloride (**10b**),

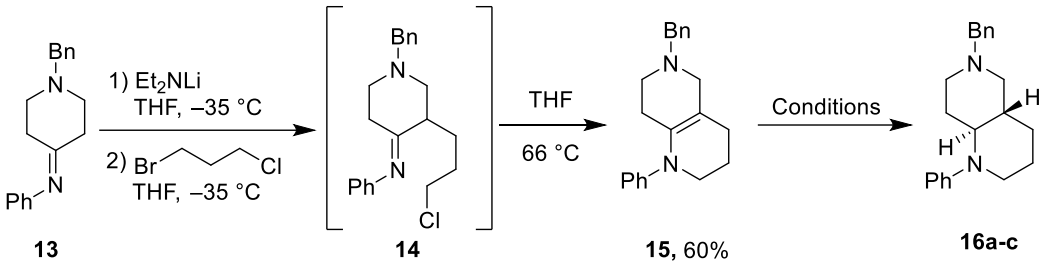
and benzoyl chloride (**10c**). Reductive cyclisation of compounds **10a-c** was accomplished with 5% palladium on carbon in glacial acetic acid under a 5 atm hydrogen pressure, yielding polycycles **11a-c** and **12a-c** in low yields (Scheme 4).



8 **9**, 62% **10a-c** **11a–c** 12 – 19% **12a–c** 8 – 11%

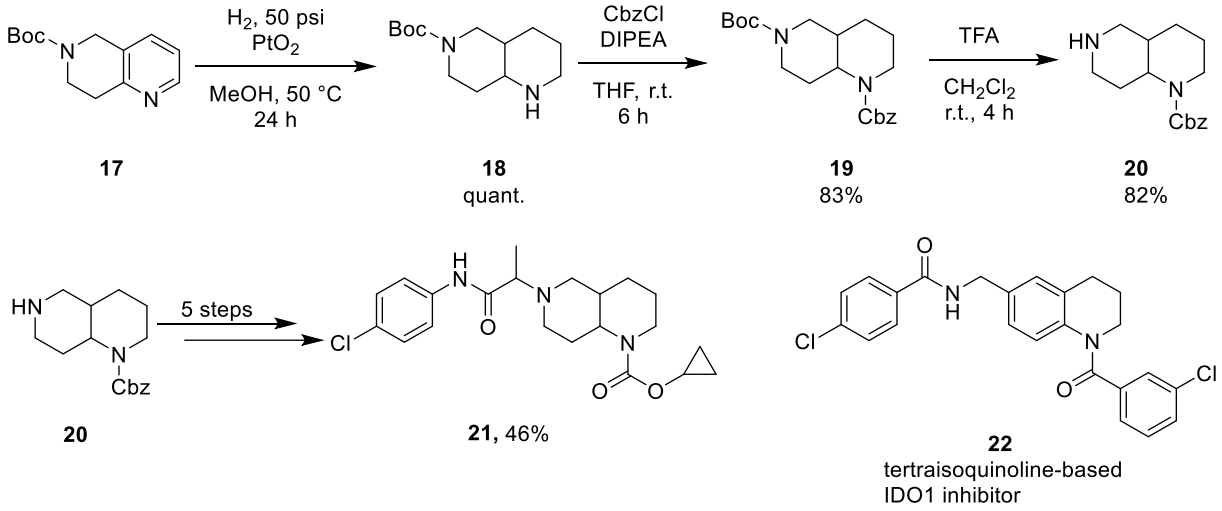
Scheme 4: Synthesis of allomatrine analogues. 63 [a]: pyrrolidine, benzene, reflux 48 h, then acrylotrile, EtOH, reflux, 48 h. [b]: H_2, $Pd(OH)_2$-C, EtOH, 24h. [c]: Ac_2O or RCOCl, Et_3N, CH_2Cl_2, 0 °C, 1H. [d]: Pd-C, AcOH, 5 atm, r.t., 48 h.

Another synthetic approach towards matrine-type core structures involved the one-pot synthesis of octahydro-1,6-naphthyridines and their reduction to decahydro-1,6-napthyridines (Scheme 5).[64, 65] Piperidone imines such as **13** were treated with lithium diethylamide and reacted *in situ* with 1-bromo-3-chloropropane affording intermediate **14**. Intramolecular cyclisation of the latter afforded the octahydro-naphthyridine core **15**.[64] Further studies uncovered the reactivity of **15** towards reduction of the enamine moiety subjected to different reductive conditions (Scheme 5). The highest diastereoselectivity in the crude mixture was obtained with $NaBH_4$ at– 60 °C and **16c** was isolated in 46% yield after column chromatography. Slightly worse results were obtained when the same reaction was carried out at room temperature (**16b**: 50%, dr of the crude mixture: 1:33). Treatment of **15** in boiling formic acid afforded a mixture of diastereoisomers (dr: 1:8) from which **16a** was isolated in 45% yield. The authors noted that both the octahydro- and decahydro-naphthyridine frameworks were underexploited at the time (2005) and could represent optimal starting points for the preparation of biologically active compounds, with a more recent study discovering that some *trans*-decahydro-1,6-napthyridine derivatives possessed anti-HIV activity.[65]



Scheme 5: Decahydro-1,6-napthyridine synthesis; ds: diastereoselectivity, refers to crude mixtures, yields to isolated trans-16.

Recently decahydro-1,6-napthyridines were studied in a SAR investigation involving the discovery of novel IDO1 inhibitors (**21**, Scheme 6) for new therapeutic treatment in cancer immunotherapy.[66] The synthesis of **21** consist of eight linear steps, with two of them dedicated to deprotecting the desired amine moiety. The synthesis begins from the PtO_2 catalysed hydrogenation of **17** to the decahydro-1,6-naphthyridine scaffold **18**. The amine is protected with a Cbz group **19** and successively the Boc group is removed to yield the key intermediate **20**. From there a 5 steps synthesis is required to install the desired substituents, yielding **21** in 46% yield over the last 5 steps (Scheme 6).

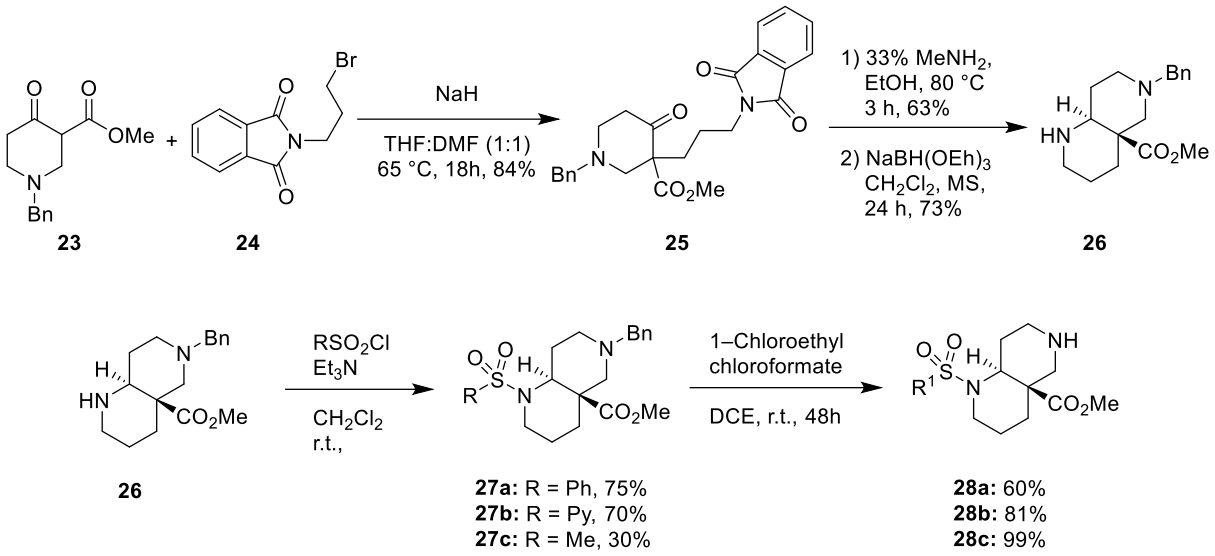


Scheme 6: Synthesis of decahydro-naphthyridine based IDO1 inhibitor.

It was noted from this investigation that compound **21** showed lead like properties due to its high potency and low clearance[c]. The authors postulated that the fully saturated bicyclic system would present better resistance to oxidative metabolism compared to a previous series of IDO1 inhibitors based on the tetrahydroquinoline **22**.[66]

Attempts to synthesise a library based on the decahydro-1,6-naphthyridine scaffolds were also undertaken as part of the effort to enrich the Joint European Compound Library (JECL) with sp^3-rich small molecules.[67] The synthesis in this case began with the commercial β -ketoester **23** that was alkylated using 1-bromo-propylpthalimide **24** in presence of NaH. The phthalimide group was removed from **25** under aminolysis conditions followed by stereoselective reductive amination using a bulky hydride source such as $NaBH(OEh)_3$ (Sodium tri(2-ethylhexanoyloxy)borohydride), leading to the formation of the bicyclic core scaffold **26** in good yields. Sulfonylation of **26** performed with 3 different sulfonyl chlorides provided compounds **27a-c** in good yields. Debenzylation was achieved by reaction with 1-chloroethyl chloroformate in DCE unmasking the second handle of scaffolds **28a-c** for the final library generation (Scheme 7). The scaffolds were decorated using three different reaction types: amide synthesis, reductive amination and sulfonylation reaction, yielding a compound collection of 354 molecules.[67]

[c] : clearance is a pharmacokinetic measure used in pharmaceutical research. It measures the removal of a drug from a measured matrix (usually blood or plasma) and has direct implications over other parameters such as elimination, half-life and efficacious dose.



Scheme 7: Synthesis of decahydro-naphthyridine scaffolds.

This method clearly represents an important addition for the synthesis of alkaloid like structures as scaffolds for a library generation, however it also bore some limitations. Only sulfonamides were shown to be applicable at the amine protection step of **26**, whilst evidence for compatibility to install functional groups to the carbon skeleton in addition to two amines already exploited for the functionalisation, left the scaffold lacking modularity in providing high skeletal diversity. Furthermore, only decahydro-1,6-napthyridines are accessible, limiting the possible chemical space coverage, while the synthesis of decahydro-1,7-napthyridines analogues would require the use of a different, even more expensive, starting material (Figure 5).

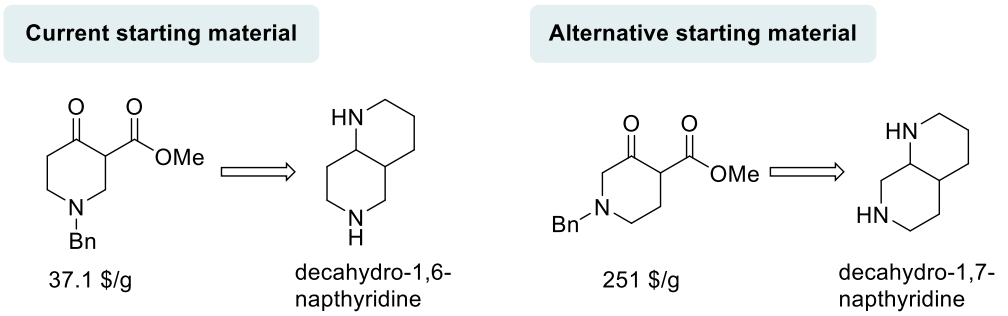


Figure 5: Starting material prices for decahydro-naphthyridines synthesis. Prices provided from Combi-Blocks website, accessed 23/9/2021.

The literature provided a limited array of possibilities for the synthesis of decahydro-naphthyridines, despite how frequently these structures are found in various NPs and their highlighted utility. A method that provided access to this useful NP-like framework in a modular and efficient fashion was desirable. Importantly, a single methodology that could grant access to various decahydro-naphthyridine frameworks with different functional group installions was sought after. Moreover, the approach should be aligned with the common strategies in drug discovery, providing useful scaffolds for the synthesis of compound libraries for early-stage drug discovery.

2.2. Gold-catalysed synthesis of epoxybridged naphthyridines

Although the methods to synthesise piperidines highlighted earlier (Figure 3), few had been explored in the successful synthesis of decahydronapthyridines outside the reduction of the naphthyridine core (Schemes 1, 6) or C-N bond formation via nucleophilic substitution (Scheme 5) or reductive amination (Schemes 4, 7). None of the methodologies explored alternative disconnections to access this important framework. To this end, the Diels–Alder reaction offers the opportunity to explore an alternative retrosynthetic approach for the synthesis of these valuable structures (Figure 6).

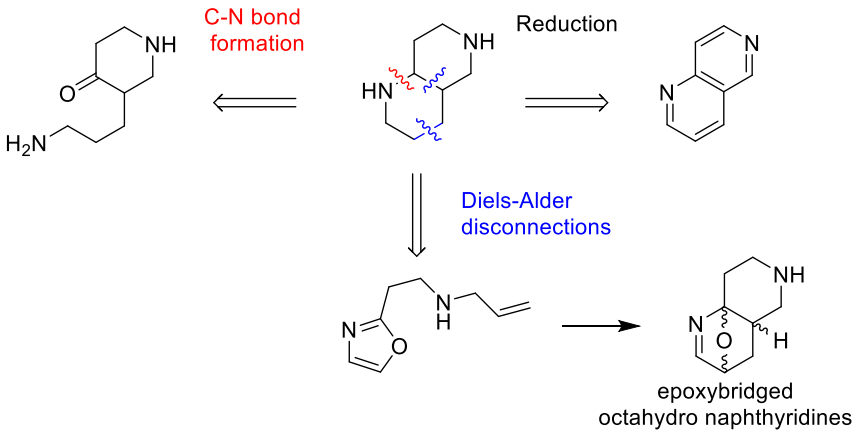
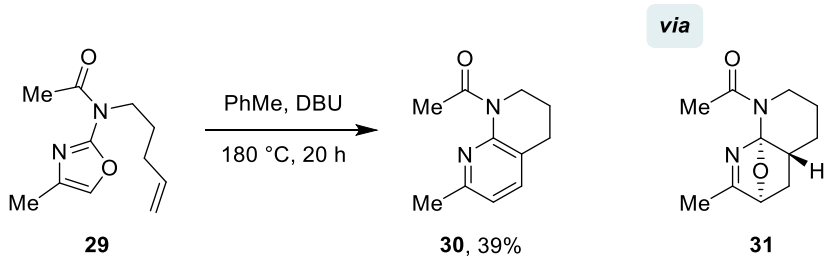


Figure 6: Retrosynthetic approach to decahydro-naphthyridine frameworks.

Since its discovery, the Diels–Alder reaction has been widely used to convert simple precursors into complex polycyclic scaffolds.[68] After Kondrat'eva's seminal paper on the synthesis of pyridines in 1957,[69] the Diels–Alder reaction of oxazoles have been extensively studied with inter- and intra-molecular reactions. A variety of polycyclic scaffolds have been accessed exploiting the reactivity of alkenes, allenes, and alkynes dienophiles.[70] As these areas have been extensively reviewed in the literature,[70] and by previous members of the Davies' group,[71, 72] the scope of this introduction will focus on intramolecular Diels–Alder reactions that result in the formation of epoxybridged octahydro naphthyridines and their derivatives.

Whilst describing the total synthesis of Hippadine, Padwa demonstrated that 2-amidooxazole **29** underwent an intramolecular Diels–Alder reaction.[73] The forcing reaction conditions and the presence of DBU favoured the spontaneous dehydration of **31** to **30** (Scheme 8).

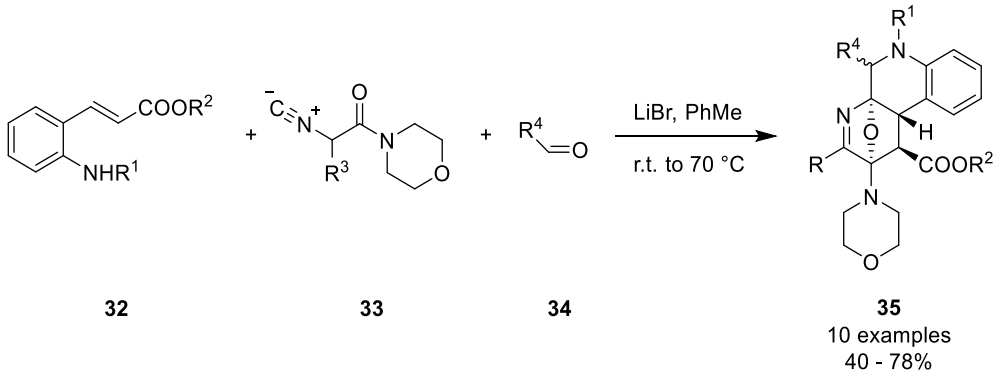


Scheme 8: Example of intramolecular Diels–Alder reaction and tethered oxazoles.

This methodology provides a novel strategy for synthesis of tetrahydro-1,8-naphthyridine frameworks, however the synthesis relied on the alkylation of prebuilt oxazoles, limiting the modular nature in which they could be functionalised at different positions.

Zhu and coworkers isolated the initial Diels–Alder product **35** as a diasteromeric mixture from the Ugi reaction-Diels–Alder cascade process shown in Scheme 9.[74] In this reaction the oxazole is synthesised in the cascade sequence and was not isolated. The desired polycyclic scaffold

was generated from vinyl aniline **32** upon short reactions time and moderate temperatures with no dehydration observed.



Scheme 9: Zhu's multicomponent reaction to access hexahydronaphthyridines scaffolds.

Zhu's multicomponent reaction provided access to decahydro-naphthyridine frameworks, while the modular nature of this methodology allowed for the synthesis of various analogues, bearing, for the first time, substitutions on the carbon skeleton. By changing one of the starting materials, the scaffold diversity of the compound collections would be greatly increased, following the Diversity Oriented Synthesis concept. This feature would be an important addition to any methodology discovered, but it is a critical factor to all strategies that aim at the generation of novel scaffolds for drug discovery.

The intramolecular Diels–Alder reaction of alkene-tethered oxazoles represents a practical methodology to rapidly assemble complex sp^3-rich frameworks bearing a decahydro-naphthyridine scaffold and might represent the answer to the gap in synthetic methodologies for the preparation of these valuable frameworks. Moreover, the Diels–Alder reaction has been demonstrated to be compliant with cascading procedures once the alkene tethered oxazole is generated *in situ*, with no additional reagents required. The ability to develop a robust strategy to access a range of diverse Diels–Alder products whilst controlling the substitution patterns would grant access to a diverse collection of decahydro-naphthyridine analogues with potential for further modification for use in library synthesis.

One such method has recently been developed within the Davies group and employs a gold-catalysed formal [3+2] dipolar cycloaddition to access 2,4,5-substituted oxazoles. By careful design of an *N*-acyl pyridinium ylide **36** or enynamide **41**, the resulting oxazoles **38** and **42** generated from the gold-catalysed cycloaddition can contain an appended alkene at C2 or C5 position. The oxazoles subsequently undergo a [4+2] Diels–Alder reaction to give polycycles **39** and **43** as racemic mixtures of single diastereomers (Figure 7). The effectiveness of the process is exemplified by the four new bonds formed and the introduction of three stereocenters. Moreover, it provides selective *trans* ring junctions and access an amidine functionality that could be exploited for further elaborations.

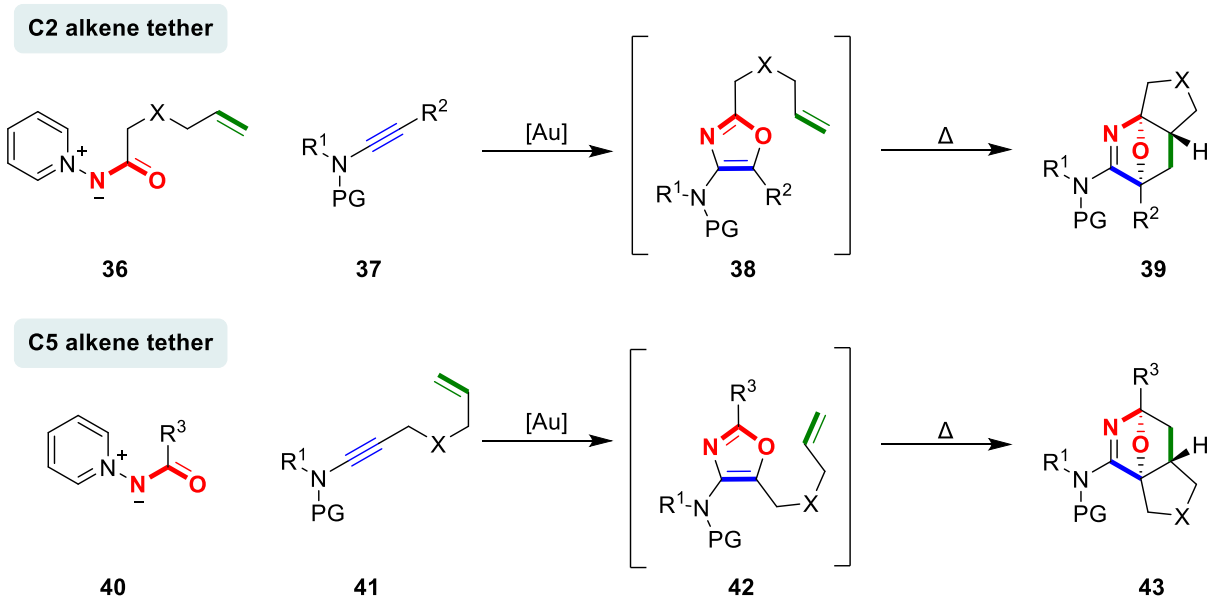


Figure 7: Overview of the gold-catalysed cascade.

The protocol was developed, and an initial substrate scope was prepared by previous member of the Davies' group to access a variety of hexahydropyrollopyridines from either the C2 or C5 series. The reaction proved general with a variety of functionality tolerated at the C-terminus of the ynamide. In these preliminary studies the nitrogen on the tethered alkene was mostly protected with a tosyl sulfonamide, due to the simple preparation of the starting materials,

however mesyl and Cbz were also employed. The substrate scope was successively expanded, and other sulfonyl chlorides were selected to install desirable functional groups for drug discovery purposes (Figure 8). Thio- and cyclopropyl- functionalised ynamides gave improved conversion to polycycles **44a-d**. Moreover, thioketal **44c** was obtained in nearly quantitative yield, even when the catalyst loading was reduced to 2 mol% highlighting the efficiency of the oxazole formation. Furan, thiophen, and alkyl polycycles **44e-l** demonstrated the capability of ynamides to undergo the desired cascade reaction providing access to a variety of different groups attached to the carbon skeleton. Electron-rich polycycle **44h** was isolated in higher yield than its electron-poor nitro analogue **44i**.

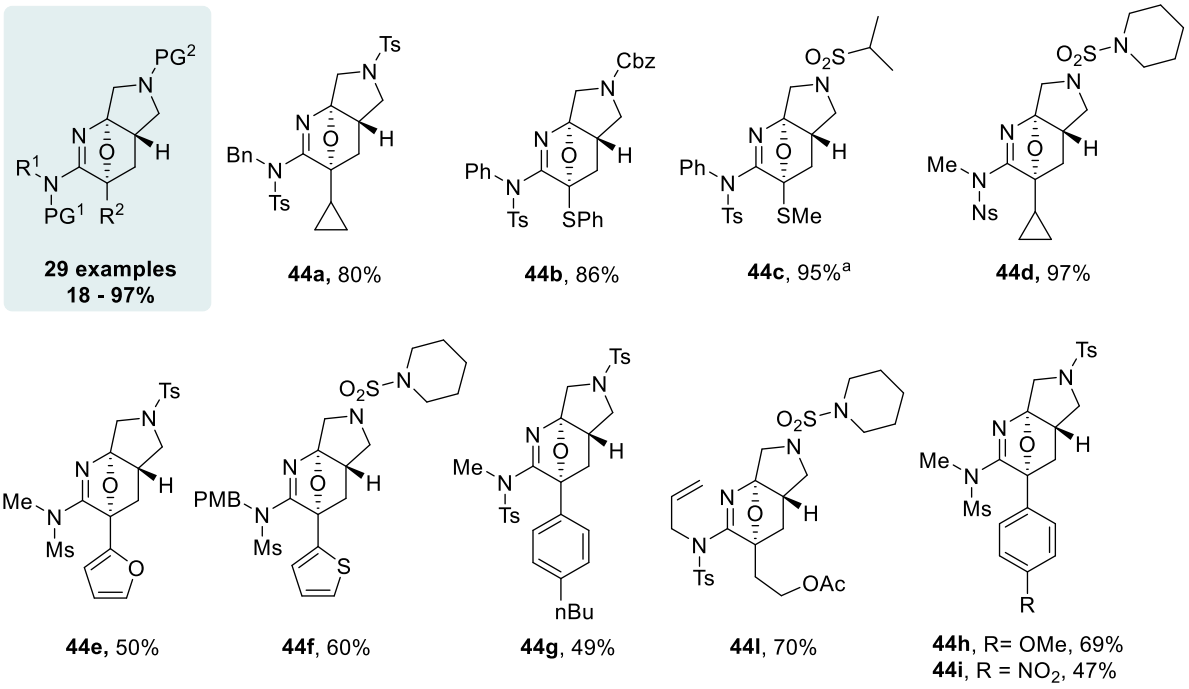


Figure 8 : Selected examples of substrate scope for 6,5 Diels–Alder reaction prepared by Matt Ball-Jones, Andrew Gillie and Matthew Wakeling. Standard reaction conditions: Ynamide (1.0 eq), ylide (1.2 eq), [Au-III] 5mol%, PhMe, 1–2 h 90 °C, 20–72 h 110 °C. [a][Au-III]

The ability of the enynamides to participate in the cascading cycloadditions was also investigated, *via* alkene tethered to the C5 position of the oxazoles. A range of functionality was found to be compatible with the cascade process. The initial substrate scope focused on the synthesis of hexahydropyrollopyridines with excellent yields obtained across the series **45a-d**.

The process was further extended to oxygen tethered alkenes to access furan derivatives such as **45e-f** and benzopyran derivative **45g** in excellent yields (Figure 9).

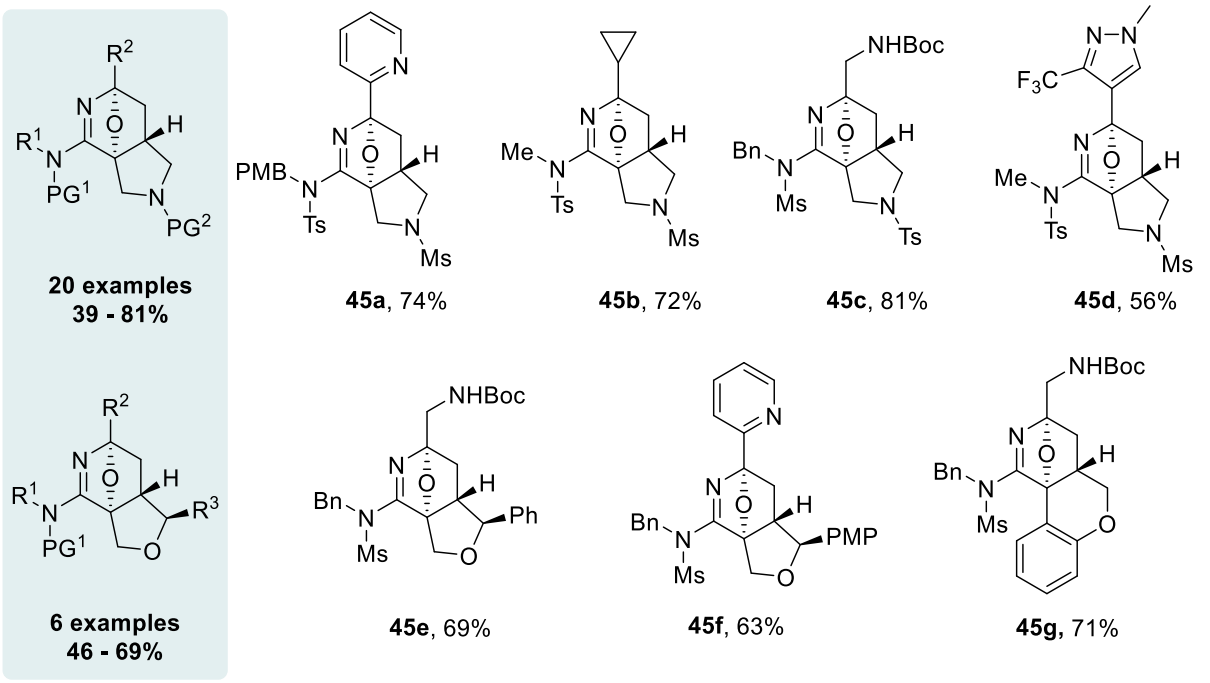


Figure 9: Selected examples from Matt Ball-Jones and Matthew Wakeling studies on the scope of the C5 Diels–Alder cascade process.

Following these results, this method was extended and homoallyl tethered alkenes were used providing access to 6,6-polycycles based on the decahydro-naphthyridine scaffold. Regarding the C2 Diels–Alder series, the nitrogen on the linker was still primarily protected with tosyl sulfonamide and thio- and cyclopropyl functionalised ynamides confirmed their role as superior coupling partners for an enhanced Diels–Alder conversion **46b-d**. All the reactions were carried out at 90 °C, except when Cbz-protected ylide was employed, a higher temperature was required for the conversion from the corresponding oxazole and hydroxypyridine **46e** was isolated *via* sulfide expulsion and aromatisation. Even if this was the only polycycle so far to undergo spontaneous degradation to the pyridine, this pathway might represent a problem to overcome in future studies with similar substrates if high temperatures are needed for the Diels–Alder

reaction to occur. In the C5 Diels–Alder series the compatibility of protecting groups bearing more desirable functionalities for drug discovery was investigated, which included cyclopropyl sulfonamides and Cbz **46g-h**. Conversion from the corresponding oxazole proceeded smoothly across all the substrates, however Cbz derivative **46i** required heating to 110 °C to achieve sufficient conversion (Figure 10)

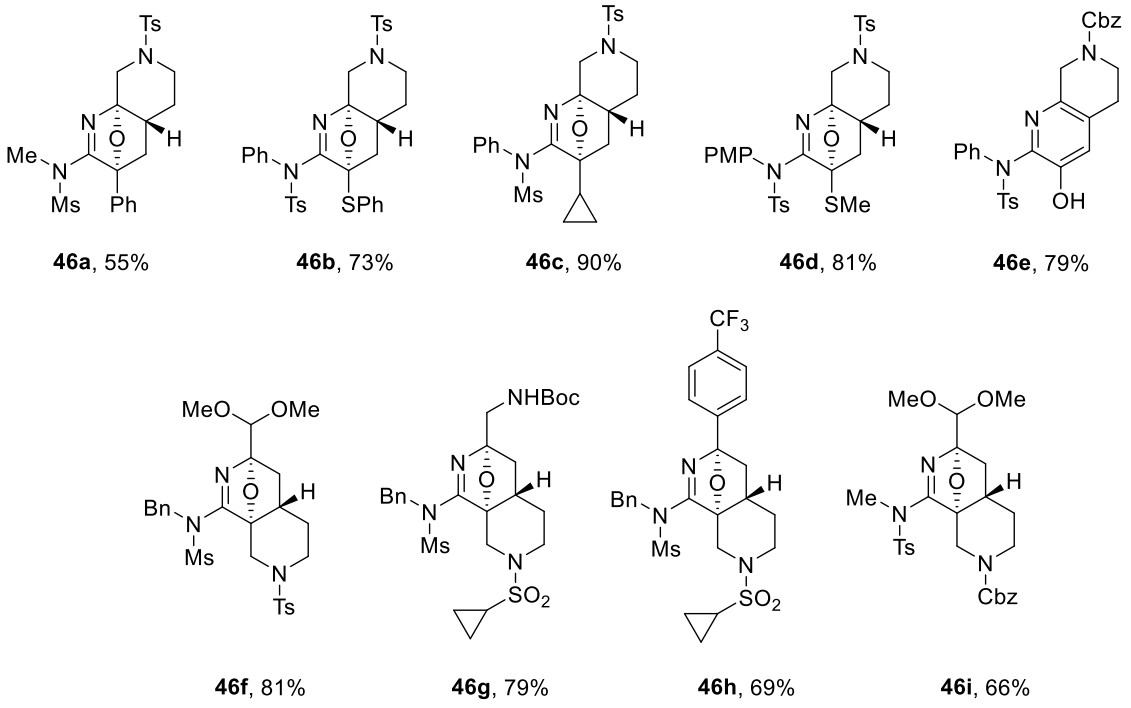


Figure 10: Selected examples from Matt Ball-Jones and Matthew Wakeling studies on the Diels–Alder process for 6,6-polycycles.

This method proved general across a variety of substrates providing access to 6,5 and 6,6-polycycles, the latter bearing a decahydro-naphthyridine core. Through careful design of the en-ylide and en-ynamide this synthetic approach could represent the answer to the methodology gap regarding the synthesis of decahydro-naphthyridine cores (Figure 11).

The flexibility of the method allows for the installation of pharmaceutically relevant substitutions attached to the carbon skeleton of the framework, increasing the diversity of the collection. The embedded reactive functionalities of these sp^3-rich frameworks represent

promising manifolds for elaboration, and the further functionalisation of such frameworks could yield NP-like scaffolds based on the desired decahydro-1,6-naphthyridine core.

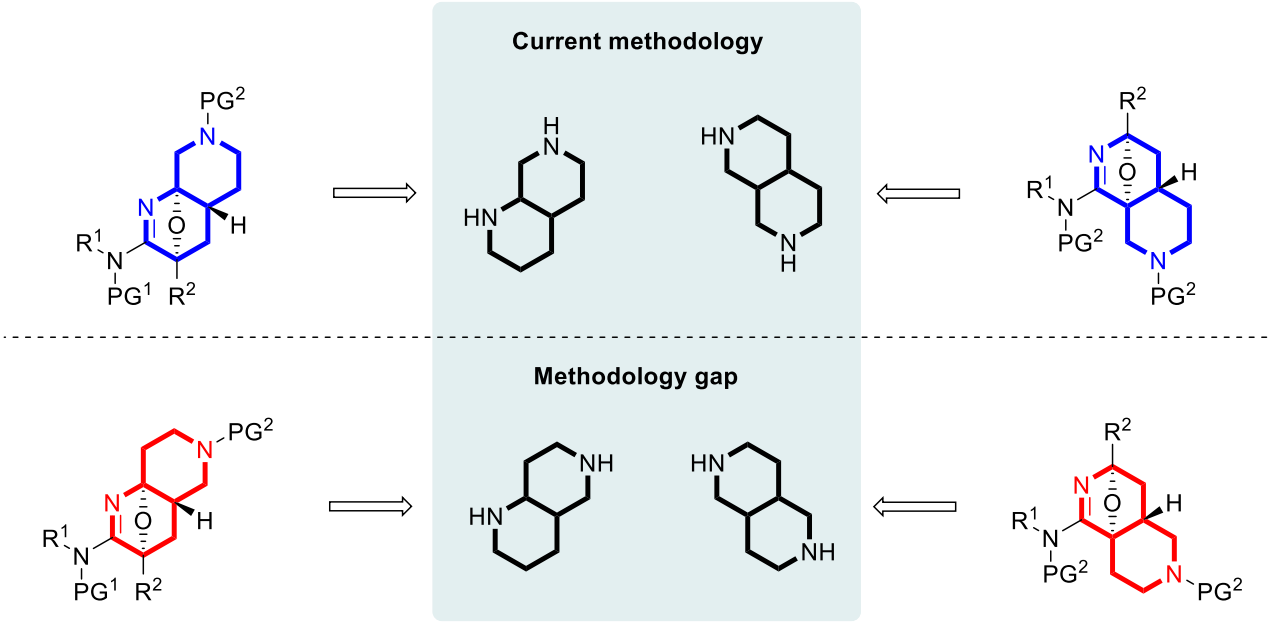


Figure 11: Overall view of the frameworks accessed via gold-catalysed cascading process.

2.3. Aim and objectives

This work aims to investigate the reactivity of the novel sp^3-rich frameworks, accessed *via* the gold-catalysed cascade methodology, and generate scaffolds suitable for the synthesis of a compound library for early-stage drug discovery. The gap in synthetic methodologies for the modular synthesis of valuable decahydro-1,6-naphthyridines derivatives was investigated. To achieve this, the approach looked at providing modular, robust, and scalable synthetic procedures, installing easily cleavable protecting groups, and developing divergent strategies to manipulate the embedded functionalities generated during the polycyclisation process, providing access to an array of diverse scaffolds based on the decahydro-1,6-napthyridine framework. To further expand the range of accessible structures and increase the chemical space coverage of the final library, the octahydro-pyranopyridine scaffold was also studied (Figure 12). The validation of the scaffolds will be investigated through the computational design and

synthesis of a compound library that should contain molecules with desirable physicochemical properties for predicted bioavailability and novel chemical space coverage.

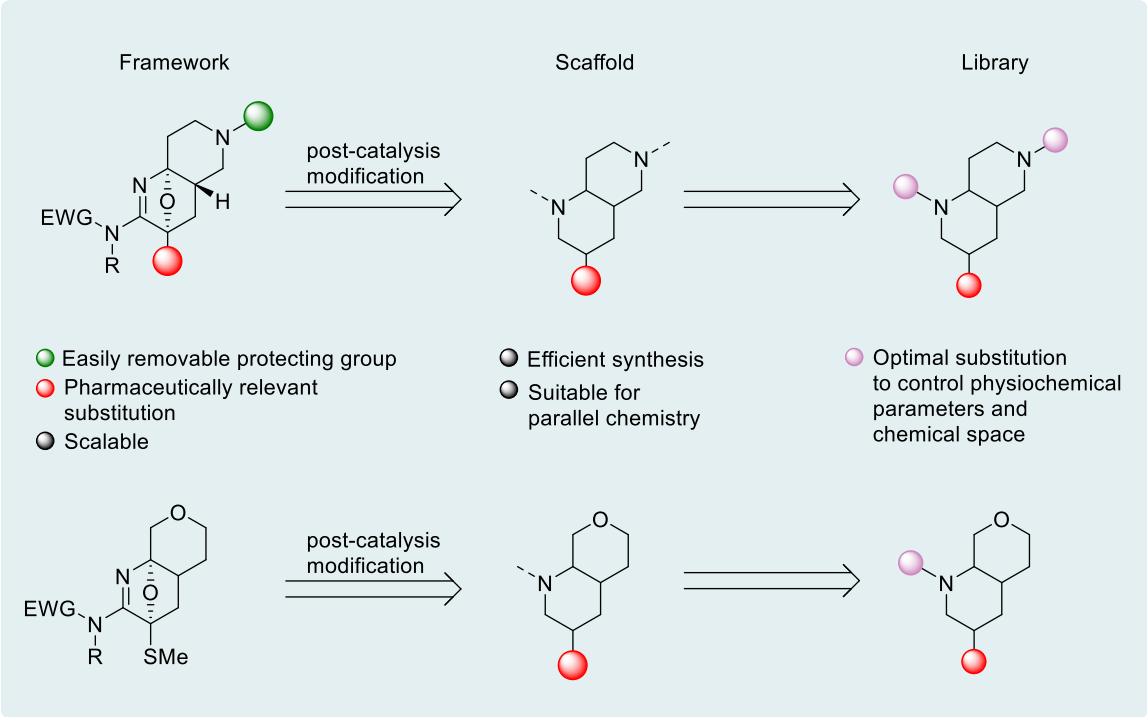


Figure 12: Aim and objectives of this work.

3. Chapter 3: Pluripotent Frameworks for Drug Discovery

Pluripotent is often used to describe the ability of stem cells to differentiate into many different cell types.[75] In a broader sense, pluripotent can be defined as something that has no fixed development potential and more than one potential outcome.[76] This adjective describe perfectly a molecular framework that via the DOS principle can develop into different scaffolds. With this concept in mind, the reactivity of novel pluripotent frameworks accessible with the gold-catalysed protocol was investigated. To this end new or improved synthesis of cyclisation precursors were developed. Novel en-ylides and en-ynamides were prepared, through changing the position of the heteroatom on the linker or changing its protecting group. A variety of pharmaceutically relevant aromatic-, heteroaromatic-, and alkyl-substitutions will be installed on the frameworks, expanding the scope of polycyclic frameworks accessible with the protocol The reactivity of the pluripotent frameworks and their embedded functionalities was investigated following the DOS principle to deliver a range of diverse scaffolds for early-stage drug discovery.

3.1. Expanding the scope: Gold-catalysed double-annulations

3.1.1. Gold-catalysed cycloaddition reaction to access 4-aminooxazoles

The key intermediate towards the synthesis of pluripotent frameworks bearing a decahydro-naphthyridine core are 2,4,5-trisubstituted oxazoles bearing a tethered alkene that subsequently undergoes Diels–Alder reaction (Figure 13).

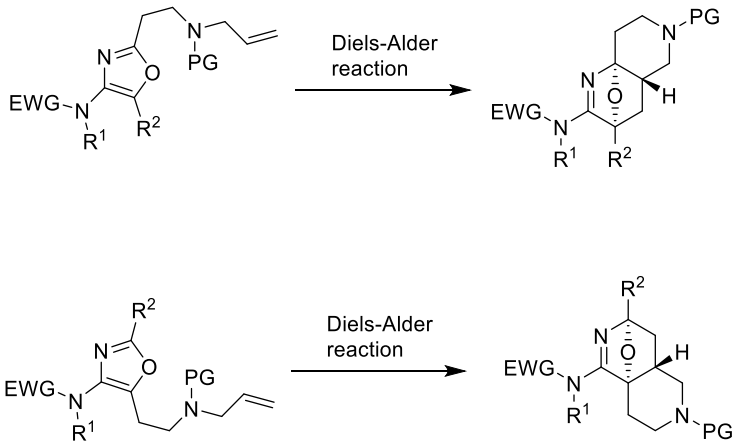
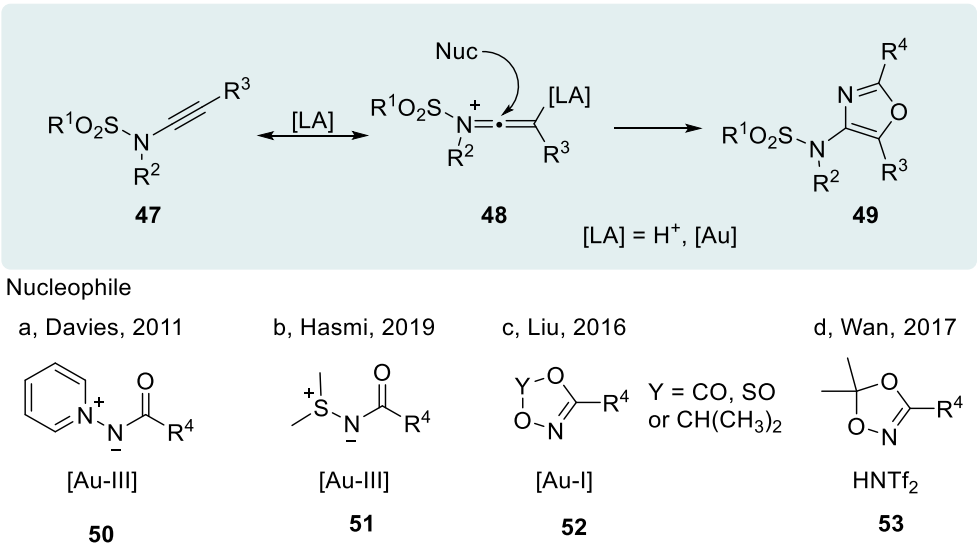


Figure 13: Diels–Alder reaction of alkene tethered oxazoles to give pluripotent frameworks bearing decahydro-napthyridine core structures.

In 2011 the Davies group published the synthesis of 4-aminooxazoles *via* a formal [3+2]-dipolar cycloaddition between ynamide **47** and *N*-acyl pyridinium *N*-aminide **50** under gold catalysis (Scheme 10a).[77-79] The key intermediate of this transformation can be visualised as a gold keteniminium **48**, this resonance species highlights the electronic bias of ynamides driving the regioselectivity of the reaction. The same reactivity was successively exploited by several groups in combination with different nucleophilic nitrenoids. Hashmi et al. reported an analogous transformation involving ynamides and *N*-acyl sulfilimines **51** (Scheme 10b),[80] using conditions similar to those reported by Davies. Dioxazolones, dioxathiazoles, and dioxazoles **52** were found to be effective coupling partners under [Au-I] catalysis (Scheme 10c).[81] A transition metal free reaction was also reported employing dioxazoles **53** and $HNTf_2$ as a super acid catalyst (Scheme 10d).[82]

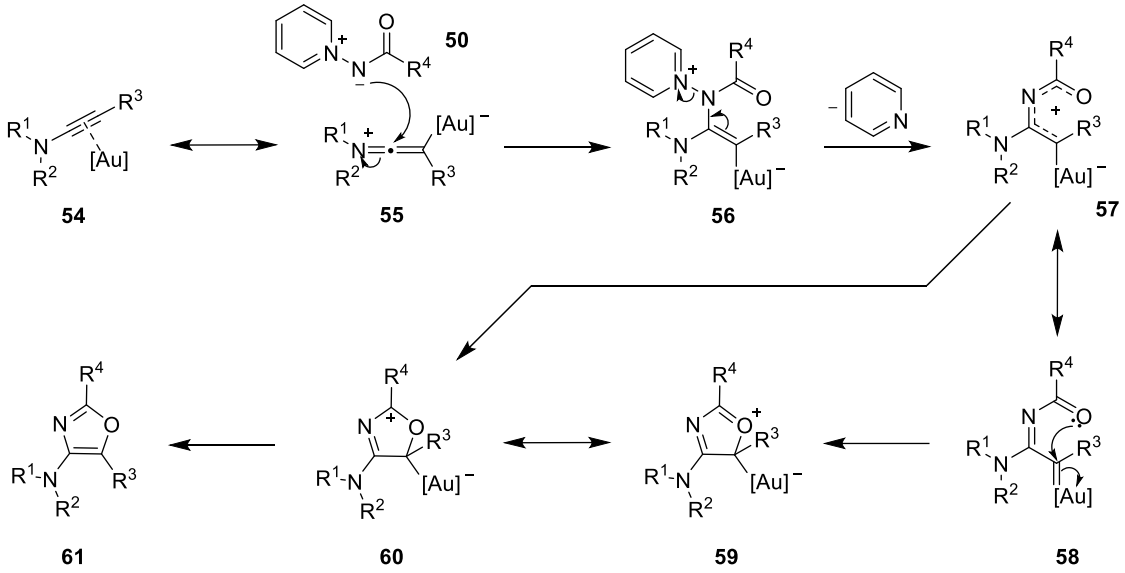


Scheme 10: Synthesis of 4-aminooxazoles from ynamides and nucleophilic nitrenoids equivalents.

Due to their simple preparation from ester derivatives and the excellent functional group compatibility, *N*-Acyl pyridinium ylides **50** were the nucleophilic nitrenoids of choice throughout the studies discussed in this thesis. The synthesis of the other nitrenoids would result in an increase of linear synthesis steps and decrease in efficiency, since accessing sulfilimines would require the conversion of an ester moiety into a primary amide, whilst dioxazoles and dioxazolone preparation would entail the conversion of acid chlorides or carboxylic acids to the corresponding hydroxamic acids. Furthermore, both [Au-I] and $HNTf_2$ methods involving the use of dioxazoles and dioxazolones as nucleophilic coupling partners employ DCE as reaction solvent, which is a known carcinogen.

The proposed mechanism for this process begins with the activation of ynamide π-system by the gold catalyst and the formation of the gold-ketenimminium species **55** as an extreme resonance form caused by the electronic bias of the appended nitrogen. Ylide **50** therefore attacks in a regioselective manner providing **56** that evolves to gold-stabilised carbocation **57** through elimination of the pyridine and undergoes cyclisation either *via* 4π electrocyclization

or *via* capturing the acyl oxygen generating **60**. Finally, deauration provides aromatisation to oxazole **61** and regenerates the gold catalyst (Scheme 11).



Scheme 11: Mechanism of gold catalysed oxazole formation between ynamides and N-acylpyridinium ylides.

3.1.2. Synthesis of cyclisation precursors

3.1.2.1. Preparation of N-acyl pyridinium ylides

A range of *N*-acylpyridinium ylides were designed and synthesised in order to access novel epoxybridged napthyridine frameworks from the C2 Diels–Alder series and address the methodology gap for the synthesis of these important NP-based structures (Figure 14).

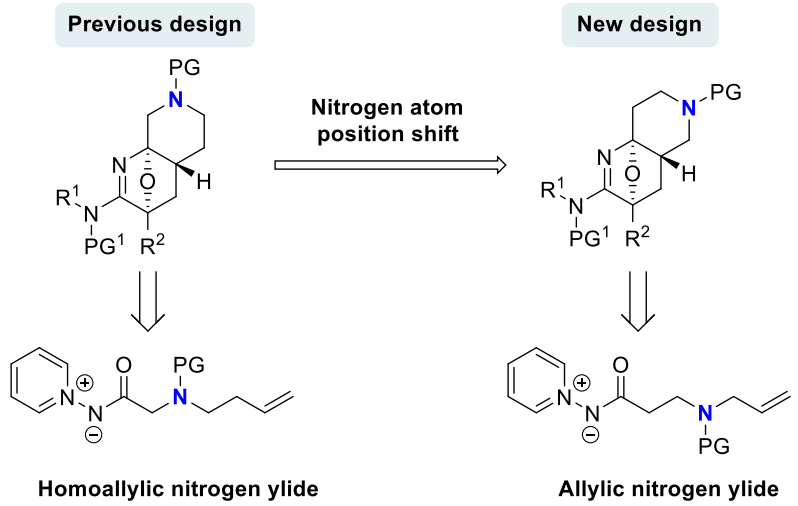
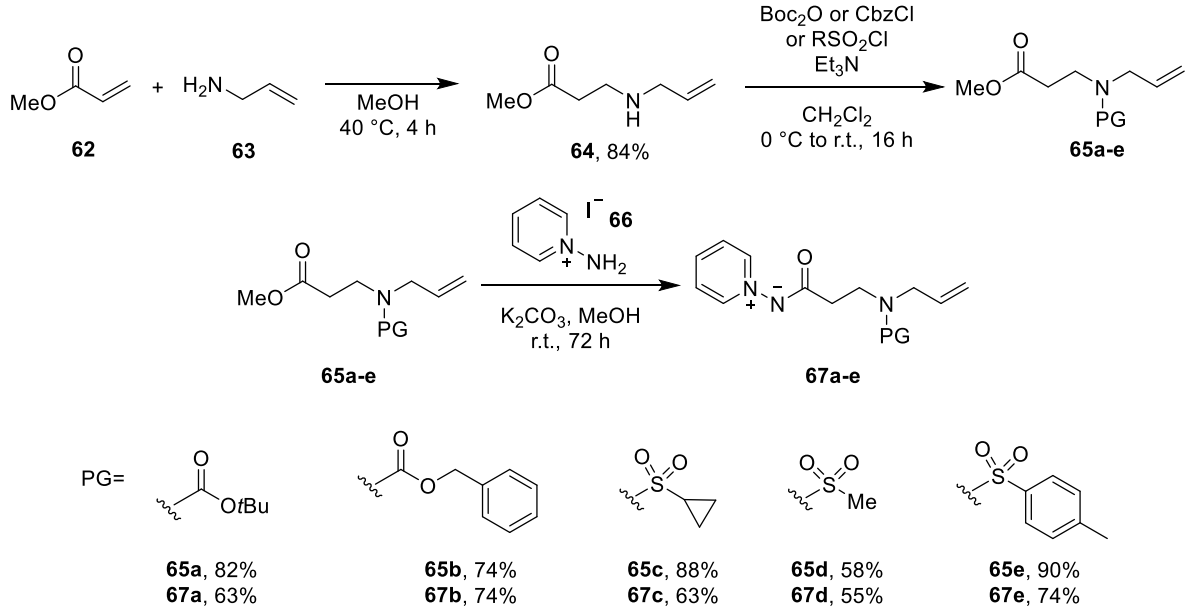


Figure 14: Different design of *N*-acylimminium ylides to access 1,6-decahydro-naphthyridine scaffolds.

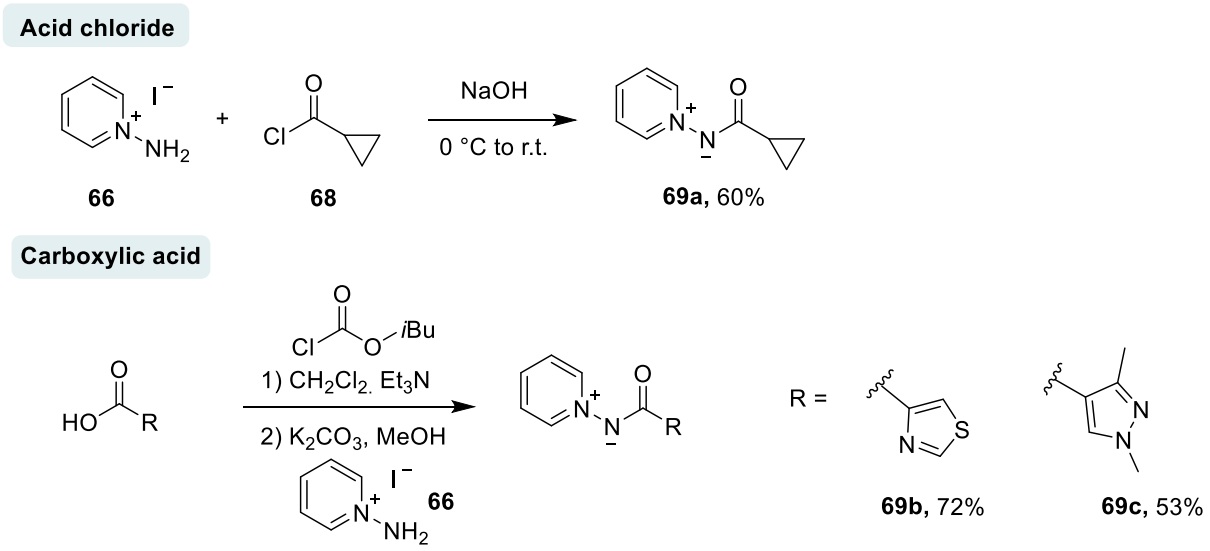
To investigate the impact on the cascading process of the nitrogen in the allylic position, a range of different protecting groups were selected. The tosyl functional group was initially tested for a direct benchmark to compare the compatibility of the allylic nitrogen against its homoallylic analogue in the cascading process. The main objective was then to introduce easily removable groups such as Boc and Cbz, to allow further decorations after the post-catalysis elaboration. Moreover, a set of sulfonyl chlorides was selected for their desirable functional groups for drug discovery purposes, such as cyclopropyl and mesyl chloride. To this end, a divergent synthesis was designed to access esters **65a-e** from a common starting material **64**, which was synthesized via aza-Michael addition between methyl acrylate and allylamine followed by protection with the corresponding sulfonyl chloride or carbamate. Esters **65a-e** were stirred with 1-aminopyridinium iodide **66** affording the *N*-acyl pyridinium *N*-aminides **67a-e** in good yields in only three steps from commercial materials (Scheme 12). The synthesis of ylide **67a** was also up scaled to 50 mmol with little loss in yield. Considering that Boc protection was performed on the crude reaction mixture of **64** and that ester **65a** was distilled under reduced pressure, this effectively reduced the chromatographic purifications to the one needed for ylide **67a**.



Scheme 12: Synthesis of ylides and their precursors.

For the C5 Diels–Alder series, ylide **69a-c** were prepared to access polycycles with desirable aliphatic and heteroaromatic groups for drug discovery purposes. Cyclopropyl ylide **69a** was prepared to access an electron-rich alkyl group to compare its beneficial effects on the Diels–Alder process found in previous studies in the C2 Diels–Alder series. Ylides **69b** and **69c** were selected in order to try and install moieties that are commonly found in a range of natural products and marketed drugs.

The *N*-acyl pyridinium ylides were prepared according to literature procedures from the reaction of acid chlorides or carboxylic acids with *N*-aminopyridinium iodide **66** and ylides **69a-c** were obtained in good yields (Scheme 13).



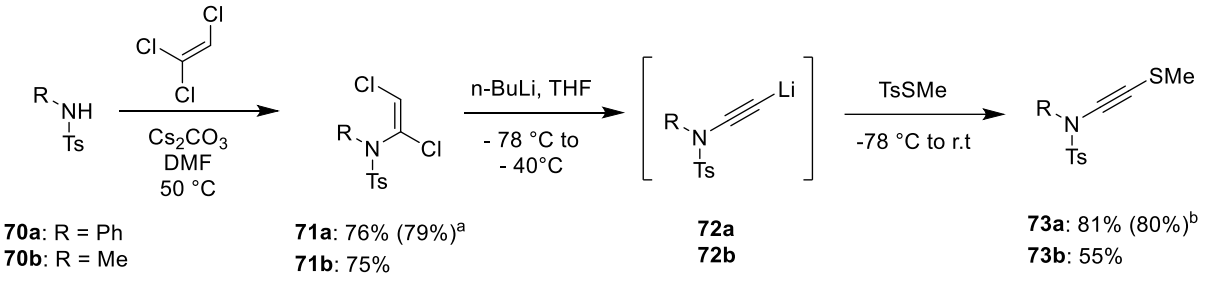
Scheme 13: Synthesis of *N*-acylimminium ylides used in the C5 Diels–Alder study.

3.1.2.2. Preparation of Ynamides

A variety of ynamides were prepared following the Hsung,[83] Stahl,[84] and Anderson[85] methods, to investigate the reactivity of the C2 Diels–Alder series. During the elaboration of the frameworks (see Chapter 3.2) the sulfonamide is typically expunged *via* reactions at the amidine

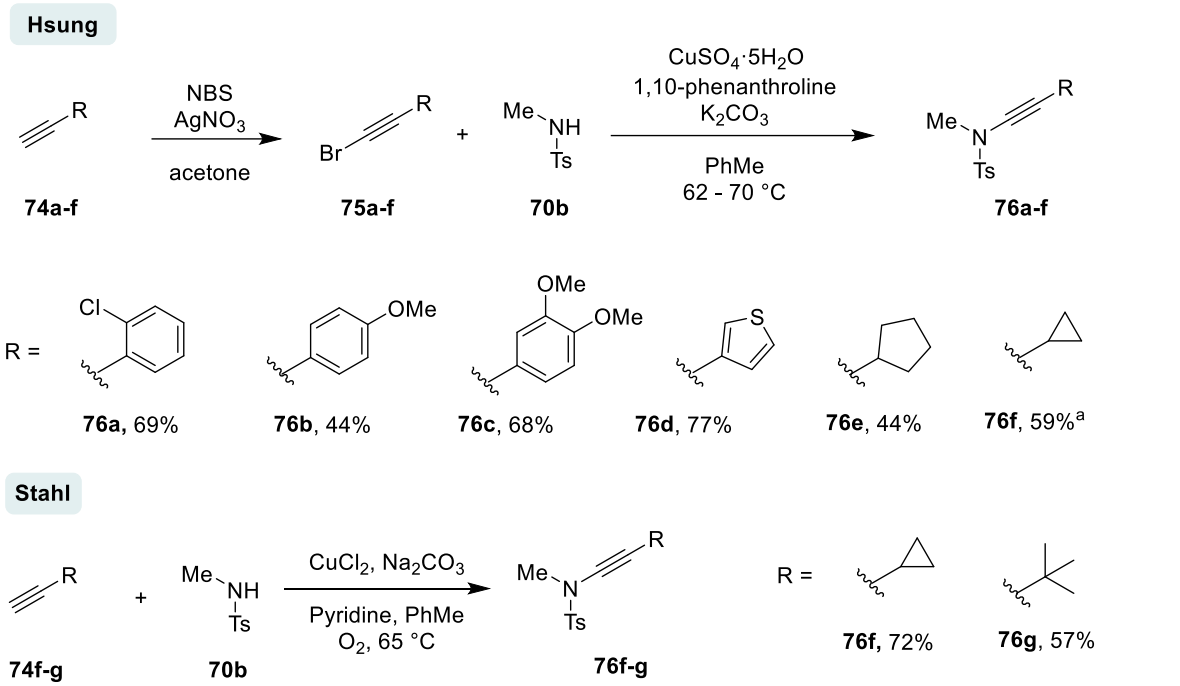
motif, therefore the choice of the sulfonamide at the ynamide was driven by the ease of handling and molecular weight, to minimise the mass loss after framework elaboration.

Thioynamides **73a-b** were prepared via Anderson's method from the corresponding sulfonamides **70a-b** to access dichloroenamide **71a-b**. Subsequent lithiation and trapping with methylthiosulfate yielded Thioynamide **73a** in excellent yield whilst **73b** was isolated in a moderately lower yield. Synthesis of thioynamide **73a** was performed on a 50 mmol scale, avoiding chromatographic purifications, as every intermediate was isolated after recrystallisation from ethanol (Scheme 14).



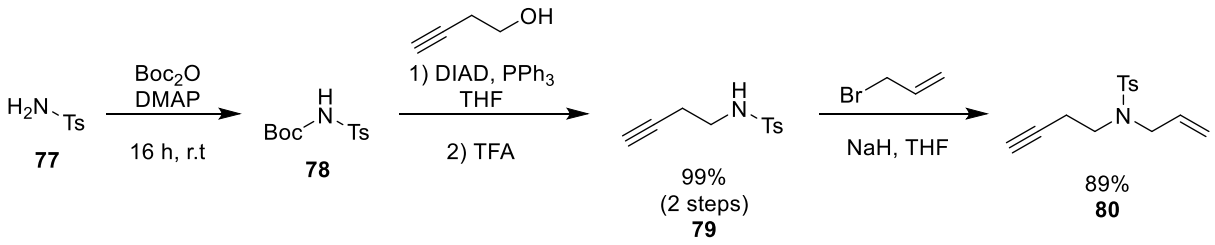
Scheme 14: Synthesis of thioynamides via Anderson's method. [a]: 81 mmol scale; [b]: 51 mmol scale.

A variety of functionalities were selected for the C-terminus of the ynamides both to investigate the effect on the Diels–Alder process and for their desirability for drug discovery purposes. The preparation of these precursors was initially approached via Stahl's method, this one step procedure avoids handling of the often volatile and light sensitive bromo-alkyne intermediates employed in Hsung's methodology.[83, 84] However, the Stahl procedure suffers from the potential Glaser–Hay oxidative competing reaction forming the diyne,[86] which is sufficiently suppressed by using 5.0 equivalents of sulfonamide and by the addition of the alkyne over several hours. These drawbacks render it unsuitable for large scale synthesis due to the large amounts of unreacted sulfonamides remaining in the reaction mixture. Nevertheless, the Stahl method was used as the first approach for the small-scale preparation of ynamides **76f** and **76g**, whilst ynamides **76a-e** were prepared via the Hsung method in good yields. (Scheme 15).



Scheme 15: Synthesis of ynamides via Hsung and Stahl methods. [a]: 50 mmol scale.

With a variety of ynamides in hand to test the C2 Diels–Alder series, attention was turned to the synthesis of homopropargyl 1,7-enynes such as **80**. This synthesis has been already attempted in the Davies group *via* a Mitsunobu reaction and subsequent allylation in excellent yield (Scheme 16).

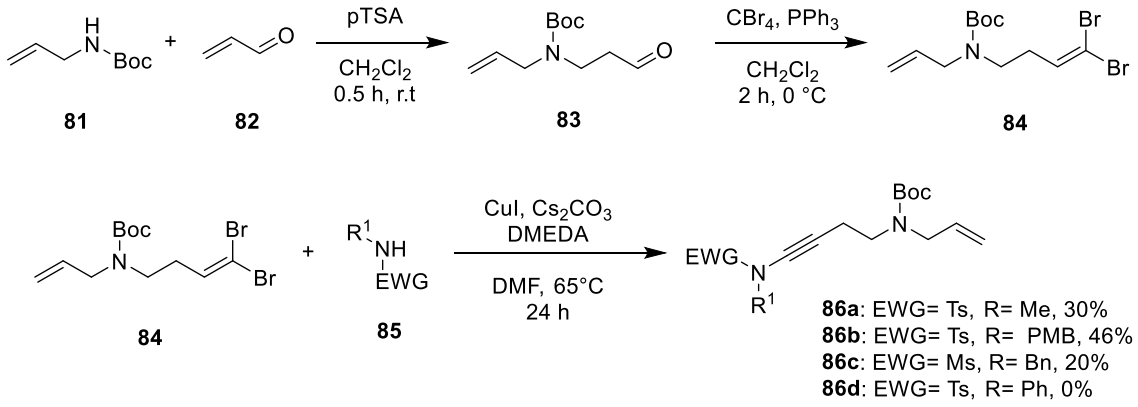


Scheme 16: Synthesis of homopropargyl 1,7-enynes used by Matt Ball-Jones.

However, the synthesis of the catalysis precursor was limited to this example and a more flexible protecting group was required to access the possibility of deprotecting and functionalising the alkyl nitrogen. Nevertheless, selective deprotection of a single Boc group from di-tert-butylimnodicarboxylate derivative **79** is reported in the literature,[87] the alkylation

of the corresponding carbamates has proven low yielding and a more efficient process was desirable for future up scale of the process.

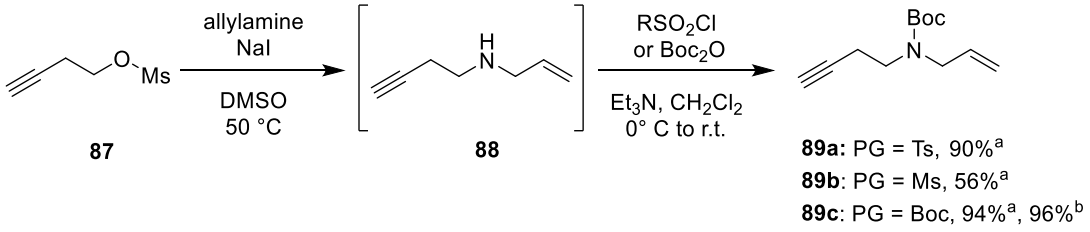
The first synthetic sequence was ideated along the lines of the *N*-acylpyridinium ylide precursors procedure (Scheme 12), aza-Michael addition between Boc-protected allylamine and acroleine yielded aldehyde **83**, that was then converted to vinyl dibromide **84** *via* the Ramirez reaction.[88] The last synthetic step was the coupling of **84** with the desired sulfonamide following Evano's method (Scheme 17).[89] Although this process consisted of a short synthetic sequence, final conversion from the vinyl dibromide yielded low amounts of the desired ynamides **86a-d** due to a very unclean conversion and a complex chromatographic separation from side products and unreacted starting materials. Moreover, Ramirez's olefination produced considerable amounts of triphenylphosphine oxide as by-product and its removal could represent an obstacle to the up scaling of the process.



Scheme 17: Initial attempts at the syntheses of homopropargyl 1,7-enynamides.

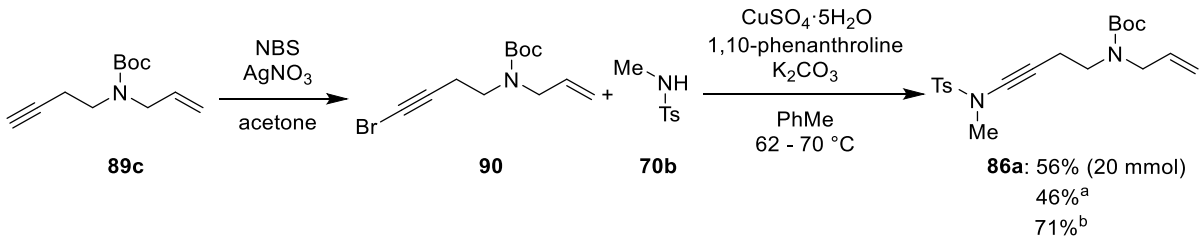
A more atom efficient process was developed by another member of the Davies group (Matthew Wakeling.[90] The synthesis involved the protection of homopropargyl alcohol with mesyl chloride to give methanesulfonate **87** which provided a suitable substrate for S_N2 alkylation. Treating **87** with excess allylamine and NaI provided secondary amine **88**, and the crude material was used to deliver enynes **89a-c** in excellent yield (Scheme 18). The efficiency of this

method is exemplified by the necessity for only one chromatographic purification after the enyne protection, whilst intermediate **87** was obtained pure after quenching and aqueous work up. For the purpose of this thesis, the synthesis of enyne **89c** was up scaled to 52 mmol in excellent yield, further confirming the efficiency of the method.



Scheme 18: Matthew Wakeling synthesis of homopropargyl 1,7-enynes; [a]: Matthew Wakeling results; [b]: 52 mmol scale attempted during this study.

Enyne **89c** was then converted to ynamide **86a** via Hsung method, crucial for the successful reaction was the synthesis of bromo-alkyne **90** employing freshly recrystallised NBS, since when an off-white solid was used, Boc removal was observed in the reaction mixture. Ynamide **86a** was obtained in moderate yield (46% over 2 steps) via Hsung's method. Whilst an higher yield was obtained by Matthew Wakeling using the Stahl procedure, due to scalability issues of the latter method Hsung methodology was preferred and ynamide **86a** was obtained in 56% yield (Scheme 19).



Scheme 19: Synthesis of homopropargyl 1,7-enynamide at 20 mmol scale. [a]: Matthew Wakeling, via Hsung method; [b]: Matthew Wakeling, via Stahl method.

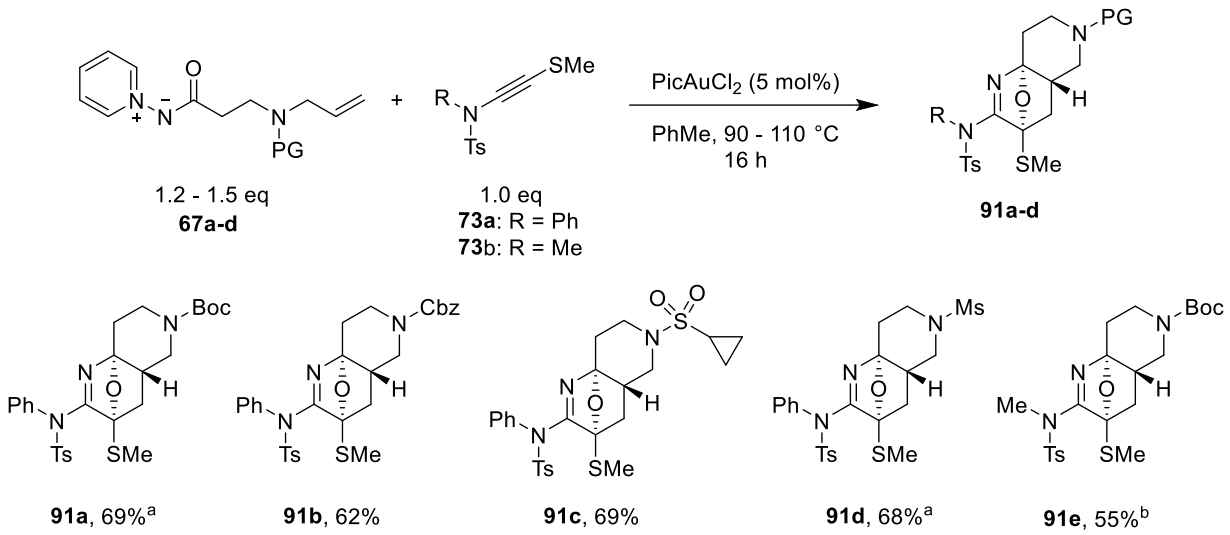
Both *N*-acyl pyridinium ylides and ynamides bearing a diverse set of protecting groups and substitution were synthesised. Ynamides **86a** and ylides **67a-e** would provide insight into the proficiency of the allylic tethered alkene in the cascading cycloaddition, whilst catalysis

precursors **69a-c**, **73a-b**, and **76a-g** will provide a diverse set of medicinally relevant substitutions. More importantly, the synthesis of catalysis precursors **67a** and **86a**, bearing a Boc group on the tethered nitrogen, will provide access to another manipulation site for functionalisation of the epoxybridged piperidine frameworks.

3.2. Diels–Alder studies to access novel pluripotent frameworks

3.2.1.1. Diels–Alder studies with en-ylides

The proficiency of the synthesised catalysis precursors was then investigated in the cascade protocol. Previous studies carried out in the Davies group highlighted the competence of homoallyl tethered ylides to undergo the desired Diels–Alder process, albeit with reduced conversions from the corresponding oxazole when a phenyl-functionalised ynamide was used as the coupling partner (Figure 10, **46a**). The increased flexibility and degrees of freedom of the longer alkene tether were thought to reduce the concentration of reactive conformation and heating to 110 °C was required for sufficient conversion. However, when thio- and cyclopropyl-functionalised ynamides were employed, a higher conversion was achieved at 90 °C (Figure 10, **46b-d**, page 24). Allyl tethered ylides share the same traits of increased flexibility and degrees of freedom, even requiring harsher conditions to achieve adequate conversion in the Diels–Alder process compared to homoallyl tethered ylides. When ylides **67a-d** were tested in the cascade reaction with thioynamides **73a-b**, in all cases consumption of the ynamide was achieved within 2 h, as monitored by TLC analysis, heating to 110 °C was required to achieve conversion from the corresponding oxazole, however gratifyingly the procedure was effective for all the ylides reacted with thioynamide **73a**, yielding polycycles **91a-d** in good yields (Scheme 20).



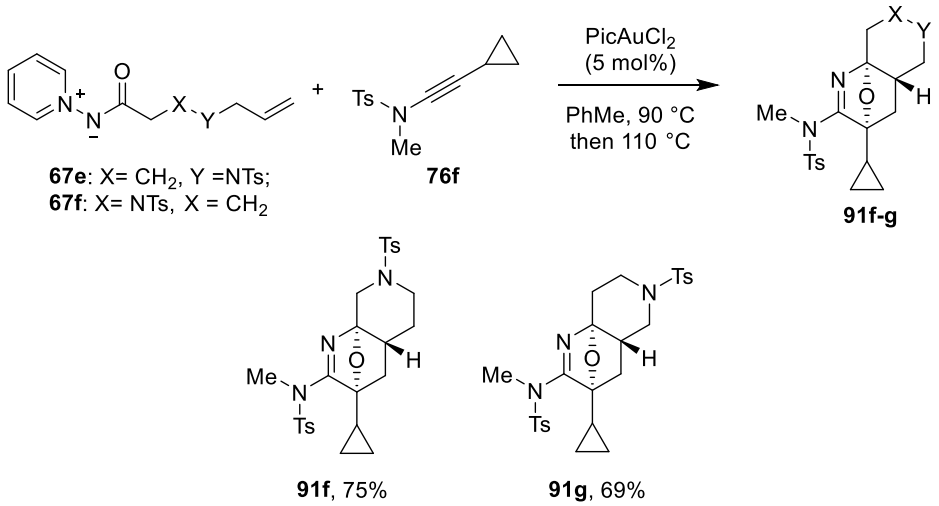
Scheme 20: Catalysis results obtained using allyl tethered ylides and thioynamides; [a]: 1.2 eq *N*-acyl pyridinium ylide; [b]: yield calculated from analysis of the ^{1}H-NMR spectra of the crude reaction mixture (internal standard: methyl 3,5-dinitrobenzoate).

Purification by flash column chromatography proved challenging for polycycles **91a-e** due to similar retention times with remaining oxazoles. Isolation of polycycles **91a-d** was achieved successfully after trituration of the mixture in hot ethanol, however **91e** could not be separated even through this procedure. Pleasingly no degradation to the hydroxypyridine *via* sulfide expulsion and aromatisation was observed in this series at 110 °C, in contrast with the previous example **46e** (Figure 10). Further studies into the fragmentation pathway *via* sulfide expulsion could represent an interesting strategy to access highly functionalised 2-amino-3-hydroxypyridines (Chapter 4.3.1). Carbamate protecting groups proved compatible with the allyl tethered ylide and were successfully installed onto polycycles **91a-b** along with desirable sulfonamides in polycycles **91c-d**.

Previous studies in the Davies group postulated that the choice of the sulfonamide at the ynamide could beneficially interfere with the polarity of the polycycles granting larger differences in the retention time on silica gel from the respective oxazole, albeit no trends were observed in order to identify an optimal sulfonamide. However, throughout the investigations

carried out for this thesis, it was found that also the position of the nitrogen on the tether could influence the polarity of the resulting polycycle relative to the remaining oxazole.

During the preparation of polycycles **91f** and **91g**, **91f** could be easily purified by flash column chromatography, whilst **91g** required trituration from hot isopropanol due to similar retention time with the remaining oxazole (Scheme 21).

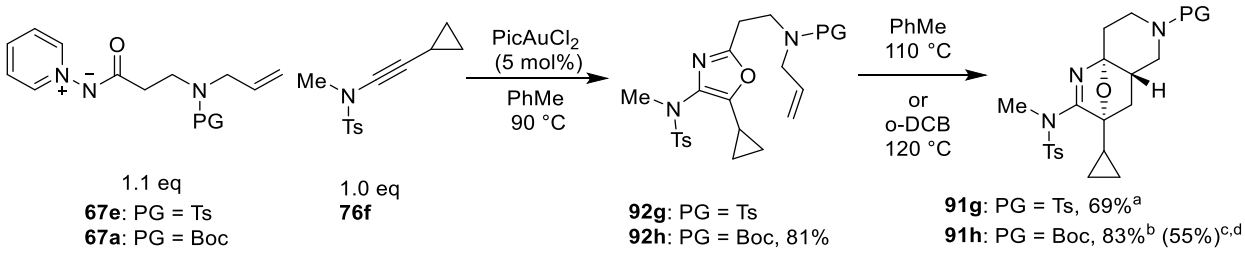


Scheme 21: Comparison between homoallyl and allyl tethered derived polycycles

Homoallyl tethered ylides generally resulted in more polar polycycles compared to their allyl tethered analogues, with the latter bearing retention factor on TLC very similar to those of the parent oxazoles, complicating the purification *via* silica gel flash column chromatography. This behaviour held true throughout the investigation of the allyl tethered series and further studies evidenced the possibility of separating the polycycles from unconverted oxazole *via* silica gel flash column chromatography using toluene: EtOAc as the eluent phase. However, this method was employed only for small scale reactions, whilst trituration from a suitable solvent was elected as the method of choice for larger scale processes.

To further expand the access to octahydronaphthyridine motifs, **67e** was tested in the cascade process with ynamide **76f** (Scheme 22). Whilst N-Ts allyl tethered oxazole **92g** successfully

provided the Diels–Alder product **91g**, moderate conversion to the desired polycycle was found from *N*-Boc allyl tethered oxazole **92h** when the Diels–Alder process was carried out at 110 °C (Scheme 22). Examination of the ^{1}H-NMR spectra of the crude reaction mixture revealed that, apart from minor impurities, the bulk of the material was a combination of the oxazole and Diels–Alder product, with conversion to the desired Diels–Alder product not exceeding 55% even after 24 h at 110 °C.[d] The reduced conversion to polycycle **91h** was tentatively attributed to the carbamate affecting the amount of reactive conformer available for the Diels–Alder reaction. An increased reaction temperature was exploited by previous member of the Davies group to enhance the rate of challenging Diels–Alder reactions and was found to have a positive effect also in this example. When the reaction between ylide **67a** and cyclopropyl-substituted ynamide **76f** was repeated, oxazole **92h** was isolated in excellent yield and resubmitted to the Diels–Alder process in o-dichlorobenzene at 120 °C, affording polycycle **91h** in excellent yield (Scheme 22).

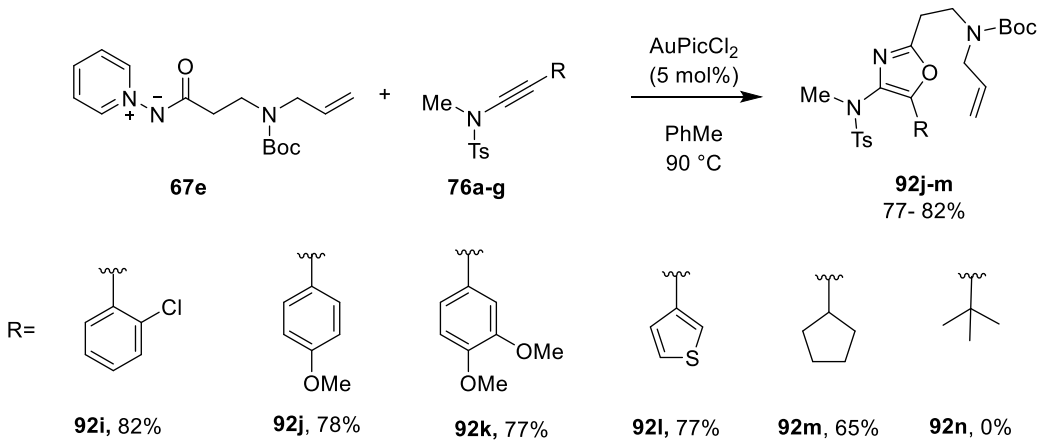


Scheme 22: Improved synthesis of 6,6-polycyclic systems in o-dcb; [a]: toluene, 110 °C, 16 h; [b]: o-DCB, 120 °C, 16 h; [c]: toluene, 110 °C, 24 h; [d]: ^{1}H-NMR conversion calculated using 3,5-dinitromethylbenzoate.

The entire synthetic sequence was also carried out in o-DCB in order to try and avoid the extra chromatographic purification at the oxazole step. Upon consumption of ynamide **76f**, temperature was raised to 120 °C to trigger the Diels–Alder reaction. Unfortunately, extensive degradation was observed by TLC analysis of the reaction mixture after 16 h at 120 °C. Since

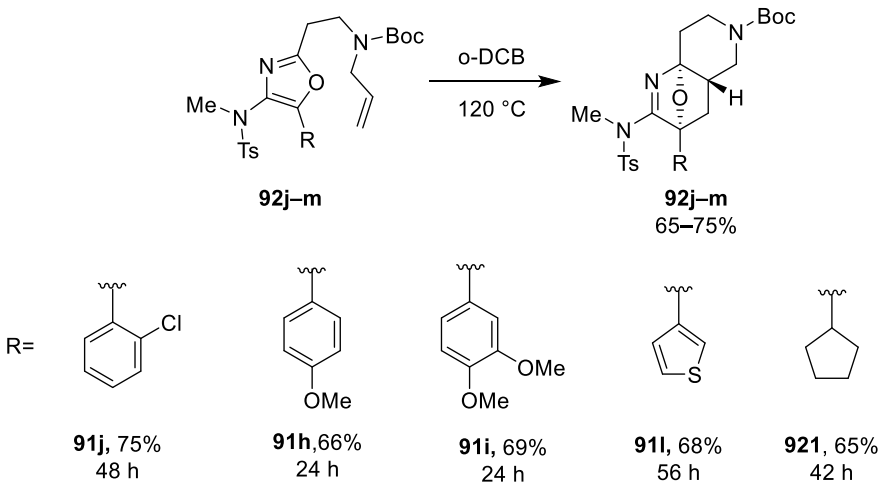
it was not possible to isolate the products derived from this reaction, a clear degradation pathway could not be elucidated, and it remained unclear if the gold catalyst could play a role in the formation of side products. However, despite the method evolving from a one-pot cascading cycloaddition to a 2-step double annulation, the process was upscaled to 21 mmol successfully. Due to the efficiency of the gold-catalysed process, oxazole **92h** was purified via a filtration through a pad of silica and **91h** was recrystallised from hot ethanol and obtained in excellent yield (repeated twice, at 21 mmol scale, 79% and 81%), completely avoiding chromatographic purifications. Thus far, these are the largest scale reactions of both the gold-catalysed 4-aminoxazole synthesis (previously: 13.0 mmol, Matt Ball-Jones)[91] and subsequent Diels–Alder process.

Ynamides **76a-g**, containing a range of alkyl, heteroaryl and functionalised aromatics, were then employed in the gold catalysed standard procedure to access oxazoles **92j-m** in good yields (Scheme 23), complete consumption of ynamides **76a-e** was achieved within 30 minutes. No oxazole formation was observed by TLC or LCMS analysis of the crude reaction mixture with *t*-butyl-substituted ynamide **76g**, this might result from the hindrance of the *t*-butyl substituent that hampered the formation of the initial ketenimminium by the gold-catalyst.



Scheme 23: Oxazole synthesis bearing a range of alkyl, heteroaryl and functionalised aromatics substitutents.

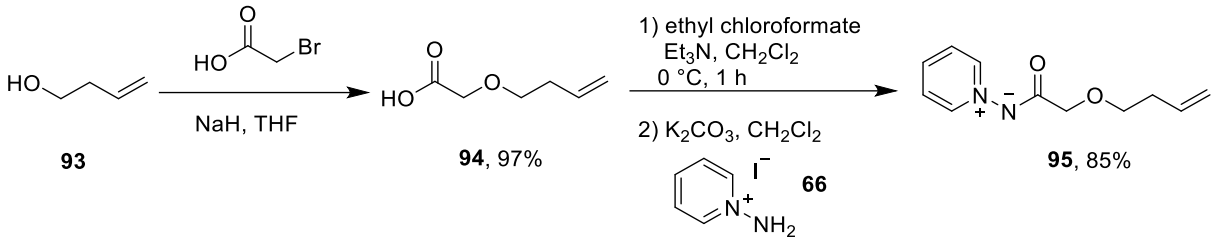
Although longer reactions time were necessary, good conversion to polycycles **92j-n** was achieved when oxazoles **91j-m** were subjected to the refined Diels–Alder conditions (Scheme 24). A variety of polycycles with aromatic-, heteroaromatic-, and alkyl-substitution were accessed bearing a carbamate protected nitrogen on the alkyl tether, proving the modularity of the method.



Scheme 24: Synthesis of epoxybridged naphthyridines.

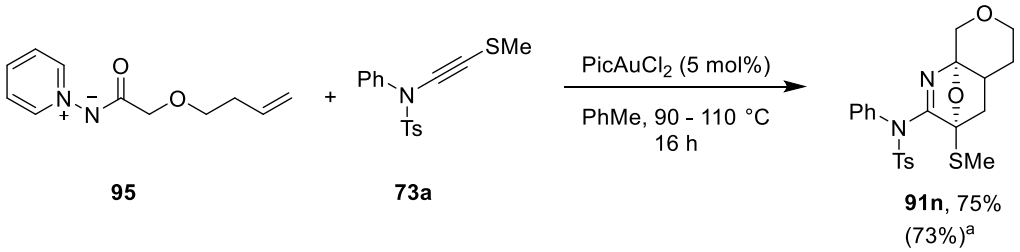
3.2.1.2. Diels–Alder studies with oxygen tethered en-ylides

To further expand the range of possible frameworks for the successive library elaboration studies, the heteroatom present of the ylide linker was changed. The synthesis of this polycyclic framework was previously successfully attempted by Matthew Wakeling.[90] For the scope of this thesis the synthesis of ylide **95** was up scaled to 78 mmol to provide enough material for the synthesis of the corresponding polycyclic framework. Starting from the alkylation of homoallyl alcohol **93** with bromoacetic acid to give acid **94**, a one pot formation of the mixed anhydride with ethyl chloroformate and successive reaction with 1-aminopyridinium iodide provided **95** in good yield (Scheme 25).



Scheme 25: Synthesis of oxygen tethered homoallyl ylide.

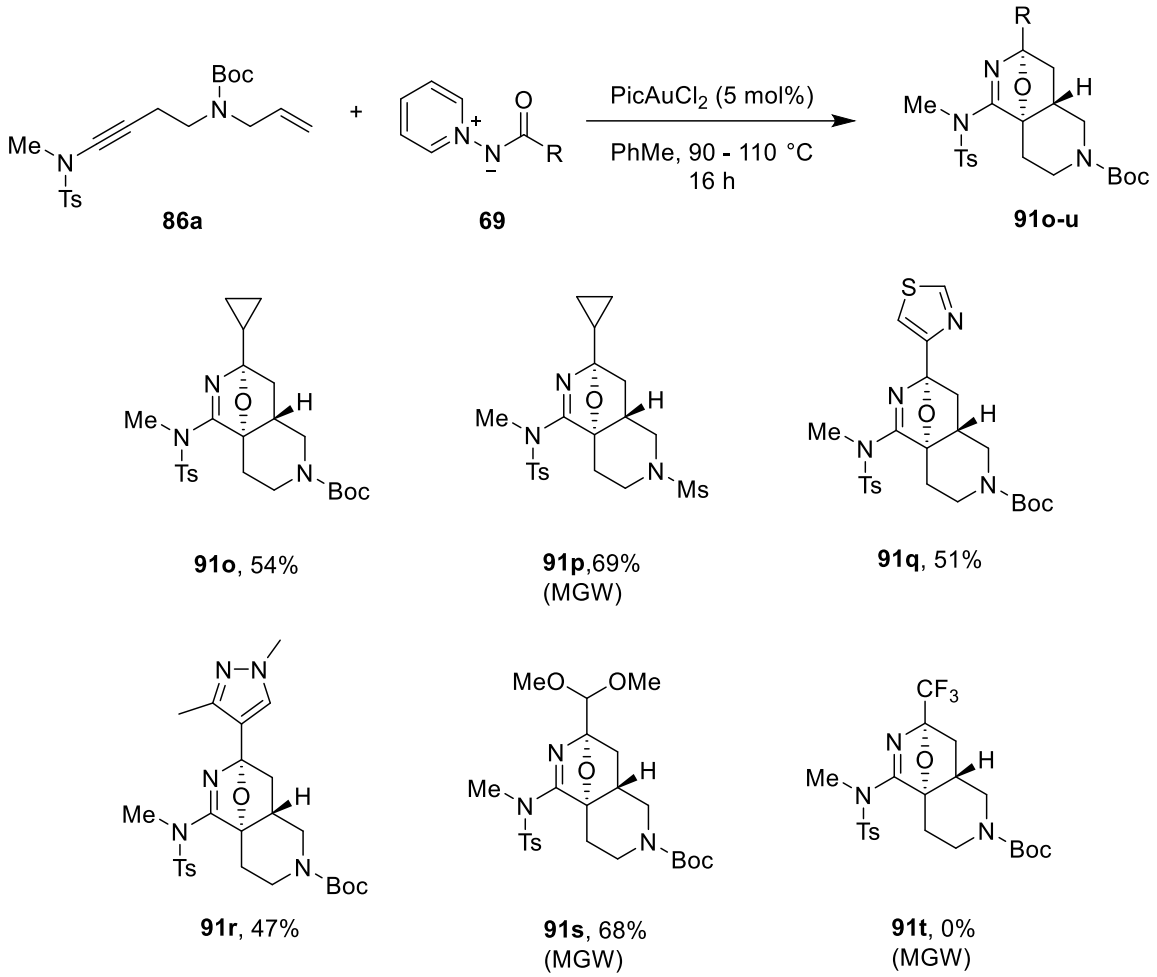
Ylide **95** was then reacted with thioynamide **73a**, oxazole formation was completed within 30 minutes and polycycle **91n** was obtained in excellent yield after heating the reaction mixture for 16 h at 110 °C. An excellent yield was also obtained when the process was up scaled to 15 mmol.



Scheme 26: Synthesis of an oxygen tethered polycycle. [a]: 15.6 mmol scale

3.2.1.3. Diels–Alder studies with en-ynamides

The C5 Diels–Alder series was investigated in a limited manner, the results presented thereafter are a combination of the joint efforts between the author and Matthew Wakeling.[90] 1,7-enynamide **86a** was tested in the cascade reaction, where raising the reaction temperature to 110 °C upon consumption of the ynamide was required for Diels–Alder reaction to occur (Scheme 27).



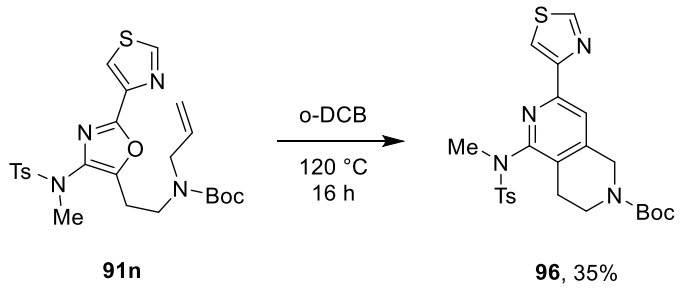
Scheme 27: Cascade products from 1,7-enynamides.

The results for this series mirrored the ones obtained for the C2 Diels–Alder series, cyclopropyl derivatives **91o**–**t** served as useful comparative tool, with the carbamate protected 1,7-enynamide **91o** yielding lower conversion compared to the sulfonamide protected enynamide **91p**. Higher temperatures were required but pleasingly did not result in decomposition.

Although moderate yields were obtained, polycycles **91q**–**r** incorporated medicinally relevant substitutions, proving the capability of the method in providing access into very highly functionalised polycycles. Polycycle **91s** was obtained in good yield, the dimethyl acetal moiety represents a masked manifold to exploit for further functionalisation after post-catalysis transformation. Trifluoromethyl ylide was tested to access polycycle **91t** in the attempt to

expand the range of medicinally chemistry substitution, however oxazole formation was not successful, and analysis of the ^{1}H-NMR spectra revealed only starting material recovery.[90]

To improve the conversion rate, the oxazole recovered from the reaction to polycycle **91q** was heated in o-DCB at 120 °C (Scheme 28). The transformation carried out at this temperature resulted in a very unclean reaction mixture, from which pyridine **96** was recovered in low yield.



91n **96**, 35%

Scheme 28: Attempted conversion at higher temperature resulted into the degradation to pyridine 92a.

These preliminary studies showed the proficiency of 1,7-enynamides in providing access into sp^{3}-rich complex frameworks bearing a decahydro-1,6-naphthyridine core, however further investigation is needed in order to improve the rate of the conversion to these highly functionalised polycycles.

3.3. Summarising the pluripotent frameworks synthesis

Allyl tethered ylides, however, proved capable coupling partners for the gold-catalysed oxazole formation and subsequent Diels–Alder process, albeit generally requiring higher temperature to access adequate conversion compared to homoallyl tethered ylides. Polycycles **91a-m** were obtained in good yields and their synthesis required only minimal optimisation of the reaction temperature moving from thioynamides to aryl-/alkyl- substituted ynamides (Figure 15). A range of different protecting groups was installed onto the tethered nitrogen, more importantly Boc-protected polycycles were successfully synthesised in combination with both thioynamides

and aryl-/alkyl- substituted ynamides, providing access to a set of highly functionalised polycycles bearing relevant medicinal chemistry substitutions and easily cleavable protecting groups.

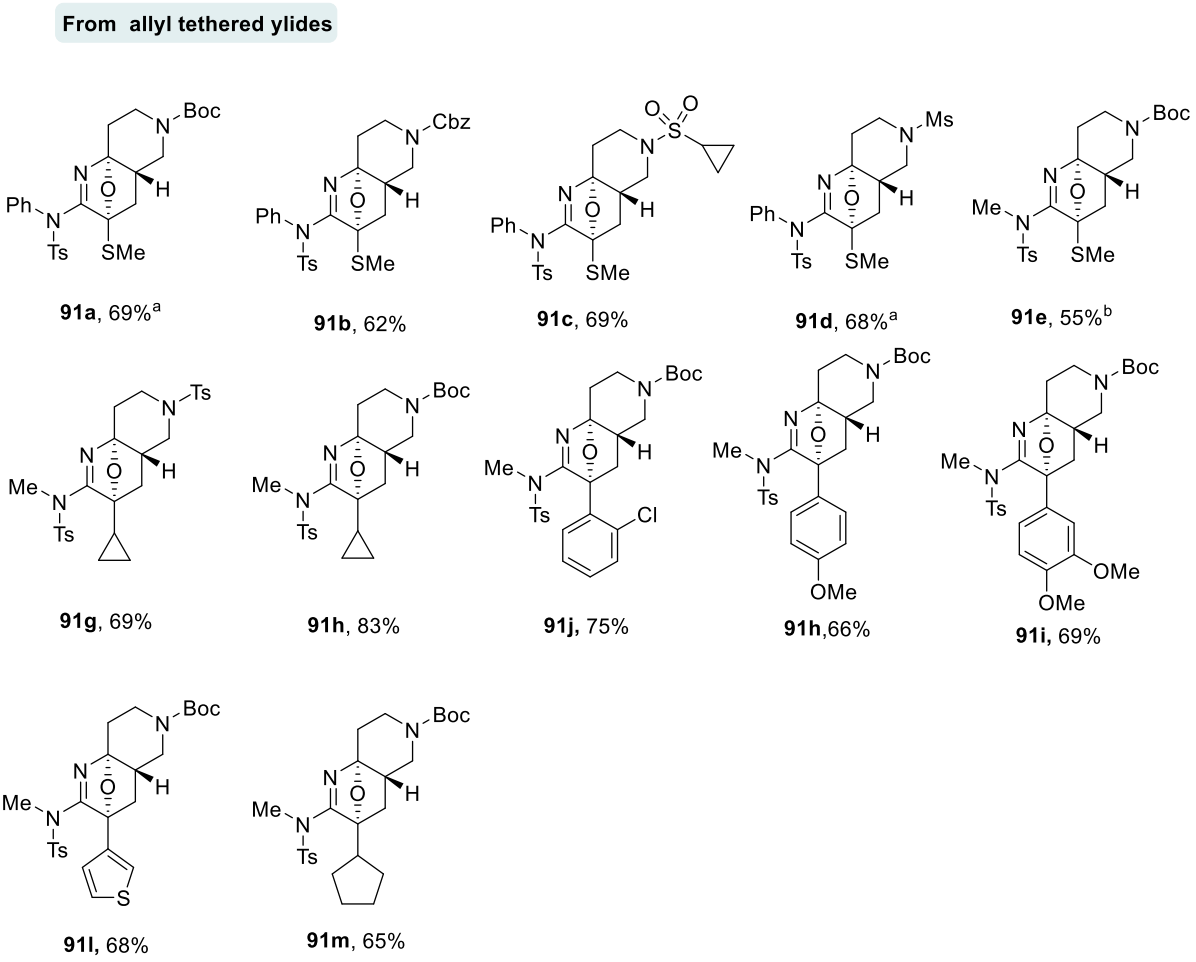


Figure 15: Summarised results for the gold-catalysed double annulation of allyl tethered ylides.

1,7-enynamides were also briefly investigated and their proficiency to undergo the gold-catalysed double annulation process was confirmed (Figure 16). A range of pharmaceutically relevant substitution was installed on this pluripotent framework, and the Boc-protected nitrogen on the alkyl tether of the ynamide was found compatible with the process. With a significant amount of material, attention was turned to post-catalysis modifications.

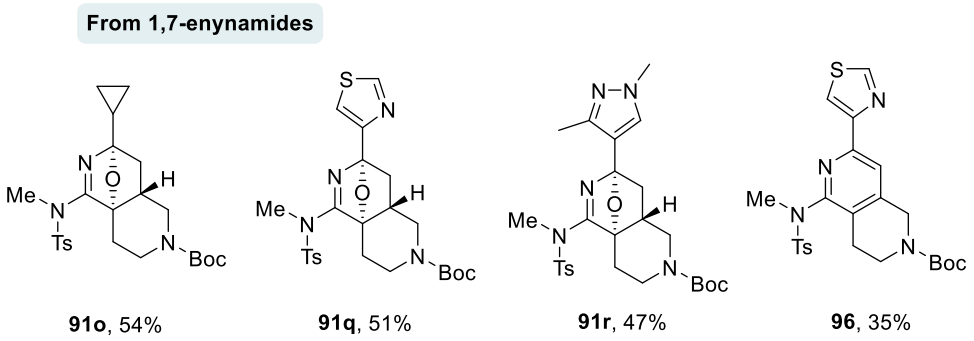


Figure 16: Summarised results for the gold-catalysed double annulation of 1,7-enynamides.

4. Chapter 4: Framework Elaboration and Scaffold Synthesis

With a range of polycycles in hand, the pluripotency of the embedded functionalities installed in the gold-catalysed transformation was investigated, with a focus on how to exploit these complex frameworks to access decahydro-1,6-napthyridine based scaffolds. The transformations described in this chapter used polycycles obtained through the C2 Diels–Alder series. Polycycle **91g** was chosen to benchmark the reactivity and optimise the reactions that were then applied to **91h** (Figure 17). These polycycles were preferred over others in the series due to the higher conversion rates and successful synthesis at multigram scale. The cyclopropyl-substitution was considered to have a positive impact to the resulting final molecules due to its reduced molecular weight, that would allow for a larger scope in library design. Furthermore, the cyclopropyl fragment has been increasingly utilised in the past years in drug discovery programs to improve pharmaceutical properties of the synthesised molecules.[92] The reactivity of thioynamide **73a** derivatives was also investigated, in particular that of **91n** (Figure 17), in order to access a diverse set of scaffolds from which a library could be elaborated.

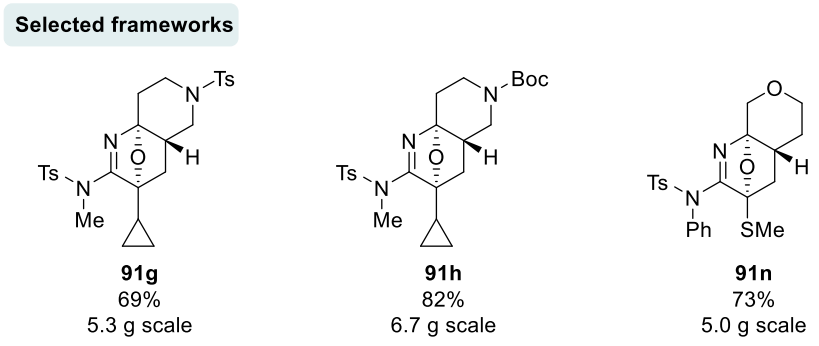
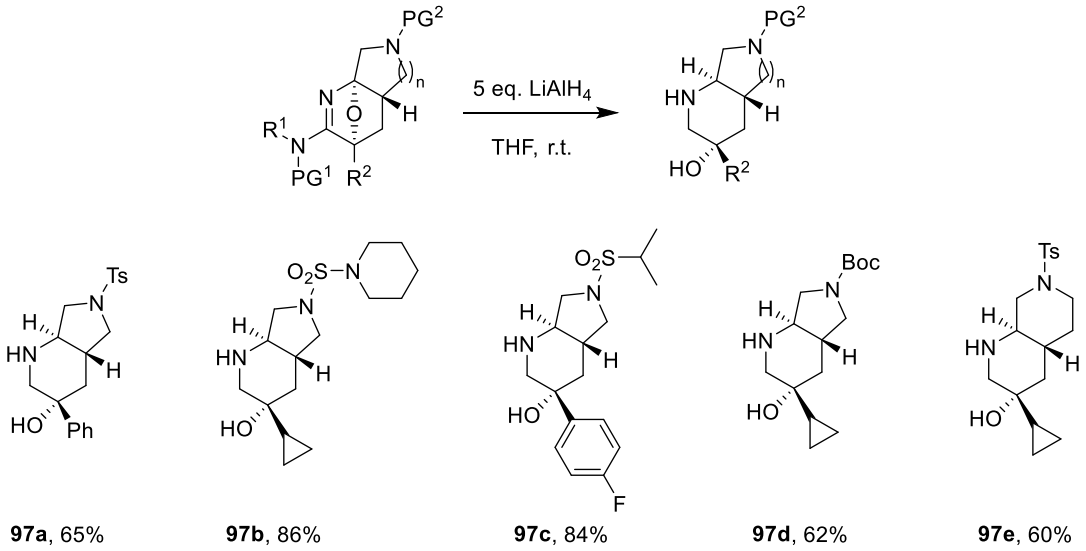


Figure 17: Selected frameworks for post-catalysis transformation. Yield is reported from the gold-catalysed step, scale is referred to amount of ynamide used.

4.1. Reductions and oxidations to decahydro-1,6-naphthyridine derivatives

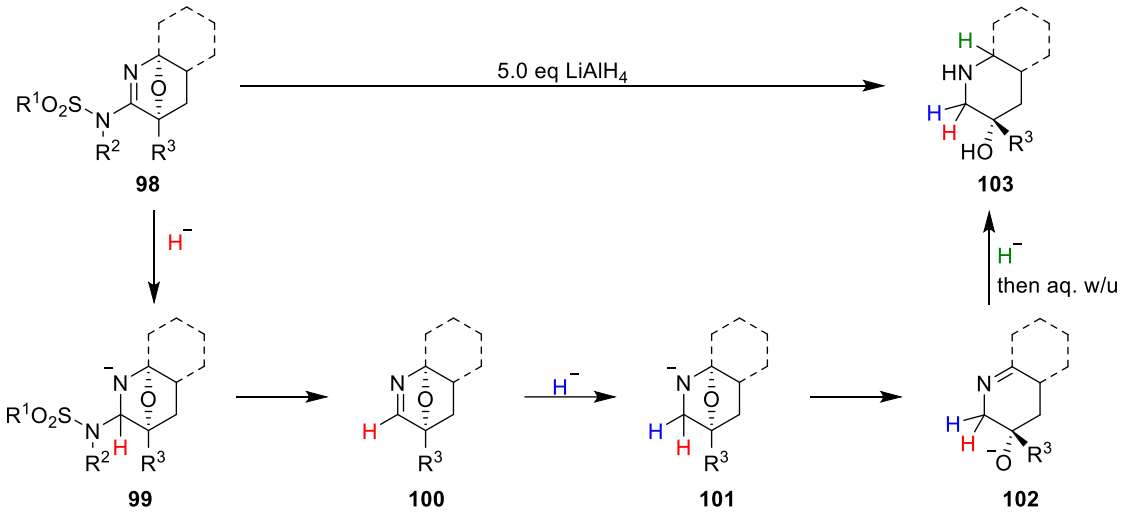
Previous results from the Davies group demonstrated the reactivity of the amidine moiety towards a reduction procedure with $LiAlH_4$ to access fused piperidines scaffolds such as **97a-e** (Scheme 29). Reduction of sulfonyl amidine motifs are known in the literature,[93, 94] but only few examples of cyclic variants are reported and none containing a cyclic ether bridge.



Scheme 29: Diastereoselective LiAlH4 reduction to access fused piperidine scaffolds.

This procedure directly and selectively provided *trans*-ring fused piperidines bearing a secondary amine and a tertiary alcohol that could be exploited as reactive points for further decoration. The protocol proved general, and a variety of functionality was tolerated affording a range of fused piperidines, bearing sulfonyl protecting groups **97a-c**. Pleasingly, the methodology worked well also to deliver Boc-protected polycycle **97d**, however this was the only example so far in which the carbamate survived reduction, whilst other examples showed inconsistent reactivity. The same stereochemical preference for a *trans* ring junction was observed when 6,6-bicyclic frameworks were used to deliver **97e** in good yield.

The reduction selectivity was rationalised by the mechanism shown in Scheme 28. The initial hydride addition to **98** was proposed to occur at the amidine moiety to give **99**, that could then evolve through the cleavage of the ether bridge or sulfonamide elimination to deliver imine **100**. The diastereoselectivity of this transformation derives from the events triggered by second hydride addition to **100** that could result in the cleavage of the cyclic ether bridge via cyclic hemiaminal **101** to give key intermediate imine **102**. Hydride addition to **102** controls the stereochemical outcome and delivers **103** upon aqueous workup.



Scheme 30: Plausible reaction mechanism for multistep reduction.

It was not completely clear whether sulfonamide expulsion happens before the cleavage of the cyclic ether bridge. The complete stereoselectivity of the process was hypothesised to derive from imine **102** adopting a half chair and twist-boat conformation for ring a and b respectively after cleavage of the ether bridge, represented in **102a** in Figure 18.[90] Hydride can approach from both faces of the reduction centre C1 that must shift to accommodate for the tetrahedral geometry. Hydride addition to the bottom face then results in a boat-chair conformation **104a**, whilst addition to the top face results in energetically disfavoured boat-skew boat conformation **105a**. Energy differences between conformations **104a** and **105a** provides complete kinetic control over the stereoselectivity of the reaction. This hypothesis is corroborated by related

examples in the literature, where *trans* ring junctions were accessed from the reduction of bicyclic imines **106**[95] and **108**[96] (Figure 18).

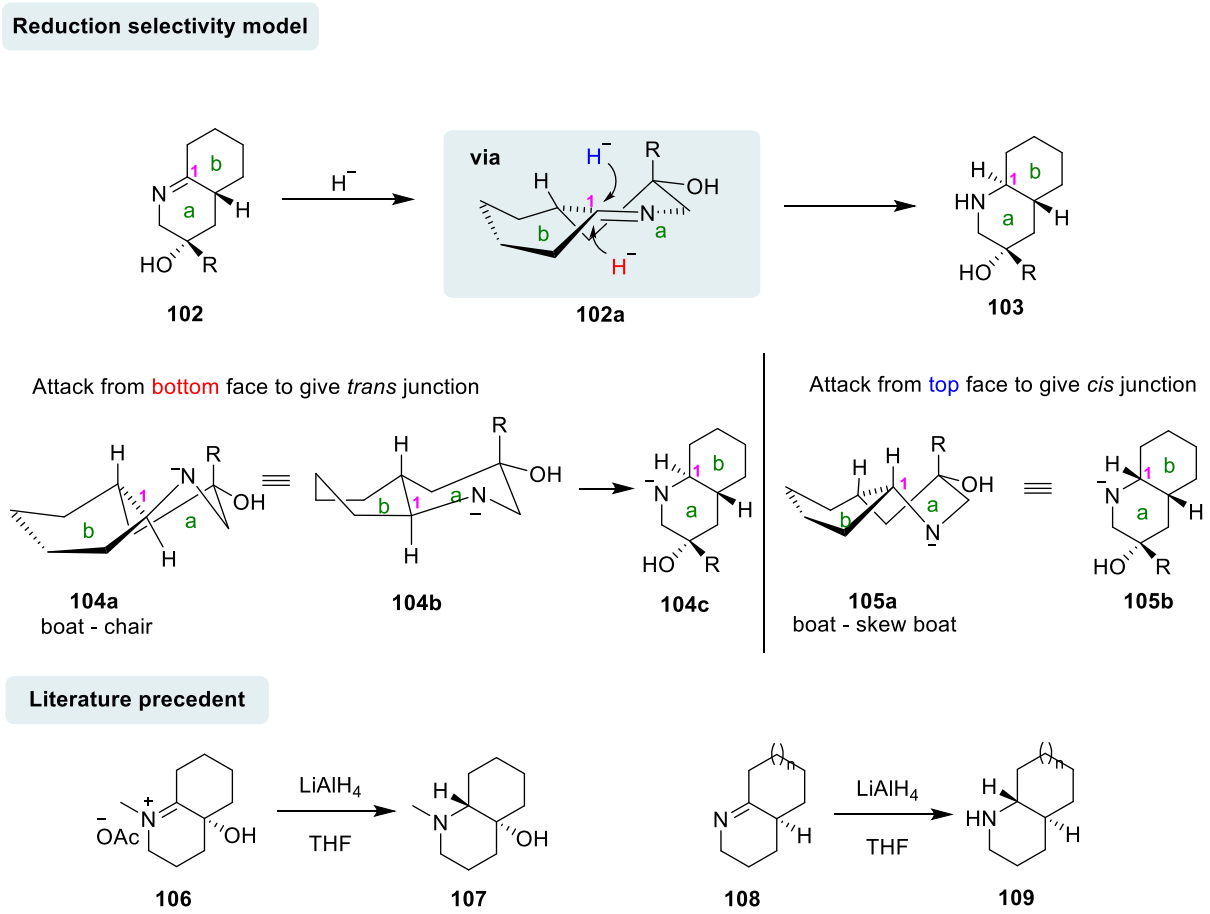
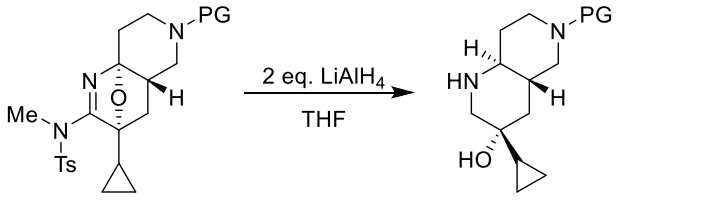


Figure 18: Reduction selectivity three-dimensional models.[90]

With these preliminary results in hand, further investigation of the process was undertaken to achieve improved yields by refining the protocol used previously within our group. These improvements looked primarily at the reduction of the equivalent of $LiAlH_4$ utilised and at the modification of the work-up procedure specifically aimed at the scaling up of the synthesis to deliver decahydro-1,6-naphthyridine derived scaffolds.

With the potential of up to four hydrides per equivalent of $LiAlH_4$, lowering the reducing agent required was explored.[97] This was particularly desirable when considering the scalability of this process, as reactive and exothermic nature of $LiAlH_4$ and its subsequent quenching became

more of a concern. Reduction of polycycle **91g** was attempted with 1 equivalent of $LiAlH_4$, after 8 hours leftover starting material was still detected *via* TLC and LCMS analysis of the crude reaction mixture (Scheme 31). However, even if mechanistically one equivalent of reducing agent should be sufficient, the reducing power of subsequent hydrides may not be as potent requiring a slight excess to achieve full conversion and the reaction was repeated with 2 equivalents of $LiAlH_4$. This time complete consumption of polycycle **91g** was achieved within 3 h. The work up procedure previously designed in our group was applied, this consisted of quenching the reaction with Rochelle's salt and subsequent extraction of the organics with a 3:1 mixture of $CHCl_3$/*i*PrOH. However, the extractive work up resulted in a poor mass recovery and subsequent low yield of 33%. The procedure was modified to a filtration work up through celite with a 3:1 mixture of $CHCl_3$/*i*PrOH upon addition to the reaction mixture of the minimal amount of water to quench the excess of reducing agent and successive addition of a 20% $NaOH_{(aq)}$ solution to break Li aggregates and trigger LiOH formation. With this new work up procedure mass recovery greatly improved and subsequently the yield increased from 33% to 88%. The same conditions were applied to polycycle **91h**, pleasingly the carbamate survived and aminoalcohol **110b** was isolated in 90% yield as a formic acid salt after acidic reverse phase column chromatography (Scheme 31).



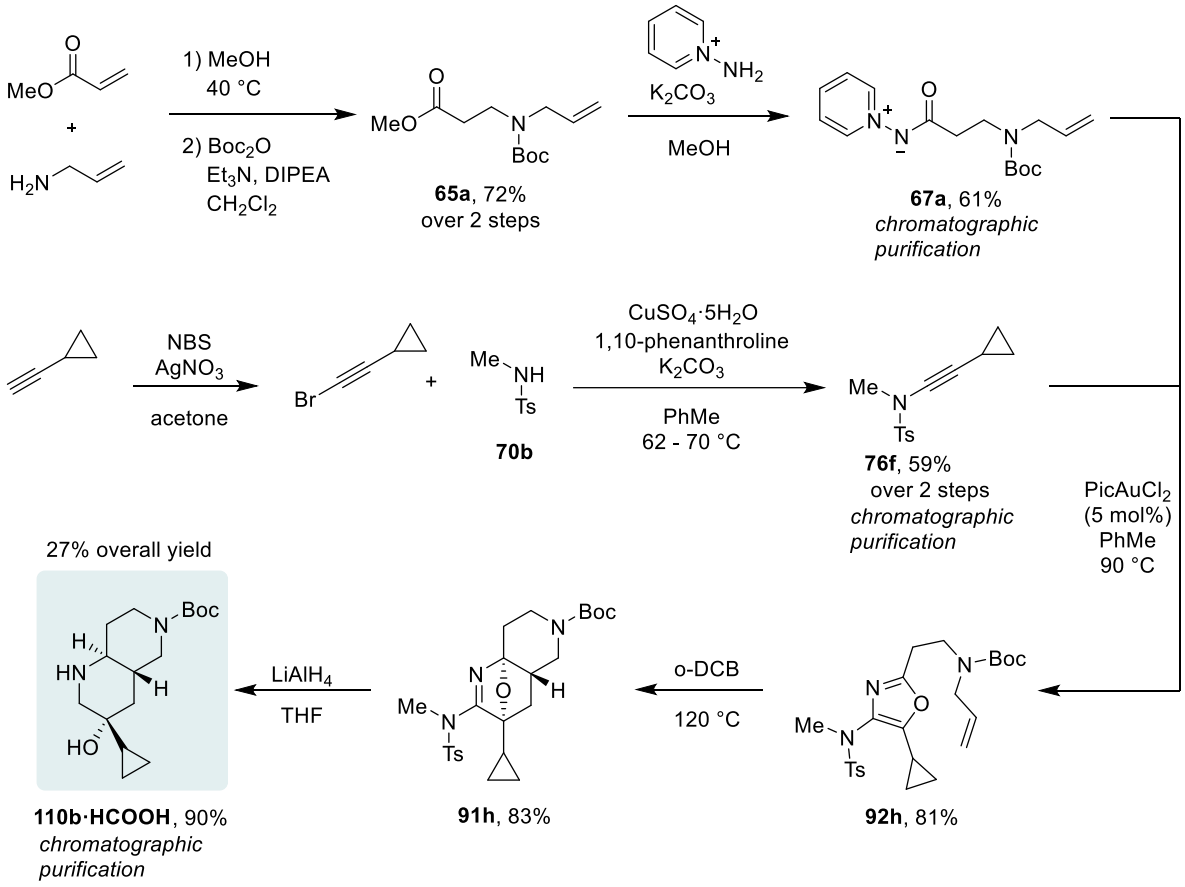
91g, PG = Ts
91h, PG = Boc

110a, PG = Ts, 88%
110b·HCOOH, PG = Boc, 90%

Scheme 31: Reduction of polycyclic frameworks to access the decahydro-1,6-napthyridine core.

With the reduction of **91h** to **110b**, the synthetic gap found in the synthesis of decahydro-1,6-naphtiridine scaffolds was addressed. The methodology provides a modular access to a NP-like

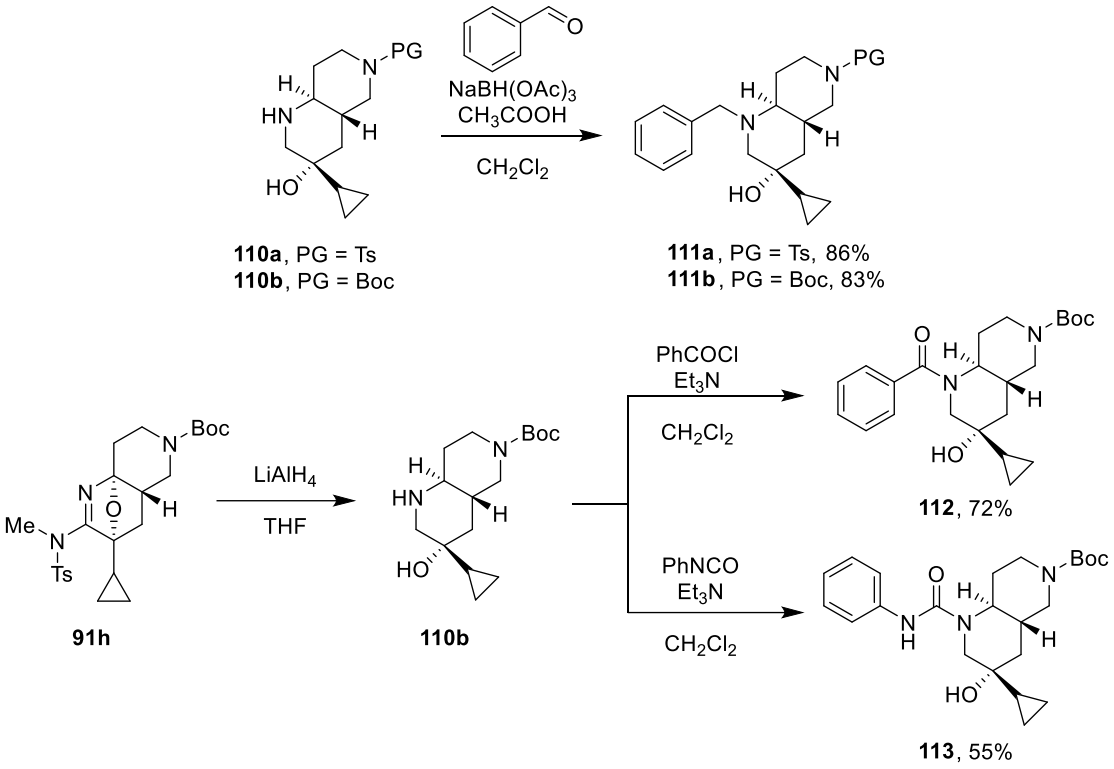
scaffold, bearing two secondary amines, one of which protected with an easily cleavable protecting group and a relevant medicinal chemistry substitution attached to the carbon skeleton. The synthesis, with the longest linear synthetic sequence of five steps, yields aminoalcohol **110b** in excellent 27% overall yield, with only three chromatographic purifications (Scheme 32).



Scheme 32: Summary synthetic scheme for aminoalcohol 110b

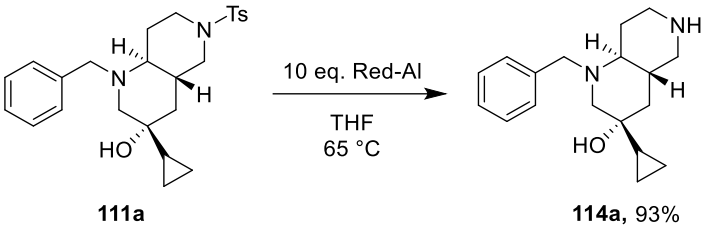
Attention then turned to the exploration of the reactivity of aminoalcohols **106a-b** towards common functionalisation reactions used in parallel chemistry and the investigation of deprotection procedures. Aminoalcohols **106a-b** were submitted to reductive amination conditions with benzaldehyde, yielding polycycles **111a-b** in excellent comparable yields (Scheme 33). Since **110b** would represent an ideal scaffold candidate, further studies into its reactivity were undertaken. The compound reacted well in both amide and urea formation

reactions yielding **112** and **113** in good yields. However, the process was modified, a two-step procedure was envisioned where the functionalisation reaction occurred directly on the crude material from the reduction of **91h**, avoiding the chromatographic purification of **110b**. This procedure performed well for both amide coupling and urea formation with good yields obtained for both **112** and **113** over two steps (Scheme 33). Disappointingly, functionalisation *via* reductive amination did not perform as well when undertaken from the crude product of **110b**. Conversion proceeded slowly, and traces of unreacted starting material could still be detected after 24 h, with purification yielding **111b** in a moderate 52%. Nevertheless, aminoalcohol **110b** showed a good comprehensive reactivity towards the most common reactions used in parallel chemistry, confirming its proficiency as a potential scaffold. The substitutions were chosen to minimize influence on the design of the future library and to maximise practicality since the benzene ring could easily be visualised under UV light. This choice was made in relation to the assessment of the purities and purifications of the compound libraries. Purity, for library compounds, was assessed *via* integration of the area under the peak detected during UPLC analysis. If no UV-active substituents were installed on the molecule, purity would have had to be assessed *via* ELSD detectors, that are not always reliable in these types of analyses. Therefore, installing an UV-active substituent on the scaffold itself left open the possibility to instal fully saturated substituents during the library synthesis step.



Scheme 33: First elaborations on the decahydro-1,6-naphtyridine scaffold.

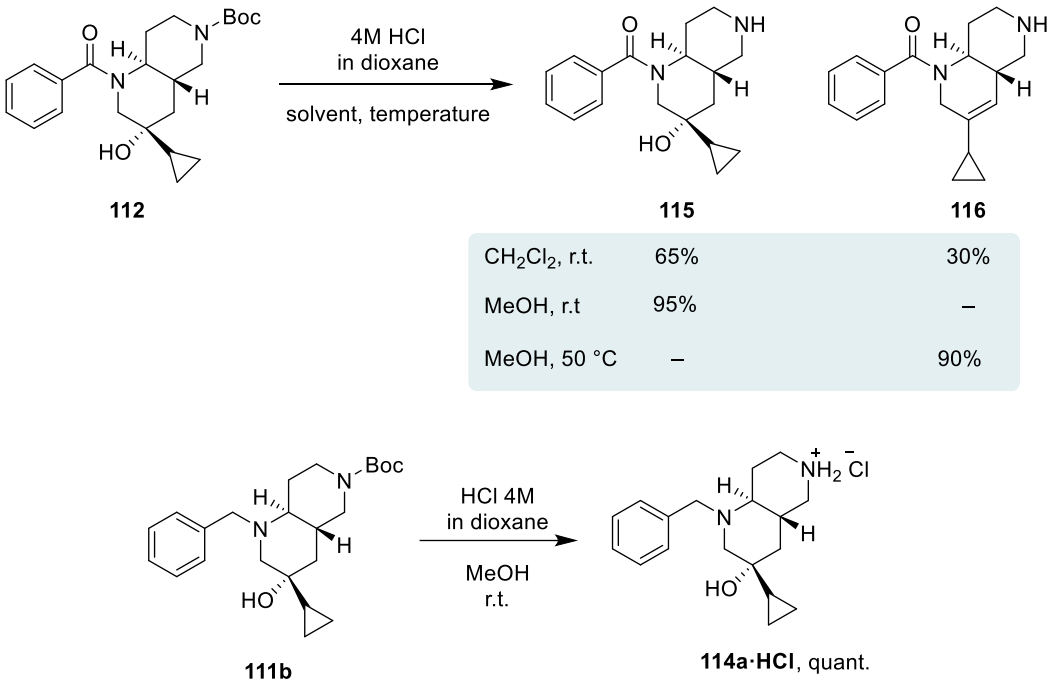
The next step in validating of **110a-b** as high quality scaffolds was the investigation of deprotection conditions. De-tosylation is known in the literature, and various methods have been reported and share either harsh conditions,[98] or the use of expensive reagents.[99] Reductive cleavage of the tosyl protecting group was attempted with Red-Al in refluxing THF,[100, 101]and polycycle **114a** was obtained in good yield upon extractive work up (Scheme 34). The deprotection gave positive results but the strong reducing environment needed for the de-tosylation procedure would present compatibility issues with substrates bearing reduction-sensitive substituents, such as amide derivatives, limiting the choice of substitution at the nitrogen next to the ring junction.



111a **114a**, 93%

Scheme 34: De–tosylation procedure.

Therefore, attention turned to the deprotection of polycycle **112**, Boc-deprotection usually offers higher functional group tolerability. When polycycle **112** was treated with HCl in CH_2Cl_2, full consumption of starting material occurred in 24 h, however elimination product **116** was also isolated alongside the desired deprotected aminoalcohol **115** (Scheme 35). Reduction of the number of equivalents of acid resulted in incomplete consumption of starting material and both products were still detected *via* LCMS analysis of the crude reaction mixture. The solvent was switched to MeOH in an attempt to favour E1 elimination to product **116**, however counterintuitively compound **115** was isolated in almost quantitative yields after 16 h at room temperature. This result was tentatively attributed to the large excess of small MeOH molecules tapering the acid ability to protonate the hindered tertiary alcohol. Repeating the reaction at 50 °C to favour the elimination furnished **116** in excellent yield. The revised conditions for Boc-deprotection were applied to polycycle **111b**, providing **114a·HCl** in quantitative yield.

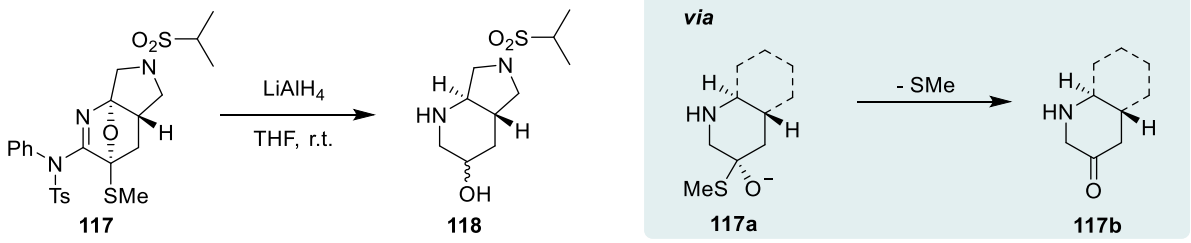


Scheme 35: Boc-deprotection conditions and results.

Compounds **114a/b**, **115** and **116** were chosen as scaffolds for a compound library which synthesis and design are described in Chapter 5.

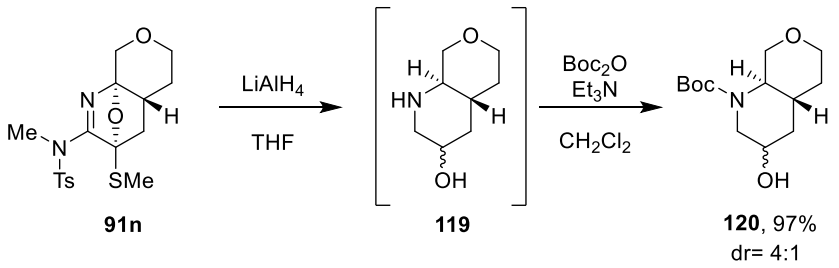
4.1.1. Exploring the reactivity of thioketals polycycles

The reduction of thioketal polycycles such as **117** was also attempted. Previous examples with similar substrates resulted in diastereomeric mixtures of aminoalcohols **118** (Scheme 36). This result is prompted by the *in-situ* expulsion of the methylsulfide moiety and subsequent formation of aminoketone **117b**, that is further reduced by $LiAlH_4$.



Scheme 36: The prior reduction of a thioketal bearing substrate by Matthew Wakeling.

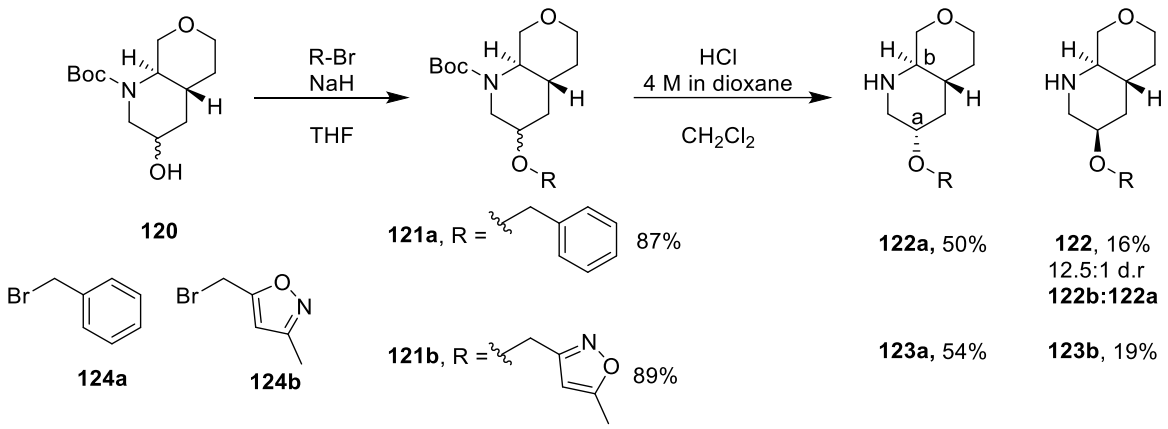
Thioketal polycycle **91n** was reduced following the initial protocol developed in our group (5.0 eq. $LiAlH_4$, aqueous work up). The reaction mixture was heated to reflux, and to achieve complete consumption of the starting material, complete reduction was obtained in 3 h. However, mass recovery for aminoalcohol **119** was poor when the standard protocol was applied. The synthesis was modified to include a Boc protection performed on the crude material of **119** after work up, in order to decrease the inherent polarity of the product molecule (Scheme 37). Following this modification polycycle **120** was obtained in 47% yield. A great improvement of the yield to 97% was obtained when the aqueous work up was changed to the filtration work up (described for **110a-b**, Scheme 31). However, separation of the diastereoisomers proved challenging *via* both silica flash column chromatography and supercritical fluid chromatography (SFC). The reduction-Boc protection two-step method was up scaled to 11.0 mmol, providing **120** was obtained in 42% overall yield with the longest synthetic sequence consisting of 6 steps.



Scheme 37: Reduction of thioketal polycycle 91n.

Functionalisation of polycycle **120** was continued as a mixture of diastereoisomers and their separation was attempted at each subsequent step. To this end, alcohol **120** was alkylated with bromoalkanes **124a-b** to yield amino ethers **121a-b**, followed by carbamate deprotection to give aminoethers **122a-b** and **123a-b**. Separation of the diastereomers was unsuccessful before carbamate deprotection, *via* both silica gel flash column chromatography and SFC, but

successful afterwards using SFC purification to give aminoethers **122a** and **123b** as the major products (Scheme 38).



Scheme 38: Aminoalchol 120 initial elaboration via ether formation and boc-deprotection.

The stereochemistry of the major product **122a** was confirmed by analysis of the ^{1}H-NMR spectrum, confirming the structure with the ether *syn* to H_b. Analysis of the coupling constants of proton H_a observed values of 10.3 and 4.5 Hz, consistent with θ = 180 ° and θ = 60 °. The other diastereomer **122b** would observe *J* values of similar magnitude from dihedral angles θ = 60 ° in the range of 2–5 Hz (Figure 19). This observation is consistent with the reduction of similar substrates attempted previously in our group.[90]

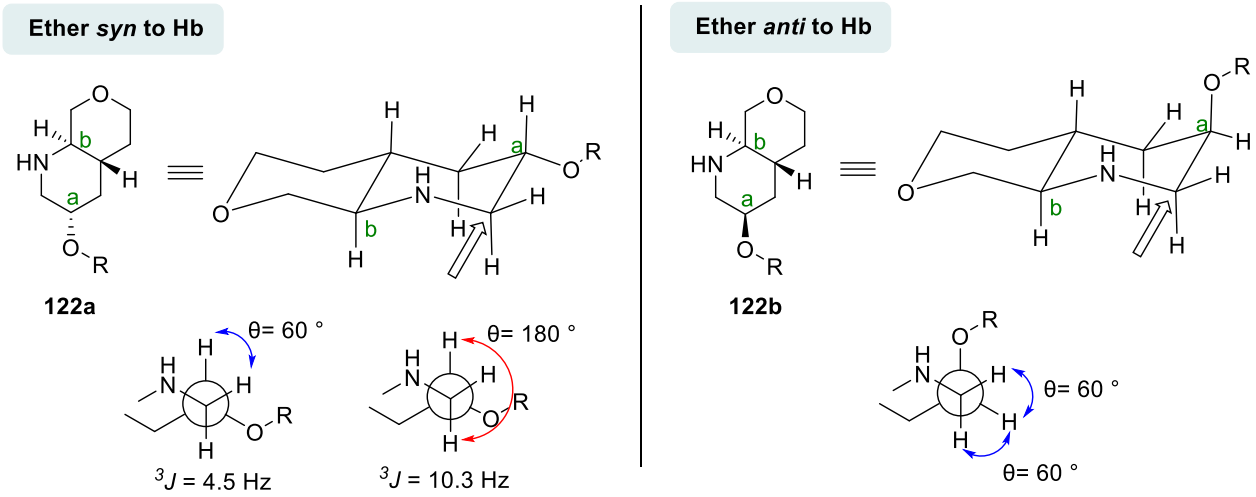
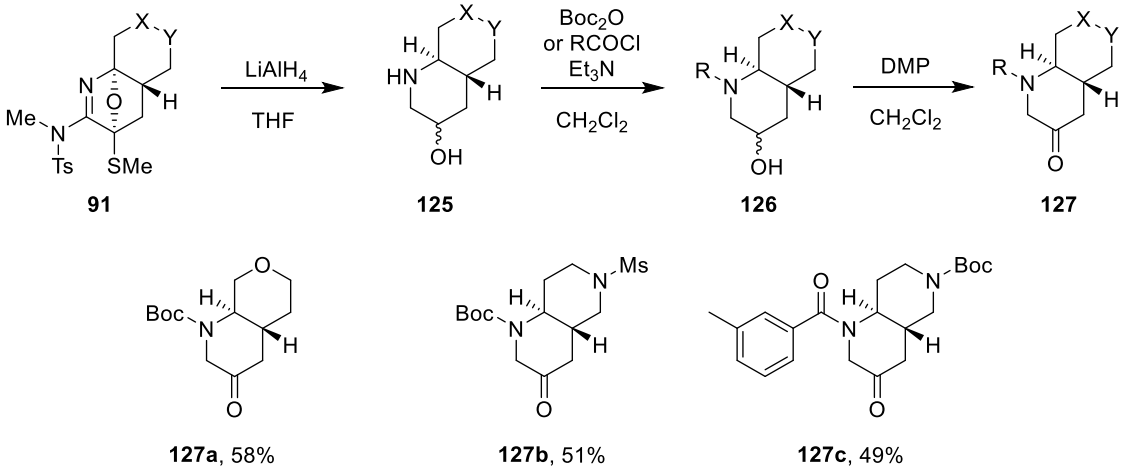


Figure 19: Model illustrating ether stereochemistry from analysis of *J* couplings in the ^{1}H-NMR spectra

A different approach was then sought that removed the need for separation of diastereoisomers. To this end, 1,3-amino ketones were prepared in a three-step reduction-amine substitution and oxidation procedure (Scheme 39), with purification only performed in the final steps affording products **127a-b**. The reaction was successful starting from three different frameworks, moreover the procedure was found to be compliant with both nitrogen protection or direct functionalisation.

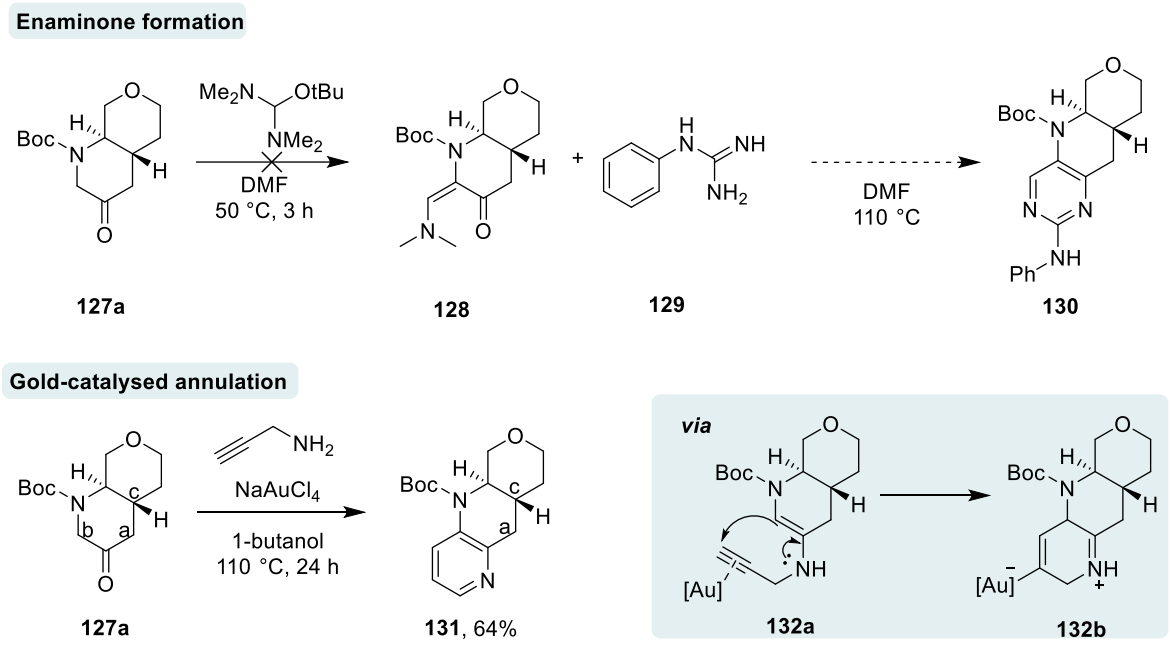


Scheme 39: Preparation of aminoketone derivatives.

The ketone functionality was exploited to increase the skeletal diversity of the scaffold rather than being used a simple point of variation. To this end, the formation of fused *N*-heteroaromatic rings from the ketone was investigated. In particular, pyridine[102] and pyrimidine[103] derived scaffolds are a class of heterocyclic molecules that possess a broad range of biological and pharmacological activities. Installing these functionalities directly fused to the carbon skeleton would represent a great opportunity to both test the reactivity of the embedded ketone and increase the skeletal diversity of the accessible scaffolds.

Enaminones are versatile functionalities in organic synthesis, especially as precursors for various heterocycles, their preparation usually involves the reaction with orthoformic acid

derivatives based on DMF or aminal derived formates.[104] Pyrimidine **130** synthesis was attempted *via* enaminone formation from ketone **127a** and then condensation with phenyl guanidine (Scheme 40). However, formation of intermediate **128** was not observed *via* TLC or LCMS analysis of the crude reaction mixture and the method was not pursued further. However, a different approach was successful in installing a pyridine ring *via* a gold-catalysed annulation between ketone **127a** and propargyl amine as a single regioisomer (Scheme 40).[105] This reaction was suggested to proceed through a sequential amination of the carbonyl compound followed by a 6-*exo-dig* cyclisation of the propargylenamine intermediate **132a** (Scheme 40) followed by aromatisation to deliver pyridine derivative **131**.[105]



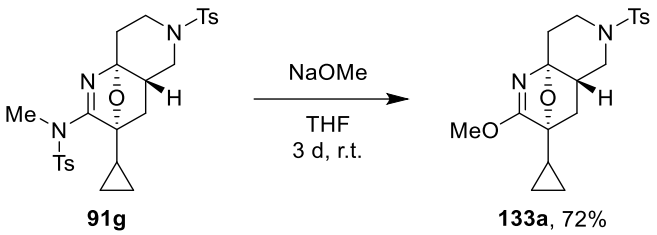
Scheme 40: Formation of a tricyclic structure from aminoketone 127a.

The regioselectivity of the reaction was confirmed comparing ^{1}H-NMR spectra of **127a** and **131**. Analysis of the COSY spectrum of **131** showed protons H_a coupled to H_c, additionally H_a resonances shifted downfield from 2.45 and 2.23 in **127a** to 2.79 and 2.61 in **131**. The regioselectivity is thought to be driven by the electronic bias of the nitrogen during the enamine

intermediate formation **132a**, and it is consistent with previous examples of reactivity of piperidonenamines.[106, 107]

4.2. Methyl imidates formation to hexahydro-triazolo-1,6-napthyridine derivatives

The ability to prepare fused rings from the amidine moiety was explored. Another elaboration was discovered, when polycycles were treated with NaOMe in THF to access the cyclic methyl imidate **133** (Scheme 41). Methyl imidates have been widely exploited for the synthesis of various heterocycles such as quinazolines,[108] triazoles,[109] imidazoles,[110] and benzimidazoles.[111] Imidates are generally synthesised via the Pinner reaction[112] involving the acid-catalysed alcoholysis of a nitrile or, most commonly, via direct alkylation of an amide.[113] However, the latter method presents the intrinsic issue of competing *N*- versus *O*-alkylation. Few examples have been reported in the literature regarding the selective *O*-alkylation of amides or lactams upon treatment with diazomethane[114] or trialkyloxonium tetrafluoroborates[115] (Meerwein's salt). Literature precedent has shown the ability of sulfonyl amidines to undergo substitution with various nucleophiles with the expulsion of the sulfonamide motif.[116] Treatment of amidines with alkoxides have been reported,[117] however the reaction between cyclic amidines with alkoxides to give cyclic methyl imidates is, to the best of our knowledge, unprecedented. This transformation allowed access to the versatile methyl imidates synthon and avoids the underlying issue of competing alkylation. Moreover, it greatly contributed to the reactive versatility of the frameworks accessed via the gold-catalysed process.



91g **133a**, 72%

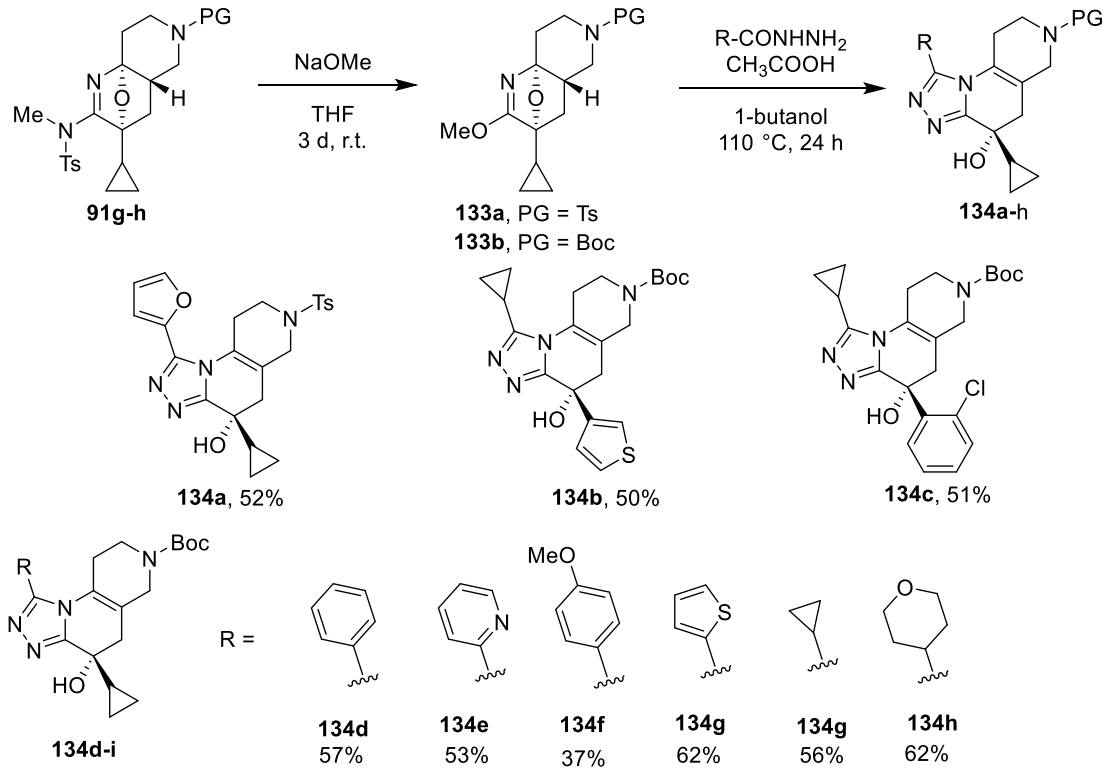
Scheme 41: Synthesis of cyclic imidate derived from cyclic amidine motifs.

The reactivity of the newly synthesised cyclic imidates was tested towards the generation of 1,2,4-triazoles in order to access another tricyclic framework with unique connectivity. Triazoles have attracted enormous attention in medicinal chemistry due to their ability to interact with enzymes *via* multiple weak interactions, and many drug candidates have been approved in the fields of cancer, fungi and viral infections treatment.[118] Aromatic heterocycles fused with saturated aliphatic rings are particularly sought after in medicinal chemistry.[119] This class of compounds bearing partially unsaturated polycyclic scaffolds have displayed bioactivity toward a variety of biological targets,[120-123] and so a series of triazole-fused tricyclic scaffolds could represent an excellent addition to a screening collection.

Pleasingly, when the cyclic imidates were treated with hydrazides in refluxing 1-butanol and catalytic acetic acid the 1,2,4-triazole-fused tricyclic scaffolds were formed in good yields. This approach was then applied to four different frameworks **91g-i** and **91l** with several different hydrazide in order to access a small library of different fused ring systems. The reactions proceeded well affording hexahydro-triazolo-1,6-napthyridine derivatives **134a-i** with aromatic-, heteroaromatic- and aliphatic-substituents in good yields over two steps.

Our approach to the synthesis of 1,2,4-triazole-fused tricyclic scaffolds consisted in the reaction of imidates **133a-b** with a diverse set of substituted hydrazides that would further contribute to the diversity of the generated scaffolds (Scheme 42). Triazolo-hexahydro-1,6-naphthyridines

134a-i were obtained in good yields across the series. The process was further modified to avoid chromatographic purification of the imidate intermediate **133b**.



Scheme 42: Synthesis of tricyclic-triazole derivatives, yields over 2 steps.

The cyclic ether bridge did not survive this transformation, in contrast with the formation of the imidate intermediate where the ether bridge was found to remain intact. This was confirmed by analysis and comparison of the ^{13}C-NMR spectra of compounds **91g**, **133a** and **134a** (Figure 20).

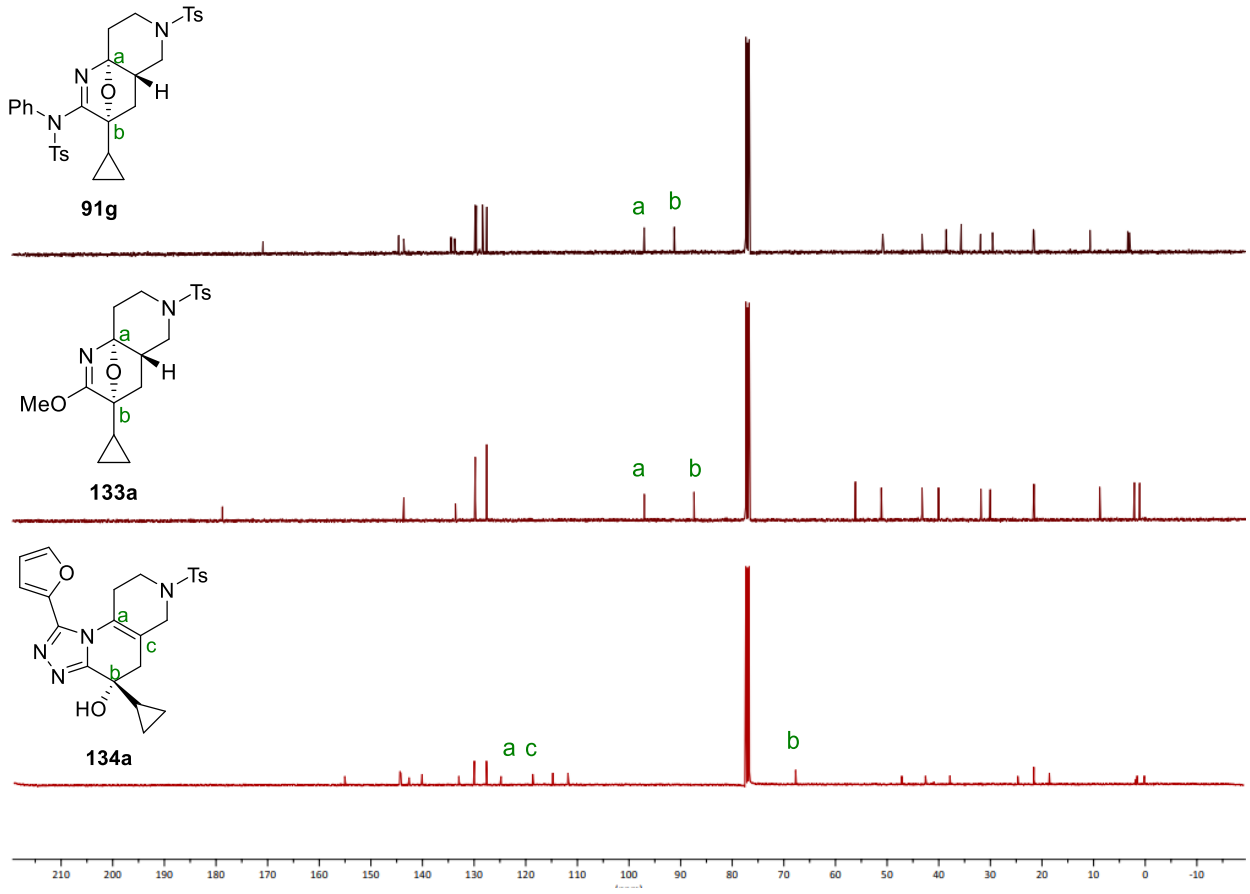
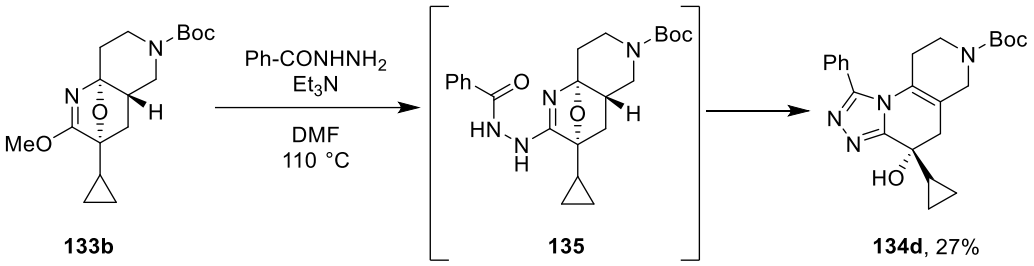


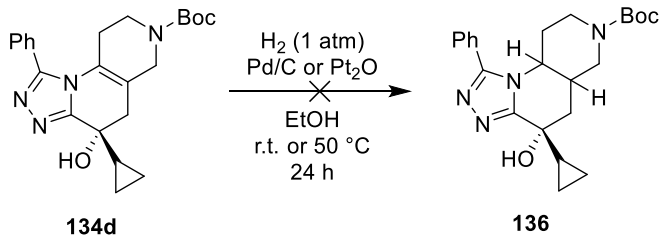
Figure 20: Comparison of the ^{13}C-NMR spectra of compounds 91g, 133a, 134a.

The slightly acidic conditions, in combination with the high temperature were initially thought to be implicate in the opening of the ether bridge. Therefore, a base-catalysed reaction was attempted, imidate **133b** was stirred in DMF with Et_3N and triazole **134d** was isolated in a modest 27% yield (Scheme 43). The reaction was also found to be slower, requiring 3 days to go to completion. Attempts to isolate possible intermediate **135** and clarify at which point the oxygen bridge collapses were unsuccessful.



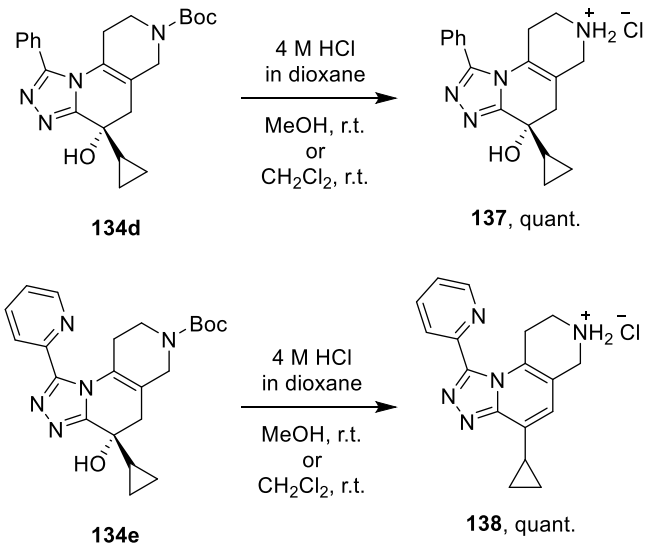
Scheme 43: Attempted basic conditions used for triazole synthesis.

The reactivity of the triazoles was then investigated. The alkene at the bicyclic junction was recognized as an opportunity to access *cis*-fused structures *via* H_2 reduction with Pd/C or Pt_2O catalysts. Triazole **134d** was not reactive towards hydrogenations under the attempted conditions, and starting material was recovered in every instance (Scheme 44); further studies are required to confirm the inactivity of this substrate towards hydrogenation reactions that might be driven from the possibility of triazole poisoning the catalyst and the very hindered position of the double bond.



Scheme 44: Attempted hydrogenation of the triazole scaffold.

Attention was then turned to the Boc-deprotection of the nitrogen on the alkyl tether in the attempt to make the secondary amine moiety accessible for further functionalisations. Triazole **137** was accessed in quantitative yield upon stirring of precursor **134d** with HCl in both MeOH and CH_2Cl_2. However, when **134e** was subjected to deprotection conditions, elimination of the tertiary alcohol prompted the formation of 1,2-diazaindolizine derivative **138** (Scheme 45).

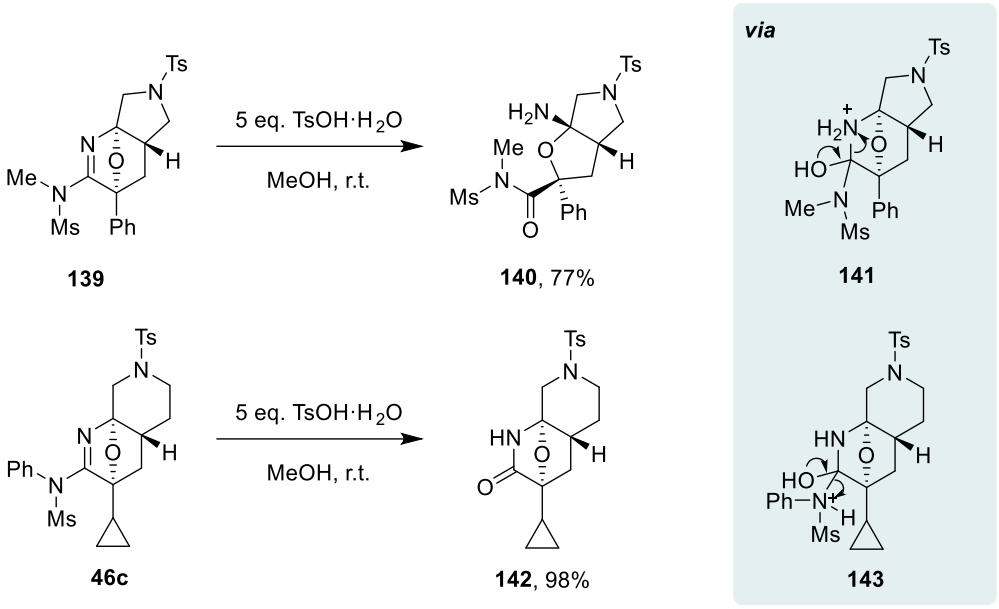


Scheme 45: Boc deprotection of selected triazole-derivative examples.

Despite the increased numbers of sp^2 carbons, polycycle **138** still possessed good physicochemical properties and was progressed with polycycle **137** for the generation of a small set of analogues, for which the synthesis and design is discussed in Chapter 5.

4.3. Brönsted and Lewis acid catalysed dehydrations and hydrolysis to hydroxypyridine and lactam derivatives

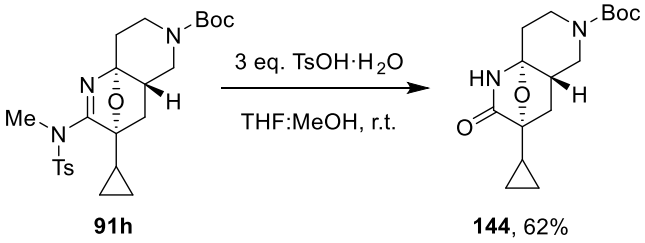
Amidine acid-catalysed hydrolysis is a known procedure in the literature[124] and previous members of the Davies group have exploited this reactivity to access either densely functionalised tetrahydrofurans motifs or lactam derivatives when 6,5-polycycles **139** or 6,6-polycycles **46c** were treated in acidic conditions (Scheme 46).[90, 91] The divergent reaction outcome was hypothesised to arise from the same reaction mechanism, involving the initial acid catalysed attack of water onto the amidine moiety to give **141** and **143**. From this point the similar intermediates would resolve following different pathways: either the amine acts as a leaving group to form THF **140**, or the sulfonamide is expelled and lactam **142** is formed.



Scheme 46: Synthesis of tetrahydrofurans and lactam motifs by Matt Ball-Jones and Matthew Wakeling

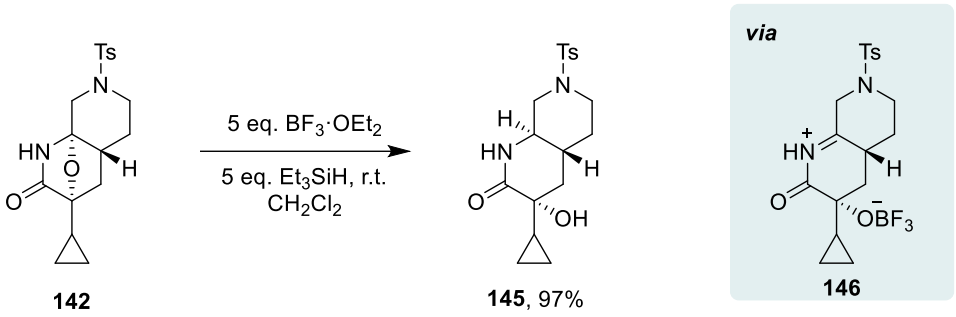
Initial rationalisations for this opposing behaviour held accountable both the leaving group ability of the sulfonamide and the different ring strain involved in the 6,5- and 6,6 fused rings systems. Further studies on the hydrolysis of the C5 Diels–Alder products employed polycycles with the same sulfonamide and the same divergent pathway was found, therefore the dominating factor was presumed to be the ring strain in the different systems.[90]

Following the procedure exploited from previous member of the Davies' group, lactam **144** was obtained in good yield from framework **91h**. THF was used a co-solvent for the reaction to increase the solubility of the starting material and its complete consumption was achieved in 1 h. The amount of TsOH was reduced to 3 equivalents showing a much cleaner conversion to lactam **144** (Scheme 47).



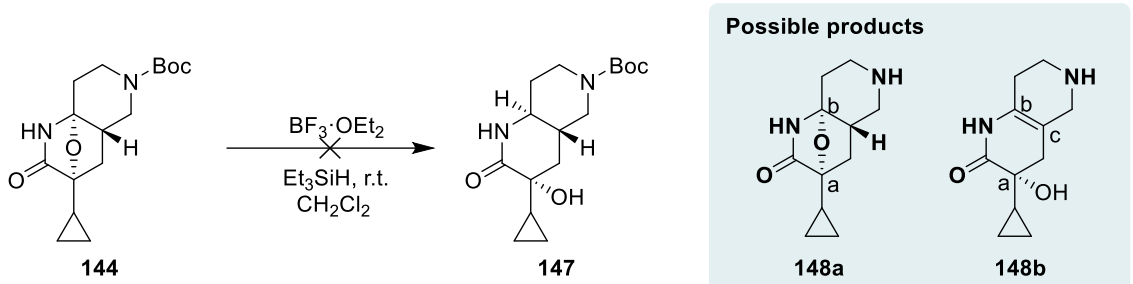
Scheme 47: Lactam formation bearing a Boc-protected secondary amine.

The embedded functionalities in the lactam constitute precursors for acyliminium formation upon treatment with a suitable Lewis acid. Acylimminiums have been reported in literature and exploited for the preparation of a diverse range of scaffolds from a diverse array of addition reactions that includes allyl silanes,[125] organotrifluoroborates,[126] and boronic acids.[127] Previous members of the Davies group also exploited this reactivity, lactam **142** was treated with triethylsilane in presence of $BF_3 \cdot OEt_2$ and **145** was isolated as a single diastereomer (Scheme 48).



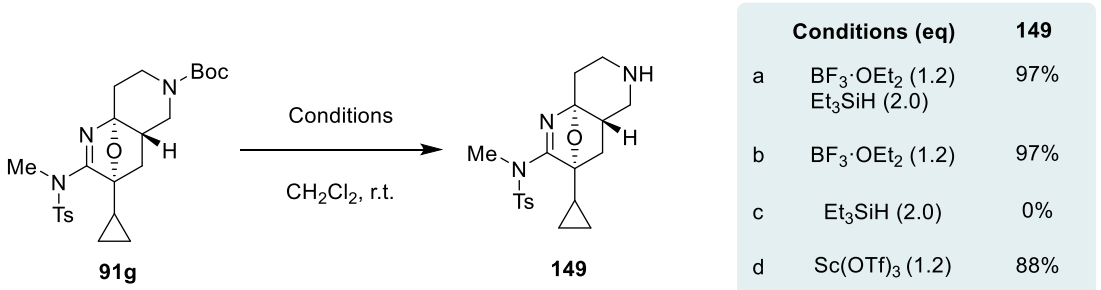
Scheme 48: Matthew Wakeling reduction of oxy-bridged lactams

However, when the reaction was repeated with lactam **144** under the same conditions, no product could be retrieved, and analysis of the LCMS and ^{1}H-NMR of the crude reaction mixture revealed that the carbamate protecting group was removed from the starting material. The same result was achieved also employing reduced equivalents of Lewis acid and silane. Unfortunately, isolation of a pure compound proved challenging, however the product of the reaction was speculative assigned to **148a** (Scheme 48), with the ether bridge still intact. Analysis of the ^{13}C-NMR spectra showed two quaternary carbons resonances, C_a and C_b found respectively at 90.7 and 87.9 ppm, consistent with ether functionality; whilst for its ring opened analogue **148b** three quaternary carbon resonances would be expected.



Scheme 49: Attempted reduction of oxy-bridged lactams

Further experiments carried out on polycycle **91g** with the Lewis acids confirmed their efficiency in carbamate removal (Scheme 50, condition a). In absence of silane, **149** was formed from **91g** in almost quantitative yield (Scheme 50, condition b). No reaction occurred when only triethylsilane was added to the mixture (Scheme 50, condition c). Other Lewis acids were tested, $Sc(OTf)_3$ gave good results albeit requiring longer reaction times (Scheme 50, condition d), whilst $Mg(OTf)_2$ showing no reaction (Scheme 50, condition e).

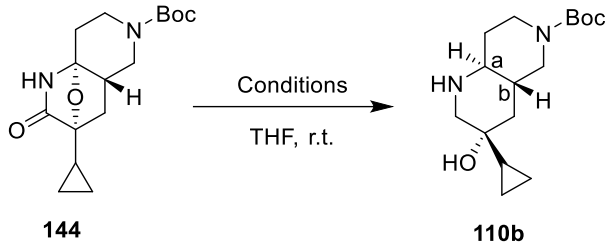


	Conditions (eq)	149
a	$BF_3{\cdot}OEt_2$ (1.2) Et_3SiH (2.0)	97%
b	$BF_3{\cdot}OEt_2$ (1.2)	97%
c	Et_3SiH (2.0)	0%
d	$Sc(OTf)_3$ (1.2)	88%
e	$Mg(OTf)_2$ (1.2)	0%

Scheme 50: Carbamate removal *via* Lewis acid.

The reactivity of lactam **144** was then tested using other reduction conditions. In particular, lactams can be reduced upon activation with a suitable Lewis acid.[128] TMSCl was employed to activate the lactam alongside various reducing agents. Its presence was necessary as reaction without the Lewis acid showed no conversion (Scheme 51, condition a), and did not trigger Boc-deprotection (scheme 51, condition b). When $LiAlH_4$ and $NaBH_4$ were used as reducing

agents, full consumption of the starting material was observed and amino alcohol **110b** was obtained in moderate yields (Scheme 51, conditions c and d). No reaction was observed when milder reducing agents were used and starting material was fully recovered (Scheme 1, conditions e and f).



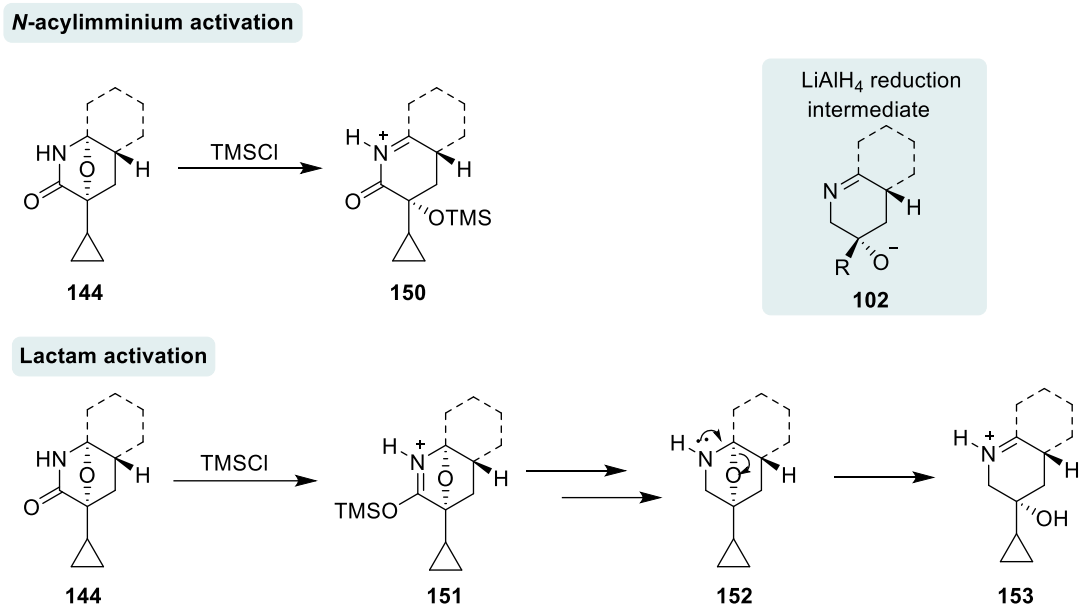
144 **110b**

Conditions

	reducing agent (eq)	additive (eq)	time (h)	yield
a	$LiAlH_4$ (2.0)	none	6	no rxn
b	none	TMSCl (1.5)	6	no rxn
c	$LiAlH_4$ (2.0)	TMSCl (1.5)	1	59%
d	$NaBH_4$ (2.0)	TMSCl (1.5)	4	57%
e	$NaBH(OAc)_3$ (2.0)	TMSCl (1.5)	6	No Rxn
f	Et_3SiH (2.0)	TMSCl (1.5)	6	No Rxn

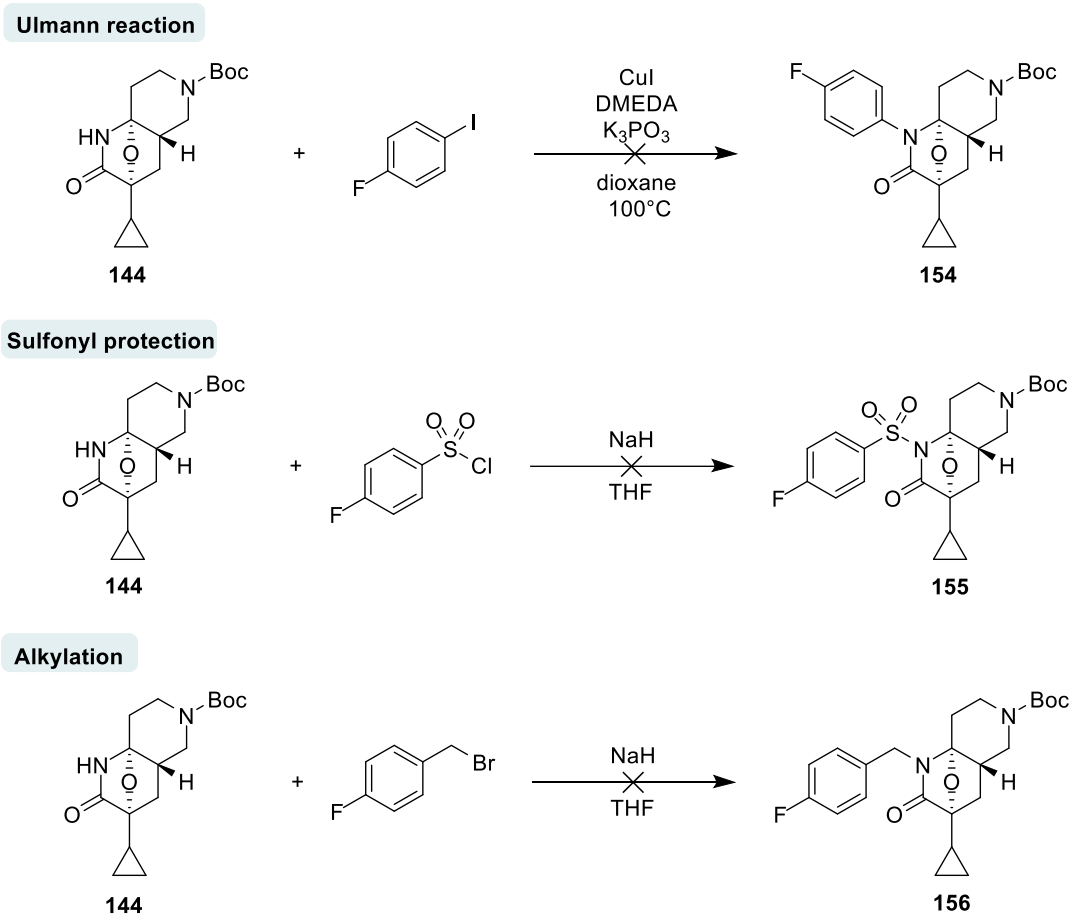
Scheme 51: Reduction conditions of the lactam motif.

The same stereoselectivity observed for previous amidine reduction (Scheme 29, Figure 19), was obtained for this procedure. The *trans* ring junction was identified via analysis of the ^{1}H-NMR spectrum that showed vicinal Ha-Hb coupling constant of 11.1 Hz, consistent with dihedral angle of 180°. Whether the reaction proceeds via *N*-acylimminium formation **150** or lactam activation **151** and reduction to hemiaminal **152** is unknown (Scheme 52). However, both intermediates **150** and **153** were predicted to adopt an analogous conformation to imine **102** from the amidine $LiAlH_4$ reduction process, and the same conformational analysis explain the *trans*-stereoselectivity.



Scheme 52: Possible intermediates in the lactam reduction

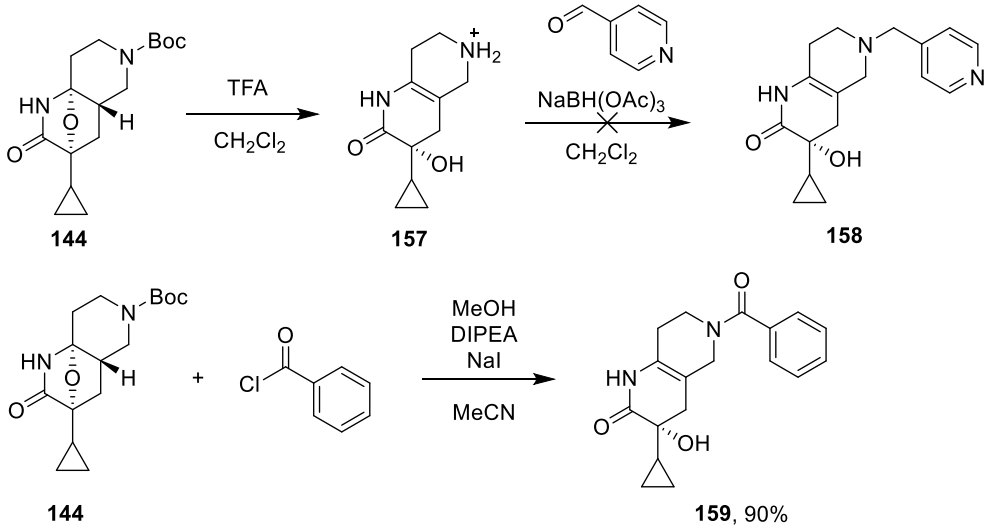
Further studies aimed at the investigation of the reactivity of **144** were carried out, with unsatisfying results regarding the *N*-functionalisation of the lactam moiety. Both Ulmann coupling and sulfonyl protection failed to yield the desired products **154** and **155**, with starting material fully recovered. Alkylation with benzylbromide showed full conversion to an alkylated product, but upon purification a single compound could not be isolated, and it was not possible to determine if the reaction produced a mixture of *N*- and *O*-alkylation products (Scheme 53).



Scheme 53: Attempted *N*-functionalisation at the lactam motif.

Attention then turned to the Boc-deprotection and functionalisation of that nitrogen atom on the alkyl tether. However, when lactam **144** was treated under acidic conditions a pure compound could not be isolated. Analysis of the ^{1}H-NMR of the crude reaction mixture showed that enamide **157** could be formed (Scheme 54). A two-step procedure was than ideated that could trap intermediate **157** via a reductive amination to form lactam **158**, however the reaction showed no conversion. Brönsted acids can also catalyse *N*-acyl iminium formation, literature precedents report the loss of a proton from the *N*-acyl iminium intermediate is possible with consequent formation of enamides *via* this pathway that would result in **157**.[129] A one-step methodology that could both trigger enamide formation and access *N*-functionalisation was sought after and enamide **159** was prepared following the method published by Nazihr and

Heissler for Boc-deprotections.[130] This method allows for the cleavage of *t*-butyl carbamates to amides *via* the *in situ* generation of hydrogen iodide from the reaction between an acyl halide and methanol. The excess of acyl halide would then react with the intermediate amine in presence of DIPEA forming an amide. Pleasingly the reaction media was acidic enough to trigger enamide formation and enamide **159** was isolated in excellent yield (Scheme 54).



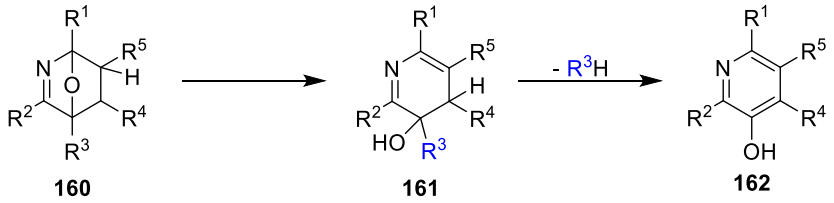
Scheme 54: Boc-deprotection attempts and enamide formation.

Despite the rich potential of the lactam and enamide motifs, further studies are needed to investigate and clarify the reactivity of these embedded functionalities. The one-pot procedure for Boc-deprotection-amide formation adds another potential scaffold accessible *via* the lactam from the initial common framework. However, the scope of this reaction toward the use of different acyl halides for the formation of enamide analogues was not investigated further. Pd-catalysed hydrogenation of enamides has been reported,[131] and this reactivity may provide access to *cis* fused ring junctions.

4.3.1. Brönsted acid dehydrations to fused hydroxypyridines

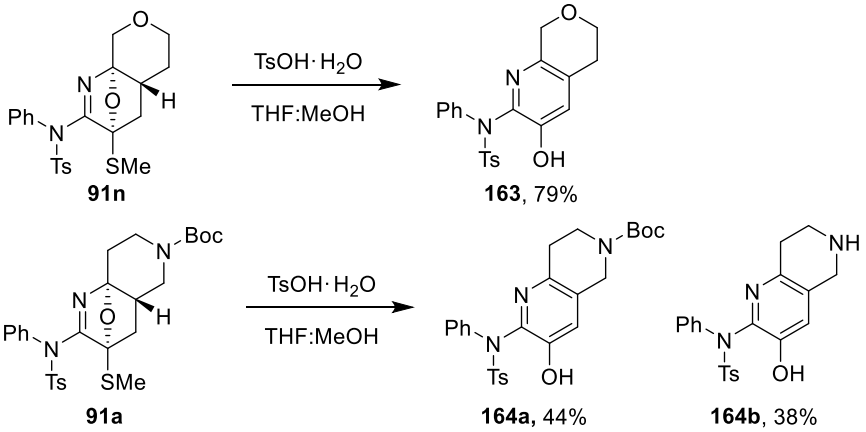
Fused polycycles like **160** accessed via a Diels–Alder reaction between an oxazole and an alkene have shown their proficiency to spontaneously ring open to azadiene **161** and further

progress to hydroxypyridine **162** if R^3 contains a suitable leaving group (Scheme 55).[132] This process, catalysed by acidic conditions, has been used to convert Diels–Alder adducts similar to those accessed via the gold-catalysed process to pyridines.[133, 134]



Scheme 55: Hydroxypyridine formation

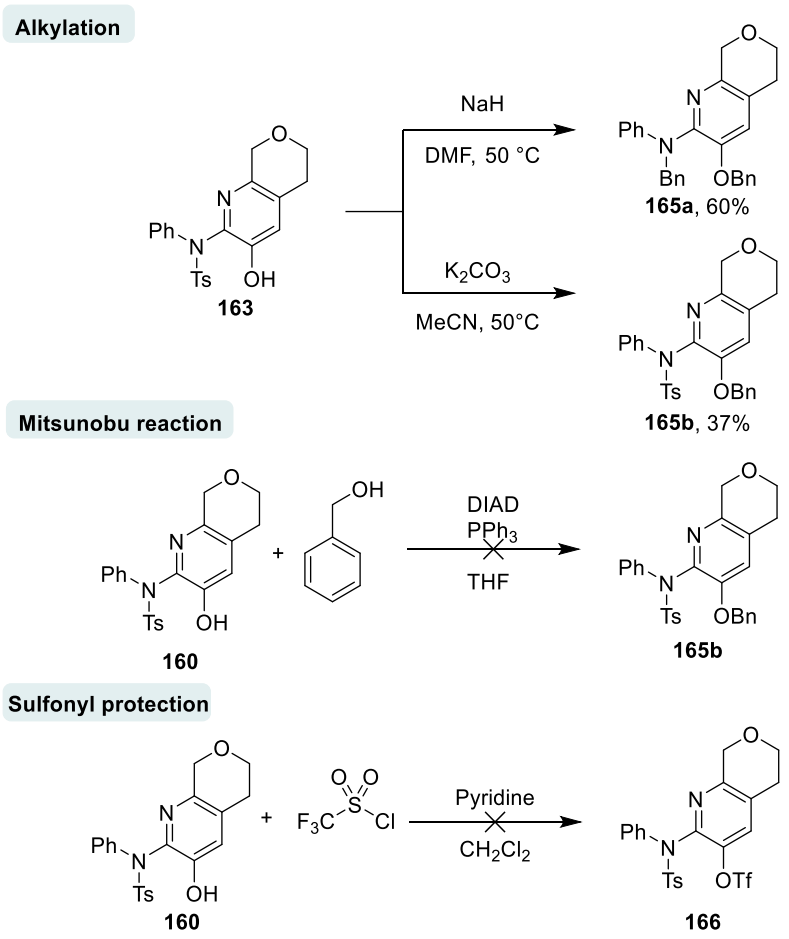
In the same way, thioketal derivatives can function as precursors to highly functionalised hydroxypyridines when treated in acid conditions. This transformation would afford yet another partially unsaturated polycyclic motif. To this end, polycycles **91a** and **91n** were treated with TsOH in THF:MeOH and hydroxypyridines **163** and **164a-b** were isolated in good yields (Scheme 56).



Scheme 56: Synthesis of hydroxypyridines from thioketals polycycles.

The reactivity of the newly synthesised hydroxypyridine **163** was tested. Ether formation was achieved both using NaH and K_2CO_3 as bases, although both reactions requiring heating to 50 °C to observe conversion from the starting material. The product obtained from the hydride reaction furnished the double alkylated **165a** product after tosyl cleavage, via a reaction

pathway similar to that operated by Red-Al in earlier examples (Scheme 57). Carbonate-mediated alkylation yielded mono-alkylated pyridine **165b** in moderate yield. Mitsunobu reaction and sulfonyl protection both failed to give the desired products, with no conversion observed *via* TLC or LCMS analysis of the crude reaction mixtures.



Scheme 57: Attempted functionalisation of the hydroxypyridine.

Further studies are needed to explore the reactivity of the hydroxypyridine derivatives. However, tosyl deprotection might not require harsh conditions to be used as encountered for previous systems. By designing different ynamides, a set of highly functionalised 3-hydroxypyridines could be synthesised in a modular manner, providing access to another scaffold with unique connectivity.

4.4. Summarising the gold-catalysed double annulation and framework elaborations

The further development of the gold-catalysed process allowed the preparation of an additional 14 examples with a range of pharmaceutically relevant substitutions and easily cleavable protecting groups. In particular, expansion was aimed at polycyclic frameworks bearing a decahydro-1,6-naphthyridine core. The newly designed ylides proved capable coupling partners, albeit requiring moderately harsher conditions compared to their homo allylic counterparts. Thio- and cyclopropyl- substituted ynamides showed the highest conversion to the corresponding polycycles, whilst aromatic-, heteroaromatic- and aliphatic substituted ynamides showed moderately reduced yields. The protocol had to be revisited to achieve adequate conversion and required higher temperatures for all the substrates in combination with longer reaction times for the most challenging ones.

The polycyclisation reaction to access framework **91h** was up scaled to 21 mmol, affording it in a 36% overall yield with only one chromatographic purification needed from commercially available starting materials. Similarly, the synthesis of thioketal derivative **91n** was up scaled up to 15.6 mmol with a 42% overall yield, once again with only one chromatographic purification needed (Chapter 3.2.1.1).

New or improved methodologies were developed to diversify the frameworks into different scaffolds for the synthesis of a compound collection. Cyclopropyl-functionalised framework **91h** was chosen as a benchmark for these transformations and 6 different scaffolds were accessed from one common intermediate, mostly *via* two-step procedures (Figure 21). All the primary modifications are the result of the reactivity of the amidine functionality towards

Brönsted acid hydrolysis to a lactam moiety **144**, alkoxide nucleophiles to methyl imidate motif **133b**, and towards hydride reduction to aminoalcohol **110b**. The only modification that did not involve amidine reactivity was the Lewis acid deprotection of **91h** to access framework **149**. Further elaboration of intermediates allowed access to a diverse range of scaffolds, bearing diverse skeletal modifications around the decahydro-1,6-naphthyridine core.

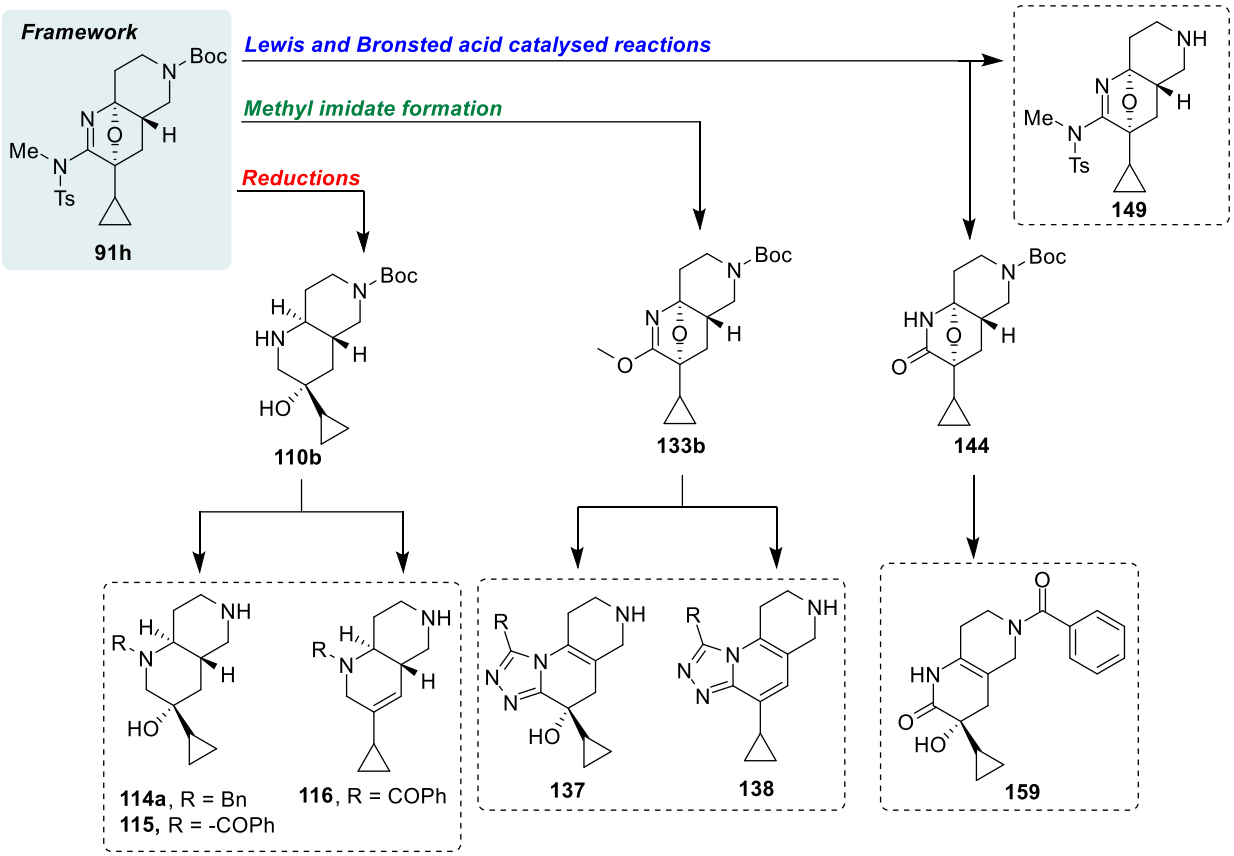


Figure 21: Reaction tree summarising framework 91h modifications.

Simultaneously, thioketal derivative **91n** was subjected to both hydride reductions and acid hydrolysis accessing aminoalcohol **120** and 3-hydroxypyridine **163**. Aminoalcohol **120** was further functionalised via oxidation to access aminoketone **127a** that functioned as an intermediate to access tricyclic pyridine framework **131**. Aminoethers **122** were also derived from aminoalcohol **120**, providing the third scaffold accessed from framework **91n** (Figure 22).

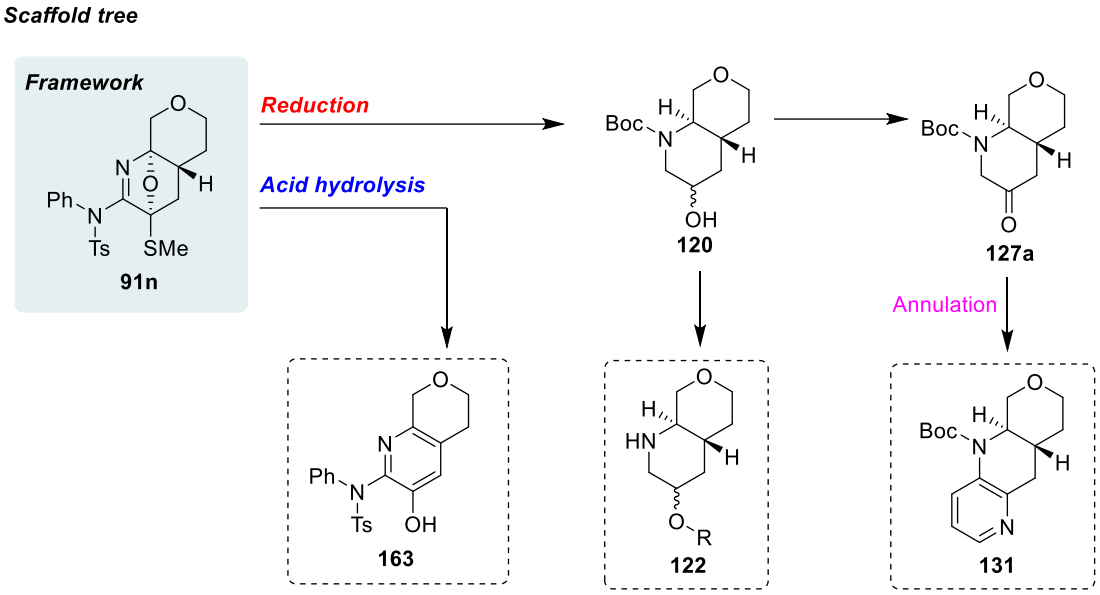


Figure 22: Scaffold tree summarising framework 91n modifications.

Exploring the reactivity of the frameworks accessed via the gold-catalysed process allowed the generation of nine unique scaffolds with a very diverse skeletal connectivity. This diversity mainly originated from the exploitation of the amidine moiety as a pluripotent functional group and its reactivity towards different reaction conditions and reagents, in a diversity oriented synthesis fashion.

With a range of novel polycycles at hand, attention then turned towards the synthesis of a compound library for early-stage drug discovery. To this end, *in silico* studies were carried out to maximise molecular diversity and to access control over the physicochemical properties of the compound collection.

5. Chapter 5: Libraries, design, and synthesis

In this chapter the design and synthesis of three compound libraries based on the developed scaffolds will be discussed. Two open-source software were used to carry out the *in silico* design. Knime[135] was used for the enumeration and physicochemical properties calculations, while DataWarrior[136] was used for filtering and visualisation of the final libraries. Each scaffold was individually analysed during the design and synthesis steps, with a comprehensive overlook of the combined final libraries presented at the end of the chapter along with final initial ADME results.

5.1. Computational design of Virtual Libraries: Knime and Datawarrior

Combinatorial chemistry has provided medicinal chemists with an unprecedented ability to synthesise large numbers of compounds. However, screening for effective hit molecules was inefficient and did not result in any real increment of candidates for lead optimisation.[2] Excluding the missed opportunity to develop a new treatment for a disease, the economic loss from a failed screening can be huge, since just the cost of making and storing the library can be significant. It was therefore necessary to develop novel methods to increase the likelihood of finding new hits and to optimise the drug discovery process so that the best molecules could be delivered in the timeliest and least wasteful fashion. To this end, chemoinformatics provides the tools to manage, visualise, and analyse chemical information.[137] The field has evolved in the past decades, and it can be defined as the application of informatic methods to solve chemical problems.[137] Amongst all the fields of chemistry, medicinal chemistry and drug discovery benefited the most from the implementation of chemoinformatics in their standard operating procedure.[138] These *in silico* techniques have helped the drug discovery process with

the enumeration of virtual libraries from which a relatively small set of molecules that, bear the desired pharmaceutical properties, could be selected and subsequently tested in biological screenings, increasing the likelihood of finding new hits containing desired physiological properties.[139]

5.1.1. Knime and Library enumeration

The enumeration of virtual libraries, intended as the virtual synthesis of a set of compounds, can be accomplished by several methods, as different computational tools have been developed.[139] However, only a few of these software packages are open source and do not require an extensive background in informatics to enumerate chemical libraries.[139] Among these, Knime offers a user-friendly workspace and presents the opportunity to virtually functionalise the selected scaffolds on specific connections points with a list of R groups, following pre-validated reactions, in a combinatorial fashion. A critical aspect of virtual libraries is that the compound generated must be synthetically feasible, and the pre-validated reaction strategy offers the opportunity to minimise the risk of unfeasible compounds using reaction approaches developed within the research group or reported in the literature.[139] For these reasons, Knime was selected as the platform to virtually compute the chemical libraries discussed in this work.

The Knime platform interface allows users to create visual workflows, where each task is represented by a node with input and output ports. The data is processed by a pipeline of connected nodes that produces results on the node outputs based on their settings. The type of data processing ranges from simple basic operations, such as filtering or merging data sets, to more complicated specific functions, for example the calculation of physicochemical properties and simulation of a reaction between two reagents to yield a product molecule. The workflow

for the enumeration of a virtual library can be conceptualised as in Figure 23. In this schematic example the reagents uploaded in Reagent Node A are reacted with the reagents in Node B in a combinatorial fashion in Reaction Node, which renders the product molecules. The output of the reaction node, the products C, can be successively processed by other node operators to filter and select the products, following parameters defined by the specific project.

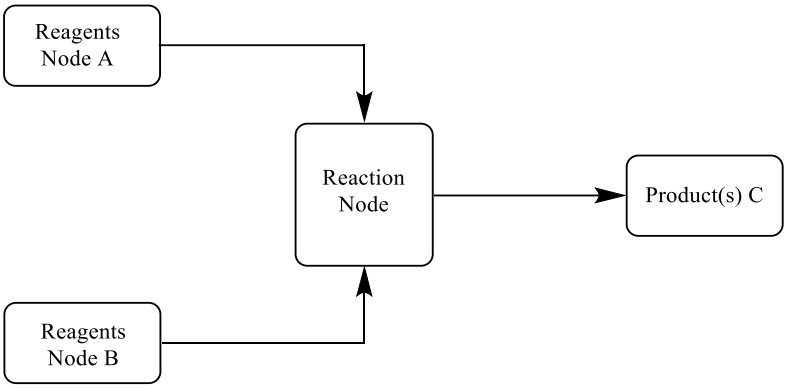


Figure 23: Schematic conceptualisation of a knime enumeration workflow.

Knime offers the opportunity to import the reagents into the reagents nodes as standard file format such as structure-data file (SDF) or comma separated value (CSV) files, which is particularly useful when elaborating huge data sets of compounds. Otherwise, when a specific molecule is to be elaborated, it can be drawn directly using a suitable node that supports 2D graphical representation. Similarly, the product node returns the product molecules that can be written in the most suitable format for visualisation.

Knime already incorporates most of the nodes used for data analysis, however, to specifically perform virtual library enumeration, third party extensions must be downloaded. To this end, RdKit[140] and ChemAxon[141] nodes were used to build the workflows utilised for this thesis, and Figure 24 shows the main workflow used for library enumeration. The workflow can be divided in three sections: the first one involving the upload of the scaffold and the reagents into the workspace; the middle one involving the reaction nodes and the virtual generation of the

products; and the last one entailing the calculation of the physicochemical properties and writing of the products file.

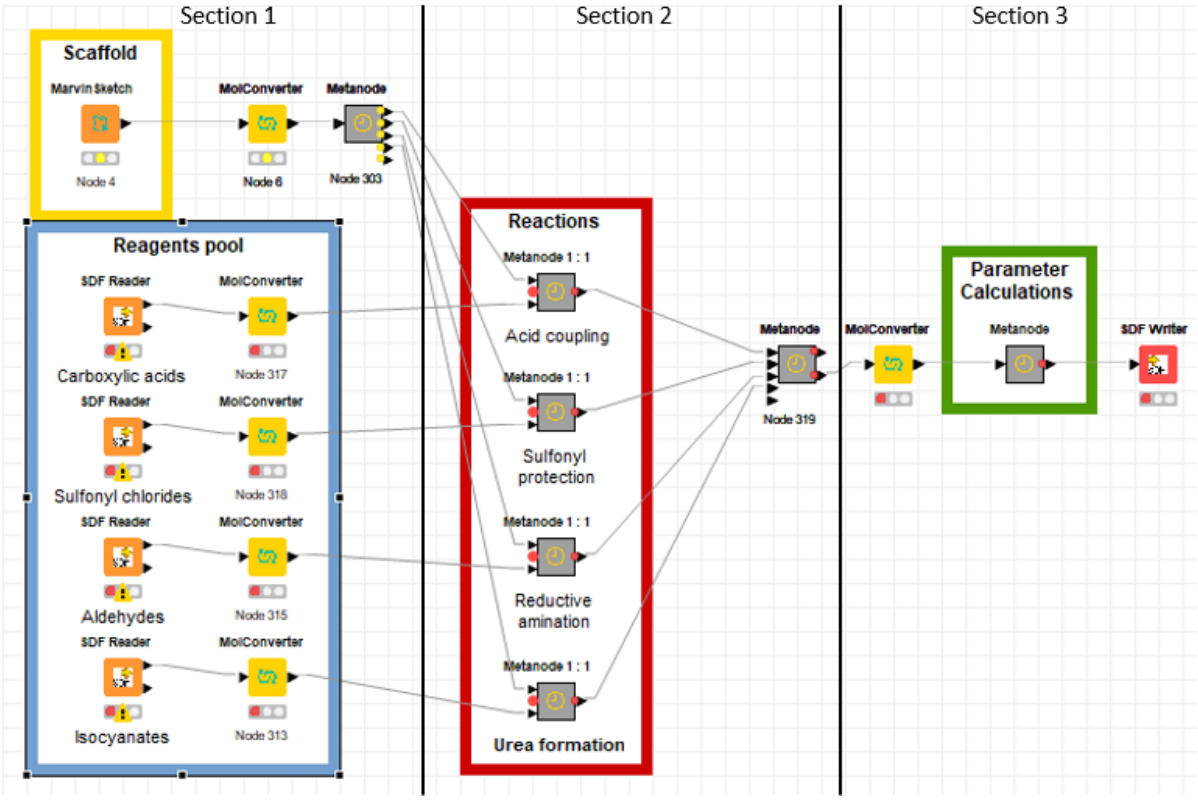


Figure 24: Representation of the workflow utilised for library enumeration.

Since the library generation revolved around the decoration of a central molecule with a range of different building blocks, the scaffold was directly drawn in the MarvinSketch node, whilst the reagents were imported using SDF files divided by functional group categories (Section 1 of the workflow). The outputs of these nodes are connected to a range of reaction metanodes in Section 2 of the workflow. Metanodes encapsulate sub-workflows that process customised specific actions, without overloading the platform workspace. The sub-workflow enclosed in the reaction metanodes is reported in Figure 25.

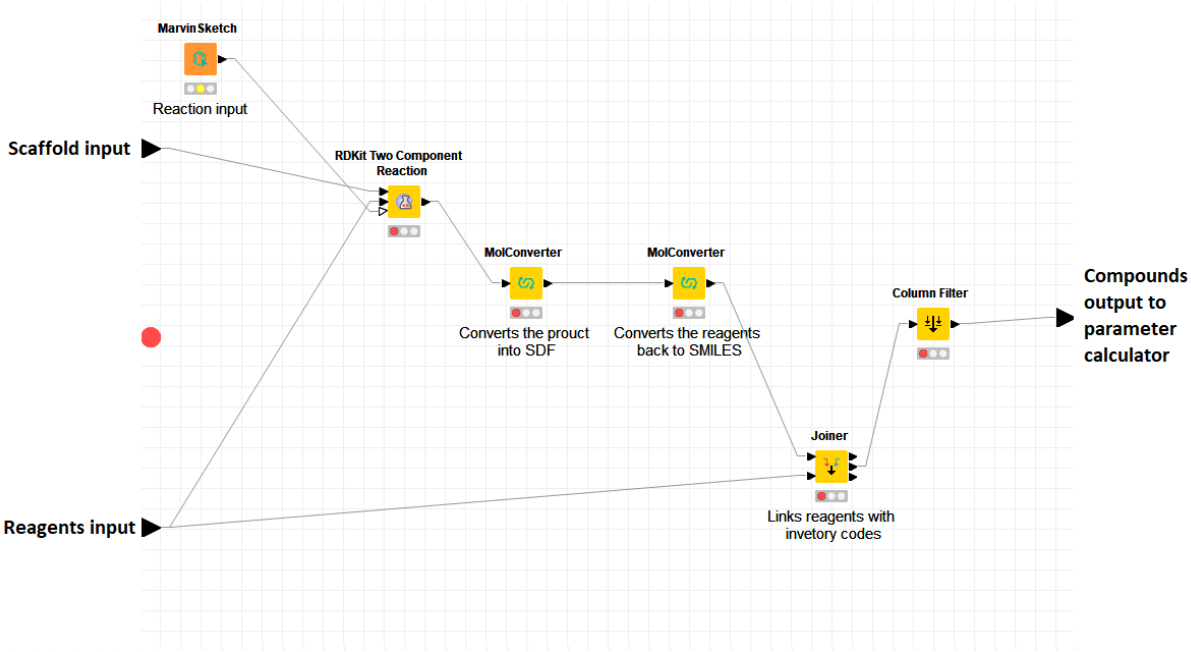


Figure 25: Reaction metanode sub-workflow.

The two main nodes of this workflow are the MarvinSketch reaction input (Figure 26), which allows the user to draw a generic example of a specific type of reaction (i.e., acid coupling, reductive amination, sulfonyl protection), and the RDKit Two component reaction node that combines the molecules incoming from the scaffold and reagents inputs, following the rules dictated by the reaction input node. Another important node was the joiner, used to assign to each product the inventory code of the reagent used for its decoration, to simplify traceability during the actual synthesis of the library.

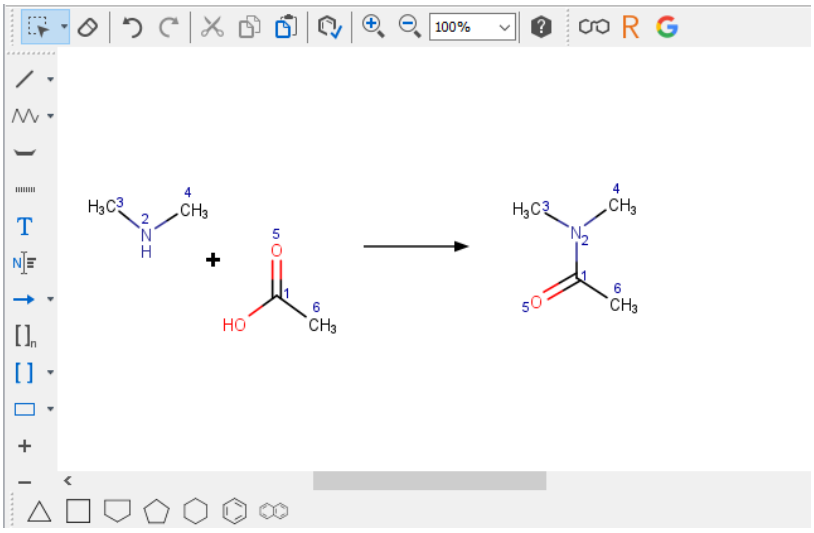


Figure 26: MarvinSketch, reaction input node settings example for acid coupling reaction.

In the last part of the workflow, the product molecules resulting from each reaction input are merged to form the final enumerated library. The physicochemical properties of the compounds are calculated in the parameter calculation metanode (Figure 27), before the final SDF file is written, embedding all the parameters calculated during the process.

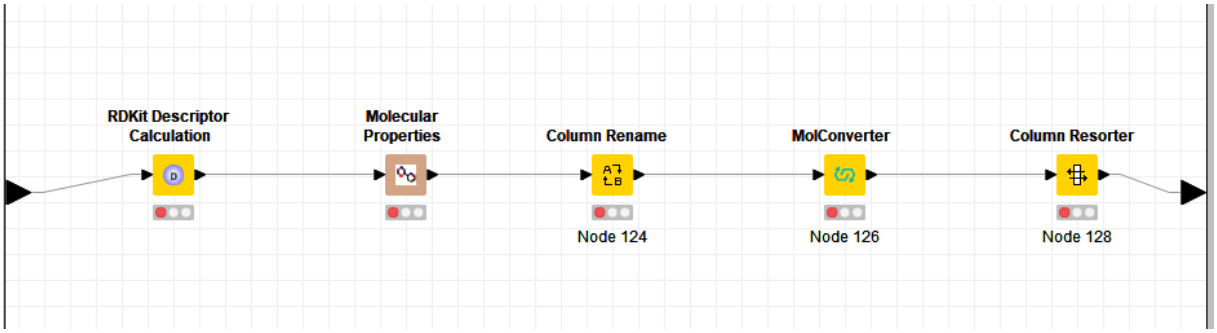


Figure 27. Sub-workflow embedded into the parameter calculation metanode.

This workflow was used to enumerate the libraries based on the synthesised scaffolds and to predict physicochemical properties for the generated molecules. However, to exploit the information generated during this step, the data should be rendered to allow its efficient manipulation and visualisation. Knime offers the possibility to generate plots, graphical views, cluster, and filter the compounds to visualise and manipulate the data, however, due to the

nature of the software, this process was too computationally demanding without additional computer resources. To this end, the data generated with Knime was instead analysed with Datawarrior. This software is specifically designed for data analysis and provides interactive views to visualise and manipulate the information from a large dataset.

5.1.2. Datawarrior-clustering and visualisation

In addition to the graphical visualisation of the chemical information, Datawarrior was used to compute and cluster the molecular diversity of the compounds and select which ones to synthesise to achieve the larges variety possible. Molecular diversity of a small molecule library has been reported as one of the most important indicators of the overall quality of the collection, granting higher hit rates across a variety of targets.[142] However, the first challenge in defining molecular diversity is the choice of molecular properties and descriptors upon which the diversity calculation is based. Several ideologies have been published on the subject of molecular descriptors, however it is not possible to conclude that a general applicable set of descriptors exists, while increasing the complexity of the descriptors does not guarantee better performance in the compound selection.[142-145] Therefore, the choice of an appropriate descriptor is highly dependent on the task of the project. In general, a descriptor can be described as a computational formulation of a molecule and its molecular properties based on physicochemical properties as well as topological and geometric substructures.[146] Descriptors can be classified according to their dimensionality, referring to the properties from which the values are calculated: one-dimensional (1D) descriptors capture bulk properties (eg. molecular weight or LogP) whilst 2D and 3D descriptors capture more complex molecular features such as molecular connectivity or conformational states.[146] In the simplest cases, 2D descriptors encode binary bit strings, called fingerprints, in which the molecule properties are written as

characteristic bit patterns,[147] whilst more complex descriptors are usually represented as mathematical vectors that represent the occurrence of different substructures in a molecule.[148] Datawarrior offers the opportunity to calculate chemical descriptors based both on fingerprints and vectors and the available descriptors are divided by increased complexity. Amongst the options offered by the software, the *SkeletonSphere* descriptor provides the best accuracy in similarity calculation without extreme computational demands.[148] This 2D topological descriptor computes molecular connectivity and stereochemistry capturing the topology around each atom of the molecule to better encode molecular structures. The *SkeletonSphere* descriptor outperforms other available descriptors in calculating similarity, such as the fragment-based descriptors *FragFp* or the *Orgfunction* that only encode whether a specific fragment (i.e. functional group) is present or not in the molecules. On the other hand, the more complex *Flexophore* is a 3D descriptor that considers molecular flexibility and spatial relationships between atoms or functional groups, it is utilised to calculate pharmacophore similarity.[149] This descriptor is the most comprehensive amongst those available in Datawarrior, which, encodes for three-dimensional binding behaviour rather than chemical similarity, and it also requires more computational power.[149] The *Flexophore* descriptor was mainly selected to compute diversity in libraries based upon a scaffolds with two points of diversity, because it will also compute the spatial relationship between the two substituents and allows for more subtle similarity calculation. When libraries based on a single point of diversity were analysed, the *SkeletonSphere* was deemed sufficient in rendering the diversity of the collection. The two descriptors were selected to compute diversity and clustering the compounds generated *via* the *in silico* library enumeration. In a cluster analysis the compounds are divided into small groups of similar compounds according to a predefined similarity criterion in this case the molecular descriptor. The native clustering algorithm in DataWarrior calculates the similarity over all the

compounds in the collection, and the most similar compounds are joined into the first cluster. The similarity matrix is updated by removing the similarity values related to the compounds joined in the first cluster and updated with a new set of similarities between the cluster centre and any other compound (Figure 28). The process continues by joining the most similar compounds/clusters and it is repeated until a stop criterion is met, two possibilities are available based on the number of clusters reached or based on the similarity between the generated clusters.

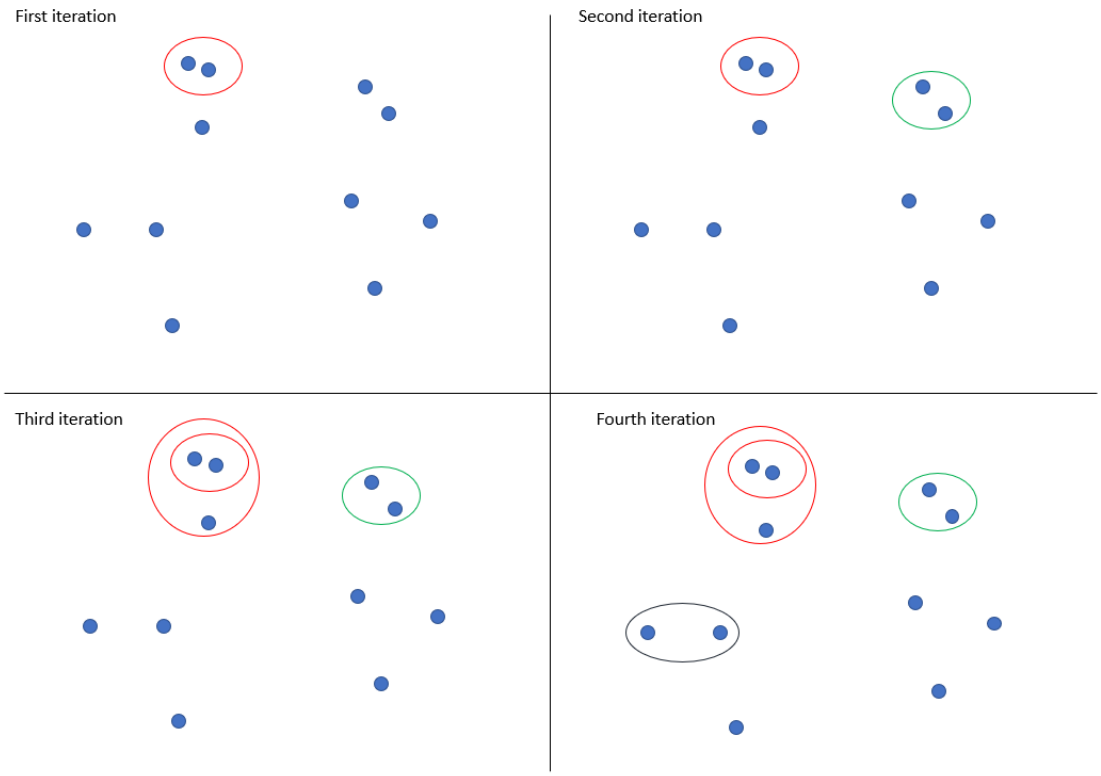


Figure 28: Schematic representation of clustering process.

Datawarrior calculates the most representative compound from each cluster, which is then selected to be synthesised. For the clustering operation the stop criterion is based upon a defined number of clusters established by the number of molecules that were to be synthesised from each individual library (i.e., if 50 molecules were to be synthesised from an enumerated set, the

clustering would stop when the number of clusters reached 50). It should be noted that the clustering operation is a very important part of the library design, however its role serves only in directing the chemist towards the informed choice of the compounds to be synthesised and, quite often, the selection is not followed strictly: compounds can be manually added or changed in order to target specific areas of the physicochemical property space and increase the range covered by the synthesised library.

Finally, Datawarrior offers the opportunity to visualise and manage the generated data through interactive plots and 2D or 3D graphical views which helps the informed selection of the compounds to be synthesised and offers an optimal view of the overall properties of the enumerated library. Examples of these graphical views were generated for each of the enumerated libraries to visualise the physicochemical properties of the compound collection.

With these chemoinformatic tools at hand, attention was turned towards the design and synthesis of a compound collection based on the scaffolds derived from the post-catalysis modification of the frameworks accessed *via* the gold-catalysed process.

5.2. Library design, synthesis, and overview

5.2.1. Analysis of polycycles physicochemical properties for potential use as scaffolds in library synthesis

The first step undertaken towards the design of the compound library was to evaluate the available scaffolds and select those with the best physicochemical properties. To this end, a chemoinformatic analysis of the compounds accessed from the post catalysis modifications was performed. Nine unique systems were analysed and their predicted molecular properties and

potential as scaffolds for drug discovery were assessed using the RdKit Descriptor calculator in Knime (Figure 29).

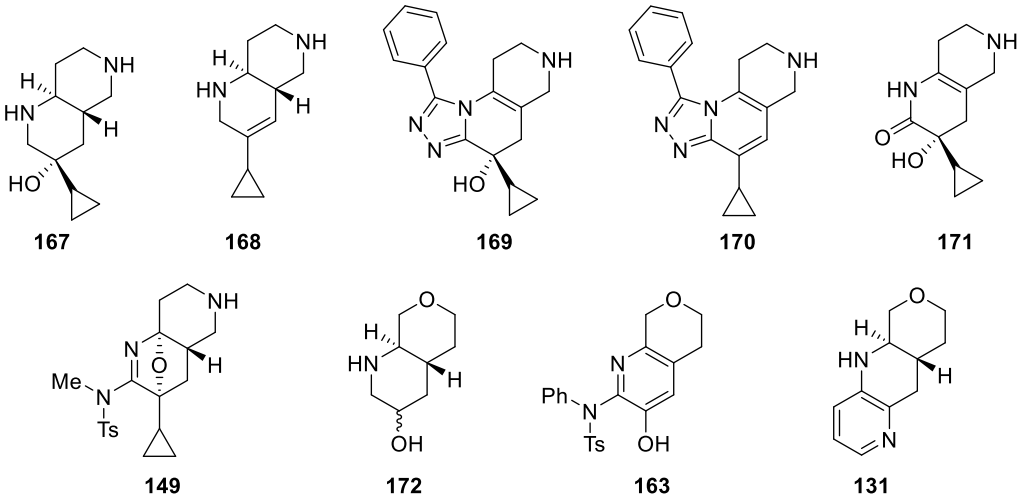


Figure 29: Compound selection for potential use as scaffolds.

The common metrics for drug discovery were calculated and compared against the guidelines from the literature (Table 1).

Table 1: Predicted molecular properties of synthesised scaffolds alongside drug discovery guidelines

Polycycle	MW	cLogP	HBD	HBA	RoB	TPSA (Å^2)	Fsp^3
Guidelines	<500[1]	≤5[1]	≤5[1]	≤10[1]	≤10[8]	≤140[9]	N/A
167	196.3	0.09	3	3	1	44.3	1.0
168	178.3	0.90	2	2	1	24.1	0.82
169	308.4	2.15	2	5	2	63.0	0.44
170	291.4	2.31	1	5	2	55.1	0.35
171	208.3	- 0.10	3	3	1	61.4	0.73
149	437.6	3.48	1	5	4	71.0	0.46
172	157.1	-0.25	2	3	0	41.5	1.0
163	396.5	3.69	1	5	4	79.7	0.19
131	190.2	1.46	1	3	0	34.1	0.55

In addition to high molecular weight, **149** and **163** showed high LogP in combination with lower Fsp^3 and were not selected.

Of the remaining systems, **167–170** and **172** physicochemical properties located optimally within the guidelines suggested from the literature and were selected as scaffolds for the generation of compound collections. It must also be noted that **171** and **131** possessed ideal physicochemical properties, however further studies were needed to assess their reactivity and were not further investigated due to time constraints.

In total, 5 unique scaffolds were selected as starting points for the generation of a compound library collection.

5.2.2. Library enumeration and synthesis

5.2.2.1. Library synthesis metrics and caveats

Library synthesis deviates from classical organic synthesis in respect of the parameters utilised to assess the performance of a reaction. When it comes to libraries the important factors revolve around how many compounds a chemist can synthesise in high purity and adequate amounts, detaching from the classical metric of chemical yield. The library synthesis process is optimised to handle huge amounts of reactions simultaneously, and reduction of the obtained yield cannot be prevented and is inherently intertwined in the process itself. As an example, UPLC analysis requires collecting samples of the crude reaction mixtures of 10 μL, which alone accounts for the 1% loss of the final yield if the analysis is performed only once. Moreover, purity is valued more than actual amount of compound obtained and some of it is lost at the purification step. This is an inevitable price to pay considering that, to ensure high purity results, the shoulder and the tail of the compound peak are usually automatically cut-off and not collected. Therefore,

Symeres in-house guidelines were utilised to evaluate the synthetic performance of a library in relation to the yields and purities of the products. The metrics are comprised of the following parameters:

- Reaction successful: Yield (mg) > 5 mg and purity (UPLC) > 90%;
- Reaction acceptable: Yield (mg) < 5 mg and purity (UPLC) > 90%;
- Reaction failed: Yield purity (UPLC) < 90%.

To express a more general synthetic performance, the "library success rate" parameter was utilized. This metric is expressed as the percentage of the sum of successful and acceptable reactions over the number of performed reactions, and based on in-house data, its values are usually found between 65–70%.

5.2.2.2. MC00985 Library design and synthesis

This library was based upon aminoalcohol **120** derived from the reduction and successive elaboration of thioketal derivative **91n** (Scheme 34, Chapter 3.2.1). Aminoalcohol **120** contained two manifolds for diversification, one at the alcohol moiety and one at the amine motif, therefore the design of MC00985 library was divided in two subsequent decoration steps (Figure 30). The first decoration involved the synthesis of ether derivatives that constituted the two scaffolds of the library (synthesis discussed in Scheme 35, Chapter 3.2.1), whilst the second decoration step at the amine motif was exploited for parallel synthesis to give the final MC00985 library. For the second elaboration five different reactions type were used with the secondary amine: amide synthesis, reductive amination, sulfonyl protection, alkylation, and urea formation.

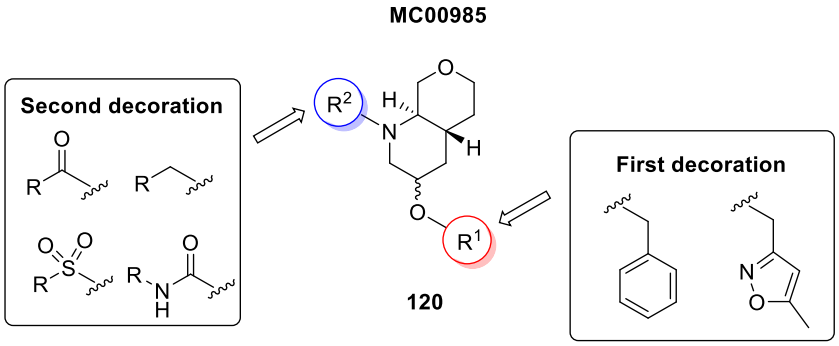


Figure 30. Schematic of decorations on MC00985.

The alkyl bromides involved in the first decoration were selected after running the native diversity algorithm present in DataWarrior on Symeres alkyl bromide database so that the two most diverse fragments were incorporated in the molecule, generating two diastereoisomers for each decoration for a total of four scaffolds. Considering the diastereomeric ratio of 4:1, most of the library was designed around the major diastereoisomer, with few selected examples generated from the minor. The reagents employed for the second decoration were selected by desired drug-like molecular properties resulting in a library compliant with Lipinski's rule. To this end, the Symeres database of preferred building-blocks[e] was filtered to remove all the fragments containing: stereogenic centres, MW > 300, and LogP > 2 resulting in a final reagent pool of 73 compounds (31 carboxylic acids, 25 aldehydes, 9 sulfonyl chlorides, 6 alkyl bromides, and 2 isocyanates).

The two building blocks **122a** and **123a** were enumerated using workflow 1 in Knime (Figure 31) generating two sets of 73 compounds each for a total of 146 molecules in the virtual library (VL). Each set was filtered and clustered using the *Flexhophore* descriptor, so that the 20 most

[e] Symeres in-house collection of building blocks with the highest rates of selection by costumers and reaction success.

diverse compounds were selected to be synthesised, for a total of 40 molecules that will constitute the physical library derived from the major diastereoisomer (M-PL).

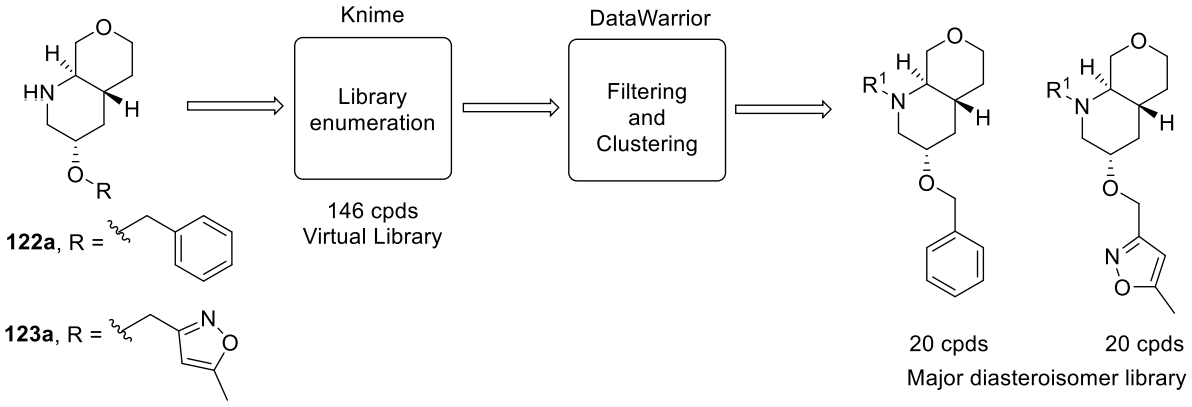


Figure 31: Schematic of *in silico* work for major diastereoisomers.

The approach towards the selection of the compounds derived from the minor diastereoisomer involved a diversity selection algorithm present in Datawarrior. This function is an efficient way of locating the most diverse subset within a given set of molecules, especially because the algorithm can be preloaded with a sample set of compounds, causing the software to select molecules which are both different from the ones in the sample and the enumerated set. A virtual library of 146 compounds was enumerated following the same procedure used for the major diastereoisomer. The enumerated compounds were filtered with the diversity algorithm preloaded with the compounds selected from the major diastereoisomer library. The algorithm was set to return the eight most diverse compounds derived from the minor diastereoisomer virtual library (Figure 32).

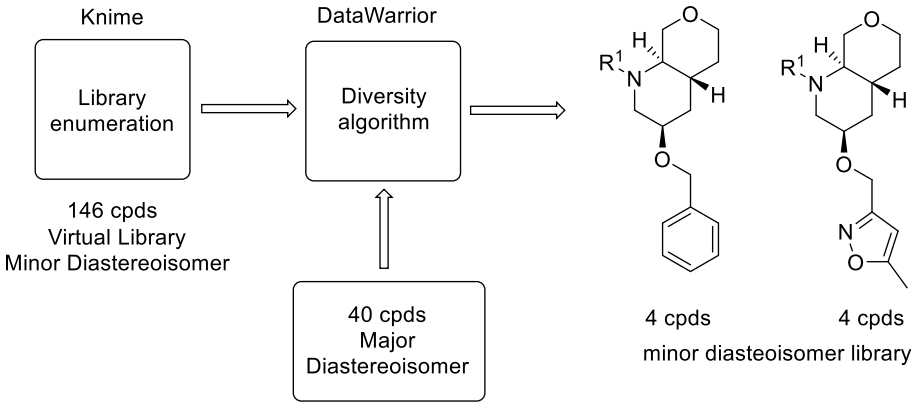


Figure 32: Schematic of *in silico* work for the selection of compounds from the minor diastereoisomer.

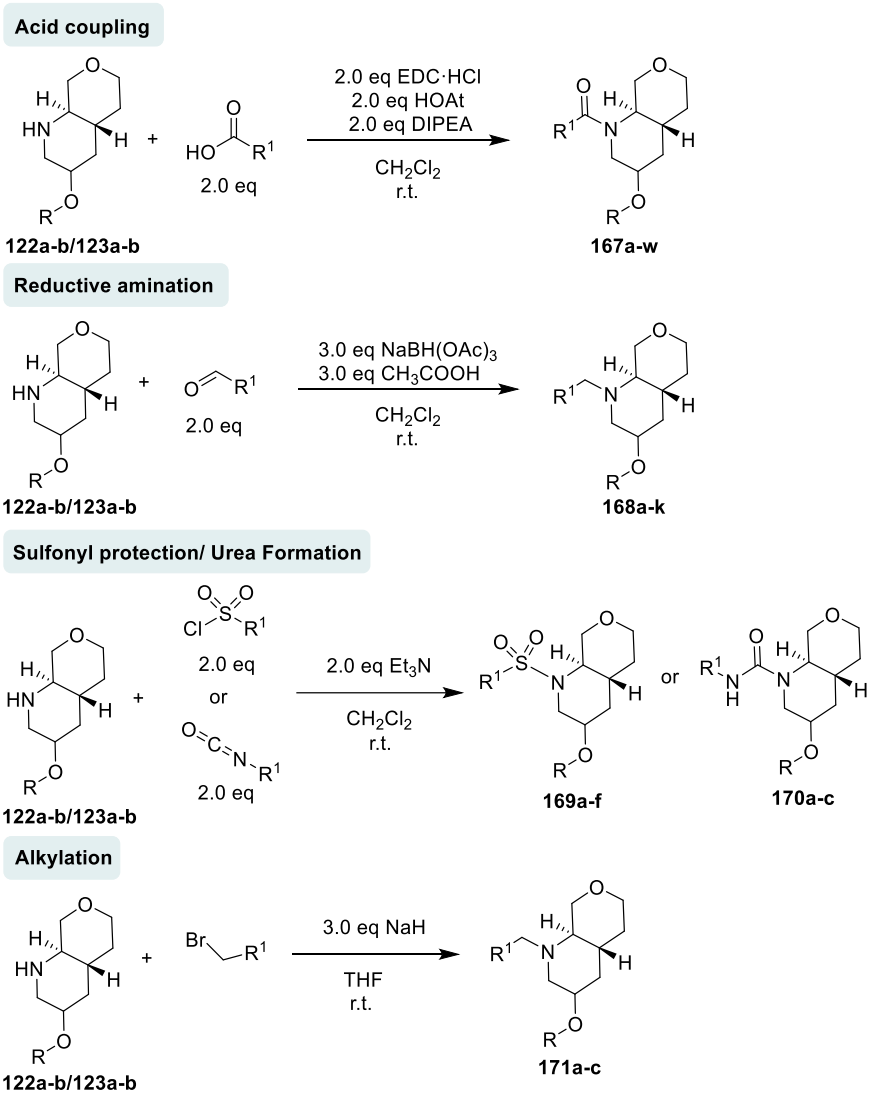
A total of 48 compounds were selected to be synthesised and represented the physical library derived from scaffold MC00985. The reactions were performed in parallel at a 0.1 mmol scale, following the library general procedures explained in the supporting information (Chapter 6.7.1). The predicted physicochemical properties of the selected compounds pleasingly fell between the guidelines suggested from the literature (Table 2).

Table 2: Predicted physicochemical properties of the selected compounds. [a]: ranges; [b]: mean values

Properties	MC00985[a]	MC00985[b]	Guidelines
MW	301.4–471.6	394.75	< 500
LogP	1.7–4.5	3.1	≤ 5
TPSA	21.7–99.7	61.3	≤ 140
Rot. Bond	4–9	5.6	≤ 10
HBD	0–1	0	≤ 5
HBA	3–8	5.6	≤ 10
Fsp^3	0.40–0.82	0.59	N/A

Having confirmed the quality of the library in respect of its calculated physicochemical properties, attention turned towards its synthesis. Early studies on the reactivity of the scaffolds

were carried out before the final library was enumerated and selected[f], with good results in terms of conversion, yields, and purity. These six compounds were included in the final library collection, as their physicochemical properties were compliant with Lipinski's rules. The conditions exploited for this first set of reactions were also employed for library synthesis and are reported in Scheme 58.



Scheme 58: Reaction conditions for library MC00985.

[f] Virtual enumeration and all the *in silico* work were developed during the lockdown, however initial attempts at the decoration of the scaffolds were already in progress.

The overall synthetic performance for library MC00985 is reported in Figure 33. Yield is reported both in weight (mg) and percentage and the results are colour coded based on Symeres library performance metrics.

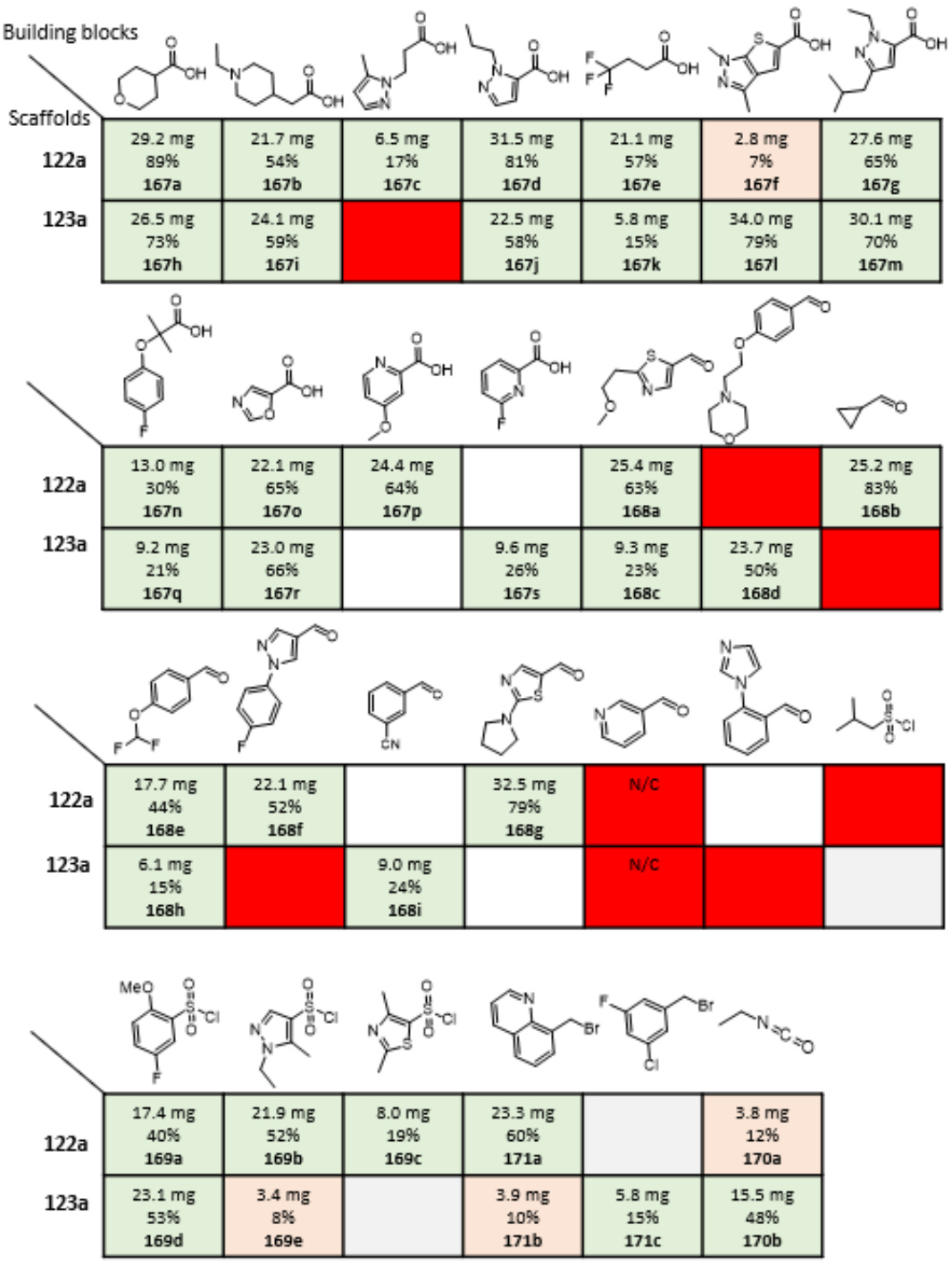


Figure 33: *Continued on next page*

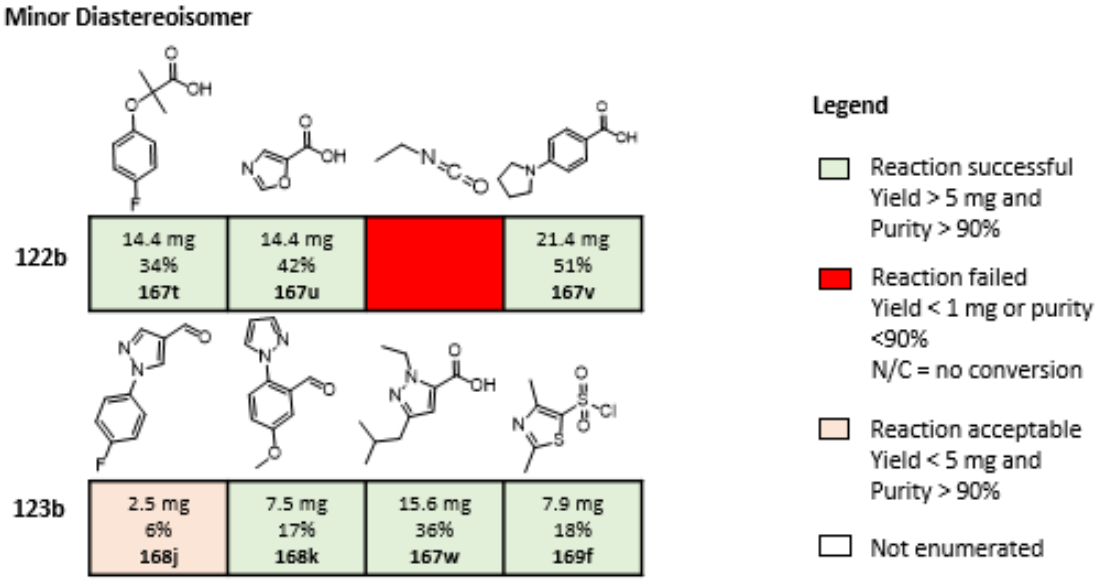


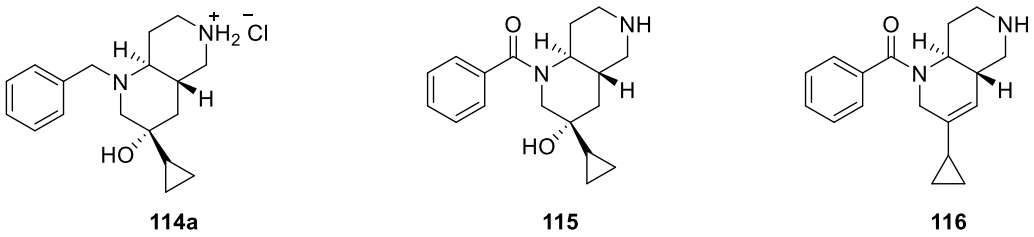
Figure 33: Overall view of the synthetic performance for library MC00985

Pleasingly, 45 reactions out of 54 were successful. Only six compounds were isolated in moderately low yields, accounting for an optimal library success rate of 83%. Reactions were monitored via UPLC analysis, with only one building block showing no conversion to the desired products when reacted with both the scaffolds, whilst the other six failed compounds were discarded due to low isolated yields and purities. However, a general trend that could explain the failed reactions could not be identified. Overall, the scaffolds showed optimal reactivity towards common reactions utilised in library synthesis, with yields spanning from the lowest of 6% to the highest of 89%. With these optimal results, attention was turned towards the design and synthesis of another library.

5.2.2.3. MC00994 Library design and synthesis

This library was based upon aminoalcohol **110b**, derived from the reduction of framework **91h** (Scheme 30, Chapter 4). Initial studies focused on derivatives **114a**, **115** and **116** of **110** (Figure 34). The scaffold was considered to possess only one point of variation, the secondary amine,

and that the same decorations will be installed on all of the three scaffolds to compare the biological results of these closely related structures.



114a 115 116

Figure 34: Scaffolds involved in library MC00994.

To this end, the design approach was slightly changed. Scaffold **114a** was enumerated and a library of 20 compounds was selected. The same 20 decorations were selected to be installed also on scaffold **115**, so that the properties of the molecules could be directly compared. Compound **116** was enumerated separately, and 10 compounds were selected from the enumeration. The molecular descriptor utilised for the clustering was the *Skelsphere* since the scaffold had only one point of diversity. The set of building blocks utilised for this enumeration was a reduced version of that used for library MC00995. Only carboxylic acids and aldehydes were initially selected, given that sulfonamides could be installed early in the synthesis of the frameworks and survive the post-catalysisis modifications, and alkylation using sodium hydride could result in the reaction at both the amine and the alcohol, possibly generating double alkylation products.

To the selection operated in Datawarrior for scaffolds **114a** and **115**, three building blocks were manually substituted because the selected compounds were not available (Figure 35). Building block **B017** could be replaced by another compound (**B022**) in its own cluster, however the same could not be applied to building blocks **B255** and **B087**, and the substitute building blocks (**B368** and **B450**) were selected by interrogation of the MW-LogP scatter plot in an attempt to

spread the library over lighter regions of the MW-LogP ranges. For the same reason building block **D001** was manually added to the selection to test the urea formation with these scaffolds. These issues were not identified with scaffold **116**, and the selection of building blocks was used without modifications.

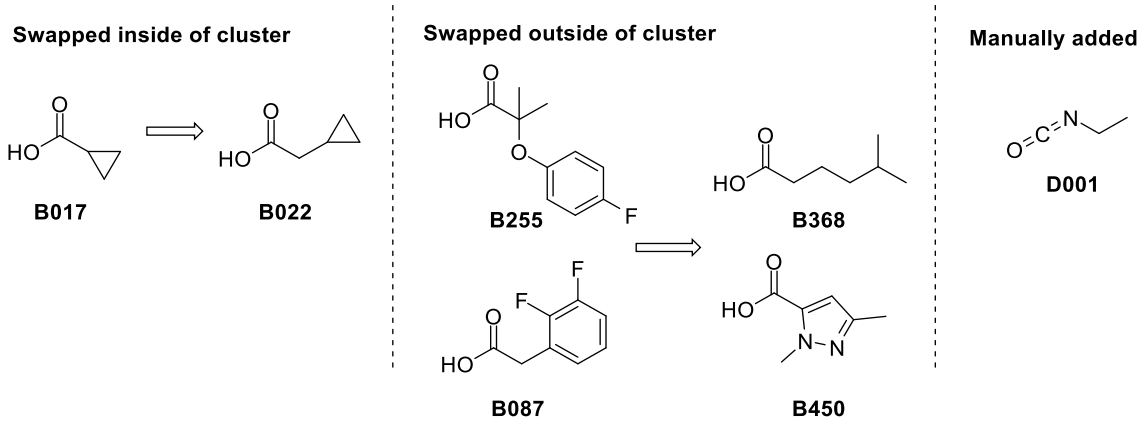


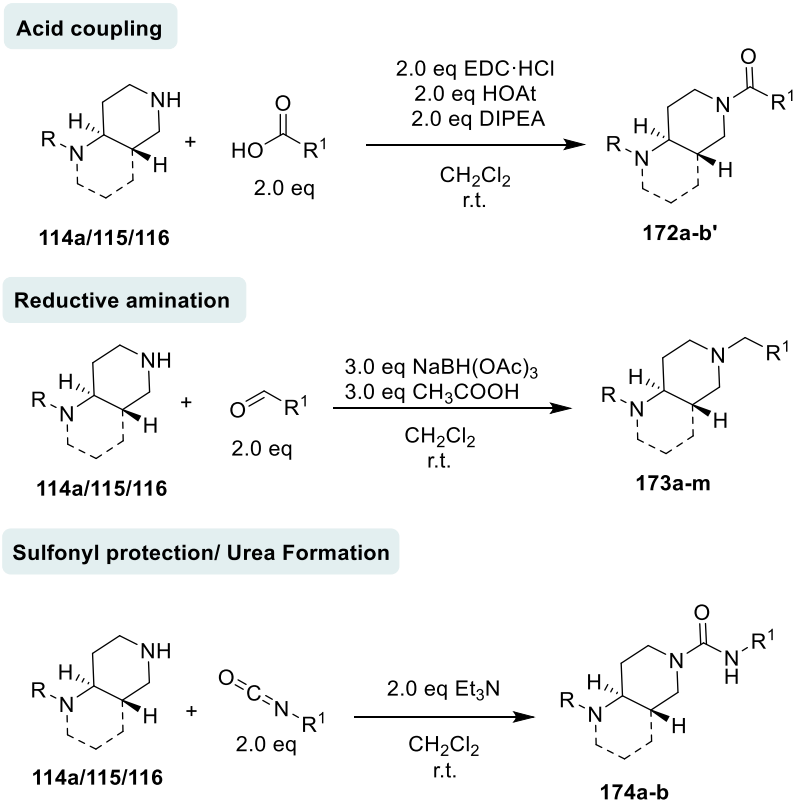
Figure 35: Modifications introduced to the Datawarrior selections.

21 reactions were performed for both scaffolds **114a** and **115** and 10 reactions for **116**, for a total of 52 reactions. The reactions were performed in parallel at a 0.1 mmol scale, following the library general procedures explained in the supporting information (Chapter 6.7.1). The predicted physicochemical properties of the selected compounds were calculated and, pleasingly, were all found compliant with the guidelines suggested from the literature (Table 3).

Table 3: Predicted physicochemical properties of the selected compounds. [a]: ranges; [b]: mean values.

Properties	MC00994[a]	MC00994[b]	Guidelines
MW	357.5–482.65	427.5	< 500
LogP	2.0–4.7	3.4	≤ 5
TPSA	36.4–86.8	59.0	≤ 140
Rot. Bond	3–7	4.7	≤ 10
HBD	0–2	1	≤ 5
HBA	2–7	4.4	≤ 10
Fsp^3	0.35–0.72	0.53	N/A

The conditions utilised for the synthesis of library MC00985 were initially tested with a validation set of 5 molecules and then utilised for the rest of library MC00994 and are summarised in Scheme 59.



Scheme 59: Reaction conditions utilised for library MC00994

The overall synthetic performance for library MC00994 is reported in Figure 36, yield is reported both in mg and percentage and the results are colour coded based on Symeres library performance metrics.

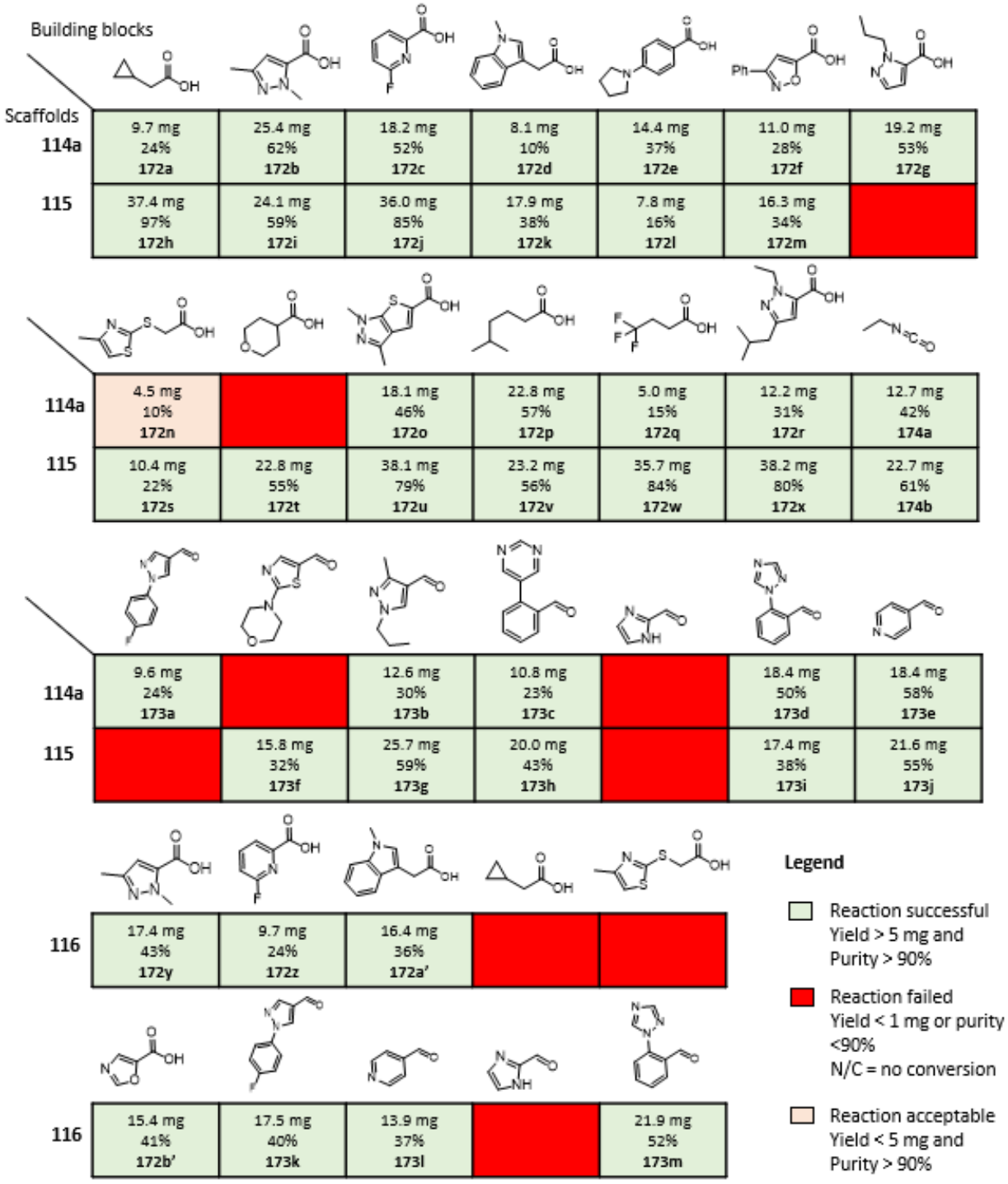


Figure 36: Overall results for library MC00994.

Pleasingly, 43 reactions out of 52 were successful, while only one compound was isolated in low yield, accounting of a library success rate of 83%. Nine reactions were unsuccessful, despite UPLC analysis of the crude reaction mixture showing complete conversion, the desired

products were isolated in low purity. Each of the three scaffolds showed good compatibility, with three of the most common reactions utilised in library synthesis,[150] with yields included in the range comprised from 10 to 97%.

The physicochemical property ranges occupied by MC00994 library are showed in Figure 37. All the compounds are found within the ranges suggested by Lipinski rules, and it can be appreciated how compounds derived from scaffold **115** show generally lower LogP than those derived from **114a**. On the other hand, the subset derived from **114a** show lower TPSA values compared to that derived from **115**. These mirrored physicochemical properties could spark the opportunity to further compare these compounds during the investigation for biological activity.

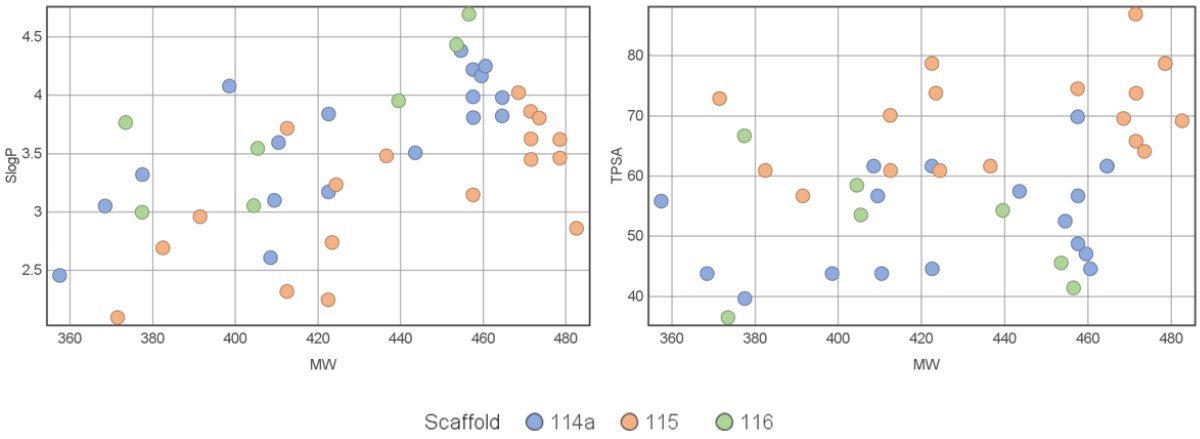


Figure 37: Scatterplots comparing the physicochemical properties of library MC00994 based on the different scaffolds.

5.2.2.4. MC01022 Library design and synthesis

The design of this library was based upon triazole derivative **137** and 1,2-diazaindolizine derivative **138** (Figure 38). However, due to time restraints only a validation set of 16 molecules was synthesised, with 10 derived from **137** and 6 from **138**.

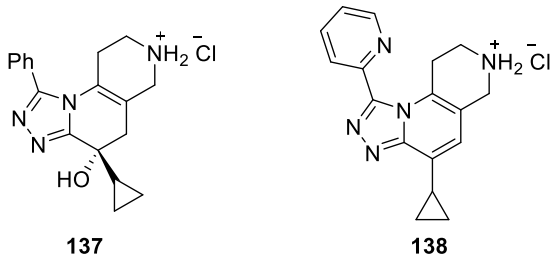
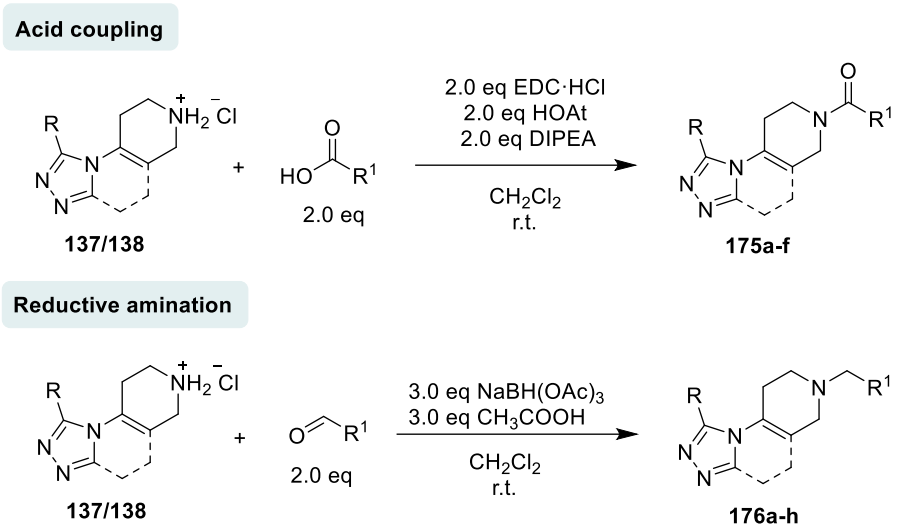


Figure 38: Initial choice of scaffolds for MC01022 library.

Given the relatively small size of this library, the building blocks utilised for the decorations of the scaffold were selected from those tested within the previous libraries. This also provided the opportunity to directly compare the physicochemical properties of the scaffolds, and to further confirm that the highest diversity across a compound collection is accessed *via* scaffold diversity rather than appendage diversity. Moreover, it would provide the opportunity to evaluate and compare the biological activity of the molecules across the libraries and to better locate if the activity is triggered from the scaffold, from the building block itself or from a combination of the two. Only one building block was newly selected. Thiazoles are very common building blocks in drug discovery, and have been reported to possess diverse biological effects including antimicrobial and anticancer activities.[151] Different examples of thiazoles were already included in previous sets, however their molecular weight was deemed too high and it would have impacted negatively with the physicochemical property of the resulting compounds. Therefore, a smaller analogue was selected from the Symeres inventory.

The conditions tested for the previous libraries were applied and are reported in Scheme 60. Previously to the library set up, scaffolds **137** and **138** were suspended in CH_2Cl_2 (0.1 M), then reacted with 1.1 equivalents of Et_3N and added to the reaction mixture as stockpile solutions.



Scheme 60: Reaction conditions for Library MC01022.

The results of the elaboration of scaffolds **137** and **138** are reported in Figure 39.

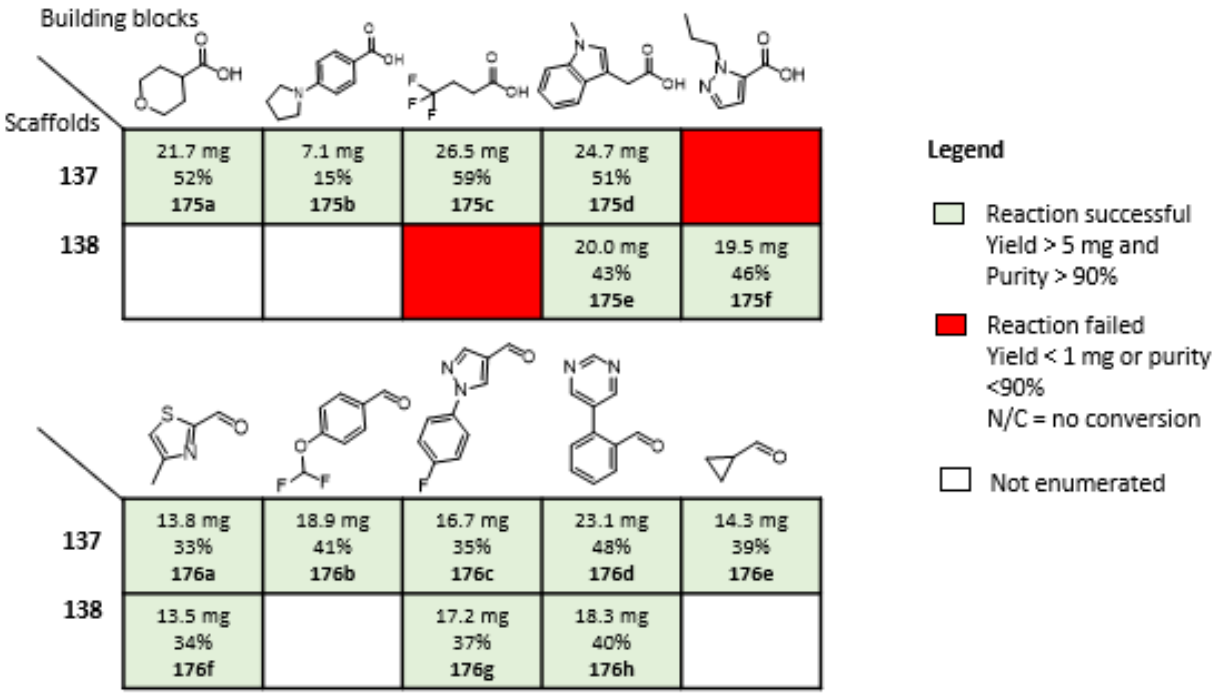


Figure 39: Overall results for library MC01022.

Overall, 14 reactions out of 16 were successful, and only two compounds were isolated in low purity and discarded from the collection. The library success rate for this set of compounds was

87%, although this set was relatively small compared to the previous two libraries it provided a good representation of the reactivity of two examined scaffolds.

With this last set of compounds, the design and synthesis work related to the selected scaffolds was concluded. Attention was then turned towards the analysis and evaluation of the physicochemical properties of the final library (ALBA library), along with computation of its chemical space coverage.

5.2.3. ALBA Library overall view

5.2.3.1. Physicochemical Properties and chemical space

Overall, 103 compounds were synthesised across 5 unique scaffolds. Evaluation of the physicochemical properties of any synthesised library is of paramount importance for the drug discovery process. Therefore, the physicochemical properties distributions were visualised using different types of plots in order to evaluate the trends found within the ALBA Library. A first example is shown in Figure 40, where the compounds were binned in histogram charts based on their physicochemical properties.

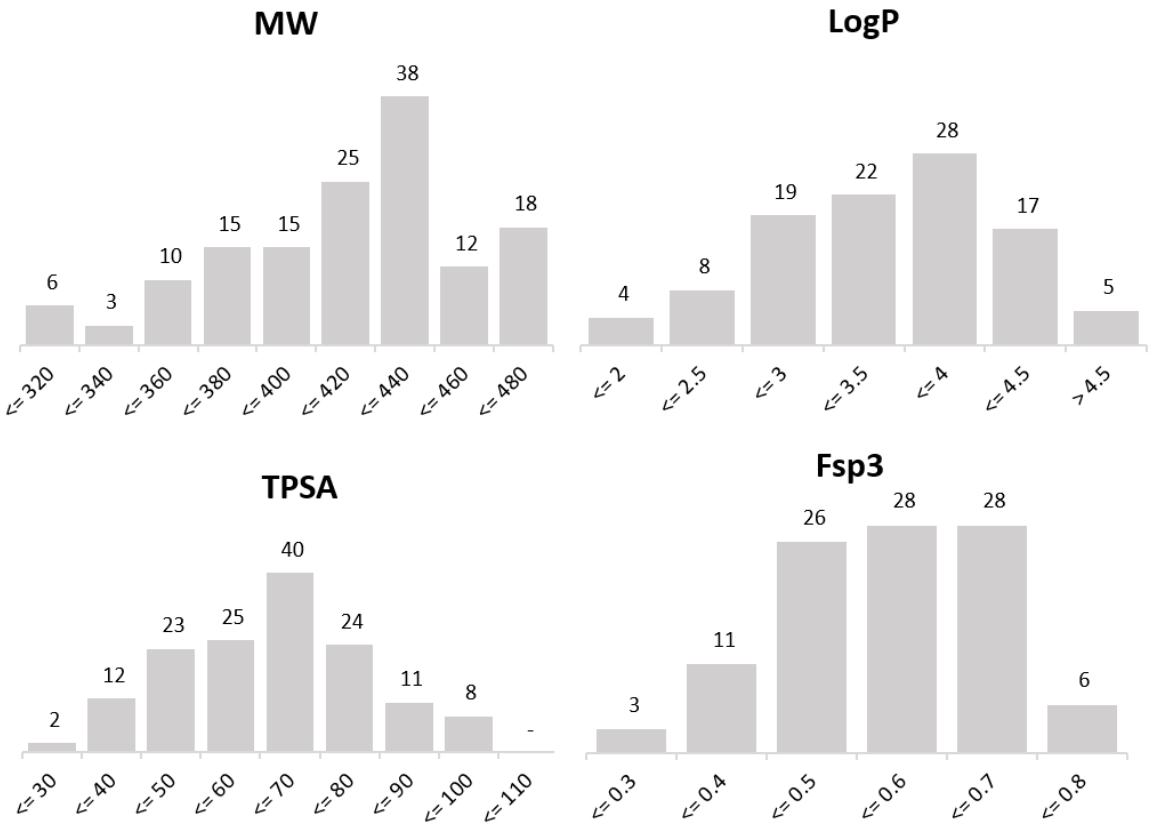


Figure 40: Physicochemical property distribution of the final library.

Pleasingly, the results showed promising trends with the molecules well distributed over the physicochemical property space defined by Lipinski's rule of 5 (including RoB: 3–9, HBD: 0–2, HBA: 3–8).[1] Althought most of the compounds showed relatively high molecular weight and LogP, the calculated values for TPSA and Fsp^3 showed an optimal distribution. The majority of the compounds possessed TPSA values ideal for blood-brain barrier permeation to target the central nervous system.[10] Moreover, the Fsp^3 distribution showed very high values, with the majority of the compounds falling within the 0.5–0.8 range.

Overall, the library possesses good physicochemical properties, however the LogP and molecular weight values linger towards the higher ends of their ranges, despite the scaffolds owning very promising physicochemical properties (see Chapter 5.2.1, table 1). The reasons for that are essentially two. The first one is that the decorations were selected from Symeres

inventory of “preferred structures”, in essence a set of molecules that are often selected by clients for their libraries and is therefore subjected to the well-known medicinal chemistry bias of flat and saturated molecules. This selection of substitutions had an impact on the physicochemical properties of the molecules in the ALBA library, that remained still between the ranges; however, the quality of the library was not affected as it will be showed later on during the studies concerning the diversity and chemical space coverage. The second reason was that most of the selected decorations carried some examples of steric hindrance around the reactive centres due to their substitutions and size. This had an impact on the final physicochemical properties of the molecules but represented a good test for the reactivity of the scaffolds towards difficult substitutions.

An alternative view of the library property distribution is shown in Figure 41, where the compounds are spread in a scatter plot based on physicochemical properties in the Lipinski rule space. These plots clearly demonstrate how the properties are well distributed after a certain threshold of molecular weight (360), covering a very broad range of LogP and TPSA. However, this result is not unexpected considering the average MW of the compounds selected as scaffolds (246.75). Further investigation aimed at expansion of the physicochemical property coverage of this library could revolve around scaffolds **171** and **131** (Figure 23), which possess relatively low MW and LogP, and could therefore represent optimal starting points to enrich the library physicochemical properties coverage.

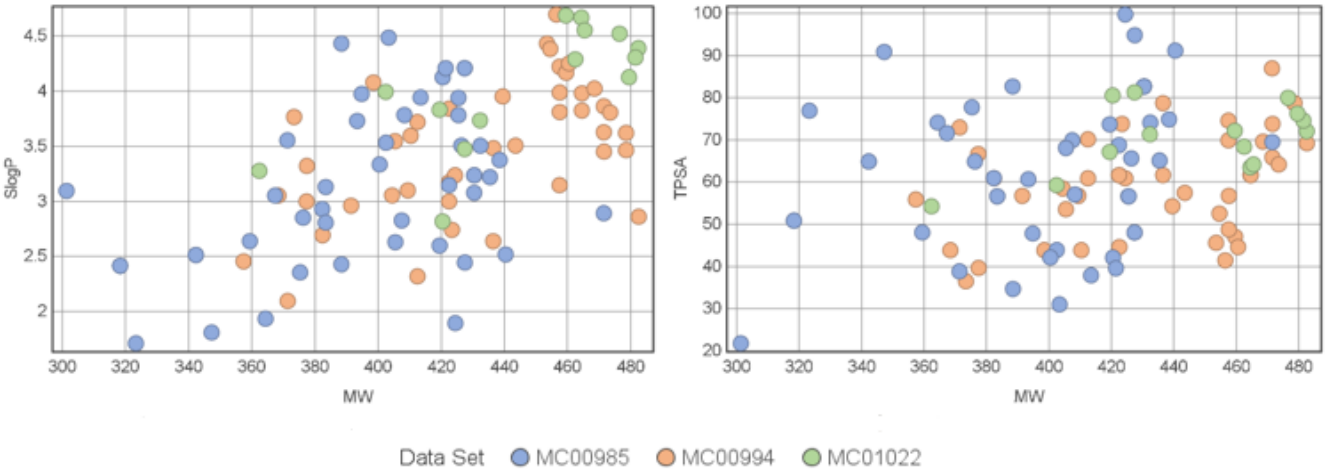


Figure 41: MW-LogP (left) and MW-TPSA (right) distributions of library compounds in the Ro5 space.

These computational results indicate that the generated library should contain molecules with reasonable bioavailability and have the potential for excellent specificity. However, possessing optimal physicochemical properties does not directly translate into a high quality compound collection, as diversity and chemical space coverage have been reported to play a major role in addressing the overall quality of the library.[42]

Diversity is always measured as a relative property of the molecules within the investigated set rather than an absolute measure, and numerous computational tools have been developed to measure diversity in a quantitative manner.[152, 153] One method often used for the diversity assessment is based around the calculation of molecular descriptors followed by principal component analysis, providing a measure of the chemical space coverage.[44, 154] Another commonly used method revolves around the calculation of the principle moment of inertia (PMI) for the assessment of molecular shape diversity.[142] PMI descriptors assess the extent to which a given molecule possess rod, disc or spherical shape. The PMI plot is usually visualised as a ternary graph where each vertex represents a specific shape (top-left: rod shape, top-right; sphere shape, bottom: disc shape). Molecules are represented in the continuum between the three vertices and their position in the plot is defined by the degree to which their structure

exhibits those shape classes.[155] A representation of the ALBA library *via* a PMI plot generated using Knime, is reported in Figure 42. The library shows a broad coverage of the plot area, with the majority of the molecules laying towards the rod-disc area, with some compounds shifted towards the center area and the sphere-like shape. It is a satisfactory result, considering that molecules derived from the same scaffold are reasonably spread over the PMI plot showing that overall the library possess good molecular diversity.

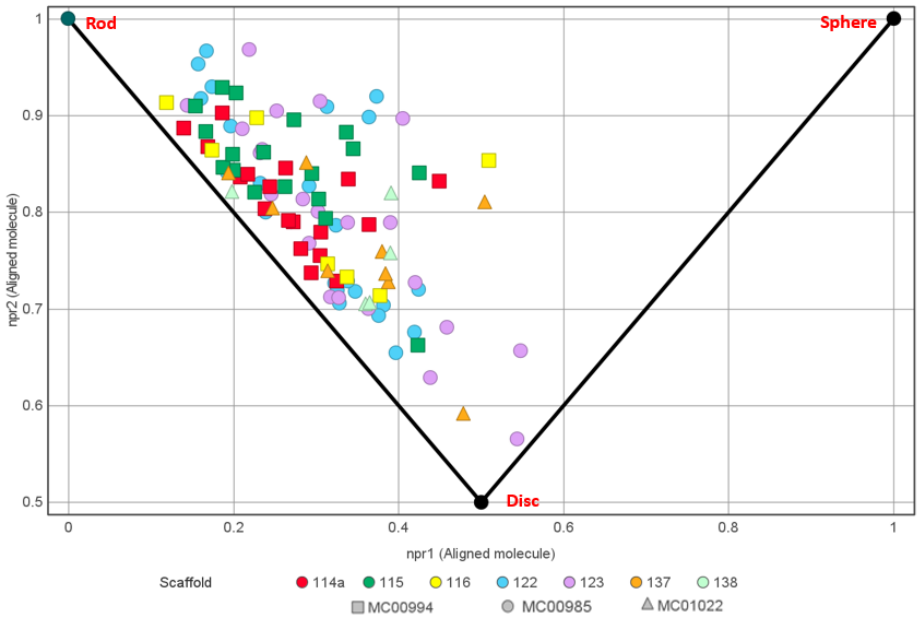


Figure 42: PMI plot representation of the ALBA library

However, the interpretation of what defines a 3D compound in a PMI plot can be somewhat subjective, as any molecule that is off the rod-disc axis may be considered to be 3D.[156] Moreover, a key characteristic, that could also represent a drawback of this visualisation method, is that PMI plots are completeley size independent. For instance, adamantane and buckminstefullerene will exhibit identical normalized PMI plots.[155] In conclusion, PMI plots provide a good approximation of the shape of the compounds, which is in line with the rigid bicyclic or tricyclic structures of the scaffolds from which the library is derived, but fails to compute their actual structural diversity.

To this end, the diversity of the compound collection was measured as a function of chemical space coverage.[44] Chemical space can be visualised in the 2- or 3-dimensional space where compounds are plotted in such a way that topological neighbourhood corresponds with compound similarity.[157] A map-based representation of the chemical space was generated in Datawarrior performing a principal component analysis (PCA) on one of the molecular descriptors. Since a molecular descriptor is nothing more than a set of variables calculated specifically for every single molecule, the *n* variables computed by the descriptor can be utilised as the *n* parameters of the data set for the PCA, therefore only binary or numerical vector descriptors can be used.[157] The *Skeletonsphere* descriptor was selected as a parameter, because it provided the best accuracy in similarity calculation amongst the binary or vector descriptors in DataWarrior.[157] The first components calculated from the PCA were used to position objects on a plane or in space such that clusters of similar objects were closely located, and dissimilarity was translated linearly into distance.

PCA analysis of the *SkeletonSphere* descriptor for the final synthesised library is depicted in Figure 43. As it can be expected, compounds deriving from the same scaffold units are clustered together, but the topological distance found within the position of each data set confirm the overall diversity of the library, as further proof that scaffold skeletal diversity is the main parameter that must be addressed to generate diversity across a library. This result aligns with the aims of the diversity oriented synthesis towards the generation of small molecule collections with a high degree of structural diversity that would explore large areas of chemical space.[42]

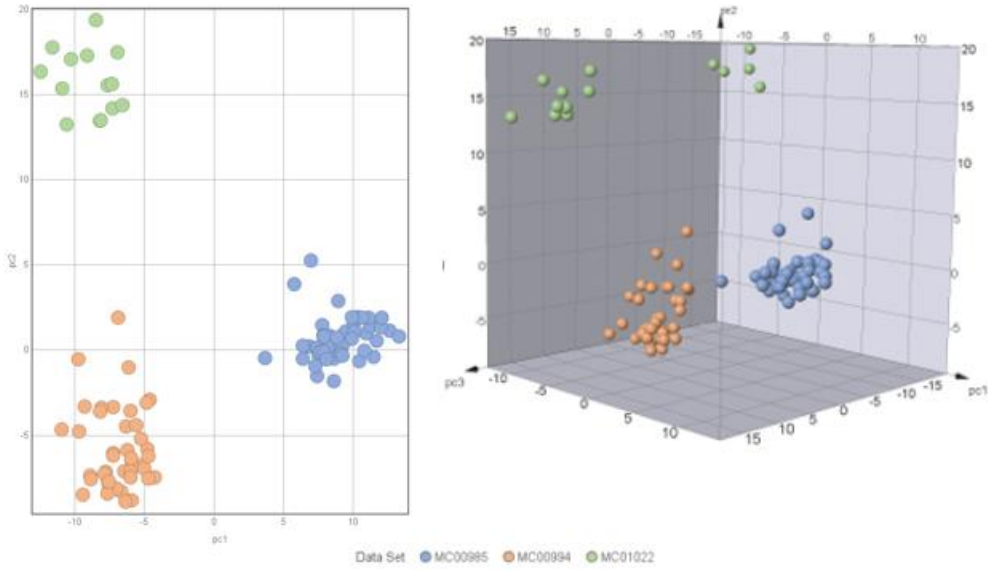


Figure 43: PCA analysis of the synthesised library showing 2D and 3D chemical space coverage.

From the results obtained by comparing the PMI and PCA plots it can be concluded that the compounds in the ALBA library, in addition to bearing optimal physicochemical properties, possess good shape diversity coverage and high structural diversity.

The last step towards the computational evaluation of the ALBA library was the comparison of the chemical space coverage against other compound collections. Comparison of compound collections is a widely accepted resource in library selection and design, and when designing new libraries, it is fundamental to assess their chemical space coverage and structural novelty.[158, 159] The exploration of uncharted portions of chemical space is highly seek within drug discovery due to the potential to identify novel compounds to probe both known and unknown biological targets.[25] To further investigate the quality of the ALBA library, its chemical space coverage was compared with that of a set of molecules from the ChEMBL database.[160] The ChEMBL dataset was filtered so that all the novel molecular entities that had entered phase 1 to 3 of the drug discovery process were selected, for a total of 1924 compounds. This specific subset of molecules would allow for the direct comparison of the molecules

included in the ALBA library with those that are currently being trialled in the drug discovery process. Assessing the diversity between these two data sets is extremely meaningful, because it will yield a direct comparison of their chemical space coverage and evaluation of their diversity. The physicochemical properties of the ChEMBL subset were calculated in Knime and compared to those of the ALBA Library (Table 4).

Table 4: Comparison of physicochemical properties between the two evaluated datasets.

Properties	ALBA Library	ChEMBL phase 1 -3	Guidelines
MW	301.4–482.65	74.1–741.2	< 500
LogP	1.7–4.7	- 8.19–5.7	≤ 5
TPSA	21.7–99.7	0–319.4	≤ 140
Rot. Bond	3–9	0–19	≤ 10
HBD	0–2	0–9	≤ 5
HBA	3–8	0–13	≤ 10
Fsp^3	0.25–0.81	0–1	N/A

The compounds included in the ChEMBL subset possess a range of physicochemical properties much wider compared to that suggested by literature guidelines. A total of 393 compounds were found to violate at least one Lipinski rule, accounting for 20% of the total dataset. However, the majority of the compounds was found to be compliant with the literature guidelines, with the spread of the physicochemical property distribution shown in Figure 43. Median values of the ChEMBL dataset for MW and LogP values were slightly lower compared to the ALBA Library, while the TPSA median value was higher. Comparison of the mean value and distribution related to the Fsp^3 parameter shows the ALBA Library is spreading more towards the higher range of the chart, showing that the molecules possess generally a higher level of saturation compared to those in the ChEMBL database. RoB and HBA parameters are very

similar in terms of median values and distributions, whilst the ALBA Library possess clearly fewer HBA donors.

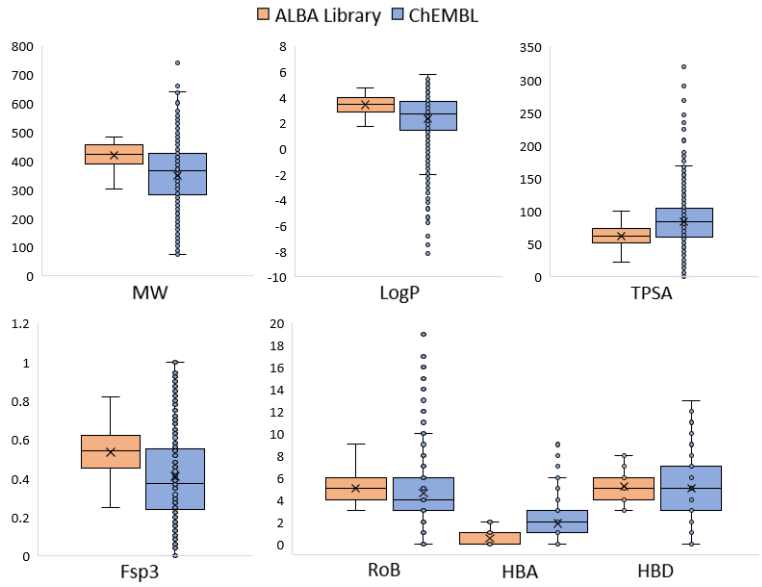


Figure 44: Physicochemical properties comparison between ALBA Library and CheMBL.

The chemical space coverage of the two datasets was computed using the *SkeletonSphere* descriptor and PCA and is depicted in Figure 45.

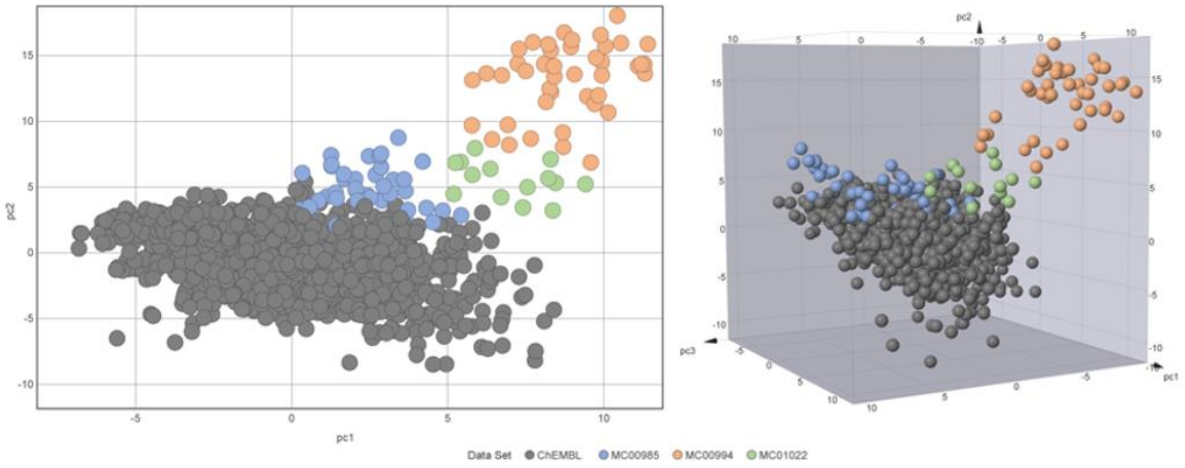


Figure 45: Chemical space coverage of the ALBA library compared to a ChEMBL subset.

The PCA shows that the ALBA Library mostly covers a different portion of chemical space compared to that of the ChEMBL dataset, and only a small portion of the space is shared

between the two datasets. In addition to the optimal physicochemical property distribution, these computational results corroborate the overall quality of the ALBA library, confirming its ability in the exploration of uncharted portion of chemical space, meeting all the requirements of medicinal chemistry for the synthesis of novel structurally diverse libraries that occupy uncharted portions of chemical space.

Next, the chemical space coverage of the ALBA Library was compared against the known medicinal chemistry space, represented by 1589 FDA approved drugs from the ZINC database (Figure 46).[161]

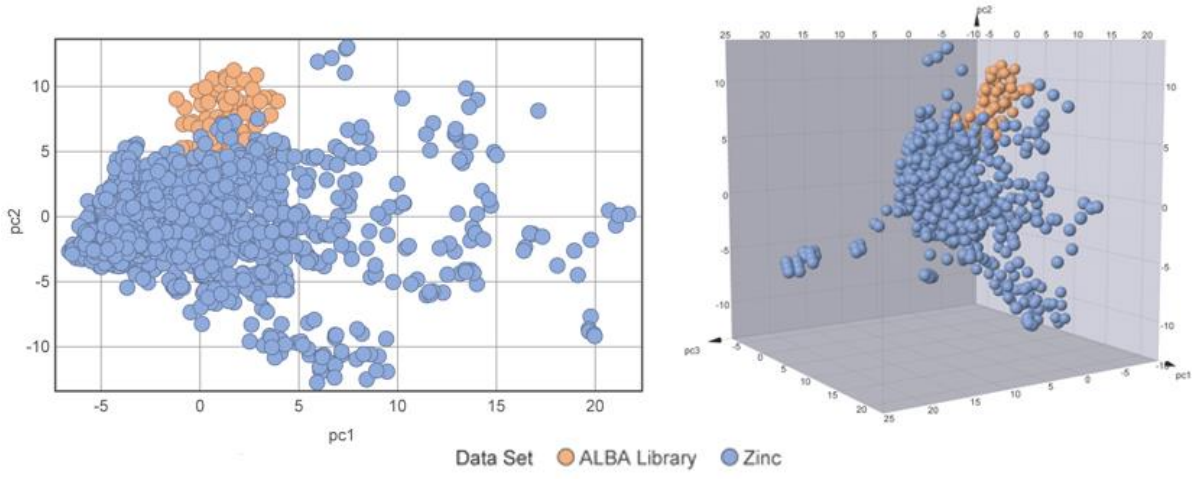


Figure 46: Comparison of chemical space coverage

Compounds included in the ALBA library occupy a portion of the chemical space situated on the outer edge of the mapped medicinal chemistry space. However, in the FDA approved drugs dataset, 615 molecules were found to violate at least one Lipinski rule accounting for the 39% of the whole dataset. Therefore, almost half of the molecules included in the dataset are lying outside the boundaries of those specific physicochemical property ranges that the ALBA library was intended to target. The analysis was repeated with the FDA dataset filtered in accordance with Lipinski rule, the results of the chemical space mapping are reported in Figure 47.

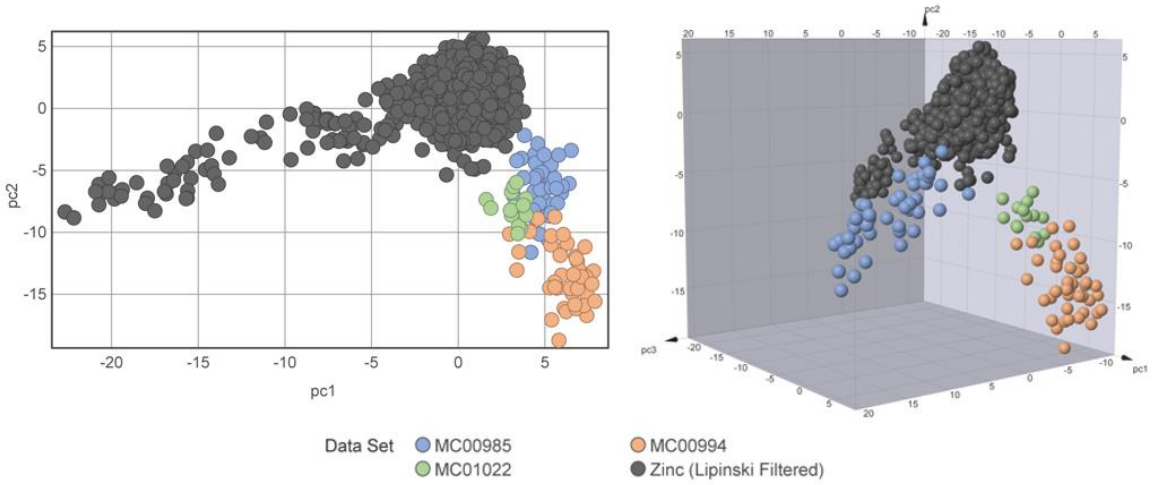


Figure 47: Comparison of chemical space coverage (compounds filtered following Lipinski rule).

From analysis of this subset the computed diversity between the ALBA library and the filtered FDA database appears clear, showing the compounds occupy a distinct portion of the chemical space. It should also be noted from both Figures 45 and 45 how the chemical space coverage differs in relation to the scaffold possessed by the molecules of the libraries. All the molecules bearing a decahydro-1,6-naphthyridine cores are clustered in two adjacent clusters (MC00994 and MC01022 libraries), whilst compounds bearing a decahydro-pyranopyridine scaffold occupy a different portion of chemical space.

Computational analysis of the synthesised compounds showed that the scaffolds derived from the modification of the polycyclic frameworks obtained via the gold-catalysed process could represent optimal starting points for the generation of a compound library for early-stage drug discovery. The diversity of the compound collection was demonstrated *via* analysis of the chemical space coverage, while the ALBA library occupied different portions of chemical space when compared to a set of investigational compounds undergoing phase 1 to 3 of the drug discovery process. The chemical space of the synthesised library was also found to be different from that of a set of FDA approved drugs, with this difference even clearer when the analysis

is carried out after a Lipinski rule filter is applied. However, these results were based upon calculated physicochemical properties and descriptors. To further validate the quality of the compounds included in the ALBA library, experimental values of some critical physicochemical properties and biological activity were investigated. In particular: ElogD and hERG inhibition.

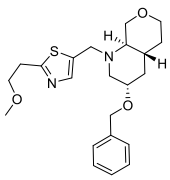
5.2.3.2. ADME studies

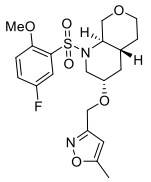
Lipophilicity is an important physicochemical parameter monitored in drug discovery, which impacts on individual ADME parameters and more widely on the overall compound quality.[162] High lipophilicity values have been linked to compromised solubility and metabolism as well as increased off-target binding and hERG inhibition.[1, 162-165] On the other hand, low lipophilicity might introduce other issues related to the difficulty of absorption through cellular membranes unless specific uptake mechanisms are in effect.[166, 167] An increasing body of literature has been published and attempted to provide where the optimum lipophilicity range lies.[168, 169] One of the most influential views was that of Lipinski, highlighted in the "Rule of 5", where the ideal value for the LogP of a drug candidate should be <5.[1]

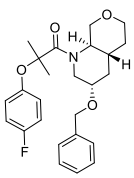
Given the importance of lipophilicity as a qualitative parameter, different computational methods have been conceived for its prediction to expedite the drug discovery process and are routinely employed by medicinal chemists.[170] However, experimental values for lipophilicity often deviate from the calculated ones as a result of the high dissimilarity between the molecules being predicted from those used in the training sets of the algorithms.[170] These methods are valuable, especially when designing libraries of compounds, however if possible computed values should be replaced by measured values,[171] particularly as many compounds are ionized at physiological pH, and the partition coefficient is effectively a distribution coefficient (D),

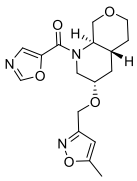
which is generally measured as the distribution between an aqueous buffer at physiological pH (7.4) and *n*-octanol.[171] This measure will offer a pH-dependent differential solubility of the species to better estimate the compounds absorption and solubility behaviour.[171] The method exploited for this measurement involved the RP-HLPC analysis from which the retention data is correlated with the relative lipophilicity of the compounds. Experimental ELogD values for a set of 11 molecules were measured and compared to the cLogP values obtained during the parameter calculation at the virtual enumeration step and are shown in Table 5.

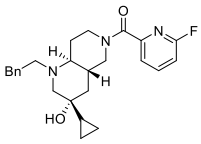
Table 5: Comparison of cLogP and ELogD for selected compounds.

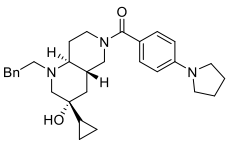

168a

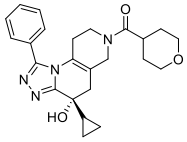

169d

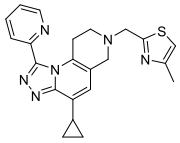

167n

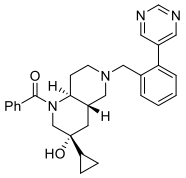

167r

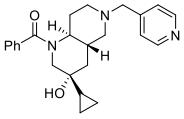

172c

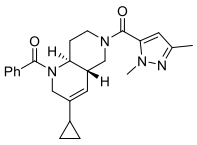

172e


175a


176f


173h


173j


172y

Compound	Calculated LogP[a]	Average ELogD[7.4]	Standard error	Δ (ElogD–LogP)
168a	3.5	3.3	0.03	-0.2
169d	2.5	3.0	0.03	0.5
167n	4.2	5.1	0.02	0.9
167r	1.8	0.6	0.01	-1.2
172c	3.1	3.7	0.02	0.6
172e	4.2	5.6	0.03	1.4
175a	2.8	2.6	0.02	-0.2
176f	4.0	2.6	0.05	-1.4
173h	4.0	3.6	0.03	-0.4
173j	2.9	2.5	0.05	-0.4
172y	3.1	3.9	0.02	0.8

[a]: calculated in KNIME using the "RDkit Descriptor calculation" node.

Apart from three measurements (Table 5, entries **167r**, **172e**, and **176f**), experimental values were all found within one unit distance from those calculated *via* di RdKit in Knime, and the calculated logP can therefore be utilised as a good approximation of the distribution for the other library compounds. Almost all the compounds were still found within ElogD < 5. Only two measurements, concerning compounds **167n** and **172e**, were found to slightly exceed the suggested guideline. However, a trend that could explain deviations of LogD from the calculated LogP could not be extrapolated from the limited number of measurements.

Further assessment of the ALBA library quality involved the estimation of possible toxicity effects. Early detection of possible toxicity effects is crucial for every drug discovery process. Toxicological profiling of drug candidates can minimise attrition and avoid late-stage failures for potential adverse effects.[172] In particular, QT interval prolongation and related Torsades de Pointes (TdP) have become the main critical issues in drug discovery.[162] In a very small percentage of patients, drug-induced QT interval prolongation might result in a potentially fatal cardiac arrythmia, called Torsades de Pointes, which can degenerate in ventricular fibrillation and sudden death.[162] As a consequence of the many withdrawn drugs that affected normal cardiac function, prediction of the fatal risk from QT prolongation in the early stage of the drug discovery process became a critical assessment, aimed to further improve the rational drug design and success rates.[162]

Drug-induced QT interval prolongation have been associated with inhibition of the hERG potassium channel.[162] Prediction of hERG inhibition is complicated, resulting from the receptor promiscuity that allows for structurally diverse drugs to block this channel.[173] As a result, most drug-like molecules tend to possess at least a modest potency for hERG inhibition, and very few are found to have little to none hERG blocking activity.[174] Some *in silico* prediction models

for hERG inhibition have been reported to help during the initial drug design and some physicochemical parameters such as lipophilicity, number of basic nitrogens and number of rotatable bonds have been linked to hERG inhibition.[175] Even if silico prediction and assessment of the physicochemical properties could provide an acceptable estimation of possible hERG inhibition, this toxic effect is usually directly measured *via* electrophysiological analysis.[176] However, despite the reasonable safety issue raised by a significant hERG inhibition, it does not automatically result in a compound being rejected in drug discovery programme. Examples of approach towards the mitigation of the hERG blocking activity usually revolve around the modification of their physicochemical parameters, such as reduction of the lipophilicity and basicity, or variation of the molecular structure towards increased rigidity.[175] These variations are usually performed at the lead-optimisation stage, and successful attempts have been reported in the literature.[175] Moreover, hERG inhibition risk assessments are not usually a clear-cut decision and the risk-benefit perspective needs to be evaluated before stopping or continuing a compound development.[177]

Given the importance of drug safety, a set of molecules from the ALBA library were analysed for their hERG inhibition. The compounds were selected based on their physicochemical properties, LogP, number of basic nitrogens and number of rotatable bonds, as these parameters have all been linked with increased hERG inhibition.[175] The distribution of these pharmaceutical properties in relation to the ALBA library was plotted in a scatter plot, the attention in the testing was mainly focused on those compounds that simultaneously possessed a combination of properties that potentially could be linked with hERG inhibition and are circled in red in Figure 48.

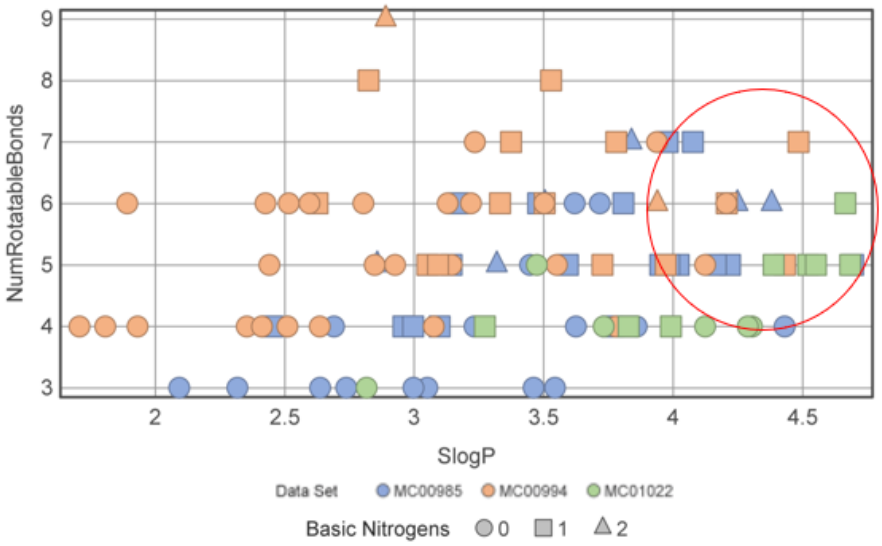


Figure 48: Compound distribution based on RoB, LogP and number of basic nitrogens.

Five compounds were selected from this area, whilst the other two compounds were selected outside based on their physicochemical properties and in such a way that almost all the scaffolds included in the ALBA library could be representatively tested. The selected molecules for the hERG inhibition analysis are shown in Figure 48. In particular **172h** was selected because it possessed low logP and RoB, and no basic nitrogens, whilst **167m** was selected because it possessed low logP and no basic nitrogens but a relatively high RoB. The selected molecules for the hERG inhibition analysis are shown in Figure 49.

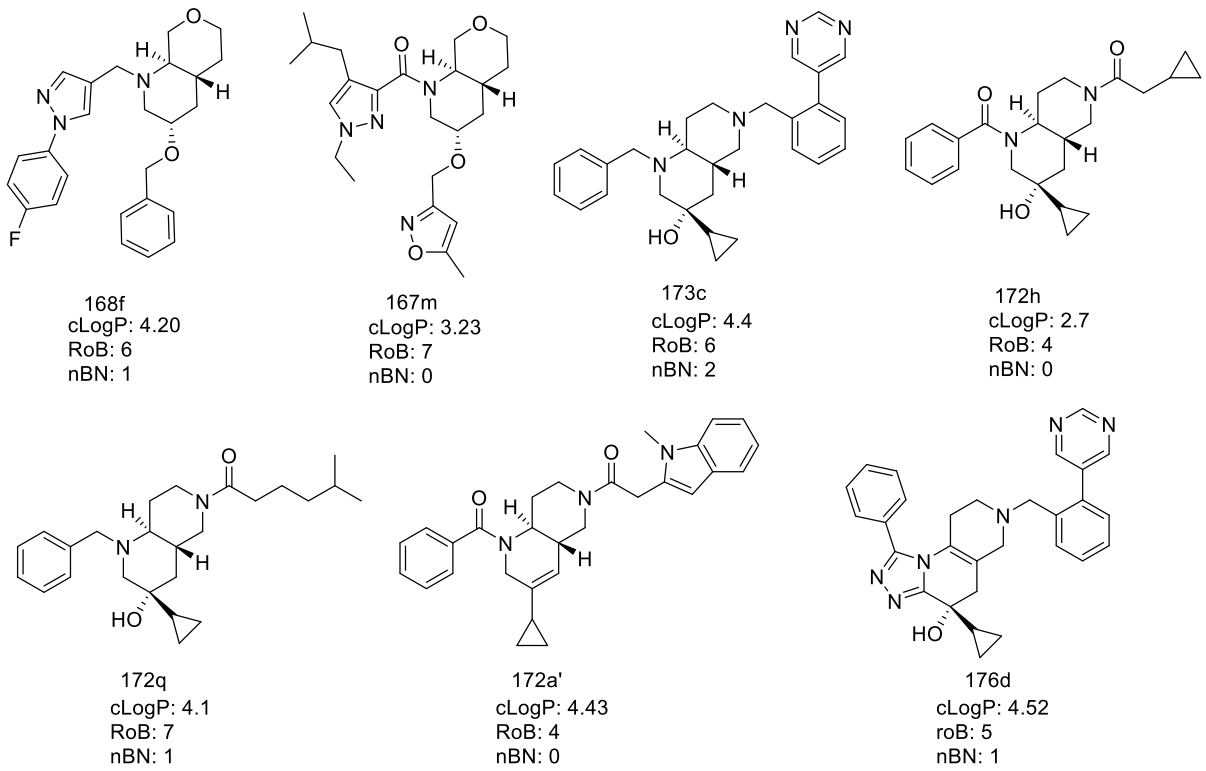


Figure 49: Compounds selected for hERG inhibition.

The selected compounds were measured at Apconix using an automated patch-clamp, at a single test concentration of 30 μM and the results are given in %hERG inhibition. A compound is considered inactive if it shows <30% inhibition, whilst it is considered active and might result in biologically significant interaction if the measured inhibition is >50%. The results regarding the selected molecules are shown in Figure 50. Each dot in the plot represents a successful measurement of current inhibition carried out on a single cell. The red line represents the mean % hERG inhibition of each compound.

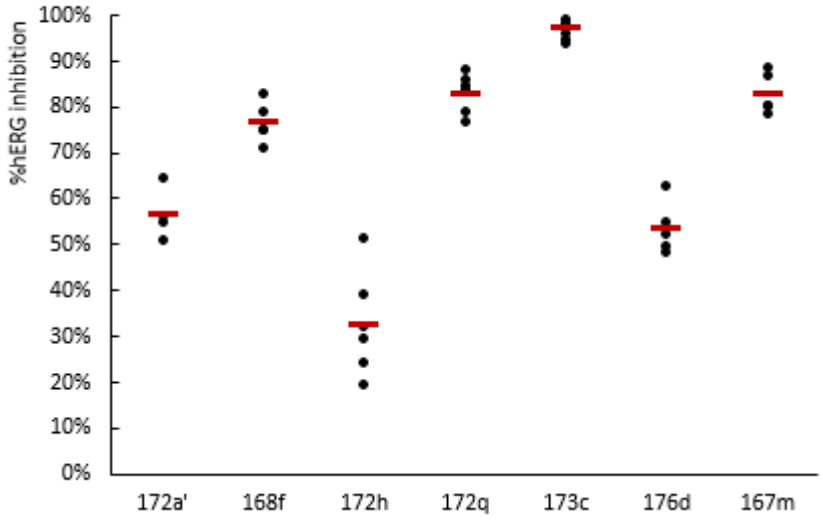


Figure 50: hERG inhibition, test concentration 30 µM

172h showed inhibition lower than 50%, confirming that the evaluation of physicochemical properties could represent a good initial assessment of the hERG inihibition. However, the estimation is not straightforward when one or more parameters approaches the highest part of the ranges. The other compounds all showed some degree of inhibition, spanning from slightly above 50% to 100%. **176d** and **172a'** showed inhibition slightly above this threshold, whilst **168f** showed around 75% hERG blockage. **172q** and **168m** showed very high hERG activity despite the latter possessing low logP and no basic nitrogens and **173c** showed the highest hERG inhibition.

The tested compounds showed moderate to high hERG inhibition, but this outcome does not automatically result in the rejection of these molecular entities from drug discovery programs. The first consideration that should be taken in account is that the compound concentration for the hERG inhibition test (30µM) is higher than the usual threshold potency of a hit molecule in a HTS screening (100nM–5µM).[178] Another important consideration is selectivity of the hit molecule towards the intended biological target over hERG binding.[175] Selectivity in drug

discovery is intended as the ability of the molecule to avoid binding with undesirable targets that could lead to adverse effects.[179] Both potency and selectivity increase as a consequence of the manipulation of the hit molecule during the hit-to-lead optimisation stage and hERG binding is effectively reduced by modification of the physicochemical parameters at this stage.[178, 179] In the event that one of the ALBA molecules was found active towards a biological target, knowing the hERG inhibition behaviour linked to some molecules present in the library is a highly valuable information that would benefit the hit-to-lead optimisation stage, so that potent, selective and safe drug candidates can be delivered.

5.3. Conclusions and future work

The drug discovery process suffered from the implementation of compound libraries with high scaffold redundancy and lack of diversity, that inevitably resulted in a limited discovery of novel molecular entities both for known and unknown biological targets. The implementation of the chemical space concept and diversity-oriented synthesis have benefited the drug discovery process through highlighting the limitation of their synthetic methodologies and paved the way towards the synthesis of more complex and diverse structures. Following these concepts, a library of 103 compounds (ALBA library) was synthesised from five selected scaffolds, bearing optimal physicochemical properties, and covering uncharted portions of chemical space. 57 of the synthesised library compounds were generated from the elaboration of four scaffolds derived from pluripotent framework **91h** (Figure 51). During this work the synthesis of **91h** was achieved in excellent yield at multigram scale *via* a gold-catalysed double annulation (Scheme 21, Chapter 3.2.2.1). Moreover, an easily removable Boc group was installed on the nitrogen on the linker and a series of pharmaceutically relevant substitutions, other than the cyclopropyl, were installed on the framework. Six unique scaffolds (**114a**, **115**,

116, **137**, **138**, **149** and **159**) were derived from **91h** exploiting primarily the chemistry of the amidine moiety embedded in its structure or from the reactivity of the Boc group. All the scaffolds in this series bear the decahydro-1,6-naphtyridine core, a motif that is often found in Nature but underrepresented in mainstream drug discovery programs. Four of the six scaffolds were selected, and following chemoinformatic studies, a virtual library was enumerated, and the most representative compounds were selected to be synthesised.

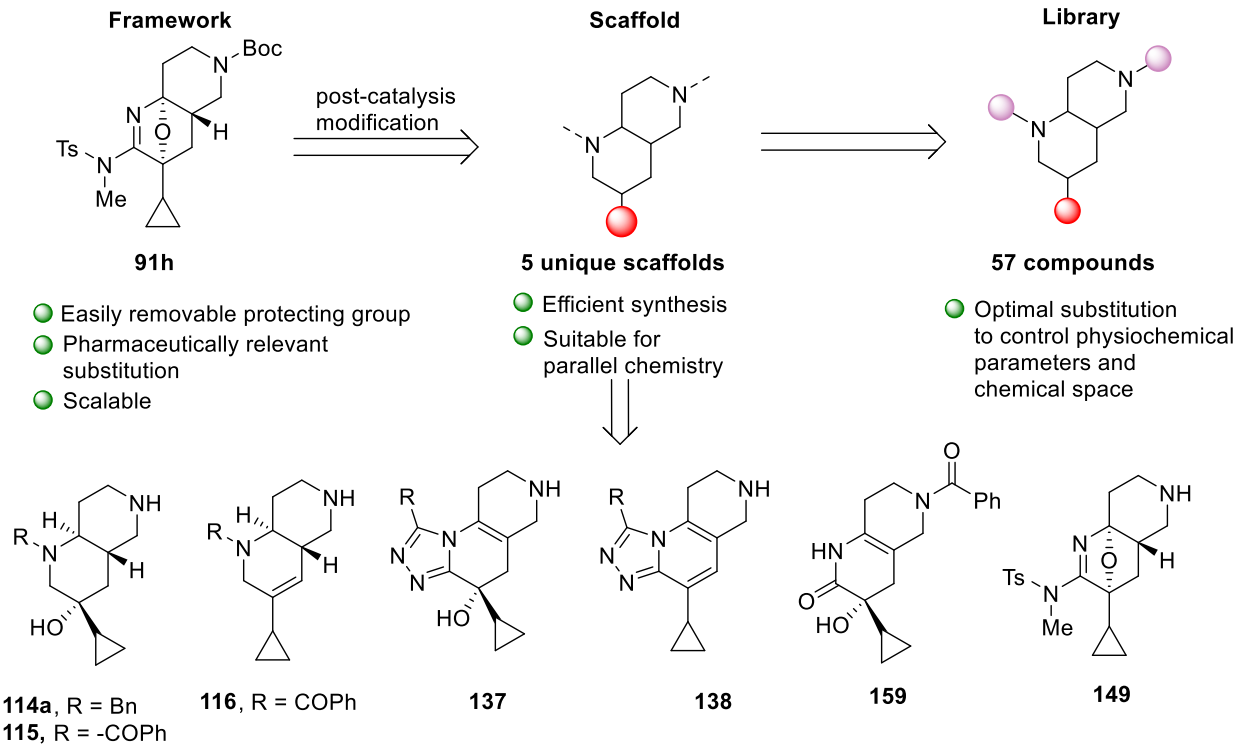


Figure 51: Summary of the work done for framework 91h.

The other 45 compounds included in the ALBA library derived from the work done on pluripotent framework **91n** (Figure 52). One of the three scaffolds derived from **91n** was selected as a starting point for a library synthesis, and following chemoinformatic studies, a virtual library was enumerated. The most representative compounds were selected and successively synthetised.

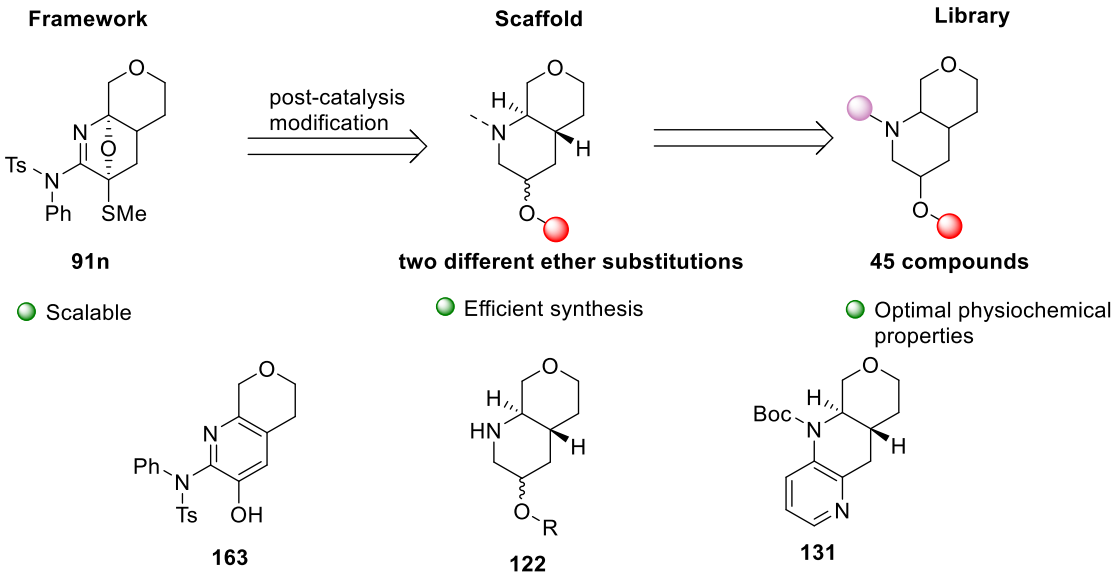


Figure 52: Summary of the work done on framework 91n.

The compound included in the ALBA library are now within the Haworth collection and their biological activity is being tested against various targets in drug discovery programs at the University of Birmingham.

Concerning future work, the gold-catalysed double annulation give access to highly functionalised frameworks whose chemistry offers a broad spectrum of possibilities for further investigations.

The chemistry explored in this thesis mostly revolved around one example of pluripotent framework, precisely **91h**. However, the C-2 gold-catalysed double annulation allowed the synthesis of other frameworks bearing pharmaceutically relevant substitutions (see chapter 3.2.1., scheme 23). To further confirm the relevancy of the chemistry developed during this work it would be interesting to see it applied to similar frameworks. The compound derived from this study would also further the diversity of the molecules included in the ALBA library, with the possibility to access diverse portions of the chemical space.

During this thesis, a limited investigation was carried out on the C-5 gold-catalysed double annulation. The possibility to apply the chemistry developed throughout this thesis to those type of pluripotent frameworks would greatly increase the scope of scaffolds accessed from the double annulation methodology.

6. Chapter 6: Supporting information

6.1. General experimental

Commercial chemicals were purchased from major suppliers (Sigma-Aldrich, Acros organics, Fisher Scientific, VWR international or Combi-Blocks) and used without prior purification, unless otherwise specified. Solvents that required to be dry were stored over activated 4 Å molecular sieves for 24 h prior use. The glassware used for reactions carried out under argon atmosphere was oven dried at 115 °C for 24 h before use and left cooling under a nitrogen stream or flame–dried with a hot air gun under vacuum at 0.1 mbar and backfilled with argon. The vacuum/argon purge was carried out three times. Reactions which required heating were submerged in preheated paraffin oil baths or aluminium heating mantles and the temperature was controlled by an external probe. For reactions above 10 g scale an internal thermometer was also introduced for better temperature control. Reactions which required cooling were submerged in the following baths: 0 °C ice/water, −41 °C dry ice/MeCN, −78 °C dry ice/acetone, −96 °C liquid N_2/methanol. Reactions were monitored using thin layer chromatography Merck silica gel 60 F_{254} (glass and aluminium support) plates which were developed using standard visualizing agents: UV fluorescence (254 nm) or potassium permanganate/Δ, vanillin/Δ or anisaldehyde/Δ. Flash chromatography was carried out on Sigma Aldrich silica gel (60 Å, 230–400 mesh, 40–63 μm), Interchim prepacked spherical silica columns (60 Å, 30 μm) or BUCHI Flashpure silica columns (irregular, 40 μm) and were run manually or with a CombiFlash® NextGen 300+ using UV detection or BUCHI® Reveleris X2 using UV and ELSD detection. Gradient eluent mixtures are described including any isocratic holds: (0→30 hold→100, hexane/EtOAc). Melting points were measured in open ended capillaries using a Stuart Scientific melting point apparatus and are uncorrected. ^{1}H-

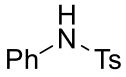
NMR and ^{13}C-NMR experiments were recorded using Bruker Neo-400 (^{1}H = 400 MHz, ^{13}C = 101 MHz), AVIII300 (^{1}H = 300 MHz), Bruker Avance or Bruker Avance II-Ultrashield 400 (^{1}H = 400 MHz, ^{13}C = 101 MHz) spectrometers at 295–300 K. 13C NMR spectra were recorded using the UDEFT, JMOD or APT pulse sequence from the Bruker standard pulse program library. 2D NMR spectra were recorded using the Bruker standard pulse program library. Spectra were processed using MestReNova 12.0. Chemical shifts (δ) are given in ppm relative to TMS and are calibrated using residual solvent peaks ($CDCl_3$: δC ≡ 77.16 ppm; MeOD: δC ≡ 49.00 ppm, DMSO–d6: δC ≡ 39.52 ppm; residual $CHCl_3$ in $CDCl_3$: δH ≡ 7.26 ppm, residual MeOH in MeOD: δH ≡ 3.31 ppm, residual DMSO in DMSO–d6: δH ≡ 2.50 ppm). Spectral data for ^{1}H-NMR are reported as follows: chemical shift (multiplicity, coupling constant, number of protons) and for ^{13}C-NMR: chemical shift. The following abbreviations were used for multiplicity in ^{1}H-NMR: s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet). Coupling constants (*J*) are quoted in Hz to one decimal place. Where restricted rotation causes broadening of the NMR resonances, the centre of the peak is reported: (br. app. s). Where AB spin systems are reported the pattern is reported as a first order (i.e. two doublets), for example: 4.38 (d, J_{AB} = 13.1, 1H), 4.18 (d, J_{AB} = 13.1, 1H). Infrared spectra were recorded neat on a Perkin Elmer or Agilent Cary 630 FTIR (ZnSe) with Diamond ATR and wavelengths (ν) are reported in cm^{-1}. Mass spectra were obtained using Waters GCT Premier (EI), Waters LCT (ES) or Waters Synapt (ES) spectrometers. LCMS analysis were performed on an Agilent 1260 Bin. equipped with Agilent G6130B ESI and column Water xSelect CSH C18 30 × 2.1 mm, 3.5 mm. Methods: SC_Base: flow: 1 mL/min, Eluent A: 10 mM ammoniumbicarbonate in water (pH = 9.0), Eluent B: acetonitrile; Gradient: t_0: 5% B, $t_{1.6min}$ = 98% B, t_{3min} = 98% B, Post-run time: 1.4 min. SC_Acid: flow: 1mL/min, Eluent A: 0.1% formic acid in water, Eluent B: 0.1 % formic acid in acetonitrile; Gradient: t_0: 5% B, $t_{1.6min}$ = 98% B, t_{3min} = 98% B, Post-run

time: 1.3 min. SFC analysis were recorded on Waters UPC2, Bin pump ACQ-ccBSM and samples were purified on Waters Prep100q SFC System, PDA: Waters 2998; MS: Waters QDa; Fraction Collector: Waters 2767. UPLC analysis were performed on Waters IClass, Bin. Pump: UPIBSM; Autosampler UPISMFTN and SO; Column oven; PDA UPPDATC; SQD2 ESI, ELSD; Eluent A1: 0.1% formic acid in acetonitrile, Eluent B1: 0.1% formic acid in water; Eluent A2: acetonitrile, Eluent B2: 10mM ammonium bicarbonate in water.

The computational studies were carried out on a Macbook Pro (2018) using Knime and Datawarrior.

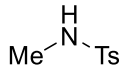
6.2. Starting Materials

4-Methyl-N-phenylbenzenesulfonamide (70a)

 *p*-toluensulfonyl chloride (3.42 g, 18.0 mmol, 1.20 eq) was added portion wise to a mixture of aniline (1.30 mL, 15.0 mmol) and pyridine (1.40 mL, 18.0 mmol, 1.2 eq) in CH_2Cl_2 (75.0 mL, 0.2 M). The reaction mixture was stirred at room temperature for 16h. The reaction mixture was then washed with 5% $HCl_{(aq)}$ (50.0 mL). The organic layer was washed with sat. $NaHCO_{3(aq)}$ (50.0 mL) and dried over anhydrous Na_2SO_4. After filtration and removal of the solvent under reduce pressure, the crude material was recrystallized from hot toluene yielding sulfonamide **70a** as white crystals (3.31 g, 89%).

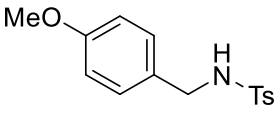
Scaling up: *p*-toluensulfonyl chloride (46.4 g, 243 mmol, 1.1 eq) was added portion wise to a mixture of aniline (20.0 mL, 221 mmol) and pyridine (21.5 mL, 265 mmol, 1.2 eq) in CH_2Cl_2 (1000 mL, 0.22 M). The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was then poured into a separating funnel and washed with 2 M $HCl_{(aq)}$ (300 mL), sat. $NaHCO_{3(aq)}$ (300 mL) and brine (300 mL) and dried over anhydrous Na_2SO_4. After filtration and removal of the solvent under reduced pressure the crude material was recrystallized from hot toluene yielding sulfonamide **70a** as white crystals (50.9 g, 93%); Purity: qNMR(methyl 3,5-dinitrobenzoate): 99.81%; mp: 102−104 °C [lit.[180] 97–99 °C]; IR (neat): *ν* (max) cm^{-1} 3246, 2899, 1947, 1598, 1482, 1415, 1433, 1154, 108; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.70–7.64 (m, 2H), 7.25–7.22 (m, 4H), 7.16–7.11 (m, 1H), 7.11–7.06 (m, 2H), 2.40 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.1 (C), 136.5 (C), 136.1 (C), 129.6 (2CH), 129.3 (2CH), 127.3 (2CH), 125.4 (CH), 121.7 (2CH), 21.7 (CH_3) ppm. Data match those reported in the literature.[180]

N,4-Dimethylbenzenesulfonamide (70b)



A solution of methylamine 2 M in THF (80.0 mL, 160 mmol, 2 eq) was added drop wise over 30 minutes to an ice cooled solution of *p*-toluensulfonyl chloride (15.3 g, 80.0 mmol) in CH_2Cl_2 (120 mL, 0.66 M) and the reaction mixture was left stirring at 0 °C for 2 h. The white precipitate formed during the reaction was filtered off and filtrated was concentrated under reduced pressure. The crude material was dissolved in EtOAc (150 mL) and washed with sat. $NaHCO_{3(aq)}$ (150 mL) and brine (150 mL) and dried over anhydrous Na_2SO_4. After filtration and removal of the solvent under reduced pressure compound **70b** was obtained as white crystals and was used in the next step without further purification (14.4 g, 78.0 mmol, 99%); mp = 75–77 °C; IR (neat): *v* (max) cm^{-1} 3265, 1595, 1315, 1155, 1058, 820; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.77–7.72 (m, 2H), 7.32 (d, *J* = 8.0, 2H), 4.31 (br. s, NH), 2.65 (d, *J* = 5.4, 3H), 2.43 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.5 (C), 135.8 (C), 129.7 (2CH), 127.3 (2CH), 29.4 (CH_3), 21.5 (CH_3). Data match those reported in the literature.[181]

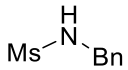
N-(4-Methoxybenzyl)-4-methylbenzenesulfonamide (85b)



4-methoxybenzylamine (2.80 mL, 22.0 mmol) was added to CH_2Cl_2 (22.0 mL, 1 M), after that Et_3N (6.10 mL, 44.0 mmol, 2 eq) was added and the solution was cooled to 0°C. *p*-toluensulfonyl chloride (8.30 g, 44.0 mmol, 2 eq) was then added portion wise at 0 °C. The reaction was then allowed to warm to room temperature and stirred for 16 h. The reaction mixture was then quenched with 1 M $HCl_{(aq)}$ (25 mL) and extracted with CH_2Cl_2 (3 × 25 mL) and dried over anhydrous Na_2SO_4. After filtration the solvent was removed under reduced pressure. The crude material was then recrystallized from hot toluene yielding sulfonamide **85b** as white crystals (4.91 g, 86%). mp = 119–121°C [lit.[182] 120 °C]; IR (neat): ν(max) cm^{-1} 3247, 2978, 2922, 1613, 1514, 1251, 1155; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 8.0 Hz, 2H) 7.31 (d, *J* = 8.0, 2H), 7.10 (d, *J* = 8.4, 2H), 6.78 (d,

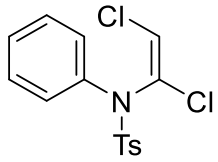
J = 8.4, 2H), 4.78 (m, 1H), 4.04 (d, *J* = 6.1, 2H), 3.76 (s, 3H), 2.43 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.3 (C), 143.4 (C), 136.9 (C), 129.7 (2CH), 129.2 (2CH), 128.3 (C), 127.2 (2CH), 114.1 (2CH), 55.3 (CH_3), 46.8 (CH_2), 21.5 (CH_3) ppm. Data match those reported in literature.[182]

N-Benzylmethanesulfonamide (85c)



Methanesulfonyl chloride (1.80 mL, 24.0 mmol, 1.2 eq) was added dropwise to an ice cooled solution of benzylamine (2.20 mL, 20.0 mmol) and Et_3N (5.60 mL, 40.0 mmol, 2.0 eq) in CH_2Cl_2 (40.0 mL, 0.5 M). After 15 minutes the cooling bath was removed and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was poured in a separating funnel and washed with 2 M $HCl_{(aq)}$ (30 mL), sat. $NaHCO_{3(aq)}$ (30 mL) and brine (30 mL) and further dried over Na_2SO_4. After filtration and removal of the solvent under reduced pressure the crude material was recrystallised from hot toluene yielding sulfonamide **85c** as white flake crystals (3.70 g, 81%); mp = 58–60 °C; IR (neat): ν(max) cm^{-1} 3224, 3019, 1453, 1293, 1183, 1058, 738; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.28 (m, 5H), 4.83 (br. s, 1H), 4.31 (d, *J* = 6.1, 2H), 2.85 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 136.7 (C), 128.9 (2CH), 128.1 (CH), 127.9 (2CH), 47.2 (CH_2), 41.1 (CH_3) ppm. Data match those reported in the literature. [183]

N-(1,2-Dichlorovinyl)-4-methyl-N-phenylbenzenesulfonamide (71a)



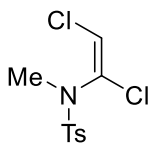
To a stirring suspension of sulfonamide **70a** (1.0 g, 4.00 mmol), Cs_2CO_3 (1.90 g, 6.10 mmol, 1.5 eq) in DMF (3.00 mL, 1.3 M) at 50 °C, TCE (0.40 mL, 4.4 mmol, 1.1 eq) was added dropwise over 10 minutes. The resulting mixture was stirred at 50 °C until reaction completion (monitored by TLC, approx. 2 h). Upon cooling to room temperature, the mixture was partitioned between of EtOAc (15 mL) and water (15 mL). The organic layer was separated and washed with brine (15 mL)

and dried over anhydrous Na_2SO_4. After removal of the solvent the pale yellow solid was recrystallized from hot ethanol to yield dichloroenamide **71a** as white crystals (1.01 g, 76%).

Scaling up: *Safety note: the reaction intermediate is dichloroacetylene which can spontaneously ignite in air (b.p. = 33 °C), therefore it is necessary to keep a positive argon pressure during the whole reaction time to prevent air intruding and ensuring vigorous stirring of the reaction mixture to prevent accumulation.*

To a stirring suspension of sulfonamide **70a** (20.0 g, 81.0 mmol), Cs_2CO_3 (39.5 g, 121 mmol, 1.5 eq) in DMF (62.0 mL, 1.3 M) at 50 °C, TCE (8.0 mL, 89 mmol, 1.1 eq) was added dropwise over 15 minutes. The resulting mixture was stirred at 50 °C until reaction completion (monitored by TLC, approx. 3 h). Upon cooling to room temperature, the mixture was partitioned between EtOAc (150 mL) and water (150 mL). The organic layer was washed with brine (2 x 150 mL) and dried over anhydrous Na_2SO_4. After removal of the solvent the pale yellow solid was recrystallized from hot ethanol to yield dichloroenamide **71a** as white crystals (22.0 g, 79%); Purity: qNMR(methyl 3,5-dinitrobenzoate): 99.01%; mp: 112−115 °C (EtOH); IR (neat): *ν*(max) cm^{-1} 3015, 2232, 1488, 1359, 1244, 1161; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 7.5, 2 H), 7.41–7.35 (m, 5 H), 7.27 (d, *J* = 7.5, 2 H), 6.48 (s, 1 H), 2.45 (s, 3 H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.6 (C), 137.7 (C), 135.6 (C), 130.7 (C), 129.6 (2CH), 129.4 (2CH), 129.1 (CH), 128.7 (2CH), 128.6 (2CH), 120.5 (CH), 21.7 (CH_3) ppm; Data match those reported in literature.[85]

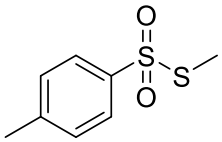
(E)-N-(1,2-dichlorovinyl)-N,4-dimethylbenzenesulfonamide (71b)



To a stirring suspension of sulfonamide **70b** (2.00 g, 10.8 mmol), Cs_2CO_3 (5.30 g, 16.2 mmol, 1.5 eq) in DMF (8.30 mL, 1.3 M) at 50 °C, TCE (1.10 mL, 11.9 mmol, 1.1 eq) was added dropwise over 10 minutes. The resulting mixture was stirred at 50 °C until reaction completion (monitored by TLC, approx. 2 h). Upon cooling to room

temperature, the mixture was partitioned between of EtOAc (15 mL) and water (15 mL). The organic layer was separated and washed with brine (15 mL) and dried over anhydrous Na_2SO_4. After removal of the solvent the crude material was purified via silica gel flash column chromatography [Heptane:EtOAc (7:3)] to give **71b** as white crystals (2.31 g, 75%); IR (neat): ν(max) cm^{-1} 3090, 1591, 1349, 1162; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 8.3, 2H), 7.33 (d, *J* = 8.3, 2H), 6.39 (s, 1H), 2.94 (s, 3H), 2.45 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.8 (C), 134.6 (C), 131.6 (C), 129.8 (2CH), 128.6 (2CH), 119.8 (CH), 35.4 (CH_3), 21.8 (CH_3) ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_{10}H_{11}Cl_2NO_2S$: 279.99603, found 256.04582 $[M+H]^+$.

Methyl thiotosylate (TsSMe)

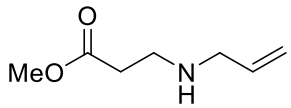


Dimethyl disulfide (0.40 mL, 5.0 mmol, 0.5 eq), sodium toluensulfonate (2.5 g, 14 mmol, 1.4 eq) and Iodine (2.5 g, 10.0 mmol, 1.0 eq) were added to CH_2Cl_2 (15 mL, 0.66 M) and stirred at room temperature overnight. The reaction mixture was then poured into a separating funnel with a solution of $Na_2S_2O_3$ (2.5 g) and NaOH (1.0 g) in 50 mL of water and then shaked until colorless. The organic phase was separated and further washed with water (25 mL). After removal of the solvent under reduced pressure, the crude material was recrystallized from hot ethanol affording **TsSMe** as white crystals (1.70 g, 90%).

Scaling up: Dimethyl disulfide (2.15 mL, 24.3 mmol, 0.5 eq), sodium toluenesulfonate (12.1 g, 67.9 mmol, 1.4 eq) and Iodine (12.3 g, 48.5 mmol, 1.0 eq) were added to CH_2Cl_2 (75 mL, 0.66 M) and stirred at room temperature overnight. A solution of $Na_2S_2O_3$ (11.0 g) in 150 mL of water was added to the reaction mixture and stirred until colourless. The organic phase was separated and further washed with water (80 mL) and brine (50 mL). After removal of the solvent under reduced pressure, the crude material was recrystallized from hot ethanol affording

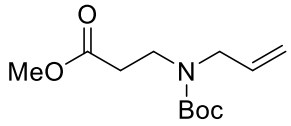
TsSMe as white crystals (8.2 g, 84 %); Purity: qNMR(methyl 3,5-dinitrobenzoate): 99.86%**;** mp: 56–57 °C (EtOH); IR (neat): *v*(max) cm^{-1} 2995, 2925, 1591, 1425, 1326, 1311, 1293, 1138; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 8.3, 2 H), 7.37 (d, *J* = 7.0, 2 H), 2.53 (s, 3 H), 2.48 (s, 3 H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.8 (C), 140.9 (C), 129.9 (2CH), 127.2 (2CH), 21.7 (CH_3), 18.0 (CH_3) ppm. Data match those reported in literature.[184]

Methyl 3-(allylamino)propanoate (64)



Methyl acrylate (1.80 mL, 20.0 mmol) was added to a solution of allylamine (2.30 mL, 30.0 mmol, 1.5 eq) in MeOH (100 mL, 0.3 M) and the reaction was stirred at 40 °C for 4 h. After which the solvent was removed under reduced pressure and the crude material was subjected to silica gel flash column chromatography [CH_2Cl_2:MeOH (9:1)] to yield ester **64** as a pale yellow liquid (2.41 g, 84%); IR (neat): *v* (max) cm^{-1} 2953, 2842, 1732, 1644, 1437, 1173; ^{1}H NMR (400 MHz, Chloroform-*d*): δ = 5.91 (ddt, *J* = 17.2, 10.2, 6.0, 1H), 5.21 (dq, *J* = 17.1, 1.6, 1 H), 5.12 (dq, *J* = 10.3, 1.4, 1 H), 3.71 (s, 3 H), 3.29 (dt, *J* = 6.0, 1.4, 2 H), 2.91 (t, *J* 6.5, 2 H), 2.56 (t, *J* = 6.5, 2 H) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*): δ 173.2 (C), 136.6 (CH), 116.0 (CH_2), 52.2 (CH_2), 51.6 (CH_2), 44.3 (CH_3), 34.5 (CH_2) ppm; LRMS (EI-TOF): 143.10 $[M+H]^+$. Data match those reported in the literature.[185]

Methyl 3-(allyl(tert-butoxycarbonil)amino)propanoate (65a)

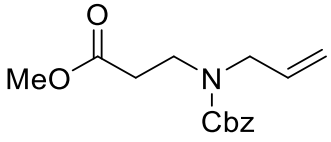


To a solution of ester **64** (1.50 g, 10.5 mmol), Et_3N (1.7 mL, 12.7 mmol, 1.2 eq) and DMAP (129 mg, 1.05 mmol, 10 mol%) in CH_2Cl_2 (11.0 mL, 0.5 M) at 0 °C, a solution on Boc_2O (2.76 g, 12.7 mmol, 1.2 eq) in CH_2Cl_2 (10.0 mL, 1.3 M) was added dropwise over 30 minutes. The reaction mixture was allowed to warm to room temperature and stirred for an additional 14h. The organic phase was washed sequentially with 1% $HCl_{(aq)}$ (20 mL), saturated $NaHCO_{3(aq)}$ (20 mL) and then brine (20 mL)

and dried over anhydrous Na_2SO_4. After filtration and removal of the solvent under reduced pressure, the crude material was subjected to silica gel flash column chromatography [hexane:EtOAc (1:1)] to yield ester **65a** as a colourless liquid (2.09 g, 82%).

Scale up: Methyl acrylate (4.5 mL, 50 mmol) was added to a solution of allylamine (5.9 mL, 100 mmol, 1.5 eq) in MeOH (250 mL, 0.2 M) and the reaction was stirred at 40 °C for 4 h. After which the solvent was removed under reduced pressure and the crude material was dissolved in CH_2Cl_2 (100 mL, 0.5 M). Et_3N (10.5 mL, 75 mmol, 1.5 eq) and DMAP (0.61 mg, 5 mmol, 10 mol%) were added and the mixture was cooled down to 0 °C. A solution on Boc_2O (12.0 g, 55 mmol, 1.1 eq) in CH_2Cl_2 (40 mL, 1.3 M) was added dropwise over 30 minutes. The reaction mixture was allowed to warm to room temperature and stirred for an additional 14h. The organic phase was washed sequentially with 1% $HCl_{(aq)}$ (100 mL), saturated $NaHCO_{3(aq)}$ (100 mL), then brine (100 mL) and dried over anhydrous Na_2SO_4. After filtration and removal of the solvent under reduced pressure, the crude material was distilled under reduced pressure (107 °C/ 1 mbar) yielding ester **65a** as a colourless liquid (8.8 g, 36.2 mmol, 72% over two steps); *The data provided thereafter were from a sample of the product purified by column chromatography*: IR (neat): *v* (max) cm^{-1} 2977, 1736, 1691, 1463, 1407, 1365, 1247, 1160; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.86–5.71 (m, 1H), 5.11 (app. d, *J* = 12.3, 2H), 3.83 (s, 2H), 3.67 (s, 3H), 3.50–3.42 (broad, 2H), 2.60 (d, *J* = 8.4, 2H), 1.63 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.2 (C), 155.2 (C), 133.1 (CH), 116.6 (CH_2), 79.9 (C), 51.7 ($2CH_2$), 42.5 (CH_3), 33.5 (CH_2), 28.4 ($3CH_3$) ppm; HRMS (ES-TOF): m/*z*: calcd for $C_{12}H_{21}NO_4Na$: 266.1371 found 266.1368 $[M+Na]^+$. Data match those reported in the literature.[185]

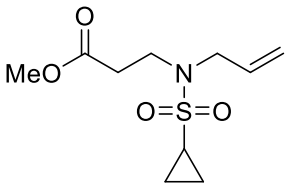
3-(Allyl((benzyloxy)carbonyl)amino)propanoate (65b)



Benzyl chloroformate (0.60 mL, 4.12 mmol, 1.2 mmol) was added to a solution of ester **64** (0.50 g, 3.49 mmol) and Et_3N (1.00 mL,

7.7 mmol, 2.2 eq) in CH_2Cl_2 (18 mL, 0.2 M). The reaction mixture was stirred overnight at room temperature. The reaction mixture was then quenched with 10 mL of 2 M $HCl_{(aq)}$. The organic phase was separated and washed with sat. $NaHCO_{3(aq)}$ (15 mL) and Brine (15 mL). The organic phase was then dried over anhydrous Na_2SO_4. After filtration and removal of the solvent under reduced pressure the crude material was subjected to silica gel flash column chromatography [hexane:EtOAc (8:2)] to yield ester **65b** as a colourless liquid (0.72 g, 74%); IR (neat): *v* (max) cm^{-1} 2952, 1735, 1696, 1469, 1413, 1240, 1171. *NMR spectrum displays broad peaks due to the rotamer effect:* ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.29 (m, 5H), 5.77 (br. s, 1H), 5.14 (br. app s, 4H), 3.92 (s, 2H), 3.65 (s, 3H), 3.55 (t, *J* = 7.1, 2H), 2.69–2.49 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.3 and 172.0 (C), 155.9 (C), 136.6 (C), 133.7 and 133.5 (CH), 128.5 (2CH), 127.9 (CH), 127.8 (2CH) , 117.3 and 116.7 (CH_2), 67.2 (CH_2), 51.7 (CH_3), 50.4 (CH_2), 43.5 and 42.4 (CH_2), 33.6 and 33.1 (CH_2) ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_{15}H_{19}NO_4$: 278.1387, found 278.1381 $[M+H]^+$.

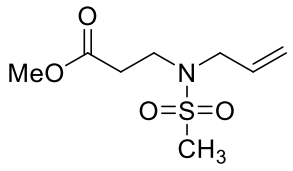
Methyl 3-(N-allylcylcopropanesulfonamido)propanoate (65c)



To a solution of ester **64** (453 mg, 3.2 mmol) and Et_3N (0.7 mL, 4.8 mmol, 1.5 eq) in CH_2Cl_2 (6.5 mL, 0.5 M), cyclopropanesulfonyl chloride (0.40 mL, 3.5 mmol, 1.1 eq) was added drop wise over 10 minutes at room temperature and the reaction mixture was stirred overnight. The reaction mixture was then washed with 2 M $HCl_{(aq)}$ (15 mL). The organic phase was then dried over anhydrous Na_2SO_4. After filtration and removal of the solvent under reduced pressure the crude material was subjected to silica gel flash column chromatography [hexane:EtOAc (8:2)] to afford ester **65c** as a colourless liquid (705 mg, 88%); IR (neat): *v* (max) cm^{-1} 2954, 1733, 1643, 1438, 1329, 1200, 1141; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.87 (ddt, *J* = 17.2, 10.1, 6.4, 1H), 5.35–5.25 (m, 2H), 3.90 (dt, *J* = 6.3, 1.4 2H), 3.71 (s, 3 H), 3.59–3.54 (m, 2H), 2.71–2.66 (m,

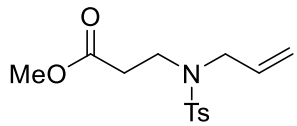
2H), 2.36 (tt, *J* = 8.0, 4.9, 1H), 1.25–1.14 (m, 2H), 1.03–0.94 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.8 (C), 133.3 (CH), 119.2 (CH_2), 51.8 (CH_3), 51.0 (CH_2), 43.0 (CH_2), 34.2 (CH), 29.6 (CH_2), 5.2 (2 CH_2) ppm; HRMS (ES-TOF): m/*z*: calcd for $C_{10}H_{17}NO_4NaS$: calcd 270.0776 found 270.0779 $[M+Na]^+$.

Methyl 3-(N-allylmethylsulfonamido)propanoate (65d)



To a solution of ester **64** (4.00 g, 28.0 mmol) and Et_3N (5.90 mL, 42.0 mmol, 1.5 eq) in CH_2Cl_2 (56 mL, 0.5 M), methanesulfonyl chloride (2.8 mL, 36 mmol, 1.3 eq) was added drop wise over 10 minutes at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was then washed with 2 M $HCl_{(aq)}$ (35.0 mL), sat. $NaHCO_{3(aq)}$ (35.0 mL) and Brine (35.0 mL). The organic phase was then dried over anhydrous Na_2SO_4. After filtration and removal of the solvent under reduced pressure the crude material was filtered through a pad of silica with 50 mL of [hexane:EtOAc (6:4)] to afford ester **65d** as a colourless liquid (3.61 g, 58%); IR (neat): *ν* (max) cm^{-1} 2954, 1732, 1643, 1438, 1318, 1201 ,1142; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.85 (ddt, *J* = 17.1, 10.2, 6.4 1H), 5.37–5.27 (m, 2H), 3.88 (dt, *J* = 6.4, 1.3, 2H), 3.71 (s, 3H), 3.52 (t, *J* = 7.1, 2H), 2.89 (s, 3H), 2.68 (t, *J* = 7.2, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.8 (C), 132.7 (CH), 119.6 (CH_2), 51.8 (CH_3), 50.8 (CH_2), 43.0 (CH_2), 39.7 (CH_3), 34.1 (CH_2) ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_8H_{15}NO_4S$: 222.0795, found 222.0792 $[M+H]^+$.

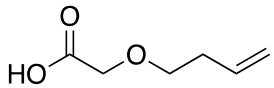
Methyl 3-((N-allyl-4-methylphenyl)sulfonamido)propanoate (65e)



Ester **64** (5.70 g, 40.0 mmol) and Et_3N (6.10 mL, 44.0 mmol, 1.1 eq) were dissolved in CH_2Cl_2 (200 mL, 0.2 M) and the mixture was cooled to 0 °C. Tosyl chloride (8.40 g, 44.0 mmol, 1.1 eq) was added portion wise over 20 minutes, and the cooling bath was removed. The reaction mixture was allowed to warm to room

temperature and stirred for 16 h. After this time 1 M $HCl_{(aq)}$ (80.0 mL) was added to the reaction mixture. The layers were separated, and the organic phase was washed with sat. $NaHCO_{3(aq)}$ (100 mL), brine (100 mL) and dried over Na_2SO_4. After filtration and removal of the solvent under reduced pressure sulfonamide **65e** was obtained as a pale yellow oil that was taken into the next step without further purification (10.6 g, 90%); IR (neat): *v* (max) cm^{-1} 1733, 1438, 1319, 1155, 745; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.72–7.68 (m, 2H), 7.31 (d, *J* = 8.1, 2H), 5.65 (ddt, *J* = 16.6, 10.1, 6.4, 1H), 5.22–5.14 (m, 2H), 3.81 (dt, *J* = 6.5, 1.4, 2H), 3.66 (s, 3H), 3.39 (dd, *J* = 8.3, 6.8, 2H), 2.64 (dd, *J* = 8.3, 6.8, 2H), 2.43 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.8 (C), 143.5 (C), 136.5 (C), 133.0 (2CH), 129.8 (2CH), 127.2 (CH), 119.3 (CH_2), 51.8 (CH_3), 51.6 (CH_2), 43.1 (CH_2), 34.1 (CH_2), 21.5 (CH_3) ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_{14}H_{19}NO_4S$: 298.1108, found 298.1102 $[M+H]^+$.

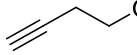
2-(But-3-en-1-yloxy)acetic acid (94)



A solution of but-3-en-1-ol (13.8 mL, 160 mmol, 2.0 eq) in dry THF (60.0 mL) was added dropwise over 15 min to a suspension of NaH (9.60 g, 240 mmol, 3.0 eq) in dry THF (380 mL) at 0°C. After 15 minutes a solution of 2-bromoacetic acid (11.2 g, 80.0 mmol) was added dropwise over 20 minutes at 0 °C. The cooling bath was then removed, and the reaction mixture was stirred at room temperature for 16 h. After which time Et_2O (150 mL) and water (150 mL) were added. The layers were separated, and the aqueous phase was further washed with Et_2O (100 mL) before being acidified with 6 M $HCl_{(aq)}$ and extracted with EtOAc (3 × 70 mL). The recombined organic phases were dried over Na_2SO_4. Filtration and removal of the solvent under reduced pressure afforded acid **94** (10.1 g, 97%) as a colourless oil that was taken into the next step without further purification; IR (neat): *v*(max) cm^{-1} 3078, 2911, 1722, 1431, 1218, 1118, 916; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.98 (s, 1H), 5.83 (ddt, *J* = 17.4, 10.2, 6.7, 1H), 5.14 (dq, *J* = 17.2, 1.7, 1H), 5.08 (dq, *J* = 10.2, 1.4,

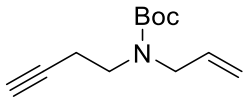
1H), 4.15 (s, 2H), 3.63 (t, *J* = 6.7, 2H), 2.40 (qt, *J* = 6.8, 1.4, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 175.0 (C), 134.4 (CH), 117.1 (CH_2), 71.2 (CH_2), 67.8 (CH_2), 33.9 (CH_2) ppm. Data match those reported in the literature.[186]

But-3-yn-1-yl methanesulfonate (87)



3–Butyn–1–ol (4.0 mL, 53 mmol) and Et_3N (8.1 mL, 58 mmol, 1.1 eq) were dissolved in CH_2Cl_2 (106 mL) and cooled to 0 °C. Methanesulfonyl chloride (4.1 mL, 53 mmol) was added dropwise over 10 min and stirred at 0 °C for 15 min before the ice bath was removed and the reaction mixture stirred for 2 h at r.t. The reaction mixture was poured into a separating funnel and washed with 1 M $HCl_{(aq)}$ (80 mL), satd $NaHCO3_{(aq)}$ (80 mL) and brine (100 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give protected alcohol **87** as a colourless oil characterised by ^{1}H NMR only and used immediately in the next reaction (7.7 g, 98%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.31 (t, *J* = 6.7, 2H), 3.05 (s, 3H), 2.66 (td, *J* = 6.7, 2.7, 2H), 2.06 (t, *J* = 2.7, 1H) ppm.

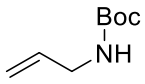
tert-Butyl allyl(but-3-yn-1-yl)carbamate (89c)



Protected alkyne **87** (7.70 g, 52.0 mmol), allylamine (11.7 mL, 156 mmol, 3.0 eq) and NaI (1.60 g, 10.0 mmol, 0.20 eq.) were combined in DMSO (87.0 mL, 0.6 M alkyne) and the mixture stirred at 50 °C overnight. The reaction mixture was poured into 2 M NaOH (100 mL) and extracted with Et2O (3 × 50 mL), before the combined organics were washed with brine, dried over Na2SO4, filtered, and concentrated under reduced pressure (10 mbar 10 min). The crude amine and Et_3N (10.9 mL, 78.0 mmol, 1.5 eq.) were dissolved in CH_2Cl_2 (87.0 mL, 0.6 M wrt alkyne) and Boc2O (12.5 g, 57.2 mmol, 1.1 eq) was added and the reaction mixture stirred for 3 h at r.t. The reaction mixture was diluted with CH_2Cl_2, washed with 2 M $HCl_{(aq)}$ (100 mL) and brine (100 mL) before drying over Na_2SO_4. After filtration and removal of the solvent under reduced pressure the crude material

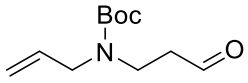
was subjected to silica gel flash column chromatography [Heptane: EtOAc (7:3)] affording enyne **89c** as a colourless liquid (10.9 g, 96%); IR (neat): *ν*(max) cm^{-1} 3306, 2978, 107, 1692, 1408, 1367, 1248, 1166, 114; *NMR spectra display a mixture of rotamers:* ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.86–5.72 (m, 1H), 5.13 (br. d, 2H), 3.90 (br. s, 2H), 3.35 (br. s, 2H), 2.42 (br. s, 2H), 1.96 (t, *J* = 2.6, 1H), 1.46 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.2 and 146.8 (C), 134.1 (CH), 116.7 and 116.1 (CH_2), 85.2 (C) , 79.8 (CH) , 69.5 (C), 50.6 and 49.7 (CH_2), 45.7 (CH_2), 28.4 and 27.4 ($3CH_3$), 18.5 (CH_2) ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_{12}H_{19}NO_2$: 154.0863, found 154.0861 $[M\text{-}tert\text{-butyl} + H]^+$.

tert-Butyl allylcarbamate (81)



To a solution of allylamine (1.00 mL, 13.3 mmol, 1.02 eq) in CH_2Cl_2 (13.0 mL, 1 M), Et_3N (1.80 mL, 13.1 mmol, 1.0 eq) followed by Boc_2O (2.85 g, 13.1 mmol, 1.0 eq) were added. The reaction mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure and the crude reaction mixture was subject to silica gel flash column chromatography [Hexane:EtoAc (9:1)] yielding carbamate **81** as a colourless solid (1.8 g, 87%). mp: 38–40 °C; IR (neat): ν(max) cm^{-1} 3340, 2980, 2911, 1677, 1523; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.77-5.90 (m, 1H), 5.11 (app. dq, *J* = 17.2, 1.6, 1H), 5.04 (app. dq, *J* = 10.2, 1.4, 1H), 4.53 (s, 1H), 3.67 (d, *J* = 6.0, 2H), 1.38 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.8 (C), 134.9 (CH), 115.7 (CH_2), 79.0 (C), 43.1 (CH_2), 28.4 ($3CH_3$) ppm. Data match those reported in the literature.[187]

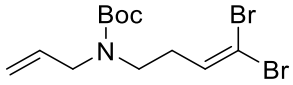
tert-Butyl allyl(3-oxopropyl)carbamate (83)



Freshly distilled acrolein (2.00 mL, 31.5 mmol, 10.0 eq) and p-toluensulphonic acid (121 mg, 0.63 mmol, 10 mol%) were added to an ice-cooled solution of carbamate **81** (495 mg, 3.15 mmol, 1.0 eq) in CH_2Cl_2 (0.4 M). The resulting solution was stirred at 0 °C for 15 minutes and for further 30 minutes at r.t. The

reaction mixture was diluted with CH_2Cl_2, poured into a separating funnel, and washed with saturated $NaHCO_{3(aq)}$ (10 mL) and brine (15 mL). The organic phase was dried over anhydrous Na_2SO_4. After filtration and removal of solvent under reduced pressure the crude material was subjected to silica gel flash column chromatography [Hexane: Petroleum ether (1:1)] yielding carbamate **83** as a colourless liquid (441 mg, 66%); IR (neat): ν(max) cm^{-1} 2977, 2727, 1728, 1686, 1407, 1385, 1147, 1144 ppm; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.72 (t, *J* = 1.7, 1H), 5.79–5.61 (m, 1H), 5.12–5.00 (m, 2H), 3.76 (s, 2H), 3.44 (t, *J* = 6.7, 2H), 2.62 (t, *J* = 6.7, 2H), 1.38 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.2 (CH), 155.2 (C), 133.9 (CH), 116.5 (CH2), 79.6 (C), 50.2(CH2), 43.1(CH_2), 40.6(CH_2), 28.1 ($3CH_3$) ppm. Data match those reported in the literature.[188]

tert-Butyl allyl(4,4-dibromobut-3-en-1-yl)carbamate (84)



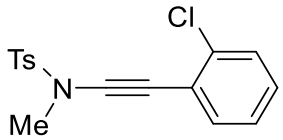
CBr_4 (1.39 g, 4.2 mmol, 2.0 eq) was added with a syringe pump over 30 minutes to an ice cooled solution solution of PPh_3 (2.19 g, 8.4 mmol, 4.0 eq) in CH_2Cl_2 (6 mL, 0.7 M). Aldehyde **83** (0.44 g, 2.1 mmol) was added and the reaction was stirred at 0 °C for further 2 h. After complete consumption of the aldehyde (checked by TLC), the reaction was quenched with water and poured into a separating funnel. The layers were separated and the organic phase was further washed with brine before being dried over Na_2SO_4. After filtration and removal of the solvent under reduced pressure the crude material was filtered through a pad of silica with [hexane: petroleum ether (9:1)] yielding dibromoolefin **84** as a colourless liquid characterised only by ^{1}H NMR before and used immediately into the next step (0.65 g, 88%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.33 (t, *J* = 7.3, 1H), 5.78–5.61 (m, 1H), 5.12–5.00 (m, 2H), 3.76 (br. app. s, 2H), 3.20 (br. app. s, 2H), 2.25 (q, *J* = 7.3, 2H), 1.40 (s, 9H) ppm.

6.3. Ynamides

General Procedure 01: Ynamide synthesis from terminal alkynes via Hsung's method (reaction scale < 5 mmol)

NBS (2 eq) and $AgNO_3$ (10 mol%) were added to a solution of the desired terminal alkyne (1 eq) in acetone (0.66 M) and the reaction mixture was stirred at room temperature for 4 h. After which time the solvent was removed under reduced pressure (300 mbar). The crude material was then suspended in Et_2O (5 mL). Pentane (10 mL) was added to the suspension and a white precipitate formed. The suspension was filtered through a pad of silica with pentane (30 mL), and the filtrate was concentrated under reduced pressure (600 mbar for 10 minutes then 400 mbar for 20 minutes). The crude material was dissolved in toluene (a portion taken from the whole reaction final volume) and added to an oven-dried 3-neck round bottom flask containing *N*,4-dimethylbenzenesulfonamide (1.0 eq), $CuSO_4 \cdot 5H_2O$ (10 mol%), 1,10-phenanthroline (20 mol%) and K_2CO_3 (2.0 eq) to dry toluene (0.1 M) and the reaction mixture was stirred at 60–65 °C for 16 h. After which time the reaction mixture was allowed to cool down to room temperature and filtered through a pad of silica with EtOAc (50 mL). The volatiles were removed under reduced pressure and the crude material was subjected to silica gel column chromatography to afford the final compounds.

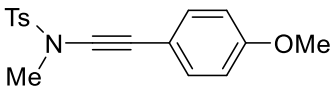
N-((2-Chlorophenyl)ethynyl)-N,4-dimethylbenzenesulfonamide (76a)



Following GP 01: NBS (1.6 g, 9.0 mmol, 2 eq), $AgNO_3$ (0.08 g, 10 mol%) and 1-chloro-2-ethynylbenzene (0.55 mL, 4.50 mmol) in acetone (6.8 mL, 0.66 M). After work-up the bromoalkyne was dissolved in toluene (5 mL) and added to N,4-dimethylbenzenesulfonamide (834 g, 4.5 mmol, 1.0 eq), $CuSO_4 \cdot 5H_2O$ (112 mg, 0.45 mmol, 10 mol%), 1,10-phenanthroline (162 mg, 0.90 mmol, 20 mol%), K_2CO_3 (1.24 g, 9.0 mmol, 2.0 eq) and dry toluene (40 mL, 0.1 M) and the reaction mixture was stirred at 60 °C

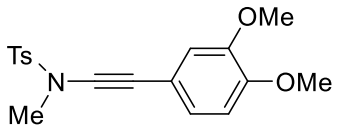
for 16 h. After work up the crude material was subjected to silica gel flash column chromatography [Heptane:EtOAc (6:4)] affording ynamide **76a** as a pale yellow solid (0.99 g, 3.1 mmol, 69%); IR (neat): *v*(max) cm^{-1} 2232, 1595, 1364, 1166, 961, 812, 752, 693; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92–7.86 (m, 2H), 7.43–7.34 (m, 4H), 7.24–7.14 (m, 2H), 3.19 (s, 3H), 2.46 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$); δ = 144.9 (C), 135.2 (C), 133.3 (C), 132.6 (CH), 129.9 (2CH), 129.2 (CH), 128.6 (CH), 127.9 (2CH), 126.4 (CH), 122.8 (C), 88.9 (C), 66.5 (C), 39.3 (CH_3), 21.7 (CH_3) ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_{16}H_{14}ClNO_2S$: 320.0506, found 320.0507 $[M+H]^+$.

N-((4-Methoxyphenyl)ethynyl)-N,4-dimethylbenzenesulfonamide (76b)



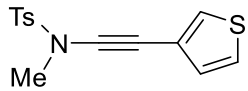
Following GP 01: NBS (1.6 g, 9.0 mmol, 2 eq), $AgNO_3$ (0.08 g, 10 mol%) and 1-ethynyl-4-methoxybenzene (0.58 mL, 4.5 mmol) in acetone (6.8 mL, 0.66 M). After work-up the bromoalkyne was dissolved in toluene (5 mL) and added to N,4-dimethylbenzenesulfonamide (834 mg, 4.5 mmol, 1.0 eq), $CuSO_4 \cdot 5H_2O$ (112 mg, 0.45 mmol, 10 mol%), 1,10-phenanthroline (162 mg, 0.90 mmol, 20 mol%) and K_2CO_3 (1.2 g, 9.0 mmol, 2.0 eq) and dry toluene (40 mL, 0.1 M) and the reaction mixture was stirred at 60 °C for 16 h. After work up the crude material was subjected to silica gel flash column chromatography [Heptane:EtOAc (6:4)] affording ynamide **76b** as a pale yellow solid (0.618 g, 1.96 mmol, 44%); IR (neat): *v*(max) cm^{-1} 2937, 2236, 1602, 1509, 1360, 1244, 1162, 831, 723; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86–7.81 (m, 2H), 7.37 (d, *J* = 8.1, 2H), 7.33–7.28 (m, 2H), 6.85–6.79 (m, 2H), 3.80 (s, 3H), 3.13 (s, 3H), 2.46 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.5 (C), 144.7 (C), 133.4 (2CH), 133.2 (C), 129.8 (2CH), 127.9 (2CH), 114.6 (C), 113.9 (2CH), 82.5 (C), 68.6 (C), 55.3 (CH_3), 39.4 (CH_3), 21.7 (CH_3) ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_{17}H_{17}NO_3S$: 316.1002, found 316.1000 $[M+H]^+$.

N-((3,4-Dimethoxyphenyl)ethynyl)-N,4-dimethylbenzenesulfonamide (76c)



Following GP 01: NBS (712 mg, 4.0 mmol, 2 eq), $AgNO_3$ (34 mg, 10 mol%) and 1-ethynyl-4-methoxybenzene (324 mg, 2.0 mmol) in acetone (3 mL, 0.66 M). After work-up the bromoalkyne was dissolved in toluene (3 mL) and added to N,4-dimethylbenzenesulfonamide (370 mg, 2.0 mmol, 1.0 eq), $CuSO_4 \cdot 5H_2O$ (50 mg, 0.20 mmol, 10 mol%), 1,10-phenanthroline (72 mg, 0.40 mmol, 20 mol%) and K_2CO_3 (553 mg, 4.0 mmol, 2.0 eq) and dry toluene (17 mL, 0.1 M) and the reaction mixture was stirred at 60 °C for 16 h. After work up the crude material was subjected to silica gel flash column chromatography [Heptane:EtOAc (6:4)] affording ynamide **76c** as a pale yellow solid (470 mg, 1.36 mmol, 68%); IR (neat): ν(max) cm^{-1} 2903, 2825, 2101, 1595, 1509, 1244, 1136, 805; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.84 (dd, *J* = 8.6, 2.0, 2H), 7.37 (d, , *J* = 8.2, 2H), 6.97 (dd, *J* = 8.2, 1.9, 1H), 6.88 (d, *J* = 1.9, 1H), 6.78 (d, *J* = 8., 1H), 3.87 (stack s., 6H), 3.14 (s, 3H), 2.46 (s, 3H) ppm; ^{13}C NMR (101 MHz, CDCl3): δ = 149.3 (C), 148.5 (C), 144.6 (C), 133.3 (C), 129.7 (CH), 127.8 (C), 125.1 (C), 114.7 (C), 110.9 (C), 82.4 (C), 68.8 (C), 55.9 ($2CH_3$), 39.3 (CH_3), 21.6 (CH_3) ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_{18}H_{19}NO_4S$: 346.1108, found 346.1100 $[M+H]^+$.

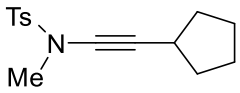
N,4-Dimethyl-N-(thiophen-3-ylethynyl)benzenesulfonamide (76d)



Following GP 01: NBS (1.6 g, 9.0 mmol, 2 eq), $AgNO_3$ (80 mg, 10 mol%) and 3-ethynylthiophene (0.44 mL, 4.5 mmol) in acetone (6.8 mL, 0.66 M). After work-up the bromoalkyne was dissolved in toluene (5 mL) and added to N,4-dimethylbenzenesulfonamide (834 mg, 4.5 mmol, 1.0 eq), $CuSO_4 \cdot 5H_2O$ (112 mg, 0.45 mmol, 10 mol%), 1,10-phenanthroline (162 mg, 0.90 mmol, 20 mol%) and K_2CO_3 (1.2 g, 9.0 mmol, 2.0 eq) to dry toluene (40 mL, 0.1 M) and the reaction mixture was stirred at 60 °C for 16 h. After work up the crude material was subjected to silica gel flash column chromatography

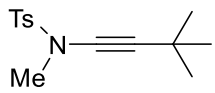
[Heptane:EtOAc (6:4)] affording ynamide **76d** as a pale yellow solid (998 mg, 3.43 mmol, 77%); IR (neat): *v*(max) cm^{-1} 3104, 2228, 1595, 1360, 1162, 1084, 812, 779; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 8.1, 2H), 7.38–7.35 (m, 3H), 7.30–7.23 (m, 1H), 7.05 (dd, *J* = 4.9, 1.2, 1H), 3.13 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.8 (C), 133.2 (C), 130.2 (CH), 129.8 (2CH), 128.8 (CH), 127.9 (2CH), 125.2 (CH), 121.4 (C), 83.2 (C), 64.1 (C), 39.3 (CH_3), 21.7 (CH_3) ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_{14}H_{13}NO_2S_2$: 292.0460, found 292.0459 $[M+H]^+$.

N-(Cyclopentylethynyl)-N,4-dimethylbenzenesulfonamide (76e)



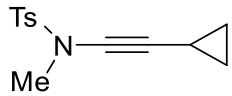
Following GP 01: NBS (1.60 g, 9.00 mmol, 2 eq), $AgNO_3$ (8.00 mg, 10 mol%) and ethynylcyclopentane (0.52 mL, 4.5 mmol) in acetone (6.80 mL, 0.66 M). After work-up the bromoalkyne was dissolved in toluene (5 mL) and added to N,4-dimethylbenzenesulfonamide (834 mg, 4.50 mmol, 1.0 eq), $CuSO_4 \cdot 5H_2O$ (112 mg, 0.45 mmol, 10 mol%), 1,10-phenanthroline (162 mg, 0.90 mmol, 20 mol%), K_2CO_3 (1.20 g, 9.00 mmol, 2.0 eq) and dry toluene (40 mL, 0.1 M) and the reaction mixture was stirred at 60 °C for 16 h. After work up the crude material was subjected to silica gel flash column chromatography [Heptane:EtOAc (6:4)] affording ynamide **76e** as a pale yellow solid (555 mg, 2.00 mmol, 45%); IR (neat): *v*(max) cm^{-1} 2967, 2243, 1595, 1360, 1166, 998, 730, 663; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.3, 2H), 7.35 (d, *J* = 8.0, 2H), 3.00 (s, 3H), 2.72–2.60 (m, 1H), 2.46 (s, 3H), 1.91–1.82 (m, 2H), 1.77–1.62 (m, 2H), 1.56–1.49 (m, 4H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.4 (C), 133.1 (C), 129.6 (2CH), 127.9 (2CH), 74.7 (C), 72.7 (C), 39.4 (CH_3), 33.9 ($2CH_2$), 29.9 (CH), 24.8 ($2CH_2$), 21.7 (CH_3)ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_{15}H_{19}NO_2S$: 278.1209, found : 278.1208 $[M+H]^+$.

N-(3,3-Dimethylbut-1-yn-1-yl)-N,4-dimethylbenzenesulfonamide (76g) Y6



Na_2CO_3 (254 mg, 2.4 mmol, 2.0 eq), sulphonamide **70b** (1.1 g, 6.0 mmol, 5.0 eq) and $CuCl_2$ (3.2 mg, 0.024 mmol, 20 mol%) were added to an oven dried 3-neck-round-bottom flask. The flask was then purged with oxygen for 60 minutes, before a solution of pyridine (0.19 mL, 2.4 mmol, 2.0 eq) in dry toluene (12 mL, 0.4 M pyridine) was added and the reaction mixture warmed to 60 °C. A solution of 3,3-dimethylbut-1-yne (0.15 mL, 1.2 mmol) in dry toluene (12 mL, 0.2 M of the alkyne) was then added over 4 h via a dropping funnel, the reaction mixture was then stirred at 60 °C for a further 16 h. After which time the reaction mixture was allowed to cool down to room temperature and was filtered through a pad of silica with EtOAc (50 mL). After removal of the solvent under reduced pressure the crude material was subjected to silica gel flash column chromatography [heptane:EtOAc (8:2)] to afford ynamide **76g** as a pale yellow solid (180 mg, 57%); IR (neat): *ν*(max) cm^{-1} 2967, 2243, 1595, 1453, 1360, 1166, 730, 663; ^1H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.4, 2H), 7.34 (d, *J* = 8.0, 2H), 2.97 (s, 3H), 2.44 (s, 3H), 1.18 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.5 (C), 132.9 (C), 129.51 (2CH), 127.9 (2CH), 76.6 (C), 74.1 (C), 39.4 (CH_3), 31.1 ($3CH_3$), 27.3 (C), 21.6 (CH_3) ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_{14}H_{19}NO_2S$: 266.1209, found : 266.1208 $[M+H]^+$.

N-(Cyclopropylethynyl)-N,4-dimethylbenzenesulfonamide (76f)



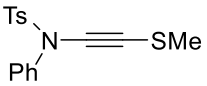
Stahl's Method: Na_2CO_3 (4.4 g, 42 mmol, 2.0 eq), sulphonamide **70b** (19.5 g, 105 mmol, 5.0 eq) and $CuCl_2$ (56 mg, 0.42 mmol, 0.02 eq) were added to an oven dried 3-neck-round-bottom flask. The flask was then purged with oxygen for 60 minutes, before a solution of pyridine (3.4 mL, 42 mmol, 2.0 eq) in dry toluene (105 mL, 0.4 M pyridine) was added and the reaction mixture warmed to 60 °C. A solution of ethynylcyclopropane (1.8 mL, 21 mmol) in dry toluene (105 mL, 0.2 M of the alkyne) was then

added over 4 h via a dropping funnel, the reaction mixture was then stirred at 60 °C for a further 16 h. After which time the reaction mixture was allowed to cool down to room temperature and was filtered through a pad of silica with EtOAc (250 mL). After removal of the solvent under reduced pressure the crude material was subjected to silica gel flash column chromatography [heptane:EtOAc (8:2)] to afford ynamide **76f** as a pale yellow solid (3.77 g, 72%);

Hsung's Method: NBS (21.4 g, 100 mmol, 2 eq) and $AgNO_3$ (850 mg, 10 mol%) were added to a solution of ethynylcyclopropane (4.2 mL, 50 mmol) in acetone (76 mL, 0.66 M) and the reaction mixture was stirred at room temperature for 4 h in darkness. After which time the solvent was removed under reduced pressure (300 mbar). The crude material was then suspended in Et_2O (25 mL). Pentane (25 mL) was added to the suspension and a white precipitate formed. The suspension was filtered through a pad of silica with pentane (60 mL), and the filtrate was concentrated under reduced pressure (600 mbar for 10 minutes then 400 mbar for 20 minutes). The crude material was dissolved in toluene (10 mL) and added to an oven-dried 3-neck round bottom flask containing *N*,4-dimethylbenzenesulfonamide (9.3 g, 50 mmol, 1.0 eq), $CuSO_4 \cdot 5H_2O$ (1.3 g, 5.0 mmol, 10 mol%), 1,10-phenanthroline (1.8 g, 10 mmol, 20 mol%) and K_2CO_3 (13.8 g, 100 mmol, 2.0 eq) to dry toluene (0.49 L, 0.1 M) and the reaction mixture was stirred at 60 °C for 16 h. After which time the reaction mixture was allowed to cool down to room temperature and transferred to single-neck round bottom flask. The reaction mixture was then concentrated under reduced pressure to approximately 1/4 of the initial volume of toluene and filtered through a pad of silica with EtOAc (300 mL). The volatiles were removed under reduced pressure and the crude material was subjected to silica gel column chromatography to afford ynamide **76f** as a pale yellow solid (7.3 g, 29.4 mmol, 59%); *The characterisation provided thereafter is related to the compound synthesized using Hsung's method:* mp: 47–49 °C; IR (neat): *ν*(max) cm^{-1} 3079, 2950, 2094, 1607; ^1H NMR (400 MHz,

$CDCl_3$): δ = 7.59 (d, *J* = 8.0, 2H), 7.17 (d, *J* = 8.0 , 2H), 2.82 (s, 3H), 2.28 (s, 3H), 1.12–1.06 (m, 1H), 0.68–0.55 (m, 2H), 0.51–0.39 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.3 (C), 134.1 (C), 130.5 ($2CH_2$), 128.7 ($2CH_2$), 73.8 (c), 71.3 (C), 40.2 (CH_3) 22.5 (CH_3), 9.5 ($2CH_2$), 0.3 (CH) ppm; Data match those reported in the literature.[189]

4-Methyl-N-((methylthio)ethynyl)-N-phenylbenzenesulfonamide (73a)

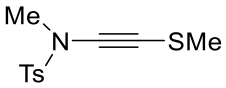


Dichloroenamide **71a** (900 mg, 2.62 mmol) was added to dry THF (10.5 mL, 0.25 M) and cooled to −78 °C for 15 minutes. Keeping the temperature below −75 °C, a solution of nBuLi 2.5 M in hexane (1.3 mL, 3.14 mmol, 1.2 eq) was added dropwise using a syringe pump over 10 minutes. After this time the reaction was stirred at −40°C for 35 minutes. Upon cooling to −78 °C for 10 minutes a second portion of nBuLi 2.5 M in hexane (1.0 mL, 2.62 mmol, 1.0 eq) was added over 5 minutes. After 10 minutes **TsSMe** (586 mg, 3.15 mmol, 1.2 eq) was added and the reaction was allowed to warm to room temperature. After 20 minutes the reaction was quenched with water (15 mL) and extracted with EtOAc (4 × 15 mL). The organic layer was dried over anhydrous Na_2SO_4. After filtration and removal of the solvent under reduced pressure the brown solid was purified by recrystallization from hot ethanol affording ynamide **73a** as pale yellow crystals (673 mg, 81%).

Scale up: To an oven dried, argon flushed 3-neck-round bottom flask was added dichloroenamide **71a** (17.5 g, 51.0 mmol) to dry THF (510 mL, 0.1 M) and cooled to -78 °C whilst stirring for 15 minutes. Keeping the temperature below −75 °C, a solution of nBuLi 1.6 M in hexane (38.4 mL, 61.4 mmol, 1.2 eq) was added dropwise via a dropping funnel over 35 minutes. After the addition the reaction mixture was allowed to stir at −75 °C for 10 minutes before being warmed up to - 40°C and additionally stirred for 45 minutes. Upon cooling to −78 °C for 10 minutes a second portion of nBuLi 1.6 M in hexane (32.0 mL, 51.1 mmol, 1.0 eq)

was added over 15 minutes. After 10 minutes **TsSMe** (12.4 g, 61.4 mmol, 1.2 eq) was added and the reaction was allowed to warm to room temperature. After 20 minutes the reaction was quenched with water (100 mL) and extracted with EtOAc (3 × 200 mL). The organic phase was further washed with brine (200 mL) and dried over anhydrous Na_2SO_4. After filtration and removal of the solvent under reduced pressure the brown solid was purified by recrystallization from hot ethanol affording ynamide **73a** as pale yellow crystals (12.9 g, 80%). Purity: qNMR(methyl 3,5-dinitrobenzoate): 99.44%; mp = 124–126 °C; IR (neat): *ν*(max) cm^{-1} 2933, 2167, 1594, 1455, 1486, 1366, 1172; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.38 (m, 2H), 7.32–7.24 (m, 4H), 7.18 (dd, *J* = 8.8, 2.5, 1H), 6.59 (d, *J* = 8.8, 1H), 5.90 (ddt, *J* = 17.2, 10.4, 5.2, 1H), 5.32 (dq, *J* = 17.1, 1.6, 1H), 5.17 (dq, *J* = 10.5, 1.5, 1H), 4.60 (s, 2H), 4.41 (dt, *J* = 5.2, 1.6, 2H), 2.81 (d, *J* = 0.9 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.5 (C), 139.1 (C), 133.3 (C), 129.5 (2CH), 129.1 (2CH), 128.3 (2CH), 128.2 (CH), 126.3 (2CH), 86.6 (C), 66.5 (C), 21.7 (CH_3), 20.5 (CH_3) ppm. Data match those reported in the literature.[190]

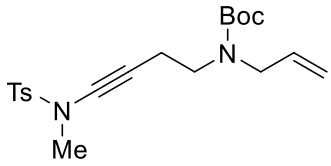
N,4-dimethyl-N-((methylthio)ethynyl)benzenesulfonamide (73b)



Dichloroenamide **71b** (1.0 g, 8.0 mmol) was added to dry THF (32 mL, 0.25 M) and cooled to −78 °C for 15 minutes. Keeping the temperature below −75 °C, a solution of nBuLi 1.6 M in hexane (6.0 mL, 9.60 mmol, 1.2 eq) was added dropwise using a syringe pump over 10 minutes. After this time the reaction was stirred at −40°C for 35 minutes. Upon cooling to −78 °C for 10 minutes a second portion of nBuLi 1.6 M in hexane (5.0 mL, 8.0 mmol, 1.0 eq) was added over 5 minutes. After 10 minutes **TsSMe** (1.9 g, 9.6 mmol, 1.2 eq) was added and the reaction was allowed to warm to room temperature. After 20 minutes the reaction was quenched with water (15 mL) and extracted with EtOAc (4 × 20 mL). The organic layer was dried over anhydrous Na_2SO_4. After filtration and removal of the solvent under reduced pressure the brown solid was purified via silica gel flash column

chromatography [heptane: EtOAc (7:3)] affording ynamide **73b** as pale yellow crystals (1.1 mg, 55%); IR (neat): *v*(max) cm^{-1} 2929, 2100, 1595, 1356, 1166; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, J = 8.2, 2H), 7.36 (d, J = 8.2, 2H), 3.09 (s, 3H), 2.45 (s, 3H), 2.31 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.9 (C), 133.7 (C), 129.9 (2CH), 127.9 (2CH), 87.9 (C), 65.1 (C), 39.6 (CH_3), 21.8 (CH_3), 20.7 (CH_3) ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_{11}H_{13}NO_2S_2$: 256.0460, found : 256.0458 $[M+H]^+$.

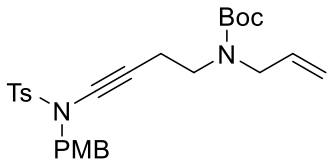
tert-Butyl allyl(4-((N,4-dimethylphenyl)sulfonamido)but-3-yn-1-yl)carbamate (86a)



Recrystallised NBS (7.12 g, 40 mmol, 2.0 eq) and $AgNO_3$ (0.340 g, 2.0 mmol, 10 mol%) were added to a solution of enyne **89c** (4.19 g, 20 mmol) in acetone (30 mL, 0.66 M) and the reaction mixture was left stirring at room temperature in darkness for 4 h. After this time the solvent was evaporated under reduced pressure and the crude material was then suspended in Et_2O (15 mL). Heptane (15 mL) was added, and the suspension was filtered through a pad of silica using [Heptane: Et_2O (1:1)] as a eluent. The filtrate was concentrated under reduced pressure, dissolved in dry toluene (5 mL) and added to an oven dried three-neck round bottom flask containing *N*,4-dimethylbenzenesulfonamide (3.70 g, 20 mmol, 1.0 eq), $CuSO_4 \cdot 5H_2O$ (0.49 g, 2 mmol, 10 mol%), 1,10-phenanthroline (0.72 g , 4 mmol, 20 mol%) and K_2CO_3 (5.5 g, 40 mmol, 2.0 eq) to dry toluene (195 mL, 0.1 M) and the reaction mixture was stirred at 70 °C for 16 h. After which time the reaction mixture was allowed to cool down to room temperature and filtered through a pad of silica with EtOAc. The filtrate was concentrated under reduced pressure and the crude material was subjected to silica gel flash column chromatography [Heptane:EtOAc (7:3)] yielding ynamide **86a** as a pale yellow oil (4.47 g, 57% over two steps); IR (neat): *v*(max) cm^{-1} 2974, 2929, 2255, 1688, 1595, 1384, 1162, 812, 670; *NMR spectra show a mixture of rotamers:* ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77–7.68 (m, 2H), 7.32 (d, *J* = 7.8,

2H), 5.77–5.66 (m, 1H), 5.08 (d, *J* = 11.4, 2H), 3.80 (br. s, 2H), 3.25 (s, 2H), 2.97 (s, 3H), 2.44–2.42 (m, 5H), 1.42 (br. s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.2 (C), 144.6 (C), 134.1 (CH), 133.2 (C), 129.7 (2CH), 127.7 (2CH), 116.5 and 116.0 (CH_2), 79.7 (C), 75.8 (C), 66.1 (C), 50.4 and 49.9 (CH_2), 46.1 (CH_2), 39.2 (CH_3), 28.36 ($3CH_3$), 21.6 (CH_3), 18.5 and 18.2 (CH_2) ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_{20}H_{28}N_2O_4S$: 293.13183, found 293.1313 $[M\text{-}Boc+H]^+$.

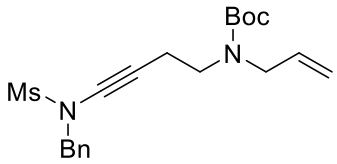
tert-Butyl allyl(4-((N-(4-methoxybenzyl)-4-methylphenyl)sulfonamido)but-3-yn-1-yl)carbamate (86b)



Recrystallised NBS (1.40 g, 7.9 mmol, 2.0 eq) and $AgNO_3$ (0.067 g, 0.39 mmol, 10 mol%) were added to a solution of enyne **89c** (0.820 g, 3.9 mmol) in acetone (6 mL, 0.66 M) and the reaction mixture was left stirring at room temperature in darkness for 4 h. After this time the solvent was evaporated under reduced pressure and the crude material was then suspended in Et_2O (5 mL). Heptane (5 mL) was added and the suspension was filtered through a pad of silica using [Heptane: Et_2O (1:1)] as a eluent. The filtrate was concentrated under reduced pressure, dissolved in dry toluene (5 mL) and added to an oven dried three-neck round bottom flask containing sulfonamide **85b** (1.14 g, 3.9 mmol, 1.0 eq), $CuSO_4{\cdot}5H_2O$ (0.098 g, 0.39 mmol, 10 mol%), 1,10-phenanthroline (0.142 g, 0.79 mmol, 20 mol%) and K_2CO_3 (1.08 g, 7.9 mmol, 2.0 eq) to dry toluene (35 mL, 0.1 M) and the reaction mixture was stirred at 70 °C for 16 h. After which time the reaction mixture was allowed to cool down to room temperature and filtered through a pad of silica with EtOAc. The filtrate was concentrated under reduced pressure and the crude material was subjected to silica gel flash column chromatography [Heptane:EtOAc (7:3)] yielding ynamide **86b** as a pale yellow oil (0.893 g, 46% over two steps); IR (neat): *ν*(max) cm^{-1} 2974, 2929, 2251, 1688, 1513, 1364, 1244, 1162, 812; *NMR spectra show a mixture of rotamers:* ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 8.0, 2H),

7.29 (d, *J* = 8.0, 2H), 7.18 (d, *J* = 8.3, 2H), 6.80 (d, *J* = 8.4, 2H), 5.67 (ddt, *J* = 16.2, 10.7, 5.5, 1H), 5.12–4.96 (m, 2H), 4.36 (s, 2H), 3.77 (s, 3H), 3.75–3.63 (m, 2H), 3.24–3.07 (m, 2H), 2.43 (s, 5H), 1.42 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.6 (C), 155.2 (C), 144.4 (C), 134.8 (C), 134.1 (CH), 130.2 (2CH), 129.7 (2CH), 127.6 (2CH), 126.7 (C), 116.4 and 115.8 (CH_2), 113.8 (2CH), 79.7 (C), 74.3 (C), 68.4 (C), 55.2 (CH_3), 55.0 (CH_2), 50.5 (CH_2), 46.1 (CH_2), 28.4 ($3CH_3$), 21.6 (CH_3), 18.6 and 18.3 (CH_2) ppm;

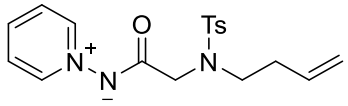
tert-Butyl allyl(4-(N-benzylmethylsulfonamido)but-3-yn-1-yl)carbamate (86c)



Dibromoolefin **84** (949 mg, 2.59 mmol, 1.3 eq), sulphonamide **85c** (368 mg, 1.99 mmol), Cs_2CO_3 (2.60 g, 7.97 mmol, 4.0 eq) and CuI (37.9 mg, 0.199 mmol, 10 mol%) were added to a Shlenck that was evacuated and refilled with argon twice. DMF (4.0 mL, 0.2 M) and DMEDA (47 µL, 0.44 mmol, 22 mol%) were added to the solid, the mixture was stirred at 60°C for 24 h. The mixture was allowed to cool to room temperature, after addition of water the mixture was extracted with EtOAc (3 × 15 mL). The combined organic phases were dried over anhydrous Na_2SO_4. After filtration and removal of the solvent under reduced pressure the crude material was subjected to silica gel flash column chromatography [Hexane: EtOAC (7.5:2.5)] to yield **86c** as a pale yellow oil (158 mg, 20%); IR (neat): ν (max) cm^{-1} 2976, 2931, 2255, 1667, 1457, 1407, 1354, 1247, 1159; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.32 (m, 5H), 5.72 (ddt, *J* = 16.2, 10.7, 5.6, 1H), 5.10–5.05 (m, 2H), 4.49 (2 s, 2H), 3.84–3.72 (m, 2H), 3.34–3.18 (m, 2H), 2.79 (s, 3H), 2.43 (t, *J* = 7.2, 2H), 1.37 (s, 9H) ppm; ^{13}C NMR (101 MHz,$CDCl_3$): δ = 155.3 (C), 134.7 (C), 134.0 (CH), 128.84 (2CH), 128.75 (2CH), 128.61 (CH), 116.6 and 116.0 (CH_2), 79.8 (C), 73.9 (C), 68.7 (C), 55.6 (CH_2), 50.3 and 49.9 (CH_2), 45.9 (CH_2), 38.5 (CH_3), 28.4 ($3CH_3$), 18.6 and 18.1 (CH_2) ppm; HRMS (ES-TOF): m/z: calcd for $C_{20}H_{28}N_2O_4NaS$: 415.1667, found 415.1663 $[M+Na]^+$.

6.4. Ylides

The following ylide was prepared by a previous member of the Davies group.



67f (Mat Ball-Jones)

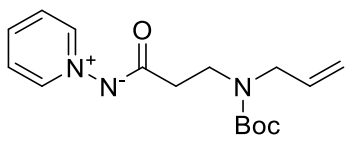
General Procedure 02: synthesis of ylides from esters

Under air, the relevant ester (1.2 eq) was added to MeOH (0.12 M). 1-Aminopyridinium iodide (1.0 eq) was added and stirred until completely dissolved. K_2CO_3 (2.4 eq) was then added and the solution was stirred for 3 days at room temperature. The solvent was removed under reduced pressure and the resulting solid was filtered through a 2 cm alumina pad with 10% MeOH in CH_2Cl_2. The crude material was subjected to silica gel flash column chromatography to give the aminide.

General Procedure 03: synthesis of ylides from acids

Et_3N (2.0 eq) was added to an ice cooled solution (or suspension, depending on the acid) of the relevant acid in CH_2Cl_2 (0.1 M). Isobutyl chloroformate (1.1 eq) was added drop wise to the mixture over 5 minutes. The reaction mixture was stirred at 0 °C for 1 h. After this time 1-Aminopyridinium iodide (1.1 eq), K2CO3 (2.4 eq) and MeOH (one quarter of the initial volume of CH_2Cl_2) and the ice bath was removed. The reaction mixture was left stirring for 16 h at room temperature. The solvents were removed under reduced pressure and the resulting solid was filtered through a 2 cm silica pad with 10% MeOH in CH_2Cl_2. The crude material was subjected to silica gel flash column chromatography to give the aminide.

(3-((Allyl-tert-butoxycarbonyl0amino)propanoyl-(pyridine-1-ium-1-yl)amide (67a)

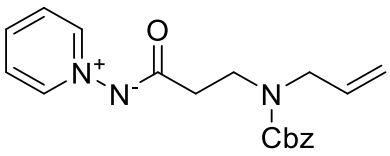


Following GP 02 using ester **65a** (900 mg, 3.72 mmol, 1.2 eq) in MeOH (25 mL, 0.12 M), 1-aminopyridinium iodide (688 mg,

3.10 mmol) and K_2CO_3 (1.00 g, 7.43 mmol, 2.4 eq). Silica gel flash column chromatography gave aminide **67a** as a brown oil (596 mg, 63%);

Scaling up: following GP 02 using ester **65a** (14.6 g, 60.0 mmol, 1.2 eq) in MeOH (500 mL), 1-aminopyridinium iodide (11.1 g, 50 mmol) and K_2CO_3 (16.6 g, 120 mmol). Filtration through a 6 cm alumina pad with 10% MeOH in CH_2Cl_2; Silica gel flash column chromatography gave aminide **67a** as a brown oil (9.3 g, 61%); IR (neat): *v*(max) cm^{-1} 3403, 2976, 1680, 1559, 1469, 1384, 1409, 1160; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.68–8.55 (m, 2H), 7.92 (t, *J* = 7.9, 1H), 7.65 (t, *J* = 7.9, 2H), 5.85–5.69 (m, 1H), 5.11 (app. t, *J* = 14.9, 2H), 3.87 (br. app. s, 2H), 3.56 (s, 2H), 2.54–2.50 (m, 2H), 1.43 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 175.0 (C), 155.5 (C), 143.1 (CH), 137.1 (2CH), 134.2 (CH), 125.9 (2CH), 115.9 (CH_2), 79.3 (C), 49.6 (CH_2), 44.3 (CH_2), 35.5 (CH_2), 28.3 ($3CH_3$); HRMS (ES-TOF): m/z: calcd for $C_{16}H_{24}N_3O_3$: 306.1818, found 306.1820 $[M+H]^+$.

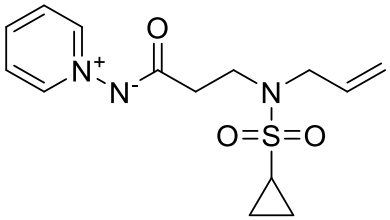
(3-(Allyl((benzyloxy)carbonyl)amino)propanoyl)(pyridine-1-ium-1-yl)amide (67b)



Following GP 02 using ester **65b** (500 mg, 1.80 mmol, 1.2 eq) in MeOH (15 mL, 0.1 M), 1-aminopyridinium iodide (333 mg, 1.50 mmol) and K_2CO_3 (500 mg, 3.60 mmol, 2.4 eq). Silica gel flash column chromatography gave aminide **67b** as a brown oil (328 mg, 0.97 mmol, 74%); IR (neat): *v*(max) cm^{-1} 3386, 3068, 1689, 1617, 1561, 1469, 1414, 1238*; NMR spectra displays a mixture of rotamers*: ^1H NMR (400 MHz, $CDCl_3$): δ = 8.54 (d, *J* = 6.1, 2H), 7.94–7.79 (m, 1H), 7.60–7.56 (m, 2H), 7.46–7.20 (m, 5H), 5.86–5.78 (m, 1H), 5.25–5.05 (m, 4H), 3.98 (br. app. s, 2H), 3.69 (br. s., 2H), 2.57 (t, *J* = 7.4, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.4 and 174.2 (C), 155.8 and 155.6 (C), 142.7 and 142.6 (2CH), 136.9 (CH), 136.6 (C), 133.5 and 133.4 (CH), 128.6 (CH), 127.9 (CH), 127.8 (CH), 127.3 (CH), 127.2 and 127.1 (CH), 125.7 (2CH), 116.3 and 115.9 (CH_2), 66.5 and 66.4 (CH_2), 49.6 and 49.2 (CH_2), 44.5 and 43.60 (CH_2),

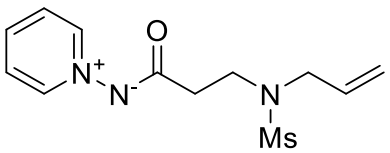
35.23 and 34.82 (CH_2) ppm; HRMS (ES-TOF): m/*z*: calcd for $C_{19}H_{22}N_3O_3$: calcd: 340.1661, found 340.1664 $[M+H]^+$.

(3-(N-Allylcyclopropanesulfonamido)propanoyl)(pyridine-1-ium-1-yl)amide (67c)



Following GP 02 using ester **65c** (700 mg, 2.8 mmol, 1.2 eq) in MeOH (20 mL, 0.12 M), 1-aminopyridinium iodide (526 mg, 2.4 mmol) and K_2CO_3 (786 mg, 5.70 mmol, 2.4 eq). Silica gel flash column chromatography gave aminide **67c** as a brown oil (458 mg, 63%); IR (neat): *v*(max) cm^{-1} 3401, 1618, 1562, 1470, 1324, 1138; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.66–8.62 (m, 2H), 7.90 (tt, *J* = 7.6, 1.3, 1H), 7.64 (t, *J* = 7.6, 2H), 5.90 (ddt, *J* = 16.9, 10.1, 6.3, 1H), 5.31 (dd, *J* = 16.9, 1.4, 1H), 5.23 (dd, *J* = 10.1, 1.4 1H), 3.96 (d, *J* = 6.3, 2H), 3.68 (t, *J* = 7.4, 2H), 2.61 (t, *J* = 7.4, 2H), 2.39 (tt, *J* = 8.0, 4.9, 1H), 1.21–1.17 (m, 2H), 0.97–0.92 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.4 (C), 143.2 (CH), 137.1 (2CH), 133.5 (2CH), 125.9 (CH), 118.6 (CH_2), 50.0 (CH_2), 44.4 (CH_2), 35.6 (CH_2), 29.8 (CH), 5.2 ($2CH_2$) ppm; HRMS (ES-TOF): m/*z*: calcd for $C_{14}H_{20}N_3O_3S$: calcd: 310.1225, found 310.1227 $[M+H]^+$.

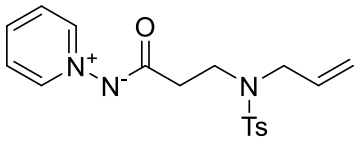
(3-(N-Allylmethylsulfonamido)propanoyl)(pyridin-1-ium-1-yl)amide (67d)



Following GP 02 using ester **65d** (2.0 g, 9.1 mmol, 1.2 eq) in MeOH (25 mL, 0.12 M), 1-aminopyridinium iodide (566 mg, 2.6 mmol) and K_2CO_3 (846 mg, 6.1 mmol, 2.4 eq). Silica gel flash column chromatography gave aminide **67d** as a brown oil (0.40 g, 55%); IR (neat): *v*(max) cm^{-1} 3308, 1558, 1468, 1312, 1140, 771, 678; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.62–8.57 (m, 2H), 7.93 (app. t, *J* = 7.5, 1H), 7.65 (t, *J* = 7.5, 2H), 5.86 (ddt, *J* = 16.9, 10.0, 6.3, 1H), 5.31 (app. d, *J* = 16.9, 1H), 5.23 (app. d, *J* = 10.0, 1H), 3.92 (d, *J* = 6.3, 2H), 3.62 (t, *J* = 7.3, 2H), 2.88 (s, 3H), 2.63–2.53 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.3 (C), 143.1 (CH),

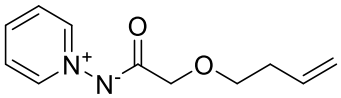
137.3 (2CH), 132.9 (2CH), 126.0 (CH), 118.9 (CH_2), 49.9 (CH_2), 44.3 (CH_2), 39.4 (CH_3), 35.4 (CH_2) ppm; HRMS (ES-orbitrap): m/*z*: calcd for $C_{12}H_{17}N_3O_3S$: calcd: 284.1063, found 284.1056 $[M+H]^+$.

(3-((N-Allyl-4-methylphenyl)sulfonamido)propanoyl)(pyridin-1-ium-1-yl)amide (67e)



Following GP 02 using ester **65e** (8.00 g, 27 mmol, 1.2 eq) in MeOH (225 mL, 0.1 M), 1-aminopyridinium iodide (5.00 g, 22.4 mmol) and K_2CO_3 (7.40 g, 53.8 mmol, 2.4 eq). Silica gel flash column chromatography gave aminide **67e** as a brown oil (5.96 mg, 74%); IR (neat): *v* (max) cm^{-1} 2922, 1561, 1468, 1323, 11448, 1088, 767; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.64–8.58 (m, 2H), 7.93 (app. t, *J* = 7.9, 1H), 7.78–7.72 (m, 2H), 7.65 (t, *J* = 7.1, 2H), 7.28 (d, *J* = 8.3, 2H), 5.69 (ddt, *J* = 16.9, 10.2, 6.3 , 1H), 5.23 (dd, *J* = 16.9, 1.6, 1H), 5.14 (dd, *J* = 10.2, 1.6, 1H), 3.90 (dd, *J* = 6.3, 1.6, 2H), 3.61–3.54 (m, 2H), 2.59–2.51 (m, 2H), 2.41 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.5 (C), 143.3 (CH), 143.0 (C), 137.3 (2CH), 133.2 (2CH), 129.6 (2CH), 127.2 (2CH), 126.1 (CH), 118.8 (CH_2), 50.6 (CH_2), 44.8 (CH_2), 35.4 (CH_2), 21.5 (CH_3) ppm; *one quaternary carbon is not observed in ^{13}C NMR spectra;* HRMS (ESI-orbitrap): m/z: calcd for $C_{18}H_{21}N_3O_3S$: 360.1376, found 360.1369 $[M+H]^+$.

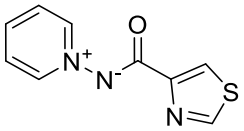
(2-(But-3-en-1-yloxy)acetyl)(pyridin-1-ium-1-yl)amide (95)



A solution of acid **93** (10.2 g, 78 mmol) in CH_2Cl_2 (780 mL, 0.1 M) was cooled to 0°C. Et_3N (21.7 mL, 156 mmol, 2.0 eq) and ethyl chloroformate (8.2 mL, 86 mmol 1.1 eq) were added dropwise via syringe over 10 minutes. After 1 h, 1-aminopyridinium iodide (19.1 g, 86 mmol, 1.1 eq), K_2CO_3 (25.9 g, 187 mmol, 2.4 eq) and MeOH (195 mL, equal to one quarter of the initial volume of CH_2Cl_2) were added and the reaction mixture was allowed to warm to room temperature and stirred for 24 h. Salts were removed by filtration thourgh a 3 cm deep pad of silica (diameter = 6.5 cm).

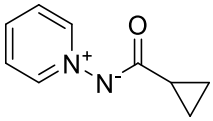
The filtrate was concentrated under reduced pressure and purified by flash column chromatography [CH_2Cl_2: MeOH (9:1)] yielding aminide **95** as a brown solid (13.7 g, 85%); IR (neat): *v*(max) cm^{-1} 3395, 2922, 2859, 1567, 1471, 1281, 1108; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.77–8.69 (m, 2 H), 7.96–7.92 (m, 1 H), 7.72–7.66 (m, 2 H), 5.88 (ddt, *J* = 17.1, 10.2, 6.8, 1H), 5.31 (app. dq, *J* = 17.1, 1H), 5.23 (ddt, *J* = 10.2, 2.3, 1.3, 1H), 4.17 (s, 2H), 3.70 (t, *J* = 7.1, 2H), 2.47 (app. qt, *J* = 7.0, 1.4 , 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.3 (C), 143.3 (2CH), 137.7 (CH), 135.2 (CH), 126.2 (2CH), 116.4 (CH_2), 71.5 (CH_2), 70.8 (CH_2), 34.1 (CH_2) ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_{11}H_{14}N_2O_2$: 207.1128, found 207.1127 $[M+H]^+$.

Pyridin-1-ium-1-yl(thiazole-4-carbonyl)amide (69b)



Following GP 03 using 1,3-thiazole-4-carboxylic acid (0.65 g, 5.0 mmol), Et_3N (1.4 mL, 10.0 mmol, 2 eq), isobutyl chloroformate (0.75 mL, 5.5 mmol, 1.1 eq) in CH_2Cl_2 (50.0 mL, 0.1 M) and 1-aminopyridinium iodide (1.2 g, 3.3 mmol, 1.1 eq), K_2CO_3 (1.7 g, 12.0 mmol, 2.4 eq) and MeOH (12.5 mL). After workup and purification via silica gel flash column chromatography ylide **69b** was obtained as a brown solid (0.79 g, 72%); mp = 243–245 °C; IR (neat): *v*(max) cm^{-1} 3104, 3060, 1561, 1461, 1319, 760; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.86 (dt, *J* = 6.9, 1.5, 2H), 8.82 (d, *J* = 2.3, 1 H), 8.13 (d, *J* = 2.3, 1H), 7.94 (tt, *J* = 7.7, 1.4, 1H), 7.75–7.65 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.2 (C), 154.9 (C), 152.4 (CH), 143.3 (CH), 137.2 (2CH), 126.1 (2CH), 122.2 (CH) ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_9H_7N_3OS$: 206.0383, found 206.0382 $[M+H]^+$.

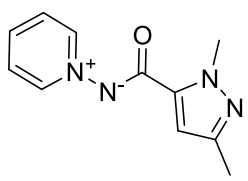
Cyclopropanecarbonyl(pyridin-1-ium-1-yl)amide (69a)



1-Aminopyridinium iodide (4.44 g, 20.0 mmol) was dissolved in in 2.5 M NaOH (200 mL) with vigorous stirring and cooled to 0 °C. After 10 min stirring at 0 °C, cyclopropanecarbonyl chloride (3.64 mL, 40.0 mmol, 2 eq) was added via

syringe pump over 20 min, the ice bath was removed, and the reaction mixture stirred at r.t. for 16 h. The organics were extracted with CH_2Cl_2 (6 × 100 mL), combined, and dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography [CH_2Cl_2 : MeOH (9:1)] gave ylide **69a** as pale yellow crystals (1.95 g, 60%); mp: 158–160 °C; IR (neat): *ν*(max) cm^{-1} 3103, 3030, 1558, 1476, 1390, 1244; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.68 (d, *J* = 6.1, 2H), 7.84 (t, *J* = 7.7, 1H), 7.59 (t, *J* = 7.1, 2H), 1.64 (tt, *J* = 8.1, 4.2, 1H), 0.95–0.84 (m, 2H), 0.75–0.62 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 177.6 (C), 143.2 (2CH), 136.5 (CH), 125.8 (2CH), 14.7 (CH), 6.4 ($2CH_2$) ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_9H_{10}N_2O$: 163.0866, found 163.0865 $[M+H]^+$.

(1,3-Dimethyl-1H-pyrazole-5-carbonyl)(pyridin-1-ium-1-yl)amide (69c)



Following GP 03 using 1,3-dimethylpyrazol-5-4-carboxylic acid (524 mg, 3.7 mmol), Et_3N (1.00 mL, 7.5 mmol, 2 eq), isobutyl chloroformate (0.540 mL, 4.1 mmol, 1.1 eq) in CH_2Cl_2 (37.0 mL, 0.1 M) and 1-aminopyridinium iodide (913 g, 3.3 mmol, 1.1 eq), K_2CO_3 (1.24 g, 8.9 mmol, 2.4 eq) and MeOH (12.5 mL). After workup and purification via silica gel flash column chromatography ylide **69c** was obtained as a brown solid (429 g, 53%); mp = 102–104 °C; IR (neat): *ν*(max) cm^{-1} 3097, 2937, 1587, 1520, 1431, 1304, 1274; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.75 (app. d, *J* = 7.4, 2H), 7.96 (app. t, *J* = 7.4, 1H), 7.70 (app. t, *J* = 7.4, 2H), 6.52, (s, 1H), 4.15 (s, 3H), 2.27 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.2 (C), 146.5 (C), 143.3 (CH), 139.2 (CH), 137.3 (CH), 126.1 (2CH), 106.9 (CH), 39.9 (CH_3), 13.4 (CH_3) ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_{11}H_{12}N_4O$: 217.1084, found 217.1083 $[M+H]^+$.

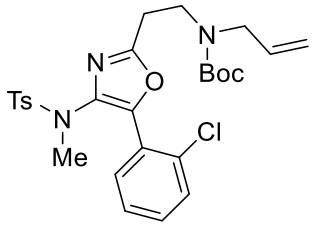
6.5. Oxazoles and double annulation products

6.5.1. Oxazoles

General Procedure 04: gold catalysed synthesis of trisubstituted oxazoles

Adapted from the method developed within our group. To an oven dried 3-neck round bottom flask were added ynamide (1.0 eq), ylide (1.1 eq) and $AuPicCl_2$ (2–5 mol%) and dry toluene (0.1 M wrt. of the ynamide). The reaction mixture was stirred at 90 °C until full consumption of the ynamide (checked by TLC or LCMS). After allowing to cool down to room temperature the reaction mixture was filtered through a pad silica with EtOAc. The volatiles were removed under reduced pressure and the crude product was subjected to silica gel flash column chromatography yielding the corresponding oxazoles.

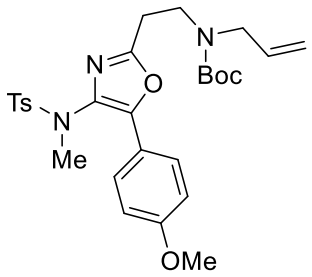
tert-Butyl allyl(2-(5-(2-chlorophenyl)-4-((N,4-dimethylphenyl)sulfonamido)oxazol-2-yl)ethyl)carbamate (92j)



Following GP 04 using ynamide **76a** (640 mg, 2.0 mmol), ylide **67a** (672 mg, 2.2 mmol, 1.1 eq) and $AuPicCl_2$ (39 mg, 5 mol%) in dry toluene (20 mL). The reaction mixture was stirred at 90 °C for 30 minutes. Purification by silica gel flash column chromatography [Heptane: EtOAc(6:4)] gave oxazole **92j** as a colourless oil (896 mg, 1.64 mmol, 82%); IR (neat): ν(max) cm^{-1} 2978, 2933, 1692, 1461, 1408, 1353, 1155, 760, 734; *NMR spectra display a mixture of rotamers:* ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71–7.62 (m , 3H), 7.48–7.43 (m, 1H), 7.37–7.32 (m, 2H), 7.25 (d, *J* = 8.3, 2H), 5.74 (br. app. s, 1H), 5.15–5.05 (m, 2H), 3.90–3.72 (m, 2H), 3.66–3.50 (m, 2H), 3.09 (s, 3H), 3.02–2.95 (m, 2H), 2.41 (s, 3H), 1.46 (br. s., 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ =160.8 (C), 155.3 (C), 143.8 (C), 143.5 (C), 135.7 (C), 134.7 (C), 133.96 and 133.88 (CH), 133.4 (C), 131.8 (CH), 130.8 (CH), 130.1 (CH), 129.5 (2CH), 128.29(2CH), 126.8 and 126.5 (CH), 116.9 and 116.3 (CH_2), 80.1 (C), 50.38 and 49.81

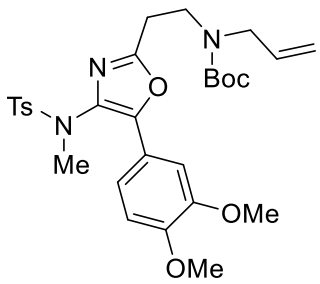
(CH_2), 44.5 and 44.28 (CH_2), 37.0 (CH_3), 28.5 ($3CH_3$), 28.18 and 27.72 (CH_2), 21.7 (CH_3) ppm; *one quaternary carbon not observed in the ^{13}C NMR spectra;* HRMS (ESI-orbitrap): m/z: calcd for $C_{27}H_{32}ClN_3O_5S$: 546.18240, found : 546.1814 $[M+H]^+$, 490.1188 [M-*tert*-butyl+H] $^+$.

tert-Butyl allyl(2-(4-((N,4-dimethylphenyl)sulfonamido)-5-(4-methoxyphenyl)oxazol-2-yl)ethyl)carbamate (92h)



Following GP 04 using ynamide **76b** (631 mg, 2.0 mmol), ylide **67a** (672 mg, 2.2 mmol, 1.1 eq) and $AuPicCl_2$ (39 mg, 5 mol%) in dry toluene (20 mL). The reaction mixture was stirred at 90 °C for 30 minutes. Purification by silica gel flash column chromatography [Heptane: EtOAC(6:4)] gave oxazole **92h** as a colourless oil (845 mg, 1.56 mmol, 78%); IR (neat): ν(max) cm^{-1} 2974, 2933, 1688, 1602, 1513, 1461, 1244, 1155, 663; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.93–7.83 (m, 2H), 7.74 (d, *J* = 8.1, 2H), 7.30 (d, *J* = 8.1, 2H), 7.05–6.93 (m, 2H), 5.74 (br. app. s, 1H), 5.20–5.02 (m, 2H), 3.84 (m, 4H), 3.76 (s, 1H), 3.57–3.50 (br. m, 2H), 3.07 (s, 3H), 2.97–2.90 (br. m, 2H), 2.43 (s, 3H), 1.44 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.0 (C), 155.3 (C), 146.0 (C), 143.9 (C), 134.6 (C), 134.0 (CH), 131.9 (C), 129.5 (2CH), 128.8 (2CH), 126.9 (2CH), 120.0 (C), 117.0 (CH_2), 114.3 (2CH), 80.2 (C), 55.4 (CH_3), 50.5 and 49.7 (CH_2), 44.6 and 44.4 (CH_2), 37.2 (CH_3), 28.5 ($3CH_3$), 28.1 and 27.7 (CH_2), 21.6 (CH_3) ppm; *one quaternary carbon not observed in the ^{13}C NMR spectra;* HRMS (ESI-orbitrap): m/z: calcd for $C_{28}H_{35}N_3O_6S$: 542.2319, found 542.2308 $[M+H]^+$, 564.2123 $[M+Na]^+$.

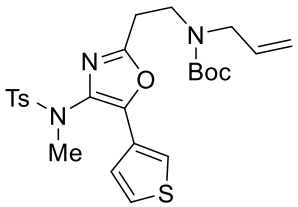
tert-Butyl allyl(2-(5-(3,4-dimethoxyphenyl)-4-((N,4-dimethylphenyl)sulfonamido)oxazol-2-yl)ethyl)carbamate (92i)



Following GP 04 using ynamide **76c** (350 mg, 1.0 mmol), ylide **67a** (340 mg, 1.1 mmol, 1.1 eq) and $AuPicCl_2$ (19 mg, 5 mol%) in dry toluene (20 mL). The reaction mixture was stirred at 90 °C for 30 minutes. Purification by silica gel flash column chromatography

[Heptane: EtOAC(6:4)] gave oxazole **92i** as a colorless oil (446 mg, 0.780 mmol, 77%); IR (neat): ν(max) cm^{-1} 2959, 2929, 1692, 1513, 1461, 1349, 1263, 1155, 812, 663; *NMR spectra display a mixture of rotamers:* ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.3, 2H), 7.57 (d, *J* = 2.2, 1H), 7.48 (dd, *J* = 8.6, 2.2, 1H), 7.30 (d, *J* = 8.3, 2H), 6.92 (d, *J* = 8.6, 1H), 5.81–5.64 (m, 1H), 5.11–5.05 (m, 2H), 3.96 (s, 3H), 3.90 (s, 3H), 3.85–3.73 (m, 2H), 3.54 (s, 2H), 3.05 (s, 3H), 2.95 (s, 2H), 2.42 (s, 3H), 1.43 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6 and 158.4 (C), 155.2 (C), 149.6 (C), 149.1 (C), 146.0 (C), 143.9 (C), 134.6 (C), 134.0 (CH), 132.1 (C), 129.5 (2CH), 128.6 (2CH), 120.1 (C), 118.2 (CH), 116.9 and 116.2 (CH_2), 111.3 (CH), 108.6 (CH), 80.0 (C), 56.1 (CH_3), 56.0 (CH_3), 50.5 and 49.7 (CH_2), 44.6 and 44.4 (CH_2), 37.2 (CH_3), 28.4 ($3CH_3$), 28.0 and 27.7 (CH_2), 21.7 (CH_3) ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_{29}H_{37}N_3O_7S$: 572.24250, found 572.2413 $[M+H]^+$, 594.2230 $[M+Na]^+$, 472.1891 [M-boc $+H]^+$.

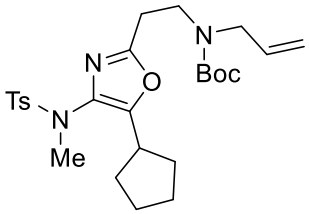
tert-Butyl allyl(2-(4-((N,4-dimethylphenyl)sulfonamido)-5-(thiophen-2-yl)oxazol-2-yl)ethyl)carbamate (92l)



Following GP 04 using ynamide **76d** (500 mg, 1.70 mmol), ylide **67a** (576 mg, 1.87 mmol, 1.1 eq) and $AuPicCl_2$ (30 mg, 5 mol%) in dry toluene (17 mL). The reaction mixture was stirred at 90 °C for 30 minutes. Purification by silica gel flash column chromatography [heptane: EtOAC(6:4)] gave oxazole **92l** as a pale yellow oil (680 mg, 1.31 mmol, 77%); IR (neat): ν(max) cm^{-1} 2974, 2929, 1681, 1613, 1423, 1349, 1162, 1080, 775, 685; *NMR spectra display a mixture of rotamers:* ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (app. d, *J* = 3.1, 1H), 7.73 (d, *J* = 8.1, 2H), 7.62 (dd, *J* = 5.1, 1.3, 1H), 7.39 (dd, *J* = 5.1, 3.1, 1H), 7.32 (d, *J* = 8.1, 2H), 5.74 (br. s, 1H), 5.14–5.06 (m, 2H), 3.90–3.74 (m, 2H), 3.59–3.50 (m, 2H), 3.07 (s, 3H), 2.99–2.90 (m, 2H), 2.44 (s, 3H), 1.45 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.0 and 158.8 (C), 155.2 (C), 144.0 (C), 143.7 (C), 134.4 (C), 134.0 (CH), 132.2 (C), 129.5 (2CH), 128.6 (2CH), 127.8 (C), 126.4 (CH), 125.3

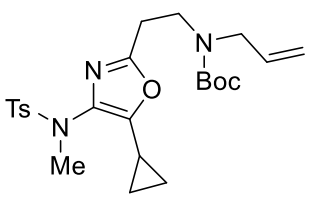
(CH), 122.7 (CH), 116.9 and 116.3 (CH_2), 80.1 (C), 50.5 and 49.7 (CH_2), 44.6 and 44.3 (CH_2), 37.2 (CH_3), 28.4 (3 CH_3), 28.0 and 27.6 (CH_2), 21.7 (CH_3) ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_{25}H_{31}N_3O_5S_2$: 518.1778, found 518.1773 $[M+H]^+$, 540.1594 $[M+Na]^+$, 418.1246 [M-boc +H]$^+$.

tert-Butyl allyl(2-(5-cyclopentyl-4-((N,4-dimethylphenyl)sulfonamido)oxazol-2-yl)ethyl)carbamate (92m)



Following GP 04 using ynamide **76e** (550 mg, 1.98 mmol), ylide **67a** (666 mg, 2.30 mmol, 1.1 eq) and $AuPicCl_2$ (0.035 mg, 5 mol%) in dry toluene (20 mL). The reaction mixture was stirred at 90 °C for 30 minutes. Purification by silica gel flash column chromatography [Heptane: EtOAC(6:4)] gave oxazole **92m** as a pale yellow oil (812 mg, 1.61 mmol, 81%); IR (neat): ν(max) cm^{-1} 2963, 2870, 1692, 1587, 1461, 1405, 1349, 1155, 667; *NMR spectra display a mixture of rotamers:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.0, 2H), 7.22 (d, *J* = 8.0, 2H), 5.70–5.60 (m, 1H), 5.10–4.94 (m, 2H), 3.77–3.61 (m, 2H), 3.46–3.38 (m, 2H), 3.25 (p, *J* = 8.3, 1H), 2.98 (s, 3H), 2.83–2.77 (m, 2H), 2.36 (s, 3H), 2.02–1.99 (m, 2H), 1.81–1.55 (stack, 6H), 1.40 (br. s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.7 and 158.5 (C), 155.1 (C), 151.7 (C), 143.6 (C), 134.4 (C), 133.9 (CH), 132.5 (C), 129.4 (2CH), 128.2 (2CH), 116.7 and 116.0 (CH_2), 79.8 (C), 50.2 and 49.6 (CH_2), 44.5 and 44.2 (CH_2), 37.2 (CH_3), 35.3 (CH), 31.4 ($2CH_2$), 28.3 ($3CH_3$), 28.0 and 27.5 (CH_2), 25.6 ($2CH_2$), 21.5 (CH_3) ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_{26}H_{37}N_3O_5S$: 504.25267, found 504.2514 $[M+H]^+$.

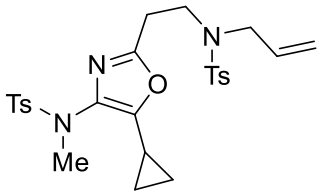
tert-Butyl allyl(2-(5-cyclopropyl-4-((N,4-dimethylphenyl)sulfonamido)oxazol-2-yl)ethyl)carbamate (92h)



Following GP 04 using ynamide **76f** (500 mg, 2.00 mmol), ylide **67a** (674 mg, 2.20 mmol, 1.1 eq) and AuPicCl2 (39 mg, 5 mol%) in dry toluene (20 mL). The reaction mixture was stirred at 90 °C for 30

minutes. Purification by silica gel flash column chromatography [Heptane: EtOAC(6:4)] gave oxazole **92h** as a pale yellow oil (839 mg, 1.76 mmol, 88%); IR (neat): ν(max) cm–1 2974, 1692, 1587, 1461, 1408, 1349, 1155, 752; *NMR spectra display a mixture of rotamers*: 1H NMR (400 MHz, $CDCl_3$): δ = 7.66–7.60 (m, 2H), 7.28 (s, 2H), 5.69 (br. s, 1H), 5.11–5.02 (m, 2H), 3.80–3.63 (m, 2H), 3.47–3.39 (m, 2H), 3.04 (s, 3H), 2.82–2.77 (m, 2H), 2.41 (s, 3H), 2.07 (tt, *J* = 8.3, 5.3, 1H), 1.44 (s, 9H), 1.03–0.86 (m, 4H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.7 (C), 155.2 (C), 149.4 (C), 143.8 (C), 134.4 (C), 134.0 (CH), 133.1 (C), 129.6 (2CH), 128.4 (2CH), 116.9 and 116.3 (CH2), 80.0 (C), 50.4 and 49.7 (CH_2), 44.5 and 44.1 (CH_2), 37.2 (CH_3), 28.5 ($3CH_3$), 27.8 and 27.4 (CH_2), 21.7 (CH_3), 6.8 ($2CH_2$), 6.1 (CH) ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_{24}H_{33}N_3O_5S$: 476.22137, found 476.2212 $[M+H]^+$, 498.2029 $[M+Na]^+$.

N-Allyl-N-(2-(5-cyclopropyl-4-((N,4-dimethylphenyl)sulfonamido)oxazol-2-yl)ethyl)-4-methylbenzenesulfonamide (92g)



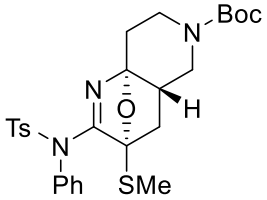
Following GP 04 using ynamide **76f** (500 mg, 2.00 mmol), ylide **67e** (793 mg, 2.21 mmol, 1.1 eq) and AuPicCl2 (0.039 mg, 5 mol%) in dry toluene (20 mL). The reaction mixture was stirred at 90 °C for 30 minutes. Purification by silica gel flash column chromatography [Heptane: EtOAC(7:3)] gave oxazole **92g** as a pale yellow oil (988 mg, 1.86 mmol, 93%); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.70–7.62 (m, 4H), 7.34–7.26 (m, 4H), 5.58 (ddt, *J* = 17.8, 9.6, 6.4, 1H), 5.14 (br. s, 1H), 5.12–5.09 (m, 1H), 3.75 (app. d, *J* = 6.3, 2H), 3.39 (t, *J* = 7.2, 2H), 3.04 (s, 3H), 2.86 (t, *J* = 7.2, 2H), 2.43 (s, 3H), 2.42 (s, 3H), 2.04 (tt, *J* = 8.4, 5.3, 1H), 1.02–0.86 (m, 4H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.1 (C), 149.5 (C), 143.8 (C), 143.6 (C), 136.9 (C), 134.8 (C), 133.2 (C), 132.9 (CH), 129.9 (2CH), 129.6 (2CH), 128.4 (2CH), 127.3 (2CH), 119.4 (CH_2), 51.3 (CH_2), 44.6 (CH_2), 37.3 (CH_3), 28.6 (CH_2), 21.72 (CH_3), 21.67 (CH_3), 7.0 ($2CH_2$), 6.3 (CH) ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_{26}H_{31}N_3O_5S_2$: 530.1778, found 530.1767 $[M+H]^+$.

6.5.2. Double annulation products

General procedure 05: gold catalysed double annulation

Adapted from the method developed within our group. To an oven dried 3-neck round bottom flask were added ynamide (1.0 eq), ylide (1.1–1.5 eq) and $AuPicCl_2$ (2–5 mol%) and dry toluene (0.1 M wrt. of the ynamide). The reaction mixture was stirred at 90 °C until full consumption of the ynamide (checked by TLC or LCMS). And then stirred at the stated temperature for the stated time. After allowing to cool down to room temperature the reaction mixture was filtered through a pad silica with EtOAc. The volatiles were removed under reduced pressure and the crude product was subjected to silica gel flash column chromatography or recrystallised, yielding the corresponding Diels–Alder products.

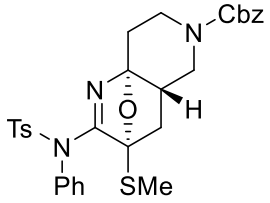
tert-Butyl (3R*,4aS*,8aR*)-2-((4-methyl-N-phenylphenyl)sulfonamido)-3-(methylthio)-3,4,4a,5,7,8-hexahydro-6H-3,8a-epoxy-1,6-naphthyridine-6-carboxylate (91a)



Following GP 05 using aminide **67a** (586 mg, 1.9 mmol, 1.2 eq), ynamide **73a** (508 mg, 1.6 mmol) and $AuPicCl_2$ (32.0 mg, 0.083 mmol, 5 mol%) then toluene (24 mL, 0.1 M aminide) and the reaction was stirred at 90 °C until complete consumption of the ynamide (40 min). After which the temperature was raised to 110 °C and the reaction mixture was stirred for 16 h. Silica gel flash column chromatography [hexane:EtOAc (8:2)] and trituration from hot ethanol gave **91a** as a white solid (599 mg, 69%); mp: 172–174°C; IR (neat): ν(max) cm^{-1} 2975, 2946, 2923, 1685, 1607, 1585, 1424, 1362, 1163; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 8.0, 2H), 7.45–7.38 (m, 1H), 7.35 (app. t, *J* = 7.6, 2H), 7.29–7.20 (m, 4H), 4.25 (br. app. s, 2H), 2.87 (s, 1H), 2.60–2.37 (stack, 5H, including: 2.42, s, 3H), 2.26 (app. d, *J* = 14.3, 1H), 2.13–2.01 (m, 1H), 1.67 (m, 4H), 1.50 (s, 9H), 1.33 (dd, *J* = 12.2, 2.9, 1H) ppm; *^{13}C NMR resonances assigned with assistance from HSQC and HMBC spectra due to the broadening of the resonances owing to the rotamer effect, shifts marked with an asterisk were extracted from HSQC analysis:* ^{13}C

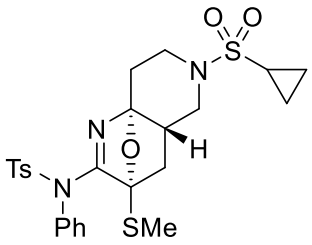
NMR (101 MHz, $CDCl_3$): δ = 165.9 (C), 154.2 (C), 144.4 (C), 135.7 (C), 134.5 (C), 130.4 (2CH), 129.8 (2CH), 129.7 (2CH), 129.5 (CH), 128.9 (2CH), 128.8 (2CH), 99.3 (C), 94.2 (C), 79.9 (C), 47.9* (CH_2), 40.6* (CH_2) 39.5 (CH), 33.9 (CH_2), 29.5* (CH_2), 28.4 ($3CH_3$), 21.7 (CH_3), 12.3 (CH_3) ppm; HRMS (ES-TOF): m/*z*: calcd for $C_{27}H_{33}N_3O_5S_2$: 544.1940, found 544.1945 $[M+H]^+$.

Benzyl (3R*,4aS*,8aR*)-2-((4-methyl-N-phenylphenyl)sulfonamido)-3-(methylthio)-3,4,4a,5,7,8-hexahydro-6H-3,8a-epoxy-1,6-naphthyridine-6-carboxylate (91b)



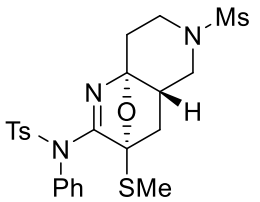
Following GP 05 using aminide **67b** (189 mg, 0.56 mmol, 1.5 eq), ynamide **73a** (118 mg, 0.37 mmol) and $AuPicCl_2$ (7.2 mg, 0.018 mmol, 5 mol%) then toluene (5.6 mL, 0.1 M aminide) and the reaction was stirred at 90 °C until complete consumption of the ynamide (2 h). After which the temperature was raised to 110 °C and the reaction mixture was stirred for 16 h. Silica gel flash column chromatography [hexane:EtOAc (8:2)] and trituration from hot ethanol gave **91b** as a white solid (133 mg, 62%); mp: 165–167°C; IR (neat): *v* (max) cm^{-1} 1695, 1606, 1589, 1476, 1431, 1356, 1237, 1163; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 8.1, 2H), 7.45–7.37 (m, 5H), 7.36–7.32 (m, 3H), 7.25–7.19 (m, 3H), 5.18 (br. app. s, 2H), 4.31 (br. s, 2H), 2.94 (br. s, 1H), 2.50 (br. s, 1H), 2.42 (s, 3H), 2.28 (app. d, *J* = 15.1, 1H), 2.16–2.05 (m, 1H), 1.92–1.59 (m, 4H), 1.32 (d, *J* = 11.6 Hz, 1H) ppm; *^{13}C NMR resonances assigned with assistance from HSQC and HMBC spectra due to the broadening of the resonances owing to the rotamer effect, shifts marked with an asterisk were exctracted from HSQC analysis:* ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.1 (C), 154.8 (C), 144.5 (C), 134.5 (C), 130.5 (2CH), 129.8 (2CH) , 129.6 (CH), 129.0 (2CH), 128.8 (2CH), 128.6 (2CH), 128.2 (2CH), 128.1 (CH), 99.2 (C), 94.3 (C), 67.4 (CH_2), 48.1 (CH_2), 40.9 (CH_2), 38.3* (CH), 34.3* (CH_2), 29.0* (CH_2), 21.7 (CH_3), 14.2 (CH_3); HRMS (ES-TOF): m/*z* calcd for $C_{30}H_{32}N_3O_5S_2$: 578.1778, found 578.1779 $[M+H]^+$.

N-((3R*,4aS*,8aR*)-6-(Cyclopropylsulfonyl)-3-(methylthio)-4,4a,5,6,7,8-hexahydro-3H-3,8a-epoxy-1,6-naphthyridin-2-yl)-4-methyl-N-phenylbenzenesulfonamide (91c)



Following GP 05 using aminide **67c** (183 mg, 0.6 mmol, 1.5 eq), ynamide **73a** (127 mg, 0.4 mmol), $AuPicCl_2$ (7.80 mg, 0.02 mmol, 5 mol%) and toluene (6 mL, 0.1 M aminide). The reaction was stirred at 90 °C until complete consumption of the ynamide (2 h). After which the temperature was raised to 110 °C and the reaction mixture was stirred for 16 h. Silica gel flash column chromatography [hexane:EtOAc (8:2)] and trituration from hot ethanol gave **91c** as a white solid (107 mg, 69%); mp: 196 –198 °C; IR (neat): *v* (max) cm^{-1} 1606, 1588, 1467, 1453, 1356, 1332, 1307, 1163, 1153, 1127; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 8.8, 2H), 7.45–7.39 (m, 1H), 7.38–7.33 (m, 2H), 7.27–7.20 (m, 4H), 3.99 (ddd, *J* = 12.3, 6.5, 2.1, 1H), 3.90 (ddt, *J* = 11.9, 5.4, 1.8, 1H), 2.99 (app. td, *J* = 12.3, 2.9, 1H), 2.71–2.62 (m, 1H), 2.57 (app. t, *J* = 11.8, 1H), 2.46–2.44 (stack, 4H, including: 2.43, s, 3H), 2.29–2.17 (m, 2H), 1.86 (dd, *J* = 12.4, 7.5, 1H), 1.72 (s, 3H), 1.31 (dd, *J* = 12.4, 2.8, 1H), 1.20–1.15 (m, 2H), 1.01–0.95 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.3 (C), 144.6 (C), 135.7 (C), 134.5 (C), 130.5 (CH), 129.9 (2CH), 129.6 (2CH) , 129.0 (2CH), 128.9 (2CH), 98.3 (C), 94.2 (C), 50.4 (CH_2), 43.2 (CH_2), 40.0 (CH), 34.4 (CH_2), 29.9 (CH_2), 26.9 (CH), 21.7 (CH_3), 12.4 (CH_3), 4.7 (CH_2), 4.6 (CH_2) ppm; HRMS (ES-TOF): m/z calcd for $C_{25}H_{30}N_3O_5S_3$: 548.1342, found 548.1345 $[M+H]^+$.

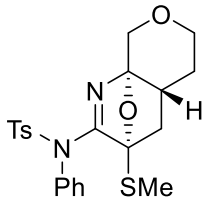
4-Methyl-N-((3R*,4aS*,8aR*)-6-(methylsulfonyl)-3-(methylthio)-4,4a,5,6,7,8-hexahydro-3H-3,8a-epoxy-1,6-naphthyridin-2-yl)-N-phenylbenzenesulfonamide (91d)



Note: *Ylide **67d** is not completely soluble in toluene, therefore a portion of the reaction volume was used to solubilise the ylide heating gently the suspension with a heat gun*; Following GP 05 using aminide **67c** (280 mg, 0.99 mmol, 1.2 eq), ynamide **73a** (262 mg, 0.83 mmol) and $AuPicCl_2$ (16 mg, 0.041 mmol, 5

mol%) then toluene (8.2 mL, 0.1 M ynamide) and the reaction was stirred at 90 °C until consumption of the ynamide (1 h). After which the temperature was raised to 110 °C and the reaction mixture was stirred for 16 h. Silica gel flash column chromatography [hexane:EtOAc (8:2)] and trituration from hot ethanol gave **91d** as a white solid (294 mg, 68%); mp: 199–201 °C; IR (neat): ν (max) cm^{-1} 1608, 1590, 1488, 1454, 1359, 1325, 1309, 1163, 1144; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72–7.68 (m, 2H), 7.45–7.40 (m, 1H), 7.38–7.33 (m, 2H), 7.27–7.22 (m, 4H), 3.99 (ddd, *J* = 12.0, 6.4, 2.0, 1H), 3.90–3.84 (m, 1H), 2.87 (td, *J* = 12.5, 2.9, 1H), 2.81 (s, 3H), 2.71–2.61 (m, 1H), 2.50–2.40 (stack, 5H, including: 2.42, s, 3H), 2.28–2.19 (m, 1H), 1.86 (dd, *J* = 12.4, 7.5, 1H), 1.72 (s, 3H), 1.31 (dd, *J* = 12.4, 2.8, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.3 (C), 144.6 (C), 135.6 (C), 134.4 (C), 130.5 (2CH), 129.8 (2CH), 129.7 (CH), 128.9 (2CH), 128.8 (2CH), 98.2 (C), 94.2 (C), 50.0 (CH_2), 42.9 (CH_2), 39.9 (CH), 36.0 (CH_3), 34.3 (CH_2), 29.7 (CH_2), 21.7 (CH_3), 12.4 (CH_3)ppm; HRMS (ES-TOF): m/z calcd for $C_{23}H_{27}N_3O_5S_3$: 522.1191, found 522.1198 $[M+H]^+$.

4-Methyl-N-((3R*,4aR*,8aS*)-3-(methylthio)-4,4a,5,6-tetrahydro-3H,8H-3,8a-epoxypyrano[3,4-b]pyridin-2-yl)-N-phenylbenzenesulfonamide (91n)

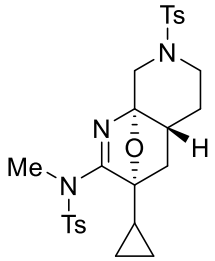


Following GP 05 using aminide **95** (1.1 g, 5.3 mmol, 1.2 eq), ynamide **73a** (1.4 g, 4.4 mmol), $AuPicCl_2$ (86 mg, 0.22 mmol, 5 mol%) and toluene (44 mL, 0.1 M ynamide). The reaction was stirred at 90 °C until complete consumption of the ynamide (30 minutes). After which the temperature was raised to 110 °C and the reaction mixture was stirred for 16 h. After allowing to cool down to room temperature the reaction mixture was filtered through a pad of silica with EtOAc (80 mL). Solvent was removed under reduced pressure and the crude material was recrystallized from hot ethanol affording **91n** as a white powder (1.4 g, 75%);

Scaling up: To an oven dried, argon flushed 3-neck round bottom flask, were added ynamide **73a** (5.00 g, 15.6 mmol), aminide **95** (3.60 g, 17.3 mmol, 1.1 eq) and $AuPicCl_2$ (123 mg, 2

mol%) to dry toluene (160 mL, 0.1 M). The reaction mixture was stirred at 90 °C until complete consumption of the ynamide (40 minutes). The temperature was then raised to 110 °C and the reaction mixture was stirred for further 16 h. After allowing to cool down to room temperature the reaction mixture was filtered through a pad of silica with EtOAC (150 mL). The volatiles were removed under reduced pressure and the crude solid was titrated from hot EtOH yielding polycyle **91n** as a white powder (5.11 g, 73%); mp(EtOH): 179–181 °C; Purity: qNMR(methyl 3,5-dinitrobenzoate): 99.71%; IR (neat): *v* (max) cm^{-1} 1745, 1606, 1532, 1344, 1310, 1217, 1154; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, *J*= 8.3, 2H), 7.44–7.38 (m, 1H), 7.37–7.32 (m, 2H), 7.24 (m, 4H), 4.38 (d, J_{AB} = 13.1, 1H), 4.18 (d, J_{AB} = 13.1, 1H), 3.97 (ddd, *J* = 11.6, 4.4, 1.8, 1H), 3.49 (td, *J* = 12.3, 11.8, 1.8, 1H), 2.42 (s, 3H), 2.11 (m, 1H), 1.94 (m, 2H), 1.72 (s, 3H), 1.68–1.56 (m, 1H), 1.51 (dd, *J* = 12.1, 2.9, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.0 (C), 144.4 (C), 135.7 (C), 134.5 (C), 130.5 (2CH), 129.7 (2CH), 129.6 (CH), 128.9 (CH), 128.8 (CH), 97.0 (C), 94.6 (C), 68.4, 66.9 (CH_2), 38.4 (CH), 36.4 (CH_2), 31.5 (CH_2), 21.7 (CH_3), 12.3 (CH_3) ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_{22}H_{24}N_2O_4S_2$: 445.1250, found 445.1242 $[M+H]^+$.

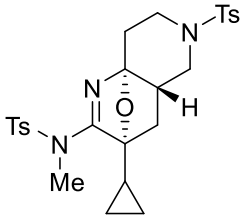
N-((3R*,4aR*,8aS*)-3-cyclopropyl-7-tosyl-4,4a,5,6,7,8-hexahydro-3H-3,8a-epoxy-1,7-naphthyridin-2-yl)-N,4-dimethylbenzenesulfonamide (91f)



Following GP 05 using aminide **67f** (431.0 mg, 1.2 mmol, 1.2 eq), ynamide **76f** (249.0 g, 1.0 mmol), $AuPicCl_2$ (20.0 mg, 0.22 mmol, 5 mol%) and toluene (10 mL, 0.1 M ynamide). The reaction was stirred at 90 °C until complete consumption of the ynamide (1 h). After which the temperature was raised to 110 °C and the reaction mixture was stirred for 16 h. After allowing to cool down to room temperature the reaction mixture was filtered through a pad of silica with EtOAc (20 mL). Solvent was removed under reduced pressure and the crude material was subjected to silica gel flash column chromatography [eptane:EtOAc (30% -> 40%)] affording **91f** as a white

powder (397 mg, 75%); IR (neat): *v* (max) cm^{-1} 2949, 2847, 1595, 1341, 1162, 1008; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.82–7.76 (m, 2H), 7.66 (d, *J* = 8.2, 2H), 7.33–7.27 (m, 4H), 4.20 (d, *J* = 13.2, 1H), 3.79 (dt, *J* = 12.4, 3.4 Hz, 1H), 3.19 (s, 3H), 3.13 (d, *J* = 13.2, 1H), 2.44 (s, 3H), 2.43 (s, 3H), 2.38 (td, *J* = 12.7, 1.7, 1H), 1.84 (dd, *J* = 12.1, 7.7, 1H), 1.70–1.62 (m, 1H), 1.56–1.48 (m, 1H), 1.41 (qd, *J* = 12.9, 3.9, 1H), 1.13 (dd, *J* = 12.1, 3.0, 1H), 0.88 (app. t, *J* = 6.7 Hz, 1H), 0.65–0.45 (m, 4H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.9 (C), 144.6 (C), 143.6 (C), 134.8 (C), 133.9 (C), 129.8 (2CH), 129.7 (2CH), 128.3 (2CH), 127.9 (2H), 96.3 (C), 91.7 (C), 48.4 (CH_2), 45.4 (CH_2), 37.7 (CH), 35.7 (CH_3), 35.1 (CH_2), 30.7 (CH_2), 21.8 (CH_3), 21.7 (CH_3), 11.2 (CH), 3.5 (CH_2), 3.4 (CH_2)ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_{26}H_{31}N_3O_5S_2$: 530.1778, found 530.1770 $[M+H]^+$.

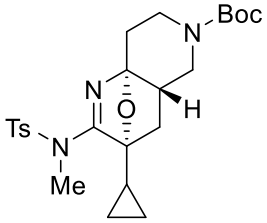
N-((3R*,4aS*,8aR*)-3-Cyclopropyl-6-tosyl-4,4a,5,6,7,8-hexahydro-3H-3,8a-epoxy-1,6-naphthyridin-2-yl)-N,4-dimethylbenzenesulfonamide (91g)



Following GP 05 using aminide **67e** (5.3 g, 14.8 mmol, 1.2 eq), ynamide **76f** (3.2 g, 12.8 mmol), $AuPicCl_2$ (0.25 g, 0.22 mmol, 5 mol%) and toluene (130 mL, 0.1 M ynamide). The reaction was stirred at 90 °C until complete consumption of the ynamide (1 h). After which the temperature was raised to 110 °C and the reaction mixture was stirred for 16 h. After allowing to cool down to room temperature the reaction mixture was filtered through a pad of silica with EtOAc (120 mL). Solvent was removed under reduced pressure and the crude material was triturated from hot isopropanol affording **91g** as a white powder (4.7 g, 69 %); mp: 199–201 °C; IR (neat): *v* (max) cm^{-1} 1599, 1345, 1166, 1088, 812, 741; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.78 (d, *J*= 8.0, 2H), 7.64 (d, *J* = 7.8, 2H), 7.38–7.32 (m, 4H), 3.93 (m, 1H), 3.81 (m, 1H), 3.19 (s, 3H), 2.53 (td, *J* = 13.8, 5.5, 1H), 2.44 (s, 6H), 2.42–2.35 (m, 1H), 2.18 (app. d, *J* = 14.3, 1H), 2.05–1.89 (m, 2H), 1.73 (dd, *J* = 12.4, 7.1, 1H), 1.53 (m, 1H), 0.95 (m, 1H), 0.59 (m, 2H), 0.47 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.9 (C), 144.6 (C), 143.5 (C), 134.5 (C), 133.8

(C), 129.8 (2CH), 129.6 (2CH), 128.4 (2CH), 127.5 (2CH), 97.1 (C), 91.2 (C), 50.9 (CH_2), 43.2 (CH_2), 38.6 (CH), 35.6 (CH_3), 31.9 (CH_2), 29.6 (CH_2), 21.7 (CH_3), 21.6 (CH_3), 10.7 (CH), 3.4 (CH_2), 3.1 (CH_2) ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_{26}H_{31}N_3O_5S_2$: 530.1778, found 530.1770 $[M+H]^+$.

tert-Butyl (3R*,4aS*,8aR*)-3-cyclopropyl-2-((N,4-dimethylphenyl)sulfonamido)-3,4,4a,5,7,8-hexahydro-6H-3,8a-epoxy-1,6-naphthyridine-6-carboxylate (91h)

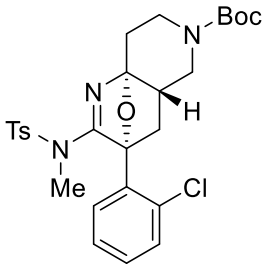


Aminide **67a** (1.0 g, 3.3 mmol, 1.1 eq), ynamide **76f** (0.75 g, 3.0 mmol), and $AuPicCl_2$ (20 mg, 0.06 mmol, 2 mol%) were dissolved in toluene (30 mL, 0.1 M) and stirred at 90 °C until complete consumption of the ynamide (40 min). The reaction mixture was allowed to cool down to room temperature and filtered through a short pad of silica using heptane: EtOAc (7:3) (80 mL). The solvents were removed under reduced pressure and the crude material was dissolved in o-dichlorobenzene (30 mL) and stirred at 120 °C for 24 h. The reaction mixture was allowed to cool to room temperature and filtered through a pad of silica that was washed further with heptane (50 mL, successively discarded) and EtOAc (100 mL). The latter aliquot was evaporated under reduced pressure yielding a pale yellow oil that solidifies upon standing into a pale yellow solid that was recrystallised from hot EtOH yielding polycycle **91h** as a white solid (1.18 g, 83%);

Scale up: Aminide **67a** (6.70 g, 22.1 mmol, 1.1 eq), ynamide **76f** (5.00 g, 22.1 mmol), and $AuPicCl_2$ (0.16 g, 0.40 mmol, 2 mol%) were dissolved in toluene (200 mL, 0.1 M) and stirred at 90 °C until complete consumption of the ynamide (40 min). The reaction mixture was allowed to cool down to room temperature and transferred to a single-neck round bottom flask. The reaction mixture was concentrated under reduced pressure to one quarter of the initial volume and filtered through a pad of silica using heptane: EtOAc (7:3) (200 mL). The solvents were removed under reduced pressure and the crude material was dissolved in o-

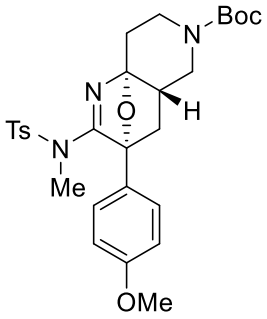
dichlorobenzene (200 mL) and stirred at 120 °C for 24 h. The reaction mixture was allowed to cool to room temperature and filtered through a pad of silica, that was washed further with heptane (350 mL, successively discarded) and EtOAc (300 mL). The latter aliquot was evaporated under reduced pressure yielding a pale yellow oil that solidifies upon standing into a pale yellow solid that was recrystallised from hot EtOH yielding polycycle **91h** as a white solid (7.8 g, 82%); *Note: it might be useful to cool down the resulting oil to help the solidification process for bigger scale reactions*. mp: 116–118 °C; IR (neat): cm^{-1} 2974, 1688, 1587, 1461, 1405, 1345, 1162, 1058, 935, 670. ^{1}H NMR (400 MHz, DMSO, 80 °C): δ = 7.85 (d, *J* = 8.1, 2H), 7.45 (d, *J* = 8.1, 2H), 4.08 (ddd, *J* = 13.4, 5.8, 1.9, 1H), 3.99–3.94 (m, 1H), 3.29 (s, 3H), 2.78 (td, *J* = 13.1, 3.4, 1H), 2.45 (s, 3H), 2.37 (app. dd, *J* = 13.4, 11.1, 1H), 2.15 (ddd, *J* = 14.7, 12.9, 5.7, 1H), 2.05–2.01 (m, 1H), 1.61 (tt, *J* = 8.3, 4.2, 1H), 1.57–1.48 (m, 2H), 1.47 (s, 9H), 1.02–0.93 (m, 1H), 0.74–0.66 (m, 1H), 0.66–0.50 (m, 3H) ppm; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (app. br. s, 2H), 7.30 (d, *J* = 8.1, 2H), 4.14 (br, 2H), 3.19 (s, 3H), 2.81 (br, 1H), 2.42 (s, 3H), 2.29 (br, 2H), 2.07 (dt, *J* = 14.2, 2.6, 1H), 1.85 (dtd, *J* = 11.4, 6.9, 2.8, 1H), 1.78–1.69 (m, 1H), 1.61 (s, 1H), 1.45 (s, 9H), 1.00 (d, *J* = 12.1, 1H), 0.68–0.63 (m, 1H), 0.63–0.52 (m, 3H) ppm; *^{13}C NMR resonances assigned with assistance from HSQC and HMBC spectra due to the broadening of the resonances owing to the rotamer effect, shifts marked with an asterisk were exctracted from HSQC analysis:* ^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.2 (C), 144.5 (C), 134.6 (C), 129.5 (2CH), 128.4 (2CH), 98.2 (C), 91.3 (C), 79.7 (C), 47.7 (CH_2)*, 40.4 (CH_2)*, 37.3 (CH)*, 35.6 (CH_3), 31.9 (CH_2), 29.5 (CH_2)*, 28.4 ($3CH_3$), 21.6 (CH_3), 10.9 (CH), 3.4 (CH_2), 3.1 (CH_2) ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_{24}H_{33}N_3O_5S$: 476.2214, found: 476.2205 $[M+H]^+$.

tert-Butyl (3R*,4aS*,8aR*)-3-(2-chlorophenyl)-2-((N,4-dimethylphenyl)sulfonamido)-3,4,4a,5,7,8-hexahydro-6H-3,8a-epoxy-1,6-naphthyridine-6-carboxylate (91j)



Oxazole **92j** (500 mg, 0.91 mmol) was dissolved in o-DCB (9.1 mL, 0.1 M) and stirred at 120 °C for 48 h. After allowing to cool down to room temperature the reaction mixture was filtered through a pad of silica with heptane (25 mL). This aliquot was discarded and the silica pad was further washed with EtOAc (50 mL). The filtrate was then concentrated under reduced pressure and subjected to silica gel flash column chromatography [toluene: EtOAc(8:2)] yielding polycycle **91j** as a white solid (371 mg, 0.68 mmol, 75%); mp = 160–162 °C; IR (neat): *v* (max) cm^{-1} 2952, 1684, 1602, 1420, 1345, 1162, 931, 816, 760; *NMR spectra display a mixture of rotamers:* ^{1}H NMR (400 MHz, DMSO, 80 °C): δ = 7.74–7.69 (m, 1H), 7.60–7.55 (m, 2H), 7.50–7.44 (m, 3H), 7.39 (d, *J* = 8.1, 2H), 4.20 (ddd, *J* = 13.4, 6.5, 1.8, 1H), 4.02 (ddt, *J* = 13.7, 5.3, 2.3, 1H), 2.88 (s, 3H), 2.87–2.79 (m, 1H), 2.52–2.45 (m, 1H), 2.44 (s, 3H), 2.35–2.19 (stack, 3H), 1.84 (dd, *J* = 12.3, 3.1, 1H), 1.75–1.68 (m, 1H), 1.49 (s, 9H) ppm; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63–7.59 (m, 1H), 7.42 (d, *J* = 8.1, 2H), 7.35–7.27 (m, 3H), 7.18 (d, *J* = 8.0, 2H), 4.47–3.99 (m, 2H), 2.92 (stack, 4H), 2.52 (stack, 3H), 2.38 (s, 3H), 2.29 (d, *J* = 13.6, 1H), 2.02 (ddt, *J* = 14.4, 7.3, 3.0, 1H), 1.75 (br. app. s, 1H), 1.47 (s, 9H) ppm; *^{13}C NMR resonances assigned with assistance from HSQC and HMBC spectra due to the broadening of the resonances owing to the rotamer effect, shifts marked with an asterisk were extracted from HSQC analysis:* ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.8 (C), 154.1 (C), 144.1 (C), 134.6 and 134.4 (C), 133.0 (C), 130.7 and 130.6 (CH), 130.1 (CH), 129.3 (2CH), 127.7 (CH), 126.6 (2CH), 99.2 (C), 90.5 (C), 79.6 (C), 48.3* (CH_2), 41.0* (CH_2), 38.1 (CH), 35.1 (CH_3), 33.1 (CH_2), 29.6* (CH_2), 28.3 ($3CH_3$), 21.4 (CH_3) ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_{27}H_{32}ClN_3O_5S$: 546.1824, found: 546.1815 $[M+H]^+$.

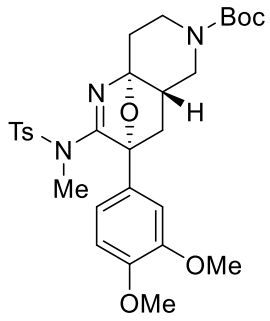
tert-Butyl (3R*,4aS*,8aR*)-2-((N,4-dimethylphenyl)sulfonamido)-3-(4-methoxyphenyl)-3,4,4a,5,7,8-hexahydro-6H-3,8a-epoxy-1,6-naphthyridine-6-carboxylate (91h)



Oxazole **92h** (500 mg, 0.92 mmol) was dissolved in o-DCB (9.2 mL, 0.2 M) and stirred at 120 °C for 24 h. After allowing to cool down to room temperature the reaction mixture was filtered through a pad of silica with heptane (25 mL). This aliquot was discarded and the silica pad was further washed with EtOAc (50 mL). The filtrate was then concentrated under reduced pressure and subjected to silica gel flash column chromatography [toluene: EtOAc(8:2)] yielding polycycle **91h** as a white solid (330 mg, 0.61 mmol, 66%); IR (neat): *v* (max) cm^{-1} 2952, 1684, 1599, 1520, 1427, 1353, 1080, 1166, 816, 678; ^{1}H NMR (400 MHz, DMSO, 80 °C): δ = 7.69 (d, *J* = 8.3, 2H), 7.43–7.37 (m, 4H), 7.01 (d, *J* = 8.8, 2H), 4.17 (ddd, *J* = 13.5, 6.5, 1.9, 1H), 4.07–3.99 (m, 1H), 3.85 (s, 3H), 2.84 (td, *J* = 12.9, 4.0 Hz, 1H), 2.72 (s, 3H), 2.50–2.46 (m, 1H),2.45 (s, 3H) 2.33–2.17 (m, 2H), 2.14 (dd, *J* = 12.2, 7.5, 1H), 1.74–1.67 (m, 1H), 1.57 (dd, *J* = 12.3, 3.1 Hz, 1H), 1.49 (s, 9H) ppm; ^{1}H NMR (400 MHz, DMSO): δ = 7.68 (d, *J* = 8.1, 2H), 7.43–7.36 (m, 4H), 7.04–6.98 (m, 2H), 4.22–3.94 (m, 2H), 3.82 (s, 3H), 2.91–2.72 (m, 1H), 2.68 (s, 3H), 2.51–2.39 (stack, 4H, including: 2.42, s, 3H), 2.24–2.18 (m, 2H), 2.10 (s, 1H), 1.68–1.55 (m, 2H), 1.46 (s, 9H) ppm; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 7.8, 2H), 7.40–7.34 (m, 2H), 7.23 (d, *J* = 8.1, 2H), 6.93–6.86 (m, 2H), 4.23 (s, 2H), 3.82 (s, 3H), 2.90 (br.s, 1 H), 2.71 (s, 3H), 2.44 (br. s, 2H), 2.41 (s, 3H), 2.33–2.21 (m, 2H), 2.08–1.98 (m, 1H), 1.48 (s, 10H) ppm; *^{13}C NMR resonances assigned with assistance from HSQC and HMBC spectra due to the broadening of the resonances owing to the rotamer effect, shifts marked with an asterisk were exctracted from HSQC analysis:* ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.5 (C), 160.0 (C), 154.2 (C), 144.3 (C), 134.8 (C), 129.3 (2CH), 128.8 (CH), 128.5 (CH), 127.6 (C), 113.9 (2CH), 99.1 (C), 91.4 (C), 79.8 (C), 55.4 (CH_3), 48.7 (CH_2),

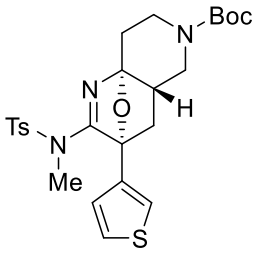
41.7* (CH_2), 38.7 (CH) 35.3 (CH_3), 32.9* (CH_2), 30.7* (CH_2), 28.5 ($3CH_3$), 21.6 (CH_3) ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_{28}H_{35}N_3O_6S$: 542.2319, found: 542.2305 $[M+H]^+$.

tert-Butyl (3R*,4aS*,8aR*)-3-(3,4-dimethoxyphenyl)-2-((N,4-dimethylphenyl)sulfonamido)-3,4,4a,5,7,8-hexahydro-6H-3,8a-epoxy-1,6-naphthyridine-6-carboxylate (91i)



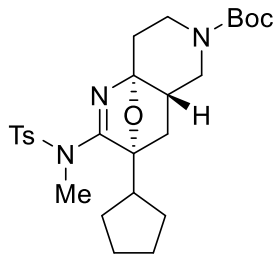
Oxazole **92i** (350 mg, 0.61 mmol) was dissolved in o-DCB (6.1 mL, 0.1 M) and stirred at 120 °C for 24 h. After allowing to cool down to room temperature the reaction mixture was filtered through a pad of silica with heptane (20 mL). This aliquot was discarded and the silica pad was further washed with EtOAc (50 mL). The filtrate was then concentrated under reduced pressure and subjected to silica gel flash column chromatography [toluene: EtOAc(8:2)] yielding polycycle **91i** as a white solid (241 mg, 0.42 mmol, 69%); IR (neat): *v* (max) cm^{-1} 2929, 1688, 1595, 1517, 1416, 1349, 1244, 1162, 1021, 808, 764; ^{1}H NMR (400 MHz, DMSO, 80 °C): δ = 7.72 (d, *J* = 8.2, 2H), 7.40 (d, *J* = 8.0, 2H), 7.04 (app. s, 2H), 6.99 (app. s, 1H), 4.17 (dd, *J* = 12.8, 6.4, 1H), 4.08–3.99 (m, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 2.85 (app. td, *J* = 12.0, 4.2, 1H), 2.73 (s, 3H), 2.49 (d, *J* = 12.4, 1H), 2.45 (s, 3H), 2.33–2.18 (m, 2H), 2.12 (dd, *J* = 12.2, 7.5, 1H), 1.70 (ddt, *J* = 14.2, 10.8, 4.8, 1H), 1.58 (dd, *J* = 12.2, 3.1, 1H), 1.49 (s, 9H) ppm; ^{1}H NMR (400 MHz, DMSO): δ = 7.69 (d, *J* = 8.3, 2H), 7.36 (d, *J* = 8.2, 2H), 7.04 (s, 2H), 6.99 (s, 1H), 4.09 (br. s, 1H), 3.93 (br. s, 1H), 3.78 (s, 3H), 3.72 (s, 3H), 2.83–2.70 (br. s, 1H), 2.66 (s, 3H), 2.39 (s, 3H), 2.24–2.15 (m, 2H), 2.07–1.98 (m, 1H), 1.63–1.50 (m, 2H), 1.43 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.9 (C), 153.4 (C), 149.3 (C), 148.5 (C), 144.2 (C), 134.6 (C), 129.2 (2CH), 128.2 (2CH), 127.3 (C), 120.0 (CH), 111.4 (CH), 110.9 (CH), 98.5 (C), 90.9 (C), 78.9 (C), 55.5 ($2CH_3$), 34.7 (CH_3), 31.8 (CH), 28.0 ($3CH_3$), 21.0 (CH_3) ppm; *Due to Boc rotamers effect four secondary carbons were not observed in in ^{13}C NMR;* HRMS (ESI-orbitrap): m/z: calcd for $C_{29}H_{37}N_3O_7S$: 572.2425, found: 572.2413 $[M+H]^+$.

tert-Butyl (3S*,4aS*,8aR*)-2-((N,4-dimethylphenyl)sulfonamido)-3-(thiophen-2-yl)-3,4,4a,5,7,8-hexahydro-6H-3,8a-epoxy-1,6-naphthyridine-6-carboxylate (91l)



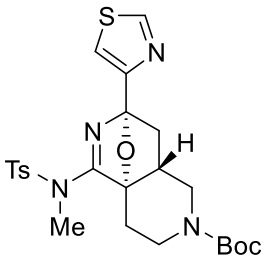
Oxazole **92l** (500 mg, 0.97 mmol) was dissolved in o-DCB (9.7 mL, 0.1 M) and stirred at 120 °C for 56 h. After allowing to cool down to room temperature the reaction mixture was filtered through a pad of silica with heptane (25 mL). This aliquot was discarded and the silica pad was further washed with EtOAc (50 mL). The filtrate was then concentrated under reduced pressure and subjected to silica gel flash column chromatography [toluene:EtOAc(8:2)] yielding polycycle **91l** as a white solid (341 mg, 0.66 mmol, 68%); IR (neat): *v* (max) cm^{-1} 2974, 2929, 1681, 1613, 1423, 1349, 1162, 1080, 816, 685; ^{1}H NMR (400 MHz, DMSO): δ = 7.72–7.67 (m, 3H), 7.62–7.60 (m, 1H), 7.37 (d, *J* = 8.1, 2H), 7.14 (app. dd, *J* = 5.0, 1.3, 1H), 4.19–3.86 (m, 2H), 2.81–2.69 (m, 1H) 2.66 (s, 3H), 2.38 (stack, 4H), 2.14 (dq, *J* = 9.2, 5.2, 2H), 2.02 (s, 1H), 1.59–1.49 (m, 2H), 1.41 (s, 9H) ppm; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 7.9, 2H), 7.40–7.39 (m, 1H), 7.36 (dd, *J* = 5.0, 2.9, 1H), 7.26 (d, *J* = 8.3, 2H), 7.15 (dd, *J* = 4.8, 1.3, 1H), 4.44–3.99 (m, 2H), 2.92–2.85 (m, 1H), 2.74 (s, 3H),2.55–2.45 (br. m, 1H), 2.42 (s, 4H), 2.33–2.21 (m, 2H), 2.02 (dtd, *J* = 10.2, 6.8, 2.9, 1H), 1.59–1.52 (br. m. 1 H), 1.49 (s, 9H) ppm; *^{13}C NMR resonances assigned with assistance from HSQC and HMBC spectra due to the broadening of the resonances owing to the rotamer effect, shifts marked with an asterisk were exctracted from HSQC analysis:* ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.0 (C), 154.3 (C), 144.5 (C), 136.8 (C), 134.8 (C), 129.5 (2CH), 128.6 (2CH), 127.1 (CH), 126.7 (CH), 124.2 (CH), 99.4 (C), 88.8 (C), 79.9 (C), 47.8* (CH_2), 40.7* (CH_2), 38.9 (CH), 35.1 (CH_3), 33.7 (CH_2), 29.8 (CH_2), 28.6 ($3CH_3$), 21.7 (CH_3) ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_{25}H_{31}N_3O_5S_2$: 518.1778, found: 518.1770 $[M+H]^+$.

tert-Butyl (3R*,4aS*,8aR*)-3-cyclopentyl-2-((N,4-dimethylphenyl)sulfonamido)-3,4,4a,5,7,8-hexahydro-6H-3,8a-epoxy-1,6-naphthyridine-6-carboxylate (91m)



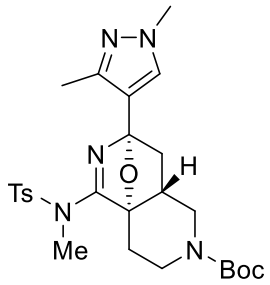
Oxazole **92m** (500 mg, 0.99 mmol) was dissolved in o-DCB (9.9 mL, 0.1 M) and stirred at 120 °C for 42 h. After allowing to cool down to room temperature the reaction mixture was filtered through a pad of silica with heptane. This aliquot was discarded, and the silica pad was further washed with EtOAc. The filtrate was then concentrated under reduced pressure and subjected to silica gel column chromatography [toluene:EtOAc (8:2)] yielding polycycle **91m** as a white solid (324 mg, 0.64 mmol, 65%); IR (neat): *v* (max) cm^{-1} 2952, 2870, 1692, 1595, 1423, 1360, 1159, 678; *NMR spectra display a mixture of rotamers:* ^{1}H NMR (400 MHz, DMSO, 80 °C): δ = 7.70 (d, *J* = 8.0, 2H), 7.42 (d, *J* = 8.0, 2H), 4.11 (ddd, *J* = 13.4, 6.4, 1.8, 1H, 3.93 (ddd, *J* = 13.4, 4.8, 2.5, 1H), 2.96 (s, 3H), 2.86 (app. q, *J* = 8.3, 1H), 2.77 (td, *J* = 13.2, 3.8, 1H), 2.40 (s, 3H), 2.12 (td, *J* = 13.6, 5.6, 1H), 2.05–2.01 (m, 1H), 1.83–1.77 (stack, 3H), 1.67–1.46 (m, 6H), 1.42 (s, 9H), 1.20 (dd, *J* = 12.5, 2.9, 1H) ppm; ^{1}H NMR (400 MHz, DMSO): δ = 7.70 (d, *J* = 8.1, 2H), 7.45 (d, *J* = 8.1, 2H), 4.12 (br.s, 1H), 3,92 (br. s, 1H), 2.92 (s, 3H), 2.89–2.83 (m, 1H), 2.41 (s, 3H), 2.16–1.98 (m, 2H), 1.90–1.72 (stack, 3H), 1.68–1.44 (stack, 6H), 1.41 (s, 9H), 1.22–1.18 (m, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.3 (C), 144.6 (C), 129.8 (2CH), 127.9 (2CH), 97.9 (C), 94.6 (C), 79.7 (C), 38.2 (CH), 37.9 (CH), 36.5 (CH_3), 31.6 (CH_2), 29.9 (CH_2), 28.4 ($3CH_3$), 28.3 ($2CH_2$), 27.7 (CH_2), 26.0 and 25.9 ($2CH_2$), 21.6 (CH_3) ppm*; three quaternary carbons not observed in ^{13}C NMR;* HRMS (ESI-orbitrap): m/z: calcd for $C_{26}H_{37}N_3O_5S$: 504.2527, found: 504.2514 $[M+H]^+$.

tert-Butyl (3S*,4aR*,8aS*)-1-((N,4-dimethylphenyl)sulfonamido)-3-(thiazol-4-yl)-3,4,4a,5,7,8-hexahydro-6H-3,8a-epoxy-2,6-naphthyridine-6-carboxylate (91q)



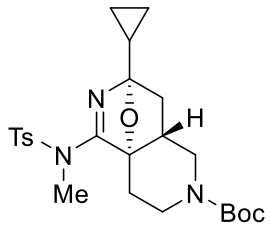
Following GP 05 using aminide **69b** (115 mg, 0.56 mmol, 1.1 eq), ynamide **86a** (200 mg, 0.51 mmol), $AuPicCl_2$ (9.94 mg, 0.025 mmol, 5 mol%) and toluene (5.1 mL, 0.1 M ynamide). The reaction was stirred at 90 °C until complete consumption of the ynamide (40 min). After which the temperature was raised to 110 °C and the reaction mixture was stirred for 36 h. After allowing to cool down to room temperature the reaction mixture was filtered through a pad of silica with EtOAc (25.0 mL). Solvent was removed under reduced pressure and the crude material was purified via silica gel flash column chromatography [heptane: EtOAc (6:4)] affording polycycle **91q** as a white powder (134 mg, 51%); IR (neat): *v* (max) cm^{-1} 2978, 2929, 1684, 1595, 1420, 1360, 1162, 730; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.86 (d, *J* = 2.2, 1H), 7.60 (d, *J* = 2.2, 1H), 7.32 (d, *J* = 8.1, 2H) 4.28 (br. s, 2H), 2.99 (stack, 5H), 2.77 (br. s, 2H), 2.43 (stack, 4H), 2.37 (br. s, 1H), 2.22–2.14 (m, 1H), 2.02 (br. s, 1H), 1.91 (dd, *J* = 12.0, 2.9, 1H), 1.49 (s, 9H) ppm; *^{13}C NMR resonances assigned with assistance from HSQC and HMBC spectra due to the broadening of the resonances owing to the rotamer effect:* ^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.4 (C), 153.8 (CH), 153.3 (C), 144.7 (C), 129.7 (2CH), 128.4 (2CH), 118.1 (CH), 100.0 (C), 88.9 (C), 79.9 (C), 37.4 (CH and CH_2), 34.2 (CH_3), 28.4 ($3CH_3$), 25.6 (CH_2), 21.6 (CH_3) ppm; *two secondary carbons not observed in ^{13}C NMR spectra, but visible in HSQC. Three quaternary carbons not observed in ^{13}C NMR spectra;* HRMS (ESI-orbitrap): m/z: calcd for $C_{24}H_{30}N_4O_5S_2$: 519.1730, found: 519.1724 $[M+H]^+$.

tert-Butyl (3S*,4aR*,8aS*)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-1-((N,4-dimethylphenyl)sulfonamido)-3,4,4a,5,7,8-hexahydro-6H-3,8a-epoxy-2,6-naphthyridine-6-carboxylate (91r)



Following GP 05 using aminide **69c** (121 mg, 0.56 mmol, 1.1 eq), ynamide **86a** (200 mg, 0.51 mmol), $AuPicCl_2$ (9.94 mg, 0.025 mmol, 5 mol%) and toluene (5.1 mL, 0.1 M ynamide). The reaction was stirred at 90 °C until complete consumption of the ynamide (40 min). After which the temperature was raised to 110 °C and the reaction mixture was stirred for 28 h. After allowing to cool down to room temperature the reaction mixture was filtered through a pad of silica with EtOAc (25.0 mL). Solvent was removed under reduced pressure and the crude material was purified via silica gel flash column chromatography [heptane: EtOAc (6:4)] affording polycycle **91r** as a white powder (128 mg, 47%); IR (neat): *v* (max) cm^{-1} 2974, 2929, 1684, 1595, 1360, 1159, 730; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.72 (br. s, 2H), 7.32 (d, *J* = 8.3, 2H), 6.18 (s, 1H), 4.39 (br. s, 2H), 3.79 (s, 3H), 2.97 (s, 3H), 2.72 (br. s, 2H), 2.43 (s, 3H), 2.26 (stack, 4H), 2.22–2.15 (m, 1H), 2.01 (br. s, 1H), 1.73–1.67 (m, 2H), 1.49 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.3 (C), 146.9 (C), 144.9 (C), 138.4 (C), 129.7 (2CH), 128.33 (2CH), 106.1 (CH), 97.1 (C), 88.6 (C), 80.1 (C), 37.9 (CH_3), 33.5 (CH_3), 31.9 (CH_2), 29.0 (CH_2), 28.4 ($3CH_3$), 25.6 (CH_2), 21.6 (CH_3), 13.3 (CH_3) ppm; *two quaternary carbons and two secondary carbons not observed in ^{13}C NMR spectra;* HRMS (ESI-orbitrap): m/z: calcd for $C_{26}H_{35}N_5O_5S$: 530.2432, found: 530.2420 $[M+H]^+$.

tert-Butyl (3S*,4aR*,8aS*)-3-cyclopropyl-1-((N,4-dimethylphenyl)sulfonamido)-3,4,4a,5,7,8-hexahydro-6H-3,8a-epoxy-2,6-naphthyridine-6-carboxylate (91o)



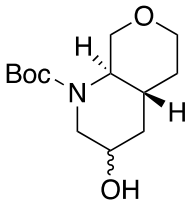
Following GP 05 using aminide **69a** (661 mg, 4.06 mmol, 1.1 eq), ynamide **86a** (1.45 g, 3.69 mmol), $AuPicCl_2$ (7.00 mg, 0.2 mmol, 5 mol%) and toluene (37.0 mL, 0.1 M ynamide). The reaction was stirred at 90 °C until complete consumption of the ynamide (40 min). The

temperature was raised to 110 °C and the reaction mixture was stirred for 24 h. After allowing to cool down to room temperature the reaction mixture was filtered through a pad of silica with EtOAc (75.0 mL). Solvent was removed under reduced pressure and the crude material was purified via silica gel flash column chromatography [heptane: EtOAc (6:4)] affording **91o** as a white powder (952 mg, 54%); IR (neat): *v* (max) cm^{-1} 2970, 2929, 2866, 1688, 1591, 1353, 1159, 1073; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80–7.57 (m, 2H), 7.30 (d, *J* = 8.2, 2H), 4.42–4.03 (m, 2H), 2.98–2.80 (m, 4H), 2.66–2.46 (m, 2H), 2.42 (s, 3H), 2.11–2.06 (m, 2H), 1.66–1.50 (m, 1H), 1.47 (s, 9H), 1.39–1.30 (m, 1H), 1.24–1.16 (m, 1H), 0.70–0.57 (m, 3H), 0.54–0.45 (m, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ =169.4 (C), 154.5 (C), 144.6 (C), 129.6 (2CH), 128.6 (2CH), 103.8 (C), 87.5 (C), 79.9 (C), 37.4 (CH_3), 35.7 (CH_2), 34.3 (CH), 28.5 ($3CH_3$), 25.8 (CH_2), 21.7 (CH_3), 13.0 (CH), 2.0 (CH_2), 1.9 (CH_2) ppm; *one quaternary and two secondary carbons are not observed in ^{13}C NMR spectra*; HRMS (ESI-orbitrap): m/z: calcd for $C_{24}H_{33}N_3O_5S$: 476.2214, found: 476.2204 $[M+H]^+$.

6.6. Post-Catalysis transformations

6.6.1. Reductions and Oxidations

tert-Butyl (4aR,8aR)-3-hydroxyoctahydro-1H-pyrano[3,4-b]pyridine-1-carboxylate (120)



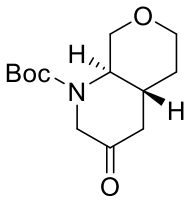
Dry THF (7.4 mL) was added to a flame dried Schlenk flask and cooled to 0 °C. $LiAlH_4$ (3.7 mL, 3.7 mmol, 5.0 eq, 1 M in THF) was added and the suspension stirred for 5 minutes. After this time compund **91n** (300 mg, 0.74 mmol) was added to the suspension and the ice bath removed after 5 minutes. The flask was then placed on a heating mantle and heated to 60 °C, the reaction mixture was stirred at this temperature for 16 h. After this time the heating mantle was removed and the reaction mixture was allowed to cool down to room temperature while stirring. A saturated solution of

Rochelle's salt$_{(aq)}$ (8 mL) was added and the mixture was stirred for 3 h at room temperature. The mixture was extracted with $CHCl_3$:IPA [3:1] (3 × 15 mL) and then with $CHCl_3$ (2 × 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered and the solvents were removed under reduced pressure. The crude material was dissolved in CH_2Cl_2 (1.5 mL). Et_3N (200 mL, 1.5 mmol, 2.0 eq) and di-*tert*-butyl dicarbonate (358 mg, 1.5 mmol, 2.0 eq) were added and the reaction mixture stirred at room temperature for 16 h. After this time the solvent was removed under reduced pressure and the crude material was subjected to silica gel flash column chromatography [EtOAc (100%)] to give amino alcohol **120** as a pale yellow oil (108 mg, 56%).

Scaling up: To an oven dried, argon flushed 3-neck-round bottom flask was added dry THF (110 mL) and cooled to 0 °C. $LiAlH_4$ (9.4 mL, 22.5 mmol, 2.0 eq, 2.4 M in THF) was added and the suspension stirred for 5 minutes. After this time compund **91n** (5.0 g, 11.3 mmol) was added to the suspension and the ice bath removed after 5 min. The reaction mixture was stirred at room temperature for 1 h and then heated to 40 °C for 3 h. After this time the heating mantle was removed and the reaction mixture was allowed to cool down to room temperature while stirring. The reaction mixture was cooled down to 0 °C and quenched with the dropwise addition in the subsequent order of water (0.85 mL), 20% $NaOH_{aq}$ (0.85 mL) and water (0.40 mL). The cooling bath was removed and the mixture was stirred at room temperature for 10 minutes, before Na_2SO_4 (5 g) was added. The resulting mixture was left stirring for an additional 20 minutes. After which time the mixture was filtered through celite and the filter was rinsed with $CHCl_3$:IPA [3:1] (2 × 50) and $CHCl_3$ (2 × 30). The filtrate was concentrated under reduced pressure and suspended in 25 mL of CH_2Cl_2. The suspension was cooled down and stirred at 0 °C before Et_3N (4.7 mL, 33.7 mmol, 3.0 eq) and Boc_2O (7.4 g, 33.7 mmol, 3.0 eq) were added. The cooling bath was removed and the reaction mixture was stirred at room

temperature for 16 h. The volatiles were removed under reduced pressure and the crude material was subjected to silica flash gel column chromatography [EtOAC 100%] to give aminoalcohol **120** as a pale yellow oil (2.8 g, 97%, dr: 4:1); *due to excessive overlap, both set of resonances are reported as a mixture:* ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.32 (dd, *J* = 10.9, 4.1, 1H), 4.26 (d, *J* = 10.7, 3.9, 1 H),4.06–4.03 (m, 1H), 3.94–3.92 (m, 2H), 3.74–3.68 (m, 1H), 3.72–3.69 (m, 1H), 3.54–3.47 (m, 1H), 3.47–3.40 (m, 1H), 3.36 (dd, *J* = 11.7, 2.3 Hz, 1H), 3.16 (dd, *J* = 13.7, 6.6 Hz, 1H), 3.06 (td, *J* = 10.5, 4.1, 1H), 3.01 (td, *J* = 10.4,4.0, 1 H) 2.14 (ddd, *J* = 13.5, 6.8, 3.7, 1H), 2.10–2.00 (m, 1H), 1.88–1.81 (m, 1H), 1.81–1.73 (m, 2H), 1.69–1.57 (m, 2H), 1.45 (stack, 14H), 1.14 (ddd, *J* = 13.4, 12.1, 7.7, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.6 (C), 80.5 and 80.3 (C), 70.6 and 70.5 (CH_2), 68.2 and 67.9 (CH_2), 66.6 and 65.5 (CH), 60.0 and 59.5 (CH), 50.2 and 48.9 (CH_2), 39.1 and 38.0 (CH), 36.6 and 33.7 (CH), 32.9 and 32.8 (CH_2), 28.4 ($3CH_3$) ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_{13}H_{23}NO_4$: 280.1519, found: 280.1514 $[M+Na]^+$.

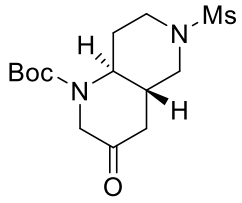
tert-Butyl (4aR*,8aR*)-3-oxooctahydro-1H-pyrano[3,4-b]pyridine-1-carboxylate (127a)



DMP (1.3 g, 3.0 mmol, 1.5 eq) was added to a solution of aminoalchol **120** (530 mg, 2.0 mmol) in CH_2Cl_2 (4.1 mL, 0.5 M) and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was poured into a separating funnel, diluted with CH_2Cl_2 and sat. Na_2CO_3 (10 mL). The organics were further extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were washed with brine (20 mL) and dried over Na_2SO_4. After filtration and removal of the solvent under reduced pressure, the crude material was subjected to silica gel column chromatography [heptane: EtOAc (1:1)] yielding aminoketone **127a** as a white solid (305 mg, 1.2 mmol, 58 %); IR (neat): *ν*(max) cm^{-1} 2977, 2956, 1723, 1683, 1396, 1361, 1153; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.4.53 (app. d, *J* = 18.4, 1H), 4.38 (dd, *J* = 10.4, 3.8, 1H), 4.02 (ddd, *J* = 11.5, 4.7, 1.4 Hz, 1H), 3.63

(m, 1H), 3.52–3.45 (m, 1H), 3.45–3.38 (m, 1H), 3.15 (app. t, *J* = 10.1, 1H), 2.45 (dd, *J* = 17.5, 2.6, 1H), 2.23 (dd, *J* = 17.4, 13.7, 1H), 2.01–1.91 (m, 1H), 1.80–1.74 (m, 1H), 1.69–1.60 (m, 1H), 1.47 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 206.5 (C), 154.8 (C), 81.1 (C),70.3 (CH_2), 67.7 (CH_2), 57.1 (CH), 50.9 (CH_2), 43.8 (CH_2), 35.9 (CH), 31.9 (CH_2), 28.3 ($3CH_3$) ppm; HRMS (ES-TOF): m/z calcd for $C_{13}H_{21}NO_4Na$: 278.1368, found 278.1370 $[M+H]^+$.

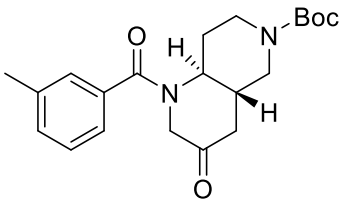
tert-Butyl (4aS*,8aS*)-6-(methylsulfonyl)-3-oxooctahydro-1,6-naphthyridine-1(2H)-carboxylate (127b) R3



To a flame dried, argon flushed Schlenk flask was added dry THF (2.7 mL) and cooled to 0 °C. $LiAlH_4$ (1.4 mL, 1.84 mmol, 5.0 eq, 2.4 M in THF) was added and the suspension stirred for 5 minutes. After this time compund **91d** (141.8 mg, 0.27 mmol) was added to the suspension and the ice bath removed after 5 minutes. The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was cooled down to 0 °C and quenched with the dropwise addition of Rochelle's salt (5 mL). The cooling bath was removed and the mixture was stirred at room temperature for 30 minutes, before being transferred into a separating funnel. The organics were extracted with [$CHCl_3$: IPA (3:1)] (4 × 15 mL). The combined organic phases were dried over Na_2SO_4. After filtration and removal of the solvents under reduced pressure the crude material was suspended in CH_2Cl_2 (1.3 mL, 0.2 M wrt of the initial polycycle). The suspension was cooled down and stirred at 0 °C before Et_3N (75 µL, 0.54 mmol, 2.0 eq) and Boc_2O (117.8 mg, 0.54 mmol, 2.0 eq) were added. The reaction mixture was stirred at 0 °C for 2 h and then allowed to warm up to room temperature over 16 h. After this time the reaction mixture was diluted with CH_2Cl_2 (10 mL), poured into a separating funnel and washed with 2 M $HCl_{(aq)}$ (15 mL). The aqueous layer was further extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were washed with brine (15 mL) and dried over Na_2SO_4. After filtration and removal fo the solvent under reduced pressure the crude material was dissolved in CH_2Cl_2 (1.3 mL, 0.2 M wrt the

initial polycycle). DMP (170.4 mg, 0.40 mmol, 1.5 eq) was added and the reaction mixture was stirred at room temperature for 3 h. Sat. Na_2CO_3 (10 mL) was added to the reaction mixture and the organics were extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried over Na_2SO_4. After filtration and removal of the solvent under reduced pressure the crude material was subjected to silica gel flash column chromatography [EtOAc 100%] yielding ketone **127b** as a white solid (45 mg, 51% over three steps); IR (neat): *v* (max) cm^{-1} 2975, 2929, 1726, 1684, 1404, 1366, 1326, 1145, 924; ^1H NMR (400 MHz, $CDCl_3$): δ = 4.48 (d, *J* = 18.3, 1H), 3.96–3.86 (m, 2H), 3.65 (d, *J* = 18.3, 1H), 3.43 (td, *J* =10.9, 3.0, 1H), 2.91–2.77 (stack, 5H), 2.64–2.55 (m, 1H), 2.51–2.39 (m, 2H), 2.21–2.10 (m, 2H), 1.70–1.56 (m, 1H), 1.45 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 205.2 (C), 154.5 (C), 81.3 (C), 57.9 (CH), 50.6 (CH_2), 50.1 (CH_2), 45.4 (CH_2), 40.9 (CH_2), 36.5 (CH), 35.6 (CH_3), 30.4 (CH_2) 28.3 ($3CH_3$) ppm; HRMS (ES-TOF): m/z calcd for $C_{14}H_{24}N_2O_5SNa$: 355.1304, found 355.1305 $[M+Na]^+$.

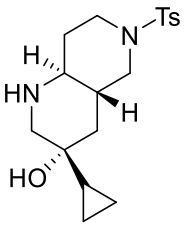
tert-Butyl (4aS*,8aS*)-1-(3-methylbenzoyl)-3-oxooctahydro-1,6-naphthyridine-6(2H)-carboxylate (127c)



To an oven dried, argon flushed 3-neck-round bottom flask was added dry THF (9.2 mL) and cooled to 0 °C. $LiAlH_4$ (0.77 mL, 1.84 mmol, 2.0 eq, 2.4 M in THF) was added and the suspension stirred for 5 minutes. After this time compund **91a** (0.5 g, 0.92 mmol) was added to the suspension and the ice bath removed after 5 minutes. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was cooled down to 0 °C and quenched with the dropwise addition in the subsequent order of water (69 µL), 20% $NaOH_{aq}$ (69 µL) and water (30 µL). The cooling bath was removed and the mixture was stirred at room temperature for 10 minutes, before Na_2SO_4 (1.0 g) was added. The resulting mixture was left stirring for an additional 20 minutes. After which time the mixture was filtered through celite and the filter was rinsed with $CHCl_3$:IPA [3:1] (2 × 20) and $CHCl_3$ (2 × 10). The filtrate was concentrated

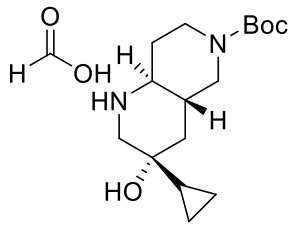
under reduced pressure and suspended in CH_2Cl_2 (4.6 mL, 0.2 M wrt of the initial polycycle). The suspension was cooled down and stirred at 0 °C before Et_3N (0.19 mL, 1.34 mmol, 1.5 eq) and 3-methylbenzoyl chloride (0.18 mL, 1.34 mmol, 1.5 eq) were added. The reaction mixture was stirred at 0 °C for 2 h. After this time the reaction mixture was diluted with CH_2Cl_2 (10 mL), poured into a separating funnel and washed with 2 M $HCl_{(aq)}$ (15 mL). The aqueous layer was further extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were washed with brine (15 mL) and dried over Na_2SO_4. After filtration and removal fo the solvent under reduced pressure the crude material was dissolved in CH_2Cl_2 (4.6 mL, 0.2 M wrt the initial polycycle). DMP (0.58 g, 1.38 mmol, 1.5 eq) was added and the reaction mixture was stirred at room temperature for 3 h. Sat. Na_2CO_3 (10 mL) was added to the reaction mixture and the organics were extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried over Na_2SO_4. After filtration and removal of the solvent under reduced pressure the crude material was subjected to silica gel flash column chromatography yielding ketone **127c** as a white solid (171 mg, 0.459 mmol, 49% over three steps); IR (neat): *ν* (max) cm^{-1} 2974, 2922, 1729, 1684, 1632, 1412, 1364, 1162, 1121, 745; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.22 (m, 2H), 7.17 (br. s, 1H), 7.15–7.11 (m, 1H), 4.26 (br. s, 2H), 4.17 (d, *J* = 17.7, 1H), 4.03–3.92 (stack, 2H), 2.99 (s, 1H), 2.64 (s, 1H), 2.54–2.43 (m, 2H), 2.37 (s, 3H), 2.20–2.16 (m, 1H), 2.13–2.00 (m, 1H), 1.48 (s, 10H) ppm; *shifts marked with an asterisk were exctracted from HSQC analysis:* ^{13}C NMR (101 MHz, $CDCl_3$): δ = 204.6 (C), 172.1 (C), 154.6 (C), 138.6 (C), 135.3 (C), 131.2 (CH), 128.5 (CH), 127.9 (CH), 124.3 (CH), 80.2 (C), 57.9 (CH), 54.4 (CH_2), 47.8* (CH_2), 42.3* (CH_2) 40.9 (CH_2), 36.2 (CH), 29.8 (CH_2), 28.4 ($3CH_3$), 21.3 (CH_3) ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_{21}H_{28}N_2O4$: 395.1941, found 395.1935 $[M+Na]^+$.

(3R*,4aS*,8aS*)-3-Cyclopropyl-6-tosyldecahydro-1,6-naphthyridin-3-ol (110a)



To an oven dried, argon flushed 3-neck-round bottom flask was added dry THF (47 mL) and cooled to 0 °C. $LiAlH_4$ (4.0 mL, 9.6 mmol, 2.0 eq, 2.4 M in THF) was added and the suspension stirred for 5 minutes. After this time compund **91g** (2.5 g, 4.7 mmol) was added to the suspension and the ice bath removed after 5 minutes. The reaction mixture was stirred at room temperature for 3 h, after this time the reaction mixture was cooled down to 0 °C and quenched with the dropwise addition in the subsequent order of water (0.40 mL), 20% $NaOH_{aq}$ (0.40 mL) and water (0.20 mL). The cooling bath was removed and the mixture was stirred at room temperature for 10 minutes, before Na_2SO_4 (2.0 g) was added. The resulting mixture was left stirring for an additional 20 minutes. After which time the mixture was filtered through celite and the filter was rinsed with $CHCl_3$:IPA [3:1] (2 × 50 mL) and $CHCl_3$ (2 × 30 mL). Volatiles were removed under reduced pressure and the crude material was subjected to silica gel flash column chromatography (CH_2Cl_2 : MeOH 9:1) yielding aminoalcohol **110a** as a white solid (1.5 g, 88%); IR (neat): *v* (max) cm^{-1} 3100, 2922, 2858, 1599, 1341, 1159, 745; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.67–7.62 (m, 2H), 7.36–7.31 (m, 2H), 3.91–3.85 (m, 1H), 3.68–3.64 (m, 1H), 2.92 (dd, *J* = 11.6, 2.2, 1H), 2.57 (d, *J* = 11.7, 1H), 2.44 (s, 3H), 2.32 (td, *J* = 12.2, 2.8, 1H), 2.02 (ddd, *J* = 11.4, 9.8, 3.9, 1H), 1.93 (t, *J* = 11.2, 1H), 1.85–1.66 (m, 3H), 1.58 (qd, *J* = 12.5, 4.4, 1H), 1.34 (ddd, *J* = 14.1, 8.4, 5.8, 1H), 1.12 (t, *J* = 11.7, 1H), 0.49–0.35 (m, 4H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.2 (C), 132.8 (C), 129.3 (2CH), 127.2 (2CH), 67.4 (C), 59.0 (CH), 57.0 (CH_2), 50.3 (CH_2), 45.4 (CH_2), 41.2 (CH_2), 38.2 (CH), 31.0 (CH_2), 21.1 (CH_3), 16.4 (CH), 0.5 ($2CH_2$); HRMS (ESI-orbitrap): m/z: calcd for $C_{18}H_{26}N_2O_3S$: 351.1737, found 351.1730 $[M+H]^+$.

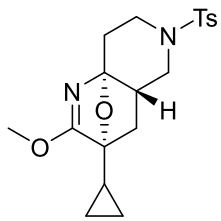
tert-Butyl (3R*,4aS*,8aS*)-3-cyclopropyl-3-hydroxyoctahydro-1,6-naphthyridine-6(2H)-carboxylate (110b)



To an oven dried, argon flushed 3-neck-round bottom flask was added dry THF (21 mL) and cooled to 0 °C. $LiAlH_4$ (1.7 mL, 4.1 mmol, 2.0 eq, 2.4 M in THF) was added and the suspension stirred for 5 minutes. After this time compund **91h** (0.958 g, 2.0 mmol) was added to the suspension and the reaction mixture was stirred for 3 h without removing the ice bath. After this time the reaction was quenched with the dropwise addition in the subsequent order of water (0.15 mL), 20% $NaOH_{(aq)}$ (0.15 mL) and water (0.10 mL). The cooling bath was removed and the mixture was stirred at room temperature for 10 minutes, before Na_2SO_4 (1.0 g) was added. The resulting mixture was left stirring for an additional 20 minutes. After which time the mixture was filtered through a pad of celite and the filter was rinsed with $CHCl_3$:IPA [3:1] (2 × 50 mL) and $CHCl_3$ (3 × 30 mL).The volatiles were removed under reduced pressure and the crude material was purified by acid reverse phase preparative chromatography to afford aminoalcohol **110b** as a formic acid salt, white solid (0.55 g, 90%); IR (neat): *v* (max) cm^{-1} 3473, 3180, 2978, 2937, 2780, 1666, 1580, 1423, 1380, 1162, 1025; ^1H NMR (400 MHz, MeOD): δ = 8.47 (s, 1H), 4.28 (d, *J* = 13.7, 1H), 4.13 (d, *J* = 13.3, 1H), 3.28 (app. d, *J* = 12.3, 1H), 3.07–2.79 (m, 3H), 2.60 (br. s, 1H), 2.05 (dd, *J* = 12.5, 3.6, 1H), 1.99–1.86 (m, 1H), 1.82 (dq, *J* = 11.2, 7.4, 5.7, 1H), 1.65 (tt, *J* = 12.2, 6.1, 1H), 1.50 (s, 9H), 1.29 (td, *J* = 8.4, 4.2, 1H), 0.62–0.53 (m , 2H), 0.51–0.42 (m, 2H) ppm; ^{13}C NMR (101 MHz, MeOD): δ = 168.1 (CH), 154.9 (C), 80.6 (C), 65.7 (C), 58.7 (CH_2), 53.3, 48.1, 47.8, 47.6, 47.4, 39.5, 35.8, 27.6 ($3CH_3$), 16.2 (CH), 0.05 ($2CH_2$) ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_{16}H_{28}N_2O_3$: 297.2173, found 297.2170 $[M+H]^+$.

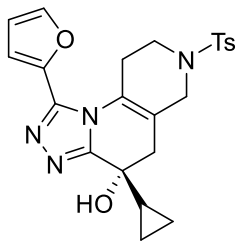
6.6.2. Triazoles

(3R*,4aS*,8aR*)-3-Cyclopropyl-2-methoxy-6-tosyl-4,4a,5,6,7,8-hexahydro-3H-3,8a-epoxy-1,6-naphthyridine (133a)



NaOMe (640 µL, 5.4 M in MeOH, 3.45 mmol, 3.0 eq) was added to a solution of polycycle **91g** (609 mg, 1.15 mmol) in THF (12.0 mL, 0.1 M) and the reaction mixture was stirred at room temperature for three days. Water (10 mL) and EtOAc (10 mL) were added, the layers were separated, and the aqueous phase was further extracted with EtOAc (3 × 15 mL). The combined organic phases were dried over Na_2SO_4. After filtration and removal of the solvent under reduced pressure the crude material was subjected to silica gel flash column chromatography [EtOAc 100%] affording **133a** as a white solid (312 mg, 72%); IR (neat): *v* (max) cm^{-1} 2937, 1625, 1345, 1162, 961, 913, 741; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 7.8, 2H), 7.31 (d, *J* = 7.8, 2H), 3.92 (ddd, *J* = 11.5, 6.3, 2.2, 1H), 3.81 (stack, 4H), 2.55–2.39 (stack, 5H), 2.26–2.20 (m, 1H), 2.18–2.11 (m, 1H), 1.96 (t, *J* = 11.5 Hz, 1H), 1.46 (dd, *J* = 12.2, 7.5, 1H), 1.24–1.16 (m, 1H), 0.91 (dd, *J* = 12.3, 2.9, 1H), 0.66–0.57 (m, 1H), 0.57–0.50 (m, 2H), 0.38–0.31 (m, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 178.9 (C), 143.7 (C), 133.7 (C), 129.9 (2CH), 127.7 (2CH), 97.1 (C), 87.5 (C), 56.3 (CH_2), 51.3 (CH_3), 43.4 (CH_2), 40.2 (CH), 31.9 (CH_2), 30.1 (CH_2), 21.7 (CH_3), 8.9 (CH), 2.2 (CH_2), 1.2 (CH_2) ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_{19}H_24N_2O_4S$: 377.1529, found 377.1523 $[M+H]^+$.

(rac)-4-Cyclopropyl-1-(furan-2-yl)-7-tosyl-4,5,6,7,8,9-hexahydro-[1,2,4]triazolo[4,3-a][1,6]naphthyridin-4-ol (134a)



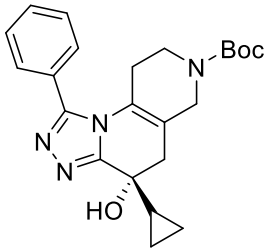
Glacial acetic (23 µL, 0.4 mmol, 0.5 eq) and 2-furoic acid hydrazide (111 mg, 0.88 mmol, 1.1 eq) were added to a solution of compound **133a** (300 mg, 0.8 mmol) in 1-butanol (8.0 mL, 0.1 M) and the reaction mixture was stirred at 110 °C for 16 h. Upon cooling to room temperature sat.

$NaHCO_{3(aq)}$ (20 mL) and EtOAc (20 mL) were added, the layers were separated and the aqueous phase was further extracted with EtOAc (3 × 20 mL). The combined organic phases were dried over Na_2SO_4. After filtration and removal of the solvent under reduced pressure the crude material was subjected to silica gel flash column chromatography [EtOAc 100%] affording **134a** as a white solid (188 mg, 52 %); IR (neat): *v* (max) cm^{-1} 2901, 1595, 1435, 1341, 1159; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 8.1, 2H), 7.58 (d, *J* = 1.8, 1H), 7.33 (d, *J* = 8.1, 2H), 6.63 (d, *J* = 3.3, 1H), 6.55 (dd, *J* = 3.4, 1.9, 1H), 3.76 (d, *J* = 16.6, 1H), 3.69–3.61 (m, 1H), 3.25 (dt, *J* = 11.4, 5.5, 1H), 3.11 (dt, *J* = 11.7, 5.7, 1H), 2.57–2.40 (stack, 5H), 2.35–2.16 (m, 2H), 1.32 (ddd, *J* = 13.9 8.2, 5.4, 1H), 0.69–0.41 (m, 4H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.9 (C), 144.2 (CH), 144.0 (C), 142.4 (C), 139.9 (C), 132.8 (C), 129.8 (2CH), 127.4 (2CH), 124.6 (C), 118.5 (C), 114.6 (CH), 111.6 (C), 67.5 (C), 46.9 (CH_2), 42.4 (CH_2), 37.7 (CH_2), 24.5 (CH_2), 21.4 (CH_3), 18.4 (CH) , 1.7 (CH_2), 1.4 (CH_2) ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_{23}H_{24}N_4O_4S$: 453.1591, found 453.1585 $[M+H]^+$.

General procedure for triazole formation from *N*-Boc protected polycycles (GP 06)

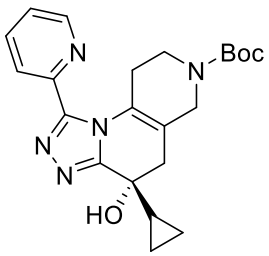
NaOMe (3 eq, 5.4 M in THF)) was added to a solution of the desired polycycle (1.0 eq) in THF (0.1 M) and the reaction mixture was stirred at room temperature for three days. Water (20 mL) and EtOAc (20 mL) were added, the layers were separated, and the aqueous phase was further extracted with EtOAc (3 × 25 mL). The combined organic phases were dried over Na_2SO_4. After filtration and removal of the solvent under reduced pressure the crude material was dissolved in 1-butanol (0.1 M wrt. The initial polycycle), the desired hydrazide (1.1 eq) and glacial acetic acid (0.5 eq) were added, and the reaction mixture was stirred at 110 °C for 24 h. Upon cooling to room temperature, the reaction mixture was poured into sat. $NaHCO_{3(aq)}$ and the organic were extracted with EtOAc. After filtration and removal of the solvent under reduced pressure the crude material was purified via silica gel flash column chromatography.

tert-Butyl (rac)-4-cyclopropyl-4-hydroxy-1-phenyl-4,5,8,9-tetrahydro-[1,2,4]triazolo[4,3-a][1,6]naphthyridine-7(6H)-carboxylate (134d)



Following GP 06 using polycycle **91h** (1.0 g, 2.10 mmol), NaOMe (1.2 mL, 6.31 mmol, 3.0 eq) in THF (21 mL). After work up and removal of the solvent under reduced pressure the crude material was dissolved in 1-butanol (21 mL), benzhydrazide (0.32 g, 2.3 mmol, 1.1 eq) and glacial acetic acid (60 µL) were added and the reaction mixture was stirred at 110 °C for 24 h. After extractive work up the crude material was subjected to silica gel flash column chromatography [EtOAc 100%] to yield compound **134d** as a white solid (0.49 g, 57% over two steps); IR (neat): *ν* (max) cm^{-1} 3295, 2974, 1695, 1412, 1237, 1144; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51–7.31 (m, 5H), 4.10–4.00 (m, 1H), 4.00–3.87 (m, 1H), 3.47 (br.s., 1H), 3.23 (br.s., 1H), 2.66 (d, *J* = 16.3, 1H), 2.43 (d, *J* = 16.3, 1H), 2.00–1.95 (m, 1H), 1.86–1.80 (m, 1H), 1.41 (s, 9H), 1.31–1.28 (m, 1H), 0.63–0.56 (m, 1H), 0.53–0.48 (m, 2H), 0.44–0.37 (m, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.0 (C), 154.2 (C), 150.7 (C), 130.2 (CH), 129.6 (2CH), 128.3 (2CH), 124.8 (C), 120.2 (C), 80.3 (C), 67.8 (C), 45.6 (CH_2), 38.2 (CH_2), 28.3 ($3CH_3$), 26.7 (CH_2), 18.5 (CH), 1.51 ($2CH_2$) ppm; *one quaternary carbon and one secondary carbon are not observed in ^{13}C NMR spectra;* HRMS (ESI-orbitrap): m/z: calcd for $C_{23}H_{28}N_4O_3$: 409.2234, found 409.2226 $[M+H]^+$.

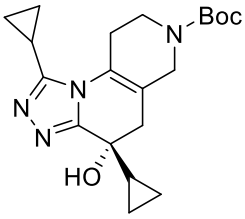
tert-Butyl (rac)-4-cyclopropyl-4-hydroxy-1-(pyridin-2-yl)-4,5,8,9-tetrahydro-[1,2,4]triazolo[4,3-a][1,6]naphthyridine-7(6H)-carboxylate (134e)



Following GP 06 using polycycle **91h** (1.0 g, 2.10 mmol), NaOMe (1.2 mL, 6.31 mmol, 3.0 eq) in THF (21 mL). After work up and removal of the solvent under reduced pressure the crude material was dissolved in 1-butanol (21 mL), 2-picolinyl hydrazide (0.32 g, 2.3 mmol, 1.1 eq) and glacial acetic acid (60 µL, 1 mmol, 0.5 eq) were added and the reaction

mixture was stirred at 110 °C for 24 h. After extractive work up the crude material was subjected to silica gel flash column chromatography [EtOAc 100%] to yield compound **134e** as a white solid (0.45 g, 53% over two steps); IR (neat): *v* (max) cm^{-1} 3246, 2974, 2926, 1692, 1416, 1241, 1148, 723; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.67–8.65 (m, 1H), 7.93 (d, *J* = 7.9, 1H), 7.84 (td, *J* = 7.7, 1H), 7.41–7.38 (m, 1H), 4.14–3.97 (m, 2H), 3.53 (br.s., 1H), 3.32 (br.s., 1H), 2.67 (d, *J* = 16.2, 1H), 2.47 (d, *J* = 16.1, 1H), 2.26 (br.s 1H), 2.08 (d, *J* = 16.4, 1H), 1.46 (s, 9H), 1.40–1.31 (m, 1H), 0.71–0.65 (m, 1H), 0.62–0.55 (m, 1H), 0.54–0.55 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.5 (C), 154.2 (C), 150.2 (C), 149.1 (CH), 137.1 (CH), 125.2 (CH), 124.6 (CH), 80.3 (C), 68.2 (C), 37.9 (CH_2), 29.6 (CH_2), 28.4 ($3CH_3$), 27.0 (CH2), 15.6 (CH), 1.6 ($2CH_2$) ppm; *three quaternary carbons are not observed in ^{13}C NMR spectra;* HRMS (ESI-orbitrap): m/z: calcd for $C_{22}H_{27}N_5O_3$: 410.2187, found 410.2178 $[M+H]^+$.

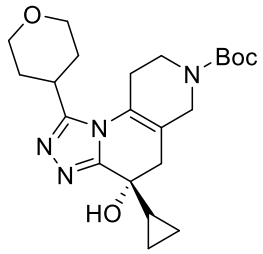
tert-Butyl (rac)-1,4-dicyclopropyl-4-hydroxy-4,5,8,9-tetrahydro-[1,2,4]triazolo[4,3-a][1,6]naphthyridine-7(6H)-carboxylate (134g)



Following GP 06 using polycycle **91h** (160 mg, 0.35 mmol), NaOMe (0.2 mL, 1.01 mmol) in THF (3.5 mL). After work up and removal of the solvent under reduced pressure the crude material was dissolved in 1-butanol (3.5 mL), cyclopropanecarboxylic acid hydrazide (40 mg, 0.39 mmol, 1.1 eq) and glacial acetic acid (10 µL, 0.17 mmol, 0.5 eq) were added and the reaction mixture was stirred at 110 °C for 24 h. After extractive work up the crude material was subjected to silica gel flash column chromatography [EtOAc 100%] to yield compound **134g** as a white solid (73 mg, 56% over two steps); IR (neat): *v* (max) cm^{-1} 3213, 3088, 2974, 1684, 1416, 1241, 1166, 726; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.12–3.91 (m, 2H), 3.75 (br.s., 1H), 3.59–3.53 (m, 1H), 2.86 (br.s., 1H), 2.78 (br.s., 1H), 2.51 (d, *J* = 16.5, 1H), 2.34 (d, *J* = 16.6, 1H), 1.89–1.83 (m, 1H), 1.48 (s, 9H), 1.33–1.26 (m, 1H), 1.16–1.12 (m, 2H), 1.00–0.97 (m, 2H), 0.50 (stack, 4H) ppm; *^{13}C NMR resonances assigned with assistance from HSQC and HMBC spectra due to the*

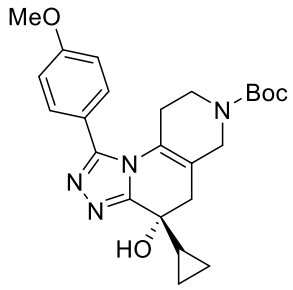
broadening of the resonances owing to the rotamer effect: ^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.6 (C), 154.2 (C), 152.8 (C), 124.9 (C), 118.7 (C), 80.4 (C), 67.5 (C), 38.1 (CH_2), 29.6 (CH_2), 28.3 ($3CH_3$), 25.9 (CH_2), 18.6 (CH), 7.6 (CH), 7.3 ($2CH_2$), 1.4 ($2CH_2$) ppm; *one secondary carbon is not observed in ^{13}C NMR spectra;* HRMS (ESI-orbitrap): m/z: calcd for $C_{20}H_{28}N_4O_3$: 373.2234, found 373.2226 $[M+H]^+$.

tert-Butyl (rac)-4-cyclopropyl-4-hydroxy-1-(tetrahydro-2H-pyran-4-yl)-4,5,8,9-tetrahydro-[1,2,4]triazolo[4,3-a][1,6]naphthyridine-7(6H)-carboxylate (134i)



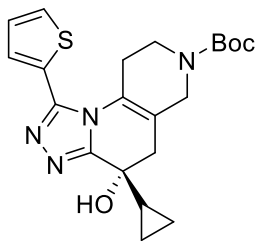
Following GP 06 using polycycle **91h** (470 mg, 0.99 mmol), NaOMe (0.55 mL, 3.0 mmol) in THF (10 mL). After work up and removal of the solvent under reduced pressure the crude material was dissolved in 1-butanol (10 mL), tetrahydro-2H-pyrancarbo hydrazide (157 mg, 1.0 mmol, 1.1 eq) and glacial acetic acid (28 µL, 0.49 mmol, 0.5 eq) were added and the reaction mixture was stirred at 110 °C for 24 h. After extractive work up the crude material was subjected to silica gel flash column chromatography [EtOAc 100%] to yield compound **134i** as a white solid (255 mg, 62% over two steps); IR (neat): *v* (max) cm^{-1} 3254, 2959, 2926, 2855, 1695, 1416, 1241, 730; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.11–3.90 (stack, 4H), 3.76 (br.s, 1H), 3.55–3.43 (stack, 3H), 3.05 (app. t, *J* = 11.0, 1H), 2.75–2.55 (m, 2H), 2.51 (d, *J* = 16.5, 1H), 2.34 (d, *J* = 16.5, 1H), 2.18–1.91 (m, 2H), 1.88–1.74 (m, 2H), 1.46 (s, 9H), 1.35–1.24 (m, 1H), 0.57–0.47 (m, 2H), 0.44–0.38 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.8 (C), 154.4 (C), 154.3 (C), 124.7 (C), 120.8 (C), 80.7 (C), 67.7 (C), 67.49 (CH_2), 67.42 (CH_2), 46.1 (CH_2), 39.7 (CH_2), 38.2 (CH_2), 33.6 (CH), 31.9 (CH_2), 31.5 (CH_2), 28.5 ($3CH_3$), 26.0 (CH_2), 18.5 (CH), 1.6 (CH_2), 0.1 (CH_2) ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_{22}H_{32}N_4O_4$: 417.2496, found 417.2488 $[M+H]^+$.

tert-Butyl (rac)-4-cyclopropyl-4-hydroxy-1-(4-methoxyphenyl)-4,5,8,9-tetrahydro-[1,2,4]triazolo[4,3-a][1,6]naphthyridine-7(6H)-carboxylate (134f)



Following GP 06 using polycycle **91h** (160 mg, 0.35 mmol), NaOMe (0.2 mL, 1.01 mmol) in THF (3.5 mL). After work up and removal of the solvent under reduced pressure the crude material was dissolved in 1-butanol (3.5 mL), 4-methoxybenzo hydrazide (65 mg, 0.39 mmol, 1.1 eq) and glacial acetic acid (10 µL, 0.17 mmol, 0.5 eq) were added and the reaction mixture was stirred at 110 °C for 24 h. After extractive work up the crude material was subjected to silica gel flash column chromatography [EtOAc 100%] to yield compound **134f** as a white solid (56 mg, 37% over two steps); IR (neat): *v* (max) cm^{-1} 3209, 2974, 2929, 1692, 1613, 1148, 1244, 723; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (d, *J* = 8.4, 2H), 6.97–6.90 (m, 2H), 4.08 (d, *J* = 18.4, 1H), 3.95 (d, *J* = 18.6, 1H), 3.86 (s, 3H), 3.51 (br.s., 1H), 3.26 (br.s., 1H), 2.65 (d, *J* = 16.4, 1H), 2.44 (d, *J* = 16.2, 1H), 2.04 (d, *J* = 16.2, 1H), 1.93–1.82 (m, 1H), 1.45 (s, 9H), 1.35 (tt, *J* = 8.3, 5.4, 1H), 0.69–0.62 (m, 1H), 0.59–0.53 (m, 1H), 0.51–0.43 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.2 (C), 155.0 (C), 154.4 (C), 150.9 (C), 131.2 (2CH), 123.5 (C), 120.3 (2CH), 114.0 (C), 80.5 (C), 68.3 (C), 55.5 (CH_3), 44.2 (CH_2), 38.4 (CH_2), 29.8 (CH_2), 28.5 ($3CH_3$), 26.8 (CH_2), 18.8 (CH), 1.8 (CH_2), 0.2 (CH_2) ppm; *one quaternary carbon is not observed in ^{13}C NMR spectra;* HRMS (ESI-orbitrap): m/z: calcd for $C_{24}H_{30}N_4O_4$: 439.2339, found 439.2330 $[M+H]^+$.

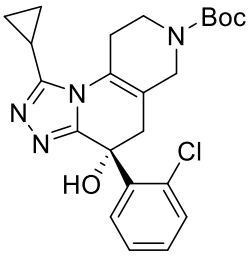
tert-Butyl (rac)-4-cyclopropyl-4-hydroxy-1-(thiophen-2-yl)-4,5,8,9-tetrahydro-[1,2,4]triazolo[4,3-a][1,6]naphthyridine-7(6H)-carboxylate (134g)



Following GP 06 using polycycle **91h** (285 mg, 0.6 mmol), NaOMe (0.3 mL, 1.8 mmol) in THF (6 mL). After work up and removal of the solvent under reduced pressure the crude material was dissolved in 1-butanol (6 mL), thiphene-2-carbo hydrazide (94 mg, 0.39 mmol, 1.1 eq)

and glacial acetic acid (17 µL, 0.3 mmol, 0.5 eq) were added and the reaction mixture was stirred at 110 °C for 24 h. After extractive work up the crude material was subjected to silica gel flash column chromatography [EtOAc 100%] to yield compound **134g** as a white solid (154 mg, 62% over two steps); IR (neat): *v* (max) cm^{-1} 3227, 3086, 2974, 2929, 1692, 1416, 1144, 726; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 5.1, 1H), 7.19 (s, 1H), 7.07 (t, *J* = 4.4, 1H), 5.01 (br.s., 1H), 4.02 (d, *J* = 18.6, 1H), 3.94 (d, *J* =18.7, 1H), 3.47 (br.s., 1H), 3.31 (br.s., 1H), 2.61 (d, *J* =16.5, 1H), 2.41 (d, *J* = 16.5, 1H), 2.15–2.11 (m, 1H), 2.04–1.99 (m, 1H), 1.42 (s, 9H), 1.32 (app. q, *J* = 6.6, 1H), 0.62–0.50 (stack, 3H), 0.45–0.38 (m, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.5 (C), 154.3 (C), 145.0 (C), 131.2 (CH), 129.1 (CH), 127.2 (CH), 125.1 (C), 120.9 (C), 80.4 (C), 67.8 (C), 45.9 (CH_2), 38.2 (CH_2), 28.4 ($3CH_3$), 25.7 (CH_2), 18.6 (CH), 1.6 (CH_2), 0.2 (CH_2) ppm; *one quaternary carbon is not observed in ^{13}C NMR spectra;* HRMS (ESI-orbitrap): m/z: calcd for $C_{21}H_{26}N_4O_3S$: 415.1798, found 415.1790 $[M+H]^+$.

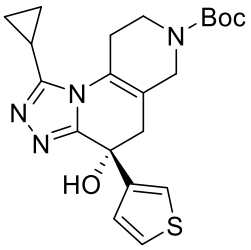
tert-Butyl (rac)-4-(2-chlorophenyl)-1-cyclopropyl-4-hydroxy-4,5,8,9-tetrahydro-[1,2,4]triazolo[4,3-a][1,6]naphthyridine-7(6H)-carboxylate (134c)



Following GP 06 using polycycle **91j** (109 mg, 0.20 mmol), NaOMe (110 µL, 0.60 mmol) in THF (2.0 mL). After work up and removal of the solvent under reduced pressure the crude material was dissolved in 1-butanol (2.0 mL), cyclopropanecarbohydrazide (22 mg, 0.22 mmol, 1.1 eq) and glacial acetic acid (6 µL, 0.10 mmol, 0.5 eq) were added and the reaction mixture was stirred at 110 °C for 24 h. After extractive work up the crude material was subjected to silica gel flash column chromatography [EtOAc 100%] to yield compound **134c** as a white solid (45 mg, 51% over two steps); IR (neat): *v* (max) cm^{-1} 3250, 2967, 2821, 1681, 1505, 1420, 1364; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93–7.90 (m, 1H), 7.37–7.21 (m, 3H), 4.22–4.05 (m, 2H), 3.82–3.68 (m, 1H), 3.32–3.18 (stack, 2H), 3.11–2.98 (m, 1H), 2.84–2.72 (m, 1H), 2.28 (d, *J* = 17.8, 1H), 1.93–1.85 (m, 1H), 1.49 (s, 9H), 1.75–1.11 (m, 2H), 1.06–1.01 (m, 2H) ppm; *^{13}C*

NMR resonances assigned with assistance from HSQC and HMBC spectra due to the broadening of the resonances owing to the rotamer effect: ^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.5 (C), 154.3 (C), 153.3 (C), 152.5 (C), 140.3 (C), 131.9 (C), 130.8 (CH), 129.3 (CH), 127.9 (CH), 126.6 (CH), 80.4 (C), 68.9 (C), 38.6 (CH_2), 28.4 ($3CH_3$), 8.2 (CH), 7.4 (CH_2), 7.1 (CH_2) ppm; *three secondary carbons are not observed in ^{13}C NMR spectra;* HRMS (ESI-orbitrap): m/z: calcd for $C_{23}H_{27}ClN_4O_3$: 443.1844, found 443.1838 $[M+H]^+$.

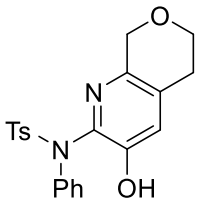
tert-Butyl (rac)-1-cyclopropyl-4-hydroxy-4-(thiophen-3-yl)-4,5,8,9-tetrahydro-[1,2,4]triazolo[4,3-a][1,6]naphthyridine-7(6H)-carboxylate (134b)



Following GP 06 using polycycle **91l** (104 mg, 0.20 mmol), NaOMe (110 µL, 0.60 mmol) in THF (2.0 mL). After work up and removal of the solvent under reduced pressure the crude material was dissolved in 1-butanol (2.0 mL), cyclopropanecarbo hydrazide (22 mg, 0.22 mmol, 1.1 eq) and glacial acetic acid (6 µL, 0.10 mmol, 0.5 eq) were added and the reaction mixture was stirred at 110 °C for 24 h. After extractive work up the crude material was subjected to silica gel flash column chromatography [EtOAc 100%] to yield compound **134b** as a white solid (41 mg, 50% over two steps); IR (neat): *v* (max) cm^{-1} 3160, 2967, 2866, 1684, 1420, 1241, 1148; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.26 (m, 2H), 7.11–7.09 (m, 1H), 4.06–3.87 (m, 2H), 3.72–3.57 (m, 2H), 2.85 (s, 2H), 2.76–2.64 (m, 2H), 1.90 (tt, *J* = 8.3, 5.0, 1H), 1.47 (s, 9H), 1.23–1.17 (m, 2H), 1.06–1.00 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.5 (C), 154.3 (C), 153.2 (C), 143.8 (C), 126.2 (CH), 126.00 (CH), 122.3 (CH), 80.5 (C), 68.6 (C), 40.4 (CH_2), 28.4 ($3CH_3$), 7.8 (CH), 7.70 (CH_2), 7.65 (CH_2)ppm; *two secondary carbons are not observed in ^{13}C NMR spectra;* HRMS (ESI-orbitrap): m/z: calcd for $C_{21}H_{26}N_4O_3S$: 415.1798, found 415.1791 $[M+H]^+$.

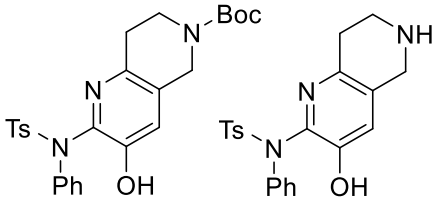
6.6.3. Brönsted-acid catalysed dehydrations and hydrolysis

N-(3-Hydroxy-5,8-dihydro-6H-pyrano[3,4-b]pyridin-2-yl)-4-methyl-N-phenylbenzenesulfonamide (163) BA1



Polycycle **91n** (100.0 mg, 0.225 mmol) and $TsOH{\cdot}H_2O$ (86.0 mg, 0.450 mmol, 2.0 eq) were dissolved in THF (1.1 mL) and MeOH (1.1 mL) and the resulting mixture was stirred at r.t. for 16 h. The mixture was diluted with CH_2Cl_2 (10 mL), poured into sat. $NaHCO_{3(aq)}$ (12 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combine organic phases were washed with brine and further dried over Na_2SO_4. After filtration and removal of the solvent under reduced pressure the crude material was subjected to silica gel flash column chromatography [heptane: EtOAc (6:4)] yielding hydroxypyridine **163** as a white solid (70.5 mg, 79%); IR (neat): *v* (max) cm^{-1} 3410, 1599, 1513,1453, 1371, 1177, 1110; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.2, 2H), 7.30–7.25 (m, 4H), 7.24–7.18 (m, 2H), 6.94 (app. t, *J* = 7.3, 1H), 6.31 (s, 1H), 4.65 (s, 2H), 3.94 (t, *J* =5.6, 2H), 2.76 (t, *J* = 5.6, 2H), 2.32 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 151.0 (C), 146.5 (C), 146.3 (C), 139.3 (C), 132.3 (C), 131.4 (C), 130.9 (CH), 130.3 (2CH), 128.8 (2CH), 128.3 (2CH), 122.1 (CH), 119.8 (C), 118.5 (2CH), 69.6 (CH_2), 65.0 (CH_2), 27.1 (CH_2), 21.8 (CH_3) ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_{21}H_{20}N_2O_4S$: 397.1216, found 397.1208 $[M+H]^+$.

tert-Butyl 3-hydroxy-2-((4-methyl-N-phenylphenyl)sulfonamido)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (164a) and N-(3-Hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridin-2-yl)-4-methyl-N-phenylbenzenesulfonamide (164b) BA2

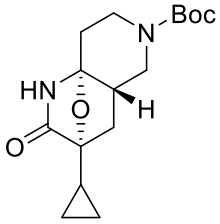


Polycycle **91h** (150.0 mg, 0.276 mmol) and $TsOH{\cdot}H_2O$ (105.0 mg, 0.552 mmol, 2.0 eq) were dissolved in THF (1.4 mL) and MeOH (1.4 mL) and the resulting mixture was stirred at r.t. for 16 h. The mixture was diluted with CH_2Cl_2 (10 mL), poured into sat.

$NaHCO_{3(aq)}$ (12 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with brine and further dried over Na_2SO_4. After filtration and removal of the solvent under reduced pressure the crude material was subjected to silica gel flash column chromatography [heptane: EtOAc (40% → 100%)] yielding hydroxypyridines **164a** (60.2 mg, 44%) and **164b** (41.5 mg, 38%) as a white solids; **164a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.11 (s, 1H), 7.94–7.88 (m, 2H), 7.59–7.45 (m, 3H), 7.40–7.28 (m, 4H), 4.80 (s, 1H), 4.08 (s, 2H), 3.57 (t, *J* = 5.9, 2H), 2.56 (t, *J* = 5.9, 2H), 2.43 (s, 3H), 1.41 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.5 (C), 154.8 (C), 144.7 (C), 136.8 (C), 136.5 (C), 130.8 (2CH), 130.2 (CH), 129.6 (2CH), 129.3 (4CH), 122.7 (C), 117.4 (C), 113.5 (CH), 79.9 (C), 41.3 (CH_2), 31.9 (CH_2), 28.4 ($3CH_3$), 22.3 (CH_2), 21.7 (CH_3) ppm; *one quaternary carbon is not observed in ^{13}C NMR spectra;* HRMS (ESI-orbitrap): m/z: calcd for $C_{26}H_{29}N_3O_5S$: 496.1901, found 496.1893 $[M+H]^+$.

164b: IR (neat): *v* (max) cm^{-1} 3309, 2832, 1651, 1453, 1349, 1297, 1162; ^{1}H NMR (400 MHz, DMSO): δ = 11.48 (s, 1H), 7.82–7.76 (m, 2H), 7.56–7.47 (m, 3H), 7.43 (d, *J* = 8.3, 2H), 7.35–7.30 (m, 2H), 4.96 (d, *J* = 2.0, 1H), 3.29 (s, 3H), 2.75 (t, *J* = 5.7, 2H), 2.41 (s, 3H), 2.38 (t, *J* = 5.7, 2H) ppm; ^{13}C NMR (101 MHz, DMSO): δ = 159.9 (C), 144.3 (C), 137.0 (C), 136.3 (C), 134.5 (C), 130.4 (2CH), 129.6 (CH), 129.4 (2CH), 129.3 (2CH), 128.6 (2CH), 121.0 (C), 119.0 (C), 113.4 (CH), 42.45 (CH_2), 42.38 (CH_2), 23.7 (CH_2), 21.1 (CH_3) ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_{21}H_{21}N_3O_3S$: 396.13764, found 396.1370 $[M+H]^+$.

tert-Butyl (3R*,4aS*,8aR*)-3-cyclopropyl-2-oxooctahydro-6H-3,8a-epoxy-1,6-naphthyridine-6-carboxylate (144) LA1

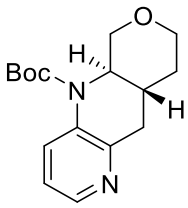


Polycycle **91h** (523.0 mg, 1.10 mmol) and $TsOH·H_2O$ (628.0 mg, 3.30 mmol, 3.0 eq) were dissolved in THF (5.5 mL) and MeOH (5.5 mL) and the resulting mixture was stirred at r.t. for 1 h. The mixture was diluted with CH_2Cl_2 (30 mL), poured into poured in sat. $NaHCO_{3(aq)}$ (20 mL) and

extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were washed with water (30 mL), brine (35 mL) and further dried over Na_2SO_4. After filtration and removal of the solvent under reduced pressure the crude material was recrystallised from hot methanol yielding lactam **144** as a white solid (210.0 mg, 62%); IR (neat): *v* (max) cm^{-1} 3384, 3153, 2974, 2929, 1688, 1416, 1241, 1166; ^1H NMR (400 MHz, DMSO): δ = 8.53, (s, 1H), 3.95 (s, 2H), 2.78 (s, 1H), 2.32 (s, 1H), 2.08–1.89 (m, 2H), 1.86–1.78 (m, 1H), 1.63–1.58 (m, 1H), 1.39 (s, 9H), 1.22–1.15 (m, 1H), 1.09–1.04 (m, 1H), 0.60–0.55 (m, 2H), 0.51–0.44 (m, 1H), 0.40–0.34 (m, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 177.9 (C), 154.1 (C), 90.9 (C), 88.0(C), 80.3 (C), 70.0 (CH_2), 43.3 (CH_2), 36.4 (CH_2), 28.0 ($3CH_3$), 19.1 (CH_2), 9.1 (CH), 1.9 (CH_2), 1.0 (CH_2) ppm; *one secondary carbon is not observed in ^{13}C NMR spectra;* HRMS (ESI-orbitrap): m/z: calcd for $C_{16}H_{24}N_2O_4$: 309.1809, found 309.1806 $[M+H]^+$.

6.6.4. Functional group manipulations

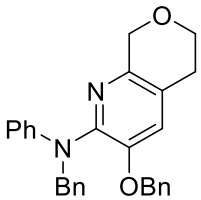
tert-Butyl (5aR,9aS*)-5a,6,8,9,9a,10-hexahydro-5H-pyrano[3,4-b][1,5]naphthyridine-5-carboxylate (131) FGM1*



$NaAuCl_4$ (20.0 mg, 0.05 mmol, 5 mol%) and propargylamine (119 µL, 1.86 mmol, 2.0 eq) were added to a solution of ketone **127a** (237.0 mg, 0.93 mmol) in 1-butanol (3.7 mL, 0.25 M) and the reaction mixture was stirred at 110 °C for 16 h in a capped 8 mL vial. After allowing to cool down to r.t. the reaction mixture was filtered through a short pad of silica with EtOAc (15 mL). The volatiles were removed under reduced pressure and the crude material was subjected to silica gel flash column chromatography yielding pyridine **131** as a pale yellow solid (173.1 mg, 64%); IR (neat): *v* (max) cm^{-1} 2974, 2926, 2847, 1699, 1448, 1319, 1159, 1125; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.13 (dd, *J* = 4.8, 1.5, 1H), 7.81 (dd, *J* = 8.3, 1.5, 1H), 7.07 (dd, *J* = 8.3, 4.8, 1H), 4.52 (dd, *J* = 10.0, 3.5, 1H), 4.02–3.94 (m, 1H), 3.55 (ddd, *J* = 11.3, 9.6, 3.5, 1H), 3.34 (td, *J* = 11.7, 2.7,

1H), 3.04 (app. t, *J* = 9.9, 1H), 2.79 (dd, *J* = 14.5, 2.6, 1H), 2.61 (dd, *J* = 14.7, 12.2, 1H), 1.88–1.80 (m, 1H), 1.80–1.65 (m, 1H), 1.65–1.51 (m, 1H), 1.48 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.2 (C), 152.3 (C), 143.5 (C), 133.8 (C), 132.9 (CH), 121.1 (C), 82.0 (C), 72.1 (CH_2), 67.8 (C), 60.2 (CH), 41.2 (CH), 37.5 (CH_2), 32.7 (CH_2), 28.2 ($3CH_3$) ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_{16}H_{22}N_2O_3$: 291.17032, found 291.1695 $[M+H]^+$, 191.1175 $[M-Boc+H]^+$.

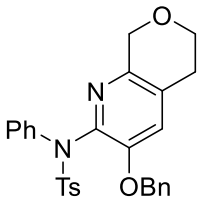
N-Benzyl-3-(benzyloxy)-N-phenyl-5,8-dihydro-6H-pyrano[3,4-b]pyridin-2-amine (165a) FGM2



NaH (20.2 mg, 0.50 mmol, 2.0 eq) was added to a suspension of hydroxypyridine **163** (100 mg, 0.25 mmol) in DMF (2.5 mL, 0.1 M), and the reaction mixture was stirred for 15 min at r.t. Benzyl bromide (45.0 µL, 0.38 mmol, 1.5 eq) was added and the reaction mixture was heated to 50 °C and stirred for 16 h. After allowing to cool down to room temperature the reaction was quenched by the addition of water (10 mL) and poured into a separating funnel and the organics were extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (2 x 10 mL) and dried over Na_2SO_4. After filtration and removal of the solvent the crude material was purified via basic reverse phase flash column chromatography yielding benzyloxypyridine **165a** as a white solid (63.9 mg, 60%); IR (neat): *ν* (max) cm^{-1} 3060, 2922, 1599, 1446, 1103, 730; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 7.4, 2H), 7.24–7.19 (m, 5H), 7.16 (t, *J* = 7.9, 3H), 6.94 (s, 1H), 6.91–6.85 (m, 3H), 6.84 (d, *J* = 8.0, 2H), 5.25 (s, 2H), 4.92 (s, 2H), 4.67 (s, 2H), 3.96 (t, *J* = 5.6, 2H), 2.80 (t, *J* = 5.6, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 148.1 (C), 146.4 (C), 144.4 (C), 140.1 (C), 136.3 (C), 128.6 (2CH), 128.25 (2CH), 128.23 (2CH), 127.6 (CH), 126.9 (2CH), 126.6 (2CH), 126.5 (CH), 123.9 (C), 121.0 (CH), 120.6 (CH), 118.3 (2CH), 70.4 (CH_2), 69.4 (CH_2), 64.9 (CH_2), 55.4 (CH_2), 27.6 (CH_2) ppm; *one quaternary carbon is not*

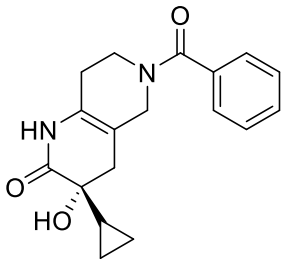
observed in ^{13}C NMR spectra; HRMS (ESI-orbitrap): m/z: calcd for $C_{28}H_{26}N_2O_2$: 423.2067, found 423.2059 $[M+H]^+$.

N-(3-(Benzyloxy)-5,8-dihydro-6H-pyrano[3,4-b]pyridin-2-yl)-4-methyl-N-phenylbenzene-sulfonamide (165b) FGM3



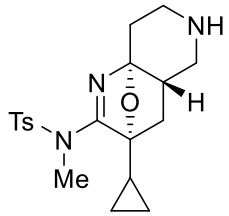
Hydroxypyridine **163** (100 mg, 0.252 mmol), K_2CO_3 (87.0 mg, 0.631 mmol, 2.5 eq) and benzyl bromide (45.0 µL, 0.378 mmol, 1.5 eq) were suspended in acetonitrile and stirred for 16 h at 50 °C. After allowing to cool down to r.t. the reaction mixture was diluted with water (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (20 mL) and dried over Na_2SO_4. After filtration and removal of the solvent under reduced pressure the crude material was purified via basic reverse phase flash column chromatography yielding pyridine **165b** as a white solid (45.4 mg, 37%); IR (neat): *v* (max) cm^{-1} 3060, 2918, 2851, 1595, 1449, 1371, 1174; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.40 (m, 2H), 7.32 (s, 1H), 7.28–7.26 (m, 1H), 7.24–7.15 (m, 5H), 7.12–7.03 (m, 2H), 6.91–6.85 (m, 1H), 6.74–6.68 (m, 2H), 5.30 (s, 1H), 4.93 (s, 2H), 4.63 (s, 2H), 3.96 (t, *J* = 5.6, 2H), 2.80 (t, *J* = 5.6, 2H), 2.42 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 151.3 (C), 148.9 (C), 146.5 (C), 145.1 (C), 139.1 (C), 135.4 (C), 132.2 (2CH), 129.4 (2CH), 128.5 (2CH), 128.2 (2CH), 128.1 (2CH), 127.6 (2CH), 126.6 (CH), 123.1 (C), 122.3 (CH), 120.7 (CH), 69.5 (CH_2), 64.8 (CH_2), 55.1 (CH_2), 27.0 (CH_2), 21.7 (CH_3) ppm; *one quaternary carbon is not observed in ^{13}C NMR spectra;* HRMS (ESI-orbitrap): m/z: calcd for $C_{28}H_{26}N_2O_4S$: 487.1686, found 487.1678 $[M+H]^+$.

(rac)-6-Benzoyl-3-cyclopropyl-3-hydroxy-3,4,5,6,7,8-hexahydro-1,6-naphthyridin-2(1H)-one (159) FGM4



Benzoyl chloride (151.0 µL, 1.30 mmol, 4.0 eq), MeOH (26.0 µL, 0.65 mmol, 2.0 eq) and NaI (97.0 mg, 0.65 mmol, 2.0 eq) were added to an ice cooled solution of lactam **144** (100.0 mg, 0.32 mmol) in MeCN (3.2 mL, 0.1 M). The reaction mixture was stirred at 0 °C for 30 min before DIPEA (227 µL, 1.3 mmol, 4.0 eq) was added and ice bath removed. The reaction mixture was further stirred for 2 h. The reaction was quenched with 6% $HCl_{(aq)}$ (10 mL) and the organics were extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with sat. $NaHCO_{3(aq)}$ (20 mL) and brine (20 mL) and further dried over Na_2SO_4. After filtration and removal of the solvent under reduced pressure the crude material was subjected to silica gel flash column chromatography [heptane: EtOAc (20%→ 100%) yielding enamide **159** as an off-white solid (90.9 mg, 90%); IR (neat): *v* (max) cm^{-1} 3227, 2929, 1666, 1610, 1431, 1289, 1252; ^1H NMR (400 MHz, DMSO): δ = 9.25 (s, 1H), 7.49–7.38 (m, 5H), 4.60–4.56 (m, 1H), 4.02 (app. s, 1H), 3.78 (d, *J* = 17.3, 1H), 3.42 (app. s, 1H), 2.15 (app. s, 2H), 1.22–1.10 (m, 1H), 0.50 (app. s, 1H), 0.33–0.12 (m, 3H) ppm; *^{13}C NMR resonances assigned with assistance from HSQC and HMBC spectra due to the broadening of the resonances owing to the rotamer effect:* ^{13}C NMR (101 MHz, DMSO): δ = 172.9 (C), 169.4 (C), 136.0 (C), 129.6 (2CH), 128.4 (2CH), 126.7 (CH), 104.3 (C), 68.6 (C), 43.5 (CH_2), 39.1 (CH_2), 36.9 (CH_2), 25.6 (CH), 0.1 (CH_2), 0.0 (CH_2) ppm; *one quaternary and one secondary carbons are not observed in ^{13}C NMR spectra;* HRMS (ESI-orbitrap): m/z: calcd for $C_{18}H_{20}N_2O_3$: 313.1547, found 313.1543 $[M+H]^+$.

N-((3R*,4aS*,8aR*)-3-Cyclopropyl-4,4a,5,6,7,8-hexahydro-3H-3,8a-epoxy-1,6-naphthyridin-2-yl)-N,4-dimethylbenzenesulfonamide (149) FGM5



$BF_3{\cdot}(OEt)_2$ (32.0 µL, 0.25 mmol, 1.2 eq) was added to a solution of polycycle **91h** (100.0 mg, 0.21 mmol) in CH_2Cl_2 (2.1 mL, 0.1 M) and the reaction mixture was stirred at r.t. for 4 h. The reaction mixture was poured into a separating funnel and diluted with CH_2Cl_2 (10 mL) and washed with sat. $NaHCO_{3(aq)}$ (10 mL). The aqueous phase was further extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over Na_2SO_4 and the crude material was purified via silica gel flash column chromatography [CH_2Cl_2: MeOH (9:1)] yielding polycycle **149** as a white solid (76.9 mg, 97%); IR (neat): *v* (max) cm^{-1} 2944, 1595, 1349, 1162, 1080; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.85–7.79 (m, 2H), 7.29 (d, *J* = 8.1, 2H), 3.20 (stack, 4H), 3.05–2.99 (m, 1H), 2.69 (td, *J* = 12.8, 3.2, 1H), 2.42 (s, 3H), 2.36–2.22 (m, 2H), 2.15–2.10 (m, 1H), 1.78–1.71 (m, 1H), 1.69–1.64 (m, 1H), 1.57–1.51 (m, 1H), 0.98 (dd, *J* = 11.9, 2.7, 1H), 0.71–0.63 (m, 1H), 0.60–0.55 (m, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.4 (C), 144.3 (C), 134.8 (C), 129.5 (2CH), 128.5 (2CH), 98.1 (C), 91.1 (C), 51.9 (CH_2), 43.1 (CH_2), 39.1(CH), 35.6 (CH_3), 32.0 (CH_2), 31.0 (CH_2), 21.6 (CH_3), 10.9 (CH), 3.4 (CH_2), 3.1(CH_2) ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_{19}H_{25}N_3O_3S$: 376.1689, found 376.1682 $[M+H]^+$.

6.7. Scaffolds elaboration and library compounds

The characterisation of the compounds included in the ALBA library followed the guidelines from Organic Letters journal:[191] for combinatorial libraries containing more than 20 compounds, a complete characterisation data must be provided for at least 20 diverse members. The compounds to be characterised from the ALBA libraries were selected in such a way that all the products of diverse reactions (for example: reductive aminations, acid couplings, etc.) were almost equally represented and fully characterised.

6.7.1. Library General procedures:

Reactions were performed in 8 mL vials and were capped with a plastic cap. The reactions were stirred using a Teflon coated stirring bar or via an orbital shaker. The desired scaffold was added to the reaction mixture as a stockpile solution. If the scaffold was in the form of HCl salt, it was pre-stirred for 30 min in CH_2Cl_2 with 1.1 eq of Et_3N before being added to the reaction mixture. Reactions were monitored via UPLC systems (Waters IClass, Bin. Pump: UPIBSM; Autosampler UPISMFTN and SO; Column oven; PDA UPPDATC; QDA ESI, Eluent A: acetonitrile, Eluent B: 10mM ammonium bicarbonate in water). Prior to purification, the solvent was evaporated under reduced pressure using GENEVAC systems, and the reaction mixture was dissolved in 1 mL of DMSO and filtered through a 0.45 μm plastic filter with a syringe. Purifications were performed on Agilent Technologies 1100 preparative LC; 2 prep pump G1361A; autosampler; 2 Prep-FC G1364B; Isopump G1310A; DAD G1315B; MSD G16120A (ESI pos/neg); fraction collection based on MS and DAD. Eluent A: 99% acetonitrile + 1% 10mM ammonium bicarbonate in water in acetonitrile, Eluent B: 10mM ammonium bicarbonate in water. Purity is detected via UPLC analysis (Waters IClass, Bin. Pump: UPIBSM; Autosampler UPISMFTN and SO; Column oven; PDA UPPDATC; QDA ESI, Eluent A: acetonitrile, Eluent B: 10mM ammonium bicarbonate in water), the samples are measured in a DMSO solution and purity is based on UV activity.

Library Procedure 1 (LP1): Acid couplings

The desired acid (2.0 eq), EDC·HCl (38.3 mg, 0.2 mmol 2.0 eq), HOAt (27.2 mg, 0.2 mmol, 2.0 eq) and DIPEA (35 μL, 0.2 mmol 2.0 eq) were dissolved in CH_2Cl_2 (1.0 mL) and stirred at room temperature for 1 h before the relevant polycycle (0.1 mmol) was added. The resulting reaction mixture was stirred at room temperature for 24 h.

Library Procedure 2 (LP2): Reductive aminations

The desired aldehyde (2.0 eq), glacial acetic acid (23 μL, 0.3 mmol, 3.0 eq) and the relevant polycycle (0.1 mmol) were dissolved in CH_2Cl_2 (1.0 mL), and the reaction mixture was stirred at room temperature for 3 h. After this time, $NaBH(OAc)_3$ (65 mg, 0.3 mmol, 3.0 eq) was added and the reaction mixture was allowed to stir at room temperature for 24 h before the reaction mixture was quenched by addition of a 0.7 M solution of NH_3 in MeOH (0.5 mL).

Library Procedure 3 (LP3): Sulfonyl protections and urea formations

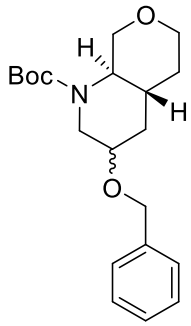
The desired sulfonyl chloride or isocyanate (2.0 eq), Et_3N (28 μL, 0.2 mmol, 2.0 eq) and the relevant polycycle were dissolved in CH_2Cl_2 (1.0 mL) and stirred for 24 h at room temperature.

Library Procedure 4 (LP4): Alkylations

NaH (65.0 mg, 0.3 mmol,3.0 eq) was added to a solution of the relevant polycycle block in THF (1.0 mL) and the reaction mixture was stirred at room temperature for 30 minutes before the desired alkyl halide (2.0 eq) was added and the reaction mixture was stirred for a further 24 h at room temperature before the reaction mixture was quenched by addition of MeOH (0.5 mL).

6.7.2. MC00985 Library

tert-Butyl (4aR,8aR)-3-(benzyloxy)octahydro-1H-pyrano[3,4-b]pyridine-1-carboxylate (121a)

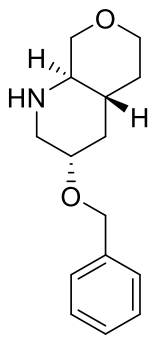


NaH (0.80 g, 20 mmol, 5.0 eq) was added to a cooled solution of aminoalcohol **120** (1.0 g, 3.9 mmol) in THF (40.0 mL, 0.1 M) and the reaction mixture was stirred for 30 minutes. After this time benzyl bromide (0.95 mL, 8.0 mmol, 2.0 eq) was added to the reaction mixture and the cooling bath was removed. The reaction mixture was allowed to warm up to room temperature and stirred for 16 h before it was quenched with water (30 mL) and extracted with EtOAc (3 x 30 mL).

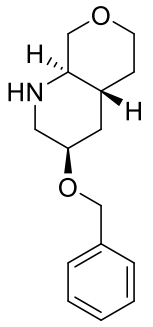
The combined organic phases were dried over Na_2SO_4, after filtration and removal of the solvent the crude material was subjected to silica gel column chromatography (EtOAc 100%) to afford compound **121a** as a colorless oil (1.2 g, 87%); IR (neat): *v* (max) cm^{-1} 2974, 2918, 2862, 1673, 1394, 1364, 1166; *due to excessive overlap, both set of resonances are reported as a mixture of diastereoisomers:* ^1H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.32 (m, $5H_{Major}$), 7.28–7.25 (m, $5H_{minor}$), 4.64 (d, J_{AB} = 11.7, $1H_{Major}$), 4.60 (d, J_{AB} = 11.8, $1H_{minor}$), 4.49 (d, J_{AB} = 11.6, $1H_{minor}$), 4.45 (d, J_{AB} = 11.8, $1H_{Major}$), 4.32 (dd, *J* = 10.8, 4.0, $1H_{Major}$), 4.26 (dd, *J* = 10.7, 3.9, $1H_{minor}$), 3.94–3.90 (stack, $1H_{Major}$ + $1H_{minor}$), 3.77–3.70 (m, $1H_{minor}$), 3.68–3.50 (stack, $3H_{Major}$ + 3_{Hminor}), 3.47–3.34 (stack, $2H_{Major}$+ $2H_{minor}$), 3.14 (td, *J* = 10.4, 4.1, $1H_{Major}$), 3.06 (td, *J* = 10.6, 4.0, $1H_{minor}$), 2.16 (ddd, *J* = 13.4, 7.4, 3.9, $1H_{Major}$), 2.06–1.98 (m, $1H_{minor}$), 1.90–1.83 (m, $1H_{minor}$), 1.75–1.57 (stack, $2H_{Major}$ + $2H_{minor}$), 1.45 (stack, $9H_{Major}$ + $9H_{minor}$), 1.32–1.21 (stack, $1H_{Major}$ + $1H_{minor}$) ppm; *only the resonances of the major diastereoisomer are reported:* ^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.5 (C), 128.5 (2CH), 127.8 (2CH), 127.7 (CH), 80.2 (C), 73.3 (CH), 70.8 (CH_2), 70.2 (CH_2), 68.1 (CH_2), 59.1 (CH), 45.7 (CH_2), 36.7 (CH), 36.3 (CH_2), 32.9 (CH_2), 28.5 ($3CH_3$) ppm; *one quaternary carbon is not observed in ^{13}C NMR spectra*; HRMS (ESI-orbitrap): m/z: calcd for $C_{20}H_{29}NO_4$: 348.2169, found 348.2168 $[M+H]^+$.

(3S*,4aR*,8aR*)-3-(Benzyloxy)octahydro-1H-pyrano[3,4-b]pyridine (122a) and (3R*,4aR*,8aR*)-3-(benzyloxy)octahydro-1H-pyrano[3,4-b]pyridine (122b)

Carbamate **121a** (1.0 g, 2.9 mmol) was dissolved in CH_2Cl_2 (5.7 mL, 0.5 M), and the mixture was cooled to 0 °C. HCl 4 M in dioxane (3.6 mL, 14.4 mmol, 5.0 eq) was added dropwise to the mixture over 5 minutes. The cooling bath was removed and the reaction mixture was allowed to warm to room temperature and stirred for 16 h. After this time the volatiles were removed under reduced pressure and the crude yellow oil was purified via SFC yielding aminoether **122a** (357 mg, 50%) and aminoether **122b** (116 mg, 16%, 12.5:1 mixture) as white solids:

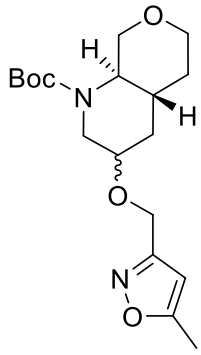


122a: IR (neat): *v* (max) cm^{-1} 3309, 2943, 2907, 2840, 1453, 1148, 1103; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.31 (m, 4H), 7.30–7.25 (m, 1H), 4.60 (d, J_{AB} = 11.9, 1H), 4.56 (d, J_{AB} = 11.9, 1H), 3.94 (ddd, *J* = 11.5, 4.5, 1.7, 1H), 3.87 (dd, *J* = 10.7, 4.4, 1H), 3.47 (tt, *J* = 10.3, 4.5, 1H), 3.41–3.32 (m, 2H), 3.05 (app. t, *J* = 10.4, 1H), 2.55 (app. t, *J* = 10.6, 1H), 2.32 (td, *J* = 9.8, 4.3, 1H), 2.16–2.11 (m, 1H), 1.57–1.43 (m, 2H), 1.43–1.32 (br.s, NH), 1.32–1.23 (m, 1H), 1.21–1.13 (m, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.6 (C), 128.4 (2CH), 127.6 (2CH), 74.9 (CH_2), 71.6 (CH), 70.4 (CH_2), 68.1 (CH_2), 58.9 (CH), 51.2 (CH_2), 39.75 (CH_2), 37.5(CH), 31.9 (CH_2) ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_{15}H_{21}NO_2$: 248.1645, found 248.1643 $[M+H]^+$.



122b: IR (neat): *v* (max) cm^{-1} 3309, 2948, 2866, 1449, 1099; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.34 (m, 4H), 7.31–7.25 (m, 1H), 4.55 (s, 2H), 4.01–3.83 (m, 2H), 3.58–3.51 (m, 1H), 3.42 (td, *J* = 11.8, 2.5, 1H), 3.08 (app. t, *J* = 10.6, 1H), 2.75 (dd, *J* = 14.0, 1.9, 1H), 2.40 (td, *J* = 10.2, 4.4, 1H), 2.03–1.97 (m, 1H), 1.75–1.58 (m, 1H), 1.51–1.23 (m, 4H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.7 (C), 128.4 (2CH), 127.6 (CH), 127.5 (2CH), 72.2 (CH), 71.5(CH_2), 70.2 (CH_2), 68.6 (CH_2), 59.3 (CH), 49.5 (CH_2), 36.1 (CH), 34.8 (CH_2), 32.2 (CH_2) ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_{15}H_{21}NO_2$: 248.1645, found 248.1643 $[M+H]^+$.

tert-Butyl(4aR,8aR)-3-((5-methylisoxazol-3-yl)methoxy)octahydro-1H-pyrano[3,4-b]pyridine-1-carboxylate (121b)



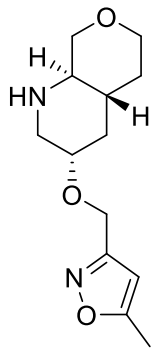
NaH (606 mg, 15.2 mmol, 5.0 eq) was added to a cooled solution of aminoalcohol **120** (780 mg, 1.44 mmol) in THF (30.0 mL, 0.1 M) and the reaction mixture was stirred for 30 minutes. After this time 3-(bromomethyl)-5-methylisoxazole (0.500 mL, 4.55 mmol, 2.0 eq) was added to the reaction mixture and the cooling bath was removed. The reaction mixture was allowed to warm up to room temperature and stirred for 16 h before it was quenched with water (30 mL)

and extracted with EtOAc (3 x 20 mL). The combined organic phases were dried over Na_2SO_4, after filtration and removal of the solvent the crude material was subjected to silica gel column chromatography (100% EtOAc) to afford compound **121b** as a colorless oil (951 mg, 89%, 4:1 mixture); *due to excessive overlap, both sets of resonances are reported as a mixture*; IR (neat): *v* (max) cm^{-1} 2974, 2918, 2802, 1677, 1606, 1401, 1364, 1110; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.02 (s, $1H_{Major}$ + $1H_{minor}$), 4.57 (stack, including: d, J_{AB} = 12.6, $1H_{Major}$ and d, J_{AB} = 12.5, $1H_{minor}$), 4.50 (stack including: d, J_{AB} = 12.5, $1H_{minor}$ and d, J_{AB}= 12.5, $1H_{Major}$), 4.30 (dd, *J* = 10.8, 4.1, $1H_{Major}$), 4.24 (dd, *J* = 10.7, 4.1, $1H_{minor}$), 3.93–3.89 (stack, $1H_{Major}$ + $1H_{minor}$), 3.70–3.55 (stack, $3H_{major}$ + $3H_{minor}$), 3.53–3.46 (stack, $2H_{Major}$ + $2H_{minor}$), 3.39 (stack, $2H_{Major}$ + $2H_{minor}$), 3.11 (td, *J* = 10.4, 4.0, $1H_{Major}$), 3.03 (td, *J* =10.5, 4.0, $1H_{minor}$), 2.40 (stack, $3H_{Major}$ + $3H_{minor}$), 2.13 (ddd, *J* = 13.7, 7.4, 3.8, $1H_{Major}$), 2.01–1.92 (m, $1H_{minor}$), 1.85–1.79 (m, $1H_{minor}$), 1.66–1.57 (m, $1H_{Major}$), 1.44 (stack, $9H_{Major}$ + $9H_{minor}$), 1.25–1.12 (stack, $1H_{Major}$ + $1H_{minor}$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.8 and 169.7 (C), 161.72 and 161.66 (C), 155.5 and 155.1 (C), 101.1 and 101.0 (CH), 80.13 (C), 73.7 and 72.3 (CH), 70.6 and 70.3 (CH_2), 68.1 and 68.0 (CH_2), 61.9 and 61.6 (CH_2), 59.6 and 59.0 (CH), 45.3 (CH_2), 36.2 (CH_2), 36.0 (CH), 32.8 and 32.7 (CH_2), 28.43 and 28.4 ($3CH_3$), 12.3 (CH_3) ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_{18}H_{28}N_2O_5$: 353.2071, found 353.2067 $[M+H]^+$.

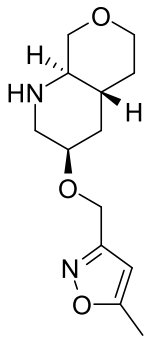
(3S*,4aR*,8aR*)-3-((5-Methylisoxazol-3-yl)methoxy)octahydro-1H-pyrano[3,4-b]pyridine (123a) and (3R*,4aR*,8aR*)-3-((5-Methylisoxazol-3-yl)methoxy)octahydro-1H-pyrano[3,4-b]pyridine (123b)

Carboxylate X (950 mg, 2.70 mmol) was dissolved in CH_2Cl_2 (5.4 mL, 0.5 M), and the mixture was cooled to 0 °C. HCl 4 M in dioxane (3.40 mL, 13.48 mmol, 5.0 eq) was added dropwise to the mixture over 5 minutes. The cooling bath was removed and the reaction mixture was allowed to warm to room temperature and stirred for 16 h. After this time the volatiles were

removed under reduced pressure and the crude yellow oil was purified via SFC yielding aminoether **123a** (367 mg, 54%) and aminoether **123b** (129 mg, 19%) as white solids:

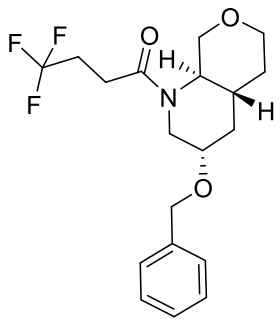


123a: IR (neat): *v* (max) cm^{-1} 2922, 2847, 1606, 1453, 1237, 1080; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.03 (s, 1H), 4.59 (s, 2H), 3.97–3.91 (m, 1H), 3.87 (dd, *J* = 10.7, 4.3, 1H), 3.50–3.40 (m, 1H), 3.40–3.30 (m, 2H), 3.04 (app. t, *J* = 10.5, 1H), 2.52 (app. t, *J* = 10.7, 1H), 2.41 (s, 3H), 2.31 (td, *J* = 9.9, 4.3, 1H), 2.12 (ddd, *J* = 12.1, 5.0, 2.6, 1H), 1.57–1.48 (m, 1H), 1.47–1.34 (stack, 1H + NH), 1.31–1.21 (m, 1H), 1.13 (app. q, *J* = 11.7, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.9 (C), 101.0 (CH), 75.2 (CH), 71.5 (CH_2), 68.1 (CH_2), 61.7 (CH_2), 58.8 (CH), 51.0 (CH_2), 39.7 (CH), 37.2 (CH_2), 31.8 (CH_2), 12.3 (CH_3) ppm; *a quaternary carbon is not observed in ^{13}C NMR spectra;* HRMS (ESI-orbitrap): m/z: calcd for $C_{13}H_{20}N_2O_3$: 253.1547, found 253.1544 $[M+H]^+$.



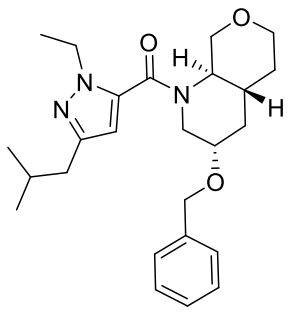
123b: IR (neat): *v* (max) cm^{-1} 2914, 2844, 1606, 1446, 1084; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.04 (s, 1H), 4.58–4.59 (m, 2H), 3.92 (ddd, *J* = 11.5, 4.5, 1.6, 1H), 3.84 (dd, *J* = 10.7, 4.4, 1H), 3.53–3.51 (m, 1H), 3.39 (td, *J* = 11.7, 2.5, 1H), 3.17 (dt, *J* = 13.8, 2.4, 1H), 3.06 (app. t, *J* = 10.5, 1H), 2.77 (dd, *J* = 13.8, 1.9, 1H), 2.40 (s, 3H), 2.39 (dd, *J* = 10.2, 4.5, 1H), 1.94 (dq, *J* = 13.8, 3.0, 1H), 1.70–1.65 (br. s, NH), 1.64–1.56 (m, 1H), 1.45–1.39 (m, 1H), 1.37–1.22 (stack, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.8 (C), 161.8 (C), 101.0 (CH), 72.6 (CH), 71.4 (CH_2), 68.5 (CH_2), 61.6 (CH_2), 59.1 (CH), 49.4 (CH_2), 35.8 (CH), 34.4 (CH_2), 32.0 (CH_2), 12.9 (CH_3) ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_{13}H_{20}N_2O_3$: 253.1547, found 253.1543 $[M+H]^+$.

1-((3S*,4aR*,8aR*)-3-(Benzyloxy)octahydro-1H-pyrano[3,4-b]pyridin-1-yl)-4,4,4-trifluoro-butan-1-one (167e)



Following LP1: **122a** (0.1 mmol) and 4,4,4-trifluorobutanoic acid (30 μL, 0.2 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **167e** as a colourless oil (21.1 mg, 57%, purity: 91.7%); Rt(UPLC): 1.61 min; IR (neat): *v* (max) cm^{-1} 2922, 2847, 1640, 1436, 1382, 1252, 1133, 1088, 738, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38–7.27 (m, 5 H), 4.56 (d, J_{AB} = 11.9, 1 H), 4.48 (d, J_{AB} = 11.9, 1 H), 4.35–4.24 (m, 1H), 3.97 (d, *J* = 11.5, 4.4 Hz, 1H), 3.75 (tt, *J* = 7.4, 3.6, 1H), 3.52–3.3 (m, 4H), 2.70–2.57 (m, 1H), 2.51–2.37 (m, 3H), 2.17 (ddd, *J* = 13.4, 7.9, 3.2, 1H), 1.77–1.60 (m, 3H), 1.51 (dtd, *J* = 13.6, 12.1, 4.6, 1H), 1.28 (app. td, *J* = 13.1, 6.7, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.4 (C), 137.8 (C), 128.53 (2CH), 128.47 (t, *J* = 276.9, CF_3) 127.9 (CH), 127.5 (2CH) ,73.6 (CH), 70.3 (CH_2), 69.4 (CH_2), 68.0 (CH_2), 59.7 (CH), 35.7 (CH), 35.1 (CH_2), 32.8 (CH_2), 30.0 (CH_2) , 29.7 (q, *J* = 29.5, CH_2), 26.6 (CH_2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ = -66.51 (t, *J* = 10.6) ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_{19}H_{25}F_3NO_3$: 372.1781, found 372.1774 $[M+H]^+$.

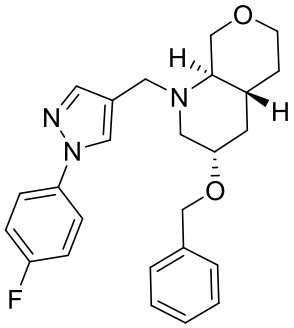
((3S*,4aR*,8aR*)-3-(benzyloxy)octahydro-1H-pyrano[3,4-b]pyridin-1-yl)(1-ethyl-3-isobutyl-1H-pyrazol-5-yl)methanone (167g)



Following LP1: **122a** (0.1 mmol) and 1-ethyl-3-isobutyl-1H-pyrazole-5-carboxylic acid (39 mg, 0.2 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **167g** as a white solid (27.6 mg, 65%, purity: 100%); Rt(UPLC): 1.84 min; IR (neat): *v* (max) cm^{-1} 2952, 2866, 1628, 1531, 1449, 1200, 1088, 734, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34–7.25 (m, 3H), 7.21–7.16 (m, 2H), 6.07 (s, 1H), 4.46 (dd, *J* = 10.6, 4.0, 1H), 4.35 (d, J_{AB} = 11.9, 1 H), 4.30 (d, J_{AB} = 11.9, 1 H), 4.11 (d, J_{AB} = 7.1, 1H), 4.07 (d, J_{AB} = 7.3, 1H), 3.99 (dd, *J* = 11.5, 4.4 , 1H), 3.74 (dd, *J* = 13.8, 4.2, 1H), 3.70–3.62 (m, 2H), 3.58 (dd, *J* = 13.8, 3.1,

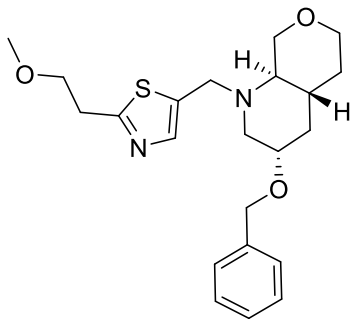
1H), 3.48–3.37 (m, 2H), 2.48 (d, *J* = 7.1, 2H), 2.19 (ddd, *J* = 13.7, 7.8, 3.8, 1H), 1.87 (dt, *J* = 13.5, 6.7, 1H), 1.82–1.68 (stack, 3H), 1.56 (td, *J* = 12.4, 4.3, 1H), 1.32 (t, *J* = 7.2, 4H), 0.93 (d, *J* = 1.6, 3H), 0.92 (d, *J* = 1.6, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 164.1 (C), 150.6 (C), 137.7 (C), 135.8 (C), 128.4 (2CH), 127.8 (CH), 127.4 (2CH), 105.6 (CH), 73.0 (CH), 70.0 (CH_2), 69.0 (CH_2), 68.0 (CH_2), 58.8 (CH), 48.4 (CH_2), 45.5 (CH_2), 37.3 (CH_2), 35.3 (CH), 35.2 (CH_2), 32.8 (CH_2), 29.1 (CH), 22.42 (CH_3), 22.41 (CH_3), 15.9 (CH_3) ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_{25}H_{36}N_3O_3$: 426.2751, found 426.2743 $[M+H]^+$.

(3S*,4aR*,8aR*)-3-(benzyloxy)-1-((1-(4-fluorophenyl)-1H-pyrazol-4-yl)methyl)octahydro-1H-pyrano[3,4-b]pyridine (168f)



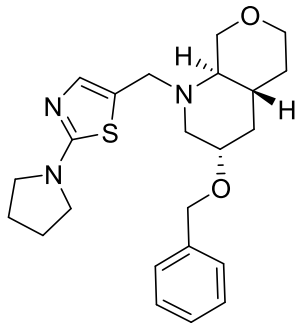
Following LP2: **122a** (0.1 mmol) and 1-(4-Fluorophenyl)pyrazole-4-carbaldehyde (38 mg, 0.2 mmol, 0.2 eq). Purification by prep-LCMS yielded compound **168f** as a pale yellow oil (22.1 mg, 52%, purity: 100%); Rt(UPLC): 1.75 min; IR (neat): *v* (max) cm^{-1} 2922, 2847, 1513, 1453, 1397, 1226, 834, 738, 697; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (s, 1H), 7.67–7.60 (m, 2H), 7.59 (s, 1H), 7.34 - 7.31 (m, 1H), 7.25 (m, 1H), 7.14 (t, *J* = 8.6, 2H), 4.58 (d, J_{AB} = 11.9, 1H), 4.50 (d, J_{AB} = 11.9, 1H), 4.38 (dd, *J* = 10.8, 4.0, 1H), 3.94 (dd, *J* = 10.9, 3.2, 1H), 3.71 (d, J_{AB} = 14.6, 1H), 3.62–3.51 (stack, 2H including: d, J_{AB} = 14.4, 1H), 3.38 (td, *J* = 11.3, 2.9, 1H), 3.22–3.11 (stack, 2H), 2.11–2.03 (m, 2H), 1.94 (td, *J* = 9.6, 3.9, 1H), 1.60–1.38 (stack, 3H), 1.05 (app. q, *J* = 11.5, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.3 (C), 159.8 (C), 141.9 (CH), 138.6 (C), 136.4 (CF), 128.4 (2CH), 127.6 (2CH), 126.6 (CH), 120.8 (CH), 120.7 (CH), 117.5 (C), 116.3 (CH), 116.1 (CH), 73.9 (CH), 70.5 (CH_2), 70.3 (CH_2), 68.1 (CH_2), 61.8 (CH), 57.6 (CH_2), 46.6 (CH_2), 38.5 (CH), 37.5 (CH_2), 32.2 (CH_2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -116.01 (m) ppm; HRMS (ESI-orbitrap): calcd for $C_{25}H_{29}FN_3O_2$: 422.2238, found 422.2232 $[M+H]^+$.

(3S*,4aR*,8aR*)-3-(benzyloxy)-1-((2-(2-methoxyethyl)thiazol-5-yl)methyl)octahydro-1H-pyrano[3,4-b]pyridine (168a)



Following LP2: **122a** (0.1 mmol) and 2-(2-methoxyethyl)-1,3-thiazole-5-carbaldehyde (34 mg, 0.2 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **168a** as a pale yellow oil (25.4 mg, 63%, purity: 100%); Rt(UPLC): 1.53 min; IR (neat): *v* (max) cm^{-1} 2922, 2847, 1453, 1375, 1110, 738, 697; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (s, 1H), 7.35–7.26 (m, 5H), 4.55 (d, J_{AB} = 11.8, 1H), 4.50 (d, J_{AB} = 11.8, 1H), 4.29 (dd, *J* = 10.7, 4.0 , 1H), 3.97–3.92 (m, 1H), 3.89 (d, J_{AB} = 15.3, 1H), 3.75 (t, *J* = 6.5, 2H), 3.70 (d, J_{AB} = 15.0, 1H), 3.54 (tt, *J* = 10.8, 4.4, 1H), 3.39 (s, 3H), 3.35 (dd, *J* = 11.2, 2.9, 1H), 3.24 (t, *J* = 6.4, 2H), 3.17–3.08 (m, 2H), 2.10–2.04 (m, 2H), 2.01 (td, *J* = 9.7, 4.0, 1H), 1.59–1.37 (stack, 3H), 1.07 (app. q, *J* = 11.7, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.1 (C), 141.0 (CH), 138.5 (C), 133.7 (C), 128.4 ($2CH_2$), 127.61 (CH), 127.58 (2CH), 73.8 (CH), 71.1 (CH_2), 70.5 (CH_2), 70.1 (CH_2), 68.1 (CH_2), 62.1 (CH), 58.8 (CH_3), 57.7 (CH_2), 48.7 (CH_2), 38.5 (CH), 37.5 (CH_2), 34.0 (CH_2), 32.1 (CH_2) ppm; HRMS (ESI-orbitrap): calcd for $C_{22}H_{31}N_2O_3S$: 403.2049, found 403.2045 $[M+H]^+$.

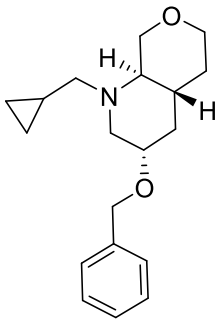
(3S*,4aR*,8aR*)-3-(benzyloxy)-1-((2-(pyrrolidin-1-yl)thiazol-5-yl)methyl)octahydro-1H-pyrano[3,4-b]pyridine (168g)



Following LP2: **122a** (0.1 mmol) and 2-Pyrrolidin-1-yl-1,3-thiazole-5-carbaldehyde (37 mg, 0.2 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **168g** as a off-white solid (32.5 mg, 79%, purity: 97.7%); Rt(UPLC): 1.65 min; IR (neat): *v* (max) cm^{-1} 2914, 2799, 2836, 1550, 1449, 1356, 1088, 734, 693; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.28 (m, 4H), 7.28–7.23 (m, 1H), 6.94 (s, 1H), 4.56 (d, J_{AB} =11.9, 1H), 4.52 (d, J_{AB} = 11.9, 1H),4.32 (dd, *J* = 10.7, 4.0, 1H), 3.93 (ddd, *J* = 11.1, 4.1, 1.6, 1H), 3.77 (d, J_{AB}

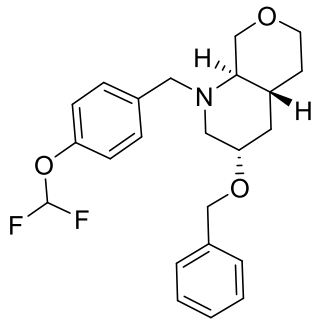
= 14.7, 1H), 3.60 (d, J_{AB} = 14.7, 1H), 3.57–3.50 (m, 1H), 3.48–3.41 (m, 4H), 3.36 (td, *J* = 11.2, 3.0, 1H), 3.20–3.10 (m, 2H), 2.11 (app. t, *J* = 10.4, 1H), 2.06–1.98 (stack, 6H), 1.55–1.51 (m, 1H), 1.49–1.45 (m, 1H), 1.44–1.36 (m, 1H), 1.08 (app. q, *J* = 11.7, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.3 (C), 138.9 (CH), 138.6 (C), 128.4 (2CH), 127.6 (CH), 127.5 (2CH), 119.8 (C), 74.0 (CH), 70.4 (CH_2), 70.2 (CH_2), 68.1 (CH_2), 62.0 (CH), 57.4 (CH_2), 49.3 ($2CH_2$), 49.2 (CH_2), 38.6 (CH), 37.7 (CH_2), 32.2 (CH_2), 25.7 ($2CH_2$) ppm; HRMS (ESI-orbitrap): calcd for $C_{23}H_{32}N_3O_2S$: 414.2209, found 414.2204 $[M+H]^+$.

(3S*,4aR*,8aR*)-3-(benzyloxy)-1-(cyclopropylmethyl)octahydro-1H-pyrano[3,4-b]pyridine (168b)



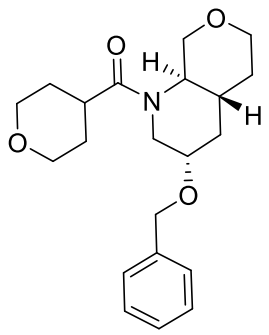
Following LP2: **122a** (0.1 mmol) and cyclopropanecarboxaldehyde (15 µL, 0.2 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **168b** as a colourless oil (25.2 mg, 83%, purity: 95.1%). Rt(UPLC): 1.59 min; *sample contains 2.2% w/w CH_2Cl_2.* IR (neat): *v* (max) cm^{-1} 2922, 2844, 1453, 1073; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.31 (m, 4H), 7.30–7.24 (m, 1H), 4.62 (d, J_{AB} = 11.8, 1H), 4.56 (d, J_{AB} = 11.9, 1H), 4.22 (dd, *J* = 10.7, 4.0, 1H), 3.93 (ddd, *J* = 11.4, 4.2, 1.7, 1H), 3.57 (tt, *J* = 10.5, 4.4, 1H), 3.41–3.37 (m, 1H), 3.37–3.41 (td, *J* = 11.0, 3.5, 1H), 3.08 (app. t, *J* = 10.5, 1H), 2.45 (dd, J_{AB} = 13.5, 6.7, 1H), 2.30 (dd, J_{AB} = 13.6, 6.3, 1H), 2.23 (app. t, *J* = 10.5, 1H), 2.12–2.00 (m, 2H), 1.59–1.46 (m, 2H), 1.46–1.34 (m, 1H), 1.12 (app. q, *J* = 11.7. 1H), 0.88–0.78 (m, 1H), 0.54–0.46 (m, 2H), 0.12–0.03 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.8 (C), 128.4 (2CH), 127.7 (2CH), 127.6 (CH), 74.2 (CH), 70.5 (CH_2), 70.3 (CH_2), 68.1 (CH_2), 62.7 (CH), 58.1 (CH_2), 57.8 (CH_2), 38.5 (CH), 37.8 (CH_2), 32.3 (CH_2), 6.6 (CH), 4.2 (CH_2), 3.8 (CH_2) ppm; HRMS (ESI-orbitrap): calcd for $C_{19}H_{27}NO_2$: 302.2115, found 302.2109 $[M+H]^+$.

(3S*,4aR*,8aR*)-3-(benzyloxy)-1-(4-(difluoromethoxy)benzyl)octahydro-1H-pyrano[3,4-b]pyridine (168e)



Following LP2: **122a** (0.1 mmol) and 3-(difluoromethoxy) benzaldehyde (34.0 mg, 0.2 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **168e** as a white solid (17.7 mg, 44%, purity: 98.2%). Rt(UPLC): 1.92 min; IR (neat): *v* (max) cm^{-1} 2926, 2847, 2795, 1587, 1118, 1073, 1039; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.21 (m, 6H), 7.10 (d, *J* = 7.6, 1H), 7.06 (br. s, 1H), 6.99 (dd, *J* = 8.2, 2.4, 1H), 6.50 (t, J_{HF} = 75.0, 1H), 4.52 (d, J_{AB} = 11.8, 1H), 4.45 (d, J_{AB} = 11.8, 1H), 4.22 (dd, *J* = 10.8, 3.9, 1H), 3.97–3.89 (m, 1H), 3.87 (d, J_{AB} = 14.0, 1H), 3.50 (tt, *J* = 10.5, 4.4, 1H), 3.36 (td, *J* = 11.1, 3.3, 1H), 3.20 (d, J_{AB} = 14.0, 1H), 3.12–3.02 (stack, 2H, including: app. t, *J* = 10.4, 1H), 2.10–2.05 (m, 1H), 2.01 (td, *J* = 9.5, 4.0, 1H), 1.93 (app. t, *J* = 10.4, 1H), 1.58–1.54 (m, 1H), 1.53–1.42 (m, 2H), 1.12 (app. q, *J* = 11.6, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 151.4 (t, *J* = 2.9, C), 141.6 (C), 138.6 (C), 129.7 (CH), 128.4 (2CH), 127.6 (3CH), 125.5 (CH), 119.5 (CH), 117.8 (CH), 116.0 (t, *J* = 260.2, CHF_2), 73.8 (CH), 70.7 (CH_2), 70.4 (CH_2), 68.1 (CH_2), 64.2 (CH), 58.4 (CH_2), 57.2 (CH_2), 38.6 (CH), 37.8 (CH_2), 32.3 (CH_2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = - 80.5 (d, *J* = 72.6) ppm; HRMS (ESI-orbitrap): calcd for $C_{23}H_{27}F_2NO_3$: 404.2032, found 404.2023 $[M+H]^+$.

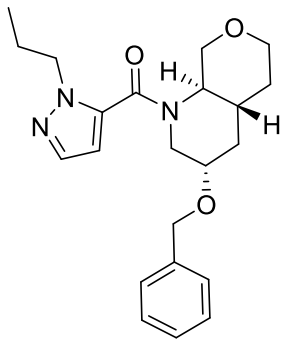
((3S*,4aR*,8aR*)-3-(benzyloxy)octahydro-1H-pyrano[3,4-b]pyridin-1-yl)(tetrahydro-2H-pyran-4-yl)methanone (167a)



Following LP1: **122a** (0.1 mmol) and Tetrahydropyran-4-yl-carboxylic acid (26.0 mg, 0.2 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **167a** as a colourless oil (29.2 mg, 89%, purity: 100%); Rt(UPLC): 1.33 min; IR (neat): *v* (max) cm^{-1} 2948, 2855, 1617, 1438, 1353, 1084, 1010, 752, 700; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.27

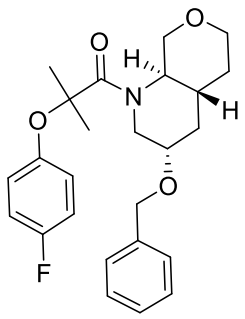
(m, 5H), 4.56 (d, J_{AB} = 11.9, 1H), 4.47 (d, J_{AB} = 11.9, 1H), 4.26 (br. s, 1H), 3.97–3.92 (stack, 3H), 3.72 (tt, *J* = 7.4, 3.7, 1H), 3.52–3.28 (m, 6H), 2.66 (tt, *J* = 11.4, 3.8, 1H), 2.19 (ddd, *J* = 13.5, 7.8, 3.3 Hz, 1H), 1.95–1.78 (stack, 3H), 1.75–1.55 (stack, 4H), 1.52–1.46 (m, 2H), 1.27 (td, *J* = 13.1, 6.9, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 175.2 (C), 138.0 (C), 128.5 (2CH), 127.8 (CH), 127.5 (2CH), 73.8 (CH), 70.2 (CH_2), 69.8 (CH_2), 68.1 (CH_2), 67.2 ($2CH_2$), 59.6 (CH), 38.5 (CH), 35.7 (CH), 35.3 (CH_2), 32.9 (CH_2), 29.5 ($2CH_2$), 29.1 (CH_2) ppm; HRMS (ESI-orbitrap): calcd for $C_{21}H_{30}NO_4$: 360.2169, found 360.2162 $[M+H]^+$.

((3S*,4aR*,8aR*)-3-(benzyloxy)octahydro-1H-pyrano[3,4-b]pyridin-1-yl)(1-propyl-1H-pyrazol-5-yl)methanone (167d)



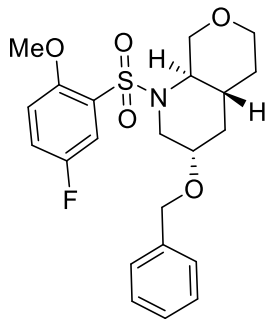
Following LP1: **122a** (0.1 mmol) and 1-propyl-1H-pyrazole-5-carboxylic acid (31.0 eq, 0.2 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **167d** as a white solid (31.5 mg, 81%, purity: 100%); Rt(UPLC): 1.75 min; IR (neat): *v* (max) cm^{-1} 2929, 2851, 1625, 1517, 1397, 1066, 734, 697; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (d, *J* = 1.9, 1H), 7.34–7.24 (m, 3H), 7.22–7.17 (m, 2H), 6.27 (d, *J* = 1.9, 1H), 4.47 (dd, *J* = 10.6, 4.0, 1H), 4.37 (d, J_{AB} = 11.9, 1H), 4.31 (d, J_{AB} = 11.9, 1H), 4.07 (ddd, *J* = 8.6, 6.8, 2.3, 2H), 4.02–3.95 (m, 1H), 3.72–3.61 (stack, 3H), 3.61–3.54 (m, 1H), 3.48–3.39 (m, 2H), 2.19 (ddd, *J* = 13.8, 7.6, 3.9, 1H), 1.84–1.76 (stack, 3H), 1.75–1.68 (m, 1H), 1.61–1.52 (m, 1H), 1.34 (td, *J* = 13.3, 6.1, 1H), 0.82 (t, *J* = 7.4, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.8 (C), 137.7 (C), 137.6 (CH), 135.8 (C), 128.5 (2CH), 127.8 (CH), 127.5 (2CH), 106.4 (CH), 72.9 (CH), 70.0 (CH_2), 68.9 (CH_2), 68.0 (CH_2), 58.8 (CH), 52.3 (CH_2), 48.6 (CH_2), 35.3 (CH), 35.2 (CH_2), 32.8 (CH_2), 23.8 (CH_2), 11.1 (CH_3) ppm; HRMS (ESI-orbitrap): calcd for $C_{22}H_{30}N_3O_3$: 384.2282, found 384.2274 $[M+H]^+$.

1-((3S*,4aR*,8aR*)-3-(benzyloxy)octahydro-1H-pyrano[3,4-b]pyridin-1-yl)-2-(4-fluorophenoxy)-2-methylpropan-1-one (167n)



Following LP1: **122a** (25 mg, 0.1 mmol) and 2-(4-fluorophenoxy)-2-methylpropanoic acid (40.0 mg, 0.2 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **167n** as a white solid (13.0 mg, 30%, purity: 100%); Rt(UPLC): 1.93 min; IR (neat): *v* (max) cm^{-1} 2933, 2844, 1628, 1502, 1416, 1207, 1148, 1108, 730, 697; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.20 (m, 5H), 6.95–6.87 (m, 2H), 6.79–6.72 (m, 2H), 4.48 (dd, *J* = 10.0, 3.4, 1H), 4.45 (d, J_{AB} = 11.9, 1H), 4.40 (d, J_{AB} = 12.0, 1H), 3.96 (td, *J* = 13.3, 12.1, 4.3, 2H), 3.76 (dd, *J* = 14.5, 4.1, 1H), 3.57–3.50 (m, 1H), 3.48 (td, *J* = 10.4, 3.9, 1H), 3.39–3.33 (m, 1H), 2.08 (ddd, *J* = 12.9, 7.5, 2.9, 1H), 1.68 (s, 3H), 1.65–1.59 (stack, 3H), 1.57–1.55 (stack, 4H, including: 1.56, s, 3H), 1.54–1.47 (m, 1H), 1.24 (td, *J* = 12.5, 7.9, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.3 (C), 158.8 (C), 151.3 (C), 138.1 (C), 128.4 (2CH), 127.6 (CH), 127.4 (2CH), 118.6 (d, *J* = 7.9, 2CH), 115.8 (d, *J* = 23.2, 2CH), 81.6 (C), 73.7 (CH), 70.2 (CH_2), 68.5 (CH_2), 67.9 (CH_2), 61.0 (CH), 47.3 (CH_2), 35.4 (CH_2), 33.1 (CH_2), 27.4 (CH), 25.4 ($2CH_3$) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ= -122.63 ppm (m) ppm; HRMS (ESI-orbitrap): calcd for $C_{25}H_{31}FNO_4$: 428.2232, found 428.2224 $[M+H]^+$.

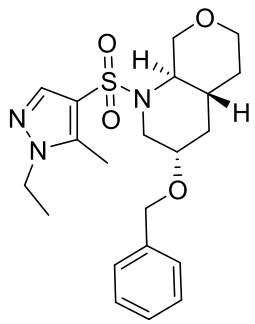
(3S*,4aR*,8aR*)-3-(benzyloxy)-1-((5-fluoro-2-methoxyphenyl)sulfonyl)octahydro-1H-pyrano[3,4-b]pyridine (169a)



Following LP3: **122a** (0.1 mmol) and 5-fluoro-2methoxybenzenesulfonlyl chloride (45.0 mg, 0.2 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **169a** as a white solid (17.4 mg, 40%, purity: 91.2%). Rt(UPLC): 1.77 min; IR (neat): *v* (max) cm^{-1} 2974, 2937, 2870, 1487, 1446, 1338, 1107; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (dd, *J* = 8.0, 3.1, 1H), 7.37–7.26 (m, 5H), 7.20 (ddd, *J* = 9.1, 7.4, 3.1, 1H),

6.93 (dd, *J* = 9.1, 3.9, 1H), 4.59 (s, 2H), 4.33–4.27 (m, 1H), 4.25 (dd, *J* = 11.6 , 4.3, 1H), 3.89 (s, 3H), 3.86 (dd, *J* = 11.4, 4.8, 1H), 3.66–3.56 (stack, 2H, including: 3.60, app. t, *J* = 10.6, 1H), 3.36 (td, *J* = 11.9, 2.4, 1H), 2.75 (td, *J* = 10.1, 4.0, 1H), 2.59 (dd, *J* = 12.3, 10.1, 1H), 2.19–2.10 (m, 1H), 1.76–1.66 (m, 1H), 1.66–1.59 (m, 1H), 1.53–1.39 (m, 1H), 1.17 (td, *J* = 12.4, 10.8, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.1 (C), 154.6 (C), 152.9 (d, *J* = 2.7, C), 138.1 (C), 129.6 (d, J = 6.5, C), 128.4 (2CH), 127.7 (CH), 127.6 (2CH), 120.9 (d, J = 23.1 , CH), 117.9 (d, J = 26.4, CH), 113.4 (d, J = 7.4, 1H), 73.4 (CH), 70.9 (CH_2), 69.7 (CH_2), 67.6 (CH_2), 61.5 (CH), 56.5 ($CH_)$, 53.1 (CH_2), 38.9 (CH_3), 38.3 (CH_2), 32.9 (CH_2) ppm; HRMS (ESI-orbitrap): calcd for $C_{22}H_{26}FNO_5S$: 436.1588, found 436.1580 $[M+H]^+$.

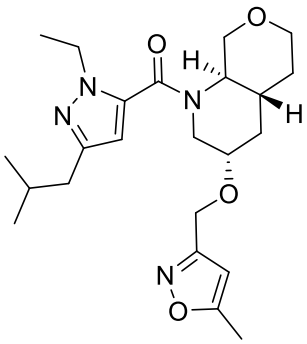
(3S*,4aR*,8aR*)-3-(benzyloxy)-1-((1-ethyl-5-methyl-1H-pyrazol-4-yl)sulfonyl)octahydro-1H-pyrano[3,4-b]pyridine (169b)



Following LP3: **122a** (0.1 mmol) and 1-ethyl-5-methyl-1H-pyrazole-4-sulfonyl chloride (42 mg, 0.2 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **169b** as a white solid (21.9 mg, 52%, purity: 98.4%). Rt(UPLC): 1.61 min; *sample contains 0.6% w/w CH_2Cl_2;* R (neat): *v* (max) cm^{-1} 2937, 2862, 1483, 1449, 1330; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (s, 1H), 7.39–7.27 (m, 5H), 4.59 (s, 2H), 4.47 (dd, *J* = 11.8, 4.0, 1H), 4.24 (ddd, *J* = 11.3, 4.6, 1.9, 1H), 4.11 (q, *J* = 7.3, 2H), 3.87 (dd, *J* = 11.4, 4.6, 1H), 3.64 (tt, *J* = 10.6, 4.5, 1H), 3.51 (dd, *J* = 11.8, 10.1, 1H), 3.36 (td, *J* = 11.8, 2.4, 1H), 2.46 (s, 3H), 2.42 (td, *J* = 9.9, 5.0, 1H), 2.36 (app. dd, *J* = 11.3, 10.1, 1H), 2.15–2.08 (m, 1H), 1.72–1.58 (m, 2H), 1.54–1.45 (m, 1H), 1.43 (t, *J* = 7.3, 3H), 1.11 (td, *J* = 12.3, 10.8, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 139.7 (C), 138.4 (CH), 138.1 (C), 128.6 (2CH), 127.9 (CH), 127.7 (2CH), 116.4 (C), 73.1 (CH), 70.9 (CH_2), 70.2 (CH_2), 67.5 (CH_2), 61.1 (CH), 52.8 (CH_2), 44.8 (CH_2), 38.4 (CH), 38.1

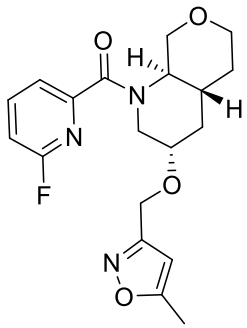
(CH_2), 32.8 (CH_2), 14.9 (CH_3), 10.2 (CH_3) ppm; HRMS (ESI-orbitrap): calcd for $C_{21}H_{29}N_3O_4S$: 420.1951, found 420.1943 $[M+H]^+$.

(1-ethyl-3-isobutyl-1H-pyrazol-5-yl)((3S*,4aR*,8aR*)-3-((5-methylisoxazol-3-yl)methoxy)octahydro-1H-pyrano[3,4-b]pyridin-1-yl)methanone (167m)



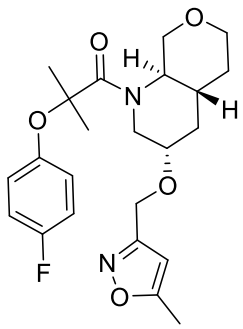
Following LP1: **123a** (25 mg, 0.1 mmol) and 1-ethyl-3-isobutyl-1H-pyrazole-5-carboxylic acid (39 mg, 0.2 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **167m** as a white solid (30.1 mg, 70%, purity: 99.0%); Rt(UPLC): 1.51 min; IR (neat): *v* (max) cm^{-1} 2952, 2870, 1628, 1446, 1006, 1084, 797, 756; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.06 (s, 1H), 5.86 (s, 1H), 4.43 (dd, *J* = 10.6, 4.0 Hz, 1H), 4.35 (s, 2H), 4.26–4.11 (m, 2H), 3.98 (dd, *J* = 11.6, 4.4 Hz, 1H), 3.74–3.67 (m, 1H), 3.67–3.59 (m, 2H), 3.57–3.50 (m, 1H), 3.45–3.33 (stack, 2H), 2.46 (d, *J* = 7.1, 2H), 2.38 (s, 3H), 2.16 (ddd, *J* = 13.7, 7.6, 3.8, 1H), 1.94–1.85 (m, 1H), 1.85–1.75 (stack, 2H), 1.75–1.67 (m, 1H), 1.60–1.50 (m, 1H), 1.36 (t, *J* = 7.2, 3H), 1.25 (td, *J* = 13.2, 5.9, 1H), 0.90 (d, *J* = 6.6 Hz, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.9 (C), 164.1 (C), 161.1 (C), 150.7 (C), 135.7 (C), 105.7 (CH), 100.8 (CH), 73.3 (CH), 68.9 (CH_2), 67.9 (CH_2), 61.4 (CH_2), 58.5 (CH), 48.2 (CH_2), 45.5 (CH_2), 37.3 (CH_2), 35.1 (CH), 34.8 (CH_2), 32.7 (CH_2), 29.0 (CH), 22.4 ($2CH_3$), 15.9 (CH_3), 12.2 (CH_3) ppm; HRMS (ESI-orbitrap): calcd for $C_{23}H_{35}N_4O_4$: 431.2653, found 431.2643 $[M+H]^+$.

(6-fluoropyridin-2-yl)((3S*,4aR*,8aR*)-3-((5-methylisoxazol-3-yl)methoxy)octahydro-1H-pyrano[3,4-b]pyridin-1-yl)methanone (167s)



Following LP1: **123a** (25 mg, 0.1 mmol) and 6-Fluoropicolinic acid (28 mg, 0.2 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **167s** as a off-white solid (9.6 mg, 26%, purity: 97.5%); Rt(UPLC): 1.19 min; IR (neat): *v* (max) cm^{-1} 2922, 2847, 1636, 1599, 1427, 1259, 1077, 991, 812, 764; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (q, *J* = 7.8, 1H), 7.51 (dd, *J* = 7.5, 2.1, 1H), 7.01 (dd, *J* = 8.2, 2.7, 1H), 5.92 (s, 1H), 4.52 (s, 1H), 4.36 (d, J_{AB} = 12.7, 1H), 4.32 (d, J_{AB} = 12.7, 1H), 3.96 (dd, *J* = 11.6, 4.6 Hz, 1H), 3.79–3.73 (m, 1H), 3.69–3.64 (m, 1H), 3.63–3.57 (m, 1H), 3.56–3.50 (m, 1H), 3.43 (td, *J* = 11.9, 2.4, 2H), 2.39 (s, 3H), 2.20 (ddd, *J* = 13.4, 7.1, 3.9, 1H), 1.84 (qt, *J* = 11.4, 3.8, 1H), 1.73–1.68 (m, 2H), 1.61–1.48 (m, 1H), 1.28 (td, *J* = 13.1, 7.1, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.9 (C), 167.9 (C), 163.1 and 160.6 (d, *J* = 245, CF), 161.4 (C), 152.9 (d, *J* = 12.5, CH), 142.3 (d, *J* = 8.0, CH), 121.4 (CH), 111.0 (d, *J* = 36.0, CH), 100.9 (CH), 73.7 (CH), 69.2 (CH_2), 67.9 (CH_2), 61.7 (CH_2), 59.9 (CH), 35.84 (CH), 35.75 (CH_2), 32.9 (CH_2), 12.3 (CH_3) ppm; *one quaternary carbon is not observed in ^{13}C NMR spectra*; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -66.85 (d, *J* = 7.4) ppm. HRMS (ESI-orbitrap): calcd for $C_{19}H_{23}FN_3O_4$: 376.1667, found 376.1656 $[M+H]^+$.

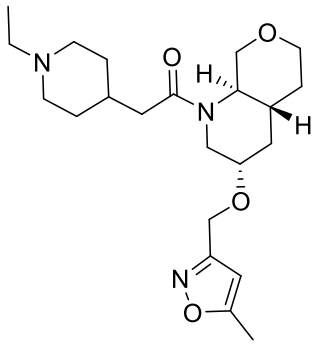
2-(4-fluorophenoxy)-2-methyl-1-((3S*,4aR*,8aR*)-3-((5-methylisoxazol-3-yl)methoxy)octahydro-1H-pyrano[3,4-b]pyridin-1-yl)propan-1-one (167q)



Following LP1: **123a** (25 mg, 0.1 mmol) and 2-(4-fluorophenoxy)-2-methylpropanoic acid (40 mg, 0.2 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **167q** as a white solid (9.2 mg, 21%, purity: 100%); Rt(UPLC): 1.64 min; IR (neat): *v* (max) cm^{-1} 2930, 2848, 1634, 1500, 1410; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.95–6.87 (m, 2H), 6.78–6.71 (m, 2H), 5.91 (s, 1H), 4.48–4.43 (stack, 2H including: 4.47, dd, *J* = 10.5, 3.8, 1H and 4.44,

d, J_{AB}= 12.7, 1H), 4.40 (d, J_{AB} = 12.7, 1H), 4.06 (dd, *J* = 14.5, 3.9, 1H), 3.94 (dd, *J* = 11.1, 4.3, 1H), 3.65 (dd, *J* = 14.5, 4.0, 1H), 3.60–3.54 (m, 1H), 3.51 (td, *J* = 10.2, 3.8, 1H), 3.36 (td, *J* = 11.6, 2.4, 1H), 3.27 (app. t, *J* = 10.2, 1H), 2.41 (s, 3H), 2.08 (ddd, *J* = 13.0, 7.7, 2.9, 1H), 1.65 (s, 3H), 1.64–1.56 (stack, 7H, including: 1.58, s, 3H), 1.54–1.47 (m, 1H), 1.18 (td, *J* = 12.6, 7.5, 1H) ppm; ^{3}C NMR (101 MHz, $CDCl_3$) δ 173.5 (C), 169.9 (C), 161.4 (C), 158.9 (C), 151.2 (C), 118.7 (d, *J* = 7.9, 2CH), 115.6 (d, = 23.4, 2CH), 100.9 (CH), 81.6 (C), 74.1(CH), 68.3 (CH_2), 68.0 (CH_2), 61.6 (CH_2), 60.6 (CH), 46.7 (CH_2), 35.2 (CH_2), 33.0 (CH_2), 27.4 (CH), 25.5 ($2CH_3$), 12.3 (CH_3) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -122.54 (m) ppm; HRMS (ESI-orbitrap): calcd for $C_{23}H_{30}FN_2O_5$: 433.2133, found 433.2127 $[M+H]^+$.

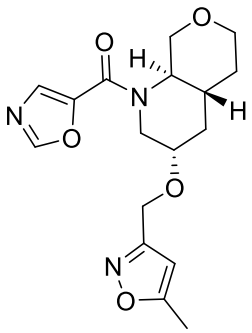
2-(1-ethylpiperidin-4-yl)-1-((3S*,4aR*,8aR*)-3-((5-methylisoxazol-3-yl)methoxy)octahydro-1H-pyrano[3,4-b]pyridin-1-yl)ethan-1-one (167i)



Following LP1: **123a** (25 mg, 0.1 mmol) and (1-Ethyl-piperidin-4-yl)-acetic acid (34 mg, 0.2 mmol, 0.2 eq). Purification by prep-LCMS yielded compound **167i** as a white solid (24.1 mg, 59%, purity: 100%); Rt(UPLC): 1.09 min; IR (neat): *v* (max) cm^{-1} 2922, 2847, 2769, 1632, 1423, 1088, 764; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.00 (s, 1H), 4.52 (s, 2H), 4.28 (b. s, 1H), 3.96 (dd, *J* = 11.4, 4.4, 1H), 3.72 (b. s, 1H), 3.47–3.34 (m, 4H), 2.91 (ddd, *J* = 10.9, 5.3, 3.1, 2H), 2.42 (s, 3H), 2.38 (q, *J* = 7.2, 2H), 2.22 (d, *J* = 6.8, 2H), 2.15 (ddd, *J* = 13.4, 7.9, 3.3, 1H), 1.99 (b. s., 2H), 1.93–1.85 (m, 2H), 1.75–1.72 (m, 2H), 1.71–1.61 (m, 2H), 1.49 (dtd, *J* = 13.5, 11.9, 4.6, 1H), 1.37–1.23 (m, 2H), 1.19 (dt, *J* = 13.1, 6.6, 1H), 1.07 (t, *J* = 7.2, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ =172.6 (C), 169.9 (C), 161.4 (C), 101.1 (CH), 74.1 (CH), 68.0 (CH_2), 61.5 (CH_2), 59.5 (CH), 53.4 ($2CH_2$), 52.6 (CH_2), 40.4 (CH_2), 35.7 (CH), 35.1 (CH_2), 32.8 (CH), 32.5 ($2CH_2$), 32.2 (CH_2), 12.3 (CH_3),

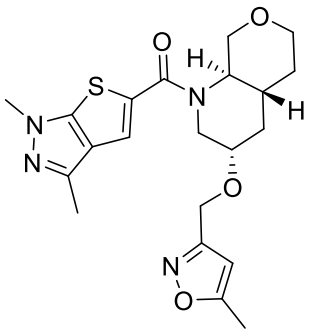
12.2 (CH_3) ppm; *two secondary carbons are not observed in ^{13}C NMR spectra*; HRMS (ESI-orbitrap): calcd for $C_{22}H_{36}N_3O_4$: 406.2700, found 406.2692 $[M+H]^+$.

((3S*,4aR*,8aR*)-3-((5-methylisoxazol-3-yl)methoxy)octahydro-1H-pyrano[3,4-b]pyridin-1-yl)(oxazol-5-yl)methanone (167r)



Following LP1: **123a** (0.1 mmol) and 5-oxazolecarboxylic acid (23.0 mg, 0.2 mmol, 0.2 eq). Purification by prep-LCMS yielded compound **167r** as a colourless oil (23.0 mg, 66%, purity: 99.6%); Rt(UPLC): 0.99 min; IR (neat): *v* (max) cm^{-1} 2922, 2851, 1625, 1420, 1080; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.94 (s, 1H), 7.58 (s, 1H), 5.92 (s, 1H), 4.48 (d, J_{AB} = 12.7, 1H), 4.45–4.39 (stack, 2H, including: 4.43, d, J_{AB} = 12.7, 1H and 4.41, dd, *J* = 10.8, 4.2, 1H), 3.97 (dd, *J* = 11.6, 4.5, 1H), 3.88–3.78 (m, 2H), 3.79–3.75 (m, 2H), 3.67–3.58 (stack, 2H, including: 3.66, dd, *J* = 14.0, 3.2, 1H and 3.6 , td, *J* = 10.8, 3.9, 1H), 3.47–3.36 (m, 2H), 2.39 (s, 3H), 2.20 (ddd, *J* = 13.5, 7.4, 3.7, 1H), 1.86–1.72 (m, 1H), 1.74–1.67 (m, 2H), 1.58–1.48 (m, 1H), 1.28 (td, *J* = 13.1, 6.3, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.9 (C), 161.1 (C), 159.3 (C), 151.4 (C), 145.4 (C), 131.5 (CH), 100.8 (CH), 73.5 (CH), 69.0 (CH), 67.9 (CH), 61.6 (CH), 59.4 (CH), 47.1 (CH_2), 35.5 (CH), 35.0 (CH_2), 32.7 (CH_2), 12.2 (CH_3) ppm; HRMS (ESI-orbitrap): calcd for $C_{17}H_{21}N_3O_5$: 348.1554, found 348.1546 $[M+H]^+$.

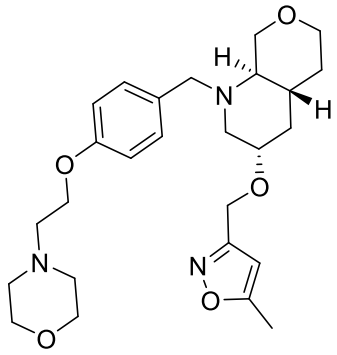
(1,3-dimethyl-1H-thieno[2,3-c]pyrazol-5-yl)((3S*,4aR*,8aR*)-3-((5-methylisoxazol-3-yl)methoxy)octahydro-1H-pyrano[3,4-b]pyridin-1-yl)methanone (167l)



Following LP1: **123a** (0.1 mmol) and 1,3-dimethyl-1H-thieno[2,3-c]pyrazole-5-carboxylic acid (39.0 mg, 0.2 mmol, 0.2 eq). Purification by prep-LCMS yielded compound **167l** as a white solid (34.0 mg, 79%, purity: 99.7%); Rt(UPLC): 1.21 min; IR (neat): *v* (max) cm^{-1} 2918, 2847, 1595, 1535, 1397, 1080; ^1H NMR (400 MHz,

$CDCl_3$): δ = 7.20 (s, 1H), 5.93 (s, 1H), 4.45 (dd, *J* = 10.7, 4.0, 1H), 4.40 (d, J_{AB} = 12.6, 1H), 4.36 (d, J_{AB} = 12.7, 1H), 3.95 (dd, *J* = 11.6, 4.0, 1H), 3.94–3.77 (stack, 5H, including 3.87, s, 3H), 3.78–3.69 (m, 1H), 3.56 (ddd, *J* = 11.4, 10.0, 4.0, 1H), 3.45–3.34 (m, 2H), 2.41 (s, 3H), 2.32 (s, 3H), 2.18 (ddd, *J* = 13.7, 7.5, 4.2, 1H), 1.86–1.75 (m, 1H), 1.74–1.64 (m, 1H), 1.58–1.43 (m, 1H), 1.27 (td, *J* = 13.1, 6.1, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.7 (C), 166.2 (C), 161.2 (C), 145.7 (C), 141.4 (C), 134.6 (C), 128.3 (C), 119.1 (CH), 100.8 (CH), 73.5 (CH), 68.9 (CH_2), 67.8 (CH_2), 61.5 (CH_2), 58.7 (CH), 49.2 (CH_2), 37.8 (CH_3), 35.3 (CH_2), 35.1 (CH), 32.7 (CH_2), 12.8 (CH_3), 12.0 (CH_3) ppm; HRMS (ESI-orbitrap): calcd for $C_{21}H_{26}N_4O_4S$: 431.1746, found 431.1741 $[M+H]^+$.

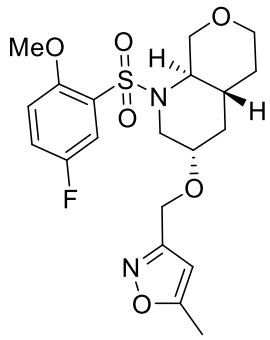
(3S*,4aR*,8aR*)-3-((5-methylisoxazol-3-yl)methoxy)-1-(4-(2-morpholinoethoxy)benzyl)octahydro-1H-pyrano[3,4-b]pyridine (168d)



Following LP2: **123a** (25 mg, 0.1 mmol) and 4-[2-morpholin-4-yl)ethoxy]benzaldehyde (47.0 mg, 0.2 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **168d** as a colourless oil (23.7 mg, 50%, purity: 99.3%). Rt(UPLC): 1.31 min; IR (neat): *v* (max) cm^{-1} 2922, 2847, 2799, 1509, 1241; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14 ($d_{AA'XX'}$, *J* = 8.4, 2H), 6.83 ($d_{AA'XX'}$, *J* = 8.6 , 2H), 5.95 (s, 1H), 4.50 (d, J_{AB} = 12.4, 1H), 4.46 (d, J_{AB} = 12.5, 1H), 4.32 (dd, *J* = 10.8, 4.0, 1H), 4.09 (t, *J* 5.7, 2H, 3.93–3.90 (m, 1H), 3.79 (d, J_{AB} = 13.4, 1H), 3.73 (t, *J* = 4.7, 4H), 3.52–3.40 (m, 1H), 3.41–3.30 (m, 1H), 3.18 (d, J_{AB} = 13.4, 1H), 3.14–3.02 (m, 2H), 3.07–2.98 (m, 1H), 2.79 (t, *J* = 5.7, 2H), 2.58 (t, *J* = 4.7, 4H), 2.38 (s, 3H), 2.05–2.00 (m, 1H), 1.95 (dt, *J* = 9.7, 4.8, 1H), 1.84 (app. t, *J* = 10.4, 1H), 1.58–1.37 (stack, 3H), 1.03 (app. q, *J* = 11.6, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.8 (C), 162.0 (C), 157.9 (C), 130.4 (C), 130.2 (2CH), 114.5 (2CH), 101.1 (CH), 74.5 (CH), 70.8 (CH_2), 68.2 (CH_2), 67.1 ($2CH_2$), 65.9 (CH_2), 63.7 (CH), 61.9 (CH_2), 57.9 (CH_2), 57.7

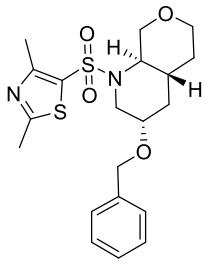
(CH_2), 56.9 (CH_2), 54.3 ($2CH_2$), 38.6 (CH), 37.5 (CH_2), 32.4 (CH_2), 12.4 (CH_3) ppm; HRMS (ESI-orbitrap): calcd for $C_{26}H_{37}N_3O_5$: 472.2806, found 472.2798 $[M+H]^+$.

(3S*,4aR*,8aR*)-1-((5-fluoro-2-methoxyphenyl)sulfonyl)-3-((5-methylisoxazol-3-yl)methoxy)octahydro-1H-pyrano[3,4-b]pyridine (169d)

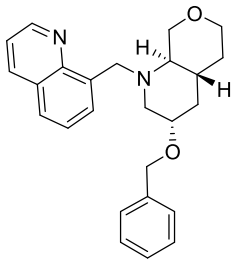


Following LP3: **123a** (25 mg, 0.1 mmol) and 5-fluoro-2methoxybenzenesulfonlyl chloride (45.0 mg, 0.2 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **169d** as a white solid (23.1 mg, 53%, purity: 91.2%). Rt(UPLC): 1.55 min; IR (neat): *v* (max) cm^{-1} 2937, 2870, 1610, 1483, 1326, 1256, 1148; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.61 (dd, 8.0, 3.1, 1H), 7.21 (ddd, *J* = 9.1, 7.4, 3.2, 1H), 6.94 (dd, *J* = 9.1, 4.0, 1H), 6.02 (s, 1H), 4.59 (s, 2H), 4.28–4.19 (m, 2H), 3.19 (s, 3H), 3.86 (dd, *J* = 11.4, 4.7, 1H), 3.65–3.53 (stack, 2H, including 3.56, dd, *J* = 11.4, 10.1, 1H), 3.35 (td, *J* = 12.1, 2.4, 1H), 2.76, (td, *J* = 10.1, 4.0, 1H), 2.62 (dd, *J* = 12.4, 10.0, 1H), 2.42 (s, 3H), 2.22–2.11 (m,1H), 1.75–1.58 (stack, 3H), 1.49–1.38 (m, 1H), 1.12 (td, *J* = 12.4, 10.6, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.9 (C), 157.0 (C), 154.6 (C), 152.9 (C), 152.9 (C), 129.5 (d, *J* = 6.9, C), 120.9 (d, *J* = 23.3, CH), 117.8 (d, *J* = 26.2, CH), 113.4 (d, *J* = 7.4, CH), 100.9 (CH), 73.6 (CH), 69.7 (CH_2), 67.6 (CH_2), 62.0 (CH_2), 61.3 (CH), 56.5 (CH), 52.7 (CH_2), 38.7 (CH_3), 37.7 (CH_2), 32.9 (CH_2), 12.2 (CH_3) ppm; HRMS (ESI-orbitrap): calcd for $C_{20}H_{25}FN_2O_6S$: 441.1490, found 441.1481 $[M+H]^+$.

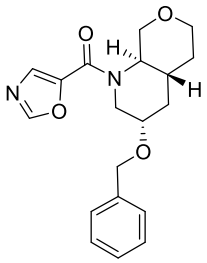
Other molecules:



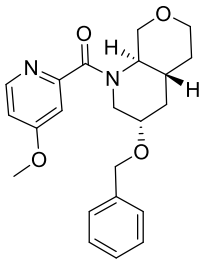
169c
LP3
8 mg, 19%
p: 87.1%
Rt= 1.69 min



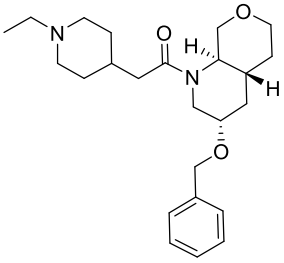
171a
LP4
23.3 mg, 60%
p: 97.4%
Rt= 1.92 min



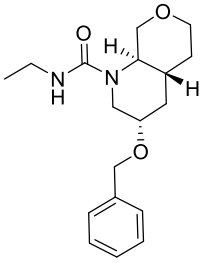
167o
LP1
22.1 mg, 65%
p: 100%
Rt= 1.27 min



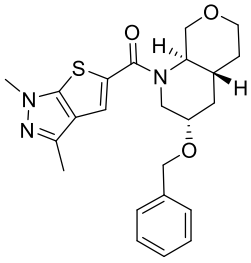
167p
LP2
24.4 mg, 64%
p: 100%
Rt= 1.36 min



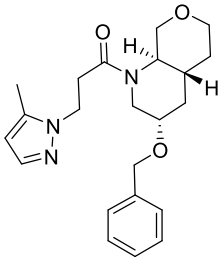
167b
LP1
21.7 mg, 54%
p: 100%
Rt= 1.34 min



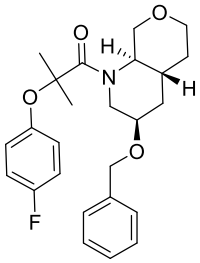
170a
LP3
3.8 mg, 12%
p: 100%
Rt= 1.28 min



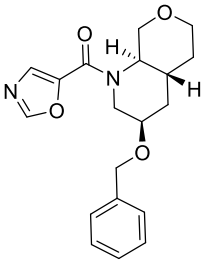
167f
LP2
2.8 mg, 7%
p: 100%
Rt= 1.49 min



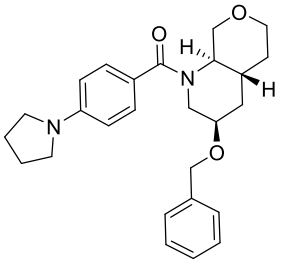
167c
LP2
6.5 mg, 17%
p: 95.88%
Rt= 1.38 min



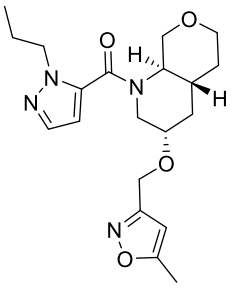
167t
LP2
14.4 mg, 34%
p: 100%
Rt= 1.91 min



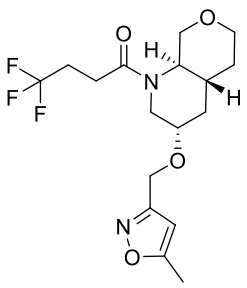
167u
LP2
14.4 mg, 42%
p: 99.6%
Rt= 1.30 min



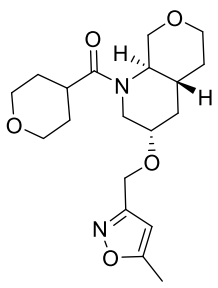
167v
LP2
21.4 mg, 51%
p: 91.0%
Rt= 1.87 min



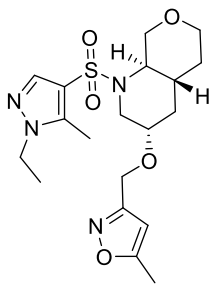
167j
LP2
22.5 mg, 58%
p: 99.19%
Rt= 1.22 min



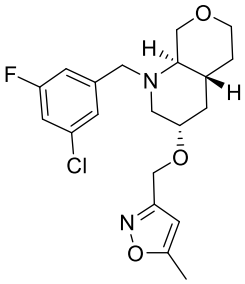
167k
LP2
5.8 mg, 15%
p: 94.8%
Rt= 1.34 min



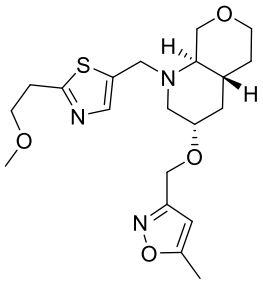
167h
LP2
26.5 mg, 73%
p: 100%
Rt= 1.06 min



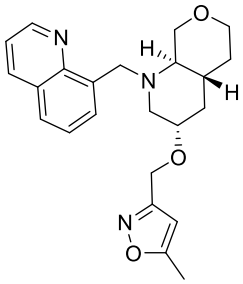
169e
LP3
3.4 mg, 8%
p: 100%
Rt= 1.34 min



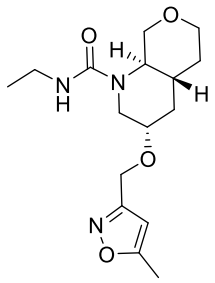
171c
LP4
5.8 mg, 15%
p: 100%
Rt= 1.82 min



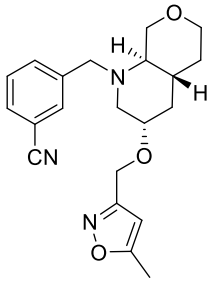
168c
LP1
9.3 mg, 23%
p: 100%
Rt= 1.18 min



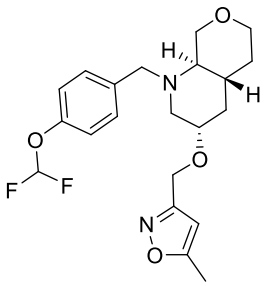
171b
LP4
3.9 mg, 10%
p: 100%
Rt= 1.52 min



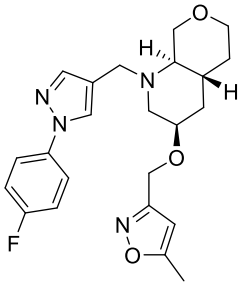
170b
LP3
15.5 mg, 48%
p: 95.75%
Rt = 1.00 min



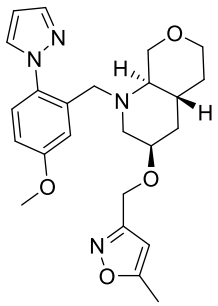
168i
LP1
9 mg, 24%
p: 100%
Rt= 1.49 min



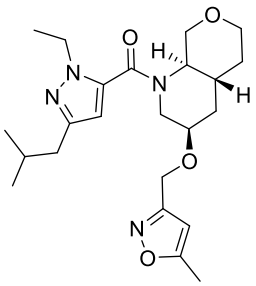
168h
LP1
6.1 mg, 15%
p: 100%
Rt= 1.65 min



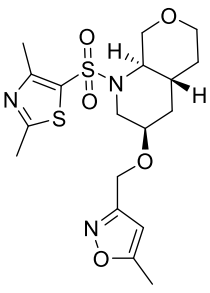
168j
LP1
2.5 mg, 6%
p: 100%
Rt= 1.52 min



168k
LP1
7.5 mg, 17%
p: 100%
Rt= 1.52 min



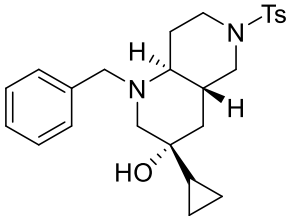
167w
LP2
15.6 mg, 36%
p: 100%
Rt= 1.55 min



169f
LP3
7.9 mg, 18%
p: 100%
Rt= 1.38 min

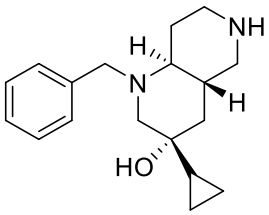
6.7.3. MC00994 Library

(3R*,4aS*,8aS*)-1-benzyl-3-cyclopropyl-6-tosyldecahydro-1,6-naphthyridin-3-ol (111a)



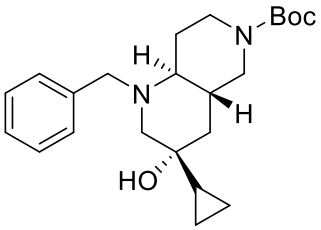
Benzhaldeyde (0.76 mL, 7.4 mmol, 2.0 eq), glacial acetic acid (0.85 mL, 14.8 mmol, 4.0 eq) and aminoalcohol **110a** (1.3 g, 3.7 mmol) were dissolved in CH_2Cl_2 (37 mL) and the reaction mixture was stirred at room temperature for 3 h. After this time, $NaBH(OAc)_3$ (2.4 g, 11.3 mmol, 3.0 eq) was added and the reaction mixture was allowed to stir at room temperature for 24 h before being quenched by addition of a 0.7 M solution of NH_3 in MeOH (5 mL). The reaction mixture was filtered through a short pad of celite with CH_2Cl_2 (40 mL). The volatiles were removed under reduced pressure and the crude material was subjected to silica gel column chromatography (Heptane : EtOAc, 50% to 100%) to afford aminoalcohol **111a** as a white solid (1.41 g, 86%); IR (neat): *v* (max) cm^{-1} 3533, 2918, 2803, 1350, 1155, 752, 700; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.65 (dd, *J* = 8.3, 1.9, 2H), 7.34 (dd, *J* = 8.3, 1.9, 2H), 7.30–7.19 (m, 5H), 4.03 (app. d, *J* = 13.6, 1H), 3.91–3.86 (m, 1H), 3.67–3.64 (m, 1H), 3.04 (app. dd, *J* = 13.6, 1.8, 1H), 2.66–2.62 (m, 1H), 2.44 (s, 3H), 2.33–2.24 (m, 1H), 2.17–2.13 (m, 1H), 2.02–1.91 (m, 2H), 1.84 (dd, *J* = 10.8, 1.8, 1H), 1.75 –1.70 (m, 1H), 1.69–1.51 (m, 3H), 1.47–1.39 (m, 1H), 1.07 (td, *J* = 12.1, 1.7 Hz, 1H), 0.45–0.19 (m, 4H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.6 (C), 138.9 (C), 132.9 (C), 129.7 (2CH), 128.5 (2CH), 128.2 (2CH), 127.7 (2CH), 126.9 (CH), 68.1 (C), 64.8 (CH), 63.5 (CH_2), 56.8 (CH_2), 50.8 (CH_2), 45.7 (CH_2), 41.9 (CH_2), 38.0 (CH), 29.5 (CH_2), 21.6 (CH_3), 17.7 (CH), 1.1 ($2CH_2$) ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_{25}H_{32}N_2O_3S$: 441.2206, found 441.2198 $[M+H]^+$.

(3R*,4aS*,8aS*)-1-benzyl-3-cyclopropyldecahydro-1,6-naphthyridin-3-ol (114a)



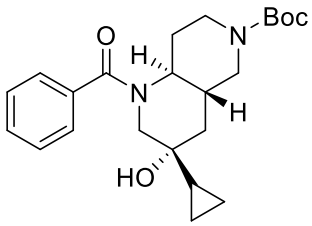
Aminoalcohol **111a** (1.1 g, 2.50 mmol) was dissolved in THF (42.0 mL, 0.06 M), the mixture was cooled to 0 °C before Red-Al (7.1 mL, 25.0 mmol, 3.5 M in toluene) was added dropwise over 5 minutes. The reaction mixture was heated to 65 °C and stirred for 24 h. After this time the reaction was allowed to cool down to room temperature and further cooled to 0 °C before being quenched with the dropwise addition of 20% $NaOH_{aq}$ (5 mL). After gas evolution stopped, the mixture was diluted with EtOAc (20 mL) and water (15 mL). The phases were separated, and the aqueous phase was further extracted with EtOAc (3 x 30 mL). The combined organic phases were washed with brine (50 mL) and dried over Na_2SO_4. After filtration and removal of the solvent under reduced pressure aminoalcohol **114a** was obtained as a white solid, that was taken into the next step without further purification (0.66 g, 93%); IR (neat): *v* (max) cm^{-1} 3233, 2922, 2814, 2407, 2322, 1446, 1066, 756, 704; ^1H NMR (400 MHz, MeOD): δ = 7.14–7.04 (m, 4H), 7.03–6.97 (m, 1H), 3.95 (d, *J* = 13.4, 1H), 2.95–2.81 (m, 1H), 2.83 (d, *J* = 13.4, 1H), 2.67–2.63 (m, 1H), 2.52 (dd, *J* = 10.7, 2.3, 1H), 2.44 (td, *J* = 12.9, 2.8, 1H), 2.13–2..07 (m, 1H), 2.00–1.95 (m, 1H), 1.69–1.61 (m, 2H), 1.61–1.50 (m, 1H), 1.49–1.45 (m, 1H), 1.33–1.26 (m, 1H), 1.21–1.08 (m, 1H), 0.92 (t, *J* = 12.2, 1H), 0.20–0.14 (m, 1H), 0.08–0.01 (m, 4H) ppm; ^{13}C NMR (101 MHz, MeOD): δ = 141.9 (C), 130.91 (2CH), 130.1 (2CH), 128.8 (CH), 69.7 (C), 68.4 (CH), 65.8 (CH_2), 58.6 (CH_2), 53.5 (CH_2), 50.9 (CH_2), 47.6 (CH_2), 44.4 (CH_2), 41.6 (CH_2), 32.7 (CH), 19.5 (CH), 2.2 (CH_2), ppm; HRMS (ESI-orbitrap): m/z: calcd for $C_{18}H_{26}N_2O$: 287.2118, found 287.2113 $[M+H]^+$.

tert-butyl (3R*,4aS*,8aS*)-1-benzyl-3-cyclopropyl-3-hydroxyoctahydro-1,6-naphthyridine-6(2H)-carboxylate (111b)



Aminoalcohol **110b** (450 mg, 1.3 mmol) was added to a stirring solution of benzhaldeyde (0.27 mL, 2.7 mmol, 2.0 eq) and glacial acetic acid (0.16 mL, 2.7 mmol, 2.0 eq) in CH_2Cl_2 (14 mL, 0.1 M) and the reaction mixture was stirred at room temperature for 3 h. After this time, $NaBH(OAc)_3$ (840 mg, 4.05 mmol, 3.0 eq) was added and the reaction mixture was allowed to stir at room temperature for 24 h before being quenched by addition of a 0.7 M solution of NH_3 in MeOH (5 mL). The reaction mixture was poured into water and the organics were extracted with EtOAc (3 x 25 mL). The volatiles were removed under reduced pressure and the crude material was subjected to silica gel column chromatography (Heptane : EtOAc, 50% to 100%) to afford aminoalcohol **111b** as a white solid (423 mg, 83%); IR (neat): *v* (max) cm^{-1} 3447, 2847, 2974, 2847, 2784, 1666, 1431, 1364, 1267, 1148, 1092, 1021, 700; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.29 (app. d, *J* = 4.3, 4H), 7.25–7.20 (m, 1H), 4.20 (br. s, 1H), 4.11 (d, *J* = 13.6, 1H), 3.09 (d, *J* = 13.6, 1H), 2.76 (br. s, 1H), 2.69 (dd, *J* = 10.6, 2.2, 1H), 2.41 (br. s, 1H), 2.10 (d, *J* = 12.7, 1H), 1.91 (d, *J* = 10.7 Hz, 1H), 1.86 (dd, *J* = 10.8, 3.4, 1H), 1.79–1.73 (m, 2H), 1.47 (stack, 9H + 1H), 1.41–1.28 (m, 1H), 1.15 (app. t, *J* = 12.8, 1H), 0.45–0.20 (m, 4H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.6 (C), 139.3 (C), 128.5 (2CH), 128.1 (2CH), 126.7 (CH), 79.6 (C), 68.0 (CH), 65.8 (CH_2), 63.6 (CH_2), 56.7 (CH_2), 42.1 (CH_2), 38.4 (CH), 28.4 ($3CH_3$), 17.7 (CH), 1.0 (CH_2), 0.6 (CH_2) ppm; HRMS (ESI-orbitrap): calcd for $C_{23}H_{34}N_2O_3$: 387.2642, found 387.2636 $[M+H]^+$.

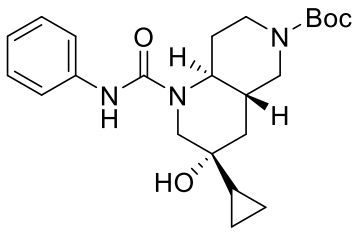
tert-butyl (3R*,4aS*,8aS*)-1-benzoyl-3-cyclopropyl-3-hydroxyoctahydro-1,6-naphthyridine-6(2H)-carboxylate (112)



To an oven dried, argon flushed 3-neck-round bottom flask was added dry THF (25 mL) and cooled to 0 °C. $LiAlH_4$ (2.1 mL, 5.0 mmol, 2.0 eq, 2.4 M in THF) was added and the suspension stirred for 5 minutes. After this time compund **91h** (1.19 g, 2.5 mmol) was added to the suspension and the reaction mixture was stirred for 3 h without removing the ice bath. After this time the reaction was quenched with the dropwise addition in the subsequent order of water (0.19 mL), 20% $NaOH_{aq}$ (0.19 mL) and water (0.10 mL). The cooling bath was removed and the mixture was stirred at room temperature for 10 minutes, before Na_2SO_4 (1.0 g) was added. The resulting mixture was left stirring for an additional 20 minutes. After which time the mixture was filtered through celite and the filter was rinsed with $CHCl_3$:IPA [3:1] (3 x 50 mL) and $CHCl_3$ (3 x 30 mL). Volatiles were removed under reduced pressure and the crude material was dissolved in CH_2Cl_2 (12 mL, 0.2 M wrt. Of the initial polycycle) and cooled to 0 °C. Et_3N (0.69 mL, 5.0 mmol, 2.0 eq) and benzoyl chloride (0.58 mL, 5.0 mmol, 2.0 eq) were added and the reaction mixture was stirred for 2 h before being poured into sat. $NaHCO_{3(aq)}$ (20 mL). The organics were extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were washed with brine (15 mL) and dired over Na_2SO_4. After filtration and removal of the solvent, the crude material was subjected to silica gel flash column chromatography [Heptane: EtOAc 0 % to 80%] affording compound **112** as a white foam (0.72 g, 72%); mp: 162–164 °C; IR (neat): *v* (max) cm^{-1} 3414, 2929, 2978, 28621692, 1610, 1438, 1408, 1166, 1092, 782; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.47–7.40 (m, 2H), 7.39–7.33 (m, 3H), 4.26–3.98 (m, 2H), 3.67 (td, *J* = 11.2, 3.4, 1H), 3.43 (d, *J* = 14.1, 1H), 3.27 (d, *J* = 14.0, 1H), 2.83 (s, 1H), 2.39–2.32 (m, 2H), 2.07–1.90 (m, 1H), 1.74 (dd, *J* = 13.7, 4.0, 1H), 1.69–1.58 (m, 1H), 1.45 (s, 10H), 1.42–1.35 (m, 1H), 1.08 (t, *J* = 13.4, 1H), 0.78 (ddd, *J* = 13.6,

8.2, 5.5, 1H), 0.37–0.17 (m, 4H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.8 (C), 154.7 (C), 136.9 (C), 129.6 (CH), 128.4 (2CH), 127.6 (2CH), 79.9 (C), 71.5 (C), 58.3 (CH_2), 54.00 (C), 48.4 (CH_2), 43.5 (CH_2), 38.7 (CH2), 36.1 (CH_2), 29.8 (CH_2), 28.4 ($3CH_3$), 19.2 (CH), -0.1 ($2CH_2$) ppm; HRMS (ESI-orbitrap): calcd for $C_{23}H_{32}N_2O_4$: 401.2435, found 401.2426 $[M+H]^+$.

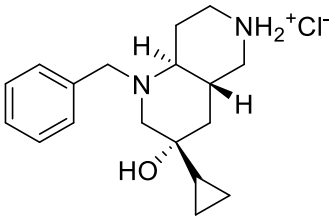
tert-butyl(3R*,4aS*,8aS*)-3-cyclopropyl-3-hydroxy-1-(phenylcarbamoyl)octahydro-1,6-naphthyridine-6(2H)-carboxylate (113)



To an oven dried, argon flushed 3-neck-round bottom flask was added dry THF (12 mL) and cooled to 0 °C. $LiAlH_4$ (1.0 mL, 2.4 mmol, 2.0 eq, 2.4 M in THF) was added and the suspension stirred for 5 minutes. After this time compund **91h** (0.57 g, 1.2 mmol) was added to the suspension and the reaction mixture was stirred for 3 h without removing the ice bath. After this time reaction was quenched with the dropwise addition in the subsequent order of water (0.1 mL), 20% $NaOH_{aq}$ (0.1 mL) and water (0.1 mL). The cooling bath was removed and the mixture was stirred at room temperature for 10 minutes, before Na_2SO_4 (0.5 g) was added. The resulting mixture was left stirring for an additional 20 minutes. After which time the mixture was filtered through celite and the filter was rinsed with $CHCl_3$:IPA [3:1] (2 x 30 mL) and $CHCl_3$ (2 x 30 mL). Volatiles were removed under reduced pressure and the crude material was dissolved in CH_2Cl_2 (6.0 mL, 0.2 M wrt. of the initial polycycle) and cooled to 0 °C. Et_3N (0.42 mL, 3.0 mmol, 2.5 eq) and phenyl isocianate (0.33 mL, 3.0 mmol, 2.5 eq) were added and the reaction mixture was stirred for 2 h before being poured into sat. $NaHCO_{3(aq)}$ (20 mL). The organics were extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were washed with brine (15 mL) and dired over Na_2SO_4. After filtration and removal of the solvent, the crude material was subjected to silica gel flash column chromatography [Heptane: EtOAc 0 % to 80%] affording compound **113** as a white

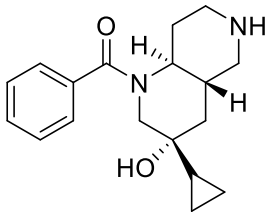
foam (0.28 g, 55 %); IR (neat): *v* (max) cm^{-1} 3339 (br.), 2974, 2922, 2855, 1640, 1528, 1438, 1155; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.23 (m, 4H), 7.03–7.00 (m, 1H), 4.15 (br. s, 2H), 3.55–3.51 (m, 1H), 3.35 (td, *J* = 11.3, 3.3, 1H), 3.15 (app. d, *J* = 15.0, 1H), 2.84 (br. s, 1H), 2.57 (br. s, OH), 2.35 (br. s, 1H), 2.25–2.20 (m, 1H), 1.74 (dd, *J* = 13.5, 3.2, 1H), 1.65–1.50 (m, 1H), 1.48 (s, 9H), 1.30 (app. t, *J* = 15.9, 1H), 0.95–0.87 (stack, 2H), 0.47–0.35 (m, 4H) ppm; *NH was not observed;* ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.1 (C), 154.6 (C), 139.2 (C), 128.7 (2CH), 122.7 (CH), 119.8 (2CH), 79.8 (C), 72.7 (C), 59.9 (CH), 51.1 (CH_2), 38.7 (CH_2), 37.2 (CH), 31.8 (CH_2), 30.9 (CH_2), 28.3 ($3CH_3$), 22.6 (CH_2), 18.7 (CH), 0.01 ($2CH_2$) ppm; HRMS (ESI-orbitrap): calcd for $C_{23}H_{33}N_3O_4$: 416.2544, found 416.2535 $[M+H]^+$.

(3R*,4aS*,8aS*)-1-benzyl-3-cyclopropyl-3-hydroxydecahydro-1,6-naphthyridin-6-ium chloride (114·HCl)



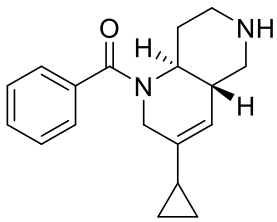
HCl (1.29 mL, 5.17 mmol, 4 M in dioxane) was added to a solution of carbamate **111b** (400 mg, 1.03 mmol) in MeOH (5.1 mL, 0.2 M). The reaction mixture was stirred at room temperature for 24 h. After this time the volatiles were removed under reduced pressure and the compound was taken into the next step without further purification; IR (neat): *v* (max) cm^{-1} 3336 (br.), 2929, 2728, 2661, 1591, 1397, 700; ^{1}H NMR (400 MHz, MeOD): δ = 8.30–8.13 (m, 2H), 8.13–7.94 (m, 3H), 5.35 (s, 2H), 4.85–4.68 (m, 1H), 4.20 (app. q, J = 13.4, 1H), 4.11–3.96 (m, 2H), 3.91–3.66 (m, 2H), 3.65–3.25 (m, 4H), 3.22–2.96 (m, 2H), 2.53–2.35 (m, 1H), 2.21–1.95 (m, 2H), 1.08–0.67 (m, 4H) ppm; ^{13}C NMR (101 MHz, MeOD): δ = 132.6 (2CH), 131.3 (CH), 130.5 (2CH), 130.2 (C), 67.0 (C), 65.5 (CH), 61.1 (CH_2), 58.2 (CH_2), 48.3 (CH_2), 44.1 (CH_2), 40.1 (CH_2), 34.3 (CH), 24.8 (CH_2), 17.6 (CH), 1.40 ($2CH_2$) ppm; HRMS (ESI-orbitrap): calcd for $C_{18}H_{26}N_2O$: 287.2118, found 287.2116 $[M+H]^+$.

((3R*,4aS*,8aS*)-3-cyclopropyl-3-hydroxyoctahydro-1,6-naphthyridin-1(2H) yl)(phenyl)methanone



HCl (1.0 mL, 4.4 mmol, 4 M in dioxane) was added to a solution of carbamate **112** (700 mg, 1.75 mmol) in MeOH (8.7 mL, 0.2 M). The reaction mixture was stirred at room temperature for 24 h. After this time the volatiles were removed under reduced pressure. The crude material was purified via basic reverse phase column chromatography [ammonium carbonate in water(pH 9): acetonitrile (20 % to 70%)] yielding **115** as a white solid; IR (neat): *v* (max) cm^{-1} 3280, 2914, 2840, 1621, 1408, 1121; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.40 (m, 2H), 7.38–7.34 (m, 3H), 3.68 (td, *J* = 12.4, 2.7, 1H), 3.44–3.39 (stack, 2H, including: 3.43, d, J_{AB} = 14.0, 1H and 3.42, s, OH), 3.33 (d, J_{AB} = 14.0, 1H), 3.11–3.06 (m, 1H), 3.01 (dd, *J* = 12.1, 3.2, 1H), 2.76 (td, *J* = 12.4, 2.7, 1H), 2.41–2.28 (m, 2H), 2.00 (br. s, NH), 1.77–1.61 (m, 2H), 1.46 (qd, *J* = 12.2, 4.2, 1H), 1.09 (app. t, *J* = 14.0, 1H), 0.79 (tt, *J* = 8.0, 5.8, 1H), 0.39–0.17 (m, 4H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.7 (C), 137.0 (C), 129.5 (CH), 128.3 (2CH), 127.5 (2CH), 71.9 (C), 58.8 (CH), 54.0 (CH_2), 51.8 (CH_2), 45.9 (CH_2), 38.9 (CH_2), 37.6 (CH_2), 31.2, 19.2 (CH), 0.0 ($2CH_2$) ppm; HRMS (ESI-orbitrap): calcd for $C_{18}H_{24}N_2O_2$: 301.1911, found 301.1904 $[M+H]^+$.

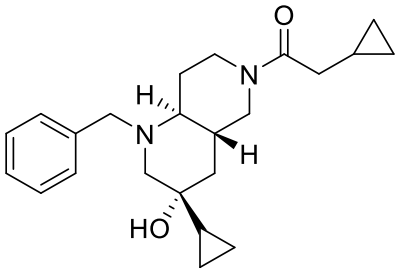
((4aS*,8aS*)-3-cyclopropyl-4a,5,6,7,8,8a-hexahydro-1,6-naphthyridin-1(2H)-yl)(phenyl)methanone (116)



HCl was added to a solution of carbamate **112** in MeOH. The reaction mixture was stirred at 50 °C for 48 h. After this time the volatiles were removed under reduced pressure. The crude material was purified by basic reverse phase column chromatography [ammonium carbonate in water (pH 9): acetonitrile (20 to 70%)] yielding compound **116** as a pale yellow solid. IR (neat):

v (max) cm^{-1} 2918, 2765, 1636, 1323, 1274; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57–7.50 (m, 2H), 7.48–7.35 (m, 3H), 6.30 (d, *J* = 2.3, 1H), 3.46 (td, *J* = 10.7, 3.3, 1H), 3.22–3.13 (m, 2H), 3.09 (app. dq, *J* = 12.7, 2.9, 1H), 2.83 (td, *J* = 12.7, 2.6, 1H), 2.50 (dd, 12.3, 10.9, 1H), 2.12 (br. s, NH), 1.83–1.73 (m, 1H), 1.67 (dd, *J* = 16.0, 4.3, 1H), 1.61–1.53 (m, 1H), 1.33–1.23 (m, 1H), 1.18 (tt, *J* = 8.3, 5.2, 1H), 0.53–0.40 (m, 2H), 0.32–0.18 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.2 (C), 136.3 (C), 130.6 (CH), 128.6 (2CH), 128.5 (2CH), 123.0 (CH), 118.5 (C), 58.02 (CH), 52.1 (CH_2), 45.9 (CH_2), 39.9 (CH), 31.5 (CH_2), 26.8 (CH_2), 15.0 (CH), 3.9 (CH_2), 3.4 (CH_2) ppm; HRMS (ESI-orbitrap): calcd for $C_{18}H_{22}N_2O$: 283.1805, found 283.1799 $[M+H]^+$.

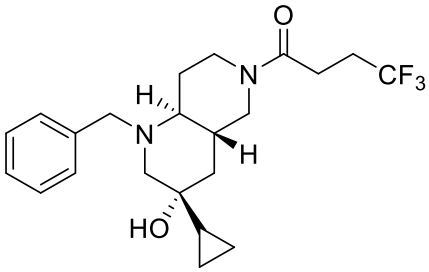
1-((3R*,4aS*,8aS*)-1-benzyl-3-cyclopropyl-3-hydroxyoctahydro-1,6-naphthyridin-6(2H)-yl)-2-cyclopropylethan-1-one (MC217) (172a)



Following LP1: **114a** (25 mg, 0.085 mmol) and cyclopropylacetic acid (18 μL, 0.17 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **172a** as a colourless oil (9.7 mg, 24%, purity: 100%); Rt(UPLC): 1.52 min; IR (neat): *v* (max) cm^{-1} 3399, 3078, 3000, 2918, 2855, 2788, 1617, 1446, 1371, 1010, 738; *NMR spectra display a mixture of rotamers*; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.27 (m, $4H_{maj}$ + $4H_{min}$), 7.25–7.19 (m, $1H_{maj}$ + $1H_{min}$), 4.83–4.76 (m, $1H_{min}$), 4.61–4.54 (m, $1H_{maj}$), 4.11 (app. t, *J* = 13.7, $2H_{maj}$ + $2H_{min}$), 3.98–3.90 (m, $1H_{maj}$), 3.70–3.62 (m, $1H_{min}$), 3.14–3.03 (m, 4H), 2.76 (dd, *J* = 13.3, 11.2, $1H_{min}$), 2.71–2.67 (m, $1H_{maj}$ + $1H_{min}$), 2.57 (td, *J* = 13.3, 2.9, $1H_{min}$), 2.39–2.21 (m, 6H), 2.19–2.13 (m, $2H_{maj}$), 1.99–1.90 (m, 4H), 1.84–1.77 (m, $1H_{maj}$), 1.76–1.68 (m, $1H_{maj}$ + $1H_{min}$), 1.44–1.38 (m, $1H_{maj}$ + $1H_{min}$), 1.37–1.29 (m, $1H_{maj}$), 1.24–1.12 (m, $1H_{maj}$ + $1H_{min}$), 1.09–0.98 (m, $1H_{maj}$ + $1H_{min}$), 0.92–0.87 (m, $1H_{maj}$ + $1H_{min}$), 0.63–0.53 (m, $2H_{maj}$ + $2H_{min}$), 0.46–0.37 (m, $1H_{maj}$ + $1H_{min}$), 0.37–0.21 (m, $3H_{maj}$ + $3H_{min}$), 0.21–0.14 (m,

$2H_{maj}$ + $2H_{min}$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.0 and 171.91 (C), 139.4 and 139.3 (C), 128.7 and 128.6 (CH), 128.3 (2CH), 127.0 (2CH), 68.20 and 68.18 (C), 66.1 and 66.0 (CH), 63.9 and 63.7 (CH_2), 57.1 and 56.8 (CH_2), 50.7 and 46.4 (CH_2), 45.3 and 41.2 (CH_2), 42.23 and 42.16 (CH_2), 39.5 and 38.6 (CH), 38.8 and 38.7 (CH_2), 30.9 and 29.9 (CH_2), 17.96 and 17.87 (CH), 7.5 (CH), 4.7 and 4.4 ($2CH_2$), 1.22 and 1.17 (CH_2), 0.2 and 0.1 (CH_2) ppm; HRMS (ESI-orbitrap): calcd for $C_{23}H_{32}N_2O_2$: 369.2536, found 369.2531 $[M+H]^+$.

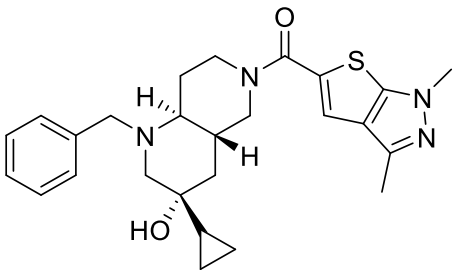
1-((3R*,4aS*,8aS*)-1-benzyl-3-cyclopropyl-3-hydroxyoctahydro-1,6-naphthyridin-6(2H)-yl)-4,4,4-trifluorobutan-1-one (MC241) (172q)



Following LP1: **114a** (25 mg, 0.085 mmol) and 4,4,4-trifluoroacetic acid (26 μL, 0.17 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **172q** as a colourless oil (5 mg, 15%, purity: 100%); Rt(UPLC): 1.65 min; IR (neat): *v* (max) cm^{-1} 3429, 3004, 2922, 2855, 2788, 1628, 1442, 1380, 1133, 1099, 700; *NMR spectra display a mixture of rotamers*; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.26 (m, $4H_{maj}$ + $4H_{min}$), 7.25–7.21 (m, $1H_{maj}$ + $1H_{min}$), 4.76 (app. d, *J* = 13.4, $1H_{min}$), 4.57–4.50 (m, $1H_{maj}$), 4.10 (app. t, *J* = 12.9, $2H_{maj}$ + $2H_{min}$), 3.92 (app. d, *J* = 13.8, $1H_{maj}$), 3.68–3.61 (m, $1H_{min}$), 3.15–3.06 (m, 4H), 2.78 (app. t, *J* = 12.4, $1H_{min}$), 2.73–2.67 (m, $1H_{maj}$ + $1H_{min}$), 2.64–2.55 (m, $2H_{maj}$ + $2H_{min}$), 2.54–2.45 (m, $2H_{maj}$ + $2H_{min}$), 2.29 (app. t, *J* = 12.3, $1H_{maj}$), 2.21–2.15 (m, $1H_{maj}$ + $1H_{min}$), 1.99–1.91 (m, $2H_{maj}$ + $2H_{min}$), 1.84–1.68 (m, $2H_{maj}$ + $2H_{min}$), 1.44–1.38 (m, $1H_{maj}$ + $1H_{min}$), 1.20 (app. q, *J* = 12.6, $1H_{maj}$ + $1H_{min}$), 0.91–0.84 (m, $1H_{maj}$ + $1H_{min}$), 0.47–0.36 (m, $1H_{maj}$ + $1H_{min}$), 0.35–0.20 (m, $3H_{maj}$ + $3H_{min}$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.0 and 167.9 (C), 139.3 and 139.1 (C), 128.7 (CH), 128.6 (CF_3), 128.5 (2CH), 127.0 (2CH), 68.2 (C), 65.7 (CH), 63.9 and 63.7 (CH_2), 57.2 and 56.8 (CH_2), 50.3 and 46.7 (CH_2), 44.9 and 41.5 (CH_2), 42.2 and 42.1 (CH_2), 39.3 and 38.6 (CH), 30.8 (CH_2), 29.9 and 29.8 (CH_2), 29.7 (CH_2),

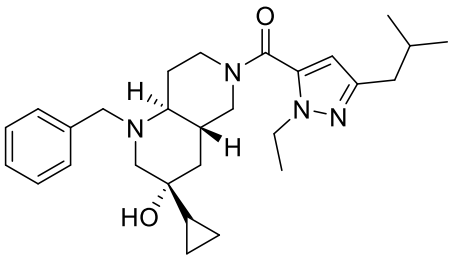
18.0 and 17.9 (CH), 1.3 and 1.2 (CH_2), 0.2 and 0.1 (CH_2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ = -66.45 (t, *J* = 10.5, $3F_{min}$), -66.55 (t, *J* = 10.5, $3F_{maj}$) ppm; HRMS (ESI-orbitrap): calcd for $C_{22}H_{29}F_3N_2O_2$: 411.2254, found 411.2247 $[M+H]^+$.

((3R*,4aS*,8aS*)-1-benzyl-3-cyclopropyl-3-hydroxyoctahydro-1,6-naphthyridin-6(2H)-yl)(1,3-dimethyl-1H-thieno[2,3-c]pyrazol-5-yl)methanone (MC242) (172o)



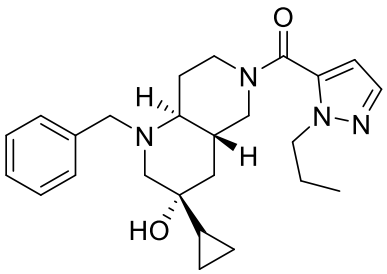
Following LP1: **114a** (25 mg, 0.085 mmol) and 1,3-dimethyl-1H-thieno[2,3-c]pyrazole-5-carboxylic acid (33 mg, 0.17 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **172o** as a white solid (18.1 mg, 46%, purity: 100%); Rt(UPLC): 1.56 min; IR (neat): *v* (max) cm^{-1} 3406, 2922, 2851, 2788, 1599, 1539, 1490, 1427, 738 ;^1H NMR (400 MHz, $CDCl_3$): δ = 7.30 (d, *J* = 4.4 Hz, 4H), 7.25–7.20 (m, 1H), 7.14 (s, 1H), 4.64 (d, *J* = 13.5 Hz, 1H), 4.44 (d, *J* = 13.2 Hz, 1H), 4.13 (d, *J* = 13.5 Hz, 1H), 3.90 (s, 3H), 3.12 (d, *J* = 13.6 Hz, 2H), 2.72 (dd, *J* = 10.6, 2.2 Hz, 2H), 2.44 (s, 3H), 2.26–2.19 (m, 1H), 2.09–2.02 (m, 1H), 1.96 (d, *J* = 10.7 Hz, 1H), 1.91–1.85 (m, 1H), 1.84–1.78 (m, 1H), 1.59–1.41 (m, 2H), 1.23 (t, *J* = 12.2 Hz, 1H), 0.46–0.20 (m, 4H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.3 (C), 145.8 (C), 141.3 (C), 139.1 (C), 133.8 (C), 128.43 (2CH), 128.36 (C), 128.2 (2CH), 126.8 (CH), 118.5 (CH), 68.0 (C), 65.8 (CH), 63.6 (CH_2), 56.8 (CH_2), 41.9 ($2CH_2$), 38.9 (CH), 37.9 (CH_3), 30.4 (CH_2), 17.7 (CH), 12.9 (CH_3), 1.8 ($2CH_2$) ppm; HRMS (ESI-orbitrap): calcd for $C_{26}H_{32}N_4O_2S$: 465.2319, found 465.2312 $[M+H]^+$.

((3R*,4aS*,8aS*)-1-benzyl-3-cyclopropyl-3-hydroxyoctahydro-1,6-naphthyridin-6(2H)-yl)(1-ethyl-3-isobutyl-1H-pyrazol-5-yl)methanone (MC221) (172r)



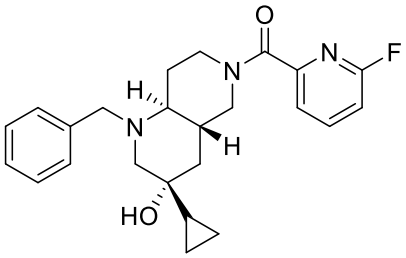
Following LP1: **114a** (25 mg, 0.085 mmol) and 1-ethyl-3-isobutyl-1H-pyrazole-5-carboxylic acid (33 mg, 0.17 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **172g** as a off-white solid (12.2 mg, 31%, purity: 99.4%); Rt(UPLC): 1.82 min; IR (neat): *v* (max) cm^{-1} 3384, 2922, 2866, 2788, 1617, 1531, 1446, 1010, 738; *NMR spectra display a mixture of rotamers* ; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.27 (m, $4H_{maj}$ + $4H_{min}$), 7.25–7.20 (m, $1H_{maj}$ + $1H_{min}$), 6.05 (s, $1H_{maj}$ + $1H_{min}$), 4.84 (br. app. s, $1H_{min}$), 4.62 (br. app. s, $1H_{maj}$), 4.23 (ABq, *J* = 7.2, $2H_{maj}$ + $2H_{min}$), 4.17 (m, 2H + $1H_{maj}$), 3.85 (br. app. s, $1H_{min}$), 3.11 (d, *J* = 13.5, $2H_{maj}$ + $2H_{min}$), 2.79 (br. app. s, $1H_{min}$), 2.74–2.67 (m, $1H_{maj}$), 2.48 (d, *J* = 7.1, $2H_{maj}$ + $2H_{min}$), 2.30–2.12 (m, $1H_{maj}$ + $1H_{min}$), 2.06–1.97 (m, $1H_{maj}$ + $1H_{min}$), 1.97–1.90 (m, 1Hmaj + 1Hmin), 1.91–1.83 (m, 2Hmaj + $2H_{min}$), 1.42 (t, *J* = 7.1, $3H_{maj}$ + $3H_{min}$), 0.93 (d, *J* = 6.6, $6H_{maj}$ + $6H_{min}$), 0.47–0.36 (m, $1H_{maj}$ + $1H_{min}$), 0.36–0.18 (m, $3H_{maj}$ +$3H_{min}$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.4 (C), 150.9 (C), 139.1 (C), 135.1 (C), 128.7 (CH), 128.4 (2CH), 127.1 (2CH), 105.5 (CH), 68.1 (C), 65.9 (CH), 63.7 (CH_2), 57.0 (CH_2), 45.7 (CH_2), 42.1 (CH_2), 37.4 (CH_2), 29.1 (CH), 22.6 ($2CH_3$), 17.9 (CH), 16.3 (CH_3), 1.2 (CH_2), 0.1 (CH_2) ppm; *three secondary and one tertiary carbon are not observed in ^{13}C NMR spectra*; HRMS (ESI-orbitrap): calcd for $C_{28}H_{40}N_4O_2$: 465.3224, found 465.3220 $[M+H]^+$.

((3R*,4aS*,8aS*)-1-benzyl-3-cyclopropyl-3-hydroxyoctahydro-1,6-naphthyridin-6(2H)-yl)(1-propyl-1H-pyrazol-5-yl)methanone (MC244) (172g)



Following LP1: **114a** (25 mg, 0.085 mmol) and 1-propyl-1H-pyrazole-5-carboxylic acid (26 mg, 0.17 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **172g** as a white solid (19.2 mg, 53%, purity: 100%); Rt(UPLC): 1.54 min; IR (neat): *v* (max) cm^{-1} 3500, 2914, 2963, 2788, 1613, 1520, 1438, 790; *NMR spectra display a mixture of rotamers, only the major is reported;* ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (s, 1H), 7.33–7.27 (m, 4H), 7.26–7.20 (m, 1H), 6.28 (d, *J* = 2.0, 1H), 4.62 (br. app. s, 1H), 4.23 (app. t, *J* = 7.2, 2H), 4.10 (br. app. s, 2H), 3.16–3.01 (m, 2H), 2.80 (br. app. s, 1H), 2.74–2.67 (m, 1H), 2.32–2.10 (m, 1H), 2.06–1.98 (m, 1H), 1.97–1.92 (m, 1H), 1.90–1.83 (m, 3H), 1.64 (br. app. s, 1H) 1.43 (br. app. s, 2H), 1.29–1.12 (br. app. s, 1H), 0.93 (br. app. s, 1H), 0.89 (t, *J* = 7.4, 3H), 0.45–0.36 (m, 1H), 0.38–0.19 (m, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.2 (C), 139.1 (C), 137.9 (CH), 135.2 (C), 128.7 (CH), 128.4 (2CH), 127.1 (2CH), 106.3 (CH), 68.1 (C), 65.9 (CH), 63.9 (CH_2), 57.1 (CH_2), 52.4 (CH_2), 42.1 (CH_2), 24.0 (CH_2), 17.9 (CH), 11.2 (CH_3), 1.2 (CH_2), 0.1 (CH_2) ppm; *one tertiary and three secondary carbons are not observed in ^{13}C NMR spectra*; HRMS (ESI-orbitrap): calcd for $C_{25}H_{34}N_4O_2$: 423.2754, found 423.2748 $[M+H]^+$.

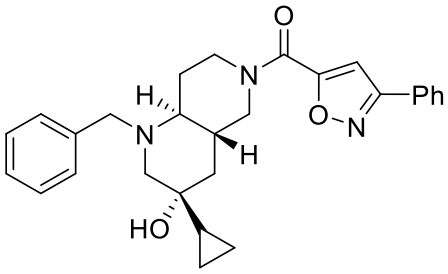
((3R*,4aS*,8aS*)-1-benzyl-3-cyclopropyl-3-hydroxyoctahydro-1,6-naphthyridin-6(2H)-yl)(6-fluoropyridin-2-yl)methanone (MC247) (172c)



Following LP1: **114a** (25 mg, 0.085 mmol) and 6-Fluoropicolinic acid (24 mg, 0.17 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **172c** as a off-white solid (18.2 mg, 52%, purity: 100%); Rt(UPLC): 1.50 min; IR (neat): *v* (max) cm^{-1} 3481, 3078 ,2922, 2788, 1610, 1435, 1241, 1073, 734; *NMR spectra display a mixture of rotamers*; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95–7.86 (m, $1H_{maj}$ + $1H_{min}$),

7.55 (td, J = 7.4, 2.2, $1H_{maj}$ + $1H_{min}$), 7.34–7.26 (m, $4H_{maj}$ + $4H_{min}$), 7.25–7.20 (m, $1H_{maj}$ + $1H_{min}$), 7.03–6.97 (m, $1H_{maj}$ + $1H_{min}$), 4.89–4.80 (m, $1H_{min}$), 4.66–4.58 (m, $1H_{maj}$), 4.17–4.02 (m, $2H_{maj}$ + $1H_{min}$), 3.83–3.74 (m, $1H_{min}$), 3.21–3.04 (m, $2H_{maj}$ +$1H_{min}$), 2.89–2.77 (m, $1H_{min}$), 2.73–2.66 (m, $1H_{maj}$ + $1H_{min}$), 2.54–2.44 (m, $1H_{maj}$), 2.28–2.21 (m, $1H_{min}$), 2.14–2.01 (m, $1H_{maj}$), 2.01–1.98 (m, $1H_{maj}$ + $1H_{min}$), 1.98–1.93 (m, $2H_{maj}$ + $2H_{min}$), 1.73–1.55 (m, $1H_{maj}$ + $1H_{min}$), 1.55–1.37 (m, $2H_{maj}$ + $2H_{min}$), 1.24 (app. t, J = 12.1, $1H_{maj}$), 1.12 (app. t, J = 12.4, $1H_{min}$), 0.99–0.92 (m, $1H_{maj}$ + $1H_{min}$), 0.46–0.17 (m, $4H_{maj}$ + $4H_{min}$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.6 (C), 162.1 (d, J = 243.5, CF), 152.6 (d, J = 12.5, C), 142.3 (d, J = 7.9, CH), 139.39 and 139.34 (C), 128.7 and 128.6 (CH), 128.3 (2CH), 127.0 (2CH), 121.5 and 121.4 (d, J = 4.2, CH), 111.1 and 110.7 (d, J = 8.5, CH), 68.21 and 68.16 (C), 66.0 (CH), 63.9 and 63.8 (CH), 57.0 and 56.9 (CH_2), 52.0 and 47.2 (CH_2), 46.7 and 41.2 (CH_2), 42.3 and 42.2 (CH_2), 39.4 and 38.6 (CH), 30.8 and 29.9 (CH_2), 17.9 (CH), 1.22 and 1.15 (CH_2), 0.21 and 0.16 (CH_2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ = -66.68 (d, J = 7.6, F_{maj}) and -66.74 (d, J = 7.6 F_{min}) ppm; HRMS (ESI-orbitrap): calcd for $C_{24}H_{28}FN_3O_2$: 410.2238, found 410.2233 $[M+H]^+$.

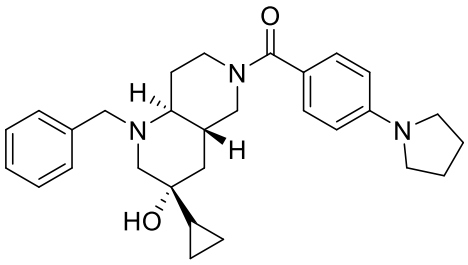
((3R*,4aS*,8aS*)-1-benzyl-3-cyclopropyl-3-hydroxyoctahydro-1,6-naphthyridin-6(2H)-yl)(3-phenylisoxazol-5-yl)methanone (MC249) (172f)



Following LP1: **114a** (25 mg, 0.085 mmol) and 3-phenylisoxazole-5-carboxylic acid (32 mg, 0.17 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **172f** as a colourless oil (11.0 mg, 28%, purity: 100%); Rt(UPLC): 1.84 min; IR (neat): v (max) cm^{-1} 3492, 2922, 2788, 1625, 1446, 1274, 738; *NMR spectra display a mixture of rotamers*; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.87–7.80 (m, $2H_{maj}$ + $2H_{min}$), 7.53–7.45 (m, $3H_{maj}$ + $3H_{min}$), 7.33–7.27 (m, $4H_{maj}$ + $4H_{min}$), 7.25–7.21 (m, $1H_{maj}$ + $1H_{min}$), 7.09 (s, $1H_{min}$), 7.07 (s, $1H_{maj}$), 4.87–4.81 (m, $1H_{min}$), 4.64–4.57 (m, $1H_{maj}$), 4.20–4.07

(stack, $1H_{maj}$ + $2H_{min}$, including: 4.12, app. t, J = 12.7, $1H_{maj}$ + $1H_{min}$), 3.24 (app. td, J = 13.5, 2.8, $1H_{maj}$), 3.12 (app. dd, J = 13.4, 2.8, $1H_{maj}$ + $1H_{min}$), 2.94 (app. dd, J = 13.6, 11.5, $1H_{min}$), 2.85 (app. td, J = 13.3, 3.0, $1H_{min}$), 2.72 (app. dd, J = 10.6, 2.1, $1H_{maj}$ + $1H_{min}$), 2.54 (app. t, J = 12.3, $1H_{maj}$), 2.32–2.20 (m, $1H_{maj}$ + $1H_{min}$), 2.11–2.02 (m, $1H_{maj}$ + $1H_{min}$), 2.00–1.93 (m, $1H_{maj}$ + $1H_{min}$), 1.92–1.84 (m, $1H_{maj}$ + $1H_{min}$), 1.80–1.74 (m, $1H_{maj}$), 1.56–1.51 (m, $1H_{maj}$ + $1H_{min}$), 1.50–1.42 (m, $1H_{maj}$ + $1H_{min}$), 1.32–1.16 (m, $2H_{maj}$ + $2H_{min}$), 0.95–0.87 (m, $2H_{maj}$ + $2H_{min}$), 0.46–0.38 (m, $1H_{maj}$ + $1H_{min}$), 0.38–0.21 (m, $2H_{maj}$ + $2H_{min}$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ =165.0 (C), 162.6 (C), 156.8 (C), 139.2 (C), 130.7 (CH), 129.2 (CH), 128.7 and 128.6 (2CH), 128.4 (2CH), 128.2 (2CH), 127.1 and 127.0 (2CH), 106.7 and 106.4 (CH), 68.2 (C), 65.9 (CH), 63.8 (CH_2), 57.1 and 57.0 (CH_2), 51.2 (CH_2), 47.6 and 46.2 (CH_2), 42.1 and 42.0 (CH_2), 39.8 and 38.7 (CH), 31.1 and 29.8 (CH_2), 17.9 (CH), 1.3 (CH_2), 0.2 (CH_2) ppm; *one quaternary carbon is not observed in ^{13}C NMR spectra*; HRMS (ESI-orbitrap): calcd for $C_{28}H_{31}N_3O_3$: 458.2438, found 458.2431 $[M+H]^+$.

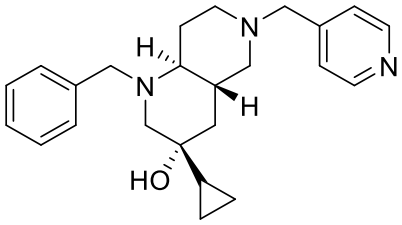
((3R*,4aS*,8aS*)-1-benzyl-3-cyclopropyl-3-hydroxyoctahydro-1,6-naphthyridin-6(2H)-yl)(4-(pyrrolidin-1-yl)phenyl)methanone (MC220) (172e)



Following LP1: **114a** (25 mg, 0.085 mmol) and 4-(1-Pyrrolidinyl)benzoic acid (32 mg, 0.17 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **172e** as a white solid (14.4 mg, 37%, purity: 93%); Rt(UPLC): 1.89 min; IR (neat): v (max) cm^{-1} 3377, 2889, 2840, 1595, 1524, 1431, 1379, 752; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (d, J = 8.8, 2H), 7.29 (d, J = 4.4 Hz, 4H), 7.22 (m, 1H), 6.56–6.47 (m, 2H), 4.11 (d, J = 13.5 Hz, 1H), 3.37–3.26 (m, 4H), 3.09 (d, J = 13.6 Hz, 1H), 2.96 (b.s, 1H), 2.70 (dd, J = 10.7, 2.2 Hz, 1H), 2.59 (b.s, 1H), 2.12 (d, J = 12.7 Hz, 1H), 2.02 (m, 5H),1.98 – 1.95 (m,1H) 1.93 (d, J = 10.7 Hz, 1H), 1.89–1.72 (m, 2H), 1.51–1.37 (m, 2H), 1.17 (t, J = 12.3

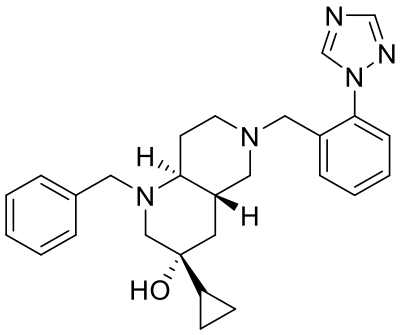
Hz, 1H), 0.43–0.20 (m, 4H). ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.9 (C), 148.8 (C), 139.3 (C), 129.4 (2CH), 128.4 (2CH), 128.1 (2CH), 126.7 (CH), 121.6 (C), 110.6 (2CH), 68.0 (C), 66.1 (CH), 63.7 (CH_2), 56.8 (CH_2), 47.4 ($2CH_2$), 42.0 (CH_2), 25.4 ($2CH_2$), 17.7 (CH), 1.8 ($2CH_2$). ppm; HRMS (ESI-orbitrap): calcd for $C_{29}H_{37}N_3O_2$: 460.2958, found 460.2952 $[M+H]^+$.

(3R*,4aS*,8aS*)-1-benzyl-3-cyclopropyl-6-(pyridin-4-ylmethyl)decahydro-1,6-naphthyridin-3-ol (MC253) (173e)



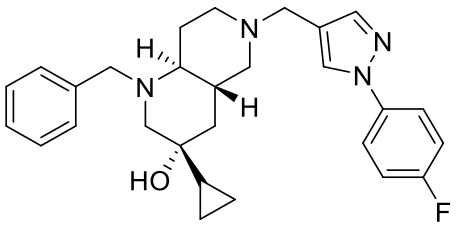
Following LP2: **114a** (25 mg, 0.085 mmol) and 4-pyridinecarboxaldehyde (17 μL, 0.17 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **173e** as a colourless oil (18.4 mg, 58%, purity: 100%); Rt(UPLC): 1.56 min; IR (neat): *v* (max) cm^{-1} 3250, 2918, 2780, 1602, 1319, 738, 697; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.57–8.48 (m, 2H), 7.31–7.25 (m, 6H), 7.24–7.19 (m, 1H), 4.10 (d, J_{AB} = 13.6 Hz, 1H), 3.51 (d, J_{AB} = 14.1, 1H), 3.46 (d, J_{AB} = 14.1, 1H), 3.07 (d, J_{AB} = 13.6 Hz, 1H), 3.01–2.91 (m, 1H), 2.73 (dt, *J* = 10.6, 2.7 Hz, 1H), 2.68 (dd, *J* = 10.6, 2.3 Hz, 1H), 2.14–2.02 (m, 2H), 2.01–1.91 (m, 1H), 1.89 (d, *J* = 10.8 Hz, 2H), 1.82 (d, *J* = 10.9 Hz, 1H), 1.76 (ddd, *J* = 13.3, 7.7, 3.5 Hz, 1H), 1.66 (ddd, *J* = 11.8, 3.5, 2.3 Hz, 1H), 1.56 –.1.54 (m, 2H), 1.16 (app. t, *J* = 12.3 Hz, 1H), 0.43–0.38 (m, 1H), 0.33–0.27 (m, 2H), 0.27–0.20 (m, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 149.7 (CH), 147.9 (C), 139.5 (C), 128.5 (2CH), 128.1 (2CH), 126.7 (CH), 123.8 (2CH), 68.2 (C), 65.7 (CH), 63.8 (CH_2), 61.7 (CH_2), 59.2 (CH_2), 56.9 (CH_2), 53.2 (CH_2), 42.6 (CH_2), 38.3 (CH), 30.1 (CH_2), 17.8 (CH), 1.0 ($2CH_2$) ppm; HRMS (ESI-orbitrap): calcd for $C_{24}H_{31}N_3O$: 378.2534, found 378.2535 $[M+H]^+$.

(3R*,4aS*,8aS*)-6-(2-(1H-1,2,4-triazol-1-yl)benzyl)-1-benzyl-3-cyclopropyldecahydro-1,6-naphthyridin-3-ol (MC255) (173d)



Following LP2: **114a** (25 mg, 0.085 mmol) and 2-(1H-1,2,4-triazol-1-yl)benzaldehyde (29 mg , 0.17 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **173d** as a white solid (18.4 mg, 50%, purity: 100 %); Rt(UPLC): 1.70 min; IR (neat): *v* (max) cm^{-1} 3380, 2918, 2776, 1509, 1453, 1274, 1010, 700; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.88 (s, 1H), 8.11 (s, 1H), 7.56–7.40 (m, 5H), 7.33–7.18 (m, 4H), 4.08 (d, J_{AB} = 13.5, 1H), 3.32 (s, 2H), 3.06 (d, J_{AB} = 13.5, 1H), 2.90 (s, 1H), 2.76–2.60 (m, 2H), 2.11–1.96 (m, 2H), 1.87 (d, *J* = 10.5, 1H),1.80–1.72 (stack, 3H), 1.69–1.62 (m, 1H), 1.49–1.44 (m, 2H), 1.14 (app. t, *J* = 12.1, 1H), 0.43–0.14 (m, 4H) ppm; *OH resonance not observed in ^{1}H NMR*; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 152.1 (CH), 145.4 (CH), 139.5 (C), 137.2 (C), 131.5 (CH), 128.8 (CH), 128.6 (2CH), 128.2 (2CH), 126.8 (CH), 126.2 (2CH), 68.3 (C), 65.9 (CH), 63.9 (CH_2), 58.6 ($2CH_2$), 57.0 (CH_2), 52.9 (CH_2), 42.6 (CH_2), 38.6 (CH), 17.9 (CH), 1.0 ($2CH_2$) ppm; *one quaternary carbon and one secondary carbon are not observed in ^{13}C NMR spectra*; HRMS (ESI-orbitrap): calcd for $C_{27}H_{33}N_5O$: 444.2758, found 444.2752 $[M+H]^+$.

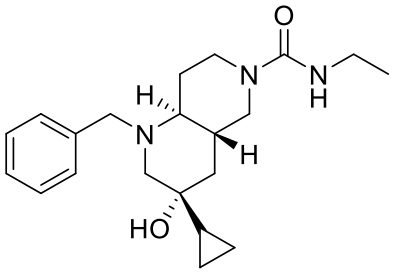
(3R*,4aS*,8aS*)-1-benzyl-3-cyclopropyl-6-((1-(4-fluorophenyl)-1H-pyrazol-4-yl)methyl)decahydro-1,6-naphthyridin-3-ol (MC223) (173a)



Following LP2: **114a** (25 mg, 0.085 mmol) and 1-(4-Fluorophenyl)pyrazole-4-carbaldehyde (32 mg, 0.17 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **173a** as a white solid (9.6 mg, 24%, purity: 99.4%); Rt(UPLC): 1.82 min; IR (neat): *v* (max) cm^{-1} 3384, 2918, 2780, 1513, 1226, 738, 697; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (s, 1H), 7.65–7.62 (m, 3H), 7.31–7.27 (m, 4H), 7.23–

7.19 (m, 1H), 7.14 (app. t, *J* = 8.5, 1H), 4.10 (d, *J* = 13.5, 1H), 3.48 (s, 2H), 3.07 (app. d, *J* = 13.5, 2H), 2.83 (app. d, *J* = 10.9, 1H), 2.66 (app. d, *J* = 10.6, 1H), 2.17–2.04 (m, 1H), 2.04–1.98 (m, 1H), 1.97–1.91 (m, 1H), 1.88 (app. d, *J* = 10.8, 1H), 1.75 (app. t, *J* = 11.1, 1H), 1.73–1.64 (m, 3H), 1.59–1.42 (m, 2H), 1.17 (app. t, *J* = 12.3, 1H), 0.84 (s, OH), 0.43–0.38 (m, 1H), 0.33–0.28 (m, 2H), 0.26–0.17 (m, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.2 (d, *J* = 246.7, CF), 142.0 (CH), 139.6 (C), 136.6 (d, *J* = 2.8, C), 128.6 (2CH), 128.1 (2CH), 126.7 (CH), 126.6 (CH), 120.7 (d, *J* = 8.3, 2CH), 120.0 (C), 116.3 (d, *J* = 23.0, 2CH), 68.3 (C), 65.8 (CH), 63.8 (CH_2), 58.8 (CH_2), 56.9 (CH_2), 53.0 (CH_2), 52.4 (CH_2), 42.7 (CH_2), 38.3 ($CH_)$, 30.2 (CH_2), 17.9 (CH), 1.1 (CH_2), 0.0 (CH_2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -116.2 (m); HRMS (ESI-orbitrap): calcd for $C_{28}H_{33}FN_4O$: 461.2711, found 461.2705 $[M+H]^+$.

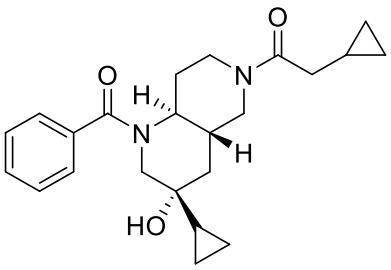
(3R*,4aS*,8aS*)-1-benzyl-3-cyclopropyl-N-ethyl-3-hydroxyoctahydro-1,6-naphthyridine-6(2H)-carboxamide (Mc261) (174a)



Following LP3: **114a** (25 mg, 0.085 mmol) and ethyl isocyanate (14 μL, 0.17 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **174a** as a colourless oil (12.7 mg, 42%, purity: 100%); Rt(UPLC): 1.32 min; IR (neat): *v* (max) cm^{-1} 3339, 2967, 2765, 1595, 1535, 1092, 1010; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (app. d, *J* = 4.1, 4H), 7.24–7.20 (m, 1H), 4.41 (t, *J* = 5.5, NH), 4.11 (d, J_{AB} = 13.6, 1H), 4.03–3.98 (m, 1H), 3.87–3.82 (m, 1H), 3.28 (dq, *J* = 7.2, 5.4, 2H), 3.10 (d, J_{AB} = 13.5, 1H), 2.83 (td, *J* =13.1, 2.8, 1H), 2.69 (dd, *J* = 10.7, 2.2, 1H), 2.47 (dd, *J* = 12.9, 11.0, 1H), 2.15–2.09 (m, 1H), 1.96–1.84 (m, 2H), 1.96–1.84 (m, 2H), 1.82–1.74 (m, 2H), 1.46 (tt, *J* = 8.7, 5.6, 1H), 1.43–1.32 (m, 1H), 1.13 (t, *J* = 4.0, 3H), 0.47–0.36 (m, 1H), 0.35–0.20 (m, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.6 (C), 139.5 (C), 128.7 (2CH), 128.3 (2CH), 126.9 (CH), 68.2 (CH_2), 65.9 (CH), 63.9 (CH_2), 57.0 (CH_2), 49.0 (CH_2), 43.6 (CH_2), 42.2 (CH_2), 38.5 (CH), 35.9 (CH_2), 30.9

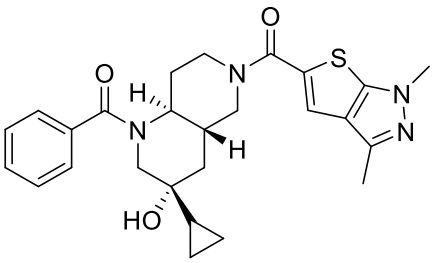
(CH_2), 17.9 (CH), 15.7 (CH_3), 1.17 ($2CH_2$)ppm; HRMS (ESI-orbitrap): calcd for $C_{21}H_{31}N_3O_2$: 358.2489, found 358.2483 $[M+H]^+$.

1-((3R*,4aS*,8aS*)-1-benzoyl-3-cyclopropyl-3-hydroxyoctahydro-1,6-naphthyridin-6(2H)-yl)-2-cyclopropylethan-1-one (MC265) (172h)



Following LP1: **115** (30 mg, 0.1 mmol) and cyclopropylacetic acid (18 μL, 0.2 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **172h** as a colourless oil (37.4 mg, 97%, purity: 100%); Rt(UPLC): 0.93 min; IR (neat): *v* (max) cm^{-1} 3388, 3004, 2926, 2862, 2236, 1613, 1423, 1211, 909, 723, 700; *NMR spectra display a mixture of rotamers, only the major rotamer is reported:* ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48–7.40 (m, 2H), 7.40–7.33 (m, 3H), 4.68–4.61 (m, 1H), 3.90–3.94 (m, 1H), 3.74 (app. td, *J* = 11.2, 3.4, 1H), 4.41 (d, J_{AB} = 13.9, 1H), 3.27 (d, J_{AB} = 14.0, 1H), 3.15 (app. td, *J* = 13.2, 2.8, 1H), 2.37–2.31 (m, 1H), 2.27 (d, *J* = 6.7, 2H), 2.17 (dd, *J* = 13.2, 10.9, 1H), 1.98 (s, OH), 1.79 (dd, *J* =13.9, 4.2, 1H), 1.72–1.56 (m, 1H), 1.49–1.33 (m, 1H), 1.30–1.20 (m, 1H), 1.10 (app. t, *J* = 13.4, 1H), 1.06–0.95 (m, 1H), 0.79–0.73 (m, 1H), 0.60–0.49 (m, 2H), 0.40–0.20 (m, 4H), 0.18–0.14 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.9 (C), 171.3 (C), 136.8 (C), 129.7 (CH), 128.4 (2CH), 127.7 (2CH), 71.5 (C), 58.2 (CH), 54.5 (CH_2), 46.4 (CH_2), 45.3 (CH_2), 38.8 (CH_2), 37.1 (CH_2), 36.1 (CH), 29.6 (CH_2), 19.3 (CH), 7.4 (CH), 4.7 ($2CH_2$), 0.0 ($2CH_2$) ppm; HRMS (ESI-orbitrap): calcd for $C_{23}H_{30}N_2O_3$: 383.2329, found 383.2322 $[M+H]^+$.

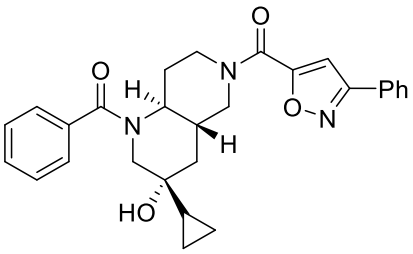
((3R*,4aS*,8aS*)-1-benzoyl-3-cyclopropyl-3-hydroxyoctahydro-1,6-naphthyridin-6(2H)-yl)(1,3-dimethyl-1H-thieno[2,3-c]pyrazol-5-yl)methanone (MC266) (172u)



Following LP1: **115** (30 mg, 0.1 mmol) and 1,3-dimethyl-1H-thieno[2,3-c]pyrazole-5-carboxylic acid (39 mg, 0.2 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **172u** as a white solid (38.1 mg, 79%, purity: 100%); Rt(UPLC): 0.96 min; IR (neat): *v* (max) cm^{-1} 3388, 3004, 2926, 2862, 2236, 1599, 1539, 1423, 1282, 909, 723; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.42 (m, 2H), 7.40–7.33 (m, 3H), 7.12 (s, 1H), 4.54–4.51 (m, 2H), 3.90–3.79 (stack, 4H, including: 3.88, s, 3H), 3.44 (d, J_{AB} = 14.0, 1H), 3.32 (d, J_{AB} = 14.0, 1H), 3.24–3.18 (m, 1H), 2.56–2.51 (m, 2H), 2.42 (s, 3H), 1.96 (s, OH), 1.87–1.74 (m, 2H), 1.64–1.46 (m, 1H), 1.15 (app. t, *J* = 14.2, 1H), 0.79 (tt, *J* = 7.8, 5.5, 1H), 0.40–0.28 (m, 1H), 0.32–0.17 (m, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.0 (C), 163.9 (C), 145.9 (C), 141.6 (C), 136.7 (C), 133.6 (C), 129.8 (CH), 128.53 (C), 128.46 (2CH), 127.7 (2CH), 119.0 (CH), 71.5 (C), 58.2 (CH), 54.2 (CH_2), 48.6 (CH_2)*, 46.3 (CH_2)*, 38.6 (CH_2), 38.1 (CH), 36.4 (CH_3), 30.4 (CH_2), 19.3 (CH), 13.0 (CH_3), 0.3 ($2CH_2$) ppm; HRMS (ESI-orbitrap): calcd for $C_{26}H_{30}N_4O_3S$: 479.2111, found 479.2105 $[M+H]^+$.

*: very low intensity signals in ^{13}C NMR spectra

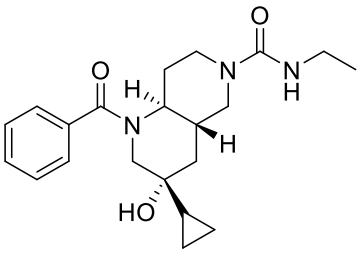
((3R*,4aS*,8aS*)-1-benzoyl-3-cyclopropyl-3-hydroxyoctahydro-1,6-naphthyridin-6(2H)-yl)(3-phenylisoxazol-5-yl)methanone (MC267) (172m)



Following LP1: **115** (30 mg, 0.1 mmol) and 3-phenylisoxazole-5-carboxylic acid (38 mg, 0.2 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **172m** as a white solid (16.3 mg, 34%, purity: 100%); Rt(UPLC): 1.15 min; IR (neat): *v* (max) cm^{-1} 3399, 3004, 2926, 2862, 1621, 1446, 1271, 1211,

909, 767, 723; *NMR spectra display a mixture of rotamers, only the major rotamer is reported:* ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87–7.78 (m, $2H_{maj}$ + $2H_{min}$), 7.52–7.43 (m, $5H_{maj}$ + $5H_{min}$), 7.42–7.36 (m, $3H_{maj}$ + $3H_{min}$), 7.10 (s, $1H_{min}$), 7.06 (s, $1H_{maj}$), 4.80 (app. d, *J* = 13.5, $1H_{min}$), 4.71 (app. d, *J* = 13.4, $1H_{maj}$), 4.33 (app. d, *J* = 13.4, $1H_{maj}$), 4.25 (app. d, *J* = 13.5, $1H_{min}$), 3.94–3.86 (m, $1H_{maj}$ + $1H_{min}$), 3.46 (d, JAB = 14.1, $1H_{maj}$ + $1H_{min}$), 3.40–3.28 (stack, $1H_{maj}$ + $2H_{min}$, including: 3.34, d, *J* = 14.1, $1H_{maj}$ + $1H_{min}$), 3.00–2.92 (m, $1H_{min}$), 2.91–2.84 (m, $1H_{min}$), 2.69–2.55 (m, $1H_{maj}$), 2.51 (app. t, *J* = 12.0, $1H_{maj}$), 1.92–1.77 (m, $2H_{maj}$ + $2H_{min}$), 1.68–1.53 (m, $2H_{maj}$ + $2H_{min}$), 1.27–1.08 (m, $1H_{maj}$ + $1H_{min}$), 0.87–0.76 (m, $1H_{maj}$ + $1H_{min}$), 0.42–0.34 (m, $1H_{maj}$ + $1H_{min}$), 0.35–0.18 (m, $3H_{maj}$ + $3H_{min}$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.1 (C), 165.1 and 164.7 (C), 162.7 and 162.6 (C), 157.3 and 156.9 (C), 136.7 (C), 130.72 and 130.66 (CH), 129.9 (CH), 129.3 and 129.2 (2CH), 128.6 (2CH), 128.2 and 128.1 (2CH), 127.0 (2CH), 106.8 and 106.3 (CH), 71.8 and 71.7 (C), 58.0 (CH), 54.2 (CH_2), 51.3 and 47.7 (CH_2), 46.3 and 42.7 (CH_2), 38.6 and 38.5 (CH_2), 37.2 and 36.2 (CH), 30.8 and 29.6 (CH_2), 19.4 (CH), 0.1 and 0.06 ($2CH_2$) ppm; *one quaternary carbon is not observed in ^{13}C NMR spectra;* HRMS (ESI-orbitrap): calcd for $C_{28}H_{29}N_3O_4$: 472.2231, found 472.2225 $[M+H]^+$.

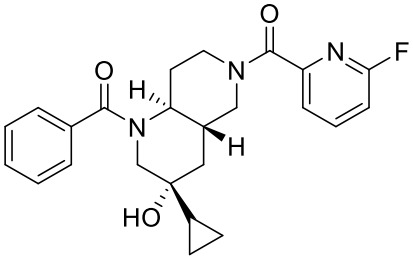
(3R*,4aS*,8aS*)-1-benzoyl-3-cyclopropyl-N-ethyl-3-hydroxyoctahydro-1,6-naphthyridine-6(2H)-carboxamide (MC269) (174b)



Following LP3: **115** (30 mg, 0.1 mmol) and ethyl isocyanate (16 μL, 0.2 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **174b** as a colourless oil (22.7 mg, 61%, purity: 100%); Rt(UPLC): 0.83 min; IR (neat): *ν* (max) cm^{-1} 3347, 2970, 2926, 2862, 1610, 1528, 1423, 1252, 1215, 909, 723; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.40 (m, 2H), 7.39–7.33 (m, 3H), 4.57 (t, *J* = 5.4, NH), 4.18–4.13 (m, 1H), 3.81–3.76 (m, 1H), 3.71 (td, *J* = 11.2, 3.5, 1H), 3.41 (d, *J* = 14.0, 1H), 3.29 (d, *J* = 13.8, 1H), 3.26–3.21 (m, 2H),

2.98 (td, *J* = 12.9, 2.8, 1H), 2.46–2.41 (m ,1H), 2.37 (dd, *J* = 12.9, 10.7, 1H), 1.88 (s, OH), 1.81–1.63 (stack, 3H), 1.55–1.40 (m, 1H), 1.12 (t, *J* = 7.2, 3H), 0.81–0.74 (m, 1H), 0.36–0.30 (m, 1H), 0.29–0.17 (m, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.0 (C), 157.6 (C), 136.9 (C), 129.7 (CH), 128.5 (2CH), 127.7 (2CH), 71.7 (C), 58.2 (CH), 54.1 (CH_2), 48.7 (CH_2), 43.9 (CH_2), 38.7 (CH_2), 36.0 (CH), 35.9 (CH_2), 29.8 (CH_2), 19.3 (CH), 15.7 (CH_3), 0.0 ($2CH_2$) ppm; HRMS (ESI-orbitrap): calcd for $C_{21}H_{29}N_3O_3$: 372.2282, found 372.2275 $[M+H]^+$.

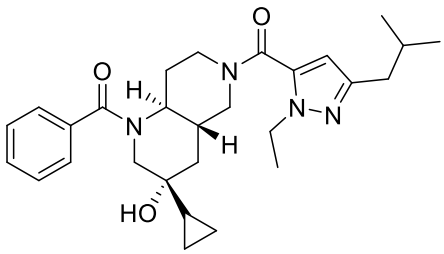
((3R*,4aS*,8aS*)-1-benzoyl-3-cyclopropyl-3-hydroxyoctahydro-1,6-naphthyridin-6(2H)-yl)(6-fluoropyridin-2-yl)methanone (MC354) (172j)



Following LP1: **115** (30 mg, 0.1 mmol) and 6-Fluoropicolinic acid (28 mg, 0.2 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **172j** as a white solid (36 mg, 85%, purity: 89%); Rt(UPLC): 1.08 min; IR (neat): *v* (max) cm^{-1} 3410, 3004, 2926, 2232, 1599, 1435, 1267, 1166, 723; *NMR spectra display a mixture of rotamers* ; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94–7.86 (m, $1H_{maj}$ + $1H_{min}$), 7.58–7.48 (m, $1H_{maj}$ + $1H_{min}$), 7.48–7.40 (m, $2H_{maj}$ + $2H_{min}$), 7.40–7.34 (m, $3H_{maj}$ + $3H_{min}$), 7.00 (dd, *J* = 8.3, 2.7, $1H_{maj}$ + $1H_{min}$), 4.85–4.76 (m, $1H_{min}$), 4.75–4.67 (m, $1H_{maj}$), 3.99–3.91 (m, $1H_{maj}$), 3.90–3.80 (m, $1H_{maj}$ + $2H_{min}$), 3.50–3.41 (m, $1H_{maj}$ + $1H_{min}$), 3.34 (app. t, *J* = 13.5, $1H_{maj}$ + $1H_{min}$), 3.21 (app. td, *J* = 13.2, 2.8, $1H_{maj}$), 2.91 (app. td, *J* = 13.2, 3.0, $1H_{min}$), 2.73 (app. dd, *J* = 13.2, 10.9, $1H_{min}$), 2.59–2.53 (m, $1H_{min}$), 2.48–2.38 (m, $2H_{maj}$), 1.99–1.76 (m, $2H_{maj}$ + $2H_{min}$), 1.68–1.52 (m, $2H_{maj}$ + $2H_{min}$), 1.17 (app. t, *J* = 14.1, $1H_{maj}$), 1.04 (app.t, *J* = 13.6, $1H_{min}$), 0.79 (tt, *J* = 7.7, 4.4, $1H_{maj}$ + $1H_{min}$), 0.40–0.31 (m, $1H_{maj}$ + $1H_{min}$), 0.31–0.38 (m, $3H_{maj}$ + $3H_{min}$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.0 and 172.9 (C), 166.6 and 165.6 (C), 162.13 and 161.8 (d, *J* = 243.4, CF), 152.4 (d, *J* = 13.0, C) , 142.45 (app. t, *J* = 7.4, CH), 136.8 (C), 129.9 (CH), 128.5 (2CH), 127.73 and 127.69 (2CH), 121.7 and 121.1 (d, *J* = 4.1, CH), 111.0 (d, *J* =

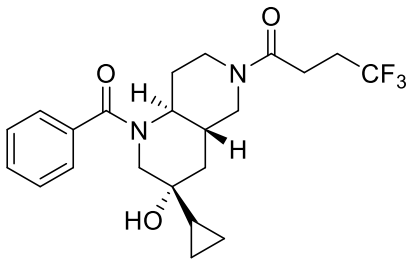
36.0, CH), 71.9 and 71.3 (C), 58.2 and 58.1 (CH), 54.1 (CH_2), 52.1 and 47.3 (CH_2), 46.9 and 42.4 (CH_2), 38.6 and 37.6 (CH_2), 36.9 and 36.1 (CH), 30.4 and 29.7 (CH_2), 19.3 and 19.1 (CH), 0.1 and 0.06 ($2CH_2$) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ = -66.45 (d, *J* = 7.8, F_{maj}), -66.78 (d, *J* = 7.8, F_{min}) ppm; HRMS (ESI-orbitrap): calcd for $C_{24}H_{26}FN_3O_3$: 424.20310, found 424.2023 $[M+H]^+$.

((3R*,4aS*,8aS*)-1-benzoyl-3-cyclopropyl-3-hydroxyoctahydro-1,6-naphthyridin-6(2H)-yl)(1-ethyl-3-isobutyl-1H-pyrazol-5-yl)methanone (MC355) (172x)



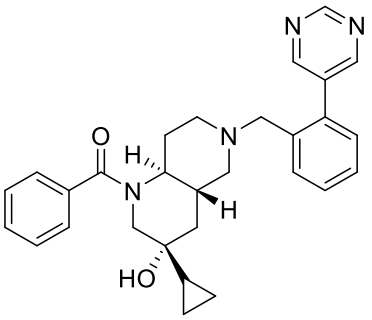
Following LP1: **115** (30 mg, 0.1 mmol) and 1-ethyl-3-isobutyl-1H-pyrazole-5-carboxylic acid (40 mg, 0.2 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **172x** as a light yellow solid (38.2 mg, 80%, purity: 97.1%); Rt(UPLC): 1.12 min; IR (neat): *v* (max) cm^{-1} 3410, 2952, 2870, 1613, 1420, 1215; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.47–7.41 (m, 2H), 7.41–7.34 (m, 3H), 6.04 (s, 1H), 4.71 (br. app. s, 1H), 4.21 (q, *J* = 7.1, 2H), 4.15–4.05 (br. app. s, 1H), 3.81 (app. td, *J* = 11.2, 3.5, 1H), 3.44 (d, J_{AB} = 13.9, 1H), 3.31 (d, J_{AB} = 13.9, 1H), 3.19 (br. app. s, 1H), 2.52 (br. app. s, 1H), 2.47 (d, *J* = 7.2, 2H), 2.40 (br. app. s, 1H), 1.91–1.71 (stack, 3H including: 1.87, app. dq, *J* = 13.3, 6.6, 1H), 1.75 (br. app. s, 1H), 1.47 (br. app. s, 1H), 1.40 (t, *J* = 7.1, 3H), 1.16 (br. app. s, 1H), 0.92 (d, *J* = 6.6, 6H), 0.78 (br. app. s, 1H), 0.38–0.31 (m, 1H), 0.30–0.16 (m, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.1 (C), 161.7 (C), 150.9 (C), 136.7 (C), 134.9 (C), 129.9 (CH), 128.5 (2CH), 127.7 (2CH), 105.6 (CH), 71.5 (C), 58.1 (CH), 54.2 (CH_2), 46.9 (CH_2), 45.7 (CH_2), 38.7 (CH_2), 36.2 (CH_2), 29.1 (CH), 22.5 ($2CH_3$), 19.3 (CH), 16.3 (CH_3), 0.1 (CH_2), 0.02 (CH_2)ppm; *two secondary and one tertiary carbon are not observed in 13C NMR spectra*; HRMS (ESI-orbitrap): calcd for $C_{28}H_{38}N_4O_3$: 479.3017, found 479.3001 $[M+H]^+$.

1-((3R*,4aS*,8aS*)-1-benzoyl-3-cyclopropyl-3-hydroxyoctahydro-1,6-naphthyridin-6(2H)-yl)-4,4,4-trifluorobutan-1-one (MC369) (172w)



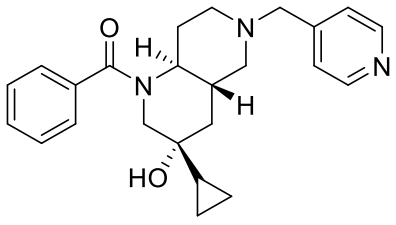
Following LP1: **115** (30 mg, 0.1 mmol) and 4,4,4-trifluoroacetic acid (28 μL, 0.2 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **172w** as a colourless oil (35.7 mg, 84%, purity: 99.6%); Rt(UPLC): 1.03 min; IR (neat): *v* (max) cm^{-1} 3459, 2929, 2855, 1658, 1617, 1438, 1125, 1252, 704; *NMR spectra display a mixture of rotamers* : ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.42 (m, 2Hmaj + 2Hmin), 7.41–7.35 (m, 3Hmaj + 3Hmin), 4.74–4.67 (m, 1Hmin), 4.66–4.60 (m, 1Hmaj), 3.92–3.83 (m, 1Hmaj), 3.81–3.70 (m, 1Hmaj + 2Hmin), 3.44 (d, JAB = 14.0, 1Hmaj + 1Hmin), 3.28 (d, JAB = 14.0, 1Hmaj + 1Hmin), 3.18 (app. td, J = 13.3, 2.8, 1Hmaj), 2.73–2.63 (m, 1Hmin), 2.61–2.52 (m, 2Hmaj + 2Hmin), 2.51–2.42 (m , 3Hmaj + 3Hmin), 2.21 (app. dd, J = 13.0, 11.0, 1Hmaj), 1.83–1.72 (m, 1Hmaj + 1Hmin), 1.73–1.65 (m, 1Hmaj + 1Hmin), 1.51–1.38 (m, 1Hmaj + 1Hmin), 1.19–1.07 (m, 1Hmaj + 1Hmin), 0.84–0.71 (m, 1Hmaj + 1Hmin), 0.40–0.30 (m, 1Hmaj + 1Hmin), 0.30–0.17 (m, 3Hmaj + 3Hmin) ppm; *OH resonance is not observed in 1H NMR*; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.0 and 172.9 (C), 168.3 and 168.0 (C), 136.7 (C), 129.8 (CH), 128.5 (2CH), 127.8 (2CH), 127.2 (q, J = 270.7, CF_3), 71.6 and 71.5 (C), 58.2 and 58.0 (CH), 54.2 and 54.1 (CH_2), 50.3 and 46.8 (CH_2), 44.9 and 41.6 (CH_2), 38.8 and 38.6 (CH_2), 36.9 and 36.0 (CH), 30.3 and 29.5 (CH_2), 29.7 (q, J = 29.4, CH_2), 26.03 and 26.00 (CH_2), 19.33 and 19.27 (CH), 0.17 and 0.04 ($2CH_2$) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ = - 66.48 (m, 3Fmaj + 3Fmin) ppm, HRMS (ESI-orbitrap): calcd for $C_{22}H_{27}F_3N_2O_3$: 425.2046, found 425.2041 $[M+H]^+$.

((3R*,4aS*,8aS*)-3-cyclopropyl-3-hydroxy-6-(2-(pyrimidin-5-yl)benzyl)octahydro-1,6-naphthyridin-1(2H)-yl)(phenyl)methanone (MC506) (173h)



Following LP2: **115** (30 mg, 0.1 mmol) and 2-(pyrimidin-5-yl)benzaldehyde (37 mg, 0.2 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **173h** as a white solid (20.0 mg, 43%, purity: 100%); Rt(UPLC): 1.45 min; IR (neat): *v* (max) cm^{-1} 3451, 2929, 1617, 1435, 1125, 726; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.19 (s, 1H), 8.85 (s, 2H), 7.42–7.38 (m, 5H), 7.37–7.34 (m, 3H), 7.28–7.24 (m, 1H), 3.54 (td, *J* = 11.1, 3.6, 1H), 3.40 (d, J_{AB}= 14.1, 1H), 3.35–3.27 (stack, 3H, including: 3.32, s, 2H and 3.30, d, J_{AB} = 13.9, 1H), 2.76–2.71 (m, 1H), 2.66–2.62 (m, 1H), 2.34–2.38 (m, 1H), 2.11 (td, *J* = 11.9, 2.7, 1H), 1.81 (s, OH), 1.72 (app. t, *J* = 10.3, 1H), 1.68–1.56 (m, 2H), 1.42 (dd, *J* = 12.0, 3.9, 1H), 1.36 (dd, *J* = 12.1, 4.0, 1H), 1.06 (app. t, *J* = 14.0, 1H) 0.78 (tt, *J* = 8.3, 5.3, 1H), 0.39–0.17 (m, 4H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.9 (C), 157.3 (CH), 156.8 (CH), 137.1 (C), 136.7 (C), 135.8 (C), 135.3 (C), 131.2 (CH), 130.5 (CH), 129.6 (CH), 128.8 (CH), 128.5 (2CH), 128.0 (CH), 127.6 (2CH), 72.0 (C), 60.6 (CH_2), 58.3 (CH), 54.0 (CH_2), 52.4 (CH_2), 39.2 (CH_2), 36.1 (CH), 30.0 (CH_2), 19.4 (CH), 0.0 ($2CH_2$) ppm; HRMS (ESI-orbitrap): calcd for $C_{29}H_{32}N_4O_2$: 469.2598, found 469.2594 $[M+H]^+$.

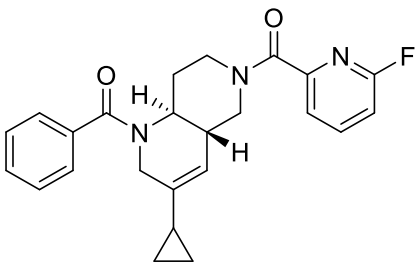
((3R*,4aS*,8aS*)-3-cyclopropyl-3-hydroxy-6-(pyridin-4-ylmethyl)octahydro-1,6-naphthyridin-1(2H)-yl)(phenyl)methanone (MC507) (173j)



Following LP2: **115** (30 mg, 0.1 mmol) and 4-pyridinecarboxaldehyde (19 μL, 0.2 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **173j** as a colourless oil (21.6 mg, 55%, purity: 98.4%); Rt(UPLC): 1.14 min; IR (neat): *v* (max) cm^{-1} 3220, 2933, 2873, 2791, 1621, 1416, 1285, 1215, 1021, 715; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.57–8.50 (m, 2H), 7.45–7.41 (m, 2H), 7.40–7.35 (m, 3H),

7.28–7.24 (m, 2H), 3.61 (td, *J* = 11.1, 3.7, 1H), 3.53 (d, J_{AB} = 14.0, 1H), 3.47 (d, J_{AB} = 13.9, 1H), 3.44 (d, J_{AB} = 13.9, 1H), 3.35 (d, J_{AB} = 14.0, 1H), 2.94–2.89 (m, 1H), 2.82–2.78 (m, 1H), 2.43–2.38 (m, 1H), 2.24 (td, *J* = 11.9, 2.7, 1H), 1.96–1.76 (stack, 3H), 1.68 (dd, *J* = 13.7, 3.6, 1H), 1.60 (td, *J* = 11.8, 3.9, 1H), 1.49 (s, 1H), 1.11 (app. t, *J* = 13.3, 1H), 0.81 (tt, *J* = 8.2, 5.4, 1H), 0.40–0.17 (m, 4H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.0 (C), 150.0 (2CH), 147.9 (C), 137.1 (C), 129.6 (CH), 128.5 (2CH), 127.6 (2CH), 124.0 (2CH), 72.0 (C), 61.7 (CH_2), 59.0 (CH_2), 58.4 (CH), 54.2 (CH_2), 53.3 (CH_2), 39.2 (CH_2), 36.1 (CH), 30.0 (CH_2), 19.4 (CH), 0.3 ($2CH_2$) ppm; HRMS (ESI-orbitrap): calcd for $C_{24}H_{29}N_3O_2$: 392.2332, found 392.2324 $[M+H]^+$.

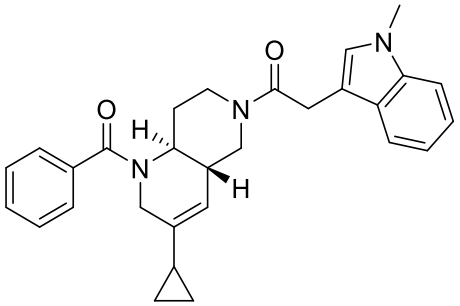
((4aS*,8aS*)-1-benzoyl-3-cyclopropyl-1,4a,5,7,8,8a-hexahydro-1,6-naphthyridin-6(2H)-yl)(6-fluoropyridin-2-yl)methanone (MC712) (172z)



Following LP1: **116** (28 mg, 0.1 mmol) and 6-fluoropicolinic acid (28 mg, 0.2 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **172z** as a whit solid (9.7 mg, 24%, purity: 100%); Rt(UPLC): 1.64 min; IR (neat): *v* (max) cm^{-1} 3000, 2907, 2862, 1632, 1431, 1237; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97–7.86 (m, 1H), 7.62–7.50 (m, 3H), 7.49–7.40 (m, 3H), 7.02 (td, *J* = 8.3, 2.6, 1H), 6.32 (d, *J* = 2.4, 1H), 4.90–4.80 (m, 1H), 4.14–4.00 (m, 1H), 3.61 (app. tt, *J* = 10.9, 3.1, 1H), 3.30 (app. td, *J* = 13.4, 2.8, 1H), 3.21–3.12 (m, 1H), 3.02–2.93 (m, 1H), 2.62 (app. dd, *J* = 13.2, 11.5, 1H), 2.09–1.91 (m, 1H), 1.91–1.82 (m, 1H), 1.77–1.54 (m, 3H), 1.45 (app. tdd, *J* = 12.7, 10.1, 4.2, 1H), 1.31–1.15 (m, 1H), 0.53–0.42 (m, 2H), 0.33–0.18 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.5 (C), 165.9 (C), 164.3 (d, *J* = 243.5, CF), 142.3 (d, *J* = 7.4, CH), 136.0 (C), 131.0 (CH), 128.8 (4CH), 123.3 and 123.1 (CH), 121.2 (d, *J* = 4.0, CH), 118.6 and 117.9 (C), 111.0 (d, *J* = 36.0, CH), 57.6 (CH), 52.0 and 47.3 (CH_2), 46.6 and 42.2 (CH_2), 39.3 and 38.6 (CH), 30.8 and 29.9 (CH_2), 26.8 and 26.6 (CH_2), 15.1 (CH), 4.1 (CH_2), 3.6 (CH_2) ppm; *one*

quaternary carbon is not observed in ^{13}C NMR spectra; ^{19}F NMR (376 MHz, $CDCl_3$) δ = -66.46 (d, *J* = 8.1, $3F_{maj}$) and–66.75 (d, = 8.1, $3F_{min}$) ppm; HRMS (ESI-orbitrap): calcd for $C_{24}H_{24}FN_3O_2$: 406.1925, found 406.1919 $[M+H]^+$.

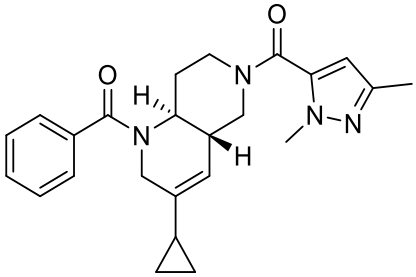
1-((4aS*,8aS*)-1-benzoyl-3-cyclopropyl-1,4a,5,7,8,8a-hexahydro-1,6-naphthyridin-6(2H)-yl)-2-(1-methyl-1H-indol-3-yl)ethan-1-one (MC709) (172a')



Following LP1: **116** (28 mg, 0.1 mmol) and 1-methyl-3-indoleacetic acid (28 mg, 0.2 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **172a'** as a white solid (16.4 mg, 36%, purity: 100%); Rt(UPLC): 1.82 min; IR (neat): *v* (max) cm^{-1} 3000, 2948, 1632, 1446, 1326; *NMR spectra display a mixture of rotamer* : ^1H NMR (400 MHz, $CDCl_3$): δ = 7.66–7.61 (m, $1H_{maj}$ + $1H_{min}$), 7.51–7.45 (m, $2H_{maj}$ + $2H_{min}$), 7.45–7.38 (m, $3H_{maj}$ + $3H_{min}$), 7.34–7.27 (m, $1H_{maj}$ + $1H_{min}$), 7.25–7.20 (m, $1H_{maj}$ + $1H_{min}$), 7.18–7.09 (m, $1H_{maj}$ + $1H_{min}$), 7.01 (s, $1H_{min}$), 6.96 (s, $1H_{maj}$), 6.29–6.26 (m, $1H_{maj}$), 6.25–6.23 (m, $1H_{min}$), 4.87–4.75 (m, $1H_{maj}$ + $1H_{min}$), 4.15–4.07 (m, $1H_{maj}$), 4.07–4.01 (m, $1H_{min}$), 3.92–3.82 (m, $2H_{maj}$ + $2H_{min}$), 3.79–3.74 (app. s, $3H_{maj}$ + $3H_{min}$), 3.53–3.43 (m, $1H_{maj}$ + $1H_{min}$), 3.26–3.20 ($1H_{maj}$), 3.15–3.05 (m, $1H_{maj}$ + $1H_{min}$), 2.87–2.69 (m, $1H_{maj}$ + $1H_{min}$), 2.38 (app. dd, *J* = 13.2, 11.0, $1H_{maj}$ + $1H_{min}$), 1.87–1.69 (m, $2H_{maj}$ + $2H_{min}$), 1.69–1.65 (m, $1H_{maj}$ + $1H_{min}$), 1.29–1.13 (m, $1H_{maj}$ + $1H_{min}$), 1.13–1.04 (m, $1H_{maj}$ + $1H_{min}$), 0.50–0.45 (m, $2H_{maj}$), 0.44–0.41 (m, $2H_{min}$), 0.33–0.18 (m, $2H_{maj}$), 0.17–0.11 (m, $1H_{min}$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.43 and 171.36 (C), 170.1 and 170.0 (C), 137.1 and 137.0 (C), 136.00 and 135.96 (C), 130.9 (CH), 128.6 (4CH), 127.7 and 127.5 (C), 127.24 and 124.16 (CH), 123.1 and 122.9 (CH), 122.0 and 121.9 (CH), 119.3 (CH), 119.1 (CH), 118.7 and 117.9 (C), 109.5 and 109.4 (CH), 107.9 and 107.8 (C), 57.6 (CH), 51.2 and 46.7 (CH_2), 45.6 and 41.3 (CH_2), 39.2 and 38.5 (CH), 32.90 and 32.97 (CH_3), 31.3 (CH_2), 30.6 and 29.9 (CH_2),

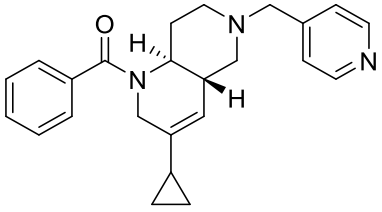
26.6 and 26.5 (CH_2), 15.0 and 14.9 (CH), 4.0 (CH_2), 3.6 (CH_2) ppm; HRMS (ESI-orbitrap): calcd for $C_{29}H_{31}N_3O_2$: 454.2489, found 454.2481 $[M+H]^+$.

((4aS*,8aS*)-1-benzoyl-3-cyclopropyl-1,4a,5,7,8,8a-hexahydro-1,6-naphthyridin-6(2H)-yl)(1,3-dimethyl-1H-pyrazol-5-yl)methanone (MC711) (172y)



Following LP1: **116** (28 mg, 0.1 mmol) and 1,3-dimethyl-1H-pyrazole-carboxylic acid (39 mg, 0.2 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **172y** as a colourless oil (17.4 mg, 43%, purity: 100%); Rt(UPLC): 1.56 min; IR (neat): *v* (max) cm^{-1} 3000, 2922, 2866, 1628, 1446, 1334, 1237; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.55–7.49 (m, 3H), 7.49–7.40 (m, 3H), 6.32 (d, *J* = 2.1, 1H), 6.08 (s, 1H), 4.82 (br. s, 1H), 4.15 (br. s, 1H), 3.89 (s, 3H), 3.60 (td, *J* = 10.7, 3.3, 1H), 3.35–3.12 (m, 2H), 2.26 (s, 3H), 1.93–1.78 (m, 2H), 1.77–1.66 (m, 2H), 1.31 (br. s, 1H), 1.23–1.16 (m, 1H), 0.50–0.47 (m, 2H), 0.31–0.14 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.5 (C), 161.2 (C), 147.1 (C), 135.8 (C), 131.1 (CH), 128.7 (4CH), 123.1 (CH), 106.2 (CH), 57.5 (CH), 46.8 (CH_2), 38.8 (CH), 37.8 (CH_3), 26.7 (CH_2), 15.0 (CH_3), 13.5 (CH), 4.1 (CH_2), 3.6 (CH_2) ppm; *two quaternary carbons are not observed in 13C NMR spectra, one secondary carbon was not observed in ^{13}C NMR spectra, but is detected in HSQC;* HRMS (ESI-orbitrap): calcd for $C_{24}H_{28}N_4O$: 405.2285, found 405.2279 $[M+H]^+$.

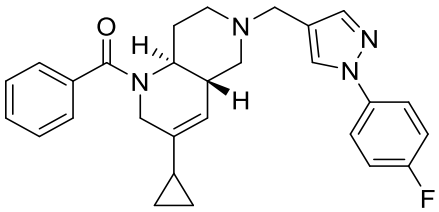
((4aS*,8aS*)-3-cyclopropyl-6-(pyridin-4-ylmethyl)-4a,5,6,7,8,8a-hexahydro-1,6-naphthyridin-1(2H)-yl)(phenyl)methanone (MC714) (173l)



Following LP2: **116** (28 mg, 0.1 mmol) and 4-pyridinecarboxaldehyde (19 μL, 0.2 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **173l** as a colourless oil (13.9 mg, 37%, purity: 100%); Rt(UPLC): 1.72 min; IR (neat): *v* (max) cm^{-1}

3000, 2922, 2803, 1640, 1315, 1274, 1226; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.58–8.53 (m, 2H), 7.56–7.51 (m, 2H), 7.48–7.39 (m, 3H), 7.32–7.28 (m, 2H), 6.31 (d, *J* = 2.1, 1H), 3.60 (d, J_{AB} = 14.1, 1H), 3.51 (d, J_{AB} = 14.1, 1H), 3.35 (td, *J* = 10.6, 3.5, 1H), 3.12 (dq, *J* = 12.7, 3.0, 1H), 3.02–2.98 (m, 1H), 2.97–2.92 (m, 1H), 2.29 (td, *J* = 12.2, 2.6, 1H), 2.02–1.98 (m, 1H), 1.99–1.87 (m, 1H), 1.70–1.57 (m, 2H), 1.58–1.42 (m, 1H), 1.18 (app. tt, *J* = 8.4, 5.2, 1H), 0.51–0.39 (m, 2H), 0.28–0.19 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.5 (C), 149.9 (2CH), 136.3 (C), 130.9 (CH), 128.7 (2CH), 128.6 (2CH), 124.1 (2CH), 123.2 (CH), 118.4 (C), 61.5 (CH_2), 58.9 (CH_2), 57.6 (CH), 53.2 (CH_2), 38.3 (CH), 30.0 (CH_2), 27.1 (CH_2), 15.1 (CH), 4.0 (CH_2), 3.5 (CH_2)ppm; *one quaternary carbon is not observed in 13C NMR spectra*; HRMS (ESI-orbitrap): calcd for $C_{24}H_{27}N_3O$: 374.2227, found 374.2219 $[M+H]^+$.

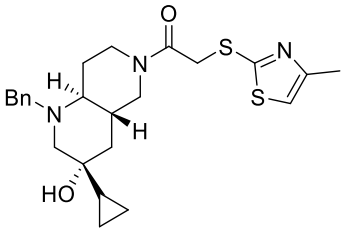
((4aS*,8aS*)-3-cyclopropyl-6-((1-(4-fluorophenyl)-1H-pyrazol-4-yl)methyl)-4a,5,6,7,8,8a-hexahydro-1,6-naphthyridin-1(2H)-yl)(phenyl)methanone (MC716) (173k)



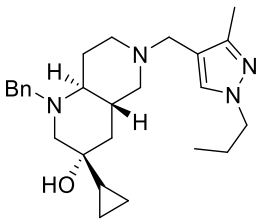
Following LP2: **116** (28 mg, 0.1 mmol) and 1-(4-fluorophenyl)pyrazole-4-carbaldehyde (38 mg, 0.2 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **173k** as a white solid (13.2 mg, 29%, purity: 100%); Rt(UPLC): 1.92 min; IR (neat): *v* (max) cm^{-1} 3000, 2899, 2780, 1636, 1513, 1222; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (s, 1H), 7.69–7.60 (m, 3H), 7.56–7.50 (m, 2H), 7.50–7.36 (m, 3H), 7.18–7.10 (m, 2H), 6.30 (d, *J* = 2.1, 1H), 3.60 (d, J_{AB} = 13.5, 1H), 3.51 (d, J_{AB} = 13.4, 1H), 3.34 (td, *J* = 10.6, 3.4, 1H), 3.18–3.11 (m, 2H), 3.10–3.05 (m, 2H), 2.29–2.21 (m, 1H), 2.04–1.92 (m, 1H), 1.88 (app. t, *J* = 10.9, 1H), 1.72–1.65 (m, 1H), 1.65–1.58 (m, 1H), 1.53–1.42 (m, 1H), 1.18 (app. tt, *J* = 8.3, 5.3, 1H), 0.49–0.41 (m, 2H), 0.32–0.17 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.5 (C), 161.2 (d, *J* = 246.3, CF), 142.0 (CH), 136.6 (d, *J* = 2.6, C), 136.3 (C) 130.8 (CH), 128.7 (2CH), 128.6 (2CH), 126.9 (CH), .123.2 (CH), 120.9 (d, *J* = 8.3, 2CH), 118.4 (C), 116.3 (d, *J* = 23, 2CH),

58.5 (CH_2), 57.7 (CH), 52.8 (CH_2), 52.2 (CH_2), 38.2 (CH), 29.9 (CH_2), 27.2 (CH_2), 15.1 (CH), 4.0 (CH_2), 3.5 (CH_2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -116.0 (m); HRMS (ESI-orbitrap): calcd for $C_{28}H_{29}FN_4O$: 457.2398, found 457.2390 $[M+H]^+$.

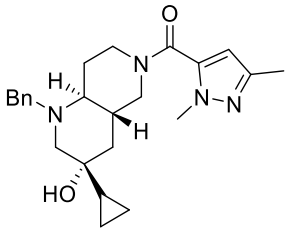
Other molecules:



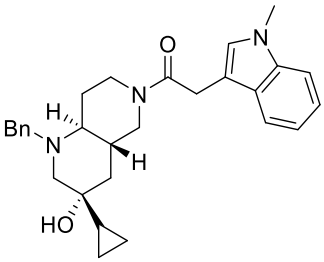
172n
LP1
4.5 mg, 10%
p: 100%
Rt: 1.60 min



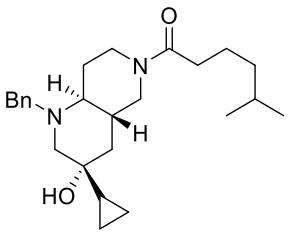
173b
LP2
12.6 mg, 30%
p: 100%
Rt: 1.55 min



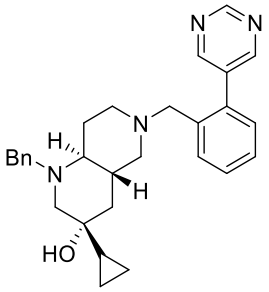
172b
LP1
25.4 mg, 62%
p: 100%
Rt: 1.43 min



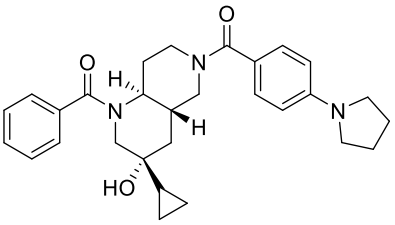
172d
LP1
8.1 mg, 10%
p: 100%
Rt: 1.68 min



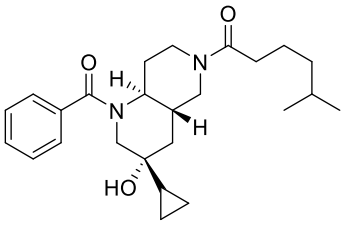
172p
LP1
22.8 mg, 57%
p: 100%
Rt: 1.90 min



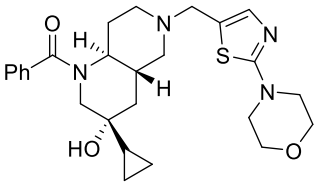
173c
LP2
10.8 mg, 23%
p: 100%
Rt: 1.90 min



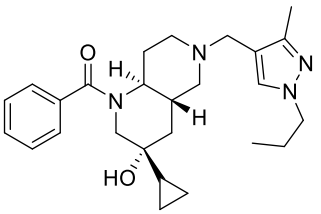
172l
LP1
7.8 mg, 16%
p: 94%
Rt: 1.15 min



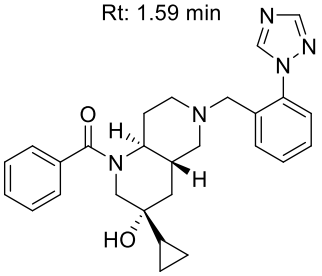
172v
LP1
23.2 mg, 56%
p: 100%
Rt: 1.59 min



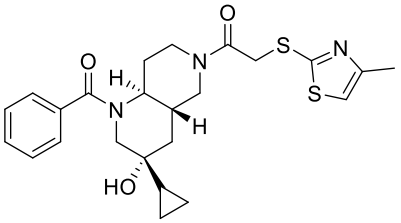
173f
LP1
15.8 mg, 32%
p: 100%
Rt: 1.21 min



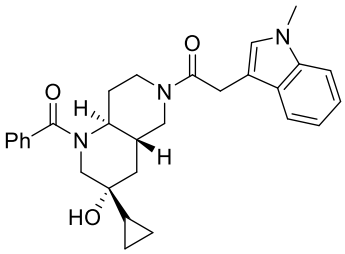
173g
LP2
25.7 mg, 59%
p: 100%
Rt: 1.22 min



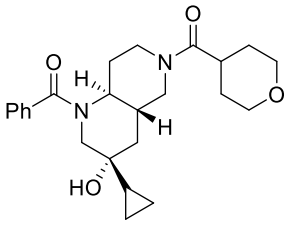
173i
LP2
17.4 mg, 38%
p: 100%
Rt: 1.35 min



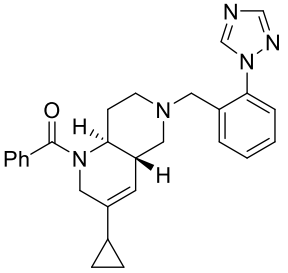
172s
LP1
10.4 mg, 22%
p: 95.7%
Rt: 1.0 min



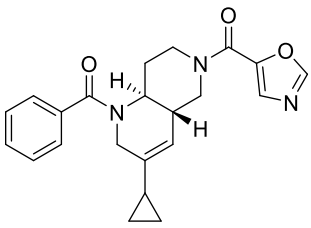
172k
LP2
17.9 mg, 38%
p: 99.4%
Rt: 1.79 min



172t
LP1
22.8 mg, 55%
p: 94.1%
Rt: 1.16 min



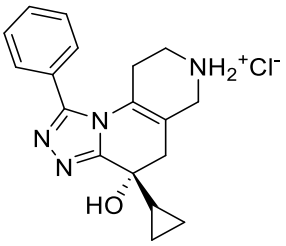
173m
LP2
17.5 mg, 40%
p: 100%
Rt: 1.85 min



172b'
LP1
15.4 mg, 41%
p: 100%
Rt: 1.46 min

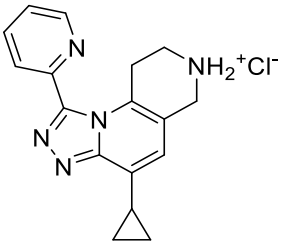
6.7.4. MC01022 Library

(Rac)-4-cyclopropyl-4-hydroxy-1-phenyl-4,5,6,7,8,9-hexahydro-[1,2,4]triazolo[4,3-a][1,6]naphthyridin-7-ium chloride (ALBA03-126) (137)



HCl 4 M in dioxane (1.37 mL, 5.51 mmol, 5.0 eq) was added to a solution of triazole **134d** (450 mg, 1.10 mmol) in MeOH (5.5 mL, 0.2 M) and stirred at r.t. for 16 h. After this time the volatiles were removed under reduced pressure and compound **137** was taken into the next step without further purification; IR (neat): *v* (max) cm^{-1} 3362 (br.), 2616, 2452, 1647, 1528, 1420; ^{1}H NMR (400 MHz, MeOD): δ = 7.91–7.84 (m, 2H), 7.80–7.76 (m, 1H), 7.70–7.76 (m, 2H), 3.98 (s, 2H), 3.44–3.55 (m, 1H), 3.28–3.22 (m, 1H), 2.89 (d, J_{AB} = 17.1, 1H), 2.73 (d, J_{AB}= 17.1, 1H), 2.55–2.43 (m, 1H), 2.39–2.28 (m, 1H), 1.53 (tt, *J* = 8.1, 4.1, 1H), 0.90–0.84 (m, 1H), 0.73–0.65 (m, 2H), 0.63–0.57 (m, 1H) ppm; ^{13}C NMR (101 MHz, MeOD): δ = 156.8 (C), 151.4 (C), 134.3 (CH), 131.6 (2CH), 130.4 (2CH), 125.2 (C), 123.6 (C), 123.2 (C), 67.3 (C), 45.0 (CH_2), 41.4 (CH_2), 38.0 (CH_2), 23.8 (CH_2), 18.0 (CH), 1.7 ($2CH_2$)ppm; HRMS (ESI-orbitrap): calcd for $C_{18}H_{20}N_4O$: 309.1710, found 309.1709 $[M+H]^+$.

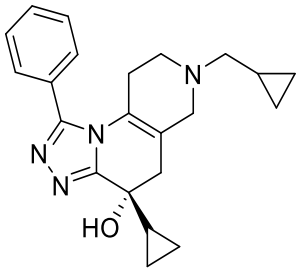
4-cyclopropyl-1-(pyridin-2-yl)-6,7,8,9-tetrahydro-[1,2,4]triazolo[4,3-a][1,6]naphthyridine (138)



HCl 4 M in dioxane (1.22 mL, 4.88 mmol, 5.0 eq) was added to a solution of triazole **134e** (400 mg, 0.98 mmol) in CH_2Cl_2 (4.9 mL, 0.2 M) and stirred at r.t. for 16 h. After this time the volatiles were removed under reduced pressure and compound **138** was taken into the next step without further purification; IR (neat): *v* (max) cm^{-1} 3309, 2970, 2926, 2407, 1695, 1423, 1166; ^{1}H NMR (400 MHz, MeOD): δ = 8.92 (dd, *J* = 4.7, 1.6, 1H), 8.26 (td, *J* = 7.7, 1.6, 2H), 8.28 (d, *J* = 7.7, 1H), 7.86 (dd, *J* = 4.7, 1.6, 1H), 7.73 (s, 1H), 4.55 (s, 2H), 3.78 (t, *J* = 6.1, 2H), 3.07, (t, *J* = 6.1, 2H), 3.08 (tt, *J* = 8.3, 4.2, 1H), 1.37–1.27 (m, 2H), 1.14–1.05 (m, 2H)

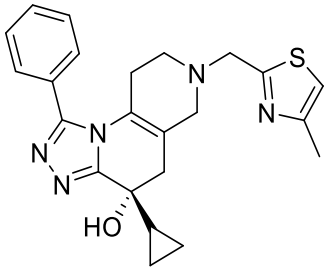
ppm; ^{13}C NMR (101 MHz, MeOD): δ = 150.2 (CH), 148.0 (C), 147.0 (C), 145.1 (C), 140.4 (CH), 132.9 (CH), 131.6 (C), 129.4 (CH), 128.4 (C), 128.3 (CH), 122.6 (C), 44.1 (CH_2), 41.1 (CH_2), 25.4 (CH_2), 11.1 (CH), 8.4 ($2CH_2$) ppm; HRMS (ESI-orbitrap): calcd for $C_{17}H_{17}N_5$: 292.1557, found 292.1549 $[M+H]^+$.

(Rac)-4-cyclopropyl-7-(cyclopropylmethyl)-1-phenyl-4,5,6,7,8,9-hexahydro-[1,2,4]triazolo[4,3-a][1,6]naphthyridin-4-ol (176e)



Following LP2: **137** (0.1 mmol) and cyclopropane carboxaldehyde (15 μL, 0.2 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **176e** as a colourless oil (14.3 mg, 39%, purity: 100%); Rt(UPLC): 1.18 min; IR (neat): *v* (max) cm^{-1} 3216, 3071, 3004, 2918, 2817, 2780, 1628, 1416; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54–7.40 (m, 5H), 3.28 (d, J_{AB} = 17.0, 1H), 3.12 (d, J_{AB} = 17.0, 1H), 2.71–2.58 (m, 2H), 2.49–2.40 (m, 2H), 2.33 (d, *J* = 6.6, 2H), 2.11 (d, J_{AB} = 16.6, 1H), 1.91 (d, J_{AB} = 16.6, 1H), 1.37 (tt, *J* = 8.2, 5.5, 1H), 0.92–0.79 (m, 1H), 0.70–0.63 (m, 1H), 0.62–0.54 (m, 1H), 0.54–0.43 (m, 4H), 0.12–0.07 (m, 2H) ppm; *OH proton is not observed;* ^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.4 (C), 151.2 (C), 130.4 (CH), 131.1 (2CH), 128.5 (2CH), 128.3 (C), 125.1 (C), 120.9 (C), 68.3 (CH_2), 62.8 (CH_2), 55.5 (CH_2), 49.6 (CH_2), 38.7 (CH_2), 27.2 (CH_2), 18.9 (CH), 8.3 (CH), 4.1 ($2CH_2$), 1.7 (CH_2), 0.5 (CH_2)ppm; HRMS (ESI-orbitrap): calcd for $C_{22}H_{26}N_4O$: 363.2179, found 363.2174 $[M+H]^+$.

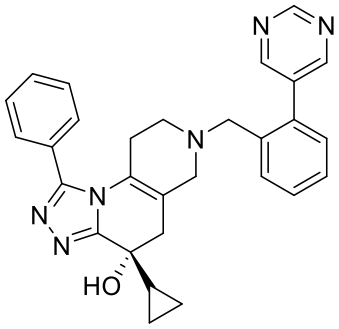
(Rac)-4-cyclopropyl-7-((4-methylthiazol-2-yl)methyl)-1-phenyl-4,5,6,7,8,9-hexahydro-[1,2,4]triazolo[4,3-a][1,6]naphthyridin-4-ol (176a)



Following LP2: **137** (0.1 mmol) and 4-methyl-1,3-thiazole-2-carboxaldehyde (22 μL, 0.2 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **176a** as a white solid(13.8 mg, 33%, purity: 93.4%); *sample contains 1.1% w/w of CH_3CN*; Rt(UPLC):

1.14 min; IR (neat): *v* (max) cm^{-1} 3209, 2922, 1684, 1418, 1300; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54–7.50 (m, 2H), 7.48–7.40 (m, 3H), 6.82 (s, 1H), 3.89 (s, 1H), 3.61 (s, OH), 3.32 (d, J_{AB} = 16.6, 1H), 3.23 (d, J_{AB} = 16.6, 1H), 2.72–2.57 (m, 2H), 2.54–2.47 (m, 1H), 2.44–2.38 (stack, 4H, including: 2.40, s, 3H), 2.10 (d, *J* = 16.3, 1H), 1.97–1.80 (m, 2H), 1.36 (tt, *J* = 8.4, 5.3, 1H), 0.69–0.63 (m, 1H), 0.62–0.54 (m, 1H), 0.53–0.43 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.0 (C), 155.3 (C), 152.8 (C), 151.2 (C), 130.3 (CH), 130.0 (2CH), 128.5 (2CH), 128.4 (C), 125.1 (C), 120.8 (C), 114.2 (CH), 68.4 (CH_2), 58.6 (CH_2), 55.5 (CH_2), 49.6 (CH_2), 35.6 (CH_2), 27.3 (CH_2), 18.9 (CH_3), 17.2 (CH), 1.8 (CH_2), 0.3 (CH_2) pm; HRMS (ESI-orbitrap): calcd for $C_{23}H_{25}N_5OS$: 420.1853, found 420.1845 $[M+H]^+$.

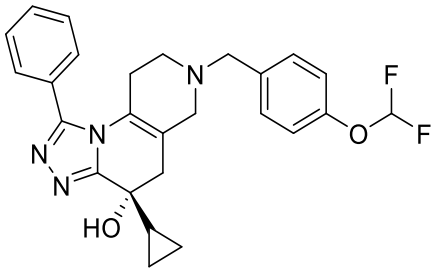
(Rac)-4-cyclopropyl-1-phenyl-7-(2-(pyrimidin-5-yl)benzyl)-4,5,6,7,8,9-hexahydro-[1,2,4]triazolo[4,3-a][1,6]naphthyridin-4-ol (176d)



Following LP2: **137** (0.1 mmol) and 2-(pyrimidin-5-yl)benzaldehyde (37 mg, 0.2 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **176d** as an off-white (23.1 mg, 48%, purity: 96.5%); Rt(UPLC): 1.29 min; IR (neat): *v* (max) cm^{-1} 3216, 3011, 1468, 1408, 1021; *sample contains 5.4% w/w;* IR (neat): *v* (max) cm^{-1} 3200, 2922, 1687, 1408, 764; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.17 (s, 1H), 8.76 (s, 2H), 7.56–7.37 (m, 9H), 3.78 (s, OH), 3.44 (s, 2H), 3.02 (d, J_{AB} = 17.0, 1H), 2.92 (d, J_{AB} = 17.0, 1H), 2.60–2.51 (m, 1H), 2.46–2.33 (m, 2H), 2.31–2.25 (m, 1H), 1.92 (d, J_{AB} = 17.2, 1H), 1.76 (d, J_{AB} = 17.2, 1H), 1.39–1.28 (m, 1H), 0.69–0.59 (m, 1H), 0.58–0.52 (m, 1H), 0.51–0.38 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.3 (CH), 156.6 (2CH), 155.2 (C), 151.1 (C), 135.8 (C), 135.6 (C), 135.1 (C), 130.9 (CH), 130.6 (CH), 130.3 (CH), 130.0 (2CH), 129.0 (CH), 128.5 (2CH), 128.4 (C), 128.2 (CH), 125.1 (C), 120.7 (C), 68.4 (CH_2), 59.6 (CH_2),

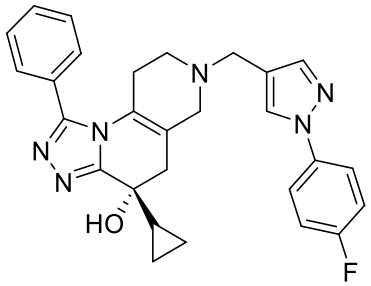
55.3 (CH_2), 48.8 (CH_2), 38.6 (CH_2), 27.3 (CH_2), 18.9 (CH), 1.8 (CH_2), 0.15 (CH_2) ppm; HRMS (ESI-orbitrap): calcd for $C_{29}H_{28}N_6O$: 477.2397, found 477.2392 $[M+H]^+$.

(Rac)-4-cyclopropyl-7-(4-(difluoromethoxy)benzyl)-1-phenyl-4,5,6,7,8,9-hexahydro-[1,2,4]triazolo[4,3-a][1,6]naphthyridin-4-ol (176b)



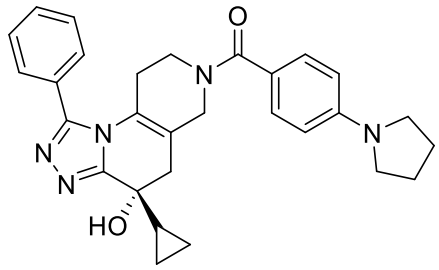
Following LP2: **137** (0.1 mmol) and 3-(difluoromethoxy)benzaldehyde (34 mg, 0.2 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **176b** as a white solid (18.9 mg, 41%, purity: 87.5%); Rt(UPLC): 1.46 min; IR (neat): *v* (max) cm^{-1} 3213, 1684, 1416, 1110, 1039; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.55–7.49 (m, 2H), 7.48–7.40 (m, 3H), 7.31–7.27 (m, 1H), 7.14 (d, *J* = 7.6, 1H), 7.02–6.99 (m, 1H), 6.51 (t, *J* = 77.9, CHF_2), 3.75 (s, OH), 3.59 (d, J_{AB} = 13.3, 1H), 3.56 (d, J_{AB} = 13.3, 1H), 3.17 (d, J_{AB} = 16.7, 1H), 3.06 (d, J_{AB} = 16.7, 1H), 2.65–2.58 (m, 1H), 2.57–2.51 (m, 1H), 2.43–2.33 (m, 2H), 2.11–1.95 (m, 2H), 1.92–1.81 (m, 1H), 1.37 (tt, *J* = 8.0, 5.7, 1H), 0.70–0.63 (m, 1H), 0.62–0.54 (m, 1H), 0.53–0.44 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.3 (C), 151.5 (t, *J* = 2.9, C), 151.2 (C), 140.2 (C), 130.3 (CH), 130.0 (2CH), 129.9 (CH), 128.5 (2CH), 126.0 (CH), 125.1 (C), 120.9 (C), 120.0 (CH), 118.4 (CH), 116.0 (t, *J* = 260.5, CHF_2), 68.4 (C), 61.7 (CH_2), 55.7 (CH_2), 49.3 (CH_2), 38.6 (CH_2), 27.4 (CH_2), 18.9 (CH), 1.77 (CH_2), 0.32 (CH_2) ppm; HRMS (ESI-orbitrap): calcd for $C_{26}H_{26}F_2N_4O_2$: 465.2097, found 465.2091 $[M+H]^+$.

(Rac)-4-cyclopropyl-7-((1-(4-fluorophenyl)-1H-pyrazol-4-yl)methyl)-1-phenyl-4,5,6,7,8,9-hexahydro-[1,2,4]triazolo[4,3-a][1,6]naphthyridin-4-ol (176c)



Following LP2: **137** (0.1 mmol) and 1-(4-fluorophenyl)pyrazole-4-carbaldehdye (38 mg, 0.2 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **176c** as a white solid (16.7 mg, 35%, purity: 100%); Rt(UPLC): 1.32 min; IR (neat): *v* (max) cm^{-1} 3198, 3071, 2937, 1513, 1401, 1211; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (s, 1H), 7.65–7.58 (m, 3H), 7.52–7.48 (m, 2H), 7.47–7.39 (m, 3H), 7.18–7.10 (m, 2H), 3.59 (d, J_{AB} = 13.5, 1H), 3.55 (d, J_{AB} = 13.5, 1H), 3.21 (d, J_{AB} = 16.6, 1H), 3.10 (d, J_{AB} = 16.6, 1H), 2.65–2.55 (m, 2H), 2.47–2.37 (m, 2H), 2.12–2.01 (m, 1H), 1.94–1.85 (m, 1H), 1.38 (tt, *J* = 7.9, 5.7, 1H), 0.71–0.62 (m, 1H), 0.64–0.54 (m, 1H), 0.54–0.43 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.2 (d, *J* = 246.9, CF), 155.2 (C), 151.2 (C), 141.8 (CH), 136.5 (d, *J* = 3.2, C), 130.3 (CH), 130.1 (2CH), 128.48 (2CH), 128.42 (C), 126.7 (CH), 125.2 (C), 120.80 (C), 120.78 (d, *J* = 8.1, 2CH), 119.3 (C), 116.4 (d, *J* = 23.3, 2CH), 68.4 (CH_2), 51.7 (CH_2), 49.1 (CH), 38.6 (CH_2), 27.5 (CH_2), 19.0 (CH), 1.8 (CH_2), 0.5 (CH_2) ppm; HRMS (ESI-orbitrap): calcd for $C_{28}H_{27}FN_6O$: 483.2303, found 483.2297 $[M+H]^+$.

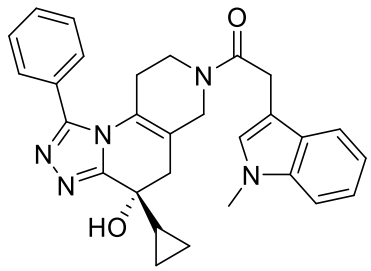
(Rac)-(4-cyclopropyl-4-hydroxy-1-phenyl-4,5,8,9-tetrahydro-[1,2,4]triazolo[4,3-a][1,6]naphthyridin-7(6H)-yl)(4-(pyrrolidin-1-yl)phenyl)methanone 175b



Following LP1: **137** (0.1 mmol) and 4-(1-pyrrolidinyl)benzoic acid (38 mg, 0.2 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **175b** as an off-white solid (7.1 mg, 15%, purity: 99.0%); Rt(UPLC): 1.36 min; IR (neat): *v* (max) cm^{-1} 3235, 3071, 2840, 1602, 1524, 1379, 1252; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57–7.43 (m, 5H), 7.33 (d, *J* = 8.4, 2H), 6.50 (d, *J* = 8.4, 2H), 4.35–4.18 (m, 2H), 3.69 (br. app. s, 1H), 3.52 (br. app. s, 1H), 3.35–3.27 (m, 4H), 2.61 (d, J_{AB} = 16.5, 1H),

2.46 (d, J_{AB}= 16.5, 1H), 2.14–2.04 (m, 2H), 2.05–1.99 (m, 4H), 1.43–1.35 (m, 1H), 0.75–0.58 (m, 2H), 0.57–0.46 (m, 2H) ppm; *OH resonance is not observed in ^{1}H NMR*; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.5 (C), 155.0 (C), 151.2 (C), 149.4 (C), 130.5 (CH), 129.9, (2CH), 129.5 (2CH), 128.7 (2CH), 128.2 (C), 120.8 (C), 110.9 (2CH), 68.4 (C), 47.7 ($2CH_2$), 38.2 (CH_2), 25.6 ($2CH_2$), 18.9 (CH), 1.8 (CH_2), 0.6 (CH_2) ppm; *three quaternary and two secondary carbons are not observed in ^{13}C NMR spectra*; HRMS (ESI-orbitrap): calcd for $C_{29}H_{31}N_5O_2$: 482.2550, found 482.2545 $[M+H]^+$.

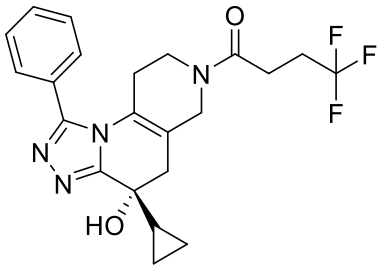
(Rac)-1-(4-cyclopropyl-4-hydroxy-1-phenyl-4,5,8,9-tetrahydro-[1,2,4]triazolo[4,3-a][1,6]naphthyridin-7(6H)-yl)-2-(1-methyl-1H-indol-3-yl)ethan-1-one (175d)



Following LP1: **137** (0.1 mmol) and 1-methyl-3-indoleacetic acid (38 mg, 0.2 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **175d** as a white solid (24.7 mg, 51%, purity: 100%); Rt(UPLC): 1.26 min; IR (neat): *v* (max) cm^{-1} 3235, 2929, 1625, 1416, 1013; *NMR spectra display a mixture of rotamers*: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (app. d, *J* = 7.9, $1H_{min}$), 7.53 (app. d, *J* = 8.0, $1H_{maj}$), 7.51–7.45 (m, $1H_{maj}$ + $1H_{min}$), 7.44–7.39 (m, $1H_{maj}$ + $1H_{min}$), 7.39–7.34 (m, $3H_{maj}$ + $3H_{min}$), 7.33–7.28 (m, $1H_{maj}$ + $1H_{min}$), 7.23 (app. d, *J* = 7.9, $1H_{maj}$ + $1H_{min}$), 7.13 (app. t, *J* = 7.4, $1H_{min}$), 7.08 (app. t, *J* = 7.4, $1H_{maj}$), 6.96 (s, $1H_{min}$), 6.89 (s, $1H_{maj}$), 4.24 (s, 2H), 4.17 (d, J_{AB} = 17.4, 1H), 4.07 (d, J_{AB} = 17.4, 1H), 3.85 (s, $2H_{min}$), 3.78 (s, $2H_{maj}$), 3.74 (s, $3H_{min}$), 3.72 (s, $3H_{maj}$), 3.52–3.45 (m, $1H_{maj}$ + $1H_{min}$), 2.63 (d, J_{AB} = 16.3, $1H_{maj}$), 2.56–2.44 (m, $1H_{maj}$ + $1H_{min}$), 2.31 (d, J_{AB} = 16.3, $1H_{min}$), 1.93–1.78 (m, 2H), 1.36 (tt, *J* = 8.2, 5.6, $1H_{maj}$ + $1H_{min}$), 0.72–0.55 (m, $2H_{maj}$ + $2H_{min}$), 0.55–0.39 (m, $2H_{maj}$ + $2H_{min}$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.4 and 170.3 (C), 155.0 and 154.9 (C), 151.1 and 150.9 (C), 137.1 And 137.0 (C), 130.6 and 130.4 (CH), 129.8 (4CH), 128.7 and 128.6 (CH), 128.1 and 128.0 (C), 127.5 and 127.4 (C), 127.2 and 127.1 (CH), 126.1

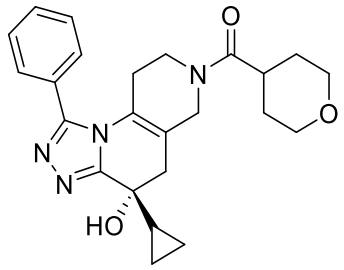
and 124.4 (C), 122.1 (CH), 120.6 and 119.2 (C), 119.4 and 118.8 (CH), 109.54 and 109.47 (CH), 107.2 and 107.1 (C), 68.12 and 68.07 (C), 47.9 and 44.5 (CH_2), 42.9 and 38.6 (CH_2), 38.2 (CH_2), 32.89 and 32.85 (CH_3), 31.8 and 31.5 (CH_2), 27.2 and 26.5 (CH_2), 18.8 and 18.7 (CH), 1.75 (CH_2), 0.3 (CH_2)ppm; HRMS (ESI-orbitrap): calcd for $C_{29}H_{29}N_5O_2$: 480.2394, found 480.2389 $[M+H]^+$.

(Rac)-1-(4-cyclopropyl-4-hydroxy-1-phenyl-4,5,8,9-tetrahydro-[1,2,4]triazolo[4,3-a][1,6]naphthyridin-7(6H)-yl)-4,4,4-trifluorobutan-1-one (175c)



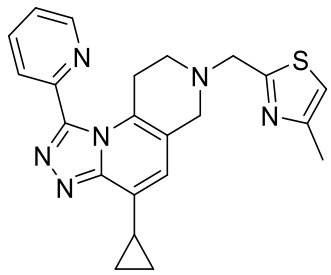
Following LP1: **137** (0.1 mmol) and 4,4,4-trifluorobutanoic acid (30 μL, 0.2 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **175c** as a white solid (25.6 mg, 59%, purity: 100%); Rt(UPLC): 1.18 min; IR (neat): *v* (max) cm^{-1} 3220, 3008, 2922, 1640, 1442, 1386, 1230; *NMR spectra display a mixture of rotamers*: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55–7.46 (m, $5H_{maj}$), 7.41–7.41 (m, $5H_{min}$), 4.21 (s, $2H_{min}$), 4.16–4.01 (m, $2H_{maj}$), 3.76–3.78 (m, $1H_{min}$), 3.53–3.37 (m, $2H_{maj}$ + $1H_{min}$), 2.72–2.57 (m, $2H_{maj}$ + $2H_{min}$), 2.55–2.44 (m, $4H_{maj}$ + $4H_{min}$), 2.15–2.08 (m, $2H_{maj}$ + $2H_{min}$), 1.43–1.34 (m, $1H_{maj}$ + $1H_{min}$), 0.72–0.59 (m, $2H_{maj}$ + $2H_{min}$), 0.59–0.45 (m, $2H_{maj}$ + $2H_{min}$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.45 and 168.43 (C), 155.04 and 154.99 (C), 151.2 and 150.1 (C), 130.7 and 129.9 (CH), 128.7 (4CH), 127.1 (q, *J* = 276.4, CF_3), 126.3 (C), 120.5 (C), 118.8 (C), 68.1 (C), 47.1 and 44.6 (CH_2), 42.0 and 38.5 (CH_2),38.3 and 38.2 (CH_2), 29.5 (q, *J* = 29.4, CH_2), 27.2 (CH_2), 26.5 and 26.1 (CH_2), 18.8 (CH), 1.8 (CH_2), 0.3 (CH_2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ = - 66.27–-66.76 (m) ppm; HRMS (ESI-orbitrap): calcd for $C_{22}H_{23}F_3N_4O_2$: 433.1846, found 433.1842 $[M+H]^+$.

(Rac)-(4-cyclopropyl-4-hydroxy-1-phenyl-4,5,8,9-tetrahydro-[1,2,4]triazolo[4,3-a][1,6]naphthyridin-7(6H)-yl)(tetrahydro-2H-pyran-4-yl)methanone (175a)



Following LP1: **137** (0.1 mmol) and tetrahydropyran-4-yl-carboxylic acid (26 mg, 0.2 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **175a** as a white solid (21.7 mg, 52%, purity: 95.7%); Rt(UPLC): 0.91 min; IR (neat): *v* (max) cm^{-1} 3276, 2948, 2840, 1625, 1442, 1125; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54–7.40 (m, 5H), 4.19 (s, 2H), 4.04–3.94 (m, 2H), 3.57–3.34 (m, 4H), 2.79–2.68 (m, 1H), 2.64 (d, J_{AB} = 16.4, 1H), 2.50 (d, J_{AB} = 16.4, 1H), 2.15–1.94 (m, 2H), 1.96–1.82 (m, 2H), 1.58 (d, J_{AB} = 13.6, 1H), 1.51 (d, J_{AB} = 13.6, 1H), 1.42–1.35 (m, 1H), 0.70–0.63 (m, 1H), 0.63–0.44 (m, 3H) ppm; *OH resonance is not observed in ^{1}H NMR spectra*; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.1 (C), 155.1 (C), 152.1 and 150.9 (C), 130.6 and 129.9 (CH), 129.8 and 128.7 (4CH), 126.4 (C), 120.9 (C), 119.0 (C), 68.0 (C), 67.2 ($2CH_2$), 47.2 and 44.6 (CH_2), 41.9 and 38.5 (CH_2), 37.8 (CH), 29.0 ($2CH_2$), 27.7 (CH_2), 26.5 (CH_2), 18.8 (CH), 1.8 (CH_2), 0.3 (CH_2) ppm; HRMS (ESI-orbitrap): calcd for $C_{24}H_{28}N_4O_3$: 421.2234, found 421.2228 $[M+H]^+$.

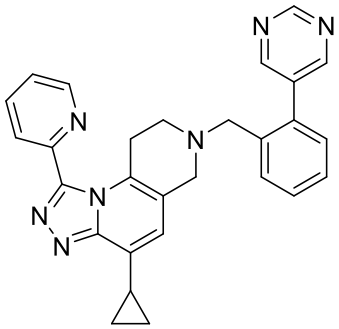
2-((4-cyclopropyl-1-(pyridin-2-yl)-8,9-dihydro-[1,2,4]triazolo[4,3-a][1,6]naphthyridin-7(6H)-yl)methyl)-4-methylthiazole (176f)



Following LP2: **138** (0.1 mmol) and 4-methyl-1,3-thiazole-2-carboxaldehyde (22 μL, 0.2 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **176f** as a white solid (13.5 mg, 34%, purity: 100%); Rt(UPLC): 1.16 min; IR (neat): *v* (max) cm^{-1} 2922, 2821, 1587, 1498, 1125; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.76–8.71 (m, 1H), 7.90 (d, *J* = 7.7, 1H), 7.84 (td, *J* = 7.7, 1.8, 1H), 7.44–7.38 (m, 1H), 6.84 (s, 1H), 6.49 (s, 1H), 3.98 (s, 2H), 3.71 (s, 2H), 2.80–2.69 (m, 4H), 2.63–2.57 (m, 1H), 2.42 (s, 3H), 1.19–1.08 (m, 2H), 1.02–0.91 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.6 (C), 152.6 (C), 151.7 (C), 149.2 (C), 148.9

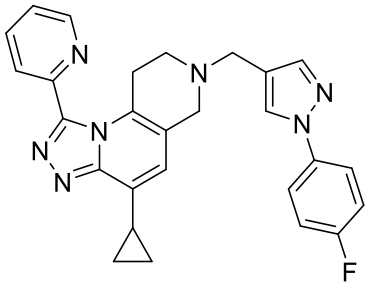
(CH), 147.2 (C), 136.7 (CH), 130.8 (C), 128.6 (C), 126.6 (CH), 124.2 (CH), 121.1 (CH), 120.9 (C), 114.3 (CH), 58.9 (CH_2), 54.3 (CH_2), 49.7 (CH_2), 28.5 (CH_2), 17.2 (CH_3), 11.3 (CH), 8.5 ($2CH_2$) ppm; HRMS (ESI-orbitrap): calcd for $C_{22}H_{22}N_6S$: 403.1699, found 403.1693 $[M+H]^+$.

4-cyclopropyl-1-(pyridin-2-yl)-7-(2-(pyrimidin-5-yl)benzyl)-6,7,8,9-tetrahydro-[1,2,4]triazolo[4,3-a][1,6]naphthyridine (176h)



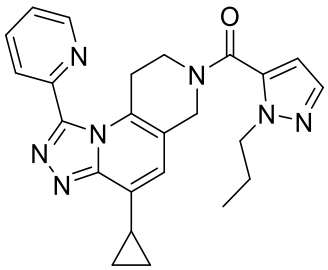
Following LP2: **138** (0.1 mmol) and 2-(pyrimidin-5-yl)benzaldehyde (37 mg, 0.2 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **176h** as a white solid (18.3 mg, 40%, purity: 99.8%); Rt(UPLC): 1.32 min; IR (neat): *v* (max) cm^{-1} 3005, 2916, 2117, 1507, 1408; ^1H NMR (400 MHz, $CDCl_3$): δ = 9.17 (s, 1H), 8.82 (s, 2H), 8.74–8.71 (m, 1H), 7.89 (d, *J* = 7.7, 1H), 7.83 (td, *J* = 7.6, 1.7, 1H), 7.54–7.48 (m, 1H), 7.48–7.37 (m, 3H), 7.30–7.28 (m, 1H), 6.43 (s, 1H), 3.49 (s, 2H), 3.45 (s, 2H), 2.62–2.57 (m, 3H), 2.56–2.52 (m, 2H), 1.15–1.08 (m, 2H), 0.96–0.90 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.5 (CH), 156.8 (CH), 151.7 (C), 149.1 (C), 148.9 (CH), 147.1 (C), 136.7 (CH), 135.8 (C), 135.7 (C), 134.9 (C), 131.1 (CH), 130.6 (CH), 129.6 (CH), 129.0 (CH), 128.6 (C), 128.2 (CH), 126.6 (CH), 124.2 (CH), 121.2 (CH), 120.8 (C), 59.7 (CH_2), 53.9 (CH_2), 49.9 (CH_2), 28.3 (CH_2), 11.3 (CH), 8.5 ($2CH_2$) ppm; one quaternary carbon is not observed in ^{13}C NMR spectra; HRMS (ESI-orbitrap): calcd for $C_{28}H_{25}N_7$: 460.2244, found 460.2239 $[M+H]^+$.

4-cyclopropyl-7-((1-(4-fluorophenyl)-1H-pyrazol-4-yl)methyl)-1-(pyridin-2-yl)-6,7,8,9-tetrahydro-[1,2,4]triazolo[4,3-a][1,6]naphthyridine (176g)



Following LP2: **138** (0.1 mmol) and 1-(4-fluorophenyl)pyrazole-4-carbaldehdye (38 mg, 0.2 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **176g** as a white solid (17.2 mg, 37%, purity: 99.1%); Rt(UPLC): 1.36 min; IR (neat): *v* (max) cm^{-1} 3004, 2922, 2780, 1513, 1401, 1222; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.71 (app. d, *J* = 4.8, 1H), 7.88 (app. d, *J* = 7.6, 1H), 7.85–7.80 (m, 2H), 7.64 (s, 1H), 7.63–7.59 (m, 2H), 7.41–7.37 (m, 1H), 7.13 (app. t, *J* = 8.5, 2H), 6.49 (s, 1H), 3.63 (s, 2H), 3.58 (s, 2H), 2.72–2.65 (m, 4H), 2.61 (tt, *J* = 8.5, 5.2, 1H), 1.19–1.08 (m, 2H), 0.98–0.90 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.2 (d, *J* = 246.8, CF), 151.7 (C), 149.2 (C), 148.9 (CH), 147.2 (C), 141.7 (CH), 136.6 (CH), 136.5 (d, *J* = 3.3, C), 130.7 (C), 128.6 (C), 126.6 (CH), 124.2 (CH), 121.2 (CH), 121.0 (C), 120.7 (d, *J* = 8.2, 2CH), 119.8 (C), 116.4 (d, *J* = 22.9, 2CH), 54.2 (CH_2), 51.8 (CH_2), 49.2 (CH_2), 28.4 (CH_2), 11.3 (CH), 8.6 ($2CH_2$) ppm; HRMS (ESI-orbitrap): calcd for $C_{27}H_{24}FN_7$: 466.2150, found 466.2142 $[M+H]^+$.

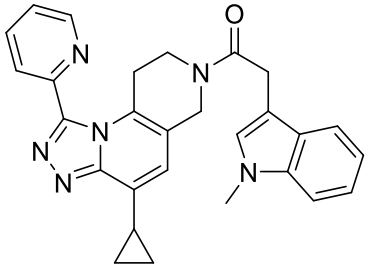
(4-cyclopropyl-1-(pyridin-2-yl)-8,9-dihydro-[1,2,4]triazolo[4,3-a][1,6]naphthyridin-7(6H)-yl)(1-propyl-1H-pyrazol-5-yl)methanone (175f)



Following LP1: **138** (0.1 mmol) and 1-propyl-1H-pyrazole-5-carboxylic acid (31 mg, 0.2 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **175f** as a white solid (19.5 mg, 46%, purity: 99.0%); Rt(UPLC): 1.10 min; IR (neat): *v* (max) cm^{-1} 2937, 1640, 1498, 1431, 1241; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.72 (br. app. s, 1H), 7.96 (app. d, *J* = 7.7, 1H), 7.87 (app. t, *J* = 7.7, 1H), 7.49 (s, 1H), 7.43 (dd, *J* = 7.7, 4.8, 1H), 6.53 (br. app. s, 1H), 6.34 (s, 1H), 4.74 (br. s, 2H), 4.22 (t, *J* = 7.2, 2H), 3.78 (br. s, 2H), 2.82–2.75 (m, 2H), 2.62 (tt, *J* = 8.5, 5.1, 1H), 1.88–1.79 (m, 2H), 1.20–1.11 (m, 2H), 1.01 (br. app. s, 2H), 0.85 (t,

J = 7.7, 3H) ppm; *^{13}C NMR resonances assigned with assistance from HSQC and HMBC spectra due to the broadening of the resonances owing to the rotamer effect, shifts marked with an asterisk were extracted from HSQC analysis:* ^{13}C NMR (101 MHz, $CDCl_3$): δ = 151.4 (C), 148.9 (CH), 148.6 (C), 147.3 (C), 137.8 (CH), 136.9 (CH), 134.3 (C), 132.2 (C), 126.3 (CH), 124.3 (CH), 106.1* (CH), 52.4 (CH_2), 31.8 (CH_2), 23.9 (CH_2), 11.3 (CH_3), 11.0 (CH), 8.7 ($2CH_2$) ppm; HRMS (ESI-orbitrap): calcd for $C_{24}H_{25}N_7O$: 428.2193, found 428.2183 $[M+H]^+$.[1]

1-(4-cyclopropyl-1-(pyridin-2-yl)-8,9-dihydro-[1,2,4]triazolo[4,3-a][1,6]naphthyridin-7(6H)-yl)-2-(1-methyl-1H-indol-3-yl)ethan-1-one (175e)



Following LP1: **138** (0.1 mmol) and 1-methyl-3-indoleacetic acid (38 mg, 0.2 mmol, 2.0 eq). Purification by prep-LCMS yielded compound **175e** as a white solid (20.0 mg, 43%, purity: 99.5%); Rt(UPLC): 1.29 min; IR (neat): *v* (max) cm^{-1} 1640, 1423, 1237, 738; *NMR spectra display a mixture of rotamers*: ^{1}H NMR (400 MHz, $CDCl_3$): δ = ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.73 (d, *J* = 5.0, $1H_{min}$), 8.52 (d, *J* = 4.9, $1H_{maj}$), 7.95–7.79 (m, $2H_{maj}$ + $2H_{min}$), 7.59 (d, *J* = 7.9, $1H_{maj}$), 7.55 (d, *J* = 7.9, $1H_{min}$), 7.39–7.33 (m, $1H_{maj}$ + $1H_{min}$), 7.30–7.20 (m, $2H_{maj}$ + $2H_{min}$), 7.16–7.06 (m, $1H_{maj}$ + $1H_{min}$), 6.96 (s, $1H_{maj}$), 6.92 (s, $1H_{min}$), 6.59 (s, $1H_{maj}$), 6.29 (s, $1H_{min}$), 4.71 (s, $2H_{maj}$), 4.55 (s, $2H_{min}$), 3.94–3.96 (m, $2H_{maj}$ + $2H_{min}$), 3.75 (s, $3H_{maj}$), 3.74–3.71 (m, $2H_{maj}$), 3.67 (s, $3H_{min}$), 3.58 (t, *J* = 5.8, $2H_{min}$), 2.67 (t, *J* = 6.0, $2H_{maj}$), 2.64–2.58 (m, $1H_{maj}$), 2.58–2.53 (m, $1H_{min}$), 2.48 (t, *J* = 5.9, $2H_{min}$), 1.24–1.08 (m, $2H_{maj}$ + $2H_{min}$), 1.05–0.96 (m, $2H_{maj}$), 0.94–0.89 (m, $2H_{min}$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.6 (C), 151.5 and 151.4 (C), 149.1 and 148.8 (CH), 147.4 and 147.2 (C), 136.9 and 136.8 (CH), 131.8 and 134.5 (C), 129.0 (C), 127.7 (CH), 127.43 and 127.40 (C), 127.2 and 127.1 (CH), 126.3 (CH), 124.4 and 124.1 (CH), 122.1 (CH), 120.6 and 120.4 (C), 119.8 and 119.5 (CH), 119.41 and 119.35 (C), 118.6 (CH), 109.6 and 109.5 (CH), 107.3 and 107.0 (C),

46.8 and 43.2 (CH_2), 42.7 and 38.6 (CH_2), 32.9 and 32.8 (CH_3), 31.7 and 31.2 (CH_2), 28.5 and 27.8 (CH_2), 11.4 (CH), 8.8 and 8.7 ($2CH_2$) ppm; *one quaternary carbon is not observed in* ^{13}C *NMR spectra*; HRMS (ESI-orbitrap): calcd for $C_{28}H_{26}N_6O$: 463.22409, found 463.2233 $[M+H]^+$.

6.8. Computational methods

6.8.1. Knime

The general method utilised for virtual library generation is explained in Chapter 5.1.1. Specific changes to the method are listen within each library design and synthesis chapter (from 5.2.2.2 to 5.2.2.4).

6.8.1.1. PMI plot workflow

The SDF file containing the compounds for the ALBA library was uploaded through the SDF reader. The second node generates 3D coordinates for each molecule in the library whilst the third calculate the optimized geometry based on the MMFF94 force field.[192] The properties are then used to calculate the principal moment of inertia and its derived properties in node 339. The plot is then generated by the last node and can be visualised by clicking and executing node 340 (Figure 53).

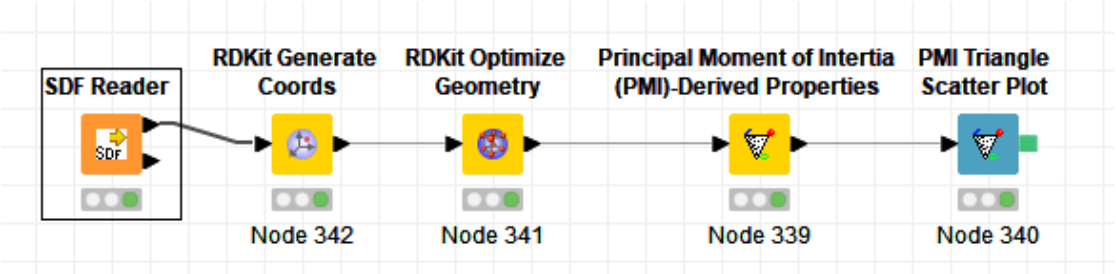


Figure 53: Knime workflow for PMI plot calculation.

6.8.1.2. List of nodes

Node	Description
SDF Reader 	Used to load Structure-Data Files (SDF) for subsequent processing. (i.e. reagent lists)
SDF Writer 	This node saves the processed molecules into Structure-Data Files at the end of the workflow.
MolConverter 	Used to convert data between different data types (i.e. from SDF to Smiles and vice versa)
Marvin Sketch 	Used to input the scaffolds into the workflows. It works as a drawing chemical editor.
Marvin Sketch  Reaction input	Used to input the reaction type into the workflows. It works as a drawing chemical editor.
RDKit Two Component Reaction 	Used to virtually perform the reaction in the workflow.
RDKit Optimize Geometry 	Optimizes the geometry for a given set of molecules and calculates the molecules energy

RDKit Generate Coords



Generates 2D or 3D coordinates for the input molecules

Principal Moment of Intertia (PMI)-Derived Properties



Calculates the PMI properties necessary to create a PMI plot

PMI Triangle Scatter Plot



Generates the PMI plot

Molecular Properties



Calculates the molecular formula

RDKit Descriptor Calculation



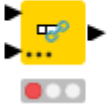
Calculates the molecular properties for Lipinski's Rules

Constant Value Column



Adds or replace a column containing a value in each row. (used to name different datasets when merging SDF files)

Concatenate



Used to merge the outputs of two nodes together

6.8.2. Datawarrior

6.8.2.1. Chemical descriptor calculation

Open in Datawarrior the desired SDF file containing the structures of the molecules you want to analyse. Select “chemistry” from the menu, then “from chemical structure”. From the list select “calculate descriptor”. Select the desired descriptor that will be calculated (Figure 54).

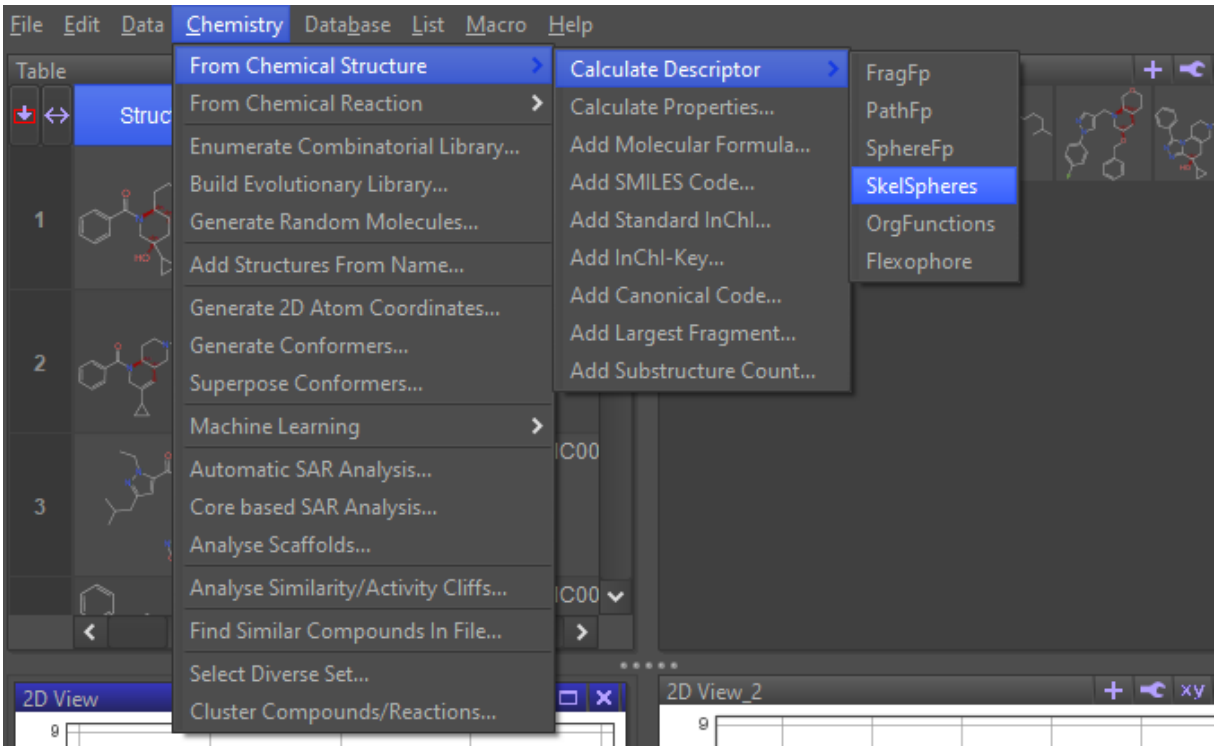


Figure 54: Screenshot of the path to follow to calculate a descriptor in Datawarrior.

The descriptor column will be added to the data and it will be available for further manipulation.

6.8.2.2. Compound filtering

The compounds were filtered using the very intuitive native function of Datawarrior. In the main Datawarrior interface, it is possible to visualise all the calculated parameters for the molecules (Figure 55).

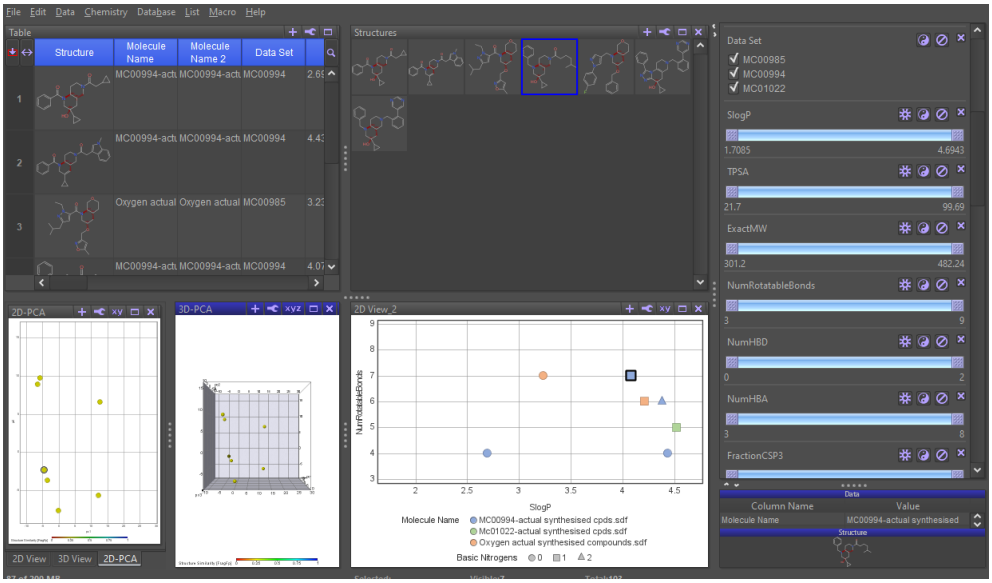


Figure 55: Main datawarrior interface.

You can modify the selection of molecules you are visualising in your interface by clicking on the numbers below the bars and typing the desired values (Figure 56).

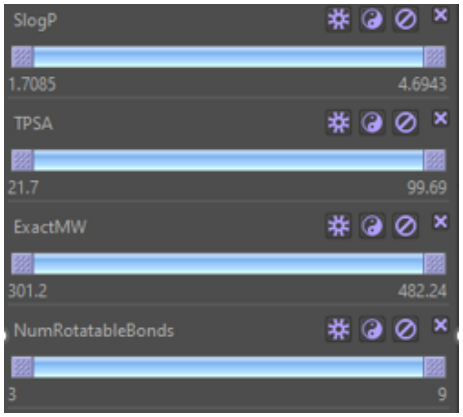


Figure 56: Parameters menu in Datawarrior.

6.8.2.3. Compound clustering

This function was used every time a virtual library was enumerated, and a selection of compound was to be selected for synthesis

Go to the “Chemistry menu”, select “Cluster Compounds/Reactions”, a new window will open (Figure 57)

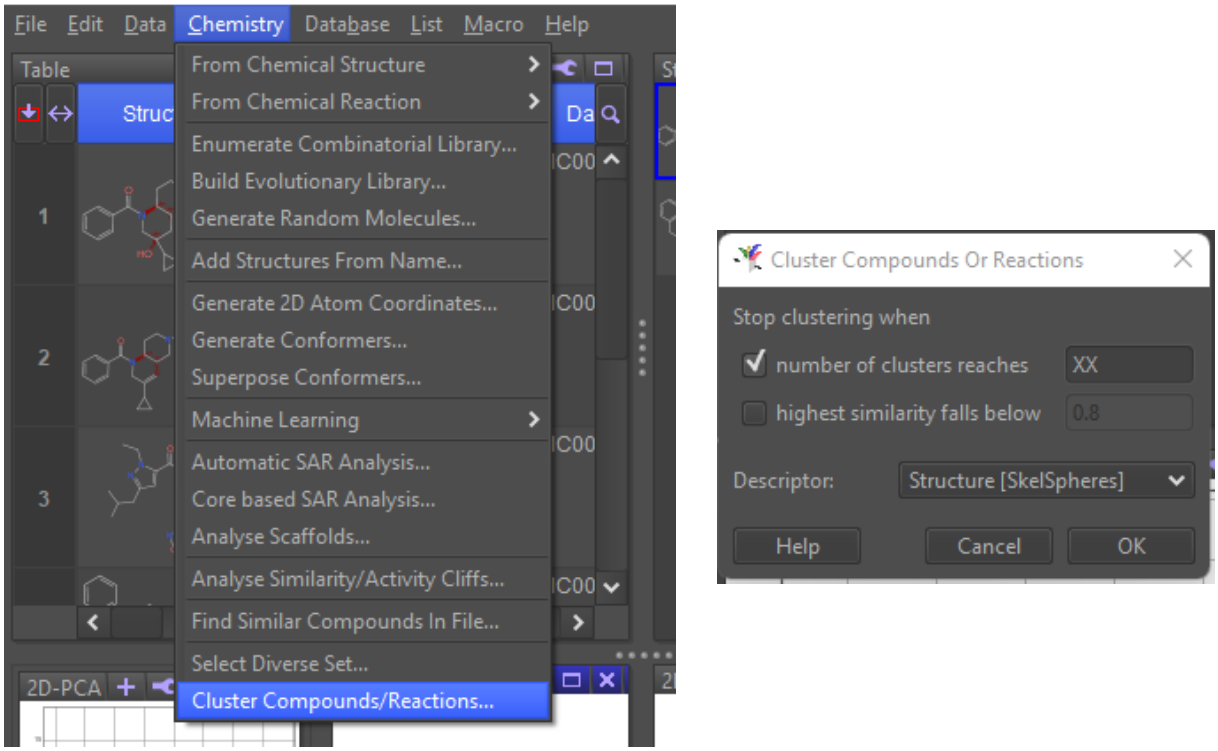


Figure 57: Cluster compound menu in Datawarrior.

In the new window you will be able to select when to stop the clustering. For this studies, the first option was selected and a desired number was inserted. In the dropdown menu, select the desired descriptor.

A new filter will appear on the right-hand side of the software interface where you can select the most representative compound from each cluster (Figure 58).



Figure 58: New filter added to select only representative compounds from clusters.

6.8.2.4. Calculate principal components

This function was used in every case a PCA analysis was performed (Chapter 5.2.3)

After the descriptor is calculated, click on “data”. A new menu will pop down. Select “Calculate principal components” (Figure 59).

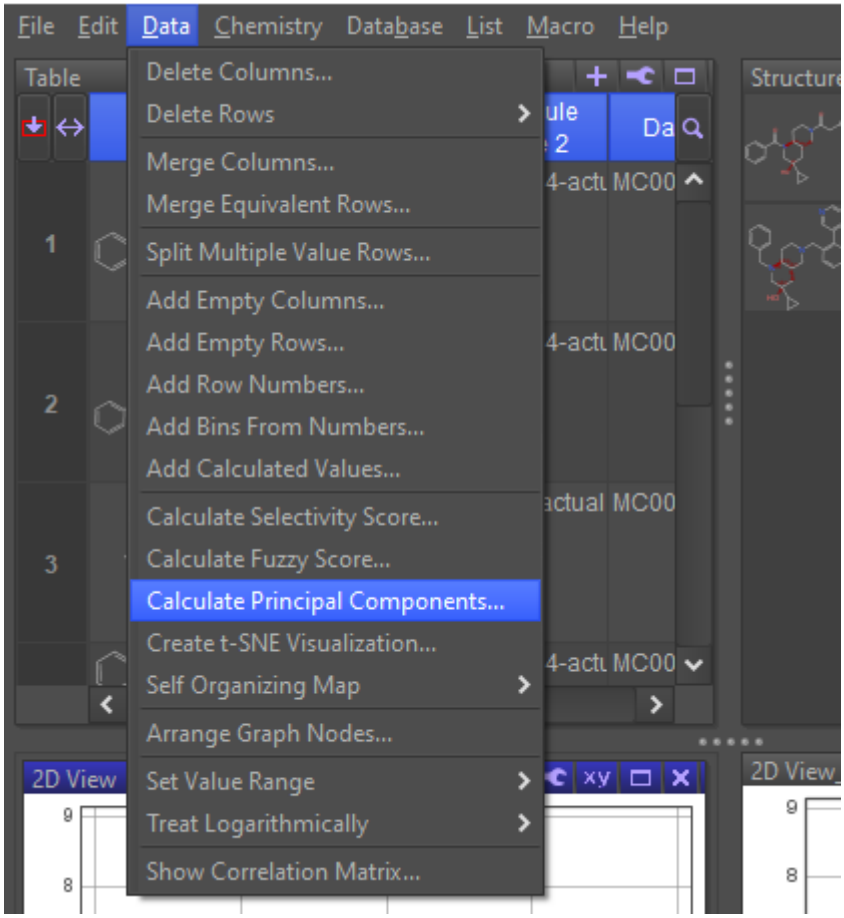


Figure 59: Principal component calculation menu in Datawarrior

A new window will open with different options to select.

N° of principal components to calculate: you can select up to 8 components. For this studies, I selected 3 components to be able to obtain 3D plots.

Used parameters: from this menu you decide upon which parameters the PCA will be calculated. Select the chemical descriptor of choice.

The software will automatically create 2D and 3D views of your results. If you want to explore the mathematical results, tick the "Open new window with eigenvalues" option. When all the parameters are chosen, press "ok" (Figure 60).

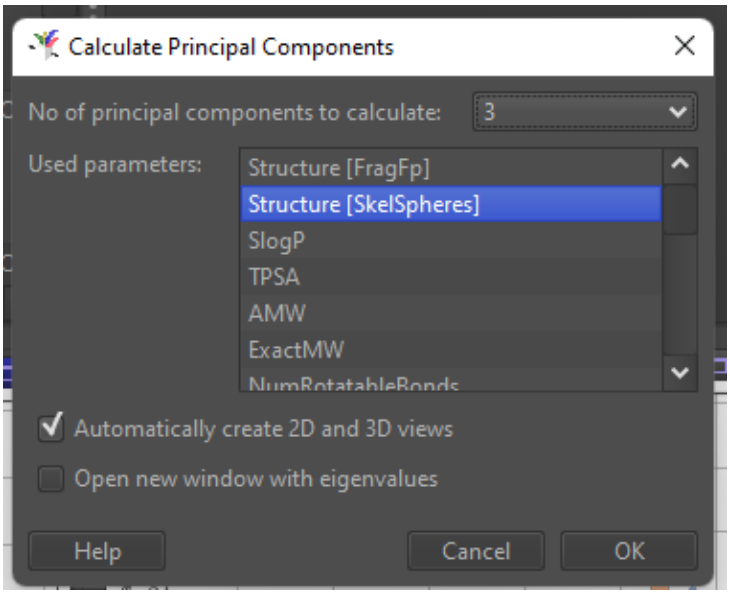


Figure 60. PCA parameters selection in Datwarrior.

The 2D and 3D views of your PCA will be showed in the main window of the software. You can then manipulate the colours, size, and shape of the objects in the plot. You can move around the 3D plot by right clicking and drag (for examples of the final plots see Figures 43, 45, 46, 47, Chapter 5.2.3.1).

6.8.2.5. Diversity Algorithm

This function was used to enumerate the compounds for the minor diastereomer of library MC00985 (Chapter 6.7.1.).

Open in Datawarrior the SDF file with the compound to be filtered. Go to the "Chemistry" menu and click on "Select diverse set". A new window will pop up (Figure 61).

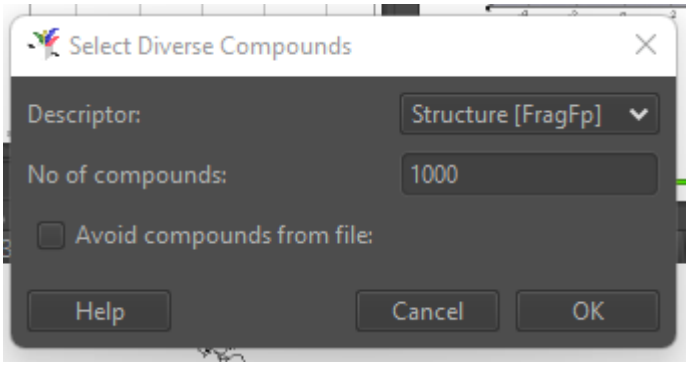


Figure 61: Diversity algorithm set up window.

In the set-up window, select the desired descriptor. For this algorithm, only fingerprint-based descriptors can be used, and tick the "avoid compounds from file option". A new window will open that allows you to upload another SDF file. Upload the file with the structures you want your new selection to be most different from (in case of library MC00985, I uploaded the enumerated virtual library relative to the major diastereomer).

The "number of compounds" option was set matching the number of compounds in the initial file to be filtered (for library MC00985 was set to 146), this was each compound will be ranked by diversity.

After pressing "ok" the software will calculate a "diversity rank", adding another column to the dataset. The progressing number in the column is the diversity rank assigned to the compound.

Compound with diversity rank 1 is the most different to all the others. Compound number 2 is the most different from compound number 1, and compound number 3 is the most different from compound 2 and 1.

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