Synthesis of medium-sized rings via nucleophile-induced cascade expansion (NICE)

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Contents

1 Acknowledgements

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Finally, to my family I would like to show my appreciation for your support and love throughout my life. I am grateful for teaching me the importance of education, enabling me to have more opportunities in life. I am looking forward to my future, excited to face new challenges and develop as a scientist.

I have truly enjoyed my experience undertaking this Master's by research project and couldn't speak more highly of the Will Unsworth group. I have regained a passion and confidence for research which is in part due to the research environment within the Unsworth group.

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.

William Glover-Humphreys

2 Abstract

This thesis details the development of a novel method for the synthesis of medium-sized lactones and lactams via a cascade process referred to in this thesis as 'Nucleophile-Induced Cyclisation Expansion' (NICE). In this approach, linear precursors are designed to contain an internal nucleophilic catalyst, to ensure the NICE proceeds via a cyclic transition state containing a 5 to 7 membered ring (*i.e.* **I → II → III**). This approach avoids the high-dilution conditions typically required to synthesise medium-sized rings by end-to-end cyclisation. The majority of the challenges associated with synthesising medium-sized rings by NICE centre on the synthesis of the linear precursor. In this thesis two different retrosynthetic approaches to synthesising linear precursors are detailed, referred to as the **EI** + **N** and **E** + **IN** approaches as summarised in Figure 1.

Section 7.2 details the synthesis of linear precursors composed of an aliphatic amine as the internal nucleophile and a primary amine as the terminal nucleophile to synthesise novel medium-sized lactams. An **EI** + **N** retrosynthetic approach was used to synthesise the linear precursors as shown in Figure 1, where a molecule composed of an electrophilic carbonyl group and aliphatic amine as the internal nucleophile (**EI**), is reacted with a molecule composed of the terminal nucleophile (**N**).

Section 7.3 also focuses on an **EI** + **N** retrosynthetic approach, but by using bromopropan-1-ol an alternative **N**-building block. The subsequent linear precursors synthesised contains an alcohol group as the terminal nucleophile. Therefore, upon NICE lactones are synthesised analogous to the lactams shown in Section 7.2.

Section 7.4 focuses on the synthesis of linear precursors by the alterative **E** + **IN** retrosynthetic approach as shown in Figure 1. A range of different **E**-building blocks were synthesised composed of an electrophilic carbonyl group. Different commercially available amino alcohols were used as the **IN**-building blocks to introduce an internal and the terminal nucleophile into the linear precursor. Upon deprotection and NICE the different linear precursors were ring expanded into a range of structurally diverse medium-sized lactones.

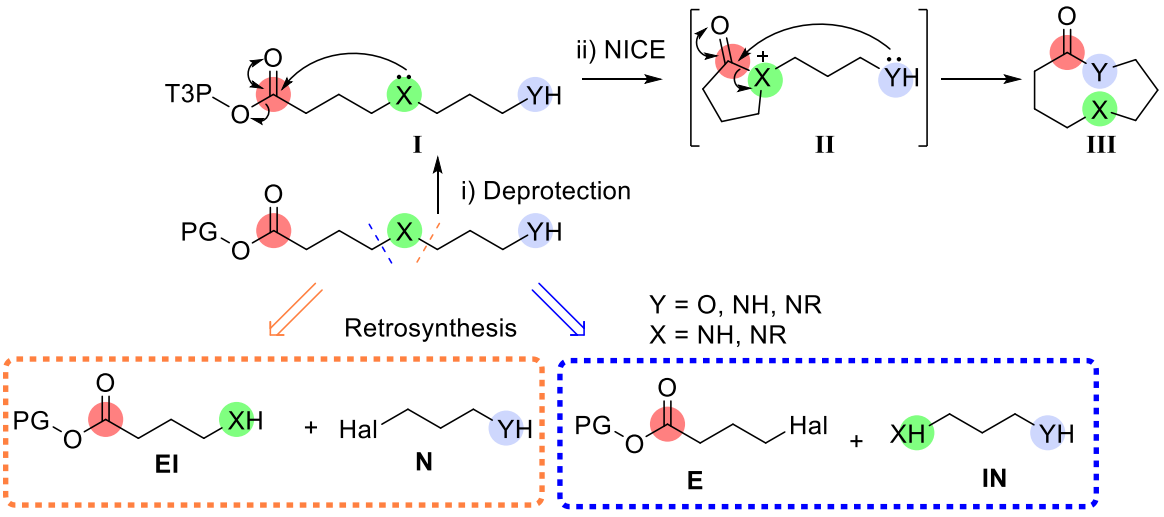


Figure 1 : - The two retrosynthetic approaches to synthesise the linear precursors to the medium-sized ring.

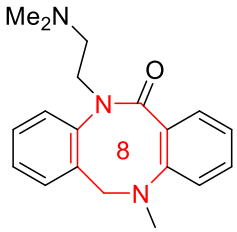
3 List of Figures

4 List of Schemes

5 Introduction

5.0 The importance of medium-sized rings

Medium-sized rings (cyclic molecules in which the ring skeleton is made up of 8 to 11 atoms) are often found in small molecules with desirable medicinal and therapeutic properties, with examples shown in Figure 2.[1] The pharmacology of these chemicals has been in part attributed to the restricted conformation of the medium-sized ring. The ring provides a degree of order and conformational rigidity to the chemical structure, resulting in key functional groups being arranged in space in a relatively predictable manner, which can be beneficial for medicinal chemistry applications.[2] Pharmaceutical compounds containing a medium-sized ring within their chemical structure have often been shown to exhibit superior bioactivity[3] and cell permeability[4] relative to their acyclic analogues structure.[5] Knowing the benefits that medium-sized rings offer, it is perhaps surprising to find that they are not as prevalent in pharmaceutical screening libraries as might be expected, which may explain why there are few examples in top-selling pharmaceuticals. The reason behind this is multifaceted, but is in part due to the challenges posed by the synthesis of medium-sized rings, which in turn restricts their application within the drug discovery field.[6]



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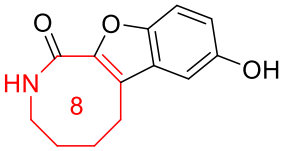

Kb-NB96-53(PKD inhibitor)

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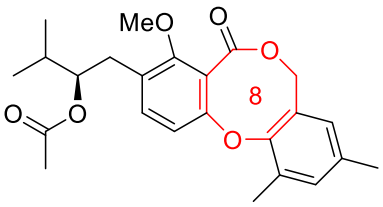

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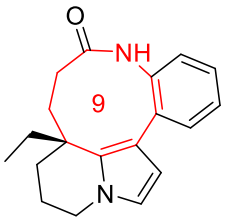

Rhazinilin (anticancer)

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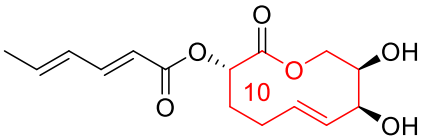

Pinolidoxin (Phytotoxin)

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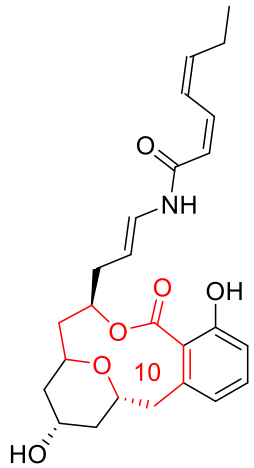


Apricularen A (anticancer)

4-6

Figure 2 : - Therapeutic and medicinally relevant compounds containing medium-sized rings.

5.1 Medium-sized ring synthesis

Traditionally, medium-sized rings have been synthesised via the end-to-end cyclisation of a linear precursor as shown in Figure 3. The likelihood that the linear precursor will orientate in a way that the two ends of the precursor will meet to form a ring can be limited however. This results in there being a competition between the desired intramolecular reaction (*i.e.,* cyclisation) and intermolecular reactions (*i.e.*, dimerization) which can lead to poor yields and unpredictable reactions. Various techniques have been implemented to favour end-to-end cyclisation such as high dilution conditions,[7, 8] pseudo-high dilution conditions[9, 10] and templated synthesis.[11] However, all these approaches aim to improve an unfavourable end to end cyclisation reaction, rather than finding an alternative, superior method to synthesise a medium-sized ring that avoids these challenges altogether.

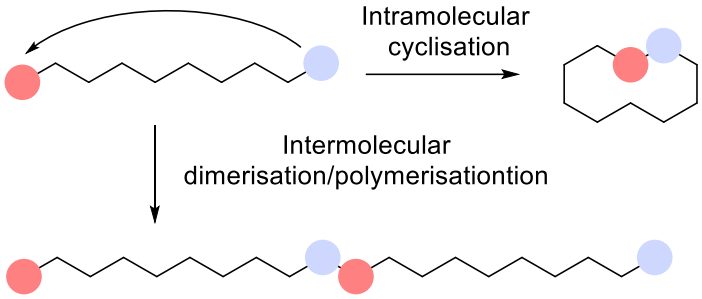


Figure 3 : - Schematic representation of the competing dimer and end to end cyclisation of medium-sized rings.

The thermodynamic and kinetic barriers to synthesising medium-sized rings are typically greater than those seen in the synthesis of smaller 5- to 7-membered rings, or in macrocycles, which are 12-membered rings and larger. As a result, medium-sized rings are commonly noted as being the most challenging ring size to synthesise.[12] This is due to medium-sized rings being large enough to experience significant loss in entropy upon cyclisation of a linear precursor, but small enough to experience ring strain and transannular strain due to the bond angle and the finite interior space within the ring.[1]

5 to 7-membered rings however are readily synthesised via cyclisation and cycloaddition reactions.[13, 14] As a result, a strategy to synthesize medium-sized rings is to expand these rings, thus avoiding the challenges associated with medium-sized ring end to end cyclisation. This approach is referred to as ring expansion.[12] Forming a medium-sized ring upon the ring expansion of a cyclic transition state rather than end to end cyclisation, resulting in a more kinetically favourable reaction course as shown in Figure 4.

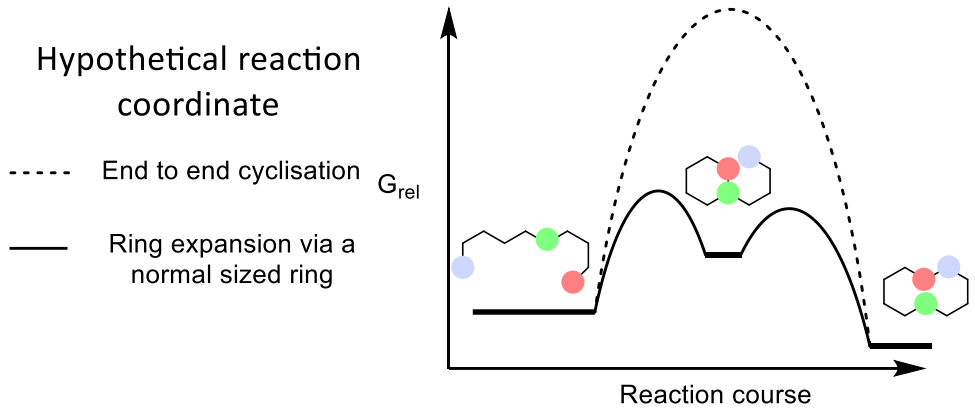


Figure 4 : - A hypothetical reaction coordinate of a linear precursor forming a medium-sized ring via ring expansion or by end-to-end cyclisation.

5.1.1 Nucleophilic catalyst Induced Cascade ring Expansion

An innovative ring expansion approach which forms medium-sized rings was pioneered by the Unsworth group and is named 'Nucleophilic catalyst Induced Cascade ring Expansion' (NICE). The method is based on the reaction of a linear precursor with an internal nucleophile that catalyses the reaction, thus ensuring the reaction proceeds via a smaller sized ring transition state, before expanding into a medium-sized ring. As shown in Figure 5 an internal nucleophile (shown in green) attacks the terminal electrophile (shown in red) forming a cyclic transition state. The terminal nucleophile (shown in blue) then attacks the electrophile and in a cascade reaction forms the desired medium-sized ring.

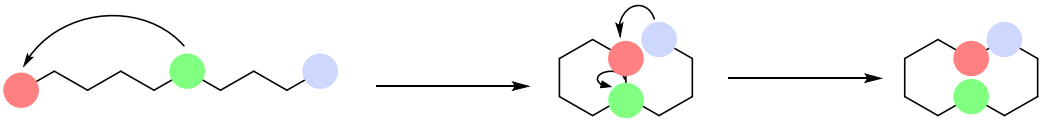
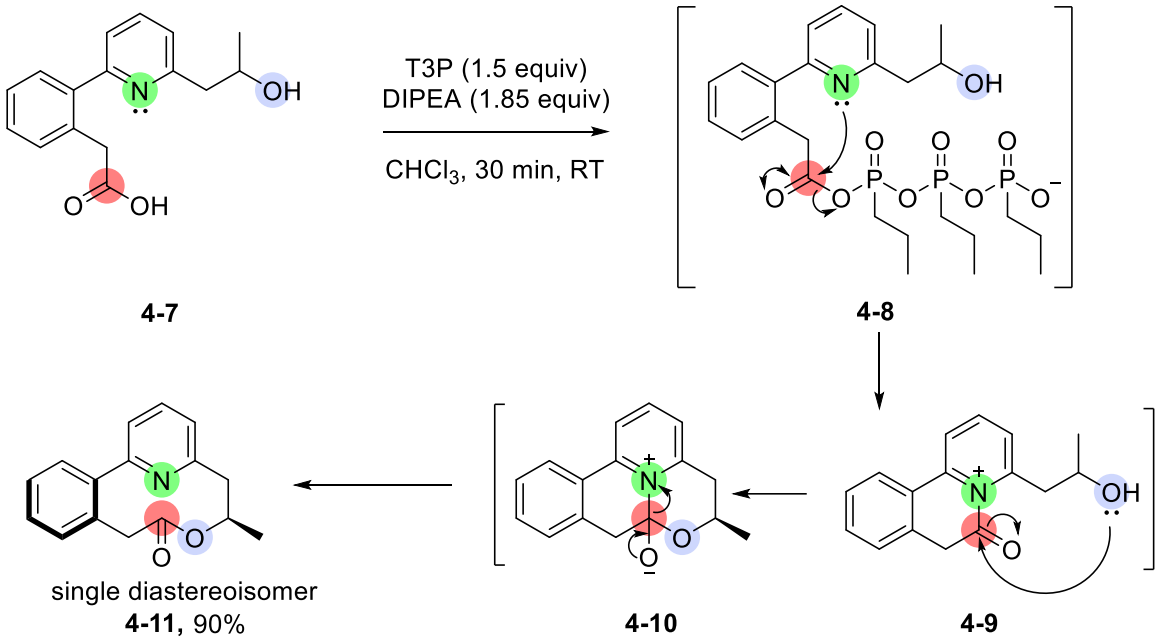


Figure 5 : - Schematic of the mechanism for nucleophile-induced cascade ring expansion reaction.

The NICE methodology was implemented by developing a precursor with a pyridine strategically incorporated within the linear structure **4-7**, as shown in Scheme 1. Following the activation of the carboxylic acid **4-7** with propane phosphonic acid anhydride (T3P) and *N*, *N*-diisopropylethylamine (DIPEA) in chloroform, the internal nucleophile attacks the activated carboxylic acid group forming the 6 membered ring shown in the reactive intermediate **4-9**. The hydroxy group, referred to as the terminal nucleophile, then proceeds to attack the acyl pyridinium species resulting in the formation of the lactone **4-11** (via **4-10**) in a cascade reaction.



Scheme 1: - The NICE mechanism forming the lactone **4-11**.

A key benefit of the ring expansion via NICE is its ability to form the product as a single diastereoisomer **4-11**. Atroposelective reactions that forms medium-sized rings are limited [15-17] and could be critical to drug discovery, as stereochemistry can considerably affect a drug's biological activity, pharmacokinetics and toxicity.[18] The atroposelectivity occurs in part due to the carbon-carbon bond between the two aryl units in compound **4-7** being prevented from freely rotating (supported by density functional theory (DFT) studies),[19] and in this case it was found that diastereoisomer **4-11** was formed exclusively in preference to isomer **4-16** as shown in Figure 6.

The proposed mechanism accounting for the selective formation of product lactone **4-11**, rather than the unobserved diastereoisomer **4-16**, is shown in Figure 6. The observed diastereoisomer **4-11** is formed from precursor **4-12**, whereby the hydroxyl selectively attacks the carbonyl *Si* face. The transition state leading to tetrahedral intermediate **4-13** is proposed to adopt a chair-boat like conformation with the methyl group in a pseudo-equatorial orientation. The intermediate **4-13** then ring expands to form the observed diastereoisomer **4-11**. The alternative approach would be the nucleophilic attack by the hydroxyl group, on to the carbonyl *Re* face of precursor **4-14**. However, for this to happen the methyl group, now in a pseudo-axial conformation, would likely be sterically hindered by the carbonyl group, resulting in a higher energy barrier to form the intermediate **4-15** compared to the alterative intermediate state **4-13**, thus resulting in an atroposelective reaction.

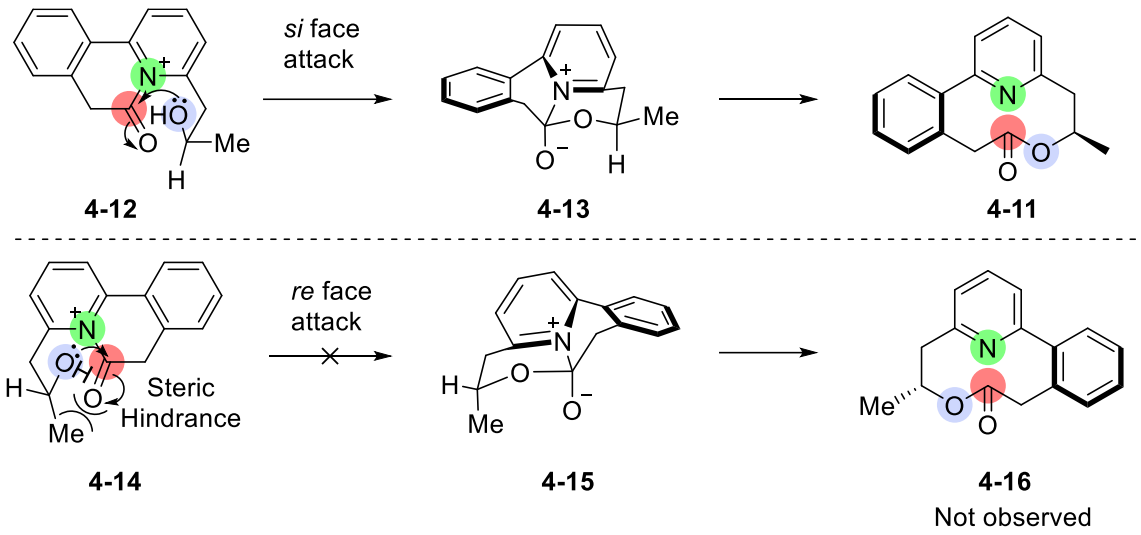


Figure 6 : - The diastereoselective nucleophilic addition reaction and ring expansion to form the lactone **4-11**.

To date, medium-sized ring synthesis carried out by the Unsworth group, has predominantly focused on the use of a pyridine as the internal nucleophile to catalyse the NICE reaction.[19] This research has resulted in an impressive number of lactones being synthesised ranging in size and functionality as shown in Figure 7 (**4-17** → **4-18**).

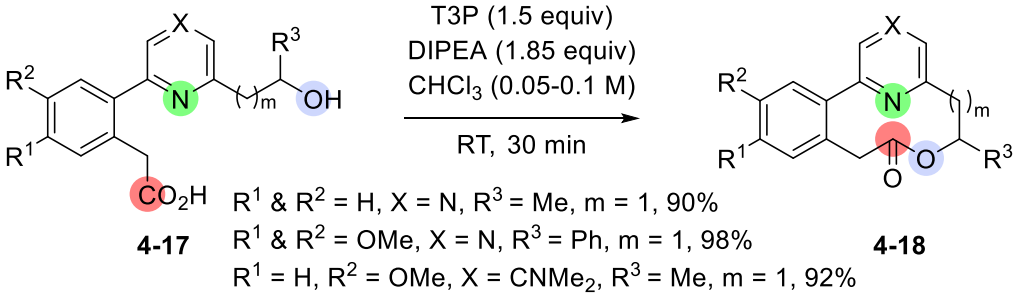


Figure 7 : - The general reaction scheme of medium-sized lactones synthesised by NICE, catalysed by an internal nucleophilic pyridine or derivative.

The use of an aliphatic amine rather than a pyridine as the internal nucleophile has also been used to catalyse the NICE reaction to synthesise a wider variety of medium-sized lactones with altered functionality, shown in Figure 8 (**4-19** → **4-20**).

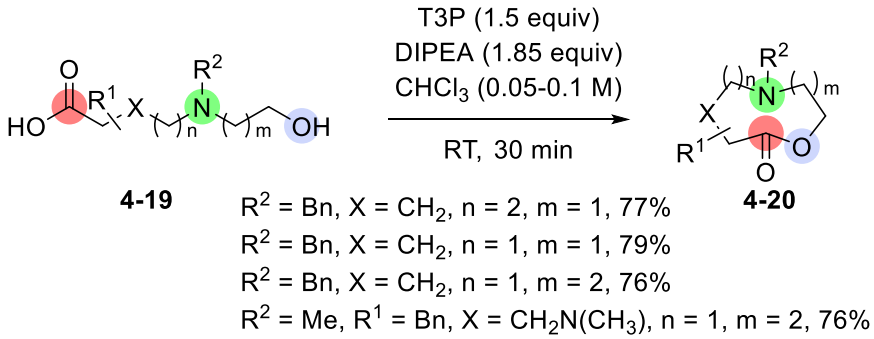


Figure 8 : - The general NICE reaction scheme catalysed by an internal aliphatic tertiary amine.

The diversity of medium-sized lactams synthesised by NICE has not been researched to the same extent as the lactones shown in Figure 7 and Figure 8. The current research solely focuses on ten membered lactams, all synthesised using a pyridine as the internal nucleophile.[19] The use of different terminal nucleophiles has been researched but predominantly focused on secondary amines, with one example utilising a primary amine, as shown in Figure 9.

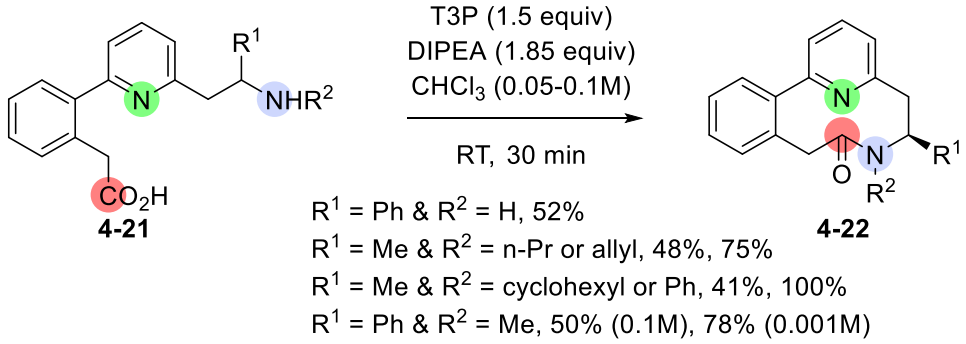


Figure 9 : - The general reaction for the synthesis of medium-sized lactams synthesised by NICE.

A logical progression of this research would be to focus on the NICE of lactams, specifically tailoring the precursor to ensure the ring expansion is catalysed by an aliphatic amine as the internal nucleophile. Additionally, the use of a primary amine as the terminal nucleophile has not been researched in great detail and would emphasize the diversity of medium-sized rings that can be synthesised by NICE.

A potential reason for the success of the NICE reactions that use a pyridine as the internal nucelophile, could be due to the restricted conformation a pyridine ring imposes on the precuror. This may result in the reactive groups being held in closer proximity and thus favouring the NICE. Conversely, the use of a pyridine could also impede on the reaction if it introduces conformation constraints, and this was indeed seen when exploring the size of the medium-sized rings accessible; for example, there was a stark contrast in yield between 9−, 10− and 11−membered lactone analogues shown in Figure 10. All the lactones, if successfully synthesised, would have been formed via an initial 6 membered ring cyclisation, yet the final ring size, and strain within it, is clearly critical to the successes of NICE in this case. In this case the most reasonable explanation for the failure to synthesise compound **4-23**, is due to the high ring strain imposed by the multiple aromatic substituents in the structure.

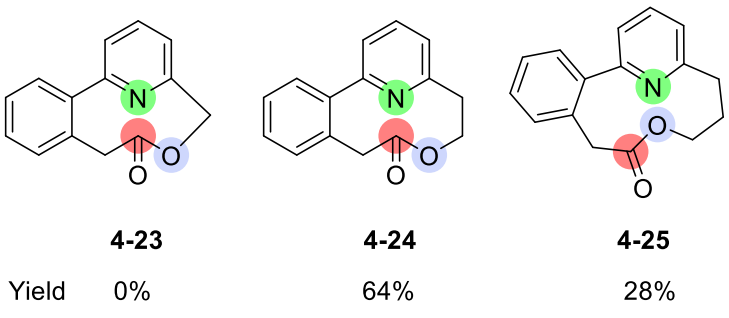


Figure 10 : - Medium-sized lactones ranging in size, containing a biaryl functionality.

In contrast using an aliphatic tertiary amine as the internal nucleophile, and no longer forming a benzo fused heterocycle, has enabled medium-sized lactones ranging in ring size to be synthesised by NICE in good yield, as shown in Figure 11.

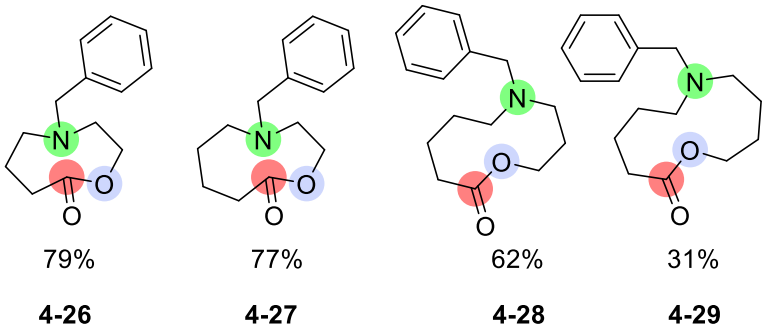
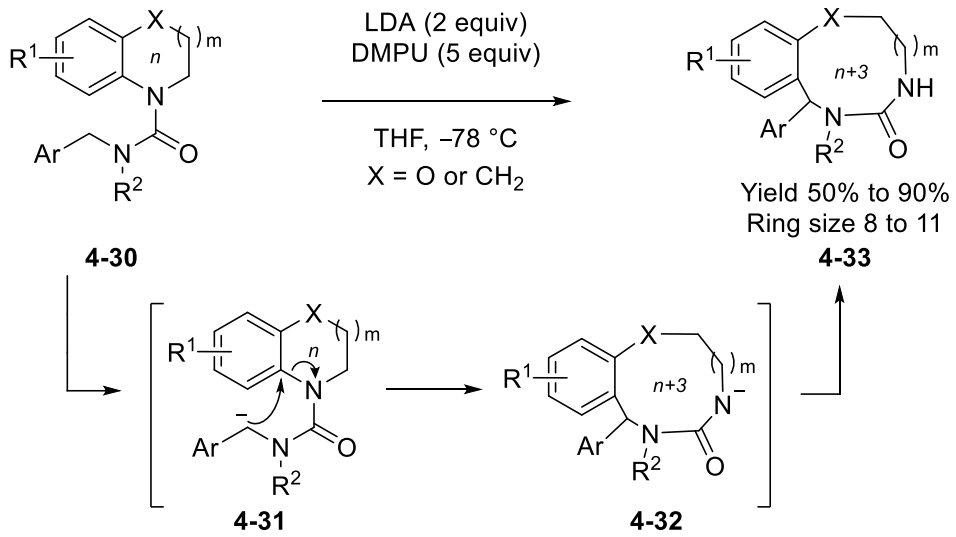


Figure 11 : - Medium-sized lactones ranging in ring size synthesised with an aliphatic tertiary amine acting as an internal nucleophile.

These observations highlight how the structure of the precursor can have beneficial or detrimental effects on the outcome of a NICE reaction. More generally, to ensure a given ring expansion reaction is successful, the reaction must be carefully designed to ensure that it is likely to be thermodynamically favourable. In most cases the change in ring size from a small to medium-sized ring is thermodynamically endergonic considering only the change in ring size in isolation.[20] Therefore, for a ring expansion reaction that results in medium-sized ring formation to be overall exergonic, additional driving forces need to ensure the thermodynamic cost associated with the change in ring size can be repaid.[1] In the following sections the design features that contribute to a thermodynamically favourable ring expansion reaction will be discussed.

5.1.2 Charged intermediates

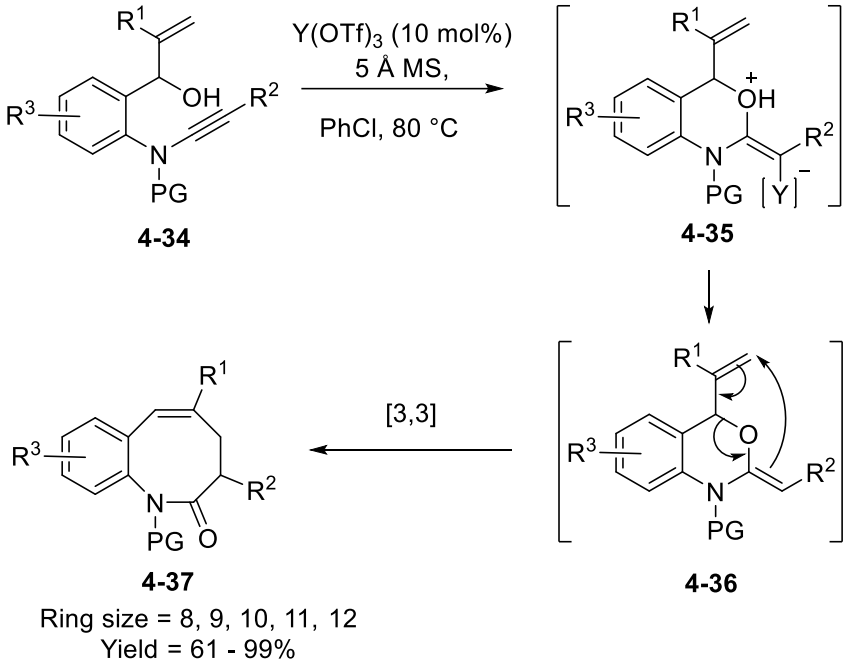
One driving force that contributes to the success of a ring expansion is the conversion of a charged unstable intermediate into a more stable neutral species. NICE reactions are an example of this whereby a quaternary ammonium cationic intermediate is formed before ring expanding it into a neutral medium-sized ring as shown earlier in Scheme 1. Similarly, Clayden and co-workers reported the synthesis of medium-sized benzo fused heterocycles via a charged reactive intermediate. The ring expansion proceeds upon the deprotonation of the benzylic acidic proton α to the nitrogen within the urea modify forming the unstable anionic intermediate **4-31**. The more stable urea intermediate **4-32** was subsequently formed via the *n* to *n+3* ring expansion before being protonated to form the medium-sized heterocycle **4-33**.



Scheme 2 : - The n to n+3 ring expansion of metalated urea.

5.1.3 Bond-dissociation energy

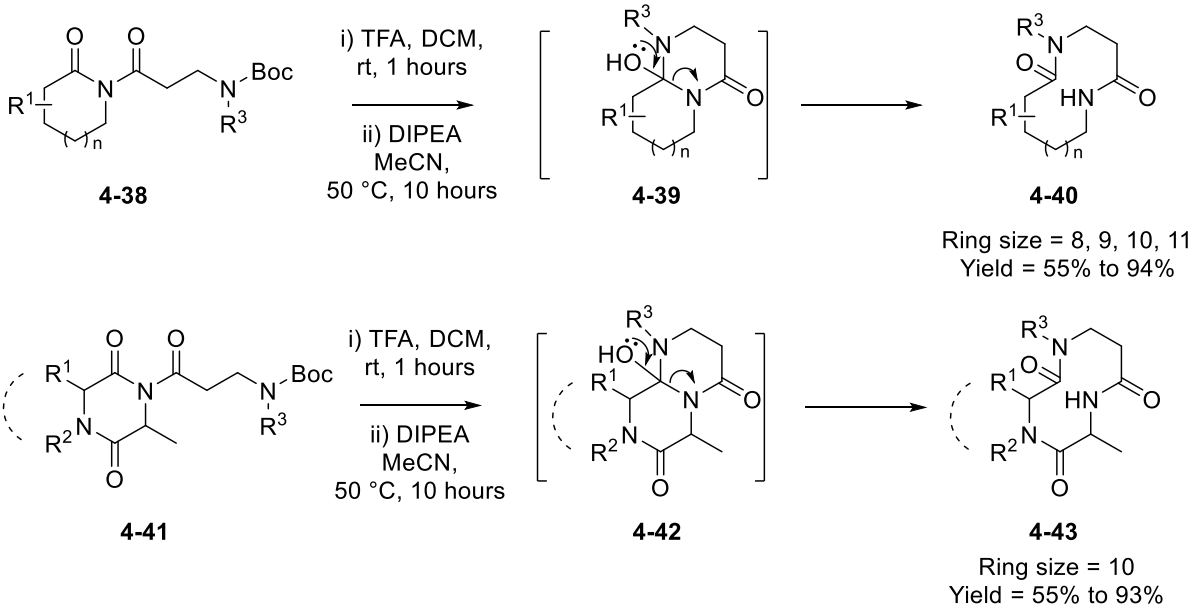
The formation of a thermodynamically stable carbonyl group upon ring expansion, especially an amide or ester group, can be a significant driver in successful ring expansion reactions. For example, Ye and co-workers reported the synthesis of benzazocinones, a structural motif present in bioactive molecules.[21] The cascade ring expansion detailed in Scheme 3 involved the yttrium(III)-catalysed intramolecular hydroalkoxylation of ynamide **4-34** to form the vinyl ether **4-36** consisting of an oxazinane ring. The intermediate **4-36** then cascades via a Claisen rearrangement to form lactam **4-37** in excellent yields. The formation of a thermodynamically stable carbonyl bond in the product is likely to be a key factor driving these reactions.



Scheme 3: - The suspected ring-expansion mechanism proposed by Ye and co-workers.

Ye and co-workers proposed the mechanism shown in Scheme 3, whereby the π-acidic yttrium(III) catalyst coordinates to and activates the alkyne in **4-34,** causing the intermediate **4-35** to be formed following nucleophilic addition of the alcohol. Lactam **4-37** is then formed upon the [3,3] sigmatropic rearrangement of the intermediate **4-36.** This reaction mechanism was proposed based on experimental observations that confirmed the carbonyl oxygen originated from the hydroxyl group and alternative intermediates were ruled out.[21]

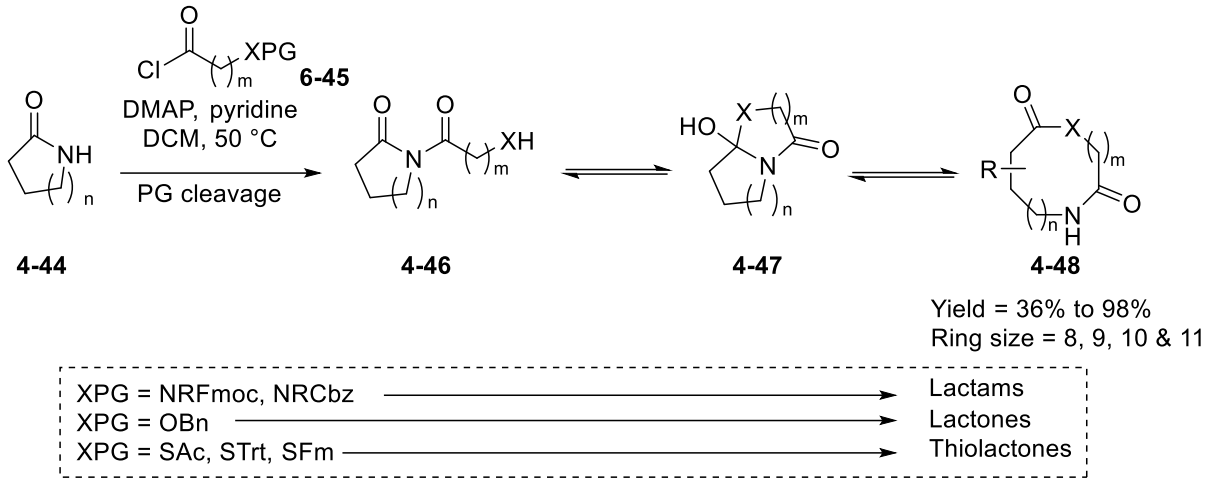
The work of Yudin and co-workers[22] also emphasized the role played by the formation of a carbonyl group in ensuring a thermodynamically favourable ring expansion reaction. Their research detailed how a range of β-amino imides **4-38** and 2,5-diketopiperazines **4-41** can be ring-expanded to form cyclic tripeptides. The approach is shown in Scheme 4; following *tert*-butyloxycarbonyl (Boc) cleavage of **4-38** and **4-41**, the deprotected amines were treated under basic conditions yielding the cyclic peptides **4-40** and **4-43** respectively, via intermediates **4-39** and **4-42**, respectfully. Computational analysis of the ring expansion concluded that the ring expansion was only successful if the reaction was exergonic by at least 16.7−50.2 kJmol^{-1}.[22] Amide formation is likely to be the main driver in ensuring these reactions are exergonic.



Scheme 4 : - The ring expansion of cyclic imides and 2,5-diketopiperazines.

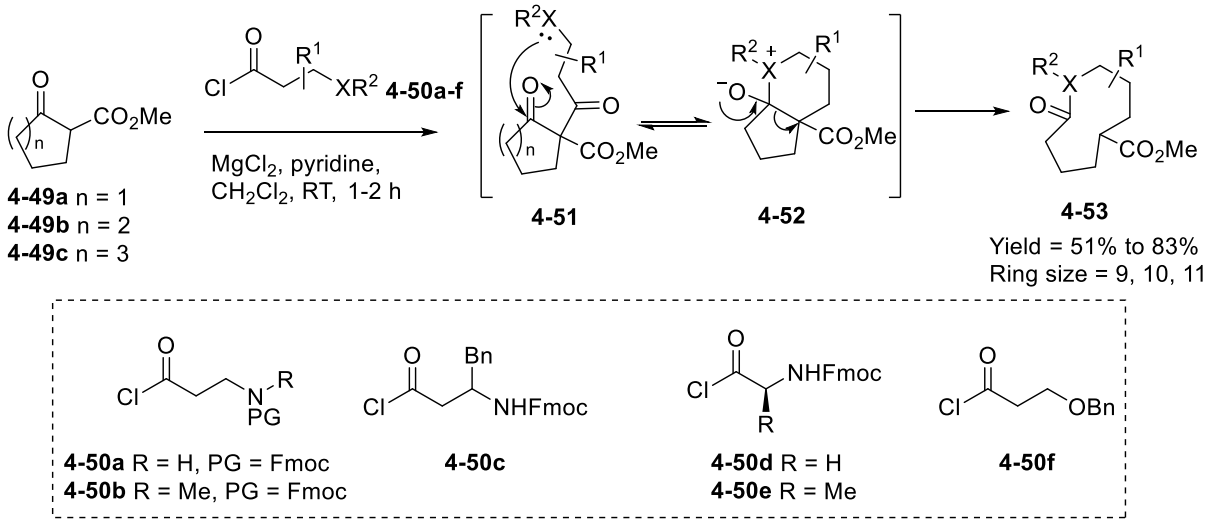
Unsworth and co-workers have also developed similar ring expansion methods, that enable the ring expansion of imides to synthesise lactones[23], lactams[24] and thiolactones[25] as shown in Scheme 5. The ring expansion involves imides **4-46** formed by an *N*-alkylation of lactam **4-44** with acyl chloride **4-45**, before ring expanding via cyclol intermediate **4-47** forming medium-sized ring **4-48**. The research was undertaken with the aim of synthesizing macrocycles via successive ring expansion (SuRE), whereby repeated ring expansion enables the synthesis of macrocycles by expanding the medium-sized rings a second (or third) time. As a result, a broad array of medium-sized rings, ranging in size and functionality were synthesized.

The research highlights how forming thermodynamically stable bonds upon ring expansion is influential in achieving a high yielding ring expansion reaction. This is evident when comparing lower yielding SuRE reactions forming thiolactones relative to analogous lactam and lactones by NICE. This is likely due to the thioester formed upon ring expansion being less stable compared to amides and esters, which benefit from greater resonance stabilisation (supported by DFT studies).[25] As a result SuRE reactions forming thiolactones are more challenging and lower yielding compared to analogous lactones and lactams.



Scheme 5 : - An *N*-acylation reaction followed by the imide ring expansion into a medium-sized ring.

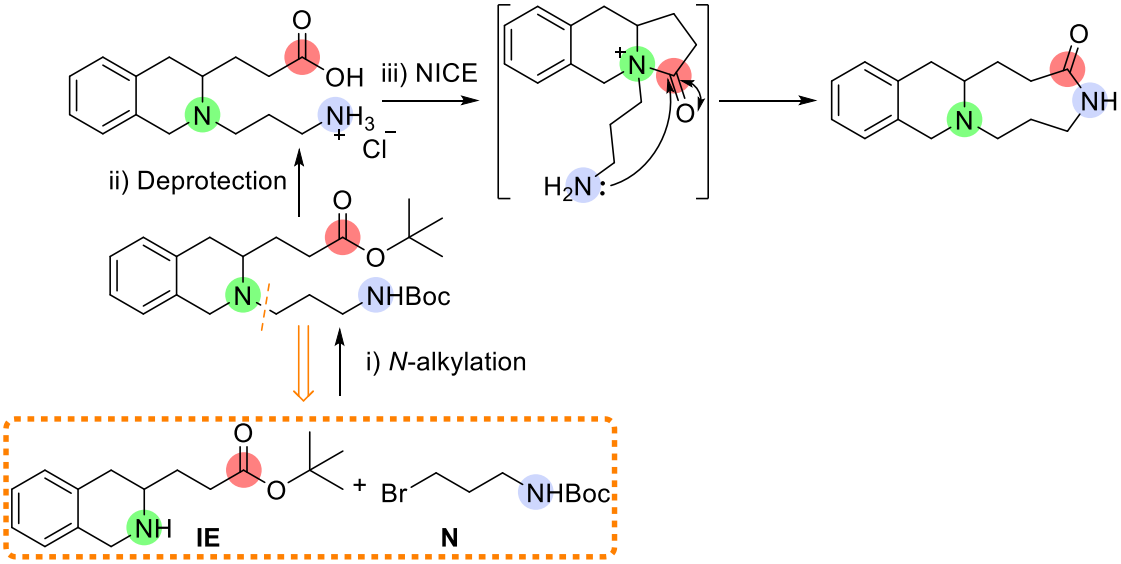
Earlier research by the Unsworth group focused on SuRE, was based on the reactions of β–ketoester motifs as shown in Scheme 6.[26] This approach involved a *C*-acylation reaction between various cyclic β-ketoesters **4-49a-c** and acyl chlorides **4-50a-f**, forming tricarbonyl species **4-51**. The addition of piperidine in dichloromethane causes the deprotection of the amine **6-45** and the reaction proceeds via a cyclisation and ring expansion, forming either an amide or ester present in the medium-sized ring **4-53**. This approach highlights the straightforward and effective approach to ring expansion, facilitating the formation of a wider range of rings.



Scheme 6 : - The structural diversity and mechanism of medium-sized rings formed via acylation/ring expansion sequence.

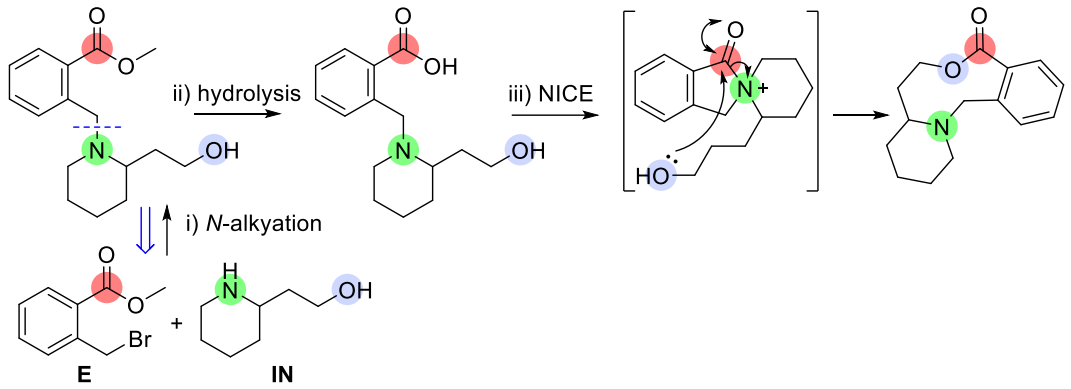
6 Project aims

Medium-sized rings act as a key structural core in an array of bioactive natural products, imparting a degree of rigidity and a unique three dimensional (3D) spatial conformation to a compound. As a result, medium-sized rings are present in medicinally important compounds as they improve various therapeutic properties.[1] Yet despite the medicinal benefits, medium-sized rings are underrepresented in pharmaceutical and drug discovery libraries due to the challenges associated with their synthesis.[1, 6, 12, 27] Therefore, the aim of this project was to expand the scope of medium-sized ring accessible via NICE. The initial focus was the synthesis of medium-sized ring lactams as they have not been researched to the same extent as lactones in previous work on NICE.[19] This was achieved by designing precursors with a primary amine as the terminal nucleophile and an aliphatic amine as the internal nucleophile as shown in Scheme 7.



Scheme 7 : - The generalised synthesis of the linear precursor with an aliphatic tertiary amine as the internal nucleophile and a primary amine as the terminal nucleophile.

The second part of this project follows the alterative **IN** + **E** retrosynthetic approach to synthesising linear precursors for NICE. The aim is to develop this retrosynthetic approach into an efficient reaction sequence to develop an array of structural diverse medium sized rings. This will be achieved by utilising the abundance of different commercially available amino alcohols to act as **IN**–building blocks, introducing the internal (**I**) and terminal nucleophiles (**N**) into the linear precursor. Further structural diversity will be achieved by development different sp2 rich esters acting as the **E**–building block that will introduce latent electrophilicity (**E**) into the linear precursor. Therefore, medium sized rings can be synthesised via an *N*-alkylation, ester sublimation and NICE reaction as shown in Scheme 8. Developing an efficient three step reaction sequence to synthesising a diverse array of medium sized rings, varying in size and functionality.

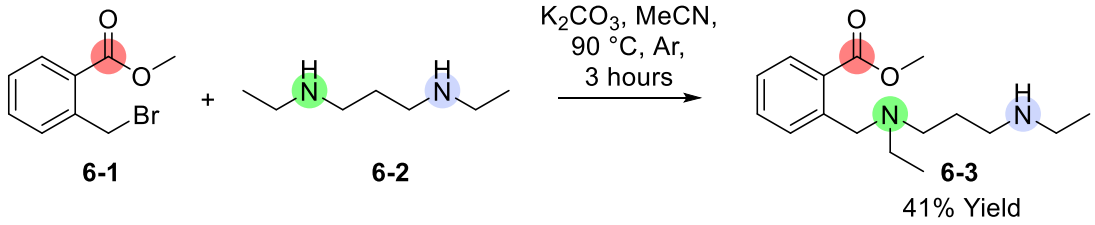


Scheme 8 : - The reaction scheme highlighting how an amino alcohol can be used to introduce an internal and terminal nucleophile into a linear precursor for NICE.

7 Experimental discussion

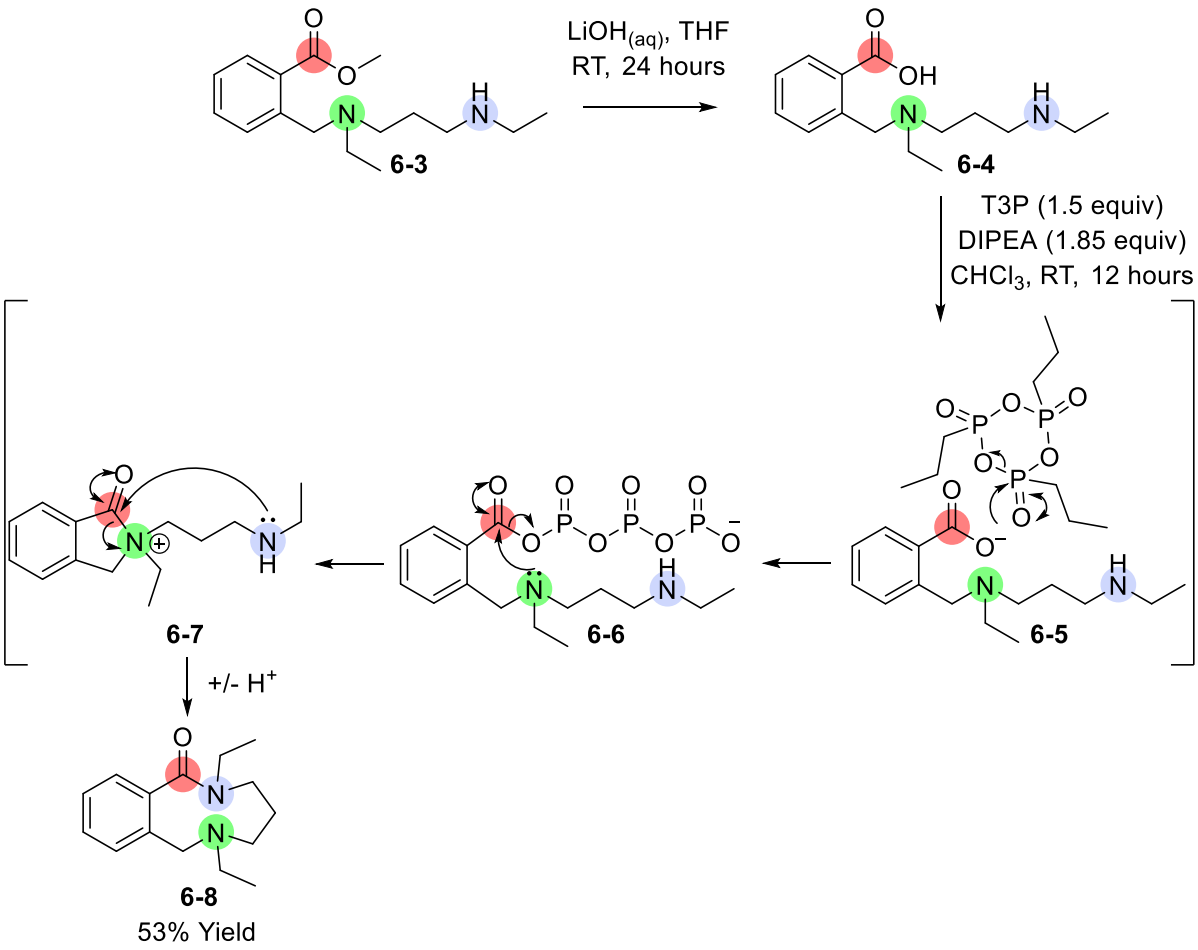
7.0 Initial research into precursor design and synthesis

The first precursor **6-3** was synthesised by an S_N2 *N*-alkylation reaction between the electrophile benzyl bromide **6-1** and the nucleophile bis-secondary amine **6-2**. This was carried out to determine if a medium-sized lactam could be synthesised by NICE from a linear precursor with an aliphatic amine as the internal nucleophile.



Scheme 9 : - The *N*-alkylation reaction to form the precursor **6-3**.

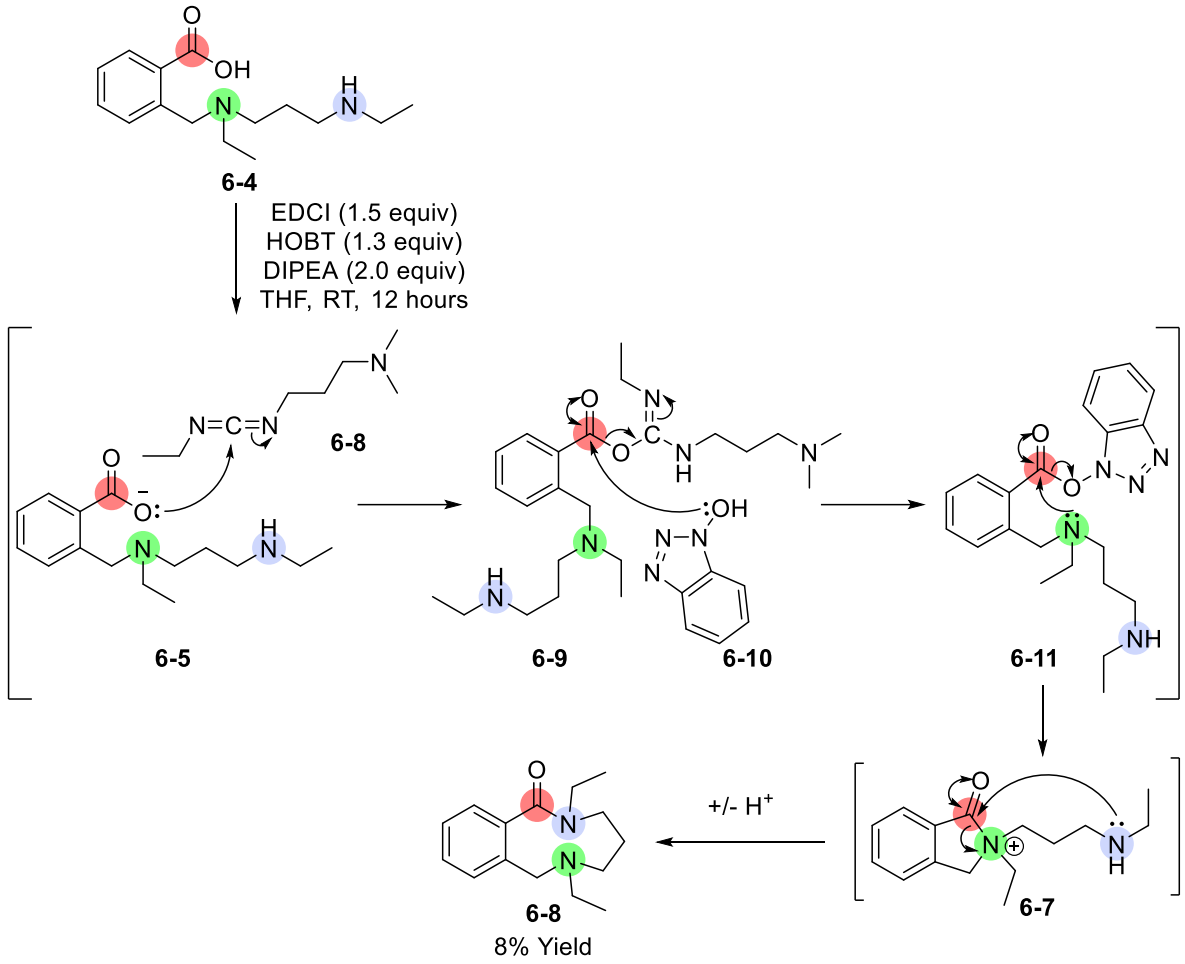
The ester **6-3** was hydrolysed by the nucleophilic addition of a hydroxide ion at the carbonyl group forming the tetrahedral alkoxide intermediate. The carbonyl group reforms and the alkoxide group is eliminated forming the desired carboxylic acid group **6-4.** The NICE reaction was then performed achieving a moderate yield of the lactam **6-8** as shown in Scheme 10. The reaction conditions were adapted from the NICE approach published by the Unsworth group,[19] that used the coupling agent T3P in DIPEA and $CHCl_3$. The NICE reaction shown in Scheme 10 takes place upon activation of the carboxylic acid group using the coupling agent T3P. This activation causes the carbonyl group to become sufficiently electrophilic to encourage the nucleophilic attack from the internal nucleophile (highlighted in green), forming the five membered acyl ammonium intermediate **6-7**. Then, the secondary amine (highlighted in blue) acts as the terminal nucleophile to attack the carbonyl group (highlighted in red) and initiate ring expansion to form the 9 membered lactam **6-8** in a 53% yield.



Scheme 10 : - The reaction mechanism of the NICE of the precursor **6-4** using the coupling agent T3P in DIPEA and $CHCl_3$.

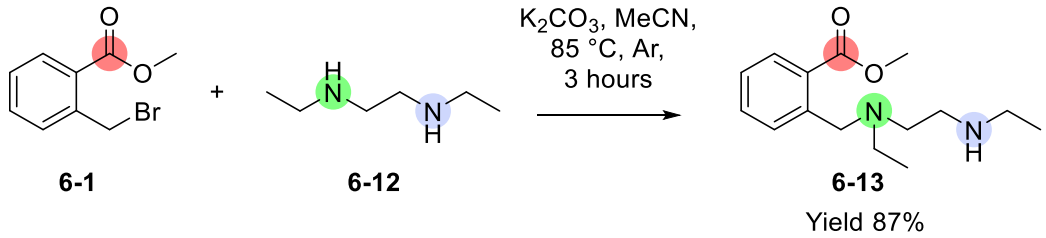
The lactam **6-8** differs from the lactams previously synthesised by NICE using the coupling agent T3P as described in Section 5.1.1, predominantly due to the internal nucleophile being an aliphatic tertiary amine rather than a pyridine. As a result, of the structural differences alternative coupling conditions were used to synthesise the lactam **6-8**. The coupling agents 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI) and hydroxybenzotriazole (HOBt) have been shown to result in a higher yielding NICE reaction when compared to using T3P in some cases. This was discovered during ongoing research in the Unsworth group, synthesising thiolactones and macrocycles by NICE.

The reaction mechanism by which the coupling agents EDCI and HOBt activate the carbonyl group to encourage the NICE of the precursor **6-4** is shown in Scheme 11. Under basic conditions the electrophilic carbodiimide is attacked by the carboxylate anion **6-5** forming the intermediate **6-9**. The more electron poor carbonyl present in the intermediate **6-9** is then attacked by HOBt **6-10** and an exchange occurs resulting in the carbamide acting as the leaving group, forming the compound **6-11**. The NICE reaction then takes place via **6-7** forming the lactam **6-8**, albeit with a low 8% yield, so this procedure was far less effective than the T3P method for this substrate. This could be due to T3P being more reactive forming the compound **6-6** more readily compared to alternative species **6-11** when using EDCI and HOBt. Therefore, hindering the NICE as the carbonyl group doesn't become electrophilic enough for the internal nucleophile to attach and start the NICE reaction to proceed.



Scheme 11 : - The reaction mechanism for the NICE of the linear precursor **6-4** using the coupling agents EDCI and HOBt in DIPEA and THF.

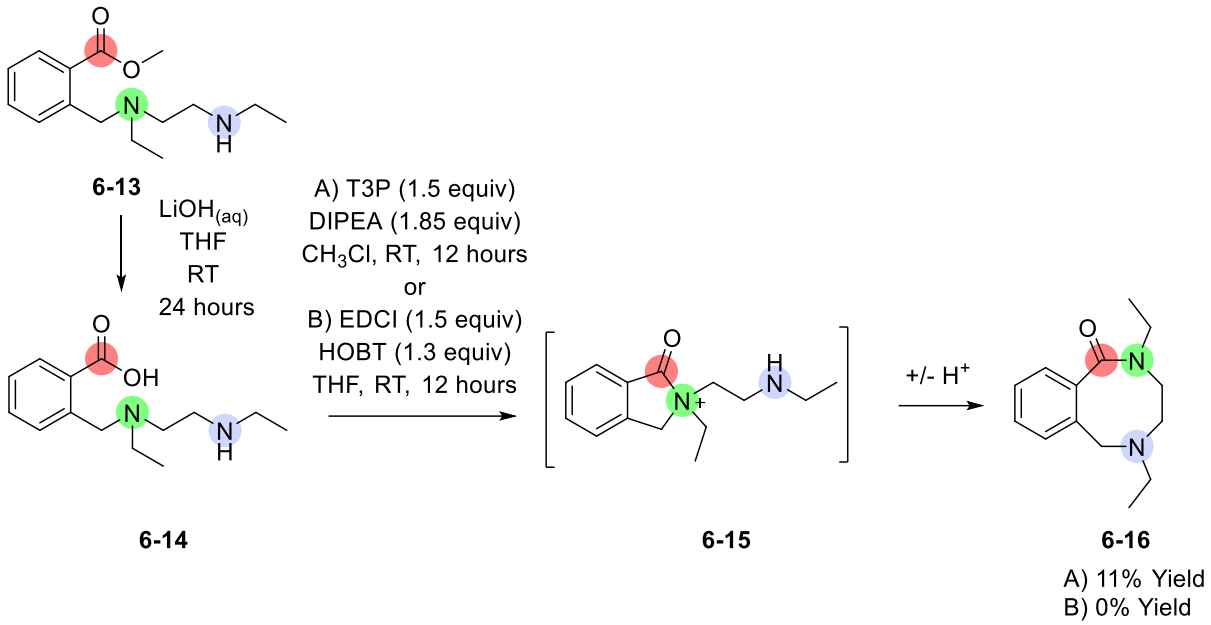
Another *N*-alkylation reaction, similar to the previous reaction shown in Scheme 9, was done using the same electrophile **6-1** but a different diamine, diethylethane-1,2-diamine **6-12** with a shorter ethyl chain separating the two amines compared diamine **6-2**. The *N*-alkylation reaction was performed with the desired compound **6-13** being formed in 87% yield.



Scheme 12 : - The *N*-alkylation reaction forming the precursor **6-13**.

The ring-expansion precursor **6-13** was then saponified to the carboxylic acid **6-14** and subjected to the same two coupling conditions previously used to synthesise the lactam **6-8** shown in Scheme 10 and Scheme 11. This resulted in the formation of lactam **6-16** which is similar in structure to lactam **6-8** but with a smaller eight membered ring. The NICE of the precursor **6-13** shown in Scheme 13 also

followed the same trend whereby the coupling conditions using T3P formed lactam **6-16** in a higher yield of 11% compared to using EDCI and HOBt. Notably the NICE reaction using EDCI and HOBt was unsuccessful in forming the lactam **6-16** achieving a 0% yield. Unable to visualise the formation of the lactam **6-16** upon monitoring the reaction via thin-layer chromatography.

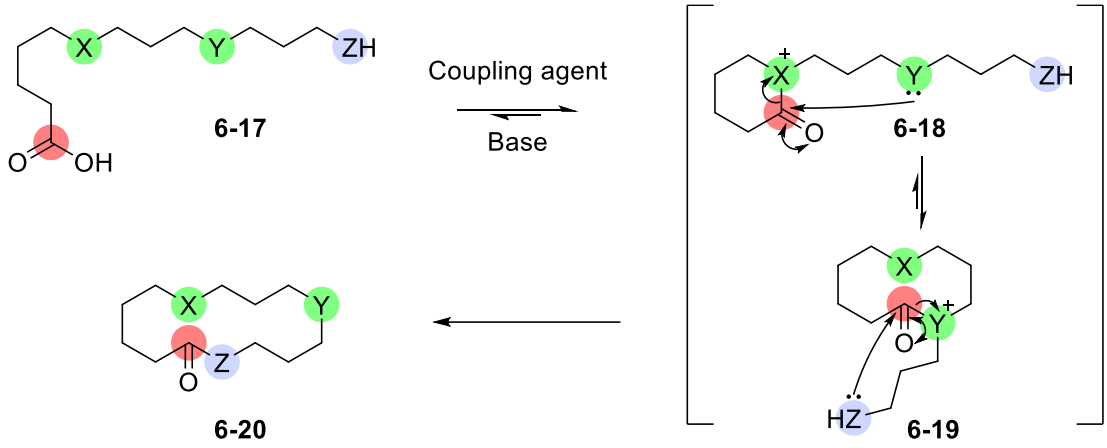


Scheme 13 : - Comparing the coupling conditions to form the lactam **6-16** by NICE.

Interestingly the larger 9-membered lactam **6-8** achieved a higher yield compared to the analogous 8-membered lactone **6-16**. This is most likely due to the lactam **6-16** having a smaller ring size and subsequently exhibiting a higher ring strain and transannular strain resulting in a lower yielding NICE when compared to the lactam **6-8**. The research into NICE by Unsworth and co-workers[19] synthesised a variety of lactones and lactams using coupling agent T3P to good effect. Particularly in the NICE of lactams, in one instance achieving quantitative yield of a medium-sized lactam, shown earlier in Figure 9.[19] Due to the results shown and the success of previous research into NICE, T3P is typically used as the coupling agent in the NICE of medium-sized rings throughout this research. However, in a few instances both reaction conditions were explored to determine which coupling conditions would achieve the highest yielding NICE reaction.

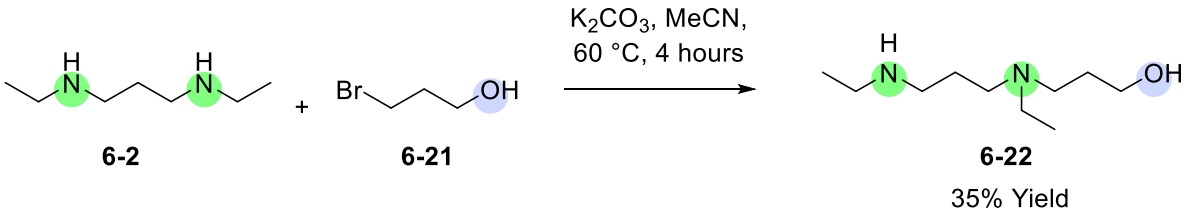
7.1 Multi Nucleophile-induced Ring Expansion

In the current published work from the Unsworth group, the NICE reactions all involved a single ring expansion step. However, work is ongoing in the group to demonstrate that larger more complex products can be made by incorporating multiple ring expansion steps into longer cascades. In this way, a macrocycle can potentially be synthesised by a multi-NICE sequence; for example, using a precursor with multiple internal nucleophiles (**X** and **Y**) like the precursor **6-17**. In theory by designing such a precursor a more complex cascade reaction sequence can take place and a macrocycle **6-20** can be formed from a linear precursor **6-17** as shown in Scheme 14.



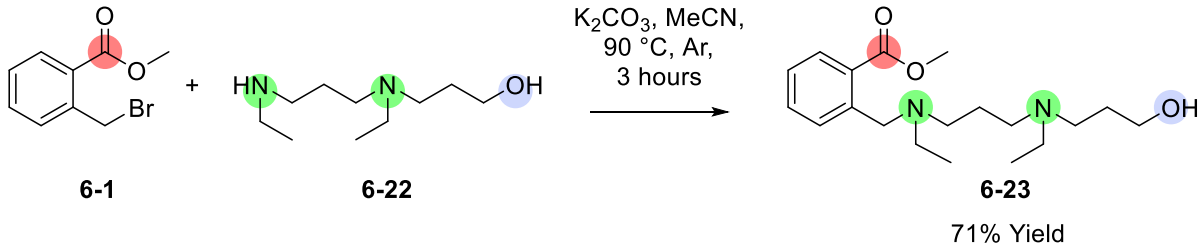
Scheme 14 : - A general reaction mechanism of a multi-NICE reaction to form a macrocycle from a linear precursor.

The first step in the reaction sequence to form the multi-NICE precursor was a *N*-alkylation reaction between diethylpropane-1,3-diamine **6-2** and 3-bromo propan-1ol **6-21** synthesising 3-(ethyl (3-(ethyl amino) propyl) amino) propan-1-ol **6-22** as shown in Scheme 15.



Scheme 15 : - The *N*-alkylation reaction to form the compound **6-22**.

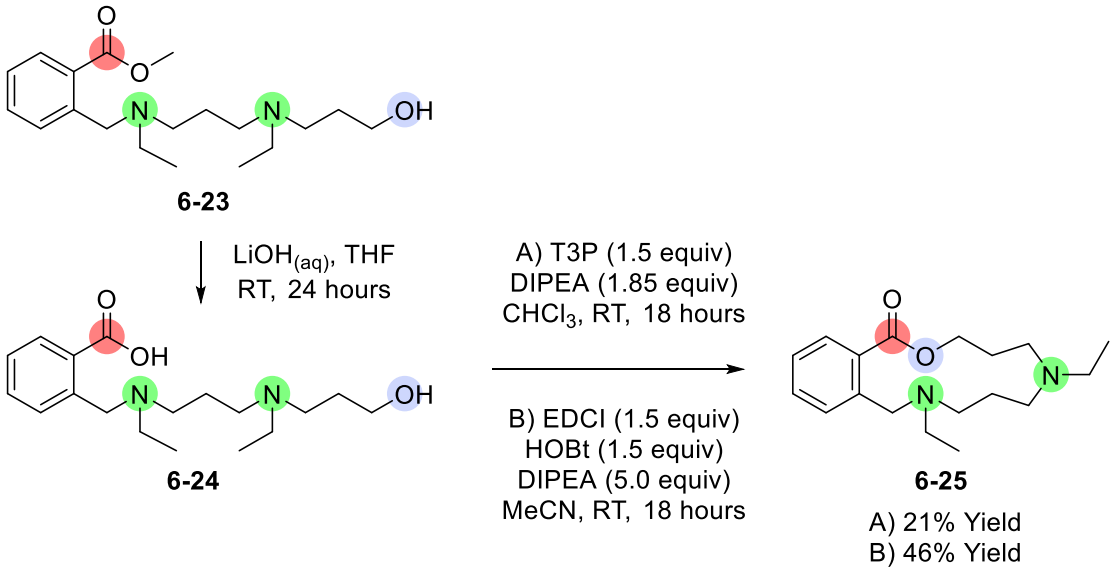
The compound **6-22** was then reacted with the electrophile **6-1** to form the linear precursor **6-23** as shown in Scheme 16. This is due to the secondary amine being more nucleophilic compared to the alcohol group and less sterically hindered compared to the tertiary amine present in the compound **6-22**.



Scheme 16 : - The *N*-alkylation reaction forming the precursor **6-23**.

Precursor **6-23** was next hydrolysed to form the carboxylic acid **6-24** and then the two different coupling conditions were used to achieve the multi-NICE reaction to form the lactone **6-25**, as shown in Scheme 17. The lactone **6-25** was synthesised in the highest yield using the coupling agents EDCI and HOBt when compared with using T3P. This demonstrates the importance of testing both coupling

conditions when developing new reaction series, to ensure the highest yielding NICE reaction is achieved.



Scheme 17 : - The Multi NICE of **6-24** via two coupling conditions forming the macrocycle **6-25**.

7.2 An alternative approach to lactam synthesis

As previously described in Section 5.1.1, research into medium-sized lactam synthesis by NICE has not been explored to the same extent as it has been for lactones. Specifically, research into the NICE of precursors composed of an aliphatic tertiary amine as the internal nucleophile and a primary amine as the terminal nucleophile had not been researched at all prior to this Master's project. Therefore, the following section will detail the synthesis of these precursors and the lactams formed using NICE.

When following a retrosynthetic approach to synthesising a linear precursor for NICE, two different approaches can be taken depending on how the precursor is deconstructed. This section will solely focus on the retrosynthetic approach **EI** + **N** as shown in Figure 12 (orange box). In this case the precursor is deconstructed into two molecules referred to as an **EI** 'building block' containing the electrophilic carbonyl group and internal nucleophile. Whereas the other molecule referred to as a **N** 'building block' contains the terminal nucleophile and a leaving group. By reacting these two molecules together the linear precursor is synthesised with all the necessary functional groups to engage in a NICE reaction.

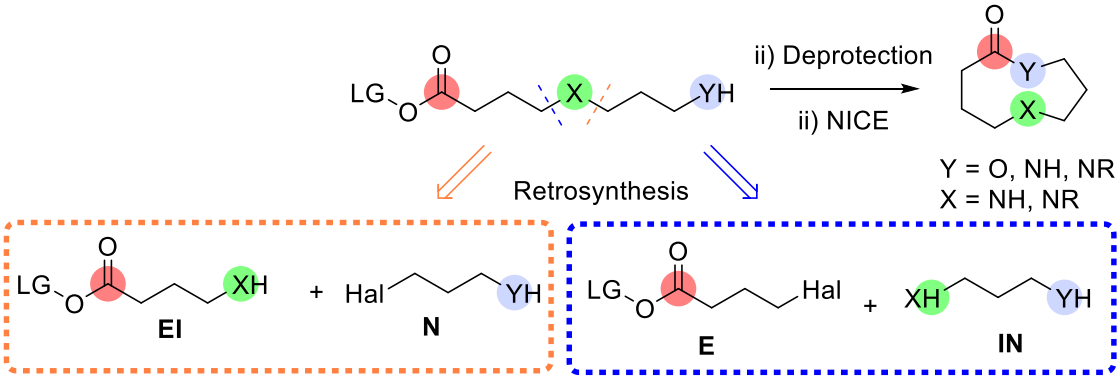
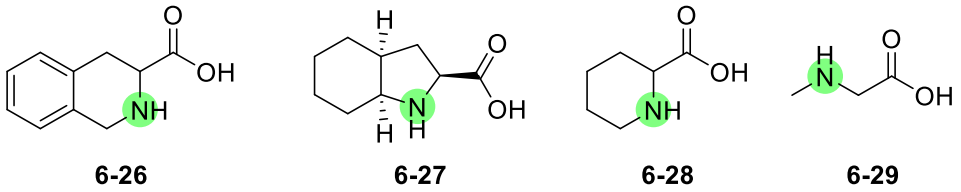


Figure 12 : - The general **EI** + **N** and **E** + **IN** retrosynthetic approach to linear precursors synthesis.

The commercially available amino acids shown in Figure 13 were all used in this work. In the case of the cyclic amino acids, these were chosen to introduce a degree of rigidity into the NICE precursor, in an effort to emulate the ability of a pyridine to restrict the conformation of the linear precursors shown in Section 5.1.1. Additionally, fused ring systems are prevalent in many pharmaceutical drugs.[28] Sarcosine **6-29**, a linear amino acid, was also used to compare the effects a cyclic fused ring system has on the NICE reaction. The same reaction sequence was performed starting from the five different amino acids shown in Figure 13. The reaction scheme employing the amino acid **6-26** will be focused on first, followed by a brief summary of the other reactions performed using the other amino acids.

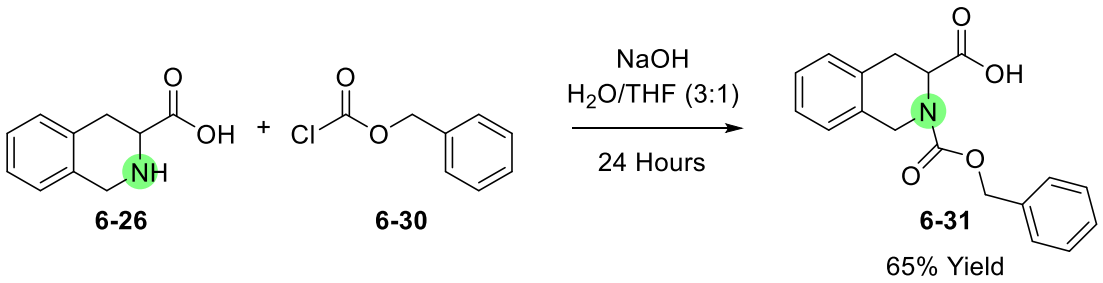


6-26 **6-27** **6-28** **6-29**

Figure 13 : - The commercially available amino acids used to introduce an aliphatic amine into the precursors.

7.2.1 Amine protection

The first reaction involved the protection of the amine group in the amino acid **6-26** using benzyl chloroformate (CbzCl) **6-30**. The reaction proceeded under basic conditions as shown in Scheme 18, forming the Cbz-protected amino acid **6-31**, in 65% yield.



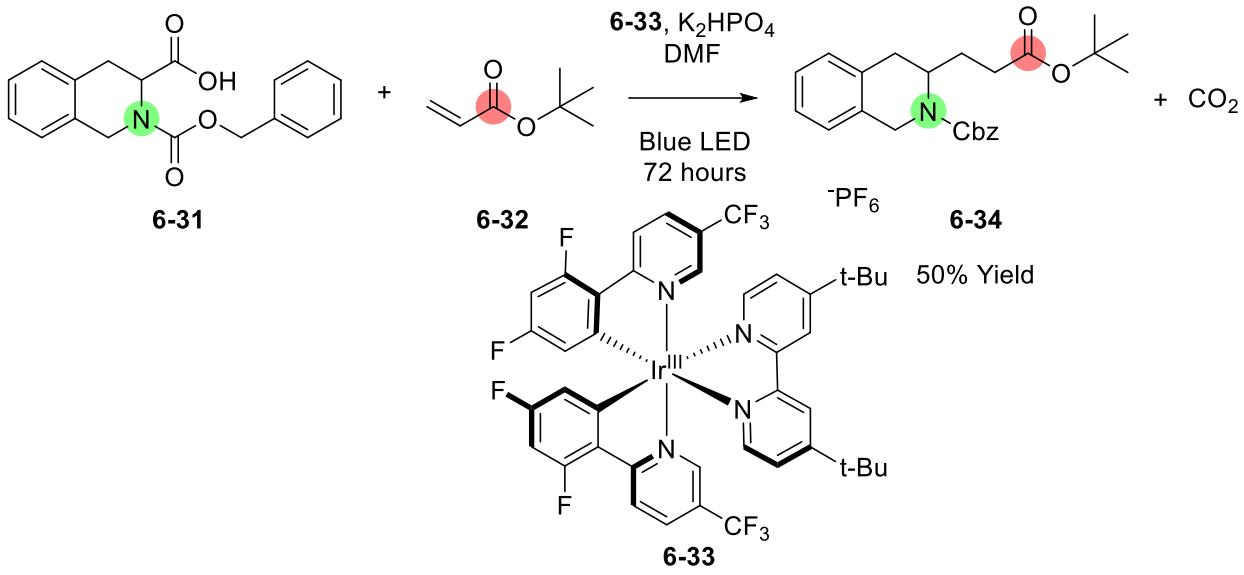
6-26 **6-30** **6-31**

65% Yield

Scheme 18 : - The amine protection of the amino acid **6-26** using benzyl chloroformate **6-30**.

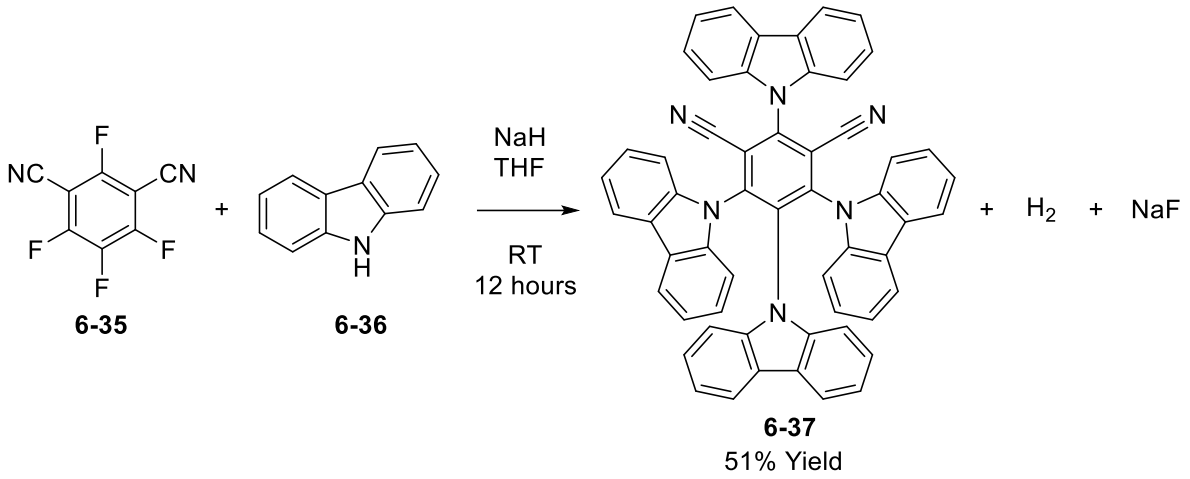
7.2.2 Photoredox 1,4-addition reaction

The Cbz-protected amino acid **6-31** was then reacted with *tert*-butyl acrylate **6-32** in a 1,4-addition reaction using the Ir (III) catalyst **6-33**. The reaction conditions were inspired by research from MacMillan and co-workers[29] to synthesise compound **6-34** in a 50% yield.



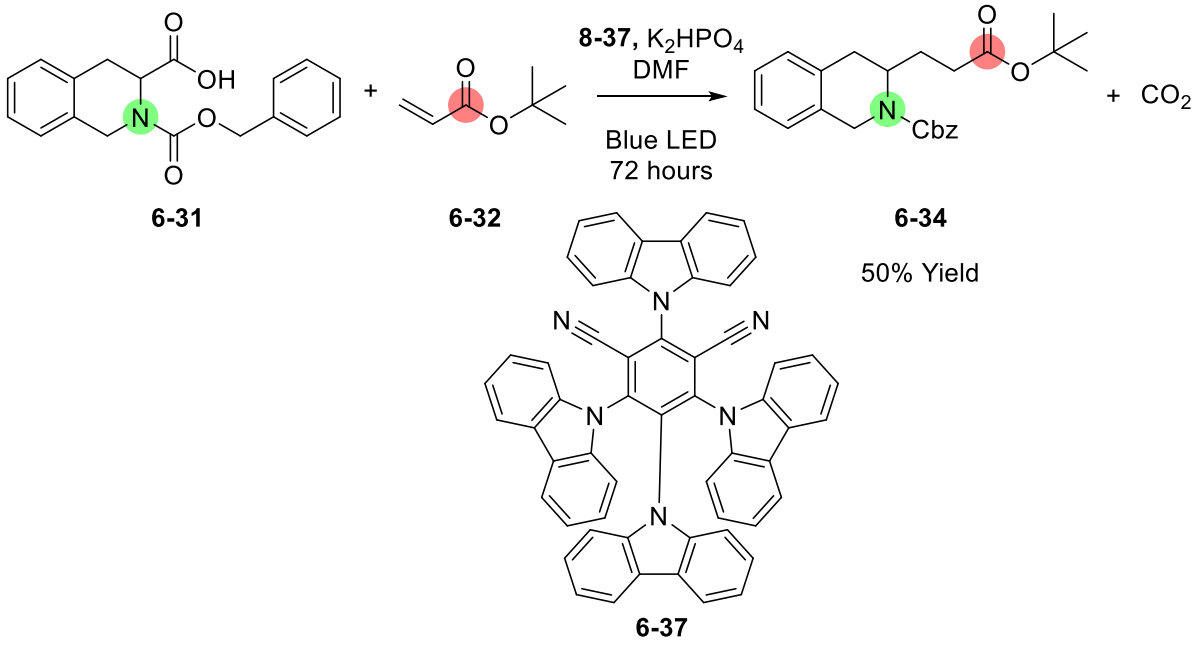
Scheme 19 : - The 1,4-addition reaction using the photocatalyst Ir [dF (CF_3) ppy]2 (dtbby) PF_6 **6-33**.

While the 1,4-addition reaction shown in Scheme 19 was high yielding, a more economical organic photocatalyst 1,2,3,5-tetrakis(carbazol-9-yl)-4,4-dicyanobenzene (4CzIPN) **6-37** was also considered to replace the expensive iridium-based catalyst **6-33**. To prepare the 4CzIPN catalyst, the following reaction sequence was performed as shown in Scheme 20.[30] Under basic conditions carbazole **6-36** attacks the electrophilic carbon atoms in 2,4,5,4-tetrafluorobenzene-1,3-dicarbonitrile **6-35** in S_NAr reactions, displacing fluoride anions forming the photo catalyst 4CzIPN **6-37** in 51% yield.



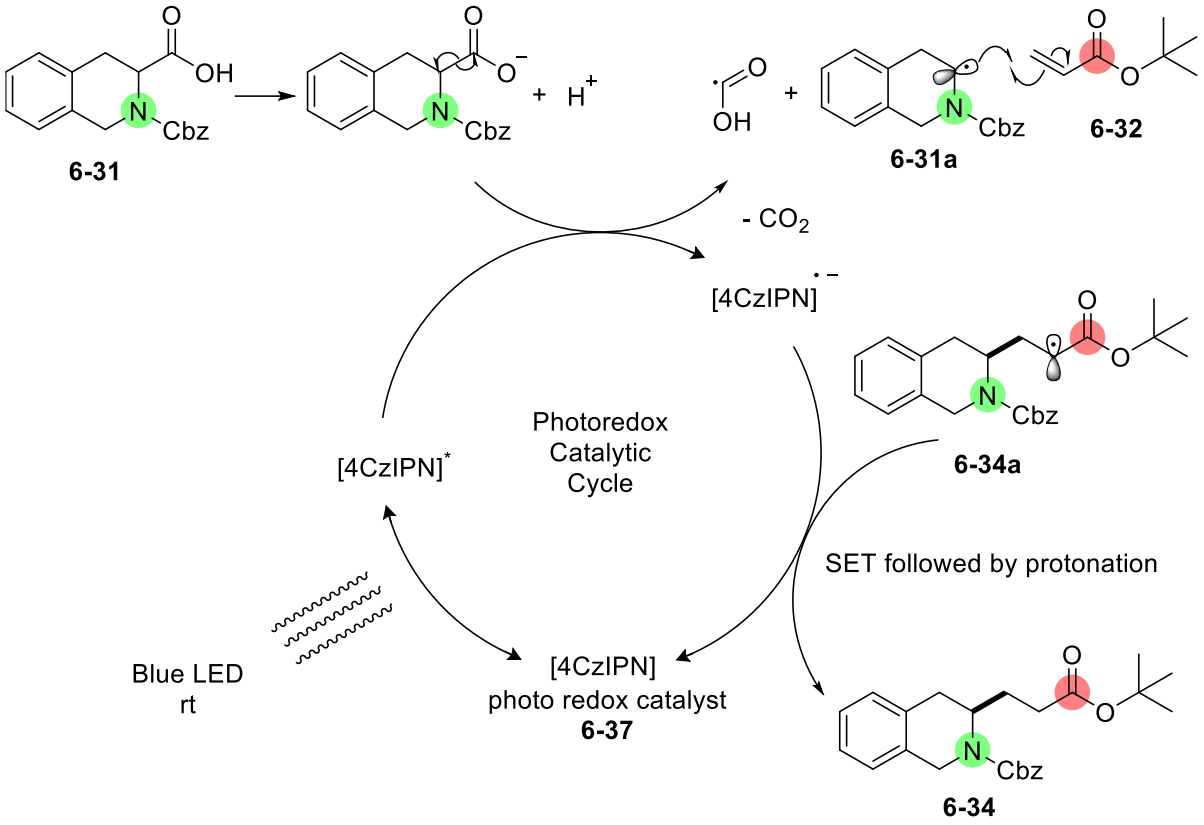
Scheme 20 : - The synthesis of the organic photocatalyst 1,2,3,5-tetrakis (carbazol-9-yl)-4,4-dicyanobenzene **6-37**.

The same photoredox 1,4-addition reaction was then repeated under the same conditions, but the iridium-based photocatalyst **6-33** was replaced with the organic photocatalyst **6-37** as shown in Scheme 21. The desired product **6-34** was formed in a 50% yield, which was exactly the same yield as the previous reaction shown in Scheme 19 using the iridium-based photocatalyst. As a result, the photocatalyst 4CzIPN **6-37** was preferred as it is markedly cheaper.



Scheme 21 : - The 1,4-addition reaction using the photocatalyst 1,2,3,5-tetrakis (carbazol-9-yl)-4,4-dicyanobenzene **6-37**.

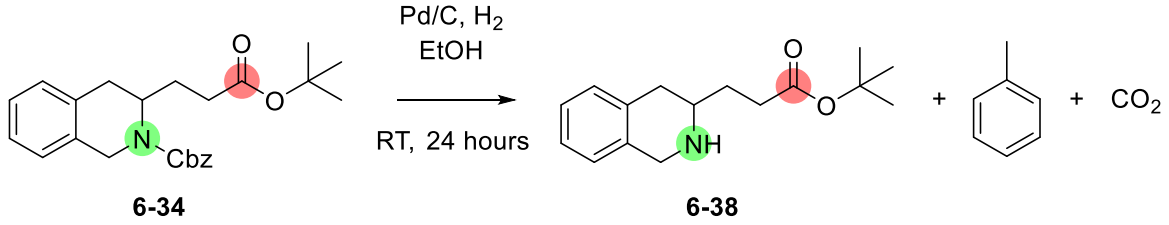
The photoredox 1,4-addition reaction takes place upon the irradiation using a blue light emitting diode (LED), causing the excitation of the photocatalyst [4CzIPN] **6-37** into its excited state 4CzIPN*. Under basic conditions the Cbz-protected amino acid forms the carboxylate ion, and when the carboxylate reacts with the photocatalyst 4CzIPN* (which in its excited state is highly oxidising) a single electron transfer (SET) reaction takes place to form a carboxyl radical, that spontaneously extrudes CO_2. As a result, the radical species **6-31a** is formed which is expected to be a nucleophilic radical and upon conjugate addition with *tertiary* butyl acrylate **6-32** a new carbon carbon bond is formed (**6-34a**). The resulting alkyl radical is then reduced by the photocatalyst species $[CzIPN]^{\cdot -}$ in a SET reaction forming the 1,4-addition product **6-34** following protonation of the resulting anion and reforming the photocatalyst **6-37** to allow the cycle to be repeated, as shown in Scheme 22.



Scheme 22 : - The photoredox catalytic cycle using the organic photocatalyst **6-37**.

7.2.3 *N*-benzyloxycarbonyl deprotection

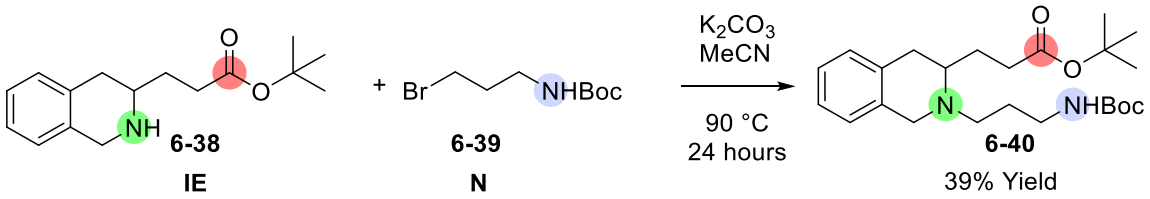
The compound **6-34** isolated from the 1,4-addition reaction was then deprotected to form the secondary amine **6-35**. This was achieved by performing a hydrogenolysis reaction on the protected amine **6-34** catalysed using palladium on carbon. This results in the formation of toluene and the carbamic acid intermediate which readily decarboxylates to yield the unprotected secondary amine **6-38** as shown in Scheme 23. At which point an **EI**-building block was synthesised containing the electrophilic carbonyl group and the internal nucleophile a secondary amine. The amine **6-38**, was not isolated but directly used in the next step of the reaction sequence.



Scheme 23 : - The hydrogenolysis of the protected amine **6-34** into the secondary amine **6-38**.

7.2.4 *N*-alkylation using 3-(Boc-amino) propyl bromide

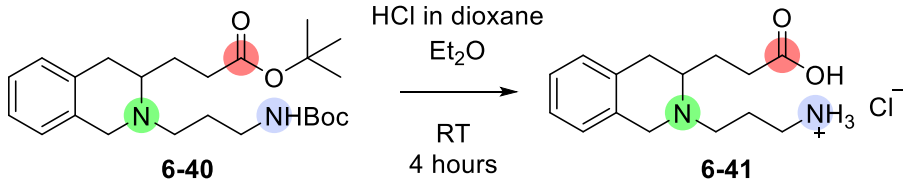
The **EI**-building block **6-38** was then reacted with the **N** building block 3-(Boc-amino) propyl bromide **6-39**, in a nucleophilic substitution S_N2 reaction forming the precursor **6-40**, as shown in Scheme 24.



Scheme 24 : - *N*-alkylation reaction between the secondary amine **6-38** and the alkyl halide **6-39** forming the product **6-40**.

7.2.5 Dual *tert*-butyoxycarbonyl deprotection

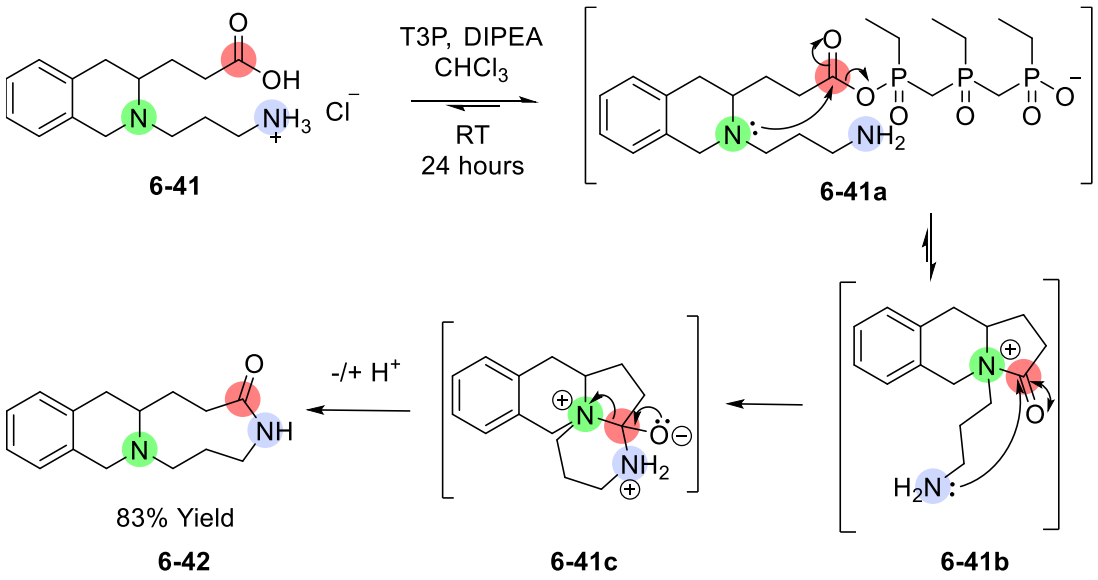
The simultaneous cleavage of the carboxylic acid and amine protecting groups was achieved under anhydrous acidic conditions using 4N HCl in dioxane, forming the compound **6-41**. The final precursor **6-41** shown in Scheme 25 was not isolated but was used directly in a NICE reaction.



Scheme 25 : - The simultaneous deprotection of a *tert*-butyl protected carboxylic acid and *tert*-butyl carbamate protected amine.

7.2.6 Cascade ring expansion

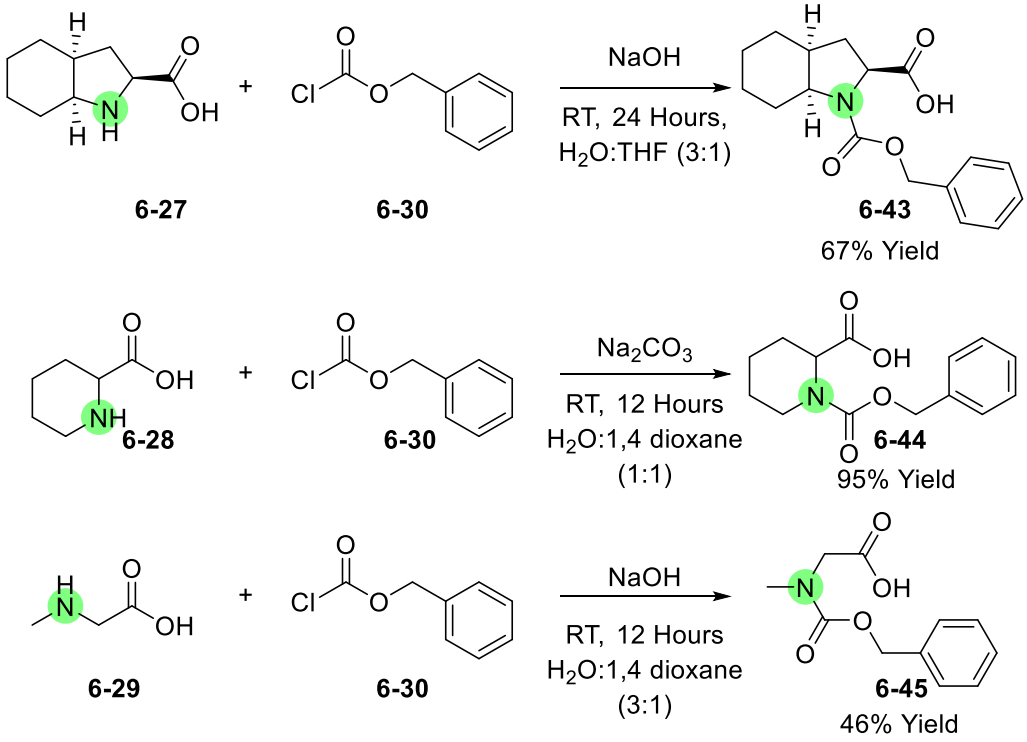
A NICE reaction was then performed using precursor **6-41** forming the lactam **6-42**, as shown in Scheme 26. The decision to use the coupling agent T3P and not EDCI and HOBt was based upon the previous research described in Section 7.0. The first step in the NICE reaction is the activation of the carbonyl group in precursor **6-41** using the coupling agent T3P, forming the intermediate **6-41a**. At this point, it is assumed that the tetrahydroisoquinoline amine acts as an internal nucleophile, attacking the activated carbonyl group. This results in a cascade sequence via the cationic 5-membered intermediate **6-41b**. The carbonyl group is then attacked by the primary amine and the reaction proceeds via the zwitterionic fused cyclic intermediate **6-41c**, before forming the 9 membered lactam **6-42**, giving an impressive 83% yield.



Scheme 26 : - The NICE reaction mechanism from the linear precursor **6-41** forming the medium-sized lactam **6-42**.

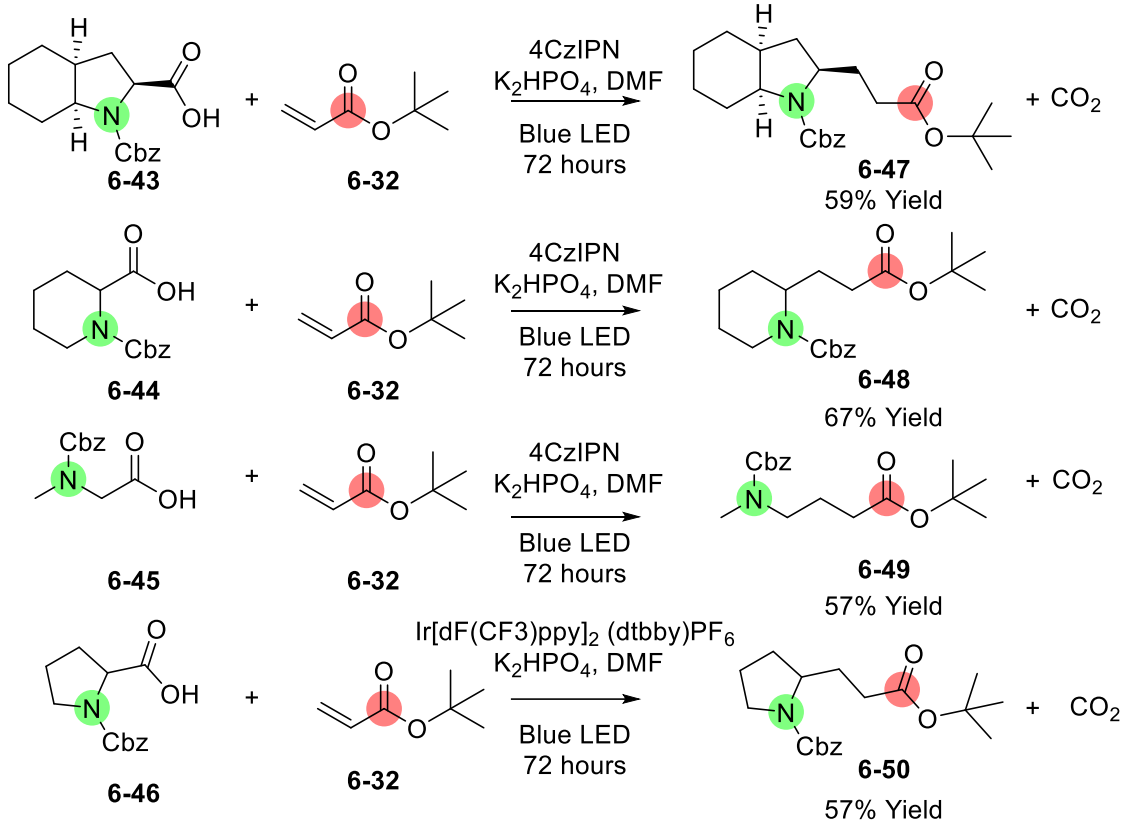
7.2.7 Repeating the reaction sequence using different amino acids

The same reaction sequence that resulted in the synthesis of lactam **6-42** was repeated using amino acids **6-27**, **6-28** and **6-29** previously shown in Figure 13. The first step required protecting the amine group using CbzCl as shown in Scheme 27.



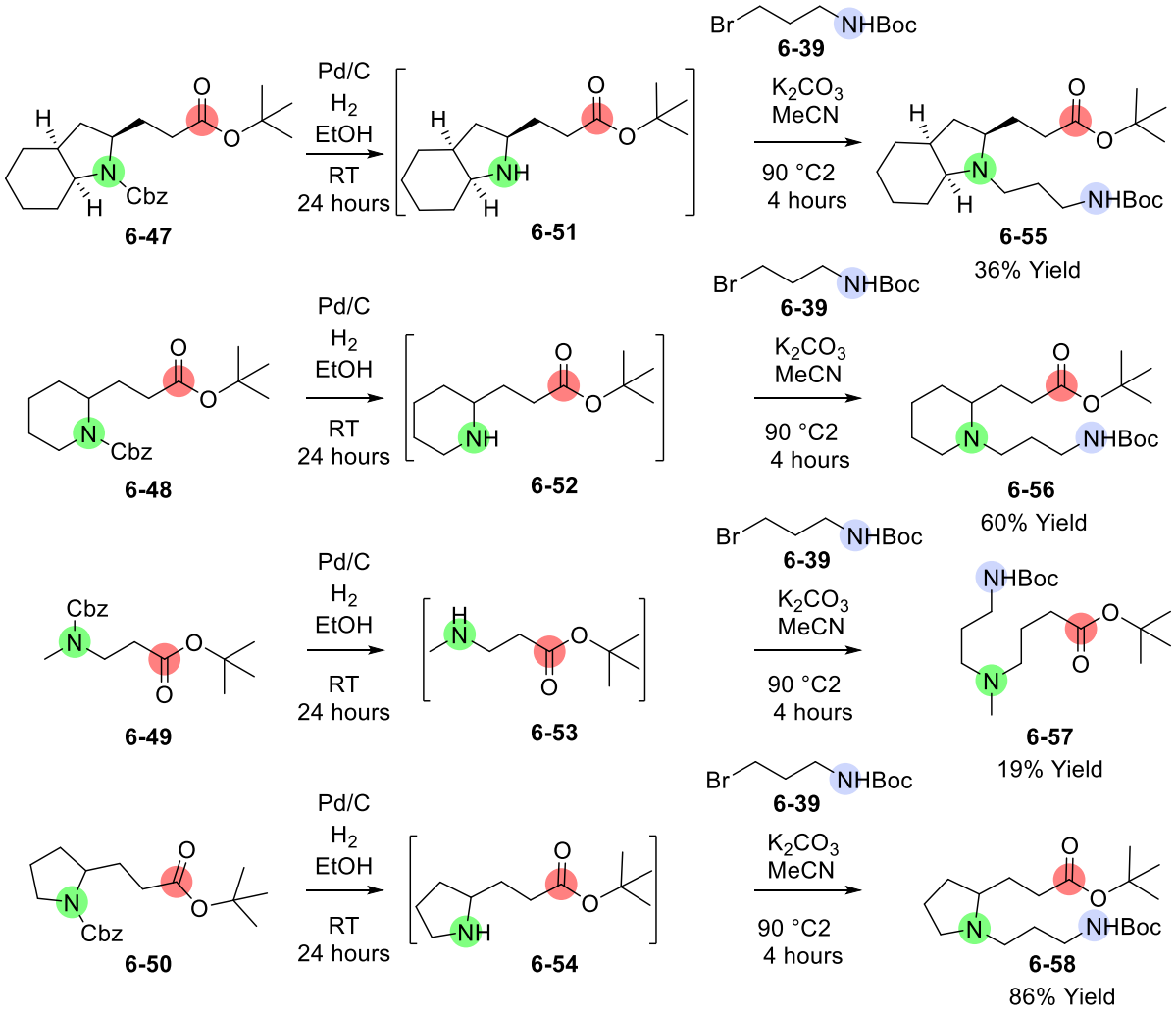
Scheme 27 : - The benzyl chloroformate protection of the amines **6-27**, **6-28** and **6-29**.

The Cbz-protected amines **6-43**, **6-44**, **6-45** and the commercially available Cbz-protected amine **6-46** were used in the next step of the reaction sequence. This involved a photo redox 1,4-addition reaction with *tert*-butyl acrylate **6-32** as shown in Scheme 28.



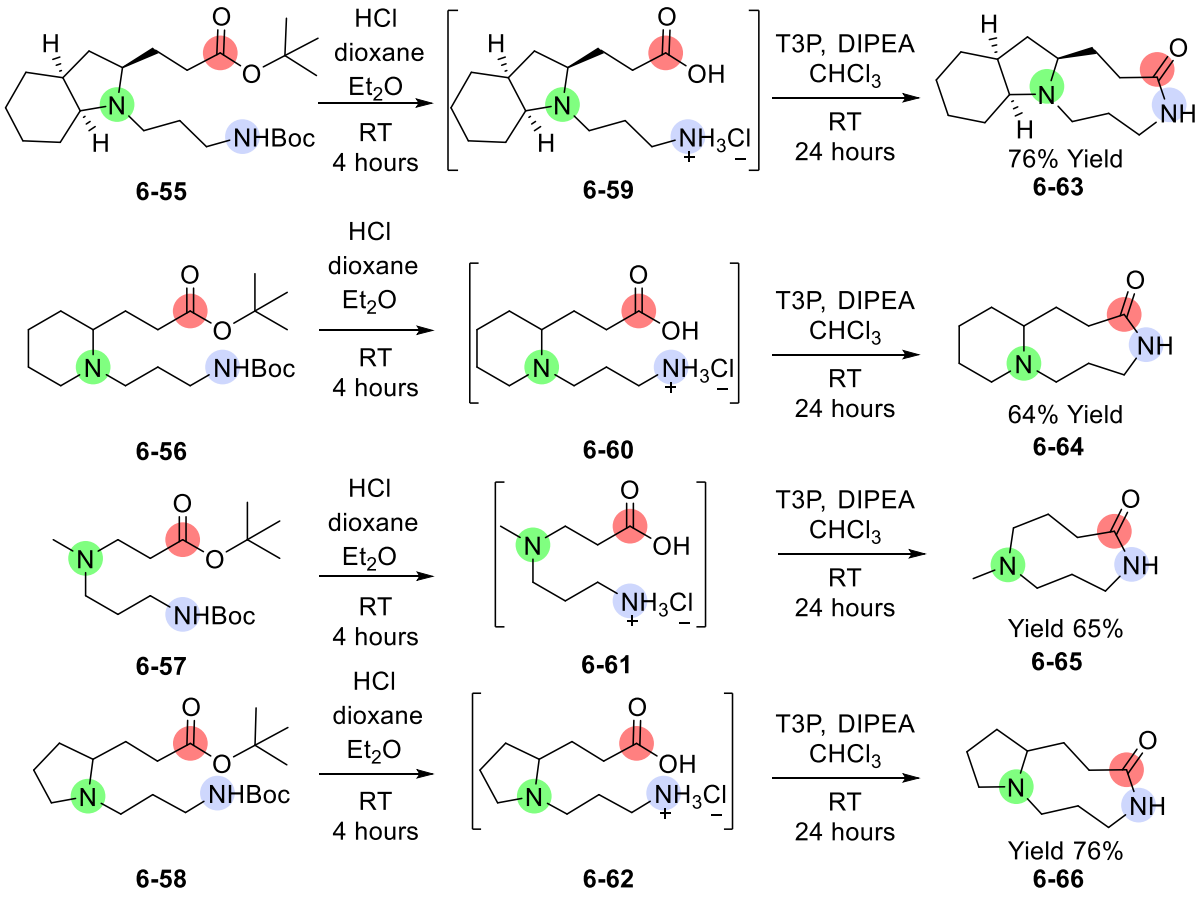
Scheme 28 : - The 1,4-addition reaction between the protected amines **6-43, 6-44, 6-45** and **6-46** and *tert*-butyl acrylate **6-32**.

The products isolated from the photoredox 1,4-additions reactions **6-47**, **6-48**, **6-49** and **6-50** were then deprotected in a hydrogenolysis reactions forming the **EI**-building blocks **6-51**, **6-52**, **6-53** and **6-54**, respectfully. The **EI**-building blocks weren't isolated but directly reacted with the **N**-building block **6-39** forming the linear precursors **6-55**, **6-56**, **6-57** and **6-58** as shown in Scheme 29.



Scheme 29 : - The hydrogenolysis of the compounds **6-47**, **6-48**, **6-49**, **6-50** forming the unprotected amines followed by an *N*-alkylation reaction with the **N**-building block **6-39**.

The *tert*-butyl ester and Boc amide groups, were simultaneously cleaved from the linear precursors **6-55**, **6-56**, **6-57** and **6-58** under anhydrous acidic conditions using 4N HCl in dioxane and diethyl ether. The intermediates **6-59**, **6-60**, **6-61** and **6-62** formed weren't isolated but used directly in the NICE reactions to form the lactams **6-63**, **6-64**, **6-65** and **6-66**, respectfully shown in Scheme 30.



Scheme 30 : - The simultaneous deprotection of the *tert*-butyl protected ester and Boc amide groups, followed by the NICE forming the lactams **6-63**, **6-64**, **6-65** and **6-66**.

7.2.8 Comparing the lactams synthesised by NICE

When comparing the five different lactams synthesised by NICE the consistent trend is the excellent yield achieved by all the lactams shown in Figure 14. The highest yielding reaction afforded lactam **6-42** in an exceptional 83% yield. Notably, this is the highest yielding NICE reaction formed from a linear precursor with a primary amine acting as the terminal nucleophile performed to date, when compared with the lactams shown in Figure 14 and those previously produced via NICE.[19] The lactams **6-42**, **6-63** and **6-66** were formed in higher yield compared to the lactam **6-65**, potentially indicating that cyclic amines as the internal nucleophile favour the NICE reaction, compared to substrates based on linear amines.

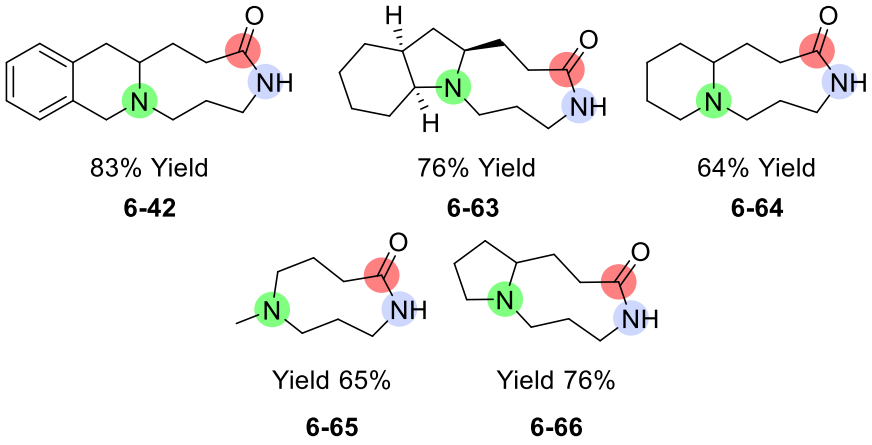
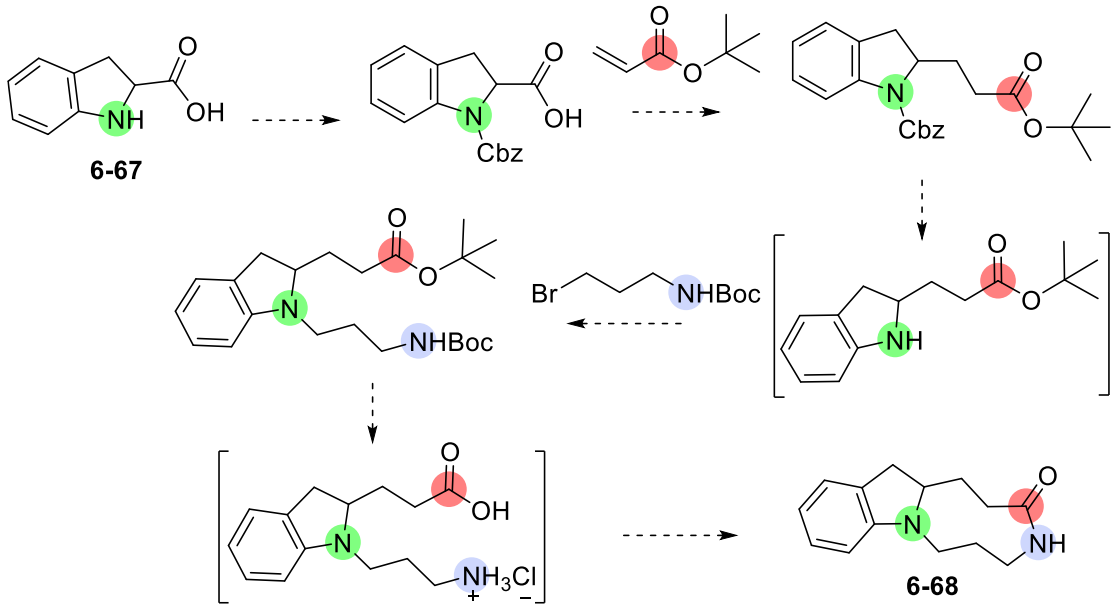


Figure 14 : - The lactams synthesised by the same reaction sequence detailed in Section 7.2.

7.2.9 Future research into the synthesis of lactams by NICE

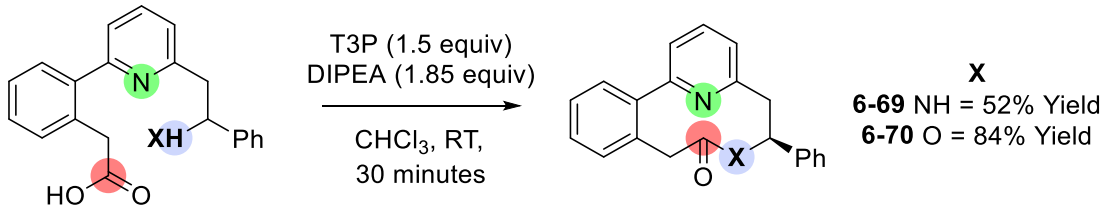
Based on the results shown in Figure 14, a proposed system that could be used to synthesise lactam **6-68** from the commercially available aniline **6-67** is summarised in Scheme 31. This starting material was designed to exhibit a benzene ring fused to the pyrrolidine ring, based on the high-yielding NICE reactions that formed the lactams **6-42** and **6-66**. This system has not been tested to date and would be an interesting example for future work. The use of an aniline as an internal nucleophile will most likely hinder the NICE reaction due to the resonance stability of the amine making it less basic compared to aliphatic tertiary amine. Yet it would be an interesting example that could be compared to the other lactams shown in Figure 14 due to the structural similarities of the fused cyclic ring systems.



Scheme 31 : - The reaction scheme for that could be followed to perform future research into synthesising the lactam **6-68**.

7.3 An alternative approach to lactone synthesis

Research was then undertaken to synthesise lactones analogous to the lactams shown in Section 7.2. The lack of research into the NICE of precursors with a primary amine as the terminal nucleophile, makes it challenging to compare analogous lactones and lactams. The only published example is shown in Scheme 32 in which the lactam **6-69** was formed in a significantly lower yield compared to the analogous lactone **6-70**. This is only one example but does shows significant promise in synthesising the targeted lactones in high yield.[19]



Scheme 32 : - The synthesis of an analogous lactam and lactone.

7.3.1 *N*-alkylation with 3-bromopropan-1-ol

The **EI**-building blocks shown in Figure 15, previously synthesised by the reaction sequence shown in Section 7.2, were used to synthesise the target lactones. The reaction sequence using the **EI**-building block **6-38** will be focused on, but the same reaction sequence was followed for all the different **EI**-building blocks shown in Figure 13.

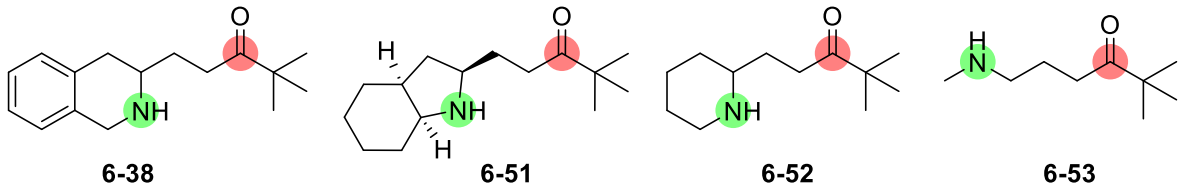
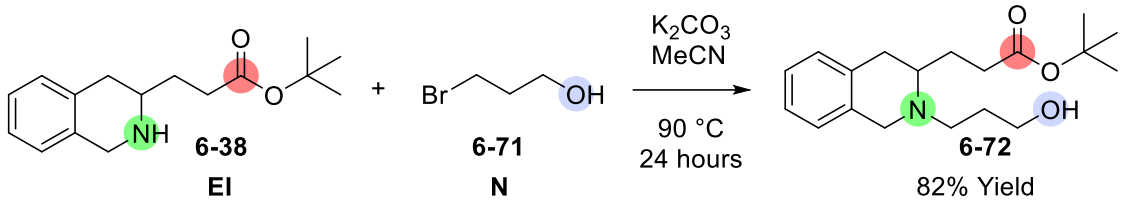


Figure 15 *:* - The **EI**-building block synthesised from the different amino acids shown in Figure 13.

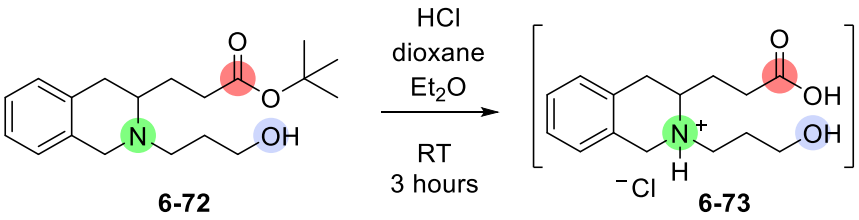
A nucleophilic substitution S_N2 reaction was performed between the **EI**-building block **6-38** and the **N**-building block, bromopropan-1-ol **6-71**. The linear precursor **6-72** crucial exhibiting an alcohol group used as the terminal nucleophile enabling the synthesis of a lactone upon NICE.



Scheme 33 : - The *N*-alkylation reaction between the **EI**-building block **6-38** and the **N**-building block **6-71**.

7.3.2 *tert*-Butyl protecting group cleavage

The cleavage of the *tert*-butyl protecting group was achieved under anhydrous acidic conditions using 4N HCl in dioxane and diethyl ether. As a result, the carboxylic acid group was deprotected forming the compound **6-73** as shown in Scheme 34. The carboxylic acid **6-73** was not isolated but transferred straight into the NICE reaction.

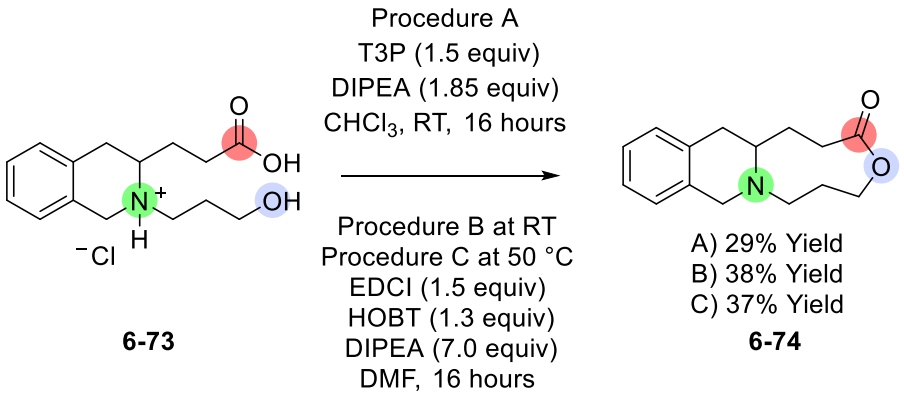


6-72 **6-73**

Scheme 34 : - The cleavage of the tert-butyl protecting group forming the precursor **6-73**.

7.3.3 The NICE reaction to form the lactone **6-74**

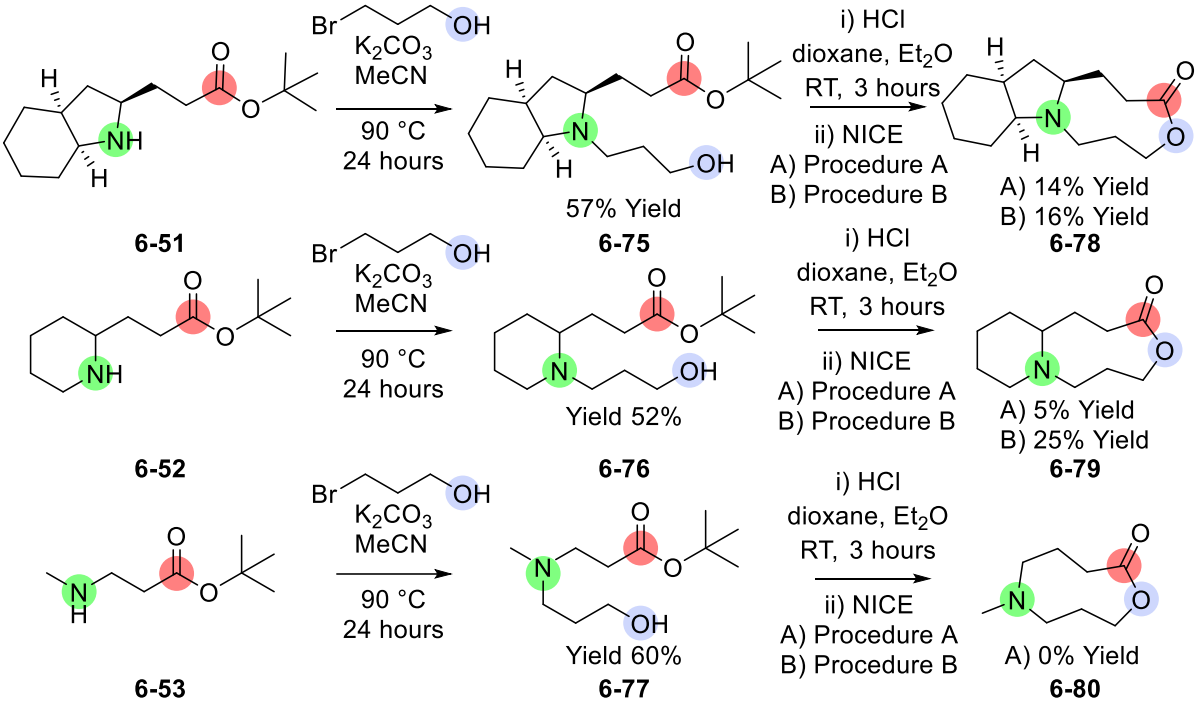
The NICE reaction of the linear precursor **6-73** was performed initially by following the same reaction conditions used to synthesise the lactams shown in Figure 14, referred to as procedure A. The lactone **6-74** was synthesised, but only in a 29% yield, which is significantly lower than the analogous lactam **6-42** that proceeded in 83% yield. As a result, different NICE conditions were tested to determine if the reaction yield could be improved. Subsequently the alternative coupling agents EDCI and HOBt were used to synthesise the lactone **6-74** in procedure B. This proved to be marginally beneficial, increasing the yield of lactone **6-74** to 38%. The temperature of the NICE was then increased from room temperature to 50 °C as shown in procedure C, which resulted in no increase in yield (37%). However, the yield of lactone **6-74** still remained significantly lower than the analogous lactam **6-42**. No more optimisation was attempted in this study, and further research is required to determine if the yield of the lactone **6-74** can be increased further.



6-73 **6-74**

Scheme 35 : - The NICE of the precursor **6-73** to synthesise the lactone **6-74**.

The same reaction sequence detailed in Section 7.3 was repeated using the different **EI**-building blocks **6-51**, **6-52** and **6-53**. As shown in Scheme 36 this involved different *N*-alkylation reactions between the **EI**-building blocks and the **N**-building block 3-bromopropan-1-ol **6-71** forming the compounds **6-75**, **6-76** and **6-77**. The cleavage of the *tert*-butyl protecting group was achieved under anhydrous acidic conditions using 4N HCl in dioxane and diethyl ether before performing the NICE reaction forming the lactones shown in Scheme 36.

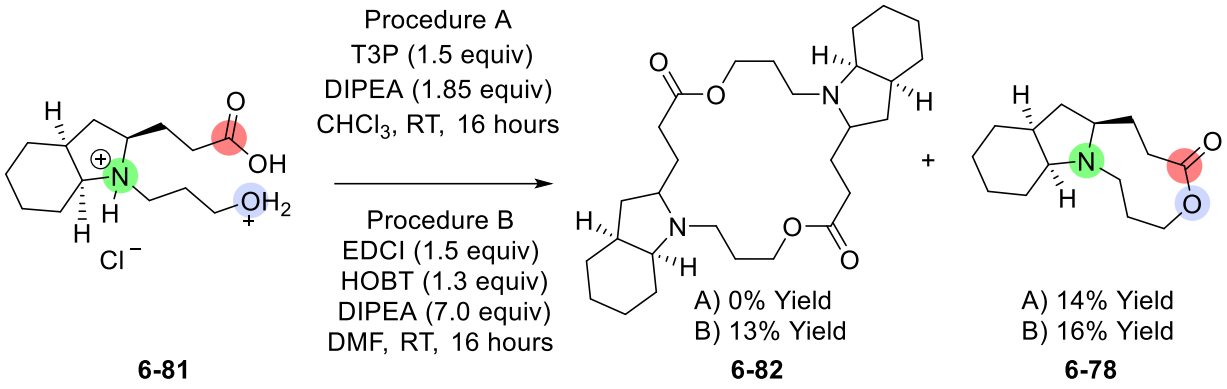


Procedure A : T3P (1.5 equiv), DIPEA (1.85 equiv), $CHCl_3$, RT, 16 hours
Procedure B : EDCI (1.5 equiv), HOBT (1.3 equiv), DIPEA (7.0 equiv), DMF, RT, 16 hours

Scheme 36 : - The *N*-alkylation of the **EI**-building blocks **6-57**, **6-58** and **6-60** with the **N**-building block **6-73**, followed by *tert*-butyl deprotection and NICE by two different procedures.

The NICE reaction conditions that proved so effective in synthesising the lactams described in Section 7.2 were used to synthesise the lactones shown in Scheme 36, referred to as procedure A. All the lactones however were formed in a considerably lower yield compared to their analogous lactams. The NICE of the linear precursor **6-77** was unsuccessful unable to observe the formation of the lactone **6-80** via thin layer chromatography nor isolated after flash column chromatography.

The NICE procedure B was also used to synthesise the lactones **6-78** and **6-79**, and in both instances the yield did increase compared to procedure A, albeit by a relatively small degree. The change in procedure caused the lactone **6-79** to achieve a 25% yield, which was the largest increase. A moderate increase in yield when compared to the 5% yield achieved using procedure A. Whereas comparing procedure A and B when synthesising the lactones **6-74** and **6-78** a minor increase in yield was achieved. When attempting the synthesis of lactone **6-78** by following procedure B, the formation of dimer **6-82** was also observed, highlighting the relative inefficiency of the NICE reaction in this case, given that NICE is designed to avoid intermolecular coupling. This reaction was also repeated at increased dilution in an attempt to reduce the competing intramolecular dimerization, yet lactone **6-78** was formed in similar yield to the previous NICE under typical conditions shown in Scheme 37.



Scheme 37 : - The competing intramolecular NICE and intermolecular dimerisation of **6-81**.

In summary different **EI**-building blocks were developed to introduce a carbonyl electrophilic group and an alkyl tertiary amine internal nucleophile into a linear precursor. Different **N**-building blocks could then be used to introduce either an alcohol or a primary amine as the terminal nucleophile. Therefore, an **EI** + **N** retrosynthetic approach was used to synthesise linear precursors and upon NICE analogous lactones and lactams were then formed successfully, as shown in Figure 16. By following the same NICE reaction conditions, lactams were synthesised in excellent yield with the lactam **6-42** achieving the highest yield at 83%. Alternative NICE reaction conditions were tested in an effort to improve the yield of the lactones, which resulted in a marginal improvement in yields. Nevertheless, the research undertaken highlighted an **EI** + **N** retrosynthetic approach to synthesising linear precursors, that upon NICE formed novel analogous lactones and lactams. Future research should focus on synthesising the lactone **6-83**, to complete the trend in synthesising analogous lactams and lactones.

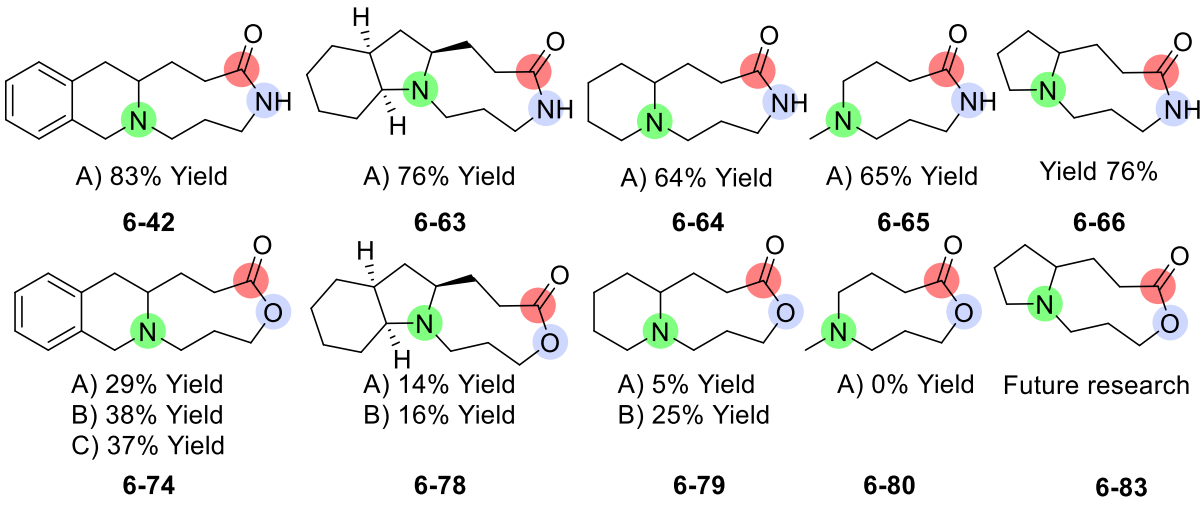


Figure 16 : - Comparing analogous lactones and lactams synthesised following the same NICE reaction conditions.

7.4 The IN + E approach to synthesising precursors

A major challenge when synthesising medium-sized rings by NICE is how to efficiently synthesise the linear precursor. When following a retrosynthetic approach to synthesising linear precursors for NICE, the disconnection of the precursor can be performed in different ways, depending on what key moieties are separated or combined into molecules. For example, the precursors that formed the lactones and lactams previously shown in Sections 7.2 and 7.3 were deconstructed as shown in Figure 17.

The terminal nucleophile was isolated into one molecule **6-39** or **6-71** referred to as a **N**-building block. The electrophilic carbonyl group and the internal nucleophile a secondary amine, were combined into molecule **6-38**, referred to as an **EI**-building block. The only major drawback to this **EI** + **N** approach is the number of reaction steps that are required to synthesise the **EI**-building block, in this case **6-38**.

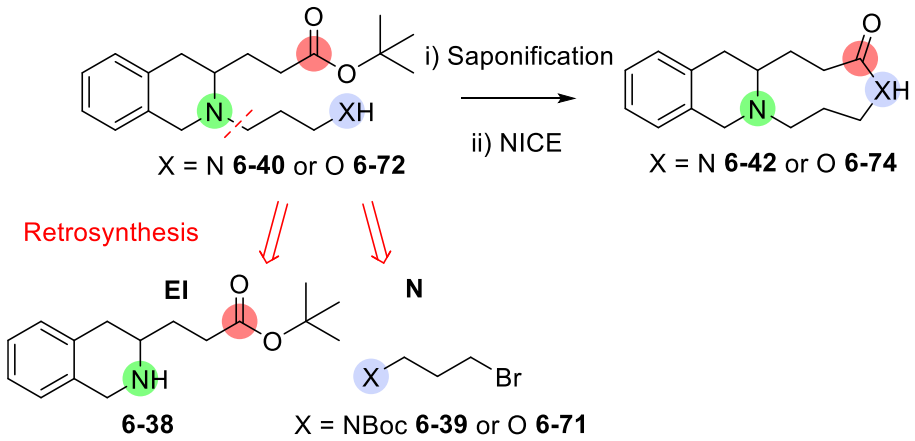
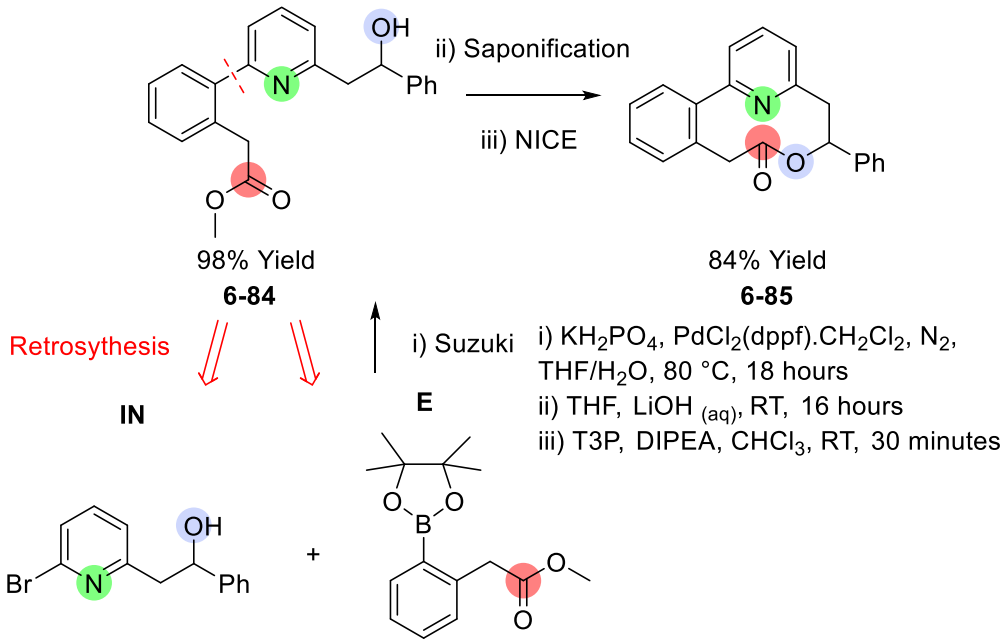


Figure 17 : - The **EI** + **N** retrosynthesis approach forming the precursors **6-40** and **6-72**.

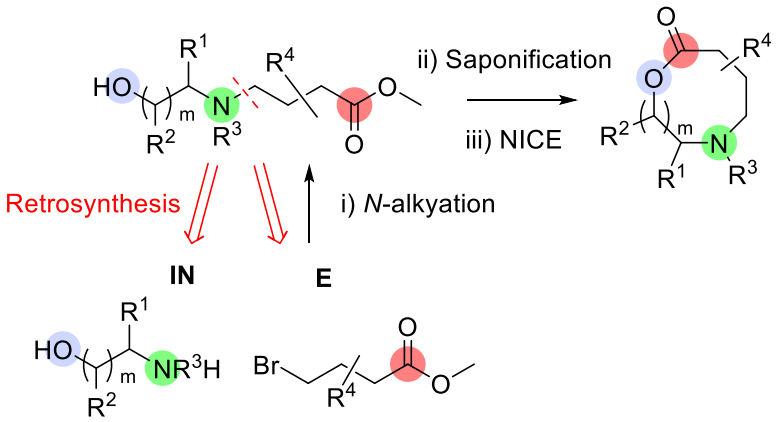
An alternative retrosynthetic approach to synthesising the NICE linear precursor is shown in Scheme 38. In this approach, the internal and terminal nucleophilic groups are both present in a single molecule referred to as an **IN**-building block. The electrophilic carbonyl group is isolated in another molecule referred to as an **E**-building block. The precursor **6-84** was synthesised by reacting the two building blocks together in a Suzuki coupling reaction. The ester **6-84** was then hydrolysed followed by the NICE, forming the lactone **6-85**, in an efficient three-step reaction sequence.



Scheme 38 : - The reaction sequence and **IN** + **E** retrosynthetic approach to synthesising the precursor **6-84**

7.4.1 Different IN-building blocks

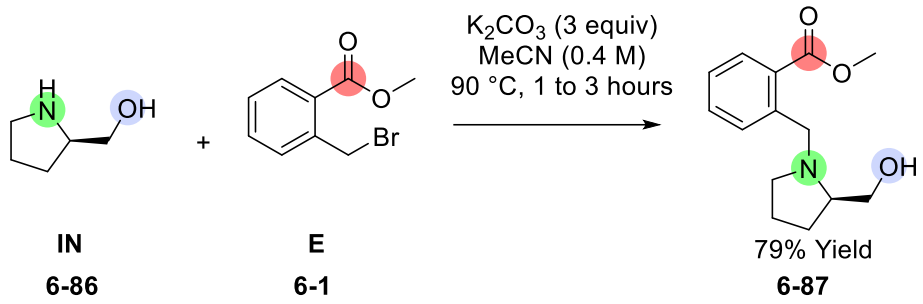
The research detailed in this section describes an alternative **IN** + **E** retrosynthetic approach for the synthesis of linear precursors, as summarised in Scheme 39.



Scheme 39 : - The general **IN** + **E** retrosynthetic approach to synthesising a precursor for NICE.

A diverse array of commercially available amino alcohols can be used as **IN**-building blocks enabling a variety of medium-sized rings ranging in size and functionality to be synthesised. Methyl 2-(bromomethyl) benzoate was initially used as the **E**-building block due to the success previously shown in Scheme 38 that utilised a *sp*2 rich **E**-building block.

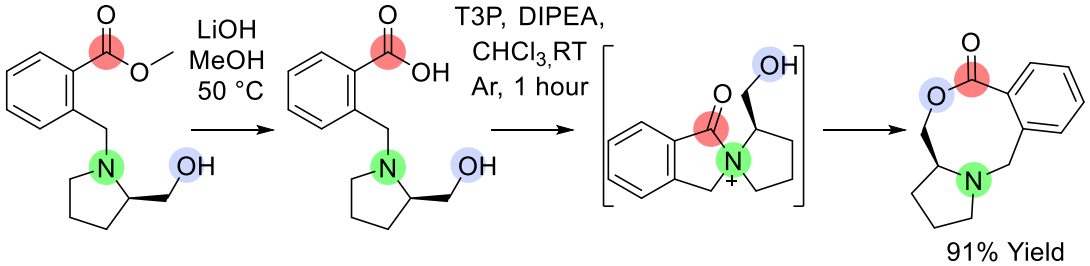
The amino alcohol **6-86** was the first compound used as an **IN**-building block reacted with the **E**-building block **6-1** in an S_N2, *N*-alkylation reaction. The linear precursor **6-87** was formed in 79% yield as shown in Scheme 40.



IN **6-86** **E** **6-1** **6-87**

Scheme 40 : - The *N*-alkylation reaction between the **IN**-building block **6-86** and the **E**-building block **6-1**.

The ester **6-87** was then hydrolysed into the carboxylic acid **6-88** and taken directly onto the NICE reaction without purification, which afforded the desired lactone **6-89** in an excellent 91% yield over the 2-step sequence, as shown in Scheme 41.



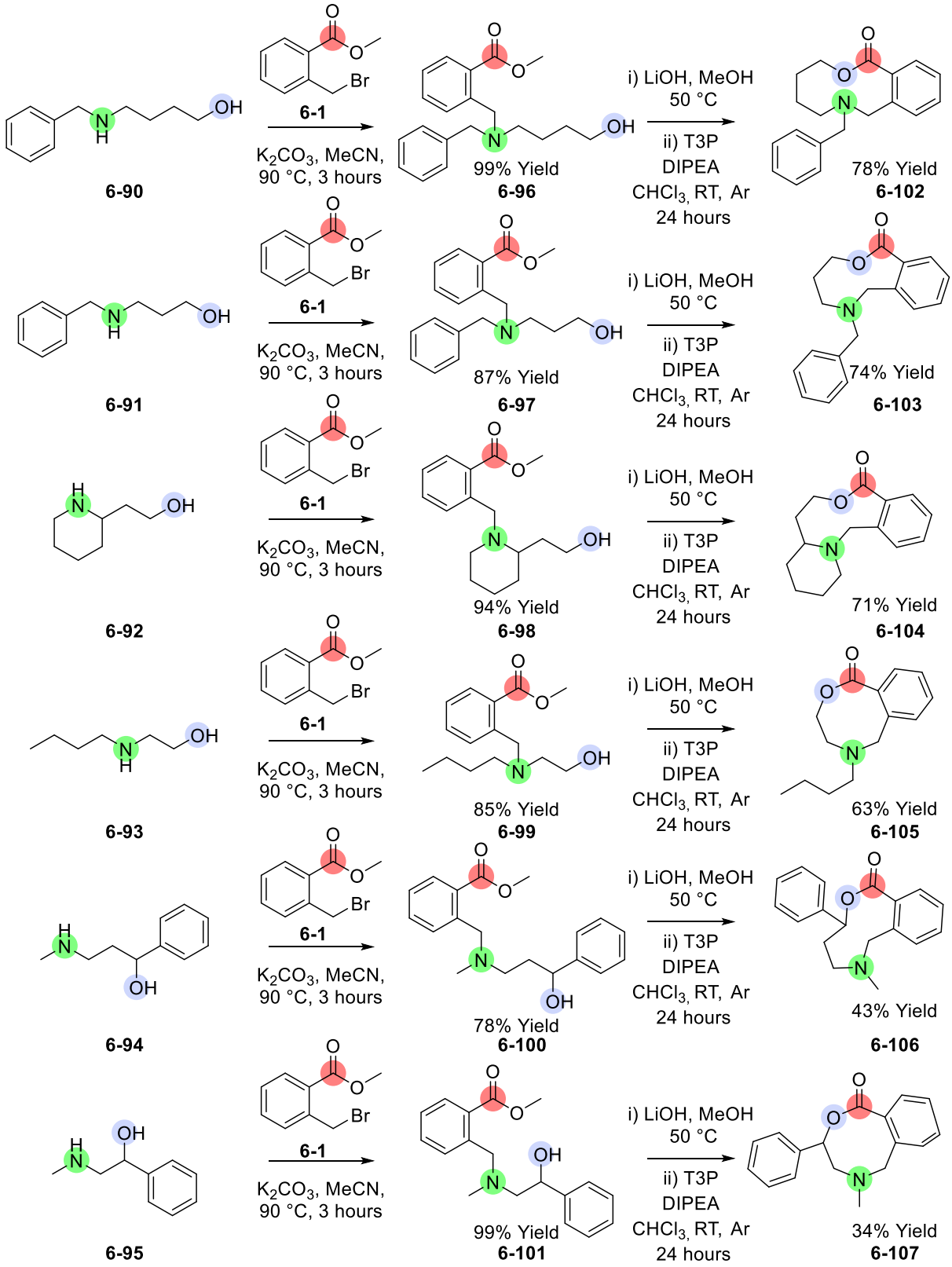
6-87 **6-88** **6-88b** **6-89**

Scheme 41 : - The ester hydrolysis of the compound **6-87** followed by the NICE of the compound **5-88**, forming the lactone **6-89**.

With a simple but effective route in place, a range of commercially available amino alcohols were then tested instead of the **IN**-building block **6-86** in the same three-step reaction sequence shown in Scheme 39. The abundance of commercially available amino alcohols that can be used as **IN**-building blocks a variety of medium-sized rings were synthesised as shown in Scheme 42. The amino alcohols were chosen to have dual reactivity at opposite ends of the molecule, with the amine expected to be much more nucleophilic compared to the alcohol. As a result, the more reactive amine takes part in the S_N2 nucleophilic substitution reaction with the **E**-building block, synthesising the linear precursor with an alcohol as the terminal nucleophile and subsequently upon NICE a lactone is formed.

When comparing the different lactones shown in Scheme 42 a few trends can be observed. For example, the lowest yielding lactones **6-106** and **6-107** were both from a linear precursor **6-94** and **6-95**, respectfully exhibiting a secondary alcohol and an amine substituted with a methyl group. Whereas the other lactones that achieved a higher yield were all synthesised from precursors with a primary alcohol group as the terminal nucleophile and larger alkyl substituents on the amine group. Unsurprisingly when comparing the analogous 8 and 9-membered lactones **6-106** and **6-107**, respectfully the more strained 8-membered lactone **6-107** achieved a lower yield compared to with

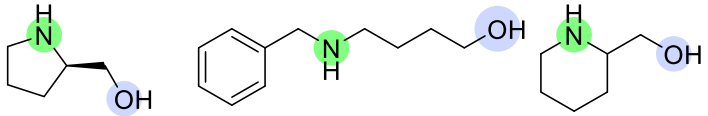
the 9-member lactone **6-106**. This trend was also observed when comparing the analogous 9 and 10-memberd lactone **6-102** and **6-103**, respectfully.



Scheme 42 : - The *N*-alkylation reaction between different **IN**-building blocks and the **E**-building block **6-1**, followed by the ester hydrolysis and NICE to form a range of structurally diverse lactones.

7.4.2 Different E-building blocks

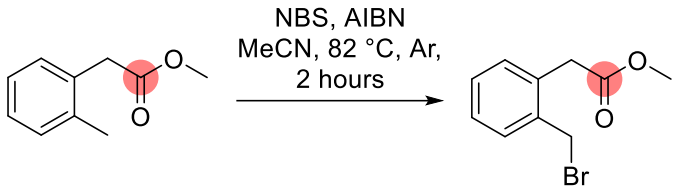
Developing different **E**-building blocks was the next logical progression for this research. The **IN**-building blocks chosen to react with the different **E**-building blocks developed, are shown in Figure 18. These **IN**-building blocks were chosen as they are significantly different in structure and worked well when compared to the other amino alcohols in the reaction sequences summarised in Scheme 39.



6-86 **6-90** **6-92**

Figure 18 : - The **IN**-building blocks chosen to react with different **E**-building blocks.

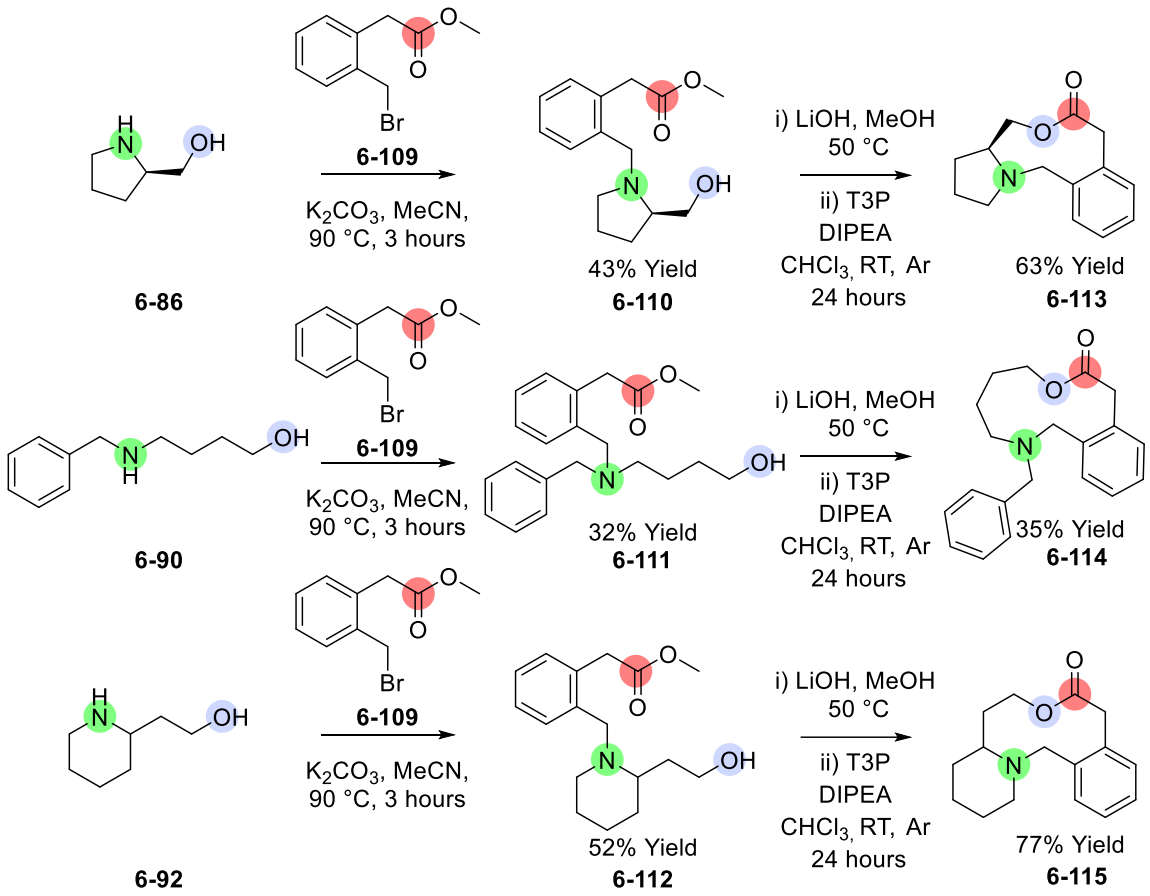
The first **E**-building block developed was methyl 2-(2-(bromomethyl)phenyl)acetate **6-109** synthesised by a Wohl-Ziegler bromination reaction[31] shown Scheme 43. This involves the benzylic bromination of methyl 2-(*o*-tolyl) acetate **6-108** using *N*-bromosuccinimide (NBS), which is used as a source of bromine radicals and azobisisobutyronitrile (AIBN) to initiate the reaction by forming radicals upon thermal homolysis.



6-108 **E** 28% Yield **6-109**

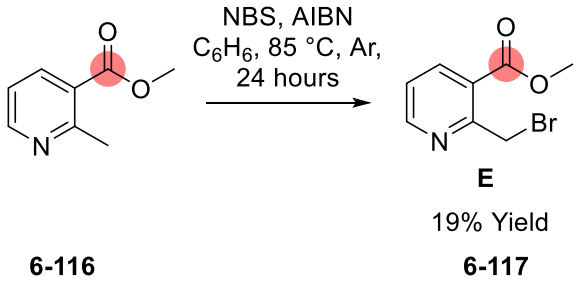
Scheme 43 : - The Wohl-Ziegler bromination of methyl 2-(o-tolyl) acetate **6-108**.

By following the reaction sequence shown in Scheme 39 starting **IN**-building blocks **6-86**, **6-90** and **6-92** and the **E**-building block **6-109**, the lactones shown in Scheme 44 were synthesised. Methyl 2-(2-(bromomethyl) phenyl) acetate **6-109** has an additional carbon atom separating the benzene ring from the carbonyl group, compared to the previous **E**-building block **6-1**. As a result, the lactones **6-113**, **6-114** and **6-115** are larger in ring size by an additional carbon atom compared to the lactones **6-89**, **6-102** and **6-104**.



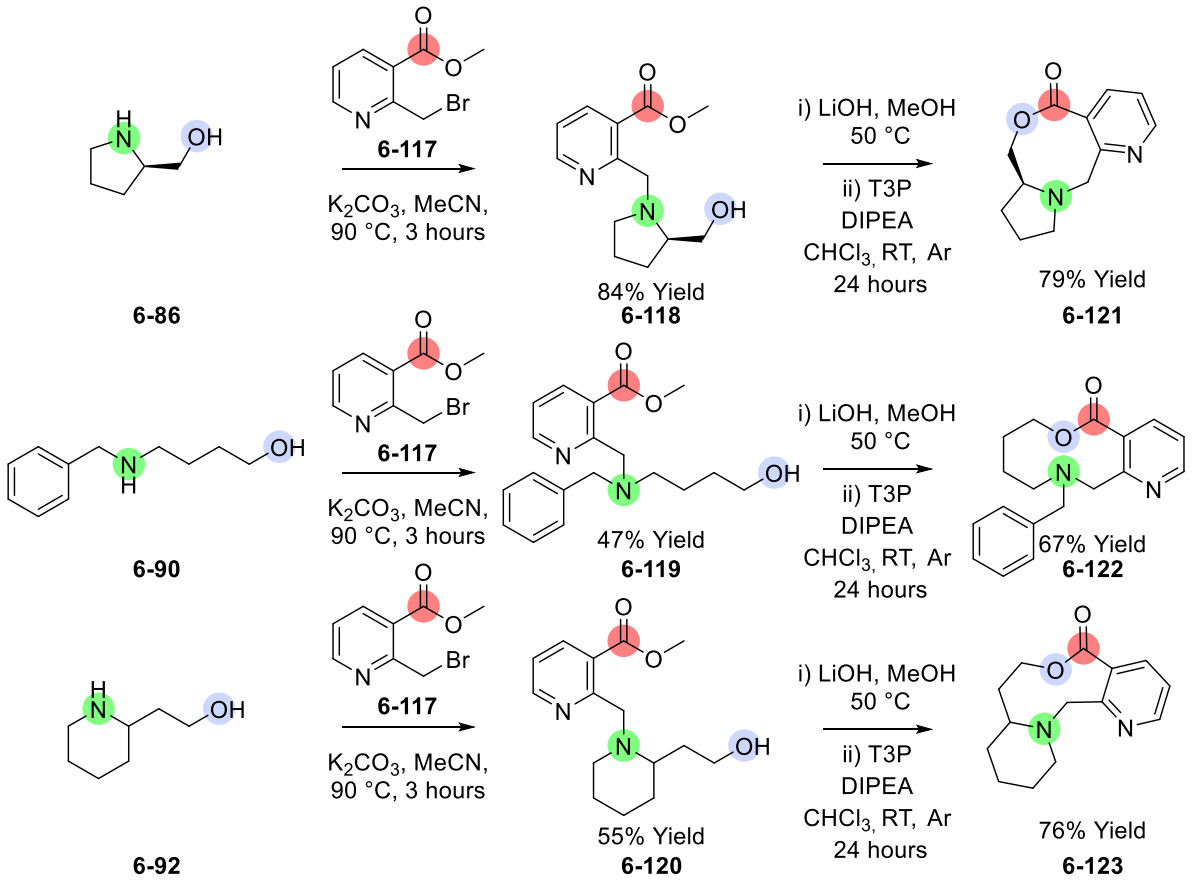
Scheme 44 : - The *N*-alkylation reaction between the IN-building blocks **6-86**, **6-90** and **6-92** and the **E**-building block **6-109**, followed by the ester hydrolysis and NICE forming the lactones **6-113**, **6-114** and **6-115**.

Methyl 2-(bromomethyl) nicotinate **6-117** was the next **E**-building block developed, again synthesised by a Wohl-Ziegler bromination reaction[31] as shown in Scheme 45. The poor yielding of **E**-building block **6-177** was partly due to the reaction not reaching completion. This could have been improved by increasing the reaction time and introducing more radical initiator throughout the reaction to ensure radicals were still being formed. The purification of compound **6-117** was challenging due to the formation of the dibrominated species that exhibited a similar retention factor to the mono brominated compound **6-117**.



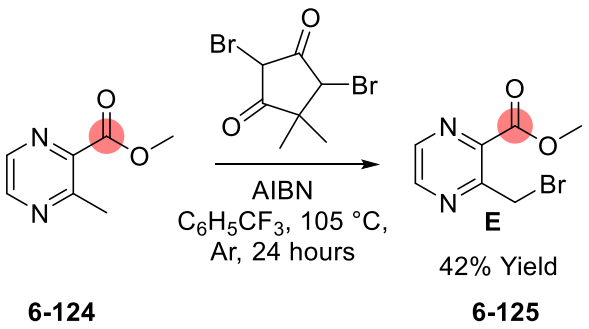
Scheme 45 : - The Wohl-Ziegler bromination of methyl 2-methylnicotinate **6-116** forming the **E**-building block **6-117**.

Each individual **IN**-building blocks **6-86**, **6-90** and **6-92** were reacted with the **E**-building block **6-117** forming the linear precursors **6-118**, **6-119** and **6-120**, respectfully. Individual ester saponification reactions was then performed followed by NICE reactions forming the lactones **6-121**, **6-122** and **6-123**, respectfully shown in Scheme 46.



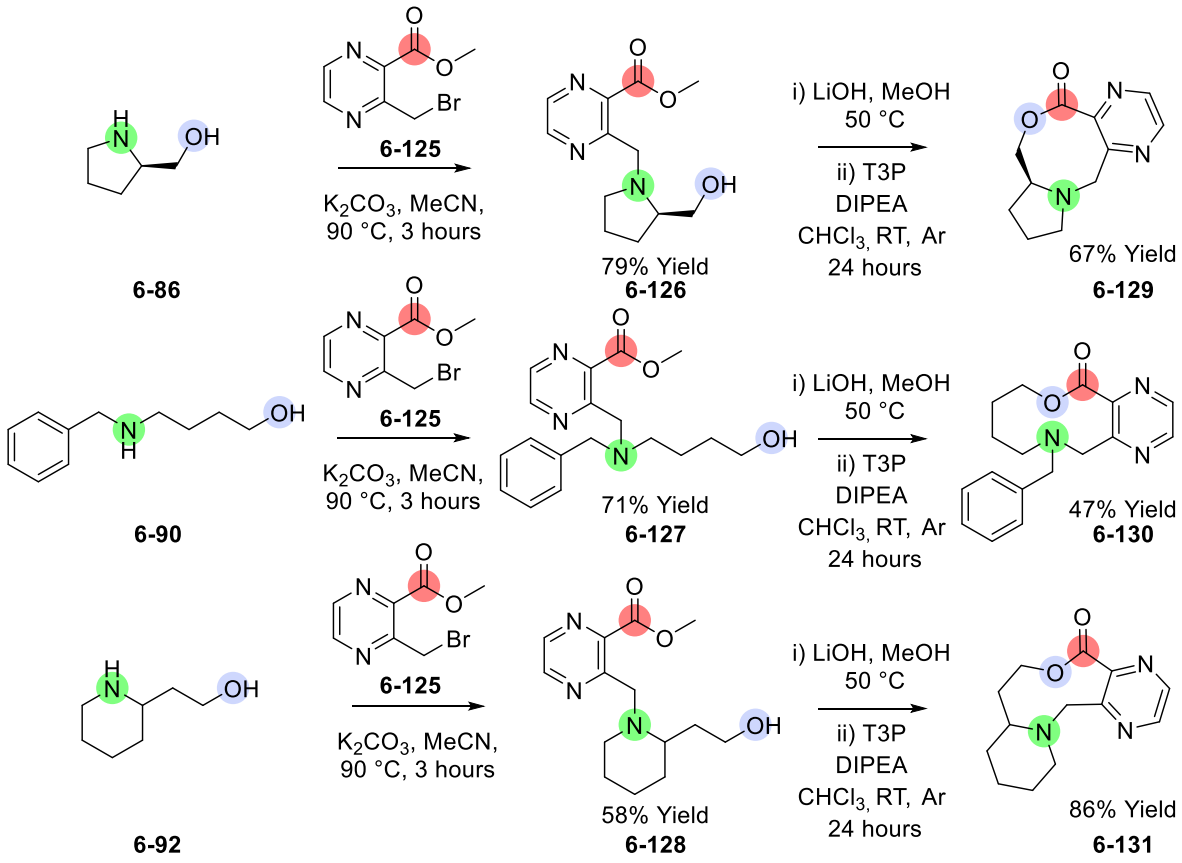
Scheme 46 : - The *N*-alkylation reaction between the **IN**-building blocks **6-86**, **6-90** and **6-92** and the **E**-building block **6-117**, followed by the ester hydrolysis and NICE forming the lactones **6-121**, **6-122** and **6-123**.

The pyrazine **E**-building block **6-125** was synthesised again by a radical bromination reaction, but 2,5-dibromo-4,4-dimethylcyclopentane-1,3-dione was used as a source of bromine radicals instead of NBS as shown in Scheme 47. To decision to use an alternative source of bromine radical was chosen due to the reaction being patented an claimed to achieve an excellent yield.[32]



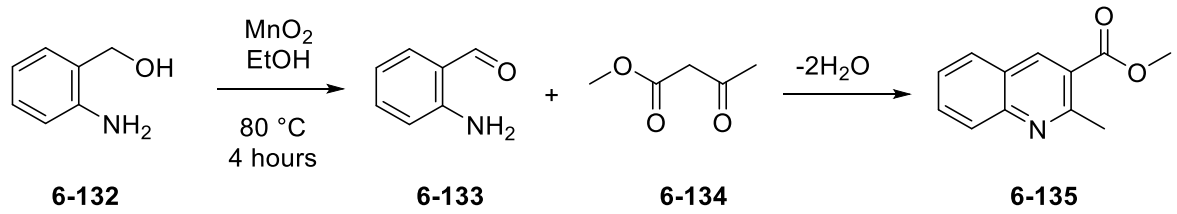
Scheme 47 : - The radical bromination of methyl 3-methylpyrazine-2-carboxylate **6-124**, forming the **E**-building block **6-125**.

Again, each individual **IN**-building blocks **6-86**, **6-90** and **6-92** were reacted with the **E**-building block **6-125** to form the linear precursors **6-126**, **6-127** and **6-128**, respectfully. Individual ester saponification reactions were performed before NICE reactions to synthesise the lactones **6-129**, **6-130** and **6-131** shown in Scheme 48.



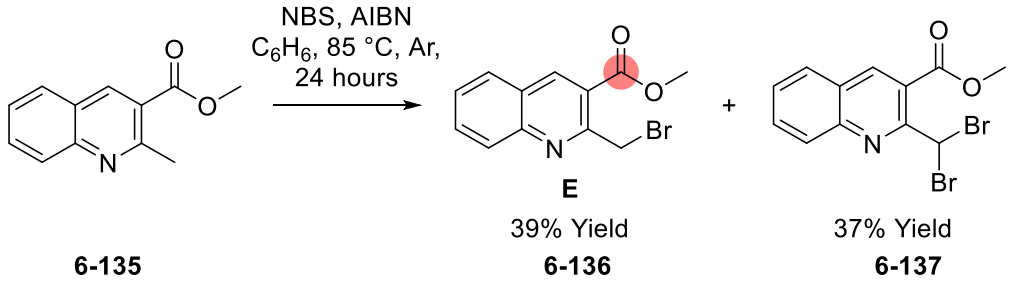
Scheme 48 : - The *N*-alkylation reaction between the **IN**-building blocks **6-86**, **6-90** and **6-92** and the **E**-building block **6-125**, followed by the ester hydrolysis and NICE forming the lactones **6-129**, **6-130** and **6-131**.

Quinoline is prevalent in many medicinal compounds that exhibit antimalarial,[33, 34] anti-inflammatory[35] and antibacterial[36] properties. Therefore, the **E**-building block **6-136** was synthesised, to show how a medium-sized ring can be synthesised with a quinoline moiety incorporated into the molecular structure. Methyl 2-methylquinoline-3-carboxylate **6-135** was first synthesised by selectively oxidising the benzylic alcohol of **6-132** into 2-aminobenzaldehyde **6-133**. A Friedländer synthesis[37] then took place between 2-aminobenzaldehyde **6-134** and methyl acetoacetate **6-133** forming the quinoline derivative **6-135** as shown in Scheme 49.



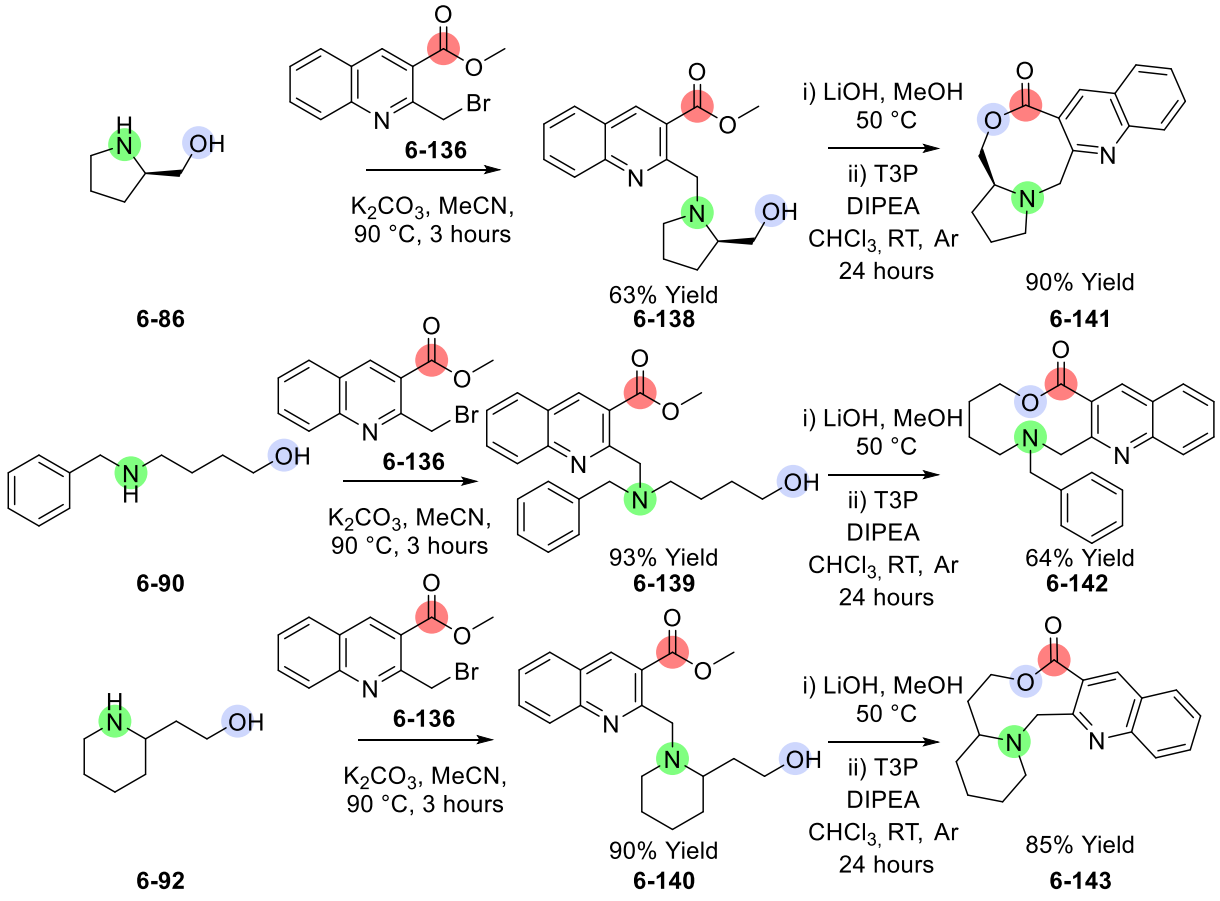
Scheme 49 : - The selective benzylic alcohol oxidation followed by a Friedländer synthesis, forming the quinoline derivative **6-135**.

A Wohl-Ziegler bromination reaction[31] was then performed on the quinoline derivative **6-135** forming both the mono and di brominated compounds **6-136** and **6-137** as shown in Scheme 50. The mono brominated quinoline derivative **6-138** was however successfully isolated following chromatography to be used as an **E**-building block.



Scheme 50 : - The Wohl-Ziegler bromination of **6-135** forming the mono and di brominated quinoline derivatives **6-136** and **6-137**.

Each individual **IN**-building blocks **6-86**, **6-90** and **6-92** were reacted with the **E**-building block **6-136** to form the linear procurers **6-138**, **6-139** and **6-140**, respectfully. Individual ester saponification reactions were performed followed by a NICE reaction forming the lactones **6-141**, **6-142** and **6-143** as shown in Scheme 51.



Scheme 51 : - The *N*-alkylation reaction between the **IN**-building blocks **6-86**, **6-90** and **6-92** and the **N**-building block **6-136**, followed by ester saponification and NICE to form the lactones **6-141**, **6-142** and **6-143**.

All the analogous lactones synthesised from the different **E**-building blocks and the three **IN**-building blocks **6-86**, **6-90** and **6-92** are shown in Figure 19. All the NICE reactions that formed the lactones shown in Figure 19 typically achieved a moderate to high yield with the exception of the lower yielding lactones **6-114** and **6-130**, both synthesised from the **IN**-building block **6-90**. Besides this there are no obvious or consistent trends when comparing the structures and yields of the analogous lactones.

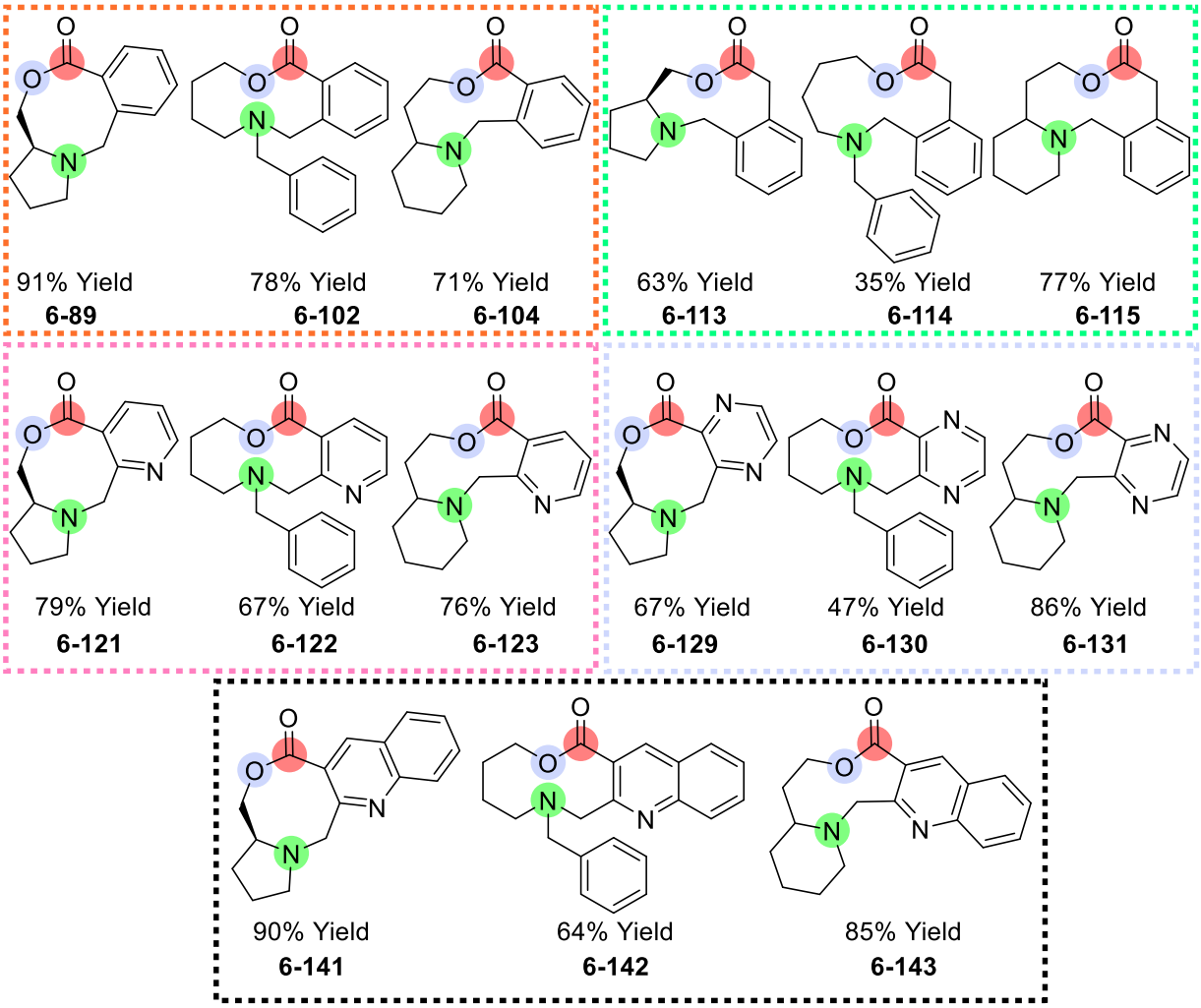
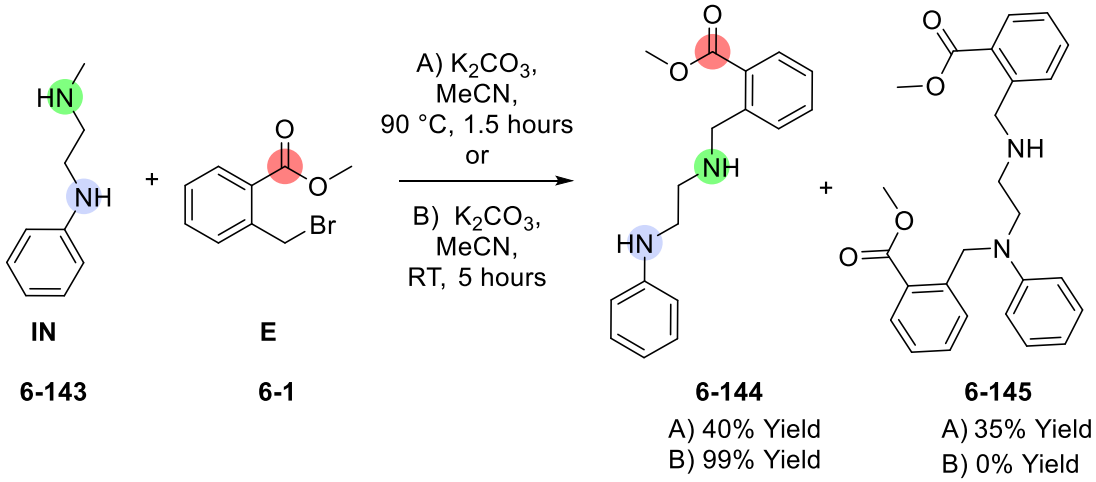


Figure 19 : - All the analogous lactones synthesised from the **IN**-blocks **6-86**, **6-90** and **6-92** and different **E**-building blocks.

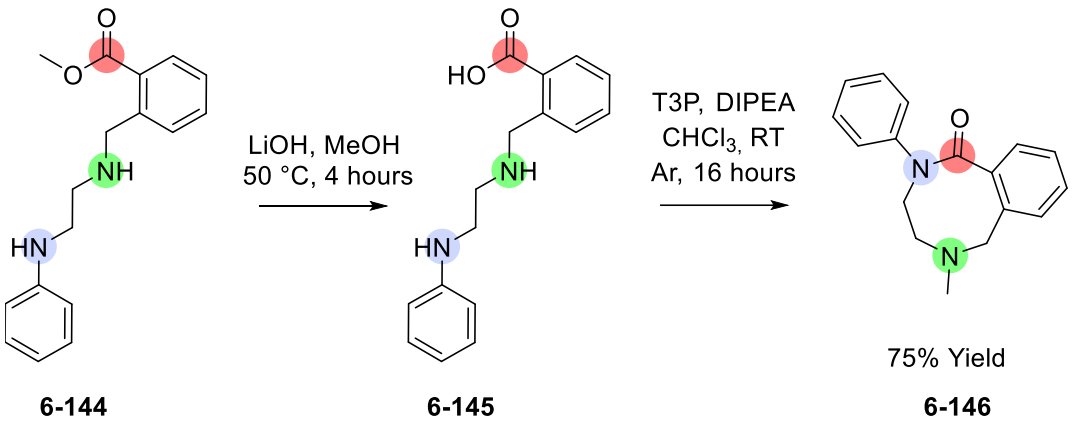
7.4.3 Lactams synthesised by the IN + E approach

The majority of medium-sized rings synthesised by the **IN** + **E** approach shown in Section 7.4 were lactones. To synthesise lactams by the **IN** + **E** approach shown in Scheme 39 a diamine needs to be used as the **IN**-building block. To ensure that only one product was formed upon the *N*-alkylation reaction, between an unsymmetrical diamine and an **E**-building block, the diamine needed to be composed of two amines with different nucleophilicities. As a result, the **IN**-building block **6-143** was chosen, due to exhibiting a secondary amine, which is likely to be much more nucleophilic compared to the resonance stabilised aniline group. The *N*-alkylation reaction conditions did however have to be optimised, to ensure both amines did not react with the **E**-building block **6-1** and form compound **6-145**, as shown in Scheme 52; a mixture of products was obtained using the standard conditions, but the desired product **6-144** was formed selectively when the alkylation reaction was performed at room temperature.



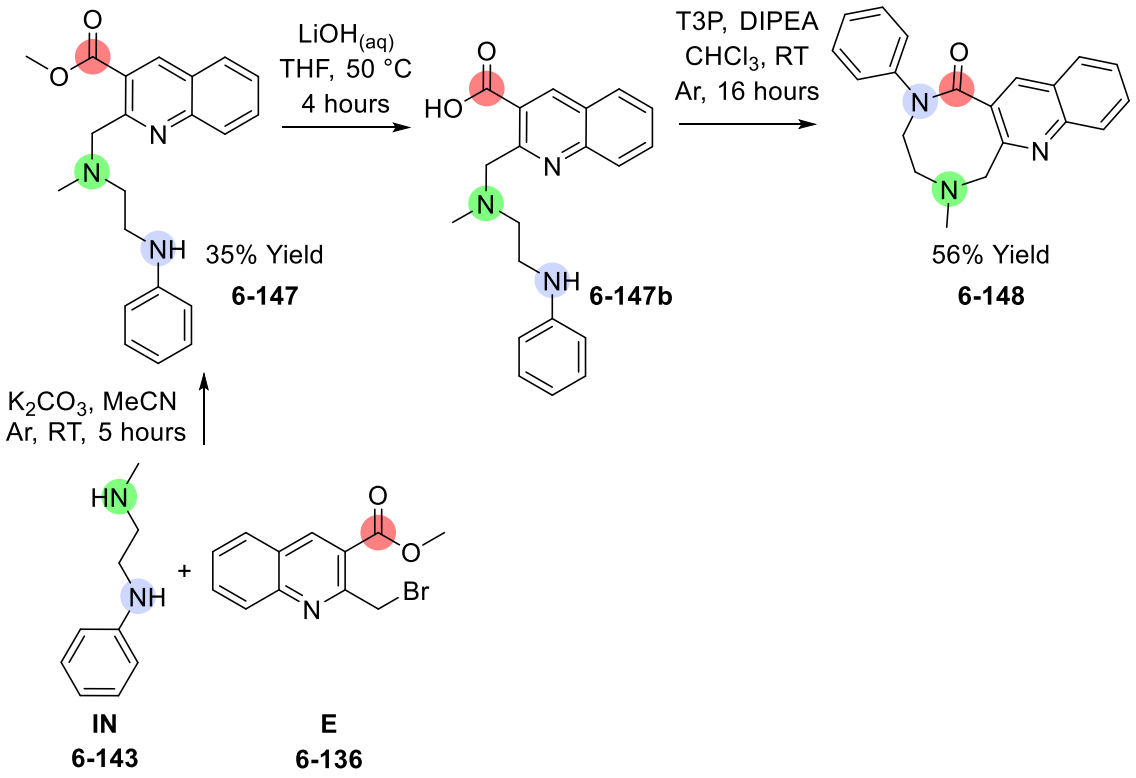
Scheme 52 : - The *N*-alkylation reaction between the diamine **IN**-building block **6-143** and the **E**-building block **6-1** to form the desired product **6-144**.

Once the NICE precursor **6-144** was successfully synthesised the same reaction conditions that synthesised the lactones shown in Section 7.4 were followed. This involved the ester saponification forming the intermediate **6-145** followed by the NICE reaction forming the lactam **6-146**, as shown in Scheme 53.



Scheme 53 : - The ester hydrolysis of **6-144** followed by the NICE of **6-145** forming the lactam **6-146**.

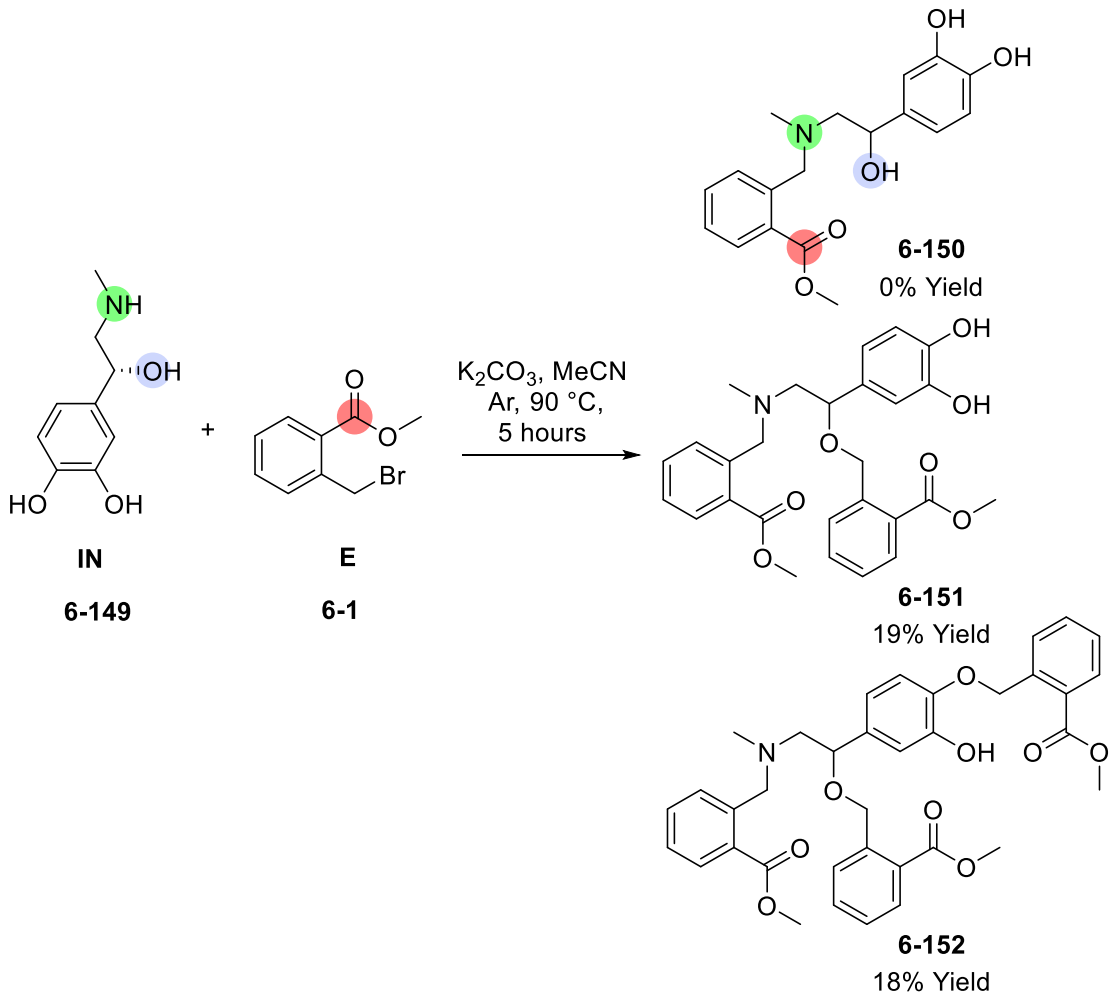
The lactam **6-148** was also synthesised by replacing the **E**-building block **6-1** with the quinoline **E**-building block **6-136** as shown in Scheme 54. The reaction scheme starts with an *N*-alkylation reaction forming the ester **6-147**. An ester saponification reaction was performed forming the carboxylic acid **6-147b**, which wasn't isolated but immediately subject to the NICE reaction conditions to form the lactone **6-148**.



Scheme 54: - The *N*-alkylation reaction between the **6-143** and **6-136**, followed by the ester hydrolysis and NICE forming the lactam **6-148**.

7.4.4 Limitation of this IN + E approach to medium-sized ring synthesis

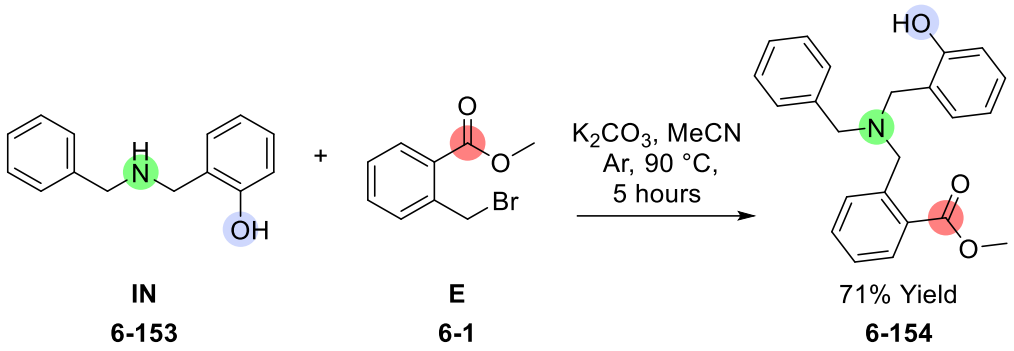
Not all amino alcohols were successfully used as **IN**-building blocks in the synthesis of linear precursors for NICE. For example, the amino alcohol adrenaline **6-149**, a hormone that is crucial to the fight-or-flight response within the human body,[38] was tested as an **IN**-building block, as shown in Scheme 55. However, upon reacting with the **E**-building block **6-1** the undesired doubly and triply alkylated products were formed and not the desired product **6-150**. The structure of the doubly alkylated product **6-151** shown in Scheme 55 was proposed due to a secondary alcohol being more nucleophilic compared to the resonance stabilised phenol group. Whereas the triply alkylated product was likely alkylated on a phenol group, although the exact one is unclear. The most likely explanation for the outcome of the reaction was due the insolubility of the adrenaline **6-149**, observed during the reaction. As a result, the **E**-building block **6-1** was in excess compared to adrenaline **6-149** causing the formation of the products **6-151** and **6-152**. Future research could be undertaken to perform the *N*-alkylation reaction trying alterative solvents to try to resolve this problem.



Scheme 55: - The *N*-alkylation reaction between the **IN**-building block Adrenaline **6-149** and the **E**-building block **6-1**, forming the undesired products **6-151** and **6-152**.

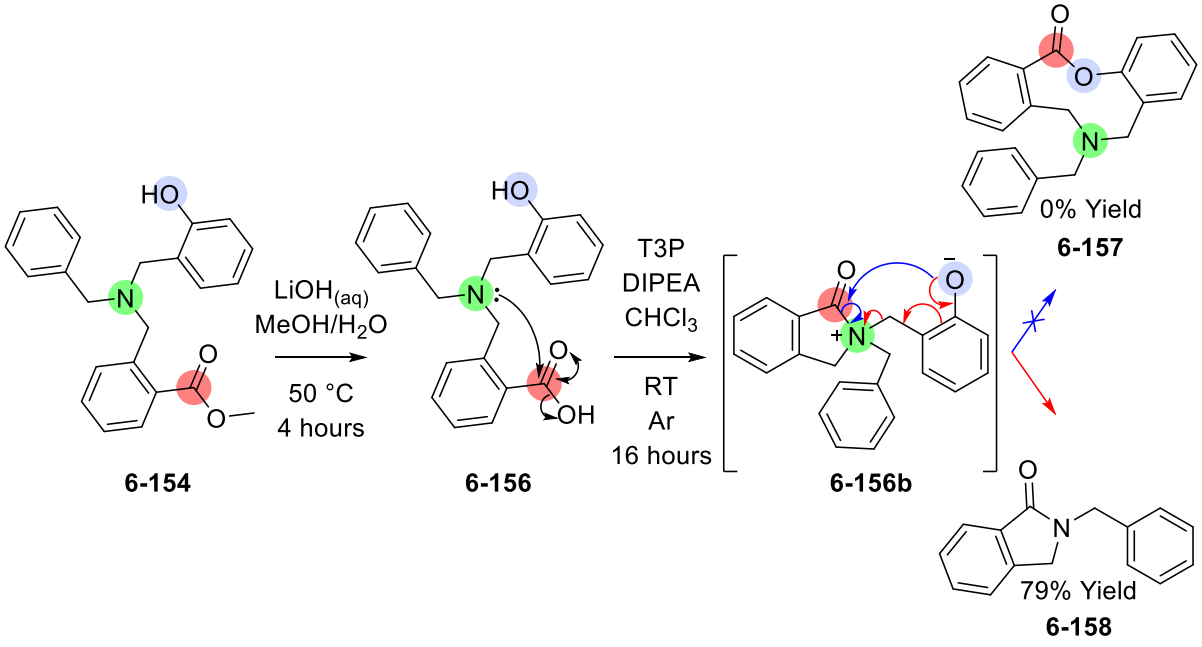
7.4.5 Alternative terminal nucleophiles to synthesise lactones by NICE

Currently research into the synthesis of lactones by NICE has solely been achieved using linear precursors with an aliphatic alcohol as the terminal nucleophile. To progress the scope of compounds synthesised by NICE the precursors **6-154** was synthesised by the *N*-alkylation reaction between the **IN**-building block **6-153** and the **E**-building block **6-1** as shown in Scheme 56.



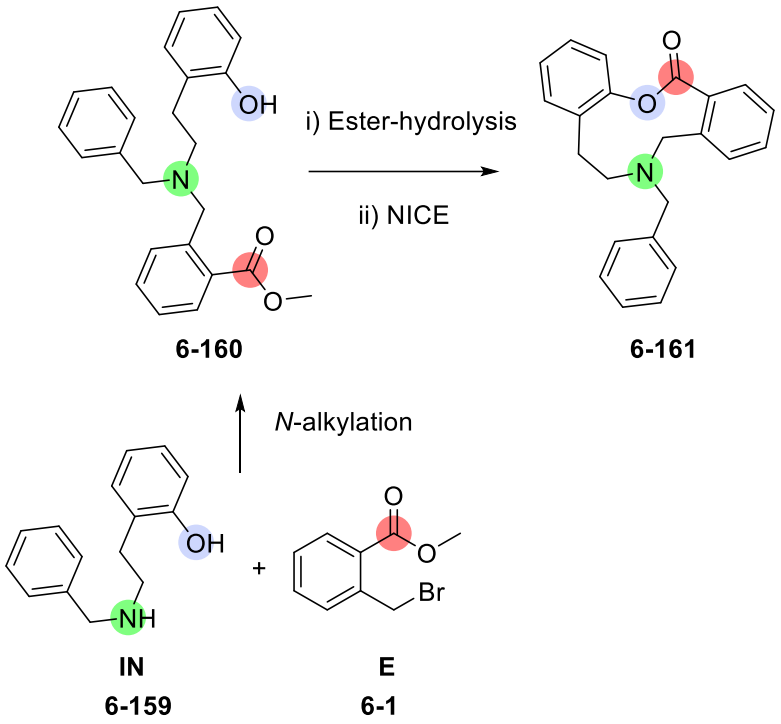
Scheme 56 : - The *N*-alkylation reaction between the **IN**-building block **6-153** and the **E**-building block **6-1**.

The precursor **6-154** has a phenol group acting as the terminal nucleophile, which has previously not yet been utilised in a NICE reaction. An ester hydrolysis reaction was then performed forming the carboxylic acid **6-156** followed by a NICE reaction. The lactone **6-157** however was not formed via the intermediate **6-156b** upon the ring expansion mechanism shown by the blue curly arrows in Scheme 57. The reaction however proceeds by the proposed mechanism shown by the red curly arrows resulting in the cleavage of a *o*-cresol derivative stabilising the quaternary amine to form the indolinone derivative **6-158**. Further research is required into this proposed mechanism, achieved by determining if a derivative of or *o*-cresol is formed achieved by taking samples of the reaction mixture for NMR analysis.



Scheme 57 : - The NICE of the precursor **6-155**, forming the undesired product **8-158**.

To prevent the cleavage of the o-cresol group and enable a successful NICE reaction, future research could focus on the synthesis of the precursor **6-160** as shown in Scheme 58. By introducing an additional carbon atom between the phenol and the amine group, resonance between the two-groups would be prevented. The NICE reaction could then take place and potentially ensure the first NICE of a precursor with a phenol group as the terminal nucleophile, forming the lactone **6-161**.



Scheme 58: - Future research synthesising the lactone **6-161**.

8 Conclusion

Medium-sized rings are often found in small molecules with desirable medicinal and therapeutic properties.[1, 6] Yet compounds containing medium-sized rings are largely underrepresented in pharmaceuticals and drug discovery libraries due to the challenges associated with synthesising them by end-to-end cyclisation.[6] As a result, a better approach to medium-sized ring synthesis is required, which was a major motivator for the development of NICE in this Master's research project.

This project has progressed research into NICE in a number of important ways, generating novel synthesis methods for medium-sized lactones and lactams via NICE. The initial research focused on synthesising precursors by an **IE** + **N** retrosynthetic approach, in which precursors were designed to include an aliphatic amine as the internal nucleophile and a primary amine as the terminal nucleophile. Following the NICE reaction, 9-membered lactams were formed in good to excellent yields. Lactones were also synthesised from similar precursors by following the same **IE** + **N** retrosynthetic approach, albeit in lower yields compared to their analogous lactams. The reason for this is unknown, and was somewhat surprising given that lactones have been synthesised by NICE in high yields in previous research, while lactam-forming NICE reactions were expected to be more difficult.[1] This highlights that trends apparent in one substrate series do not necessarily manifest in others. Changes to the NICE reaction conditions were made, aiming to improve the yield of the lactones synthesised, but only marginal improvements in yield were achieved. In total 9 novel medium-sized rings were made using this approach shown in Figure 20.

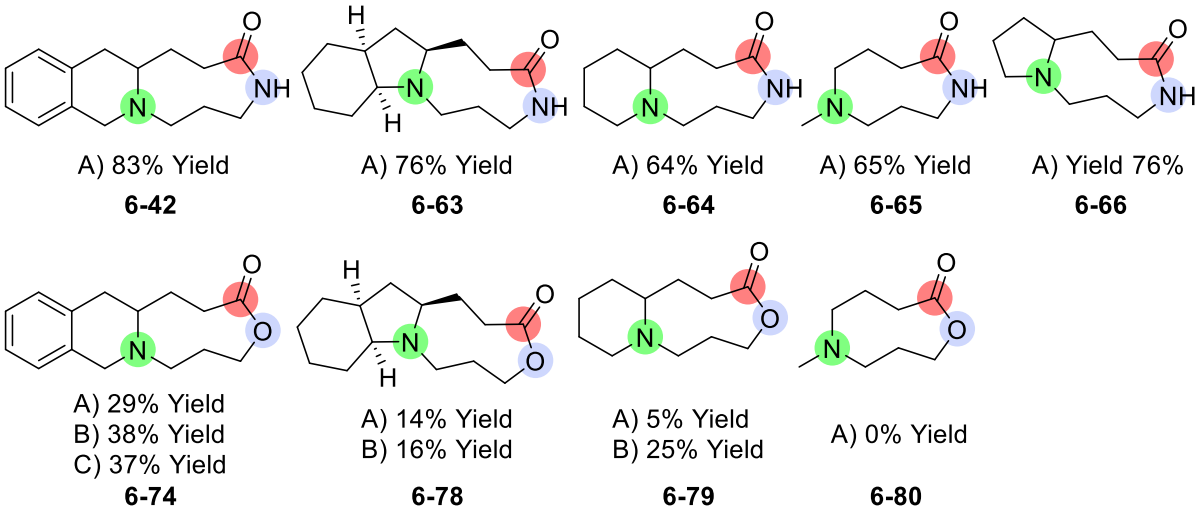


Figure 20 : - The lactams and lactones synthesised by the **IE** + **N** retrosynthetic approach.

The alternative **IN** + **E** retrosynthetic approach was then used to synthesise linear precursors to enable the formation of medium-sized lactones and lactams by NICE. The approach utilised commercially available amino alcohols as the **IN**-building blocks, introducing the internal and terminal nucleophile into the linear precursor. Different **E**-building blocks were also developed introducing the electrophilic carbonyl group into the linear precursor. This approach was very successful, with a range of lactones and lactams successfully synthesised, predominantly in good to excellent yield, varying in size and

functionality, by a very effective and straightforward three-step reaction sequence. In total 21 novel medium-sized rings were made using this approach shown in Figure 21 .

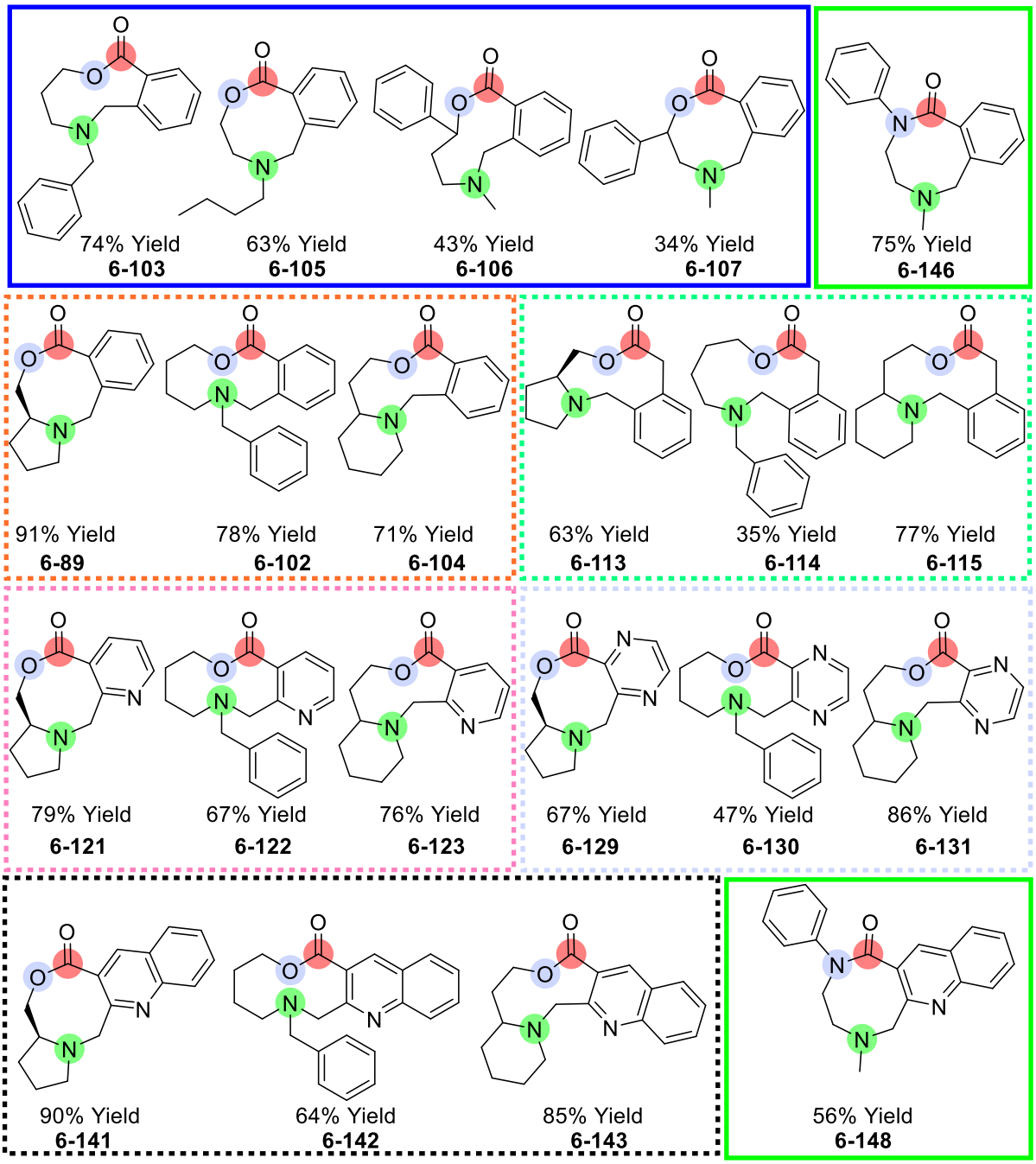


Figure 21 : - All the lactones and lactams synthesised by the **IE** + **N** retrosynthetic approach.

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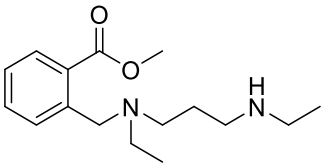
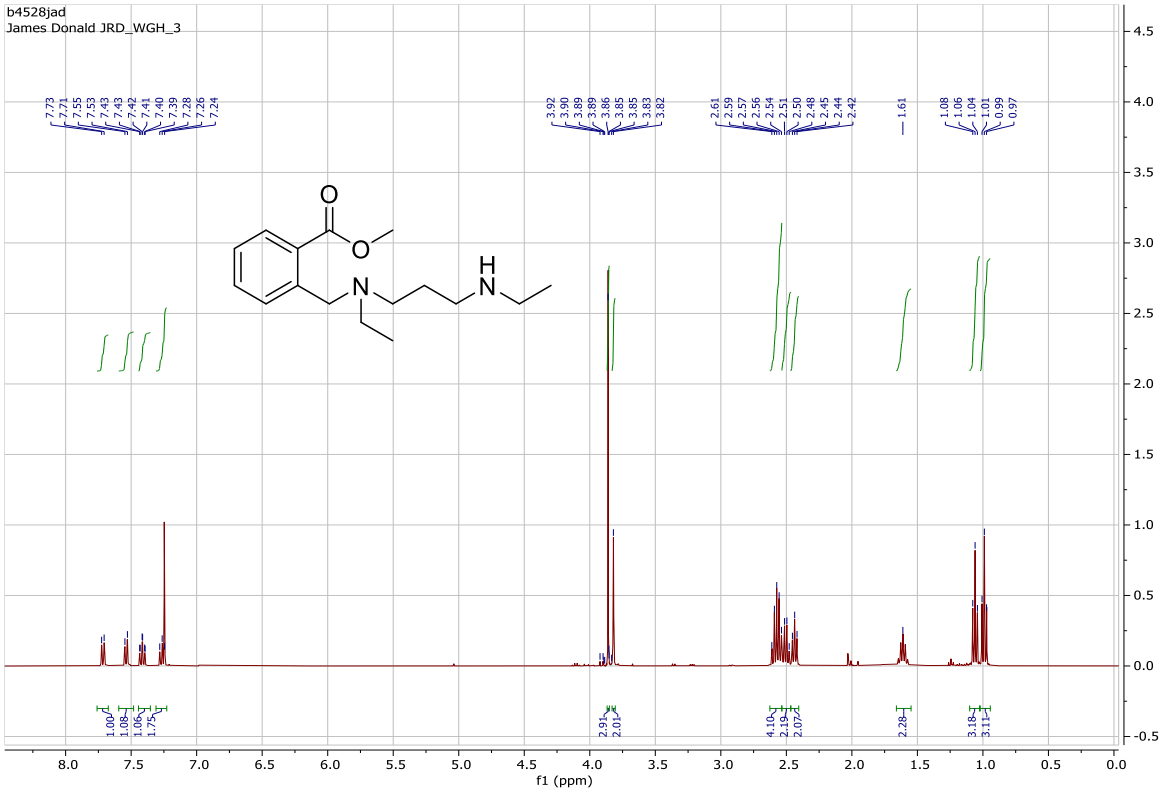
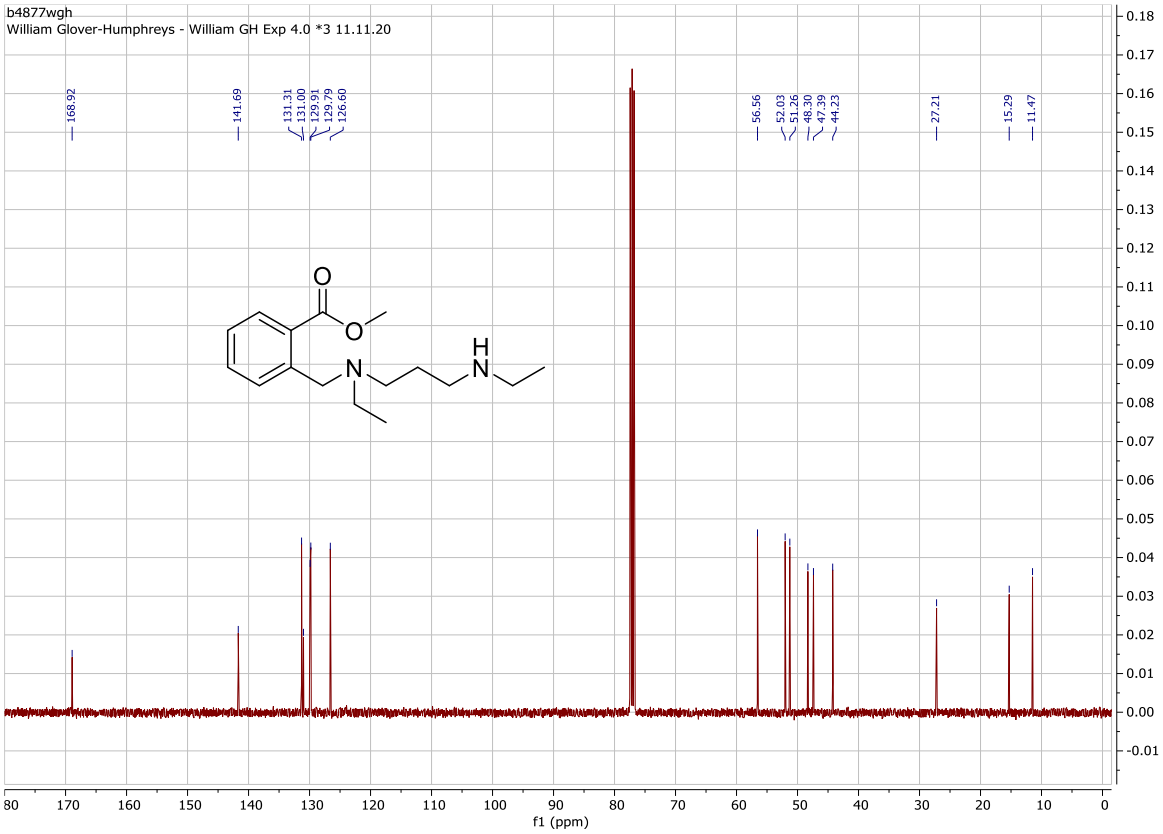
10 Experimental data

Methyl 2-((ethyl (3-(ethyl amino) propyl) amino) methyl) benzoate (6-3)



To a stirring solution of *N*,*N*'-diethyl-1,3-propanediamine **(6-2)** (0.260 g, 2.00 mmol) in acetonitrile (5.00 mL) under argon, potassium carbonate (0.690 g, 5.00 mmol) was added. Methyl 2-bromomethylbenzoate **(6-1)** (0.229 g, 1.00 mmol) was then added and the reaction mixture was heated at reflux at 90 °C for 3 hours under argon. The reaction was cooled to room temperature before it was filtered through Celite, washed with acetonitrile (200 mL), concentrated under vacuum and purified via flash column chromatography (17:2:1 ethyl acetate:methanol:triethylamine) to afford the title compound as a colourless oil (114 mg, 41%); R_f = 0.33 (17:2:1 ethyl acetate:methanol:triethylamine); ν_{max}/cm^{-1} (thin film) 2968, 2807, 1722, 1434, 1371, 1262, 1190, 1127, 1082, 1045, 967, 737; δ_H (400 MHz, $CDCl_3$) 7.72 (1H, d, *J* = 7.7 Hz, Ar**H**), 7.54 (1H, d, *J* = 7.7 Hz, Ar**H**), 7.41 (1H, app td, *J* = 7.7, 1.4 Hz, Ar**H**), 7.26 (1H, app t, *J* = 7.7 Hz, Ar**H**), 3.86 (3H, s, OC**H**$_3$), 3.82 (2H, s, ArC**H**$_2$N), 2.60−2.54 (4H, m, 2 × NHC**H**$_2$CH$_3$), 2.53−2.48 (2H, m, NC**H**$_2$CH$_2$), 2.44 (2H, t, *J* = 6.9 Hz, NHC**H**$_2$CH$_2$), 1.61 (2H, app quintet , *J* = 6.9 Hz, CH$_2$C**H**$_2$CH$_2$), 1.06 (3H, t, *J* = 7.2 Hz, NCH$_2$C**H**$_3$), 0.99 (3H, t, *J* = 7.1 Hz, NHCH$_2$C**H**$_3$); δ_c (100 MHz, $CDCl_3$) 169.9 (**C**O), 141.7 (Ar**C**), 131.3 (Ar**C**H), 131.0 (Ar**C**), 129.9 (Ar**C**H), 129.8 (Ar**C**H), 126.6 (Ar**C**H), 56.6 (Ar**C**H$_2$N), 52.0 (COO**C**H$_3$), 51.3 (CH$_2$**C**H$_2$NH), 48.3 (CH$_3$**C**H$_2$N), 47.4 (CH$_2$**C**H$_2$N), 44.2 (CH$_3$**C**H$_2$NH), 27.2 (CH$_2$C**H**$_2$CH$_2$), 15.3 (**C**H$_3$CH$_2$N), 11.5 (**C**H$_3$CH$_2$NH); HRMS (ESI): calcd. for $C_{16}H_{27}N_2O_2$ 279.2072. Found $[MH]^+$ 279.2065 (−2.5 ppm error).


b4528jad
James Donald JRD_WGH_3
f1 (ppm)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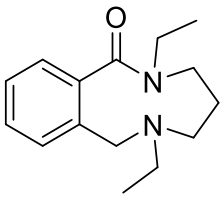
William Glover-Humphreys - William GH Exp 4.0 *3 11.11.20
f1 (ppm)

2,4-Diethyl-2,3,4,5,6,7-hexahydro-1*H*-2,4-benzodiazonin-1-one (6-8)

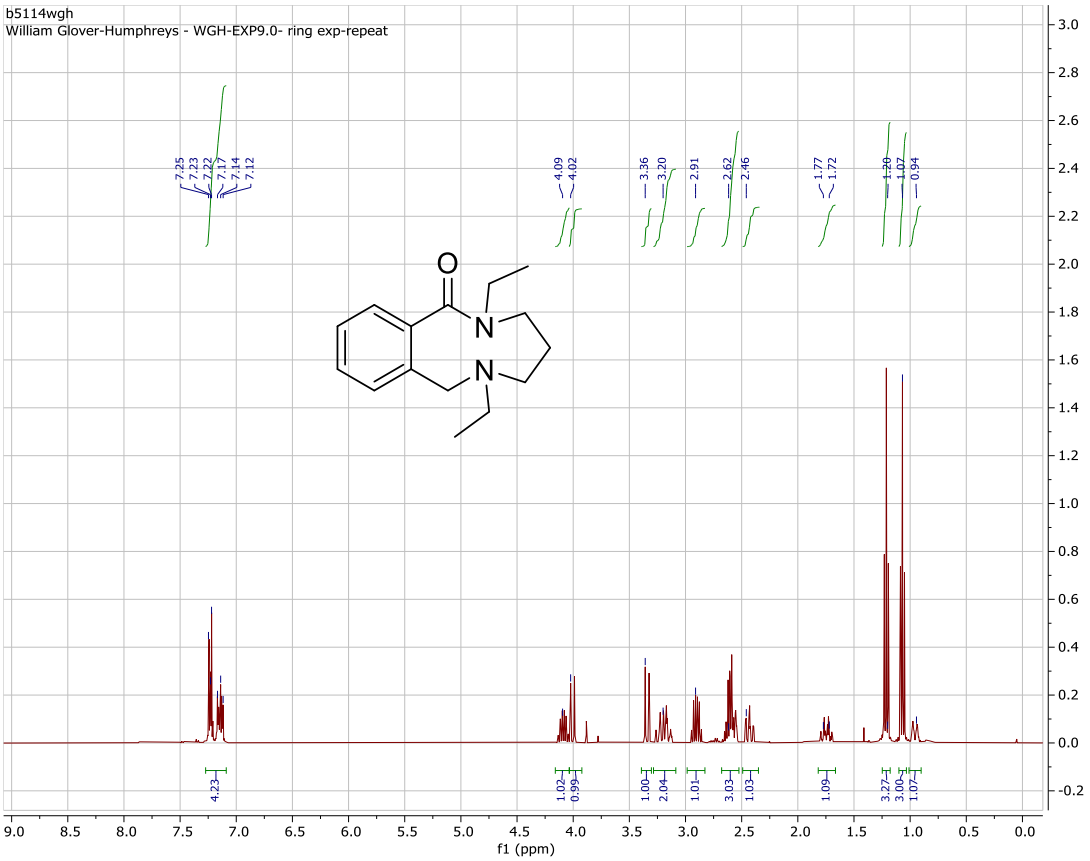


Procedure A

Methyl 2-((ethyl(3-(ethylamino) propyl) amino) methyl) benzoate **(6-3)** (0.100 g, 0.360 mmol) and lithium hydroxide (0.530 mmol, 1.30 mL of 0.500 M $LiOH_{(aq)}$) were mixed at room temperature in tetrahydrofuran (0.500 mL) for 24 hours. The solvent was then removed under vacuum. The intermediate lithium 2-((ethyl(3-(ethylamino) propyl) amino) methyl) benzoate **(6-4)** (assumed to be 0.360 mmol) was dissolved in dimethylformamide (3.00 mL) before the addition of hydroxybenzotriazole (HOBt) (0.0610 g, 0.450 mmol) followed by 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI) (0.0950 g, 0.540 mmol) and the reaction mixture was stirred for 24 hours. The reaction mixture was washed sequentially with diethyl ether (100 mL) and brine (100 mL). The aqueous phase was back extracted with diethyl ether (100 mL). The organic phases were combined, dried with sodium sulfate, filtered, concentrated under vacuum, and purified via flash column chromatography (13:6:1 hexane:ethyl acetate:triethylamine) to afford the title compound as a dark orange oil (6.6 mg, 8%); R_f = 0.24 (13:6:1 hexane:diethyl ether:triethylamine).

Procedure B

Methyl 2-((ethyl(3-(ethylamino) propyl) amino) methyl) benzoate **(6-3)** (0.114 g, 0.411 mmol) and lithium hydroxide (0.600 mmol, 1.20 mL of 0.500 M $LiOH_{(aq)}$) were stirred at room temperature in tetrahydrofuran (0.600 mL) for 24 hours. The solvent was then removed under vacuum. The intermediate lithium 2-((ethyl(3-(ethylamino) propyl) amino) methyl) benzoate **(6-4)** was dissolved in chloroform (9.00 mL) before DIPEA (0.0983 g, 0.760 mmol) was added dropwise over 2 minutes and the mixture stirred until a homogeneous solution was observed (30 minutes). Propane phosphonic acid anhydride (T3P) in ethyl acetate 50% w/v (0.412 g, 0.620 mmol) was then added dropwise over 2 minutes and the reaction mixture was stirred overnight at room temperature. The solvent was then removed under vacuum and the residue was purified via flash column chromatography (13:6:1 hexane:diethyl ether:triethylamine) to afford the title compound as a dark orange oil (54.8 mg, 54%); R_f = 0.24 (13:6:1 hexane:diethyl ether:triethylamine); ν_{max}/cm^{-1} (thin film) 2965, 2930, 1631, 1420, 1368, 1170, 1061, 959, 848, 765, 730; δ_H (400 MHz, $CDCl_3$) 7.25–7.12 (4H, m, ArC**H**), 4.13−4.04 (1H, m, CONC$\mathbf{H_a}H_bCH_3$), 4.00 (1H, d, *J* = 13.6 Hz, ArC$\mathbf{H_a}H_bN$), 3.34 (1H, d, *J* = 13.6 Hz, ArC$H_a\mathbf{H_b}$N), 3.27−3.12 (2H, m, NC$\mathbf{H}_2CH_2$), 2.95−2.85 (1H, m, CONC$H_a\mathbf{H_b}CH_3$), 2.67−2.54 (3H, m, NC$\mathbf{H}_2CH_3$ & NC$\mathbf{H_a}H_bCH_3$), 2.43 (1H, ddd, *J* = 14.4 Hz, 12.3 Hz, 2.5 Hz, NC$H_a\mathbf{H_b}CH_3$), 1.80−1.69 (1H, m, $CH_2C\mathbf{H_a}H_bCH_2$), 1.21 (3H, t, *J* = 8.0 Hz, $CONCH_2C\mathbf{H}_3$), 1.07 (3H, t, *J* = 8.0 Hz, $NCH_2C\mathbf{H}_3$), 0.99−0.92 (1H, m, $CH_2CH_a\mathbf{H_b}CH_2$); δ_c (100 MHz, $CDCl_3$) 172.9 (**C**O), 138.4 (Ar**C**), 138.3 (Ar**C**), 129.2 (Ar**C**H), 128.1 (Ar**C**H), 127.3 (Ar**C**H), 126.4 (Ar**C**H), 57.8 (Ar**C**H_2N), 52.4 (N**C**H_2CH_2), 49.4 (N**C**H_2CH_3), 48.4 (N**C**H_2CH_2), 38.5 (CON**C**H_2CH_3), 24.3 (CH_2**C**H_2CH_2), 13.1 ($CONCH_2$**C**H_3), 12.1 (NCH_2**C**H_3); HRMS (ESI): calcd. for $C_{15}H_{23}N_2O$. Found 247.1810 $[MH]^+$, 247.1800 (–4.06 ppm error).


b5114wgh
William Glover-Humphreys - WGH-EXP9.0- ring exp-repeat
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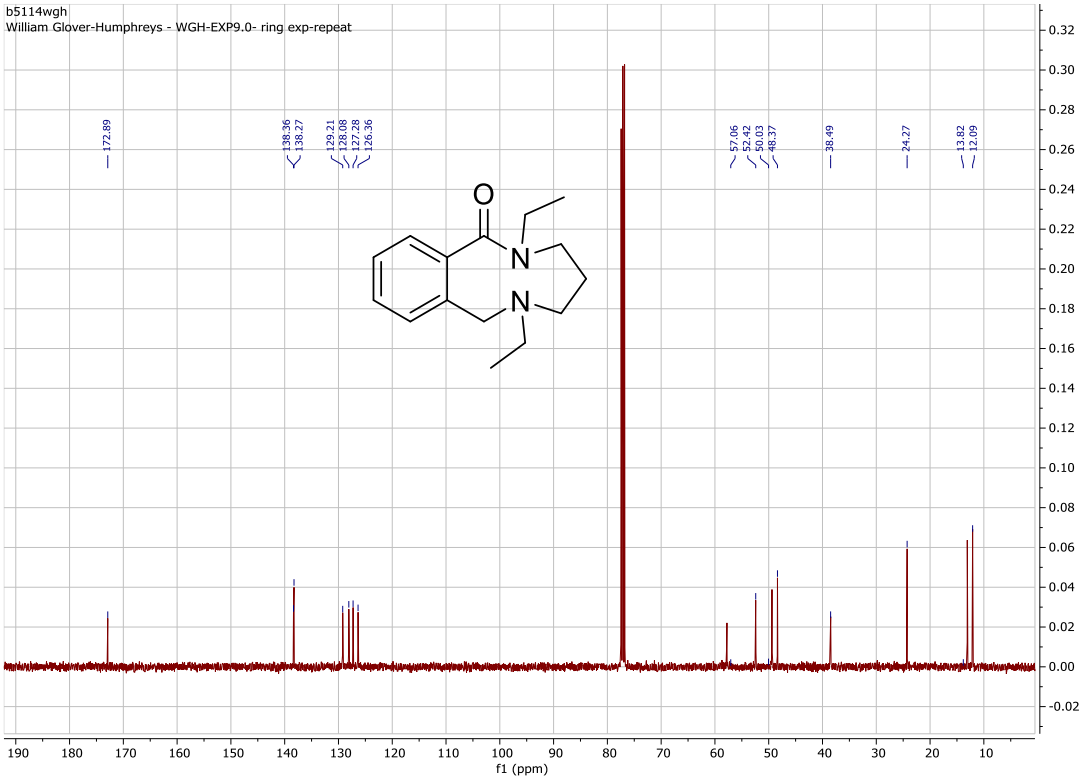
7.23
7.22
7.17
7.14
7.12
4.09
4.02
3.36
3.20
2.91
2.62
2.46
1.77
1.72
1.29
1.07
0.94
O
N
N
4.23
1.02
0.99
1.00
2.04
1.01
3.03
1.03
1.09
3.27
3.00
1.07
f1 (ppm)


b5114wgh
William Glover-Humphreys - WGH-EXP9.0- ring exp-repeat
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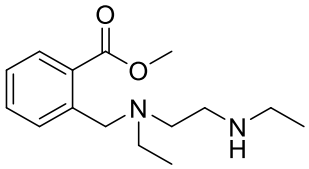
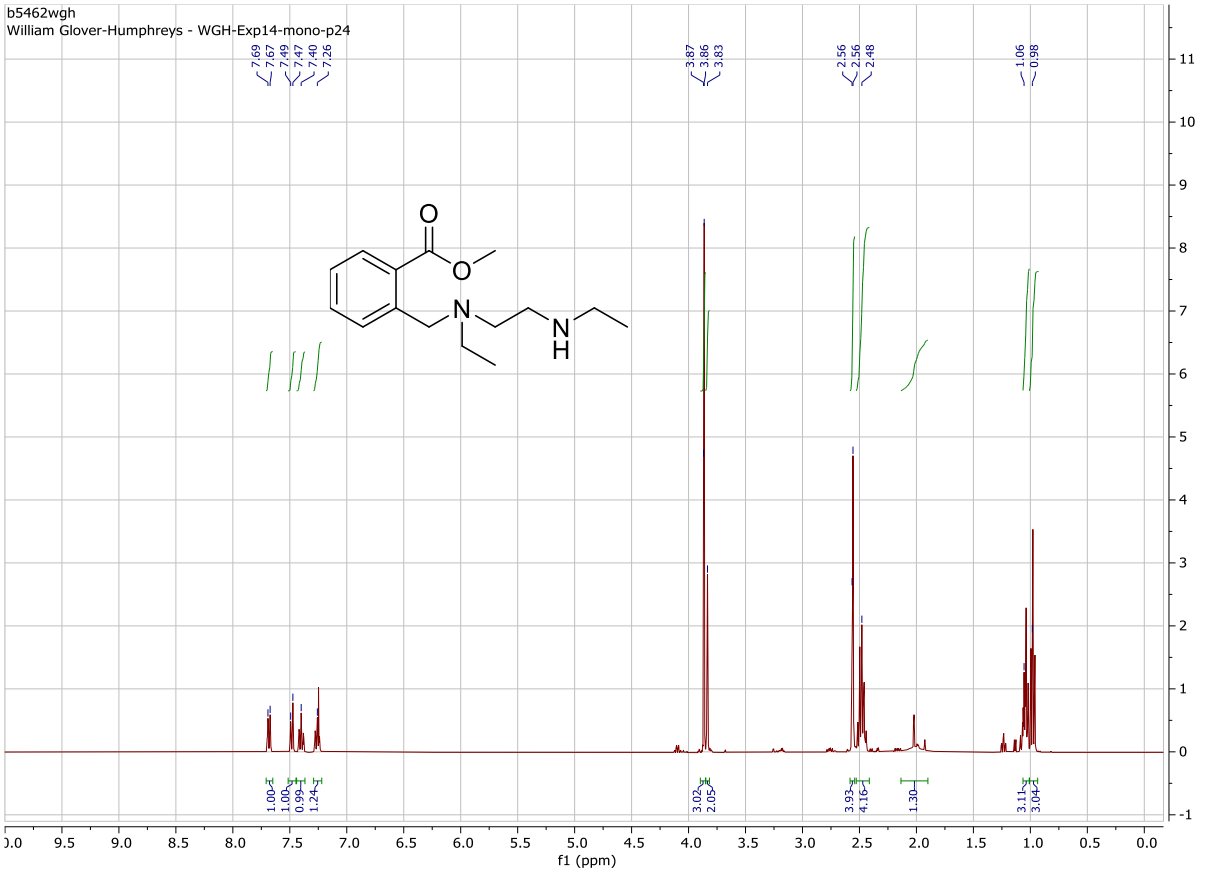
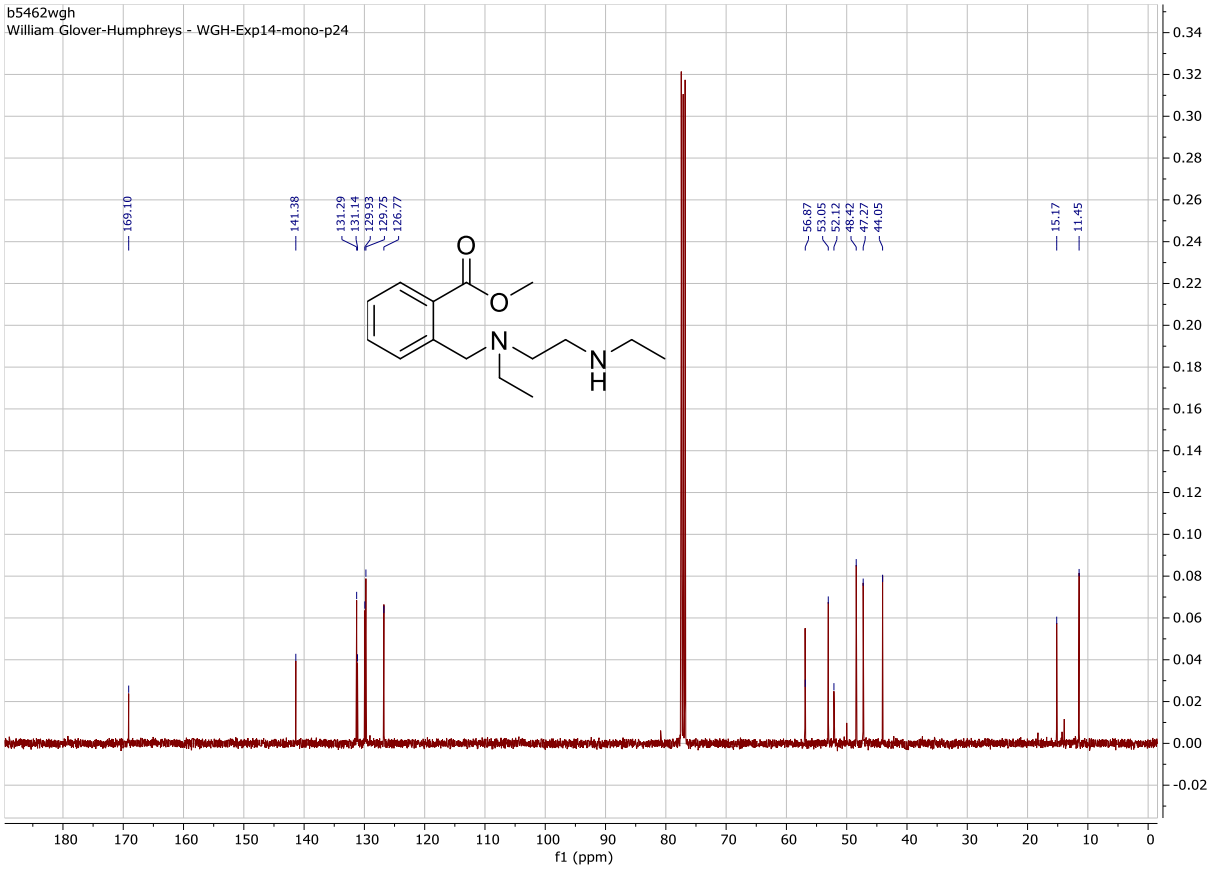
138.36
138.27
129.21
128.08
127.28
126.36
57.06
52.42
50.03
48.37
38.49
24.27
13.82
12.09
O
N
N
f1 (ppm)

Methyl 2-((ethyl[2-(ethylamino) ethyl] amino) methyl) benzoate (6-13)

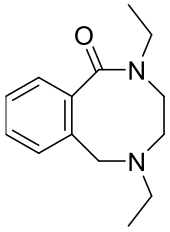


To a stirring solution of *N*, *N*'-diethylethylenediamine **(6-12)** (1.66 g, 14.3 mmol) in acetonitrile (10 mL), under argon, potassium carbonate (2.76 g, 20.0 mmol) was added. Methyl 2-bromomethylbenzoate **(6-1)** (0.430 g, 1.88 mmol) was then added and the reaction was refluxed at 85 °C for 1.5 hours under argon. The reaction was cooled to room temperature, the solvent was removed under vacuum and purified by flash column chromatography (17:2:1 ethyl acetate:menthanol:triethylamine) to afford the title compound (0.43 g, 87%); R_f = 0.4 (17:2:1 ethyl acetate:menthanol:triethylamine); ν_{max}/cm^{-1} (thin film) 2965, 2813, 1722, 1434, 1373, 1267, 1199, 1126, 1082, 967, 782, 737; δ_H (400 MHz, $CDCl_3$) 7.70−7.66 (1H, m, ArC**H**), 7.50−7.47 (1H, m, ArC**H**), 7.43−7.38 (1H, m, ArC**H**), 7.28−7.24 (1H, m, ArC**H**), 3.87−3.86 (3H, m, OC**H**$_3$), 3.83 (2H, s, ArC**H**$_2$N), 2.57−2.55 (4H, m, NC**H**$_2$C**H**$_2$N), 2.52−2.44 (4H, m, × 2 NC**H**$_2$CH$_3$), 2.05 (1H, bs, N**H**), 1.07−1.02 (3H, m, HNCH$_2$C**H**$_3$), 1.00−0.96 (3H, m, NCH$_2$C**H**$_3$); δ_c (100 MHz, $CDCl_3$) 169.1 (**C**O), 141.4 (Ar**C**), 131.3 (Ar**C**H), 131.1 (Ar**C**), 129.9 (Ar**C**H), 129.8 (Ar**C**H), 126.8 (Ar**C**H), 56.9 (Ar**C**H$_2$N), 53.1 (N**C**H$_2$CH$_2$N), 52.1 (O**C**H$_3$), 48.4 (N**C**H$_2$CH$_3$), 47.3 (NCH$_2$**C**H$_2$N), 44.1 (HN**C**H$_2$CH$_3$), 15.2 (NCH$_2$**C**H$_3$), 11.5 (HNCH$_2$**C**H$_3$); HRMS (ESI): calcd. for $C_{15}H_{25}N_2O_2$ 265.1916. Found $[MH]^+$, 265.1908 (−3.02 ppm error).


b5462wgh
William Glover-Humphreys - WGH-Exp14-mono-p24
7.69
7.67
7.49
7.47
7.40
7.26
3.87
3.86
3.83
2.56
2.56
2.48
1.06
0.98
1.00
1.00
0.99
1.24
3.02
2.05
3.93
4.16
1.30
3.11
3.04
f1 (ppm)


b5462wgh
William Glover-Humphreys - WGH-Exp14-mono-p24
169.10
141.38
131.29
131.14
129.93
129.75
126.77
56.87
53.05
52.12
48.42
47.27
44.05
15.17
11.45
f1 (ppm)

2,5-diethyl-3,4,5,4-tetrahydro-2,5-benzodiazocin-1(2*H*)-one (6-16)

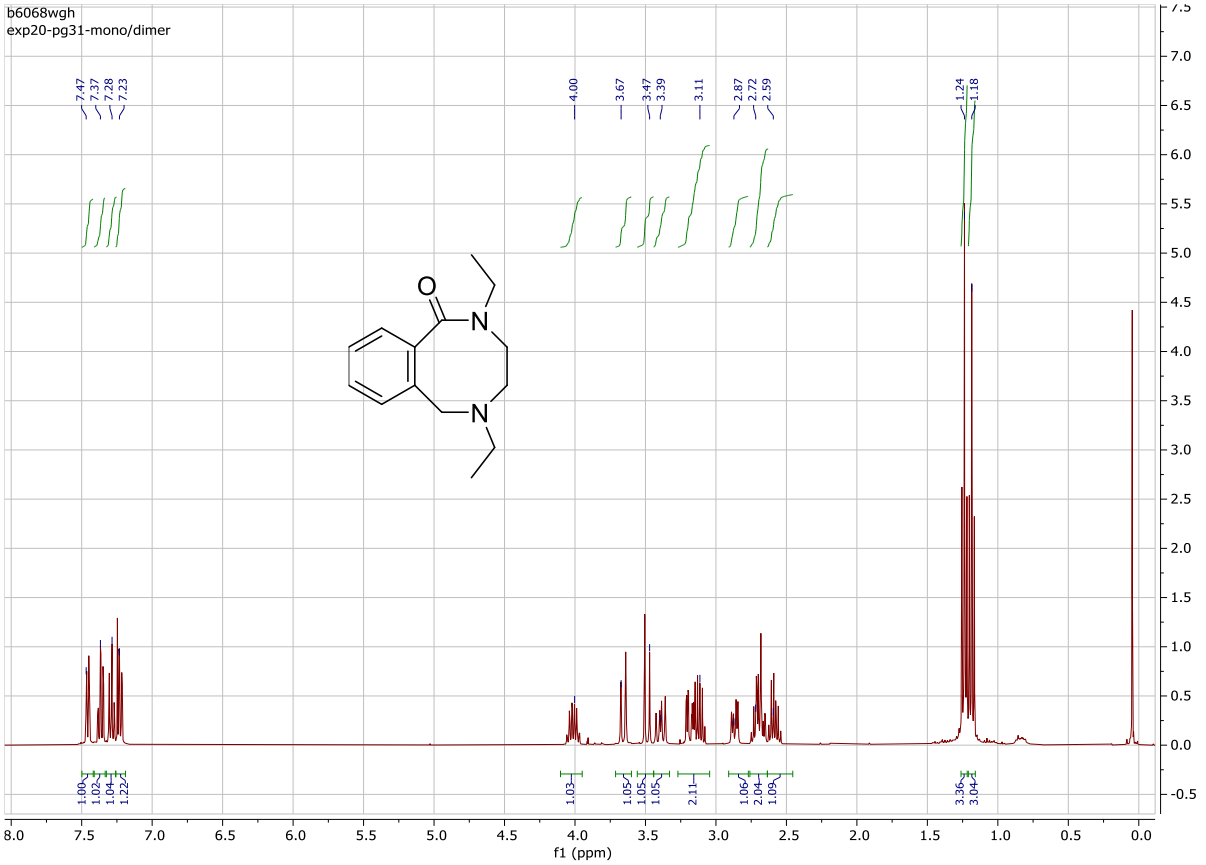


Procedure A

Methyl 2-((ethyl[2-(ethylamino) ethyl] amino) methyl) benzoate **(6-13)** (0.528 g, 2.00 mmol) and lithium hydroxide (2.60 mmol, 5.20 mL of 0.500 M LiOH(aq)) were mixed at room temperature in tetrahydrofuran (3.00 mL) for 24 hours, the solvent was then removed under vacuum. The intermediate lithium (2-((2-carboxylatobenzyl) (ethyl) amino) ethyl) (ethyl)amide **(6-14)** was dissolved in dimethylformamide (20.00 mL) before the addition of HOBt (0.350 g, 2.60 mmol) followed by EDCI 0.466 g, 3.00 mmol) and the reaction mixture was stirred for 24 hours. The reaction was monitored via TLC (10:9:1 hexane:ethyl acetate:triethylamine) and after 24 hours no spot could be identified indicating the ring expansion was unsuccessful, 0% Yield.

Procedure B

Methyl 2-((ethyl[2-(ethylamino) ethyl] amino) methyl) benzoate **(6-13)** (0.528 g, 2.00 mmol) and lithium hydroxide (2.60 mmol, 5.20 mL of 0.500 M $LiOH_{(aq)}$) were mixed at room temperature in tetrahydrofuran (3.00 mL) for 24 hours before removing the solvent under vacuum. The intermediate lithium 2-((ethyl(2-(ethylamino) ethyl) amino) methyl) benzoate was dissolved in chloroform (20 mL) before adding DIPEA (0.478 g, 3.70 mmol) dropwise over 2 minutes and the reaction mixture was stirred until homogeneous (30 minutes). T3P in ethyl acetate 50% w/v (1.91 g, 3.00 mmol) was then added dropwise over 2 minutes and the reaction mixture was stirred overnight at room temperature. The reaction mixture was then concentrated under vacuum and purified via flash column chromatography (10:9:1 hexane:ethyl acetate:triethylamine) to afford the title compound as a dark orange oil (50.0 mg, 11%), R_f = 0.4 (10:9:1 hexane:ethyl acetate:triethylamine); ν_{max}/cm^{-1} (thin film) 2966, 2929, 2818, 1628, 1472, 1423, 1374, 1262, 1138, 1083, 791, 744; δ_H (400 MHz, $CDCl_3$) rotameric in a 1:1 ratio 7.46 (1H, dd, *J* = 7.5 Hz, 1.3 Hz, ArC**H**), 7.37 (1H, td, *J* = 7.5 Hz, 1.3 Hz, ArC**H**), 7.28 (1H, td, *J* = 7.5 Hz, 1.3 Hz, ArC**H**), 7.22 (1H, d, *J* = 7.5 Hz, ArC**H**), 4.06−3.97 (1H, m, CONC$\mathbf{H_a}H_bCH_3$), 3.66 (1H, d, *J* = 14.0 Hz, ArC$H_a\mathbf{H_b}$N), 3.49 (1H, d, *J* = 14.0 Hz, ArC$\mathbf{H_a}H_b$N), 3.43−3.36 (1H, m, CONC$\mathbf{H_a}H_bCH_2$N), 3.21−3.16 (1H, m, CONC$H_a\mathbf{H_b}CH_2$N), 3.15−3.08 (1H, m, CONC$H_a\mathbf{H_b}CH_3$), 2.89−2.84 (1H, m, CONCH_2C$\mathbf{H_a}H_b$N), 2.75−2.68 (1H, m, NC$\mathbf{H_a}H_bCH_3$), 2.70−2.65 (1H, m, CONCH_2C$\mathbf{H_a}H_b$N), 2.62−2.54 (1H, m, NC$H_a\mathbf{H_b}CH_3$), 1.24 (3H, t, J = 7.1 Hz), 1.18 (3H, t, J = 7.1 Hz); δ_c (100 MHz, $CDCl_3$) 170.8 (**C**O), 137.1 (Ar**C**), 135.3 (Ar**C**), 130.5 (Ar**C**H), 129.9 (Ar**C**H), 128.4 (Ar**C**H), 127.8 (Ar**C**H), 55.6 (Ar**C**H_2N), 54.2 (CONCH_2**C**H_2N), 52.2 (N**C**H_2CH_3), 47.24 (CON**C**H_2CH_2N), 41.0 (CON**C**H_2CH_3), 12.7 (NCH_2**C**H_3), 12.6 (NCH_2**C**H_3); HRMS (ESI): calcd. for $C_{14}H_{21}N_2O$ 233.1654 & $C_{14}H_{21}N_2NaO$ 255.1473 Found $[MH]^+$, 233.1650 (error –1.7 ppm) & $[MNa]^+$, 255.1467 (error –3.0 ppm).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7.28
7.23
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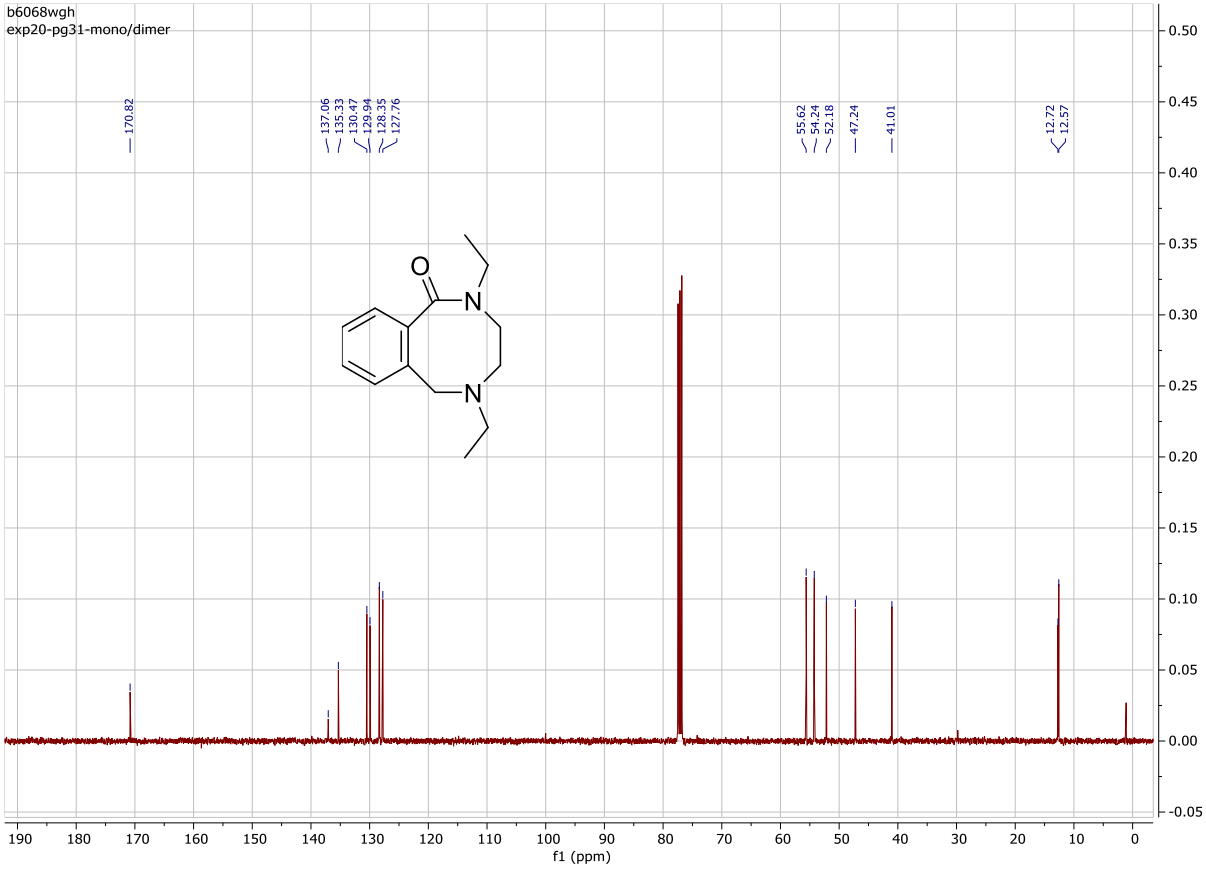
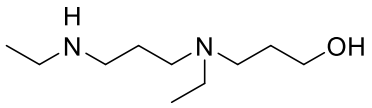
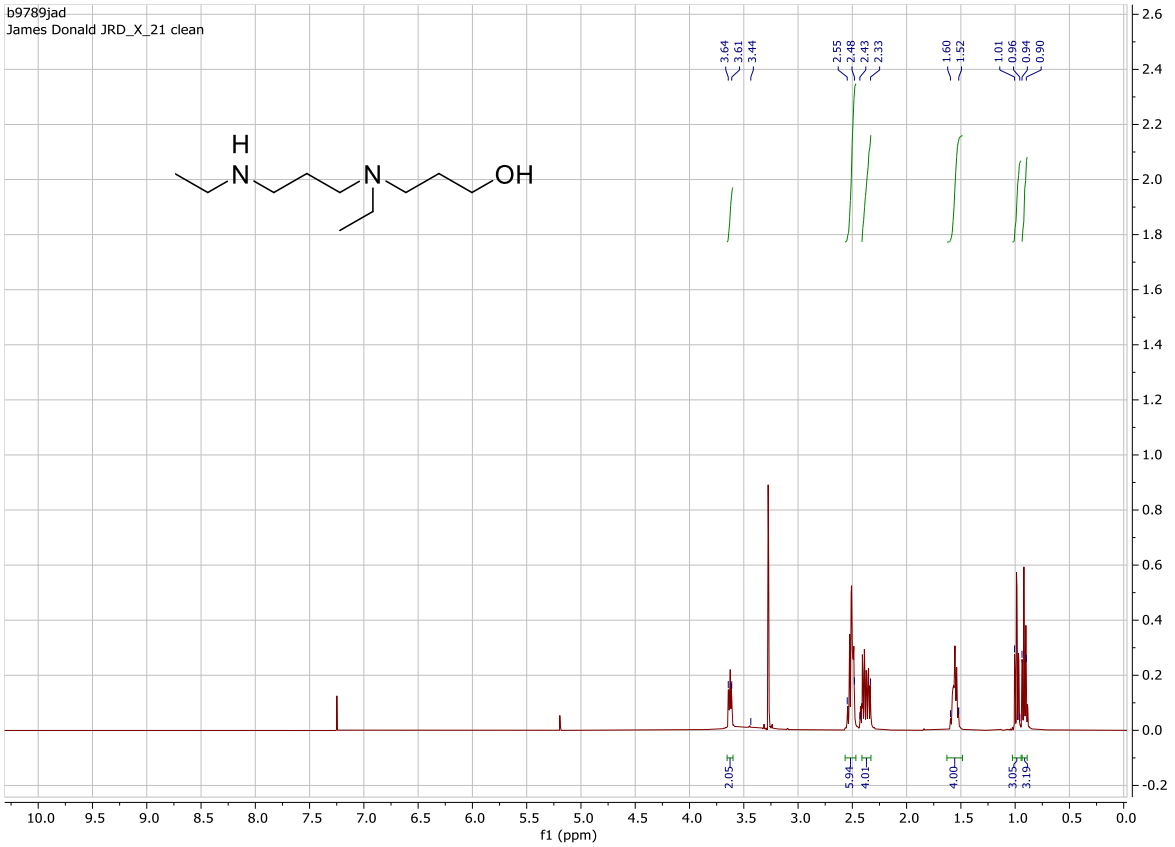
3.67
3.47
3.39
3.11
2.87
2.72
2.59
1.24
1.18
O
N
N
1.00
1.02
1.04
1.22
1.03
1.05
1.05
1.05
2.11
1.06
2.04
1.09
3.36
3.04
f1 (ppm)


b6068wgh
exp20-pg31-mono/dimer
170.82
137.06
135.33
130.47
129.94
128.35
127.76
55.62
54.24
52.18
47.24
41.01
12.72
12.57
O
N
N
f1 (ppm)

3-(Ethyl(3-(ethylamino) propyl) amino) propan-1-ol (6-22)



3-Bromopropanol **(6-21)** (904 μL, 1.31 g, 10.0 mmol) was added to a mixture of *N*, *N´*-diethyl-1,3-propanediamine **(6-2)** (3.18 mL, 2.61 g, 20.0 mmol) and potassium carbonate (6.91 g, 50.0 mmol) in acetonitrile (50 mL) and the mixture was heated at 60 °C for 4 hours. After cooling to room temperature, the mixture was filtered through Celite, washing with MeCN (50 mL) and the filtrate concentrated under reduce pressure. The residue was purified by silica gel flash column chromatography, eluting with CH_2Cl_2:MeOH:Et_3N (50:45:5), to give the product as a colourless oil (1.31 g, 70%), R_f = 0.29 (CH_2Cl_2:MeOH:Et_3N 50:45:5); ν_{max}/cm^{-1} (thin film) 3271, 2965, 2934, 2811, 1461, 1376, 1295, 1117, 1043, 922, 800, 735; δ_H (400 MHz, $CDCl_3$) 0.90−0.94 (3H, m, C**H**$_3$CH$_2$N), 0.96−1.01 (3H, m, C**H**$_3$CH$_2$N), 1.60−1.52 (4H, m, 2× CH$_2$C**H**$_2$CH$_2$), 2.43−2.33 (4H, m, 2× CH$_3$C**H**$_2$N), 2.55−2.48 (6H, m, 3× C**H**$_2$N), 3.44 (1H, bs, N**H**), 3.64−3.61 (2H, m, C**H**$_2$OH); δ_c (100 MHz, $CDCl_3$) 15.1 (**C**H$_3$CH$_2$N), 11.5 (**C**H$_3$CH$_2$N), 27.2 (CH$_2$**C**H$_2$CH$_2$), 28.0 (CH$_2$**C**H$_2$CH$_2$), 44.1 (**C**H$_2$N), 47.2 (**C**H$_2$N), 48.1 (**C**H$_2$N), 51.7 (**C**H$_2$N), 53.6 (**C**H$_2$N), 63.7 (CH$_2$**C**H$_2$OH); HRMS (ESI) calcd. for $C_{10}H_{25}N_2O$ 189.1967. Found 189.1966 $[MH]^+$ (−0.53 ppm error).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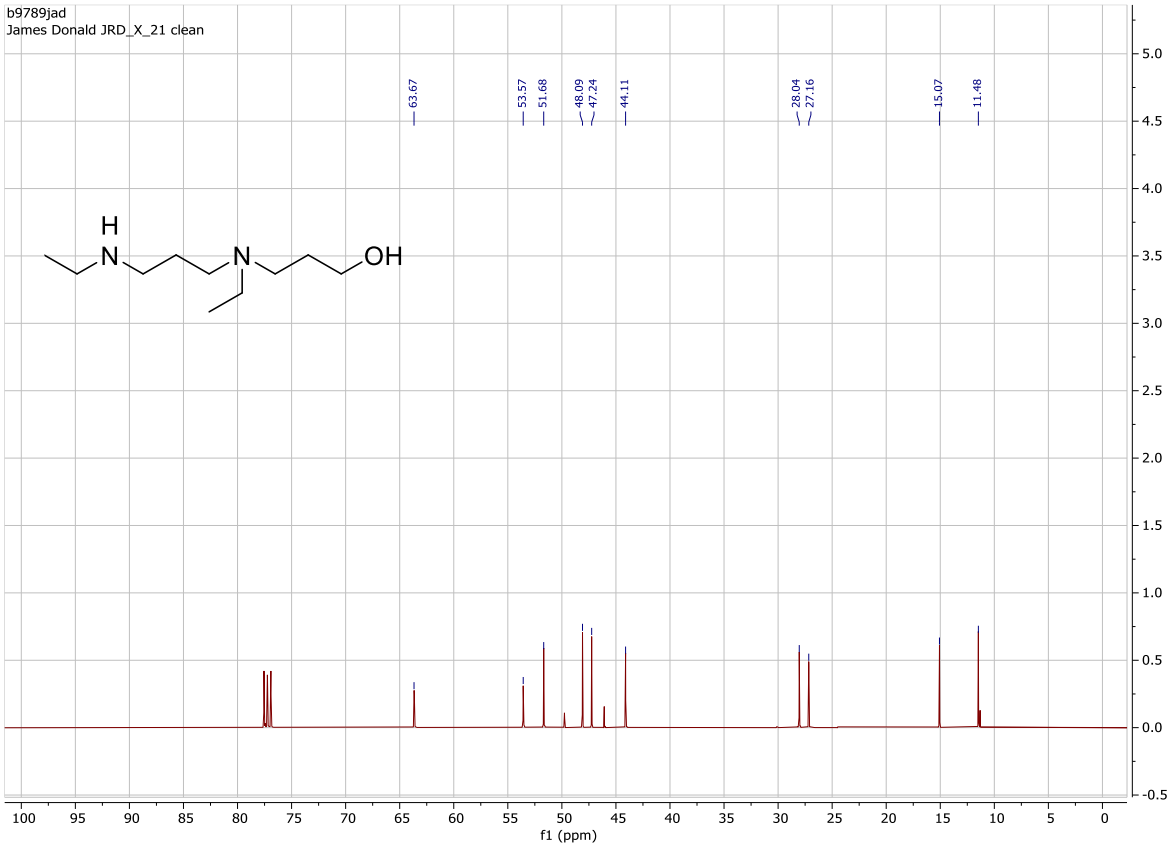
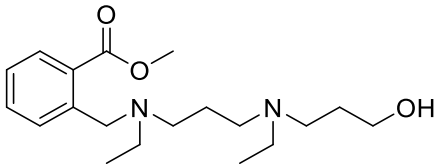
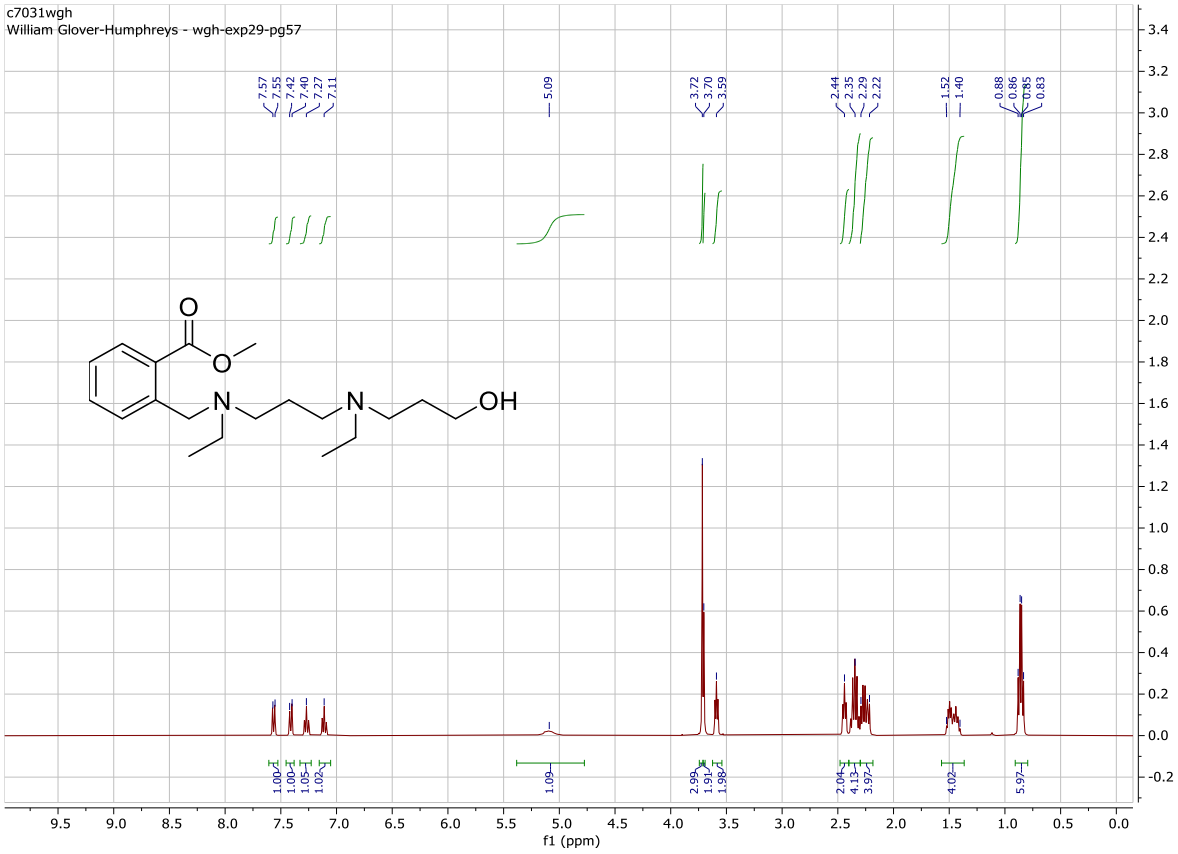
James Donald JRD_X_21 clean
H
N
N
OH
3.64
3.61
3.44
2.55
2.48
2.43
2.33
1.60
1.52
1.01
0.96
0.94
0.90
2.05
5.94
4.01
4.00
3.05
3.19
f1 (ppm)


b9789jad
James Donald JRD_X_21 clean
H
N
N
OH
63.67
53.57
51.68
48.09
47.24
44.11
28.04
27.16
15.07
11.48
f1 (ppm)

Methyl 2-((ethyl(3-(ethyl(3-hydroxypropyl) amino) propyl) amino) methyl) benzoate (6-23)



To a stirring solution of potassium carbonate (0.415 g, 3.00 mmol) in acetonitrile (5.00 mL), 3-(ethyl(3-(ethylamino) propyl) amino) propan-1-ol **(6-22)** (0.188 g, 1.00 mmol) was added followed by methyl 2-(bromomethyl) benzoate **(6-1)** (0.230 g, 1.00 mmol). The reaction mixture was heated to reflux at 90 °C for 3 hours under argon before filtering through Celite washing with dichloromethane, concentrating under vacuum and purifying by flash column chromatography (hexane:methanol:triethylamine 17:2:1) to afford the title compound as a clear oil (0.238 g, 71%) R_f = 0.20 (hexane:methanol:triethylamine 17:2:1) ν_{max}/cm^{-1} (thin film) 2950, 2814, 2238, 1721, 1449, 1372, 1268, 1128, 1081, 910, 729; δ_H (400 MHz, $CDCl_3$) 7.56 (1H, d, *J* = 7.6 Hz, Ar**H**), 7.41 (1H, d, *J* = 7.6 Hz, Ar**H**), 7.27 (1H, t, *J* = 7.6 Hz, Ar**H**), 7.11 (1H, t, *J* = 7.6 Hz, Ar**H**), 5.09 (1H, bs, O**H**), 3.72 (3H, s, OC$\mathbf{H}_3$), 3.70 (2H, s, ArC$\mathbf{H}_2$N), 3.59 (2H, t, *J* = 5.2 Hz, C$\mathbf{H}_2$OH), 2.44 (2H, t, *J* = 5.8 Hz, C$\mathbf{H}_2$N), 2.39−2.31 (4H, m, 2× NC$\mathbf{H}_2$$CH_3$), 2.29−2.22 (4H, m, C$\mathbf{H}_2$N), 1.49 (2H, quintet, *J* = 5.8 Hz, CH_2C$\mathbf{H}_2$$CH_2$), 1.46−1.40 (2H, m, CH_2C$\mathbf{H}_2$$CH_2$), 0.88−0.83 (4H, m, C$\mathbf{H}_3$$CH_2$N); δ_c (100 MHz, $CDCl_3$) 168.8 (**C**O), 141.5 (Ar**C**), 131.1 (Ar**C**H), 131.0 (Ar**C**), 129.8 (Ar**C**H), 129.6 (Ar**C**H), 126.5 (Ar**C**H), 64.0 (C$\mathbf{H}_2$OH), 56.6 (Ar**C**H_2), 53.9 (**C**H_2N), 51.8 (**C**H_3O), 51.7 (**C**H_2N), 51.2(**C**H_2N), 47.5 (CH_3**C**H_2N), 47.3 (CH_3**C**H_2N), 27.9 (CH_2**C**H_2CH_2), 24.2 (CH_2**C**H_2CH_2), 11.5 (2 × **C**H_3CH_2N); HRMS (ESI) calcd. for $C_{19}H_{33}N_2O_3$ 337.2491. Found $[MH]^+$ 337.2478 (−3.87 ppm error).


c7031wgh
William Glover-Humphreys - wgh-exp29-pg57
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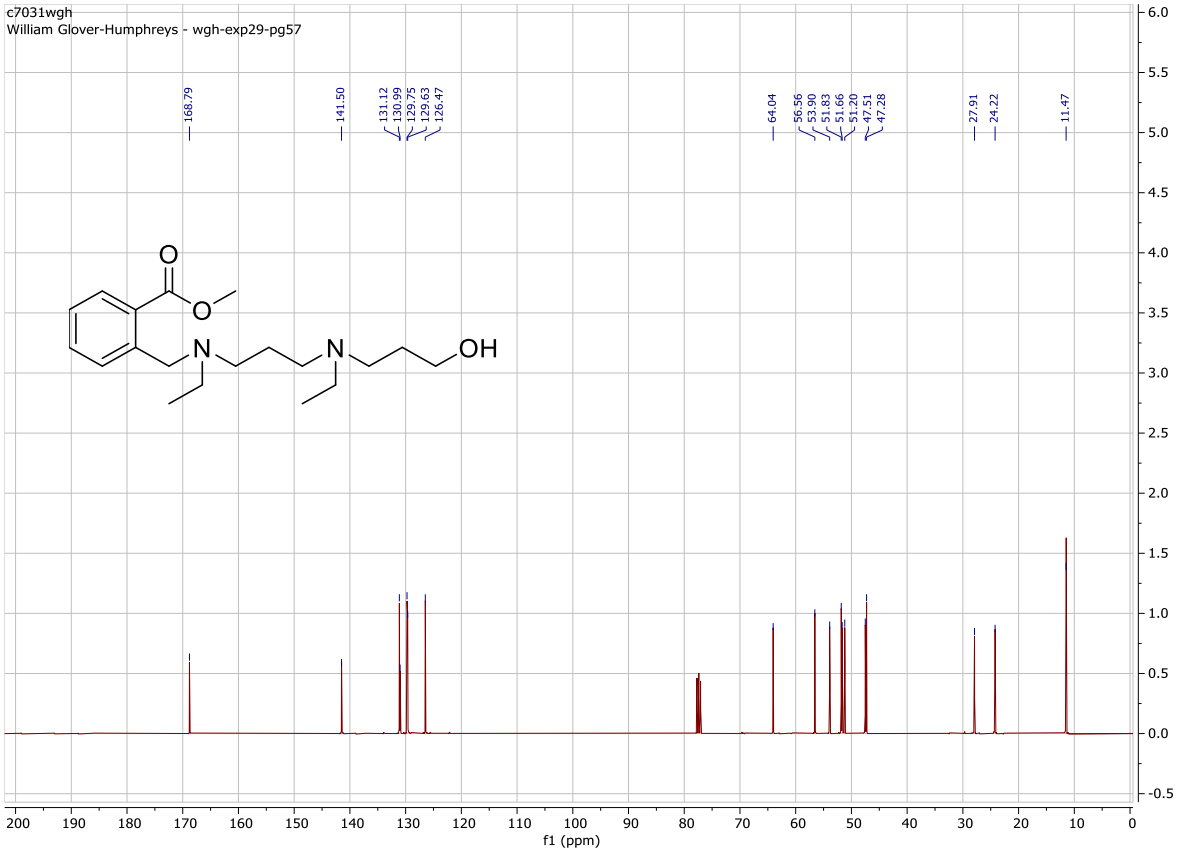
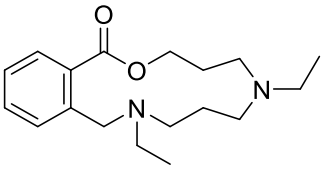
7.55
7.42
7.40
7.27
7.11
5.09
3.72
3.70
3.59
2.44
2.35
2.29
2.22
1.52
1.40
0.88
0.86
0.85
0.83
O
O
N
N
OH
1.00
1.00
1.05
1.02
1.09
2.99
1.91
1.98
2.04
4.13
3.97
4.02
5.97
f1 (ppm)


c7031wgh
William Glover-Humphreys - wgh-exp29-pg57
168.79
141.50
131.12
130.99
129.75
129.63
126.47
64.04
56.56
53.90
51.83
51.66
51.20
47.51
47.28
27.91
24.22
11.47
O
O
N
N
OH
f1 (ppm)

6,10-Diethyl-4,5,6,7,8,9,10,11-octahydrobenzo[*k*][1] oxa [5,9] diazacyclotridecin-1(3*H*)-one (6-25)

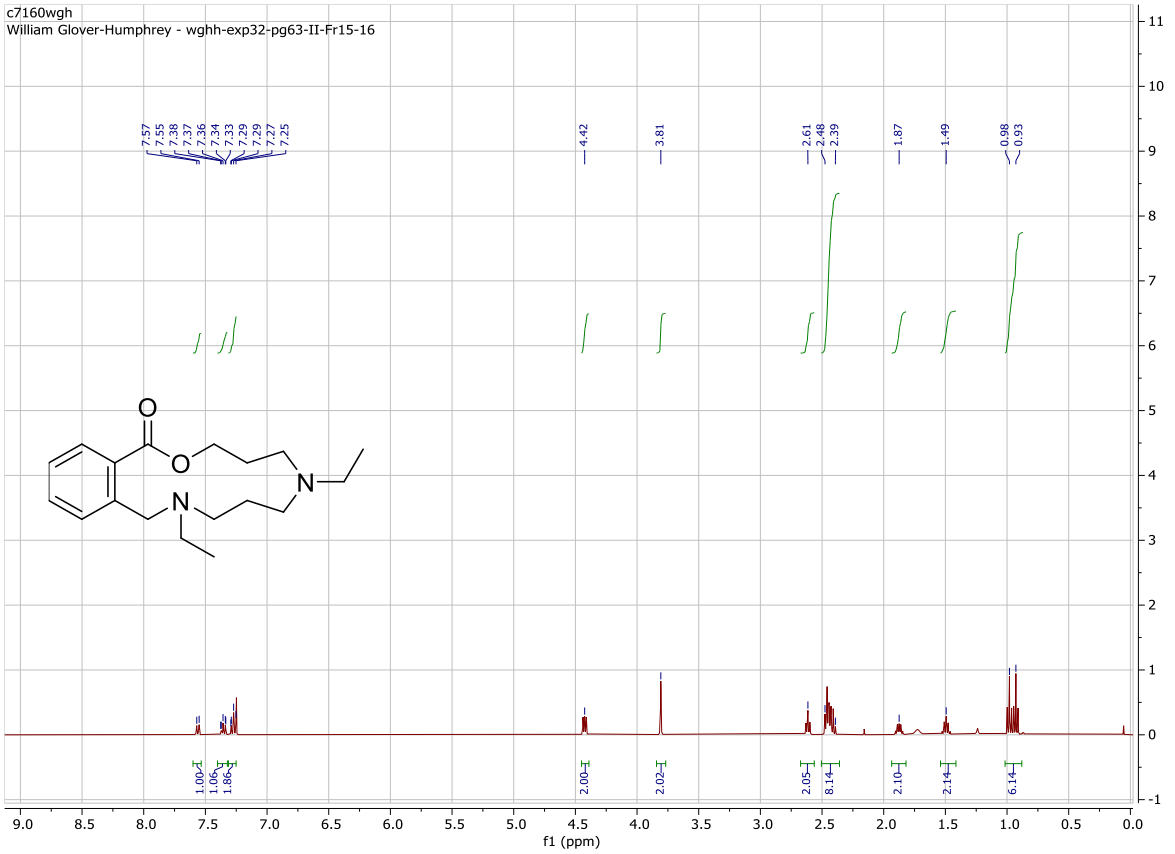


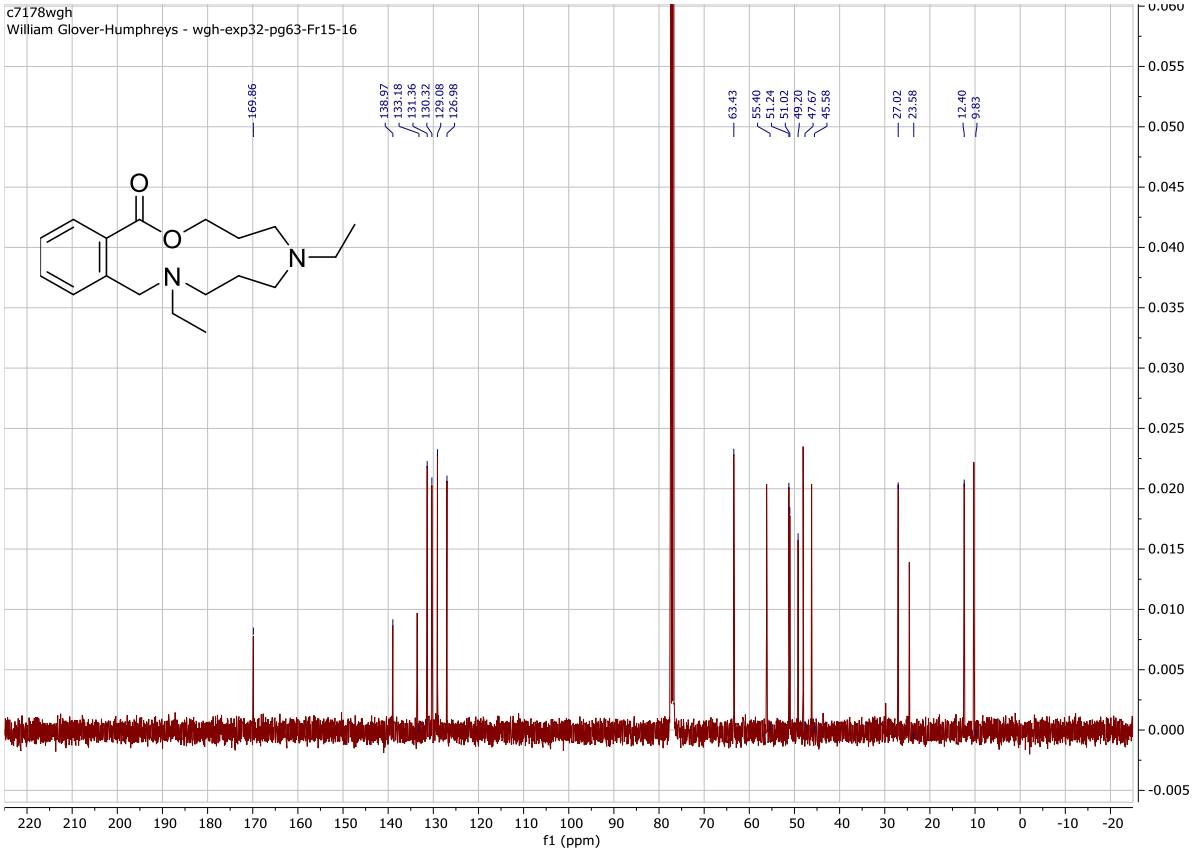
Procedure A

To a stirring solution of methyl 2-((ethyl(3-(ethyl(3-hydroxypropyl) amino) propyl) amino) methyl) benzoate (**6-23**) (0.115 g, 0.341 mmol) in tetrahydrofuran (0.8 mL), aqueous lithium hydroxide (0.5 M) (0.800 mL, 0.400 mmol) was added and heated for at 50 °C for 3 hours. The solvent was removed under vacuum using dichloromethane (5 × 50 mL) to form an azeotropic mixture. The intermediate lithium 2-((ethyl(3-(ethyl(3-oxidopropyl) amino) propyl) amino) methyl) benzoate was dissolved in chloroform (3.4 mL) and DIPEA (0.082 g, 0.11 mL, 0.630 mmol) was added followed by T3P in ethylacetate 50% w/v (0.334 g, 0.540 mmol) to stir at room temperature for 18 hours under argon. The reaction mixture was repeatedly washed sequentially in brine (100 mL) and dichloromethane (100 mL) and the organic phases combined dried with sodium sulfate, filtered, concentrated under vacuum, and purified via flash column chromatography (hexane:dichloromethane:triethylamine 10:9:1) to afford the title compound (21.8 mg, 21%) R_f = 0.54 (hexane:dichloromethane:triethylamine 10:9:1).

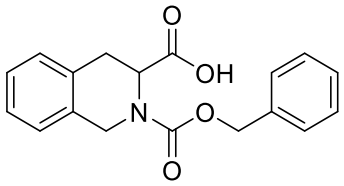
Procedure B

To a stirring solution of methyl 2-((ethyl(3-(ethyl(3-hydroxypropyl) amino) propyl) amino) methyl) benzoate (**6-23**) (0.112 g, 0.332 mmol) in tetrahydrofuran (0.8 mL), aqueous lithium hydroxide (0.5 M) (0.800 mL, 0.400 mmol) was added and heated for at 50 °C for 3 hours. The solvent was removed under vacuum using dichloromethane (5 × 50 mL) to form an azeotropic mixture. The intermediate lithium 2-((ethyl (3-(ethyl (3-oxidopropyl) amino) propyl) amino) methyl) benzoate was dissolved in acetonitrile (3.3 mL) and DIPEA (0.233 g, 0.310 mL, 1.80 mmol) was added followed by HOBt (0.0680 g, 0.500 mmol) and EDCI (0.0780 g, 0.500 mmol) and left to stir at room temperature for 18 hours under argon. The reaction mixture was washed sequentially in brine (50 mL) and diethyl ether (3 × 50 mL) and the organic phases combined dried with sodium sulfate, filtered, concentrated under vacuum and purified via flash column chromatography (hexane:dichloromethane:triethylamine 10:9:1) to afford the title compound (46.4 mg, 46%) R_f = 0.54 (hexane:dichloromethane:triethylamine 10:9:1); ν_{max}/cm^{-1} (thin film) 2965, 2801, 1723, 1457, 1375, 1271, 1127, 1085, 787, 743; δ_H (400 MHz, $CDCl_3$) 7.57−7.55 (1H, m, Ar**H**), 7.36 (1H, td, *J* = 7.6 Hz, 1.5 Hz, Ar**H**), 7.29−7.25 (2H, m, 2 × Ar**H**), 4.42 (2H, t, *J* = 5.5 Hz, OC**H**$_2$CH$_2$), 3.81 (2H, s, ArC**H**$_2$N), 2.61 (2H, t, *J* = 6.5 Hz, CH$_2$C**H**$_2$N), 2.47−2.39 (8H, m, C**H**$_2$N), 1.87 (2H, quintet, *J* = 6.4 Hz, CH$_2$C**H**$_2$CH$_2$), 1.49 (2H, quintet, *J* = 6.4 Hz, CH$_2$C**H**$_2$CH$_2$), 0.98 (3H, t, *J* = 7.0 Hz, C**H**$_3$CH$_2$O), 0.93 (3H, t, *J* = 7.3 Hz, C**H**$_3$CH$_2$O); δ_c (100 MHz, $CDCl_3$) 169.9 (**C**O), 139.0 (Ar**C**), 133.2 (Ar**C**), 131.4 (Ar**C**H), 130.3 (Ar**C**H), 129.1 (Ar**C**H), 127.0 (Ar**C**H), 63.4 (O**C**H$_2$CH$_2$)), 55.4 (Ar**C**H$_2$N), 51.2 (CH$_2$**C**H$_2$N), 51.0 (**C**H$_2$N), 49.2 (**C**H$_2$N), 45.6(**C**H$_2$N), 27.0 (CH$_2$**C**H$_2$CH$_2$), 23.6 (CH$_2$**C**H$_2$CH$_2$), 12.4 (**C**H$_3$CH$_2$N), 9.8 (**C**H$_3$CH$_2$N); HRMS (ESI) calcd. for $C_{18}H_{29}N_2O_2$, 305.2229. Found $[MH]^+$ 305.2223 (−1.97 ppm error).

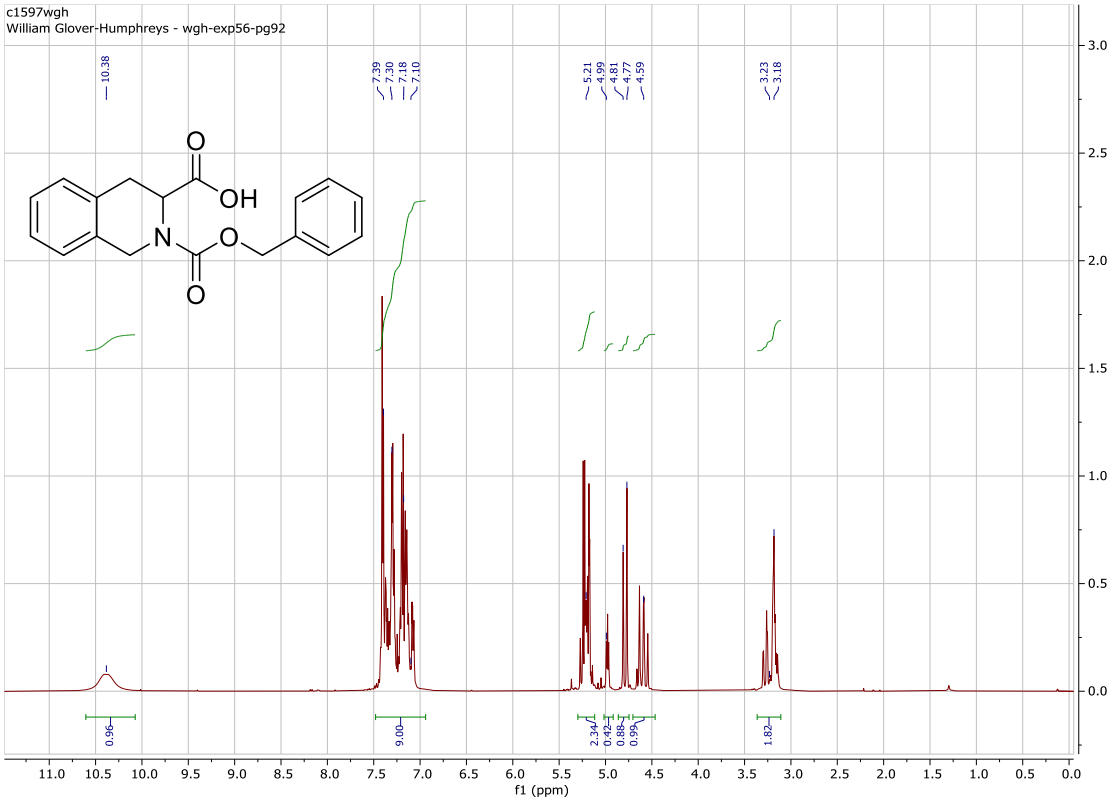

c7160wgh
William Glover-Humphrey - wghh-exp32-pg63-II-Fr15-16
7.57
7.55
7.38
7.37
7.36
7.34
7.33
7.29
7.29
7.27
7.25
4.42
3.81
2.61
2.48
2.39
1.87
1.49
0.98
0.93
1.00
1.06
1.86
2.00
2.02
2.05
8.14
2.10
2.14
6.14
f1 (ppm)

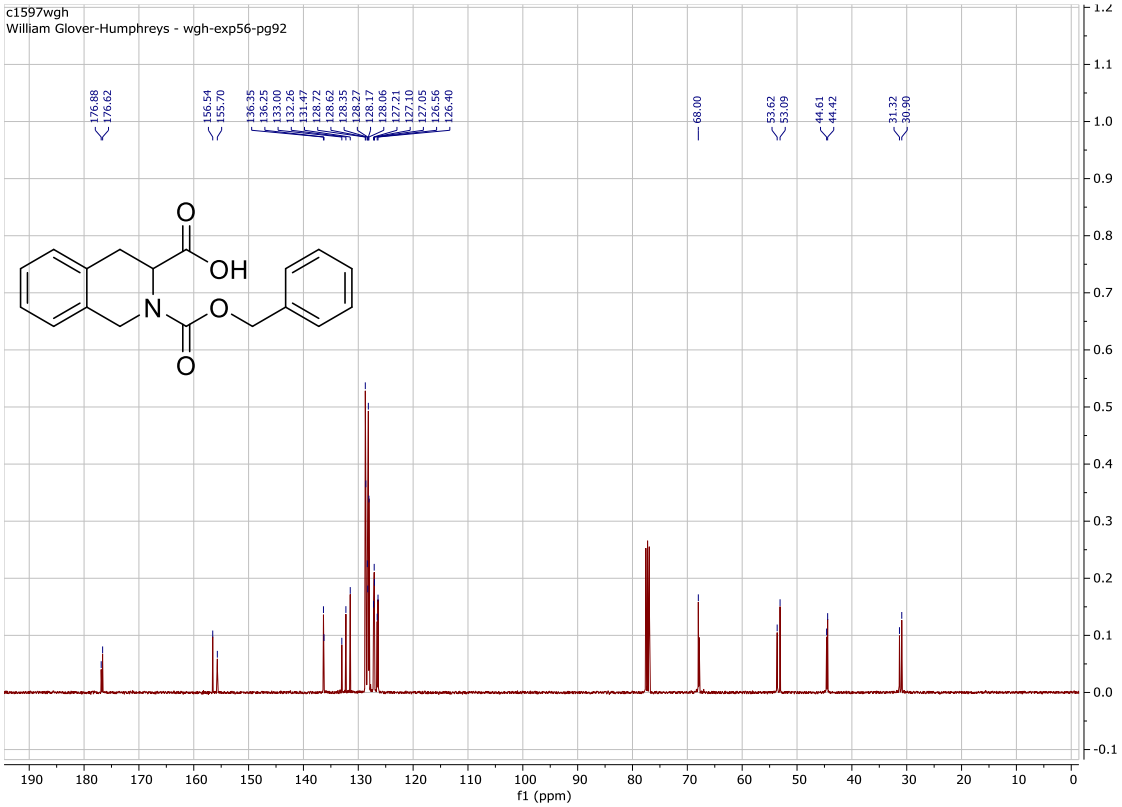

c7178wgh
William Glover-Humphreys - wgh-exp32-pg63-Fr15-16
169.86
138.97
133.18
131.36
130.32
129.08
126.98
63.43
55.40
51.24
51.02
49.20
47.67
45.58
27.02
23.58
12.40
9.83
f1 (ppm)

2-[(Benzyloxy)carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (6-31)

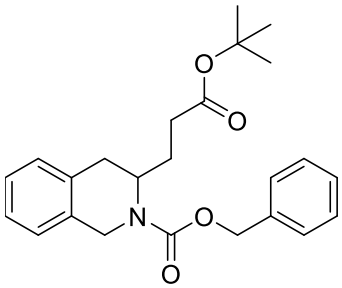


To a stirring solution of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid **(6-26)** (5.00 g, 28.2 mmol) in THF (50 mL) and DI water (150 mL), solid sodium hydroxide (2.26 g, 56.4 mmol) was added, and the reaction mixture was cooled in an ice bath. Benzyl chloroformate **(6-30)** (5.77 g, 33.8 mmol) was added dropwise over an hour and left stirring at room temperature overnight. The reaction mixture was cooled in an ice bath and 10% HCl (approximately 70 mL) solution was added dropwise until the reaction mixture reached pH 2 tested by pH indicator sticks. The solution was extracted in ethyl acetate (80 mL × 3) and the organic phases combined and washed sequentially with brine (100 mL × 3). The aqueous phase was then back extracted with ethyl acetate (100 mL × 2). The organic phases were combined, dried with sodium sulfate, filtered and the solvent removed under vacuum. The reaction mixture was purified via flash column chromatography (8:1 dichloromethane:methanol) isolating a very viscous orange oil (5.71 g, 65%); R_f = 0.27 (8:1 dichloromethane:methanol); ν_{max}/cm^{-1} (thin film) 3439, 3031, 2968, 2579, 1697, 1419, 1318, 1220, 1122, 747, 698; δ_H (400 MHz, $CDCl_3$) 10.80 (1H, bs, COO**H**)**,** 7.39−7.06 (m, 9H, Ar**H**), 5.26−5.19 (2H, m, OC$\mathbf{H}_2$), 5.26−5.19 (0.5H, m, C**H**), 4.96 (0.5H, app t, *J* = 5.1 Hz, C**H**), 4.82−4.76 (1H, m, C$\mathbf{H_a}H_b$N), 4.66−4.54 (1H, m, $CH_a\mathbf{H_b}$N), 3.30−3.14 (2H, m, C$\mathbf{H}_2$CH); δ_c (100 MHz, $CDCl_3$) rotameric ratio 3:4 176.9_{minor} & 176.7_{major} (**C**OOH), 156.5_{major} & 155.7_{minor} (N**C**O), 136.4_{major} & 136.3_{minor} (Ar**C**), 133.0_{minor} & 132.3_{major} (Ar**C**), 131.5 (Ar**C**), 128.7_{major} & 128.6_{minor} (Ar**C**H), 128.4 (Ar**C**H), 128.3 (Ar**C**H), 128.2_{major} & 128.1_{minor} (Ar**C**H), 127.1 (Ar**C**H), 127.2_{minor} & 127.0_{major} (Ar**C**H), 126.6_{minor} & 126.4_{major} (Ar**C**H), 68.0_{major} & 67.9_{minor} (O**C**H_2), 53.6_{minor} & 53.1_{major} (**C**H), 44.6_{minor} & 44.4_{major} (**C**H_2N), 31.3_{minor} & 30.9_{major} (**C**H_2); HRMS (ESI): calcd. for $C_{18}H_{18}NO_4$ 334.1055. Found $[MNa]^+$ 334.1051 (−0.32 ppm error).


c1597wgh
William Glover-Humphreys - wgh-exp56-pg92
10.38
7.39
7.30
7.18
7.10
5.21
4.99
4.81
4.77
4.59
3.23
3.18
OH
N
O
O
O
0.96
9.00
2.34
0.42
0.88
0.99
1.82
f1 (ppm)


c1597wgh
William Glover-Humphreys - wgh-exp56-pg92
176.88
176.62
156.54
155.70
136.35
136.25
133.00
132.26
131.47
128.72
128.62
128.35
128.27
128.17
128.06
127.21
127.10
127.05
126.56
126.40
68.00
53.62
53.09
44.61
44.42
31.32
30.90
OH
N
O
O
O
f1 (ppm)

Benzyl 3-(3-*tert*-butoxy-3-oxopropyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (6-34)



To a 250 mL round bottom flask Isolating 2-[(benzyloxy)carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**6-31**) (3.74 g, 12.0 mmol), IrdF(CF)$_3$ppy)$_2$(dtbbpy)]PF$_6$ **(6-33)** (0.135 g, 0.120 mmol) and dipotassium phosphate (2.51 g, 14.4 mmol) was added to DMF (30 mL) and degassed for 15 minutes using argon. Separately *tert*-butyl acrylate **(6-32)** (3.00 mL) was degassed again for 15 minutes using argon. *tert*-Butyl acrylate (12.0 mmol, 1.54 g) was then added to the 250 mL round bottom flask topped with a septum wrapped with parafilm several times. The reaction mixture was irradiated with blue LED light for 72 hours whilst stirring, setup as shown in Figure 22. The reaction was quenched in saturated $NaHCO_3$ aqueous solution (100 mL) and extracted in Et_2O (3 × 50 mL). The organic layers were collected and washed sequentially with saturated NaCl aqueous solution (2 × 100 mL) and water (2 × 100 mL). The organic phases were collected and dried with sodium sulfate and the solvent removed under vacuum. The reaction mixture was purified via flash column chromatography (8:2 hexane:ethyl acetate) to afford the title compound as a clear yellow oil (2.36 g, 50%); R_f = 0.36 (8:2 hexane:ethyl acetate); ν_{max}/cm^{-1} (thin film) 2976, 2933, 1725, 1695, 1416, 1242, 1144, 846, 749, 697; δ_H (400 MHz, $CDCl_3$) rotameric ratio 1:1 7.41−7.29 (5H, m, Ar**H**), 7.19−7.02 (4H, m, Ar**H**), 5.18 (2H, s, OC**H**$_2$Ar), 5.05−4.87 (1H, m, ArC**H**$_a$H$_b$N), 4.68−4.51 (1H, m, C**H**N), 4.34−4.21 (1H, m, CH$_a$**H$_b$**), 3.15−3.06 (1H, m, C**H**$_a$H$_b$CO), 2.69−2.60 (1H, m, CH$_a$**H$_b$**CO), 2.34−2.15 (2H, m, ArC**H**$_2$CH), 1.83−1.70 (1H, m, C**H**$_a$H$_b$), 1.69−1.53 (1H, m, CH$_a$**H$_b$**), 1.43 (9H, s, OC(C**H**$_3$)$_3$); δ_c (100 MHz, $CDCl_3$) rotomeric ratio 1:1 172.5 & 172.4 (N**C**O), 155.8 & 155.7 (O**C**O), 136.80 (Ar**C**), 132.6 & 132.4 (Ar**C**), 132.2 & 132.1 (Ar**C**), 129.5 & 129.3 (Ar**C**H), 128.7 (Ar**C**H), 128.2 (Ar**C**H), 128.1 (Ar**C**H), 126.8 (Ar**C**H), 126.4 (Ar**C**H), 126.3 & 126.1 (Ar**C**H), 80.5 (O**C**(CH$_3$)$_3$), 67.4 (Ar**C**H$_2$O), 49.5 & 49.2 (N**C**H), 42.6 & 42.5 (**C**H$_2$N), 33.5 & 33.1 (**C**H$_2$), 32.5 & 32.3 (**C**H$_2$), 28.2 (OC(**C**H$_3$)$_3$), 27.1 (**C**H$_2$); HRMS (ESI): calcd. for $C_{24}H_{29}NNaO_4$ 418.1994. Found $[MNa]^+$ 418.1994 (0.00 ppm error).

The same procedure was followed but IrdF(CF)$_3$ppy)$_2$(dtbbpy)]PF$_6$ **(6-33)** was replaced with 2,4,5,4-tetrakis(carbazol-9-yl)-1,3-dicyanobenze (4CzIPN) **(6-37)** (0.095g, 0.120 mmol) to afford the title compound as a clear yellow oil (2.42 g, 50%).

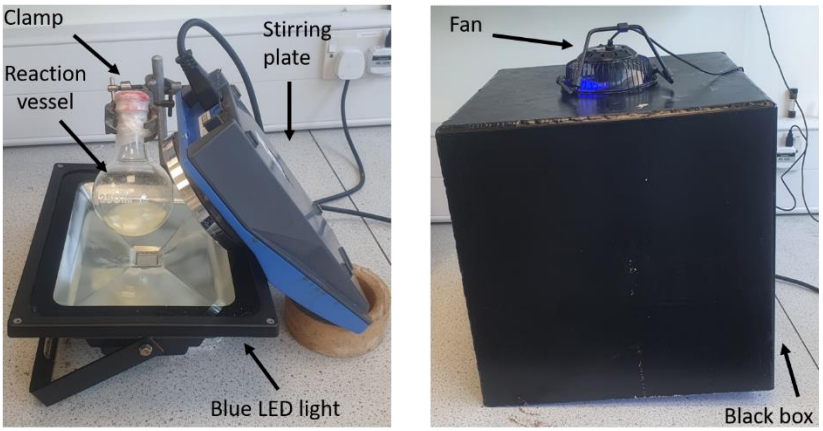
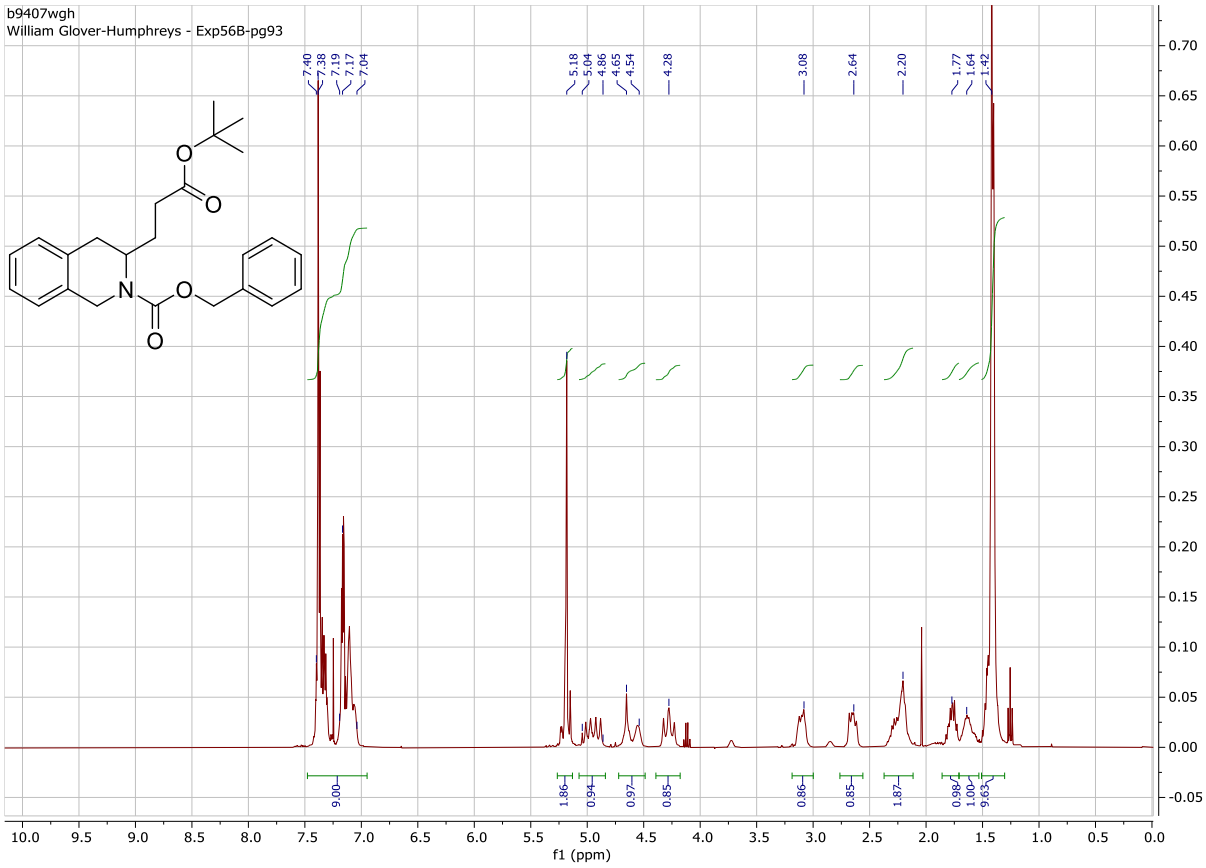
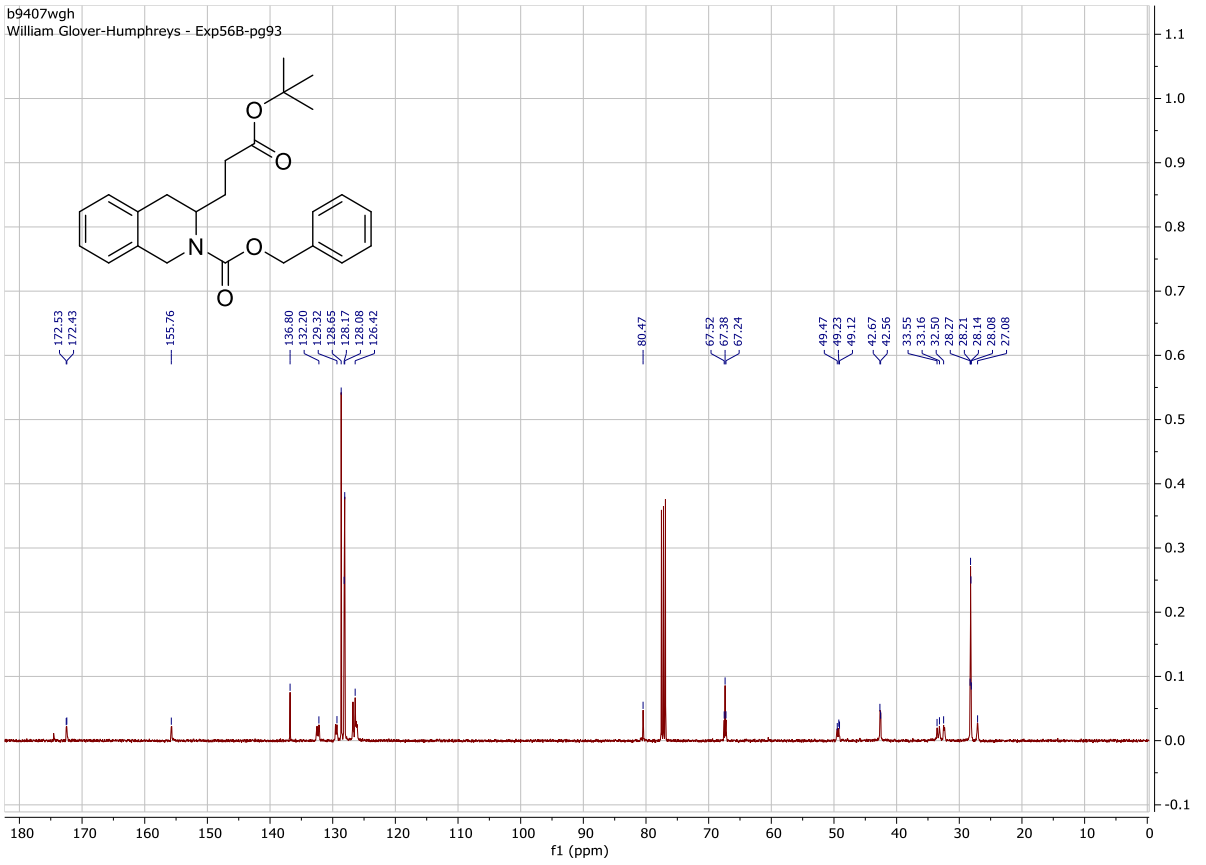
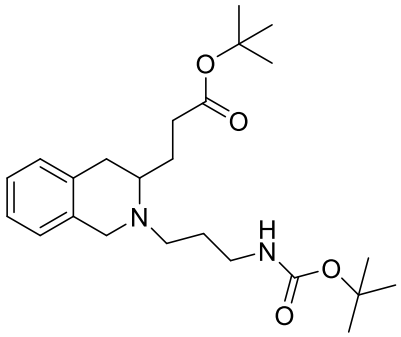


Figure 22 : - Photoredox reaction set up using blue LED light box.

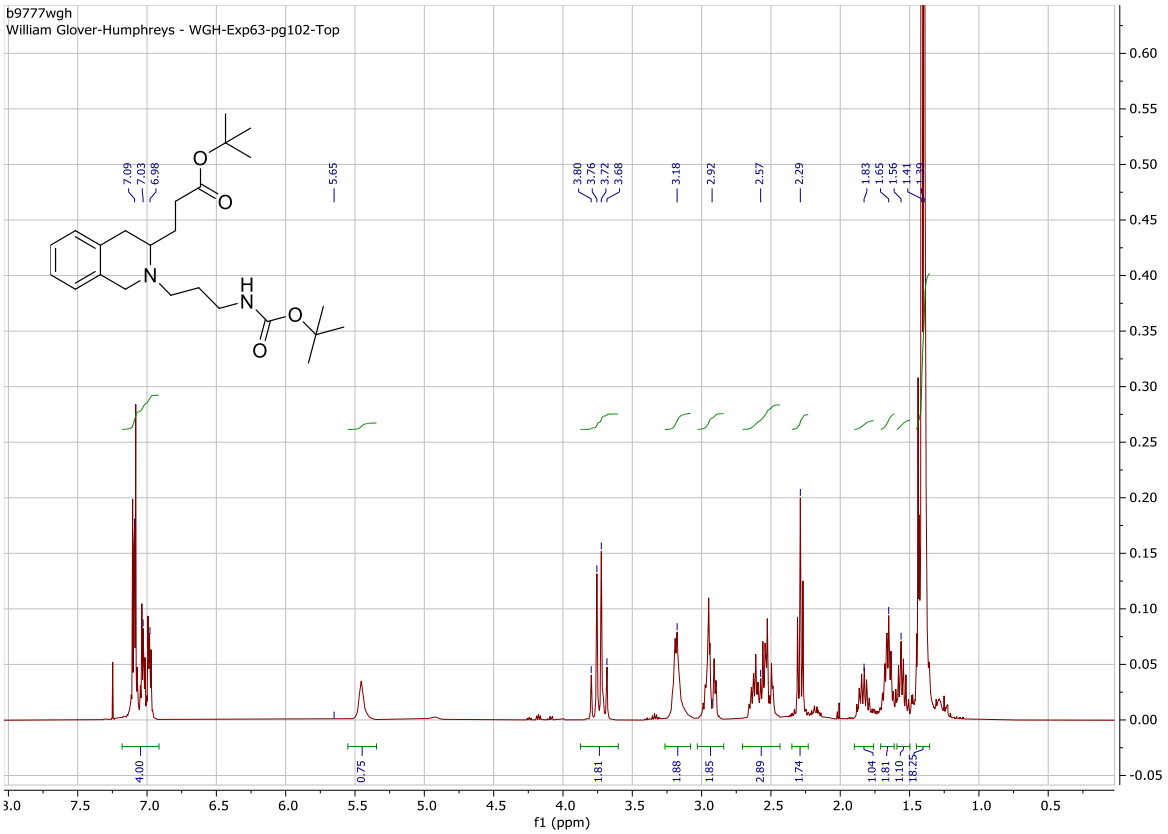

b9407wgh
William Glover-Humphreys - Exp56B-pg93
7.40
7.38
7.19
7.17
7.04
5.18
5.04
4.86
4.65
4.54
4.28
3.08
2.64
2.20
1.77
1.64
1.42
9.00
1.86
0.94
0.97
0.85
0.86
0.85
1.87
0.98
1.00
9.63
f1 (ppm)

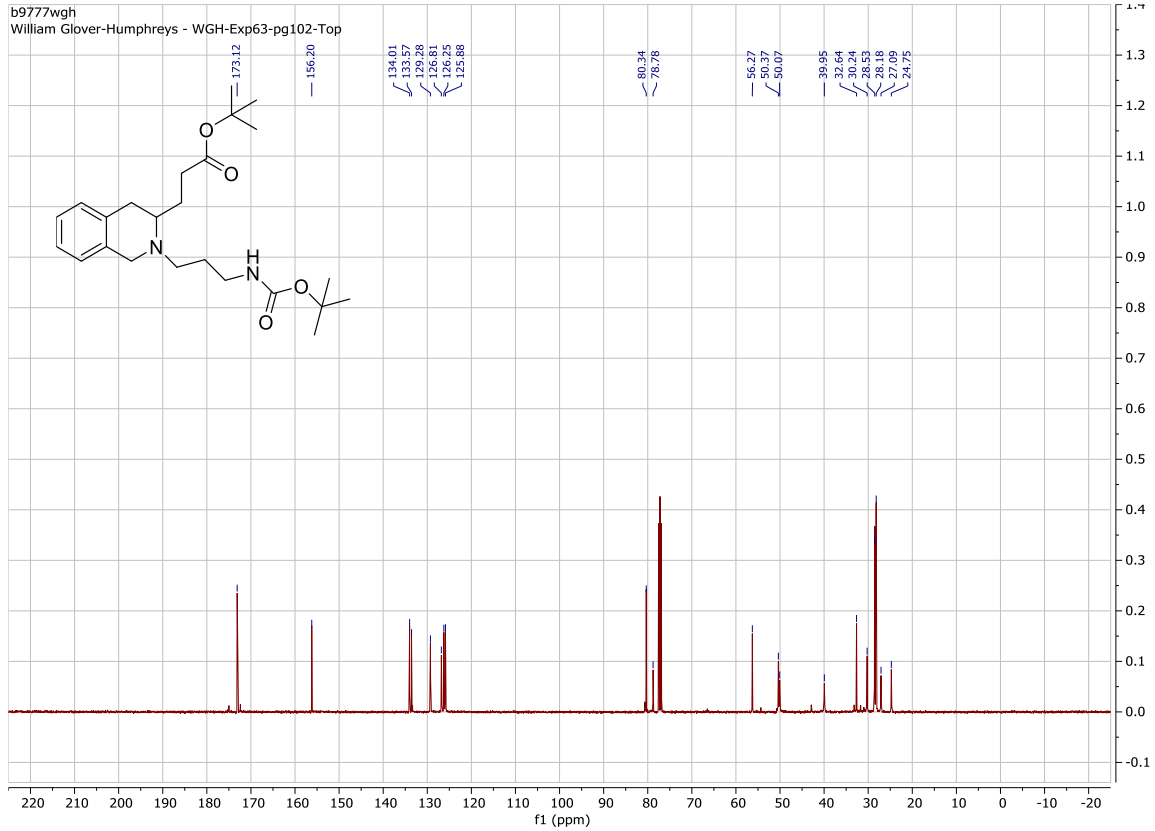

b9407wgh
William Glover-Humphreys - Exp56B-pg93
172.53
172.43
155.76
136.80
132.20
129.32
128.65
128.17
128.08
126.42
80.47
67.52
67.38
67.24
49.47
49.23
49.12
42.67
42.56
33.55
33.16
32.50
28.27
28.21
28.14
28.08
27.08
f1 (ppm)

***tert*-Butyl 3-(2-(3-[(*tert*-butoxycarbonyl) amino] propyl)-1,2,3,4-tetrahydroisoquinolin-3-yl) propanoate (6-40)**

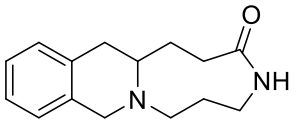


10% Palladium on carbon (0.230 g) was added to benzyl 3-(3-*tert*-butoxy-3-oxopropyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate **(6-34)** (2.98 g, 7.54 mmol) in ethanol (30 mL) under argon. The solution was evacuated and refilled with hydrogen (× 3) then stirred at room temperature overnight whilst excess hydrogen refills the reaction vessel. The mixture was filtered through Celite and washed with ethanol (100 mL) and the solvent was removed under vacuum using acetonitrile (3 × 15 mL) to make an azeotropic mixture. The mixture was redissolved in acetonitrile (30 mL) then potassium carbonate (2.08 g, 15.1 mmol) and 3-(Boc-amino) propyl bromide **(6-39)** (1.80 g, 7.54 mmol) was added and refluxed overnight under argon. The reaction mixture was diluted with EtOAc (250 mL) and washed with saturated $NaHCO_3$ aqueous solution (200 mL) then back extracted with EtOAc (2 × 150 mL). The organic phases were collected and dried using sodium sulfate, filtered and the solvent removed under vacuum. The reaction mixture was purified via flash column chromatography (15:2:1 hexane:ethyl acetate:triethylamine) to afford the title compound as a colourless oil (1.23 g, 39%); R_f = 0.53 (15:2:1 hexane:ethyl acetate:triethylamine); ν_{max}/cm^{-1} (thin film) 3369, 2976, 2932, 2249, 1709, 1504, 1454, 1391, 1365, 1248, 1149, 735; δ_H (400 MHz, $CDCl_3$) 7.11−6.96 (4H, m, ArC**H**), 5.46 (1H, bs, N**H**), 3.80−3.67 (2H, m, NC**H**$_2$), 3.22−3.13 (2H, m, C**H**$_2$NH), 2.99−2.89 (1H, m, C**H**N), 2.99−2.89 (1H, m, ArC**H**$_a$H$_b$), 2.65−2.48 (1H, m, ArCH$_a$**H**$_b$), 2.65−2.48 (2H, m, NC**H**$_2$), 2.29 (2H, t, *J* = 7.65 Hz, C**H**$_2$CO), 1.88−1.79 (1H, m, CHC**H**$_a$H$_b$), 1.69−1.61 (2H, m, CH$_2$C**H**$_2$CH$_2$), 1.59−1.50 (1H, m, CHCH$_a$**H**$_b$), 1.41 (9H, s, OC(C**H**$_3$)$_3$), 1.39 (9H, bs, OC(C**H**$_3$)$_3$); δ_c (100 MHz, $CDCl_3$) 173.1 (CH$_2$**C**O), 156.1 (NH**C**O), 134.0 (Ar**C**), 133.6 (Ar**C**), 129.3 (Ar**C**H), 126.8 (Ar**C**H), 126.2 (Ar**C**H), 125.9 (Ar**C**H), 80.3 (O**C**(CH$_3$)$_3$), 78.8 (O**C**(CH$_3$)$_3$), 56.3 (**C**HN), 50.4 (Ar**C**H$_2$N) 50.1 (**C**H$_2$N), 39.9 (**C**H$_2$NH), 32.6 (**C**H$_2$CO), 30.2 (ArC**H**$_2$), 28.5 (OC(**C**H$_3$)$_3$), 28.2 (OC(**C**H$_3$)$_3$), 27.1 (**C**H$_2$), 24.8 (**C**H$_2$); HRMS (ESI): calcd. for $C_{24}H_{39}N_2O_4$ 419.2910. Found $[MH]^+$ 419.2912 (0.48 ppm error).

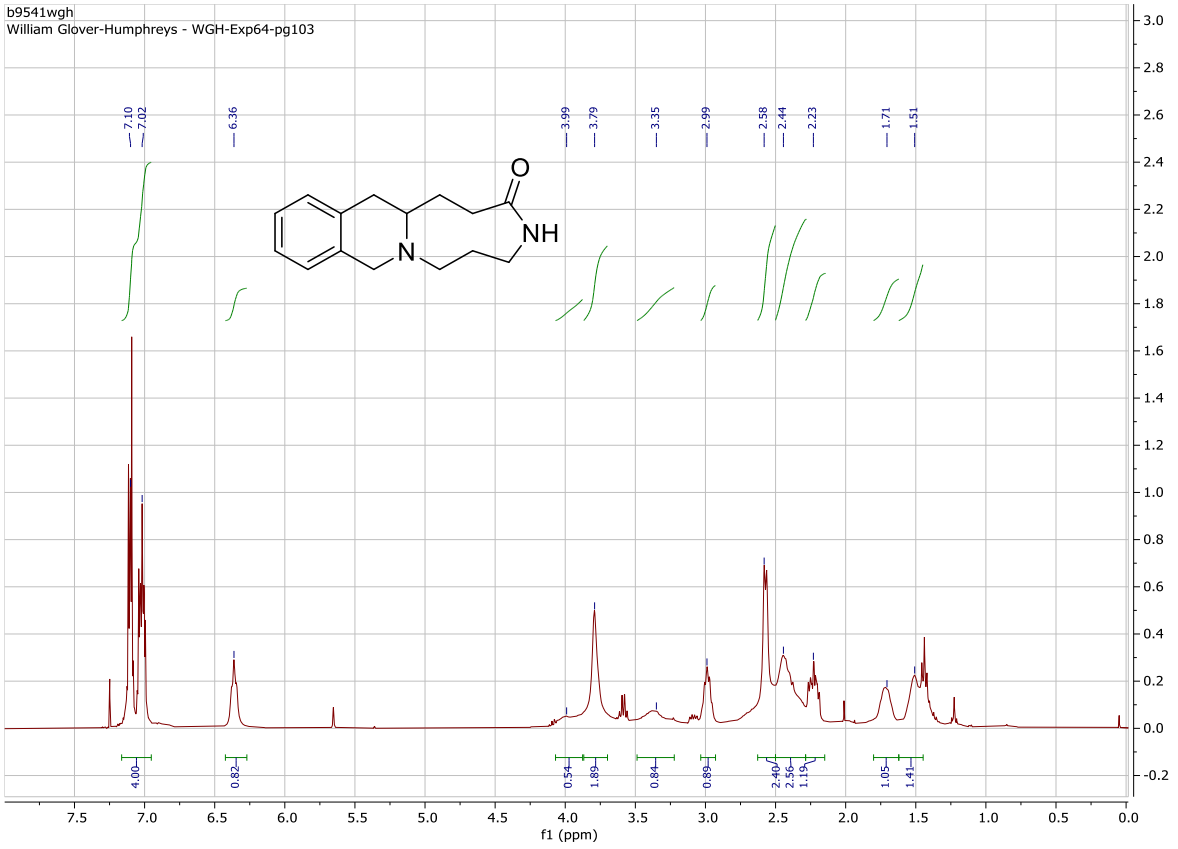

b9777wgh
William Glover-Humphreys - WGH-Exp63-pg102-Top
7.09
7.03
6.98
5.65
3.80
3.76
3.72
3.68
3.18
2.92
2.57
2.29
1.83
1.65
1.56
1.41
1.39
4.00
0.75
1.81
1.88
1.85
2.89
1.74
1.04
1.81
1.10
18.25
f1 (ppm)

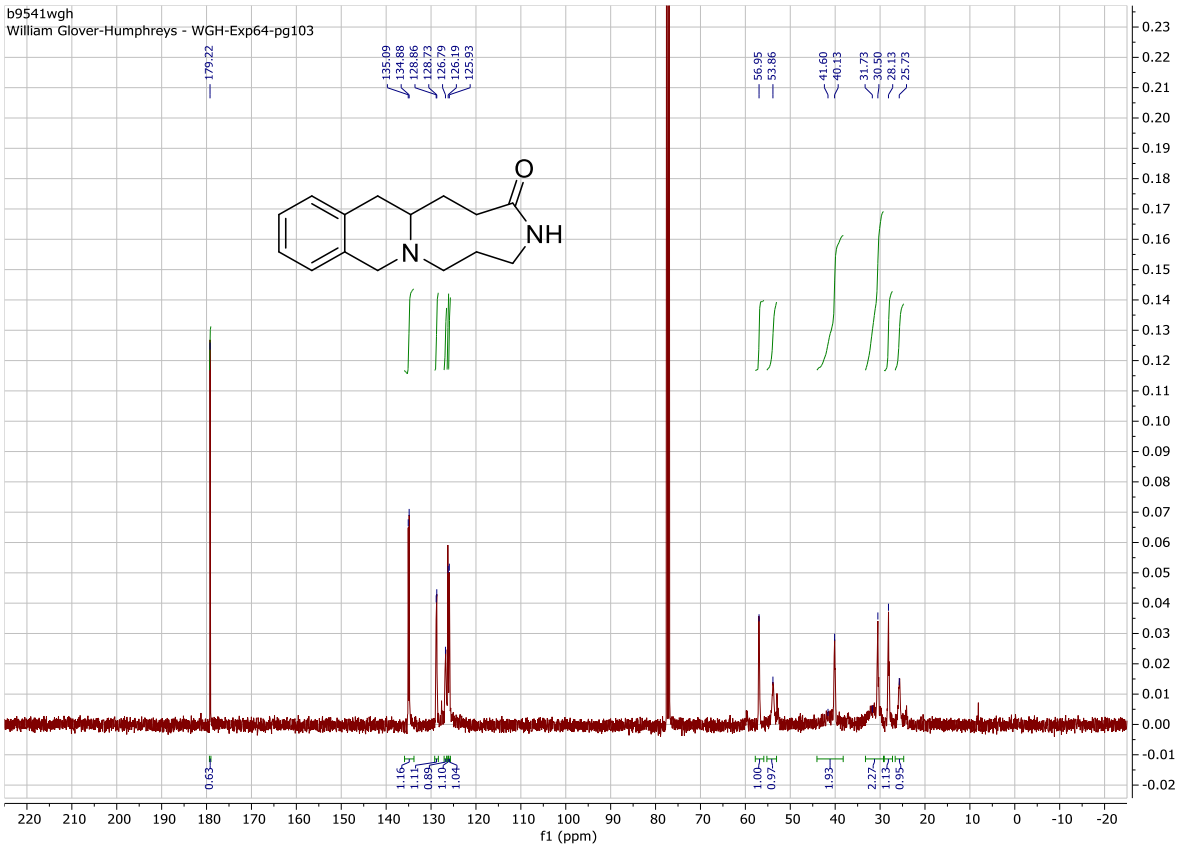

b9777wgh
William Glover-Humphreys - WGH-Exp63-pg102-Top
173.12
156.20
134.01
133.57
129.28
126.81
126.25
125.88
80.34
78.78
56.27
50.37
50.07
39.95
32.64
30.24
28.53
28.18
27.09
24.75
f1 (ppm)

1,4,5,6,7,9,14,14a-octahydro [1,5] diazonino[1,9-*b*] isoquinolin-3(2*H*)-one (6-42)

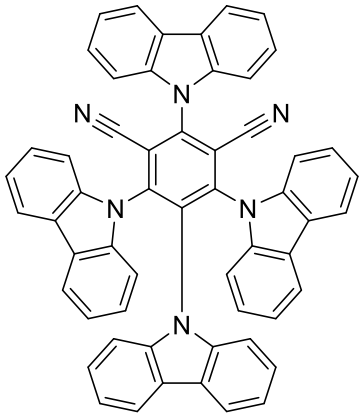


To a stirring solution of *tert*-butyl 3-(2-(3-[(*tert*-butoxycarbonyl) amino] propyl)-1,2,3,4-tetrahydroisoquinolin-3-yl) propanoate (**6-40**) (0.155 g, 0.370 mmol) in diethyl ether (1.00 mL), a solution of 4.0 M hydrochloric acid in 1,4 dioxane (1.85 mL, 7.2 mmol) was added dropwise and the reaction was left stirring at room temperature for 3 hours. The reaction mixture was concentrated under vacuum using chloroform (3 × 10 mL) to make an azeotropic solution. The intermediate 3-[2-(3-aminopropyl)-1,2,3,4-tetrahydroisoquinolin-3-yl] propanoic acid (**6-41**) was dissolved in chloroform (13 mL) and DIPEA (0.48 g, 3.7 mmol) under argon, until all the reagents dissolved into solution (30 minutes). T3P (0.353 g, 0.56 mmol) was then added and the reaction left to stir over night at room temperature. The solvent was removed under vacuum and the reaction mixture was purified via flash column chromatography (70:25:5 dichloromethane:hexane:triethylamine) forming the product a clear oil (75.1 mg, 83%); R_f = 0.47 (70:25:5 dichloromethane:hexane:triethylamine); ν_{max}/cm^{-1} (thin film) 3281, 3206, 2928, 2841, 2225 1646, 1473, 1449 1127, 908, 725; δ_H (400 MHz, $CDCl_3$) significant rotameric broadening of NMR signals was observed 7.12−7.00 (4H, m, Ar**H**), 6.36 (1H, t, *J* = 6.68 Hz, CON**H**), 4.08−3.85 (1H, bm, C**H**$_a$H$_b$N), 3.79−3.69 (2H, bs, ArC**H**$_2$N), 3.48−3.23 (1H, bm, C**H**$_a$H$_b$N), 2.98 (1H, q, *J* = 7.11 Hz, C**H**N), 2.57 (2H, d, *J* = 7.06 Hz, ArC**H**$_2$CH), 2.50−2.28 (2H, m, C**H**$_2$CO), 2.28−2.16 (1H, m, C**H**$_a$H$_b$N), 1.79−1.66 (1H, m, CH$_a$**H**$_b$N), 1.57−1.44 (2H, bm, C**H**$_2$); δ_c (100 MHz, $CDCl_3$) 179.2 (**C**O), 135.1 (Ar**C**), 134.9 (Ar**C**), 128.9 & 128.7 (Ar**C**H), 126.8 (Ar**C**H), 126.2 (Ar**C**H), 125.9 (Ar**C**H), 57.0 (**C**HN), 53.9 (Ar**C**H$_2$N), 41.6 (**C**H$_2$N), 40.1 (**C**H$_2$NH), 31.7 (**C**H$_2$CO), 30.5 (Ar**C**H$_2$CH), 28.1 (C**H**$_2$), 25.7 (C**H**$_2$); HRMS (ESI): calcd for $C_{15}H_{21}N_2O$ 245.1654. Found $[MH]^+$ 245.1646 (−3.26 ppm error).

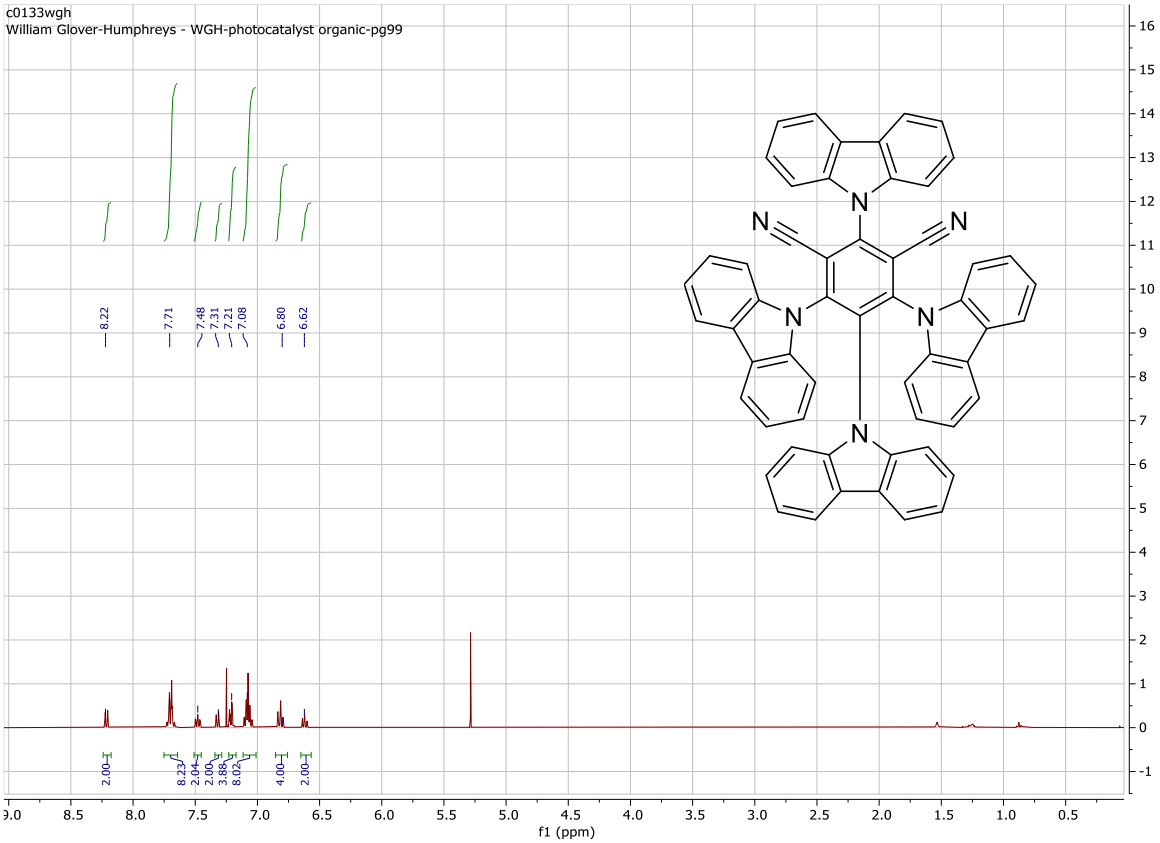

b9541wgh
William Glover-Humphreys - WGH-Exp64-pg103
7.10
7.02
6.36
3.99
3.79
3.35
2.99
2.58
2.44
2.23
1.71
1.51
O
NH
N
4.00
0.82
0.54
1.89
0.84
0.89
2.40
2.56
1.19
1.05
1.41
f1 (ppm)


b9541wgh
William Glover-Humphreys - WGH-Exp64-pg103
179.22
135.09
134.88
128.86
128.73
126.79
126.19
125.93
56.95
53.86
41.60
40.13
31.73
30.50
28.13
25.73
O
NH
N
0.63
1.16
1.11
0.89
1.10
1.04
1.00
0.97
1.93
2.27
1.13
0.95
f1 (ppm)

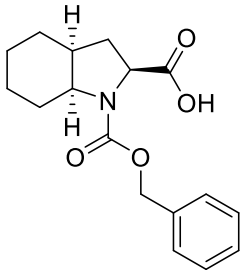
2,4,5,4-Tetra(9*H*-carbazol-9-yl)benzene-1,3-dicarbonitrile[30] (6-37)



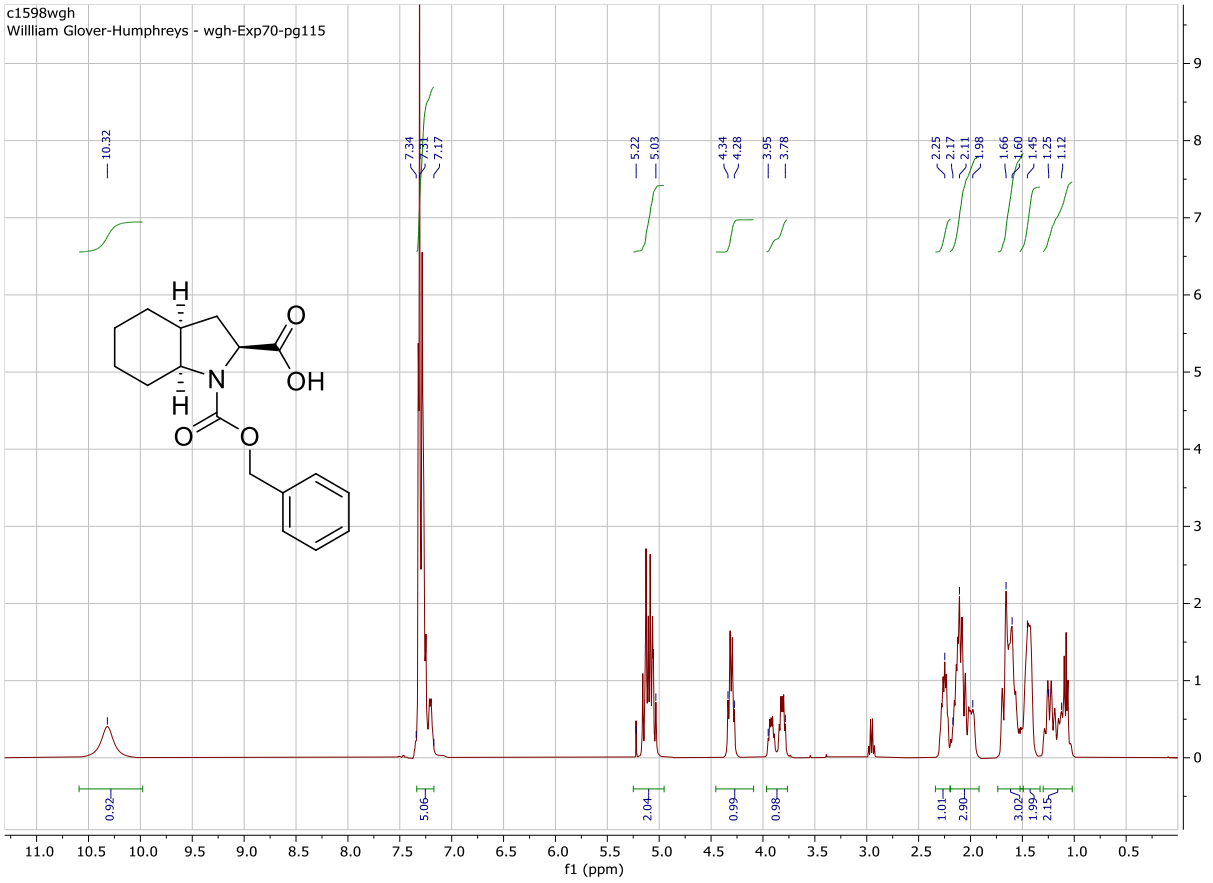
To a stirring solution of carbazole **(6-36)** (1.67 g, 10.0 mmol) in THF (40 mL) under argon, sodium hydride (60% w/w in mineral oil) (0.600 g, 15.0 mmol) was added in small amounts. After half an hour tetrafluoroisophthalonitrile **(6-35)** (0.400 g, 2.00 mmol) was added and the reaction mixture was stirred for 16 hours at room temperature. Water (2.00 mL) was added dropwise over a 10-minute period, before removing the solvent under vacuum and washing sequentially with water (100 mL) and ethanol (100 mL). The crude mixture was recrystallised by dissolving the solid in a minimal amount of chloroform before delicately layering hexane on top. The solution was left undisturbed for 2 days at which point yellow crystals precipitated out surrounded by a ring of undesired orange product. The yellow crystals were isolated upon letting the solvent evaporate at room temperature before carefully scraping the yellow crystals away from the undesired orange crystals. The isolated product were dried to afford the title compound as a yellow crystalline solid (80.5 mg, 51%); δ_H (400 MHz, $CDCl_3$) 8.22 (2H, dt, *J* = 7.8 Hz, 0.9 Hz, Ar**H**), 7.73−7.67 (8H, m, Ar**H**), 7.50−7.46 (2H, d, *J* = 7.6 Hz, Ar**H**), 7.32 (2H, d, *J* = 7.5 Hz, Ar**H**), 7.22−7.20 (4H, m, Ar**H**), 7.11−7.04 (8H, m, Ar**H**), 6.81 (4H, app t, *J* = 7.7 Hz, Ar**H**), 6.62 (2H, app td, *J* = 7.9 Hz, 1.2 Hz, Ar**H**); NMR data were consistent with those reported in the literature.[39]

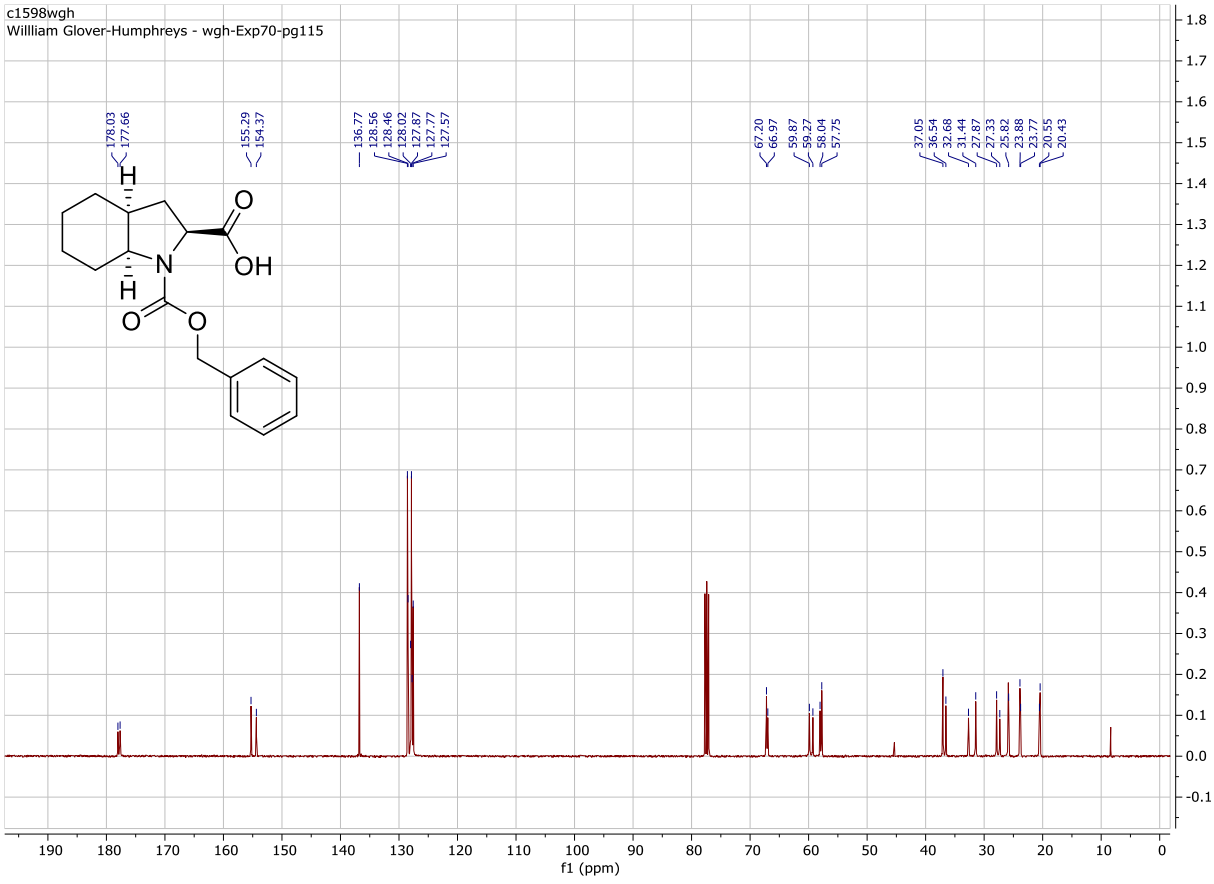

c0133wgh
William Glover-Humphreys - WGH-photocatalyst organic-pg99
8.22
7.71
7.48
7.31
7.21
7.08
6.80
6.62
2.00
8.23
2.04
2.00
3.88
8.02
4.00
2.00
f1 (ppm)
N
N
N
N
N

(2*S*,3a*S*,7a*S*)-1-((benzyloxy) carbonyl) octahydro-1*H*-indole-2-carboxylic acid (6-43)

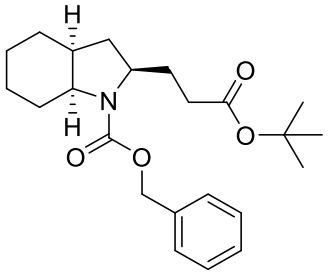


To a stirring solution of (2*S*,3a*S*,7a*S*)-2-carboxyoctahydroindole **(6-27)** (5.00 g, 29.5 mmol) and sodium hydroxide (2.36 g, 59.0 mmol) in a THF (50 mL) and deionised water (150 mL), cooled in an ice bath under argon. Benzyl chloroformate **(6-30)** (6.04 g, 35.4 mmol) was added dropwise and the reaction mixture was stirred over night at room temperature. The reaction mixture was cooled in an ice bath and 10% aq. HCl (approximately 70 mL) solution was added dropwise until the reaction mixture reached pH = 2, tested with pH indicator sticks. The solution was extracted with ethyl acetate (80 mL × 3) and the organic phases were combined and washed with sat. brine (100 mL × 3). The aqueous phase was then back extracted with ethyl acetate (100 mL × 2). The organic phases were combined, dried with sodium sulfate, filtered, concentrated under vacuum and purification via flash column chromatography (19:1 dichloromethane:methanol) afforded the title compound as a pale yellow viscous oil (5.99 g, 67%); R_f = 0.25 (19:1 dichloromethane:methanol); ν_{max}/cm^{-1} (thin film) 3450, 2931, 2853, 2579, 1982, 1693, 1420, 1358, 1178, 1123; δ_H (400 MHz, $CDCl_3$) rotamers were observed in a 4:6 ratio 10.32 (1H, bs, COO**H**), 7.34−7.17 (5H, m, ArC**H**), 5.22−5.03 (2H, m, ArC**H**$_2$O), 4.34−4.28 (1H, m, NC**H**COOH), 3.95−3.78 (1H, m, C**H**N), 2.30−2.22 (1H, m, C**H**), 2.18−1.95 (3H, m, CHC**H**$_2$CH & CH$_2$C**H**$_a$H$_b$CH), 1.72−1.56 (3H, m, C**H**$_2$CH, CH$_2$CH$_a$**H**$_b$CH) 1.48−1.40 (m, 2H, CH$_2$C**H**$_2$CH$_2$), 1.30−1.03 (m, 2H, CH$_2$C**H**$_2$CH$_2$); δ_c (100 MHz, $CDCl_3$) 178.0 (**C**O)$_{major}$, 177.7 (**C**O)$_{minor}$, 155.3 (N**C**OOH)$_{major}$, & 154.4 (N**C**OOH)$_{minor}$, 136.8 (Ar**C**)$_{both\ rotamers}$, 128.6 (Ar**C**H)$_{major}$, 128.5 (Ar**C**H)$_{minor}$, 128.0 (Ar**C**H)$_{minor}$, 127.9 (Ar**C**H)$_{major}$, 127.8 (Ar**C**H)$_{minor}$, 127.6 (Ar**C**H)$_{major}$, 67.2 (O**C**H$_2$Ar)$_{major}$, 67.0 (O**C**H$_2$Ar)$_{minor}$, 59.9 (O**C**H$_2$Ar)$_{major}$, 59.3 (O**C**H$_2$Ar)$_{minor}$, (N**C**HCOOH) 58.1 (N**C**H)$_{minor}$, 57.8 (N**C**H)$_{major}$, 37.0 (**C**H)$_{major}$, 36.5 (**C**H)$_{minor}$, 32.7 (CH**C**H$_2$CH)$_{minor}$, 31.4 (CH**C**H$_2$CH)$_{major}$, 27.9 (CH$_2$**C**H$_2$CH$_2$)$_{major}$, 27.3 (CH$_2$**C**H$_2$CH$_2$)$_{minor}$, 25.9 (CH$_2$**C**H$_2$CH)$_{both\ rotamers}$, 23.9 (CH$_2$**C**H$_2$CH)$_{major}$, 23.8 (CH$_2$**C**H$_2$CH)$_{minor}$, 20.6 (CH$_2$**C**H$_2$CH$_2$)$_{minor}$, 20.4 (CH$_2$**C**H$_2$CH$_2$)$_{major}$; HRMS (ESI): calcd. for $C_{17}H_{22}NO_4$ 304.1549. Found $[MH]^+$ 304.1547, (−0.66 ppm error).

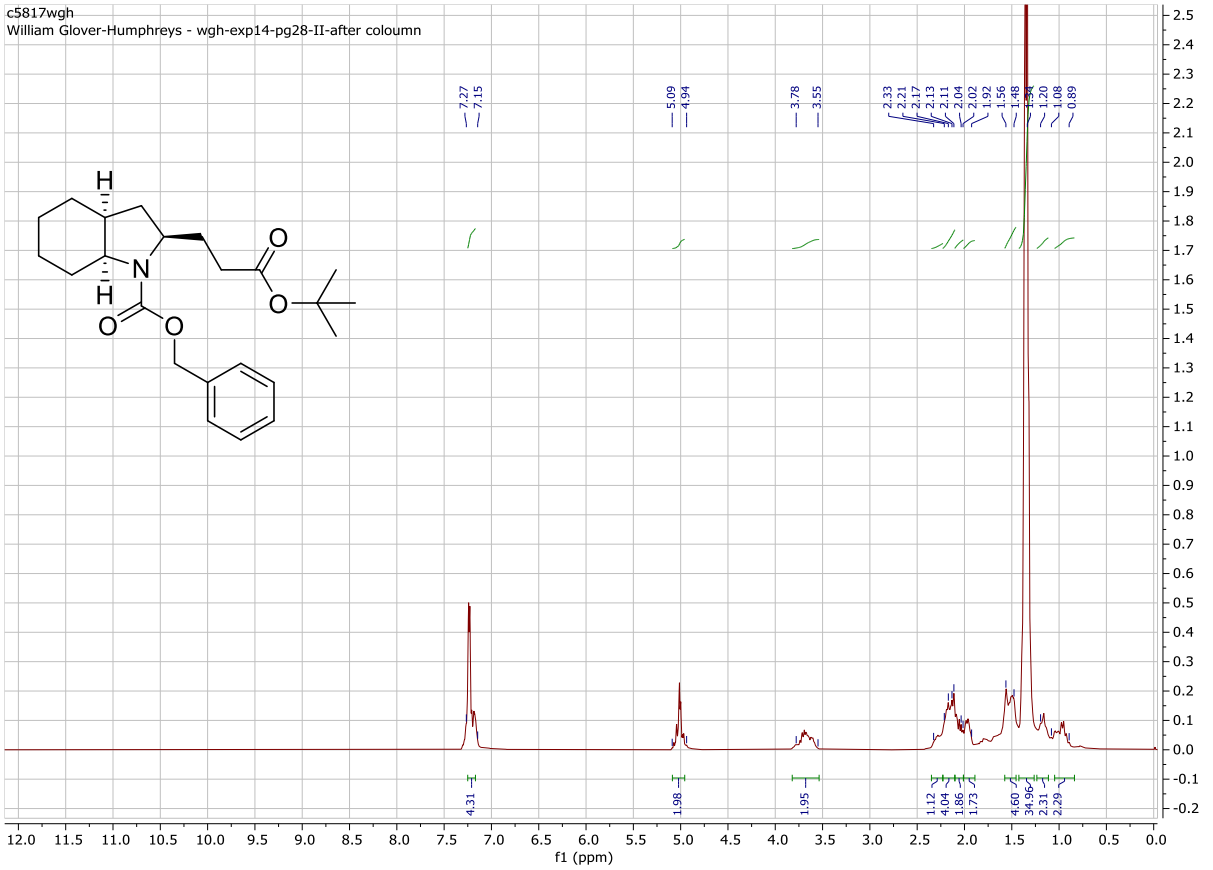

c1598wgh
Willliam Glover-Humphreys - wgh-Exp70-pg115
10.32
7.34
7.31
7.17
5.22
5.03
4.34
4.28
3.95
3.78
2.25
2.17
2.11
1.98
1.66
1.60
1.45
1.25
1.12
0.92
5.06
2.04
0.99
0.98
1.01
2.90
3.02
1.99
2.15
f1 (ppm)


c1598wgh
Willliam Glover-Humphreys - wgh-Exp70-pg115
178.03
177.66
155.29
154.37
136.77
128.56
128.46
128.02
127.87
127.77
127.57
67.20
66.97
59.87
59.27
58.04
57.75
37.05
36.54
32.68
31.44
27.87
27.33
25.82
23.88
23.77
20.55
20.43
f1 (ppm)

Benzyl (2*R*,3a*S*,7a*S*)-2-(3-(*tert*-butoxy)-3-oxopropyl) octahydro-1*H*-indole-1-carboxylate (6-47)



To a 250 mL round bottom flask containing (2*S*,3a*S*,7a*S*)-1-((benzyloxy) carbonyl) octahydro-1*H*-indole-2-carboxylic acid **(6-43)** (3.64 g, 12.0 mmol), 4CzIPN **(6-37)** (0.095 g, 0.120 mmol) and dipotassium phosphate (2.51 g, 14.4 mmol) was added to DMF (30 mL), and the resulting mixture was degassed for 15 minutes under argon. Separately *tert*-butyl acrylate **(6-32)** (3.00 mL) was degassed again for 15 minutes using argon. *tert*-Butyl acrylate (1.54 g, 12.0 mmol) was then added to the 250 mL round bottom flask topped with a septum wrapped with parafilm several times. The reaction mixture was irradiated with blue LED light for 72 hours whilst stirring, set up as shown in
. The reaction was quenched with saturated $NaHCO_3$ aqueous solution (100 mL) and extracted with Et_2O (3 × 50 mL). The organic layers were collected and washed sequentially with saturated NaCl aqueous solution (2 × 100 mL) and water (2 × 100 mL). The organic phases were collected, dried with sodium sulfate, the solvent removed under vacuum and purification via flash column chromatography (8:2 hexane:ethyl acetate) afforded the title compound as a clear oil (2.80 g, 59%). A single diastereoisomer was formed but rotameric in an approximate 10:1 ratio based on the ^{13}C NMR data, R_f = 0.4 (8:2 hexane:ethylacetate); ν_{max}/cm^{-1} (thin film) 3031, 2976, 2933, 1725, 1695, 1537, 1498, 1416, 1242, 1144, 1097; δ_H (400 MHz, $CDCl_3$) 7.29−7.15 (5H, m, Ar**C**H), 5.10−5.94 (2H, m, OC**H**$_2$Ar), 3.78−3.55 (1H, m C**H**N), 3.78−3.55 (1H, m C**H**N), 2.34−2.22 (1H, m, C**H**), 2.20−2.10 (2H, m, CHC**H**$_2$CH$_2$COO), 2.08−2.01 (2H, m, CH$_2$C**H**$_2$COO), 1.98−1.91 (2H, m, C**H**$_2$CHN), 1.58−1.53 (2H, m, CHC**H**$_2$CH), 1.52−1.47 (2H, m, CH$_2$C**H**$_2$CH), 1.34 (9H, s, OC(C**H**$_3$)$_3$), 1.18−1.10 (2H, m, CH$_2$C**H**$_2$CH$_2$), 1.02−0.89 (2H, m, CH$_2$C**H**$_2$CH$_2$); δ_c (100 MHz, $CDCl_3$) 172.8$_{major}$ & 172.6$_{minor}$ (**C**O), 154.8$_{major}$ & 154.5$_{minor}$ (N**C**OO), 137.2$_{major}$, 137.1$_{minor}$ (Ar**C**), 128.5 (Ar**C**H), 128.0 (Ar**C**H), 127.9 (Ar**C**H), 80.3 (O**C**(CH$_3$)$_3$), 66.5 (O**C**H$_2$Ar), 57.5$_{minor}$ & 57.2$_{major}$ (**C**HN), 56.8$_{major}$ & 56.2$_{minor}$ (**C**HN), 35.0$_{major}$ & 34.1$_{minor}$ (C**H**), 33.1 (**C**H$_2$COO), 31.5$_{minor}$ & 30.5$_{major}$ (CH$_2$C**H**CH$_2$), 29.2 (CHC**H**$_2$CH$_2$), 28.2 (OC(**C**H$_3$)$_3$), 27.9 (CH$_2$**C**H$_2$CH), 26.9$_{minor}$, 26.0$_{major}$ (CH$_2$**C**H$_2$CH$_2$), 24.2$_{minor}$, 23.9$_{major}$ & 23.6$_{minor}$ (CH$_2$**C**H$_2$CH), 21.0$_{minor}$, 20.70$_{major}$ & 20.58$_{minor}$ (CH$_2$**C**H$_2$CH$_2$); HRMS (ESI): calcd. for $C_{23}H_{34}NO_4$ 388.2488 & $C_{23}H_{34}NNaO_4$ 410.2307. Found $[MH]^+$, 388.2489 (0.258 ppm error), $[MNa]^+$, 410.2306 (– 0.244 ppm error).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William Glover-Humphreys - wgh-exp14-pg28-II-after coloumn
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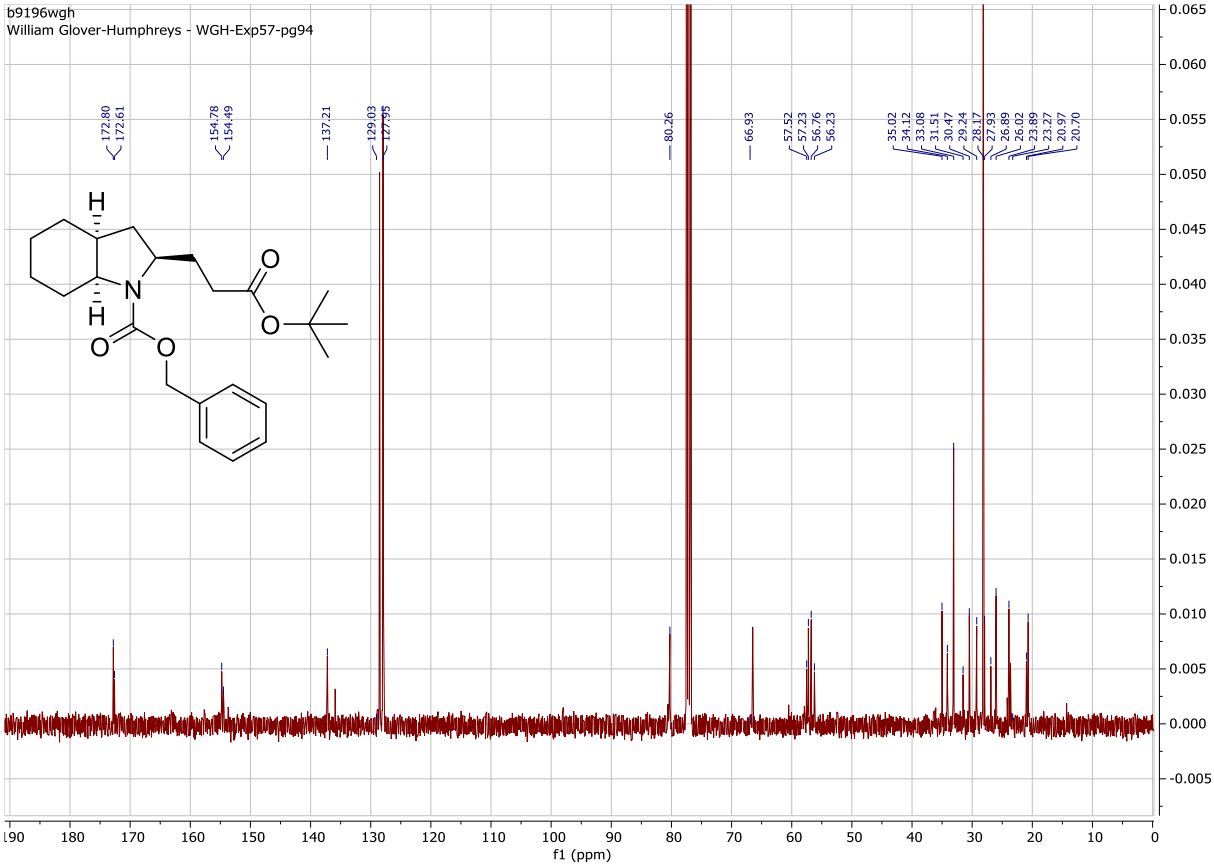
7.15
5.09
4.94
3.78
3.55
2.33
2.21
2.17
2.13
2.11
2.04
2.02
1.92
1.56
1.48
1.34
1.20
1.08
0.89
4.31
1.98
1.95
1.12
4.04
1.86
1.73
4.60
34.96
2.31
2.29
f1 (ppm)


b9196wgh
William Glover-Humphreys - WGH-Exp57-pg94
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154.78
154.49
137.21
129.03
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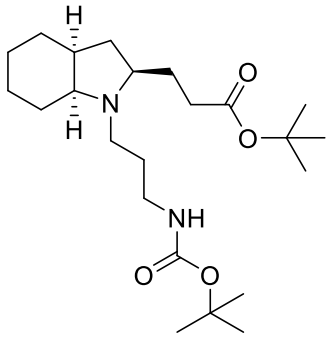
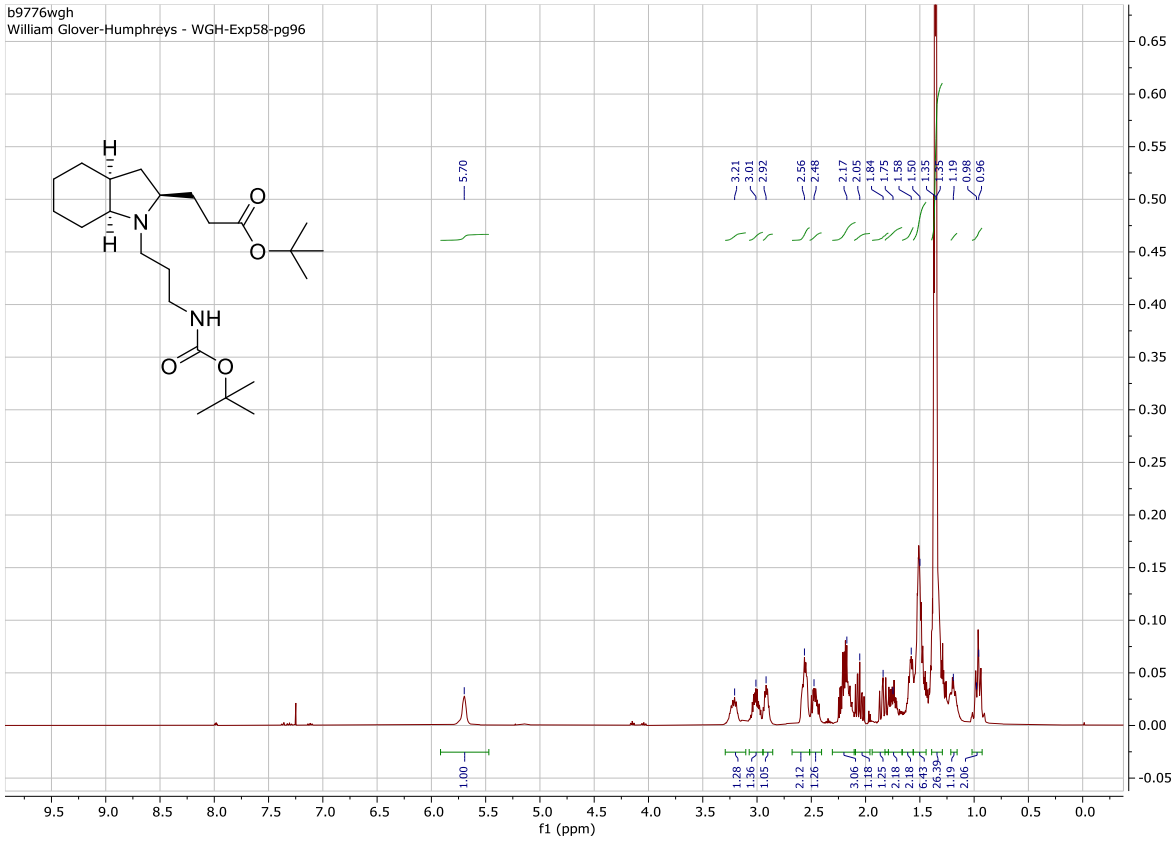
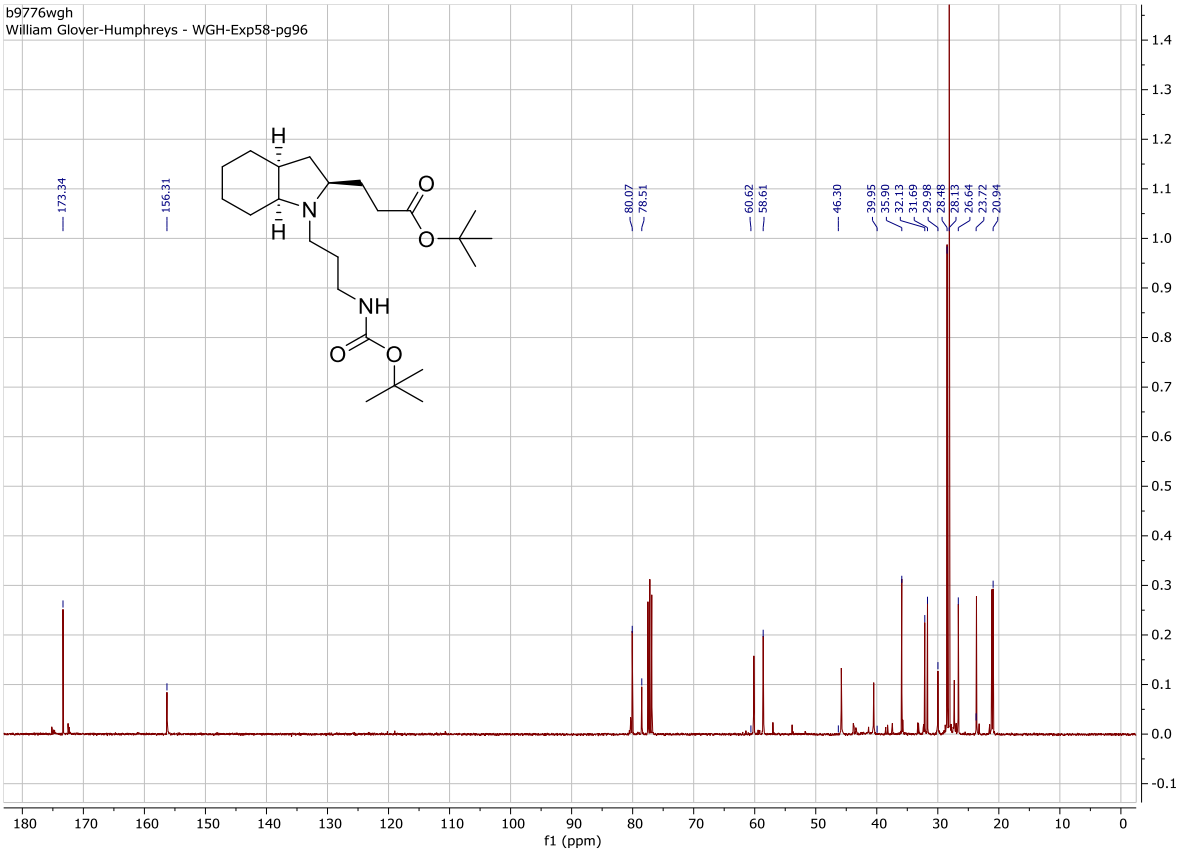
66.93
57.52
57.23
56.76
56.23
35.02
34.12
33.08
31.51
30.47
29.24
28.17
27.93
26.89
26.02
23.89
23.27
20.97
20.70
f1 (ppm)

***tert*-Butyl 3-((2*R*,3a*S*,7a*S*)-1-(3-((*tert*-butoxy carbonyl) amino) propyl) octahydro-1*H*-indol-2-yl) propanoate (6-55)**

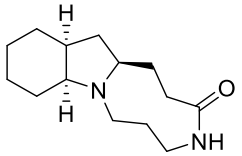


10% Palladium on carbon (0.320 g) was added to benzyl (2R,3aS,7aS)-2-(3-(*tert*-butoxy)-3-oxopropyl) octahydro-1*H*-indole-1-carboxylate **(6-47)** (3.20 g, 8.30 mmol) in ethanol (30 mL) under argon. The solution was evacuated under vacuum and refilled with hydrogen (×3) then stirred at room temperature overnight whilst excess hydrogen refills the reaction vessel. The reaction mixture was filtered through Celite and washed with ethanol (100 mL) and the solvent was removed under vacuum using acetonitrile (3 × 15.0 mL) to make an azeotropic mixture isolating the intermediate *tert*-butyl 3-(octahydro-1H-indol-2-yl) propanoate **(6-51)**. *tert*-Butyl 3-(octahydro-1H-indol-2-yl) propanoate was dissolved in acetonitrile (30 mL) then potassium carbonate (1.95 g, 14.12 mmol) and 3-(Boc-amino) propyl bromide **(6-39)** (1.98 g, 8.30 mmol) was added, and the reaction mixture refluxed (100 °C) overnight under argon. The reaction mixture was diluted with EtOAc (250 mL) and washed with saturated $NaHCO_3$ aqueous solution (200 mL) then back extracted with (EtOAc 2 ×150 mL). The organic phases were combined and dried using sodium sulfate, filtered and the solvent removed under vacuum. The reaction mixture was purified via flash column chromatography (20:75:5 hexane:ethyl acetate:triethylamine) afforded the title compound as a brown oil (1.22 g, 36%) R_f = 0.37 (20:75:5 hexane:ethyl acetate:triethylamine); ν_{max}/cm^{-1} (thin film) 3386, 2977, 2928, 2857, 1716, 1512, 1449, 1366, 1238, 1147, 1046, 847; δ_H (400 MHz, $CDCl_3$) 5.70 (1H, bs, N**H**COO), 3.27−3.17 (1H, m, NC**H$_a$**H$_b$), 3.06−2.97 (1H, m, NCH$_a$**H$_b$**), 2.92 (1H, quintet, *J* = 5.3 Hz, C**H**N), 2.60−2.53 (1H, m, C**H**N), 2.60−2.53 (1H, m, C**H$_a$**H$_b$N), 2.50−2.43 (1H, m, CH$_a$**H$_b$**N), 2.25−2.16 (1H, m, C**H$_a$**H$_b$CO), 2.21−2.11 (1H, m, C**H**), 2.09−2.01 (1H, m, CH$_a$**H$_b$**CO), 1.61−1.56 (2H, m, CHC**H**$_2$CH), 1.54−1.46 (4H, m, CH$_2$C**H**$_2$CH), 1.54−1.46 (1H, m, CH$_2$C**H$_a$**H$_b$CH$_2$), 1.36 (9H, s, COOC(C**H**$_3$)$_3$), 1.35 (9H, s, NCOOC(C**H**$_3$)$_3$), 1.22−1.14 (1H, m, CH$_2$CH$_a$**H$_b$**CH$_2$), 1.03−0.91 (2H, m, CH$_2$C**H**$_2$CH); δ_c (100 MHz, $CDCl_3$) 173.3 (CH$_3$**C**O), 156.3 (NH**C**O), 80.1 (COO**C**(CH$_3$)$_3$), 78.5 (NHCOO**C**(CH$_3$)$_3$), 60.1 (**C**HN), 58.6 (**C**HN), 45.8 (**C**H$_2$NH), 40.5 (**C**H$_2$N), 35.8 (CH$_2$**C**HCH$_2$), 32.1 (**C**H$_2$COO), 31.7 (CH**C**H$_2$CH), 30.0 (CHC**H**$_2$CH$_2$), 28.5 (NHOOC(**C**H$_3$)$_3$), 28.1 ((COO**C**(CH$_3$)$_3$), 27.3 (CH$_2$**C**H$_2$CH), 26.6 (CH$_2$**C**H$_2$CH), 23.7 (CH$_2$**C**H$_2$CH$_2$), 21.1 (NCH$_2$**C**H$_2$CH$_2$NH), 20.9 (CH$_2$**C**H$_2$CH$_2$); HRMS (ESI): calcd. for $C_{23}H_{43}N_2O_4$ 411.3223. Found $[MH]^+$, 411.3218 (−1.22 ppm error).

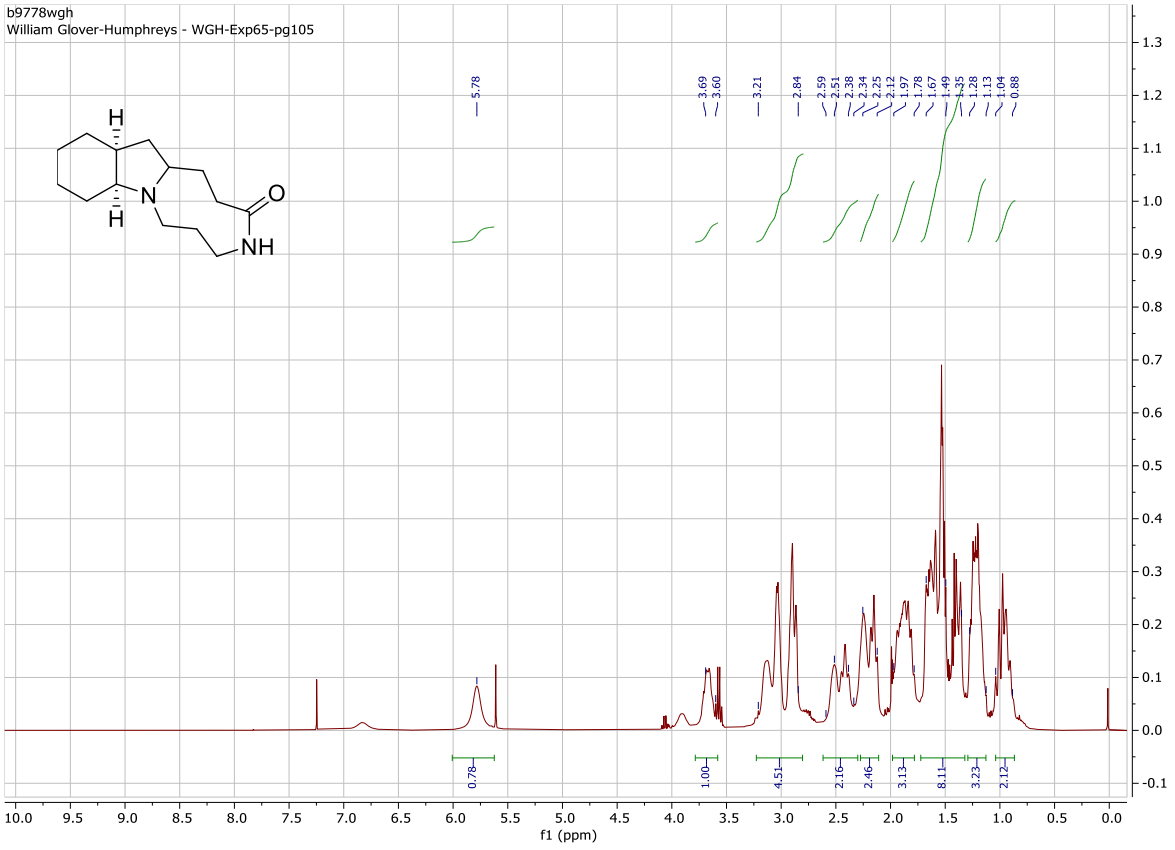

b9776wgh
William Glover-Humphreys - WGH-Exp58-pg96
f1 (ppm)

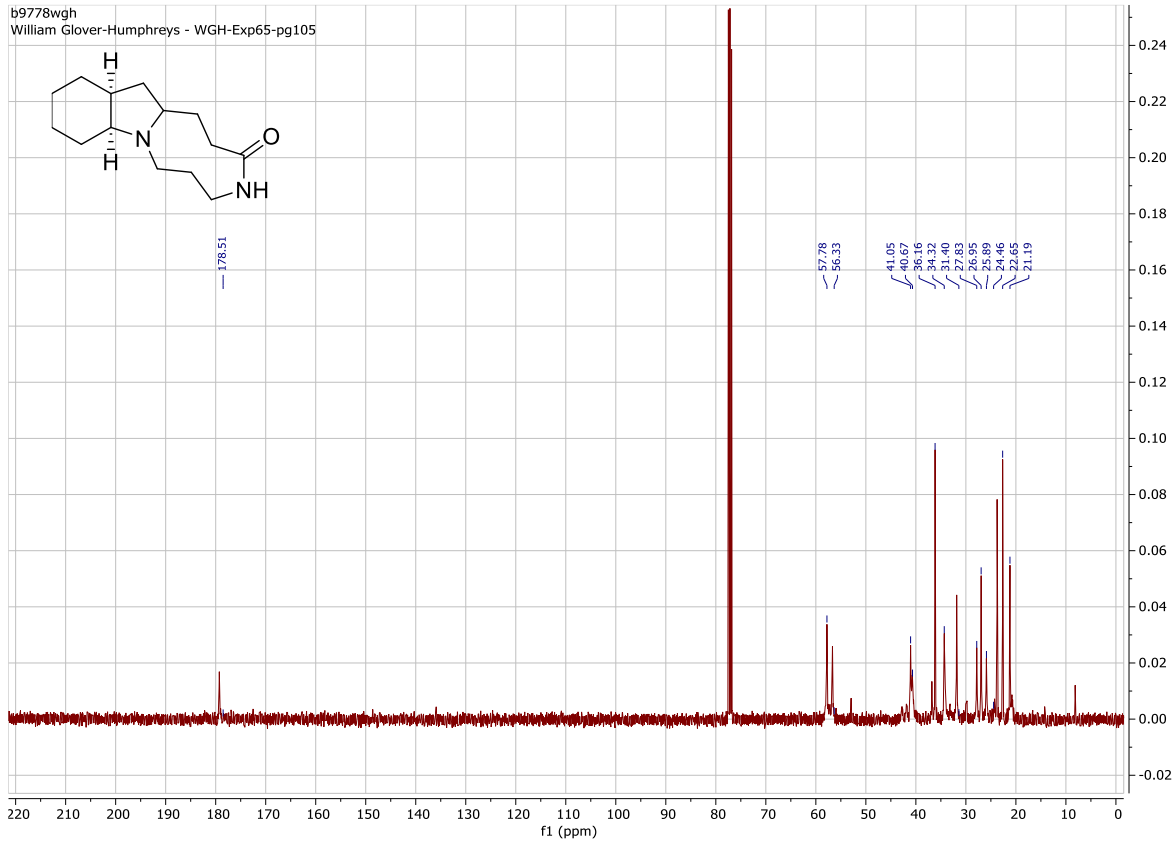

b9776wgh
William Glover-Humphreys - WGH-Exp58-pg96
f1 (ppm)

(8a*S*,12a*S*,13a*R*)-tetradecahydro-3*H*- [1,5] diazonino[1,9-a] indol-3-one (6-63)

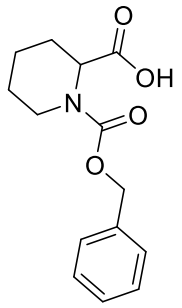


To a stirring solution of *tert*-Butyl 3-((2*R*,3a*S*,7a*S*)-1-(3-((*tert*-butoxy carbonyl) amino) propyl) octahydro-1*H*-indol-2-yl) propanoate **(6-55)** (0.164 g, 0.400 mmol) in Et_2O (12.0 mL), hydrochloric acid in 1,4-dioxane (4.00 M) (80.0 mmol, 2.00 mL) was added dropwise and left to stir for 4 hours at room temperature. The reaction mixture was concentrated under vacuum using chloroform (3 × 10 mL) to make an azeotropic solution. Chloroform was added (13.0 mL) and DIPEA (0.517 g, 0.700 mL and 4.00 mmol) and stirred until all the reagents dissolved in solution (30 minutes). T3P (0.382 g, 0.600 mmol) was then added, and the reaction was left to stir over night at room temperature. The solvent was removed under vacuum and the reaction mixture purified via flash column chromatography (50:45:5 dichloromethane:hexane:triethylamine) to afford the title compound an oily solid (71.8 mg, 76%); R_f = 0.29 (50:45:5 dichloromethane:hexane:triethylamine); ν_{max}/cm^{-1} (thin film) 3287, 2922, 2852, 1652, 1468, 1445, 1361, 1269, 1149, 794; δ_H (400 MHz, $CDCl_3$) significant rotameric broadening was observed, only the major rotamer detailed 5.78 (1H, bs, CON**H**), 3.76−3.60 (1H, m, NC**H**$_a$H$_b$), 3.22−3.29 (4H, m, 2 × C**H**N, NC**H**$_a$H$_b$, NCH$_a$**H**$_b$), 2.59−2.38 (2H, m, NCH$_a$**H**$_b$ & C**H**$_a$H$_b$CO), 2.30−2.11 (2H, m, C**H** & CH$_a$**H**$_b$CO), 1.97−1.78 (3H, m, C**H**$_2$, C**H$_a$**H$_b$), 1.67−0.86 [13H, m, 6 × C**H**$_2$, CH$_a$**H$_b$**], 1.67−1.35 (8H, m), 1.28−1.13 (3H, m), 1.04−0.88 (2H, m); δ_c (100 MHz, $CDCl_3$) 179.3 (**C**O), 57.8 (N**C**H), 56.7 (N**C**H), 41.1 (N**C**H$_2$), 40.7 (**C**H$_2$NHCO), 36.1 (CH**C**H$_2$CH), 34.3 (**C**H$_2$), 31.8 (**C**H$_2$), 27.8 (**C**H$_2$), 26.9 (**C**H$_2$), 25.9 (**C**H$_2$CO), 23.8 (**C**H$_2$), 22.7 (**C**H$_2$), 21.2 (**C**H$_2$); HRMS (ESI): calcd. for $C_{14}H_{25}N_2O$ 237.1967. Found $[MH]^+$ 237.1961 (−2.53 ppm error).

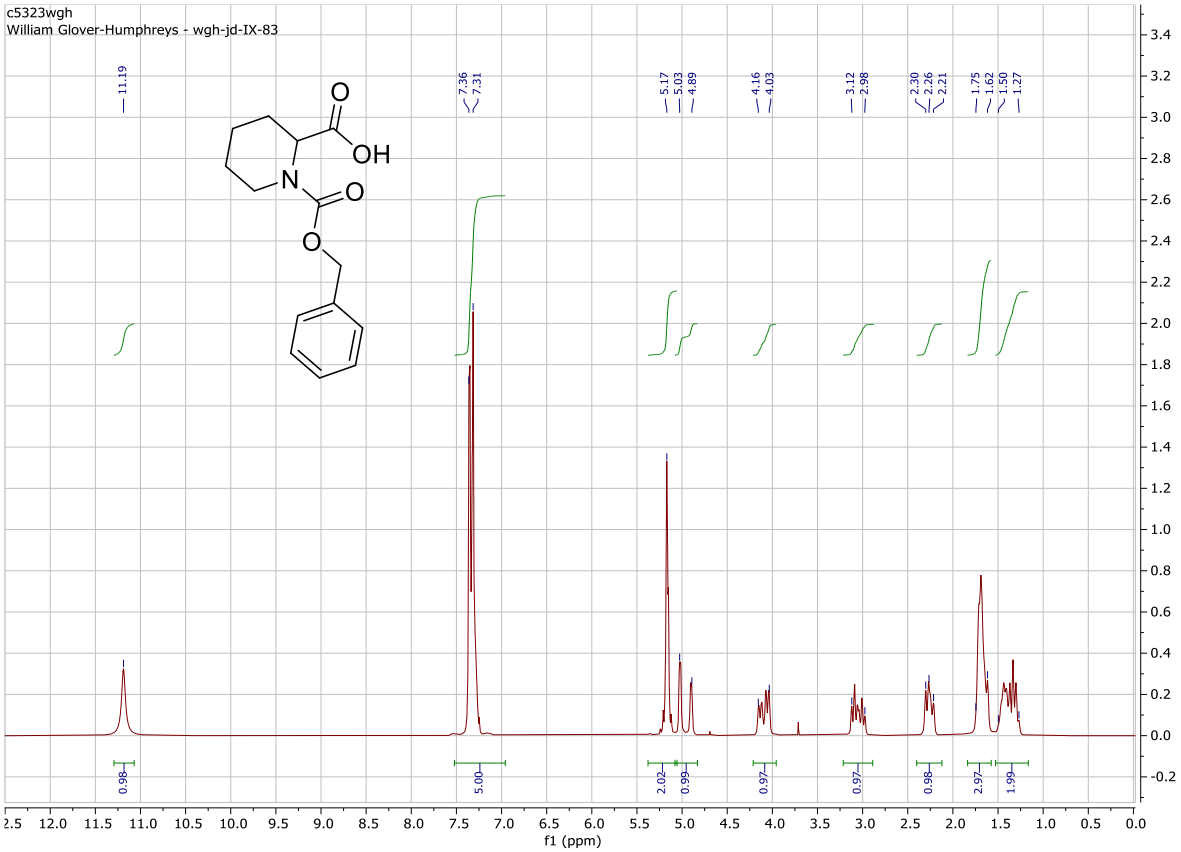

b9778wgh
William Glover-Humphreys - WGH-Exp65-pg105
5.78
3.69
3.60
3.21
2.84
2.59
2.51
2.38
2.34
2.25
2.12
1.97
1.78
1.67
1.49
1.35
1.28
1.13
1.04
0.88
0.78
1.00
4.51
2.16
2.46
3.13
8.11
3.23
2.12
f1 (ppm)

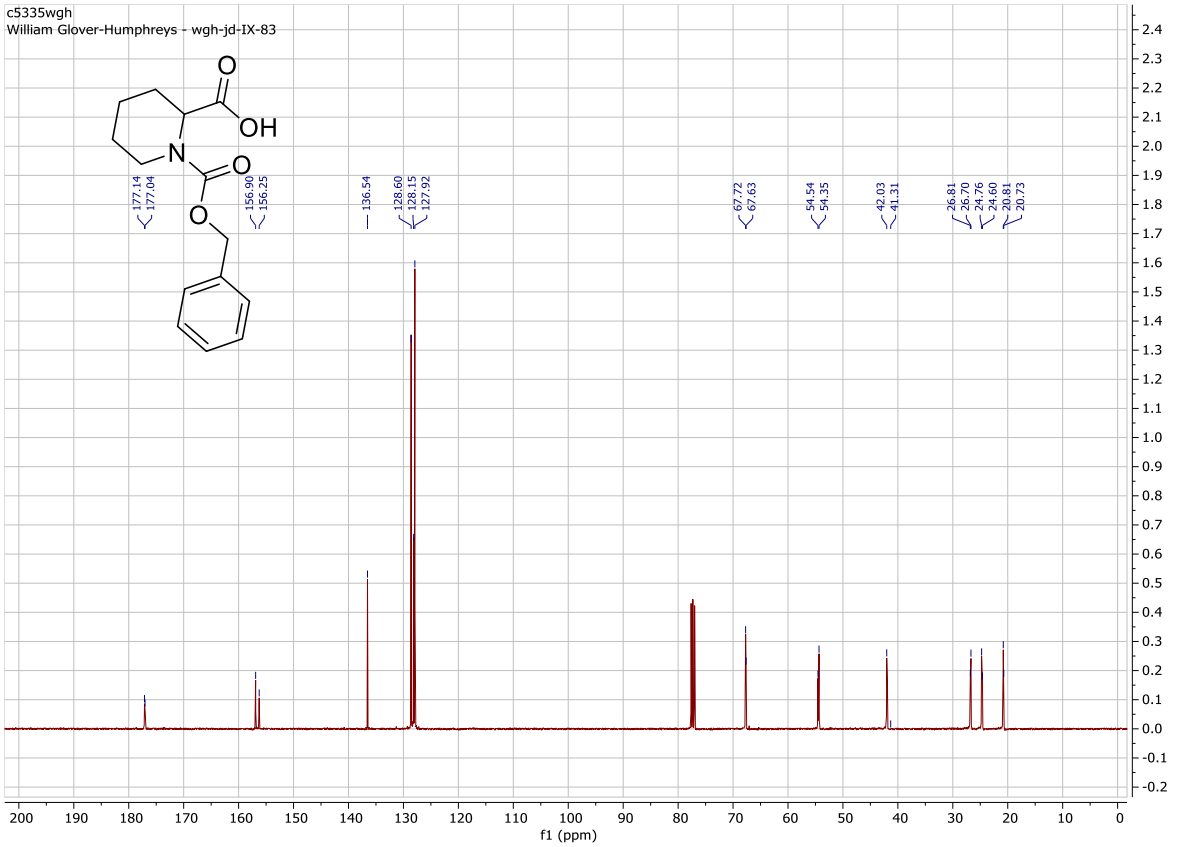

b9778wgh
William Glover-Humphreys - WGH-Exp65-pg105
178.51
57.78
56.33
41.05
40.67
36.16
34.22
31.40
27.83
26.95
25.89
24.46
22.65
21.19
f1 (ppm)

1-[(Benzyloxy) carbonyl] piperidine-2-carboxylic acid (6-44)

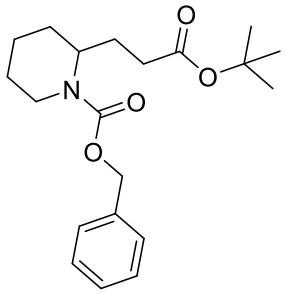


To a stirring solution of piperidine-2-carboxylic acid (**6-28**) (10.0 g, 77.4 mmol) in water (155 mL) and 1,4 dioxane (155 mL), sodium carbonate (18.9 g, 178 mmol) was added. Benzyl chloroformate **(6-30)** (15.8 g, 92.9 mmol) was then added dropwise and the reaction was left to stir over night at room temperature. The reaction was concentrated under vacuum using dichloromethane to make an azeotropic mixture. 10% HCl was added until the reaction mixture reached pH = 2. tested by pH indicator sticks. The solution was extracted in dichloromethane (200 mL × 3), the organic phases were combined, dried with sodium sulfate, filtered and the solvent removed under vacuum. To afford the title, compound as a colourless viscous oil (19.32 g, 95%); ν_{max}/cm^{-1} (thin film) 2941, 2861, 2542, 1704, 1671, 1423, 1353, 1256, 1165, 1042, 864, 740, 697, 603; δ_H (400 MHz, $CDCl_3$) 11.19 (1H, bs, COO**H**), 7.36−7.31 (5H, m, ArC**H**), 5.20−5.12 (2H, m, ArC**H**$_2$O), 5.03−4.89 (1H, m, C**H**), 4.17−4.02 (1H, m, C**H$_a$**H$_b$N), 3.16−2.96 (1H, m, CH$_a$**H$_b$**N), 2.32−2.20 (1H, m, C**H**$_a$H$_b$), 1.75−1.60 (1H, m, CH$_a$**H**$_b$), 1.75−1.60 (1H, m, C**H**$_a$H$_b$), 1.75−1.60 (1H, m, C**H**$_a$H$_b$), 1.49−1.26 (1H, m, CH$_a$**H**$_b$), 1.49−1.26 (1H, m, CH$_a$**H**$_b$); δ_c (100 MHz, $CDCl_3$) 177.1 & 177.0 (**C**OOH), 156.9 & 156.3 (**C**O), 136.5 (Ar**C**), 128.6 (Ar**C**H), 128.2 (Ar**C**H), 127.9 (Ar**C**H), 67.7 & 67.3 (Ar**C**H$_2$O), 54.5 & 54.4 (**C**H), 40.0 & 40.3 (**C**H$_2$), 26.8 & 26.7 (**C**H$_2$), 24.8 & 24.6 (**C**H$_2$), 20.8 & 20.7 (**C**H$_2$); HRMS (ESI) calcd. for $C_{14}H_{17}NNaO_4$ 286.1055 & $C_{14}H_{17}NKO_4$ 302.0795. Found $[MNa]^+$ 286.1057 (0.70 ppm error) & $[MK]^+$ 302.0781 (−4.63 ppm error).


c5323wgh
William Glover-Humphreys - wgh-jd-IX-83
11.19
7.36
7.31
5.17
5.03
4.89
4.16
4.03
3.12
2.98
2.30
2.26
2.21
1.75
1.62
1.50
1.27
0.98
5.00
2.02
0.99
0.97
0.97
0.98
2.97
1.99
f1 (ppm)

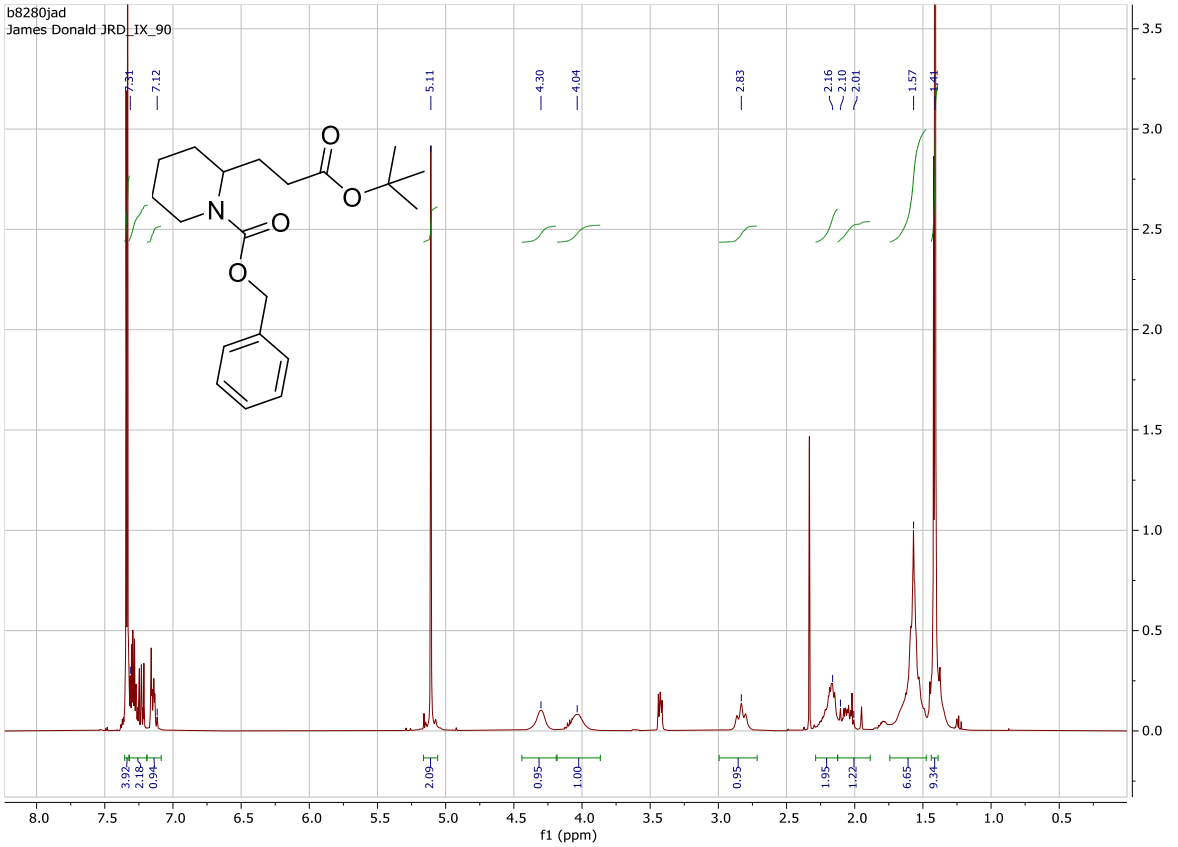

c5335wgh
William Glover-Humphreys - wgh-jd-IX-83
177.14
177.04
156.90
156.25
136.54
128.60
128.15
127.92
67.72
67.63
54.54
54.35
42.03
41.31
26.81
26.70
24.76
24.60
20.81
20.73
f1 (ppm)

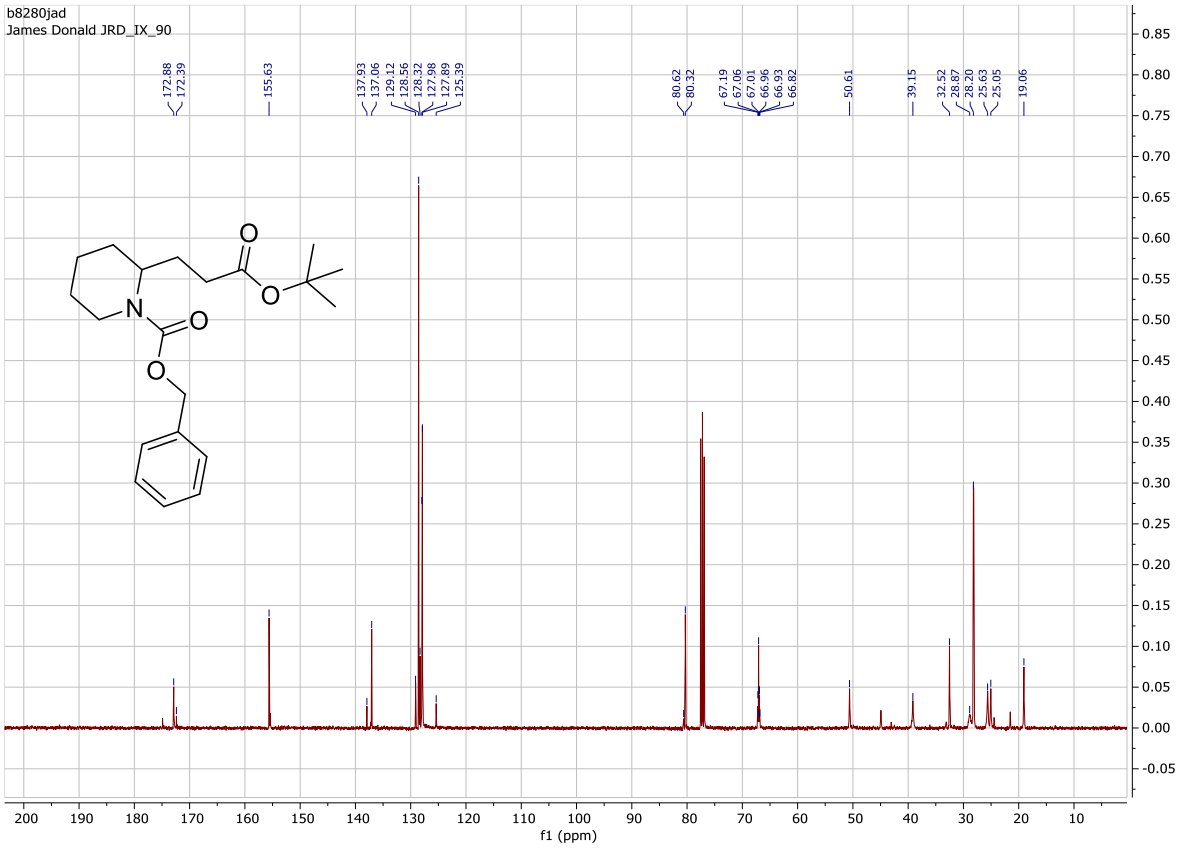
Benzyl 2-(3-*tert*-butoxy-3-oxopropyl) piperidine-1-carboxylate (6-48)



To a 250 mL round bottom flask of 1-[(benzyloxy)carbonyl] piperidine-2-carboxylic acid (**6-44**) (2.77 g, 8.00 mmol), 4CzIPN **(6-37)** (0.063 g, 0.08 mmol) and dipotassium phosphate (1.67 g, 9.6 mmol) was added to DMF (15.0 mL) and degassed for 15 minutes using argon. Separately *tert*-butyl acrylate **(6-32)** (3.00 mL) was degassed again for 15 minutes using argon. *tert*-Butyl acrylate **(6-32)** (1.03 g ,8.00 mmol) was then added to the 250 mL round bottom flask topped with a septum wrapped with parafilm several times. The reaction mixture was irradiated with blue LED light for 72 hours whilst stirring, set up as shown in

. The reaction was quenched in saturated $NaHCO_3$ aqueous solution (100 mL) and extracted in Et_2O (3 × 50 mL). The organic layers were collected and washed sequentially in saturated NaCl aqueous solution (2 × 100 mL) and water (2 × 100 mL). The organic phases were collected and dried with sodium sulfate and the solvent removed under vacuum. Purification via flash column chromatography (15:4:1 hexane:ethyl acetate:triethylamine) afforded the title compound as a clear oil (1.85 g, 67%); R_f = 0.42 (15:4:1 hexane:ethyl acetate:triethylamine); ν_{max}/cm^{-1} (thin film) 2935, 2864, 1726, 1693, 1422, 1350, 1256, 1150, 847, 731, 696; δ_H (400 MHz, $CDCl_3$) 7.30−7.11 (5H, m, Ar**H**), 5.11 (2H, s, ArC**H**$_2$O), 4.36−4.23 (1H, bm, C**H**$_a$H$_b$N), 2.83 (1H, t, *J* = 12.0 Hz), 2.26−2.13 (2H, m, C**H**$_2$CO), 2.11−2.00 (1H, m, C**H**$_a$H$_b$), 1.70−1.48 (1H, m, CH$_a$**H**$_b$) 1.70−1.48 (1H, m, C**H**$_a$H$_b$), 1.70−1.48 (1H, m, C**H**$_2$), 1.70−1.48 (1H, m, C**H**$_2$), 1.70−1.48 (1H, m, C**H**$_2$), 1.41 (9H, s, OC(C**H**$_3$)$_3$); δ_c (100 MHz, $CDCl_3$) 172.9 & 172.4 (N**C**OO), 155.6 & 155.4 (CH$_2$**C**OO), 137.9 & 137.1 (Ar**C**) 128.12 & 128.6 (Ar**C**H), 128.3 & 128.0 (Ar**C**H), 127.9 & 125.4 (Ar**C**H), 80.6 & 80.3 (O**C**(CH$_3$)$_3$), 67.0 (Ar**C**H$_2$O), 50.6 (**C**HN), 39.9 (C**H**$_2$N), 32.5 (**C**H$_2$COO),28.9 (**C**H$_2$), 28.2 (OC(**C**H$_3$)$_3$), 25.6 (**C**H$_2$), 25.1 (**C**H$_2$), 19.1 (**C**H$_2$); HRMS (ESI) calcd. for $C_{20}H_{29}NNaO_4$ 370.1994. Found $[MNa]^+$, 370.1988 (−1.62 ppm error).


b8280jad
James Donald JRD_IX_90
7.31
7.12
5.11
4.30
4.04
2.83
2.16
2.10
2.01
1.57
1.41
3.92
2.18
0.94
2.09
0.95
1.00
0.95
1.95
1.22
6.65
9.34
f1 (ppm)


b8280jad
James Donald JRD_IX_90
172.88
172.39
155.63
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137.06
129.12
128.56
128.32
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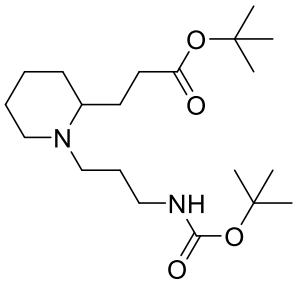
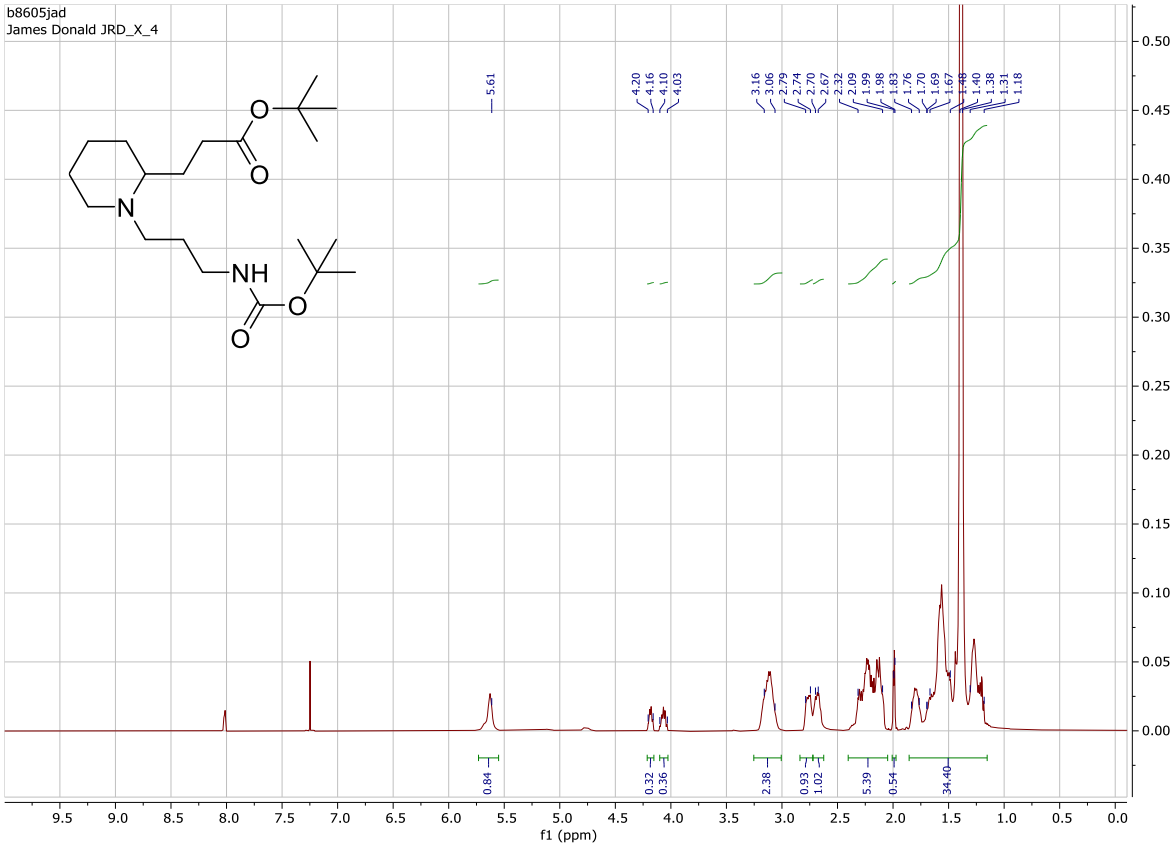
127.89
125.39
80.62
80.32
67.19
67.06
67.01
66.96
66.93
66.82
50.61
39.15
32.52
28.87
28.20
25.63
25.05
19.06
f1 (ppm)

***tert*-Butyl 3-(1-(3-((tert-butoxycarbonyl) amino) propyl) piperidin-2-yl) propanoate (6-56)**



10% Palladium on carbon (0.215 g) was added to benzyl 2-(3-*tert*-butoxy-3-oxopropyl) piperidine-1-carboxylate **(6-48)** (2.15 g, 6.19 mmol) in ethanol (62.0 mL) under argon. The solution was evacuated and refilled with hydrogen (× 3) then stirred at room temperature overnight whilst excess hydrogen refills the reaction vessel. The mixture was filtered through Celite and washed with ethanol (100 mL) and the solvent was removed under vacuum using acetonitrile (3 × 15.0 mL) to make an azeotropic mixture. The mixture was redissolved in acetonitrile (31.0 mL) then potassium carbonate (1.71 g, 12.4 mmol) and 3-(Boc-amino) propyl bromide **(6-39)** (1.48 g, 6.19 mmol) was added and refluxed overnight under argon. The reaction mixture was diluted with EtOAc (250 mL) and washed with saturated $NaHCO_3$ aqueous solution (200 mL) then back extracted with (EtOAc 2 × 150 mL). The organic phases were collected and dried using sodium sulfate, filtered and the solvent removed under vacuum. The reaction mixture was purified via flash column chromatography (75:20:5 hexane:ethyl acetate:triethylamine) to afford the title compound as a pale yellow oil (1.38 g, 60%); R_f = 0.24 (75:20:5 hexane:ethyl acetate:triethylamine); ν_{max}/cm^{-1} (thin film) 3369, 2976, 2932, 1713, 1513, 1454, 1366, 1248, 1152, 1046, 849, 780, 608; δ_H (400 MHz, $CDCl_3$) rotamers observed in a 4:1 ratio 5.61 (bs, 1H, N**H**), 4.20−4.16 (1H, m, C**H**$_a$H$_b$N)$_{minor}$, 4.10−4.03 (1H, m, CH$_a$**H**$_b$N)$_{minor}$, 3.16−3.06 (2H, m, C**H**$_2$N)$_{both\ rotamers}$, 2.79−2.74 (1H, m, C**H**$_a$H$_b$N)$_{major}$, 2.70−2.67 (1H, m, C**H**$_a$H$_b$N)$_{major}$, 2.32−2.09 [(5H, m, C**H**N, CH$_a$**H**$_b$N, CH$_a$**H**$_b$N, C**H**$_2$COO)$_{major\ rotamers}$, (1H, m, C**H**N)$_{minor}$], 1.99−1.98 (2H, m, C**H**$_2$N)$_{minor}$, 1.83−1.18 [(10H, m C**H**$_2$)$_{both\ rotamers}$ 1.83−1.76 (m), 1.70−1.48 (m), 1.31−1.18 (m), 1.40−1.38 (18H, m COOC(C**H**$_3$)$_3$, NHCOOC(C**H**$_3$)$_3$)$_{both\ rotamers}$; δ_C (100 MHz, $CDCl_3$) only the major rotamer detailed 173.4 (**C**O), 156.2 (**C**O), 80.2 (O**C**(CH$_3$)$_3$, 78.7 (O**C**(CH$_3$)$_3$, 59.5 (**C**H), 52.1 (**C**H$_2$N), 50.6 (**C**H$_2$N), 40.3 (**C**H$_2$NH), 31.8 (**C**H$_2$COO), 29.7 (**C**H$_2$), 28.5 (OC(**C**H$_3$)$_3$), 28.4 (**C**H$_2$), 28.2 (OC(**C**H$_3$)$_3$), 26.0 (**C**H$_2$), 25.3 (**C**H$_2$), 22.8 (**C**H$_2$); HRMS (ESI): calcd. for $C_{20}H_{38}N_2O_4$ 371.2910. Found $[MH]^+$ 371.2904 (−1.62 ppm error).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James Donald JRD_X_4
5.61
4.20
4.16
4.10
4.03
3.16
3.06
2.79
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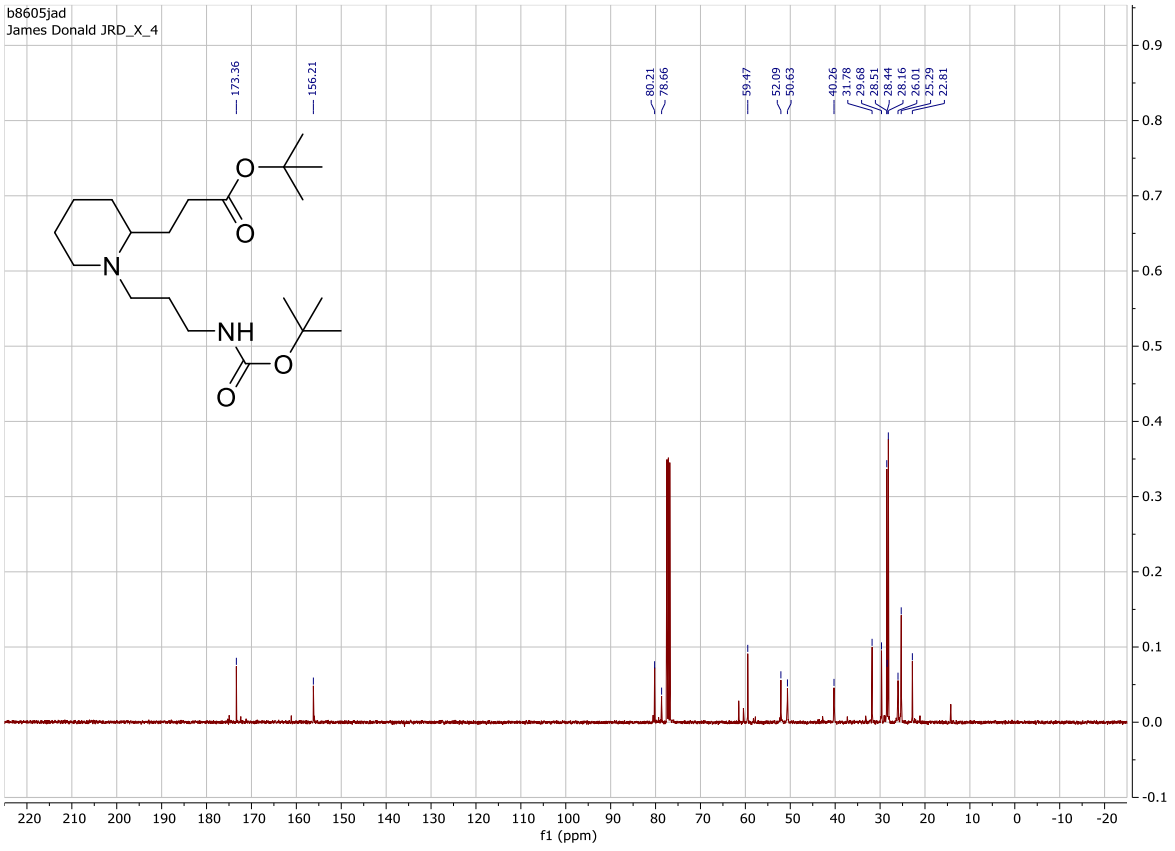
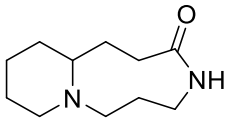
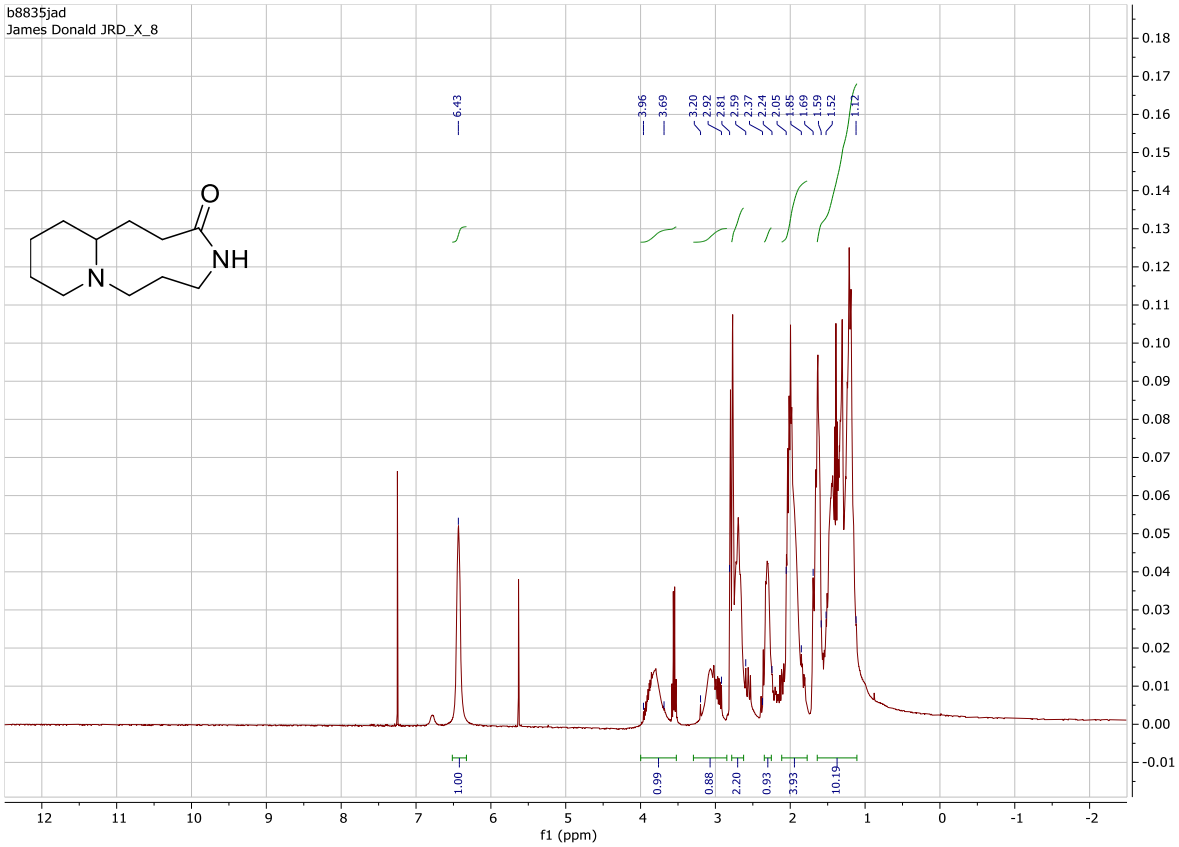
2.67
2.32
2.09
1.99
1.98
1.83
1.76
1.70
1.69
1.67
1.40
1.38
1.31
1.18
0.84
0.32
0.36
2.38
0.93
1.02
5.39
0.54
34.40
f1 (ppm)


b8605jad
James Donald JRD_X_4
173.36
156.21
80.21
78.66
59.47
52.09
50.63
40.26
31.78
29.68
28.51
28.44
28.16
26.01
25.29
22.81
f1 (ppm)

Decahydropyrido[1,2-e] [1,5] diazonin-3(2H)-one (6-64)



To a stirring solution of *tert*-butyl 3-(1-(3-((*tert*-butoxycarbonyl) amino) propyl) pyrrolidin-2-yl) propanoate **(6-56)** (0.138 g, 3.73 mmol) in diethyl ether (9.30 mL), a solution of 4.0 M hydrochloric acid in 1,4 dioxane (18.7 mL, 74.8 mmol) was added dropwise and the reaction was left stirring at room temperature for 4 hours. The reaction mixture was concentrated under vacuum using chloroform (3 × 5.00 mL) to make an azeotropic solution. The intermediate lithium 3-(1-(3-aminopropyl) piperidin-2-yl) propanoate was dissolved in chloroform (93 mL) and DIPEA (4.82 g, 6.49 mL, 37.3 mmol) under argon, until all the reagents dissolved into solution (30 minutes). T3P (3.56 g, 5.59 mmol) was then added, and the reaction left to stir over night at room temperature. The solvent was removed under vacuum and the reaction mixture was purified via flash column chromatography (70:25:5 dichloromethane:hexane:triethylamine) forming a colourless solid (0.466 g, 64%), R_f = 0.32 (70:25:5 dichloromethane:hexane:triethylamine); ν_{max}/cm^{-1} (thin film) 3189, 3060, 2925, 2841, 2796, 1654, 1439, 1398, 1180, 1027, 950, 832, 580, 482; δ_H (400 MHz, $CDCl_3$) 6.43 (1H, s, N**H**), 3.96−3.69 (1H, m, C**H**$_a$H$_b$N), 3.20−2.92 (1H, m, CH$_a$**H**$_b$N), 2.92−2.59 (2H, m, C**H**$_2$N), 2.37−2.24 (1H, m, C**H**N), 2.05−1.85 (4H, m, C**H**$_2$CO, C**H**$_2$N), 1.85−1.12 (10H, m, 5 × C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 179.7 (**C**O), 59.5 (**C**HN), 52.9 (**C**H$_2$N), 46.2 (**C**H$_2$N), 40.1 (**C**H$_2$NH), 32.4 (**C**H$_2$CO), 30.6 (**C**H$_2$), 28.1 (**C**H$_2$), 26.1 (**C**H$_2$), 24.8 (**C**H$_2$), 24.4 (**C**H$_2$); HRMS (ESI): calcd. for $C_{11}H_{21}N_2O$ 197.1654. Found $[MH]^+$ 197.1651 (−1.52 ppm error).


b8835jad
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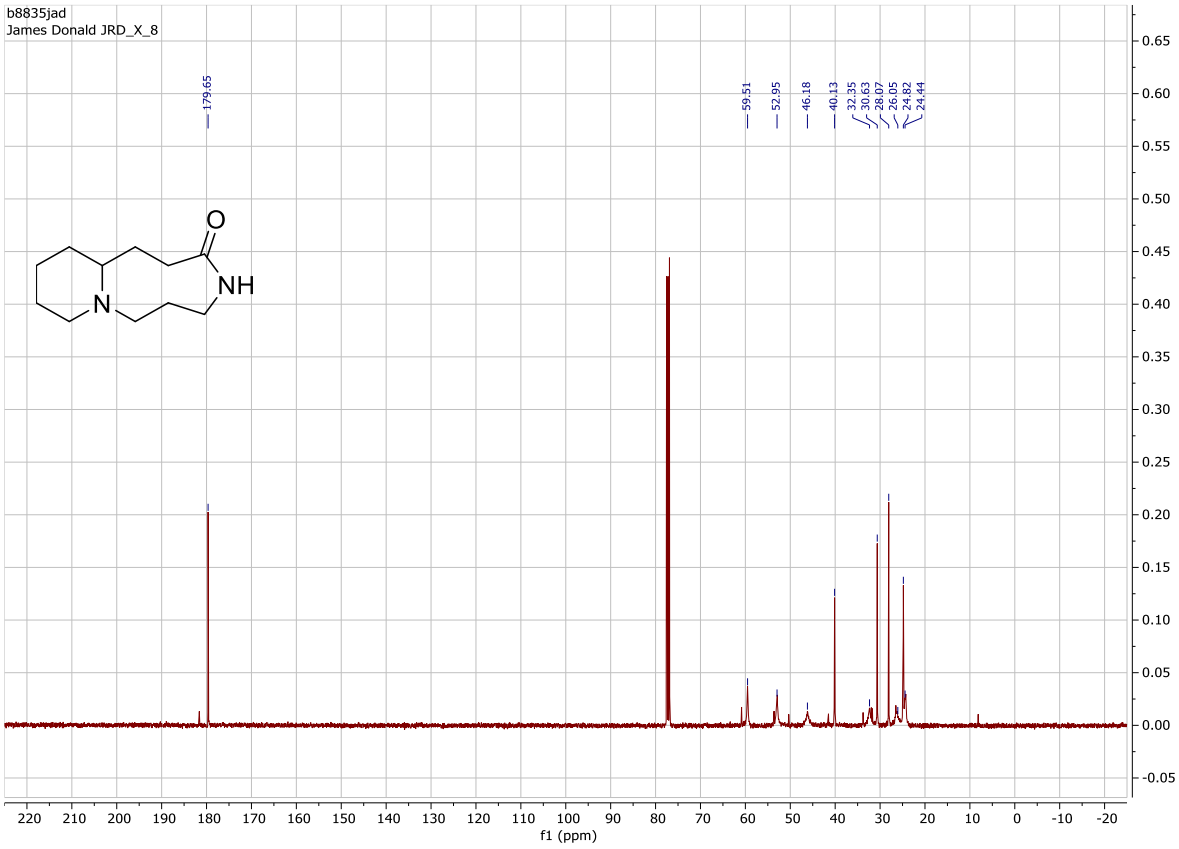
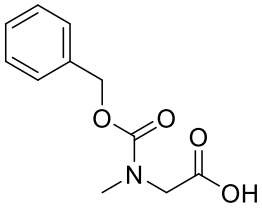
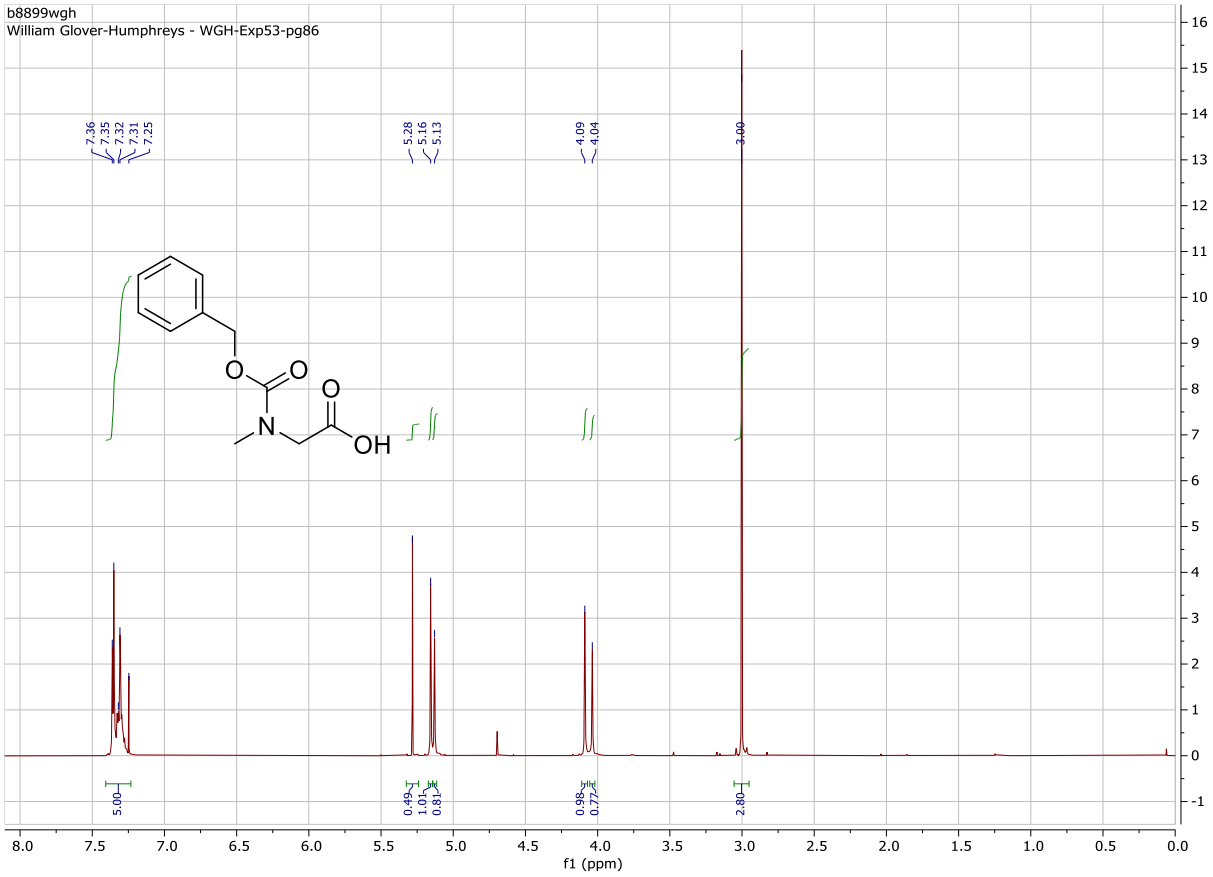
6.43
3.96
3.69
3.20
2.92
2.81
2.59
2.37
2.24
2.05
1.85
1.69
1.59
1.52
1.12
O
NH
N
1.00
0.99
0.88
2.20
0.93
3.93
10.19
f1 (ppm)


b8835jad
James Donald JRD_X_8
179.65
59.51
52.95
46.18
40.13
32.35
30.63
28.07
26.05
24.82
24.44
O
NH
N
f1 (ppm)

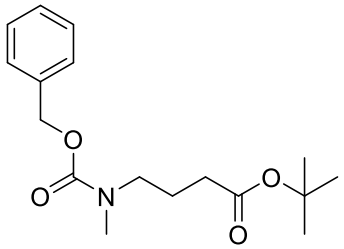
***N*-[(benzyloxy)carbonyl]-*N*-methylglycine[40] (6-45)**



To a stirring solution of sarcosine (**6-29**) (5.00 g, 56.1 mmol) and sodium hydroxide (4.48 g, 112 mmol) in 1,4 dioxane (50 mL) and deionised water (150 mL) within an ice bath, benzyl chloroformate **(6-30)** (11.5 g, 67.34 mmol) was added dropwise. The reaction mixture was left to stir overnight at room temperature. The reaction mixture was cooled in an ice bath and 10% HCl (approximately 70 mL) solution was added dropwise until the reaction mixture reached pH = 2. tested via pH indicator sticks. The solution was extracted in ethyl acetate (80 mL × 3) and the organic phases combined and washed with brine (100 mL × 3). The aqueous phase was then back extracted with ethyl acetate (100 mL × 2). The organic phases were combined, dried with sodium sulfate, filtered, the solvent removed under vacuum and purification by flash column chromatography (19:2 dichloromethane:methanol) to afford the title compound as a clear very viscous oil (5.76 g, 46%); R_f = 0.38 (19:2 dichloromethane:methanol; δ_H (400 MHz, $CDCl_3$) 7.36−7.25 (5H, m, ArC**H**), 5.28 (1H, s, COO**H**), 5.16 (1H, s, ArC$\mathbf{H_a}H_b$O), 5.13 (1H, s, Ar$CH_a\mathbf{H_b}$O), 4.09 (1H, s, NC$\mathbf{H_a}H_b$COOH), 4.04 (1H, s, N$CH_a\mathbf{H_b}$COOH), 3.00 (3H, s C$\mathbf{H}_3$N).

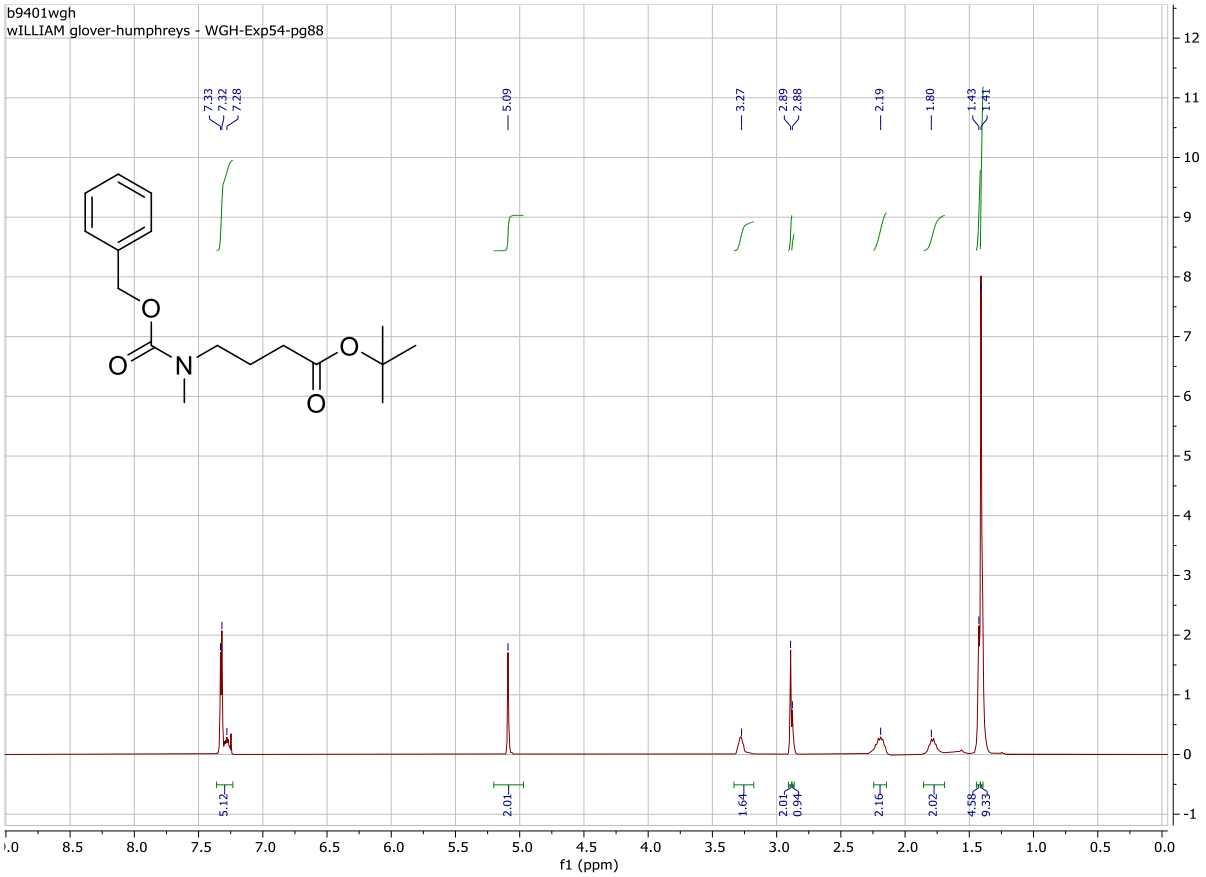


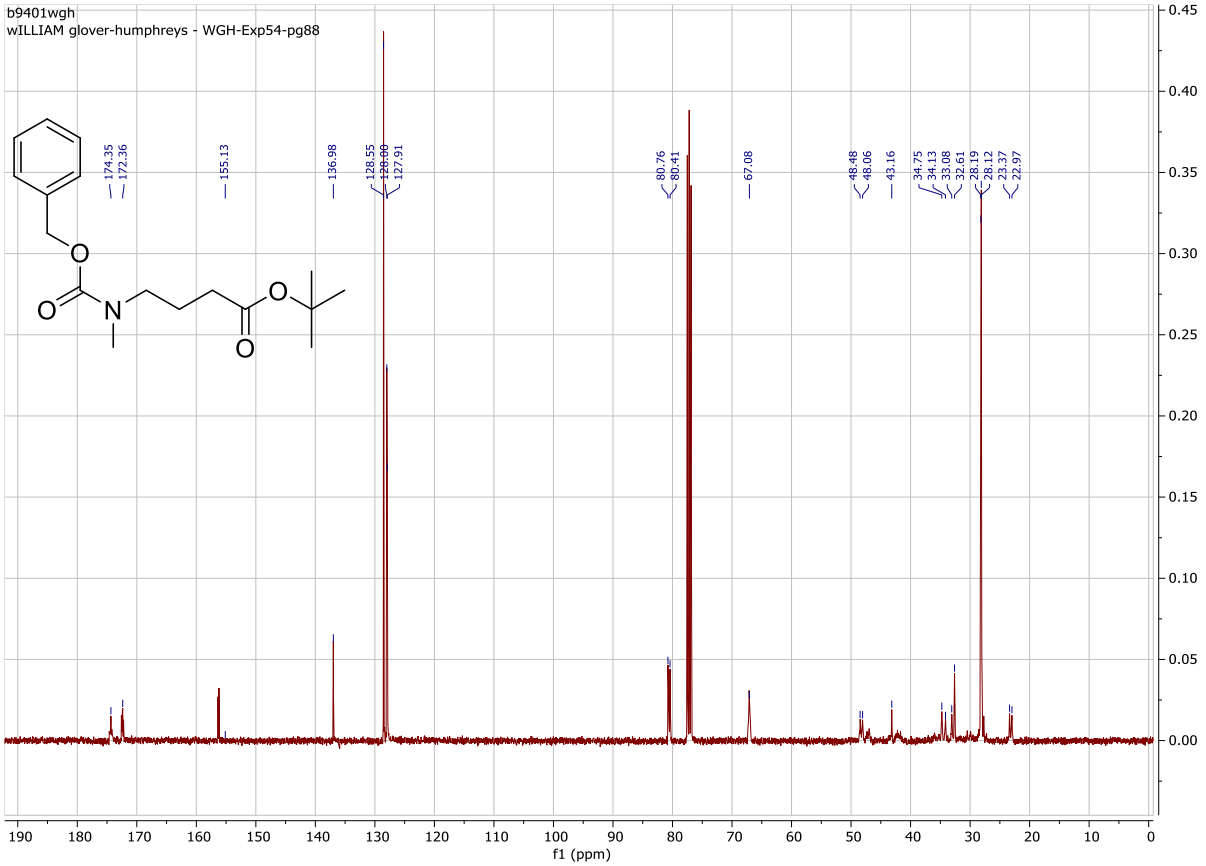
***tert*-Butyl 4-([(benzyloxy)carbonyl] (methyl)amino) butanoate (6-49)**



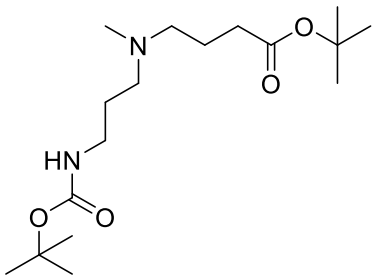
To a 250 mL round bottom flask of *N*-[(benzyloxy)carbonyl]-*N*-methylglycine **(6-45)** (2.70 g, 12.0 mmol), 4CzIPN **(6-37)** (0.095 g, 0.120 mmol) and dipotassium phosphate (2.51 g, 14.4 mmol) was added to DMF (30 mL) and degassed for 15 minutes using argon. Separately, *tert*-butyl acrylate **(6-32)** (3.00 mL) was degassed again for 15 minutes using argon. *tert*-Butyl acrylate **(6-32)** (1.54 g, 12.0 mmol) was then added to the 250 mL round bottom flask topped with a septum wrapped with parafilm several times. The reaction mixture was irradiated with blue LED light for 72 hours whilst stirring, setup as shown in

. The reaction was quenched in saturated $NaHCO_3$ aqueous solution (100 mL) and extracted in Et_2O (3 × 50 mL). The organic layers were collected and washed sequentially with saturated NaCl aqueous solution (2 × 100 mL) and water (2 × 100 mL). The organic phases were collected dried with sodium sulfate, the solvent removed under vacuum and purification via flash column chromatography (15:4:1 hexane:ethyl acetate:triethylamine) afforded the title compound as a clear oil (2.10 g, 57%); R_f = 0.32 (15:4:1 hexane:ethyl acetate:triethylamine); ν_{max}/cm^{-1} (thin film) 2977, 2934, 1724, 1702, 1455, 1366, 1145, 1055, 846, 768, 752, 698; δ_H (400 MHz, $CDCl_3$) rotamers observed in a 2:1 ratio 7.35−7.25 (5H, m, ArC**H**), 5.10 (s, 2H ArC**H**$_2$O), 3.30−3.26 (2H, m, NC**H**$_2$), 2.89$_{major}$ (3H, s, NC**H**$_3$), 2.88$_{minor}$ (3H, s, NC**H**$_3$), 2.24−2.15 (2H, m, C**H**$_2$COO), 1.83−1.75 (2H, m, CH$_2$C**H**$_2$CH$_2$), 1.43$_{minor}$ (9H, s, OC(C**H**$_3$)$_3$), 1.42$_{major}$ (9H, s, OC(C**H**$_3$)$_3$; δ_c (100 MHz, $CDCl_3$) rotamers observed in a 1:1 ratio 174.4 & 172.4 (CH$_3$**C**OO), 156.4 & 156.2 (O**C**ON), 137.0 (Ar**C**), 128.6 (ArC**H**), 128.0 (ArC**H**), 127.9 (ArC**H**), 80.8 & 80.5 (O**C**(CH$_3$)$_3$), 67.1 (Ar**C**H$_2$O), 48.5 & 48.1 (N**C**H$_2$), 43.2 (**C**H$_2$CO), 34.8 (**C**H$_2$), 34.1 (**C**H$_2$), 33.1 & 32.6 (N**C**H$_3$), 28.2 & 28.1 (OC(**C**H$_3$)$_3$), 23.4 & 23.0 (CH$_2$**C**H$_2$CH$_2$); HRMS (ESI): calcd. for $C_{17}H_{26}NO_4$ 308.1862. Found $[MH]^+$ 308.1854 (−2.60 ppm error).

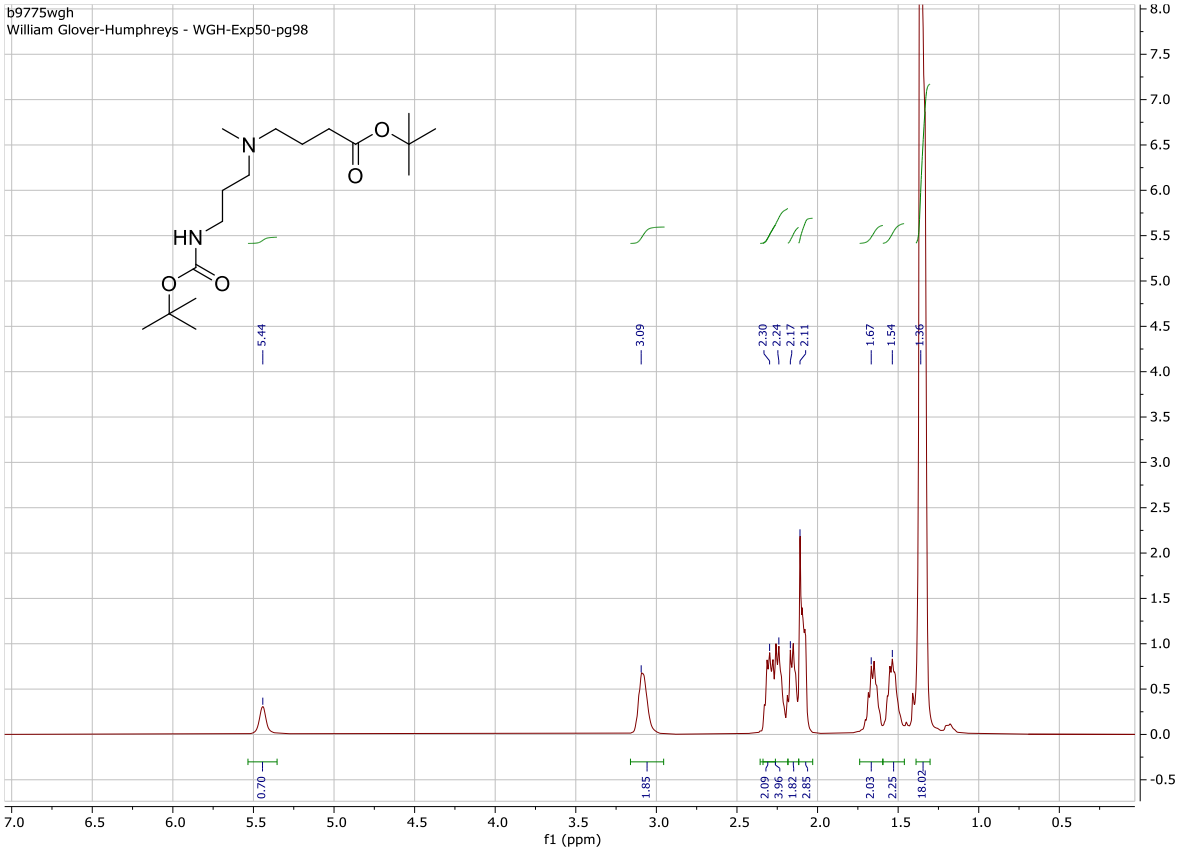

b9401wgh
wILLIAM glover-humphreys - WGH-Exp54-pg88
7.33
7.32
7.28
5.09
3.27
2.89
2.88
2.19
1.80
1.43
1.41
5.12
2.01
1.64
2.01
0.94
2.16
2.02
4.58
9.33
f1 (ppm)

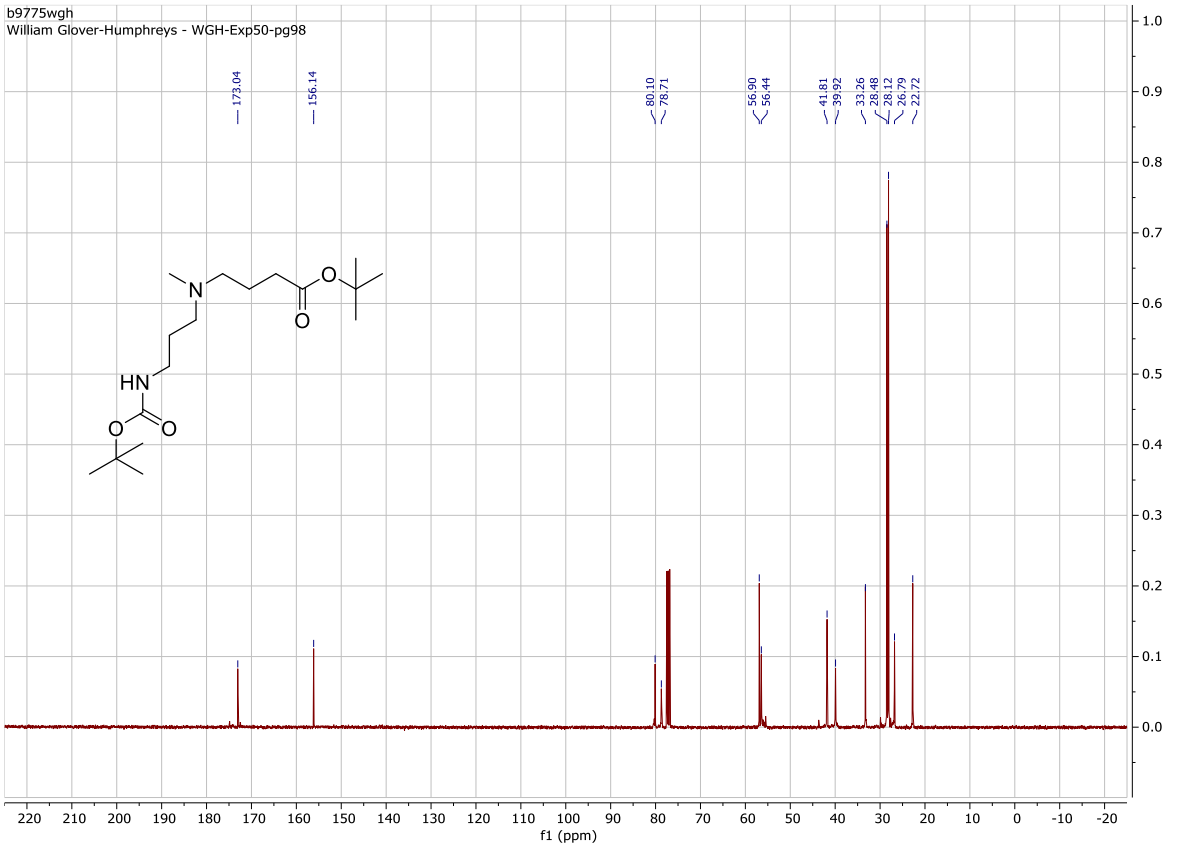

b9401wgh
wILLIAM glover-humphreys - WGH-Exp54-pg88
174.35
172.36
155.13
136.98
128.55
128.00
127.91
80.76
80.41
67.08
48.48
48.06
43.16
34.75
34.13
33.08
32.61
28.19
28.12
23.37
22.97
f1 (ppm)

***tert*-Butyl 4-[(3-[(tert-butoxycarbonyl) amino] propyl) (methyl) amino] butanoate (6-57)**

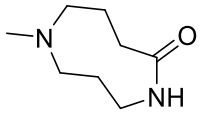


10% Palladium on carbon (0.202 g) was added to *tert*-butyl 4-[(benzyloxy)carbonyl] (methyl) amino) butanoate **(6-57)** (2.02 g, 6.89 mmol) in ethanol (60 mL) under argon. The solution was evacuated and refilled with hydrogen (× 3) then stirred at room temperature overnight whilst excess hydrogen refills the reaction vessel. The reaction mixture was filtered through Celite and washed with ethanol (100 mL) and the solvent was removed under vacuum using acetonitrile (3 × 15.0 mL) to make an azeotropic mixture. *tert*-Butyl 4-(methylamino) butanoate **(6-53)** was dissolved in acetonitrile (30 mL) then potassium carbonate (1.91 g, 13.8 mmol) and 3-(boc-amino) propyl bromide **(6-39)** (1.64 g, 6.89 mmol) was added and refluxed overnight under argon. The reaction mixture was diluted with EtOAc (250 mL) and washed with saturated $NaHCO_3$ aqueous solution (200 mL) was then back extracted with EtOAc (150 mL × 2). The organic phases were collected, dried using sodium sulfate, filtered, the solvent removed under vacuum and purified via flash column chromatography (15:4:1 hexane:ethyl acetate:triethylamine) afforded the title compound as a clear viscous oil (0.432 g, 19%); ν_{max}/cm^{-1} (thin film) 3369, 2976, 2934, 2796, 1710, 1514, 1456, 1366, 1249, 1154, 1047, 847, 733; δ_H (400 MHz, $CDCl_3$) 5.44 (1H, bs, N**H**), 3.13−3.05 (2H, bm, C**H**$_2$NH), 2.33−2.27 (2H, m, C**H**$_2$N), 2.27−2.21 (2H, m, C**H**$_2$N), 2.19−2.12 (2H, m, C**H**$_2$CO), 2.12−2.07 (3H, m, C**H**$_3$N), 1.71−1.61 (2H, m, C**H**$_2$), 1.57−1.48 (2H, m, C**H**$_2$), 1.35 (18H, bs, OC(C**H**$_3$)$_3$); δ_c (100 MHz, $CDCl_3$) 173.0 (CH_2**C**OO), 156.1 (NH**C**OO), 80.0 (O**C**(CH_3)$_3$), 78.7 ((O**C**(CH_3)$_3$), 56.9 (**C**H$_2$N), 56.5 (**C**H$_2$N), 41.8 (**C**H$_3$N), 39.9 (**C**H$_2$NH), 33.3 (**C**H$_2$COO), 28.5 (OC(**C**H$_3$)$_3$), 28.1 ((OC(**C**H$_3$)$_3$), 26.8 (**C**H$_2$), 22.7 (**C**H$_2$); HRMS (ESI): calcd. for $C_{17}H_{35}N_2O_4$ 331.2597. Found $[MH]^+$ 331.2595 (−0.60 ppm error).

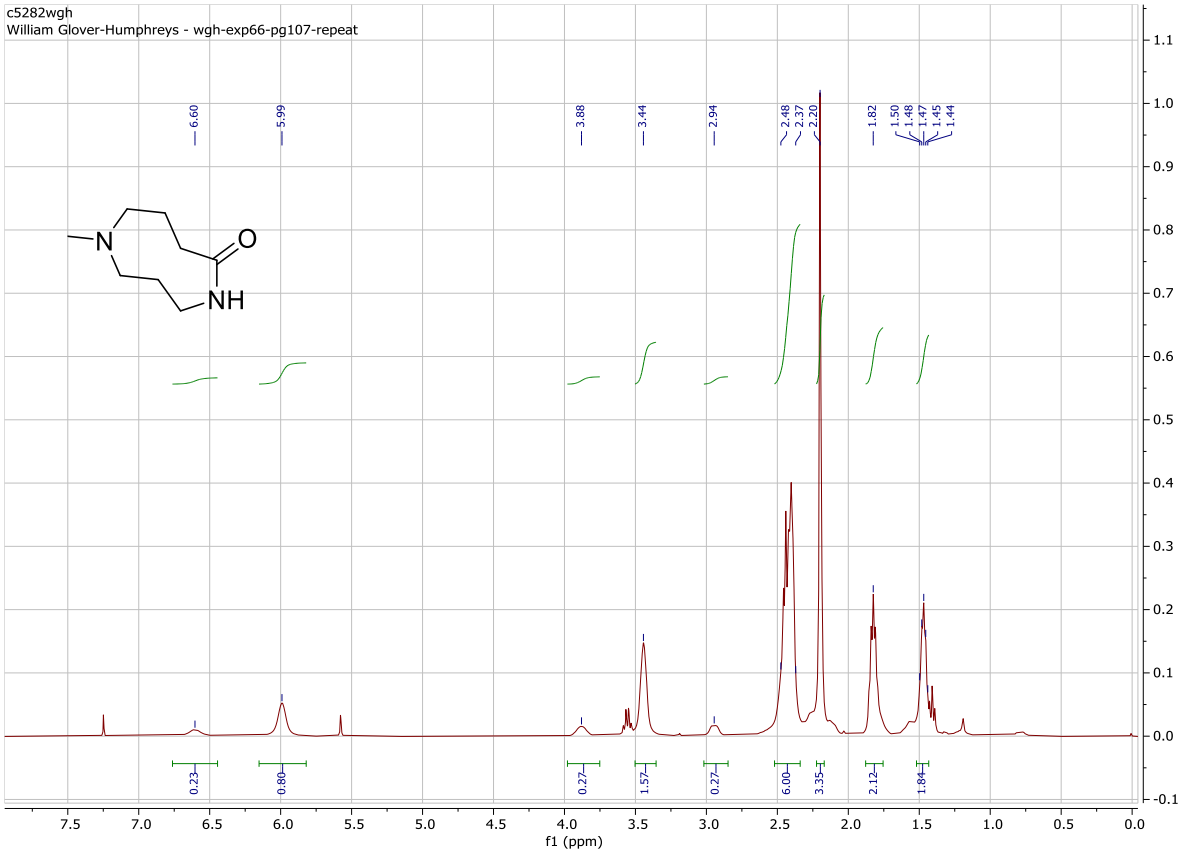

b9775wgh
William Glover-Humphreys - WGH-Exp50-pg98
5.44
3.09
2.30
2.24
2.17
2.11
1.67
1.54
1.36
0.70
1.85
2.09
3.96
1.82
2.85
2.03
2.25
18.02
f1 (ppm)

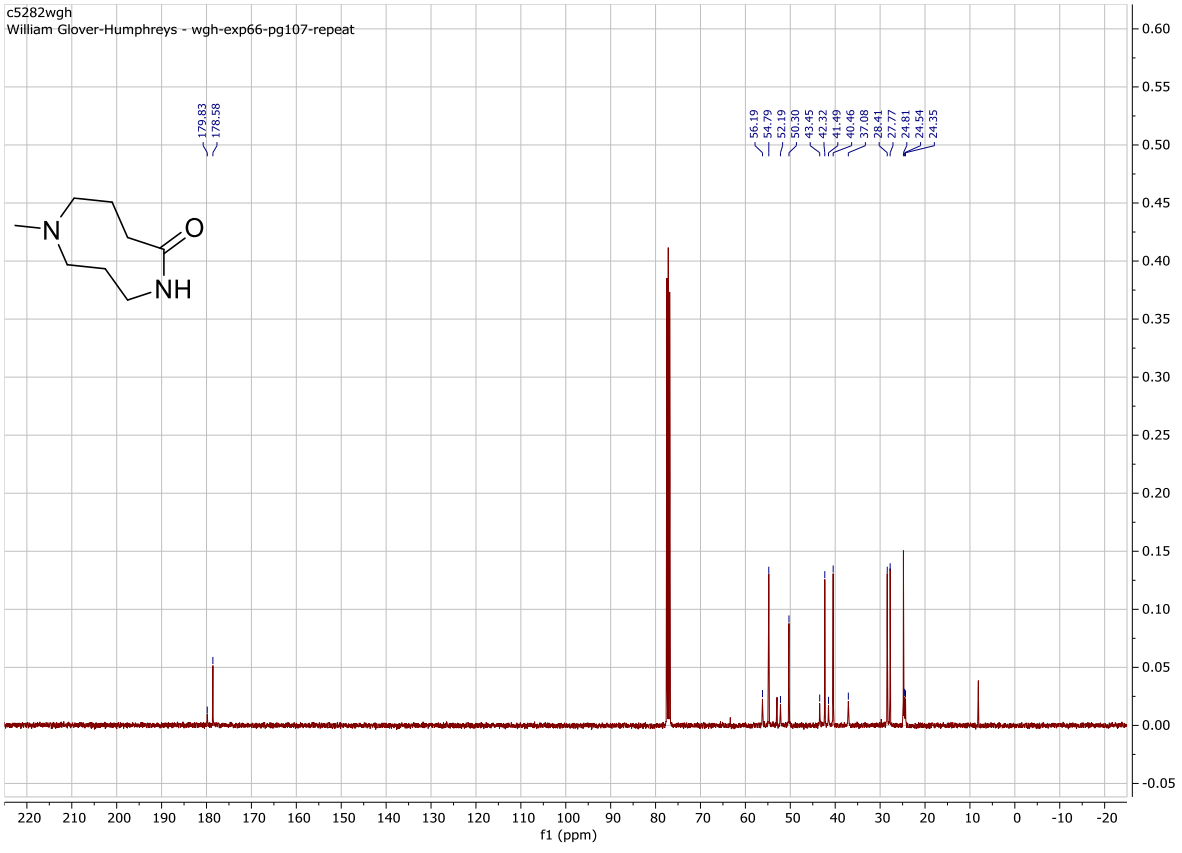

b9775wgh
William Glover-Humphreys - WGH-Exp50-pg98
173.04
156.14
80.10
78.71
55.90
56.44
41.81
39.92
33.26
28.48
28.12
26.79
22.72
f1 (ppm)

1-Methyl-1,5-diazonan-4-one (6-65)

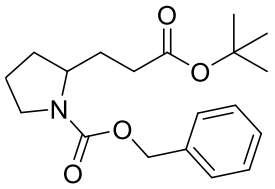


To a stirring solution of *tert*-butyl 4-[(3-[(*tert*-butoxycarbonyl) amino] propyl) (methyl) amino] butanoate **(6-57)** (0.250 g, 0.757 mmol) in Et_2O (2.00 mL), HCl in 1,4-dioxane 4.00 M solution (3.80 mL) was added dropwise and left to stir for 4 hours at room temperature. The reaction mixture was concentrated under vacuum using chloroform (3 × 10 mL) to make an azeotropic solution. Chloroform was added (19.0 mL) followed by DIPEA (0.980 g, 7.60 mmol) then stirred until all the reagents dissolved into solution (30 minutes). T3P (0.720 g, 1.14 mmol) was then added, and the reaction was left to stir over night at room temperature. The solvent was then removed under vacuum and the reaction mixture purified via flash column chromatography (10:9:1 dichloromethane:hexane:triethylamine) to afforded the title compound as a white solid, (76.8 mg, 65%); R_f = 0.28 (10:9:1 dichloromethane:hexane:triethylamine); ν_{max}/cm^{-1} (thin film) 3286, 2936, 2786, 1634, 1544, 1450, 1353, 1341, 1288, 1180, 1146, 1068, 969, 732, 580; δ_H (400 MHz, $CDCl_3$) rotomers were observed in a 1:4 ratio, 6.72−6.49$_{minor}$ (0.2H, bs, N**H**), 6.13−5.84$_{major}$ (0.8H, bs N**H**), 3.94−3.80 (bm, 0.25H, C**H**$_2$NH), 3.49−3.37 (bm, 1.5H, CH_2NH), 2.99−2.89 (bm, 0.25H, C**H$_a$**H$_b$NH), 2.50−2.40 (1H, m, CH$_a$**H$_b$**N), 2.50−2.40 (2H, m, C**H**$_2$N), 2.50−2.40 (2H, m, C**H**$_2$), 2.23 (3H, s, C**H**$_3$N), 1.86−1.79 (2H, m, C**H**$_2$CO), 1.49 (2H, pen, *J* = 6.5 Hz, C**H**$_2$); δ_c (100 MHz, $CDCl_3$) 179.8$_{minor}$ (**C**O), 178.6$_{major}$ (**C**O), 56.2$_{minor}$ (**C**H$_2$N), 54.8$_{major}$ (**C**H$_2$N), 52.2$_{minor}$ (**C**H$_2$N), 50.3 (**C**H$_2$N), 43.5$_{minor}$ (**C**H$_3$N), 42.3$_{major}$ (**C**H$_3$N), 41.5$_{minor}$ (**C**H$_2$N), 40.5$_{major}$ (**C**H$_2$NCO), 37.1$_{minor}$ (**C**H$_2$NCO), 28.5$_{major}$ (**C**H$_2$), 27.8$_{major}$ (**C**H$_2$), 24.8$_{major}$ (**C**H$_2$CO), 24.5$_{minor}$ (**C**H$_2$), 24.4$_{minor}$ (**C**H$_2$); HRMS (ESI): calcd. for $C_8H_{17}N_2O$ 157.1341. Found $[MH]^+$ 157.1336 (–3.18 ppm error).


c5282wgh
William Glover-Humphreys - wgh-exp66-pg107-repeat
6.60
5.99
3.88
3.44
2.94
2.48
2.37
2.20
1.82
1.50
1.48
1.47
1.45
1.44
N
O
NH
0.23
0.80
0.27
1.57
0.27
6.00
3.35
2.12
1.84
f1 (ppm)

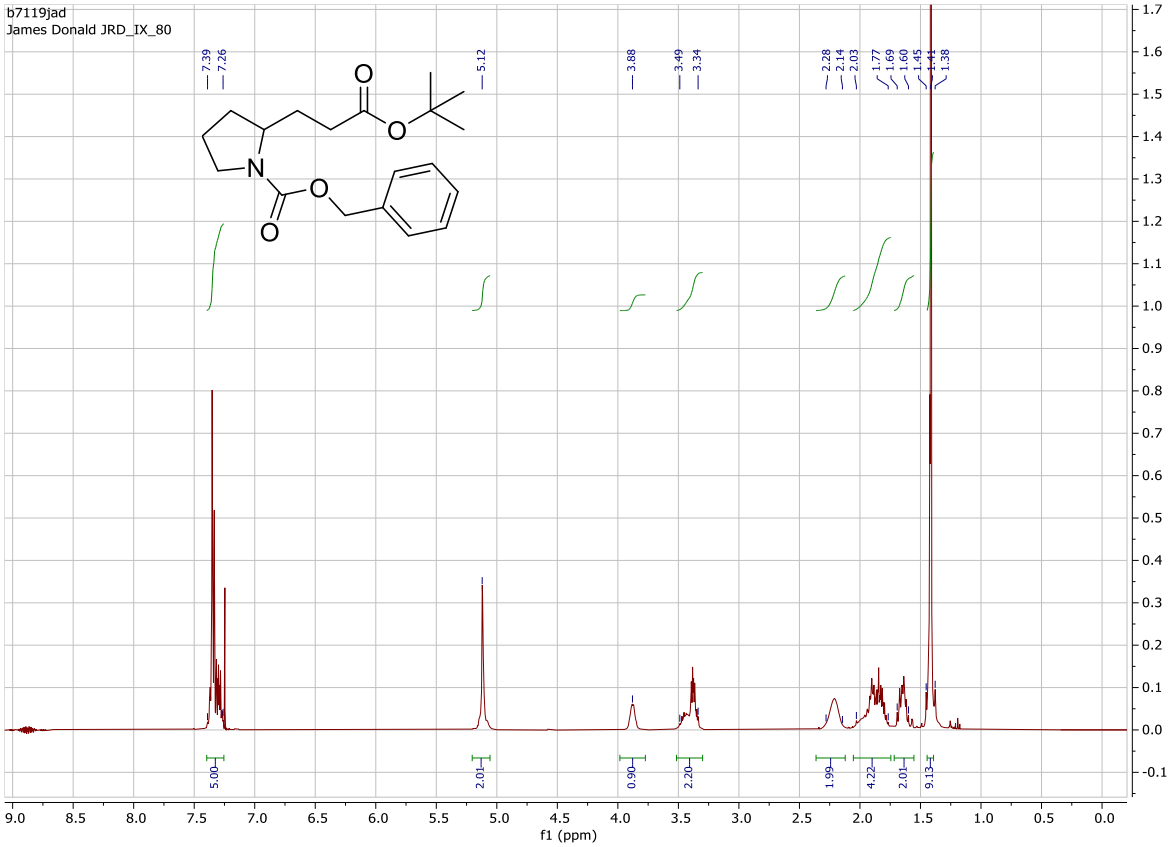

c5282wgh
William Glover-Humphreys - wgh-exp66-pg107-repeat
179.83
178.58
56.19
54.79
52.19
50.30
43.45
42.32
41.49
40.46
37.08
28.41
27.77
24.81
24.54
24.35
N
O
NH
f1 (ppm)

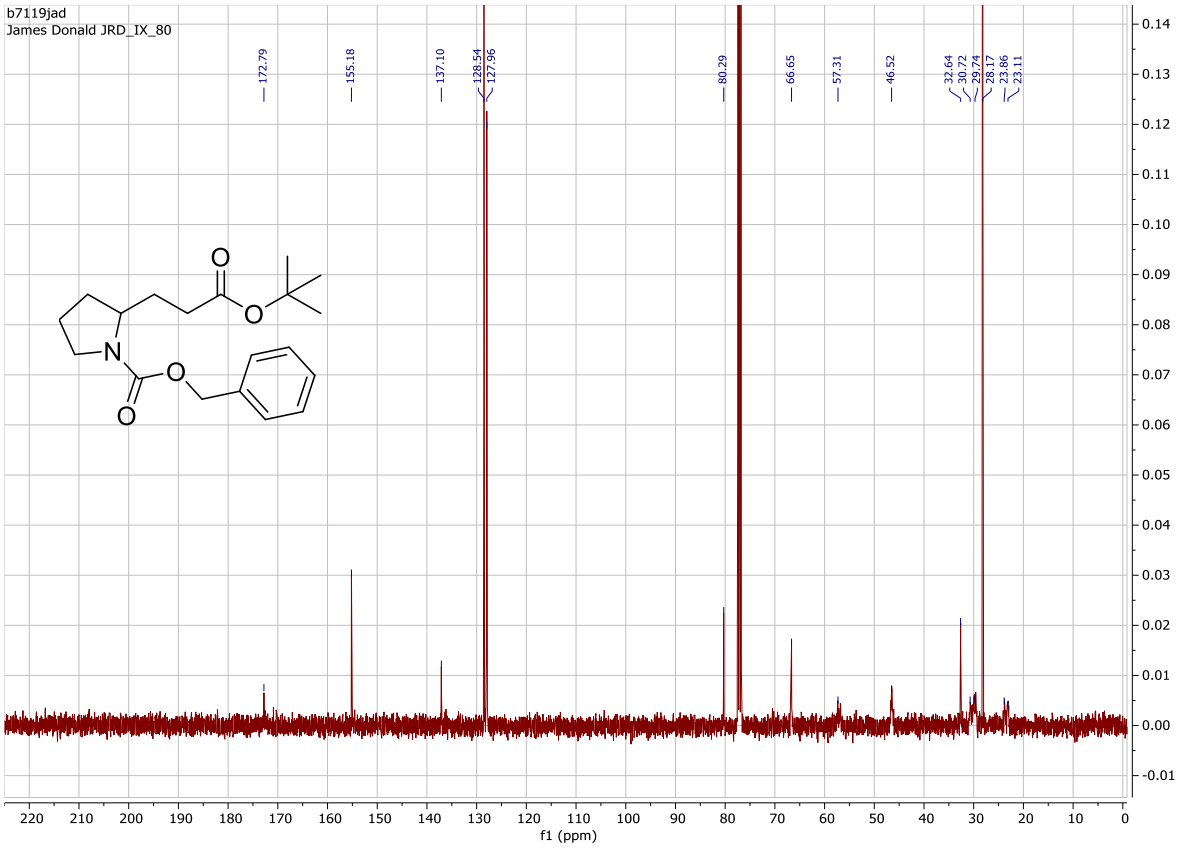
Benzyl 2-(3-(*tert*-butoxy)-3-oxopropyl) pyrrolidine-1-carboxylate (6-50)



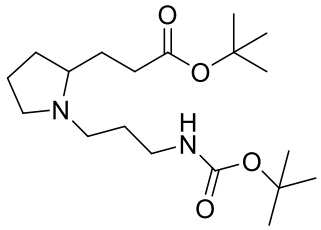
To a 250 mL round bottom flask Isolating ((benzyloxy)carbonyl) proline (**6-46**) (2.89 g, 12.0 mmol), Ir[df (CF_3)ppy]$_2$ (dtbby)PF_6 **(6-33)** (0.135 g, 0.120 mmol) and dipotassium phosphate (2.51 g, 14.4 mmol) was added to DMF (30 mL) and degassed for 10 minutes using argon. Separately *tert*-butyl acrylate **(6-32)** (3.00 mL) was degassed again for 10 minutes using argon. *tert*-Butyl acrylate **(6-32)** (1.54 g, 1.76 mL, 12.0 mmol) was then added to the 250 mL round bottom flask topped with a septum wrapped with parafilm several times. The reaction mixture was irradiated with blue LED light for 63 hours whilst stirring, setup as shown in

. The reaction was quenched in saturated $NaHCO_3$ aqueous solution (150 mL) and extracted in Et_2O (3 × 100 mL). The organic phases were collected and dried with sodium sulfate and the solvent removed under vacuum. The reaction mixture was purified via flash column chromatography (8:2 hexane:ethyl acetate) to afford the title compound as a pale yellow oil (2.30 g, 57%); R_f = 0.23 (8:2 hexane:ethyl acetate); ν_{max}/cm^{-1} (thin film) 2930, 1700, 1279, 1159; δ_H (400 MHz, $CDCl_3$) 7-39−7.26 (5H, m, 5 × Ar**H**), 5.12 (2H, s, OC**H**$_2$Ar), 3.88 (1H, s, C**H**N), 3.49−3.34 (2H, m, C**H**$_2$N), 2.88−2.14 (2H, m, CH_2C**H**$_2$CO), 2.02−1.77 (4H, m, 2× C**H**$_2$), 1.69−1.60 (2H, m, C**H**$_2$), 1.41 (9H, s, (C**H**$_3$)$_3$C); δ_C (100 MHz, $CDCl_3$) 172.8 (**C**O), 155.2 (Ar**C**H), 137.1 (Ar**C**), 128.5 (Ar**C**H), 128.0 (Ar**C**H), 80.3 (O**C**CH_3)$_3$, 66.7 (OC**H**$_2$Ar), 57.2 (N**C**H), 46.5 (**C**H_2N), 32.6 (**C**H_2CO), 30.7 (**C**H_2), 29.7 (**C**H_2), 28.2 ((**C**H_3)$_3$C), 23.9 (**C**H_2), 23.1 (**C**H_2); HRMS (ESI): calcd for $C_{19}H_{28}NO_4$ 334.2018 & $C_{19}H_{28}NNaO_4$. 356.1838. Found $[MH]^+$, 334.2007 (−3.29 ppm error) & $[MNa]^+$, 356.1830 (−2.24 ppm error).

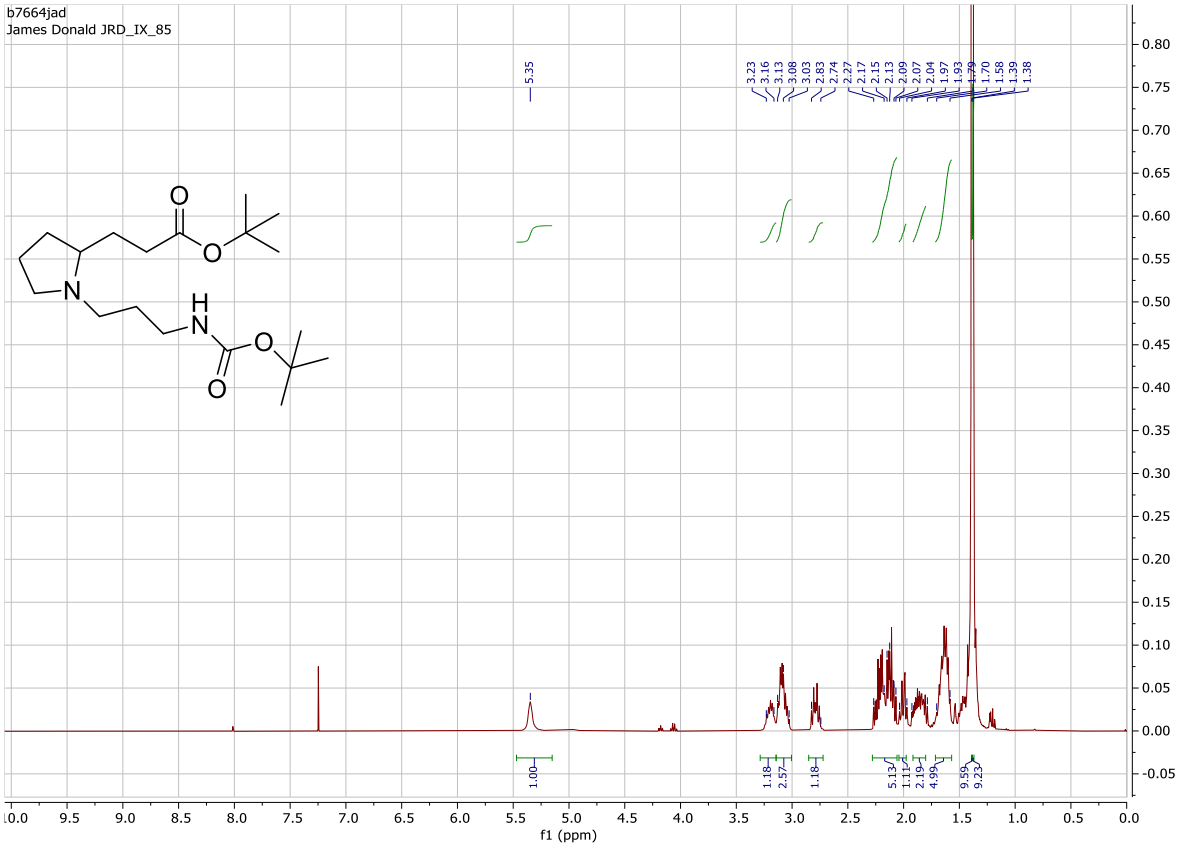

b7119jad
James Donald JRD_IX_80
7.39
7.26
5.12
3.88
3.49
3.34
2.28
2.14
2.03
1.77
1.69
1.60
1.45
1.44
1.38
5.00
2.01
0.90
2.20
1.99
4.22
2.01
9.13
f1 (ppm)


b7119jad
James Donald JRD_IX_80
172.79
155.18
137.10
128.54
127.96
80.29
66.65
57.31
46.52
32.64
30.72
29.74
28.17
23.86
23.11
f1 (ppm)

***tert*-Butyl 3-(1-(3-((*tert*-butoxycarbonyl) amino) propyl) pyrrolidin-2-yl) propanoate (6-58)**



10% Palladium on carbon (0.200 g) was added to a solution of benzyl 2-(3-(*tert*-butoxy)-3-oxopropyl) pyrrolidine-1-carboxylate **(6-50)** (2.01 g, 6.03 mmol) in ethanol (60 mL) under argon. The solution was evacuated and refilled with hydrogen (× 3) then stirred at room temperature overnight whilst excess hydrogen refills the reaction vessel. The mixture was filtered through Celite and washed with ethanol (100 mL) and the solvent was removed under vacuum using acetonitrile (3 × 15 mL) to make an azeotropic mixture. The mixture was redissolved in acetonitrile (30 mL) then potassium carbonate (1.67 g, 12.1 mmol) and 3-(Boc-amino) propyl bromide **(6-39)** (1.44 g, 6.03 mmol) was added and the reaction mixture heated to reflux overnight under argon. The reaction mixture was diluted with EtOAc (250 mL) and washed with saturated $NaHCO_3$ aqueous solution (200 mL) then back extracted with (EtOAc 2 × 150 mL). The organic phases were collected and dried using sodium sulfate, filtered and the solvent removed under vacuum. The reaction mixture was purified via flash column chromatography (75:20:5 hexane:ethyl acetate:triethylamine) to afford the title compound as a yellow oil (1.85 g, 86%); ν_{max}/cm^{-1} (thin film) 3365, 2972, 2796, 1709, 1515, 1454, 1366, 1249, 1148, 848, 732; δ_H (400 MHz, $CDCl_3$) 5.35 (1H, s, N**H**), 3.23−3.16 (1H, m, C**H**$_a$H$_b$N), 3.13−3.08 (1H, m, C**H**$_a$H$_b$N), 3.08−3.03 (1H, m, CH$_a$**H**$_b$N), 2.83−2.72 (1H, m, C**H**$_a$H$_b$N), 2.27−2.07 (5H, m, CH$_a$**H**$_b$N, C**H**$_2$CO, NC**H,** C**H**$_a$H$_b$), 2.04−1.97 (1H, m, CH$_a$**H**$_b$N), 1.93−1.79 (2H, m, CH$_2$C**H**$_2$CH$_2$), 1.70−1.58 (5H, m, CHC**H**$_2$CH$_2$, CH$_2$C**H**$_2$CH$_2$, CH$_a$**H**$_b$), 1.39 (9H, s, (C**H**$_3$)$_3$O), 1.38 (9H, s, (C**H**$_3$)$_3$O); δ_C (100 MHz, $CDCl_3$) 173.2 (CH$_2$**C**OOC(CH$_3$)$_3$), 156.2 (NH**C**OOC(CH$_3$)$_3$), 80.2 (CH$_2$COO**C**(CH$_3$)$_3$), 78.8 (NHCOO**C**(CH$_3$)$_3$), 64.1 (**C**H), 53.9 (**C**H$_2$N), 52.7 (**C**H$_2$N), 39.9 (**C**H$_2$NH), 32.3 (**C**H$_2$COO), 29.9 (CH$_2$**C**H$_2$CH), 29.1 (CH**C**H$_2$CH$_2$), 28.5 ((**C**H$_3$)$_3$O), 28.3 (CH$_2$**C**H$_2$CH$_2$), 28.2 ((**C**H$_3$)$_3$O); HRMS (ESI): calcd. for $C_{19}H_{37}N_2O_4$ 357.2753. Found $[MH]^+$ 357.2754 (0.280 ppm error).


b7664jad
James Donald JRD_IX_85
5.35
3.23
3.16
3.13
3.08
3.03
2.83
2.74
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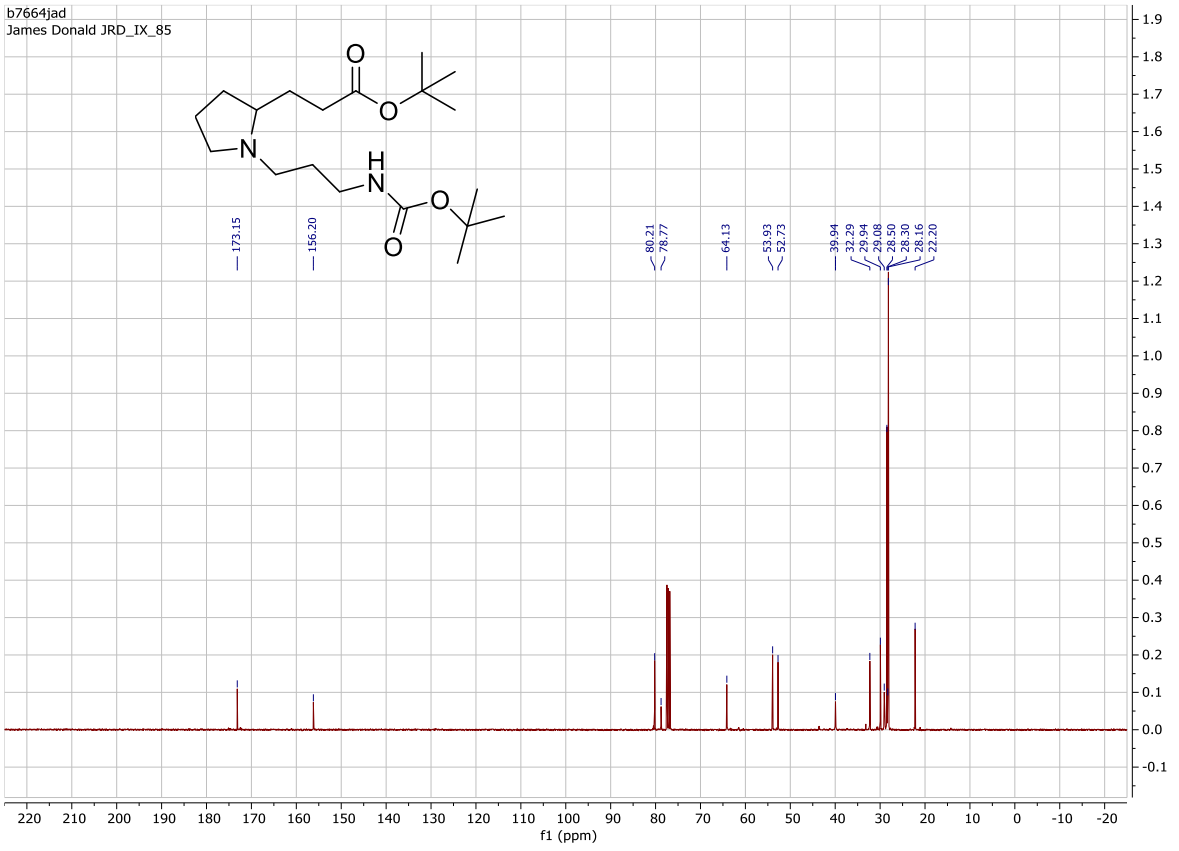
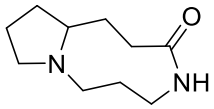
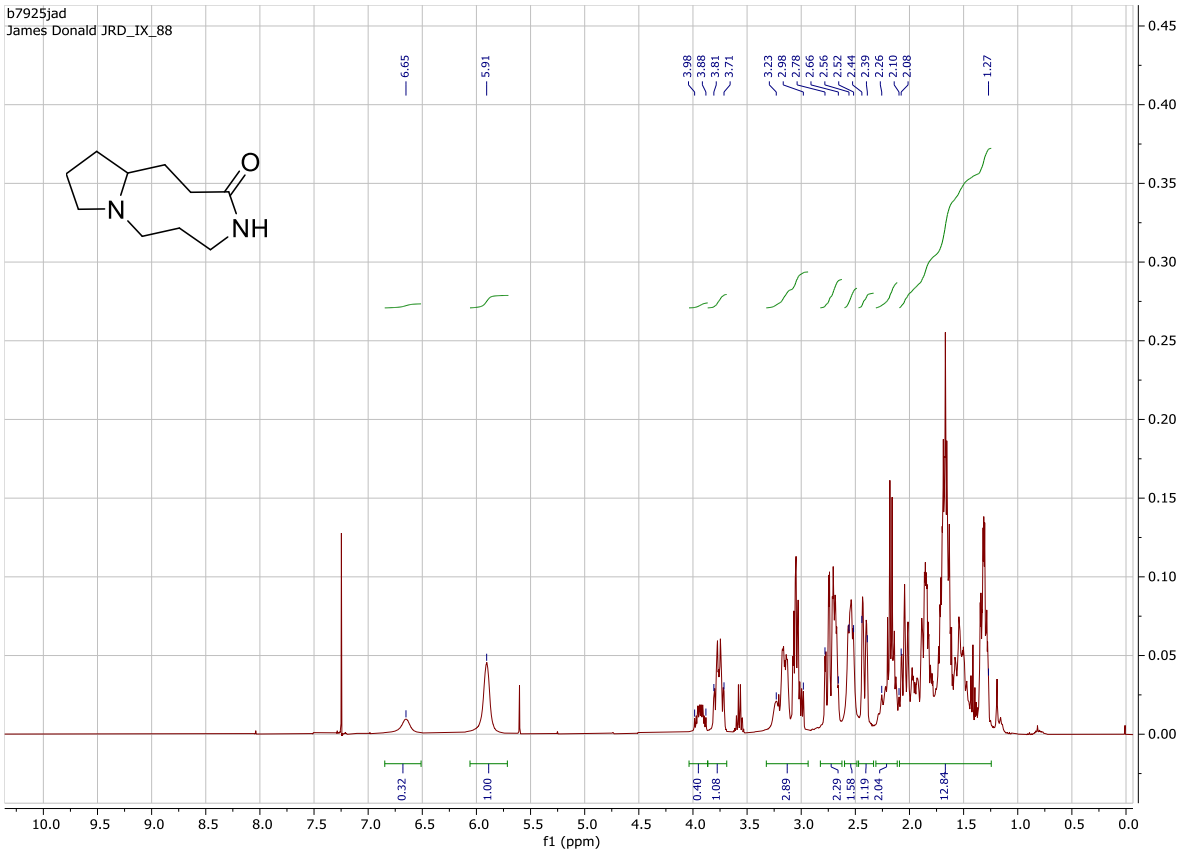
2.15
2.13
2.09
2.07
2.04
1.97
1.93
1.70
1.58
1.39
1.38
1.00
1.18
2.57
1.18
5.13
1.11
2.19
4.99
9.59
9.23
f1 (ppm)

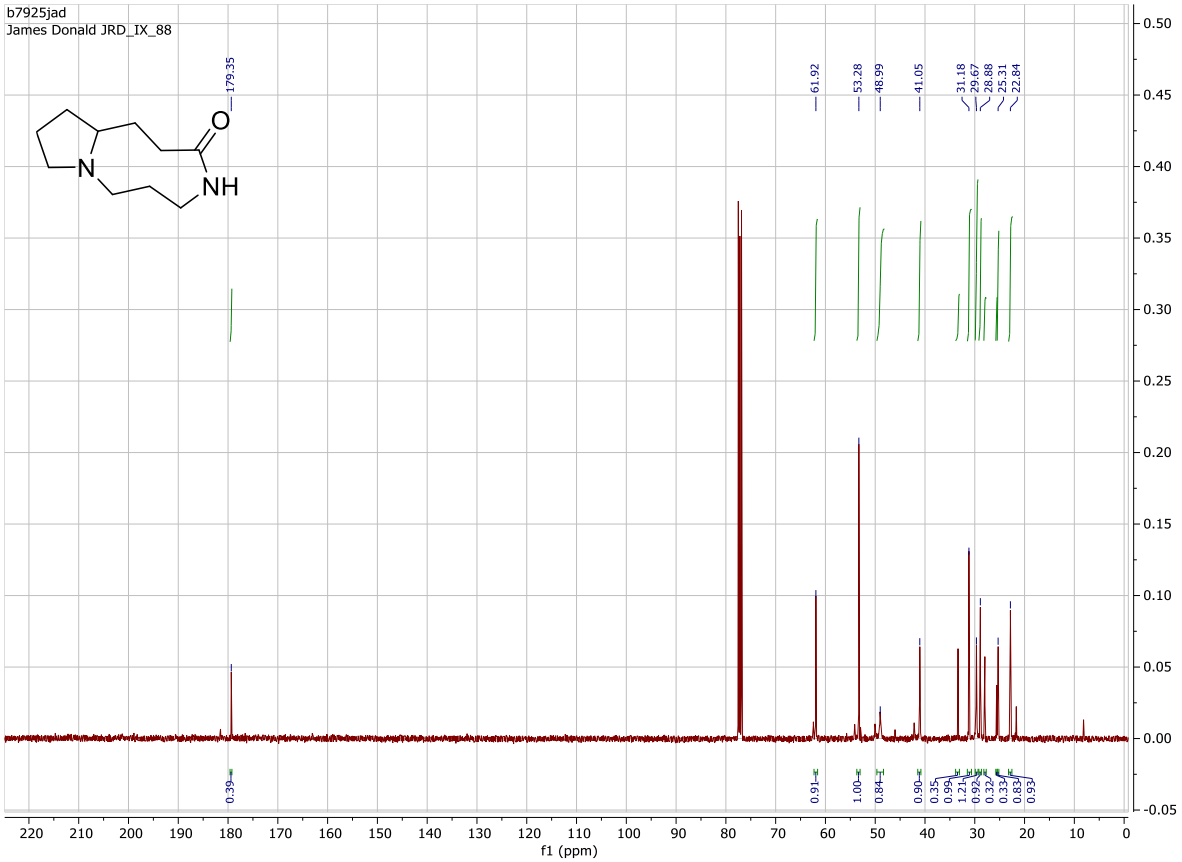

b7664jad
James Donald JRD_IX_85
173.15
156.20
80.21
78.77
64.13
53.93
52.73
39.94
32.29
29.94
29.08
28.50
28.30
28.16
22.20
f1 (ppm)

Decahydro-9H-pyrrolo[1,2-e] [1,5] diazonin-9-one (6-66)

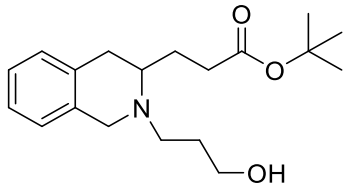


To a stirring solution of *tert*-butyl 3-(1-(3-((*tert*-butoxycarbonyl) amino) propyl) pyrrolidin-2-yl) propanoate **(6-58)** (0.183 g, 5.15 mmol) in diethyl ether (13.0 mL), a solution of 4.0 M hydrochloric acid in 1,4 dioxane (26.0 mL, 104.0 mmol) was added dropwise and the reaction was left stirring at room temperature for 4 hours. The reaction mixture was concentrated under vacuum using chloroform (3 × 5.00 mL) to make an azeotropic solution. The intermediate lithium 3-(1-(3-aminopropyl) pyrrolidin-2-yl) propanoate was dissolved in chloroform (129.0 mL) and DIPEA (6.65 g, 8.97 mL, 5.15 mmol) under argon, until all the reagents dissolved into solution (30 minutes). T3P (4.91 g, 7.72 mmol) was then added and the reaction left to stir over night at room temperature. The solvent was removed under vacuum and the reaction mixture was purified via flash column chromatography (50:45:5 dichloromethane:hexane:triethylamine) forming a colourless solid (0.715 g, 76%); R_f = 0.22 (70:25:5 dichloromethane:hexane:triethylamine); ν_{max}/cm^{-1} (thin film) 3281, 2944, 2791, 1641, 1467, 1444, 1365, 1293, 1170; δ_H (400 MHz, $CDCl_3$) rotameric mixture 3:1 ratio, 6.65 (1H, s, N**H**)$_{minor}$, 5.91 (1H, s, N**H**)$_{major}$, 3.98−3.88 (1H, m, C**H**$_a$H$_b$N)$_{minor}$, 3.81−3.71 (1H, m, C**H**$_a$H$_b$N)$_{major}$, 3.23−2.98 [4H, m (CH$_a$-**H**$_b$N)$_{both\ rotamers}$, (C**H**$_a$H$_b$N)$_{both\ rotamers}$], 2.78−2.66 (3H, m, (C**H**N)$_{major}$, (C**H**$_a$H$_b$N)$_{both\ rotamers}$), 2.56−2.52 (2H, m, (C**H**$_a$H$_b$)$_{both\ rotamers}$, (C**H**$_a$H$_b$N)$_{minor}$, 2.44−2.39 (2H, m, (C**H**N)$_{minor}$, (CH$_a$**H**$_b$N)$_{major}$), 2.26−2.10 (4H, m, CH$_a$-**H**$_b$N)$_{both\ rotamers}$, (C**H**$_2$)$_{minor}$) 2.07−1.27 [18H, m, C**H**$_2$]$_{both\ rotamers}$; δ_C (100 MHz, $CDCl_3$) the major rotamer 179.4 (**C**O), 61.9 (**C**H), 53.3 (**C**H$_2$N), 49.0 (**C**H$_2$N), 41.1 (**C**H$_2$NH), 31.1 (**C**H$_2$CO), 29.7 (NCH$_2$**C**H$_2$CH$_2$N), 28.9 (CH**C**H$_2$CH$_2$), 25.3 (CH**C**H$_2$CH$_2$), 22.8 (CH$_2$**C**H$_2$CH$_2$); HRMS (ESI): calcd. for $C_{10}H_{18}N_2O$ 183.1497. Found $[MH]^+$ 183.1492 (−2.73 ppm error).

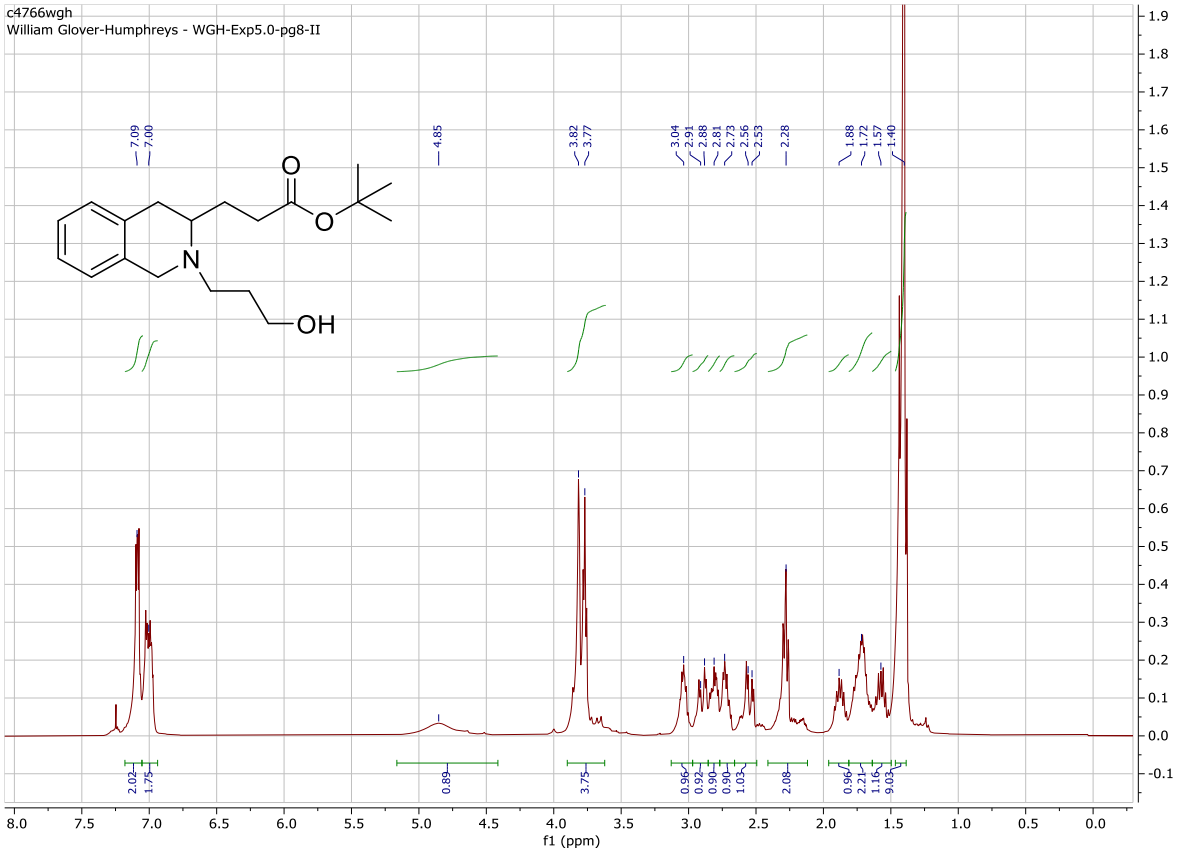

b7925jad
James Donald JRD_IX_88
6.65
5.91
3.98
3.88
3.81
3.71
3.23
2.98
2.78
2.66
2.56
2.52
2.44
2.39
2.26
2.10
2.08
1.27
O
N
NH
0.32
1.00
0.40
1.08
2.89
2.29
1.58
1.19
2.04
12.84
f1 (ppm)

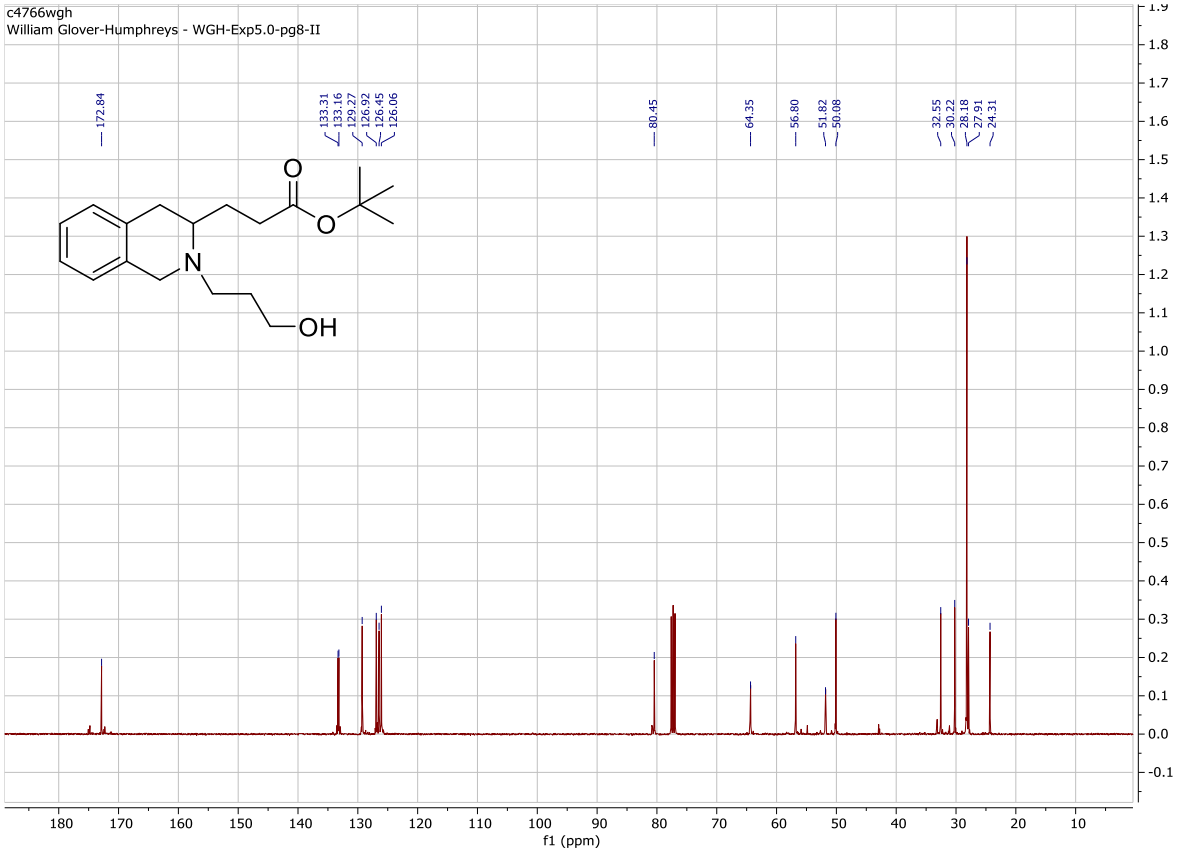

b7925jad
James Donald JRD_IX_88
179.35
61.92
53.28
48.99
41.05
31.18
29.67
28.88
25.31
22.84
O
N
NH
0.39
0.91
1.00
0.84
0.90
0.35
0.99
1.21
0.92
0.32
0.33
0.83
0.93
f1 (ppm)

***tert*-Butyl 3-[2-(3-hydroxypropyl)-1,2,3,4-tetrahydroisoquinolin-3-yl] propanoate (6-72)**

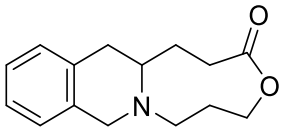


To a stirring solution of *tert*-butyl 3-(1,2,3,4-tetrahydroisoquinolin-3-yl) propanoate (**6-38**) (1.10 g, 4.00 mmol) in dry acetonitrile (33.0 mL), potassium carbonate (0.830 g, 6.00 mmol) and sodium iodide (0.12 g, 0.80 mmol) was added. Bromopropanol **(6-71)** (0.552 g, 4.00 mmol) was then added, and the resulting mixture was stirred at 100 °C for 24 hours. After allowing to cool to room temperature the reaction mixture was diluted with EtOAc (100 mL) and washed with saturated $NaHCO_3$ aqueous solution (100 mL) then back extracted with EtOAc (100 mL). The organic phases were combined dried using sodium sulfate, filtered and the solvent removed under vacuum. The reaction mixture went to completion and further purification wasn't required, with the product isolated as a brown oil (1.05 g, 82%); ν_{max}/cm^{-1} (thin film) 3390, 2975, 2931, 1724, 1454, 1367, 1147, 743; δH (400MHz, $CDCl_3$) 7.15−7.05 (2H, m, 2 × Ar**H**), 7.05−6.95 (2H, m, Ar**H**), 4.86 (1H, bs, O**H**), 3.82 (2H, bs, ArC$\mathbf{H}_2$N), 3.80−3.72 (2H, m, ArC$\mathbf{H}_2$), 3.09−2.99 (1H, m, C**H**N), 2.96−2.85 (1H, m, C$\mathbf{H_a}H_b$N), 2.85−2.77 (1H, m C$\mathbf{H_a}H_b$OH), 2.76−2.67 (1H, m $CH_a\mathbf{H_b}$OH), 2.58−2.50 (1H, m, $CH_a\mathbf{H_b}$N), 2.31−2.25 (2H, m, C$\mathbf{H}_2$CO), 1.92−1.82 (1H, m, C$\mathbf{H}_a H_b$), 1.80−1.64 (2H, m, C$\mathbf{H}_2$), 1.62−1.52 (1H, m, $CH_a\mathbf{H}_b$), 1.40 (9H, s, C(C$\mathbf{H}_3)_3$); δ_C (100 MHz, $CDCl_3$) 172.8 (**C**O), 133.3 (Ar**C**), 133.2 (Ar**C**), 129.3 (Ar**C**H), 126.9 (Ar**C**H), 126.5 (Ar**C**H), 126.1 (Ar**C**H), 80.5 (O**C**$(CH_3)_3$), 65.4 (Ar**C**H_2), 56.8 (**C**HN), 51.8 (**C**H_2OH), 50.1 (Ar**C**H_2N), 32.6 (**C**H_2CO), 30.2 (H_2N), 28.2 ((OC(**C**$H_3)_3$), 27.9 (**C**H_2), 24.3 (**C**H_2); HRMS (ESI): calcd. for $C_{19}H_{30}NO_3$ 320.2226. Found $[MH]^+$ 320.2223, (−0.94 ppm error).


c4766wgh
William Glover-Humphreys - WGH-Exp5.0-pg8-II
7.09
7.00
4.85
3.82
3.77
3.04
2.91
2.88
2.81
2.73
2.56
2.53
2.28
1.88
1.72
1.57
1.40
O
O
N
OH
2.02
1.75
0.89
3.75
0.96
0.92
0.90
0.90
1.03
2.08
0.96
2.21
1.16
9.03
f1 (ppm)


c4766wgh
William Glover-Humphreys - WGH-Exp5.0-pg8-II
172.84
133.31
133.16
129.27
126.92
126.45
126.06
80.45
64.35
56.80
51.82
50.08
32.55
30.22
28.18
27.91
24.31
O
O
N
OH
f1 (ppm)

1,6,7,9,14,14a-hexahydro-5*H*- [1,5] oxazonino[5,4-*b*] isoquinolin-3 (2*H*)-one (6-74)



Procedure A

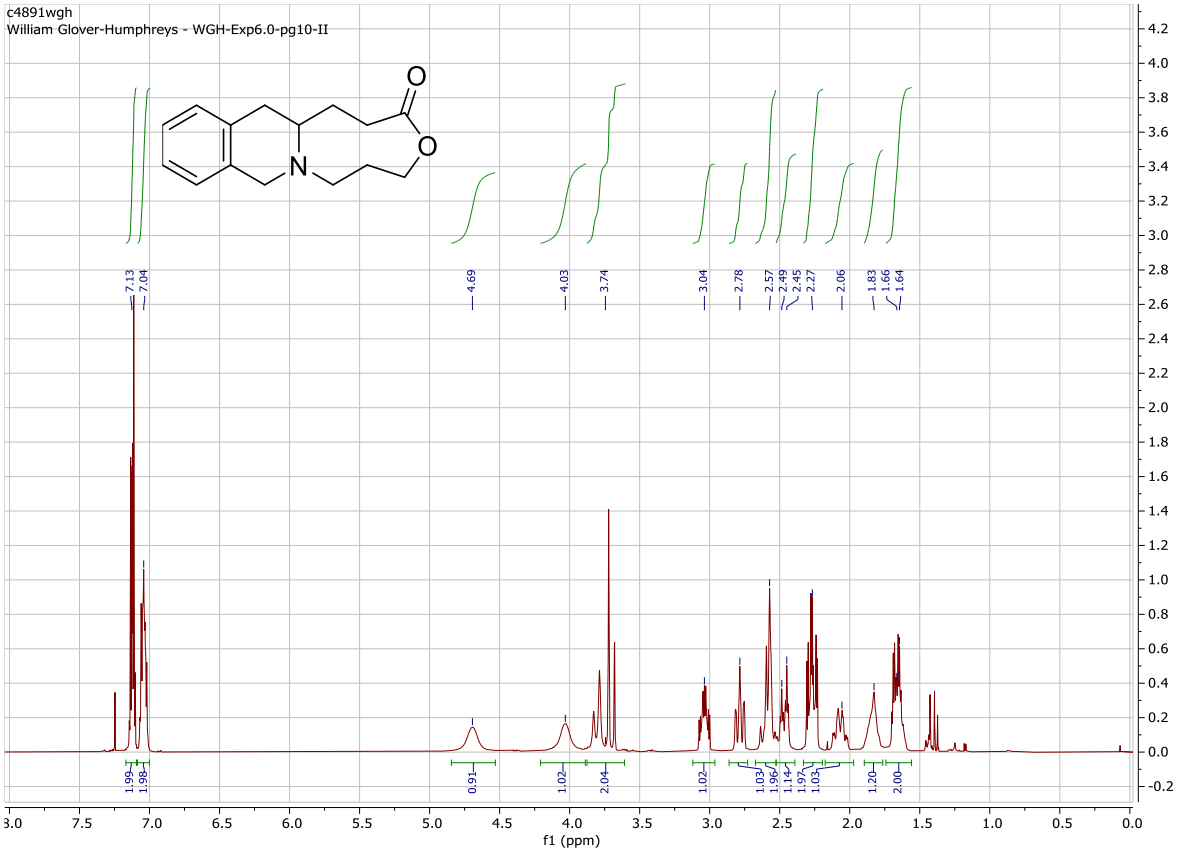
To a stirring solution of *tert*-butyl 3-[2-(3-hydroxypropyl)-1,2,3,4-tetrahydroisoquinolin-3-yl] propanoate (**6-72**) (0.300 g, 0.940 mmol) in diethyl ether (1.88 mL), a solution of 4.0 M hydrochloric acid in 1,4 dioxane (4.7 mL, 18.8 mmol) was added dropwise and the reaction was left stirring at room temperature for 3 hours. The reaction mixture was concentrated under vacuum using chloroform (3 × 20 mL) to make an azeotropic solution. The intermediate 3-[2-(3-hydroxypropyl)-1,2,3,4-tetrahydroisoquinolin-3-yl] propanoic acid (**6-73**) was dissolved in chloroform (37.6 mL) and DIPEA (2.43 g, 3.3 mL, 18.8 mmol) under argon, until all the reagents dissolved into solution (30 minutes). T3P 50% w/v in ethyl acetate (0.897 g, 1.41 mmol) was added dropwise and the reaction left to stir over night at room temperature. The reaction mixture was concentrated under vacuum and purified via flash column chromatography (85:10:5 hexane:ethyl acetate:triethylamine) forming the product a crystalline white solid (0.067 g, 29%), R_f = 0.43 (85:10:5 hexane:ethyl acetate:triethylamine)

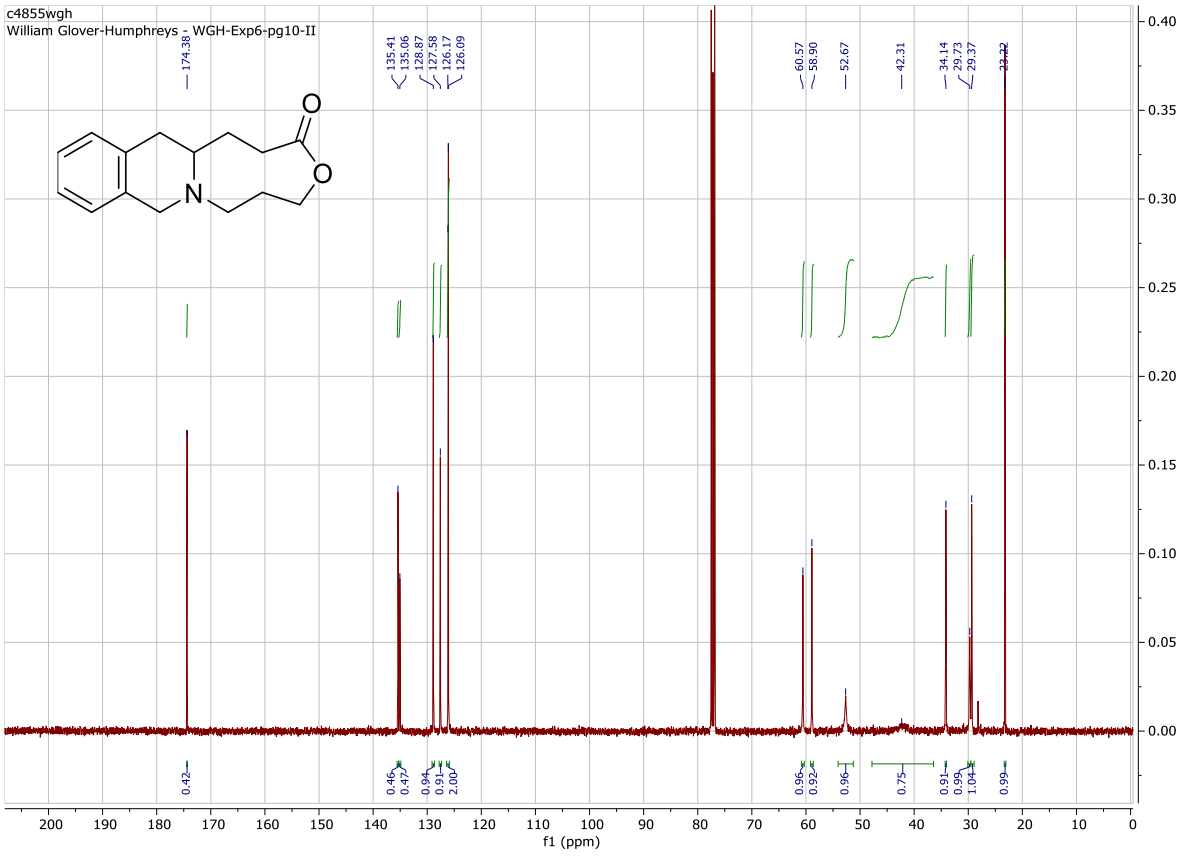
Procedure B

To a stirring solution of *tert*-butyl 3-[2-(3-hydroxypropyl)-1,2,3,4-tetrahydroisoquinolin-3-yl] propanoate (**6-72**) (0.261 g, 0.820 mmol) in diethyl ether (1.88 mL), 4.0 M hydrochloric acid in 1,4 dioxane (4.7 mL, 18.8 mmol) was added dropwise and the reaction was left stirring at room temperature for 3 hours. The reaction mixture was concentrated under vacuum using chloroform (3 × 20 mL) to make an azeotropic solution. The intermediate 3-[2-(3-hydroxypropyl)-1,2,3,4-tetrahydroisoquinolin-3-yl] propanoic acid (**6-73**) was dissolved in dimethyl formamide (37.6 mL) and DIPEA (0.851 g, 1.15 mL, 6.58 mmol) under argon, until all the reagents dissolved into solution (30 minutes). 1-Ethyl-3-(3-imethylaminopropyl) carbodiimide was (0.44 g, 2.82 mmol) and hydroxybenzotriazole (0.305 g, 2.26 mmol) were then added and the reaction left to stir over night at room temperature. The reaction mixture was washed sequentially in diethyl ether (100 mL) and brine (100 mL) the aqueous phase was back washed again with diethyl ether (100 mL). The organic phases were combined dried with sodium sulfate, filtered, concentrated under vacuum and purified via flash column chromatography (85:10:5 hexane:ethyl acetate:triethylamine) forming the product a crystalline solid (76.3 mg, 38%) R_f = 0.43 (85:10:5 hexane:ethyl acetate:triethylamine), ν_{max}/cm^{-1} (thin film) 2919, 1733, 1442, 1337, 1230, 1109, 1070, 988, 744, 663; δ_H (400 MHz, $CDCl_3$) 7.14−7.09 (2H, m, Ar**H**), 7.07−7.01 (2H, m, Ar**H**), 4.77−4.58, (1H, bm, C**H**$_a$H$_b$OCO), 4.13−3.96 (1H, bm, CH$_a$**H**$_b$O), 3.75 (2H, m, ArC**H**$_2$N), 3.84−3.66 (1H, m, C**H**N), 2.82−2.75 (2H, m, NC**H**$_2$), 2.64−2.51 (2H, m, ArC**H**$_2$), 2.47 (1H, dt, *J* = 14.4 Hz, 4.0, C**H**$_a$H$_b$COO), 2.32−2.23 (2H, m, CH$_a$**H**$_b$COO), 2.12−2.01 (m, 1H, CHC**H**$_a$H$_b$CH$_2$), 1.88−1.78 (1H, m, CH$_2$C**H**$_a$H$_b$CH$_2$), 1.71−1.59 (2H, m, CHCH$_a$**H**$_b$CH$_2$, CH$_2$CH$_a$**H**$_b$CH$_2$); δ_C (100 MHz, $CDCl_3$) 174.4 (**C**O), 135.4 (Ar**C**), 135.1 (Ar**C**), 128.9 (Ar**C**H), 127.6 (Ar**C**H), 126.2 (Ar**C**H), 126.1 (Ar**C**H), 60.6 (**C**H$_2$O), 58.9 (**C**HN), 52.7 (Ar**C**H$_2$N), 42.2 (C**H**$_2$N), 33.8 (**C**H$_2$COO), 30.2 (Ar**C**H$_2$), 29.7 (**C**H$_2$), 23.2 (**C**H$_2$); HRMS (ESI):246.1494 calcd. for $C_{15}H_{20}NO_2$. Found 246.1487 $[MH]^+$, (−2.8 ppm error).

Procedure C

To a stirring solution of *tert*-butyl 3-[2-(3-hydroxypropyl)-1,2,3,4-tetrahydroisoquinolin-3-yl] propanoate (**6-72**) (0.162 g, 0.507 mmol) in diethyl ether (5.1 mL), a solution of 4.0 M hydrochloric acid in 1,4 dioxane (1.27 mL, 5.07 mmol) was added dropwise and the reaction was left stirring at room temperature for 4 hours. The reaction mixture was concentrated under vacuum using chloroform (3 × 20 mL) to make an azeotropic solution. The intermediate 3-[2-(3-hydroxypropyl)-1,2,3,4-tetrahydroisoquinolin-3-yl] propanoic acid (**6-73**) was dissolved in dimethyl formamide (10.4 mL) and DIPEA (0.460 g, 0.62 mL, 3.55 mmol) under argon, until all the reagents dissolved into solution (30 minutes). 1-Ethyl-3-(3-imethylaminopropyl) carbodiimide was (0.118 g, 0.76 mmol) and hydroxybenzotriazole (0.082 g, 0.61 mmol) were then added and the reaction left to stir over night at 50 °C under argon. The reaction mixture was washed sequentially in diethyl ether (50 mL) and brine (50 mL) the aqueous phase was back washed again with diethyl ether (50 mL). The organic phases were combined dried with sodium sulfate, filtered, concentrated under vacuum, and purified via flash column chromatography (85:10:5 hexane:ethyl acetate:triethylamine) forming the product a crystalline white solid (46 mg, 37%), R_f = 0.43 (85:10:5 hexane:ethyl acetate:triethylamine).


c4891wgh
William Glover-Humphreys - WGH-Exp6.0-pg10-II
7.13
7.04
4.69
4.03
3.74
3.04
2.78
2.57
2.49
2.45
2.27
2.06
1.83
1.66
1.64
1.99
1.98
0.91
1.02
2.04
1.02
1.03
1.96
1.14
1.97
1.03
1.20
2.00
f1 (ppm)


c4855wgh
William Glover-Humphreys - WGH-Exp6-pg10-II
174.38
135.41
135.06
128.87
127.58
126.17
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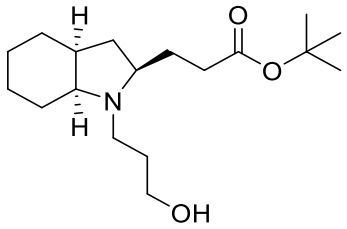
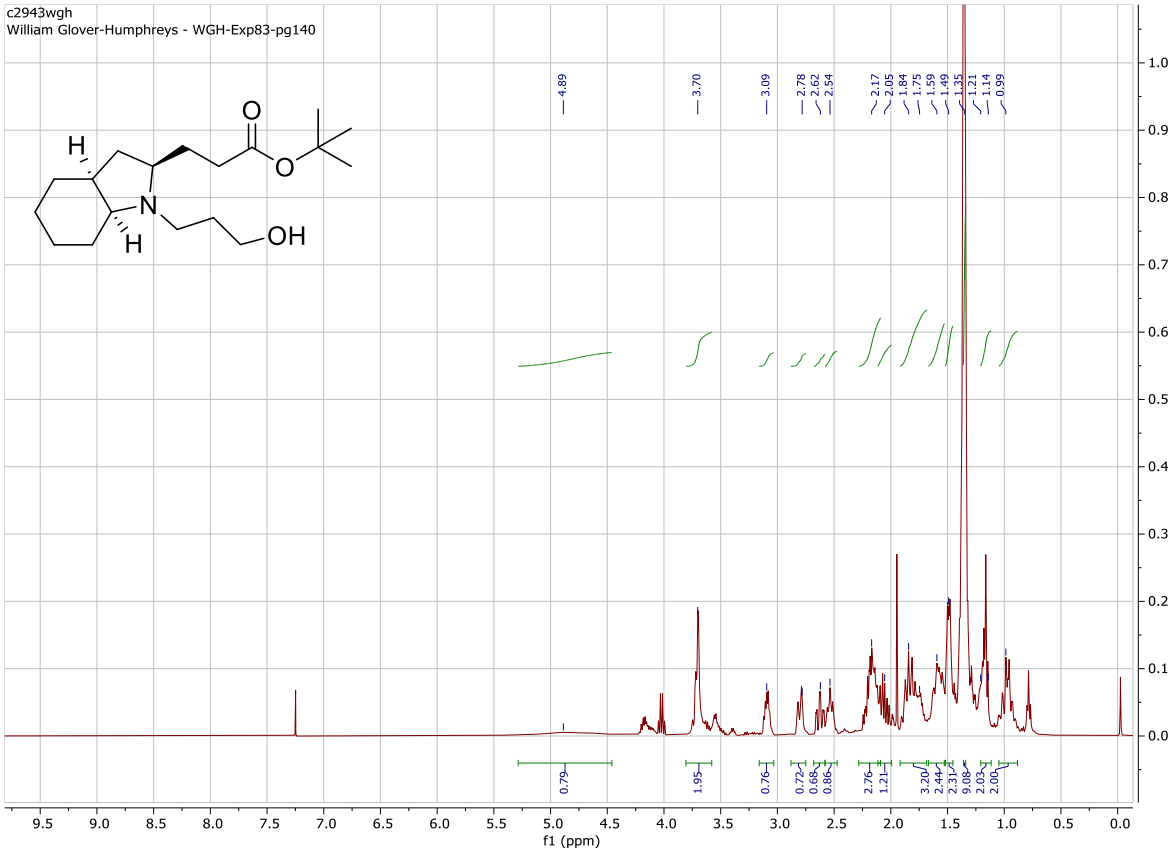
60.57
58.90
52.67
42.31
34.14
29.73
29.37
23.22
0.42
0.46
0.47
0.94
0.91
2.00
0.96
0.92
0.96
0.75
0.91
0.99
1.04
0.99
f1 (ppm)

***tert*-Butyl 3-((2*R*,3a*S*,7a*S*)-1-(3-hydroxypropyl) octahydro-1*H*-indol-2-yl) propanoate (6-75)**



To a stirring solution of *tert*-butyl 3-((2R,3aS,7aS)-octahydro-1*H*-indol-2-yl) propanoate **(6-51)** (0.578 g, 2.28 mmol) in dry acetonitrile (32.5 mL) potassium carbonate (0.473 g, 3.42 mmol) and sodium iodide (0.068 g, 0.456 mmol) were added. Bromopropanol **(6-71)** (0.378 g, 2.74 mmol) was then added, and the resulting mixture was heated to reflux at 100 °C for 24 hours. After allowing to cool to room temperature the reaction mixture was diluted with EtOAc (100 mL) and washed with saturated $NaHCO_3$ aqueous solution (100 mL) then back extracted with EtOAc (100 mL). The organic phases were collected, dried using sodium sulfate, filtered and the solvent removed under vacuum. The reaction mixture was purified by flash column chromatography (hexane:ethyl acetate:triethylamine 75:20:5) to afford the compound as an brown oil (401 mg, 57% yield), based on ^{13}C NMR it is believed a single diastereoisomer was isolated, R_f = 0.22 (hexane:ethyl acetate:triethylamine 75:20:5).; ν_{max}/cm^{-1} (thin film) 3425, 2925, 2856, 2856, 1727, 1448, 1366, 1255, 1148, 1061, 846, 1755, 596; δ_H (400 MHz, $CDCl_3$) 4.82 (1H, bs, O**H**), 3.73−3.65 (2H, m, C$\mathbf{H}_2$OH), 3.12−3.05 (1H, m, C**H**N), 2.84−2.77 (1H, m, C$\mathbf{H_a}H_b$N), 2.62 (1H, dt, *J* = 12.2 Hz, 3.7 Hz, $CH_a\mathbf{H_b}$N), 2.57−2.54 (1H, m, C**H**N), 2.28−2.20 (2H, m, C$\mathbf{H}_2$), 2.28−2.20 (1H, m, C**H**), 2.09−2.05 (2H, m, C$\mathbf{H}_2$CO), 1.90−1.78 (2H, m, C$\mathbf{H}_2$), 1.74−1.71 (2H, m, C$\mathbf{H}_2$), 1.65−1.53 (1H, m, ^{a}C$\mathbf{H_a}H_b$), 1.65−1.53 (1H, m, ^{b}C$\mathbf{H_a}H_b$), 1.50−1.47 (2H, m, C$\mathbf{H}_2$), 1.35 (9H, s, (C(C$\mathbf{H}_3$)$_3$), 1.21−1.14 (2H, m, C$\mathbf{H}_2$), 1.00−0.90 (2H, m, ^{a}C$H_a\mathbf{H_b}$ & ^{b}C$\mathbf{H_a}H_b$); δ_C (100 MHz, $CDCl_3$) 173.0 (**C**O), 80.2 (**C**$(CH_3)_3$, 64.9 (**C**H_2OH), 60.5 (**C**HN), 58.5 (**C**HN), 47.3 (**C**H_2N), 35.8 (**C**H), 32.4 (**C**H_2CO), 31.5 (CH**C**H_2CH), 30.3 (**C**H_2), 28.2 (**C**H_2), 28.1 (C(**C**H_3)$_3$, 26.4 (**C**H_2), 23.7 (**C**H_2), 21.2 (**C**H_2), 20.8 (**C**H_2); HRMS (ESI): calcd. for $C_{18}H_{33}NO_3$ 311.2460. Found $[MH]^+$ 311.2458 (−0.64 ppm error).


c2943wgh
William Glover-Humphreys - WGH-Exp83-pg140
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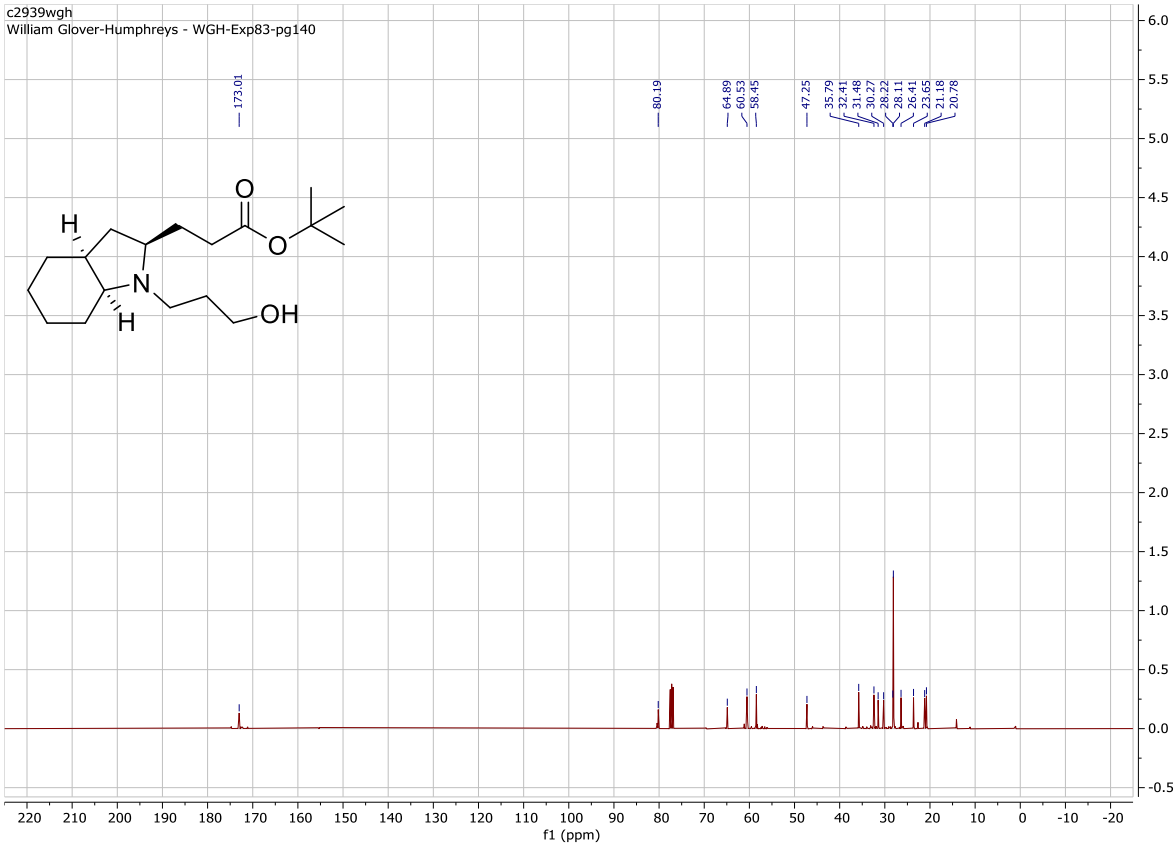
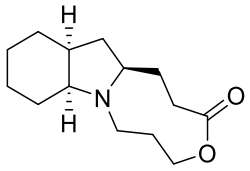
3.70
3.09
2.78
2.62
2.54
2.17
2.05
1.84
1.75
1.59
1.49
1.35
1.21
1.14
0.99
0.79
1.95
0.76
0.72
0.68
0.86
2.76
1.21
3.20
2.44
2.31
9.08
2.03
2.00
f1 (ppm)


c2939wgh
William Glover-Humphreys - WGH-Exp83-pg140
173.01
80.19
64.89
60.53
58.45
47.25
35.79
32.41
31.48
30.27
28.22
28.11
26.41
23.65
21.18
20.78
f1 (ppm)

(8aS,12a*S*,13a*R*)-dodecahydro-3*H*, 5*H*- [1,5] oxazonino [5,6-a] indol-3-one (6-78)

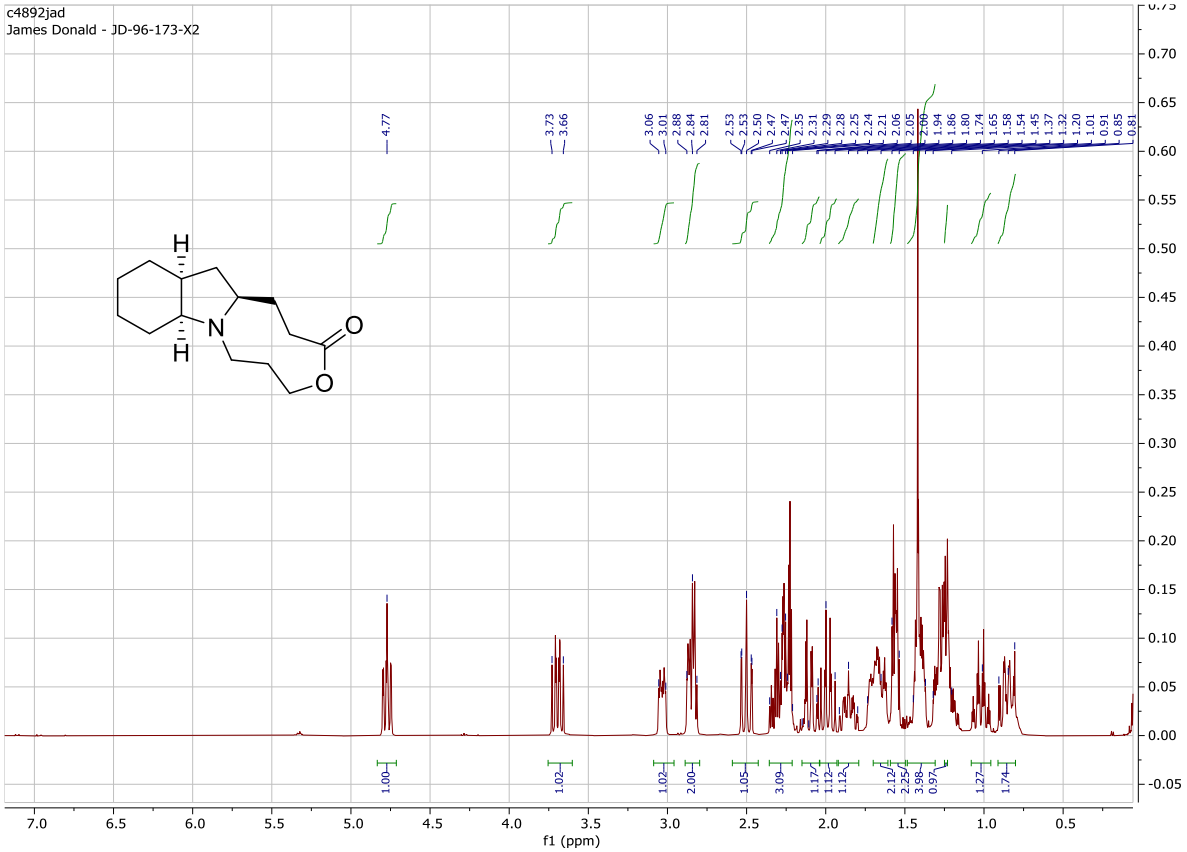


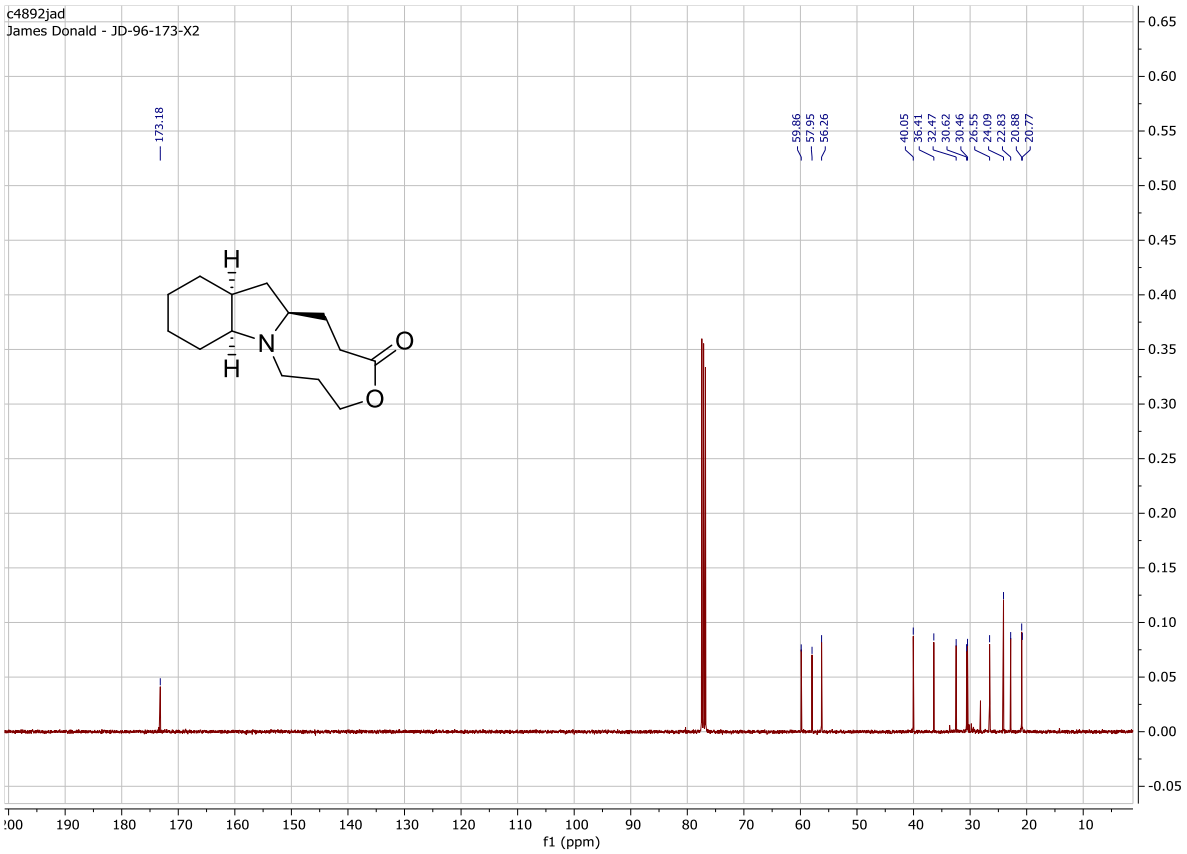
Procedure A

To a stirring solution of *tert*-butyl 3-[1-(3-hydroxypropyl) octahydro-1H-indol-2-yl] propanoate **(6-75)** (0.200 g, 0.640 mmol) in diethyl ether (0.600 mL), a solution of 4.0 M hydrochloric acid in 1,4 dioxane (1.6 mL, 6.4 mmol) was added dropwise and the reaction was left stirring at room temperature for 3 hours. The reaction mixture was concentrated under vacuum using chloroform (3 × 10 mL) to make an azeotropic solution. The intermediate 3-[(3aS,7aS)-1-(3-hydroxypropyl) octahydro-1H-indol-2-yl] propanoic acid was dissolved in chloroform (13.0 mL) and DIPEA (0.480 g, 3.70 mmol) under argon, until all the reagents dissolved into solution (30 minutes). T3P (0.612 g, 0.960 mmol) was then added, and the reaction left to stir over night at room temperature. The solvent was removed under vacuum and the reaction mixture was purified via flash column chromatography (84:15:1 hexane:diethyl ether:triethylamine) forming the product a clear oil (21.8 mg, 14%), R_f = 0.43 (84:15:1 hexane:diethyl ether:triethylamine).

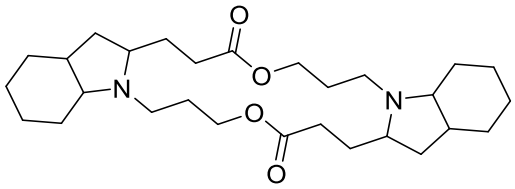
Procedure B

To a stirring solution of *tert*-butyl 3-[1-(3-hydroxypropyl) octahydro-1H-indol-2-yl] propanoate **(6-75)** (0.200 g, 0.640 mmol) in diethyl ether (0.6 mL), a solution of 4.0 M hydrochloric acid in 1,4 dioxane (1.6 mL, 6.4 mmol) was added dropwise and the reaction was left stirring at room temperature for 3 hours. The reaction mixture was concentrated under vacuum using chloroform (3 × 10 mL) to make an azeotropic solution. The intermediate 3-[(3aS,7aS)-1-(3-hydroxypropyl) octahydro-1H-indol-2-yl] propanoic acid was dissolved in dimethylformamide (13 mL) and DIPEA (0.48 g, 3.7 mmol) under argon, until all the reagents dissolved into solution (30 minutes). 1-Ethyl-3-(3-methylaminopropyl) carbodiimide was (0.150 g, 0.96 mmol) and hydroxybenzotriazole (0.104 g, 0.77 mmol) were then added and the reaction left to stir over night at room temperature. The reaction mixture was washed sequentially in diethyl ether (100 mL) and brine (100 mL) the aqueous phase was back washed again with diethyl ether (100 mL). The organic phases were combined dried with sodium sulfate, filtered, concentrated under vacuum and purified via flash column chromatography (84:15:1 hexane:diethyl ether:triethylamine) forming the product a crystalline solid (23.5 mg, 16%) R_f = 0.43 (84:15:1 hexane:diethyl ether:triethylamine); ν_{max}/cm^{-1} (thin film) 2923, 2853, 1727, 1463, 1366, 1179, 1142, 1071, 944; δ_H (400 MHz, $CDCl_3$) 4.77 (1H, ddd, *J* = 10.9 Hz, 8.8 Hz, 2.0 Hz, C**H$_a$**H$_b$O), 3.73−3.66 (1H, m, CH$_a$**H$_b$**O), 3.06−3.01 (1H, m, C**H**N), 2.88−2.81 (2H, m, C**H**N & C**H$_a$**H$_b$N), 2.50 (1H, ddd, *J* = 13.7 Hz, 12.3 Hz, 1.6 Hz, CH$_a$**H$_b$**N), 2.35−2.29 (3H, m, ^{a}C**H$_a$**H$_b$ & C**H**, C**H$_a$**H$_b$CO), 2.15−2.06 (1H, m, CH$_a$**H$_b$**CO), 2.05−1.94 (1H, m, ^{b}C**H$_a$**H$_b$), 1.91−1.80 (1H, m, ^{c}C**H$_a$**H$_b$), 1.74−1.65 (m, 2H, ^{d}C**H$_a$**CH$_b$ & ^{e}C**H$_a$**H$_b$), 1.58−1.54 (2H, m, C**H**$_2$), 1.45−1.37 (4H, m, C**H**$_2$ & ^{a}CH$_a$**H$_b$**, ^{c}CH$_a$**H$_b$**), 1.32−1.20 (1H, m, ^{b}CH$_a$C**H$_b$**), 1.00 (1H, qt, *J* = 15.9 Hz, 12.9 Hz, 3.0 Hz, ^{e}CH$_a$**H$_b$**), 0.91−0.81 (1H, m, ^{d}CH$_a$**H$_b$**); δ_C (100 MHz, $CDCl_3$) 173.2 (**C**O), 60.5 (**C**H$_2$O), 58.0 (**C**HN), 56.3 (**C**H$_2$N), 40.1 (**C**H$_2$N), 36.5 (**C**H), 32.5 (**C**H$_2$CO), 30.7 (**C**H$_2$), 30.5 (**C**H$_2$), 26.6 (**C**H$_2$), 24.2 (**C**H$_2$), 22.9 (**C**H$_2$), 20.9 (**C**H$_2$), 20.8 (**C**H$_2$); HRMS (ESI): calcd. for $C_{14}H_{24}NO_2$ 238.1807. Found $[MH]^+$, 238.1802 (−2.10 ppm error).

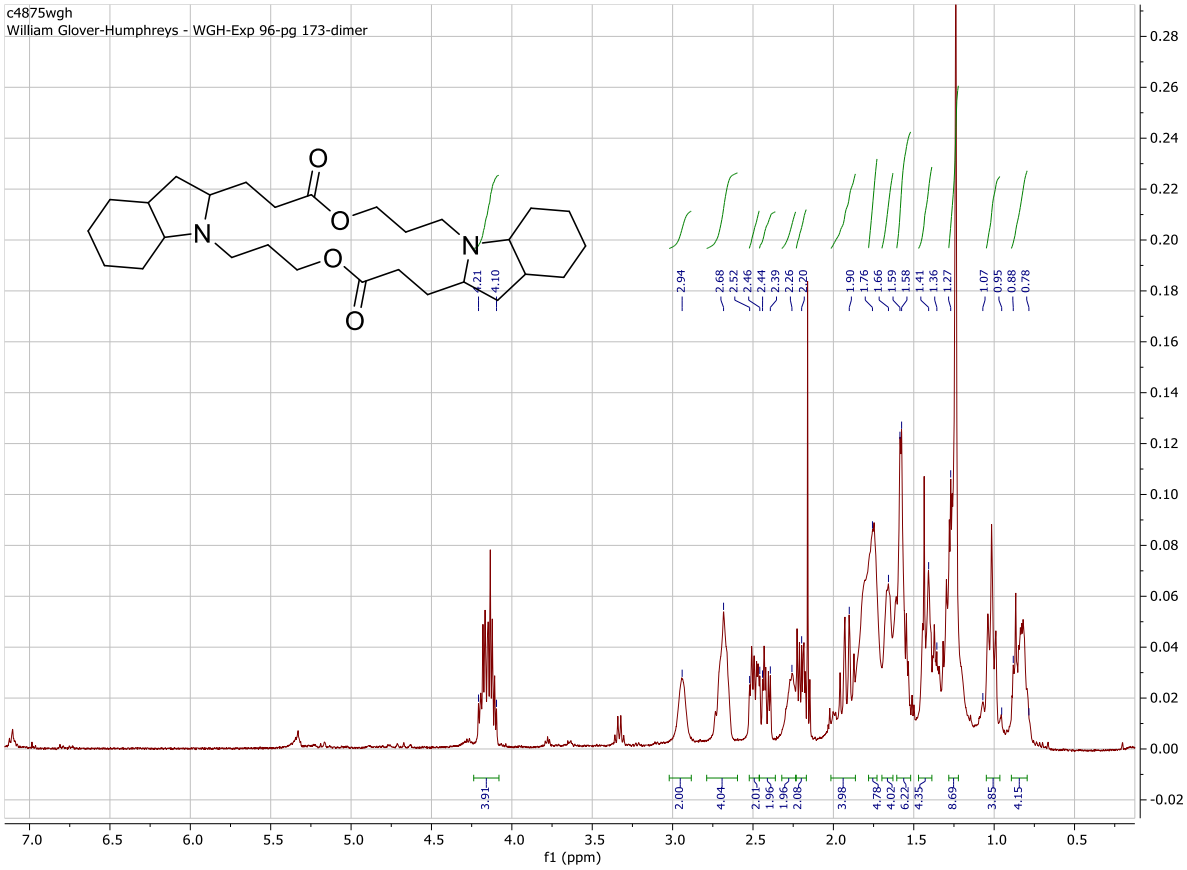

c4892jad
James Donald - JD-96-173-X2
4.77
3.73
3.66
3.06
3.01
2.88
2.84
2.81
2.53
2.53
2.50
2.47
2.47
2.35
2.31
2.29
2.28
2.25
2.24
2.21
2.06
2.05
2.00
1.94
1.86
1.80
1.74
1.65
1.58
1.54
1.45
1.37
1.32
1.20
1.01
0.91
0.85
0.81
1.00
1.02
1.02
2.00
1.05
3.09
1.17
1.12
1.12
2.12
2.25
3.98
0.97
1.27
1.74
H
N
H
O
O
f1 (ppm)

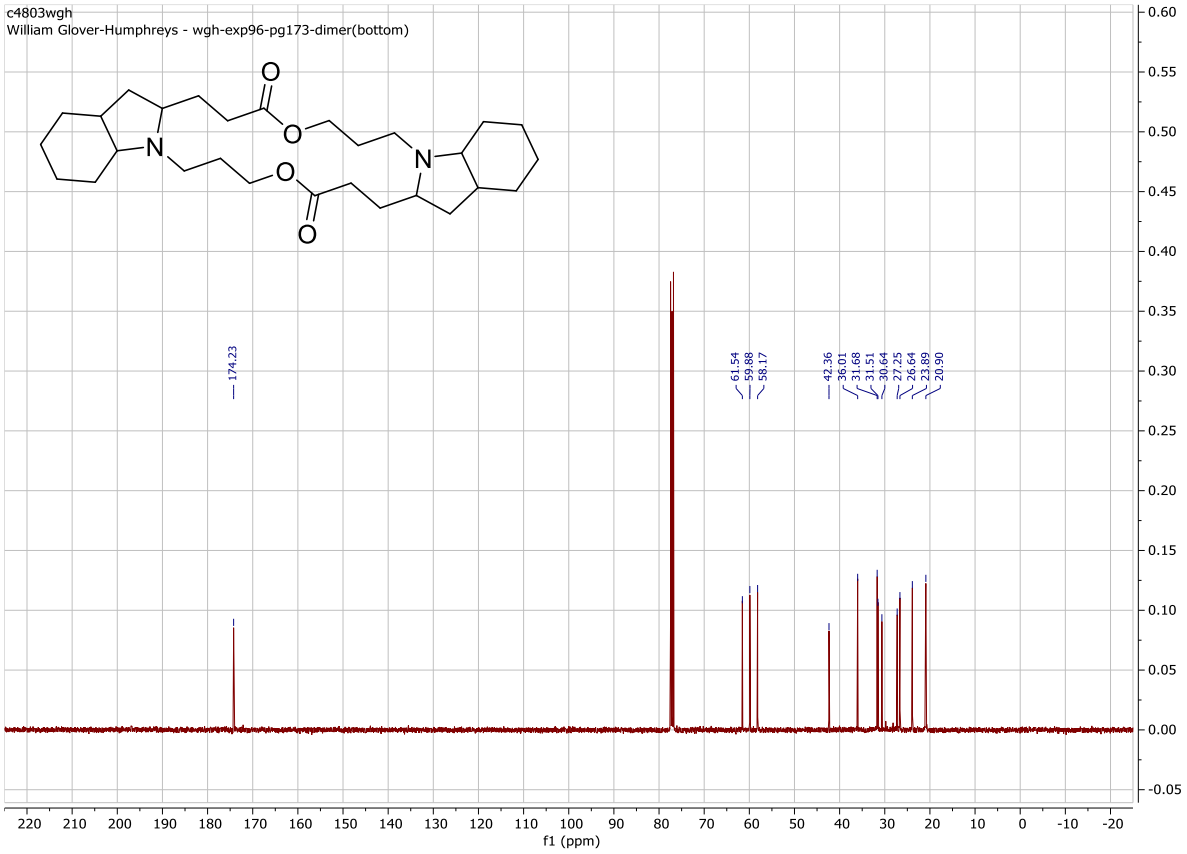

c4892jad
James Donald - JD-96-173-X2
173.18
59.86
57.95
56.26
40.05
36.41
32.47
30.62
30.46
26.55
24.09
22.83
20.88
20.77
H
N
H
O
O
f1 (ppm)

Tetracosahydro-6H,10H,19H,23H- [1,10,5,14] dioxadiazacyclooctadecino[14,15-a:5,4-a'] diindole-10,23-dione (6-82)

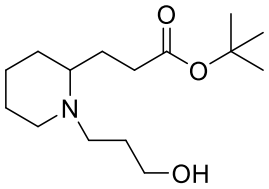


Crystalline solid (40.1 mg, 13%), R_f = 0.29 (84:15:1 hexane:diethyl ether:triethylamine); ν_{max}/cm^{-1} (thin film) 2924, 2853, 2804, 1719, 1467, 1445, 1343, 1247, 1158, 1076, 980, 891; δ_H (400 MHz, $CDCl_3$) 4.21−4.10 (4H, m, C**H**$_2$O), 2.99−2.90 (2H, bm, 2 × C**H**N), 2.73−2.64 (4H, bm, 2 × C**H**N & 2 × C**H**$_a$H$_b$N), 2.53−2.45 (2H, m, 2 × CH$_a$**H**$_b$N), 2.44−2.39 (m, 2H, 2 × C**H**$_a$H$_b$CO), 2.32−2.17 (4H, m, 2 × C**H**, 2 × CH$_a$**H**$_b$CO), 2.01−1.86 (4H, m, ^{a}C**H**$_a$H$_b$), 1.81−1.71 (4H, m, 2 × C**H**$_2$), 1.69−1.62 (4H, m, 2 × C**H**$_2$), 1.39−1.33 (2H, m, 2 × ^{b}C**H**$_a$H$_b$), 1.70−1.60 (m, 2H, 2 × ^{c}C**H**$_a$H$_b$), 1.62−1.52 (4H, m, 2 × C**H**$_2$), 1.45−1.35 (m, 4H, 2 × C**H**$_2$), 1.30−1.21 (8H, m, 2 × C**H**$_2$, 2 × ^{a}CH$_a$**H**$_b$**,** 2 × CH$_a$**H**$_b$), 1.07−0.95 (m, 2H, 2 × ^{c}C**H**$_a$H$_b$), 0.89−0.78 (m, 2H, ^{b}CH$_a$**H**$_b$); δ_C (100 MHz, $CDCl_3$) 174.2 (**C**O), 61.5, (**C**H$_2$O), 59.9 (**C**HN), 58.2 (**C**HN), 42.4 (**C**H$_2$N), 36.0 (**C**H), 31.7 (**C**H$_2$CO), 30.64 (**C**H$_2$), 27.3 (**C**H$_2$), 26.6 (**C**H$_2$), 23.9 (**C**H$_2$), 20.9 (**C**H$_2$); HRMS (ESI): calcd. for $C_{28}H_{47}N_2O_4$ 475.3536. Found $[MH]^+$, 475.3532 (−0.841 ppm error).

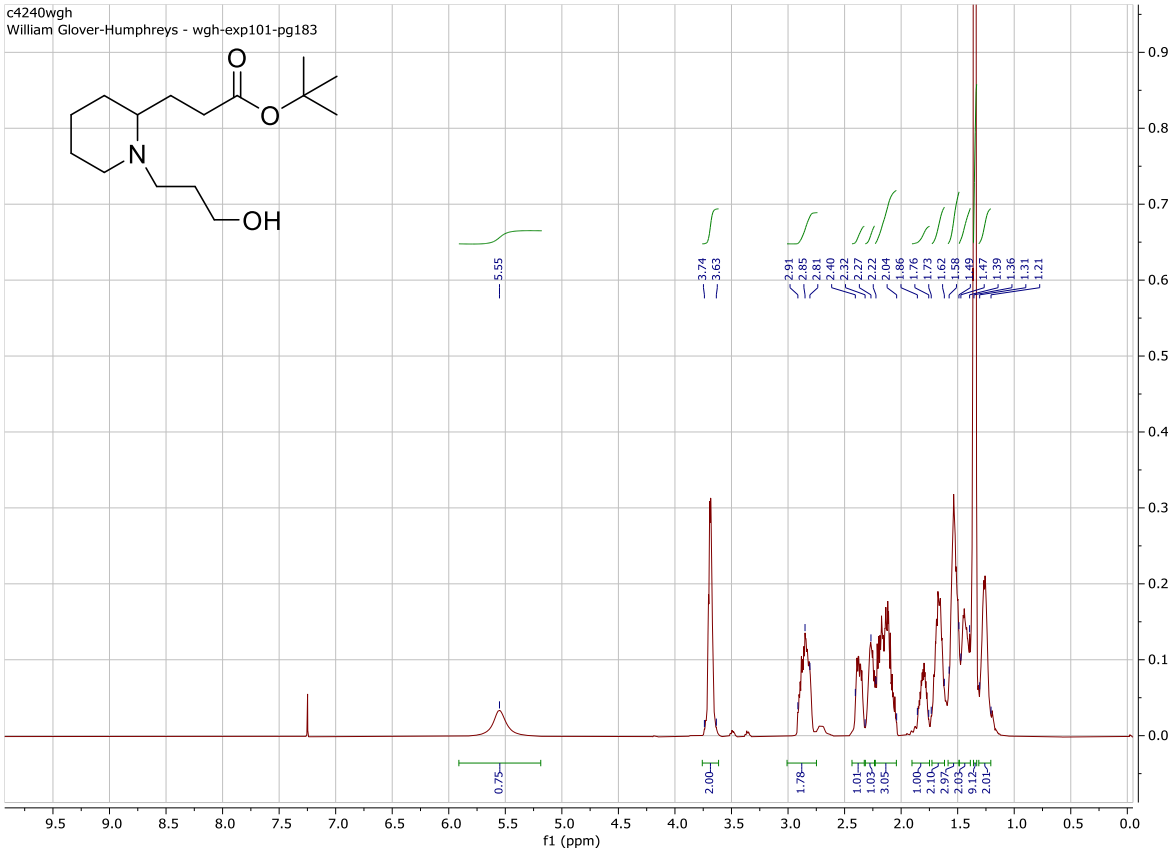

c4875wgh
William Glover-Humphreys - WGH-Exp 96-pg 173-dimer
f1 (ppm)

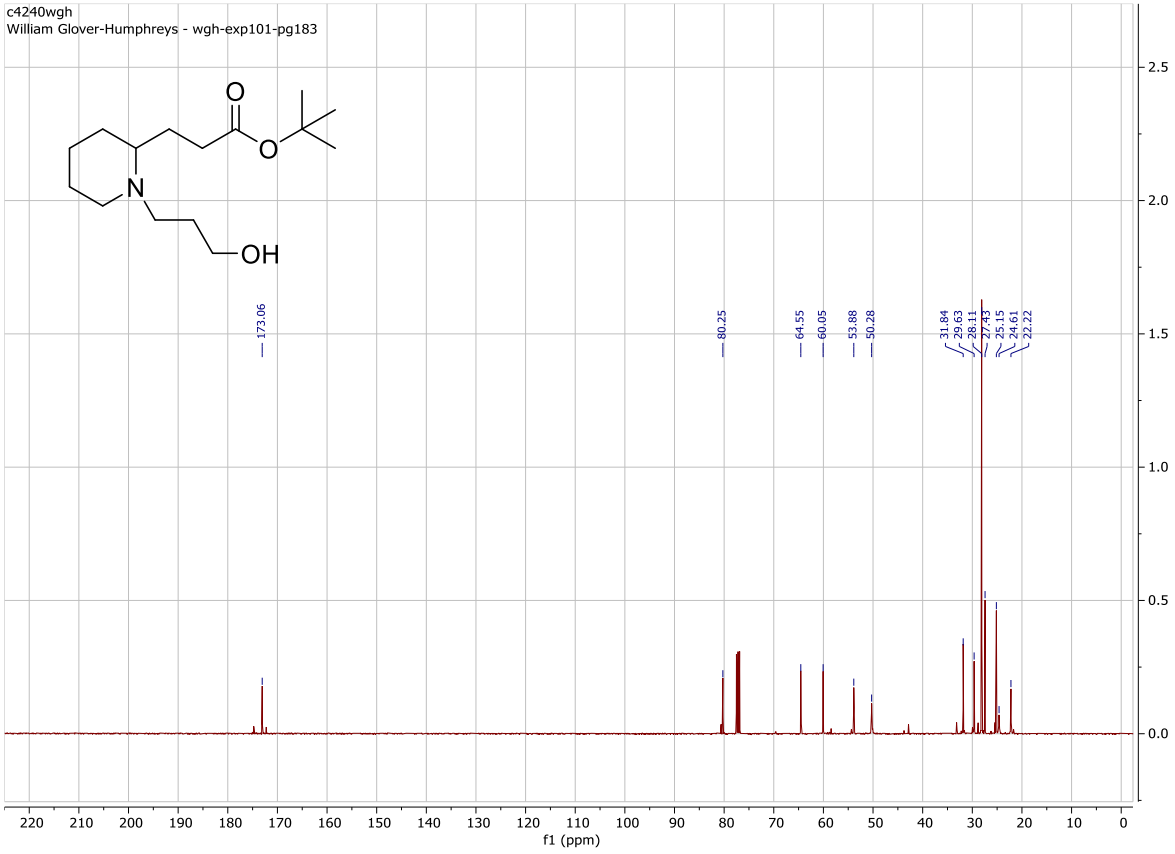

c4803wgh
William Glover-Humphreys - wgh-exp96-pg173-dimer(bottom)
f1 (ppm)

***tert*-Butyl 3-[1-(3-hydroxypropyl) piperidin-2-yl] propanoate (6-76)**

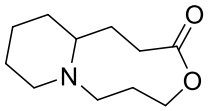


To a solution of *tert*-butyl 3-(piperidin-2-yl) propanoate (1.07 g, 5.00 mmol) **(6-52)** potassium carbonate (1.00 g, 7.50 mmol) and sodium iodide (0.150 g, 1.00 mmol) in dry acetonitrile 33.0 mL). Bromopropanol **(6-71)** (0.830 g, 6.00 mmol) was added, and the resulting mixture was stirred at 100 °C for 24 hours. After allowing to cool to room temperature the reaction mixture was diluted with EtOAc (100 mL) and washed with saturated $NaHCO_3$ aqueous solution (100 mL) then back extracted with (EtOAc 100 mL). The organic phases were collected and dried using sodium sulfate, filtered and the solvent removed under vacuum. The reaction mixture was purified by flash chromatography (hexane:ethyl acetate:triethylamine 75:20:5) isolating the produce a clear oil (70.7 mg, 52% yield); R_f = 0.25 (hexane:ethyl acetate:triethylamine 75:20:5); ν_{max}/cm^{-1} (neat) 3394, 2932, 2858, 1727, 1453, 1367, 1256, 1150, 1063, 848; δ_H (400 MHz, $CDCl_3$) 5.55 (1H, bs, O**H**), 3.74−3.63 (2H, m, C$\mathbf{H}_2$OH), 2.91−2.81 (1H, m, C$\mathbf{H_a}H_b$N), 2.91−2.81 (1H, m, C$\mathbf{H_a}H_b$N), 2.40−2.32 (1H, m, $CH_a\mathbf{H_b}$N), 2.30−2.23 (1H, m, C**H**N), 2.22−2.04 (3H, m, C$\mathbf{H}_2$COO & $CH_a\mathbf{H_b}$N), 1.86−1.76 (1H, m, C$\mathbf{H_a}H_b$), 1.73−1.62 (2H, m, $CH_a\mathbf{H_b}$, C$\mathbf{H_a}H_b$), 1.58−1.47 (3H, m, C$\mathbf{H}_2$ & C$\mathbf{H_a}H_b$), 1.46−1.40 (2H, m, $CH_a\mathbf{H_b}$, $CH_a\mathbf{H_b}$), 1.36 (9H, bs C(C$\mathbf{H}_3$)$_3$), 1.31−1.21 (2H, m, C$\mathbf{H}_2$); δ_c (100 MHz, $CDCl_3$) 173.1 (**C**O), 80.3 (**C**$(CH_3)_3$), 64.6 (**C**H_2OH), 60.1 (**C**HN), 53.9 (**C**H_2N), 50.3 (**C**H_2N), 31.8 (**C**H_2COO), 29.6 (**C**H_2), 28.1 (C(**C**H_3)$_3$), 27.4 (**C**H_2), 25.2 (**C**H_2), 24.6 (**C**H_2), 22.2 (**C**H_2); HRMS (ESI) calcd. for $C_{15}H_{30}NO_3$ 272.2226. Found $[MH]^+$ 272.2223 (−1.10 ppm error).


c4240wgh
William Glover-Humphreys - wgh-exp101-pg183
O
O
N
OH
5.55
3.74
3.63
2.91
2.85
2.81
2.40
2.32
2.27
2.22
2.04
1.86
1.76
1.73
1.62
1.58
1.49
1.47
1.39
1.36
1.31
1.21
0.75
2.00
1.78
1.01
1.03
3.05
1.00
2.10
2.97
2.03
9.12
2.01
f1 (ppm)


c4240wgh
William Glover-Humphreys - wgh-exp101-pg183
O
O
N
OH
173.06
80.25
64.55
60.05
53.88
50.28
31.84
29.63
28.11
27.43
25.15
24.61
22.22
f1 (ppm)

Octahydro-5H-pyrido[1,2-e] [1,5] oxazonin-3(2H)-one (6-79)

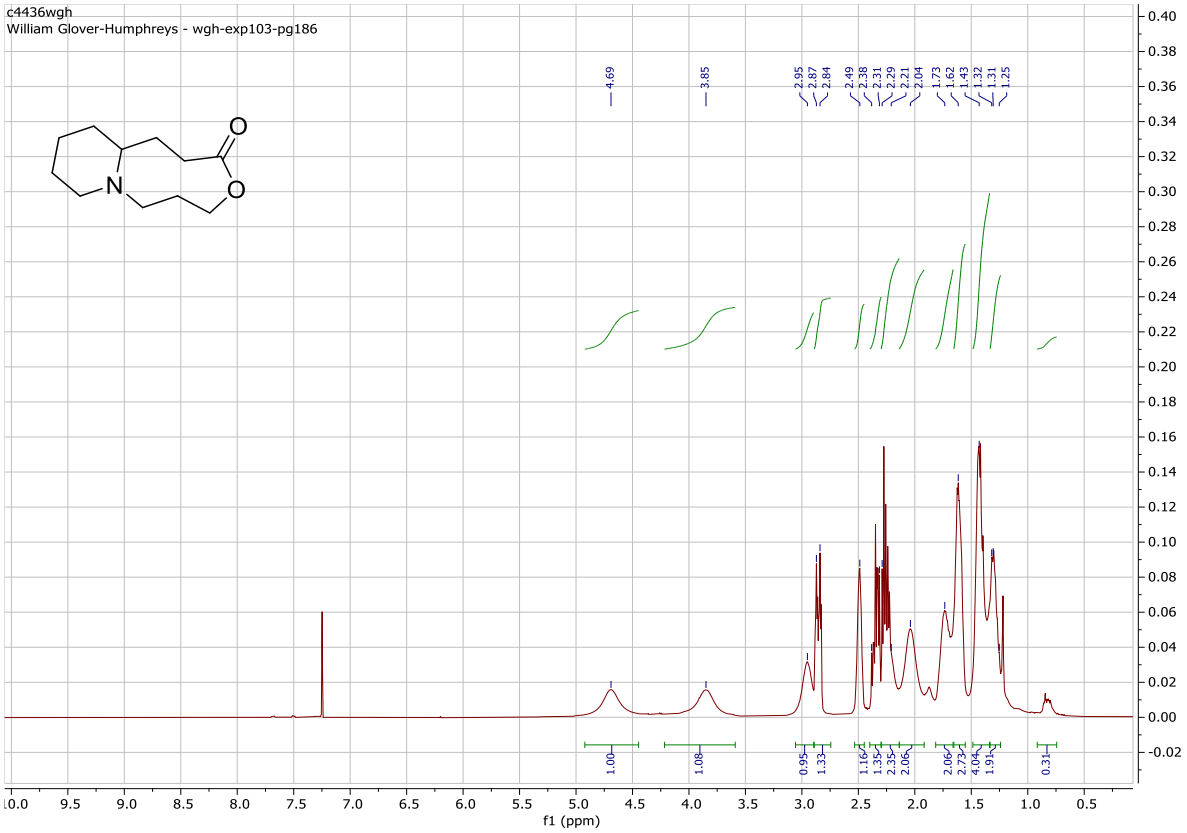


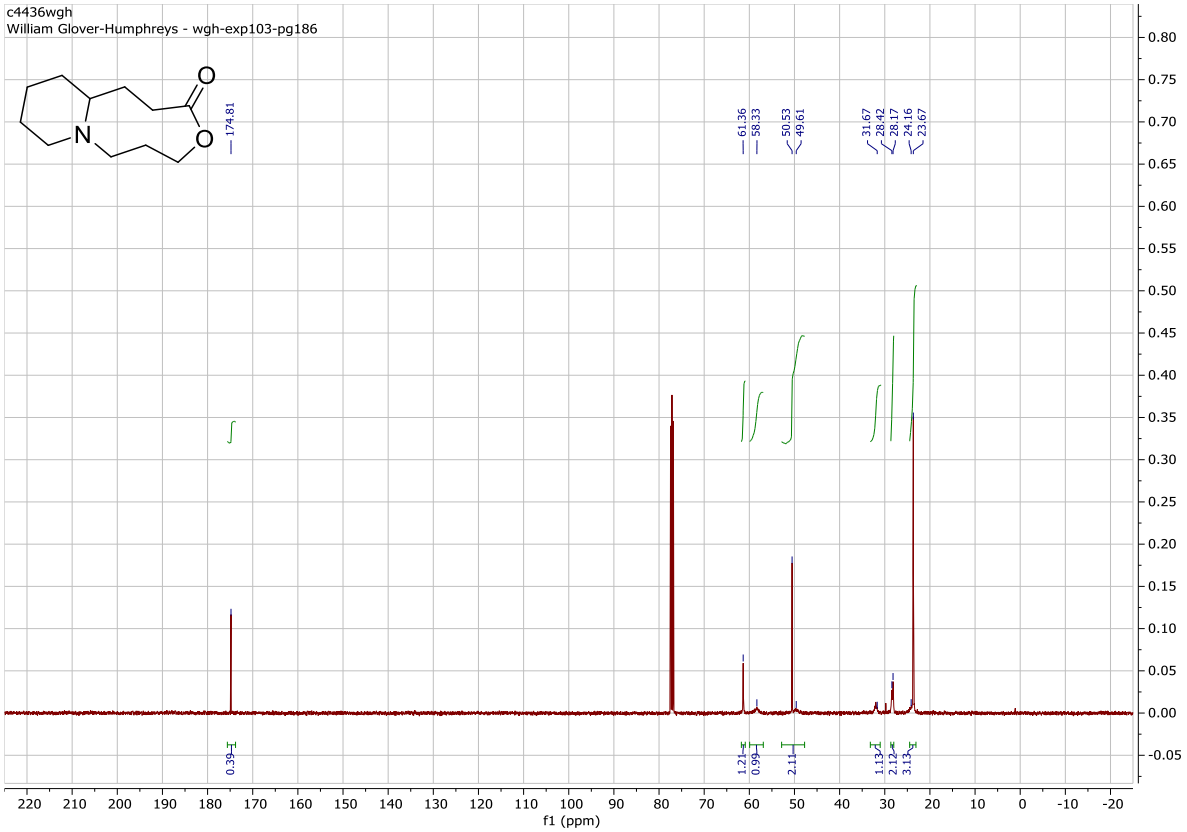
Procedure A

To a stirring solution of *tert*-butyl 3-[1-(3-hydroxypropyl) piperidin-2-yl] propanoate **(6-76)** (0.150 g, 0.553 mmol) in diethyl ether (0.6 mL), a solution of 4.0 M hydrochloric acid in 1,4 dioxane (1.38 mL, 5.53 mmol) was added dropwise and the reaction was left stirring at room temperature for 3 hours. The reaction mixture was concentrated under vacuum using chloroform (3 × 20 mL) to make an azeotropic solution. The intermediate 3-[1-(3-hydroxypropyl) piperidin-2-yl] propanoic acid was dissolved in chloroform (5.53 mL) and DIPEA (0.713 g, 5.53 mmol) under argon, until all the reagents dissolved into solution (30 minutes). T3P 50% w/v in ethyl acetate (0.528 g, 0.83 mmol) was added dropwise and the reaction left to stir over night at room temperature. The reaction mixture was concentrated under vacuum and purified via flash column chromatography (85:10:5 hexane:ethyl acetate:triethylamine) to afford the title compound (5.1 mg, 5%); R_f = 0.53 (85:10:5 hexane:ethyl acetate:triethylamine).

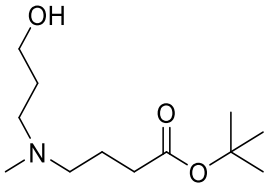
Procedure B

To a stirring solution of *tert*-butyl 3-[2-(3-hydroxypropyl)-1,2,3,4-tetrahydroisoquinolin-3-yl] propanoate **(6-76)** (0.150 g, 0.553 mmol) in diethyl ether (0.6 mL), a solution of 4.0 M hydrochloric acid in 1,4 dioxane (1.38 mL, 5.53 mmol) was added dropwise and the reaction was left stirring at room temperature for 3 hours. The reaction mixture was concentrated under vacuum using chloroform (3 × 20 mL) to make an azeotropic solution. The intermediate 3-[1-(3-hydroxypropyl) piperidin-2-yl] propanoic acid was dissolved in dimethyl formamide (10.1 mL) and DIPEA (0.500 g, 3.87 mmol) under argon, until all the reagents dissolved into solution (30 minutes). 1-Ethyl-3-(3-imethylaminopropyl) carbodiimide was (0.09 g, 0.66 mmol) and hydroxybenzotriazole (0.129 g, 0.83 mmol) were then added and the reaction left to stir over night at room temperature. The reaction mixture was washed sequentially in diethyl ether (100 mL) and brine (100 mL) the aqueous phase was back washed again with diethyl ether (100 mL). The organic phases were combined dried with sodium sulfate, filtered, concentrated under vacuum and purified via flash column chromatography (85:10:5 hexane:ethyl acetate:triethylamine) forming the product (27.3 mg, 25%); R_f = 0.43 (85:10:5 hexane:ethyl acetate:triethylamine); ν_{max}/cm^{-1} (thin film) 2928, 2855, 1735, 1444, 1343, 1242, 1059, 545; δ_H (400 MHz, $CDCl_3$) 4.88−4.48 (1H, bm, C**H**$_a$H$_b$O), 3.93−3.71 (1H, bm, CH$_a$**H**$_b$O), 3.04−2.88 (1H, bm, C**H**N), 2.84 (1H, dt, *J* = 12 Hz, 4 Hz C**H**$_a$H$_b$N), 2.55−2.45 (1H, bm CH$_a$**H**$_b$N), 2.38−2.30 (1H, m, C**H**$_a$H$_b$CO), 2.28−2.21 (1H, m, CH$_a$**H**$_b$CO), 2.12−1.95 (2H, bm, C**H**$_2$N), 1.81−1.66 (2H, bm, C**H**$_2$), 1.66−1.56 (2H, m, C**H**$_2$), 1.49−1.37 (4H, m, C**H**$_a$H$_b$, C**H**$_2$ & CH$_a$**H**$_b$), 1.32−1.23 (2H, m, C**H**$_2$); δ_c (100 MHz, $CDCl_3$) 174.8 (**C**O), 61.4 (**C**H$_2$O), 58.3 (**C**HN), 50.5 (**C**H$_2$N), 49.6 (**C**H$_2$N), 31.7 (**C**H$_2$CO), 28.4 (**C**H$_2$), 28.2 (**C**H$_2$), 24.2 (2 x **C**H$_2$), 23.7 (**C**H$_2$); HRMS (ESI) calcd. for $C_{11}H_{20}NO_2$ 198.149494. Found $[MH]^+$ 198.1490 (−2.02 ppm error).


c4436wgh
William Glover-Humphreys - wgh-exp103-pg186
4.69
3.85
2.95
2.87
2.84
2.49
2.38
2.31
2.29
2.21
2.04
1.73
1.62
1.43
1.32
1.31
1.25
1.00
1.08
0.95
1.33
1.16
1.35
2.35
2.06
2.06
2.73
4.04
1.91
0.31
f1 (ppm)

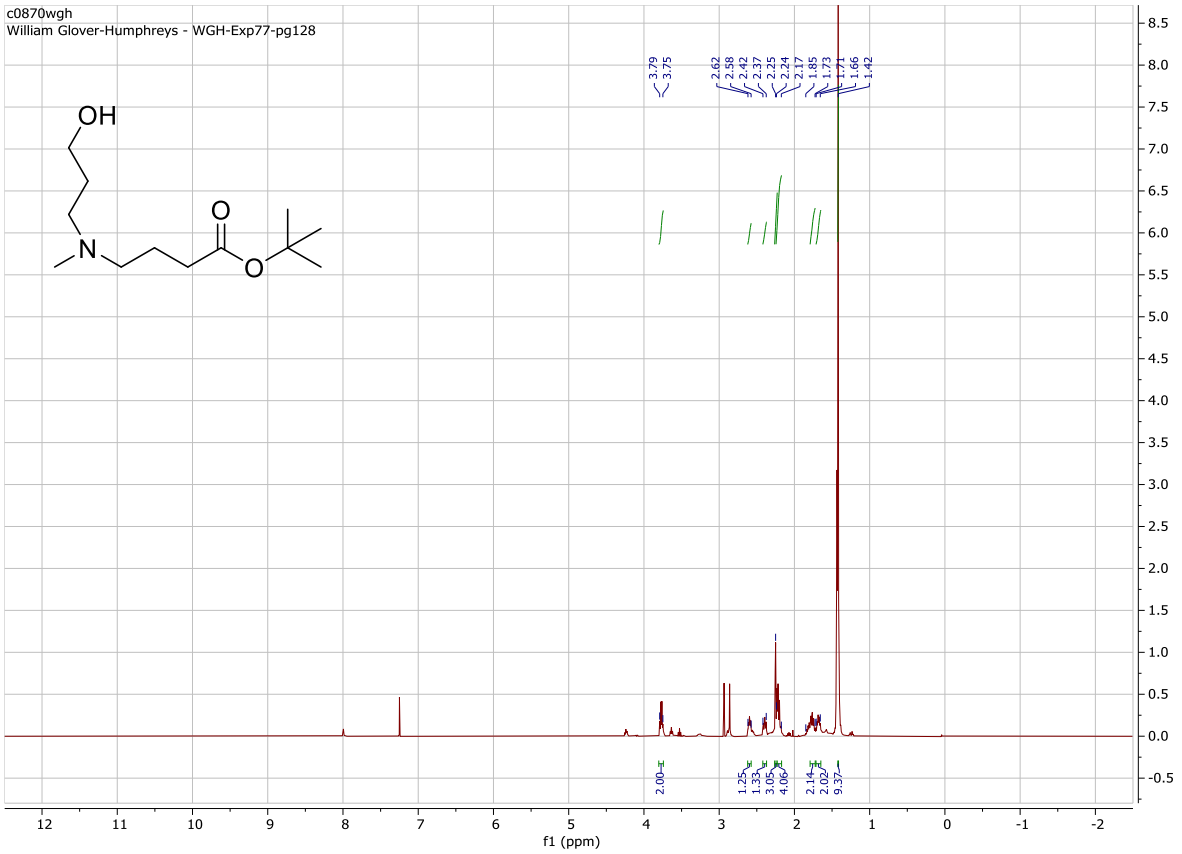

c4436wgh
William Glover-Humphreys - wgh-exp103-pg186
174.81
61.36
58.33
50.53
49.61
31.67
28.42
28.17
24.16
23.67
0.39
1.21
0.99
2.11
1.13
2.12
3.13
f1 (ppm)

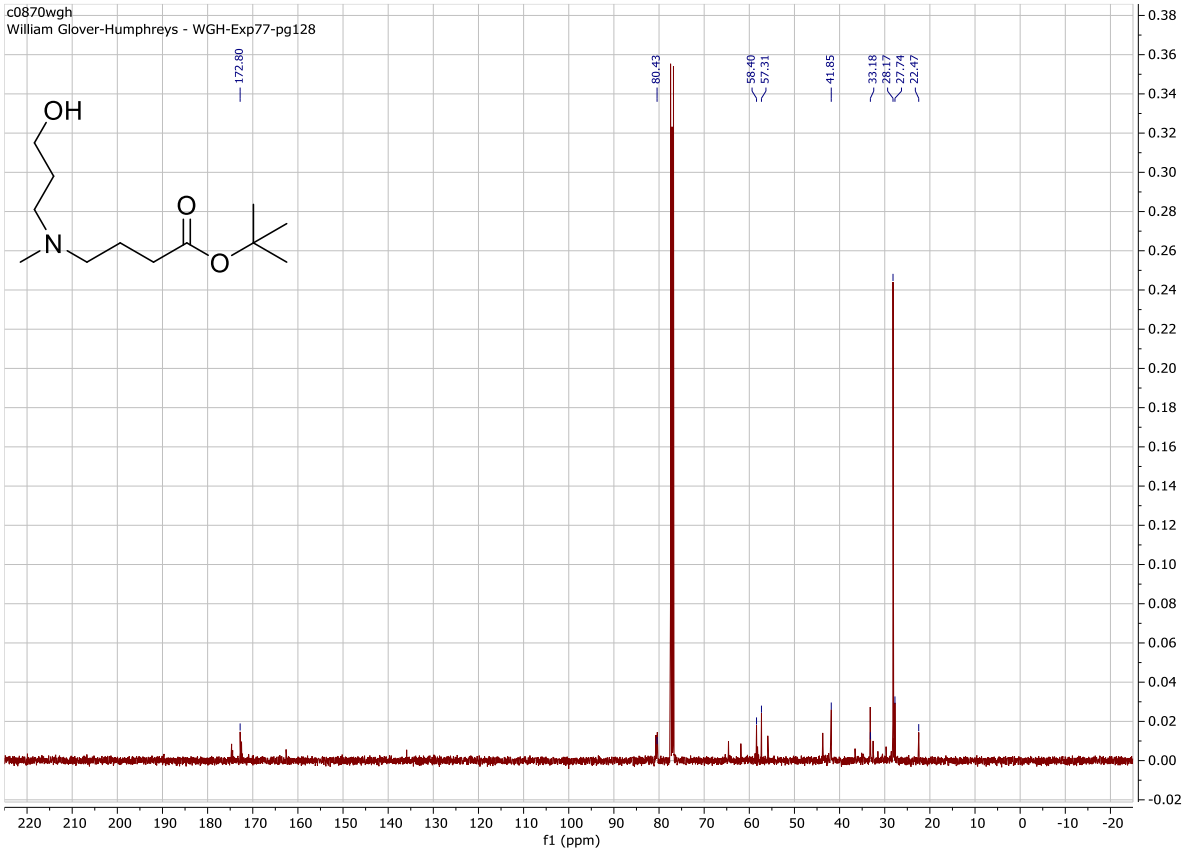
***tert*-Butyl 4-((3-hydroxypropyl) (methyl) amino) butanoate (6-77)**



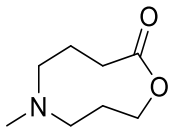
To a solution of *tert*-butyl 4-(methylamino) butanoate **(6-53)** (0.173 g, 1.00 mmol) potassium carbonate (0.138 g, 1.00 mmol) and sodium iodide (2 mg, 0.01 mmol) in dimethylformamide (10 mL). Bromopropanol **(6-71)** (0.138 g, 1.00 mmol) was added, and the resulting mixture was stirred at room temperature for 48 hours. After the reaction mixture was diluted with Et_2O (2 × 50 mL) and washed with brine solution (2 × 50 mL). The organic phases were collected and dried using sodium sulfate, filtered and the solvent removed under vacuum. The reaction mixture was purified by flash chromatography (hexane:ethyl acetate:triethylamine 75:20:5) isolating the produce the desired product (138 mg, 60%); ν_{max}/cm^{-1} 3425, 2976, 2801, 1725, 1367, 1147, 1060, 847; δ_H (400 MHz, $CDCl_3$) 3.79−3.75 (2H, m, C**H**$_2$OH), 2.62−2.58 (1H, m, C**H**$_a$H$_b$N), 2.42−2.37 (1H, m, CH$_a$**H**$_b$N), 2.26−2.22 (4H, m, C**H**$_2$N, **CH**$_2$CO), 2.25 (3H, s, C**H**$_3$N), 2.24−2.17 1.85−1.73 (2H, m, C**H**$_2$), 1.71−1.66 (2H, m, C**H**$_2$), 1.48 (9H, s, C(C**H**$_3$)$_3$); δ_c (100 MHz, $CDCl_3$) rotamers observed in a 3:2 ratio 174.7$_{minor}$, 172.8$_{major}$ (**C**O), 80.7$_{minor}$, 80.4$_{major}$ (OC(**C**H$_3$)$_3$, 61.9$_{minor}$, 58.4$_{major}$ (**C**H$_2$N), 57.3$_{major}$, 55.9$_{minor}$ (**C**H$_2$N),42.0$_{minor}$, 41.9$_{major}$ (**C**H$_3$N), 33.2$_{major}$, 32.6$_{minor}$ (CH$_2$**C**O), 28.2$_{both\ rotamers}$ (OC(**C**H$_3$)$_3$, 22.7$_{both\ rotamers}$ (**C**H$_2$), 27.9$_{minor}$, 22.5$_{major}$ (**C**H$_2$); HRMS (ESI) calcd. for $C_{12}H_{26}NO_3$ 232.1913. Found $[MH]^+$, 232.1911 (−0.861 ppm error).

During the write up the NMR data was closely examined and additional peaks in the ^{13}CNMR spectra were identified, questioning the purity of the sample. A potential reason for the subsequent failed NICE, forming the lactone **(6-80)**. Additional research is required into synthesising the compound **(6-77)** and the lactone **(6-80)**.


c0870wgh
William Glover-Humphreys - WGH-Exp77-pg128
OH
N
O
O
3.79
3.75
2.62
2.58
2.42
2.37
2.25
2.24
2.17
1.85
1.73
1.71
1.66
1.42
2.00
1.25
1.33
3.05
4.06
2.14
2.02
9.37
f1 (ppm)

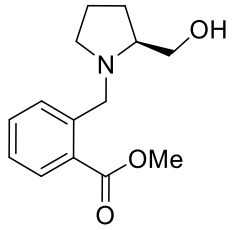

c0870wgh
William Glover-Humphreys - WGH-Exp77-pg128
OH
N
O
O
172.80
80.43
58.40
57.31
41.85
33.18
28.17
27.74
22.47
f1 (ppm)

5-Methyl-1,5-oxazonan-9-one (6-80)

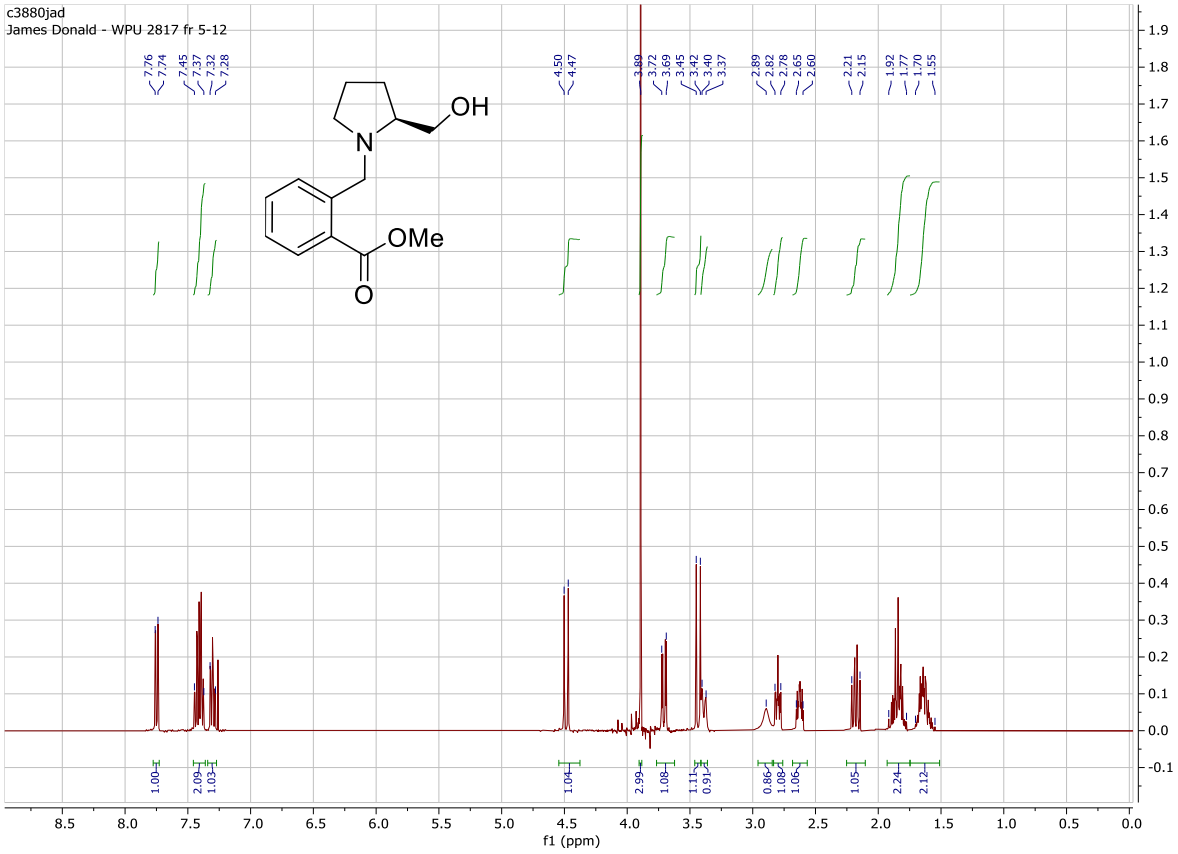


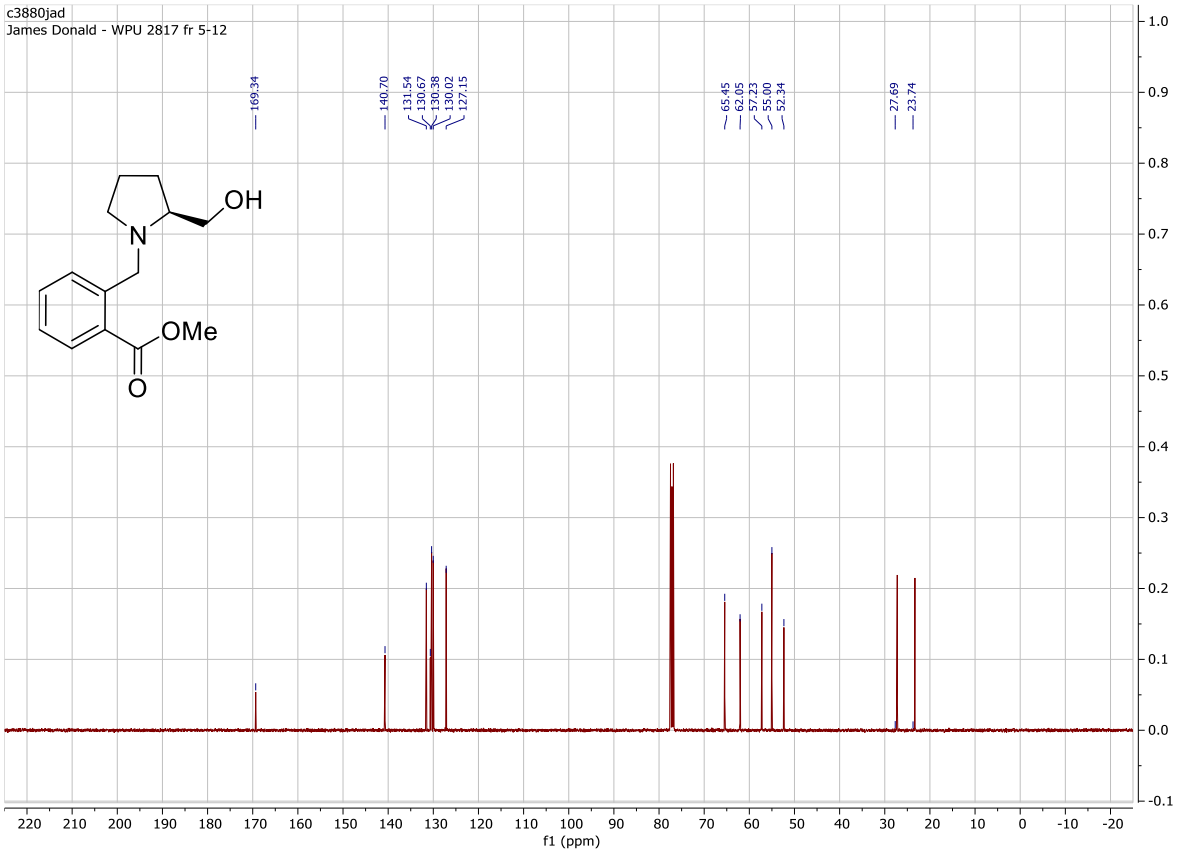
To a stirring solution of *tert*-butyl 4-((3-hydroxypropyl) (methyl) amino) butanoate **(6-77)** (0.138 g, 0.596 mmol) in diethyl ether (2.00 mL), a solution of 4.0 M hydrochloric acid in 1,4 dioxane (3.0 mL, 12.0 mmol) was added dropwise and the reaction was left stirring at room temperature for 3 hours. The reaction mixture was concentrated under vacuum using chloroform (3 × 10 mL) to make an azeotropic solution. The intermediate lithium 4-(methyl(3-oxidopropyl) amino) butanoate was dissolved in chloroform (15 mL) and DIPEA (0.115 g, 5.96 mmol) under argon, until all the reagents dissolved into solution (30 minutes). T3P (0.569 g, 0.89 mmol) was then added, and the reaction left to stir over night at room temperature. The reaction mixture was monitored by TLC after 24 hours (hexane:ethyl acetate:triethylamine 75:20:5) but there was no evidence to suggest the NICE proceeded. The reaction mixture was purified by flash column chromatography (14:4:1 dichlormethane:hexane:triethylamine) no identifiable product isolated so a 0% yield was recorded.

Methyl (*S*)-2-((2-(hydroxymethyl) pyrrolidin-1-yl) methyl) benzoate (6-87)

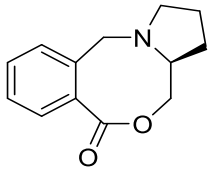


To a stirring solution of potassium carbonate (0.415 g, 3.00 mmol) in acetonitrile (5.00 mL), (*S*)-pyrrolidin-2-yl methanol **(6-86)** (0.101 g, 0.099 mL, 1.00 mmol) was added followed by methyl 2-(bromomethyl) benzoate **(6-1)** (0.229 g, 1.00 mmol). The reaction mixture was heated to reflux at 90 °C for 1 hours before filtering through Celite washing with dichloromethane, concentrating under vacuum and purifying by flash column chromatography (1:2 hexane:ethyl acetate ⟶ ethyl acetate) to afford the title compound as a yellow oil (0.197 g, 79%), R_f = 0.2 (ethyl acetate - streak); ν_{max}/cm^{-1} (thin film) 3505, 2950, 1717, 1269, 1079, 743; δ_H (400 MHz, $CDCl_3$) 7.76 (1H, d, *J* = 7.3 Hz, Ar**H**), 7.47–7.37 (2H, m, 2 × Ar**H**), 7.34–7.28 (2H, m, 2 × Ar**H**), 4.50 (1H, d, *J* = 13.3 Hz, ArC**H**$_a$H$_b$N), 3.90 (3H, s, OC**H**$_3$), 3.72 (1H, dd, *J* = 13.5 Hz, 3.2 Hz, C**H**$_a$H$_b$OH), 3.45 (1H, d, *J* = 13.3 Hz, ArCH$_a$**H**$_b$N), 3.42–3.36 (1H, m, CH$_a$**H**$_b$OH), 2.90 (1H, br s, O**H**), 2.83–2.79 (1H, m, C**H**$_a$H$_b$N), 2.67–2.61 (1H, m, NC**H**), 2.24–2.20 (1H, m, CH$_a$**H**$_b$N), 1.92–1.77 (2H, m, C**H**$_2$), 1.70–1.55 (2H, m, C**H**$_2$); δ_c (100 MHz, $CDCl_3$) 169.2 (**C**O), 140.6 (Ar**C**), 131.4 (Ar**C**H), 130.5 (Ar**C**), 130.2 (Ar**C**H), 129.9 (Ar**C**H), 127.0 (Ar**C**H), 65.3 (N**C**H), 61.9 (**C**H$_2$OH), 57.1 (Ar**C**H$_2$N), 54.9 (**C**H$_2$N), 52.2 (O**C**H$_3$), 27.1 (**C**H$_2$), 23.2 (**C**H$_2$); HRMS (ESI) calcd. for $C_{14}H_{20}NO_3$ 250.1443. Found $[MH]^+$, 250.1440 (−1.20 ppm error).

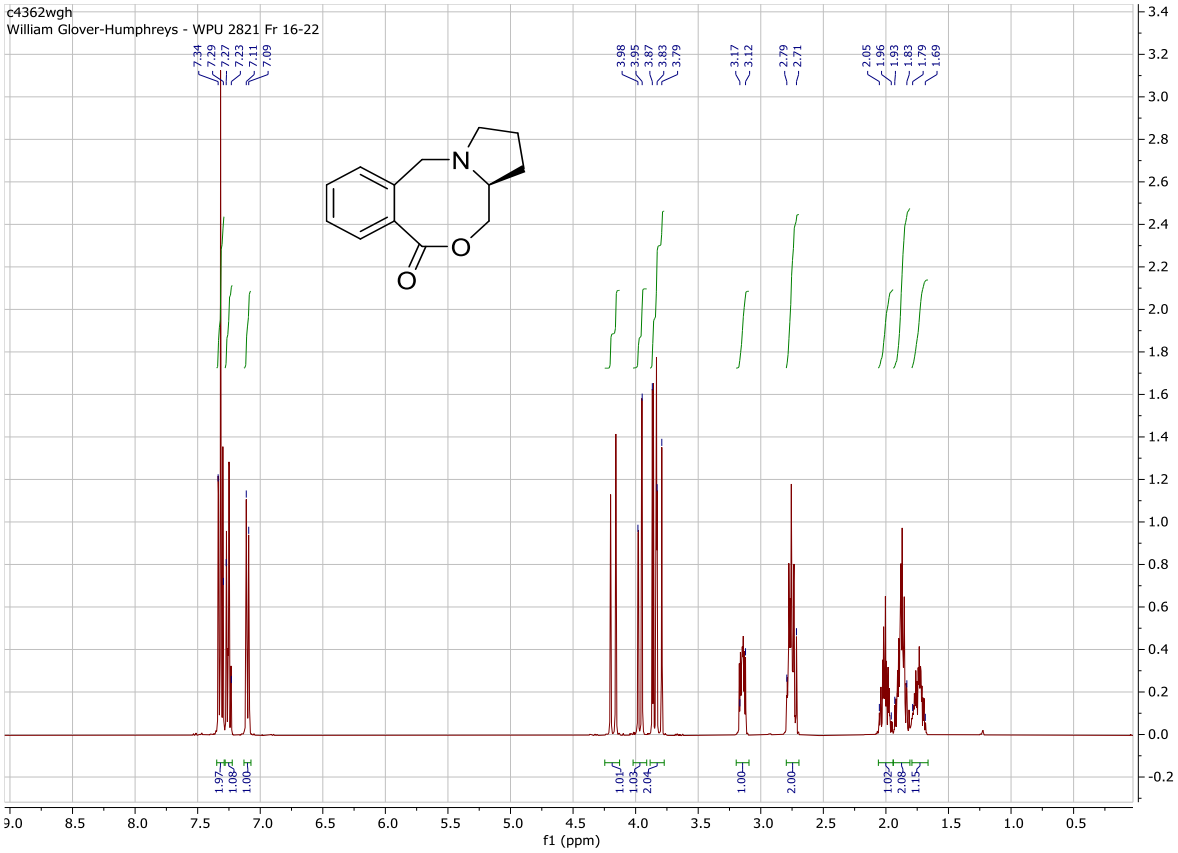

c3880jad
James Donald - WPU 2817 fr 5-12
7.76
7.74
7.45
7.37
7.32
7.28
4.50
4.47
3.89
3.72
3.69
3.45
3.42
3.40
3.37
2.89
2.82
2.78
2.65
2.60
2.21
2.15
1.92
1.77
1.70
1.55
OH
N
OMe
O
1.00
2.09
1.03
1.04
2.99
1.08
1.11
0.91
0.86
1.08
1.06
1.05
2.24
2.12
f1 (ppm)


c3880jad
James Donald - WPU 2817 fr 5-12
169.34
140.70
131.54
130.67
130.38
130.02
127.15
65.45
62.05
57.23
55.00
52.34
27.69
23.74
OH
N
OMe
O
f1 (ppm)

(*S*)-2,3,3*a*,4-Tetrahydro-1*H*-benzo[f]pyrrole [2,1-*c*] [1,4] oxazocin-6 (11*H*)-one (6-89)



To a stirring solution of methyl (*S*)-2-((2-(hydroxymethyl) pyrrolidin-1-yl) methyl) benzoate **(6-87)** (0.132 g, 0.529 mmol) in methanol (1.16 mL), aqueous lithium hydroxide (0.5 M) was added (1.16 mL, 0.582 mmol) and heated for at 50 °C for 1 hours. The solvent was removed under vacuum using chloroform (5 × 50 mL) to form an azeotropic mixture. The intermediate lithium (S)-2-((2-(oxidomethyl) pyrrolidin-1-yl) methyl) benzoate was dissolved in chloroform (5.20 mL) and DIPEA (0.17 mL, 0.979 mmol) was added followed by T3P 50% w/v in ethyl acetate (0.505 g, 0.794 mmol) and stirred at room temperature for 1 hours under argon. The reaction mixture was washed sequentially in dichloromethane (3 × 20 mL) and water (20 mL) and the organic phases combined dried with magnesium sulfate, filtered, concentrated under vacuum and purified via flash column chromatography (4:1 → 1:1 hexane:ethyl acetate) to afford the title compound (0.105 g, 91%) R_f = 0.45 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 2962, 1715, 1271, 1093, 737; δ_H (400 MHz, $CDCl_3$) 7.34–7.29 (2H, m, 2 × Ar**H**), 7.27−7.23 (1H, m, Ar**H**), 7.10 (1H, d, *J* = 7.8 Hz, Ar**H**), 4.18 (1H, d, *J* = 16.9, ArC**H**$_a$H$_b$N), 3.98–3.95 (1H, OC**H**$_a$H$_b$CH), 3.87–3.85 (1H, OCH$_a$**H**$_b$CH), 3.81 (1H, d, *J* = 16.9, ArCH$_a$**H**$_b$N), 3.19–3.12 (1H, m, NC**H**$_a$H$_b$), 2.80–2.71 (2H, m, NC**H**$_a$H$_b$, N**H**), 2.06–1.68 (4H, m, 2 × C**H**$_2$); δ_c (100 MHz, $CDCl_3$) 173.7 (**C**O), 139.3 (Ar**C**), 130.9 (Ar**C**), 129.8 (Ar**C**H), 128.9 (Ar**C**H), 127.4 (Ar**C**H), 126.0 (Ar**C**H), 68.8 (O**C**H$_2$CH), 64.3 (N**C**H), 56.1 (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 $C_{13}H_{16}NO_2$ 218.118. Found $[MH]^+$ 218.1177 (−1.84 ppm error).


c4362wgh
William Glover-Humphreys - WPU 2821 Fr 16-22
7.34
7.29
7.27
7.23
7.11
7.09
3.98
3.95
3.87
3.83
3.79
3.17
3.12
2.79
2.71
2.05
1.96
1.93
1.83
1.79
1.69
1.97
1.08
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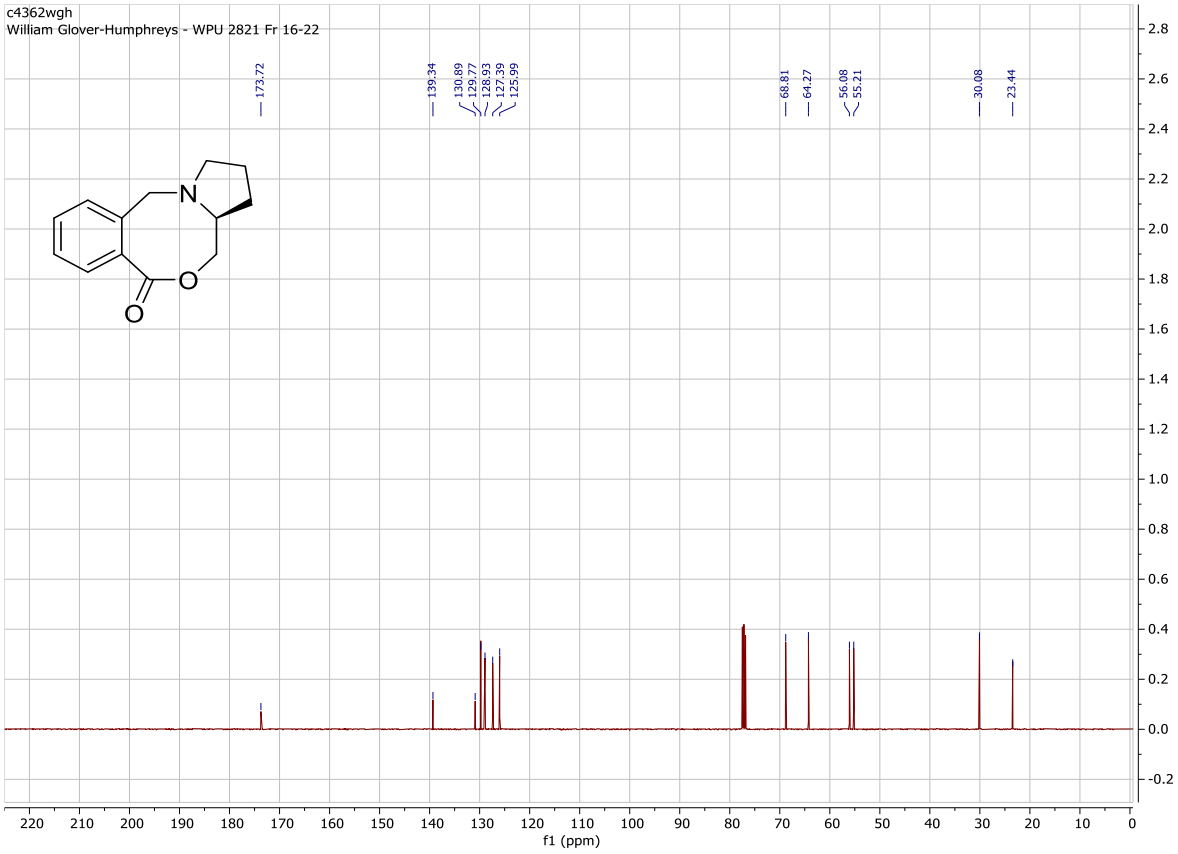
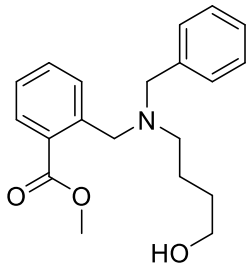
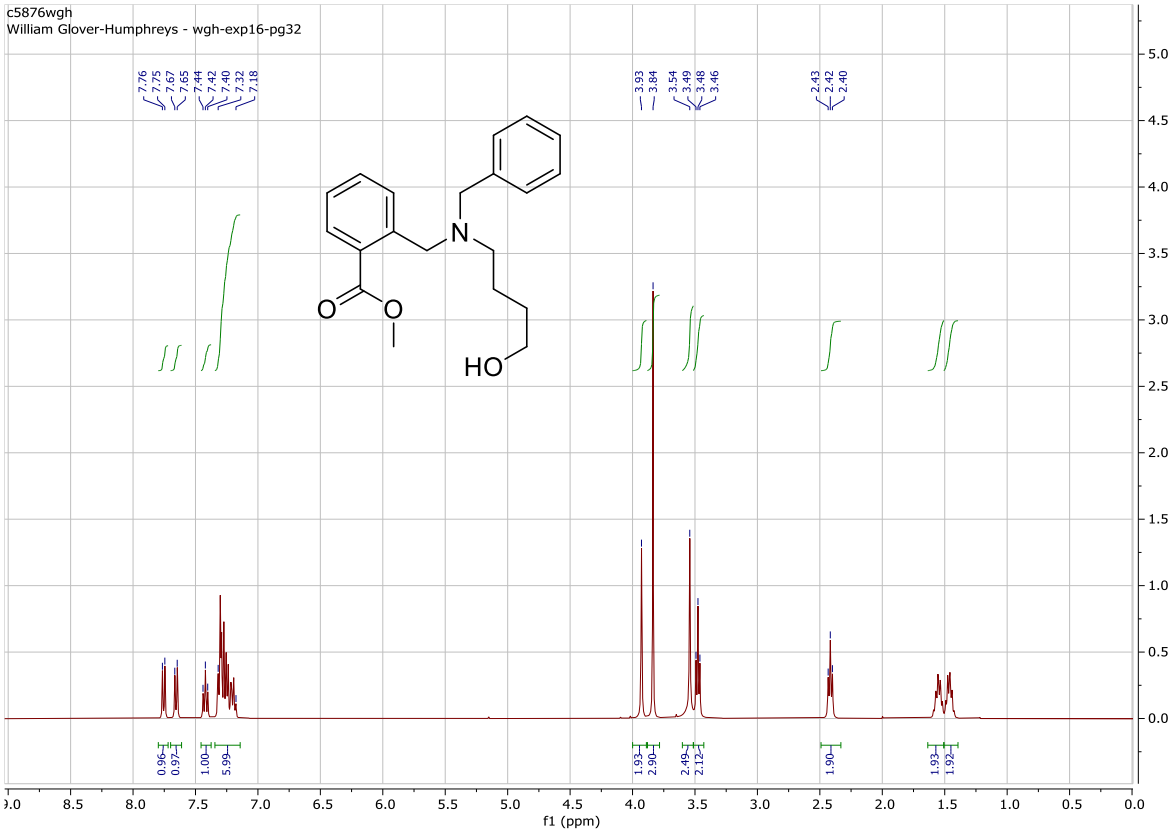
1.01
1.03
2.04
1.00
2.00
1.02
2.08
1.15
f1 (ppm)

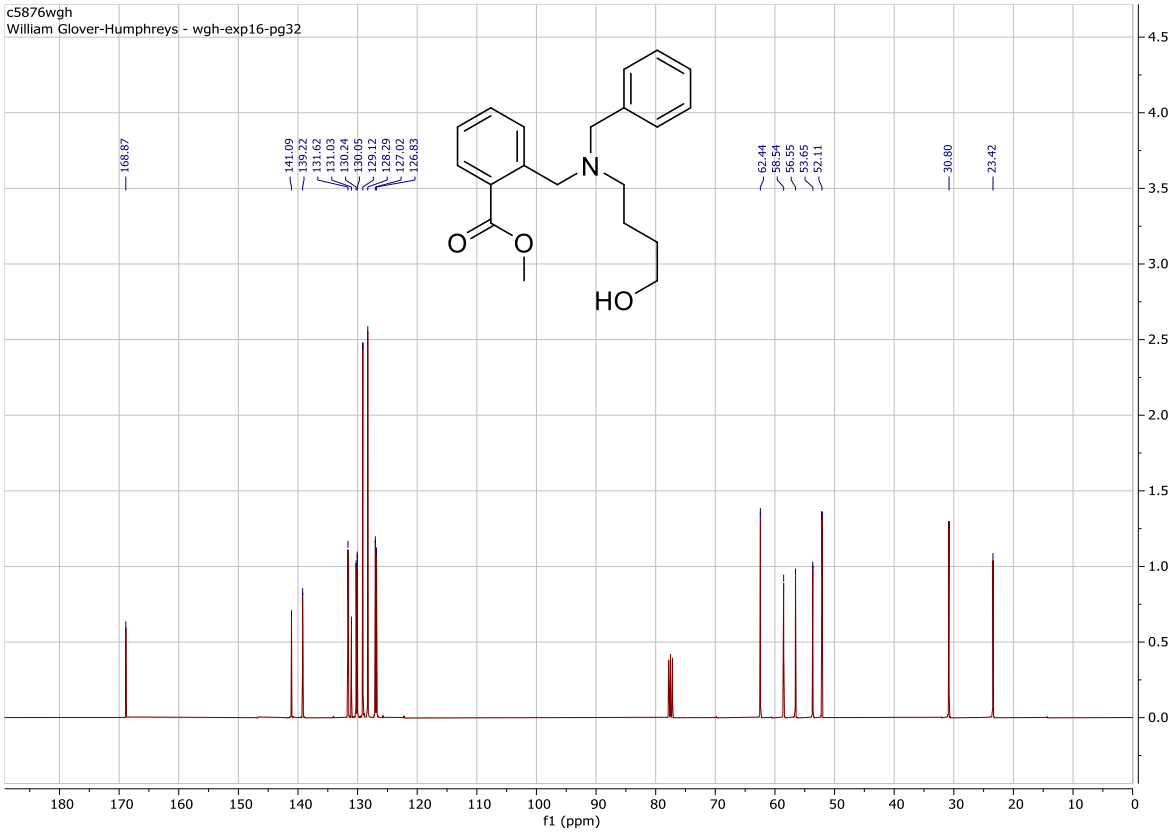

c4362wgh
William Glover-Humphreys - WPU 2821 Fr 16-22
173.72
139.34
130.89
129.77
128.93
127.39
125.99
68.81
64.27
56.08
55.21
30.08
23.44
f1 (ppm)

Methyl 2-((benzyl (4-hydroxybutyl) amino) methyl) benzoate (6-96)

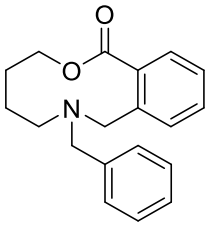


To a stirring solution of potassium carbonate (0.415 g, 3.00 mmol) in acetonitrile (5.00 mL), 4-(benzylamino) butan-1-ol **(6-90)** (0.179 g, 1.00 mmol) was added followed by methyl 2-(bromomethyl) benzoate **(6-1)** (0.229 g, 1.00 mmol). The reaction mixture was heated to reflux at 90 °C for 3 hours under argon before filtering through Celite washing with dichloromethane, concentrating under vacuum and purifying by flash column chromatography (10:9:1 ethyl acetate:hexane:triethylamine) to afford the title compound as a clear oil (0.327 g, 99%) R_f = 0.22 (14:5:1 hexane:ethyl acetate:triethylamine); ν_{max}/cm^{-1} (thin film) 3391, 2945, 2803, 1718, 14334, 1265, 1081, 909, 729; δ_H (400 MHz, $CDCl_3$) 7.75 (1H, d, *J* = 7.81 Hz, ArC**H**), 7.66 (1H, d, *J* = 7.8 Hz, ArC**H**), 7.42 (1H, t, *J* = 7.5 Hz), 7.32−7.17 (6H, m, ArC**H**), 3.93 (2H, s, ArC**H**$_2$N), 3.84 (3H, s, ArC**H**$_2$N), 3.54 (2H, s, ArC**H**$_2$N), 3.48 (2H, t, *J* = 6.2 Hz, $CH_2C\mathbf{H}_2N$), 2.42 (2H, t, *J* = 6.8 Hz, $CH_2C\mathbf{H}_2OH$), 1.55 (2H, quintet, *J* = 6.6 Hz, $CH_2C\mathbf{H}_2CH_2$), 1.49−1.42 (2H, m, $CH_2C\mathbf{H}_2CH_2$); δ_c (100 MHz, $CDCl_3$) 168.9 (**C**O), 141.1 (Ar**C**), 139.2 (Ar**C**), 131.6 (Ar**C**H), 131.0 (Ar**C**), 130.2 (Ar**C**H), 130.1 (Ar**C**H), 129.1 (Ar**C**H), 128.3 (Ar**C**H), 127.0 (Ar**C**H), 126.8 (Ar**C**H), 62.4 (**C**H_2N), 58.5 (Ar**C**H_2N), 56.6 (Ar**C**H_2N), 53.7 ($CH_2\mathbf{C}H_2OH$), 52.1 (COO**C**H_3), 30.8 (**C**H_2), 23.4 (**C**H_2); HRMS (ESI) calcd. for $C_{20}H_{26}NO_3$ 328.1913. Found $[MH]^+$ 328.1909 (−1.22 ppm error).

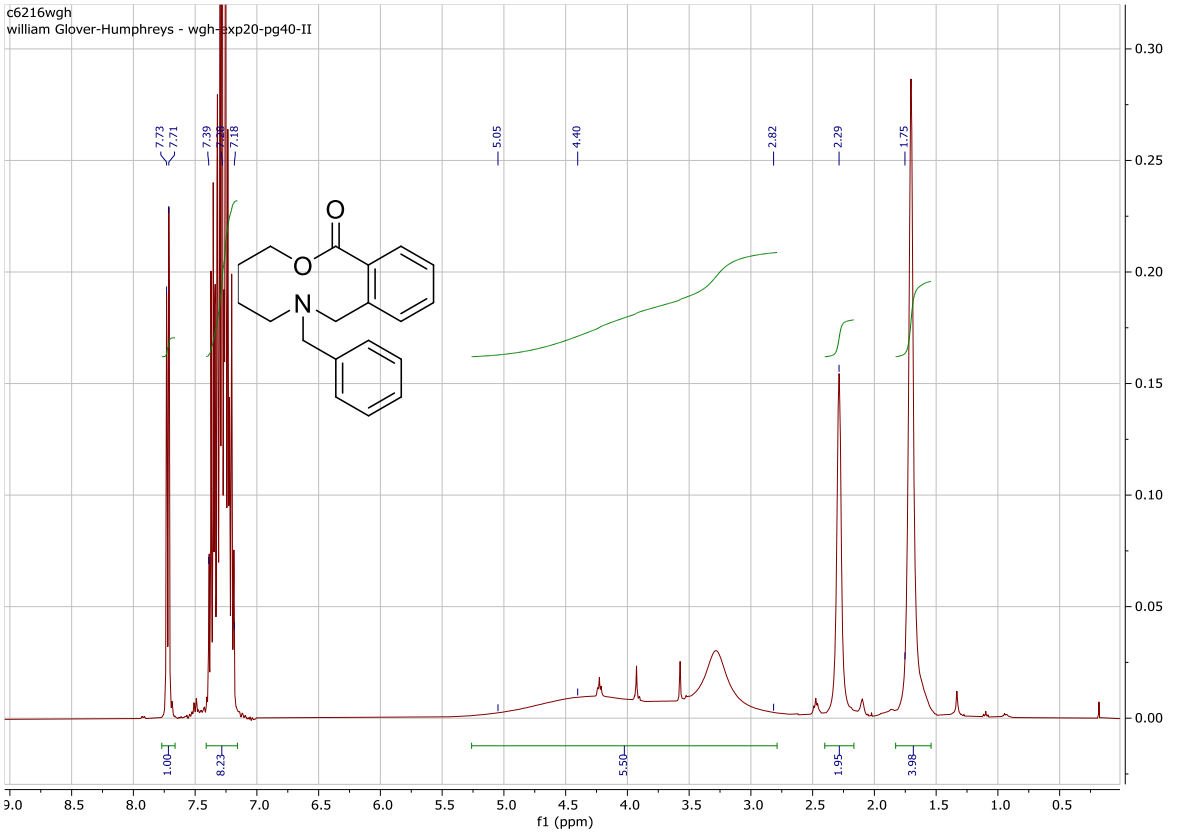

c5876wgh
William Glover-Humphreys - wgh-exp16-pg32
7.76
7.75
7.67
7.65
7.44
7.42
7.40
7.32
7.18
3.93
3.84
3.54
3.49
3.48
3.46
2.43
2.42
2.40
N
O
O
HO
0.96
0.97
1.00
5.99
1.93
2.90
2.49
2.12
1.90
1.93
1.92
f1 (ppm)

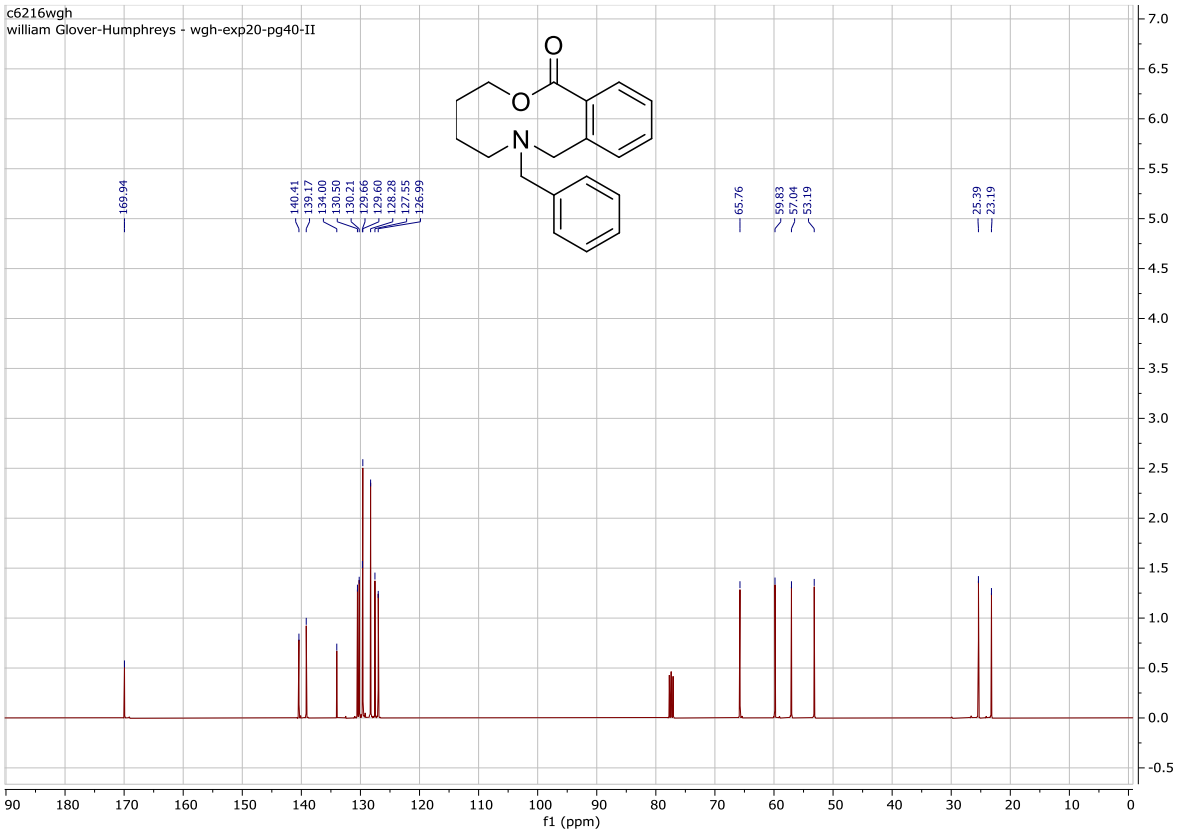

c5876wgh
William Glover-Humphreys - wgh-exp16-pg32
168.87
141.09
139.22
131.62
131.03
130.24
130.05
129.12
128.29
127.02
126.83
62.44
58.54
56.55
53.65
52.11
30.80
23.42
N
O
O
HO
f1 (ppm)

7-Benzyl-3,4,5,6,7,6-hexahydro-1*H*-benzo[*c*] [1,6] oxazecin-1-one (6-102)

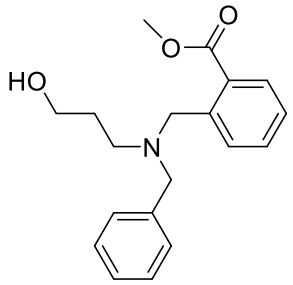


To a stirring solution of methyl 2-((benzyl (4-hydroxybutyl) amino) methyl) benzoate **(6-96)** (0.327 g, 0.998 mmol) in tetrahydrofuran (2.20 mL), aqueous lithium hydroxide (0.5 M) was added (0.323 g, 2.7 mL, 1.35 mmol) and heated for at 50 °C for 2 hours. The solvent was removed under vacuum using dichloromethane (5 × 50 mL) to form an azeotropic mixture. The intermediate lithium 2-(((3-hydroxy-3-phenylpropyl) (methyl)amino) methyl) benzoate was dissolved in chloroform (9.98 mL) and DIPEA (0.303 g, 0.445 mL, 2.35 mmol) was added followed by T3P 50% w/v in ethyl acetate (0.127 g, 2.00 mmol) and stirred at room temperature for 2 hours under argon. The reaction mixture was washed sequentially in dichloromethane (2 × 100 mL) and brine (50 mL), the organic phases combined dried with sodium sulfate, filtered, concentrated under vacuum and purified via flash column chromatography (15:4:1 hexane:ethyl acetate:triethylamine) to afford the title compound (0.230 g, 78%) R_f = 0.49 (15:4:1 hexane:ethyl acetate:triethylamine); ν_{max}/cm^{-1} (thin film) 3063, 2954, 2799, 2251, 1717, 1452, 1294, 1266, 1131, 1091, 908, 725; δ_H (400 MHz, $CDCl_3$) 7.72 (1H, dd, *J* = 7.7 Hz, 1.4 Hz, Ar**H**), 7.39−7.18 (8H, m, Ar**H**), 5.05−2.82 (6H, bm, NC**H**$_2$, NC**H**$_2$Ar, NC**H**$_2$Ar), 2.34−2.13 (2H, m, C**H**$_2$O), 1.89−1.54 (4H, m, C**H**$_2$C**H**$_2$); δ_c (100 MHz, $CDCl_3$) 169.9 (**C**O), 140.4 (Ar**C**), 139.2 (Ar**C**), 134.0 (Ar**C**), 130.5 (Ar**C**H), 130.2 (Ar**C**H), 129.7 (Ar**C**H), 129.6 (Ar**C**H), 128.3 (Ar**C**H) 127.6(Ar**C**H), 127.6 (Ar**C**H), 127.0 (Ar**C**H), 65.8 (**C**H$_2$N), 59.8 (**C**H$_2$O), 57.0 (**C**H$_2$N), 53.2 (**C**H$_2$N), 25.4 (**C**H$_2$), 23.19 (**C**H$_2$); HRMS (ESI) calcd. for $C_{19}H_{22}NO_2$ 296.1651. Found $[MH]^+$ 296.1643 (−2.70 ppm error).

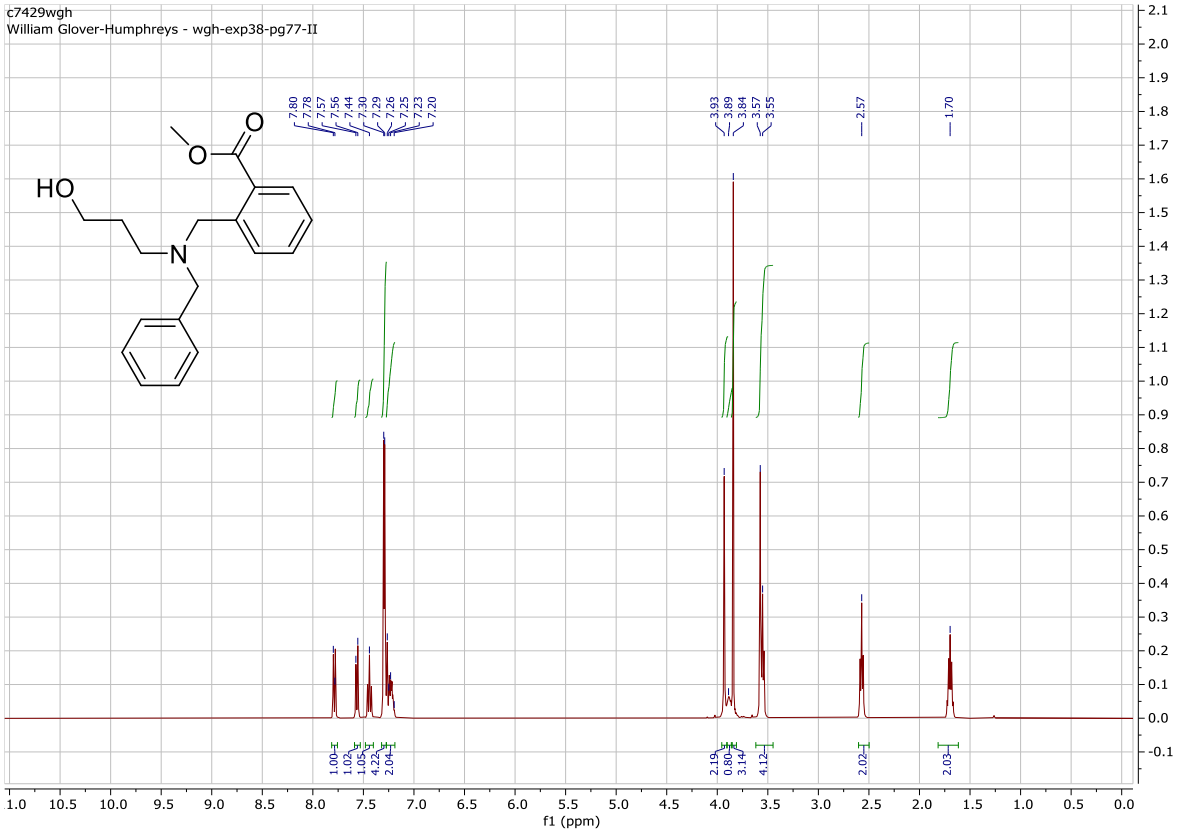

c6216wgh
william Glover-Humphreys - wgh-exp20-pg40-II
7.73
7.71
7.39
7.38
7.18
5.05
4.40
2.82
2.29
1.75
1.00
8.23
5.50
1.95
3.98
f1 (ppm)

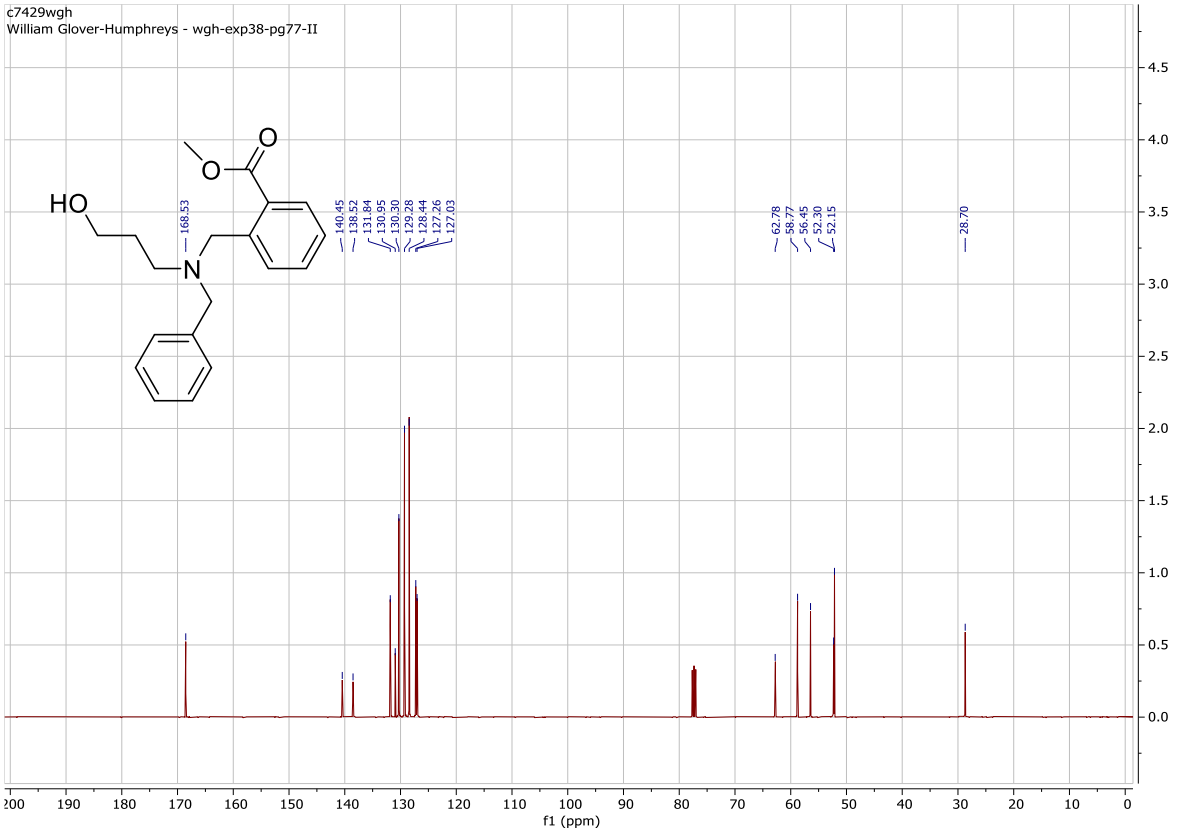

c6216wgh
william Glover-Humphreys - wgh-exp20-pg40-II
169.94
140.41
139.17
134.00
130.50
130.21
129.66
129.60
128.28
127.55
126.99
65.76
59.83
57.04
53.19
25.39
23.19
f1 (ppm)

Methyl 2-((benzyl(3-hydroxypropyl) amino) methyl) benzoate (6-97)

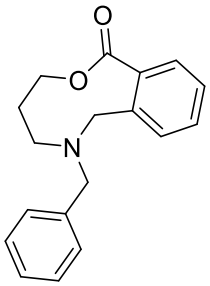


To a stirring solution of potassium carbonate (0.415 g, 3.00 mmol) in acetonitrile (5 mL), (3-(benzylamino) propan-1-ol **(6-91)** (0.165 g, 1.00 mmol) was added followed by methyl 2-(bromomethyl) benzoate **(6-1)** (0.230 g, 1.00 mmol). The reaction mixture was heated to reflux at 90 °C for 3 hours under argon before filtering through Celite washing with dichloromethane, concentrating under vacuum and purifying by flash column chromatography (8:2 hexane:ethyl acetate) to afford the title compound as a clear oil (0.272 g, 87%) R_f = 0.54 (8:2 hexane:diethyl ether); ν_{max}/cm^{-1} (thin film) 3402, 2949, 2242, 1718, 1434, 1264, 1130, 1078, 909, 729, 699; δ_H (400 MHz, $CDCl_3$) 7.79 (1H, d, *J* = 7.7 Hz, Ar**H**), 7.57 (1H, d, *J* = 7.8 Hz, Ar**H**), 7.44 (1H, t, *J* = 7.5 Hz, Ar**H**), 7.30−7.28 (4H, m, Ar**H**), 7.27−7.20 (2H, m, Ar**H**), 3.93 (2H, s, ArC**H**$_2$N), 3.89 (1H, bs, O**H**), 3.84 (3H, s, OC**H**$_3$), 3.57 (2H, s, ArC**H**$_2$N), 3.55 (2H, t, *J* = 5.4 Hz, $CH_2C\mathbf{H}_2OH$), 2.57 (2H, t, *J* = 6.3 Hz, NC**H**$_2CH_2$), 1.70 (2H, quintet, *J* = 6.0 Hz, $CH_2C\mathbf{H}_2CH_2$); δ_c (100 MHz, $CDCl_3$) 168.5 (**C**O), 140.5 (Ar**C**), 138.5 (Ar**C**), 131.8 (Ar**C**H), 131.0 (Ar**C**), 130.3 (Ar**C**H), 129.3 (Ar**C**H), 128.4 (Ar**C**H), 127.3 (Ar**C**H), 127.0 (Ar**C**H), 62.8 ($CH_2\mathbf{C}H_2OH$), 58.8 (Ar**C**H$_2$N), 56.5 (Ar**C**H$_2$N), 52.3 ($CH_2C\mathbf{H}_2N$), 52.2 (**C**H$_3$O), 28.7 ($CH_2\mathbf{C}H_2CH_2$); HRMS (ESI) calcd. for $C_{19}H_{24}NO_3$ 314.1756. Found $[MH]^+$ 314.1745 (−3.51 ppm error).

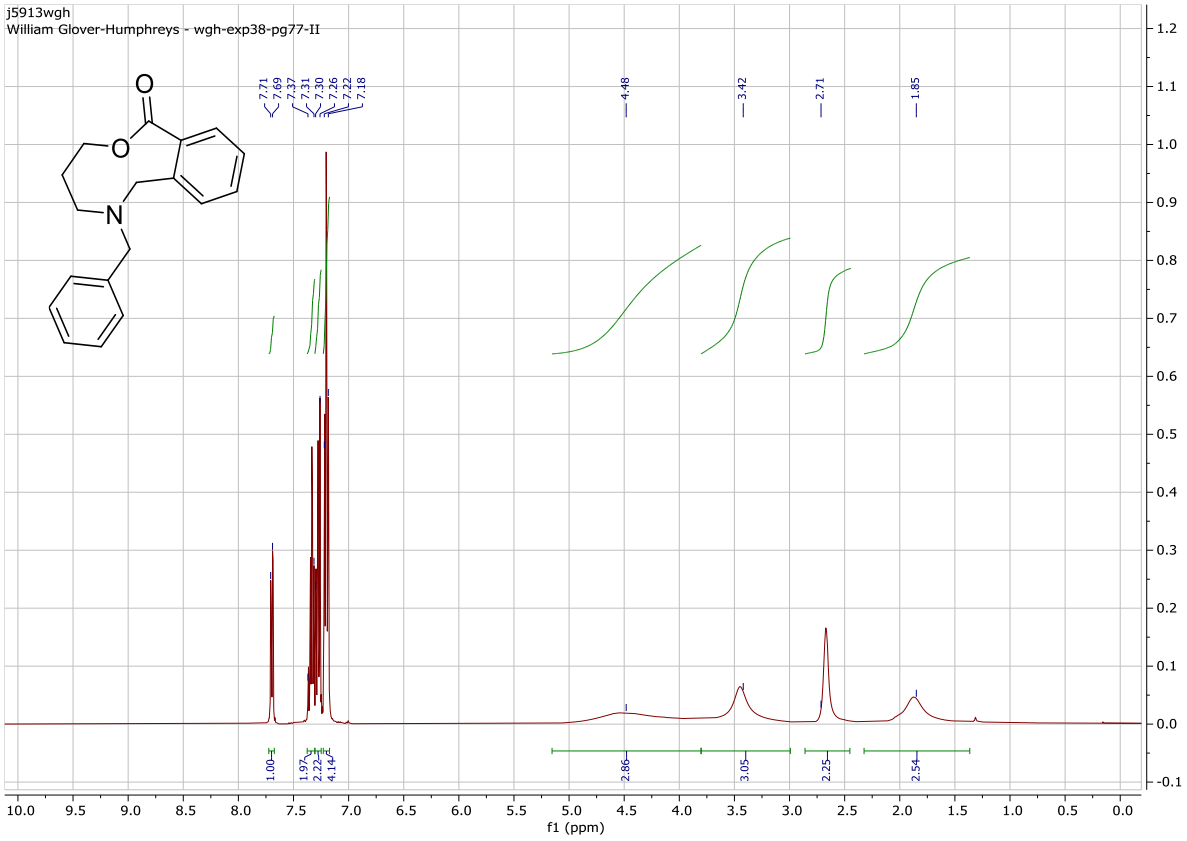

c7429wgh
William Glover-Humphreys - wgh-exp38-pg77-II
HO
O
O
N
7.80
7.78
7.57
7.56
7.44
7.30
7.29
7.26
7.25
7.23
7.20
3.93
3.89
3.84
3.57
3.55
2.57
1.70
1.00
1.02
1.05
4.22
2.04
2.19
0.80
3.14
4.12
2.02
2.03
f1 (ppm)

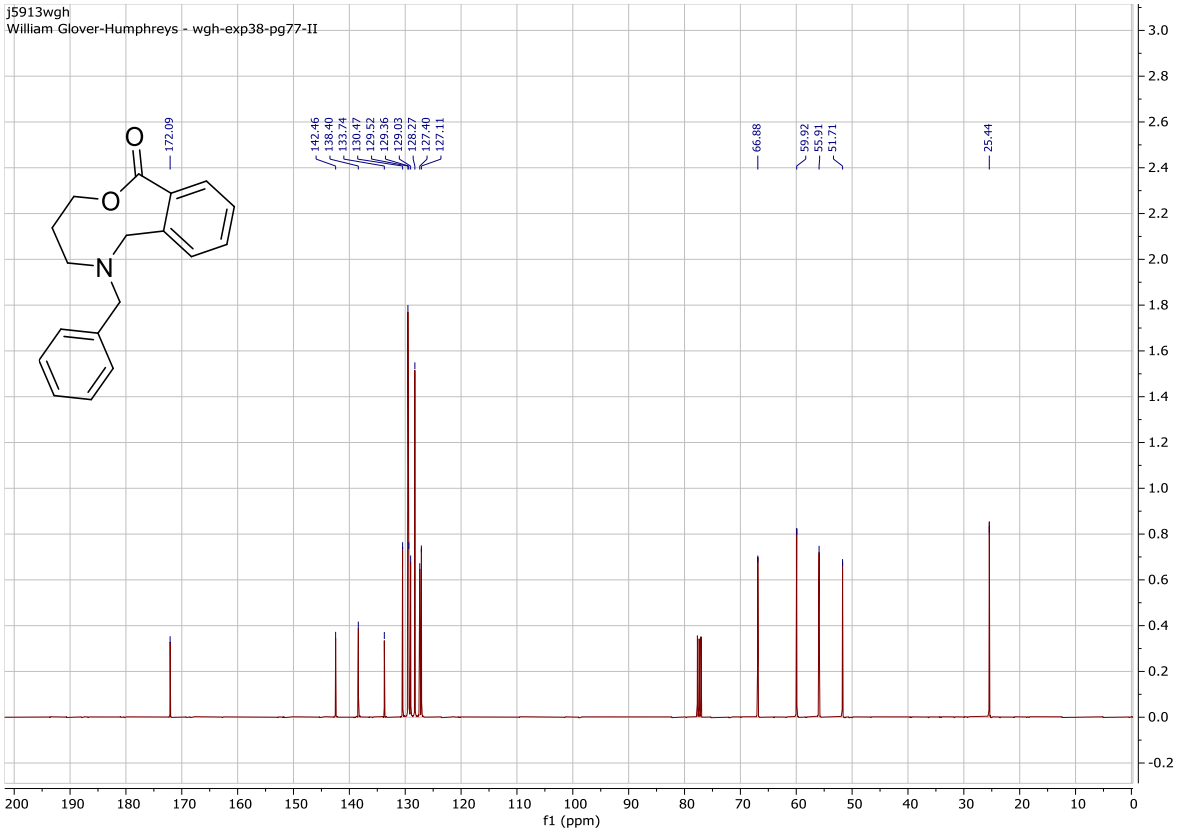

c7429wgh
William Glover-Humphreys - wgh-exp38-pg77-II
HO
O
O
N
168.53
140.45
138.52
131.84
130.95
130.30
129.28
128.44
127.26
127.03
62.78
58.77
56.45
52.30
52.15
28.70
f1 (ppm)

4-Benzyl-4,5,6,7-tetrahydrobenzo[*g*] [1,5] oxazonin-1(3*H*)-one (6-103)

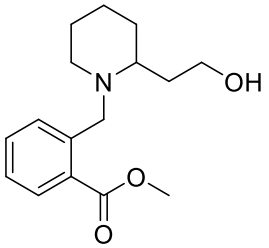


To a stirring solution of methyl 2-((benzyl(3-hydroxypropyl) amino) methyl) benzoate **(6-97)** (0.272 g, 0.869 mmol) in tetrahydrofuran (8.70 mL), aqueous lithium hydroxide (0.5 M) (2.00 mL, 1.04 mmol) was added and the resulting mixture was heated at 50 °C for 3 hours. The solvent was removed under vacuum using dichloromethane (5 × 50 mL) to form an azeotropic mixture. The intermediate lithium 2-((benzyl(3-oxidopropyl) amino) methyl) benzoate was dissolved in chloroform (8.70 mL) and DIPEA (0.208 g, 0.280 mL, 1.61 mmol) was added followed by T3P 50% w/v in ethyl acetate (0.830 g, 1.30 mmol). The mixture was stirred at room temperature for 3 hours under argon. The reaction mixture was washed sequentially in dichloromethane (2 × 100 mL) and brine (50 mL) and the organic phases combined dried with sodium sulfate, filtered, concentrated under vacuum and purified via flash column chromatography (8:2 hexane:ethyl acetate) to afford the title compound (0.181 g, 74%) R_f = 0.52 (8:2 hexane:ethyl acetate); ν_{max}/cm^{-1} (thin film) 2956, 2803, 2251, 1719, 1605, 1450, 1352, 1265, 1239, 1136, 1067, 989, 909, 767, 727, 699; δ_H (400 MHz, $CDCl_3$) 7.70 (1H, dd, *J* = 6.9 Hz, 2.1 Hz, Ar**H**), 7.37−7.31 (2H, m, 2 × Ar**H**), 7.30−7.25 (2H, m, 2 × Ar**H**), 7.21−7.18 (4H, m, 4 × Ar**H**), 4.96−3.80 (3H, m, C**H**$_2$O & C**H**$_a$H$_b$N), 3.75−3.16 (3H, CH$_a$**H**$_b$N, ArC**H**$_2$N), 2.67 (2H, s, Ar**C**H$_2$N), 2.04−1.60 (CH$_2$C**H**$_2$CH$_2$); δ_c (100 MHz, $CDCl_3$) 172.1 (**C**O), 142.5 (Ar**C**), 138.4 (Ar**C**), 133.7 (Ar**C**), 130.5 (Ar**C**H), 129.5 (Ar**C**H), 129.4 (Ar**C**H), 129.0 (Ar**C**H), 128.3 (Ar**C**H), 127.4 (Ar**C**H), 127.1 (Ar**C**H), 66.9 (**C**H$_2$O), 59.92 (Ar**C**H$_2$N), 55.91 (Ar**C**H$_2$N), 51.7 (CH$_2$**C**H$_2$N), 25.4 (CH$_2$**C**H$_2$CH$_2$); HRMS (ESI) calcd. for $C_{18}H_{20}NO_2$ 282.1494. Found $[MH]^+$ 282.1485 (−3.19 ppm error).

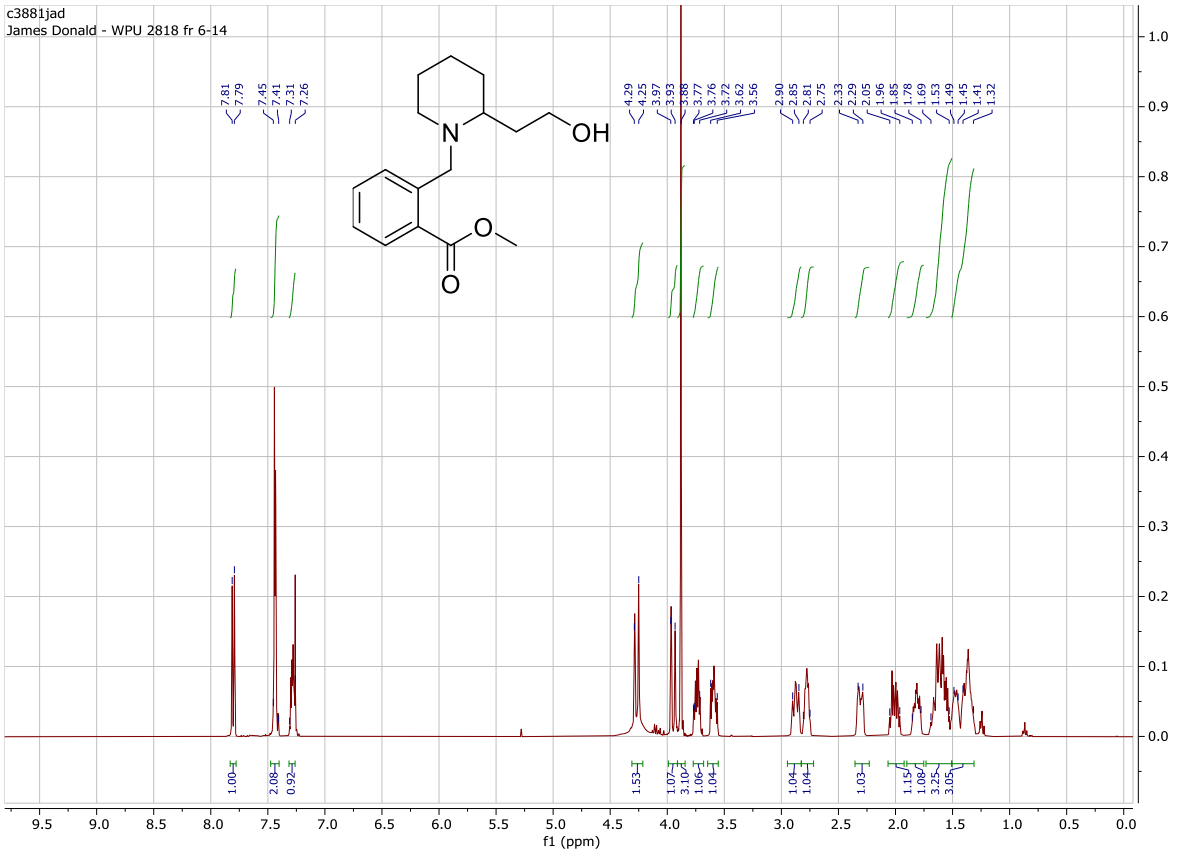

j5913wgh
William Glover-Humphreys - wgh-exp38-pg77-II
7.71
7.69
7.37
7.31
7.30
7.26
7.22
7.18
4.48
3.42
2.71
1.85
1.00
1.97
2.22
4.14
2.86
3.05
2.25
2.54
f1 (ppm)

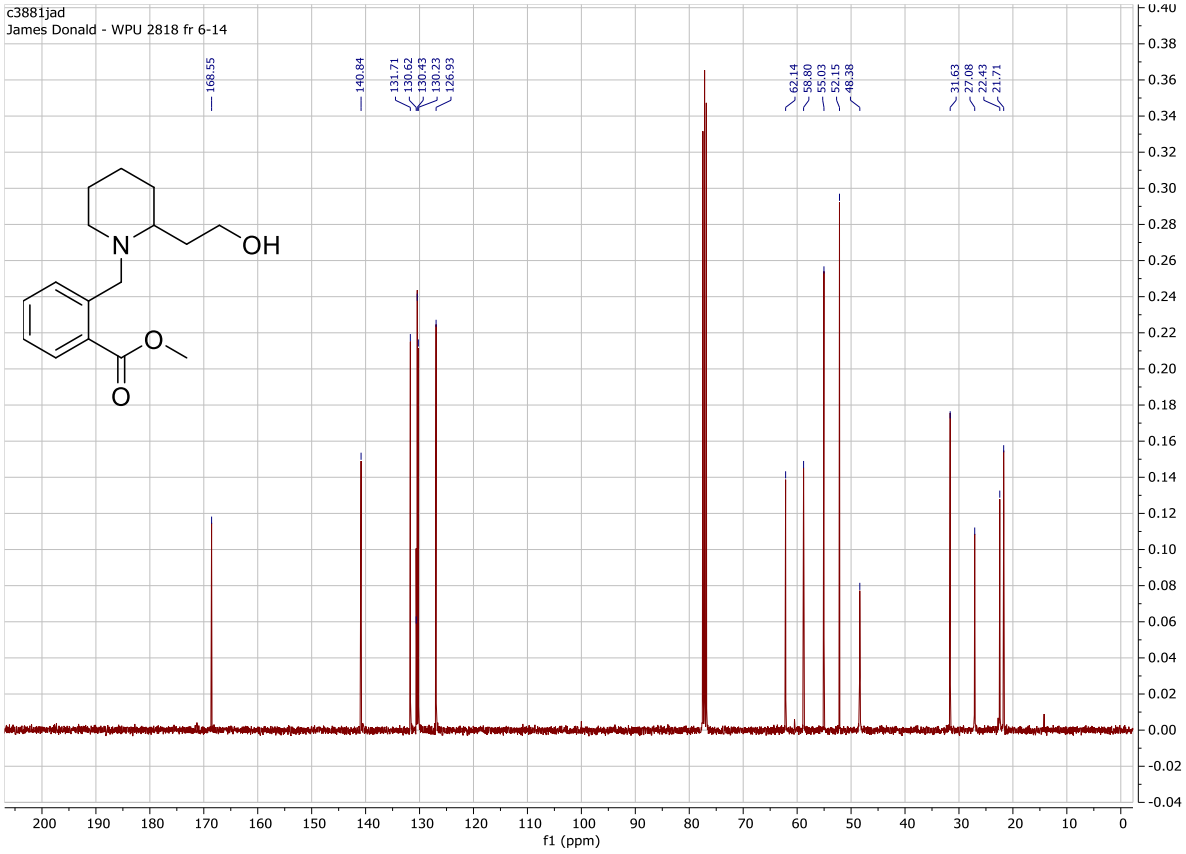

j5913wgh
William Glover-Humphreys - wgh-exp38-pg77-II
172.09
142.46
138.40
133.74
130.47
129.52
129.36
129.03
128.27
127.40
127.11
66.88
59.92
55.91
51.71
25.44
f1 (ppm)

Methyl 2-((2-(2-hydroxyethyl) piperidin-1-yl) methyl) benzoate (6-98)

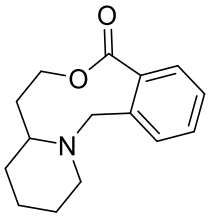


To a stirring solution of potassium carbonate (0.416 g, 3.00 mmol) in acetonitrile (5.00 mL), 2-(piperidin-2-yl) ethan-1-ol (**6-92**) (0.129 g, 1.00 mmol) was added followed by methyl 2-(bromomethyl) benzoate **(6-1)** (0.229 g, 1.00 mmol). The reaction mixture was heated to reflux at 90 °C for 1 hours before filtering through Celite washing with dichloromethane, concentrating under vacuum and purifying by flash column chromatography (1:2 hexane:ethyl acetate ⟶ ethyl acetate) to afford the title compound as a yellow oil (0.262 g, 94%) R_f = 0.2 (ethyl acetate - streaks); ν_{max}/cm^{-1} (thin film) 3417, 2932, 1721, 1264, 1085, 739; δH (400 MHz, $CDCl_3$); 7.79 (1H, d, *J* = 7.8 Hz, ArC**H**), 7.44–7.40 (2H, m, 2 × ArC**H**), 7.30–7.24 (1H, m, ArC**H**), 4.26 (1H, d, *J* = 13.7, ArC$\mathbf{H_a}H_b$N), 3.94 (1H, d, *J* = 13.7, ArC$H_a\mathbf{H_b}$N), 3.87 (3H, s, OC$\mathbf{H}_3$), 3.77–3.70 (1H, m, C$\mathbf{H_a}H_b$OH), 3.63–3.55 (1H, m, C$H_a\mathbf{H_b}$OH), 2.91–2.84 (1H, m, C$\mathbf{H_a}H_b$N), 2.81−2.75 (1H, m, C**H**N), 2.33−2.29 (1H, m, C$H_a\mathbf{H_b}$N), 2.05−2.29 (1H, m, C$\mathbf{H_a}H_b$), 1.85−1.78 (1H, m, C$H_a\mathbf{H_b}$), [1.69–1.32 (6H, m, 3 × C$\mathbf{H}_2$)]; δ_c (100 MHz, $CDCl_3$); 168.6 (**C**O), 140.8 (Ar**C**), 131.7 (Ar**C**H), 130.6 (Ar**C**), 130.4 (Ar**C**H), 130.2 (Ar**C**H), 126.9 (Ar**C**H), 62.1 (**C**H_2OH), 58.8 (**C**HN), 55.0 (Ar**C**H_2N), 52.2 (O**C**H_3), 48.4 (**C**H_2N), 31.6 (**C**H_2), 27.1 (**C**H_2), 22.4 (**C**H_2), 21.7 (**C**H_2); HRMS (ESI) calcd. for $C_{16}H_{24}NO_3$ 278.1756. Found $[MH]^+$, 278.1745 (1.5 ppm error).

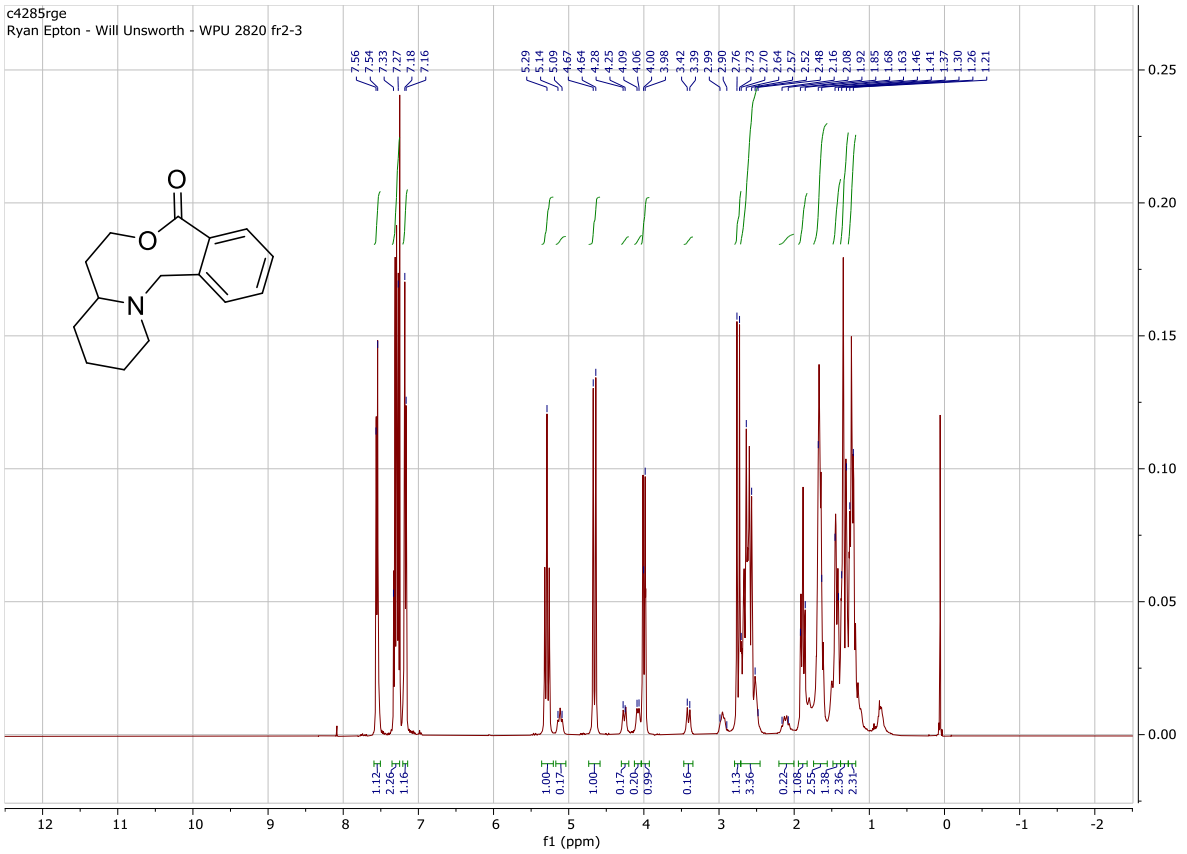

c3881jad
James Donald - WPU 2818 fr 6-14
7.81
7.79
7.45
7.41
7.31
7.26
4.29
4.25
3.97
3.93
3.88
3.77
3.76
3.72
3.62
3.56
2.90
2.85
2.81
2.75
2.33
2.29
2.05
1.96
1.85
1.78
1.69
1.53
1.49
1.45
1.41
1.32
N
OH
O
O
1.00
2.08
0.92
1.53
1.07
3.10
1.06
1.04
1.04
1.04
1.03
1.15
1.08
3.25
3.05
f1 (ppm)

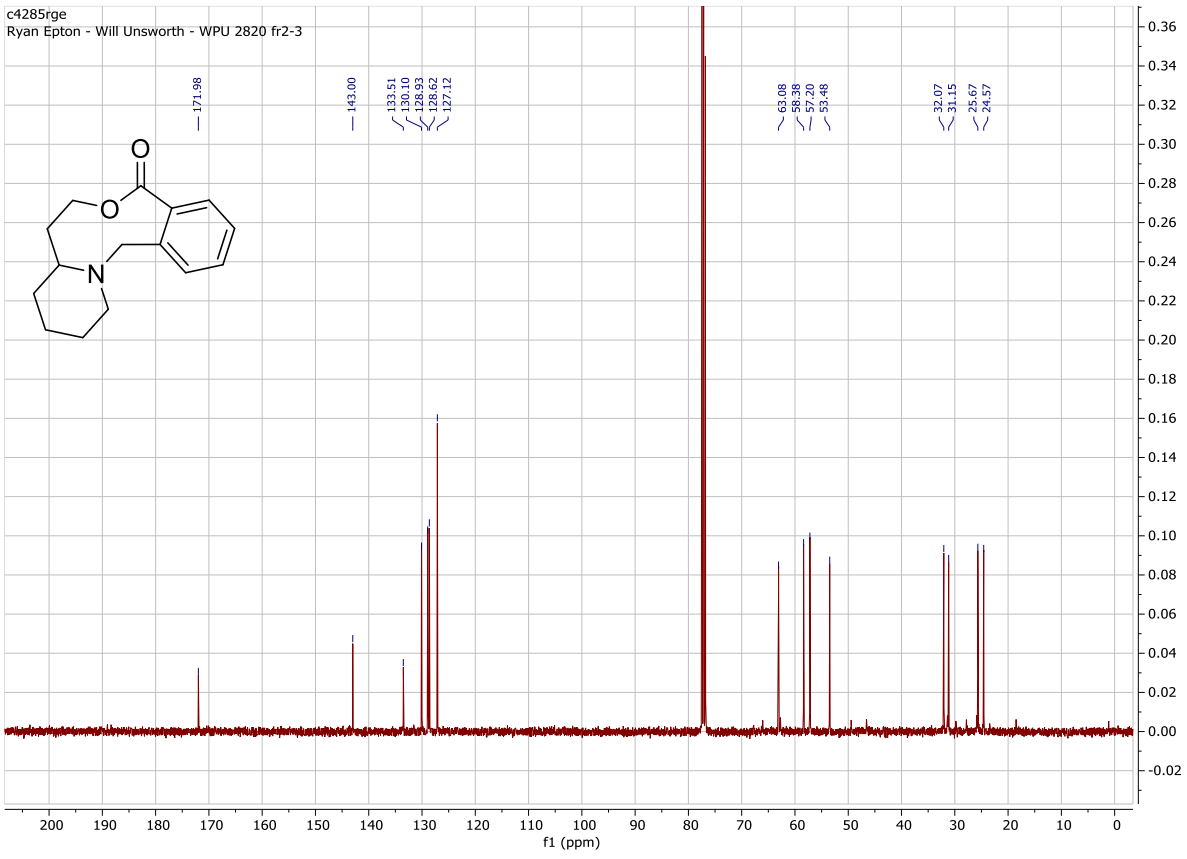

c3881jad
James Donald - WPU 2818 fr 6-14
168.55
140.84
131.71
130.62
130.43
130.23
126.93
62.14
58.80
55.03
52.15
48.38
31.63
27.08
22.43
21.71
N
OH
O
O
f1 (ppm)

8,8a,9,10,11,12-Hexahydro-7*H*-benzo [*g*]pyrido[2,1-*d*] [1,5] oxazonin-5 (14*H*)-one (6-104)

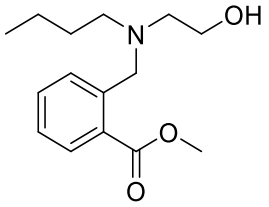


To a stirring solution of methyl 2-((2-(2-hydroxyethyl) piperidin-1-yl) methyl) benzoate (**6-98**) (0.245 g, 0.883 mmol) in methanol (1.94 mL), aqueous lithium hydroxide (0.5 M) was added (1.94 mL, 0.971 mmol) and heated for at 50 °C for 1 hours. The solvent was removed under vacuum using chloroform (5 × 50 mL) to form an azeotropic mixture. The intermediate lithium 2-((2-(2-oxidoethyl) piperidin-1-yl) methyl) benzoate was dissolved in chloroform (8.8 mL) and DIPEA (0.285 mL, 1.63 mmol) was added followed by T3P 50% w/v in ethyl acetate (0.834 g, 1.32 mmol) and stirred at room temperature for 1 hours under argon. The reaction mixture was washed sequentially in dichloromethane (3 × 20 mL) and water (20 mL) and the organic phases combined dried with magnesium sulfate, filtered, concentrated under vacuum and purified via flash column chromatography (3:1 → 1:1 hexane:ethyl acetate) to afford the title compound as a colourless oil (0.154 g, 71%) as a roughly 6:1 mixture of rotamers R_f = 0.5 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 2932, 1727, 1121, 1086, 734; δ_H (400 MHz, $CDCl_3$); 7.55 (1H, d, *J* = 7.3, ArC**H**)$_{\text{both rotamers}}$, 7.33–7.27 (2H, m, 2× ArC**H**)$_{\text{both rotamers}}$, 7.14 (1H, d, *J* = 7.8 Hz, ArC**H**)$_{\text{both rotamers}}$, 5.32–5.25 (1H, m, C**H$_a$**H$_b$O)$_{\text{major rotamer}}$, 5.15–5.09 (1H, m, C**H$_a$**H$_b$O)$_{\text{minor rotamer}}$, 4.65 (1H, d, *J* = 13.7, ArC**H$_a$**H$_b$N)$_{\text{major rotamer}}$, 4.26 (1H, d, *J* = 14.2, ArC**H$_a$**H$_b$N)$_{\text{minor rotamer}}$, 4.09–4.06 (1H, m, ArCH$_a$**H$_b$**N)$_{\text{minor rotamer}}$, 3.99 (1H, d, *J* = 13.7 CH$_a$**H$_b$**O)$_{\text{major rotamer}}$, 3.40 (1H, d, *J* = 14.2, ArCH$_a$**H$_b$**N)$_{\text{minor rotamer}}$, 2.99−2.00 (1H, m, C**H**N)$_{\text{minor rotamer}}$, 2.74 (1H, d, *J* = 13.7, ArCH$_a$**H$_b$**N)$_{\text{major rotamer}}$, [2.70−2.48 (3H, m, C**H**$_2$N, C**H**N)]$_{\text{both rotamers}}$, [16H in total 2.16−1.21 (m) $_{\text{both rotamers}}$]; δ_c (100 MHz, $CDCl_3$); data for the major rotamer only 172.0 (**C**O), 143.0 (Ar**C**), 133.5 (Ar**C**), 130.1 (Ar**C**H), 128.9 (Ar**C**H), 128.6 (Ar**C**H), 127.1 (Ar**C**H), 63.1 (O**C**H$_2$CH$_2$), 58.4 (N**C**H), 57.2 (Ar**C**H$_2$N), 53.5 (**C**H$_2$N), 32.1 (**C**H$_2$), 31.2 (**C**H$_2$), 25.7 (**C**H$_2$), 24.6 (**C**H$_2$); HRMS (ESI): calcd. for $C_{15}H_{20}NO_2$, 246.1494. Found $[MH]^+$, 246.1481 (−5.28 ppm error).

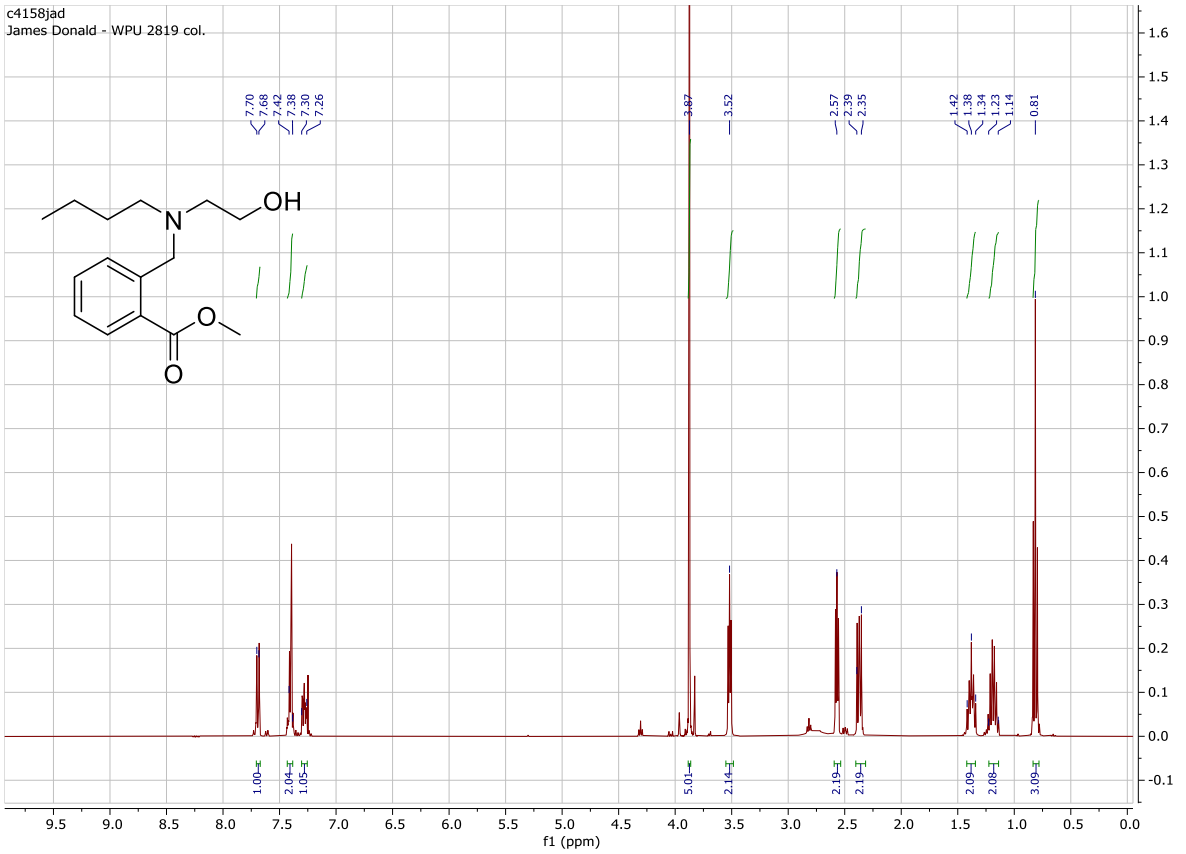

c4285rge
Ryan Epton - Will Unsworth - WPU 2820 fr2-3
7.56
7.54
7.33
7.27
7.18
7.16
5.29
5.14
5.09
4.67
4.64
4.28
4.25
4.09
4.06
4.00
3.98
3.42
3.39
2.99
2.90
2.76
2.73
2.70
2.64
2.57
2.52
2.48
2.16
2.08
1.92
1.85
1.68
1.63
1.46
1.41
1.37
1.30
1.26
1.21
1.12
2.26
1.16
1.00
0.17
1.00
0.17
0.20
0.99
0.16
1.13
3.36
0.22
1.08
2.55
1.38
2.36
2.31
f1 (ppm)


c4285rge
Ryan Epton - Will Unsworth - WPU 2820 fr2-3
171.98
143.00
133.51
130.10
128.93
128.62
127.12
63.08
58.38
57.20
53.48
32.07
31.15
25.67
24.57
f1 (ppm)

Methyl 2-((butyl (2-hydroxyethyl) amino) methyl) benzoate (6-99)



To a stirring solution of potassium carbonate (0.416 g, 3.00 mmol) in acetonitrile (5.00 mL), 2-(butylamino) ethan-1-ol **(6-93)** (0.151 g, 1.30 mmol) was added followed by methyl 2-(bromomethyl) benzoate **(6-1)** (0.229 g, 1.00 mmol). The reaction mixture was heated to reflux at 90 °C for 1 hours before filtering through Celite washing with dichloromethane, concentrating under vacuum and purifying by flash column chromatography (1:2 hexane:ethyl acetate ⟶ ethyl acetate) to afford the title compound as a yellow oil (0.225 g, 85%) R_f = 0.3 (ethyl acetate - streak); ν_{max}/cm^{-1} (thin film) 3443, 2953, 1719, 1267, 1044, 740; δ_H (400 MHz, $CDCl_3$) 7.69 (1H, d, *J* = 7.8 Hz, ArC**H**), 7.44–7.37 (2H, m, 2 × ArC**H**), 7.30–7.26 (1H, m, ArC**H**), 3.87 (5H, s, OC**H**$_2$, OC**H**$_3$), 3.52 (2H, t, *J* = 5.1, C**H**$_2$OH), 2.57 (2H, t, *J* = 5.1, C**H**$_2$N), 2.39–2.35 (2H, m, C**H**$_2$N), 1.42–1.34 (2H, m, C**H**$_2$), 1.24–1.14 (2H, m, C**H**$_2$), 0.81 (3H, t, *J* = 7.3, C**H**$_3$CH$_2$); δ_c (100 MHz, $CDCl_3$) 169.4 (**C**O), 140.4 (Ar**C**), 135.4 (Ar**C**H), 131.3 (Ar**C**), 130.5 (Ar**C**H), 129.9 (Ar**C**H), 127.1 (Ar**C**H), 50.0 (C**H**$_2$OH), 57.1 (Ar**C**H$_2$N), 55.8 (**C**H$_2$N), 54.0 (**C**H$_2$N), 52.3 (O**C**H$_3$), 28.6 (**C**H$_2$), 20.6 (**C**H$_2$), 14.1 (**C**H$_3$); HRMS (ESI) calcd. for $C_{15}H_{24}NO_3$ 266.1756. Found $[MH]^+$ 266.1745 (−4.13 ppm error).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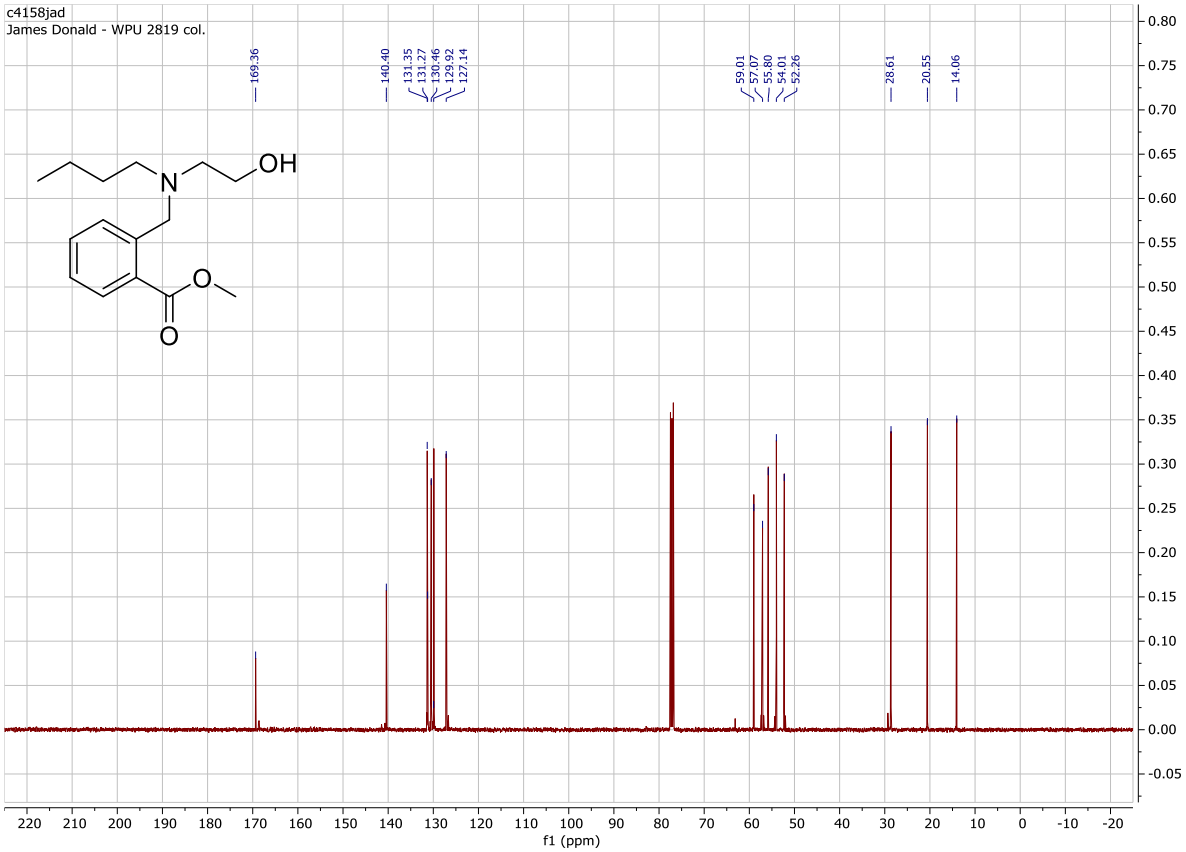
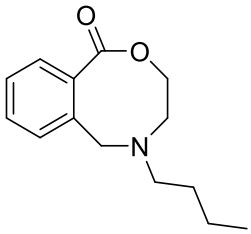
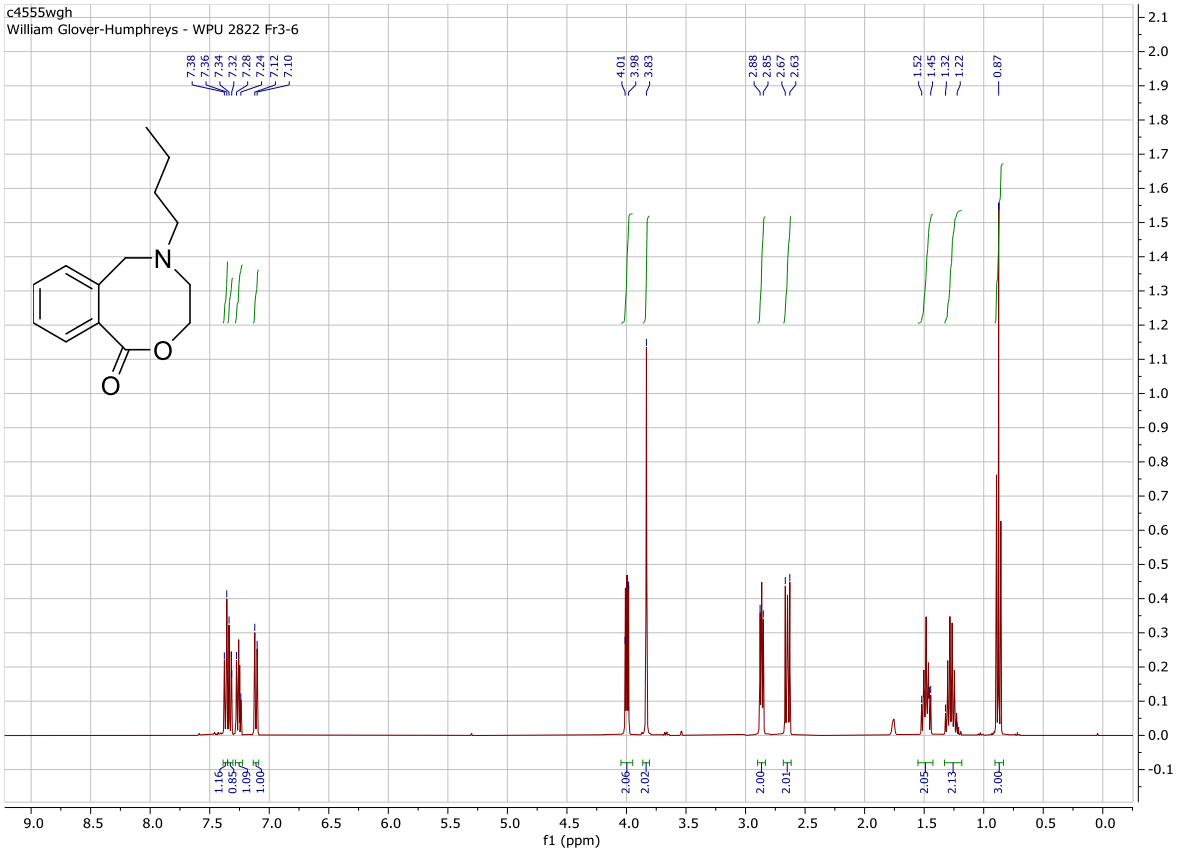
James Donald - WPU 2819 col.
7.70
7.68
7.42
7.38
7.30
7.26
3.87
3.52
2.57
2.39
2.35
1.42
1.38
1.34
1.23
1.14
0.81
OH
N
O
O
1.00
2.04
1.05
5.01
2.14
2.19
2.19
2.09
2.08
3.09
f1 (ppm)

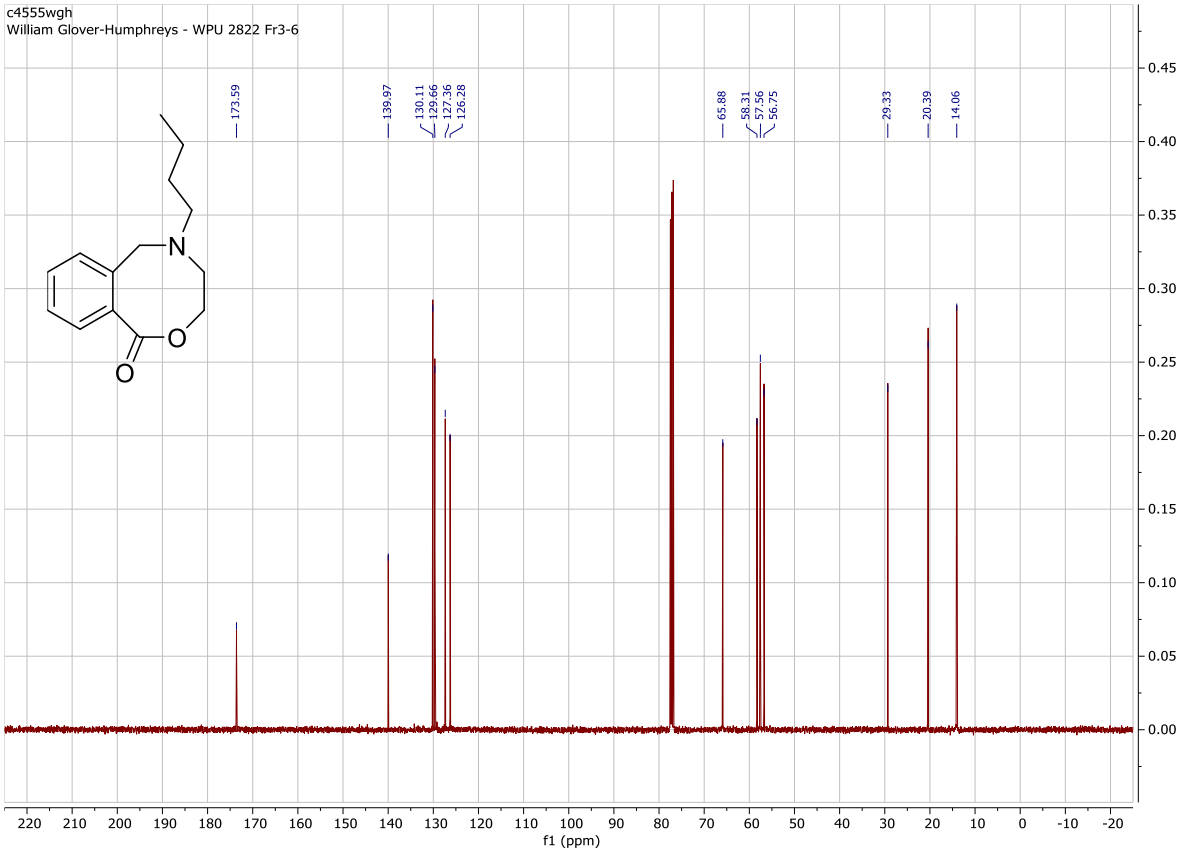

c4158jad
James Donald - WPU 2819 col.
169.36
140.40
131.35
131.27
130.46
129.92
127.14
59.01
57.07
55.80
54.01
52.26
28.61
20.55
14.06
OH
N
O
O
f1 (ppm)

5-Butyl-3,4,5,4-tetrahydro-1*H*-benzo[*f*] [1,4] oxazocin-1-one (6-105)

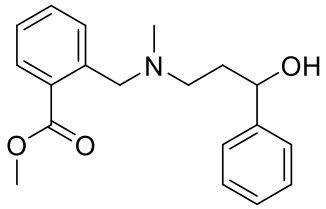


To a stirring solution of methyl 2-((butyl(2-hydroxyethyl) amino) methyl) benzoate **(6-99)** (0.176 g, 0.663 mmol) in methanol (1.46 mL), aqueous lithium hydroxide (0.5 M) was added (1.46 mL, 0.730 mmol) and heated for at 50 °C for 1 hours. The solvent was removed under vacuum using chloroform (5 × 50 mL) to form an azeotropic mixture. The intermediate lithium 2-((butyl(2-oxidoethyl) amino) methyl) benzoate was dissolved in chloroform (6.60 mL) and DIPEA (0.214 mL, 1.23 mmol) was added followed by T3P 50% w/v in ethyl acetate (0.633 g, 0.995 mmol) and stirred at room temperature for 1 hours under argon. The reaction mixture was washed sequentially in dichloromethane (3 × 20 mL) and water (20 mL) and the organic phases combined dried with magnesium sulfate, filtered, concentrated under vacuum and purified via flash column chromatography (3:1 → 1:1 hexane:ethyl acetate) to afford the title compound as a colourless oil (0.097 g, 63%); ν_{max}/cm^{-1} (thin film) 2956, 1714, 1276, 1112, 736; δ_H (400 MHz, $CDCl_3$) 7.38−7.36 (1H, m, ArC**H**), 7.34−7.32 (1H, m, ArC**H**), 7.28−7.24 (1H, m, ArC**H**), 7.11 (1H, d, *J* = 7.8 Hz, ArC**H**) 4.00 (2H, t, *J* = 5.5, OC**H**$_2$CH$_2$), 3.83 (2H, s, ArC**H**$_2$N), 2.86 (2H, t, *J* = 5.5, C**H**$_2$N), 2.64 (2H, t, *J* = 7.5, C**H**$_2$N), 1.52−1.45 (2H, m, C**H**$_2$), 1.32−1.22 (2H, m, C**H**$_2$), 0.87 (3H, t, *J* = 7.3, CH$_2$C**H**$_3$); δ_c (100 MHz, $CDCl_3$) 173.6 (**C**O), 139.8 (Ar**C**), 130.1 (Ar**C** & Ar**C**H), 129.7 (Ar**C**H), 127.4 (Ar**C**H), 126.3 (Ar**C**H), 65.9 (**C**H$_2$O), 58.3 (Ar**C**H$_2$N), 57.6 (**C**H$_2$N), 56.8 (**C**H$_2$N), 29.3 (**C**H$_2$), 20.4 (**C**H$_2$), 14.1 (**C**H$_3$); HRMS (ESI) calcd. for $C_{14}H_{20}NO_2$ 234.1494. Found $[MH]^+$ 234.1487 (−2.99 ppm error).

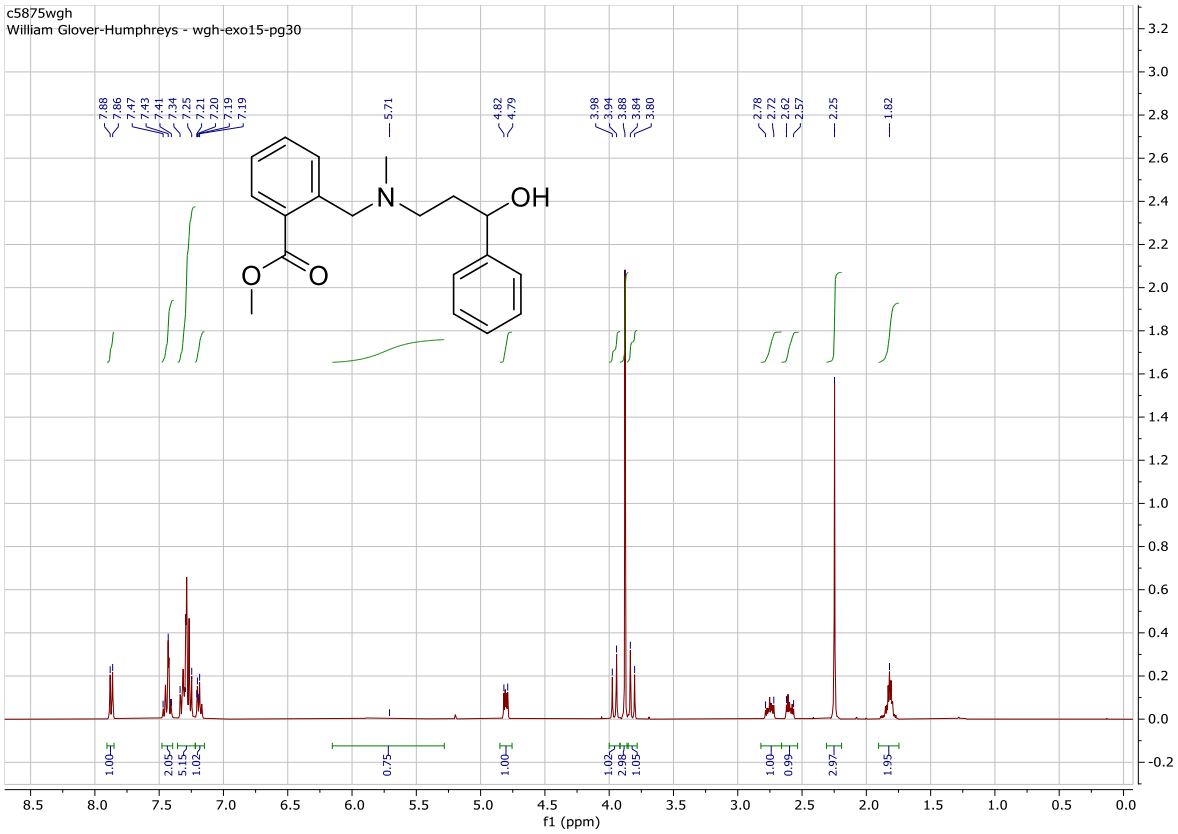

c4555wgh
William Glover-Humphreys - WPU 2822 Fr3-6
7.38
7.36
7.34
7.32
7.28
7.24
7.12
7.10
4.01
3.98
3.83
2.88
2.85
2.67
2.63
1.52
1.45
1.32
1.22
0.87
1.16
0.85
1.09
1.00
2.06
2.02
2.00
2.01
2.05
2.13
3.00
N
O
O
f1 (ppm)

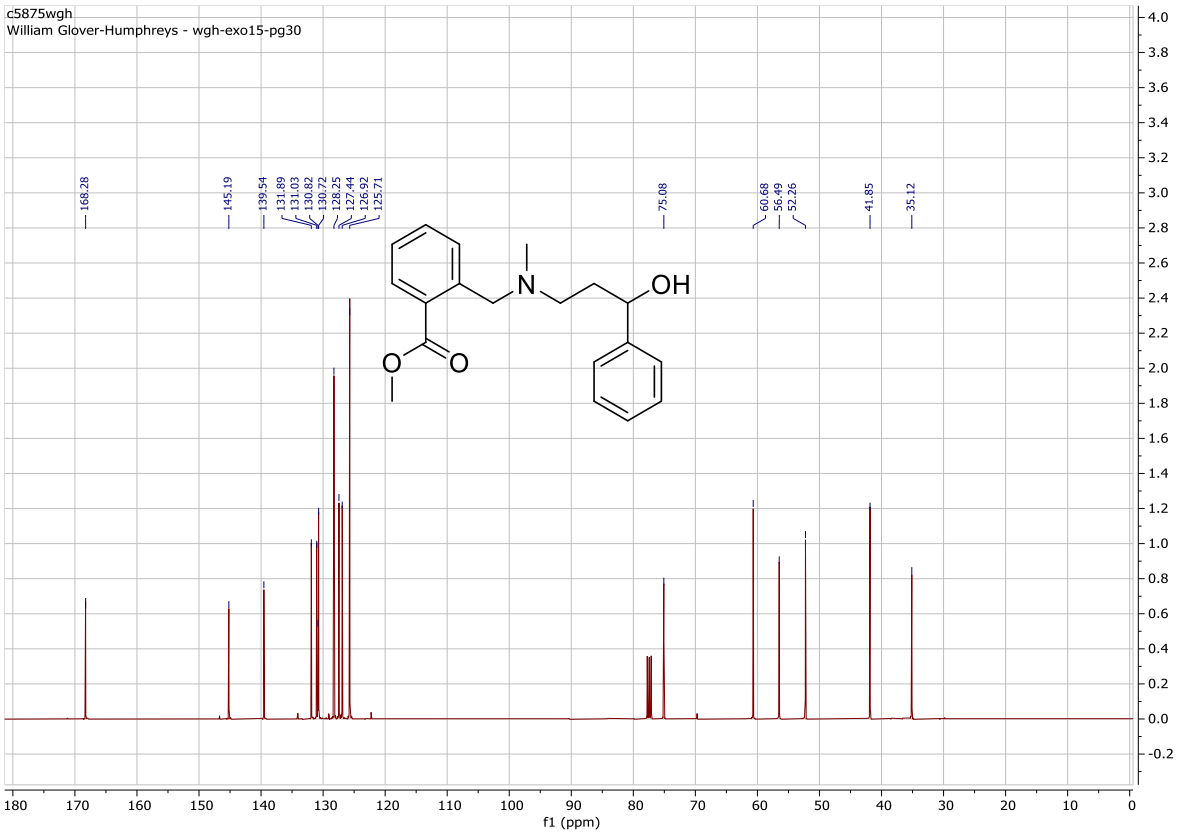

c4555wgh
William Glover-Humphreys - WPU 2822 Fr3-6
173.59
139.97
130.11
129.66
127.36
126.28
65.88
58.31
57.56
56.75
29.33
20.39
14.06
N
O
O
f1 (ppm)

Methyl 2-(((3-hydroxy-3-phenylpropyl) (methyl) amino) methyl) benzoate (6-94)

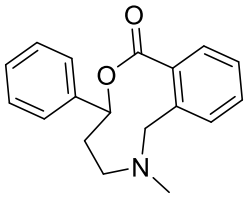


To a stirring solution of potassium carbonate (0.415 g, 3.00 mmol) in acetonitrile (5.00 mL), 3-(methylamino)-1-phenylpropan-1-ol **(6-94)** (0.165 g, 1.00 mmol) was added followed by methyl 2-(bromomethyl) benzoate **(6-1)** (0.229 g, 1.00 mmol). The reaction mixture was heated to reflux at 90 °C for 3 hours under argon before filtering through Celite washing with dichloromethane, concentrating under vacuum and purifying by flash column chromatography (10:9:1 ethyl acetate:hexane:triethylamine) to afford the title compound as a clear oil (0.244 g, 78%) R_f = 0.54 (10:9:1 ethyl acetate:hexane:triethylamine); ν_{max}/cm^{-1} (thin film) 3028, 2950, 2842, 2245, 1720, 1451, 1269, 1083, 909, 730; δ_H (400 MHz, $CDCl_3$) 7.87 (1H, dd, *J* = 7.8 Hz, 1.2 Hz, Ar**H**), 7.47−7.40 (2H, m, Ar**H**), 7.33−7.24 (5H, m, Ar**H**), 7.19 (1H, tt, *J* = 6.1 Hz, 1.70 Hz , Ar**H**), 5.74 (1H, bs, O**H**), 4.82−4.79 (1H, m, C**H**OH), 3.96 (1H, d, *J* = 13.2 Hz, ArC$\mathbf{H}_a$$H_b$N), 3.88 (3H, s, NC$\mathbf{H}_3$), 3.82 (1H, d, *J* = 13.2 Hz, ArC$H_a$$\mathbf{H}_b$N), 2.78−2.71 (1H, m, NC$\mathbf{H}_a$$H_b$), 2.63−2.56 (1H, m, NC$H_a$$\mathbf{H}_b$), 2.25 (3H, s, NC$\mathbf{H}_3$), 1.89−1.77 (2H, m, CH_2C$\mathbf{H}_2$CH); δ_c (100 MHz, $CDCl_3$) 168.3 (**C**O), 145.2 (Ar**C**), 139.5 (Ar**C**), 131.9 (Ar**C**H), 131.0 (Ar**C**H), 130.8 (Ar**C**), 130.7 (Ar**C**H), 128.3 (Ar**C**H), 127.4 (Ar**C**H), 126.9 (Ar**C**H), 125.7 (Ar**C**H), 75.1 (**C**HOH), 60.7 (Ar**C**H_2N), 56.5 (N**C**$H_2$$CH_2$), 52.3 (COO**C**$H_3$), 41.9 (N**C**$H_3$), 35.1 ($CH_2$**C**$H_2$CH); HRMS (ESI) calcd. for $C_{19}H_{24}NO_3$ 314.1756. Found $[MH]^+$, 314.1751 (−2.99 ppm error).

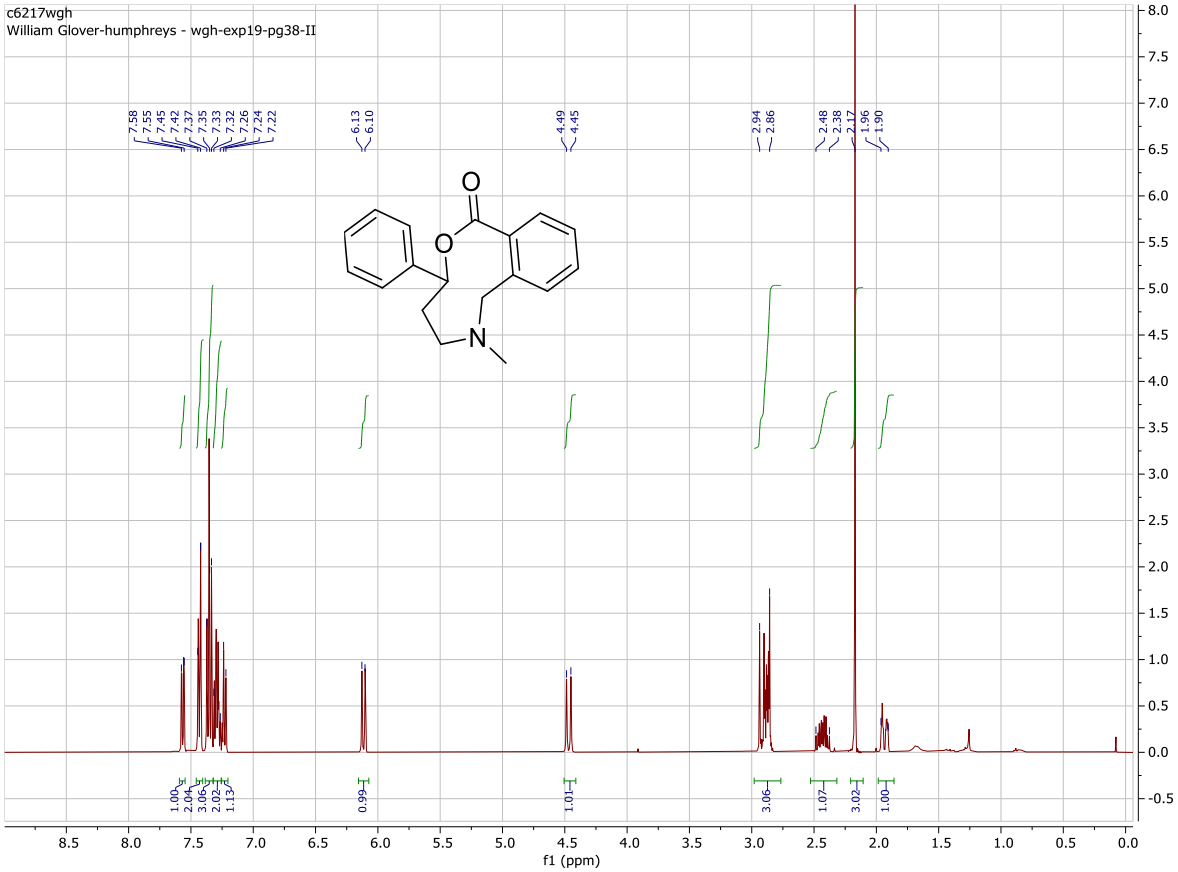

c5875wgh
William Glover-Humphreys - wgh-exo15-pg30
7.88
7.86
7.47
7.43
7.41
7.34
7.25
7.21
7.20
7.19
7.19
5.71
4.82
4.79
3.98
3.94
3.88
3.84
3.80
2.78
2.72
2.62
2.57
2.25
1.82
N
OH
O
O
1.00
2.05
5.15
1.02
0.75
1.00
1.02
2.98
1.05
1.00
0.99
2.97
1.95
f1 (ppm)

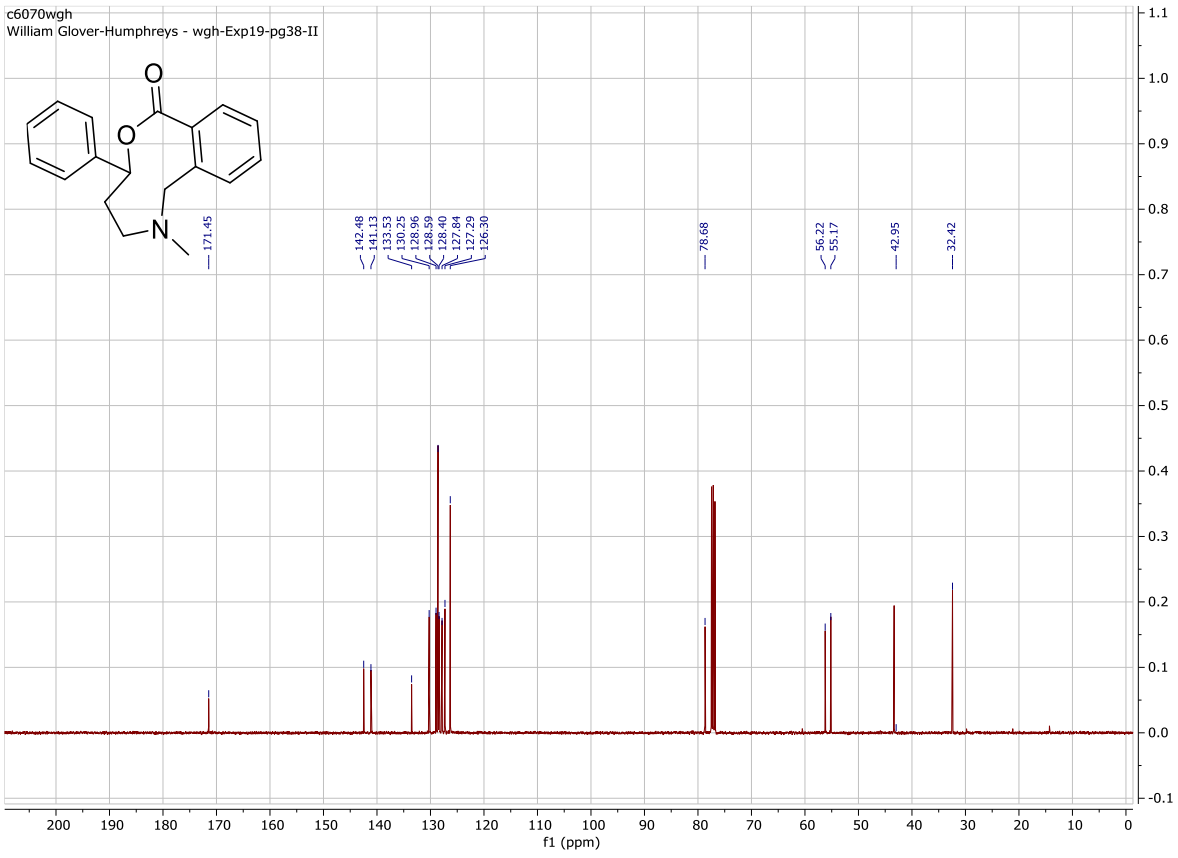

c5875wgh
William Glover-Humphreys - wgh-exo15-pg30
168.28
145.19
139.54
131.89
131.03
130.82
130.72
128.25
127.44
126.92
125.71
75.08
60.68
56.49
52.26
41.85
35.12
N
OH
O
O
f1 (ppm)

4-Methyl-3-phenyl-4,5,6,7-tetrahydrobenzo[*g*] [1,5] oxazonin-1(3*H*)-one (6-106)

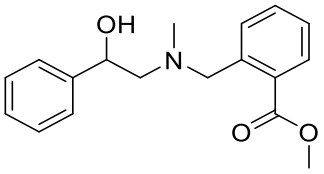


To a stirring solution of methyl 2-(((3-hydroxy-3-phenylpropyl) (methyl)amino) methyl) benzoate **(6-100)** (0.088 g, 0.280 mmol) in tetrahydrofuran (0.70 mL), aqueous lithium hydroxide (0.5 M) was added (0.670 mL, 0.336 mmol) and heated for at 50 °C for 3 hours. The solvent was removed under vacuum using chloroform (5 × 50 mL) to form an azeotropic mixture. The intermediate lithium 2-((benzyl(4-oxidobutyl) amino) methyl) benzoate was dissolved in chloroform (2.8 mL) and DIPEA (0.067 g, 0.09 mL, 0.518 mmol) was added followed by T3P 50% w/v in ethyl acetate (0.267 g, 0.420 mmol) and stirred at room temperature for 24 hours under argon. The reaction mixture was washed sequentially in dichloromethane (2 × 100 mL) and brine (50 mL) and the organic phases combined dried with sodium sulfate, filtered, concentrated under vacuum and purified via flash column chromatography (15:4:1 hexane:ethyl acetate:triethylamine) to afford the title compound (0.034 g, 43%) R_f = 0.52 (15:4:1 hexane:ethyl acetate:triethylamine); ν_{max}/cm^{-1} (thin film) 3030, 2941, 2844, 2794, 1718, 1449, 1271, 1239, 1112, 1019, 841, 733; δ_H (400 MHz, $CDCl_3$) 7.65 (1H, d, *J* = 7.19 Hz, ArC**H**), 7.43 (2H, d, *J* = 7.73 Hz, ArC**H**), 7.38−7.33 (3H, m, ArC**H**), 7.31−7.26 (2H, m, ArC**H**), 7.23 (1H, d, *J* = 7.36 Hz, ArC**H**), 6.12 (1H, d, *J* = 10.3 Hz, ArC**H**O), 4.47 (1H, d, *J* = 13.8 Hz, ArC$\mathbf{H}_a$$H_b$N), 2.92 (1H, d, *J* = 13.8 Hz, ArC$H_a$$\mathbf{H}_b$N), 2.90−2.85 (2H, m, C$\mathbf{H}_2$N), 2.49−2.37 (1H, m, CH_2C$\mathbf{H}_a$$H_b$CH), 2.17 (3H, s, C$\mathbf{H}_3$N), 1.96−1.90 (1H, m, $CH_2CH_a\mathbf{H}_b$CH); δ_c (100 MHz, $CDCl_3$) 171.5 (**C**O), 142.5 (Ar**C**), 141.1 (Ar**C**), 133.5 (Ar**C**), 130.3 (Ar**C**H), 129.0 (Ar**C**H), 128.6 (Ar**C**H), 128.4 (Ar**C**H), 127.8 (Ar**C**H), 127.3 (Ar**C**H), 126.3 (Ar**C**H), 78.7 (**C**HO), 56.2 (Ar**C**H_2N), 55.2 (**C**H_2N), 43.0 (**C**H_3N), 32.4 (CH_2**C**H_2CH); HRMS (ESI) calcd. for $C_{18}H_{20}NO_2$ 282.1498. Found $[MH]^+$ 282.1487 (−3.90 ppm error).

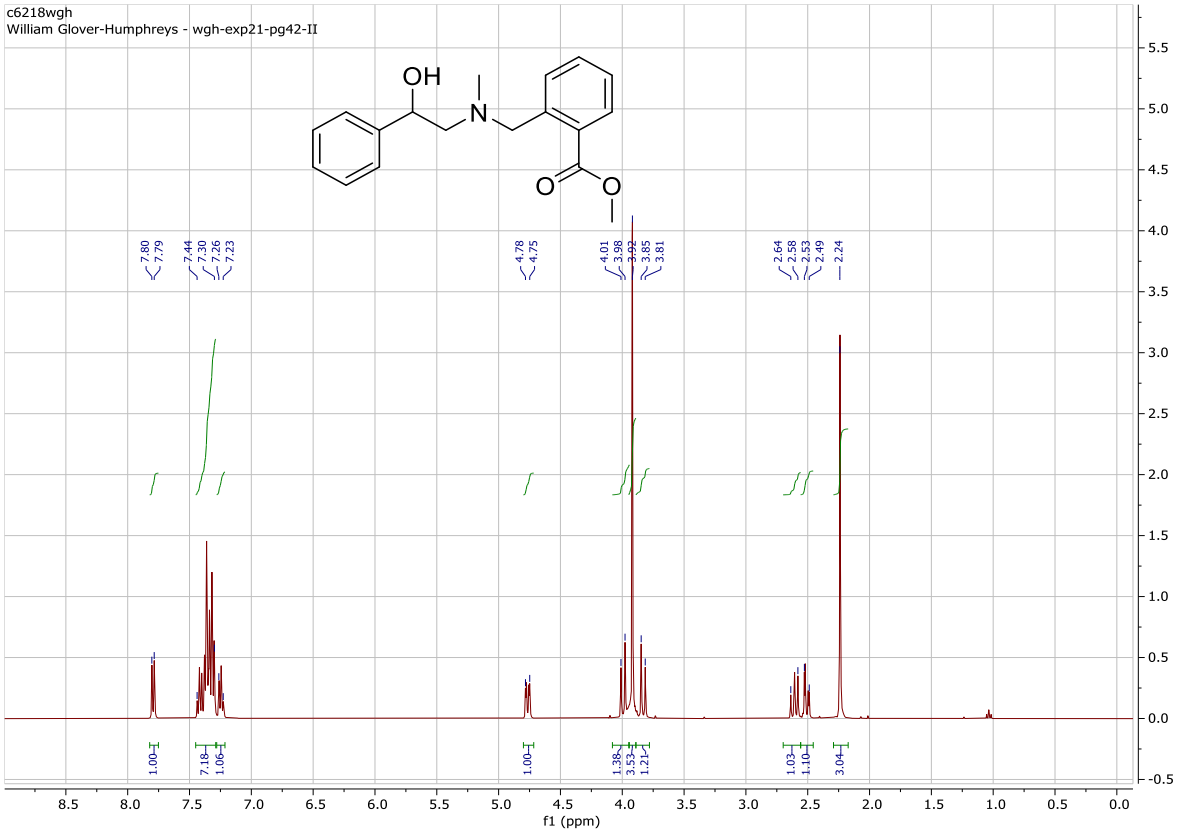

c6217wgh
William Glover-humphreys - wgh-exp19-pg38-II
7.58
7.55
7.45
7.42
7.37
7.35
7.33
7.32
7.26
7.24
7.22
6.13
6.10
4.49
4.45
2.94
2.86
2.48
2.38
2.17
1.96
1.90
O
O
N
1.00
2.04
3.06
2.02
1.13
0.99
1.01
3.06
1.07
3.02
1.00
f1 (ppm)

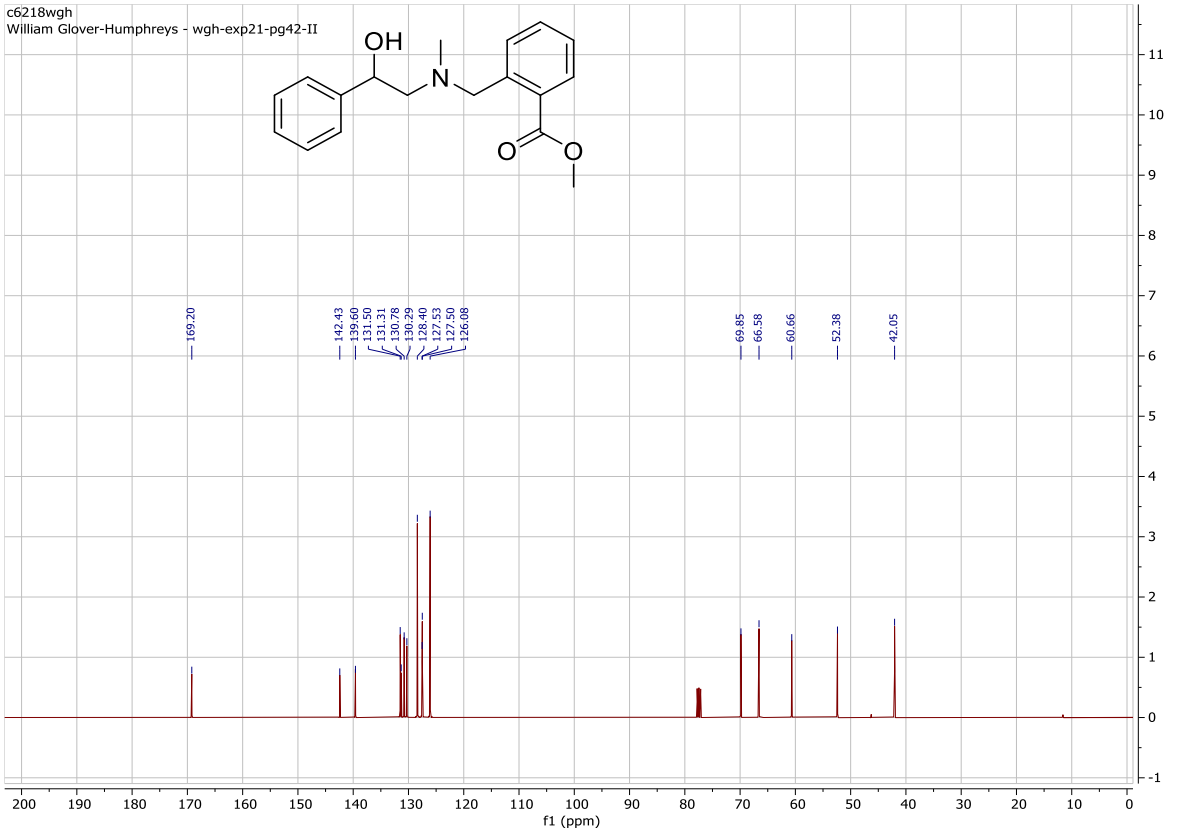

c6070wgh
William Glover-Humphreys - wgh-Exp19-pg38-II
O
O
N
171.45
142.48
141.13
133.53
130.25
128.96
128.59
128.40
127.84
127.29
126.30
78.68
56.22
55.17
42.95
32.42
f1 (ppm)

Methyl 2-(((2-hydroxy-2-phenylethyl) (methyl) amino) methyl) benzoate (6-101)

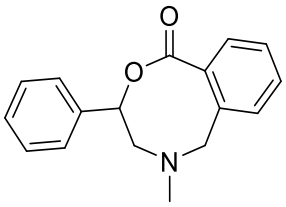


To a stirring solution of potassium carbonate (0.415 g, 3.00 mmol) in acetonitrile (5.00 mL), *N*-methylphenylethanolamine **(6-95)** (0.151 g, 1.00 mmol) was added followed by methyl 2-(bromomethyl) benzoate **(6-1)** (0.229 g, 1.00 mmol). The reaction mixture was heated to reflux at 90 °C for 3 hours under argon before filtering through Celite washing with dichloromethane, concentrating under vacuum and purifying by flash column chromatography (15:4:1 hexane:ethyl acetate:triethylamine) to afford the title compound as a clear oil (0.299 g, 99%) R_f = 0.34 (14:5:1 hexane:ethyl acetate:triethylamine); ν_{max}/cm^{-1} (thin film) 3494, 3029, 2951, 2843, 1718, 1443, 1249, 1269, 1082, 1017, 869,743; δ_H (400 MHz, $CDCl_3$) 7.79 (1H, d, *J* = 7.6 Hz, Ar**H**), 7.44−7.30 (7H, m, Ar**H**), 7.27−7.22 (1H, m, Ar**H**), 4.76 (1H, dd, *J* = 10.5 Hz, 3.1 Hz, ArC**H**OH), 4.00 (1H, d, *J* = 13.1 Hz, NC**H**$_a$H$_b$Ar), 3.91 (3H, s, C**H**$_3$O), 3.83 (1H, d, *J* = 13.1 Hz, NCH$_a$**H**$_b$Ar), 2.64−2.58 (1H, m, CHC**H**$_a$H$_b$N), 2.53−2.48 (1H, m, CHCH$_a$**H**$_b$N), 2.24 (3H, s, C**H**$_3$N);δ_c (100 MHz, $CDCl_3$) 169.2 (**C**O), 142.4 (Ar**C**), 139.6 (Ar**C**), 131.5 (Ar**C**H), 131.3 (Ar**C**), 130.8 (Ar**C**H), 130.3 (Ar**C**H), 128.4 (Ar**C**H), 127.5 (2× Ar**C**H), 126.1 (Ar**C**H), 69.9 (Ar**C**HOH), 66.6 (CH**C**H$_2$N), 60.7 (N**C**H$_2$Ar), 52.4 (**C**H$_3$O), 42.1 (**C**H$_3$N); HRMS (ESI) calcd. for $C_{18}H_{22}NO_3$ 300.1600. Found $[MH]^+$, 300.1587 (−4.33 ppm error).

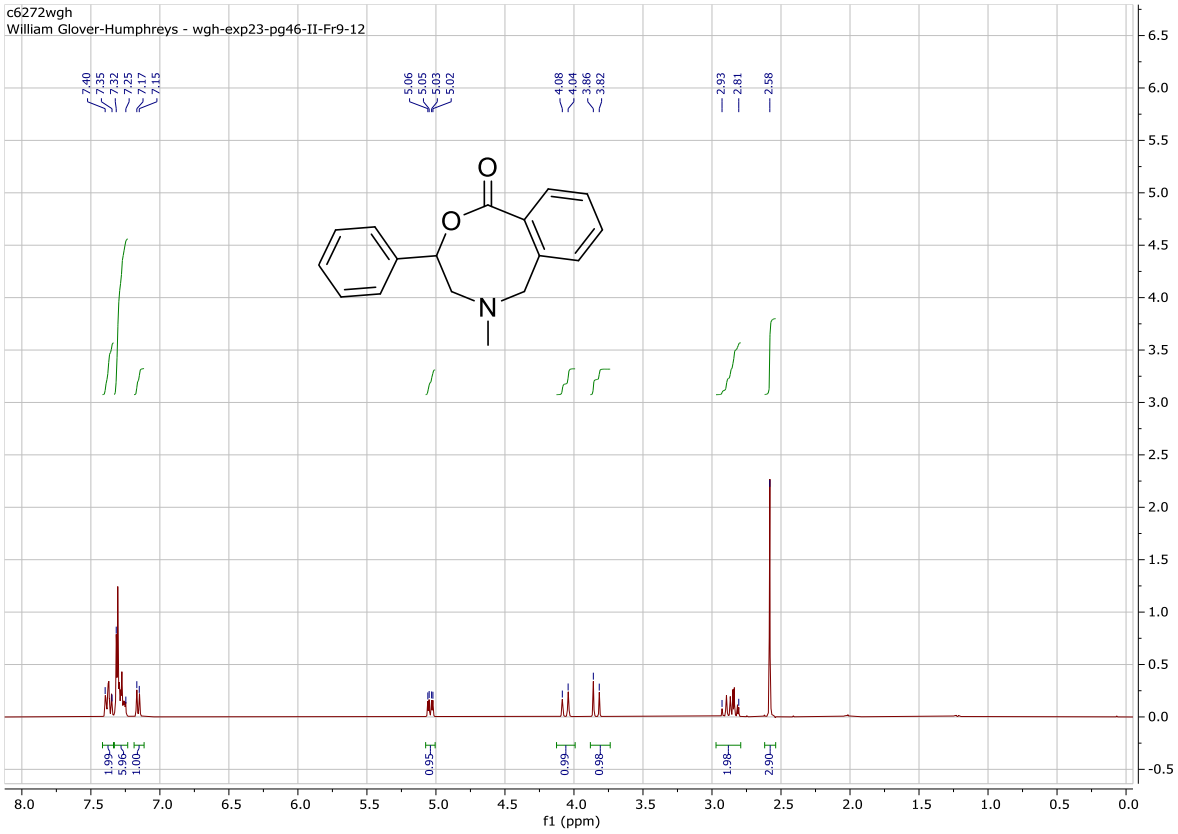

c6218wgh
William Glover-Humphreys - wgh-exp21-pg42-II
OH
N
O
O
7.80
7.79
7.44
7.30
7.26
7.23
4.78
4.75
4.01
3.98
3.92
3.85
3.81
2.64
2.58
2.53
2.49
2.24
1.00
7.18
1.06
1.00
1.38
3.53
1.21
1.03
1.10
3.04
f1 (ppm)

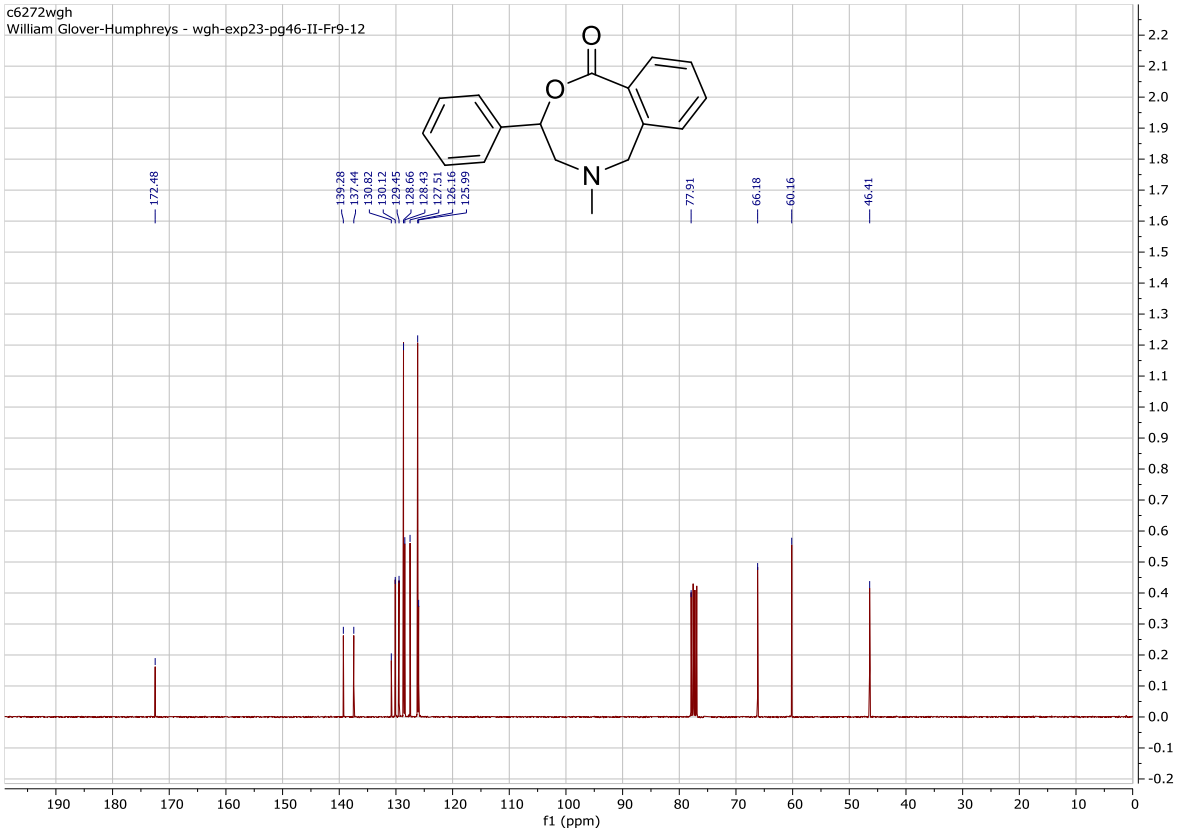

c6218wgh
William Glover-Humphreys - wgh-exp21-pg42-II
OH
N
O
O
169.20
142.43
139.60
131.50
131.31
130.78
130.29
128.40
127.53
127.50
126.08
69.85
66.58
60.66
52.38
42.05
f1 (ppm)

5-Methyl-3-phenyl-3,4,5,4-tetrahydro-1H-benzo[*f*] [1,4] oxazocin-1-one (6-107)

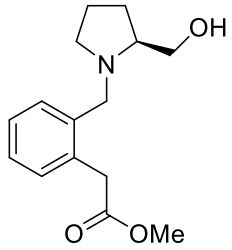


To a stirring solution of methyl 2-(((2-hydroxy-2-phenyl ethyl) (methyl) amino) methyl) benzoate **(6-101)** (0.299 g, 1.00 mmol) in tetrahydrofuran (2.20 mL), aqueous lithium hydroxide (0.5 M) (2.2 mL, 1.1 mmol) was added and heated for at 50 °C for 3 hours. The solvent was removed under vacuum using dichloromethane (5 × 50 mL) to form an azeotropic mixture. The intermediate lithium 2-((methyl(2-oxido-2-phenylethyl) amino) methyl) benzoate was dissolved in chloroform (10 mL) and DIPEA (0.239 g, 0.322 mL, 1.85 mmol) was added followed by T3P 50% w/v in ethyl acetate (0.955 g, 1.50 mmol) and stirred at room temperature for 2 hours under argon. The reaction mixture was washed sequentially in dichloromethane (2 × 100 mL) and brine (50 mL) and the organic phases combined dried with sodium sulfate, filtered, concentrated under vacuum and purified via flash column chromatography (15:4:1 hexane:ethyl acetate:triethylamine) to afford the title compound (0.0904 g, 34%) R_f = 0.39 (15:4:1 hexane:ethyl acetate:triethylamine); ν_{max}/cm^{-1} (thin film) 3063, 2948, 2848, 2808, 1714, 1455, 1267, 1230, 1114, 1078, 1031, 920, 776, 745, 727; δ_H (400 MHz, $CDCl_3$) 7.40−7.34 (2H, m, Ar**H**), 7.32−7.24 (6H, m, Ar**H**), 7.16 (1H, d, *J* = 7.7 Hz, Ar**H**), 5.04 (1H, dd, *J* = 11.0 Hz, 3.7 Hz, C**H**), 4.06 (1H, d, *J* = 17.1 Hz, NC**H**$_a$CH$_b$Ar), 3.84 (1H, d, *J* = 17.1 Hz, NCH$_a$C**H**$_b$Ar), 2.93−2.80 (2H, m, NC**H**$_2$CH), 2.58 (3H, s, C**H**$_3$N); δ_c (100 MHz, $CDCl_3$) 172.5 (**C**O), 139.3 (Ar**C**), 137.4 (Ar**C**), 130.8 (Ar**C**), 130.1 (Ar**C**H), 129.5 (Ar**C**H), 128.7 (Ar**C**H), 128.4 (Ar**C**H), 127.5 (Ar**C**H), 126.2 (Ar**C**H), 126.0 (Ar**C**H), 77.9(**C**H), 66.2 (N**C**H$_2$CH), 60.2 (N**C**H$_2$Ar), 46.4 (**C**H$_3$N); HRMS (ESI) calcd. for $C_{17}H_{18}NO_2$ 268.1338. Found $[MH]^+$ 268.1332 (−2.24 ppm error).

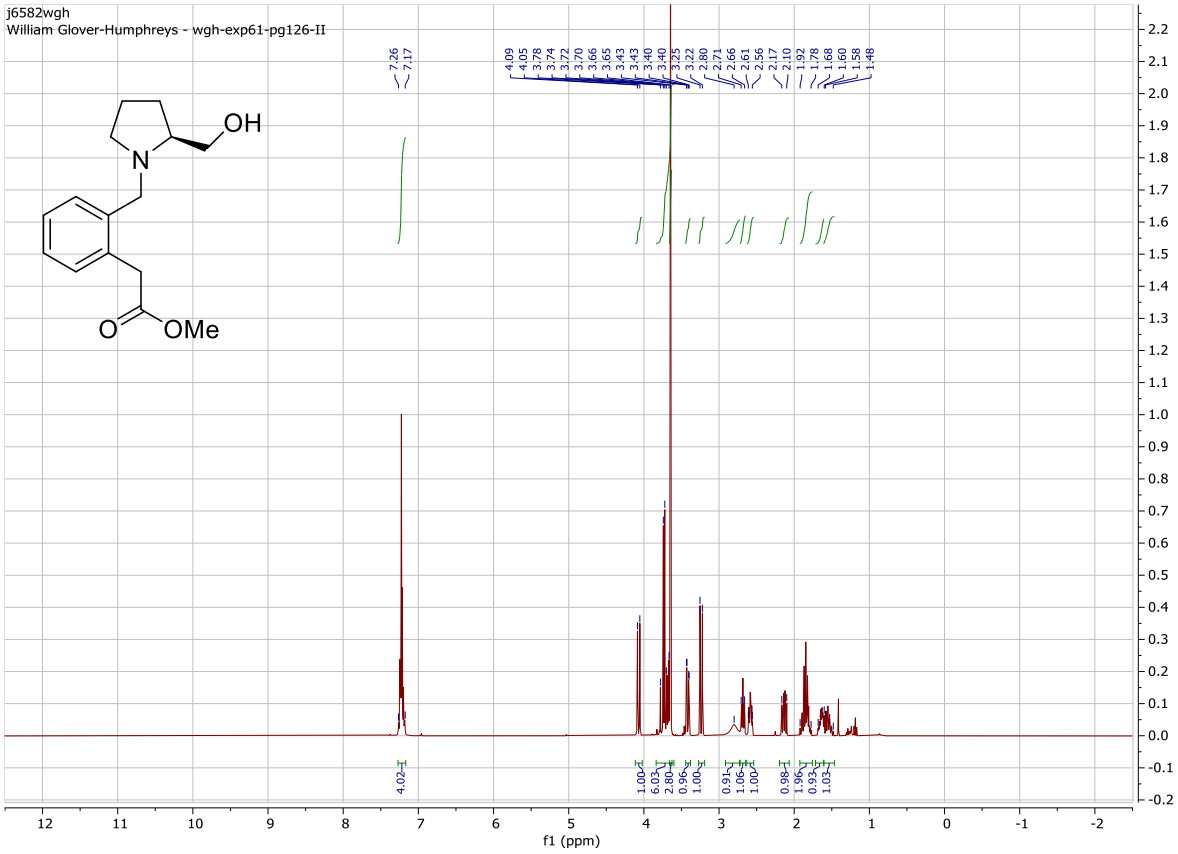

c6272wgh
William Glover-Humphreys - wgh-exp23-pg46-II-Fr9-12
7.40
7.35
7.32
7.25
7.17
7.15
5.06
5.05
5.03
5.02
4.08
4.04
3.86
3.82
2.93
2.81
2.58
O
O
N
1.99
5.96
1.00
0.95
0.99
0.98
1.98
2.90
f1 (ppm)

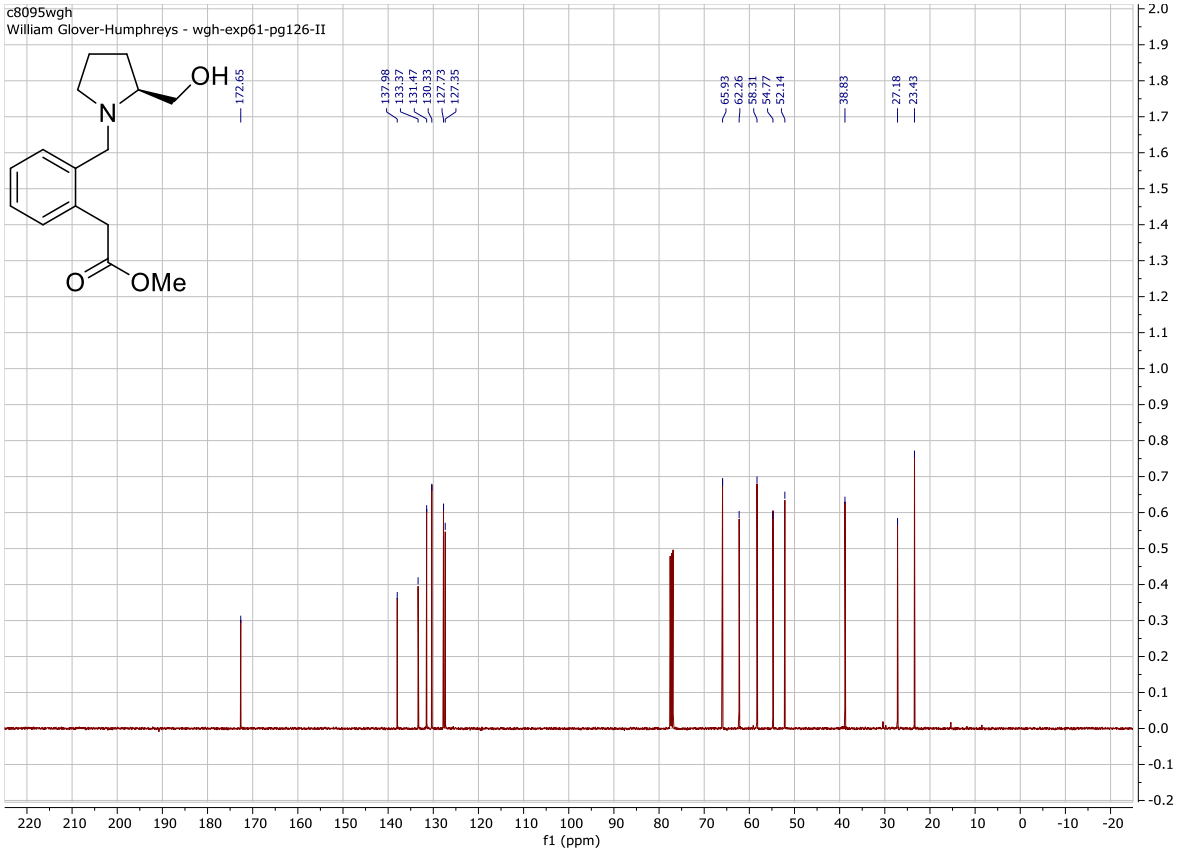

c6272wgh
William Glover-Humphreys - wgh-exp23-pg46-II-Fr9-12
172.48
139.28
137.44
130.82
130.12
129.45
128.66
128.43
127.51
126.16
125.99
77.91
66.18
60.16
46.41
O
O
N
f1 (ppm)

Methyl (*S*)-2-(2-((2-(hydroxymethyl) pyrrolidin-1-yl) methyl) phenyl) acetate (6-110)

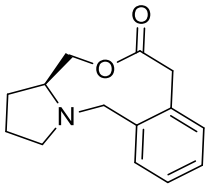


To a stirring solution of potassium carbonate (0.207 g, 1.50 mmol) in acetonitrile (5.00 mL), (*S*)-pyrrolidin-2-yl methanol (**6-86**) (0.101 g, 1.00 mmol) was added followed by methyl 2-(2-(bromomethyl) phenyl) acetate (**6-109**) (0.243 g, 1.00 mmol). The reaction mixture was heated to reflux at 90 °C for 3 hours under argon before filtering through Celite washing with dichloromethane, concentrating under vacuum and purifying by flash column chromatography (15:4:1 hexane:ethyl acetate:triethylamine) to afford the title compound an oil (0.114 g, 43%) R_f = 0.3 (15:4:1 hexane:ethyl acetate:triethylamine); ν_{max}/cm^{-1} (thin film) 365, 2953, 2799, 1735, 1441,1336, 1266, 1159, 1020, 754; δ_H (400 MHz, $CDCl_3$) 7.26−7.17 (4H, m, 4 × Ar**H**), 4.07 (1H, d, *J* = 12.7 Hz, ArC**H**$_a$H$_b$N), 3.76 (1H, d, *J* = 15.6 Hz, ArC**H**$_a$H$_b$COOMe), 3.70 (1H, d, *J* = 15.6 Hz, ArCH$_a$**H**$_b$COOMe), 3.68 (1H, dd, *J* = 11.4 Hz, 3.0 Hz, CHC**H**$_a$H$_b$OH), 3.65 (3H, s, O**C**H$_3$), 3.42 (1H, dd, *J* = 11.4 Hz, 3.0 Hz, CHCH$_a$**H**$_b$OH), 3.24 (1H, d, *J* = 12.7 Hz, ArCH$_a$**H**$_b$N), 2.80 (1H, bs, O**H**), 2.71−2.66 (1H, m, C**H**$_a$H$_b$N), 2.61−2.56 (1H, m, C**H**N), 2.71−2.10 (1H, m, CH$_a$**H**$_b$N), 1.92−1.78 (1H, m, C**H**$_2$), 1.68−1.60 (1H, m, C**H**$_a$H$_b$), 1.58−1.48 (1H, m, CH$_a$**H**$_b$); δ_c (100 MHz, $CDCl_3$) 172.7 (**C**O), 138.0 (Ar**C**), 133.4 (Ar**C**), 131.5 (Ar**C**H), 130.3 (Ar**C**H), 127.7 (Ar**C**H), 127.4 (Ar**C**H), 65.9 (**C**H), 62.3 (CH**C**H$_2$OH), 58.3 (Ar**C**H$_2$N), 54.8 (**C**H$_2$N), 52.1 (O**C**H$_3$), 38.8 (Ar**C**H$_2$COOMe), 27.2 (**C**H$_2$), 23.4 (**C**H$_2$); HRMS (ESI) calcd. for $C_{15}H_{22}NO_3$ 264.1600. Found $[MH]^+$ 264.1597 (−1.14 ppm error).

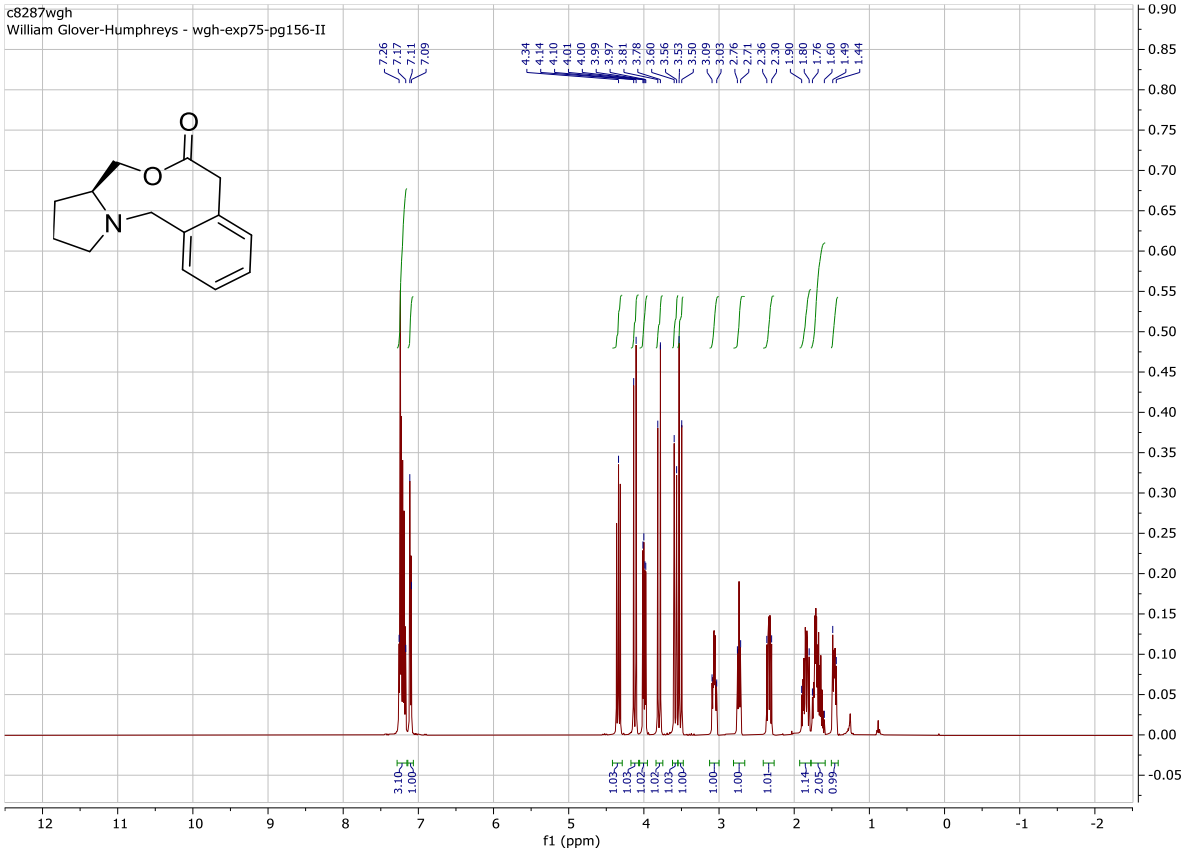

j6582wgh
William Glover-Humphreys - wgh-exp61-pg126-II
OH
N
O
OMe
7.26
7.17
4.09
4.05
3.78
3.74
3.72
3.70
3.66
3.65
3.43
3.43
3.40
3.40
3.25
3.22
2.80
2.71
2.66
2.61
2.56
2.17
2.10
1.92
1.78
1.68
1.60
1.58
1.48
4.02
1.00
6.03
2.80
0.96
1.00
0.91
1.06
1.00
0.98
1.96
0.93
1.03
f1 (ppm)

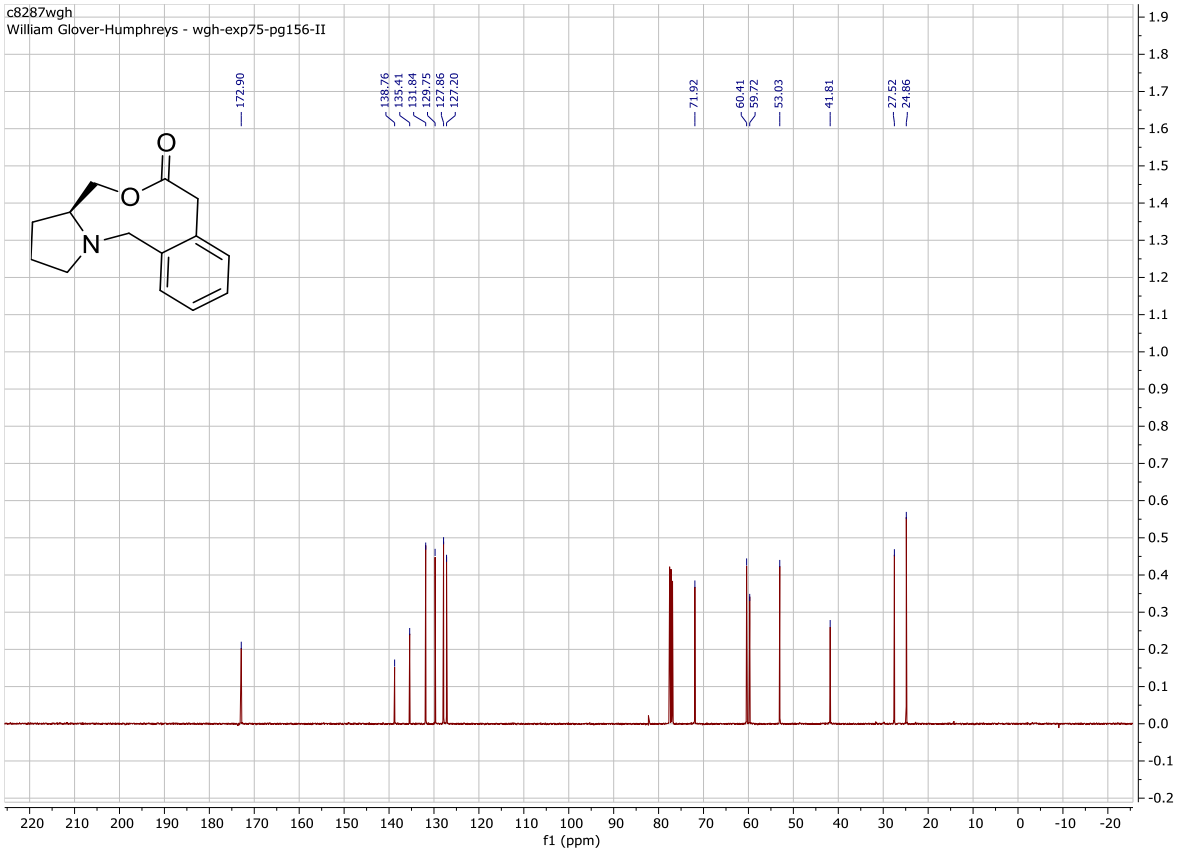

c8095wgh
William Glover-Humphreys - wgh-exp61-pg126-II
OH
N
O
OMe
172.65
137.98
133.37
131.47
130.33
127.73
127.35
65.93
62.26
58.31
54.77
52.14
38.83
27.18
23.43
f1 (ppm)

(*S*)-2,3,3a,4,7,12-Hexahydro-1*H*,6*H*-benzo[*f*]pyrrole [2,1-*c*] [1,4] oxazonin-4-one (6-113)

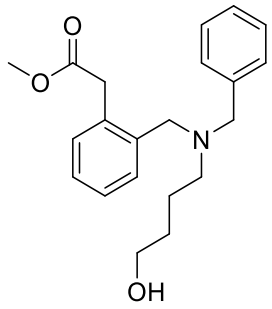


To a stirring solution of methyl (*S*)-2-(2-((2-(hydroxymethyl) pyrrolidin-1-yl) methyl) phenyl) acetate **(6-110)** (0.114 g, 0.432 mmol) in tetrahydrofuran (1.12 mL), aqueous lithium hydroxide (0.5 M) (1.12 mL, 0.562 mmol) was added and heated for at 50 °C for 3 hours. The solvent was removed under vacuum using dichloromethane (5 × 50 mL) to form an azeotropic mixture. The intermediate lithium (S)-2-(2-((2-(oxidomethyl) pyrrolidin-1-yl) methyl) phenyl) acetate was dissolved in chloroform (4.32 mL) and DIPEA (0.103 g, 0.139 mL, 0.799 mmol) was added followed by T3P 50% w/v in ethyl acetate (0.412 g, 0.648 mmol) and stirred at room temperature for 24 hours under argon. The reaction mixture was washed sequentially in dichloromethane (2 × 100 mL) and brine (50 mL), and the organic phases combined dried with sodium sulfate, filtered, concentrated under vacuum and purified via flash column chromatography (10:9:1 hexane:ethyl acetate:triethylamine) to afford the title compound (0.0625 g, 63%) R_f = 0.39 (10:9:1 hexane:ethyl acetate:triethylamine); ν_{max}/cm^{-1} (thin film) 2950, 1732, 1554, 1329, 1142, 1095, 744; δ_H (400 MHz, $CDCl_3$) 7.25−7.17 (3H, m, 3 × Ar**H**), 7.11−7.09 (1H, m, Ar**H**), 4.34 (1H, dd, *J* = 10.4 Hz, 4.7 Hz C**H**$_a$H$_b$O), 4.12 (1H, d, *J* = 13.0 Hz, ArC**H**$_a$H$_b$N), 4.00 (1H, dd, *J* = 10.4 Hz, 4.7 Hz, CH$_a$**H**$_b$O), 3.80 (1H, d, *J* = 14.0 Hz, ArC**H**$_a$H$_b$CO), 3.58 (1H, d, *J* = 13.0 Hz, ArCH$_a$**H**$_b$N), 3.51 (1H, d, *J* = 14.0 Hz, ArCH$_a$**H**$_b$CO), 3.09−3.03 (1H, m, C**H**), 2.76 (1H, m, C**H**$_a$H$_b$N), 2.36−2.30 (1H, m, CH$_a$**H**$_b$N), 1.90−1.80 (1H, m, C**H**$_a$H$_b$), 1.76−1.60 (2H, m, C**H**$_2$), 1.49−1.44 (1H, m, CH$_a$**H**$_b$); δ_c (100 MHz, $CDCl_3$) 172.9 (**C**O), 138.8 (Ar**C**), 135.4 (Ar**C**), 131.8 (Ar**C**H), 129.8 (Ar**C**H), 127.9 (Ar**C**H), 127.2 (Ar**C**H), 71.9 (**C**H$_2$O), 60.4 (**C**HN), 59.7 (Ar**C**H$_2$N), 50.0 (CH$_2$**C**H$_2$N), 41.8 (Ar**C**H$_2$O), 27.5 (**C**H$_2$), 24.9 (**C**H$_2$); HRMS (ESI) calcd. for $C_{14}H_{18}NO_2$ 232.1338. Found $[MH]^+$ 232.1335 (−1.29 ppm error); $[\alpha]_D^{20}$ = 25.9 (c = 1.0, dichloromethane), recorded using a Bellingham + Stanley RFM340-T refractometer.

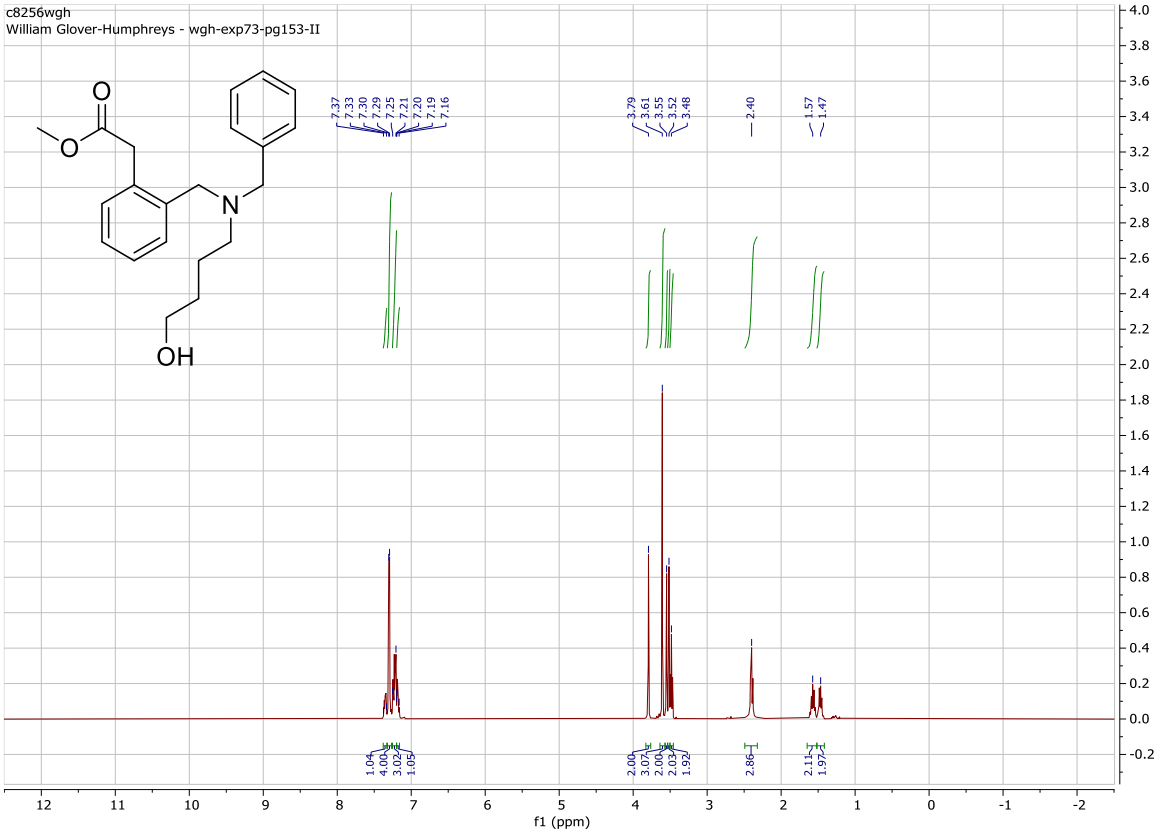

c8287wgh
William Glover-Humphreys - wgh-exp75-pg156-II
7.26
7.17
7.11
7.09
4.34
4.14
4.10
4.01
4.00
3.99
3.97
3.81
3.78
3.60
3.56
3.53
3.50
3.09
3.03
2.76
2.71
2.36
2.30
1.90
1.80
1.76
1.60
1.49
1.44
3.10
1.00
1.03
1.03
1.02
1.02
1.03
1.00
1.00
1.00
1.01
1.14
2.05
0.99
f1 (ppm)


c8287wgh
William Glover-Humphreys - wgh-exp75-pg156-II
172.90
138.76
135.41
131.84
129.75
127.86
127.20
71.92
60.41
59.72
53.03
41.81
27.52
24.86
f1 (ppm)

Methyl 2-(2-((benzyl(4-hydroxybutyl) amino) methyl) phenyl) acetate (6-111)



To a stirring solution of potassium carbonate (0.415 g, 3.00 mmol) in acetonitrile (5.00 mL), 4-benzylamino butan-1-ol (**6-90**) (0.179 g, 1.00 mmol) was added followed by methyl 2-(2-(bromomethyl) phenyl) acetate (**6-109**) (0.243 g, 1.00 mmol). The reaction mixture was heated to reflux at 90 °C for 3 hours under argon before filtering through Celite washing with dichloromethane, concentrating under vacuum and purifying by flash column chromatography (10:9:1 hexane:ethyl acetate:triethylamine) to afford the title compound as a clear oil (0.110 g, 32%) R_f = 0.5 (10:9:1 hexane:ethyl acetate:triethylamine); ν_{max}/cm^{-1} (thin film) 3418, 2943, 1734, 1453, 1162, 1056, 745, 700; δ_H (400 MHz, $CDCl_3$) 7.37−7.33 (1H, m, Ar**H**), 7.31−7.27 (4H, m, 4× Ar**H**), 7.25−7.30 (3H, m, 3× Ar**H**), 7.19 −7.16 (1H, m, Ar**H**), 3.79 (2H, s, ArC**H**$_2$COOCH$_3$), 3.61 (3H, s, OC**H**$_3$), 3.55 (2H, s, ArC**H**$_2$N), 3.52 (2H, s, ArC**H**$_2$N), 3.48 (2H, t, *J* = 6.0 Hz, CH$_2$C**H**$_2$OH), 2.40 (2H, t, *J* = 6.8 Hz, CH$_2$C**H**$_2$N), 1.57 (2H, quintet, *J* = 6.8 Hz, CH$_2$C**H**$_2$CH$_2$), 1.47 (2H, quintet, *J* = 6.0 Hz, CH$_2$C**H**$_2$CH$_2$); δ_c (100 MHz, $CDCl_3$) 172.5 (**C**O), 139.2 (Ar**C**), 137.7 (Ar**C**), 133.8 (Ar**C**), 131.0 (Ar**C**H), 131.0 (Ar**C**H), 129.4 (Ar**C**H), 128.3 (Ar**C**), 127.5 (Ar**C**H), 127.2 (Ar**C**H), 127.1 (Ar**C**H), 62.5 (CH$_2$**C**H$_2$OH), 58.9 (Ar**C**H$_2$N), 57.3 (Ar**C**H$_2$N), 53.6(CH$_2$**C**H$_2$N), 52.0 (O**C**H$_3$), 38.0 (Ar**C**H$_2$COOCH$_3$), 30.8 (**C**H$_2$), 23.4 (**C**H$_2$); HRMS (ESI) calcd. for $C_{21}H_{28}NO_3$ 342.2069. Found $[MH]^+$ 342.2065 (−1.17 ppm error).


c8256wgh
William Glover-Humphreys - wgh-exp73-pg153-II
O
O
N
OH
7.37
7.33
7.30
7.29
7.25
7.21
7.20
7.19
7.16
3.79
3.61
3.55
3.52
3.48
2.40
1.57
1.47
1.04
4.00
3.02
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3.07
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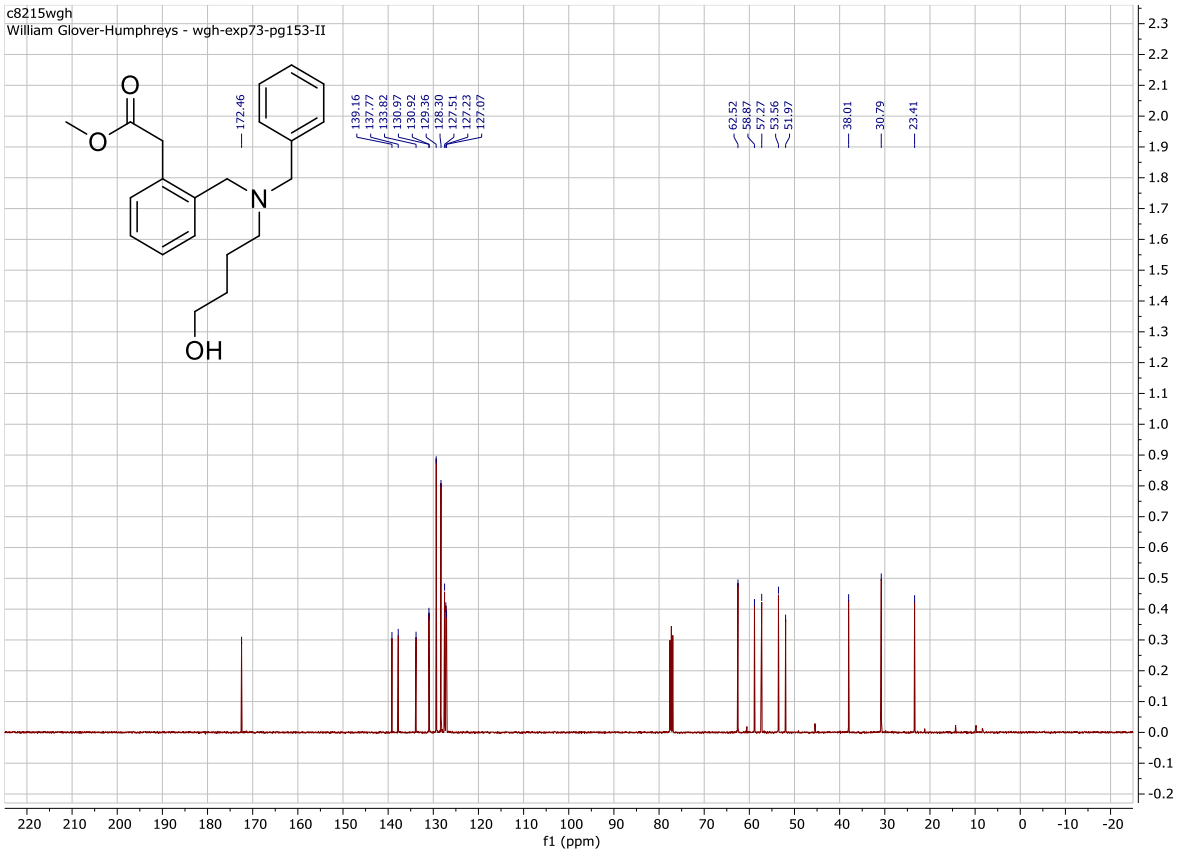
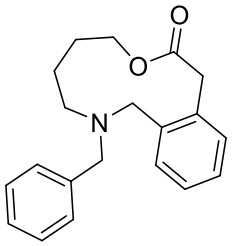
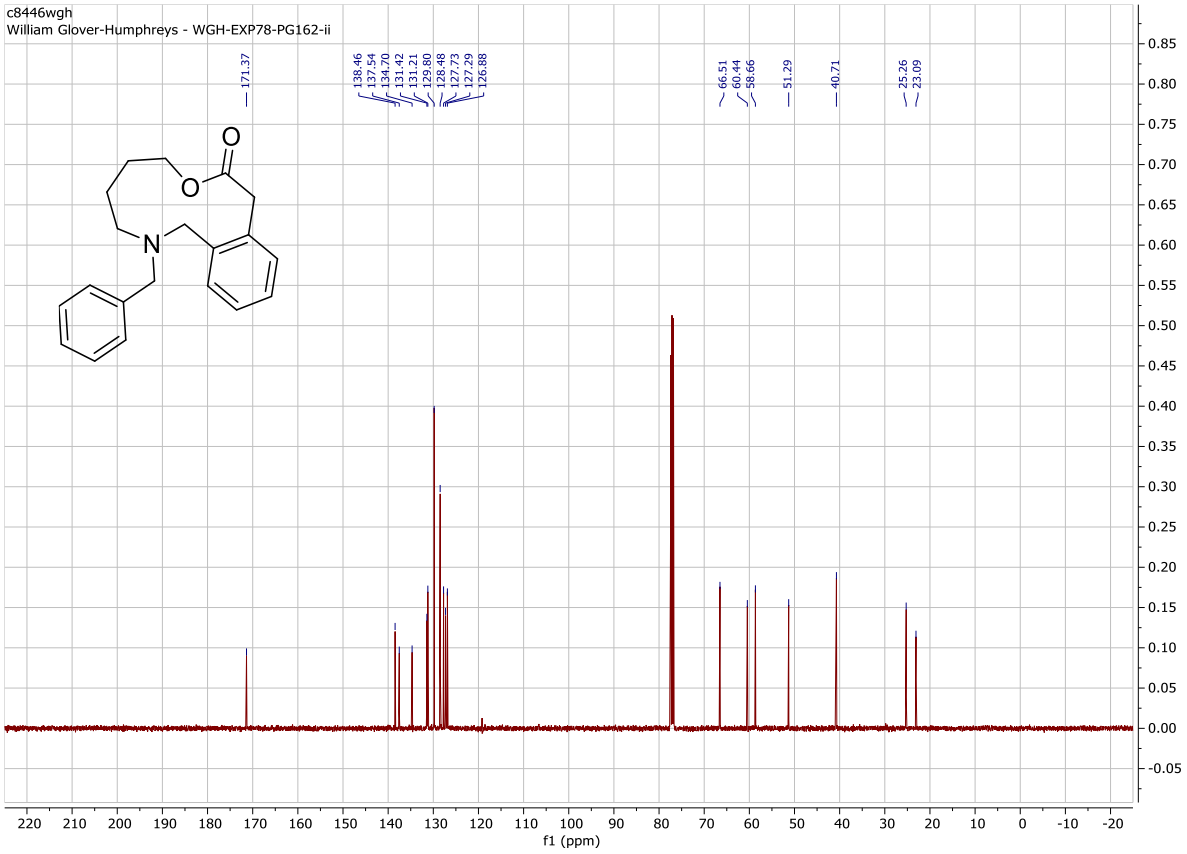
1.92
2.86
2.11
1.97
f1 (ppm)


c8215wgh
William Glover-Humphreys - wgh-exp73-pg153-II
O
O
N
OH
172.46
139.16
137.77
133.82
130.97
130.92
129.36
128.30
127.51
127.23
127.07
62.52
58.87
57.27
53.56
51.97
38.01
30.79
23.41
f1 (ppm)

2-Benzyl-1,3,4,5,6,9-hexahydrobenzo[*h*][1] oxa [6] azacycloundecin-8 (2*H*)-one (6-114)



To a stirring solution of methyl 2-(2-((benzyl (4-hydroxy butyl) amino) methyl) phenyl) acetate **(6-111)** (0.109 g, 0.320 mmol) in tetrahydrofuran (0.830 mL), aqueous lithium hydroxide (0.5 M) (0.830 mL, 0.417 mmol) was added and heated for at 50 °C for 3 hours. The solvent was removed under vacuum using dichloromethane (5 × 50 mL) to form an azeotropic mixture. The intermediate lithium 2-(2-((benzyl(4-oxidobutyl) amino) methyl) phenyl) acetate was dissolved in chloroform (3.12 mL) and DIPEA (0.077 g, 0.103 mL, 0.592 mmol) was added followed by T3P 50% w/v in ethyl acetate (0.306 g, 0.480 mmol) and stirred at room temperature for 24 hours under argon. The reaction mixture was washed sequentially in dichloromethane (2 × 100 mL) and brine (50 mL) and the organic phases combined dried with sodium sulfate, filtered, concentrated under vacuum and purified via flash column chromatography (10:9:1 hexane:ethyl acetate:triethylamine) to afford the title compound (0.035 g, 35%) R_f = 0.70 (10:9:1 hexane:ethyl acetate:triethylamine); ν_{max}/cm^{-1} (thin film) 2942, 1793, 1721, 1452, 1244, 749; δ_H (400 MHz, $CDCl_3$) 7.45−7.43 (2H, m, 2× ArC**H**), 7.39−7.35 (2H, m, 2× ArC**H**), 7.27 (1H, tt, *J* = 7.39 Hz, 1.30 Hz, ArC**H**), 7.21 (1H, td, *J* = 7.30 Hz, 1.80 Hz, ArC**H**), 7.15 (1H, td, *J* = 7.30 Hz, 1.80 Hz, ArC**H**), 7.13−7.10 (1H, m, ArC**H**), 7.06 (1H, dd, *J* = 7.39 Hz, 1.30 Hz, ArC**H**), 4.43−3.97 (1H, m, C$\mathbf{H}_2$O), 3.62−3.38 (4H, m, 2× ArC$\mathbf{H}_2$N), 3.47 (4H, s, ArC$\mathbf{H}_2$N), 3.55−3.23 (2H, m, ArC$\mathbf{H}_2$CO), 2.32-2.24 (2H, m, C$\mathbf{H}_2$N), 1.92-1.64 (4H, m, 2 × C$\mathbf{H}_2$); δ_c (100 MHz, $CDCl_3$) 171.4 (**C**O), 138.5 (Ar**C**), 137.5 (Ar**C**), 134.7 (Ar**C**), 131.4 (Ar**C**H), 131.2 (Ar**C**H), 129.8 (Ar**C**H), 128.5 (Ar**C**), 127.7 (Ar**C**H), 127.3 (Ar**C**H), 126.9 (Ar**C**H), 66.5 ($CH_2\mathbf{C}H_2O$), 60.4 (Ar**C**H_2N), 58.7 (Ar**C**H_2N), 51.3 ($CH_2\mathbf{C}H_2$N), 40.7 (Ar**C**H_2COO), 25.3 (**C**H_2), 23.1 (**C**H_2); HRMS (ESI) calcd. for for $C_{20}H_{24}NO_2$ 310.1807. Found $[MH]^+$ 310.1809 (0.650 ppm error).


c8446wgh
William Glover-Humphreys - WGH-EXP78-PG162-ii
171.37
138.46
137.54
134.70
131.42
131.21
129.60
128.48
127.73
127.29
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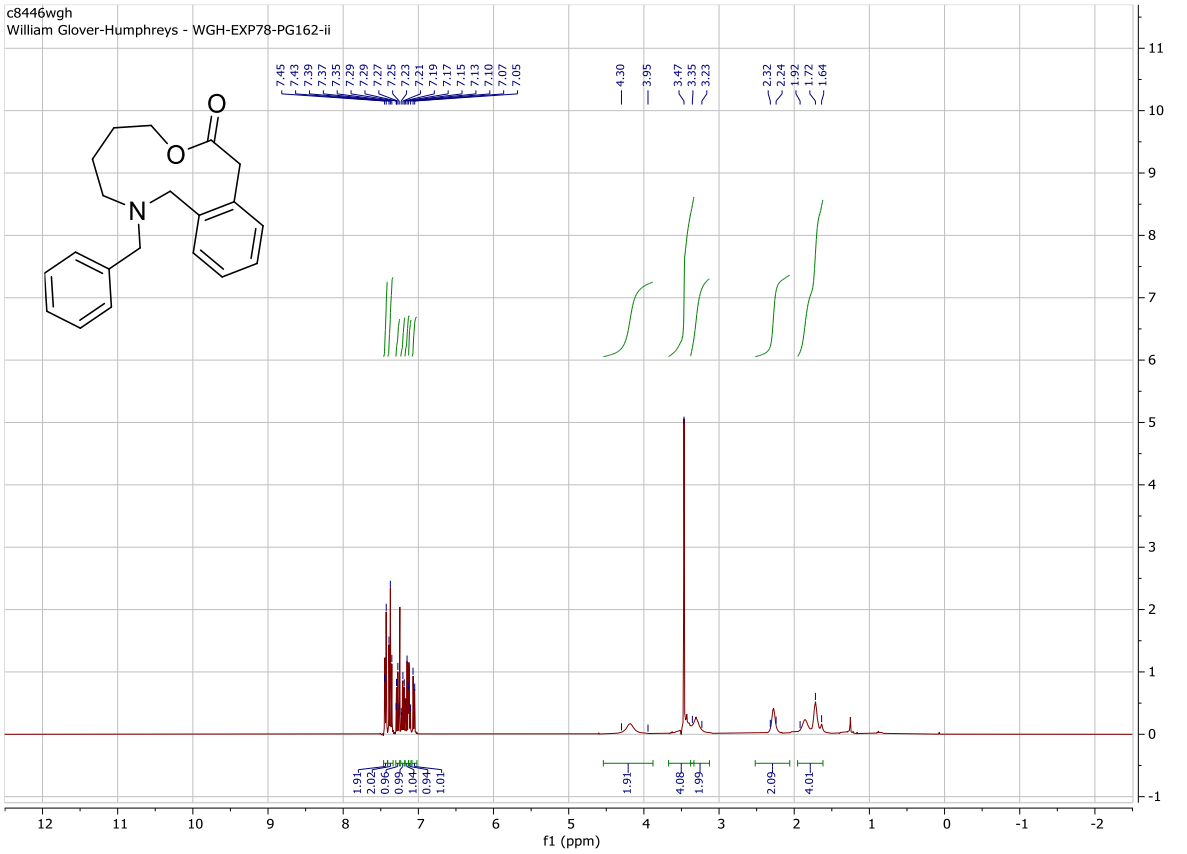
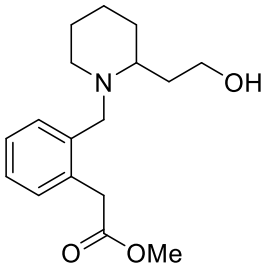
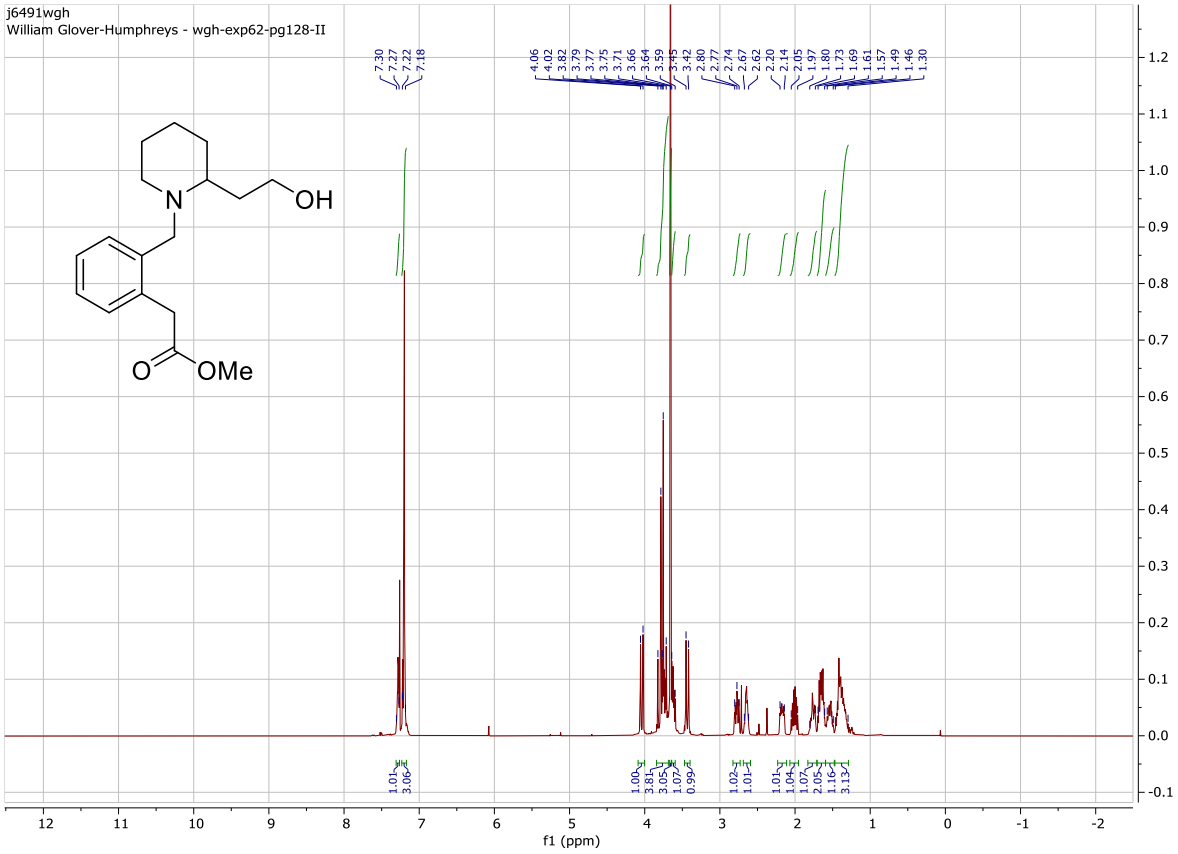
60.44
58.66
51.29
40.71
25.26
23.09
O
O
N
f1 (ppm)

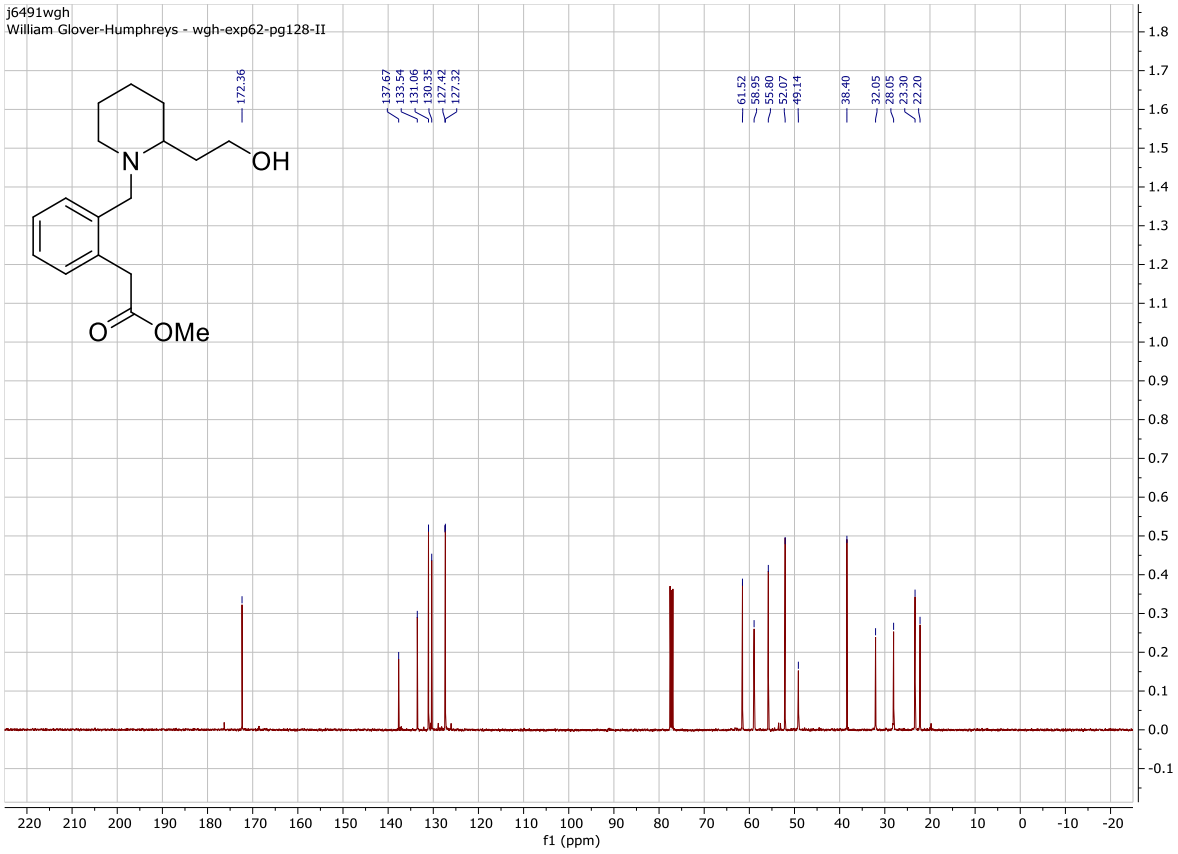

c8446wgh
William Glover-Humphreys - WGH-EXP78-PG162-ii
7.45
7.43
7.39
7.37
7.35
7.29
7.29
7.27
7.25
7.23
7.21
7.19
7.17
7.15
7.13
7.10
7.07
7.05
4.30
3.95
3.47
3.35
3.23
2.32
2.24
1.92
1.72
1.64
1.91
2.02
0.96
0.99
1.04
0.94
1.01
1.91
4.08
1.99
2.09
4.01
O
O
N
f1 (ppm)

Methyl 2-(2-((2-(2-hydroxyethyl) piperidin-1-yl) methyl) phenyl) acetate (6-112)

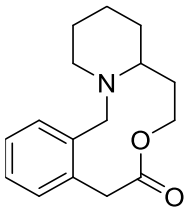


To a stirring solution of potassium carbonate (0.415 g, 3.00 mmol) in acetonitrile (5 mL), 2-(piperidin-2-yl) ethan-1-ol **(6-92)** (0.129 g, 1.00 mmol) was added followed by methyl 2-(2-(bromomethyl) phenyl) acetate **(6-109)** (0.243 g, 1.00 mmol). The reaction mixture was heated to reflux at 90 °C for 3 hours under argon before filtering through Celite washing with dichloromethane, concentrating under vacuum and purifying by flash column chromatography (10:9:1 hexane:ethyl acetate:triethylamine) to afford the title compound an oil (0.151 g, 52%) R_f = 0.46 (10:9:1 hexane:ethyl acetate:triethylamine); ν_{max}/cm^{-1} (thin film) 3396, 2933, 2252, 1734, 1425, 1157, 730; δ_H (400 MHz, $CDCl_3$) 7.30−7.27 (1H, m, ArC**H**), 7.22−7.18 (3H, m, ArC**H**), 4.04 (1H, d, *J* = 13.4 Hz, ArC**H**$_a$H$_b$N), 3.82−3.59 (5H, m, ArC**H**$_2$COOMe, C**H**$_2$OH, O**H**), 3.66 (3H, s, OC**H**$_3$), 3.42 (1H, d, *J* = 13.4 Hz, ArCH$_a$**H**$_b$N), 2.80−2.74 (1H, m, C**H**$_a$H$_b$N), 2.65 (1H, quintet, *J* = 5.2 Hz, C**H**), 2.20-2.14 (1H, m, CH$_a$**H**$_b$N), 2.00 (1H, quintet, *J* = 6.4 Hz, C**H**$_a$H$_b$CH$_2$OH), 1.80−1.73 (1H, m, C**H**$_a$H$_b$), 1.69−1.61 (1H, m, CH$_a$**H**$_b$CH$_2$OH), 1.69−1.61 (1H, m, C**H**$_a$H$_b$'), 1.57−1.49 (1H, m, CH$_a$**H**$_b$'), 1.46−1.30 (2H, m, C**H**$_2$), 1.46−1.30 (1H, m, CH$_a$**H**$_b$); δ_c (100 MHz, $CDCl_3$) 172.4 (**C**O), 137.7 (Ar**C**), 133.5 (Ar**C**), 131.1 (Ar**C**H), 130.4 (Ar**C**H), 127.4 (Ar**C**H), 127.3 (Ar**C**H), 61.5 (**C**H$_2$OH), 59.0 (**C**H), 55.8 (Ar**C**H$_2$N), 52.1 (O**C**H$_3$), 49.1 (Ar**C**H$_2$COOMe), 38.4 (**C**H$_2$N), 32.1 (CH**C**H$_2$CH$_2$OH), 28.1 (**C**H$_2$), 23.3 (**C**H$_2$), 22.2 (**C**H$_2$); HRMS (ESI) calcd. for $C_{17}H_{26}NO_3$ 292.1913. Found $[MH]^+$ 292.1910 (−1.03 ppm error).

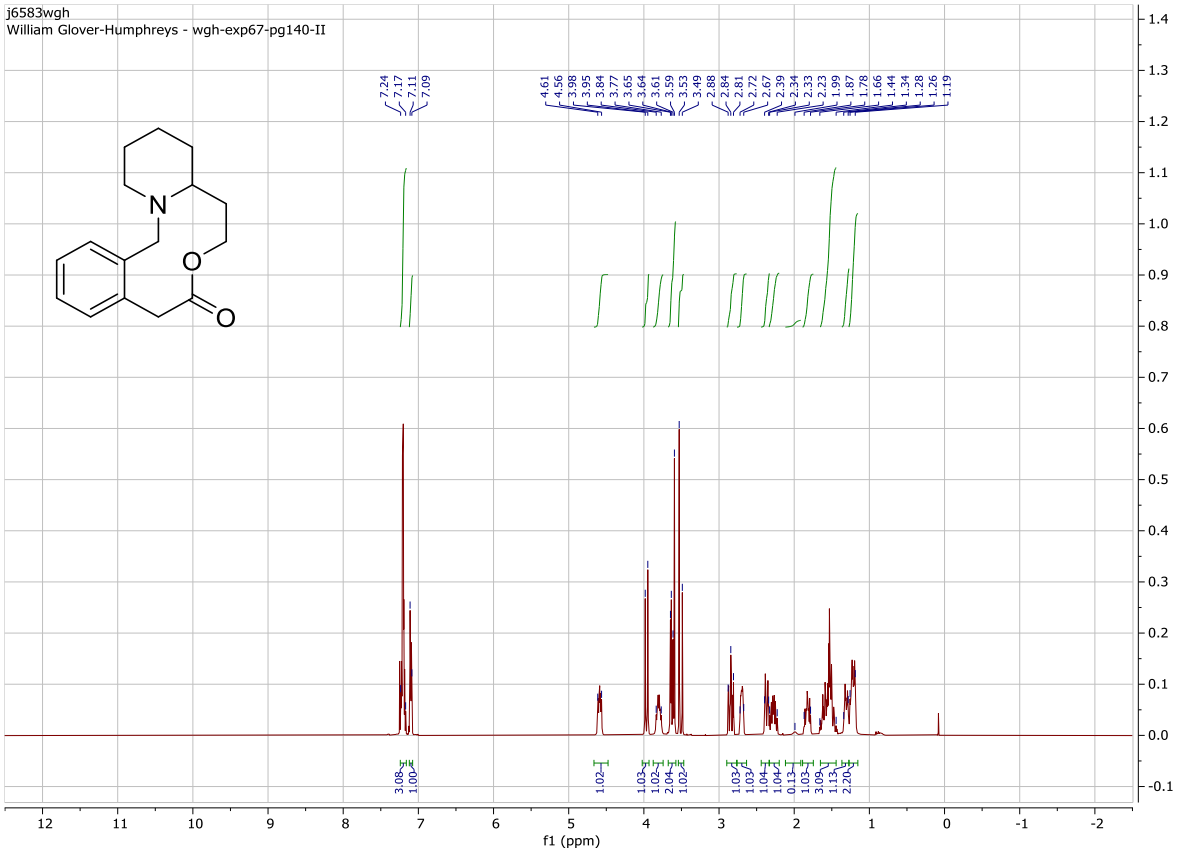

j6491wgh
William Glover-Humphreys - wgh-exp62-pg128-II
7.30
7.27
7.22
7.18
4.06
4.02
3.82
3.79
3.77
3.75
3.71
3.66
3.64
3.59
3.45
3.42
2.80
2.77
2.74
2.67
2.62
2.20
2.14
2.05
1.97
1.80
1.73
1.69
1.61
1.57
1.49
1.46
1.30
N
OH
O
OMe
1.01
3.06
1.00
3.81
3.05
1.07
0.99
1.02
1.01
1.01
1.04
1.07
2.05
1.16
3.13
f1 (ppm)

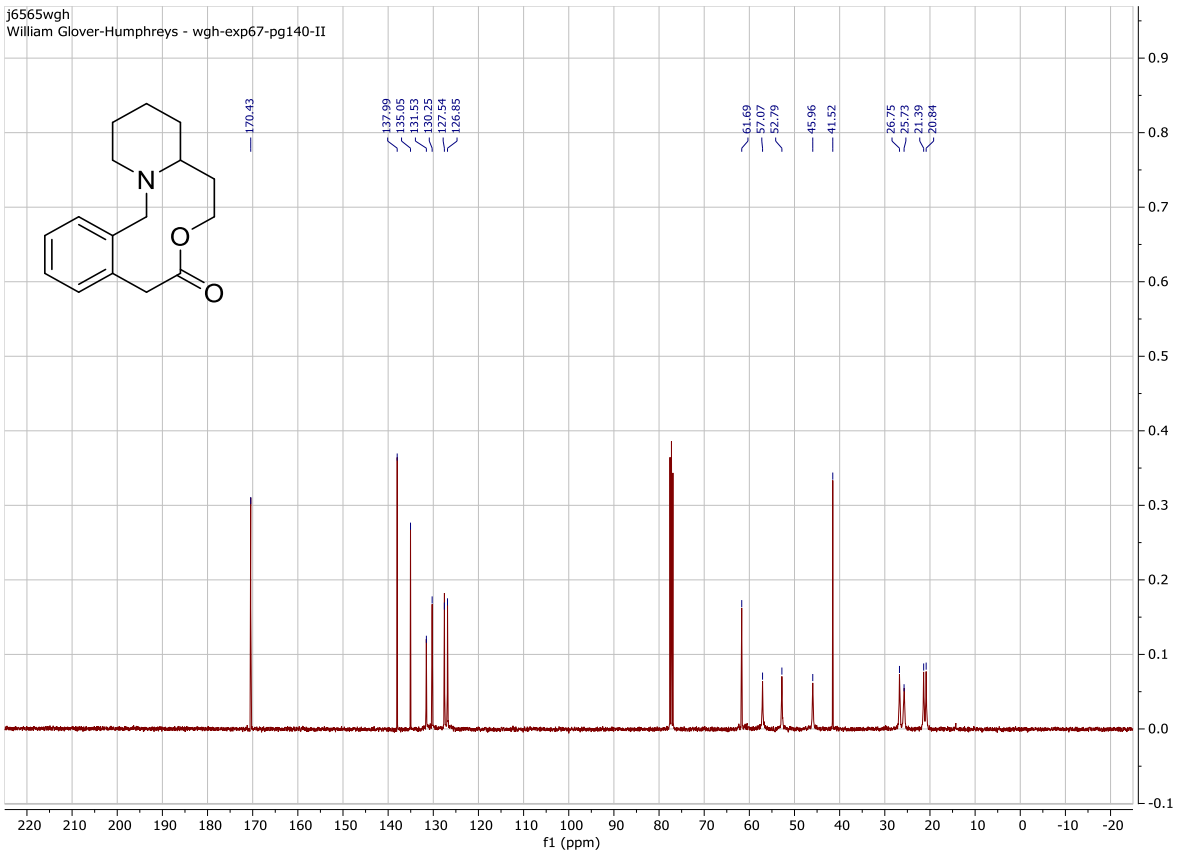

j6491wgh
William Glover-Humphreys - wgh-exp62-pg128-II
172.36
137.67
133.54
131.06
130.35
127.42
127.32
61.52
58.95
55.80
52.07
49.14
38.40
32.05
28.95
23.30
22.20
N
OH
O
OMe
f1 (ppm)

5,9,9a,10,11,12,13,15-Octahydro-6*H*,8*H*-benzo[*g*]pyrido[2,1-*d*] [1,5] oxazecin-4-one (6-115)

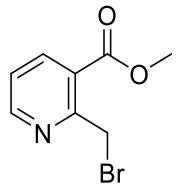


To a stirring solution of methyl 2-(2-((2-(2-hydroxyethyl) piperidin-1-yl) methyl) phenyl) acetate **(6-112)** (0.150 g, 0.515 mmol) in tetrahydrofuran (1.34 mL), aqueous lithium hydroxide (0.5 M) (1.34 mL, 0.670 mmol) was added and heated for at 50 °C for 3 hours. The solvent was removed under vacuum using dichloromethane (5 × 50 mL) to form an azeotropic mixture. The intermediate lithium 2-(2-((2-(2-oxidoethyl) piperidin-1-yl) methyl) phenyl) acetate was dissolved in chloroform (5.15 mL) and DIPEA (0.123 g, 0.166 mL, 0.953 mmol) was added followed by T3P 50% w/v in ethyl acetate (0.492 g, 0.773 mmol) and stirred at room temperature for 24 hours under argon. The reaction mixture was washed sequentially in dichloromethane (2 × 100 mL) and brine (50 mL), and the organic phases combined dried with sodium sulfate, filtered, concentrated under vacuum and purified via flash column chromatography (10:9:1 hexane:ethyl acetate:triethylamine) to afford the title compound (0.103 g, 77%) R_f = 0.63 (10:9:1 hexane:ethyl acetate:triethylamine); ν_{max}/cm^{-1} (thin film) 2930, 2249, 1728, 1452, 1372, 1233, 1044, 1101, 1045, 728; δ_H (400 MHz, $CDCl_3$) 7.25−7.18 (3H, m, 3× Ar**H**), 7.12−7.10 (1H, m, Ar**H**), 4.62−4.57 (1H, m, C**H**$_a$H$_b$O), 3.98 (1H, d, *J* = 13.7 Hz, ArC**H**$_a$H$_b$N) 3.85−3.78 (1H, m, CH$_a$**H**$_b$O), 3.64 (1H, d, *J* = 13.7 Hz, ArC**H**$_a$H$_b$N), 3.63 (1H, d, *J* = 16.6 Hz, ArC**H**$_a$H$_b$CO), 3.52 (1H, d, *J* = 16.6 Hz, ArCH$_a$**H**$_b$CO), 2.89−2.82 (1H, m, C**H**$_a$H$_b$N), 2.72−2.68 (1H, m, C**H**), 2.38 (1H, dt, *J* = 13.9 Hz, 4.1Hz, CH$_a$**H**$_b$N), 2.34−2.24 (1H, m CHC**H**$_a$H$_b$CH$_2$O), 1.88−1.79 (1H, m CHCH$_a$**H**$_b$CH$_2$O), 1.67−1.45 (1H, m, C**H**$_a$H$_b$), 1.67−1.45 (2H, m, C**H**$_2$), 1.35−1.29 (1H, m, CH$_a$**H**$_b$), 1.27−1.20 (2H, m, C**H**$_2$); δ_c (100 MHz, $CDCl_3$) 170.4 (**C**O), 138.0 (Ar**C**), 135.1 (Ar**C**), 131.5 (Ar**C**H), 130.3 (Ar**C**H), 127.5 (Ar**C**H), 126.9 (Ar**C**H), 61.7 (O**C**H$_2$), 57.1 (Ar**C**H$_2$N), 52.8 (**C**H), 46.0 (**C**H$_2$N), 41.5 (Ar**C**H$_2$CO), 26.8 (**C**H$_2$), 25.7 (**C**H$_2$), 21.4 (**C**H$_2$), 20.8 (**C**H$_2$); HRMS (ESI) calcd. for $C_{16}H_{22}NO_2$ 260.1651. Found $[MH]^+$ 260.1643 (−3.8 ppm error).

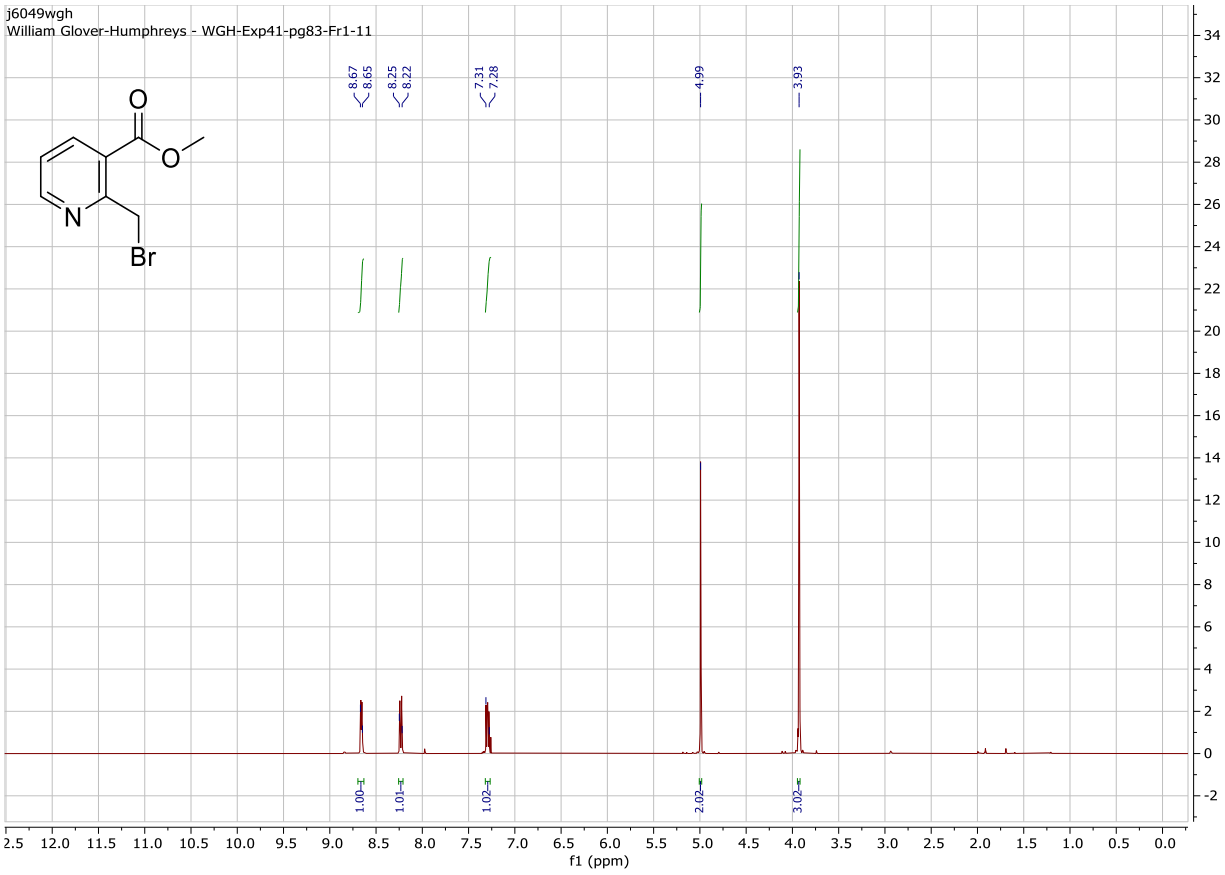

j6583wgh
William Glover-Humphreys - wgh-exp67-pg140-II
7.24
7.17
7.11
7.09
4.61
4.56
3.98
3.95
3.84
3.77
3.65
3.64
3.61
3.59
3.53
3.49
2.88
2.84
2.81
2.72
2.67
2.39
2.34
2.33
2.23
1.99
1.87
1.78
1.66
1.44
1.34
1.28
1.26
1.19
N
O
O
3.08
1.00
1.02
1.03
1.02
2.04
1.02
1.03
1.02
1.04
0.13
1.03
3.09
1.13
2.20
f1 (ppm)


j6565wgh
William Glover-Humphreys - wgh-exp67-pg140-II
170.43
137.99
135.05
131.53
130.25
127.54
126.85
61.69
57.07
52.79
45.96
41.52
26.75
25.73
21.39
20.84
N
O
O
f1 (ppm)

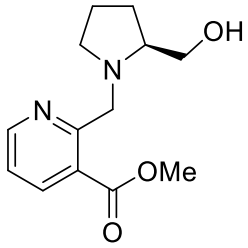
Methyl 2-(bromomethyl) nicotinate (6-117)



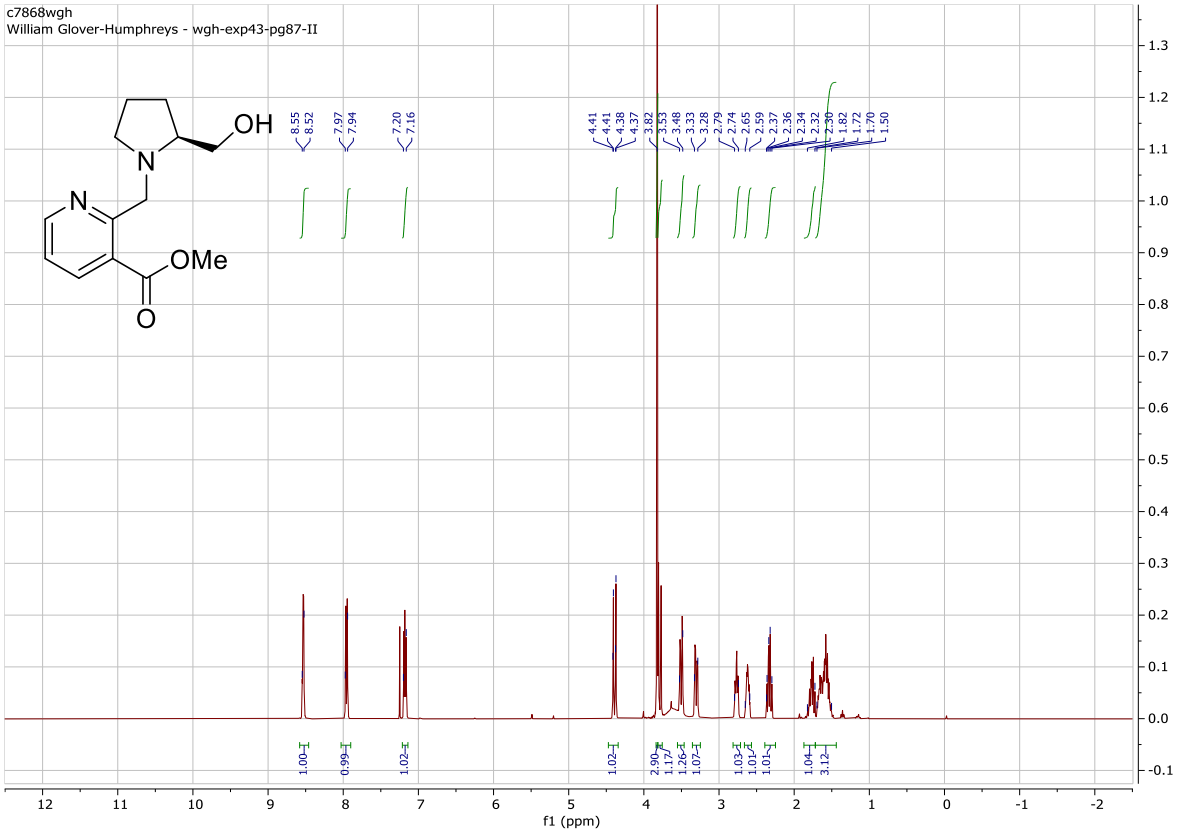
Benzene (13.0 mL) was degassed with argon for 20 minutes then added to a mixture of methyl 2-methylnicotinate **(6-116)** (1.00 g, 6.62 mmol), *N*-bromosuccinimide (1.30 g, 7.26 mmol) and azobisisobutyronitrile (0.054 g, 0.330 mmol) under argon. The reaction mixture was heated to reflux at 85 °C for 24 hours. The reaction mixture was filtered through Celite washing with dichloromethane, before removing the solvent under vacuum and purification via flash column chromatography (1:1 hexane:ethyl acetate) to afford the title compound as a brown solid (0.289 g, 19%), R_f = 0.48 (1:1 hexane:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 8.66 (1H, dd, *J* = 4.8 Hz, 1.76 Hz, Ar**H**), 8.23 (1H, dd, *J* = 7.8 Hz, 1.8 Hz, Ar**H**), 7.31−7.28 (1H, m, Ar**H**), 4.99 (2H, C**H**$_2$Br), 3.93 (3H, OC**H**$_3$). Data were consistent with those reported in the literature.[41]

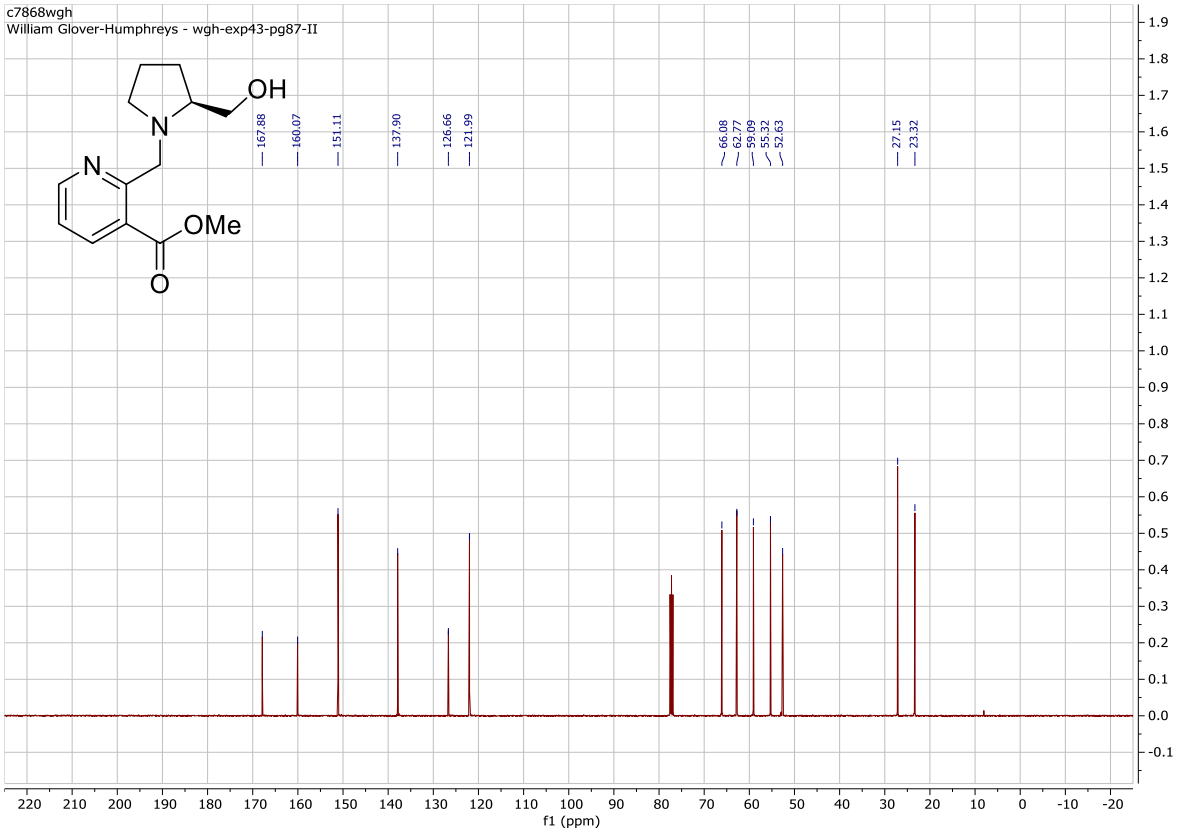


Methyl (*S*)-2-((2-(hydroxymethyl) pyrrolidin-1-yl) methyl) nicotinate (6-118)

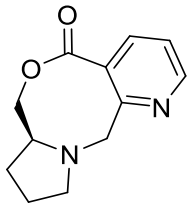


To a stirring solution of potassium carbonate (0.126 g, 0.912 mmol) in acetonitrile (6.90 mL), (*S*)-pyrrolidin-2-ylmethanol (**6-86**) (0.0615 g, 0.608 mmol) was added followed by methyl 2-(bromo methyl) nicotinate (**6-117**) (0.140 g, 0.608 mmol). The reaction mixture was heated to reflux at 90 °C for 3 hours under argon before filtering through Celite washing with dichloromethane, concentrating under vacuum and purifying by flash column chromatography (16:3:1 dichloromethane:ethyl acetate:triethylamine) to afford the title compound as a dark red oil (0.128 g, 84%) R_f = 0.39 (16:3:1 dichloromethane:ethyl acetate:triethylamine); ν_{max}/cm^{-1} (thin film) 3378, 2952, 2872, 2809, 1722, 1574, 1431, 1279, 1083, 756; δ_H (400 MHz, $CDCl_3$) 8.55−8.52 (1H, m, Ar**H**), 7.97−7.94 (1H, m, Ar**H**), 7.20−7.16 (1H, m, Ar**H**), 4.39 (1H, d, *J* = 13.6 Hz, ArC**H**$_a$H$_b$N), 3.18 (3H, s, OC**H**$_3$), 3.79 (1H, d, *J* = 13.6 Hz, ArCH$_a$**H**$_b$N), 3.53−3.48 (1H, m, CHC**H**$_a$H$_b$OH), 3.33−3.28 (1H, m, CHCH$_a$**H**$_b$OH), 2.79−2.74 (1H, m, CH$_2$C**H**$_a$H$_b$N), 2.65−2.59 (1H, m, NC**H**(CH$_2$)$_2$), 2.37−2.30 (1H, m, CH$_2$CH$_a$**H**$_b$N), 1.82−1.72 (1H, m, C**H**$_a$H$_b$), 1.70−1.50 (1H, m, CH$_a$**H**$_b$) 1.70−1.50 (1H, m, C**H**$_2$); δ_c (100 MHz, $CDCl_3$) 167.9 (**C**O), 160.1 (Ar**C**), 151.1 (Ar**C**H), 137.9 (Ar**C**H), 126.7 (Ar**C**), 122.0 (Ar**C**H), 66.1 (O**C**H$_3$), 62.8 (**C**H$_2$OH), 59.1 (Ar**C**H$_2$N) 55.3 (**C**H$_2$N), 52.6 (**C**HN), 27.2 (**C**H$_2$), 23.3 (**C**H$_2$); HRMS (ESI) calcd. for $C_{13}H_{19}N_2O_3$ 251.1396. Found $[MH]^+$ 251.1391 (−1.99 ppm error).

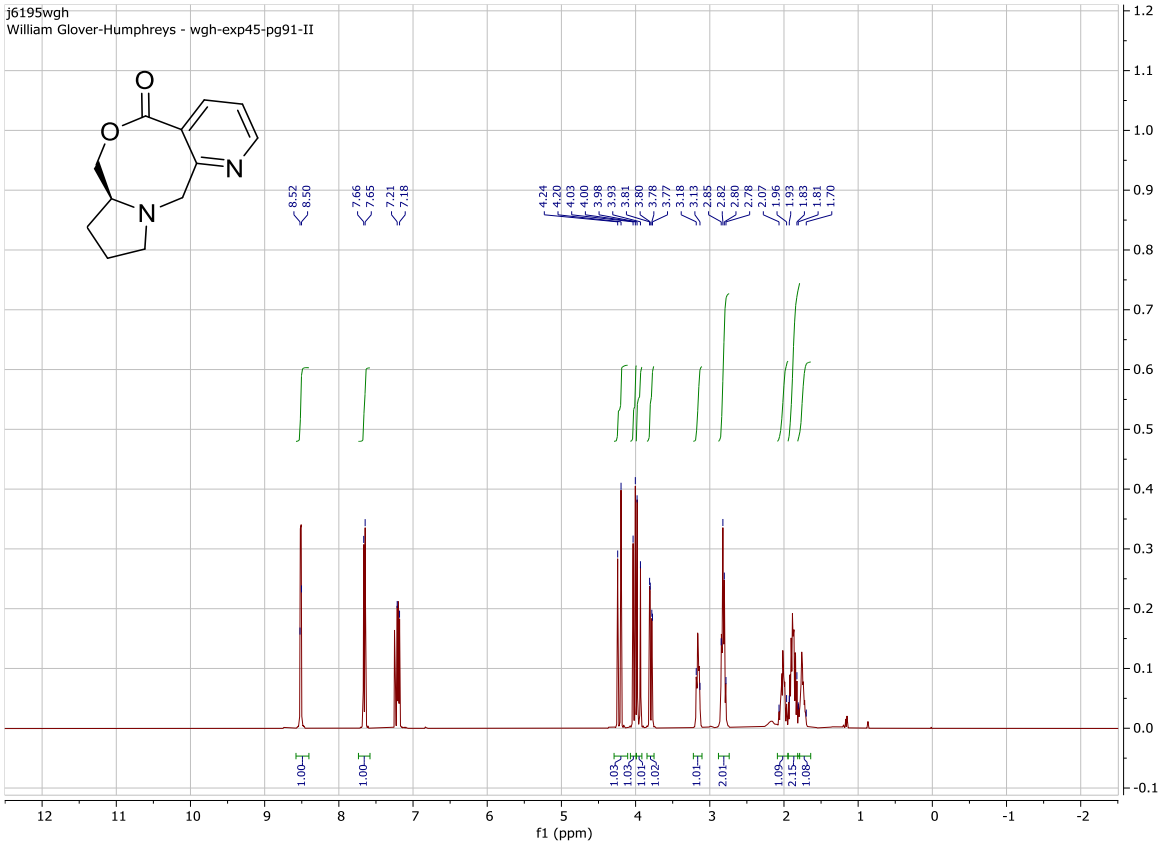

c7868wgh
William Glover-Humphreys - wgh-exp43-pg87-II
OH
N
N
OMe
O
8.55
8.52
7.97
7.94
7.20
7.16
4.41
4.41
4.38
4.37
3.82
3.53
3.48
3.33
3.28
2.79
2.74
2.65
2.59
2.37
2.36
2.34
2.32
2.30
1.82
1.72
1.70
1.50
1.00
0.99
1.02
1.02
2.90
1.17
1.26
1.07
1.03
1.01
1.01
1.04
3.12
f1 (ppm)


c7868wgh
William Glover-Humphreys - wgh-exp43-pg87-II
OH
N
N
OMe
O
167.88
160.07
151.11
137.90
126.66
121.99
66.08
62.77
59.09
55.32
52.83
27.15
23.32
f1 (ppm)

(*S*)-7a,8,9,10-Tetrahydro-7H-pyrido[2,3-*f*] pyrrolo [2,1-*c*] [1,4] oxazocin-5(12*H*)-one (6-121)



To a stirring solution of methyl (*S*)-2-((2-(hydroxymethyl) pyrrolidin-1-yl) methyl) nicotinate **(6-118)** (0.125 g, 0.50 mmol) in tetrahydrofuran (1.20 mL), aqueous lithium hydroxide (0.5 M) (1.20 mL, 0.60 mmol) was added and heated at 50 °C for 3 hours. The solvent was removed under vacuum using dichloromethane (5 × 50 mL) to form an azeotropic mixture. The intermediate lithium 2-((2-(2-oxidoethyl) piperidin-1-yl) methyl) nicotinate was dissolved in chloroform (5.00 mL) and DIPEA (0.120 g, 0.162 mL, 0.925 mmol) was added followed by T3P 50% w/v in ethyl acetate (0.477 g, 0.750 mmol) The reaction mixture was stirred at room temperature for 2 hours under argon then washed sequentially in dichloromethane (2 × 100 mL) and brine (50 mL) and the organic phases combined dried with sodium sulfate, filtered, concentrated under vacuum and purified via flash column chromatography (16:3:1 dichloromethane:ethyl acetate:triethylamine) to afford the title compound as a white solid (0.0864 g, 79%) R_f = 0.32 (16:3:1 dichloromethane:ethyl acetate:triethylamine); ν_{max}/cm^{-1} (thin film) 3424, 2926, 1708, 1422, 1275, 1094, 738; δ_H (400 MHz, $CDCl_3$) 8.52−8.50 (1H, m, Ar**H**), 7.65 (1H, d, *J* = 7.8 Hz), 7.21−7.18 (1H, m, *J* = 7.8 Hz, *J* = 4.6 Hz, Ar**H**), 4.21 (1H, d, *J* = 18.1 Hz, ArC**H**$_a$H$_b$N), 4.02 (1H, d, *J* = 12.1 Hz, C**H**$_a$H$_b$O), 3.96 (1H, d, *J* = 18.1 Hz, ArCH$_a$**H**$_b$N), 3.81−3.77 (1H, m, CH$_a$**H**$_b$O), 3.17−3.14 (1H, m, NC**H**$_a$H$_b$CH$_2$), 2.84−2.78 (1H, m, NCH$_a$**H**$_b$CH$_2$), 2.84−2.78 (1H, m, NC**H**(CH$_2$)$_2$) 2.07−1.96 (1H, m, C**H**$_a$H$_b$), 1.94−1.82 (2H, m, C**H**$_2$), 1.80−1.70 (1H, m, CH$_a$**H**$_b$); δ_c (100 MHz, $CDCl_3$) 171.1 (**C**O), 159.3 (Ar**C**), 150.4 (Ar**C**H), 137.3 (Ar**C**H), 126.6 (Ar**C**), 122.1 (Ar**C**H), 68.7 (O**C**H$_2$), 64.3 (**C**H), 58.5 (Ar**C**H$_2$N), 55.1 (N**C**H$_2$CH$_2$), 29.8 (**C**H$_2$), 23.7 (**C**H$_2$); HRMS (ESI) calcd. for $C_{12}H_{15}N_2O_2$ 219.1134. Found $[MH]^+$ 219.1132 (−0.913 ppm error); $[\alpha]_D^{20}$ = 16.3 (c = 1.0, dichloromethane), recorded using a Bellingham + Stanley RFM340-T refractometer.


j6195wgh
William Glover-Humphreys - wgh-exp45-pg91-II
O
O
N
N
8.52
8.50
7.66
7.65
7.21
7.18
4.24
4.20
4.03
4.00
3.98
3.93
3.81
3.80
3.78
3.77
3.18
3.13
2.85
2.82
2.80
2.78
2.07
1.96
1.93
1.83
1.81
1.70
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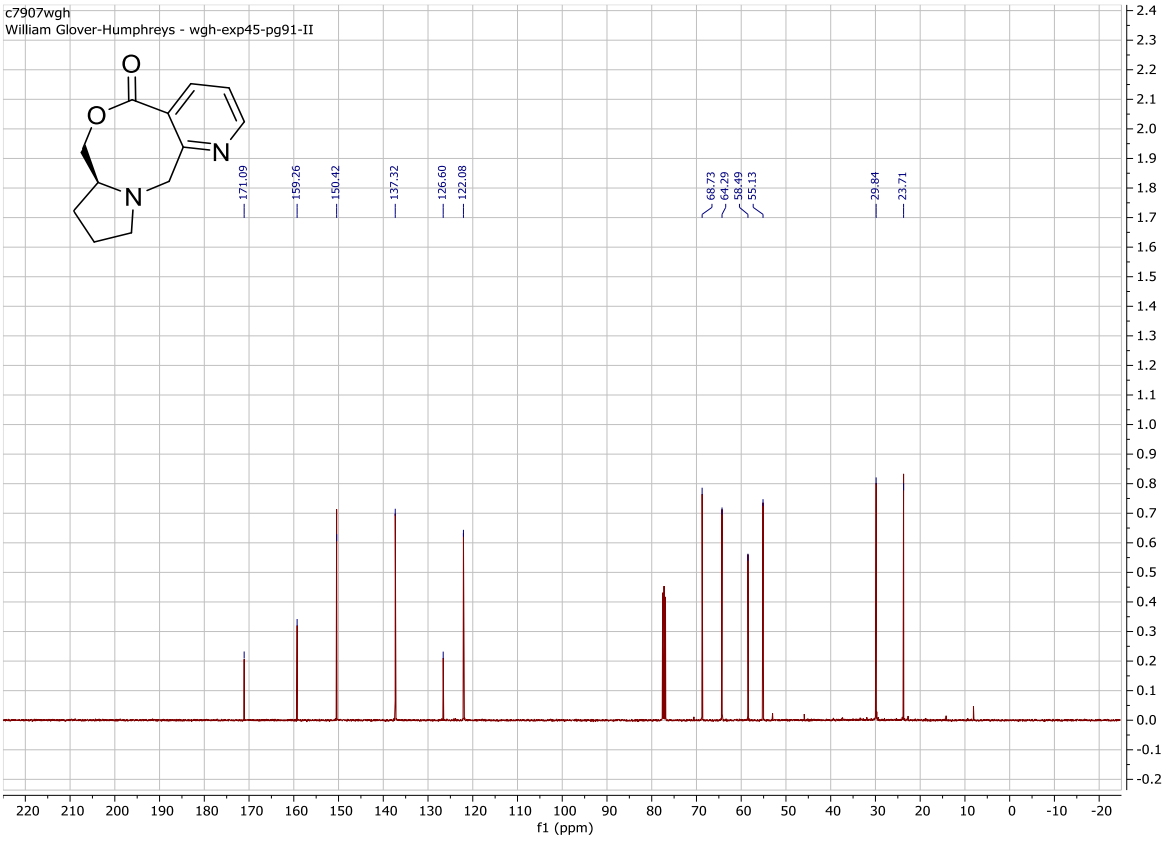
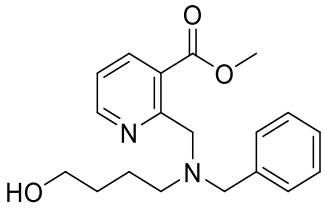
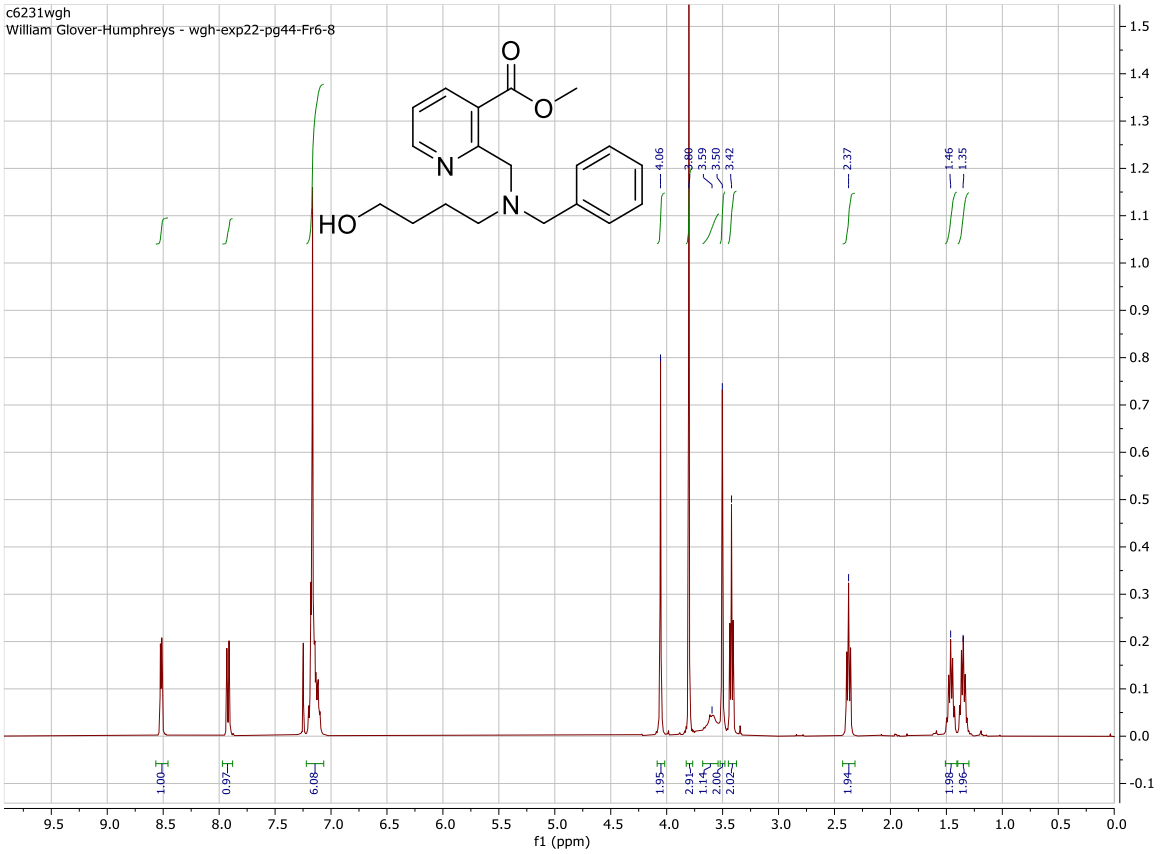
1.01
1.02
1.01
2.01
1.09
2.15
1.08
f1 (ppm)

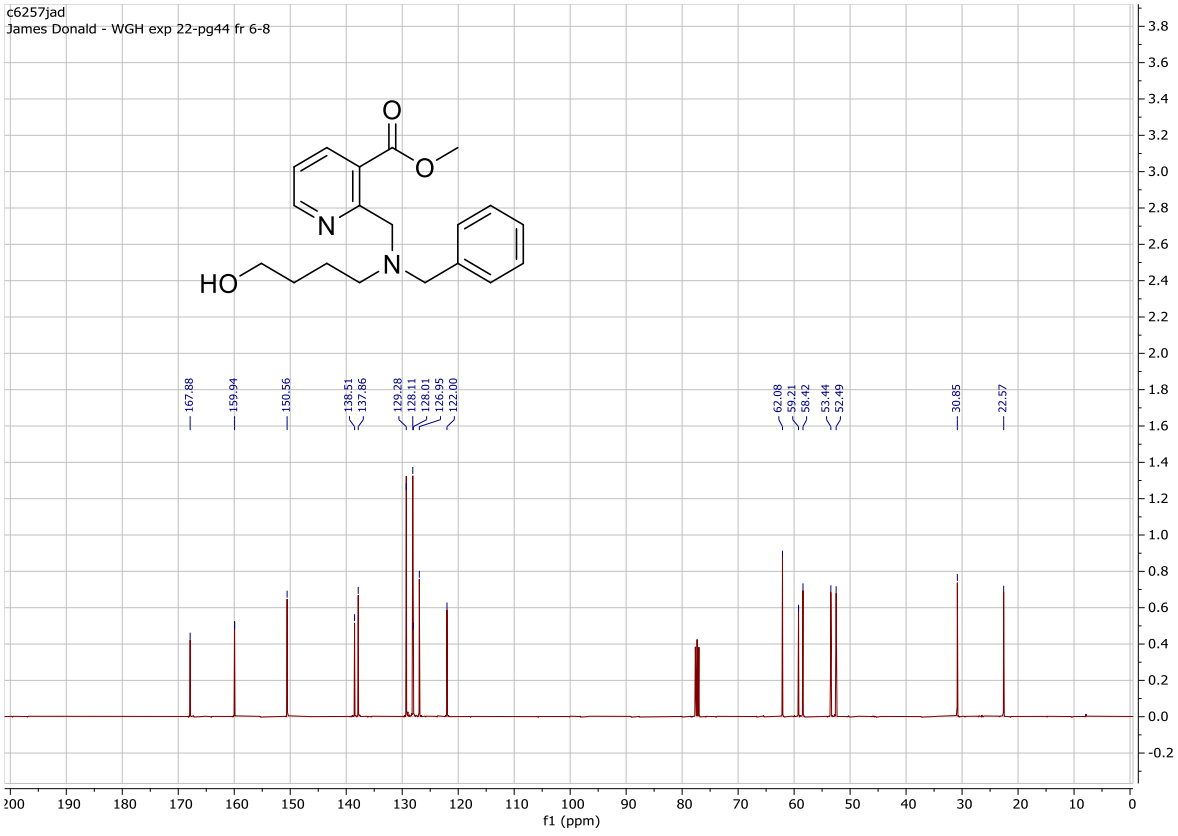

c7907wgh
William Glover-Humphreys - wgh-exp45-pg91-II
O
O
N
N
171.09
159.26
150.42
137.32
126.60
122.08
68.73
64.29
58.49
55.13
29.84
23.71
f1 (ppm)

Methyl 2-((benzyl(4-hydroxybutyl) amino) methyl) nicotinate (6-119)

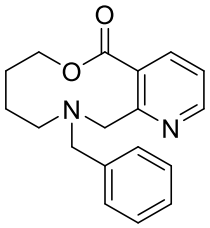


To a stirring solution of potassium carbonate (0.415 g, 3.00 mmol) in acetonitrile (5.00 mL), 4-benzylamino butan-1-ol (**6-90**) (0.179 g, 1.00 mmol) was added followed by methyl 2-(bromo methyl) nicotinate (**6-117**) (0.230 g, 1.00 mmol). The reaction mixture was heated to reflux at 90 °C for 3 hours under argon before filtering through Celite washing with dichloromethane, concentrating under vacuum and purifying by flash column chromatography (15:4:1 dichloromethane:ethyl acetate:triethylamine) to afford the title compound as a clear oil (0.153 g, 47%) R_f = 0.47 (15:4:1 dichloromethane:ethyl acetate:triethylamine); ν_{max}/cm^{-1} (thin film) 3357, 2948, 2864, 2238, 1726, 1575, 1431, 1136, 1086, 1057, 910, 728; δ_H (400 MHz, $CDCl_3$) 8.53−8.51 (1H, m, Ar**H**), 7.94−7.91 (1H, m, Ar**H**), 7.20−7.09 (6H, m, Ar**H**), 4.06 (2H, s, ArC**H**$_2$N), 3.80 (3H, s, OC**H**$_3$), 3.56 (1H, bs, O**H**), 3.50 (2H, s, ArC**H**$_2$N), 3.42 (2H, t, *J* = 6.9 Hz, $CH_2C\mathbf{H}_2OH$), 2.37 (2H, t, *J* = 6.1 Hz, $CH_2C\mathbf{H}_2N$), 1.46 (2H, quintet, *J* = 6.9 Hz, $CH_2C\mathbf{H}_2CH_2$), 1.35 (2H, quintet, *J* = 6.1 Hz, $CH_2C\mathbf{H}_2CH_2$); δ_c (100 MHz, $CDCl_3$) 167.9 (**C**O), 159.9 (Ar**C**), 150.6 (Ar**C**H), 138.5 (Ar**C**), 137.9 (Ar**C**H), 129.3 (Ar**C**H), 128.1 (Ar**C**), 128.0 (Ar**C**H), 127.0 (Ar**C**H), 122.0 (Ar**C**H), 62.1 (**C**H$_2$OH), 59.2 (Ar**C**H$_2$N), 58.4 (Ar**C**H$_2$N), 53.4 ($CH_2\mathbf{C}H_2N$), 52.5 (O**C**H$_3$), 30.9 (**C**H$_2$), 22.6 (**C**H$_2$); HRMS (ESI) calcd. for $C_{19}H_{25}N_2O_3$ 329.1865. Found $[MH]^+$, 329.1858 (−2.13 ppm error).

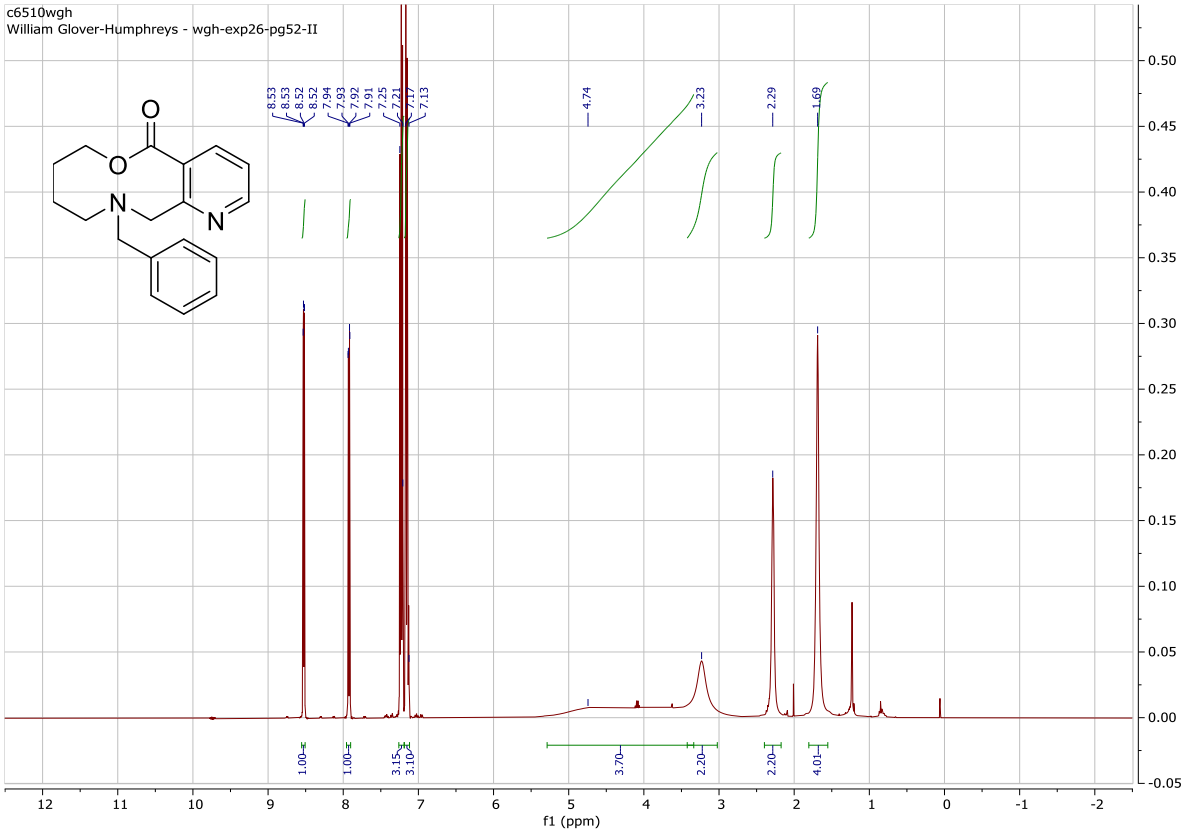

c6231wgh
William Glover-Humphreys - wgh-exp22-pg44-Fr6-8
O
O
N
N
HO
4.06
3.80
3.59
3.50
3.42
2.37
1.46
1.35
1.00
0.97
6.08
1.95
2.91
1.14
2.00
2.02
1.94
1.98
1.96
f1 (ppm)

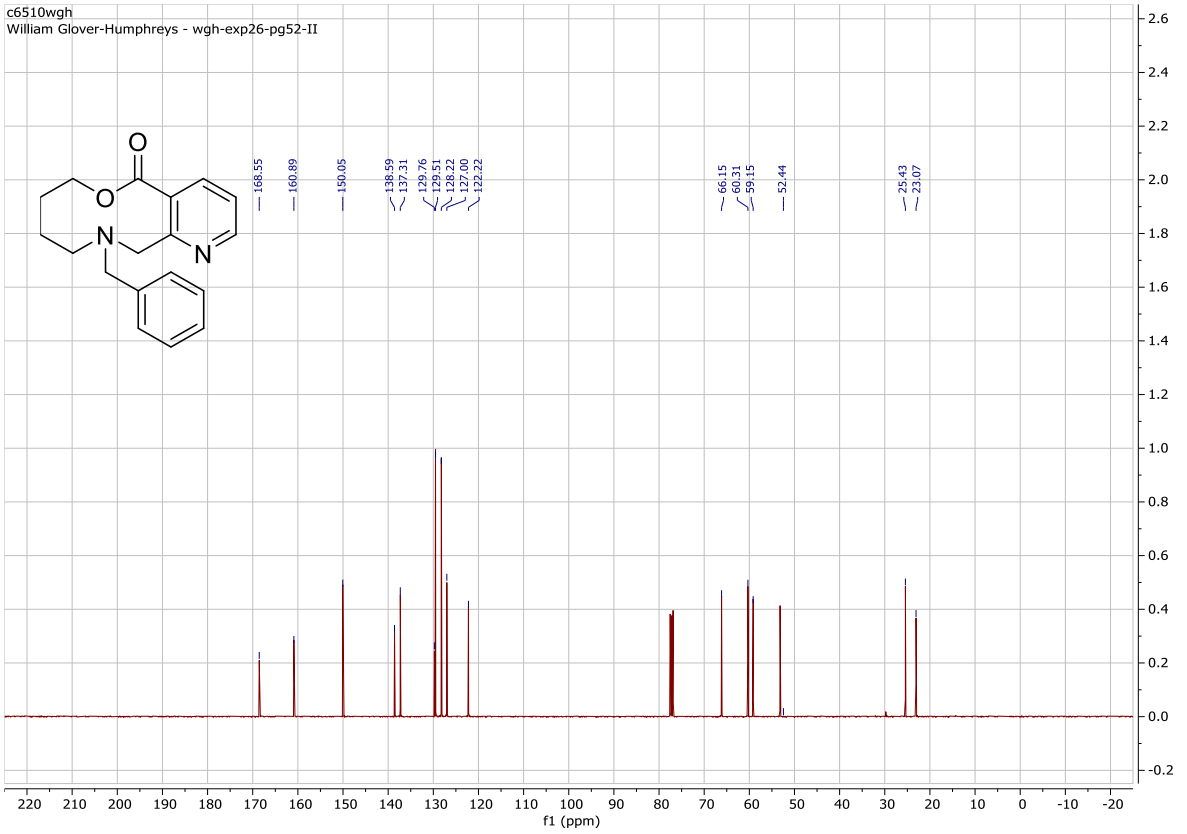

c6257jad
James Donald - WGH exp 22-pg44 fr 6-8
O
O
N
N
HO
167.88
159.94
150.56
138.51
137.86
129.28
128.11
128.01
126.95
122.00
62.08
59.21
58.42
53.44
52.49
30.85
22.57
f1 (ppm)

11-Benzyl-7,8,9,10,11,12-hexahydro-5*H*-pyrido[4,3-*c*] [1,6] oxazecin-5-one (6-122)

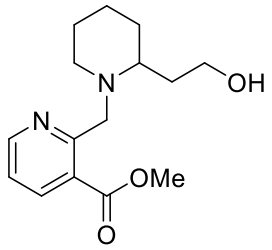


To a stirring solution of methyl 2-((benzyl (4-hydroxy butyl) amino) methyl) nicotinate **(6-119)** (0.153 g, 0.465 mmol) in tetrahydrofuran (1.10 mL), aqueous lithium hydroxide (0.5 M) (1.10 mL, 0.558 mmol) was added and heated for at 50 °C for 3 hours. The solvent was removed under vacuum using dichloromethane (5 × 50 mL) to form an azeotropic mixture. The intermediate lithium 2-((benzyl(4-oxidobutyl) amino) methyl) nicotinate was dissolved in chloroform (4.65 mL) and DIPEA (0.117 g, 0.158 mL, 0.907 mmol) was added followed by T3P 50% w/v in ethyl acetate (0.473 g, 0.744 mmol) and stirred at room temperature for 2 hours under argon. The reaction mixture was washed sequentially in dichloromethane (2 × 100 mL) and brine (50 mL) and the organic phases combined dried with sodium sulfate, filtered, concentrated under vacuum and purified via flash column chromatography (8:2 dichloromethane:ethyl acetate) to afford the title compound (0.0926 g, 67%) R_f = 0.67 (8:2 dichloromethane:ethyl acetate); ν_{max}/cm^{-1} (thin film) 3065, 2955, 2802, 1720, 1588, 1453, 1434, 1295, 1201, 1133, 1092, 954, 789, 729; δ_H (400 MHz, $CDCl_3$) 8.52 (1H, dd, *J* = 5.0 Hz, 1.7 Hz, ArC**H**), 7.93 (1H, dd, *J* = 7.7 Hz, 1.7 Hz, ArC**H**), 7.25−7.21 (3H, m, ArC**H**), 7.17−7.13 (3H, m, ArC**H**), 5.15−3.40 (4H, m, 2 × C**H**$_2$N), 3.40−2.98 (2H, m, C**H**$_2$N), 2.33−2.22 (2H, m, C**H**$_2$), 1.75−1.60 (4H, m, 2 × C**H**$_2$); δ_c (100 MHz, $CDCl_3$) 168.6 (**C**O), 160.9 (Ar**C**), 150.1 (Ar**C**H), 138.6 (Ar**C**), 137.3 (Ar**C**H), 129.8 (Ar**C**), 129.5 (Ar**C**H), 128.2 (Ar**C**H), 127.0 (Ar**C**H), 122.2 (Ar**C**H), 66.2 (**C**H$_2$N), 60.3 (**C**H$_2$O), 59.2 (**C**H$_2$N), 52.4 (**C**H$_2$N), 25.4 (**C**H$_2$), 23.1 (**C**H$_2$); HRMS (ESI) calcd. for $C_{18}H_{21}N_2O_2$ 297.1603. Found $[MH]^+$ 297.1588 (−5.05 ppm error).

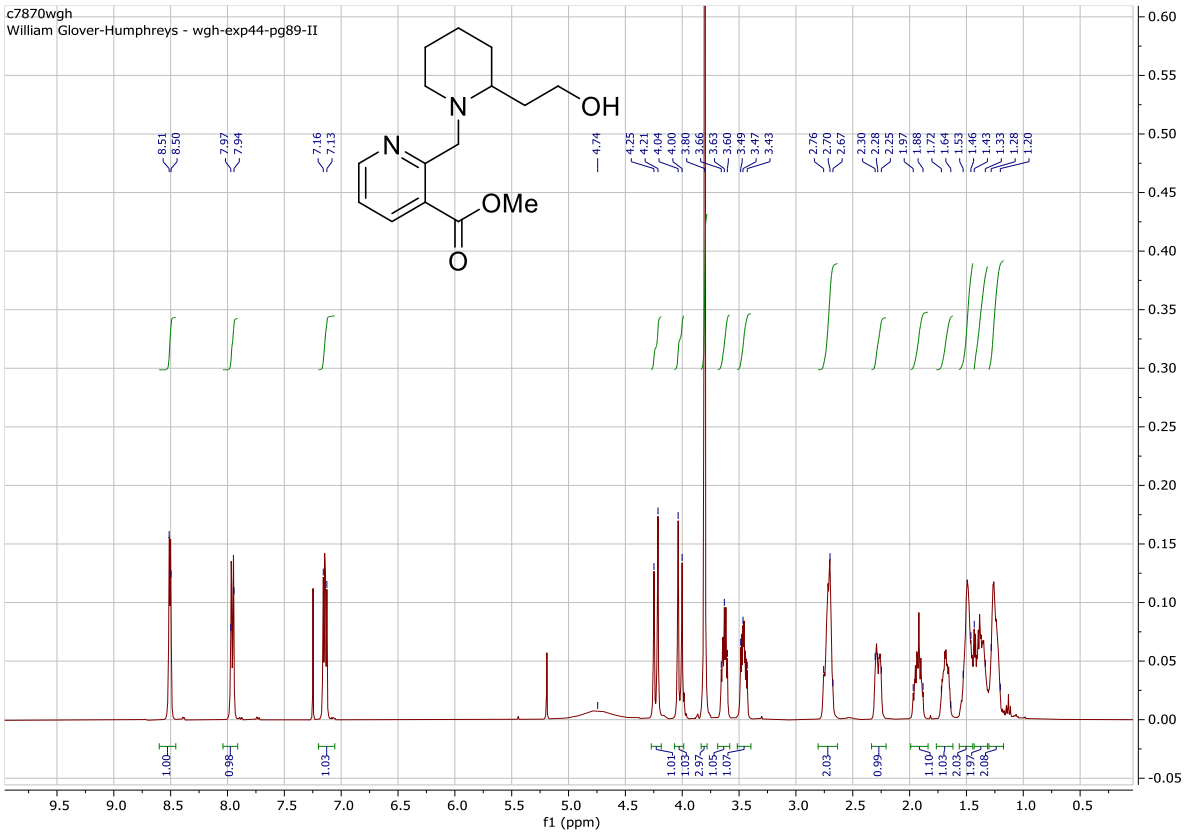

c6510wgh
William Glover-Humphreys - wgh-exp26-pg52-II
8.53
8.53
8.52
8.52
7.94
7.93
7.92
7.91
7.25
7.21
7.17
7.13
4.74
3.23
2.29
1.69
1.00
1.00
3.15
3.10
3.70
2.20
2.20
4.01
f1 (ppm)

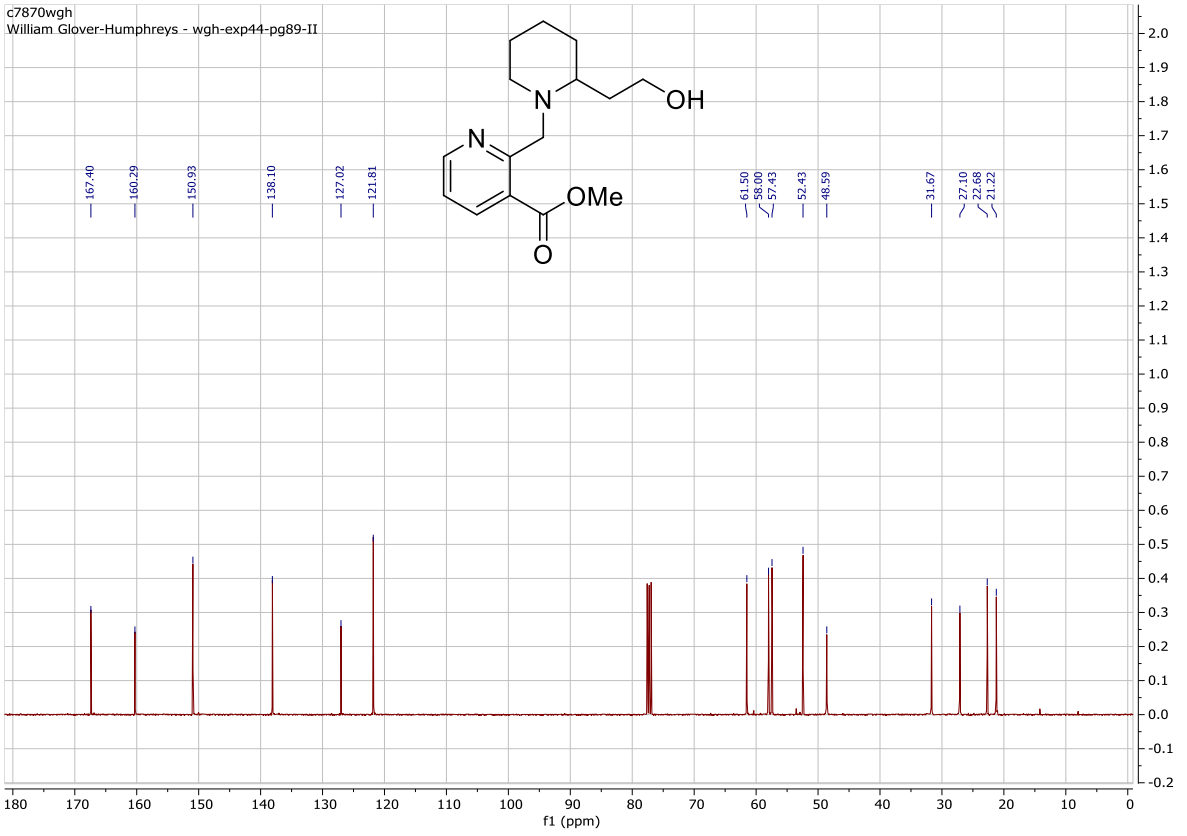

c6510wgh
William Glover-Humphreys - wgh-exp26-pg52-II
168.55
160.89
150.05
138.59
137.31
129.76
129.51
128.22
127.00
122.22
66.15
60.31
59.15
52.44
25.43
23.07
f1 (ppm)

Methyl 2-((2-(2-hydroxyethyl) piperidin-1-yl) methyl) nicotinate (6-120)



To a stirring solution of potassium carbonate (0.415 g, 3.00 mmol) in acetonitrile (5.00 mL), 2-(piperidin-2-yl) ethan-1-ol **(6-92)** (0.129 g, 1.00 mmol) was added followed by methyl 2-(bromo methyl) nicotinate **(6-117)** (0.230 g, 1.00 mmol). The reaction mixture was heated to reflux at 90 °C for 3 hours under argon before filtering through Celite washing with dichloromethane, concentrating under vacuum and purifying by flash column chromatography (15:4:1 dichloromethane:ethyl acetate:triethylamine) to afford the title compound as a dark red oil (0.153 g, 55%) R_f = 0.47 (15:4:1 dichloromethane:ethyl acetate:triethylamine); ν_{max}/cm^{-1} (thin film) 3365, 2935, 2238, 1725, 15779, 1430, 1283, 1087, 728; δ_H (400 MHz, $CDCl_3$) 8.50 (1H, m, Ar**H**), 7.96 (1H, d, *J* = 7.8 Hz, Ar**H**), 7.14 (1H, m,Ar**H**), 4.74 (1H, bs, O**H**), 4.23 (1H, d, *J* = 14.1 Hz ArC**H**$_a$H$_b$N), 4.02 (1H, d, *J* = 14.1 Hz ArCH$_a$**H**$_b$N), 3.80 (3H, s, OC**H**$_3$), 3.66−3.60 (1H, m, C**H**$_a$H$_b$OH), 3.49−3.43 (1H, m, CH$_a$**H**$_b$OH), 2.76−2.67 (1H, m, NC**H**(CH$_2$)$_2$), 2.76−2.67 (1H, m, NC**H**$_a$H$_b$), 2.31−2.25 (1H, m, NCH$_a$**H**$_b$), 1.97−1.88 (1H, m, C**H**$_a$H$_b$CH$_2$OH), 1.72−1.64 (1H, m, C**H**$_a$H$_b$), 1.53−1.46 (1H, m, C**H**$_a$H$_b$), 1.53−1.46 (1H, m, C**H**$_a$H$_b$), 1.43−1.33 (2H, m, CH$_a$**H**$_b$CH$_2$OH), 1.43−1.33 (1H, m, CH$_a$**H**$_b$), 1.28−1.20 (1H, m, CH$_a$**H**$_b$); δ_c (100 MHz, $CDCl_3$) 167.4 (**C**O), 160.3 (Ar**C**), 150.9 (Ar**C**), 138.1 (Ar**C**H), 127.1 (Ar**C**H), 121.8 (Ar**C**H), 61.5 (**C**H$_2$OH), 58.0 (N**C**H), 57.3 (Ar**C**H$_2$N), 52.4 (O**C**H$_3$), 48.6 (**C**H$_2$N), 31.7 (CH**C**H$_2$CH$_2$), 27.1 (**C**H$_2$), 22.7 (**C**H$_2$), 21.2 (**C**H$_2$); HRMS (ESI) calcd. for $C_{15}H_{23}N_2O_3$ 279.1709. Found $[MH]^+$ 279.1708 (−0.358 ppm error).


c7870wgh
William Glover-Humphreys - wgh-exp44-pg89-II
N
OH
N
OMe
O
8.51
8.50
7.97
7.94
7.16
7.13
4.74
4.25
4.21
4.04
4.00
3.80
3.66
3.63
3.60
3.49
3.47
3.43
2.76
2.70
2.67
2.30
2.28
2.25
1.97
1.88
1.72
1.64
1.53
1.46
1.43
1.33
1.28
1.20
1.00
0.98
1.03
1.01
1.03
2.97
1.05
1.07
2.03
0.99
1.10
1.03
2.03
1.97
2.08
f1 (ppm)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William Glover-Humphreys - wgh-exp44-pg89-II
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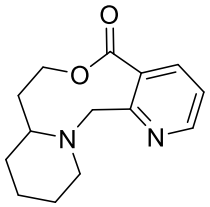
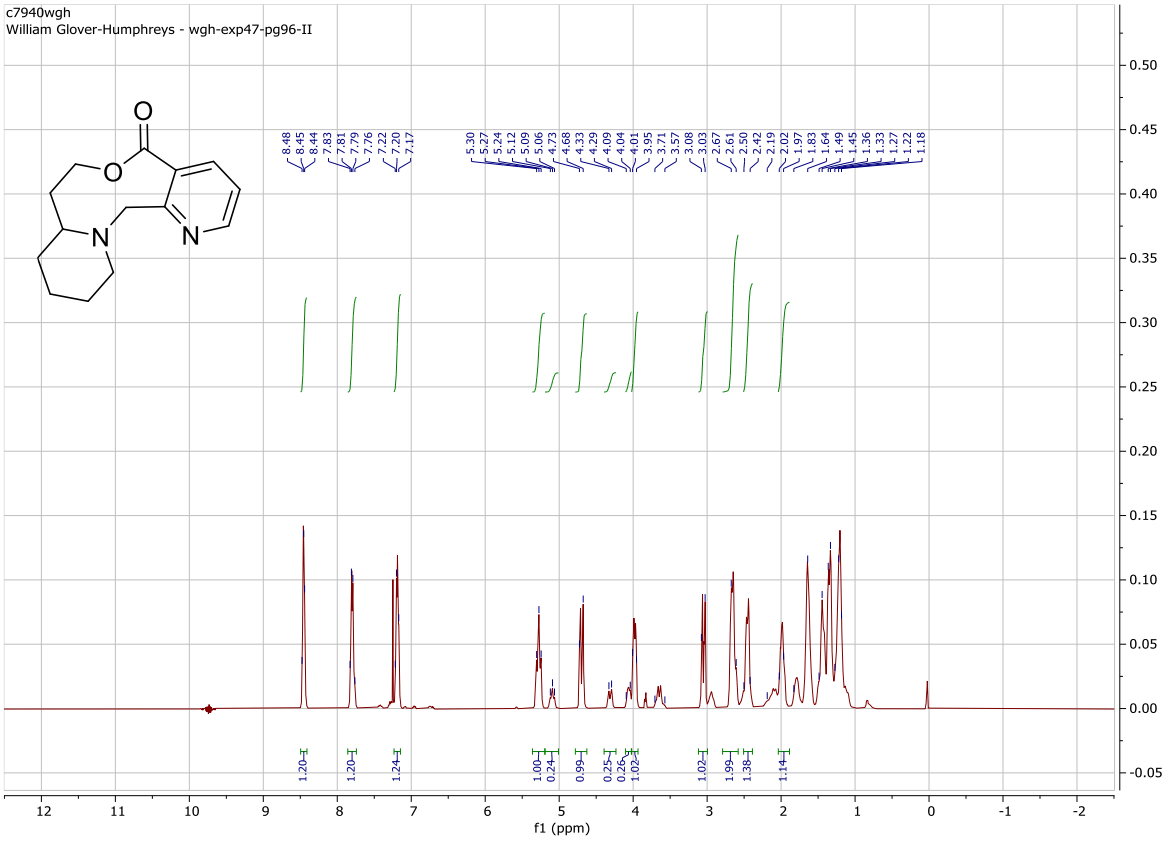
N
OMe
O
167.40
160.29
150.93
138.10
127.02
121.81
61.50
58.00
57.43
52.43
48.59
31.67
27.10
22.68
21.22
f1 (ppm)

8,8a,9,10,11,12-Hexahydro-7*H*-dipyrido[2,1-d:2',3'-*g*] [1,5] oxazonin-5 (14*H*)-one (6-123)



To a stirring solution of methyl 2-((2-(2-hydroxy ethyl) piperidin-1-yl) methyl) nicotinate **(6-120)** (0.129 g, 0.463 mmol) in tetrahydrofuran (1.40 mL), aqueous lithium hydroxide (0.5 M) (1.39 mL, 0.695 mmol) was added and heated for at 50 °C for 3 hours. The solvent was removed under vacuum using dichloromethane (5 × 50 mL) to form an azeotropic mixture. The intermediate lithium 2-((2-(2-oxidoethyl) piperidin-1-yl) methyl) nicotinate was dissolved in chloroform (4.60 mL) and DIPEA (0.110 g, 0.140 mL, 0.851 mmol) was added followed by T3P 50% w/v in ethyl acetate (0.446 g, 0.700 mmol) and stirred at room temperature for 2 hours under argon. The reaction mixture was washed sequentially in dichloromethane (2 × 100 mL) and brine (50 mL) and the organic phases combined dried with sodium sulfate, filtered, concentrated under vacuum and purified via flash column chromatography (8:2 dichloromethane:ethyl acetate) to afford the title compound (0.0869 g, 76%) R_f = 0.77 (16:3:1 dichloromethane:ethyl acetate:triethylamine); ν_{max}/cm^{-1} (thin film) 3431, 2930, 1727, 1429, 1282, 1122, 1087, 792, 707; δ_H (400 MHz, $CDCl_3$) Rotamers observed in a 4:1 ratio 8.48−8.44 (1H, m, Ar**H**), 7.83−7.76 (1H, m, Ar**H**), 7.22−7.17 (1H, m, Ar**H**), 5.27 (1H, t, *J* = 12.2 Hz, C**H**$_a$H$_b$OH) $_{major}$, 5.09 (1H, t, *J* = 11.2 Hz, C**H**$_a$H$_b$OH) $_{minor}$, 4.73−4.68 (1H, m, ArC**H**$_a$H$_b$N) $_{major}$, 4.33−4.29 (1H, m, ArC**H**$_a$H$_b$N) $_{minor}$, 4.09−4.04 (1H, m, CH$_a$**H**$_b$OH) $_{minor}$, 4.01−3.95 (1H, m, CH$_a$**H**$_b$OH) $_{major}$, 3.71−3.57 (1H, m, ArCH$_a$**H**$_b$N) $_{minor}$, 3.08−3.03 (1H ,m, ArCH$_a$**H**$_b$N) $_{major}$, 2.99−2.91 (1H, m, C**H**) $_{minor}$, 2.67−2.61 (1H, m, C**H**) $_{major,}$ 2.67−2.61 (1H, m, C**H**$_a$H$_b$) $_{major}$, 2.52−2.42 (1H, m, C**H**$_a$H$_b$N) $_{both\ rotamers}$, 2.17−2.06 (1H, m C**H**$_a$H$_b$) $_{minor}$, 2.02−1.95 (1H, m, CH$_a$**H**$_b$N) $_{major}$, 1.83−1.07 (7H in total) $_{both\ rotamers}$,[1.82−1.79 (2H, m) $_{minor}$, 1.68−1.56 (2H, m) $_{major}$, 1.50−1.19 (5H, m) $_{both\ rotamers}$, 1.15−1.07 (1H, m) $_{minor}$]; δ_c (100 MHz, $CDCl_3$) 170.4 (**C**O) $_{major}$, 170.1 (**C**O) $_{minor}$, 164.3 (Ar**C**) $_{major}$, 163.5 (Ar**C**) $_{minor}$, 149.6 (Ar**C**H) $_{major}$, 149.4 (Ar**C**H) $_{minor}$, 136.2 (Ar**C**H) $_{major}$, 136.1 (Ar**C**H) $_{minor}$, 129.4 (Ar**C**) $_{major}$, 121.9 (Ar**C**H) $_{major}$, 121.8 (Ar**C**H) $_{minor}$, 66.2 (O**C**H$_2$) $_{minor}$, 63.1 (O**C**H$_2$) $_{major}$, 62.7 (**C**H) $_{minor}$, 59.3 (Ar**C**H$_2$N) $_{major}$, 58.2 (**C**H) $_{major}$, 53.8 (N**C**H$_2$CH$_2$) $_{major}$, 50.1 (Ar**C**H$_2$N) $_{minor}$, 49.2 (N**C**H$_2$CH$_2$) $_{minor}$, 31.7 (**C**H$_2$) $_{major}$, 31.1 (**C**H$_2$) $_{minor}$, 31.0 (**C**H$_2$) $_{major}$, 28.0 (**C**H$_2$) $_{minor}$ 25.8 (**C**H$_2$) $_{minor}$, 25.5 (**C**H$_2$) $_{major}$, 13.4 (**C**H$_2$) $_{major}$, 18.6 (**C**H$_2$) $_{minor}$; HRMS (ESI) calcd. for $C_{14}H_{19}N_2O_2$ 247.1447. Found $[MH]^+$ 247.1441 (−2.43 ppm error).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William Glover-Humphreys - wgh-exp47-pg96-II
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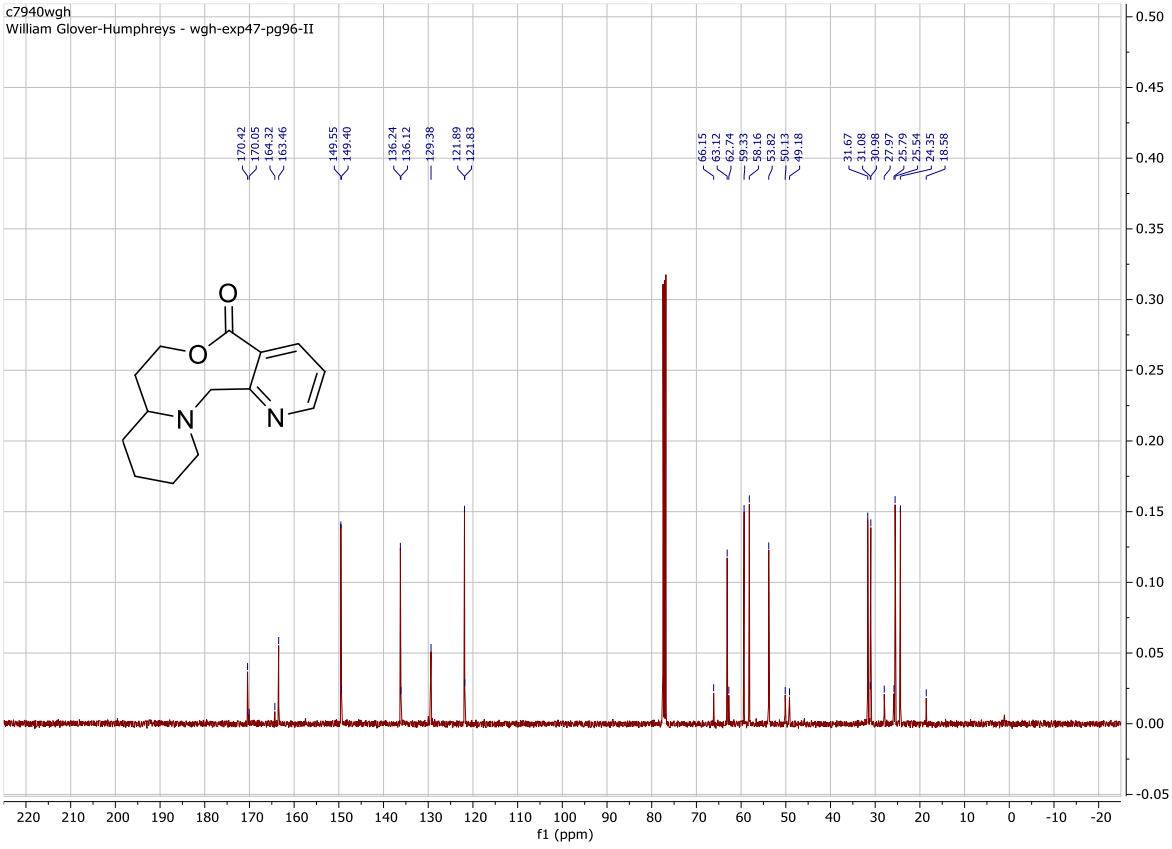
8.45
8.44
7.83
7.81
7.79
7.76
7.22
7.20
7.17
5.30
5.27
5.24
5.12
5.09
5.06
4.73
4.68
4.33
4.29
4.09
4.04
4.01
3.95
3.71
3.57
3.08
3.03
2.67
2.61
2.50
2.42
2.19
2.02
1.97
1.83
1.64
1.49
1.45
1.36
1.33
1.27
1.22
1.18
1.20
1.20
1.24
1.00
0.24
0.99
0.25
0.26
1.02
1.02
1.99
1.38
1.14
f1 (ppm)


c7940wgh
William Glover-Humphreys - wgh-exp47-pg96-II
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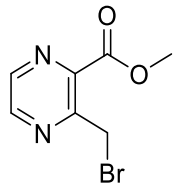
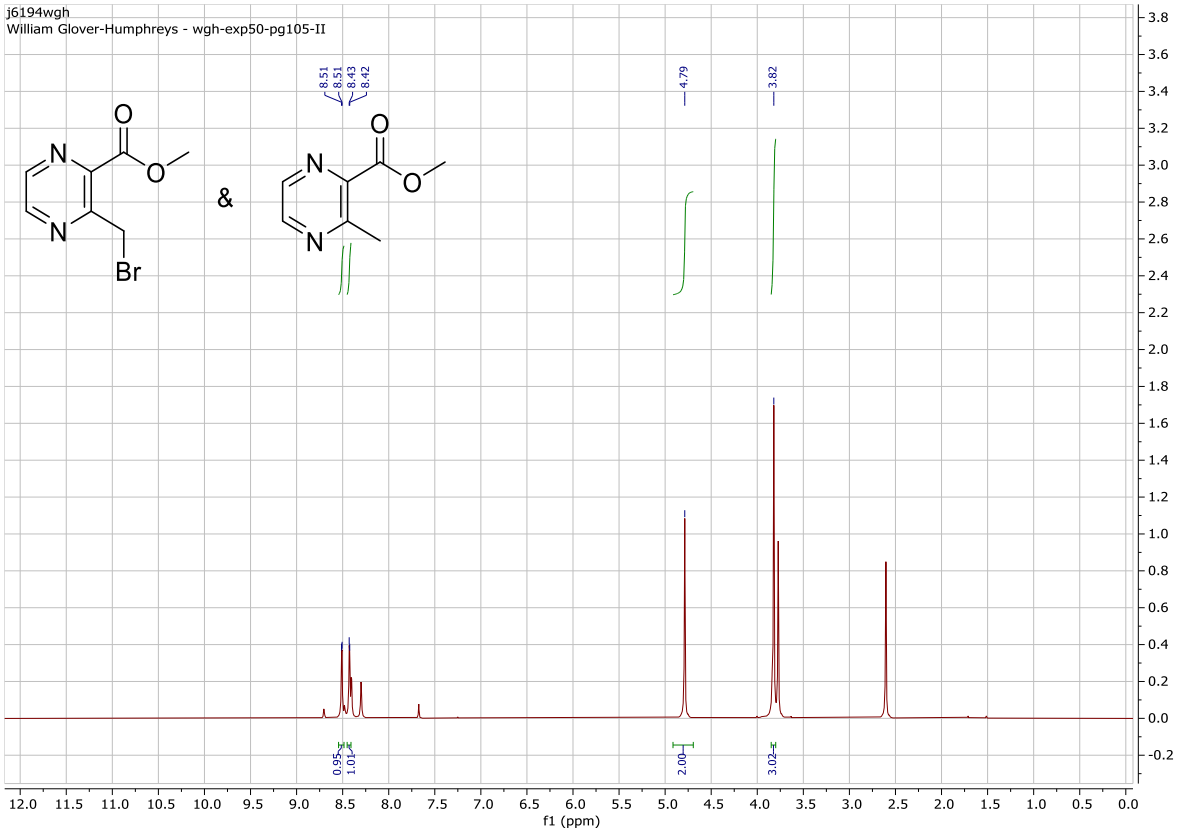
170.05
164.32
163.46
149.55
149.40
136.24
136.12
129.38
121.89
121.83
66.15
63.12
62.74
59.33
58.16
53.82
50.13
49.18
31.67
31.08
30.98
27.97
25.79
25.54
24.35
18.58
f1 (ppm)

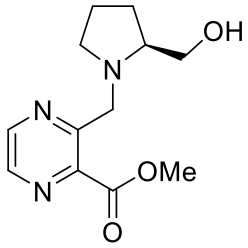
Methyl 3-(bromomethyl)pyrazine-2-carboxylate[42] (6-125)



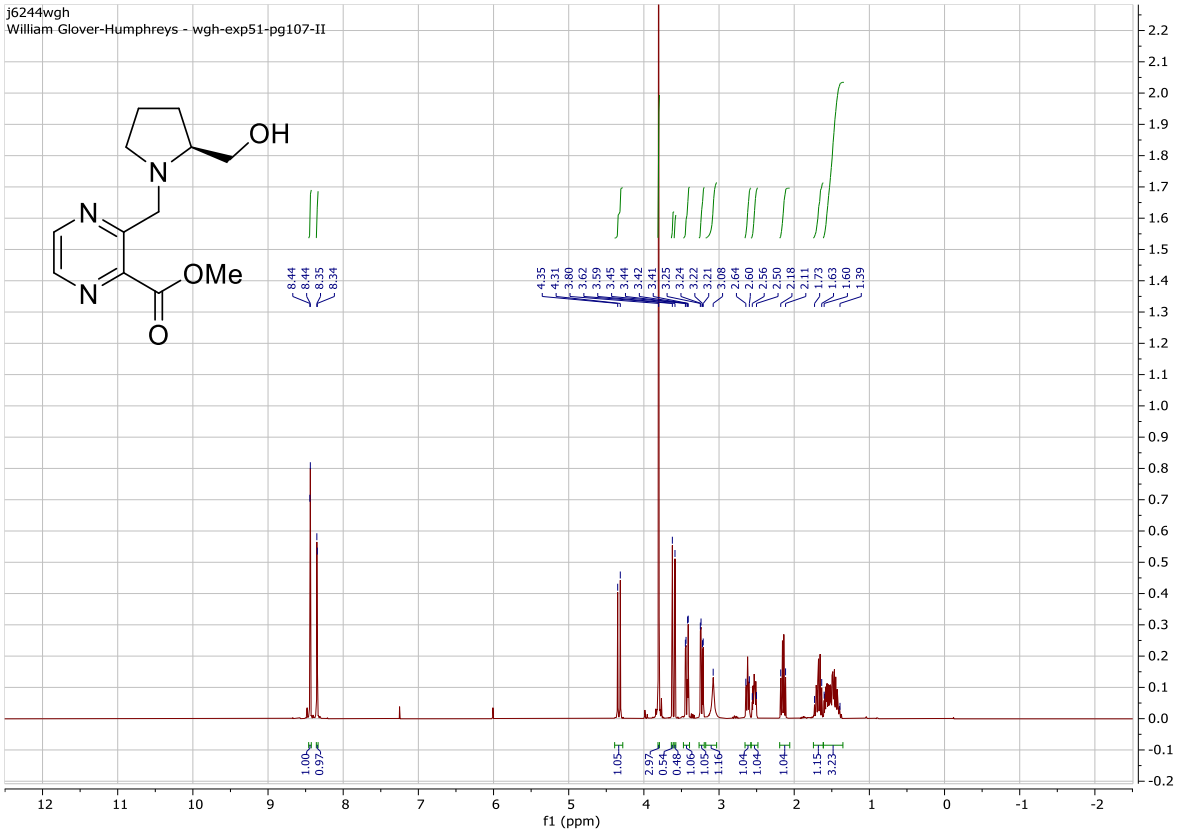
Trifluorotoluene (19.3 mL) was degassed with argon for 20 minutes and then added to a mixture of methyl 3-methylpyrazine-2-carboxylate **(6-124)** (1.00 g, 6.57 mmol), 2,5-dibromo-4,4-dimethylcyclopentane-1,3-dione (1.03 g, 3.61) and azobisisobutyronitrile (0.110 g, 0.657 mmol) under argon. The reaction mixture was heated to reflux at 105 °C for 24 hours. The reaction mixture was filtered through Celite washing with dichloromethane, before removing the solvent under vacuum and purification via flash column chromatography (6:4 hexane:ethyl acetate) to afford an impure sample composed of the title compound and methyl 3-methylpyrazine-2-carboxylate in a 73:27 mass ratio as a brown oil (0.636 g, 42%), R_f = 0.25 (6:4 hexane:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 8.51 (1H, d, *J* = 2.1 Hz, Ar**H**), 8.42 (1H, d, *J* = 2.1 Hz, Ar**H**), 4.79 (2H, s, C$\mathbf{H}_2$Br), 3.82 (3H, s, O**C**H_3). The NMR spectrum shows a mixture of methyl 3-methylpyrazine-2-carboxylate and methyl 3-(bromomethyl) pyrazine-2-carboxylate.



Methyl (*S*)-3-((2-(hydroxymethyl) pyrrolidin-1-yl) methyl) pyrazine-2-carboxylate (6-126)



To a stirring solution of potassium carbonate (0.207 g, 1.50 mmol) in acetonitrile (5.00 mL), (*S*)-pyrrolidin-2-yl methanol (**6-86**) (0.101 g, 1.00 mmol) was added followed by 3-(bromo methyl) pyrazine-2-carboxylate (**6-125**) (0.231 g, 1.00 mmol). The reaction mixture was heated to reflux at 90 °C for 3 hours under argon before filtering through Celite washing with dichloromethane, concentrating under vacuum and purifying by flash column chromatography (10:9:1 hexane:ethyl acetate:triethylamine) to afford the title compound an oil (0.198 g, 79%) R_f = 0.16 (10:9:1 hexane:ethyl acetate:triethylamine); ν_{max}/cm^{-1} (thin film) 3421, 2952, 1728, 1400, 1104, 733; δ_H (400 MHz, $CDCl_3$) 8.44 (1H, d, *J* = 2.6 Hz, Ar**H**), 8.35 (1H, d, *J* = 2.6 Hz, Ar**H**), 4.33 (1H, d, *J* = 14.0 Hz, ArC**H**$_a$H$_b$N), 3.80 (3H, s, OC**H**$_3$), 3.60 (1H, d, *J* = 14.0 Hz, ArCH$_a$**H**$_b$N), 3.43 (1H, dd, *J* = 11.6 Hz, 3.6 Hz, CHC**H**$_a$H$_b$OH), 3.23 (1H, dd, *J* = 11.6 Hz, 3.6 Hz, CHC**H**$_a$H$_b$OH), 3.08 (1H, bs, O**H**), 2.64−2.60 (1H, m, CH$_2$C**H**$_a$H$_b$N), 2.56−2.50 (1H, m, NC**H**(CH$_2$)$_2$), 2.18−2.11 (1H, m, CH$_2$CH$_a$**H**$_b$N), 1. 73−1.63 (1H, m, C**H**$_a$H$_b$), 1.60−1.39 (1H, m, CH$_a$**H**$_b$) 1.60−1.39 (1H, m, C**H**$_2$); δ_c (100 MHz, $CDCl_3$) 165.7 (**C**O), 154.4 (Ar**C**), 144.4 (Ar**C**H), 143.9 (Ar**C**), 141.4 (Ar**C**H), 64.9 (OC**H**$_3$), 61.8 (**C**H$_2$OH), 57.1 (Ar**C**H$_2$N) 54.2 (**C**H$_2$N), 52.3 (**C**HN), 26.1 (**C**H$_2$), 22.4 (**C**H$_2$); HRMS (ESI) calcd. for $C_{12}H_{18}N_3O_3$ 252.1348. Found $[MH]^+$ 252.1348 (0.00 ppm error).


j6244wgh
William Glover-Humphreys - wgh-exp51-pg107-II
OH
N
N
N
OMe
O
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8.44
8.35
8.34
4.35
4.31
3.80
3.62
3.59
3.45
3.44
3.42
3.41
3.25
3.24
3.22
3.21
3.08
2.64
2.60
2.56
2.50
2.18
2.11
1.73
1.63
1.60
1.39
1.00
0.97
1.05
2.97
0.54
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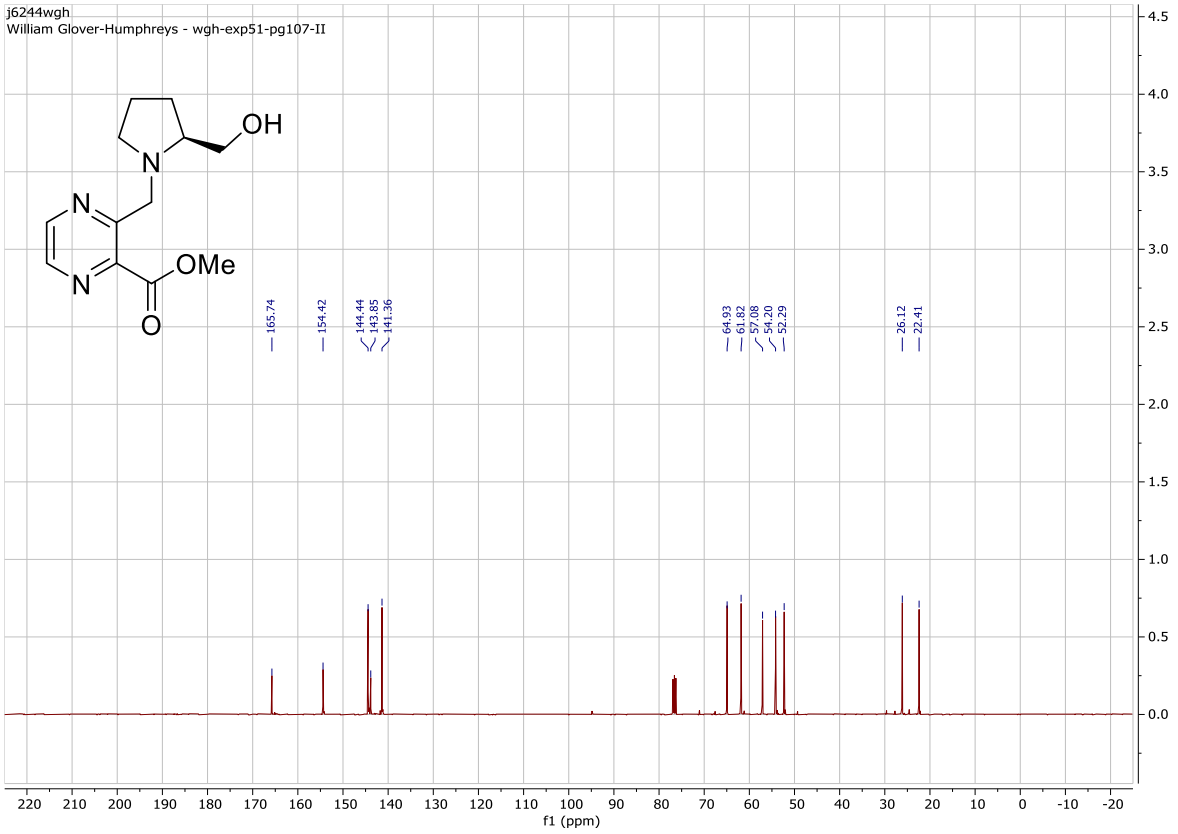
1.06
1.05
1.16
1.04
1.04
1.04
1.15
3.23
f1 (ppm)


j6244wgh
William Glover-Humphreys - wgh-exp51-pg107-II
OH
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OMe
O
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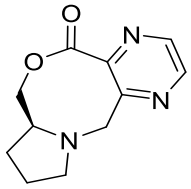
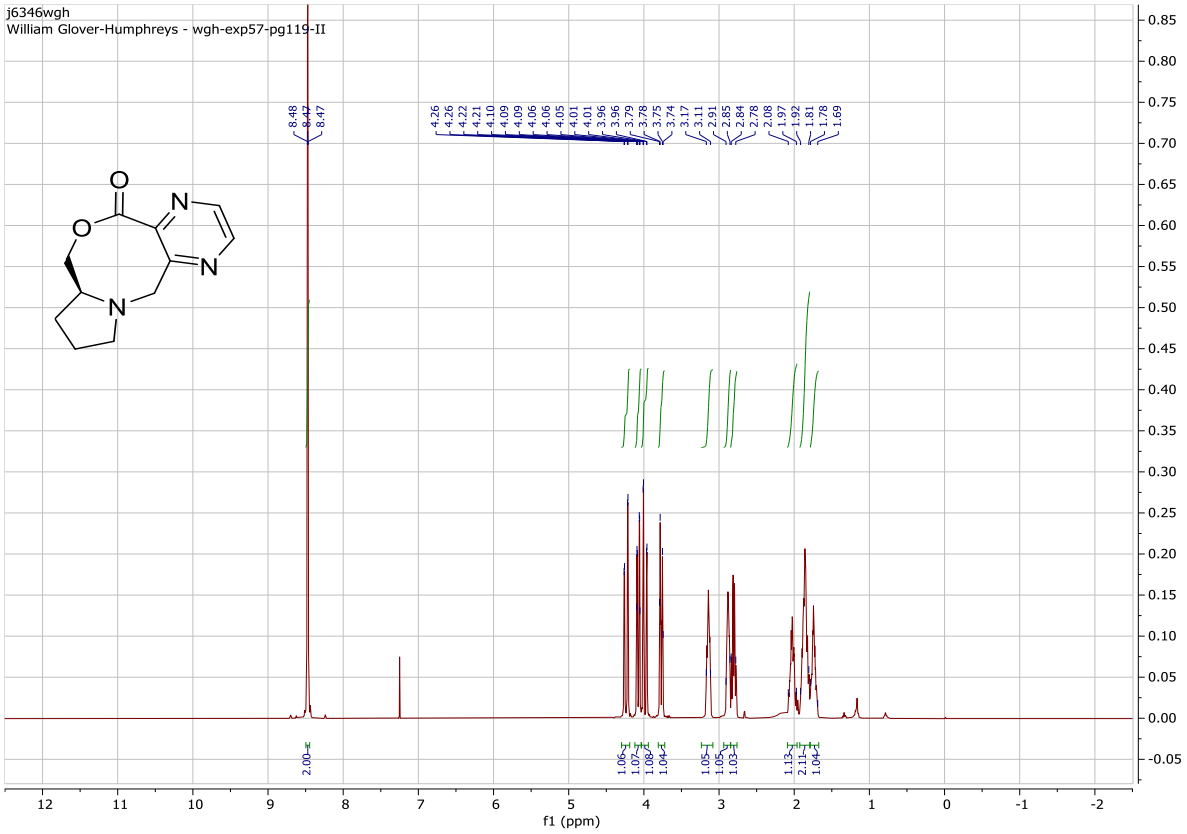
154.42
144.44
143.85
141.36
64.93
61.82
57.08
54.20
52.29
26.12
22.41
f1 (ppm)

(*S*)-7a,8,9,10-Tetrahydro-7H-pyrazino[2,3-*f*] pyrrole [2,1-*c*] [1,4] oxazocin-5 (12*H*)-one (6-129)



To a stirring solution of methyl (*S*)-3-((2-(hydroxy methyl) pyrrolidin-1-yl) methyl) pyrazine-2-carboxylate **(6-126)** (0.153 g, 0.607 mmol) in tetrahydrofuran (2.00 mL), aqueous lithium hydroxide (0.5 M) (2.00 mL, 1.02 mmol) was added and heated at 50 °C for 3 hours. The solvent was removed under vacuum using dichloromethane (5 × 50 mL) to form an azeotropic mixture. The intermediate lithium (*S*)-3-((2-(oxidomethyl) pyrrolidin-1-yl) methyl) pyrazine-2-carboxylate was dissolved in chloroform (7.9 mL) and DIPEA (0.188 g, 0.250 mL, 1.45 mmol) was added followed by T3P 50% w/v in ethyl acetate (0.750 g, 1.18 mmol) and stirred at room temperature for 24 hours under argon. The reaction mixture was washed sequentially in dichloromethane (2 × 100 mL) and brine (50 mL) and the organic phases combined dried with sodium sulfate, filtered, concentrated under vacuum and purified via flash column chromatography (10:9:1 hexane:ethyl acetate:triethylamine) to afford the title compound (0.0892 g, 67%) R_f = 0.21 (10:9:1 hexane:ethyl acetate:triethylamine); ν_{max}/cm^{-1} (thin film) 3386.7, 2951.7, 1701.5, 1397.4, 1343.5, 1276.7, 1153.4, 858.4, 733.7; δ_H (400 MHz, $CDCl_3$) 8.48−8.47 (2H, m, 2 × ArC**H**), 4.24 (1H, dd , *J* = 18.4 Hz, *J* = 2.1 Hz, ArC**H**$_a$H$_b$N), 4.10−4.05 (1H, m, C**H**$_a$H$_b$O), 3.98 (1H, dd , *J* = 18.4 Hz, *J* = 2.1 Hz, ArCH$_a$**H**$_b$N), 3.79−3.74 (1H, m, CH$_a$**H**$_b$O), 3.17−3.11 (1H, m, NC**H**$_a$H$_b$CH$_2$), 2.91−2.85 (1H, m, NC**H**(CH$_2$)$_2$), 2.84−2.78 (1H, m, NCH$_a$**H**$_b$CH$_2$), 2.08−1.97 (1H, m, C**H**$_a$H$_b$), 1.92 −1.81 (1H, m, CH$_a$**H**$_b$), 1.92 −1.81 (1H, m, C**H**$_a$H$_b$), 1.78−1.69 (1H, m, CH$_a$**H**$_b$); δ_c (100 MHz, $CDCl_3$) 168.3 (**C**O), 155.0 (Ar**C**), 144.8 (Ar**C**), 144.7 (Ar**C**H), 143.4 (Ar**C**H), 69.3 (O**C**H$_2$), 64.3 (**C**H), 57.0 (Ar**C**H$_2$N), 55.3 (N**C**H$_2$CH$_2$), 30.0 (**C**H$_2$), 22.9 (**C**H$_2$); HRMS (ESI) calcd. for $C_{11}H_{14}N_3O_2$ 220.1086. Found $[MH]^+$ 220.1087 (0.454 ppm error); $[\alpha]_D^{20}$ = −22.0 (c = 1.0, dichloromethane), recorded using a Bellingham + Stanley RFM340-T refractometer.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William Glover-Humphreys - wgh-exp57-pg119-II
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8.42
8.47
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4.26
4.22
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4.10
4.09
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4.06
4.05
4.01
4.01
3.96
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2.85
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2.78
2.08
1.97
1.92
1.81
1.78
1.69
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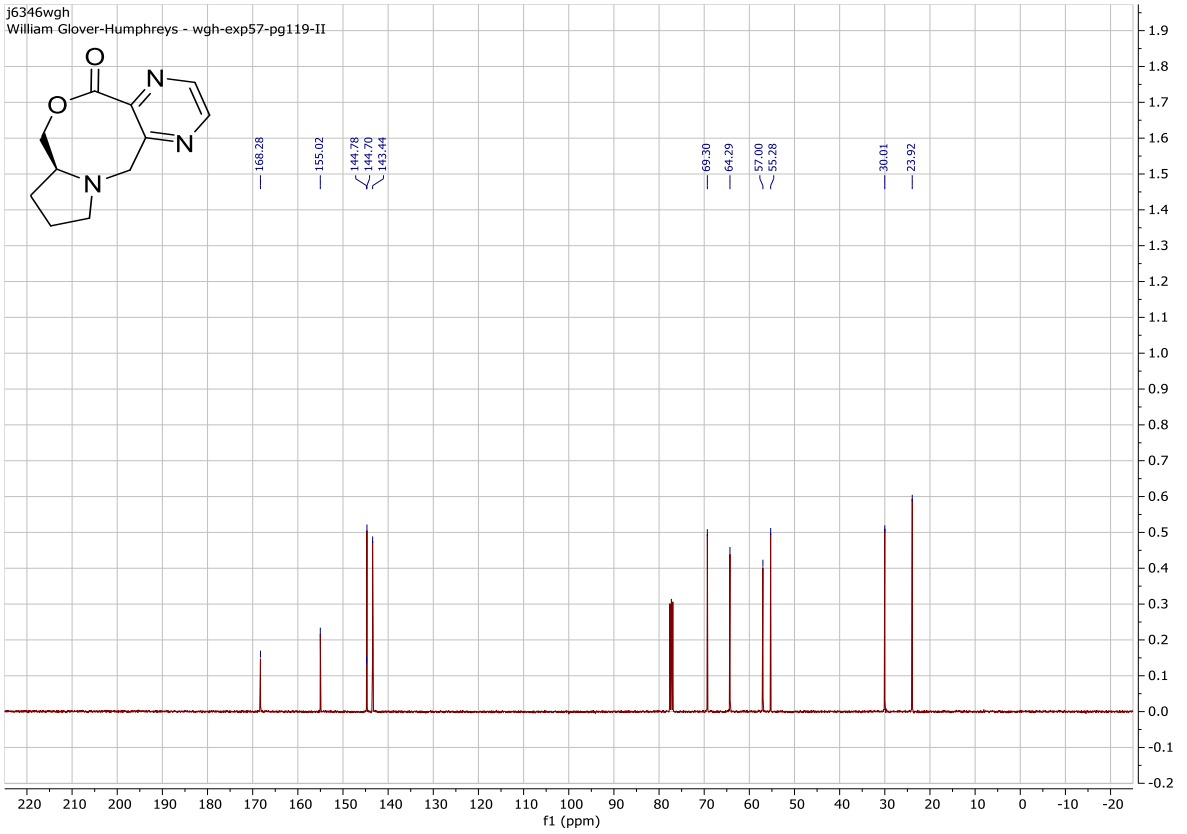
1.03
1.13
2.11
1.04
f1 (ppm)


j6346wgh
William Glover-Humphreys - wgh-exp57-pg119-II
168.28
155.02
144.78
144.70
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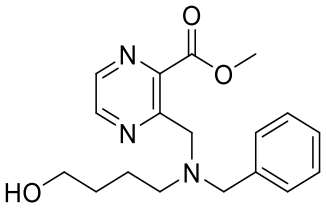
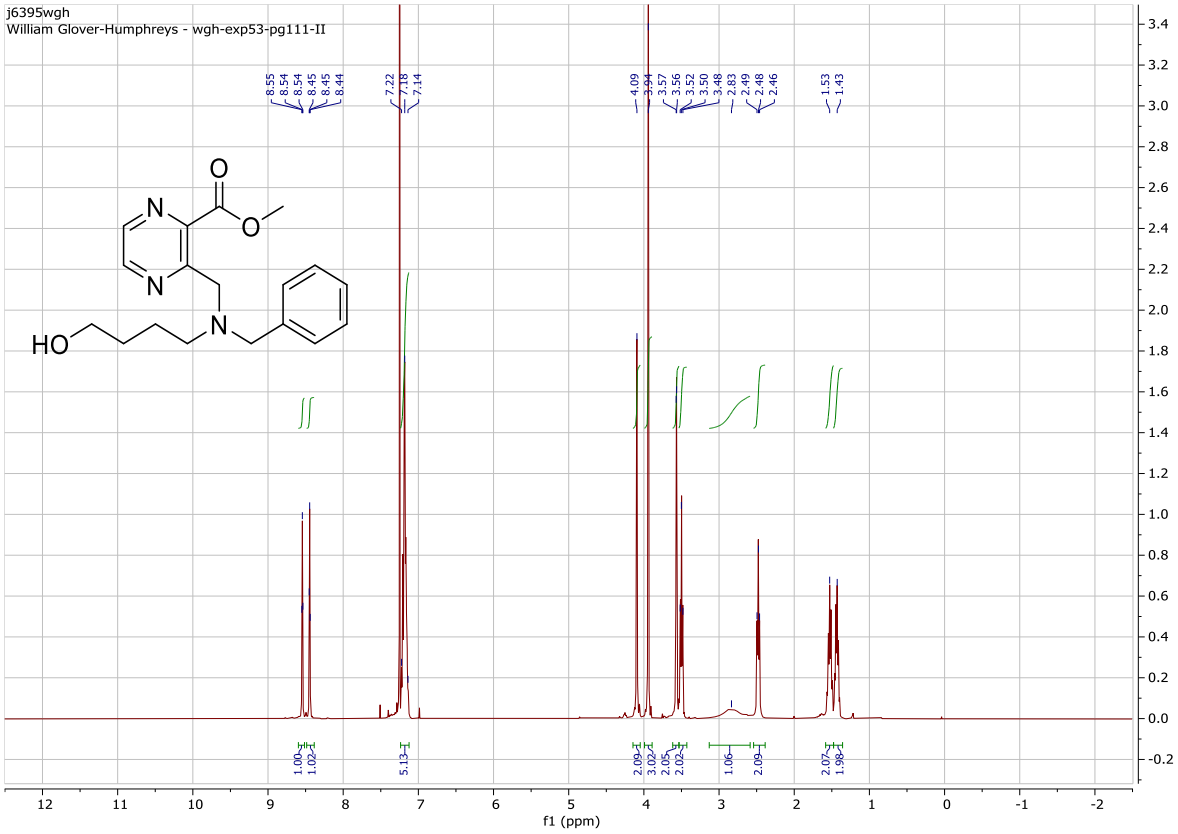
64.29
57.00
55.28
30.01
23.92
f1 (ppm)

Methyl 3-((benzyl(4-hydroxybutyl) amino) methyl) pyrazine-2-carboxylate (6-127)



To a stirring solution of potassium carbonate (0.228 g, 1.65 mmol) in acetonitrile (5.50 mL), 4-benzylamino butan-1-ol (**6-90**) (0.197 g, 1.10 mmol) was added followed methyl 3-(bromo methyl) pyrazine-2-carboxylate (**6-125**) (0.255 g, 1.10 mmol). The reaction mixture was heated to reflux at 90 °C for 3 hours under argon before filtering through Celite washing with dichloromethane, concentrating under vacuum and purifying by flash column chromatography (10:9:1 hexane:ethyl acetate:triethylamine) to afford the title compound as a clear oil (0.256 g, 71%) R_f = 0.40 (10:9:1 hexane:ethyl acetate:triethylamine); ν_{max}/cm^{-1} (thin film) 3406, 2949, 2243, 1733, 1301, 1106, 908, 726; δ_H (400 MHz, $CDCl_3$) 8.55−8.54 (1H, m, ArC**H**), 8.45−8.44 (1H, m, ArC**H**), 7.22−7.14 (5H, m, 5 × ArC**H**), 4.09 (2H, s, NC**H**$_2$Ar), 3.94 (s, 3H, OC**H**$_3$), 3.57 (2H, s, NC**H**$_2$Ar), 3.50 (2H, t, *J* = 6.5 Hz, $CH_2C\mathbf{H}_2OH$), 2.83 (1H, bs, O**H**), 2.48 (2H, t, *J* = 6.5 Hz, $CH_2C\mathbf{H}_2N$), 1.53 (2H, quintet, *J* = 6.5 Hz $CH_2C\mathbf{H}_2CH_2$), 1.43 (2H, quintet, *J* = 6.5 Hz $CH_2C\mathbf{H}_2CH_2$); δ_c (100 MHz, $CDCl_3$) 166.1 (**C**O), 155.8 (Ar**C**), 145.6 (Ar**C**), 144.8 (Ar**C**H), 142.0 (Ar**C**H), 138.0 (Ar**C**), 129.2 (Ar**C**H), 128.1 (Ar**C**H), 127.1 (Ar**C**H), 62.1 ($CH_2\mathbf{C}H_2OH$) 58.5 (N**C**H$_2$Ar), 58.1 (N**C**H$_2$Ar), 54.0 ($CH_2\mathbf{C}H_2N$), 52.9 (O**C**H$_3$), 30.7 ($CH_2\mathbf{C}H_2CH_2$), 22.7 ($CH_2\mathbf{C}H_2CH_2$); HRMS (ESI) calcd. for $C_{18}H_{24}N_3O_3$ 330.1818. Found $[MH]^+$ 330.1814 (−1.21 ppm error).


j6395wgh
William Glover-Humphreys - wgh-exp53-pg111-II
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8.54
8.54
8.45
8.45
8.44
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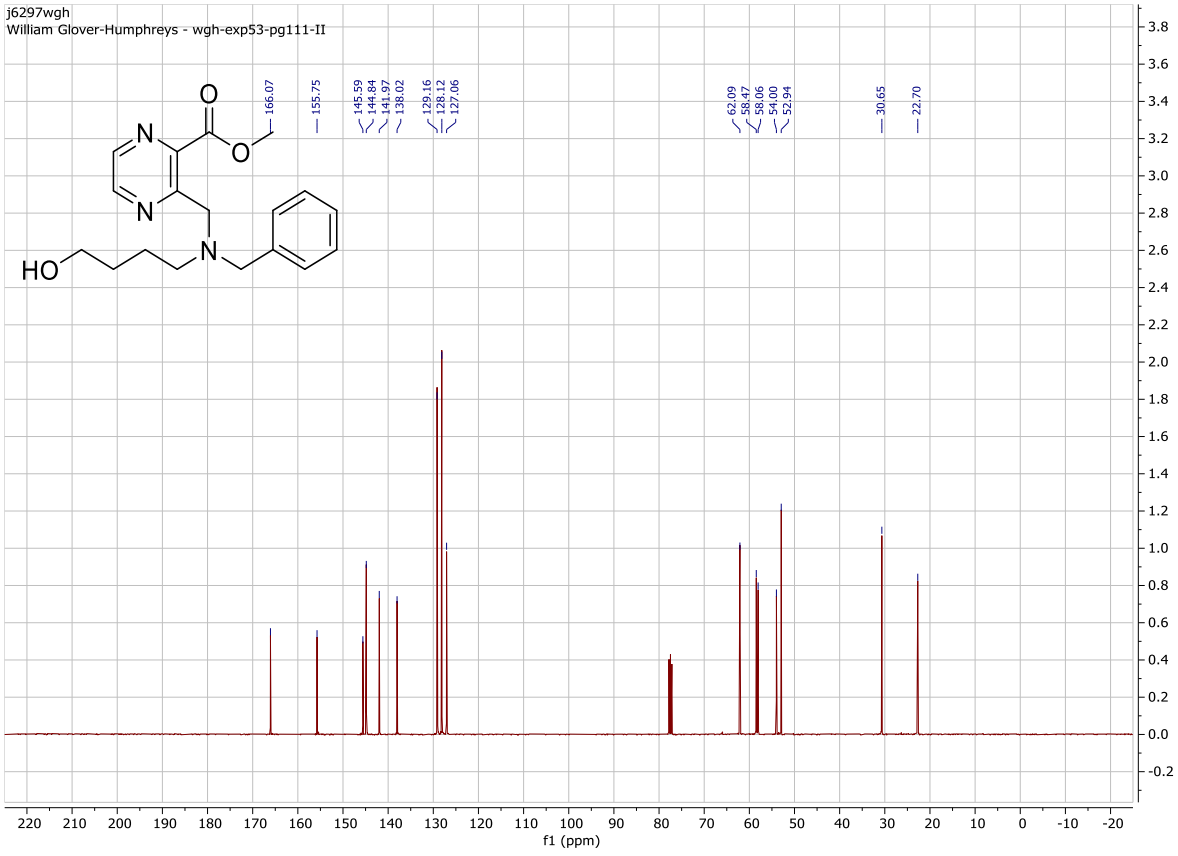
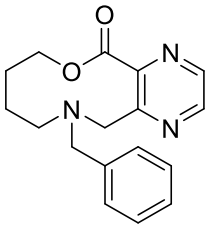
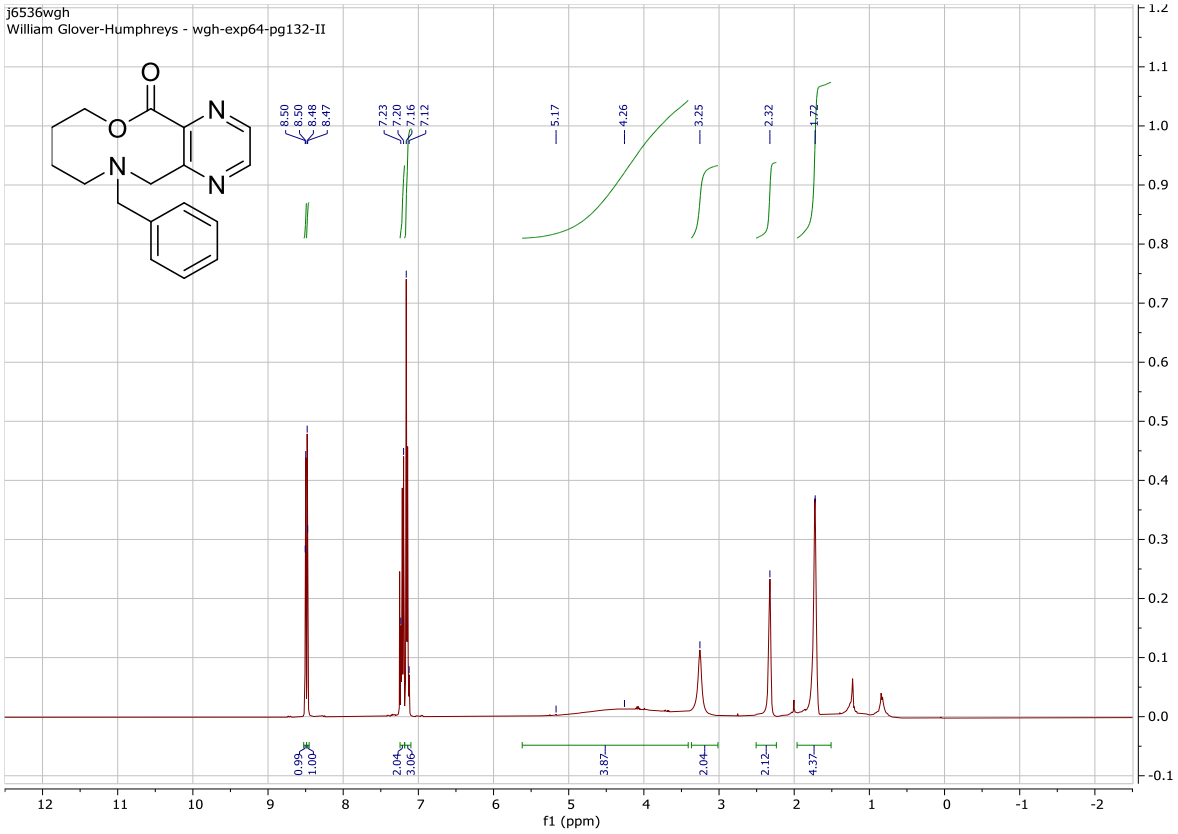
7.18
7.14
4.09
3.94
3.57
3.56
3.52
3.50
3.48
2.83
2.49
2.48
2.46
1.53
1.43
1.00
1.02
5.13
2.09
3.02
2.05
2.02
1.06
2.09
2.07
1.98
f1 (ppm)


j6297wgh
William Glover-Humphreys - wgh-exp53-pg111-II
166.07
155.75
145.59
145.84
141.97
138.02
129.16
128.12
127.06
62.09
58.47
58.06
54.00
52.94
30.65
22.70
f1 (ppm)

11-Benzyl-7,8,9,10,11,12-hexahydro-5*H*-pyrazino[2,3-*c*] [1,6] oxazecin-5-one (6-130)



To a stirring solution of methyl 3-((benzyl (4-hydroxy butyl) amino) methyl) pyrazine-2-carboxylate **(6-127)** (0.256 g, 0.776 mmol) in tetrahydrofuran (2.20 mL), aqueous lithium hydroxide (0.5 M) (2.20 mL, 1.01 mmol) was added and heated for at 50 °C for 3 hours. The solvent was removed under vacuum using dichloromethane (5 × 50 mL) to form an azeotropic mixture. The intermediate l lithium 3-((benzyl(4-oxidobutyl) amino) methyl) pyrazine-2-carboxylate was dissolved in chloroform (7.76 mL) and DIPEA (0.186 g, 0.250 mL, 1.44 mmol) was added followed by T3P 50% w/v in ethyl acetate (0.741 g, 1.16 mmol) and stirred at room temperature for 24 hours under argon. The reaction mixture was washed sequentially in dichloromethane (2 × 100 mL) and brine (50 mL) and the organic phases combined dried with sodium sulfate, filtered, concentrated under vacuum and purified via flash column chromatography (10:9:1 hexane:ethyl acetate:triethylamine) to afford the title compound (0.109 g, 47%) R_f = 0.51 (10:9:1 hexane:ethyl acetate:triethylamine); ν_{max}/cm^{-1} (thin film) 2924, 2244, 1737, 1452, 1300, 1110, 724, 699; δ_H (400 MHz, $CDCl_3$) 8.51−8.50 (1H, m, ArC**H**), 8.49−8.47 (1H, m, ArC**H**), 7.23−7.20 (2H, m, 2× ArC**H**), 7.16−7.12 (3H, m, 3 × ArC**H**), 5.17−3.40 (4H, m, 2 × C**H**$_2$N), 3.35−3.20 (2H, m, C**H**$_2$N), 2.33−2.22 (2H, m, C**H**$_2$), 1.75−1.60 (4H, m, 2 × C**H**$_2$); δ_c (100 MHz, $CDCl_3$) 168.8 (**C**O), 156.7 (Ar**C**), 147.7 (Ar**C**H), 144.3 (Ar**C**H), 142.7 (Ar**C**H), 137.8 (Ar**C**), 129.6 (Ar**C**H), 128.3 (Ar**C**H), 127.2 (Ar**C**H), 66.6 (**C**H$_2$N), 60.7 (**C**H$_2$O), 57.8 (**C**H$_2$N), 53.5 (**C**H$_2$N), 25.3 (**C**H$_2$), 23.0 (**C**H$_2$); HRMS (ESI) calcd. for $C_{17}H_{20}N_3O_2$ 298.1556. Found $[MH]^+$ 298.1551 (−1.68 ppm error).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William Glover-Humphreys - wgh-exp64-pg132-II
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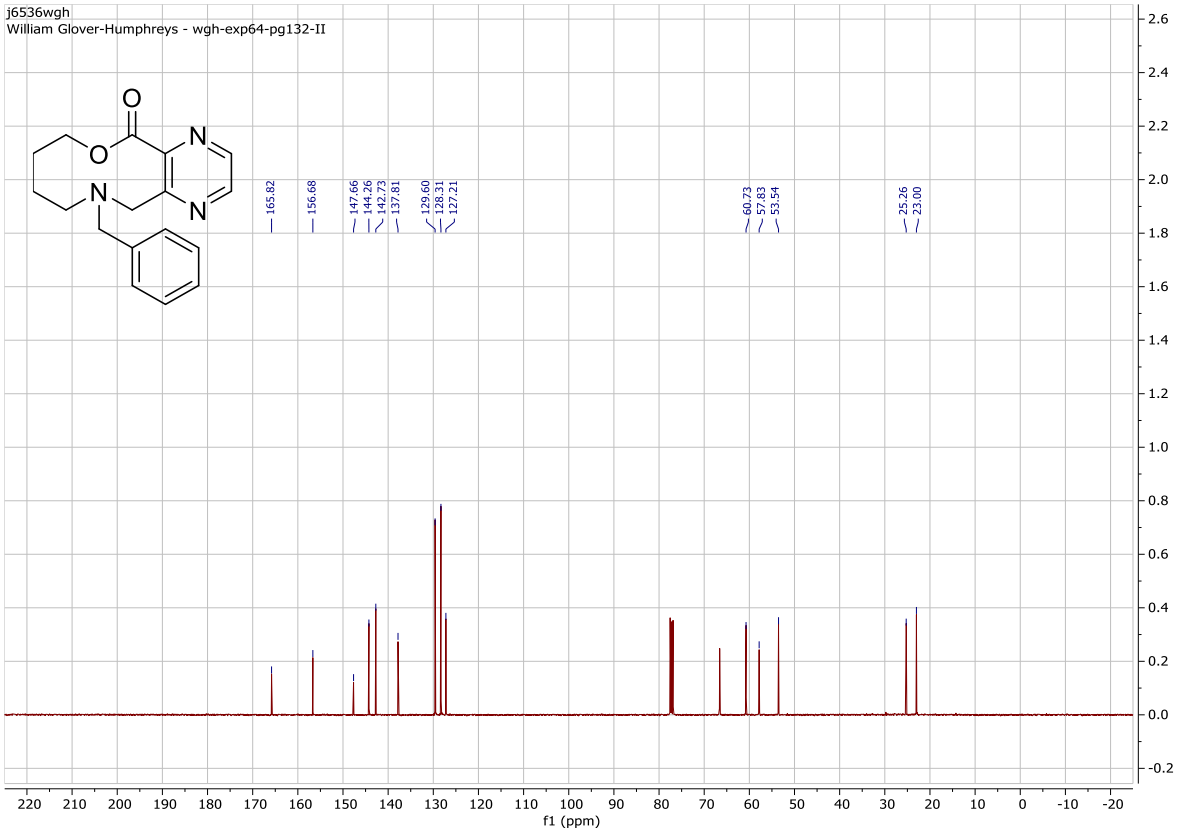
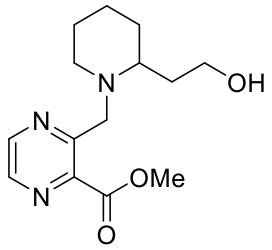
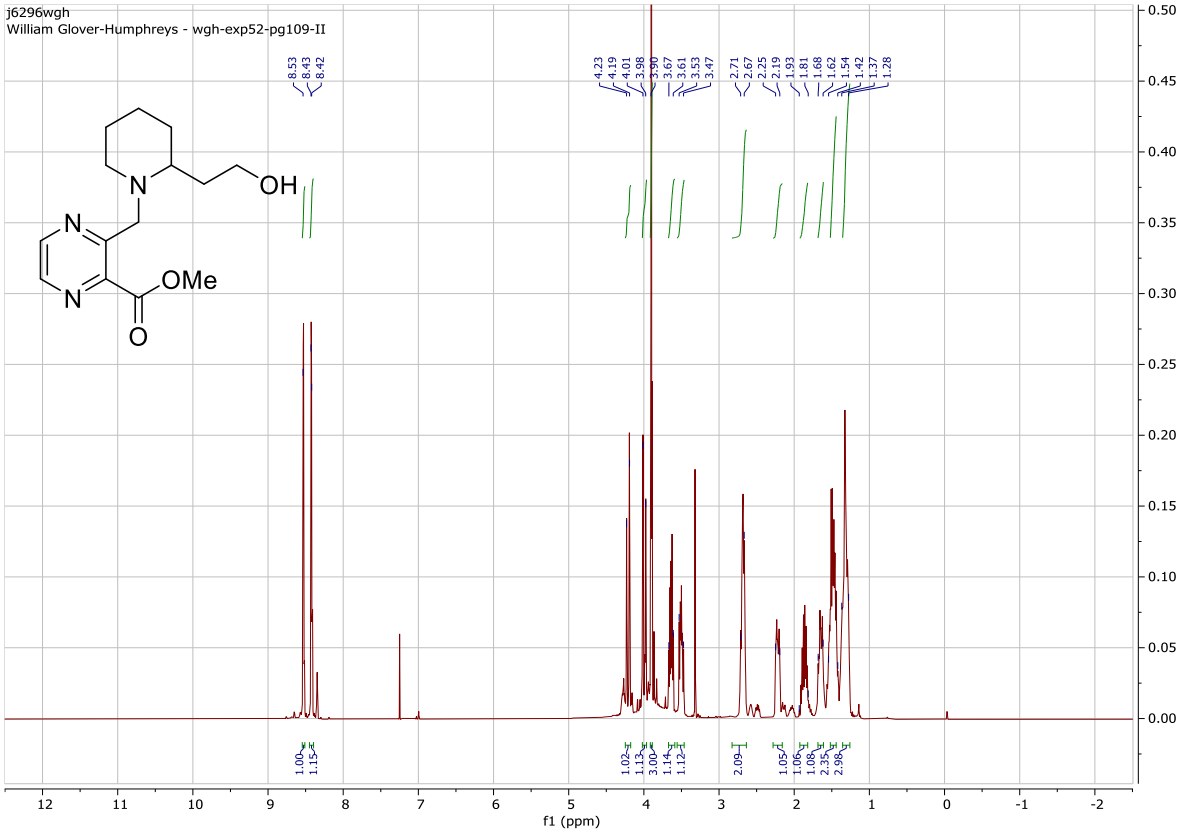
8.50
8.48
8.47
7.23
7.20
7.16
7.12
5.17
4.26
3.25
2.32
1.72
0.99
1.00
2.04
3.06
3.87
2.04
2.12
4.37
f1 (ppm)


j6536wgh
William Glover-Humphreys - wgh-exp64-pg132-II
165.82
156.68
147.66
144.26
142.73
137.81
129.60
128.31
127.21
60.73
57.83
53.54
25.26
23.00
f1 (ppm)

Methyl 3-((2-(2-hydroxyethyl) piperidin-1-yl) methyl) pyrazine-2-carboxylate (6-128)



To a stirring solution of potassium carbonate (0.138 g, 1.00 mmol) in acetonitrile (5.00 mL), 2-(piperidin-2-yl) ethan-1-ol **(6-92)** (0.089 g, 0.690 mmol) was added followed by 3-(bromo methyl) pyrazine-2-carboxylate **(6-125)** (0.160 g, 0.690 mmol). The reaction mixture was heated to reflux at 90 °C for 3 hours under argon before filtering through Celite washing with dichloromethane, concentrating under vacuum and purifying by flash column chromatography (10:9:1 hexane:ethyl acetate:triethylamine) to afford the title compound an oil (0.112 g, 58%) R_f = 0.17 (10:9:1 hexane:ethyl acetate:triethylamine); ν_{max}/cm^{-1} (thin film) 3394, 2936, 2241, 1732, 1301, 1105, 729; δ_H (400 MHz, $CDCl_3$) 8.53−8.52 (1H, m, Ar**H**), 8.43−8.42 (1H, m, Ar**H**), 4.21 (1H, d, *J* = 14.7 Hz, ArC**H**$_a$H$_b$N), 3.99 (1H, d, *J* = 14.7 Hz, ArCH$_a$**H**$_b$N), 3.90 (3H, s, OC**H**$_3$), 3.67−3.61 (1H, m, C**H**$_a$H$_b$OH), 3.53−3.47 (1H, m, CH$_a$**H**$_b$OH), 2.71−2.67 (1H, m NC**H**(CH$_2$)$_2$), 2.71−2.67 (1H, m, NC**H**$_a$H$_b$), 2.25−2.19 (1H, m, NCH$_a$**H**$_b$), 1.93−1.88 (1H, m, C**H**$_a$H$_b$CH$_2$OH), 1.68−1.62 (1H, m, C**H**$_a$H$_b$), 1.68−1.62 (1H, m, C**H**$_a$H$_b$), 1.54−1.42 (2H, m, CH$_a$**H**$_b$CH$_2$OH), 1.54−1.42 (1H, m, C**H**$_a$H$_b$), 1.54−1.42 (1H, m, C**H**$_a$H$_b$), 1.37−1.28 (1H, m, CH$_a$**H**$_b$), 1.37−1.28 (1H, m, CH$_a$**H**$_b$), 1.37−1.28 (1H, m, CH$_a$**H**$_b$); δ_c (100 MHz, $CDCl_3$) 166.0 (**C**O), 155.9 (Ar**C**), 150.9 (Ar**C**), 145.3 (Ar**C**H), 144.9 (Ar**C**), 142.0 (Ar**C**H), 61.2 (**C**H$_2$OH), 58.6 (N**C**H), 56.6 (Ar**C**H$_2$N), 53.0 (O**C**H$_3$), 49.2 (**C**H$_2$N), 31.6 (CH**C**H$_2$CH$_2$), 27.7 (**C**H$_2$), 23.1 (**C**H$_2$), 21.3 (**C**H$_2$); HRMS (ESI) calcd. for $C_{14}H_{22}N_3O_3$ 280.1661. Found $[MH]^+$ 280.1652 (−3.21ppm error).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William Glover-Humphreys - wgh-exp52-pg109-II
8.53
8.43
8.42
4.23
4.19
4.01
3.98
3.90
3.67
3.61
3.53
3.47
2.71
2.67
2.25
2.19
1.93
1.81
1.68
1.62
1.54
1.42
1.37
1.28
N
OH
N
OMe
O
1.00
1.15
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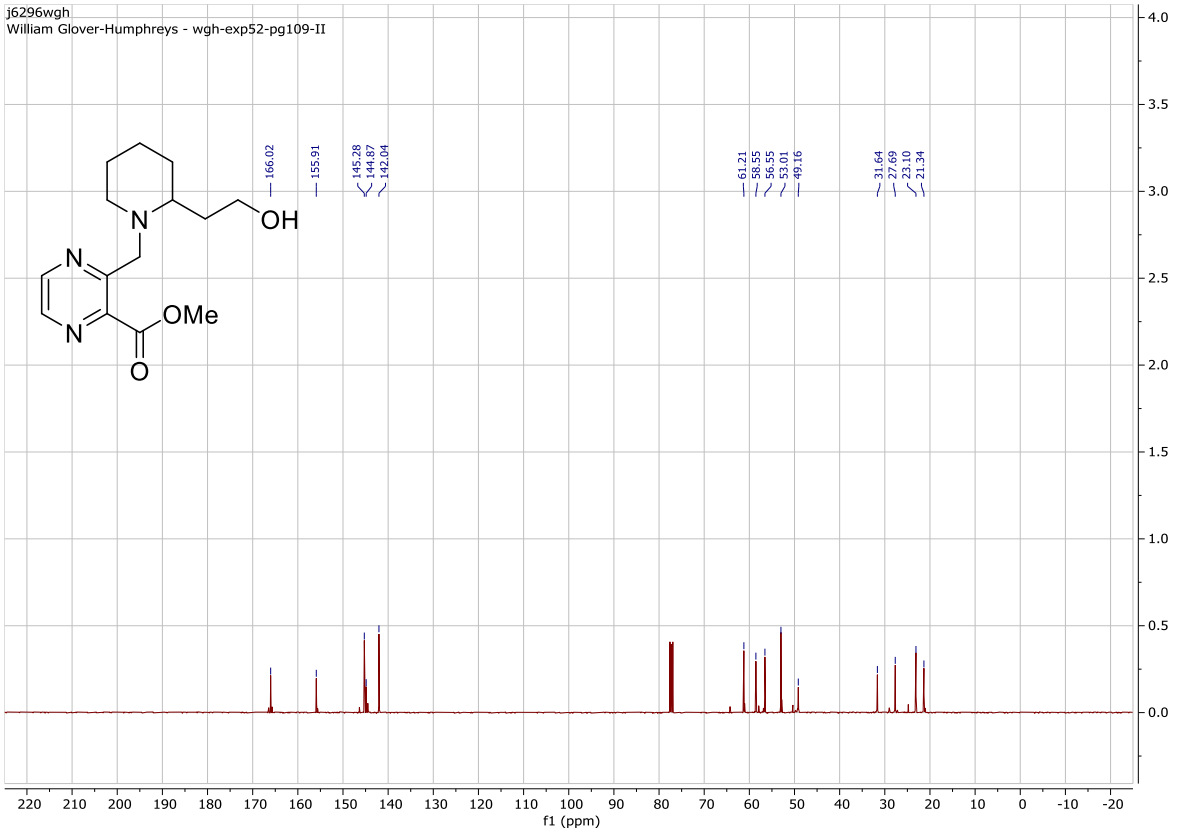
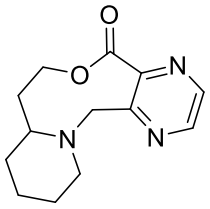
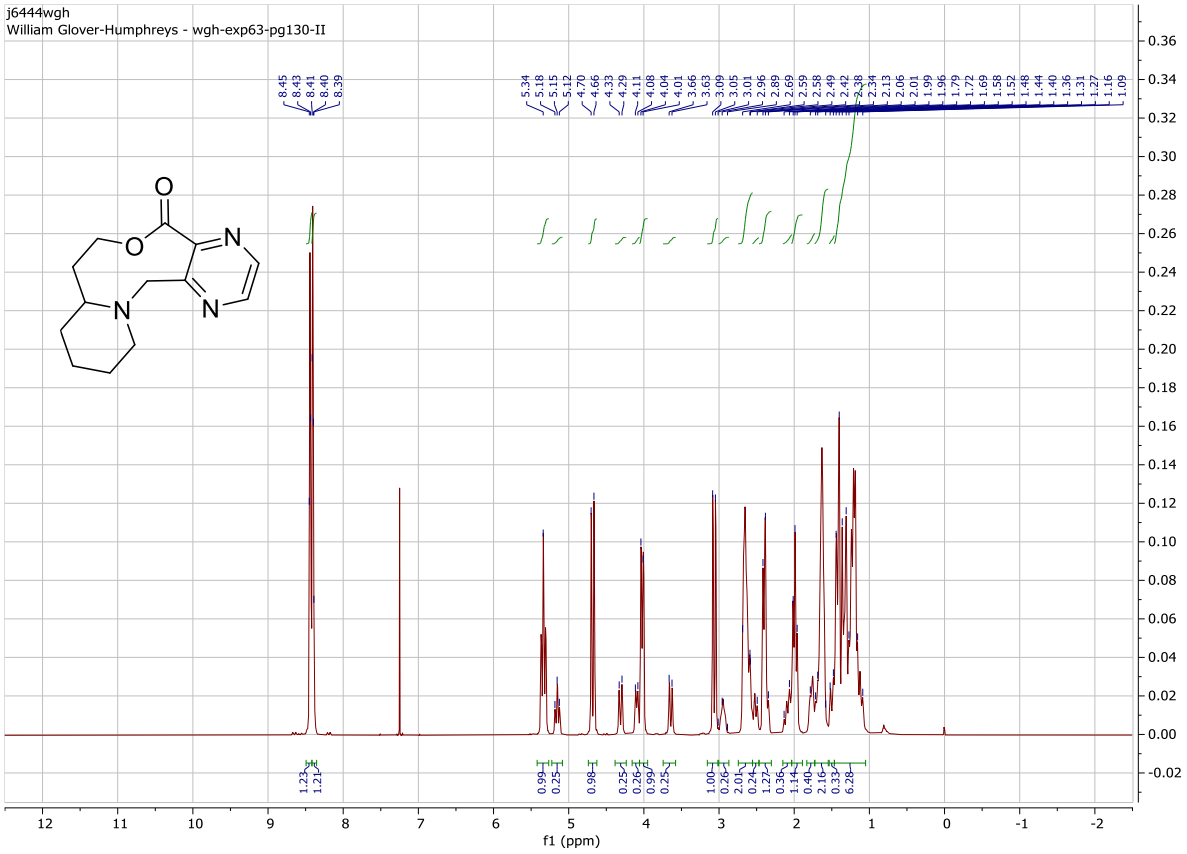
1.06
1.08
2.35
2.98
f1 (ppm)

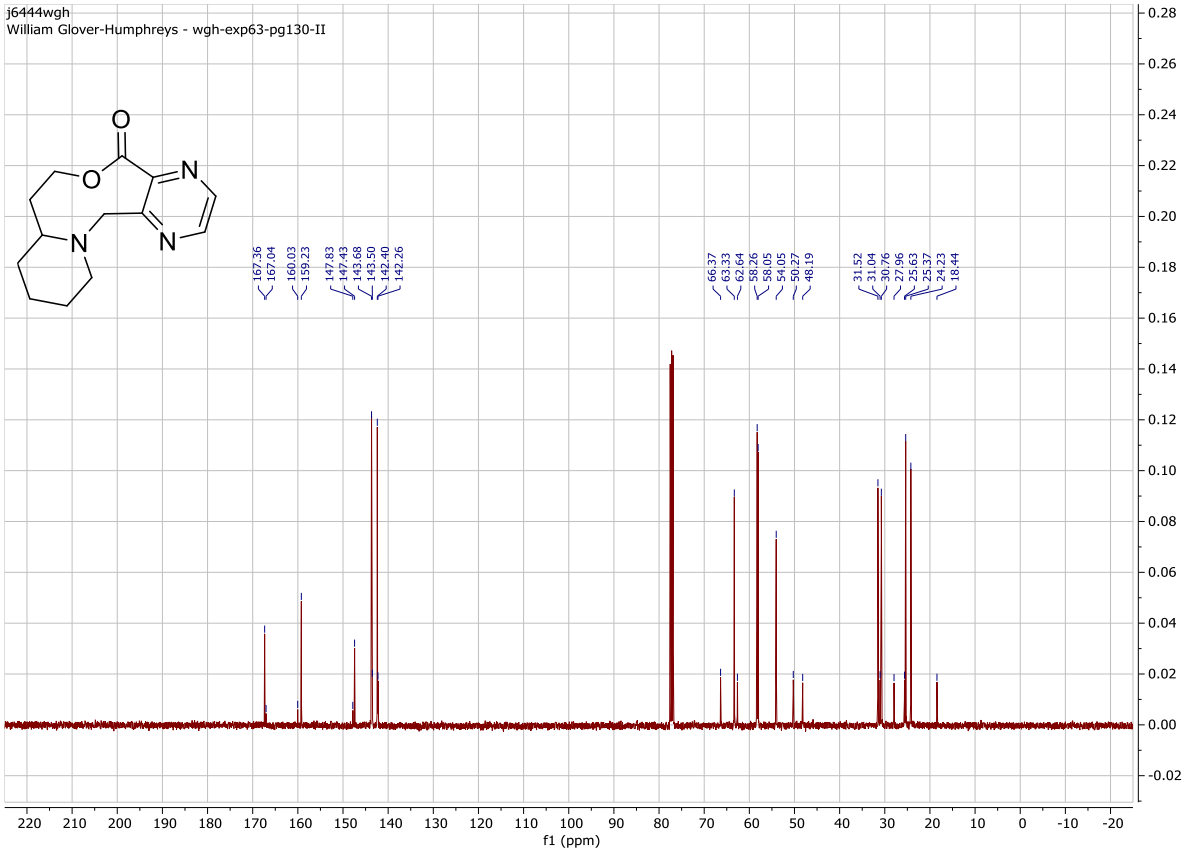

j6296wgh
William Glover-Humphreys - wgh-exp52-pg109-II
166.02
155.91
145.28
144.87
142.04
61.21
58.55
56.55
53.01
49.16
31.64
27.69
23.10
21.34
N
OH
N
OMe
O
f1 (ppm)

8,8a,9,10,11,12-Hexahydro-7*H*-pyrazino[2,3-*g*] pyrido[2,1-*d*] [1,5] oxazonin-5(14*H*)-one (6-131)

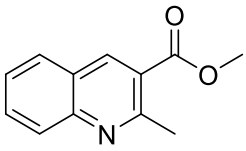


To a stirring solution of methyl 3-((2-(2-hydroxyethyl) piperidin-1-yl) methyl) pyrazine-2-carboxylate **(6-128)** (0.112 g, 0.400 mmol) in tetrahydrofuran (1.84 mL), aqueous lithium hydroxide (0.5 M) (1.84 mL, 0.920 mmol) was added and heated for at 50 °C for 3 hours. The solvent was removed under vacuum using dichloromethane (5 × 50 mL) to form an azeotropic mixture. The intermediate lithium 3-((2-(2-oxidoethyl) piperidin-1-yl) methyl) pyrazine-2-carboxylate was dissolved in chloroform (4.0 mL) and DIPEA (0.095 g, 0.130 mL, 0.600 mmol) was added followed by T3P 50% w/v in ethyl acetate (0.382 g, 0.600 mmol) and stirred at room temperature for 2 hours under argon. The reaction mixture was washed sequentially in dichloromethane (2 × 100 mL) and brine (50 mL) and the organic phases combined dried with sodium sulfate, filtered, concentrated under vacuum and purified via flash column chromatography (10:9:1 hexane:ethyl acetate:triethylamine) to afford the title compound (0.0846 g, 86%) R_f = 0.40 (10:9:1 hexane:ethyl acetate:triethylamine); ν_{max}/cm^{-1} (thin film) 2931, 1744, 1454, 1291, 1104, 708; δ_H (400 MHz, $CDCl_3$) Rotamers observed in a 4:1 ratio 8.45−8.43 (1H, m, Ar**H**)$_{\text{both rotamers}}$, 8.41−8.39 (1H, m, Ar**H**)$_{\text{both rotamers}}$, 5.34 (1H, t, *J* = 11.8 Hz, OC**H**$_a$H$_b$CH$_2$)$_{\text{major}}$, 5.15 (1H, t, *J* = 11.8 Hz, OC**H**$_a$H$_b$CH$_2$)$_{\text{minor}}$, 4.68 (1H, d, *J* = 15.0 Hz, ArC**H**$_a$H$_b$N)$_{\text{major}}$, 4.31 (1H, d, *J* = 15.0 Hz, ArC**H**$_a$H$_b$N)$_{\text{minor}}$, 4.09 (1H, d, *J* = 11.8 Hz, OCH$_a$**H**$_b$CH$_2$)$_{\text{minor}}$, 4.05−3.99 (1H, m, OCH$_a$**H**$_b$CH$_2$)$_{\text{major}}$, 3.65 (1H, d, *J* = 15.0 Hz, ArCH$_a$**H**$_b$N)$_{\text{minor}}$, 3.06 (1H, d, *J* = 14.7 Hz, ArCH$_a$**H**$_b$N)$_{\text{major}}$, 2.99−2.91 (1H, m, C**H**)$_{\text{minor}}$ 2.69−2.58 (1H, m, C**H**)$_{\text{major}}$, 2.69−2.58 (1H, m, C**H**$_a$H$_b$)$_{\text{major}}$, 2.56−2.49 (1H, m, CH$_a$**H**$_b$N)$_{\text{minor}}$, 2.42−2.34 (1H, m, C**H**$_a$H$_b$N)$_{\text{both rotamers}}$, 2.13−2.06 (1H, m, C**H**$_a$H$_b$)$_{\text{minor}}$, 1.99 (1H, t, *J* = 10.5 Hz, CH$_a$**H**$_b$N)$_{\text{major}}$, 1.80−1.09 (7H in total)$_{\text{both rotamers}}$ [1.80−1.72 (1H, m)$_{\text{minor}}$, 1.69−1.58 (2H, m)$_{\text{major}}$, 1.52−1.48 (1H, m)$_{\text{minor}}$, 1.44−1.09 (5H, m)$_{\text{both rotamers}}$]; δ_c (100 MHz, $CDCl_3$) 167.4 (**C**O)$_{\text{major}}$, 167.0 (**C**O)$_{\text{minor}}$, 160.0 (Ar**C**)$_{\text{minor}}$, 159.2(Ar**C**)$_{\text{major}}$, 147.8 (Ar**C**)$_{\text{minor}}$, 147.4 (Ar**C**)$_{\text{major}}$, 143.7 (Ar**C**H)$_{\text{major}}$, 143.5 (Ar**C**H)$_{\text{minor}}$, 142.4 (Ar**C**H)$_{\text{major}}$, 142.3 (Ar**C**H)$_{\text{minor}}$, 66.4 (O**C**H$_2$)$_{\text{minor}}$, 63.3 (O**C**H$_2$)$_{\text{major}}$, 62.6 (N**C**H)$_{\text{minor}}$, 58.3 (N**C**H)$_{\text{major}}$, 58.1 (Ar**C**H$_2$N)$_{\text{major}}$, 54.05 (N**C**H$_2$CH$_2$)$_{\text{major}}$, 50.3 (Ar**C**H$_2$N)$_{\text{minor}}$, 48.2 (N**C**H$_2$CH$_2$)$_{\text{minor}}$, 31.5 (**C**H$_2$)$_{\text{major}}$, 31.0 (**C**H$_2$)$_{\text{minor}}$, 30.8 (**C**H$_2$)$_{\text{major}}$, 28.0 (**C**H$_2$)$_{\text{minor}}$, 25.6 (**C**H$_2$)$_{\text{minor}}$, 25.4 (**C**H$_2$)$_{\text{major}}$, 24.2 (**C**H$_2$)$_{\text{major}}$, 18.4 (**C**H$_2$)$_{\text{minor}}$; HRMS (ESI) calcd. for $C_{13}H_{18}N_3O_2$ 248.1399. Found $[MH]^+$ 248.1395 (−1.61 ppm error).

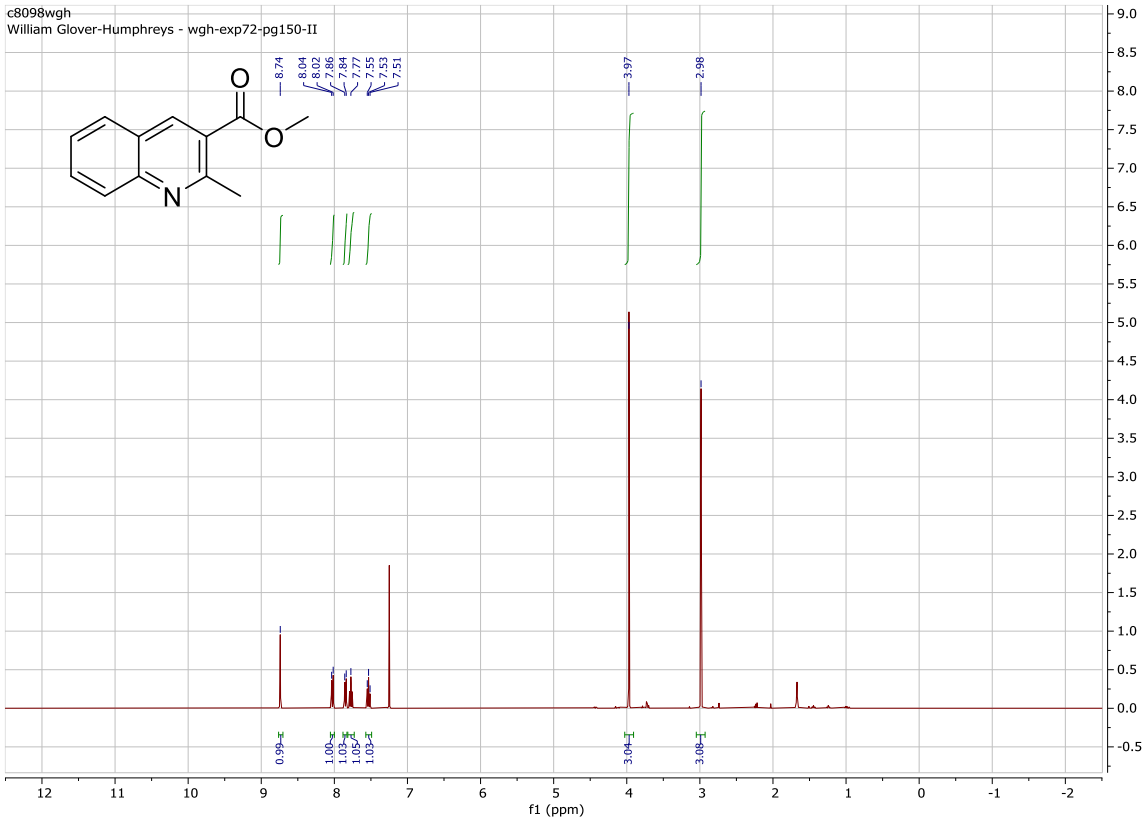

j6444wgh
William Glover-Humphreys - wgh-exp63-pg130-II
f1 (ppm)


j6444wgh
William Glover-Humphreys - wgh-exp63-pg130-II
f1 (ppm)

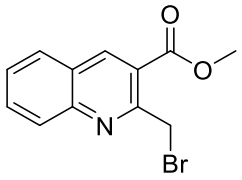
Methyl 2-methylquinoline-3-carboxylate[43] (6-135)



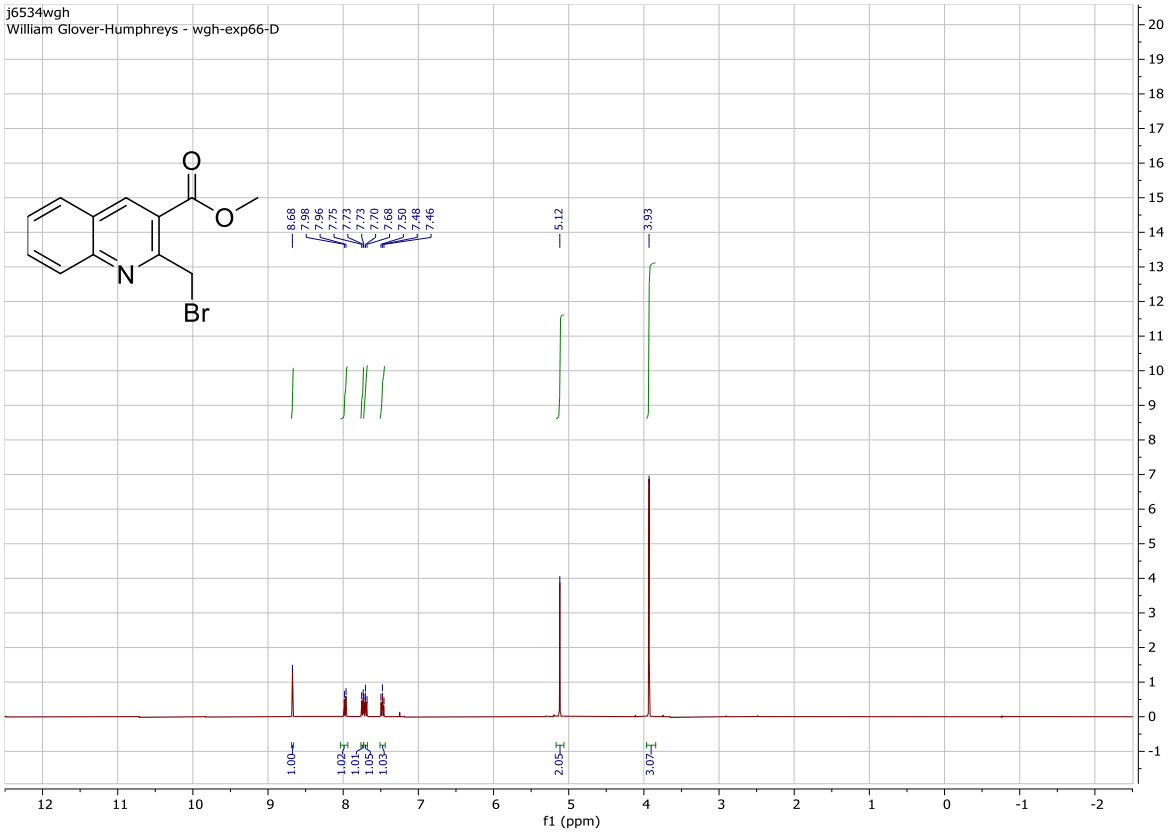
(2-aminophenyl) methanol **(6-132)** (2.00 g, 16.2 mmol), methyl 3-oxobutanoate (**6-134**) (1.88 g, 16.2 mmol) and activated magnesium (IV) oxide (4.24 g, 48.2 mmol) were refluxed in ethanol (10 mL) for 4 hours at 80 °C. Before filtering the reaction mixture through Celite washing with ethanol, concentrating under vacuum and purifying by flash column chromatography (1:1 dichloromethane:hexane) to afford the title compound as a yellow solid (1.13 g, 35%) R_f = 0.09 (1:1 dichloromethane:hexane); δ_H (400 MHz, $CDCl_3$) 8.74 (1H, s, Ar**H**), 8.03 (1H, d, *J* = 8.3 Hz, Ar**H**), 7.85 (1H, d, *J* = 8.3 Hz, Ar**H**), 7.77 (1H, t, *J* = 8.5 Hz, *J* = 8.3 Hz, Ar**H**), 7.53 (1H, t, *J* = 8.3 Hz, Ar**H**), 3.97 (3H, s, OC**H**$_3$), 2.98 (3H, s, ArC**H**$_3$). Data were consistent with those reported in the literature.[43]

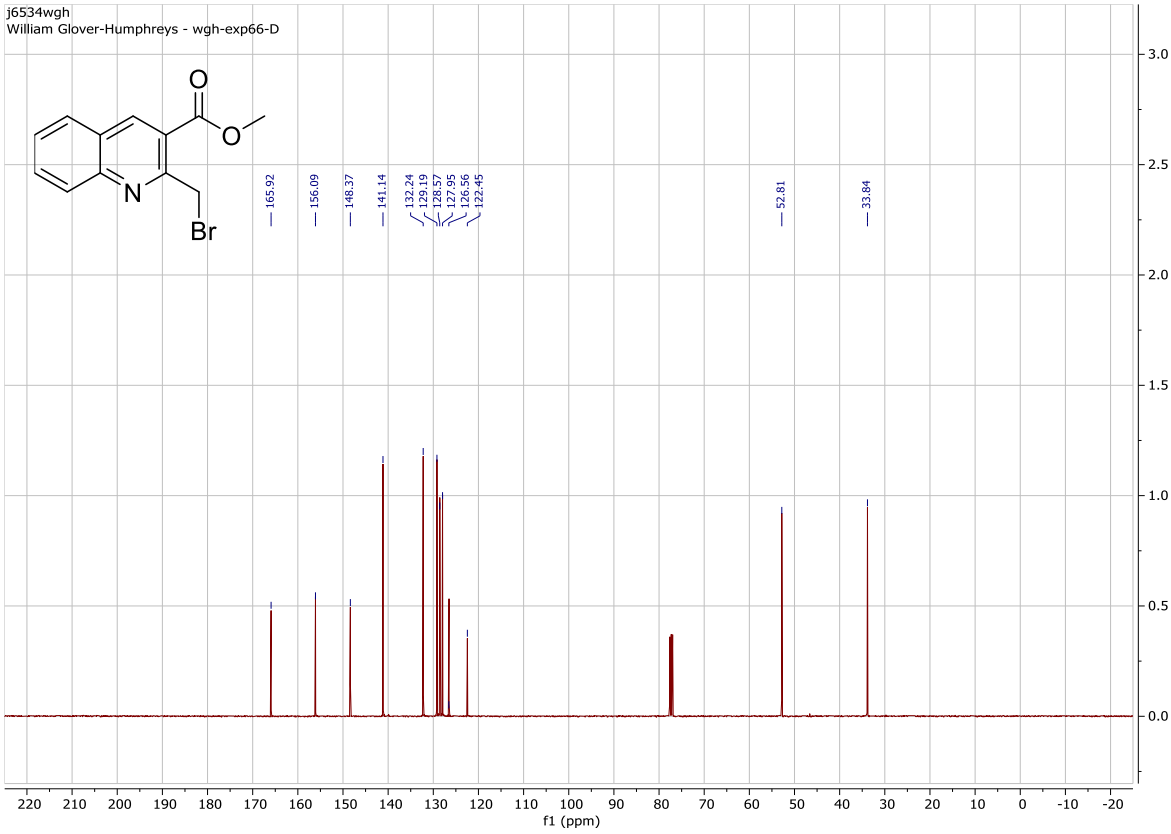


Methyl 2-(bromomethyl) quinoline-3-carboxylate (6-136)

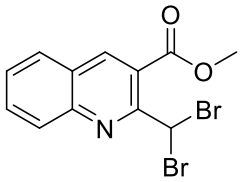


Benzene was degassed for 20 minutes using argon before adding it to a mixture of methyl 2-methylquinoline-3-carboxylate (**6-135**) (0.614 g, 3.05 mmol), azobisisobutyronitrile (0.025 g, 0.153 mmol) and *N*-bromosuccinimide (0.710 g, 3.97 mmol) and refluxed at 85 °C for 24 hours. The reaction mixture was filtered through Celite and washed with dichloromethane, concentrated under vacuum and purified by flash column chromatography (98:2 toluene:ethyl acetate) to afford the title compounds (0.335 g, 39%) R_f = 0.45 (98:2 toluene:ethyl acetate); ν_{max}/cm^{-1} (thin film) 2950, 1719, 1437, 1252, 1204, 1062, 802, 756, 594; δ_H (400 MHz, $CDCl_3$) 8.68 (1H, s, Ar**H**), 7.97 (1H, d, *J* = 8.5 Hz, Ar**H**), 7.74 (1H, d, *J* = 8.5 Hz, Ar**H**), 7.70 (1H, t, *J* = 8.5 Hz, Ar**H**), 7.48 (1H, t, *J* = 8.5 Hz, Ar**H**), 5.12 (2H, s, ArC**H**$_2$Br), 3.93 (3H, s, OC**H**$_3$); δ_c (100 MHz, $CDCl_3$) 165.9 (**C**O), 156.1 (Ar**C**), 148.4 (Ar**C**), 141.1 (Ar**C**H), 132.2 (Ar**C**H), 129.2 (Ar**C**H), 128.6 (Ar**C**H), 128.0 (Ar**C**H), 126.6 (Ar**C**), 122.5 (Ar**C**), 52.8 (O**C**H$_3$), 33.8 (Ar**C**H$_2$Br), HRMS (ESI) calcd. for $C_{12}H_{11}BrNO_2$ 279.9973. Found $[MH]^+$ 279.9964 (−3.22 ppm error);

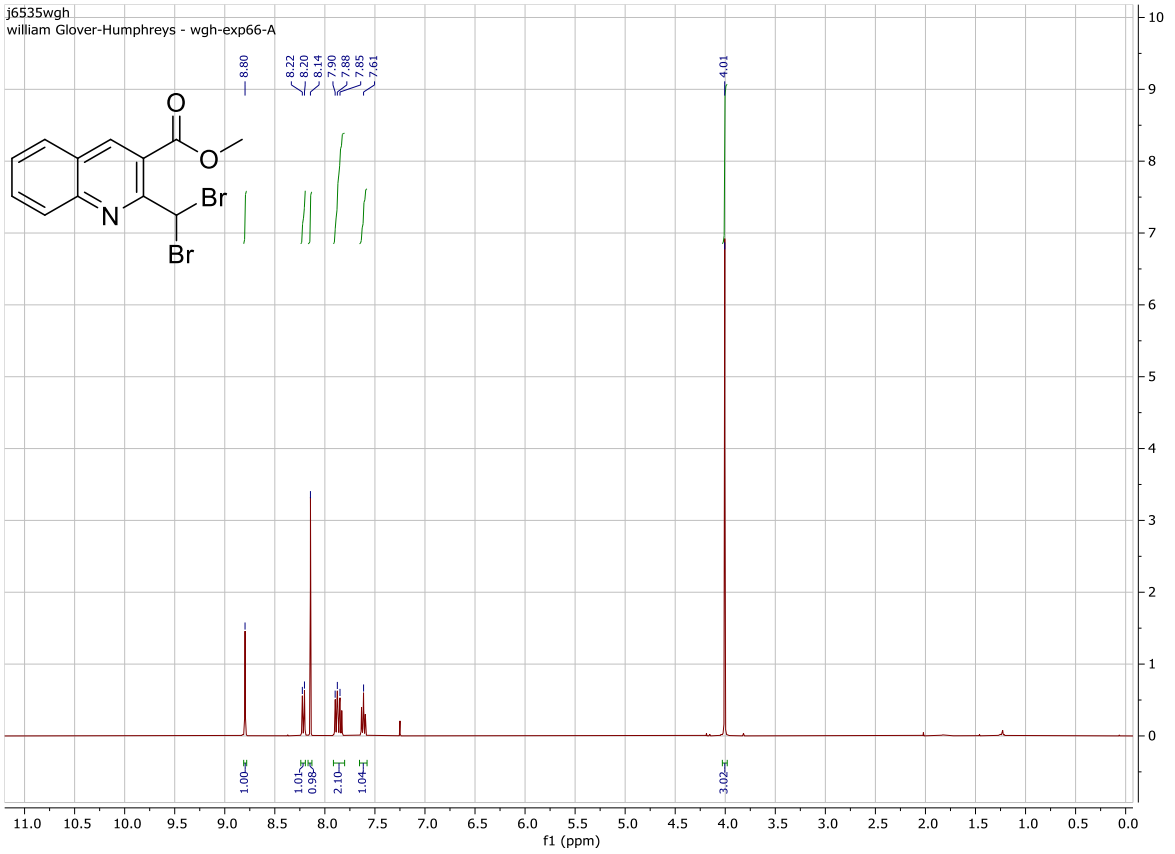

j6534wgh
William Glover-Humphreys - wgh-exp66-D
O
O
N
Br
8.68
7.98
7.96
7.75
7.73
7.73
7.70
7.68
7.50
7.48
7.46
5.12
3.93
1.00
1.02
1.01
1.05
1.03
2.05
3.07
f1 (ppm)

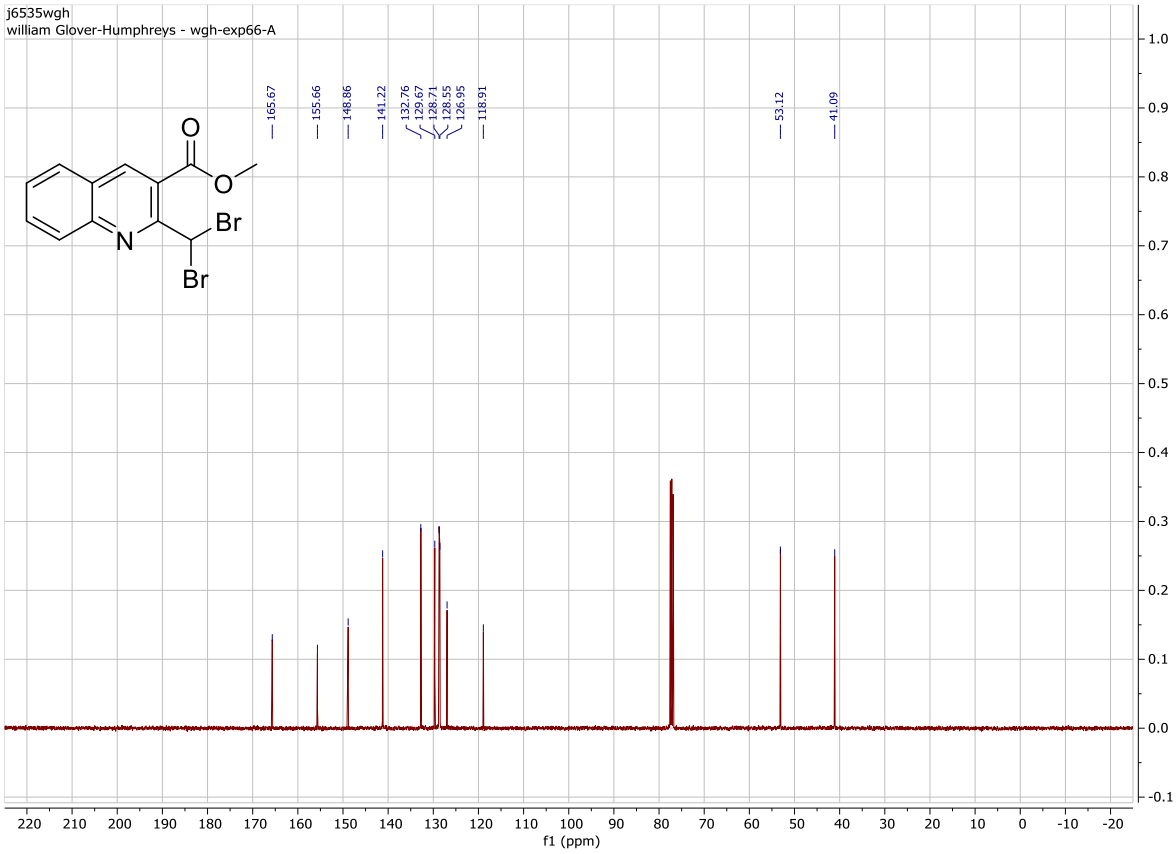

j6534wgh
William Glover-Humphreys - wgh-exp66-D
O
O
N
Br
165.92
156.09
148.37
141.14
132.24
129.19
128.57
127.95
126.56
122.45
52.81
33.84
f1 (ppm)

Methyl 2-(dibromomethyl) quinoline-3-carboxylate (6-137)

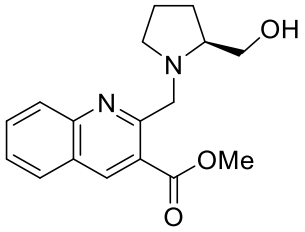


The same procedure that synthesised the mono brominated product **(6-136)** also formed the dibrominated product **(6-137)** (0.407 g, 37%) R_f = 0.63 (98:2 toluene:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 8.08 (1H, s, Ar**H**), 8.21 (1H, d, *J* = 8.5 Hz, Ar**H**), 8.14 (1H, s, C**H**$(Br)_2$), 7.89 (1H, d, *J* = 8.5 Hz, Ar**H**), 7.87−7.82 (1H, m, Ar**H**), 4.01 (3H, s, COOC**H**$_3$); δ_c (100 MHz, $CDCl_3$) 156.7 (**C**O), 155.6 (Ar**C**), 148.9 (Ar**C**), 141.2 (Ar**C**H), 132.8 (Ar**C**H), 129.7 (Ar**C**H), 128.7 (Ar**C**H), 128.6 (Ar**C**H), 127.0 (Ar**C**), 118.9 (Ar**C**), 53.1 (COO**C**H_3), 41.1 (**C**H$(Br)_2$); HRMS (ESI) calcd. for $C_{12}H_{10}Br_2NO_2$ 357.9078. Found $[MH]^+$ 357.9073 (−1.40 ppm error).

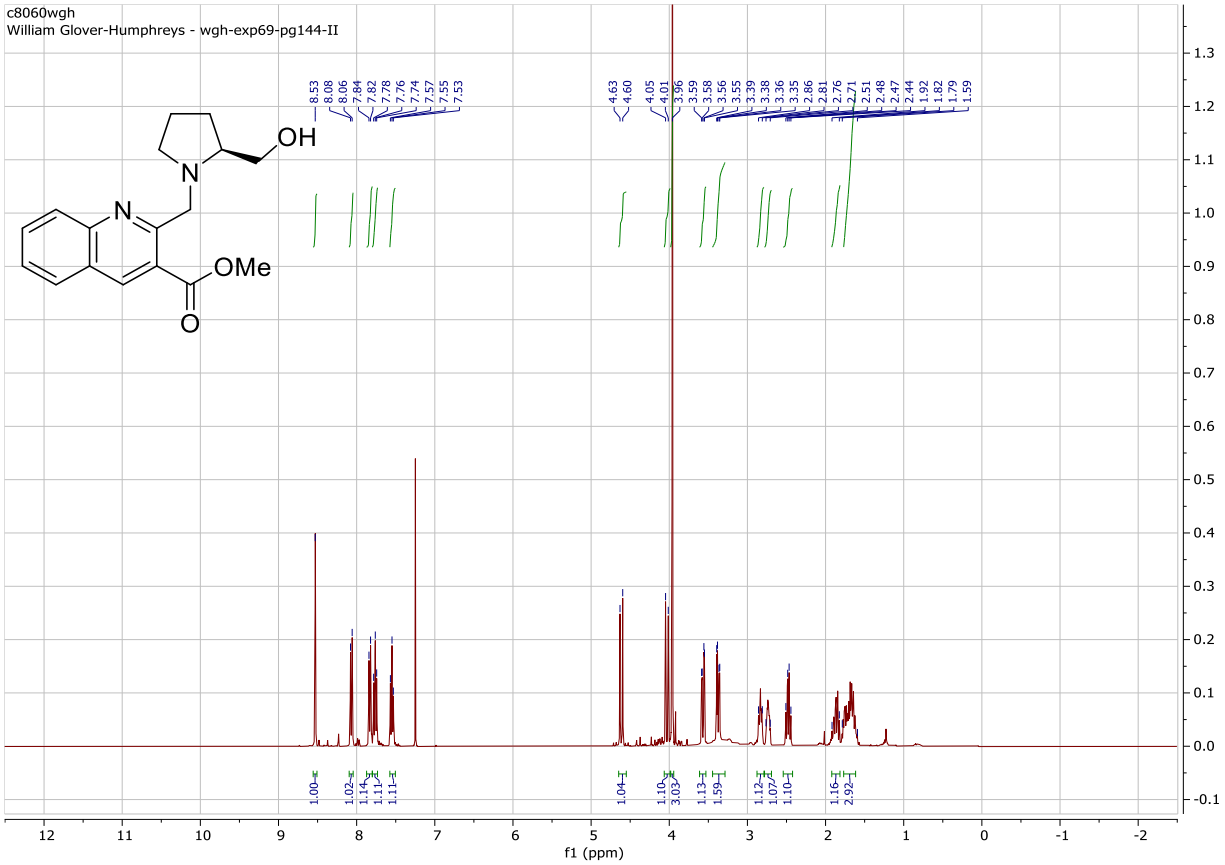

j6535wgh
william Glover-Humphreys - wgh-exp66-A
8.80
8.22
8.20
8.14
7.90
7.88
7.85
7.61
4.01
1.00
1.01
0.98
2.10
1.04
3.02
f1 (ppm)

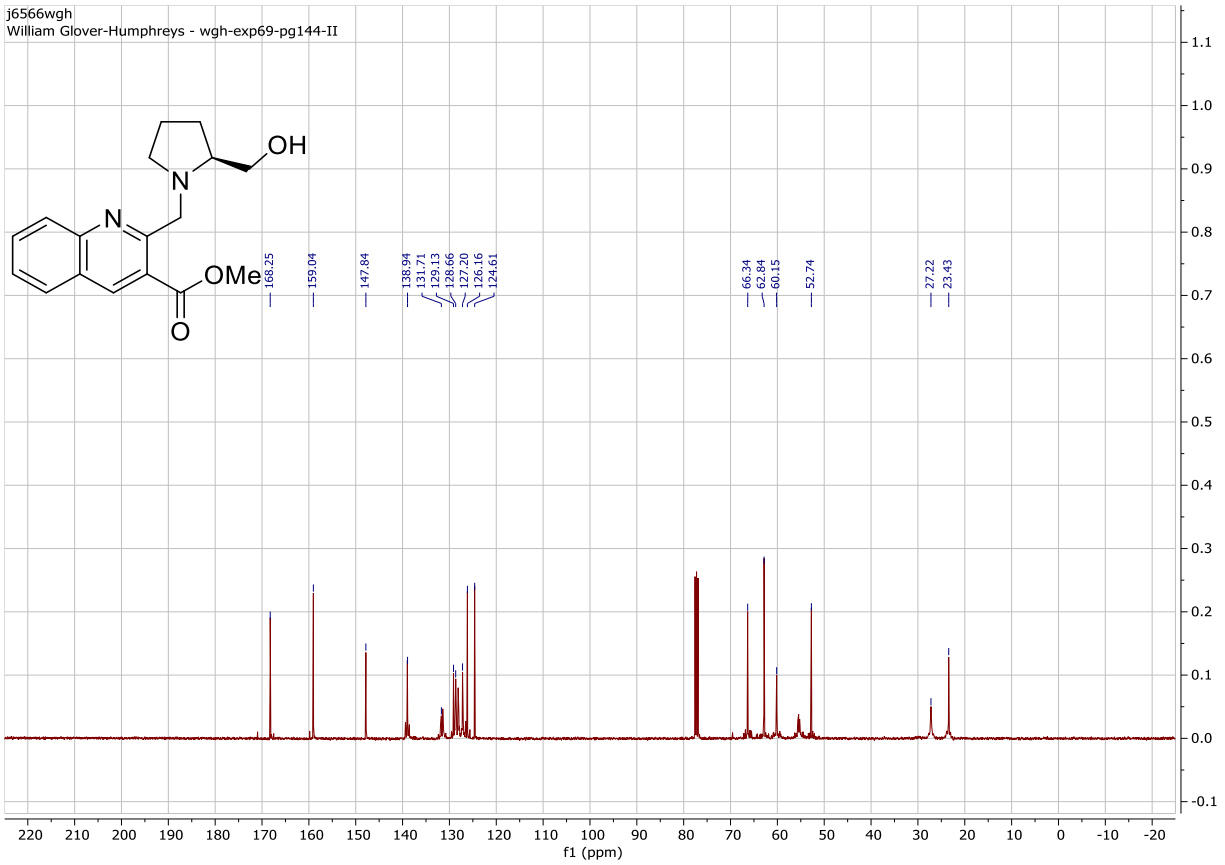

j6535wgh
william Glover-Humphreys - wgh-exp66-A
165.67
155.66
148.86
141.22
132.76
129.67
128.71
128.55
126.95
118.91
53.12
41.09
f1 (ppm)

Methyl (*S*)-2-((2-(hydroxymethyl) pyrrolidin-1-yl) methyl) quinoline-3-carboxylate (6-138)

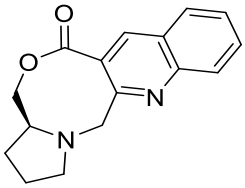


To a stirring solution of potassium carbonate (0.123 g, 0.891 mmol) in acetonitrile (2.98 mL), (*S*)-pyrrolidin-2-ylmethanol (**6-86**) (0.060 g, 0.594 mmol) was added followed by methyl 2-(bromomethyl) quinoline-3-carboxylate (**6-136**) (0.166 g, 0.594 mmol). The reaction mixture was heated to reflux at 90 °C for 3 hours under argon before filtering through Celite washing with dichloromethane, concentrating under vacuum and purifying by flash column chromatography (10:9:1 hexane:ethyl acetate:triethylamine) to afford the title compound an oil (0.112 g, 63%) R_f = 0.3 (10:9:1 hexane:ethyl acetate:triethylamine); ν_{max}/cm^{-1} (thin film) 3455, 2959, 1722, 1439, 1248, 1064, 757, 757; δ_H (400 MHz, $CDCl_3$) 8.53 (1H, s, Ar**H**), 8.07 (1H, d, *J* = 8.5 Hz, Ar**H**), 7.83 (1H, d, *J* = 8.1 Hz, Ar**H**), 7.76 (1H, m, Ar**H**), 7.57−7.53 (1H, m, Ar**H**), 4.62 (1H, d, *J* = 13.9 Hz, ArC**H**$_a$H$_b$N), 4.03 (1H, d, *J* = 13.9 Hz, ArC**H**$_a$H$_b$N), 3.95 (3H, s, OC**H**$_3$), 3.57 (1H, dd, *J* = 11.6 Hz, *J* = 3.2 Hz, C**H**$_a$H$_b$OH), 3.37 (1H, dd, *J* = 11.6 Hz, *J* = 3.2 Hz, CH$_a$**H**$_b$OH), 2.86−2.81 (1H, m, C**H**$_a$H$_b$N), 2.76−2.71 (1H, m, CH$_a$**H**$_b$N), 2.51−2.44 (1H, m, NC**H**), 1.19−1.82 (1H, m, C**H**$_a$H$_b$), 1.79−1.59 (1H, m, CH$_a$**H**$_b$), 1.79−1.59 (2H, m, C**H**$_2$); δ_c (100 MHz, $CDCl_3$) 168.3 (**C**O), 159.0 (Ar**C**), 147.8 (Ar**C**), 138.9 (Ar**C**H), 131.7 (Ar**C**H), 129.1 (Ar**C**H), 128.7 (Ar**C**H), 127.2 (Ar**C**H), 126.2 (Ar**C**), 124.6 (Ar**C**), 66.3 (O**C**H$_3$), 62.8 (ArC**H**$_2$N), 60.2 (N**C**H$_2$), 52.7 (**C**H), 27.2 (**C**H$_2$), 23.4 (**C**H$_2$); HRMS (ESI) calcd. for $C_{17}H_{21}N_2O_3$ 301.1552. Found $[MH]^+$ 301.1548 (−1.33 ppm error).

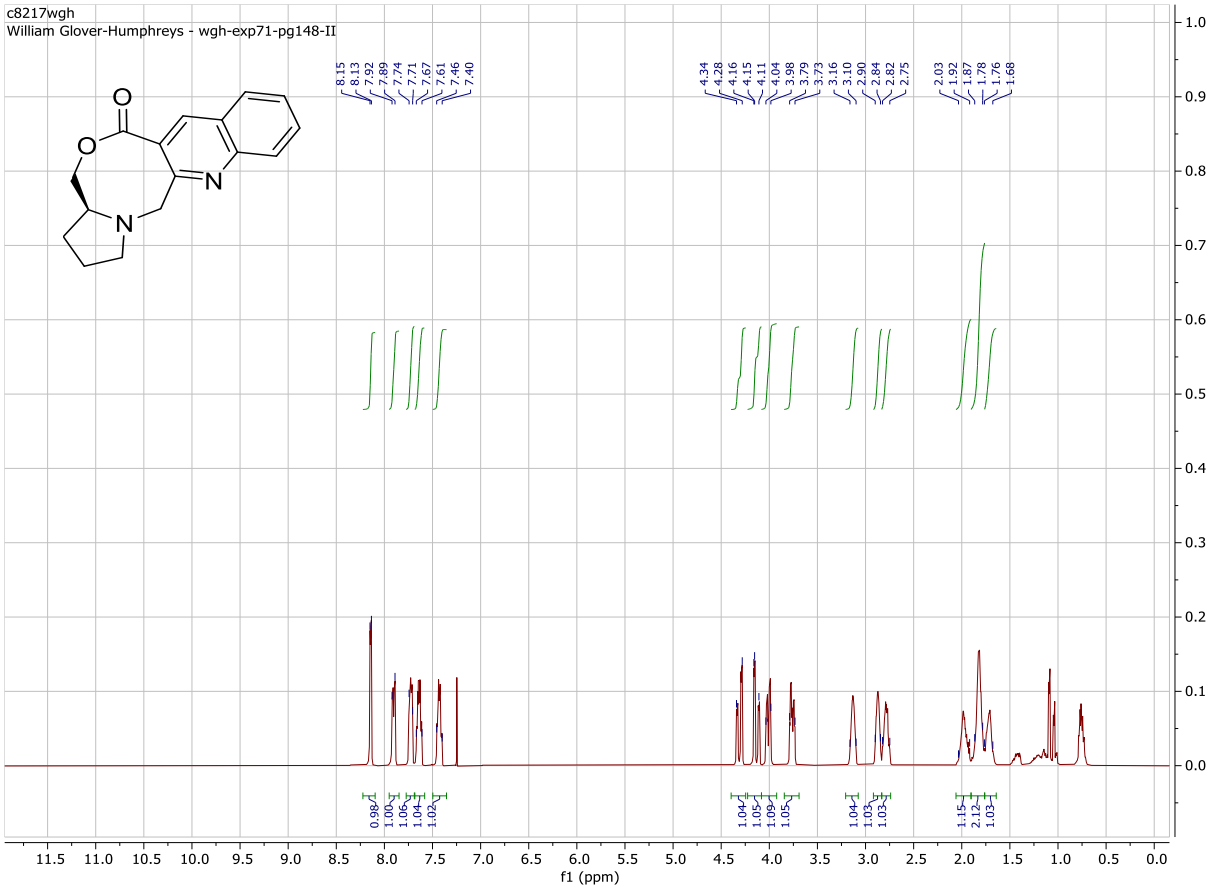

c8060wgh
William Glover-Humphreys - wgh-exp69-pg144-II
OH
N
N
OMe
O
f1 (ppm)

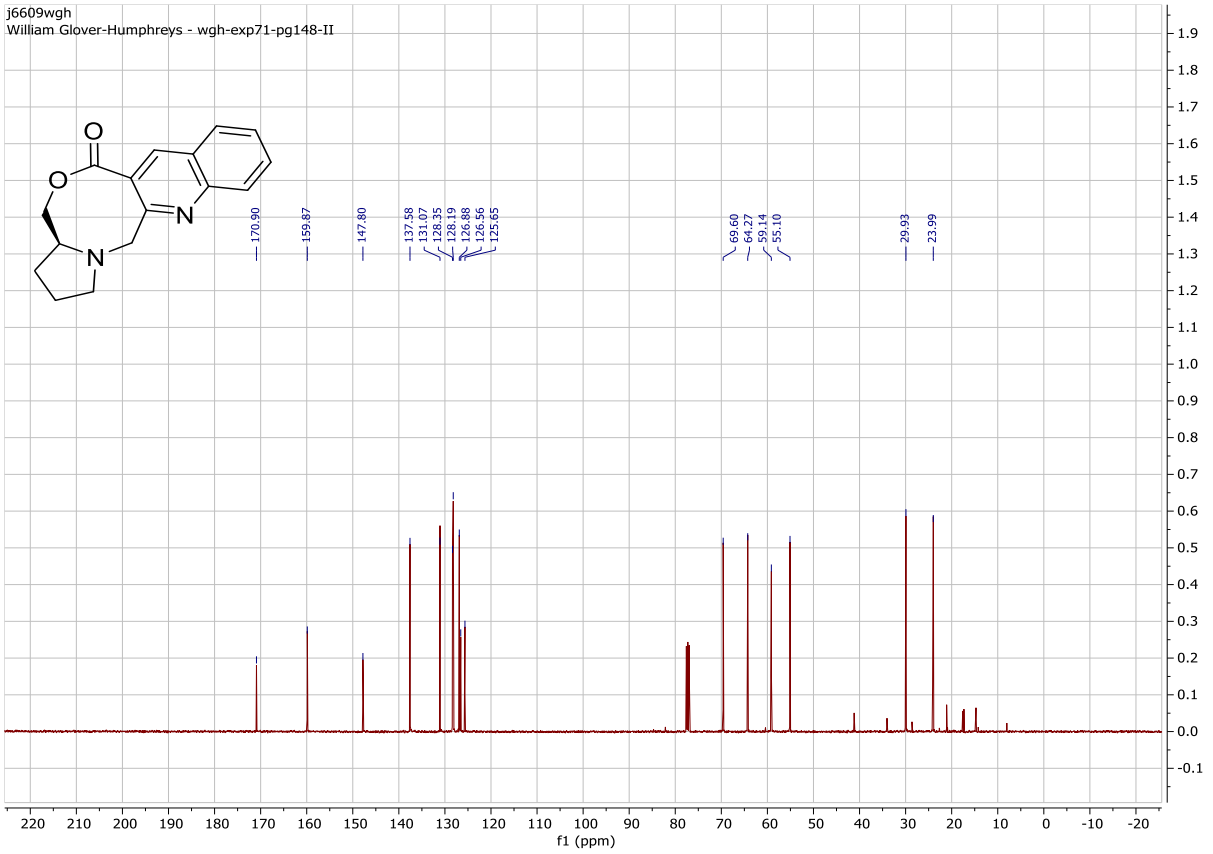

j6566wgh
William Glover-Humphreys - wgh-exp69-pg144-II
OH
N
N
OMe
O
168.25
159.04
147.84
138.94
131.71
129.13
128.66
127.20
126.16
124.61
66.34
62.84
60.15
52.74
27.22
23.43
f1 (ppm)

(*S*)-2,3,3a,4-Tetrahydro-1*H*-pyrrolo [2',1':3,4] [1,4] oxazocino [6,7-*b*] quinolin-6(13*H*)-one (6-141)

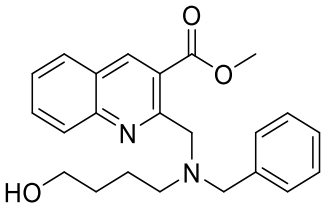


To a stirring solution of methyl (*S*)-2-((2-(hydroxy methyl) pyrrolidin-1-yl) methyl) quinoline-3-carboxylate **(6-138)** (0.133 g, 0.444 mmol) in tetrahydrofuran (1.15 mL), aqueous lithium hydroxide (0.5 M) (1.15 mL, 0.577 mmol) was added and heated for at 50 °C for 3 hours. The solvent was removed under vacuum using dichloromethane (5 × 50 mL) to form an azeotropic mixture. The intermediate lithium (*S*)-2-((2-(oxidomethyl) pyrrolidin-1-yl) methyl) quinoline-3-carboxylate was dissolved in chloroform (2.22 mL) and DIPEA (0.106 g, 0.143 mL, 0.822 mmol) was added followed by T3P 50% w/v in ethyl acetate (0.424 g, 0.666 mmol) and stirred at room temperature for 24 hours under argon. The reaction mixture was washed sequentially in dichloromethane (2 × 100 mL) and brine (50 mL) and the organic phases combined dried with sodium sulfate, filtered, concentrated under vacuum and purified via flash column chromatography (10:9:1 hexane:ethyl acetate:triethylamine) to afford the title compound (0.107 g, 90%) R_f = 0.35 (10:9:1 hexane:ethyl acetate:triethylamine); ν_{max}/cm^{-1} (thin film) 2960, 2247, 1708, 1491. 1178, 915, 728; δ_H (400 MHz, $CDCl_3$) 8.15−8.13 (1H, m, Ar**H**), 7.92−7.89 (1H, m, Ar**H**), 7.74−7.71 (1H, m, Ar**H**), 7.67−7.61 (1H, m, Ar**H**), 7.46−7.40 (1H, m, Ar**H**), 4.31 (1H, d, *J* = 18.2 Hz, ArC**H**$_a$H$_b$N), 4.13 (1H, d, *J* = 18.2 Hz, ArCH$_a$**H**$_b$N), 4.04−3.98 (1H, m, OC**H**$_a$H$_b$CH), 3.79−3.73 (1H, m, OCH$_a$**H**$_b$CH), 3.16−3.10 (1H, m, CH$_2$C**H**$_a$H$_b$N), 2.90−2.84 (1H, m, NC**H**), 2.82−2.75 (1H, m, CH$_2$CH$_a$**H**$_b$N), 2.03−1.92 (1H, m, C**H**$_a$H$_b$), 1.87−1.78 (1H, m, CH$_a$**H**$_b$), 1.87−1.78 (1H, m, C**H**$_a$H$_b$), 1.76−1.68 (1H, m, CH$_a$**H**$_b$); δ_c (100 MHz, $CDCl_3$) 170.9 (**C**O), 159.9 (Ar**C**), 147.8 (Ar**C**), 137.6 (Ar**C**H), 131.1 (Ar**C**H), 128.4 (Ar**C**H), 128.2 (Ar**C**H), 126.9 (Ar**C**H), 126.6 (Ar**C**), 125.7 (Ar**C**), 69.6 (O**C**H$_2$), 64.3 (**C**H), 59.1 (Ar**C**H$_2$N), 55.1 (CH$_2$**C**H$_2$N), 29.9 (**C**H$_2$), 24.0 (**C**H$_2$); HRMS (ESI) calcd. for $C_{16}H_{17}N_2O_2$ 269.1290. Found $[MH]^+$ 269.1286 (−1.49 ppm error); $[\alpha]_D^{20}$ = 33.62 (c = 1.0, dichloromethane), recorded using a Bellingham + Stanley RFM340-T refractometer.

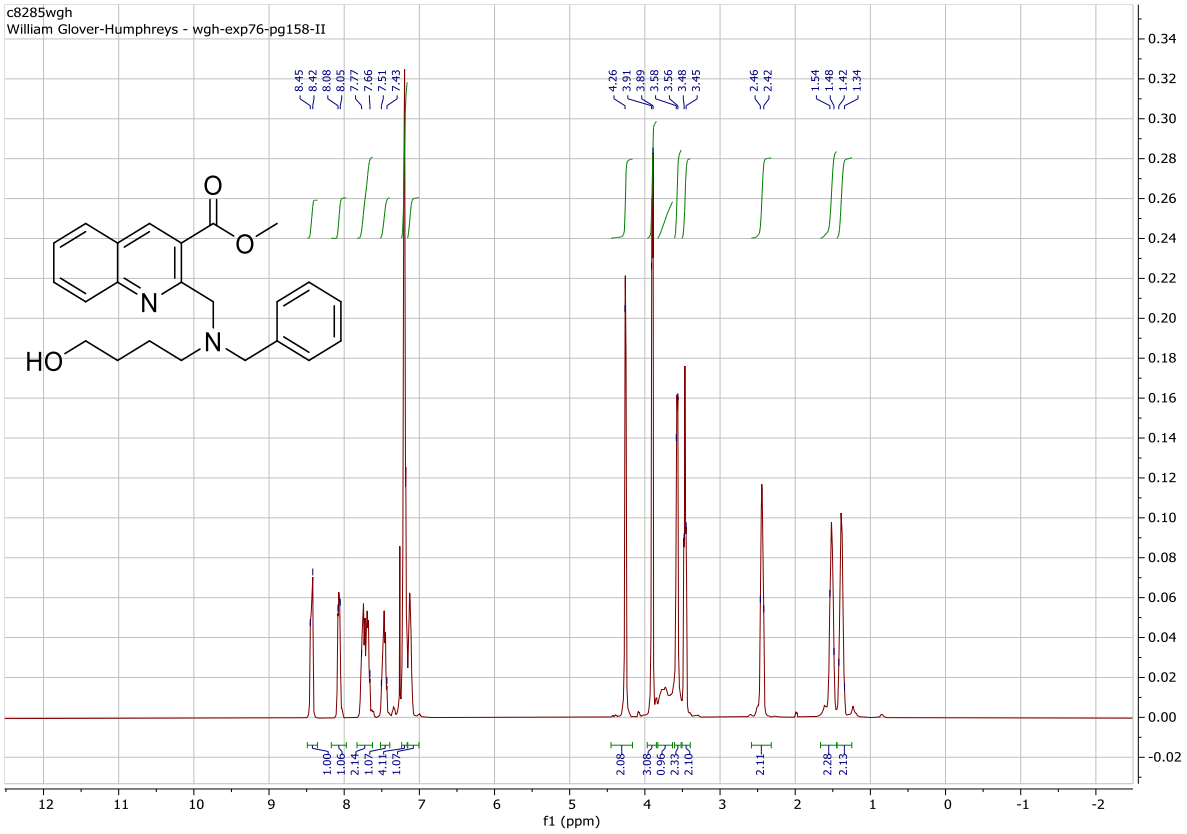

c8217wgh
William Glover-Humphreys - wgh-exp71-pg148-II
8.15
8.13
7.92
7.89
7.74
7.71
7.67
7.61
7.46
7.40
4.34
4.28
4.16
4.15
4.11
4.04
3.98
3.79
3.73
3.16
3.10
2.90
2.84
2.82
2.75
2.03
1.92
1.87
1.78
1.76
1.68
0.98
1.00
1.06
1.04
1.02
1.04
1.05
1.09
1.05
1.04
1.03
1.03
1.15
2.12
1.03
f1 (ppm)

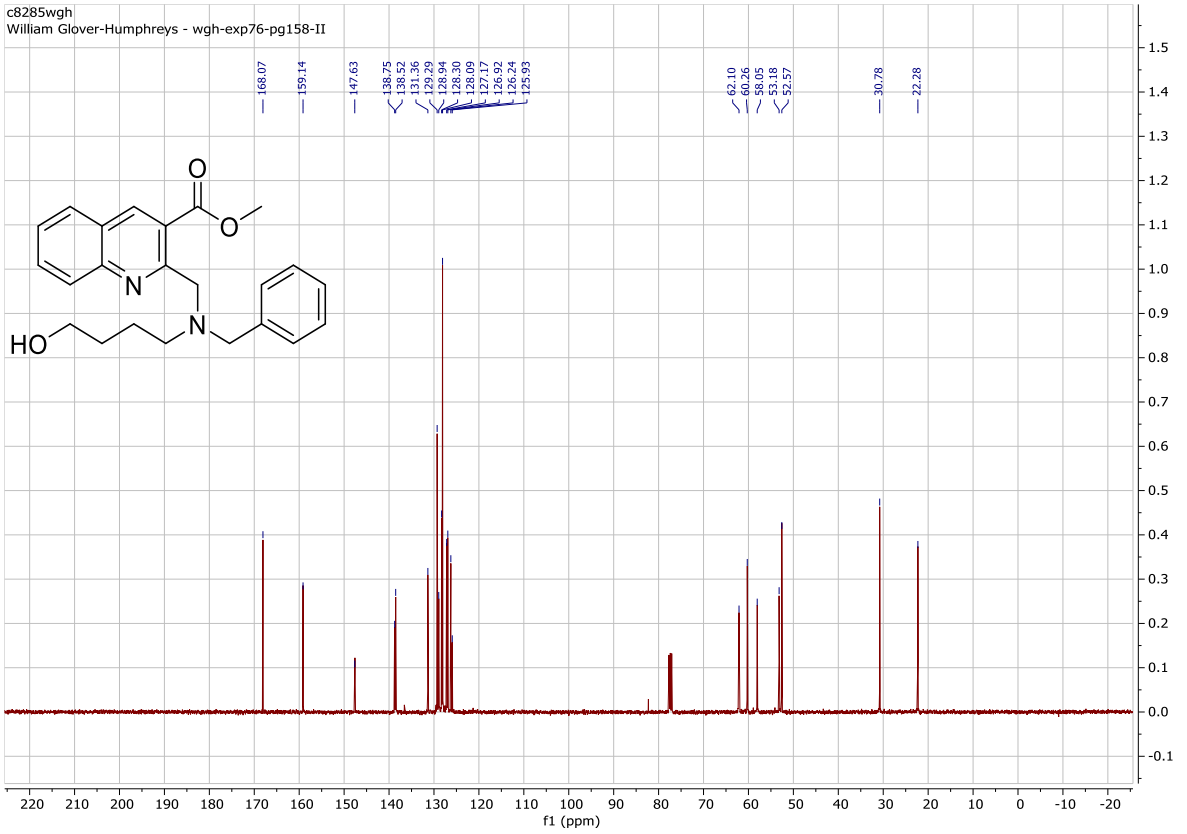

j6609wgh
William Glover-Humphreys - wgh-exp71-pg148-II
170.90
159.87
147.80
137.58
131.07
128.35
128.19
126.88
126.56
125.65
69.60
64.27
59.14
55.10
29.93
23.99
f1 (ppm)

Methyl 3-((benzyl(4-hydroxybutyl) amino) methyl) isoquinoline-4-carboxylate (6-139)

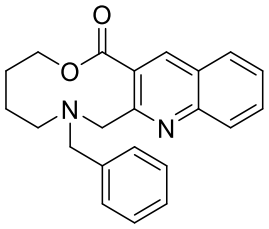


To a stirring solution of potassium carbonate (0.160 g, 1.16 mmol) in acetonitrile (3.90 mL), (4-(benzylamino) butan-1-ol (**6-90**) (0.139 g, 0.773 mmol) was added followed by methyl 2-(bromomethyl) quinoline-3-carboxylate (**6-136**) (0.216 g, 0.773 mmol). The reaction mixture was heated to reflux at 90 °C for 3 hours under argon before filtering through Celite washing with dichloromethane, concentrating under vacuum and purifying by flash column chromatography (10:9:1 hexane:ethyl acetate:triethylamine) to afford the title compound as oil (0.271 g, 93%) R_f = 0.4 (10:9:1 hexane:ethyl acetate:triethylamine); ν_{max}/cm^{-1} (thin film) 3383, 2944, 1727, 1439, 1247, 1067, 757; δ_H (400 MHz, $CDCl_3$) 8.43−8.40 (1H, m, Ar**H**), 8.08−8.04 (1H, m, Ar**H**), 7.77−7.64 (2H, m, 2× Ar**H**), 7.49−7.42 (1H, m, Ar**H**), 7.20−7.15 (4H, m, Ar**H**), 7.15−7.10 (1H, m, Ar**H**), 4.25 (2H, s, ArC**H**$_2$N), 3.89 (3H, s, OC**H**$_3$), 3.72 (1H, bs, O**H**), 3.56 (2H, s, ArC**H**$_2$N), 3.45 (2H, t, *J* = 6.4 Hz, $CH_2C\mathbf{H}_2OH$), 2.45−2.40 (2H, m, $CH_2C\mathbf{H}_2N$), 1.53−1.46 (2H, m, $CH_2C\mathbf{H}_2CH_2$), 1.41−1.33 (2H, m, $CH_2C\mathbf{H}_2CH_2$); δ_c (100 MHz, $CDCl_3$) 168.1 (**C**O), 159.2 (Ar**C**), 147.6 (Ar**C**), 138.8 (Ar**C**), 138.5 (Ar**C**H), 131.4 (Ar**C**H), 129.3 (Ar**C**H), 128.9 (Ar**C**H), 128.3 (Ar**C**H), 120.1 (Ar**C**H), 127.2 (Ar**C**H), 126.9 (Ar**C**H), 126.2 (Ar**C**), 125.9 (Ar**C**), 62.1 (**C**H$_2$OH), 60.3 (Ar**C**H$_2$N), 58.1 (Ar**C**H$_2$N), 53.2 ($CH_2\mathbf{C}H_2N$), 52.6 (O**C**H$_3$), 30.8 (**C**H$_2$), 22.3 (**C**H$_2$); HRMS (ESI) calcd. for $C_{23}H_{27}N_2O_3$ 379.2022. Found $[MH]^+$ 379.2010 (−3.16 ppm error).

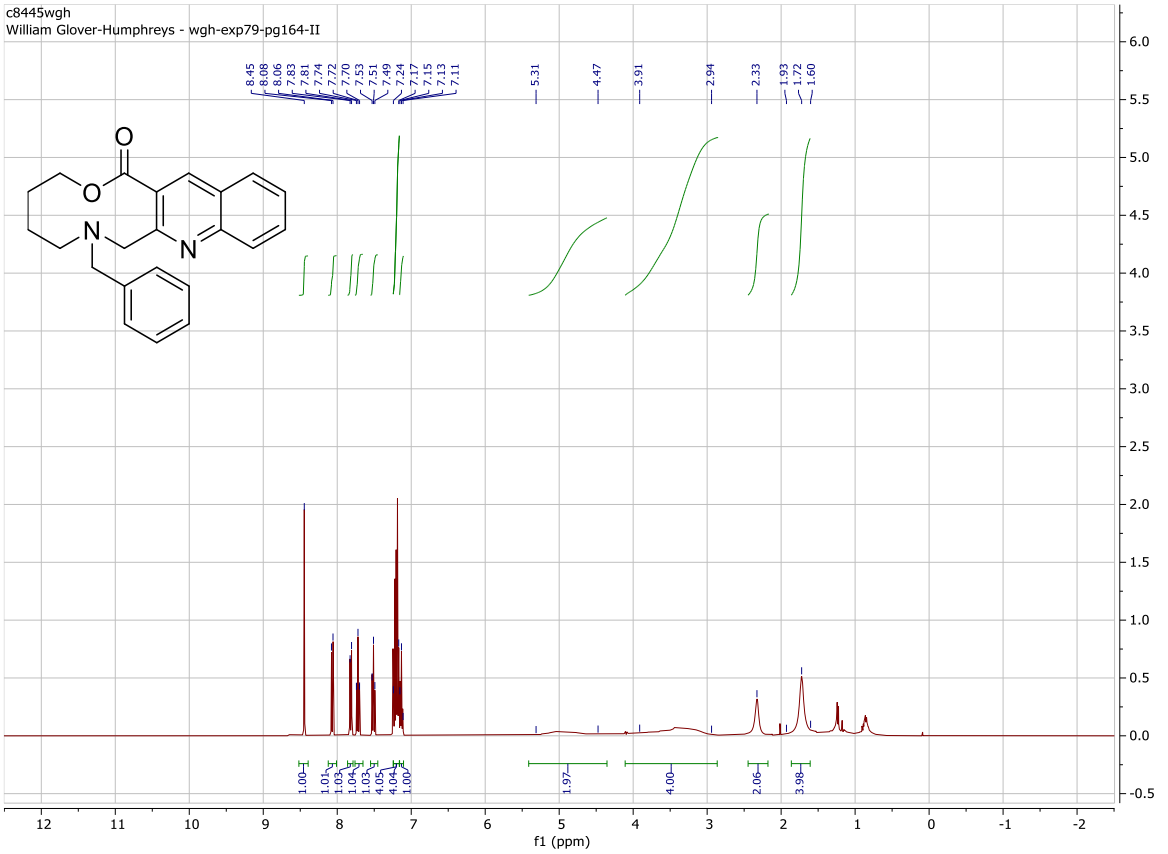

c8285wgh
William Glover-Humphreys - wgh-exp76-pg158-II
8.45
8.42
8.08
8.05
7.77
7.66
7.51
7.43
4.26
3.91
3.89
3.58
3.56
3.48
3.45
2.46
2.42
1.54
1.48
1.42
1.34
O
O
N
N
HO
1.00
1.06
2.14
1.07
4.11
1.07
2.08
3.08
0.96
2.33
2.10
2.11
2.28
2.13
f1 (ppm)


c8285wgh
William Glover-Humphreys - wgh-exp76-pg158-II
168.07
159.14
147.63
138.75
138.52
131.36
129.29
128.94
128.30
128.09
127.17
126.92
126.24
125.93
62.10
60.26
58.05
53.18
52.57
30.78
22.28
O
O
N
N
HO
f1 (ppm)

7-Benzyl-3,4,5,6,7,6-hexahydro-1*H*- [1,6] oxazecino [4,3-*b*] quinolin-1-one (6-142)



To a stirring solution of methyl 3-((benzyl (4-hydroxy butyl) amino) methyl) isoquinoline-4-carboxylate **(6-139)** (0.271 g, 0.715 mmol) in tetrahydrofuran (1.90 mL), aqueous lithium hydroxide (0.5 M) (1.90 mL, 0.930 mmol) was added and heated for at 50 °C for 3 hours. The solvent was removed under vacuum using dichloromethane (5 × 50 mL) to form an azeotropic mixture. The intermediate lithium 3-((benzyl(4-oxidobutyl) amino) methyl) isoquinoline-4-carboxylate was dissolved in chloroform (7.32 mL) and DIPEA (0.171 g, 0.231 mL, 1.32 mmol) was added followed by T3P 50% w/v in ethyl acetate (0.683 g, 1.07 mmol) and stirred at room temperature for 24 hours under argon. The reaction mixture was washed sequentially in dichloromethane (2 × 100 mL) and brine (50 mL) and the organic phases combined dried with sodium sulfate, filtered, concentrated under vacuum and purified via flash column chromatography (10:9:1 hexane:ethyl acetate:triethylamine) to afford the title compound (0.158 g, 64%) R_f = 0.61 (10:9:1 hexane:ethyl acetate:triethylamine); ν_{max}/cm^{-1} (thin film) 2954, 2251, 1719, 1236, 1212, 1058, 729, 699; δ_H (400 MHz, $CDCl_3$) 8.45 (1H, s, Ar**H**), 8.07 (1H, d, *J* = 8.1 Hz, Ar**H**), 7.82 (1H, d, *J* = 8.1 Hz, Ar**H**), 7.72 (1H, t, *J* = 8.1 Hz, Ar**H**), 7.51 (1H, t, *J* = 8.1 Hz, Ar**H**), 7.24−7.17 (4H, m, 4 × Ar**H**), 7.13 (1H, tt, *J* = 6.7 Hz, 1.6 Hz, Ar**H**), 5.31−4.47 (2H, m, C$\mathbf{H}_2$O), 3.91−2.94 (4H, m, 2 × ArC$\mathbf{H}_2$N), 2.40−2.25 (2H, m, C$\mathbf{H}_2$N), 1.93−1.60 (4H, m, 2 × C$\mathbf{H}_2$); δ_c (100 MHz, $CDCl_3$) 168.5 (**C**O), 160.1 (Ar**C**), 127.7 (Ar**C**), 138.6 (Ar**C**), 138.2 (Ar**C**H), 131.0 (Ar**C**H), 129.5 (Ar**C**H), 128.9 (Ar**C**H), 128.4 (Ar**C**H), 128.2 (Ar**C**H), 127.6 (Ar**C**), 127.1 (Ar**C**H), 127.0 (Ar**C**H), 126.7 (Ar**C**), 66.5 (O**C**H_2), 60.3 (Ar**C**H_2N), 59.6 (Ar**C**H_2N), 53.4 (**C**H_2N), 25.5 (**C**H_2), 23.2 (**C**H_2); HRMS (ESI) calcd. for $C_{22}H_{23}N_2O_2$ 347.1760. Found $[MH]^+$ 347.1756 (−1.15 ppm error).


c8445wgh
William Glover-Humphreys - wgh-exp79-pg164-II
8.45
8.08
8.06
7.83
7.81
7.74
7.72
7.70
7.53
7.51
7.49
7.24
7.17
7.15
7.13
7.11
5.31
4.47
3.91
2.94
2.33
1.93
1.72
1.60
O
O
N
N
1.00
1.01
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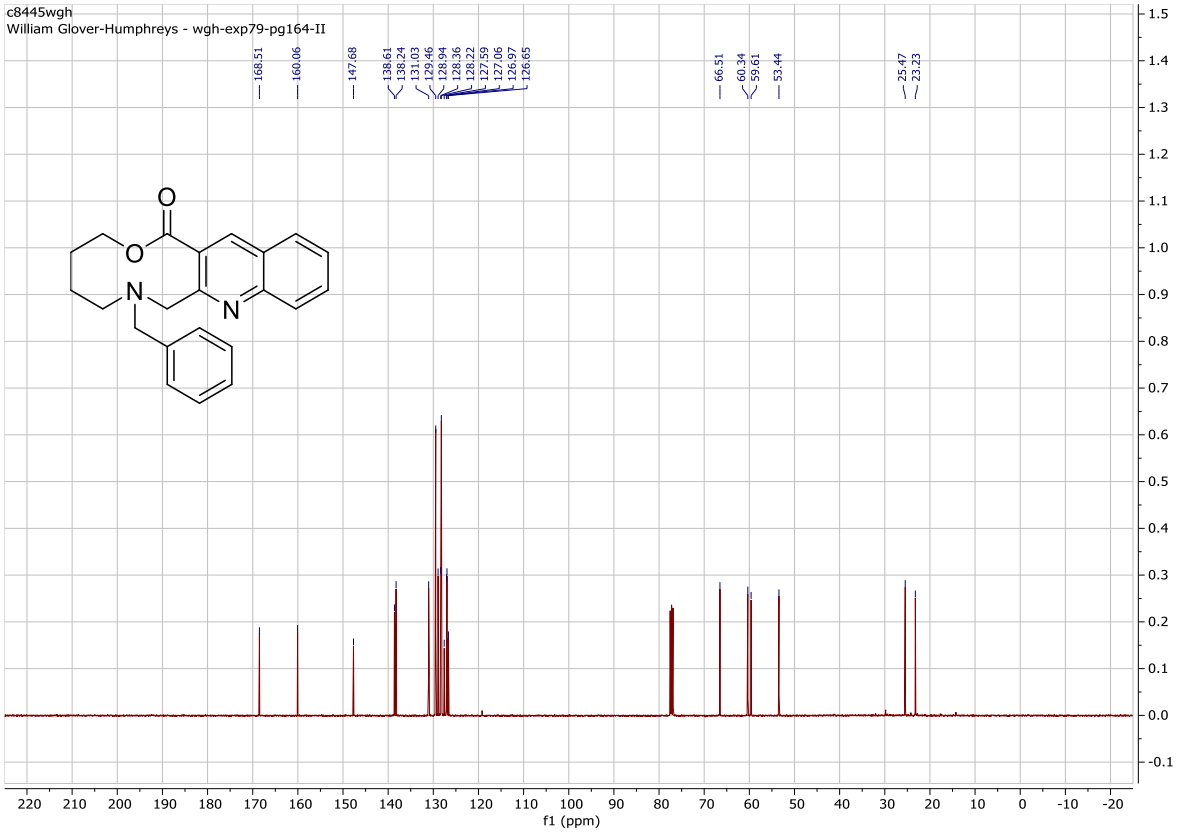
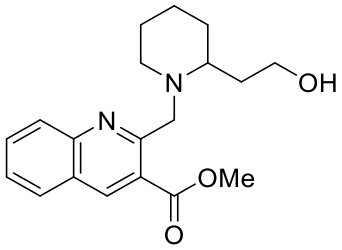
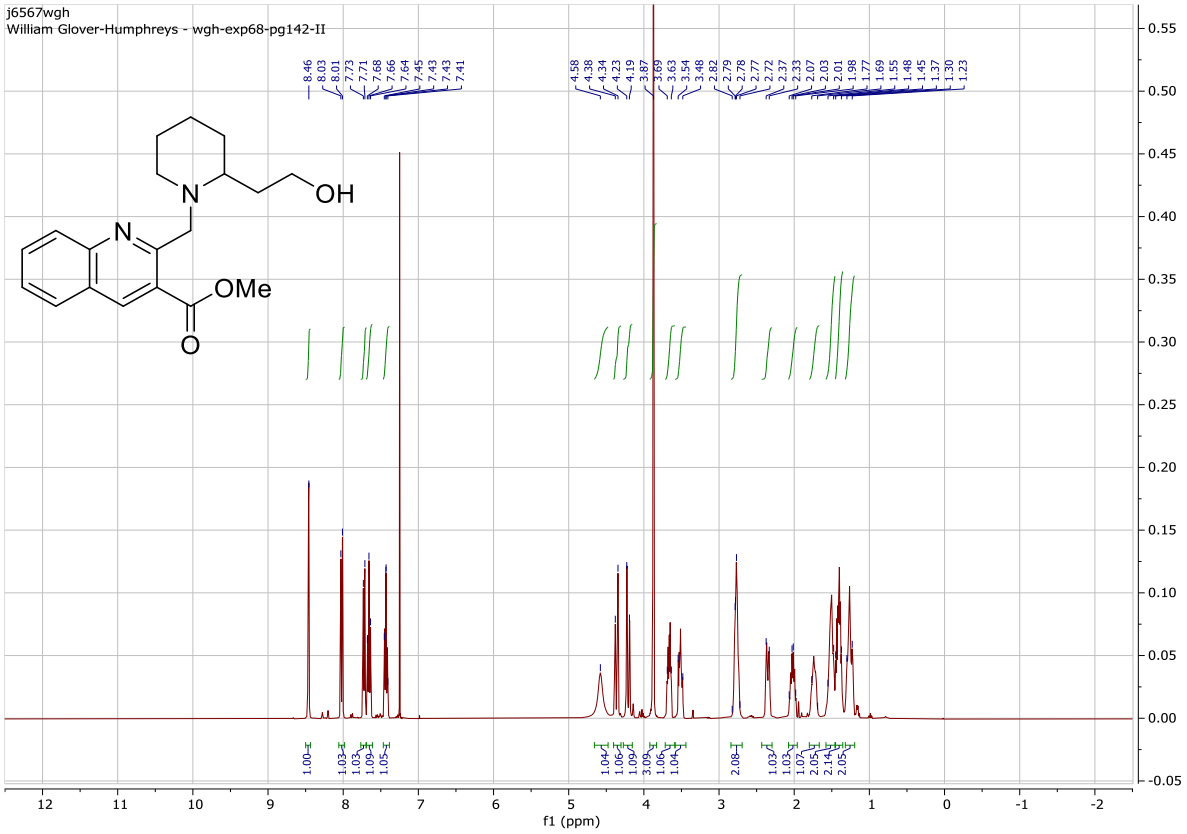
4.04
1.00
1.97
4.00
2.06
3.98
f1 (ppm)


c8445wgh
William Glover-Humphreys - wgh-exp79-pg164-II
168.51
160.06
147.68
138.61
138.24
131.03
129.46
128.94
128.36
128.22
127.59
127.06
126.97
126.65
66.51
60.34
59.61
53.44
25.47
23.23
O
O
N
N
f1 (ppm)

Methyl 2-((2-(2-hydroxyethyl) piperidin-1-yl) methyl) quinoline-3-carboxylate (6-140)



To a stirring solution of potassium carbonate (0.131 g, 0.945 mmol) in acetonitrile (3.15 mL), 2-(piperidin-2-yl) ethan-1-ol **(6-92)** (0.082 g, 0.630 mmol) was added followed by methyl 2-(bromomethyl) quinoline-3-carboxylate **(6-136)** (0.177 g, 0.630 mmol). The reaction mixture was heated to reflux at 90 °C for 3 hours under argon before filtering through Celite washing with dichloromethane, concentrating under vacuum and purifying by flash column chromatography (10:9:1 hexane:ethyl acetate:triethylamine) to afford the title compound an oil (0.186 g, 90%) R_f = 0.22 (10:9:1 hexane:ethyl acetate:triethylamine); ν_{max}/cm^{-1} (thin film) 3375, 2936, 1726, 1445, 1247, 1065, 763; δ_H (400 MHz, $CDCl_3$) 8.46 (1H, s, Ar**H**), 8.02 (1H, d, *J* = 8.5 Hz, Ar**H**), 7.72 (1H, d, *J* = 8.1 Hz, Ar**H**), 7.68−7.63 (1H, m, Ar**H**), 7.46−7.40 (1H, m, Ar**H**), 4.58 (1H, s, O**H**), 4.26 (1H, d, *J* = 14.2 Hz, ArC**H**$_a$H$_b$N), 4.21 (1H, d, *J* = 14.2 Hz, ArCH$_a$**H**$_b$N), 3.97 (3H, s, OC**H**$_3$), 3.70−3.63 (1H, m, C**H**$_a$H$_b$OH), 3.54−3.48 (1H, m, CH$_a$**H**$_b$OH), 2.81−2.72 (1H, m, C**H**), 2.81−2.72 (1H, m, CH$_2$C**H**$_a$H$_b$N), 2.37−2.33 (1H, m, CH$_2$CH$_a$**H**$_b$N), 2.07−1.98 (1H, m, C**H**$_a$H$_b$CH$_2$OH), 1.77−1.69 (1H, m, C**H**$_a$H$_b$), 1.55−1.48 (1H, m, C**H**$_a$H$_b$), 1.55−1.48 (1H, m, C**H**$_a$H$_b$), 1.45−1.37 (1H, m, CH$_a$**H**$_b$CH$_2$OH), 1.45−1.37 (1H, m, CH$_a$**H**$_b$), 1.30−1.23 (1H, m, CH$_a$**H**$_b$), 1.30−1.23 (1H, m, CH$_a$**H**$_b$); δ_c (100 MHz, $CDCl_3$) 167.6 (**C**O), 159.3 (Ar**C**), 147.8 (Ar**C**), 139.2 (Ar**C**H), 131.4 (Ar**C**H), 128.9 (Ar**C**H), 128.3 (Ar**C**H), 127.1 (Ar**C**H), 126.1 (Ar**C**), 124.9 (Ar**C**), 61.7 (O**C**H$_2$), 58.7 (Ar**C**H$_2$N), 57.3 (N**C**H), 52.5 (O**C**H$_3$), 48.1 (CH$_2$**C**H$_2$N), 31.1 (**C**H$_2$), 27.1 (**C**H$_2$), 22.9 (**C**H$_2$), 20.7 (**C**H$_2$); HRMS (ESI) calcd. for $C_{19}H_{25}N_2O_3$ 329.1865. Found $[MH]^+$ 329.1863 (−0.608 ppm error).


j6567wgh
William Glover-Humphreys - wgh-exp68-pg142-II
8.46
8.03
8.01
7.73
7.71
7.68
7.66
7.64
7.45
7.43
7.41
4.58
4.38
4.34
4.23
4.19
3.87
3.69
3.63
3.54
3.48
2.82
2.79
2.78
2.77
2.72
2.37
2.33
2.07
2.03
2.01
1.98
1.77
1.69
1.55
1.48
1.45
1.37
1.30
1.23
N
OH
N
OMe
O
1.00
1.03
1.03
1.09
1.05
1.04
1.06
1.09
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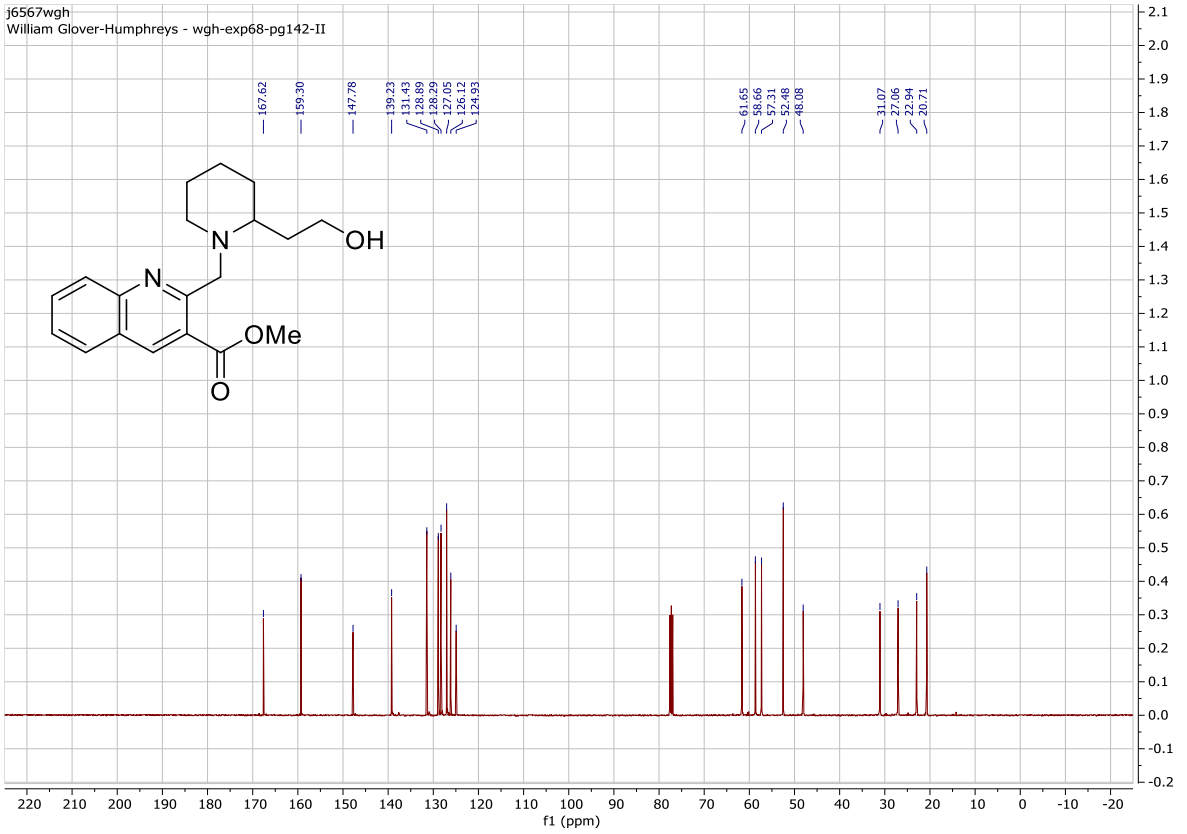
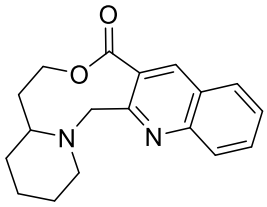
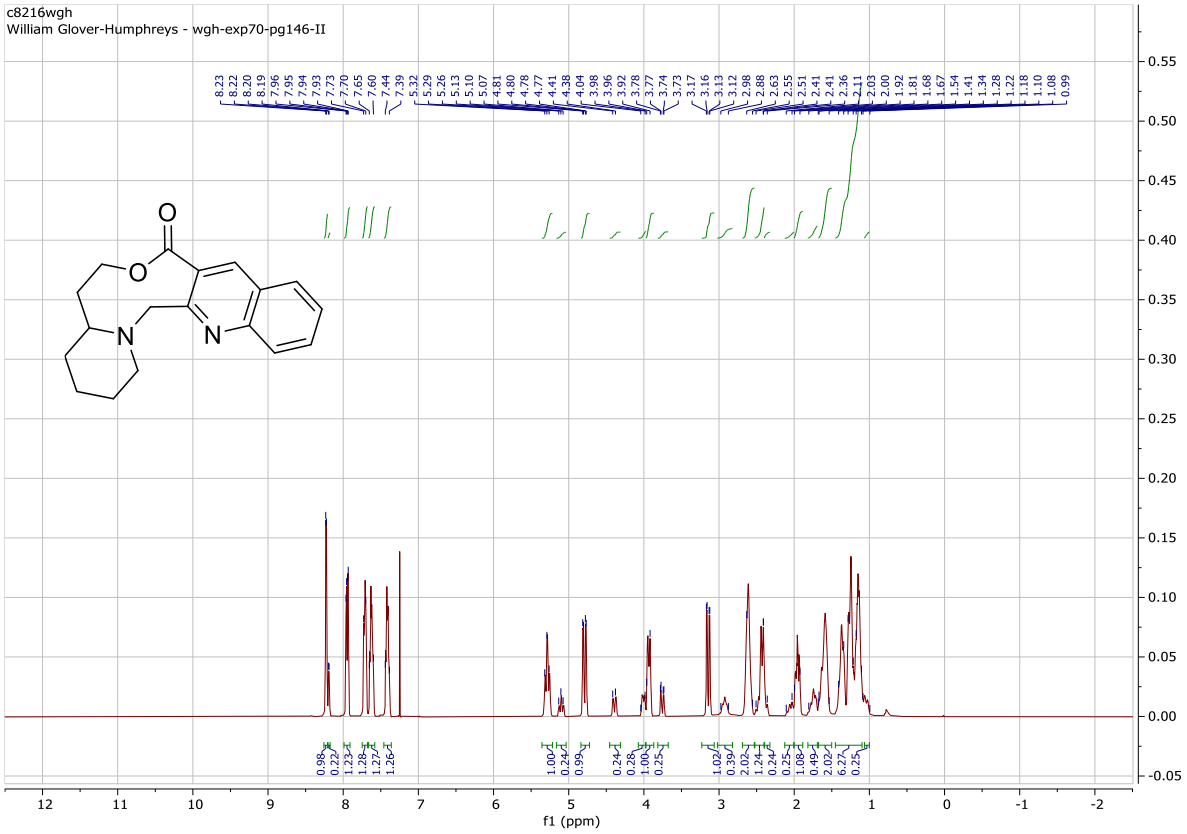
1.07
2.05
2.14
2.05
f1 (ppm)

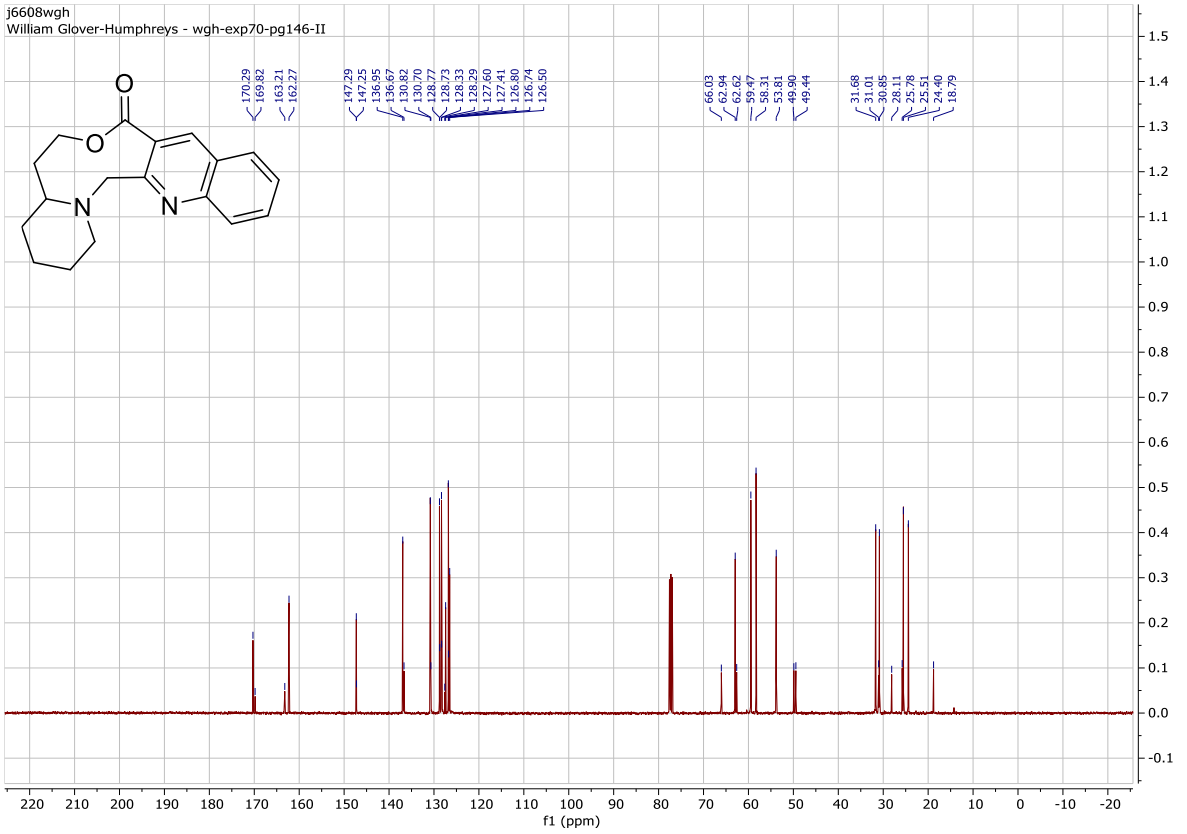

j6567wgh
William Glover-Humphreys - wgh-exp68-pg142-II
167.62
159.30
147.78
139.23
131.43
128.89
128.29
127.05
126.12
124.93
61.65
58.66
57.31
52.48
48.08
31.07
27.06
22.94
20.71
N
OH
N
OMe
O
f1 (ppm)

2,3,4,4a,5,4-Hexahydro-1*H*-pyrido [2',1':4,5] [1,5] oxazonino [7,6-*b*] quinolin-8 (15*H*)-one (6-143)

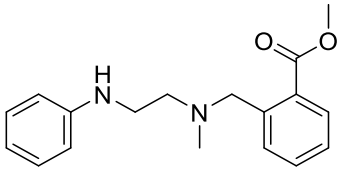


To a stirring solution of methyl 2-((2-(2-hydroxyethyl) piperidin-1-yl) methyl) quinoline-3-carboxylate **(6-140)** (0.186 g, 0.565 mmol) in tetrahydrofuran (1.47 mL), aqueous lithium hydroxide (0.5 M) (1.47 mL, 0.735 mmol) was added and heated for at 50 °C for 3 hours. The solvent was removed under vacuum using dichloromethane (5 × 50 mL) to form an azeotropic mixture. The intermediate lithium 2-((2-(2-oxidoethyl) piperidin-1-yl) methyl) quinoline-3-carboxylate was dissolved in chloroform (2.83 mL) and DIPEA (0.135 g, 0.182 mL, 1.05 mmol) was added followed by T3P 50% w/v in ethyl acetate (0.539 g, 0.848 mmol) and stirred at room temperature for 24 hours under argon. The reaction mixture was washed sequentially in dichloromethane (2 × 100 mL) and brine (50 mL) and the organic phases combined dried with sodium sulfate, filtered, concentrated under vacuum and purified via flash column chromatography (10:9:1 hexane:ethyl acetate:triethylamine) to afford the title compound (0.1414 g, 85%) R_f = 0.64 (10:9:1 hexane:ethyl acetate:triethylamine); ν_{max}/cm^{-1} (thin film) 2933, 2252, 1725, 1204, 1059, 909, 727; Rotameric observed in a 1:4 ratio, δ_H (400 MHz, $CDCl_3$) 8.21 (1H, d, *J* = 3.8 Hz, Ar**H**) $_{major}$, 9.20 (1H, d, *J* = 3.4 Hz, Ar**H**) $_{minor}$, 7.95 (1H, dd, *J* = 8.6 Hz, *J* = 3.4 Hz, Ar**H**) $_{both\ rotamers}$, 7.73-7.70 (1H, m, Ar**H**) $_{both\ rotamers}$, 7.65−7.60 (1H, m, Ar**H**) $_{both\ rotamers}$, 7.44−7.39 (1H, m, Ar**H**) $_{both\ rotamers}$, 5.29 (1H, td, *J* = 11.8 Hz, *J* = 3.0 Hz, OC**H**$_a$H$_b$CH$_2$) $_{major}$, 5.10 (1H, t, *J* = 11.8 Hz, OC**H**$_a$H$_b$CH$_2$) $_{minor}$, 4.79 (1H, dd, *J* = 14.3 Hz, *J* = 3.5 Hz, ArC**H**$_a$H$_b$N) $_{major}$, 4.39 (1H, dd, *J* = 14.3 Hz, ArC**H**$_a$H$_b$N) $_{minor}$, 4.04−3.98 (1H, m, OCH$_a$**H**$_b$CH$_2$) $_{minor}$, 3.96−3.92 (1H, m, OCH$_a$**H**$_b$CH$_2$) $_{major}$, 3.75 (1H, dd, *J* = 15.1 Hz, *J* = 3.3 Hz, ArCH$_a$**H**$_b$N) $_{minor}$, 3.14 (1H, dd, *J* = 14.3 Hz, *J* = 3.5 Hz, ArCH$_a$**H**$_b$N) $_{major}$, 2.98−2.88 (1H, m, C**H**N)$_{minor}$, 2.66−2.57 (1H, m, C**H**N)$_{major}$, 2.66−2.57 (1H, m, CHC**H**$_a$H$_b$CH$_2$), 2.51−2.41 (1H, m, CH$_2$C**H**$_a$H$_b$N) $_{both\ rotamers}$, 2.41−2.36 (1H, m, CH$_2$CH$_a$**H**$_b$N) $_{minor}$, 2.11−2.03 (1H, m, C**H**$_a$H$_b$)$_{minor}$, 2.00−1.92 (1H, m, CH$_2$CH$_a$**H**$_b$N) $_{major}$, 1.81−1.08 (7H in total, C**H**$_2$) $_{both\ rotamers}$ [1.81−1.67 (2H, m) $_{minor}$, 1.67−1.54 (2H, m) $_{major}$, 1.41−1.11 (5H, m) $_{both\ rotamers}$, 1.08−0.99 (1H, m)$_{major}$; δ_c (100 MHz, $CDCl_3$) 170.3 (**C**O) $_{major}$, 169.8 (**C**O) $_{minor}$, 163.2 (Ar**C**) $_{minor}$, 162.3 (Ar**C**) $_{major}$, 147.3 (Ar**C**) $_{major}$, 147.2 (Ar**C**) $_{minor}$, 137.0 (Ar**C**H) $_{major}$, 136.7 (Ar**C**H) $_{minor}$, 130.8 (Ar**C**H) $_{major}$, 130.7 (Ar**C**H) $_{minor}$, 128.8 (Ar**C**H) $_{major}$, 128.7 (Ar**C**H) $_{minor}$, 128.33 (Ar**C**H) $_{major}$, 128.29 (Ar**C**H) $_{minor}$, 127.6 (Ar**C**) $_{minor}$, 127.4 (Ar**C**) $_{major}$, 126.8 (Ar**C**H) $_{major}$, 126.7 (Ar**C**H) $_{minor}$, 126.5 (Ar**C**) $_{major}$, 66.0 (O**C**H$_2$) $_{minor}$, 62.9 (O**C**H$_2$) $_{major}$, 62.6 (N**C**H) $_{minor}$, 59.5 (N**C**H$_2$) $_{major}$, 58.3 (**C**HN) $_{major}$, 53.8 (N**C**H$_2$) $_{major}$, 49.9 (N**C**H$_2$) $_{minor}$, 49.4 (N**C**H$_2$) $_{minor}$, 31.7 (**C**H$_2$) $_{major}$, 31.0 (**C**H$_2$) $_{minor}$, 30.9 (**C**H$_2$) $_{major}$, 28.1 (**C**H$_2$) $_{major}$, 25.8 (**C**H$_2$) $_{minor}$, 25.5 (**C**H$_2$) $_{major}$, 24.4 (**C**H$_2$) $_{major}$, 18.8 (**C**H$_2$) $_{minor}$; HRMS (ESI) calcd. for $C_{18}H_{21}N_2O_2$ 297.1603. Found $[MH]^+$ 297.1597 (−2.02 ppm error).

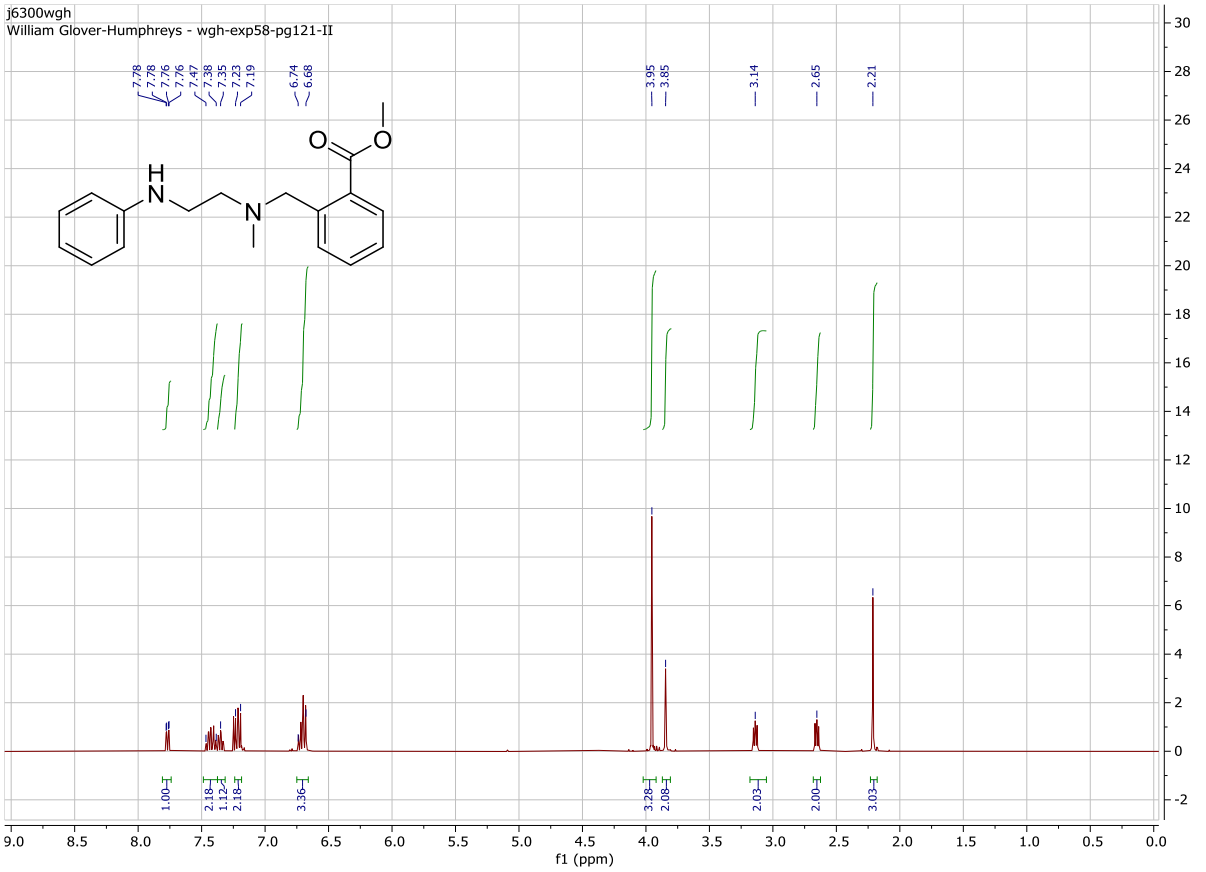

c8216wgh
William Glover-Humphreys - wgh-exp70-pg146-II
f1 (ppm)

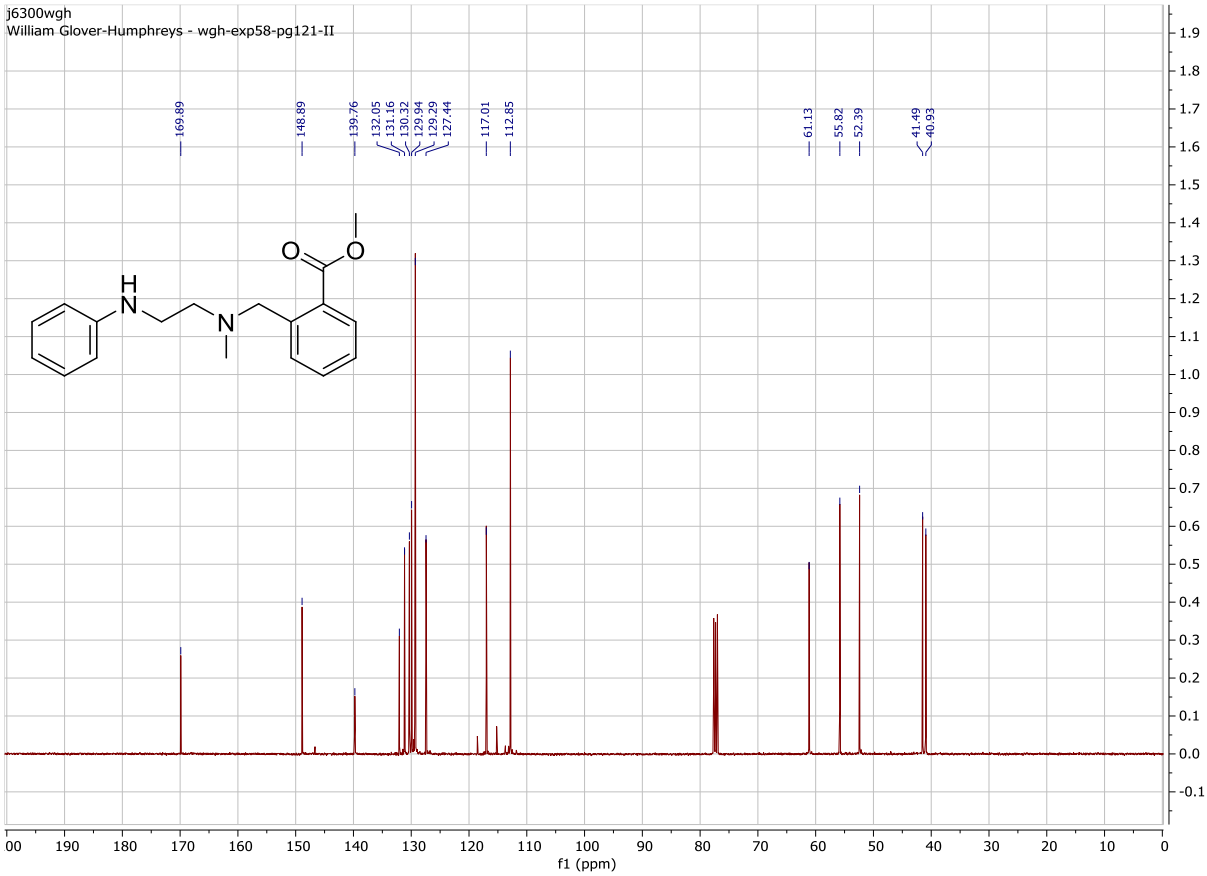

j6608wgh
William Glover-Humphreys - wgh-exp70-pg146-II
f1 (ppm)

Methyl 2-((methyl(2-(phenylamino) ethyl) amino) methyl) benzoate (6-144)

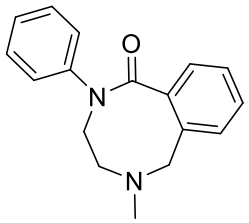


To a stirring solution of potassium carbonate (0.104 g, 0.75 mmol) in acetonitrile (7.50 mL), N^1-methyl-N^2-phenylethane-1,2-diamine (**9-143**) (0.225 g, 1.50 mmol) was added followed by methyl 2-(bromomethyl) benzoate (**6-1**) (0.115 g, 0.500 mmol). The reaction mixture was stirred at room temperature for 5 hours under argon before filtering through Celite washing with dichloromethane, concentrating under vacuum and purifying by flash column chromatography (hexane:ethyl acetate 1:1) to afford the title compound as a yellow oil (0.149 g, 99%) R_f = 0.59 streek (1:1 hexane:ethyl acetate); ν_{max}/cm^{-1} (thin film) 3391, 2949, 2798, 1717, 1602, 1505, 1431, 1273, 1249, 1082, 741; δ_H (400 MHz, $CDCl_3$) 7.77 (1H, dd, *J* = 7.5 Hz, *J* = 1.4 Hz, Ar**H**), 7.47−7.38 (2H, m, Ar**H**), 7.35(1H, td, *J* = 7.5 Hz, 1.6 Hz, Ar**H**), 7.23−7.19 (2H, m, Ar**H**), 6.74−6.68 (3H, m, Ar**H**), 3.95 (3H, s, OC**H**$_3$), 3.85 (2H, s, NC**H**$_2$Ar), 3.14 (2H, t, *J* = 5.9 Hz, NC**H**$_2$CH$_2$N), 2.65 (2H, t, *J* = 5.9 Hz, NCH$_2$C**H**$_2$N), 2.21 (3H, s, NC**H**$_3$); δ_c (100 MHz, $CDCl_3$) 170.0 (**C**O), 148.9 (Ar**C**), 139.8 (Ar**C**), 130.1 (Ar**C**), 131.2 (Ar**C**H), 130.3 (Ar**C**H), 129.9 (Ar**C**H), 129.3 (Ar**C**H), 127.4 (Ar**C**H), 117.0 (Ar**C**H), 112.9 (Ar**C**H), 61.1 (Ar**C**H$_2$N), 55.8 (**C**H$_2$N), 52.4 (**C**H$_3$O), 41.5 (**C**H$_2$NH), 40.9 (N**C**H$_3$); HRMS (ESI) calcd. for $C_{18}H_{23}N_2O_2$ 299.1760. Found $[MH]^+$ 299.1751 (−3.01 ppm error).

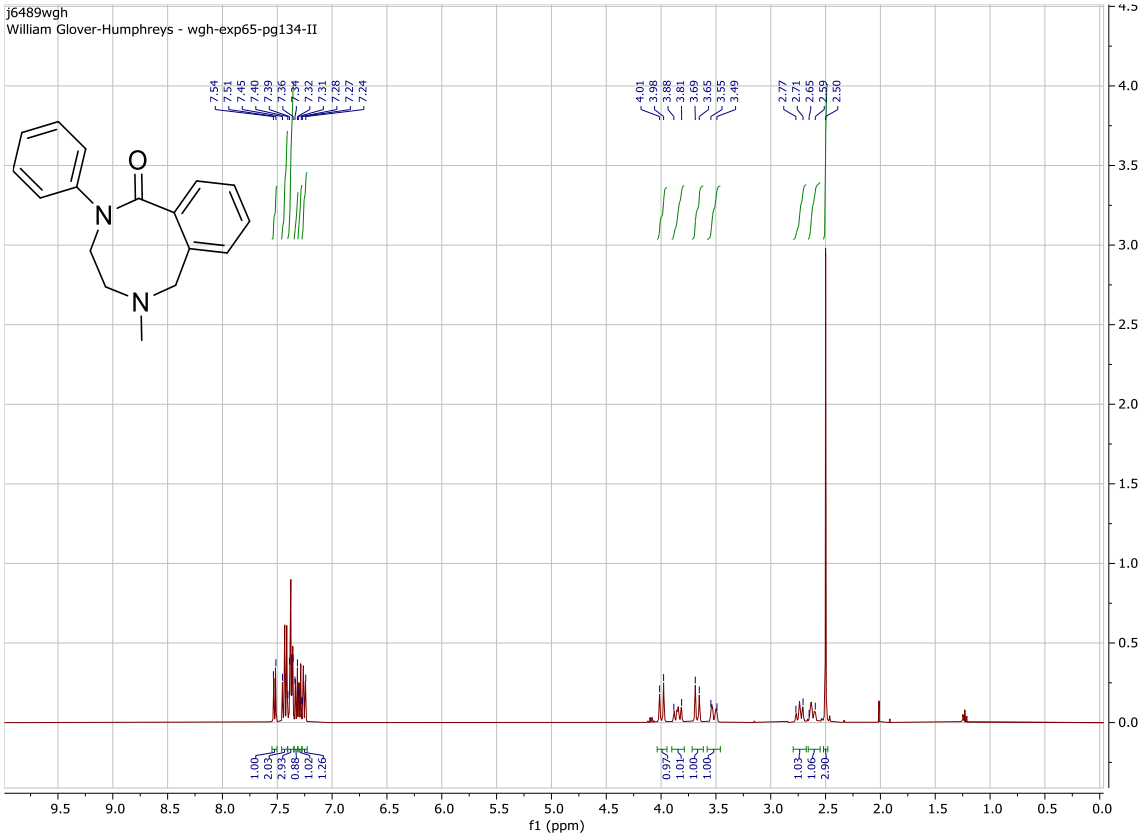

j6300wgh
William Glover-Humphreys - wgh-exp58-pg121-II
7.78
7.78
7.76
7.76
7.47
7.38
7.35
7.23
7.19
6.74
6.68
3.95
3.85
3.14
2.65
2.21
1.00
2.18
1.12
2.18
3.36
3.28
2.08
2.03
2.00
3.03
f1 (ppm)

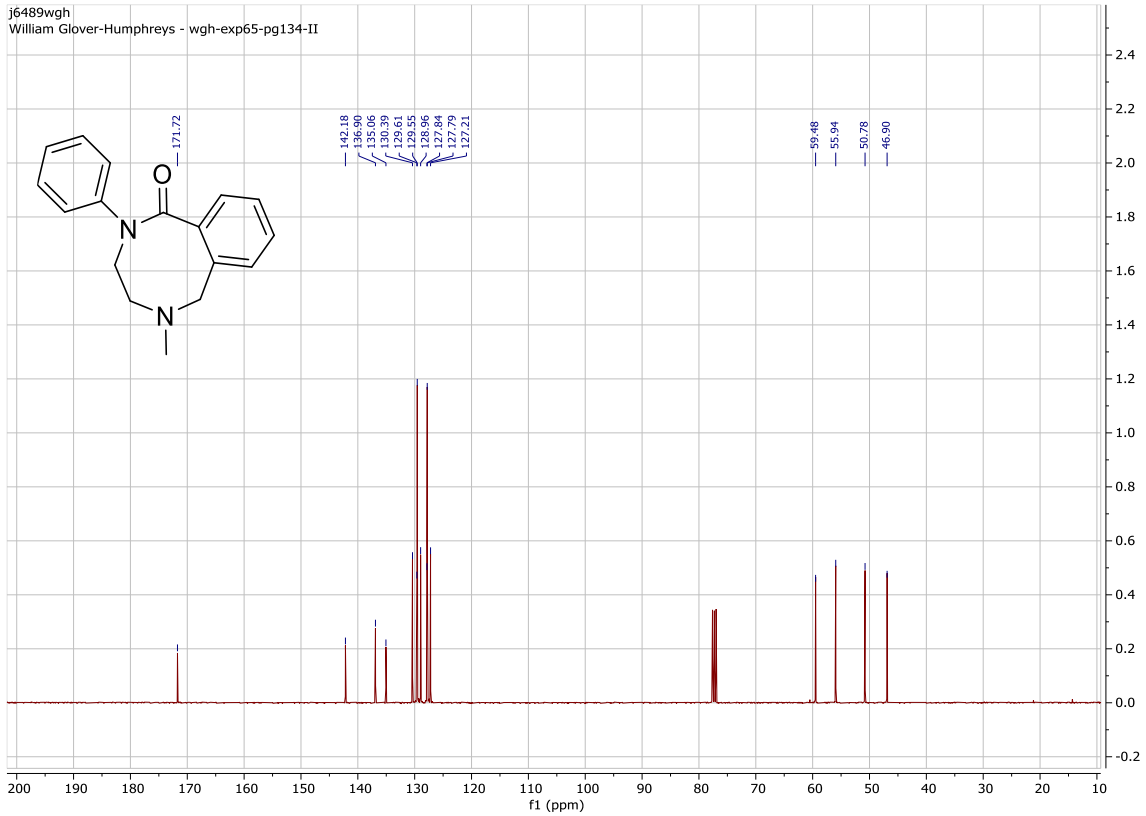

j6300wgh
William Glover-Humphreys - wgh-exp58-pg121-II
169.89
148.89
139.76
132.05
131.16
130.32
129.94
129.29
127.44
117.01
112.85
61.13
55.82
52.39
41.49
40.93
f1 (ppm)

5-Methyl-2-phenyl-3,4,5,4-tetrahydrobenzo[*f*] [1,4] diazocin-1(2*H*)-one (6-146)

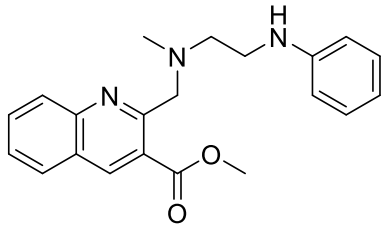


To a stirring solution of methyl 2-((methyl (2-(phenylamino) ethyl) amino) methyl) benzoate (**6-144**) (0.129 g, 0.433 mmol) in tetrahydrofuran (1.07 mL), aqueous lithium hydroxide (0.5 M) (1.07 mL, 0.563 mmol) was added and heated for at 50 °C for 3 hours. The solvent was removed under vacuum using dichloromethane (5 × 50 mL) to form an azeotropic mixture. The intermediate lithium (2-((2-carboxylatobenzyl) (methyl) amino) ethyl) (phenyl) amide was dissolved in chloroform (4.3 mL) and DIPEA (0.100 g, 0.135 mL, 0.800 mmol) was added followed by T3P 50% w/v in ethyl acetate (0.420 g, 0.650 mmol) and stirred at room temperature for 3 hours under argon. The reaction mixture was washed sequentially in dichloromethane (2 × 100 mL) and brine (50 mL) and the organic phases combined dried with sodium sulfate, filtered, concentrated under vacuum and purified via flash column chromatography (10:9:1 hexane:ethylacetate:triethylamine) to afford the title compound (0.0860 g, 75%) R_f = 0.3 (10:9:1 hexane:ethylacetate:triethylamine; ν_{max}/cm^{-1} (thin film) 2946, 2240, 1638, 1401, 1029, 727, 697; δ_H (400 MHz, $CDCl_3$) 7.52 (1H, dd, *J* = 7.5 Hz, 1.4 Hz, Ar**H**), 7.45−7.40 (2H, m, 2× Ar**H**), 7.39−7.36 (3H, m, 3× Ar**H**), 7.33 (1H, dd, *J* = 7.5 Hz, 1.4 Hz, Ar**H**), 7.31−7.28 (1H, m, Ar**H**), 7.27−7.24 (1H, m, Ar**H**), 3.99 (1H, d, *J* = 14.5 Hz, ArC**H**$_a$H$_b$N), 3.88−3.81 (1H, m, C**H**$_a$H$_b$N), 3.67 (1H, d, *J* = 14.5 Hz, ArCH$_a$**H**$_b$N), 3.55−3.49 (1H, m, CH$_a$**H**$_b$N), 2.77−2.71 (1H, m, C**H**$_a$H$_b$N), 2.65−2.59 (1H, m, CH$_a$**H**$_b$N), 2.50 (3H, s, C**H**$_3$N); δ_C (100 MHz, $CDCl_3$) 171.7 (**C**O), 142.2 (Ar**C**), 136.9 (Ar**C**), 135.1 (Ar**C**), 130.4 (Ar**C**H), 129.6 (Ar**C**H), 129.5 (Ar**C**H), 129.0 (Ar**C**H), 127.9 (Ar**C**H), 127.8 (Ar**C**H), 127.2 (Ar**C**H), 59.5 (Ar**C**H$_2$N), 55.9 (**C**H$_2$N), 50.8 (**C**H$_2$N), 46.9 (N**C**H$_3$); HRMS (ESI) calcd. for $C_{17}H_{19}N_2O$ 267.1497. Found $[MH]^+$ 267.1491 (−2.25 ppm error).

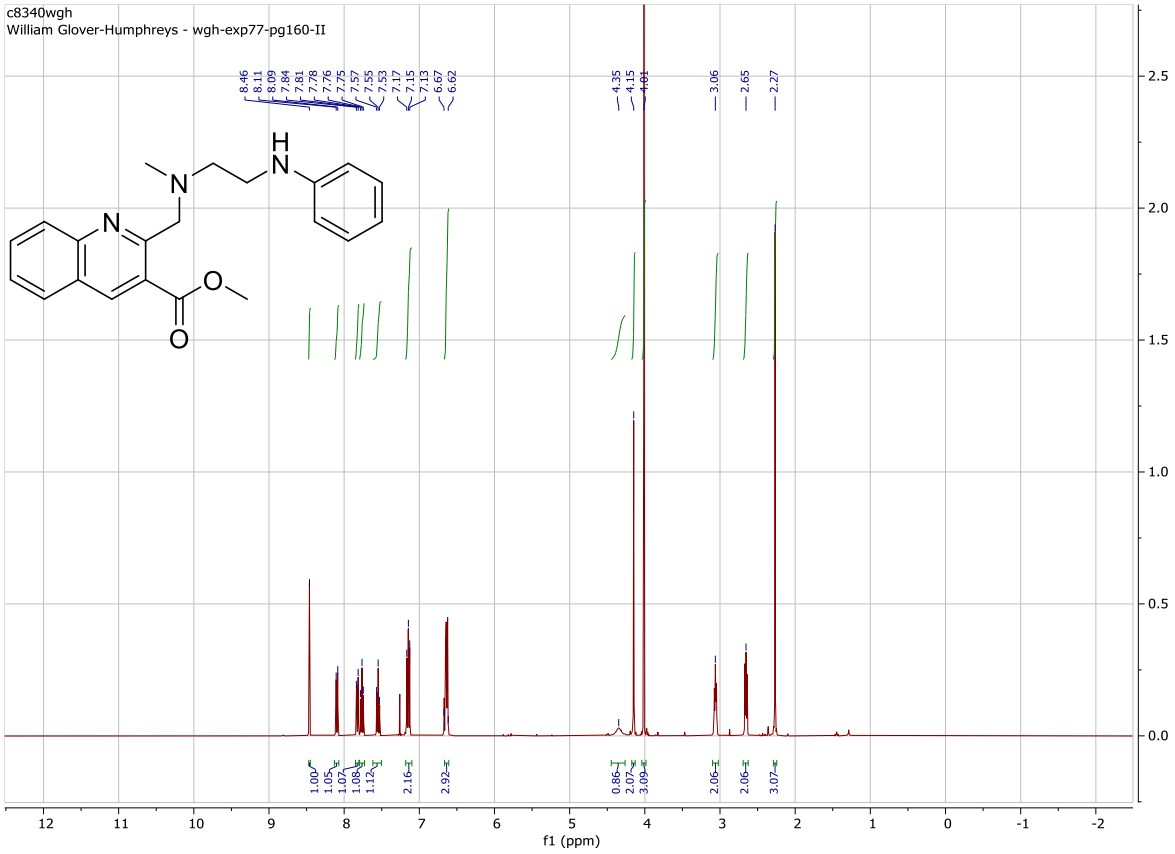

j6489wgh
William Glover-Humphreys - wgh-exp65-pg134-II
7.54
7.51
7.45
7.40
7.39
7.36
7.34
7.32
7.31
7.28
7.27
7.24
4.01
3.98
3.88
3.81
3.69
3.65
3.55
3.49
2.77
2.71
2.65
2.59
2.50
O
N
N
1.00
2.03
2.93
0.88
1.02
1.26
0.97
1.01
1.00
1.00
1.03
1.06
2.90
f1 (ppm)

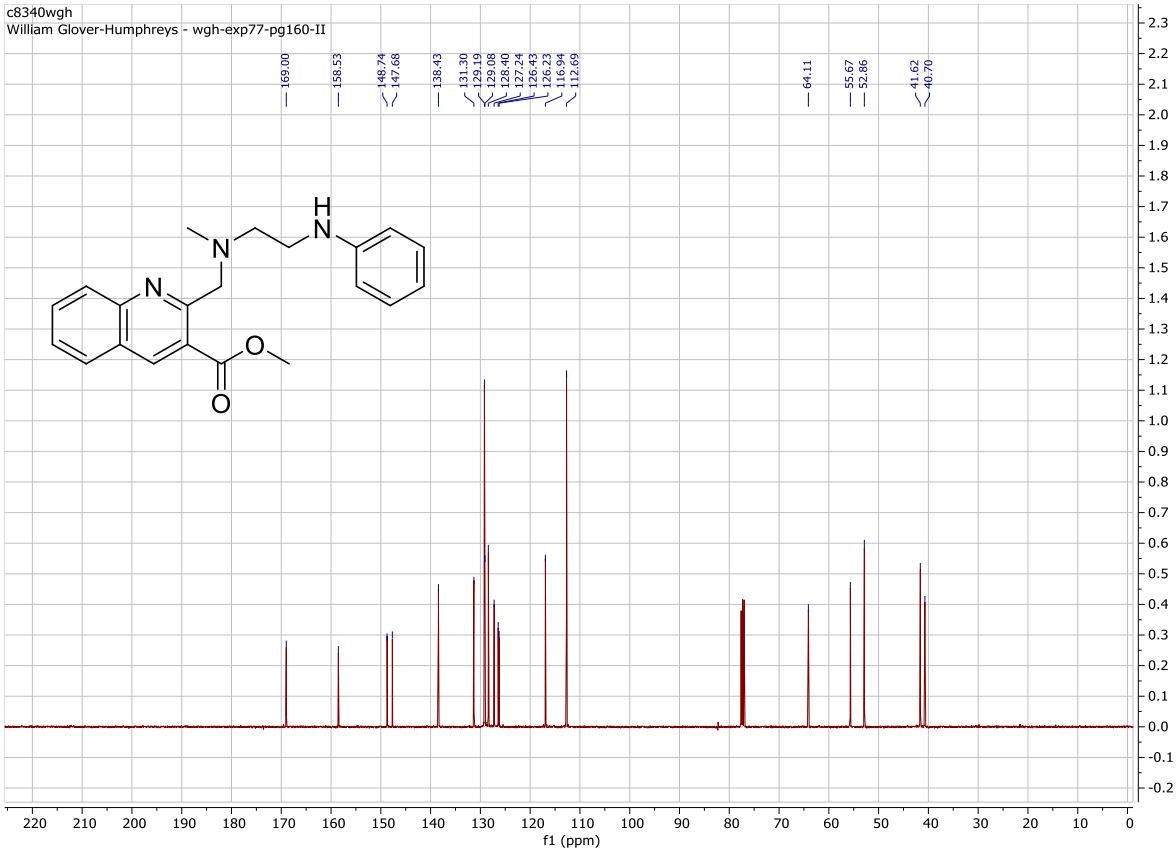

j6489wgh
William Glover-Humphreys - wgh-exp65-pg134-II
171.72
142.18
136.90
135.06
130.39
129.61
129.55
128.96
127.84
127.79
127.21
59.48
55.94
50.78
46.90
O
N
N
f1 (ppm)

Methyl 2-((methyl (2-(phenylamino) ethyl) amino) methyl) quinoline-3-carboxylate (6-147)

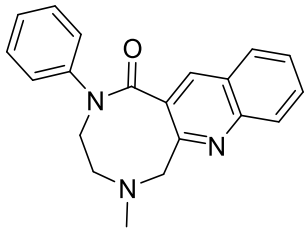


To a stirring solution of potassium carbonate (0.194 g, 1.41 mmol) in acetonitrile (4.70 mL), N^1-methyl-N^2-phenylethane-1,2-diamine (**6-143**) (0.141 g, 0.938 mmol) was added followed by methyl 2-(bromomethyl) quinoline-3-carboxylate (**6-136**) (0.222 g, 0.938 mmol). The reaction mixture was stirred at room temperature for 5 hours under argon before filtering through Celite washing with dichloromethane, concentrating under vacuum and purifying by flash column chromatography (19:1 toluene:methanol) to afford the title compound as a yellow oil (0.113 g, 35%) R_f = 0.43 streek (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3399, 2955, 2850, 1724, 1603, 1507, 1247, 1065, 751, 697; δ_H (400 MHz, $CDCl_3$) 8.46 (1H, s, Ar**H**), 8.10 (1H, d, *J* = 8.3 Hz, Ar**H**), 7.82 (1H, d, *J* = 8.3 Hz, Ar**H**), 7.76-7.75 (1H, m, Ar**H**), 7.56−7.53 (1H, m, Ar**H**), 7.17−7.13 (2H, m, 2 × Ar**H**), 6.67−6.62 (3H, m, 3 × Ar**H**), 4.35 (1H, s, N**H**), 4.15 (2H, s, ArC$\mathbf{H}_2$), 4.01 (3H, s, OC$\mathbf{H}_3$), 3.06 (2H, t, *J* = 5.6 Hz, NC$\mathbf{H}_2$CH$_2$), 2.65 (2H, t, *J* = 5.6 Hz, NC$\mathbf{H}_2$CH$_2$), 2.27 (3H, s, C$\mathbf{H}_3$N); δ_C (100 MHz, $CDCl_3$) 169.0 (**C**O), 158.5 (Ar**C**), 148.7 (Ar**C**), 147.7 (Ar**C**), 138.4 (Ar**C**H), 131.3 (Ar**C**H), 129.2 (Ar**C**H), 129.1 (Ar**C**H), 128.4 (Ar**C**H), 127.2 (Ar**C**H), 126.4 (Ar**C**), 126.2 (Ar**C**), 116.9 (Ar**C**H), 112.7 (Ar**C**H), 64.1 (Ar**C**H$_2$N), 55.7 (N**C**H$_2$), 52.9 (N**C**H$_3$), 41.6 (O**C**H$_3$), 40.7 (NH**C**H$_2$); HRMS (ESI) calcd. for $C_{21}H_{24}N_3O_2$ 350.1869. Found $[MH]^+$ 350.1854 (−4.28 ppm error).

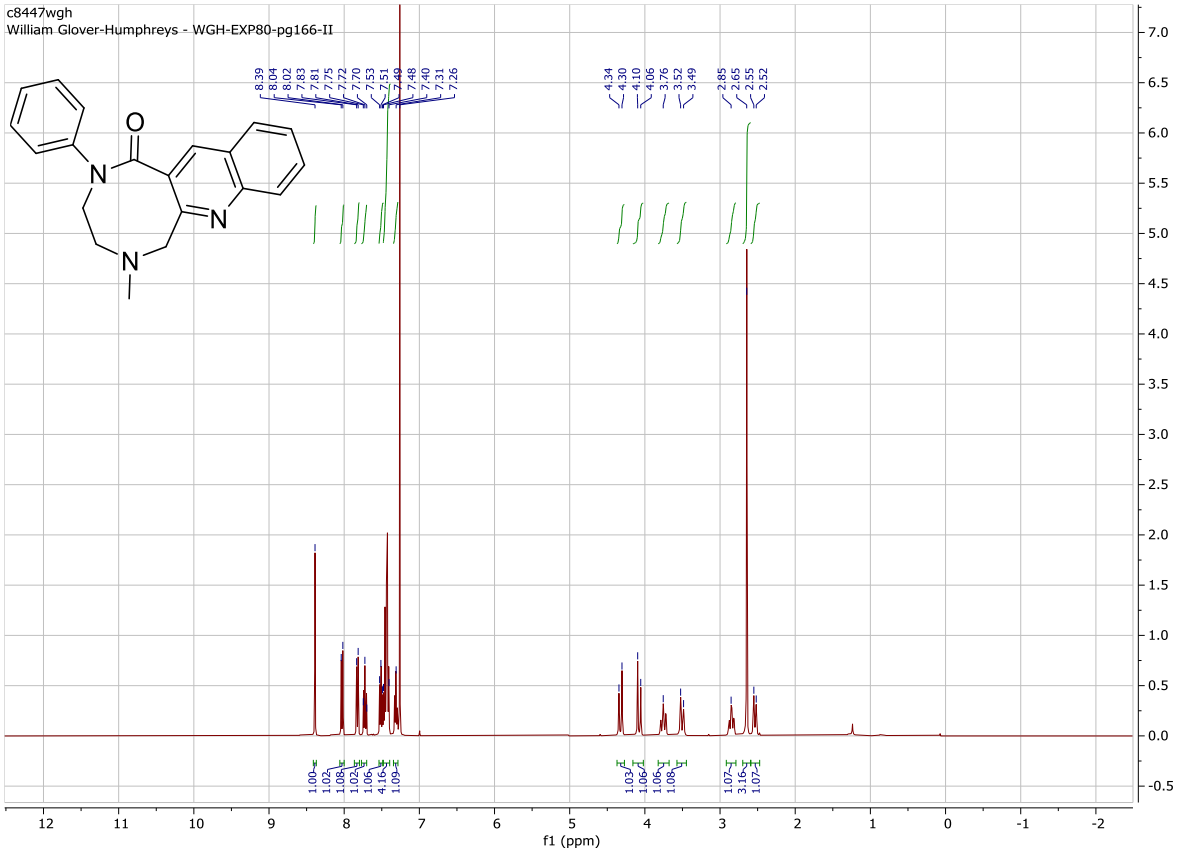

c8340wgh
William Glover-Humphreys - wgh-exp77-pg160-II
8.46
8.11
8.09
7.84
7.81
7.78
7.76
7.75
7.57
7.55
7.53
7.17
7.15
7.13
6.67
6.62
4.35
4.15
4.01
3.06
2.65
2.27
1.00
1.05
1.07
1.08
1.12
2.16
2.92
0.86
2.07
3.09
2.06
2.06
3.07
f1 (ppm)

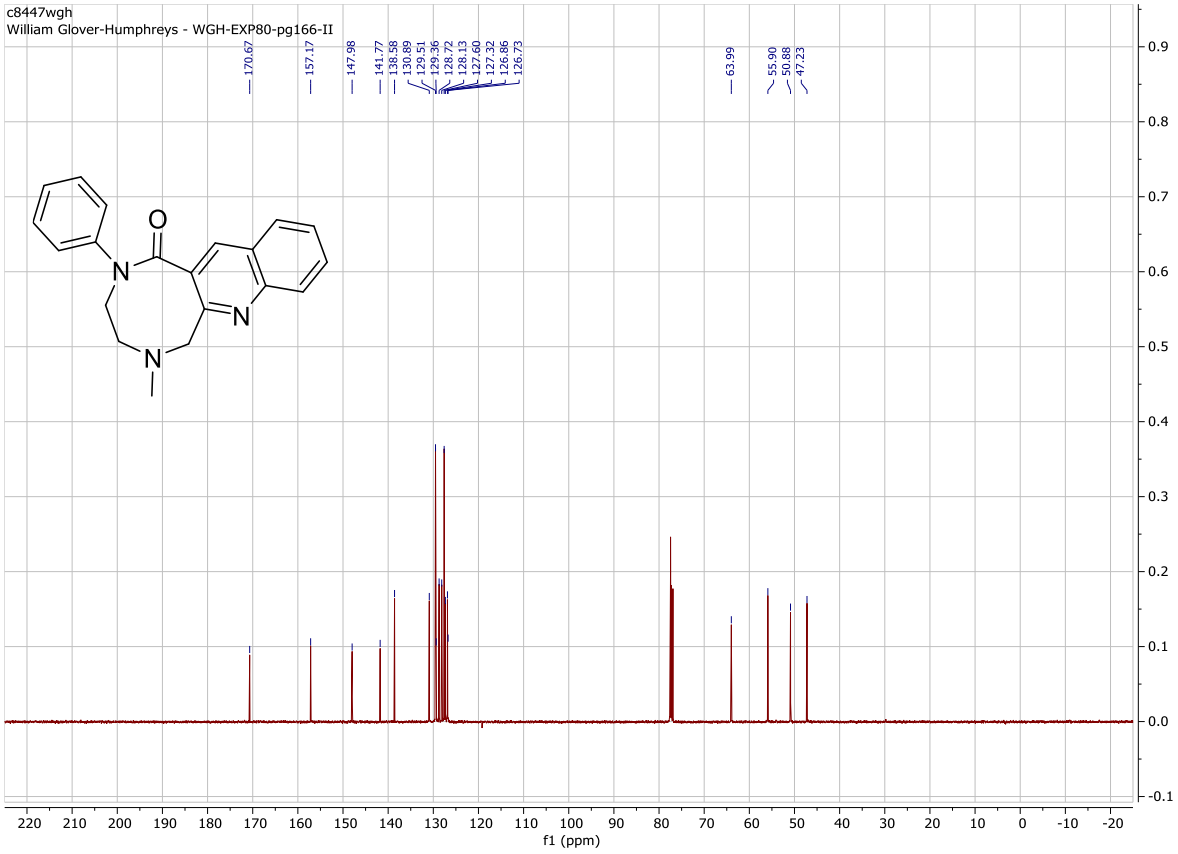

c8340wgh
William Glover-Humphreys - wgh-exp77-pg160-II
169.00
158.53
148.74
147.68
138.43
131.30
129.19
129.08
128.40
127.24
126.43
126.23
116.94
112.69
64.11
55.67
52.86
41.62
40.70
f1 (ppm)

5-Methyl-2-phenyl-3,4,5,4-tetrahydro- [1,4] diazocino [6,7-*b*] quinolin-1 (2*H*)-one (6-148)

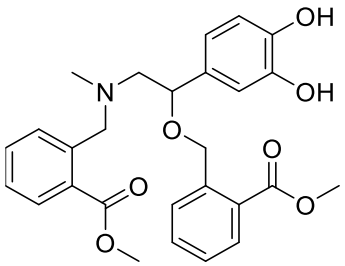


To a stirring solution of methyl 2-((methyl (2-(phenylamino) ethyl) amino) methyl) quinoline-3-carboxylate (**6-147**) (0.113 g, 0.324 mmol) in tetrahydrofuran (0.842 mL), aqueous lithium hydroxide (0.5 M) (0.842 mL, 0.421 mmol) was added and heated for at 50 °C for 3 hours. The solvent was removed under vacuum using dichloromethane (5 × 50 mL) to form an azeotropic mixture. The intermediate lithium (2-(((3-carboxylatoquinolin-2-yl) methyl) (methyl) amino) ethyl) (phenyl) amide was dissolved in chloroform (3.24 mL) and DIPEA (0.0775 g, 0.105 mL, 0.599 mmol) was added followed by T3P 50% w/v in ethyl acetate (0.309 g, 0.487 mmol) and stirred at room temperature for 24 hours under argon. The reaction mixture was washed sequentially in dichloromethane (2 × 100 mL) and brine (50 mL), and the organic phases combined dried with sodium sulfate, filtered, concentrated under vacuum and purified via flash column chromatography (10:9:1 hexane:ethyl acetate:triethylamine) to afford the title compound (0.058 g, 56%) R_f = 0.29 (10:9:1 hexane:ethyl acetate:triethylamine); ν_{max}/cm^{-1} (thin film) 2944, 2802, 2241, 1642, 1491, 1397, 1192, 1062, 921, 792, 700, 728; δ_H (400 MHz, $CDCl_3$); 8.39 (1H, s, Ar**H**), 8.03 (1H, d, *J* = 8.4 Hz, Ar**H**), 7.82 (1H, d, *J* = 8.1 Hz, Ar**H**), 7.72 (1H, t, *J* = 7.1 Hz, Ar**H**), 7.51 (1H, t, *J* = 7.6 Hz, Ar**H**), 7.46-7.40 (4H, m, 4 × Ar**H**), 7.31 (1H, t, *J* = 7.1 Hz, Ar**H**), 4.32 (1H, d, *J* = 16.1 Hz, ArC**H**$_a$H$_b$N), 4.08 (1H, d, *J* = 16.1 Hz, ArCH$_a$**H**$_b$N), 3.76 (1H, t, *J* = 14.0 Hz, ArC**H**$_a$H$_b$N), 3.51 (1H, d, *J* = 14.0 Hz, ArCH$_a$**H**$_b$N), 2.85 (1H, td, *J* = 12.6 Hz, *J* = 3.4 Hz, CH$_a$**H**$_b$NCH$_3$), 2.65 (3H, s, NC**H**$_3$), 2.53 (1H, d, *J* = 12.6 Hz, CH$_a$**H**$_b$NCH$_3$); δ_C (100 MHz, $CDCl_3$) 170.7 (**C**O) 157.2 (Ar**C**), 148.0 (Ar**C**), 141.8 (Ar**C**), 138.6 (Ar**C**H), 130.9 (Ar**C**H), 129.5 (Ar**C**H), 129.4 (Ar**C**), 128.7 (Ar**C**H), 128.1 (Ar**C**H), 127.6 (Ar**C**H), 127.3 (Ar**C**H), 126.9 (Ar**C**H), 126.7 (Ar**C**), 63.4 (Ar**C**H$_2$N), 55.9 (**C**H$_2$NCH$_3$), 50.9 (**C**H$_2$NAr), 47.2 (N**C**H$_3$); HRMS (ESI) calcd. for $C_{20}H_{20}N_3O$ 318.1606. Found $[MH]^+$ 318.1609 (0.943 ppm error).

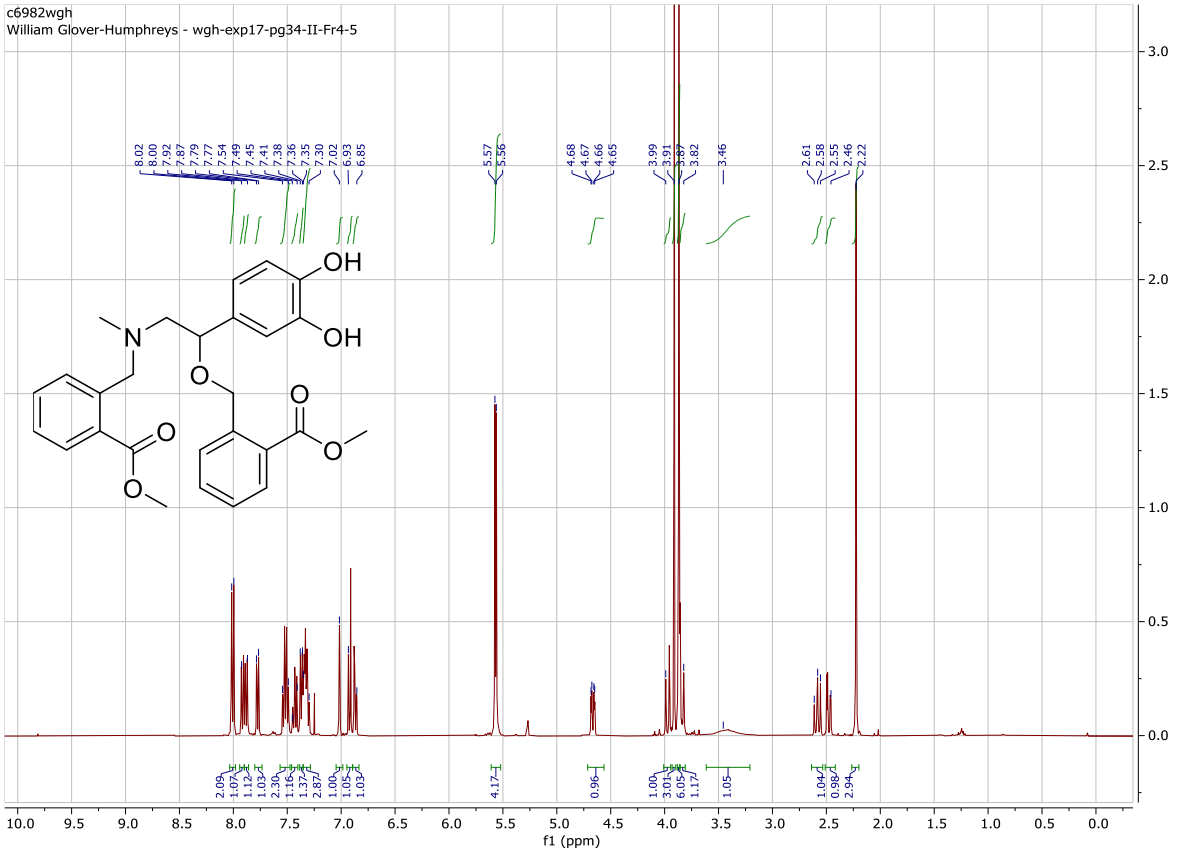

c8447wgh
William Glover-Humphreys - WGH-EXP80-pg166-II
8.39
8.04
8.02
7.83
7.81
7.75
7.72
7.70
7.53
7.51
7.48
7.40
7.31
7.26
4.34
4.30
4.10
4.06
3.76
3.52
3.49
2.85
2.65
2.55
2.52
1.00
1.02
1.08
1.02
1.06
4.16
1.09
1.03
1.06
1.06
1.08
1.07
3.16
1.07
f1 (ppm)

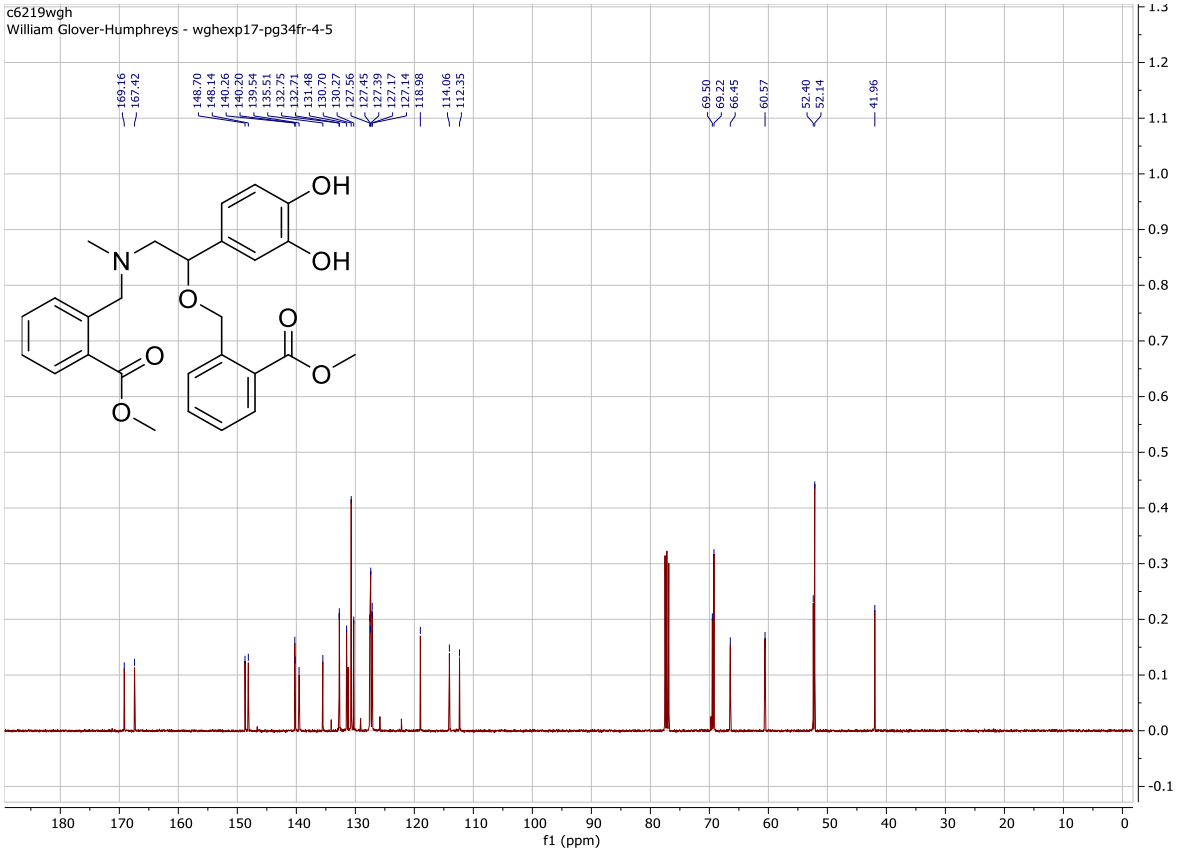

c8447wgh
William Glover-Humphreys - WGH-EXP80-pg166-II
170.67
157.17
147.98
141.77
138.58
130.89
129.51
129.36
128.72
128.13
127.60
127.32
126.86
126.73
63.99
55.90
50.88
47.23
f1 (ppm)

Methyl 2-(((2-hydroxy-2-(4-hydroxy-3-((2-(methoxycarbonyl) benzyl) oxy) phenyl) ethyl) (methyl)amino) methyl) benzoate (6-151)

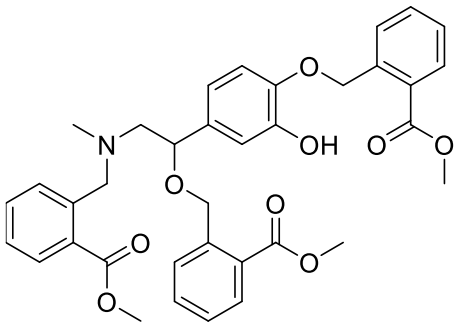


To a stirring solution of potassium carbonate (0.415 g, 3.00 mmol) in acetonitrile (5.00 mL), 4-(1-hydroxy-2-(methylamino) ethyl) benzene-1,2-diol (0.183 g, 1.00 mmol) was added followed by methyl 2-(bromomethyl) benzoate (0.230 g, 1.00 mmol). The reaction mixture was heated to reflux at 90 °C for 3 hours under argon before filtering through Celite washing with dichloromethane, concentrating under vacuum and purifying by flash column chromatography (14:4:1 dichloromethane:ethyl acetate:triethylamine) to afford the **(6-151)** (90 mg, 19%) R_f = 0.77 (14:4:1 dichloromethane:ethyl acetate:triethylamine) ν_{max}/cm^{-1} (thin film) 3433, 2952, 2250, 1714, 1511, 1434, 1264, 1083, 732; δ_H (400 MHz, $CDCl_3$) 7.99 (1H, d, *J* = 7.7 Hz, Ar**H**), 7.76 (1H, d, *J* = 7.8 Hz, Ar**H**), 7.75−7.6 (1H, m, Ar**H**), 7.54−7.47 (1H, m, Ar**H**), 7.48−7.34 (3H, m, Ar**H**), 7.31 (1H, t, *J* = 7.3 Hz, Ar**H**), 6.98−6.94 (1H, m, Ar**H**), 6.90−6.76 (1H, m, Ar**H**), 6.85−6.83 (1H, m, Ar**H**), 5.42 (2H, s, OC**H**$_2$Ar), 4.65−4.61 (1H, m, CH_2C**H**OAr), 3.98−3.80 (2H, m, NC**H**$_2$Ar), 3.91−3.90 (3H, m, C**H**$_3$O), 3.87−3.86 (3H, m, C**H**$_3$O), 2.60−2.43 (2H, m, NC**H**$_2$CH), 2.22−2.21 (3H, m, C**H**$_3$N); δ_c (100 MHz, $CDCl_3$) rotamers observed in a 1:1 ratio 169.2 & 169.2 (**C**O), 167.7 & 167.7 (**C**O), 146.5 & 246.0 (Ar**C**), 145.8 & 145.1 (Ar**C**), 139.5 &139.5 (Ar**C**), 138.6 & 138.4 (Ar**C**), 136.5 & 134.2 (Ar**C**), 132.8 & 132.7 (Ar**C**H), 131.5 & 131.4 (Ar**C**H), 131.3 & 131.2 (Ar**C**), 131.0 & 130.9 (Ar**C**H), 130.7 (Ar**C**H), 130.3 & 130.2 (Ar**C**H), 128.9 & 128.5 (Ar**C**H), 128.8 & 128.5 (Ar**C**), 128.1 &128.0 (Ar**C**H), 127.5 (Ar**C**H), 120.0 & 117.7 (Ar**C**H), 114.9 & 113.8 (Ar**C**H), 113.1 & 112.0 (Ar**C**H), 70.4 & 70.3 (Ar**C**H$_2$N), 69.5 & 69.4 (**C**H), 66.5 & 66.4 (N**C**H$_2$CH), 60.6 (N**C**H$_2$Ar), 52.4 (O**C**H$_3$), 42.0 (N**C**H$_3$); HRMS (ESI) calcd. for $C_{27}H_{30}NO_9$ 480.2022. Found 480.2016 $[MH]^+$ (−1.25 ppm error).

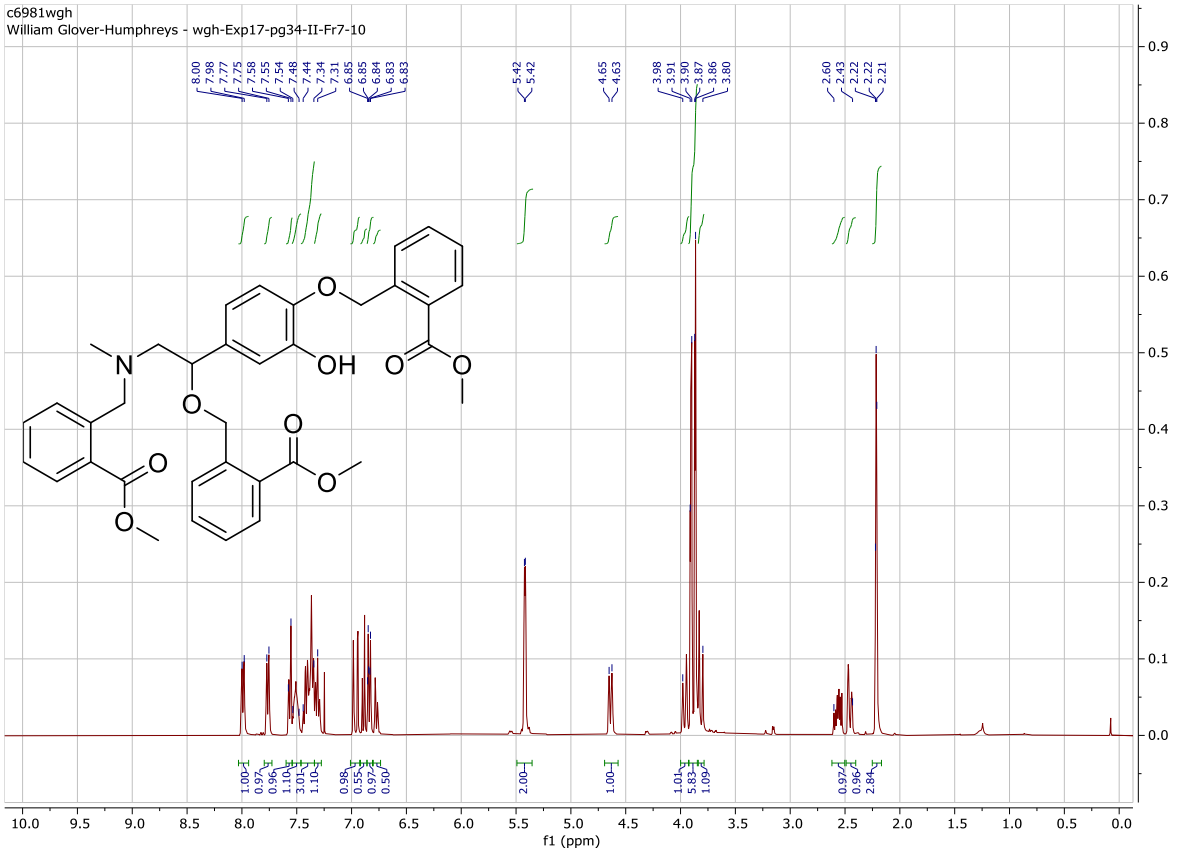

c6982wgh
William Glover-Humphreys - wgh-exp17-pg34-II-Fr4-5
8.02
8.00
7.92
7.87
7.79
7.77
7.54
7.49
7.45
7.41
7.38
7.36
7.35
7.30
7.02
6.93
6.85
5.57
5.56
4.68
4.67
4.66
4.65
3.99
3.91
3.87
3.82
3.46
2.61
2.58
2.55
2.46
2.22
OH
OH
N
O
O
O
O
O
2.09
1.07
1.12
1.03
2.30
1.16
1.37
2.87
1.06
1.05
1.03
4.17
0.96
1.00
3.01
6.05
1.17
1.05
1.04
0.98
2.94
f1 (ppm)

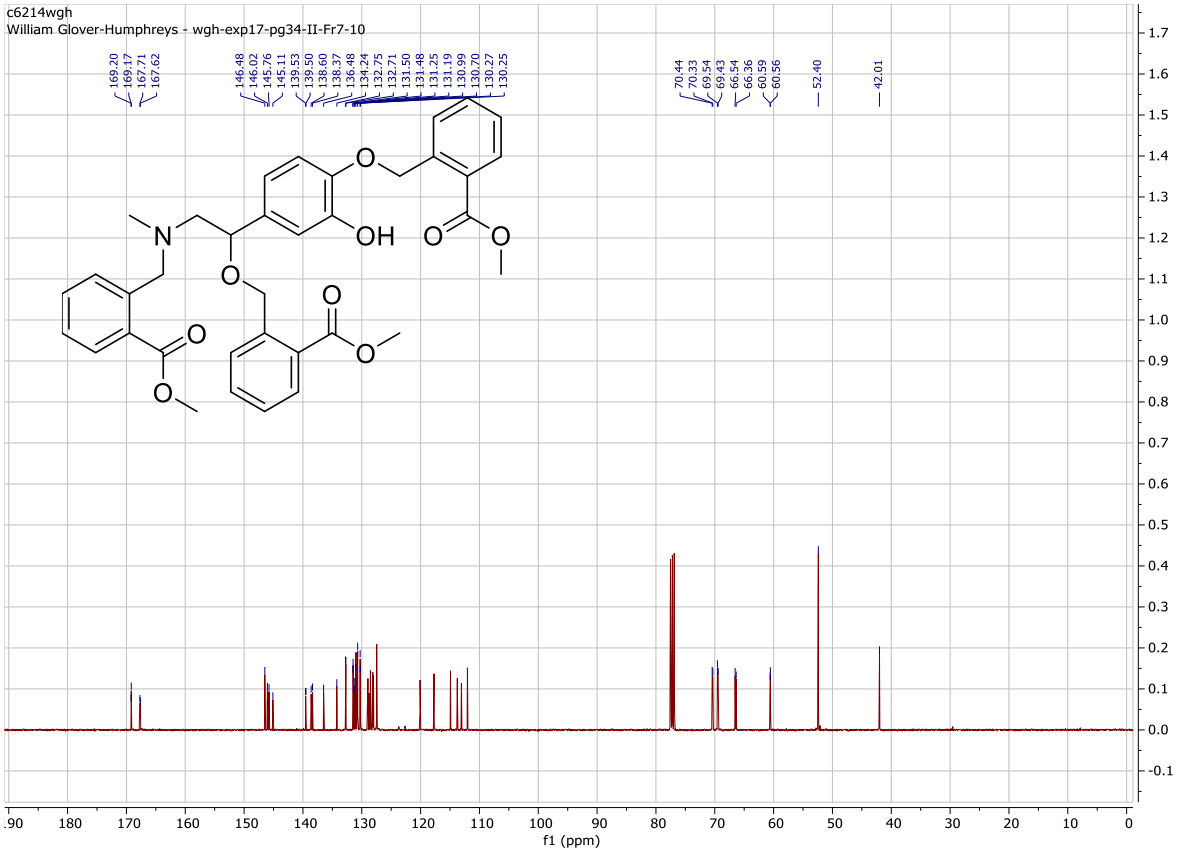

c6219wgh
William Glover-Humphreys - wghexp17-pg34fr-4-5
169.16
167.42
148.70
148.14
140.26
140.20
139.54
135.51
132.75
132.71
131.48
130.70
130.27
127.56
127.45
127.39
127.17
127.14
118.98
114.06
112.35
69.50
69.22
66.45
60.57
52.40
52.14
41.96
OH
OH
N
O
O
O
O
O
f1 (ppm)

Dimethyl 2,2'-(((4-(1-hydroxy-2-((2-(methoxycarbonyl) benzyl) (methyl)amino) ethyl)-1,2-phenylene) bis(oxy)) bis(methylene)) dibenzoate (6-152)

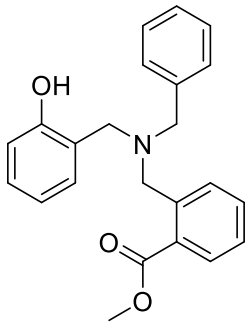


The same procedure that formed **(6-151)** also formed **(6-152)** (113 mg, 18%) R_f = 0.59 (14:4:1 dichloromethane:ethyl acetate:triethylamine); ν_{max}/cm^{-1} (thin film) 3488, 2952, 2253, 1715, 1262, 906, 725; δ_H (400 MHz, $CDCl_3$) 8.01 (2H, d, *J* = 7.9 Hz, 2 × Ar**H**), 7.91 (1H, d, *J* = 7.9 Hz, Ar**H**), 7.88 (1H, d, *J* = 7.8 Hz, Ar**H**), 7.77 (1H, dd, *J* = 7.8 Hz, *J* = 1.4 Hz, Ar**H**), 7.54−7.48 (2H, m, Ar**H**), 7.45−7.40 (1H, m, Ar**H**), 7.37 (1H, d, *J* = 7.5 Hz, Ar**H**), 7.35−7.29 (3H, m, Ar**H**), 7.02 (1H, s, Ar**H**), 6.93−6.91 (1H, m, Ar**H**), 6.88 (1H, dd, *J* = 7.9 Hz, J = 1.9 Hz Ar**H**), 5.57 (s, 2H, OC**H**$_2$Ar), 5.56 (s, 2H, OC**H**$_2$Ar), 4.67 (1H, dd, *J* = 10.5 Hz, 3.1 Hz, ArC**H**OCH$_2$), 3.99−3.82 (2H, m, ArC**H**$_2$N), 3.90 (3H, s, C**H**$_3$O), 3.87 (6H, s, C**H**$_3$O), 3.46 (1H, bs, OH), 2.61−2.24 (2H, m, NC**H**$_2$CH), 2.22 (3H, s, NC**H**$_3$); δ_C (100 MHz, $CDCl_3$) 169.2, (**C**O), 167.4 (**C**O), 167.4 (**C**O), 148.7 (Ar**C**), 148.1 (Ar**C**), 140.3 (Ar**C**), 140.2 (Ar**C**), 139.5 (Ar**C**), 135.5 (Ar**C**), 132.8 (Ar**C**H), 132.7 (Ar**C**H), 131.5 (Ar**C**H), 131.2 (Ar**C**), 130.7 (Ar**C**H), 130.7 (Ar**C**H), 130.7 (Ar**C**H), 130.7 (Ar**C**), 130.3 (Ar**C**H), 127.6 (Ar**C**), 127.6 (Ar**C**H),127.5 (Ar**C**H), 127.4 (Ar**C**H), 127.4 (Ar**C**), 127.2 (Ar**C**H), 127.1 (Ar**C**H), 119.0 (Ar**C**H), 114.1 (Ar**C**H), 112.3 (Ar**C**H), 69.5 (**C**H), 69.2 (2 × O**C**H$_2$Ar), 66.4 (N**C**H$_2$CH), 60.7 (Ar**C**H$_2$N), 52.4 (O**C**H$_3$), 52.1 (O**C**H$_3$), 42.0 (**C**H$_3$N); HRMS (ESI) calcd. for $C_{36}H_{38}NO_9$. Found 628.2547 $[MH]^+$ 628.2548 (0.159 ppm error).

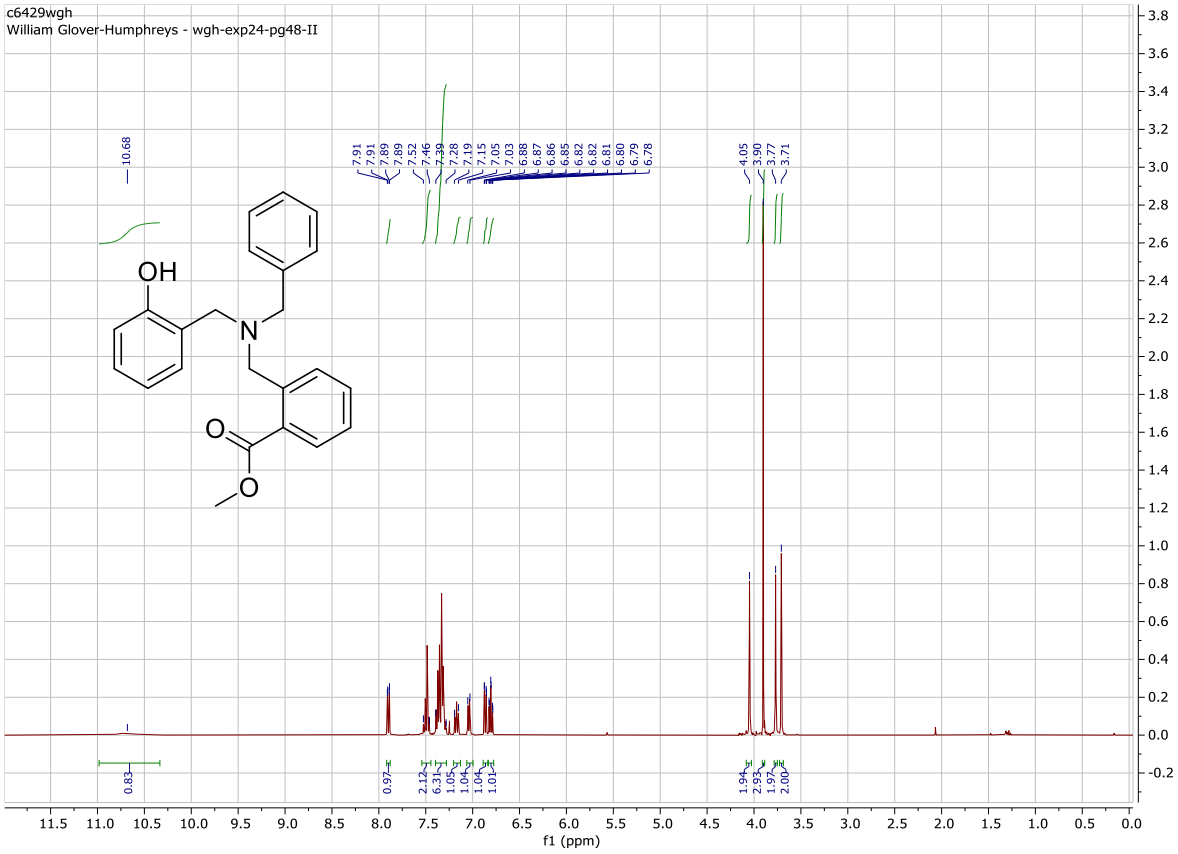

c6981wgh
William Glover-Humphreys - wgh-Exp17-pg34-II-Fr7-10
f1 (ppm)

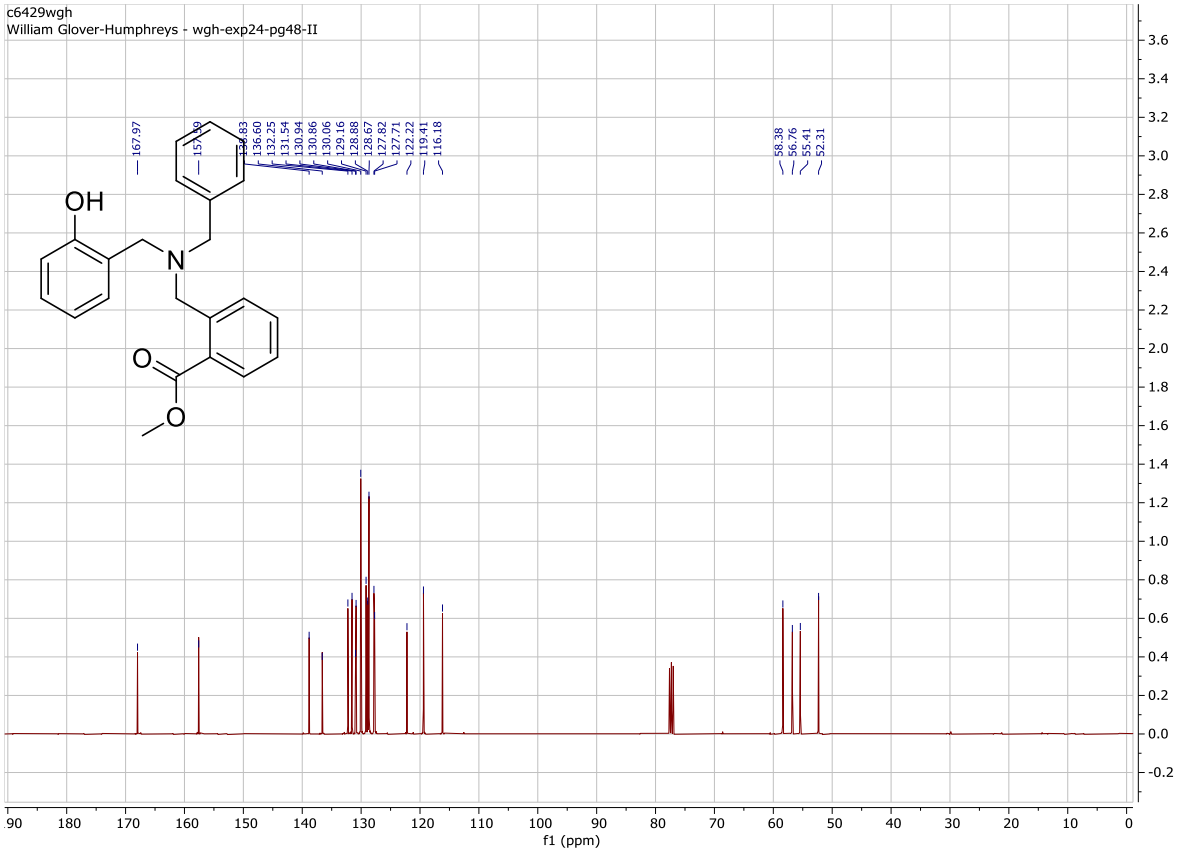

c6214wgh
William Glover-Humphreys - wgh-exp17-pg34-II-Fr7-10
f1 (ppm)

Methyl 2-((benzyl (2-hydroxybenzyl amino) methyl) benzoate (6-154)

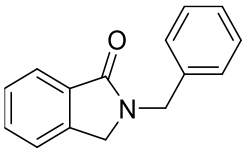


To a stirring solution of potassium carbonate (0.415 g, 3.00 mmol) in acetonitrile (5.00 mL), 2-((benzylamino) methyl) phenol (**6-153**) (0.2133 g, 1.00 mmol) was added followed by methyl 2-(bromomethyl) benzoate (**6-1**) (0.230 g, 1.00 mmol). The reaction mixture was heated to reflux at 90 °C for 3 hours under argon before filtering through Celite washing with dichloromethane, concentrating under vacuum and purifying by flash column chromatography (8:2 hexane:diethyl ether) to afford the title compound as a clear oil (0.2552 g, 71%) R_f = 0.27 (8:2 hexane:diethyl ether) ν_{max}/cm^{-1} (thin film) 3029, 2956, 2838, 2255, 1719, 1588, 1488, 1434, 1453, 1254, 1079, 909, 729; δ_H (400 MHz, $CDCl_3$) 10.68 (1H, bs, O**H**), 7.90 (1H, d, *J* = 7.4 Hz, *J* = 1.2 Hz, Ar**H**), 7.52−7.46 (2H, m, Ar**H**), 7.39−7.28 (6H, m, Ar**H**), 7.17 (1H, td, *J* = 8.0 Hz, 1.5 Hz, Ar**H**), 7.04 (1H, dd, *J* = 7.4 Hz, 1.2 Hz), 6.86 (1H, dd, *J* = 8.0 Hz, 1.5 Hz, Ar**H**), 6.81 (1H, td, *J* = 7.4 Hz, 1.2 Hz, Ar**H**), 4.05 (2H, s, ArC$\mathbf{H}_2$N), 3.90 (3H, s, C$\mathbf{H}_3$O), 3.77 (2H, s, ArC$\mathbf{H}_2$N), 3.71 (2H, s, ArC$\mathbf{H}_2$N); δ_c (100 MHz, $CDCl_3$) 168.0 (**C**O), 157.6 (Ar**C**), 138.8 (Ar**C**), 136.6 (Ar**C**), 132.3 (Ar**C**H), 131.5 (Ar**C**H), 131.0 (Ar**C**H), 130.9 (Ar**C**H), 130.1 (Ar**C**H), 129.2 (Ar**C**H), 128.9 (Ar**C**H), 128.7 (Ar**C**H), 127.8 (Ar**C**H), 127.7 (Ar**C**H), 122.2 (Ar**C**), 119.4 (Ar**C**H), 116.2 (Ar**C**H), 58.4 (ArC$\mathbf{H}_2$N), 56.8 (ArC$\mathbf{H}_2$N), 55.4 (ArC$\mathbf{H}_2$N), 52.3 (OC$\mathbf{H}_3$); HRMS (ESI) calcd. for $C_{23}H_{24}NO_3$ 362.1756. Found $[MH]^+$ 362.1748 (−2.21 ppm error).

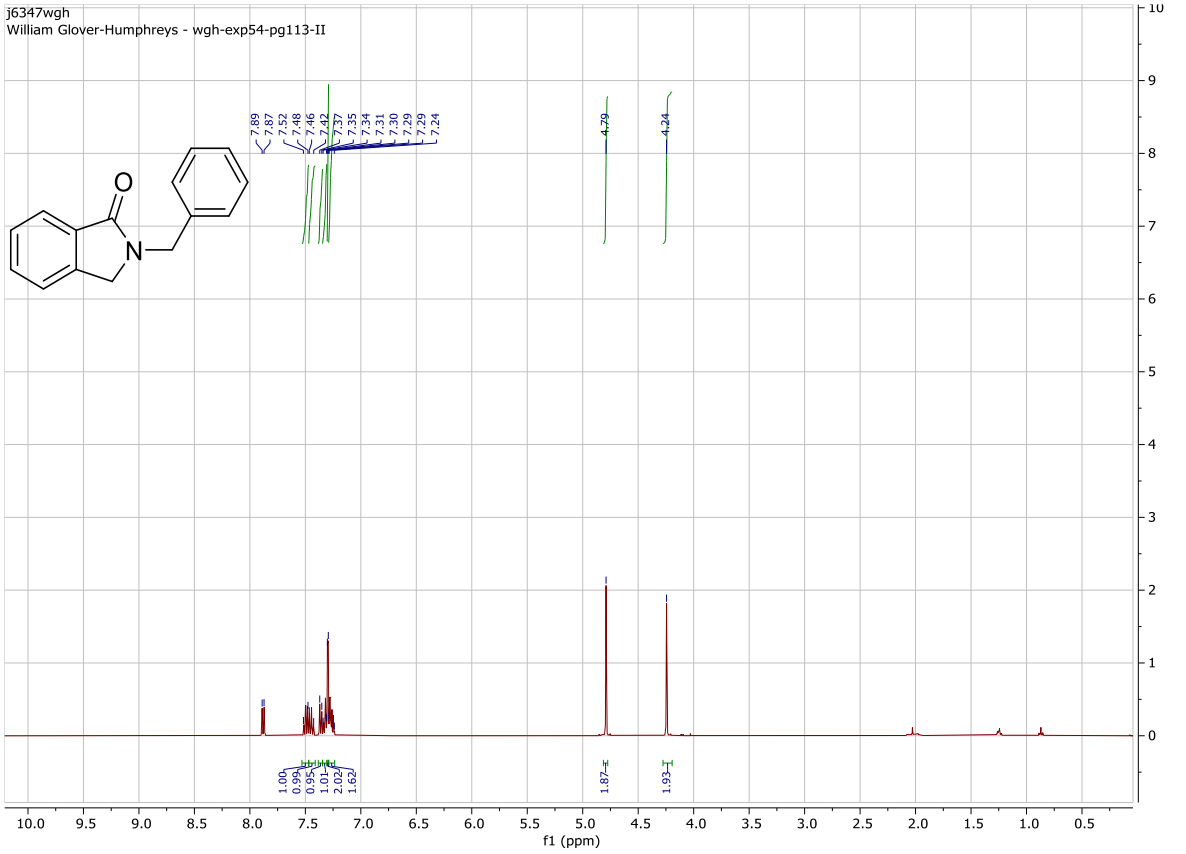

c6429wgh
William Glover-Humphreys - wgh-exp24-pg48-II
OH
N
O
O
f1 (ppm)

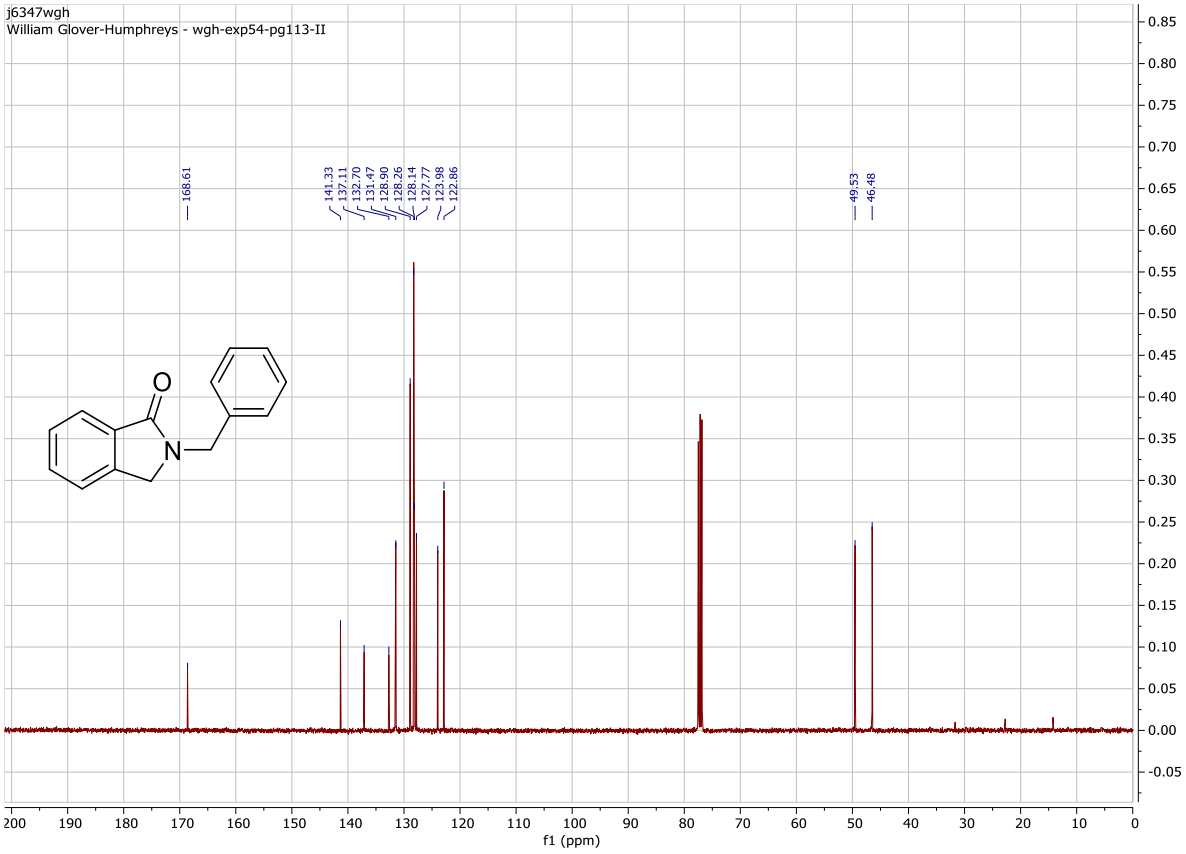

c6429wgh
William Glover-Humphreys - wgh-exp24-pg48-II
OH
N
O
O
f1 (ppm)

2-Benzylisoindolin-1-one (6-158)



To a stirring solution of 2-((benzyl(2-(methoxycarbonyl) benzyl) amino) methyl) benzoic acid (**6-154**) (0.100 g, 0.277 mmol) in methanol (10 mL) and water (5 mL), aqueous lithium hydroxide (0.5 M) (1.27 mL, 0.637mmol) was added and heated for at 50 °C for 3 hours. The solvent was removed under vacuum using dichloromethane (5 × 50 mL) to form an azeotropic mixture. The intermediate lithium 2-((benzyl(2-oxidobenzyl) amino) methyl) benzoate was dissolved in chloroform (2.80 mL) and DIPEA (0.0663 g, 0.090 mL, 0.513 mmol) was added followed by T3P 50% w/v in ethyl acetate (0.220 g, 0.693 mmol) and stirred at room temperature for 24 hours under argon. The reaction mixture was washed sequentially in dichloromethane (2 × 100 mL) and brine (50 mL) and the organic phases combined dried with sodium sulfate, filtered, concentrated under vacuum and purified via flash column chromatography (6:4 hexane:ethyl acetate) to afford the title compound (0.0490 g, 79%) R_f = 0.25 (6:4 hexane:ethyl acetate); ν_{max}/cm^{-1} (thin film) 3481, 3031, 2915, 1674, 1452, 733, 701; δ_H (400 MHz, $CDCl_3$) 7.88 (1H, d, *J* = 6.8 Hz, Ar**H**), 7.52−7.48 (1H, td, *J* = 7.3 Hz, *J* = 1.3 Hz, Ar**H**), 7.46−7.42 (1H, m, Ar**H**), 7.36 (1H, d, *J* = 7.3 Hz, Ar**H**), 7.34−7.31 (1H, m, Ar**H**), 7.30−7.29 (2H, m, Ar**H**) 7.29−7.24 (1H, m, Ar**H**), 4.79 (2H, s, NC**H**$_2$Ar), 4.24 (2H, s, ArC**H**$_2$N); δ_c (100 MHz, $CDCl_3$) 168.6 (**C**O), 141.3 (Ar**C**), 137.1 (Ar**C**), 132.7 (Ar**C**), 131.5 (Ar**C**H), 128.9 (Ar**C**H), 128.3 (Ar**C**H), 128.1 (Ar**C**H), 127.8 (Ar**C**H), 124.0 (Ar**C**H), 122.9 (Ar**C**H), 49.5, (N**C**H$_2$Ar), 46.5 (Ar**C**H$_2$N); The NMR data are consistent with literature data.[44] HRMS (ESI) calcd. for $C_{15}H_{14}NO$ 224.1075. Found $[MH]^+$ 224.1074 (−0.446 ppm error).


j6347wgh
William Glover-Humphreys - wgh-exp54-pg113-II
7.89
7.87
7.52
7.48
7.46
7.42
7.37
7.35
7.34
7.31
7.30
7.29
7.29
7.24
4.79
4.24
1.00
0.99
0.95
1.01
2.02
1.62
1.87
1.93
f1 (ppm)


j6347wgh
William Glover-Humphreys - wgh-exp54-pg113-II
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141.33
137.11
132.70
131.47
128.90
128.26
128.14
127.77
123.98
122.86
49.53
46.48
f1 (ppm)

The end, thank you for reading.