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Investigations of Indole-Alkaloid Biogenesis

Through Synthesis

Jake Stuart



Degree of Doctor of Philosophy

The University of Edinburgh

2022

Declaration

I declare that this thesis has been composed solely by myself, that the work contained herein is my own except where explicitly stated otherwise in the text, and that this work has not been submitted for any other degree or professional qualification.

Jake Stuart, 31/08/2022

Abstract

Biomimetic synthesis is a blanket term used to describe a great number of synthetic endeavours, broadly encapsulated by using reactions and materials available during organic metabolism. Herein, we will be utilising biomimicry to interrogate hypotheses for the biogenesis a complex bis-indole natural product; (+)-dievodiamine. As well as this, we will share our attempts to synthesise natural products in a concise way, with high atom economy.

Chapter 1 is an introduction to metabolism and the biogenesis of natural products derived from the shikimic acid pathway. Biomimetic syntheses of related natural products will be discussed, as well as a literature review summarising the synthesis of pentacyclic, quinazolinocarboline natural products related to (+)-dievodiamine. The isolation and only known synthesis (+)-dievodiamine will be discussed, as well as our proposed biosynthetic pathway and synthetic plan towards (+)-dievodiamine.

Chapter 2 describes the discovery of a unique deprotonation/retro-6 π electrocyclisation cascade which supports our proposed biogenesis of (+)-dievodiamine. As well as this, attempts to synthesise (+)-dievodiamine *via* a vinylogous Mannich reaction are presented, which provides insights into the redox chemistry of evodiamine (the formal monomer of (+)-dievodiamine).

Chapter 3 focuses on a route towards (+)-dievodiamine based on nonribosomal peptide synthetase mediated alkaloids. The synthesis of a tri-amide oligomer composed of tryptophan, tryptamine and two units of *N*-methyl anthranilic acid will be discussed. Beyond that, attempted functionalisation and cyclisation chemistry on a model peptide intermediate will be discussed. Finally, attempts to install a C₁-unit within the mature peptide oligomer will be described.

Chapter 4 follows-on in our attempts in the synthesis of (+)-dievodiamine by late-stage cyclisation, described in the chapter prior. This strategy we labelled the convergent route, it focuses on a synthesis of (+)-dievodiamine from a pre-functionalised the oligomer from Chapter 3. We will also show that some of the chemistry attempted prior can be achieved

simply by removal of a methyl group from the intermediate. We will attempt to complete the synthesis of the natural product through a Pictet–Spengler cyclisation and late-stage ring closure.

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1. Introduction – Biogenesis as inspiration for chemical synthesis

1.1. Metabolism and life

Organisms use chemical transformations to interconvert and transform the vast number of compounds required for sustaining life. Through the lengthy process of natural selection, the evolution of integrated and carefully regulated pathways has allowed for this chemistry to flourish within an array of organic life. These pathways are collectively referred to as metabolic pathways and are used to provide organisms with the energy required to continue life through the various processes of metabolism.

1.1.1. Primary metabolism

Importantly, organisms have almost universally evolved to use adenine triphosphate (ATP) as the currency of energy in metabolism. The use of ATP for energy has fuelled the biogenesis of the other crucial classes of organic molecules: carbohydrates, proteins, nucleic acids and fats. With the exception of fats, these molecules are all polymeric. Carbohydrates are made from sugar units, proteins from amino acids and nucleic acids from nucleotides. It is the numerous combinations of these building blocks that leads to the vast complexity observed within our biosphere.

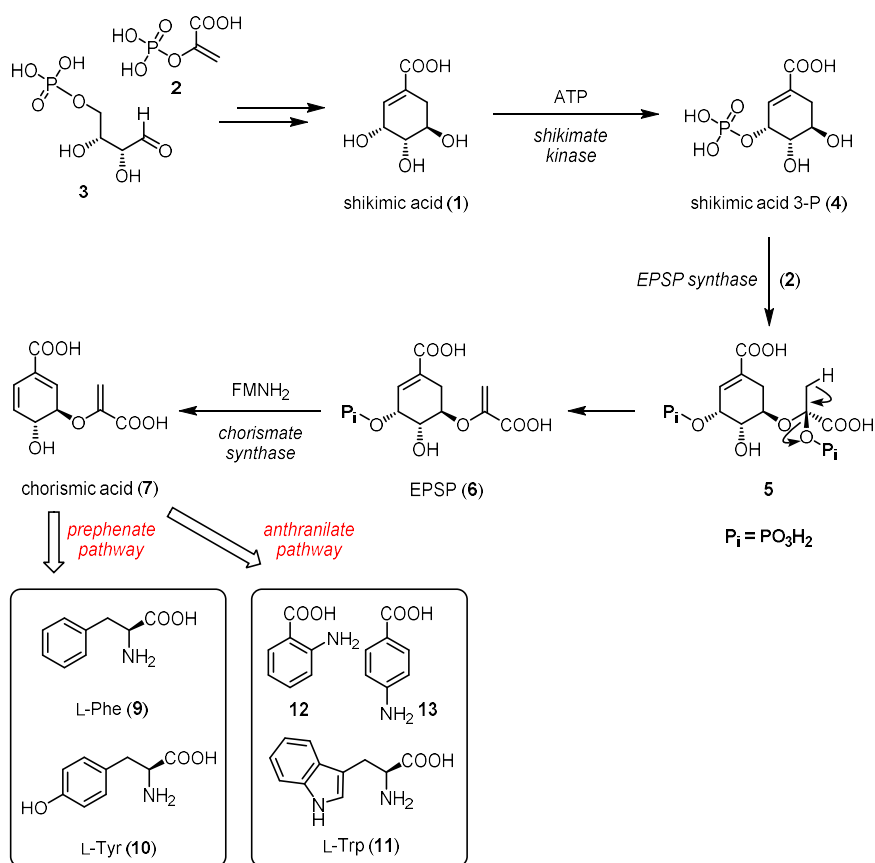
Although the complexity of organic compounds in nature is vast, the pathways for converting these building blocks into the complex molecules of life remain reasonably similar between organisms. These processes are collectively known as primary metabolism, with the compounds being known as primary metabolites. These pathways involve the degradation of carbohydrates by glycolysis and the Krebs cycle. Fats release energy by β -oxidation and oxidative phosphorylation (in aerobic organisms). Whereas proteins, taken in the diet, can be broken down to amino acids that can be interconverted to make new proteins or degraded for more energy.

1.1.2. Secondary metabolism

Primary metabolic pathways are involved in the synthesis, interconversion and degradation of commonly encountered compounds. Some compounds have a much more limited distribution in nature, these are known as secondary metabolites or natural products. These compounds are not necessarily produced under all conditions and are often organism-specific. Reasons for these include: protection from predators and attraction of the same or other species. Although the use of some secondary metabolites are unknown, it is assumed that most have some evolutionary reason for their syntheses. As synthetic chemists we can take inspiration from nature and these metabolism pathways, to perform concise synthesis of these complex molecules.

1.2. Shikimic acid pathway

Shikimic acid (**1**), derived from the combination of phosphoenol pyruvate (PEP, **2**) and erythrose 4-phosphate (**3**), is the eponymous intermediate of the shikimate pathway (Scheme 1). Shikimic acid is phosphorylated at the C3 alcohol by an ATP-mediated enzyme (shikimate kinase), to give the activated shikimic acid 3-P (**4**). A further catalysed addition of PEP (**2**) to the alcohol at C5, followed by the elimination of the phosphate unit in intermediate **5**, gives 5-enolpyruvylshikimic acid 3-P (EPSP, **6**). Finally, the phosphate unit at the C3 position of EPSP (**6**) is reductively eliminated to give chorismic acid (**7**), which acts the divergent point in the biosynthesis of the aromatic amino acids: phenylalanine (L-Phe, **8**), tyrosine (L-Tyr, **10**) and tryptophan (L-Trp, **11**).

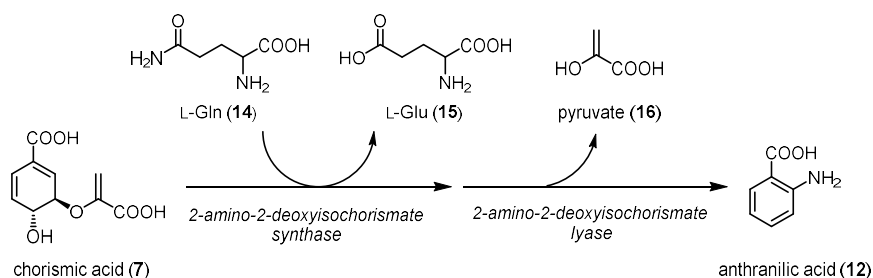


Scheme 1. Simplified shikimic acid pathway

Chorismic acid (7) is the chemical precursor to a vast number of simple secondary metabolites and the aromatic amino acids (mentioned earlier). The pathways unto which these aromatic amino acids are made diverges at chorismic acid (7):

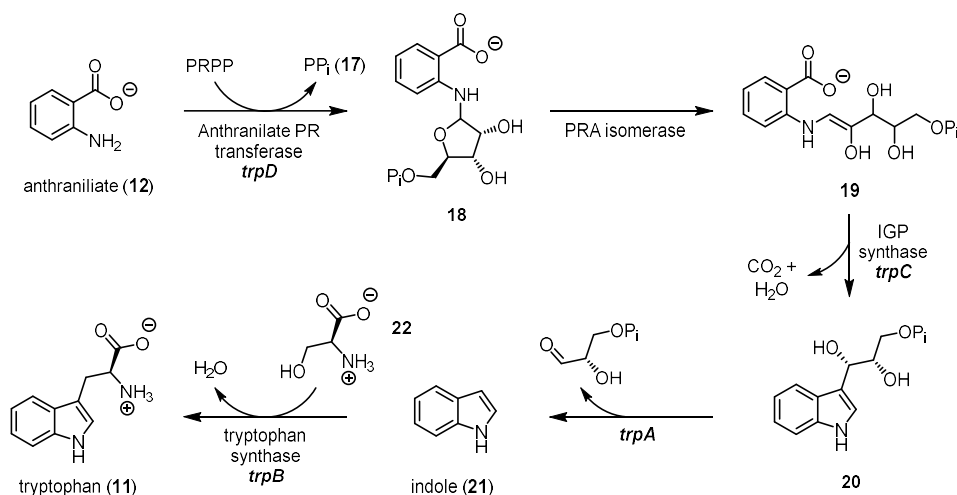
- Prephenate branch – phenylalanine (9), tyrosine (10), etc.
- Anthranilate branch – tryptophan (11), anthranilic acid (12), *p*-aminobenzoic acid (13) etc.

The anthranilate branch is of particular importance to this project and is thus discussed in further detail. The synthesis of anthranilic acid (12) from chorismic acid (7) is achieved through a two-step biosynthetic process (Scheme 2). The addition of the relevant 2-amino group is achieved using glutamine (L-Gln, 14) as the nucleophilic amino-donor, losing a unit of glutamic acid (L-Glu, 15) and furthermore by the loss of a pyruvate (16) unit (catalysed by the 2-amino-2-deoxyisochorismate synthase/lyase couple), to give anthranilic acid (12).



Scheme 2. Biosynthesis of anthranilic acid (12) from chorismic acid (7)

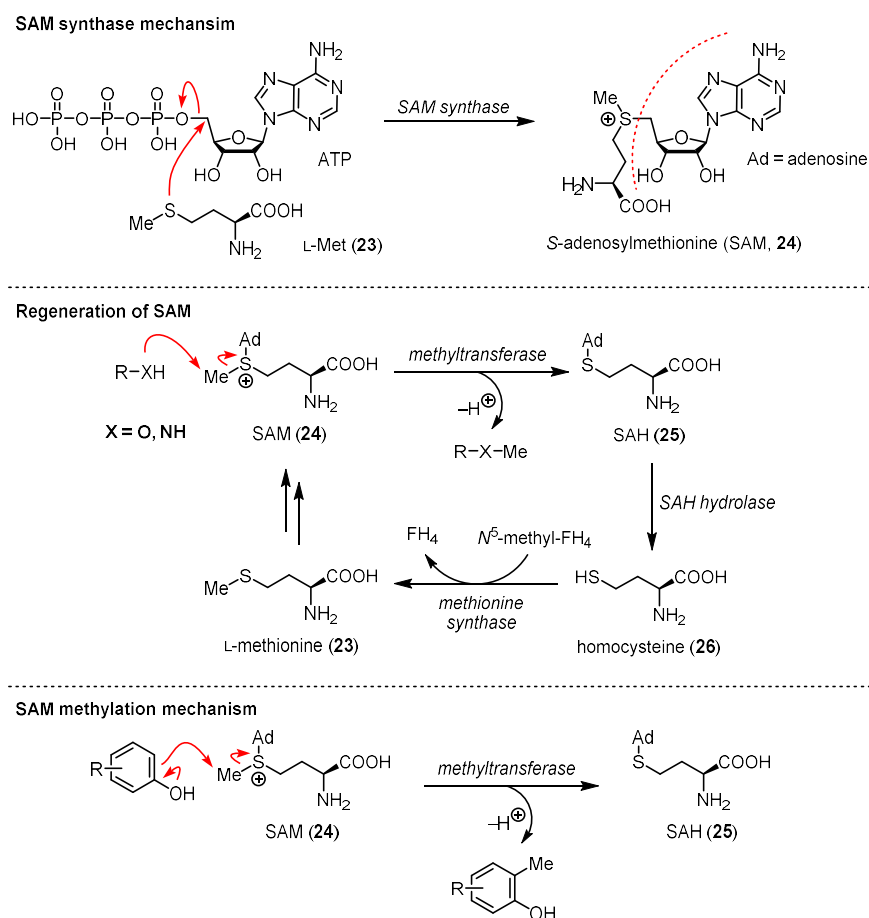
Anthranilic acid (12) can be converted to L-tryptophan (11) over the course of a complex biosynthetic pathway, using four key enzyme pathways labelled **TrpA–D** (Scheme 3. L-Tryptophan (11) biosynthesis). The first step is the S_N2 -reaction (catalysed by anthranilate phosphoribosyltransferase, **TrpD**) of the amino group with an active ribose unit, phosphoribosyl diphosphate (PPi, 17), to give phosphoribosylanthranilic acid (18). The ribose ring is opened to give the corresponding imine isomer (catalysed by phosphoribosylanthranilate isomerase,), which is quickly tautomerised to enamine 19 and condensed (catalysed by indole-3-glycerol phosphate synthase, **TrpC**) to form the necessary indolic compound, indole-3-glycerol phosphate (20). The glycerol phosphate unit is subsequently lost by a reverse aldol reaction (catalysed by tryptophan synthase, **TrpA/B**), to give the enzyme-bound indole (21). Through a PLP-mediated transformation, the indole is functionalised at the C3 position, using serine (L-Ser, 22) as a donor, to give L-tryptophan (11).



Scheme 3. L-Tryptophan (11) biosynthesis

1.3. Biological C₁-units

The supply of the C₁-methyl unit in natural product biosynthesis is often supplied by L-methionine (L-Met, **23**). Moreover, the L-Met (**23**) amino acid is converted into a more potent electrophile by enhancement of the sulfide leaving group to a sulfonium (Scheme 4). The utilised sulfonium is known as S-adenosylmethionine (SAM, **24**), which is formed through an enzyme-mediated S_N2 reaction between L-Met (**23**) and ATP.¹



Scheme 4. Biogenesis of SAM and its utility for methylation in secondary metabolism

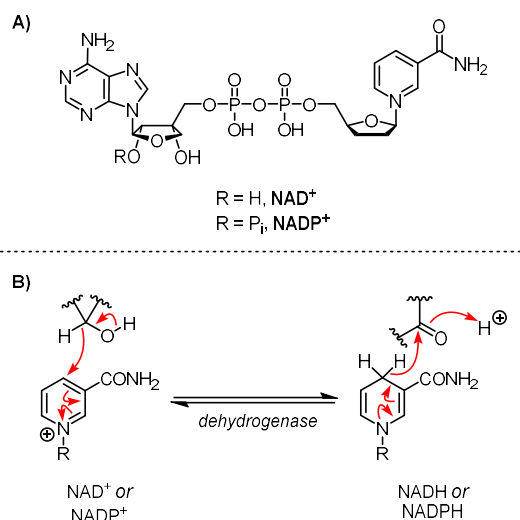
The use of SAM is well known to undergo reactions with hydroxyl and amino functionalities as nucleophiles. The methyltransferase (MT) enzyme-mediated nucleophilic substitution generates the new O/N-methyl linkage as well as S-adenosylhomocysteine (SAH, **25**), which is an excellent leaving group. SAH (**25**) rapidly undergoes the enzyme-mediated loss of an

adenosine group to give homocysteine (**26**), which can then be regenerated back to L-Met (**23**) using *N*⁵-methyl-tetrahydrofolate (*N*⁵-methyl-FH₄) as the methyl donor. C-Methylation is also observed in biological systems, yet the requirement of a nucleophilic carbon for addition of a methyl group by SAM-mediated MTs. Therefore, it is common for *para* and *ortho* positions of phenolic compounds to be methylated, as well as the α-positions of carbonyl compounds. There are also rare, but important, examples of sulphur and other heteroatoms MTs used in nature, mostly by bacteria and plants.²⁻⁴

A branch of methyltransferases, known as natural product methyltransferases (NPMTs), are responsible for the biosynthesis and modification of several branches of secondary metabolites, as well as specialised primary metabolites.⁵⁻⁷

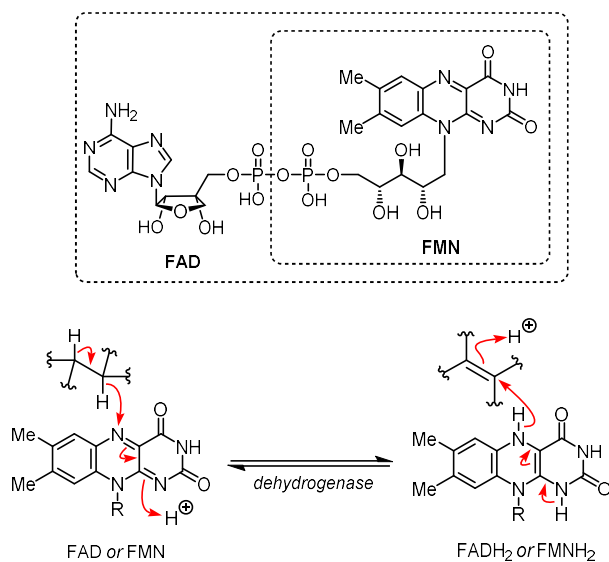
1.4. Redox Chemistry in Biological Systems

Changes in the oxidation state of secondary metabolites are regularly observed but not always thoroughly understood due to the numerous, complex pathways often involved. The enzymes involved in bio-redox chemistry can help identify the processes involved in metabolite biosynthesis. Classes of enzymes are defined by the mechanism of action by which they change the oxidation state of the target compound. Such is the case that dehydrogenases formally remove two hydrogen atoms using a cofactor acceptor, which is reduced in the process. The cofactor used depends on the substrate, for example nicotinamide adenine dinucleotide (NAD⁺) or nicotinamide adenine dinucleotide phosphate (NADP⁺) is used for the oxidation of a secondary alcohol (Scheme 5).



Scheme 5. NAD(P)⁺-mediated reduction of carbonyls

Such is the case with any catalyst, dehydrogenase enzymes can catalyse the reverse reaction using the redox partner of the relevant cofactor. Alternatively, dehydrogenation reactions in which alkanes are the substrate can be catalysed by dehydrogenases using flavin adenine dinucleotide (FAD) or flavin mononucleotide (FMN) as the oxidative cofactor (Scheme 6).



Scheme 6. FAD/FMN-mediated oxidation of alkanes

1.5. Quinazolinocarboline chemistry

1.5.1. Natural products extracted from *Evodia rutaecarpa*

A vast number of related natural products have been isolated from the fruits of *Evodia rutaecarpa* (Juss.) Benth., some examples of which are shown in Figure 1.⁸ These examples all contain the most common motif of these alkaloids; a pentacyclic framework, which contains a fused indole (red, Figure 1) and quinazolinone ring (blue, Figure 1). Due to this structural framework, these alkaloids are commonly referred to as quinazolinocarbolines.⁹ Also shown is the commonly used ring-labelling convention of A-E, with the AB indole rings being fused to the quinazolinone DE-rings, though the centre C-ring. (+)-Evodiamine (**27**) and rutaecarpine (**28**) were the first natural products of this type to be isolated from *E. rutaecarpa* in 1915.¹⁰ It is currently unknown whether (+)-evodiamine (**27**) is a result of a decarboxylation of (+)-carboxyevodiamine (**29**), or whether they are the result of parallel linear synthesis from L-tryptophan (**11**) and tryptamine (**30**), respectively. Dehydroevodiamine (**31**) is the result of (+)-evodiamine (**27**) undergoing a selective oxidation, and will be discussed in detail later. Finally, rutaecarpine (**28**) can be reduced to yield the isolated to dihydrorutaecarpine (**32**). Again this compound and its importance will be further discussed in Chapter 4.

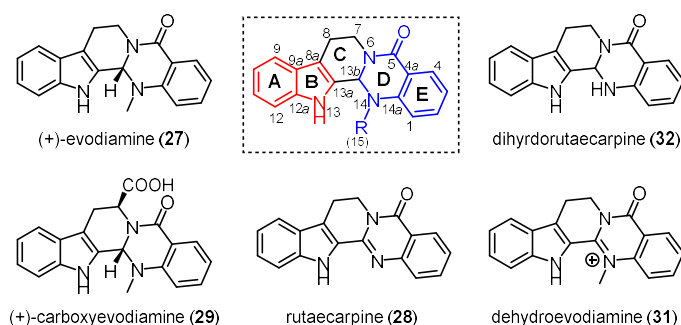
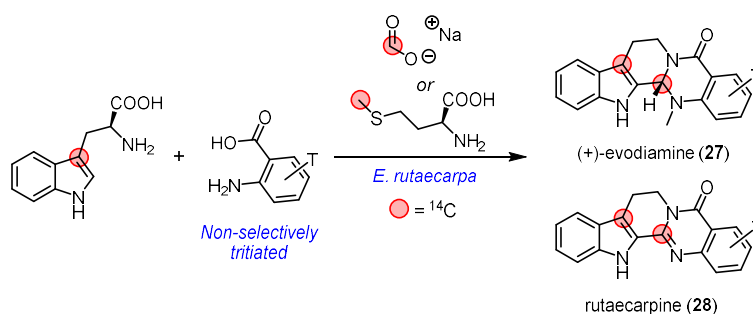


Figure 1. Natural products isolated from *Evodia rutaecarpa*, as well as the accepted numbering system

1.5.2. (+)-Evodiamine biogenesis

In order to understand the biogenesis of secondary metabolites the sequence of reactions, and the enzymes that catalyse these reactions, must be delineated. The difficulty in which this is done is dependent on the complexity of the metabolite and the producing organism. In order to test whether a speculated pathway is biosynthetically viable, methods have been created to “follow” the progress of precursors through biosynthetic pathways. These methods usually involve the labelling of atoms within these precursors, a process known as isotopic labelling. The feeding of these isotopically labelled compounds into the tissue of an organism can be tracked to the final metabolite, given that the extraction procedure of said metabolite is known.

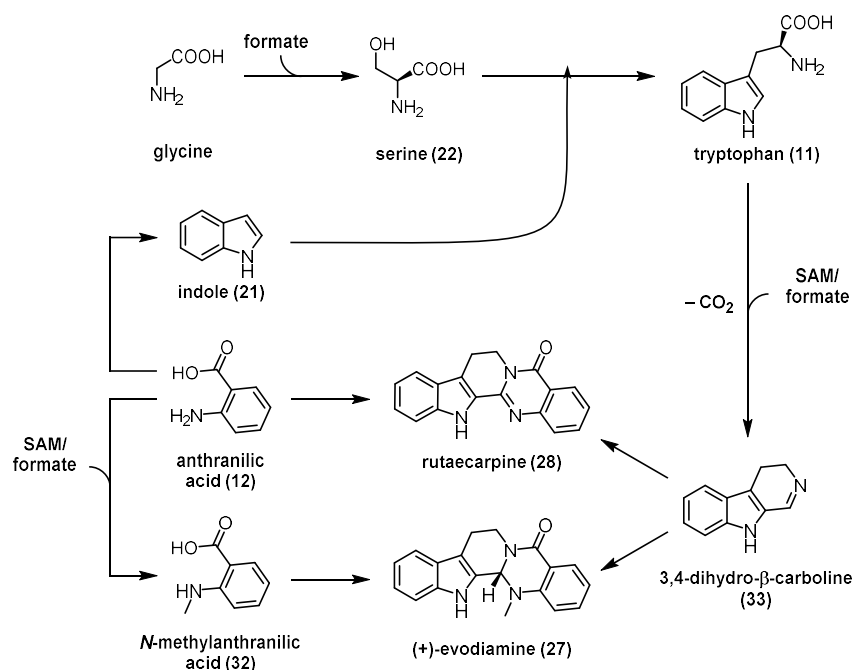
Yamazaki and co-workers, through 1966–1967, investigated the biogenesis of the (+)-evodiamine (**27**) and rutaecarpine (**28**) through such procedures.¹¹⁻¹² Experiments involving feeding *E. rutaecarpa* with radioactive isotopic labelled 3-[¹⁴C]-tryptophan (**11**), sodium [¹⁴C]-formate (or methionine-¹⁴C) and [³H]-anthranilic acid were first achieved (Scheme 7). The degradation studies showed that all of the labels were incorporated into both rutaecarpine (**28**) and (+)-evodiamine (**27**).



Scheme 7. Method for tracking the pathways involved in the biosynthesis of (+)-evodiamine (**27**) and rutaecarpine (**28**)

By analysing the isolated products obtained from *Evodia rutaecarpa* a biosynthetic pathway could be postulated (Scheme 8). Both fragments of the products (3,4-dihydro- β -carboline **33** and *N*-methyl anthranilic acid **34**) start from anthranilic acid (**12**). From the shikimic acid pathway, anthranilic acid (**12**) is converted to indole (**21**), which is further reacted with

L-serine (**22**) to give L-tryptophan (**11**). A C₁-unit is then installed, most likely using SAM. The resulting intermediate can be oxidised, cyclised and decarboxylated to give 3,4-dihydro- β -carboline (**33**). This is then coupled with a molecule of anthranilic acid (**12**) or 3,4-dihydro- β -carboline (**33**) to give rutaecarpine (**28**) or (+)-evodiamine (**27**), respectively. It should be noted that the synthesis of rutaecarpine (**28**) requires a formal oxidation after the combination of the two fragments. During our synthetic investigations, this study would prove pivotal in our inspiration for a dimeric strategy towards the synthesis of (+)-dievodimaine (**35**) (Chapter 2).



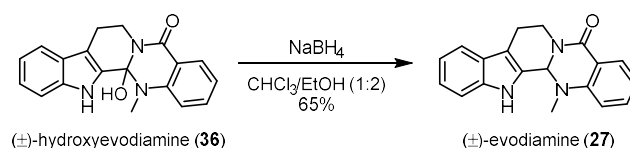
*Scheme 8. Suggested biosynthesis of (+)-evodiamine (**27**) and rutaecarpine (**28**), as concluded by Yamazaki and co-workers*

1.6. Synthesis of ($\pm$)-evodiamine

In terms of literature studies, evodiamine (**27**) has furnished the greatest interest from the scientific community. Much of the work undertaken in this area has been based upon the robust anti-cancer properties of the natural product. It is believed that evodiamine (**27**) affects the progression of numerous cancer cell lines through a varied mode of action. These include: increasing the rate of cancer cell apoptosis, interrupting the cell cycle at the C2 phase (leading to cell cycle arrest), hindering the metathesis of cancer cell lines; and suppressing

angiogenesis. In addition to the varied anti-tumour properties, evodiamine (**27**) exhibits a multitude of other pharmacological properties: anti-inflammatory, anti-obesity, cardiovascular disease prevention, anti-Alzheimer and anti-microbial.

Due to the great level of interest in the biological properties of evodiamine (**27**), a vast amount of research has been undertaken into its chemical synthesis. The first synthesis of evodiamine (**27**) was achieved by Ghosh and co-workers in 1959 (Scheme 9) and should be considered a semi-synthesis.¹³ During this synthesis, an isolated sample of (±)-hydroxyevodiamine (**36**) was reduced with sodium borohydride resulting in the first synthetic isolation of (±)-evodiamine (**27**).[†]

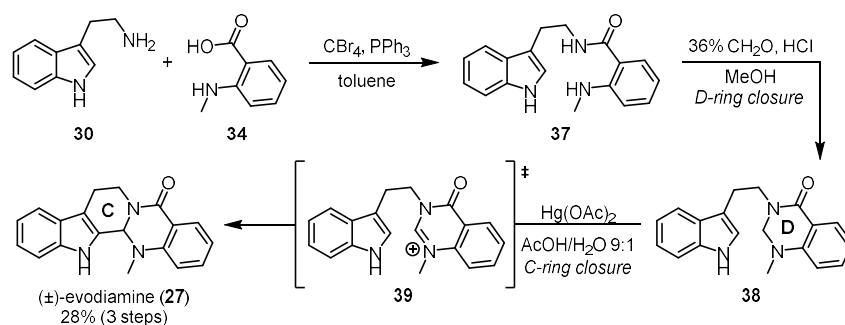


Scheme 9. Synthesis of (±)-evodiamine (**27**) by reduction of (±)-hydroxyevodiamine (**36**)

1.6.1. Late-stage C-ring formation

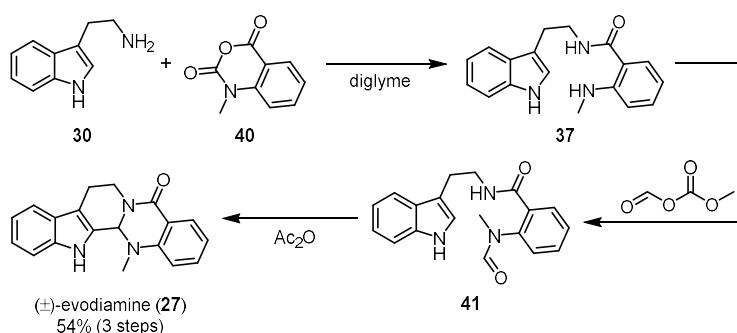
The first synthesis of (±)-evodiamine (**27**) from tryptamine (**30**) was achieved by Danieli and co-workers in 1978 (Scheme 10).¹⁴ The first step of this synthesis involved an amide bond formation between tryptamine (**30**) and 3,4-dihydro-β-carboline (**33**), giving amide **37**. This amide has become a common intermediate in various syntheses of evodiamine (**27**), in this case the intermediate was made using triphenylphosphine (PPh₃) and tetrabromomethane (CBr₄) for Appel-type activation of the carboxylic acid. From amide **37**, the required C₁-unit was installed through condensation with formaldehyde (CH₂O) in acidic methanol, giving the tetracyclic intermediate **38**. This was oxidised to the intermediate **39**. Finally, ring fusion between the indole and quinazolinonium rings (formed *in situ*) was furnished under acidic conditions, giving (±)-evodiamine (**27**).

[†] In this report, (±)-hydroxyevodiamine and (±)-evodiamine were labelled as rhetsinine and rhetsine respectively. This nomenclature is not observed elsewhere in the literature



Scheme 10. Synthesis of (±)-evodiamine (**27**), Danieli and co-workers (1978)

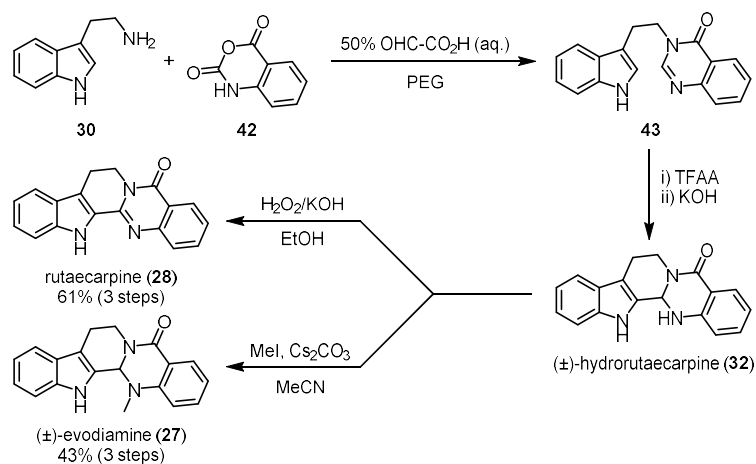
Therefore, Danieli and co-workers demonstrated that (±)-evodiamine (**27**) can be synthesised through a late-stage formation of the C-ring. Other examples of this methodology can be found throughout the literature. Bergman and co-workers, developed a greener and more efficient method for synthesising amide **37**.¹⁵ Starting from tryptamine (**30**) and methyl isatoic anhydride (**40**), the required amide bond was made by refluxing in diglyme (Scheme 11). Addition of the C_1 -unit was achieved by addition of formic acid in acetic anhydride to give formamide **41**. Finally, the late-stage formation of the C-ring was achieved through cyclisation by refluxing formamide **41** in acetic anhydride, giving (±)-evodiamine (**27**) in 54% yield over three steps.



Scheme 11. Synthesis of (±)-evodiamine (**27**), Bergman and co-workers (1985)

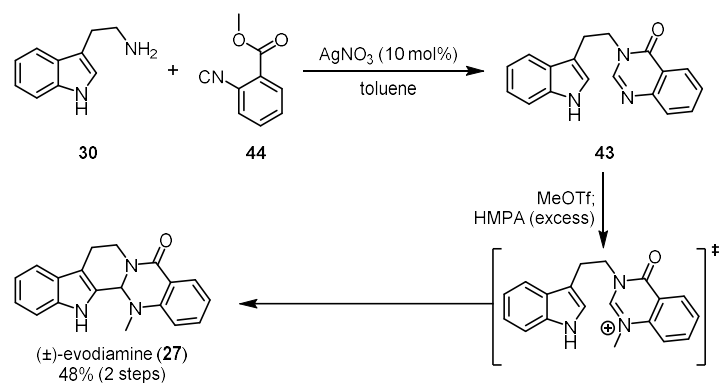
Pal and co-workers would go on to utilise (±)-dihydrorutaecarpine (**32**) as a common intermediate to synthesise both (±)-evodiamine (**27**) and rutaecarpine (**28**) (Scheme 12).¹⁶ Tryptamine (**30**) and isatoic anhydride (**42**) were reacted in the presence of aqueous glyoxylic acid to give imine **43**. Reaction of imine **43** with TFAA, then potassium hydroxide cleanly gave

($\pm$)-dihydrorutaecarpine (**32**). From here the synthesis diverges, either refluxing with hydrogen peroxide/potassium hydroxide to give rutaecarpine (**28**) or addition of methyl iodide under basic conditions to give ($\pm$)-evodiamine (**27**).



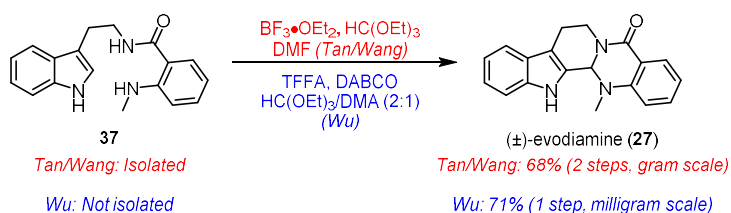
Scheme 12. Synthesis of rutaecarpine (**28**) and ($\pm$)-evodiamine (**27**), Pal and co-workers (2014)

The key downfall in these syntheses is the difficult purification of the intermediates formed in each step. In order to overcome this issue, Zhu and co-workers developed a strategy for the synthesis of ($\pm$)-evodiamine (**27**) without the need to purify intermediates (Scheme 13).¹⁷ In order to achieve this, tryptamine (**30**) was condensed with isocyanide **44** through a silver-mediated reaction. The crude imine intermediate **43** was then cyclised, by the stepwise addition of methyl triflate and hexamethylphosphoramide (HMPA), to give ($\pm$)-evodiamine (**27**) in 48% yield without purification of intermediates.



Scheme 13. Synthesis of ($\pm$)-evodiamine (**27**), Zhu and co-workers (2017)

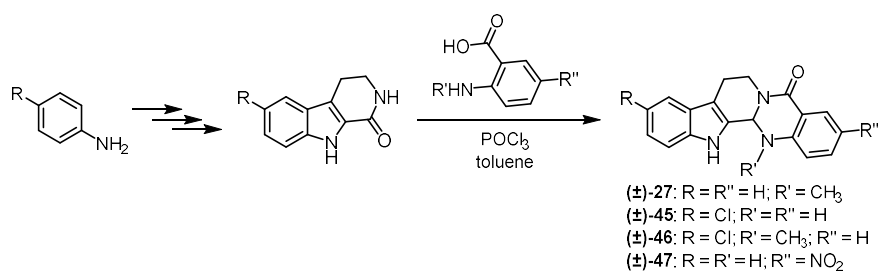
In the most modern methods for synthesis of (±)-evodiamine (**27**), the use of triethyl orthoformate seems to be the favoured C₁-unit for the late-stage formation of the C-ring. This is used, in part, as the reagent is in the correct oxidation state for the addition and cyclisation steps to occur, within the same acid-mediated reaction. The work of Tan/Wang and co-workers showed that the use of a Lewis acid catalyst (boron trifluoride etherate) can induce the addition/cyclisation of triethyl orthoformate in a single step, to give (±)-evodiamine (**27**) on a gram scale (Scheme 14).¹⁸ Alternatively, the reaction of tryptamine (**30**) and *N*-methyl isatoic anhydride (**40**) with triethyl orthoformate can be done in one-pot, as shown by Wu and co-workers.¹⁹ This was achieved using a stepwise addition of TFAA and 1,4-diazabicyclo[2.2.2]octane (DABCO) at high temperatures in dimethylacetamide (DMA). The authors also ran the reaction excluding the orthoformate reagent, which showed the formation of amide **37**.



Scheme 14. Synthesis of (±)-evodiamine (**27**); Tan/Wang and co-workers (2019, red), Wu and co-workers (2018)

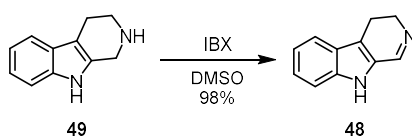
1.6.2. Late-stage D-ring formation

An alternative method for the synthesis of (±)-evodiamine (**27**) involves the late-stage formation of the D-ring. This methodology was first utilised by Yeleswarapu and co-workers in order to produce evodiamine-inspired scaffolds for cytotoxicity studies.²⁰ In order to achieve this, substituted lactams were made over three steps from their corresponding *para*-substituted anilines (Scheme 15). These were combined with functionalised anthranilic acids to quickly obtain a small library of evodiamine-type compounds, which were screened against a selection of cytotypes.



Scheme 15. Synthesis of $(\pm)$ -evodiamine (**27**) and notable derivatives, Yeleswarapu and co-workers (2004)

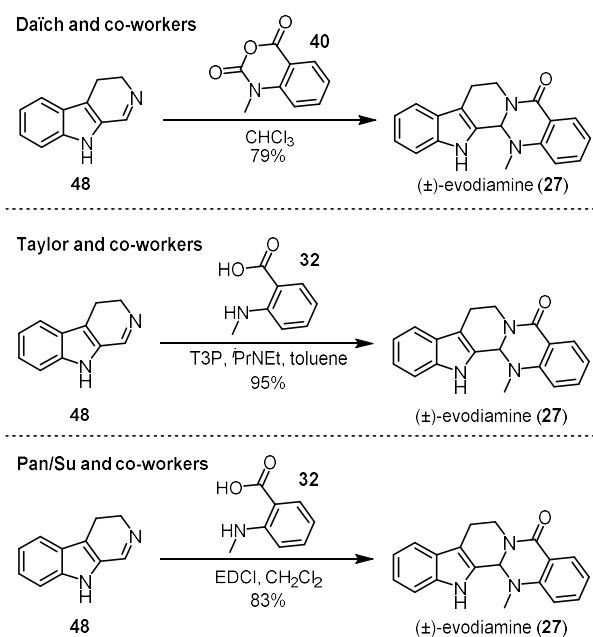
One of the drawbacks of this work is the longer synthesis of the required lactam intermediates and the harsh conditions required to undergo the addition/cyclisation/dehydration cascade in the final step. These issues have been overcome by using tricyclic imine **48** for the late-stage D-ring formation pathway. There are a number of ways to synthesise this intermediate, however, Nicolaou and co-workers showed that commercially available amine **49** could be selectively oxidised by 2-iodoxybenzoic acid (IBX), giving imine **48** in one step (Scheme 16).²¹



Scheme 16. Nicolaou and co-worker's amine oxidation using IBX

From this intermediate imine **48** several pathways are known to get to $(\pm)$ -evodiamine (**27**) (Scheme 17). Daïch and co-workers, showed that heating imine **48** with *N*-methyl isatoic anhydride (**40**) in chloroform would result in $(\pm)$ -evodiamine (**27**) crashing out of solution upon cooling.²² Alternative syntheses use 3,4-dihydro- β -carboline (**33**) as the coupling partner. Taylor and co-workers would develop direct imine acylation methodology, in which the synthesis of $(\pm)$ -evodiamine (**27**) showed the complexity that could be produced using the methodology.²³ Here, $(\pm)$ -evodiamine (**27**) was synthesised using propanephosphonic acid anhydride (T3P), in the presence of base (*N,N*-diisopropylethylamine, DIPEA), as the coupling reagent. Finally, Pan, Su and co-workers would remove the need for base in the reaction using

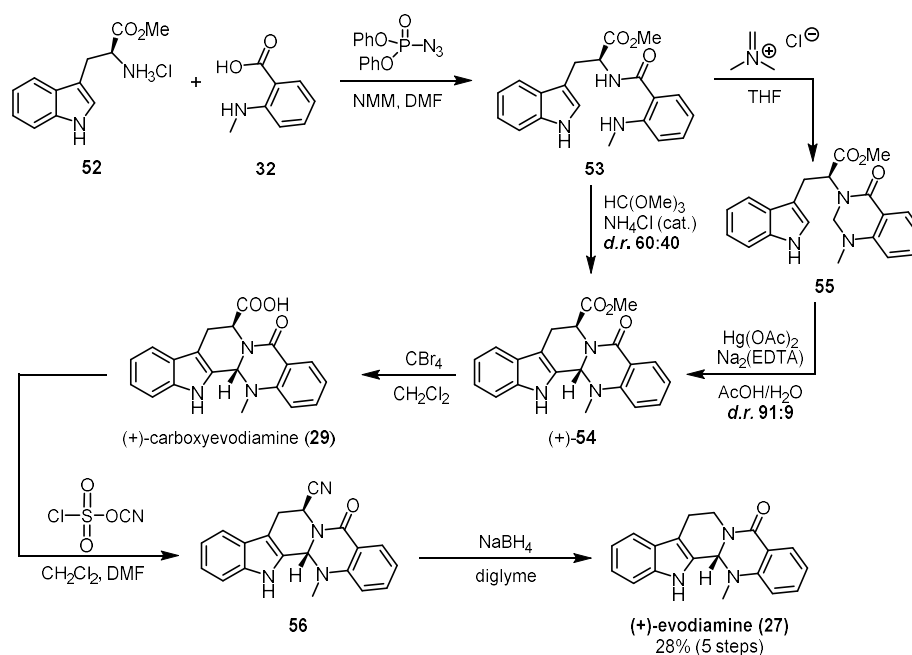
the same reagents as Taylor. In this example *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDCI) was utilised as the coupling reagent for the transformation.



Scheme 17. Using imine **48** as the starting material for the late-stage D-ring formation of (±)-evodiamine (**27**)

1.7. Stereoselective synthesis of evodiamine

Although a great multitude of syntheses of (±)-evodiamine (**27**) have been achieved, it has been shown that the biological activity of the natural product is very much dependant on the absolute configuration of the material. This means that any use of (±)-evodiamine (**27**) scaffolds in medicinal chemistry will result in half the material being non-bioactive and thus higher doses being required. This also assumes that the non-natural enantiomer, (–)-evodiamine (**27**), would have no biological activity, when it is very plausible that this enantiomer could result in side-effects occurring when used. It has been shown by Passarella and co-workers that use of a chiral sulfonyl chloride **50** yielded sulfamide **51** as a 1:1 mixture of diastereomers, that were separable by careful column chromatography (Scheme 18).²⁴ Upon base-mediated hydrolysis, (+)-evodiamine (**27**) can be obtained. However, the obvious downfall of this strategy is that half of the material is lost in the chiral resolution.



Scheme 19. Synthesis of (+)-evodiamine (27) from L-tryptophan (11)

1.8. Dievodiamine

(+)-Dievodiamine (35) was isolated from the fruits of *E. rutaecarpa*, by Feng and co-workers in 2010 (Figure 2).²⁶ It was co-isolated alongside evodiagenine (57), which was fully characterised by Feng and co-workers.

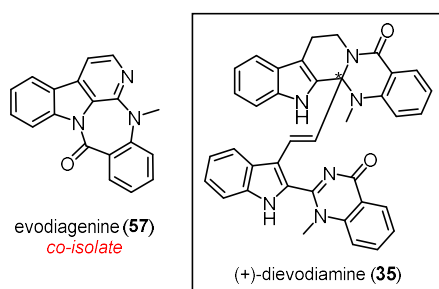


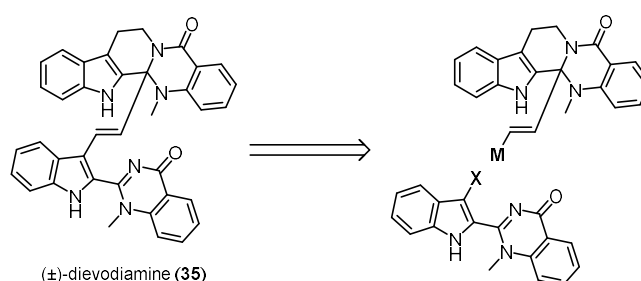
Figure 2. Structure of (+)-dievodiamine (35) and co-isolate evodiagenine (57)

The structure of (+)-dievodiamine (35) was elucidated through mass spectrometry and UV/IR/NMR spectroscopy. The product was also observed to have an optical activity of $[\alpha]_D^{24} + 48.9^\circ$ ($c = 0.1$, CHCl_3). However, the enantiopurity of the isolated material is not known, let alone the absolute configuration of the major enantiomer. Despite reporting an X-ray crystal structure for the achiral co-isolate, evodiagenine (57), the isolation chemists were unable to

report the corresponding structure for (+)-dievodiamine (**35**). Although Feng and co-workers were able to elucidate the majority of the structural features of (+)-dievodiamine (**35**), the absolute stereochemistry remains unknown.

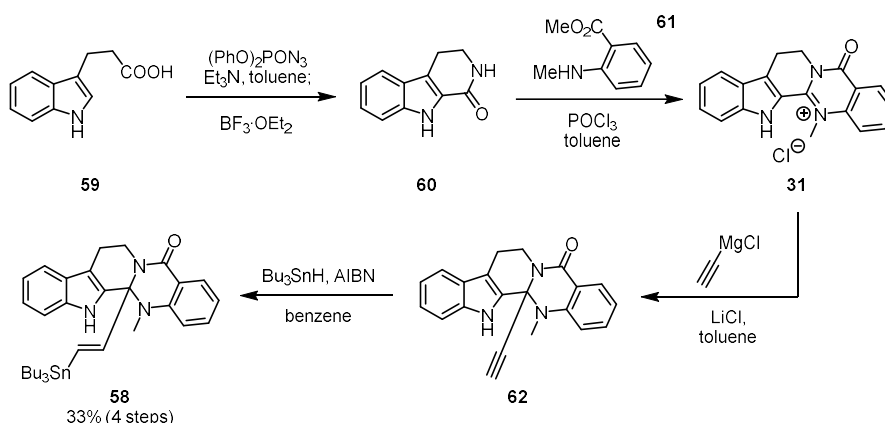
1.9. Known synthesis of (±)-dievodiamine

To date, only one total synthesis of racemic (±)-dievodiamine (**35**) has been reported.²⁷ This synthesis was achieved by Taylor/Unsworth and co-workers, in a 5-step convergent approach and 17% overall yield (9 steps in total). The synthesis was concluded with formation of the ethylene tether, prepared by a Stille cross-coupling reaction (Scheme 20).



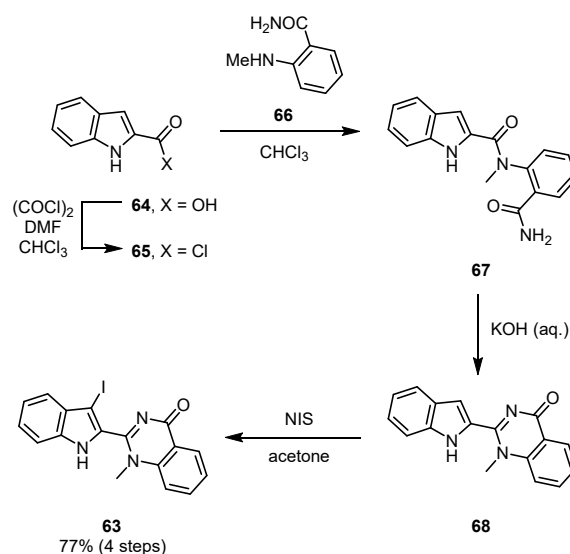
*Scheme 20. Key retrosynthetic disconnection employed by Taylor/Unsworth and co-workers for the synthesis of (±)-dievodiamine (**35**)*

The required stannane coupling partner **58** was prepared in four steps, from commercially available indole-3-propanoic acid (**59**) (Scheme 21). This synthesis progressed through lactam intermediate **60**, which was furthermore added to dimethyl anthranilate (**61**) to give dehydroevodiamine (**31**), a natural product also isolated from *E. rutaecarpa*. Addition of the acetylene group into the iminium gave alkyne **62**, which was finally transformed to the required stannane partner **58** by azobisisobutyronitrile-mediated hydrostannylation.



Scheme 21. Synthesis of stannane partner **58**, Taylor/Unsworth and co-workers

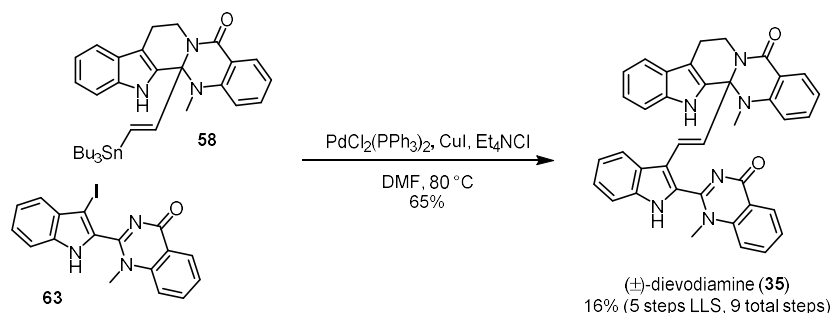
The required iodine-containing coupling partner **63** was also synthesised in four steps, from indole-2-carboxylic acid (**64**) (Scheme 22). The carboxylic acid **64** was converted to the corresponding acid chloride **65** and coupled with amine **66** to give the diamide **67**. The required ring closure was achieved under basic conditions, giving intermediate **68**. The final iodination step was done using *N*-iodosuccinimide (NIS).



Scheme 22. Synthesis of iodinated partner **63**, Taylor/Unsworth and co-workers

Finally, the Stille cross-coupling reaction was achieved between partners **58** and **63** (Scheme 23). It was found that two additives (CuI and Et₄NCl) were required to overcome the steric clash, which was suggested to be limiting the rate of transmetalation.²⁸ When Stille cross-coupling is done in highly polar solvent, such as DMF, the use of CuI is used to form a more

reactive organocopper species through transmetallation of the stannane, increasing the overall rate of reaction. The rate of transmetallation is further increased by the use of Et₄NCl, as the formation of a Sn–Cl bond is favoured.

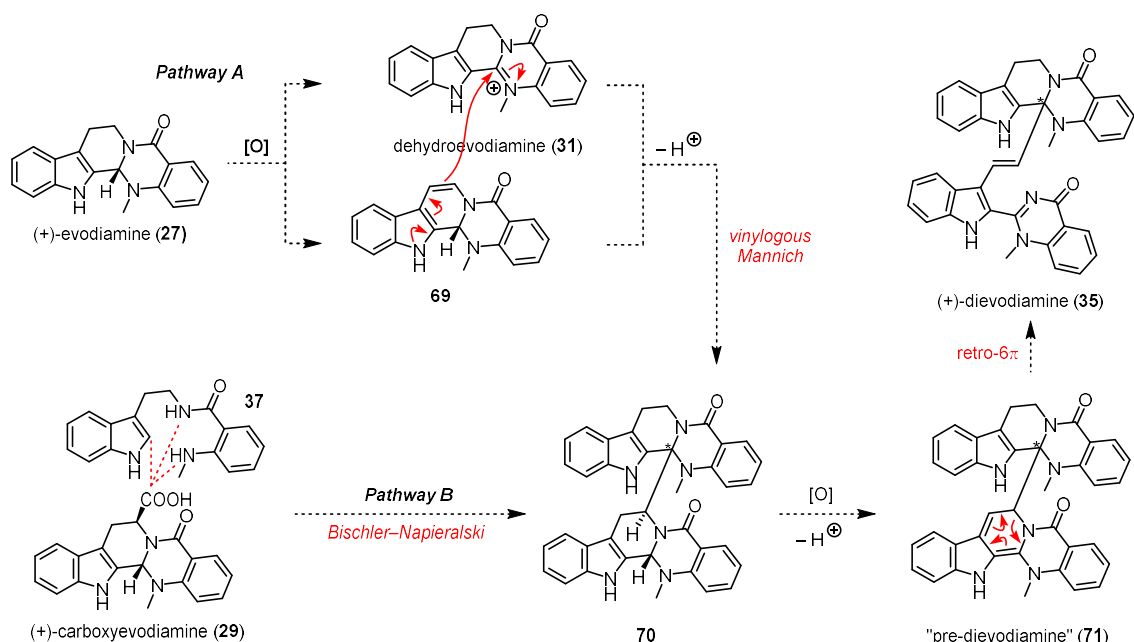


*Scheme 23. Stille coupling of stannane **58** and iodo-indole **63**, Taylor/Unsworth and co-workers*

Although this synthesis is non-enantioselective, it still represents the first total synthesis of (±)-dievodiamine (**35**) in an impressive convergent synthesis, requiring only 9 steps in total. However, the reliance on toxic organotin compounds, complicates application of this synthesis for a pharmaceutical or biological screening.²⁹⁻³¹

1.10. Project aims

The synthesis of (±)-dievodiamine (**35**), described by Taylor, Unsworth and co-workers represents an excellent synthetic strategy towards the natural product. We decided to pursue a biomimetic synthesis of (+)-dievodiamine (**35**) to probe the chemical feasibility of several proposed biosynthetic pathways (Scheme 24). For example, one possibility involves divergent oxidations of (+)-evodiamine (**27**) to give dehydroevodiamine (**31**, a known co-isolate) and alkene **69**, which is currently unknown (Scheme 24, Pathway A). Combination of these intermediates, through a vinylogous Mannich reaction, would give intermediate **70**.



Scheme 24. Proposed biogenesis of (+)-dievodiamine (35)

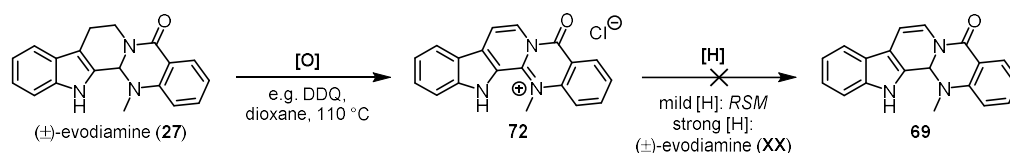
Alternatively, the biogenesis could involve the co-isolated (+)-carboxyevodiamine (29) as an intermediate (Scheme 24, Pathway B). Specifically, a domino condensation/Bischler–Napieralski-type reaction sequence between (+)-carboxyevodiamine (29) and tryptamine/*N*-methyl anthranilate amide 37 would yield the pseudo dimer 70. An oxidation and deprotonation would produce an intermediate we have labelled, pre-dievodiamine 71. Finally, a unique retro-*aza*-6 π electrocyclisation of pre-dievodiamine 71 is then proposed to be the final step, in both biosynthetic pathways, to give (+)-dievodiamine (35).

It was envisaged that the first synthesis (+)-dievodiamine (35) in enantioenriched form could be achieved following either of these biosynthetic proposals (Scheme 24, Pathway A or B). That is to say, the absolute configuration of the single stereogenic centre in (+)-dievodiamine (35) might be set entirely under substrate-controlled diastereoselectivity, through point-to-point chirality transfers, rather than through enzyme-controlled selectivity. Thus, this work may allow the absolute configuration of (+)-dievodiamine (35) to be assigned for the first time.

Successful completion of a tin-free, stereoselective, biomimetic total synthesis of (+)-dievodiamine (**35**), in a convergent and efficient manner, could also facilitate biological activity screening and follow-up SAR studies.

1.11. Prior work (Jake Stuart, Masters project)

I completed preliminary work on this project during my undergraduate MChem research project, focused primarily on investigating Pathway A (Scheme 24). A preliminary study was performed into the selectivity of various oxidations of evodiamine (**27**) (Scheme 25). Results from this study indicate that selective oxidation of evodiamine (**27**) to give alkene **69** is not possible, as various oxidative conditions resulted in over-oxidation to give the unsaturated product **72**. Selective reduction of this aromatic iminium ion **72** to access alkene **69** was also not possible; No reaction was observed with mild reducing agents (e.g., sodium triacetoxyborohydride) whereas over-reduction back to (±)-evodiamine (**27**) was observed with stronger reductants (e.g., sodium borohydride), albeit in low yield.



*Scheme 25. Prior attempts to selectively oxidise (±)-evodiamine (**27**)*

2. Dimerisation strategy

2.1. Introduction – Dimeric Natural Products

Complex dimeric natural products arise when two units of a secondary metabolite are connected through a bond-forming transformation.³² This characterisation was recently summarised excellently by Hu and co-workers, who described these dimers as fitting into two categories: homo- or heterodimers; the latter of which could further be split by how similar their skeletal structure are: identical/similar- or distinct-skeletons (Figure 3).

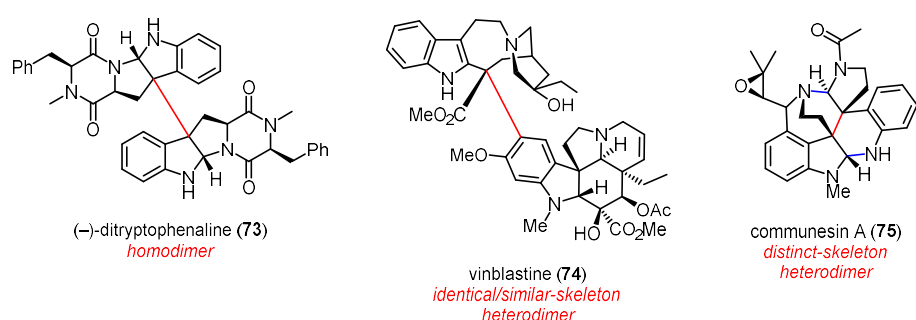


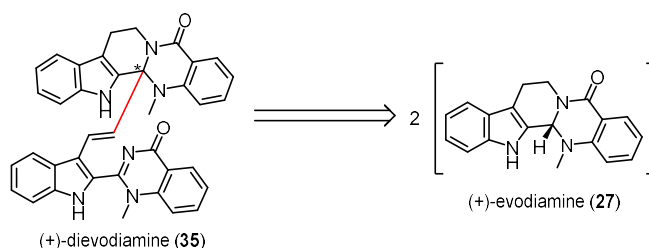
Figure 3. Examples of complex dimerisations in natural products

The examples shown in Figure 3 are representative bis-alkaloids that can be characterised using Hu's method. It is generally considered that homodimeric natural products, such as (-)-ditryptophenaline (**73**),³³ are the most simple to identify, as the two units are identical and give rise to clear symmetry. However, when dimers are formed through heterodimerisations, higher orders of complexity are generally observed. It can be inferred that there is a dimeric relationship within hetero-dimers by analysis of the skeletal structure, such is the case in the example of vinblastine (**74**, *vide supra*). By understanding the biosynthetic pathways of these secondary metabolites, bio-retrosyntheses of these dimers back to the corresponding monomer(s) can be proposed.³⁴ However, this is often not the case for the most complex class of dimeric natural products, such as communesin A (**75**), in which the dimerisation is often followed by multiple post-combinatorial functionalisations. In this example, it is perhaps easy to see that the product is tryptophan-derived, but not simple to understand the dimeric nature

of the compound is a result of three C–C bond formations, resulting in extensive structural complexity.³⁵

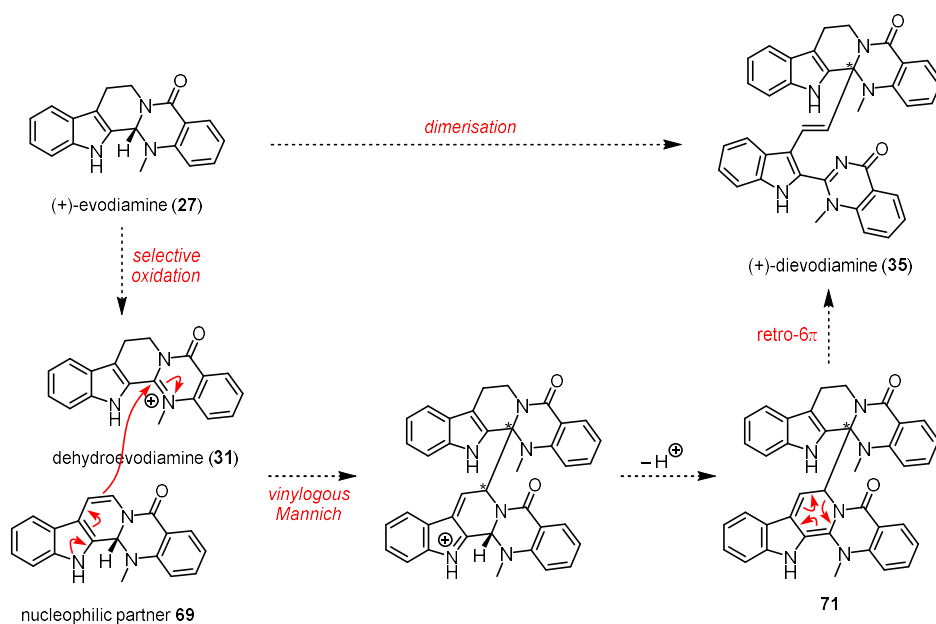
2.2. Planned dimerisation of (+)-evodiamine

Upon careful consideration of the structure of (+)-dievodiamine (**35**), it has been speculated that it is an identical/similar-skeleton, hetero-dimeric, natural product derived from two units of (+)-evodiamine (**27**) (Scheme 26).



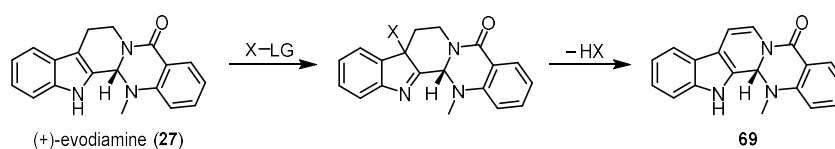
*Scheme 26. Proposed dimeric relationship between (+)-evodiamine (**27**) and (+)-dievodiamine (**35**)*

However, this dimerisation is not immediately obvious and required further analysis. We postulate that the natural product could be traced to a dimerisation through a vinylogous Mannich/retro-6 π electrocyclisation reaction cascade (Scheme 27). In order to get to the dimeric intermediate **71**, we proposed that (+)-evodiamine (**27**) would undergo selective oxidations to give the known electrophile, dehydroevodiamine (**31**), and the proposed nucleophilic alkene **69**.



Scheme 27. Proposed biosynthesis of (+)-dievodiamine (35) through a vinylogous Mannich/retro-6 π electrocyculation cascade pathway

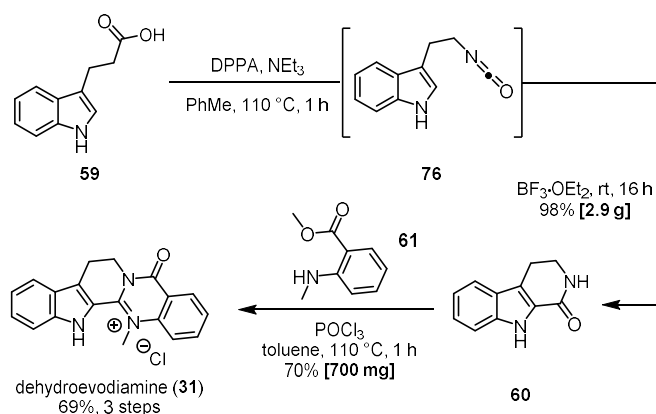
In order to investigate the synthesis of dehydroevodiamine (31) the synthesis of the novel nucleophilic partner 69 will require investigation. We knew from past studies that this cannot be achieved through simple dehydrogenation of (+)-evodiamine (27). Therefore, a stepwise functionalisation/elimination pathway to synthesise nucleophilic alkene 69 would require investigation using an indolenine with a good leaving group as an intermediate (Scheme 28). Once we have achieved this, it should be possible for the combination of this unit with dehydroevodiamine (31) to occur under basic conditions, through a vinylogous Mannich reaction. The synthesis of dehydroevodiamine (31) is well known, however we would have to synthesise it to investigate its viability as an electrophile in the synthesis.



Scheme 28 Planned synthesis of nucleophilic alkene 69

2.3. Synthesis of dehydroevodiamine as an electrophilic partner

In order to achieve our dimerisation strategy, the synthesis of the electrophilic compound, dehydroevodiamine (DHED, **31**), was replicated from the work of Taylor, Unsworth and co-workers (Scheme 29).²⁷ Conversion of indole-3-propanoic acid (**59**) to lactam **60** was achieved by activating the acid with diphenylphosphoryl azide (DPPA) to undergo a Curtius rearrangement.³⁶⁻³⁷ The crude isocyanate **76** was then subjected to Lewis acid-mediated electrophilic aromatic substitution in neat $\text{BF}_3 \cdot \text{OEt}_2$, resulting in lactam **60**. Condensing the newly formed lactam with dimethyl anthranilate (**61**), using POCl_3 as a dehydrating agent, gave dehydroevodiamine (**31**) in a 69% overall yield.³⁸ This synthetic route offered a reproducible route to our required electrophilic partner for the proposed vinylogous Mannich reaction on 700 mg scale.

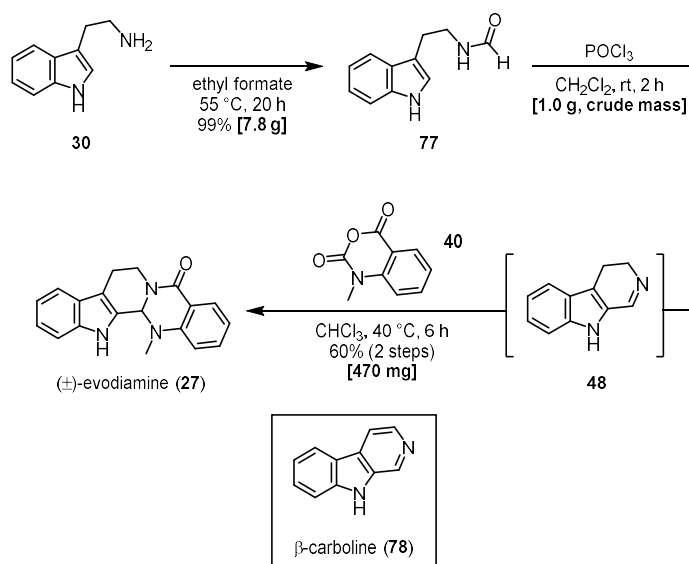


Scheme 29. Synthesis of dehydroevodiamine (**31**) from indole-3-propanoic acid (**59**)

2.4. Efforts towards selective oxidation of evodiamine

In order to achieve the synthesis of the nucleophilic partner **69**, we required a suitable way to synthesise large quantities of ($\pm$)-evodiamine (**27**) from commercially available starting materials. We chose to follow the procedure outlined by Zhang and co-workers, as the reagents needed are cheaply accessible in bulk and the chemistry has been proven to be scalable on a multigram scale.³⁹

The synthesis starts by *N*-formylation of tryptamine (**30**) to give formamide **77** (Scheme 30). The resulting carbonyl group was activated, by POCl₃, and cyclised through a Bischler–Napieralski reaction, to give imine **48** in good enough purity for the crude to be used directly in the following step. It was found that attempting to purify this imine through column chromatography led to a facile auto-oxidation to give β-carboline (**78**). It was also known, from the work of Zhang and co-workers, that (±)-evodiamine (**27**) was likely to precipitate out of chloroform in the following step of the synthesis. When we subjected the freshly synthesised crude imine (**48**) to *N*-methyl isatoic anhydride (**40**) as a refluxing solution in chloroform, the imine was fully consumed. Upon cooling (±)-evodiamine (**27**) indeed precipitated out of solution in good overall yield and purity (60%, 3 steps).



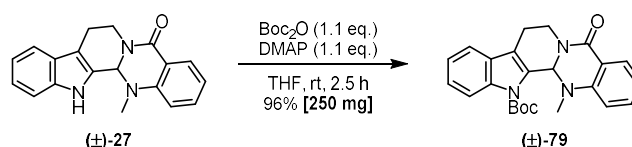
Scheme 30. Synthesis of (±)-evodiamine (**27**) from tryptamine (**30**)

2.5. Dehydrogenation of (±)-evodiamine

We knew, from past studies (see Chapter 1.11), that when (±)-evodiamine (**27**) was exposed to oxidation conditions (DDQ; Pd/C, air) that dehydrogenation would proceed to give unsaturated iminium **72**. In order to achieve a selective oxidation, we anticipated that functionalising the indole nitrogen with an electron-withdrawing group would help stabilise the methine towards oxidation. Addition of such a group draws electron density from the indole

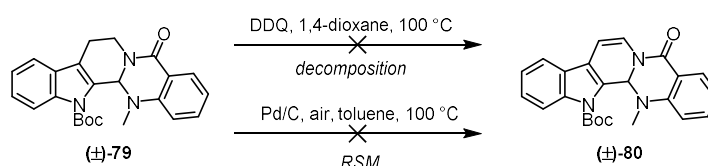
and thus reduces the likelihood of over-oxidation. In turn, minimising unselective oxidation when using charge-transfer or heterogeneous catalytic oxidants.⁴⁰

With this in mind, it was decided that installing a *tert*-butyloxycarbonyl (Boc) moiety at the indole nitrogen would suffice. The carbamate group is electron-withdrawing and can be removed under mild acidic conditions. Protection of (±)-evodiamine (**27**) is not well-explored in the literature, with only methylation reported.⁴¹⁻⁴³ However, subjecting (±)-evodiamine (**27**) to standard Boc-protection conditions (Boc₂O, DMAP, Scheme 31) gave (±)-Boc-evodiamine (**79**) in excellent yield (96%).



Scheme 31. Synthesis of (±)-Boc-evodiamine (**79**)

With the protected starting material in hand, several oxidants were trialled in order to obtain Boc-protected alkene **80** (Scheme 32).⁴⁴⁻⁴⁷ To our disappointment, the conditions trialled were unsuccessful, only resulting in decomposition or recovery of the starting material **79**.



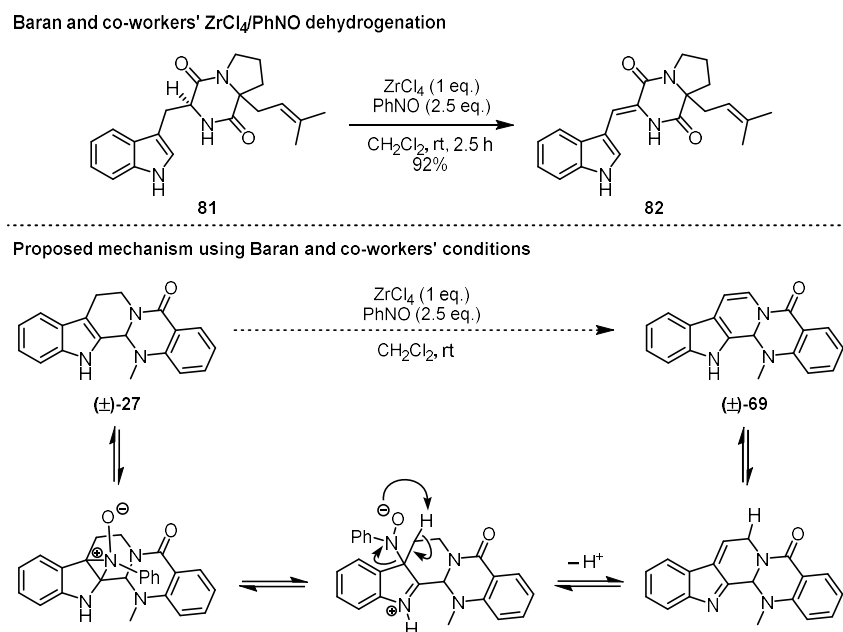
Scheme 32. Investigating the effect of indole-protection with electron-withdrawing group

Following these studies, we were convinced that introducing selective unsaturation of (±)-evodiamine (**27**), using the conditions discussed, not plausible. Other electron-withdrawing auxiliary groups could be explored. However, it seems that introduction of a Boc-group has deactivated the requisite C–H bond towards oxidation by DDQ (unless oxidation was followed by decomposition). The electron-withdrawing effect of the carbamate seems to stabilise the molecule towards oxidation too greatly, as the required unsaturation was not observed. Running the reaction at higher temperatures unfortunately resulted only in decomposition.

Upon completion of this study, it was decided that other methods of introducing unsaturation would be investigated.

2.6. Zirconium-mediated oxidation strategy

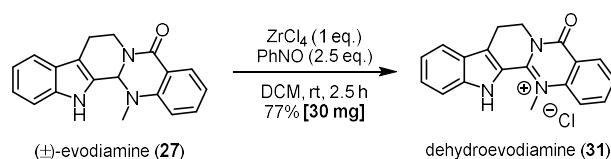
With attempts to use dehydrogenation reagents to oxidise (±)-evodiamine (**27**) proving to be unsuccessful, our efforts turned to inducing the desired reactivity through activation by zirconium(IV) chloride. This methodology was developed by Baran and co-workers in order to achieve the syntheses of avrainvillamide and various stephacidins.⁴⁸ A screen of oxidants including: DDQ, ceric ammonium nitrate (CAN), IBX and Pd/C (O₂), were screened on their model tryptophan moiety **81** (Scheme 33), to no avail. In order to overcome this, it was hypothesised that activation of the indole “enopholic” π -bond, with ZrCl₄/PhNO, would give an adduct which was susceptible to a cascade of reactions (ene-like group transfer/tautomerisation) giving the corresponding α,β -unsaturated ester **82**.



Scheme 33. Proposed conditions and mechanistic rationale Baran and co-workers' dehydrogenation methodology

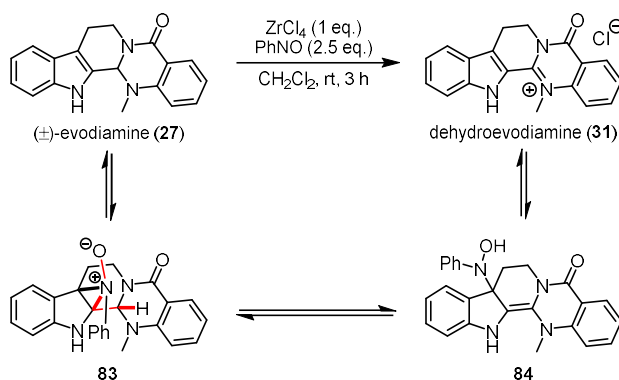
Our proposal similarly included using these conditions, to activate the corresponding indole π -bond in (±)-evodiamine (**27**), towards an overall elimination of molecular hydrogen. When

the reaction conditions were reproduced, using ($\pm$)-evodiamine (**27**) as the starting material, the only product obtained was dehydroevodiamine (**31**) (Scheme 34).



Scheme 34. Synthesis of dehydroevodiamine (**31**) using Baran and co-workers' conditions

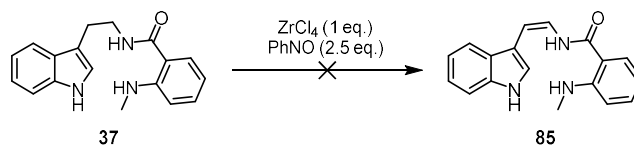
It is possible that this is the result of the transient 3-nitroso intermediate proceeding through a 5-membered transition state with the C–H proton, activating oxidation at this position (Scheme 35). Therefore, deprotonation of the aziridinium **83** by the nitroso oxygen, would give the indolenine **84**. The oxidation is likely to occur when the stereochemistry of the aziridinium and the methine were *syn* and the convex face is accessible. Upon elimination of the corresponding hydroxyamine (PhNHOH), dehydroevodiamine (**31**) was isolated. It was not too surprising that oxidation was occurring at this position rather than at the α -C–H to C3, due to its susceptibility towards oxidation in solution.



Scheme 35. Proposed mechanism for formation of dehydroevodiamine (**31**) from ($\pm$)-evodiamine (**27**) using Baran's $\text{ZrCl}_4/\text{PhNO}$ conditions

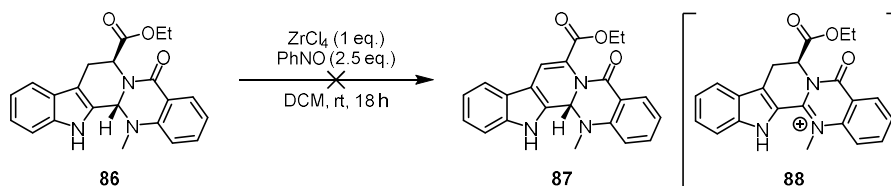
We attempted to introduce the required unsaturation onto a precursor of ($\pm$)-evodiamine (**27**) that did not have the labile, stereogenic methine proton (Scheme 36). If the oxidation chemistry were successful, we hope to introduce the required C₁-unit through a condensation with triethylorthoformate with the resulting enamide **85**. However, attempts to oxidise intermediate

amide **37** using $\text{ZrCl}_4/\text{PhNO}$ proved unsuccessful. Changing the solvent to a higher boiling solvent (DCE, toluene or xylenes) and running the reaction at higher temperatures, resulted in only recovery of starting material or a small amount of amide bond cleavage.



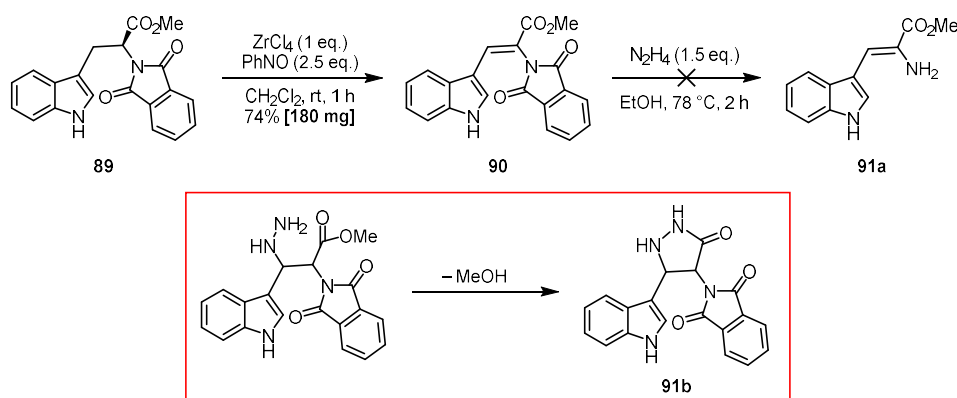
*Scheme 36. Attempts to oxidise amide **37** using Baran and co-workers' $\text{ZrCl}_4/\text{PhNO}$ methodology*

It should also be noted that subjecting (+)-carboxyevodiamine ethyl ester (**86**) to these conditions (see Chapter 4.2 for synthesis) resulted only in the recovery of starting material (Scheme 37). This showed that the issue with the $\text{ZrCl}_4/\text{PhNO}$ oxidation strategy was not simply a result of the product not having the stability of an α,β -unsaturated ester (as would be the case in the product **87**). It was also interesting to observe that the corresponding iminium **88** was not being observed by the same conditions that oxidised ($\pm$)-evodiamine (**27**).



*Scheme 37. Attempts to oxidise (+)-carboxyevodiamine ethyl ester (**86**) using Baran and co-workers' $\text{ZrCl}_4/\text{PhNO}$ methodology*

Although our prior test reactions were not fruitful, we were confident that the zirconium-mediated ene reaction with nitrosobenzene was occurring (by TLC analysis and unexpected synthesis of dehydroevodiamine **31**). Baran and co-workers showed that their conditions were amenable to a number of protected tryptophan methyl ester derivatives, including a phthalimide-protected derivative **89**. As we had large quantities of this material to hand, we envisioned oxidising a step earlier in the potential synthesis (Scheme 38). Although, we would have to decarboxylate the resulting product at some stage,⁴⁹⁻⁵¹ we believed it was worth trying just to test the reproducibility of the methodology in our hands.

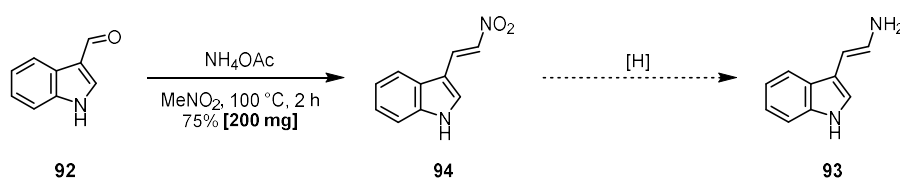


Scheme 38. Oxidation of phthalimide-protected tryptophan methyl ester (**89**), followed by attempted deprotection of α,β -unsaturated ester **90**

Replicating the literature conditions was successful, giving α,β -unsaturated ester **90** in 74% yield (compared to 82%, as reported by Baran and co-workers). However, the deprotection of the phthalimide group with hydrazine did not result in the isolation of enamine **91a**. It is hypothesised that using hydrazine may have led to a 1,3-addition to the α,β -unsaturated ester group, further cyclising to give pyrazolidine **91b**.

2.7. An alternative approach to early-stage oxidation

Another route trialled towards the synthesis of enamine **85** was to install the required unsaturation through a Henry condensation reaction. Starting from indole-3-carboxaldehyde (**92**) we were hoping to follow a reported synthesis of enamine **93** from Harishkumar and co-workers (Scheme 39).⁵² However, there was limited experimental data provided for their synthetic work, and we had to screen conditions ourselves to investigate this. In particular the reduction chemistry quoted by the authors is a unique $\text{SnCl}_2 \cdot \text{H}_2\text{O}$ /acid-mediated reaction, which we wanted to reproduce.

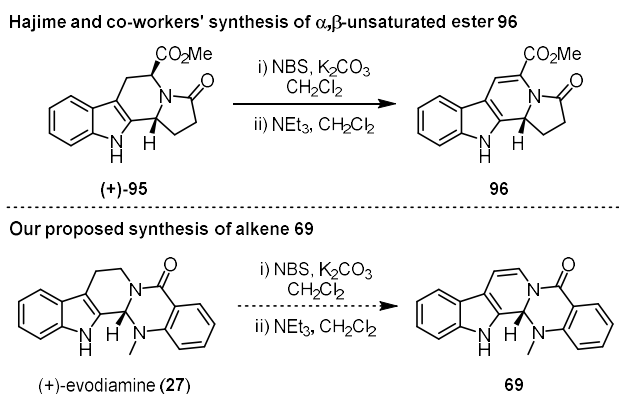


Scheme 39. Synthesis of nitroolefin **94** and proposed selective reduction of the resulting nitro-group

The synthesis of nitroolefin **94** was achieved in reasonable yield and scale, following a reported procedure from Jiang and co-workers.⁵³ This allowed us to investigate the reduction of the nitro group, starting with the conditions reported by Harishkumar and co-workers. Surprisingly, the nitroolefin starting material **94**, when treated with stannous chloride in acidic ethanolic medium, was remarkably stable and full recovery of starting material was observed regardless of acid concentration or quantity of $\text{SnCl}_2 \cdot \text{H}_2\text{O}$ used. Other mild reducing conditions, such as Zn/HCl were tried, but the stability of nitroolefin **94** thwarted our efforts. When stronger reducing reagents were employed, such as LiAlH_4 or NaBH_4 , we were able to force a reaction to occur. Disappointingly, the only product formed was the over-reduced adduct, tryptamine (**30**). When we controlled the equivalents of reducing reagent, we were not able to stunt the reduction at the enamine stage. Instead, we would only see the greater recovery of starting material alongside the formation of tryptamine (**30**).

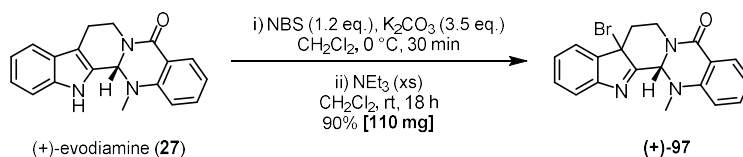
2.8. Installation of heteroatoms to ($\pm$)-evodiamine as leaving groups

Having thoroughly investigated the use of $\text{ZrCl}_4/\text{PhNO}$ to oxidise ($\pm$)-evodiamine (**27**) and its precursors, through functionalisation/elimination, we turned our attention towards alternative functionalisation approaches. During our literature search, we were pleased to find a procedure of indole activation by bromination, achieved by Hajime and co-workers (Scheme 40).⁵⁴ During their investigations, the group observed the formal elimination of hydrogen by treatment of methyl ester **95** with *N*-bromosuccinimide (NBS), followed by addition of triethylamine giving α,β -unsaturated ester **96**.



*Scheme 40. Inspiration and proposed synthesis of alkene **69** using Hajime and co-workers' NBS activation/basic elimination conditions*

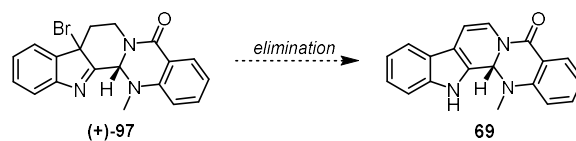
In order to test these conditions, we decided to use the natural enantiomer (+)-evodiamine (**27**) as the starting material. To our disappointment, the reaction of (+)-evodiamine (**27**) with NBS had cleanly converted the starting material to the corresponding 3-bromo-indolenine **97**, rather than full conversion to the corresponding alkene elimination product **69** (Scheme 41).



*Scheme 41. Synthesis of 3-bromo-indolenine **97***

Undeterred by this result, we subjected the 3-bromo-indolenine **97** product to a variety of bases in order to eliminate a molecule of hydrogen bromide and tautomerise to alkene **69** (Table 1).

Table 1. Trialled conditions for the elimination of hydrogen bromide from 3-bromo-indolenine **97**



Entry	Reagent ^a	Conditions ^b	Result ^c
1	NEt ₃	CH ₂ Cl ₂ , rt, 2 h	RSM
2	NaO ^t Bu	^t BuOH, rt, 2 h	evodiamine (50%)/RSM (46%)
3	DBN	CH ₂ Cl ₂ , rt, 2 h	evodiamine (94%)
4	DBU	CH ₂ Cl ₂ , rt, 0.5 h	complex mixture
5	Barton's base	MeOH, 50 °C, 2 h	evodiamine (84%)
6	AgOAc	MeOH, 50 °C, 2 h	evodiamine (97%)
7	TFA	MeOH, rt, 18 h	RSM

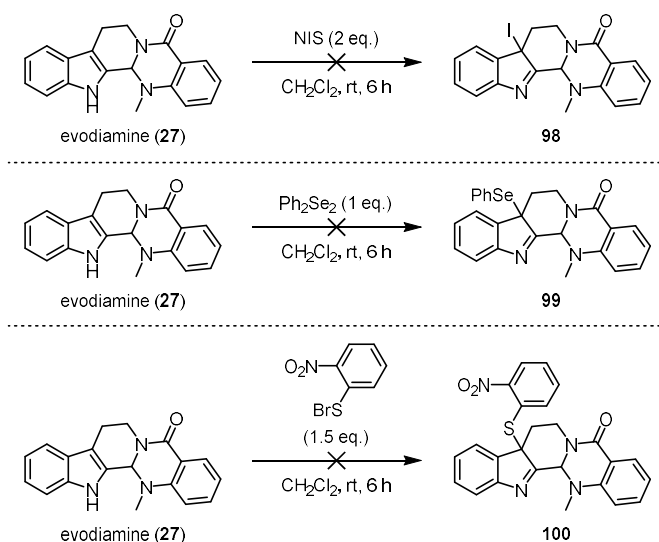
^a all reactions were run using 1.5 eq. of the stated reagent

^b all reactions were run at [0.1 M]

^c yields given in brackets, by internal standard NMR (durene)

Attempts to use non-nucleophilic bases, of increasing basicity (entries 1-3, 5-6; Table 1), to trigger an elimination reaction gave mixtures of (+)-evodiamine (**27**) and recovered starting material. The proto-dehalogenation of 3-bromo-indolenine **97** in these cases was rapid and unfortunately occurred prior to any anticipated elimination. Where proto-dehalogenation is occurring, it is speculated that the base acting as a nucleophile to extract the bromide and reform evodiamine (**27**). We attempted to overcome this by using a softer halogen (e.g. chlorine) but the reaction with *N*-chlorosuccinimide (NCS) did not result in chlorination. Use of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, entry 4, Table 1) gave a complex mixture of products, however we were unable to observe any of the expected signals from an elimination product in the ¹H NMR spectrum of the crude mixture. We finally treated the 3-bromo-indolenine **97** with acid in an attempt to stabilise any tertiary carbocation and allow time for elimination of HBr. However, use of TFA (entry 7, Table 1) only gave recovered starting material, therefore showing good acidic stability.

It should also be noted that attempts were made to synthesise the corresponding iodo-indolenine **98**, seleno-indolenine **99** and thio-indolenine **100** (Scheme 42). However, these attempts did not yield the desired outcome. All the reactions shown resulted in the recovery of the (±)-evodiamine (**27**) starting material.

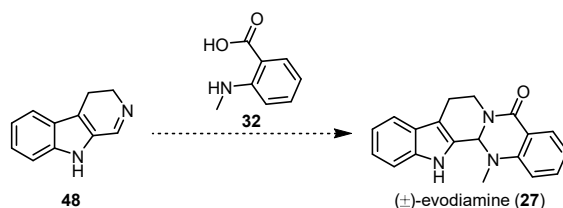


Scheme 42. Screen of alternative electrophiles

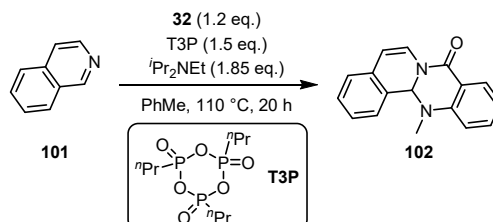
2.9. *N*-Acylation of β -carboline

As the required selective oxidation of ($\pm$)-evodiamine (**27**) at a late-stage in the synthesis was not achieved, we turned our attentions to an alternative synthesis of ($\pm$)-evodiamine (**27**), shown in Scheme 30, using β -carboline (**78**) in place of 3,4-dihydro- β -carboline (**48**) (Scheme 43). We were also encouraged by the example of isoquinoline (**101**) being converted to the unsaturated product **102**.

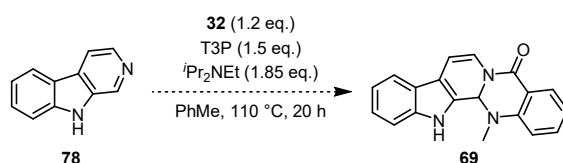
Taylor and co-workers' synthesis of evodiamine



Taylor's direct imine acylation methodology



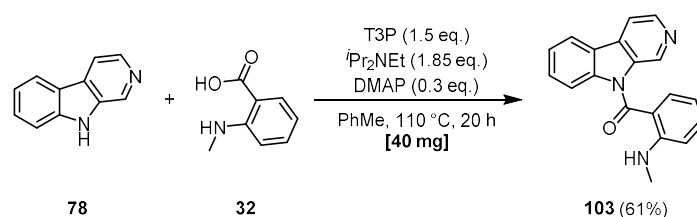
Adaptation using β-carboline substrate



Scheme 43. Synthetic inspiration and strategy for nucleophilic partner **69** using Taylor and co-workers' direct imine acylation/cyclisation cascade

In order to investigate this, we attempted to mimic conditions developed by Taylor and co-workers. In their methodology, propanephosphonic acid anhydride (T3P) was used to activate 3,4-dihydro-β-carboline (**33**) towards amide bond formation with a series of imines. This would form a transient amide intermediate which would undergo an intramolecular 6-*endo-trig* cyclisation to form the new 6-membered ring.

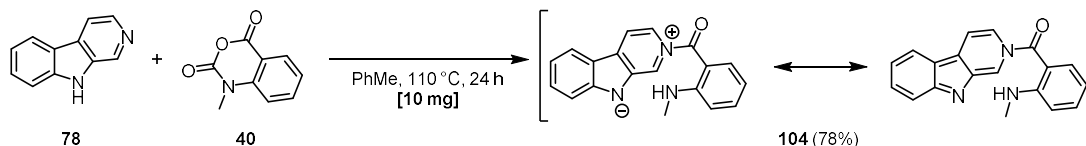
When we subjected β-carboline (**78**) to the reaction conditions, there was no reaction and only starting materials were recovered. The reaction was repeated in higher boiling point solvents with a variety of polarities (xylenes, DMF and 1,4-dioxane), with no observed change in the result. Addition of catalytic DMAP (Scheme 44) to the reaction led to some dimerisation of 3,4-dihydro-β-carboline (**33**), but also promoted the reaction of the two units. However, it was observed that the β-carboline (**78**) was reacting with the 3,4-dihydro-β-carboline (**33**) through the indole nitrogen.



*Scheme 44. Synthesis of N_α -acylated β -carboline **78***

The resulting benzoyl amide was unstable to the basic work-up, however, quenching the excess T3P with water and purifying the crude directly allowed for the isolation of amide **103** in 61% yield. This result allowed us to conclude that this method was not suitable for the synthesis of the required alkene **69**.

Following on from this, the combination of β -carboline (**78**) and *N*-methyl isatoic anhydride (**40**) was trialled (Scheme 45). The use of T3P was not necessary as the acid was pre-activated as an anhydride. Heating these two reactants together at reflux, in toluene, resulted in the formation of the unusual *N*-acylated adduct **104**.



*Scheme 45. Synthesis of zwitterionic N_β -acyl- β -carboline **104***

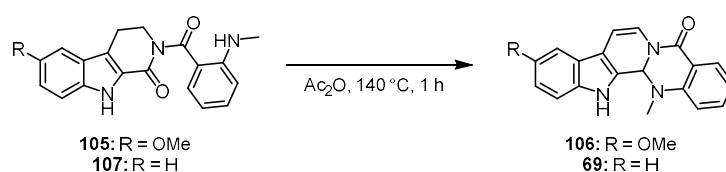
This compound was surprisingly stable towards basic conditions, as resubmitting this to the reaction conditions with excess DIPEA lead to recovery of the substrate. This further supports the mechanistic rationale of Taylor and co-workers' original findings, as it was reported that a transient *N*-acyliminium intermediate was observed using IR reaction monitoring. However, it was not isolated, as has been achieved here.

2.10. Evidence of the hypothesised retro-6 π electrocyclization

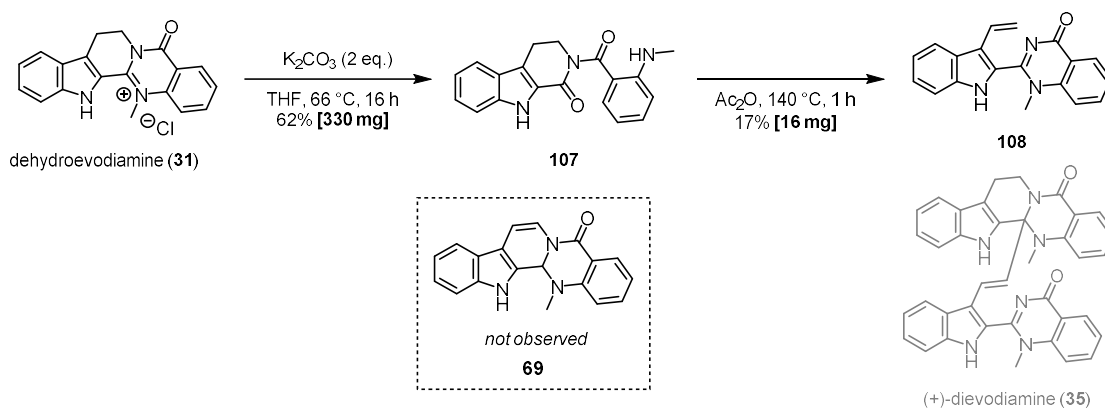
After further searching of the literature, a paper by Pachter and co-workers, that appeared to contain a synthesis of our desired alkene **69**, was found. This was missed in earlier literature searches (prior to 2019) using Reaxys and Scifinder, as a structure search did not yield any

results. So it was fortunate that this important reference was discovered. Interestingly, if the search is run using Scifinderⁿ (June 2022), the structure now yields this reference. Pachter and co-workers report a reaction in which 5-methoxyrhetsinine (**105**)[‡] was refluxed in acetic anhydride giving enamide **106** (isohortiamine).⁵⁵ When treated in the same way, the authors suggest that rhetsinine (**107**) proceeds through the same reaction pathway to give the corresponding desmethoxyisohortiamine (alkene **69**) (Scheme 46). We, therefore, immediately set out to reproduce this result.

Pachter and co-workers' investigative studies



Result of repeating Pachter and co-workers' experiment



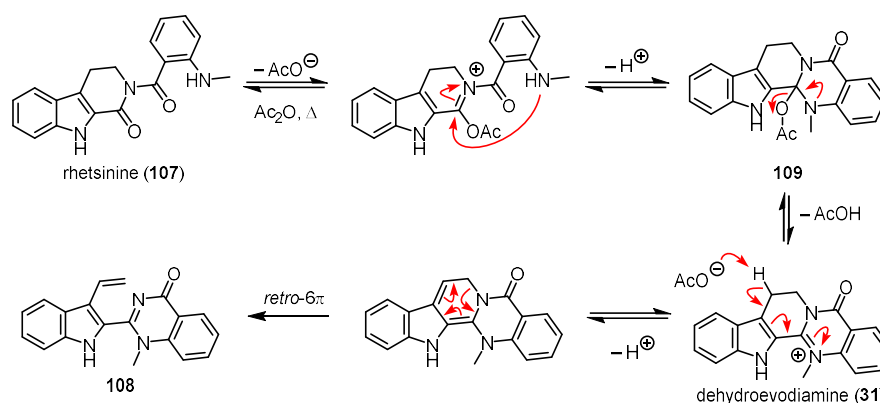
Scheme 46. Inspiration and inadvertent synthesis of alkene **108**

The synthesis of rhetsinine (**107**) was performed by treatment of dehydroevodiamine (**31**) with potassium carbonate in “wet” THF (not distilled). Upon repetition of the conditions within the paper, using rhetsinine (**107**), the expected product was not observed in the crude material. Instead, we observed and isolated alkene **108**, which is structurally similar to the core structure of (+)-dievodiamine (**35**). This product has been made previously through cross-coupling chemistry by Taylor, Unsworth and co-workers.²⁷ The UV/Vis spectral data for the compound

[‡] Labelled as 6-methoxyrhetsinine, however no nomenclature is stated and this numbering is not accepted elsewhere in the literature

obtained in this experiment [$\lambda_{\text{max}} = 317 \text{ nm}$ (EtOH)] were in agreement with those reported by Pachter and co-workers for their proposed product, alkene **69**. This was an unexpected result that provides evidence to support the chemical feasibility of our proposed biosynthetic hypothesis.

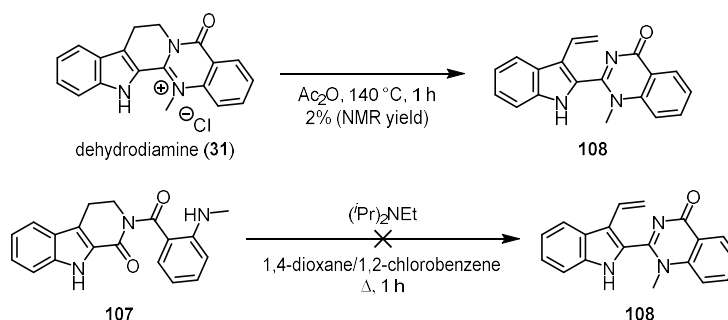
We hypothesised that the first step of this reaction involves the formation of dehydroevodiamine (**31**) through a transient imidoyl acetate intermediate (Scheme 47). The acetate counter-ion can then deprotonate alpha to the indole C3 position, giving an intermediate which is primed for the required retro-aza-6 π electrocyclicization. It should also be noted that by following the reaction by NMR spectroscopy of aliquots, we can see protection of the indole nitrogen within rhetsinine (**107**) with an acetate group. However, these compounds were not stable towards aqueous work-up and were not isolated.



*Scheme 47. First proposed mechanism for the synthesis of alkene **108** from rhetsinine (**107**)*

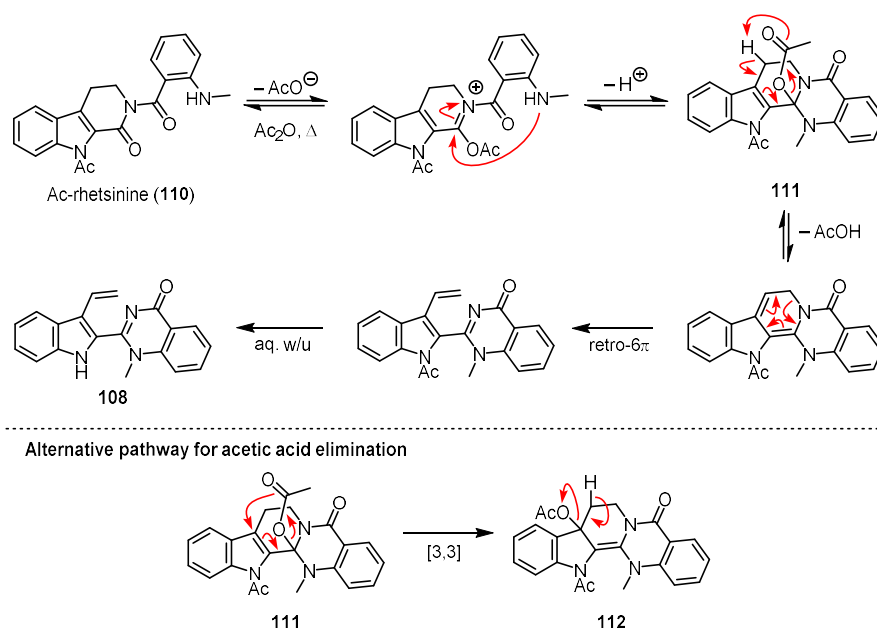
In order to test this, we subjected dehydroevodiamine (**31**) – a possible intermediate in the pathway – to refluxing acetic anhydride (Scheme 48). Although alkene **108** was formed in this reaction the yield was very low (approximately 2% by internal standard NMR spectroscopy). Dehydroevodiamine (**31**) formation through the imadoyl acetate intermediate **109** could be necessary for the formation of the observed product (at a reasonable rate). It is possible that acetylation of the indole-*N*, which might be important for this reaction, is not occurring when starting with dehydroevodiamine (**31**). No acetylation of dehydroevodiamine (**31**) was observed when refluxed in acetic anhydride. Furthermore, heating rhetsinine (**107**) in other

high-boiling solvents (1,4-dioxane/1,2-dichlorobenzene) at reflux, even in the presence of base, gave no trace of the alkene product **108**.



*Scheme 48. Experiments gauging mechanistic insight towards the synthesis of alkene **108***

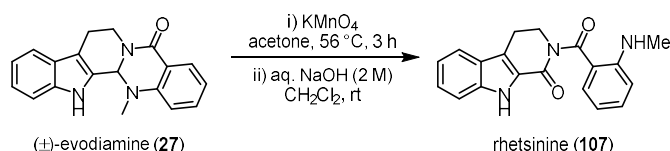
In our revised mechanism, rhetsinine (**107**) is first protected with an acetate group, giving us Ac-rhetsinine (**110**) (Scheme 49). This step should be expected as we see protection of the indole within rhetsinine (**107**) in our aliquots, mentioned earlier. This is not possible using the charged intermediate, dehydroevodiamine (**31**), and it's possibly required to act as an electron-withdrawing group to increase the acidity of the abstracted proton later in the mechanism. The acetylation could also reduce the aromaticity of the indole, which requires interruption later in the mechanism. After cyclisation, the hemi-acetate **111** undergoes an intramolecular deprotonation, through an 8-membered transition state, eliminating acetic acid and priming for the retro-*aza*-6 π electrocyclicisation. Alternatively, hemi-acetate **111** could undergo a [3,3]-sigmatropic rearrangement, followed by *syn*-elimination of the acetate to give intermediate **112**. Finally, aqueous work-up then deprotects the indole, resulting in the isolation of alkene **108**.



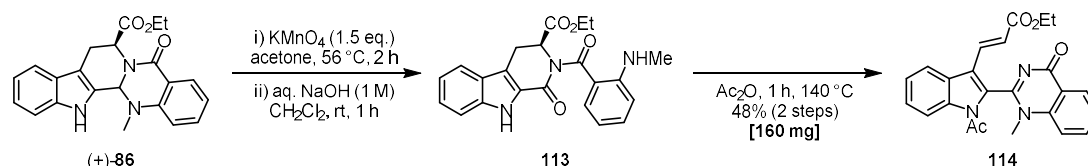
Scheme 49. Revised mechanistic speculation based on experimental data for the synthesis of alkene **108**

Furthermore, we hypothesised that if the methodology was extended towards formation of a more thermodynamically favoured α,β -unsaturated ester, we could improve the yield of the reaction. In order to achieve this, we first needed to access the relevant rhetsinine-derived ester **113** (Scheme 50). We envisioned that oxidation of (+)-carboxyevodiamine ethyl ester (**86**) could be achieved using conditions taken from Decker and co-workers.⁵⁶ Treatment of (+)-carboxyevodiamine ethyl ester (**86**) with potassium permanganate, followed by basic hydrolysis of the quinazolinium intermediate would give us access to carboxyrhetsinine ethyl ester (**113**). With this in hand, we could attempt our strategy of activation to achieve the cyclisation/retro-*aza*-6 π electrocyclic cascade.

Synthesis of rhetsine from evodiamine, Decker and co-workers (2016)



Synthesis of α,β -unsaturated ester **114**



*Scheme 50. Inspiration and synthesis of carboxyrhetsinine ethyl ester (**113**) and α,β -unsaturated ester **114***

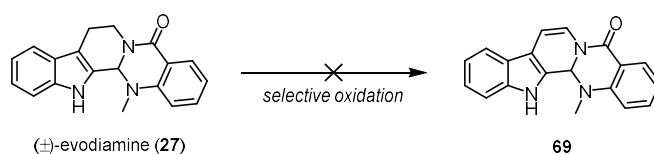
Synthesis of carboxyrhetsinine ethyl ester (**113**) using our proposed route was shown to be successful, however, the crude product proved difficult to purify by column chromatography. The result seemed to be relatively low mass recovery from the silica column. We attributed this to the acidic nature of the silica gel, perhaps initiating the cyclisation/condensation of the secondary amine, giving an iminium ion that was unable to pass through the column. In order to counteract this, we attempted to neutralise the silica prior to purification, however this affected the amount of separation we could achieve. In order to maximise potential yield of our entire reaction process, we decided to telescope the reactions together. To our delight, when the crude carboxyrhetsinine ethyl ester (**113**) was heated to reflux in acetic anhydride, we were pleased to be able to isolate the product of the condensation/retro-*aza*- 6π electrocyclicization. In this case the α,β -unsaturated ester **114** was observed to be isolated with the indole nitrogen acylated. Nonetheless, this product was significantly less polar than the rhetsinine-derived alkene **108**, and thus the crude could be purified without the need for an aqueous work-up. This could also attribute to the isolation of α,β -unsaturated ester **114** in significantly higher yields (48% over two steps) than were possible for alkene **108**.

2.11. Conclusion

In order to investigate the dimerisation of evodiamine through a vinylogous Mannich approach, we synthesised the required electrophilic partner, dehydroevodiamine (**31**), in 69% yield over

three steps. Thus, we have a scalable and reproducible strategy to the required electrophile for our vinylogous-Mannich reaction pathway.

Through attempts to synthesise the proposed nucleophilic partner **69**, we investigated a number of possible synthetic routes. This included initiating the required oxidation at both an early-stage during known syntheses of (±)-evodiamine (**27**), as well as doing late-stage functionalisation of the natural product itself (Scheme 51).



*Scheme 51. Unsuccessful strategy for the selective oxidation of evodiamine (**27**)*

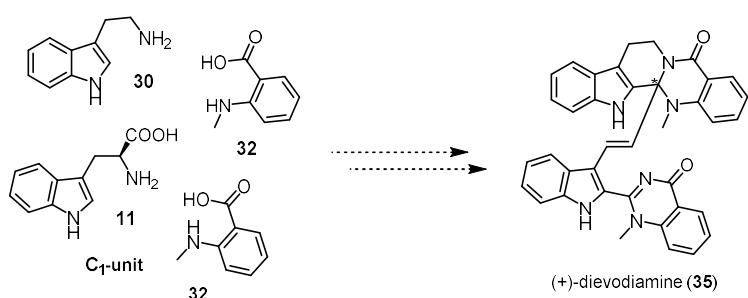
Although our synthetic strategies were not fruitful, we were able to study the chemistry of evodiamine-derived natural product scaffolds in depth. We showed that functionalising the scaffold with an electron-withdrawing group, reduces the reactivity of the system towards oxidation chemistry. This is known to be a very common issue arising with the synthesis and storage of evodiamine and its derivatives.

Finally, we were able to show that the retro-*aza*-6 π electrocyclisation of rhetsinine (**107**) was possible simply by stirring in refluxing acetic anhydride. A mechanistic rationale has been presented, which indicates the importance of an imidoyl acetal intermediate that can undergo intramolecular elimination. The low yields of this transformation can be boosted by formation of an α,β -unsaturated ester functionality. However, future work can be done to enforce this phenomenon is not actually due to the removal of a required work-up—in this example.

3. Linear Strategy

3.1. Introduction: Nonribosomal peptide synthetase inspiration

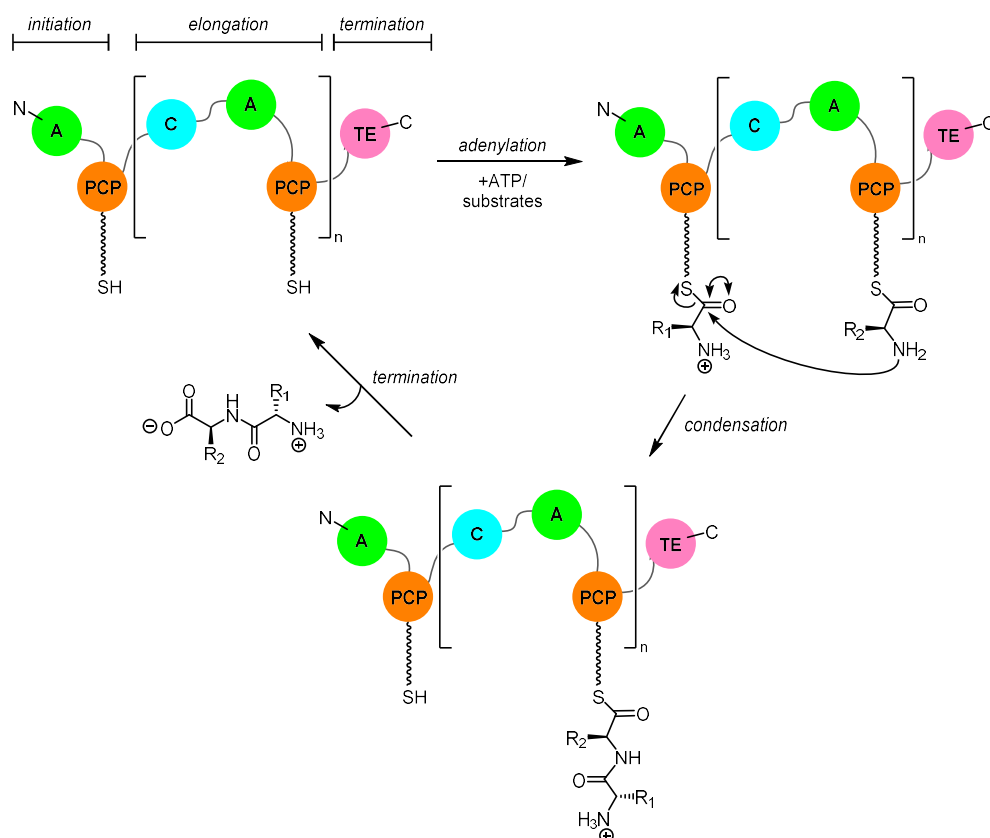
We have thus far thought of (+)-dievodiamine (**35**) as a dimer comprising of two units of (+)-evodiamine (**27**). In this case we have to assume that the stereochemistry of the natural product is induced through a chiral environment (enzymatic control) and point-to-point chirality transfer. However, it is also possible to introduce the requisite stereochemistry by utilising a chiral pool approach starting from L-tryptophan (**11**) (Scheme 52).



*Scheme 52. (+)-Dievodiamine (**35**) as a sum of its biosynthetic components*

A new strategy was envisioned to mimic the possibility that (+)-dievodiamine (**35**) could be a pseudo-dimer resulting from post-translational modifications of a peptidic oligomer, formed by combination of tryptophan (**11**), tryptamine (**30**) and two units of *N*-methyl anthranilic acid (**32**).

Our new synthetic strategy was inspired by the biochemistry of nonribosomal peptide (NRP) synthetases. NRP synthetases contain three key domains: adenylation (A), condensation (C) and peptidyl carrier proteins (PCP), which are responsible for the elongation of natural product peptidic backbone (Scheme 53).⁵⁷⁻⁵⁹



Scheme 53. General chemical logic of nonribosomal peptide (NRP) synthetases

The basic chemical logic starts with initiation at the A-domain, which is crucial for substrate recognition and control.⁶⁰ Adenosine triphosphate (ATP) is used as the energy currency for the loading and activation of the carboxylate group, as a mixed anhydride/adenosine monophosphate (AMP) ester. The activated acids are passed to the PCP-module, resulting in the formation of a covalent thioester adduct. Finally, the C-domain catalyses the coupling of this to an amino group of an upstream thioester, releasing the free thiol-terminated phosphopantetheine arm and forming the required amide linkage. Once the elongation of the peptide is complete, the mature peptide is released from the PCP-domain, through a catalytically controlled mechanism at the C-terminal thioesterase (TE) domain.

NRP natural products are numerous in their structural diversity and biological/therapeutic activity.⁶¹⁻⁶³ All of these compounds are based on peptide scaffolds using α -amino acids as core building blocks, through the formation of amide linkages. Some examples of NRP natural

products include antibiotics such as the β -lactam penicillins and the glycopeptide, colistin (**115**) (Figure 4).

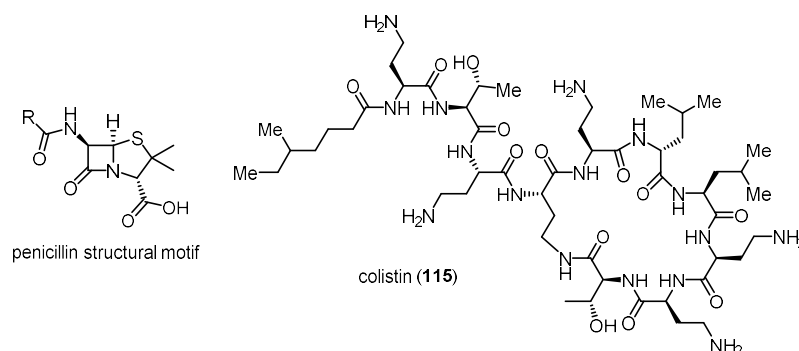


Figure 4. Structures of the penicillins and colistin (**115**)

In many cases the structural diversity represented within NRP natural products is a by-product of integration of non- α -amino acid residues into the structural core. Some particularly relevant examples of this diversification can be found in the pyrrolo[1,4]benzodiazepines (PBDs) group of natural products.⁶⁴ These feature a common core PBD ring system, with many natural products exhibiting a variety of substitution motifs about this core (Figure 5).⁶⁵⁻⁶⁶

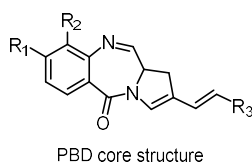
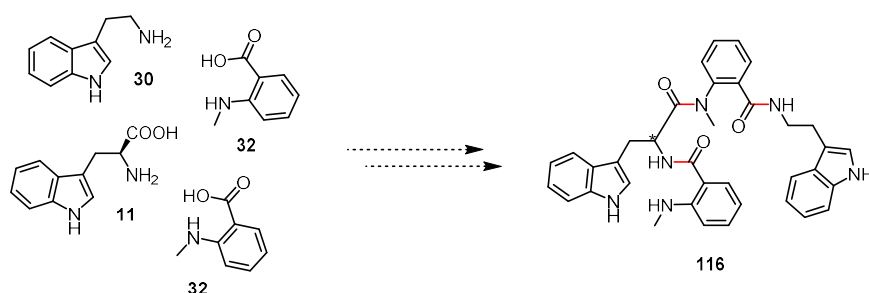


Figure 5. The core structure of the pyrrolo[1,4]benzodiazepines

Interestingly for us, the PBDs are found to contain an anthranilate, as well as a dihydropyrrole or pyrrolidine, moiety fused either side of the diazepine ring. The imine carbon is often the site of alkylation, therefore these compounds have been investigated for bioactivity. Most notably PBDs analogues have shown to slow cell proliferation of cancer lines through alkylation of DNA/RNA.⁶⁷

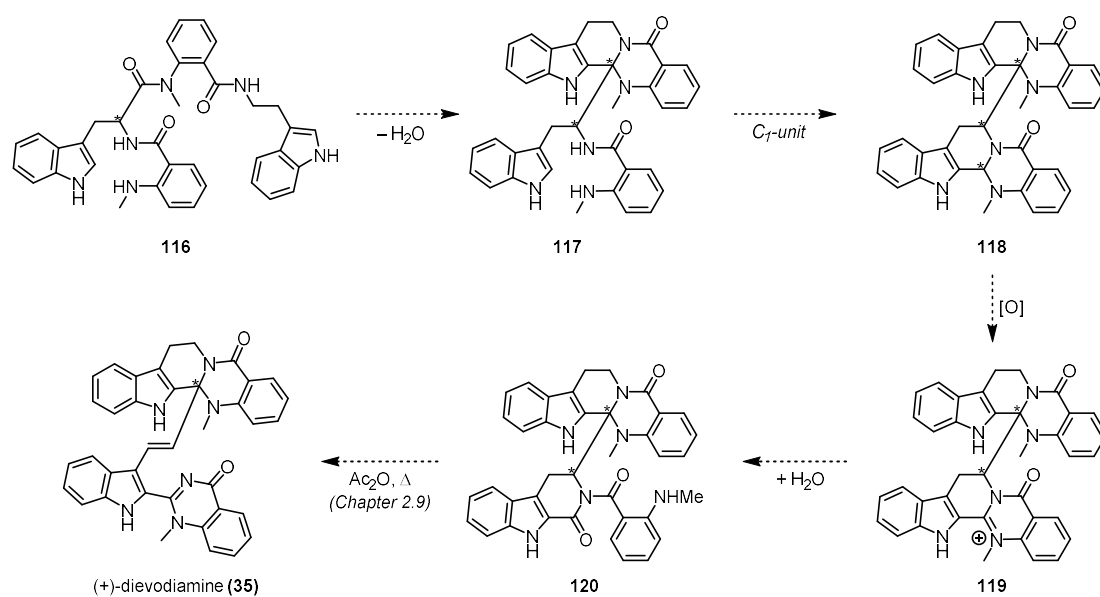
3.2. Linear strategy: synthetic plan

With our knowledge that both L-tryptophan (**11**) and anthranilates are common substrates for NRP synthetases,⁶⁸ we envisioned an alternative strategy that mimicked the possibility that (+)-dievodiamine (**35**) could be a pseudo-dimer resulting from post-translational modifications of a peptidic oligomer **116**. The functionalisation of the mature peptidic oligomer **116** could also be completed, biosynthetically, at the NRP synthetase as the relevant domains are often found within the elongation domain: *N*-methylation, cyclisation, formyltransferases, reductases, dehydratases etc.⁶⁹ This oligomer could be synthesised by combining tryptophan (**11**), tryptamine (**30**) and two units of *N*-methyl anthranilic acid (**32**) (Scheme 54), although the best sequence of reactions would require investigation.



Scheme 54. Linear strategy: Proposed combinatorial chemistry required to synthesise peptidic oligomer 116

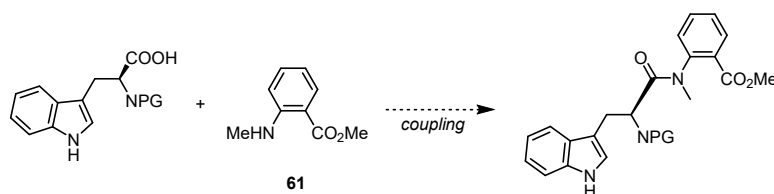
Following the synthesis of oligomer **116**, it was envisioned that the amide linkage formed from the tryptophan carboxy-group and the methyl-aniline could undergo a condensation reaction of the top ring (intermediate **117**), fixing the stereochemistry that is retained in the natural product (Scheme 55). Subsequently, the “bottom” unit would be completed by addition of a C₁-unit, through another condensation reaction to give intermediate **118**. Oxidation would afford the corresponding quinoxolinium **119**, giving the rhetsinine-like lactam **120** upon hydrolysis. Finally, this intermediate could be subjected to the same conditions that initiated the cyclisation/retro-*aza*-6 π electrocyclisation cascade outlined in Chapter 2.10.



Scheme 55. Linear strategy: Functionalising peptidic oligomer **116**

3.3. Synthesis of the peptidic oligomer

As outlined previously, we believed that early introduction of L-tryptophan (**11**) in the synthetic sequence would influence the stereochemical outcome of subsequent reactions. With this in mind, the amide linkage between L-tryptophan (**11**) and *N*-methyl anthranilic acid (**32**) (protected as the methyl ester **61**) would preferably be installed early in the synthesis and the rest of the peptide constructed from the resulting amide (Scheme 56). We envisioned that once this linkage was formed, we could then add the other molecule of *N*-methyl anthranilic acid (**32**) and tryptamine (**30**) in an inconsequential order.



Scheme 56. Planned coupling of a protected tryptophan derivative and dimethyl anthranilate (**61**)

Formation of the amide linkage, as outlined in Scheme 56, was investigated using a number of different protected tryptophan derivatives. The first protecting group we screened was the *tert*-butoxycarbonyl (Boc) group, which was proposed due to the ease with which it can be

removed under mild acidic conditions. By using a group that was stable to base, we could be sure that either the Boc or methoxy group could be orthogonally removed in the next step.

Table 2. Screening amide coupling between L-Boc-Trp-OH (**121**) and dimethyl anthranilate (**61**)

Entry	Reagents	Solvents	Temperature / °C	Time / h	Result
1	DCC, DMAP	CH ₂ Cl ₂	rt	3	N.R.
2	EEDQ	CH ₂ Cl ₂	rt	24	N.R.
3	DCC, DMAP, HOBT	CH ₂ Cl ₂	rt	5	N.R.
4	DCC, DMAP, HOBT	CH ₂ Cl ₂	40 °C	5	Observed acid activation (MeOH quench)
5	DIC, DMAP, HOBT	DMF	rt	24	Observed acid activation (MeOH quench)
6	EDCI, DIPEA, DMAP, HOBT	CH ₂ Cl ₂	rt	24	Observed acid activation (MeOH quench)
7	T3P, DIPEA	2-Me-THF	90 °C	1.5	Observed acid activation (MeOH quench)
8	HATU, DIPEA	CH ₂ Cl ₂	rt	24	Observed acid activation (MeNH ₂ quench)
9	COMU, DIPEA	CH ₂ Cl ₂	rt	24	N.R.
10	COMU, DIPEA	EtOAc	rt	24	N.R.
11	COMU, DIPEA	2-Me-THF	rt	24	Observed acid activation (MeOH quench)
12	SOCl ₂ , NEt ₃	CH ₂ Cl ₂	rt	5	Deprotection, tryptophan (11) (34%)

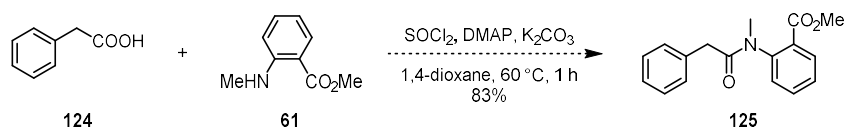
To investigate this potential bond formation, we treated L-Boc-Trp-OH (**121**) and dimethyl anthranilate (**61**) with a variety of coupling reagents (Table 2). The first thing to note was that none of the conditions trialled yielded the expected product, amide **122**. It was confirmed that L-Boc-Trp-OH (**121**) has the capability to couple with numerous nucleophiles as the activated

acids were reactive to methanol or methylamine quenches (Table 2; entries 4-8, 11). Formation of an acid chloride was considered a last resort for our synthesis, although we were concerned about racemisation of the starting material. However, formation of the expected product was not observed, even when the acid was activated through a Fisher esterification pathway using thionyl chloride (Table 2; entry 12). In this particular case, we observed some deprotection of the Boc-group in the starting material, as the formation of tryptophan methyl ester (**52**) was observed when analysing the crude reaction mixture by ^1H NMR spectra. Thus, we moved onto another base-stable amino protecting group.

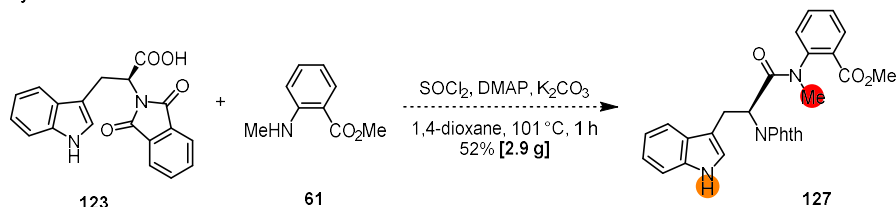
We decided to move onto protecting tryptophan as the corresponding phthalamide, L-Phth-Trp-OH (**123**). We chose the phthalamide group for three reasons: mild aqueous basic conditions would be unlikely to deprotect the amine group over the methyl ester, the group is stable under the strong acidic conditions (potentially needed for coupling).⁷⁰⁻⁷¹

Using information learnt from the study using L-Boc-Trp-OH (**121**), it was clear that activation of the acid as a strong electrophile was required. Modified conditions inspired from Dudley and co-workers were trialled.⁷² In their work, they used dimethyl anthranilate (**61**) as a nucleophile for an amide coupling reaction with phenylacetic acid (**124**), giving amide **125** in an excellent yield (83%, Scheme 57). In our hands, the modified reaction afforded the desired amide product **126** as a 1:1 mixture of rotomers in a reasonable yield of 52% on gram-scale. The reaction was required to run at higher temperatures to avoid long reaction times, which would decompose the product. Evidence of rotomers was seen through variable temperature NMR experiments, as coalescence of the N-H and N-CH₃ protons was observed. This type of restricted rotation, on the NMR time-scale, is common-place when synthesising tertiary amides, and was a recurring issue throughout this project when using dimethyl anthranilate (**61**) as a nucleophile.⁷³

Inspiration for coupling using dimethyl anthranilate (**61**) as a nucleophile



Synthesis of amide **127**

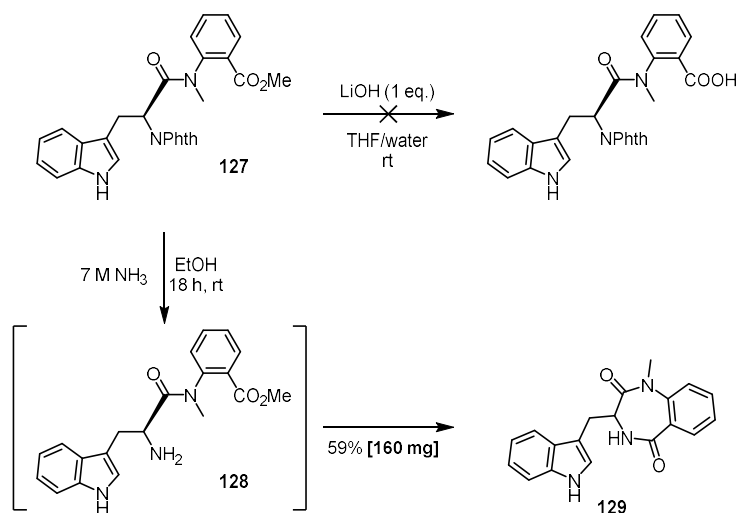


VT ^1H NMR experiment showing 1:1 ratio of amide **127** rotomers



Scheme 57. Inspiration, synthesis and assignment of amide **127**

With a scalable method to obtain amide **127** now in hand, we were able to move through the synthesis of oligomer **116**. The first observation we made was that the phthalamide group must be removed before hydrolysing the methyl ester. This is due to instability of the phthalamide group towards ring-opening under basic conditions (Scheme 58). Thus, we decided to start our synthetic efforts with the removal of the phthalamide group.

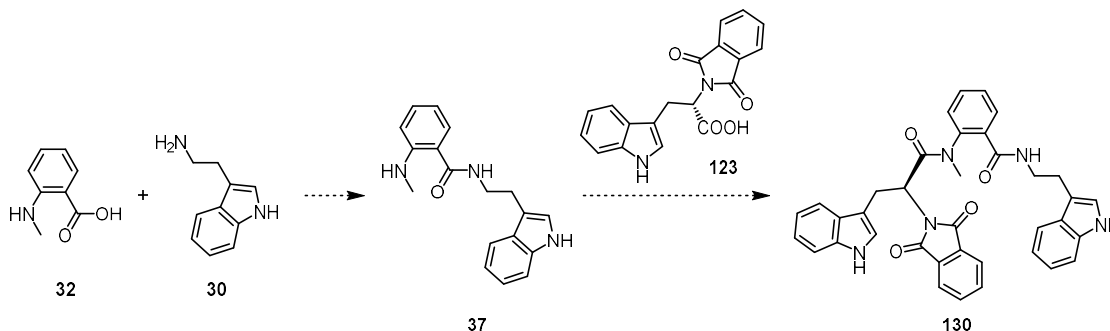


Scheme 58. Studies towards deprotection of amide **127**

Upon exposure of amide **127** to mild phthalamide deprotection conditions, 7 M NH_3 (EtOH), full consumption of the starting material to one major product was observed. However, we were surprised to find that this product was not the expected amine **128**. Instead, this intermediate had undergone a *7-exo-trig* ring closure to give the known cyclic product **129**.⁷⁴⁻
⁷⁶ Although this cyclisation is undesired, it is not too unexpected as this type of ethanolic ammonia-induced cyclisation is known.⁷⁰ However, this is the first example – to our knowledge – of a *7-exo-trig* ring closure and amide formation directly from the ester, without the need to install a *gem*-methyl group (Thorpe–Ingold effect).⁷⁷⁻⁷⁹

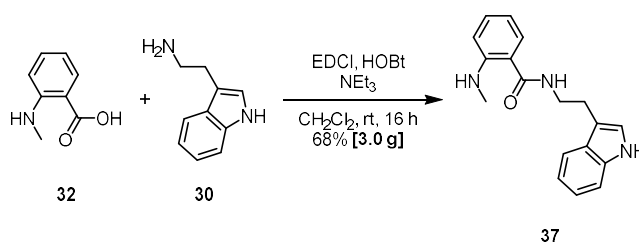
From this study we were able to conclude two key findings: the anthranilate methyl aniline was a very poor nucleophile requiring activation of the acid unit as a strong electrophile, and the carboxy group on the anthranilate unit must be blocked with an alternative to an ester, in order to selectively deprotect the primary amine on the tryptophan unit. Ultimately, the use of a phthalimide protecting group is not ideal. As a protecting group, it is not as trivial to remove as other amine protecting groups,⁸⁰ and requires refluxing in toluene to install or pre-formation of an activated reagent (poor step/atom economy).⁸¹⁻⁸⁴ However, due to the rather harsh conditions needed to achieve the relevant amide coupling chemistry, it is an acceptable protecting group as it is stable to both acid and non-nucleophilic bases.

An alternative route was investigated, in which the amide bond between *N*-methyl anthranilic acid (**32**) and tryptamine (**30**) was pre-installed, thereby using the required tryptamine unit as a pseudo-protecting group (Scheme 59).



Scheme 59. Proposed synthesis of Phth-protected diamide **130**

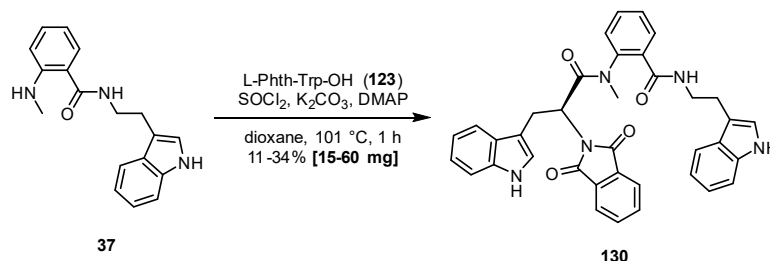
The synthesis began with the synthesis of amide **37**, from *N*-methyl anthranilic acid (**32**) and tryptamine (**30**) (Scheme 60), on a multigram scale.⁸⁵ Purification at this larger scale was aided by trituration of the crude mixture, from EtOAc, which was found to remove most of the unreacted starting materials and allowed the remaining residue to be easily purified by column chromatography. As expected, the dimerisation of *N*-methyl anthranilic acid (**32**) under these conditions, was negligible due to the weak nucleophilic nature of the methylated aniline.



Scheme 60. Synthesis of amide **37**

With the required amide **37** in hand, we could plan a coupling of itself and L-Phth-Trp-OH (**123**). We expected that amide **37** would be a poor nucleophile, as the amide group would still be in conjugation with the aniline reducing electron density on the nitrogen. Therefore, activation of the carboxylic acid as an acid chloride, in attempt to facilitate the desired reaction, was attempted. Pleasingly, activation of the acid with thionyl chloride did

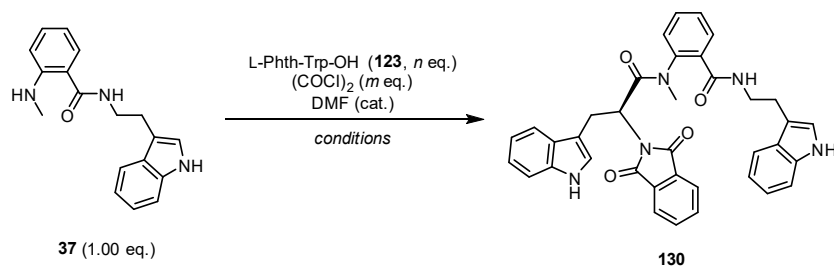
indeed provide the expected diamide product **130** (Scheme 61). However, the yields of this reaction were low and the chemistry proved unreliable to reproduce. Hence, attempts to scale up this chemistry did not proceed.



Scheme 61. Small-scale synthesis of diamide **130**, using thionyl chloride as an acid activation reagent

The formation of the acid chloride using milder conditions was trialled, by *in situ* formation of a Vilsmeier–Haack reagent from oxalyl chloride and catalytic dimethylformamide. This methodology would prove to be the best method for formation of the strenuous amide linkage, although significant investigation was required to optimise this approach (Table 3).

Table 3. Selected entries of screen for conditions of coupling of aniline **37** and L-Phth-Trp-OH (**123**) using oxalyl chloride/DMF (cat.)



Entry ^a	Acid <i>n</i> eq.	(COCl) ₂ eq. ^b	Base (<i>m</i> eq.)	Solvent	[reaction] / M ^c	Temp. / °C	Time / h	Yield XX / %
1	1.50	1.50	NEt ₃ (5.0)	CH ₂ Cl ₂	0.10	rt	2	16
2	1.00	1.05	DMAP (2.5)	CH ₂ Cl ₂	0.10	rt	18	12
3	1.00	2.00	DMAP (4.0)	CH ₂ Cl ₂	0.15	rt	20	21
4	1.10	1.50	NEt ₃ (4.0)	CH ₂ Cl ₂	0.15	40	20	32
5	1.10	1.50	NEt ₃ (4.0)	THF	0.08	50	3	54
6	1.30	2.00	NEt ₃ (4.0)	THF	0.08	50	24	69
7 ^d	1.30	2.00	NEt ₃ (3.5)	THF	0.08	50	18	84

^a All the reactions proceeded through pre-activation of L-Phth-Trp-OH (**123**) as the acid chloride by addition of (COCl)₂ and DMF (3 drops) at 0 °C for 1 h, after which time the solution was allowed to warm to rt and a solution of amide **37** and base in the required solvent was added dropwise.

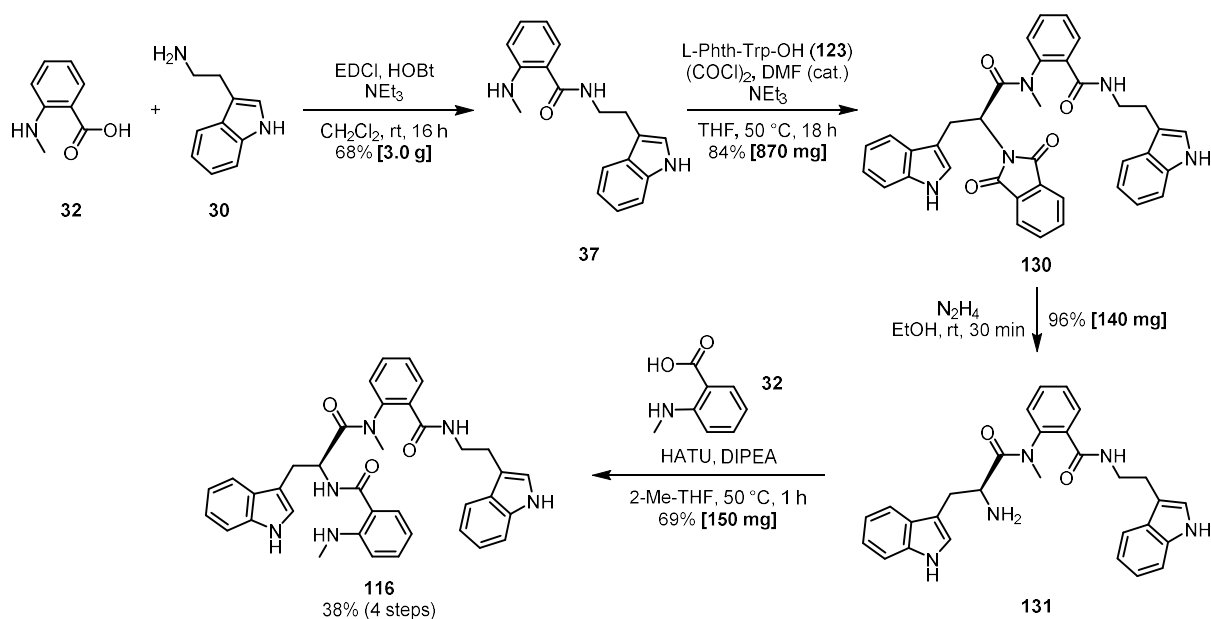
^b 2 M oxalyl chloride as a solution in CH₂Cl₂ was used.

^c Unless stated otherwise, reactions were run using 100 mg of amide **37**.

^d Entry 7 was run on a multigram scale, resulting in 870 mg of diamide **130**.

It was surprising to observe quite a low yield of the expected product **130** using the first set of coupling conditions, when activating with oxalyl chloride (Table 3, entry 1). TLC analysis of the activation step showed almost complete conversion to tryptophan methyl ester (**52**), when an aliquot was quenched with MeOH. Therefore, the observed reactivity was attributed to the poor nucleophilicity of the aniline nucleophile **37**. By using DMAP as the base, it was anticipated to further activate the acid chloride by nucleophilic catalysis (Table 3, entry 2). Surprisingly, the yield of the resulting reaction was slightly lower than the preceding entry. This prompted an increase the equivalents of oxalyl chloride used (Table 3, entry 3), which almost doubled the yield of diamide **130**, from the entry before. From this observation, it was proposed that the acid was being activated as the corresponding acid chloride, however, the latter was prone to degradation. Therefore, promotion of the reaction between the nucleophilic aniline **37** and the corresponding acid chloride was achieved by heating to reflux. This was shown to slightly increase the yield of the desired product (Table 3, entry 4).

With all this mind, we decided to change the solvent to the more polar tetrahydrofuran (THF), which we hoped would stabilise charged intermediates and increase the solubilities of the reactants (Table 3, entry 5). To our delight, this resulted in much better yield of the expected product. Furthermore, when the equivalency of the acid was increased to 1.3 and the reaction was allowed to proceed overnight (Table 3, entry 6), the yield increased and the reproducibility of the reaction was improved. Fortunately, upon scaling up (Table 3, entry 7), the reaction was shown to proceed with an even higher yield of diamide **130** and shorter reaction times.



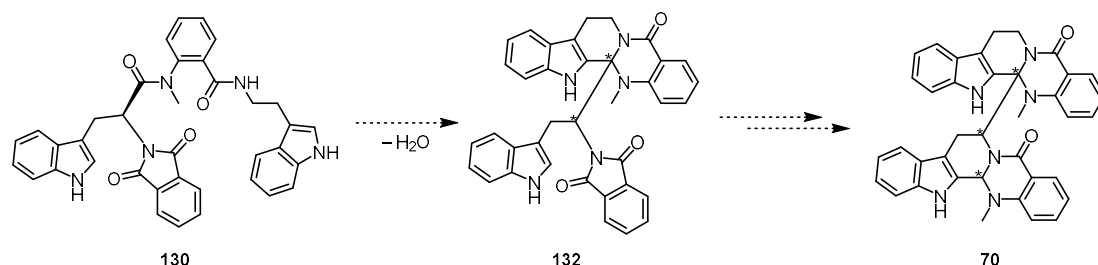
Scheme 62. Completed synthesis of triamide oligomer **116**

The deprotection of the phthalimide group went smoothly, when diamide **130** was treated with hydrazine in ethanolic solution, giving access to primary amine **131** – ready to undergo the last amide bond formation (Scheme 62). Coupling of the final unit of *N*-methyl anthranilic acid (**32**) was hampered initially by the insolubility of the starting primary amine **131**. Although DMF could be used as a solvent, we were unable to remove it from any of the products of amide formation without significant degradation of the product. Hence, it was proposed to use of 2-methyltetrahydrofuran (2-MeTHF) as the solvent for the screening of coupling conditions for this amide formation. Not only did 2-MeTHF fully solubilise amine **131**, but it is generally a great option for amide coupling chemistry, as heating will help eliminate water.⁸⁶⁻⁸⁷ Some coupling conditions were screened according to the methodology described by Watson and co-workers. It was observed that we were able to obtain the required oligomer **116**, quickly and reliably, using HATU. In this case we were able to obtain reasonable amounts of the required oligomer intermediate **116**, using a much milder and simpler procedure (compared to when using dimethyl anthranilate **61**) owing to the much more reactive nature of the primary amine **131**.

3.4. Functionalising oligomer **116**: Amide activation/dehydrative cyclisation

With our synthesis of oligomer **116** complete, we needed to develop a methodology applicable to activation of the tertiary amide carbonyl group. In order to first investigate this transformation, it was decided not to employ the complex peptidic oligomer **116**. We believed that the free aniline could interfere, as it is the most nucleophilic functional group. Also, using the most advanced and valuable intermediate for small-scale test reactions would require a great deal of time.

With this in mind, it was beneficial to investigate the cyclisation chemistry using the less-complex phthalimide protected diamide **130** as a model substrate. This intermediate was readily accessible, at large-scale, through the two-step sequence described in the prior section. If we could successfully perform the dehydrative cyclisation chemistry on this intermediate, then we could easily take the corresponding pentacycle **132** through an alternative synthetic pathway (Scheme 63).

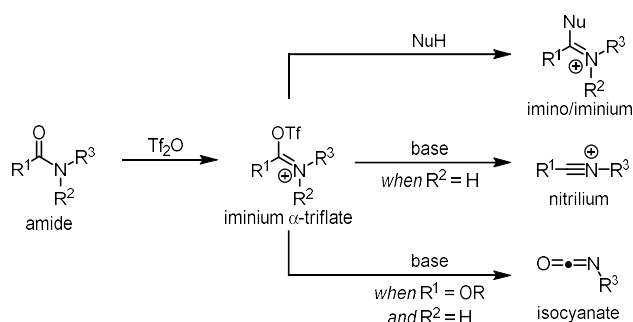


*Scheme 63. Planned dehydrative cyclisation of phthalimide protected diamide **130**, along with a representative progression of the synthesis from the cyclised product **132***

The obvious issue with this strategy is the reactivity of amides towards nucleophilic addition, as well as the tendency for them to react as nucleophiles through the oxygen atom.⁸⁸⁻⁸⁹ It is this reactivity that must be exploited when considering amide activation strategies.⁹⁰⁻⁹² Furthermore, we will discuss the attempts and rationale of activating our amide towards intramolecular nucleophilic addition.

3.5. Activation of tertiary amide 130 by triflic anhydride

Triflic anhydride is a frequently employed electrophilic reagent which activates multiple functional groups towards nucleophilic addition. This is due to the strong electron-withdrawing effect of the triflate (OTf) group. One of the most prevalent uses of triflic anhydride is the activation of amides. This activation can proceed with or without the use of base, due to highly electrophilic nature of the reagent. The activation of primary amides with triflic anhydride typically results in the formation of nitriles.⁹³ However, the activation of secondary or tertiary amides can afford a variety of products (Scheme 64).

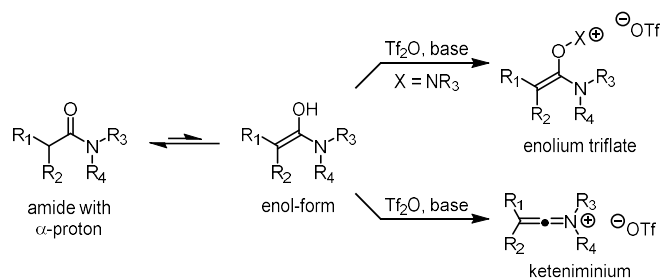


Scheme 64. Activation and reactivity of secondary/tertiary amides with triflic anhydride

The activation of amides proceeds first with the formation of a iminium α -triflate. Without base, the resulting iminium α -triflate can react with a relevant nucleophile, giving imino/iminium products.⁹⁴ Treatment of secondary amides with triflic anhydride and a base will generally form the corresponding nitrilium product.⁹⁵ When carbamates are treated with triflic anhydride/base, the elimination of the alkoxy group can occur, giving the corresponding isocyanate product.⁹⁶

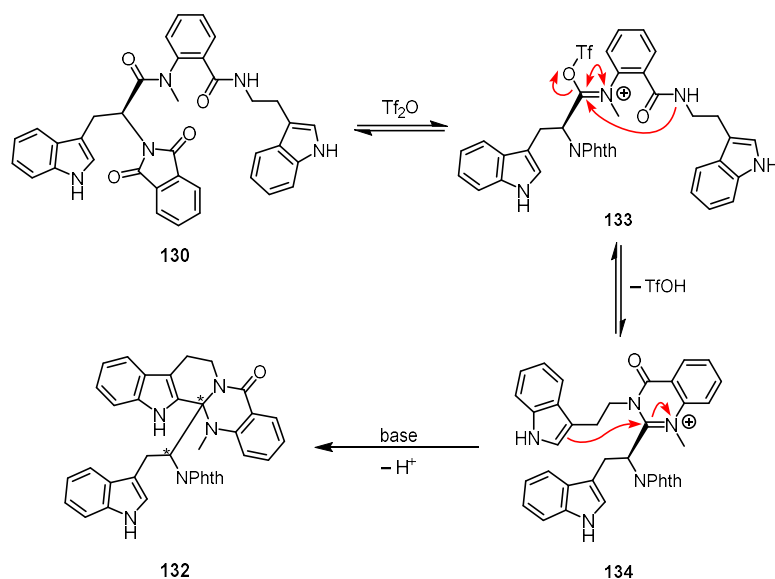
Alternatively, if the secondary or tertiary amide has an α -proton, it can be converted to its enol-form. In this case the effect of triflic anhydride, under basic conditions, can give rise to the formation of a range of different products (Scheme 65). If the utilised base is able to stabilise the positive charge efficiently, then it is possible to synthesise enolium triflates.⁹⁷ These tend to be transient intermediates, which are not isolated. Instead, a nucleophile is usually added at the α -position, reforming the carbonyl in the process. If the R^3/R^4 are sufficiently electron-

donating, the formation of a keteniminium intermediate is favoured.⁹⁸ Again these are usually transient and are made *en route* towards the synthesis of nitrogen-containing heterocycles.



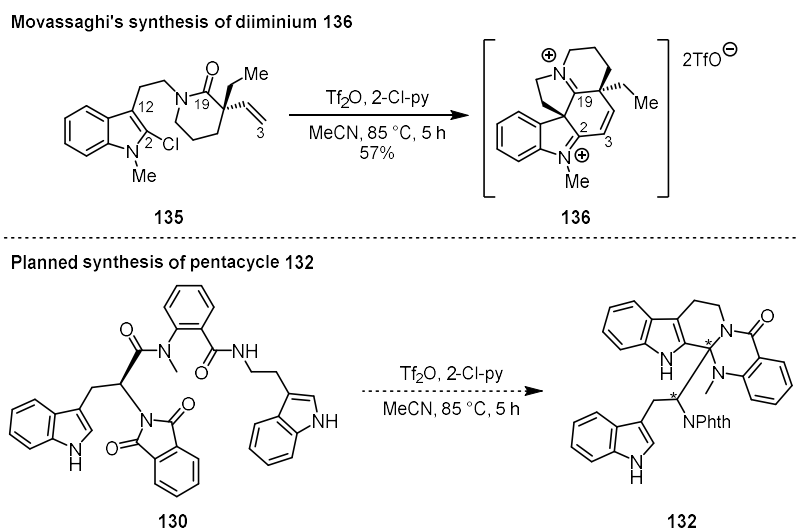
Scheme 65. Activation and reactivity of secondary/tertiary enolisable-amides with triflic anhydride/base

In our case, we hypothesised that activation of the tertiary amide **130**, as the triflate **133**, would yield an intermediate iminium **134** that would be sufficiently electrophilic for cyclisation. We hoped that the secondary amide nitrogen would undergo the first nucleophilic addition to the iminium (Scheme 66). Despite the poor nucleophilicity of the amide nitrogen, we anticipated that the formation of a 6-membered ring, the elimination of the triflate leaving group and the addition to a highly activated iminium would facilitate the desired reactivity. As the C3-position of the indole is substituted, substitution at the C2-position should occur to give the required pentacyclic product **132** (presumably *via* C3 addition followed by [1,2]-migration).



*Scheme 66. Our proposed mechanism of activation and cyclisation of phthalimide-protected diamide **130***

The conditions we decided to employ for our initial activation strategy were inspired by previous work from Movassaghi and co-workers.⁹⁹ In their synthesis of a number of aspidosperm-type natural products, amide activation by Tf_2O afforded the desired iminium products (Scheme 67). The base chosen was 2-chloropyridine, which is a commonly used base for this activation as it is known to facilitate the elimination of the triflate leaving group.¹⁰⁰ Following activation of chloride **135**, the authors suggest that the indole reacts as a nucleophile at C12. Upon completion of the cyclisation step, the base-mediated cyclisation between carbons C2 and C3 then occurs. The diiminium **136** was not isolated by the authors but subsequent products in their synthesis are likely to stem from this central intermediate.



*Scheme 67. Movassaghi and co-workers' synthesis of diiminium **136** as inspiration for our triflic anhydride amide activation and cyclisation cascade*

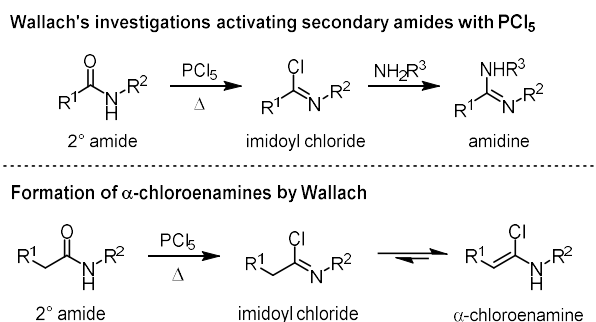
When we treated our starting material with triflic anhydride, at $-78\text{ }^{\circ}\text{C}$, a colour change was observed. However, adding 2-chloropyridine and heating the resulting mixture did not result in the formation of the expected pentacycle **132**. To our disappointment, there was no evidence of any new products in the crude material. It is possible that the observed colour change was due to the activation of the tertiary amide, and that the activated amide was insufficiently electrophilic to undergo the desired transformation.

The base used in the reaction was also varied, as well its equivalency with respect to triflic anhydride and diamide **130**. It has been shown that when undergoing triflic anhydride activation it is beneficial to use pyridine-containing base.¹⁰¹ We found that the use of pyridine, or DMAP, resulted in full recovery of the starting material.

3.6. Activation as imidoyl chlorides

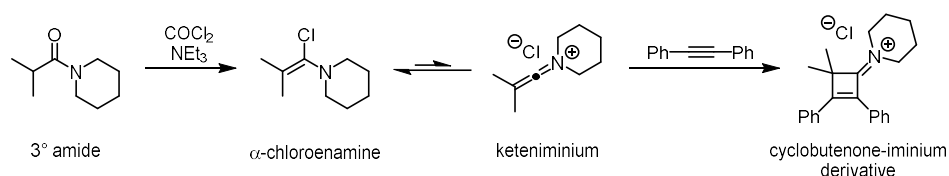
Activation of secondary and tertiary amides as imidoyl chlorides is well reported. In fact it was first noted in 1877, by Otto Wallach, that treatment of secondary amides with phosphorous pentachloride resulted in the formation of the corresponding imidoyl chlorides, which could act as strong electrophiles (Scheme 68 68).^{92, 102} The latter was showcased by reacting the corresponding imidoyl chlorides with primary amines, resulting in the formation of amidines.

He was also able to show that the corresponding α -chloroenamines could be isolated, if there was an available α -proton for deprotonation.



Scheme 68. Wallach's investigations using phosphorus pentachloride as an activation reagent for secondary amides

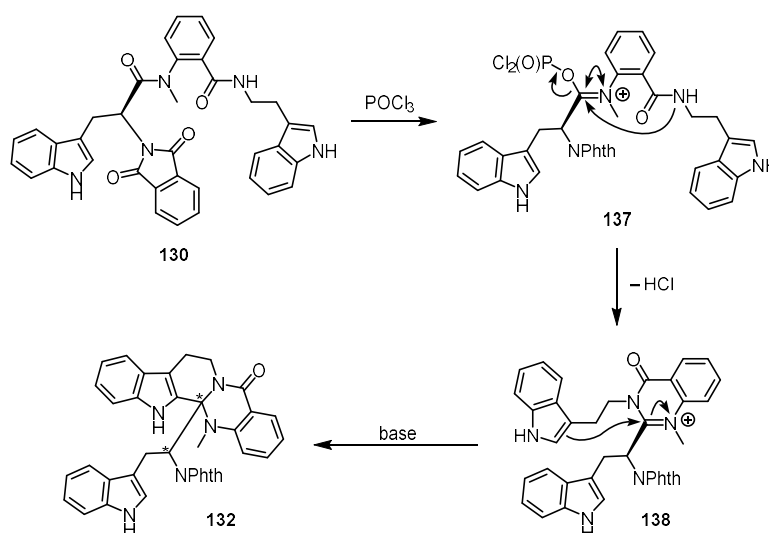
It was suggested, by Heymons and co-workers, that tertiary amides could also form the corresponding imidoyl chlorides/ α -chloroenamines when treated with phosphorus pentachloride.¹⁰³ These claims were later substantiated by Viehe and co-workers who activated tertiary amides using phosgene followed by treatment with triethylamine (Scheme 69).¹⁰⁴ Furthermore, these α -chloroenamines were shown to undergo [2+2] cycloadditions with acetylenes, giving the corresponding cyclobutenone derivatives. This would suggest that the α -chloroenamines are in equilibrium with the corresponding keteniminiums by reversible elimination of chloride.¹⁰⁵



Scheme 69. Activation of tertiary amides and an example the corresponding keteniminium reactivity

In order to investigate activating our required tertiary amide as an imidoyl chloride, we decided to react the phthalimide protected diamine **130** with various phosphorus-based activating reagents. We hoped that the required cyclisation would be more viable through this method, due to the favourable, and irreversible, formation of a $\text{P}=\text{O}$ bond.¹⁰⁶ We proposed, upon formation of imidoyl species **137**, an intramolecular substitution *via* a 6-*endo-trig* cyclisation

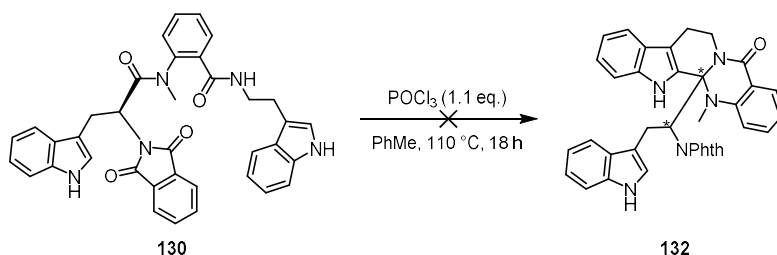
would occur (Scheme 70). This hypothesis is strengthened by the recent work of Ábrányi–Balogh and co-workers.¹⁰⁶ In this earliest density functional theory (DFT) study of the Bischler–Napieralski (BN) reaction, the group showed that the formation of imidoyl chlorides, during the reactions of amides with POCl_3 or T3P, was not favoured. This is understandably due to the increased rate of intramolecular addition, as well as the formation of the energetically favoured $\text{P}=\text{O}$ bond. The resulting iminium product **138** should then undergo a similar reaction as seen earlier (Scheme 66), to result in the pentacyclic product **132**.



Scheme 70. Proposed mechanism for phosphorus(V) induced BN/cyclisation cascade, shown using POCl_3 as the example reagent

Toluene was chosen as the solvent for the reaction, to assist with the elimination of water using a Dean-Stark set-up. Use of phosphorus(V) oxychloride (POCl_3) as a dehydration reagent for the synthesis of quinazolinones from amides is well documented.¹⁰⁷⁻¹¹⁰ Starting with this reagent, we found that the addition of POCl_3 , even at low temperatures, resulted in the decomposition of the starting material (Scheme 71). We were encouraged that there was apparently no reactivity of the reagent with the phthalimide protecting group, which was observed to be intact in the recovered starting material. This was even the case when the

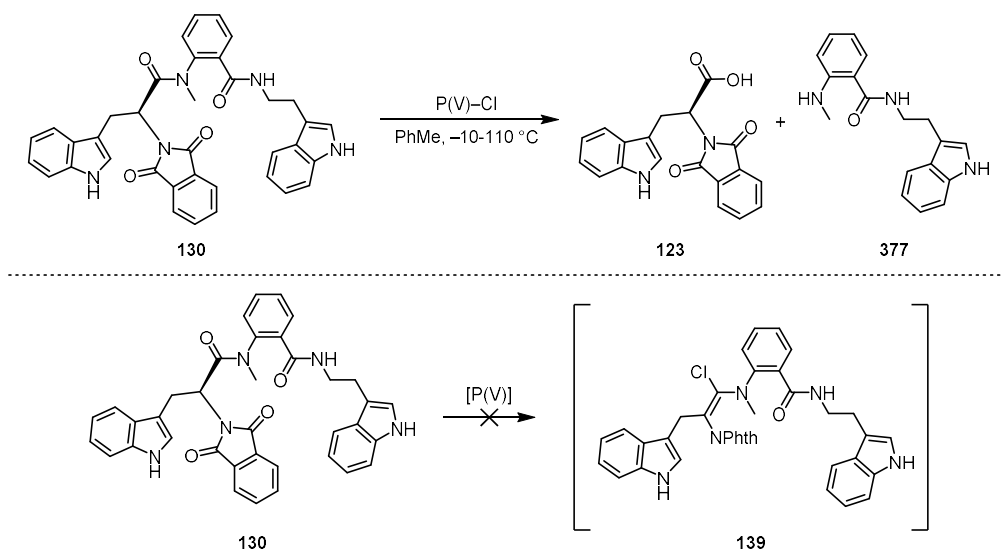
phthalimide starting material **130** was subjected to POCl₃ at elevated temperatures over a prolonged period of time.



Scheme 71. Example attempt to induce a Bischler–Napieralski reaction with POCl₃

Attempts using an alternative reagent for this transformation were also unsuccessful. Some examples of the reagents used include: POCl₃/NEt₃, POCl₃ (excess/solvent), PCl₅, P₂O₅/PCl₅, T3P/DIPEA.

The use of all the P(V)–Cl reagents, resulted in decomposition of the starting material, by the amide hydrolysis mentioned earlier (Scheme 72). This would suggest that the starting material is not stable in the presence of strong acid (in this case, HCl). This decomposition was not observed when triethylamine was used alongside the POCl₃ or when T3P was used as a reagent. In these examples, only recovered starting material was observed. Additionally, any recovered starting materials from these reactions were shown to not have altered optical rotation values. Thus, if the activation of the amide is occurring, it is not forming the corresponding α-chloroenamine **139**. This would result in racemisation through equilibrium. This furthers our confidence in the stereochemical stability of the stereogenic centre derived from L-tryptophan (**11**).

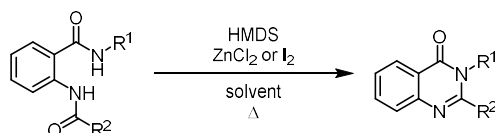


Scheme 72. Conclusions from attempts to activate diamide **130** with phosphorus(V) reagents

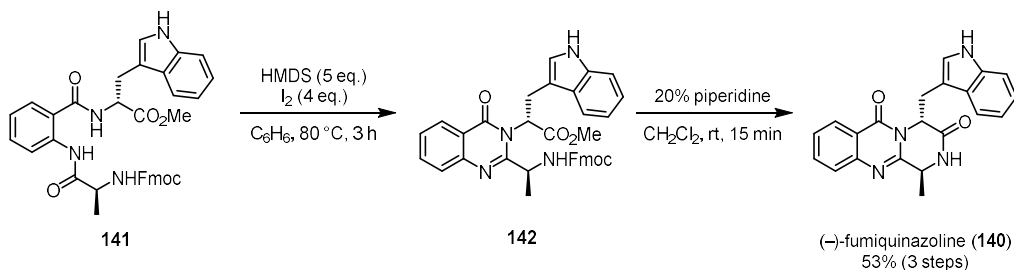
3.7. Activation by Lewis-acid mediated silylation

Knowing that the phthalimide starting material **130** was unstable to acidic conditions, we needed to change our strategy to avoid this. It was at this point we noticed the work originating from the group of Narshinha Argade. While attempting to synthesise a series of natural products, all containing a quinazolinone core, Argade and co-workers utilised mild conditions for the required quinazolinone-ring closure (Scheme 73).¹¹¹ By activating the amide with ZnCl_2 and hexamethyldisilazane (HMDS), it was shown that the required reaction could occur with a high functional group tolerance. Examples of HMDS mediated quinazolinone ring closures can be found in the synthesis of nucleosides, however Argade expanded this to mediate the synthesis of more complex alkaloids.¹¹² From this methodology, the group have been able to publish the concise syntheses of numerous quinazolinone natural products, including the indole-alkaloid (–)-fumiquinazoline (**140**).^{113–115} The final two steps of this synthesis is shown in Scheme 73. The cyclisation occurred well, even in the presence of an unprotected indole (diamide **141**), to give the complex quinazolinone **142**. They were also able to show that the method can work by utilising molecular iodine (I_2) as a soft Lewis acid.

General scheme for activation of diamides using Lewis acids and HMDS

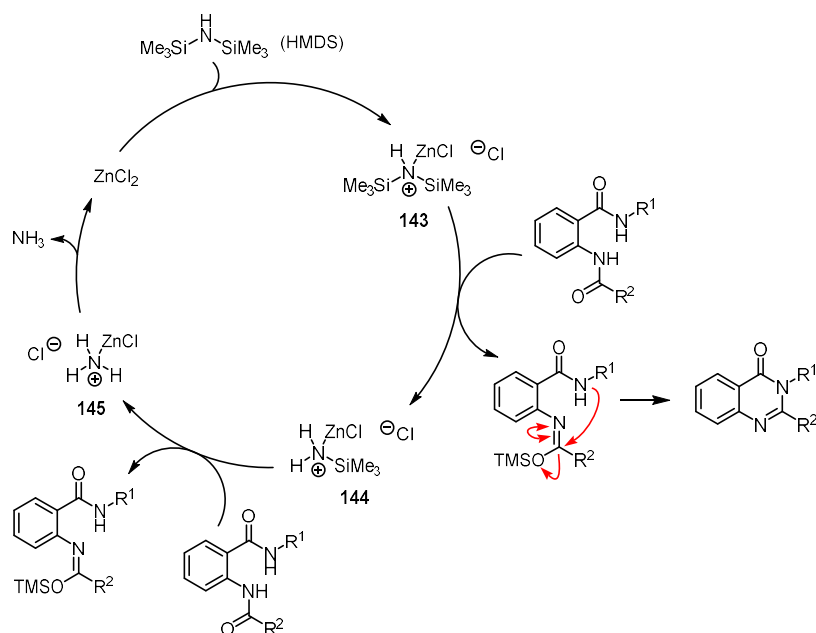


Synthesis of (–)-fumiquinazoline (**140**)



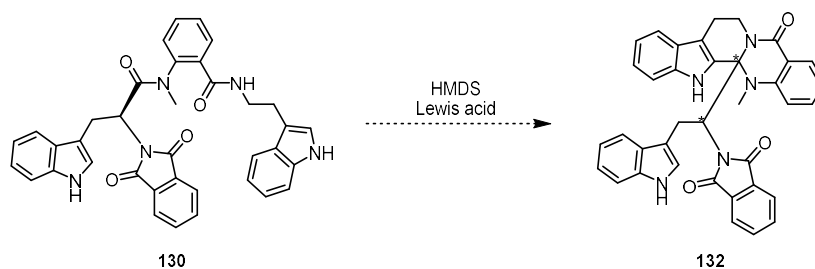
*Scheme 73. Use of Lewis acids and HMDS to synthesise quinazolinones from diamides, and the synthesis of (–)-fumiquinazoline (**140**) from Argade and co-workers*

A mechanism has been proposed for this transformation based on complementary work by Golshani and co-workers.¹¹⁶ The first step involves ligand exchange at zinc, giving the tertiary ammonium salt **143** (Scheme 74). The required amide can then extract the electrophilic trimethylsilane (TMS) through the anilide oxygen, giving the required imidoyl silane and the secondary ammonium salt **144**. The other electrophilic TMS group can then be extracted by another diamide molecule to give the ammonia-ZnCl₂ couple **145**. Upon dissociation of ammonia, which leaves as a gas, the ZnCl₂ catalyst is regenerated. It can also be assumed that, due to the excess ZnCl₂ used in the reaction, the amide carbonyl groups would also be activated by the Lewis acid throughout the mechanism.



Scheme 74. Proposed mechanism for diamide activation using ZnCl_2 /HMDS

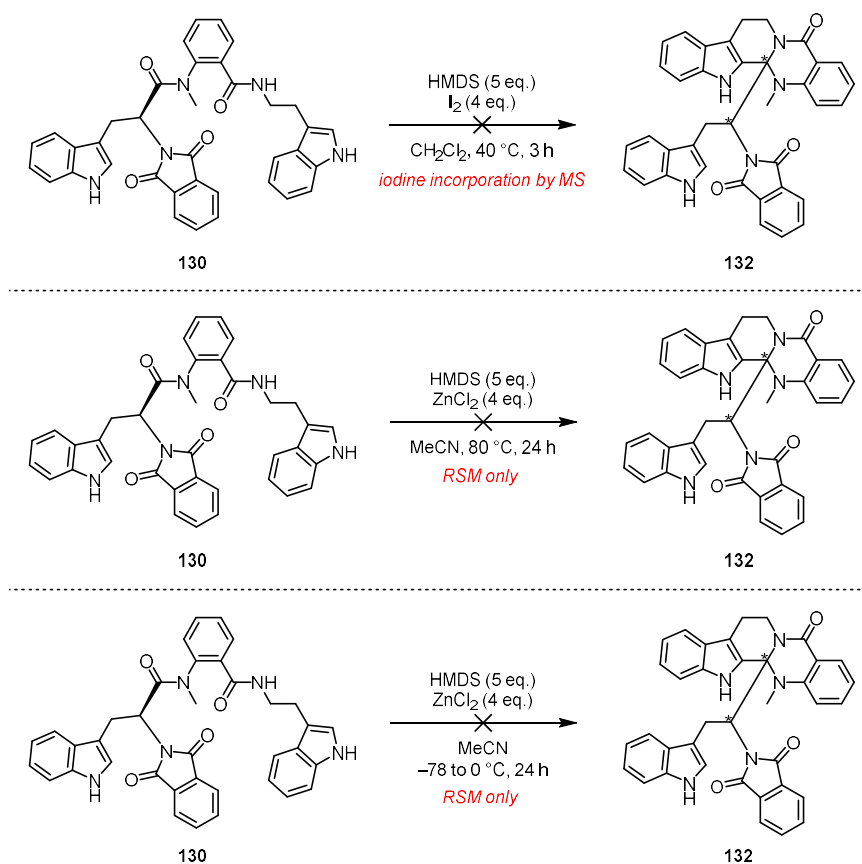
Although there is some similarity between the system reported above and our system, it was unclear whether this chemistry could be readily adapted as activation of a tertiary amide through this method is not reported within the literature (Scheme 75). Nevertheless, we decided to pursue this as a new strategy for the formation of pentacycle **132**.



Scheme 75. Planned synthesis of pentacycle **132** using HMDS and Lewis acids

Direct replication of Argade's conditions (Scheme 73) was not possible, due to the low solubility of the starting phthalimide protected diamide **130** in benzene. Therefore, we began our investigation by using dichloromethane and acetonitrile as the solvent. Upon treating diamide **130** with HMDS/ I_2 we observed a somewhat predictable mixture of iodinated products (Scheme 76). In order to avoid this, we opted instead to use ZnCl_2 as the Lewis acid for the reaction. Unfortunately, we could not force any reactivity between diamide **130** and HMDS

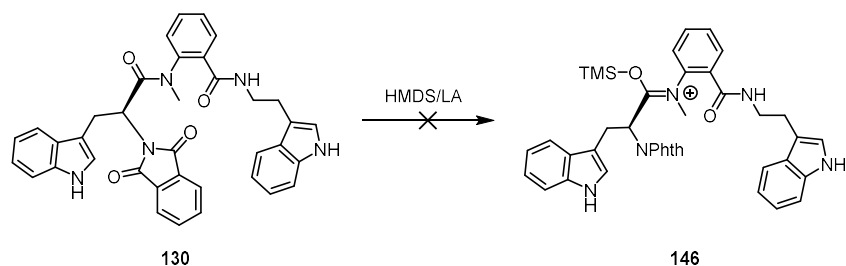
when using ZnCl_2 . Whenever ZnCl_2 was used as the Lewis acid, we were able to recover the starting material in full. We found that changing the source of TMS to the more electrophilic trimethylsilyl triflate (TMSOTf) was not able to push the reaction towards the expected product. In this case, the reaction seemed to be progressing cleanly, by TLC analysis, to a less polar product. Frustratingly, upon aqueous work-up, new products in the ^1H NMR spectrum were not observed. Presumably, the reactivity in this case could be due to the indole groups being protected with a TMS group, which would likely be cleaved during the aqueous work-up.



*Scheme 76. Selected attempts to use Lewis acid/HMDS to activate diamide **130** and form pentacycle **132***

This result led us to believe that the activation of the required tertiary amide, which would proceed through a charged intermediate **146**, may simply be too high in energy to access through this approach (Scheme 77). It should be noted that when a secondary amide is activated through this method, the resulting intermediate can be deprotonated by the excess

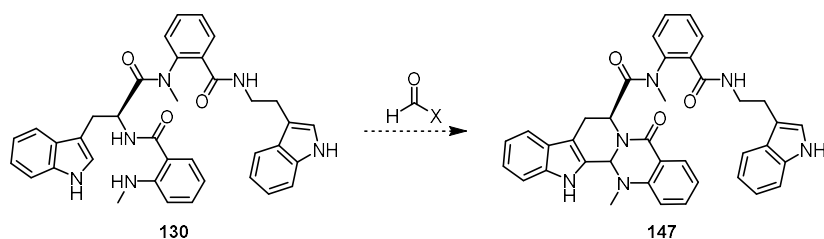
HMDS. In Chapter 4.6 we will discuss the implications of removing the methyl group and attempting this cyclisation again on an analogous secondary amide substrate.



Scheme 77. None obtainable charged intermediate using Lewis acid/HMDS conditions

3.8. Functionalising oligomer 116: C₁-unit addition

Thus far, cyclising the “top” ring early in the sequence was proving very challenging. One of the issues we did not foresee was degradation of the phthalimide protecting group during some of the initial attempts. Therefore, we next turned our efforts to the installation of the C₁-unit into the “bottom” fragment earlier in the synthesis (Scheme 78). Using the resulting diamide **147** as a reactant would overcome the need for protecting groups during cyclisation of the “top” ring, as the tryptophan amine group would be fully substituted as a lactam in the “bottom” ring.

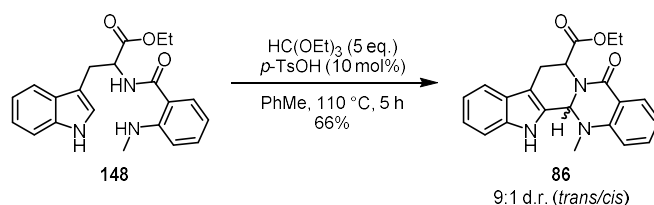


Scheme 78. Installing the C₁-unit at an earlier point in the linear synthetic route

When looking for conditions to install the required C₁-unit we decided that the best model substrate was (+)-carboxyevodiamine (**29**). It became obvious to us that the synthesis of (+)-carboxyevodiamine (**29**) has been relatively under-explored in the literature, especially when compared to many known syntheses of evodiamine (**27**) and its derivatives. It was

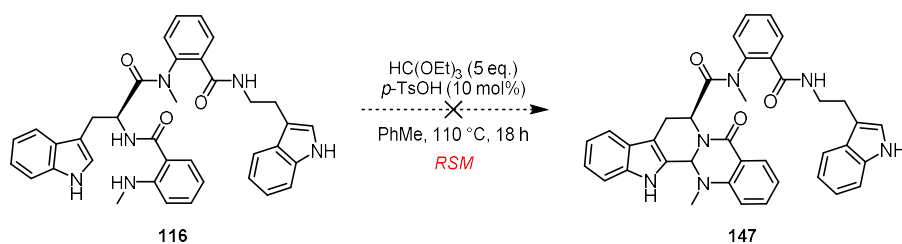
decided that investigation of two complementary strategies to access (+)-carboxyevodiamine (**29**) would be undertaken.

The first involved adapting the work of Beugelmans-Verrier and co-workers, who prepared carboxyevodiamine ethyl ester (**86**) as the product of an acid-catalysed (*p*-toluenesulfonic acid, *p*-TsOH) addition/cyclisation cascade (Scheme 79).¹¹⁷ In this reaction the electrophile used was triethyl orthoformate, a common reactive substitute for formic acid. Upon addition of triethyl orthoformate to the ester precursor **148**, the authors also note that there is good levels of substrate-controlled diastereoselectivity in this reaction (9:1 *trans/cis*).



*Scheme 79. The synthesis of carboxyevodiamine ethyl ester (**86**), as described by Beugelmans-Verrier and co-workers*

With this work in mind, we were cognisant that acidic conditions have broken down our phthalimide protected diamide **130**. However, it was decided to employ the conditions on our triamide oligomer **116**, as we hoped that the changes in molecular structure and the relatively small amount of acid added for the transformation would facilitate the reaction without decomposing the starting material. When we subjected our triamide **116** to Beugelmans-Verrier's conditions, we were disappointed to find that there was no reaction, even when left at reflux in toluene overnight (Scheme 80). Unfortunately, when we tried to increase the catalyst-loading (over 30 mol% *p*-TsOH) we started to observe some decomposition of starting material. Attempts to replace the Brønsted acid with a Lewis acid, such as boron trifluoride etherate or aluminium chloride, also resulted in the recovery of starting material only.

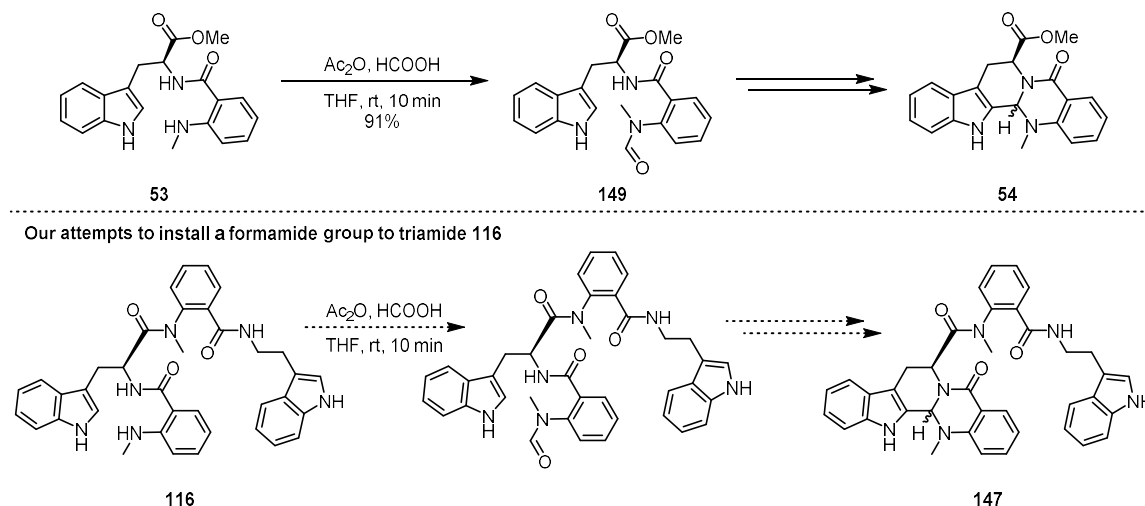


Scheme 80. Treatment of triamide **116** with triethyl orthoformate using acid catalysis

The second strategy involved the use of more steps in the addition of the C_1 -unit, but was also based on the synthesis of a carboxyevodiamine ester, in this case the methyl ester **54** (Scheme 81). The synthesis of (+)-carboxyevodiamine (**29**) will be discussed in greater depth in Chapter 4.2. However, we were confident at this stage that the conditions described by Passarella and co-workers were reproducible, in our hands.²⁴ The first step of the pentacycle formation is the formation of a formamide **149** from methyl ester **53**, and it was this transformation that we first wanted to replicate on triamide **116**. If we could install the required formyl group at the secondary aniline, it would be possible to follow the procedure through to the corresponding pentacycle **147**.

We were apprehensive of utilising these conditions on triamide **116** because we were aware that the inclusion of a greater number of functional groups (compared to methyl ester **53**) could cause complications. So it was not too surprising when the reaction yielded a complex mixture of products. Attempts to separate out these products by preparative thin layer chromatography were ultimately unsuccessful, due to the small quantities of product formed.

Synthesis of carboxyevodiamine methyl ester **54**, as described by Passarella and co-workers

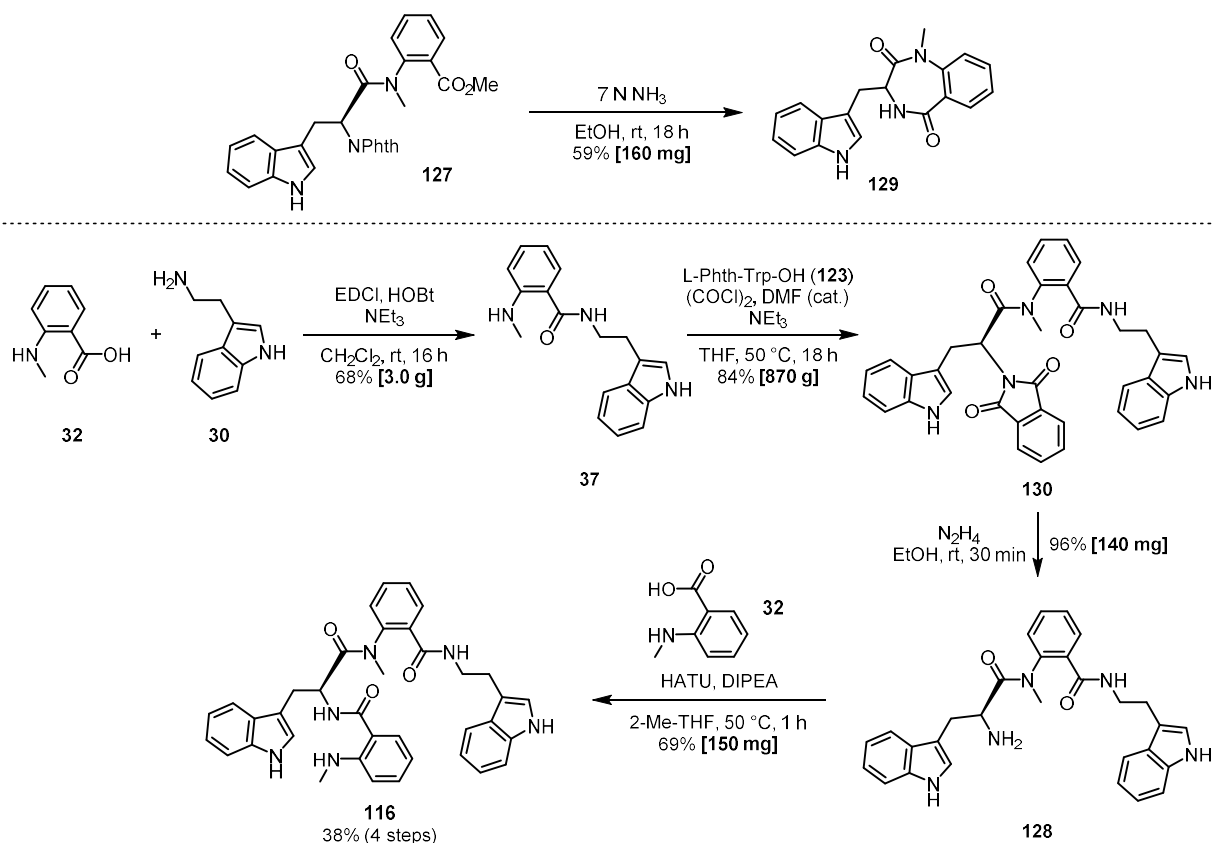


Scheme 81. Inspiration and attempts to install a formamide group to triamide **116**

3.9. Conclusion

Through this chapter we have presented a synthetic plan and the subsequent investigations towards (+)-dievodiamine (**35**). We have taken inspiration from the biology of non-ribosomal peptide synthases.

In order to investigate this, we have developed the synthesis of the mature peptide backbone **116** (Scheme 82). We had to reconsider the original synthetic route due to the unexpected formation of the 7-membered ring **129**. Nevertheless, we were able to make the oligomer **116** in a 38% overall yield (4 steps).



Scheme 82. Summary of the synthetic efforts towards oligomer **116**

Upon trying to functionalise the mature peptide scaffold, we were surprised by its apparent stability to various reaction conditions. Whilst attempting to cyclise the protected peptide **130** with various amide activation methodologies, only hydrolytic cleavage of the starting material under acidic conditions was observed. Nonetheless, we are confident the amide is being activated in some cases, but the combination of a weak nucleophile (amide nitrogen) and the requisite progression through a high energy iminium intermediate prevented any cyclisation from occurring. Attempts to install a C_1 -unit to oligomer **116** were not fruitful. We believe that the use of Lewis acids to activate the electrophilic orthoformate was difficult due to the potential coordinating interactions with the starting material. These, in turn, reduced the nucleophilic starting material's reactivity towards addition to the orthoformate.

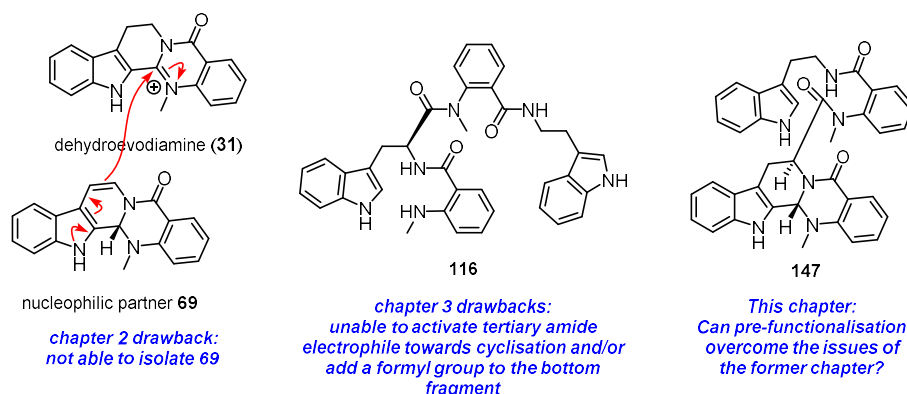
It should be noted that these investigations were not for nought. We were able to conclude that the early installation of the C_1 -unit was necessary to push forward the synthetic effort. As well as this, we are now able to suggest the need for later-stage methyl addition. This would

allow for the cyclisation chemistry discussed in this chapter to be re-investigated by activation of a more reasonable secondary amide electrophile.

4. Convergent Strategy

4.1. Introduction: a revised synthesis starting from (+)-carboxyevodiamine

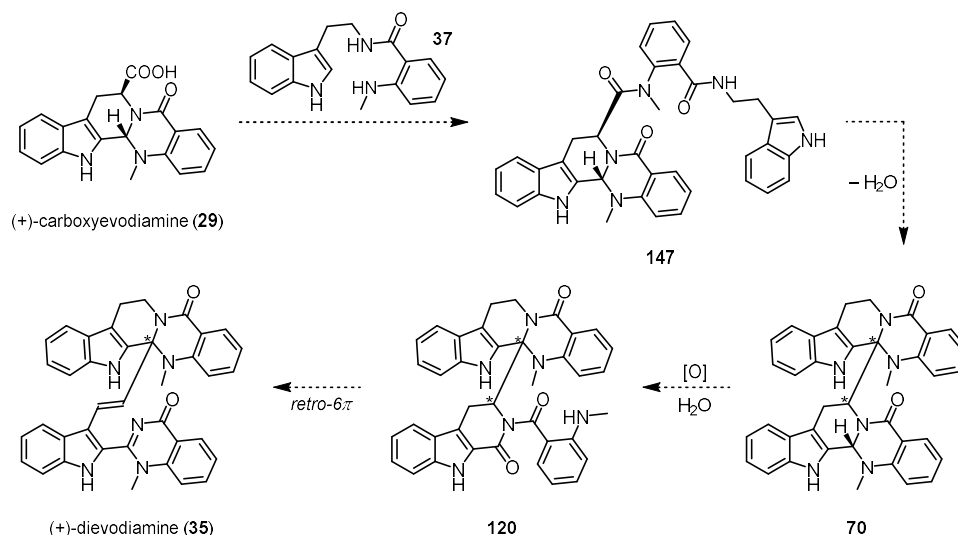
In our previous attempts to synthesise (+)-dievodiamine (**35**) we have focused on dimerisation of two selectively oxidised units of (+)-evodiamine (**27**) (dehydroevodiamine **31** and alkene **69**) or building the complexity out from a peptidic-like backbone **116** (Scheme 83). In the latter study, we had significant issues installing the required C₁-unit to the oligomer **116**. In order to overcome this, we wanted to install the required pentacyclic framework earlier in the synthesis. Therefore, we needed to propose a synthetic strategy in which this complexity is pre-installed before the combination of the two indole-containing units.



Scheme 83. Summary of the aforementioned synthetic challenges and aim of this chapter

A new synthetic route was proposed starting from (+)-carboxyevodiamine (**29**), a known natural product from the *evodia* genus of plants.¹¹⁸ In this proposed biosynthesis, we first form an amide bond between (+)-carboxyevodiamine (**29**) and diamide **37** (Scheme 84). The resulting tertiary amide **147** will have a carbonyl group, which can then act as the corresponding electrophilic carbonyl for the cyclisation of the “top” ring of the natural product. In this proposed route, it was anticipated that point-to-point chirality transfer could be achieved from the stereogenic centre in L-tryptophan (**11**), used to make (+)-carboxyevodiamine (**29**). Cyclisation of the top fragment of intermediate **147** can afford the heterodimer **70**. Furthermore, an oxidation of the bottom ring, followed by hydrolysis would afford a lactam **120**

that is primed to undergo the required cyclisation/retro-6 π cascade, resulting in the formation of (+)-dievodiamine (**35**). Due to the nature of the late-stage combination of the top and bottom fragments of the natural product, our approach can be classified as a convergent strategy.

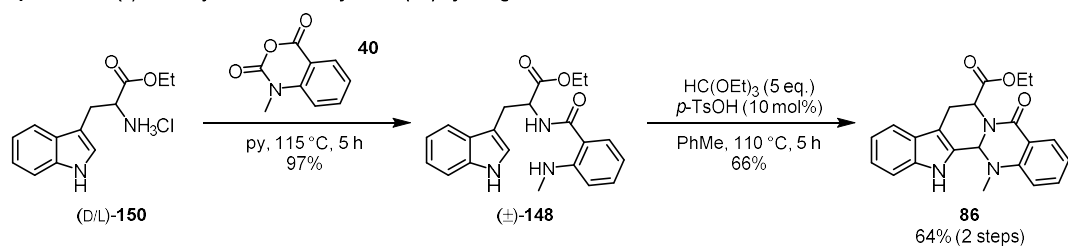


Scheme 84. Proposed "convergent" biosynthesis of (+)-dievodiamine (**35**)

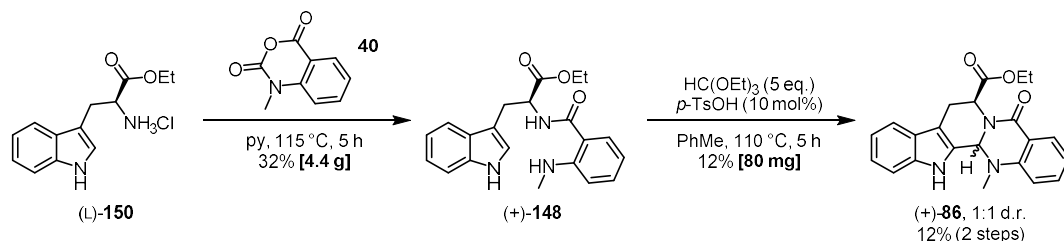
4.2. Synthesis of (+)-carboxyevodiamine

In Chapter 1.7, some of the known strategies towards the synthesis of (+)-carboxyevodiamine (**29**) were briefly mentioned. The shortest formal synthesis of the corresponding ethyl ester **86** was described by Beugelmans–Verrier and co-workers (Scheme 85).¹¹⁷ In this example, carboxyevodiamine ethyl ester (**86**) was synthesised in two steps from the commercially available ($\pm$)-tryptophan ethyl ester hydrochloride (**150**), with an overall yield of 64%. The known intermediate **148** was made through a combination of ($\pm$)-tryptophan ethyl ester hydrochloride (**150**) and *N*-methyl isatoic anhydride (**40**). After this, the aforementioned acid-mediated addition of triethyl orthoformate, followed by cyclisation, gave ($\pm$)-carboxyevodiamine ethyl ester (**86**). Although ($\pm$)-carboxyevodiamine (**29**) was never formally produced by the authors of this paper, a base-mediated hydrolysis of the ester would yield this product.

Synthesis of (±)-carboxyevodiamine ethyl ester (**86**) by Beugelmans–Verrier and co-workers



Attempts to reproduce Beugelmans–Verrier's work using L-tryptophan ethyl ester hydrochloride (**150**)

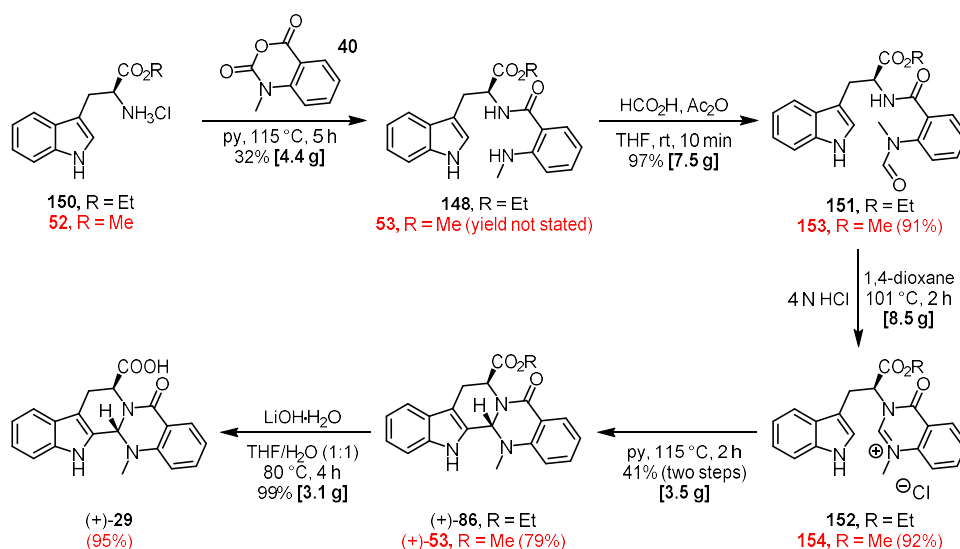


Scheme 85. Inspiration and attempted synthesis of (+)-carboxyevodiamine ethyl ester (**86**) using Beugelmans-Verrier's method

The initial aim was to make the naturally occurring enantiomer (+)-carboxyevodiamine (**29**) and so would need to reproduce the synthesis described by Beugelmans-Verrier and co-worker using the natural, enantiopure L-tryptophan ethyl ester hydrochloride (**150**). Starting the synthesis, we found the conditions for purifying the product obtained from the first reaction to be unreliable, as we only produced 32% yield from the combination of L-tryptophan ethyl ester hydrochloride (**150**) and *N*-methyl isatoic anhydride (**40**). We were not overly concerned about this. The triturated, non-crystalline, product was also of sufficient purity to use. When we tried to add the triethyl orthoformate electrophile, using a *p*-toluenesulfonic acid catalyst, we were met with sluggish reactivity and an overall much lower yield than that reported by Beugelmans-Verrier. However, before chromatographic separation, the overall crude yield of the combined diastereomers was only 12%. Additionally, the diastereomeric ratio was shown to be 1:1 by ¹H NMR analysis. This means that the yield of the desired natural diastereomer was only 6% in the final step. Considering we were not able to reproduce the high yields reported by Beugelmans-Verrier, we opted to move onto an alternative method for preparing (+)-carboxyevodiamine (**29**), previously reported by Passarella and co-workers.²⁴ Although we

mentioned this synthesis earlier (see chapter 3.8), it is sensible to describe the synthesis in more detail and in the context of our own attempts to reproduce the chemistry.

The synthesis starts with the aforementioned combination of L-tryptophan ethyl ester hydrochloride (**150**) and *N*-methyl isatoic anhydride (**40**) (Scheme 86). The resulting amide **148** was formylated almost quantitatively, giving formamide **151**. This material was then cyclised under acidic conditions and the resulting crude quinazolinium chloride **152** underwent a further cyclisation when heated in pyridine, giving (+)-carboxyevodiamine ethyl ester (**86**) (41%, over two steps). Finally, the ester was hydrolysed to give the natural product, (+)-carboxyevodiamine (**29**) in an overall yield of 13% (5 steps). This yield is deflated by the purification of pristine amide **148** (as mentioned earlier), but the chemistry was, most importantly, scalable and reproducible. Where our method differed from that described by Passarella and co-workers, was simply in the choice of ester. Passarella described the synthesis of the corresponding methyl ester **54**, prior to hydrolysis (starting from tryptophan methyl ester **52** and proceeding through intermediates **53**, **153-154**). We found that both esters gave very similar yields and identical diastereomeric ratios (5:1 *cis:trans*). However, the separation of the two diastereomers on a silica column was far easier when the ethyl ester was used. This meant that purification was much easier and required a far lesser weight of silica per column to achieve the required separation.



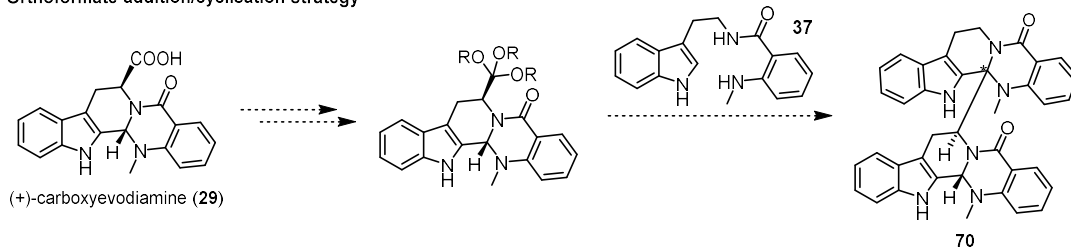
Scheme 86. Our synthesis of (+)-carboxyevodiamine (**29**), with Passarella's method and yields shown in red

With a good method for the synthesis of (+)-carboxyevodiamine (**29**) now available to us, we turned our attention to combining this “bottom” fragment with the “top” fragment.

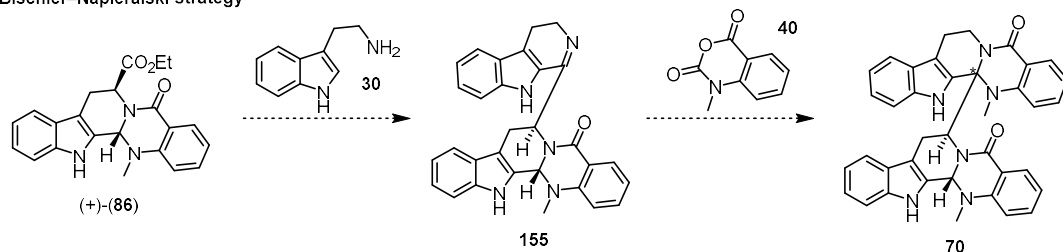
4.3. Direct addition/cyclisation of (+)-carboxyevodiamine to amide **37**

We first wanted to try a one-pot strategy for the combination of the two fragments (+)-**29** and **37**. The two routes available to us were: to convert (+)-carboxyevodiamine (**29**) to a corresponding orthoester to act as the electrophile, or to use (+)-carboxyevodiamine ethyl ester (**86**) as the electrophile in a Bischler–Napieralski type reaction (Scheme 87).

Orthoformate addition/cyclisation strategy



Bischler–Napieralski strategy



*Scheme 87. Two strategies for integrating the (+)-carboxyevodiamine (**29**) carbonyl group into the top-fragment of the natural product scaffold*

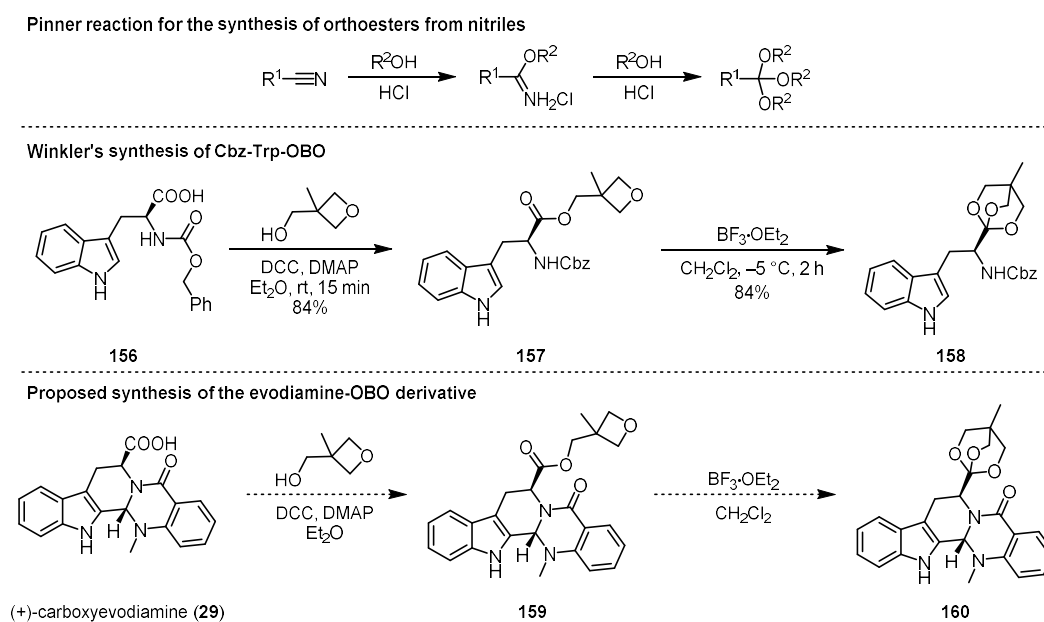
In order to get to the key evodiamine heterodimer **70**, we could try either of these routes. Using the orthoformate strategy would first involve converting (+)-carboxyevodiamine (**29**) to the respective orthoester. The resulting product could then act as a more effective electrophile than the acid itself, or the ethyl ester, in the addition/cyclisation cascade to give the evodiamine heterodimer **70**. The alternative Bischler–Napieralski chemistry is speculative, as we will firstly have to form the amide linkage directly from the ethyl ester (+)-**86** to the amine in tryptamine (**30**), followed by a dehydrative cyclisation to give imine **155**. This route potentially overcomes the issues we saw in Chapter 3.6, as the required cyclisation would use a secondary amide as the electrophile and not have to proceed through a charged iminium intermediate. This could undergo a direct imine acylation reaction with *N*-methyl isatoic anhydride (**40**), followed by cyclisation, to give the key heterodimer **70**.

4.4. Synthesis of (+)-carboxyevodiamine orthoester derivative

Orthoesters have been utilised extensively as a electrophiles for the synthesis of evodiamine. We hypothesis that by synthesising a derivative of (+)-carboxyevodiamine (**29**), in which the

carboxylic acid had been converted to an orthoester, we could activate the compound enough to act as the electrophilic masked-carbonyl for the synthesis of (+)-dievodiamine (**35**).

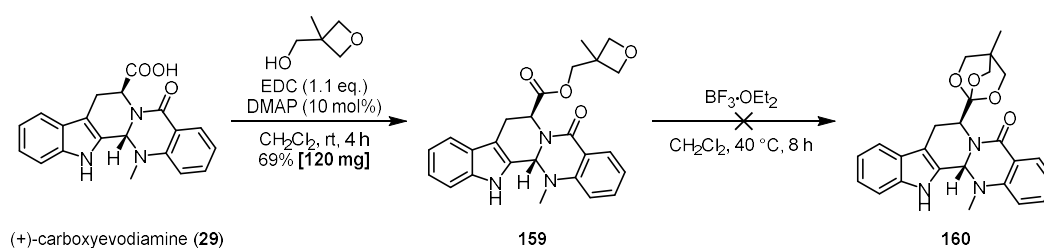
Classically, orthoesters are produced through a Pinner reaction, starting from the corresponding nitrile, using an excess of an alcohol (Scheme 88). This is a simple procedure but it is limited. The harsh acidic conditions required to make orthoesters in this way are not usually compatible with highly functionalised starting materials. We were able to find alternative conditions for the formation of tryptophan-derived orthoesters from Winkler and co-workers.¹¹⁹ In their work, the authors described the conversion of benzyloxycarbonyl protected tryptophan (Cbz-Trp-OH, **156**) to the corresponding oxetane ester **157**. In turn, this was treated with a Lewis acid at low temperature to give the corresponding orthoester **158** in excellent overall yield (71%, 2 steps). The orthoester used here is a common carboxylic acid protecting group, OBO (4-methyl-2,6,7-trioxa-bicyclo[2.2.2]octan-1-yl). This bicyclic orthoester is stable to basic conditions but can be deprotected under acidic conditions.



Scheme 88. Inspiration and proposed synthesis of evodiamine orthoester derivative **160**

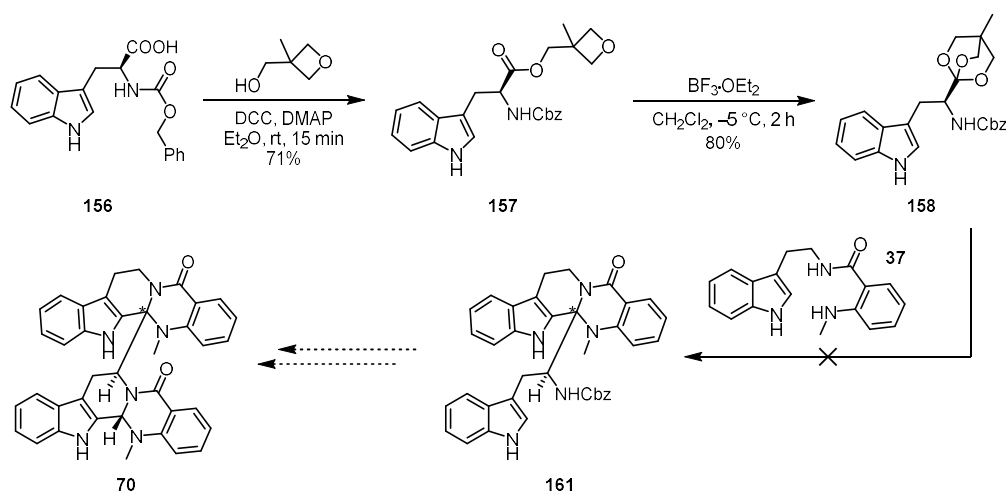
Synthesis of the required carboxyevodiamine oxetane ester **159** with *N,N'*-dicyclohexylcarbodiimide (DCC), using the conditions described by Winkler and co-workers, did not furnish the expected product. This was most likely due to the poor solubility

of (+)-carboxyevodiamine (**29**) in diethyl ether. When changing the solvent to dichloromethane, the required esterification was performed using *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC) (Scheme 89). These subtle changes allowed for the isolation of the required ester in 69% yield. With access to the required oxetane ester **159**, treatment with boron trifluoride etherate was trialled under low temperature. However, the oxetane was stable towards the treatment with Lewis acid and when raising the temperature to 40 °C, only recovery of unreacted starting material was observed.



*Scheme 89. Attempted synthesis of evodiamine OBO orthoester **160***

The Cbz-protected, OBO orthoester **158** was made to test whether the orthoester could act as an electrophile for the required reaction with amide **37**. Following Winkler's procedure, we were able to synthesise the OBO orthoester **158** in 57% yield (2 steps, Scheme 90).¹¹⁹ Adding the required electrophile at this stage means that the bottom fragment would have to be built up from the protected intermediate **161**.



Scheme 90. Planned synthesis of heterodimer **70** from Cbz-Trp-OBO (**158**)

Using acidic conditions (such as *p*-TsOH) to activate the orthoester **158** led to degradation, as the functional group is unstable towards acidic conditions. The use of boron trifluoride etherate to activate orthoesters for addition to amide **37** was also trialled. The orthoester starting material did not degrade using this method, however the anticipated addition was also not observed, and only recovery of the starting materials was obtained.

Using the OBO orthoester **158** as an electrophile was not possible using the conditions trialled. It could be that OBO orthoesters are simply too robust and the desired transformation may only occur if a more reactive trimethyl- or triethyl-orthoester was used instead.¹²⁰⁻¹²¹ With no obvious way to access such orthoesters it was decided that the alternative strategy based on the well-established Bischler–Napieralski reaction should be investigated instead.

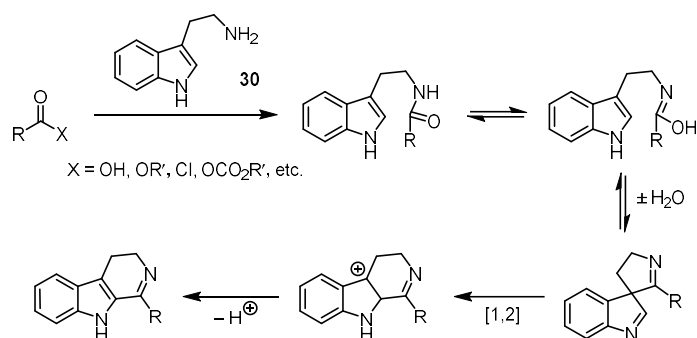
4.5. Bischler–Napieralski strategy

The Bischler–Napieralski reaction has been used extensively in the synthesis of 3,4-dihydro- β -carbolines.¹²²⁻¹²³ In order to utilise the reaction in the synthesis of (+)-dievodiamine (**35**), a number of steps is required (Scheme 91). Firstly, an amide bond has to be formed between tryptamine (**30**) and (+)-carboxyevodiamine (**29**). Ideally, we could install the required linkage directly from (+)-carboxyevodiamine ethyl ester (**86**), to avoid the extra step needed for ester hydrolysis. Following this, the amide carbonyl will require activation

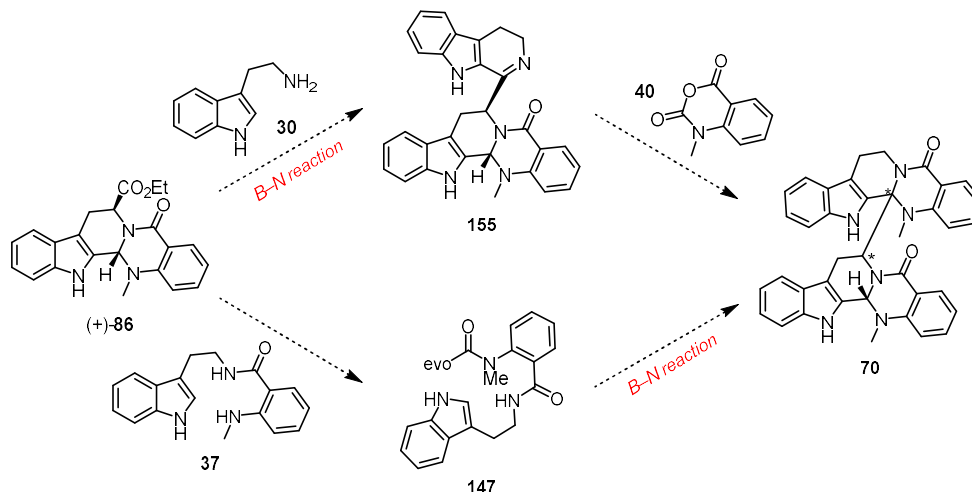
so cyclisation can occur, usually through the C3-position of the indole.¹²⁴⁻¹²⁵ Finally, the reaction will conclude with a [1,2]-shift and the aromaticity is re-established to give the expected product.

The plan for our synthesis was therefore to first prepare the corresponding amide. Either tryptamine (**30**) or amide **37** can be used as the amine for this linkage. If tryptamine (**30**) is used, then the Bischler–Napieralski cyclisation will have to be completed at an early stage. Following this, a unit of *N*-methyl isatoic anhydride (**40**) would have to be added to the resulting imine. However, if amide **37** is to form the amide linkage, then the anthranilate group will already be installed and the Bischler–Napieralski reaction can be considered late-stage in the mechanism.

Bischler–Napieralski reaction mechanism



Proposed synthesis of evodiamine (evo) heterodimer **70** using a Bischler–Napieralski cyclisation



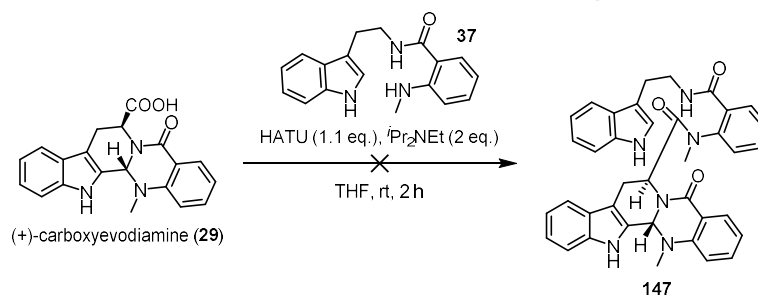
*Scheme 91. Bischler–Napieralski (B–N) reaction mechanism for the synthesis of 3,4-dihydro-β-carbolines, and the proposed strategies for the synthesis of the evodiamine heterodimer **70***

In order to investigate whether either of these routes would yield the desired heterodimer **70**, we screened a number of reaction conditions in parallel using tryptamine (**30**) and amide **37**. Firstly, we tried to simply heat the required coupling partners in toluene using a Dean–Stark set-up. However, our attempts to force the reaction to completion by removal of ethanol was not fruitful.

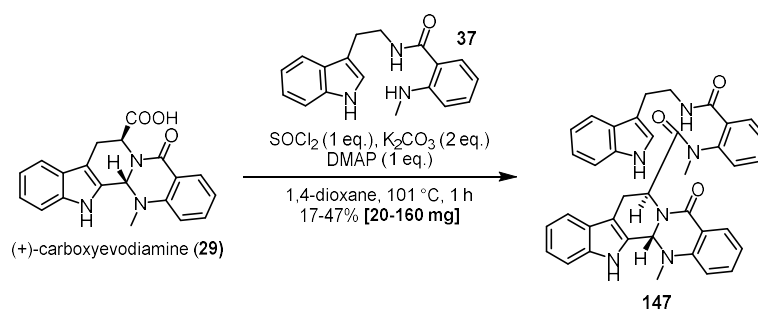
Therefore, we attempted to activate the ester carbonyl group by use of Lewis acids. Our hope was that the required amide would be formed, however if we could force a reaction using amide **37** as the nucleophile then the Lewis acid could also activate the required Bischler–Napieralski reaction. The use of zinc(II) chloride to promote amide formation from esters has been described by Qais and co-workers.¹²⁶ Qais showed that phosphorus oxychloride could be added to initiate a Bischler–Napieralski reaction of the resulting amide. When the conditions were trialled in our systems, we observed no formation of the required amine when using amide **37**. When using tryptamine (**30**) as the amine coupling partner we observed a slow formation of the required amide **147** (8%, after 24 h). This gave us scope for activating the esters directly towards amide bond formation, however the low yield made this method impractical.

In order to explore, more completely, the conditions for a Bischler–Napieralski reaction, a route towards the tertiary amide **147** was required. As shown in Chapter 3.3, the route to synthesise the difficult tertiary amide linkage in the phthalimide protected diamide **130** required the formation of the corresponding acid chloride. The use of thionyl chloride to activate (+)-carboxyevodiamine (**29**) towards the coupling to amide **37**, did not yield consistent results (Scheme 92). Variable yields (17–47%) and issues with scalability of tertiary amide **147** led us to rethink the strategy for this example. It should be noted that (+)-carboxyevodiamine (**29**) has been derivatised by formation of amides using HATU as an activation reagent.²⁴ However, attempts to use these conditions for the coupling with the nucleophile amide **37** resulted in no reaction. Therefore, activation as the acid chloride was still preferable.

Attempt to prepare tertiary amide **147** using HATU as an activation reagent



Preparation of tertiary amide **147** using thionyl chloride

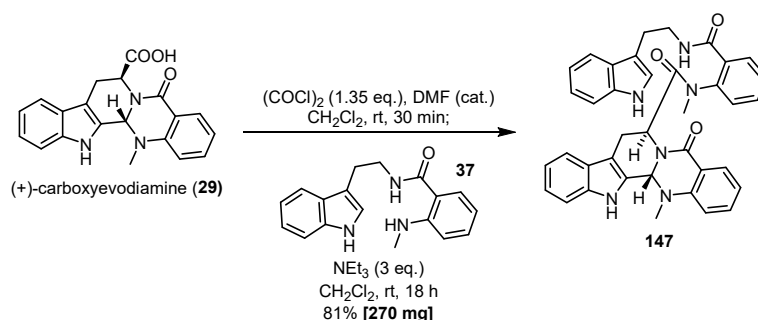


*Scheme 92. Early attempts to prepare tertiary amide **147***

One key observation of our thionyl chloride-mediated chlorination was the effect of dilution on the reaction. The greater the dilution of the reaction, the greater the yield of the isolated product (**147**). The hypothesis was that the formation of acid chlorides could lead to the formation of the lesser electrophilic anhydride. At lower concentrations this dimerisation is disfavoured and so the yield was inflated. It should be noted that the scales for this study were always kept at 50 mg of (+)-carboxyevodiamine (**29**). When scaling up the reaction to 250 mg using our optimised conditions ($c = 0.05\text{ M}$), the yield decreased dramatically to 21%.

Therefore, a method was required for the synthesis of the tertiary amide **147** that could avoid this competing dimerisation pathway. The plan was to slowly produce the acid chloride using a Vilsmeier–Haack reagent. The hypothesis being that by pre-forming the Vilsmeier–Haack reagent and slowly adding (+)-carboxyevodiamine (**29**), the selectivity for formation of the acid chloride over the anhydride could be increased. To our delight, the reaction conversion to the activated species was complete in approx. 1 h, by TLC analysis. After this time, the nucleophilic amide **37** was added alongside triethylamine as a base to quench the formed HCl.

Slow addition of amide **37** allowed for the consistent formation of tertiary amide **147** (81% yield, Scheme 93).

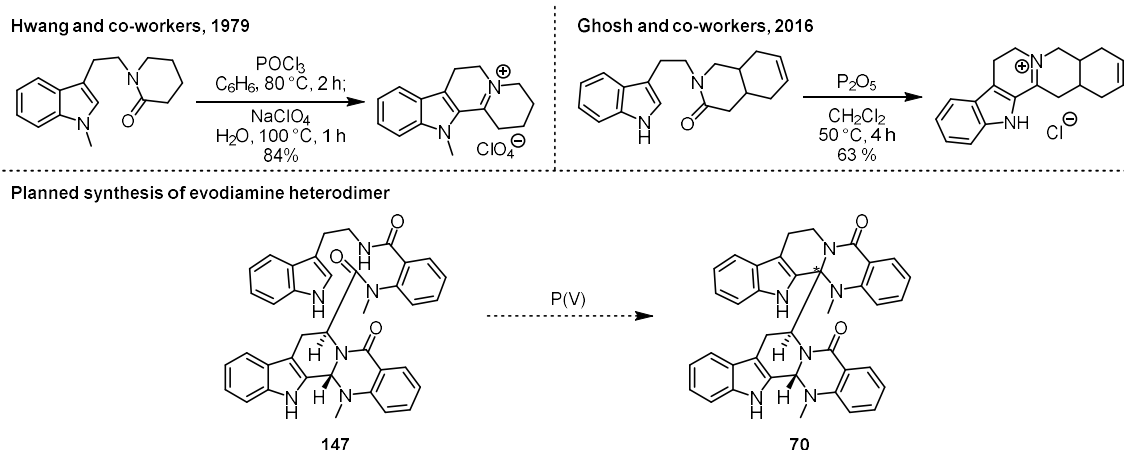


Scheme 93. Synthesis of tertiary amide **147**

With the required starting material in hand, the issue of installing the C₁-unit (as in Chapter 3.8) has been circumvented. The scalability of the reaction was also good enough for screening of Bischler–Napieralski cyclisation.

Of the conditions trialled, some of these conditions involved treating tertiary amide **147** with acid at high temperature.¹²⁷⁻¹²⁸ The material was rather stable to acidic medium, in stark contrast to diamide **130**, with the only result being protonation of the material when hydrochloric (4 M in 1,4-dioxane) or conc. sulfuric acid was used.

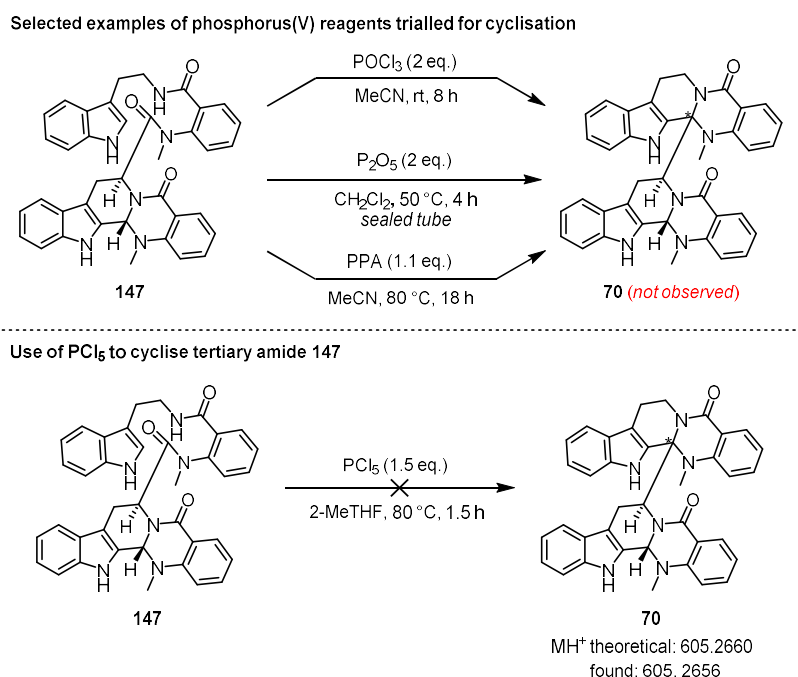
The use of phosphorus reagents for the synthesis of isoquinolines/ β -carboline through the Bischler–Napieralski reaction is well documented. In order to test this using our substrate, we treated tertiary amide **147** with various phosphorus reagents under the conditions known to undergo similar cyclisations at tertiary amides (Scheme 94).



*Scheme 94. Example activation of tertiary amides with phosphorus(V) reagents and our planned synthesis of heterodimer **70** using these reagents*

The use of phosphorus oxychloride was trialled first, as there was good precedent for this reagent facilitating the required reaction. Attempting to heat the tertiary amide **147** with phosphorus oxychloride in benzene, as described by Hwang and co-workers, was not possible due to the insolubility of the starting material in this solvent.¹²⁹ However, changing the solvent to acetonitrile allowed for greater solubility (Scheme 95).¹³⁰⁻¹³² The TLC analysis of this reaction did show full consumption of the starting material. Upon aqueous work-up, the reaction was shown to have returned back to the starting material, as well as some loss of material through complex decomposition. Using phosphorus pentoxide, as described by Ghosh and co-workers, or polyphosphoric acid (PPA) did not result in any reactivity with the starting material.¹³³⁻¹³⁵ Finally, we subjected the starting material to heating with phosphorus pentachloride, which also resulted in the full consumption of the starting material after aqueous work-up. Due to the small scale these test reactions were run at, all of the fractions obtained from the resulting preparative-TLC (PTLC) were analysed by mass spectrometry. The most polar band from the PTLC purification ($R_f = 0.09$, 3% $\text{MeOH}/\text{CH}_2\text{Cl}_2$) was shown to have an exact mass of 605.2656, matching that of the expected heterodimeric product **70** (ESI^+ HRMS, theoretical molecular mass of the expected product **70** is 605.2660, error -0.35 ppm). However, there was not enough material obtained to run the analytical experiments required to verify the expected heterodimeric product **70** was synthesised. When the reaction was

scaled up, in order to obtain more material, the reported reaction could not be repeated. Therefore, the lack of reproducibility with this transformation led us to conclude that the use of phosphorus(V) reagents to facilitate the required Bischler–Napieralski cyclisation., was unlikely to be unsuccessful.



Scheme 95. Attempts to use phosphorus(V) reagents for the cyclisation of tertiary amide **147**

4.6. Cyclisation of the D-ring by methyl group exclusion

Amides are better electrophiles towards addition reactions when they are less substituted (Figure 6). Therefore, trying to activate a tertiary amide towards addition, especially by the poor nucleophiles required to synthesise the required heterodimer precursor **70** (amide nitrogen and indole carbon), was proving to be challenging. To overcome this challenge, it was proposed that removal of the methyl group from the anthranilate aniline could increase the ability of cyclisation. Using the secondary amide **162** means that the required methyl group would simply needed to added at a later-stage in the synthesis.

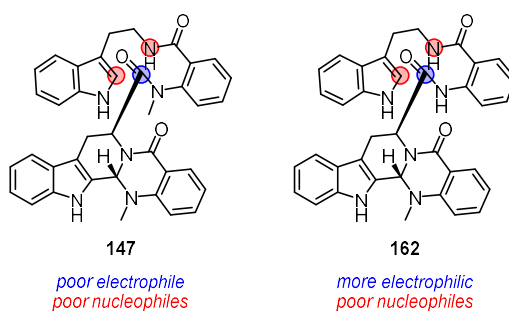
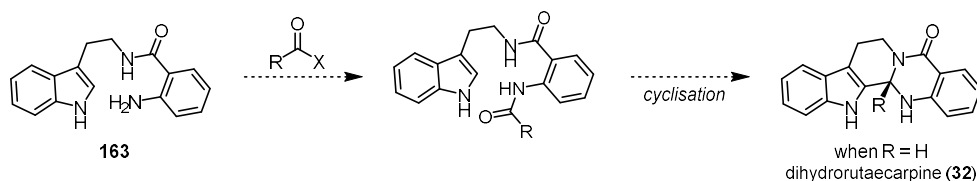


Figure 6. Comparison of tertiary and secondary amides as electrophiles

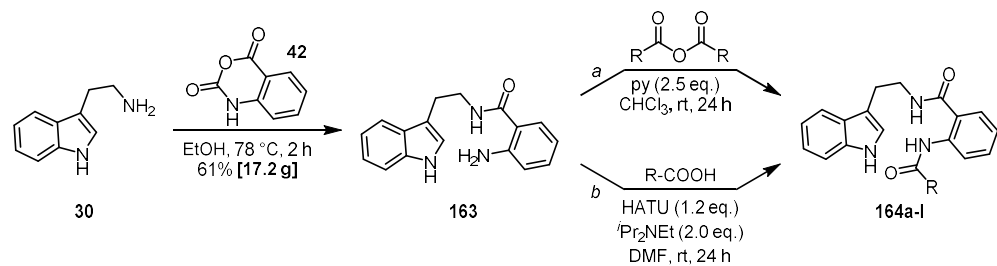
In order to investigate the viability of this hypothesis, a series of model substrates were synthesised. Formally, these compounds would be derivatives of the bioactive natural product, dihydrorutecarpine (**32**) (Scheme 97).¹³⁶ We have proposed a synthesis of dihydrorutaecarpine (**32**) from diamide **163**. Should this cyclisation methodology be successfully developed, a series of natural product derived compounds would result, which could be prepared for bioactivity screening efforts.



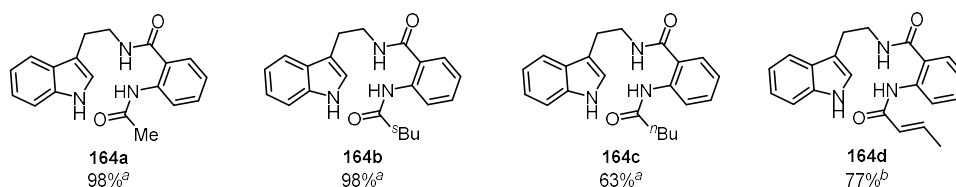
Scheme 96. Proposed synthesis of dihydrorutecarpine-derivatives

The synthesis of the required diamides was achieved through a two-step synthesis starting with the known coupling of tryptamine (**30**) and isatoic anhydride (**42**) (Scheme 97).^{15, 137} Once the primary aniline **163** was synthesised on large-scale, the second step was performed through a coupling with either: a) the corresponding anhydride or b) carboxylic acid using HATU to activate the acid.²⁴

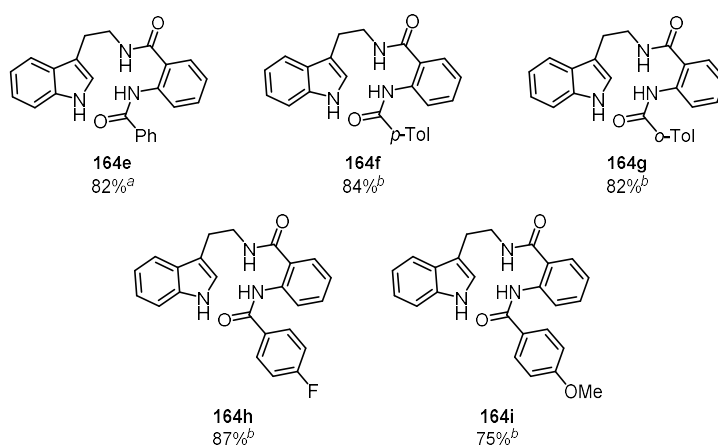
General procedure for the synthesis of diamides **164a-l**



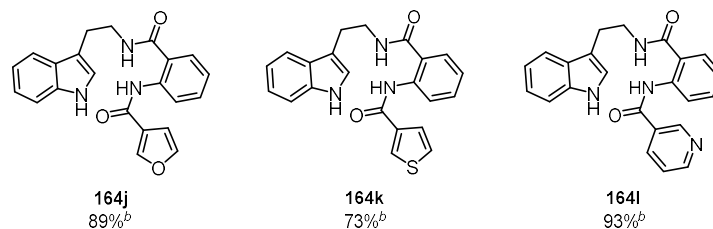
Aliphatics



Aromatics

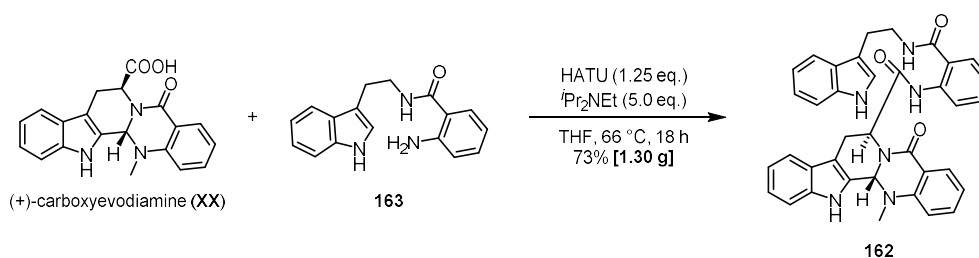


Heterocycles



Scheme 97. Synthesis of diamides **164a-l**

With the view of expanding this methodology beyond the synthesis of (+)-dievodiamine (**35**), we decided to synthesise a variety of diamides **164a-l**. The substrates chosen were designed to fall into three categories of common pharmaceutically relevant substituents: aliphatic (**164a-d**), aromatic (**164e-i**) and heterocycles (**164j-l**). With a variety of diamides in hand, we also synthesised the corresponding (+)-dievodiamine (**35**) entry, using (+)-carboxyevodiamine (**29**) as the respective substituent (Scheme 98).

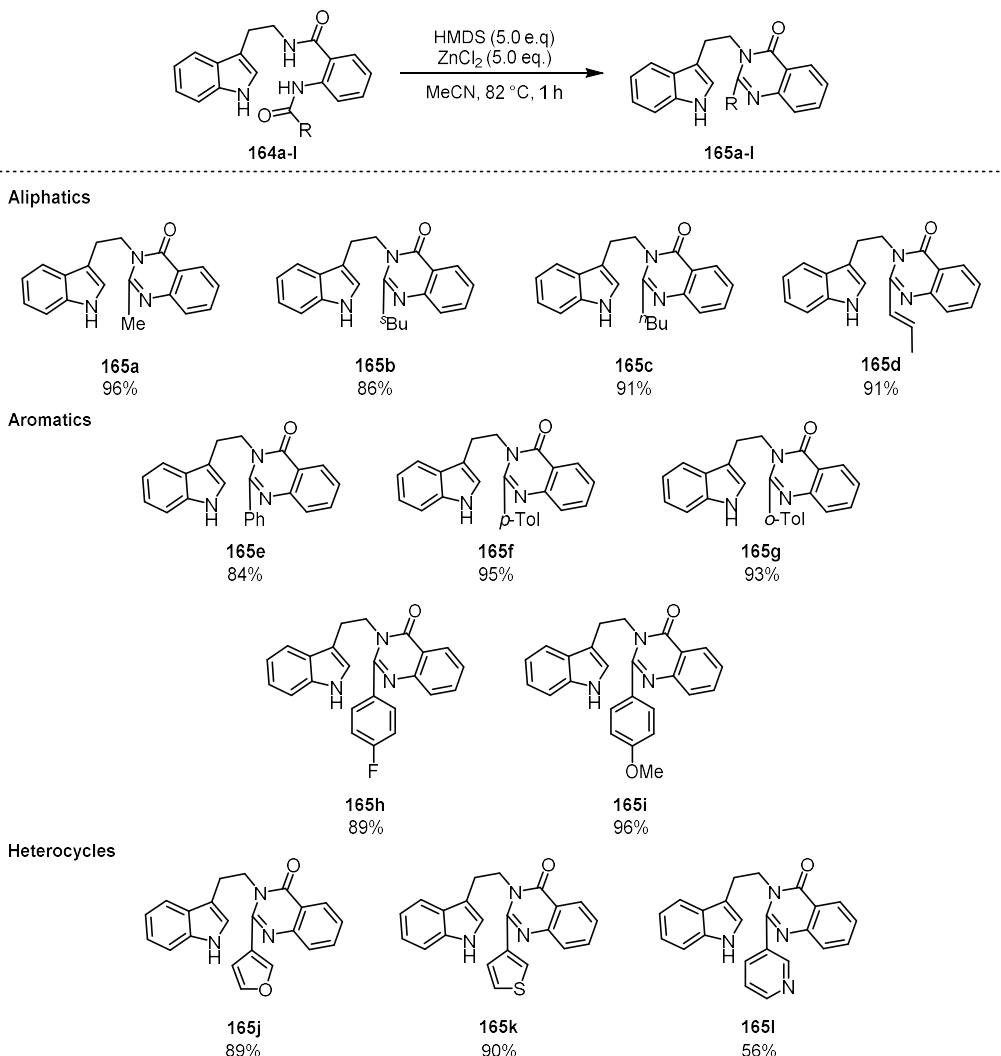


*Scheme 98. Synthesis of the demethylated (+)-dievodiamine diamide precursor **162***

With a number of accessible diamides, conditions for triggering a cyclisation were required. Starting with $\text{ZnCl}_2/\text{HMDS}$, as described by Argade and co-workers, proved to be fruitful.^{111, 114} Upon first screening the required conditions with diamide **164a** ($\text{R} = \text{Me}$), the reaction was found to be complete by TLC analysis within an hour. Upon isolation of the major product, it was interesting to observe that the double cyclisation had not occurred, but rather the formation of quinazolinone **165a** was achieved (Scheme 99). The reaction did require a large excess of the reagents to push the reaction to completion. However, this is offset by excellent yields throughout and the larger variety of non-participating functional groups.

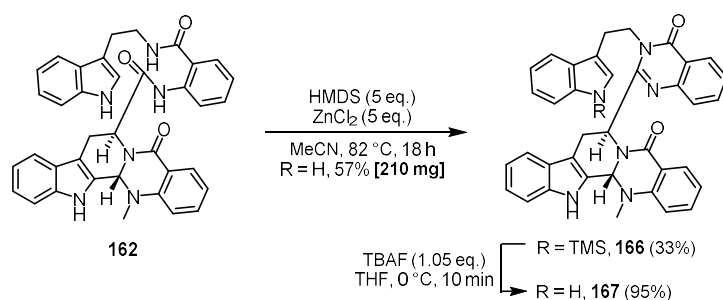
One of the most important observations made from this substrate screen is that these conditions have good functional group tolerance. Furans and thiophenes in particular are not always stable in the presence of Lewis acids. However, with this cyclisation reaction, the quinazolinones **165j** and **165k** were easily synthesised with no major decomposition side-products. Most of the entries required no further purification beyond passing the crude reaction through a silica plug to remove the zinc waste. Even the more sterically hindered entries, such as quinazolones **165b** and **165g**, were isolated in excellent yields. It should be noted that the only reaction that proceeded with <80% yield was the pyridine entry, quinazolinone **165l**.

General procedure for the synthesis of quinazolinones **165a-l**



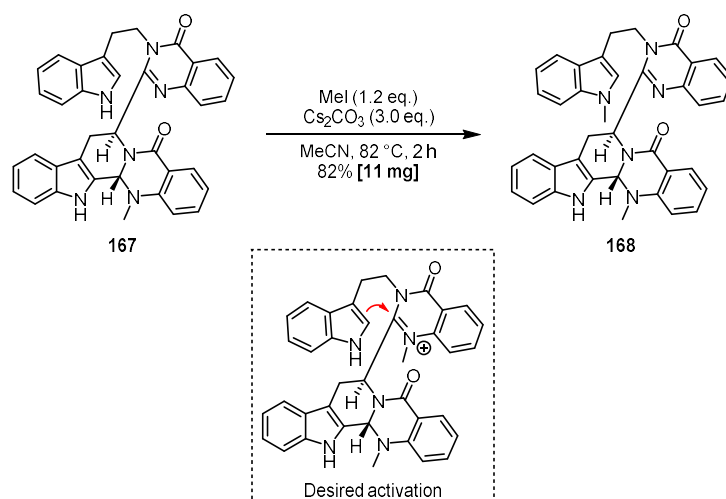
Scheme 99. Synthesis of quinazolinones **165a-l**

Interestingly, when the natural product derived diamide **162** was subject to the same conditions, the TMS-protected product **166** was also observed (Scheme 100). Analysis of the ^1H NMR spectrum showed that this TMS group was bound to the indole nitrogen of the top fragment. This allows us to form a hypothesis that the nitrogen can “extract” the TMS group from the activated amide, possibly under the required longer reaction time. It is also possible that all the quinazolinones synthesised were TMS protected during the reaction, but quinazolinone **166** may be less susceptible desilylation during the basic aqueous work-up. Nevertheless, the TMS group could be easily removed by treatment with tetra-*N*-butylammonium fluoride (TBAF), giving the corresponding free bis-indole quinalzolinone **167**.



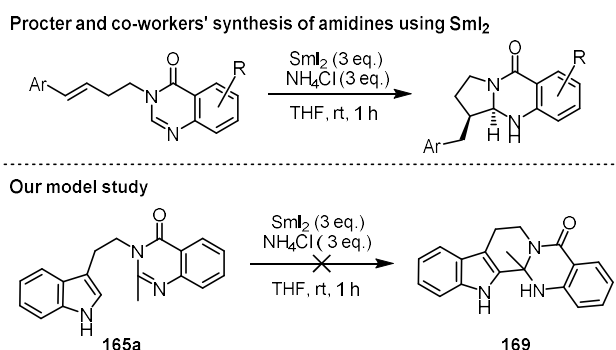
Scheme 100. Synthesis of quinazolinone **167** and TMS-protected quinazolinone **166**

Although the required dehydration and first cyclisation was achieved, the isolated quinazolinones needed to be further activated towards cyclisation with the indole. First, protonation of the quinazolinone nitrogen was investigated as a method for activating the functional group further as an electrophile.^{24, 127} Treatment of the substrate with both acidified methanol (HCl/MeOH) and dry HCl (4 M in 1,4-dioxane) showed the compound was very stable to these conditions. Heating the substrate at reflux in acidic 1,4-dioxane over 3 days, still allowed for almost quantitative recovery of starting material. Treatment of the quinazolinone **167** with Lewis acidic boron trifluoride etherate was attempted, but resulted in no reaction. We would have anticipated that if Lewis acidic conditions would facilitate this reaction, then it would have occurred during the prior step, when excess zinc(II) chloride was used. However, trialling a vastly different Lewis acid was necessary to investigate this route fully. Finally, it was envisioned that activation of the quinazolinone nitrogen by methylation could trigger the cyclisation (Scheme 101). Doing this would also result in a product with the methyl group installed at the required position for the natural product. Treatment of the starting material with methyl iodide and caesium carbonate resulted in the formation of the methylated indole product **168**.¹⁶ Interestingly, only the methylation of the top fragment indole was observed, similar to the TMS protection noted earlier.



Scheme 101. Observed vs desired reactivity of quinazolinone **167** with MeI/Cs₂CO₃

We next moved our attention towards the use of radical-mediated cyclisation of quinazolinone **167**. Use of samarium(II) iodide as a radical initiator for cyclisation chemistry in natural product synthesis is well documented and has been the subject of numerous excellent reviews.¹³⁸⁻¹⁴¹ Taking inspiration from the work of Procter and co-workers, slow addition of SmI₂ in the presence of ammonium chloride (proton source) was trialled using **165a** as a model substrate.¹⁴² Although a non-persistent colour change was observed upon addition of SmI₂ at low temperature, suggesting the formation of a reactive radical species, there was no reactivity observed using this method (no **169** being formed). It is possible that the rate of radical quenching was much faster than that of cyclisation, considering that Procter and co-workers exclusively reported the formation of more kinetically favoured ring closures.

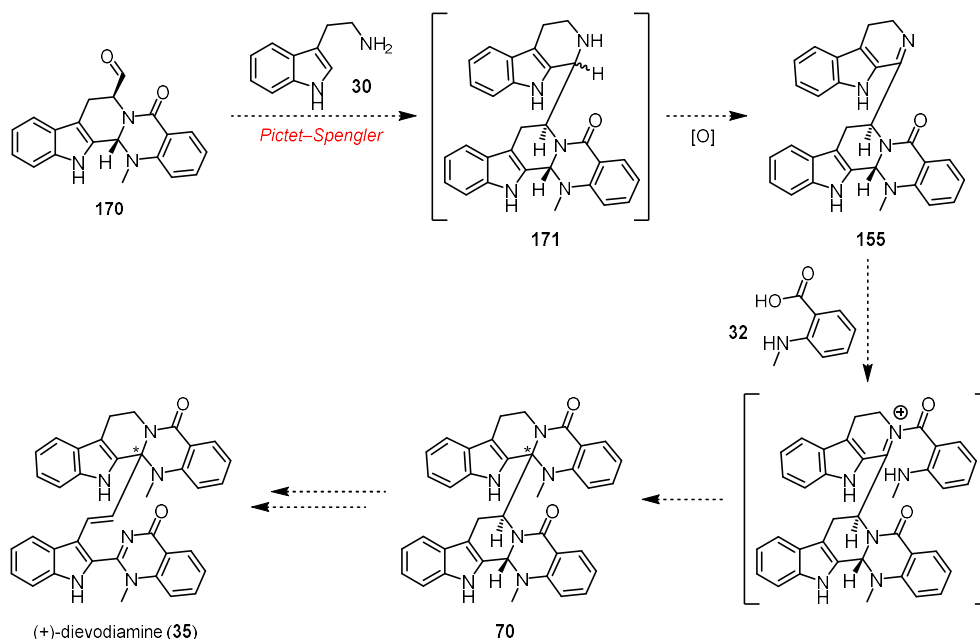


Scheme 102. Model study of SmI₂-mediated reductive cyclisations

It should be mentioned that all of the trialled cyclisation strategies were run in duplicate alongside quinazolinone **165a** (R = Me) and no difference in reactivity was observed.

4.7. Using a Pictet–Spengler strategy for cyclisation of the C-ring

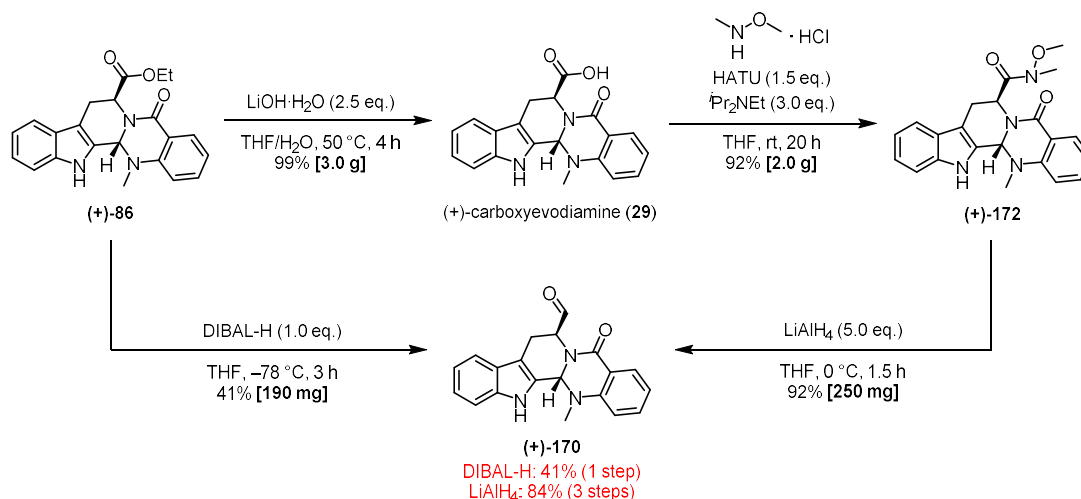
As the quinazolinone intermediate seemed to be stable towards a late-stage C-ring closure, our attention turned to closing this ring earlier in the synthesis. In order to achieve this, a route was envisaged starting with the formation of an aldehyde **170** derived from (+)-carboxyevodiamine (**29**) (Scheme 103). Following this, a Pictet–Spengler reaction between aldehyde **170** and tryptamine (**30**) would give tetrahydro- β -carboline **171**. Following an oxidation the corresponding cyclic imine **155** could be obtained. From here, activation of the compound as an acyl iminium using *N*-methyl anthranilic acid (**32**) could result in D-ring cyclisation. Finally, the evodiamine heterodimer **70** could be oxidised further and undergo the required deprotonation/retro-*aza*-6 π electrocyclicisation to give (+)-dievodiamine (**35**).



Scheme 103. Pictet–Spengler strategy for the synthesis of (+)-dievodiamine (**35**)

The synthesis of aldehyde **170** started first from (+)-carboxyevodiamine (**29**) by formation of the corresponding Weinreb amide (**172**) (Scheme 104). This was achieved by activation of the acid (+)-**29** with HATU and coupling with *N,O*-dimethylhydroxylamine hydrochloride, to give a

single diastereomer (*trans*). This material was converted to the required aldehyde **170** by reduction, using modified conditions from Sperry and co-workers, with lithium aluminium hydride.¹⁴³ Using this method, aldehyde **170** was obtainable in 84% yield, over three steps.



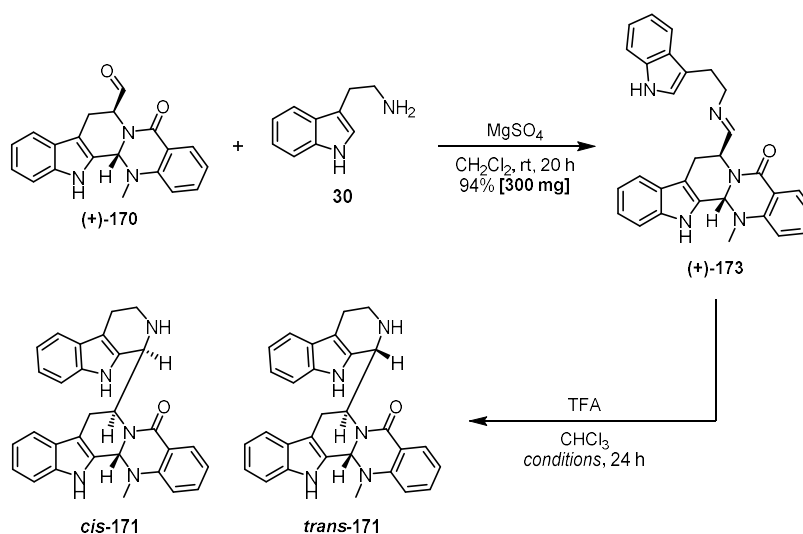
Scheme 104. Synthesis of aldehyde **170**

In order to investigate the possibility of lowering the step-count, a direct reduction of (+)-carboxyevodiamine ethyl ester (**84**) was trialed. By dropwise addition of DIBAL-H to a cooled solution of ethyl ester (+)-**84**, the corresponding aldehyde **170** was isolated in 41% yield. During this synthesis the yield was affected by mass being lost in the work-up, as well as over-reduction to the corresponding alcohol after 3 hours which hindered the full conversion of the starting material.

The resulting aldehyde **170** was unable to undergo the required Pictet–Spengler reaction with tryptamine (**30**), when stirred with various acid catalysts. It was theorised that this was due to the tryptamine (**30**) being readily protonated, thereby preventing reactivity. Removal of the acid and simply stirring the components overnight, in the presence of excess magnesium sulfate, allowed for the quantitative isolation of imine **173** (Table 4). Treatment of this with trifluoroacetic acid (TFA) resulted in the stepwise formation of the expected Pictet–Spengler cyclisation product, 1,2,3,4-tetrahydrocarboline **171**. However, depending on the equivalents of TFA used and whether molecular sieves were added, significantly different results were

observed. If catalytic TFA was used (Table 4, entries a/d), no reaction was observed on the allowed time-scale and the resulting crude mixture was hydrolysed back to aldehyde **170** and tryptamine (**30**) upon aqueous work-up. When one equivalent of TFA was employed, the reaction occurred smoothly and gave a 2.9:1 mixture of *cis/trans* diastereomers (Table 4, entry b). Using excess TFA drastically reduced the yield of the reaction due to the formation decomposition products (Table 4, entry c), although a greater proportion of the desired product was shown to be the *cis* isomer (d.r. 6.5:1 *cis/trans*). Addition of molecular sieves did not affect the outcome of the reactions (Table 4, entries e-f). Having screened the equivalents of acid, an attempt of the reaction at larger scale was shown to require a small excess of TFA to allow for the complete conversion of starting material. In this case 1.5 equivalents of TFA were used and the reaction was high yielding and resulted in the same d.r. as when 1 equivalent was used (Table 4, entry g).

Table 4. Synthesis of 1,2,3,4-tetrahydrocarboline **171** by a stepwise Pictet–Spengler reaction and effect of reaction conditions on yield and diastereomeric ratio of *cis:trans* isomers



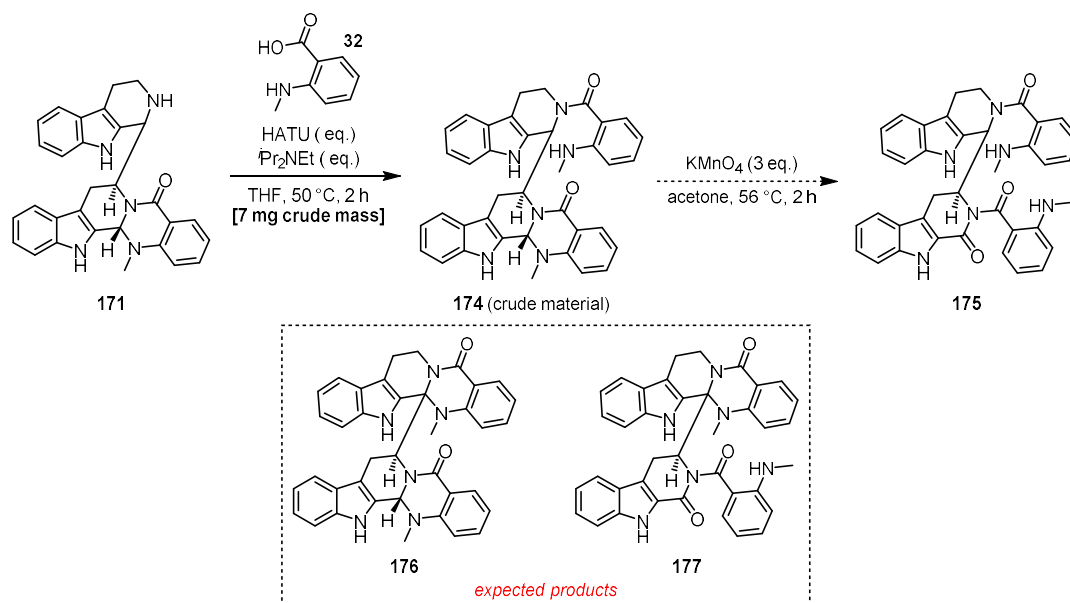
Entry	eq. TFA	Conditions	XX Yield / %	Observations ^a
a	0.1	0 °C to rt, 10 mg scale	0	After work-up, only hydrolysis back to 170
b	1.0	0 °C to rt, 10 mg scale	71	d.r. 2.9:1 (<i>cis:trans</i>)
c	10	0 °C to rt, 10 mg scale	34	d.r. 6.5:1 (<i>cis:trans</i>) Some decomposition observed
d	0.1	0 °C to rt, mol. sieves 10 mg scale	0	After work-up, only hydrolysis back to 170
e	1.0	0 °C to rt, mol. sieves 10 mg scale	67	d.r. 2.5:1 (<i>cis:trans</i>)
f	10	0 °C to rt, mol. sieves 10 mg scale	22	No <i>trans</i> isomer observed More decomposition observed
g	1.5	0 °C to rt, 200 mg scale	83	d.r. 2.9:1 (<i>cis:trans</i>) ^b

^a All ratios from ^1H NMR spectra after purification by PTLC

^b Entry g was purified by flash column chromatography

From this intermediate, it was proposed that the required oxidation chemistry be done after the addition of the second *N*-methyl anthranilic acid (**32**) unit. This was achieved using our established HATU coupling conditions, to give access to tertiary amide **174** (Scheme 105). The product of this reaction was analysed by NMR spectroscopy and mass spectrometry. Although, sufficient evidence was gathered that the reaction was successful (exact mass found = 607.2719 ppm, 1.32 ppm mass error), the complex mixture of diastereomers isolated were not separated and full characterisation was not possible. With a crude sample of this advanced intermediate **174** in hand, it was proposed that treatment with potassium permanganate would facilitate the required oxidation chemistry. Treatment of the

substrate to the oxidation conditions from Chapter 2.10, gave a mixture of products. One of these compounds was tentatively assigned as the lactam **175**. Unfortunately, this compound was not able to be fully characterised due to time constraints, however the mass spectroscopy matched that of oxidised product **175** (0.23 ppm mass error). There was no evidence of oxidation of the top fragment seen by the mass spectroscopy of any of the isolated products.



Scheme 105. Synthesis of tertiary amide **174** and proposed oxidative cyclisation products **176** and

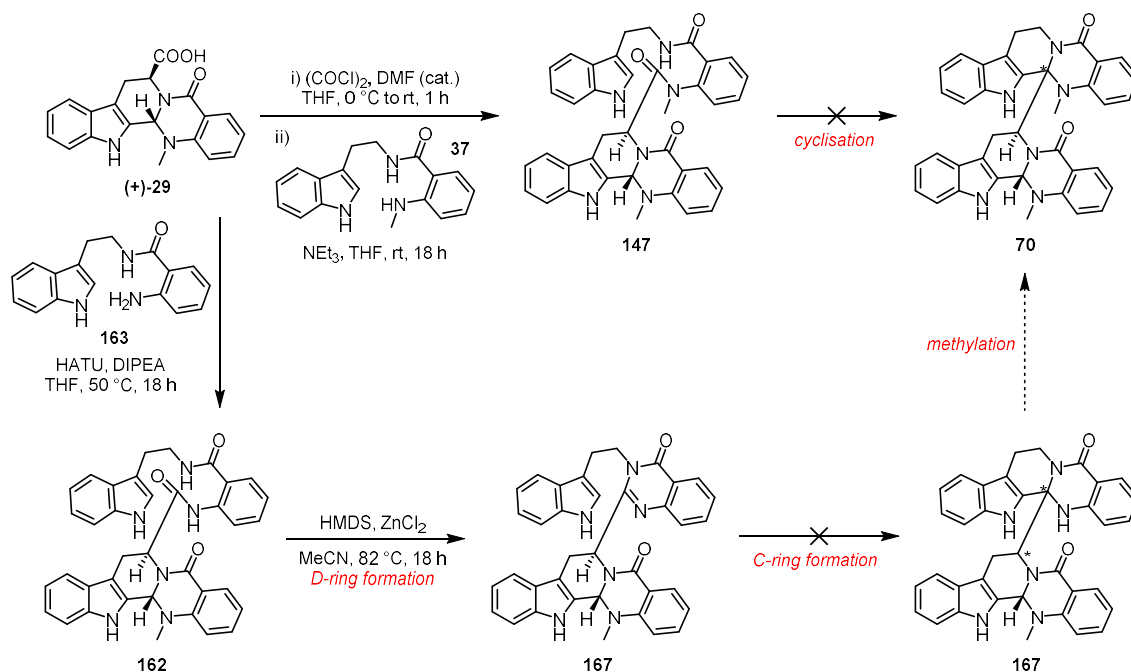
177

4.8. Conclusion

In this chapter, the use of (+)-caroxyevodiamine (**29**) was conceptualised as the electrophilic partner for the synthesis of (+)-dievodiamine (**35**). The synthesis of (+)-caroxyevodiamine (**29**) was achieved in a 5-step sequence, with an overall yield of 13% yield. The ethyl ester precursor (+)-**86** was utilised during the synthesis due to ease of separation of the resulting diastereomers.

The addition of the (+)-caroxyevodiamine (**29**) unit to the tryptamine/anthranilate amide **37** was achieved by formation of the corresponding acid chloride (Scheme 106). Attempts to cyclise the top fragment of the resulting diamide **147** through a Bischler–Napieralski reaction was shown to be unsuccessful. However, by using the corresponding secondary amide **162**,

without the methyl group, it was possible to trigger a cyclisation using a combination of HMDS/ZnCl₂. This would suggest that the activation of this tertiary amide was difficult when attempting carbonyl activation with phosphorous(V) reagents. Either way, the C-ring was unable to be formed even when starting from the secondary amide, suggesting that the resulting quinazolinone **167** required further activation to cyclise with the indole moiety.



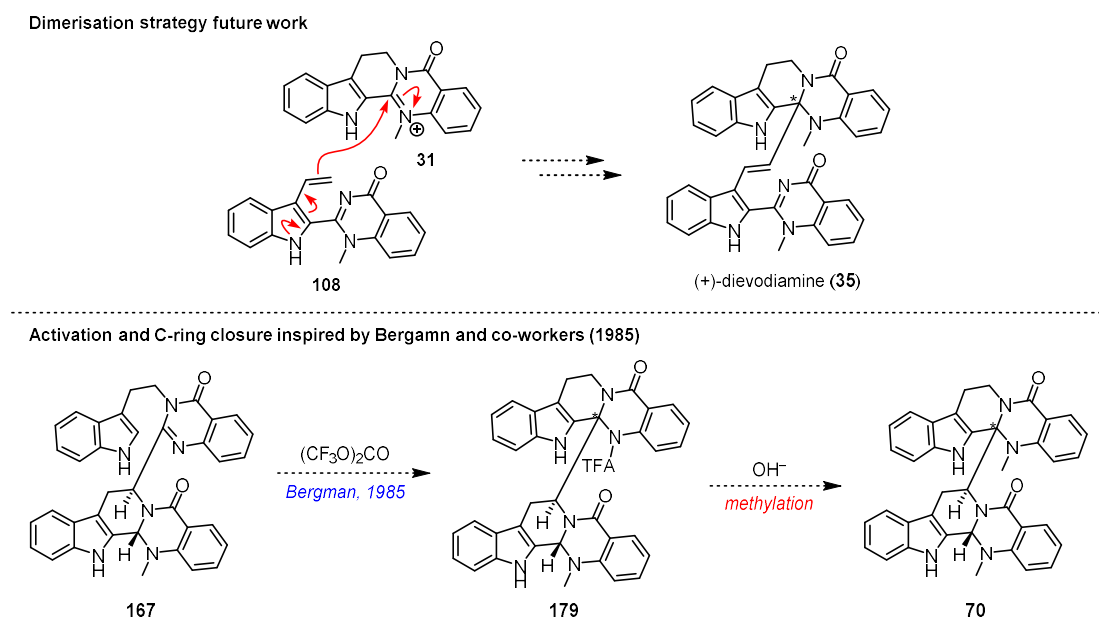
Scheme 106. Summary of top fragment cyclisation chemistry

An alternative route was also presented in which the C-ring was cyclised before the D-ring, by utilisation of a Pictet–Spengler reaction. In order to achieve this, the reduction of (+)-carboxyevodiamine (**29**) to the corresponding aldehyde **170** was achieved in an excellent yield of 81%, over 3 steps. Having cyclised the C-ring, addition of the anthranilate group to the corresponding 1,2,3,4-tetrahydrocarboline **171** was achieved. However, the initial oxidation chemistry attempted lead to decomposition of the small amount of material available with no time remaining in the laboratory to proceed.

4.9. (+)-Dievodiamine future work

The synthesis of (+)-dievodiamine (**35**) has been investigated through three major routes: dimerisation of selectively oxidised evodiamine derivatives (Chapter 2), linear peptidic backbone functionalisation (Chapter 3), and convergent coupling of (+)-carboxyevodiamine (**29**) to the top fragment (Chapter 4).

The dimerisation route was shown to be unsuccessful as the nucleophilic alkene partner **69** was difficult to isolate. In order to further pursue this route, it would be necessary to synthesise this intermediate. Once achieved, the dimerisation could be investigated, although the reaction would have to be rendered enantioselective through manipulation of the reaction environment (chiral auxiliaries/additives).¹⁴⁴⁻¹⁴⁸ Furthermore, the use of alkene **108**, the product of the initial deprotonation/retro-6 π electrocyclic ring-opening discovery, as a nucleophile for the vinylogous Mannich reaction could be explored (Scheme 107).



Scheme 107. Potential future work towards the synthesis of (+)-dievodiamine (**35**)

Attempts to install the required C₁-unit to the oligomeric intermediate **116** were shown to only result in recovery of starting material. As well as this, efforts towards the cyclisation of the top fragment were unfruitful leading to the use of (+)-carboxyevodiamine (**29**) as a functionalised

C₁-unit. Coupling this with aniline **163** gave a secondary amide **162** that was further cyclised using HMDS/ZnCl₂, giving quinazolinone **167**. Efforts are ongoing to facilitate the cyclisation of the C-ring. Thus far, the activation of the electrophilic quinazolinone **167** by acid catalysis, or deprotonation of the indole to increase the relative nucleophilicity, has been trialled. Alternatively, the quinazolinone **167** could be activated through the formation of the corresponding TFA tetravalent species (Scheme 107).¹⁴⁹⁻¹⁵³ Bergman and co-workers used this strategy for the closure of the C-ring in the synthesis of rutaecarpine (**28**).¹⁵ The cyclisation mechanism has not been explored but is suggested to go through an *N*-acyl iminium species. Therefore, it would be possible that the TFA protected species **179** would be formed in the process, however this is expected to be cleavable by base hydrolysis.

5. Experimental

^1H NMR spectra were recorded at 600 MHz on a Bruker 600 spectrometer with a AVANCE 3HD console, at 500MHz on Ascend 500 spectrometers with AVANCE 3 and AVANCE 3HD consoles, and at 400MHz on a Bruker 400 spectrometer with AVANCE 3 console. Residual solvent peaks were used as an internal reference for ^1H NMR spectra (CDCl_3 δ 7.26 ppm, CD_2Cl_2 δ 5.32 ppm and $(\text{CD}_3)_2\text{SO}$ δ 2.50 ppm). Coupling constants (J) are quoted to the nearest 0.1 Hz. ^{13}C NMR spectra were recorded at 151 MHz on a Bruker 600 spectrometer with an AVANCE 3HD console, 126 MHz on Ascend 500 spectrometers with AVANCE 3 and AVANCE 3HD consoles, and at 101 MHz on a Bruker 400 spectrometer with AVANCE 3 console. Solvent peaks were used as an internal reference for ^{13}C NMR spectra (CDCl_3 δ 77.16 ppm, CD_2Cl_2 δ 54.00 ppm and $(\text{CD}_3)_2\text{SO}$ δ 39.52 ppm).

IR spectra were recorded as neat samples on a Shimadzu IR affinity-1 FTIR spectrometer fitted with an ATR attachment. Unless stated otherwise, the IR spectra were run as thin film directly applied to the ATR attachment.

ESI spectra were recorded on a Bruker microTOF, calibrated with sodium formate clusters, with data analysis performed using Data Analysis 4.1 (Bruker Daltonics).

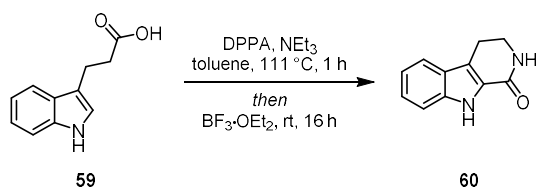
TLC analyses were performed on Merck silica plates coated with silica gel 60 F254 (0.2mm) and were visualised with UV light and by staining with *p*-anisaldehyde or KMnO_4 standard TLC stain solutions, followed by heating. Flash chromatography was performed using Merck silica gel 60 (40–63 μm).

Optical rotations were recorded using a Bellingham Stanley ADP450 polarimeter with a Bellingham Stanley 0.5 mL cell ($l = 0.25$ dm). Concentrations (c) are reported in g/100 mL.

Analytical chiral HPLC was conducted using a modular Shimadzu system using a LC-20AD pump, DGU-20A5R degassing unit, SIL-20A HT autosampler, CTO-20A column oven, SPD-20A UV/Vis detector and CDM-20A communications module.

Unless stated otherwise, reactions were performed under a positive pressure of dry nitrogen. For reactions performed under anhydrous reaction conditions, reaction vessels were dried with a heat gun under vacuum prior to use, and anhydrous solvents were used throughout. Reactions were run using freshly distilled solvents, unless stated otherwise. Solvents and reagents dried over 4 Å molecular sieves were dried for at least 24 h before use. "Wet" solvent refers to non-distilled solvents taken from bottles at least 1 month after opening.

5.1. 1,2,3,4-Tetrahydronorharman-1-one (60)



Compound **60** was made according to known literature procedure from Taylor/Unsworth and co-workers.²⁷ All the data below matches those reported in the literature for the title compound.

Diphenylphosphoryl azide (DPPA, 3.42 mL, 15.9 mmol) was added dropwise to a stirred solution of indole-3-propanoic acid (3.00 g, 15.9 mmol) and triethylamine (2.24 mL, 15.9 mmol) in toluene (50 mL). This was stirred at reflux for 1 h, after which the solvent was removed under reduced pressure. The resulting residue was cooled in an ice-bath and BF₃·OEt₂ (7.95 mL, 193 mmol) was added. Upon formation of a homogenous solution, the reaction was slowly warmed to room temperature and stirred for 16 h, after which aq. NaOH (1 M, approx. 100 mL) until pH 9 and EtOAc (70 mL) was added. The resulting solution was stirred vigorously for 1 h, after which extraction from EtOAc (3 × 70 mL) was performed. The combined organic extracts were washed with brine (100 mL), dried over Na₂SO₄ and the filtrate concentrated under reduced pressure. The resulting solid was recrystallised, by slow-evaporation from EtOAc, to give the title compound as a crystalline white solid (2.80 g 14.9 mmol, 94 %).

¹H NMR (500 MHz, DMSO-*d*₆) δ 11.57 (s, 1H), 7.58 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.54 (d, *J* = 2.7 Hz, 1H), 7.39 (dt, *J* = 8.3, 1.0 Hz, 1H), 7.21 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.05 (ddd, *J* = 8.0, 6.9, 1.0 Hz, 1H), 3.51 (td, *J* = 7.0, 2.6 Hz, 2H), 2.91 (t, *J* = 6.9 Hz, 2H);

¹³C NMR (126 MHz, DMSO) δ 161.6, 136.9, 127.0, 124.7, 123.8, 119.9, 119.2, 117.9, 112.3, 40.9, 20.1;

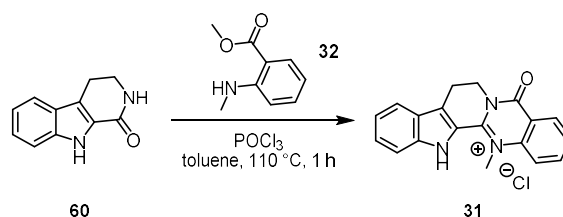
HRMS (ESI) *m/z* calcd for C₁₁H₁₁N₂O⁺ [*M* + *H*]⁺ 187.0866, found 187.0870 (mass error 2.14 ppm);

IR 3481, 2930, 2863, 1656, 1550, 1517, 1452, 1411, 1302, 872, 756 cm⁻¹;

R_f 0.35 (EtOAc);

M.P. 183-185 °C (EtOAc).

5.2. Dehydroevodiamine (**31**)



Compound **31** was made according to known literature procedure from Taylor/Unsworth and co-workers.²⁷ All the data below matches those reported in the literature for the title compound.

Dimethyl anthranilate (0.64 mL, 4.36 mmol) was added to a stirred solution of lactam **60** (600 mg, 3.26 mmol) in toluene (30 mL). To this solution, phosphorus(V) oxychloride (2.05 mL, 21.8 mmol) was added dropwise and the resulting mixture heated for 1 h. After this time, the solution was cooled and poured into ice-water (130 mL). The resulting precipitate was isolated by filtration and washed with water (75 mL). The product was collected with MeOH (100 mL), concentrated under reduced pressure and dried under high vacuum to give the title compound as a yellow solid (707 mg, 2.28 mmol, 70%).

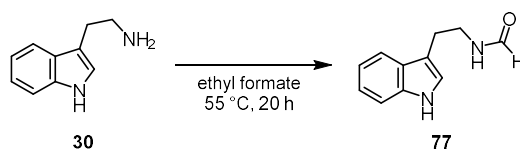
¹H NMR (400 MHz, $\text{DMSO}-d_6$) δ 12.95 (s, 1H), 8.34 (dd, $J = 7.9, 1.5$ Hz, 1H), 8.23 – 8.07 (m, 2H), 7.87 (d, $J = 8.1$ Hz, 1H), 7.80 (ddd, $J = 8.0, 7.0, 1.0$ Hz, 1H), 7.76 – 7.72 (m, 1H), 7.51 (ddd, $J = 8.4, 6.9, 1.1$ Hz, 1H), 7.26 (ddd, $J = 8.0, 6.9, 0.9$ Hz, 1H), 4.46 (dd, $J = 7.6, 6.3$ Hz, 2H), 4.43 (s, 3H), 3.38 – 3.26 (m, 2H);

¹³C NMR (126 MHz, DMSO) δ 158.29, 150.08, 141.50, 139.73, 136.73, 130.24, 128.73, 128.67, 127.74, 123.36, 121.63, 121.60, 120.17, 118.78, 118.61, 113.68, 42.12, 41.02, 18.56;

HRMS (ESI) m/z calcd for $\text{C}_{19}\text{H}_{17}\text{N}_3\text{O}^+$ $[\text{M} + \text{H}]^+$ 302.1288, found 302.1292 (mass error 1.32 ppm);

IR 1697, 1549, 1504, 1332, 1202, 1111, 769, 697 cm^{-1} .

5.3. Formamide **77**



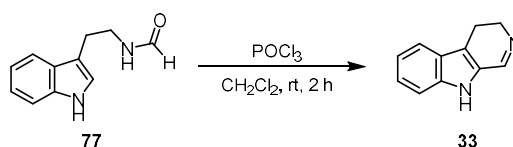
Compound **77** was made according to known literature procedure from Pérez-Castells and co-workers.¹⁵⁴ The data below matches those reported in the literature for the title compound.

A stirred suspension of tryptamine (1.00 g, 6.24 mmol) in ethyl formate (8 mL) was heated to reflux for 20 h. The resulting homogenous solution was concentrated under reduced pressure and dried under high vacuum. The resulting oil (1.40 g, mixture of rotamers 1:0.23) was of sufficient purity to be used in the following reaction.

¹H NMR (500 MHz, CDCl₃) δ 8.16 (br. s, 1H, major/minor), 8.12 (q, J = 0.9 Hz, major, 1H), 8.04 (q, J = 0.8 Hz, minor, 1H), 7.92 (d, J = 12.0 Hz, minor, 1H), 7.61 (dd, J = 7.9, 1.0 Hz, major, 1H), 7.56 (dq, J = 7.8, 0.8 Hz, minor, 1H), 7.38 (m, major/minor, 1H), 7.22 (m, major/minor, 1H), 7.14 (m, major/minor 1H), 7.05 (dd, J = 2.3, 1.1 Hz, major, 1H), 7.02 (d, J = 2.3 Hz, minor, 1H), 5.60 (s, major/minor, 1H), 3.69 – 3.62 (q, J = 6.4 Hz, major, 2H), 3.53 (q, J = 6.5 Hz, minor, 2H), 3.01 (td, J = 6.7, 0.9 Hz, major, 2H), 2.97 (td, J = 6.5, 0.8 Hz, minor, 2H);

¹³C NMR (126 MHz, CDCl₃) δ 151.7, 137.0, 128.3, 125.5, 124.8, 120.6, 120.2, 116.4, 112.2, 48.7, 19.2.

5.4. 3,4-dihydro- β -carboline (33)



Compound **33** was made according to known literature procedure from Decker and co-workers.¹⁵⁵ The data below matches those reported in the literature for the title compound.

A solution of crude formamide **77** (1.40 g) was dissolved in DCM (5 mL). The solution was cooled in an ice-bath and phosphorus oxychloride (1.84 mL, 19.8 mmol) was added dropwise. The resulting solution was slowly warmed to room temperature and stirred for 2 h, after which the solvent was removed under reduced pressure. The resulting residue was dissolved in ethyl acetate (75 mL) and extraction from 10% AcOH/H₂O (4 × 50 mL). The combined acidic fractions were basified to pH 9 with sat. aq. NH₄OH (some precipitation observed). Following extraction from DCM (3 × 100 mL) and the combined organic layers were dried with Na₂SO₄. The filtrate was collected and concentrated under reduced pressure to give the title compound as a yellow solid (969 mg, 5.69 mmol, 91% over two steps).

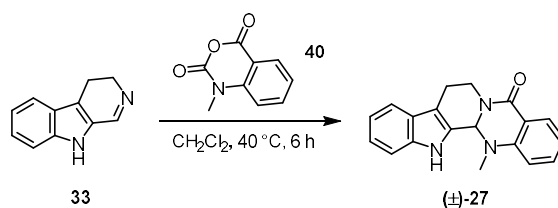
¹H NMR (500 MHz, CDCl₃) δ 8.47 (s, 1H), 8.39 (s, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.38 (dt, J = 8.3, 0.9 Hz, 1H), 7.29 (d, J = 7.1 Hz, 1H), 7.16 (ddd, J = 8.0, 6.9, 1.0 Hz, 1H), 4.01 – 3.88 (m, 2H), 2.91 (t, J = 8.7 Hz, 2H);

¹³C NMR (126 MHz, CDCl₃) δ 151.70, 137.04, 128.28, 125.54, 124.81, 120.62, 120.17, 116.43, 112.19, 77.41, 77.36, 77.16, 76.91, 48.69, 19.24;

HRMS (ESI) m/z calcd for C₁₁H₁₁N₂⁺ [M + H]⁺ 171.0916, found 171.0899 (ppm mass error -1.78);

IR 2920, 2848, 1633, 1542, 1453, 1322, 1155, 742 cm⁻¹.

5.5. (±)-Evodiamine (27)



Compound **27** was made according to known literature procedure from Decker and co-workers.¹⁵⁵ The below data matches those reported in the literature for the title compound.

A solution of 3,4-dihydro-β-carboline (**33**, 340 mg, 2.00 mmol) and methyl isatoic anhydride (**40**, 360 mg, 2.00 mmol) in dichloromethane (10 mL) were stirred at reflux for 6 h. The reaction was cooled to rt, then further cooled to −10 °C, upon which the product precipitated as an off-white solid (470 mg, 1.55 mmol, 78%).

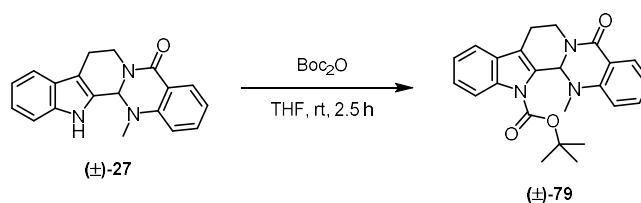
¹H NMR (601 MHz, DMSO-*d*₆) δ 11.06 (s, 1H), 7.80 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.54 – 7.44 (m, 2H), 7.36 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.11 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 7.06 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.01 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 1H), 6.97 (td, *J* = 7.4, 1.0 Hz, 1H), 6.12 (t, *J* = 1.5 Hz, 1H), 4.64 (ddd, *J* = 12.9, 5.6, 1.5 Hz, 1H), 3.20 (ddd, *J* = 12.7, 11.4, 4.6 Hz, 1H), 2.96 – 2.88 (m, 1H), 2.88 (s, 3H), 2.83 – 2.76 (m, 1H);

¹³C NMR (151 MHz, DMSO) δ 164.2, 148.8, 136.5, 133.4, 130.6, 128.0, 125.9, 121.8, 120.3, 119.3, 118.9, 118.2, 117.5, 111.6, 111.5, 69.7, 40.8, 36.4, 19.5;

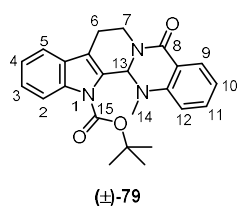
HRMS (ESI) *m/z* calcd for C₁₉H₁₈N₃O⁺ [*M* + *H*]⁺ 304.1444, found 304.1440 (ppm mass error −0.44);

IR 3244 (br), 2922, 1730, 1635, 1608, 1471, 1166, 900, 749, 606.

5.6. (±)-Boc-evodiamine (**27**)



Di-*tert*-butyl dicarbonate (160 mg, 0.73 mmol) and dimethylaminopyridine (DMAP, 89 mg, 0.73 mmol) were added sequentially to a solution of (±)-evodiamine (**27**, 200 mg, 0.66 mmol) in THF (4 mL). The resulting solution was stirred at room temperature for 2.5 h, after which the solvent was removed under reduced pressure. The resulting residue was suspended in water (15 mL) and extracted from DCM (3 × 10 mL). The combined organic extracts were washed with brine (30 mL), dried over Na₂SO₄ and the resulting filtrate was concentrated under reduced pressure. Purification by flash column chromatography (3:1 EtOAc/petroleum ether) gave the title compound as a clear oil (256 mmg, 0.63 mmol, 96%).



¹H NMR (601 MHz, CDCl₃) δ 8.28 (dt, *J* = 8.4, 0.9 Hz, 1H, **H-9**), 8.11 (ddd, *J* = 7.8, 1.6, 0.5 Hz, 1H, **H-3**), 7.56 (dt, *J* = 7.8, 1.0 Hz, 1H, **H-5**), 7.47 (ddd, *J* = 8.1, 7.2, 1.6 Hz, 1H, **H-11**), 7.41 (ddd, *J* = 8.5, 7.2, 1.3 Hz, 1H, **H-10**), 7.32 (ddd, *J* = 8.2, 7.3, 1.0 Hz, 1H, **H-12**), 7.13 (ddd, *J* = 7.8, 7.2, 1.1 Hz, 1H, **H-4**), 7.08 – 7.03 (m, 1H, **H-2**), 6.25 (t, *J* = 1.6 Hz, 1H, **H-13**), 4.91 (ddd, *J* = 12.7, 5.2, 1.6 Hz, 1H, **H-7**), 3.21 (ddd, *J* = 12.7, 11.8, 3.8 Hz, 1H, **H-7**), 3.00 (ddt, *J* = 15.8, 3.8, 1.5 Hz, 1H, **H-6**), 2.85 (dddd, *J* = 15.8, 11.9, 5.2, 2.0 Hz, 1H, **H-6**), 2.46 (s, 3H, **CH₃-14**), 1.53 (s, 9H, **Boc-(CH₃)₃**);

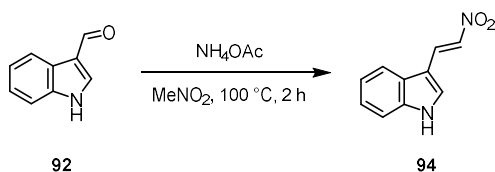
¹³C NMR (151 MHz, CDCl₃) δ 164.6, 150.5, 149.5, 137.1, 132.9, 129.1, 127.9, 127.3, 125.7, 123.1, 122.5, 122.5, 121.6, 120.3, 118.7, 115.7, 84.3, 68.4, 38.2, 35.4, 27.9, 27.8, 20.7;

HRMS (ESI) m/z calcd for $\text{C}_{24}\text{H}_{26}\text{N}_3\text{O}_3^+$ $[\text{M} + \text{H}]^+$ 404.1969, found 404.1972 (mass error 0.74 ppm);

IR 3244 (br), 2897, 1709, 1737, 1639, 1598, 1470, 1161, 954, 888, 601;

R_f 0.41 (3:1 EtOAc:petroleum ether).

5.7. 3-[(*E*)-2-nitroeth-1-enyl]-1H-indole (94)



All the above data matches those reported in the literature for the title compound.¹⁵⁶

Ammonium acetate (75 mg, 0.97 mmol) was added to a vigorously stirred suspension of indole-3-carbaldehyde (200 mg, 1.38 mmol) in nitromethane (3.5 mL). The reaction was heated to reflux and stirred for 2 h. The mixture was allowed to cool to room temperature and the solvent removed under reduced pressure. Water (7 mL) was added to the resulting residue and extraction was performed from EtOAc (4 × 10 mL). The combined organic layers were dried over Na₂SO₄ and the resulting filtrate was purified by flash column chromatography (3:1 petroleum ether/EtOAc) to give the title compound as an orange solid (195 mg, 1.04 mmol, 75%).

¹H NMR (500 MHz, CDCl₃) δ 8.75 (s, 1H), 8.29 (d, *J* = 13.4 Hz, 1H), 7.83 – 7.77 (m, 2H), 7.68 (d, *J* = 3.0 Hz, 1H), 7.50 – 7.45 (m, 1H), 7.39 – 7.31 (m, 2H);

¹³C NMR (126 MHz, CDCl₃) δ 137.16, 133.25, 132.99, 132.12, 124.60, 124.22, 122.56, 120.47, 112.16, 109.68;

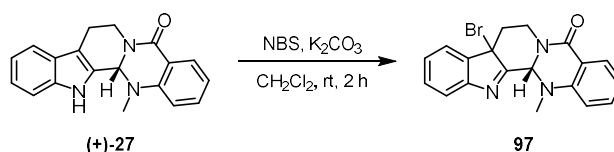
HRMS (ESI) *m/z* calcd for C₁₀H₉N₂O₂⁺ [*M* + *H*]⁺ 189.0659, found 189.0651 (mass error –0.75 ppm);

IR 3375 (br), 2733, 1600, 1485, 1322, 1301, 1285, 1210, 1109, 975, 892, 804 cm^{–1};

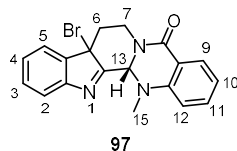
R_f 0.23 (3:1 petroleum ether/EtOAc);

M.P. 156 °C (acetone/hexane);

5.8. Bromo-indoleidine 97



To a suspension of evodiamine (100 mg, 0.33 mmol) and K_2CO_3 (160 mg) in CH_2Cl_2 (10 mL) was slowly added *N*-bromosuccinimide (71 mg, 0.66 mmol) as a solution in DCM (2 mL). This resulting mixture was stirred at room temperature until complete by TLC analysis (c.a. 2 h). The solution was diluted with DCM (10 mL) and washed with water. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give a yellow solid (113 mg, 0.30 mmol, 90%).



^1H NMR (601 MHz, $DMSO-d_6$) δ 7.69 – 7.66 (m, 1H, **H-9**), 7.60 (dd, J = 7.7, 1.7 Hz, 1H, **H-5**), 7.55 – 7.51 (m, 1H, **H-12**), 7.44 (ddd, J = 8.7, 7.3, 1.7 Hz, 1H, **H-3**), 7.39 (td, J = 7.6, 1.4 Hz, 1H, **H-11**), 7.35 (td, J = 7.5, 1.2 Hz, 1H, **H-10**), 6.89 (dd, J = 8.5, 1.0 Hz, 1H, **H-2**), 6.73 (td, J = 7.4, 1.0 Hz, 1H, **H-4**), 6.44 (s, 1H, **H-13**), 4.55 (ddd, J = 13.9, 5.0, 1.8 Hz, 1H, **H-7**), 3.33 (ddd, J = 14.0, 12.0, 2.3 Hz, 1H, **H-7**), 3.14 (s, 3H, **CH₃**), 2.87 (dt, J = 15.3, 2.0 Hz, 1H, **H-6**), 1.76 (ddd, J = 16.7, 10.3, 4.7 Hz, 1H, **H-6**);

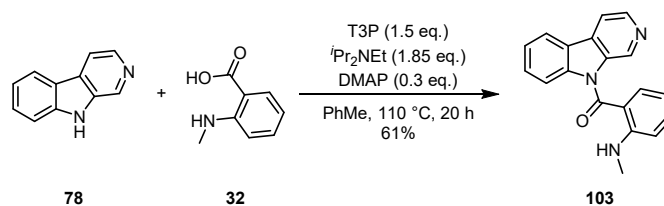
^{13}C NMR (151 MHz, DMSO) δ 173.8, 162.1, 151.0, 147.6, 140.2, 134.6, 130.2, 127.9, 127.4, 123.5, 121.6, 117.2, 113.2, 111.8, 72.6, 62.6, 40.3, 40.1, 35.5;

HRMS (ESI) m/z calcd for $C_{19}H_{17}N_3OBr^+$ $[M + H]^+$ 382.0550, found 382.0563 (mass error 1.35 ppm);

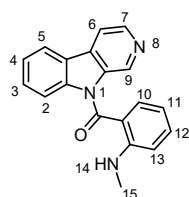
IR 2928, 1697, 1674, 1636, 1570, 1298, 1032, 774 cm^{-1} ;

R_f 0.45 (1% MeOH/ CH_2Cl_2).

5.9. *N*-acyl- β -carboline **103**



A solution of *N*-methyl anthranilic acid (**32**, 33 mg, 0.22 mmol), T3P (50% solution in toluene, 210 μ L, 0.33 mmol), DIPEA (71 μ L, 0.41 mmol) and DMAP (8 mg, 0.07 mmol) were stirred at room temperature in toluene (4 mL) for 30 min. After this time, β -carboline (**78**, 37 mg, 0.22 mmol) was added. The resulting solution was heated to reflux and stirred for 20 h, after which time, the solution was cooled and the solvent removed under reduced pressure. The resulting crude material was dissolved in EtOAc (10 mL) and washed with sat. aq. NaHCO₃ (5 mL). The organic layer was purified by flash column chromatography (3:1 PE/EtOAc) to give the title compound as an off-white solid (61%, 40 mg, 0.13 mmol).



¹H NMR (500 MHz, CDCl₃) δ 8.89 (d, *J* = 1.1 Hz, 1H, **H-9**), 8.56 (d, *J* = 5.2 Hz, 1H, **H-6**), 8.09 (ddd, *J* = 7.8, 1.3, 0.7 Hz, 1H, **H-5**), 7.92 (dd, *J* = 5.2, 1.1 Hz, 1H, **H-7**), 7.62 (dt, *J* = 8.4, 0.9 Hz, 1H, **H-3**), 7.54 – 7.45 (m, 2H, **H-2/12**), 7.40 (ddd, *J* = 8.0, 7.2, 1.0 Hz, 1H, **H-4**), 7.32 (dd, *J* = 8.0, 1.6 Hz, 1H, **H-10**), 6.99 (dd, *J* = 6.6, 3.8 Hz, 1H, **H-14**), 6.87 (dd, *J* = 8.7, 1.0 Hz, 1H, **H-13**), 6.59 (ddd, *J* = 8.1, 7.1, 1.0 Hz, 1H, **H-11**), 2.99 (d, *J* = 5.0 Hz, 3H, **H-15**);

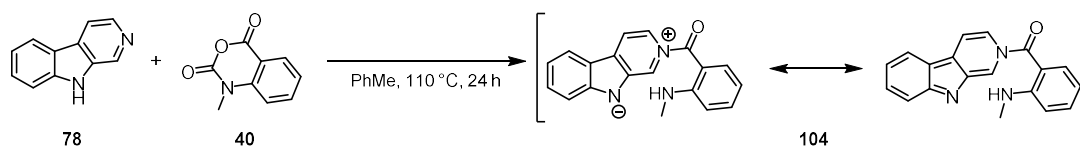
¹³C NMR (126 MHz, CDCl₃) δ 170.3 (**C=O**), 151.8, 142.6 (**C6**), 140.2, 137.8 (**C9**), 136.1, 135.7 (**C2/12**), 132.8 (**C10**), 131.7, 129.2 (**C2/12**), 123.8, 123.3 (**C4**), 121.4 (**C5**), 115.9, 115.4 (**C11**), 114.3 (**C7**), 111.9 (**C13**), 29.9 (**C15**);

HRMS (ESI) *m/z* calcd for C₁₉H₁₆N₃O⁺ [*M* + *H*]⁺ 302.1288, found 302.1291 (0.99 ppm mass error);

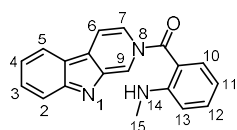
IR 1660, 1631, 1569, 1517, 1421, 1322, 1294, 750 cm⁻¹.

R_f 0.21 (3:1 PE/EtOAc).

5.10. Tertiary amide 104



A solution of β -carboline (**78**, 6.4 mg, 38 μ mol) and *N*-methyl isatoic anhydride (**40**, 6.7 mg, 38 μ mol) in toluene (3 mL) was heated to 110 °C for 1 h with stirring. After this time, the solution was passed through a pad of silica and washed with ethyl acetate (2 $\times$ 5 mL). The resulting filtrate was concentrated under reduced volume to give the title compound as a yellow oil (9 mg, 30 μ mmol, 78%).



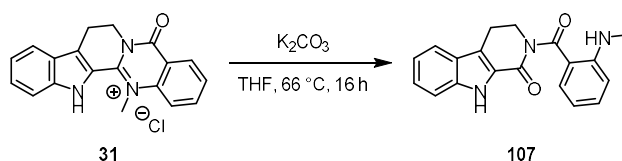
^1H NMR (601 MHz, CDCl_3) δ 9.12 (s, 1H, **H-9**), 8.71 (d, J = 6.0 Hz, 1H, **H-6**), 8.46 (d, J = 5.9 Hz, 1H, **H-7**), 8.34 – 8.28 (m, 1H, **H-5**), 7.72 (ddd, J = 8.6, 7.2, 1.2 Hz, 1H, **H-3**), 7.62 – 7.54 (m, 3H, **H-2/4/12**), 7.25 (dd, J = 8.2, 1.8 Hz, 1H, **H-10**), 6.94 (dd, J = 8.7, 1.1 Hz, 1H, **H-13**), 6.61 (ddd, J = 8.1, 7.0, 1.1 Hz, 1H, **H-11**), 3.06 (d, J = 1.2 Hz, 3H, **H-15**);

^{13}C NMR (151 MHz, CDCl_3) δ 168.4 (**C=O**), 152.8, 142.9, 137.2 (**C12**), 135.4, 133.3 (**C6**), 132.7 (**C3**), 132.4 (**C10**), 129.6 (**C9**), 124.5 (**C2**), 122.9, 121.1, 116.8 (**C7**), 115.7 (**C4**), 115.5 (**C11**), 112.6 (**C5**), 111.2, 29.8 (**C15**);

HRMS (ESI) m/z calcd for $\text{C}_{19}\text{H}_{16}\text{N}_3\text{O}^+$ [$\text{M} + \text{H}$] $^+$ 302.1288, found 302.1288 (0.03 ppm mass error);

IR 2855, 1656, 1602, 1572, 1488, 1420, 1303, 1187, 753, 699 cm^{-1} .

5.11. Rhetsinine (107)



All the above data matches those reported in the literature for the title compound.⁵⁶

Potassium carbonate (457 mg, 3.31 mmol) was added to a stirred suspension of dehydroevodiamine chloride (**31**, 500 mg, 1.66 mmol) in 'wet' THF. This suspension was heated to reflux for 16 h, after which time the solvent was removed under reduced pressure. Water (25 mL) was added to the resulting residue and extraction from CH_2Cl_2 ($4 \times 20\text{ mL}$) was performed. The combined organic extracts were washed with brine (40 mL), dried with Na_2SO_4 and the filtrate was concentrated under reduced pressure. The resulting solid was dried under high vacuum to give the title compound as an orange solid (330 mg, 1.03 mmol, 62%).

^1H NMR (500 MHz, $DMSO-d_6$) δ 11.72 (s, 1H), 7.69 (dt, $J = 8.1, 1.0\text{ Hz}$, 1H), 7.42 (dt, $J = 8.3, 0.9\text{ Hz}$, 1H), 7.31 (m, 3H), 7.12 (ddd, $J = 8.1, 6.9, 1.0\text{ Hz}$, 1H), 6.88 (q, $J = 4.9\text{ Hz}$, 1H), 6.70 (dd, $J = 8.5, 1.1\text{ Hz}$, 1H), 6.49 (ddd, $J = 8.0, 7.1, 1.1\text{ Hz}$, 1H), 4.12 (t, $J = 6.3\text{ Hz}$, 2H), 3.18 (t, $J = 6.4\text{ Hz}$, 2H), 2.82 (d, $J = 5.0\text{ Hz}$, 3H);

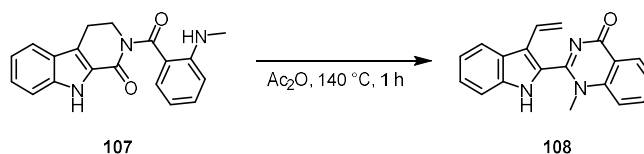
^{13}C NMR (126 MHz, $DMSO$) δ 174.64, 161.00, 149.69, 138.38, 133.43, 131.40, 125.99, 125.59, 124.42, 122.46, 120.84, 119.98, 116.97, 114.16, 112.75, 110.84, 46.82, 29.51, 20.51;

HRMS (ESI) m/z calcd for $C_{19}H_{18}N_3O_2^+$ [$M + H$] $^+$ 320.1394, found 320.1385 (mass error -0.85 ppm);

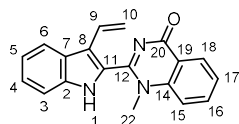
IR 3398, 3263, 2807, 2370 (br), 2352 (sh), 1661, 1575, 1551, 1421, 1368, 1267, 1203, 1174, 1103, 1001, 892, 746, 758, 657 cm^{-1} ;

R_f 0.19 (EtOAc).

5.12. Alkene 108



Rhetsinine (**107**, 100 mg, 0.31 mmol) was dissolved in acetic anhydride (2 mL) and heated to reflux with stirring. After 1 h, the acetic anhydride was removed under reduced pressure and the crude residue was purified by flash column chromatography (3:1 EtOAc/petroleum ether) to give the title compound as a yellow solid (16 mg, 0.05 mmol, 17%).



¹H NMR (601 MHz, DMSO-*d*₆) δ 11.97 (s, 1H, **NH-1**), 8.17 (dd, *J* = 7.9, 1.6 Hz, 1H, **H-18**), 7.98 (dd, *J* = 8.0, 1.1 Hz, 1H, **H-6**), 7.92 (ddd, *J* = 8.7, 7.2, 1.7 Hz, 1H, **H-16**), 7.82 (d, *J* = 8.5 Hz, 1H, **H-15**), 7.62 (ddd, *J* = 8.0, 7.2, 1.0 Hz, 1H, **H-17**), 7.51 (d, *J* = 8.2 Hz, 1H, **H-3**), 7.30 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H, **H-4**), 7.19 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H, **H-5**), 6.91 (dd, *J* = 17.8, 11.5 Hz, 1H, **H-9**), 5.73 (dd, *J* = 17.9, 1.4 Hz, 1H, **trans-CH₂-10**), 5.28 (dd, *J* = 11.5, 1.3 Hz, 1H, **cis-CH₂-10**), 3.70 (s, 3H, **CH₃**);

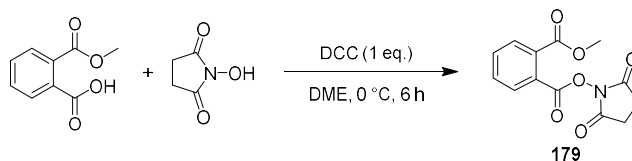
¹³C NMR (151 MHz, DMSO) δ 167.4 (**C20**), 155.2 (quat.), 141.6 (quat.), 136.4 (quat.), 134.1 (**C16**), 128.8 (**C9**), 127.1 (**C18**), 126.4 (**C17**), 124.8 (quat.), 123.7 (**C4**), 120.7 (2C, **C5/6**), 119.9 (quat.), 117.0 (**C15**), 114.7 (quat.), 113.6 (**C10**), 112.3 (**C3**), 59.7 (quat.), 37.4 (**C22**);

HRMS (ESI) *m/z* calcd for C₁₉H₁₆N₃O⁺ [*M* + *H*]⁺ 302.1288, found 302.1292 (mass error 0.41 ppm);

UV/Vis λ_{max} 317, 340 (sh) nm (EtOH);

R_f 0.12 (3:1 EtOAc/petroleum ether).

5.13. Ester 179



Compound **179** was made according to known literature procedure from Perrin and co-workers.⁸⁴ The data below matches those in the literature for the title compound.

DCC (8.25 g, 40.0 mmol) was added to a cooled solution of monomethyl phthalate (7.21 g, 40.0 mmol) and *N*-hydroxysuccinimide (4.61 g, 40 mmol) in DME (15 mL). This resulting solution was stirred at 0 °C for 4 h, after which the reaction was allowed to stand at 0 °C for a further 2 h. The resulting precipitate was filtered away and the resulting filtrate was concentrated under reduced pressure. The residue formed was triturated with 1:2 ether/hexanes, filtered and dried under high vacuum. The resulting white powder was assigned as the title compound (75%, 8.37 g, 30.2 mmol).

¹H NMR (500 MHz, CDCl₃) δ 7.95 – 7.92 (m, 1H), 7.90 – 7.87 (m, 1H), 7.69 – 7.61 (m, 2H), 3.94 (s, 3H), 2.91 (s, 4H);

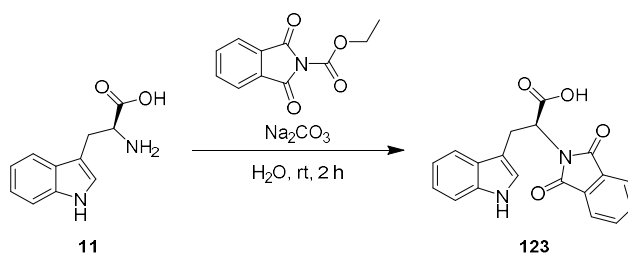
¹³C NMR (126 MHz, CDCl₃) δ 168.98, 166.57, 163.40, 132.61, 131.90, 131.67, 130.16, 129.75, 127.87, 53.16, 25.85;

M.P. 75 – 77 °C;

R_f 0.45 (Pet/EtOAc).

5.14. Phth-(L)-Trp-OH (**123**)

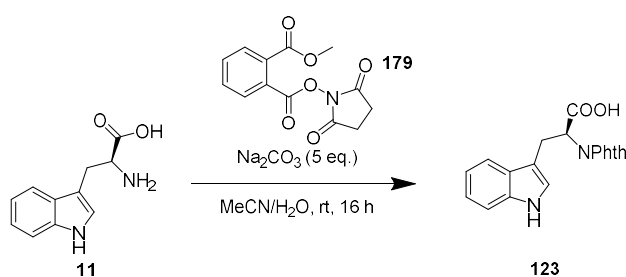
Method A:



Compound **123** was made according to known literature procedure from de Kiff and co-workers.⁸³

Tryptophan (5.00 g, 24.5 mmol) was added to stirring solution of Na_2CO_3 (5.20 g, 49.0 mmol) in water (100 mL). Upon complete solvation of tryptophan, ester (5.90 g, 26.9 mmol) was added and the solution stirred for 2 h at room temperature. The resulting solution was acidified until pH 2 (1 N HCl) and extracted with ethyl acetate (3 × 150 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and the solvent removed under reduced pressure. The resulting residue was purified by column chromatography (4:1:0.01 EtOAc/hexane/AcOH). The combined product fractions were washed with water, brine, dried over Na_2SO_4 and the solvent removed under reduced pressure to give the title compound as a yellow foam (78%, 6.406 g, 19.2 mmol).

Method B:



Compound **123** was made according to known literature procedure from Briand and co-workers.¹⁵⁷ The data below matches those reported in the literature for the title compound.

Ester **179** (2.75 g, 9.92) was added to a solution of tryptophan (2.07 g, 9.92 mmol) and Na_2CO_3 (5.26 g, 49.6 mmol) in 5:3 MeCN/ H_2O (200 mL). The resulting solution was stirred at room temperature for 16 h, after which 2 N HCl was added until acidified to pH 2. The resulting solution was diluted with EtOAc (100 mL), washed with 1 N HCl (2×100 mL), water (2×100 mL) and the combined organic fractions dried over Na_2SO_4 . Upon filtration, concentration and drying under high vacuum, the title compound was obtained as a yellow foam (96%, 3.18 g, 9.53 mmol).

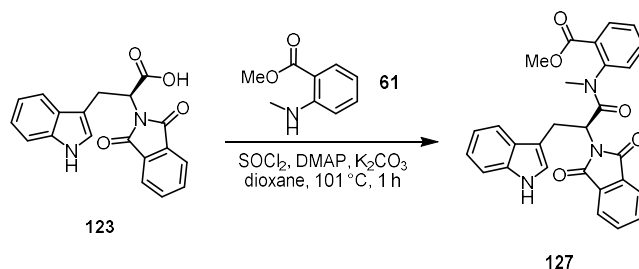
^1H NMR (500 MHz, CDCl_3) δ 7.97 (s, 1H), 7.74 (dd, $J = 5.5, 3.1$ Hz, 2H), 7.65 (dd, $J = 5.5, 3.0$ Hz, 2H), 7.60 (dt, $J = 7.9, 0.9$ Hz, 1H), 7.25 (dt, $J = 7.3, 0.9$ Hz, 1H), 7.12 (ddd, $J = 8.1, 7.0, 1.2$ Hz, 1H), 7.05 (ddd, $J = 8.0, 7.0, 1.1$ Hz, 1H), 6.99 (d, $J = 2.3$ Hz, 1H), 5.28 (dd, $J = 9.9, 6.1$ Hz, 1H), 3.79 (s, 3H), 3.78 – 3.70 (m, 2H);

^{13}C NMR (126 MHz, CDCl_3) δ 169.78, 167.68, 136.19, 134.12, 131.83, 127.29, 123.50, 122.66, 122.22, 119.65, 118.61, 111.23, 111.21, 77.41, 77.36, 77.16, 76.91, 52.96, 52.73, 24.93;

HRMS (ESI) m/z calcd for $\text{C}_{19}\text{H}_{15}\text{N}_2\text{O}_4^+$ $[\text{M} + \text{H}]^+$ 335.1026, found 335.1004 (ppm mass error -2.23);

IR 3391, 1771, 1738, 1705, 1614, 1591, 1132, 904, 669 cm^{-1} .

5.15. Amide 127



Thionyl chloride (1.42 mL, 19.6 mmol) was added dropwise to a solution of Phth-Trp-OH (6.64 g, 19.6) in dioxane (65 mL). This was allowed to stir at 60 ° for 1 h, after which time the carboxylic acid was fully consumed by TLC. The solution was cooled to room temperature and dimethyl anthranilate (1.69 mL, 11.5 mmol), potassium carbonate (5.42 g, 39.2 mmol) and dimethylaminopyridine (2.40 g, 19.6 mmol) were added to the solution. The resulting solution was headed to reflux for 1 h, after which time the resulting solution was cooled and quenched with sat. aq. NaHCO₃ (100 mL). The resulting mixture was extracted from EtOAc (3 × 200 mL), the combined organic extracts were washed with brine and dried over Na₂CO₃. The filtrate was concentrated under reduced pressure and purified by flash column chromatography (1:1 → 2:1 EtOAc/petroleum ether) to give the title compound as a yellow solid (2.87 g, 5.96 mmol, 52%, 1:1 mixture of rotomers).

¹H NMR (601 MHz, DMSO-*d*₆) δ 10.63 (d, *J* = 2.4 Hz, 1H), 10.60 (d, *J* = 2.5 Hz, 1H), 7.91 (ddd, *J* = 8.2, 6.8, 1.6 Hz, 2H), 7.80 – 7.72 (m, 5H), 7.67 (dtd, *J* = 8.1, 5.2, 2.0 Hz, 4H), 7.62 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.55 (td, *J* = 7.6, 1.3 Hz, 1H), 7.36 (td, *J* = 7.6, 1.3 Hz, 1H), 7.24 – 7.15 (m, 3H), 7.05 – 6.97 (m, 2H), 6.94 (dddd, *J* = 10.6, 8.1, 6.9, 1.2 Hz, 2H), 6.87 – 6.71 (m, 5H), 4.99 (dd, *J* = 11.1, 4.8 Hz, 1H), 4.90 (dd, *J* = 8.7, 6.4 Hz, 1H), 3.69 (s, 3H), 3.51 (s, 3H), 3.38 – 3.34 (m, 2H), 3.30 – 3.25 (m, 2H), 3.12 (s, 3H), 3.10 (s, 3H);

¹³C NMR (151 MHz, DMSO) δ 167.2, 167.0, 166.4, 166.2, 165.1, 164.1, 142.3, 141.8, 135.8, 135.7, 134.5, 134.4, 134.3, 131.8, 130.8, 130.6, 130.6, 129.6, 128.6, 128.3, 127.2, 126.8, 126.5, 123.5, 123.1, 122.8, 122.7, 120.7, 120.6, 118.0, 117.4, 117.2, 111.2, 109.3, 109.2, 79.0, 52.2, 51.8, 51.8, 51.6, 37.9, 37.8, 24.1, 23.7;

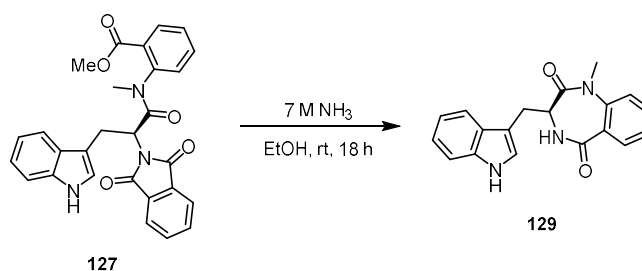
HRMS (ESI) m/z calcd for $C_{28}H_{24}N_3O_5^+$ $[M + H]^+$ 482.1638, found 282.1644 (mass error 1.24 ppm);

IR 1710, 1664, 1389, 1288, 1124, 739 cm^{-1} ;

R_f 0.22 (2:1 EtoAc/petroleum ether);

$[\alpha]_D^{21}$ -44° (c 0.50, DMSO).

5.16. Cyclic diamide 129



The data below matches those in the literature for the title compound.⁷⁶

Amide **127** (412 mg, 0.86 mmol) was dissolved in NH_3 solution (7 M in MeOH, 20 mL) and allowed to stir at room temperature for 18 h. After this time the solvent was removed under reduced pressure. The resulting crude residue was purified by column chromatography (1:1 $\rightarrow$ 2:1 EtOAc/petroleum ether) to give the title compound as a white solid (161 mg, 0.50 mmol, 59%).

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.81 (s, 1H), 8.58 (d, $J = 6.1$ Hz, 1H), 7.61 – 7.53 (m, 2H), 7.47 (dd, $J = 7.8, 1.0$ Hz, 1H), 7.41 (dd, $J = 8.3, 1.1$ Hz, 1H), 7.33 – 7.29 (m, 1H), 7.26 (td, $J = 7.5, 1.1$ Hz, 1H), 7.21 (d, $J = 2.4$ Hz, 1H), 7.01 (ddd, $J = 8.2, 7.0, 1.2$ Hz, 1H), 6.88 (ddd, $J = 8.0, 6.9, 1.1$ Hz, 1H), 3.88 (dt, $J = 8.8, 5.8$ Hz, 1H), 3.34 (s, 3H), 3.29 – 3.23 (m, 1H), 3.04 (dd, $J = 14.9, 8.8$ Hz, 1H);

^{13}C NMR (151 MHz, DMSO) δ 170.5, 167.5, 140.8, 136.0, 132.1, 129.4, 128.6, 126.9, 125.1, 124.4, 122.0, 120.8, 118.3, 118.2, 111.3, 109.7, 52.6, 35.0, 23.8;

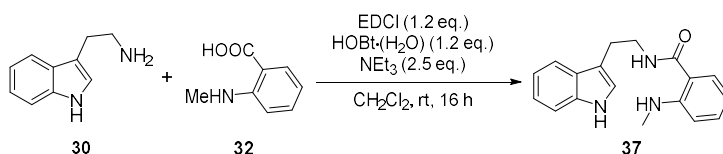
HRMS (ESI) m/z calcd for $\text{C}_{19}\text{H}_{18}\text{N}_3\text{O}_2^+$ $[\text{M} + \text{H}]^+$ 320.1394, found 320.1408 (mass error 1.45 ppm);

IR 3431 (br), 1667, 1470, 1394, 1357, 1320, 1040, 1027, 998, 770, 704;

R_f 0.35 (2:1 EtOAc/petroleum ether);

$[\alpha]_D^{21}$ +30.6 $^\circ$ (c 0.72, DMSO).

5.17. Amide 37



All the above data matched those found in the literature for the title compound.⁸⁵

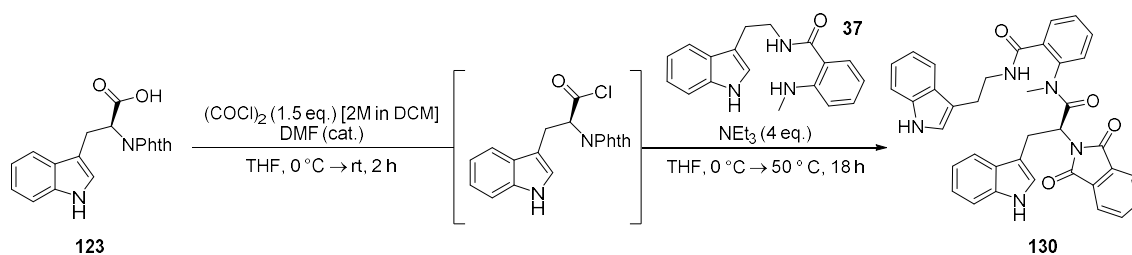
Triethylamine (5.44 mL, 39.0 mmol) was added to a solution of tryptamine (2.50 g, 15.6 mmol), *N*-methyl anthranilic acid (2.36 g, 15.6 mmol), EDCI (2.90 g, 18.7 mmol) and HOBt·H₂O (2.53 g, 18.7 mmol) in DCM (150 mL). The solution was stirred for 16 h, following which a solution of water (375 mL) and brine (150 mL) was added. The resulting solution was extracted from DCM (3 × 200 mL) and the combined organic extracts were dried over Na₂SO₄. The solvent was removed under reduced pressure and the crude material was obtained through trituration (EtOAc). The resulting crude solid was purified by column chromatography (0.5% MeOH/DCM) to give the title compound as a white solid (3.09 g, 10.5 mmol, 68%).

¹H NMR (500 MHz, DMSO-*d*₆) δ 10.79 (s, 1H), 8.38 (t, *J* = 5.6 Hz, 1H), 7.67 (q, *J* = 5.1 Hz, 1H), 7.58 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.50 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.34 (dt, *J* = 7.9, 0.9 Hz, 1H), 7.28 (ddd, *J* = 8.5, 7.1, 1.6 Hz, 1H), 7.17 (d, *J* = 2.3 Hz, 1H), 7.07 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 6.98 (ddd, *J* = 7.9, 7.0, 1.1 Hz, 1H), 6.62 (dd, *J* = 8.4, 1.1 Hz, 1H), 6.54 (ddd, *J* = 8.0, 7.2, 1.1 Hz, 1H), 3.49 (td, *J* = 7.6, 5.6 Hz, 2H), 2.99 – 2.84 (m, 2H), 2.77 (d, *J* = 5.0 Hz, 3H);

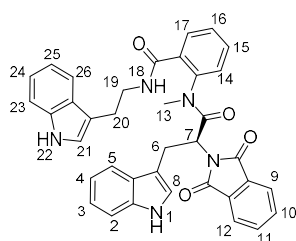
¹³C NMR (126 MHz, DMSO) δ 169.4, 150.4, 136.3, 132.9, 128.8, 127.2, 123.8, 121.1, 118.6, 118.1, 114.1, 113.9, 111.6, 110.7, 110.2, 53.7, 52.0, 29.4;

HRMS (ESI) *m/z* calcd for C₁₈H₂₀N₃O⁺ [*M* + *H*]⁺ 294.1601, found 294.1591 (mass error –0.99 ppm);

5.18. Diamide 130



To a cooled solution of oxalyl chloride (2M solution in DCM, 1.63 mL, 3.25 mmol), three drops of anhydrous DMF were added. A solution of Phth-Trp-OH (741 mg, 2.22 mmol) in freshly distilled THF (15 mL) was added dropwise to the preformed Vilsmeier reagent solution. The resulting solution was allowed to return to room temperature and stirred for 2 h, until complete by TLC analysis. This solution was cooled and a solution of amide **37** (500 mg, 1.71 mmol) and triethylamine (0.84 mL, 6.00 mmol) in anhydrous THF (15 mL) was added dropwise. Upon addition of amide **37** the resulting solution was allowed to return to room temperature gradually, then heated at 50 °C until complete by TLC analysis (*c.a.* 18 h). The solvent was removed under reduced pressure and the crude residue was dissolved in DCM (100 mL), aq. HCl (1 M, 100 mL) was added and extracted from DCM (3 × 100 mL). The combined organic layers were washed sequentially with NaHCO₃, water and brine. The organic layer was dried with Na₂SO₄, filtrated and the solvent removed under reduced pressure. The resulting residue was purified by column chromatography (1:50 crude/silica weight, 1% MeOH/DCM) to give the title compound as an orange foam (870 mg, 0.52 mmol, 84%).



¹H NMR (601 MHz, DMSO-*d*₆) δ 10.83 (s, 1H, **H-22**), 10.55 (d, *J* = 2.5 Hz, 1H, **H-1**), 8.51 (t, *J* = 5.7 Hz, 1H, **H-18**), 7.77 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.60 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.53 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.37 – 7.33 (m, 2H), 7.22 (d, *J* = 2.3 Hz, 1H, **H-21**), 7.17 – 7.11 (m, 2H),

7.07 (dtd, $J = 8.5, 7.2, 1.2$ Hz, 2H), 7.01 (dd, $J = 8.0, 1.2$ Hz, 2H), 6.98 – 6.94 (m, 2H), 6.90 (ddd, $J = 8.1, 7.0, 1.1$ Hz, 1H), 6.77 (d, $J = 2.4$ Hz, 1H, **H-8**), 6.73 (ddd, $J = 8.0, 7.0, 1.0$ Hz, 1H), 5.36 (dd, $J = 11.4, 4.2$ Hz, 1H, **H-7**), 3.60 – 3.49 (m, 3H, **H-6/19**), 3.45 – 3.37 (m, 1H, **H-6**), 3.06 (s, 3H, **H-13**), 2.96 (td, $J = 7.2, 6.6, 3.0$ Hz, 2H, **H-20**);

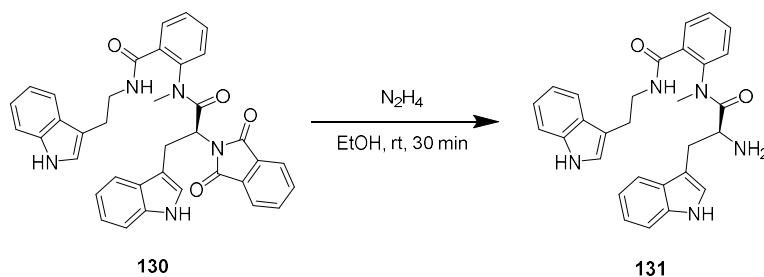
^{13}C NMR (151 MHz, DMSO) δ 168.0, 166.7, 166.6, 140.1, 136.3, 135.8, 134.7, 134.5, 130.8, 130.7, 129.1, 128.1, 127.2, 127.0, 123.2, 122.9, 122.6, 120.9, 120.7, 118.2, 118.0, 117.7, 111.6, 111.4, 111.1, 109.7, 52.3, 37.8, 25.0, 23.6;

HRMS (ESI) m/z calcd for $\text{C}_{37}\text{H}_{32}\text{N}_5\text{O}_4^+$ $[\text{M} + \text{H}]^+$ 610.2449, found 610.2457 (mass error 0.82 ppm);

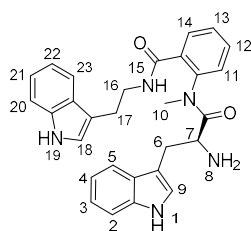
IR 3280, 1724, 1633, 1515, 680 cm^{-1} ;

$[\alpha]_{\text{D}}^{21}$ -278.8° (c 1.04, DMSO).

5.19. Amine 131



Hydrazine monohydrate (110 μL , 2.26 mmol) was added to a solution stirring solution of diamide **130** (180 mg, 0.30 mmol) in ethanol (8 mL). The resulting solution was stirred at room temperature for approx. 30 min (until complete by TLC analysis). The solvent/excess reagent was removed under reduced pressure and the resulting solid washed with dichloromethane ($3 \times 5 \text{ mL}$) to give the title compound as a yellow solid (135 mg, 0.28 mmol, 96%).



^1H NMR (500 MHz, CD_2Cl_2) δ 8.47 (s, 1H, **H-15**), 8.17 (s, 1H, **H-19**), 8.12 (s, 1H, **H-1**), 7.59 (dq, $J = 7.9, 0.9 \text{ Hz}$, 1H, **H-14**), 7.51 (dd, $J = 7.7, 1.6 \text{ Hz}$, 1H, **H-5**), 7.38 (dt, $J = 8.1, 0.9 \text{ Hz}$, 1H, **H-11**), 7.35 (dt, $J = 8.2, 0.9 \text{ Hz}$, 1H, **H-23**), 7.29 (td, $J = 7.6, 1.2 \text{ Hz}$, 1H, **H-4**), 7.23 (dq, $J = 7.9, 0.9 \text{ Hz}$, 1H, **H-20**), 7.15 (dddd, $J = 8.2, 6.4, 5.2, 1.2 \text{ Hz}$, 2H, **H-12/22**), 7.09 – 7.04 (m, 3H, **H-3/9/13**), 7.00 (ddd, $J = 8.0, 7.1, 1.0 \text{ Hz}$, 1H, **H-21**), 6.96 (d, $J = 2.4 \text{ Hz}$, 1H, **H-18**), 6.30 (dd, $J = 7.9, 1.2 \text{ Hz}$, 1H, **H-2**), 3.74 – 3.61 (m, 2H, **CH₂-16**), 3.50 (t, $J = 7.1 \text{ Hz}$, 1H, **H-7**), 3.16 (ddd, $J = 14.0, 7.2, 0.8 \text{ Hz}$, 1H, **H-6**), 3.04 (s, 3H, **CH₃**), 3.03 – 2.92 (m, 2H, **CH₂-17**), 2.77 (dd, $J = 14.0, 7.2 \text{ Hz}$, 1H, **H-6**);

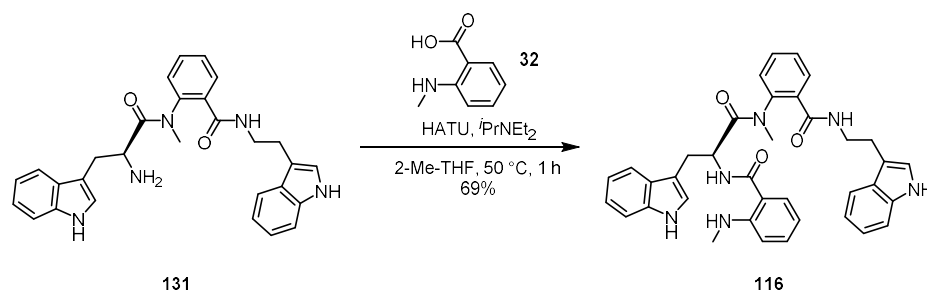
^{13}C NMR (126 MHz, CD_2Cl_2) δ 173.6, 166.9, 139.7, 136.3, 136.3, 136.1, 130.7, 129.9, 128.9, 128.3, 127.4, 127.3, 123.1, 122.2, 121.9, 121.9, 119.2, 119.2, 118.7, 118.6, 113.3, 111.7, 111.1, 111.0, 52.2, 40.0, 36.4, 31.6, 25.3;

HRMS (ESI) m/z calcd for $C_{29}H_{30}N_5O_2^+$ $[M + H]^+$ 480.2394, found 480.2405 (mass error 1.10 ppm);

IR 3228, 1644, 1598, 1512, 1256, 904 cm^{-1} ;

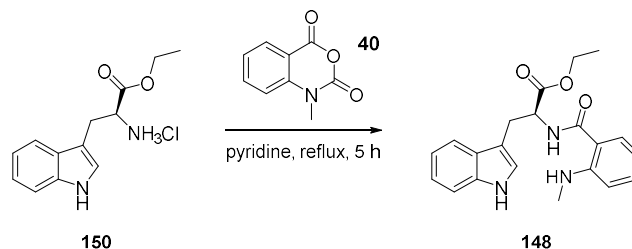
$[\alpha]_D^{20}$ +165.4 ° (c 1.10, MeOH).

5.20. Oligomer 116

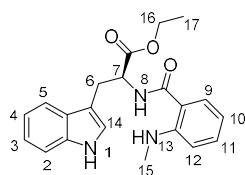


A solution of *N*-methyl anthranlic acid (**32**, 64 mg, 0.42 mmol), HATU (160 mg, 0.42 mmol) and DIPEA (152 μ L, 0.88 mmol) was stirred for 30 min in 2-Me-THF (5 mL) at room temperature. After this time, amine **131** (170 mg, 0.35 mmol) was added to the solution and the resulting solution was stirred at 50 °C for 1 h. After this time, the reaction was cooled, EtOAc (20 mL) and sat. aq. NaHCO₃ (20 mL) was added, and the mixture was extracted from EtOAc (3 $\times$ 20 mL). The combined organic extracted were washed with 1 N HCl (50 mL), water (25 mL) and brine (50 mL). The organic layer was concentrated under reduced pressure and purified by flash column chromatography (0.5% MeOH/CH₂Cl₂) to give the title compound as yellow solid (150 mg, 0.24 mmol, 69%).

5.21. Ester 148



A solution of L-tryptophan ethyl ester hydrochloride (10.00 g, 37.2 mmol) and methyl isatoic anhydride (6.60 g, 37.2 mmol) in pyridine (50 mL) was refluxed for 5 h. Upon cooling, the solvent was removed under reduced pressure, taken up in DCM and washed with sat. aq. NaHCO₃. The resulting organic layer was concentrated and purified by flash chromatography (0 → 0.5% MeOH/DCM) to give the title compound as an amorphous, white solid (32%, 4.42 g, 12.1 mmol).



¹H NMR (600 MHz, CDCl₃) δ 8.06 (s, 1H, **NH-1**), 7.58 (d, *J* = 7.9 Hz, 1H, **H-9**), 7.46 (s, 1H, **NH-13**), 7.35 (d, *J* = 8.1 Hz, 1H, **H-5**), 7.29 (ddd, *J* = 8.5, 7.1, 1.6 Hz, 1H, **H-11**), 7.21 – 7.17 (m, 2H, **H-10/12**), 7.10 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H, **H-3**), 7.03 (d, *J* = 2.4 Hz, 1H, **H-14**), 6.65 (d, *J* = 8.4 Hz, 1H, **H-2**), 6.57 (d, *J* = 7.4 Hz, 1H, **NH-8**), 6.50 (ddd, *J* = 8.1, 7.2, 1.1 Hz, 1H, **H-4**), 5.03 (dt, *J* = 7.5, 5.5 Hz, 1H, **H-7**), 4.22 – 4.08 (m, 2H, **H-16**), 3.46 – 3.37 (m, 2H, **H-6**), 2.85 (d, *J* = 3.8 Hz, 3H, **H-15**), 1.23 (t, *J* = 7.1 Hz, 3H, **H-17**);

¹³C NMR (150 MHz, CDCl₃) δ 172.24, 169.47, 150.88, 136.26, 133.19, 127.83, 127.76, 122.89, 122.47, 119.88, 118.93, 114.57, 114.49, 111.34, 111.19, 110.50, 61.66, 53.30, 29.79, 27.86, 14.25;

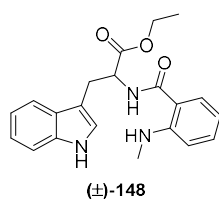
HRMS (ESI) m/z calcd for $C_{21}H_{23}N_3O_3$ $[M + H]^+$ 366.1773, found 366.1772 (mass error -0.22 ppm);

IR 3473, 1730, 1641 cm^{-1} (DCM);

M.P. 162-163 $^{\circ}\text{C}$ (hexane/DCM);

Chiral HPLC Chiralpak AD-H, 85:15 Hexane/IPA, 1.00 mL min^{-1} , injection volume 10 μL , run time 45 min, $\lambda = 235 \text{ nm}$ and 258 nm, $t_{1(R)} = 17.288$, $t_{2(S)} = 23.242$.

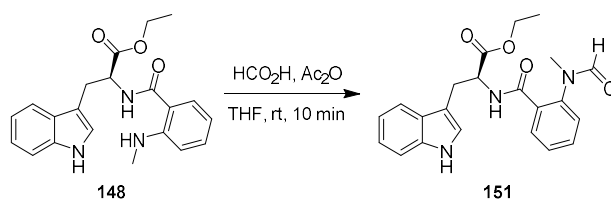
Procedure for synthesis of ($\pm$)-148:



Following the procedure for the synthesis of *R*-**128**, the title compound was obtained as an amorphous, white solid (79%, 2.37 g, 6.49 mmol).

Chiral HPLC Chiralpak AD-H, 85:15 Hexane/IPA, 1.00 mL min^{-1} , injection volume 10 μL , run time 45 min, $\lambda = 235 \text{ nm}$ and 258 nm, $t_{1(R)} = 17.265$, $t_{2(S)} = 23.409$.

5.22. Formamide 151



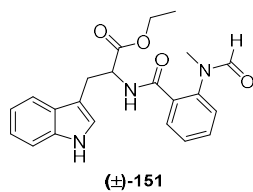
Acetic anhydride (9.00 mL) was added to formic acid (5.00 mL) and allowed to stir at rt for 10 min. To this solution, a solution of aniline **148** (3.18 g, 8.71 mmol) in dioxane (20 mL) was added and allowed to stir for 10 min. Upon stirring at rt, a white precipitate formed and was isolated by vacuum filtration. The precipitate was washed with diethyl ether (2×10 mL) and dried under reduced pressure to give the product as an amorphous white solid (97%, 3.32 g, 8.44 mmol).

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.87 (s, 1H), 8.91 (d, $J = 7.7$ Hz, 1H), 8.07 (s, 1H), 7.56 – 7.50 (m, 2H), 7.39 (td, $J = 7.5, 1.2$ Hz, 1H), 7.36 – 7.31 (m, 3H), 7.19 (d, $J = 2.4$ Hz, 1H), 7.08 (ddd, $J = 8.1, 6.9, 1.2$ Hz, 1H), 7.00 (ddd, $J = 8.0, 7.0, 1.1$ Hz, 1H), 4.63 (ddd, $J = 9.2, 7.7, 5.6$ Hz, 1H), 4.08 (q, $J = 7.1$ Hz, 2H), 3.24 (dd, $J = 14.4, 5.9$ Hz, 1H), 3.15 – 3.07 (m, 1H), 2.92 (s, 3H), 1.14 (t, $J = 7.1$ Hz, 3H);

^{13}C NMR (126 MHz, DMSO) δ 171.52, 167.04, 162.00, 139.50, 136.16, 133.53, 130.90, 128.74, 127.21, 127.09, 127.05, 123.72, 120.97, 118.37, 118.00, 111.43, 109.63, 60.60, 53.49, 32.64, 26.70, 13.90;

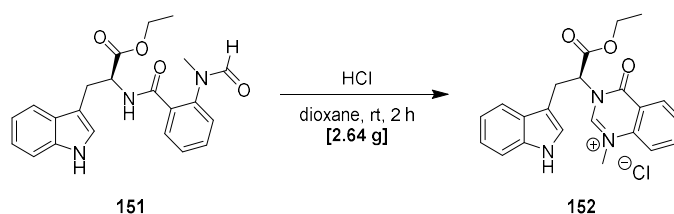
HRMS (ESI) m/z calcd for $\text{C}_{22}\text{H}_{23}\text{N}_3\text{O}_4$ $[\text{M} + \text{H}]^+$ 394.1761, found 394.1750 (mass error –2.79 ppm).

Procedure for synthesis of (±)-151:



Following the procedure for the synthesis of (*R*)-**151**, the title compound was obtained as an amorphous, white solid (94%, 2.13 g, 5.14 mmol).

5.23. Iminium chloride **152**

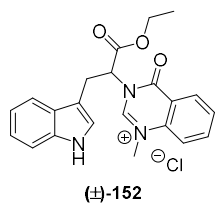


A solution of HCl (4 N, 20 mL) in anhydrous dioxane was added to a solution of **151** (2.15 g, 5.46 mmol) in anhydrous dioxane (20 mL) and allowed to heat to 50 °C for 2 h. Upon cooling, the solvent was removed under reduced pressure to give the title iminium salt **152** (2.64 g) as a yellow foam deemed suitably pure for full spectroscopic analysis.

¹H NMR (500 MHz, DMSO-*d*₆) δ 11.09 (s, 1H), 10.21 (s, 1H), 8.33 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.19 (ddd, *J* = 8.7, 7.3, 1.5 Hz, 1H), 8.03 (d, *J* = 8.3 Hz, 1H), 7.89 (ddd, *J* = 8.2, 7.3, 0.9 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.38 – 7.27 (m, 2H), 7.04 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 6.90 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 5.74 (dd, *J* = 8.3, 7.1 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.10 (s, 3H), 3.82 – 3.74 (m, 1H), 3.68 – 3.61 (m, 1H), 1.13 (t, *J* = 7.1 Hz, 3H);

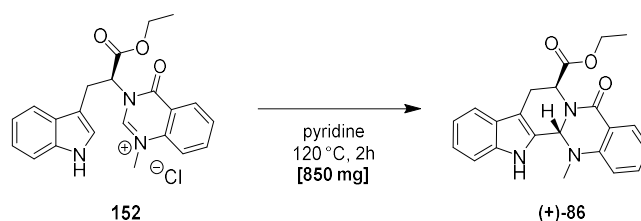
¹³C NMR (125 MHz, DMSO) δ 167.64, 157.15, 152.62, 137.55, 137.34, 136.10, 130.52, 128.09, 126.64, 124.70, 121.21, 119.06, 118.87, 118.58, 117.68, 111.59, 107.51, 62.12, 60.20, 40.47, 25.72, 13.73.

Procedure for synthesis of (±)-152:



Following the procedure for the synthesis of *R*-**152**, the title compound was obtained as an amorphous, yellow solid (88%, 1.86 g, 4.52 mmol).

5.24. Ethyl ester (+)-86



The above data matches that reported in the literature.¹¹⁸

A solution of crude **152** (2.64 g) in pyridine (12 mL) was stirred at reflux for 2 h. After cooling, the pyridine was removed under reduced pressure and the crude residue was purified by flash chromatography (3:1 Pet:EtOAc) to provide the product as a white amorphous solid (41% over two steps, 850 mg, 2.26 mmol).

¹H NMR (500 MHz, DMSO-*d*₆) δ 11.09 (s, 1H), 10.22 (s, 1H), 8.33 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.19 (ddd, *J* = 8.7, 7.3, 1.5 Hz, 1H), 8.03 (d, *J* = 8.3 Hz, 1H), 7.89 (ddd, *J* = 8.2, 7.3, 0.9 Hz, 1H), 7.48 (dt, *J* = 8.0, 0.9 Hz, 1H), 7.36 – 7.27 (m, 2H), 7.04 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 1H), 6.90 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 5.74 (dd, *J* = 8.3, 7.0 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.10 (s, 3H), 3.81 – 3.74 (m, 1H), 3.69 – 3.61 (m, 1H), 1.13 (t, *J* = 7.1 Hz, 3H);

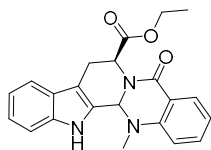
¹³C NMR (125 MHz, DMSO) δ 167.64, 157.15, 152.62, 137.55, 137.34, 136.10, 130.52, 128.09, 126.64, 124.70, 121.21, 119.06, 118.87, 118.58, 117.68, 111.59, 107.51, 62.12, 60.20, 40.47, 25.72, 13.73;

HRMS (ESI) *m/z* calcd for C₂₂H₂₁N₃O₃ [M + H]⁺ 376.1656, found 376.1666 (mass error

IR 3470, 1749, 1665, 1487, 1143, 951, 699 cm⁻¹;

$[\alpha]_D^{20}$ +60° (c 1.10, CHCl₃);

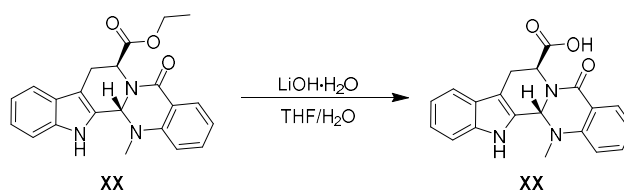
Ethyl ester (-)-86



Isolated from the flash column chromatography as described above, the title compound was a yellow solid (10% over two steps, 204 mg, 0.54 mmol)

$[\alpha]_D^{20} - 58^\circ$ (*c* 1.10, CHCl₃)

5.25. (+)-Carboxyevodiamine (29)



The above data matches that reported in the literature.²⁴

Lithium hydroxide monohydrate (537 mg, 12.8 mmol) was added to a solution of ethyl ester (+)-86 (3.20 g, 8.52 mmol) in 1:1 THF/water (70 mL) and this was stirred at reflux for 4 h. Upon cooling, THF was removed under reduced pressure and the resulting aqueous solution was acidified to approx. pH 2 with aq. 1 M HCl. The resulting solid was filtered, washed with water and dried under high vacuum to give the title compound as a yellow solid (99%, 2.95 g, 8.50 mmol).

¹H NMR ¹H NMR (500 MHz, CDCl₃) δ 8.50 (s, 1H), 8.08 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.56 (d, *J* = 7.9, 1H), 7.49 (dt, *J* = 7.6, 1.6 Hz, 1H), 7.36 (d, *J* = 8.1, 1H), 7.25 – 7.21 (m, 1H), 7.21 – 7.18 (m, 1H), 7.17 – 7.13 (m, 1H), 6.13 (s, 1H), 5.70 (dd, *J* = 6.3, 1.6 Hz, 1H), 3.53 (d, *J* = 15.7, 1H), 3.15 (ddd, *J* = 15.7, 6.3, 1.9 Hz, 1H), 2.41 (s, 3H);

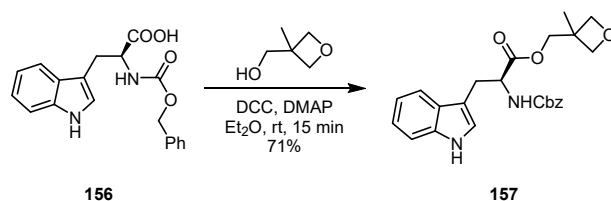
¹³C NMR (126 MHz, CDCl₃) δ 174.87, 165.35, 137.12, 133.91, 129.62, 126.04, 123.60, 123.25, 122.93, 120.32, 119.10, 111.79, 110.96, 68.37, 52.10, 36.99, 31.07, 29.86, 22.83;

HRMS (ESI) *m/z* calcd for C₂₂H₁₈N₃O₃ [M + H]⁺ 348.1343, found 348.1329 (ppm mass error –3.94)

IR 3246, 2871, 1718, 1637, 1420, 1197, 636 cm⁻¹;

[α]_D²⁰ +330° (c 1.10, DMSO);

5.26. Ester **157**



Compound **157** was synthesised according to the procedure described by Winkler and co-workers.¹¹⁹ The data below matches those reported in the literature for the title compound.

A solution of EDC (68 mg, 440 μ mol), 3-hydroxymethyl-3-methyloxethane (35 μ L, 325 μ mol) and DMAP (4 mg, 32 μ mol) was made up in dichloromethane (3 mL). This solution was cooled in an ice bath and a solution of Cbz-Trp-OH **156** (100 mg, 296 μ mol) in dichloromethane (2 mL) was slowly added. Upon complete addition, the new solution was allowed to return to room temperature and stirred until complete by TLC analysis (c.a. 4 h). The reaction was diluted with DCM (10 mL) and washed sequentially with sat. NaHCO₃ (aq.), water and brine. The organic layer was dried over Na₂SO₄ and purified by column chromatography (3:2 PE/EtOAc), to give the title compound as a white foam (71 mg, 167 μ mol, 71%).

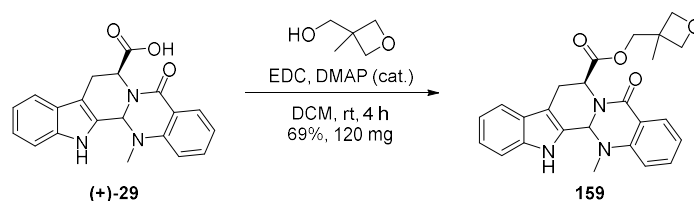
¹H NMR (601 MHz, CDCl₃) δ 8.42 (d, J = 5.8 Hz, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.38 – 7.29 (m, 8H), 7.19 (t, J = 7.6 Hz, 1H), 7.11 (t, J = 7.5 Hz, 1H), 6.97 – 6.92 (m, 1H), 5.60 – 5.41 (m, 1H), 5.17 – 5.02 (m, 2H), 4.76 (q, J = 6.6 Hz, 1H), 4.33 – 4.20 (m, 4H), 4.18 – 3.97 (m, 1H), 3.36 – 3.19 (m, 2H), 1.15 (s, 2H);

¹³C NMR (151 MHz, CDCl₃) δ 172.2, 155.7, 136.1, 136.1, 128.4, 128.4, 128.1, 128.0, 127.2, 122.8, 122.1, 119.5, 118.4, 111.2, 109.4, 79.4, 79.1, 79.1, 69.4, 66.9, 54.5, 38.6, 28.1, 20.6.

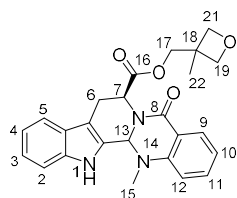
To a cooled solution of ester **157** (60 mg, 0.14 mmol) in CH₂Cl₂ (2 mL) was added boron trifluoride diethyl etherate (52 μL, 0.42 mmol) dropwise. The resulting solution was stirred at this temperature for 2 h, after which time water (5 mL) was added and the resulting solution was extracted from DCM (3 × 10 mL). The combined organic layers were concentrated under reduced pressure giving the title compound as a white oil (49 mg, 0.11 mmol, 82%).

¹³C NMR (126 MHz, CDCl₃) δ 156.5, 136.2, 128.5, 128.3, 127.9, 122.2, 121.8, 119.2, 119.0, 112.4, 111.1, 108.7, 72.9, 66.6, 55.3, 46.3, 30.8, 25.6, 14.5, 11.0.

5.28. Ester 159



A solution of EDC (79 mg, 415 μmol), 3-hydroxymethyl-3-methyloxethane (39 μL , 379 μmol) and DMAP (5 mg, 34 μmol) was made up in dichloromethane (2 mL). This solution was cooled in an ice bath and a solution of (+)-carboxyevodiamine **29** (120 mg, 346 μmol) in dichloromethane (1 mL) was slowly added. Upon complete addition, the new solution was allowed to return to room temperature and stirred until complete by TLC analysis (c.a. 4 h). The reaction was diluted with DCM (10 mL) and washed sequentially with sat. NaHCO_3 (aq.), water and brine. The organic layer was dried over Na_2SO_4 and purified by column chromatography (3:2 PE/EtOAc), to give the title compound as an off-white foam (103 mg, 239 μmol , 69%).



^1H NMR (600 MHz, CDCl_3) δ 8.50 (s, 1H, **NH-1**), 8.15 (dd, $J = 7.8, 1.6$ Hz, 1H, **H-9**), 7.58 (dd, $J = 7.9, 1.1$ Hz, 1H, **H-5**), 7.53 (ddd, $J = 8.0, 7.3, 1.6$ Hz, 1H, **H-11**), 7.40 (dt, $J = 8.2, 0.9$ Hz, 1H, **H-2**), 7.29 – 7.22 (m, 2H, **H-3/10**), 7.22 – 7.14 (m, 2H, **H-4/12**), 6.24 (d, $J = 1.5$ Hz, 1H, **H-13**), 5.80 (dd, $J = 6.1, 1.6$ Hz, 1H, **H-7**), 4.31 (d, $J = 6.1$ Hz, 1H, **CH₂-19/21**), 4.20 – 4.17 (m, 2H, **CH₂-19/21**), 4.15 (d, $J = 6.1$ Hz, 1H, **CH₂-19/21**), 4.07 – 3.99 (m, 2H, **H-17**), 3.60 (dt, $J = 15.6, 1.4$ Hz, 1H, **H-6**), 3.23 (ddd, $J = 15.6, 6.1, 1.9$ Hz, 1H, **H-6**), 2.49 (s, 3H, **CH₃-15**), 1.13 (s, 3H, **CH₃-22**);

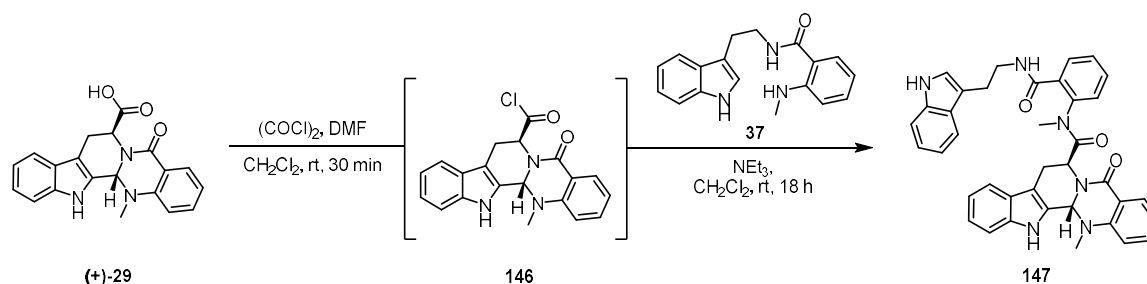
^{13}C NMR (150 MHz, CDCl_3) δ 171.37, 165.38, 137.06, 133.63, 129.36, 127.70, 126.16, 124.57, 123.52, 123.46, 122.96, 120.34, 118.97, 111.59, 110.67, 79.30, 79.20, 69.24, 68.23, 52.41, 39.05, 36.87, 24.01, 23.33, 21.08;

HRMS (ESI) m/z calcd for **159** $[\text{M} + \text{H}]^+$ 432.1917, found 432.1918

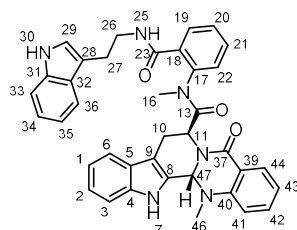
IR 3285, 2814, 1708, 1522, 1481, 1202, 1092, 750 cm^{-1} ;

$[\alpha]_{\text{D}}^{21}$ +76° (c = 1.05, CDCl_3).

5.29. Diamide 147



To an ice-cooled solution of oxalyl chloride (2 M solution in CH_2Cl_2 , 374 μL , 0.74 mmol) in CH_2Cl_2 (8 mL) was added a catalytic amount of DMF (2 drops). To the resulting solution was added, dropwise, a further solution of (+)-carboxyevodiamine (235 mg, 0.68 mmol) in CH_2Cl_2 (8 mL). After warming to room temperature, the resulting solution was stirred for 30 min. After this time the reaction was cooled to 0 °C. A solution of amide **37** (160 mg, 0.54 mmol) and triethylamine (235 μL , 1.69 mmol) in CH_2Cl_2 (10 mL) was added dropwise. The resulting solution was slowly heated to room temperature and stirred at this temperature for 18 h. After this time, the reaction was quenched with aq. HCl (1 M, 30 mL) and extracted with CH_2Cl_2 (3 $\times$ 30 mL). The combined organic layers were washed with sat. aq. NaHCO_3 (50 mL), brine (50 mL) and dried over Na_2SO_4 . The resulting filtrate was concentrated under reduced pressure and purified by flash column chromatography ($\text{CH}_2\text{Cl}_2 \rightarrow 1\% \text{ MeOH}/\text{CH}_2\text{Cl}_2$) to give the title compound as a yellow solid (7:3 mixture of rotomers, 271 mg, 0.44 mmol, 81%).



^1H NMR (601 MHz, $\text{DMSO}-d_6$) δ 11.08 (*minor*, s, 1H), 10.96 (*major*, s, 1H, *NH*-7), 10.82 (*major*, d, J = 2.5 Hz, 1H, *NH*-30), 10.81 (*minor*, appr. s, 1H), 8.65 (t, J = 5.7 Hz, 1H, *NH*-25), 7.72 (dd, J = 7.8, 1.6 Hz, 1H, *ArH*-44), 7.69 (*minor*, d, J = 7.9 Hz, 1H), 7.66 (*minor*, dd, J = 7.7, 1.6 Hz, 1H), 7.58 (*minor*, m, 2H), 7.55 (d, J = 7.9 Hz, 1H), 7.49 (dt, J = 7.6, 3.1 Hz, 1H), 7.48 – 7.39 (m, 5H), 7.35 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 8.1 Hz, 1H), 7.26 (*minor*, d, J = 8.0 Hz, 1H),

7.21 (d, $J = 2.3$ Hz, 1H, CH-29), 7.14 (*minor*, d, $J = 2.3$ Hz, 1H), 7.11 (*minor*, t, $J = 7.5$ Hz, 1H), 7.10 – 7.04 (m, 2H), 7.03 (t, $J = 7.6$ Hz, 1H), 7.00 – 6.94 (m, 3H), 6.89 (t, $J = 7.5$ Hz, 1H), 6.17 (*minor*, s, 1H), 5.53 (s, 1H, CH-47), 4.87 (*minor*, m, 1H), 4.55 (dd, $J = 9.0, 5.6$ Hz, 1H, CH-11), 3.60 (ddd, $J = 13.1, 6.6, 2.2$ Hz, 1H, CH₂-26), 3.57 (*minor*, s, 3H), 3.49 (ddt, $J = 12.3, 8.7, 6.0$ Hz, 1H, CH₂-26), 3.42 (*minor*, m, 1H), 3.36 – 3.27 (m, 1H, *cis*-CH₂-10), 3.15 (s, 3H, CH₃-16), 3.05 (*minor*, s, 3H), 2.94 (s, 3H, CH₃-46), 2.95 – 2.85 (m, 3H, *trans*-CH₂-10; CH₂-27), 2.80 (*minor*, m, 1H);

¹³C NMR (126 MHz, DMSO) δ 168.9 (C-13), 167.4 (C-23), 164.3 (C-37), 148.1 (*minor*), 140.8 (quat.), 136.4 (quat.), 136.2 (quat.), 136.2 (quat.), 135.3 (Ar-C), 133.5 (Ar-C), 130.6 (*minor*), 130.3 (*minor*), 129.4 (Ar-C), 128.2 (Ar-C), 127.9 (C-44), 127.7 (Ar-C), 127.2 (quat.), 127.1 (*minor*), 126.0 (quat.), 122.6 (C-29), 122.6 (quat.), 121.7 (Ar-C), 121.1 (Ar-C), 120.9 (quat.), 119.5 (Ar-C), 118.9 (Ar-C), 118.8 (Ar-C), 118.3 (Ar-C), 118.2 (Ar-C), 118.1 (Ar-C), 117.9 (Ar-C), 116.8 (*minor*), 111.6 (*minor*), 111.5 (*minor*), 111.5 (Ar-C), 111.4 (Ar-C), 111.4 (quat.), 111.4 (quat.), 109.8 (quat.), 70.6 (C-47), 66.3 (*minor*), 54.9 (C-11), 40.2 (*minor*), 40.1 (C-26), 37.6 (C-16), 37.3 (C-46), 25.1 (C-27), 21.7 (C-10);

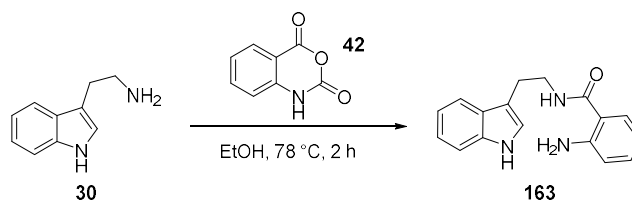
HRMS (ESI) m/z calcd for C₃₈H₃₅N₆O₃⁺ [M + H]⁺ 623.2765, found 623.2747 (mass error –1.82 ppm);

IR 3224 (br), 2363, 1638, 1624, 1607, 1489, 1431, 1210, 1020, 743 cm⁻¹;

α_D^{25} ($c = 0.1$, DMSO) +121 °

R_f 0.27 (2% MeOH/CH₂Cl₂).

5.30. Amide 163



Compound **163** was made according to known literature procedure from Chu and co-workers.¹⁵⁸ The data below matches those reported in the literature for the title compound.

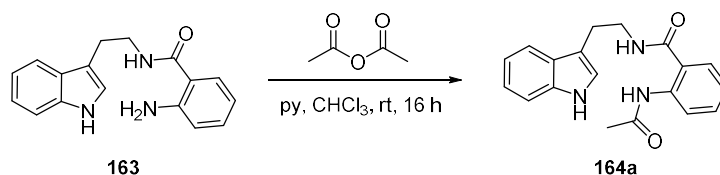
Isatoic anhydride (16.5 g, 100 mmol) was added to a stirring solution of tryptamine (16.0 g, 100 mmol) in ethanol (130 mL) and stirred at reflux for 2 h. The resulting solution was allowed to cool to room temperature and the resulting precipitate collected by filtration. The filtrate was recrystallized from ethanol to give the title compound as beige needles (61%, 17.2 g, 62 mmol).

¹H NMR (500 MHz, DMSO-*d*₆) δ 10.80 (s, 1H), 8.31 (t, *J* = 5.7 Hz, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.45 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.34 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.18 (d, *J* = 2.3 Hz, 1H), 7.12 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 7.07 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 6.99 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.69 (dd, *J* = 8.2, 1.2 Hz, 1H), 6.50 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 6.39 (s, 2H), 3.52 – 3.43 (m, 2H), 2.93 (t, *J* = 7.6 Hz, 2H);

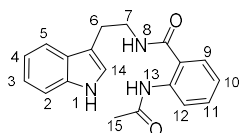
¹³C NMR (126 MHz, DMSO) δ 168.80, 149.58, 136.23, 131.48, 127.98, 127.28, 122.54, 120.89, 118.29, 118.18, 116.29, 114.97, 114.50, 111.97, 111.34, 39.77, 25.19;

M.P. 159 – 160 °C (ethanol).

5.31. Diamide 164a



Acetic anhydride (0.34 mL, 3.60 mmol) was added to a cooled solution of amide **163** (232 mg, 0.83 mmol) and pyridine (0.18 mL, 2.16 mmol) in chloroform (5 mL). This was stirred at room temperature overnight, after which the solution was concentrated under reduced pressure. Upon extensive drying under high vacuum, the title compound was obtained without further purification as a white solid (265 mg, 0.82 mmol, 98%).



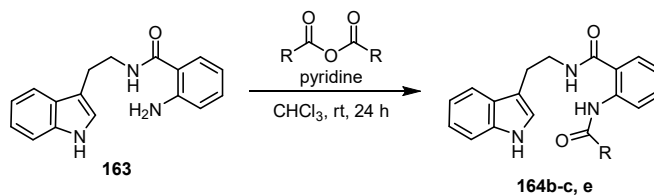
¹H NMR (600 MHz, DMSO-*d*₆) δ 11.22 (s, 1H, **H-13**), 10.82 (s, 1H, **H-1**), 8.83 (t, *J* = 5.7 Hz, 1H, **H-8**), 8.38 (d, *J* = 8.3 Hz, 1H, **H-9**), 7.68 (dd, *J* = 7.9, 1.6 Hz, 1H, **H-12**), 7.58 (dd, *J* = 7.8, 1.2 Hz, 1H, **H-5**), 7.47 (ddd, *J* = 8.5, 7.3, 1.5 Hz, 1H, **H-10**), 7.35 (dt, *J* = 8.1, 0.9 Hz, 1H, **H-2**), 7.20 (d, *J* = 2.3 Hz, 1H, **H-14**), 7.15 – 7.04 (m, 2H, **H-3/11**), 6.99 (ddd, *J* = 7.9, 6.9, 1.0 Hz, 1H, **H-4**), 3.56 (td, *J* = 7.6, 5.7 Hz, 2H, **H-6**), 2.98 (t, *J* = 7.5 Hz, 2H, **H-7**), 2.09 (s, 3H, **H-15**);

¹³C NMR (150 MHz, DMSO) δ 168.1, 138.9, 136.2, 131.6, 127.9, 127.2, 122.7, 122.4, 120.9, 120.4, 118.2, 111.7, 111.4, 40.1, 24.8;

HRMS (ESI) *m/z* calcd for C₁₉H₂₀N₃O₂ [*M* + *H*]⁺ 322.1511, found 322.1512 (mass error 0.30 ppm);

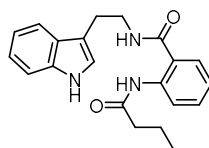
M.P. 150 – 152 °C.

5.32. General Procedure A for the synthesis of diamides **164b-c**, **164e**



A solution of aniline **163** (250 mg, 0.90 mmol) and pyridine (0.18 mL, 2.24 mmol) in chloroform (5 mL) was cooled to 0 °C. To this solution, the corresponding anhydride (3.58 mmol) was added and the solution was allowed to slowly heat to room temperature. After stirring for 24 h, the solutions were concentrated under reduced pressure and purified directly by flash column chromatography.

5.32.1. Diamide 164c (JS-E-65)



Synthesised from valeric anhydride. The crude material was purified by column chromatography (2:1 petroleum ether/ethyl acetate) to give the product as a clear oil (205 mg, 0.56 mmol, 63%).

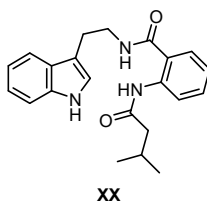
¹H NMR (601 MHz, DMSO-*d*₆) δ 11.28 (s, 1H), 10.81 (s, 1H), 8.83 (t, *J* = 5.7 Hz, 1H), 8.40 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.68 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.57 (dq, *J* = 7.9, 0.9 Hz, 1H), 7.46 (ddd, *J* = 8.6, 7.4, 1.6 Hz, 1H), 7.34 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.18 (d, *J* = 2.3 Hz, 1H), 7.11 (td, *J* = 7.6, 1.2 Hz, 1H), 7.06 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 6.97 (ddd, *J* = 7.9, 6.9, 1.0 Hz, 1H), 3.55 (td, *J* = 7.5, 5.5 Hz, 2H), 2.97 (t, *J* = 7.5 Hz, 2H), 2.33 (t, *J* = 7.5 Hz, 2H), 1.64 – 1.55 (m, 2H), 1.37 – 1.30 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H);

¹³C NMR (151 MHz, DMSO) δ 171.03, 168.23, 138.93, 136.25, 131.71, 127.95, 127.26, 122.67, 122.40, 120.94, 120.40, 118.23, 111.72, 111.39, 40.16, 40.05, 37.20, 33.38, 27.10, 24.84, 21.70, 13.69;

HRMS (ESI) *m/z* calcd for **164c** [M + H]⁺ 364.2020, found 364.2029 (2.47 ppm mass error);

IR 3377 (sh), 3300 (br), 3199 (sh), 2955, 2929, 2871, 1664, 1513 (br), 1445, 732 cm⁻¹.

5.32.2. Diamide 164b (JS-E-66)



Synthesised from isovaleric anhydride. The crude material was purified by column chromatography (3:1 petroleum ether/ethyl acetate) to give the product as a clear oil (330 mg, 0.90 mmol, 98%).

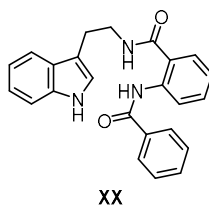
¹H NMR (601 MHz, DMSO-*d*₆) δ 11.26 (s, 1H), 10.81 (s, 1H), 8.83 (t, *J* = 5.7 Hz, 1H), 8.40 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.68 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.57 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.46 (ddd, *J* = 8.6, 7.4, 1.5 Hz, 1H), 7.34 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.18 (d, *J* = 2.3 Hz, 1H), 7.11 (td, *J* = 7.6, 1.2 Hz, 1H), 7.07 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 6.98 (ddd, *J* = 7.9, 6.9, 1.0 Hz, 1H), 3.55 (td, *J* = 7.6, 5.6 Hz, 2H), 2.97 (t, *J* = 7.5 Hz, 2H), 2.50 (p, *J* = 1.8 Hz, 4H), 2.20 (d, *J* = 7.2 Hz, 2H), 2.13 – 2.03 (m, 1H), 0.94 (d, *J* = 6.6 Hz, 6H);

¹³C NMR (151 MHz, DMSO) δ 170.42, 168.25, 138.87, 136.26, 131.71, 127.95, 127.27, 122.68, 122.46, 121.11, 120.95, 120.45, 118.25, 118.23, 111.73, 111.41, 46.80, 40.16, 25.61, 24.83, 22.22;

HRMS (ESI) *m/z* calcd for **164b** [*M* + *H*]⁺ 364.2020, found 364.2024 (0.45 ppm mass error);

IR 3293, 2962, 2927, 2874, 1676, 1508, 1435, 742 cm⁻¹.

5.32.3. Diamide 164e



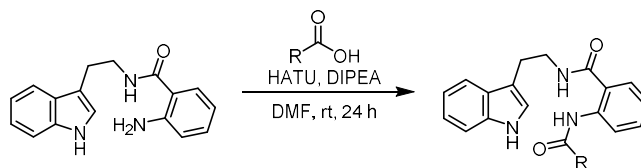
Synthesised from benzoic anhydride. The crude material was purified by column chromatography (2:1 petroleum ether/ethyl acetate) to give the product as a white foam (280 mg, 0.73 mmol, 82%).

¹H NMR (400 MHz, DMSO-*d*₆) δ 12.62 (s, 1H), 11.15 – 10.61 (m, 1H), 9.01 (t, *J* = 5.6 Hz, 1H), 8.66 (dd, *J* = 8.4, 1.2 Hz, 1H), 8.04 – 7.91 (m, 2H), 7.81 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.67 – 7.51 (m, 5H), 7.33 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.24 – 7.14 (m, 2H), 7.06 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 6.97 (ddd, *J* = 7.9, 6.9, 1.1 Hz, 1H), 3.65 – 3.53 (m, 2H), 2.99 (t, *J* = 7.4 Hz, 2H);

MS (ESI⁺) *m/z* calcd for C₂₄H₂₂N₃O₂ [M + H]⁺ 384.1634, found 384.1639 (1.30 ppm mass error);

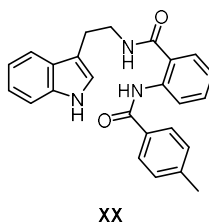
IR 3393 (sh), 3332 (sh), 3286 (br), 3198 (sh), 2925, 2854, 1632, 1518, 1449 cm⁻¹

5.33. General Procedure B for the synthesis of diamides **164d**, **164f-l**



Aniline **163** (200 mg, 0.72 mmol) was added to a solution of carboxylic acid (0.86 mmol), HATU (327 mg, 0.86 mmol), DIPEA (250 μL , 1.43 mmol) in DMF (4.5 mL) at room temperature. This was allowed to stir overnight, after which the solution was diluted with EtOAc (20 mL). The resulting solution was washed with 10% aq. NaHCO_3 , water and brine. The organic fraction was dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and purified by flash column chromatography to give the corresponding diamide products.

5.33.1. Diamide 164f (JS-E-121)



Synthesised from *p*-toluic acid (117 mg, 0.86 mmol). The crude residue was purified by flash column chromatography (2:1 petroleum ether/ethyl acetate) to give the product as a white solid (239 mg, 0.60 mmol, 84%).

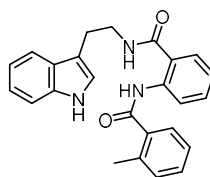
¹H NMR (500 MHz, DMSO-*d*₆) δ 12.57 (s, 1H), 10.90 – 10.75 (m, 1H), 9.01 (t, *J* = 5.7 Hz, 1H), 8.66 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.85 (d, *J* = 8.2 Hz, 2H), 7.80 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.62 – 7.55 (m, 2H), 7.42 – 7.37 (m, 2H), 7.34 (dt, *J* = 8.0, 0.9 Hz, 1H), 7.22 – 7.15 (m, 2H), 7.07 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 6.98 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 3.65 – 3.56 (m, 2H), 3.00 (t, *J* = 7.4 Hz, 2H), 2.40 (s, 3H);

¹³C NMR (126 MHz, DMSO) δ 169.07, 164.78, 142.64, 139.99, 136.72, 132.62, 132.29, 129.98, 129.80, 129.59, 128.61, 127.74, 127.43, 123.17, 123.10, 121.41, 120.79, 120.67, 118.71, 112.17, 111.87, 40.73, 38.72, 25.24, 21.50;

HRMS (ESI) *m/z* calcd for C₂₅H₂₄N₃O₂ [M + H]⁺ 398.1863, found 398.1857 (1.51 ppm mass error);

IR 3356, 3313, 3043, 2920, 1633, 1543, 1511, 1450, 1301, 1232, 755, 701 cm⁻¹.

5.33.2. Diamide 164g (JS-E-122)



XX

Synthesised from *o*-toluic acid (117 mg, 0.86 mmol). The crude residue was purified by flash column chromatography (2:1 petroleum ether/ethyl acetate) to give the product as a white solid (234 mg, 0.59 mmol, 82%).

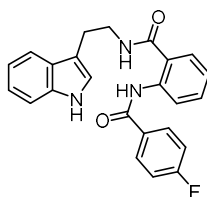
¹H NMR (500 MHz, DMSO-*d*₆) δ 11.90 (s, 1H), 10.89 (s, 1H), 8.93 (t, *J* = 5.7 Hz, 1H), 8.60 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.76 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.58 – 7.53 (m, 3H), 7.43 (td, *J* = 7.5, 1.4 Hz, 1H), 7.37 – 7.30 (m, 3H), 7.22 – 7.16 (m, 2H), 7.06 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 6.96 (ddd, *J* = 8.0, 6.9, 1.0 Hz, 1H), 3.53 (td, *J* = 7.4, 5.6 Hz, 2H), 2.95 (t, *J* = 7.4 Hz, 2H), 2.45 (s, 3H);

¹³C NMR (126 MHz, DMSO) δ 168.74, 167.62, 139.62, 136.98, 136.71, 136.38, 132.48, 131.66, 130.75, 128.58, 127.70, 127.31, 126.60, 123.35, 123.16, 121.40, 121.34, 120.76, 118.70, 118.68, 112.13, 111.86, 40.64, 25.26, 20.12;

HRMS (ESI) m/z calcd for C₂₅H₂₄N₃O₂ [M + H]⁺ 398.1863, found 398.1861 (0.50 ppm mass error);

IR 3340, 3317, 3051, 2965, 2921, 1633, 1586, 1585, 1514, 1443, 1308, 1232, 748, 726 cm⁻¹.

5.33.3. Diamide 164h (JS-E-123)



xx

Synthesised from 4-fluorobenzoic acid (120 mg, 0.86 mmol). The crude residue was purified by flash column chromatography (2:1 petroleum ether/ethyl acetate) to give the product as a white solid (250 mg, 0.62 mmol, 87%).

¹H NMR (500 MHz, DMSO-*d*₆) δ 12.61 (s, 1H), 10.81 (s, 1H), 9.01 (t, *J* = 5.7 Hz, 1H), 8.62 (dd, *J* = 8.4, 1.2 Hz, 1H), 8.07 – 7.94 (m, 2H), 7.81 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.59 – 7.53 (m, 2H), 7.43 (t, *J* = 8.8 Hz, 2H), 7.32 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.22 – 7.17 (m, 2H), 7.06 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 6.97 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 3.64 – 3.56 (m, 2H), 2.99 (t, *J* = 7.4 Hz, 2H);

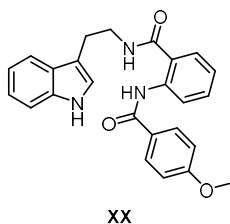
¹³C NMR (126 MHz, DMSO) δ 168.54, 165.27, 163.30, 139.33, 136.21, 132.16, 131.11, 131.08, 129.67, 129.60, 128.13, 127.24, 122.84, 122.68, 120.91, 120.42, 120.25, 118.21, 116.07, 115.89, 111.68, 111.36, 40.22, 24.74;

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -108.12 (tt, *J* = 8.8, 5.4 Hz);

HRMS (ESI) *m/z* calcd for C₂₄H₂₁N₃O₂F [*M* + *H*]⁺ 402.1612, found 402.1612 (0.07 ppm mass error);

IR 3313 (br), 1663, 1626, 2596, 1500, 1443, 1285, 1227, 1157, 747 cm⁻¹.

5.33.4. Diamide 164i (JS-E-136)



Synthesised from 4-methoxybenzoic acid (130 mg, 0.86 mmol). The crude residue was purified by flash column chromatography (2:1 petroleum ether/ethyl acetate). The resulting oil was triturated from water and washed with pentane to give the product as a white solid (221 mg, 0.53 mmol, 75%).

¹H NMR (601 MHz, DMSO-*d*₆) δ 12.53 (s, 1H), 10.82 (s, 1H), 9.00 (t, *J* = 5.6 Hz, 1H), 8.66 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.93 – 7.90 (m, 2H), 7.80 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.59 (dq, *J* = 7.9, 0.9 Hz, 1H), 7.55 (ddd, *J* = 8.6, 7.3, 1.5 Hz, 1H), 7.34 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.21 (d, *J* = 2.3 Hz, 1H), 7.17 (td, *J* = 7.6, 1.2 Hz, 1H), 7.14 – 7.12 (m, 2H), 7.07 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 6.98 (ddd, *J* = 7.9, 6.9, 1.0 Hz, 1H), 3.86 (s, 3H), 3.61 (td, *J* = 7.4, 5.6 Hz, 2H), 3.00 (t, *J* = 7.3 Hz, 2H);

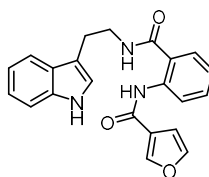
¹³C NMR (151 MHz, DMSO) δ 169.12, 164.40, 162.69, 140.15, 136.71, 132.61, 129.33, 128.59, 127.74, 127.20, 123.17, 122.93, 121.41, 120.64, 120.58, 118.71, 114.70, 112.19, 111.87, 55.96, 40.71, 25.24.;

HRMS (ESI) *m/z* calcd for C₂₅H₂₄N₃O₃ [*M* + *H*]⁺ 414.1812, found 414.1810 (0.53 ppm mass error);

IR 3419, 3268 (br), 3088, 2922, 2852, 1637, 1600, 1506, 1441, 1299, 1254, 1187, 740 cm⁻¹;

R_f 0.28 (2:1 Petroleum ether/EtOAc).

5.33.5. Diamide 164j (JS-E-137)



Synthesised from 3-furoic acid (96 mg, 0.86 mmol). The crude residue was purified by flash column chromatography (2:1 petroleum ether/ethyl acetate) to give the product as a white solid (226 mg, 0.64 mmol, 89%).

¹H NMR (500 MHz, DMSO-*d*₆) δ 12.25 (s, 1H), 10.88 – 10.73 (m, 1H), 8.98 (t, *J* = 5.7 Hz, 1H), 8.54 (dd, *J* = 8.4, 1.2 Hz, 1H), 8.30 (t, *J* = 1.2 Hz, 1H), 7.86 (t, *J* = 1.7 Hz, 1H), 7.79 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.58 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.54 (ddd, *J* = 8.6, 7.3, 1.5 Hz, 1H), 7.33 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.20 (d, *J* = 2.4 Hz, 1H), 7.17 (td, *J* = 7.6, 1.2 Hz, 1H), 7.06 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 6.97 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.82 (dd, *J* = 1.9, 1.0 Hz, 1H), 3.65 – 3.47 (m, 2H), 2.99 (t, *J* = 7.4 Hz, 2H);

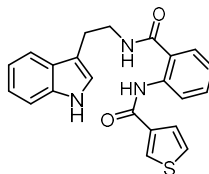
¹³C NMR (126 MHz, DMSO) δ 168.46, 159.89, 145.81, 144.99, 139.20, 136.22, 132.12, 128.10, 127.25, 123.45, 122.68, 122.65, 120.91, 120.17, 120.15, 118.21, 111.68, 111.37, 108.20, 40.22, 24.76;

HRMS (ESI) *m/z* calcd for C₂₂H₂₀N₃O₃ [M + H]⁺ 374.1499, found 374.1504 (1.28 ppm mass error);

IR 3337 (sh), 3296 (br), 2922, 2852, 1630, 1603, 1508, 1449, 1330, 1159, 744 cm⁻¹;

R_f 0.33 (2:1 Petroleum ether/EtOAc).

5.33.6. Diamide 164k (JS-E-138)



Synthesised from 3-thiophenecarboxylic acid (110 mg, 0.86 mmol). The crude residue was purified by flash column chromatography (2:1 petroleum ether/ethyl acetate) to give the product as a beige solid (203 mg, 0.52 mmol, 73%).

¹H NMR (601 MHz, DMSO-*d*₆) δ 12.46 (s, 1H), 10.85 – 10.68 (m, 1H), 9.00 (t, *J* = 5.6 Hz, 1H), 8.60 (dd, *J* = 8.4, 1.2 Hz, 1H), 8.20 (dd, *J* = 3.0, 1.3 Hz, 1H), 7.80 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.74 (dd, *J* = 5.1, 3.0 Hz, 1H), 7.59 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.57 – 7.54 (m, 1H), 7.53 (dd, *J* = 5.1, 1.4 Hz, 1H), 7.34 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.21 (d, *J* = 2.4 Hz, 1H), 7.18 (td, *J* = 7.6, 1.2 Hz, 1H), 7.07 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 6.98 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 3.66 – 3.57 (m, 2H), 3.00 (t, *J* = 7.5, 6.9 Hz, 2H);

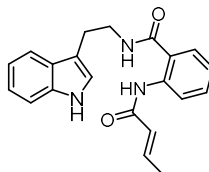
¹³C NMR (151 MHz, DMSO) δ 169.02, 160.67, 139.89, 138.48, 136.71, 132.64, 130.30, 128.61, 128.58, 127.74, 126.39, 123.18, 123.10, 121.41, 120.63, 120.59, 118.72, 118.70, 112.18, 111.86, 40.71, 25.25;

HRMS (ESI) *m/z* calcd for C₂₂H₂₀H₃O₂S [M + H]⁺ 390.1271, found 390.1275 (1.10 ppm mass error);

IR 3287 (sh), 3270 (br), 2852, 1641, 1489, 1443, 1308, 1122, 753 cm⁻¹;

R_f .023 (2:1 Petroleum ether/EtOAc).

5.33.7. Diamide 164d (JS-E-139)



Synthesised from crotonic acid (110 mg, 0.86 mmol). The crude residue was purified by flash column chromatography (5:2 petroleum ether/ethyl acetate) to give the product as a clear oil (191 mg, 0.55 mmol, 77%).

¹H NMR (601 MHz, DMSO-*d*₆) δ 11.48 (s, 1H), 10.81 (s, 1H), 8.87 (t, *J* = 5.6 Hz, 1H), 8.48 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.71 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.57 (dt, *J* = 7.9, 0.9 Hz, 1H), 7.48 (ddd, *J* = 8.6, 7.3, 1.5 Hz, 1H), 7.34 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.19 (d, *J* = 2.3 Hz, 1H), 7.13 (td, *J* = 7.6, 1.3 Hz, 1H), 7.07 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 6.98 (ddd, *J* = 7.9, 6.9, 1.0 Hz, 1H), 6.80 (dq, *J* = 15.2, 6.8 Hz, 1H), 6.09 – 6.01 (m, 1H), 3.59 – 3.53 (m, 2H), 2.98 (t, *J* = 7.5 Hz, 2H), 1.88 (dd, *J* = 6.8, 1.7 Hz, 3H);

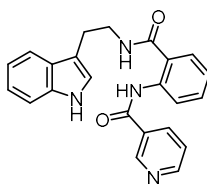
¹³C NMR (151 MHz, DMSO) δ 168.22, 163.30, 140.41, 139.11, 136.23, 131.77, 128.00, 127.23, 126.65, 122.66, 122.49, 120.91, 120.82, 120.41, 118.21, 111.69, 111.37, 40.15, 24.81, 24.08, 17.44;

HRMS (ESI) *m/z* calcd for C₂₁H₂₂N₃O₂ [*M* + *H*]⁺ 348.17065, found 348.1707 (0.14 ppm mass error);

IR 3289 (br), 2937 (br), 1670, 1624, 1599, 1515, 1446, 1276, 1054, 1033, 960, 737 cm⁻¹;

R_f 0.32 (2:1 Petroleum ether/EtOAc).

5.33.8. Diamide 164I (JS-G-5)



Synthesised from nicotinic acid (106 mg, 0.86 mmol). The crude residue was purified by flash column chromatography (2:1 ethyl acetate/petroleum ether) to give the product as a beige solid (256 mg, 0.67 mmol, 93%).

¹H NMR (601 MHz, DMSO-*d*₆) δ 12.71 (s, 1H), 10.85 – 10.76 (m, 1H), 9.13 (dd, *J* = 2.4, 0.9 Hz, 1H), 9.03 (t, *J* = 5.7 Hz, 1H), 8.82 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.61 (dd, *J* = 8.3, 1.2 Hz, 1H), 8.26 (ddd, *J* = 8.0, 2.4, 1.7 Hz, 1H), 7.83 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.64 (ddd, *J* = 7.9, 4.8, 0.9 Hz, 1H), 7.61 – 7.54 (m, 2H), 7.32 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.23 (td, *J* = 7.6, 1.2 Hz, 1H), 7.21 (d, *J* = 2.3 Hz, 1H), 7.06 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 6.97 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 1H), 3.69 – 3.55 (m, 2H), 3.10 – 2.95 (m, 2H);

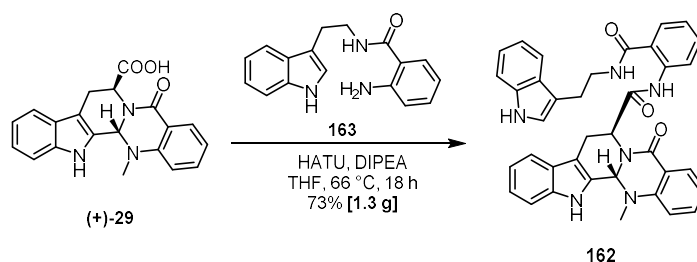
¹³C NMR (151 MHz, DMSO) δ 168.95, 163.43, 153.05, 148.62, 139.52, 136.71, 135.21, 132.68, 130.68, 128.66, 127.73, 124.47, 123.67, 123.19, 121.40, 121.22, 120.96, 118.70, 112.15, 111.85, 40.75, 25.25, 24.57;

HRMS (ESI) *m/z* calcd for **164I** [*M* + *H*]⁺ 385.1586, found 385.1588 (0.52 ppm mass error);

IR 3258 (br), 2918, 1631, 1576, 1404, 1333, 1120, 1090, 722 cm⁻¹

R_f 0.41 (2:1 EtOAc/Petroleum ether).

5.34. Diamide 162



To a solution of (+)-caroxyevodiamine (**29**, 1.13 g, 3.25 mmol) in THF (80 mL), HATU (1.42 g, 3.74 mmol) and DIPEA (2.83 mL, 16.3 mmol) was sequentially added. The solution was stirred for 15 min, after which time amide **163** (0.82 g, 2.93 mmol) was added to the solution. The resulting mixture was refluxed for 18 h, after which time the solvent was removed under reduced pressure. The residue was dissolved in CH₂Cl₂ (100 mL) and NaHCO₃ (100 mL) was added. Extraction was performed from CH₂Cl₂ (3 x 100 mL), the combined organic layers were washed sequentially with sat. aq. NH₄Cl (150 mL) and brine (150 mL). The organic layer was dried over Na₂SO₄ and the filtrate concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (CH₂Cl₂ → 1% MeOH/CH₂Cl₂) to give the product as a yellow solid (1.30 g, 2.15 mmol, 73%).

¹H NMR (500 MHz, DMSO-*d*₆) δ 11.96 (s, 1H), 11.45 (s, 1H), 10.84 (d, *J* = 2.4 Hz, 1H), 8.87 (t, *J* = 5.7 Hz, 1H), 8.31 (dd, *J* = 8.5, 1.2 Hz, 1H), 7.95 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.64 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.59 – 7.54 (m, 2H), 7.52 – 7.48 (m, 1H), 7.40 – 7.32 (m, 3H), 7.26 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.13 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H), 7.11 – 7.05 (m, 4H), 7.03 – 6.96 (m, 2H), 6.36 (s, 1H), 5.54 (dd, *J* = 6.0, 1.6 Hz, 1H), 3.65 (d, *J* = 15.6 Hz, 1H), 3.53 – 3.32 (m, 2H), 3.21 (ddd, *J* = 15.5, 6.1, 1.5 Hz, 1H), 2.89 (t, *J* = 7.6 Hz, 2H), 2.69 (s, 3H);

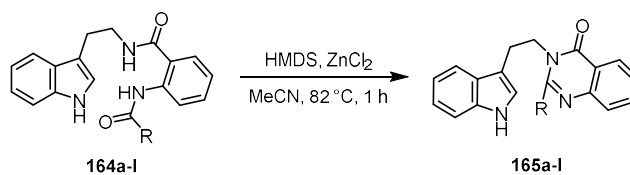
¹³C NMR (126 MHz, DMSO) δ 169.2, 168.1, 164.2, 150.4, 138.3, 136.8, 136.2, 133.3, 131.9, 128.5, 127.9, 127.5, 127.2, 125.5, 122.8, 122.6, 122.3, 122.2, 122.0, 120.9, 120.6, 120.4, 119.8, 119.0, 118.5, 118.3, 118.2, 111.7, 111.6, 111.4, 109.3, 67.3, 54.6, 40.1, 38.2, 24.7, 22.7;

HRMS (ESI) m/z calcd for $C_{37}H_{32}N_6O_3Na^+$ $[M + Na]^+$ 631.2428, found 631.2429 (ppm mass error 0.09);

IR 3222, 1677, 1578, 1441, 1256, 1107, 989, 661 cm^{-1} ;

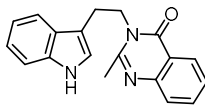
$[\alpha]_D^{20}$ +46 ° (0.90, DMSO).

5.35. General procedure for the synthesis of 4-quinazolinones **165a-l**



To a stirring solution of the corresponding diamide **164a-l** (c.a. 100 mg) and HMDS (5 eq.) in acetonitrile (5 mL) was added ZnCl (1 M solution in diethyl ether, 5 eq.). The corresponding solutions/suspensions were heated to reflux until completion (1 h, unless stated otherwise). The reactions were quenched with 10% aq. NaHCO₃ and the resulting solid removed by vacuum filtration. The filtrates were diluted with EtOAc, washed with water and brine, dried over Na₂SO₄ and filtered. The filtrates were concentrated and purified by column chromatography to give the title compounds.

5.35.1. 4-quinazolinone **165a** (JS-E-109)



Diamide **164a** (109 mg, 0.34 mmol) was used for this reaction. The crude was triturated with water and washed with pentane to give the title compound as a beige solid (99 mg, 0.33 mmol, 96%).

¹H NMR (500 MHz, DMSO-*d*₆) δ 10.89 (s, 1H), 8.17 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.80 (ddd, *J* = 8.4, 7.1, 1.5 Hz, 1H), 7.65 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.58 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.51 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 7.37 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.19 (d, *J* = 2.3 Hz, 1H), 7.10 – 7.06 (m, 1H), 6.99 (ddd, *J* = 7.9, 6.9, 1.0 Hz, 1H), 4.34 – 4.19 (m, 2H), 3.17 – 3.06 (m, 2H), 2.49 (s, 3H);

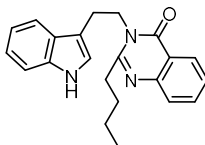
¹³C NMR (126 MHz, DMSO) δ 161.14, 154.96, 147.09, 136.22, 134.22, 127.08, 126.48, 126.17, 126.13, 123.24, 121.10, 120.05, 118.46, 118.18, 111.48, 110.58, 45.10, 23.66, 22.68;

HRMS (ESI) *m/z* calcd for C₁₉H₁₈N₃O⁺ [*M* + *H*]⁺ 304.1405, found 304.1407 (0.77 ppm mass error);

IR 3339, 2967, 2919, 1663, 1590, 1388, 1338, 777, 735 cm⁻¹;

R_f 0.27 (2:1 Petroleum ether/EtOAc).

5.35.2. 4-quinazolinone **165c** (JS-E-69)



Diamide **164c** (100 mg, 0.28 mmol) used in this reaction. The crude material was purified by column chromatography (2:1 petroleum ether/EtOAc) to give the title compound as a white solid (88 mg, 0.26 mmol, 91%).

¹H NMR (601 MHz, DMSO-*d*₆) δ 10.94 – 10.75 (m, 1H), 8.17 (ddd, *J* = 7.9, 1.5, 0.6 Hz, 1H), 7.79 (ddd, *J* = 8.5, 7.1, 1.6 Hz, 1H), 7.62 (dq, *J* = 7.9, 0.9 Hz, 1H), 7.59 (dt, *J* = 8.0, 0.9 Hz, 1H), 7.50 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H), 7.36 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.15 (d, *J* = 2.3 Hz, 1H), 7.08 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 6.98 (ddd, *J* = 7.9, 6.9, 1.0 Hz, 1H), 4.32 – 4.19 (m, 2H), 3.18 – 2.96 (m, 2H), 2.69 – 2.59 (m, 2H), 1.79 – 1.57 (m, 2H), 1.27 (h, *J* = 7.4 Hz, 2H), 0.85 (t, *J* = 7.4 Hz, 3H);

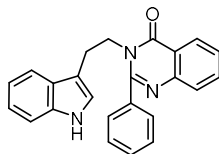
¹³C NMR (151 MHz, DMSO) δ 161.27, 157.25, 146.94, 136.26, 134.18, 127.07, 126.71, 126.17, 126.11, 123.22, 121.10, 119.98, 118.45, 118.09, 111.48, 110.54, 44.23, 33.47, 28.31, 23.89, 21.69, 13.70;

HRMS (ESI) *m/z* calcd for **165c** [*M* + *H*]⁺ 346.1914, found 346.1917 (0.31 ppm mass error);

IR 3363, 2961, 2928, 1667, 1589, 1099, 770, 735 cm⁻¹;

R_f 0.35 (2:1 Petroleum ether/EtOAc).

5.35.3. 4-quinazolinone **165e** (JS-E-70)



Diamide **164e** (100 mg, 0.26 mmol) used in this reaction. The crude material was purified by column chromatography (3:1 petroleum ether/EtOAc) to give the title compound as a white solid (80 mg, 0.22 mmol, 84%).

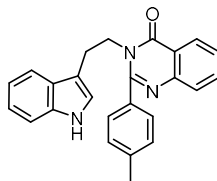
¹H NMR (500 MHz, DMSO-*d*₆) δ 10.79 – 10.75 (m, 1H), 8.26 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.87 (ddd, *J* = 8.4, 7.1, 1.6 Hz, 1H), 7.71 – 7.65 (m, 1H), 7.63 – 7.48 (m, 6H), 7.29 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.01 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 6.91 (d, *J* = 2.3 Hz, 1H), 6.85 – 6.76 (m, 2H), 4.18 – 4.08 (m, 2H), 2.98 – 2.88 (m, 2H);

¹³C NMR (151 MHz, CDCl₃) δ 162.6, 156.5, 147.4, 136.5, 134.2, 127.4, 127.0, 126.8, 126.4, 122.5, 122.4, 120.6, 119.8, 118.7, 112.2, 111.5, 45.0, 43.7, 27.3, 24.7, 22.5;

MS (ESI⁺) *m/z* calcd for C₂₄H₂₀N₃O⁺ [*M* + *H*]⁺ 366.1562, found 366.1559 (–0.82 ppm mass error);

IR 3297, 2924, 2867, 1664, 1584, 1406, 1308, 1257, 1111, 800,, 699 cm^{–1}.

5.35.4. 4-quinazolinone **165f** (JS-E-132)



Diamide **164f** (100 mg, 0.25 mmol) used in this reaction. The crude material was purified by column chromatography (3:1 petroleum ether/EtOAc) to give the title compound as a white solid (91 mg, 0.24 mmol, 95%).

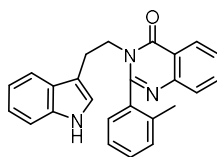
¹H NMR (601 MHz, DMSO-*d*₆) δ 10.78 (s, 1H), 8.25 (ddd, *J* = 7.9, 1.5, 0.6 Hz, 1H), 7.86 (ddd, *J* = 8.1, 7.1, 1.6 Hz, 1H), 7.67 (dt, *J* = 8.0, 0.9 Hz, 1H), 7.59 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H), 7.45 – 7.41 (m, 2H), 7.34 – 7.31 (m, 2H), 7.29 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.01 (ddd, *J* = 8.1, 5.6, 2.4 Hz, 1H), 6.94 (d, *J* = 2.3 Hz, 1H), 6.80 – 6.76 (m, 2H), 4.18 – 4.11 (m, 2H), 2.98 – 2.86 (m, 2H), 2.43 (s, 3H);

¹³C NMR (151 MHz, DMSO) δ 161.4, 156.3, 147.1, 139.2, 136.3, 134.6, 132.8, 129.0, 128.8, 128.1, 127.3, 127.0, 126.9, 126.3, 123.0, 121.1, 120.6, 118.2, 118.0, 111.5, 110.3, 46.3, 24.1, 21.1;

MS (ESI⁺) *m/z* calcd for C₂₅H₂₂N₃O [M + H]⁺ 380.1718, found 380.1719 (0.22 ppm mass error);

IR 3327, 2943 (sh), 2921, 2852, 1664, 1586, 1459 (br), 1336, 1237, 1108, 1003, 818, 772, 735 cm⁻¹.

5.35.5. 4-Quinazolinone **165g** (JS-E-132)



Diamide **164g** (100 mg, 0.25 mmol) used in this reaction. The crude material was purified by column chromatography (3:1 petroleum ether/EtOAc) to give the title compound as a white solid (88 mg, 0.23 mmol, 93%).

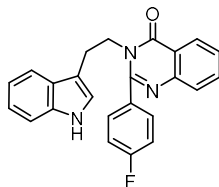
¹H NMR (500 MHz, DMSO-*d*₆) δ 10.85 – 10.70 (m, 1H), 8.28 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.88 (ddd, *J* = 8.5, 7.1, 1.6 Hz, 1H), 7.69 (dt, *J* = 8.1, 0.8 Hz, 1H), 7.62 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.51 (td, *J* = 7.6, 1.4 Hz, 1H), 7.41 (td, *J* = 6.2, 5.6, 3.0 Hz, 2H), 7.35 (tt, *J* = 7.1, 1.1 Hz, 1H), 7.28 (dt, *J* = 8.0, 0.9 Hz, 1H), 7.00 (ddd, *J* = 8.1, 6.7, 1.3 Hz, 1H), 6.93 (d, *J* = 2.4 Hz, 1H), 6.83 – 6.72 (m, 2H), 4.28 (ddd, *J* = 13.2, 11.0, 5.1 Hz, 1H), 3.69 (ddd, *J* = 13.1, 11.0, 5.7 Hz, 1H), 2.92 (dddd, *J* = 39.1, 13.5, 10.9, 5.3 Hz, 2H), 2.15 (s, 3H);

¹³C NMR (126 MHz, DMSO) δ 161.1, 155.4, 147.0, 136.1, 135.1, 134.8, 134.5, 130.2, 129.5, 128.1, 127.2, 127.1, 126.7, 126.2, 125.9, 122.9, 121.0, 120.6, 118.2, 117.7, 111.4, 110.1, 45.9, 23.8, 18.7;

MS (ESI⁺) *m/z* calcd for C₂₅H₂₂N₃O [M + H]⁺ 380.1718, found 380.1721 (0.79 ppm mass error);

IR 3314, 2930, 2866, 1665, 1577, 1447, 1326, 1099, 1012, 822, 755, 699 cm⁻¹.

5.35.6. 4-quinazolinone **165h** (JS-E-134)



Diamide **164h** (100 mg, 0.25 mmol) used in this reaction. The crude material was purified by column chromatography (3:1 petroleum ether/EtOAc) to give the title compound as a white solid (85 mg, 0.22 mmol, 89%).

¹H NMR (601 MHz, DMSO-*d*₆) δ 10.75 (s, 1H), 8.26 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.86 (ddd, *J* = 8.4, 7.1, 1.5 Hz, 1H), 7.69 – 7.65 (m, 1H), 7.60 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 7.57 – 7.46 (m, 2H), 7.32 – 7.22 (m, 3H), 7.02 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H), 6.97 – 6.87 (m, 2H), 6.80 (ddd, *J* = 7.9, 6.9, 1.0 Hz, 1H), 4.20 – 4.06 (m, 2H), 2.99 – 2.87 (m, 2H);

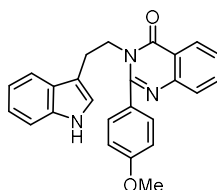
¹³C NMR (151 MHz, DMSO) δ 161.1, 155.1, 146.8, 136.1, 134.4, 131.8, 130.4, 130.4, 127.1, 126.9, 126.8, 126.1, 122.8, 120.9, 120.5, 118.1, 117.5, 115.2, 115.1, 111.3, 110.1, 46.2, 40.1, 23.7;

¹⁹F NMR (151 MHz DMSO) δ 111.4;

MS (ESI⁺) *m/z* calcd for C₂₄H₁₉N₃OF [M + H]⁺ 384.1467, found 384.1470 (0.74 ppm mass error);

IR 3362, 2945 (sh), 2918, 2851, 1669, 1602, 1583, 1506, 1221, 1095, 827, 774, 739 cm⁻¹.

5.35.7. 4-quinazolinone **165i** (JS-E-142)



Diamide **164i** (104 mg, 0.25 mmol) used in this reaction. The crude material was purified by passing the crude material through a plug of celite, after the standard work-up, to give the title compound as a beige solid (97 mg, 0.24 mmol, 96%).

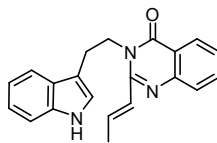
¹H NMR (601 MHz, DMSO-*d*₆) δ 10.79 (d, *J* = 2.1 Hz, 1H), 8.25 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.86 (ddd, *J* = 8.4, 7.1, 1.6 Hz, 1H), 7.64 (dd, *J* = 8.0, 2.1 Hz, 1H), 7.59 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 7.51 – 7.42 (m, 2H), 7.30 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.08 – 6.98 (m, 3H), 6.95 (d, *J* = 2.3 Hz, 1H), 6.88 (dd, *J* = 7.9, 1.2 Hz, 1H), 6.79 (ddd, *J* = 7.9, 6.9, 1.0 Hz, 1H), 4.26 – 4.09 (m, 2H), 3.86 (s, 3H), 3.03 – 2.85 (m, 2H);

¹³C NMR (151 MHz, DMSO) δ 161.35, 160.02, 156.00, 146.97, 136.14, 134.42, 129.66, 127.78, 127.14, 126.81, 126.17, 122.87, 120.97, 120.43, 118.09, 117.82, 113.65, 111.34, 110.21, 55.35, 46.21, 40.06, 23.96;

HRMS (ESI) *m/z* calcd for C₂₅H₂₂N₃O₂ [*M* + *H*]⁺ 396.1707, found 396.1714 (1.89 ppm mass error);

IR 3331, 2902, 2841, 1687, 1600, 1555, 1481, 1288, 1202, 797 cm⁻¹.

5.35.8. 4-quinazolinone **165d** (JS-E-143)



Diamide **164d** (95 mg, 0.27 mmol) used in this reaction. The crude material was purified by passing the crude material through a plug of celite, after the standard work-up, to give the title compound as a beige solid (82 mg, 0.25 mmol, 91%).

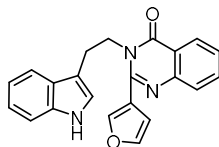
¹H NMR (601 MHz, DMSO-*d*₆) δ 10.87 (s, 1H), 8.16 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.80 (ddd, *J* = 8.4, 7.1, 1.6 Hz, 1H), 7.66 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.61 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.49 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 7.36 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.18 (d, *J* = 2.3 Hz, 1H), 7.10 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 7.01 (ddd, *J* = 7.9, 6.9, 1.0 Hz, 1H), 6.92 (dq, *J* = 14.9, 6.9 Hz, 1H), 6.53 (dq, *J* = 14.8, 1.7 Hz, 1H), 4.38 (t, *J* = 7.7 Hz, 2H), 3.08 (t, *J* = 7.5 Hz, 2H), 1.81 (dd, *J* = 6.9, 1.7 Hz, 3H);

¹³C NMR (151 MHz, DMSO) δ 161.7, 152.6, 147.7, 139.9, 136.8, 134.8, 127.7, 127.4, 126.7, 126.6, 123.8, 123.7, 121.6, 120.4, 118.9, 118.6, 111.9, 110.8, 44.2, 24.8, 18.6;

HRMS (ESI) *m/z* calcd for C₂₁H₂₀N₃O [*M* + *H*]⁺ 330.1601, found 330.1602 (0.30 ppm mass error);

IR 3352, 2943, 2917, 1669, 1597, 1117, 887, 714 cm⁻¹;

5.35.9. 4-quinazolinone **165j** (JS-E-144)

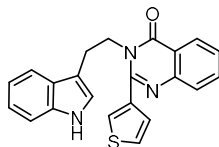


Diamide **164j** (35 mg, 0.094 mmol) used in this reaction. The crude material was purified by passing the crude material through a plug of celite, after the standard work-up, to give the title compound as a beige solid (30 mg, 0.084 mmol, 89%).

¹H NMR (601 MHz, CDCl₃) δ 8.37 (dd, *J* = 8.1, 1.5 Hz, 1H), 8.06 (s, 1H), 7.77 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1H), 7.71 (d, *J* = 8.1 Hz, 1H), 7.67 – 7.64 (m, 1H), 7.56 – 7.50 (m, 1H), 7.50 – 7.48 (m, 1H), 7.42 (d, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.93 (d, *J* = 2.3 Hz, 1H), 6.64 (d, *J* = 1.8 Hz, 1H), 4.73 – 4.24 (m, 2H), 3.37 – 3.07 (m, 2H);

¹³C NMR (151 MHz, CDCl₃) δ 162.3, 149.7, 147.4, 143.4, 143.0, 136.2, 134.4, 127.4, 127.3, 127.1, 126.8, 122.3, 122.0, 121.3, 120.8, 119.7, 118.6, 112.1, 111.1, 110.5, 46.4, 24.6.

5.35.10. 4-quinazolinone 165k (JS-E-145)

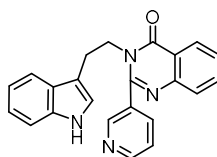


Diamide **164k** (94 mg, 0.24 mmol) used in this reaction. The crude material was purified by passing the crude material through a plug of celite, after the standard work-up, to give the title compound as a beige solid (81 mg, 0.22 mmol, 90%).

¹H NMR (601 MHz, Chloroform-*d*) δ 8.39 (ddd, J = 8.1, 1.6, 0.6 Hz, 1H), 7.96 (s, 1H), 7.80 – 7.72 (m, 2H), 7.54 (ddd, J = 8.1, 6.9, 1.3 Hz, 1H), 7.46 (dd, J = 3.0, 1.3 Hz, 1H), 7.42 (dd, J = 4.9, 3.0 Hz, 1H), 7.33 (dt, J = 8.1, 0.9 Hz, 1H), 7.21 – 7.14 (m, 3H), 7.01 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H), 6.87 (d, J = 2.3 Hz, 1H), 4.53 – 4.34 (m, 2H), 3.22 – 3.00 (m, 2H);

¹³C NMR (151 MHz, CDCl₃) δ 162.2, 152.2, 136.2, 134.4, 127.4, 127.2, 127.2, 127.1, 126.8, 126.8, 126.7, 122.2, 122.2, 121.0, 119.6, 118.5, 112.1, 111.1, 46.7, 24.6.

5.35.11. 4-quinazolinone **165I** (JS-G-8)



Diamide **164I** (100 mg, 0.26 mmol) used in this reaction. The crude material was purified by passing the crude material through a plug of celite, after the standard work-up, to give the title compound as a beige solid (53 mg, 0.15 mmol, 56%).

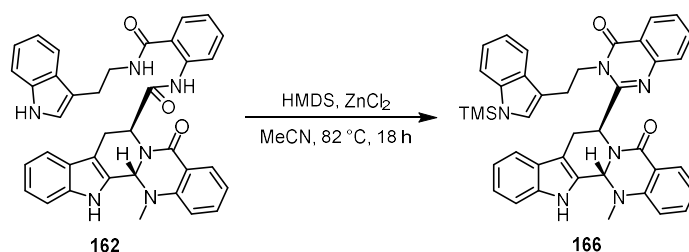
¹H NMR (601 MHz, DMSO-*d*₆) δ 10.90 – 10.62 (m, 1H), 8.71 (dd, *J* = 4.9, 1.6 Hz, 1H), 8.69 (dd, *J* = 2.4, 0.9 Hz, 1H), 8.29 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.89 (ddd, *J* = 8.4, 7.1, 1.6 Hz, 1H), 7.85 (dt, *J* = 7.8, 2.0 Hz, 1H), 7.70 (dt, *J* = 8.4, 0.8 Hz, 1H), 7.65 – 7.60 (m, 1H), 7.46 (ddd, *J* = 7.8, 4.9, 0.9 Hz, 1H), 7.33 – 7.27 (m, 1H), 7.02 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 6.90 (d, *J* = 2.4 Hz, 1H), 6.89 – 6.86 (m, 1H), 6.79 (ddd, *J* = 7.9, 6.9, 1.0 Hz, 1H), 4.20 – 4.03 (m, 2H), 3.00 – 2.92 (m, 2H);

¹³C NMR (126 MHz, DMSO) δ 161.11, 153.74, 150.23, 148.37, 146.80, 136.12, 135.61, 134.59, 131.44, 127.28, 127.25, 126.77, 126.22, 123.10, 122.93, 121.00, 120.63, 118.27, 117.50, 111.42, 110.04, 46.42, 23.73;

HRMS (ESI) *m/z* calcd for C₂₃H₁₉N₄O [M + H]⁺ 367.1514, found 367.1516 (0.54 ppm mass error);

IR 3332, 2839 (sh), 2817, 1671, 1555, 1419, 1210, 1134, 985, 697 cm⁻¹.

5.36. TMS protected 4-quinazolinone **166**



Hexamethyldisilazane (21 μ L, 100 μ mol) and ZnCl₂ (1 M solution in diethyl ether, 100 mL, 100 μ mol) were added sequentially to a solution of diamide **162** (20 mg, 33 μ mol) in 0.5 mL acetonitrile. The resulting suspension was heated to reflux for 18 h, after which the starting material was consumed. The solution was cooled and quenched with 10% aq. NaHCO₃ (5 mL). The resulting precipitate was removed by filtration and washed with EtOAc (3 $\times$ 5 mL). The filtrate was washed with water (10 mL) and brine (10 mL). The organic fraction was dried over Na₂SO₃ and the filtrate was concentrated to give a crude residue. This residue was purified by column chromatography (3:1 petroleum ether/ethyl acetate) to give the title compound as a yellow solid (7 mg, 11 μ mol, 33%).

¹H NMR (601 MHz, Chloroform-*d*) δ 8.42 (s, 1H), 8.22 (dd, *J* = 7.9, 1.5 Hz, 1H), 8.12 (dd, *J* = 7.8, 1.6 Hz, 1H), 8.10 – 7.96 (m, 1H), 7.58 – 7.53 (m, 1H), 7.53 – 7.48 (m, 2H), 7.40 (dd, *J* = 15.4, 7.9 Hz, 2H), 7.32 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H), 7.29 – 7.16 (m, 6H), 7.09 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.85 (d, *J* = 1.4 Hz, 1H), 6.51 (d, *J* = 7.4 Hz, 1H), 5.19 – 5.01 (m, 1H), 4.14 – 3.99 (m, 1H), 3.72 – 3.65 (m, 1H), 3.55 (ddd, *J* = 15.9, 7.5, 1.7 Hz, 1H), 3.46 (td, *J* = 12.9, 5.1 Hz, 1H), 3.25 (d, *J* = 15.9 Hz, 1H), 2.61 (s, 3H), 1.22 (d, *J* = 5.1 Hz, 1H), 0.57 (s, 9H);

¹³C NMR (151 MHz, CDCl₃) δ 165.8, 162.3, 155.8, 151.5, 146.6, 140.7, 136.9, 133.7, 133.5, 131.1, 129.2, 128.8, 128.1, 127.6, 126.6, 126.3, 124.2, 123.7, 122.9, 122.8, 121.7, 121.0, 120.0, 119.6, 118.5, 114.2, 113.0, 111.4, 107.6, 69.4, 51.0, 44.8, 37.2, 24.6, 24.1, 0.3;

HRMS (ESI) *m/z* calcd for **166** [M + H]⁺ 663.2859, found 663.2862 (0.56 ppm mass error);

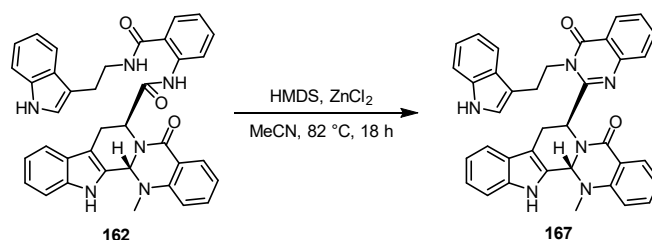
IR 3290, 2957, 1646, 1607, 1596, 1475, 1453, 1161, 1145, 844, 742 cm⁻¹;

R_f 0.42 (EtOAc/petroleum ether);

$[\alpha]_D^{20} +159.0^\circ$ (c 1.03, CHCl_3).

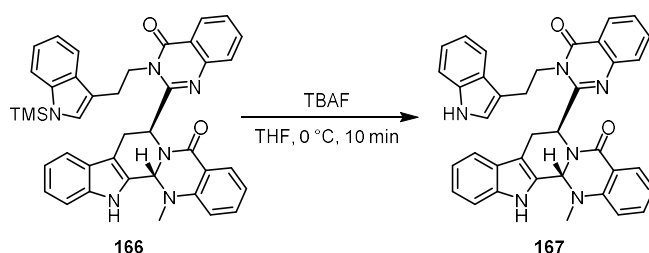
5.37. Bisindole 4-quinazolinone **167**

Method A:



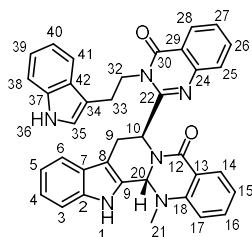
Hexamethyldisilazane (0.69 mL, 3.30 mmol) and ZnCl₂ (1 M solution in diethyl ether, 3.3 mL, 3.30 mmol) were added sequentially to a solution of diamide **162** (381 mg, 0.63 mmol) in 12 mL acetonitrile. The resulting suspension was heated to reflux for 18 h, after which the starting material was consumed. The solution was cooled and quenched with 10% aq. NaHCO₃ (20 mL). The resulting precipitate was removed by filtration and washed with EtOAc (3 × 20 mL). The filtrate was washed with water (40 mL) and brine (40 mL). The organic fraction was dried over Na₂SO₃ and the filtrate was concentrated to give a crude residue. This residue was purified by column chromatography (3:1 petroleum ether/ethyl acetate) to give the title compound as a yellow solid (211 mg, 0.36 mmol, 57%).

Method B:



To an ice-bath cooled solution of quinazolinone **166** (20 mg, 30 μmol) in THF (1 mL), tetrabutylammonium fluoride solution (1 M in THF, 33 μL, 33 μmol) was added. The resulting solution was stirred at this temperature for 10 min, after which time the reaction was quenched with sat. aq. NaHCO₃ (5 mL). The resulting solution was extracted with EtOAc (3 x 5 mL), the combined organic extracts were washed with water (10 mL) and brine (10 mL). The organic

layer was dried over Na₂SO₄ and the filtrate concentrated under reduced pressure. The resulting residue was purified through a silica plug (1:1 EtOAc/petroleum ether) to give the title compound as a yellow foam (16 mg, 28 μmol, 93%).



¹H NMR (601 MHz, DMSO-*d*₆) δ 11.33 (s, 1H), 10.92 (d, *J* = 2.4 Hz, 1H), 8.10 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.92 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.79 (d, *J* = 7.8 Hz, 1H), 7.65 (ddd, *J* = 8.4, 7.1, 1.5 Hz, 1H), 7.60 (ddd, *J* = 8.6, 7.2, 1.6 Hz, 1H), 7.47 – 7.41 (m, 2H), 7.40 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.38 – 7.34 (m, 1H), 7.33 – 7.28 (m, 3H), 7.17 – 7.13 (m, 1H), 7.12 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 7.08 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 1H), 7.05 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 1H), 6.95 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.59 (s, 1H), 6.37 (d, *J* = 7.2 Hz, 1H), 4.86 (ddd, *J* = 13.6, 11.8, 5.3 Hz, 1H), 4.12 (ddd, *J* = 13.5, 11.6, 4.8 Hz, 1H), 3.58 – 3.49 (m, 2H), 3.44 (d, *J* = 16.1 Hz, 1H), 3.29 – 3.19 (m, 1H), 2.73 (s, 3H);

¹³C NMR (151 MHz, DMSO) δ 164.7, 161.0, 156.5, 150.6, 145.9, 136.9, 136.2, 134.2, 133.6, 128.7, 128.4, 127.1, 126.7, 126.1, 125.8, 123.1, 121.9, 121.8, 121.0, 121.0, 120.3, 120.2, 118.6, 118.5, 118.4, 118.2, 111.5, 111.4, 110.5, 106.8, 68.8, 51.1, 44.2, 35.9, 24.0, 22.8;

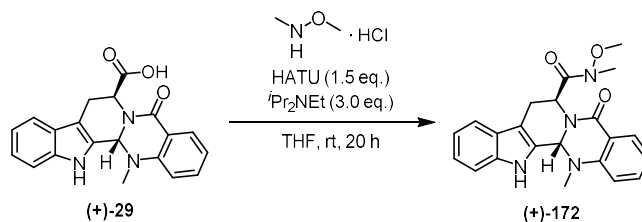
HRMS (ESI) *m/z* calcd for C₃₇H₂₉N₆O₂[−] [*M* − *H*][−] 589.2347, found 589.2375 (2.85 ppm mass error);

IR 3341, 2897, 1644, 1584, 1465, 1401, 1180, 1087, 840, 704 cm^{−1};

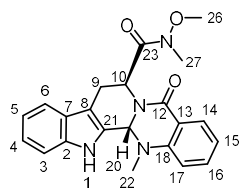
R_f 0.24 (1:1 EtOAc/petroleum ether);

[α]_D²⁰ +95° (c 1.12, DMSO).

5.38. Weinreb amide **172**



To a room temperature solution of (+)-carboxyevodiamine (**29**, 1.90 g, 5.47 mmol) in THF (80 mL), HATU (3.12 g, 8.20 mmol) and DIPEA (2.86 mL, 16.4 mmol) were sequentially added. The resulting solution was allowed to stir at this temperature for 15 min, after which time *N,O*-dimethylhydroxylamine hydrochloride (0.80 g, 8.20 mmol) was added. This was allowed to stir for 20 h at room temperature, after which time the solvent was removed under reduced pressure. The resulting residue was dissolved in CH_2Cl_2 (50 mL), sat. aq. NaHCO_3 (50 mL) was added and extraction from CH_2Cl_2 (3 $\times$ 50 mL) was performed. The combined organic layers were washed with water (100 mL), brine (100 mL) and dried over Na_2SO_4 . The resulting filtrate was concentrated under reduced pressure and purified by flash column chromatography (2:1 petroleum ether/EtOAc) to give the title compound as a white powder (1.97 g, 5.04 mmol, 92%).



^1H NMR (601 MHz, CDCl_3) δ 8.39 (s, 1H, **NH-1**), 8.09 (dd, $J = 7.8, 1.6$ Hz, 1H, **CH-14**), 7.55 (dd, $J = 7.9, 1.0$ Hz, 1H), 7.49 (ddd, $J = 8.0, 7.3, 1.6$ Hz, 1H), 7.36 (dt, $J = 8.1, 0.9$ Hz, 1H), 7.21 (tdd, $J = 7.6, 5.2, 1.2$ Hz, 2H), 7.17 (dd, $J = 8.0, 1.1$ Hz, 1H), 7.14 (ddd, $J = 8.0, 7.0, 1.0$ Hz, 1H), 6.45 (s, 1H, **CH-20**), 5.94 (dd, $J = 7.1, 1.5$ Hz, 1H, **CH-10**), 3.98 (s, 3H, **CH₃-26**), 3.39 – 3.34 (dd, $J = 16.4, 1.4$ Hz, 1H, **trans-CH-9**), 3.30 (ddd, $J = 16.2, 7.1, 1.7$ Hz, 1H, **cis-CH-9**), 3.14 (s, 3H, **CH₃-22**), 2.48 (s, 3H, **CH₃-27**);

^{13}C NMR (151 MHz, CDCl_3) δ 166.0, 151.6, 137.1, 133.4, 129.1, 128.3, 126.5, 124.3, 123.8, 123.0, 123.0, 119.9, 118.8, 111.6, 109.0, 68.8, 61.6, 50.6, 36.8, 22.6;

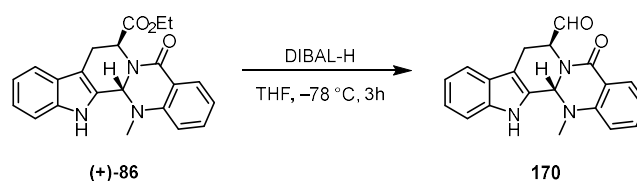
HRMS (ESI) m/z calcd for $\text{C}_{22}\text{H}_{23}\text{N}_4\text{O}_3^+$ $[\text{M}+\text{H}]^+$ 391.1725, found 391.1727 (0.51 ppm mass error);

IR 3282, 1640, 1605, 1403, 1324, 909, 723 cm^{-1} ;

$[\alpha]_{\text{D}}^{20}$ +59.0° (c 1.00, MeOH)

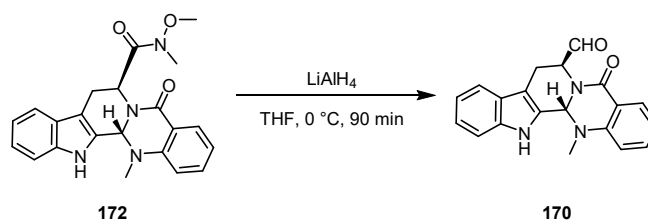
5.39. Aldehyde 170

Method A:



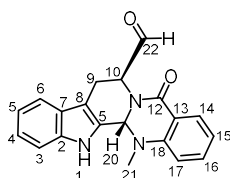
To a solution of ethyl ester **(+)-86** (500 mg, 1.36 mmol) in THF (20 mL) was stirred at -78 °C for 30 min. After this time, a solution DIBAL-H (1 M solution in THF; 1.36 mL, 1.36 mmol) was added slowly at this temperature, over 30 min. The reaction was allowed to proceed over for 3 h, after which methanol (10 mL) was added. The solution was allowed to return to room temperature and a saturated solution of Rochelle's salt (30 mL) was added. Extraction was performed with EtOAc (3 × 30 mL), the organic layers were combined and washed with brine. The organic layer was dried with Na₂SO₄, filtered, and the resulting filtrate was concentrated under reduced pressure. The resulting crude solid was purified by flash column chromatography (2:1 petroleum ether/ethyl acetate) to give the title compound as a yellow solid (187 mg, 0.56 mmol, 41%). As well as this, the starting material was recovered in 32% yield.

Method B (from Weinreb amide **172**):



A solution of Weinreb amide **172** (320 mg, 0.82 mmol) in THF (10 mL) was cooled to 0 °C and lithium aluminium hydride (1 M solution in THF; 4.1 mL, 4.1 mmol) was added over 10 min. The reaction was allowed to proceed at the temperature for 90 min, before being quenched with EtOAc (20 mL). The resulting solution was allowed to warm to room temperature and a saturated solution of Rochelle's salt (30 mL) was added. The resulting slurry was passed

through a pad of celite and water (20 mL) was added to the resulting filtrate. Extraction was performed with EtOAc (3 × 20 mL). The combined organic layers were washed with aq. HCl (1 M, 3 × 30 mL), sat. aq. NaHCO₃ (3 × 30 mL) and brine (30 mL). The organic layer was dried with Na₂CO₃, filtered and the filtrate concentrated under reduced pressure to give the title compound as a yellow solid (251 mg, 0.757 mmol, 92%).



¹H NMR (601 MHz, CDCl₃) δ 9.59 (s, 1H, *CH*-22), 8.26 (s, 1H, *NH*-1), 8.15 (dd, *J* = 7.8, 1.6 Hz, 1H, *CH*-14), 7.61 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.53 (ddd, *J* = 8.0, 7.3, 1.6 Hz, 1H), 7.40 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.27 (qd, *J* = 7.6, 7.2, 1.1 Hz, 2H), 7.22 – 7.16 (m, 2H), 6.17 (t, *J* = 1.6 Hz, 1H, *CH*-20), 5.73 (dd, *J* = 6.8, 1.5 Hz, 1H, *CH*-10), 3.58 (dt, *J* = 15.9, 1.4 Hz, 1H, *trans-CH*-10), 3.24 (ddd, *J* = 15.9, 6.9, 1.9 Hz, 1H, *cis-CH*-10), 2.44 (s, 3H, *CH*₃-21);

¹³C NMR (151 MHz, CDCl₃) δ 198.4, 165.2, 151.3, 137.0, 133.6, 129.4, 128.2, 126.1, 124.7, 123.8, 123.6, 123.2, 120.4, 119.0, 111.6, 109.9, 68.0, 58.9, 37.1, 19.4;

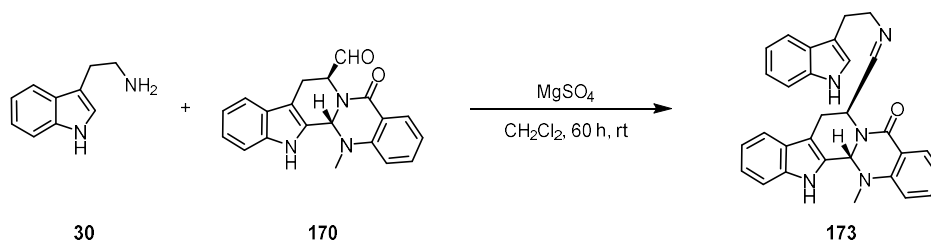
HRMS (ESI) *m/z* calcd for C₂₀H₁₈N₃O₂⁺ [*M* + *H*]⁺ 332.1394, found 332.1402 (2.56 ppm mass error);

IR 3214, 2875, 2730, 1778, 1651, 1548, 1266, 1173, 952, 701, 742 cm⁻¹;

R_f 0.14 (2:1 petroleum ether/EtOAc);

[α]_D²⁰ +37° (*c* 0.95, CHCl₃).

5.40. Imine 173



Tryptamine (106 mg, 0.664 mmol) was added to a solution of aldehyde **170** (220 mg, 0.664 mmol) in DCM (10 mL). To this solution, magnesium sulfate was added, until the powder was free-flowing. The resulting suspension was stirred at room temperature for 24 h, after which the MgSO_4 was removed by vacuum filtration. The resulting filtrate was concentrated under reduced pressure and further dried under high vacuum to give the title compound as a yellow solid (295 mg, 0.623 mmol, 94%).

^1H NMR (601 MHz, CDCl_3) δ 8.36 (s, 1H), 8.19 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.59 (dt, $J = 7.8, 0.9$ Hz, 1H), 7.55 – 7.50 (m, 1H), 7.49 – 7.45 (m, 1H), 7.42 (dd, $J = 7.9, 0.9$ Hz, 1H), 7.38 (ddd, $J = 8.2, 7.1, 1.2$ Hz, 1H), 7.32 – 7.27 (m, 1H), 7.25 (td, $J = 7.5, 1.1$ Hz, 1H), 7.21 – 7.16 (m, 2H), 7.14 – 7.10 (m, 2H), 7.01 (ddd, $J = 7.9, 5.7, 2.3$ Hz, 1H), 6.63 (s, 1H), 6.13 (t, $J = 1.5$ Hz, 1H), 5.78 (d, $J = 2.3$ Hz, 1H), 5.73 – 5.68 (m, 1H), 3.75 (dddd, $J = 12.7, 6.2, 3.4, 1.1$ Hz, 1H), 3.44 – 3.31 (m, 1H), 3.11 (ddd, $J = 15.6, 6.2, 1.8$ Hz, 1H), 3.05 (dt, $J = 15.5, 1.5$ Hz, 1H), 2.85 (dddd, $J = 14.7, 6.2, 4.1, 0.9$ Hz, 1H), 2.79 – 2.69 (m, 1H), 2.46 (s, 3H);

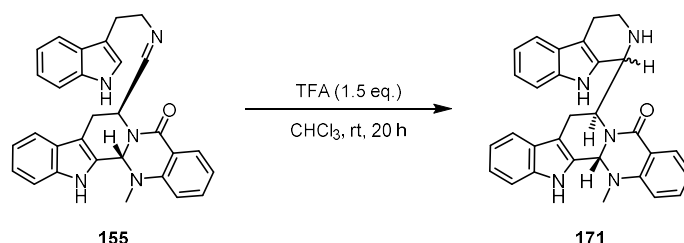
^{13}C NMR (151 MHz, CDCl_3) δ 164.8, 161.6, 151.0, 136.8, 135.7, 133.0, 129.1, 128.6, 126.9, 126.7, 124.2, 124.0, 122.8, 122.8, 122.6, 121.2, 119.7, 119.0, 118.6, 118.3, 112.5, 111.4, 110.8, 110.3, 67.7, 59.8, 52.5, 37.0;

HMRS (ESI $^+$) m/z calcd for $\text{C}_{30}\text{H}_{28}\text{N}_5\text{O}^+$ $[\text{M} + \text{H}]^+$ 474.2249, found 474.2254 (1.05 ppm mass error);

IR 3407, 3275, 2919, 2851, 1635, 1605, 1456, 1335, 762 cm^{-1} ;

$[\alpha]_{\text{D}}^{20}$ +39° ($c = 1.00$, CHCl_3).

5.41. Tetrahydro- β -carboline 171



Trifluoroacetic acid (0.12 mL, 1.50 mmol) was added to a stirred solution of imine **173** (200 mg, 0.42 mmol) in chloroform (10 mL) at 0 °C. The reaction was allowed to slowly return to room temperature and stirred at this temperature for 20 h. The resulting solution was cooled to 0 °C and sat. aq. solution of NaHCO₃ (10 mL) was added with stirring. The biphasic mixture was diluted with DCM (5 mL) and water (5 mL). Extraction from DCM (3 × 10) followed by washing with brine (25 mL) and drying of the combined organic layers with Na₂SO₄ was performed. The crude residue was obtained from concentration of the filtrate under reduced pressure and purified by flash column chromatography to give the title compound as an amorphous pale-yellow solid (mixture of *cis:trans* isomers 2.9:1; 163 mg, 0.34 mmol, 83%).

¹H NMR (601 MHz, CDCl₃) δ 9.10 (s, 1H), 8.04 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.66 – 7.63 (m, 1H), 7.59 (s, 1H), 7.46 (d, *J* = 7.4 Hz, 1H), 7.45 – 7.38 (m, 2H), 7.33 – 7.30 (m, 2H), 7.16 (d, *J* = 7.4 Hz, 1H), 7.15 – 7.10 (m, 2H), 7.07 (ddd, *J* = 7.9, 6.2, 1.9 Hz, 1H), 7.02 (d, *J* = 7.4 Hz, 1H), 6.04 (d, *J* = 1.4 Hz, 1H), 5.61 (ddd, *J* = 7.4, 4.4, 2.4 Hz, 1H), 4.11 (d, *J* = 7.9 Hz, 1H), 3.50 (ddd, *J* = 13.3, 7.7, 5.9 Hz, 1H), 3.16 – 3.09 (m, 3H), 2.76 (t, *J* = 4.7 Hz, 2H), 2.42 (s, 3H);

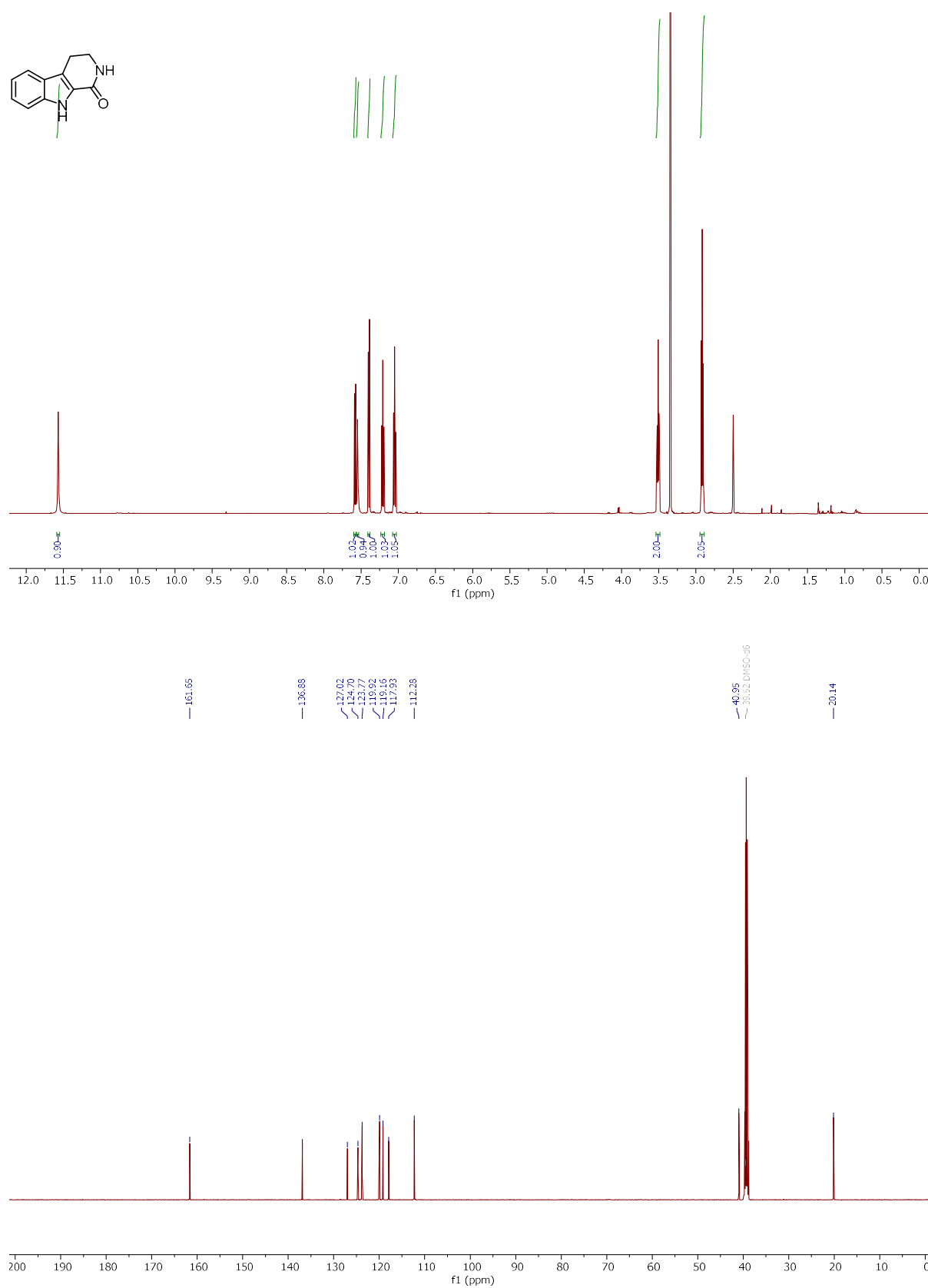
¹³C NMR (126 MHz, CDCl₃) δ 150.52, 137.26, 136.10, 133.44, 129.38, 128.83, 127.16, 125.60, 124.47, 123.85, 122.42, 122.11, 121.01, 119.54, 118.43, 118.38, 112.27, 111.05, 110.92, 110.72, 67.85, 55.75, 51.89, 40.42, 37.56, 29.85, 23.76;

HRMS (ESI) *m/z* calcd for C₃₀H₂₈N₅O⁺ [*M* + *H*]⁺ 474.2288, found 474.2278 (2.19 ppm mass error)

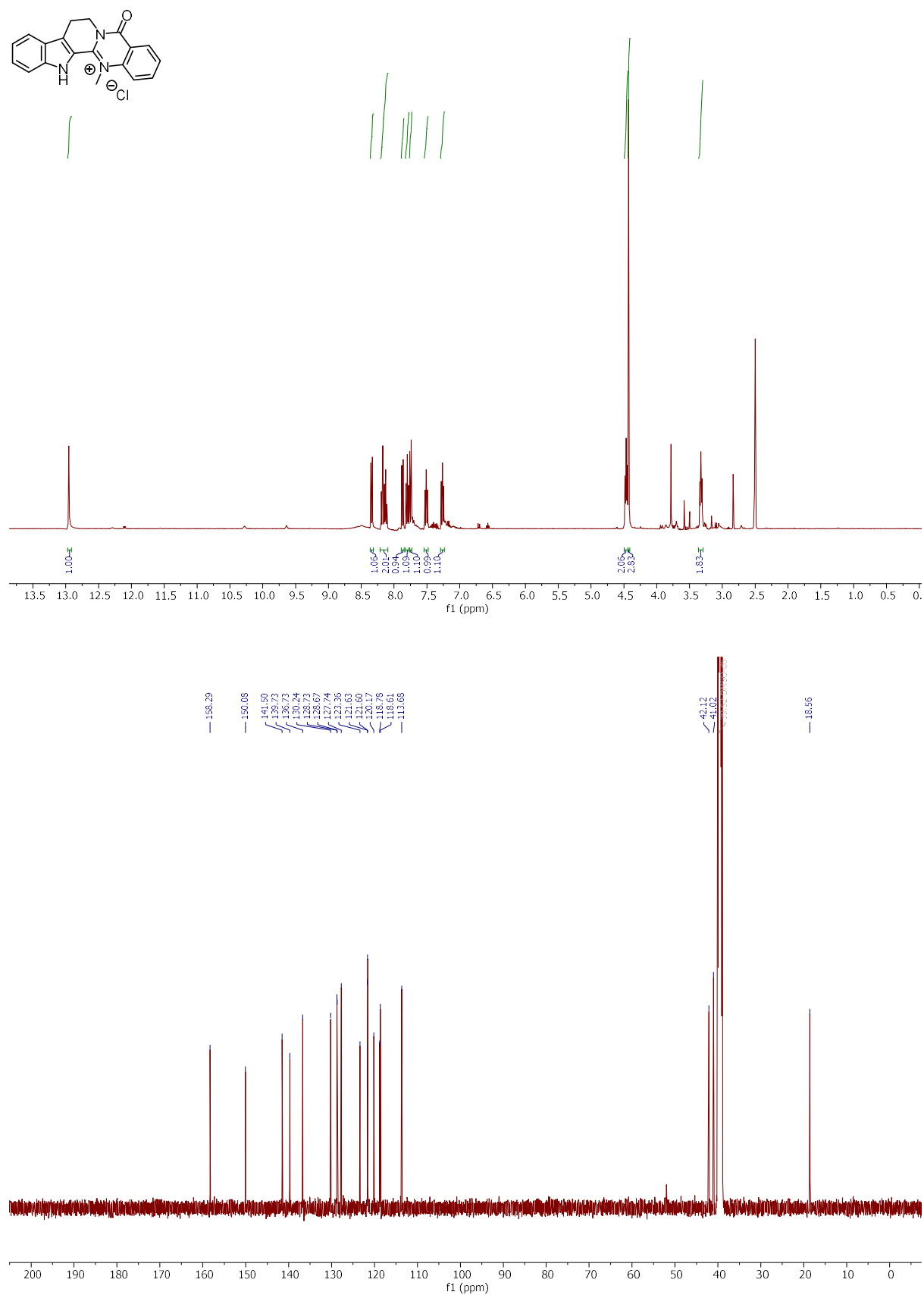
IR 3221, 2954, 2930, 1633, 1421, 1316, 708 cm⁻¹.

6. Appendices

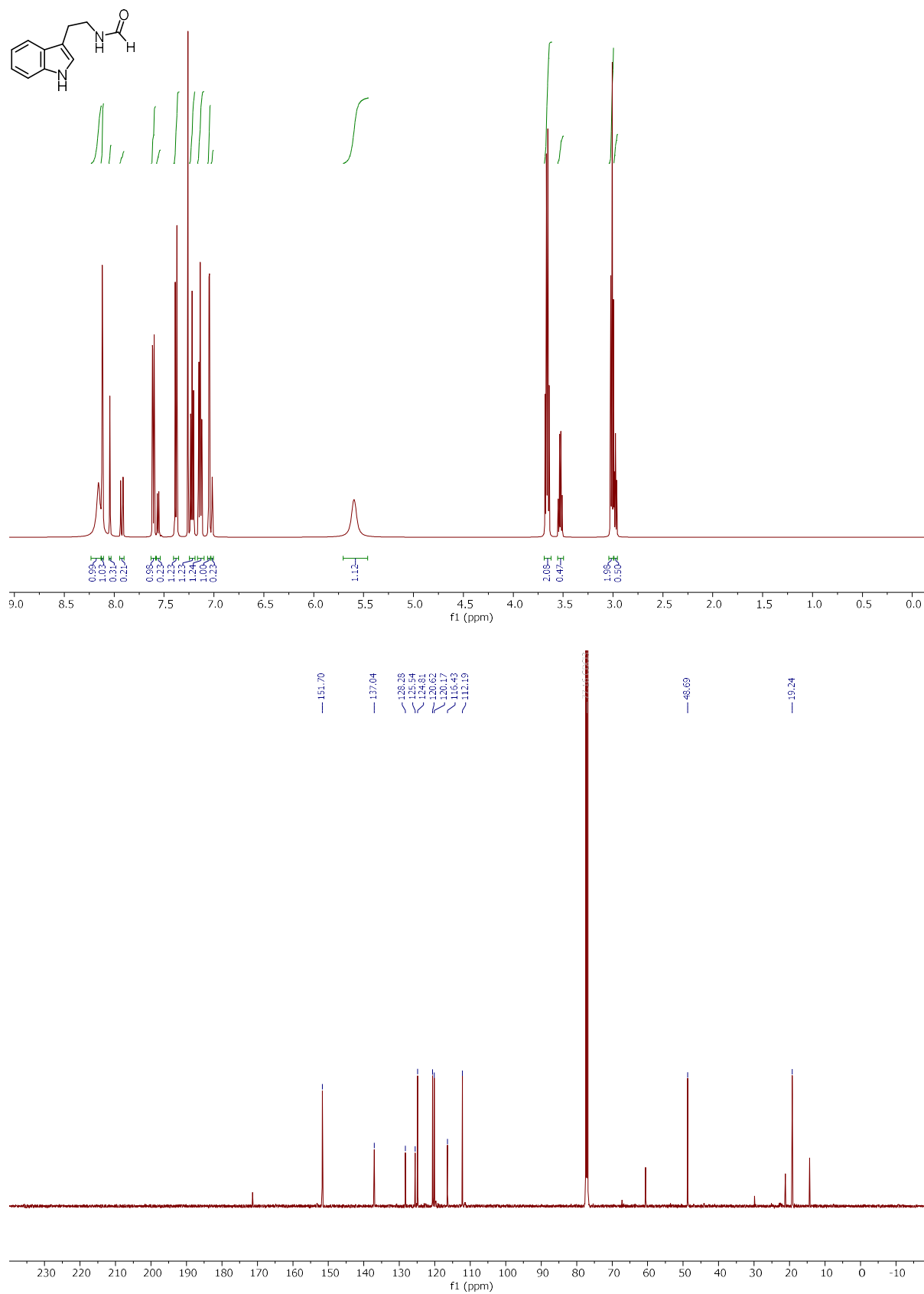
6.1. $^1\text{H}/^{13}\text{C}$ NMR spectra: 1,2,3,4-tetrahydronorharman-1-one (60)



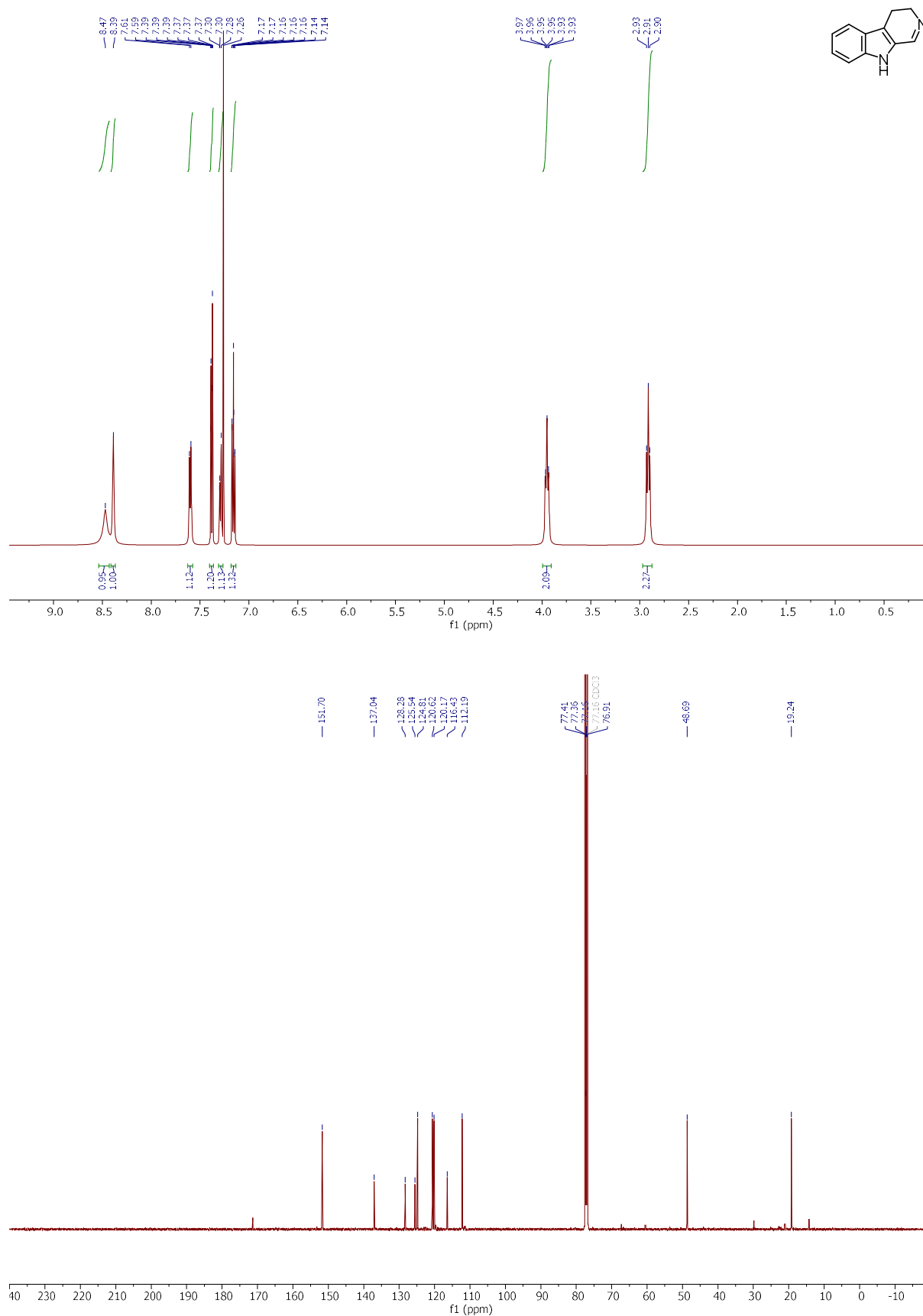
6.2. $^1\text{H}/^{13}\text{C}$ NMR spectra: Dehydroevodiamine chloride (31)



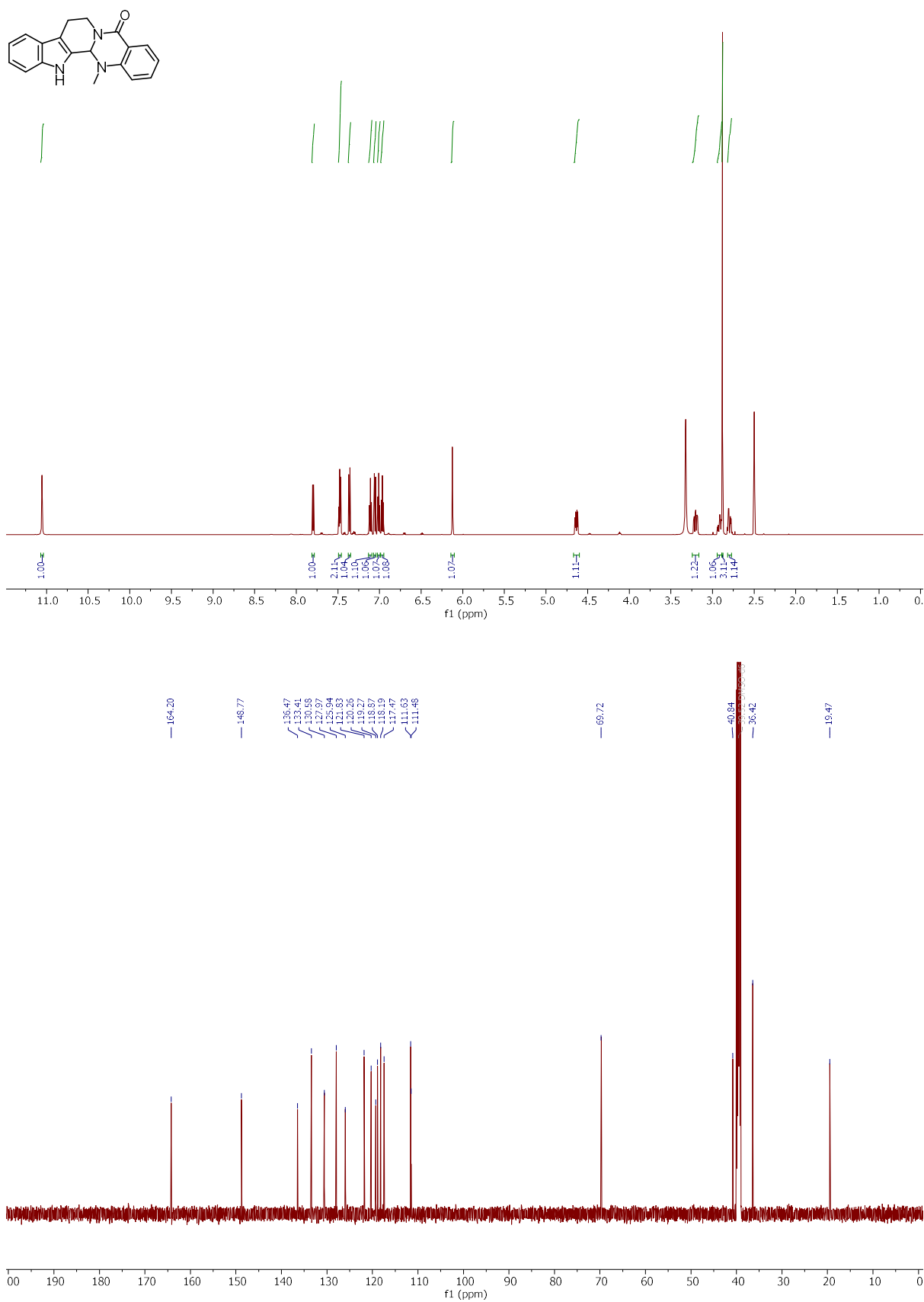
6.3. $^1\text{H}/^{13}\text{C}$ NMR spectra: Formamide 77



6.4. $^1\text{H}/^{13}\text{C}$ NMR spectra: 3,4-dihydro- β -carboline (33)

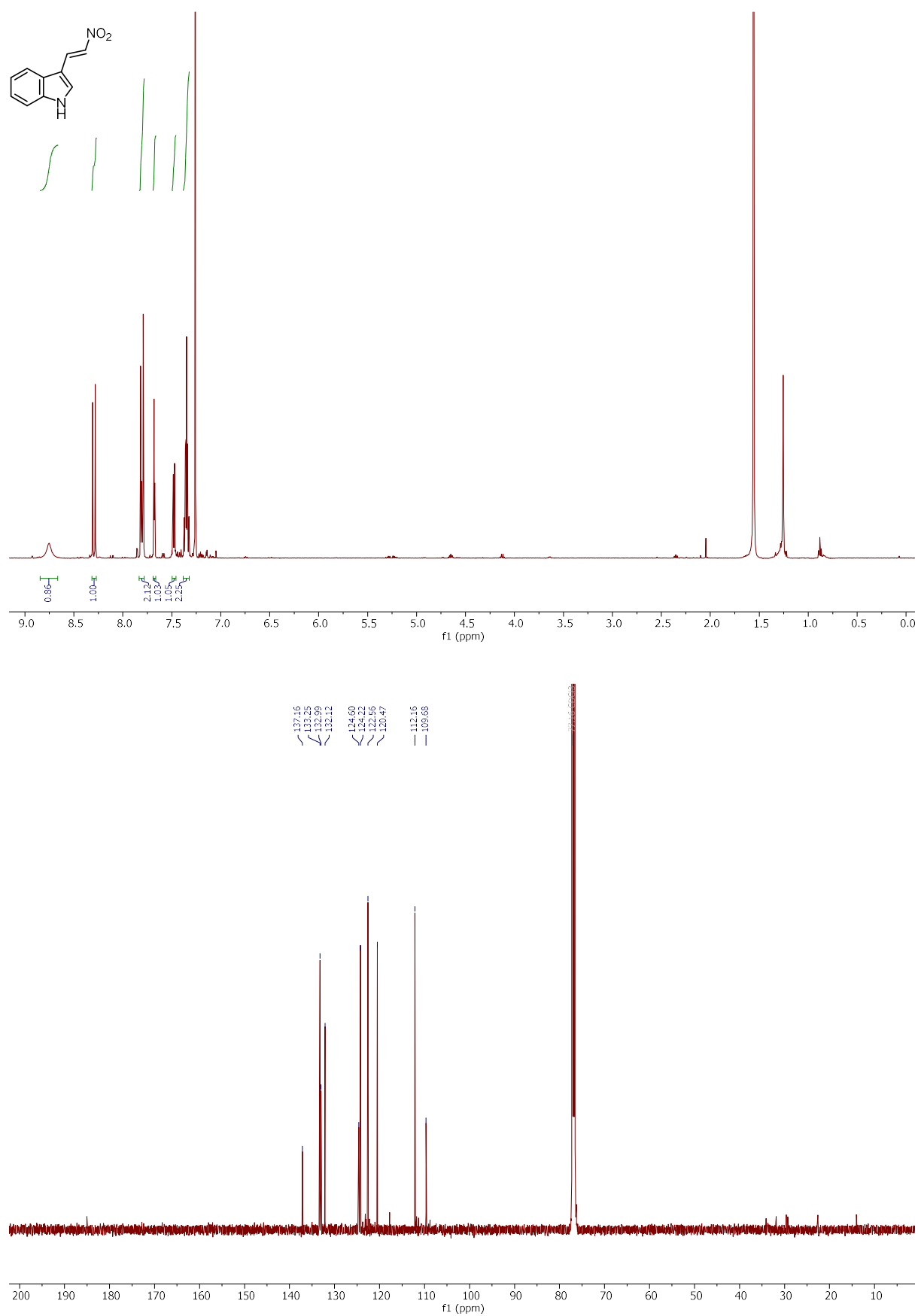


6.5. $^1\text{H}/^{13}\text{C}$ NMR spectra: ($\pm$)-Evodiamine (27)

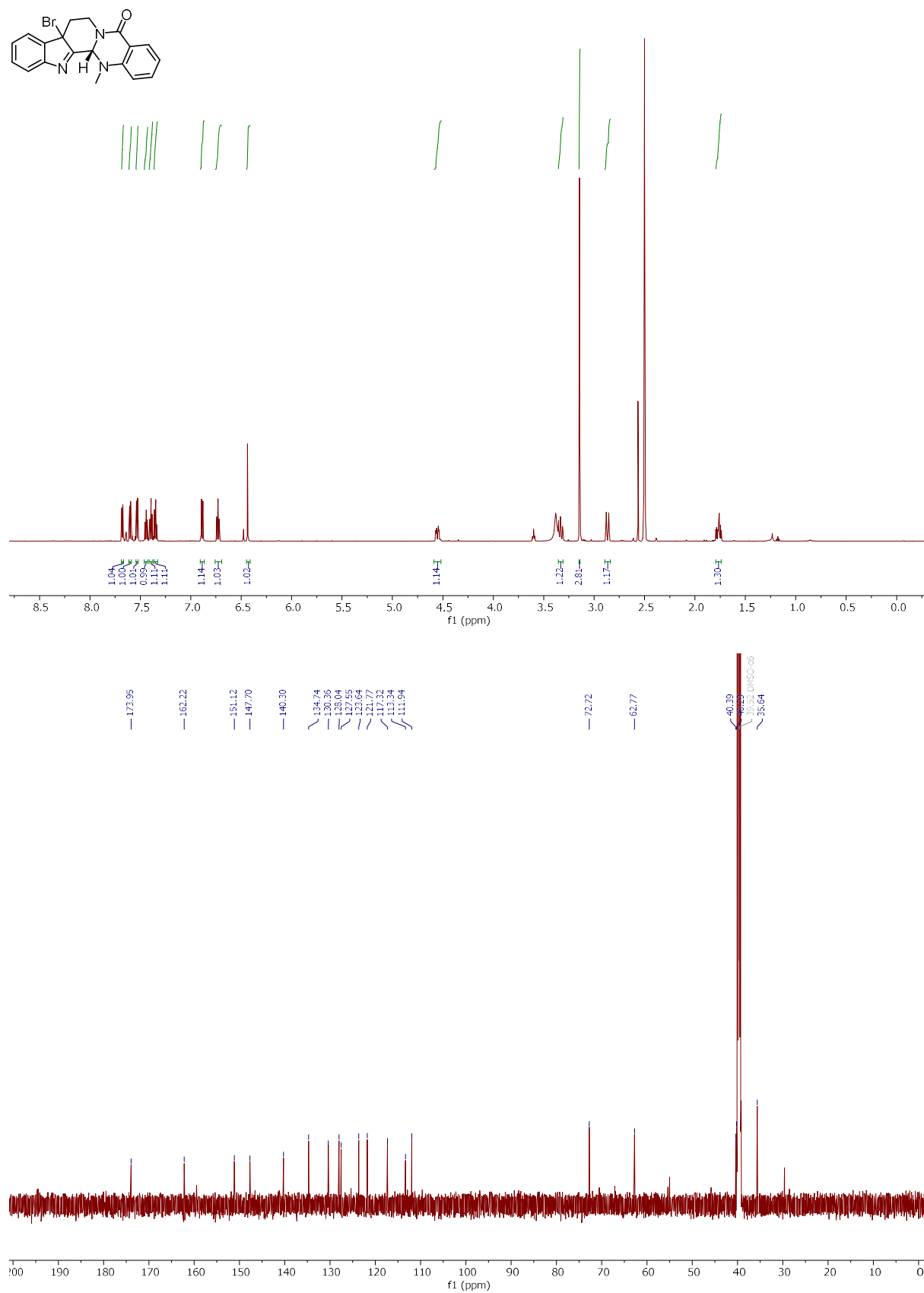




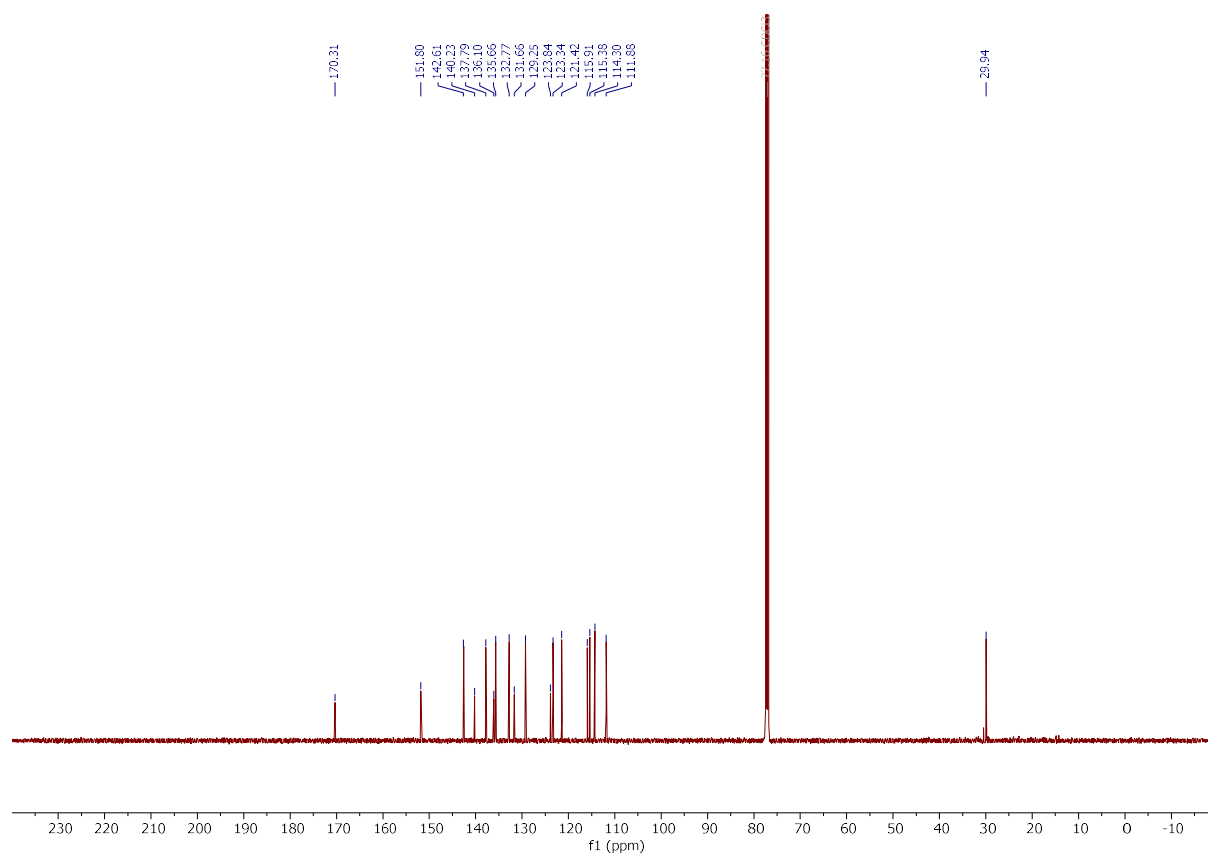
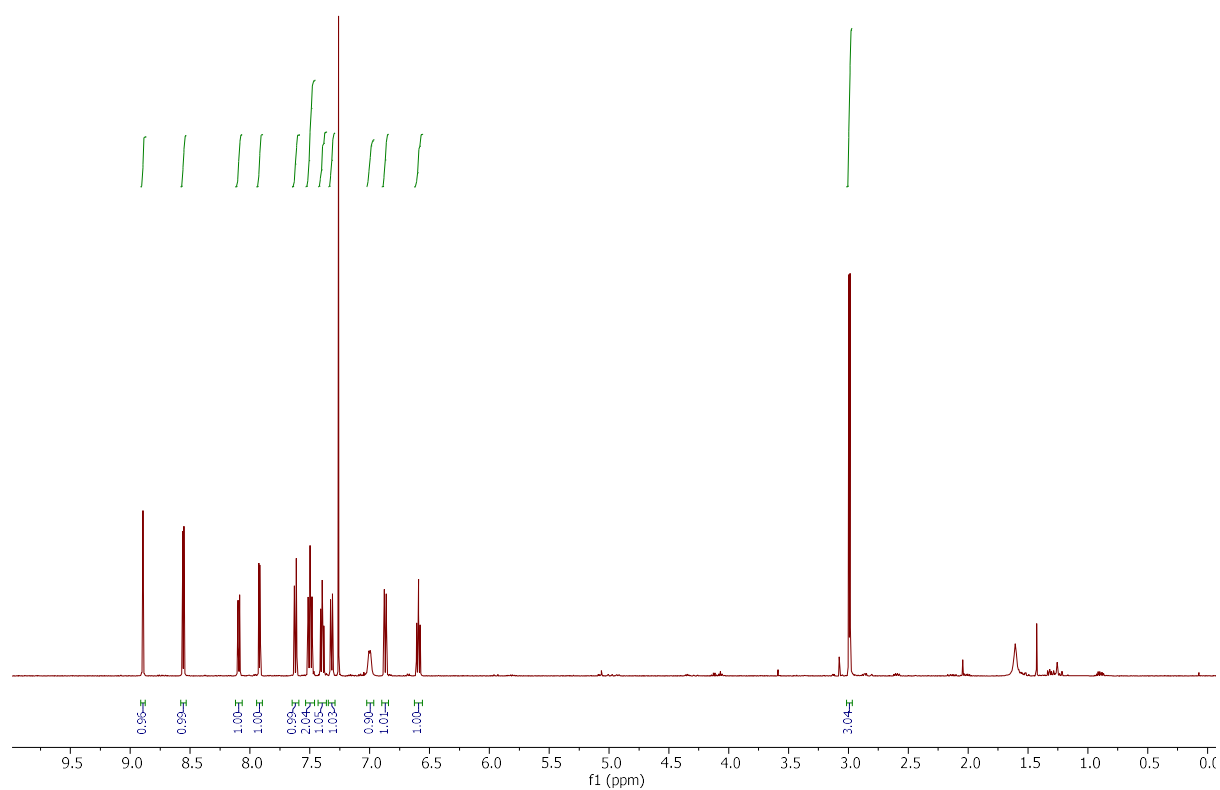
6.7. $^1\text{H}/^{13}\text{C}$ NMR spectra: 3-[(*E*)-2-nitroeth-1-enyl]-1H-indole (74)



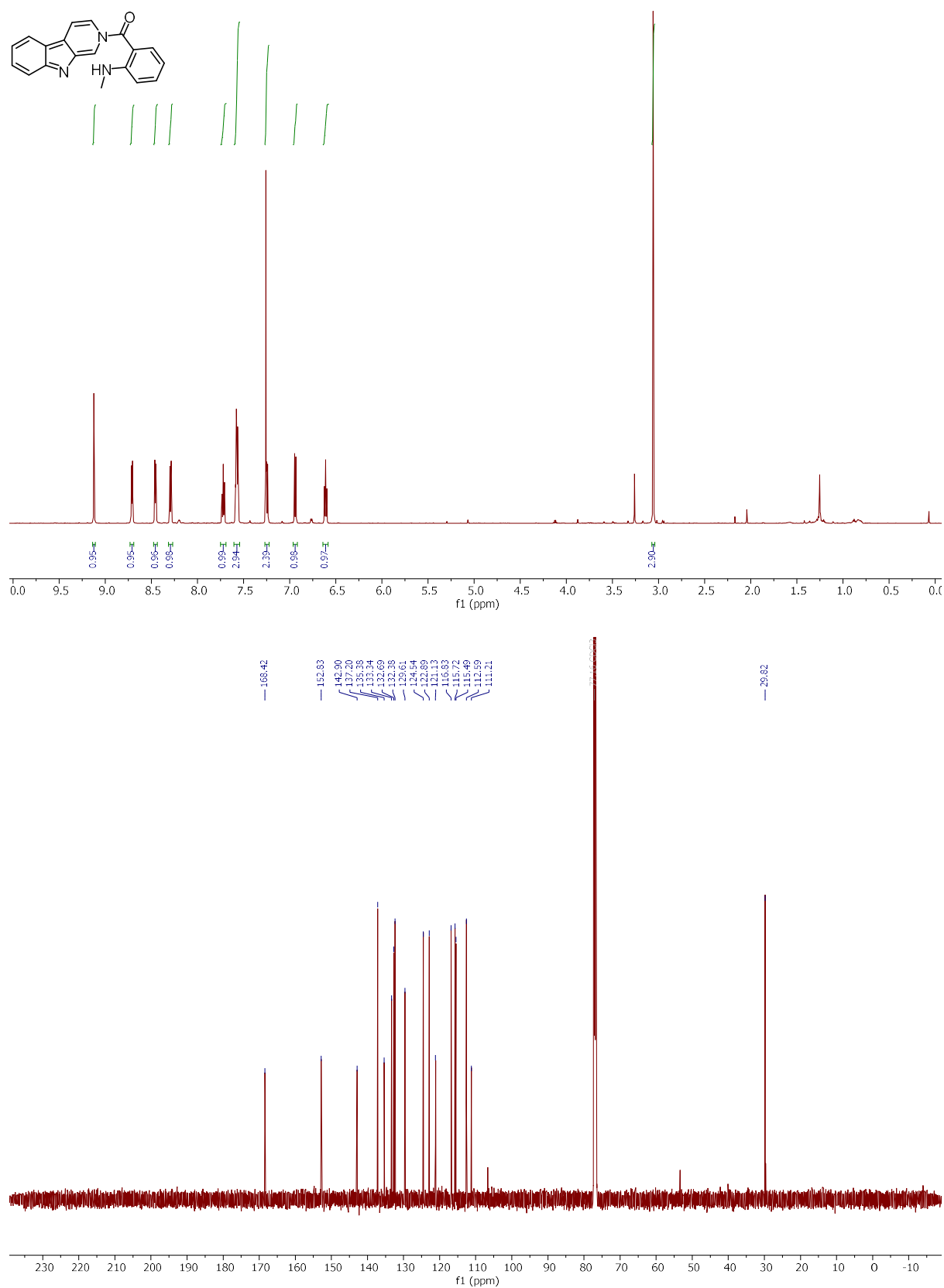
6.8. $^1\text{H}/^{13}\text{C}$ NMR spectra: Bromo-indoladine 97



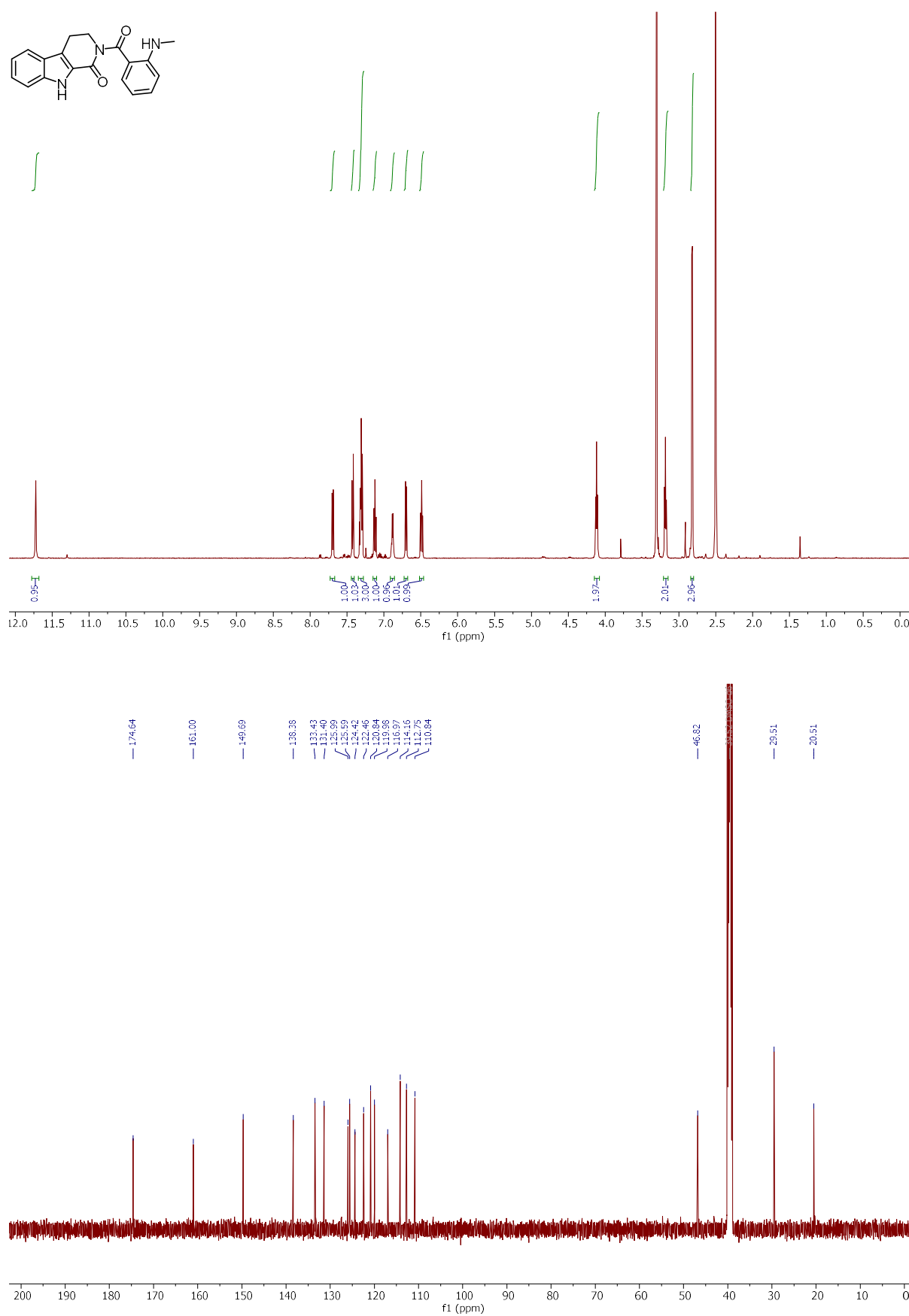
6.9. *N*-acyl- β -carboline 103



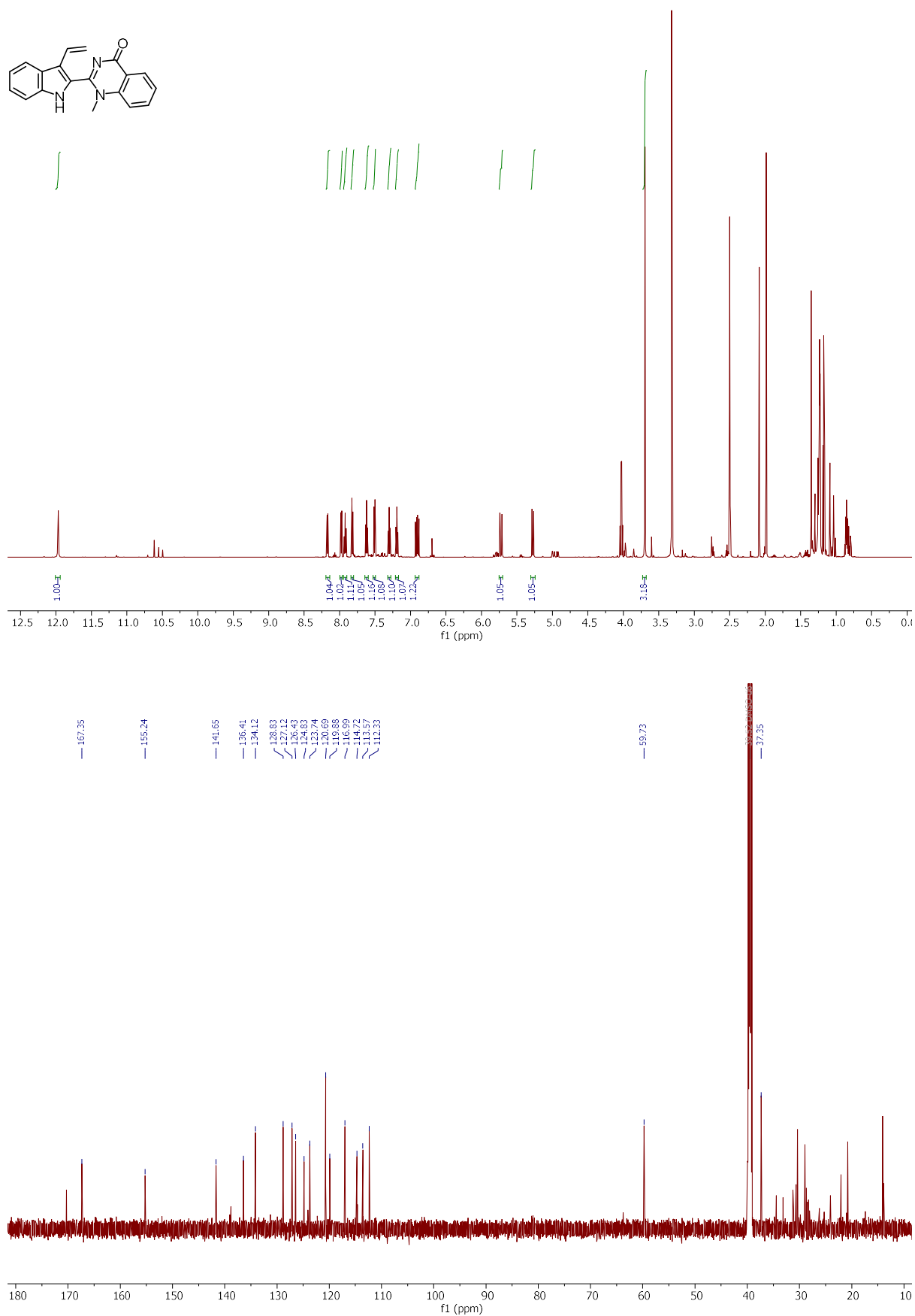
6.10. $^1\text{H}/^{13}\text{C}$ NMR spectra: Tertiary amide 104



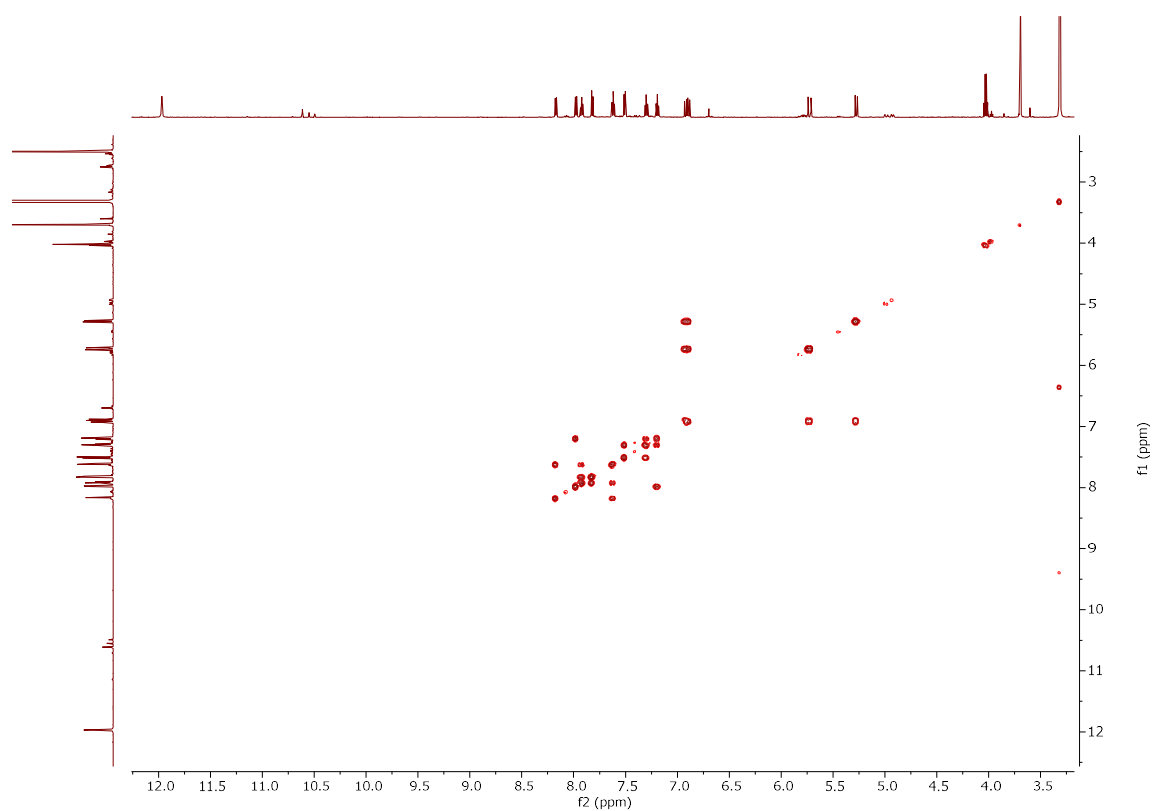
6.11. $^1\text{H}/^{13}\text{C}$ NMR spectra: Rhetsinine (107)



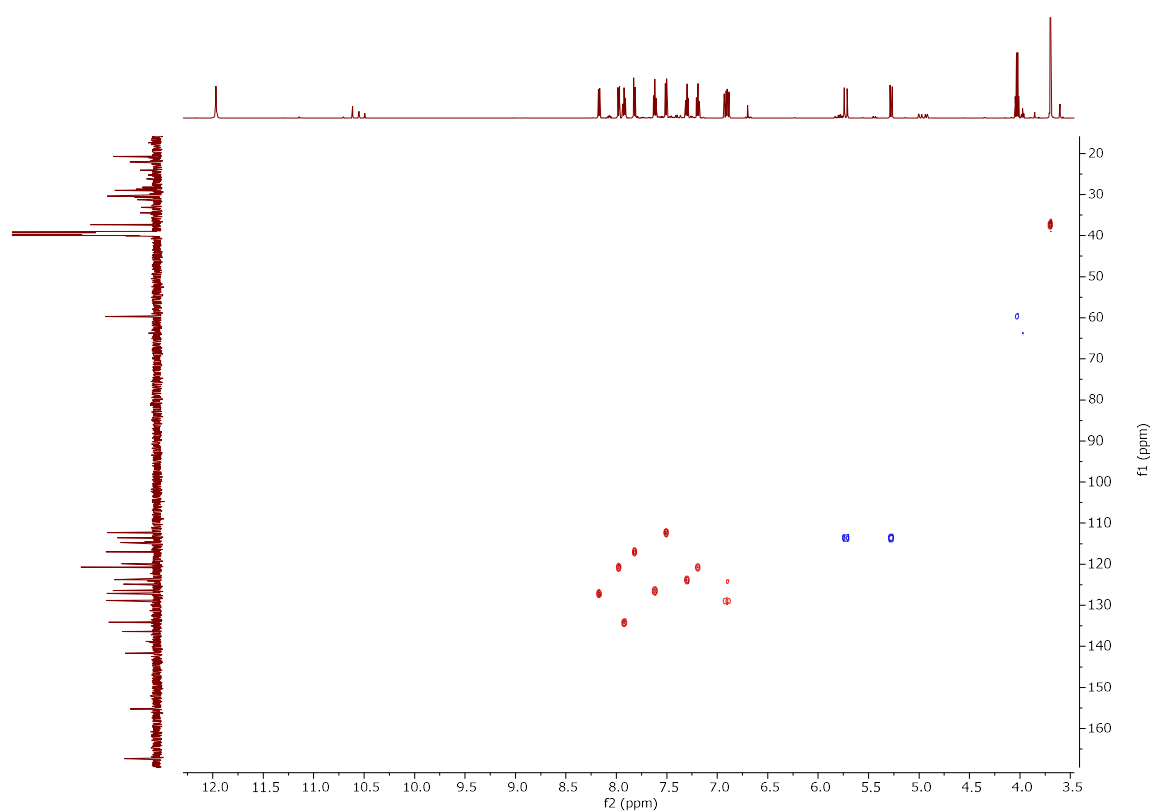
6.12. $^1\text{H}/^{13}\text{C}$ NMR spectra: Alkene 108



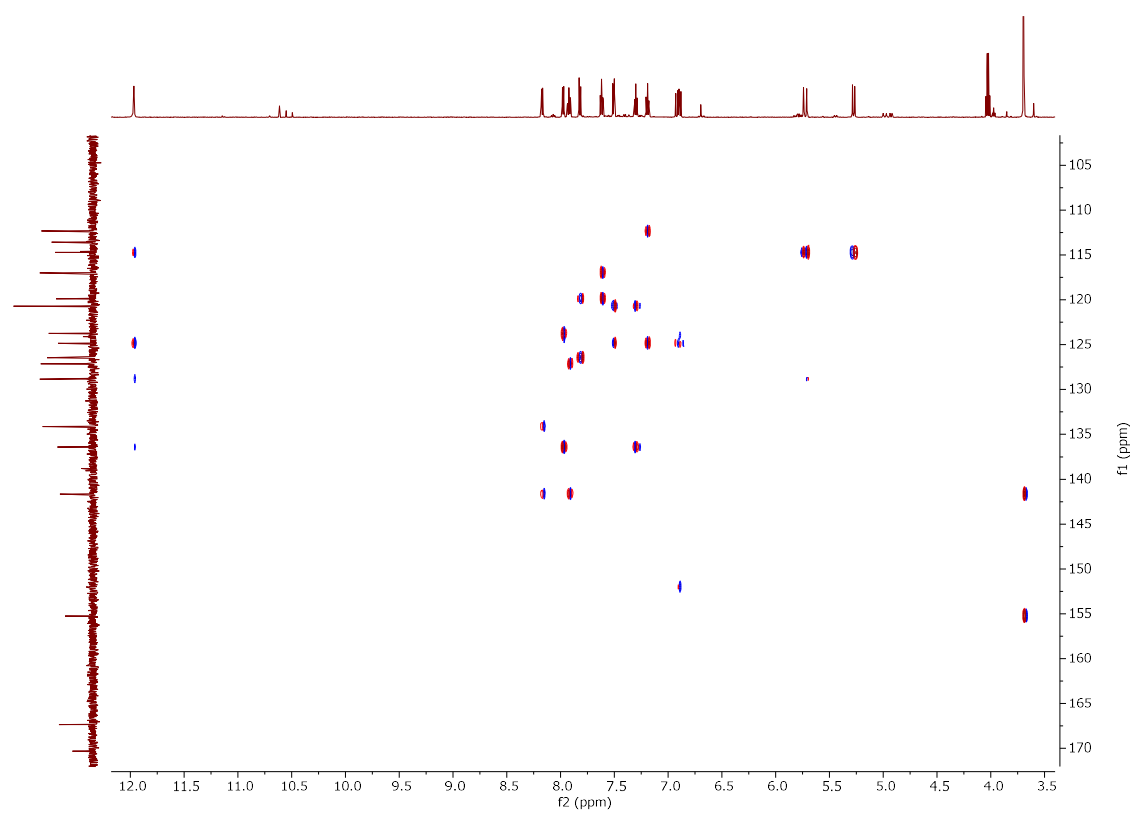
$^1\text{H}/^1\text{H}$ COSY spectra



$^1\text{H}/^{13}\text{C}$ HSQC



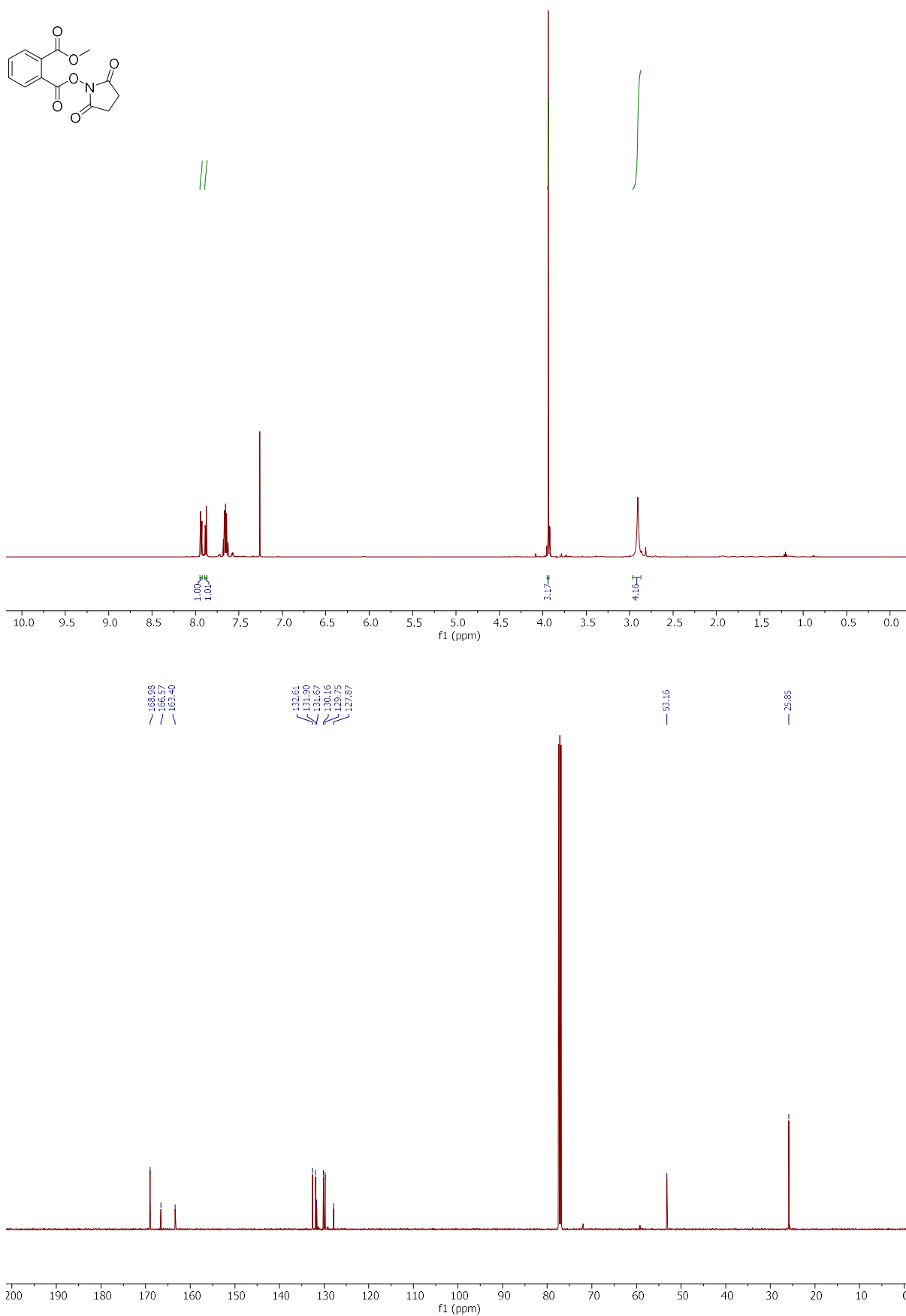
$^1\text{H}/^{13}\text{C}$ HMBC spectra



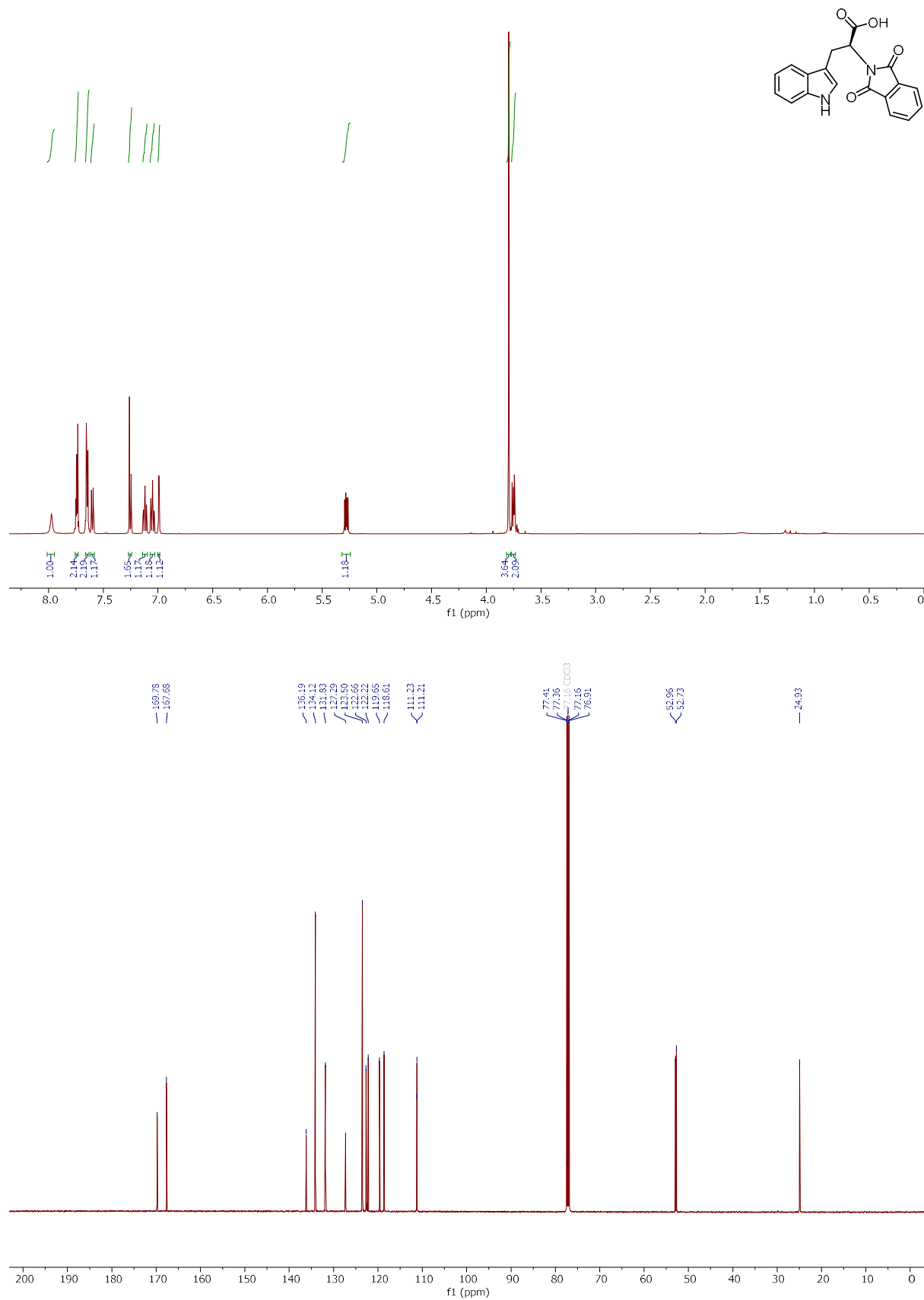
Assignment Table for alkene 108

Label	¹ H Shift / ppm	Multiplicity	J / Hz	# of Hs	COSY	HSQC	HMBC
A	11.97	s	--	1	--	--	J , 136.4, 124.8, 114.7
B	8.17	dd	7.9, 1.6	1	F	127.1	D , 167.4, 141.6
C	7.98	dd	8.0, 1.1	1	I	120.7	H , 136.4
D	7.92	ddd	8.7, 7.2, 1.7	1	E, F	134.1	B , 141.6
E	7.82	d	8.5	1	D	117.0	F , 119.9
F	7.62	ddd	8.0, 7.2, 1.0	1	D, B	126.4	E , 119.9
G	7.51	d	8.2	1	H	112.3	C , 124.8
H	7.30	ddd	8.1, 7.0, 1.1	1	G, I	123.7	C , 136.4
I	7.19	ddd	8.1, 7.0, 1.1	1	C, H	120.7	G , 124.8
J	6.91	dd	17.8, 11.5	1	K, L	128.8	J , 124.8
K	5.73	dd	17.9, 1.4	1	J	113.7	J , 114.7
L	5.28	dd	11.5, 1.3	1	J	113.7	114.7
M	3.70	s	--	3	--	37.4	141.6, 155.2

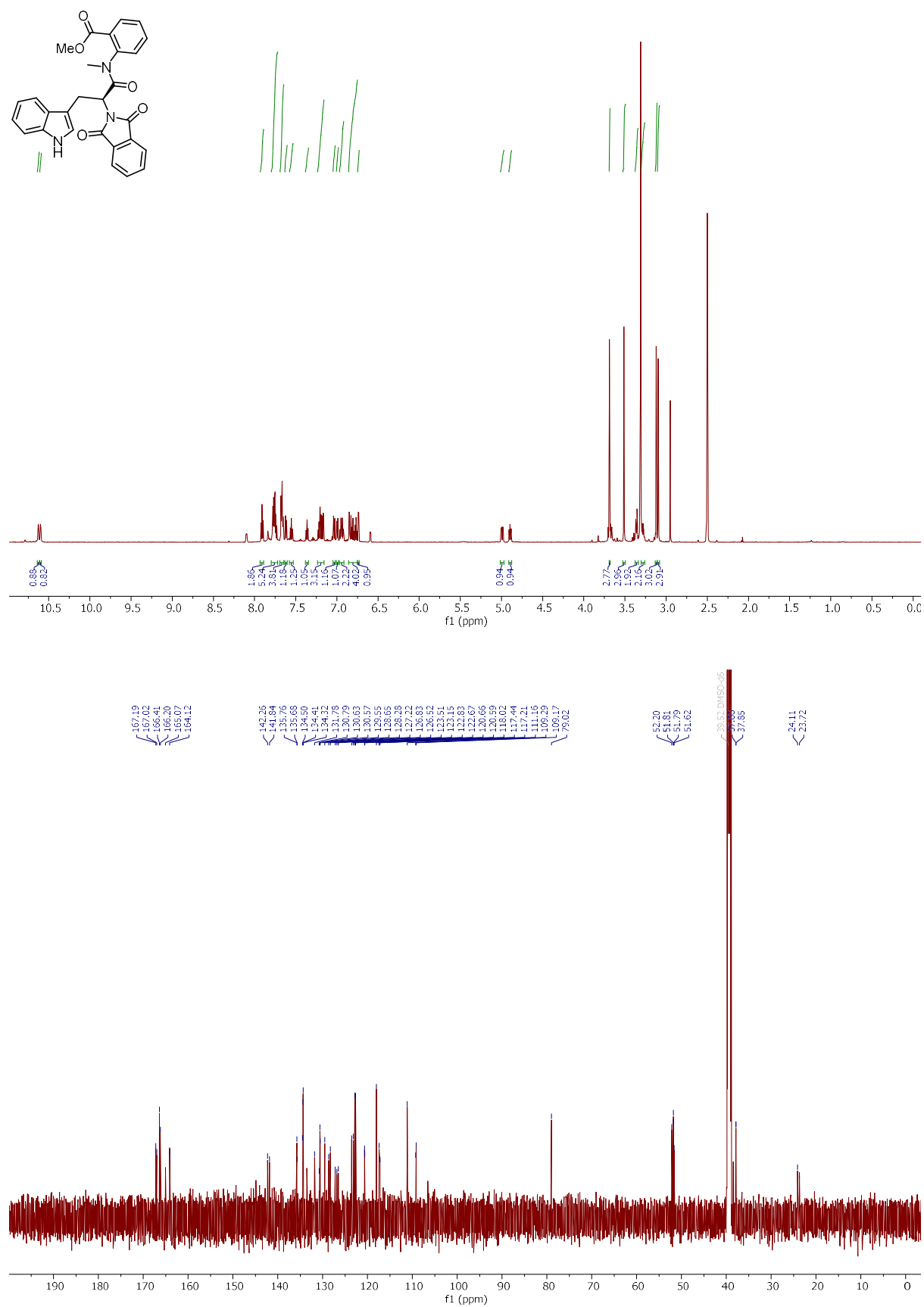
6.13. $^1\text{H}/^{13}\text{C}$ NMR spectra: Ester 179



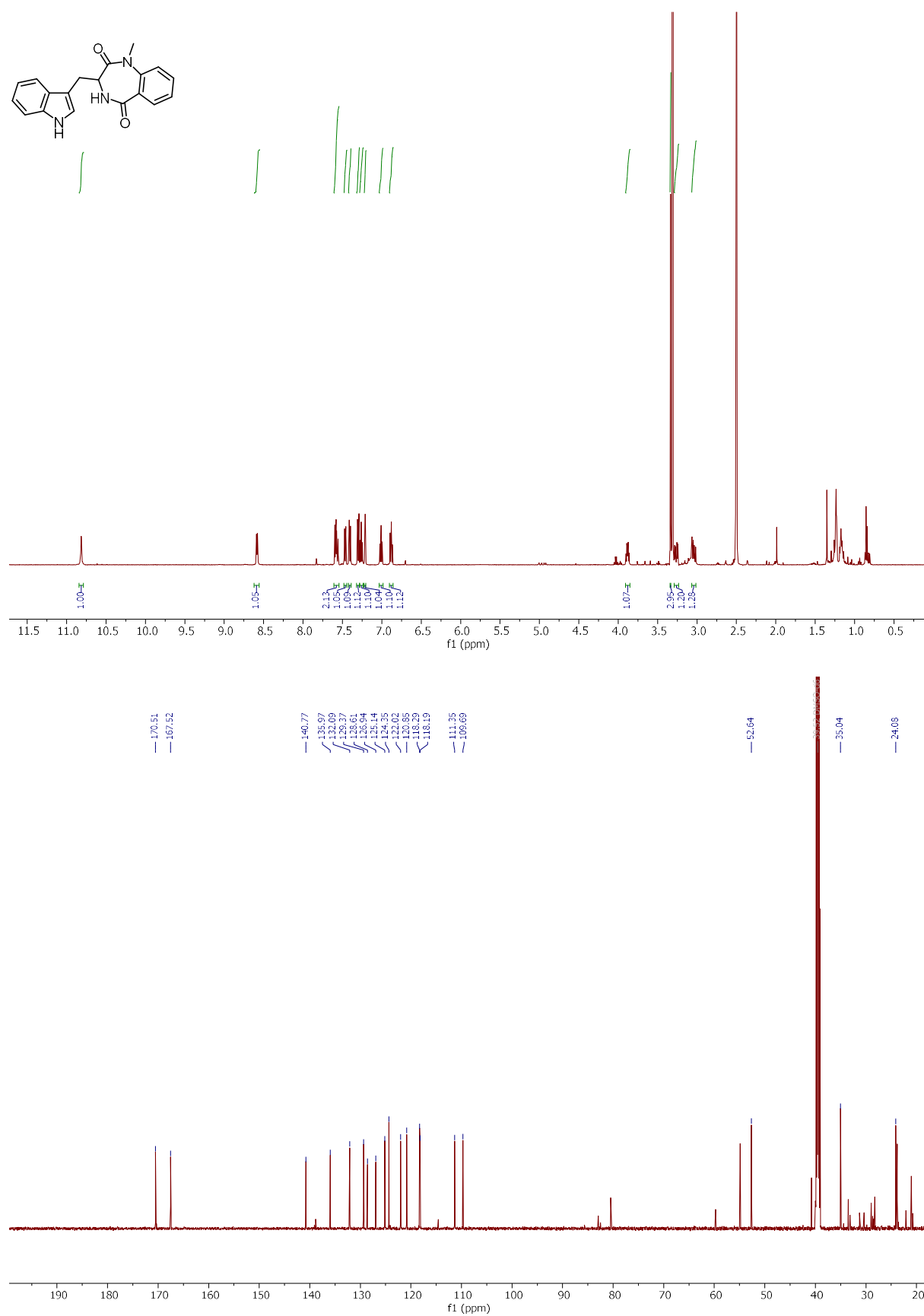
6.14. $^1\text{H}/^{13}\text{C}$ NMR spectra: L-Phth-Trp-OH (123)



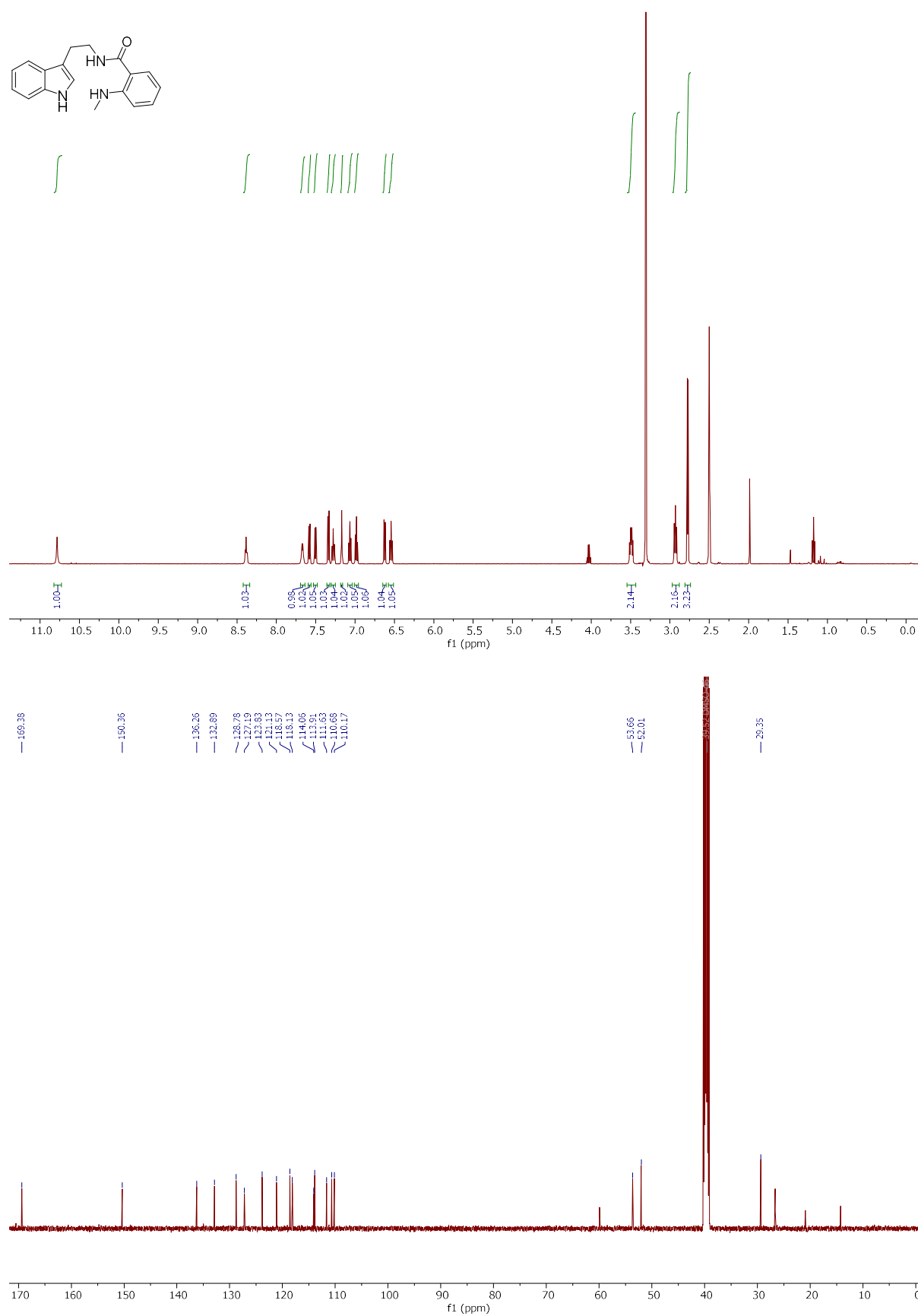
6.15. $^1\text{H}/^{13}\text{C}$ NMR spectra: Amide 127



6.16. $^1\text{H}/^{13}\text{C}$ NMR spectra: Cyclic diamide 129



6.17. $^1\text{H}/^{13}\text{C}$ NMR spectra: Amide 37

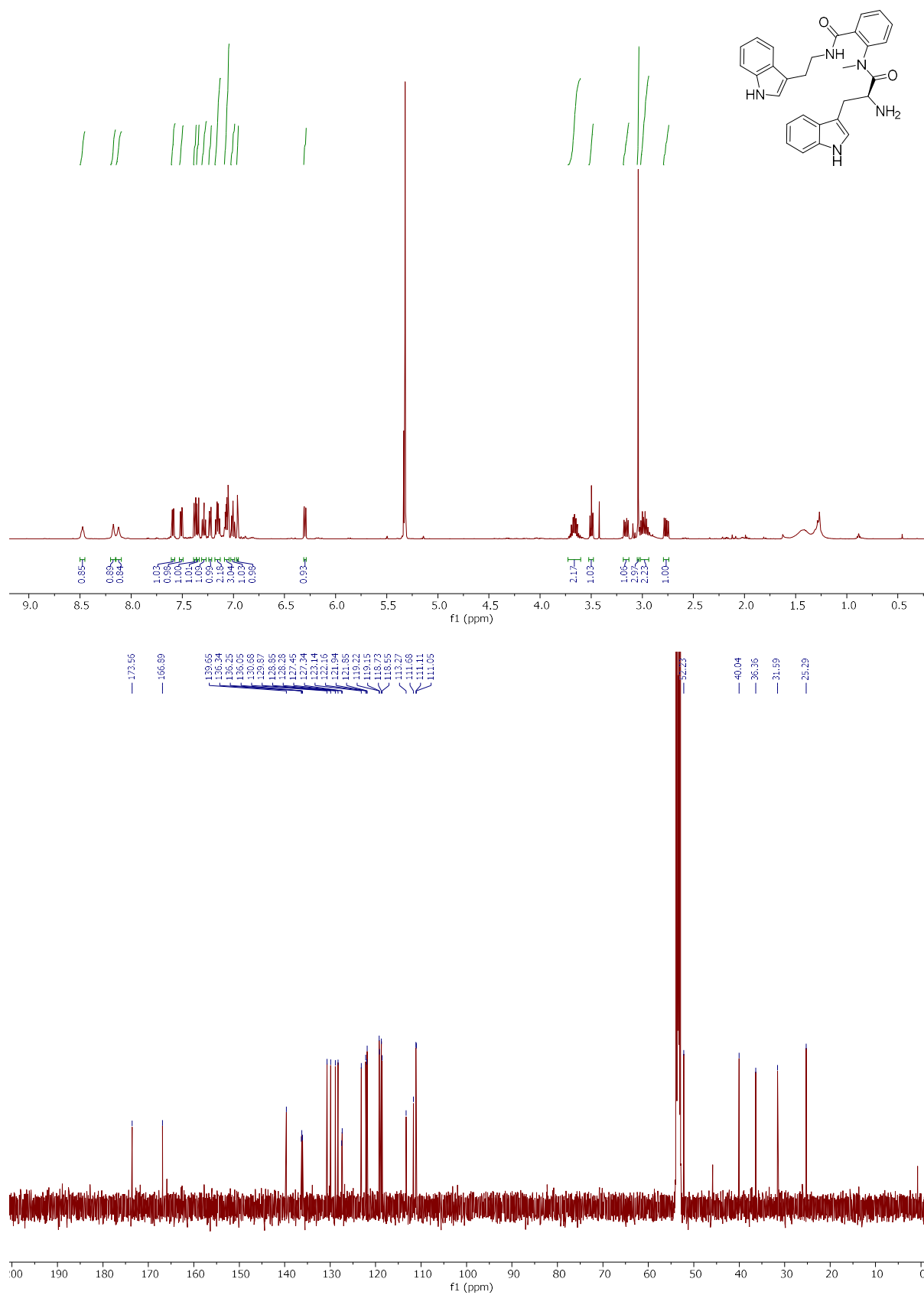


Chemical structure of compound 10 is shown in the top left corner. The structure is a complex molecule featuring a central benzene ring substituted with a 1H-indol-3-ylmethyl group, a 1H-indol-3-ylmethyl group, and a 1H-indol-3-ylmethyl group. The molecule also contains a 1H-indol-3-ylmethyl group and a 1H-indol-3-ylmethyl group.

¹H NMR (400 MHz, CDCl₃) spectrum is shown above the chemical structure. The x-axis is labeled f1 (ppm) and ranges from 2.0 to 11.5. The spectrum displays several peaks, with integration values provided below the baseline: 0.95, 0.93, 0.87, 1.90, 1.26, 1.24, 1.24, 0.89, 1.35, 1.84, 1.27, 0.92, 0.86, 1.09, 0.88, 2.89, 0.90, 2.57, and 1.84.

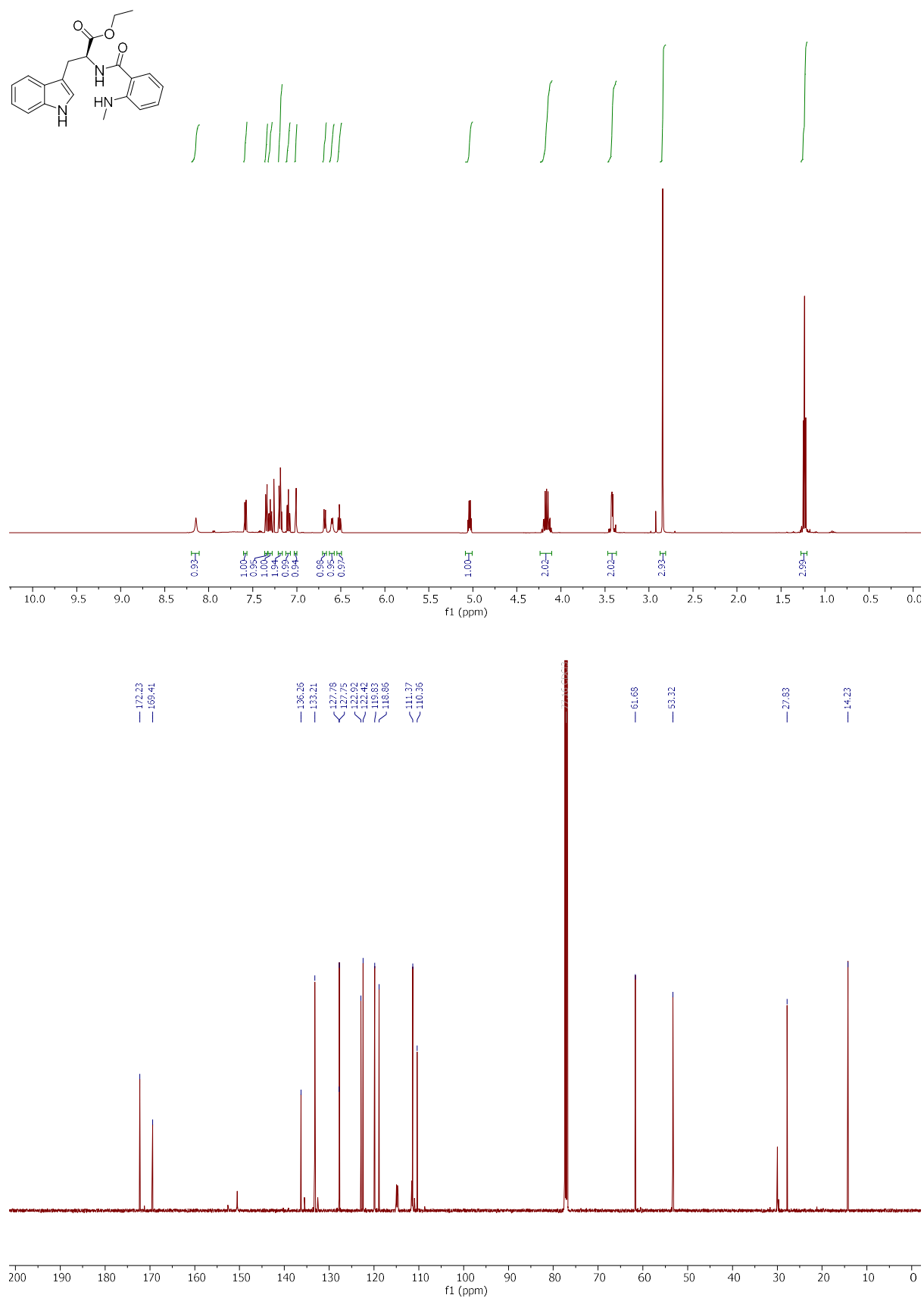
¹³C NMR (100 MHz, CDCl₃) spectrum is shown below the chemical structure. The x-axis is labeled f1 (ppm) and ranges from 20 to 190. The spectrum displays several peaks, with chemical shift values provided above the baseline: 168.46, 167.17, 167.06, 140.55, 138.76, 136.33, 135.15, 134.95, 131.32, 131.20, 128.62, 128.35, 128.61, 127.72, 127.42, 123.75, 123.40, 123.14, 121.43, 121.15, 118.73, 118.74, 118.21, 112.14, 111.87, 111.65, 110.23, 55.38, 52.82, 38.28, 25.54, and 24.09.

6.19. $^1\text{H}/^{13}\text{C}$ NMR spectra: Amine 131

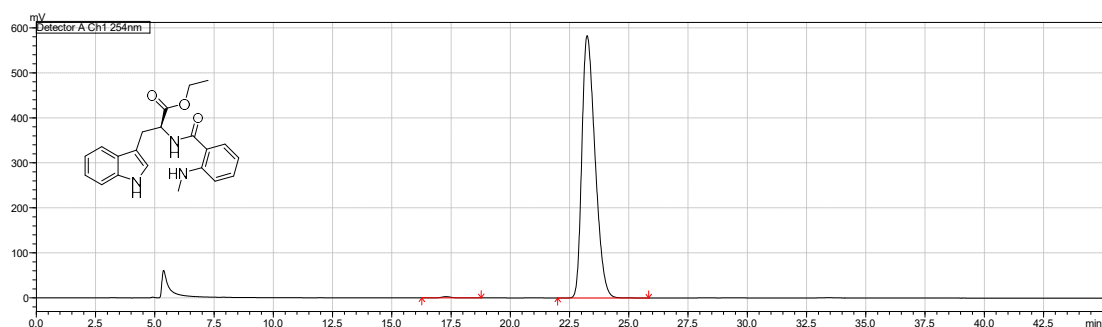


6.20. $^1\text{H}/^{13}\text{C}$ NMR spectra: Oligomer 116

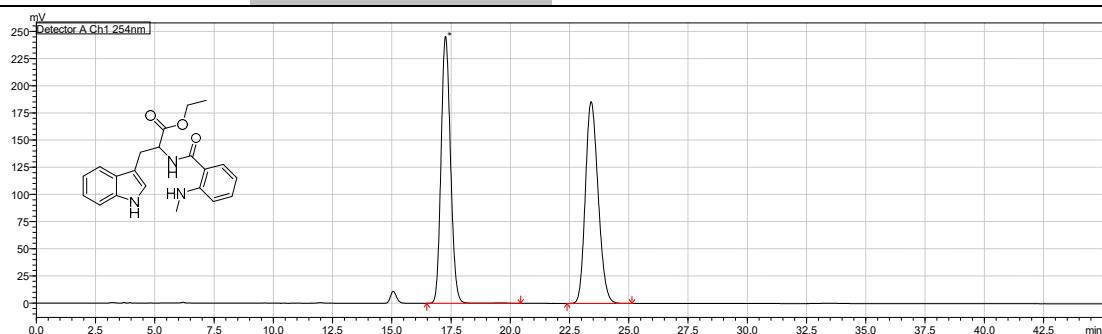
6.21. $^1\text{H}/^{13}\text{C}$ NMR spectra: Ester 148



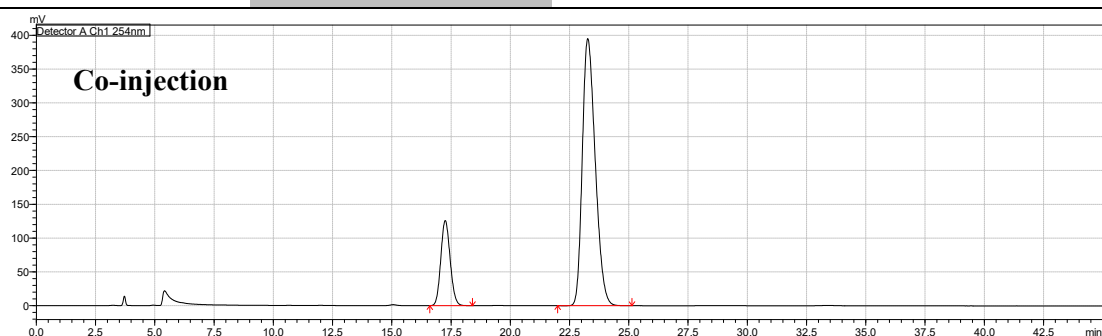
Ester 148 HPLC data



Peak Number	Retention Time	Area	Area %
1	17.288	74574	0.330
2	23.242	22515005	99.670
3		22589579	100.000

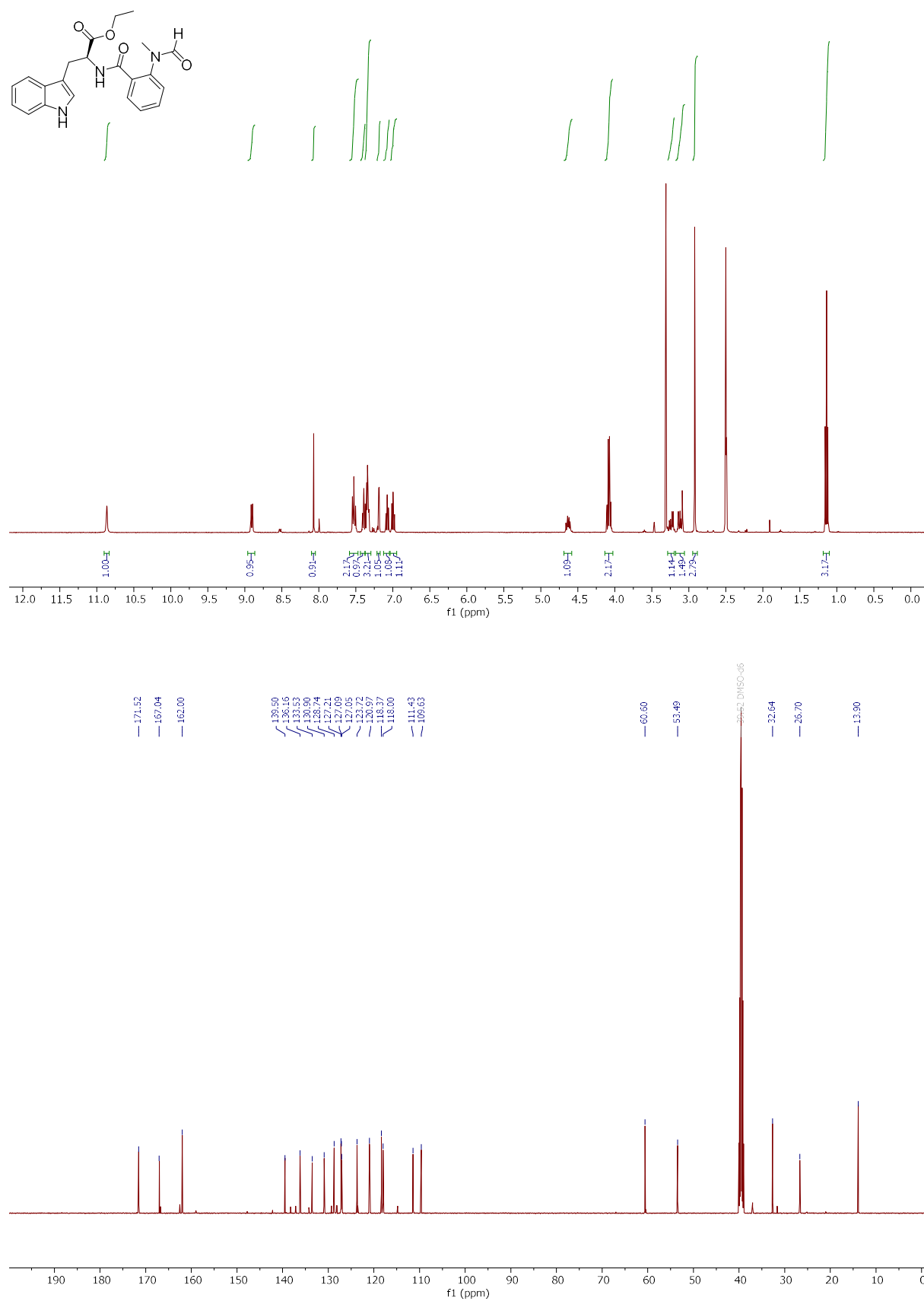


Peak Number	Retention Time	Area	Area %
1	17.265	6803651	49.412
2	23.409	6965656	50.588
3		13769307	100.000

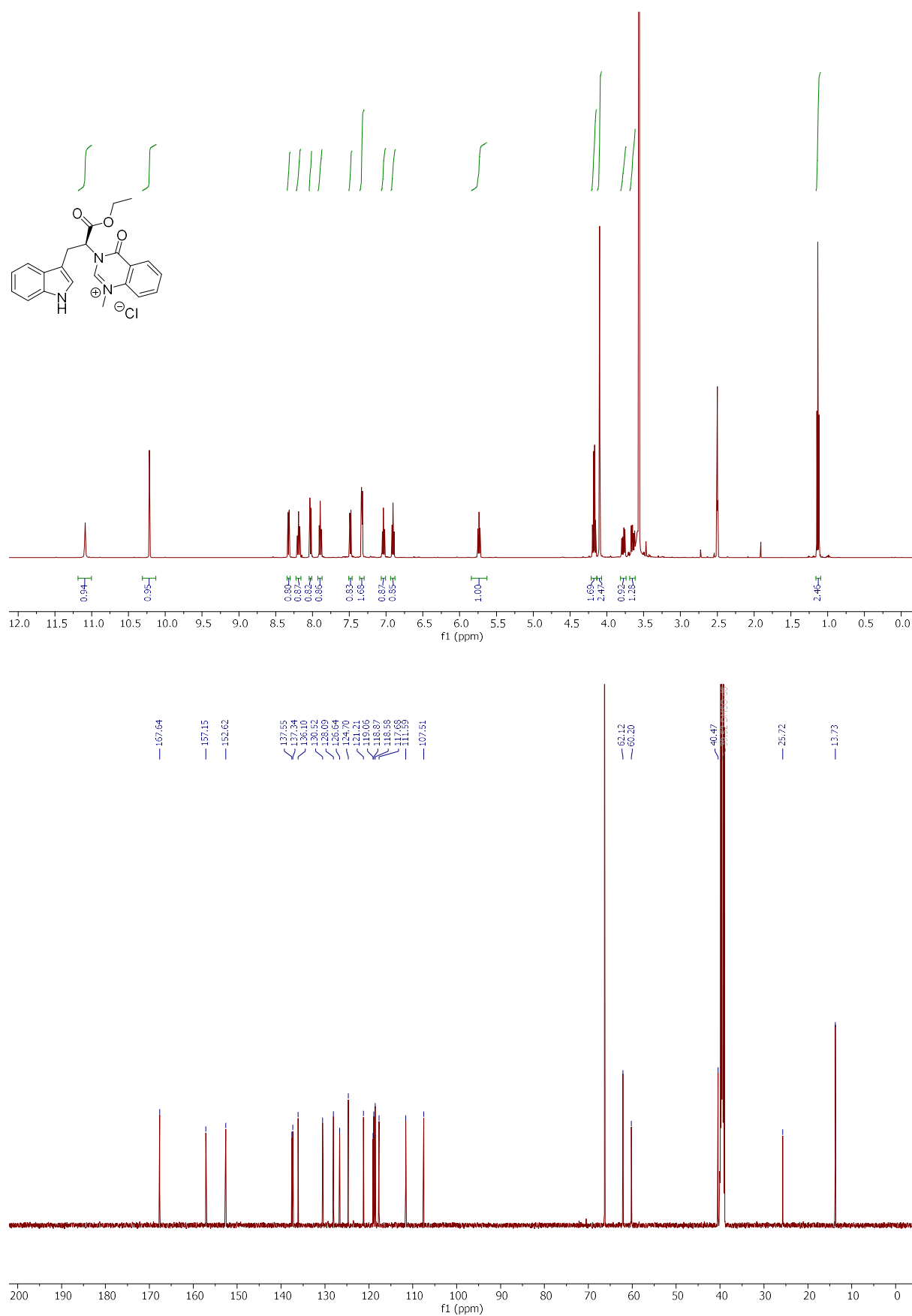


Peak Number	Retention Time	Area	Area %
1	17.254	3455262	18.711
2	23.268	15011022	81.289
3		18466283	100.000

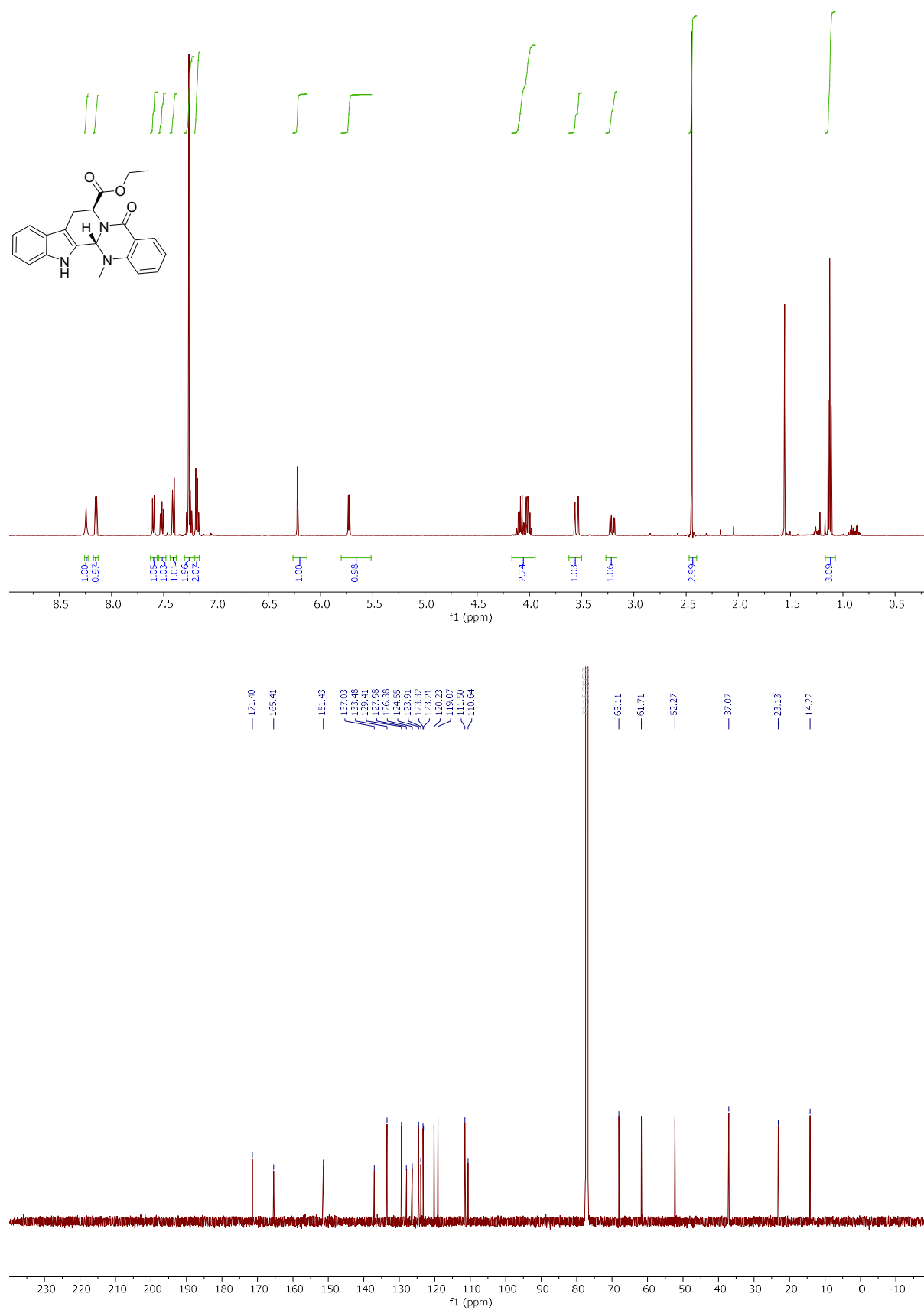
6.22. $^1\text{H}/^{13}\text{C}$ NMR spectra: Formamide 151



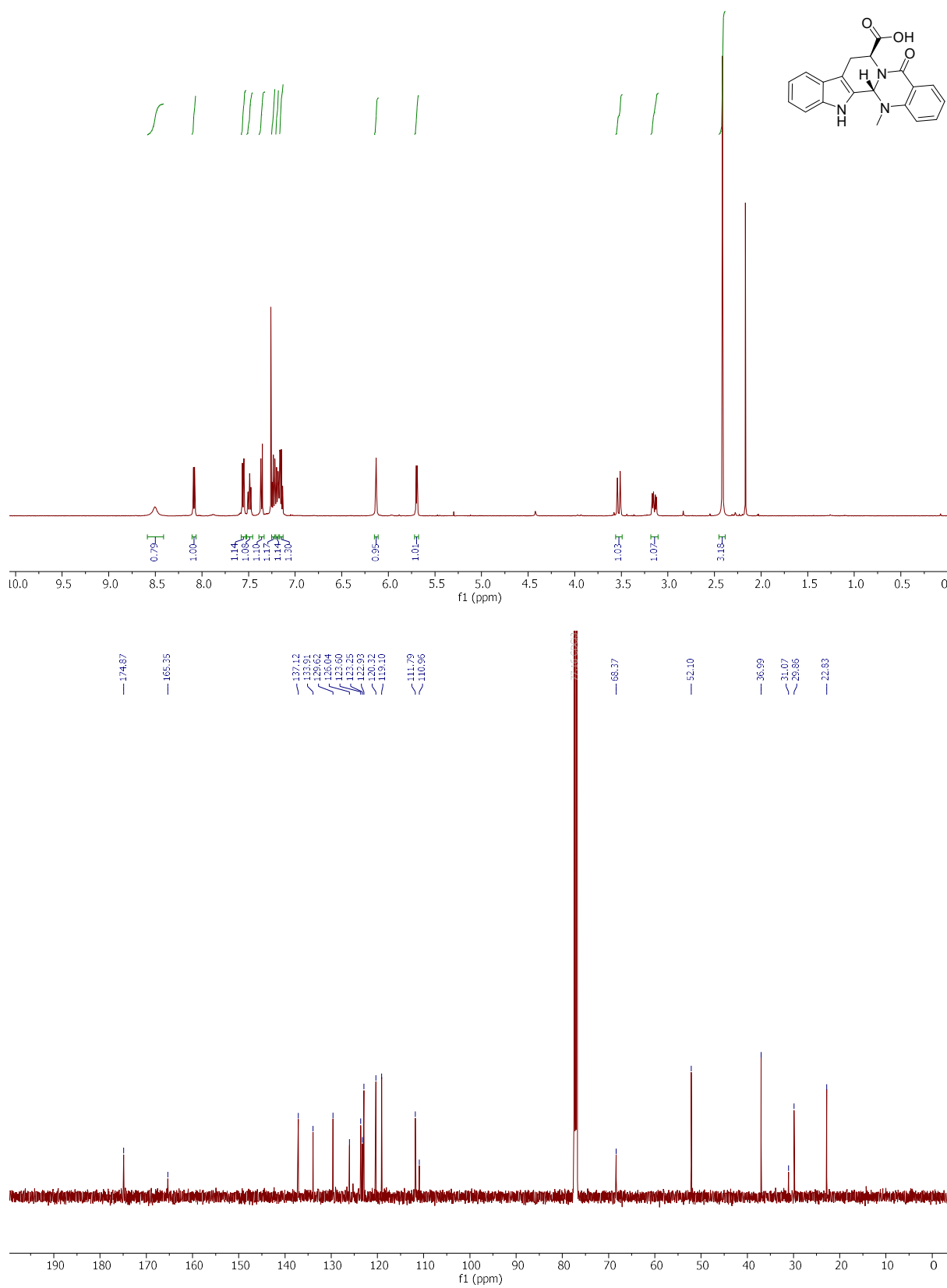
6.23. $^1\text{H}/^{13}\text{C}$ NMR spectra: iminium chloride 152



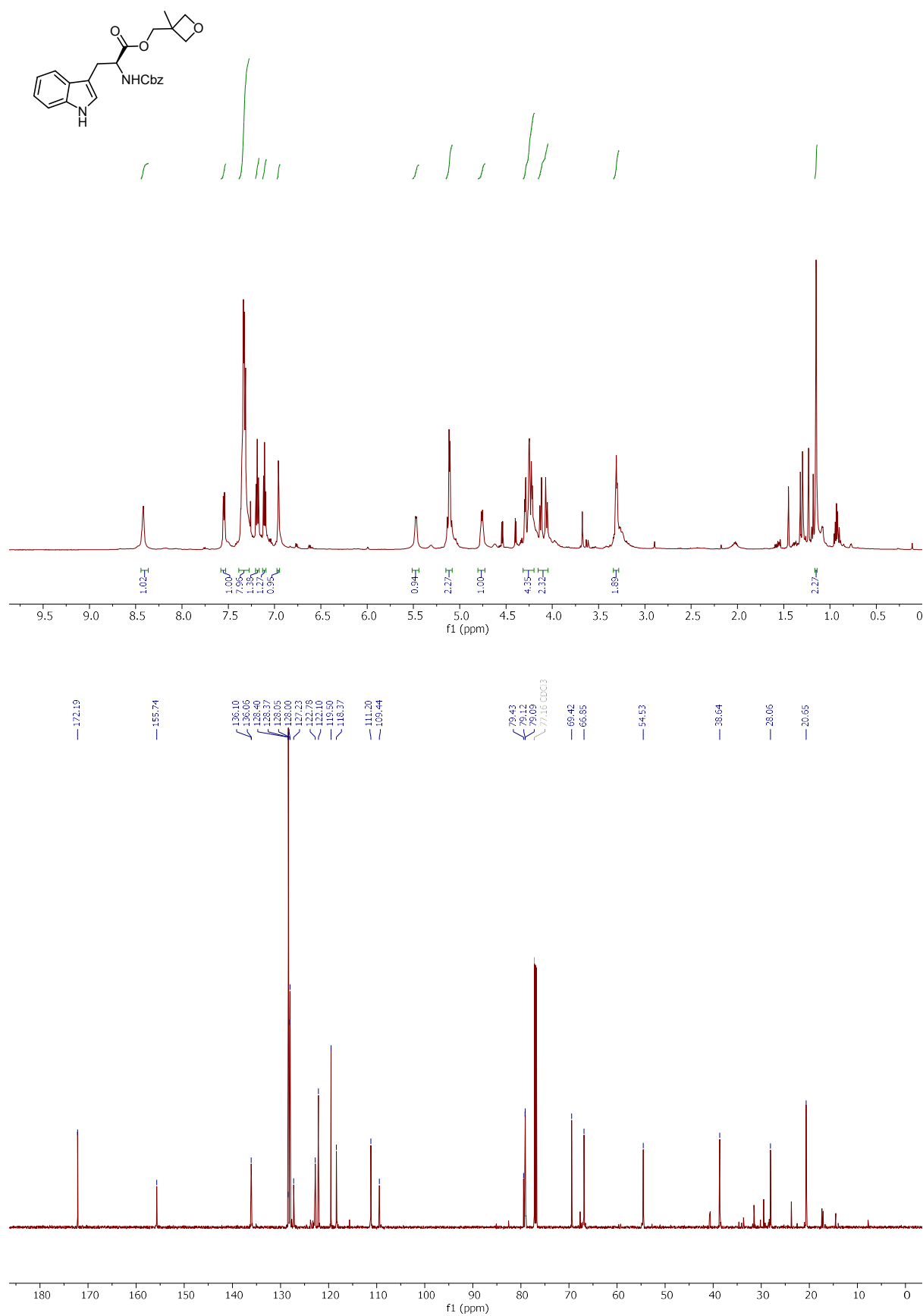
6.24. $^1\text{H}/^{13}\text{C}$ NMR spectra: ethyl ester (+)-86



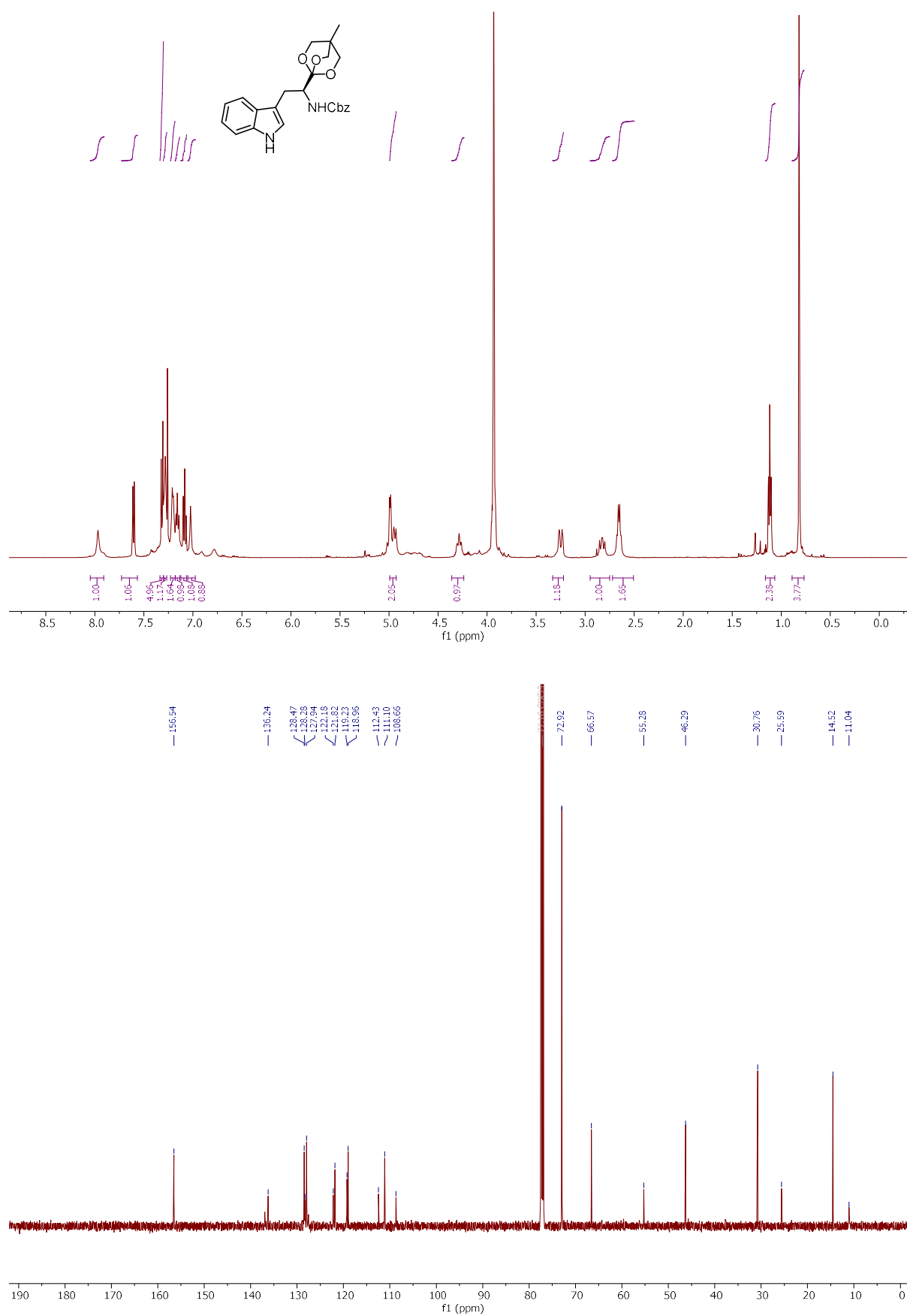
6.25. $^1\text{H}/^{13}\text{C}$ NMR spectra: (+)-caroxyevodiamine (29)



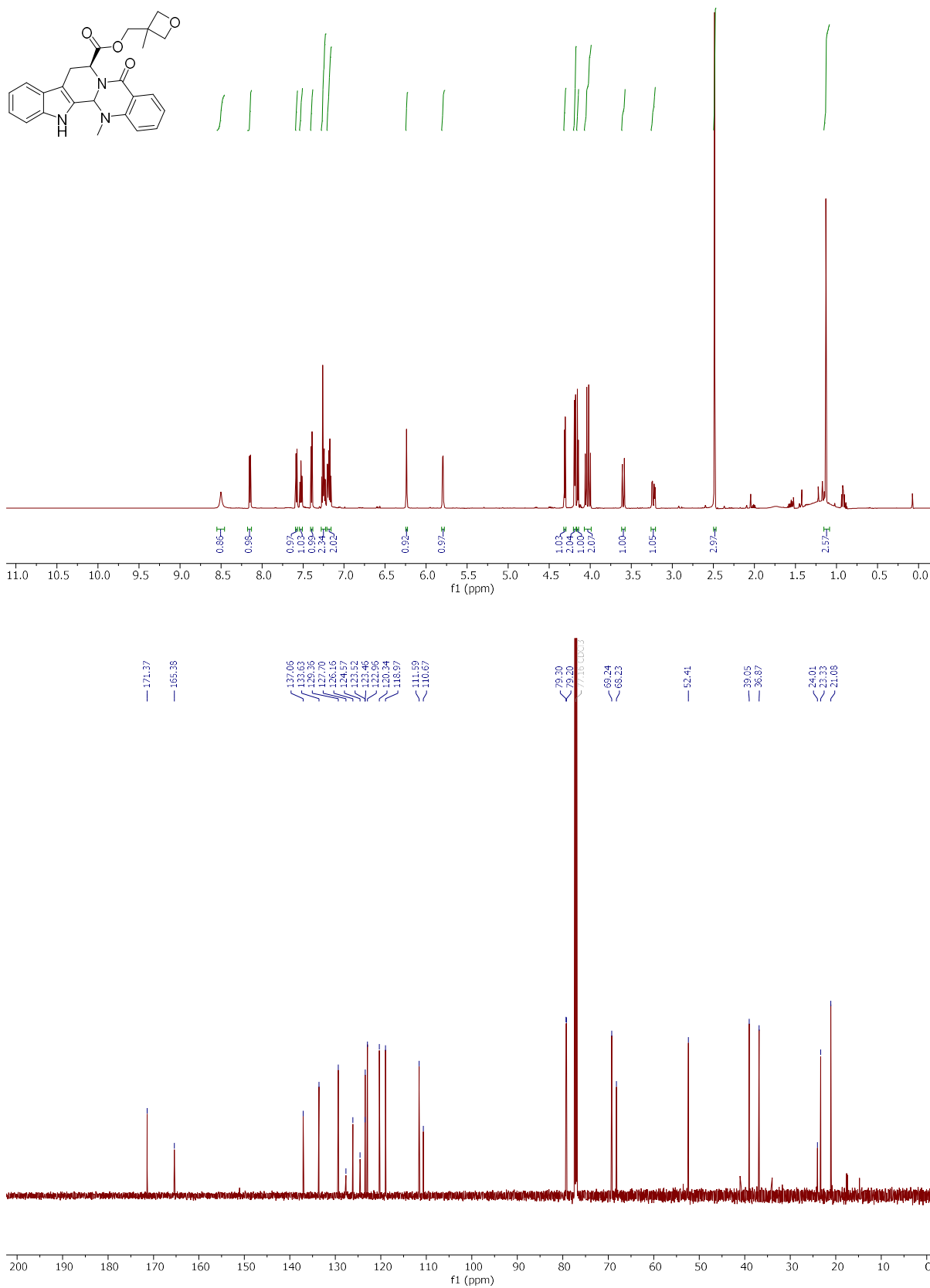
6.26. $^1\text{H}/^{13}\text{C}$ NMR spectra: ester 157



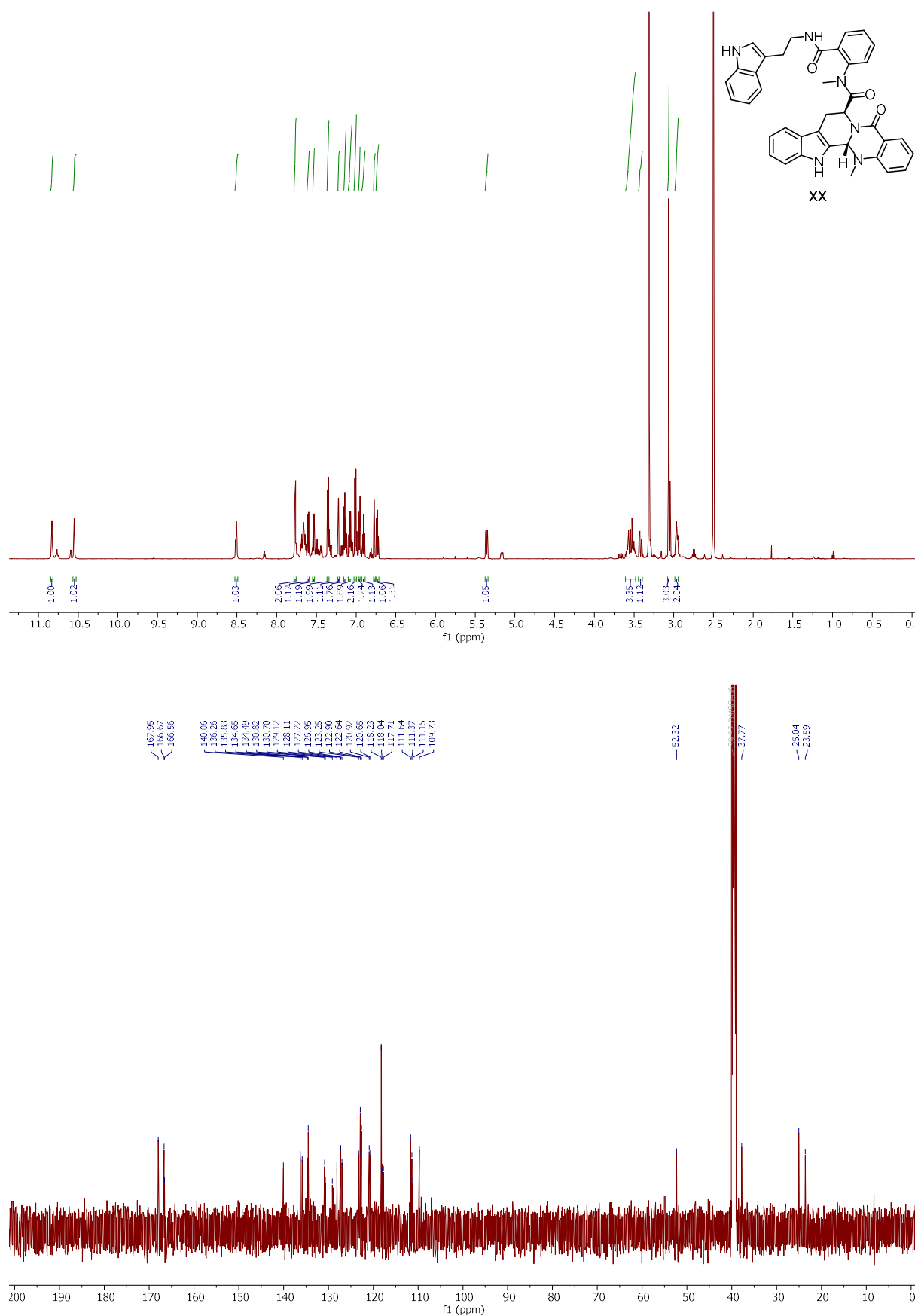
6.27. $^1\text{H}/^{13}\text{C}$ NMR spectra: OBO orthoester 158



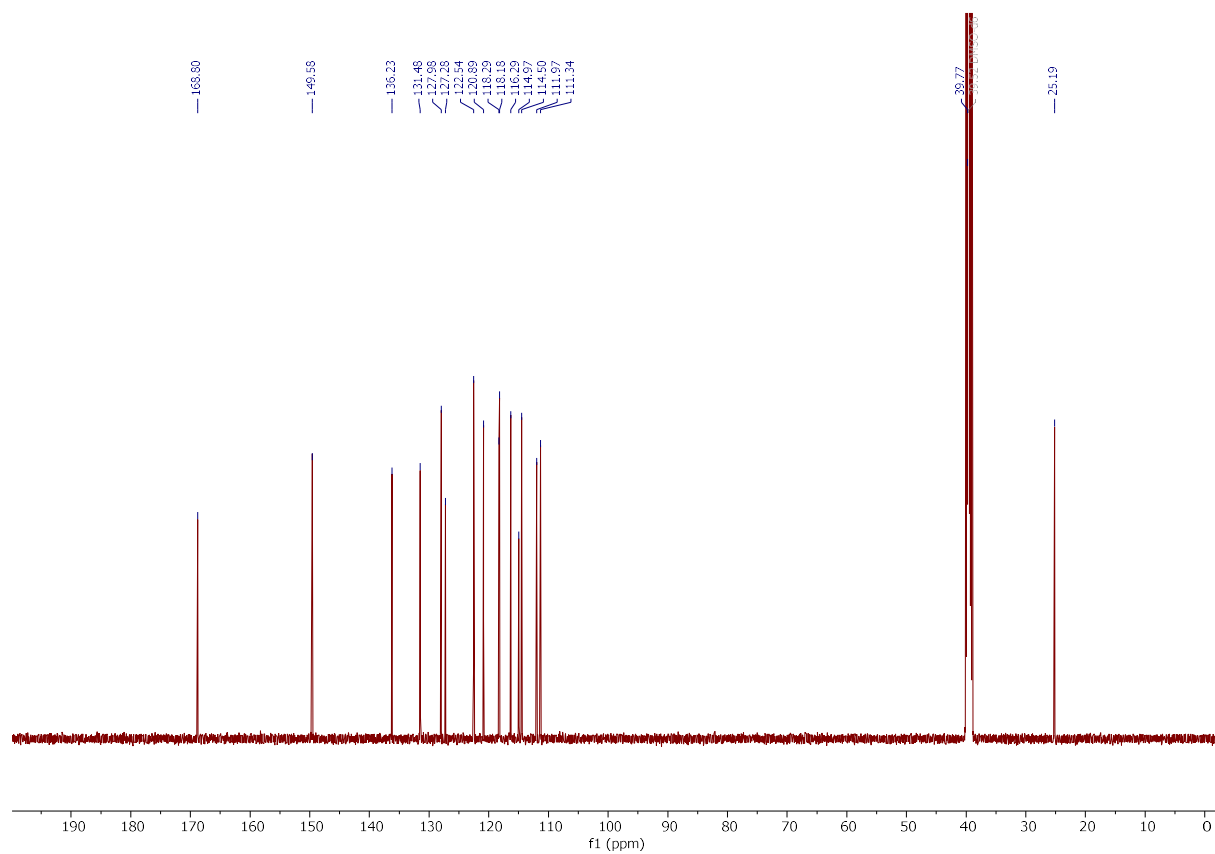
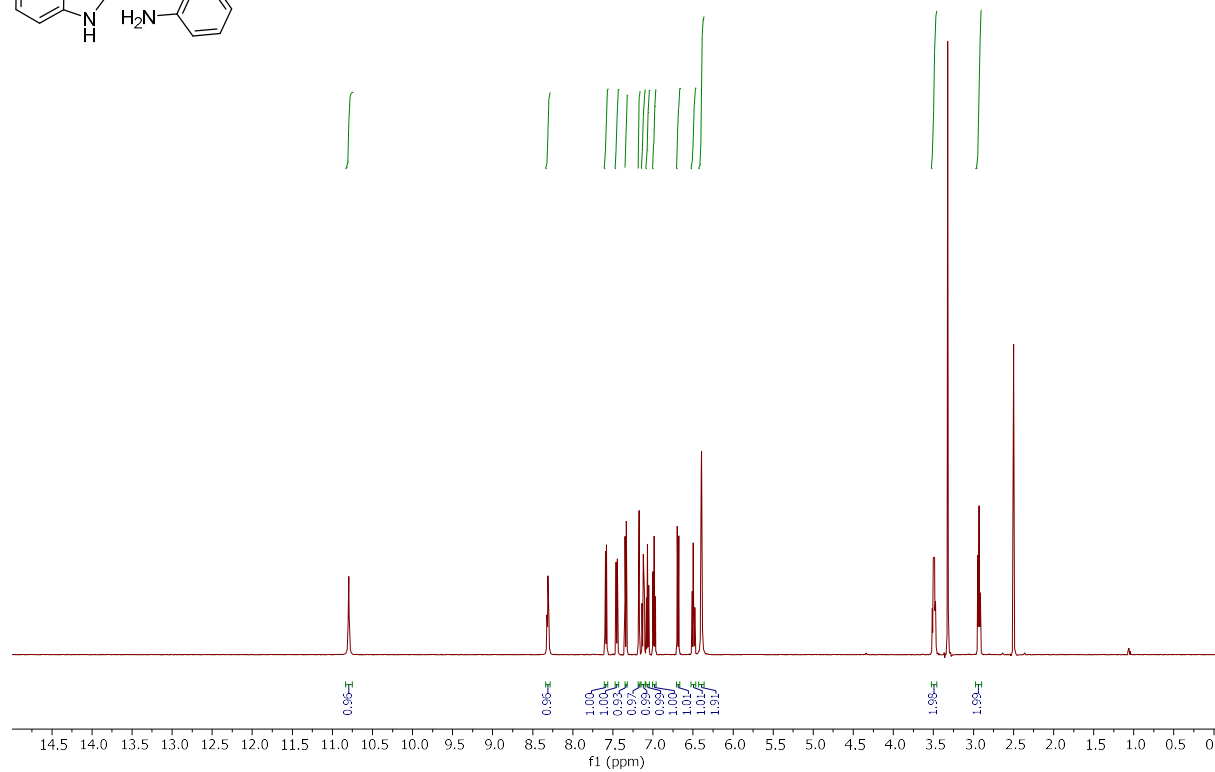
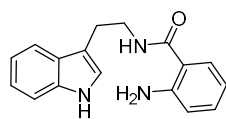
6.28. $^1\text{H}/^{13}\text{C}$ NMR spectra: ester 159



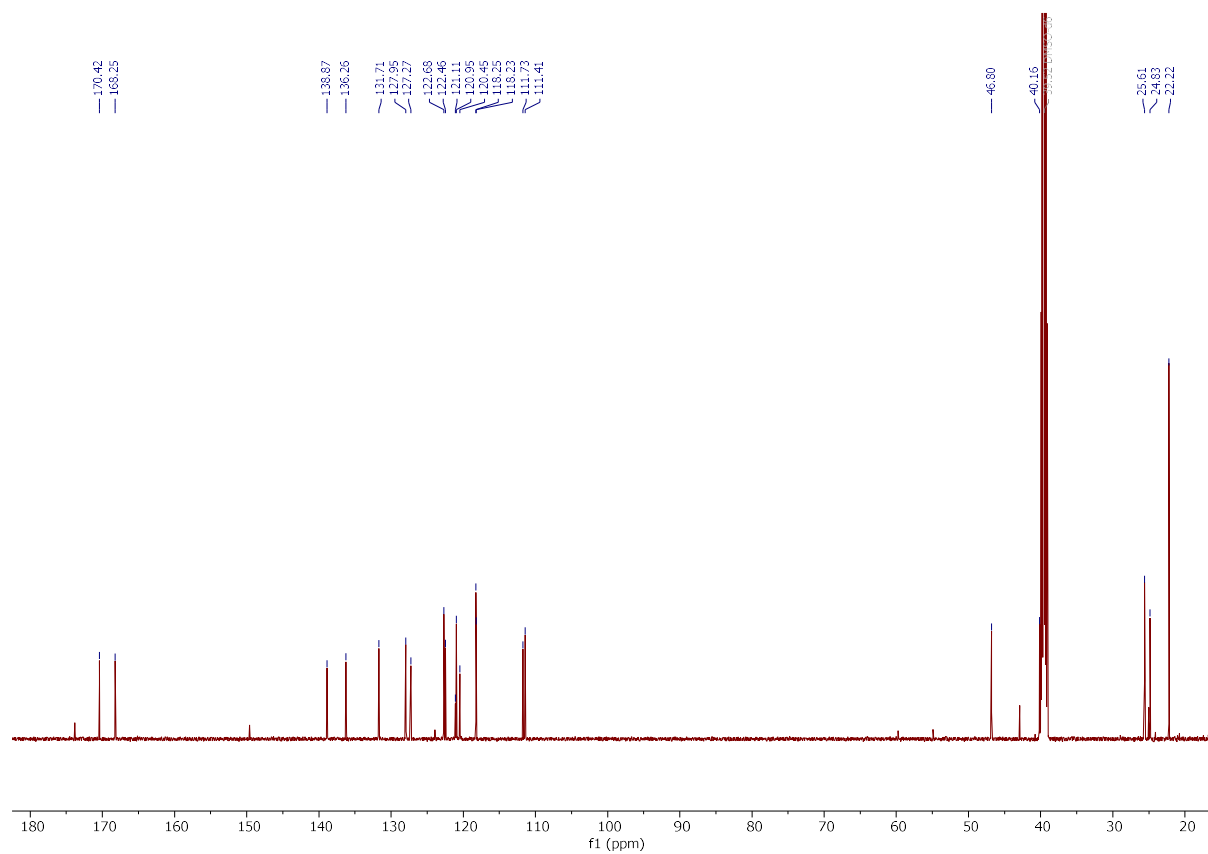
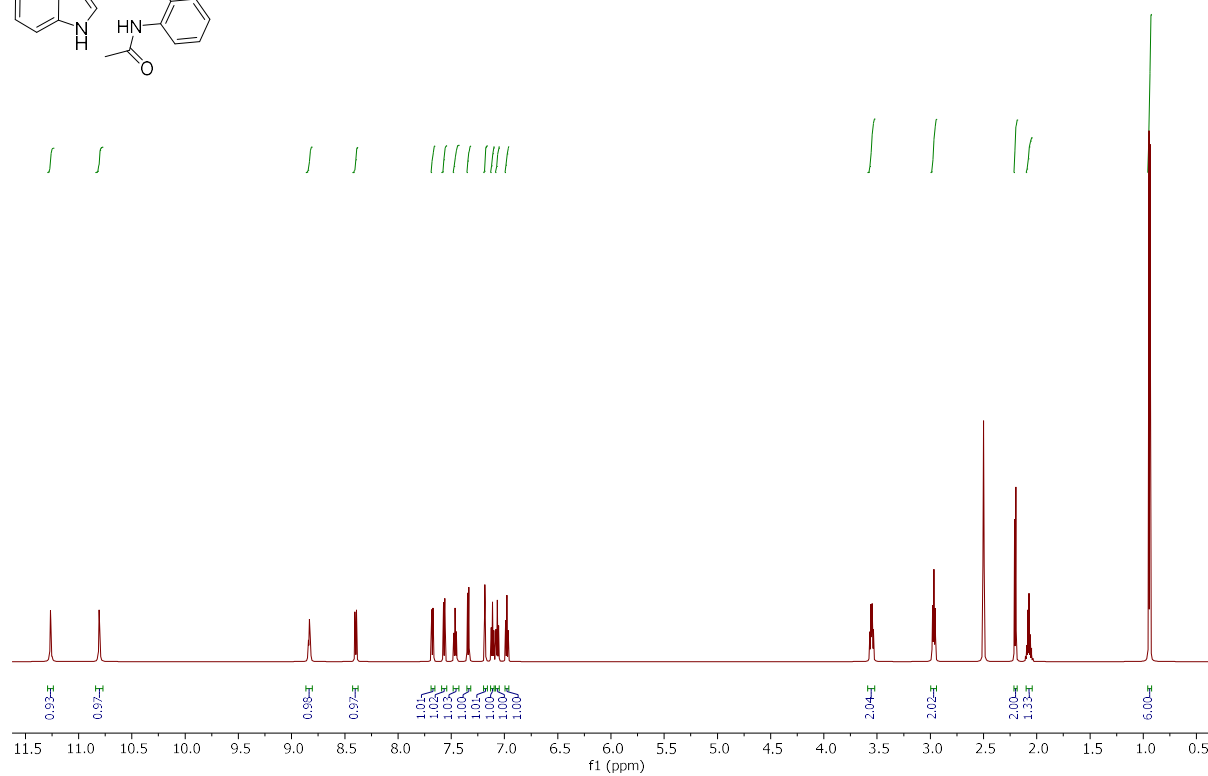
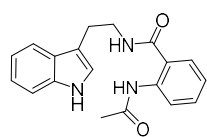
6.29. $^1\text{H}/^{13}\text{C}$ NMR spectra: Diamide 147



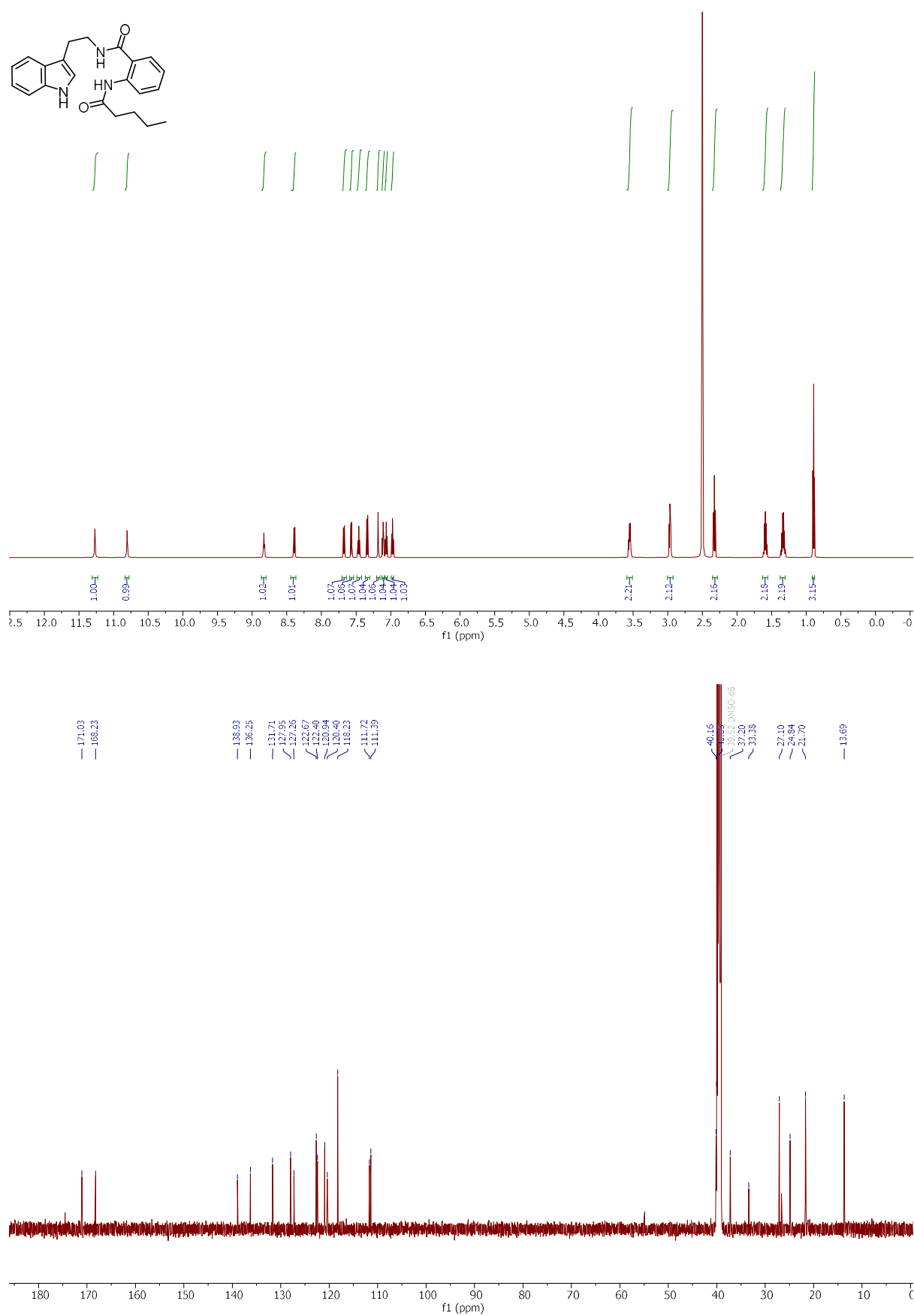
6.30. $^1\text{H}/^{13}\text{C}$ NMR spectra: Amide 163



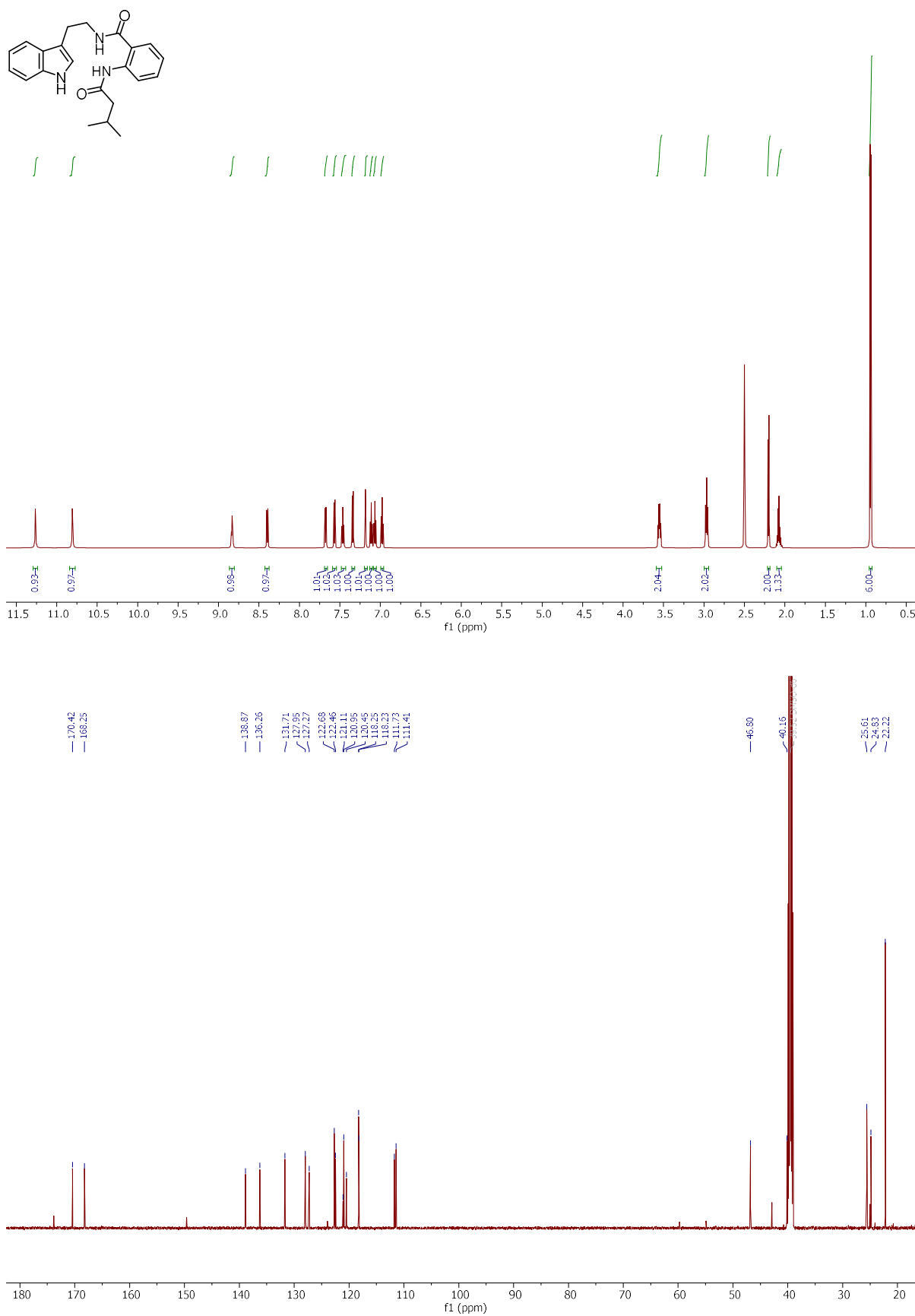
6.31. $^1\text{H}/^{13}\text{C}$ NMR spectra: diamide 164a



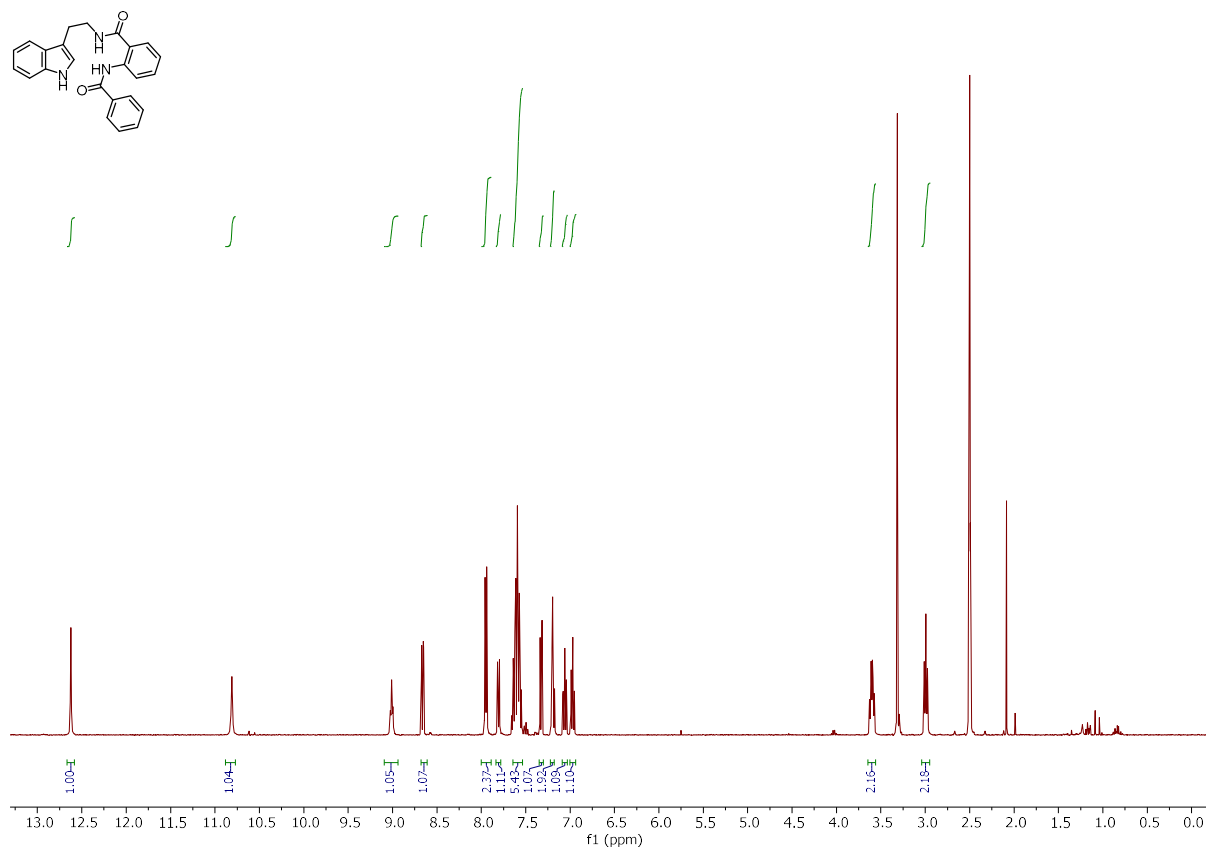
6.32. $^1\text{H}/^{13}\text{C}$ NMR spectra: diamide 164c



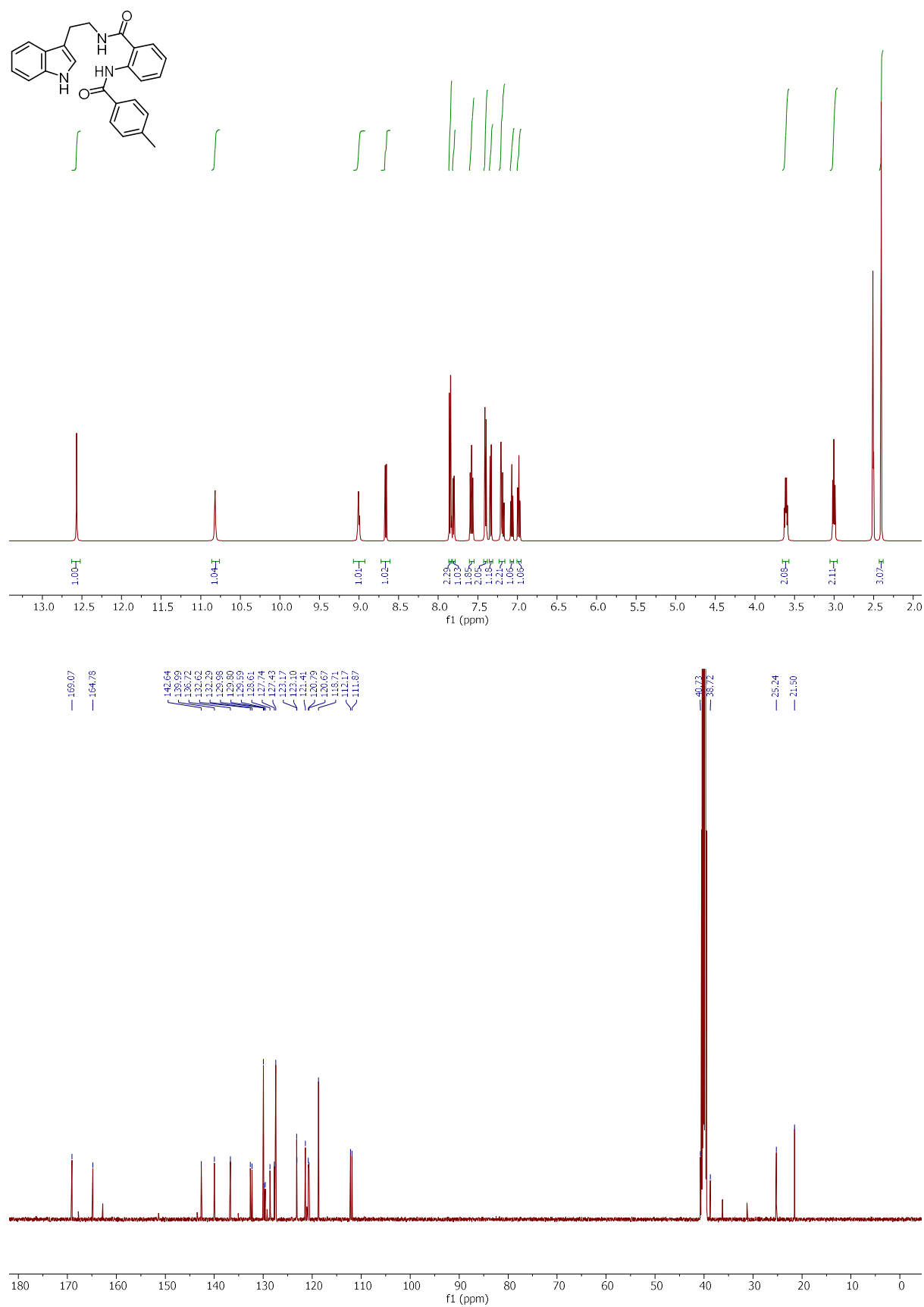
6.33. $^1\text{H}/^{13}\text{C}$ NMR spectra: diamide 164b



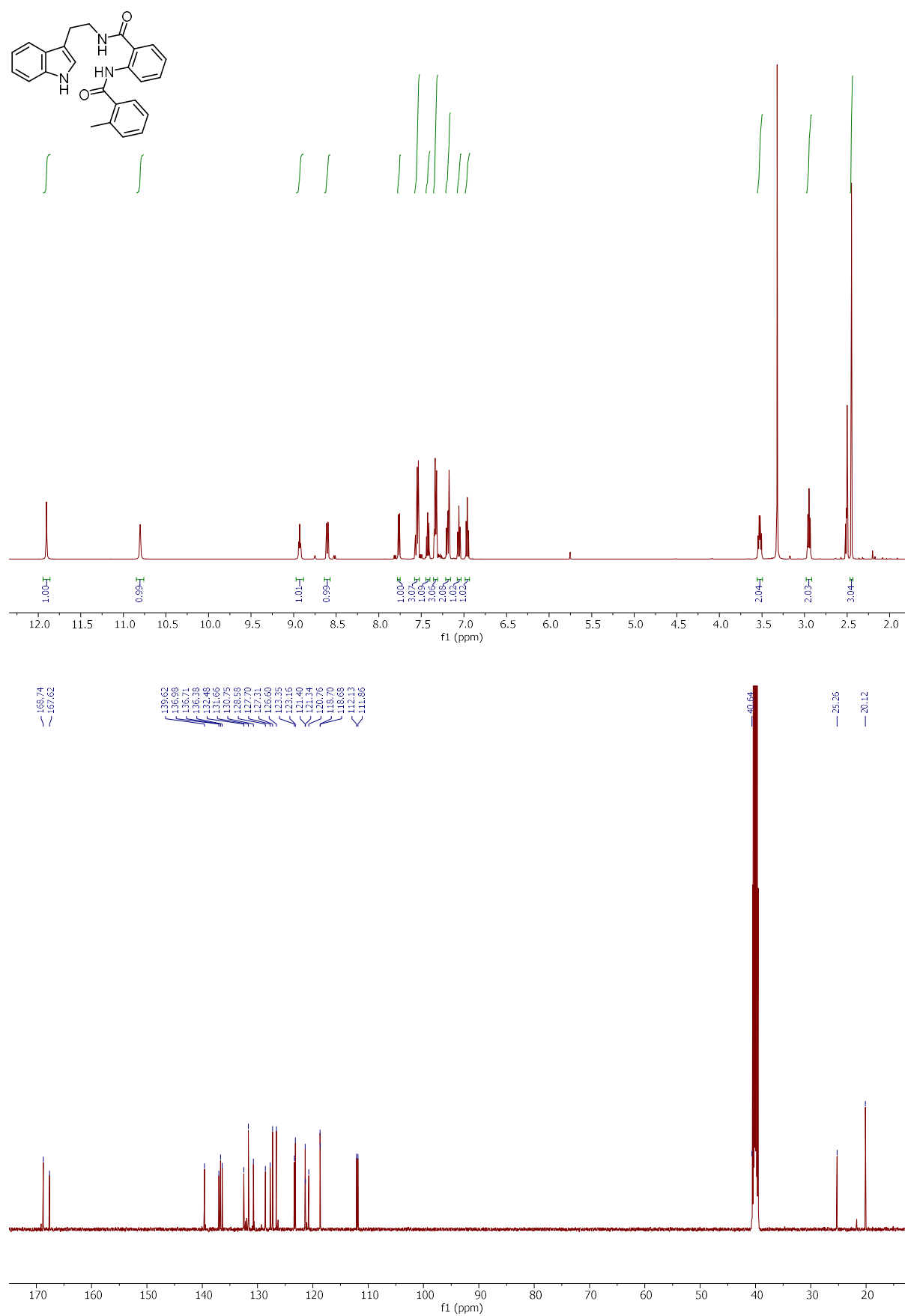
6.34. $^1\text{H}/^{13}\text{C}$ NMR spectra: diamide 164e



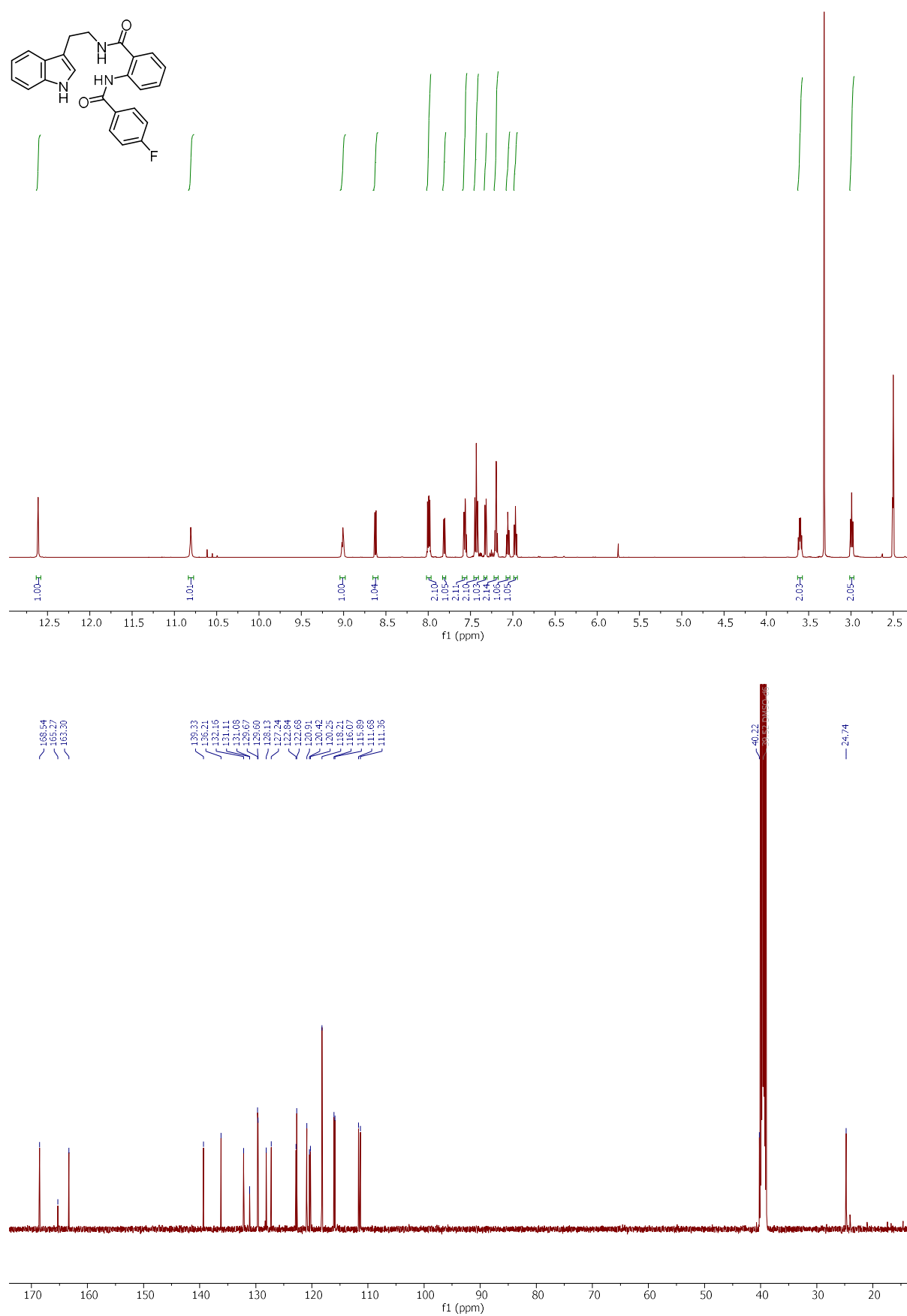
6.35. $^1\text{H}/^{13}\text{C}$ NMR spectra: diamide 164f



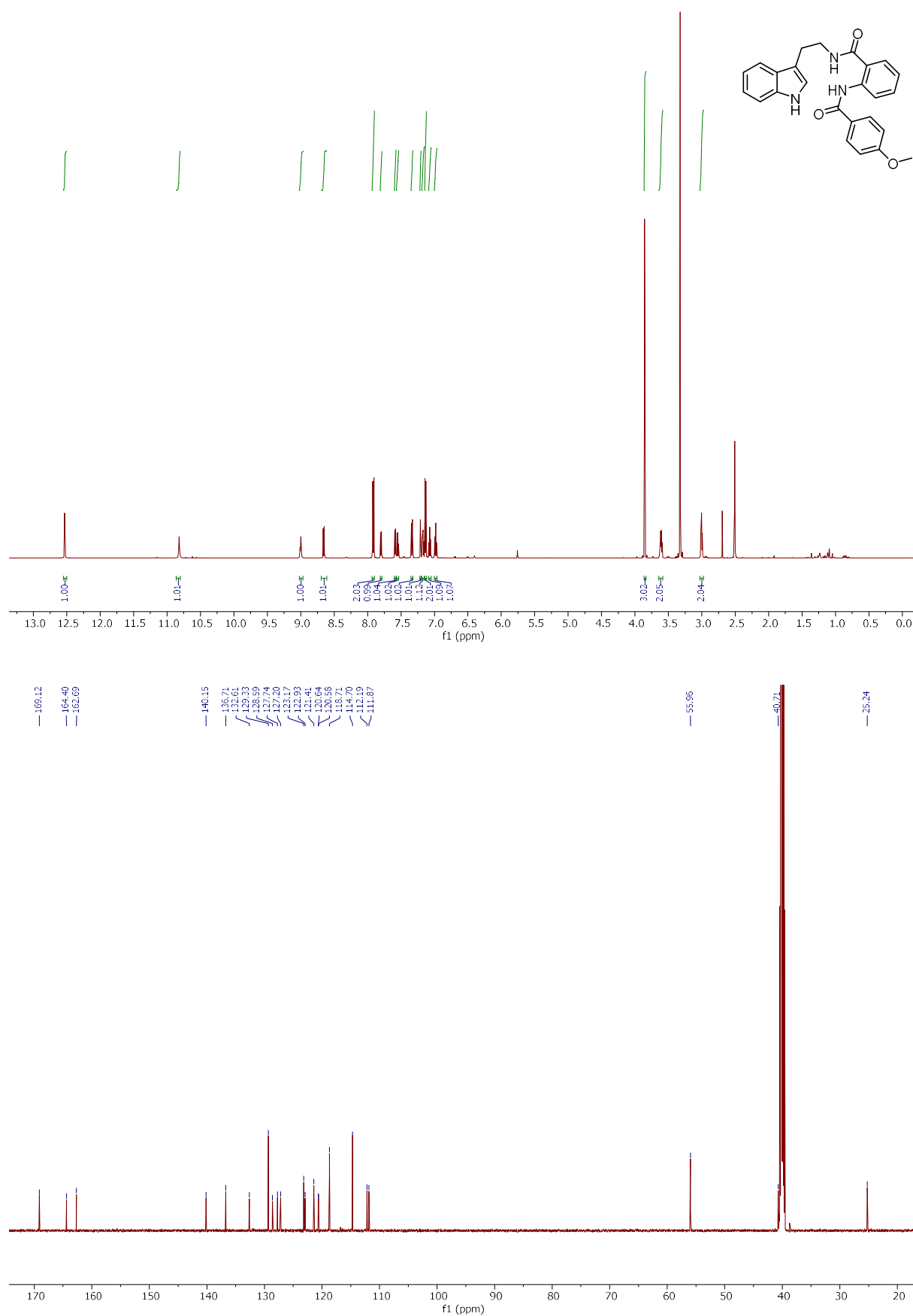
6.36. $^1\text{H}/^{13}\text{C}$ NMR spectra: diamide 164g



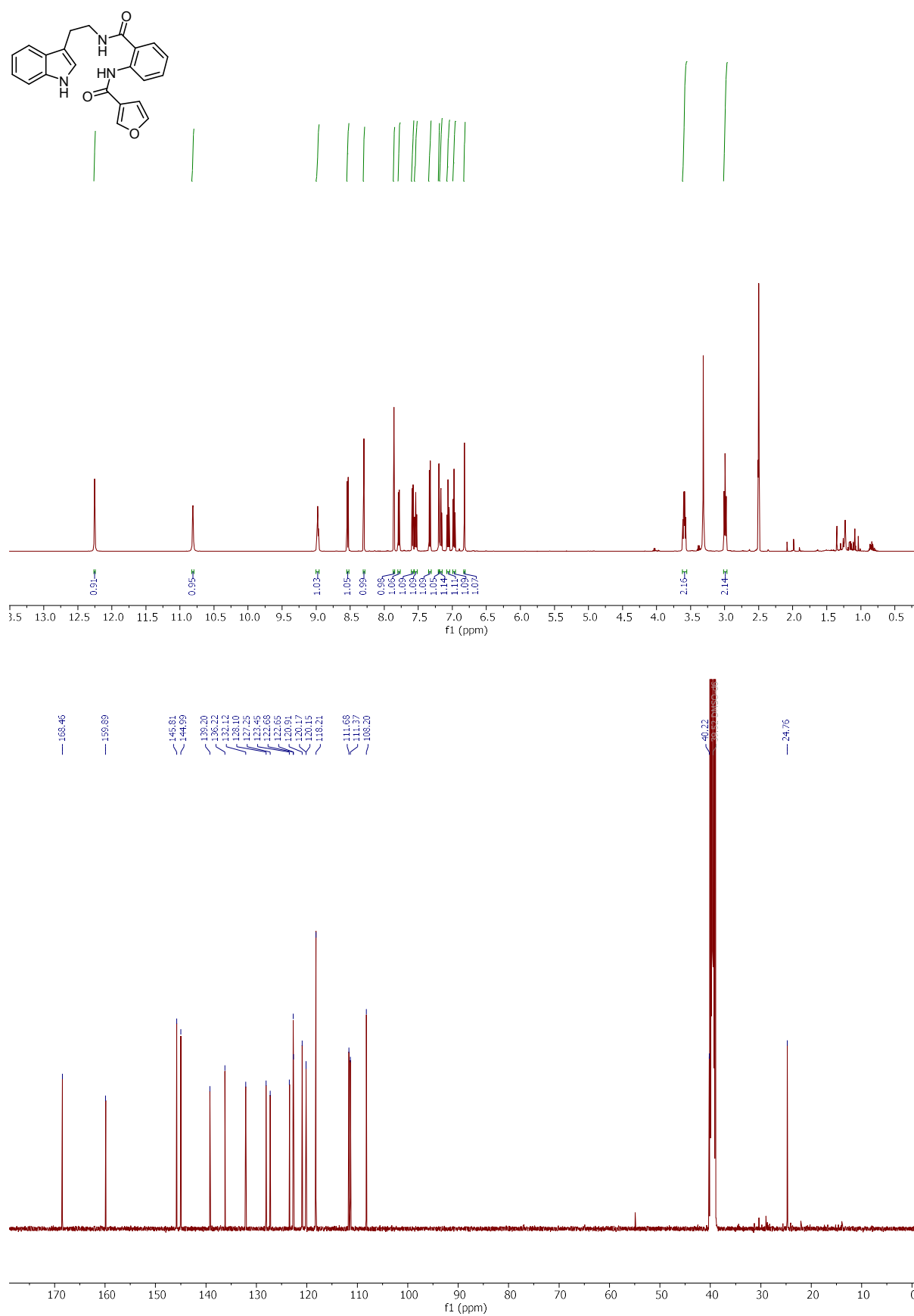
6.37. $^1\text{H}/^{13}\text{C}$ NMR spectra: diamide 164h



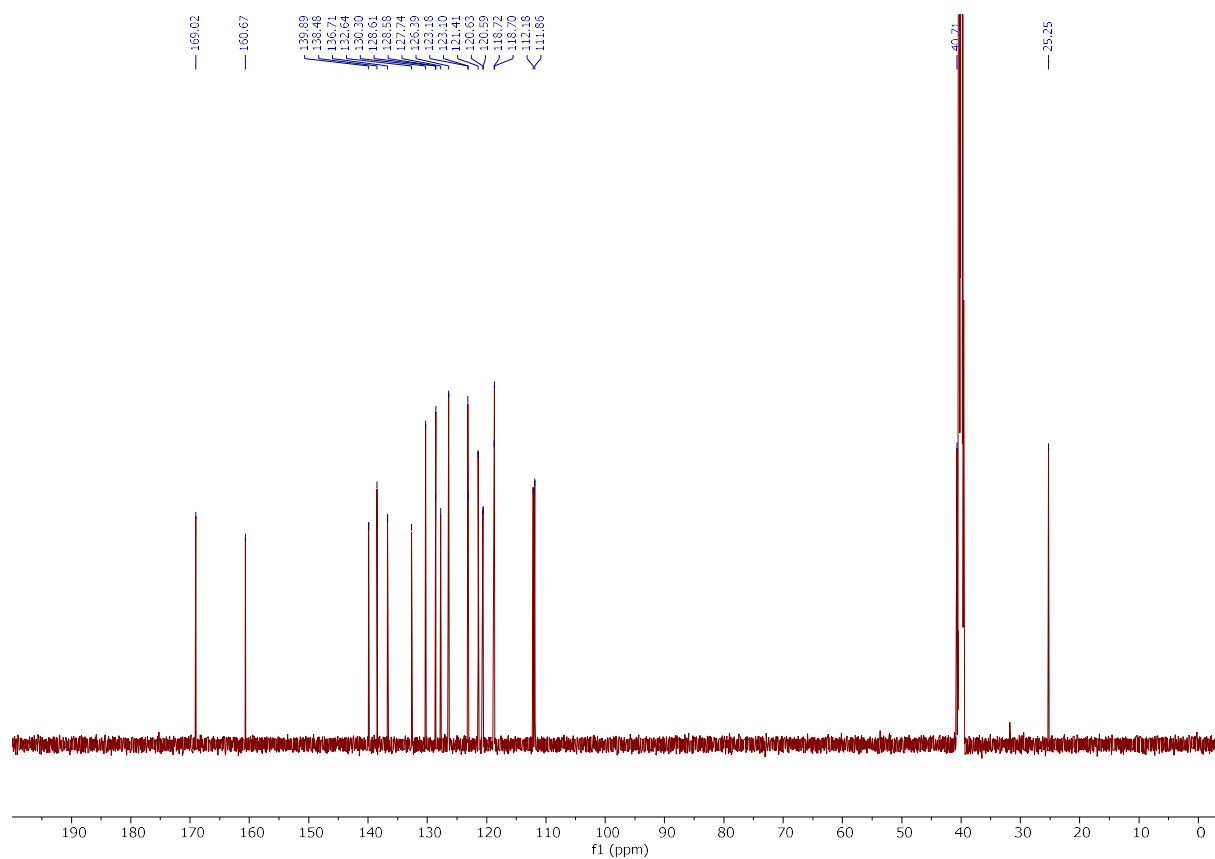
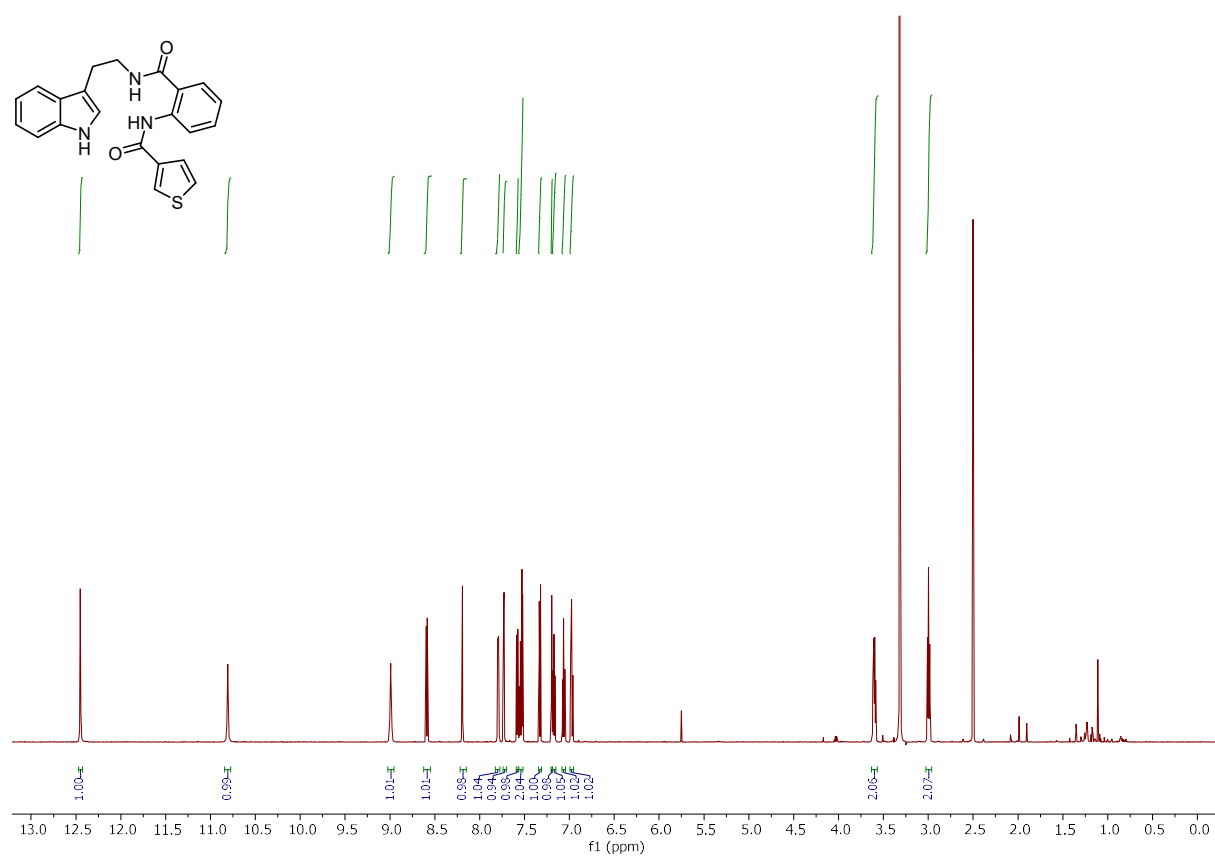
6.38. $^1\text{H}/^{13}\text{C}$ NMR spectra: diamide 164i



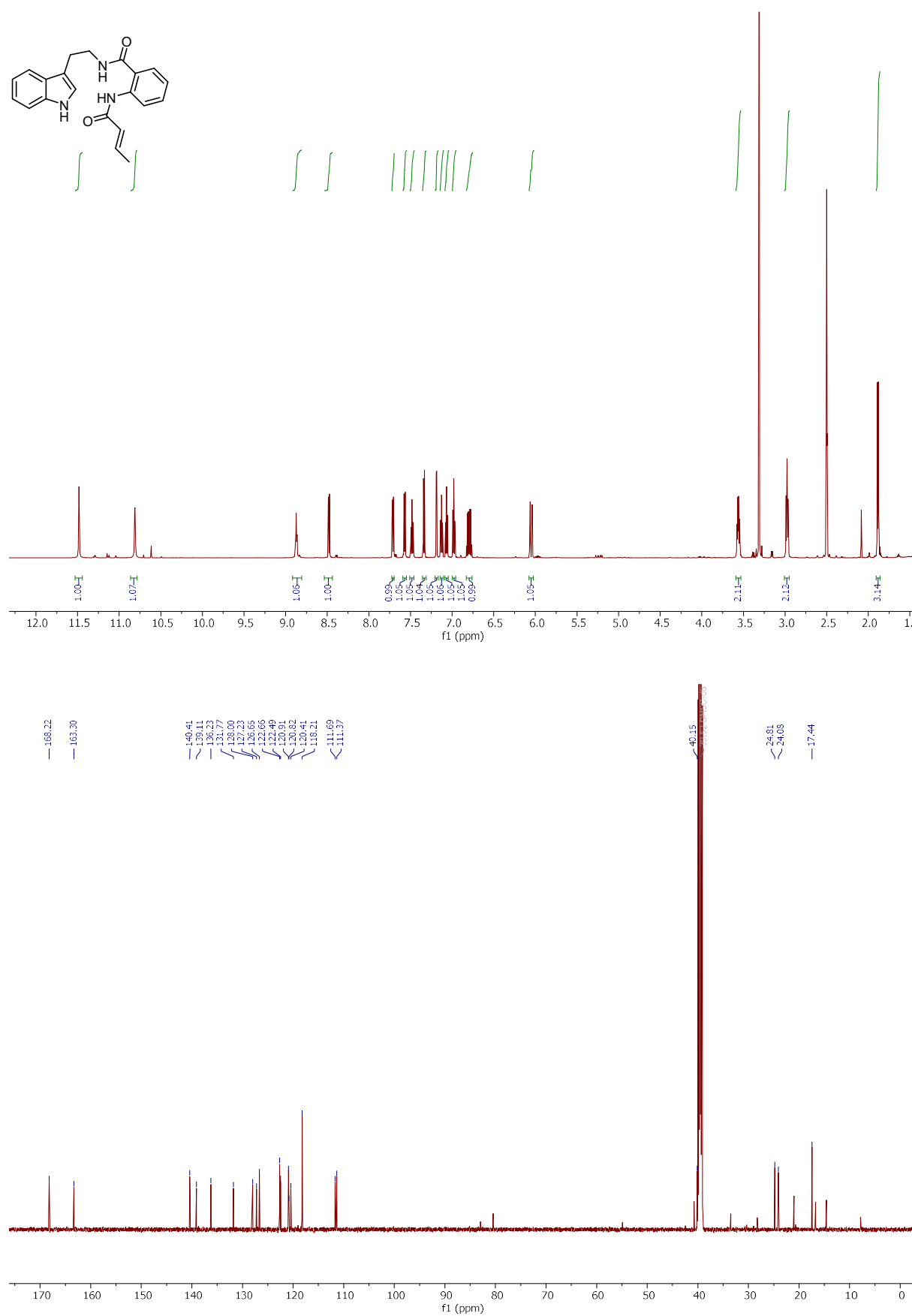
6.39. $^1\text{H}/^{13}\text{C}$ NMR spectra: diamide 164j



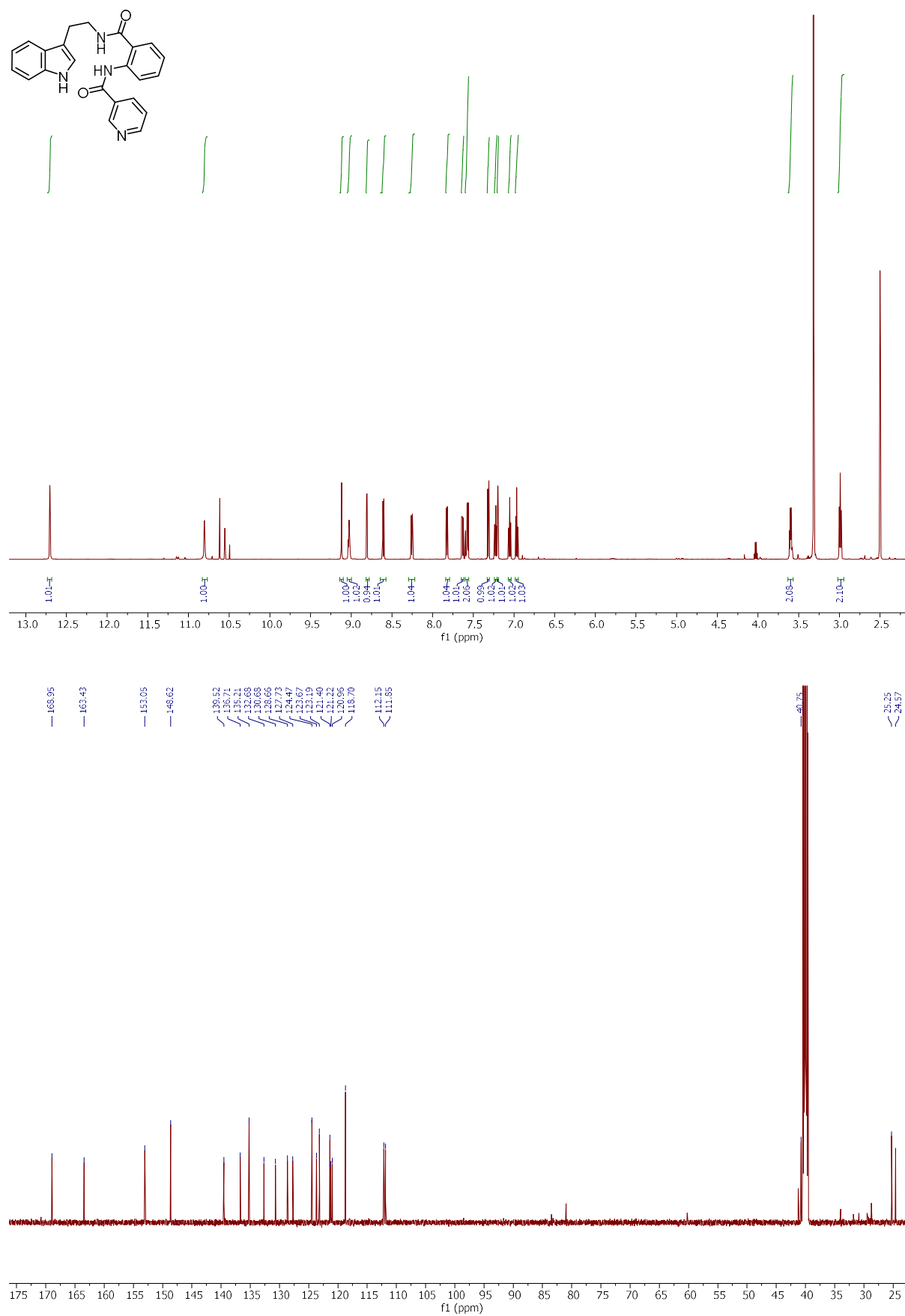
6.40. $^1\text{H}/^{13}\text{C}$ NMR spectra: diamide 164k



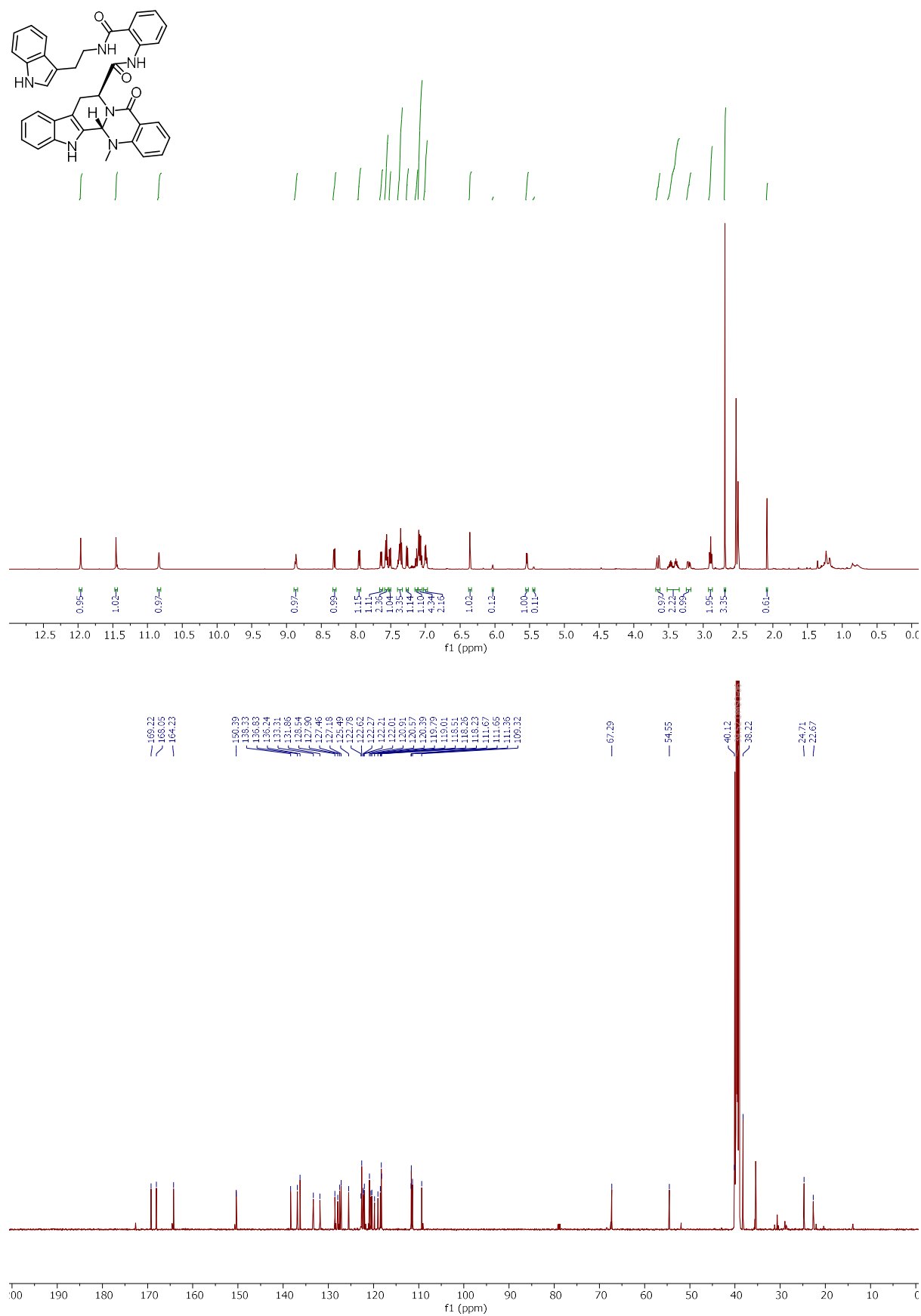
6.41. $^1\text{H}/^{13}\text{C}$ NMR spectra: diamide 164d (JS-E-139)



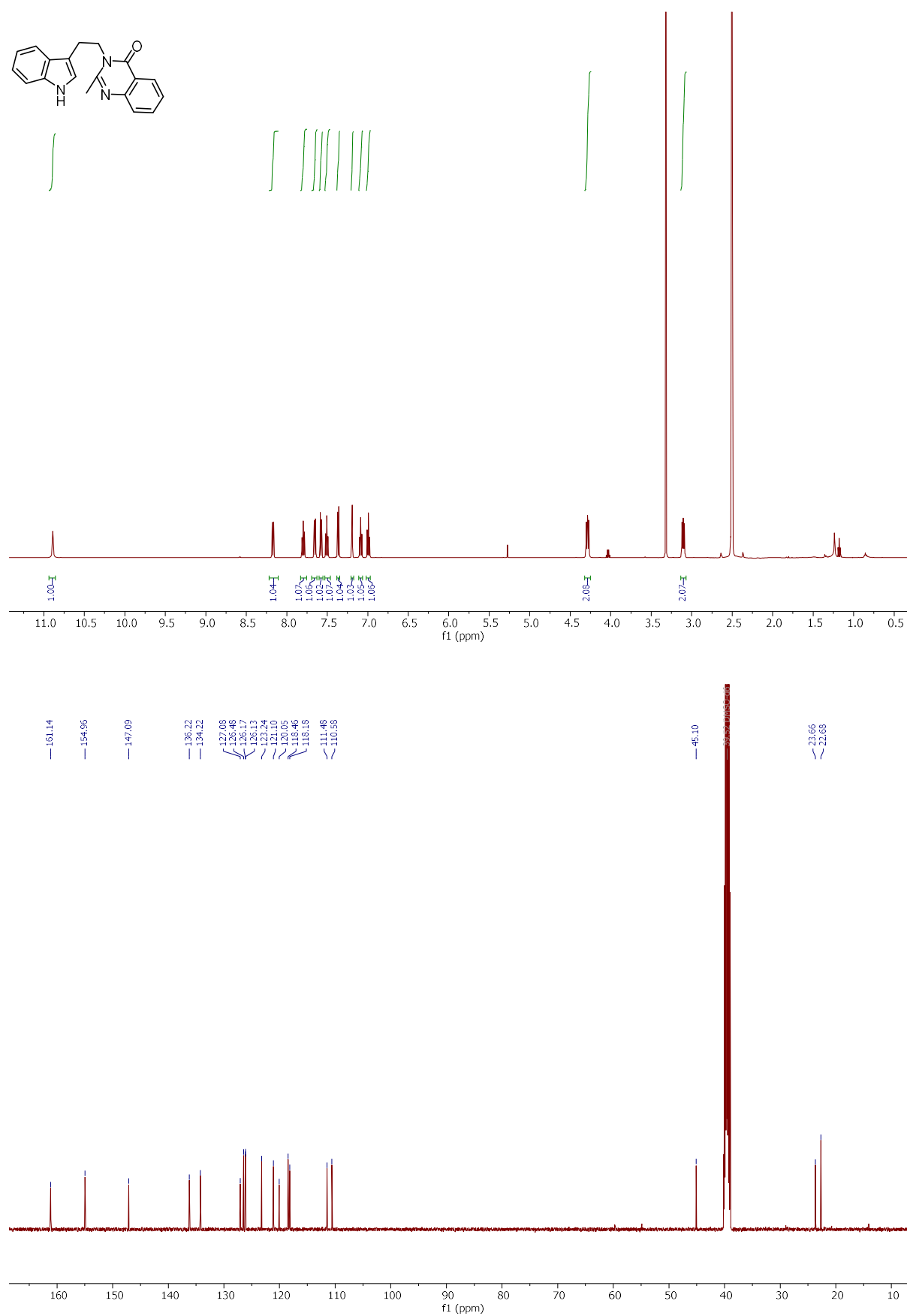
6.42. $^1\text{H}/^{13}\text{C}$ NMR spectra: diamide 164I (JS-G-5)



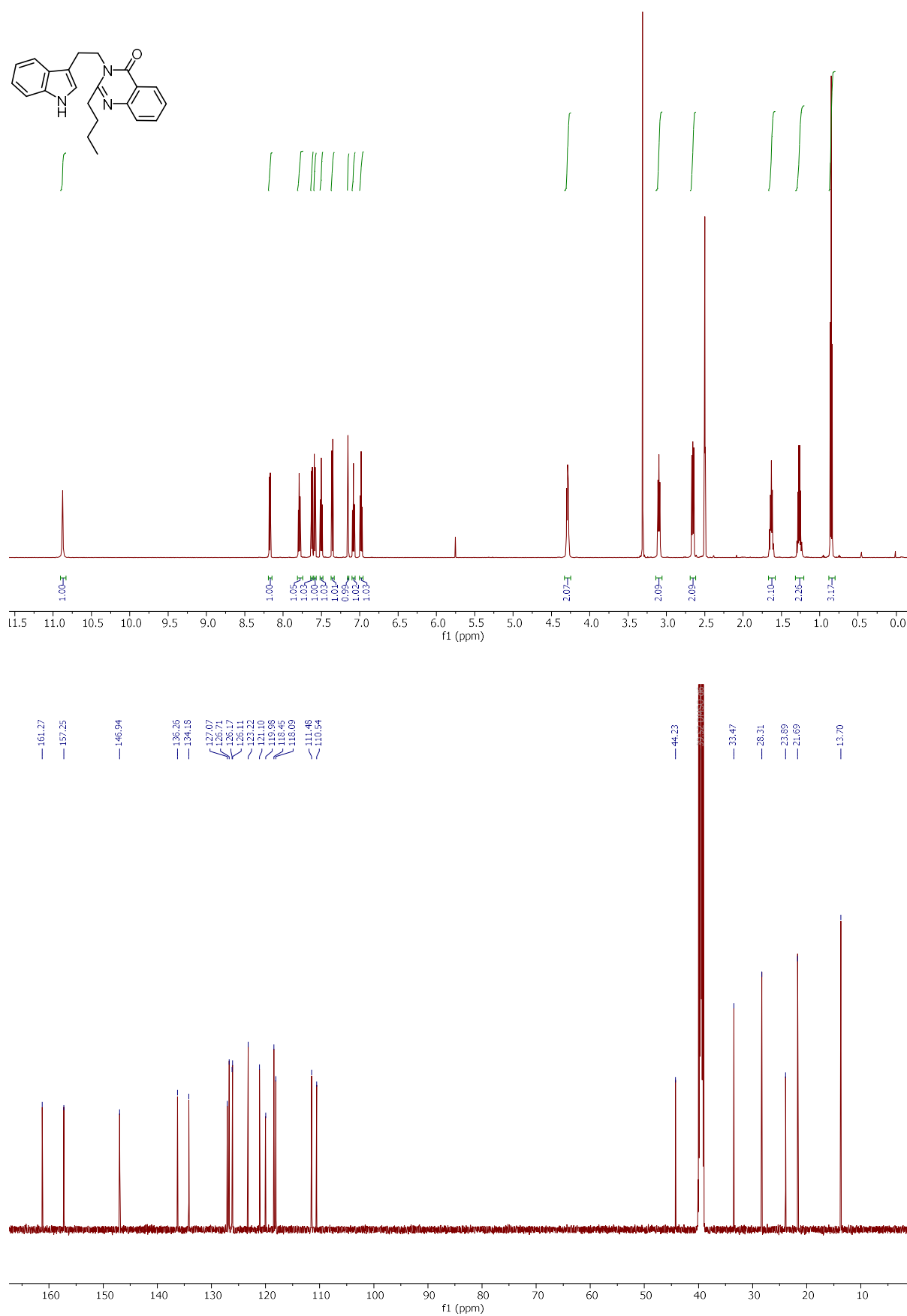
6.43. $^1\text{H}/^{13}\text{C}$ NMR spectra: diamide 162



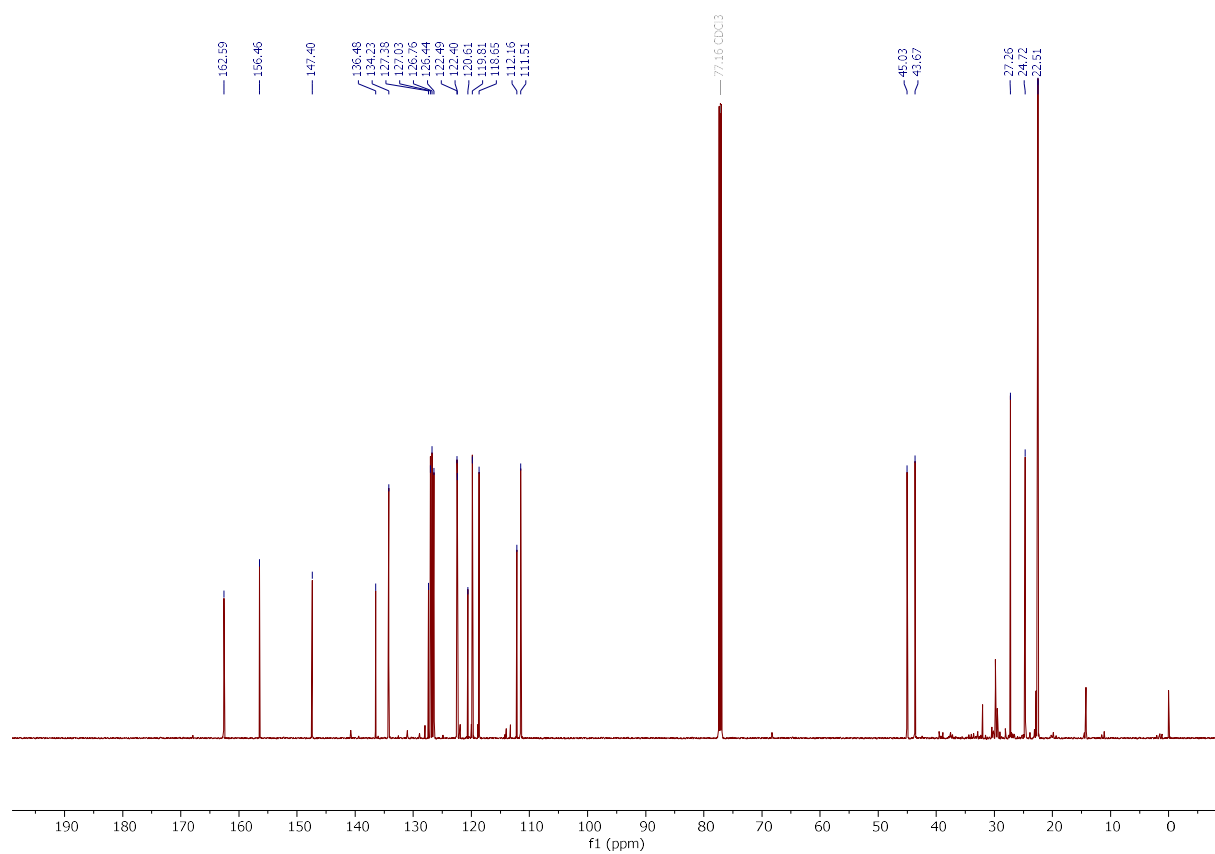
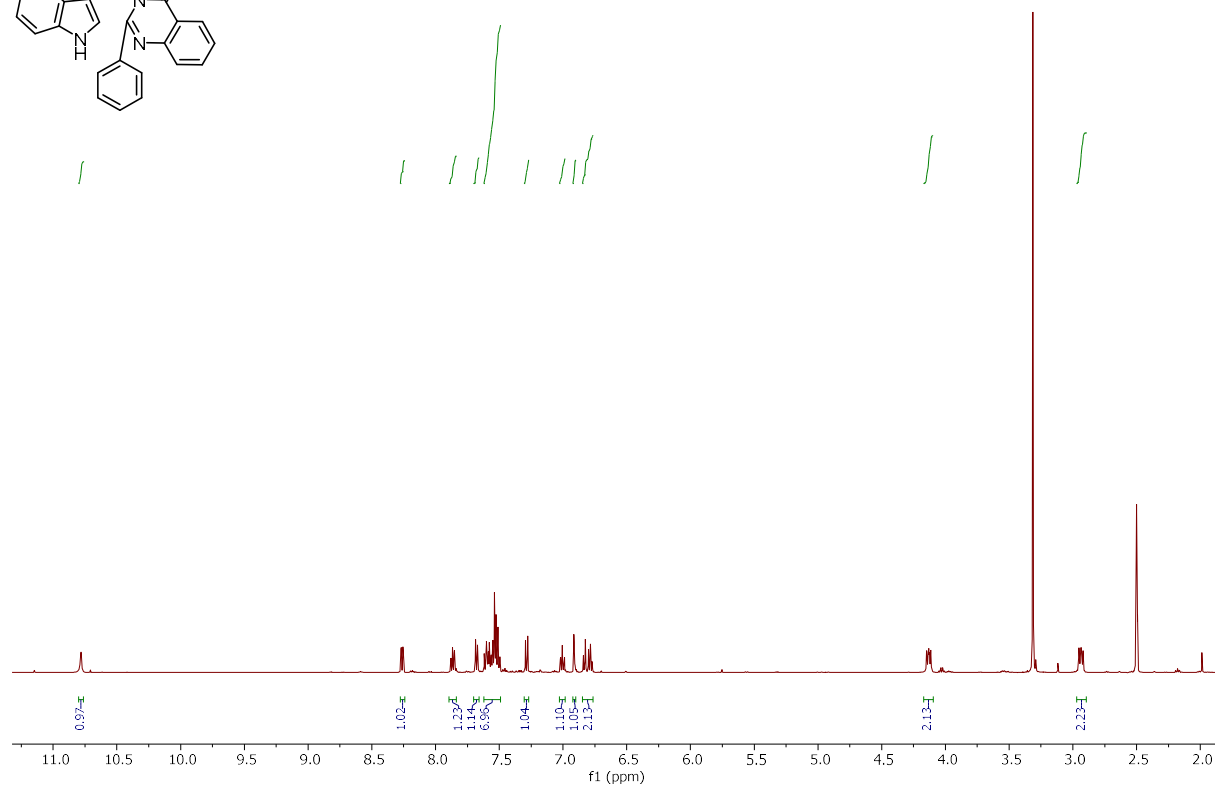
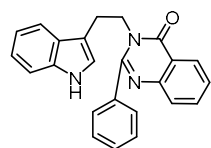
6.44. $^1\text{H}/^{13}\text{C}$ NMR spectra: 4-quinazolinone 165a



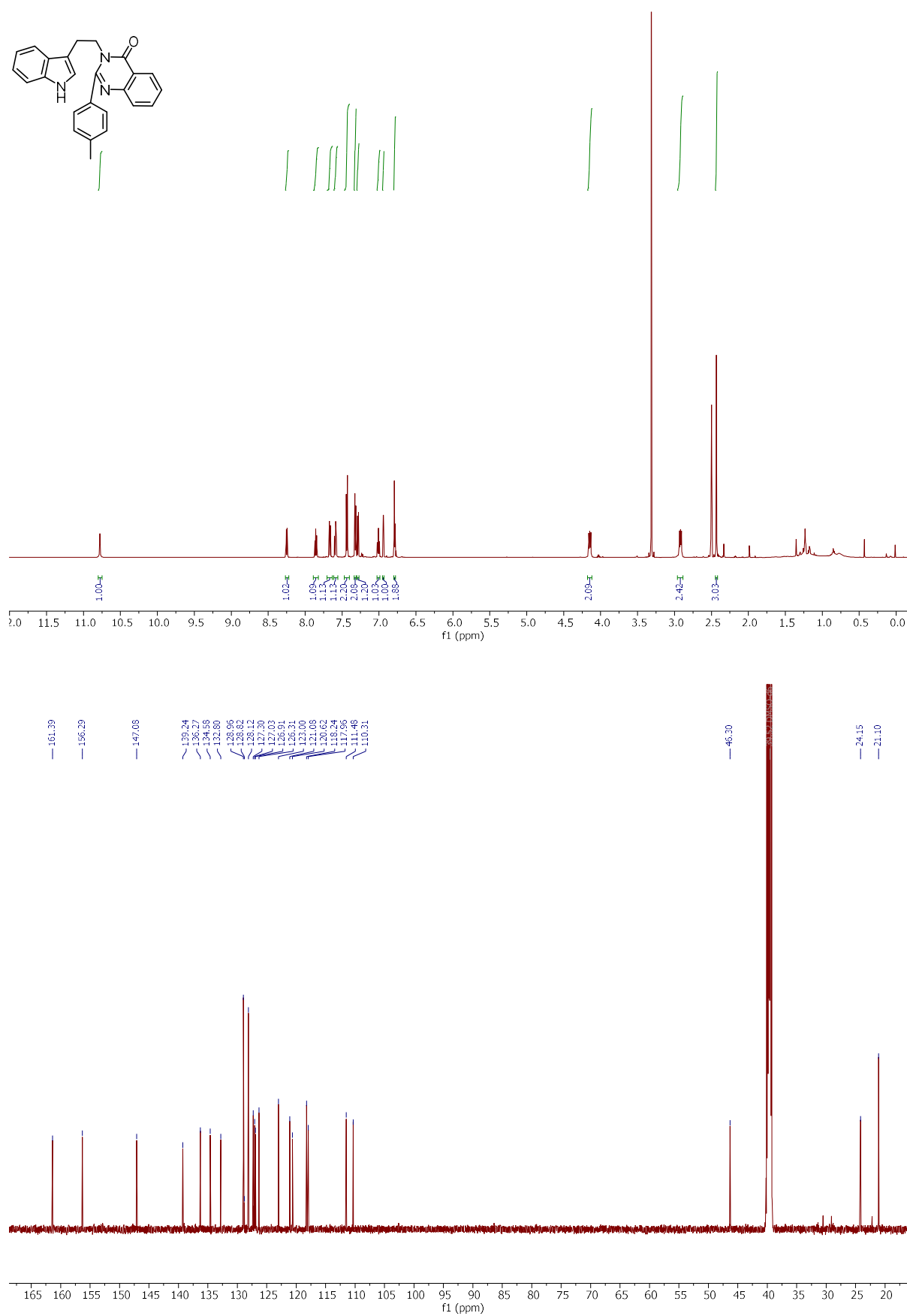
6.45. $^1\text{H}/^{13}\text{C}$ NMR spectra: 4-quinazolinone 165c



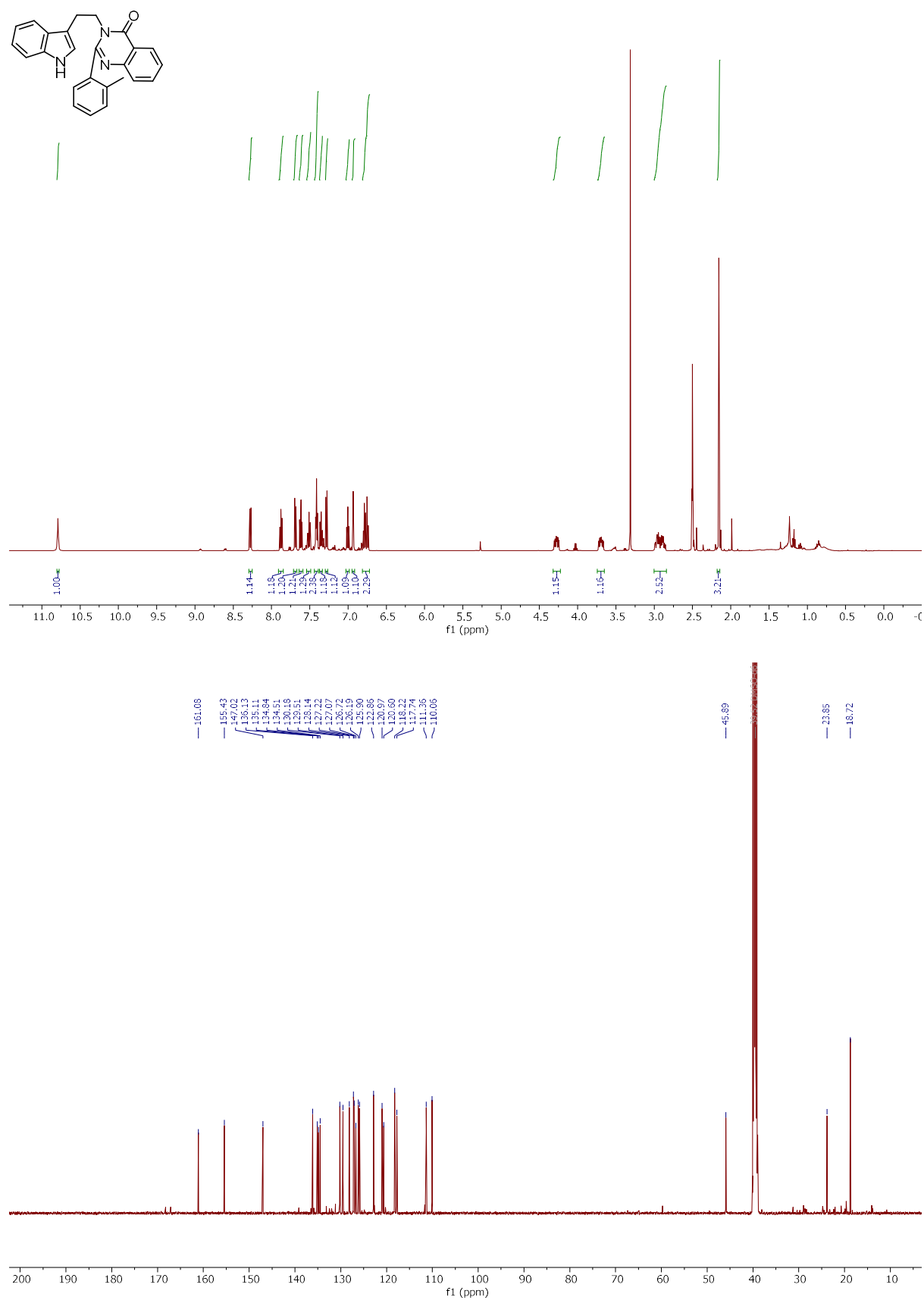
6.46. ¹H NMR spectra: 4-quinazolinone 165e



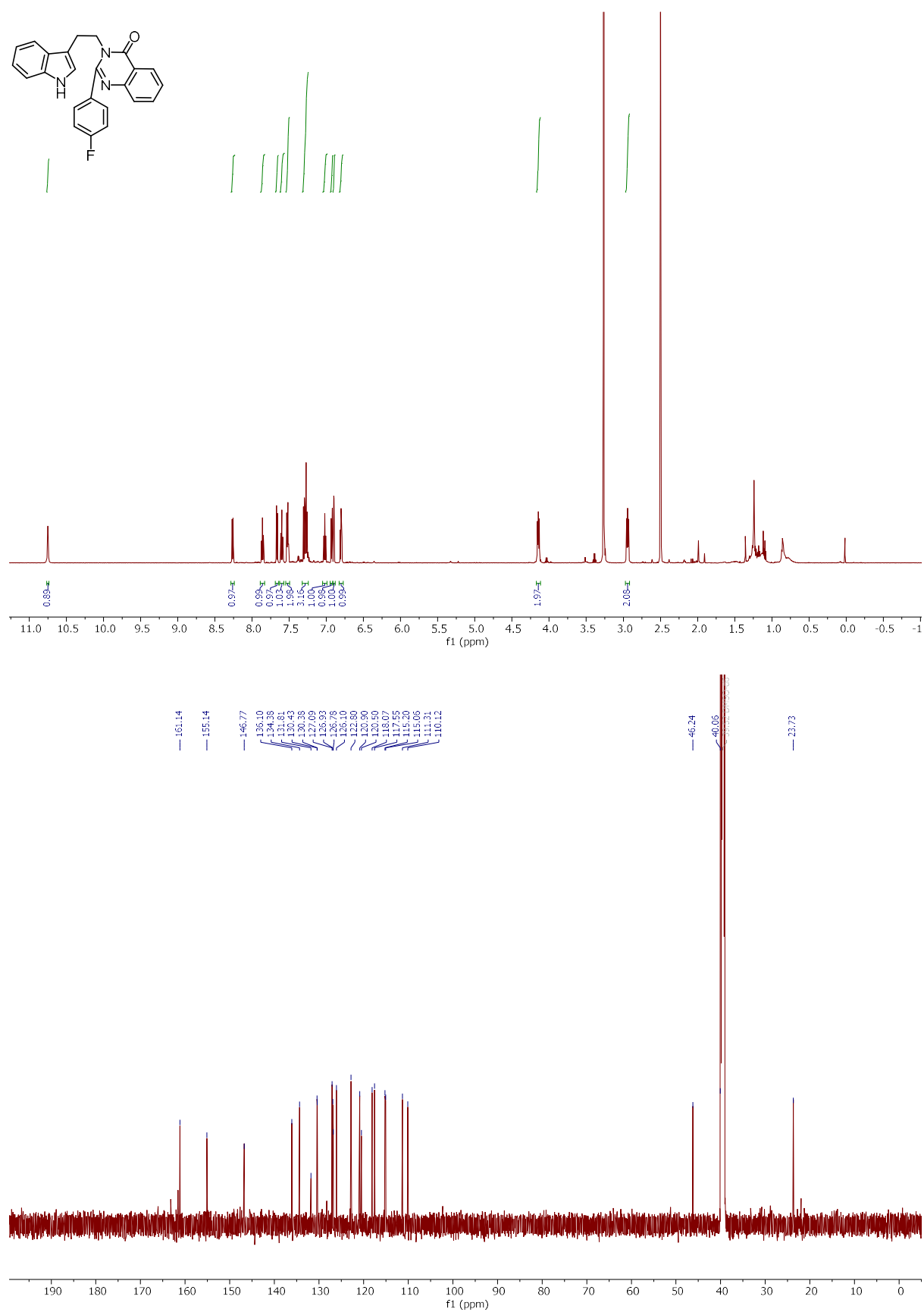
6.47. $^1\text{H}/^{13}\text{C}$ NMR spectra: 4-quinazolinone 165f



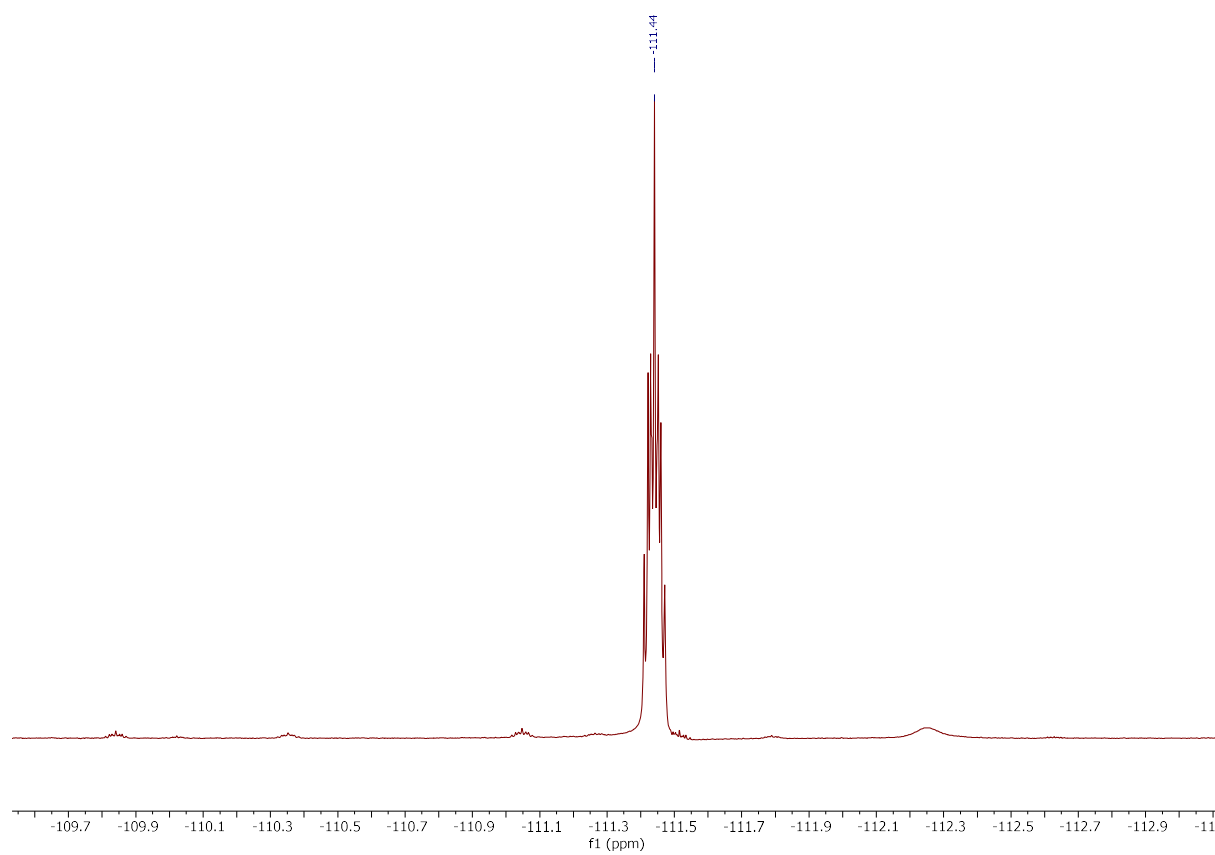
6.48. $^1\text{H}/^{13}\text{C}$ NMR spectra: 4-quinazolinone 165g



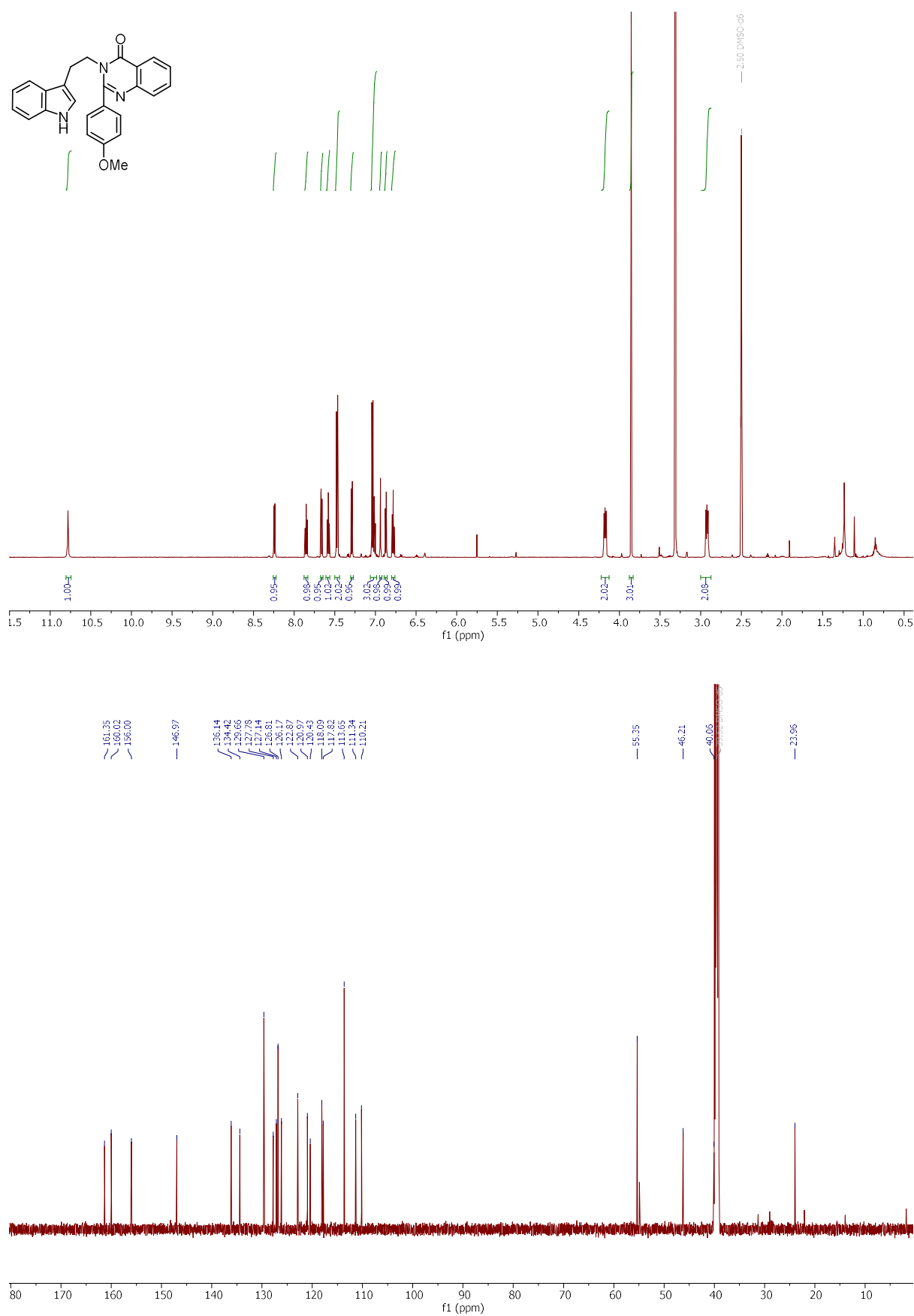
6.49. $^1\text{H}/^{13}\text{C}$ NMR spectra: 4-quinazolinone 165h



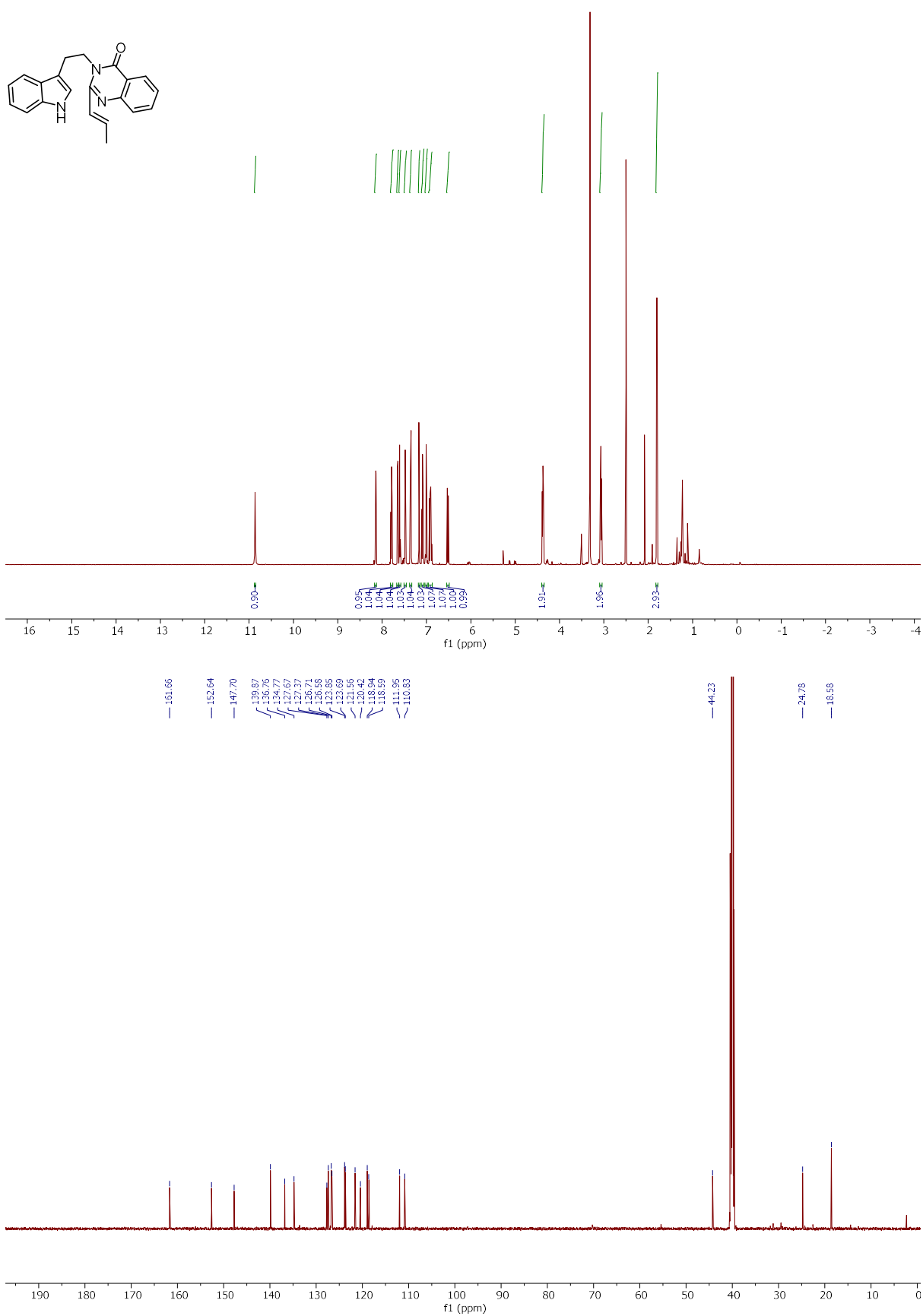
^{19}F NMR spectrum



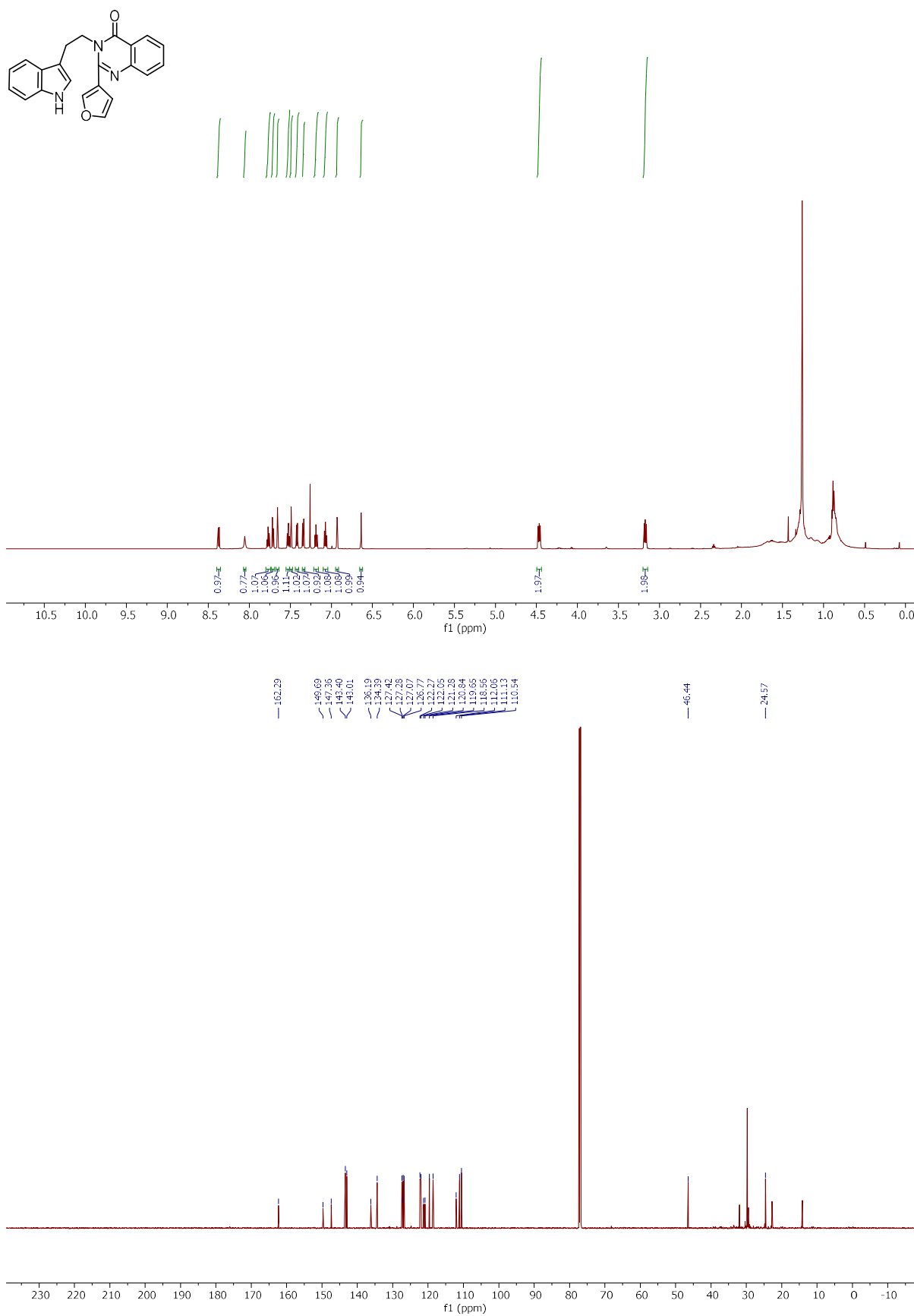
6.50. $^1\text{H}/^{13}\text{C}$ NMR spectra: 4-quinazolinone 165i



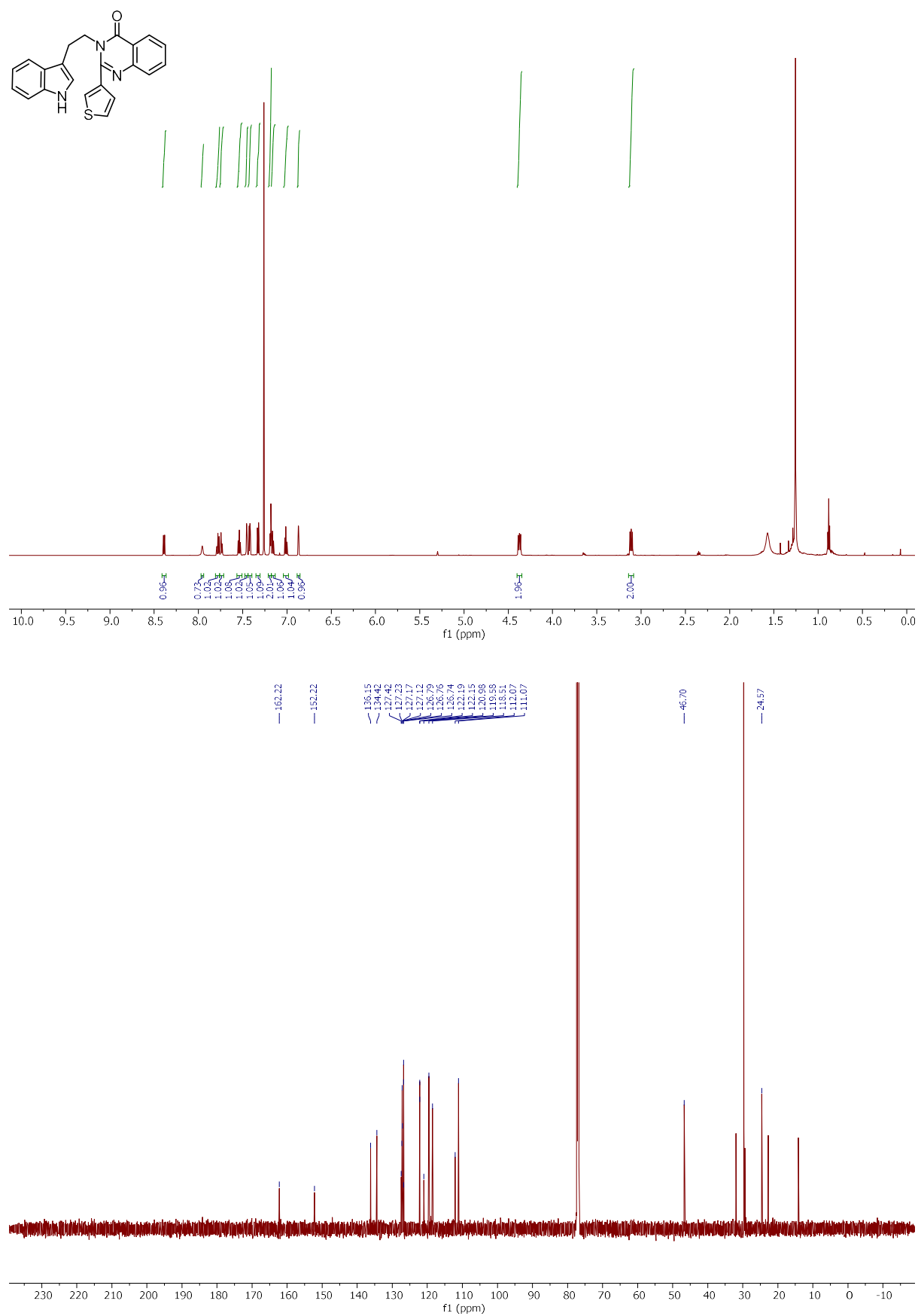
6.51. $^1\text{H}/^{13}\text{C}$ NMR spectra: 4-quinazolinone 165d



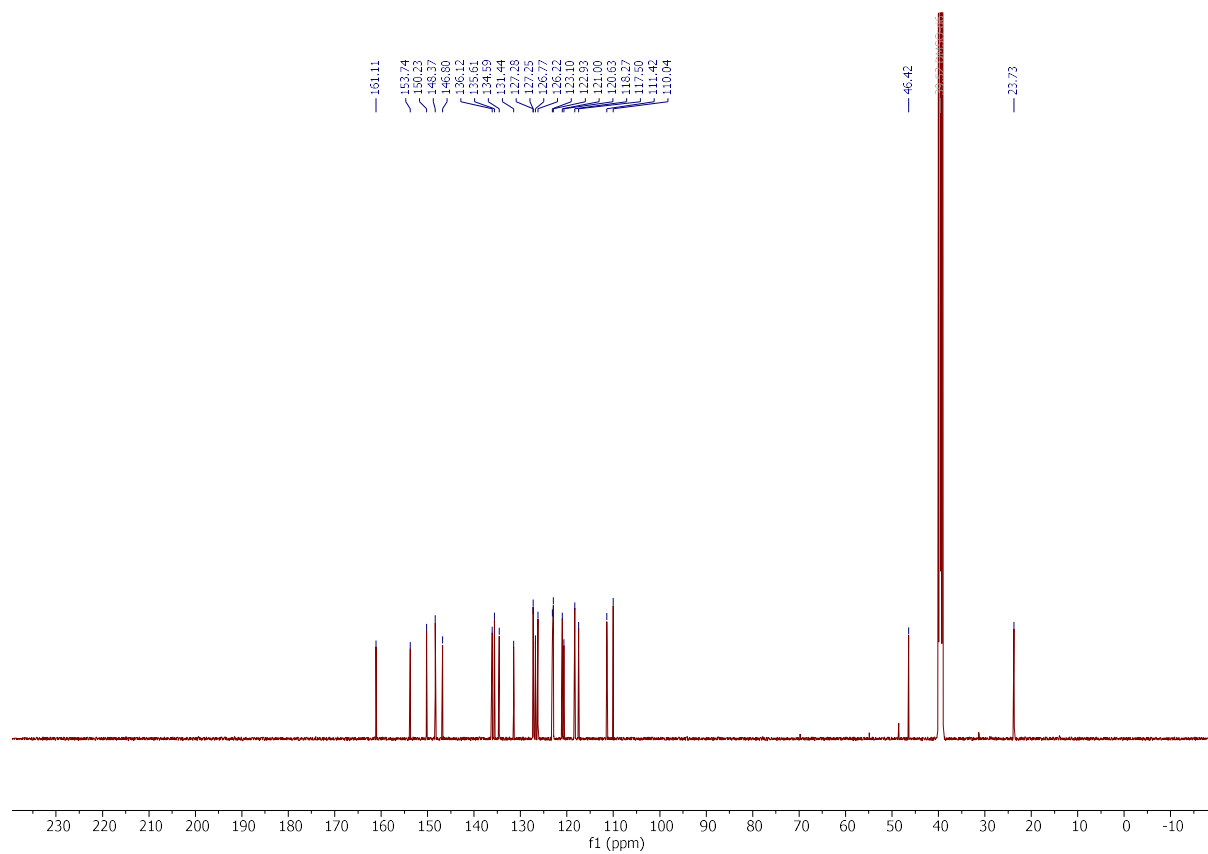
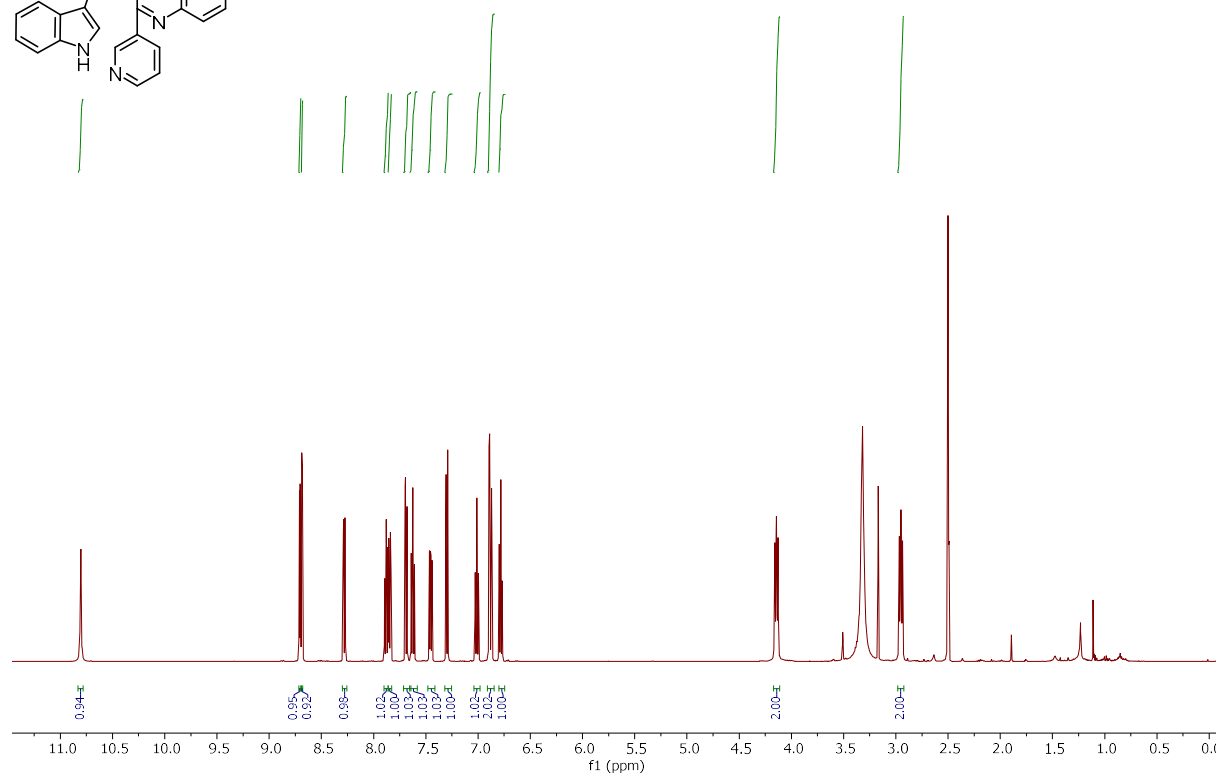
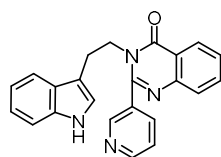
6.52. $^1\text{H}/^{13}\text{C}$ NMR spectra: 4-quinazolinone 165j



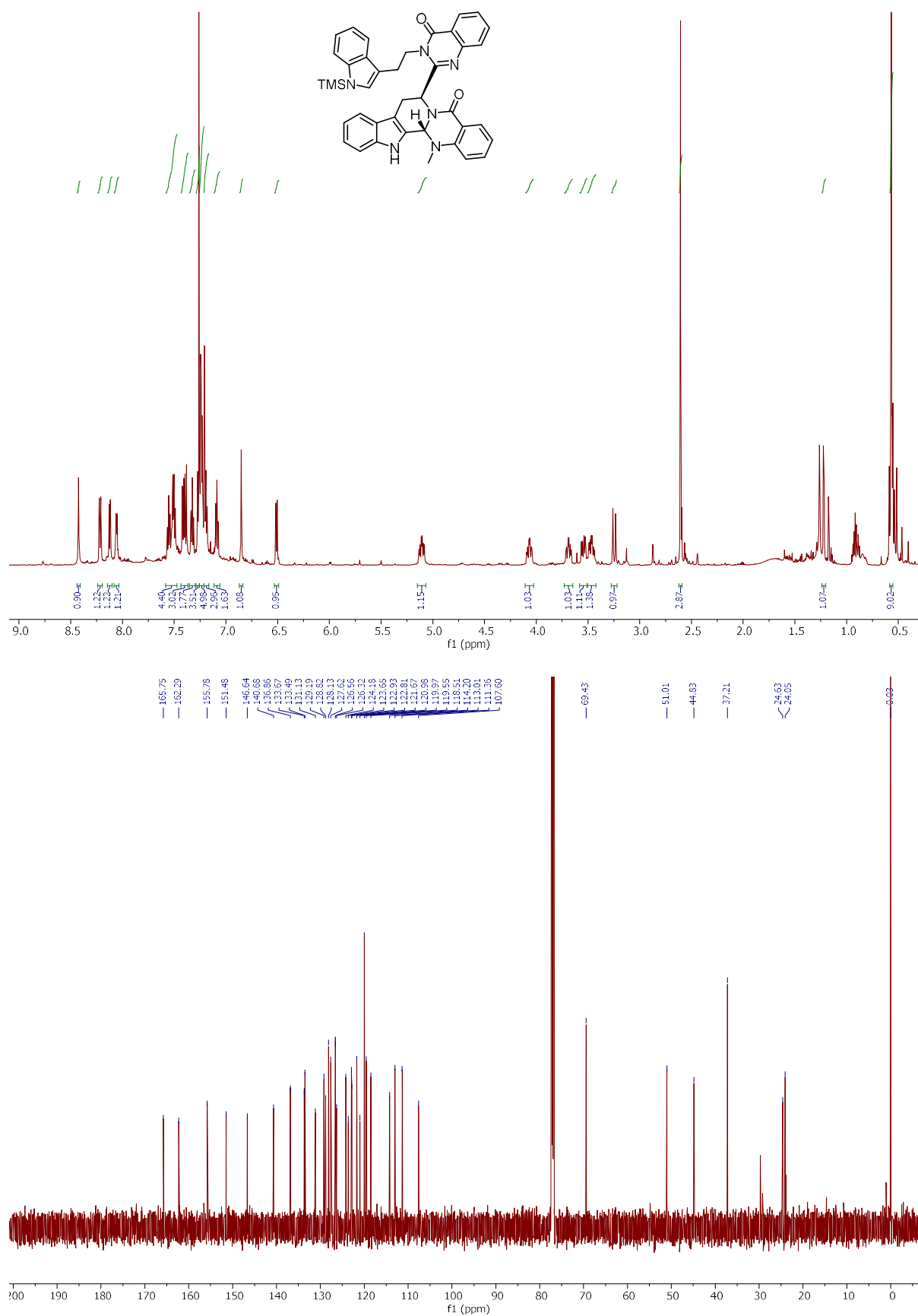
6.53. $^1\text{H}/^{13}\text{C}$ NMR spectra: 4-quinazolinone 165k



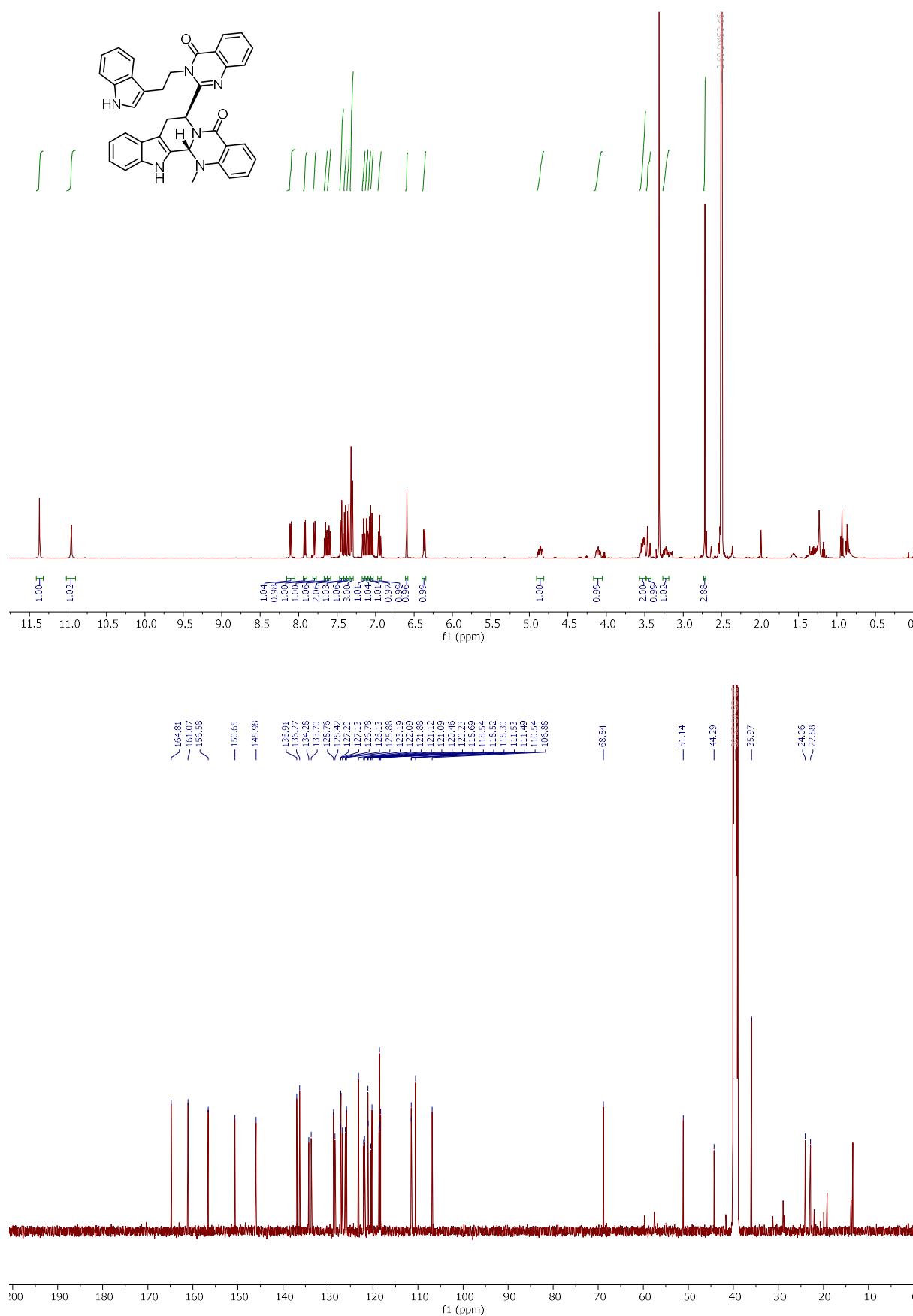
6.54. $^1\text{H}/^{13}\text{C}$ NMR spectra: 4-quinazolinone 165I



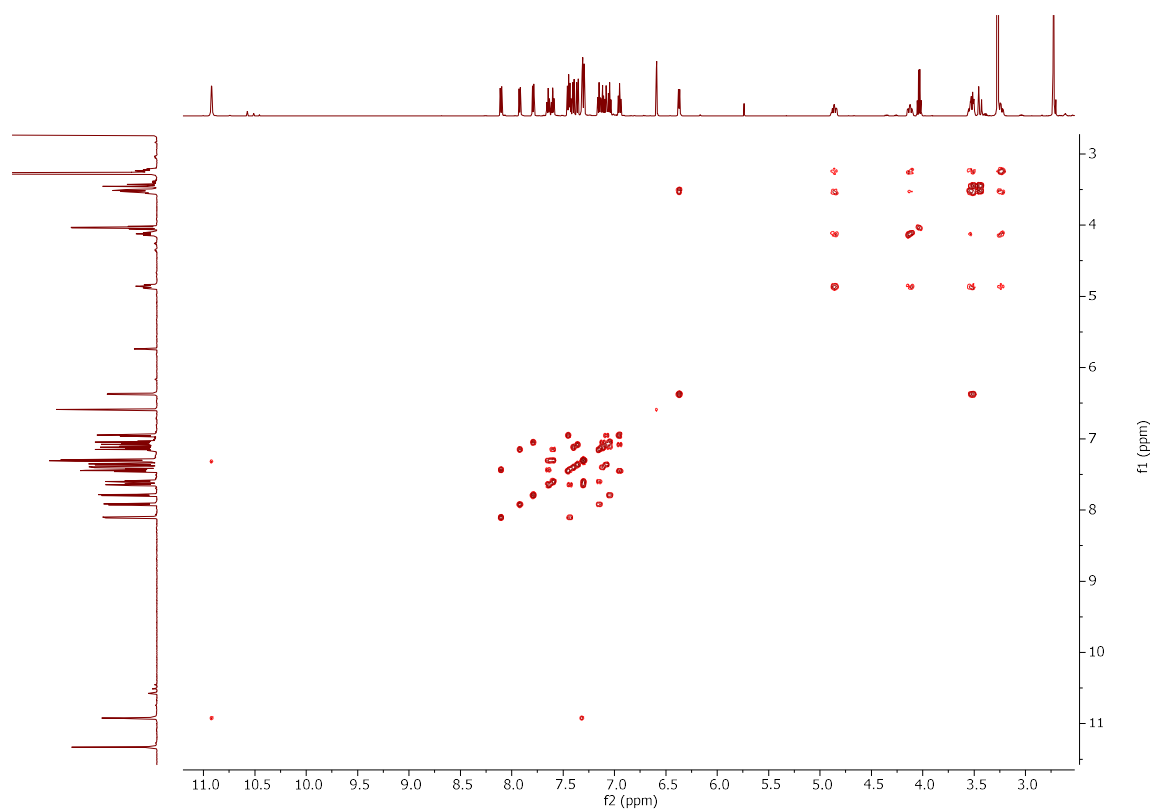
6.55. $^1\text{H}/^{13}\text{C}$ NMR spectra: TMS-protected bisindole quinazolinone 166



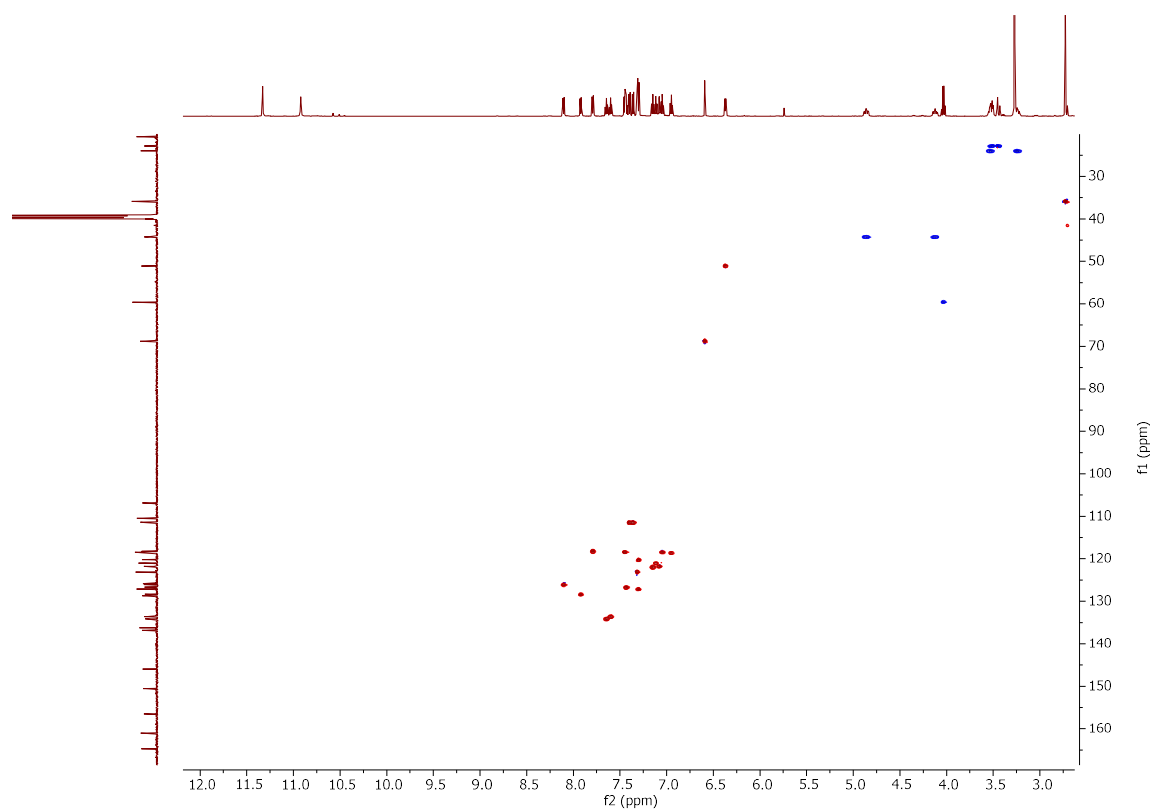
6.56. $^1\text{H}/^{13}\text{C}$ NMR spectra: bisindole quinazolinone 167



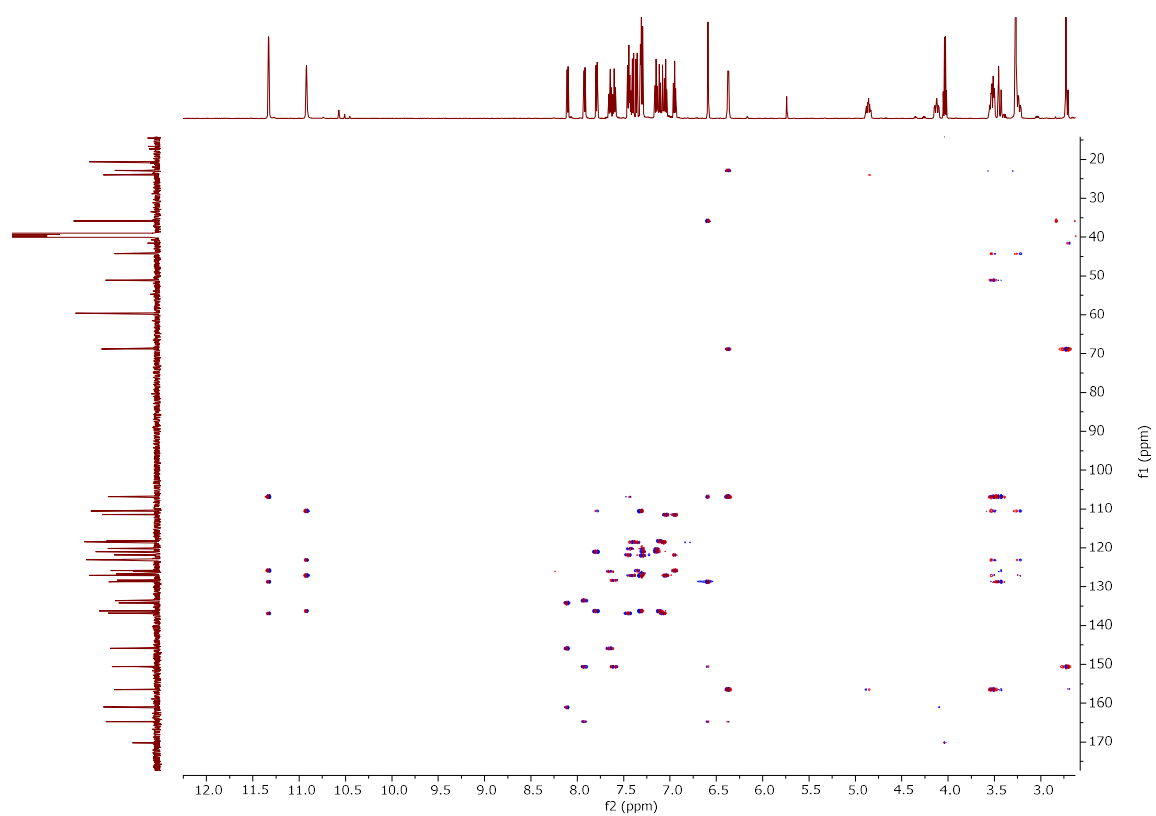
$^1\text{H}/^1\text{H}$ COSY



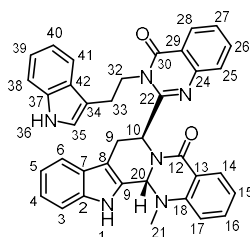
$^1\text{H}/^{13}\text{C}$ HSQC spectrum



$^1\text{H}/^{13}\text{C}$ HMBC spectrum

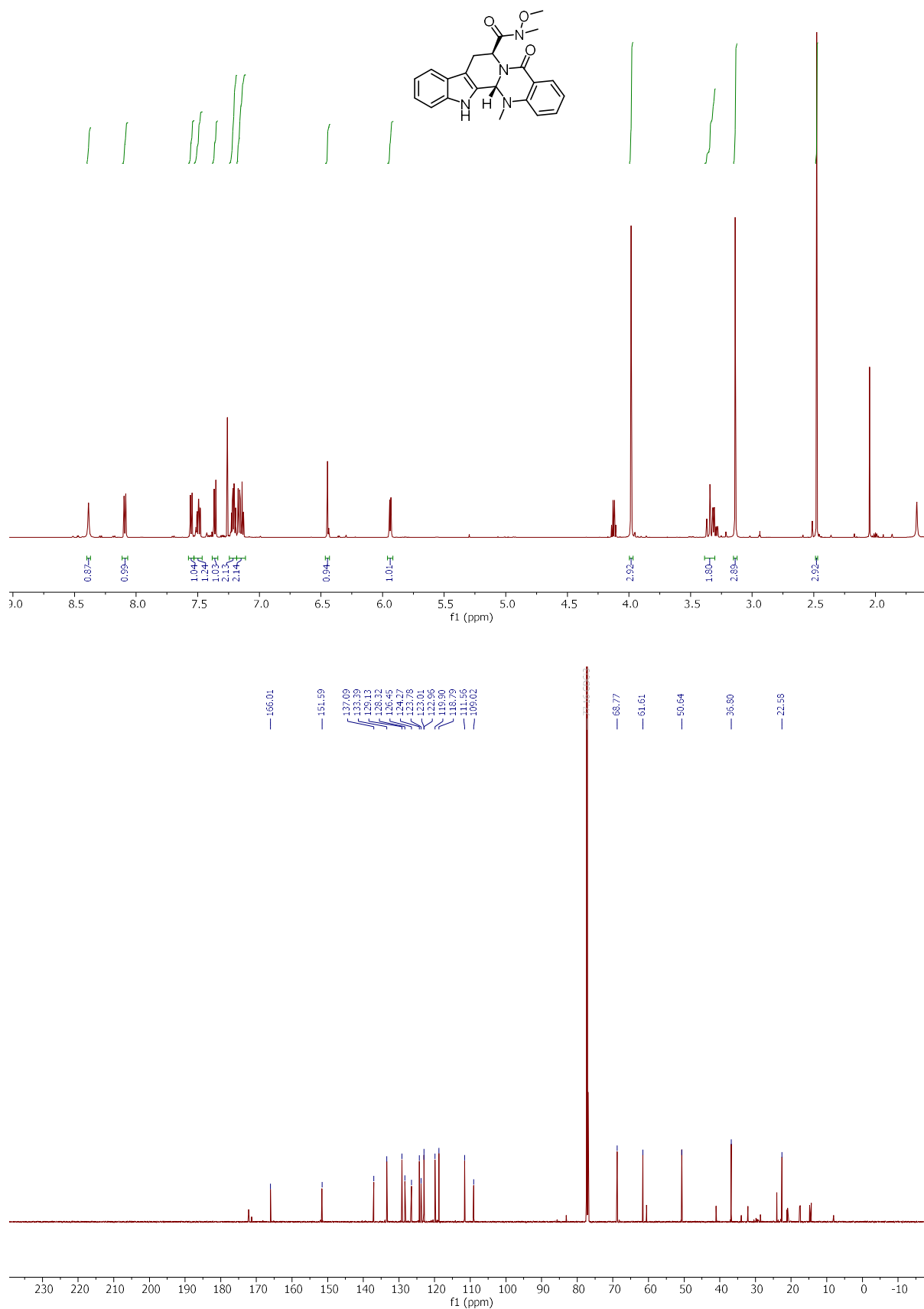


Bisindole quinazolinone 167: 2D NMR characterisation table

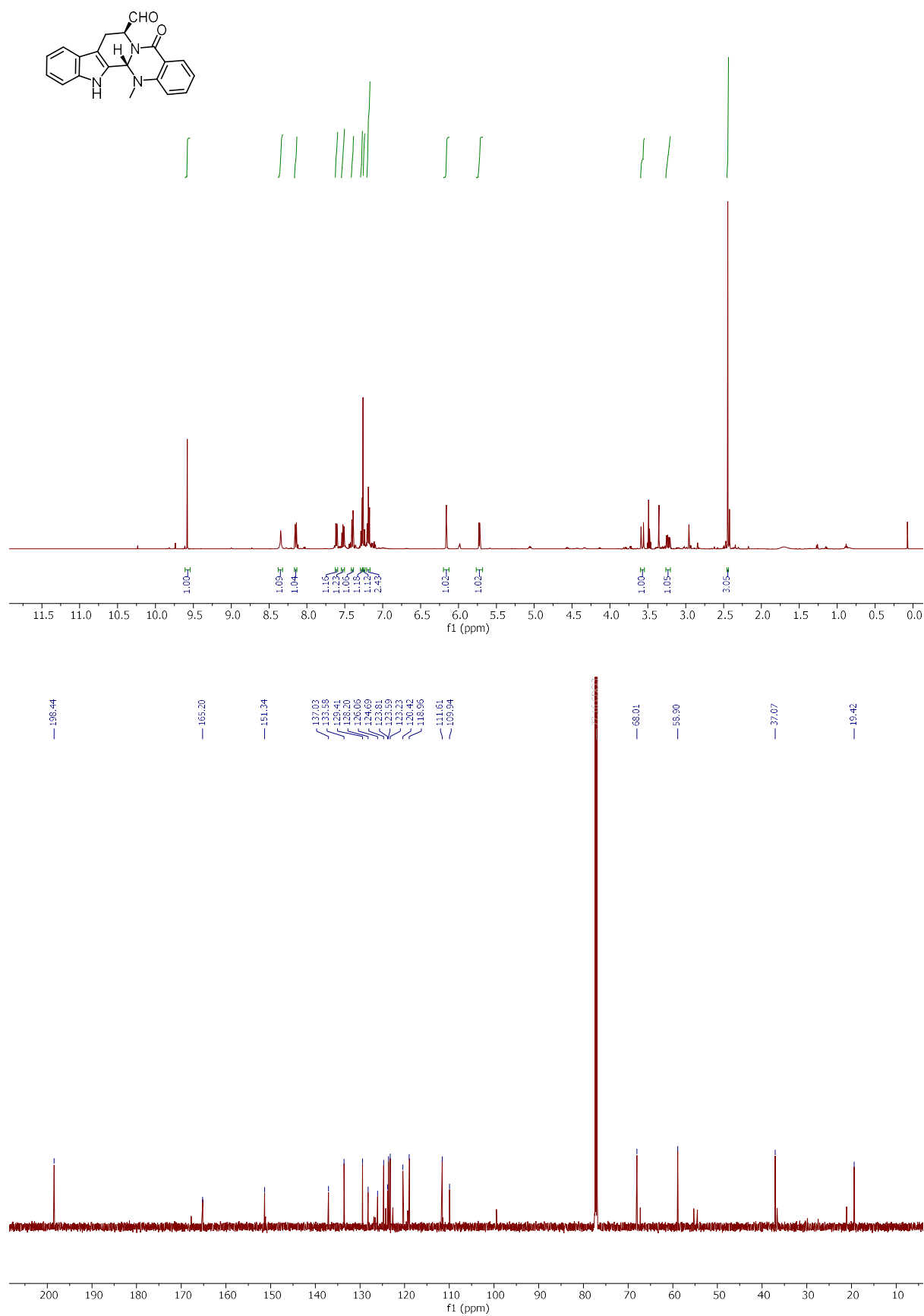


¹ H δ / ppm (multiplicity)	# Hs	J / Hz	¹³ C HSQC / ppm	¹ H- ¹ H COSY / ppm	¹ H- ¹³ C HMBC / ppm	Assignment
11.83 (s)	1	—	—	—	136.9; 128.7; 125.8; 106.8	NH-1
10.92 (d)	1	2.4	—	7.31	136.2; 127.1; 123.1; 110.5	NH-36
8.10 (dd)	1	1.5, 8.0	126.1	7.44	161.0; 145.9; 134.2	
7.92 (dd)	1	1.6, 7.8	128.4	7.15	164.7; 150.6; 133.6	
7.79 (d)	1	7.8	118.2	7.05	136.2; 121.0	
7.65 (ddd)	1	1.5, 7.1, 8.4	134.6	7.44; 7.31	145.9; 126.1	
7.60 (ddd)	1	1.6, 7.2, 8.6	133.6	7.31; 7.15	150.6; 128.4	
7.44 (m)	2	—	118.4; 126.7	8.10; 7.65; 6.95	136.9; 121.8; 120.2	
7.40 (dt)	1	0.9, 8.1	111.4	7.12	127.1; 118.5	
7.36 (m)	1	—	111.5	7.08	125.8; 118.6	
7.31 (m)	3	—	127.1; 123.1; 120.3	10.92; 7.65; 7.60	136.2; 127.1; 126.7; 121.9; 121.0; 120.2; 110.5	CH-35
7.15 (m)	1	—	121.9	7.92; 7.60	120.3; 120.0	
7.12 (ddd)	1	1.1, 7.0, 8.1	121.0	7.40	136.2; 118.2	
7.08 (ddd)	1	1.1, 7.0, 8.2	121.8	7.36; 6.95	136.2; 118.4	
7.05 (ddd)	1	1.0, 7.0, 8.0	118.5	7.79	127.1; 111.4	
6.95 (ddd)	1	1.0, 7.0, 8.0	118.6	7.44; 7.08	125.8; 121.8; 111.5	
6.59 (s)	1	—	68.8	—	164.7; 150.6; 128.7; 106.8; 35.9	CH-20
6.37 (d)	1	7.2	51.1	3.52	164.7; 156.5; 128.7; 68.8; 22.8	CH-10
4.86 (ddd)	1	5.4, 11.8, 13.6	44.3	4.12; 3.52; 3.24	161.0; 156.5	CH ₂ -9
4.12 (ddd)	1	4.8, 11.6, 13.5	44.3	4.86; 3.52; 3.24	161.0	CH ₂ -9
3.52 (m)	2	—	22.8; 24.0	6.37; 4.86; (4.12; 3.24)	156.5; 123.1; 110.5; 106.8; 51.1; 44.2	CH ₂ -33; CH ₂ -32
3.44 (d)	1	16.1	22.8	3.52	128.7; 106.8	CH ₂ -32
3.24 (m)	1	—	24.0	4.86; 4.12; 3.52	123.1; 110.5; 44.2	CH ₂ -33
2.73 (s)	3	—	35.9	—	150.6; 68.8	CH ₃ -21

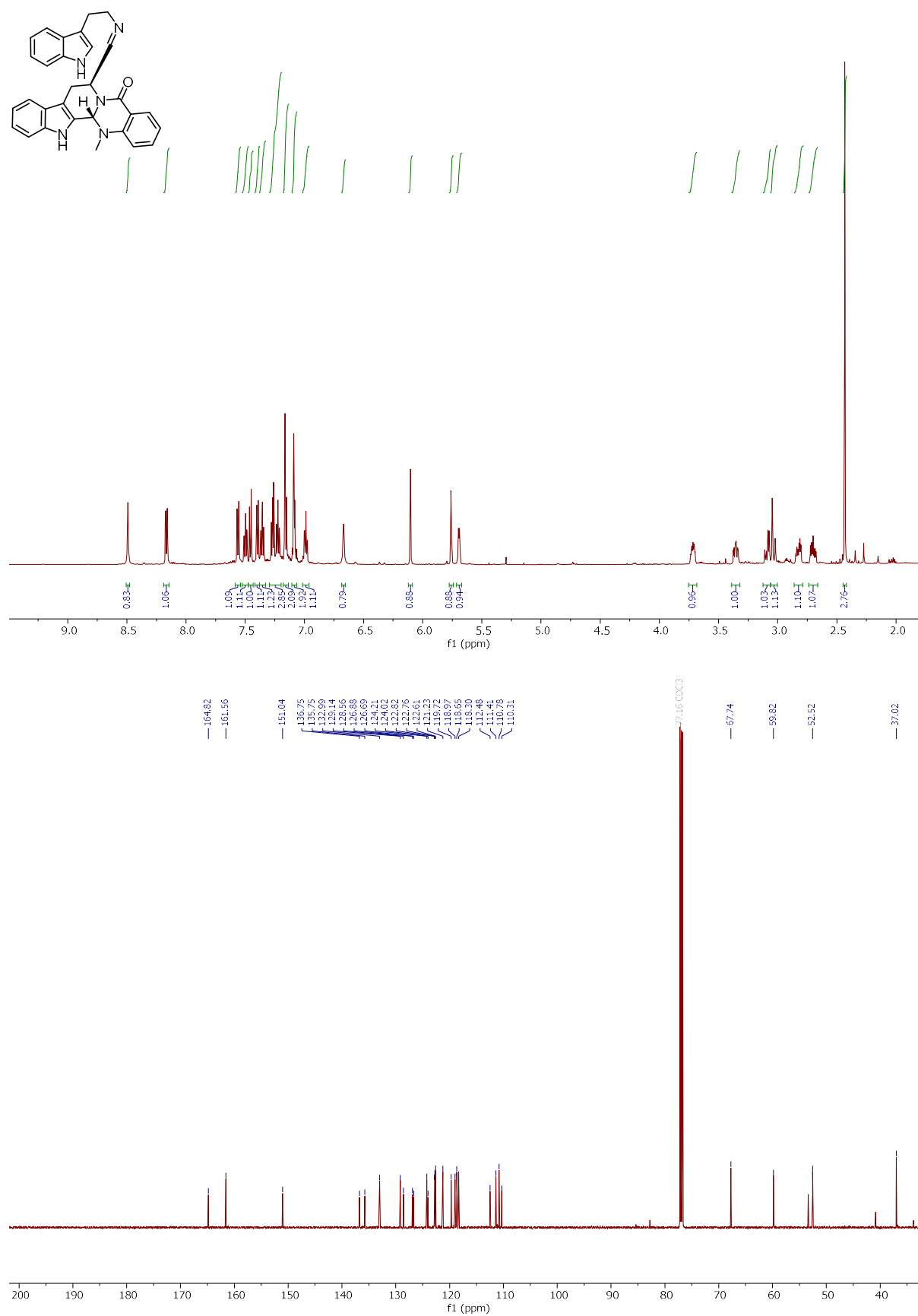
6.57. $^1\text{H}/^{13}\text{C}$ NMR spectra: Weinreb amide 172



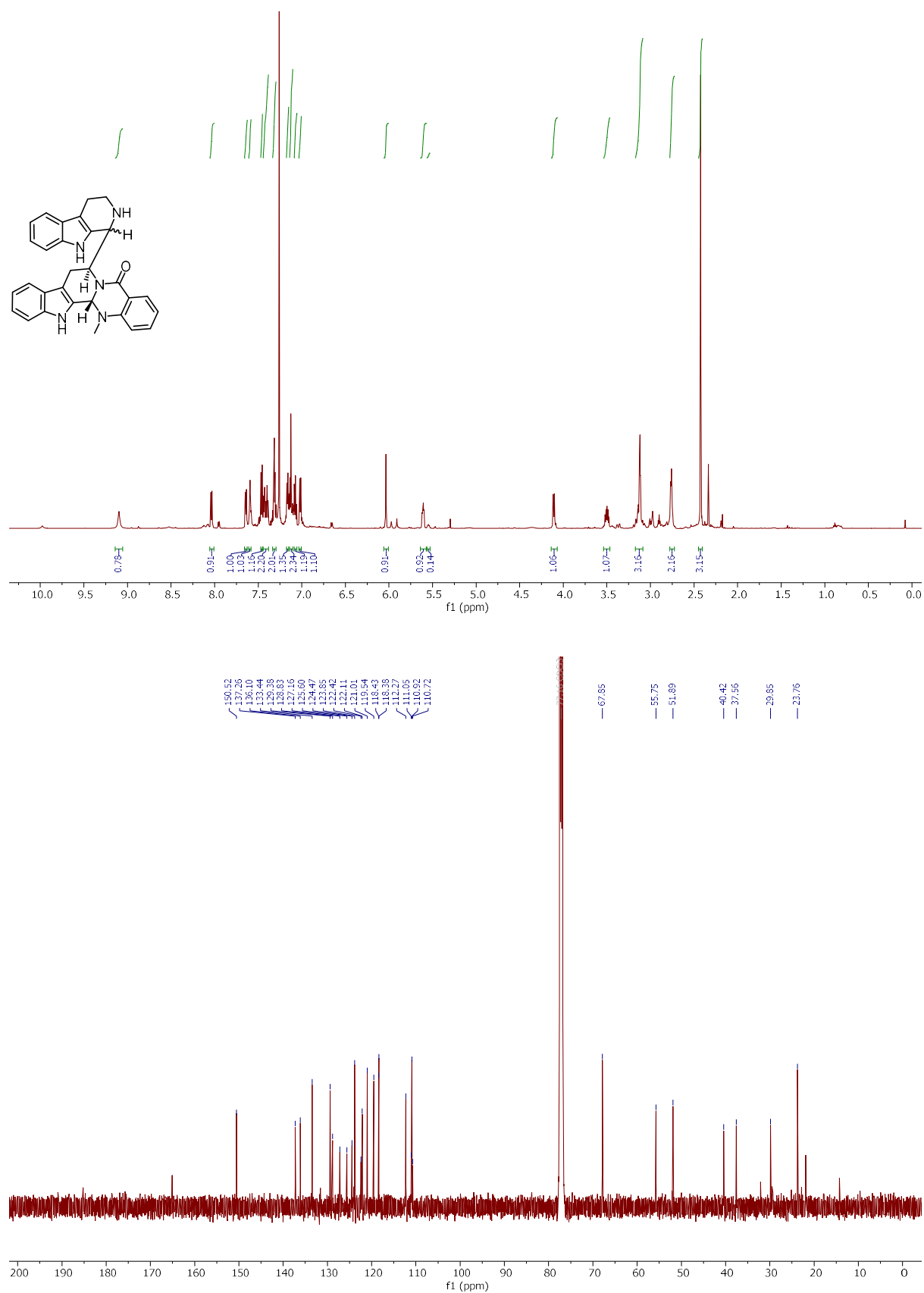
6.58. $^1\text{H}/^{13}\text{C}$ NMR spectra: aldehyde 170



6.59. $^1\text{H}/^{13}\text{C}$ NMR spectra: imine 173



6.60. $^1\text{H}/^{13}\text{C}$ NMR spectra: tetrahydro- β -carboline 171



7. References

1. O'Hagan, D.; Schmidberger, J. W., Enzymes that catalyse SN2 reaction mechanisms. *Nat. Prod. Rep.* **2010**, *27*, 900-918.
2. Coiner, H.; Schröder, G.; Wehinger, E.; Liu, C.-J.; Noel, J. P.; Schwab, W.; Schröder, J., Methylation of sulfhydryl groups: a new function for a family of small molecule plant O-methyltransferases. *Plant J.* **2006**, *46*, 193-205.
3. Peng, Y.; Feng, Q.; Wilk, D.; Adjei, A. A.; Salavaggione, O. E.; Weinshilboum, R. M.; Yee, V. C., Structural Basis of Substrate Recognition in Thiopurine S-Methyltransferase. *Biochemistry* **2008**, *47*, 6216-6225.
4. Lomax, C.; Liu, W.-J.; Wu, L.; Xue, K.; Xiong, J.; Zhou, J.; McGrath, S. P.; Meharg, A. A.; Miller, A. J.; Zhao, F.-J., Methylated arsenic species in plants originate from soil microorganisms. *New Phytol.* **2012**, *193*, 665-672.
5. Martin, J. L.; McMillan, F. M., SAM (dependent) I AM: the S-adenosylmethionine-dependent methyltransferase fold. *Curr. Opin. Struc. Biol.* **2002**, *12*, 783-793.
6. Schubert, H. L.; Blumenthal, R. M.; Cheng, X., Many paths to methyltransfer: a chronicle of convergence. *Trends Biochem. Sci.* **2003**, *28*, 329-335.
7. Liscombe, D. K.; Louie, G. V.; Noel, J. P., Architectures, mechanisms and molecular evolution of natural product methyltransferases. *Nat. Prod. Rep.* **2012**, *29*, 1238-1250.
8. Chuang, W.-C.; Cheng, C.-M.; Chang, H.-C.; Chen, Y.-P.; Sheu, S.-J., Contents of constituents in mature and immature fruits of *Evodia* species. *Planta medica* **1999**, *65*, 567-571.
9. Bergman, J., The Quinazolinocarboline Alkaloids. In *The Alkaloids, Chemistry and Pharmacology*, 1 ed.; Brossi, A., Ed. Academic Press: 1983; Vol. 21, pp 29-54.

10. Asahina, Y.; Kashiwaki, K., Chemical constituents of the fruits of *Evodia rutaecarpa*. *Yakugaku Zasshi* **1915**, 405, 1293.
11. Yamazaki, M.; Ikuta, A., Biosynthesis of evodia alkaloids. *Tetrahedron Lett.* **1966**, 7, 3221-3224.
12. Yamazaki, M.; Ikuta, A.; Mori, T.; Kawana, T., Biosynthesis of evodia alkaloids. II. The participation of C1-unit to the formation of indoloquinazoline alkaloids. *Tetrahedron Lett.* **1967**, 8, 3317-3320.
13. Chatterjee, A.; Bose, S.; Ghosh, C., Rhetsine and rhetsinine: the quinazoline alkaloids of *Xanthoxylum rhetsa*. *Tetrahedron* **1959**, 7, 257-261.
14. Danieli, B.; Palmisano, G., A New Approach to Quinazolinocarboline Alkaloids: Synthesis of (±)-Evodiamine, Rutaecarpine and Dehydroevodiamine. *Heterocycles* **1978**, 9, 803-806.
15. Bergman, J.; Bergman, S., Studies of rutaecarpine and related quinazolinocarboline alkaloids. *J. Org. Chem.* **1985**, 50, 1246-1255.
16. Rao, K. R.; Raghunadh, A.; Mekala, R.; Meruva, S. B.; Pratap, T. V.; Krishna, T.; Kalita, D.; Laxminarayana, E.; Prasad, B.; Pal, M., Glyoxylic acid in the reaction of isatoic anhydride with amines: a rapid synthesis of 3-(un)substituted quinazolin-4(3H)-ones leading to rutaecarpine and evodiamine. *Tetrahedron Lett.* **2014**, 55, 6004-6006.
17. Clemenceau, A.; Wang, Q.; Zhu, J., Silver Nitrate-Catalyzed Isocyanide Insertion/Lactamization Sequence to Imidazolones and Quinazolin-4-ones: Development and Application in Natural Product Synthesis. *Org. Lett.* **2017**, 19, 4872-4875.
18. Deng, J.-D.; Lei, S.; Jiang, Y.; Zhang, H.-H.; Hu, X.-L.; Wen, H.-X.; Tan, W.; Wang, Z., A concise synthesis and biological study of evodiamine and its analogues. *Chem. Commun.* **2019**, 55, 3089-3092.

19. Wang, Z.-X.; Xiang, J.-C.; Wang, M.; Ma, J.-T.; Wu, Y.-D.; Wu, A.-X., One-Pot Total Synthesis of Evodiamine and Its Analogues through a Continuous Biscyclization Reaction. *Org. Lett.* **2018**, *20*, 6380-6383.
20. Baruah, B.; Dasu, K.; Vaitilingam, B.; Mamnoor, P.; Venkata, P. P.; Rajagopal, S.; Yeleswarapu, K. R., Synthesis and cytotoxic activity of novel quinazolino- β -carboline-5-one derivatives. *Bioorg. Med. Chem.* **2004**, *12*, 1991-1994.
21. Nicolaou, K.; Mathison, C. J.; Montagnon, T., New Reactions of IBX: Oxidation of Nitrogen-and Sulfur-Containing Substrates To Afford Useful Synthetic Intermediates. *Angew. Chem. Int. Ed.* **2003**, *42*, 4077-4082.
22. Pin, F.; Comesse, S.; Daïch, A., Intramolecular N-aza-amidoalkylation in association with Witkop–Winterfeldt oxidation as the key step to synthesize Luotonin-A analogues. *Tetrahedron* **2011**, *67*, 5564-5571.
23. Unsworth, W. P.; Kitsiou, C.; Taylor, R. J. K., Direct Imine Acylation: Rapid Access to Diverse Heterocyclic Scaffolds. *Org. Lett.* **2013**, *15*, 258-261.
24. Christodoulou, M. S.; Sacchetti, A.; Ronchetti, V.; Caufin, S.; Silvani, A.; Lesma, G.; Fontana, G.; Minicone, F.; Riva, B.; Ventura, M.; Lahtela-Kakkonen, M.; Jarho, E.; Zuco, V.; Zunino, F.; Martinet, N.; Dapiaggi, F.; Pieraccini, S.; Sironi, M.; Dalla Via, L.; Gia, O. M.; Passarella, D., Quinazolinecarboline alkaloid evodiamine as scaffold for targeting topoisomerase I and sirtuins. *Bioorgan. Med. Chem.* **2013**, *21*, 6920-6928.
25. Danieli, B.; Lesma, G.; Palmisano, G., The configuration of (+)-evodiamine: a long-standing problem in the chemistry of indole alkaloids. *J. Chem. Soc. Chem. Commun.* **1982**, *19*, 1092-1093.
26. Wang, Q. Z.; Liang, J. Y.; Feng, X., Evodiagenine and dievodiamine, two new indole alkaloids from *Evodia rutaecarpa*. *Chin. Chem. Lett.* **2010**, *21*, 596-599.

27. Unsworth, W. P.; Kitsiou, C.; Taylor, R. J. K., An Expedient Protecting-Group-Free Total Synthesis of (±)-Dievodiamine. *Org. Lett.* **2013**, *15*, 3302-3305.
28. Mee, S. P. H.; Lee, V.; Baldwin, J. E., Stille Coupling Made Easier—The Synergic Effect of Copper(I) Salts and the Fluoride Ion. *Angew. Chem. Int. Ed.* **2004**, *43*, 1132-1136.
29. Jeffery, T., On the efficiency of tetraalkylammonium salts in Heck type reactions. *Tetrahedron* **1996**, *52*, 10113-10130.
30. Kanekiyo, N.; Kuwada, T.; Choshi, T.; Nobuhiro, J.; Hibino, S., Total Syntheses of β -Carboline Alkaloids, (R)-(-)-Pyridindolol K1, (R)-(-)-Pyridindolol K2, and (R)-(-)-Pyridindolol. *J. Org. Chem.* **2001**, *66*, 8793-8798.
31. Han, X.; Stoltz, B. M.; Corey, E., Cuprous chloride accelerated Stille reactions. A general and effective coupling system for sterically congested substrates and for enantioselective synthesis. *J. Am. Chem. Soc.* **1999**, *121*, 7600-7605.
32. Liu, J.; Liu, A.; Hu, Y., Enzymatic dimerization in the biosynthetic pathway of microbial natural products. *Nat. Prod. Rep.* **2021**, *38*, 1469-1505.
33. Barrow, C. J.; Sedlock, D. M., 1'-(2-Phenyl-ethylene)-ditryptophenaline, a New Dimeric Diketopiperazine from *Aspergillus flavus*. *J. Nat. Prod.* **1994**, *57*, 1239-1244.
34. O'Connor, S. E.; Maresh, J. J., Chemistry and biology of monoterpene indole alkaloid biosynthesis. *Nat. Prod. Rep.* **2006**, *23*, 532-547.
35. Wigley, L. J.; Mantle, P. G.; Perry, D. A., Natural and directed biosynthesis of communesin alkaloids. *Phytochemistry* **2006**, *67*, 561-569.
36. Curtius, T., Ueber Stickstoffwasserstoffsäure (Azoimid) N₃H. *Ber. Dtsch Chem. Ges.* **1890**, *23*, 3023-3033.
37. Curtius, T., 20. Hydrazide und Azide organischer Säuren I. Abhandlung. *J. Prsch Chem.* **1894**, *50*, 275-294.

38. Decker, M., Novel inhibitors of acetyl- and butyrylcholinesterase derived from the alkaloids dehydroevodiamine and rutaecarpine. *Eur. J. Med. Chem.* **2005**, *40*, 305-313.
39. Dong, G.; Sheng, C.; Wang, S.; Miao, Z.; Yao, J.; Zhang, W., Selection of Evodiamine as a Novel Topoisomerase I Inhibitor by Structure-Based Virtual Screening and Hit Optimization of Evodiamine Derivatives as Antitumor Agents. *J. Med. Chem.* **2010**, *53*, 7521-7531.
40. Oikawa, Y.; Yonemitsu, O., Selective oxidation of the side chain at C-3 of indoles. *J. Org. Chem.* **1977**, *42*, 1213-1216.
41. Guo, W.; Wang, X.; Zhang, J.; Zhang, T.; Lv, H.; Zhao, C., Synthesis of ring opening of evodiamine derivatives and evaluation on their biological activity. *Chem. Biol. Drug Des.* **2022**, *99*, 535-546.
42. Mei, H.; Wang, N.; Li, Z.; Han, J., Intramolecular Appel Reaction of Trifluoromethylated β -Keto Diazos Enabling Assembly of Trifluoromethylpyrazoles. *Org. Lett.* **2022**, *24*, 2258-2263.
43. Su, Y.; Huang, G.; Ye, F.; Qiao, P.; Ye, J.; Gao, Y.; Chen, H., Facile access to evodiakine enabled by aerobic copper-catalyzed oxidative rearrangement. *Org. Biomol. Chem.* **2019**, *17*, 8811-8815.
44. Otto, R.; Penzis, R.; Gaube, F.; Winckler, T.; Appenroth, D.; Fleck, C.; Tränkle, C.; Lehmann, J.; Enzensperger, C., Beta and gamma carboline derivatives as potential anti-Alzheimer agents: A comparison. *Eur. J. Med. Chem.* **2014**, *87*, 63-70.
45. Hawkins, A.; Jakubec, P.; Ironmonger, A.; Dixon, D. J., An expedient stereoselective route to the ACE tricyclic core of manzamine A via a palladium-catalysed arylation allene spirocyclisation cascade. *Tetrahedron Lett.* **2013**, *54*, 365-369.

46. Ma, C.; Cao, R.; Shi, B.; Zhou, X.; Ma, Q.; Sun, J.; Guo, L.; Yi, W.; Chen, Z.; Song, H., Synthesis and cytotoxic evaluation of 1-carboxamide and 1-amino side chain substituted β -carbolines. *Eur. J. Med. Chem.* **2010**, *45*, 5513-5519.
47. Roggero, C. M.; Giulietti, J. M.; Mulcahy, S. P., Efficient synthesis of eudistomin U and evaluation of its cytotoxicity. *Bioorgan. Med. Chem. Lett.* **2014**, *24*, 3549-3551.
48. Baran, P. S.; Hafensteiner, B. D.; Ambhaikar, N. B.; Guerrero, C. A.; Gallagher, J. D., Enantioselective Total Synthesis of Avrainvillamide and the Stephacidins. *J. Am. Chem. Soc.* **2006**, *128*, 8678-8693.
49. Wu, N.; Song, F.; Yan, L.; Li, J.; You, J., Transition-Metal-Catalyzed C–H Bond Functionalizations: Feasible Access to a Diversity-Oriented β -Carboline Library. *Chem. A - Eur. J.* **2014**, *20*, 3408-3414.
50. Ramesh, S.; Nagarajan, R., A Formal Synthesis of Lavendamycin Methyl Ester, Nitramarine, and Their Analogues: A Povarov Approach. *J. Org. Chem.* **2013**, *78*, 545-558.
51. Nissen, F.; Richard, V.; Alayrac, C.; Witulski, B., Synthesis of β - and γ -carbolines via ruthenium and rhodium catalysed [2+2+2] cycloadditions of yne-ynamides with methylcyanoformate. *Chem. Commun.* **2011**, *47*, 6656-6658.
52. Manjunatha, K. S.; Satyanarayan, N. D.; Harishkumar, S., ANTIMICROBIAL AND IN SILICO ADMET SCREENING OF NOVEL (E)-N-(2-(1H-INDOL-3-YL-AMINO) VINYL)-3-(1-METHYL-1H-INDOL-3-YL)-3-PHENYLPROPANAMIDE DERIVATIVES. *Int. J. Pharm. Pharmac. Sci.* **2016**, *8*, 251-256.
53. Jin, H.; Zhang, P.; Bijian, K.; Ren, S.; Wan, S.; Alaoui-Jamali, M. A.; Jiang, T., Total Synthesis and Biological Activity of Marine Alkaloid Eudistomins Y1–Y7 and Their Analogues. *Marine Drugs* **2013**, *11*, 1427-1439.

54. Hajime, I.; Susumu, M.; Masahiro, U.; Yasuaki, O., Reaction of Methyl 2,3,5,6,11,11b-Hexahydro-3-oxo-1H-indolizino[8,7-b]indole-5-carboxylate and Its Derivatives with N-Bromosuccinimide. *Bull. Chem. Soc. Jap.* **1989**, 62, 3031-3033.
55. Pachter, I. J.; Mohrbacher, R. J.; Zacharias, D. E., The Chemistry of Hortiamine and 6-Methoxyrhetsinine. *J. Am. Chem. Soc.* **1961**, 83, 8.
56. Wehle, S.; Espargaró, A.; Sabaté, R.; Decker, M., Investigation into the stability and reactivity of the pentacyclic alkaloid dehydroevodiamine and the benz-analog thereof. *Tetrahedron* **2016**, 72, 2535-2543.
57. Hur, G. H.; Vickery, C. R.; Burkart, M. D., Explorations of catalytic domains in non-ribosomal peptide synthetase enzymology. *Nat. Prod. Rep.* **2012**, 29, 1074-1098.
58. Walsh, C. T., Insights into the chemical logic and enzymatic machinery of NRPS assembly lines. *Nat. Prod. Rep.* **2016**, 33, 127-135.
59. Meier, J. L.; Burkart, M. D., The chemical biology of modular biosynthetic enzymes. *Chem. Soc. Rev.* **2009**, 38, 2012-2045.
60. Zagulyaeva, A. A.; Bruner, S. D., 2.11 - Structural Biology of Nonribosomal Peptide Synthetases. In *Comprehensive Natural Products III*, Liu, H.-W.; Begley, T. P., Eds. Elsevier: Oxford, 2020; pp 229-246.
61. Süssmuth, R. D.; Mainz, A., Nonribosomal Peptide Synthesis—Principles and Prospects. *Angew. Chem. Int. Ed.* **2017**, 56, 3770-3821.
62. Walsh, C. T., Polyketide and Nonribosomal Peptide Antibiotics: Modularity and Versatility. *Science* **2004**, 303, 1805-1810.
63. Schwarzer, D.; Finking, R.; Marahiel, M. A., Nonribosomal peptides: from genes to products. *Nat. Prod. Rep.* **2003**, 20, 275-287.

64. Antonow, D.; Thurston, D. E., Synthesis of DNA-Interactive Pyrrolo[2,1-c][1,4]benzodiazepines (PBDs). *Chem. Rev.* **2011**, *111*, 2815-2864.
65. Gregson, S. J.; Howard, P. W.; Hartley, J. A.; Brooks, N. A.; Adams, L. J.; Jenkins, T. C.; Kelland, L. R.; Thurston, D. E., Design, Synthesis, and Evaluation of a Novel Pyrrolobenzodiazepine DNA-Interactive Agent with Highly Efficient Cross-Linking Ability and Potent Cytotoxicity. *J. Med. Chem.* **2001**, *44*, 737-748.
66. Nepali, K.; Sharma, S.; Sharma, M.; Bedi, P. M. S.; Dhar, K. L., Rational approaches, design strategies, structure activity relationship and mechanistic insights for anticancer hybrids. *Eur. J. Med. Chem.* **2014**, *77*, 422-487.
67. Kumar, R.; Lown, W. J., Recent Developments in Novel Pyrrolo[2,1-c][1,4]Benzodiazepine Conjugates: Synthesis and Biological Evaluation. *Mini-Rev. Med. Chem.* **2003**, *3*, 323-339.
68. Giessen, T. W.; Kraas, F. I.; Marahiel, M. A., A Four-Enzyme Pathway for 3,5-Dihydroxy-4-methylantranilic Acid Formation and Incorporation into the Antitumor Antibiotic Sibiromycin. *Biochemistry* **2011**, *50*, 5680-5692.
69. Schaub, A. J.; Moreno, G. O.; Zhao, S.; Truong, H. V.; Luo, R.; Tsai, S.-C., Chapter Seventeen - Computational structural enzymology methodologies for the study and engineering of fatty acid synthases, polyketide synthases and nonribosomal peptide synthetases. In *Methods in Enzymology*, Shukla, A. K., Ed. Academic Press: 2019; Vol. 622, pp 375-409.
70. Godfrey, R. C.; Green, N. J.; Nichol, G. S.; Lawrence, A. L., Total synthesis of brevianamide A. *Nature Chem.* **2020**, *12*, 615-619.
71. Godfrey, R. C.; Jones, H. E.; Green, N. J.; Lawrence, A. L., Unified total synthesis of the brevianamide alkaloids enabled by chemical investigations into their biosynthesis. *Chem. Sci.* **2022**, *13*, 1313-1322.

72. Tummatorn, J.; Dudley, G. B., Stereodefined Homopropargyl Amines by Tandem Nucleophilic Addition/Fragmentation of Dihydropyridone Triflates. *Org. Lett.* **2011**, *13*, 158-160.
73. Laursen, J. S.; Engel-Andreasen, J.; Fristrup, P.; Harris, P.; Olsen, C. A., Cis–Trans Amide Bond Rotamers in β -Peptoids and Peptoids: Evaluation of Stereoelectronic Effects in Backbone and Side Chains. *J. Am. Chem. Soc.* **2013**, *135*, 2835-2844.
74. Nigst, T. A.; Antipova, A.; Mayr, H., Nucleophilic Reactivities of Hydrazines and Amines: The Futile Search for the α -Effect in Hydrazine Reactivities. *J. Org. Chem.* **2012**, *77*, 8142-8155.
75. Rebollar-Ramos, D.; Macías-Ruvalcaba, M. L.; Figueroa, M.; Raja, H. A.; González-Andrade, M.; Mata, R., Additional α -glucosidase inhibitors from *Malbranchea flavorosea* (Leotiomycetes, Ascomycota). *J. Antibiot.* **2018**, *71*, 862-871.
76. Akssira, M.; Boumzebra, M.; Kasmi, H.; Dahdouh, A.; Roumestant, M. L.; Viallefont, P., New routes to 1,4- benzodiazepin-2,5-diones. *Tetrahedron* **1994**, *50*, 9051-9060.
77. Barlind, J. G.; Buckett, L. K.; Crosby, S. G.; Davidsson, Ö.; Emtenäs, H.; Ertan, A.; Jurva, U.; Lemurell, M.; Gutierrez, P. M.; Nilsson, K.; O'Mahony, G.; Petersson, A. U.; Redzic, A.; Wågberg, F.; Yuan, Z.-Q., Identification and design of a novel series of MGAT2 inhibitors. *Bioorgan. Med. Chem. Lett.* **2013**, *23*, 2721-2726.
78. Gordon-Wylie, S. W.; Teplin, E.; Morris, J. C.; Trombley, M. I.; McCarthy, S. M.; Cleaver, W. M.; Clark, G. R., Exploring Hydrogen-Bonded Structures: Synthesis and X-ray Crystallographic Screening of a Cisoid Cyclic Dipeptide Mini-Library. *Cryst. Growth Des.* **2004**, *4*, 789-797.
79. Yongpeng, Z.; Jiaxi, X., Thorpe-Ingold Effect and Its Application in Cyclizations in Organic Chemistry. *Prog. Chem.* **2014**, *26*, 1471-1491.

80. Isidro-Llobet, A.; Álvarez, M.; Albericio, F., Amino Acid-Protecting Groups. *Chem. Rev.* **2009**, *109*, 2455-2504.
81. Newhouse, T.; Baran, P. S.; Hoffmann, R. W., The economies of synthesis. *Chem. Soc. Rev.* **2009**, *38*, 3010-3021.
82. Chen, D.; Po, K. H. L.; Blasco, P.; Chen, S.; Li, X., Convergent Synthesis of Calcium-Dependent Antibiotic CDA3a and Analogues with Improved Antibacterial Activity via Late-Stage Serine Ligation. *Org. Lett.* **2020**, *22*, 4749-4753.
83. Griesbeck, A. G.; Neudörfl, J.; de Kiff, A., Photoinduced electron-transfer chemistry of the bielectrophoric N-phthaloyl derivatives of the amino acids tyrosine, histidine and tryptophan. *Beilstein J. Org. Chem.* **2011**, *7*, 518-524.
84. Zhao, L.; May, J. P.; Huang, J.; Perrin, D. M., Stereoselective Synthesis of Brevianamide E. *Org. Lett.* **2012**, *14*, 90-93.
85. Fan, X.; Li, J.; Deng, X.; Lu, Y.; Feng, Y.; Ma, S.; Wen, H.; Zhao, Q.; Tan, W.; Shi, T.; Wang, Z., Design, synthesis and bioactivity study of N-salicyloyl tryptamine derivatives as multifunctional agents for the treatment of neuroinflammation. *Eur. J. Med. Chem.* **2020**, *193*, 112217.
86. MacMillan, D. S.; Murray, J.; Sneddon, H. F.; Jamieson, C.; Watson, A. J. B., Evaluation of alternative solvents in common amide coupling reactions: replacement of dichloromethane and N,N-dimethylformamide. *Green Chem.* **2013**, *15*, 596-600.
87. Procopio, D.; Siciliano, C.; Trombino, S.; Dumitrescu, D. E.; Suci, F.; Di Gioia, M. L., Green solvents for the formation of amide linkages. *Org. Biomol. Chem.* **2022**, *20*, 1137-1149.
88. Slebocka-Tilk, H.; Brown, R. S., Effect of distortion on the hydrolytic reactivity of amides. 2. N-Pyramidalization: decomposition of N-benzoylaziridines in aqueous media. *J. Org. Chem.* **1987**, *52*, 805-808.

89. Bennet, A. J.; Wang, Q. P.; Slebocka-Tilk, H.; Somayaji, V.; Brown, R. S.; Santarsiero, B. D., Relationship between amidic distortion and ease of hydrolysis in base. If amidic resonance does not exist, then what accounts for the accelerated hydrolysis of distorted amides? *J. Am. Chem. Soc.* **1990**, *112*, 6383-6385.
90. Baraznenok, I. L.; Nenajdenko, V. G.; Balenkova, E. S., Chemical Transformations Induced by Triflic Anhydride. *Tetrahedron* **2000**, *56*, 3077-3119.
91. Kumagai, N.; Shibasaki, M., Nucleophilic and Electrophilic Activation of Non-Heteroaromatic Amides in Atom-Economical Asymmetric Catalysis. *Chem. – A Eur. J.* **2016**, *22*, 15192-15200.
92. Kaiser, D.; Bauer, A.; Lemmerer, M.; Maulide, N., Amide activation: an emerging tool for chemoselective synthesis. *Chem. Soc. Rev.* **2018**, *47*, 7899-7925.
93. Bose, D. S.; Jayalakshmi, B., Reagents for Organic Synthesis: Use of Organostannyl Oxides as Catalytic Neutral Agents in the Preparation of Nitriles from Primary Amides under Microwave Irradiation. *J. Org. Chem.* **1999**, *64*, 1713-1714.
94. Movassaghi, M.; Hill, M. D., Single-Step Synthesis of Pyrimidine Derivatives. *J. Am. Chem. Soc.* **2006**, *128*, 14254-14255.
95. Geng, H.; Huang, P.-Q., Versatile and chemoselective transformation of aliphatic and aromatic secondary amides to nitriles. *Tetrahedron* **2015**, *71*, 3795-3801.
96. In, J.; Hwang, S.; Kim, C.; Seo, J. H.; Kim, S., Synthesis of 3,4-Dihydroisoquinolin-1-ones from N-Boc-(β -Arylethyl)carbamates via Isocyanate Intermediates. *Eur. J. Org. Chem.* **2013**, *2013*, 965-971.
97. Di Mauro, G.; Maryasin, B.; Kaiser, D.; Shaaban, S.; González, L.; Maulide, N., Mechanistic Pathways in Amide Activation: Flexible Synthesis of Oxazoles and Imidazoles. *Org. Lett.* **2017**, *19*, 3815-3818.

98. Zhang, H.; Riomet, M.; Roller, A.; Maulide, N., Synthesis of Novel Heterocycles by Amide Activation and Umpolung Cyclization. *Org. Lett.* **2020**, *22*, 2376-2380.
99. Medley, J. W.; Movassaghi, M., A Concise and Versatile Double-Cyclization Strategy for the Highly Stereoselective Synthesis and Arylative Dimerization of Aspidosperma Alkaloids. *Angew. Chem. Int. Ed.* **2012**, *51*, 4572-4576.
100. Záborský, O.; Šoral, M.; Fischer, R., Application of the Tf₂O/2-chloropyridine couple in the synthesis of novel 4,5-unsubstituted N-carbamoyl-2,3-dihydroisoxazoles. *Tetrahedron Lett.* **2015**, *56*, 2155-2158.
101. Garcia, B. A.; Poole, J. L.; Gin, D. Y., Direct Glycosylations with 1-Hydroxy Glycosyl Donors using Trifluoromethanesulfonic Anhydride and Diphenyl Sulfoxide. *J. Am. Chem. Soc.* **1997**, *119*, 7597-7598.
102. Wallach, O., Ueber die Einwirkung von Phosphorpentachlorid auf Säureamide. *Justus Liebigs Annal. Chem.* **1877**, *184*, 1-127.
103. v. Braun, J.; Heymons, A., Imid- und Amidchloride nicht-aromatischer Säuren (III. Mitteilung). *Berch Deut. Chem. Ges.* **1929**, *62*, 409-413.
104. Ghosez, L.; Haveaux, B.; Viehe, H. G., Alkyl and Aryl α -Chloro Enamines. *Angew. Chem. Int. Ed.* **1969**, *8*, 454-455.
105. Kaiser, D.; Maulide, N., Making the Least Reactive Electrophile the First in Class: Domino Electrophilic Activation of Amides. *J. Org. Chem.* **2016**, *81*, 4421-4428.
106. Ábrányi-Balogh, P.; Volk, B.; Keglevich, G.; Milen, M., Computational study on the synthesis of 1-phenyl-3,4-dihydro- β -carboline: T3P®-promoted one-pot formation from tryptamine vs. POCl₃-mediated ring closure of Nb-benzoyltryptamine. The first DFT investigation of the Bischler-Napieralski reaction. *Comput. Theor. Chem.* **2016**, *1097*, 48-60.

107. Ban, Y.; Kimura, M.; Kobayashi, H.; Mori, M., One Pot Synthesis of Quinazoline Derivatives by Use of Palladium Catalyzed Carbonylation. *Heterocycles* **1985**, 23, 2803 - 2806.
108. Lee, E. S.; Park, J.-G.; Jahng, Y., A facile synthesis of simple alkaloids—synthesis of 2,3-polymethylene-4(3H)-quinazolinones and related alkaloids. *Tetrahedron Lett.* **2003**, 44, 1883-1886.
109. Lee, C.-S.; Liu, C.-K.; Chiang, Y.-L.; Cheng, Y.-Y., One-pot reductive-cyclization as key step for the synthesis of rutaecarpine alkaloids. *Tetrahedron Lett.* **2008**, 49, 481-484.
110. Mhaske, S. B.; Argade, N. P., The chemistry of recently isolated naturally occurring quinazolinone alkaloids. *Tetrahedron* **2006**, 62, 9787-9826.
111. Kshirsagar, U. A.; Mhaske, S. B.; Argade, N. P., Hexamethyldisilazane-iodine induced intramolecular dehydrative cyclization of diamides: a general access to natural and unnatural quinazolinones. *Tetrahedron Lett.* **2007**, 48, 3243-3246.
112. Vorbrueggen, H., Adventures in silicon-organic chemistry. *Acc. Chem. Res.* **1995**, 28, 509-520.
113. Kshirsagar, U. A.; Argade, N. P., Copper-Catalyzed Intramolecular N-Arylation of Quinazolinones: Facile Convergent Approach to (–)-Circumdatins H and J. *Org. Lett.* **2010**, 12, 3716-3719.
114. Vaidya, S. D.; Argade, N. P., A Biomimetic Synthesis of Phaitanthrin E Involving a Fragmentation of sp³ Carbon–Carbon Bond: Synthesis and Rearrangement of Phaitanthrin D to Phaitanthrin E. *Org. Lett.* **2015**, 17, 6218-6221.
115. Vaidya, S. D.; Argade, N. P., Synthesis of (–)-Phaitanthrin D and (+)-Dihydropyrroloindoloquinazolinone. *Synthesis* **2016**, 48, 2896-2903.

116. Karimi, B.; Golshani, B., Mild and Highly Efficient Method for the Silylation of Alcohols Using Hexamethyldisilazane Catalyzed by Iodine under Nearly Neutral Reaction Conditions. *J. Org. Chem.* **2000**, *65*, 7228-7230.
117. Beugelmans-Verrier, M.; Potier, P., Sythesis of pentacyclic β -carbolike and 1,4-benzodiazepine hybrid molecules by dehydrogenatioh-trahsamidation of quinazolino-tetrahydro- β -carboline. *Tetrahedron* **1987**, *43*, 3465-3470.
118. Danieli, B.; Lesma, G.; Palmisano, G., A new tryptophan derived alkaloid from *Evodia rutaecarpa* (Juss.) Benth. et Hook. *Experientia* **1979**, *35*, 156-156.
119. Winkler, J. D.; Scott, R. D.; Williard, P. G., Asymmetric induction in the vinylogous amide photocycloaddition reaction. A formal synthesis of vindorosine. *J. Am. Chem. Soc.* **1990**, *112*, 8971-8975.
120. Shirley, H. J.; Koyioni, M.; Muncan, F.; Donohoe, T. J., Synthesis of lamellarin alkaloids using orthoester-masked α -keto acids. *Chem. Sci.* **2019**, *10*, 4334-4338.
121. Khademi, Z.; Nikoofar, K., Applications of alkyl orthoesters as valuable substrates in organic transformations, focusing on reaction media. *RSC Advances* **2020**, *10*, 30314-30397.
122. Love, B. E., SYNTHESIS OF β -CARBOLINES. A REVIEW. *Org. Prep. Proc. Int.* **1996**, *28*, 1-64.
123. M. Heravi, M.; Nazari, N., Bischler-Napieralski Reaction in Total Synthesis of Isoquinoline-based Natural Products. An Old Reaction, a New Application. *Curr. Org. Chem.* **2015**, *19*, 2358-2408.
124. Nagubandi, S.; Fodor, G., The mechanism of the bischler-napieralski reaction. *J. Heterocyclic Chem.* **1980**, *17*, 1457-1463.
125. White, K. L.; Mewald, M.; Movassaghi, M., Direct Observation of Intermediates Involved in the Interruption of the Bischler–Napieralski Reaction. *J. Org. Chem.* **2015**, *80*, 7403-7411.

126. Qais, N.; Jahan, N., Synthesis of di-1-(4-hydroxybenzyl)-1,2,3,4-tetrahydro- β -carboline and evaluation of its biological activity *World J. Pharm. Res.* **2020**, *9*, 203-211.
127. Putkonen, T.; Tolvanen, A.; Jokela, R., First total synthesis of ($\pm$)-tangutorine. *Tetrahedron Lett.* **2001**, *42*, 6593-6594.
128. Seganish, W. M.; Bercovici, A.; Ho, G. D.; Loozen, H. J. J.; Timmers, C. M.; Tulshian, D., A synthesis of dihydroimidazo[5,1-a]isoquinolines using a sequential Ugi-Bischler-Napieralski reaction sequence. *Tetrahedron Lett.* **2012**, *53*, 903-905.
129. Hwang, D.-Y.; Chen, S.-S.; Gu, J.-T., The Synthesis of 12-Methyl-1, 2, 3, 4, 6, 7, 12, 12B-Octahydroindolo [2,3-A]Quinolizine (1), 1-Benzoyl-1, 2, 3, 4, 6, 7, 12, 12B-Octahydroindolo[2, 3-A]Quinolizine (2), and 1-Phenylcarbinol-1, 2, 3, 4, 6, 7, 12, 12B-Octahydroindolo[2, 3-A]Quinolizine (3). *J. Chin. Chem. Soc.* **1979**, *26*, 49-52.
130. Vilhanová, B.; Matoušek, V.; Václavík, J.; Syslová, K.; Přech, J.; Pecháček, J.; Šot, P.; Januščák, J.; Toman, J.; Zápál, J.; Kuzma, M.; Kačer, P., Two optimized synthetic pathways toward a chiral precursor of Mivacurium chloride and other skeletal muscle relaxants. *Tetrahedron: Asymmetry* **2013**, *24*, 50-55.
131. Abu-Safieh, K. A.; El-Abadelah, M. M.; Sabri, S. S.; Voelter, W.; Moessmer, C. M.; Stroebele, M., Bischler-Napieralski synthesis of some new pyrazole-fused β -carbolines. *Zeitschrift Nat. B* **2002**, *57*, 1327-1332.
132. Safieh, K. A. A.; El-Abadelah, M. M.; Zarga, M. H. A.; Sabri, S. S.; Voelter, W.; Mössmer, C. M., Synthesis of pyrazole-fused azepino[5,4,3-cd]indoles. *Journal of Heterocyclic Chem.* **2001**, *38*, 623-628.
133. Ghosh, A. K.; Sarkar, A., Enantioselective Syntheses of (–)-Alloyohimbane and (–)-Yohimbane by an Efficient Enzymatic Desymmetrization Process. *Eur. J. Org. Chem.* **2016**, *2016*, 6001-6009.

134. Koo, J., Studies in Polyphosphoric Acid Cyclizations. *J. Am. Chem. Soc.* **1953**, *75*, 1891-1895.
135. Fodor, G.; Nagubandi, S., Correlation of the von Braun, Ritter, Bischler-Napieralski, Beckmann and Schmidt reactions via nitrilium salt intermediates. *Tetrahedron* **1980**, *36*, 1279-1300.
136. Li, D.-W.; Zhang, M.; Feng, L.; Huang, S.-S.; Zhang, B.-J.; Liu, S.-S.; Deng, S.; Wang, C.; Ma, X.-C.; Leng, A.-J., Alkaloids from the nearly ripe fruits of *Evodia rutaecarpa* and their bioactivities. *Fitoterapia* **2020**, *146*, 104668.
137. Li, Y.; Feng, T.; Liu, P.; Liu, C.; Wang, X.; Li, D.; Li, N.; Chen, M.; Xu, Y.; Si, S., Optimization of Rutaecarpine as ABCA1 Up-Regulator for Treating Atherosclerosis. *ACS Med. Chem. Lett.* **2014**, *5*, 884-888.
138. Molander, G. A.; Harris, C. R., Sequencing Reactions with Samarium(II) Iodide. *Chem. Rev.* **1996**, *96*, 307-338.
139. Edmonds, D. J.; Johnston, D.; Procter, D. J., Samarium(II)-Iodide-Mediated Cyclizations in Natural Product Synthesis. *Chem. Rev.* **2004**, *104*, 3371-3404.
140. Nicolaou, K. C.; Ellery, S. P.; Chen, J. S., Samarium Diiodide Mediated Reactions in Total Synthesis. *Angew. Chem. Int. Ed.* **2009**, *48*, 7140-7165.
141. Szostak, M.; Fazakerley, N. J.; Parmar, D.; Procter, D. J., Cross-Coupling Reactions Using Samarium(II) Iodide. *Chem. Rev.* **2014**, *114*, 5959-6039.
142. Huang, H.-M.; Adams, R. W.; Procter, D. J., Reductive cyclisations of amidines involving amination radicals. *Chem. Commun.* **2018**, *54*, 10160-10163.
143. Badrinarayanan, S.; Sperry, J., Biomimetic Synthesis of 2,5-Bis(indol-3-ylmethyl)pyrazine via Intermolecular Amino Aldehyde Cyclization. *Synlett* **2011**, *2011*, 2339-2342.

144. Verkade, J. M. M.; Hemert, L. J. C. v.; Quaedflieg, P. J. L. M.; Rutjes, F. P. J. T., Organocatalysed asymmetric Mannich reactions. *Chem. Soc. Rev.* **2008**, 37, 29-41.
145. Ruan, S.-T.; Luo, J.-M.; Du, Y.; Huang, P.-Q., Asymmetric Vinylogous Mannich Reactions: A Versatile Approach to Functionalized Heterocycles. *Org. Lett.* **2011**, 13, 4938-4941.
146. Cheng, C.; Lu, X.; Ge, L.; Chen, J.; Cao, W.; Wu, X.; Zhao, G., Effective asymmetric vinylogous Mannich reaction of isatin imines with α,α -dicyanoolefins in the presence of a simple chiral amide phosphonium bifunctional phase transfer catalyst. *Org. Chem. Front.* **2017**, 4, 101-114.
147. Fang, Y.; Wei, Z.; Wang, Y.; Liu, S.; Cao, J.; Liang, D.; Lin, Y.; Duan, H., The asymmetric vinylogous Mannich reaction of noncyclic dicyanoolefins catalyzed by a bifunctional thiourea–ammonium salt phase transfer catalyst. *New J. Chem.* **2019**, 43, 10012-10016.
148. Rostoll-Berenguer, J.; Blay, G.; Pedro, J. R.; Vila, C., Asymmetric Oxidative Mannich Reactions. *Adv. Synth. Catal.* **2021**, 363, 602-628.
149. Wu, M.; Ma, J.; Ji, L.; Wang, M.; Han, J.; Li, Z., Design, synthesis, and biological evaluation of rutacecarpine derivatives as multitarget-directed ligands for the treatment of Alzheimer's disease. *Eur. J. Med. Chem.* **2019**, 177, 198-211.
150. Wang, B.; Mai, Y.-C.; Li, Y.; Hou, J.-Q.; Huang, S.-L.; Ou, T.-M.; Tan, J.-H.; An, L.-K.; Li, D.; Gu, L.-Q.; Huang, Z.-S., Synthesis and evaluation of novel rutaecarpine derivatives and related alkaloids derivatives as selective acetylcholinesterase inhibitors. *Eur. J. Med. Chem.* **2010**, 45, 1415-1423.
151. Chen, Z.; Hu, G.; Li, D.; Chen, J.; Li, Y.; Zhou, H.; Xie, Y., Synthesis and vasodilator effects of rutaecarpine analogues which might be involved transient receptor potential vanilloid subfamily, member 1 (TRPV1). *Bioorgan. Med. Chem.* **2009**, 17, 2351-2359.

152. Huang, G.; Roos, D.; Stadtmüller, P.; Decker, M., A simple heterocyclic fusion reaction and its application for expeditious syntheses of rutaecarpine and its analogs. *Tetrahedron Lett.* **2014**, *55*, 3607-3609.
153. Kingi, N.; Bergman, J., Thionation of Tryptanthrin, Rutaecarpine, and Related Molecules with a Reagent Prepared from P4S10 and Pyridine. *J. Org. Chem.* **2016**, *81*, 7711-7716.
154. González-Gómez, Á.; Domínguez, G.; Pérez-Castells, J., Novel chemistry of β -carbolines. Expedient synthesis of polycyclic scaffolds. *Tetrahedron* **2009**, *65*, 3378-3391.
155. Huang, G.; Kling, B.; Darras, F. H.; Heilmann, J.; Decker, M., Identification of a neuroprotective and selective butyrylcholinesterase inhibitor derived from the natural alkaloid evodiamine. *Eur. J. Med. Chem.* **2014**, *81*, 15-21.
156. Ertugrul, B.; Kilic, H.; Lafzi, F.; Saracoglu, N., Access to C5-Alkylated Indolines/Indoles via Michael-Type Friedel–Crafts Alkylation Using Aryl-Nitroolefins. *J. Org. Chem.* **2018**, *83*, 9018-9038.
157. Casimir, J. R.; Guichard, G.; Briand, J.-P., Methyl 2-((Succinimidooxy)carbonyl)benzoate (MSB): A New, Efficient Reagent for N-Phthaloylation of Amino Acid and Peptide Derivatives. *J. Org. Chem.* **2002**, *67*, 3764-3768.
158. Tseng, M.-C.; Cheng, H.-T.; Shen, M.-J.; Chu, Y.-H., Bicyclic 1,2,3-Triazolium Ionic Liquids: Synthesis, Characterization, and Application to Rutaecarpine Synthesis. *Org. Lett.* **2011**, *13*, 4434-4437.