Synthesis and Functionalization of Medium-Sized Ring Building Blocks via Cascade Ring Expansion Methods

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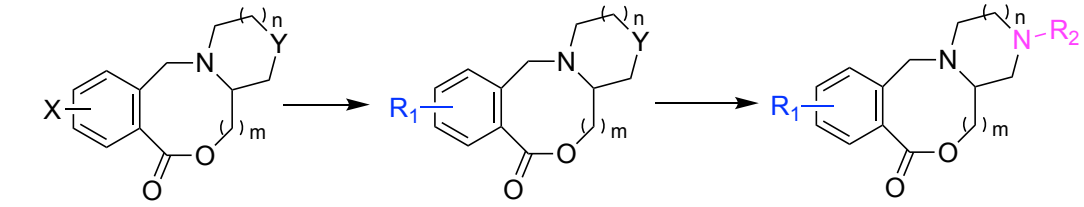
Abstract

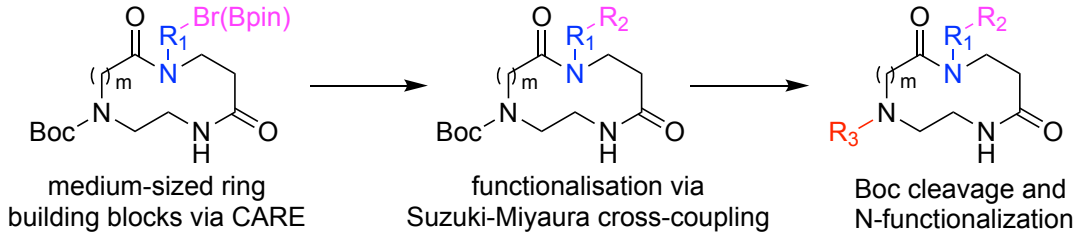
This thesis describes the synthesis and application of 3-D medium-sized ring building blocks using cascade ring expansion methods. The "Nucleophilic catalyst Induced Cascade ring Expansion (NICE)" method is the primary research approach used for the synthesis of medium-sized ring structures in this project, with additional work exploring the "Conjugate Addition/Ring Expansion (CARE)" method also described. Functionalization of the medium-sized ring building blocks generated was also explored using Suzuki-Miyaura cross-coupling and *N*-functionalisation reactions.

Chapter 2.1 describes the development of reaction pathway for the synthesis of medium-sized lactone ring building blocks using the NICE method. In this route, bromination and *N*-alkylation reactions were first employed to synthesize linear precursors containing both internal and terminal nucleophilic groups. These were then subjected to the NICE reaction to yield various mono-functionalised and difunctionalised medium-sized ring building blocks.

Chapter 2.2 provides detailed research on the functionalization reactions of these medium-sized ring building blocks obtained from the NICE method. Two approaches were used to explore Suzuki-Miyaura cross-coupling. First, bromine-containing medium-sized ring building blocks were cross-coupled with arylboronic acids. Then, some of the building blocks underwent Miyaura borylation to introduce Bpin groups, which were then cross-coupled with bromoaryl groups. Additionally, six different types of *N*-functionalization reactions were employed, and 10 different medicinally relevant groups were successfully combined with these medium-sized ring building blocks.



Chapters 2.3 and 2.4 focus on exploring the CARE method. Using a similar research process, a series of medium-sized lactam rings weas synthesized.



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Author's Declaration

I declare that this thesis is a presentation of original work and I am the sole author. This work has not previously been presented for an award at this, or any other, University. All sources are acknowledged as references.

Haimei Zhou

Abbreviations

s	singlet
d	doublet
m	multiplet
t	triplet
h	hour
min	minute
BPin	Boronic Pinacol Ester
S_N2	Substitution Nucleophilic Bimolecular reaction
SMCC	Suzuki-Miyaura cross-coupling
NICE	Nucleophilic catalyst Induced Cascade ring Expansion
CARE	Conjugate Addition/Ring Expansion
S_NAr	Substitution Nucleophilic Aromatic reaction
BINAP	2,2’-bis(diphenylphosphino)-1,1’-binaphthalene
Boc	tert-butoxycarbonyl
Ph	phenyl
t-Bu	tert-Butyl
T3P	Propanephosonic Acid Anhydride
eq.	equivalent
Hz	Hertz
IR	infra-red
J	coupling constant in Hz
rt	room temperature
dba	Dibenzylideneacetone
DIPEA	Diisopropylethylamine
dppf	1,1'-Bis(diphenylphosphino)ferrocene
DCM	Dichloromethane
Pd	palladium
M, mol	molar

Me	methyl
MP	melting point
MS	mass spectrometry
m/z	mass to charge ratio
NBS	N-bromosuccinimide
NMR	nuclear magnetic resonance
THF	Tetrahydrofuran
DMF	Dimethylformamide
$[\alpha]_D^{20}$	Specific rotation
HCl	Hydrogen chloride
Et_3N	Triethylamine
CDI	Carbonyldiimidazole
DMAP	4-Dimethylaminopyridine
BPO	Benzoyl peroxide
BOP	(Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate

1. Introduction

1.1 The Importance of Medium-sized Rings

Medium-sized rings are generally most commonly defined to be cyclic structures based on rings of 8–11 members. Medium-sized ring structures generally possess a certain rigidity and a distinctive 3-D conformation,[1] serving as a crucial structural core in a series of biologically active natural products [2] and synthetic molecules with useful medicinal properties[3] (see Figure 1 for examples). Medium-sized ring compounds show a variety of biological activities, such as anti-cancer effects,[4] anti-epileptic properties,[5] and the ability to inhibit enzymes.[6] However, due to the challenges associated with their synthesis, there are comparatively few examples showcasing medium-sized ring structures in pharmaceutical discovery.[7]

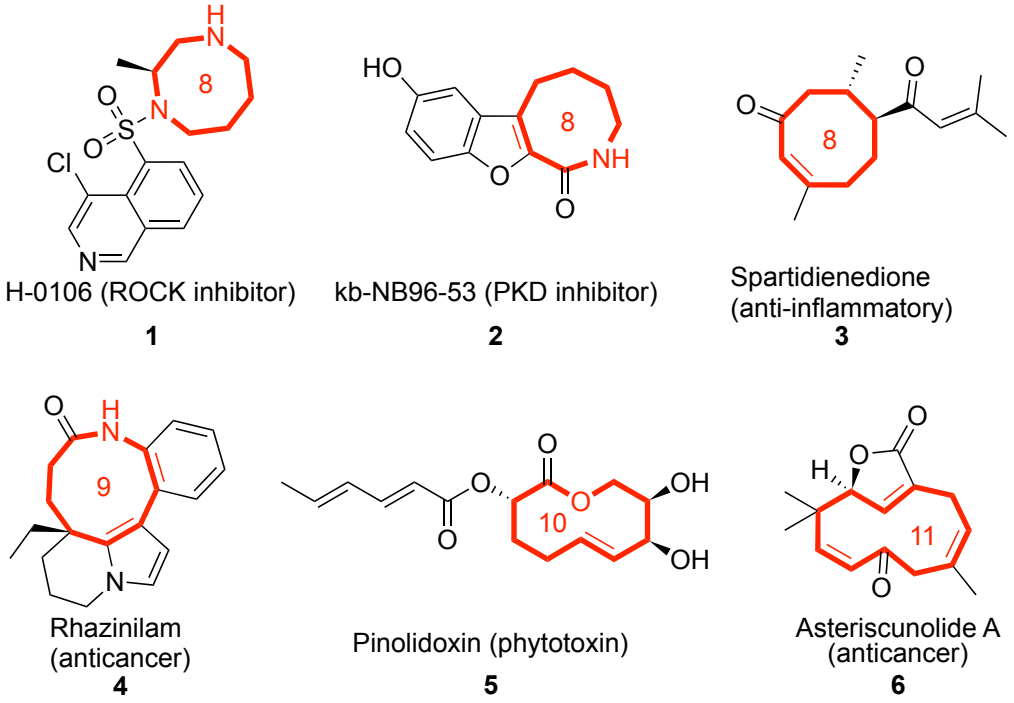


Figure 1. Bioactive molecules containing medium-sized rings.

Compound **1** features an eight-membered ring in its core structure and is a novel Rho-associated coiled-coil kinase (ROCK) inhibitor with potent intraocular pressure (IOP) lowering effects.[8] Compound **2**, a protein kinase D (PKD) inhibitor, also has an eight-membered ring structure. PKD is involved in numerous biological processes in the human body, including cell proliferation, differentiation, and signal transduction,[9] which makes PKD inhibitors important for applications in inhibiting cancer cell growth and metastasis. Similarly, natural product **3**, with an eight-membered ring as its core structure, is a non-steroidal anti-inflammatory drug (NSAID), which is widely used for pain relief, anti-inflammatory, antibacterial, and antipyretic effects.[10] Compound **4**, containing a nine-membered ring lactam structure, exhibits unique anti-mitotic activity and is a promising new candidate for anticancer drugs.[11] Natural product **5**, a ten-membered ring lactone produced by fungi, is a plant toxin.[12] As a natural product extract, compound **6** with an eleven-membered ring shows various biological activities,

including the induction of apoptosis in tumor cells and strong anticancer properties. Research is ongoing into its effects on tumor cell and leukemia cell viability.[13]

1.2 Challenges in Medium-sized Ring Synthesis and Unsworth Group Approaches using Ring Expansion

Traditional synthetic methods to prepare medium-sized rings involve the end-to-end cyclization of linear precursors. However, in such reactions there is a competition between intramolecular reactions (end-to-end cyclisation reactions) and intermolecular reactions (dimerization), as depicted in Figure 2. This competition often results in low reaction yields and other undesired side reactions. Various methods have been implemented to improve the efficiency of end-to-end cyclization, and some methods have proven effective, such as the use of highly diluted reaction conditions.[14] High dilution approaches can be successful in minimising competing intermolecular side reactions. However, they have notable drawbacks, especially in terms of scalability, practicality and the green/economic factors, considering the large amount of solvent waste generated.

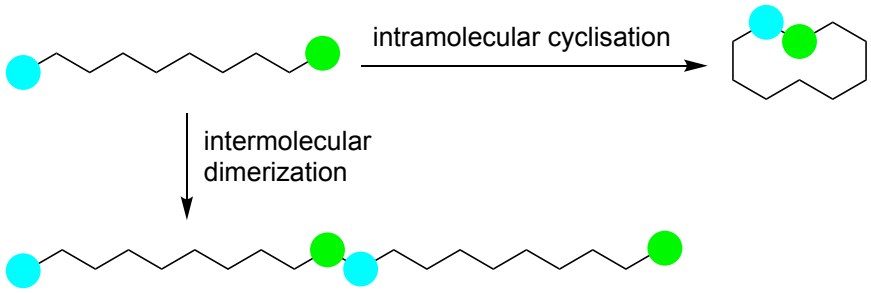


Figure 2. End-end cyclisation and competing dimerization of medium sized rings.

Due to ring strain and unfavourable entropic and enthalpic factors relative to normal-sized rings (5-7 membered rings),[15] the synthesis of medium-sized rings (8-11 membered rings) constitutes a formidable challenge in organic chemistry.[16] Given that normal-sized ring cyclisation reactions typically benefit from higher reactivity and lower kinetic barriers,[17] organic chemists have developed innovative ways to access medium-sized rings via ring expansion strategies that operate via normal-sized ring cyclisation steps.[18] These strategies involve using normal-sized rings as intermediates to form medium-sized rings,[19] thus avoiding the disadvantages associated with direct end-to-end cyclization.

1.2.1 Nucleophilic catalyst Induced Cascade ring Expansion (NICE)

A new method for the synthesis of medium-sized rings was reported by the Unsworth group in 2019, named internally in the group as “Nucleophilic catalyst Induced Cascade ring Expansion” (NICE). The NICE method involves a cascade ring expansion that completely avoids direct end-to-end cyclization.[20] The activation energy required to synthesize “normal” sized 5-7 membered rings via end-to-end cyclisation is typically lower than that for medium sized rings.[21] The NICE strategy is effective because it allows medium sized rings to be made by expanding normal sized ring intermediates formed in situ. NICE reactions are designed to operate exclusively via normal-sized ring transition states, as shown in Figure 3, which tends to make them much more kinetically favourable.

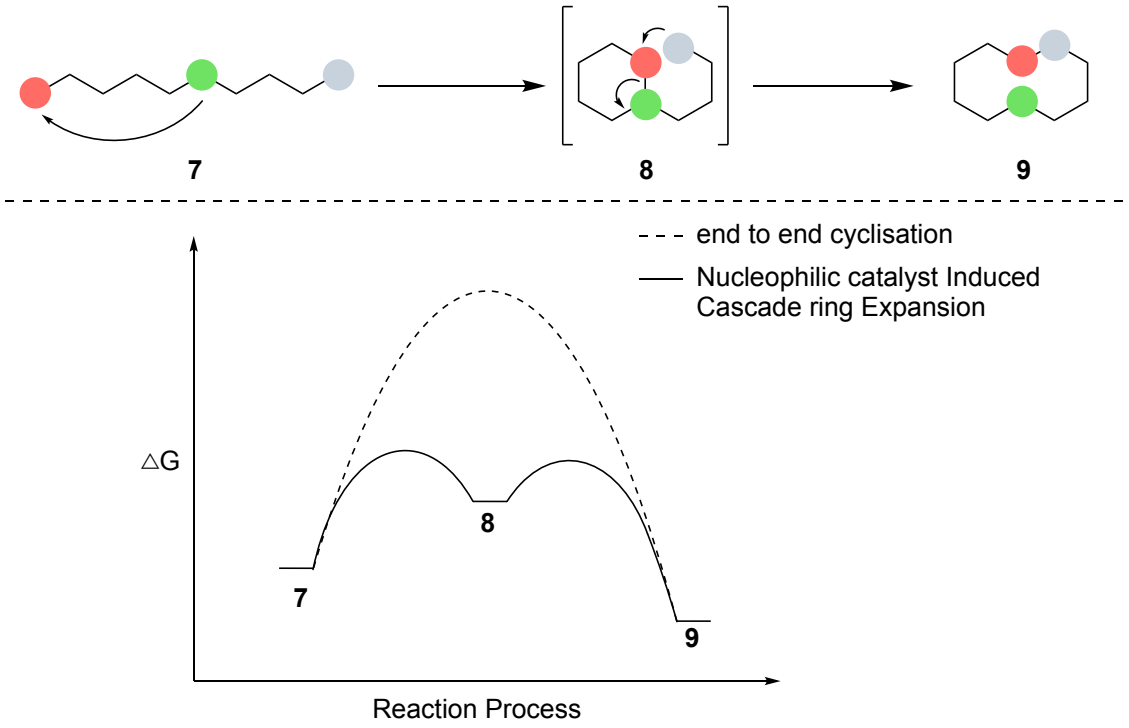


Figure 3. Schematic of the mechanism for NICE and hypothetical reaction coordinates for end-end cyclisation and ring expansion cascade.

The proposed reaction mechanism for a published NICE reaction is shown in Figure 4. The Unsworth group first investigated the cyclisation of linear precursor **10**, which contains a strategically placed pyridine group, when developing the NICE method. After ester group hydrolysis to form a carboxylic acid, a cascade ring expansion was initiated. Under the influence of the *N*,*N*-diisopropylethylamine (DIPEA) as a base, propane phosphonic acid anhydride (T3P) activates the carboxylic acid (highlighted in red), rendering it sufficiently electrophilic to form a six-membered ring intermediate **12** with the internal nucleophile (the pyridine nitrogen, highlighted in green). Subsequently, the terminal nucleophile (the alcohol, highlighted in blue) attacks the carbonyl group, and following fragmentation enables N-C bond cleavage and the expansion of the six-membered ring into a ten-membered ring **14**, which was formed in 90% yield.

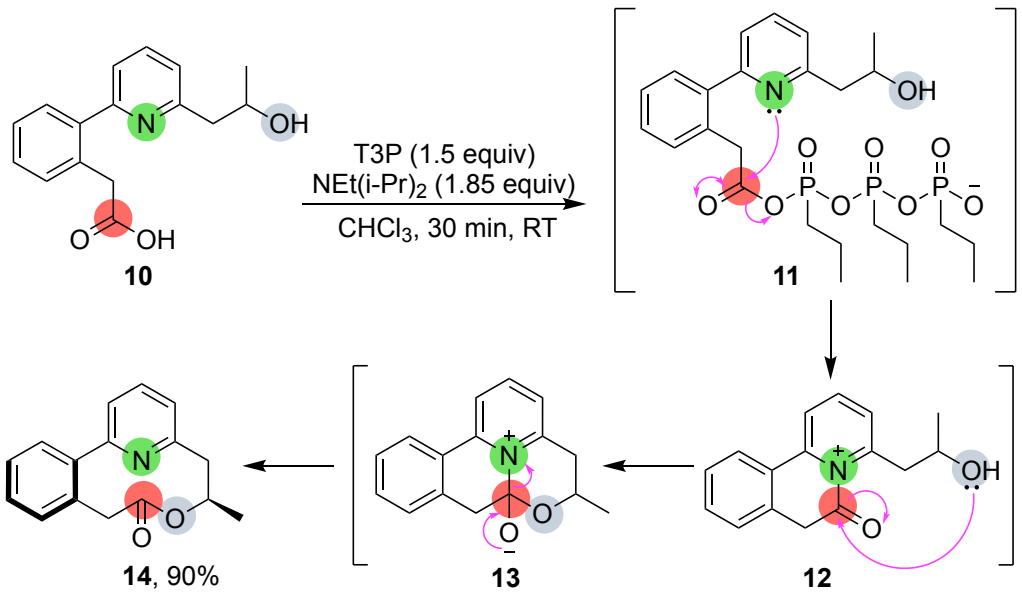


Figure 4. Schematic of the mechanism for NICE.

An important feature of some examples of the medium-sized rings obtained through the NICE method is the excellent diastereoselectivity of the products formed; in the example above, **14** was isolated as a single atropisomer. Stereoselectivity is important in drug discovery, as stereochemistry can greatly influence a drug's bioactivity, pharmacokinetics and toxicity.[22] However, the stereoselective synthesis of medium-sized rings is very rare in ring expansion methods, which makes the application of the NICE method in medicinal chemistry potentially significant.

Using high temperature NMR studies and DFT (Density Functional Theory) simulations,[23] the Unsworth group concluded that the barrier to rotation of the biaryl C–C bond in **15** is very high and that atropisomer **14** formed is very stable at room temperature. A proposed kinetic argument for the selective formation of atropisomer is presented in Figure 5, which explains why the reaction forms the product lactone **14** rather than the alternative atropisomer **19**. The observed stereochemical outcome aligns with the *N*-acylammonium ion in **15** being attacked by the alcohol on the Si-face, with the methyl group adopting a pseudo-equatorial orientation in a chair/boat conformation in transition state **16**. Conversely, forming the unobserved isomer **19** would require attacking the opposite face of the N-acylammonium ion, steric clashes with the methyl group in this orientation result in a higher energy barrier for the **17** → **19** reaction, making it less feasible.

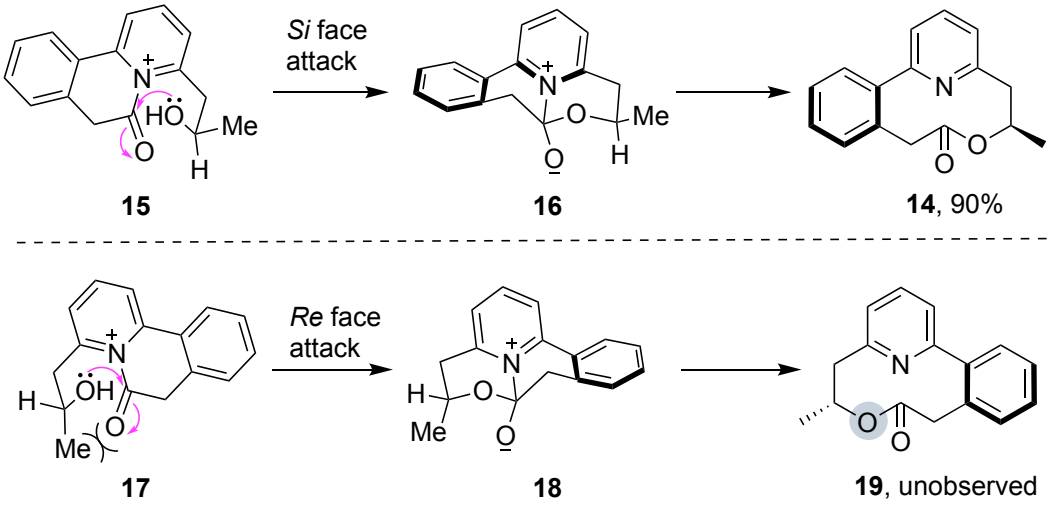


Figure 5. The mechanism and stereochemistry of the diastereoselective ring expansion.

As a control reaction, hydroxy acid **20**, which does not contain the internal pyridine nucleophile, was substituted for **10** and reacted under the same conditions to verify the proposed reaction mechanism. As expected, the ten-membered lactone did not form (Figure 6). The only isolated product was the twenty-membered lactone **21**, supporting the notion that the nitrogen atom in pyridine acts as the internal nucleophile in the NICE method.

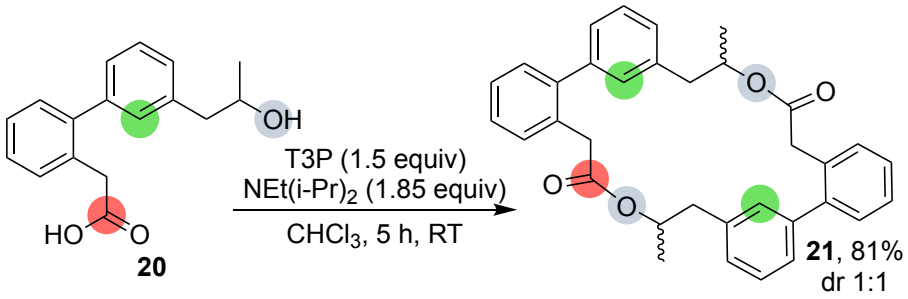


Figure 6. Results of NICE reaction without the internal pyridine nucleophile.

Further research revealed that substituting pyridine with aliphatic tertiary amines as the internal nucleophile also successfully catalysed the NICE reaction (Figure 7).[20] This allowed the synthesis of several low-molecular-weight medium-sized rings and significantly expanded the applicability of the NICE reaction. Similarly, when X = CH_2, the starting material lacks the internal nucleophile and the corresponding medium-sized ring product was not obtained. This once again indicates the vital importance of the internal nucleophile's presence for the success of the NICE reaction.

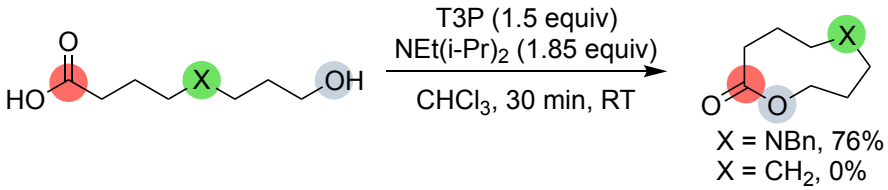


Figure 7. Comparison of the NICE results with and without the internal nucleophile.

Using the NICE approach, medium sized ring lactones can be formed in high yield, under mild conditions, without using high dilution conditions. To further expand the scope of this method, the Unsworth group performed several more NICE reactions. Initial experiments involved using pyridine derivatives as the internal nucleophile, with selected examples shown in Figure 8. Some excellent results were obtained, showing that the NICE method is highly versatile in its application.

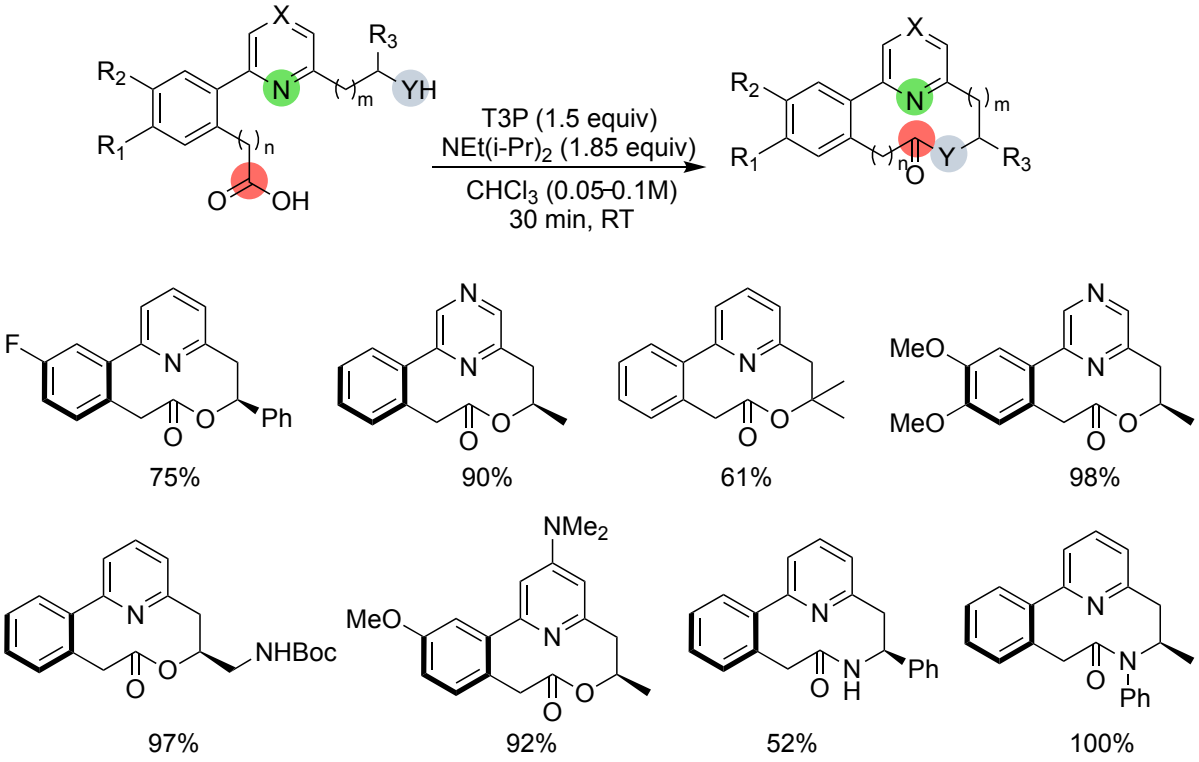


Figure 8. The general reaction scheme of medium sized lactones synthesised by NICE, catalysed by an internal nucleophilic pyridine.

Next, to determine whether the NICE method had even more general applicability, the Unsworth group successfully demonstrated a series of NICE reactions using aliphatic amines as the starting materials (for selected examples, see Figure 9). These initial explorations laid the groundwork for investigating the wider applicability of the NICE method in this thesis.

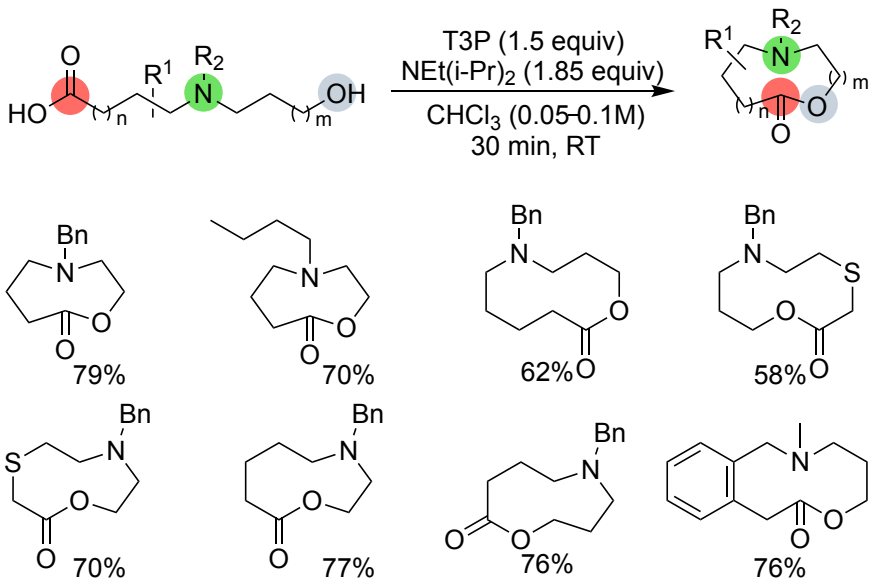


Figure 9. The general reaction scheme of medium sized lactones synthesised by NICE catalysed by an aliphatic amine as the internal nucleophile.

1.2.2 Conjugate Addition/Ring Expansion (CARE) Cascade Reaction

The Unsworth group first reported a novel conjugate addition/ring expansion (CARE) cascade reaction in 2021.[24] This reaction is simple to perform, typically gives high yields of products, and can be used to prepare medium-sized ring lactams from imides.

The proposed reaction pathway for the published CARE methods is shown in Figure 10. It begins with the reaction of a simple acryloyl chloride derivative in an *N*-acylation with lactam **22** to form imide **23** under basic conditions. Subsequently, this Michael acceptor is reacted with a primary amine nucleophile in a conjugate addition reaction (**23** → **24**), followed by a ring expansion cascade reaction (**24** → **25** → **26**), yielding a medium-sized cyclic lactam **26**.

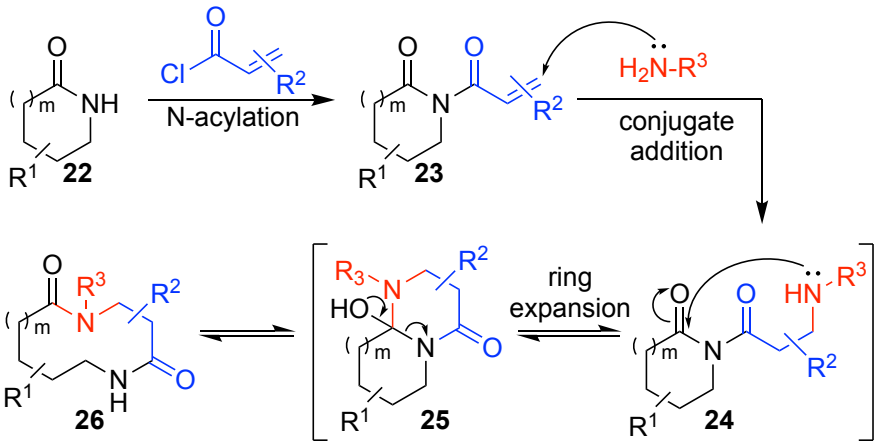


Figure 10. Schematic of the mechanism for CARE.

The Unsworth group has extensively explored the CARE reaction with many good results (Figure 11).[24] According to the group's previous findings, this reaction shows high compatibility with a wide range of functional groups, including esters, halides, various heterocycles, cycloalkanes, alkynes, and hydroxylamine derivatives. These results highlight

the powerful ability of the CARE reaction to incorporate different primary amine groups into medium-sized ring lactams. But at the same time, some failed and low-yield results indicate that steric hindrance has a significant impact on the experimental yield. This finding also provides guidance for the selection of target compounds in future research. The ease of operation and favourable reaction outcomes make the CARE method highly promising for applications in medical and biochemical fields.

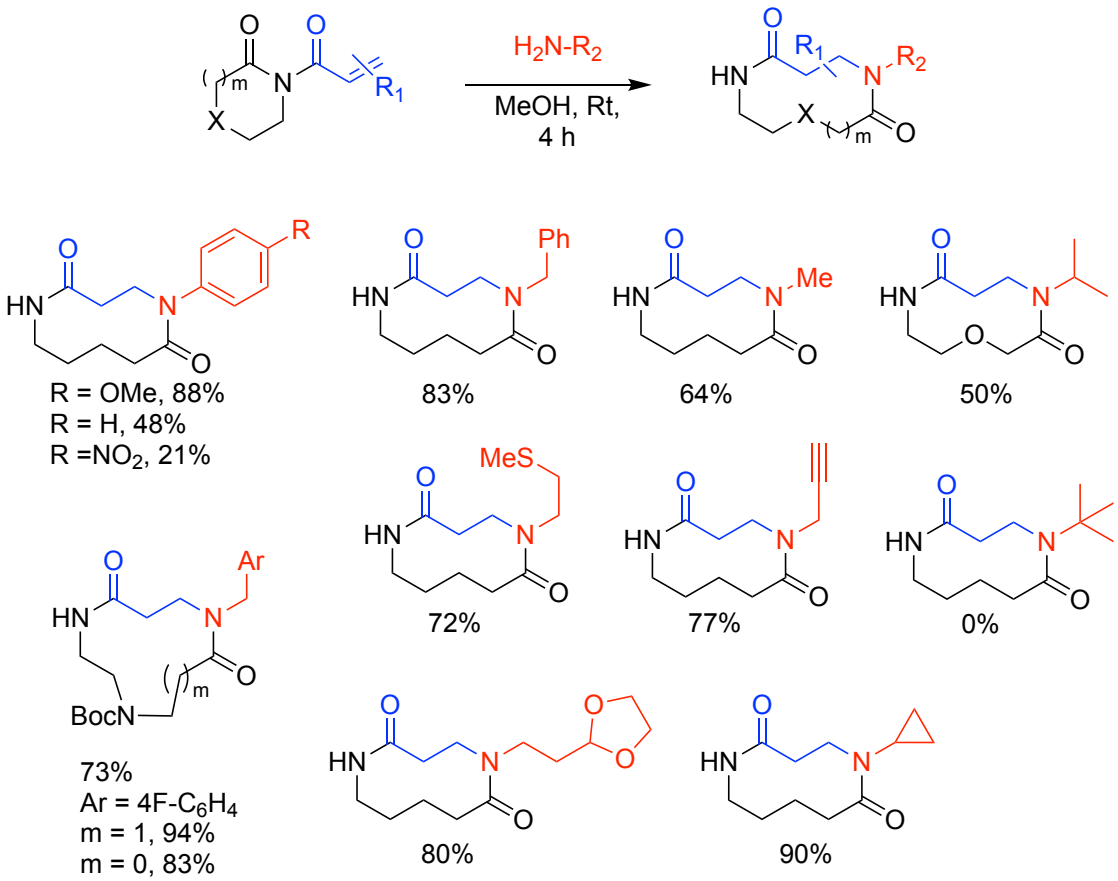


Figure 11. The general reaction scheme of medium sized lactams synthesised by CARE.

1.2.3 Other methods for synthesizing medium-sized rings in the Unsworth group

Recently, variants of the NICE method have been developed, with nine different NICE reaction modes now confirmed. Selected examples are shown in Figure 12.[25] For instance, diamino alcohol **27** reacts with thiophosgene at room temperature, forming a medium-sized ring product **30** through a five-membered ring cationic intermediate **29** via a NICE cascade. Similarly, both diol **32** and diamine **37** were converted into medium-sized ring products **35** and **40** through cationic intermediates **34** and **39**. When X = CH_2, the substrates **28**, **33**, and **38**, which then lack an internal nucleophile, do not produce medium-sized ring products **31**, **36**, and **41** under the same reaction conditions, which is given as supporting evidence that these reactions proceed via a NICE cascade.

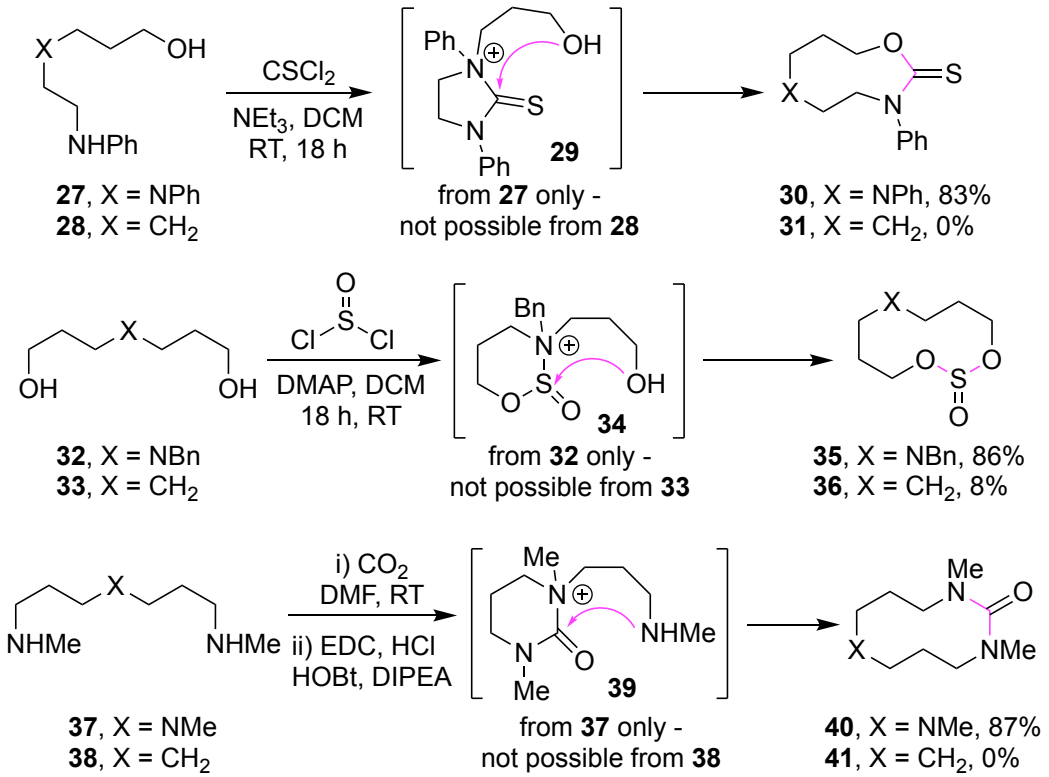


Figure 12. Selected examples of CRE cascade reactions in Unsworth group.

In 2015, the Unsworth group proposed a method for expanding lactam rings to medium-sized rings and large-ring lactones via side-chain insertion, named the Sequential Ring Expansion (SuRE) reaction.[26] As shown in Figure 13, lactam **42** reacts with acyl chloride **43** through an *N*-acylation reaction to form imide **44**, which then experiences sequential protecting group cleavage and ring expansion to yield the medium-sized ring **45**. Methods based on N-, O- and S-nucleophiles have all been reported. In the case when X is a sulfur atom, the reaction product is a thiolactone, and the yield of the SuRE reaction is typically lower, likely due to there being a lower thermodynamic driving force for formation of a thiolactone, compared to more stable lactam and lactone products formed in the N- and O-variants. This reflects the significant impact that the formation of thermodynamically stable bonds during ring expansion has on the yield of the SuRE method.

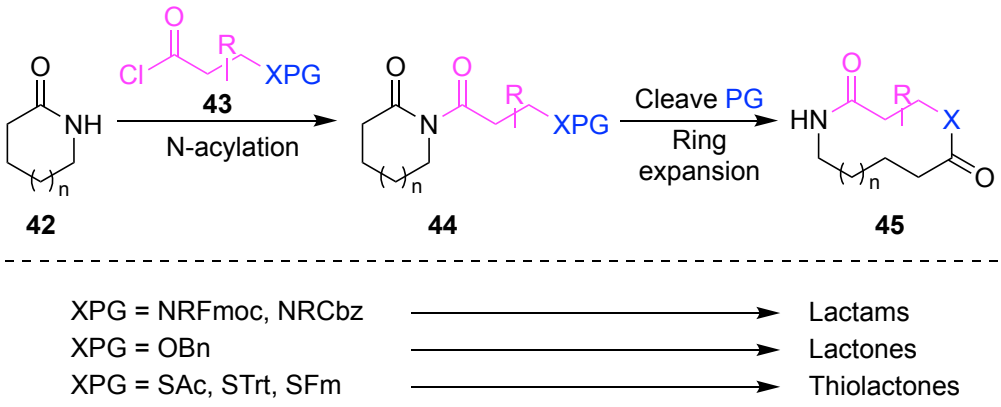


Figure 13. Schematic diagram of the SuRE method process

In addition, in 2023, the Unsworth group introduced two new ring expansion methods for the synthesis of medium-sized and large-sized ring sulfonamides **48**, as well as phosphate and phosphoramidate esters **53**.[27] In both methods, a ring strain-assisted cascade ring expansion approach is employed. Similar to the CARE method, Figure 14 shows the cascade ring expansion reactions involving sulfonamide and P=O systems. First, a primary amine nucleophile experiences a conjugate addition with cyclic vinyl sulfonamide **46**, resulting in the formation of a medium-sized ring sulfonamide **48** (Figure 14-a).

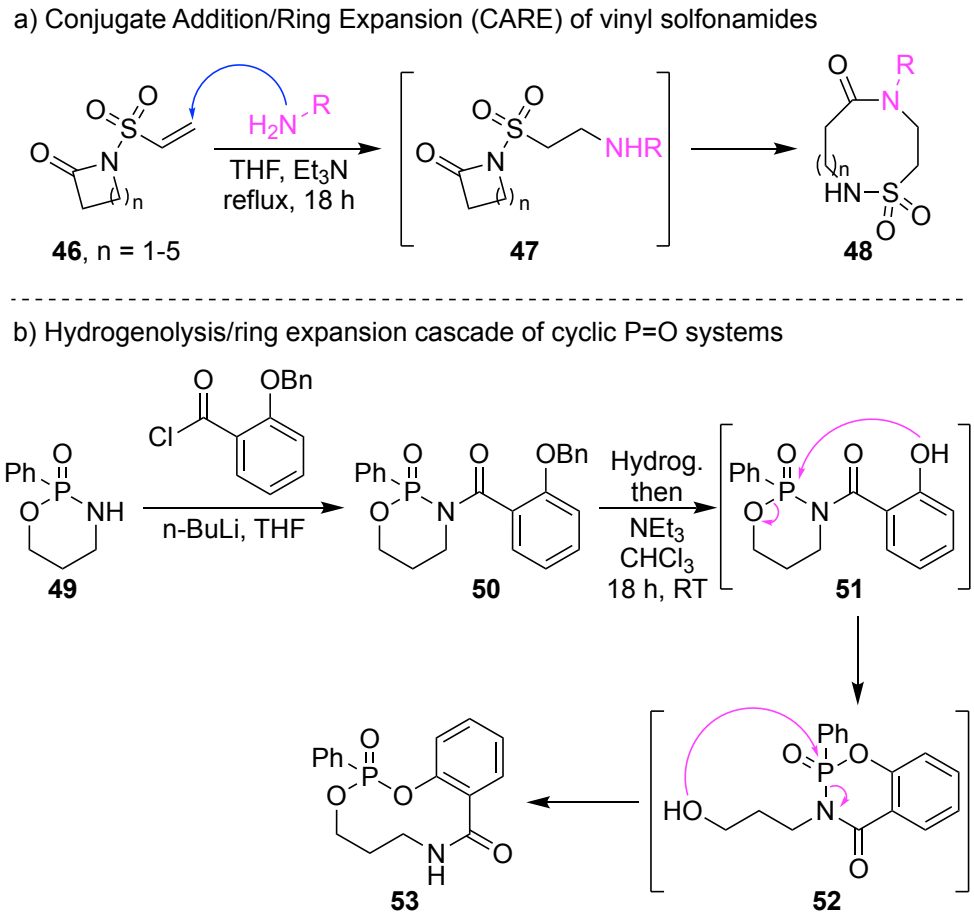


Figure 14. Schematic diagram of the CARE method of sulfonamides and phosphoramidate

This approach is also applicable to initial materials containing P=O groups (Figure 14-b). In this case, phosphoramidate **49** first undergoes N-acylation, followed by benzyl cleavage via hydrogenation, which initiates the cascade ring expansion. Based on the isolation of intermediates, a surprising result was shown. A rearrangement from **51** to **52** occurs before the ring expands to form **53**, which is different from other ring expansion reaction mechanisms. This rearrangement is believed to be driven by the cleavage of the weaker phosphorus-nitrogen bond to form a stronger phosphorus-oxygen bond, providing the driving force for the ring expansion in this case.

1.3 Other Methods for Synthesizing Medium-sized Rings

Aside from the ring expansion methods used by the Unsworth group, other strategies for synthesizing medium-sized rings include intramolecular cyclization, ring addition reactions, multicomponent cyclization reactions, and metal-catalyzed reactions. For example, Kitsiou and co-workers reported a method for the enantioselective synthesis of medium-sized ring lactones via iridium-catalyzed *Z*-selective asymmetric allylic substitution (Figure 15).[28] This method employs a series of α-benzyl-β-ketoesters, 1,3-diesters, and β-sulfonyl esters as intramolecular nucleophiles to obtain the corresponding medium-sized ring compounds (**55**). This approach provides a range of eight to eleven-membered ring lactones with good yields and excellent enantioselectivity.

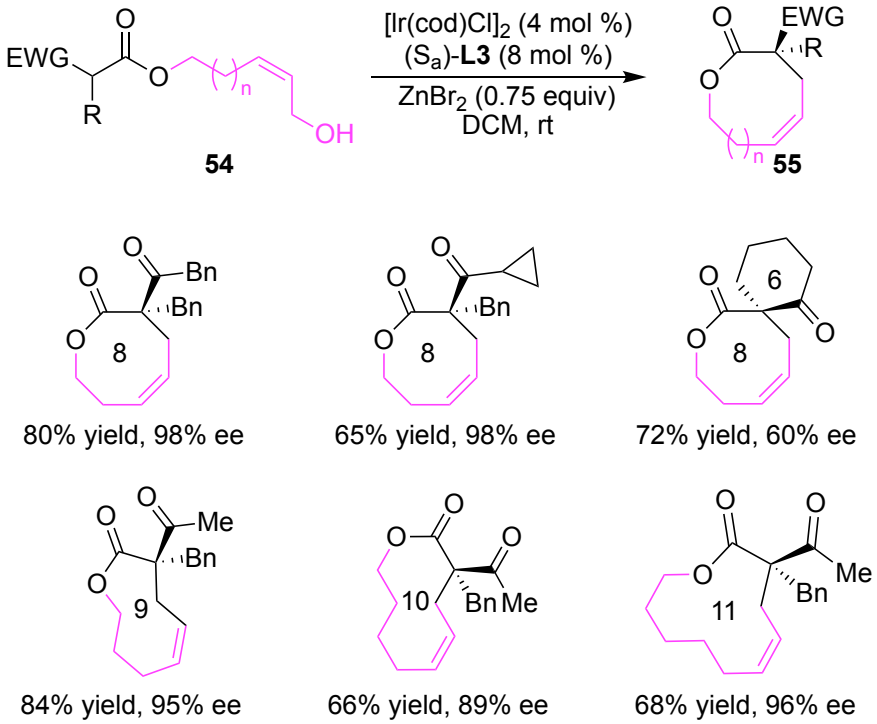


Figure 15. Schematic diagram of the iridium-catalyzed ring expansion

Clayden and colleagues developed a method for obtaining medium-sized rings based on ring expansion, initiated by lithiation (shown in Figure 16).[29] This method involves the selective deprotonation/lithiation of compound **56** using lithium diisopropylamide (LDA) and N,N'-dimethylpropyleneurea (DMPU) to form an organolithium intermediate **57**. Subsequently, an intramolecular anionic nucleophilic attack happened, leading to N-C bond cleavage and the formation of the n+3 membered ring compound **58**. This approach not only enables the efficient synthesis of medium-sized lactams but also shows adaptability to various substituents, and highlights its potential for applications in industrial synthesis and medicinal chemistry.

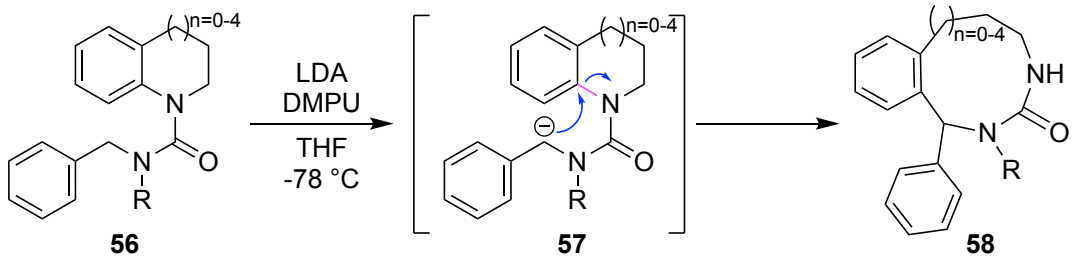


Figure 16. Schematic diagram of the Migratory ring expansion.

In 2023, Aleksandr and co-workers proposed a new method for synthesizing medium-sized ring azasulatams.[30] This method uses reductive cleavage to achieve ring expansion, differing from the method developed by the Unsworth group described earlier, which formed medium-sized sulfonamides through intramolecular nucleophilic attack. The process for this approach is shown in Figure 17. First, cyclic imidate **59** reacts with a taurine derivative to yield sulfonamide **60** containing two "normal" sized rings. Then the C-N bond between the two rings is cleaved under the action of sodium cyanoborohydride and acetic acid, resulting in medium-sized ring sulfonamide **61**.

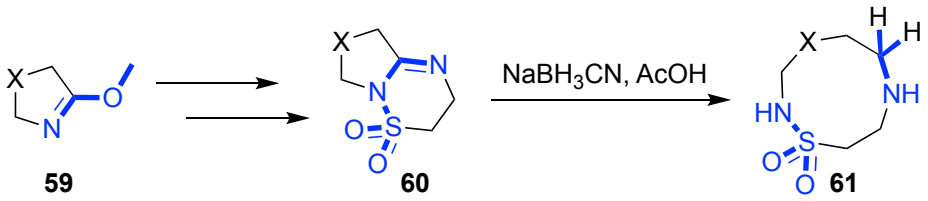


Figure 17. Schematic diagram of the $NaBH_3CN/AcOH$ reduction method ring expansion.

1.4 Building Blocks in Drug Discovery

During the process of drug design and discovery, there has been a predominant focus on optimizing synthetic routes based on the final structure of compounds, while the selection and design of building blocks have been relatively neglected.[31] Nowadays, it is recognized that purposefully designing new building blocks can enhance the diversity and novelty of small molecules to be assessed in bioassays, thereby improving the quality of drug candidates.[32]

Some examples of building blocks containing small and normal sized rings are shown in Figure 18. However, the synthesis and application of new building blocks containing medium-sized rings has not been reported. Addressing this, by actively targeting the design and synthesis of new medium-sized ring building blocks, as we have done in the work described in this Thesis, has the potential to offer new perspectives and opportunities in drug discovery.

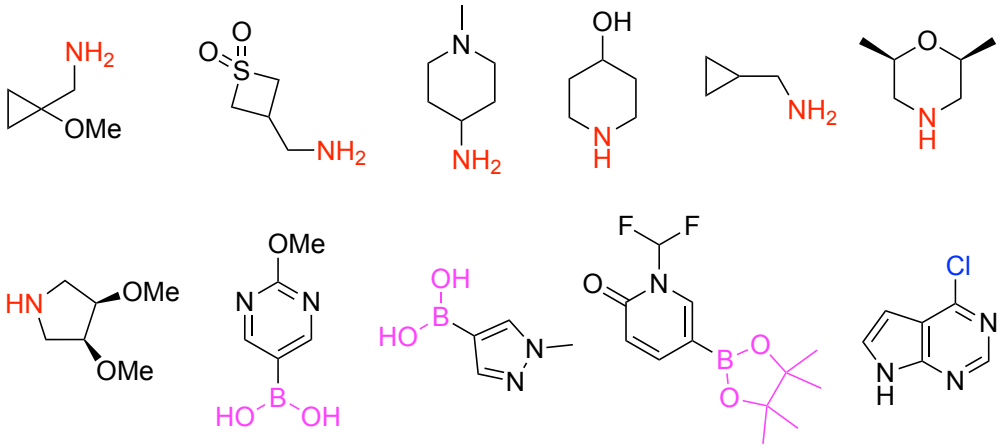


Figure 18. Building blocks from AstraZeneca.[33]

To potentially shorten the drug discovery process, the O'Brien group has been developing a modular synthetic platform and, as part of this methodology, various types of 3-D building blocks have been designed. A key consideration in designing these building blocks is that they should include structures common in drug candidates, such as saturated nitrogen heterocycles. These building blocks not only have distinct 3-D configurations but also contain two functionalities that can be connected with different types of groups, which could increase the efficiency of drug discovery.

In unpublished work, the O'Brien group has successfully developed several 3-D building blocks (Figure 19) which each contain a Boc-protected cyclic amine group and a cyclopropyl BMIDA part (MIDA = N-methyliminodiacetic acid), which can be used to combine various medicinally relevant groups. For example, using Pd-catalysed Suzuki-Miyaura cross-coupling reactions and *N*-functionalization reactions (including amidation, sulfonamidation, reductive amination, S_N2, S_NAr and Buchwald-Hartwig amination) following Boc group removal, approximately 30 compounds ready for testing were generated in a short time in the O'Brien group.

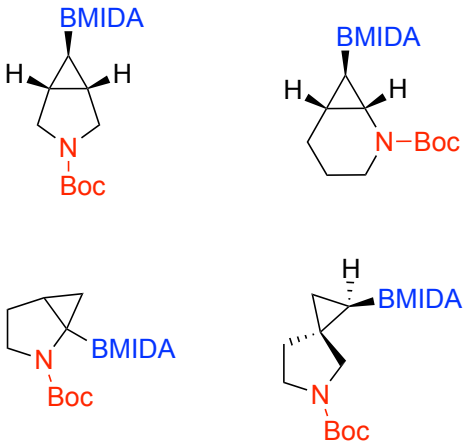


Figure 19. Difunctionalised building blocks in the O'Brien group.

1.5 Project Outline

The objective of this project is to develop efficient methods for the synthesis of medium-sized ring 3-D building blocks using ring expansion methods adapted from those developed in the Unsworth group. Additionally, these scaffolds will be functionalized into a range of compounds with the medium-sized ring as a core using the O'Brien group approach briefly mentioned above. Ultimately, this could allow for the rapid synthesis of diversely functionalised medium-szied ring compounds with potential applications in medicinal chemistry.[34]

1.5.1. Synthesis and Functionalization of Medium-Sized Ring Building Blocks via NICE

One general route used in this project is shown in Figure 20. It begins with a bromination reaction to introduce a bromide synthetic handle to the starting materials (**62** → **63**). Next, an S_N2 N-alkylation reaction (**63** → **65**) is performed, followed by ester hydrolysis to afford the key NICE reaction precursors (**65** → **66**). Then, the Unsworth group's approach (NICE), would be applied to synthesize a series of medium-sized ring building blocks (**66** → **67**). By designing these building blocks to include bromide substituents, this would then provide a handle for further functionalisation reactions. For example, the bromide can be converted into Bpin through borylation reactions (**67** → **68**), facilitating their combination with a wider range of functional groups. Other reactions including Suzuki-Miyaura cross-coupling (**67** → **71**, **68** → **71**), Boc cleavage, and N-functionalization will be applied to introduce various medicinally relevant groups, exploring the functionalization scope of the medium sized ring building blocks.

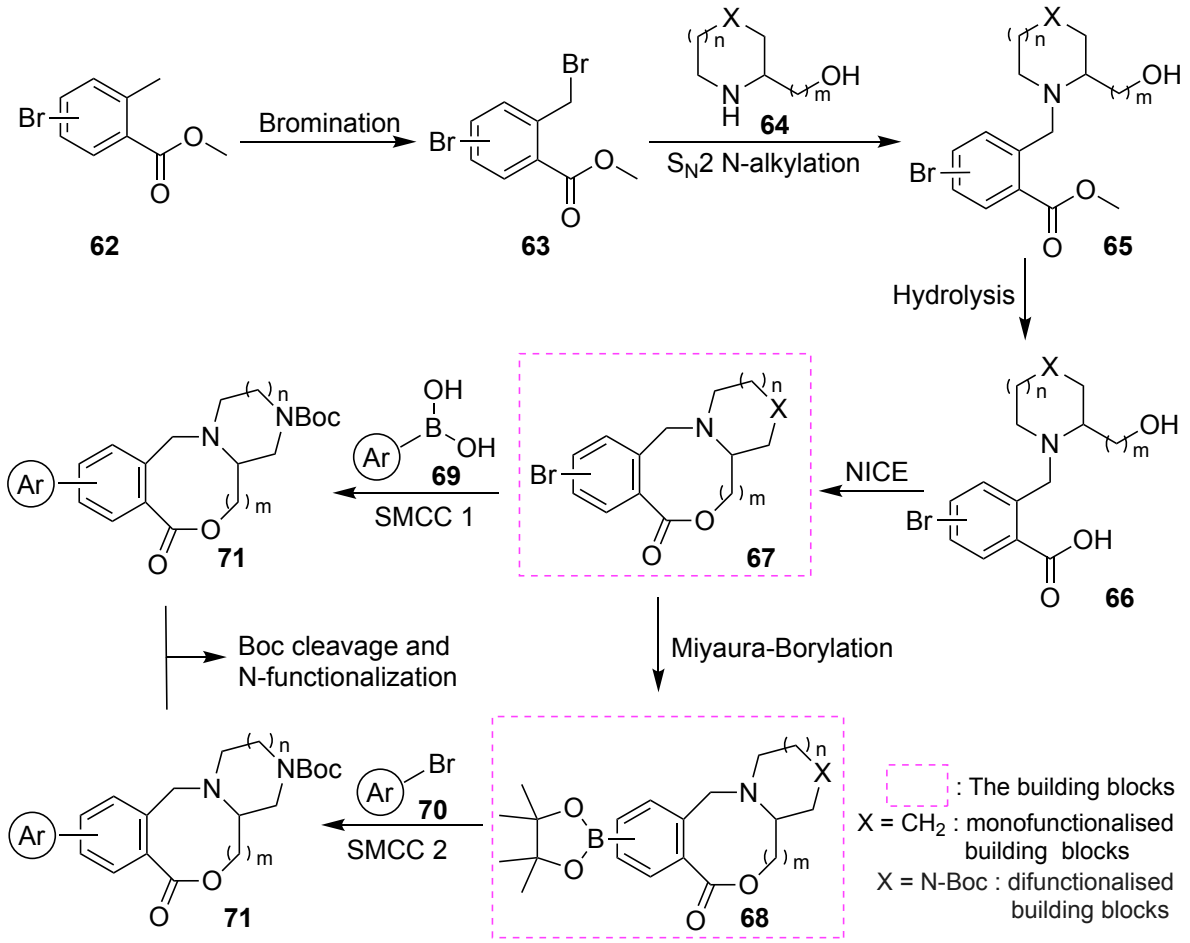


Figure 20. The general synthesis route of NICE approach to synthesis and functionalize 3-D medium ring building blocks.

1.5.2. Synthesis and Functionalization of Medium-Sized Ring Building Blocks via CARE

The general pathway of the project using the CARE method is shown in Figure 21. First, N-acylation of the Boc-protected lactam **72** using acryloyl chloride should form the imide **73**. Subsequently, the terminal double bond of **73** would undergo a conjugate addition reaction with a primary amine nucleophile. Following this, **73** would experience a Conjugate Addition/Ring Expansion reaction (CARE), yielding the building block **74**. Unlike most of the CARE reactions previously conducted by the Unsworth group, the starting material lactam used in this project will contain a N-Boc group. When the primary amine nucleophile used in the conjugate addition reaction has an additional functional group (bromine or Bpin), the product building block **74** can then carry two functional groups. This difunctionalised building block can then be further varied by Suzuki-Miyaura cross-coupling and N-functionalization after deprotection, efficiently producing a wide variety of target compounds.

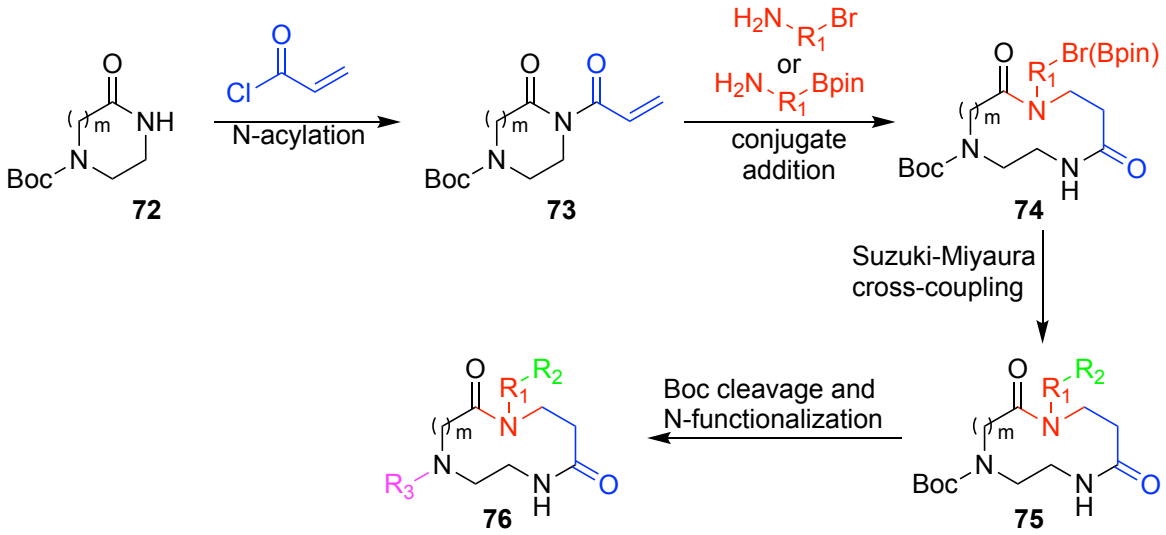


Figure 21. General route for the CARE approach to synthesis and functionalization of 3-D medium-ring building blocks.

2. Results and Discussion

2.1 Synthesis of 3-D medium ring Building Blocks via NICE Method

2.1.1 Selection of target building blocks and preliminary experiments

As outlined in the project outline, the plan was to explore the synthesis of two different types of building blocks. The structures are shown in Figure 22. Monofunctionalised building blocks would have bromide or Bpin group attached to the aromatic ring. Difunctionalised building blocks would be similar in structure but would also have a NBoc ring as part of a piperazine scaffold. As illustrated in Figure 22, when m = 1, n = 1, and X = NBoc, this difunctionalized building block will consist of an eight-membered ring as the core structure and a piperazine, which is also the primary building block of interest in this project. Additionally, when m = 2, the core ring structure of the medium-sized ring building block will be a nine-membered ring. And when n = 0 or 1, X = CH_2, the building block will be monofunctionalized, with a medium-sized ring and a pyrrolidine or a piperidine as the core structure. All of these scenarios will be explored in this project. To incorporate aromatic functional groups into the building blocks and considering the availability and reactivity of various halogen-containing compounds, an aryl bromide was selected as the functional group for the building blocks in this project. The design of these initial targets was based on the favorable outcomes of previous NICE reactions in the Unsworth group.

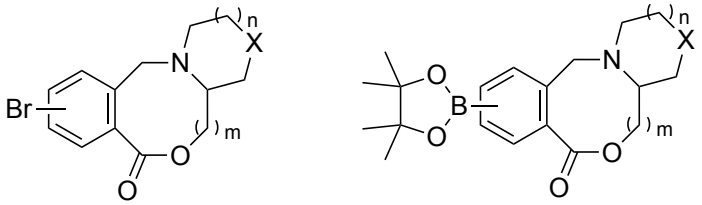


Figure 22. Selected target building block structure

Before starting on the synthesis of the targeted building blocks, the synthesis and ring expansion of a similar structure to known compounds from previous work in the Unsworth group[35] was carried out. This was done to learn and verify the steps required to execute the building block synthesis. The project's first reactions involved N-alkylation, hydrolysis, and cyclization/ring expansion of a methyl benzoate, which is also structurally similar to the planned target building blocks, differing by only one bromine atom. Through these experiments, we aimed to assess the feasibility of applying the NICE method to the selected target products.

The first step in synthesizing medium-sized ring products is an S_N2 N-alkylation reaction to obtain the internal nucleophilic part necessary for the upcoming NICE method. The S_N2 N-alkylation reaction refers to a process in which an alkyl group is transferred to a nitrogen atom via nucleophilic substitution thereby forming a new N-alkyl compound. The reactants in an S_N2 N-alkylation reaction typically include a nucleophile containing a lone pair of electrons (such as ammonia, amines, or nitrogen-containing compounds) and an alkylating agent with a good leaving group (such as a halide R-X). Thus, bromomethyl benzoate **77** was reacted with amino alcohol **78** in acetonitrile at 90 °C for 18 hours in the presence of the base, K_2CO_3. After

work-up and purification by chromatography, tertiary amine **80** was obtained in 51% yield (Figure 23). The mechanism of the S_N2 N-alkylation reaction is also shown in Figure 23. S_N2 is a one-step reaction involving two molecules. First, the lone pair of electrons of nitrogen in the nucleophile attacks the carbon atom of the alkylating agent. At the same time, the leaving group (Br) departs from the carbon, forming a positively charged intermediate **79**. Subsequently, a basic anion removes the proton and breaks the nitrogen-hydrogen bond. This forms N-alkylated compound **80** while releasing the leaving group as a Br^- ion.

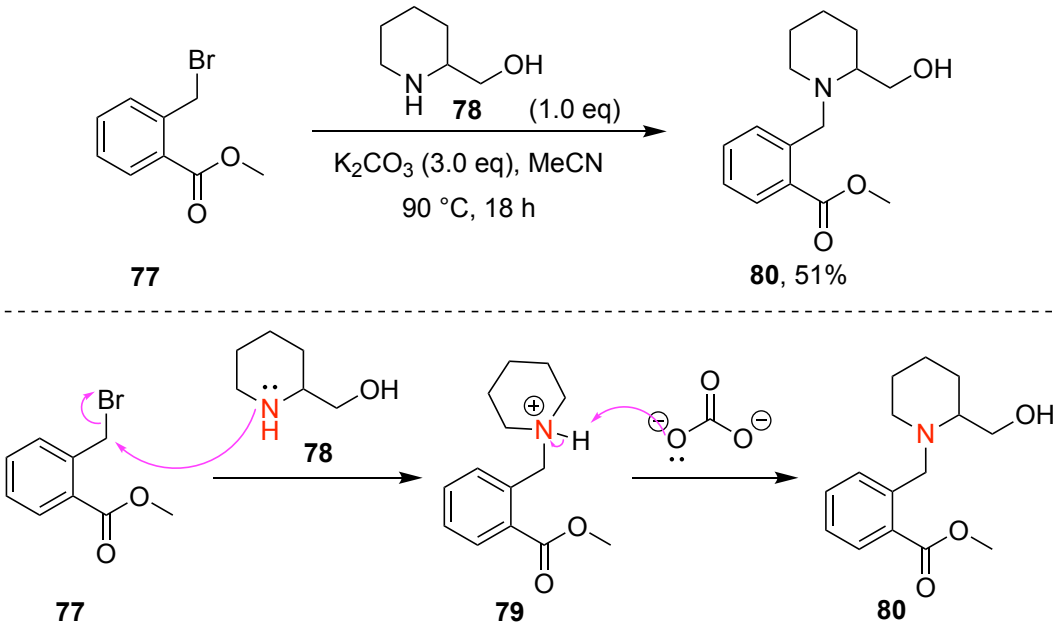


Figure 23. Conditions, results and mechanism of S_N2 N-alkylation.

The next two steps involve the hydrolysis of the ester group, followed by a NICE reaction. First, for the hydrolysis reaction, methyl benzoate **80** was reacted with lithium hydroxide in a water/methanol mixed solvent at 50°C for one hour. After ester group hydrolysis to form carboxylic acid **81**, a cascade ring expansion was initiated using conditions derived from the Unsworth group's NICE approach. The proposed reaction mechanism is shown in Figure 24. Under the influence of the N,N-diisopropylethylamine (DIPEA), the propane phosphonic acid anhydride (T3P) activates the carboxylic acid (highlighted in red), rendering it sufficiently electrophilic to form a five-membered ring intermediate **83** with the internal nucleophile (highlighted in green). Subsequently, the terminal nucleophile attacks the carbonyl group, leading to N-C bond cleavage and the expansion of the five-membered ring into an eight-membered ring **85**. The NICE reaction in the project pathway progressed smoothly, and the medium-sized ring product **85** was isolated after chromatography with an impressive yield of 96%, marking a promising start to the project.

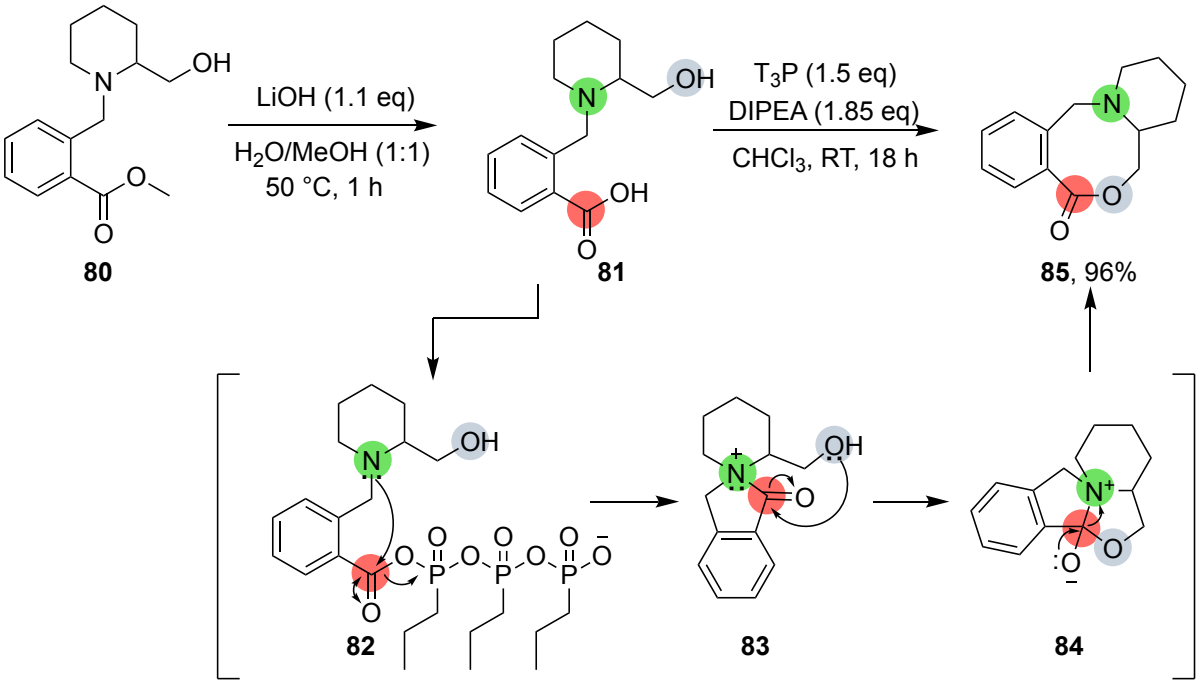


Figure 24. Conditions, results and mechanism of NICE approach.

2.1.2 Bromination of methyl benzoates

For our synthetic route to medium-ring building blocks, it was first necessary to prepare a set of benzyl bromides using a benzylic bromination reaction of methyl benzoates. In 1919, Wohl studied the reaction of 2,3-dimethyl-2-butene with N-bromoacetamide in ether and discovered that a proton in one of the methyl groups in the substrate was replaced by a bromide, while the double bond remained unchanged.[36] In 1942, Ziegler conducted comprehensive research on the application of N-bromosuccinimide (NBS) in allylic bromination of alkenes.[37] Since then, this bromination reaction, involving the use of NBS and radical initiators, has been named the Wohl-Ziegler reaction. It is an efficient strategy for introducing bromine at the allylic position of alkenes or the benzylic position of aromatic compounds.

The mechanism of the Wohl-Ziegler reaction using AIBN is shown in Figure 25. Firstly, AIBN is thermally decomposed to give a radical which reacts with NBS to give a bromide radical (Br·). Then, the bromide radical (Br·) extracts a hydrogen from the benzylic or allylic position. The hydrogen atoms at these positions are more easily abstracted because the resulting radical intermediates are resonance-stabilized. Subsequently, bromine radicals are regenerated, and the resulting radical reacts with Br_2 to form the brominated product and new bromine radicals. These processes repeat until the reaction terminates.

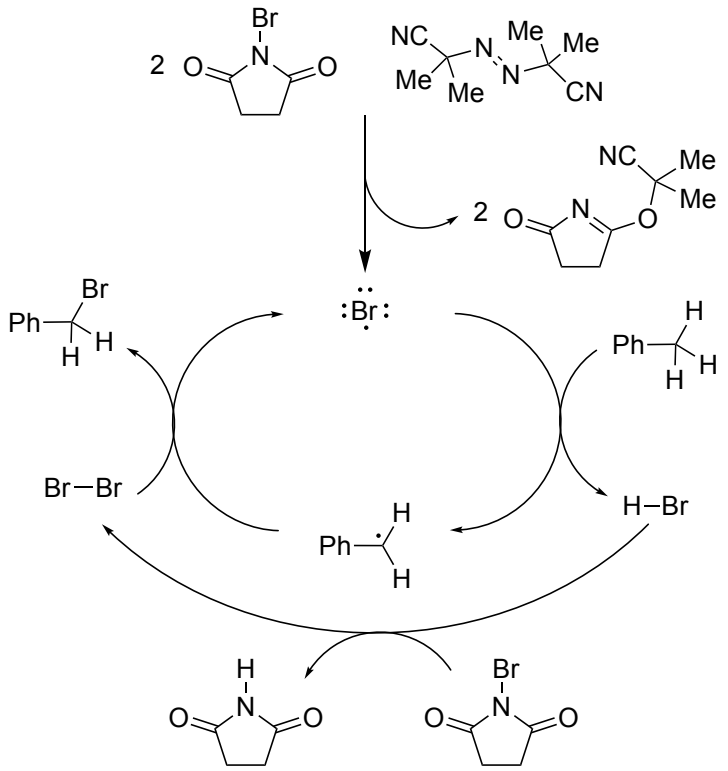
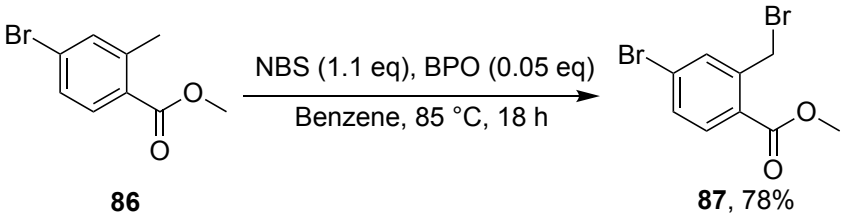


Figure 25. The mechanism of *Wohl-Ziegler* reaction.[38]

The first step in making the medium-sized ring building blocks in this project involves the Wohl-Ziegler bromination reaction. The bromination reaction in this project used NBS with benzoyl peroxide (BPO) as the radical initiator and was conducted at 85 °C in benzene for 18 hours. Using methyl 4-bromo-2-methylbenzoate **86** as the starting material, a satisfactory 78% yield of brominated product **87** was achieved after purification by chromatography (Figure 26).



86 **87**, 78%

Figure 26. Results of the first bromination reaction.

Figure 27 explains the reaction mechanism that this reaction undergoes. The free radical reaction proceeds through chain initiation, chain propagation, and chain termination steps. First, the free radical initiator dissociates into two benzoyl radicals after heating. Since there are some Br_2 molecules present in NBS at the beginning of the reaction, the benzoyl radicals initiate the cleavage of the Br_2 bond, and form a bromine radical.

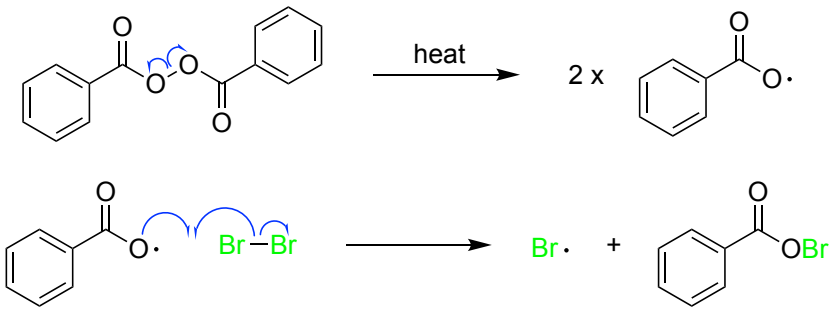


Figure 27. The chain initiation mechanism in free radical reactions

Subsequently, the bromine radical breaks the C-H bond, forming a benzylic radical and a hydrogen bromide molecule. The benzylic radical then attacks Br_2 to regenerate the bromine radical. These two chain propagation steps repeat until the concentration of Br_2 decreases, leading to chain termination and the completion of the reaction.

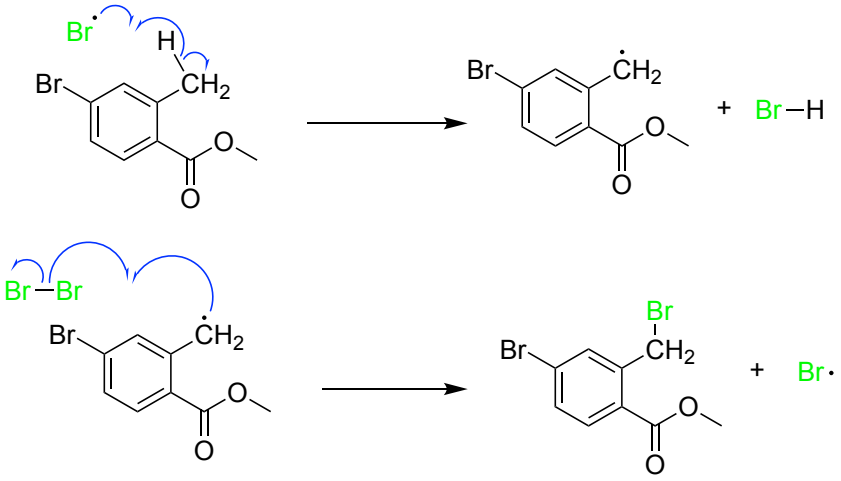


Figure 28. Mechanism of chain propagation in free radical reactions.

It is noteworthy that the hydrogen bromide molecules produced in the previous step react with NBS to generate Br_2, providing the Br_2 molecules needed for the subsequent reaction cycles.

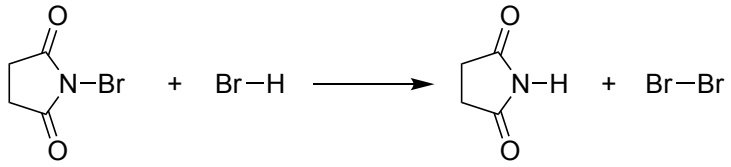


Figure 29. Mechanism of the process generating Br_2 in free radical reactions.

From the reaction mechanism, it is evident that the actual brominating agent in the reaction is the Br_2 molecule present in the system, and not NBS. When excess bromine is present in the system, side reactions are inevitable. Therefore, some dibromo-substituted side-products are often produced in most Wohl-Ziegler reactions.[39] Interestingly, real-time monitoring of this reaction using TLC showed three spots under 254 nm fluorescence, corresponding to the side product, starting material, and product from top to bottom. After reacting the starting material with 1.1 equivalents of NBS and 0.05 equivalents of BPO in benzene at 85 °C for 18

hours, about 5% of the starting material remained (assessed by NMR). Extending the reaction time or adding more NBS reduced the starting material but increased the proportion of by-products. Thus, balancing the starting material, product, and by-products is crucial to achieve the highest yield in the experiment. Generally, the substrate used in this project can achieve a yield of around 75% under the selected reaction conditions.

The ^{1}H NMR spectrum of brominated methyl benzoate **87** is shown in Figure 30. Due to the presence of a large coupling (^{3}J) the H_A proton likely appears at δ_H 7.84 (d, J = 8.5 Hz). Similarly, inferenced by a large coupling (^{3}J) and a small coupling (^{2}J, W-coupling), the H_B proton appears at δ_H 7.51 (dd, J = 8.0, 2.0 Hz). The H_C proton, which has one small coupling, is theoretically expected to show as a doublet, and in this NMR spectrum, H_C appears at δ_H 7.63 (d, J = 2.0 Hz). The CH_2 and CH_3 protons appear as two distinct singlets, located at δ_H 4.89 (s, CH_2) and δ_H 3.94 (s, CH_3) respectively.

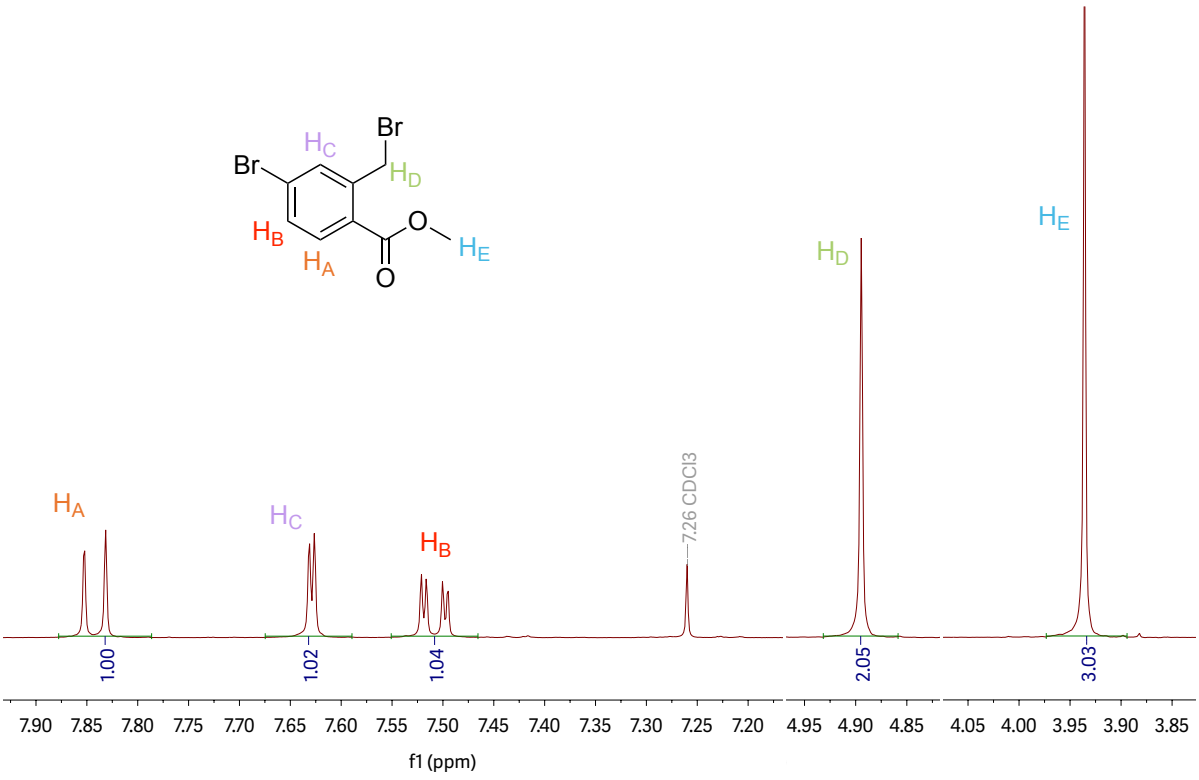


Figure 30. ^{1}H NMR spectrum of compound **87**.

Next, three other methyl benzoate derivatives were used as substrates for bromination, with the bromine group positioned at the ortho and two meta positions relative to the ester group. The results are shown in Figure 31. All reactions proceeded well, and the expected products **88** to **90** were obtained on a gram scale with good yields. Notably, the yield of product **90** differed from the others, reaching an impressive 91%.

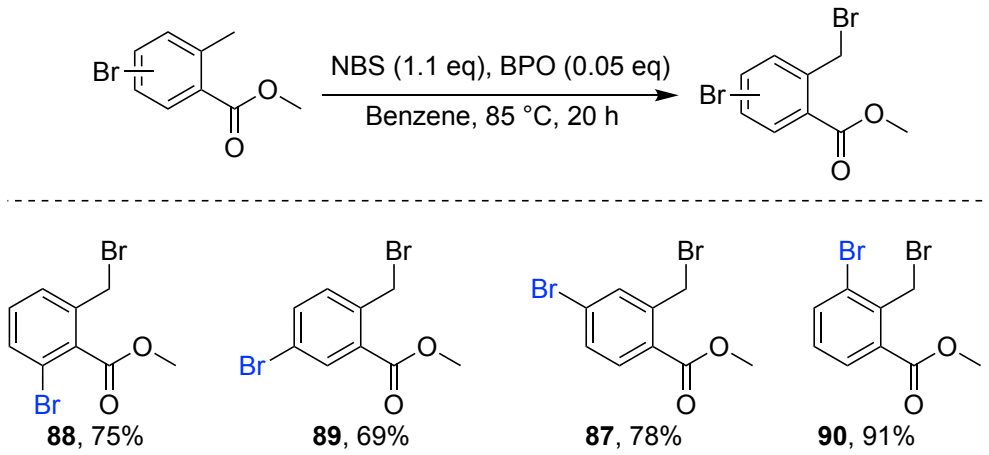


Figure 31. Results and yields of bromination.

The comparative ^{1}H NMR spectra of the aromatic region of these four products are shown in Figure 32. All H_E are located at δ_H 3.9 – 4.0, appearing as a distinct singlet. The chemical shift range of H_D is between δ_H 4.8 and 5.2. From the figure, it can be clearly observed that the aromatic hydrogens exhibit different multiplicities due to the different couplings they experience. Notably, in Figure 32-b, H_A, being positioned between the bromine and ester groups (both highly electronegative), has a chemical shift of δ_H 8.11 (d, J = 2.0 Hz), which is much higher than the typical chemical shift for aromatic ring hydrogens.

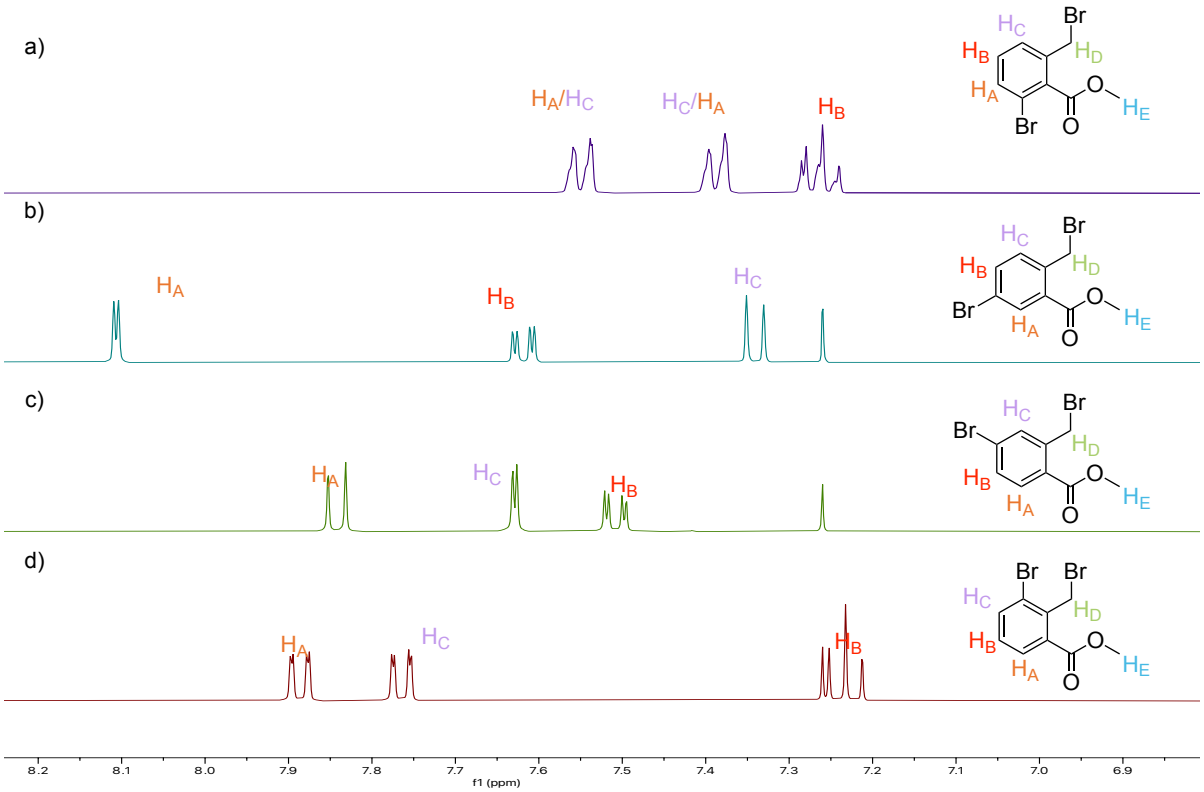


Figure 32. ^{1}H NMR spectrum of compounds **87**, **88**, **89** and **90**.

2.1.3 S_N2 N-alkylation reactions

With these four brominated methyl benzoate products **87-90** in hand, S_N2 N-alkylation reactions with different amines were performed, leading to a series of amine products containing the internal nucleophilic parts necessary for the NICE reaction to synthesize medium-sized rings.

Each reaction followed the same conditions as the initial experiment on the model system (see Figure 33). The brominated methyl benzoates and amines experienced S_N2 N-alkylation in acetonitrile at 90 °C with K_2CO_3 (3.0 equivalents) for 18 hours.[40] All reactions proceeded smoothly, and after chromatographic purification, seven different compounds (**91** - **97**) were obtained with yields ranging from 31% to 87%. The lowest yield (31%) was observed for compound **92**, where the bromine is located at the 2-position of the benzene ring in the figure below. However, good yields were obtained with two other amines and so it cannot only be the position of the bromine that is influencing the yields. In contrast, compound **94** exhibited a relatively high yield (74%), with bromine at the 4-position. For comparison, compounds with bromine at 1-position and 4-position showed similar yields in the bromination reaction.

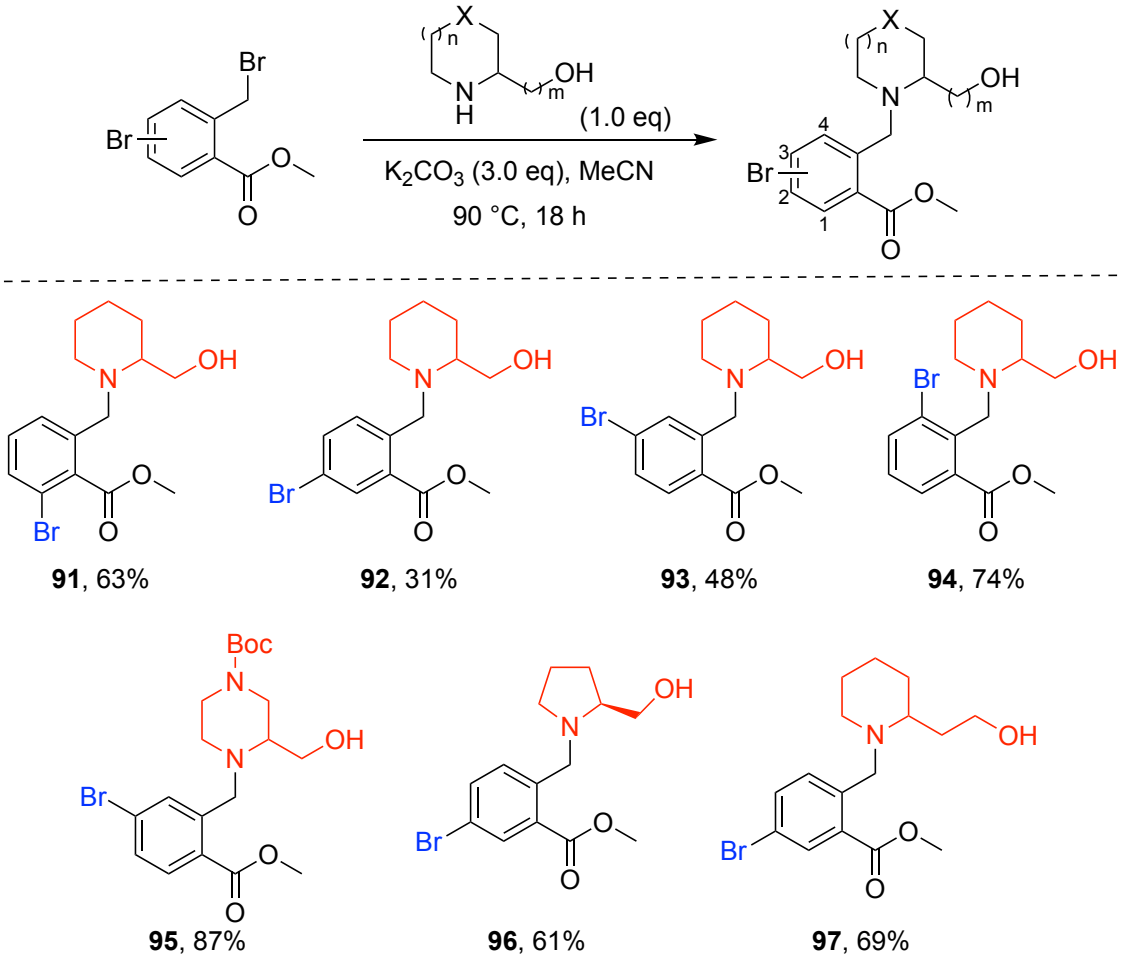


Figure 33. S_N2 N-alkylation reactions of amino alcohols and benzyl bromides.

The ^1H NMR spectrum of the S_N2 N-alkylation product **91** is shown in Figure 34. The H_D protons are diastereotopic due to the stereogenic centre in compound **91**. Thus, the H_D protons

appear as a pair of doublets (^2J = 13.5 Hz) at δ_H 4.30 and 3.09. Similarly, the two diastereotopic protons of H_J appear as two doublet of doublet (dd) peaks at δ_H 3.91 (dd, J = 12.0, 3.0 Hz) and 3.40 (dd, J = 12.0, 3.0 Hz), because they couple not only with each other with a large coupling (^2J), but also with the adjacent H_I protons. Additionally, H_E and H_I were assigned using the HMQC spectrum. The three methylene protons H_F, H_G, and H_H in the piperidine ring appear as a series of multiplets between δ_H 1.23 and 1.75, which could not be resolved and assigned.

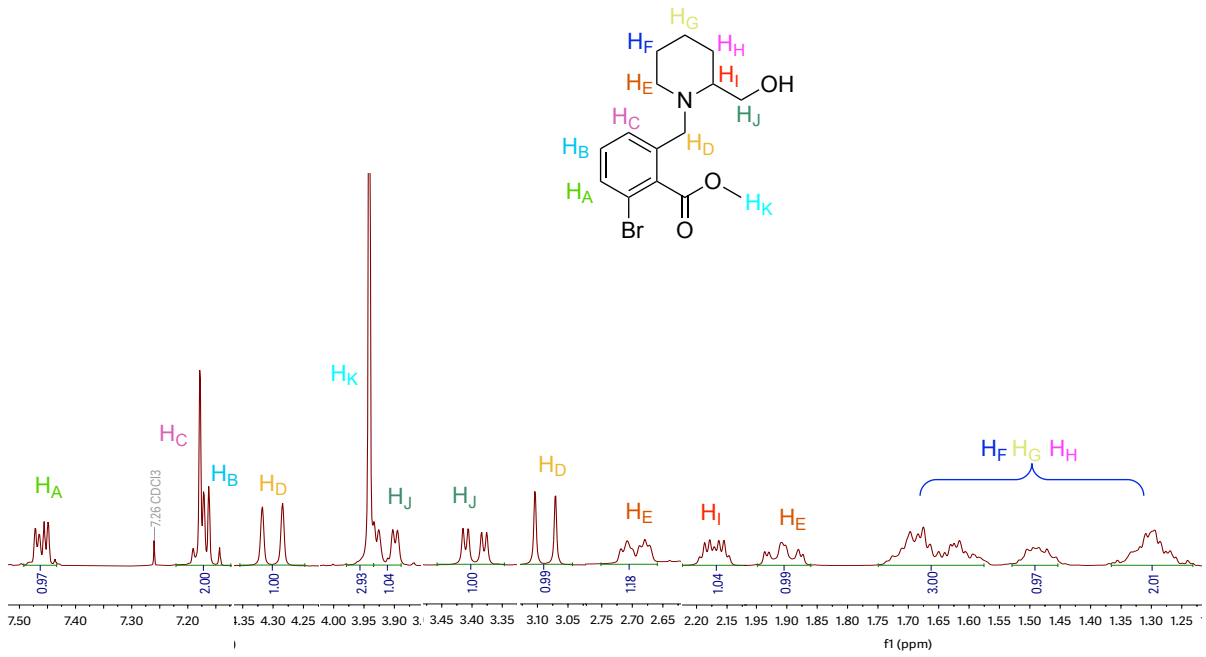


Figure 34. ^{1}H NMR spectrum of compound **91**.

2.1.4 Hydrolysis and ring expansion

According to the project pathway, following the general reaction mechanism discussed previously, the subsequent hydrolysis and cyclization reactions were carried out as shown in Figure 35. When the initial materials correspond to those illustrated as **65**, changing m, n, and X, a total of seven first batch building blocks with medium-sized rings (**98 - 104**) were successfully synthesized. As shown in Figure 35, all the hydrolysis and cyclization reactions involving **66 → 67** resulted in good to excellent overall yields over two steps. Particularly notable is the synthesis of the monofunctionalised building block **100** (with a yield of 97%) and the difunctionalised building block **104** (with a yield of 93%).

During this reaction process, it was noted that when the bromide group is positioned *ortho* to the methoxycarbonyl group, the ester hydrolysis proved to be more challenging compared to other positions, leading to relatively lower yields in these two steps (**98** with a yield of 64%). Moreover, the nine-membered ring building block with a bromide group in the same position exhibited lower yields compared to the eight-membered ring building block (**101** with a yield of 61% and **99** with a yield of 80%, respectively). Increased steric hindrance around the carbonyl is a possible explanation for the lower yield in the *ortho*-substituted case.

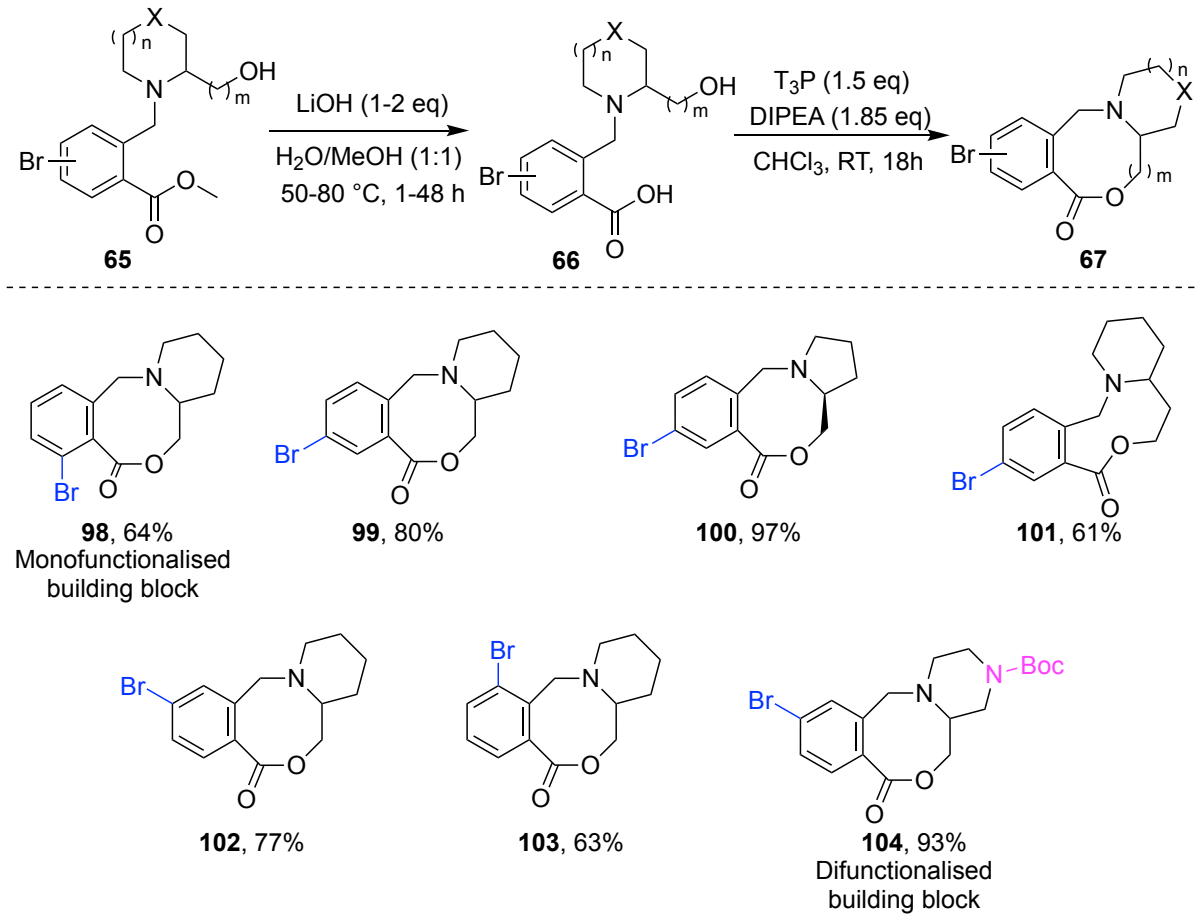


Figure 35. Results for the synthesis of the building blocks through the NICE approach

The ^{1}H NMR spectrum of the product **99** obtained from the NICE reaction is shown in Figure 36. Proton H_A appears at δ_H 7.61 (d, J = 2.0 Hz) as a doublet peak. This is due to a small coupling (^{4}J, W-coupling) between H_A and H_B, with a coupling constant generally ranging from 0 - 3 Hz. In addition to the small coupling with H_A, H_B also exhibits a large coupling with H_C (^{3}J, coupling constant 8 - 10 Hz), resulting in a double doublet peak at δ_H 7.53 (dd, J = 8.0, 2.0 Hz). Similarly, H_C shows a doublet peak with a coupling constant of 8.0 Hz due to coupling with H_B. Apart from the hydrogens on the aromatic ring, H_J, being adjacent to an oxygen atom that is part of an electron withdrawing ester group, appears most downfield among the remaining hydrogens. The two hydrogens are located in different spatial locations, leading to differences in coupling constants: δ_H 4.04 (dd, J = 12.5, 2.0 Hz) and δ_H 3.98 (dd, J = 12.5, 5.0 Hz). The diastereotopic methylene group H_D, situated between the aromatic ring and the nitrogen atom, appears as a pair of highly roofed doublets at δ_H 3.64. In addition, the higher field signals correspond to the methylene groups H_E and methine H_I connected to the nitrogen atom and alkyl group. The three methylene groups H_F, H_G, and H_H appear as multiplets at δ_H1.2 − 1.8 ppm, which were not resolved.

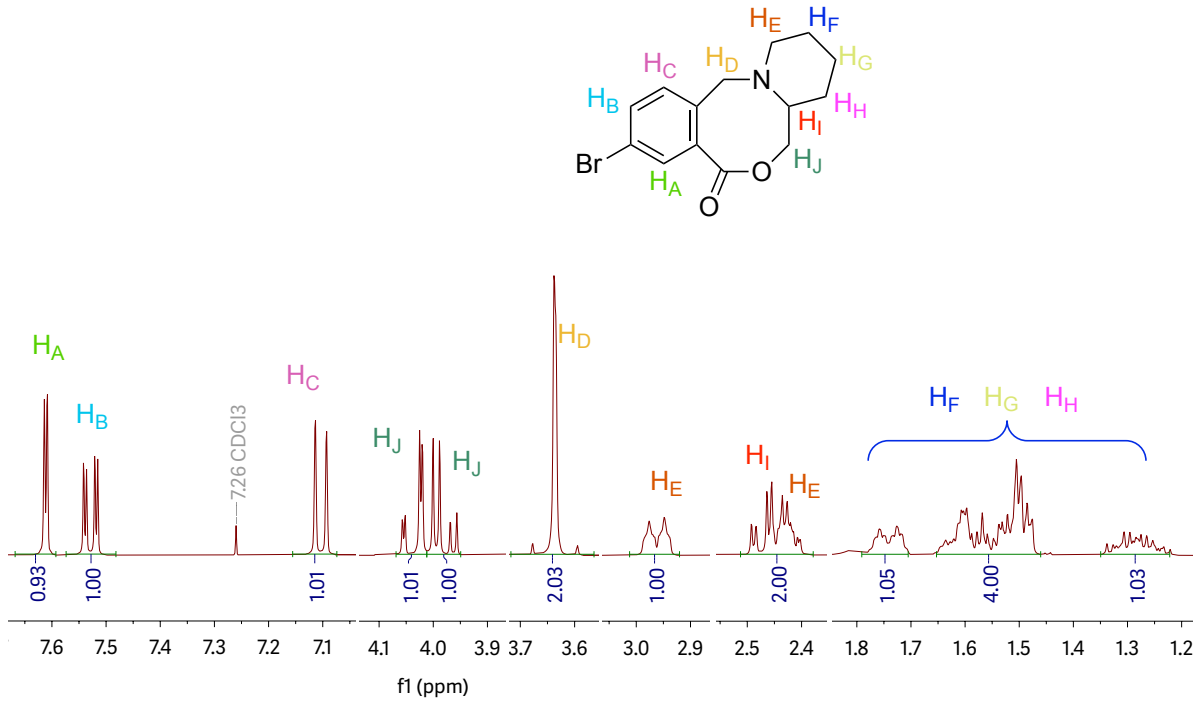


Figure 36. ^{1}H NMR spectrum of compound **99**.

Figure 37 shows the ^{1}H NMR spectrum of the difunctionalised building block **104** containing an aryl bromide and a N-Boc. Based on the spectroscopic data, the expected three signals H_A, H_B and H_C were observed in the aromatic region. A 9H singlet at δ_H 1.40 (s) corresponding to the *t*-butyl group in the Boc group. Finally, the assignment of other hydrogens was determined using the 2D NMR spectra.

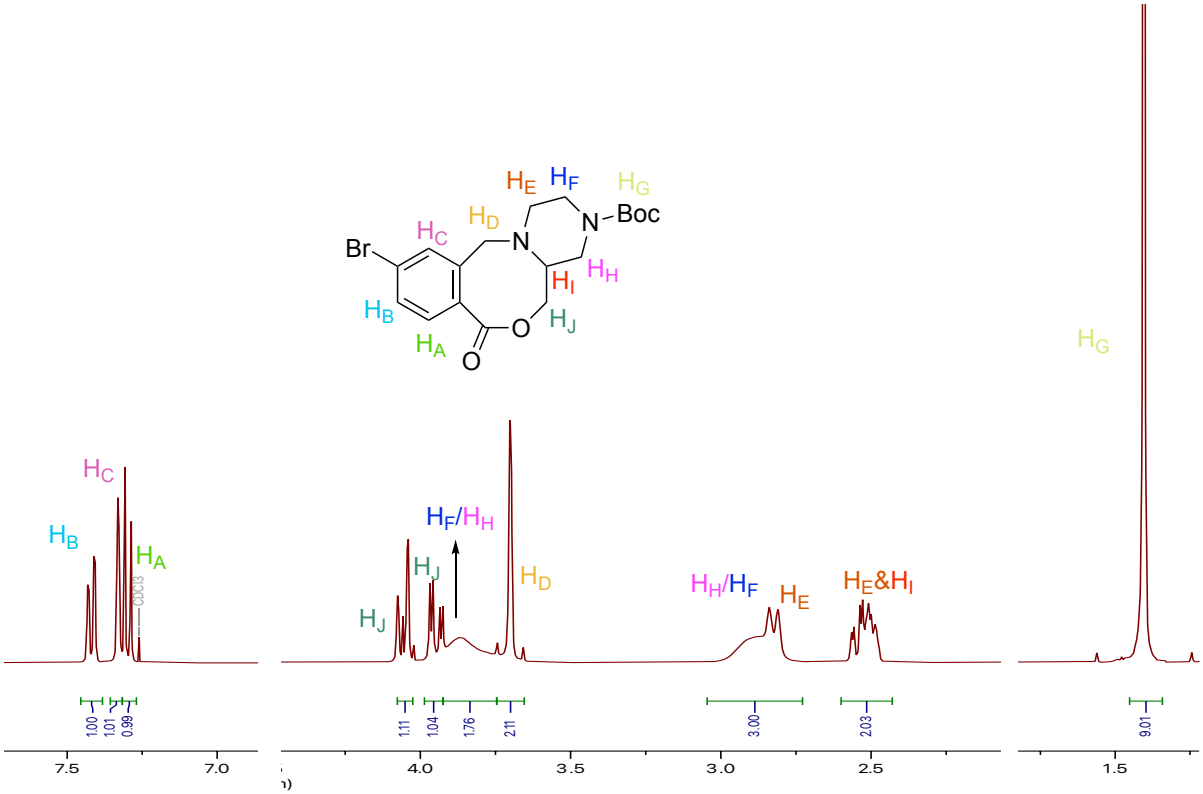


Figure 37. ^{1}H NMR spectrum of compound **104**

Overall, the use of the NICE method to synthesize medium-sized ring lactone building blocks was really effective. All attempted substrates yielded the expected products, with yields of over 60% for the two-step synthesis involving hydrolysis and ring expansion (see Figure 35). This shows that introducing internal and terminal nucleophiles into a linear precursor and preparing medium-sized lactone ring building blocks through the NICE method is a highly efficient approach.

2.2 Application of the 3-D medium ring Building Blocks Synthesized by NICE Method

2.2.1 Suzuki-Miyaura cross-coupling of boronic acids

After successfully synthesizing some aryl bromide-containing medium-sized ring building blocks, efforts were made to conduct cross-coupling with aryl boronic acids to explore the potential of these functionalized building blocks. The Suzuki-Miyaura cross-coupling reaction, first reported in 1979,[41] involves the coupling of aryl or alkenyl boronic acids or boronates with halogenated (chlorine, bromine, iodine) aromatic or alkenyl compounds under the catalysis of a palladium(0) complex. Due to the high tolerance of the Suzuki-Miyaura reaction of substrates and their functional groups, it has found extensive application in the synthesis of natural products, pharmaceuticals and organic materials.[42]

The mechanism of the Suzuki-Miyaura cross-coupling reaction is shown in Figure 38. First, the halogenated hydrocarbon R_1-X undergoes oxidative addition with palladium(0), generating a highly electrophilic palladium(II) intermediate. Next, the halogen (X) in the palladium(II) intermediate is substituted by a base, forming a new highly active palladium(II) complex. Subsequently, the arylboronic acid reacts with the palladium(II) complex, transferring the organic group R_2 onto the palladium atom. This step is called transmetallation. Through reductive elimination, the desired product is formed along with the regeneration of the palladium(0) catalyst, completing the catalytic cycle.

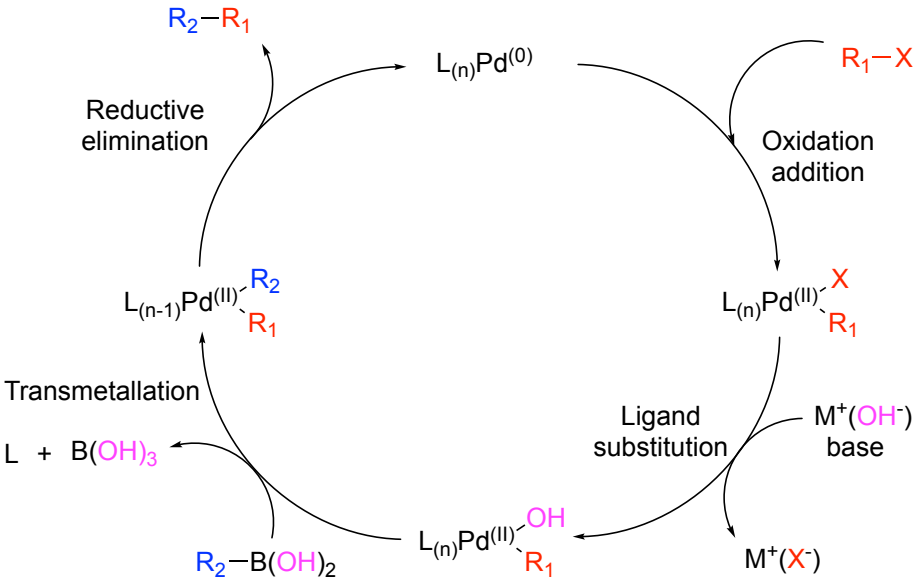


Figure 38. Conditions and results of SMCC between building blocks and phenylboronic acid.[43]

The first step was to explore the applicability of medium-sized ring structures to the Suzuki-Miyaura cross-coupling reaction by attaching a phenyl group to the ring. A Suzuki-Miyaura cross-coupling reaction of a structurally related example was found in the literature (Figure 39).[44] The starting material **105** contained a seven-membered ring and a carbonyl group (ketone, not an ester) and cross-coupling with phenyl boronic acid was described. Substrate **105** was reacted with phenyl boronic acid at 110 °C using DMF and water as solvents, potassium carbonate as the base and tetrakis(triphenylphosphine)palladium as the catalyst.

The reaction was carried out under a nitrogen atmosphere for 5 hours, yielding product **106** with a 90% yield.

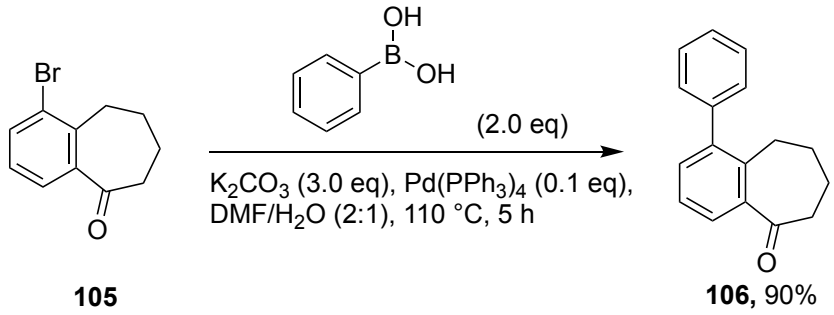


Figure 39. SMCC conditions and results of literature example.

Unexpectedly, when these reaction conditions were applied to the eight-membered lactone **102** from this project, the desired product **107** was not obtained. Data analysis of the compound separated via column chromatography revealed that the main product was **108**, indicating that the medium-sized ring in the molecule had been broken (shown in Figure 40). After further analysis, it is suggested that the possible cause of the ring opening was the high reaction temperature, which probably led to the hydrolysis of the lactone under the basic reaction conditions. High temperature provides the energy required for the hydrolysis of the lactone in the eight-membered ring building block, and contributes to the activation and nucleophilic attack of the hydroxide ions. This suggests that for medium-sized ring building blocks obtained through the NICE method, milder reaction conditions needed to be considered when doing the Suzuki-Miyaura cross-coupling reaction.

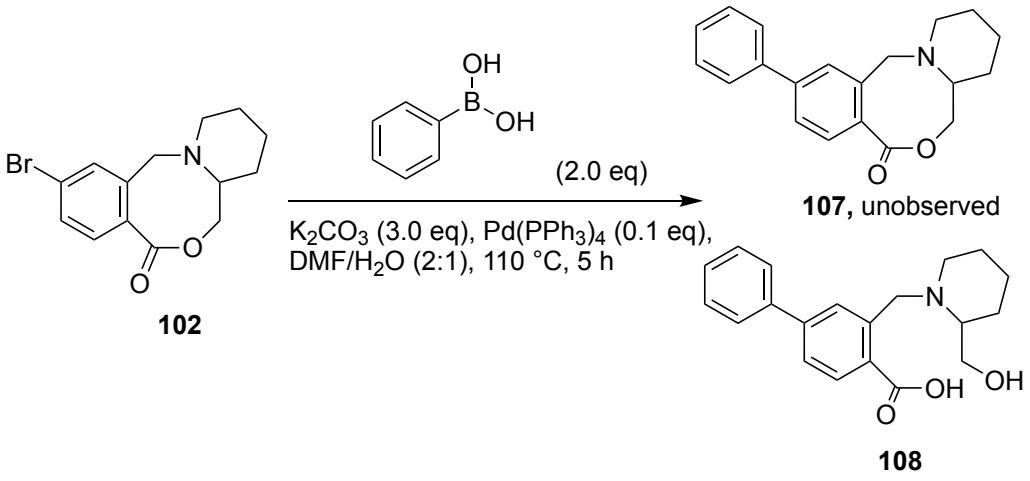


Figure 40. Unsuccessful results of the first SMCC.

To avoid the hydrolysis of medium-sized lactone rings during the Suzuki-Miyaura cross-coupling reaction, the reaction needed to be carried out under milder conditions. The selected reaction conditions are shown in Figure 41.[45] Starting material **109** and phenyl boronic acid were dissolved in a solvent mixture of dioxane and water (2:1), with sodium carbonate as the base and $Pd(dppf)Cl_2$ as the catalyst. The reaction was heated at 50 °C under a nitrogen atmosphere for 16 hours, yielding the coupled products **110**.

By changing the m, n, and X units in the previously obtained medium-sized ring building blocks, seven products were coupled with phenyl boronic acid (**107**, **111** to **116**). All products had yields of 69% or higher; compound **116** with a nine-membered ring core achieved an impressive yield of 91%. The coupling product **114** of the difunctionalised building block, which is the primary focus of this project, also achieved a yield of 82%. Additionally, no side-product from ring-opening of the lactone was observed in these reactions. These satisfactory results show the excellent performance of the Suzuki-Miyaura cross-coupling reaction in medium-sized ring building blocks synthesized through the NICE method. These results marked a promising start in the exploration of the functionalization potential of the new building blocks.

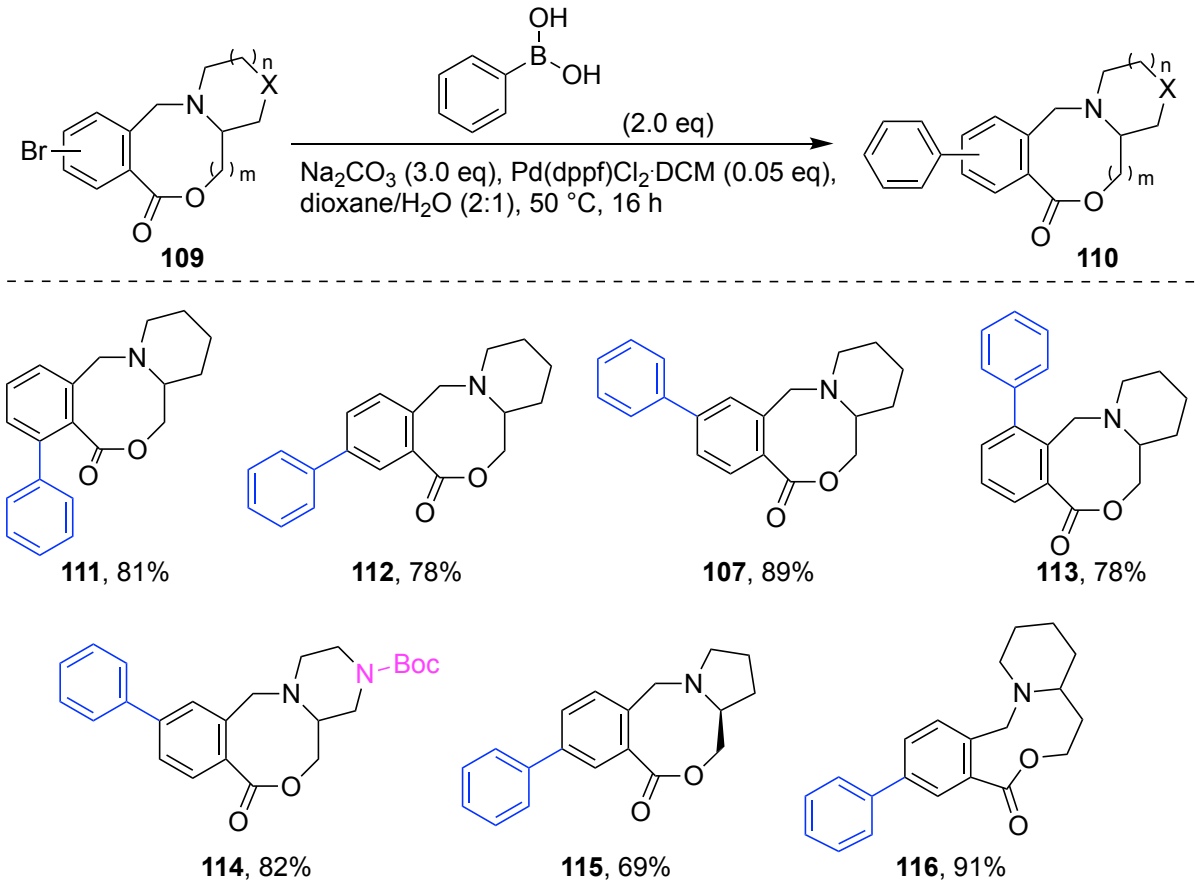


Figure 41. Conditions and results of SMCC between building blocks and phenylboronic acid.

However, considering the application of medium-sized ring building blocks in drug discovery, unsubstituted phenyl groups are unattractive functional groups in drug molecules. Therefore, we aimed to introduce non-phenyl aromatic rings to improve the potential binding affinity and solubility of any drug molecules that could be targeted using this methodology. As a result, we continued to study the Suzuki-Miyaura cross-coupling reaction of the difunctionalised medium-sized ring building block **104** with a series of heteroaromatic boronic acids and a fluorinated aromatic ring (Figure 42). This would allow us to explore the reactivity of the difunctionalised medium-sized ring building block with different groups.

Including the previously mentioned reaction with phenyl boronic acid, the difunctionalised medium-sized ring building block **104** was subjected to Suzuki-Miyaura cross-coupling

reactions with six different aryl boronic acids, yielding products **114** and **118** to **122**. Pleasingly, each reaction produced the relevant product, with yields even reaching 96% for the reaction with benzo[d]thiazole boronic acid. This indicates that the medium-sized ring building blocks obtained through the NICE method in this project have good functional group tolerance in SMCC reactions. Additionally, it is notable that when the aryl ring directly connected to the boronic acid contains nitrogen, the yields are often lower compared to other cases, as shown by products **118** and **121** in Figure 42, with yields of only 40% and 54%, respectively. Finally, the synthesis of **120** was scaled up to provide enough material for subsequent N-functionalisation studies (see Section 2.2.4).

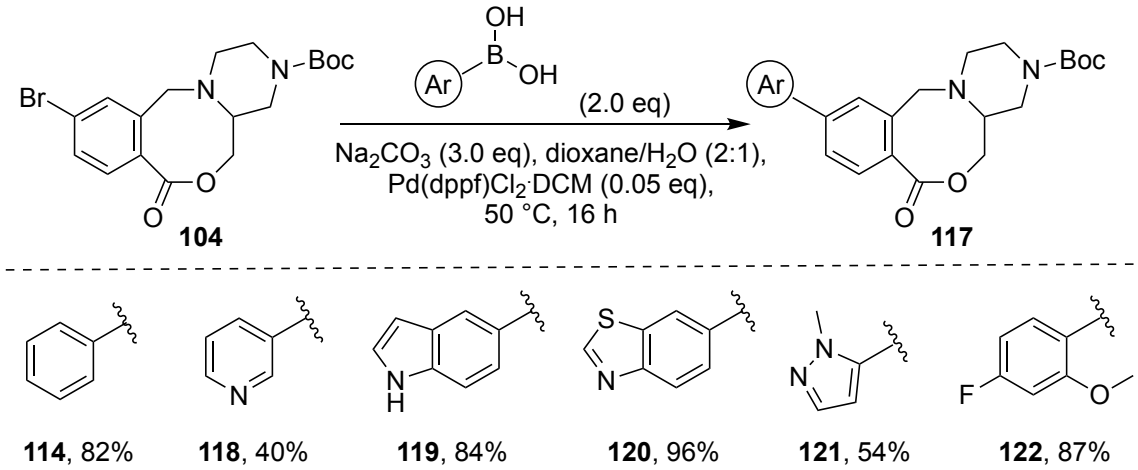


Figure 42. Results for all SMCC reactions of building block **104**.

Figure 43 shows the ^{1}H NMR spectrum of the Suzuki-Miyaura cross-coupled reaction product **121**. Compared to the benzene ring, the hydrogens on the pyrazole ring are typically more upfield due to the weaker aromaticity. Protons H_C and H_D couple with each other, appearing as doublets at δ_H 7.27 (d, J = 2.0 Hz) and δ_H 6.35 (d, J = 2.0 Hz) respectively. Proton H_A, due to its large coupling with H_B (^{3}J, coupling constant 8 - 10 Hz), appears at δ_H 7.59 (d, J = 8.0 Hz). H_B, in addition to its coupling with H_A, also has a small coupling with H_E (^{4}J, W-coupling), appearing at δ_H 7.41 (dd, J = 8.0, 2.0 Hz). H_C is observed at δ_H 7.53 (d, J = 2.0 Hz). Additionally, the methyl group H_F and the three methyl groups of the Boc group H_J all appear as singlets. However, since H_F is on the pyrazole ring, it appears more downfield at δ_H 3.91 (s), while H_J appears at δ_H 1.46 (s). Apart from the new aromatic groups introduced by the coupling reaction, the chemical shifts and peak shapes of other hydrogen atoms show no significant difference compared to the difunctionalised medium-sized ring building block **104** in Figure 37.

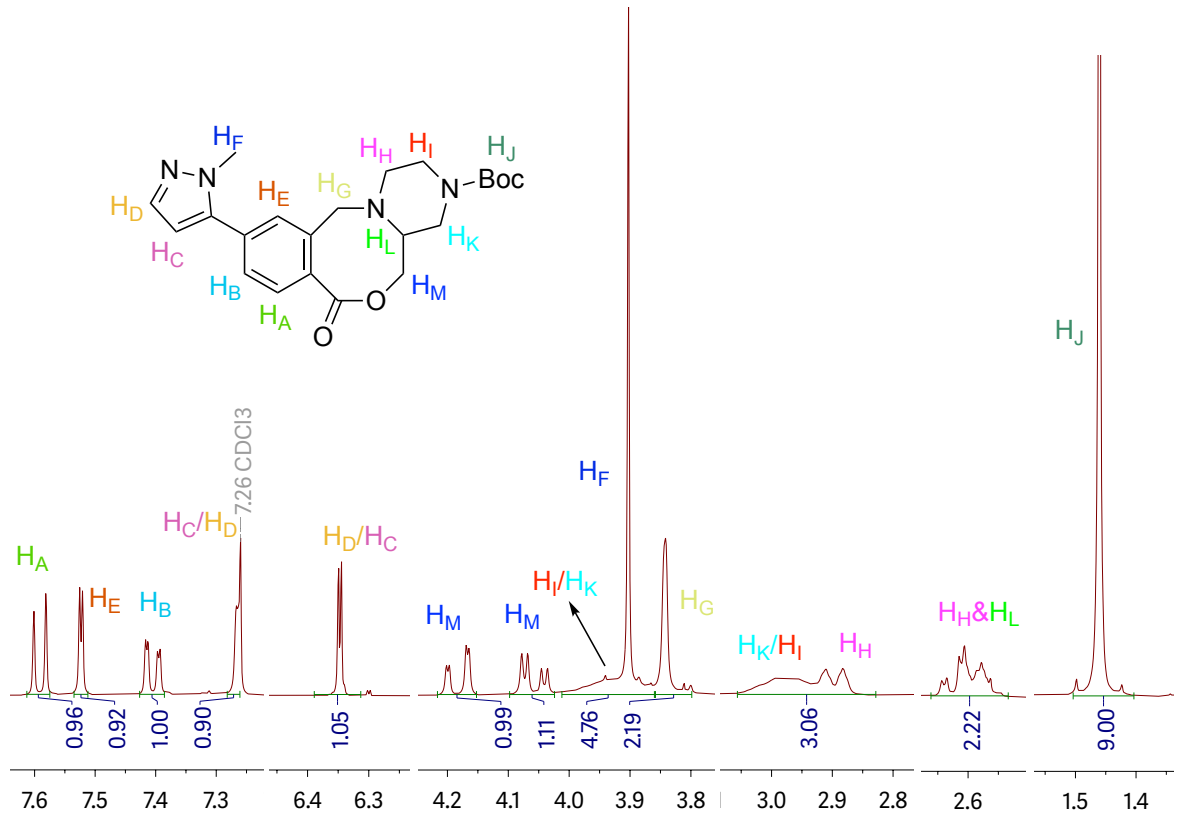


Figure 43. ^{1}H NMR spectrum of compound **121**.

2.2.2 Miyaura borylation and Suzuki-Miyaura cross-coupling of Bpin compounds

In terms of confirming the applicability of these 3-D medium-sized ring building blocks for functionalization reactions, a significant next step was taken by converting the bromide substituent into a Bpin group on the building blocks through a borylation reaction. The decision to make this functional group interconversion was motivated by the fact that, commercially, there are considerably more functionalized aryl bromides available, compared to the analogous boronated compounds. Therefore, achieving this objective has the potential to significantly broaden the functionalization scope of these medium-sized ring building blocks for use in Suzuki–Miyaura cross coupling reactions.

A monofunctionalised building block **101** and a difunctionalized building block **104** were selected to carry out Miyaura borylation.[46] Unlike Suzuki-Miyaura coupling reactions, Miyaura borylation is carried out in the absence of water, eliminating potential hydrolysis issues during the reaction. However, relatively mild reaction conditions were still chosen. As shown in Figure 44, the initial brominated material **67** and the B_2pin_2 were dissolved in dioxane, with potassium acetate as the base and Pd(dppf)Cl_2 as the catalyst. The reaction was conducted under nitrogen protection at 60 °C for 18 hours.[47] Due to the acidic nature of the silica gel used in the separation and purification, and some water is unavoidably present in solvents such as ethyl acetate and n-hexane, it is important to process the separation of Bpin-containing products quickly to prevent hydrolysis to a boronic acid during long-time contact with the column. Using Miyaura borylation, two different new medium-sized ring building

blocks were obtained: the monofunctional building block **123** (yield 63%) and the difunctional building block **124** (yield 86%).

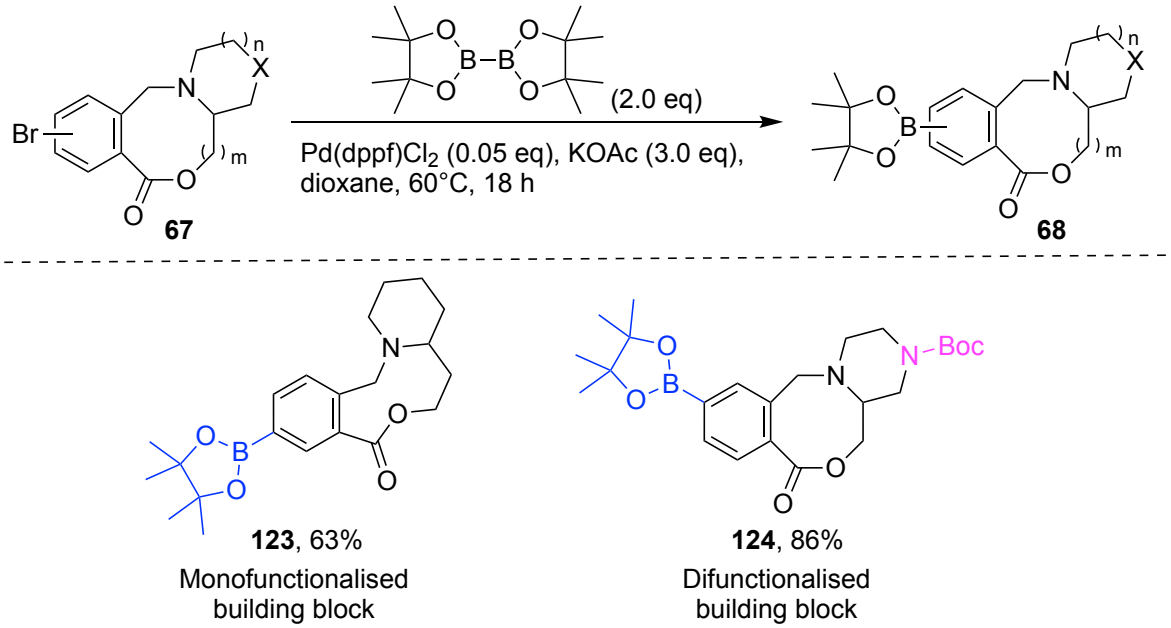


Figure 44. Conditions and results of Miyaura borylation.

Figure 45 shows the ^{1}H NMR spectrum of the difunctionalized building block **124** obtained from the Miyaura borylation reaction. The four methyl protons in the Bpin group - H_K δ_H 1.32 (s) and the *tert*-butyl group of the Boc group - H_G δ_H 1.43 (s) are the most upfield signals. H_A and H_B appear at δ_H 7.73 (d, J = 7.5 Hz) and δ_H 7.45 (d, J = 7.5 Hz) respectively, with H_B also showing as a doublet peak similar to H_A, making it difficult to distinguish between them. H_C shows as a singlet at δ_H 7.63. Other protons do not differ significantly from the building block before the Miyaura borylation reaction.

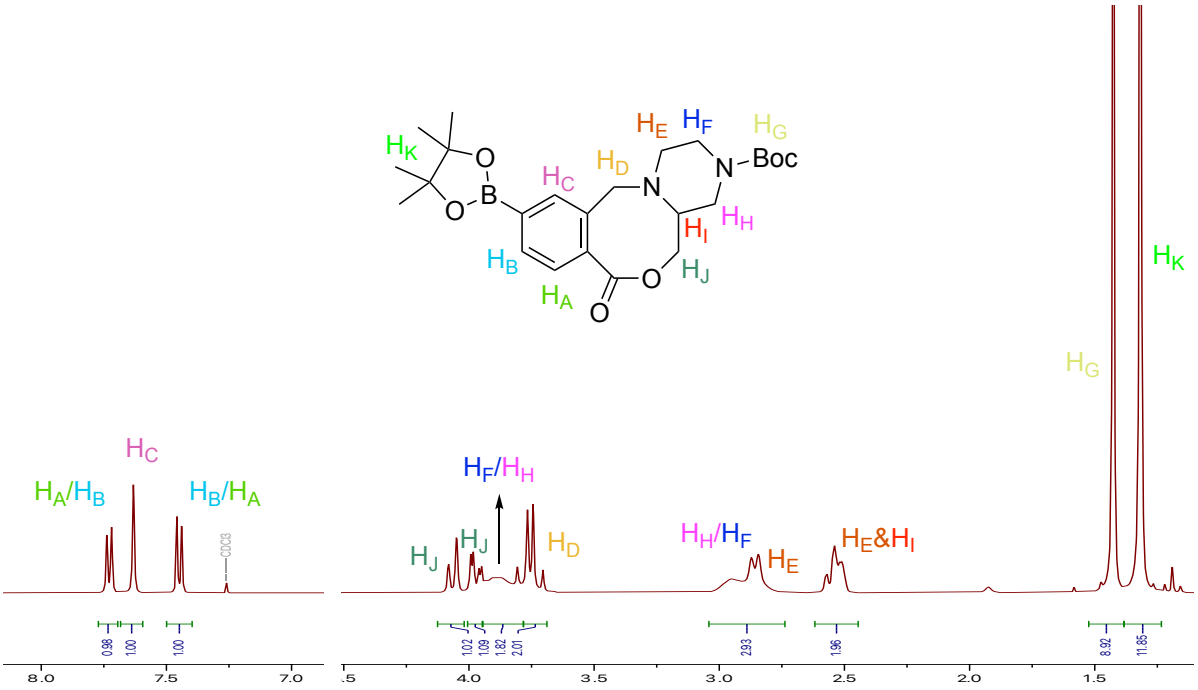


Figure 45. ^{1}H NMR spectrum of compound **124**.

Subsequently, a wide range of aryl bromides (to give products in Figure 46) was chosen for a series of Suzuki-Miyaura cross-coupling reactions with the Bpin functionality of the difunctionalized building block **124**. Pleasingly, all the Suzuki-Miyaura cross-coupling reactions provided the relevant products in 25-68% yields. The yields were generally lower than those obtained from cross-coupling of aryl boronic acids with the brominated building block **104** (see Figure 42). However, the diversity of functionalized aryl bromides greatly expands the applicability of medium-sized ring building blocks synthesized through the NICE method in Suzuki-Miyaura cross-coupling reactions. Additionally, a similar observation to previous aryl boronic acid Suzuki-Miyaura cross-coupling reactions was noted — when the aryl group directly connected to the bromine contains nitrogen (**118**, **130** to **133**), the yields tended to be lower than those with other groups.

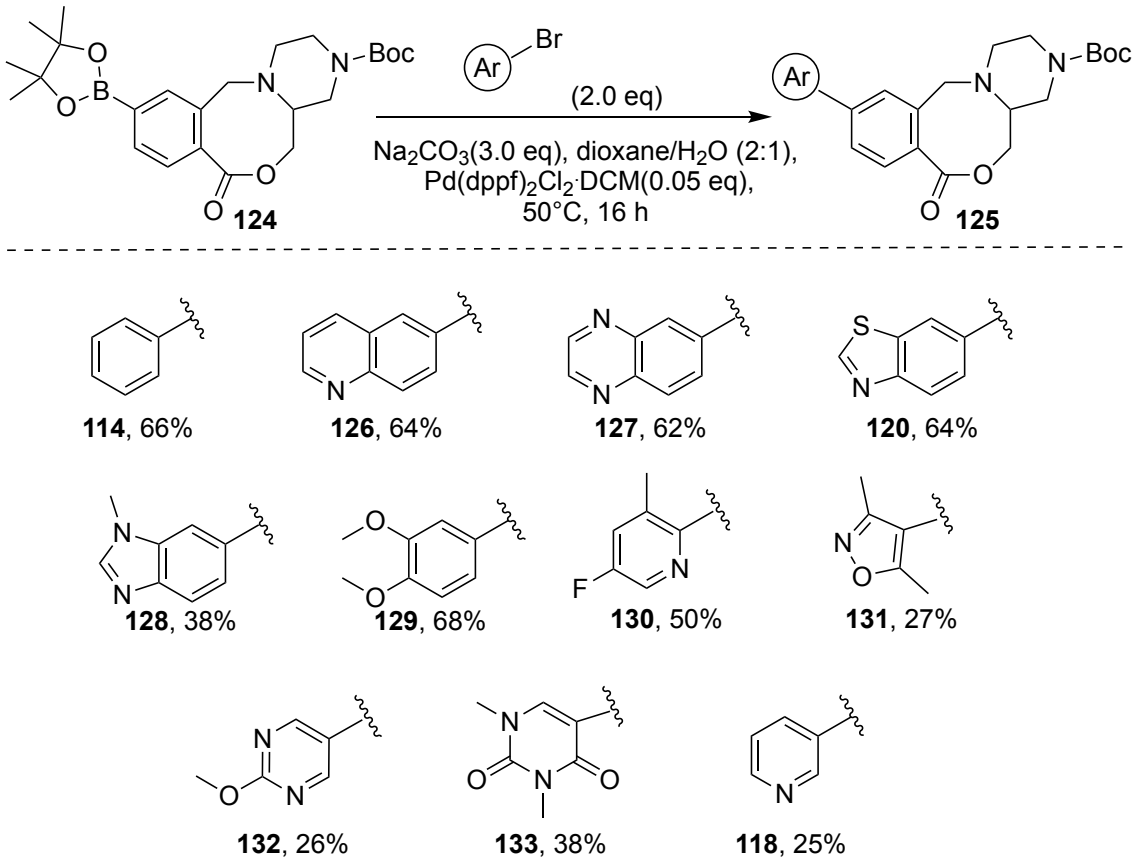


Figure 46. Results for all SMCC reactions of building block **124**.

Pleasingly, using the brominated building block **104** and the Bpin building block **124**, more than 20 Suzuki-Miyaura cross-coupling reactions aimed at exploring the functionalization range of medium-sized ring-building units have successfully produced the target products. This marks a very successful part of the project.

We also targeted cross-coupled product **120** for further N-functionalisation reactions and therefore the scale-up of its synthesis was explored. However, when scaling up the reaction of the Bpin-containing difunctionalised building block **124** with 6-bromobenzo[d]thiazole, it consistently failed to achieve the same good results as the initial attempt. Compared to the previous 64% yield, the subsequent repeated experiments only achieved yields of 20% to 30%.

It was therefore decided to synthesise the benzothiazole containing building block **120** using the medium-sized ring building block **104**, which contains a bromine functional group, to solve the issue of preparing reaction materials. As shown in Figure 47, bromobenzothiazole was first converted into Bpin **134** on a larger scale under the same conditions as the previous Miyaura borylation reaction. Then, Bpin **134** was hydrolyzed in a 6M HCl aqueous solution at 120 °C for 3 hours[48] to yield boronic acid **135**. After separation and purification, the yields of these two steps were 92% and 95% respectively. The subsequent Suzuki-Miyaura cross-coupling reaction gave product **120** in 96% yield (see Figure 42). On a 200 mg scale-up, the yield was 94%, successfully resolving the issue of preparing enough material for the N-functionalization reactions.

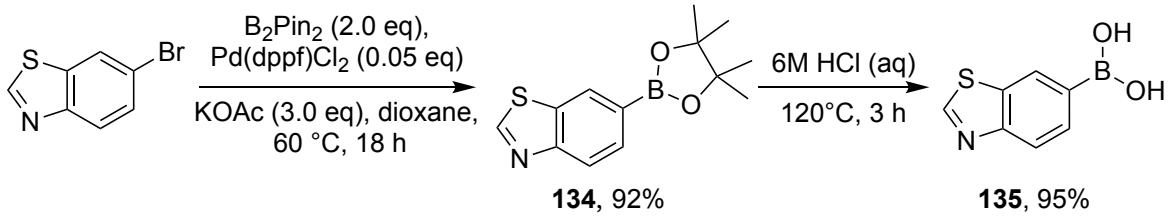


Figure 47. Results of Bromobenzothiazole Miyaura Borylation and Hydrolysis.

2.2.3 Comparison of Suzuki-Miyaura cross-coupling with boronic acids and Bpins

Both the benzothiazole and pyridine groups in the forms of brominated and boronic acid compounds were used in Suzuki-Miyaura cross-coupling reactions with difunctionalised building blocks **104** and **124**, functionalized with either bromine or Bpin (Figure 48). The yields for coupling the benzothiazole group to the two building blocks were 96% and 64% respectively, both higher than the yields for coupling the pyridine group, which were 40% and 25%. Additionally, the two reactions with the bromine containing difunctionalised building block **104** yielded 96% and 40%, both higher than the yields with the Bpin difunctionalised building block **124**. To ensure sufficient reaction of the more challenging compounds **104** and **124**, 2 equivalents of boronic acid were used in reaction Figure 48-a, while 2 equivalents of aryl bromide were used in reaction Figure 48-b. Typically, more side reactions consume the boronic acid coupling partner, leading to its common overuse. This could be one of the reasons why bromides performed better than Bpin in the Suzuki-Miyaura cross-coupling reactions for building blocks in this project.

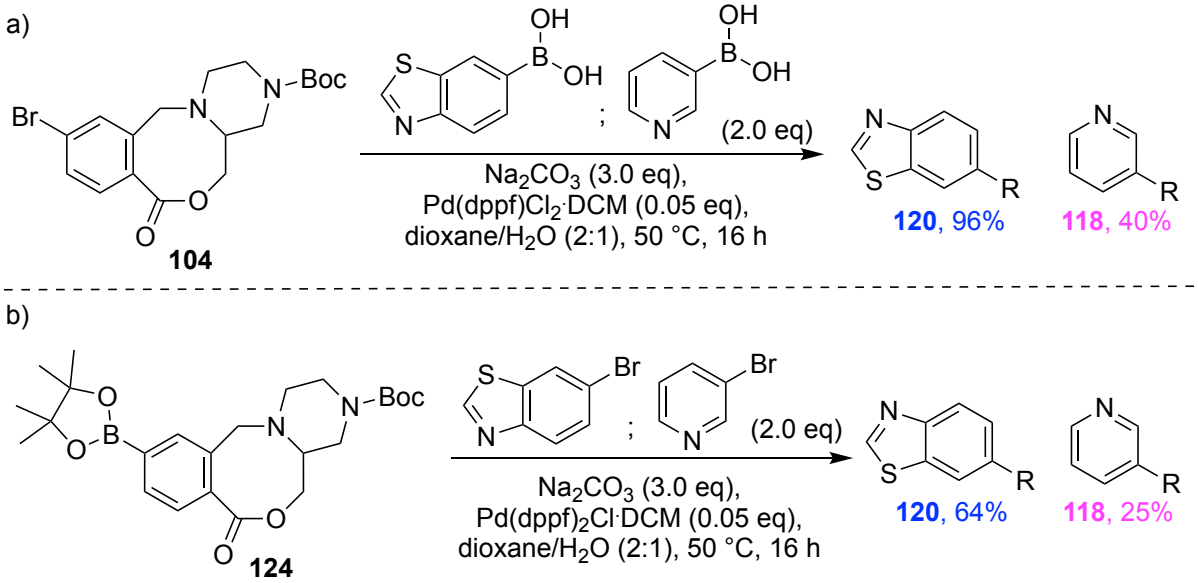


Figure 48. Comparison of SMCC with Boronic Acid building block and Bpin building block.

2.2.4 N-Functionalisation of medium-sized ring Suzuki-Miyaura products

Common reaction types used for N-functionalization include amide bond formation, nucleophilic substitution, sulfonamide formation, reductive amination, S_NAr, and Buchwald-Hartwig reactions. In this project, we selected some of these methods to combine with pharmaceutically relevant groups to further explore the potential of medium-sized ring

building blocks obtained by the NICE method in medicinal chemistry. First, we choose compounds **120** and **122**, which contain the benzothiazole group and 4-fluoro-2-methoxyphenyl group respectively. As discussed above, larger quantities were synthesized as the starting materials for the subsequent N-functionalization reactions. The benzothiazole and 4-fluoro-2-methoxyphenyl groups are heterocyclic aryl and aryl groups respectively. In addition, thiazole, fluorine atoms, and methoxy groups are common structural units in bioactive molecules which is why these two compounds were chosen for further exploration.

The removal of the Boc group was the first step in the N-functionalization process. Compound **122** was dissolved in dioxane with 4 N HCl, and the solution was stirred at room temperature for 1 hour to remove the Boc group. The reaction mixture was then concentrated to obtain hydrochloride salt **136**. Then, a sodium bicarbonate aqueous solution was added to the salt product, adjusting the pH to 7-8. After extraction and concentration, the crude product was purified by column chromatography yielding amine **137** with a yield of 74% (Figure 49).

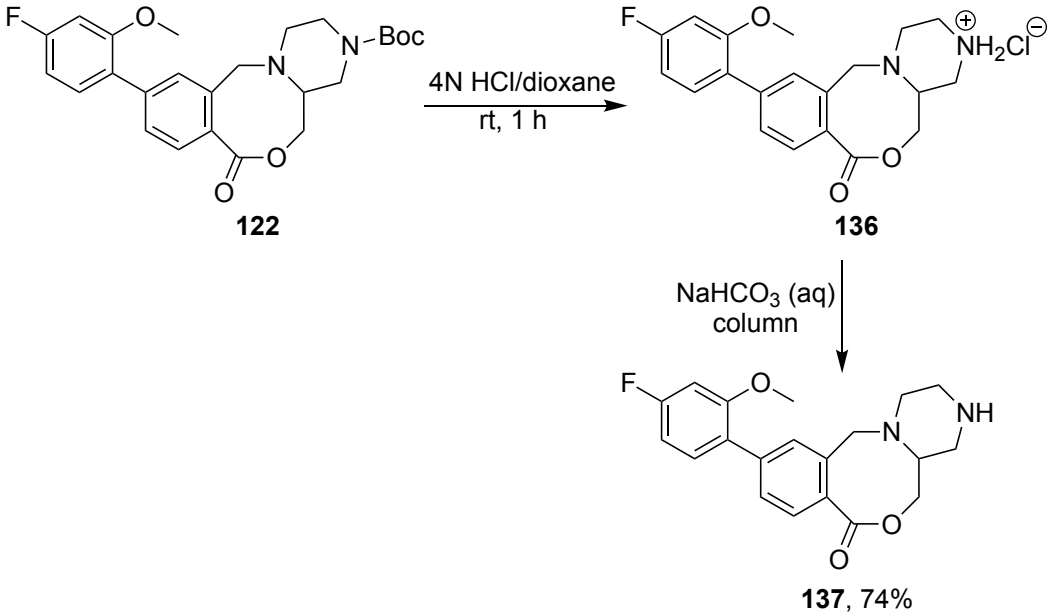


Figure 49. Boc deprotection process and results of compound **122**.

Subsequently, compound **120** containing the benzothiazole group was used in the Boc group deprotection under the same conditions. After separation and purification, amine **139** was obtained in 62% yield (Figure 50). At this point, both selected compounds for the N-functionalization reaction were successfully deprotected. The reactions proceeded smoothly, yielding clean products, and no ring-opening of the medium-sized ring structures was observed during the reactions. These make a successful beginning for the N-functionalization reactions.

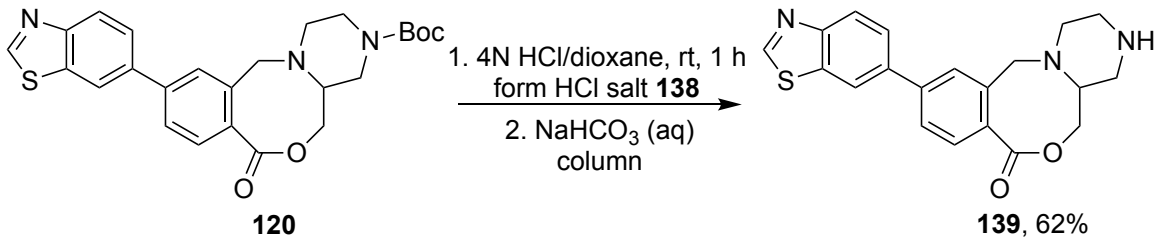


Figure 50. Boc deprotection process and results of compound **120**.

Figure 51 shows the ^{1}H NMR spectrum of amine **139** in DMSO-d_6. The NH in the structure does not appear in the NMR spectrum. Additionally, a key feature of this spectrum is the absence of the Boc signal around δ_H 1.4, and the number of other hydrogen atoms is consistent with the starting material **120**. The H_D proton appears at the most downfield area of the spectrum due to the -I inductive effects of the sulfur and nitrogen atoms, showing as a singlet at δ_H 9.45 (s). Next, there are three similar protons on both the phenyl ring and the benzothiazole ring, and it is difficult to accurately assign them. The signal at δ_H 8.57 (d, J = 2.0 Hz) is assigned to the H_C proton or the H_G proton, as both have small coupling constants of 0–3 Hz (^{4}J, W-coupling), but there is not enough information to distinguish between them. Similarly, the two doublet signals at δ_H 8.20 (d, J = 8.5 Hz) and δ_H 7.52 (d, J = 8.0 Hz) are assigned to the H_A or H_E proton, based on the large coupling constants (8–10 Hz, ^{3}J) with neighboring protons. The δ_H 7.91 (dd, J = 8.5, 2.0 Hz) appears as a doublet of doublets, which is assigned to H_B or H_F based on proton coupling. The other two aromatic proton peaks, theoretically expected as a doublet and a doublet of doublets, overlap at δ_H 7.81–7.74 (m). In the upfield region of the spectrum, the behavior of protons is consistent with those commonly seen in compounds of this series. Due to the stereogenic centre, the two protons of H_N and H_H, which are in non-equivalent environments, do not exhibit the same chemical shifts. As for the protons on the piperazine ring, based on the 2D NMR spectrum, only H_M can be assigned, which corresponds to one of the four hydrogens in the multiplet at δ_H 2.88–2.68 (m).

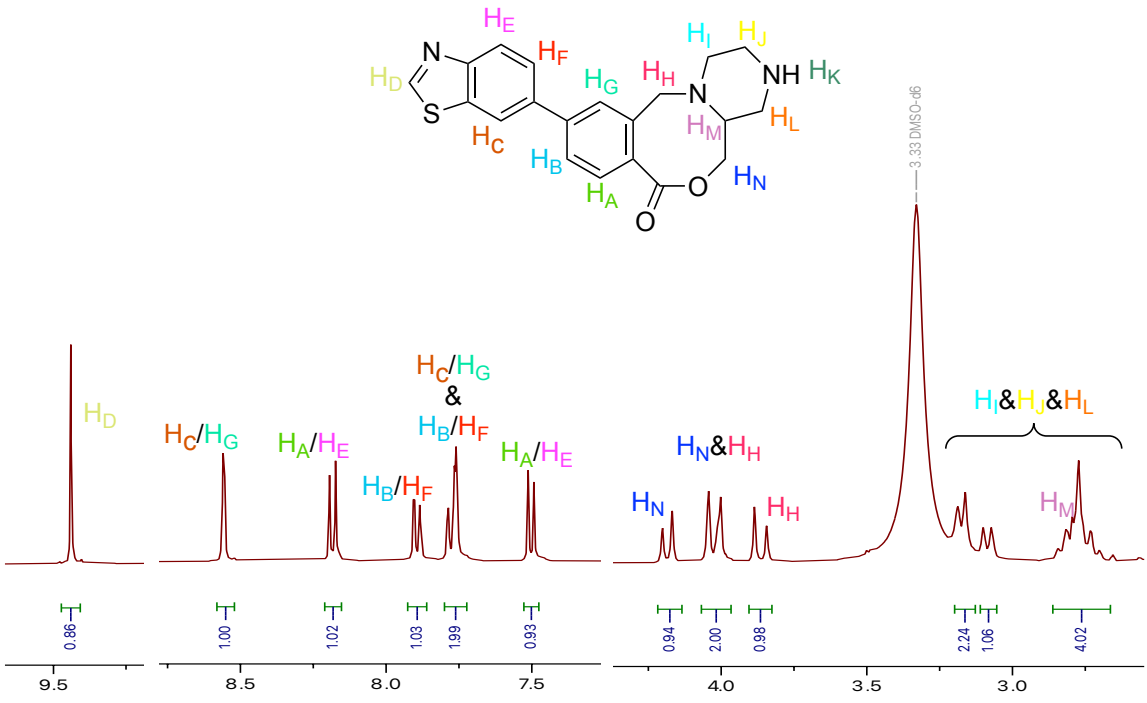


Figure 51. ^{1}H NMR spectrum of compound **139**.

After successfully showing that the Boc group could be removed from each of **120** and **122**, the plan was to carry out a series of N-functionalization reactions, with sulfonamide formation being the first one to be attempted. Sulfonamide formation is a method in which sulfonyl chlorides react with amines via nucleophilic substitution to form sulfonamides. As an important structure of sulfonamide drugs, the sulfonamide functional group is widely used in medicinal chemistry.[49] Since the secondary amine has relatively weak nucleophilicity, 4-dimethylaminopyridine (DMAP) is typically added as a catalyst. Sulfonyl chloride can be converted into a sulfonyl-DMAP intermediate in the presence of DMAP, which enhances the electrophilicity of the sulfur atom. Subsequently, the amine, acting as a nucleophile, attacks the sulfur atom in the sulfonyl group, producing the sulfonamide product while regenerating the DMAP catalyst and releasing one molecule of HCl, which is absorbed by a base.

First, starting from **122** containing the 4-fluoro-2-methoxyphenyl group, the deprotection reaction was carried out to remove the Boc group under the previously described conditions. The crude hydrochloride salt intermediate was reacted with 3,5-dimethylisoxazole-4-sulfonyl chloride **140**, triethylamine and catalyst DMAP in dichloromethane at 0 °C and then at room temperature for 18 hours. An excess of triethylamine was added during the reaction to neutralize the hydrochloride intermediate obtained after Boc removal, allowing the reaction to proceed directly from the hydrochloride salt. Finally, after purification by chromatography, the product **141** was obtained with a significant yield of 96% (Figure 52-a).

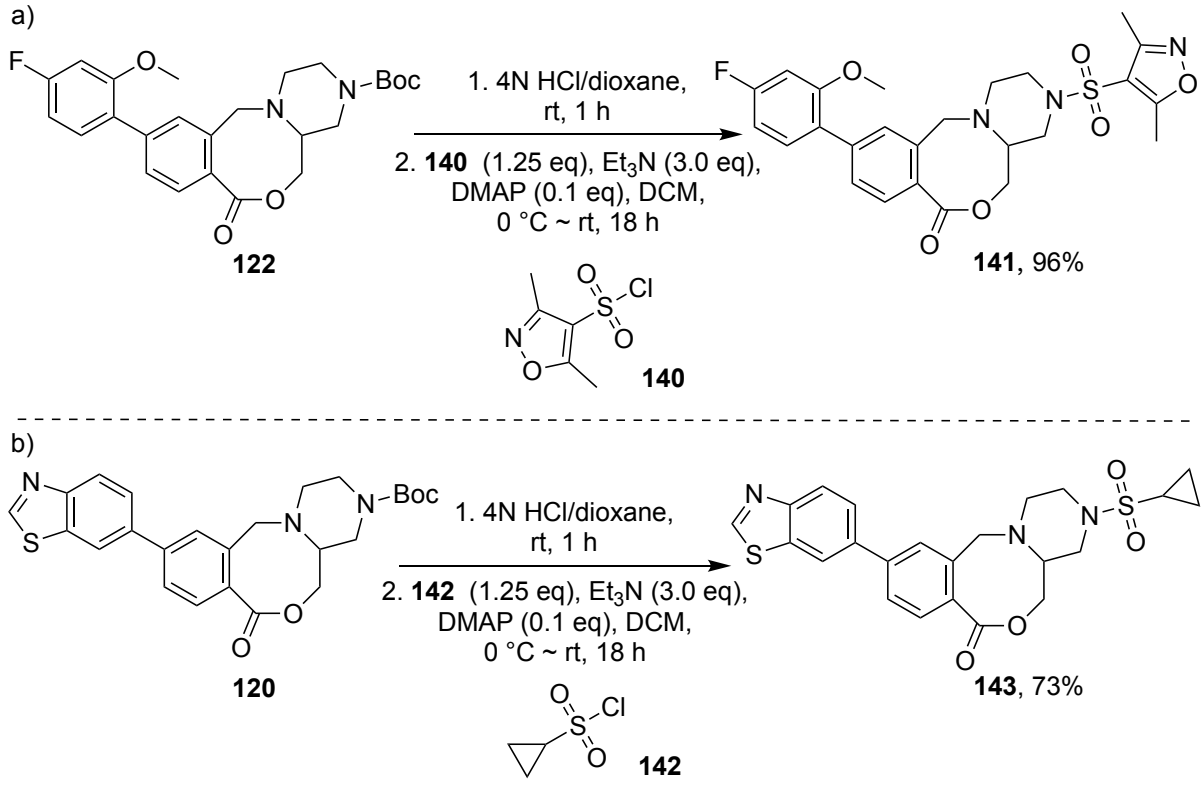


Figure 52. Results of sulfonamide formation.

Next, the sulfonamide formation was also attempted on compound **120** containing the benzothiazole group under the same conditions, but the sulfonyl chloride group was changed to cyclopropanesulfonyl chloride **142** (Figure 52-b). After the reaction and subsequent

purification by column chromatography, sulfonamide compound **143** was obtained with a yield of 73%. Based on these two highly successful sulfonamide formation results, it was confirmed that sulfonamide formation shows good compatibility with medium-sized ring compounds synthesized by the NICE method.

With the successful production of the two sulfonamide compounds **141** and **143**, different N-functionalization reactions were carried out to further prove the versatility of the medium-sized ring building blocks. Reductive amination was chosen to investigate next. Reductive amination is a method used to obtain amine compounds by reacting ammonia, primary amines, or secondary amines with aldehydes or ketones. This reaction takes place in the presence of a reducing agent, typically as a one-pot process, but it consists of two steps. First, the carbonyl group of the aldehyde or ketone experiences nucleophilic addition with the amine to form an imine, followed by the removal of a water molecule to generate the Schiff base intermediate structure. Finally, the nucleophilic attack by the hydride ion provided by the reducing agent results in the formation of the amine product. Common reducing agents include $NaBH_4$, $NaBH_3CN$, $NaBH(OAc)_3$ and 2-picoline-borane. Additionally, a small amount of acetic acid is added to the reductive amination reaction to provide a mildly acidic environment. If the acidity is too strong, the starting amine material may become overly protonated, reducing its nucleophilicity. While under basic conditions, the OH group cannot be protonated into a leaving group to facilitate the reaction.

The first reductive amination was explored with compound **122** containing the 4-fluoro-2-methoxyphenyl group. After deprotecting the Boc group, the obtained hydrochloride salt was subjected to reductive amination conditions using 5-methylfuran-2-carbaldehyde **144**, 1 equivalent of acetic acid and 2 equivalents of $NaBH(OAc)_3$ in tetrahydrofuran at room temperature for 18 hours.[50] After completion, the product was purified by silica gel chromatography, yielding amine **145** with an impressive 95% yield (Figure 53-a). Similarly, the eight-membered ring compound **120** containing the benzothiazole group was deprotected and reductive amination was carried out with pyrrolopyridine-carbaldehyde **146** under the same conditions, producing amine **147** in 51% yield (Figure 53-b).

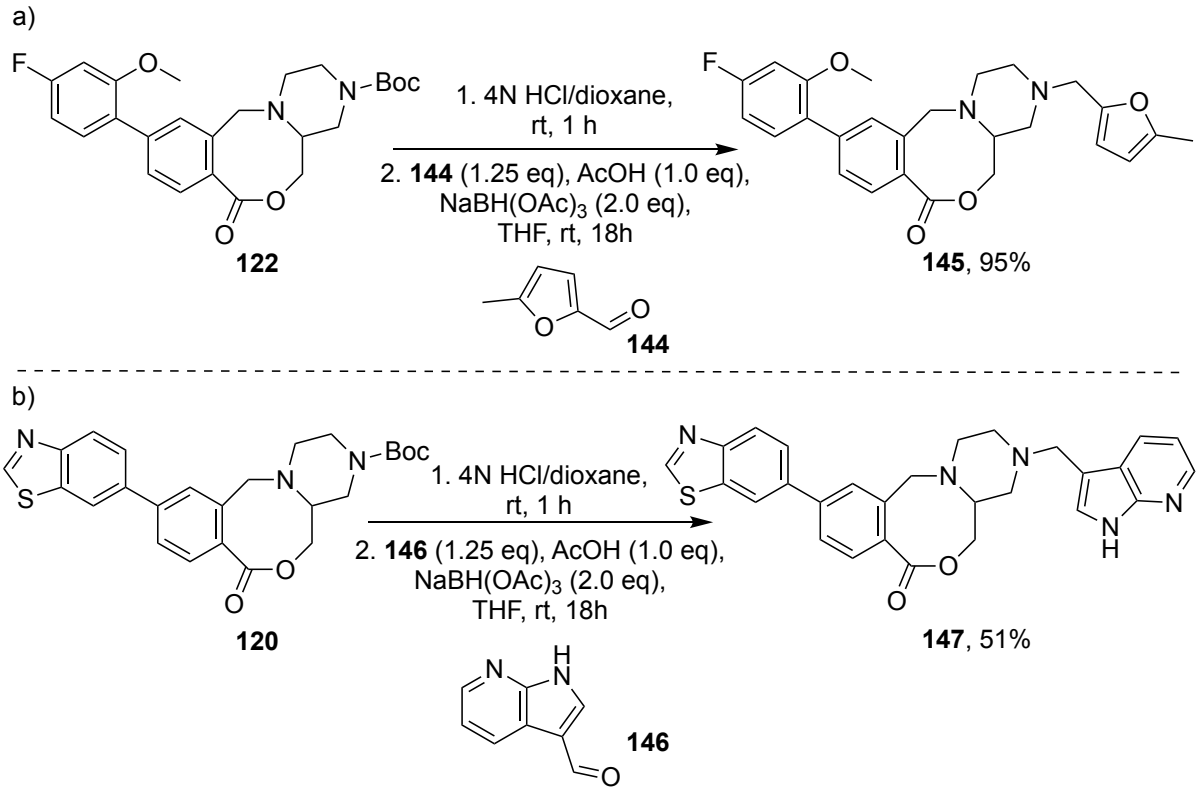


Figure 53. Results of reductive amination.

The next N-functionalization reaction on the NBoc medium-sized ring compound was amide bond formation, which is similar to the mechanism of sulfonamide formation. After removing the Boc group from **122**, the hydrochloride salt was reacted with acyl chloride **148**, triethylamine and DMAP in dichloromethane at 0 °C to room temperature. After purification by chromatography, amide **149** was isolated with a high yield of 95% (Figure 54).

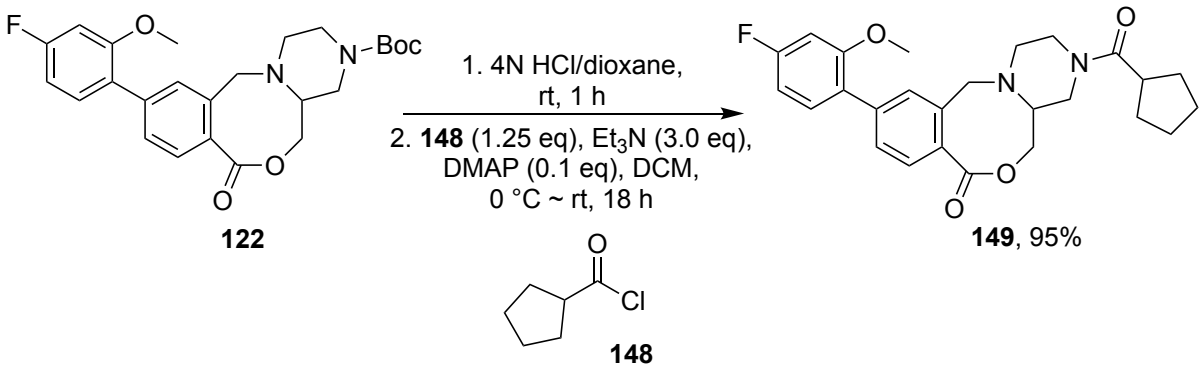


Figure 54. Results of amide bond formation with acyl chloride.

Amide bond formation using carboxylic acids was also explored. When the substrate is a carboxylic acid rather than an acyl chloride, condensation agents such as BPO, CDI, or T3P need to be added to the reaction to convert the hydroxyl group into a better leaving group to facilitate the reaction. As shown in Figure 55-a, the reaction conditions were derived from Glinka *et al.*[51] The hydrochloride salt of the deprotected product from **122** and carboxylic acid **150** were treated with 1.5 equivalents of BOP and an excess of triethylamine in DMF at room temperature for 18 hours. However, product **151** was not successfully obtained.

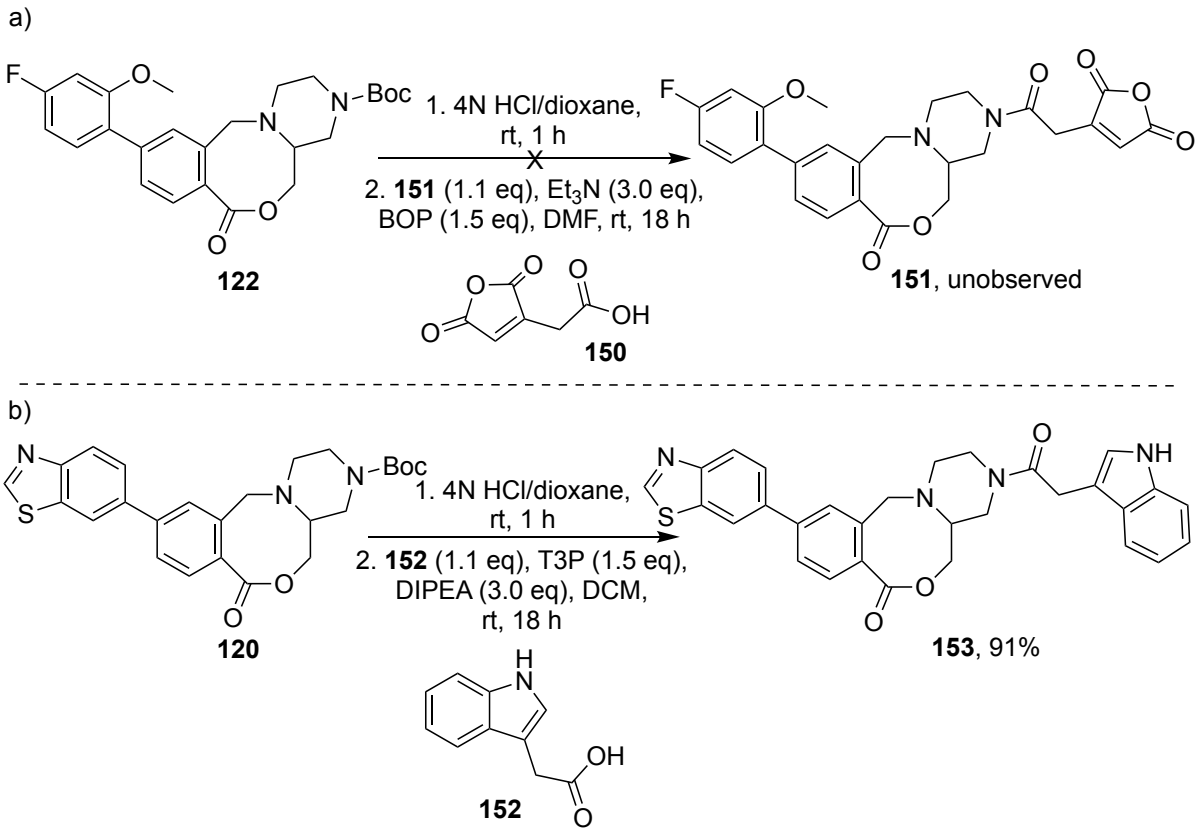


Figure 55. Results of amide bond formation with carboxylic acid.

A different carboxyl group was selected – indole acetic acid **152** (Figure 55-b) – along with reaction conditions that successfully allowed indole acetic acid to complete amide bond formation.[52] The hydrochloride salt derived from **120**, carboxylic acid **152**, T3P, and DIPEA were reacted in dichloromethane at room temperature for 18 hours. Amide **153** was then obtained via chromatography, in 91% yield. This reaction with carboxylic acid **152** yielded a good result, while the previous carboxylic acid **150** did not, and the reason for this remains unclear. Therefore, it is necessary to select an appropriate carboxylic acid for the amide bond formation reaction of building blocks.

The S_N2 N-alkylation reaction between amines and alkyl halides is also a common reaction for introducing amino groups into molecules. The S_N2 N-alkylation is a nucleophilic substitution reaction and its mechanism was described earlier in the synthesis of linear precursors containing internal nucleophiles (see Figure 56). Bromomethylbenzene **154**, containing a trifluoromethyl group, was selected for the first exploration of this reaction. After the usual preparation of the hydrochloride salt from **122**, relatively mild reaction conditions were chosen to maintain the stability of the eight-membered ring. The secondary amine hydrochloride salt and bromomethylbenzene **154** were reacted in THF in the presence of triethylamine at 70 °C for 18 hours. After separation and purification, tertiary amine **155** was successfully obtained in 78% yield.

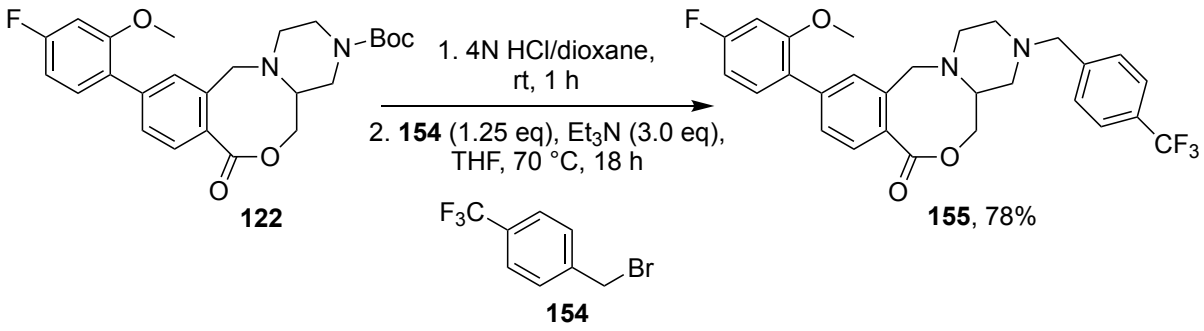


Figure 56. Result of S_N2 N-alkylation.

Next, N-functionalization using nucleophilic aromatic substitution (S_NAr) was explored. S_NAr is a reaction between nucleophiles and aryl halides that proceeds via an addition-elimination mechanism. The reaction requires an electron-withdrawing group (such as nitro, trifluoromethyl, sulfonyl) at the ortho or para position on the halogenated aromatic ring. S_NAr reactions also occur in 2- and 4-halopyridines, where the nitrogen on the pyridine acts as an electron-withdrawing group to facilitate the reaction.

Under general conditions, the Boc group was removed from the medium-sized ring compound **120** and to obtain the crude hydrochloride salt. 2-Chloro-4-methoxypyridine **156** was chosen for the first attempt as there were a few examples of S_NAr reactions with amines.[53] The reaction conditions used the secondary amine HCl salt, chloropyridine **156** and potassium carbonate in acetonitrile at 70 °C for 18 hours, but no product **157** was observed (Figure 57-a). Based on the S_NAr reaction mechanism, it was speculated that the electron donating methoxy group made this a more challenging S_NAr substrate. Therefore, 2-chloro-5-nitropyridine **158**, with a strong electron-withdrawing group NO_2, was selected for a S_NAr reaction with the deprotected HCl salt using the same reaction conditions. After chromatographic purification, the N-functionalized compound **159** was obtained with a yield of 82% (Figure 57-b). This result indicates that S_NAr reactions are also applicable to the medium-sized ring building blocks in this project when the appropriate substrate is selected.

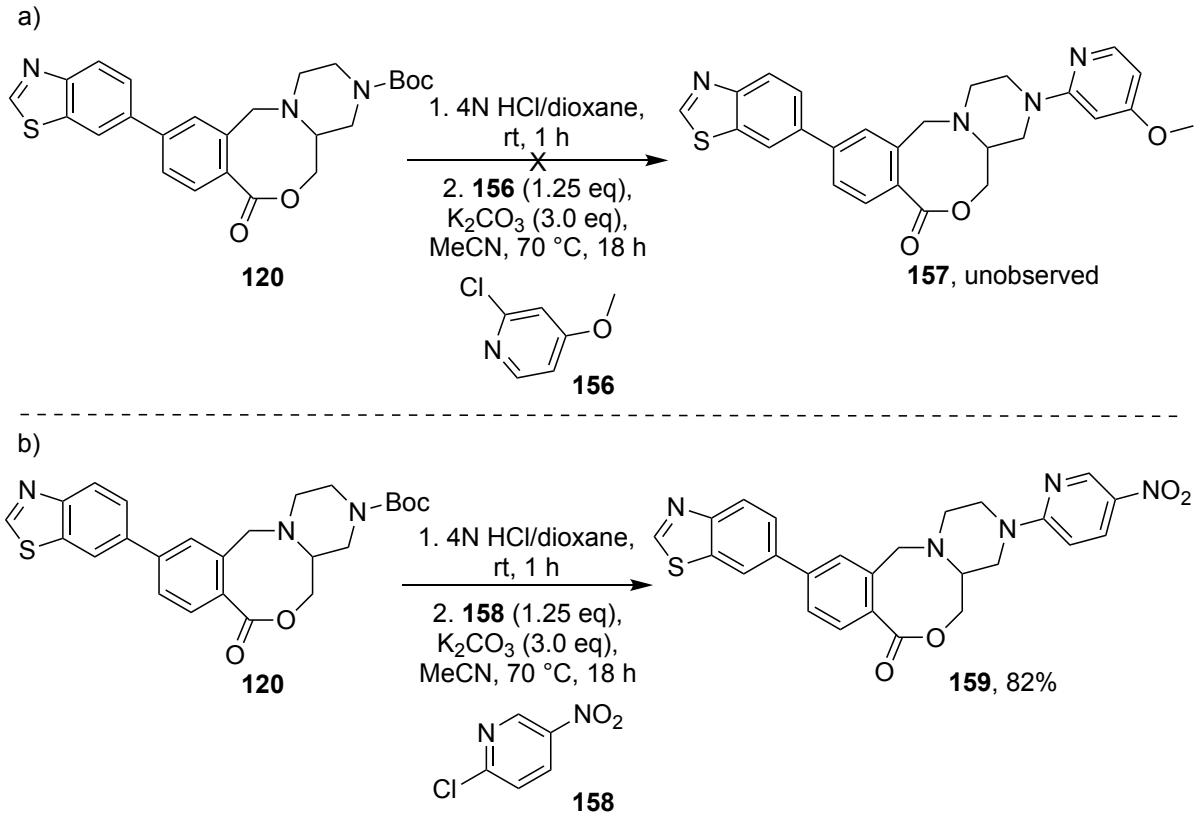


Figure 57. Results of S_NAr reactions.

Buchwald-Hartwig arylation is a cross-coupling reaction between amines and aryl halides catalyzed by palladium, and was the next N-functionalisation reaction to be explored. The reaction mechanism is similar to most palladium-catalyzed cross-coupling reactions, involving oxidative addition, ligand substitution, deprotonation, and reductive elimination. The Pd(0) catalyst undergoes oxidative addition with the aryl halide to form a Pd(II) complex. The amine, in the presence of a base, then attacks the Pd(II) complex, and the halide leaves as the leaving group. Finally, deprotonation and reductive elimination happen, yielding the product and regenerating the palladium(0) catalyst to start the cycle again.

The reaction conditions shown in Figure 58 were applied to the Buchwald-Hartwig arylation of pyrrolidine and 4-bromobenzaldehyde, yielding good results.[54] These reaction conditions were selected because the piperazine ring to be used has a structure similar to pyrrolidine. Additionally, (±)-BINAP is a commonly used bidentate ligand in Buchwald-Hartwig arylation, which can prevent palladium dimerization during the reaction and speed up the reaction. However, after deprotection of N-Boc compound **122** to obtain the hydrochloride salt, cross-coupling with 5-bromopyrimidine **160** in toluene at 70 °C using $Pd_2(dba)_3$, (±)-BINAP and NaO-t-Bu for 18 hours did not yield product **161**. Another reaction was carried out at a higher reaction temperature (110° C) but, unfortunately, no product formation was shown by ^1H NMR spectroscopy or mass spectrometry.

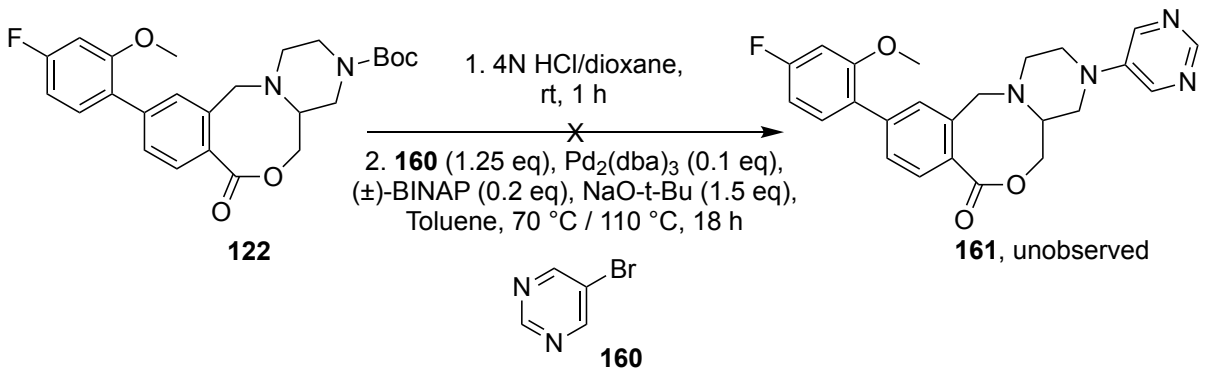


Figure 58. Unsuccessful attempt of Buchwald-Hartwig arylation.

After the failure of the reaction between the amine with a medium-sized ring and aryl bromide, some other conditions for successful Buchwald-Hartwig arylations of amines and 5-bromopyrimidine were found.[55] The failure of the cross-coupling reaction may have been caused by the strong basicity of NaO-t-Bu, which could have led to ring-opening by nucleophilic attack on the carbonyl group of the eight-membered ring. Therefore, the reaction conditions were revisited, and NaO-t-Bu was replaced with the milder base Cs_2CO_3. The starting material hydrochloride salt from **122**, aryl bromide **160**, $Pd_2(dba)_3$, (±)-BINAP and Cs_2CO_3 were reacted in toluene at 110°C for 65 hours. To our delight, product **161** was successfully obtained by chromatographic purification with a yield of 61% (Figure 59-a).

With this success, we further explored the scope of the Buchwald-Hartwig arylation on the medium-sized ring building blocks in this project. As shown in Figure 59-b, the N-Boc compound **120** was deprotected and the resulting hydrochloride salt was then subjected to the same reaction conditions, cross-coupling aryl bromide **162**. Finally, compound **163** was obtained through chromatography, with a yield of 73%. Thus, the successful reactions of two different amines and two different aryl bromides demonstrated that, with the appropriate reaction conditions, Buchwald-Hartwig arylation is also applicable to medium-sized ring building blocks synthesized by NICE.

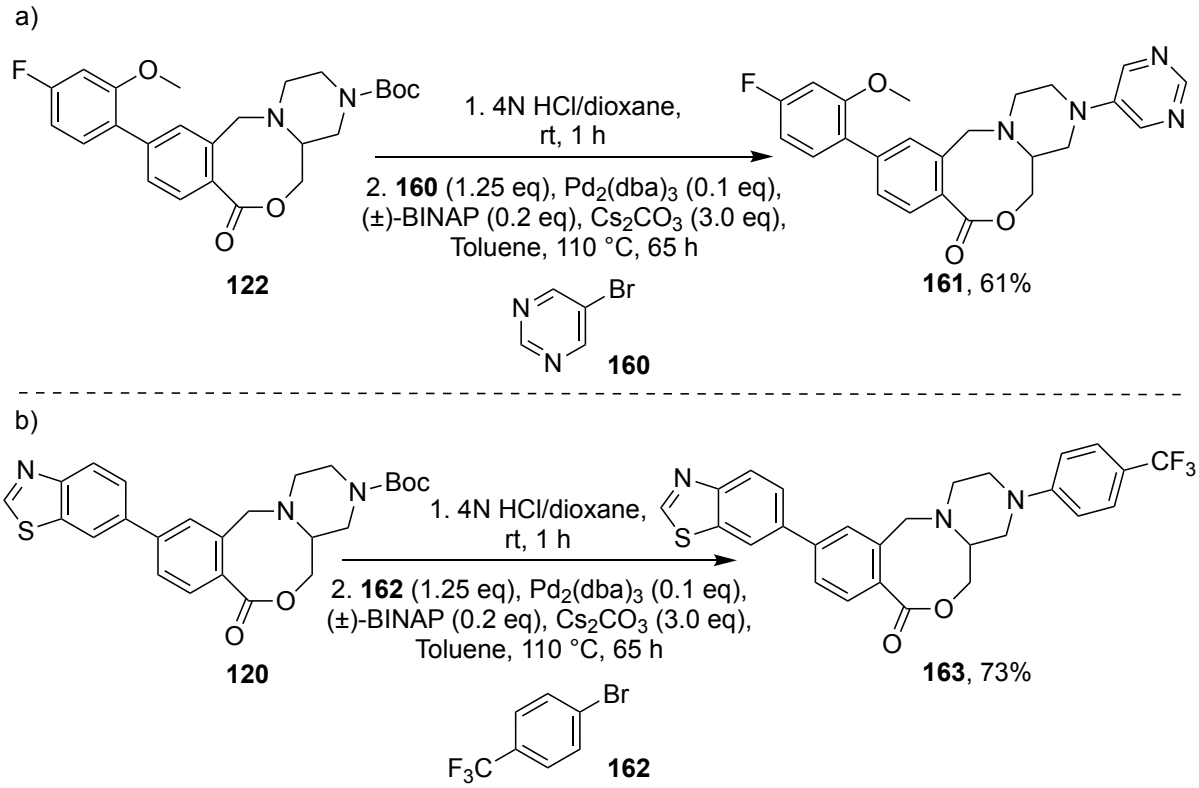


Figure 59. Successful Results of Buchwald-Hartwig arylation.

Figure 60 shows the ^{1}H NMR spectrum of amine **145** obtained through reductive amination. The downfield part of the spectrum corresponds to the three protons on the benzene ring: H_A, H_B, and H_G. H_A appears at δ_H 7.49 (d, J = 8.0 Hz). H_B, due to coupling with both H_A and H_G, is assigned to δ_H 7.43 (dd, J = 8.0, 1.5 Hz), and H_G appears at δ_H 7.27 (d, J = 1.5 Hz). Next, the three protons on the fluoro and methoxy-substituted benzene ring are H_C, H_D, and H_E. H_E, due to coupling with both H_D and the fluorine atom, shows a double doublet at δ_H 7.23. H_C and H_D overlap between δ_H 6.76 – 6.67 (m), making it difficult to calculate the coupling constants. Due to weaker aromaticity, the two protons on the furan group, H_M and H_N, appear more upfield than the protons on the benzene ring at δ_H 6.06 (d, J = 2.5 Hz) and δ_H 5.87 (dd, J = 2.5, 1.5 Hz) respectively. In addition to the two methyl groups which are easily identifiable, H_F and H_L, the methylene group between the nitrogen atom and the benzene ring H_H, appears more downfield than H_K, the methylene group between the nitrogen atom and the furan ring. Furthermore, the remaining protons in compound **145** exhibit similar characteristics in the ^{1}H NMR spectrum as other NICE series medium-sized ring compounds in this project.

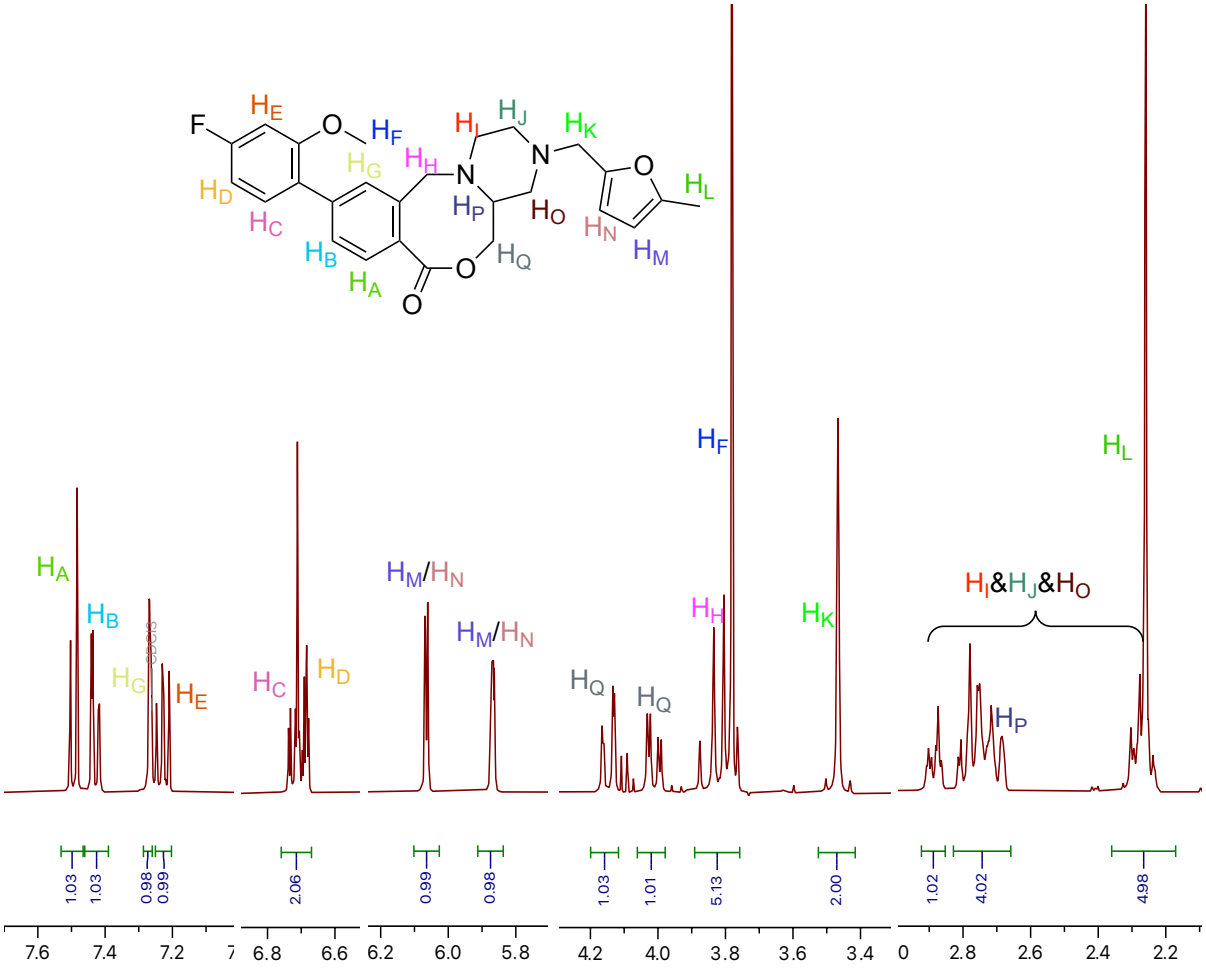


Figure 60. ^{1}H NMR spectrum of compound **145**.

Overall, a total of six different types of N-functionalization reactions have been successfully carried out using medium-sized ring building blocks up to this point - sulfonamide formation, reductive amination, nucleophilic substitution, amide bond formation, S_NAr and Buchwald-Hartwig. Numerous reaction conditions were explored, and, finally, 10 different N-functionalised compounds were obtained, all with satisfactory yields (ranging from 51% to 96%). Additionally, various types of groups were selected for attachment during the N-functionalization reactions, notably sulfonamide groups and heteroaromatic groups, which are widely used in medicinal chemistry. These successful results indicate that the medium-sized ring building blocks obtained through the NICE method exhibit broad compatibility both in terms of reaction and reactive group types. This demonstrates their potential for broader applications in drug design and discovery.

2.3 Synthesis of 3-D medium ring Building Blocks via CARE Method

The conjugate addition/ring expansion (CARE) cascade reaction sequence, previously mentioned and published by the Unsworth group as a method for synthesizing medium-sized lactams, was also studied following the completion of the synthesis and application exploration of medium-sized ring building blocks through the NICE method. The same research approach was used, involving the synthesis of medium-sized ring building blocks, together with their application in Suzuki-Miyaura cross-coupling reactions, and N-functionalization reactions.

First, a 6-membered ring amide which had been widely used in CARE reactions by the Unsworth group,[24] was selected as the precursor for constructing medium-sized ring building blocks. To include the amine functionality required for N-functionalization reactions, the selected lactam contained an additional NBoc structure compared to the lactams used in previous CARE methods. The preparation process for the CARE reaction starting material **166** is shown in Figure 61, where N-acylation of lactam **164** with acryloyl chloride **165** yielded imide **166** with a yield of 87% after chromatography.

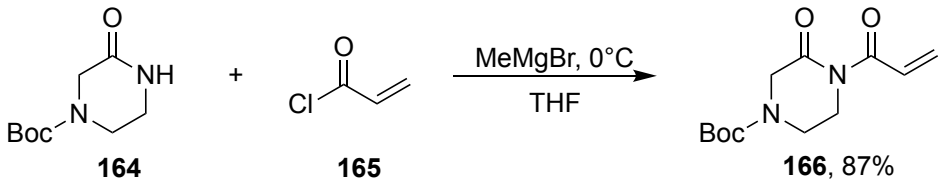


Figure 61. N-acylation of valerolactam **164**.

Next, we addressed the key step proposed by the CARE method, with the reaction mechanism shown in Figure 62. After the primary amine nucleophile attacks the Michael acceptor **73**, the cascade ring expansion begins. In this process, the internal nucleophile attacks the carbonyl group of the imide in **167**, forming an intermediate **168** containing two six-membered rings. Subsequently, the N-C bond breaks, and the six-membered ring expands into the ten-membered ring **169**.

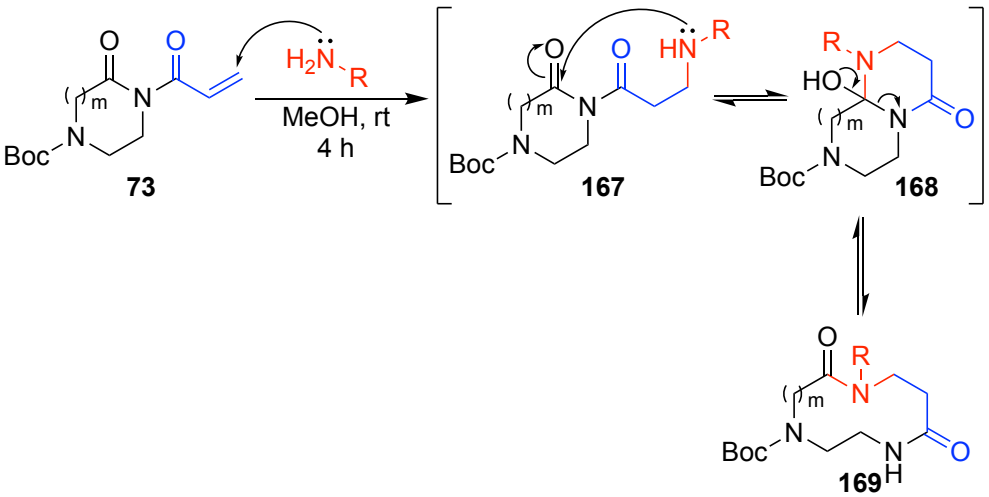


Figure 62. The CARE mechanism forming the lactam.

Bromoaniline **170** was first reacted with imide **166** in methanol, stirring at room temperature for three days. However, no product **171** was detected (Figure 63). Based on analysis, the likely reason was the conjugation effect of the benzene ring and the electron-withdrawing effect of the bromine atom, which reduced the nucleophilicity of the nitrogen atom on the primary amine. According to NMR spectroscopy and mass spectrometry, **172** and **173** were the main side products in this reaction. After methanol, acting as a nucleophile, attacks the carbonyl group of the 6-membered lactam **166**, the ring is broken to generate **172**. Then, aniline **170** further attacks this by-product **172** to form **173**, alternatively, the opposite order of steps may have occurred to give the same product **173**.

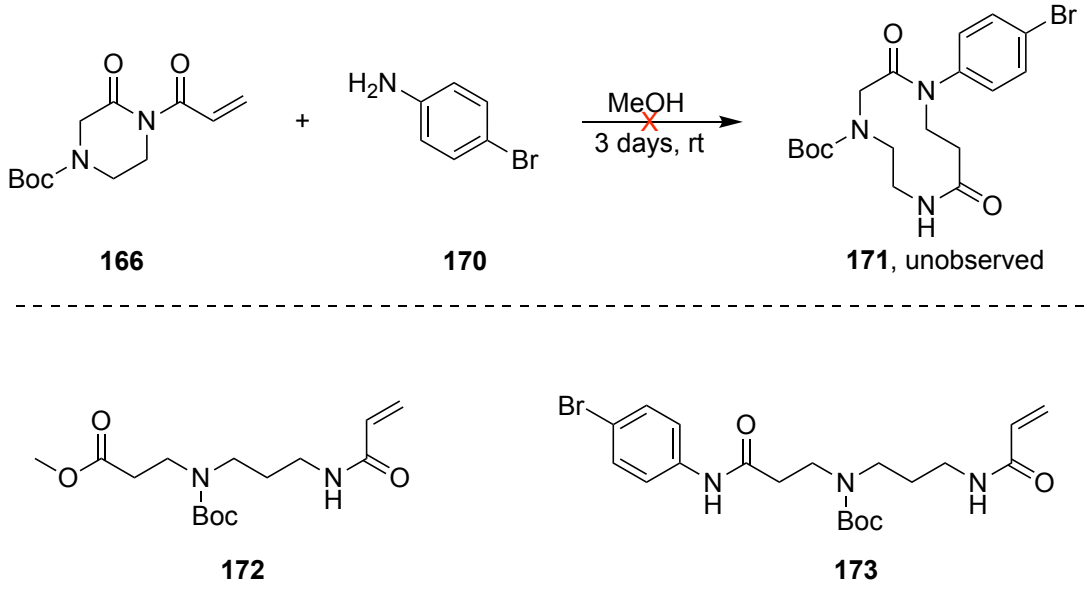


Figure 63. CARE reaction of bromoaniline.

Attempts were also made with Bpin containing aniline **174** and aniline **176**. However, no product **175** or **177** was obtained from this change either (Figure 64).

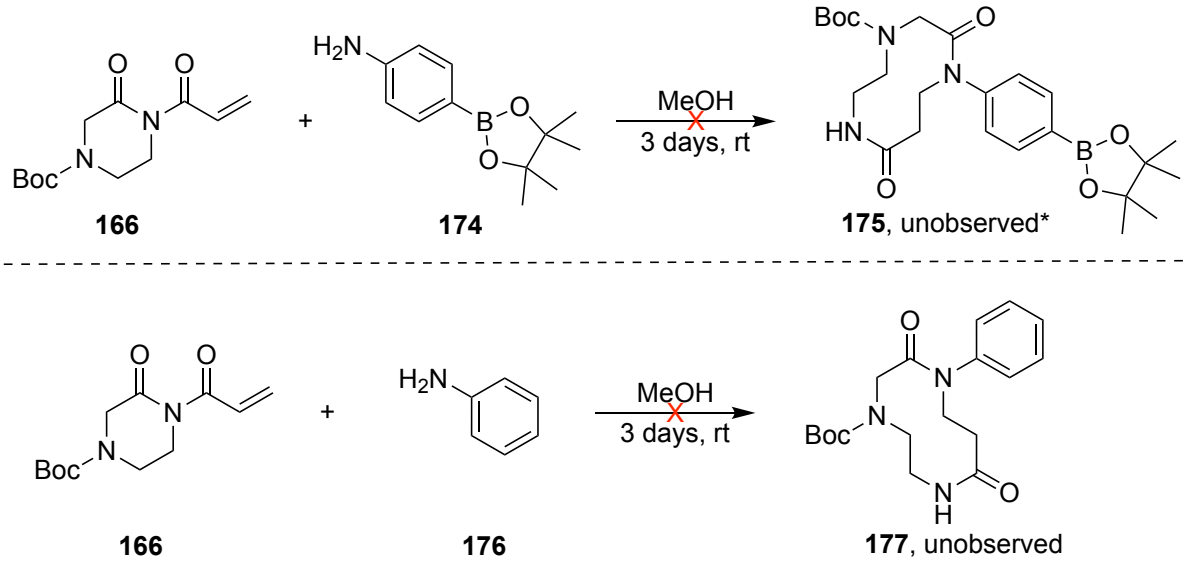


Figure 64. CARE reaction of aniline and Bpin aniline (*Result from Selin Yilmaz).

Similarly, the previously reported CARE reactions using anilines have been shown to be slower or unsuccessful.[24] It was concluded that the failure of these reactions was likely due to the resonance effect of the benzene reducing the nucleophilicity of the nitrogen atom. Therefore, it was decided to add a carbon between the benzene and the amino group, connecting them via a methylene group to address this issue. As shown in Figure 65, bromophenyl methanamine **178** and Bpin-phenyl methanamine **180** were reacted with acryloyl piperazine **166** in methanol at room temperature for 4 hours. After column chromatography, the 10-membered ring difunctionalised building blocks **179** and **181** were obtained with yields of 81% and 69% respectively. The reaction to give product **181** was carried out by a co-worker in the group, Selin Yilmaz.

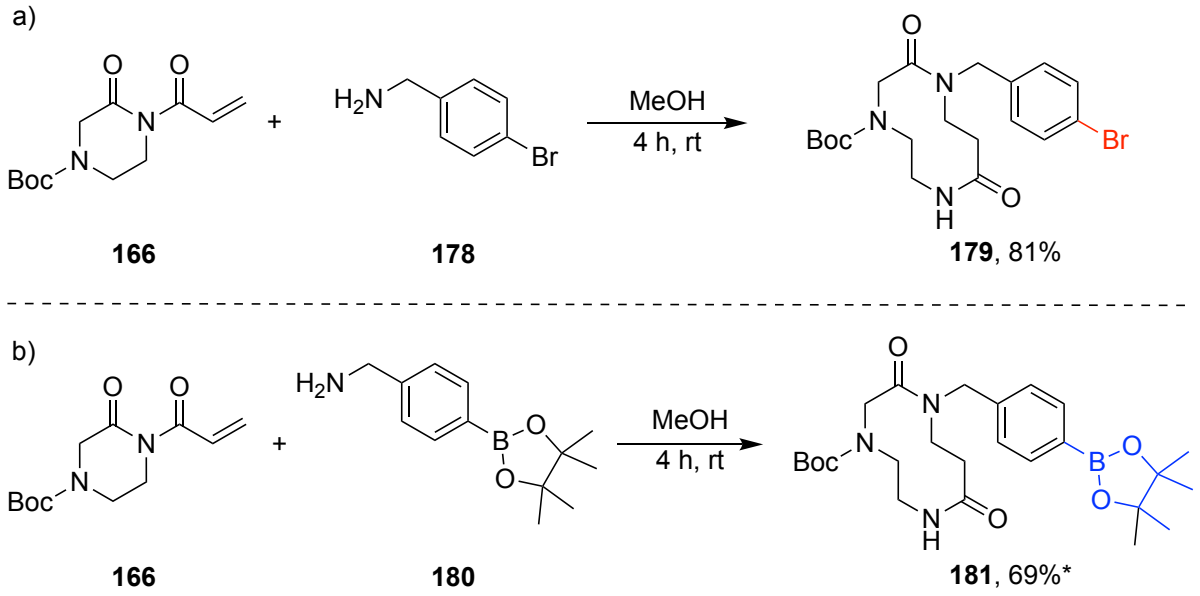


Figure 65. CARE reaction of 6-membered ring imide and phenyl methanamines (*Result from Selin Yilmaz).

With successful reaction results in hand, we continued to explore the CARE reaction with a 7-membered imide **182** (Figure 66). Two 11-membered ring difunctionalised building blocks **183** and **184** were successfully obtained after purification, with yields as 92% and 66%. Product **184** was synthesised by a co-worker in the group, Selin Yilmaz. These results confirmed the feasibility of synthesizing medium-sized ring building blocks using the CARE method.

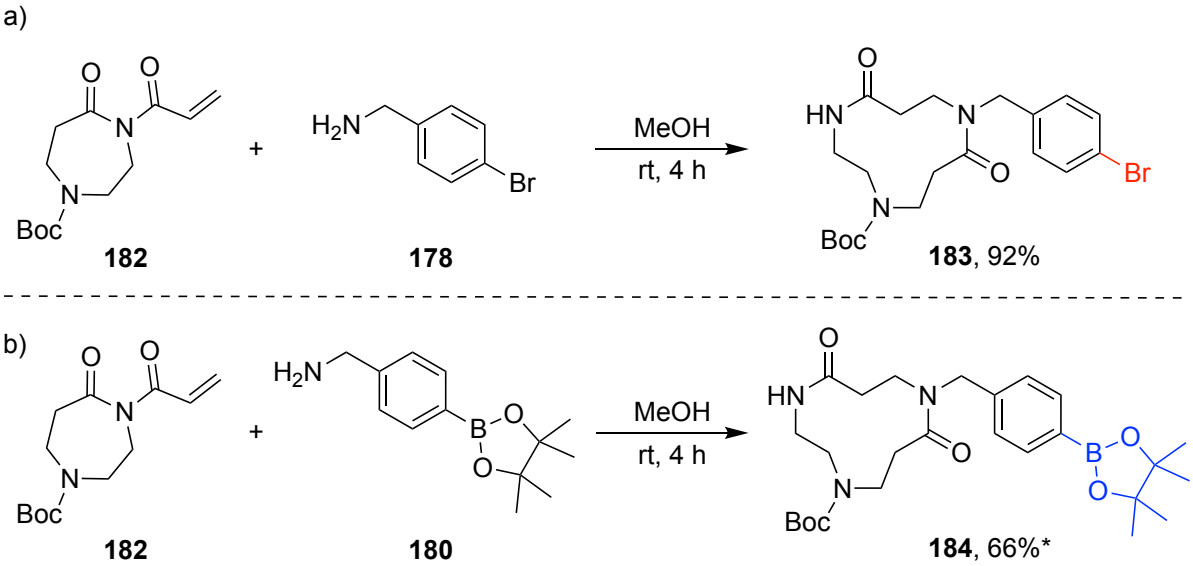


Figure 66. CARE reaction of 7-membered ring lactam and phenyl methanamine (*Result from Selin Yilmaz).

The ^{1}H NMR spectrum of the difunctionalised building block **179** is shown in Figure 67. This series of compounds shows complex NMR spectra due to the presence of rotamers from the two amides and the Boc group. First, four protons were successfully observed in the aromatic region. Among them, H_F and H_G each integrate for two protons. These are observed at δ_H 7.44 (d, *J* = 8.0 Hz, minor rotamer), δ_H 7.40 (d, *J* = 8.0 Hz, major rotamer) and δ_H 7.10 (d, *J* = 8.0 Hz, minor rotamer), δ_H 7.03 (d, *J* = 8.0 Hz, major rotamer). H_J appears at δ_H 5.84 representing the NH group. The non-equivalent methylene group H_E appears at δ_H 5.06 (d, *J* = 16.5 Hz) and δ_H 4.07 (d, *J* = 16.5 Hz) – this is presumably due to some type of restricted rotation or slow conformational changes on the NMR timescale, most one of the amide C–N bonds, imparting planar chirality on the molecule.[24] Similarly, the methylene group between the carbonyl group and NBoc, H_D, appears at δ_H 4.96 (d, *J* = 14.0 Hz) and δ_H 3.22 (d, *J* = 14.0 Hz). As for the nine protons on the tert-butyl group of the NBoc group, three distinct singlets can be observed at δ_H 1.31–1.49 which correspond to three rotamers. The remaining protons are heavily overlapped and difficult to distinguish, so only a basic assignment was made using 2D NMR spectra.

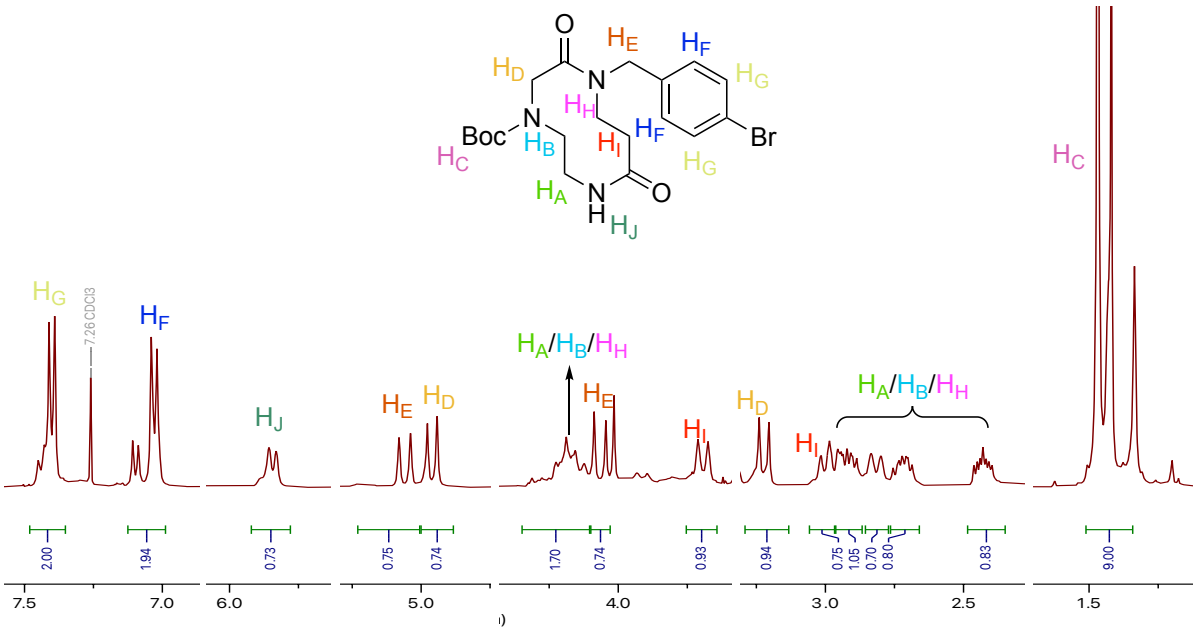


Figure 67. ^{1}H NMR spectrum of compound **179**.

2.4 Application of the 3-D medium ring Building Blocks Synthesized by CARE Method

2.4.1 Suzuki-Miyaura cross-coupling of building blocks from CARE method

Suzuki-Miyaura cross-coupling reactions were also explored on the medium-ring building blocks synthesized by the CARE method. The cross-coupling reaction conditions from earlier were applied to building blocks **179** and **181** (Figure 68). Pleasingly, these reaction conditions were equally applicable to the building blocks obtained through the CARE method. As shown in Figure 68-a, starting material **179** was separately reacted with phenyl boronic acid and pyridyl boronic acid in a 2:1 solvent mixture of dioxane and water with Na_2CO_3 and $Pd(dppf)Cl_2 \cdot DCM$ at 50 °C for 16 hours. After separation by chromatography, products **185** and **186** were obtained with yields of 90% and 52% respectively. Coupling with Bpin-containing building block **181** and phenyl bromide also yielded product **185** in 53% yield (Figure 68-b). The reaction to give product **185** from **181** was carried out by Selin Yilmaz. These results are similar to the results of the Suzuki Miyaura cross-coupling from the NICE method – the yields with the bromine-containing building blocks were higher than those with the Bpin-containing ones, and reactions with phenyl boronic acid produced better results than those with heteroaromatic boronic acids.

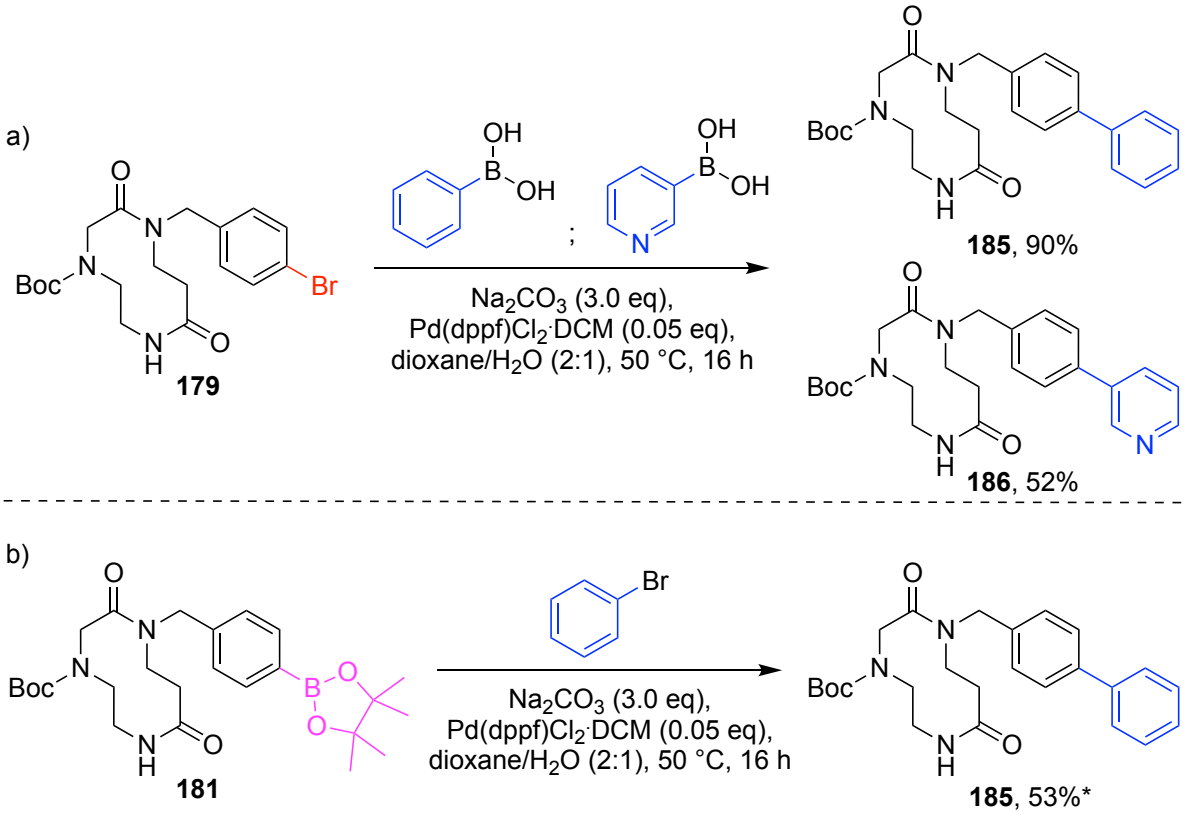


Figure 68. Results for all SMCC reactions of building blocks **179** and **181** (*Result from Selin Yilmaz).

Subsequently, Suzuki-Miyaura cross-coupling reactions were also successfully performed on the 11-membered lactam ring building blocks **183** and **184**, yielding product **187** (carried out by Selin Yilmaz) with 79% and 62% yields respectively (Figure 69). Thus, all Suzuki-Miyaura cross-coupling reactions on the medium-sized ring building blocks synthesized by the CARE

method were successful. This demonstrates that these building blocks exhibit adaptability in functionalization reactions via cross-coupling.

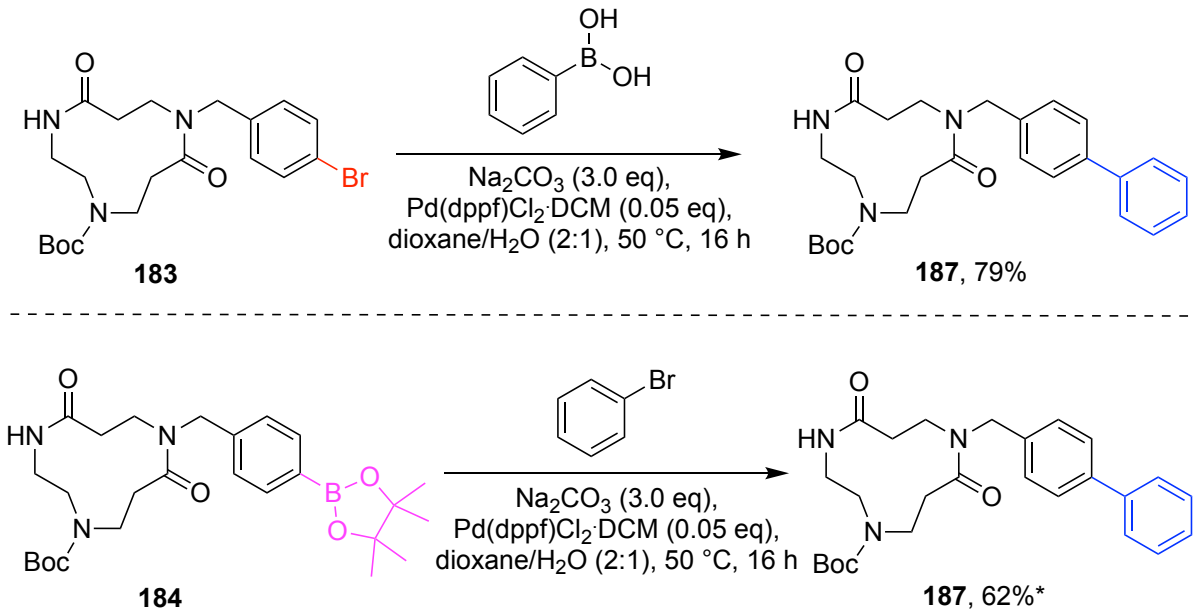


Figure 69. Results for SMCC reactions of building block **183** and **184** (*Result from Selin Yilmaz).

2.4.2 N-funtionalisation of building blocks from CARE method

Even though the yields of Suzuki-Miyaura cross-coupling with phenyl boronic acid were higher compared to those with pyridine, considering the broader application of heteroaromatic groups in medicinal chemistry, compound **186** was ultimately chosen for further N-functionalisation reactions. Additionally, since compound **186** contains an amide group, which could potentially undergo amination under Buchwald-Hartwig-type reaction conditions[56], the N-functionalization reaction of this 10-membered ring lactam were limited to amide and sulfonamide formation, together with reductive amination.

Our studies began with amide bond formation under relatively mild conditions. As shown in Figure 70, the same conditions were used for amide bond formation as in the previous work. After Boc deprotection of reactant **186**, the hydrochloride salt **189** was reacted with acyl chloride **188** in dichloromethane, with DMAP and triethylamine, at room temperature for 18 hours. After purification by silica gel column chromatography, compound **190** was obtained with a yield of 74%.

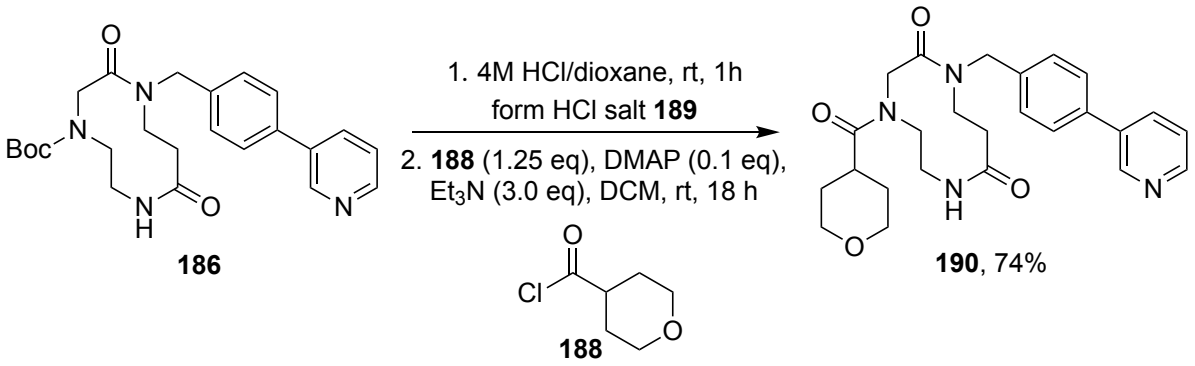


Figure 70. Results for amide bond formation of compound **186**.

A reductive amination reaction was also attempted under the previously successful conditions (see Figure 71), but no product **192** was detected.

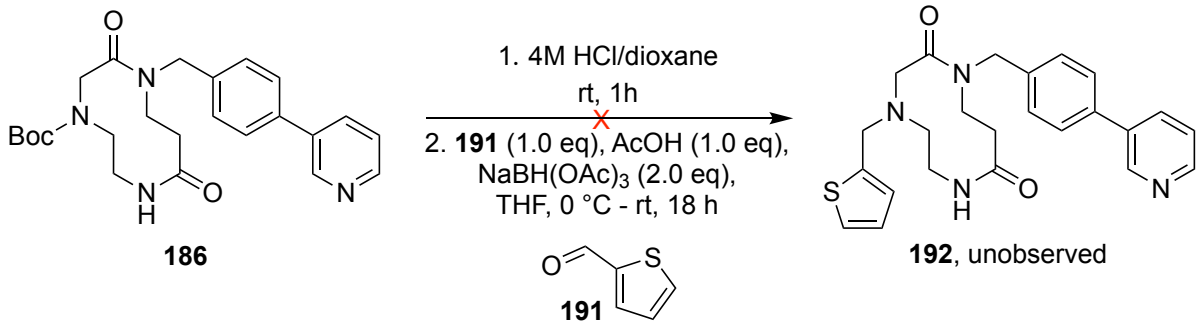


Figure 71. Results for reductive amination of building block **186**.

However, after NMR monitoring, significant differences were observed between the ^{1}H NMR spectra of the hydrochloride salts obtained during amide bond formation reaction (Figure 70) and that from the reductive amination reaction (Figure 71) even though the same reactions conditions for Boc group removal were used. The spectra were similar in the aromatic region, but in the upfield region, there were notable differences. The two hydrogens on each methylene group in hydrochloride salt were displayed as separate signals in Figure 72-a, with complex coupling. In contrast, in Figure 72-b, the two protons of the methylene groups appeared as singlets at δ_H 4.74 and δ_H 4.41. Figure 72-a corresponds to the ^{1}H NMR spectrum of the hydrochloride salt from the amide bond formation reaction which gave amide **190** successfully, confirming that Figure 72-a represents the correct spectrum for the hydrochloride salt. The presence of singlets for the methylene groups after Boc group removal from the reductive amination reaction suggested that some kind of ring opening of the medium-ring lactam had occurred. We wondered if this was during the work-up and removal of the dioxane on the rotary evaporator – maybe in this case, the crude product was heated higher or longer than in the Boc deprotection that had worked. Therefore, for the failure of the reductive amination reaction, it was concluded that the opening of the lactam ring during the Boc deprotection reaction might be the reason for the failure.

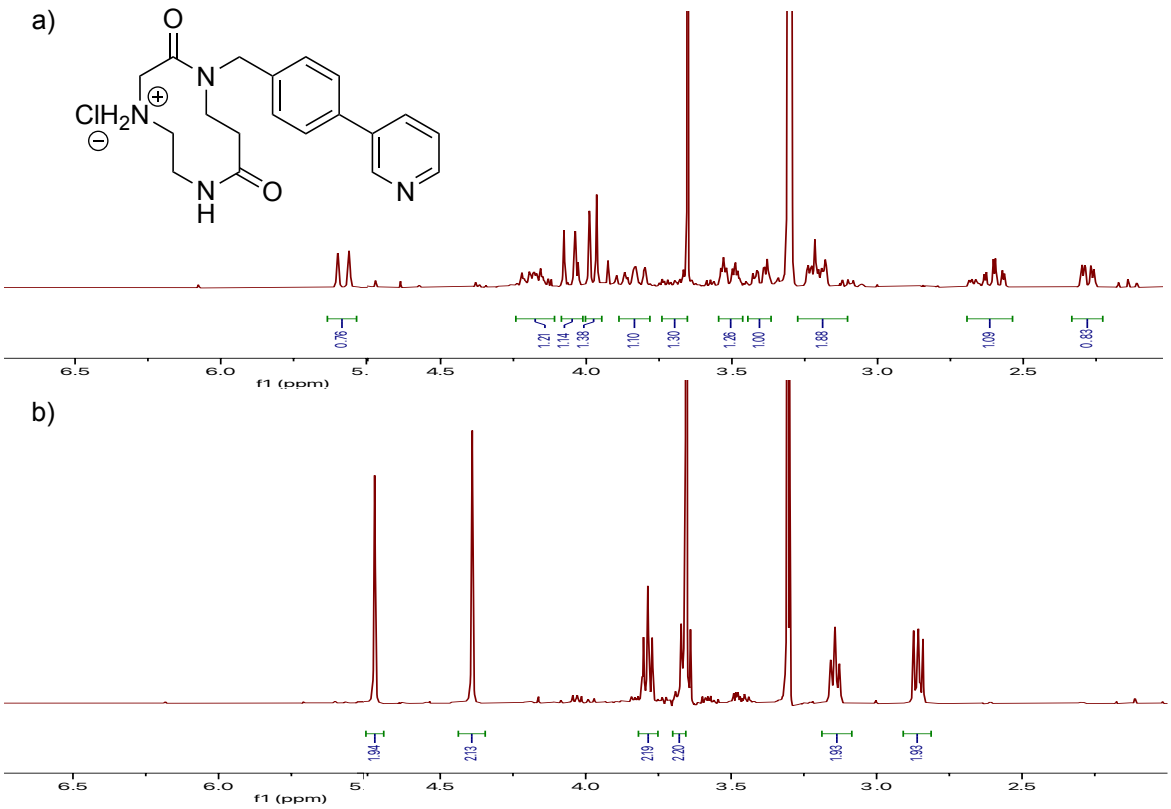


Figure 72. Comparison of the correct a) and incorrect b) ^{1}H NMR spectra of HCl salt **189**.

It was necessary to explore the Boc deprotection conditions more carefully in order to avoid ring opening of the lactam in the work-up and the lack of reproducibility in the Boc removal. (Figure 73). Eventually, under reaction conditions ii, where 4 M HCl in dioxane was used as the solvent and the reaction was carried out at 0 °C for ten minutes, followed by evaporation at room temperature (rather than at 40°C), hydrochloride salt **189** with the ^{1}H NMR spectrum corresponding to Figure 72-a could be reproducibly obtained. The reductive amination reaction in Figure 71 was then reattempted, but, frustratingly, no reaction product was detected.

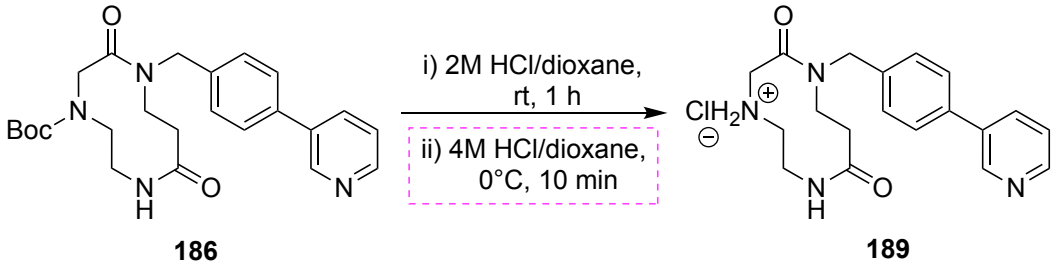


Figure 73. Exploration of deprotection reaction conditions.

Finally, two sulfonamide formation reactions were attempted starting from building block **186** using sulfonyl chloride groups **193** and **195** (Figure 74). Under the same reaction conditions as before, sulfonamide compound **196** was obtained with a 53% yield after chromatography purification (Figure 74-b). However, no compound **194** was obtained (Figure 74-a).

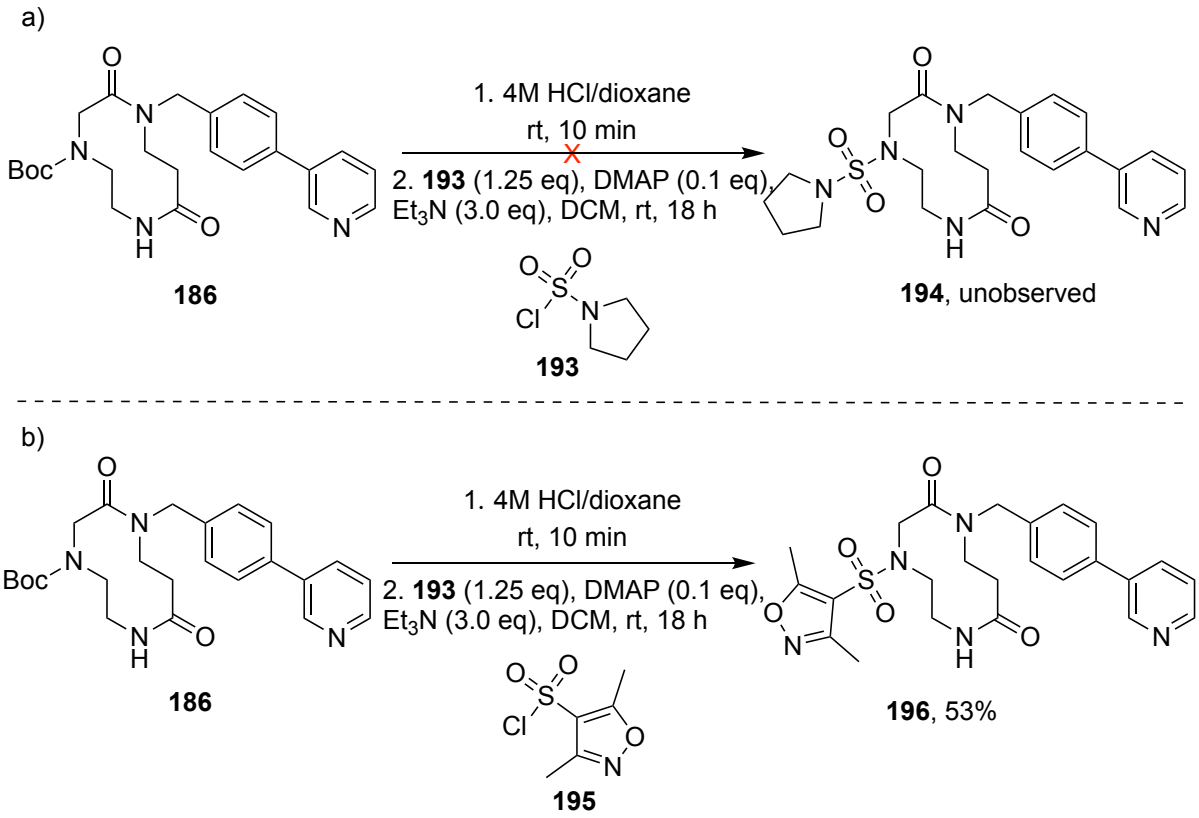


Figure 74. Results for sulfonamide formation compound **194** and **196**.

The ^{1}H NMR spectrum of N-functionalised compound **196** is shown in Figure 75. The presence of rotamers makes the NMR spectrum difficult to analyze and complicates the calculation of coupling constants. The number of protons is correct in the aromatic area—a total of nine protons. H_J representing the NH, appears at δ_H 6.37 (s, rotamer) and δ_H 6.17 (s, rotamer). Based on the 2D NMR spectra, the non-equivalent methylene group H_G is assigned to δ_H 5.12–5.28 (m) and δ_H 4.04–4.23 (m), while δ_H 4.41–4.53 (m) and δ_H 3.13–3.25 (m) are assigned to H_M. Despite overlapping with some of the methylene protons, some distinct singlets at upfield (δ_H 2.1–2.7) can be observed, which correspond to two methyl groups H_N and H_O. The remaining methylene protons are overlapped and difficult to distinguish.

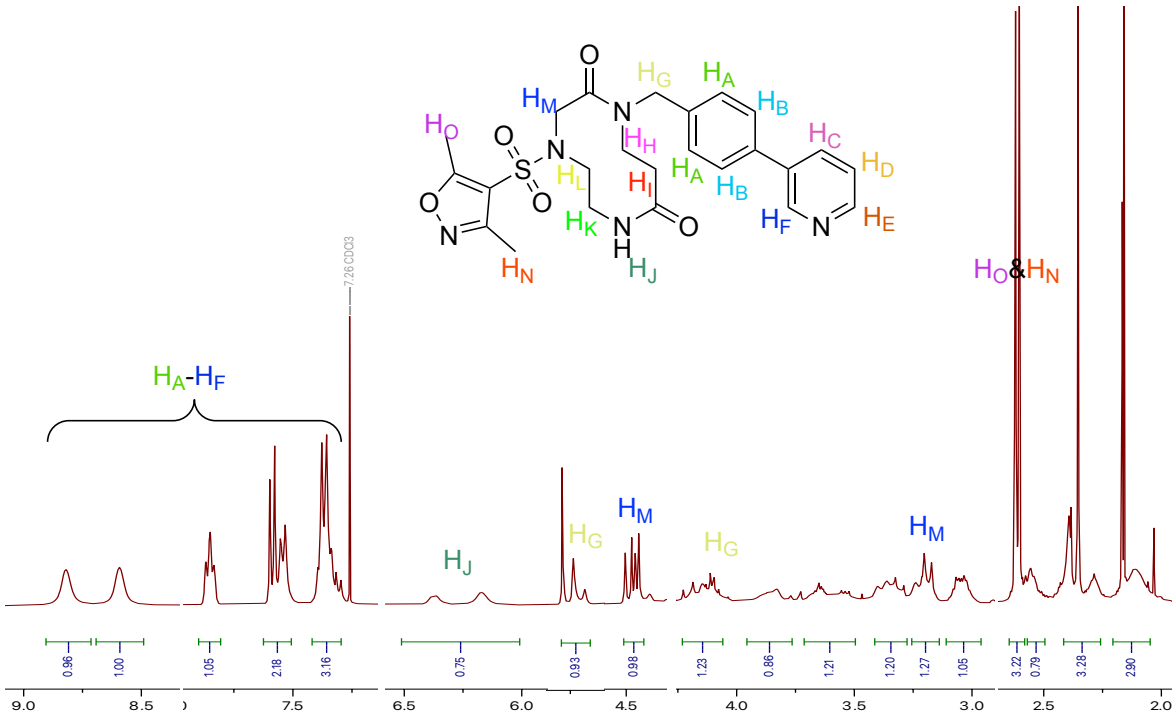


Figure 75. ^{1}H NMR spectrum of compound **196**.

3. Conclusion and Future work

Medium-sized ring structures have important applications in medicinal chemistry, but due to the challenges in their synthesis, they are underrepresented in drug discovery libraries.[57] The goal of this project was to combine new methods for synthesizing medium-sized ring structures with building blocks that can significantly enhance drug discovery efficiency, synthesizing 3-D building blocks centered on medium-sized rings and exploring their adaptability in various functionalization reactions.

The general approach in the NICE method involved bromination reactions, followed by S_N2 nucleophilic substitution, hydrolysis and ring expansion reactions, finally yielding 13 medium-sized ring building blocks. Most of the building blocks (**98** to **104**, **123** to **124**) were obtained using the NICE method (Figure 76-a), which was a key focus of this project's research. These gram-scale syntheses are achieved with overall yields of 61%-97% in two steps of hydrolysis and cyclization. Additionally, some work was done using the CARE method, resulting in a few additional building blocks **179**, **181**, **183** and **184** (Figure 76-b). Reactions to give products **181** and **184** were carried out by a co-worker in the group, Selin Yilmaz. The work in this thesis has shown that both methods are efficient for constructing a wide variety of building blocks.

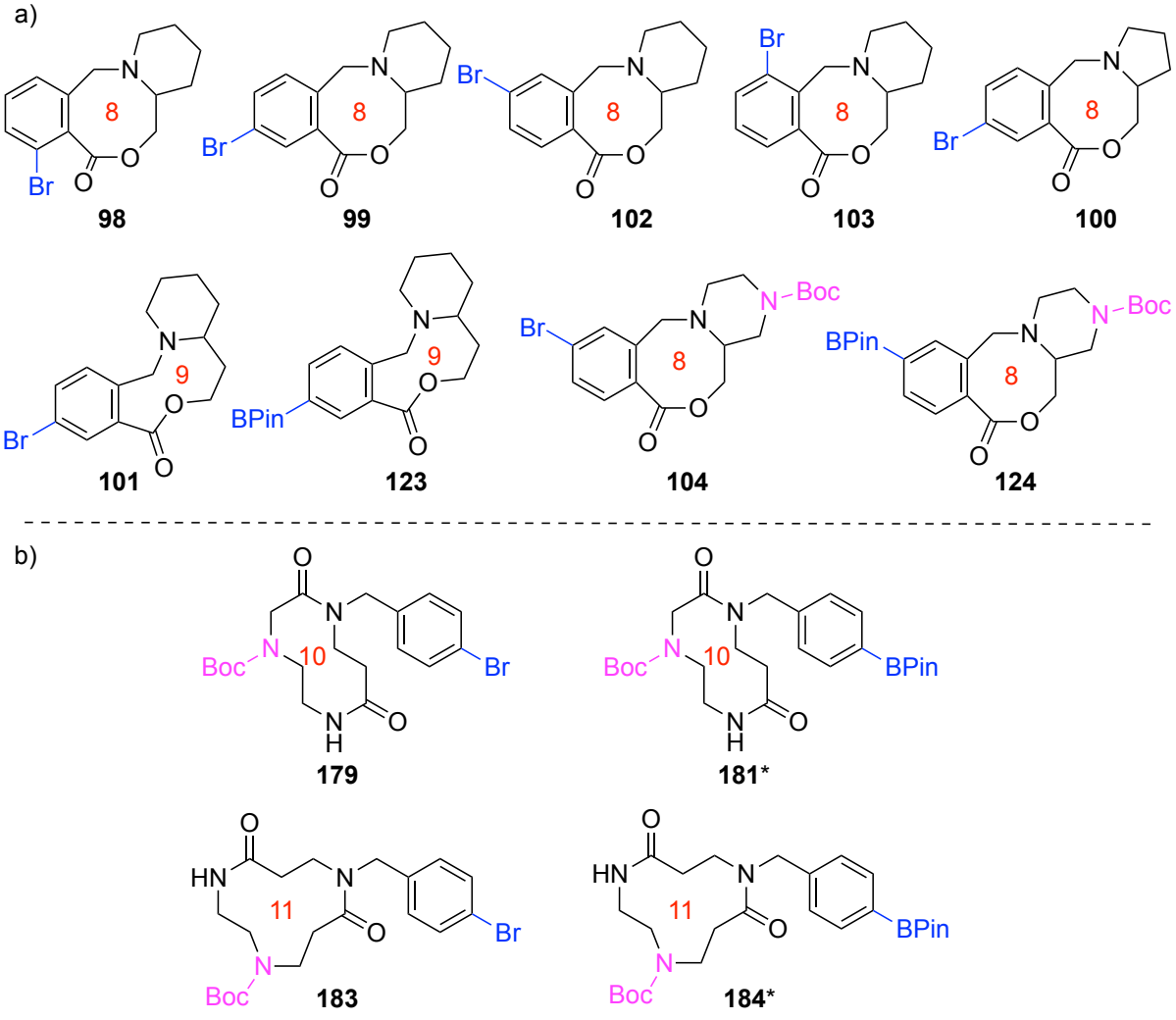


Figure 76. A summary of all obtained medium-sized ring building blocks (*Result from Selin Yilmaz).

A series of Suzuki-Miyaura cross-coupling reactions were successfully performed with the various medium-sized ring building blocks obtained (Figure 77). A phenyl group was successfully connected to all of the building blocks. More than ten reactions were completed, but as unsubstituted phenyl rings are less useful in medicinal chemistry, no N-functionalisation reactions were carried out with those products. These Suzuki-Miyaura reactions were conducted to explore the functionalization potential of medium-sized ring building blocks. Then, the results from this process were applied to Suzuki Miyaura cross-coupling reactions between the building blocks and heteroaromatic groups or substituted phenyl rings, which have broader applications in medicinal chemistry.

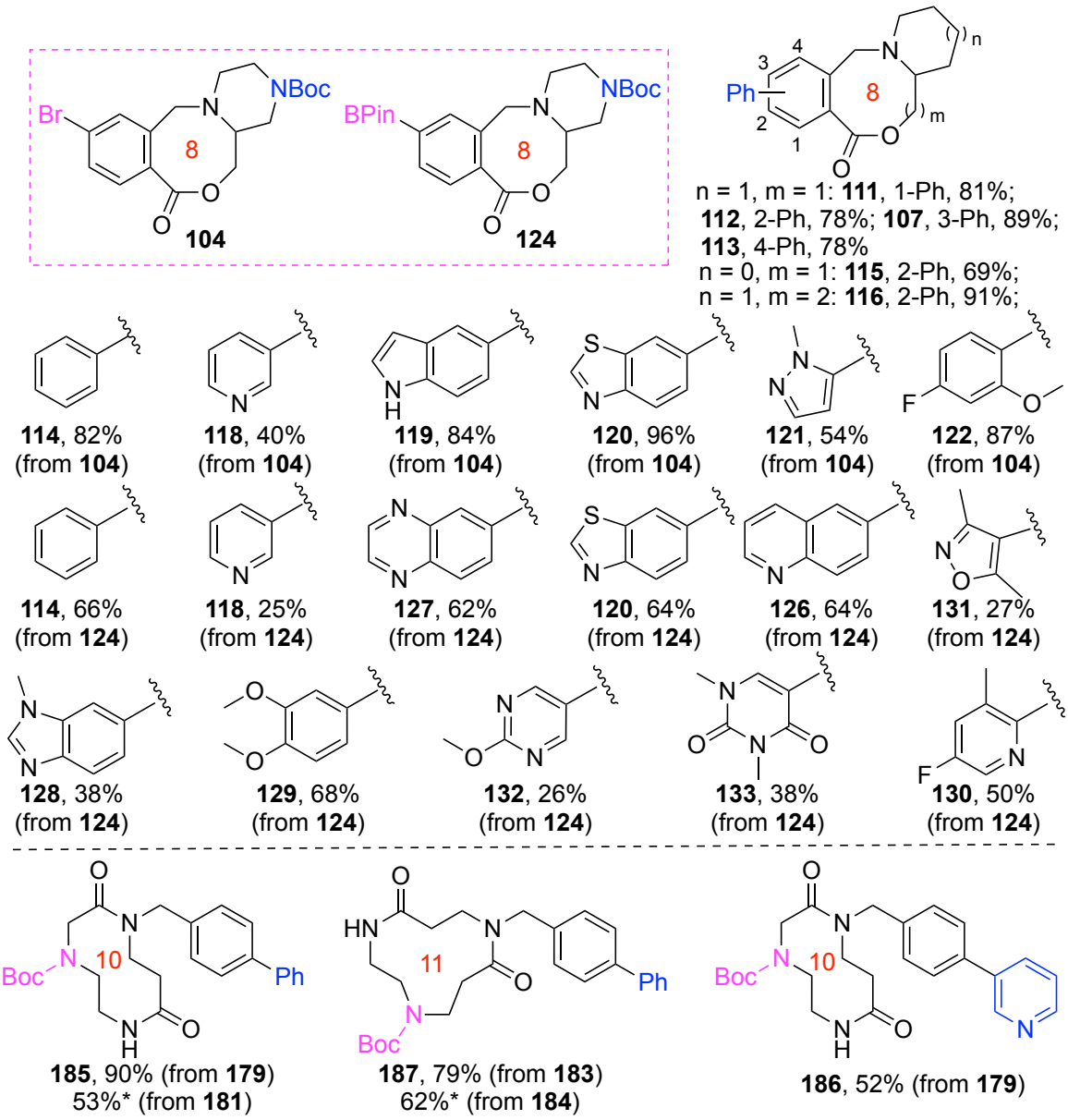


Figure 77. A summary of the Suzuki Miyaura cross-coupling results (*Result from Selin Yilmaz).

Additionally, some compounds obtained from Suzuki Miyaura cross-coupling were selected, displaying examples of their N-functionalization reactions, including sulfonamide formation, reductive amination, amide formation, S_N2 nucleophilic substitution, S_NAr and Buchwald-Hartwig arylation. The results are presented in Figure 78.

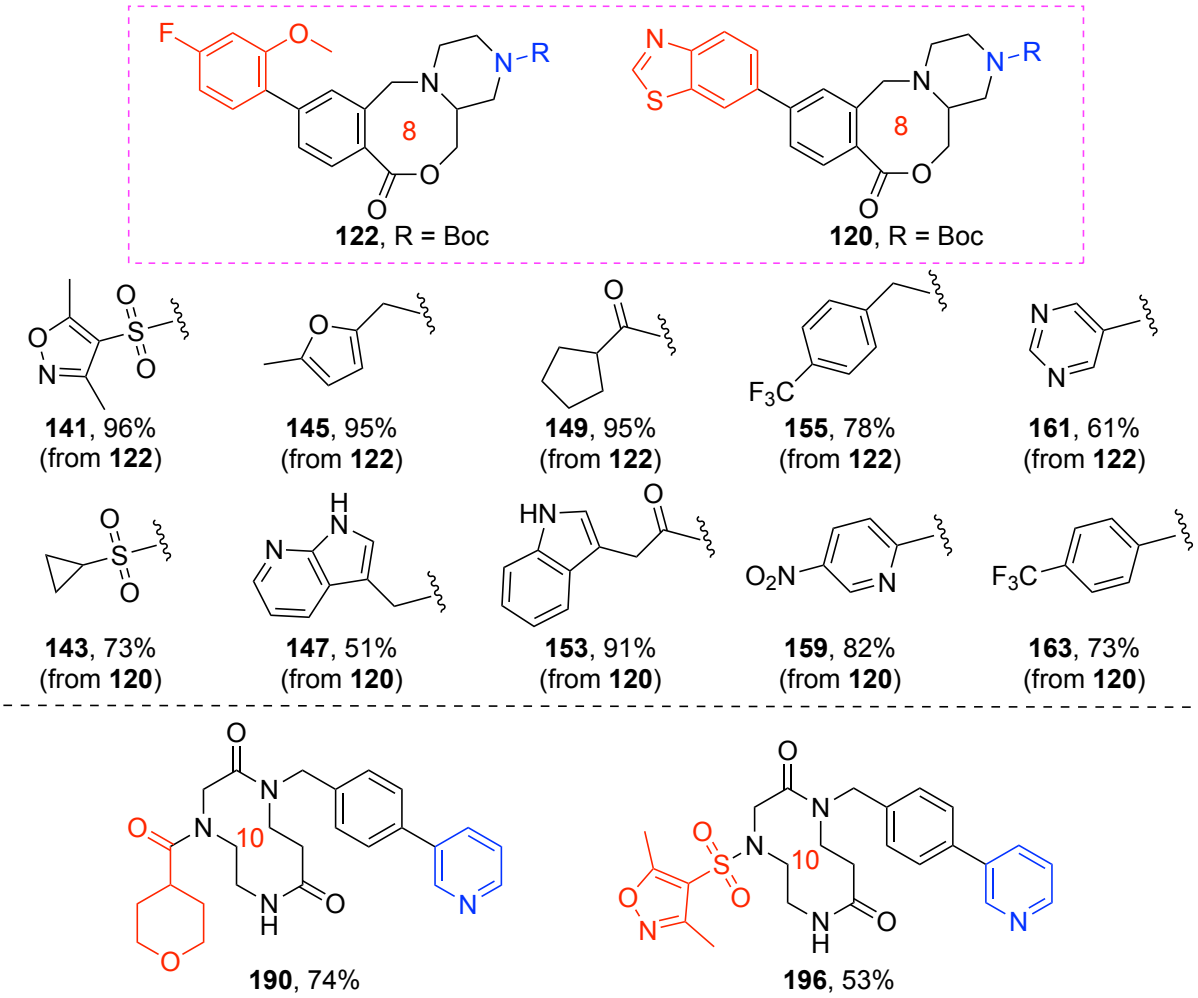


Figure 78. A summary of the N-functionalization results.

Regarding the research direction of synthesizing medium-sized ring building blocks using new methods and exploring their applications in medicinal chemistry, there is still great potential for development and research motivation. First, this project represents a practical attempt at applying the medium-sized ring synthesis methods from the Unsworth group. The primary research effort was dedicated to the difunctionalised eight-membered ring building blocks synthesized via the NICE method, as shown in Figure 79. However, in addition to these, there are also nine-, ten-, and eleven-membered ring building blocks that can be subjected to further studies. Alternatively, the aromatic on building block in Figure 79 could be removed and replaced with alkyl or cycloalkyl groups. These modifications could reduce the molecular weight of the compounds and increase their potential applications in medicinal chemistry. At the same time, there are many other methods for synthesizing medium-sized rings that could be applied, such as the SURE and other cascade ring expansion methods from the Unsworth group. These are all ideas worth exploring.

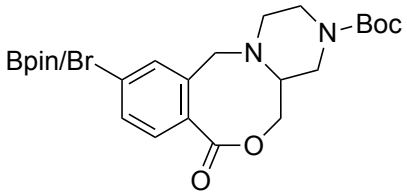


Figure 79. The primary focus structure of the building blocks in this project.

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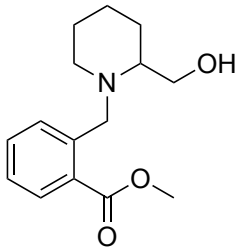
5. Experimental Data

5.1 General Synthetic Information

Anhydrous DCM, THF and Et_2O were obtained from a PureSolv MD 5 solvent purification system/anhydrous solvent dispenser & pump. All other reagents and solvents were purchased from commercial sources and used directly without further purification. All experiments were carried out in oven-dried glassware under inert atmosphere (Argon) unless otherwise stated. Thin layer chromatography was carried out using Merck silica gel $60F_{254}$ pre-coated aluminium foil sheets and were visualised using UV light (254 nm) and stained with basic aqueous potassium permanganate. Flash column chromatography was carried out using Sigma-Aldrich high-purity grade silica gel (SiO_2) 35–70 µm, 60 Å, under a light positive pressure, eluting with the specified solvent system. ^1H and ^{13}C NMR experiments were recorded on a JEOL ECS400 spectrometer operating at 400 MHz and 100 MHz respectively. All spectral data was acquired at 298 K unless stated otherwise. Chemical shifts (δ) are quoted in parts per million (ppm). The residual solvent peaks δ_H 7.27 and δ_C 77.16 for $CDCl_3$ were used as a reference. Coupling constants (*J*) are reported in Hertz (Hz) to the nearest 0.5 Hz. The multiplicity abbreviations used are: s singlet, d doublet, t triplet, q quartet, m multiplet, dd doublet of doublets, td triplet of doublets, ddd doublet of doublets of doublets; where br indicates a broad signal. Signal assignment was achieved by analysis of COSY, HSQC and HMBC experiments where required. Infrared (IR) spectra were recorded on a PerkinElmer IR UATR 2 spectrometer as a thin film dispersed from either CH_2Cl_2 or $CDCl_3$. High resolution mass spectra (HRMS) were obtained by the University of York Mass Spectrometry Service, using Electrospray Ionisation (ESI) on a Bruker Daltonics, Micro-tof spectrometer.

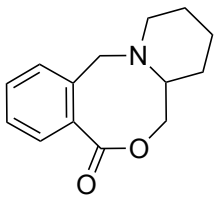
5.2 Experimental Procedures and Characterisation Data

Methyl 2-((2-(hydroxymethyl)piperidin-1-yl)methyl)benzoate (80)



To a stirring solution of potassium carbonate (830 mg, 6.00 mmol) in acetonitrile (10.0 mL), 2-piperidinemethanol (230 mg, 2.00 mmol) was added followed by methyl 2-bromo-6-(bromomethyl)benzoate (458 mg, 2.00 mmol). The reaction mixture was refluxed at 90 °C for 18 hours under argon. Then the reaction mixture was allowed to cool to RT, filtered and washed with dichloromethane, concentrated under vacuum and purified by column chromatography (SiO_2, 50:49:1 → 0:99:1 hexane : ethyl acetate : triethylamine) to afford the title compound (269 mg, 51%) as a yellow oil. R_f = 0.23 (99:1 ethyl acetate : triethylamine); ν_{max}/cm^{-1} (thin film) 2933, 1718, 1434, 1273, 1129, 1086, 741; δ_H (400 MHz, $CDCl_3$) 7.67 (1H, dd, *J* = 7.5, 1.5 Hz, Ar**H**), 7.44 – 7.36 (2H, m, 2 x Ar**H**), 7.30 (1H, td, *J* = 7.5, 1.5 Hz, Ar**H**), 4.56 (1H, d, *J* = 13.5 Hz, ArC**H$_a$**H$_b$N), 3.95 (1H, dd, *J* = 12.0, 3.5 Hz, C**H$_a$**H$_b$OH), 3.93 – 3.85 (3H, m, OC**H$_3$**), 3.44 (1H, dd, *J* = 12.0, 3.5 Hz, CH$_a$**H$_b$**OH), 3.34 (1H, d, *J* = 13.5 Hz, ArCH$_a$**H$_b$**N), 2.64 (1H, dt, *J* = 12.0, 4.5 Hz, NC**H$_a$**H$_b$), 2.33 – 2.26 (1H, m, NC**H**), 2.02 – 1.95 (1H, m, NCH$_a$**H$_b$**), 1.72 – 1.63 (3H, m, C**H$_2$**, C**H$_a$**H$_b$), 1.53 – 1.47 (1H, m, CH$_a$**H$_b$**), 1.38 – 1.28 (2H, m, C**H$_2$**); δ_C (100 MHz, $CDCl_3$) 170.0 (**C**O), 140.2 (Ar**C**), 131.3 (Ar**C**H), 131.2 (Ar**C**), 130.5 (Ar**C**H), 129.6 (Ar**C**H), 127.1 (Ar**C**H), 63.0 (N**C**H), 62.7 (**C**H$_2$OH), 56.2 (Ar**C**H$_2$N), 52.5 (O**C**H$_3$), 51.9 (N**C**H$_2$), 27.5 (**C**H$_2$), 24.7 (**C**H$_2$), 23.8 (**C**H$_2$); HRMS (ESI) calcd. for $C_{15}H_{22}NO_3^+$, 264.1594. Found: $[MH]^+$ 264.1594 (+0.1 ppm error).

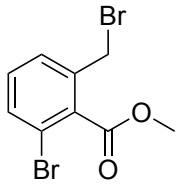
7,7a,8,9,10,11-Hexahydrobenzo[*f*]pyrido[2,1-*c*][1,4]oxazocin-5(13*H*)-one (85)



To a stirring solution of methyl 2-((2-(hydroxymethyl)piperidin-1-yl)methyl)benzoate **80** (200 mg, 0.759 mmol) in methanol (1.7 mL), aqueous lithium hydroxide (0.5 M) was added (1.7 mL, 0.835 mmol) and the reaction mixture was heated to 50 °C for 1 hour. The reaction was then allowed to cool to RT, and the solvent was removed under vacuum using chloroform (5 × 50 mL) to form an azeotropic mixture. The intermediate 2-((2-(hydroxymethyl)piperidin-1-yl)methyl)benzoic acid was dissolved in chloroform (7.5 mL) and DIPEA (0.25 mL, 1.40 mmol) was added followed by T3P (50% w/v in ethyl acetate, 725 mg, 1.14 mmol) and the mixture was stirred at room temperature for 18 hours under argon. The reaction mixture was then transferred into a separating funnel and water (20 mL) was added, and extracted with dichloromethane (3 × 20 mL). The organic phases were then combined, dried with magnesium

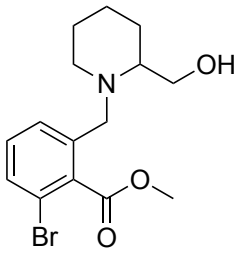
sulphate, filtered and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, 6:1 → 2:1 hexane : ethyl acetate) to afford the title compound (170 mg, 96%) as a white solid. R_f = 0.42 (1:1 hexane : ethyl acetate); m.p. 80–83 °C; ν_{max}/cm^{-1} (thin film) 2936, 1719, 1294, 1242, 1090, 742; δ_H (400 MHz, $CDCl_3$) 7.51 (1H, dd, *J* = 7.5, 1.5 Hz, Ar**H**), 7.46 (1H, td, *J* = 7.5, 1.5 Hz, Ar**H**), 7.34 (1H, t, *J* = 7.5 Hz, Ar**H**), 7.26 (1H, d, *J* = 7.5 Hz, Ar**H**), 4.04 (2H, d, *J* = 3.5 Hz, OC**H₂**), 3.76 – 3.64 (2H, m, ArC**H₂**N), 3.01 (1H, dt, *J* = 11.0, 3.5 Hz, NC**H$_a$**H$_b$), 2.49 (2H, td, *J* = 11.0, 3.5 Hz, NCH$_a$**H$_b$**, NC**H**), 1.76 (1H, dt, *J* = 12.5, 3.5 Hz, C**H$_a$**H$_b$), 1.62 – 1.58 (2H, m, C**H₂**), 1.53 – 1.45 (2H, m, C**H₂**), 1.36 – 1.26 (1H, m, CH$_a$**H$_b$**); δ_C (100 MHz, $CDCl_3$) 172.2 (**C**O), 138.7 (Ar**C**), 131.5 (Ar**C**H), 129.8 (Ar**C**H), 129.4 (Ar**C**), 129.2 (Ar**C**H), 127.7 (Ar**C**H), 72.4 (O**C**H$_2$), 64.7 (N**C**H), 60.7 (Ar**C**H$_2$N), 57.7 (N**C**H$_2$), 29.1 (**C**H$_2$), 25.9 (**C**H$_2$), 23.9 (**C**H$_2$); HRMS (ESI) calcd. for $C_{14}H_{18}NO_2^+$, 232.1332. Found: $[MH]^+$ 232.1336 (−1.6 ppm error).

Methyl 2-bromo-6-(bromomethyl)benzoate (88)



A round-bottomed flask was charged with benzene (20.0 mL), *N*-bromosuccinimide (855mg, 4.80 mmol), benzoyl peroxide (76.0 mg, 0.218 mmol) and methyl 2-bromo-6-methylbenzoate (1.00 g, 4.37 mmol). The solution was stirred and heated at 85°C for 22 hours under argon. Then, the round-bottomed flask was removed from the heating block, after being allowed to cool to RT, the mixture was filtered. The filtrate was transferred into a separating funnel and water (20 mL) was added, and extracted with dichloromethane (3 × 20 mL). The combined organic phases were dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, 5:1 → 2:1 hexane : dichloromethane) to afford the title compound (1.01 g, 75%) as a colourless oil. R_f = 0.43 (2:1 hexane : dichloromethane); ν_{max}/cm^{-1} (thin film) 1729, 1444, 1277, 1103, 1059, 954, 773; δ_H (400 MHz, $CDCl_3$) 7.55 (1H, dt, *J* = 8.0, 1.5 Hz, Ar**H**), 7.39 (1H, dt, *J* = 8.0, 1.5 Hz, Ar**H**), 7.26 (1H, td, *J* = 8.0, 1.5 Hz, Ar**H**), 4.50 (2H, s, ArC**H₂**Br), 4.01 (3H, s, OC**H₃**); δ_C (100 MHz, $CDCl_3$) 167.3 (**C**O), 137.2 (Ar**C**), 135.5 (Ar**C**), 133.0 (Ar**C**H), 131.2 (Ar**C**H), 129.2 (Ar**C**H), 120.19 (Ar**C**), 52.9 (O**C**H$_3$), 29.6 (Ar**C**H$_2$Br); HRMS (ESI) calcd. for $C_9H_8{}^{79}Br_2NaO_2^+$, 328.8783. Found: $[MH]^+$ 328.8778 (+1.5 ppm error). Characterisation data matched those reported in the literature.[25]

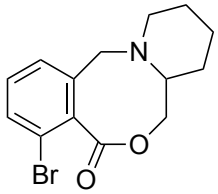
Methyl 2-bromo-6-((2-(hydroxymethyl)piperidin-1-yl)methyl)benzoate (91)



To a stirring solution of potassium carbonate (1.21 g, 8.77 mmol) in acetonitrile (20.0 mL), 2-piperidinemethanol (337 mg, 2.92 mmol) was added followed by methyl 2-bromo-6-

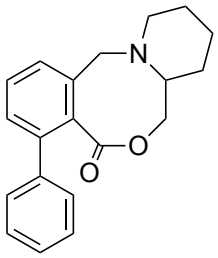
(bromomethyl)benzoate **88** (900 mg, 2.92 mmol). The reaction mixture was refluxed at 90 °C for 17 hours under argon. Then the reaction mixture was allowed to cool to RT, filtered and washed with dichloromethane, concentrated under vacuum and purified by column chromatography (SiO_2, 3:1 → 1:1 hexane : ethyl acetate) to afford the title compound (634 mg, 63%) as a yellow oil. R_f = 0.68 (1:1 hexane : ethyl acetate); v_{max}/cm^{-1} (thin film) 2936, 1732, 1718, 1446, 1278, 1150, 1107, 1063; δ_H (400 MHz, $CDCl_3$) 7.46 (1H, dd, *J* = 6.5, 3.0 Hz, Ar**H**), 7.22 – 7.11 (2H, m, 2 x Ar**H**), 4.30 (1H, d, *J* = 13.5 Hz, ArC**H$_a$**H$_b$N), 3.94 (3H, s, OC**H$_3$**), 3.91 (1H, dd, *J* = 12.0, 3.0 Hz, C**H$_a$**H$_b$OH), 3.40 (1H, dd, *J* = 12.0, 3.0 Hz, CH$_a$**H$_b$**OH), 3.09 (1H, d, *J* = 13.5 Hz, ArCH$_a$**H$_b$**N), 2.69 (1H, dt, *J* = 11.5, 3.5 Hz, NC**H$_a$**H$_b$), 2.17 (1H, dq, *J* = 10.0, 3.5 Hz, NC**H**), 1.91 (1H, td, *J* = 11.5, 3.5 Hz, NCH$_a$**H$_b$**), 1.75 – 1.58 (3H, m, C**H$_2$**, C**H$_a$**H$_b$), 1.53 – 1.45 (1H, m, CH$_a$**H$_b$**), 1.37 – 1.23 (2H, m, C**H$_2$**); δ_C (100 MHz, $CDCl_3$) 169.9 (**C**O), 140.0 (Ar**C**), 134.7 (Ar**C**), 131.7 (Ar**C**H), 130.6 (Ar**C**H), 128.4 (Ar**C**H), 120.3 (Ar**C**), 63.3 (N**C**H), 62.8 (**C**H$_2$OH), 56.9 (Ar**C**H$_2$N), 52.7 (O**C**H$_3$), 52.6 (N**C**H$_2$), 27.7 (**C**H$_2$), 24.7 (**C**H$_2$), 23.9 (**C**H$_2$); HRMS (ESI) calcd. for $C_{15}H_{21}{}^{79}BrNO_3{}^+$, 342.0699. Found: $[MH]^+$ 342.0696 (+1.1 ppm error).

4-Bromo-7,7a,8,9,10,11-hexahydrobenzo[*f*]pyrido[2,1-*c*][1,4]oxazocin-5(13*H*)-one (98)



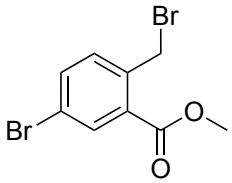
To a stirring solution of methyl 2-bromo-6-((2-(hydroxymethyl)piperidin-1-yl)methyl) benzoate **88** (500 mg, 1.46 mmol) in methanol (3.2 mL), aqueous lithium hydroxide (0.5 M) was added (9.6 mL, 4.80 mmol) and the reaction mixture was heated to 80 °C for 49 hours. The reaction was then allowed to cool to RT, and the solvent was removed under vacuum using chloroform (5 × 100 mL) to form an azeotropic mixture. The intermediate 2-bromo-6-((2-(hydroxymethyl)piperidin-1-yl)methyl)benzoic acid was dissolved in chloroform (15 mL) and DIPEA (0.47 mL, 2.70 mmol) was added followed by T3P (50% w/v in ethyl acetate, 1.39 g, 2.19 mmol) and the mixture was stirred at room temperature for 16 hours under argon. The reaction mixture was then transferred into a separating funnel and water (30 mL) was added, and extracted with ethyl acetate (3 × 30 mL). The organic phases were then combined, dried with magnesium sulphate, filtered and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, 2:1 hexane : ethyl acetate) to afford the title compound (291 mg, 64%) as a white solid. R_f = 0.35 (2:1 hexane : ethyl acetate); m.p. 62–66 °C; v_{max}/cm^{-1} (thin film) 2936, 1733, 1563, 1428, 1344, 1212, 1101, 1064, 992, 757; δ_H (400 MHz, $CDCl_3$) 7.57 (1H, dd, *J* = 7.5, 1.5 Hz, Ar**H**), 7.30 – 7.26 (1H, m, Ar**H**), 7.23 (1H, d, *J* = 7.5 Hz, Ar**H**), 4.09 (1H, dd, *J* = 13.0, 6.5 Hz, OC**H$_a$**H$_b$), 3.99 (1H, dd, *J* = 13.0, 1.5 Hz, OCH$_a$**H$_b$**), 3.66 (2H, d, *J* = 4.5 Hz, ArC**H$_2$**N), 2.98 (1H, dt, *J* = 11.5, 3.5 Hz, NC**H$_a$**H$_b$), 2.57 – 2.43 (2H, m, NC**H**, NCH$_a$**H$_b$**), 1.74 (1H, dt, *J* = 13.0, 4.0 Hz, C**H$_a$**H$_b$), 1.66 – 1.57 (3H, m, C**H$_2$**, C**H$_a$**H$_b$), 1.55 – 1.47 (1H, m, CH$_a$**H$_b$**), 1.37 – 1.28 (1H, m, CH$_a$**H$_b$**); δ_C (100 MHz, $CDCl_3$) 168.6 (**C**O), 140.5 (Ar**C**), 132.4 (Ar**C**H), 131.7 (Ar**C**H), 131.1 (Ar**C**), 128.3 (Ar**C**H), 120.5 (Ar**C**), 72.6 (O**C**H$_2$), 64.5 (N**C**H), 60.3 (Ar**C**H$_2$N), 57.6 (N**C**H$_2$), 29.2 (**C**H$_2$), 25.8 (**C**H$_2$), 23.7 (**C**H$_2$); HRMS (ESI) calcd. for $C_{14}H_{17}{}^{79}BrNO_2{}^+$, 310.0437. Found: $[MH]^+$ 310.0434 (−1.1 ppm error).

4-Phenyl-7,7a,8,9,10,11-hexahydrobenzo[*f*]pyrido[2,1-*c*][1,4]oxazocin-5(13*H*)-one (111)



4-Bromo-7,7a,8,9,10,11-hexahydrobenzo[*f*]pyrido [2,1-*c*][1,4]oxazocin-5(13*H*)-one **98** (100 mg, 0.322 mmol) and phenylboronic acid (78.6 mg, 0.644 mmol) were dissolved in 1,4-dioxane (5.0 mL). Then Na_2CO_3 (103 mg, 0.967 mmol) which dissolved in water (2.5 mL) was added followed by $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (13.1 mg, 0.016 mmol) and the resulting mixture was purged with argon for 10 minutes. The mixture was stirred and heated at 50 °C for 16 hours under argon. After being allowed to cool to RT, water (20 mL) was added and the two layers were separated. The aqueous layer was extracted with dichloromethane (3 x 20 mL) and the combined organic phases were dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, 3:1 → 2:1 hexane : ethyl acetate) to afford the title compound (80.5 mg, 81%) as a white solid. R_f = 0.52 (2:1 hexane : ethyl acetate); m.p. 101–104 °C; ν_{max}/cm^{-1} (thin film) 2935, 1731, 1457, 1266, 1234, 1105, 1066, 1010, 755, 728, 699; δ_H (400 MHz, $CDCl_3$) 7.49 (1H, t, *J* = 7.5 Hz, Ar**H**), 7.43 – 7.34 (4H, m, 4 x Ar**H**), 7.34 – 7.27 (3H, m, 3 x Ar**H**), 4.48 (1H, dd, *J* = 12.5, 7.0 Hz, OC**H**$_a$H$_b$), 4.14 (1H, d, *J* = 12.5 Hz, OH$_a$**H**$_b$), 3.73 (1H, d, *J* = 14.5 Hz, ArC**H**$_a$H$_b$N), 3.64 (1H, d, *J* = 14.5 Hz, ArCH$_a$**H**$_b$N), 3.03 (1H, dt, *J* = 11.5, 4.0 Hz, NC**H**$_a$H$_b$), 2.62 (1H, ddd, *J* = 10.5, 7.0, 3.0 Hz, NC**H**), 2.52 (1H, td, *J* = 11.5, 4.0 Hz, NCH$_a$**H**$_b$), 1.79 – 1.71 (1H, m, C**H**$_a$H$_b$), 1.69 – 1.56 (2H, m, C**H**$_2$), 1.56 – 1.48 (1H, m, C**H**$_a$H$_b$), 1.44 – 1.28 (2H, m, CH$_a$**H**$_b$, CH$_a$**H**$_b$); δ_C (100 MHz, $CDCl_3$) 170.5 (**C**O), 141.5 (Ar**C**), 140.1 (Ar**C**), 138.1 (Ar**C**), 131.0 (Ar**C**H), 129.7 (Ar**C**H), 129.3 (Ar**C**H), 129.3 (Ar**C**), 128.6 (Ar**C**H), 128.3 (Ar**C**H), 127.8 (Ar**C**H), 73.0 (O**C**H$_2$), 65.0 (N**C**H), 60.3 (Ar**C**H$_2$N), 58.2 (N**C**H$_2$), 29.5 (**C**H$_2$), 26.1 (**C**H$_2$), 24.0 (**C**H$_2$); HRMS (ESI) calcd. for $C_{20}H_{22}NO_2^+$, 308.1645. Found: $[MH]^+$ 308.1647 (−0.5 ppm error).

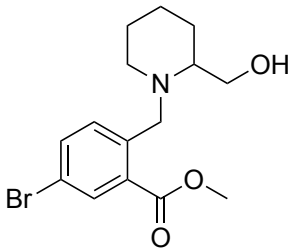
Methyl 5-bromo-2-(bromomethyl)benzoate (89)



A round-bottomed flask was charged with benzene (80.0 mL), *N*-bromosuccinimide (4.27 g, 24.0 mmol), benzoyl peroxide (378 mg, 1.09 mmol) and methyl 5-bromo-2-methylbenzoate (5.00 g, 21.8 mmol). The solution was stirred and heated at 85 °C for 16 hours under argon. Then, the round-bottomed flask was removed from the heating block, after being allowed to cool to RT, the mixture was filtered. The filtrate was transferred into a separating funnel and water (50 mL) was added, and extracted with dichloromethane (3 × 50 mL). The combined organic phases were dried with magnesium sulphate, filtered and concentrated in vacuo to

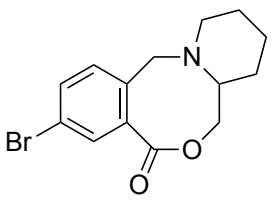
give the crude product. The product was purified by column chromatography (SiO_2, 2:1 → 1:1 hexane : dichloromethane) to afford the title compound (4.66 g, 69%) as a colourless oil. R_f = 0.44 (2:1 hexane : dichloromethane); ν_{max}/cm^{-1} (thin film) 1721, 1433, 1285, 1254, 1119, 1076, 967, 856, 829, 800; δ_H (400 MHz, $CDCl_3$) 8.11 (1H, d, *J* = 2.0 Hz, Ar**H**), 7.62 (1H, dd, *J* = 8.0, 2.0 Hz, Ar**H**), 7.34 (1H, d, *J* = 8.0 Hz, Ar**H**), 4.90 (2H, s, ArC**H₂**Br), 3.95 (3H, s, OC**H₃**); δ_C (100 MHz, $CDCl_3$) 165.8 (**C**O), 138.4 (Ar**C**), 135.6 (Ar**C**H), 134.3 (Ar**C**H), 133.3 (Ar**C**H), 130.7 (Ar**C**), 122.5 (Ar**C**), 52.7 (O**C**H_3), 30.6 (Ar**C**H_2Br); HRMS (ESI) calcd. for $C_9H_8{}^{79}Br_2NaO_2^+$, 328.8783. Found: $[MH]^+$ 328.8780 (+0.9 ppm error). Characterisation data matched those reported in the literature.[58]

Methyl 5-bromo-2-((2-(hydroxymethyl)piperidin-1-yl)methyl)benzoate (92)



To a stirring solution of potassium carbonate (1.21 g, 8.77 mmol) in acetonitrile (20.0 mL), 2-piperidinemethanol (337 mg, 2.92 mmol) was added followed by methyl 5-bromo-2-(bromomethyl)benzoate **89** (900 mg, 2.92 mmol). The reaction mixture was refluxed at 90 °C for 19 hours under argon. Then the reaction mixture was allowed to cool to RT, filtered and washed with dichloromethane, concentrated under vacuum and purified by column chromatography (SiO_2, 90:9:1 → 75:24:1 dichloromethane : acetone : triethylamine) to afford the title compound (306 mg, 31%) as a yellow oil. R_f = 0.36 (75:24:1 dichloromethane : acetone : triethylamine); ν_{max}/cm^{-1} (thin film) 2933, 1721, 1435, 1288, 1257, 1143, 1093, 968, 831, 778; δ_H (400 MHz, $CDCl_3$) 7.81 (1H, d, *J* = 2.0 Hz, Ar**H**), 7.53 (1H, dd, *J* = 8.0, 2.0 Hz, Ar**H**), 7.27 (1H, d, *J* = 8.0 Hz, Ar**H**), 4.47 (1H, d, *J* = 13.5 Hz, ArC**H$_a$**H$_b$N), 3.96 – 3.86 (4H, m, C**H$_a$**H$_b$OH, OC**H₃**), 3.45 (1H, dd, *J* = 12.0, 4.0 Hz, CH$_a$**H$_b$**OH), 3.32 (1H, d, *J* = 13.5 Hz, ArCH$_a$**H$_b$**N), 2.68 – 2.57 (1H, m, NC**H$_a$**H$_b$), 2.33 – 2.26 (1H, m, NC**H**), 1.99 (1H, t, *J* = 11.0 Hz, NCH$_a$**H$_b$**), 1.72 – 1.63 (3H, m, C**H$_a$**H$_b$, C**H₂**), 1.54 – 1.47 (1H, m, C**H$_a$**H$_b$), 1.37 – 1.25 (2H, m, CH$_a$**H$_b$**, CH$_a$**H$_b$**); δ_C (100 MHz, $CDCl_3$) 168.5 (**C**O), 139.4 (Ar**C**), 134.2 (Ar**C**H), 132.7 (Ar**C**), 132.5 (Ar**C**H), 132.0 (Ar**C**H), 120.6 (Ar**C**), 62.9 (N**C**H), 62.7 (**C**H_2OH), 55.6 (Ar**C**H_2N), 52.7 (O**C**H_3), 51.8 (N**C**H_2), 27.5 (**C**H_2), 24.6 (**C**H_2), 23.7 (**C**H_2); HRMS (ESI) calcd. for $C_{15}H_{21}{}^{79}BrNO_3^+$, 342.0699. Found: $[MH]^+$ 342.0697 (+0.6 ppm error).

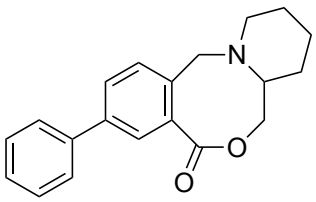
3-Bromo-7,7a,8,9,10,11-hexahydrobenzo[*f*]pyrido[2,1-*c*][1,4]oxazocin-5(13*H*)-one (99)



To a stirring solution of methyl 5-bromo-2-((2-(hydroxymethyl)piperidin-1-yl)methyl) benzoate **92** (200 mg, 0.584 mmol) in methanol (1.3 mL), aqueous lithium hydroxide (0.5 M)

was added (1.3 mL, 0.643 mmol) and the reaction mixture was heated to 50 °C for 1 hour. The reaction was then allowed to cool to RT, and the solvent was removed under vacuum using chloroform (5 × 50 mL) to form an azeotropic mixture. The intermediate 5-bromo-2-((2-(hydroxymethyl)piperidin-1-yl)methyl)benzoic acid was dissolved in chloroform (6.0 mL) and DIPEA (0.19 mL, 1.08 mmol) was added followed by T3P (50% w/v in ethyl acetate, 558 mg, 0.877 mmol) and the mixture was stirred at room temperature for 18 hours under argon. The reaction mixture was then transferred into a separating funnel and water (10 mL) was added, and extracted with dichloromethane (3 × 10 mL). The organic phases were then combined, dried with magnesium sulphate, filtered and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, 5:1 → 2:1 hexane : ethyl acetate) to afford the title compound (144 mg, 80%) as a white solid. R_f = 0.62 (2:1 hexane : ethyl acetate); m.p. 81–85 °C; ν_{max}/cm^{-1} (thin film) 2937, 1719, 1465, 1369, 1267, 1090, 996, 820; δ_H (400 MHz, $CDCl_3$) 7.61 (1H, d, *J* = 2.0 Hz, Ar**H**), 7.53 (1H, dd, *J* = 8.0, 2.0 Hz, Ar**H**), 7.10 (1H, d, *J* = 8.0 Hz, Ar**H**), 4.04 (1H, dd, *J* = 12.5, 2.0 Hz, OC**H**$_a$H$_b$), 3.98 (1H, dd, *J* = 12.5, 5.0 Hz, OCH$_a$**H$_b$**), 3.64 (2H, s, ArC**H$_2$**N), 2.96 (1H, dt, *J* = 11.5, 4.0 Hz, NC**H**$_a$H$_b$), 2.51 – 2.38 (2H, m, NC**H**, NCH$_a$**H$_b$**), 1.74 (1H, dt, *J* = 13.0, 4.0 Hz, C**H**$_a$H$_b$), 1.65 – 1.46 (4H, m, 2 x C**H$_2$**), 1.35 – 1.22 (1H, m, CH$_a$**H$_b$**); δ_C (100 MHz, $CDCl_3$) 170.6 (**C**O), 137.9 (Ar**C**), 134.3 (Ar**C**H), 132.5 (Ar**C**H), 131.2 (Ar**C**), 130.5 (Ar**C**H), 121.2 (Ar**C**), 72.2 (O**C**H$_2$), 64.4 (N**C**H), 60.2 (Ar**C**H$_2$N), 57.6 (N**C**H$_2$), 29.0 (**C**H$_2$), 25.9 (**C**H$_2$), 23.8 (**C**H$_2$); HRMS (ESI) calcd. for $C_{14}H_{17}{}^{79}BrNO_2^+$, 310.0437. Found: $[MH]^+$ 310.0435 (−0.6 ppm error).

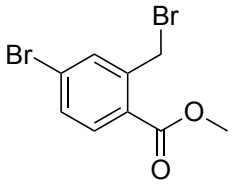
3-Phenyl-7,7a,8,9,10,11-hexahydrobenzo[*f*]pyrido[2,1-*c*][1,4]oxazocin-5(13*H*)-one (112)



3-Bromo-7,7a,8,9,10,11-hexahydrobenzo[*f*]pyrido[2,1-*c*][1,4]oxazocin-5(13*H*)-one **99** (100 mg, 0.322 mmol) and phenylboronic acid (78.6 mg, 0.644 mmol) were dissolved in 1,4-dioxane (5.0 mL). Then Na_2CO_3 (103 mg, 0.967 mmol) which dissolved in water (2.5 mL) was added followed by Pd(dppf)Cl_2·CH_2Cl_2 (13.1 mg, 0.016 mmol) and the resulting mixture was purged with argon for 10 minutes. The mixture was stirred and heated at 50 °C for 18 hours under argon. After being allowed to cool to RT, water (20 mL) was added and the two layers were separated. The aqueous layer was extracted with dichloromethane (3 x 20 mL) and the combined organic phases were dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, 5:1 → 2:1 hexane : ethyl acetate) to afford the title compound (77.0 mg, 78%) as a yellow solid. R_f = 0.53 (2:1 hexane : ethyl acetate); m.p. 104–107 °C; ν_{max}/cm^{-1} (thin film) 2937, 1718, 1485, 1312, 1228, 1122, 1089, 757, 698; δ_H (400 MHz, $CDCl_3$) 7.74 (1H, d, *J* = 2.0 Hz, Ar**H**), 7.67 (1H, dd, *J* = 8.0, 2.0 Hz, Ar**H**), 7.58 (2H, dd, *J* = 7.5, 2.0 Hz, 2 x Ar**H**), 7.43 (2H, t, *J* = 7.5 Hz, 2 x Ar**H**), 7.39 – 7.30 (2H, m, 2 x Ar**H**), 4.08 (2H, d, *J* = 3.5 Hz, OC**H$_2$**), 3.79 – 3.65 (2H, m, ArC**H$_2$**N), 3.02 (1H, dt, *J* = 10.0, 3.5 Hz, NC**H**$_a$H$_b$), 2.49 (2H, td, *J* = 10.0, 3.5 Hz, NC**H**, NCH$_a$**H$_b$**), 1.76 (1H, dt, *J* = 13.0, 3.5 Hz, C**H**$_a$H$_b$), 1.69 – 1.56 (2H, m, C**H$_2$**), 1.51 (2H, td, *J* = 10.0, 3.5 Hz, C**H$_2$**), 1.38 –

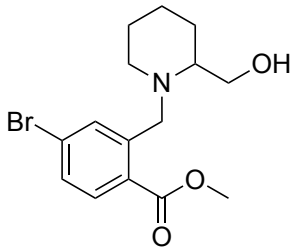
1.27 (1H, m, $CH_a\mathbf{H_b}$); δ_C (100 MHz, $CDCl_3$) 172.2 (**C**O), 140.8 (Ar**C**), 139.6 (Ar**C**), 137.6 (Ar**C**), 130.1 (Ar**C**H), 129.9 (Ar**C**), 129.8 (Ar**C**H), 129.0 (Ar**C**H), 128.3 (Ar**C**H), 127.9 (Ar**C**H), 127.0 (Ar**C**H), 72.5 (O**C**H_2), 64.7 (N**C**H), 60.4 (Ar**C**H_2N), 57.7 (N**C**H_2), 29.2 (**C**H_2), 26.0 (**C**H_2), 23.9 (**C**H_2); HRMS (ESI) calcd. for $C_{20}H_{22}NO_2^+$, 308.1645. Found: $[MH]^+$ 308.1649 (−1.4 ppm error).

Methyl 4-bromo-2-(bromomethyl)benzoate (87)



A round-bottomed flask was charged with benzene (60.0 mL), *N*-bromosuccinimide (2.56 g, 14.4 mmol), benzoyl peroxide (227 mg, 0.655 mmol) and methyl 4-bromo-2-methylbenzoate (3.00 g, 13.1 mmol). The solution was stirred and heated at 85 °C for 23 hours under argon. Then, the round-bottomed flask was removed from the heating block, after being allowed to cool to RT, the mixture was filtered. The filtrate was transferred into a separating funnel and water (60 mL) was added, and extracted with dichloromethane (3 × 60 mL). The combined organic phases were dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, 5:1 → 2:1 hexane : dichloromethane) to afford the title compound (3.15 g, 78%) as a colourless oil. R_f = 0.56 (2:1 hexane : dichloromethane); ν_{max}/cm^{-1} (thin film) 1717, 1587, 1433, 1259, 1118, 1093, 868, 779, 704; δ_H (400 MHz, $CDCl_3$) 7.84 (1H, d, *J* = 8.5 Hz, Ar**H**), 7.63 (1H, d, *J* = 2.0 Hz, Ar**H**), 7.51 (1H, dd, *J* = 8.5, 2.0 Hz, Ar**H**), 4.89 (2H, s, ArC$\mathbf{H_2}$Br), 3.94 (3H, s, OC$\mathbf{H_3}$); δ_C (100 MHz, $CDCl_3$) 166.3 (**C**O), 141.3 (Ar**C**), 134.7 (Ar**C**H), 132.9 (Ar**C**H), 131.8 (Ar**C**H), 127.8 (Ar**C**), 127.2 (Ar**C**), 52.6 (O**C**H_3), 30.4 (Ar**C**H_2Br). Characterisation data matched those reported in the literature.[59]

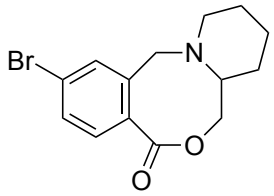
Methyl 4-bromo-2-((2-(hydroxymethyl)piperidin-1-yl)methyl)benzoate (93)



To a stirring solution of potassium carbonate (1.08 g, 7.79 mmol) in acetonitrile (20.0 mL), 2-piperidinemethanol (299 mg, 2.60 mmol) was added followed by methyl 4-bromo-2-(bromomethyl)benzoate **87** (800 mg, 2.60 mmol). The reaction mixture was refluxed at 90 °C for 18 hours under argon. Then the reaction mixture was allowed to cool to RT, filtered and washed with dichloromethane, concentrated under vacuum and purified by column chromatography (SiO_2, 1:1 hexane : ethyl acetate) to afford the title compound (430 mg, 48%) as a yellow oil. R_f = 0.27 (1:1 hexane : ethyl acetate); ν_{max}/cm^{-1} (thin film) 2933, 1718, 1587, 1434, 1289, 1235, 1090, 868, 768; δ_H (400 MHz, $CDCl_3$) 7.59 – 7.51 (2H, m, 2 x Ar**H**), 7.42 (1H, dd, *J* = 8.5, 2.0 Hz, Ar**H**), 4.48 (1H, d, *J* = 14.0 Hz, ArC$\mathbf{H_a}H_b$N), 3.91 – 3.83 (4H, m, C$\mathbf{H_a}H_b$OH, OC$\mathbf{H_3}$), 3.45 (1H, dd, *J* = 11.5, 4.0 Hz, $CH_a\mathbf{H_b}$OH), 3.34 (1H, d, *J* = 14.0 Hz, Ar$CH_a\mathbf{H_b}$N), 2.63 (1H,

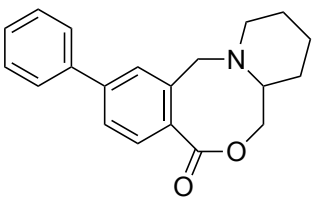
ddd, *J* = 11.5, 5.0, 3.0 Hz, NC**H**$_a$H$_b$), 2.30 (1H, dt, *J* = 8.0, 4.0 Hz, NC**H**), 2.04 – 1.95 (1H, m, NCH$_a$**H$_b$**), 1.72 – 1.59 (3H, m, C**H**$_a$H$_b$, C**H$_2$**), 1.54 – 1.46 (1H, m, C**H**$_a$H$_b$), 1.40 – 1.27 (2H, m, C**H**$_a$H$_b$, CH$_a$**H$_b$**); δ_C (100 MHz, $CDCl_3$) 169.0 (**C**O), 142.9 (Ar**C**), 133.1 (Ar**C**H), 131.2 (Ar**C**H), 130.2 (Ar**C**H), 129.7 (Ar**C**), 126.0 (Ar**C**), 62.9 (N**C**H), 62.7 (**C**H$_2$OH), 55.8 (Ar**C**H$_2$N), 52.6 (O**C**H$_3$), 52.0 (N**C**H$_2$), 27.5 (**C**H$_2$), 24.6 (**C**H$_2$), 23.7 (**C**H$_2$); HRMS (ESI) calcd. for $C_{15}H_{21}{}^{79}BrNO_3{}^+$, 342.0699. Found: $[MH]^+$ 342.0692 (+2.0 ppm error).

2-Bromo-7,7a,8,9,10,11-hexahydrobenzo[*f*]pyrido[2,1-*c*][1,4]oxazocin-5(13*H*)-one (102)



To a stirring solution of methyl 4-bromo-2-((2-(hydroxymethyl)piperidin-1-yl)methyl) benzoate **87** (400 mg, 1.17 mmol) in methanol (2.6 mL), aqueous lithium hydroxide (0.5 M) was added (2.6 mL, 1.29 mmol) and the reaction mixture was heated to 50 °C for 4.5 hours. The reaction was then allowed to cool to RT, and the solvent was removed under vacuum using chloroform (5 × 50 mL) to form an azeotropic mixture. The intermediate 4-bromo-2-((2-(hydroxymethyl)piperidin-1-yl)methyl)benzoic acid was dissolved in chloroform (12 mL) and DIPEA (0.38 mL, 2.16 mmol) was added followed by T3P (50% w/v in ethyl acetate, 1.12 g, 1.75 mmol) and the mixture was stirred at room temperature for 16 hours under argon. The reaction mixture was then transferred into a separating funnel and water (30 mL) was added, and extracted with dichloromethane (3 × 30 mL). The organic phases were then combined, dried with magnesium sulphate, filtered and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, 5:1 → 2:1 hexane : ethyl acetate) to afford the title compound (279 mg, 77%) as a white solid. R_f = 0.66 (2:1 hexane : ethyl acetate); m.p. 79–82 °C; ν_{max}/cm^{-1} (thin film) 2937, 1716, 1588, 1464, 1270, 1094, 994, 910, 727; δ_H (400 MHz, $CDCl_3$) 7.43 (1H, dd, *J* = 8.5, 2.0 Hz, Ar**H**), 7.38 (1H, d, *J* = 2.0 Hz, Ar**H**), 7.34 (1H, d, *J* = 8.5 Hz, Ar**H**), 4.11 – 3.92 (2H, m, OC**H$_2$**), 3.72 – 3.56 (2H, m, ArC**H$_2$**N), 2.96 (1H, dt, *J* = 11.0, 3.5 Hz, NC**H**$_a$H$_b$), 2.53 – 2.33 (2H, m, NCH$_a$**H$_b$**, NC**H**), 1.73 (1H, dt, *J* = 12.5, 3.5 Hz, C**H**$_a$H$_b$), 1.65 – 1.44 (4H, m, 2 x C**H$_2$**), 1.35 – 1.20 (1H, m, CH$_a$**H$_b$**); δ_C (100 MHz, $CDCl_3$) 171.2 (**C**O), 140.9 (Ar**C**), 131.9 (Ar**C**H), 131.5 (Ar**C**H), 130.9 (Ar**C**H), 128.3 (Ar**C**), 125.7 (Ar**C**), 72.3 (O**C**H$_2$), 64.4 (N**C**H), 60.2 (Ar**C**H$_2$N), 57.6 (N**C**H$_2$), 28.9 (**C**H$_2$), 25.8 (**C**H$_2$), 23.8 (**C**H$_2$); HRMS (ESI) calcd. for $C_{14}H_{17}{}^{79}BrNO_2{}^+$, 310.0437. Found: $[MH]^+$ 310.0444 (−2.3 ppm error).

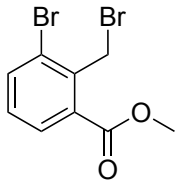
2-Phenyl-7,7a,8,9,10,11-hexahydrobenzo[*f*]pyrido[2,1-*c*][1,4]oxazocin-5(13*H*)-one (107)



2-Bromo-7,7a,8,9,10,11-hexahydrobenzo[*f*]pyrido[2,1-*c*][1,4]oxazocin-5(13*H*)-one **102** (100 mg, 0.322 mmol) and phenylboronic acid (78.6 mg, 0.644 mmol) were dissolved in 1,4-

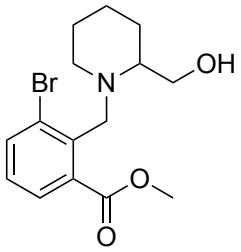
dioxane (5.0 mL). Then Na_2CO_3 (103 mg, 0.967 mmol) which dissolved in water (2.5 mL) was added followed by Pd(dppf)Cl_2·CH_2Cl_2 (13.1 mg, 0.016 mmol) and the resulting mixture was purged with argon for 10 minutes. The mixture was stirred and heated at 50 °C for 16 hours under argon. After being allowed to cool to RT, water (20 mL) was added and the two layers were separated. The aqueous layer was extracted with dichloromethane (3 x 20 mL) and the combined organic phases were dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, 5:1 → 3:1 hexane : ethyl acetate) to afford the title compound (88.0 mg, 89%) as a white solid. R_f = 0.55 (3:1 hexane : ethyl acetate); m.p. 111–114 °C; ν_{max}/cm^{-1} (thin film) 2937, 1713, 1609, 1449, 1277, 1240, 1092, 993, 912, 754, 730, 697; 7.63 – 7.51 (4H, m, 4 x Ar**H**), 7.49 – 7.40 (3H, m, 3 x Ar**H**), 7.42 – 7.32 (1H, m, Ar**H**), 4.16 – 4.04 (2H, m, OC**H₂**), 3.75 (2H, d, *J* = 3.0 Hz, ArC**H₂**N), 3.01 (1H, d, *J* = 11.5 Hz, NC**H**$_a$H$_b$), 2.49 (2H, td, *J* = 11.5, 4.0 Hz, NC**H**, NCH$_a$**H$_b$**), 1.75 (1H, dt, *J* = 13.0, 4.0 Hz, C**H**$_a$H$_b$), 1.69 – 1.54 (2H, m, C**H₂**), 1.57 – 1.47 (2H, m, C**H₂**), 1.39 – 1.23 (1H, m, CH$_a$**H$_b$**); δ_C (100 MHz, $CDCl_3$) 172.1 (**C**O), 144.2 (Ar**C**), 139.8 (Ar**C**), 139.3 (Ar**C**), 130.5 (Ar**C**H), 128.9 (Ar**C**H), 128.1 (Ar**C**), 128.1 (Ar**C**H), 127.8 (Ar**C**H), 127.2 (Ar**C**H), 126.3 (Ar**C**H), 72.4 (O**C**H$_2$), 64.6 (N**C**H), 60.8 (Ar**C**H$_2$N), 57.7 (N**C**H$_2$), 29.0 (**C**H$_2$), 25.9 (**C**H$_2$), 23.8 (**C**H$_2$); HRMS (ESI) calcd. for $C_{20}H_{22}NO_2^+$, 308.1645. Found: $[MH]^+$ 308.1643 (+0.6 ppm error).

Methyl 3-bromo-2-(bromomethyl)benzoate (90)



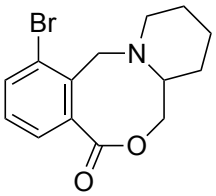
A round-bottomed flask was charged with benzene (20.0 mL), *N*-bromosuccinimide (855mg, 4.80 mmol), benzoyl peroxide (76.0 mg, 0.218 mmol) and methyl 3-bromo-2-methylbenzoate (1.00 g, 4.37 mmol). The solution was stirred and heated at 85 °C for 16.5 hours under argon. Then, the round-bottomed flask was removed from the heating block, after being allowed to cool to RT, the mixture was filtered. The filtrate was transferred into a separating funnel and water (20 mL) was added, and extracted with dichloromethane (3 × 20 mL). The combined organic phases were dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, 5:1 → 2:1 hexane : dichloromethane) to afford the title compound (1.22 g, 91%) as a colourless oil. R_f = 0.32 (3:1 hexane : dichloromethane); ν_{max}/cm^{-1} (thin film) 1721, 1434, 1259, 1222, 1113, 970, 759, 705; δ_H (400 MHz, $CDCl_3$) 7.89 (1H, dd, *J* = 8.0, 1.5 Hz, Ar**H**), 7.76 (1H, dd, *J* = 8.0, 1.5 Hz, Ar**H**), 7.23 (1H, t, *J* = 8.0 Hz, Ar**H**), 5.13 (2H, s, ArC**H₂**Br), 3.95 (3H, s, OC**H₃**); δ_C (100 MHz, $CDCl_3$) 166.6 (**C**O), 138.0 (Ar**C**), 137.2 (Ar**C**H), 131.7 (Ar**C**), 130.5 (Ar**C**H), 129.6 (Ar**C**H), 127.2 (Ar**C**), 52.8 (O**C**H$_3$), 30.2 (Ar**C**H$_2$Br). HRMS (ESI) calcd. for $C_9H_8{}^{79}Br_2NaO_2^+$, 328.8783. Found: $[MH]^+$ 328.8778 (-1.6 ppm error). Characterisation data matched those reported in the literature.[59]

Methyl 3-bromo-2-((2-(hydroxymethyl)piperidin-1-yl)methyl)benzoate (94)



To a stirring solution of potassium carbonate (1.35 g, 9.74 mmol) in acetonitrile (20.0 mL), 2-piperidinemethanol (374 mg, 3.25 mmol) was added followed by methyl 3-bromo-2-(bromomethyl)benzoate **90** (1.00 g, 3.25 mmol). The reaction mixture was refluxed at 90 °C for 18 hours under argon. Then the reaction mixture was allowed to cool to RT, filtered and washed with dichloromethane, concentrated under vacuum and purified by column chromatography (SiO_2, 5:1 → 2:1 hexane : ethyl acetate) to afford the title compound (818 mg, 74%) as a yellow oil. R_f = 0.54 (1:1 hexane : ethyl acetate); ν_{max}/cm^{-1} (thin film) 2936, 1714, 1432, 1279, 1208, 1150, 1093, 908, 753, 728; δ_H (400 MHz, $CDCl_3$) 7.61 (1H, dd, *J* = 8.0, 1.5 Hz, Ar**H**), 7.40 (1H, dd, *J* = 8.0, 1.5 Hz, Ar**H**), 7.13 (1H, t, *J* = 8.0 Hz, Ar**H**), 4.43 (1H, d, *J* = 13.5 Hz, ArC$\mathbf{H_a}H_b$N), 3.90 (3H, s, OC$\mathbf{H_3}$), 3.81 (1H, dd, *J* = 12.0, 4.0 Hz, C$\mathbf{H_a}H_b$OH), 3.75 (1H, d, *J* = 13.5 Hz, ArC$H_a\mathbf{H_b}$N), 3.45 (1H, dd, *J* = 12.0, 4.0 Hz, C$H_a\mathbf{H_b}$OH), 2.60 (1H, ddd, *J* = 12.0, 7.0, 4.0 Hz, NC$\mathbf{H_a}H_b$), 2.28 (1H, dq, *J* = 7.0, 4.0 Hz, NC**H**), 2.09 (1H, ddd, *J* = 12.0, 9.0, 4.0 Hz, NC$H_a\mathbf{H_b}$), 1.72 – 1.56 (3H, m, C$\mathbf{H_a}H_b$, C$\mathbf{H_2}$), 1.55 – 1.47 (1H, m, C$\mathbf{H_a}H_b$), 1.43 – 1.31 (1H, m, C$H_a\mathbf{H_b}$), 1.29 – 1.19 (1H, m, C$H_a\mathbf{H_b}$); δ_C (100 MHz, $CDCl_3$) 170.4 (**C**O), 138.2 (Ar**C**), 135.0 (Ar**C**H), 134.9 (Ar**C**), 128.3 (Ar**C**H), 127.6 (Ar**C**H), 125.6 (Ar**C**), 62.8 (N**C**H), 62.3 (**C**H_2OH), 54.6 (Ar**C**H_2N), 52.8 (O**C**H_3), 51.1 (N**C**H_2), 26.6 (**C**H_2), 24.4 (**C**H_2), 23.3 (**C**H_2); HRMS (ESI) calcd. for $C_{15}H_{21}{}^{79}BrNO_3{}^+$, 342.0699. Found: $[MH]^+$ 342.0697 (–0.5ppm error).

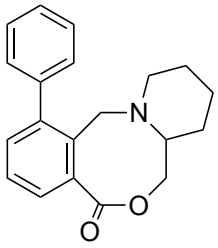
1-Bromo-7,7a,8,9,10,11-hexahydrobenzo[*f*]pyrido[2,1-*c*][1,4]oxazocin-5(13*H*)-one (103)



To a stirring solution of methyl 3-bromo-2-((2-(hydroxymethyl)piperidin-1-yl)methyl) benzoate **94** (500 mg, 1.46 mmol) in methanol (3.2 mL), aqueous lithium hydroxide (0.5 M) was added (3.2 mL, 1.61 mmol) and the reaction mixture was heated to 50 °C for 3 hours. The reaction was then allowed to cool to RT, and the solvent was removed under vacuum using chloroform (5 × 100 mL) to form an azeotropic mixture. The intermediate 3-bromo-2-((2-(hydroxymethyl)piperidin-1-yl)methyl)benzoic acid was dissolved in chloroform (15 mL) and DIPEA (0.47 mL, 2.70 mmol) was added followed by T3P (50% w/v in ethyl acetate, 1.40 g, 2.19 mmol) and the mixture was stirred at room temperature for 16.5 hours under argon. The reaction mixture was then transferred into a separating funnel and water (30 mL) was added, and extracted with dichloromethane (3 × 30 mL). The organic phases were then combined, dried with magnesium sulphate, filtered and concentrated in vacuo. The crude product was

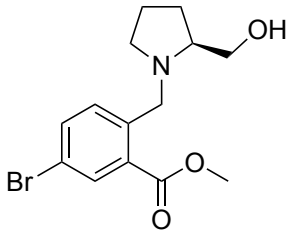
purified by column chromatography (SiO_2, 5:1 →3:1 hexane : ethyl acetate) to afford the title compound (285 mg, 63%) as a white solid. R_f = 0.58 (3:1 hexane : ethyl acetate); m.p. 104–107 °C; ν_{max}/cm^{-1} (thin film) 2937, 1722, 1465, 1285, 1093, 751; δ_H (400 MHz, $CDCl_3$) 7.66 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.41 (1H, d, *J* = 7.5 Hz, Ar**H**), 7.18 (1H, t, *J* = 8.0 Hz, Ar**H**), 3.95 (2H, qd, *J* = 12.5, 3.5 Hz, OC**H₂**), 3.77 (1H, d, *J* = 16.0 Hz, ArC**H$_a$**H$_b$N), 3.61 (1H, d, *J* = 16.0 Hz, ArCH$_a$**H$_b$**N), 3.13 (1H, dt, *J* = 11.5, 3.0 Hz, NC**H$_a$**H$_b$), 2.58 – 2.41 (2H, m, NCH$_a$**H$_b$**, NC**H**), 1.75 (1H, dt, *J* = 12.5, 3.5 Hz, C**H$_a$**H$_b$), 1.66 – 1.43 (4H, m, 2 x C**H₂**), 1.36 – 1.20 (1H, m, CH$_a$**H$_b$**); δ_C (100 MHz, $CDCl_3$) 171.2 (**C**O), 137.9 (Ar**C**), 135.4 (Ar**C**H), 131.9 (Ar**C**), 128.9 (Ar**C**H), 128.8 (Ar**C**H), 124.3 (Ar**C**), 72.0 (O**C**H$_2$), 64.1 (N**C**H), 60.5 (Ar**C**H$_2$N), 57.0 (N**C**H$_2$), 28.7 (**C**H$_2$), 25.8 (**C**H$_2$), 23.8 (**C**H$_2$); HRMS (ESI) calcd. for $C_{14}H_{17}{}^{79}BrNO_2{}^+$, 310.0437. Found: $[MH]^+$ 310.0441 (−1.1 ppm error).

1-Phenyl-7,7a,8,9,10,11-hexahydrobenzo[*f*]pyrido[2,1-*c*][1,4]oxazocin-5(13*H*)-one (113)



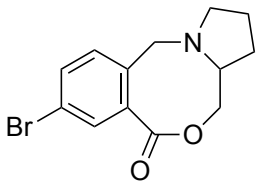
1-Bromo-7,7a,8,9,10,11-hexahydrobenzo[*f*]pyrido[2,1-*c*][1,4]oxazocin-5(13*H*)-one **103** (100 mg, 0.322 mmol) and phenylboronic acid (78.6 mg, 0.644 mmol) were dissolved in 1,4-dioxane (5.0 mL). Then Na_2CO_3 (103 mg, 0.967 mmol) which dissolved in water (2.5 mL) was added followed by Pd(dppf)Cl_2·CH_2Cl_2 (13.1 mg, 0.016 mmol) and the resulting mixture was purged with argon for 10 minutes. The mixture was stirred and heated at 50 °C for 17.5 hours under argon. After being allowed to cool to RT, water (20 mL) was added and the two layers were separated. The aqueous layer was extracted with dichloromethane (3 x 20 mL) and the combined organic phases were dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, 8:1 → 4:1 hexane : ethyl acetate) to afford the title compound (77.5 mg, 78%) as a white solid. R_f = 0.51 (4:1 hexane : ethyl acetate); m.p. 130–133 °C; ν_{max}/cm^{-1} (thin film) 2931, 1721, 1464, 1303, 1269, 1109, 1071, 750, 702; δ_H (400 MHz, $CDCl_3$) 7.51 (1H, dd, *J* = 6.5, 3.0 Hz, Ar**H**), 7.46 (2H, d, *J* = 6.5 Hz, 2 x Ar**H**), 7.43 – 7.35 (5H, m, 5 x Ar**H**), 4.25 (1H, dd, *J* = 12.5, 7.0 Hz, OC**H$_a$**H$_b$), 4.01 (1H, d, *J* = 12.5 Hz, OCH$_a$**H$_b$**), 3.45 (1H, d, *J* = 14.5 Hz, ArC**H$_a$**H$_b$N), 3.29 (1H, d, *J* = 14.5 Hz, ArCH$_a$**H$_b$**N), 2.52 (1H, ddd, *J* = 10.5, 7.0, 2.5 Hz, NC**H**), 2.38 (1H, dt, *J* = 11.5, 3.5 Hz, NC**H$_a$**H$_b$), 2.14 (1H, td, *J* = 11.5, 3.5 Hz, NCH$_a$**H$_b$**), 1.80 – 1.70 (1H, m, C**H$_a$**H$_b$), 1.59 – 1.41 (3H, m, C**H₂**, C**H$_a$**H$_b$), 1.38 – 1.21 (2H, m, 2 x CH$_a$**H$_b$**); δ_C (100 MHz, $CDCl_3$) 172.2 (**C**O), 143.4 (Ar**C**), 140.6 (Ar**C**), 136.2 (Ar**C**), 133.3 (Ar**C**H), 130.6 (Ar**C**), 129.8 (Ar**C**H), 128.3 (Ar**C**H), 127.9 (Ar**C**H), 127.7 (Ar**C**H), 127.5 (Ar**C**H), 73.6 (O**C**H$_2$), 64.3 (N**C**H), 56.9 (Ar**C**H$_2$N), 56.5 (N**C**H$_2$), 29.6 (**C**H$_2$), 26.1 (**C**H$_2$), 24.2 (**C**H$_2$); HRMS (ESI) calcd. for $C_{20}H_{22}NO_2{}^+$, 308.1645. Found: $[MH]^+$ 308.1653 (−2.7 ppm error).

Methyl (*S*)-5-bromo-2-((2-(hydroxymethyl)pyrrolidin-1-yl)methyl)benzoate (96)



To a stirring solution of potassium carbonate (1.34 g, 9.74 mmol) in acetonitrile (20.0 mL), (*R*)-pyrrolidin-2-ylmethanol (328 mg, 3.25 mmol) was added followed by methyl 5-bromo-2-(bromomethyl)benzoate **89** (1.00 g, 3.25 mmol). The reaction mixture was refluxed at 90 °C for 16 hours under argon. Then the reaction mixture was allowed to cool to RT, filtered and washed with dichloromethane, concentrated under vacuum and purified by column chromatography (SiO_2, 99:1 ethyl acetate : triethylamine) to afford the title compound (654 mg, 61%) as a yellow oil. R_f = 0.31 (99:1 ethyl acetate : triethylamine); ν_{max}/cm^{-1} (thin film) 2951, 1723, 1435, 1287, 1258, 1077; δ_H (400 MHz, $CDCl_3$) 7.89 – 7.83 (1H, m, Ar**H**), 7.54 – 7.49 (1H, m, Ar**H**), 7.25 (1H, d, *J* = 8.0 Hz, Ar**H**), 4.38 (1H, d, *J* = 13.5 Hz, ArC**H$_a$**H$_b$N), 3.86 (3H, s, OC**H$_3$**), 3.68 – 3.63 (1H, m, C**H$_a$**H$_b$OH), 3.42 – 3.33 (2H, m, ArCH$_a$**H$_b$**N, CH$_a$**H$_b$**OH), 2.75 (1H, t, *J* = 6.5 Hz, NC**H$_a$**H$_b$), 2.62 – 2.56 (1H, m, NC**H**), 2.16 – 2.08 (1H, m, NCH$_a$**H$_b$**), 1.87 – 1.70 (2H, m, C**H$_2$**), 1.68 – 1.52 (2H, m, C**H$_2$**); δ_C (100 MHz, $CDCl_3$) 167.8 (**C**O), 139.8 (Ar**C**), 134.4 (Ar**C**H), 132.9 (Ar**C**H), 132.3 (Ar**C**), 131.9 (Ar**C**H), 120.7 (Ar**C**), 65.5 (N**C**H), 62.1 (**C**H$_2$OH), 56.7 (Ar**C**H$_2$N), 54.9 (N**C**H$_2$), 52.6 (O**C**H$_3$), 27.2 (**C**H$_2$), 23.3 (**C**H$_2$); HRMS (ESI) calcd. for $C_{14}H_{19}{}^{79}BrNO_3{}^+$, 328.0543. Found: $[MH]^+$ 328.0536 (+2.1 ppm error).

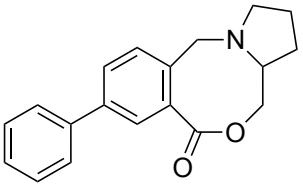
8-Bromo-2,3,3a,4-tetrahydro-1H-benzo[*f*]pyrrolo[2,1-*c*][1,4]oxazocin-6(11*H*)-one (100)



To a stirring solution of methyl (*S*)-5-bromo-2-((2-(hydroxymethyl)pyrrolidin-1-yl)methyl) benzoate **96** (500 mg, 1.52 mmol) in methanol (3.3 mL), aqueous lithium hydroxide (0.5 M) was added (3.3 mL, 1.68 mmol) and the reaction mixture was heated to 50 °C for 2 hours. The reaction was then allowed to cool to RT, and the solvent was removed under vacuum using chloroform (5 × 100 mL) to form an azeotropic mixture. The intermediate (*S*)-5-bromo-2-((2-(hydroxymethyl)pyrrolidin-1-yl)methyl)benzoic acid was dissolved in chloroform (15 mL) and DIPEA (0.49 mL, 2.82 mmol) was added followed by T3P (50% w/v in ethyl acetate, 1.45 g, 2.28 mmol) and the mixture was stirred at room temperature for 17 hours under argon. The reaction mixture was then transferred into a separating funnel and water (30 mL) was added, and extracted with ethyl acetate (3 × 30 mL). The organic phases were then combined, dried with magnesium sulphate, filtered and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, 2:1 → 1:1 hexane : ethyl acetate) to afford the title compound (439 mg, 97%) as a white solid. R_f = 0.52 (2:1 hexane : ethyl acetate); m.p. 93–96 °C; ν_{max}/cm^{-1} (thin film) 2954, 2817, 1712, 1477, 1344, 1258, 1204, 1092, 1045, 840; δ_H

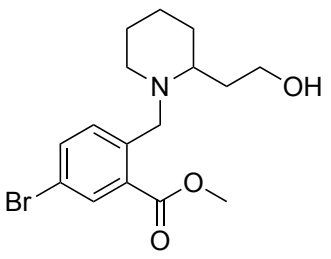
(400 MHz, $CDCl_3$) 7.49 (1H, d, *J* = 2.0 Hz, Ar**H**), 7.45 (1H, dd, *J* = 8.0, 2.0 Hz, Ar**H**), 7.00 (1H, d, *J* = 8.0 Hz, Ar**H**), 4.13 (1H, d, *J* = 16.5 Hz, ArC**H$_a$**H$_b$N), 4.01 (1H, dd, *J* = 12.0, 1.5 Hz, OC**H$_a$**H$_b$), 3.89 – 3.77 (2H, m, OCH$_a$**H$_b$**, ArCH$_a$**H$_b$**N), 3.21 – 3.13 (1H, m, NC**H$_a$**H$_b$), 2.87 – 2.72 (2H, m, NC**H**, NCH$_a$**H$_b$**), 2.10 – 1.99 (1H, m, C**H$_a$**H$_b$), 1.95 – 1.83 (2H, m, C**H$_a$**H$_b$, CH$_a$**H$_b$**), 1.82 – 1.71 (1H, m, CH$_a$**H$_b$**); δ_C (100 MHz, $CDCl_3$) 171.7 (**C**O), 138.6 (Ar**C**), 132.9 (Ar**C**), 132.7 (Ar**C**H), 131.5 (Ar**C**H), 127.3 (Ar**C**H), 120.7 (Ar**C**), 69.1 (O**C**H$_2$), 64.2 (N**C**H), 55.6 (Ar**C**H$_2$N), 55.2 (N**C**H$_2$), 30.2 (**C**H$_2$), 23.6 (**C**H$_2$); HRMS (ESI) calcd. for $C_{13}H_{15}{}^{79}BrNO_2^+$, 296.0281. Found: $[MH]^+$ 296.0275 (−1.9 ppm error); $[\alpha]_D^{20}$ = 16.4 (c = 1.0, $CHCl_3$).

8-Phenyl-2,3,3a,4-tetrahydro-1H-benzo[*f*]pyrrolo[2,1-*c*][1,4]oxazocin-6(11*H*)-one (115)



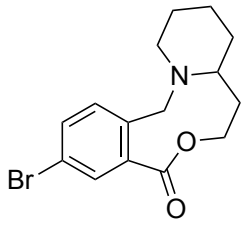
8-Bromo-2,3,3a,4-tetrahydro-1H-benzo[*f*]pyrrolo[2,1-*c*][1,4]oxazocin-6(11*H*)-one **100** (100 mg, 0.338 mmol) and phenylboronic acid (82.3 mg, 0.675 mmol) were dissolved in 1,4-dioxane (5.0 mL). Then Na_2CO_3 (107 mg, 1.01 mmol) which dissolved in water (2.5 mL) was added followed by Pd(dppf)Cl_2·CH_2Cl_2 (13.7 mg, 0.017 mmol) and the resulting mixture was purged with argon for 10 minutes. The mixture was stirred and heated at 50 °C for 18 hours under argon. After being allowed to cool to RT, water (20 mL) was added and the two layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 20 mL) and the combined organic phases were dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, 2:1 → 1:1 hexane : ethyl acetate) to afford the title compound (67.9 mg, 69%) as a white solid. R_f = 0.62 (1:1 hexane : ethyl acetate); m.p. 131–138 °C; v_{max}/cm^{-1} (thin film) 2966, 1714, 1485, 1345, 1304, 1203, 1093, 1043, 759, 699; δ_H (400 MHz, $CDCl_3$) 7.66 – 7.52 (4H, m, 4 x Ar**H**), 7.43 (2H, t, *J* = 7.5 Hz, Ar**H**), 7.38 – 7.30 (1H, m, Ar**H**), 7.20 (1H, d, *J* = 8.0 Hz, Ar**H**), 4.24 (1H, d, *J* = 17.0 Hz, ArC**H$_a$**H$_b$N), 4.03 (1H, dd, *J* = 12.0, 2.0 Hz, OC**H$_a$**H$_b$), 3.95 (1H, dd, *J* = 12.0, 3.5 Hz, OCH$_a$**H$_b$**), 3.88 (1H, d, *J* = 17.0 Hz, ArCH$_a$**H$_b$**N), 3.26 – 3.14 (1H, m, NC**H$_a$**H$_b$), 2.87 – 2.72 (2H, m, NC**H**, NH$_a$**H$_b$**), 2.12 – 2.00 (1H, m, C**H$_a$**H$_b$), 1.98 – 1.86 (2H, m, C**H$_a$**H$_b$, CH$_a$**H$_b$**), 1.84 – 1.71 (1H, m, CH$_a$**H$_b$**); δ_C (100 MHz, $CDCl_3$) 173.6 (**C**O), 140.5 (Ar**C**), 139.8 (Ar**C**), 138.3 (Ar**C**), 131.4 (Ar**C**), 128.9 (Ar**C**H), 128.5 (Ar**C**H), 127.7 (Ar**C**H), 127.4 (Ar**C**H), 127.0 (Ar**C**H), 126.5 (Ar**C**H), 68.9 (O**C**H$_2$), 64.3 (N**C**H), 55.8 (Ar**C**H$_2$N), 55.2 (N**C**H$_2$), 30.1 (**C**H$_2$), 23.4 (**C**H$_2$); HRMS (ESI) calcd. for $C_{19}H_{20}NO_2^+$, 294.1489. Found: $[MH]^+$ 294.1486 (+0.7 ppm error); $[\alpha]_D^{20}$ = 24.9 (c = 1.0, $CHCl_3$).

Methyl 5-bromo-2-((2-(2-hydroxyethyl)piperidin-1-yl)methyl)benzoate (97)



To a stirring solution of potassium carbonate (4.71 g, 34.1 mmol) in acetonitrile (70.0 mL), 2-(piperidin-2-yl)ethan-1-ol (1.47 g, 11.4 mmol) was added followed by methyl 5-bromo-2-(bromomethyl)benzoate **89** (3.50 mg, 11.4 mmol). The reaction mixture was refluxed at 90 °C for 17 hours under argon. Then the reaction mixture was allowed to cool to RT, filtered and washed with dichloromethane, concentrated under vacuum and purified by column chromatography (SiO_2, 99:1 ethyl acetate : triethylamine) to afford the title compound (2.77g, 69%) as a yellow oil. R_f = 0.39 (99:1 ethyl acetate : triethylamine); ν_{max}/cm^{-1} (thin film) 2933, 1725, 1435, 1287, 1242, 1094, 1076, 971, 830, 778; δ_H (400 MHz, $CDCl_3$) 7.96 (1H, d, *J* = 2.0 Hz, Ar**H**), 7.57 (1H, dd, *J* = 8.5, 2.0 Hz, Ar**H**), 7.36 (1H, d, *J* = 8.5 Hz, Ar**H**), 4.23 (1H, d, *J* = 14.0 Hz, ArC$\mathbf{H_a}H_b$N), 3.90 (4H, s, OC$\mathbf{H_3}$, ArC$H_a\mathbf{H_b}$N), 3.76 (1H, dt, *J* = 11.0, 5.0 Hz, C$\mathbf{H_a}H_b$OH), 3.62 (1H, ddd, *J* = 11.0, 7.5, 5.0 Hz, C$H_a\mathbf{H_b}$OH), 2.86 (1H, ddd, *J* = 13.0, 9.0, 3.0 Hz, NC$\mathbf{H_a}H_b$), 2.78 (1H, s, NC**H**), 2.32 (1H, s, NC$H_a\mathbf{H_b}$), 1.98 (1H, ddd, *J* = 13.0, 7.5, 5.0 Hz, C$\mathbf{H_a}H_b$), 1.80 (1H, ddd, *J* = 13.0, 9.0, 4.0 Hz, C$\mathbf{H_a}H_b$), 1.69 – 1.56 (3H, m, 2 x C$\mathbf{H_a}H_b$, 1 x C$H_a\mathbf{H_b}$), 1.52 – 1.35 (3H, m, 3 x C$H_a\mathbf{H_b}$); δ_C (100 MHz, $CDCl_3$) 167.1 (**C**O), 140.1 (Ar**C**), 134.6 (Ar**C**H), 133.2 (Ar**C**H), 132.3 (Ar**C**), 131.9 (Ar**C**H), 120.5 (Ar**C**), 61.9 (**C**H_2OH), 58.8 (N**C**H), 54.6 (Ar**C**H_2N), 52.4 (O**C**H_3), 48.7 (N**C**H_2), 31.7 (**C**H_2), 27.4 (**C**H_2), 22.7 (**C**H_2), 21.7 (**C**H_2); HRMS (ESI) calcd. for $C_{16}H_{23}{}^{79}BrNO_3{}^+$, 356.0856. Found: $[MH]^+$ 358.0830 (+2.1 ppm error).

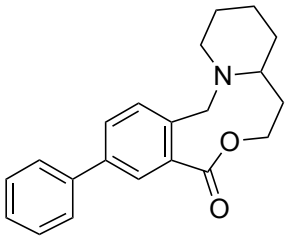
3-Bromo-8,8a,9,10,11,12-hexahydro-7H-benzo[*g*]pyrido[2,1-*d*][1,5]oxazonin-5(14*H*)-one (101)



To a stirring solution of methyl 5-bromo-2-((2-(2-hydroxyethyl)piperidin-1-yl)methyl) benzoate **97** (2.50 g, 7.02 mmol) in methanol (15.4 mL), aqueous lithium hydroxide (0.5 M) was added (15.4 mL, 7.72 mmol) and the reaction mixture was heated to 50 °C for 2 hours. The reaction was then allowed to cool to RT, and the solvent was removed under vacuum using chloroform (5 × 200 mL) to form an azeotropic mixture. The intermediate 5-bromo-2-((2-(2-hydroxyethyl)piperidin-1-yl)methyl)benzoic acid was dissolved in chloroform (70 mL) and DIPEA (2.3 mL, 13.0 mmol) was added followed by T3P (50% w/v in ethyl acetate, 6.70 g, 10.5 mmol) and the mixture was stirred at room temperature for 17 hours under argon. The reaction mixture was then transferred into a separating funnel and water (80 mL) was added, and extracted with ethyl acetate (3 × 80 mL). The organic phases were then combined, dried with magnesium sulphate, filtered and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, 20:1 → 10:1 hexane : ethyl acetate) to afford the title compound (1.38 g, 61%) as a white solid. R_f = 0.42 (10:1 hexane : ethyl acetate); m.p. 99–102 °C; ν_{max}/cm^{-1} (thin film) 2931, 1726, 1462, 1257, 1138, 1090, 998, 814, 745; δ_H (400 MHz, $CDCl_3$) 7.66 (1H, d, *J* = 2.5 Hz, Ar**H**), 7.42 (1H, dd, *J* = 8.0, 2.5 Hz, Ar**H**), 7.05 (1H, d, *J* = 8.0 Hz, Ar**H**), 5.27 (1H, t, *J* = 12.0 Hz, OC$\mathbf{H_a}H_b$), 4.55 (1H, d, *J* = 14.0 Hz, ArC$\mathbf{H_a}H_b$N), 4.00 (1H, dt, *J* = 12.0, 3.0 Hz, OC$H_a\mathbf{H_b}$), 2.72 (1H, d, *J* = 14.0 Hz, ArC$H_a\mathbf{H_b}$N), 2.68 – 2.44 (3H, m, NC**H**, NC$\mathbf{H_a}H_b$, C$\mathbf{H_a}H_b$), 1.88 (1H, td, *J* = 11.5, 3.0 Hz, NC$H_a\mathbf{H_b}$), 1.70 – 1.57 (2H, m, 2 x C$\mathbf{H_a}H_b$), 1.46 – 1.30 (3H,

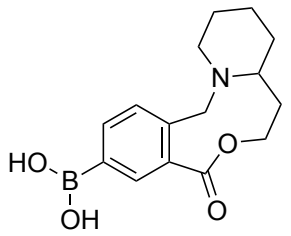
m, 2 x $CH_a\mathbf{H_b}$, $\mathbf{C}H_aH_b$), 1.27 – 1.15 (2H, m, 2 x $CH_a\mathbf{H_b}$); δ_C (100 MHz, $CDCl_3$) 170.3 (**C**O), 142.0 (Ar**C**), 135.3 (Ar**C**), 132.8 (Ar**C**H), 131.6 (Ar**C**H), 130.5 (Ar**C**H), 120.5 (Ar**C**), 63.3 (O**C**H_2), 58.3 (N**C**H), 56.6 (Ar**C**H_2N), 53.4 (N**C**H_2), 31.9 (**C**H_2), 31.0 (**C**H_2), 25.6 (**C**H_2), 24.5 (**C**H_2); HRMS (ESI) calcd. for $C_{15}H_{19}{}^{79}BrNO_2{}^+$, 324.0594. Found: $[MH]^+$ 324.0580 (−4.3 ppm error).

3-Phenyl-8,8a,9,10,11,12-hexahydro-7H-benzo[*g*]pyrido[2,1-*d*][1,5]oxazonin-5(14*H*)-one (116)



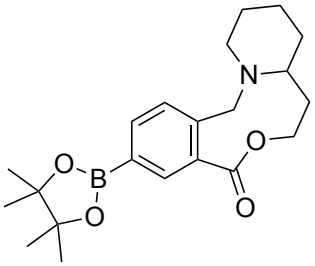
3-Bromo-8,8a,9,10,11,12-hexahydro-7H-benzo[*g*]pyrido[2,1-*d*][1,5]oxazonin-5(14*H*)-one **101** (100 mg, 0.308 mmol) and phenylboronic acid (75.2 mg, 0.617 mmol) were dissolved in 1,4-dioxane (5.0 mL). Then Na_2CO_3 (98.1 mg, 0.925 mmol) which dissolved in water (2.5 mL) was added followed by $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (12.5 mg, 0.015 mmol) and the resulting mixture was purged with argon for 10 minutes. The mixture was stirred and heated at 50 °C for 16 hours under argon. After being allowed to cool to RT, water (20 mL) was added and the two layers were separated. The aqueous layer was extracted with dichloromethane (3 x 20 mL) and the combined organic phases were dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, 20:1 → 10:1 hexane : ethyl acetate) to afford the title compound (90.2 mg, 91%) as a white solid. R_f = 0.32 (10:1 hexane : ethyl acetate); m.p. 185–191 °C; ν_{max}/cm^{-1} (thin film) 1717, 1587, 1433, 1260, 1118, 1094, 869, 779, 704; δ_H (400 MHz, $CDCl_3$) 7.81 (1H, d, *J* = 2.0 Hz, Ar**H**), 7.62 – 7.59 (2H, m, 2 x Ar**H**), 7.56 (1H, dd, *J* = 8.0, 2.0 Hz, Ar**H**), 7.43 (2H, t, *J* = 7.5 Hz, 2 x Ar**H**), 7.34 (1H, t, *J* = 7.5 Hz, Ar**H**), 7.26 (1H, d, *J* = 8.0 Hz, Ar**H**), 5.33 (1H, t, *J* = 11.5 Hz, OC$\mathbf{H}_aH_b$), 4.69 (1H, d, *J* = 14.0 Hz, ArC$\mathbf{H}_aH_b$N), 4.04 (1H, dt, *J* = 11.5, 3.0 Hz, OC$H_a\mathbf{H_b}$), 2.81 (1H, d, *J* = 14.0 Hz, Ar$CH_a\mathbf{H_b}$N), 2.76 – 2.62 (3H, m, NC$\mathbf{H}_aH_b$, NC**H**, C$\mathbf{H}_aH_b$), 1.94 (1H, td, *J* = 11.5, 3.0 Hz, N$CH_a\mathbf{H_b}$), 1.74 – 1.63 (2H, m, 2 x C$\mathbf{H}_aH_b$), 1.49 – 1.24 (5H, m, 3 x $CH_a\mathbf{H_b}$, C$\mathbf{H_2}$); δ_C (100 MHz, $CDCl_3$) 171.9 (**C**O), 142.0 (Ar**C**), 140.2 (Ar**C**), 134.0 (Ar**C**), 129.4 (Ar**C**H), 128.9 (Ar**C**H), 128.9 (Ar**C**), 128.6 (Ar**C**H), 127.6 (Ar**C**H), 127.4 (Ar**C**H), 127.1 (Ar**C**H), 63.2 (O**C**H_2), 58.4 (N**C**H), 57.0 (Ar**C**H_2N), 53.6 (N**C**H_2), 32.1 (**C**H_2), 31.2 (**C**H_2), 25.8 (**C**H_2), 24.6 (**C**H_2); HRMS (ESI) calcd. for $C_{21}H_{24}NO_2{}^+$, 322.1802. Found: $[MH]^+$ 322.1798 (−0.5 ppm error).

(5-Oxo-5,8,8a,9,10,11,12,14-octahydro-7H-benzo[*g*]pyrido[2,1-*d*][1,5]oxazonin-3-yl) boronic acid (Not shown in the thesis)



3-Bromo-8,8a,9,10,11,12-hexahydro-7H-benzo[*g*]pyrido[2,1-*d*][1,5]oxazonin-5(14*H*)-one **101** (1.00 g, 3.08 mmol) and bis(pinacolato)diboron (1.57g, 6.17 mmol) were dissolved in 1,4-dioxane (20 mL). Then Na_2CO_3 (981 mg, 9.25 mmol) which dissolved in water (10 mL) was added followed by $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (125 mg, 0.154 mmol) and the resulting mixture was purged with argon for 10 minutes. The mixture was stirred and heated at 50 °C for 16.5 hours under argon. After being allowed to cool to RT, water (50 mL) was added and the two layers were separated. The aqueous layer was extracted with dichloromethane (3 x 50 mL) and the combined organic phases were dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, 5:1 hexane : ethyl acetate) to afford the title compound (365 mg, 41%) as a white solid. R_f = 0.23 (5:1 hexane : ethyl acetate); m.p. 201–206 °C; ν_{max}/cm^{-1} (thin film) 2931, 1725, 1462, 1262, 1139, 1087, 997, 816, 734, 701; δ_H (400 MHz, $CDCl_3$) 7.78 (1H, s, Ar**H**), 7.54 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.23 (1H, d, *J* = 8.0 Hz, Ar**H**), 5.35 – 5.26 (1H, m, OC**H$_a$**H$_b$), 4.65 (1H, d, *J* = 14.0 Hz, ArC**H$_a$**H$_b$N), 4.00 (1H, d, *J* = 11.5 Hz, OCH$_a$**H$_b$**), 2.77 (1H, d, *J* = 14.0 Hz, ArCH$_a$**H$_b$**N), 2.73 – 2.57 (3H, m, NC**H$_a$**H$_b$, NC**H**, C**H$_a$**H$_b$), 1.90 (1H, t, *J* = 11.0 Hz, NCH$_a$**H$_b$**), 1.73 – 1.57 (2H, m, 2 x C**H$_a$**H$_b$), 1.47 – 1.19 (5H, m, 3 x CH$_a$**H$_b$**, C**H$_2$**); δ_C (100 MHz, $CDCl_3$) 171.7 (**C**O), 142.2 (Ar**C**), 139.0(Ar**C**), 134.0 (Ar**C**), 129.5 (Ar**C**H), 128.3 (Ar**C**H), 127.1 (Ar**C**H), 63.1 (O**C**H$_2$), 58.3 (N**C**H), 56.8 (Ar**C**H$_2$N), 53.5 (N**C**H$_2$), 32.0 (**C**H$_2$), 31.1 (**C**H$_2$), 25.7 (**C**H$_2$), 24.5 (**C**H$_2$); HRMS (ESI) calcd. for $C_{15}H_{20}BNO_4^+$, 290.1558. Found: $[MH]^+$ 290.1561.

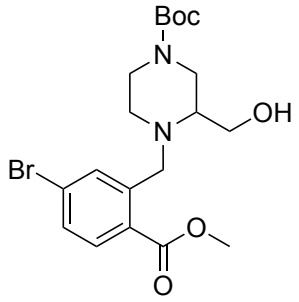
3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-8,8a,9,10,11,12-hexahydro-7H-benzo[*g*] pyrido[2,1-*d*][1,5]oxazonin-5(14*H*)-one (123)



3-Bromo-8,8a,9,10,11,12-hexahydro-7H-benzo[*g*]pyrido[2,1-*d*][1,5]oxazonin-5(14*H*)-one **101** (100 mg, 0.308 mmol), bis(pinacolato)diboron (156.6 mg, 0.716 mmol), $Pd(dppf)Cl_2$ (22.7 mg, 0.031 mmol) and potassium acetate (60.6 mg, 0.617 mmol) were added to a round-bottomed flask. The round-bottomed flask was purged with argon and then 1,4-dioxane (3 mL) was added. The resulting mixture was stirred and heated at 60 °C for 23 hours under argon. After being allowed to cool to RT, the solids were removed by filtration and washed with dichloromethane (10 mL). The solvents were evaporated under reduced pressure to give the crude product. The crude product was purified by column chromatography (SiO_2, 10:1 hexane : ethyl acetate) to afford the title compound (72.1 mg, 63%) as a white solid. R_f = 0.59 (10:1 hexane : ethyl acetate); m.p. 120–124 °C; ν_{max}/cm^{-1} (thin film) 2979, 1730, 1612, 1355, 1280, 1258, 1122, 1078, 963, 848, 731, 669; δ_H (400 MHz, $CDCl_3$) 8.01 (1H, s, Ar**H**), 7.75 (1H, d, *J* = 7.5 Hz, Ar**H**), 7.19 (1H, d, *J* = 7.5 Hz, Ar**H**), 5.29 (1H, t, *J* = 12.0 Hz, OC**H$_a$**H$_b$), 4.66 (1H, d, *J* = 14.0 Hz, ArC**H$_a$**H$_b$N), 4.19 – 3.82 (1H, m, OCH$_a$**H$_b$**), 2.76 (1H, d, *J* = 14.0 Hz, ArCH$_a$**H$_b$**N), 2.72 – 2.43 (3H, m, NC**H**, NC**H$_a$**H$_b$, C**H$_a$**H$_b$), 1.88 (1H, t, *J* = 11.0 Hz, NCH$_a$**H$_b$**), 1.76 – 1.59 (2H, m, 2 x C**H$_a$**H$_b$), 1.48 – 1.40 (1H, m, CH$_a$**H$_b$**), 1.32 (14H, s, 4 x C**H$_3$**, C**H$_2$**), 1.25 – 1.14 (2H, m, 2 x CH$_a$**H$_b$**); δ_C (100

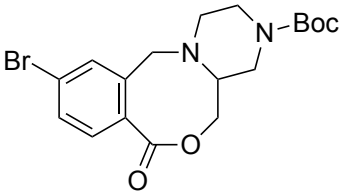
MHz, $CDCl_3$) 171.9 (**C**O), 146.2 (Ar**C**), 136.6 (Ar**C**), 136.6 (Ar**C**H), 135.0 (Ar**C**H), 133.1 (Ar**C**), 128.4 (Ar**C**H), 84.1 (2 x BO**C**(CH_2)), 63.0 (O**C**H_2), 58.4 (N**C**H), 57.3 (Ar**C**H_2N), 53.6 (N**C**H_2), 32.1 (**C**H_2), 31.1 (**C**H_2), 25.7 (**C**H_2), 25.0 (4 x **C**H_3), 24.6 (**C**H_2); HRMS (ESI) calcd. for $C_{21}H_{31}BNO_4^+$, 372.2341. Found: $[MH]^+$ 372.2349 (–1.1 ppm error).

tert-Butyl 4-(5-bromo-2-(methoxycarbonyl)benzyl)-3-(hydroxymethyl)piperazine-1-carboxylate (95)



To a stirring solution of potassium carbonate (2.69 g, 19.5 mmol) in acetonitrile (40.0 mL), *tert*-butyl 3-(hydroxymethyl)piperazine-1-carboxylate (1.40 g, 6.49 mmol) was added followed by methyl 4-bromo-2-(bromomethyl)benzoate **87** (2.00 g, 6.49 mmol). The reaction mixture was refluxed at 90 °C for 17 hours under argon. Then the reaction mixture was allowed to cool to RT, filtered and washed with dichloromethane, concentrated under vacuum and purified by column chromatography (SiO_2, 5:1 → 2:1 hexane : ethyl acetate) to afford the title compound (2.49 g, 87%) as a colourless oil. R_f = 0.33 (2:1 hexane : ethyl acetate); ν_{max}/cm^{-1} (thin film) 2976, 1720, 1673, 1588, 1431, 1366, 1272, 1169, 1125, 1091, 865, 770, 730; δ_H (400 MHz, $CDCl_3$) 7.57 – 7.43 (2H, m, 2 x Ar**H**), 7.34 (1H, dd, *J* = 8.0, 2.5 Hz, Ar**H**), 4.35 (1H, s, ArC**H$_a$**H$_b$N), 3.77 (4H, s, C**H$_a$**H$_b$OH, OC**H$_3$**), 3.58 – 3,26 (4H, m, BocNC**H$_2$**, CH$_a$**H$_b$**OH, ArCH$_a$**H$_b$**N), 3.04 (2H, s, BocNC**H$_2$**), 2.52 – 2.40 (1H, m, NC**H$_a$**H$_b$), 2.34 (1H, s, NC**H**), 2.01 (1H, ddd, *J* = 11.5, 8.5, 3.0 Hz, NCH$_a$**H$_b$**), 1.34 (9H, s, 3 x C**H$_3$**); δ_C (100 MHz, $CDCl_3$) 168.4 (O**C**O), 154.9 (N**C**O), 141.8 (Ar**C**), 133.1 (Ar**C**H), 131.3 (Ar**C**H), 130.2 (Ar**C**H), 129.5 (Ar**C**), 125.9 (Ar**C**), 79.7 (O**C**(CH_3)$_3$), 61.1 (N**C**H), 59.5 (**C**H_2OH), 55.7 (Ar**C**H_2N), 52.3 (O**C**H_3), 49.5 (N**C**H_2), 44.2 (BocN**C**H_2), 42.3 (BocN**C**H_2), 28.3 (3 x **C**H_3); HRMS (ESI) calcd. for $C_{19}H_{28}{}^{79}BrN_2O_5^+$, 443.1176. Found: $[MH]^+$ 443.1162 (+3.2 ppm error).

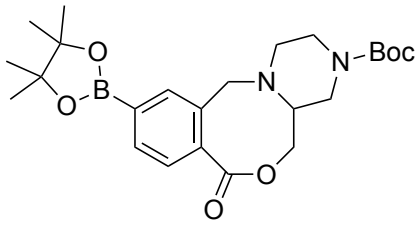
tert-Butyl 10-bromo-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[*f*]pyrazino[2,1-*c*][1,4] oxazocine-3(4*H*)-carboxylate (104)



To a stirring solution of methyl *tert*-Butyl 4-(5-bromo-2-(methoxycarbonyl)benzyl)-3-(hydroxymethyl)piperazine-1-carboxylate **95** (2.20g, 4.96 mmol) in methanol (10.9 mL), aqueous lithium hydroxide (0.5 M) was added (10.9 mL, 5.46 mmol) and the reaction mixture was heated to 50 °C for 29.5 hours. The reaction was then allowed to cool to RT, and the solvent was removed under vacuum using chloroform (5 × 200 mL) to form an azeotropic

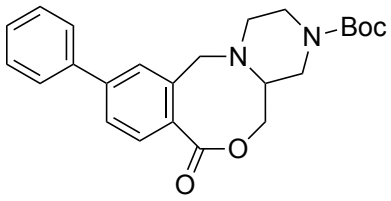
mixture. The intermediate 4-Bromo-2-((4-(*tert*-butoxycarbonyl)-2-(hydroxymethyl)piperazin-1-yl)methyl)benzoic acid was dissolved in chloroform (60 mL) and DIPEA (1.60 mL, 9.18 mmol) was added followed by T3P (50% w/v in ethyl acetate, 4.74 g, 7.44 mmol) and the mixture was stirred at room temperature for 15.5 hours under argon. The reaction mixture was then transferred into a separating funnel and water (50 mL) was added, and extracted with dichloromethane (3 × 50 mL). The organic phases were then combined, dried with magnesium sulphate, filtered and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, 2:1 hexane : ethyl acetate) to afford the title compound (1.90 g, 93%) as a yellow solid. R_f = 0.53 (2:1 hexane : ethyl acetate); m.p. 99–103 °C; ν_{max}/cm^{-1} (thin film) 2976, 1724, 1688, 1588, 1456, 1271, 1241, 1168, 1114, 1090, 1012, 734; δ_H (400 MHz, $CDCl_3$) 7.42 (1H, dt, *J* = 8.0, 1.5 Hz, Ar**H**), 7.33 (1H, d, *J* = 1.5 Hz, Ar**H**), 7.30 (1H, dd, *J* = 8.0, 1.5 Hz, Ar**H**), 4.08 – 4.03 (1H, m, OC**H$_a$**H$_b$), 4.02 – 3.75 (3H, m, OCH$_a$**H$_b$**, BocNC**H$_2$**), 3.70 (2H, d, *J* = 2.0 Hz, ArC**H$_2$**N), 3.05 – 2.73 (3H, m, NC**H$_a$**H$_b$, BocNC**H$_2$**), 2.60 – 2.43 (2H, m, NCH$_a$**H$_b$**, NC**H**), 1.40 (9H, d, *J* = 1.3 Hz, 3 x C**H$_3$**); δ_C (100 MHz, $CDCl_3$) 171.0 (O**C**O), 154.5 (N**C**O), 140.1 (Ar**C**), 131.7 (Ar**C**H), 131.1 (Ar**C**H), 131.0 (Ar**C**H), 127.8 (Ar**C**), 125.5 (Ar**C**), 80.1 (O**C**(CH$_3$)$_3$), 68.5 (O**C**H$_2$), 62.5 (N**C**H), 59.8 (Ar**C**H$_2$N), 54.8 (N**C**H$_2$), 44.7(BocN**C**H$_2$), 42.9(BocN**C**H$_2$), 28.4 (3 x **C**H$_3$); HRMS (ESI) calcd. for $C_{18}H_{23}{}^{79}BrN_2NaO_4^+$, 411.0914. Found: $[MH]^+$ 411.0912 (0.5 ppm error).

***tert*-Butyl 7-oxo-10-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,4a,5,7,12-hexahydrobenzo[*f*]pyrazino[2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate (124)**



tert-Butyl 10-bromo-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[*f*]pyrazino[2,1-*c*][1,4] oxazocine-3(4*H*)-carboxylate **104** (1.00 g, 2.43 mmol), bis(pinacolato)diboron (1.23 mg, 4.86 mmol), Pd(dppf)Cl_2 (88.9 mg, 0.122 mmol) and potassium acetate (716 mg, 7.29 mmol) were added to a round-bottomed flask. The round-bottomed flask was purged with argon and then 1,4-dioxane (20 mL) was added. The resulting mixture was stirred and heated at 60 °C for 19 hours under argon. After being allowed to cool to rt, the solids were removed by filtration and washed with dichloromethane (30 mL). The solvents were evaporated under reduced pressure to give the crude product. The crude product was purified by column chromatography (SiO_2, 4:1 hexane : ethyl acetate) to afford the title compound (959 mg, 86%) as a white solid. R_f = 0.50 (2:1 hexane : ethyl acetate); m.p. 162–165 °C; ν_{max}/cm^{-1} (thin film) 2977, 1731, 1695, 1391, 1361, 1275, 1243, 1169, 1114, 1013, 965, 732; δ_H (400 MHz, $CDCl_3$) 7.73 (1H, d, *J* = 7.5 Hz, Ar**H**), 7.63 (1H, s, Ar**H**), 7.45 (1H, d, *J* = 7.5 Hz, Ar**H**), 4.07 (1H, d, *J* = 12.5 Hz, OC**H$_a$**H$_b$), 4.01 – 3.67 (5H, m, OCH$_a$**H$_b$**, BocNC**H$_2$**, ArC**H$_2$**N), 3.04 – 2.74 (3H, m, BocNC**H$_2$**, NC**H$_a$**H$_b$), 2.54 (2H, td, *J* = 12.0, 4.0 Hz, NC**H**, NCH$_a$**H$_b$**), 1.43 (9H, s, 3 x C**H$_3$**), 1.32 (12H, s, 4 x C**H$_3$**); δ_C (100 MHz, $CDCl_3$) 168.8 (O**C**O), 151.4 (N**C**O), 133.9 (Ar**C**), 131.7 (Ar**C**H), 130.8 (Ar**C**H), 129.2 (Ar**C**), 128.2 (Ar**C**), 126.1 (Ar**C**H), 81.2 (O**C**(CH$_3$)$_3$), 77.0 (2 x BO**C**(CH$_2$)), 65.6 (O**C**H$_2$), 59.6 (N**C**H), 57.2 (Ar**C**H$_2$N), 51.8 (N**C**H$_2$), 41.7 (BocN**C**H$_2$), 40.8 (BocN**C**H$_2$), 25.3 (3 x **C**H$_3$), 21.8 (4 x **C**H$_3$); HRMS (ESI) calcd. for $C_{24}H_{36}BN_2O_6^+$, 459.2661. Found: $[MH]^+$ 459.2678 (–2.8 ppm error).

***tert*-Butyl 7-oxo-10-phenyl-1,2,4a,5,7,12-hexahydrobenzo[*f*]pyrazino[2,1-*c*][1,4] oxazocine-3(4*H*)-carboxylate (114)**

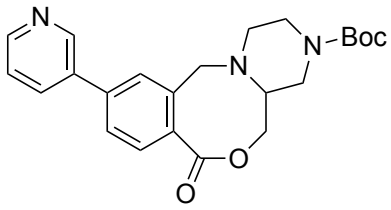


Method 1: *tert*-Butyl 10-bromo-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[*f*]pyrazino[2,1-*c*][1,4] oxazocine-3 (4*H*)-carboxylate **104** (80.0 mg, 0.194 mmol) and phenylboronic acid (49.4 mg, 0.389 mmol) were dissolved in 1,4-dioxane (4.0 mL). Then Na_2CO_3 (61.8 mg, 0.584 mmol) which dissolved in water (2.0 mL) was added followed by $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (7.9 mg, 0.010 mmol) and the resulting mixture was purged with argon for 10 minutes. The mixture was stirred and heated at 50 °C for 17 hours under argon. After being allowed to cool to RT, water (10 mL) was added and the two layers were separated. The aqueous layer was extracted with dichloromethane (3 x 10 mL) and the combined organic phases were dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, 5:1 → 3:1 hexane : ethyl acetate) to afford the title compound (65.0 mg, 82%) as a white solid.

Method 2: *tert*-Butyl 7-oxo-10-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,4a,5,7,12-hexahydro benzo[*f*]pyrazino[2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate **124** (90.0 mg, 0.196 mmol) and bromobenzene (61.7 mg, 0.393 mmol) were dissolved in 1,4-dioxane (4.0 mL). Then Na_2CO_3 (62.4 mg, 0.589 mmol) which dissolved in water (2.0 mL) was added followed by $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (8.0 mg, 0.010 mmol) and the resulting mixture was purged with argon for 10 minutes. The mixture was stirred and heated at 50 °C for 18 hours under argon. After being allowed to cool to RT, water (10 mL) was added and the two layers were separated. The aqueous layer was extracted with dichloromethane (3 x 10 mL) and the combined organic phases were dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, 5:1 → 3:1 hexane : ethyl acetate) to afford the title compound (52.7 mg, 66%) as a white solid.

Data for **5g**: R_f = 0.56 (2:1 hexane : ethyl acetate); m.p. 155–158 °C; ν_{max}/cm^{-1} (thin film) 2975, 2928, 1720, 1688, 1424, 1271, 1241, 1169, 1121, 1089, 755, 735, 698; δ_H (400 MHz, $CDCl_3$) 7.66 – 7.52 (4H, m, 4 x Ar**H**), 7.49 – 7.34 (4H, m, 4 x Ar**H**), 4.16 (1H, d, *J* = 13.0 Hz, OC**H**$_a$H$_b$), 4.05 (1H, dd, *J* = 13.0, 4.0 Hz, OCH$_a$**H$_b$**), 4.00 – 3.66 (4H, m, BocNC**H$_2$**, ArC**H$_2$**N), 3.02 – 2.85 (3H, m, BocNC**H$_2$**, NC**H$_a$**H$_b$), 2.59 (2H, td, *J* = 11.5, 3.0 Hz, NC**H**, NCH$_a$**H$_b$**), 1.46 (9H, s, 3 x C**H$_3$**); δ_C (100 MHz, $CDCl_3$) 172.0 (O**C**O), 154.6 (N**C**O), 144.2(Ar**C**), 139.6(Ar**C**), 138.6 (Ar**C**), 130.8 (Ar**C**H), 129.0 (Ar**C**H), 128.2 (Ar**C**H), 127.7 (Ar**C**), 127.2 (Ar**C**H), 127.1 (Ar**C**H), 126.5 (Ar**C**H), 80.2 (O**C**(CH$_3$)$_3$), 68.7 (O**C**H$_2$), 62.7 (N**C**H), 60.6 (Ar**C**H$_2$N), 55.0 (N**C**H$_2$), 45.9 (BocN**C**H$_2$), 43.9 (BocN**C**H$_2$), 28.4 (3 x **C**H$_3$); HRMS (ESI) calcd. for $C_{24}H_{29}N_2O_4^+$, 409.2122. Found: $[MH]^+$ 409.2127 (−1.1 ppm error).

***tert*-Butyl 7-oxo-10-(pyridin-3-yl)-1,2,4a,5,7,12-hexahydrobenzo[*f*]pyrazino[2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate (118)**

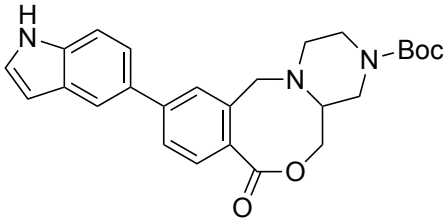


Method 1: *tert*-Butyl 10-bromo-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[*f*]pyrazino[2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate **104** (80.0 mg, 0.194 mmol) and pyridin-3-ylboronic acid (47.8 mg, 0.389 mmol) were dissolved in 1,4-dioxane (4.0 mL). Then Na_2CO_3 (61.8 mg, 0.584 mmol) which dissolved in water (2.0 mL) was added followed by $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (7.9 mg, 0.010 mmol) and the resulting mixture was purged with argon for 10 minutes. The mixture was stirred and heated at 50 °C for 18 hours under argon. After being allowed to cool to RT, water (10 mL) was added and the two layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 10 mL) and the combined organic phases were dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, 2:1 → 0:1 hexane : ethyl acetate) to afford the title compound (32.0 mg, 40%) as a yellow solid.

Method 2: *tert*-Butyl 7-oxo-10-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,4a,5,7,12-hexahydro benzo[*f*]pyrazino[2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate **124** (140 mg, 0.305 mmol) and 3-bromopyridine (96.5 mg, 0.611 mmol) were dissolved in 1,4-dioxane (6.0 mL). Then Na_2CO_3 (97.1 mg, 0.916 mmol) which dissolved in water (3.0 mL) was added followed by $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (12.2 mg, 0.015 mmol) and the resulting mixture was purged with argon for 10 minutes. The mixture was stirred and heated at 50 °C for 18 hours under argon. After being allowed to cool to RT, water (10 mL) was added and the two layers were separated. The aqueous layer was extracted with dichloromethane (3 x 10 mL) and the combined organic phases were dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, 1:1 → 0:1 hexane : ethyl acetate) to afford the title compound (31.1 mg, 25%) as a yellow solid.

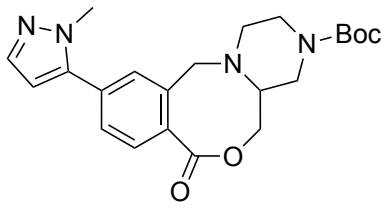
Data for **5h**: R_f = 0.30 (ethyl acetate); m.p. 131–135 °C; ν_{max}/cm^{-1} (thin film) 2976, 1721, 1692, 1611, 1456, 1426, 1280, 1243, 1170, 1124, 1021, 729; δ_H (400 MHz, $CDCl_3$) 8.83 (1H, d, *J* = 2.0 Hz, Ar**H**), 8.62 (1H, dd, *J* = 5.0, 1.5 Hz, Ar**H**), 7.87 (1H, dt, *J* = 8.0, 2.0 Hz, Ar**H**), 7.60 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.55 (1H, dd, *J* = 8.0, 2.0 Hz, Ar**H**), 7.41 (1H, d, *J* = 1.5 Hz, Ar**H**), 7.38 (1H, dd, *J* = 8.0, 5.0 Hz, Ar**H**), 4.16 (1H, dd, *J* = 13.0, 2.0 Hz, OC**H$_a$**H$_b$), 4.05 (1H, dd, *J* = 13.0, 4.0 Hz, OCH$_a$**H$_b$**), 4.01 – 3.74 (4H, m, BocNC**H$_2$**, ArC**H$_2$**N), 2.90 (3H, dd, *J* = 8.5, 6.0 Hz, BocNC**H$_2$**, NC**H$_a$**H$_b$), 2.67 – 2.53 (2H, m, NC**H**, NCH$_a$**H$_b$**), 1.45 (9H, s, 3 x C**H$_3$**); δ_C (100 MHz, $CDCl_3$) 171.7 (O**C**O), 154.6 (N**C**O), 149.4 (Ar**C**H), 148.3 (Ar**C**H), 140.8 (Ar**C**), 139.1 (Ar**C**), 135.3 (Ar**C**), 134.6 (Ar**C**H), 131.2 (Ar**C**H), 128.7 (Ar**C**), 127.0 (Ar**C**H), 126.6 (Ar**C**H), 123.8 (Ar**C**H), 80.3 (O**C**$(CH_3)_3$), 68.7 (O**C**H_2), 62.8 (N**C**H), 60.6 (Ar**C**H_2N), 55.0 (N**C**H_2), 45.5 (BocN**C**H_2), 44.0 (BocN**C**H_2), 28.5 (3 x **C**H_3); HRMS (ESI) calcd. for $C_{23}H_{27}N_3O_4^+$, 410.2074. Found: $[MH]^+$ 410.2082 (−1.8 ppm error).

***tert*-Butyl 10-(1H-indol-5-yl)-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[*f*]pyrazino[2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate (119)**



tert-Butyl 10-bromo-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[*f*]pyrazino[2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate **104** (80.0 mg, 0.194 mmol) and (1H-indol-5-yl)boronic acid (62.6 mg, 0.389 mmol) were dissolved in 1,4-dioxane (4.0 mL). Then Na_2CO_3 (61.8 mg, 0.584 mmol) which dissolved in water (2.0 mL) was added followed by $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (7.9 mg, 0.010 mmol) and the resulting mixture was purged with argon for 10 minutes. The mixture was stirred and heated at 50 °C for 18 hours under argon. After being allowed to cool to RT, water (10 mL) was added and the two layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 10 mL) and the combined organic phases were dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, 3:1 → 1:1 hexane : ethyl acetate) to afford the title compound (73.1 mg, 84%) as a white solid. R_f = 0.29 (1:1 hexane : ethyl acetate); m.p. 202–206 °C; ν_{max}/cm^{-1} (thin film) 3320, 2977, 1688, 1606, 1456, 1427, 1366, 1282, 1244, 1169, 1123, 1091, 1011, 910, 729; δ_H (400 MHz, $CDCl_3$) 8.71 (1H, s, N**H**), 7.87 (1H, d, *J* = 1.5 Hz, Ar**H**), 7.62 (1H, dd, *J* = 8.0, 1.5 Hz, Ar**H**), 7.57 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.50 – 7.39 (3H, m, 3 x Ar**H**), 7.25 (1H, t, *J* = 2.5 Hz, Ar**H**), 6.60 (1H, t, *J* = 2.5 Hz, Ar**H**), 4.18 (1H, dd, *J* = 13.0, 2.0 Hz, OC**H**$_a$H$_b$), 4.07 (1H, dd, *J* = 13.0, 4.5 Hz, OCH$_a$**H$_b$**), 4.03 – 3.71 (4H, m, BocNC**H$_2$**, ArC**H$_2$**N), 3.10 – 2.79 (3H, m, BocNC**H$_2$**, NC**H$_a$**H$_b$), 2.67 – 2.53 (2H, m, NC**H**, NCH$_a$**H$_b$**), 1.48 (9H, s, 3 x C**H$_3$**); δ_C (100 MHz, $CDCl_3$) 172.5 (O**C**O), 154.7 (N**C**O), 145.7 (Ar**C**), 138.4 (Ar**C**), 135.9 (Ar**C**), 131.4 (Ar**C**), 130.8 (Ar**CH**), 128.5 (Ar**C**), 127.2 (Ar**C**H), 126.7 (Ar**C**H), 126.6 (Ar**C**), 125.5 (Ar**C**H), 121.5 (Ar**C**H), 119.5 (Ar**C**H), 111.7 (Ar**C**H), 102.9 (Ar**C**H) 80.3 (O**C**$(CH_3)_3$), 68.8 (O**C**H_2), 62.8 (N**C**H), 60.7 (Ar**C**H_2N), 54.9 (N**C**H_2), 45.6 (BocN**C**H_2), 44.1 (BocN**C**H_2), 28.5 (3 x **C**H_3); HRMS (ESI) calcd. for $C_{26}H_{30}N_3O_4^+$, 448.2231. Found: $[MH]^+$ 448.2238 (−1.5 ppm error).

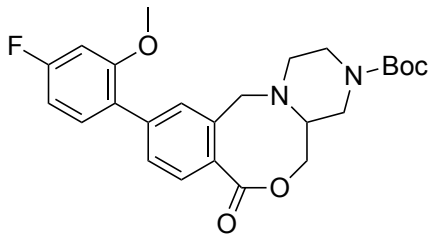
***tert*-Butyl 10-(1-methyl-1H-pyrazol-5-yl)-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[*f*]pyrazino[2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate (121)**



tert-Butyl 10-bromo-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[*f*]pyrazino[2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate **104** (80.0 mg, 0.194 mmol) and (1-methyl-1H-pyrazol-5-yl)boronic acid (49.0 mg, 0.389 mmol) were dissolved in 1,4-dioxane (4.0 mL). Then Na_2CO_3 (61.8 mg, 0.584 mmol) which dissolved in water (2.0 mL) was added followed by $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (7.9 mg, 0.010 mmol) and the resulting mixture was purged with argon for 10 minutes. The mixture

was stirred and heated at 50 °C for 18 hours under argon. After being allowed to cool to RT, water (10 mL) was added and the two layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 10 mL) and the combined organic phases were dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, 2:1 → 0:1 hexane : ethyl acetate) to afford the title compound (40.2 mg, 50%) as a yellow solid. R_f = 0.51 (ethyl acetate); m.p. 147–152 °C; ν_{max}/cm^{-1} (thin film) 2924, 1721, 1690, 1458, 1425, 1366, 1280, 1244, 1171, 1123, 1091, 1013, 761; δ_H (400 MHz, $CDCl_3$) 7.59 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.53 (1H, d, *J* = 2.0 Hz, Ar**H**), 7.41 (1H, dd, *J* = 8.0, 2.0 Hz, Ar**H**), 7.27 (1H, d, *J* = 2.0 Hz, Ar**H**), 6.35 (1H, d, *J* = 2.0 Hz, Ar**H**), 4.18 (1H, dd, *J* = 13.0, 2.0 Hz, OC**H**$_a$H$_b$), 4.06 (1H, dd, *J* = 13.0, 4.0 Hz, OCH$_a$**H$_b$**), 3.97 – 3.79 (7H, m, BocNC**H$_2$**, ArC**H$_2$**N, C**H$_3$**), 3.01 – 2.84 (3H, m, BocNC**H$_2$**, NC**H**$_a$H$_b$), 2.67 – 2.54 (2H, m, NC**H**, NCH$_a$**H$_b$**), 1.46 (9H, s, 3 x C**H$_3$**); δ_C (100 MHz, $CDCl_3$) 171.6 (O**C**O), 154.7 (N**C**O), 142.2(Ar**C**), 138.9(Ar**C**H), 133.7 (Ar**C**), 132.0 (Ar**C**), 130.8 (Ar**C**H), 129.0 (Ar**C**), 128.5 (Ar**C**H), 127.9 (Ar**C**H), 106.7 (Ar**C**H), 80.4 (O**C**(CH$_3$)$_3$), 68.6 (O**C**H$_2$), 62.8 (N**C**H), 60.5 (Ar**C**H$_2$N), 55.0 (N**C**H$_2$), 44.7 (BocN**C**H$_2$), 43.0 (BocN**C**H$_2$), 37.8 (N**C**H$_3$). 28.5 (3 x **C**H$_3$); HRMS (ESI) calcd. for $C_{26}H_{31}N_4O_4^+$, 463.2340. Found: $[MH]^+$ 463.2356 (−3.4 ppm error).

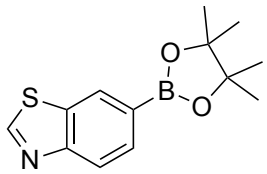
tert-Butyl 10-(4-fluoro-2-methoxyphenyl)-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[*f*] pyrazino[2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate (122)



tert-Butyl 10-bromo-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[*f*]pyrazino[2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate **104** (120 mg, 0.292 mmol) and (4-fluoro-2-methoxyphenyl)boronic acid (99.3 mg, 0.584 mmol) were dissolved in 1,4-dioxane (6.0 mL). Then Na_2CO_3 (92.7 mg, 0.875 mmol) which dissolved in water (3.0 mL) was added followed by Pd(dppf)Cl_2·CH_2Cl_2 (12.2 mg, 0.015 mmol) and the resulting mixture was purged with argon for 10 minutes. The mixture was stirred and heated at 50 °C for 18 hours under argon. After being allowed to cool to RT, water (10 mL) was added and the two layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 10 mL) and the combined organic phases were dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, 5:1 → 2:1 hexane : ethyl acetate) to afford the title compound (116 mg, 87%) as a white solid. R_f = 0.40 (2:1 hexane : ethyl acetate); m.p. 109–113 °C; ν_{max}/cm^{-1} (thin film) 2975, 1721, 1692, 1607, 1455, 1424, 1281, 1241, 1170, 1155, 1090, 1032, 955, 836, 768, 735; δ_H (400 MHz, $CDCl_3$) 7.48 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.43 (1H, dd, *J* = 8.0, 1.5 Hz, Ar**H**), 7.28 (1H, s, Ar**H**), 7.21 (1H, dd, *J* = 8.5, 6.5 Hz, Ar**H**), 6.74 – 6.64 (2H, m, 2 x Ar**H**), 4.16 (1H, dd, *J* = 13.0, 2.0 Hz, OC**H**$_a$H$_b$), 4.03 (1H, dd, *J* = 13.0, 4.0 Hz, OCH$_a$**H$_b$**), 3.98 – 3.72 (7H, m, BocNC**H$_2$**, ArC**H$_2$**N, OC**H$_3$**), 3.05 – 2.77 (3H, m, BocNC**H$_2$**, NC**H**$_a$H$_b$), 2.55 (2H, td, *J* = 11.5, 3.0 Hz, NC**H**, NCH$_a$**H$_b$**), 1.43 (9H, s, 3 x C**H$_3$**); δ_C (100 MHz, $CDCl_3$) 172.0 (O**C**O), 163.4 ($J_{F\text{-}C}$ = 246 Hz, N**C**O), 157.6($J_{F\text{-}C}$ = 9.8 Hz, Ar**C**), 154.5(Ar**C**), 140.7 (Ar**C**), 137.8 (Ar**C**), 131.4 ($J_{F\text{-}C}$ =

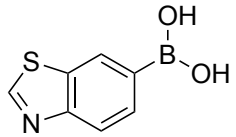
9.7 Hz, Ar**C**H), 129.9 (Ar**C**H), 129.1 (Ar**C**H), 128.9 (Ar**C**H), 127.3 (Ar**C**), 125.0 (J_{F-C} = 3.1 Hz, Ar**C**), 107.3 (J_{F-C} = 21.0 Hz, Ar**C**H), 99.5 (J_{F-C} = 25.6 Hz, Ar**C**H), 80.0 (O**C**$(CH_3)_3$), 68.5 (O**C**H_2), 62.6 (N**C**H), 60.5 (Ar**C**H_2N), 55.8 (O**C**H_3), 54.7 (N**C**H_2), 44.8 (BocN**C**H_2), 43.8 (BocN**C**H_2), 28.4 (3 x **C**H_3); HRMS (ESI) calcd. for $C_{25}H_{30}FN_2O_5^+$, 457.2133. Found: $[MH]^+$ 457.2130 (+0.7 ppm error).

6-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]thiazole (134)



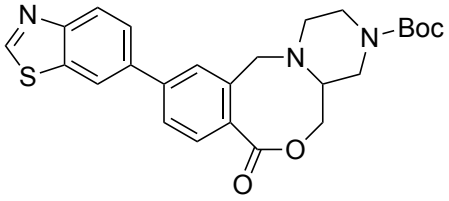
6-Bromobenzo[*d*]thiazole (800 mg, 3.74 mmol), bis(pinacolato)diboron (1.04 g, 4.11 mmol), Pd(dppf)Cl_2 (55.0 mg, 0.075 mmol) and potassium acetate (1.10 g, 11.2 mmol) were added to a round-bottomed flask. The round-bottomed flask was purged with argon and then 1,4-dioxane (20 mL) was added. The resulting mixture was stirred and heated at 60 °C for 18 hours under argon. After being allowed to cool to RT, the solids were removed by filtration and washed with dichloromethane (10 mL). The solvents were evaporated under reduced pressure to give the crude product. The crude product was purified by column chromatography (SiO_2, 10:1 hexane : ethyl acetate) to afford the title compound (898 mg, 92%) as a white solid. R_f = 0.32 (10:1 hexane : ethyl acetate); m.p. 93–95 °C; ν_{max}/cm^{-1} (thin film) 2977, 1596, 1474, 1441, 1386, 1345, 1287, 1143, 1095, 964, 894, 856, 674; δ_H (400 MHz, $CDCl_3$) 9.04 (1H, s, Ar**H**), 8.45 (1H, s, Ar**H**), 8.12 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.93 (1H, dd, *J* = 8.0, 1.0 Hz, Ar**H**), 1.36 (12H, s, 4 x C**H₃**); δ_C (100 MHz, $CDCl_3$) 155.5 (Ar**C**H), 155.3 (Ar**C**), 133.4 (Ar**C**), 132.1 (Ar**C**H), 129.1 (Ar**C**H), 123.0 (Ar**C**H), 84.24 (BO**C**), 25.0 (4 x **C**H_3); HRMS (ESI) calcd. for $C_{13}H_{17}BNO_2S^+$, 262.1068. Found: $[MH]^+$ 262.1070 (+0.1 ppm error). Characterisation data matched those reported in the literature.[60]

Benzo[*d*]thiazol-6-ylboronic acid (135)



6-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]thiazole **134** (400 mg, 1.53 mmol) was dissolved in 6 M HCl aqueous solution (4.0 mL). The solution was heated to reflux at 120 °C for 3 hours, after which the solution was concentrated in vacuo to give the crude product. The product was triturated in DCM (4.0 mL) for 20 mins, filtered and concentrated in vacuo to afford the title compound (314 mg, HCl salt, 95%) as a white solid; m.p. 267–273 °C; ν_{max}/cm^{-1} (thin film) 3347, 2635, 1596, 1397, 1337, 1310, 1191, 1119, 1057, 1035, 841, 768, 691, 668; δ_H (400 MHz, Methanol-*D4*) 10.24 (1H, s, Ar**H**), 8.55 (1H, s, Ar**H**), 8.07 (2H, s, 2 x Ar**H**); δ_C (101 MHz, Methanol-*D4*) 163.1 (Ar**C**H), 145.4 (Ar**C**), 135.1 (Ar**C**H), 132.4 (Ar**C**H), 130.2 (Ar**C**), 119.0 (Ar**C**H); HRMS (ESI) calcd. for $C_7H_7BNO_2S^+$, 180.0286. Found: $[MH]^+$ 180.0294 (−1.1 ppm error). Characterisation data matched those reported in the literature.[61]

***tert*-Butyl 10-(benzo[*d*]thiazol-6-yl)-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[*f*]pyrazino [2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate (120)**



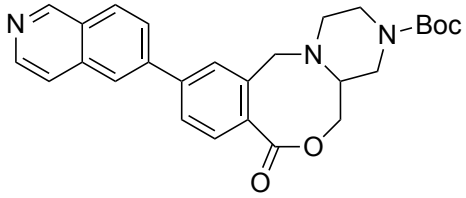
Method 1: *tert*-Butyl 10-bromo-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[*f*]pyrazino[2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate **104** (90.0 mg, 0.219 mmol) and benzo[d]thiazol-6-ylboronic acid **135** (HCl salt, 70.7 mg, 0.328 mmol) were dissolved in 1,4-dioxane (2.0 mL). Then Na_2CO_3 (69.5 mg, 0.656 mmol) which dissolved in water (1.0 mL) was added followed by $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (8.9 mg, 0.011 mmol) and the resulting mixture was purged with argon for 10 minutes. The mixture was stirred and heated at 50 °C for 18 hours under argon. After being allowed to cool to RT, water (10 mL) was added and the two layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 10 mL) and the combined organic phases were dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, 3:1 → 1:1 hexane : ethyl acetate) to afford the title compound (93.6 mg, 94%) as a yellow solid.

Method 2: *tert*-Butyl 10-bromo-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[*f*]pyrazino[2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate **104** (90.0 mg, 0.328 mmol) and 6-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[d]thiazole (85.7 mg, 0.393 mmol) were dissolved in 1,4-dioxane (2.0 mL). Then Na_2CO_3 (69.5 mg, 0.656 mmol) which dissolved in water (1.0 mL) was added followed by $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (8.9 mg, 0.011 mmol) and the resulting mixture was purged with argon for 10 minutes. The mixture was stirred and heated at 50 °C for 18 hours under argon. After being allowed to cool to RT, water (10 mL) was added and the two layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 10 mL) and the combined organic phases were dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, 3:1 → 1:1 hexane : ethyl acetate) to afford the title compound (98.7 mg, 99%) as a yellow solid.

Method 3: *tert*-Butyl 7-oxo-10-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,4a,5,7,12-hexahydro benzo[*f*]pyrazino[2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate **124** (90.0 mg, 0.196 mmol) and 6-bromobenzo[d]thiazole (84.1 mg, 0.393 mmol) were dissolved in 1,4-dioxane (4.0 mL). Then Na_2CO_3 (62.4 mg, 0.589 mmol) which dissolved in water (2.0 mL) was added followed by $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (8.0 mg, 0.010 mmol) and the resulting mixture was purged with argon for 10 minutes. The mixture was stirred and heated at 50 °C for 18 hours under argon. After being allowed to cool to RT, water (10 mL) was added and the two layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 10 mL) and the combined organic phases were dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, 3:1 → 1:1 hexane : ethyl acetate) to afford the title compound (58.7 mg, 64%) as a yellow solid.

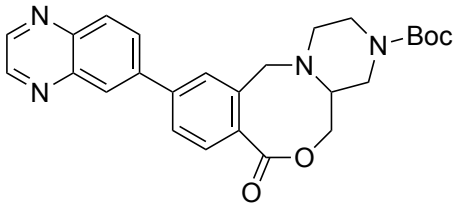
Data for **120**: R_f = 0.30 (1:1 hexane : ethyl acetate); m.p. 170–173 °C; ν_{max}/cm^{-1} (thin film) 2976, 1718, 1688, 1465, 1427, 1366, 1280, 1242, 1170, 1122, 1090, 1011, 868, 836, 732; δ_H (400 MHz, $CDCl_3$) 9.01 (1H, s, Ar**H**), 8.23 – 8.09 (2H, m, Ar**H**), 7.71 (1H, dt, *J* = 8.5, 2.5 Hz, Ar**H**), 7.58 (2H, d, *J* = 3.0 Hz, 2 x Ar**H**), 7.46 (1H, s, Ar**H**), 4.15 (1H, d, *J* = 13.0 Hz, OC**H$_a$**H$_b$), 4.05 (1H, dd, *J* = 13.0, 4.0 Hz, OCH$_a$**H$_b$**), 4.02 – 3.72 (4H, m, BocNC**H$_2$**, ArC**H$_2$**N), 3.08 – 2.79 (3H, m, BocNC**H$_2$**, NC**H$_a$**H$_b$), 2.58 (2H, td, *J* = 10.0, 6.0 Hz, NC**H**, NCH$_a$**H$_b$**), 1.44 (9H, s, 3 x C**H$_3$**); δ_C (100 MHz, $CDCl_3$) 171.8 (O**C**O), 154.8 (Ar**C**H), 154.5 (N**C**O), 153.0 (Ar**C**), 143.4 (Ar**C**), 138.8 (Ar**C**), 137.3 (Ar**C**), 134.7 (Ar**C**), 131.0 (Ar**C**H), 128.1 (Ar**C**), 127.4 (Ar**C**H), 126.8 (Ar**C**H), 125.8 (Ar**C**H), 123.9 (Ar**C**H), 120.4 (Ar**C**H), 80.2 (O**C**(CH$_3$)$_3$), 68.7 (O**C**H$_2$), 62.7 (N**C**H), 60.5 (Ar**C**H$_2$N), 55.0 (N**C**H$_2$), 45.7 (BocN**C**H$_2$), 43.9 (BocN**C**H$_2$), 28.4 (3 x **C**H$_3$); HRMS (ESI) calcd. for $C_{25}H_{28}N_3O_4S^+$, 466.1795. Found: $[MH]^+$ 466.1830 (−7.4 ppm error).

***tert*-Butyl 10-(isoquinolin-6-yl)-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[*f*]pyrazino[2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate (126)**



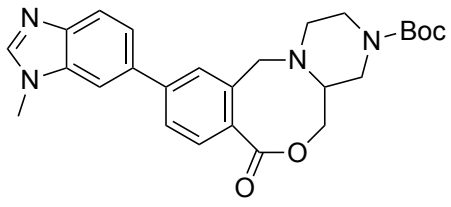
tert-Butyl 7-oxo-10-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,4a,5,7,12-hexahydro benzo[*f*]pyrazino[2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate **124** (90.0 mg, 0.196 mmol) and 6-bromoisoquinoline (81.8 mg, 0.393 mmol) were dissolved in 1,4-dioxane (4.0 mL). Then Na_2CO_3 (62.4 mg, 0.589 mmol) which dissolved in water (2.0 mL) was added followed by Pd(dppf)Cl_2·CH_2Cl_2 (8.0 mg, 0.010 mmol) and the resulting mixture was purged with argon for 10 minutes. The mixture was stirred and heated at 50 °C for 18 hours under argon. After being allowed to cool to RT, water (10 mL) was added and the two layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 10 mL) and the combined organic phases were dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, 2:1 → 0:1 hexane : ethyl acetate) to afford the title compound (58.0 mg, 64%) as a yellow solid. R_f = 0.34 (ethyl acetate); m.p. 216–219 °C; ν_{max}/cm^{-1} (thin film) 2976, 1718, 1687, 1421, 1279, 1243, 1169, 1122, 1090, 911, 829, 728; δ_H (400 MHz, $CDCl_3$) δ 9.31 (1H, s, Ar**H**), 8.58 (1H, d, *J* = 5.5 Hz, Ar**H**), 8.08 (1H, d, *J* = 8.5 Hz, Ar**H**), 8.02 (1H, d, *J* = 1.5 Hz, Ar**H**), 7.85 (1H, dd, *J* = 8.5, 1.5 Hz, Ar**H**), 7.75 – 7.64 (3H, m, 3 x Ar**H**), 7.56 (1H, d, *J* = 1.5 Hz, Ar**H**), 4.20 (1H, dd, *J* = 13.0, 2.0 Hz, OC**H$_a$**H$_b$), 4.09 (1H, dd, *J* = 13.0, 4.0 Hz, OCH$_a$**H$_b$**), 4.04 – 3.72 (4H, m, BocNC**H$_2$**, ArC**H$_2$**N), 3.11 – 2.82 (3H, m, BocNC**H$_2$**, NC**H$_a$**H$_b$), 2.70 – 2.55 (2H, m, NC**H**, NCH$_a$**H$_b$**), 1.47 (9H, s, 3 x C**H$_3$**); δ_C (100 MHz, $CDCl_3$) 171.7 (O**C**O), 154.6 (N**C**O), 152.4 (Ar**C**H), 143.8 (Ar**C**H), 141.5 (Ar**C**), 139.0 (Ar**C**), 136.0 (Ar**C**), 131.1 (Ar**C**H), 128.7 (Ar**C**), 128.5 (Ar**C**H), 128.0 (Ar**C**), 127.5 (Ar**C**H), 127.0 (Ar**C**H), 126.8 (Ar**C**H), 124.8 (Ar**C**H), 120.7 (Ar**C**H), 80.3 (O**C**(CH$_3$)$_3$), 68.7 (O**C**H$_2$), 62.8 (N**C**H), 60.6 (Ar**C**H$_2$N), 55.0 (N**C**H$_2$), 45.6 (BocN**C**H$_2$), 44.0 (BocN**C**H$_2$) 28.5 (3 x **C**H$_3$); HRMS (ESI) calcd. for $C_{27}H_{30}N_3O_4^+$, 460.2231. Found: $[MH]^+$ 460.2233 (−0.6 ppm error).

***tert*-Butyl 7-oxo-10-(quinoxalin-6-yl)-1,2,4a,5,7,12-hexahydrobenzo[*f*]pyrazino[2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate (127)**



tert-Butyl 7-oxo-10-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,4a,5,7,12-hexahydro benzo[*f*]pyrazino[2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate **124** (90.0 mg, 0.196 mmol) and 6-bromoquinoxaline (82.2 mg, 0.393 mmol) were dissolved in 1,4-dioxane (4.0 mL). Then Na_2CO_3 (62.4 mg, 0.589 mmol) which dissolved in water (2.0 mL) was added followed by $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (8.0 mg, 0.010 mmol) and the resulting mixture was purged with argon for 10 minutes. The mixture was stirred and heated at 50 °C for 18 hours under argon. After being allowed to cool to RT, water (10 mL) was added and the two layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 10 mL) and the combined organic phases were dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, 2:1 → 0:1 hexane : ethyl acetate) to afford the title compound (56.2 mg, 62%) as a yellow solid. R_f = 0.56 (ethyl acetate); m.p. 155–159 °C; ν_{max}/cm^{-1} (thin film) 2975, 1720, 1687, 1424, 1366, 1279, 1241, 1167, 1121, 1089, 1021, 866, 837, 764, 732; δ_H (400 MHz, $CDCl_3$) 8.89 – 8.78 (2H, m, 2 x Ar**H**), 8.28 (1H, d, *J* = 2.0 Hz, Ar**H**), 8.15 (1H, d, *J* = 8.5 Hz, Ar**H**), 7.99 (1H, dd, *J* = 8.5, 2.0 Hz, Ar**H**), 7.69 (1H, dd, *J* = 8.0, 2.0 Hz, Ar**H**), 7.61 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.57 (1H, d, *J* = 2.0 Hz, Ar**H**), 4.17 (1H, dd, *J* = 13.0, 2.0 Hz, OC**H$_a$**H$_b$), 4.06 (1H, dd, *J* = 13.0, 4.0 Hz, OCH$_a$**H$_b$**), 4.02 – 3.74 (4H, m, BocNC**H$_2$**, ArC**H$_2$**N), 3.01 – 2.86 (3H, m, BocNC**H$_2$**, NC**H$_a$**H$_b$), 2.60 (2H, td, *J* = 11.5, 3.0 Hz, NC**H**, NCH$_a$**H$_b$**), 1.43 (9H, s, 3 x C**H$_3$**); δ_C (100 MHz, $CDCl_3$) 171.6 (O**C**O), 154.6 (N**C**O), 145.7(Ar**C**H), 145.3(Ar**C**H), 143.1 (Ar**C**), 142.7 (Ar**C**), 142.4 (Ar**C**), 141.2 (Ar**C**), 139.0 (Ar**C**), 131.1 (Ar**C**H), 130.2 (Ar**C**H), 129.4 (Ar**C**H), 128.8 (Ar**C**), 127.5 (Ar**C**H), 127.5 (Ar**C**H), 126.9 (Ar**C**H), 80.2 (O**C**$(CH_3)_3$), 68.8 (O**C**H_2), 62.7 (N**C**H), 60.5 (Ar**C**H_2N), 55.0 (N**C**H_2), 45.7 (BocN**C**H_2), 43.9 (BocN**C**H_2), 28.4 (3 x **C**H_3); HRMS (ESI) calcd. for $C_{26}H_{28}N_4NaO_4^+$, 483.2003. Found: $[MH]^+$ 483.2015 (−2.5 ppm error).

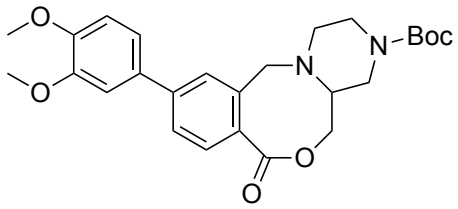
***tert*-Butyl 10-(1-methyl-1H-benzo[d]imidazol-6-yl)-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[*f*] pyrazino[2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate (128)**



tert-Butyl 7-oxo-10-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,4a,5,7,12-hexahydro benzo[*f*]pyrazino[2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate **124** (90.0 mg, 0.196 mmol) and 6-bromo-1-methyl-1H-benzo[d]imidazole (82.9 mg, 0.393 mmol) were dissolved in 1,4-dioxane (4.0 mL). Then Na_2CO_3 (62.4 mg, 0.589 mmol) which dissolved in water (2.0 mL) was added followed by $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (8.0 mg, 0.010 mmol) and the resulting mixture was purged

with argon for 10 minutes. The mixture was stirred and heated at 50 °C for 18 hours under argon. After being allowed to cool to RT, water (10 mL) was added and the two layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 10 mL) and the combined organic phases were dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, 10:1 → 3:1 dichloromethane : acetone) to afford the title compound (34.0 mg, 38%) as a brown solid. R_f = 0.21 (3:1 dichloromethane : acetone); m.p. 184–189 °C; ν_{max}/cm^{-1} (thin film) 3404, 2974, 1690, 1607, 1461, 1424, 1365, 1283, 1242, 1169, 1122, 1090, 1012, 820, 768; δ_H (400 MHz, $CDCl_3$) 7.93 (1H, s, Ar**H**), 7.84 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.60 (1H, dd, *J* = 8.0, 1.5 Hz, Ar**H**), 7.55 (2H, dd, *J* = 5.0, 3.0 Hz, 2 x Ar**H**), 7.50 (1H, dd, *J* = 8.0, 1.5 Hz, Ar**H**), 7.45 (1H, d, *J* = 1.5 Hz, Ar**H**), 4.16 (1H, dd, *J* = 13.0, 2.0 Hz, OC**H$_a$**H$_b$), 4.08 – 4.02 (1H, m, OCH$_a$**H$_b$**), 4.00 – 3.77 (7H, m, BocNC**H$_2$**, ArC**H$_2$**N, NC**H$_3$**), 2.91 – 2.84 (3H, m, BocNC**H$_2$**, NC**H$_a$**H$_b$), 2.58 (2H, td, *J* = 11.5, 3.0 Hz, NC**H**, NCH$_a$**H$_b$**), 1.44 (9H, s, 3 x **C**H$_3$); δ_C (100 MHz, $CDCl_3$) 172.0 (O**C**O), 154.6 (N**C**O), 144.9 (Ar**C**H), 144.6 (Ar**C**), 143.3 (Ar**C**), 138.7 (Ar**C**), 135.3 (Ar**C**), 135.1 (Ar**C**), 131.0 (Ar**C**H), 127.6 (Ar**C**), 127.4 (Ar**C**H), 126.9 (Ar**C**H), 122.3 (Ar**C**H), 120.6 (Ar**C**H), 108.3 (Ar**C**H), 80.3 (O**C**(CH$_3$)$_3$), 68.8 (O**C**H$_2$), 62.8 (N**C**H), 60.7 (Ar**C**H$_2$N), 55.0 (N**C**H$_2$), 44.9 (BocN**C**H$_2$), 44.1 (BocN**C**H$_2$), 31.4 (N**C**H$_3$), 28.4 (3 x **C**H$_3$); HRMS (ESI) calcd. for $C_{26}H_{31}N_4O_4^+$, 463.2340. Found: $[MH]^+$ 463.2356 (−3.4 ppm error).

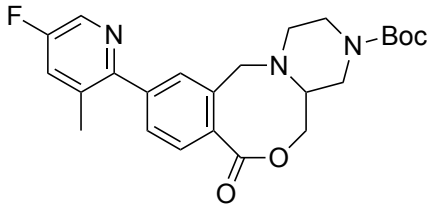
***tert*-Butyl 10-(3,4-dimethoxyphenyl)-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[*f*] pyrazino[2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate (129)**



tert-Butyl 7-oxo-10-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,4a,5,7,12-hexahydro benzo[*f*]pyrazino[2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate **124** (140 mg, 0.305 mmol) and 4-bromo-1,2-dimethoxybenzene (133 mg, 0.611 mmol) were dissolved in 1,4-dioxane (6.0 mL). Then Na_2CO_3 (97.1 mg, 0.916 mmol) which dissolved in water (3.0 mL) was added followed by Pd(dppf)Cl_2·CH_2Cl_2 (12.2 mg, 0.015 mmol) and the resulting mixture was purged with argon for 10 minutes. The mixture was stirred and heated at 50 °C for 18 hours under argon. After being allowed to cool to RT, water (10 mL) was added and the two layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 10 mL) and the combined organic phases were dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, 2:1 → 1:1 hexane : ethyl acetate) to afford the title compound (97.2 mg, 68%) as a white solid. R_f = 0.42 (1:1 hexane : ethyl acetate); m.p. 99–103 °C; ν_{max}/cm^{-1} (thin film) 2974, 2836, 1718, 1689, 1606, 1521, 1494, 1462, 1425, 1267, 1250, 1222, 1170, 1122, 1090, 1023, 915, 764, 729; δ_H (400 MHz, $CDCl_3$) 7.57 – 7.43 (2H, m, 2 x Ar**H**), 7.34 (1H, s, Ar**H**), 7.12 (1H, dd, *J* = 8.5, 2.0 Hz, Ar**H**), 7.06 (1H, d, *J* = 2.0 Hz, Ar**H**), 6.91 (1H, d, *J* = 8.5 Hz, Ar**H**), 4.13 (1H, dd, *J* = 13.0, 2.0 Hz, OC**H$_a$**H$_b$), 4.02 (1H, dd, *J* = 13.0, 4.0 Hz, OCH$_a$**H$_b$**), 3.97 – 3.73 (10H, m, 2 x OC**H$_3$**, BocNC**H$_2$**, ArC**H$_2$**N), 3.06 – 2.79 (3H, m, BocNC**H$_2$**, NC**H$_a$**H$_b$), 2.61 – 2.47 (2H, m, NC**H**, NCH$_a$**H$_b$**), 1.43 (9H, s, 3 x C**H$_3$**); δ_C (100

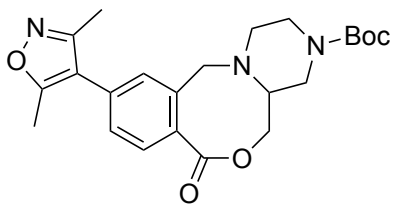
MHz, $CDCl_3$) 171.9 (O**C**O), 154.5 (N**C**O), 149.3 (Ar**C**), 149.3 (Ar**C**), 143.9 (Ar**C**), 138.5 (Ar**C**), 132.4 (Ar**C**), 130.8 (Ar**C**H), 127.2 (Ar**C**), 126.5 (Ar**C**H), 126.1 (Ar**C**H), 119.7 (Ar**C**H), 111.5 (Ar**C**H), 110.3 (Ar**C**H), 80.1 (O**C**$(CH_3)_3$), 68.6 (O**C**H_2), 62.7 (N**C**H), 60.5 (Ar**C**H_2N), 56.0 (O**C**H_3), 56.0 (O**C**H_3), 54.9 (N**C**H_2), 44.8 (BocN**C**H_2), 43.0 (BocN**C**H_2), 28.4 (3 x **C**H_3); HRMS (ESI) calcd. for $C_{26}H_{33}N_2O_6^+$, 469.2333. Found: $[MH]^+$ 469.2337 (−0.8 ppm error).

***tert*-Butyl 10-(5-fluoro-3-methylpyridin-2-yl)-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[*f*] pyrazino[2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate (130)**



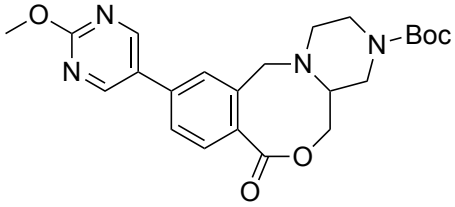
tert-Butyl 7-oxo-10-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,4a,5,7,12-hexahydro benzo[*f*]pyrazino[2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate **124** (140 mg, 0.305 mmol) and 2-bromo-5-fluoro-3-methylpyridine (116 mg, 0.611 mmol) were dissolved in 1,4-dioxane (6.0 mL). Then Na_2CO_3 (97.1 mg, 0.916 mmol) which dissolved in water (3.0 mL) was added followed by Pd(dppf)Cl_2·CH_2Cl_2 (12.2 mg, 0.015 mmol) and the resulting mixture was purged with argon for 10 minutes. The mixture was stirred and heated at 50 °C for 18 hours under argon. After being allowed to cool to RT, water (10 mL) was added and the two layers were separated. The aqueous layer was extracted with dichloromethane (3 x 10 mL) and the combined organic phases were dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, 3:1 → 1:1 hexane : ethyl acetate) to afford the title compound (67.0 mg, 50%) as a white solid. R_f = 0.47 (1:1 hexane : ethyl acetate); m.p. 126–128 °C; ν_{max}/cm^{-1} (thin film) 2975, 2929, 1722, 1691, 1461, 1427, 1366, 1276, 1242, 1171, 1122, 1090, 1011, 886, 735; δ_H (400 MHz, $CDCl_3$) 8.36 (1H, d, *J* = 3.0 Hz, Ar**H**), 7.54 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.42 (1H, dd, *J* = 8.0, 1.5 Hz, Ar**H**), 7.37 – 7.30 (2H, m, 2 x Ar**H**), 4.16 (1H, dd, *J* = 13.0, 2.0 Hz, OC**H**$_a$H$_b$), 4.01 (1H, dd, *J* = 13.0, 4.0 Hz, OCH$_a$**H**$_b$), 3.98 – 3.74 (4H, m, BocNC**H**$_2$, ArC**H**$_2$N), 3.08 – 2.79 (3H, m, BocNC**H**$_2$, NC**H**$_a$H$_b$), 2.63 – 2.48 (2H, m, NC**H**, NCH$_a$**H**$_b$), 2.34 (3H, s, ArC**H**$_3$), 1.43 (9H, s, 3 x **C**H_3); δ_C (100 MHz, $CDCl_3$) 171.9 (O**C**O), 158.8 (d, J_{F-C} = 257 Hz, N**C**O), 154.6 (Ar**C**), 153.4 (d, J_{F-C} = 3.7 Hz, Ar**C**), 142.5 (Ar**C**), 138.5 (Ar**C**), 135.3 (d, J_{F-C} = 22.9 Hz, Ar**C**H), 133.0 (d, J_{F-C} = 3.9 Hz, Ar**C**), 130.1 (Ar**C**H), 128.8 (Ar**C**H), 128.6 (Ar**C**), 128.2 (Ar**C**H), 125.2 (d, J_{F-C} = 17.9 Hz, Ar**C**H), 80.2 (O**C**$(CH_3)_3$), 68.4 (O**C**H_2), 62.7 (N**C**H), 60.6 (Ar**C**H_2N), 54.9 (N**C**H_2), 44.8 (BocN**C**H_2), 43.8 (BocN**C**H_2), 28.4 (3 x **C**H_3), 20.1 (**C**H_3); HRMS (ESI) calcd. for $C_{24}H_{29}FN_3O_4^+$, 442.2137. Found: $[MH]^+$ 442.2137 (−0.2 ppm error).

***tert*-Butyl 10-(3,5-dimethylisoxazol-4-yl)-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[*f*]pyrazino [2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate (131)**



tert-Butyl 7-oxo-10-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,4a,5,7,12-hexahydro benzo[*f*]pyrazino[2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate **124** (140 mg, 0.305 mmol) and 4-bromo-3,5-dimethylisoxazole (108 mg, 0.611 mmol) were dissolved in 1,4-dioxane (6.0 mL). Then Na_2CO_3 (97.1 mg, 0.916 mmol) which dissolved in water (3.0 mL) was added followed by Pd(dppf)Cl_2·CH_2Cl_2 (12.2 mg, 0.015 mmol) and the resulting mixture was purged with argon for 10 minutes. The mixture was stirred and heated at 50 °C for 18 hours under argon. After being allowed to cool to RT, water (10 mL) was added and the two layers were separated. The aqueous layer was extracted with dichloromethane (3 x 10 mL) and the combined organic phases were dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, 3:1 → 1:1 hexane : ethyl acetate) to afford the title compound (35.3 mg, 27%) as a white solid. R_f = 0.16 (2:1 hexane : ethyl acetate); m.p. 111–115 °C; ν_{max}/cm^{-1} (thin film) 2924, 2853, 1721, 1692, 1456, 1425, 1366, 1281, 1241, 1171, 1123, 1091, 1048, 1014, 873, 756; δ_H (400 MHz, $CDCl_3$) δ 7.58 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.24 (1H, dd, *J* = 8.0, 2.0 Hz, Ar**H**), 7.08 (1H, d, *J* = 2.0 Hz, Ar**H**), 4.20 (1H, dd, *J* = 13.0, 2.0 Hz, OC**H**$_a$H$_b$), 4.06 (1H, dd, *J* = 13.0, 4.0 Hz, OCH$_a$**H**$_b$), 4.00 – 3.78 (4H, m, BocNC**H**$_2$, ArC**H**$_2$N), 3.06 – 2.86 (3H, m, BocNC**H**$_2$, NC**H**$_a$H$_b$), 2.66 – 2.55 (2H, m, NC**H**, NCH$_a$**H**$_b$), 2.42 (3H, s, C**H**$_3$), 2.28 (3H, s, C**H**$_3$), 1.46 (9H, s, 3 x C**H**$_3$); δ_C (100 MHz, $CDCl_3$) 171.8 (O**C**O), 165.9 (N**C**O), 158.4 (Ar**C**), 154.7 (Ar**C**), 138.9 (Ar**C**), 133.8 (Ar**C**), 131.0 (Ar**C**H), 128.6 (Ar**C**H), 128.5 (Ar**C**H), 128.3 (Ar**C**), 111.7 (Ar**C**), 80.4 (O**C**(CH_3)$_3$), 68.6 (O**C**H_2), 62.8 (N**C**H), 60.6 (Ar**C**H_2N), 54.9 (N**C**H_2), 44.9 (BocN**C**H_2), 43.2 (BocN**C**H_2), 28.5 (3 x **C**H_3), 11.8 (**C**H_3), 11.0 (**C**H_3); HRMS (ESI) calcd. for $C_{23}H_{29}N_3NaO_5^+$, 450.1999. Found: $[MH]^+$ 450.2010 (−2.3 ppm error).

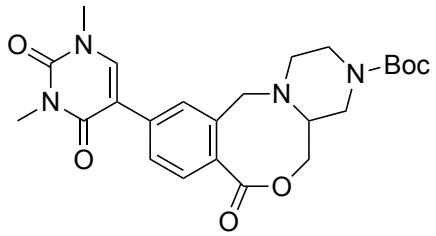
***tert*-Butyl 10-(2-methoxypyrimidin-5-yl)-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[*f*]pyrazino [2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate (132)**



tert-Butyl 7-oxo-10-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,4a,5,7,12-hexahydro benzo[*f*]pyrazino[2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate **124** (140 mg, 0.305 mmol) and 5-bromo-2-methoxypyrimidine (116 mg, 0.611 mmol) were dissolved in 1,4-dioxane (6.0 mL). Then Na_2CO_3 (97.1 mg, 0.916 mmol) which dissolved in water (3.0 mL) was added followed by Pd(dppf)Cl_2·CH_2Cl_2 (12.2 mg, 0.015 mmol) and the resulting mixture was purged with argon for 10 minutes. The mixture was stirred and heated at 50 °C for 18 hours under argon. After being allowed to cool to RT, water (10 mL) was added and the two layers were separated. The aqueous layer was extracted with dichloromethane (3 x 10 mL) and the combined organic phases were dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, 1:1 → 1:2 hexane : ethyl acetate) to afford the title compound (35.0 mg, 26%) as a yellow solid. R_f = 0.31 (1:2 hexane : ethyl acetate); m.p. 104–107 °C; ν_{max}/cm^{-1} (thin film) 2975, 2932, 1720, 1693, 1596, 1473, 1411, 1334, 1281, 1243, 1170, 1124, 1091, 1034, 802, 766; δ_H (400 MHz, $CDCl_3$) 8.72 (2H, s, 2 x Ar**H**), 7.60 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.49 (1H, dd, *J* = 8.0, 2.0 Hz, Ar**H**), 7.35 (1H, d, *J* =

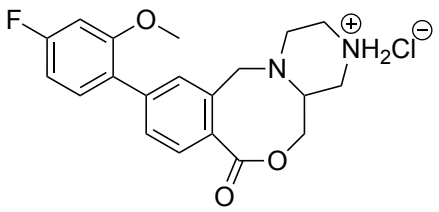
2.0 Hz, Ar**H**), 4.16 (1H, dd, *J* = 13.0, 2.0 Hz, OC**H**$_a$H$_b$), 4.05 (4H, s, OC**H$_3$**, OCH$_a$**H$_b$**), 3.96 – 3.78 (4H, m, BocNC**H$_2$**, ArC**H$_2$**N), 3.08 – 2.79 (3H, m, BocNC**H$_2$**, NC**H$_a$**H$_b$), 2.60 (2H, ddd, *J* = 15.0, 9.0, 3.5 Hz, NC**H**, NCH$_a$**H$_b$**), 1.45 (9H, s, 3 x C**H$_3$**); δ_C (100 MHz, $CDCl_3$) 171.5 (O**C**O), 165.6 (N**C**O), 157.5 (Ar**C**H), 157.0 (Ar**C**H), 154.6 (Ar**C**), 139.3 (Ar**C**), 137.5 (Ar**C**), 131.4 (Ar**C**H), 128.8 (Ar**C**), 127.0 (Ar**C**), 126.2 (Ar**C**H), 125.9 (Ar**C**H), 80.3 (O**C**$(CH_3)_3$), 68.7 (O**C**H$_2$), 62.8 (N**C**H), 60.5 (Ar**C**H$_2$N), 55.4 (O**C**H$_3$), 55.1 (N**C**H$_2$), 45.6 (BocN**C**H$_2$), 43.9 (BocN**C**H$_2$), 28.5 (3 x **C**H$_3$); HRMS (ESI) calcd. for $C_{23}H_{28}N_4NaO_5^+$, 463.1952. Found: $[MH]^+$ 463.1954 (−0.5 ppm error).

***tert*-Butyl 10-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[*f*]pyrazino[2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate (133)**



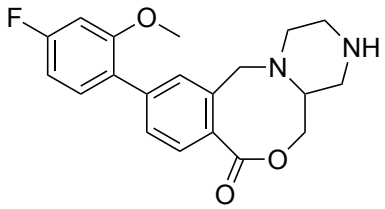
tert-Butyl 7-oxo-10-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,4a,5,7,12-hexahydro benzo[*f*]pyrazino[2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate **124** (140 mg, 0.305 mmol) and 5-bromo-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (134 mg, 0.611 mmol) were dissolved in 1,4-dioxane (6.0 mL). Then Na_2CO_3 (97.1 mg, 0.916 mmol) which dissolved in water (3.0 mL) was added followed by Pd(dppf)Cl_2·CH_2Cl_2 (12.2 mg, 0.015 mmol) and the resulting mixture was purged with argon for 10 minutes. The mixture was stirred and heated at 50 °C for 18 hours under argon. After being allowed to cool to RT, water (10 mL) was added and the two layers were separated. The aqueous layer was extracted with dichloromethane (3 x 10 mL) and the combined organic phases were dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, 1:1 → 0:1 hexane : ethyl acetate) to afford the title compound (54.9 mg, 38%) as a brown solid. R_f = 0.30 (ethyl acetate); m.p. 117–123 °C; ν_{max}/cm^{-1} (thin film) 2976, 1698, 1650, 1455, 1429, 1365, 1281, 1243, 1170, 1122, 1021, 918, 756, 730; δ_H (400 MHz, $CDCl_3$) 7.51 – 7.33 (4H, m, 4 x Ar**H**), 4.11 (1H, d, *J* = 13.0 Hz, OC**H**$_a$H$_b$), 3.97 (1H, dd, *J* = 13.0, 4.0 Hz, OCH$_a$**H$_b$**), 3.94 – 3.68 (4H, m, BocNC**H$_2$**, ArC**H$_2$**N), 3.47 (3H, s, NC**H$_3$**), 3.37 (3H, s, NC**H$_3$**), 3.02 – 2.76 (3H, m, BocNC**H$_2$**, NC**H$_a$**H$_b$), 2.53 (2H, td, *J* = 12.5, 4.5 Hz, NC**H**, NCH$_a$**H$_b$**), 1.42 (9H, s, 3 x C**H$_3$**); δ_C (100 MHz, $CDCl_3$) 171.8 (O**C**O), 162.1 (N**C**O), 154.5 (Ar**C**), 151.2 (Ar**C**), 141.5 (Ar**C**H), 138.2 (Ar**C**), 136.0 (Ar**C**), 130.4 (Ar**C**H), 128.1 (Ar**C**H), 128.1 (Ar**C**), 127.1 (Ar**C**H), 112.6 (Ar**C**), 80.2 (O**C**$(CH_3)_3$), 68.5 (O**C**H$_2$), 62.6 (N**C**H), 60.4 (Ar**C**H$_2$N), 54.8 (N**C**H$_2$), 44.7 (BocN**C**H$_2$), 43.8 (BocN**C**H$_2$), 37.3 (N**C**H$_3$), 28.4 (3 x **C**H$_3$), 28.3 (N**C**H$_3$); HRMS (ESI) calcd. for $C_{24}H_{31}N_4O_6^+$, 471.2238. Found: $[MH]^+$ 471.2243 (−1.1 ppm error).

10-(4-Fluoro-2-methoxyphenyl)-7-oxo-1,2,3,4,4a,5,7,12-octahydrobenzo[*f*]pyrazino [2,1-*c*][1,4]oxazocin-3-ium chloride (136)



tert-Butyl 10-(4-fluoro-2-methoxyphenyl)-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[*f*]pyrazino [2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate **122** (50 mg, 0.110 mmol) was dissolved in 4 M HCl in dioxane (4.0 mL). The solution was stirred at room temperature for 1 hour, after which the solution was concentrated in vacuo to afford the title compound (49 mg, 116%) as a white solid. R_f = 0 (10:1 dichloromethane : methanol); m.p. 201–205 °C; ν_{max}/cm^{-1} (thin film) 3387, 2943, 1711, 1607, 1452, 1281, 1154, 1085, 1030, 956, 837; δ_H (400 MHz, Methanol-*D*$_4$) 7.56 (1H, dd, *J* = 8.0, 1.5 Hz, Ar**H**), 7.53 – 7.47 (2H, m, 2 x Ar**H**), 7.36 (1H, dd, *J* = 8.5, 6.5 Hz, Ar**H**), 6.92 (1H, dd, *J* = 11.0, 2.5 Hz, Ar**H**), 6.79 (1H, td, *J* = 8.5, 2.5 Hz, Ar**H**), 4.38 (1H, dd, *J* = 13.5, 2.0 Hz, OC**H$_a$**H$_b$), 4.23 – 4.05 (3H, m, OCH$_a$**H$_b$**, ArC**H$_2$**N), 3.83 (3H, s, OC**H$_3$**), 3.45 (2H, dd, *J* = 12.5, 3.0 Hz, 2 x NC**H$_a$**H$_b$), 3.39 (1H, d, *J* = 13.0 Hz, NC**H$_a$**H$_b$), 3.24 (2H, td, *J* = 12.5, 4.0 Hz, 2 x NCH$_a$**H$_b$**), 3.15 – 2.99 (2H, m, NC**H**, NCH$_a$**H$_b$**); ^{13}C NMR signal is too weak to distinguish because the compound is difficult to dissolve in the solvent; HRMS (ESI) calcd. for $C_{20}H_{22}FN_2O_3^+$, 357.1609. Found: $[MH]^+$ 357.1617 (−2.2 ppm error).

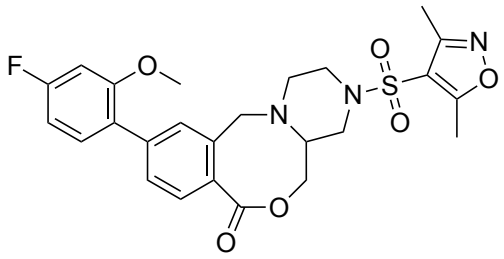
10-(4-Fluoro-2-methoxyphenyl)-1,2,3,4,4a,5-hexahydrobenzo[*f*]pyrazino[2,1-*c*][1,4] oxazocin-7(12*H*)-one (137)



tert-Butyl 10-(4-fluoro-2-methoxyphenyl)-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[*f*]pyrazino [2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate **122** (50 mg, 0.110 mmol) was dissolved in 4 M HCl in dioxane (4.0 mL). The solution was stirred at room temperature for 1 hour, after which the solution was concentrated in vacuo to yield the salt product **136**. Sodium bicarbonate solution was added while stirring until the pH is adjusted to 7-8. The aqueous layer was extracted with ethyl acetate (3 x 10 mL) and the combined organic phases were dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, 50:1 → 10:1 dichloromethane : methanol) to afford the title compound (29.0 mg, 74%) as a white solid. R_f = 0.10 (10:1 dichloromethane : methanol); m.p. 206–210 °C; ν_{max}/cm^{-1} (thin film) 2949, 2760, 1715, 1607, 1455, 1378, 1347, 1278, 1231, 1148, 1098, 1031, 955, 829, 803, 765; δ_H (400 MHz, $CDCl_3$) 7.54 – 7.47 (1H, m, Ar**H**), 7.44 (1H, dd, *J* = 8.0, 1.5 Hz, Ar**H**), 7.31 – 7.20 (2H, m, 2 x Ar**H**), 6.77 – 6.65 (2H, m, 2 x Ar**H**), 5.59 (1H, s, N**H**), 4.22 (1H, dd, *J* = 13.0, 2.0 Hz, OC**H$_a$**H$_b$), 4.04 (1H, dd, *J* = 13.0, 3.5 Hz, OCH$_a$**H$_b$**), 3.93 – 3.80 (2H, m, ArC**H$_2$**N), 3.79 (3H, s, OC**H$_3$**), 3.17 – 3.05 (2H, m, 2 x NC**H$_a$**H$_b$),

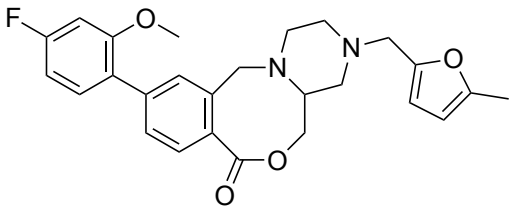
3.04 – 2.87 (3H, m, NC**H**$_a$H$_b$, 2 x NCH$_a$**H$_b$**), 2.86 – 2.65 (2H, m, NC**H**, NCH$_a$**H$_b$**); δ_C (100 MHz, $CDCl_3$) 172.2 (O**C**O), 163.6 (d, J_{F-C} = 246 Hz, Ar**C**), 157.7 (d, J_{F-C} = 10.0 Hz, Ar**C**), 140.8 (Ar**C**), 138.0 (Ar**C**), 131.5 (d, J_{F-C} = 10.1 Hz, Ar**C**H), 130.2 (Ar**C**H), 129.0 (Ar**C**H), 128.8 (Ar**C**H), 127.2 (Ar**C**), 125.1 (d, J_{F-C} = 3.5 Hz, Ar**C**), 107.4 (d, J_{F-C} = 21.0 Hz, Ar**C**H), 99.6 (d, J_{F-C} = 25.7 Hz, Ar**C**H), 68.3 (O**C**H$_2$), 62.5 (N**C**H), 60.9 (Ar**C**H$_2$N), 55.9 (O**C**H$_3$), 54.3 (N**C**H$_2$), 46.5 (N**C**H$_2$), 45.0 (N**C**H$_2$); HRMS (ESI) calcd. for $C_{20}H_{22}FN_2O_3^+$, 357.1609. Found: $[MH]^+$ 357.1613 (−1.2 ppm error).

3-((3,5-Dimethylisoxazol-4-yl)sulfonyl)-10-(4-fluoro-2-methoxyphenyl)-1,2,3,4,4a,5-hexahydrobenzo[*f*]pyrazino[2,1-*c*][1,4]oxazocin-7(12*H*)-one (141)



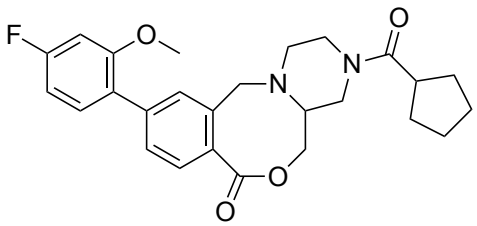
tert-Butyl 10-(4-fluoro-2-methoxyphenyl)-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[*f*]pyrazino [2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate **122** (50 mg, 0.110 mmol) was dissolved in 4 M HCl in dioxane (4.0 mL). The solution was stirred at room temperature for 1 hour, after which the solution was concentrated in vacuo to yield the salt product **136**. This salt was dissolved in anhydrous DCM (3.0 mL) at room temperature and the solution was cooled to 0 °C using an ice bath. Triethylamine (0.05 mL, 0.329 mmol) was added dropwise, followed by 3,5-dimethylisoxazole-4-sulfonyl chloride (26.8 mg, 0.137 mmol) and DMAP (1.4 mg, 0.011 mmol). The solution was allowed to gradually warm to room temperature while being stirred for 18 hours. The solution was diluted with ethyl acetate (10 mL) and washed with brine (10 mL). The aqueous layer was then extracted with ethyl acetate (3 x 10 mL). The organic layers were then combined, dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, 2:1 → 1:1 hexane : ethyl acetate) to afford the title compound (54.4 mg, 96%) as a white solid. R_f = 0.55 (1:1 hexane : ethyl acetate); m.p. 177–183 °C; ν_{max}/cm^{-1} (thin film) 2855, 1710, 1597, 1454, 1407, 1325, 1308, 1281, 1268, 1185, 1152, 1123, 1109, 1090, 1025, 975, 952, 913, 831, 766, 690, 664; δ_H (400 MHz, $CDCl_3$) 7.50 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.46 (1H, dd, *J* = 8.0, 1.5 Hz, Ar**H**), 7.27 (1H, d, *J* = 1.5 Hz, Ar**H**), 7.22 (1H, dd, *J* = 8.5, 6.5 Hz, Ar**H**), 6.77 – 6.68 (2H, m, 2 x Ar**H**), 4.25 (1H, d, *J* = 13.0 Hz, OC**H$_a$**H$_b$), 4.05 (1H, dd, *J* = 13.0, 3.0 Hz, OCH$_a$**H$_b$**), 3.88 (2H, d, *J* = 3.0 Hz, ArC**H$_2$**N), 3.79 (3H, s, OC**H**$_3$), 3.65 – 3.57 (1H, m, NC**H$_a$**H$_b$), 3.54 (1H, dd, *J* = 8.0, 2.0 Hz, NC**H$_a$**H$_b$), 3.05 – 2.96 (1H, m, NC**H$_a$**H$_b$), 2.85 – 2.69 (4H, m, 3 x NCH$_a$**H$_b$**, NC**H**), 2.63 (3H, s, C**H**$_3$), 2.38 (3H, s, C**H**$_3$); δ_C (100 MHz, $CDCl_3$) 172.9 (d, J_{F-C} = 218 Hz, O**C**O), 163.6 (d, J_{F-C} = 252 Hz, Ar**C**), 157.9 (Ar**C**), 157.6 (d, J_{F-C} = 9.6 Hz, Ar**C**), 141.0 (Ar**C**), 137.4 (Ar**C**), 131.5 (d, J_{F-C} = 9.9 Hz, Ar**C**H), 130.3 (Ar**C**H), 129.1 (Ar**C**H), 128.7 (Ar**C**H), 126.9 (Ar**C**), 125.0 (Ar**C**), 124.9 (Ar**C**), 113.2 (Ar**C**), 107.4 (d, J_{F-C} = 21.1 Hz, Ar**C**H), 99.7 (d, J_{F-C} = 25.9 Hz, Ar**C**H), 67.9 (O**C**H$_2$), 62.3 (N**C**H), 60.3 (Ar**C**H$_2$N), 55.9 (O**C**H$_3$), 54.2 (N**C**H$_2$), 47.1 (N**C**H$_2$), 45.3 (N**C**H$_2$), 13.1 (**C**H$_3$), 11.5 (**C**H$_3$); HRMS (ESI) calcd. for $C_{25}H_{27}FN_3O_6S^+$, 516.1599. Found: $[MH]^+$ 516.1617 (−3.4 ppm error).

10-(4-Fluoro-2-methoxyphenyl)-3-((5-methylfuran-2-yl)methyl)-1,2,3,4,4a,5-hexahydrobenzo[*f*]pyrazino[2,1-*c*][1,4]oxazocin-7(12*H*)-one (145)



tert-Butyl 10-(4-fluoro-2-methoxyphenyl)-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[*f*]pyrazino [2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate **122** (80 mg, 0.175 mmol) was dissolved in 4 M HCl in dioxane (6.0 mL). The solution was stirred at room temperature for 1 hour, after which the solution was concentrated in vacuo to yield the salt product **136**. This salt was dissolved in anhydrous THF (2.0 mL), 5-methylfuran-2-carbaldehyde (19.3 mg, 0.175 mmol) was added, followed by acetic acid (0.01 mL, 0.175 mmol) and the solution was stirred for 10 minutes. Then sodium triacetoxyborohydride (74.3 mg, 0.350 mmol) was added and the reaction mixture was stirred at room temperature for 18 hours. The mixture was diluted with ethyl acetate (10 mL) and washed with sodium bicarbonate solution (10 mL). The aqueous layer was then extracted with ethyl acetate (3 x 10 mL). The organic layers were then combined, dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, 2:1 → 1:1 hexane : ethyl acetate) to afford the title compound (75.2 mg, 95%) as a white solid. R_f = 0.16 (1:1 hexane : ethyl acetate); m.p. 97–101 °C; v_{max}/cm^{-1} (thin film) 1718, 1606, 1512, 1488, 1458, 1278, 1153, 1114, 1025, 955, 836, 735; δ_H (400 MHz, $CDCl_3$) 7.49 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.43 (1H, dd, *J* = 8.0, 1.5 Hz, Ar**H**), 7.30 – 7.20 (2H, m, 2 x Ar**H**), 6.76 – 6.67 (2H, m, 2 x Ar**H**), 6.06 (1H, d, *J* = 3.0 Hz, Ar**H**), 5.87 (1H, dd, *J* = 2.5, 1.5 Hz, Ar**H**), 4.15 (1H, dd, *J* = 13.0, 2.0 Hz, OC**H$_a$**H$_b$), 4.01 (1H, dd, *J* = 13.0, 3.5 Hz, OCH$_a$**H$_b$**), 3.89 – 3.76 (5H, m, ArC**H$_2$**N, OC**H$_3$**), 3.47 (2H, s, 2 x NC**H$_a$**H$_b$), 2.89 (1H, dt, *J* = 12.0, 3.0 Hz, NC**H$_a$**H$_b$), 2.83 – 2.66 (4H, m, NC**H$_a$**H$_b$, NC**H**, 2 x NCH$_a$**H$_b$**), 2.36 – 2.17 (5H, m, 2 x NCH$_a$**H$_b$**, C**H$_3$**); δ_C (100 MHz, $CDCl_3$) 172.4 (O**C**O), 163.5 (d, J_{F-C} = 245 Hz, Ar**C**), 157.6 (d, J_{F-C}= 9.6 Hz, Ar**C**), 152.2 (Ar**C**), 149.2 (Ar**C**), 140.6 (Ar**C**), 138.1 (Ar**C**), 131.5 (d, J_{F-C} = 9.9 Hz, Ar**C**H), 130.1 (Ar**C**H), 128.9 (Ar**C**H), 128.8 (Ar**C**H), 127.5 (Ar**C**), 125.2 (d, J_{F-C} = 3.0 Hz, Ar**C**), 110.1 (Ar**C**H), 107.4 (d, J_{F-C} = 21.1 Hz, Ar**C**H), 106.1 (Ar**C**H), 99.6 (d, J_{F-C} = 25.7 Hz, Ar**C**H), 69.2 (O**C**H$_2$), 62.8 (N**C**H), 60.5 (Ar**C**H$_2$N), 55.8 (O**C**H$_3$), 55.1 (N**C**H$_2$), 54.9 (N**C**H$_2$), 54.8 (N**C**H$_2$), 52.7 (N**C**H$_2$), 13.8 (**C**H$_3$); HRMS (ESI) calcd. for $C_{26}H_{28}FN_2O_4^+$, 451.2028. Found: $[MH]^+$ 451.2031 (−0.8 ppm error).

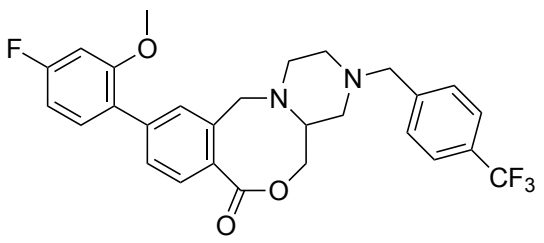
3-(Cyclopentanecarbonyl)-10-(4-fluoro-2-methoxyphenyl)-1,2,3,4,4a,5hexahydrobenzo [*f*]pyrazino[2,1-*c*][1,4]oxazocin-7(12*H*)-one (149)



tert-Butyl 10-(4-fluoro-2-methoxyphenyl)-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[*f*]pyrazino [2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate **122** (50 mg, 0.110 mmol) was dissolved in 4 M HCl in

dioxane (4.0 mL). The solution was stirred at room temperature for 1 hour, after which the solution was concentrated in vacuo to yield the salt product **136**. This salt was dissolved in anhydrous DCM (3.0 mL) at room temperature and the solution was cooled to 0 °C using an ice bath. Triethylamine (0.05 mL, 0.329 mmol) was added dropwise, followed by cyclopentane carbonyl chloride (18.2 mg, 0.137 mmol) and DMAP (1.4 mg, 0.011 mmol). The solution was allowed to gradually warm to room temperature while being stirred for 18 hours. The solution was diluted with ethyl acetate (10 mL) and washed with brine (10 mL). The aqueous layer was then extracted with ethyl acetate (3 x 10 mL). The organic layers were then combined, dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, 1:1 hexane : ethyl acetate) to afford the title compound (47.5 mg, 95%) as a white solid, which exists in solution as a roughly 1:1 mixture of amide rotamers. R_f = 0.37 (1:1 hexane : ethyl acetate); m.p. 90–98 °C; ν_{max}/cm^{-1} (thin film) 2951, 1719, 1636, 1607, 1450, 1279, 1228, 1153, 1112, 1091, 954, 836, 734; δ_H (400 MHz, $CDCl_3$) 7.51 (1H, dd, *J* = 8.0, 2.5 Hz, Ar**H**), 7.45 (1H, dd, *J* = 8.0, 2.0 Hz, Ar**H**), 7.28 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.23 (1H, t, *J* = 7.5 Hz, Ar**H**), 6.81 – 6.63 (2H, m, 2 x Ar**H**), 4.54 – 4.37 (1H, m, NC**H$_a$**H$_b$), 4.24 (1H, ddd, *J* = 13.0, 6.5, 2.0 Hz, OC**H$_a$**H$_b$), 4.13 – 4.01 (1H, m, OCH$_a$**H$_b$**), 3.92 – 3.65 (6H, m, ArC**H$_2$**N, OC**H$_3$**, NC**H$_a$**H$_b$), 3.28 (1H, tt, *J* = 13.0, 2.5 Hz, NCH$_a$**H$_b$**), 2.95 (1H, tt, *J* = 10.5, 2.5 Hz, NC**H$_a$**H$_b$), 2.92 – 2.74 (2H, m, C**H**, NCH$_a$**H$_b$**), 2.67 – 2.46 (2H, m, NC**H**, NCH$_a$**H$_b$**), 1.91 – 1.64 (6H, m, 3 x C**H$_2$**), 1.63 – 1.47 (2H, m, C**H$_2$**); δ_C (100 MHz, $CDCl_3$) 174.7 (O**C**O, rotamer A), 174.5 (O**C**O, rotamer B), 172.2 (N**C**O, rotamer A), 172.0 (N**C**O, rotamer B), 164.8 (Ar**C**, rotamer A), 162.3 (Ar**C**, rotamer B), 157.6 (d, J_{F-C} = 9.6 Hz, Ar**C**, both rotamers), 140.9 ((Ar**C**, rotamer A), 140.7 (Ar**C**, rotamer B), 137.9 ((Ar**C**, rotamer A), 137.8 (Ar**C**, rotamer B), 131.5 (Ar**C**H, rotamer A), 131.4 (Ar**C**H, rotamer B), 130.2 (Ar**C**H, rotamer A), 130.1 (Ar**C**H, rotamer B), 129.0 (Ar**C**H, both rotamers), 128.8 (Ar**C**H, rotamer A), 128.7 (Ar**C**H, rotamer B), 127.4 (Ar**C**, rotamer A), 127.1 (Ar**C**, rotamer B), 125.1 (Ar**C**, rotamer A), 125.0 (Ar**C**, rotamer B), 107.4 (d, J_{F-C} = 21.1 Hz, Ar**C**H, both rotamers), 99.6 (d, J_{F-C} = 25.7 Hz, Ar**C**H, both rotamers), 68.3 (O**C**H$_2$, rotamer A), 68.2 (O**C**H$_2$, rotamer B), 63.4 (N**C**H, rotamer A), 62.7 (N**C**H, rotamer B), 60.7 (Ar**C**H$_2$N, rotamer A), 60.6 (Ar**C**H$_2$N, rotamer B), 55.9 (O**C**H$_3$, both rotamers), 55.4 (N**C**H$_2$, rotamer A), 54.9 (N**C**H$_2$, rotamer B), 44.6 (q, *J* = 194.6 Hz, N**C**H$_2$, both rotamers), 41.0 (**C**H, both rotamers), 30.4 (**C**H$_2$, both rotamers), 30.0 (**C**H$_2$, rotamer A), 30.0 (**C**H$_2$, rotamer B), 26.1 (**C**H$_2$, rotamer A), 26.1 (**C**H$_2$, rotamer B); HRMS (ESI) calcd. for $C_{26}H_{30}FN_2O_4^+$, 453.2184. Found: $[MH]^+$ 453.2180 (+0.9 ppm error).

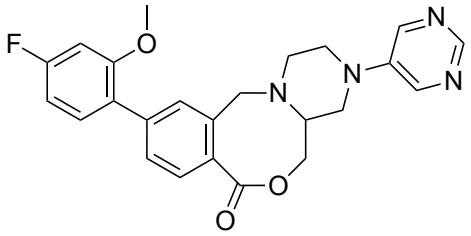
10-(4-Fluoro-2-methoxyphenyl)-3-(4-(trifluoromethyl)benzyl)-1,2,3,4,4a,5-hexahydrobenzo[*f*]pyrazino[2,1-*c*][1,4]oxazocin-7(12*H*)-one (155)



tert-Butyl 10-(4-fluoro-2-methoxyphenyl)-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[*f*]pyrazino [2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate **122** (50 mg, 0.110 mmol) was dissolved in 4 M HCl in dioxane (4.0 mL). The solution was stirred at room temperature for 1 hour, after which the

solution was concentrated in vacuo to yield the salt product **136**. This salt was dissolved in anhydrous THF (5.0 mL), 1-(bromomethyl)-4-(trifluoromethyl) benzene (25.5 mg, 0.137 mmol) was added followed by triethylamine (0.05 mL, 0.329 mmol). The reaction mixture was refluxed at 70 °C for 18 hours under argon. Then the reaction mixture was allowed to cool to RT, filtered and washed with dichloromethane, concentrated under vacuum and purified by column chromatography (SiO_2, 2:1 → 1:1 hexane : ethyl acetate) to afford the title compound (44.3 mg, 78%) as a white solid. R_f = 0.49 (1:1 hexane : ethyl acetate); m.p. 125–128 °C; ν_{max}/cm^{-1} (thin film) 2982, 1720, 1607, 1325, 1281, 1156, 1118, 1066, 955, 836; δ_H (400 MHz, $CDCl_3$) 7.57 (2H, d, *J* = 8.0 Hz, 2 x Ar**H**), 7.52 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.48 – 7.42 (3H, m, 3 x Ar**H**), 7.29 (1H, d, *J* = 1.5 Hz, Ar**H**), 7.25 (1H, dd, *J* = 8.0, 6.5 Hz, Ar**H**), 6.78 – 6.69 (2H, m, 2 x Ar**H**), 4.15 (1H, dd, *J* = 13.0, 2.0 Hz, OC**H**$_a$H$_b$), 4.02 (1H, dd, *J* = 13.0, 3.5 Hz, OCH$_a$**H$_b$**), 3.92 – 3.78 (5H, m, ArC**H$_2$**N, OC**H**$_3$), 3.55 (2H, d, *J* = 3.0 Hz, ArC**H$_2$**N), 2.94 – 2.85 (1H, m, NC**H**$_a$H$_b$), 2.77 (1H, dd, *J* = 11.0, 3.0 Hz, NC**H**$_a$H$_b$), 2.74 – 2.68 (2H, m, NC**H**, NCH$_a$**H$_b$**), 2.64 (1H, ddd, *J* = 11.0, 3.0, 1.5 Hz, NC**H**$_a$H$_b$), 2.38 – 2.27 (2H, m, 2 x NCH$_a$**H$_b$**); δ_C (100 MHz, $CDCl_3$) 172.4 (O**C**O), 164.8 (Ar**C**), 162.3 (Ar**C**), 157.7 (d, J_{F-C} = 9.9 Hz, Ar**C**), 142.4 (Ar**C**), 140.6 (Ar**C**), 138.1 (Ar**C**), 131.5 (d, J_{F-C} = 9.8 Hz, Ar**C**H), 130.2 (Ar**C**H), 129.6 (q, J_{F-C} = 31.9 Hz, **C**F$_3$), 129.3 (Ar**C**H), 129.0 (Ar**C**H), 128.9 (Ar**C**H), 125.4 (d, J_{F-C} = 3.7 Hz, Ar**C**H), 125.3 (Ar**C**), 124.3 (Ar**C**), 107.4 (d, J_{F-C} = 21.1 Hz, Ar**C**H), 99.7 (d, J_{F-C} = 25.7 Hz, Ar**C**H), 69.1 (O**C**H$_2$), 63.1 (N**C**H), 62.3 (Ar**C**H$_2$N), 60.6 (Ar**C**H$_2$N), 55.9 (O**C**H$_3$), 55.4 (N**C**H$_2$), 54.9 (N**C**H$_2$), 53.0 (N**C**H$_2$); HRMS (ESI) calcd. for $C_{28}H_{27}F_4N_2O_3^+$, 515.1952. Found: $[MH]^+$ 515.1950 (+0.4 ppm error).

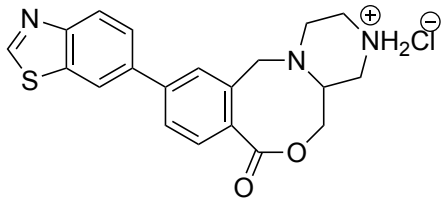
10-(4-Fluoro-2-methoxyphenyl)-3-(pyrimidin-5-yl)-1,2,3,4,4a,5-hexahydrobenzo[*f*] pyrazino[2,1-*c*][1,4]oxazocin-7(12*H*)-one (161)



tert-Butyl 10-(4-fluoro-2-methoxyphenyl)-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[*f*]pyrazino [2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate **122** (50 mg, 0.110 mmol) was dissolved in 4 M HCl in dioxane (4.0 mL). The solution was stirred at room temperature for 1 hour, after which the solution was concentrated in vacuo to yield the salt product **136**. This salt and 5-bromopyrimidine (21.8 mg, 0.137 mmol) were dissolved in toluene (2.0 mL). Then Cs_2CO_3 (107 mg, 0.330 mmol) and (±)-BINAP (15.8 mg, 0.016 mmol) were added followed by $Pd_2(dba)_3$ (10.1 mg, 0.011 mmol) and the resulting mixture was purged with argon for 10 minutes. The mixture was stirred and heated at 110 °C for 65 hours under argon. After being allowed to cool to RT, water (10 mL) was added and the two layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 10 mL) and the combined organic phases were dried with magnesium sulphate, concentrated under vacuum and purified by column chromatography (SiO_2, 2:1 → 0:1 hexane : ethyl acetate) to afford the title compound (28.9 mg, 61%) as a yellow solid. R_f = 0.48 (ethyl acetate); m.p. 176–180 °C; ν_{max}/cm^{-1} (thin film) 2925, 2845, 1718, 1606, 1568, 1513, 1488, 1448, 1280, 1241, 1192, 1153, 1115, 1089, 1031, 955, 837, 726; δ_H (400 MHz, $CDCl_3$) 8.72 (1H, s, Ar**H**), 8.38 (2H, s, 2 x Ar**H**), 7.54 (1H, d, *J* = 8.0

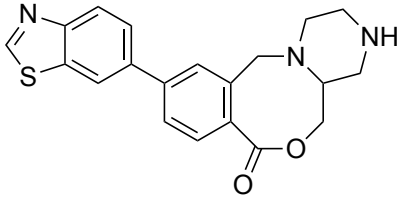
Hz, Ar**H**), 7.48 (1H, dd, *J* = 8.0, 1.5 Hz, Ar**H**), 7.33 (1H, d, *J* = 1.5 Hz, Ar**H**), 7.26 – 7.22 (1H, m, Ar**H**), 6.79 – 6.68 (2H, m, 2 x Ar**H**), 4.28 (1H, dd, *J* = 13.0, 2.0 Hz, OC**H$_a$**H$_b$), 4.16 (1H, dd, *J* = 13.0, 4.0 Hz, OCH$_a$**H$_b$**), 3.90 (2H, d, *J* = 3.0 Hz, ArC**H$_2$**N), 3.80 (3H, s, OC**H$_3$**), 3.57 (1H, dd, *J* = 11.5, 2.5 Hz, NC**H$_a$**H$_b$), 3.48 (1H, ddd, *J* = 11.5, 3.5, 1.5 Hz, NC**H$_a$**H$_b$), 3.14 – 2.95 (3H, m, NC**H$_a$**H$_b$, 2 x NCH$_a$**H$_b$**), 2.90 – 2.77 (2H, m, NC**H**, NCH$_a$**H$_b$**); δ_C (100 MHz, $CDCl_3$) 172.0 (O**C**O), 164.9 (Ar**C**), 162.4 (Ar**C**), 157.7 (d, $J_{F\text{-}C}$ = 9.6 Hz, Ar**C**), 150.3 (Ar**C**H), 144.1 (Ar**C**H), 144.0 (Ar**C**H), 141.0 (Ar**C**), 137.7 (Ar**C**), 131.6 (d, $J_{F\text{-}C}$ = 9.8 Hz, Ar**C**H), 130.2 (Ar**C**H), 129.2 (Ar**C**H), 127.3 (Ar**C**H), 125.1 (d, $J_{F\text{-}C}$ = 3.1 Hz, Ar**C**), 107.5 (d, $J_{F\text{-}C}$ = 9.8 Hz,Ar**C**), 99.7 (d, $J_{F\text{-}C}$ = 25.7 Hz, Ar**C**H), 68.7 (O**C**H$_2$), 62.6 (N**C**H), 60.6 (Ar**C**H$_2$N), 55.9 (O**C**H$_3$), 54.6 (N**C**H$_2$), 49.6 (N**C**H$_2$), 47.7 (N**C**H$_2$); HRMS (ESI) calcd. for $C_{24}H_{23}FN_4NaO_3^+$, 457.1646. Found: $[MH]^+$ 457.1652 (−1.3 ppm error).

10-(Benzo[d]thiazol-6-yl)-7-oxo-1,2,3,4,4a,5,7,12-octahydrobenzo[*f*]pyrazino[2,1-*c*] [1,4]oxazocin-3-ium chloride (138)



tert-Butyl 10-(benzo[*d*]thiazol-6-yl)-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[*f*]pyrazino[2,1-*c*] [1,4]oxazocine-3(4*H*)-carboxylate **120** (50 mg, 0.110 mmol) was dissolved in 4 M HCl in dioxane (4.0 mL). The solution was stirred at room temperature for 1 hour, after which the solution was concentrated in vacuo to afford the title compound (49.5 mg, 112%) as a white solid. R_f = 0 (10:1 dichloromethane : methanol); m.p. 244–251 °C; δ_H (400 MHz, Methanol-*D*$_4$) 9.34 (1H, s,), 8.43 (1H, d, *J* = 2.0 Hz, Ar**H**), 8.16 (1H, d, *J* = 8.5 Hz, Ar**H**), 7.90 (1H, dd, *J* = 8.5, 2.0 Hz, Ar**H**), 7.82 – 7.72 (2H, m, 2 x Ar**H**), 7.58 (1H, d, *J* = 8.0 Hz, Ar**H**), 4.39 – 4.33 (1H, m, OC**H$_a$**H$_b$), 4.22 – 4.07 (3H, m, OCH$_a$**H$_b$**, ArC**H$_2$**N), 3.68 – 3.60 (3H, m, 3 x NC**H$_a$**H$_b$), 3.45 – 3.38 (2H, m, 2 x NCH$_a$**H$_b$**), 3.24 – 3.18 (1H, m, NC**H**), 3.05 – 3.00 (1H, m, NCH$_a$**H$_b$**); ^{13}C NMR signal is too weak to distinguish because the compound is difficult to dissolve in the solvent; HRMS (ESI) calcd. for $C_{20}H_{20}N_3O_2S^+$, 366.1271. Found: $[MH]^+$ 366.1280 (−2.5 ppm error).

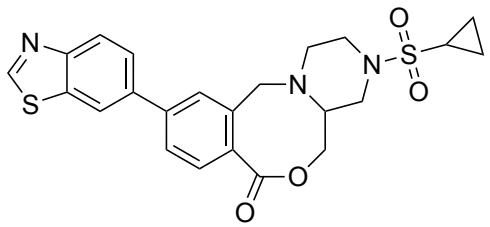
10-(Benzo[*d*]thiazol-6-yl)-1,2,3,4,4a,5-hexahydrobenzo[*f*]pyrazino[2,1-*c*][1,4] oxazocin-7(12*H*)-one (139)



tert-Butyl 10-(benzo[*d*]thiazol-6-yl)-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[*f*]pyrazino[2,1-*c*] [1,4]oxazocine-3(4*H*)-carboxylate **120** (50 mg, 0.110 mmol) was dissolved in 4 M HCl in dioxane (4.0 mL). The solution was stirred at room temperature for 1 hour, after which the solution was concentrated in vacuo to yield the salt product **138**. Sodium bicarbonate solution was added while stirring until the pH is adjusted to 7-8. The aqueous layer was extracted with ethyl acetate (3 x 10 mL) and the combined organic phases were dried with magnesium

sulphate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, 10:1 dichloromethane: methanol) to afford the title compound (25.1 mg, 62%) as a white solid. R_f = 0.40 (50:1 → 10:1 methanol : dichloromethane); m.p. 144–149 °C; ν_{max}/cm^{-1} (thin film) 2923, 1712, 1607, 1462, 1440, 1378, 1354, 1277, 1255, 1233, 1126, 1095, 1023, 1002, 867, 833, 807, 767; δ_H (400 MHz, DMSO-*D*$_6$) 9.45 (1H, s, Ar**H**), 8.57 (1H, d, *J* = 2.0 Hz, Ar**H**), 8.20 (1H, d, *J* = 8.5 Hz, Ar**H**), 7.91 (1H, dd, *J* = 8.5, 2.0 Hz, Ar**H**), 7.81 – 7.74 (2H, m, 2 x Ar**H**), 7.52 (1H, d, *J* = 8.0 Hz, Ar**H**), 4.20 (1H, d, *J* = 13.0 Hz, OC**H$_a$**H$_b$), 4.08 – 3.98 (2H, m, OCH$_a$**H$_b$**, ArC**H$_a$**H$_b$N), 3.88 (1H, d, *J* = 16.5 Hz, ArCH$_a$**H$_b$**N), 3.19 (2H, d, *J* = 10.5 Hz, 2 x NC**H$_a$**H$_b$), 3.10 (1H, d, *J* = 11.5 Hz, NC**H$_a$**H$_b$), 2.88 – 2.68 (4H, m, NC**H**, 3 x NCH$_a$**H$_b$**); δ_C (101 MHz, DMSO-*D*$_6$) 171.1 (O**C**O), 157.2 (Ar**C**H), 152.9 (Ar**C**), 141.7 (Ar**C**), 139.3 (Ar**C**), 136.1 (Ar**C**), 134.7 (Ar**C**), 130.8 (Ar**C**H), 127.6 (Ar**C**), 126.6 (Ar**C**H), 125.9 (Ar**C**H), 125.4 (Ar**C**H), 123.4 (Ar**C**H), 120.8(Ar**C**H), 67.3 (O**C**H$_2$), 60.2 (N**C**H), 59.2 (Ar**C**H$_2$N), 51.6 (N**C**H$_2$), 44.4 (N**C**H$_2$), 43.3 (N**C**H$_2$); HRMS (ESI) calcd. for $C_{20}H_{20}N_3O_2S^+$, 366.1271. Found: $[MH]^+$ 366.1275 (−1.0 ppm error).

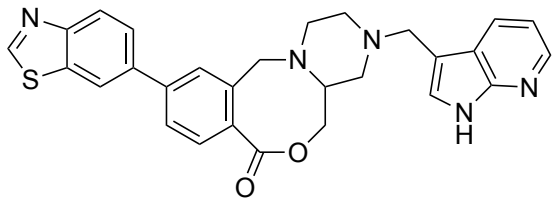
10-(Benzo[*d*]thiazol-6-yl)-3-(cyclopropylsulfonyl)-1,2,3,4,4a,5-hexahydrobenzo[*f*] pyrazino[2,1-*c*][1,4]oxazocin-7(12*H*)-one (143)



tert-Butyl 10-(benzo[*d*]thiazol-6-yl)-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[*f*]pyrazino[2,1-*c*] [1,4]oxazocine-3(4*H*)-carboxylate **120** (50 mg, 0.110 mmol) was dissolved in 4 M HCl in dioxane (4.0 mL). The solution was stirred at room temperature for 1 hour, after which the solution was concentrated in vacuo to yield the salt product **138**. This salt was dissolved in anhydrous DCM (3.0 mL) at room temperature and the solution was cooled to 0 °C using an ice bath. Triethylamine (0.05 mL, 0.329 mmol) was added dropwise, followed by cyclopropanesulfonyl chloride (19.3 mg, 0.137 mmol) and DMAP (1.4 mg, 0.011 mmol). The solution was allowed to gradually warm to room temperature while being stirred for 18 hours. The solution was diluted with ethyl acetate (10 mL) and washed with brine (10 mL). The aqueous layer was then extracted with ethyl acetate (3 x 10 mL). The organic layers were then combined, dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, 1:1 → 0:1 hexane : ethyl acetate) to afford the title compound (38.2 mg, 74%) as a white solid. R_f = 0.51 (ethyl acetate); m.p. 206–210 °C; ν_{max}/cm^{-1} (thin film) 2923, 2853, 1717, 1608, 1464, 1335, 1309, 1287, 1153, 1119, 1010, 990, 769, 734; δ_H (400 MHz, $CDCl_3$) 9.04 (1H, s, NC**H**S), 8.20 (1H, d, *J* = 8.5 Hz, Ar**H**), 8.16 (1H, d, *J* = 2.0 Hz, Ar**H**), 7.73 (1H, dd, *J* = 8.5, 2.0 Hz, Ar**H**), 7.67 – 7.56 (2H, m, 2 x Ar**H**), 7.46 (1H, d, *J* = 1.5 Hz, Ar**H**), 4.28 (1H, dd, *J* = 13.0, 2.0 Hz, OC**H$_a$**H$_b$), 4.05 (1H, dd, *J* = 13.0, 3.0 Hz, OCH$_a$**H$_b$**), 4.02 – 3.87 (2H, m, ArC**H$_2$**N), 3.63 (2H, ddt, *J* = 17.0, 11.5, 2.5 Hz, 2 x NC**H$_a$**H$_b$), 3.18 – 2.95 (3H, m, NC**H$_a$**H$_b$, 2 x NCH$_a$**H$_b$**), 2.90 – 2.69 (2H, m, NC**H**, NCH$_a$**H$_b$**), 2.27 (1H, tt, *J* = 8.0, 5.0 Hz, C**H**), 1.22 – 1.10 (2H, m, C**H$_2$**), 1.07 – 0.94 (2H, m, C**H$_2$**); δ_C (100 MHz, $CDCl_3$) 171.9 (O**C**O), 154.9 (N**C**HS), 153.2 (Ar**C**), 143.3 (Ar**C**), 138.8 (Ar**C**), 137.3 (Ar**C**), 134.8

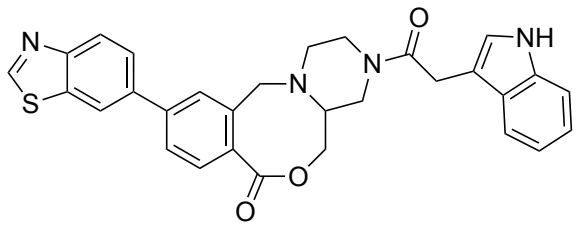
(Ar**C**), 131.4 (Ar**C**H), 127.7 (Ar**C**), 126.9 (Ar**C**H), 126.5 (Ar**C**H), 125.8 (Ar**C**H), 124.1 (Ar**C**H), 120.5 (Ar**C**H), 67.9 (O**C**H_2), 62.6 (N**C**H), 60.6 (Ar**C**H_2N), 54.7 (N**C**H_2), 47.8 (N**C**H_2), 45.0 (N**C**H_2), 25.5 (**C**H), 4.6 (**C**H_2), 4.5 (**C**H_2); HRMS (ESI) calcd. for $C_{23}H_{24}N_3O_4S_2^+$, 470.1203. Found: $[MH]^+$ 470.1237 (−7.4 ppm error).

3-((1H-Pyrrolo[2,3-*b*]pyridin-3-yl)methyl)-10-(benzo[*d*]thiazol-6-yl)-1,2,3,4,4a,5-hexahydrobenzo[*f*]pyrazino[2,1-*c*][1,4]oxazocin-7(12*H*)-one (147)



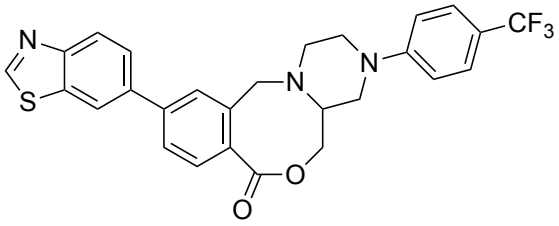
tert-Butyl 10-(benzo[*d*]thiazol-6-yl)-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[*f*]pyrazino[2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate **120** (50 mg, 0.110 mmol) was dissolved in 4 M HCl in dioxane (4.0 mL). The solution was stirred at room temperature for 1 hour, after which the solution was concentrated in vacuo to yield the salt product **138**. This salt was dissolved in anhydrous THF (2.0 mL), 1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde (12.6 mg, 0.110 mmol) was added, followed by acetic acid (0.007 mL, 0.110 mmol) and the solution was stirred for 10 minutes. Then sodium triacetoxyborohydride (46.4 mg, 0.219 mmol) was added and the reaction mixture was stirred at room temperature for 18 hours. The mixture was diluted with ethyl acetate (10 mL) and washed with sodium bicarbonate solution (10 mL). The aqueous layer was then extracted with ethyl acetate (3 x 10 mL). The organic layers were then combined, dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, 90:9:1 dichloromethane : methanol : triethylamine) to afford the title compound (27.8 mg, 51%) as a yellow solid. R_f = 0.58 (90:9:1 dichloromethane : methanol : triethylamine); m.p. 237–241 °C; ν_{max}/cm^{-1} (thin film) 3130, 2528, 1702, 1606,1466, 1438, 1383, 1350, 1281, 1236, 1129, 1095, 988, 865, 805, 760; δ_H (400 MHz, DMSO-*D_6*) 10.63 (1H, s, N**H**), 9.28 (1H, s, NC**H**S), 8.52 (1H, d, *J* = 5.0 Hz, Ar**H**), 8.47 – 8.36 (2H, m, 2 x Ar**H**), 8.30 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.97 (1H, dd, *J* = 9.0, 2.0 Hz, Ar**H**), 7.90 – 7.76 (2H, m, 2 x Ar**H**), 7.71 (1H, s, Ar**H**), 7.54 (1H, d, *J* = 3.0 Hz, Ar**H**), 7.31 (1H, dd, *J* = 8.0, 5.0 Hz, Ar**H**), 4.36 (1H, d, *J* = 13.0 Hz, OC**H**$_a$H$_b$), 4.25 (1H, dd, *J* = 13.0, 3.5 Hz, OCH$_a$**H$_b$**), 4.12 (2H, q, *J* = 16.0 Hz, ArC**H$_2$**N), 4.00 – 3.72 (3H, m, C**H$_2$**, NC**H$_a$**H$_b$), 3.17 (1H, d, *J* = 11.5 Hz, NC**H$_a$**H$_b$), 3.09 – 2.91 (3H, m, NC**H$_a$**H$_b$, 2 x NCH$_a$**H$_b$**), 2.69 – 2.44 (2H, m, NC**H**, NCH$_a$**H$_b$**); δ_C (101 MHz, DMSO-*D_6*) 171.1 (O**C**O), 157.2 (N**C**HS), 152.9 (Ar**C**), 148.3 (Ar**C**), 143.2 (Ar**C**H), 141.6 (Ar**C**), 139.3 (Ar**C**), 136.1 (Ar**C**), 134.7 (Ar**C**), 130.9 (Ar**C**H), 129.8 (Ar**C**H), 127.5 (Ar**C**H), 127.3 (Ar**C**), 126.3 (Ar**C**H), 125.8 (Ar**C**H), 125.3 (Ar**C**H) 123.4 (Ar**C**H), 120.8 (Ar**C**H), 119.8 (Ar**C**), 116.0 (Ar**C**H), 101.2 (Ar**C**), 79.2 (O**C**H_2), 66.8 (N**C**H), 59.4 (N**C**H_2), 58.6 (N**C**H_2), 51.0 (N**C**H_2), 50.1 (N**C**H_2), 49.7 (**C**H_2); HRMS (ESI) calcd. for $C_{28}H_{26}N_5O_2S^+$, 496.1802. Found: $[MH]^+$ 496.1820 (-3.6 ppm error).

3-(2-(1H-Indol-3-yl)acetyl)-10-(benzo[*d*]thiazol-6-yl)-1,2,3,4,4a,5-hexahydrobenzo[*f*] pyrazino[2,1-*c*][1,4]oxazocin-7(12*H*)-one (153)



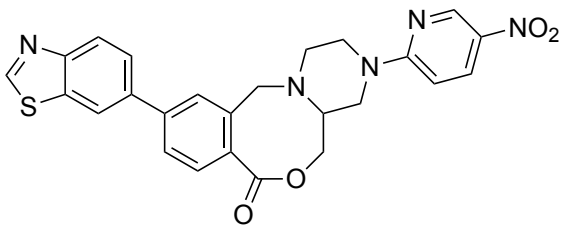
tert-Butyl 10-(benzo[*d*]thiazol-6-yl)-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[*f*]pyrazino[2,1-*c*] [1,4]oxazocine-3(4*H*)-carboxylate **120** (50 mg, 0.110 mmol) was dissolved in 4 M HCl in dioxane (4.0 mL). The solution was stirred at room temperature for 1 hour, after which the solution was concentrated in vacuo to yield the salt product **138**. This salt was dissolved in anhydrous DCM (2.0 mL), DIPEA (0.06 mL, 0.330 mmol) was added dropwise, followed by cyclopentane carbonyl chloride (21.1 mg, 0.120 mmol) and T3P (50% w/v in ethyl acetate, 105 mg, 0.165 mmol). The reaction solution was then stirred at room temperature for 18 hours under argon. The solution was diluted with ethyl acetate (10 mL) and washed with brine (10 mL). The aqueous layer was then extracted with ethyl acetate (3 x 10 mL). The organic layers were then combined, dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, 10:1 → 3:1 dichloromethane : acetone) to afford the title compound (52.4 mg, 91%) as a gray solid. R_f = 0.53 (3:1 dichloromethane : acetone); m.p. 167–174 °C; ν_{max}/cm^{-1} (thin film) 3269, 2923, 1710, 1617, 1457, 1346, 1278, 1227, 1010, 834, 807, 743; δ_H (400 MHz, DMSO-*D*$_6$) 10.90 (1H, s, N**H**), 9.43 (1H, s, NC**H**S), 8.55 (1H, d, *J* = 3.0 Hz, Ar**H**), 8.17 (1H, d, *J* = 8.5 Hz, Ar**H**), 7.89 (1H, dt, *J* = 8.5, 2.0 Hz, Ar**H**), 7.74 (2H, dd, *J* = 13.0, 7.0 Hz, 2 x Ar**H**), 7.56 (1H, t, *J* = 8.0 Hz, Ar**H**), 7.48 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.33 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.23 (1H, dd, *J* = 19.0, 2.0 Hz, Ar**H**), 7.11 – 7.03 (1H, m, Ar**H**), 6.96 (1H, t, *J* = 7.0 Hz, Ar**H**), 4.30 (1H, d, *J* = 13.0 Hz, NC**H$_a$**H$_b$), 4.18 – 3.94 (4H, m, OC**H$_2$**, ArC**H$_a$**H$_b$N, NC**H$_a$**H$_b$), 3.85 – 3.68 (3H, m, C**H$_2$**, ArCH$_a$**H$_b$**N), 3.11 – 2.87 (2H, m, NC**H$_a$**H$_b$, NCH$_a$**H$_b$**), 2.70 – 2.57 (1H, m, NCH$_a$**H$_b$**), 2.44 – 2.28 (2H, m, NC**H**, NCH$_a$**H$_b$**); δ_C (101 MHz, DMSO-*D*$_6$) 171.2 (O**C**O, both rotamers), 169.4 (N**C**O, rotamer A), 169.2 (N**C**O, rotamer B), 157.1 (N**C**HS, both), 152.8(Ar**C**, both), 141.6(Ar**C**, both), 139.4 (Ar**C**, both), 136.1 (Ar**C**, both), 134.6 (Ar**C**, both), 130.6 (Ar**C**H, both), 130.1(Ar**C**, both), 127.8 (Ar**C**, rotamer A), 127.7 (Ar**C**, rotamer B), 127.2 (Ar**C**, rotamer A), 127.1 (Ar**C**, rotamer B), 126.6 (Ar**C**H, both), 125.8 (Ar**C**H, both), 125.4 (Ar**C**H, both), 123.6 (Ar**C**H, rotamer A), 123.5 (Ar**C**H, rotamer B), 123.4 (Ar**C**H, both), 121.1 (Ar**C**H, both), 120.8 (Ar**C**H, both), 118.8 (Ar**C**H, rotamer A), 118.7 (Ar**C**H, rotamer B), 118.4 (Ar**C**H, both), 111.4 (Ar**C**H, both), 108.1 (Ar**C**, rotamer A), 108.0 (Ar**C**, rotamer B), 67.9 (O**C**H$_2$, rotamer A), 67.7 (O**C**H$_2$, rotamer B), 62.6 (N**C**H, rotamer A), 62.1 (N**C**H, rotamer B), 59.4 (Ar**C**H$_2$N, rotamer A), 59.2 (Ar**C**H$_2$N, rotamer B), 54.4 (N**C**H$_2$, rotamer A), 54.1 (N**C**H$_2$, rotamer B), 46.9 (N**C**H$_2$, rotamer A), 45.4 (N**C**H$_2$, rotamer B), 42.7 (N**C**H$_2$, rotamer A), 41.1 (N**C**H$_2$, rotamer B), 30.7 (**C**H$_2$, rotamer A), 30.6 (**C**H$_2$, rotamer B); HRMS (ESI) calcd. for $C_{30}H_{26}N_4NaO_3S^+$, 545.1618. Found: $[MH]^+$ 545.1611 (+1.3 ppm error).

10-(Benzo[*d*]thiazol-6-yl)-3-(4-(trifluoromethyl)phenyl)-1,2,3,4,4a,5-hexahydrobenzo [*f*]pyrazino[2,1-*c*][1,4]oxazocin-7(12*H*)-one (163)



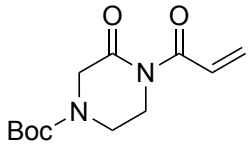
tert-Butyl 10-(benzo[*d*]thiazol-6-yl)-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[*f*]pyrazino[2,1-*c*] [1,4]oxazocine-3(4*H*)-carboxylate **120** (50 mg, 0.110 mmol) was dissolved in 4 M HCl in dioxane (4.0 mL). The solution was stirred at room temperature for 1 hour, after which the solution was concentrated in vacuo to yield the salt product **138**. This salt and 1-bromo-4-(trifluoromethyl)benzene (30.8 mg, 0.137 mmol) were dissolved in toluene (2.0 mL). Then Cs_2CO_3 (107 mg, 0.330 mmol) and (±)-BINAP (15.8 mg, 0.016 mmol) were added followed by $Pd_2(dba)_3$ (10.1 mg, 0.011 mmol) and the resulting mixture was purged with argon for 10 minutes. The mixture was stirred and heated at 110 °C for 65 hours under argon. After being allowed to cool to RT, water (10 mL) was added and the two layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 10 mL) and the combined organic phases were dried with magnesium sulphate, concentrated under vacuum and purified by column chromatography (SiO_2, 3:1 → 1:1 hexane : ethyl acetate) to afford the title compound (41.1 mg, 73%) as a yellow solid. R_f = 0.50 (1:1 hexane : ethyl acetate); m.p. 145–149 °C; v_{max}/cm^{-1} (thin film) 2836, 1718, 1613, 1525, 1466, 1330, 1237, 1162, 1113, 1071, 1012, 830, 732; δ_H (400 MHz, $CDCl_3$) 9.09 (1H, s, NC**H**S), 8.25 (1H, d, *J* = 8.5 Hz, Ar**H**), 8.19 (1H, d, *J* = 2.0 Hz, Ar**H**), 7.76 (1H, dd, *J* = 8.5, 2.0 Hz, Ar**H**), 7.64 (2H, s, Ar**H**), 7.53 (1H, s, Ar**H**), 7.49 (2H, d, *J* = 8.5 Hz, Ar**H**), 6.93 (2H, d, *J* = 8.5 Hz, Ar**H**), 4.26 (1H, dd, *J* = 13.0, 2.0 Hz, OC**H$_a$**H$_b$), 4.18 (1H, dd, *J* = 13.0, 4.0 Hz, OCH$_a$**H$_b$**), 4.01 – 3.87 (2H, m, ArC**H$_2$**N), 3.69 – 3.61 (1H, m, NC**H$_a$**H$_b$), 3.54 (1H, dt, *J* = 11.5, 2.5 Hz, NC**H$_a$**H$_b$), 3.12 – 2.93 (3H, m, NC**H$_a$**H$_b$, 2 x NCH$_a$**H$_b$**), 2.92 – 2.81 (2H, m, NC**H**, NCH$_a$**H$_b$**); δ_C (100 MHz, $CDCl_3$) 171.8 (O**C**O), 155.3 (N**C**HS), 152.9 (Ar**C**), 143.5 (Ar**C**), 138.8 (Ar**C**), 137.6 (Ar**C**), 134.8 (Ar**C**), 131.1 (Ar**C**H), 128.2 (Ar**C**), 127.5 (Ar**C**H), 127.0 (Ar**C**H), 126.6 (d, $J_{F\text{-}C}$= 35.9 Hz, Ar**C**H), 126.1 (Ar**C**), 126.0 (Ar**C**H), 124.0 (Ar**C**H), 123.4 (Ar**C**), 121.2 (q, $J_{F\text{-}C}$ = 32.5 Hz, **C**F$_3$), 120.6 (Ar**C**H), 115.1 (Ar**C**H), 69.2 (O**C**H$_2$), 62.8 (N**C**H), 60.6 (Ar**C**H$_2$N), 55.0 (N**C**H$_2$), 50.3 (N**C**H$_2$), 48.3 (N**C**H$_2$); HRMS (ESI) calcd. for $C_{27}H_{23}F_3N_3O_2S^+$, 510.1458. Found: $[MH]^+$ 510.1464 (−1.2 ppm error).

10-(Benzo[*d*]thiazol-6-yl)-3-(5-nitropyridin-2-yl)-1,2,3,4,4a,5-hexahydrobenzo[*f*] pyrazino[2,1-*c*][1,4]oxazocin-7(12*H*)-one (159)



tert-Butyl 10-(benzo[*d*]thiazol-6-yl)-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[*f*]pyrazino[2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate **120** (50 mg, 0.110 mmol) was dissolved in 4 M HCl in dioxane (4.0 mL). The solution was stirred at room temperature for 1 hour, after which the solution was concentrated in vacuo to yield the salt product **138**. This salt was dissolved in anhydrous MeCN (3.0 mL), 2-chloro-5-nitropyridine (21.9 mg, 0.138 mmol) was added followed by potassium carbonate (45.5 mg, 0.329 mmol). The reaction mixture was heated to 70 °C for 18 hours under argon. Then the reaction mixture was allowed to cool to RT, filtered and washed with dichloromethane, concentrated under vacuum and purified by column chromatography (SiO_2, 2:1 → 1:1 hexane : ethyl acetate) to afford the title compound (44.1 mg, 82%) as a white solid. R_f = 0.22 (1:1 hexane : ethyl acetate); m.p. 256–258 °C; ν_{max}/cm^{-1} (thin film) 3061, 2837, 1716, 1574, 1512, 1486, 1468, 1430, 1334, 1314, 1298, 1266, 1234,1095, 1085, 999, 977, 866, 822, 802, 762, 658 ; δ_H (400 MHz, DMSO-*D*$_6$) 9.45 (1H, s, NC**H**S), 8.98 (1H, d, *J* = 3.0 Hz, Ar**H**), 8.59 (1H, d, *J* = 2.0 Hz, Ar**H**), 8.26 (1H, dd, *J* = 9.5, 3.0 Hz, Ar**H**), 8.20 (1H, d, *J* = 8.5 Hz, Ar**H**), 7.92 (1H, dd, *J* = 8.5, 2.0 Hz, Ar**H**), 7.83 – 7.75 (2H, m, 2 x Ar**H**), 7.53 (1H, d, *J* = 8.5 Hz, Ar**H**), 7.02 (1H, d, *J* = 9.5 Hz, Ar**H**), 4.59 – 4.36 (2H, m, 2 x NC**H$_a$**H$_b$), 4.26 (1H, dd, *J* = 13.0, 2.5 Hz, OC**H$_a$**H$_b$), 4.15 (1H, dd, *J* = 13.0, 3.5 Hz, OCH$_a$**H$_b$**), 4.08 (1H, d, *J* = 16.5 Hz, ArC**H$_a$**H$_b$N), 3.86 (1H, d, *J* = 16.5 Hz, ArCH$_a$**H$_b$**N), 3.19 – 3.04 (3H, m, NC**H$_a$**H$_b$, 2 x NCH$_a$**H$_b$**), 2.74 – 2.60 (2H, m, NC**H**, NCH$_a$**H$_b$**); δ_C (101 MHz, DMSO-*D*$_6$) 171.3 (O**C**O), 160.0 (Ar**C**), 157.1 (Ar**C**), 152.9(Ar**C**), 146.0(N**C**HS), 141.7(Ar**C**), 139.5 (Ar**C**H), 136.2 (Ar**C**), 134.7 (Ar**C**), 134.4 (Ar**C**H), 132.9 (Ar**C**), 130.6 (Ar**C**), 127.9 (Ar**C**H), 126.7 (Ar**C**H), 125.9 (Ar**C**H), 125.4 (Ar**C**H), 123.4 (Ar**C**H), 120.8 (Ar**C**H), 105.8 (Ar**C**H), 68.0 (O**C**H$_2$), 62.0 (N**C**H), 59.2 (Ar**C**H$_2$N), 53.7 (N**C**H$_2$), 44.5 (N**C**H$_2$); HRMS (ESI) calcd. for $C_{25}H_{22}N_5O_4S^+$, 488.1387. Found: $[MH]^+$ 488.1398 (−2.2 ppm error).

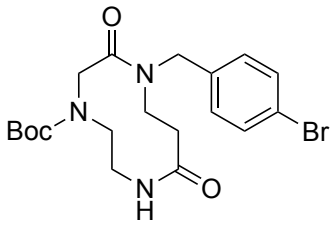
***tert*-Butyl 4-acryloyl-3-oxopiperazine-1-carboxylate (166)**



To a stirring solution of tert-butyl 3-oxopiperazine-1-carboxylate (1.0 g, 5.00 mmol) in dry THF (18.0 mL) cooled to 0 °C was added a solution of MeMgBr (3.0 M in diethyl ether, 1.8 mL) via dropwise addition using a syringe pump over 30 min. The reaction mixture was allowed to stir for 10 min at 0 °C after addition was completed. Acryloyl chloride (0.6 mL, 7.50 mmol) was then added in a single portion and the reaction was stirred for an additional 30 min at 0 °C. The reaction was then quenched with sat. aq. NH_4Cl (35 mL) and the mixture was extracted with Et_2O (35 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (2 × 35 mL), and organic extracts dried over $MgSO_4$ and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 1:1 diethyl ether: hexane) afforded the title compound as a colourless oil (1.104 g, 87%); R_f = 0.25 (1:1 hexane: diethyl ether); ν_{max}/cm^{-1} (thin film) 1685, 1616, 1406, 1389, 1365, 1303, 1243, 1160, 1131, 1097, 1021, 974, 919, 864, 795, 769; δ_H (400 MHz, $CDCl_3$) 7.15 (1H, dd, *J* = 17.0, 10.5 Hz, NCOC**H**CH$_2$), 6.43 (1H, dd, *J* = 17.0, 1.5 Hz, NCOCHC**H$_a$**H$_b$), 5.81 (1H, dd, *J* = 10.5, 1.5 Hz, NCOCHCH$_a$**H$_b$**), 4.23 (2H, s, N(Boc)C**H$_2$**CON), 3.93 – 3.86 (2H, m, C**H$_2$**), 3.67 – 3.58 (2H, m, C**H$_2$**), 1.45 (9H, s, 3 × C**H$_3$**); δ_C (100 MHz, $CDCl_3$) 168.8 (**C**O), 168.0 (**C**O), 153.7 (t-BuO-**C**O), 131.1 (NCO**C**H$_2$), 130.2 (NCO**C**H), 81.3 (O**C**(CH$_3$)), 49.3 (**C**H$_2$), 42.3 (**C**H$_2$), 41.7

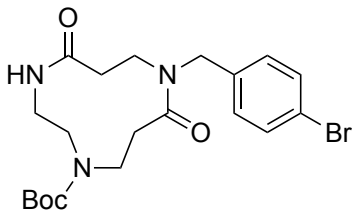
(**C**H_2), 28.4 (3 × **C**H_3), ^{13}C NMR data are from the published literature;[24] HRMS (ESI) calcd. for $C_{12}H_{18}N_2NaO_4$, 277.1159. Found: $[MNa]^+$, 277.1156 (+1.0 ppm error). Characterisation data matched those reported in the literature.[24]

***tert*-Butyl 1-(4-bromobenzyl)-2,8-dioxo-1,4,7-triazecane-4-carboxylate (179)**



To a solution of *tert*-butyl 4-acryloyl-3-oxopiperazine-1-carboxylate **166** (100 mg, 0.393 mmol) in dry methanol (1.0 mL) was added 4-bromobenzylamine (80.5 mg, 0.433 mmol) in a single portion. The reaction mixture was allowed to stir for 4 hours at RT and then the solvent was removed in vacuo. Purification by column chromatography (SiO_2, 1:1 ethyl acetate: hexane → 2:1 ethyl acetate: hexane → 3:1 dichloromethane : acetone) afforded the title compound as a white solid (140 mg, 81%). In solution in $CDCl_3$, this compound exists as a mixture of 3 rotameric forms; R_f = 0.27 (3:1 dichloromethane : acetone); m.p. 128–131 °C; νmax/cm–1 (thin film) 1650, 1548, 1405, 1366, 1245, 1161, 1128, 1070, 733; ^{1}H and ^{13}C NMR data for the major rotamer: δ_H (400 MHz, $CDCl_3$) 7.44 (2H, d, *J* = 8.0 Hz, 2 x Ar**H**, minor rotamer), 7.40 (2H, d, *J* = 8.0 Hz, 2 x Ar**H**, major rotamer), 7.10 (2H, d, *J* = 8.0 Hz, 2 x Ar**H**, minor rotamer), 7.03 (2H, d, *J* = 8.0 Hz, 2 x Ar**H**, major rotamer), 5.84 (1H, d, *J* = 10.5 Hz, N**H**, major rotamer), 5.06 (1H, d, *J* = 16.5 Hz, C**H₂**, major rotamer), 4.96 (1H, d, *J* = 14.0 Hz, C**H₂**, major rotamer), 4.28 – 4.10 (2H, m, C**H₂**, major rotamer), 4.07 (1H, d, *J* = 16.5 Hz, C**H₂**, major rotamer), 3.69 (1H, dt, *J* = 14.0, 2.5 Hz, C**H₂**, major rotamer), 3.22 (1H, d, *J* = 14.0 Hz, C**H₂**, major rotamer), 3.10 – 2.58 (4H, m, 2 x C**H₂**, both rotamers), 2.43 (1H, ddd, J = 13.0, 8.5, 4.5 Hz, C**H₂**, major rotamer), 1.47 (9H, s, 3 × C**H₃**, major rotamer), 1.42 (9H, s, 3 × C**H₃**, minor rotamer), 1.34 (9H, s, 3 × C**H₃**, minor rotamer); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 172.6 (**C**O), 170.7 (**C**O), 155.1 (**C**O), 136.1 (Ar**C**), 131.9 (Ar**C**), 128.8 (2 × Ar**C**H), 121.5 (2 × Ar**C**H), 81.3 (**C**(CH_3)), 52.3 (**C**H_2), 51.6 (**C**H_2), 49.2 (**C**H_2), 41.7 (**C**H_2), 38.7 (**C**H_2), 35.1 (**C**H_2), 28.3 (3 × **C**H_3); HRMS (ESI) calcd.for $C_{19}H_{27}{}^{79}BrN_3O_4$, 440.1179. Found: [MNa]+, 440.1185 (−1.3 ppm error).

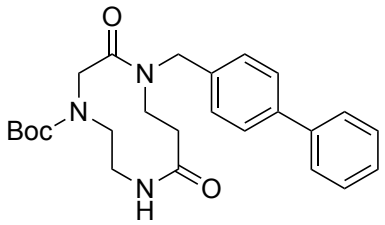
***tert*-Butyl 8-(4-bromobenzyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate (183)**



To a solution of *tert*-butyl 4-acryloyl-5-oxo-1,4-diazepane-1-carboxylate **182** (100 mg, 0.373 mmol) in dry methanol (1.0 mL), was added 4-bromobenzylamine (76.3 mg, 0.410 mmol) in a single portion. The reaction mixture was allowed to stir for 4 h at RT and then the solvent was removed in vacuo. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate: hexane → 2:1 ethyl acetate: hexane → 3:1 dichloromethane : acetone) afforded the title

compound as a white solid (158 mg, 92%). In solution in $CDCl_3$, this compound exists as a mixture of 3 rotameric forms; R_f = 0.21 (3:1 dichloromethane : acetone); m.p. 132–136 °C; vmax/cm–1 (thin film) 3336, 2930, 1641, 1555, 1481, 1455, 1406, 1366, 1352, 1246, 1166, 1139, 1071, 1011, 797, 730; δ_H (400 MHz, $CDCl_3$) 7.50 – 7.36 (2H, m, 2 x Ar**H**, both rotamers), 7.14 (1H, d, *J* = 8.0 Hz, Ar**H**, major rotamer), 7.02 (1H, d, *J* = 8.0 Hz, Ar**H**, minor rotamer), 6.98 (1H, d, *J* = 8.0 Hz, Ar**H**, major rotamer), 5.99 (1H, d, *J* = 10.5 Hz, N**H**, major rotamer), 4.92 – 4.66 (1H, m, C**H₂**, both rotamers), 4.43 – 4.09 (2H, m, C**H₂**, both rotamers), 3.75 (1H, dt, *J* = 13.0, 3.5 Hz, C**H₂**, major rotamer), 3.66 – 3.42 (2H, m, C**H₂**, both rotamers), 3.37 – 3.16 (2H, m, C**H₂**, both rotamers), 2.95 (1H, dt, *J* = 13.5, 7.5 Hz, C**H₂**, major rotamer), 2.90 – 2.70 (2H, m, C**H₂**, major rotamer), 2.45 – 2.35 (1H, m, C**H₂**, major rotamer), 2.30 – 2.17 (1H, m, C**H₂**, major rotamer), 2.09 (1H, dt, *J* = 13.5, 3.5 Hz, C**H₂**, major rotamer), 1.55 – 1.38 (9H, m, 3 x C**H₃**, both rotamers); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 174.7 (**C**O), 171.4 (**C**O), 170.4 (**C**O), 156.5 (Ar**C**), 132.1 (Ar**C**), 129.9 (2 × Ar**C**H), 121.8 (2 x Ar**C**H), 80.4 (**C**(CH_3)), 53.2 (**C**H_2), 52.8 (**C**H_2), 51.8 (**C**H_2), 43.0 (**C**H_2), 39.0 (**C**H_2), 35.3 (**C**H_2), 32.7 (**C**H_2), 28.4 (3 × **C**H_3); HRMS (ESI): calcd. for $C_{20}H_{29}{}^{79}BrN_3O_4$, 454.1336. Found: $[MNa]^+$, 456.1310 (–1.0 ppm error).

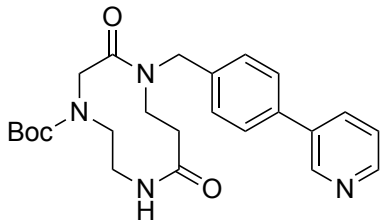
***tert*-Butyl 1-([1,1'-biphenyl]-4-ylmethyl)-2,8-dioxo-1,4,7-triazecane-4-carboxylate (185)**



tert-Butyl 1-(4-bromobenzyl)-2,8-dioxo-1,4,7-triazecane-4-carboxylate **179** (60 mg, 0.136 mmol) and phenylboronic acid (24.9 mg, 0.204 mmol) were dissolved in 1,4-dioxane (2.0 mL). Then Na_2CO_3 (43.3 mg, 0.409 mmol) which dissolved in water (1.0 mL) was added followed by Pd(dppf)Cl_2·CH_2Cl_2 (5.5 mg, 0.007 mmol) and the resulting mixture was purged with argon for 10 minutes. The mixture was stirred and heated at 50 °C for 18 hours under argon. After being allowed to cool to RT, water (10 mL) was added and the two layers were separated. The aqueous layer was extracted with dichloromethane (3 x 10 mL) and the combined organic phases were dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, 1:1 hexane : ethyl acetate → ethyl acetate → 3:1 dichloromethane : acetone) to afford the title compound (53.6 mg, 90%) as a yellow solid. R_f = 0.25 (3:1 dichloromethane : acetone); m.p. 145–149 °C; ν_{max}/cm^{-1} (thin film) 3314, 2975, 1648, 1554, 1455, 1435, 1408, 1366, 1247, 1162, 1129, 1071, 950, 759, 698; δ_H (400 MHz, $CDCl_3$) 7.60 – 7.51 (4H, m, 4 x Ar**H**, both rotamers), 7.42 (2H, m, 2 x Ar**H**, both rotamers), 7.33 (1H, m, Ar**H**, both rotamers), 7.29 – 7.21 (2H, m,2 x Ar**H**, both rotamers), 5.79 (1H, d, J = 8.5 Hz, N**H**, major rotamer), 5.19 (1H, d, *J* = 16.5 Hz, C**H₂**, major rotamer), 5.07 (1H, d, *J* = 14.0 Hz, C**H₂**, major rotamer), 4.35 – 4.23 (1H, m, C**H₂**, both rotamers), 4.19 (1H, d, *J* = 16.5 Hz, C**H₂**, major rotamer), 3.73 (1H, dt, *J* = 14.0, 2.5 Hz, C**H₂**, major rotamer), 3.43 – 3.34 (1H, m, C**H₂**, major rotamer), 3.31 (1H, d, *J* = 14.0 Hz, C**H₂**, major rotamer), 3.16 – 2.97 (2H, m, C**H₂**, major rotamer), 2.88 (1H, d, *J* = 14.0 Hz, C**H₂**, major rotamer), 2.78 (1H, ddd, *J* = 13.0, 8.5, 6.0 Hz, C**H₂**, major rotamer), 2.50 (1H, ddd, *J* = 13.0, 8.5, 4.5 Hz, C**H₂**, major rotamer), 1.52 (9H, s, 3 x C**H₃**, major rotamer), 1.49 (9H, s, 3 x C**H₃**, minor rotamer), 1.46 (9H,

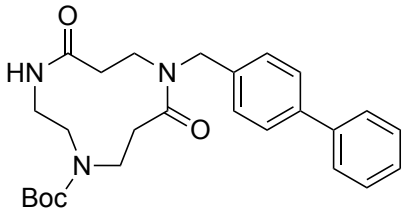
s, 3 x C**H₃**, minor rotamer), 1.40 (9H, s, 3 x C**H₃**, minor rotamer); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 172.7 (**C**O), 170.9 (**C**O), 155.2 (**C**O), 140.7 (Ar**C**), 136.0 (Ar**C**), 128.9 (Ar**C**), 128.8 (Ar**C**H), 127.6 (Ar**C**H), 127.6 (Ar**C**H), 127.4 (Ar**C**H), 127.1 (Ar**C**), 80.2 (O**C**$(CH_3)_3$), 52.6 (**C**H_2), 51.6 (**C**H_2), 49.1 (**C**H_2), 41.7 (**C**H_2), 38.8 (**C**H_2), 35.2 (**C**H_2), 28.3 (3 x **C**H_3); HRMS (ESI) calcd. for $C_{25}H_{31}N_3NaO_4^+$, 460.2207. Found: $[MH]^+$ 460.2214 (−1.6 ppm error).

***tert*-Butyl 2,8-dioxo-1-(4-(pyridin-3-yl)benzyl)-1,4,7-triazecane-4-carboxylate (186)**



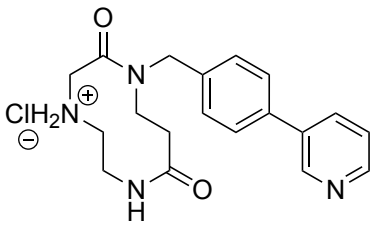
tert-Butyl 1-(4-bromobenzyl)-2,8-dioxo-1,4,7-triazecane-4-carboxylate **179** (60 mg, 0.136 mmol) and pyridine boronic acid (25.1 mg, 0.204 mmol) were dissolved in 1,4-dioxane (2.0 mL). Then Na_2CO_3 (43.3 mg, 0.409 mmol) which dissolved in water (1.0 mL) was added followed by Pd(dppf)Cl_2·CH_2Cl_2 (5.5 mg, 0.007 mmol) and the resulting mixture was purged with argon for 10 minutes. The mixture was stirred and heated at 50 °C for 18 hours under argon. After being allowed to cool to RT, water (10 mL) was added and the two layers were separated. The aqueous layer was extracted with dichloromethane (3 x 10 mL) and the combined organic phases were dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, ethyl acetate → 1:1 dichloromethane : acetone → 1:3 dichloromethane : acetone) to afford the title compound (31.2 mg, 52%) as a yellow solid. R_f = 0.33 (1:3 dichloromethane : acetone); m.p. 134–138 °C; ν_{max}/cm^{-1} (thin film) 3303, 2972, 2928, 1649, 1453, 1430, 1402, 1366, 1246, 1161, 1128, 1070, 1002, 798, 731, 711; δ_H (400 MHz, $CDCl_3$) 8.92 – 8.76 (1H, m, Ar**H**, both rotamers), 8.67 – 8.53 (1H, m, Ar**H**, both rotamers), 7.95 – 7.79 (1H, m, Ar**H**, both rotamers), 7.61 – 7.51 (2H, m, 2 x Ar**H**, both rotamers), 7.44 – 7.29 (3H, m, 3 x Ar**H**, both rotamers), 5.63 (1H, d, *J* = 10.5 Hz, N**H**, major rotamer), 5.23 (1H, d, *J* = 16.5 Hz, C**H₂**, major rotamer), 5.07 (1H, d, *J* = 14.0 Hz, C**H₂**, major rotamer), 4.39 – 4.24 (2H, m, C**H₂**, both rotamers), 4.20 (1H, d, *J* = 16.5 Hz, C**H₂**, major rotamer), 3.85 – 3.72 (1H, m, C**H₂**, major rotamer), 3.31 (1H, d, *J* = 14.0 Hz, C**H₂**, major rotamer), 3.13 – 2.98 (2H, m, C**H₂**, both rotamers), 2.93 – 2.75 (2H, m, C**H₂**, major rotamer), 2.52 (1H, ddd, *J* = 13.5, 9.0, 5.0 Hz, C**H₂**, major rotamer), 1.67 (9H, s, 3 x C**H₃**, minor rotamer), 1.54 (9H, s, 3 x C**H₃**, major rotamer), 1.51 (9H, s, 3 x C**H₃**, minor rotamer), 1.50 (9H, s, 3 x C**H₃**, minor rotamer), 1.42 (9H, s, 3 x C**H₃**, minor rotamer); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 172.8 (**C**O), 170.9 (**C**O), 155.2 (**C**O), 148.5(Ar**C**H), 148.2(Ar**C**H), 137.3(Ar**C**), 137.1 (Ar**C**), 136.4 (Ar**C**H), 134.8 (Ar**C**), 128.0 (Ar**C**H), 127.7 (Ar**C**H), 127.1 (Ar**C**), 123.9 (Ar**C**H), 81.5 (O**C**$(CH_3)_3$), 52.7 (**C**H_2), 51.7 (**C**H_2), 49.3 (**C**H_2), 41.9 (**C**H_2), 38.9 (**C**H_2), 35.4 (**C**H_2), 28.4 (3 x **C**H_3); HRMS (ESI) calcd. for $C_{24}H_{31}N_4O_4^+$, 439.2340. Found: $[MH]^+$ 439.2340 (0.1 ppm error).

***tert*-Butyl 8-([1,1'-biphenyl]-4-ylmethyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate (187)**



tert-Butyl 8-(4-bromobenzyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate **183** (100 mg, 0.220 mmol) and phenylboronic acid (40.2 mg, 0.330 mmol) were dissolved in 1,4-dioxane (2.0 mL). Then Na_2CO_3 (70.0 mg, 0.660 mmol) which dissolved in water (1.0 mL) was added followed by $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (8.9 mg, 0.011 mmol) and the resulting mixture was purged with argon for 10 minutes. The mixture was stirred and heated at 50 °C for 18 hours under argon. After being allowed to cool to RT, water (10 mL) was added and the two layers were separated. The aqueous layer was extracted with dichloromethane (3 x 10 mL) and the combined organic phases were dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, 1:1 hexane : ethyl acetate → ethyl acetate → 3:1 dichloromethane : acetone) to afford the title compound (78.5 mg, 79%) as a yellow solid. R_f = 0.27 (3:1 dichloromethane : acetone); m.p. 126–128 °C; v_{max}/cm^{-1} (thin film) 3340, 1975, 1629, 1477, 1434, 1358, 1262, 1243, 1190, 1129, 1082, 1006, 985, 797; δ_H (400 MHz, $CDCl_3$) data for the major rotamer only: 7.58 – 7.52 (4H, m, 4 x Ar**H**), 7.42 (2H, t, *J* = 7.5 Hz, 2 x Ar**H**), 7.39 – 7.31 (2H, m, 2 x Ar**H**), 7.24 – 7.17 (1H, m, Ar**H**), 6.04 (1H, d, *J* = 10.0 Hz, N**H**), 4.92 (1H, d, *J* = 17.1 Hz, C**H₂**), 4.71 (1H, s, C**H₂**), 4.52 – 4.20 (2H, m, C**H₂**), 3.78 (1H, dt, *J* = 13.5, 3.5 Hz, C**H₂**), 3.65 – 3.25 (4H, m, C**H₂**), 3.09 – 2.97 (1H, m, C**H₂**), 2.96 – 2.80 (2H, m, C**H₂**), 2.52 – 2.36 (1H, m, C**H₂**), 2.28 – 2.17 (1H, m, C**H₂**), 1.54 – 1.46 (9H, m, 3 x C**H₃**); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 174.7 (**C**O), 170.5 (**C**O), 156.5 (**C**O), 140.9 (Ar**C**), 135.8 (Ar**C**), 128.9 (Ar**C**), 128.9 (Ar**C**H), 127.7 (Ar**C**H), 127.6 (Ar**C**H), 127.1 (Ar**C**H), 127.1 (Ar**C**), 80.0 (O**C**$(CH_3)_3$), 53.1 (**C**H_2), 52.8 (**C**H_2), 51.8 (**C**H_2), 42.7 (**C**H_2), 39.1 (**C**H_2), 35.3 (**C**H_2), 32.8 (**C**H_2), 28.5 (3 x **C**H_3); HRMS (ESI) calcd. for $C_{26}H_{33}N_3NaO_4^+$, 474.2363. Found: $[MH]^+$ 474.2355 (1.7 ppm error).

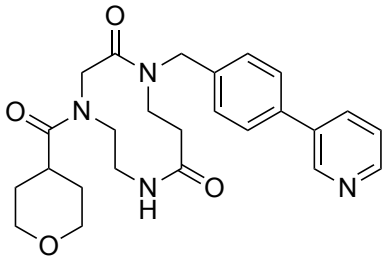
2,8-Dioxo-1-(4-(pyridin-3-yl)benzyl)-1,4,7-triazecan-4-ium chloride (189)



tert-Butyl 2,8-dioxo-1-(4-(pyridin-3-yl)benzyl)-1,4,7-triazecane-4-carboxylate **186** (50 mg, 0.114 mmol) was dissolved in 4 M HCl in dioxane (3.0 mL). The solution was stirred at room temperature for 10 min, after which the solution was concentrated in vacuo to afford the title compound (47 mg, 110%) as a white solid. R_f = 0 (10:1 dichloromethane : methanol); m.p. 189–195 °C; δ_H (400 MHz, Methanol-*D₄*) data for the major rotamer only: 9.20 (1H, d, *J* = 2.0 Hz, Ar**H**), 8.98 – 8.91 (1H, m, Ar**H**), 8.85 (1H, d, *J* = 5.5 Hz, Ar**H**), 8.19 (1H, dd, *J* = 8.5, 5.5 Hz,

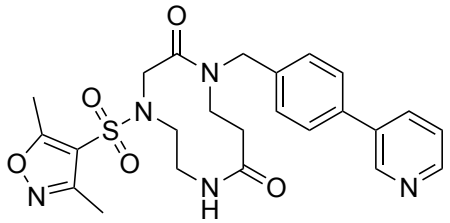
Ar**H**), 7.89 – 7.81 (2H, m, 2 x Ar**H**), 7.60 – 7.52 (2H, m, 2 x Ar**H**), 5.59 (1H, d, *J* = 15.5 Hz, C**H₂**), 4.26 – 4.13 (1H, m, C**H₂**), 4.07 (1H, d, *J* = 15.5 Hz, C**H₂**), 4.04 – 3.93 (2H, m, C**H₂**), 3.92 – 3.81 (1H, m, C**H₂**), 3.52 (1H, dt, *J* = 16.0, 3.5 Hz, C**H₂**), 3.45 – 3.38 (1H, m, C**H₂**), 3.26 – 3.09 (2H, m, C**H₂**), 2.61 (1H, td, *J* = 12.5, 3.0 Hz, C**H₂**), 2.29 (1H, dd, *J* = 12.5, 4.0 Hz, C**H₂**); ^{13}C NMR signal is too weak to distinguish because the compound is difficult to dissolve in the solvent; HRMS (ESI) calcd. for $C_{19}H_{23}N_4O_2^+$, 339.1816. Found: $[MH]^+$ 339.1811 (1.2 ppm error).

1-(4-(Pyridin-3-yl)benzyl)-4-(tetrahydro-2H-pyran-4-carbonyl)-1,4,7-triazecane-2,8-dione (190)



tert-Butyl 2,8-dioxo-1-(4-(pyridin-3-yl)benzyl)-1,4,7-triazecane-4-carboxylate **186** (50 mg, 0.114 mmol) was dissolved in 4 M HCl in dioxane (3.0 mL). The solution was stirred at room temperature for 10 min, after which the solution was concentrated in vacuo to yield the salt product **189**. This salt was dissolved in anhydrous DCM (3.0 mL) at room temperature and the solution was cooled to 0 °C using an ice bath. Triethylamine (0.05 mL, 0.342 mmol) was added dropwise, followed by tetrahydro-*2H*-pyran-4-carbonyl chloride (21.2 mg, 0.143 mmol) and DMAP (1.4 mg, 0.011 mmol). The solution was allowed to gradually warm to room temperature while being stirred for 18 hours. The solution was diluted with ethyl acetate (10 mL) and washed with brine (10 mL). The aqueous layer was then extracted with ethyl acetate (3 x 10 mL). The organic layers were then combined, dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, ethyl acetate → 50:1 dichloromethane : methanol → 20:1 dichloromethane : methanol) to afford the title compound (38.0 mg, 74%) as a yellow solid. R_f = 0.45 (20:1 dichloromethane : methanol); m.p. 159–162 °C; ν_{max}/cm^{-1} (thin film) 3318, 2930, 1641, 1479, 1408, 1365, 1353, 1245, 1165, 1138, 759, 731, 698; δ_H (400 MHz, $CDCl_3$) data for the major rotamer only: 8.88 – 8.81 (1H, m, Ar**H**), 8.65 – 8.59 (1H, m, Ar**H**), 7.93 – 7.86 (1H, m, Ar**H**), 7.60 – 7.49 (2H, m,2 x Ar**H**), 7.45 – 7.36 (2H, m, 2 x Ar**H**), 7.35 – 7.27 (1H, m, Ar**H**), 6.45 – 6.19 (1H, m, N**H**), 4.27 – 4.20 (1H, m, C**H**), 4.13 – 3.81 (4H, m, 2 x C**H₂**), 3.70 – 3.59 (1H, m, C**H₂**), 3.53 – 3.29 (4H, m,2 x C**H₂**), 3.16 (1H, t, *J* = 7.5 Hz, C**H₂**), 3.02 (1H, ddd, *J* = 14.0, 9.0, 5.5 Hz, C**H₂**), 2.85 – 2.71 (1H, m, C**H₂**), 2.37 – 2.20 (1H, m, C**H₂**), 2.04 – 1.80 (2H, m, C**H₂**), 1.70 (2H, td, *J* = 9.0, 4.0 Hz, C**H₂**), 1.61 – 1.50 (1H, m, C**H₂**), 0.93 – 0.75 (2H, m, C**H₂**); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 175.0 (**C**O), 171.9 (**C**O), 167.6 (**C**O), 148.4 (Ar**C**H), 148.0 (Ar**C**H), 135.2 (Ar**C**), 129.2 (Ar**C**), 129.0 (Ar**C**H), 128.0 (Ar**C**), 127.8 (Ar**C**), 127.7 (Ar**C**H), 124.1 (Ar**C**H), 67.3 (**C**H), 54.1 (**C**H$_2$), 50.9 (**C**H$_2$), 48.6 (**C**H$_2$), 46.3 (**C**H$_2$), 44.9 (**C**H$_2$), 42.1 (**C**H$_2$), 38.9 (**C**H$_2$), 34.8 (**C**H$_2$), 29.7 (**C**H$_2$), 29.2 (**C**H$_2$); HRMS (ESI) calcd. for $C_{25}H_{31}N_4O_4^+$, 451.2340. Found: $[MH]^+$ 451.2371 (−6.8 ppm error).

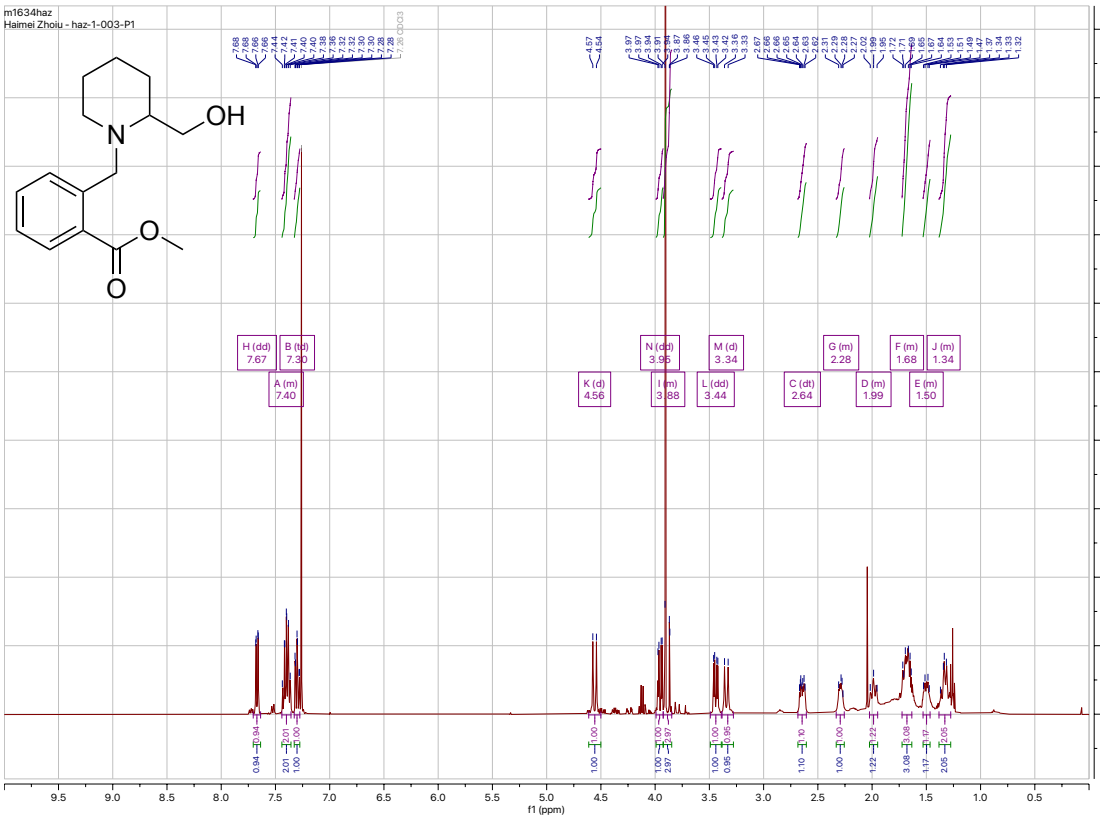
4-((3,5-Dimethylisoxazol-4-yl)sulfonyl)-1-(4-(pyridin-3-yl)benzyl)-1,4,7-triazecane-2,8-dione (196)

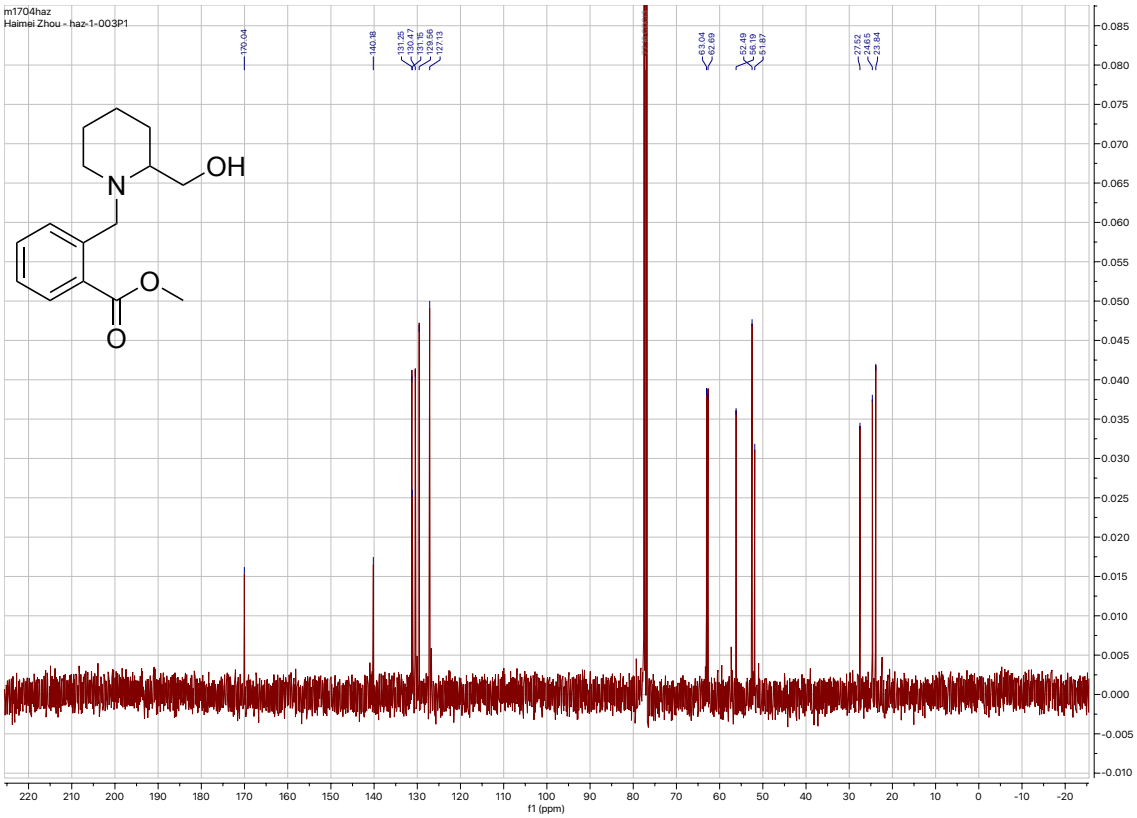


tert-Butyl 2,8-dioxo-1-(4-(pyridin-3-yl)benzyl)-1,4,7-triazecane-4-carboxylate **186** (50 mg, 0.114 mmol) was dissolved in 4 M HCl in dioxane (3.0 mL). The solution was stirred at room temperature for 10 minutes, after which the solution was concentrated in vacuo to yield the salt product **189**. This salt was dissolved in anhydrous DCM (3.0 mL) at room temperature and the solution was cooled to 0 °C using an ice bath. Triethylamine (0.05 mL, 0.342 mmol) was added dropwise, followed by 3,5-dimethylisoxazole-4-sulfonyl chloride (28.0 mg, 0.143 mmol) and DMAP (1.4 mg, 0.011 mmol). The solution was allowed to gradually warm to room temperature while being stirred for 18 hours. The solution was diluted with ethyl acetate (10 mL) and washed with brine (10 mL). The aqueous layer was then extracted with ethyl acetate (3 x 10 mL). The organic layers were then combined, dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, ethyl acetate → 50:1 dichloromethane : methanol → 20:1 dichloromethane : methanol) to afford the title compound (30.1 mg, 53%) as a brown solid. R_f = 0.35 (20:1 dichloromethane : methanol); m.p. 173–177 °C; ν_{max}/cm^{-1} (thin film) 2926, 1647, 1432, 1337, 1262, 1176, 1125, 798, 755; δ_H (400 MHz, $CDCl_3$) data for the major rotamer only: 8.82 (1H, s, Ar**H**), 8.59 (1H, s, Ar**H**), 7.86 (1H, ddd, *J* = 8.0, 5.0, 3.0 Hz, Ar**H**), 7.61 – 7.56 (1H, m, Ar**H**), 7.56 – 7.49 (1H, m, Ar**H**), 7.42 – 7.29 (3H, m, 3 x Ar**H**), 6.27 (1H, d, *J* = 8.0 Hz, N**H**), 5.24 (1H, t, *J* = 18.5 Hz, C**H₂**), 4.51 – 4.42 (1H, m, C**H₂**), 4.22 – 4.05 (1H, m, C**H₂**), 3.92 – 3.77 (1H, m, C**H₂**), 3.70 – 3.49 (1H, m, C**H₂**), 3.43 – 3.15 (3H, m, C**H₃**), 3.10 – 2.97 (1H, m, C**H₂**), 2.61 (3H, d, *J* = 6.5 Hz, C**H₃**), 2.58 – 2.47 (1H, m, C**H₂**), 2.37 (3H, d, *J* = 15.5 Hz, C**H₂**), 2.16 (2H, d, *J* = 15.5 Hz, C**H₂**); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 174.4 (**C**O), 170.9 (**C**O), 157.5 (Ar**C**), 148.8 (Ar**C**H), 148.2(Ar**C**H), 137.7(Ar**C**), 136.5 (Ar**C**), 134.4 (Ar**C**H), 129.1 (Ar**C**), 127.9 (Ar**C**H), 127.7 (Ar**C**H), 127.5 (Ar**C**), 123.8 (Ar**C**H), 113.8 (Ar**C**) 53.9 (**C**H_2), 53.1 (**C**H_2), 43.1 (**C**H_2), 35.2 (**C**H_2), 29.4 (**C**H_2), 28.4 (**C**H_2), 13.3 (**C**H_3), 11.7 (**C**H_3); HRMS (ESI) calcd. for $C_{24}H_{28}N_5O_5S^+$, 498.1806. Found: $[MH]^+$ 498.1788 (3.5 ppm error).

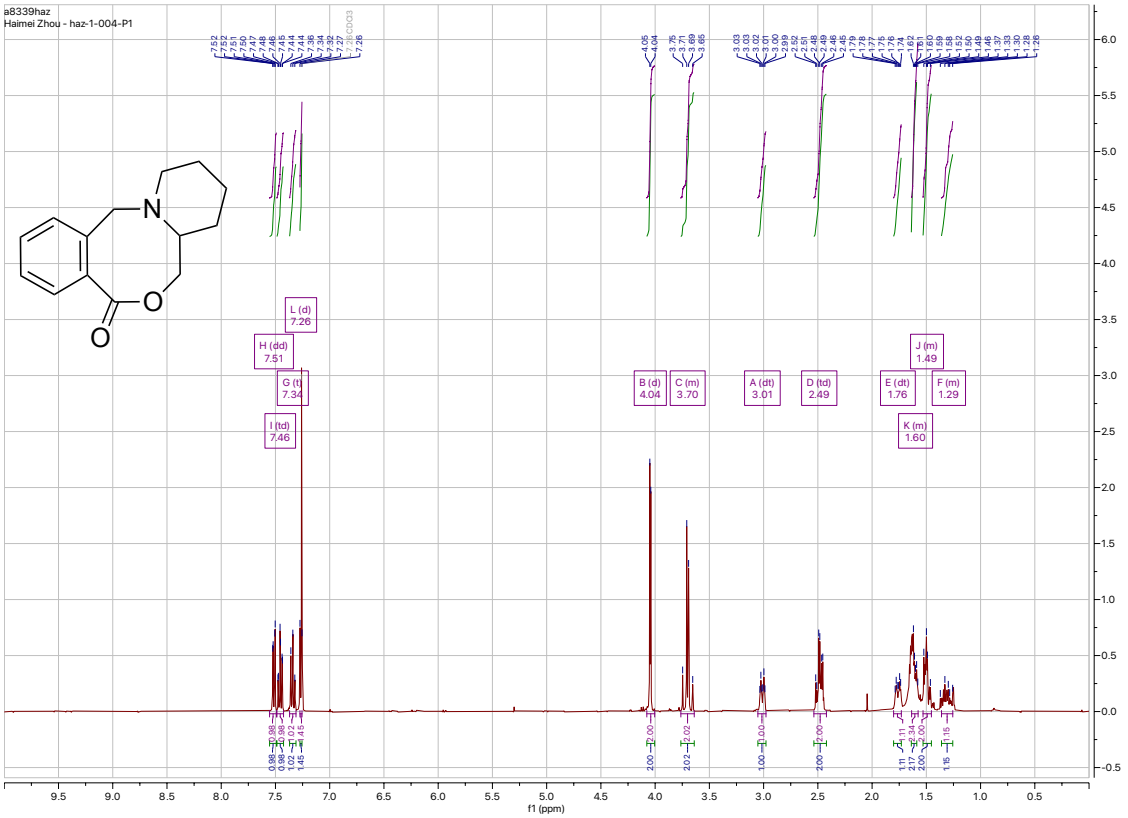
5.3 NMR Spectra

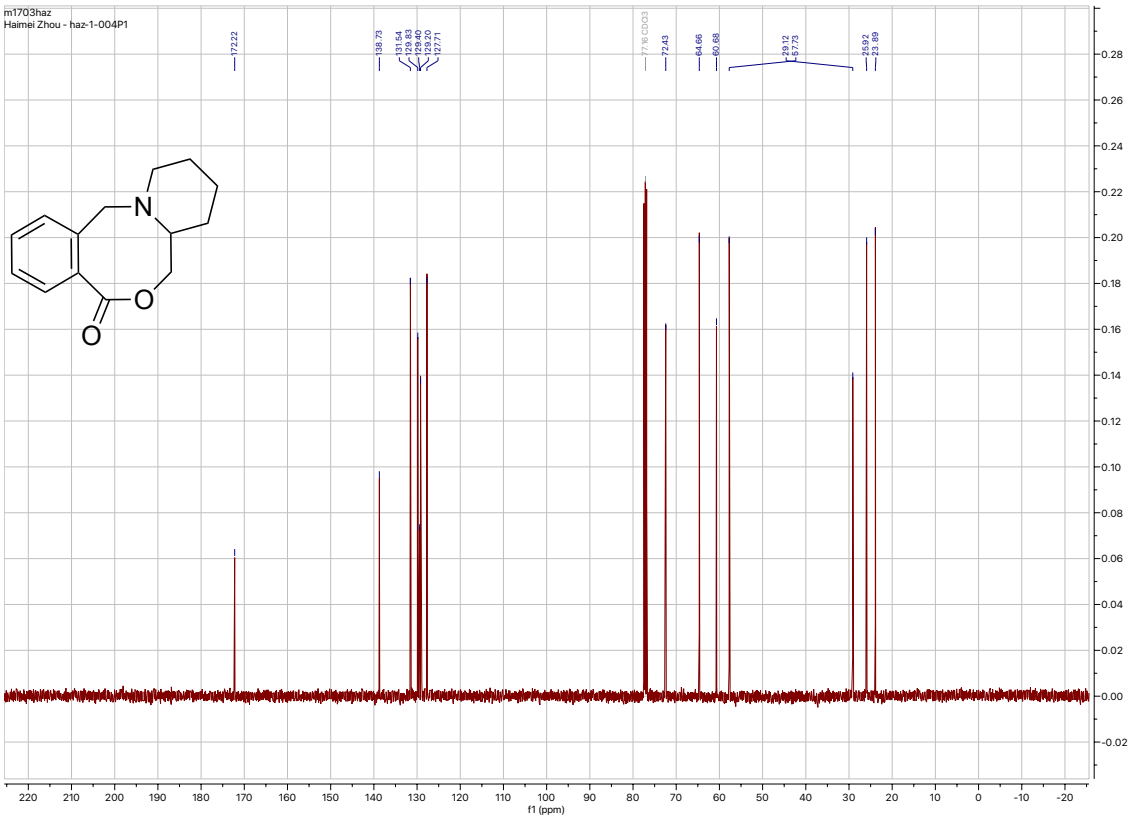
Methyl 2-((2-(hydroxymethyl)piperidin-1-yl)methyl)benzoate (80)



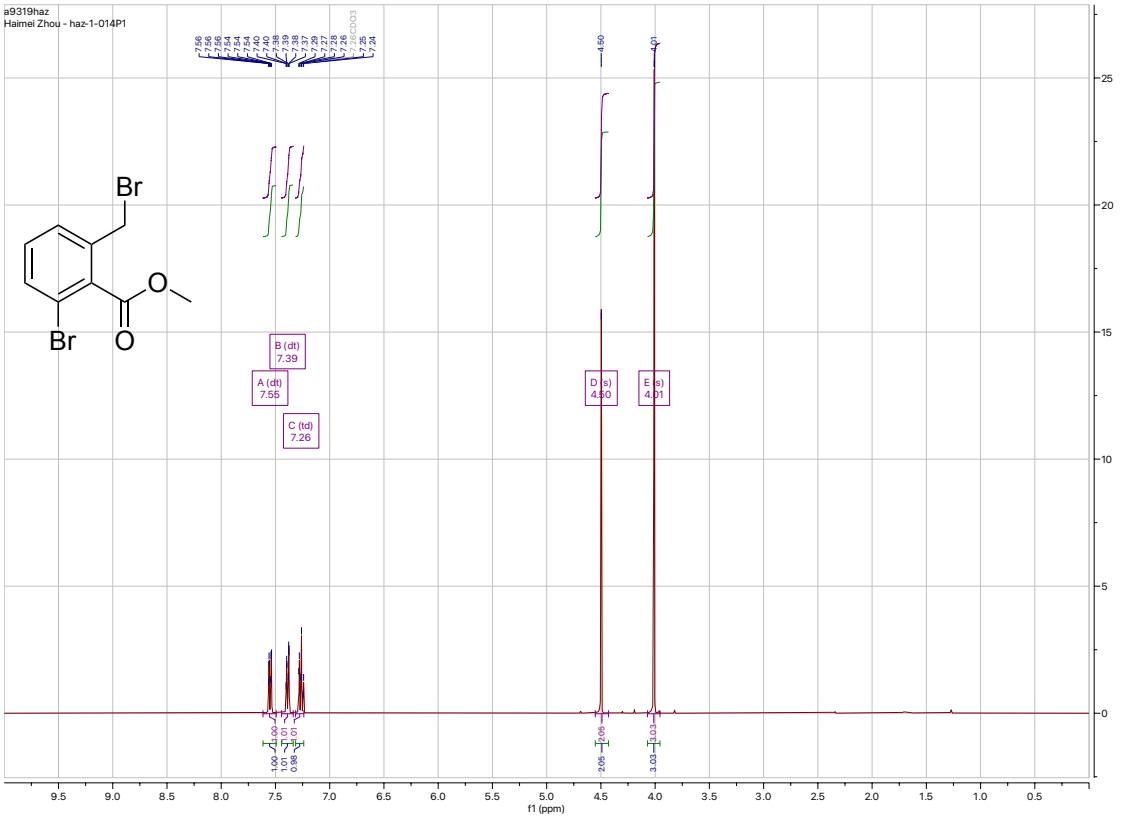


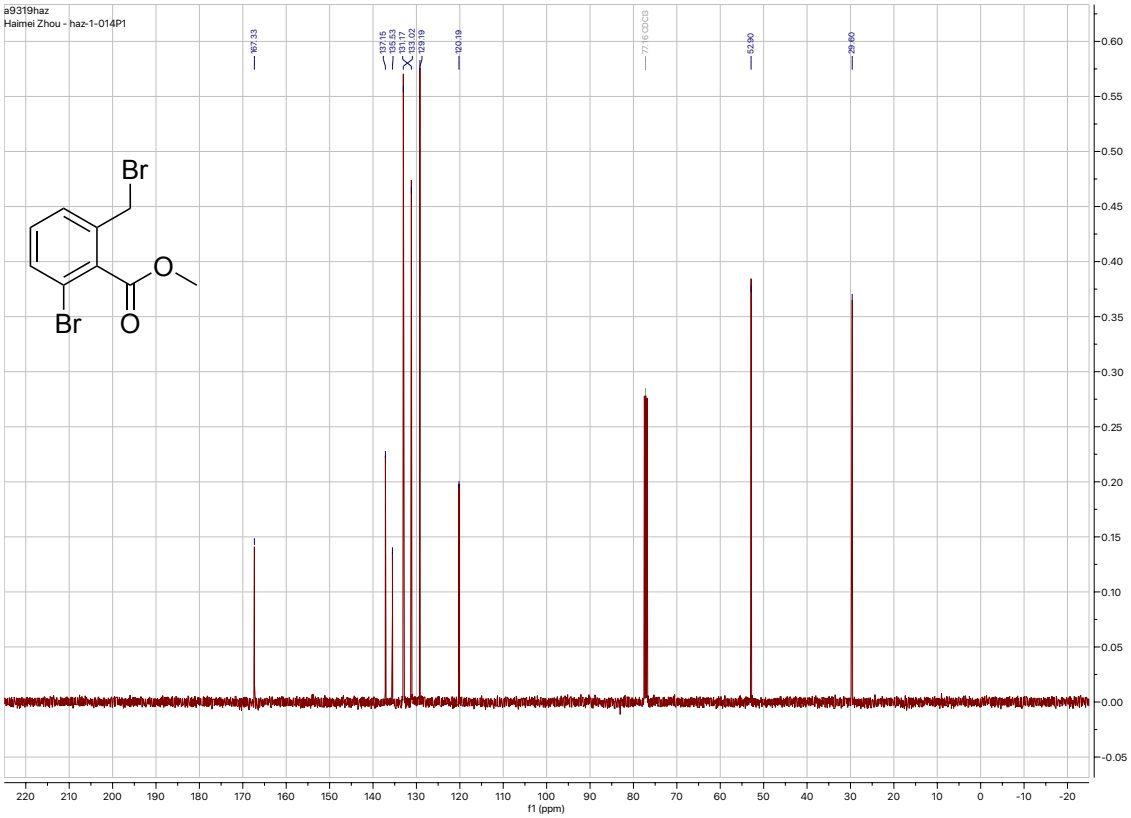
7,7a,8,9,10,11-Hexahydrobenzo[*f*]pyrido[2,1-*c*][1,4]oxazocin-5(13*H*)-one (85)



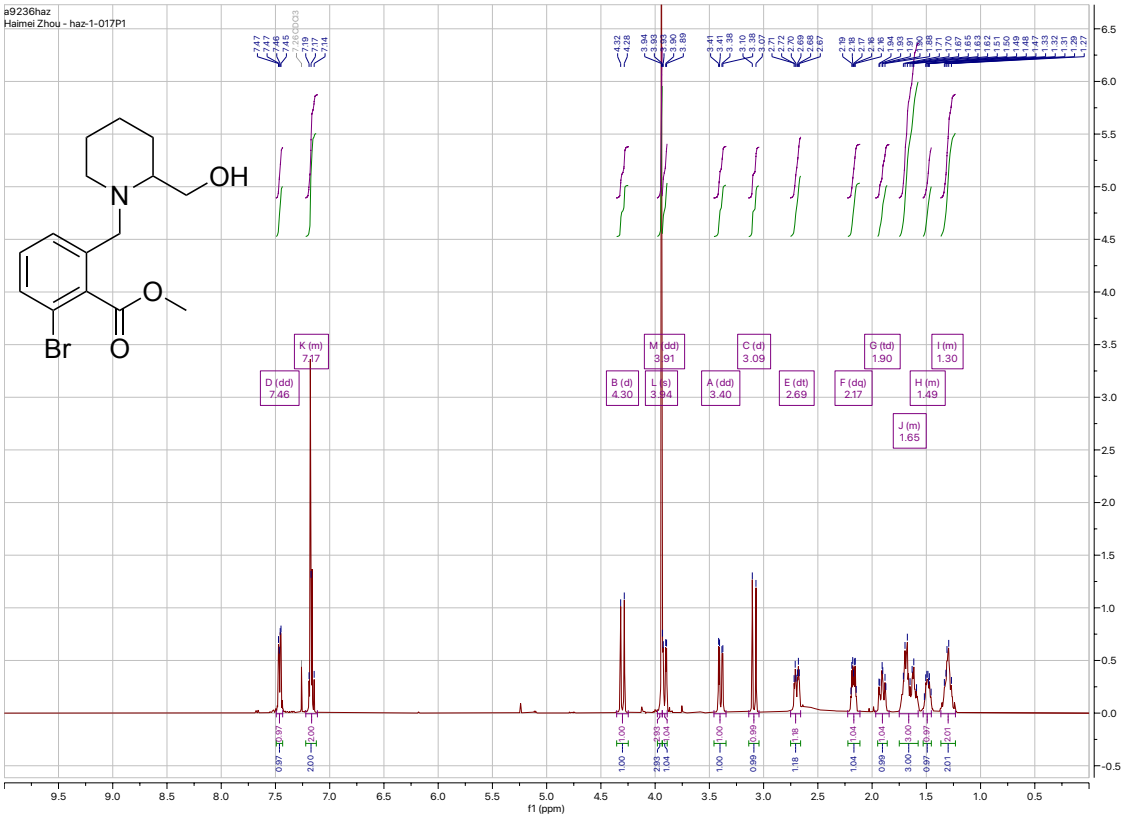


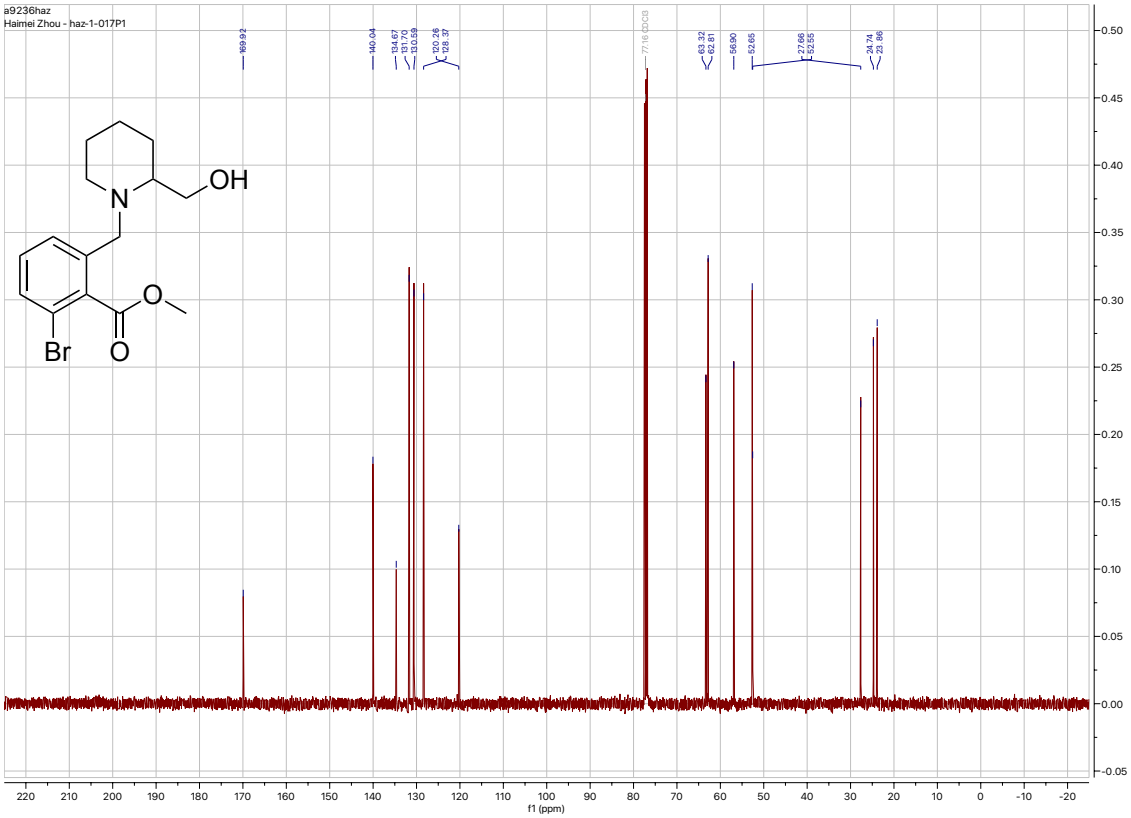
Methyl 2-bromo-6-(bromomethyl)benzoate (88)



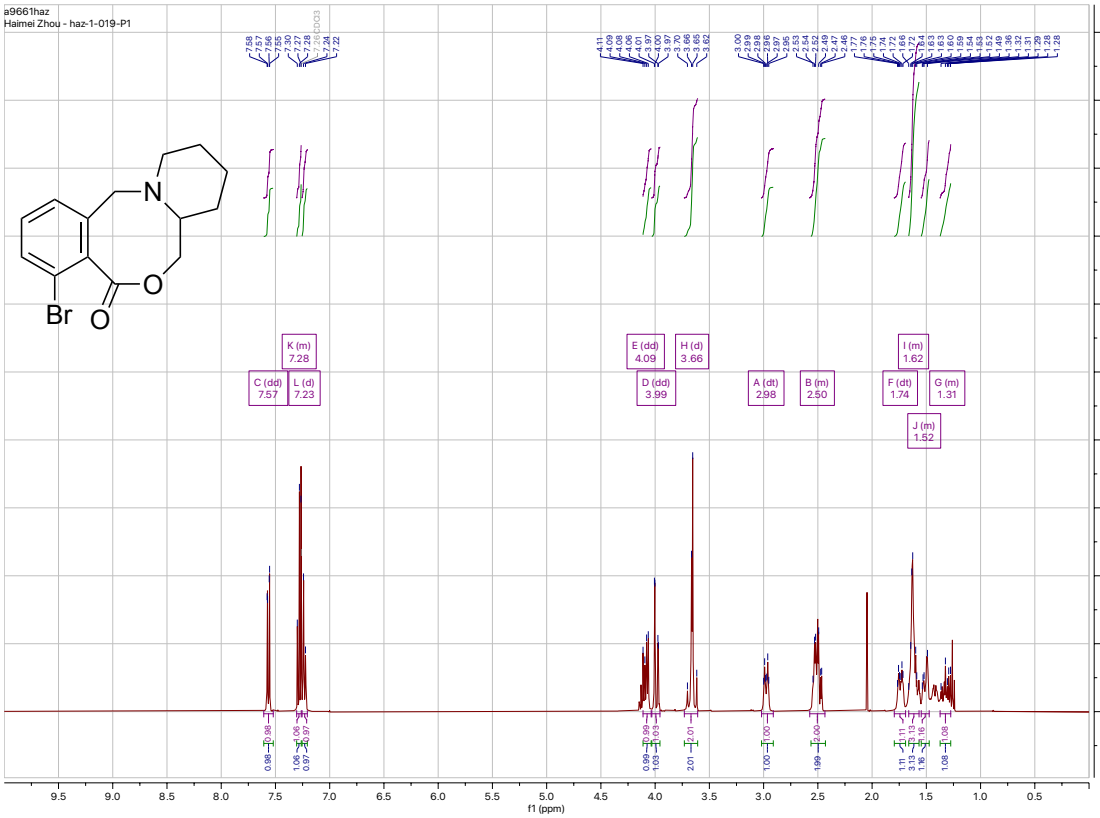


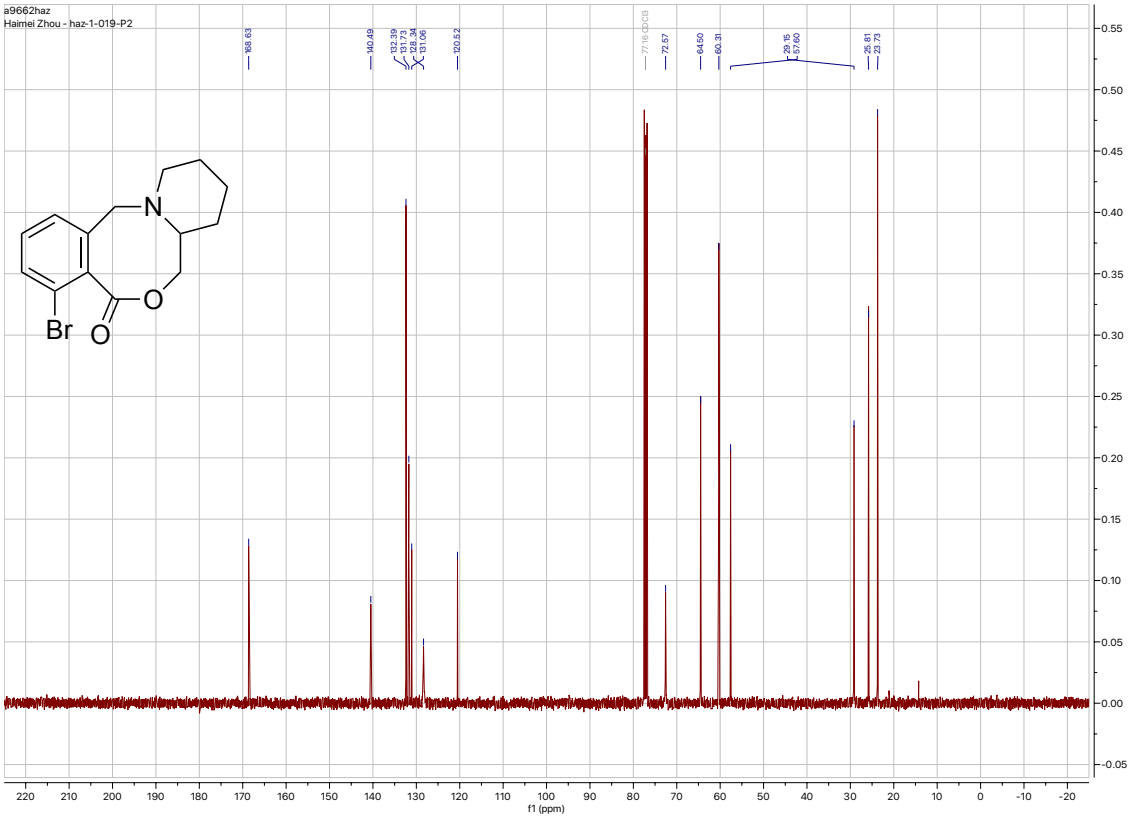
Methyl 2-bromo-6-((2-(hydroxymethyl)piperidin-1-yl)methyl)benzoate (91)



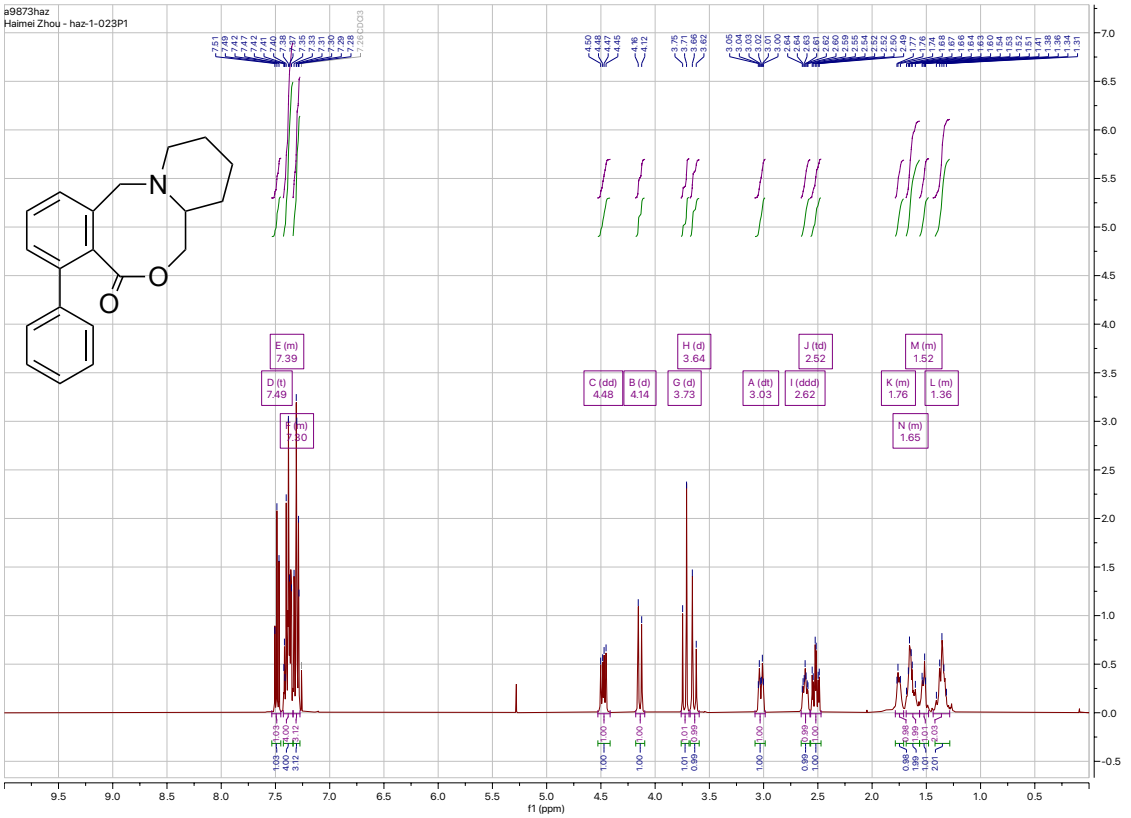


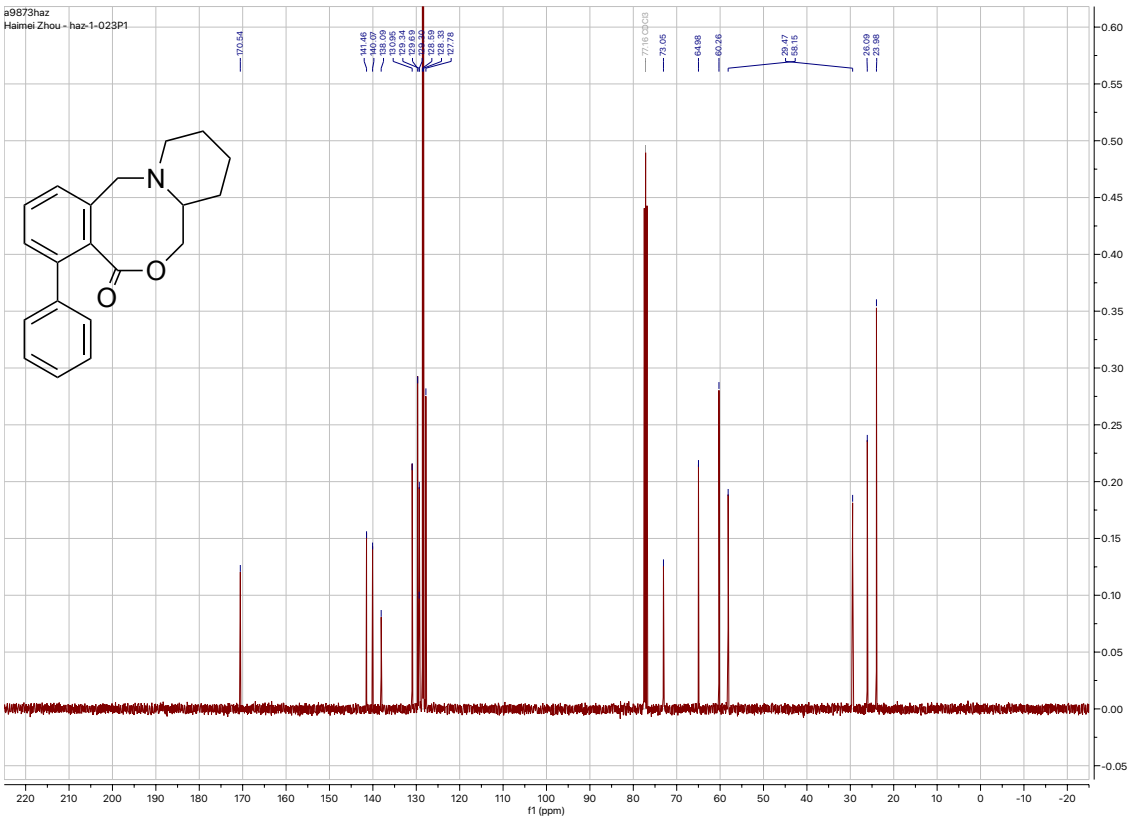
4-Bromo-7,7a,8,9,10,11-hexahydrobenzo[*f*]pyrido[2,1-*c*][1,4]oxazocin-5(13*H*)-one (98)



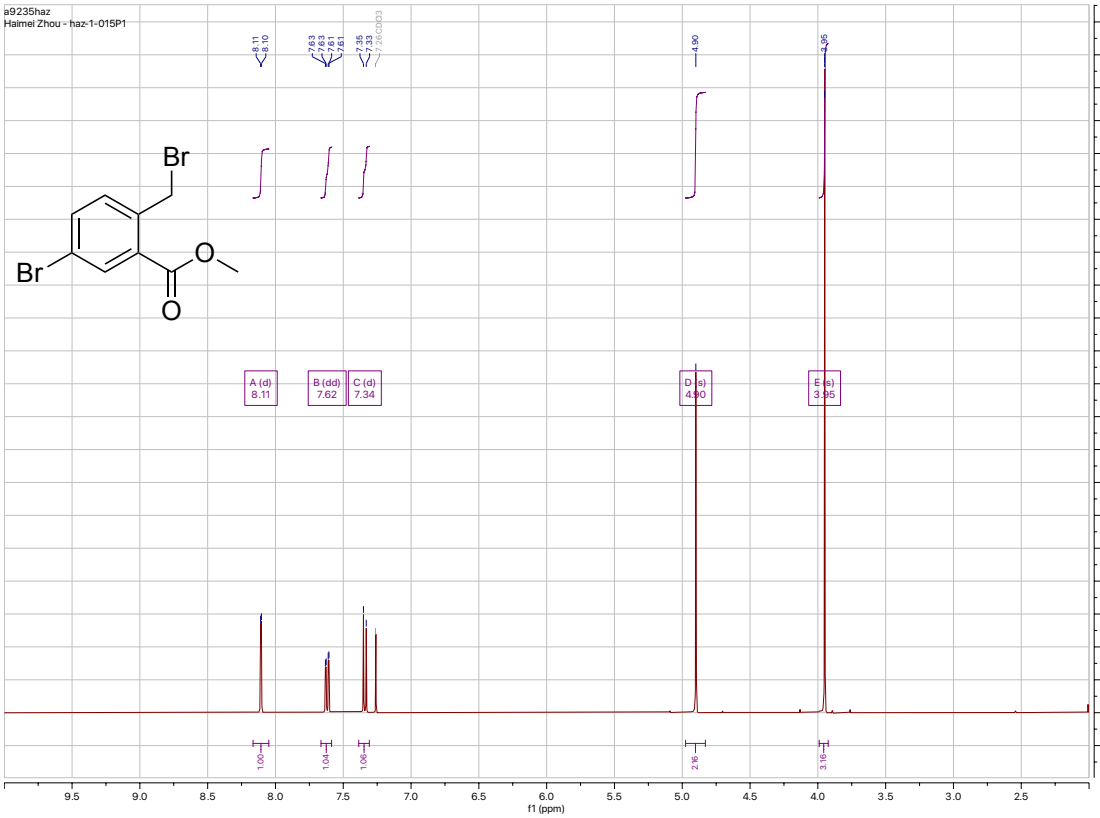


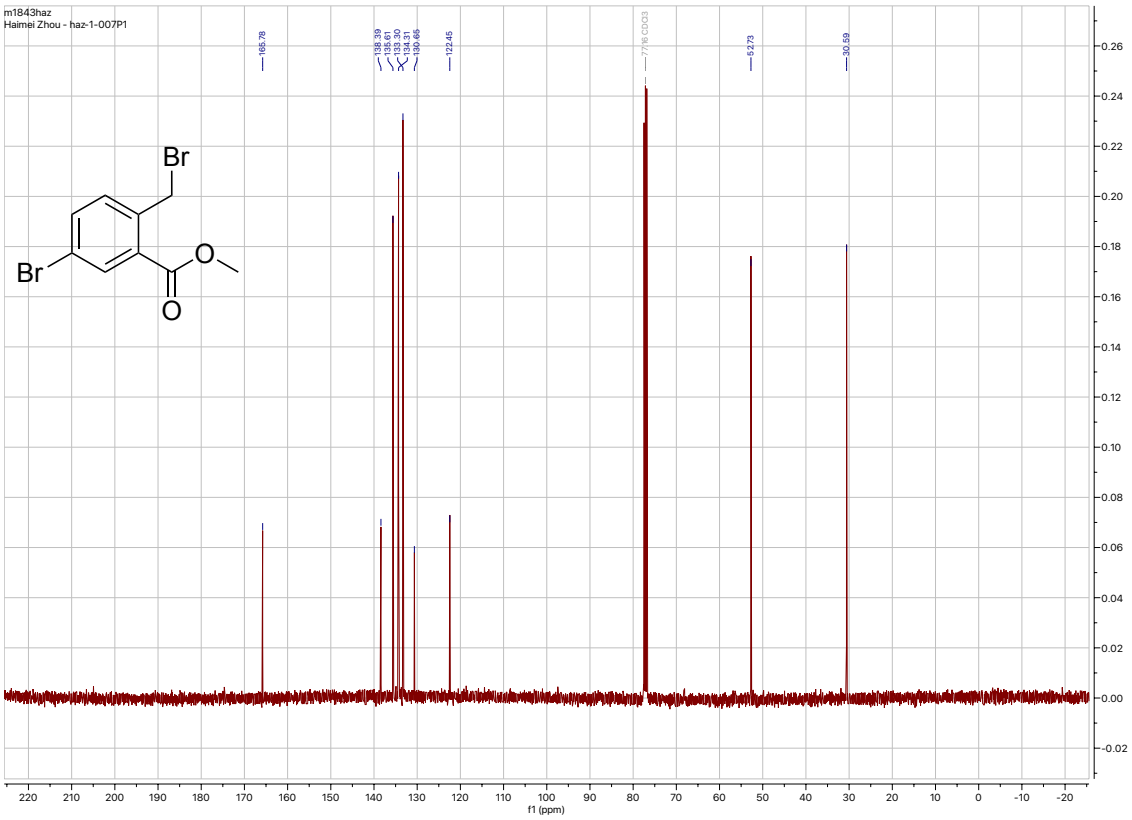
4-Phenyl-7,7a,8,9,10,11-hexahydrobenzo[*f*]pyrido[2,1-*c*][1,4]oxazocin-5(13*H*)-one (111)



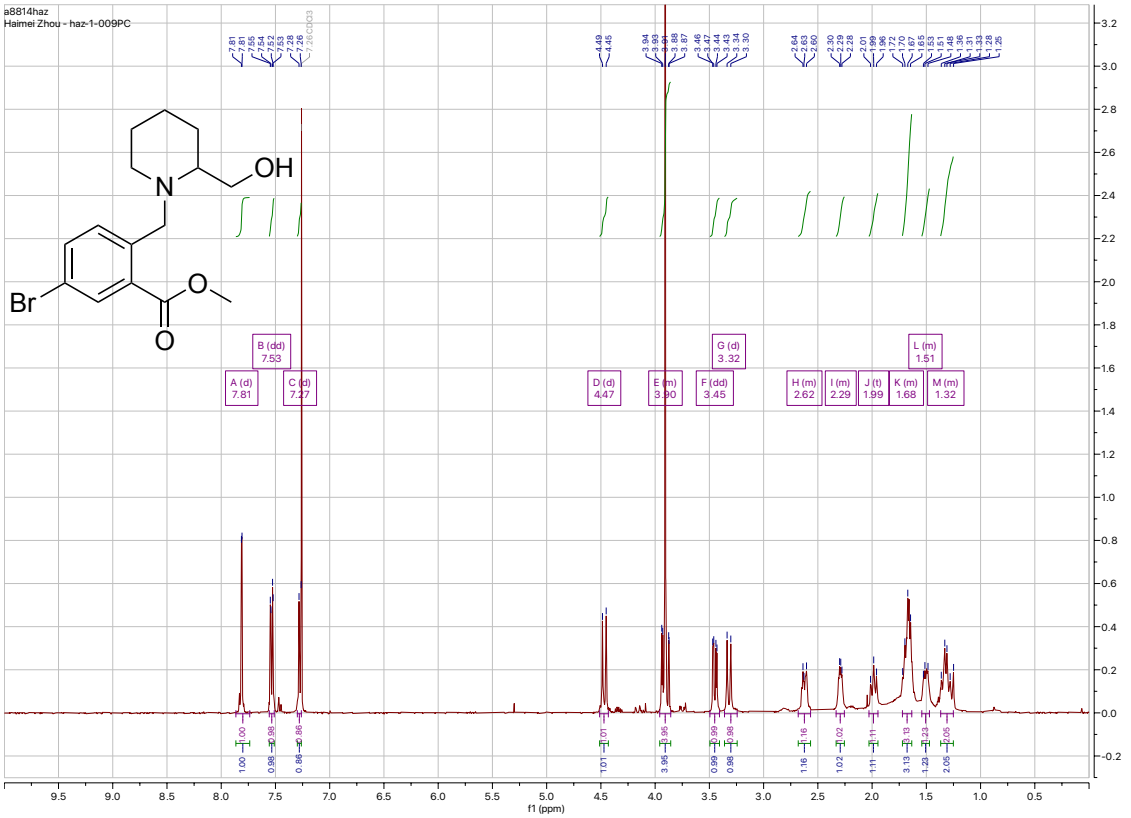


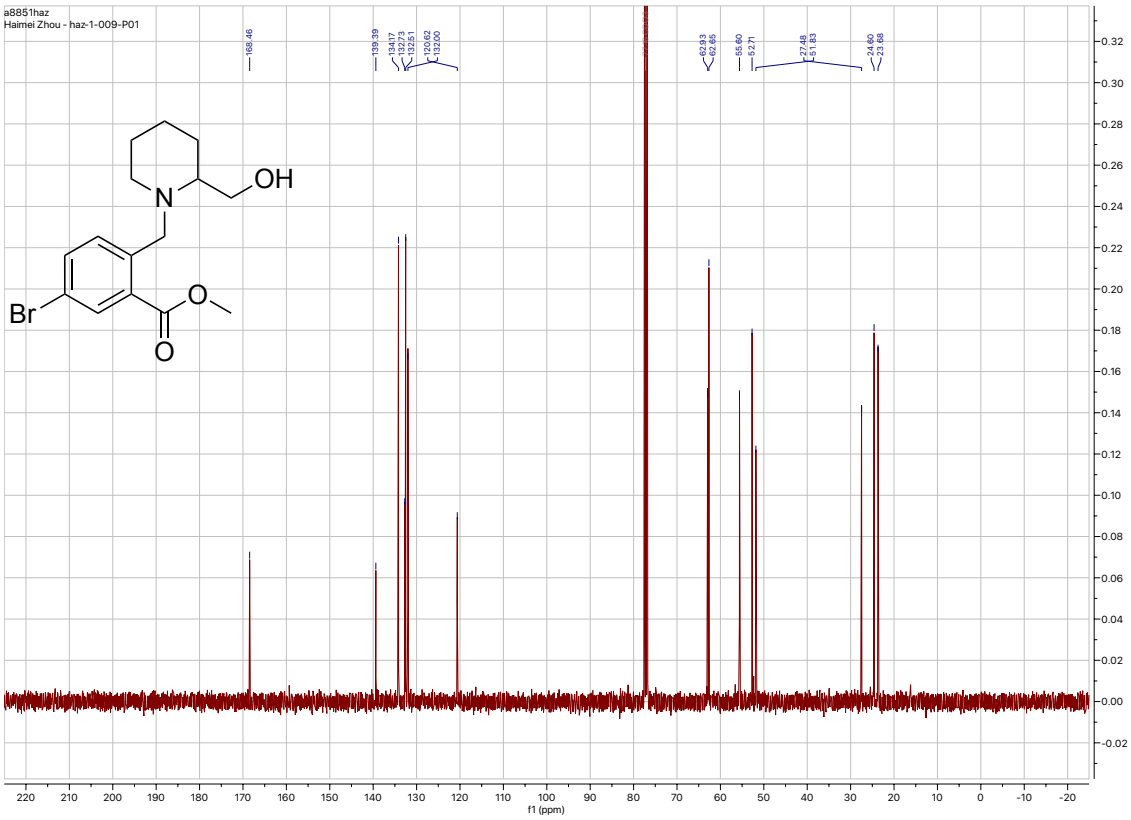
Methyl 5-bromo-2-(bromomethyl)benzoate (89)



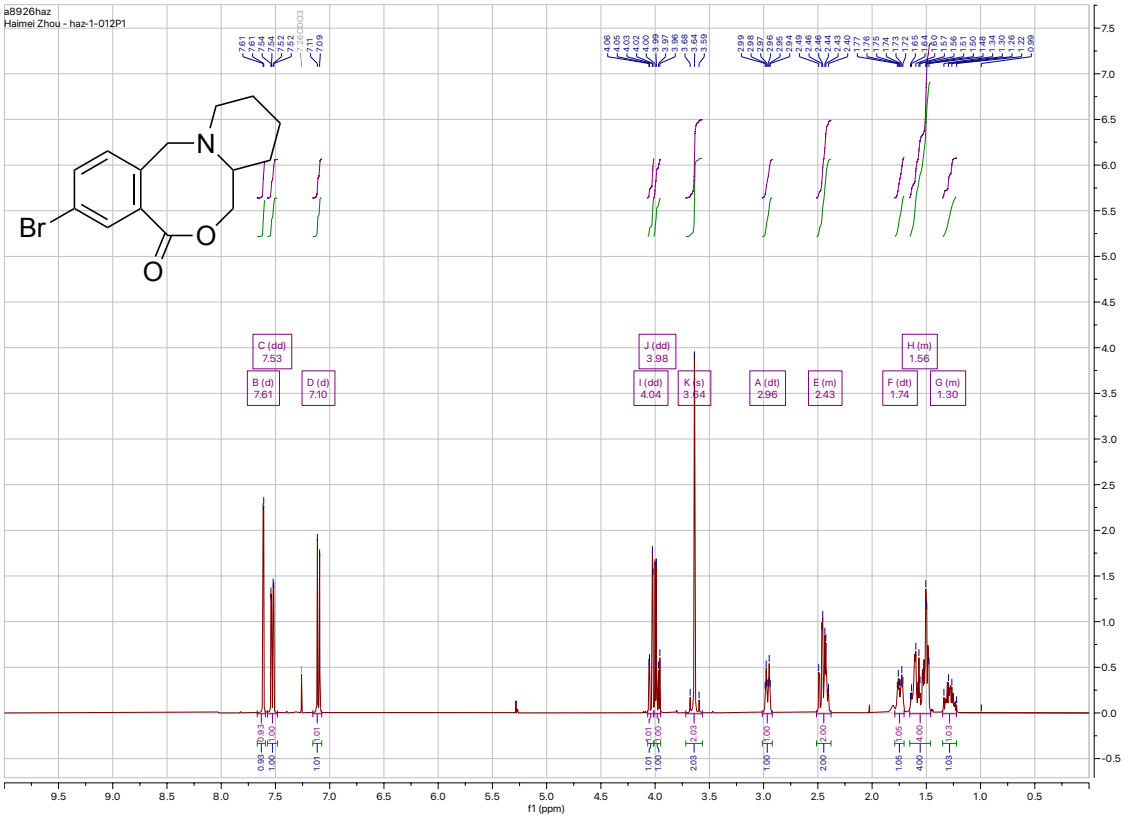


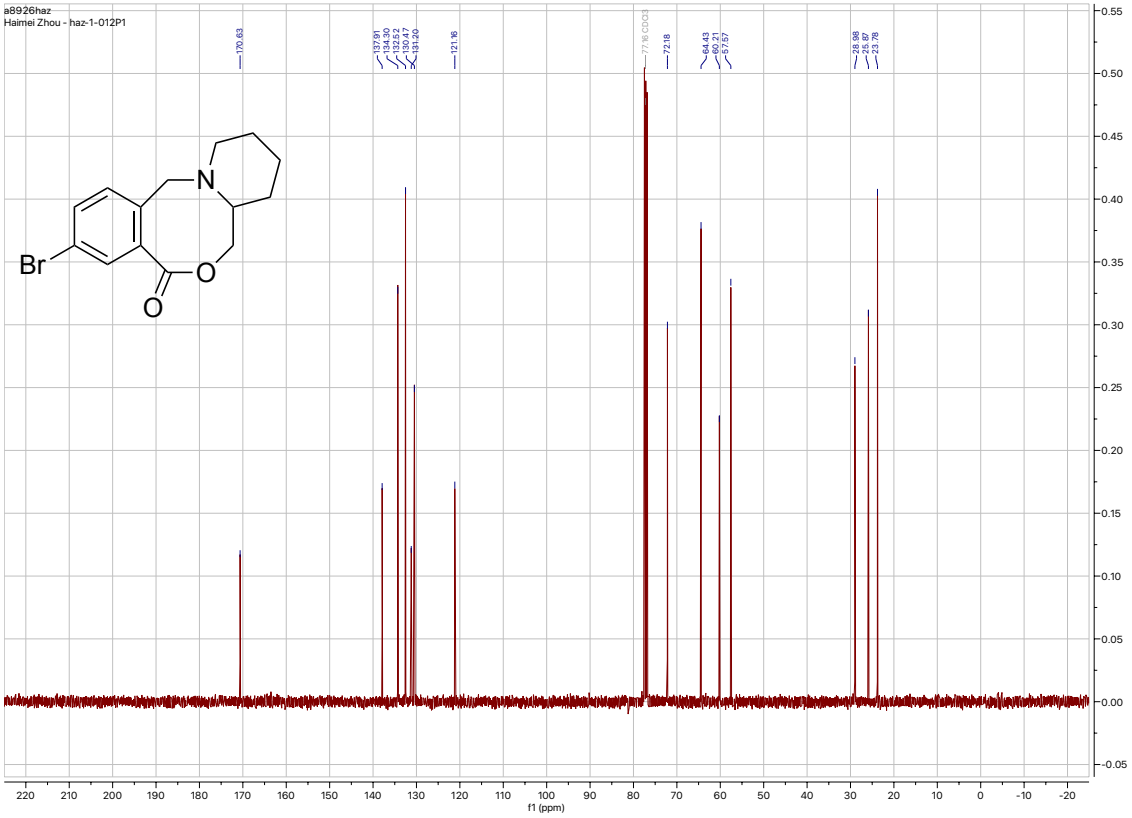
Methyl 5-bromo-2-((2-(hydroxymethyl)piperidin-1-yl)methyl)benzoate (92)



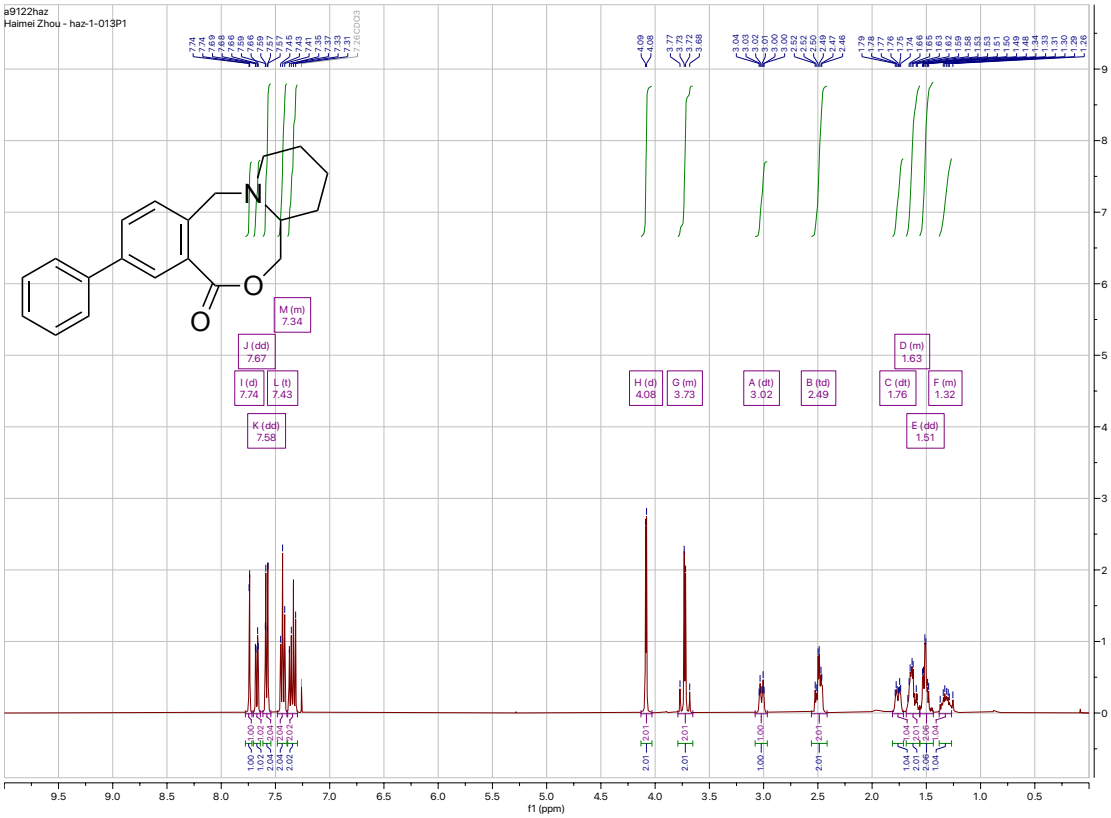


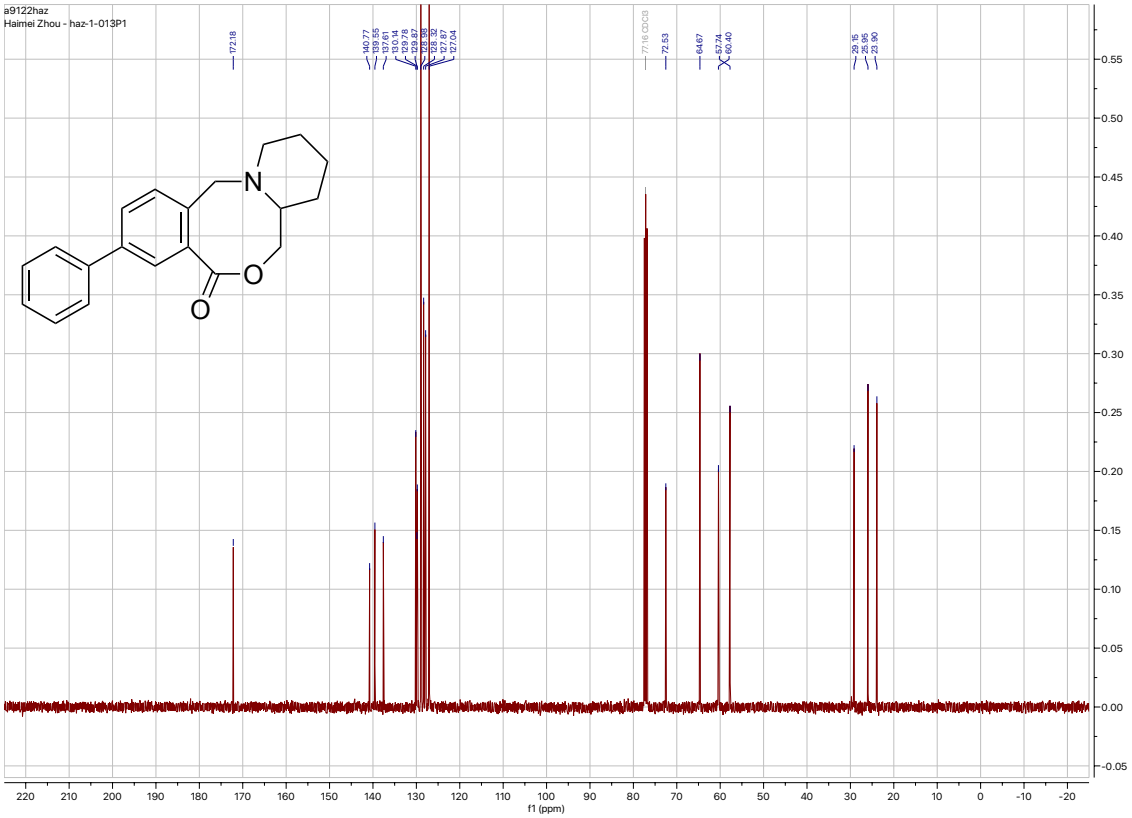
3-Bromo-7,7a,8,9,10,11-hexahydrobenzo[*f*]pyrido[2,1-*c*][1,4]oxazocin-5(13*H*)-one (99)



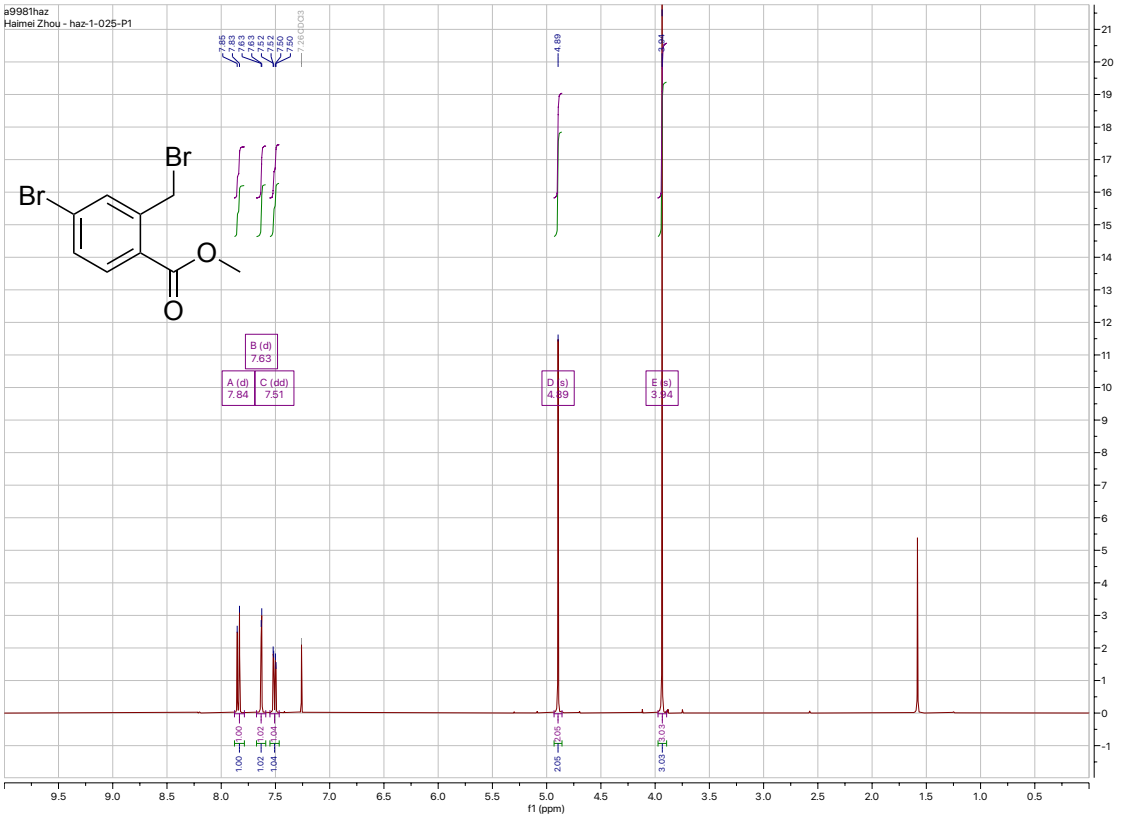


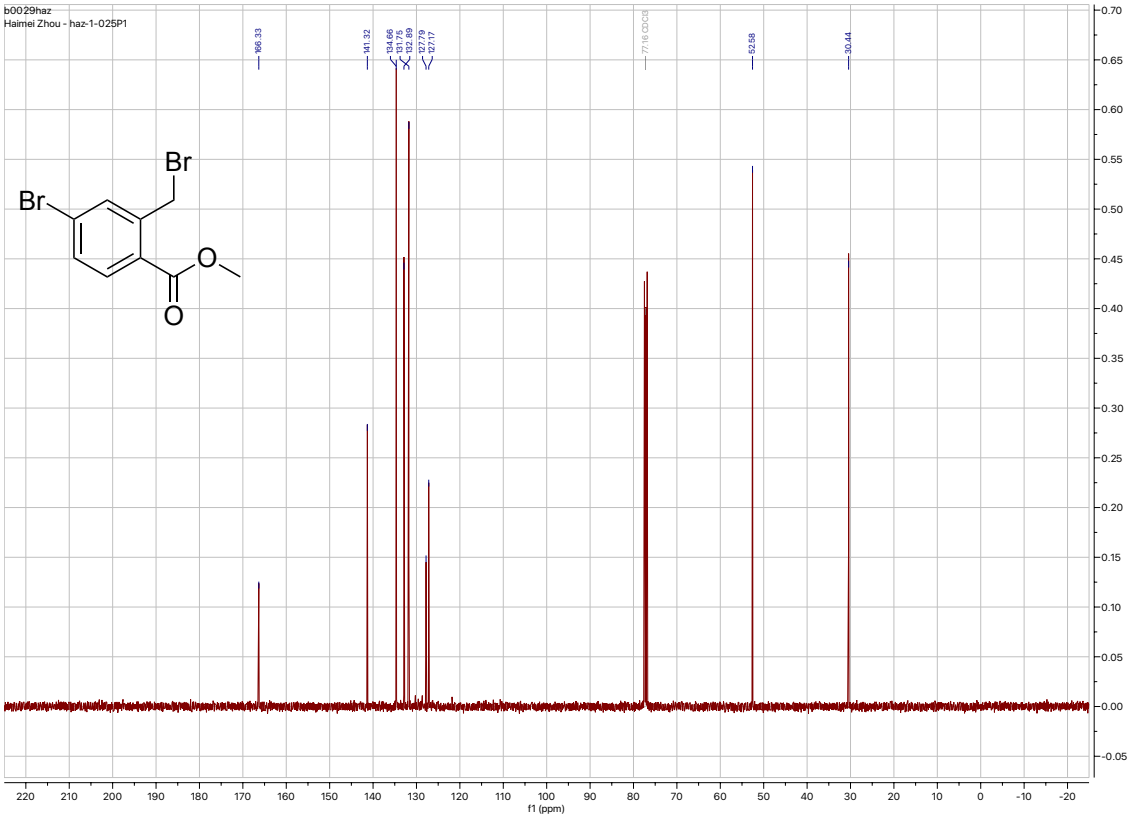
3-Phenyl-7,7a,8,9,10,11-hexahydrobenzo[*f*]pyrido[2,1-*c*][1,4]oxazocin-5(13*H*)-one (112)



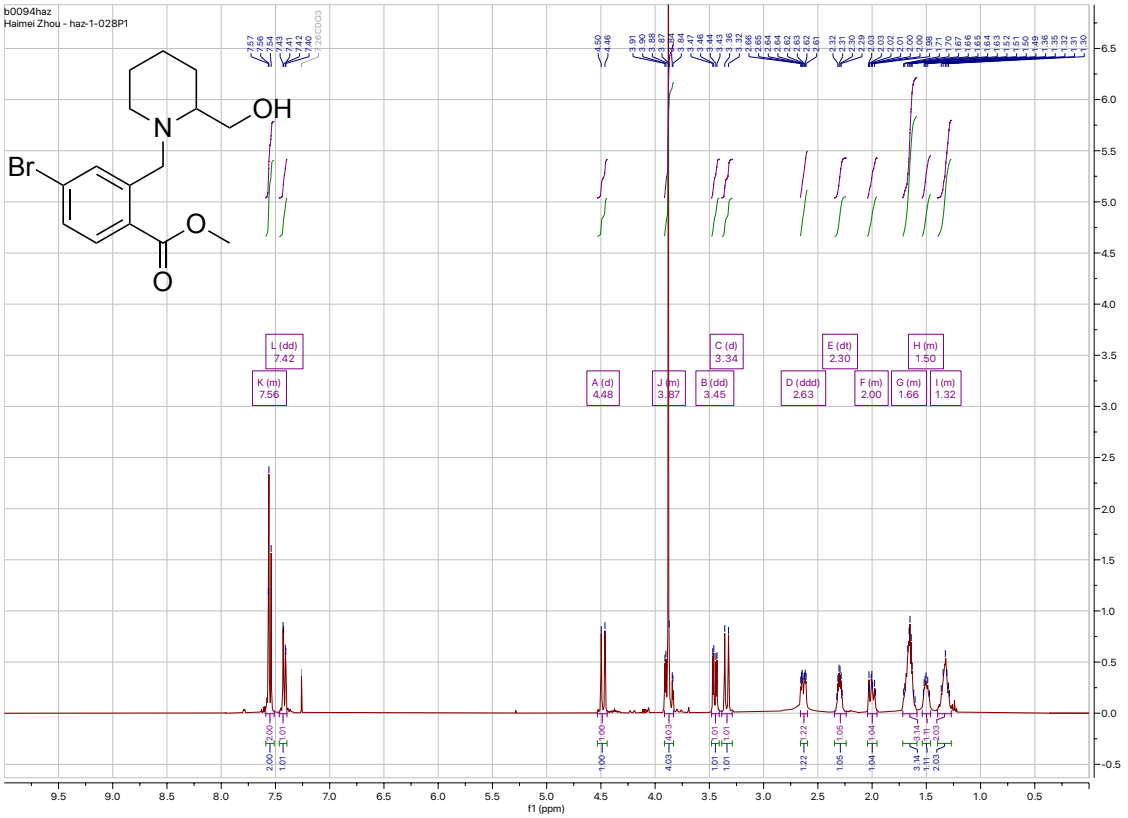


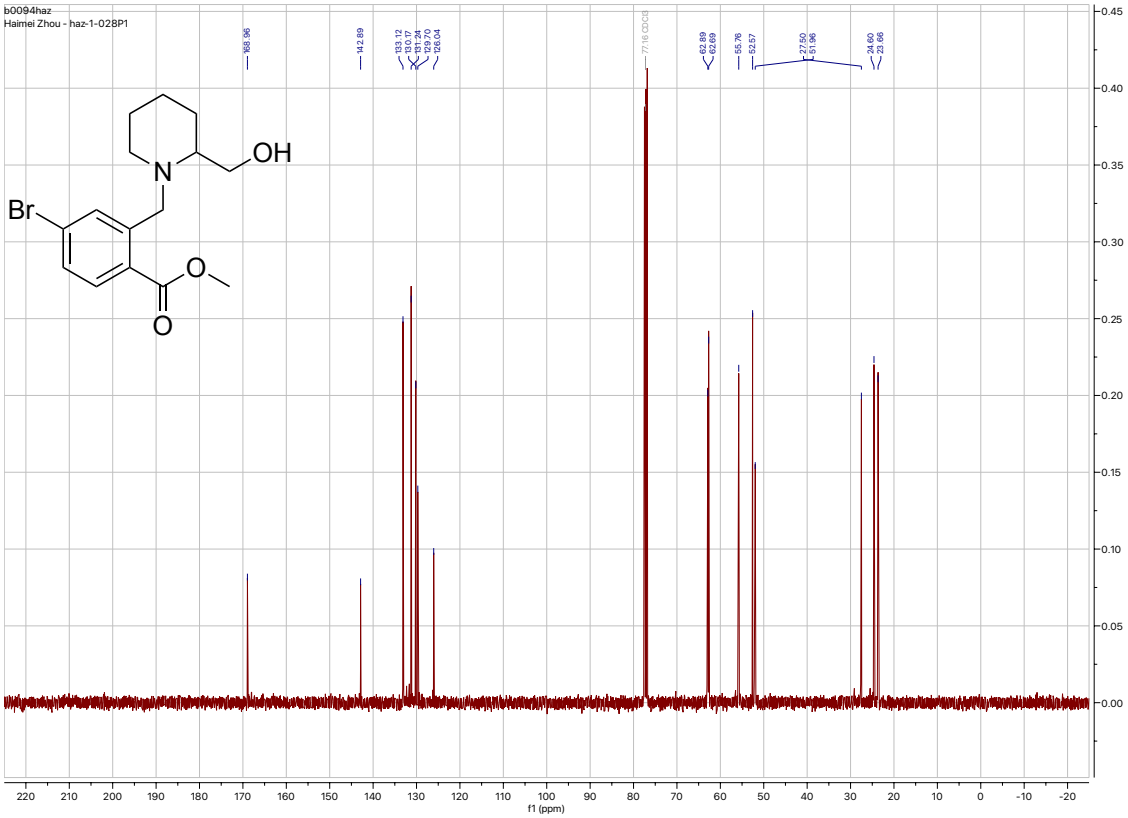
Methyl 4-bromo-2-(bromomethyl)benzoate (87)



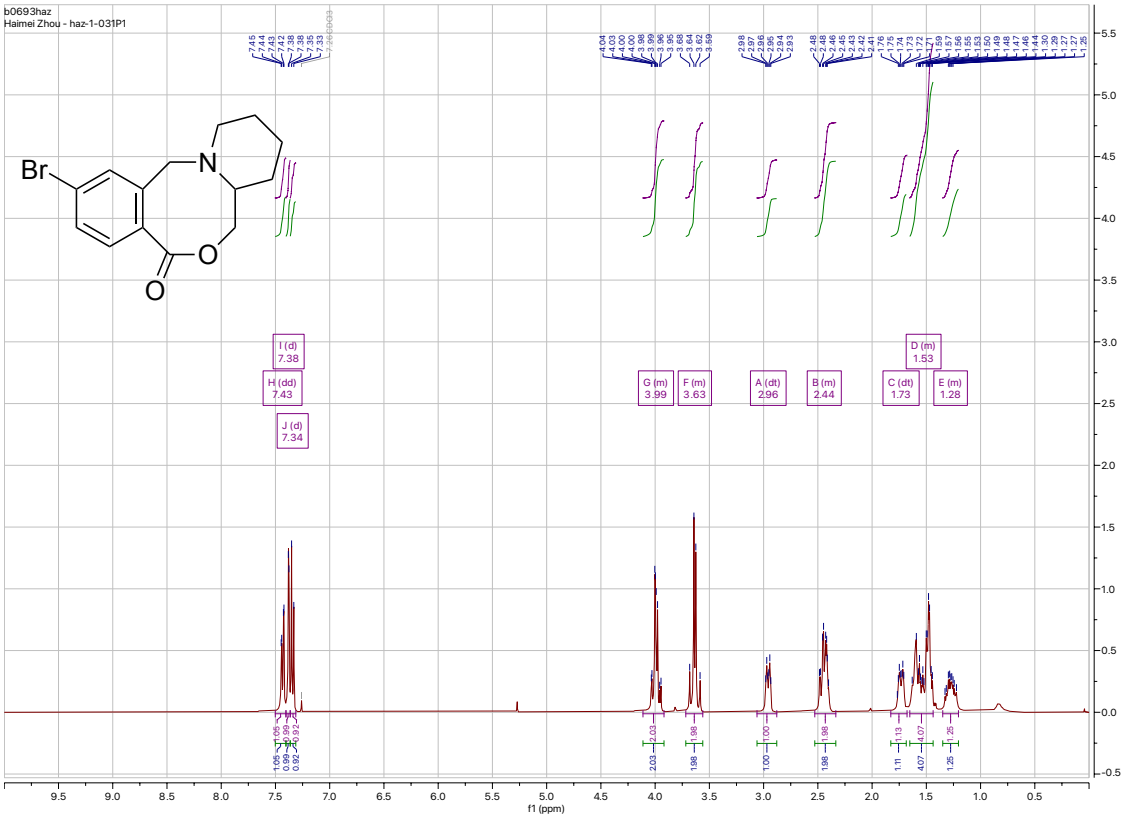


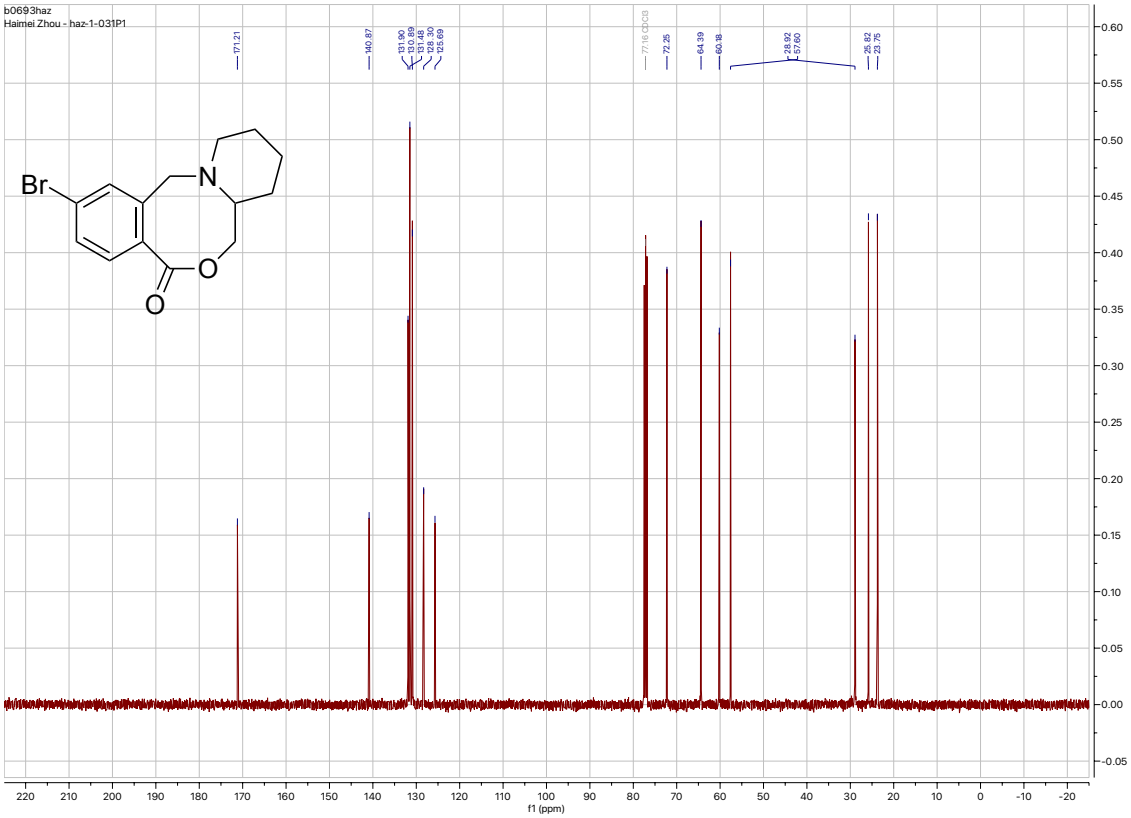
Methyl 4-bromo-2-((2-(hydroxymethyl)piperidin-1-yl)methyl)benzoate (93)



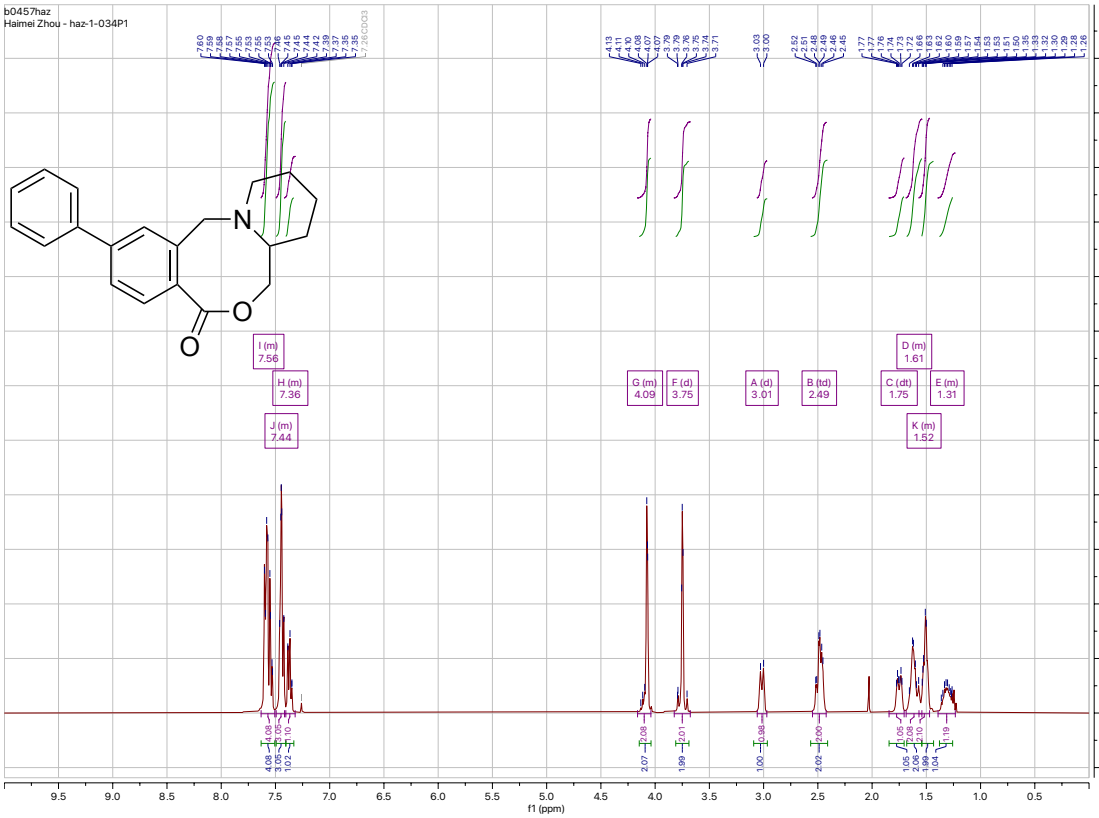


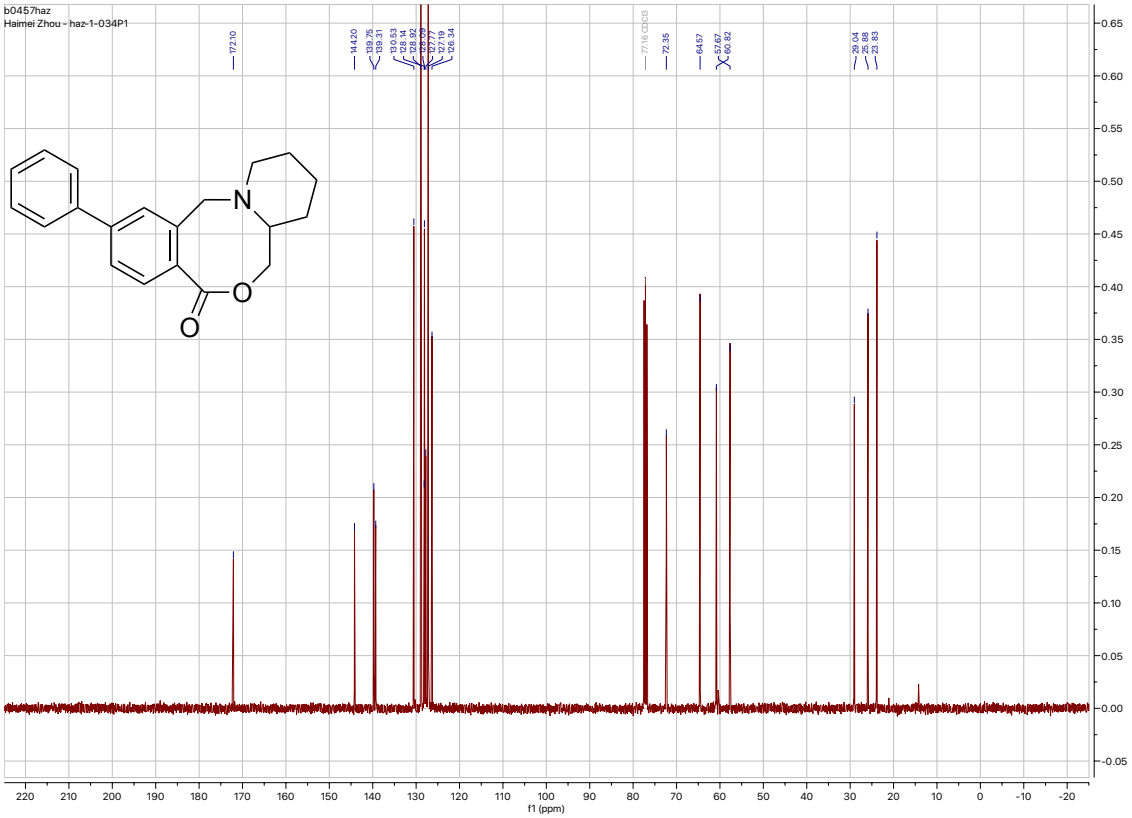
2-Bromo-7,7a,8,9,10,11-hexahydrobenzo[*f*]pyrido[2,1-*c*][1,4]oxazocin-5(13*H*)-one (102)



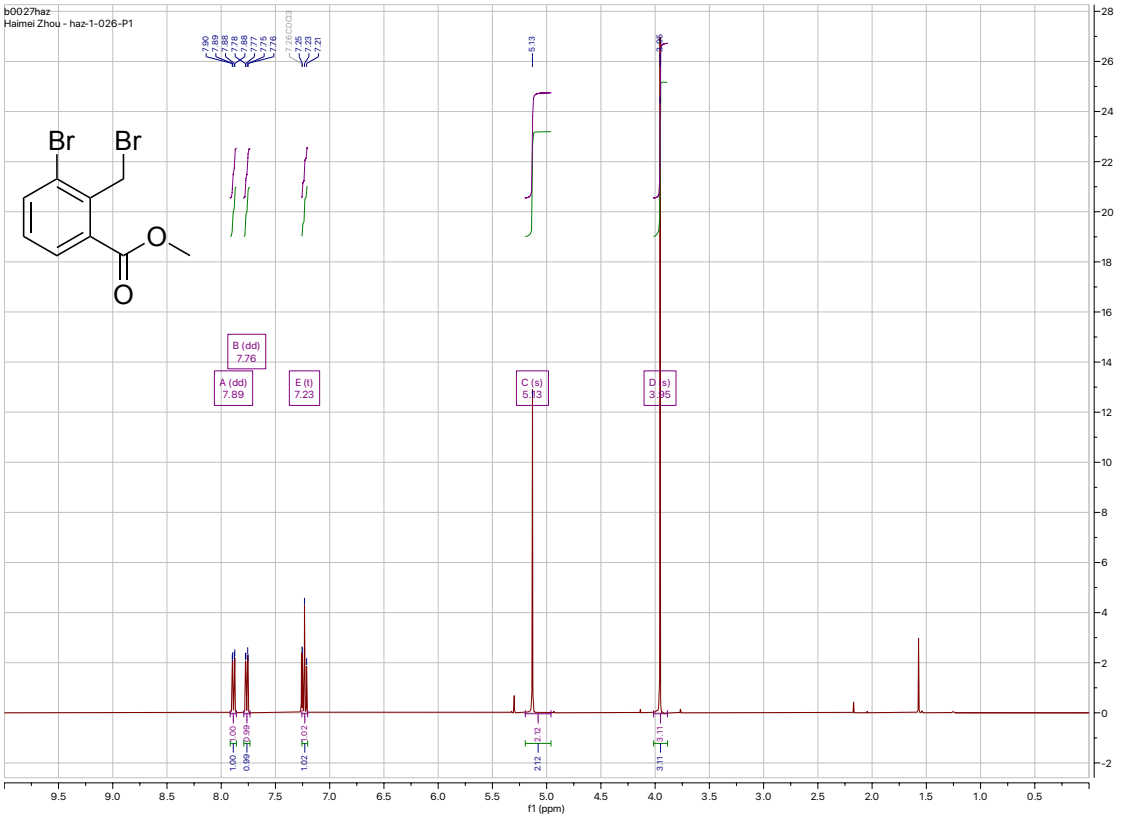


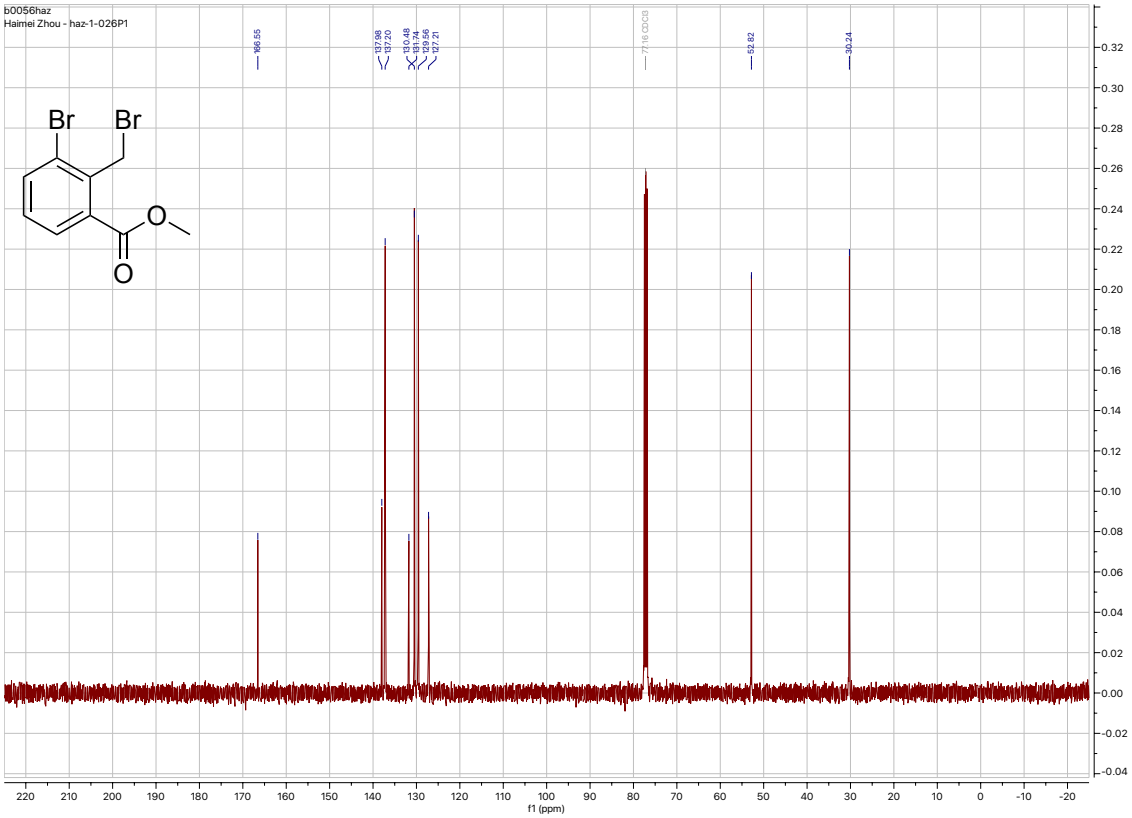
2-Phenyl-7,7a,8,9,10,11-hexahydrobenzo[*f*]pyrido[2,1-*c*][1,4]oxazocin-5(13*H*)-one (107)



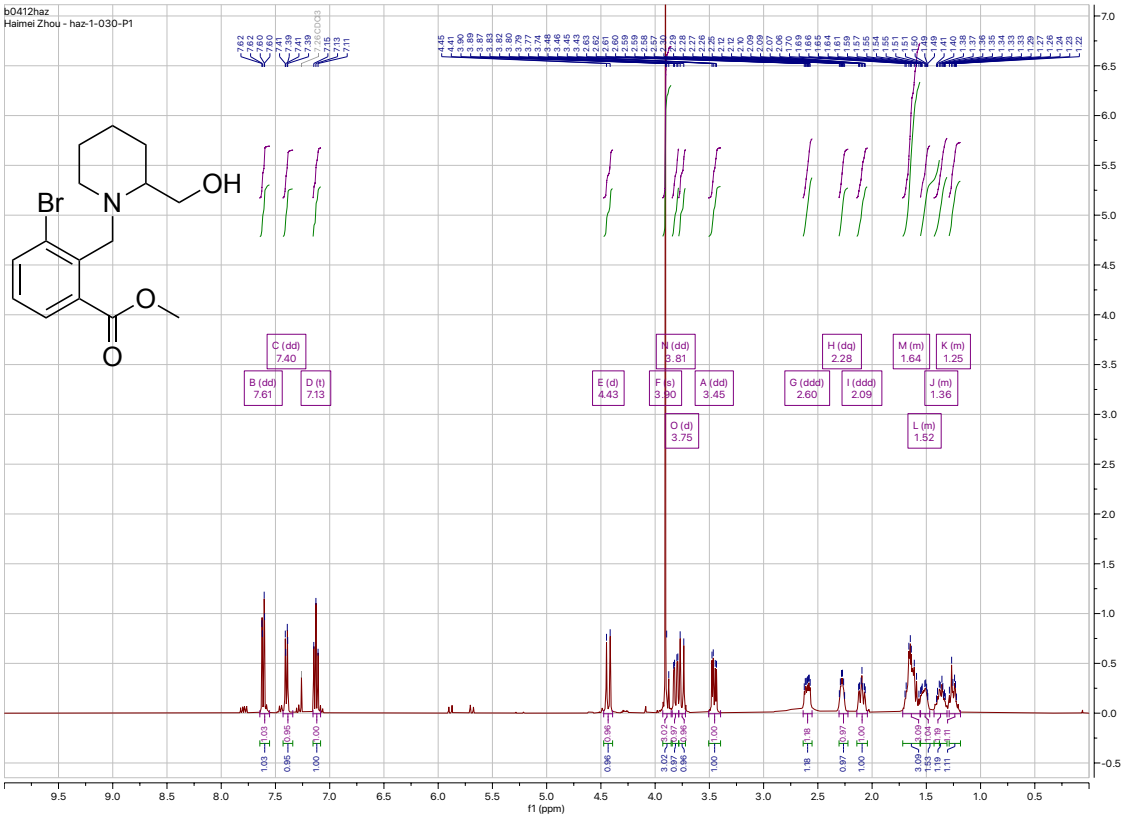


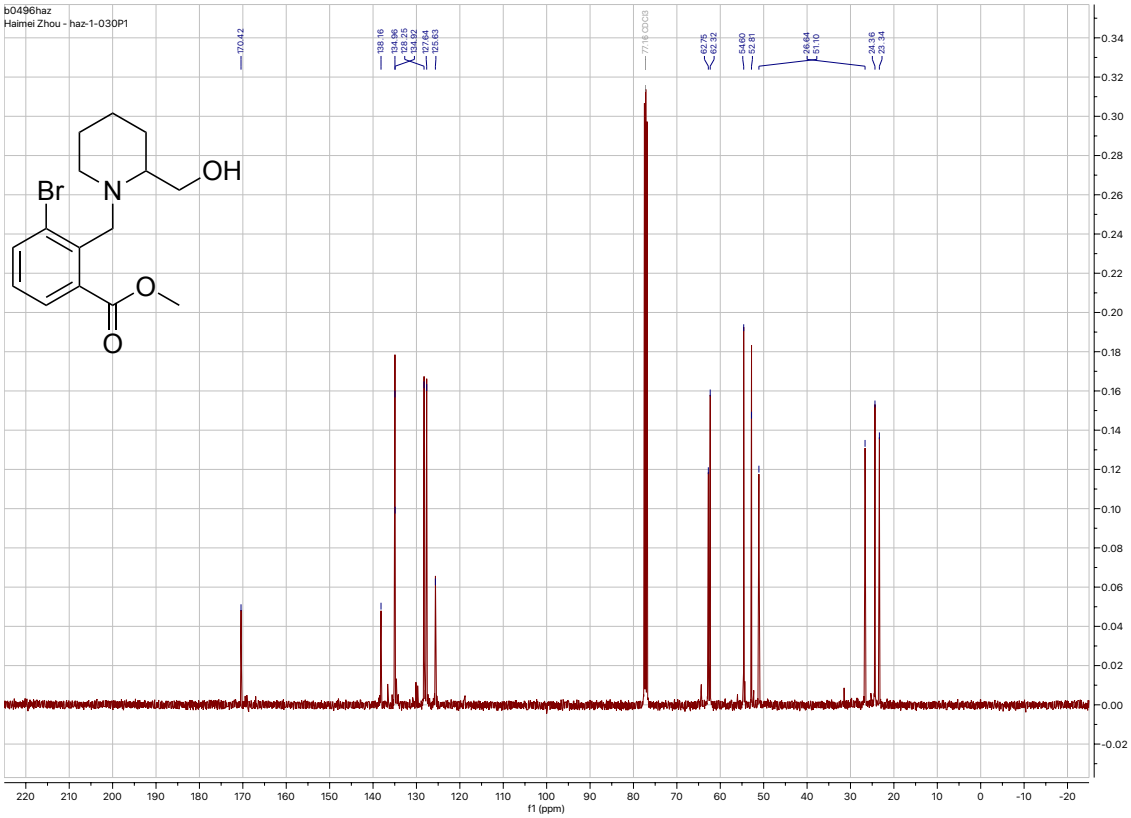
Methyl 3-bromo-2-(bromomethyl)benzoate (90)



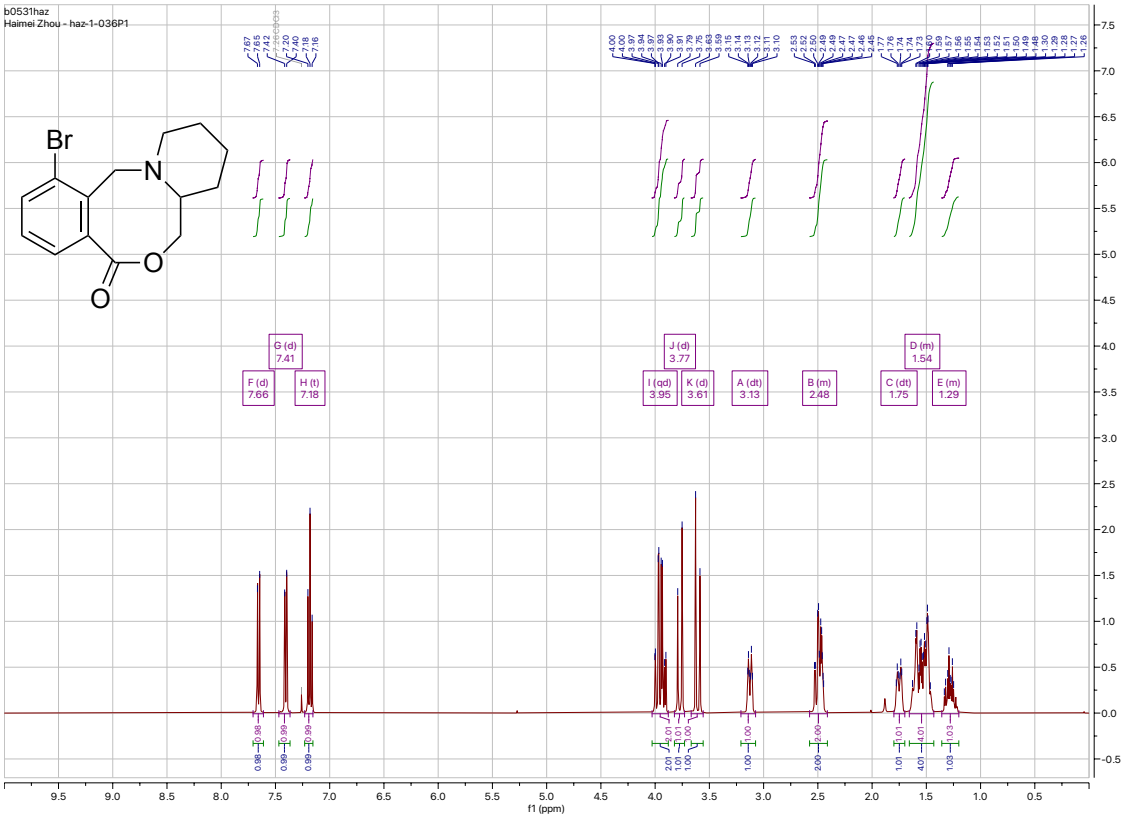


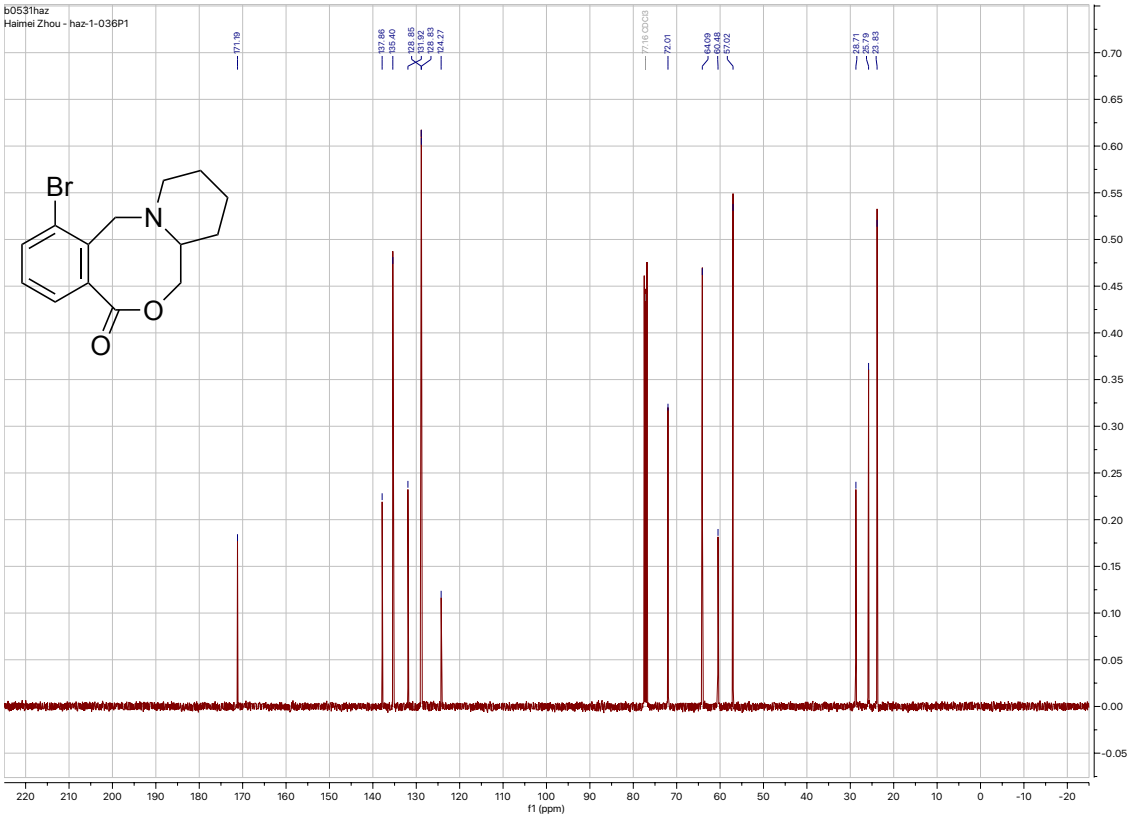
Methyl 3-bromo-2-((2-(hydroxymethyl)piperidin-1-yl)methyl)benzoate (94)



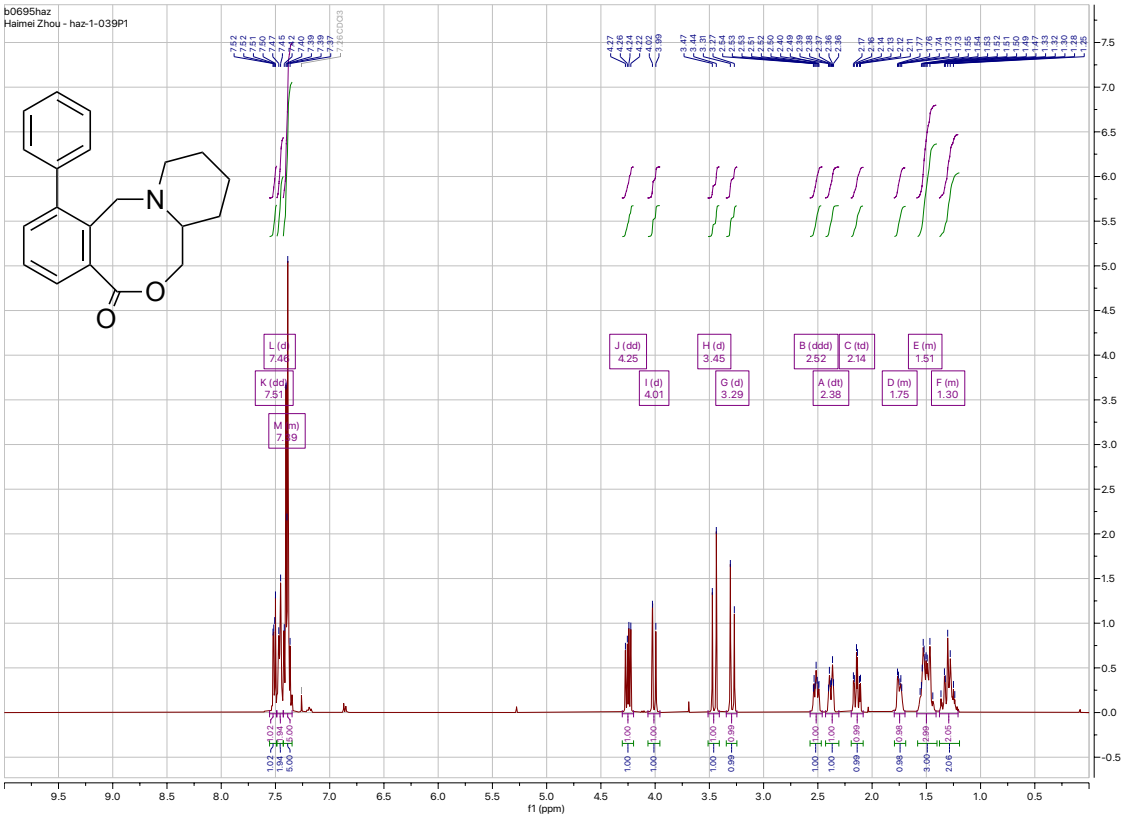


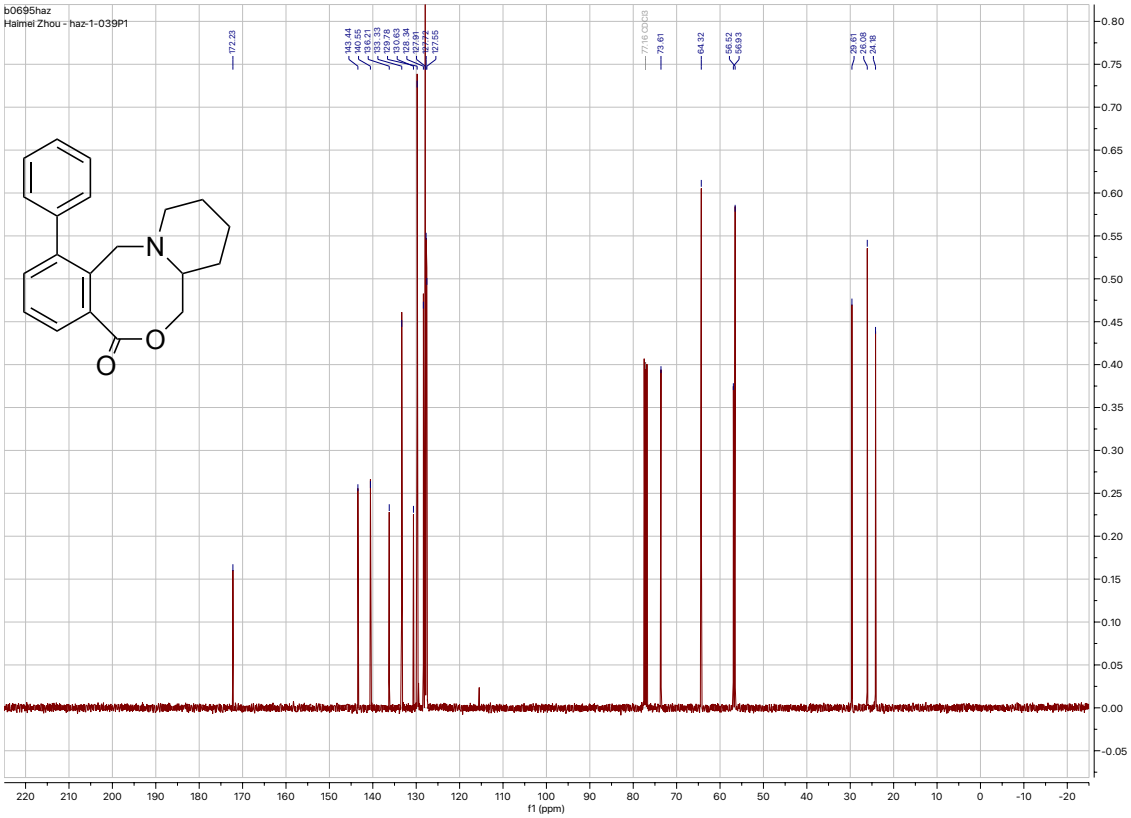
1-Bromo-7,7a,8,9,10,11-hexahydrobenzo[*f*]pyrido[2,1-*c*][1,4]oxazocin-5(13*H*)-one (103)



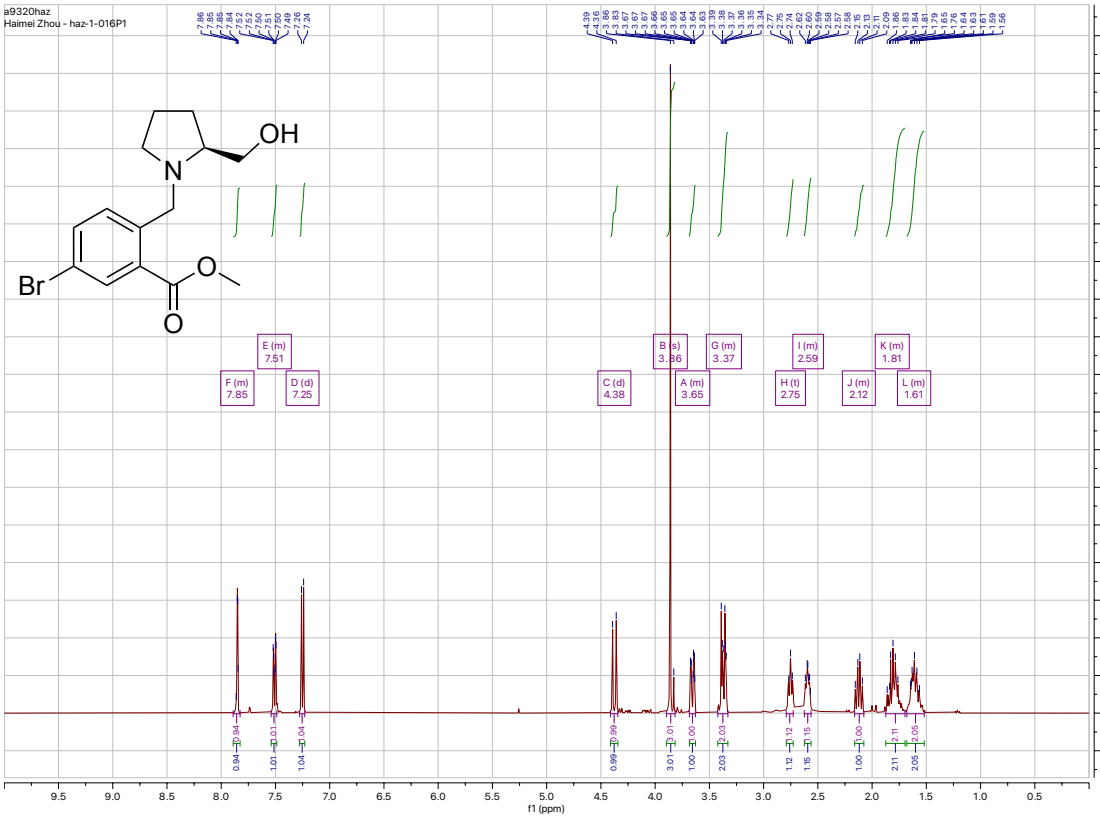


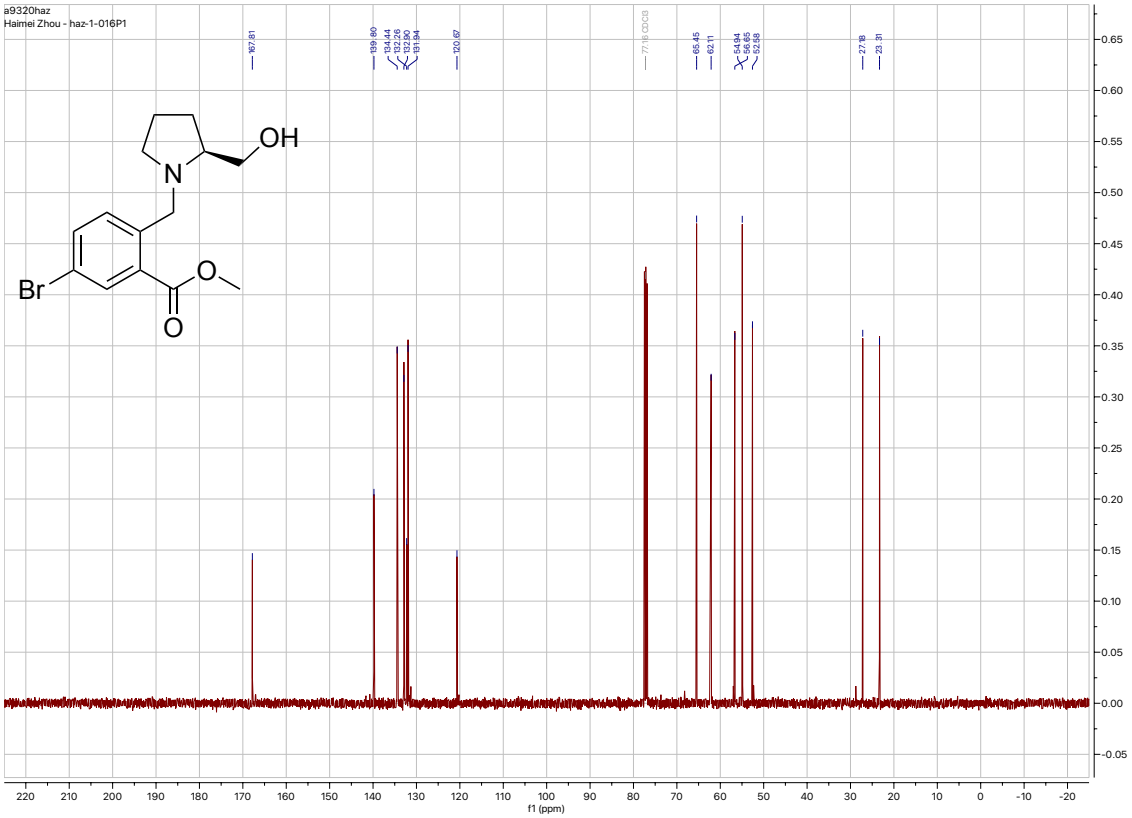
1-Phenyl-7,7a,8,9,10,11-hexahydrobenzo[*f*]pyrido[2,1-*c*][1,4]oxazocin-5(13*H*)-one (113)



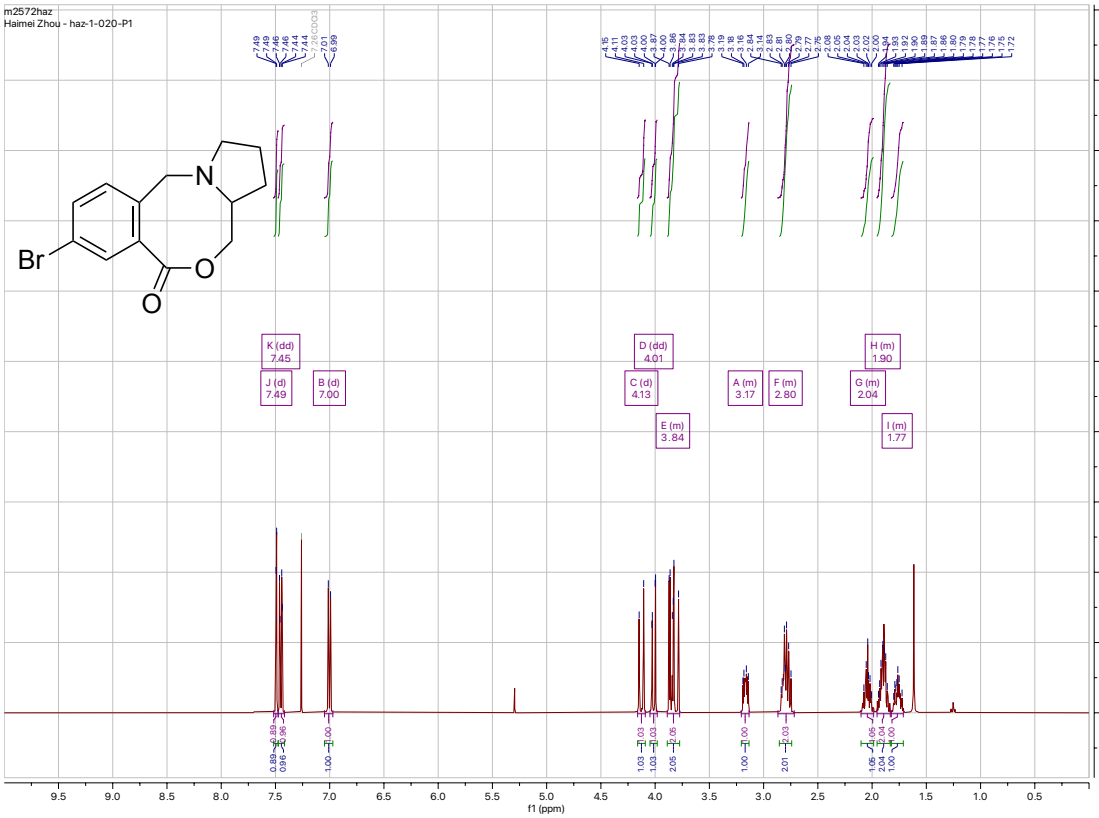


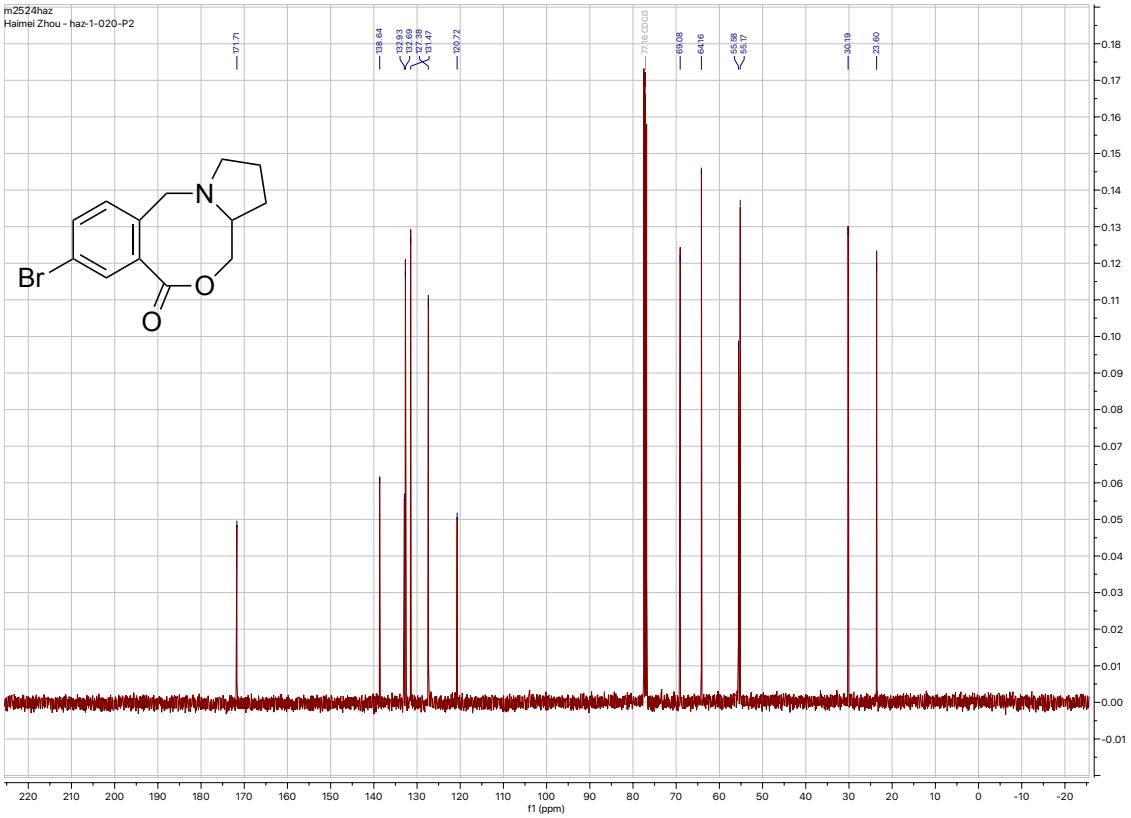
Methyl (*S*)-5-bromo-2-((2-(hydroxymethyl)pyrrolidin-1-yl)methyl)benzoate (96)



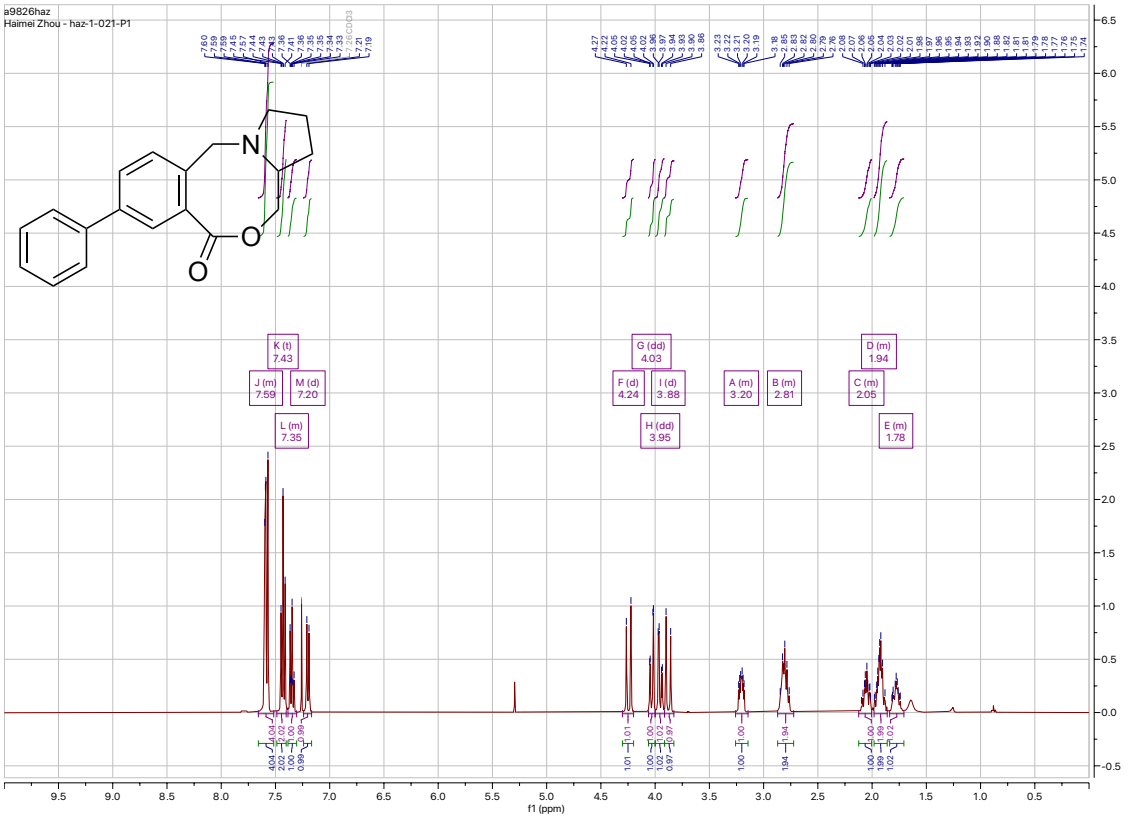


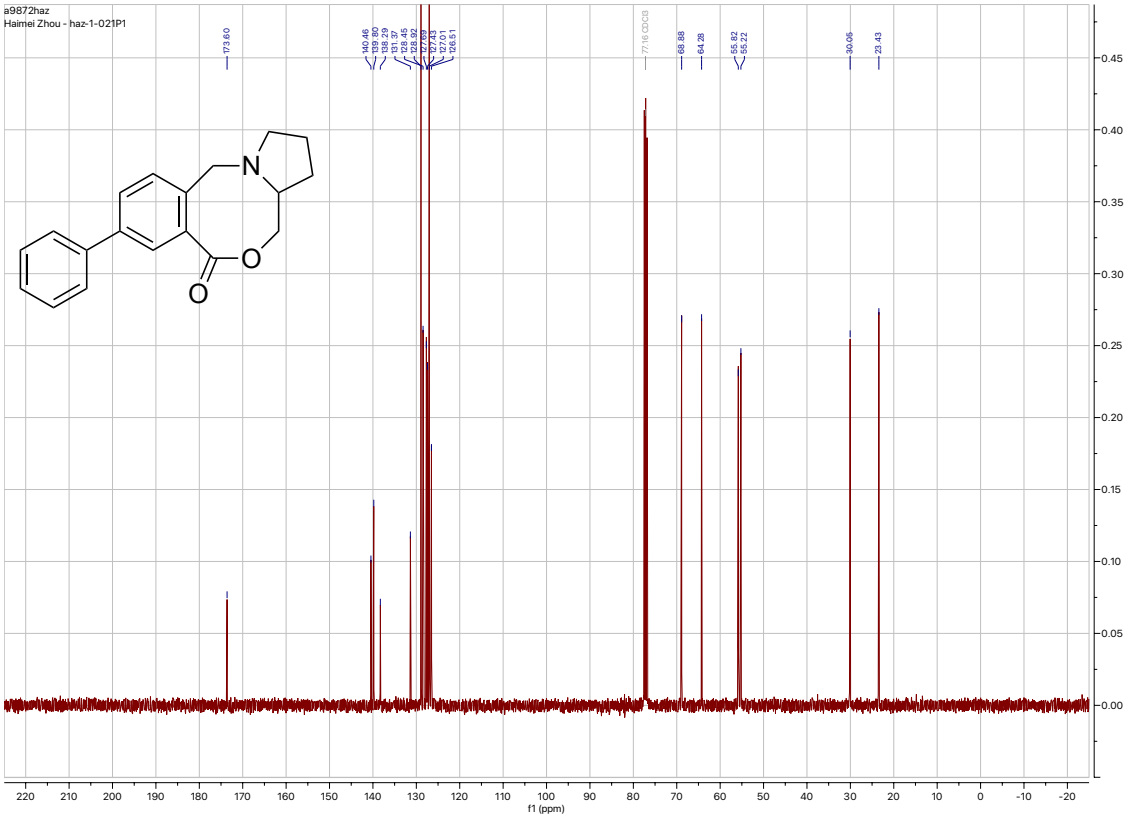
8-Bromo-2,3,3a,4-tetrahydro-1H-benzo[*f*]pyrrolo[2,1-*c*][1,4]oxazocin-6(11*H*)-one (100)



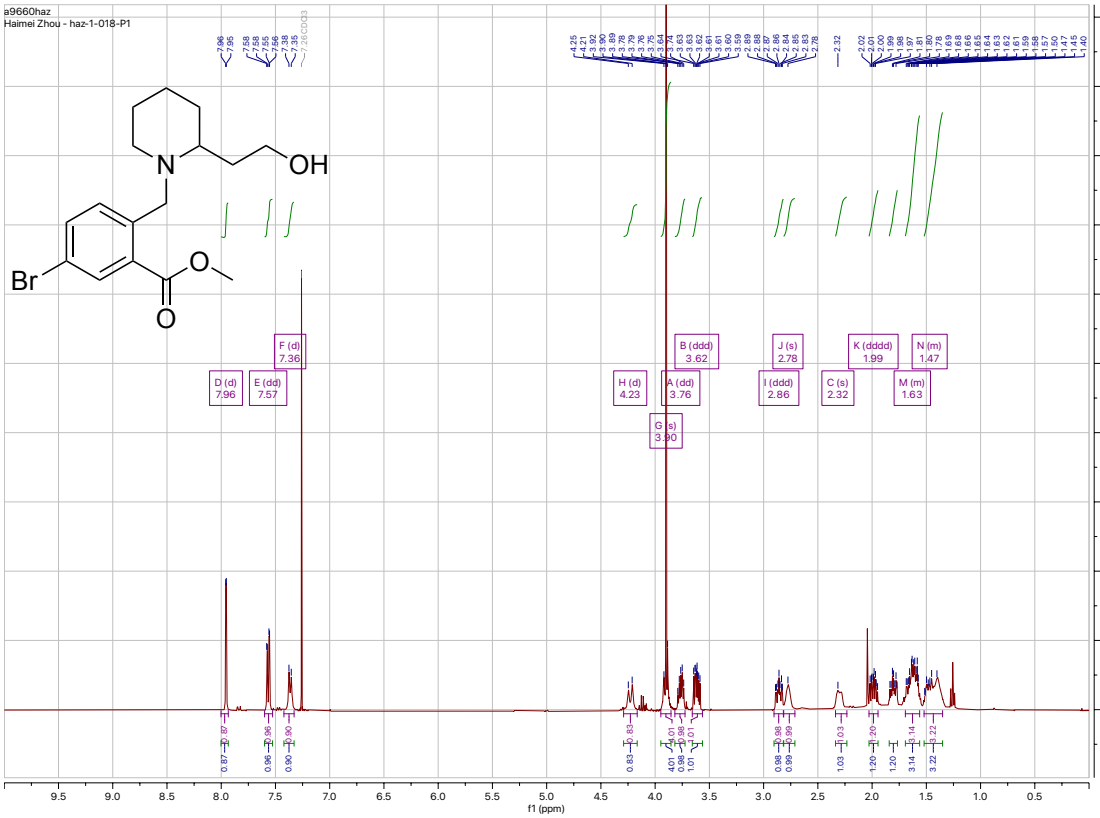


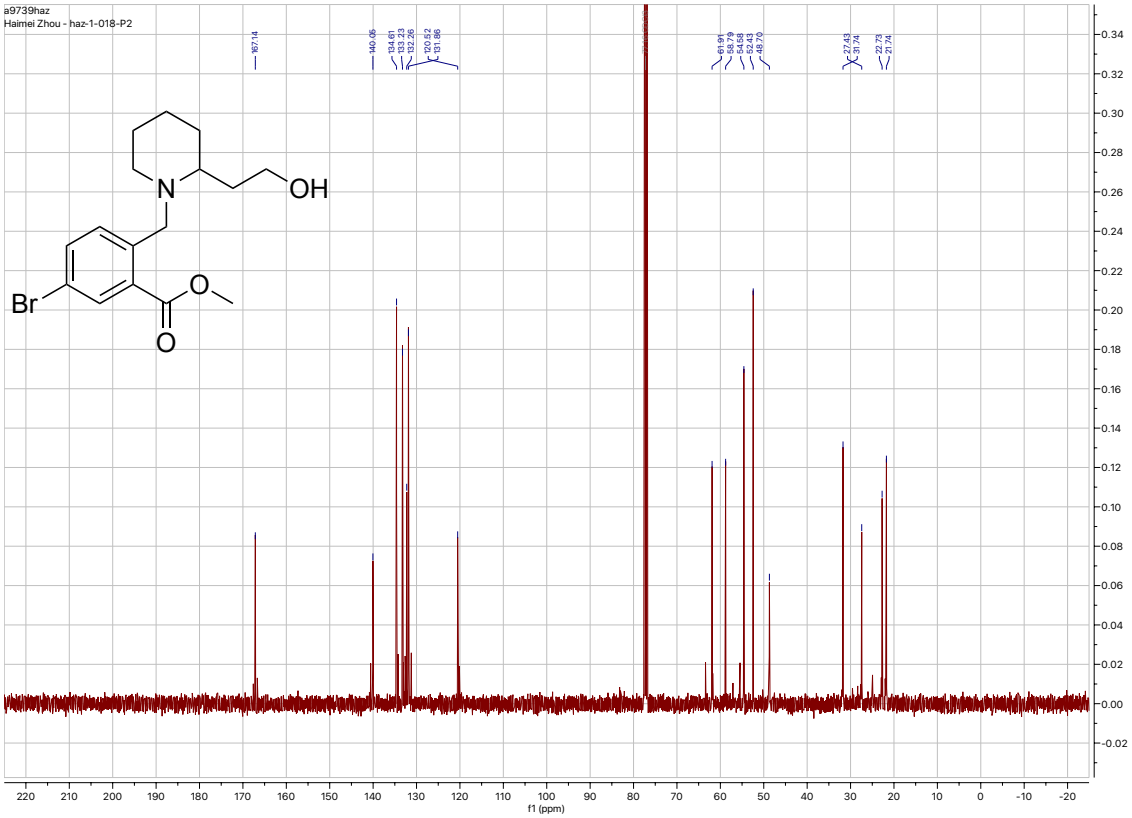
8-Phenyl-2,3,3a,4-tetrahydro-1H-benzo[*f*]pyrrolo[2,1-*c*][1,4]oxazocin-6(11*H*)-one (115)



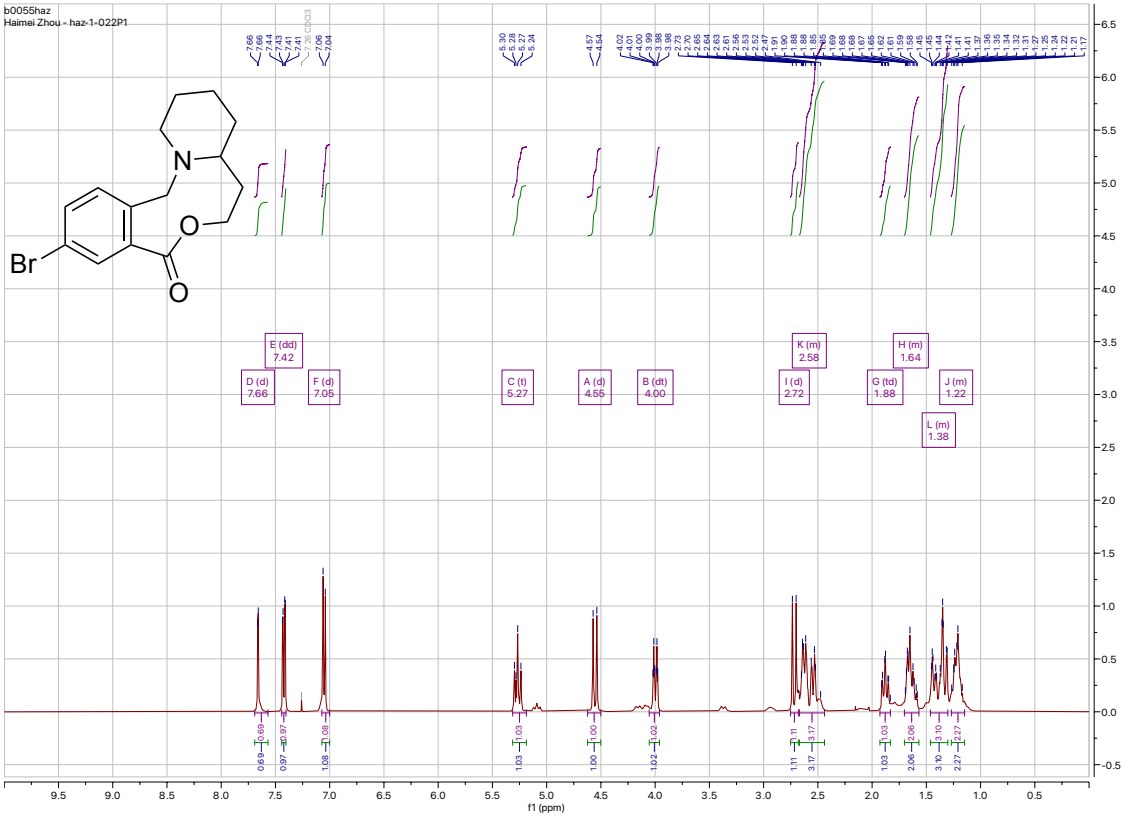


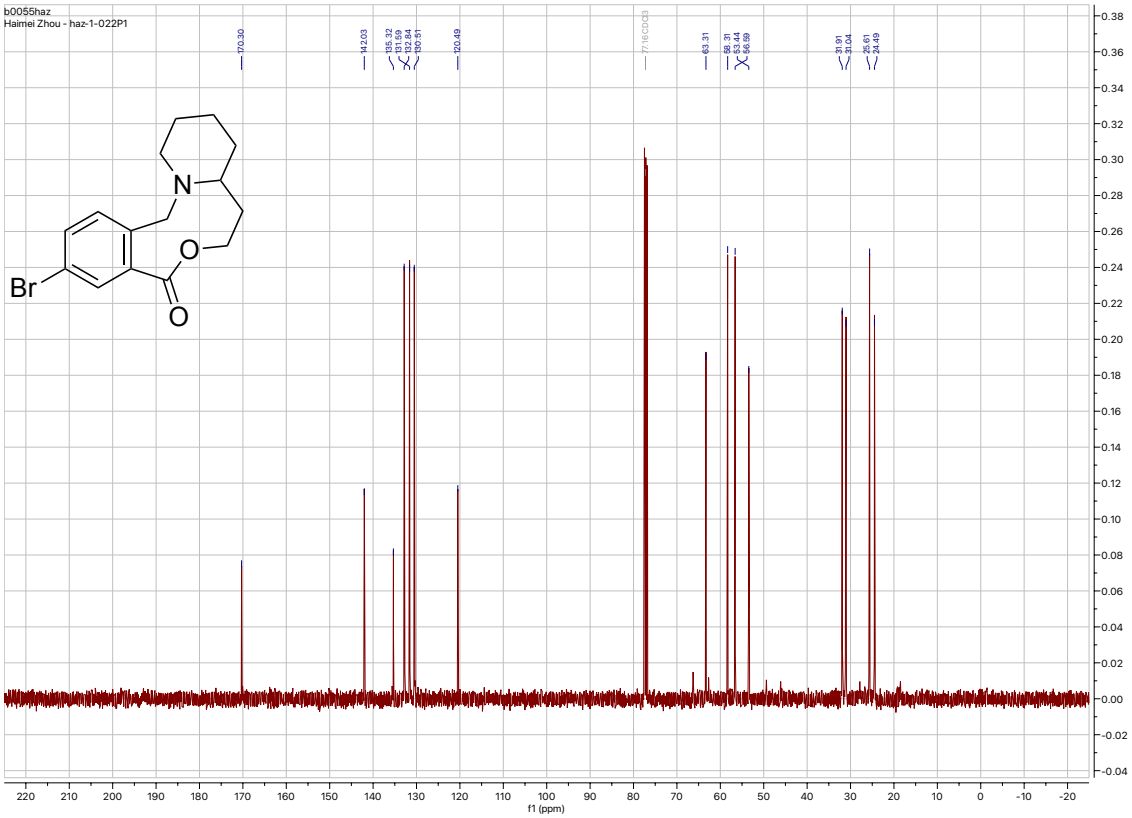
Methyl 5-bromo-2-((2-(2-hydroxyethyl)piperidin-1-yl)methyl)benzoate (97)



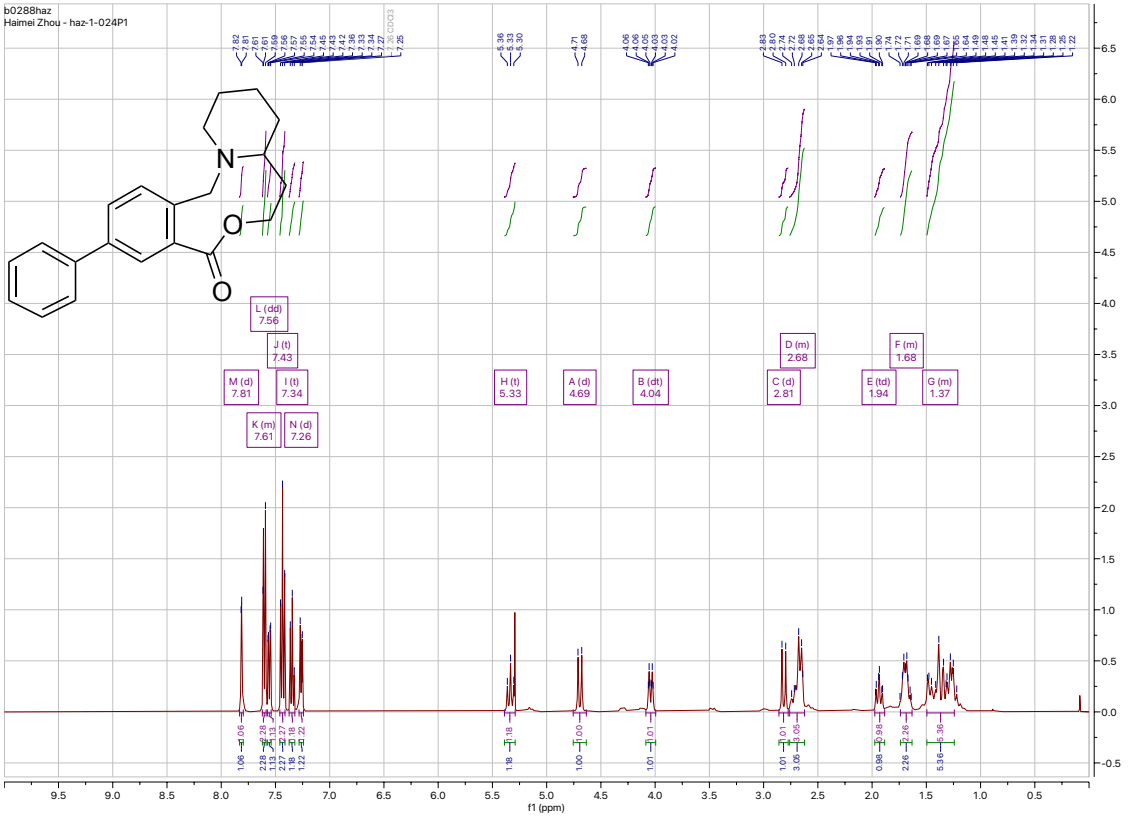


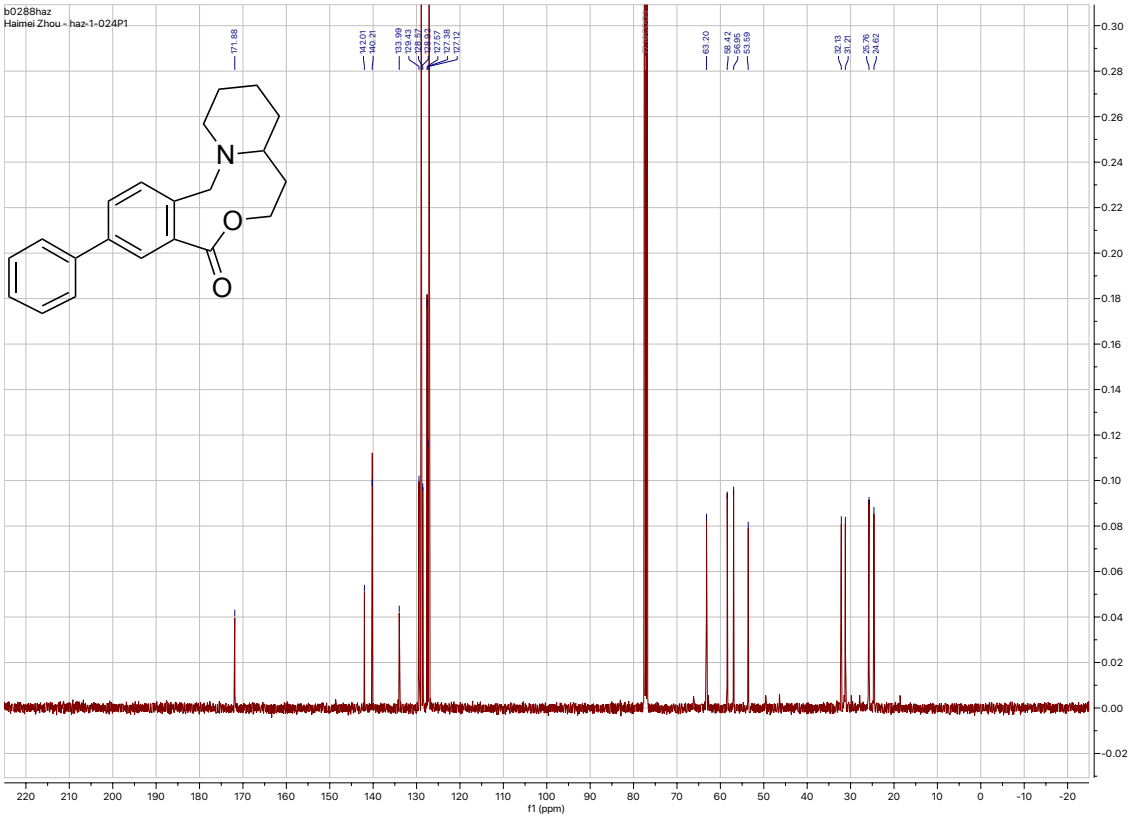
3-Bromo-8,8a,9,10,11,12-hexahydro-7H-benzo[*g*]pyrido[2,1-*d*][1,5]oxazonin-5(14*H*)-one (101)



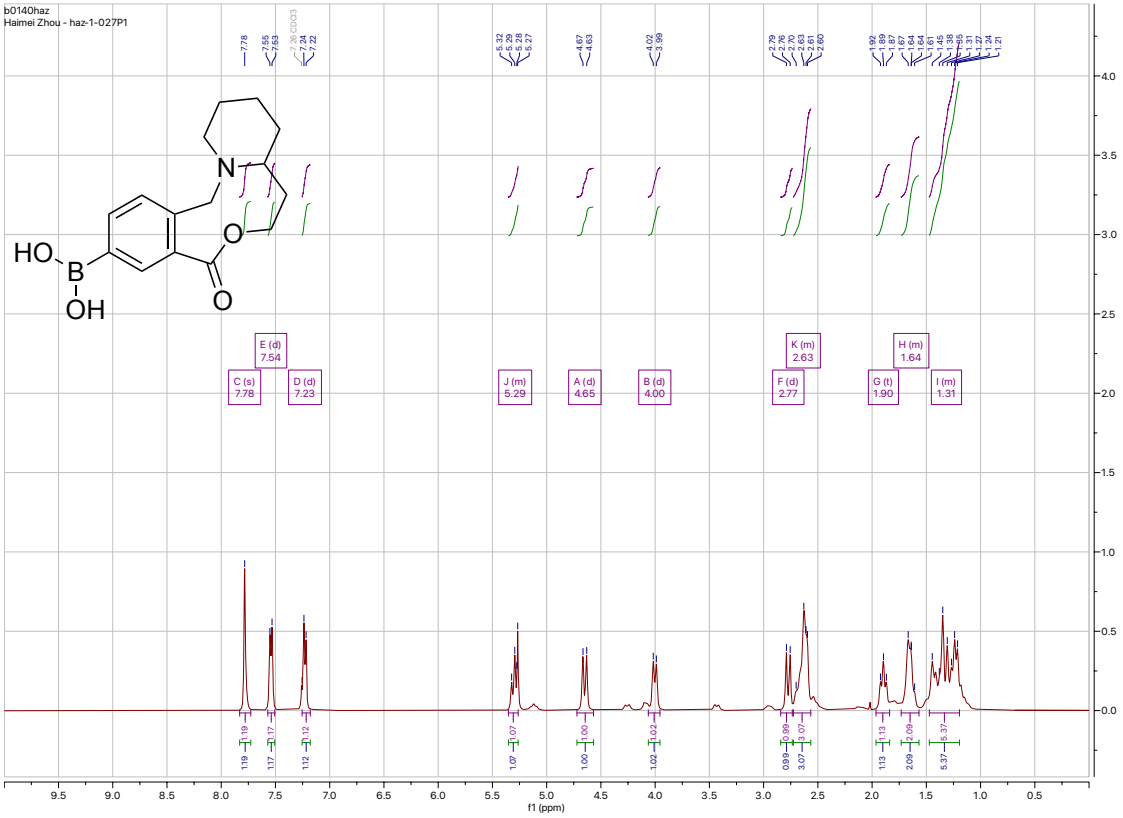


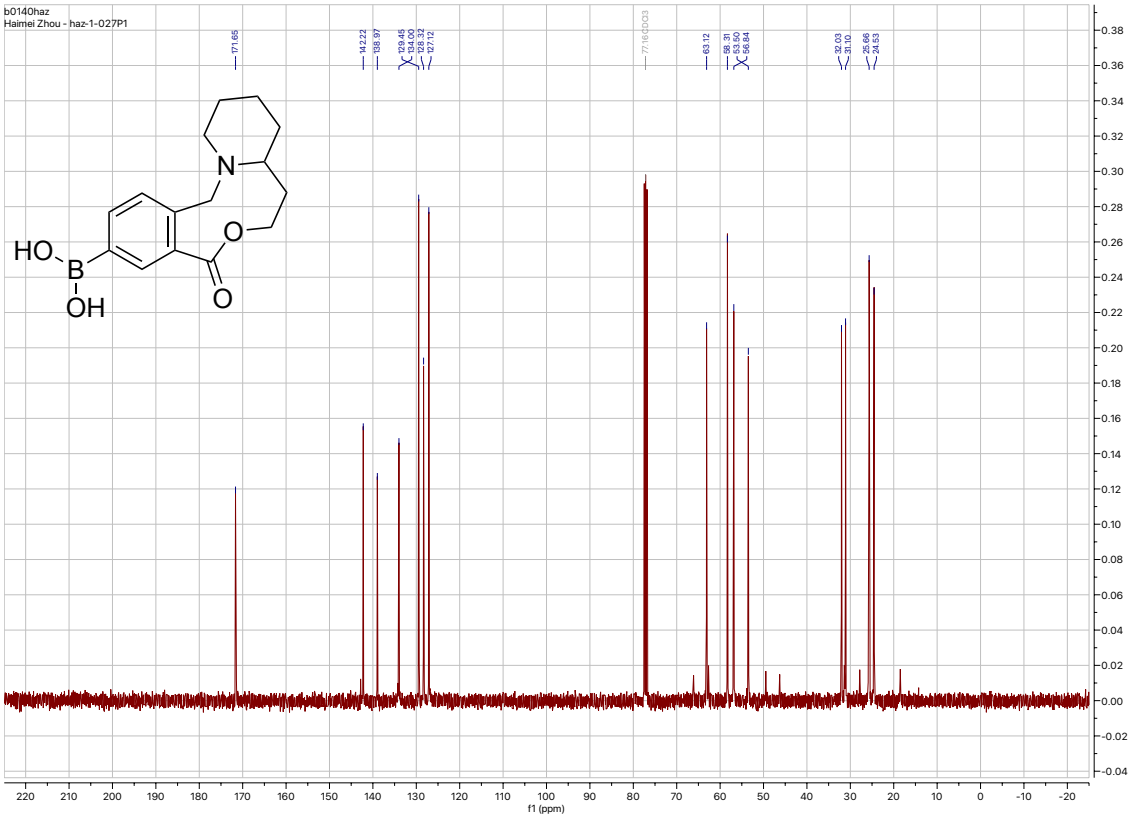
3-Phenyl-8,8a,9,10,11,12-hexahydro-7H-benzo[*g*]pyrido[2,1-*d*][1,5]oxazonin-5(14*H*)-one (116)



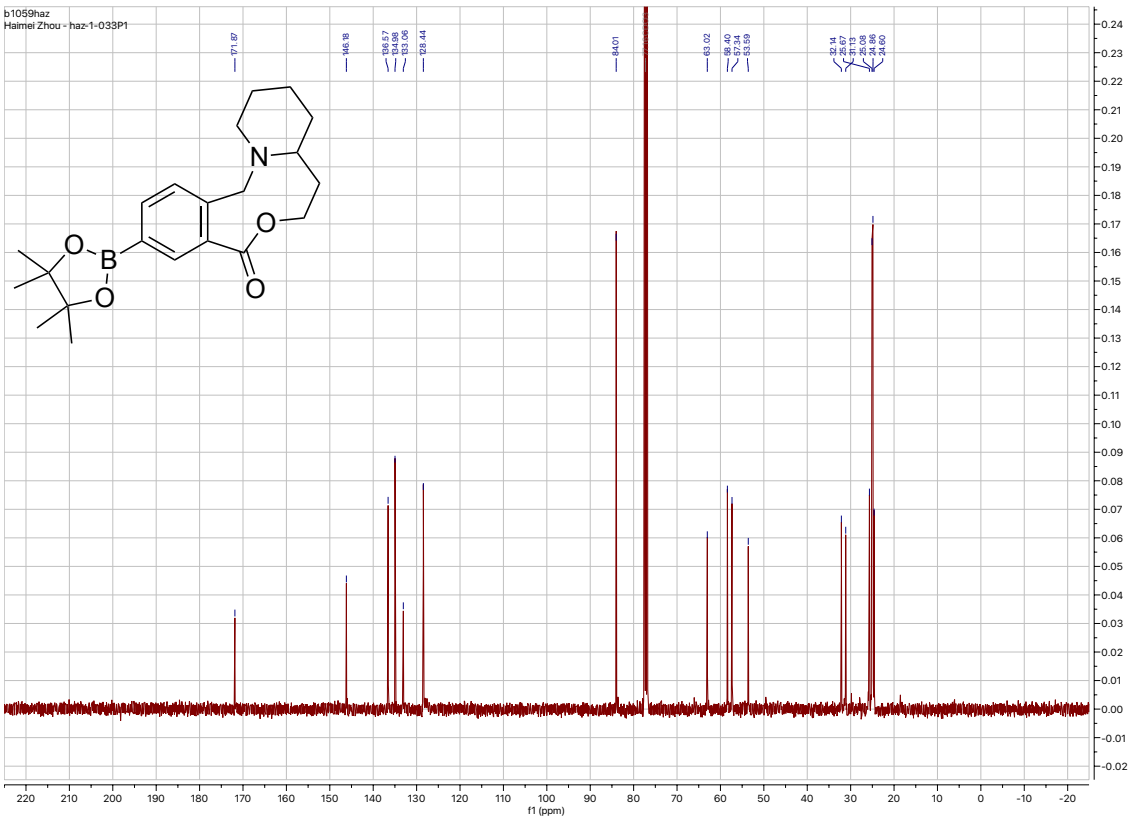


(5-Oxo-5,8,8a,9,10,11,12,14-octahydro-7H-benzo[*g*]pyrido[2,1-*d*][1,5]oxazonin-3-yl) boronic acid (Not shown in the thesis)

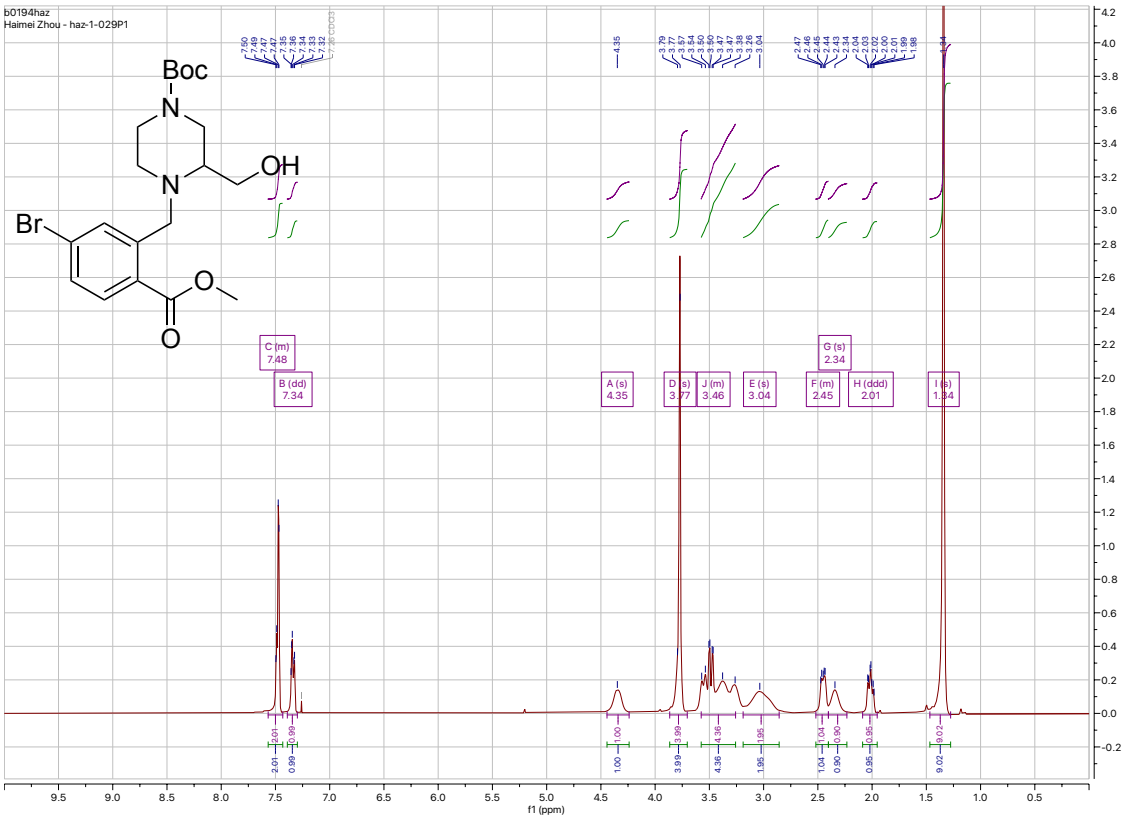


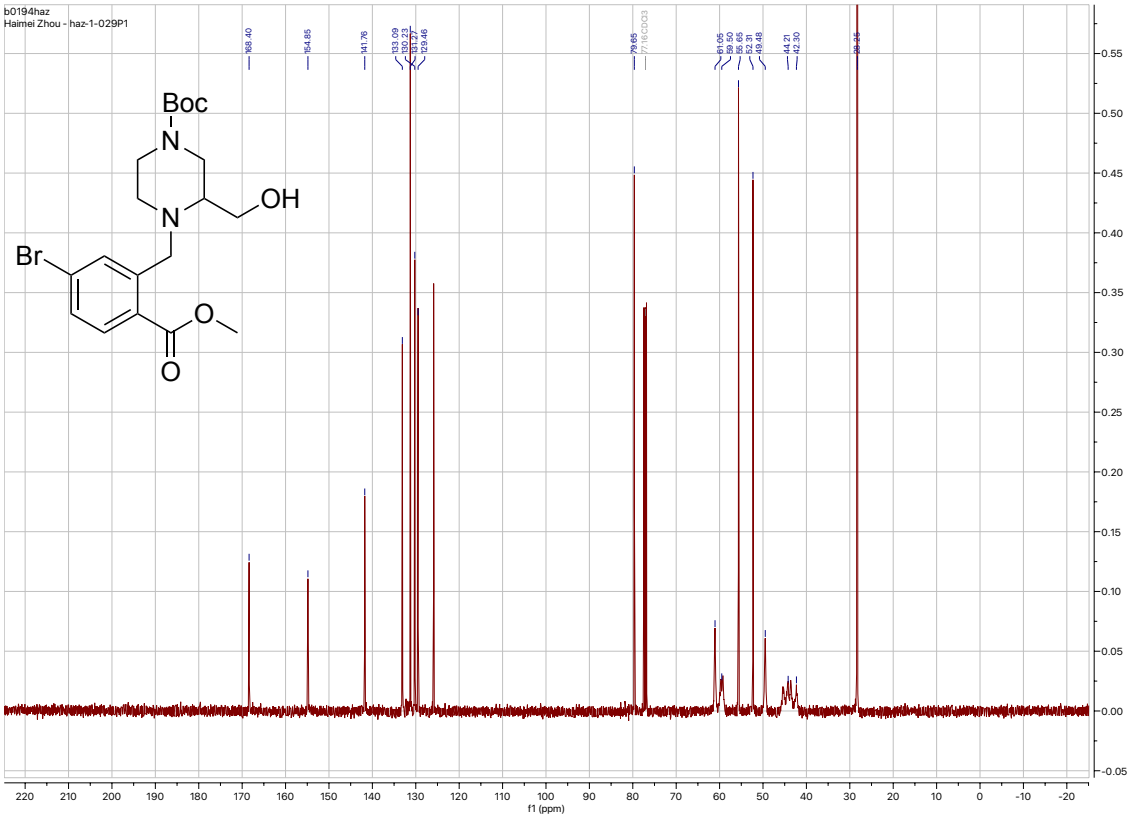


3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-8,8a,9,10,11,12-hexahydro-7H-benzo[*g*]pyrido[2,1-*d*][1,5]oxazonin-5(14*H*)-one (123)

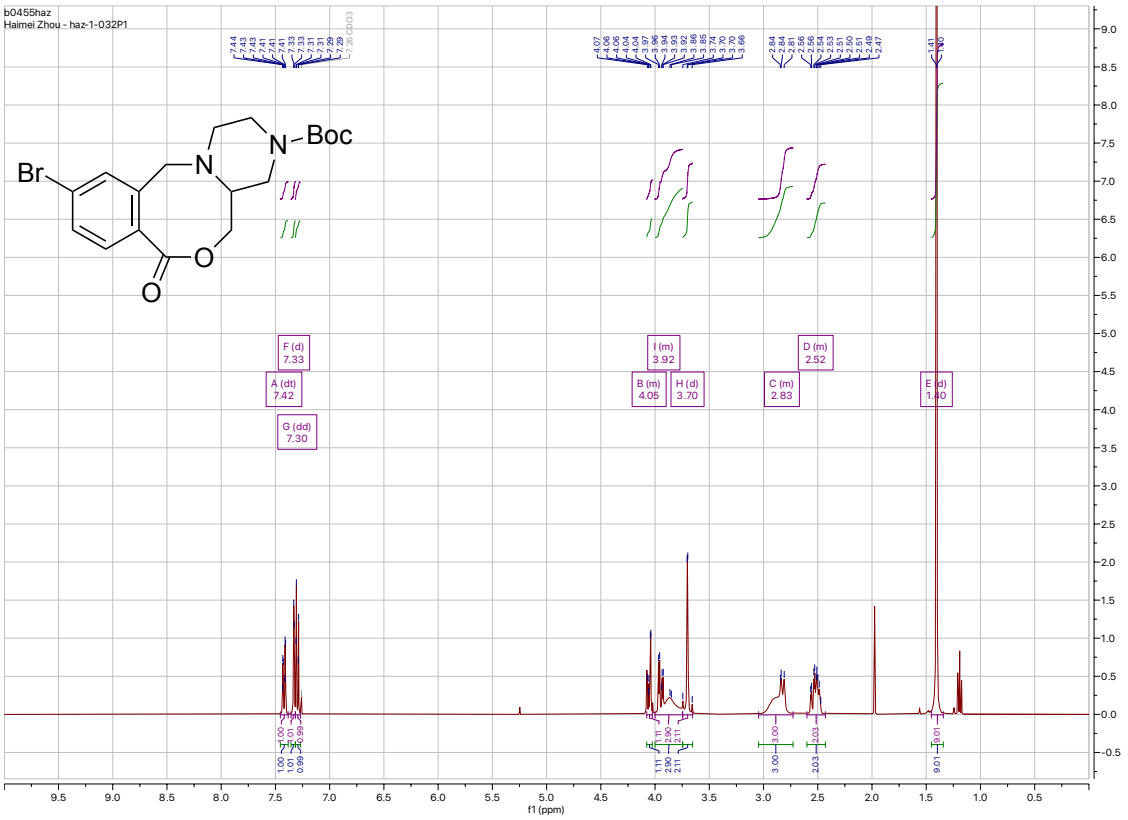


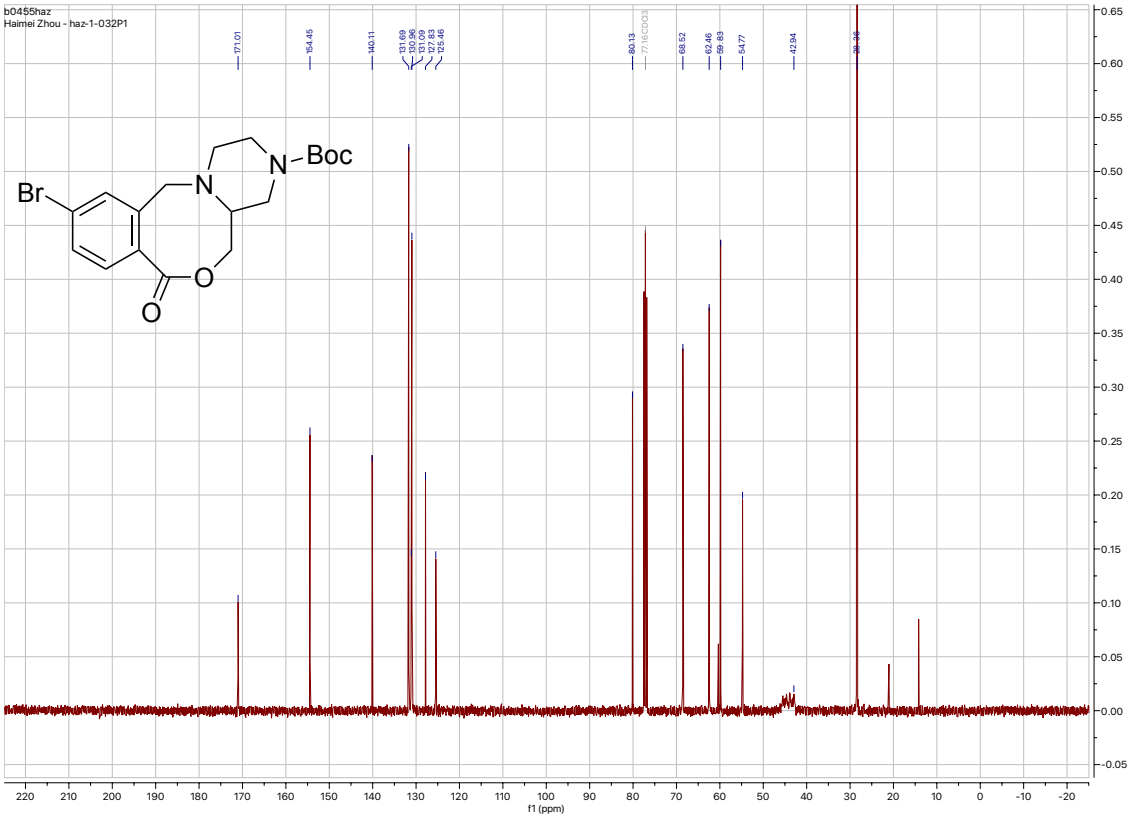
***tert*-Butyl 4-(5-bromo-2-(methoxycarbonyl)benzyl)-3-(hydroxymethyl)piperazine-1-carboxylate (95)**



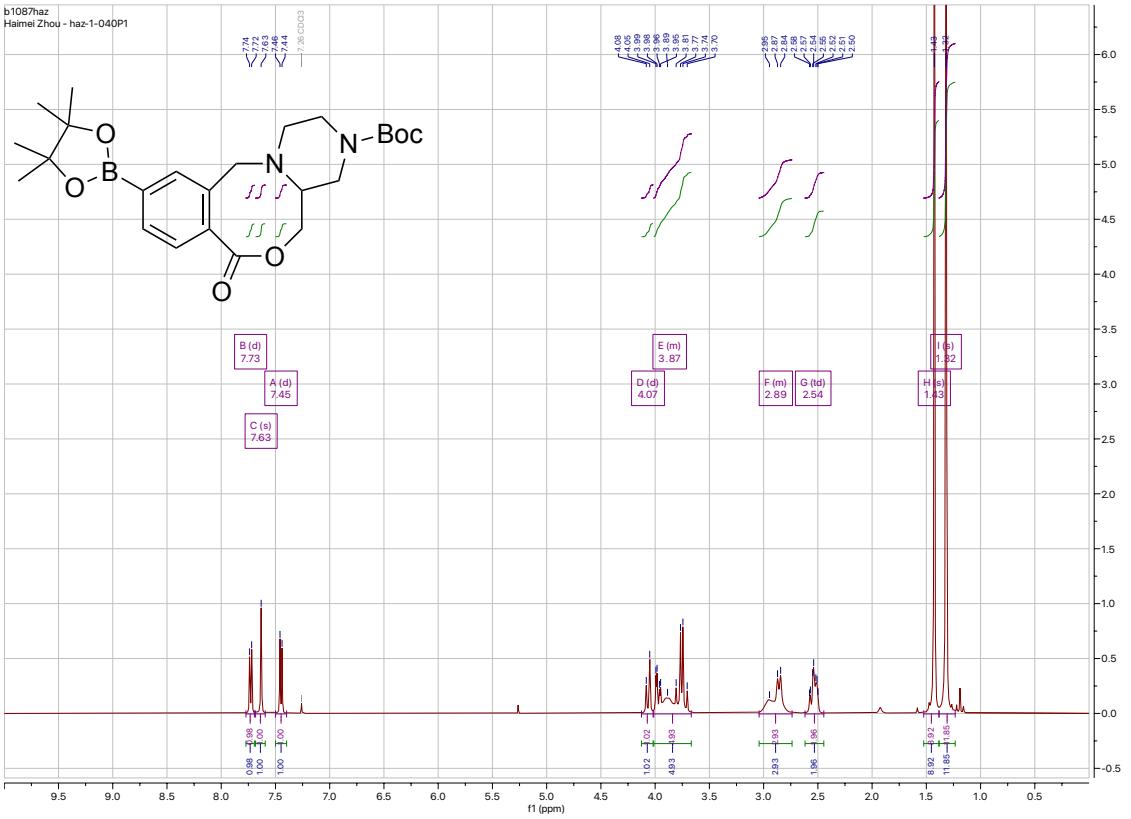


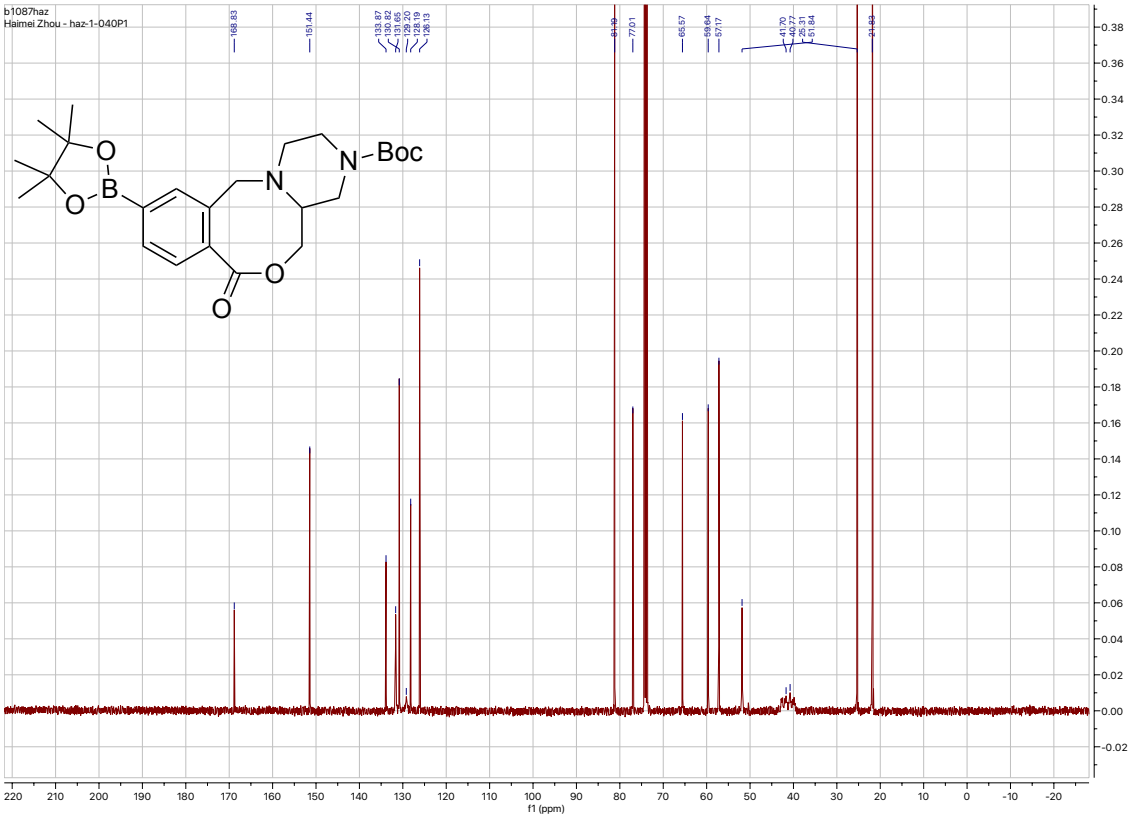
tert-Butyl 10-bromo-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[_f_]pyrazino[2,1-_c_][1,4] oxazocine-3(4_H_)-carboxylate (104)



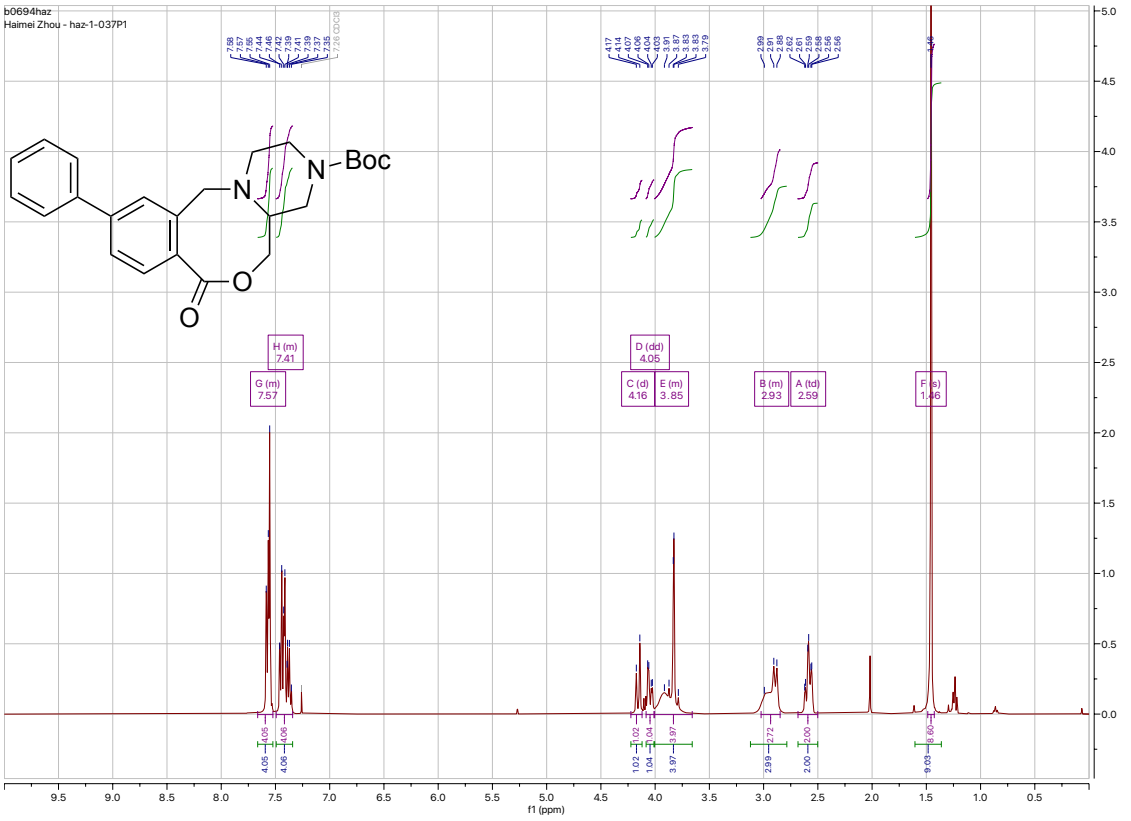


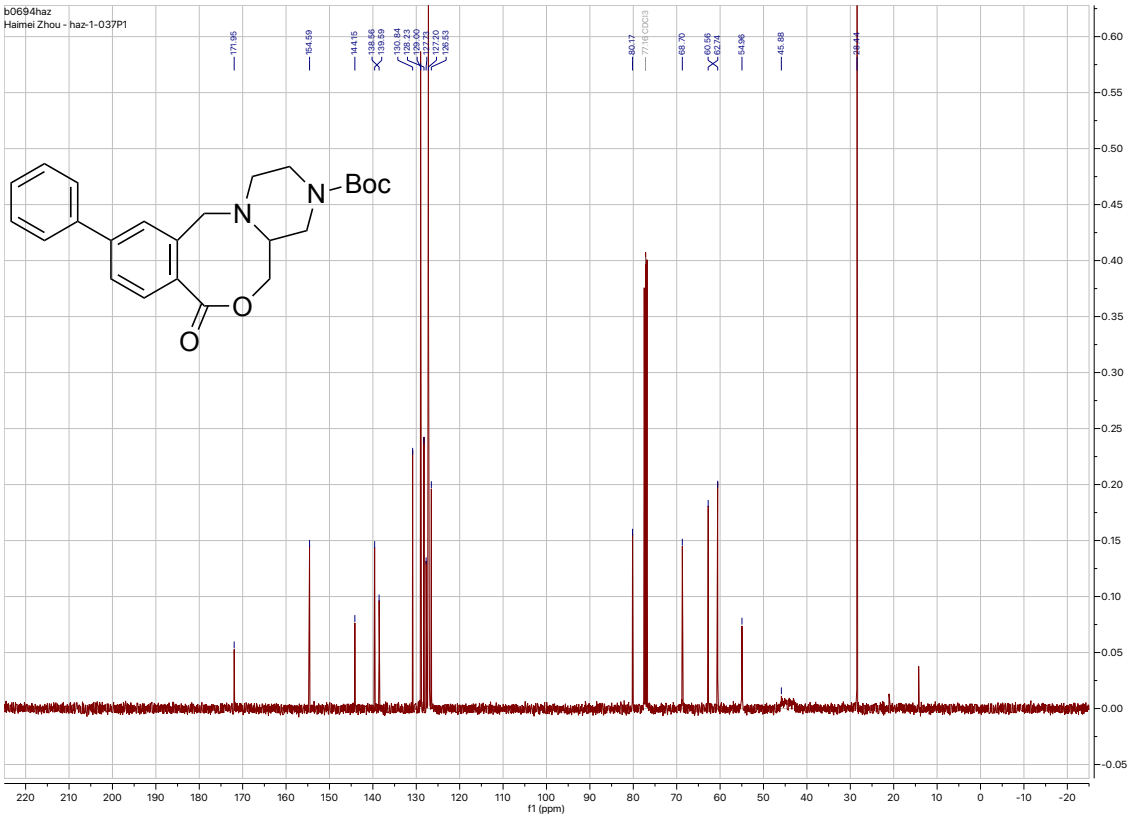
***tert*-Butyl 7-oxo-10-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,4a,5,7,12-hexahydrobenzo[*f*]pyrazino[2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate (124)**



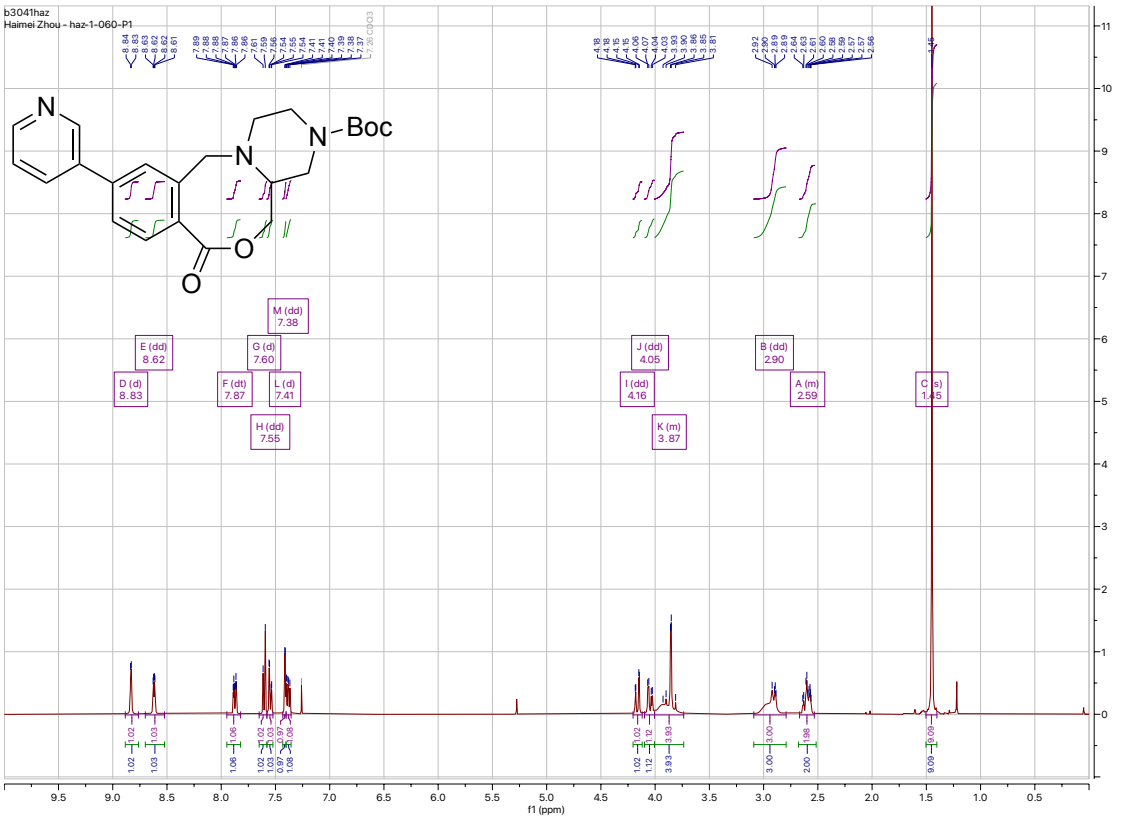


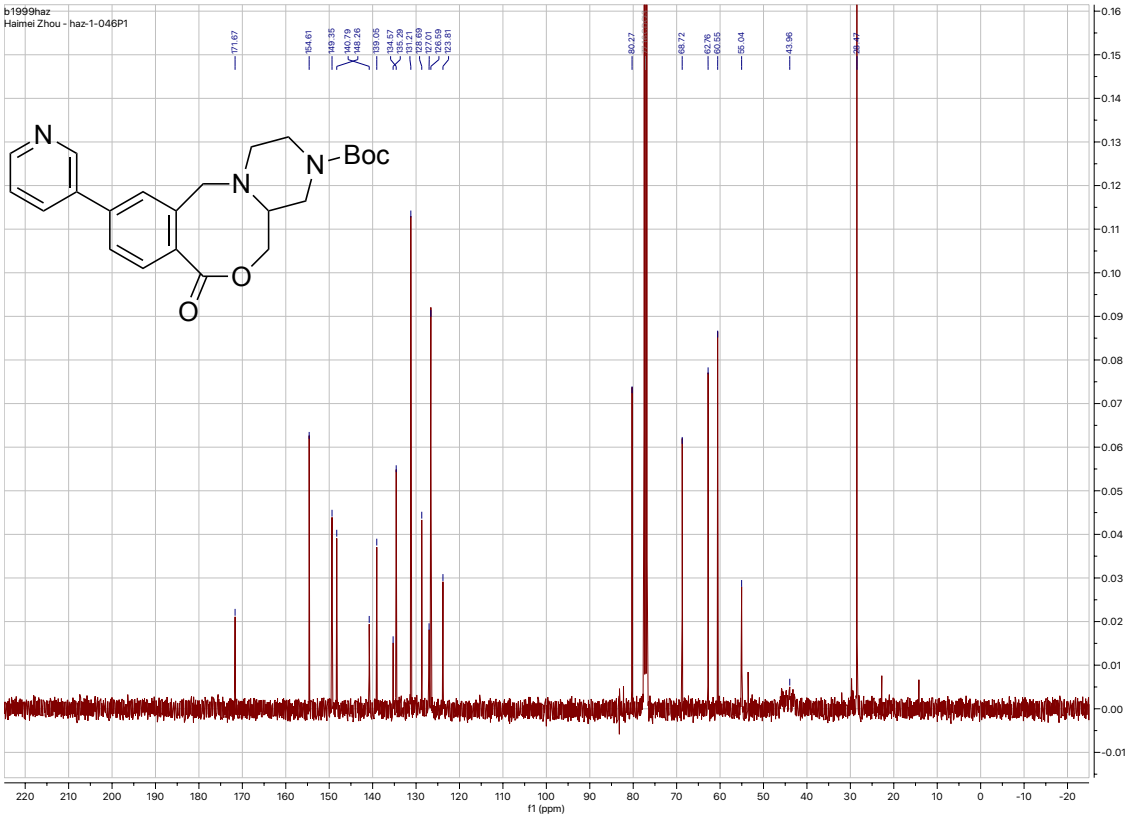
***tert*-Butyl 7-oxo-10-phenyl-1,2,4a,5,7,12-hexahydrobenzo[*f*]pyrazino[2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate (114)**



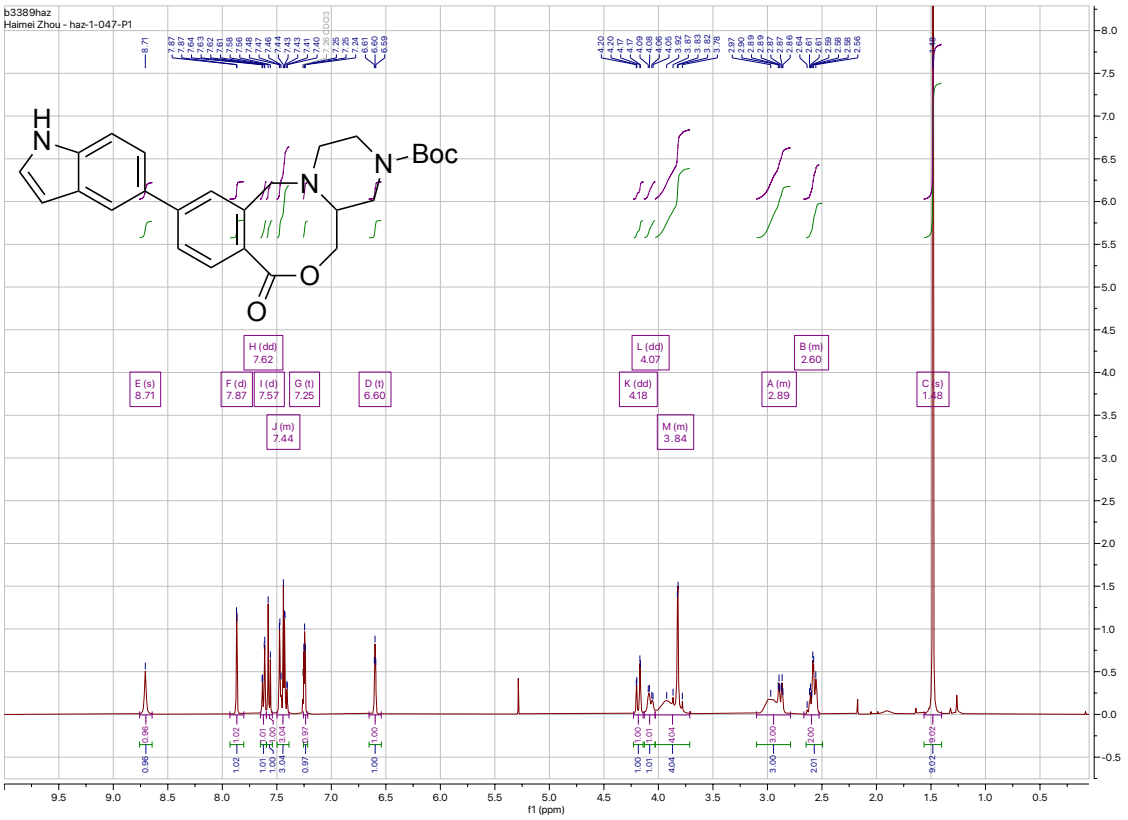


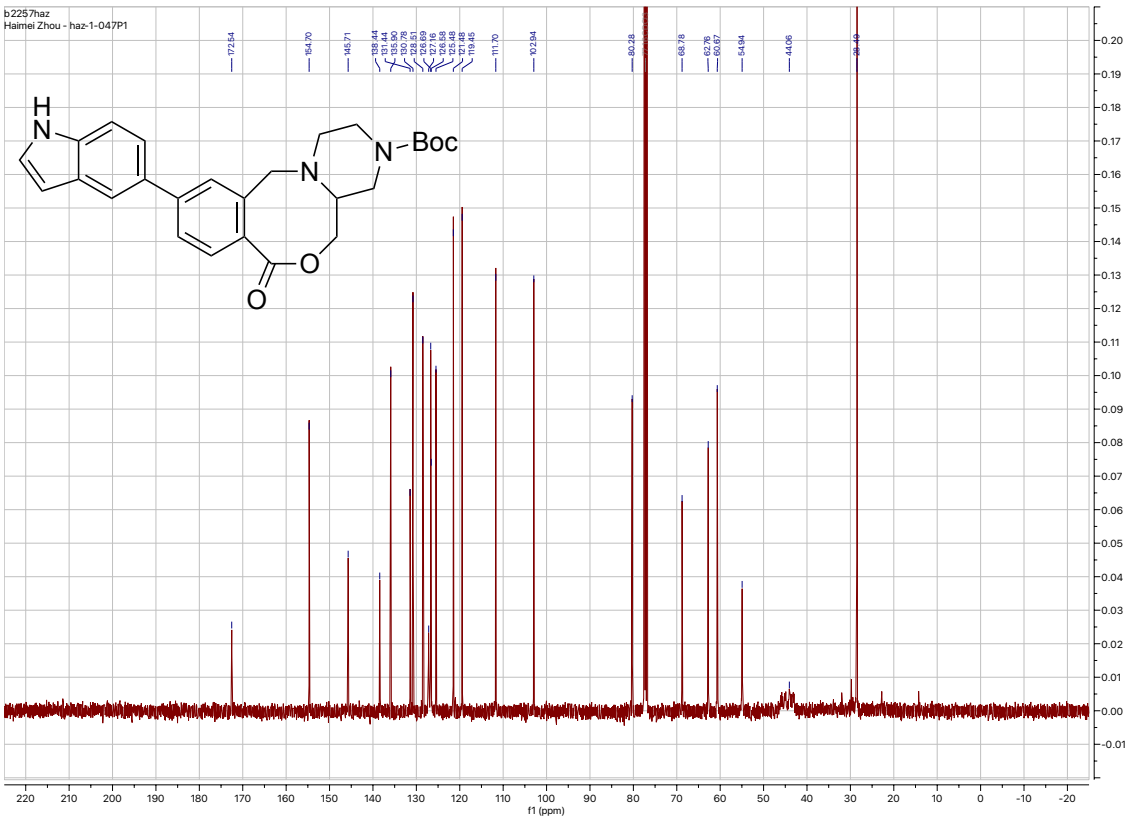
tert-Butyl 7-oxo-10-(pyridin-3-yl)-1,2,4a,5,7,12-hexahydrobenzo[_f_]pyrazino[2,1-_c_][1,4]oxazocine-3(4_H_)-carboxylate (118)



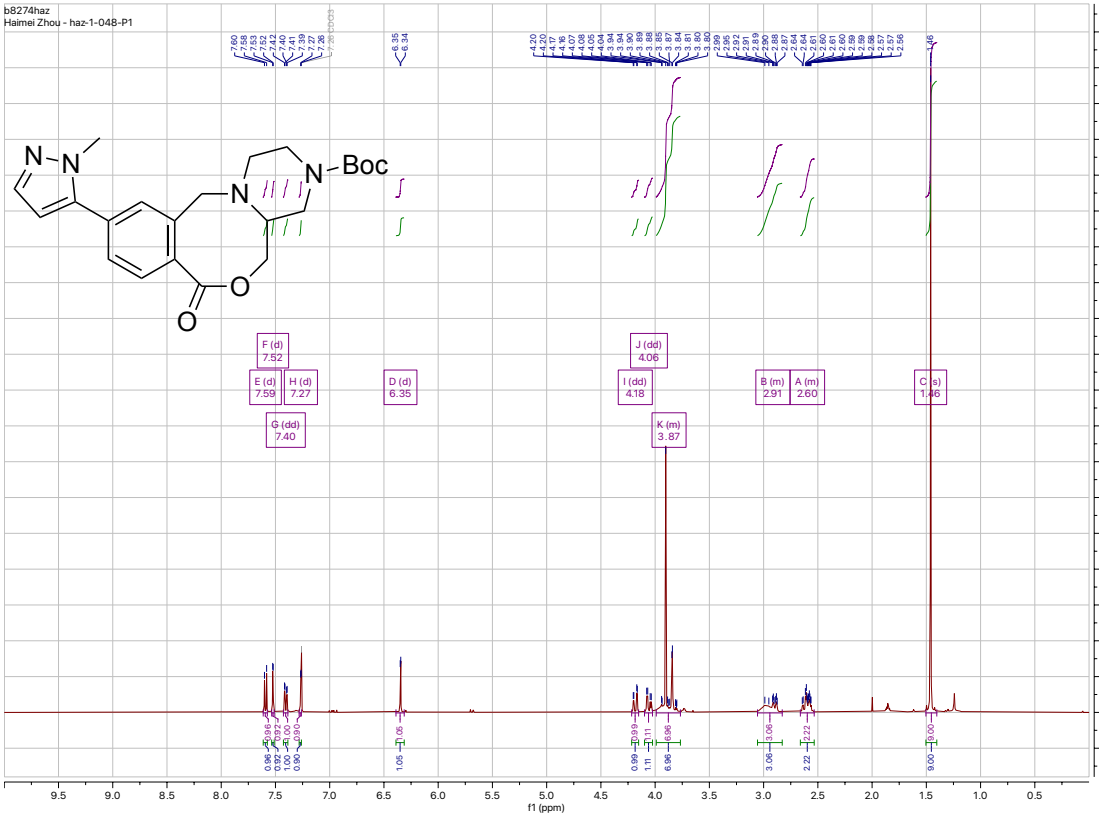


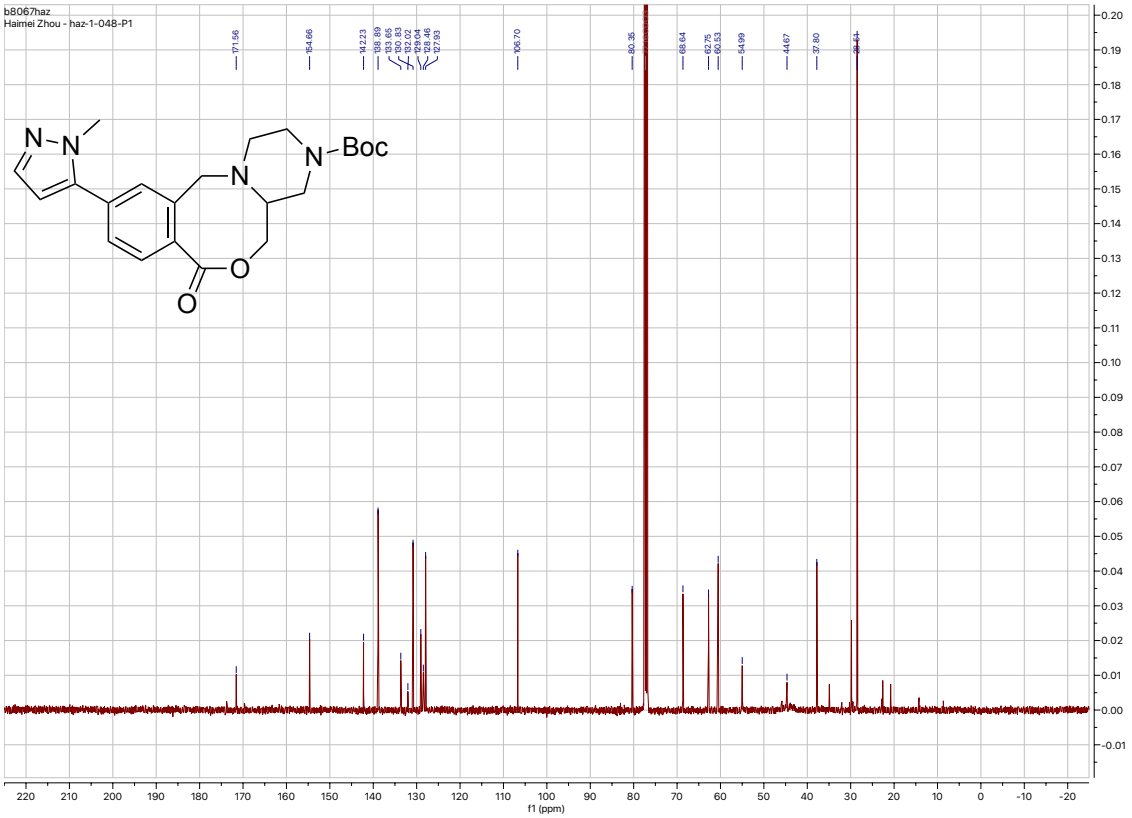
***tert*-Butyl 10-(1H-indol-5-yl)-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[*f*]pyrazino[2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate (119)**



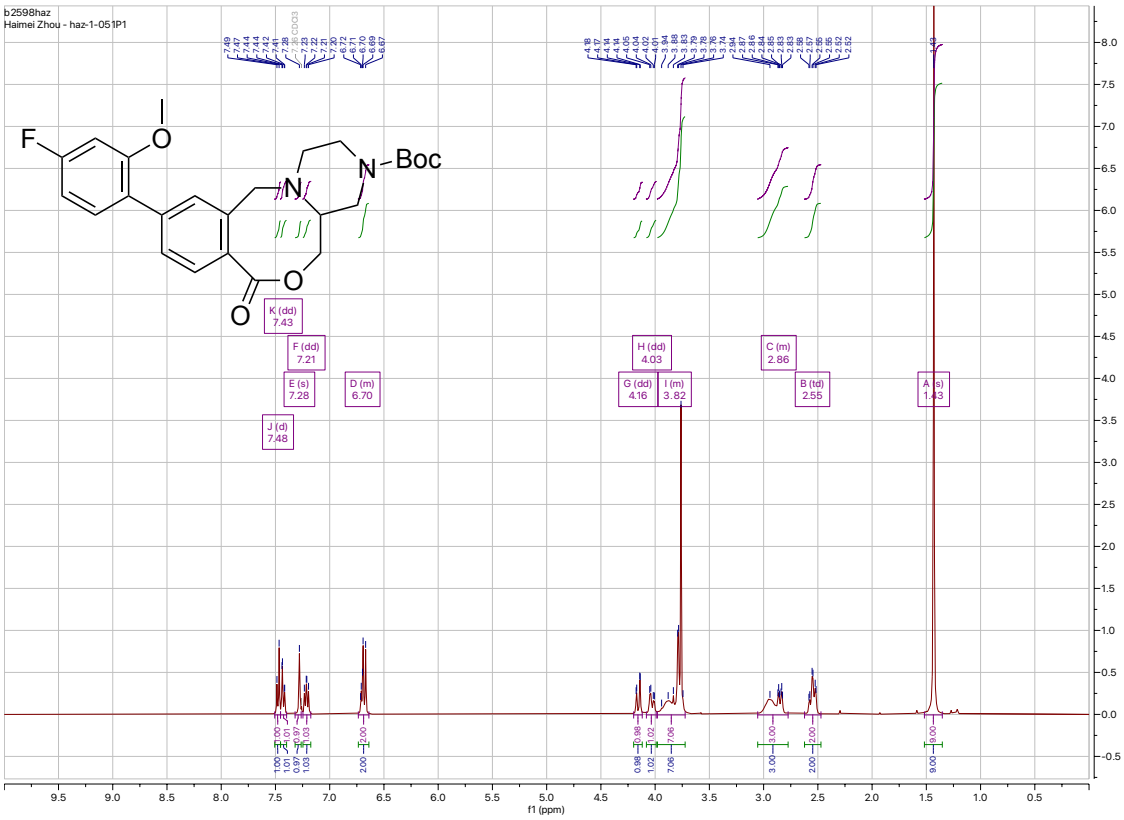


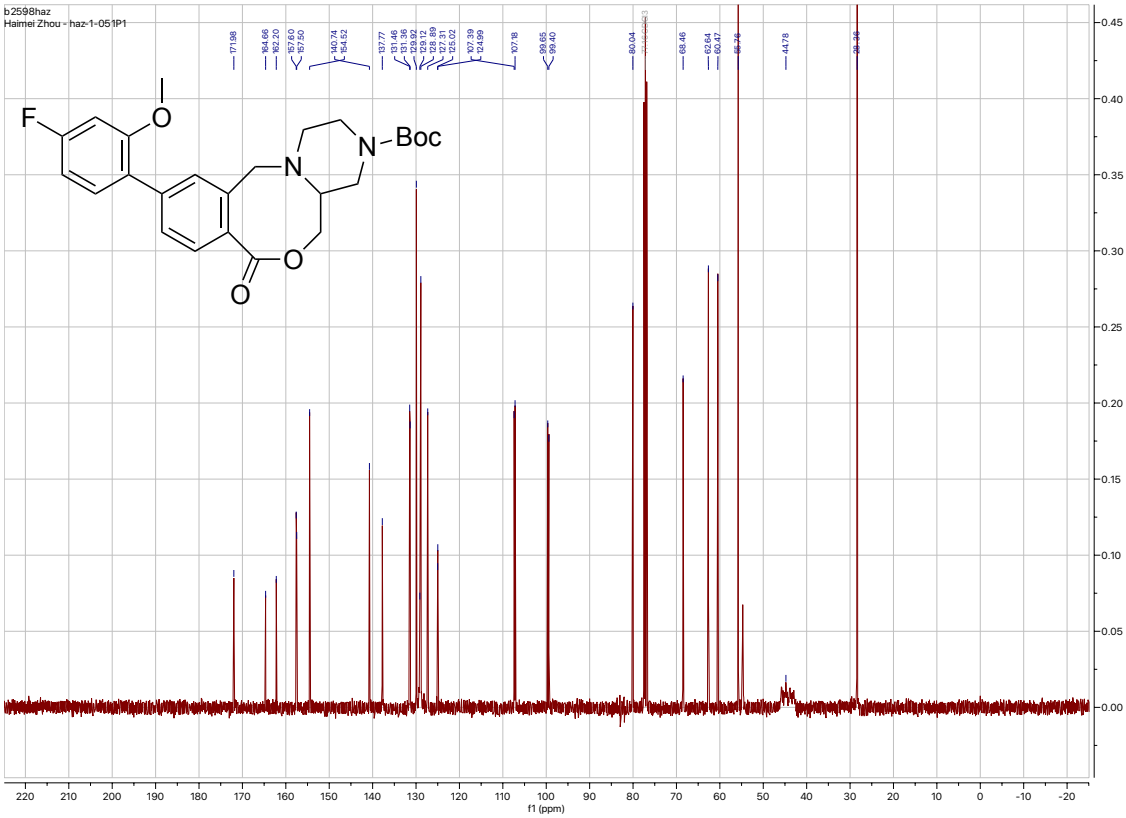
***tert*-Butyl 10-(1-methyl-1H-pyrazol-5-yl)-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[*f*]pyrazino [2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate (121)**



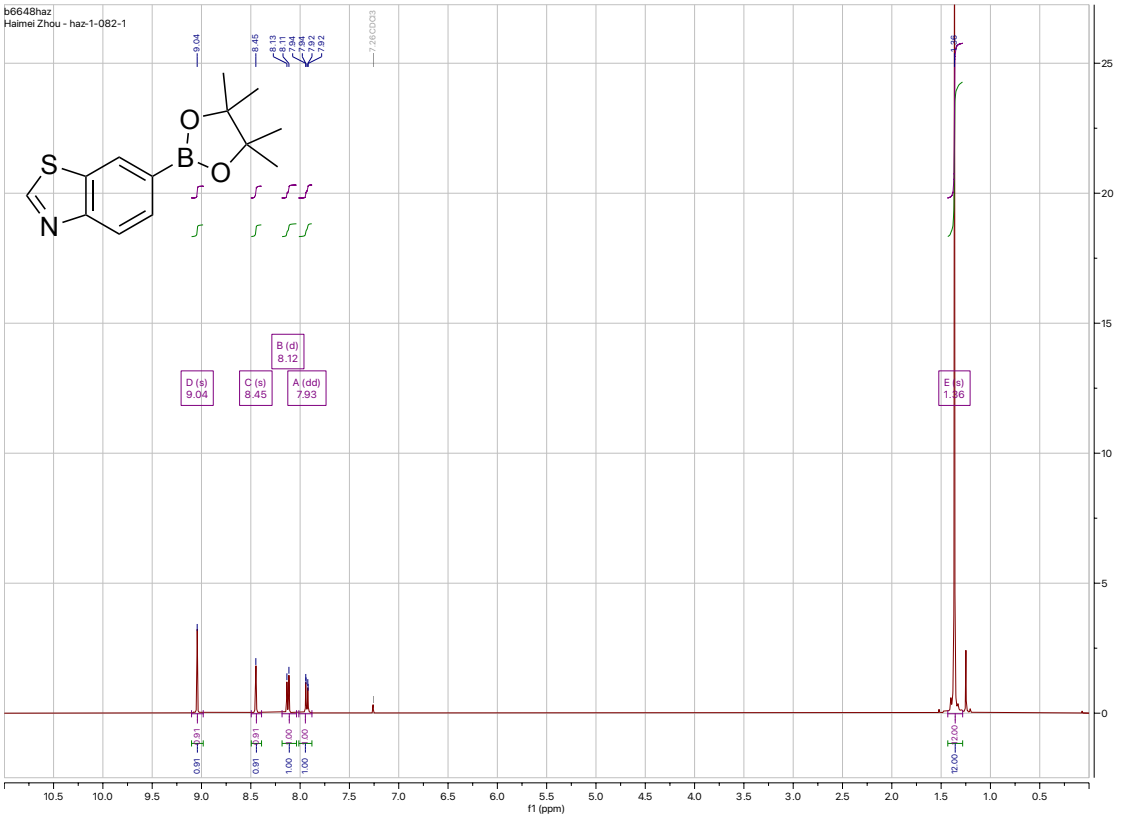


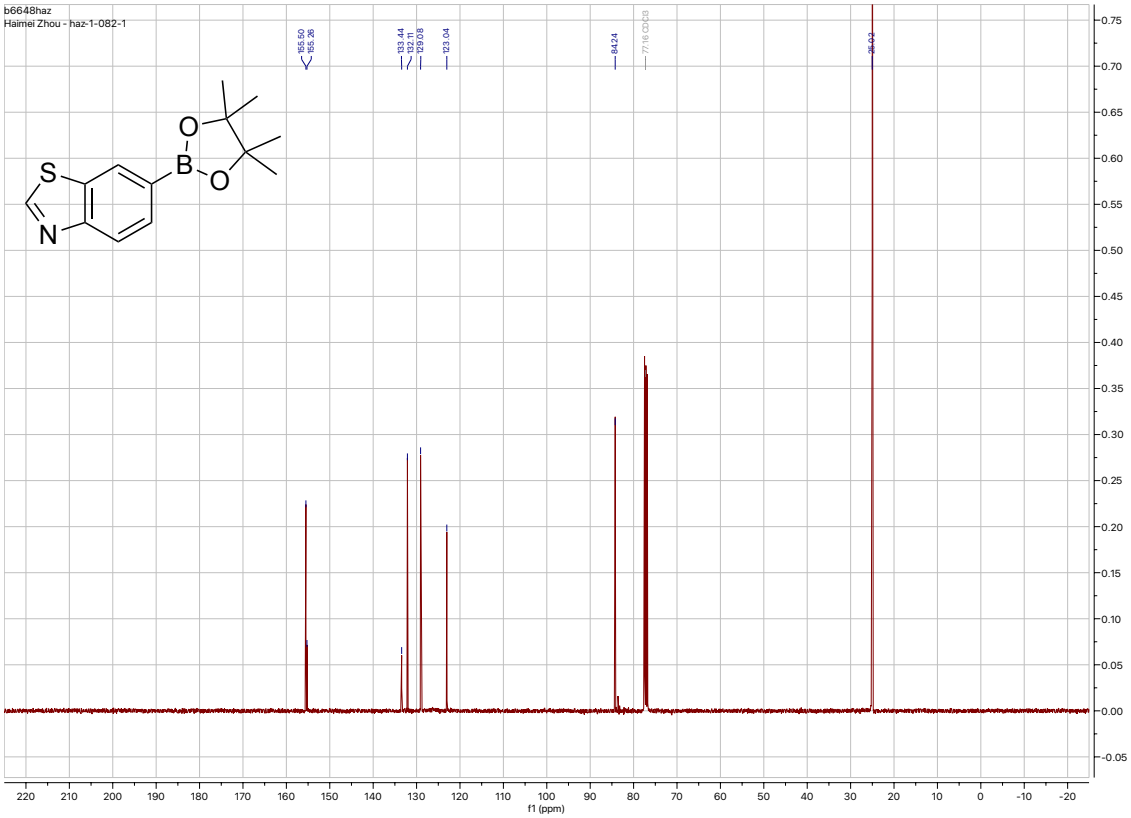
tert-Butyl 10-(4-fluoro-2-methoxyphenyl)-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[_f_]pyrazino[2,1-_c_][1,4]oxazocine-3(4_H_)-carboxylate (122)



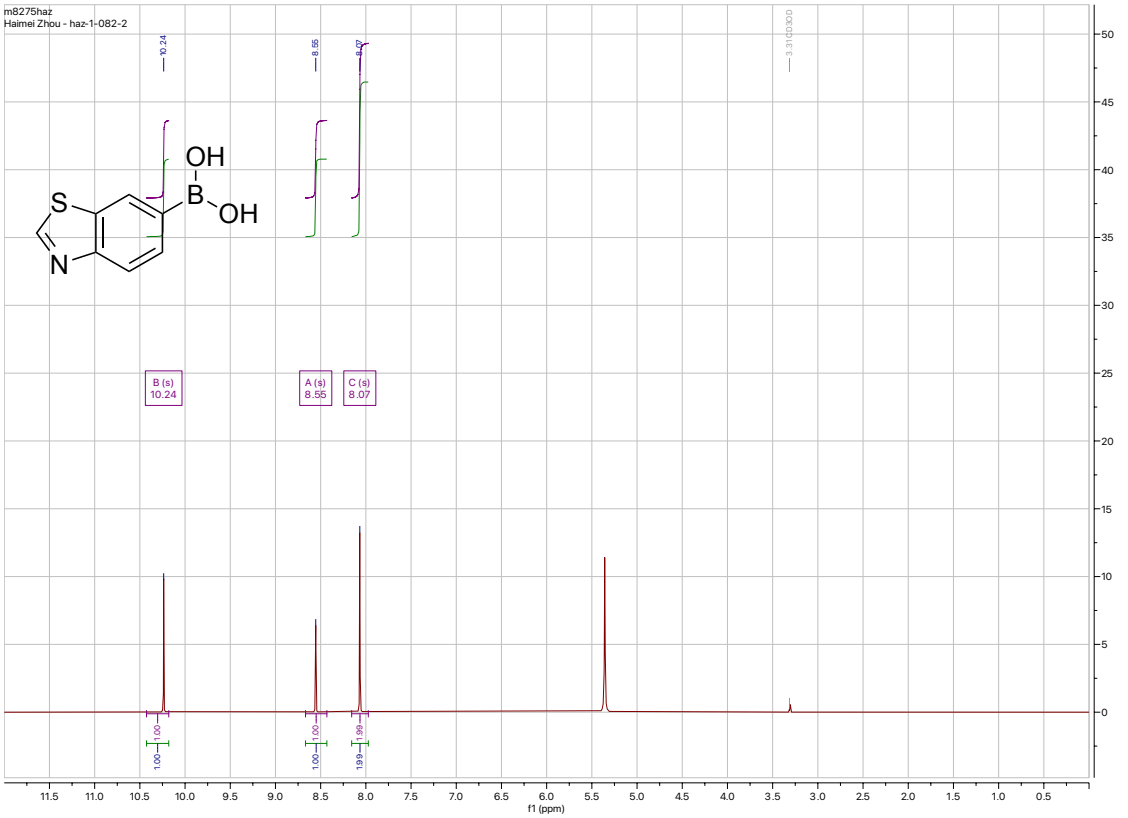


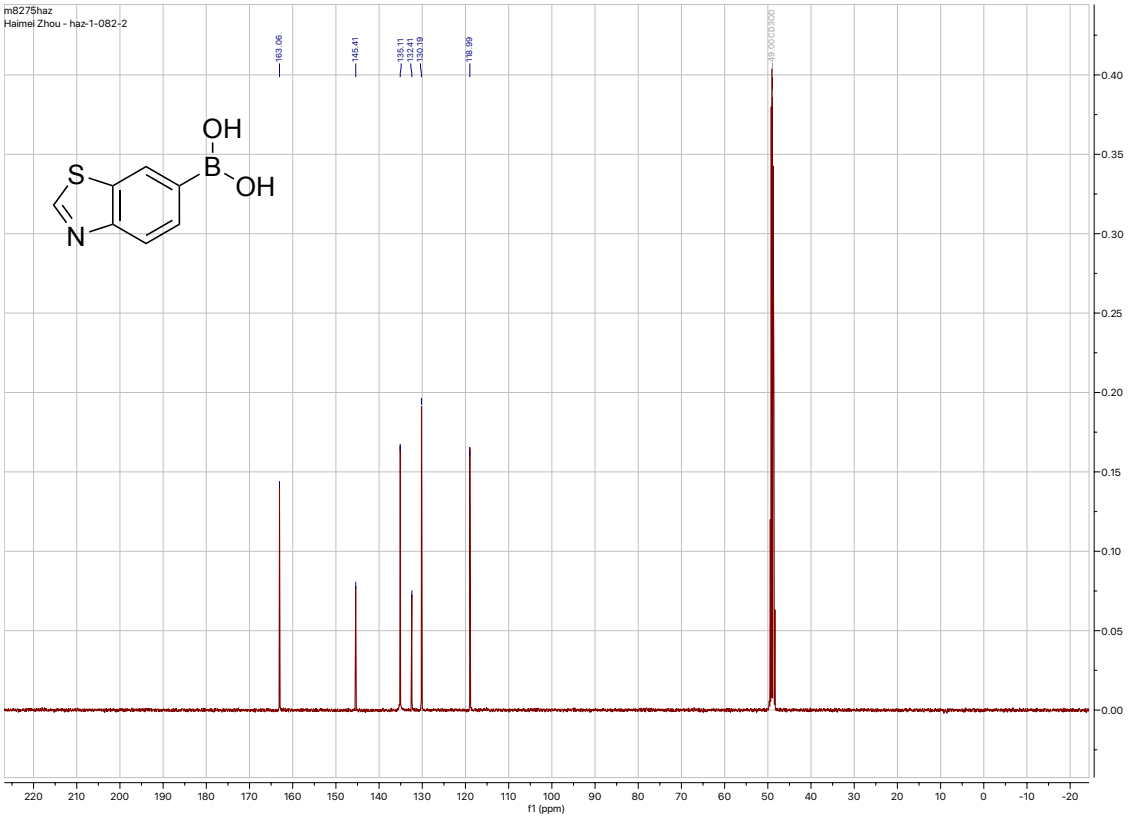
6-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]thiazole (134)



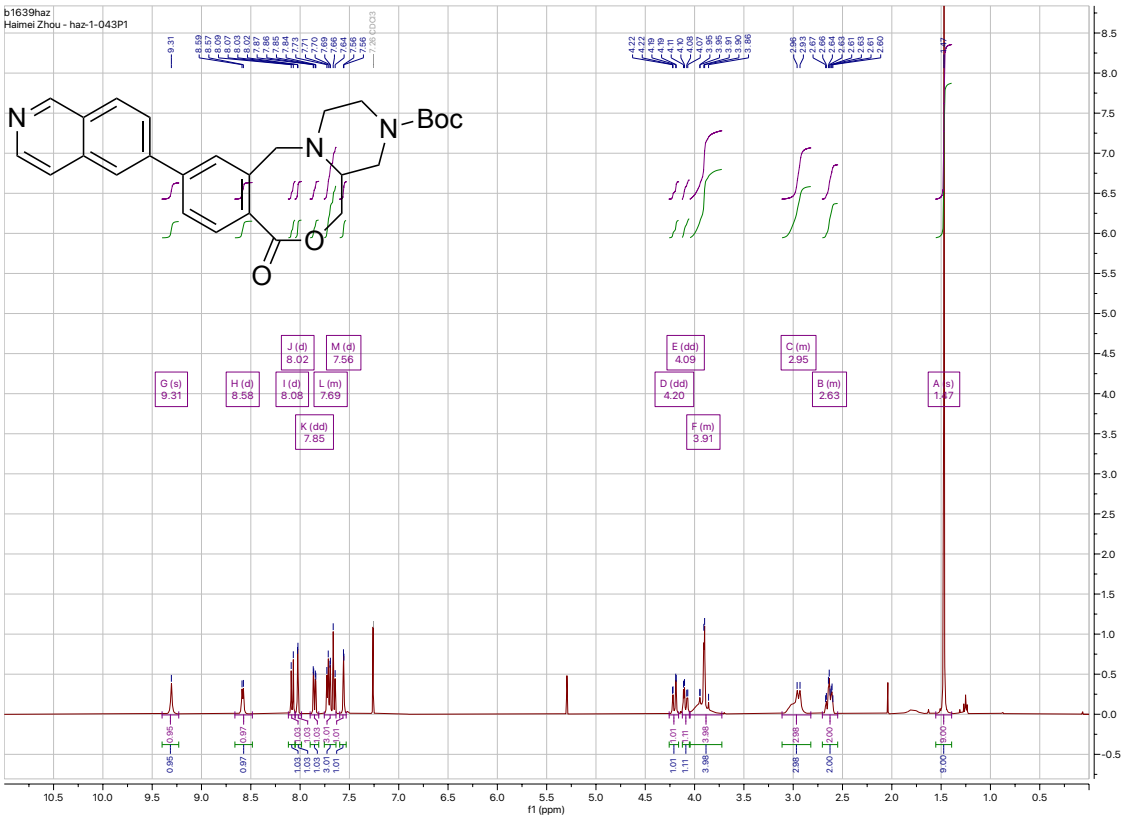


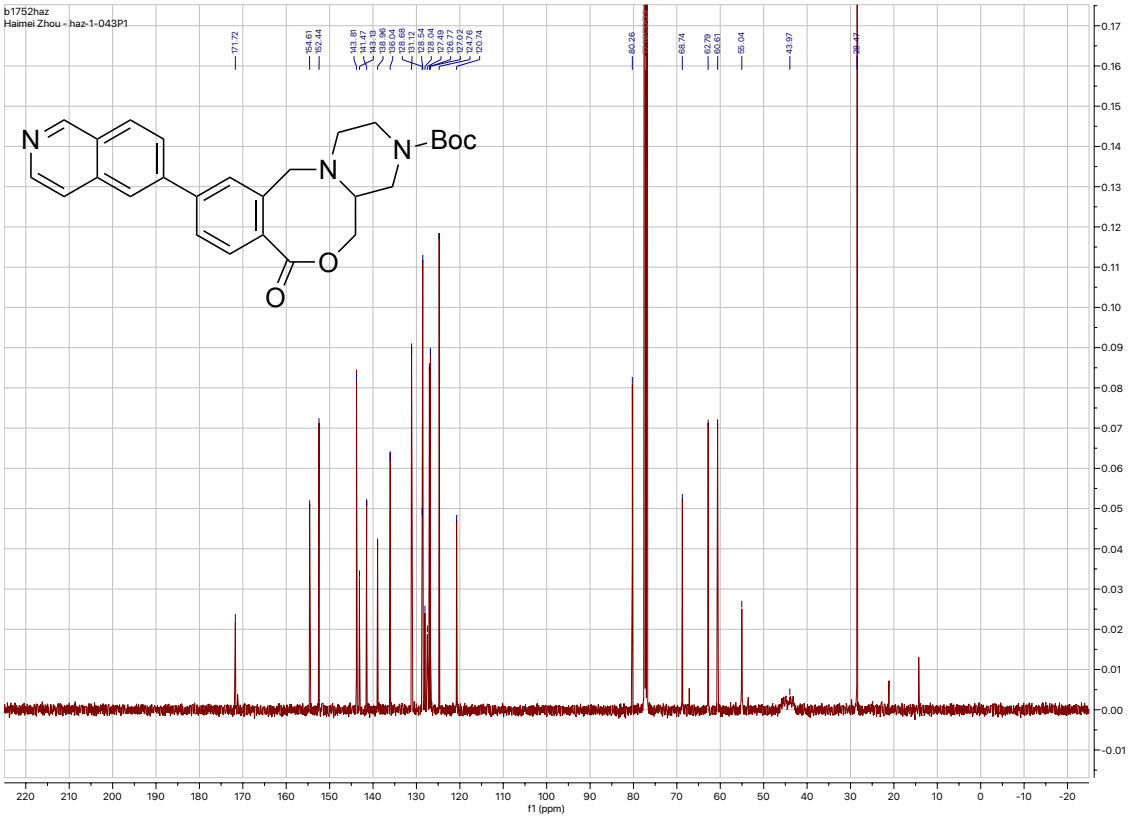
Benzo[*d*]thiazol-6-ylboronic acid (135)



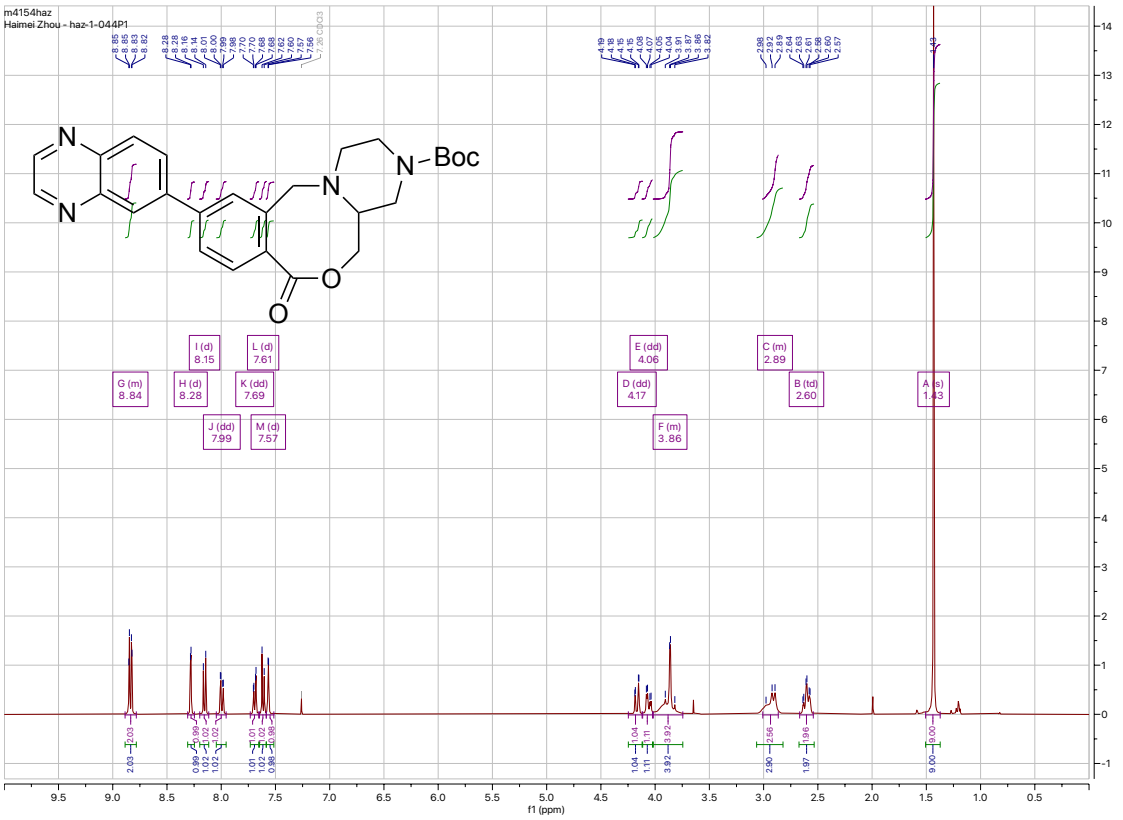


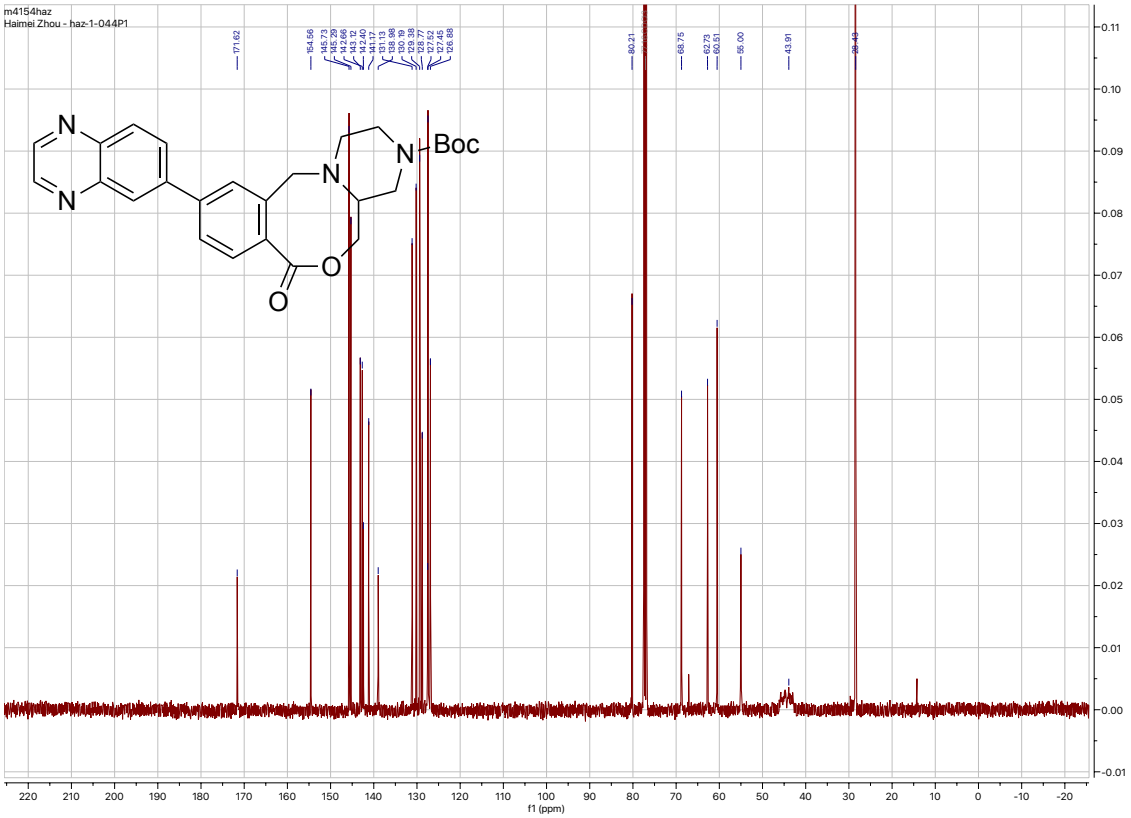
***tert*-Butyl 10-(isoquinolin-6-yl)-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[*f*]pyrazino[2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate (120)**



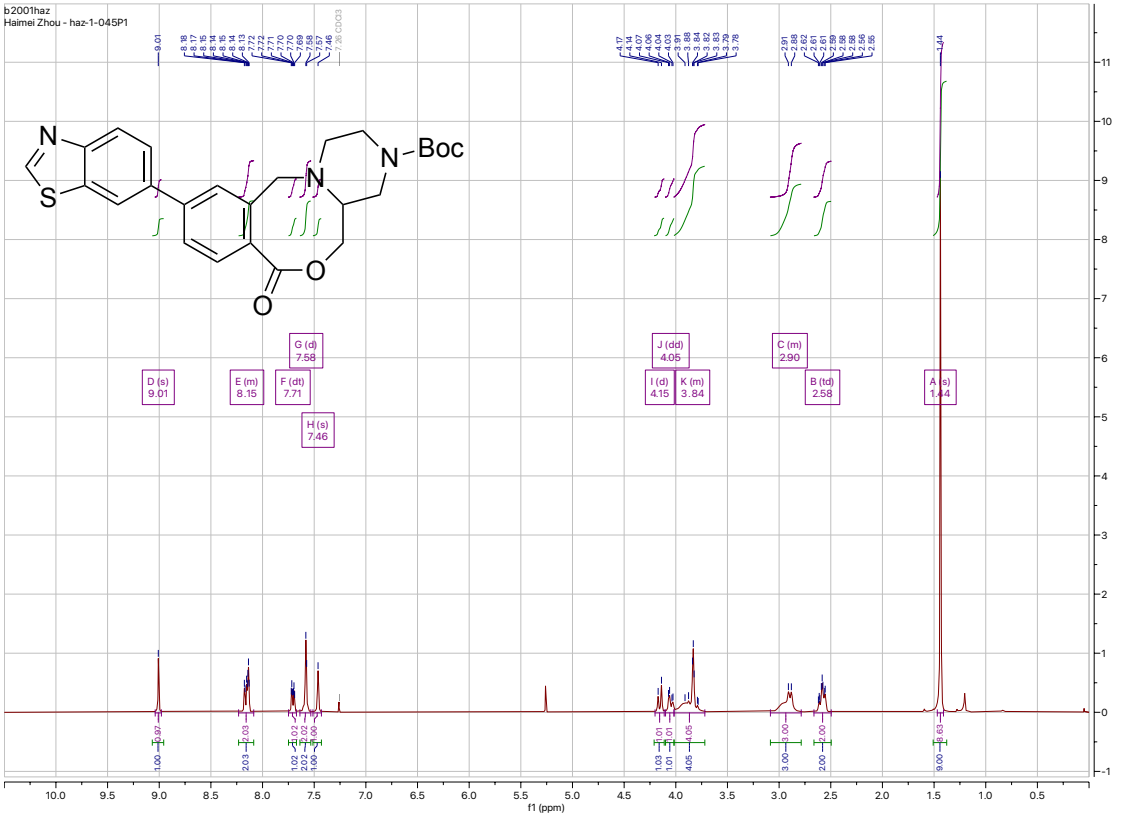


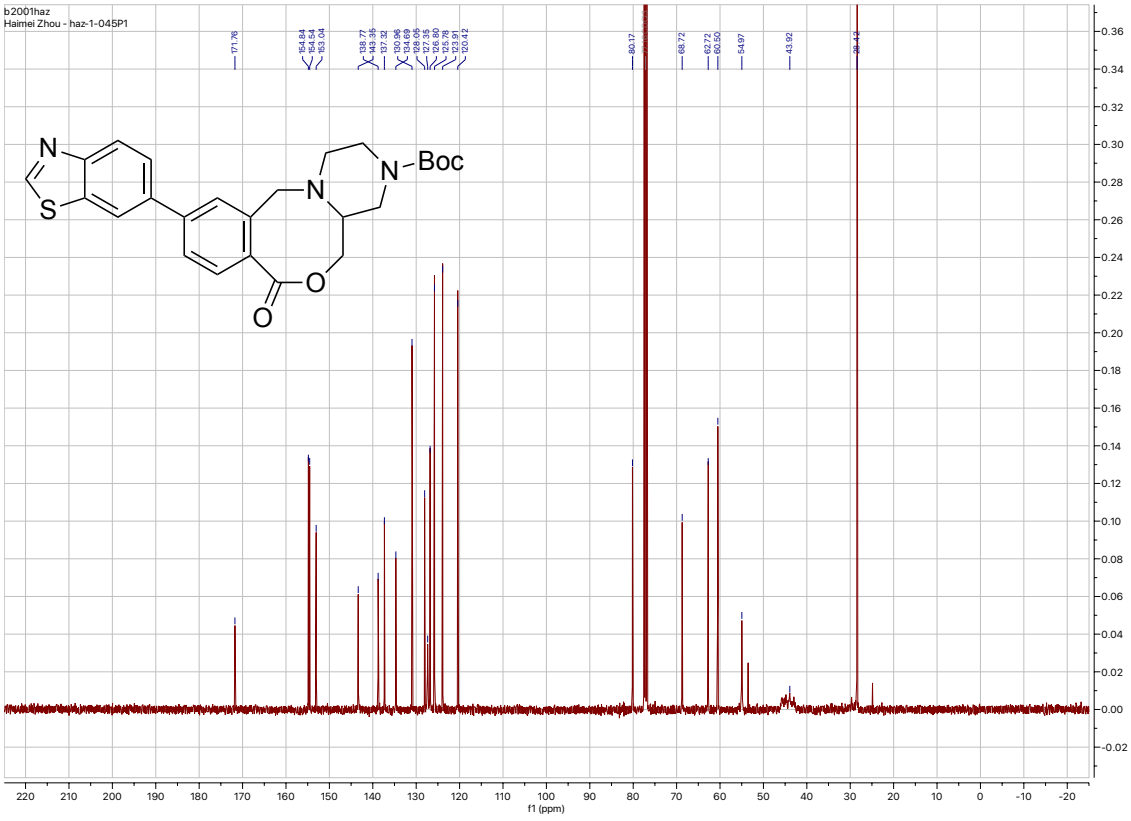
tert-Butyl 7-oxo-10-(quinoxalin-6-yl)-1,2,4a,5,7,12-hexahydrobenzo[_f_]pyrazino[2,1-_c_][1,4]oxazocine-3(4_H_)-carboxylate (126)



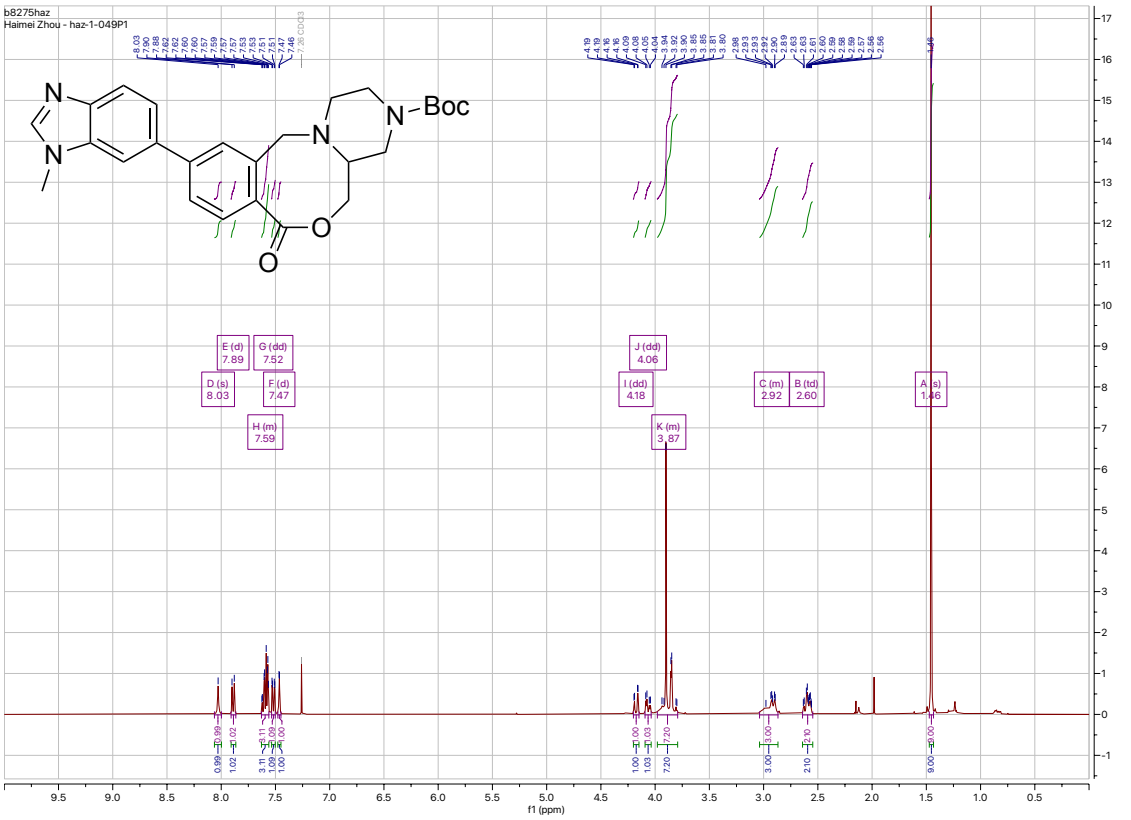


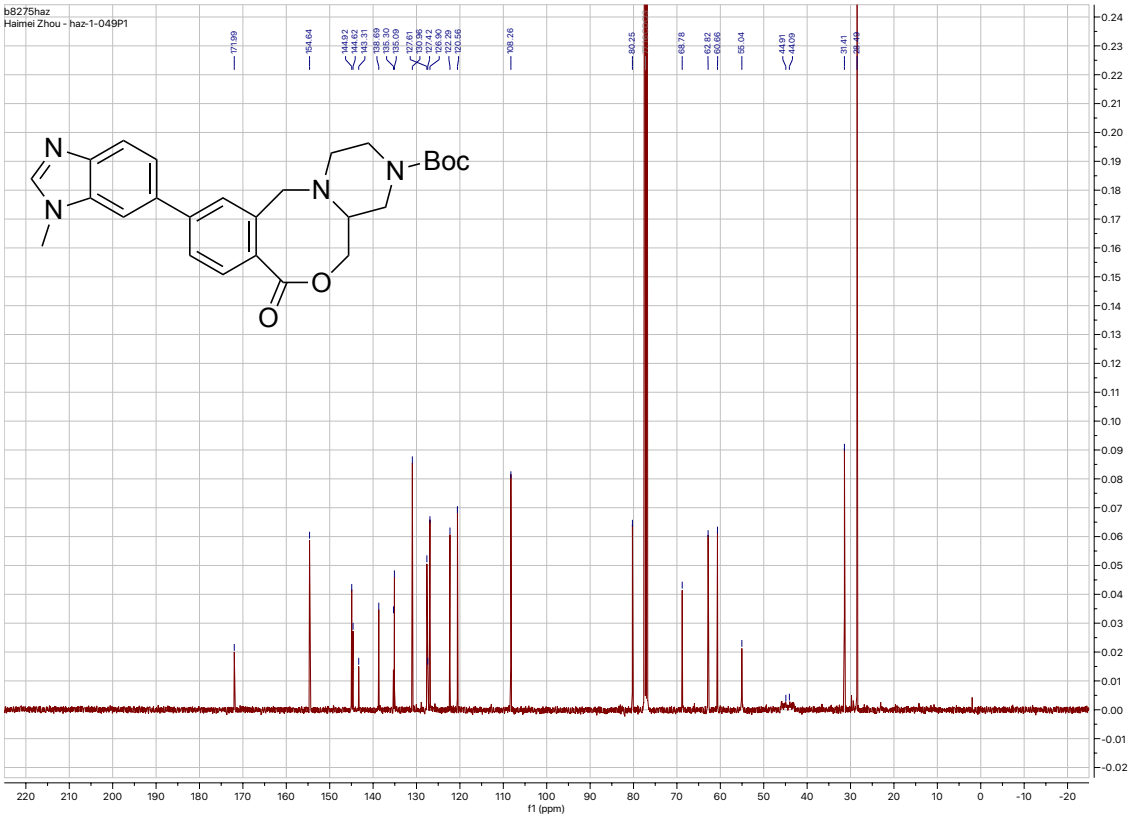
***tert*-Butyl 10-(benzo[d]thiazol-6-yl)-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[*f*]pyrazino [2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate (127)**



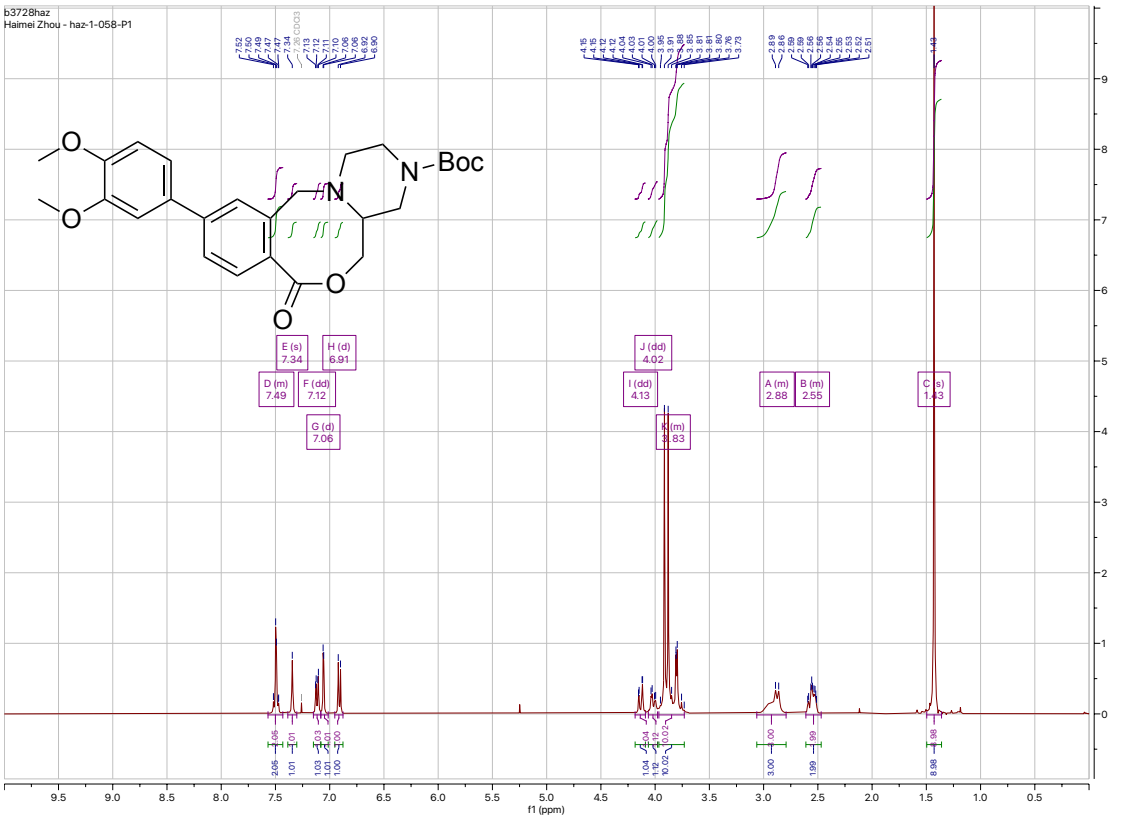


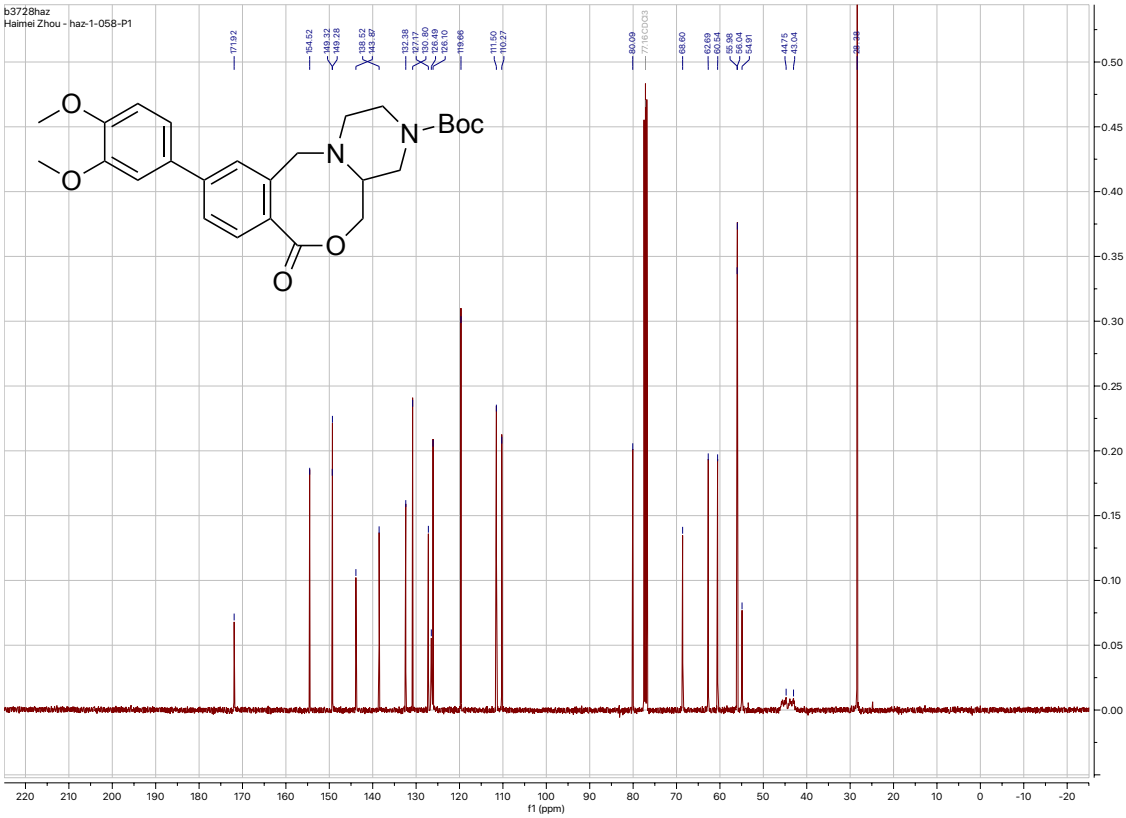
***tert*-Butyl 10-(1-methyl-1H-benzo[d]imidazol-6-yl)-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[*f*] pyrazino[2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate (128)**



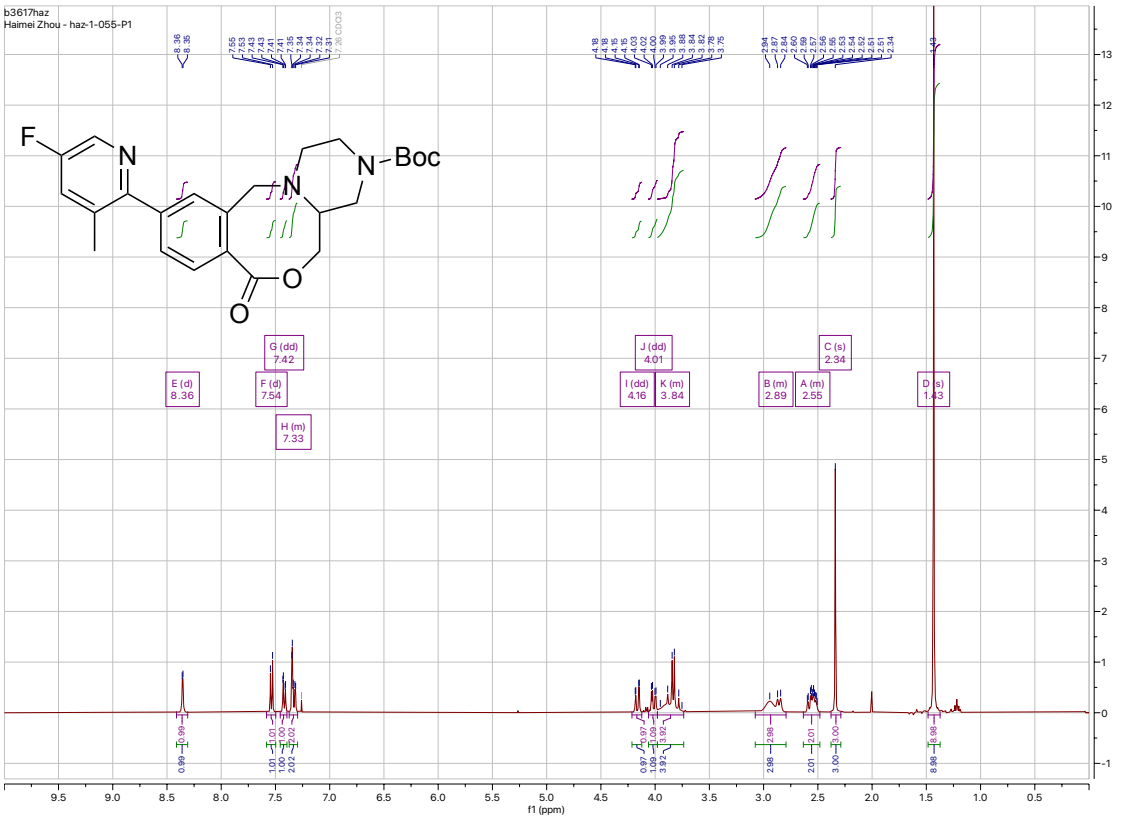


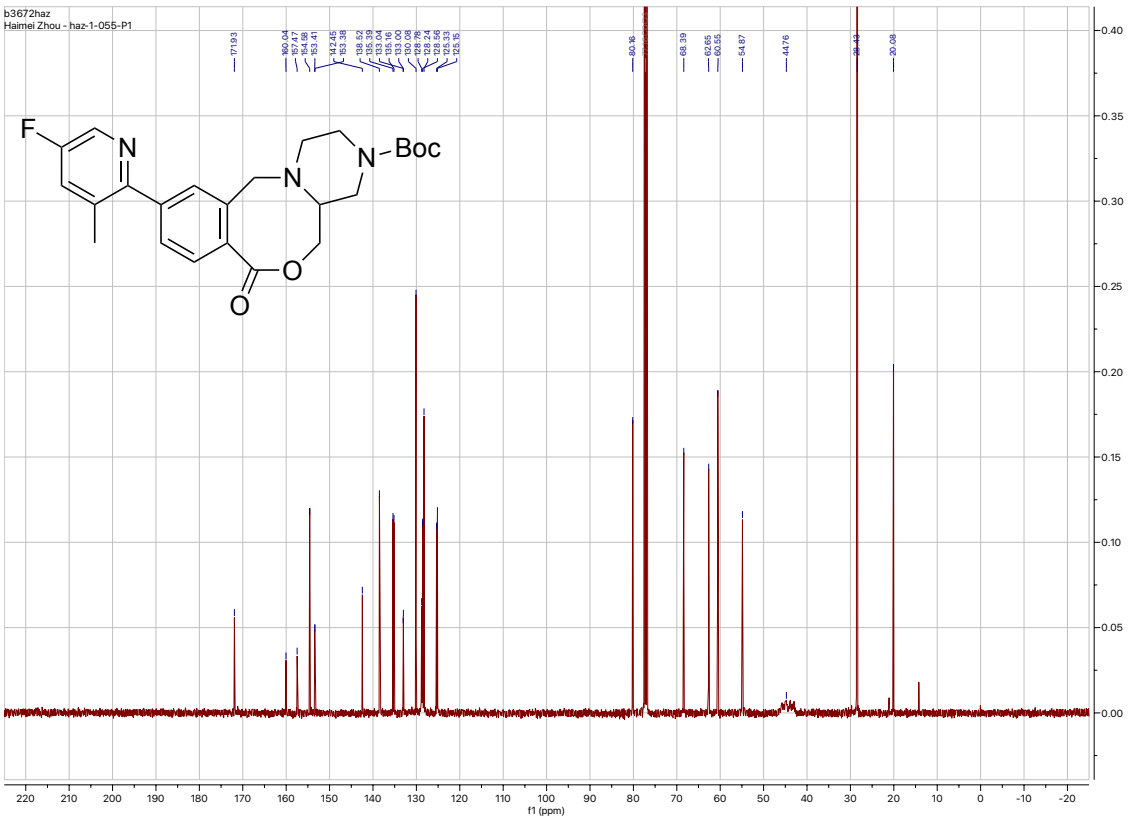
***tert*-Butyl 10-(3,4-dimethoxyphenyl)-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[*f*] pyrazino [2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate (129)**



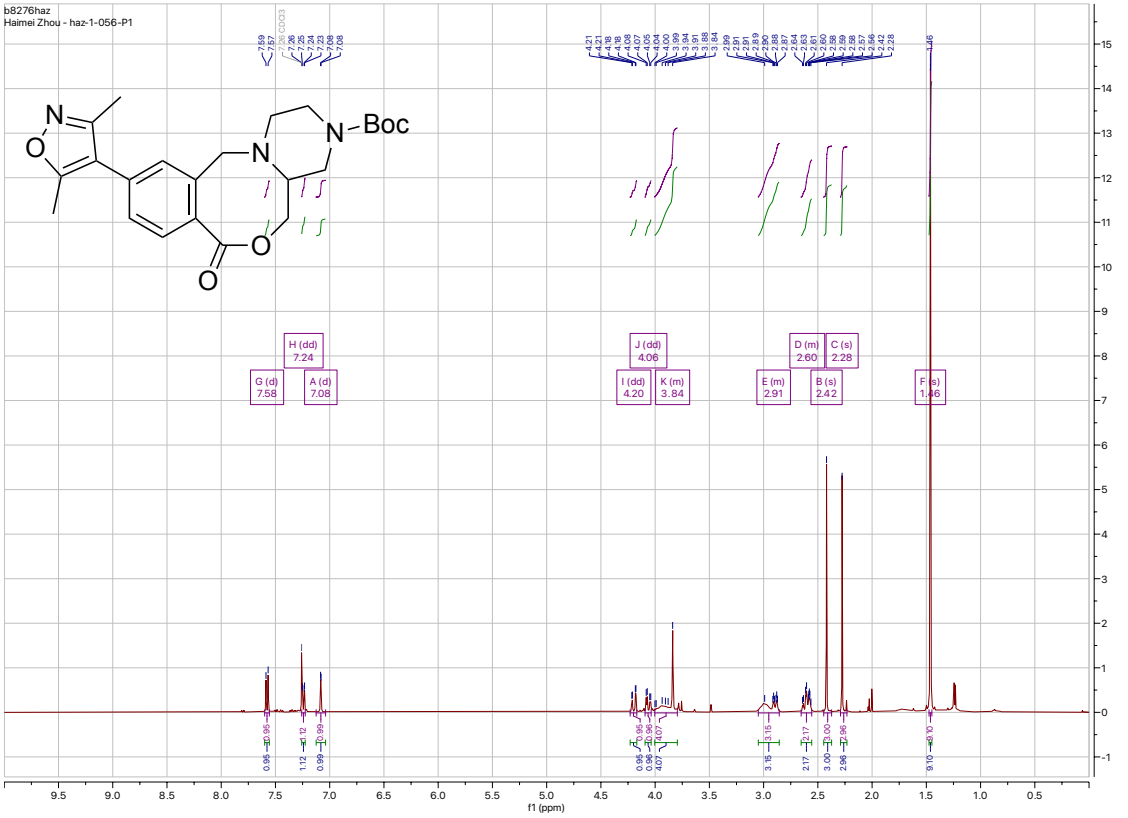


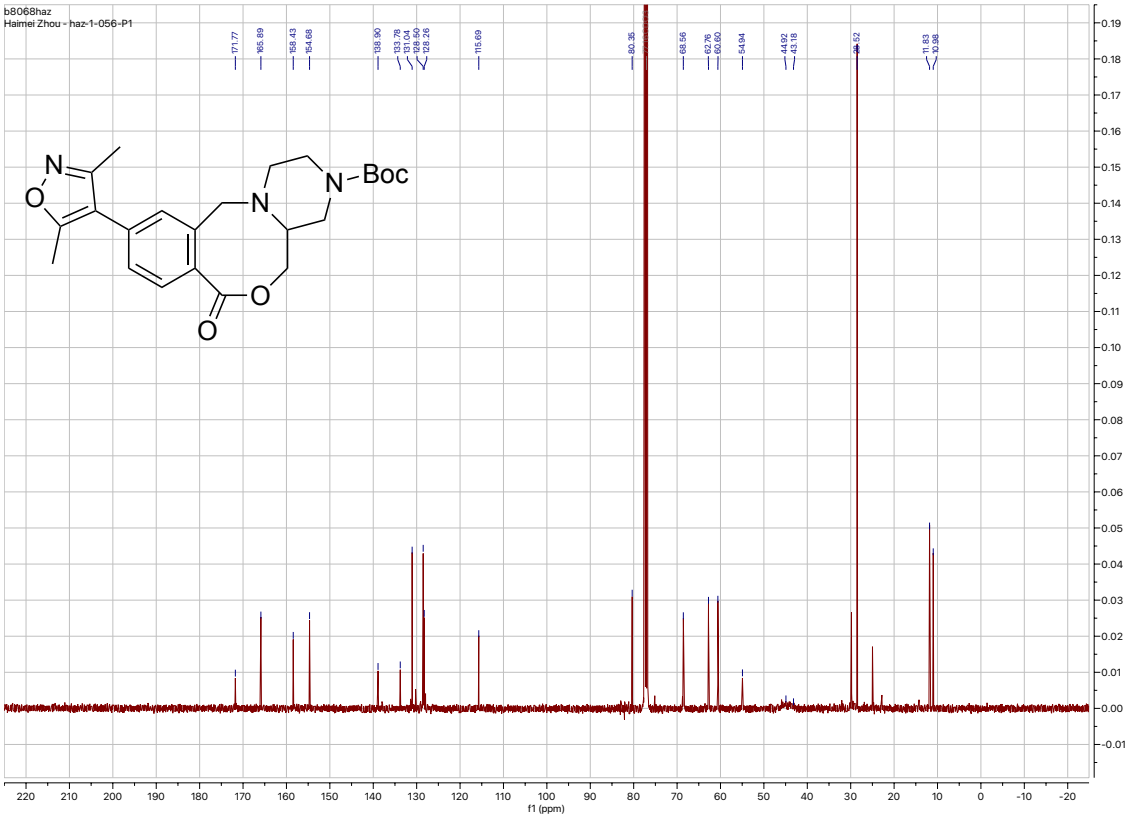
tert-Butyl 10-(5-fluoro-3-methylpyridin-2-yl)-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[_f_]pyrazino[2,1-_c_][1,4]oxazocine-3(4_H_)-carboxylate (130)



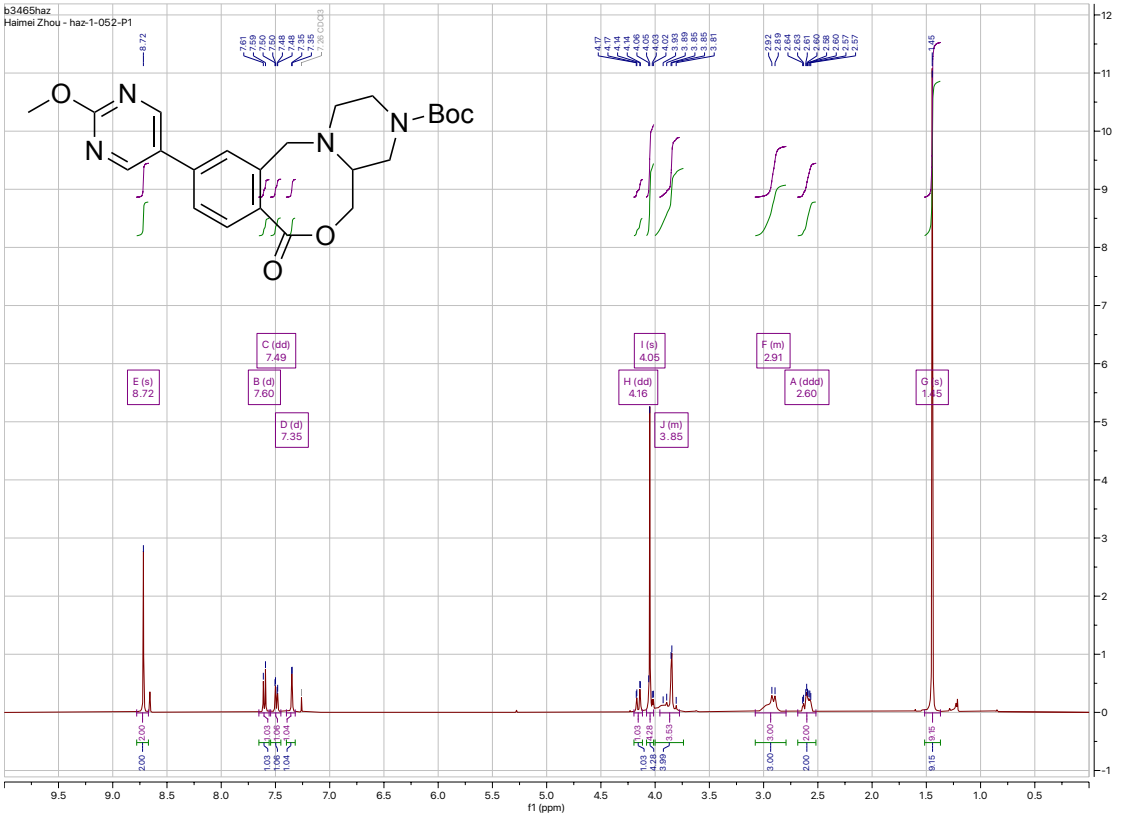


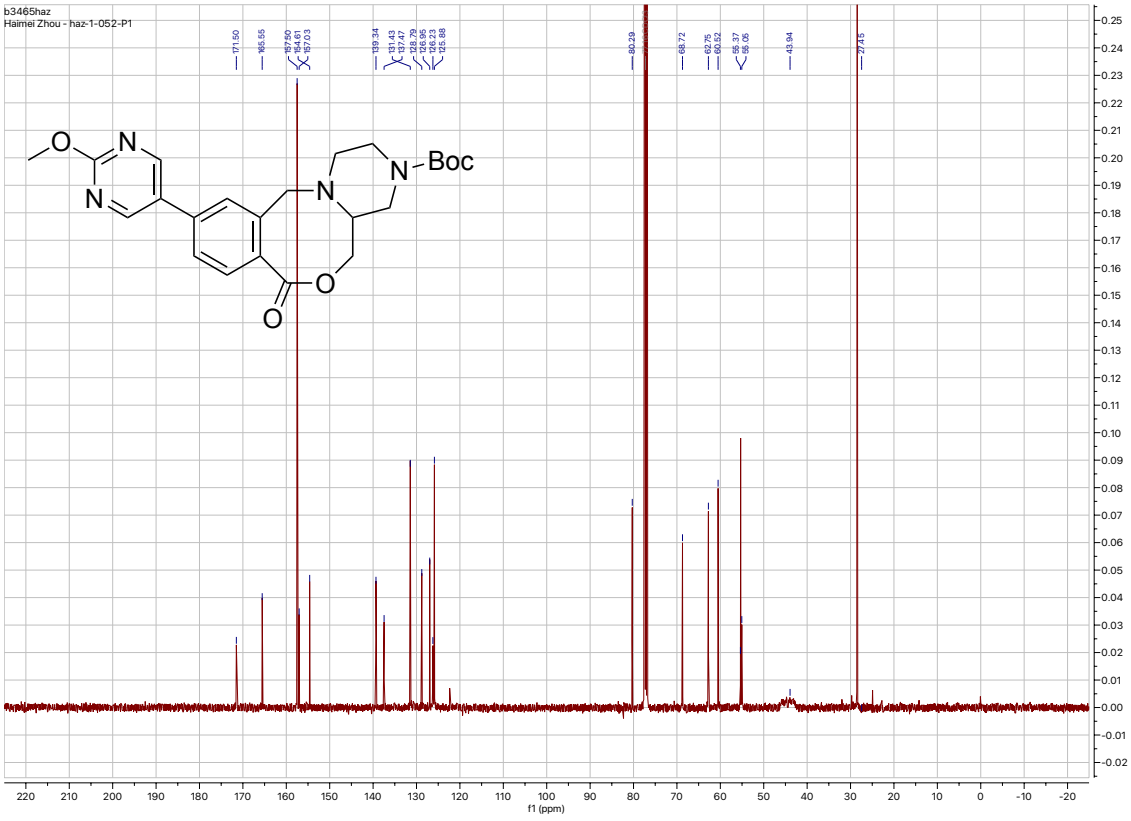
***tert*-Butyl 10-(3,5-dimethylisoxazol-4-yl)-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[*f*]pyrazino [2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate (131)**



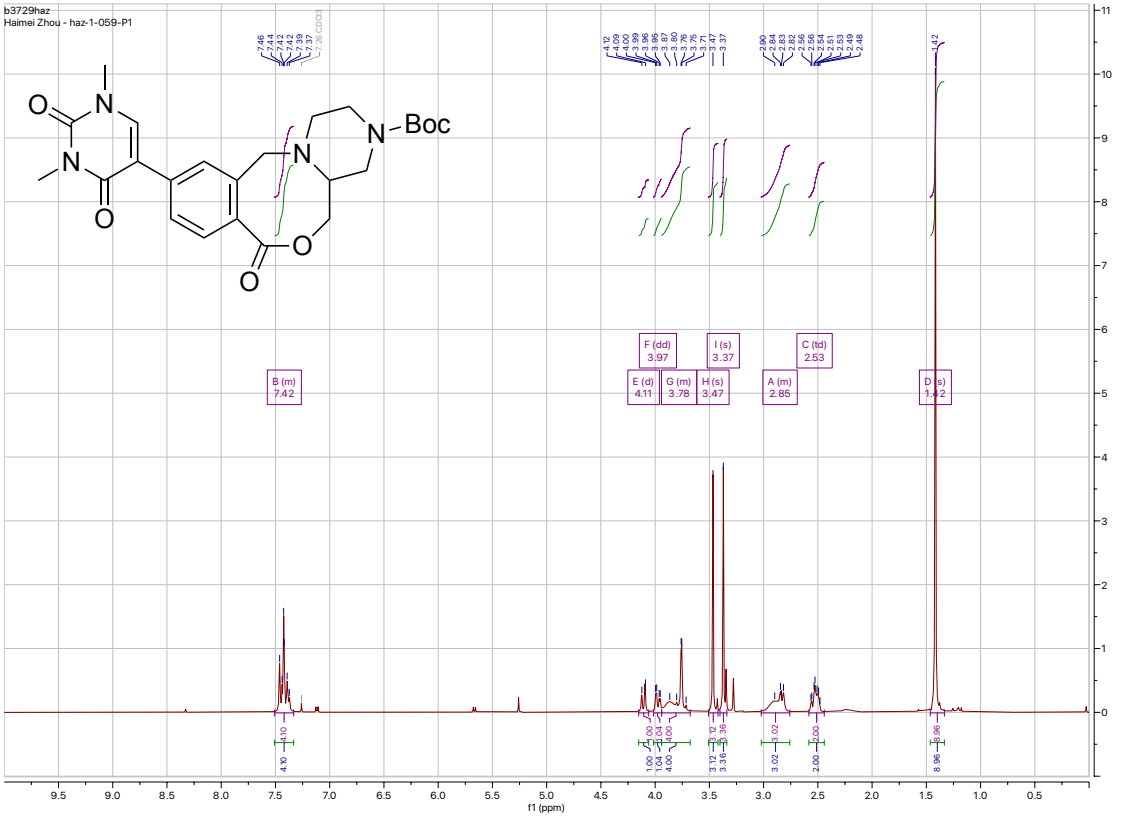


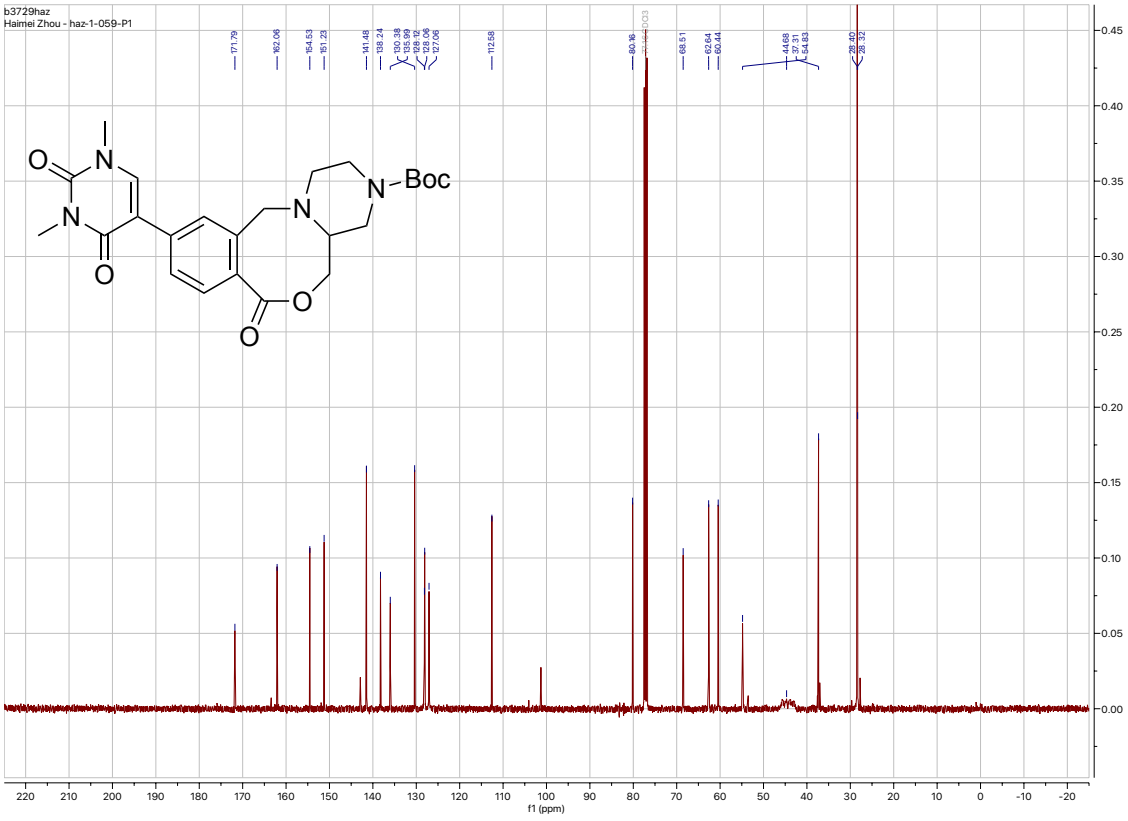
tert-Butyl 10-(2-methoxypyrimidin-5-yl)-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[_f_]pyrazino [2,1-_c_][1,4]oxazocine-3(4_H_)-carboxylate (132)



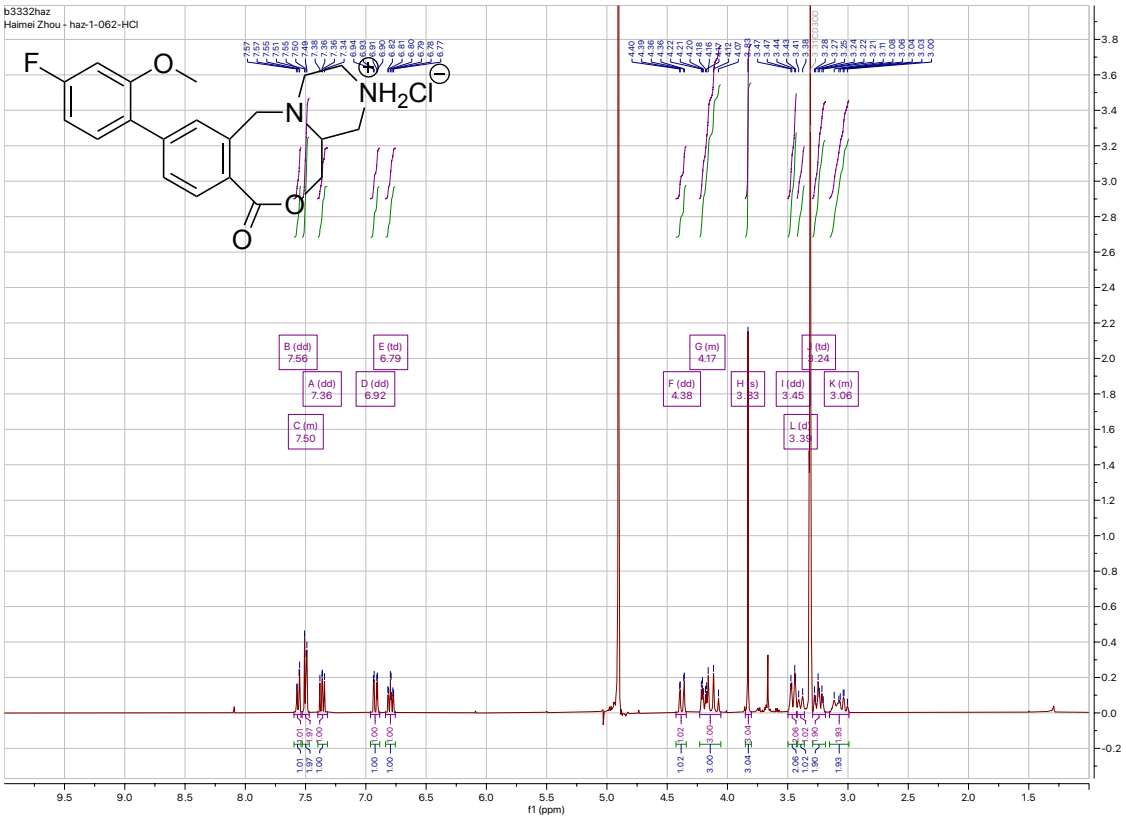


***tert*-Butyl 10-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-7-oxo-1,2,4a,5,7,12-hexahydrobenzo[*f*]pyrazino[2,1-*c*][1,4]oxazocine-3(4*H*)-carboxylate (133)**

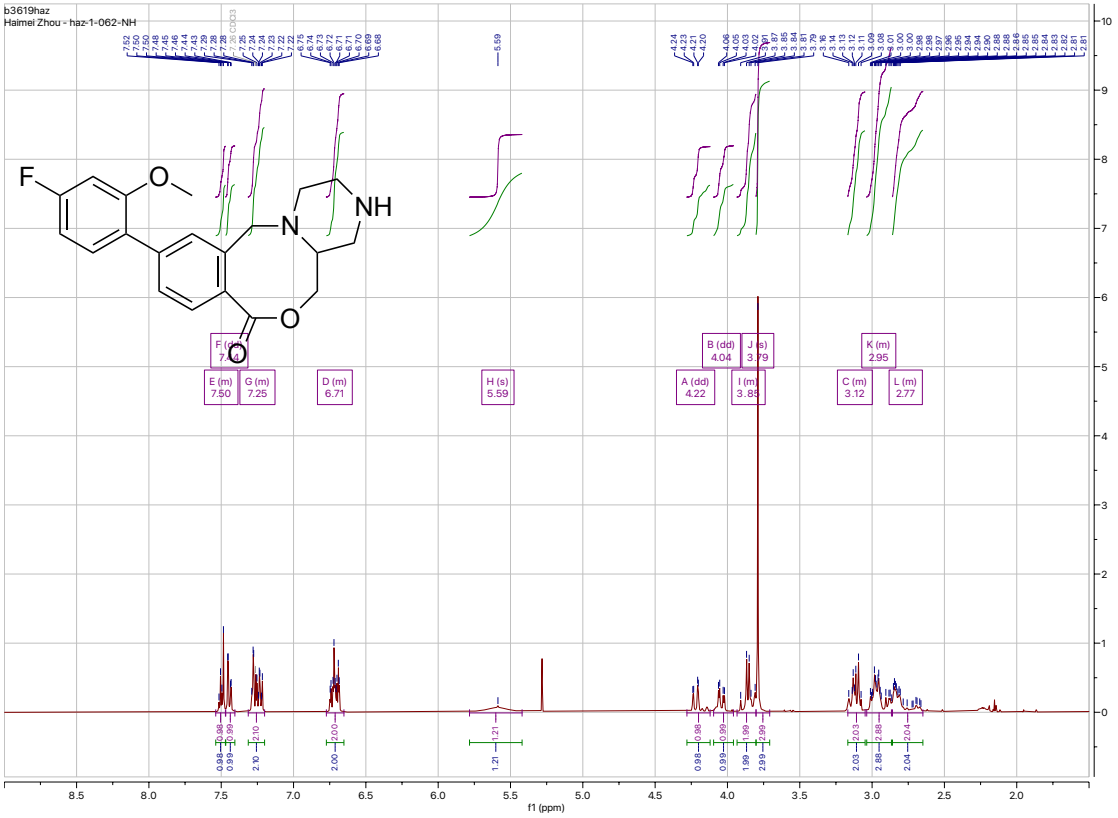


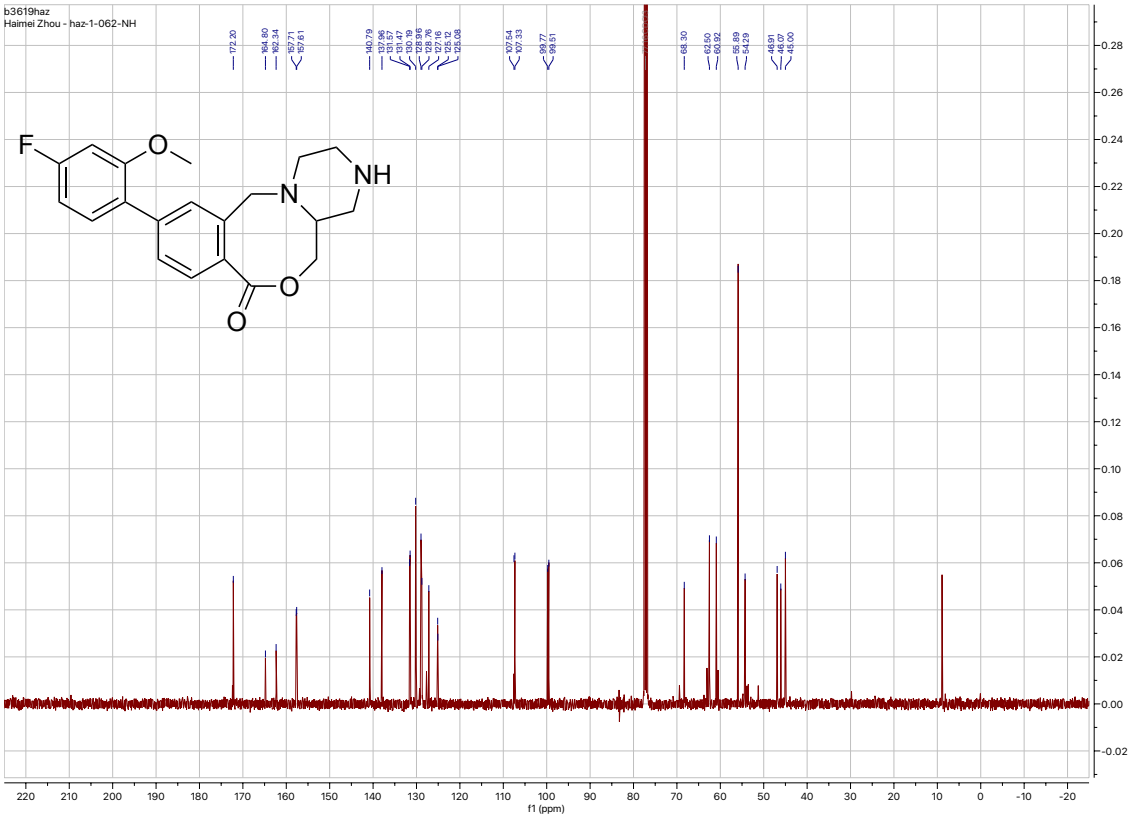


10-(4-Fluoro-2-methoxyphenyl)-7-oxo-1,2,3,4,4a,5,7,12-octahydrobenzo[*f*]pyrazino [2,1-*c*][1,4]oxazocin-3-ium chloride (136)

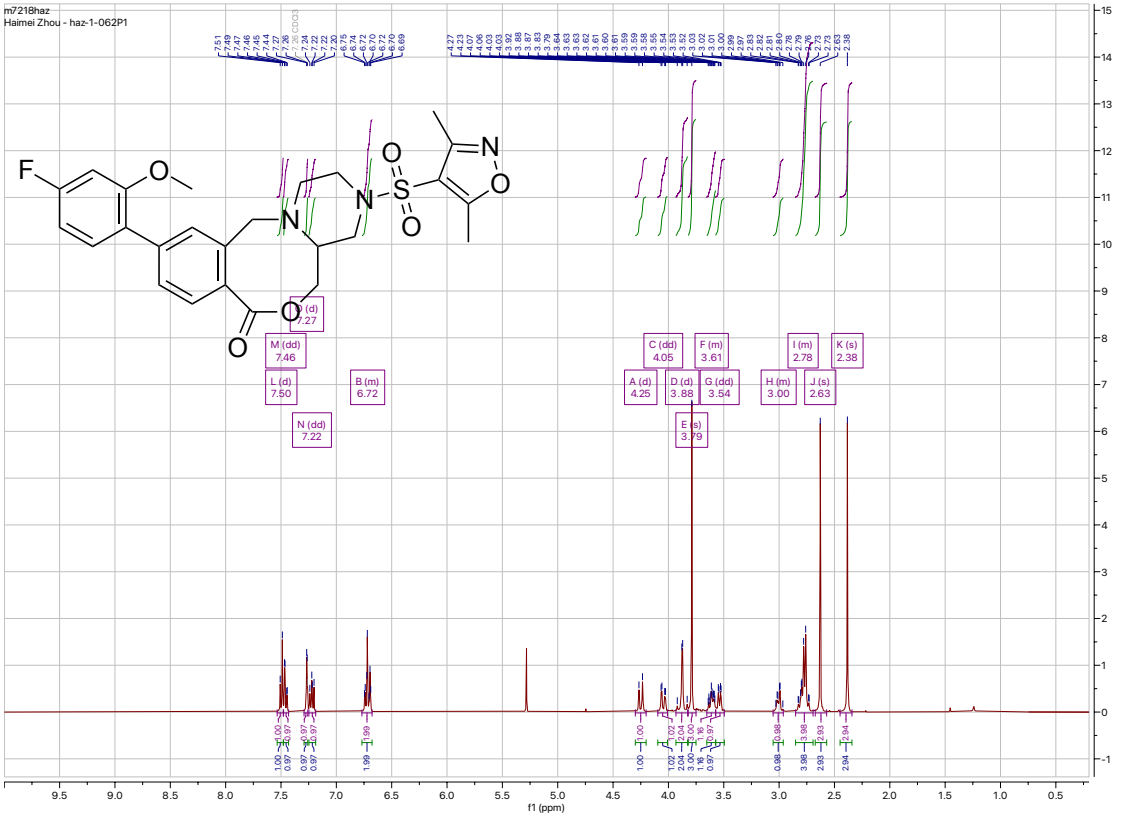


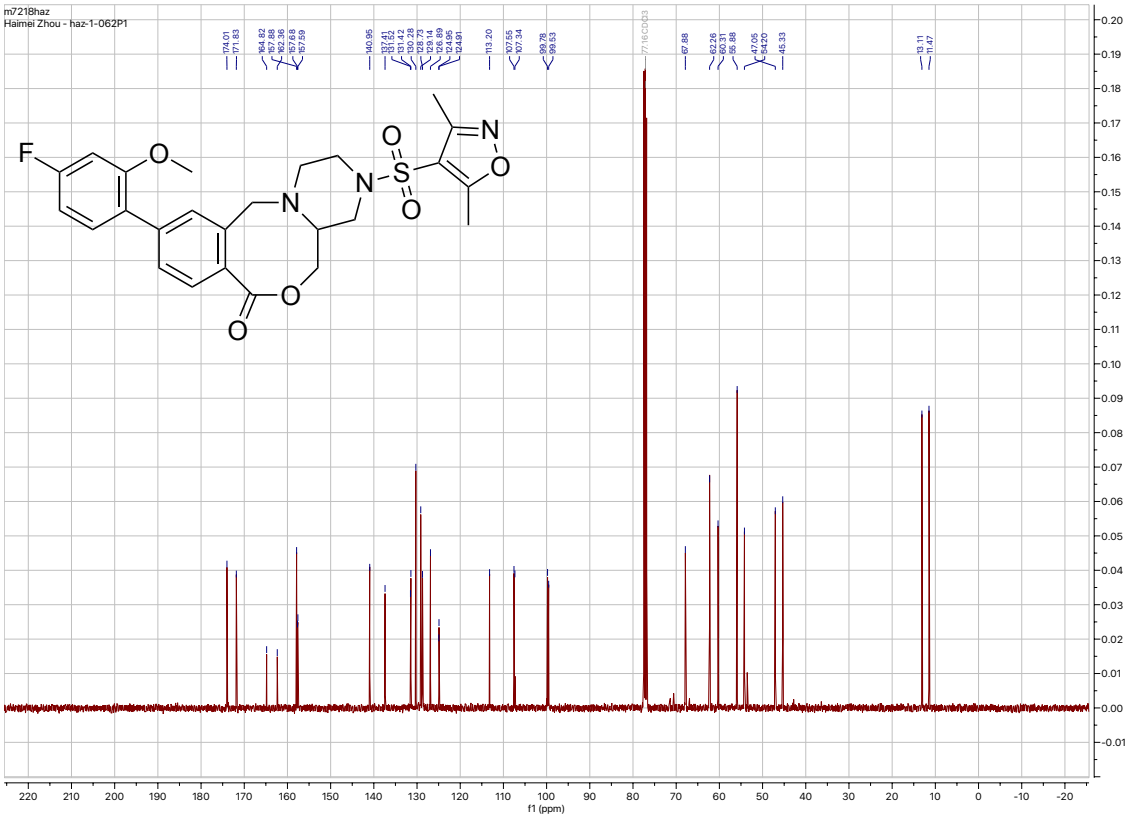
10-(4-Fluoro-2-methoxyphenyl)-1,2,3,4,4a,5-hexahydrobenzo[*f*]pyrazino[2,1-*c*][1,4]oxazocin-7(12*H*)-one (137)



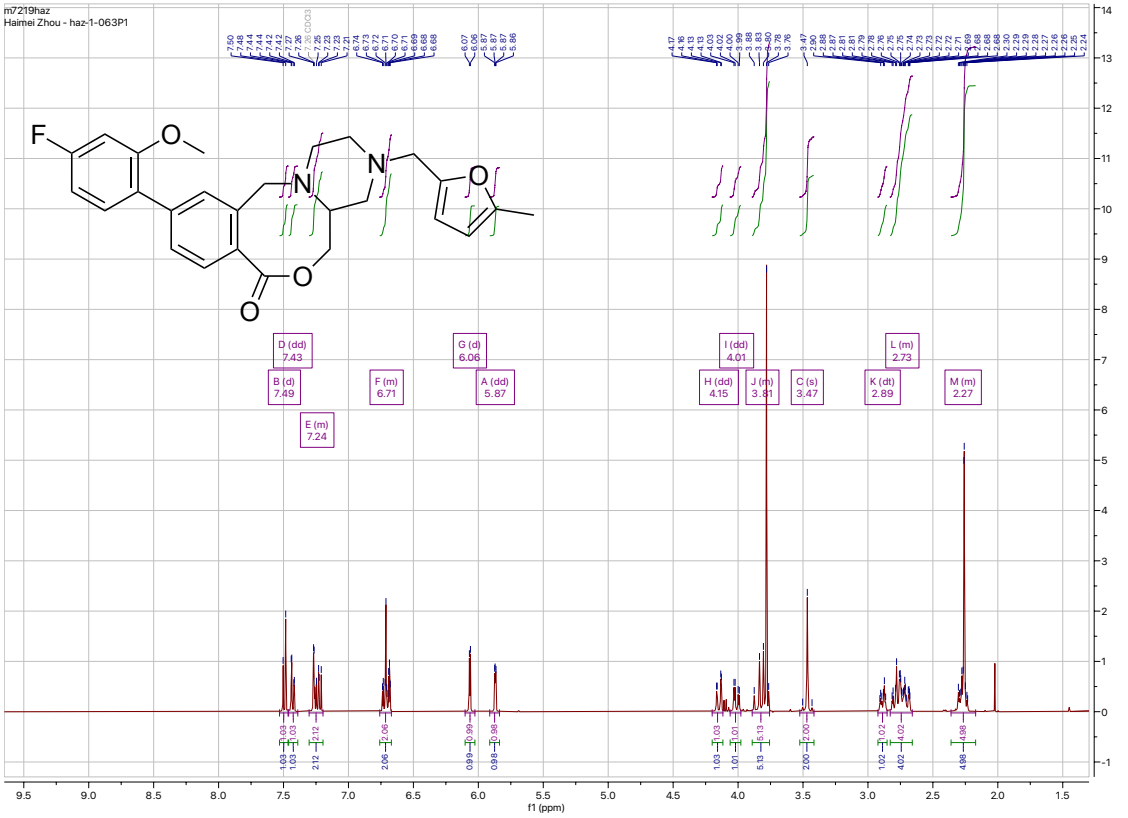


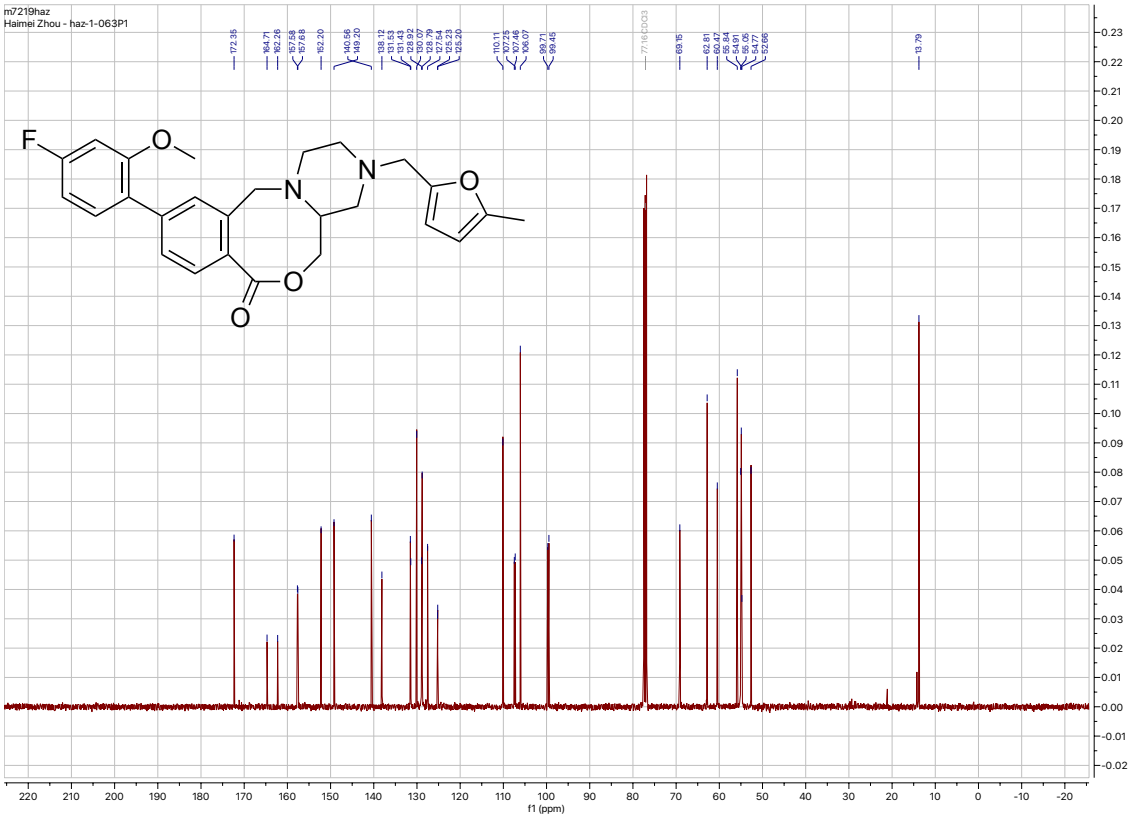
3-((3,5-Dimethylisoxazol-4-yl)ulfonyl)-10-(4-fluoro-2-methoxyphenyl)-1,2,3,4,4a,5-hexahydrobenzo[*f*]pyrazino[2,1-*c*][1,4]oxazocin-7(12*H*)-one (141)



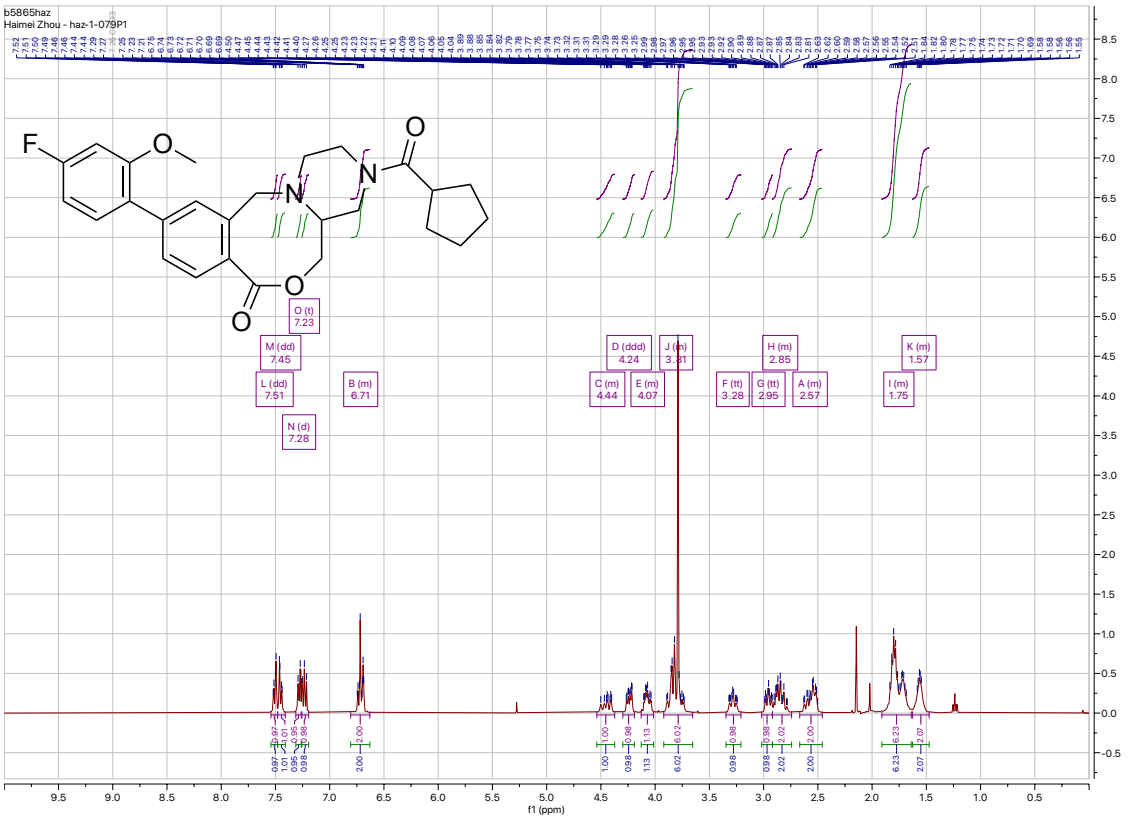


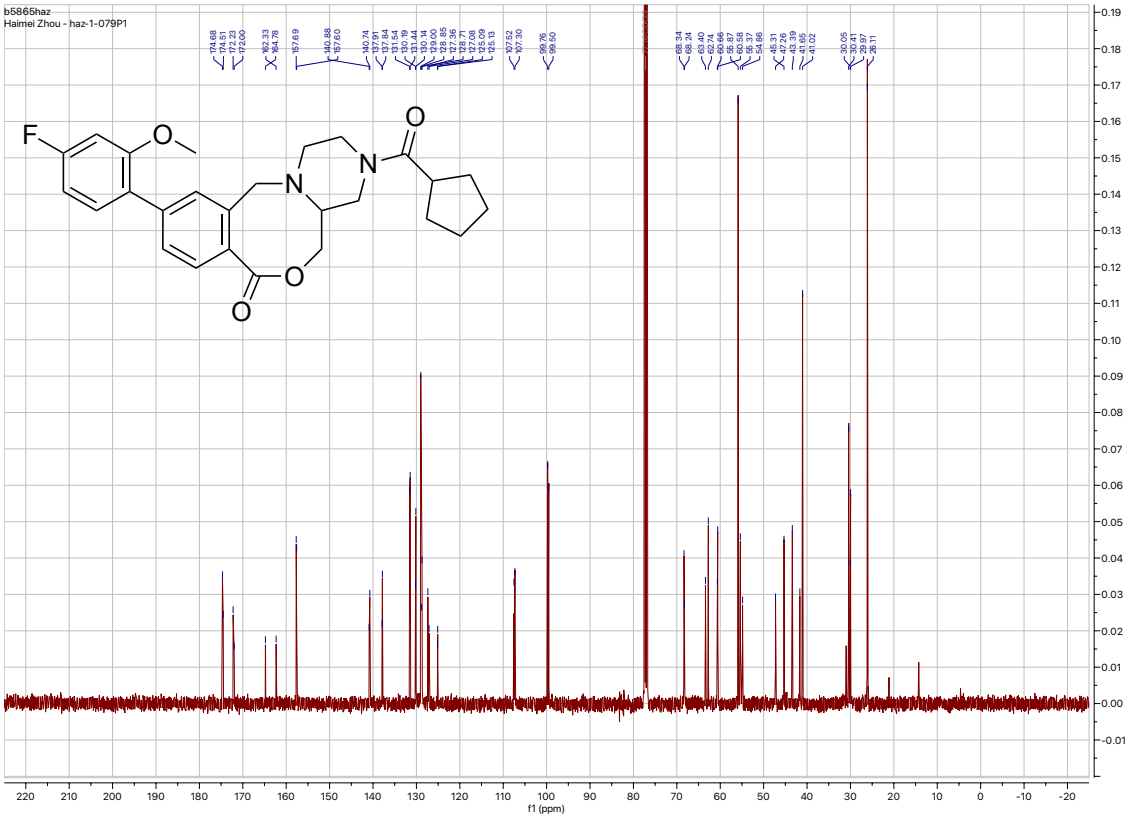
10-(4-Fluoro-2-methoxyphenyl)-3-((5-methylfuran-2-yl)methyl)-1,2,3,4,4a,5-hexahydrobenzo[*f*]pyrazino[2,1-*c*][1,4]oxazocin-7(12*H*)-one (145)



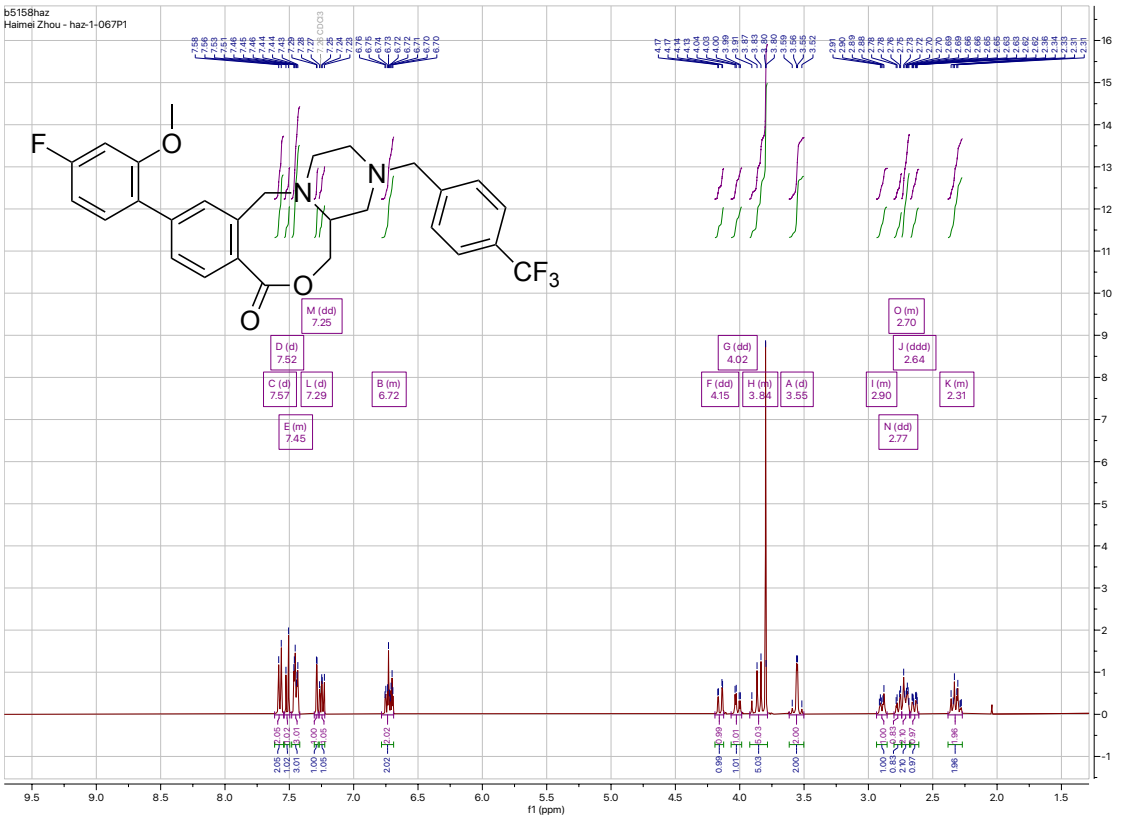


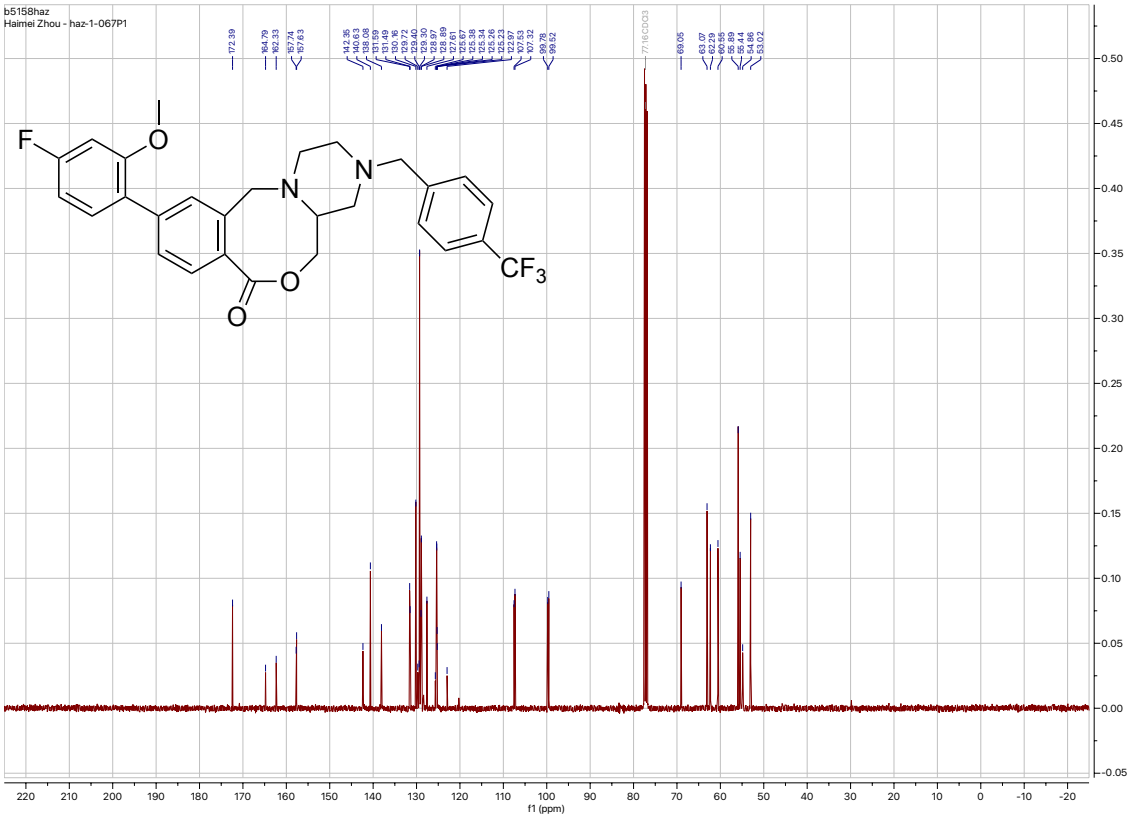
3-(cyclopentanecarbonyl)-10-(4-fluoro-2-methoxyphenyl)-1,2,3,4,4a,5-hexahydrobenzo[*f*]pyrazino[2,1-*c*][1,4]oxazocin-7(12*H*)-one (149)



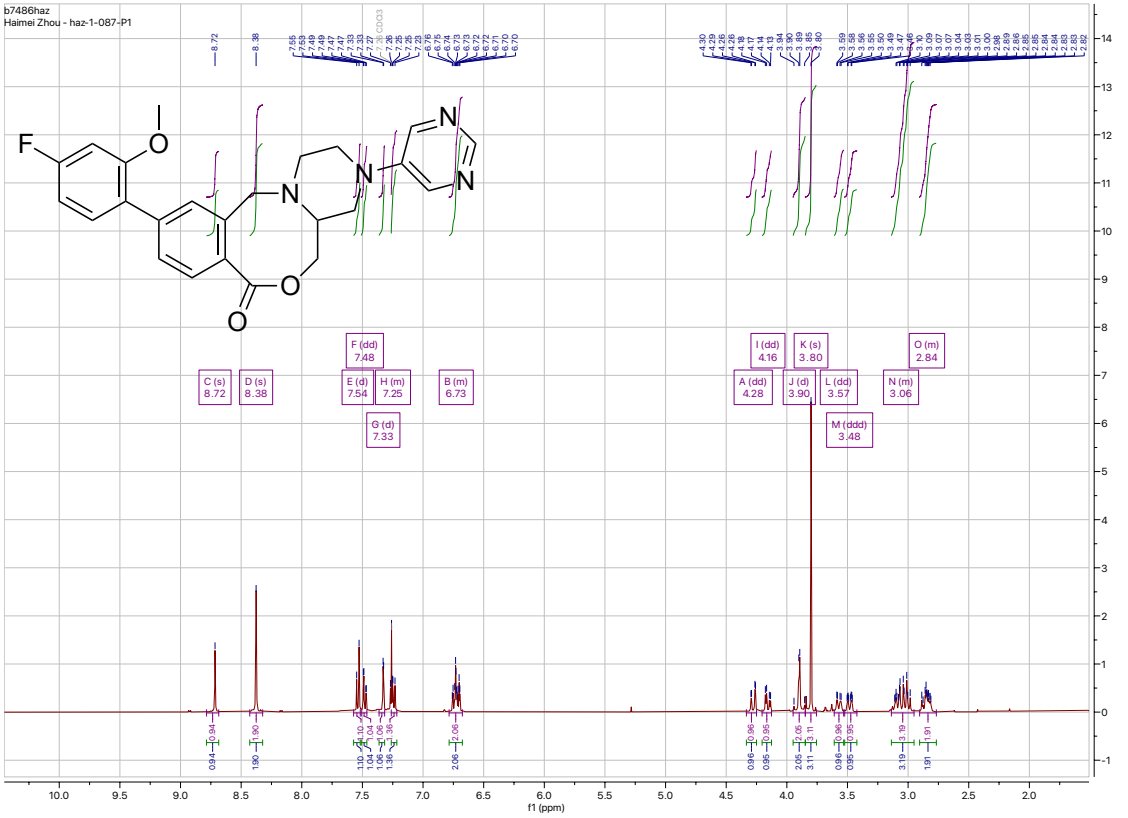


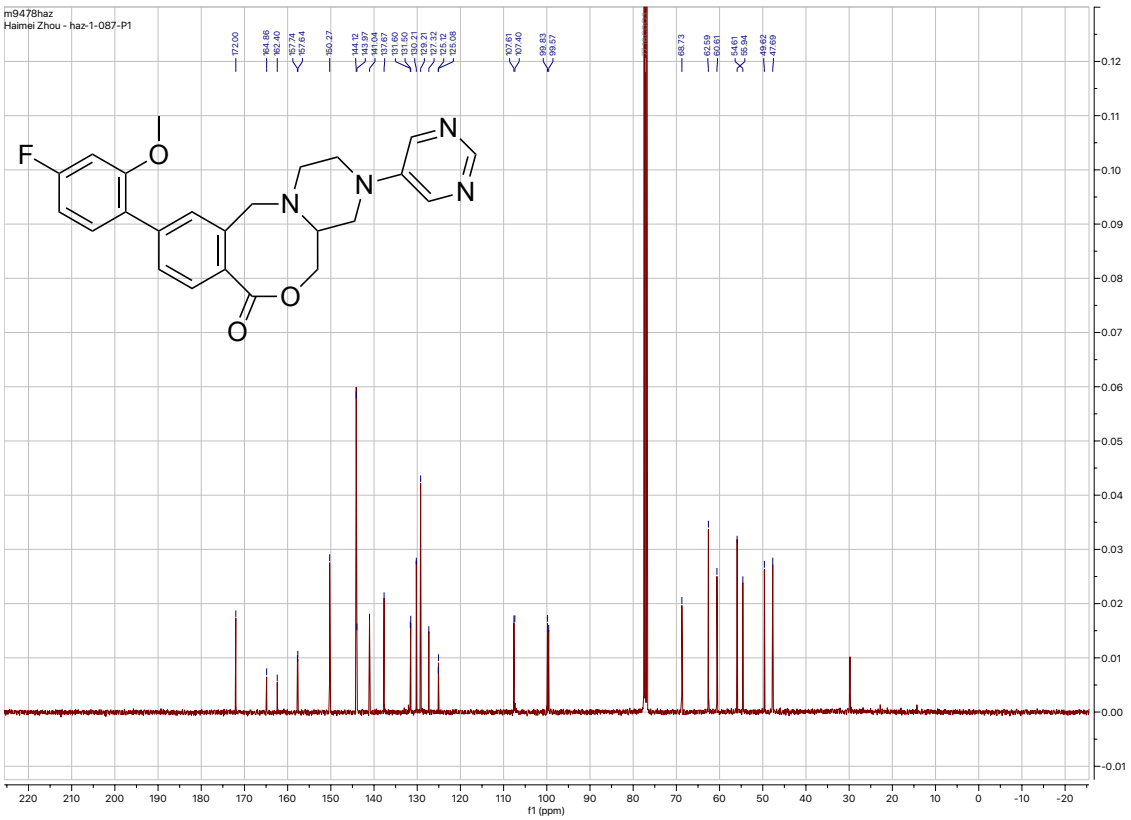
10-(4-Fluoro-2-methoxyphenyl)-3-(4-(trifluoromethyl)benzyl)-1,2,3,4,4a,5-hexahydrobenzo[*f*]pyrazino[2,1-*c*][1,4]oxazocin-7(12*H*)-one (155)



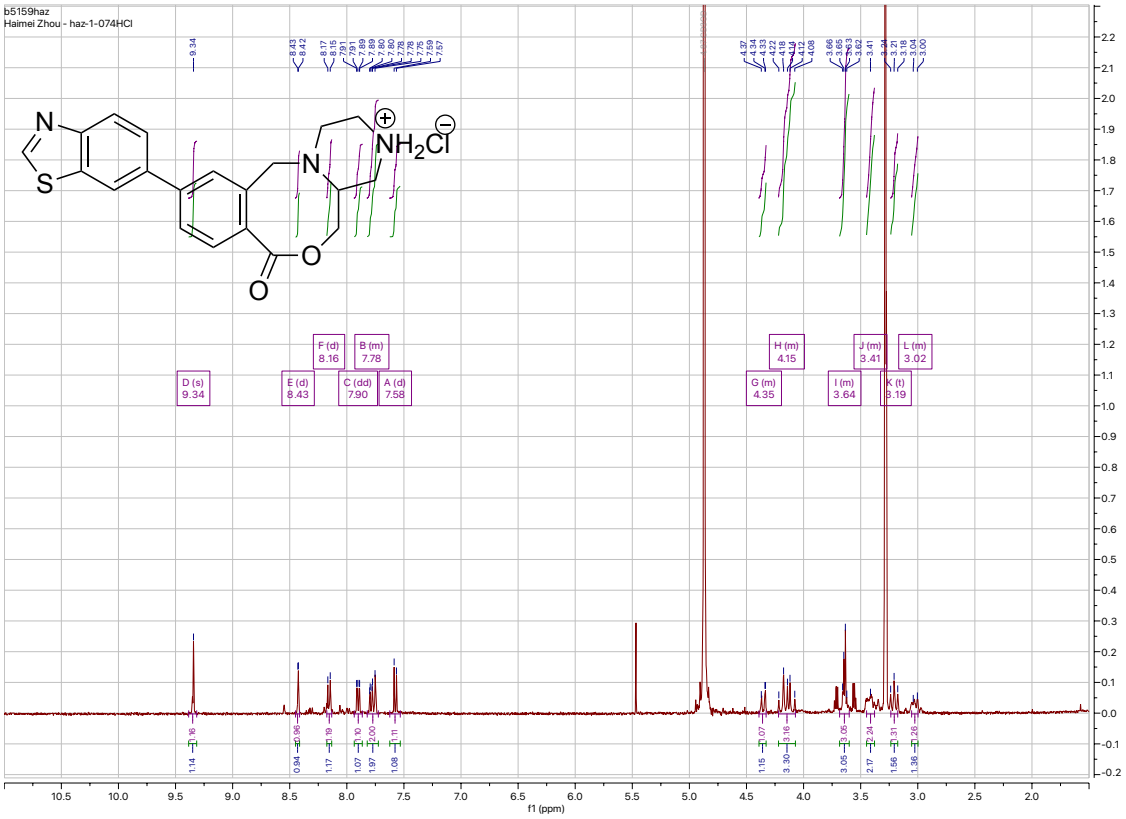


10-(4-fluoro-2-methoxyphenyl)-3-(pyrimidin-5-yl)-1,2,3,4,4a,5-hexahydrobenzo[*f*] pyrazino[2,1-*c*][1,4]oxazocin-7(12*H*)-one (161)

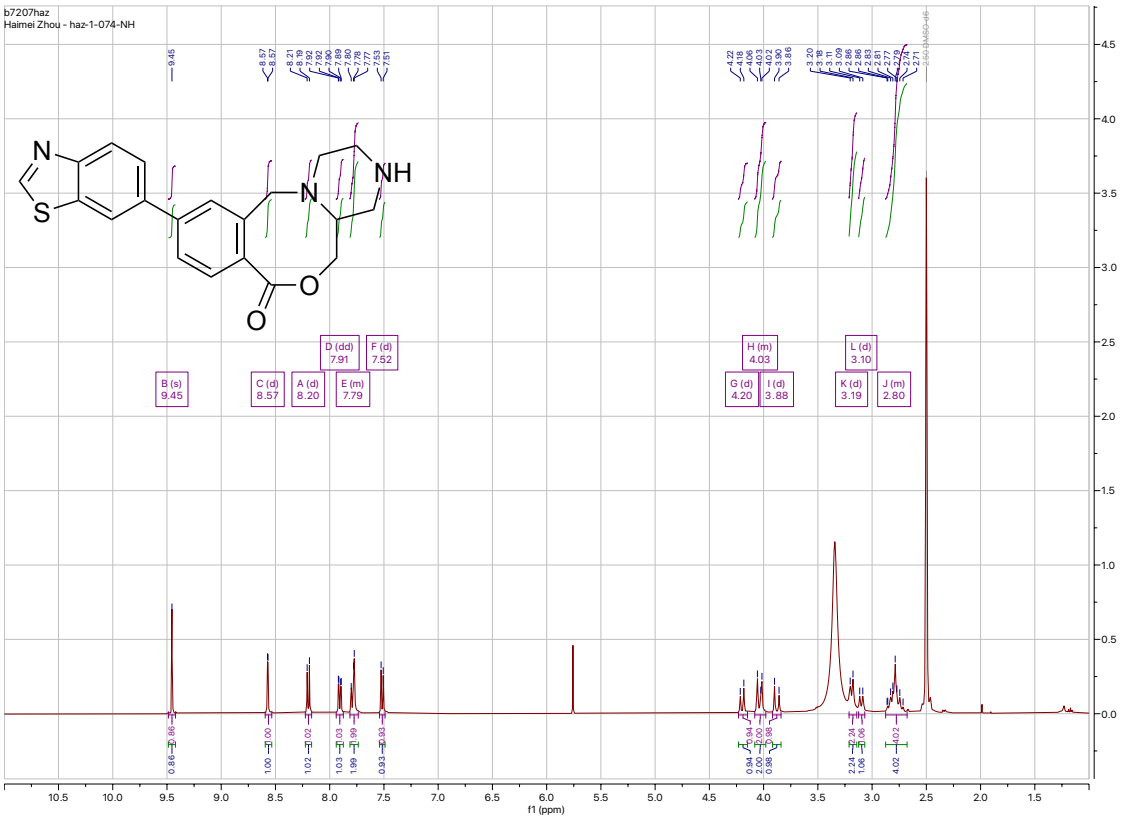


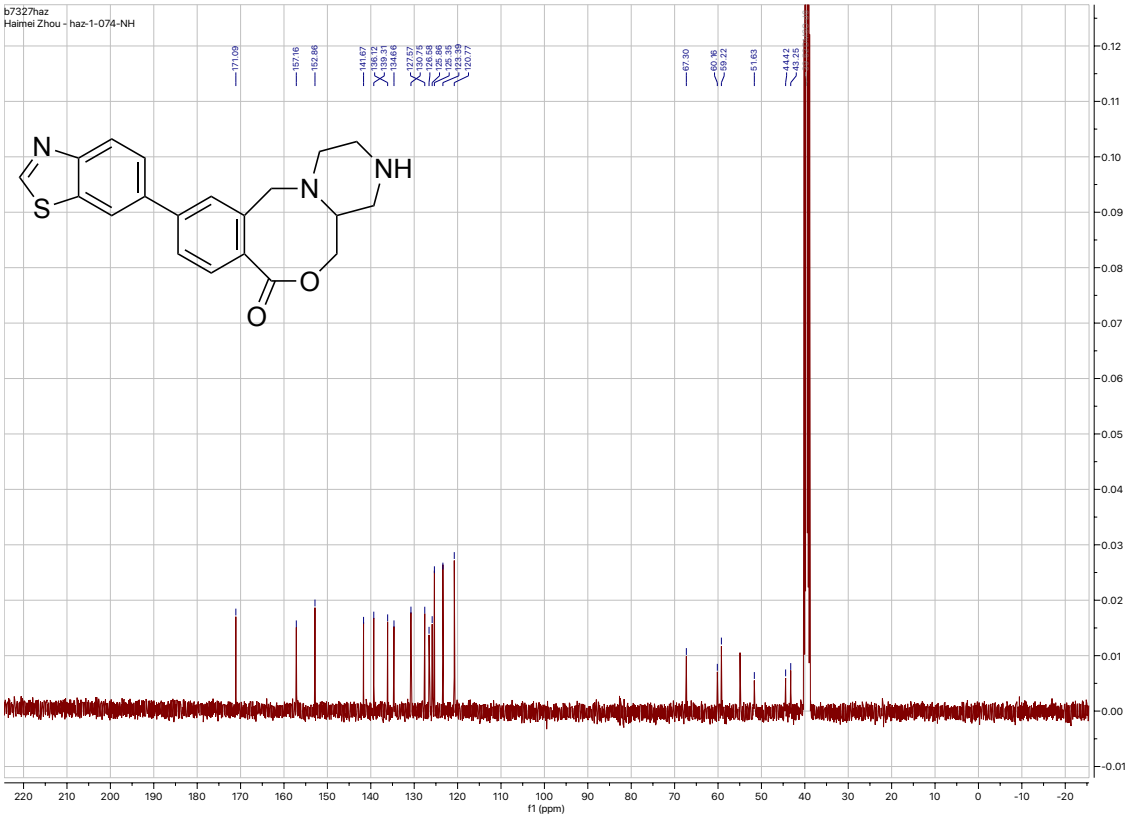


10-(Benzo[*d*]thiazol-6-yl)-7-oxo-1,2,3,4,4a,5,7,12-octahydrobenzo[*f*]pyrazino[2,1-*c*][1,4]oxazocin-3-ium chloride (138)

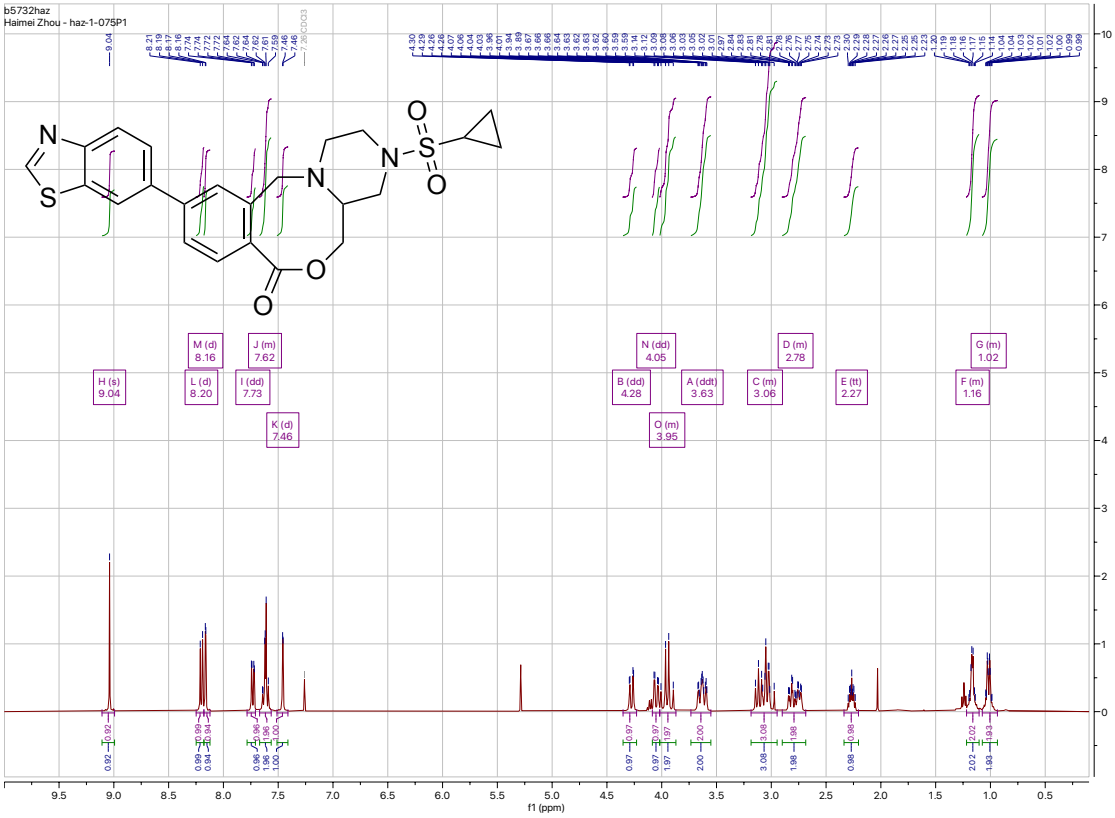


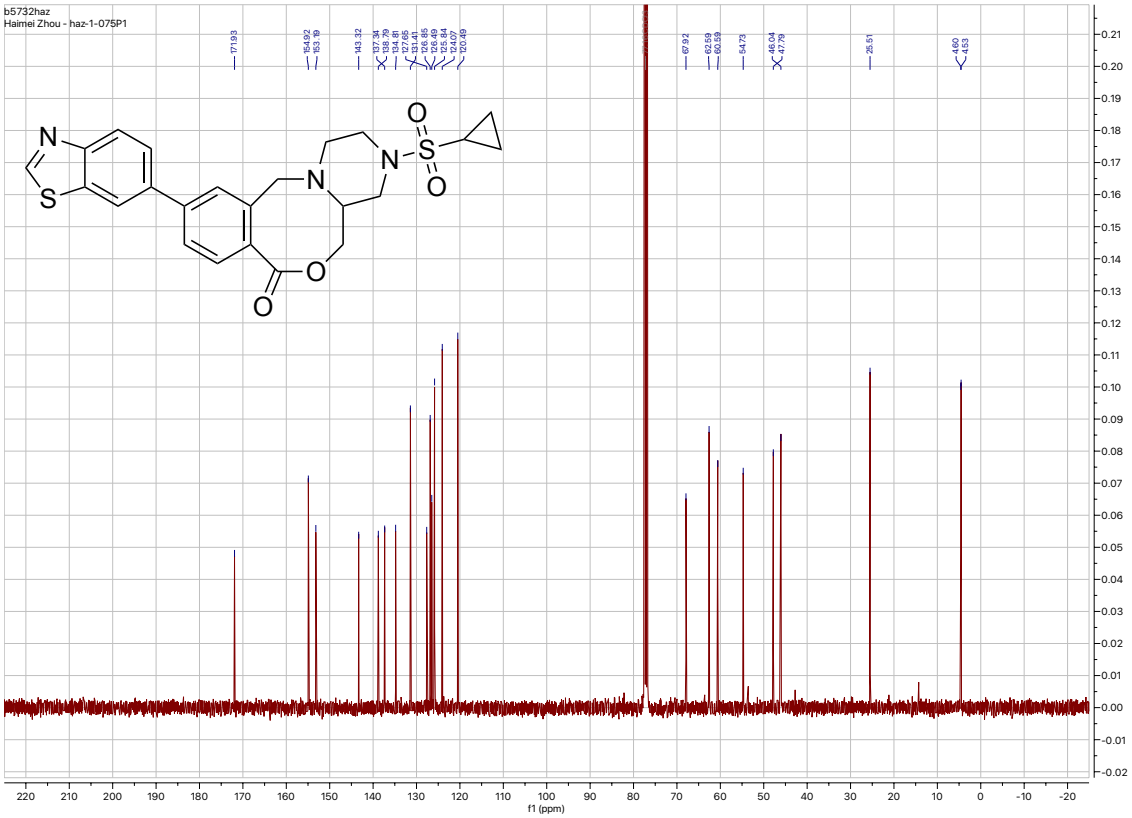
10-(Benzo[*d*]thiazol-6-yl)-1,2,3,4,4a,5-hexahydrobenzo[*f*]pyrazino[2,1-*c*][1,4] oxazocin-7(12*H*)-one (139)



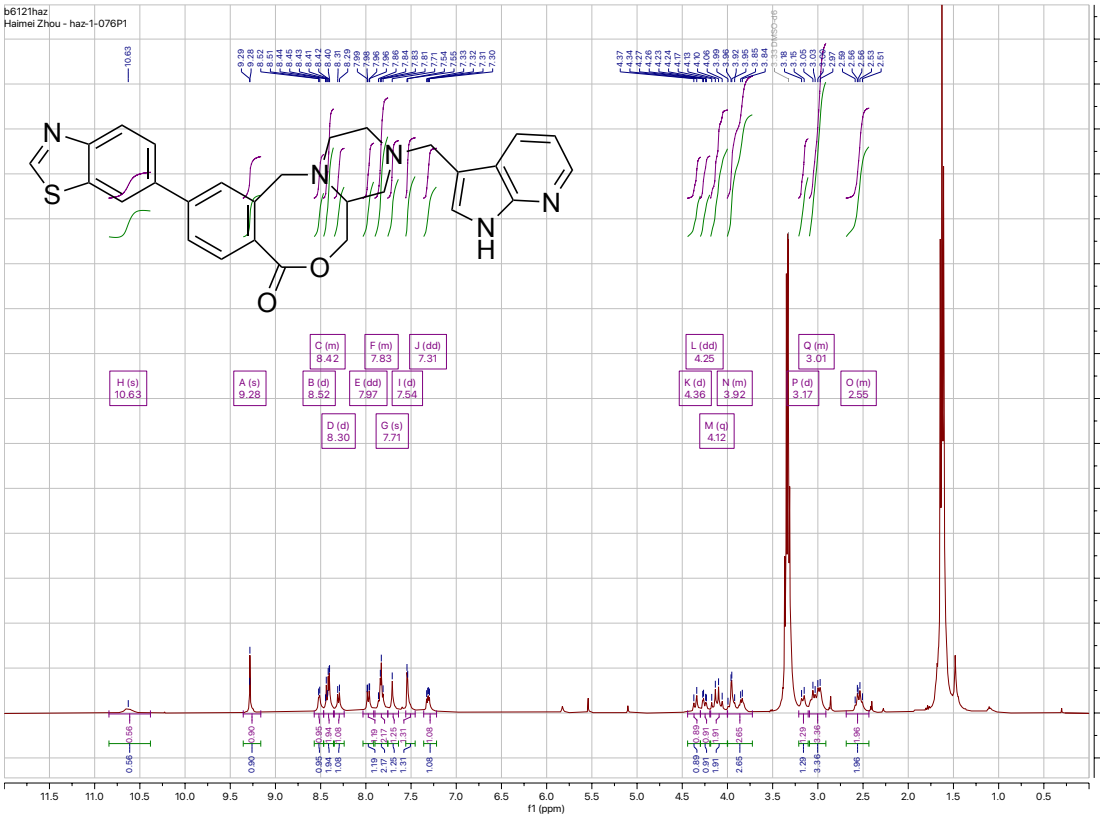


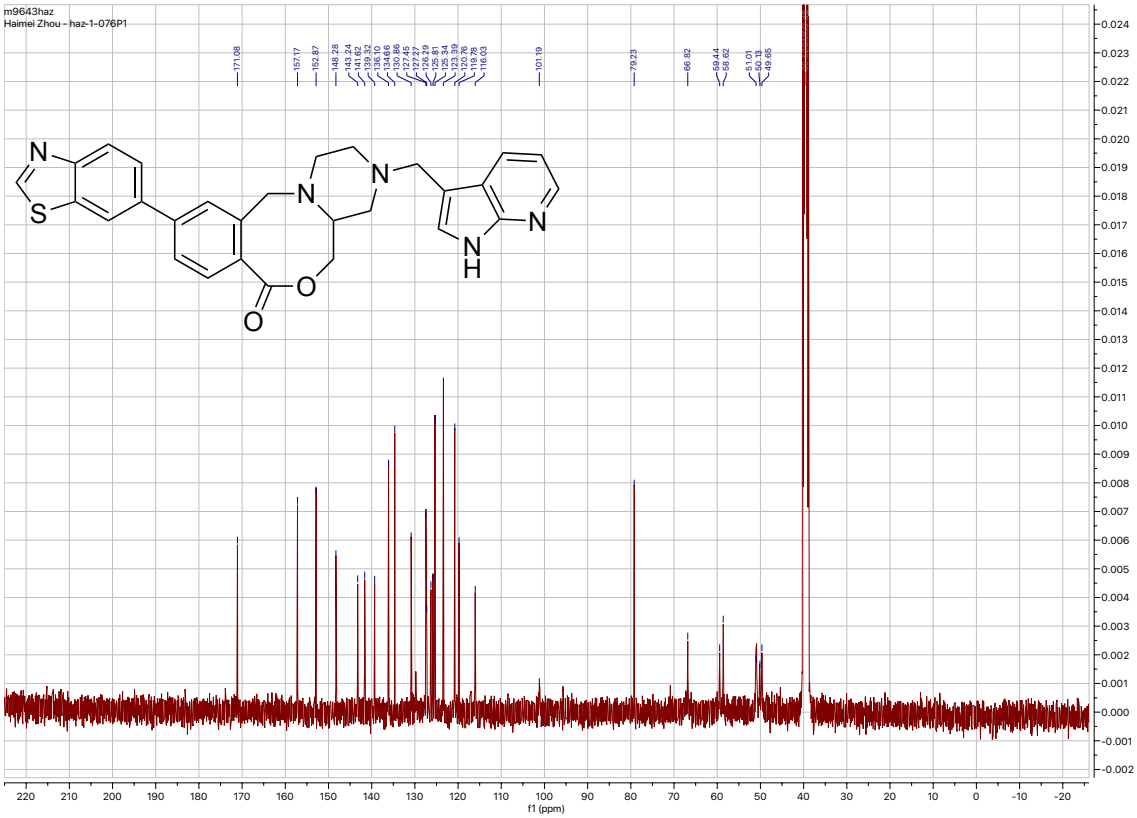
10-(Benzo[*d*]thiazol-6-yl)-3-(cyclopropylsulfonyl)-1,2,3,4,4a,5-hexahydrobenzo[*f*] pyrazino[2,1-*c*][1,4]oxazocin-7(12*H*)-one (143)



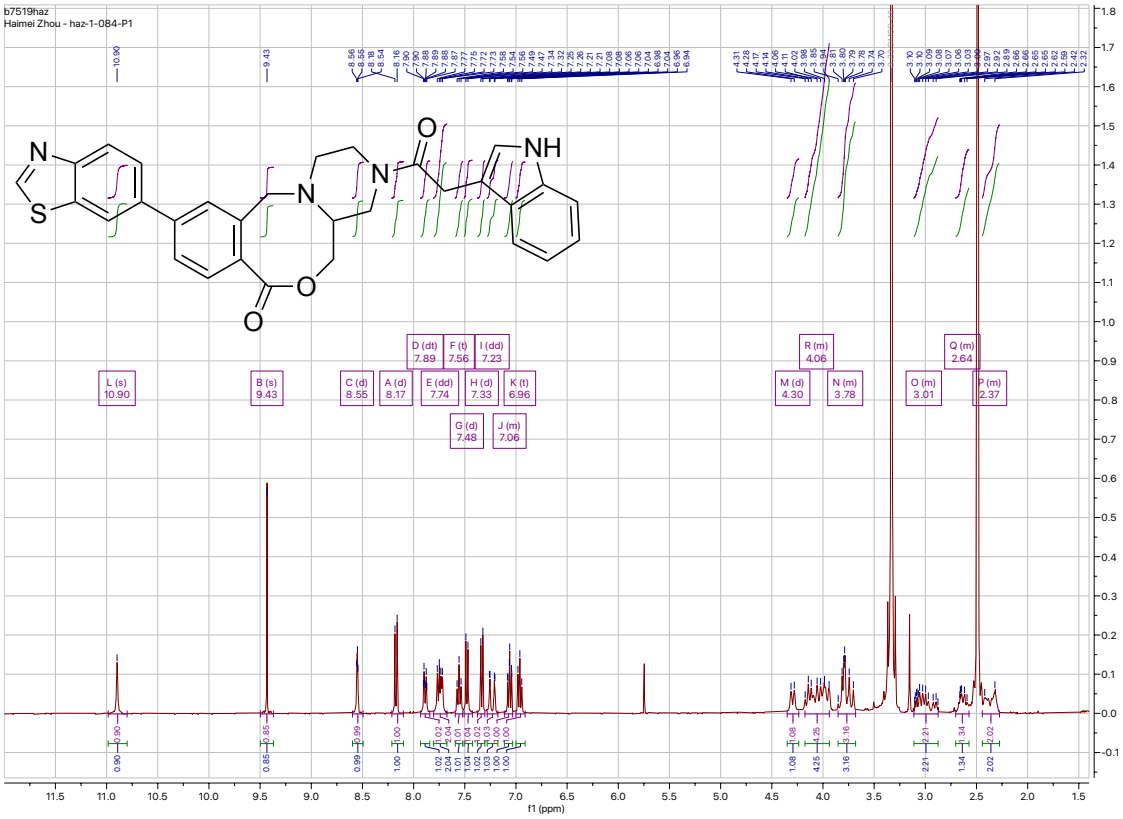


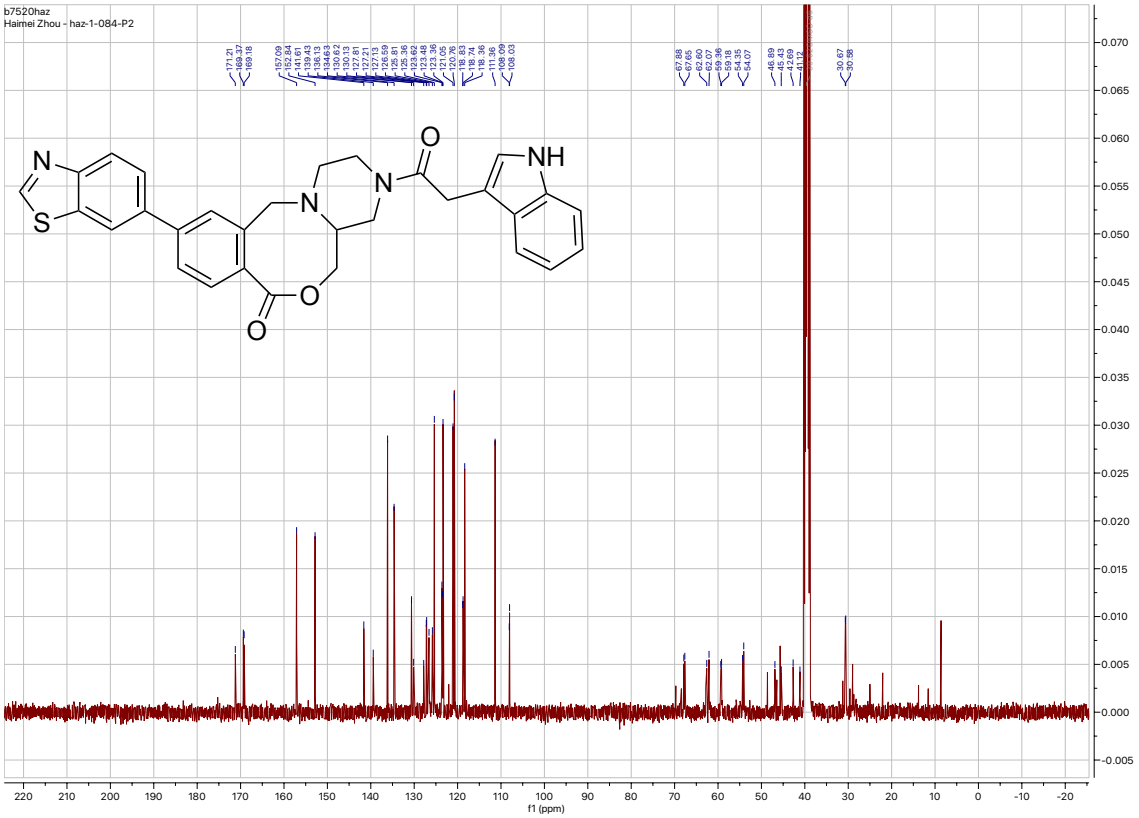
3-((1H-Pyrrolo[2,3-*b*]pyridin-3-yl)methyl)-10-(benzo[*d*]thiazol-6-yl)-1,2,3,4,4a,5-hexahydrobenzo[*f*]pyrazino[2,1-*c*][1,4]oxazocin-7(12*H*)-one (147)



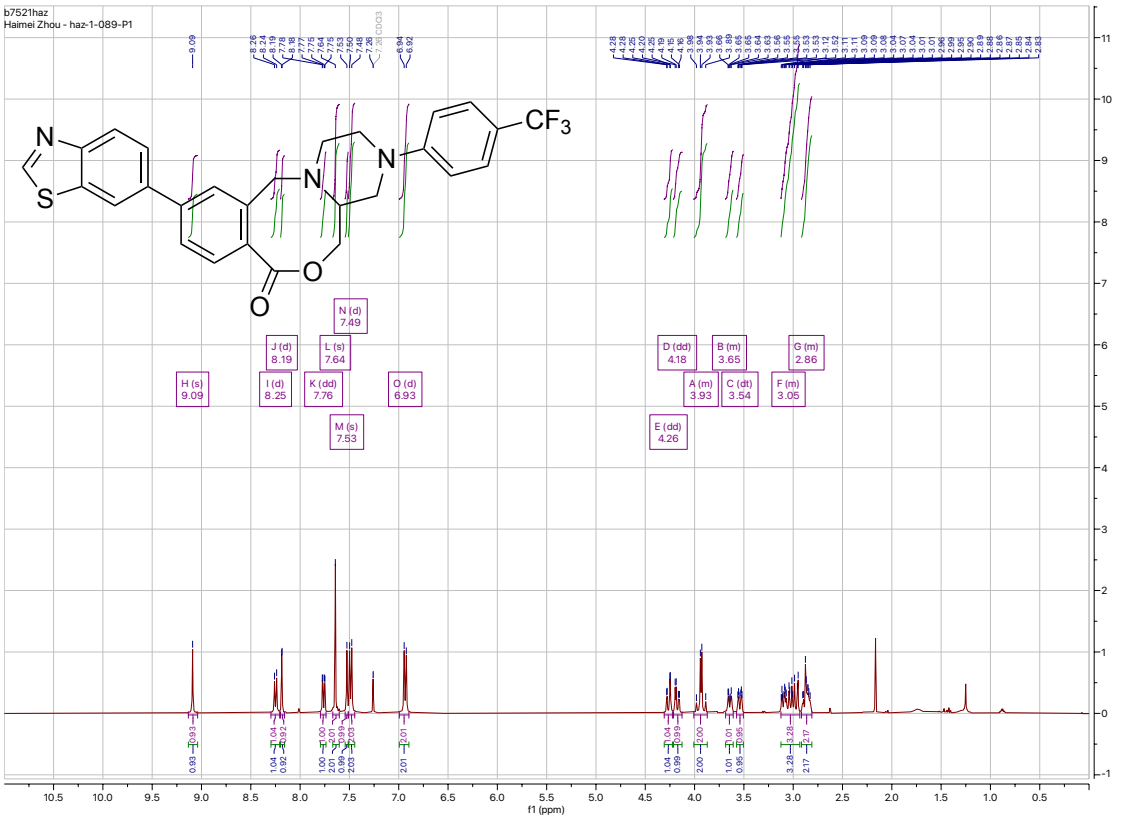


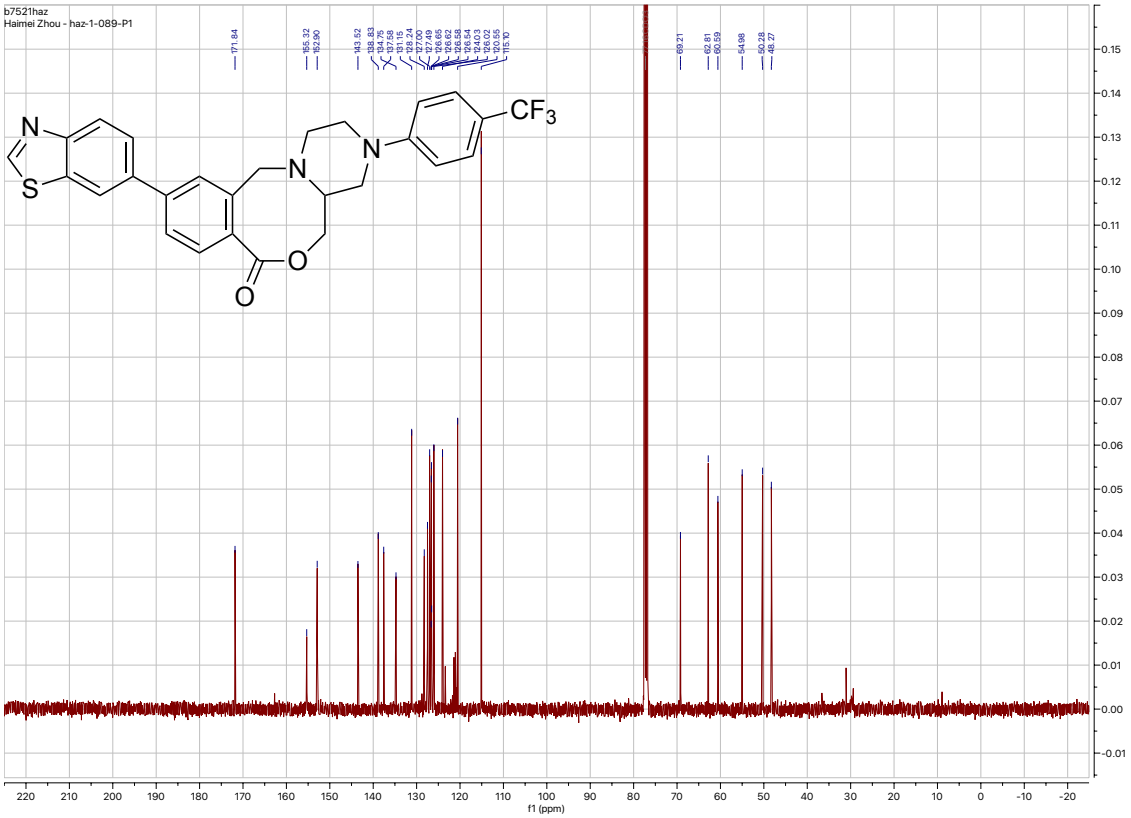
3-(2-(1H-Indol-3-yl)acetyl)-10-(benzo[*d*]thiazol-6-yl)-1,2,3,4,4a,5-hexahydrobenzo[*f*] pyrazino[2,1-*c*][1,4]oxazocin-7(12*H*)-one (153)



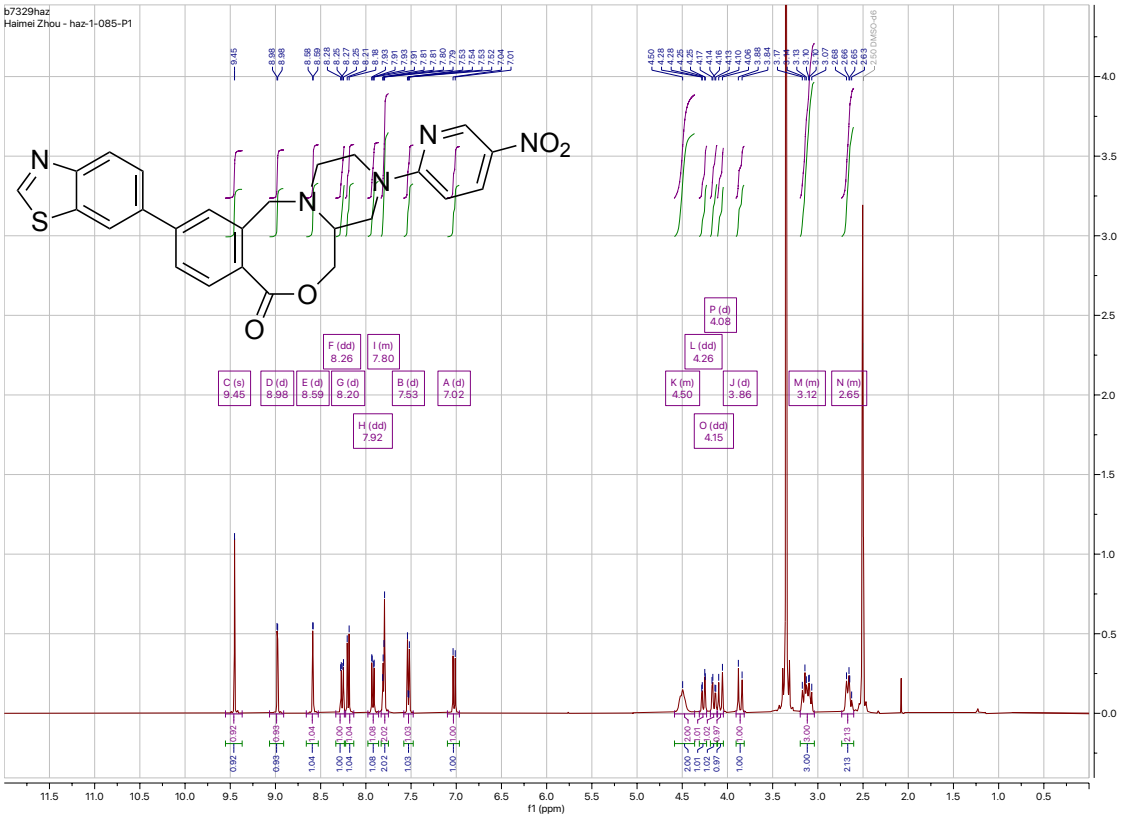


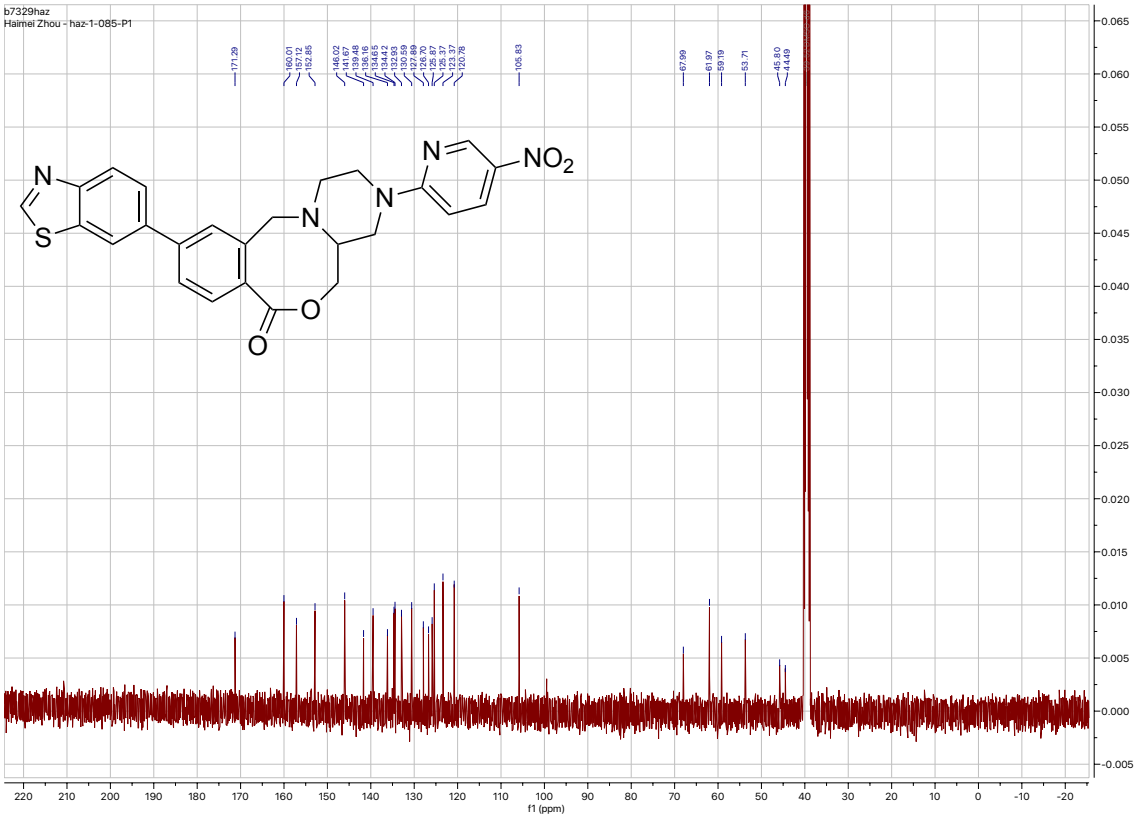
10-(Benzo[*d*]thiazol-6-yl)-3-(4-(trifluoromethyl)phenyl)-1,2,3,4,4a,5-hexahydrobenzo[*f*]pyrazino[2,1-*c*][1,4]oxazocin-7(12*H*)-one (163)



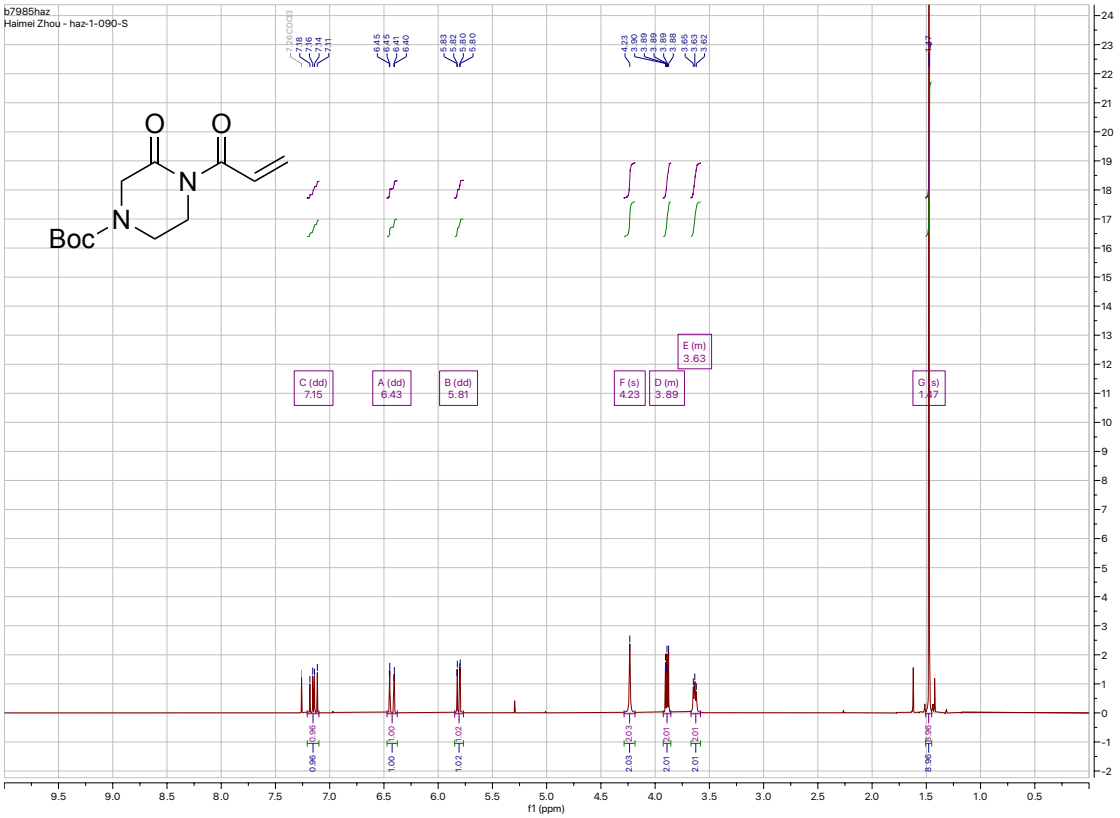


10-(benzo[*d*]thiazol-6-yl)-3-(5-nitropyridin-2-yl)-1,2,3,4,4a,5-hexahydrobenzo[*f*] pyrazino[2,1-*c*][1,4]oxazocin-7(12*H*)-one (159)

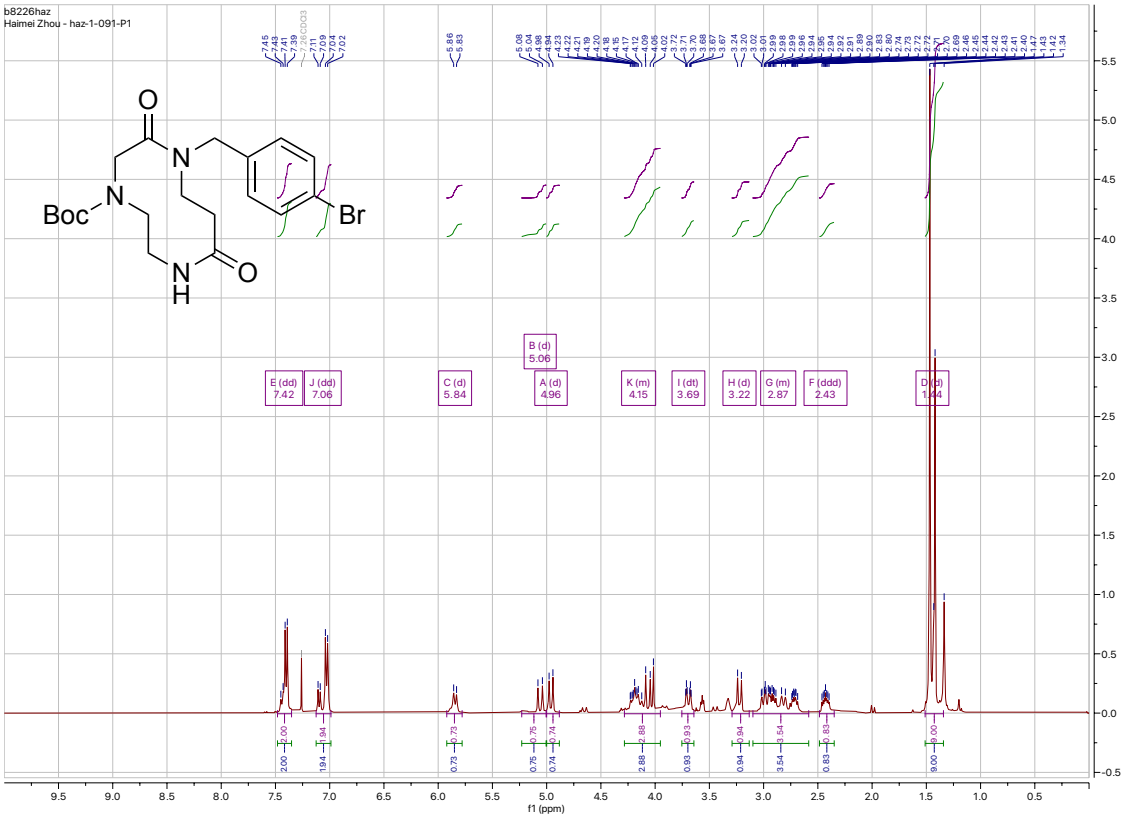


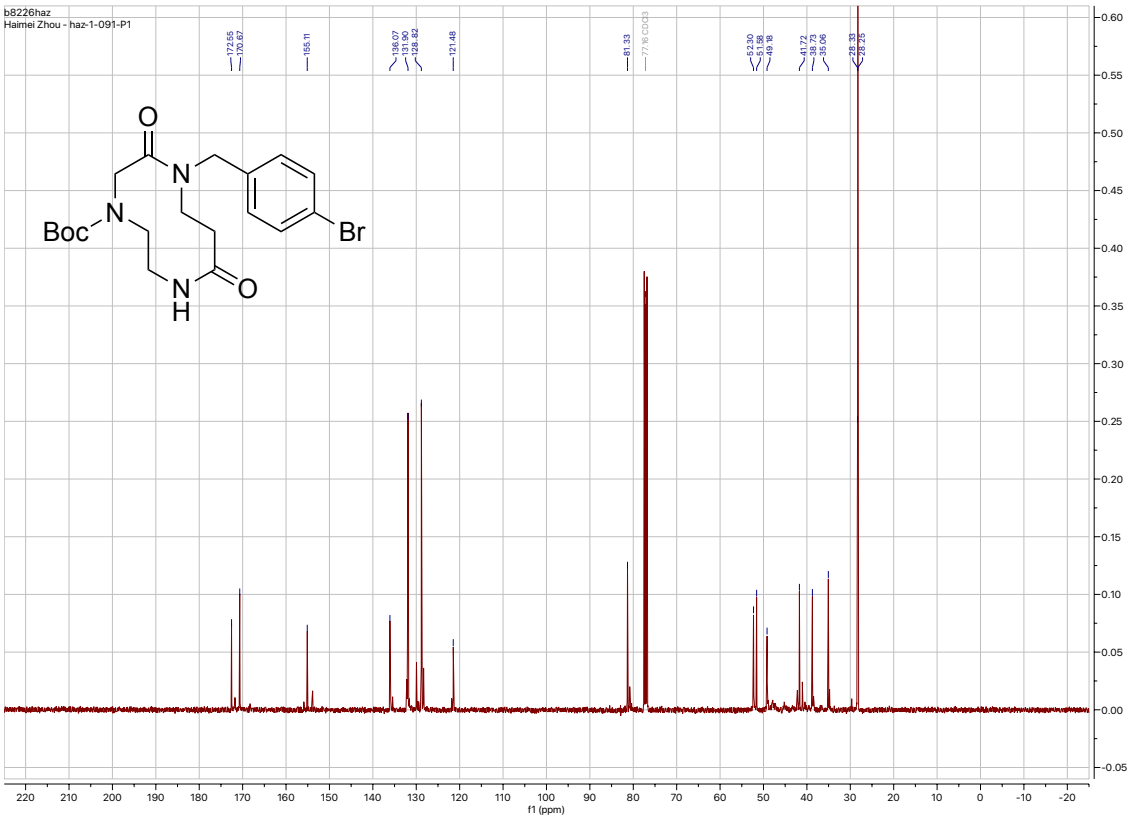


tert-Butyl 4-acryloyl-3-oxopiperazine-1-carboxylate (166)

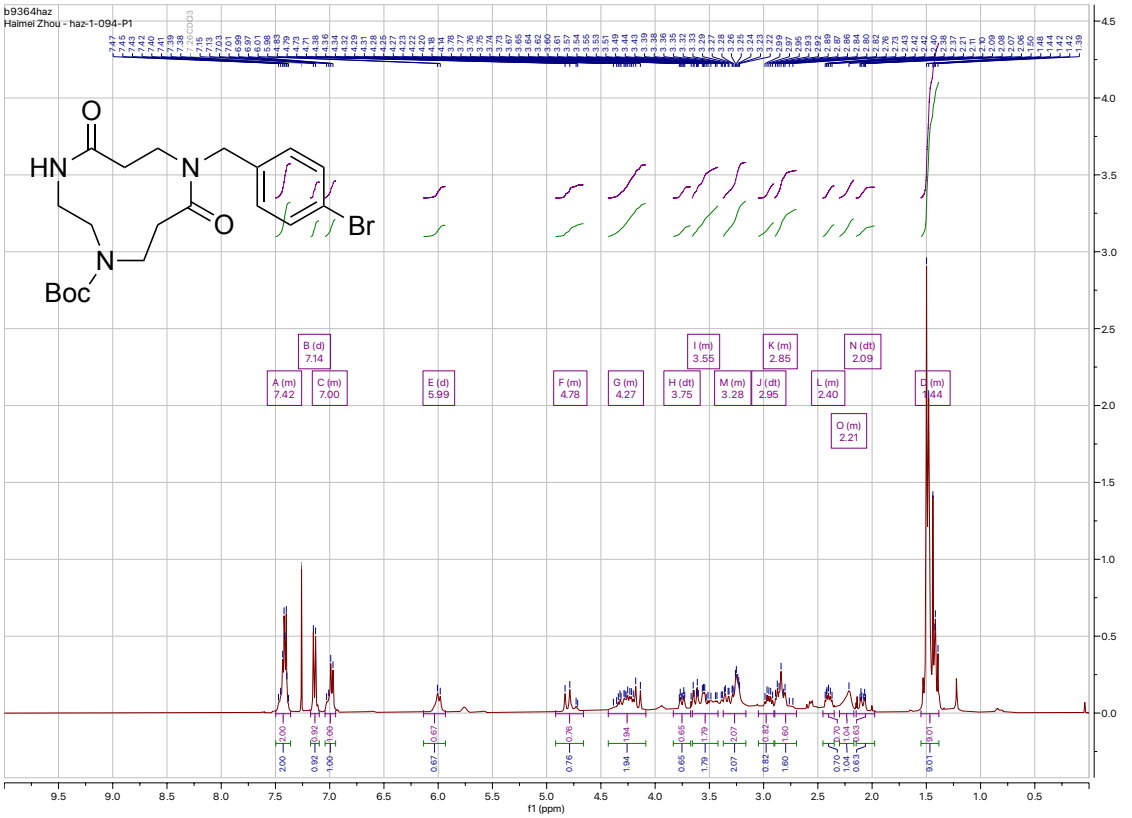


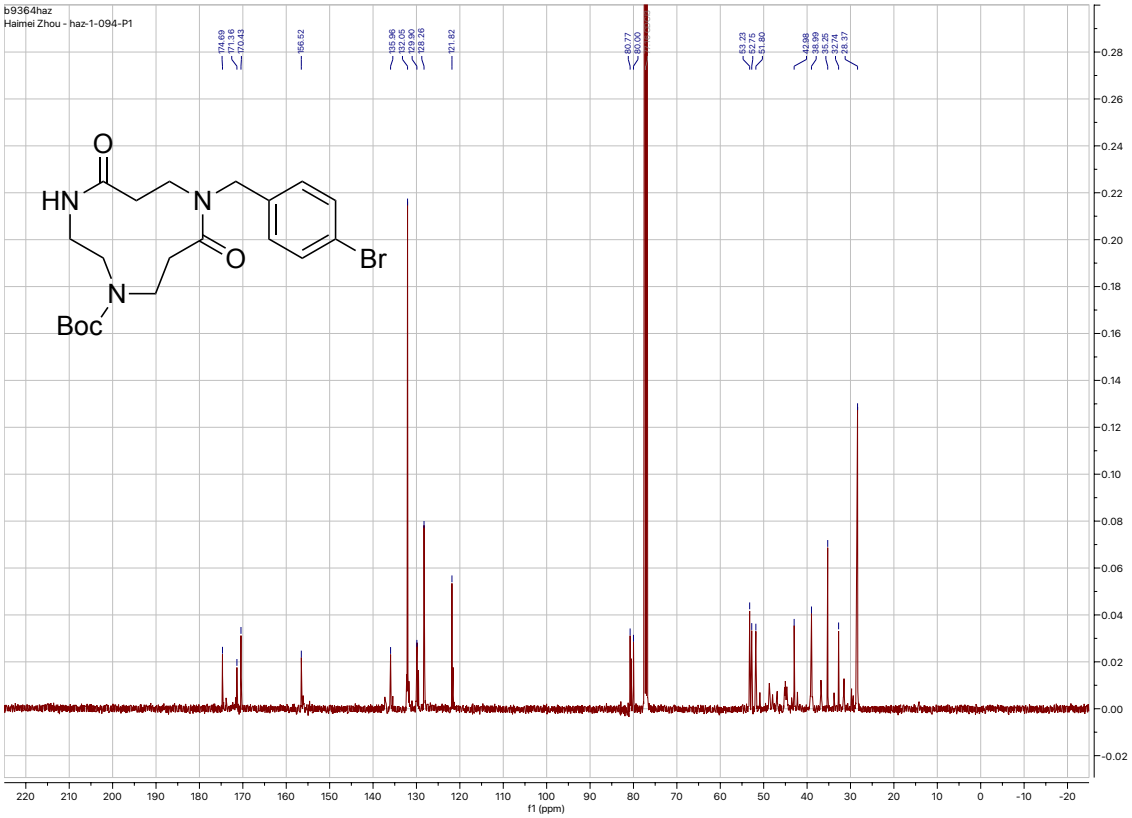
tert-Butyl 1-(4-bromobenzyl)-2,8-dioxo-1,4,7-triazecane-4-carboxylate (179)



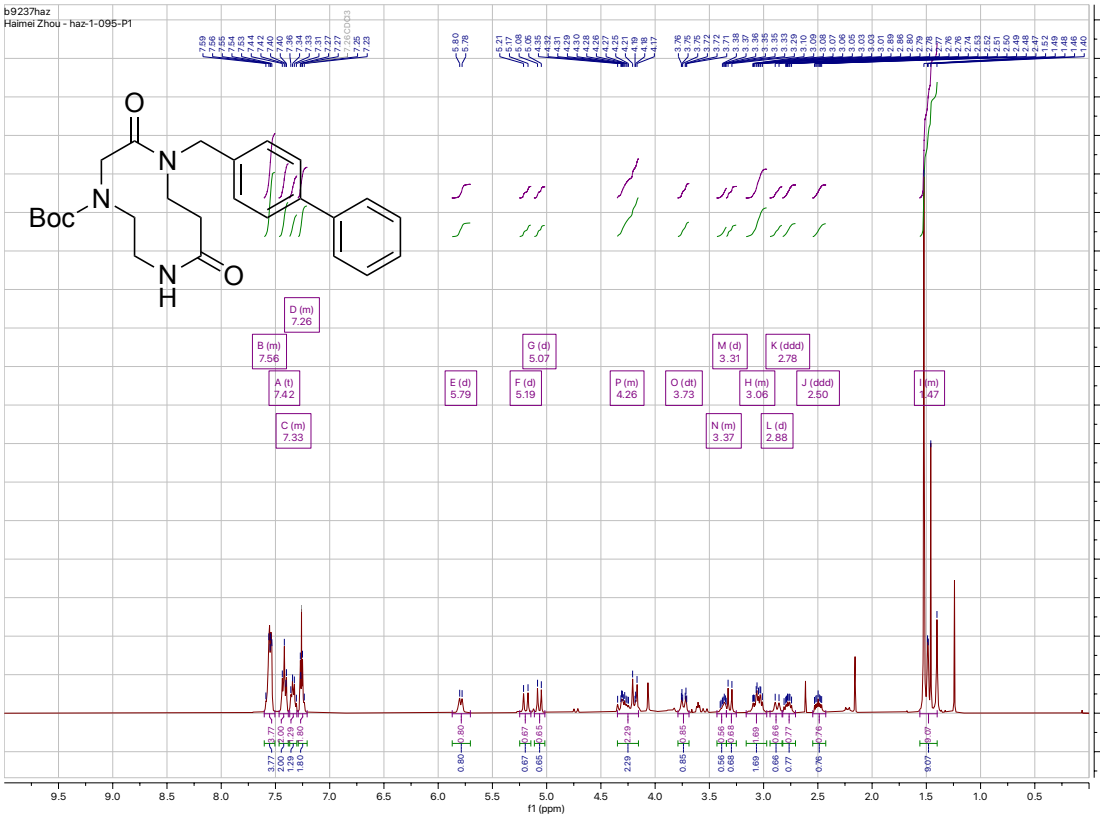


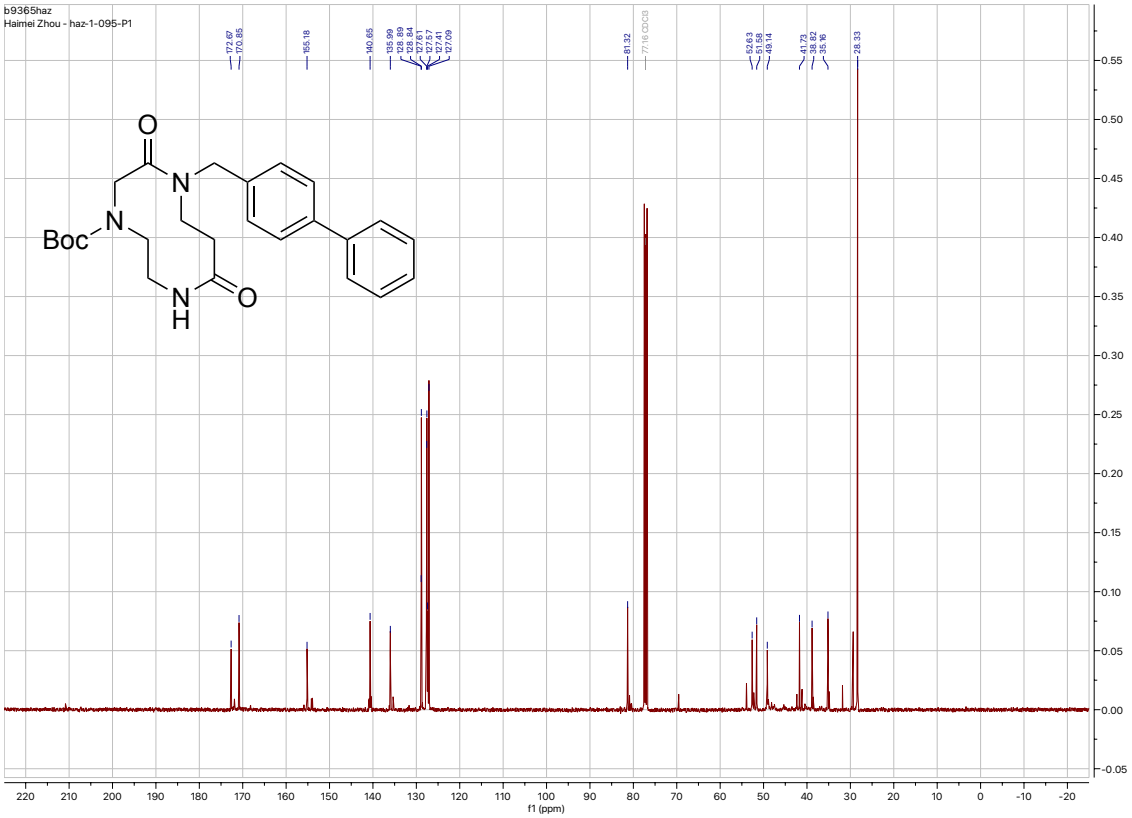
tert-Butyl 8-(4-bromobenzyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate (183)



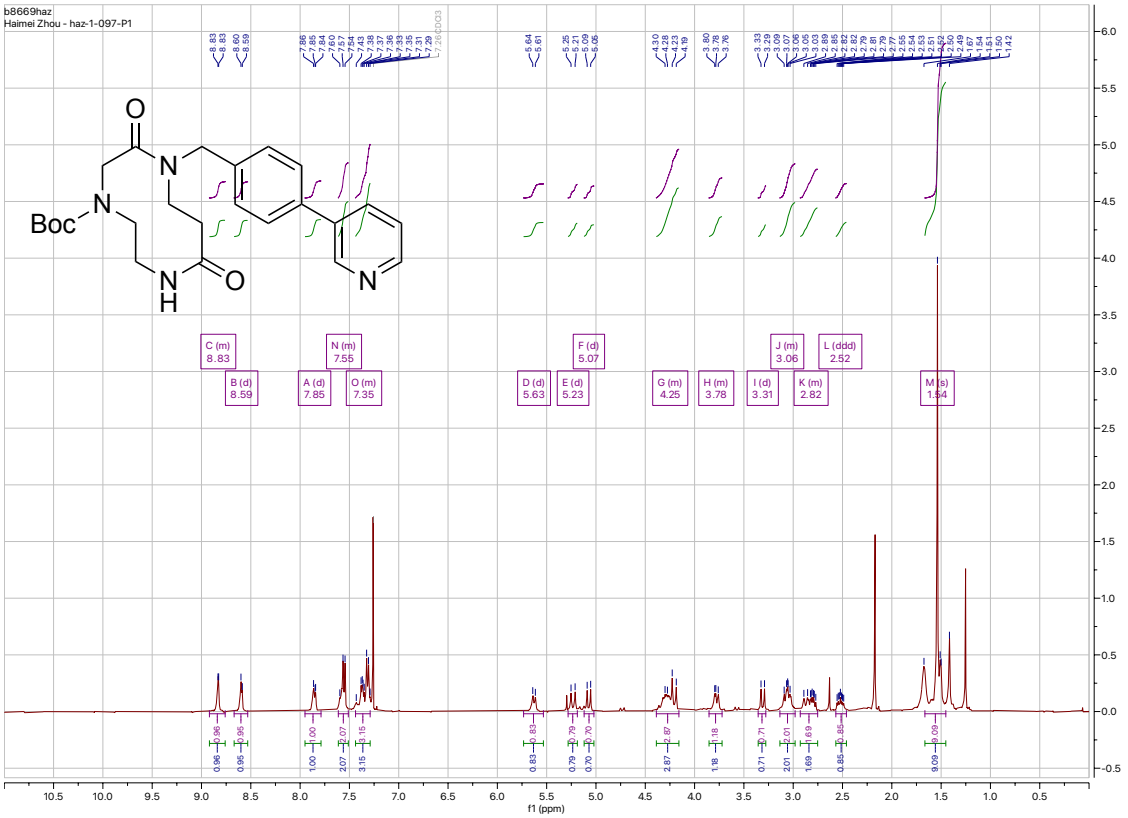


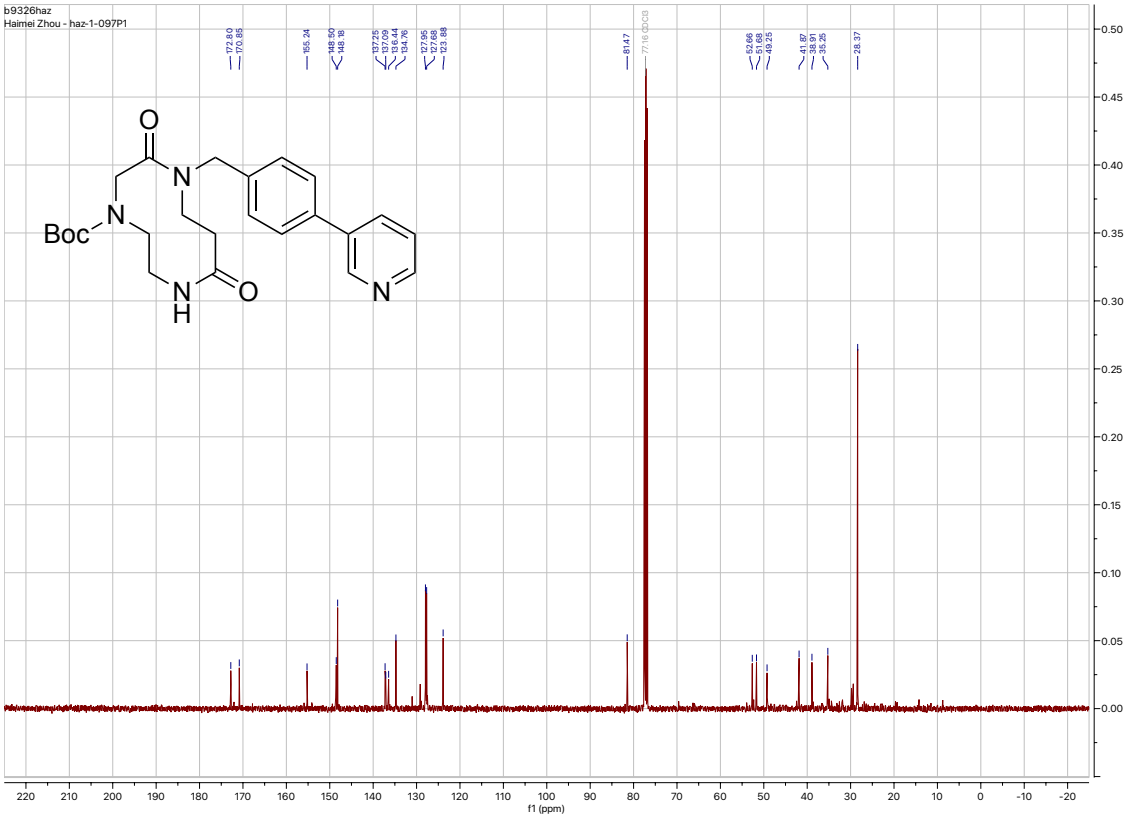
tert-Butyl 1-([1,1'-biphenyl]-4-ylmethyl)-2,8-dioxo-1,4,7-triazecane-4-carboxylate (185)



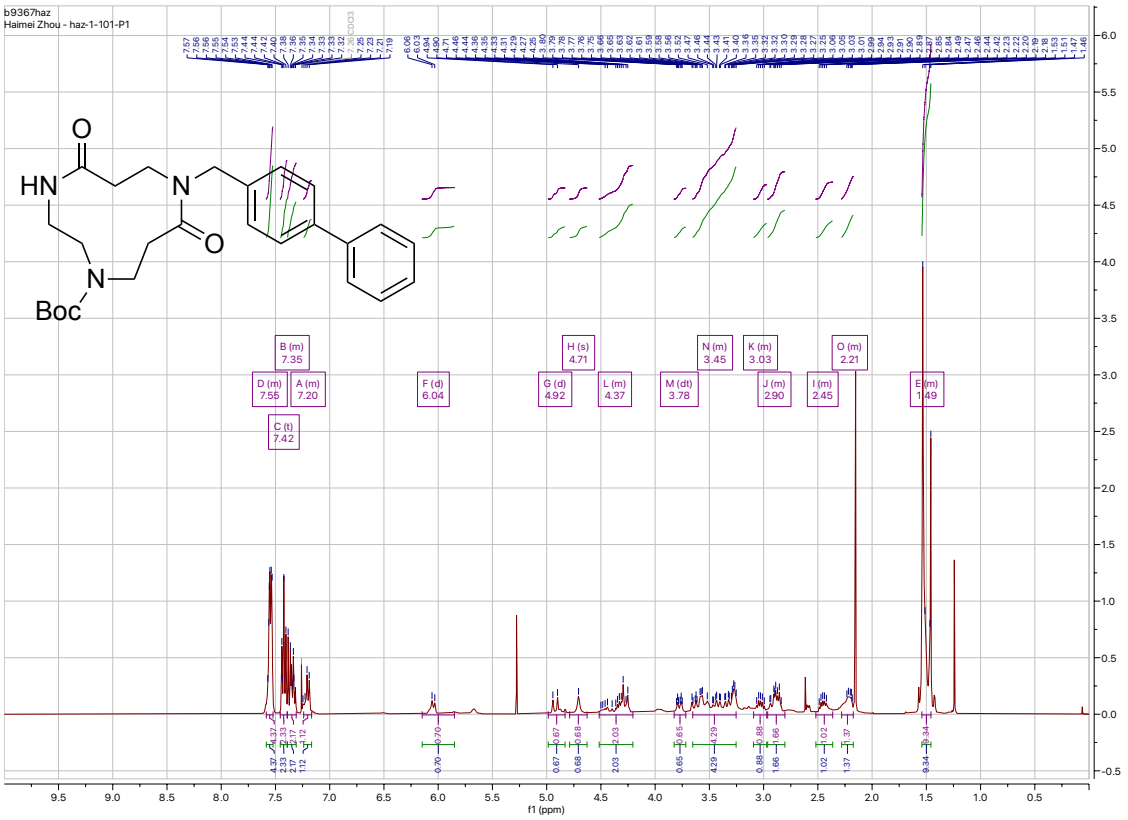


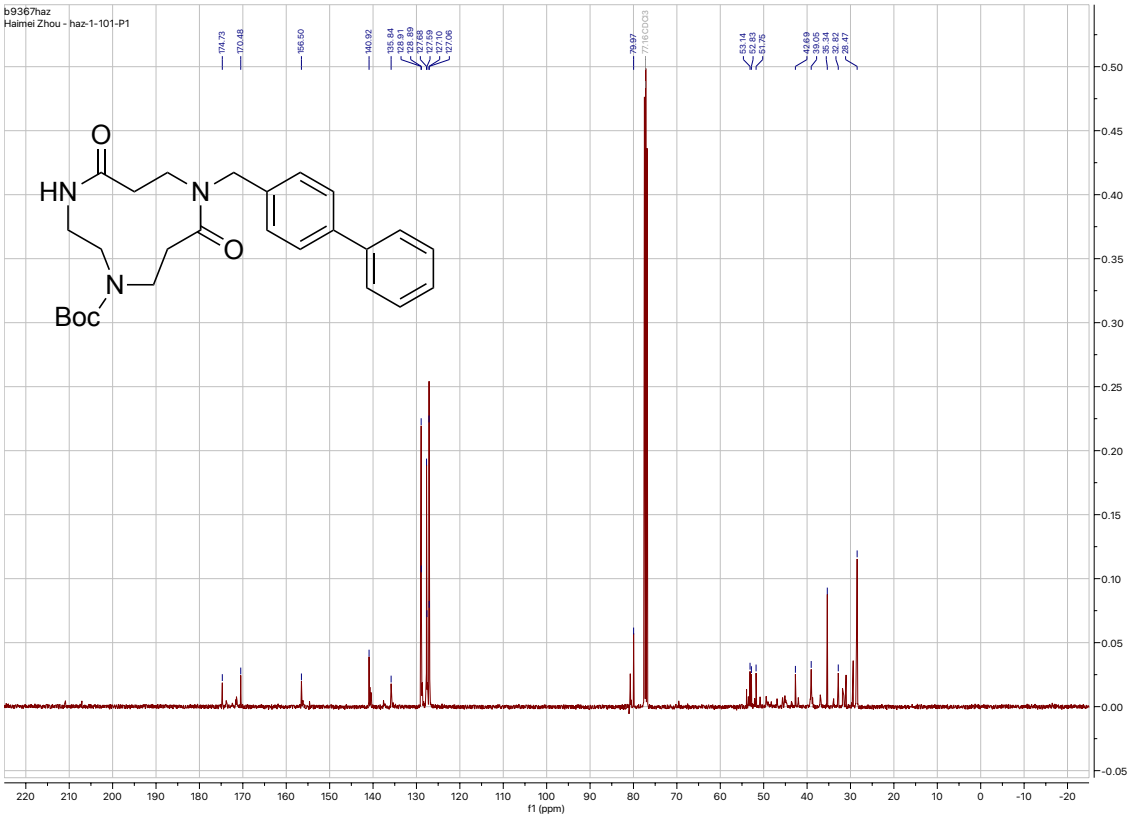
tert-Butyl 2,8-dioxo-1-(4-(pyridin-3-yl)benzyl)-1,4,7-triazecane-4-carboxylate (186)



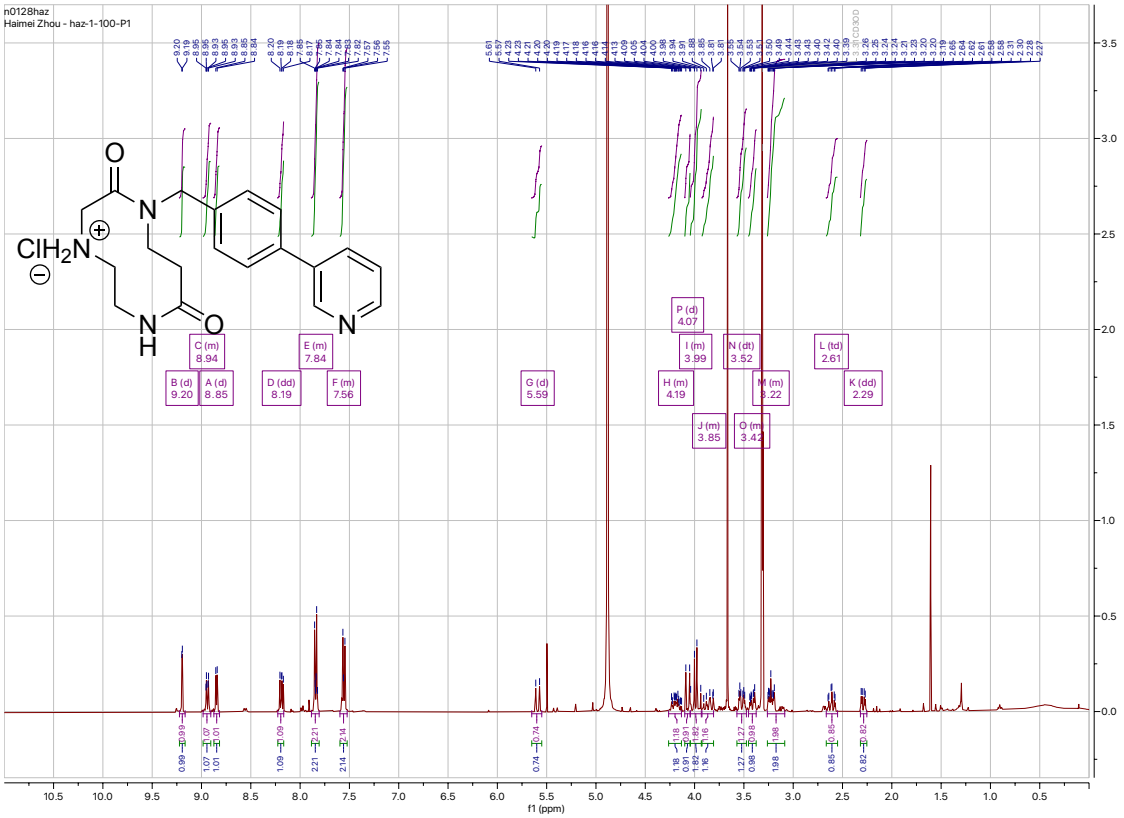


***tert*-Butyl 8-([1,1'-biphenyl]-4-ylmethyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate (187)**

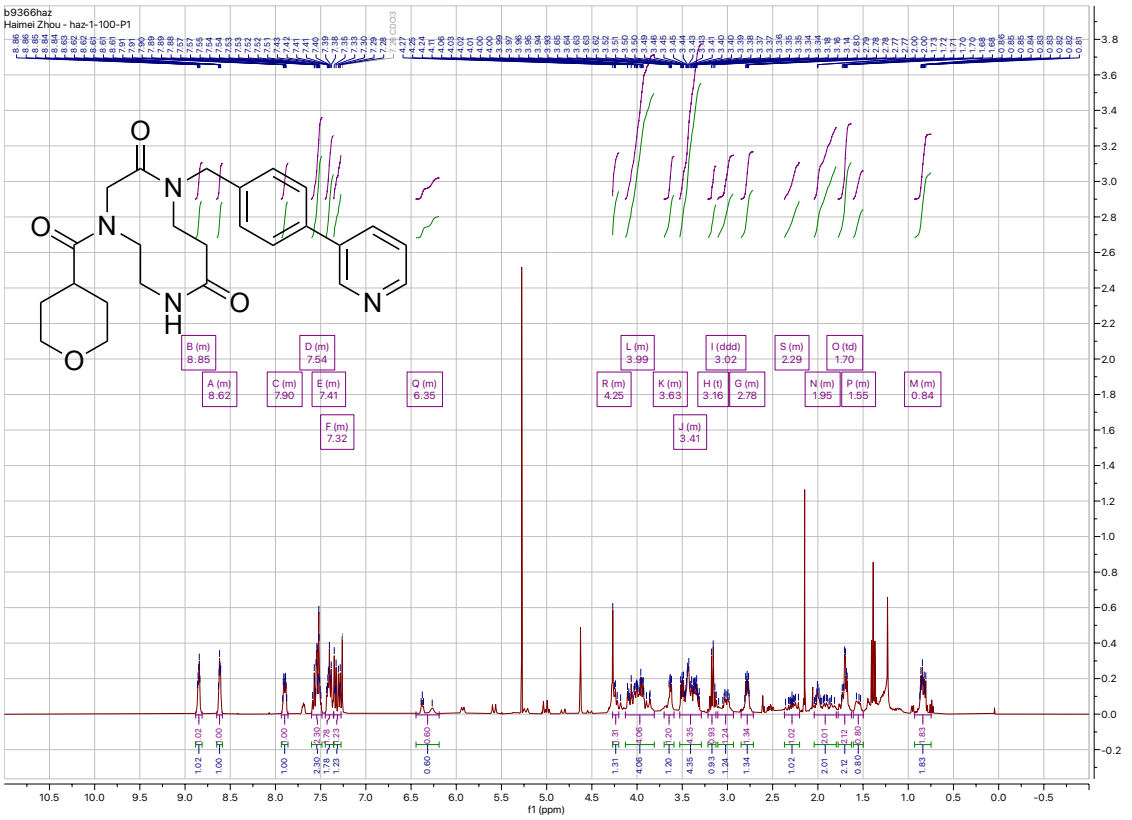


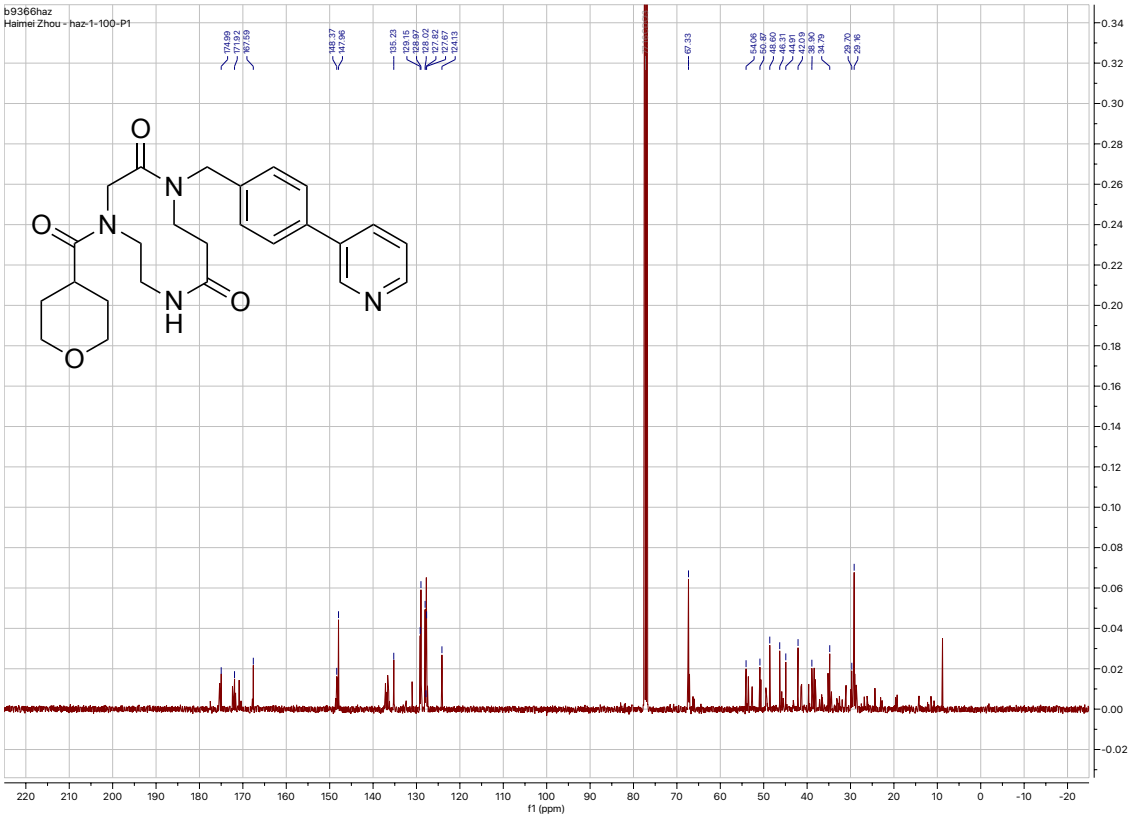


2,8-Dioxo-1-(4-(pyridin-3-yl)benzyl)-1,4,7-triazecan-4-ium chloride (189)



1-(4-(Pyridin-3-yl)benzyl)-4-(tetrahydro-2H-pyran-4-carbonyl)-1,4,7-triazecane-2,8-dione (190)





4-((3,5-Dimethylisoxazol-4-yl)sulfonyl)-1-(4-(pyridin-3-yl)benzyl)-1,4,7-triazecane-2,8-dione (196)