

Decarboxylative C–C and C–Heteroatom Bond Forming Reactions: New Methods and Their Application in Total Synthesis

By

Sonavane Sameer Raghunath
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DOCTOR OF PHILOSOPHY
in
SCIENCE

Under the supervision of

Dr. Santosh B. Mhaske



CSIR- National Chemical Laboratory, Pune



Academy of Scientific and Innovative Research AcSIR
Headquarters, CSIR-HRDC Campus
Sector 19, Kamla Nehru Nagar
Ghaziabad, U.P. – 201 002, India

December-2024

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Mr. Sonavane Sameer Raghunath

Research Student

Date 26-12-2024.



Dr. Santosh B. Mhaske

Research Supervisor

Date 26-12-2024

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Dedicated to My Beloved Family

"Dedicated to my Parents, wife, and beloved son, whose unwavering love, support, and encouragement have been the foundation of my strength and perseverance. This work is a testament to their sacrifices and belief in me"



“Dedicated to the Great Social Leader, Visionary and Reformer of Modern Bharat, Dr. Babasaheb Ambedkar”

- **सामाजिक समानता आणि न्याय:** डॉ. आंबेडकर नेहमीच सामाजिक समानतेचा पुरस्कार करत होते. त्यांनी भारतीय समाजात जातिवाद, अस्पृश्यता आणि धार्मिक विषमता निर्मूलनाचे प्रयत्न केले. त्यांचा विश्वास होता की समाजातील प्रत्येक व्यक्तीला समान अधिकार मिळाले पाहिजेत, त्याच्या जात, धर्म, आणि आर्थिक स्थितीच्या आधारावर त्याला भेदभाव होणं समर्पक नाही.
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- **भारतीय संविधान:** डॉ. बाबासाहेब आंबेडकर हे भारतीय संविधानाचे शिल्पकार होते. त्यांनी भारतीय संविधानात समानता, धर्मनिरपेक्षता, आणि सर्व नागरिकांना समान हक्क देणारी तरतुदी ठरवली. त्यांनी अस्पृश्यतेचे निर्मूलन, धर्माच्या आधारावर भेदभाव रोखणे आणि सर्व नागरिकांना समान हक्क देणे यासाठी संविधानाच्या माध्यमातून कायदेशीर संरचना तयार केली.

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Ph.D. is like a long journey, a unique experience that takes you through the untraversed path, to conquer the final goal fixed in mind. Once you achieve the target and turn back, you realize that all your efforts and the pain were worth going through. The small successes & the serendipitous discoveries, the frustrating failures & unexpected crystallizations, the imparted chemical wisdom & the laboratory camaraderie; they are all important parts of this beautiful voyage. But one can't succeed in this journey without the guidance and support of the research supervisor, friends, and well-wishers. At this juncture of my doctorate, I would like to express my sincere gratitude to everyone who has helped and supported me throughout my research journey directly or indirectly.

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Thesis Abstract

List of publications and posters/presentations

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Abbreviations

Units	
°C	Degree centigrade
mg	Milligram
h	Hour
min	Minutes
mL	Millilitre
µg	Microgram
Hz	Hertz
MHz	Megahertz
mmol	Millimole
ppm	Parts per million
mol	Mole
NR	No reaction
CR	Complex reaction mixture

Chemical Notations	
Ac	Acetyl
AcOH	Acetic Acid
ACN	Acetonitrile
Ar	Aryl
APS	Ammonium persulfate
BHT	Butylated hydroxytoluene
CCDC	Cambridge Crystallographic Data centre
CDCl ₃	Deuterated Chloroform
DCM	Dichloromethane
DCE	Dichloethane
DMF	Dimethyl formamide
DMSO	Dimethyl sulphoxide
Et	Ethyl
EtOH	Ethanol
EtOAc	Ethyl acetate
LCMS	Liquid chromatography–mass spectrometry
Ph	Phenyl

<i>p</i> -TSA	<i>p</i> -Toluene sulfonic acid
RFTA	Riboflavin tetraacetate
SAR	Structure activity relation
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TFA	Trifluoroacetic acid
TMS	Trimethylsilyl
TLC	Thin layer chromatography
THF	Tetrahydrofuran
TPPO	Triphenylphosphine oxide

Other Notations

calcd	Calculated
δ	Chemical shift
<i>J</i>	Coupling constant in NMR
equiv.	Equivalents
eq.	Equitation
ESI	Electrospray ionization Mass spectrometry
HRMS	High Resolution Mass Spectrometry
<i>m/z</i>	Mass-to-charge ratio
MS	Molecular sieves
mp	Melting Point
NMR	Nuclear Magnetic Resonance
rt	Room temperature

General information

All reagents and solvents were used as received from commercial sources. All experiments were carried out under argon atmosphere unless otherwise noted. Pre-coated plates (silica gel 60 PF254, 0.25 mm or 0.5 mm) were utilized for thin layer chromatography (TLC). Column chromatographic purifications were carried out on flash silica-gel (240–400 mesh) using petroleum ether and ethyl acetate as eluents unless otherwise noted. The ^1H , ^{13}C NMR spectra were recorded on 200/400/500 MHz, and 50/100/125 MHz NMR spectrometers, respectively in $\text{CDCl}_3/\text{DMSO}-d_6/\text{acetone}-d_6$. Chemical shifts were reported as δ values from standard peaks. Melting points recorded are uncorrected. Optical rotations were measured on ADP 220 polarimeter (Bellingham + Stanley Ltd). Chiral HPLC analysis was performed on the Agilent Technologies 1260 infinity instrument with a UV detector. Mass spectra were taken on LC-MS (ESI) or GCMS spectrometer. HRMS were scanned on Quadrupole-Orbitrap Mass Spectrometer available at NCL, Pune.

	Synopsis of the thesis to be submitted to the Academy of Scientific and Innovative Research for award of the degree of Doctor of philosophy in Chemical Science
Name of Candidate	Mr. Sameer Raghunath Sonavane
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Title of the Thesis	Decarboxylative C–C and C–Heteroatom Bond Forming Reactions: New Methods and Their Application in Total Synthesis
Research Supervisor	Dr. Santosh B. Mhaske

1. Introduction: The present thesis describes the development of novel decarboxylative C–C and C–heteroatom bond-forming reactions and their application in the synthesis of natural products, biologically active molecules, and Active Pharmaceutical Ingredients (APIs). The thesis is categorized into four chapters. The first chapter provide a general introduction to decarboxylative C–C and C–heteroatom bond-forming reactions. Particularly, it describe decarboxylative C–H bond functionalization of nitrogen-containing heteroarenes and their applications. The second chapter encompasses the development of new protocol for decarboxylative C–H bond functionalization of quinazolinones with amino acids by visible light photoredox catalysis. We also present the application of the protocol in the total synthesis of circumdatin class of quinazolinone natural products and their congeners. The third chapter demonstrates our studies toward the asymmetric synthesis of the key intermediate of dextromethorphan API *via* the decarboxylative C–C bond-forming reaction. Dextromethorphan is commonly used as a cough suppressant. The fourth chapter deals with the organophotoredox-catalyzed decarboxylative C–heteroatom bond formation for the synthesis of biologically important Ampakine APIs and quinazolinone based natural products such as deoxyvasicinone, and mackinazolinone. The developed protocol was applied in the synthesis of the drug molecules CX-614, and CX-554, which are used in the treatment of neurodegenerative diseases such as Alzheimer's and Parkinson's. Overall, this thesis summarises new scalable approaches on decarboxylative C–C and C-heteroatom bond formation reactions for synthesizing various structurally complex and bioactive scaffolds of pharmaceutical importance.



Mr. Sameer R. Sonavane
(Student)



Dr. Santosh B. Mhaske
(Supervisor)

2. Statement of the problem: Efficient construction of bioactive scaffolds using economical and environmentally friendly processes is highly valued in organic synthesis and pharmaceuticals. We planned to explore two of the most popular and contemporary synthetic tools viz C–H bond functionalization of heteroaromatic compounds and photoredox catalysis to achieve this goal. Decarboxylative C–C and C–heteroatom bond formation is a crucial tool in the synthesis of bioactive molecules and drug discovery. Constructing a Csp^3 – Csp^2 and Csp^3 –X– Csp^2 (X = O, N, and S) bonds remains a challenging task in organic synthesis using classical methods. These bonds are prevalent in natural products and pharmaceuticals. Therefore, there is a need to discover novel protocols for these bond formations, particularly using easily accessible carboxylic acids and efficient organophotocatalysts. While significant progress has been made in decarboxylative C–C and C-heteroatom bond formations, especially using photochemical, radical, metal-catalyzed, and electrochemical approaches, many challenges still persist. These include developing reactions that can construct structurally complex organic molecules under ambient conditions.

3. Objectives:

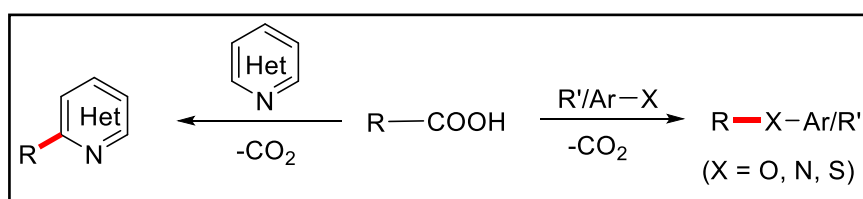
- 1) Development of enantioselective intramolecular decarboxylative C–H bond functionalization of quinazolinones with amino acids by visible light photoredox catalysis and its application in the synthesis of natural products.
- 2) Asymmetric synthesis of a key dextromethorphan intermediate by decarboxylative C–C bond formation.
- 3) Exploration of new synthetic transformations employing Csp^3 –X– Csp^2 (X = O, N, S) bond formation using intramolecular photodecarboxylative cyclization of salicylic acid derivatives.

4. Methodology and result:

Chapter 1: Decarboxylative C–C and C–Heteroatom Bond Forming Reactions and Their Application in the Synthesis of Bioactive Molecules

Chapter 1 provide introduction to the area of decarboxylative C–C and C–heteroatom bond forming reactions and its applications. Decarboxylation is a chemical process which involves extrusion of carbon dioxide from organic molecules. The decarboxylative C–C and C–heteroatom bond formation reaction have long history. The Kolbe electrolysis (1848) is the oldest decarboxylative C–C bond forming reaction in which radicals are generated and get dimerized.¹ Another classical decarboxylation method, was developed by the Hunsdiecker² in which stoichiometric amount of silver salt enables oxidative decarboxylation with subsequent trapping of the alkyl radicals by halides. Moreover, the Barton decarboxylation represents an interesting decarboxylative reduction process.³ The forerunner of modern, metal-catalyzed decarboxylative chemistry is the decarboxylative Ullman cross-coupling between two aromatic compounds, which was reported by Nilsson et al. in 1966.⁴

Over the past few decades, decarboxylative C–C and C–heteroatom bond forming reactions are intensively studied by synthetic organic chemists. There are plethora of reactions that have been developed by researchers *via* classical two electron as well as radical pathway. For example, Minisci type reactions for decarboxylative C–H bond functionalization of nitrogen-containing heteroarene and C–heteroatom bond forming reactions (Scheme 1). In the last few years decarboxylation reaction has emerged as a powerful tool in the synthesis of various bioactive molecules, natural products, and pharmaceuticals (Figure 1A).



Scheme 1. Decarboxylative C–C bond formation and C–heteroatom bond forming reactions

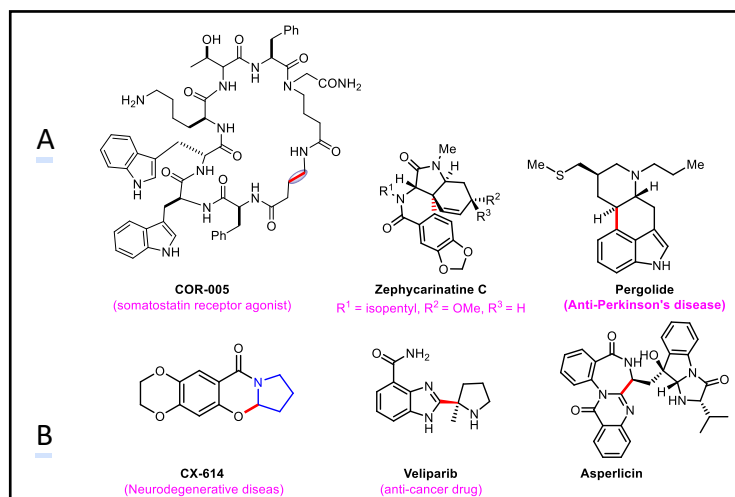
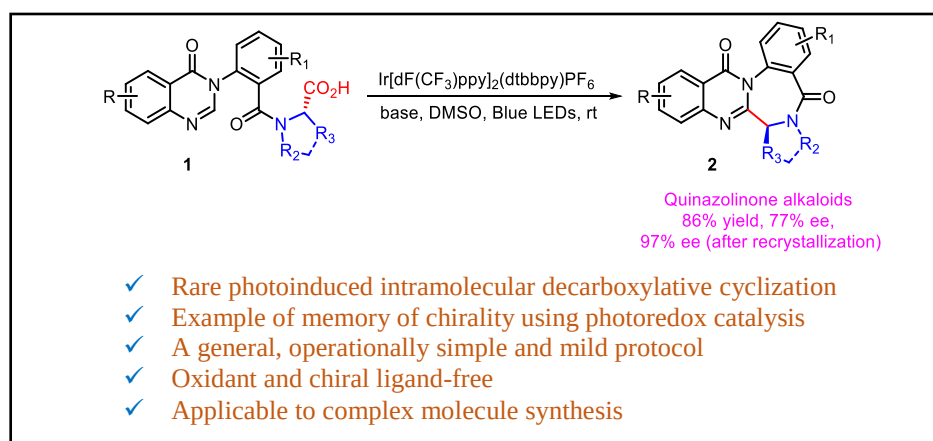


Figure 1. Decarboxylative C–C bond formation and C–heteroatom bond forming reactions to access natural products and drug molecules.

This chapter deals with the account of the significant organic transformations reported in the literature utilizing decarboxylative C–C and C–heteroatom bond formation and provide necessary background for the working chapters 2-4. We believe that the processes will be applicable to APIs and bioactive natural products (Figure 1B)

Chapter 2: Enantioselective Intramolecular Decarboxylative C–H Bond Functionalization of Quinazolinones with Amino Acids by Visible Light Photoredox catalysis

The visible light-mediated intramolecular decarboxylative C–H functionalization of Csp²–H bond adjacent to the nitrogen of a heteroarene has been achieved by iridium-catalyzed photodecarboxylative radical cyclization (Scheme 2).⁵



Scheme 2. Intramolecular decarboxylative C–H functionalization of Csp²–H bond of quinazolinone

This method offers rapid entry to the synthesis of quinazolinone scaffolds from easily accessible starting materials. The newly developed protocol is mild, operationally simple, oxidant free and general. The utility of this unique Csp^3-Csp^2 bond forming reaction has been demonstrated in the syntheses of Circumdatin, Sclerotigenine and Benzomalvin A class of quinazolinone natural products and their congeners. The present work represents an interesting example of the use of memory of chirality in decarboxylative C–C bond forming enantioselective photoredox reaction.

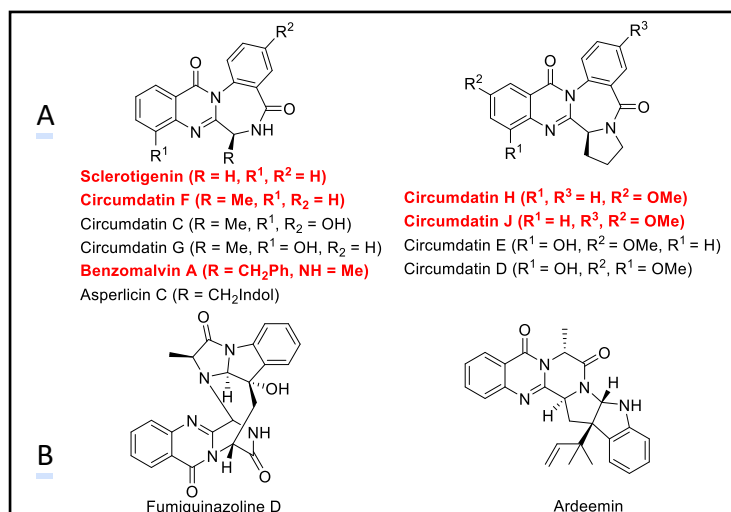


Figure 2. Quinazolinone based bioactive natural products

We have disclosed the first oxidant and chiral ligand free C–C bond functionalization of quinazolinone heteroarenes by Iridium-catalyzed intramolecular photodecarboxylative cyclization method and its application. This straightforward approach provides a facile access to biologically active quinazolinone natural products (Figure 2A) ⁶ and their analogues using commercially available α -amino acids as coupling partners. We believe that the optimized protocol can be applied to the total synthesis of complex quinazolinone bioactive natural products (Figure 2B)

Chapter 3: Studies Towards the Asymmetric Synthesis of Dextromethorphan Key Intermediate by Decarboxylative C–C Bond Forming Reaction

This chapter demonstrates our attempts towards the development of decarboxylative C–C bond formation method and its application in the synthesis of dextromethorphan key intermediate. Here, we describe our two attempts towards its asymmetric synthesis (Figure 3) by decarboxylative C–H bond functionalization of unactivated olefin.

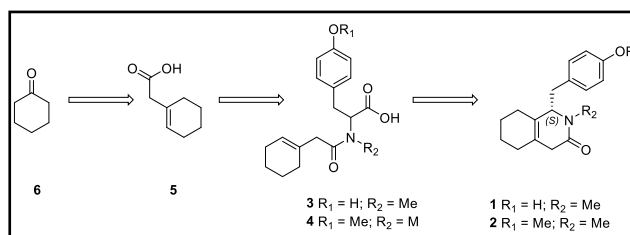
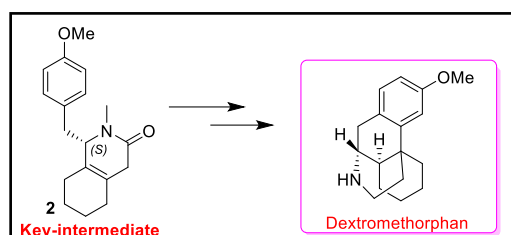
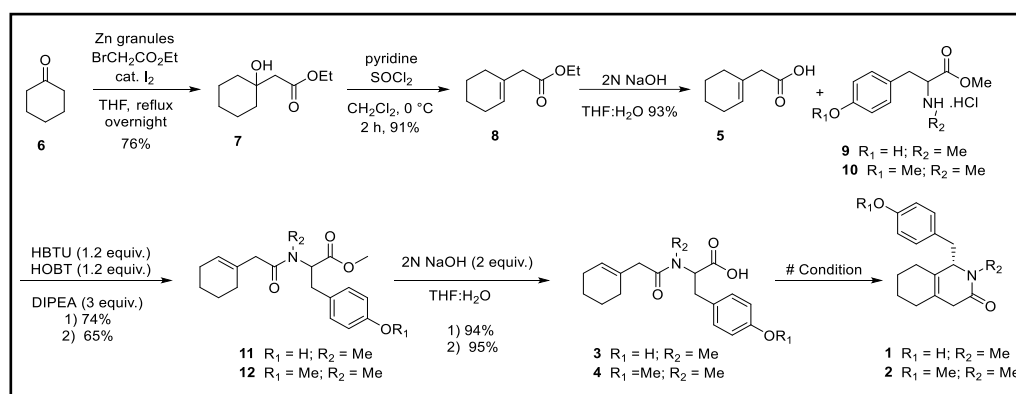
Route A:

Figure 3. Key intermediate of dextromethorphan **Scheme 3.** Retrosynthesis for dextromethorphan intermediate

The first designed retrosynthesis of dextromethorphan involves utilization of olefin activation with metal as well as photoredox catalyzed tandem cyclization strategy. The key intermediate **1/2** could be obtained by decarboxylative C–H bond functionalization of olefin. The acid **5** (derived from cyclohexanone) could lead us to the formation of coupling intermediates **3/4** using tyrosine as coupling partner. (Scheme 3).

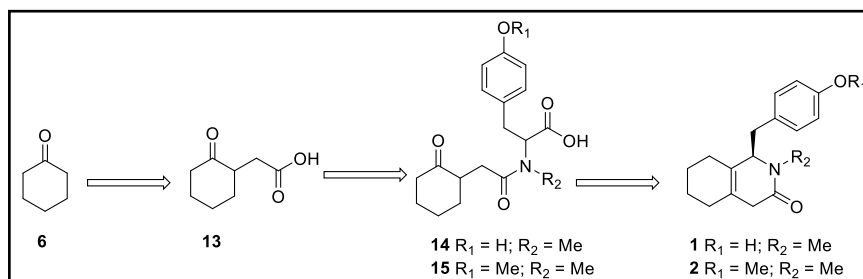


Scheme 4. Synthetic route A for the dextromethorphan

The synthesis of the dextromethorphan key intermediate began from commercially available cyclohexanone. The alkene compound **3/4** was synthesized starting from cyclohexanone **6** in six steps with good yields. However, in the decarboxylative cyclization reaction, we observed the formation of undesired products or no product, when the alkene acids **3/4** were subjected to various known and new reaction conditions (Scheme 4). Our next target is to find a suitable condition for the required transformation. Alternately, we planned to modify the route A (Scheme 4) to avoid the formation of undesired products.

Route B:

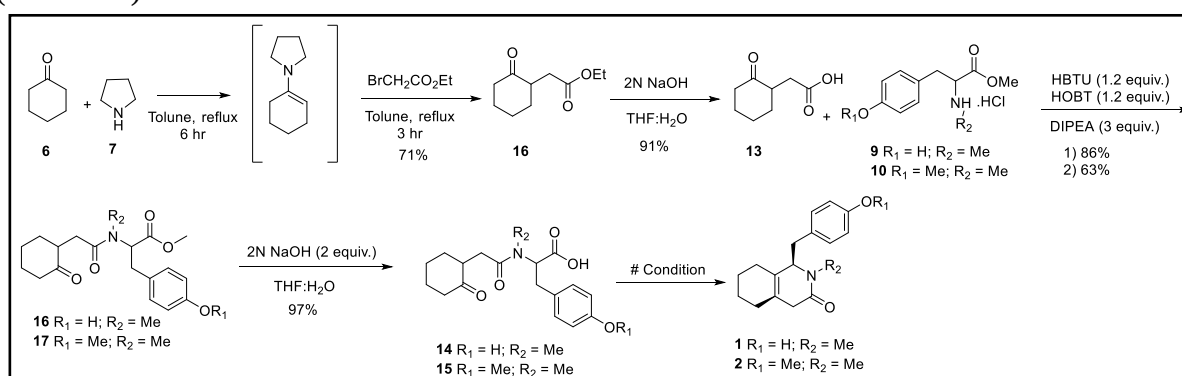
After several attempts on Route A, we moved towards Route B. In this context, we have designed retrosynthetic plan for dextromethorphan key intermediate considering the utilization of ketonic substrate and its electrophilic reaction to get cyclized product formation **1/2** (Scheme 5).



Scheme 5. Retrosynthetic strategy for dextromethorphan.

The key dextromethorphan intermediate **1/2** could be obtained from **14/15** by using decarboxylative C–C bond forming reaction. The ketonic acid **13** (derived from cyclohexanone **6**) could lead us to the formation of coupling intermediates **14/15** using tyrosine as coupling partner (Scheme 5).

The **Route B** started with cyclohexanone. The keto products **14/15** were synthesized starting from the cyclohexanone **6** in five steps with good yields. After getting key intermediate in hand, we tried several reaction conditions. We did not observe the formation of expected product when the ketone **14/15** was subjected to various known and new reaction conditions (Scheme 6).

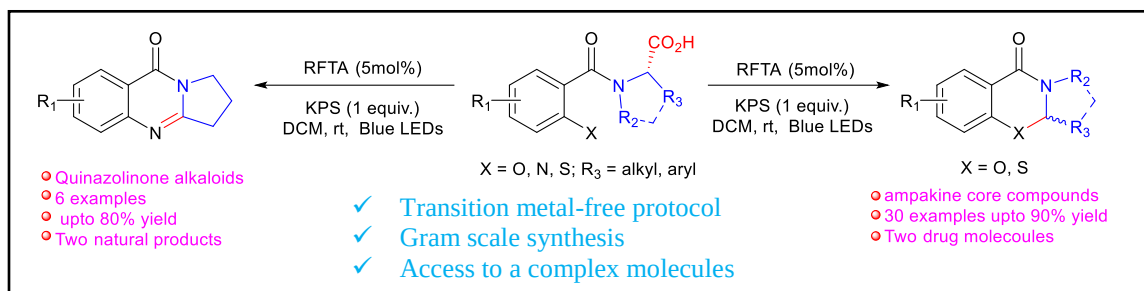


Scheme 6. Synthetic route B for the dextromethorphan

Our next target is to find a suitable condition for the required transformation. We believe that Route B might work and provide cyclized product **1/2**. Currently, we are working on both routes.

Chapter 4: Organophotoredox-Catalyzed Decarboxylative C–X Bond Formation: Synthesis of Ampikine APIs, and Quinazolinone Alkaloids

Chapter 4 describes the detailed study on organophotoredox-catalyzed intramolecular decarboxylative C–X (X = O, N, S) bond formation of salicylic/anthracitic acid derivatives with natural/unnatural amino acids (Scheme 7).



Scheme 7. Intramolecular decarboxylative Csp³–X–Csp² bond forming reaction

This intramolecular C–heteroatom bond formation reaction provides an important class of ampakines and quinazolinone derivatives. This protocol does not require any pre-functionalization on natural/unnatural amino acids and leverages commercially available acids. Moreover, this method provides a convenient synthesis of new drug molecules CX-614 and CX-554, which have potential in the treatment of Alzheimer's and Parkinson's diseases. Diflunisal drug hybrid as well as quinazolinone alkaloids such as deoxyvasicinone and mackinazolinone were synthesised using our protocol. This method exhibits high functional group tolerance and convenient scalability.

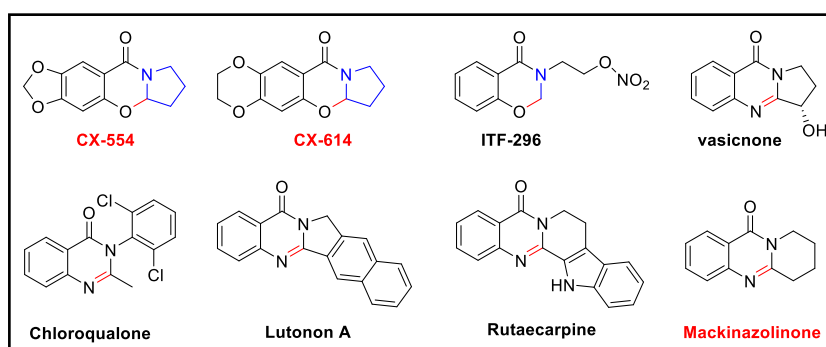


Figure 4. Ampikine and quinazolinone based bioactive molecules

Moreover, C–S bond-forming reaction also worked under the standard protocol to obtain novel scaffolds, which may have promising bioactivity.

Summary/Conclusion:

In summary, we have disclosed the first oxidant and chiral ligand-free C–H bond functionalization of quinazolinone heteroarenes by Iridium-catalyzed intramolecular photo decarboxylative cyclization method and its application in the synthesis of quinazolinone alkaloids. We have developed two synthetic routes to achieve the dextromethorphan key intermediate. We tried different reaction conditions on the key precursor but the expected product could not be observed. Currently, we are working on it, and we believe that we will soon achieve it. The protocol will be also useful for the synthesis of related core. The work on the decarboxylative $Csp^3-X-Csp^2$ bond formation is significant advancement in the synthesis of bioactive and complex molecules. The application of the protocol in the drug molecules CX-614 and CX-554 as well as quinazolinone bioactive molecule synthesis proves the importance of this protocol.

Future directions:

The decarboxylative C–H bond functionalization protocol developed herein can be explored in the asymmetric synthesis of complex molecules such as Asperlicin and its derivatives. The synthesis of dextromethorphan key intermediate may need the development of a novel photocatalyst. The $Csp^3-X-Csp^2$ bond forming reaction developed can be optimized further for industrial application, particularly ampakine class of APIs.

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Publications and patents:

- 1) **S. R. Sonavane**, S. B. Mhaske., Enantioselective Intramolecular Decarboxylative C–H Bond Functionalization of Quinazolinones with Amino Acids by Visible Light Photoredox Catalysis. *Chem. Asian J.* **2023**, *18*, e202300235.
- 2) S. B. Mhaske, **S. R. Sonavane**. *Indian patent*, 2024-NF-0101.
- 3) **Sonavane, S. R.**, Kale, T. B., Bhatt, G. J., Mhaske, S. B. Organophotoredox-Catalyzed Decarboxylative C(sp³)–X Bond Formation: Facile Access to Ampikine APIs and Quinazolinone Alkaloids. *manuscript communicated*.
- 4) S. B. Mhaske, **S. R. Sonavane**. Filed patent no. 2023-NF-0177.
- 5) Viveki, A. B., Pol, M. D., Halder, P., **Sonavane, S. R.**, Mhaske, S. B, Annulation of Enals with Carbamoylpropiolates via NHC-Catalyzed Enolate Pathway: Access to Functionalized Maleimides/Iso-maleimides and Synthesis of Aspergillus FH-X-213. *J. Org. Chem.* **2021**, *86*, 9466–9477.

Poster/oral presentations:

- 1) Poster presentation on Enantioselective Intramolecular Decarboxylative C–H Bond Functionalization of Quinazolinones with Amino Acids by Visible Light Photoredox Catalysis, NCL RF Annual student conference, Pune, Maharashtra, Nov, 2022
- 2) Oral presentation on Enantioselective Intramolecular Decarboxylative C–H Bond Functionalization of Quinazolinones with Amino Acids by Visible Light Photoredox Catalysis, NCL RF Annual student conference, Pune, Maharashtra, Dec, 2023 (**Best oral presentation award**)
- 3) Oral presentation on Organophotoredox-Catalyzed Decarboxylative C(sp³)–X–Csp² Bond Formation: Facile Access to Ampikine APIs and Deoxyvasicinone Quinazolinone Alkaloids, XVIII J-NOST 2023 conference from October 10-12, 2023, @IISERPune
- 4) Flash talk presentation on Organophotoredox-Catalyzed Decarboxylative C(sp³)–X – Csp² Bond Formation: Facile Access to Ampikine APIs and Deoxyvasicinone Quinazolinone Alkaloids, Humboldt Kolleg conference, Goa, Feb, 2024



Mr. Sameer R. Sonavane
(Student)



Dr. Santosh B. Mhaske
(Supervisor)

Chapter 1

Decarboxylative C–C and C–Heteroatom Bond Forming Reactions and Their Application in the Synthesis of Bioactive Molecules

Decarboxylative C–C and C–Heteroatom Bond Forming Reactions and Their Application in the Synthesis of Bioactive Molecules

The key focus of the present thesis is the controlled extraction of CO₂ from organic compounds, a process termed as decarboxylation, which leads to reactive intermediate and further functionalization. Carboxylic acids, with their natural availability, structural diversity and ease of handling, serve as vital and stable feedstock chemicals in synthetic organic chemistry. Decarboxylative reactions, particularly those forming Carbon-Carbon and Carbon–Heteroatom bonds, play a crucial role in the construction of natural products, bioactive molecules and potent drugs. This chapter provides an introduction to decarboxylative bond constructing reactions, laying the groundwork for the subsequent working chapters.

This chapter is organized into two sections: The first section provides an overview of decarboxylative C–C bond construction through C–H bond functionalization of nitrogen-containing heteroarenes, while the second section focuses on decarboxylative C–heteroatom bond-forming reactions. Together, these sections highlight the importance and versatility of decarboxylative bond-forming processes in advancing synthetic strategies for drug and natural product synthesis.

Section 1.1 Decarboxylative C–H bond functionalization to form C–C bond formation

In recent years, decarboxylative C–H functionalization has evolved as a dominant strategy for synthesizing C–C bond.^[1] This innovative approach harnesses the inherent reactivity of carboxylic acids, enabling the selective removal of carbon dioxide while simultaneously facilitating Carbon–Carbon bond formation via C–H bond activation.^[2] The structural diversity and stability of carboxylic acids make them ideal precursors in synthetic organic

chemistry, enhancing their value in this context. The decarboxylative process streamlines synthetic pathways and allows for the formation of complex molecules that are crucial in drug discovery and development.^[3] This section will discuss various methodologies that utilize decarboxylative C–H bond functionalization of heteroarenes for C–C bond formation, emphasizing key reactions, mechanistic insights, and applications in synthesizing pharmacologically relevant compounds.^[4] By examining the complexity of these reactions, researchers can better leverage the potential of decarboxylation to innovate and optimize synthetic strategies in organic chemistry. C–H functionalization refers to the transformation of unreactive carbon-hydrogen (C–H) bonds into functionalized organic molecules. Over the past few decades, this field has significantly expanded, yielding innovative methods that impact organic synthesis, materials science, drug discovery, and catalysis.^[4-5] One of the primary advantages of C–H functionalization is its economic efficiency; it enables the formation of both C–C and carbon-heteroatom bonds from C–H bonds directly, often without requiring pre-functionalized substrates. This aspect provides well-organized synthetic routes and reduces waste, making it a promising method in the field of green chemistry.^[6]

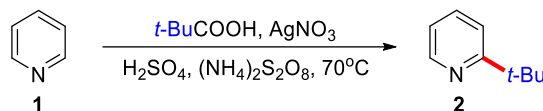
Recent advancements in C–H functionalization have emphasized the fine-tuning of reactions involving organic molecules with sensitive functional groups. Researchers have developed sophisticated directing group strategies and catalytic systems that enhance selectivity and efficiency in these transformations.^[7] The capability to selectively functionalize C–H bonds in complex molecules holds great potential for the development of new pharmaceuticals and advanced materials. However, challenges persist, particularly regarding the C–H bond functionalization without directing groups.^[8] To address these challenges, the exploration of novel catalysts, reaction conditions, and methodologies is essential to broaden the utility of C–H bond functionalization reactions. As the field continues to evolve, ongoing innovation is expected to unlock further applications and overcome existing limitations, paving the way for

transformative developments in chemistry. Collectively, these advancements highlight the potential of decarboxylative C–H functionalization as a keystone of modern synthetic organic chemistry. In this context, nitrogen-containing heteroarenes are of particular significance due to their occurrence in bioactive natural products as well as pharmaceutical compounds.^[9] This has prompted considerable interest in developing methodologies for the selective functionalization of these heteroarenes, enabling the direct modification of complex molecules.^[10] Such strategies not only streamline synthetic routes but also reduce reliance on pre-functionalized starting materials.

Among the various techniques available, the Minisci reaction, first reported in 1971 by F. Minisci, stands out as a prominent method for the C–H functionalization of nitrogen-containing heteroarenes.^[11] While it shares similarities with classical Friedel–Crafts alkylation, the Minisci reaction exhibits distinct reactivity and selectivity. Specifically, while Friedel–Crafts reactions typically favour electron-rich arenes, the Minisci reaction is considered by its preference for electron-deficient heteroarenes. The Minisci reaction involves nucleophilic addition of carbon-centred radicals to the nitrogen-containing electron-deficient heteroarenes, such as isoquinolines, pyridines, and quinolones (Scheme 1.1).^[12] This innovative approach marked a remarkable advancement in the direct C–H functionalization field, proposing adaptable method for modifying heterocycles under mild conditions. Consequently, it has become an essential tool in both synthetic and medicinal chemistry.

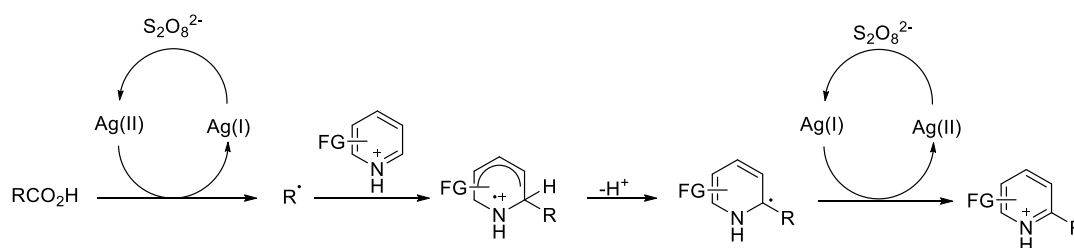
Since its inception, the Minisci reaction has continually evolved, strengthening its position as a fundamental technique in C–H functionalization.^[10,12] Over the past fifty years, it has expanded beyond its original parameters, with numerous advancements enhancing our understanding of its mechanisms and broadening its applications. These developments have further established the Minisci reaction as a versatile platform for the construction and enantioselective functionalization of nitrogen-containing heterocycles,^[13] making it

indispensable in contemporary synthetic strategies. Together, these innovations underscore the importance of decarboxylative C–H bond functionalization in advancing modern organic chemistry and drug discovery.



Scheme 1.1 Minisci reaction: decarboxylative alkylation of heteroarenes^[13]

Mechanistically, these reactions begin with the silver(I) oxidation to a silver(II) species facilitated by a persulfate (Scheme 1.2). The silver(II) intermediate species then promotes decarboxylation of alkyl carboxylic acids, leading to the formation of a carbon-centered radical. This radical then interacts with protonated pyridines, generating a radical cation. The final product is formed through subsequent deprotonation and oxidation processes.



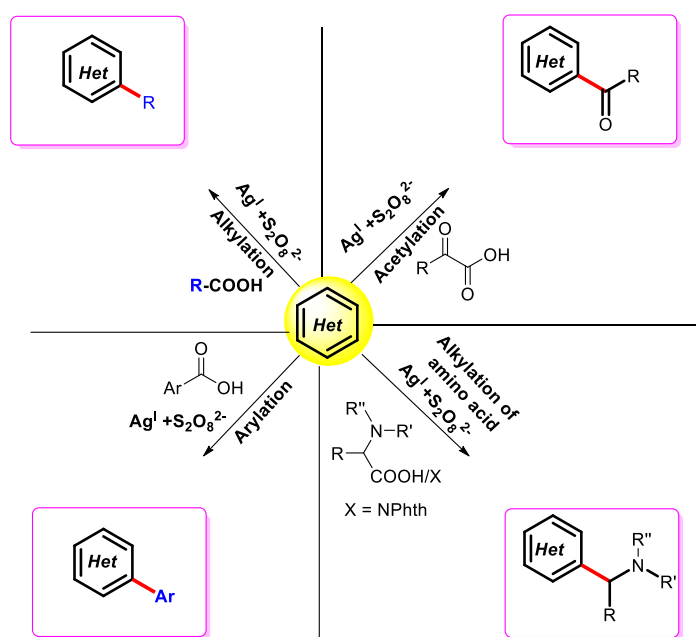
Scheme 1.2 Nucleophilic radical addition to protonated pyridines (Minisci Reaction)^[13]

Since its inception, the Minisci reaction has experienced significant advancements, which have broadened its applicability to include both classical and modern photocatalyzed reactions.

1.1.1 Classical decarboxylative C–H functionalization of heteroarens

In the classical decarboxylative C–H functionalization of heteroarens,^[10a] several key methods for a radical generation have been developed since the late 1960s, particularly by Minisci and others.^[4,10,12-13] This section provides an extensive review of these methodologies and their significance in the evolution of C–H bond functionalization strategies of nitrogen containing heteroarens. Researchers have expanded its applicability to a wide variety of

substrates and functional groups, enhancing its versatility. This broadened scope now encompasses alkylation, arylation, acetylation, and even the alkylation of amino acids.^[1,4,10] Notable approaches include oxidative addition, hydrogen atom transfer or single electron transfer (SET) and photochemical processes,^[4] all of which have laid the milestone for innovative techniques in the functionalization of nitrogen-containing heteroarenes. By examining these foundational advancements, we aim to clarify how earlier methodologies have guided the more recent developments, discussed in this chapter.



Scheme 1.3 Decarboxylative radical generation from various substrates in Minisci-type reactions^[10b]

This context will enhance the appreciation of ongoing progress in the field and illustrate the interconnected nature of these radical generation techniques (Scheme 1.3).^[10b] Such an understanding underscores the continuity and evolution of research in decarboxylative C–H functionalization, highlighting its relevance in the broader landscape of synthetic organic chemistry. Classical decarboxylative C–H functionalization of heteroarenes is a key method in synthetic organic chemistry for modifying complex molecules. Additionally, its applications in medicinal chemistry will further underscore its importance. Future

advancements will likely focus on developing new radical precursors, enhancing selectivity, integrating with other synthetic strategies, promoting sustainability, and deepening mechanistic insights. These efforts will collectively enhance the efficiency and versatility of this valuable technique, solidifying its role as a keystone of modern chemical synthesis.

1.1.2 Photodecarboxylative C–H functionalization of nitrogen containing heteroarenes

Over the past few decades, photoredox catalysis has become a valuable technique in the field of synthetic organic chemistry, particularly for constructing C–C and C–heteroatom bonds.^[10b, 12-14] Among these transformations, C–H bond functionalization has gained significant attention. Visible light-mediated radical decarboxylative C–H bond functionalization is a crucial reaction in the selective functionalization of natural products and late-stage derivatization of pharmaceuticals and agrochemicals.^[15] Chemists have dedicated considerable attention to the field of C–H bond functionalization, particularly in the advancement of new methodologies for functionalizing nitrogen-containing heteroarenes.

This approach has become increasingly relevant for the decarboxylative C–H bond functionalization of nitrogen-containing heteroarenes, an appealing area in natural products and drug molecule synthesis. The C–H alkylation of *N*-heteroarenes using amino acids as coupling partners is particularly significant in the pharmaceutical industry due to the widespread presence of functionalized *N*-heteroarenes in medicinal compounds.^[16] In the broader field of C–H functionalization, photodecarboxylative reactions that form C–C and C–heteroatom bonds play a crucial role. These reactions facilitate the efficient construction of complex molecular frameworks by directly transforming C–H bonds, offering a streamlined approach to accessing bioactive compounds. In photoredox catalysis methods,^[14e] inorganic and organometallic photocatalysts^[17] offer several advantages, such as high molar absorptivity, efficient intersystem crossing (ISC), and triplet-state (T_1) lifetimes ranging from approximately 100 nanoseconds to 1 millisecond. Numerous Ru(II) and Ir(III) photocatalysts

have been synthesized, as the ligand environment of these complexes can be easily modified using commercially available or readily synthesized ligands. This flexibility allows fine-tuning of their absorption and excited-state properties. While these catalysts typically absorb in the 390–480 nm range. Organic photocatalysts possess a broader redox window compared to their inorganic or organometallic counterparts, enabling them to facilitate specific classes of transformation that may not be accessible with other catalysts.

1.1.2.1 Photoredox catalytic cycle

The photodecarboxylative catalytic cycle is crucial because it explains the fundamental mechanisms behind light-driven reactions, which can significantly enhance the efficiency and selectivity of synthetic processes. By understanding this cycle, chemists can design innovative methodologies that influence light as a clean energy source, opening new avenues in organic synthesis and materials science. This knowledge not only nurtures progresses in reaction design but also contributes to the development of sustainable practices in chemical manufacturing. Photodecarboxylative C–H bond functionalization via a radical intermediate is an important transformation for C–C bond formation, particularly with nitrogen-containing heteroarenes. Conventional methods for generating carbon centred radicals often rely on toxic and explosive reagents, such as tributyltin hydride, peroxides, and diazo compounds.^[18] A safer and more efficient alternative is photodecarboxylation, as they are particularly well-suited for generating sp^3 carbon-centered radicals. The photoredox catalytic reaction follows one of the two mechanistic pathways illustrated in Figure 1.1^[19]

The excited state of the catalyst (cat*) is deactivated in an oxidative quenching cycle, through electron transfer (ET) to either the substrate or an oxidizing agent (oxi) in the reaction mixture. When the catalyst is oxidized by donating an electron to the substrate, this process is termed oxidative quenching.

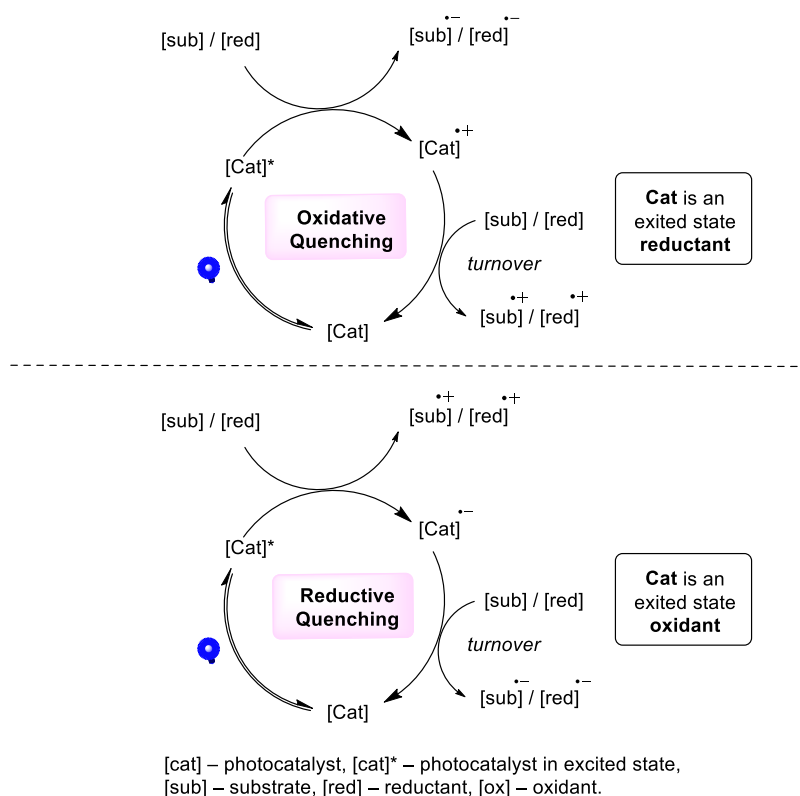


Figure 1.1: Oxidative and reductive quenching cycles of photoredox catalyst^[19]

Alternatively, the reductive quenching cycle takes place when (cat^*) is quenched by receiving an electron from either the substrate or a reducing agent (red). The catalyst-turnover step includes the reduction of the oxidized catalyst ($cat^{•+}$) in the oxidative cycle and the oxidation of the reduced catalyst ($[cat]^{•-}$) in the reductive cycle. In both cycles, the turnover of the catalyst can be aided by an external redox-active reagent, the substrate or an intermediate.

1.1.3 Features of C–H bond functionalization of heterocycle via photoredox catalysis

Over the past few decades, several research groups viz. MacMillan,^[14d, 20] Frank Glorius,^[14a, 21] Stephenson,^[22] and Tunge,^[23] have made remarkable development in the field of photocatalysis. Their pioneering contributions have greatly advanced the use of photocatalysis in synthetic organic chemistry, enhancing its role in developing efficient and sustainable methodologies for complex and bioactive molecule synthesis. These efforts have

wide scope of photocatalysis, making it a vital tool in the creation of pharmaceuticals, fine chemicals, and materials.

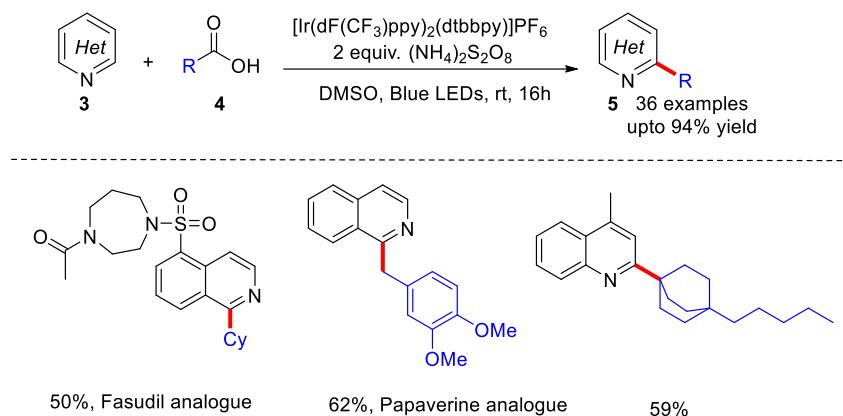
Photocatalytic C–H bond functionalization of heterocycles is an innovative technique in organic synthesis, providing benefits like mild reaction conditions, precise selectivity, and alignment with sustainable practices. As the development of photocatalysts, optimization of reactions, and incorporation of new technologies advance, the possibilities for novel chemical synthesis continue to grow. This rapidly developing field is poised to make significant contributions to future progress in synthetic chemistry, materials science, and other related disciplines.

1.1.4 Photodecarboxylative C–H Bond functionalization of (Hetero)Arenes

The photoredox catalysis has evolved as a sustainable and eco-friendly approach for demonstrating C–H functionalization in efficient synthetic methodologies, enabling to drive a wide range of transformations in synthetic organic chemistry.^[8-10] These synthetic strategies open new avenues by using excited (energetically or electronically) reactive intermediates, providing a complementary approach to traditional thermal pathways.^[11] Consequently, this allows the response to change through completely different mechanistic pathways.^[12] Significant efforts have been made to explore photocatalysis in the organic chemistry for the synthesis of pharmaceuticals, fine chemicals, polymers, and more.^[13]

The direct modification of heteroarene C–H bonds is of excessive interest in organic synthesis, with regioselective alkylation of heteroarene C–H bonds emerging as a crucial research area over recent decades in organic chemistry. Various groups have developed alkylation methodologies using advanced photo decarboxylative coupling methods and also some enantioselective Minisci-type photodecarboxylative reactions invented under mild conditions. Despite these advancements, these methods are subject to various limitations. While intermolecular decarboxylative cyclization reactions have been extensively studied, as

compared to intramolecular decarboxylative cyclizations remain less explored. Despite their potential for synthesizing complex cyclic structures, these reactions face significant challenges, particularly in achieving high regioselectivity and stereoselectivity. To fully harness the potential of intramolecular decarboxylative cyclizations in synthetic chemistry, further research is needed to refine the methodology.



Scheme 1.4. Decarboxylative C–H Alkylation of *N*-Heteroarenes^[24]

This includes gaining a deeper understanding of the underlying mechanistic pathways and developing new catalysts and optimized reaction conditions. Overcoming these hurdles will be key to expanding the applications of this approach in achieving target molecules.

The first photodecarboxylative C–H functionalization of heteroarenes containing nitrogen was reported by Frank Glorius in 2017 (Scheme 1.4).^[24] The alkylation of heteroarenes using aliphatic carboxylic acids mediated by visible light is a mild approach that operates efficiently at lower catalyst loading (0.5 mol%). This method demonstrates excellent tolerance toward a variety of functional groups and exhibits wide substrate compatibility.

It includes a range of moieties, such as phthalazine, pyridine, benzothiazole, isoquinoline, and several heterocyclic derivatives, which were alkylated using both cyclic and acyclic carboxylic acids (primary, secondary, and tertiary).

In their proposed mechanism, the photocatalyst (Ir-PC) is get excited from ground state to an excited state [$^*\text{Ir}^{\text{III}}$] under irradiation by blue LED light. This excited Ir^{III} complex undergoes

single-electron reduction of the persulfate anion, resulting in the formation of oxidized species Ir^{IV} , sulfate radical anion, and sulfate dianion [**D**]. Subsequently, a hydrogen atom transfer (HAT) occurs among the carboxylic acid **6** and the sulfate radical anion [**D**], leading to the decarboxylation and generation of the corresponding alkyl radical (**A**) (Figure 1.2).

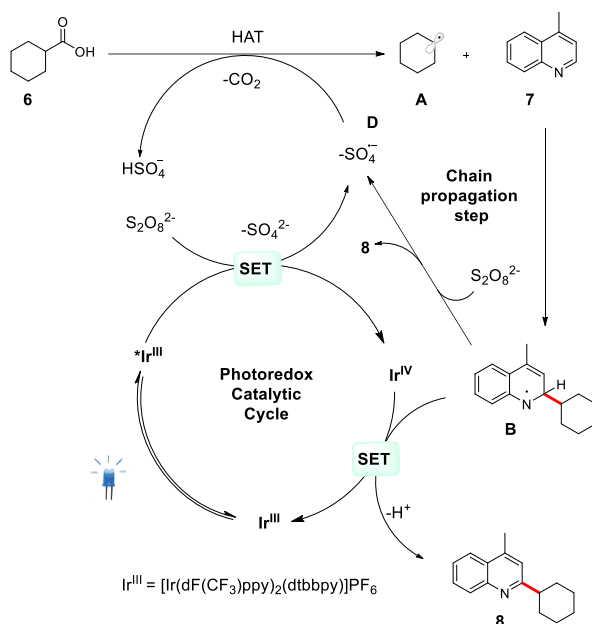
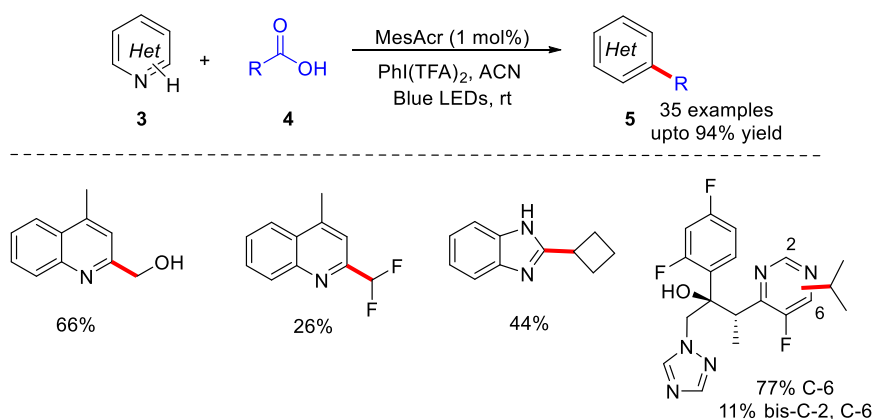


Figure 1.2. Decarboxylative Minisci Reaction of Alkyl Carboxylic Acids ^[24]

The radical species (**A**) then add to 4-methyl quinoline (**7**), forming nitrogen-centred radical intermediate (**B**). This intermediate undergoes deprotonation to furnish the anticipated product (**8**), with the revival of the Ir^{III} photocatalyst, completing the catalytic cycle. The authors proposed that the persulfate anion could act as a chain carrier in the reaction (Figure 1.2).

In 2018, Genovino, Frenette, and collaborators reported a reductive decarboxylation method using in situ-generated phenyliodine(III) diacetate (PIDA) analogs, which effectively generates radical nucleophiles for Minisci-type reactions (Scheme 1.5)^[25]. This approach utilizes the Fukuzumi organic photoredox catalyst Mes-Acr (9-mesityl-10-methyl acridinium) to start a process that is believed to occur through a chain reaction mechanism.

The reported protocol outlines a metal-free C–H bond alkylation of heteroaromatic compounds by photoredox catalysis using easily accessible carboxylic acids. The reaction is catalyzed by hypervalent iodine reagents and an organic photocatalyst, activated by blue LED light exposure. This innovative approach streamlines the process by eliminating the requirement of transition-metal catalysts, thereby enhancing sustainability and reducing potential environmental impact. The developed methodology exhibits broad tolerance for various functional groups, this makes it ideal for the late-stage modification of drugs and drug-like compounds.



Scheme 1.5 Hypervalent iodine dicarboxylates in Minisci type transformation ^[25]

In the proposed catalytic mechanism, the photoexcited catalyst (MesAcr⁺) was unable to reduce adduct of hypervalent iodine dicarboxylate because of its high ($E^*_{\text{red}} > +2.0$ V) redox potential. The exact identity of the species responsible for reducing (MesAcr⁺) is not fully determined. It is speculated that the inefficient oxidation of trace carboxylates or neutral heteroaromatic compounds may generate small quantities of MesAcr•, which could serve as the initiating species. After reduction, MesAcr• is capable of transferring an electron to adduct of hypervalent iodine (as shown in Figure 1.3), thus initiating the catalytic cycle and regenerating the MesAcr⁺ photocatalyst. The resulting hypervalent iodine radical anion, [PhI(O₂CR)₂]^{•−}, is predicted to quickly collapse, to form the alkyl radical R• (Figure 1.3).

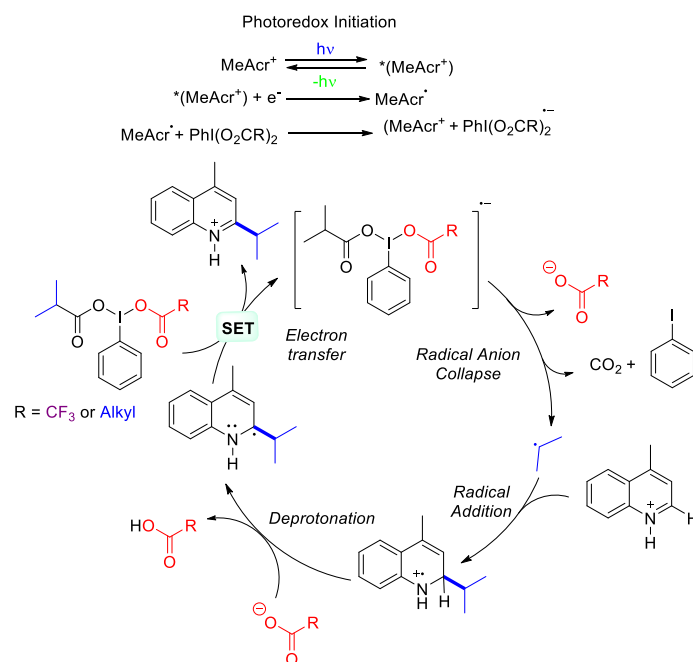
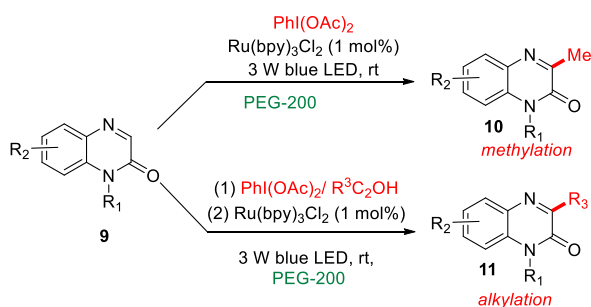


Figure 1.3. Proposed mechanism for decarboxylative alkylation^[25]

In solution, the reduction potentials of protonated lepidine and PIFA are -1.34 V and -0.527 V versus ferrocene, respectively. These values suggest a highly favorable single-electron transfer (SET) process, with a driving force of +2.05 V.

In 2019, He and his team described a decarboxylative alkylation reaction of quinoxalin-2(1H)-ones and phenyliodine(III) dicarboxylates, employing a recyclable ruthenium(II) catalyst (Scheme 1.6)^[26]. This photocatalytic reaction was conducted at room temperature using an environmentally friendly solvent. A range of 3-alkylquinoxalin-2(1H)-ones were efficiently synthesized using this ruthenium(II) catalytic system, which demonstrated the ability to be recycled up to five times without a significant loss of catalytic efficiency.



Scheme 1.6 Decarboxylative alkylation of quinoxalin-2(1H)-ones^[26]

Their anticipated reaction pathway is demonstrated in Figure 1.4. The process begins with the creation of the excited $^*\text{Ru}(\text{ppy})_3^{2+}$ species upon exposure to visible light. This is followed by a single-electron transfer (SET) from $^*\text{Ru}(\text{ppy})_3^{2+}$ to $\text{PhI}(\text{OAc})_2$ **12**, generating radical intermediate **E** and $\text{Ru}(\text{ppy})_3^{3+}$. The radical intermediate **E** then undergoes cleavage of the I–O bond, yielding an acyloxy radical that decarboxylates to produce methyl radical **F** and generate CO_2 as byproduct. Subsequently, methyl radical **F** adds to substrate **9** to form nitrogen-centred radical **G**.

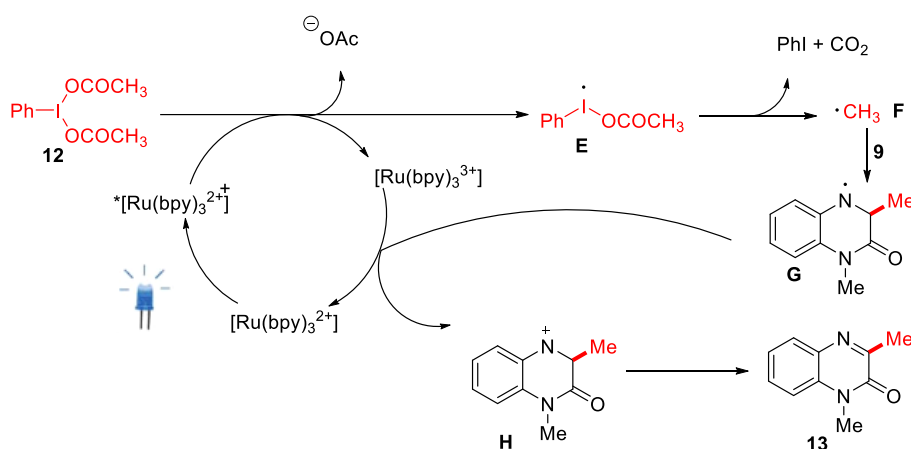
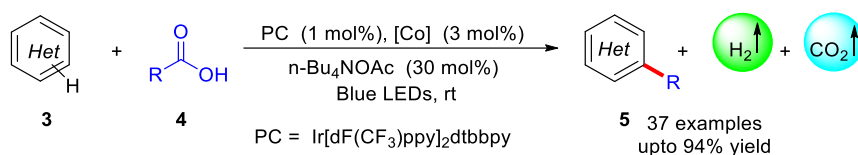


Figure 1.4. Proposed mechanism for decarboxylative alkylation^[26]

The nitrogen radical **G** is get oxidized by $\text{Ru}(\text{ppy})_3^{3+}$, resulting in the generation of the cation **H**. Subsequently, a β -hydrogen is abstracted from **H** by a carboxylate anion, to provide the product **13**.

Li and co-workers established a visible light-mediated alkylation of heteroarenes under mild reaction conditions in 2019 via decarboxylative reaction (Scheme 1.7).^[27] This method represents a noteworthy advance in photoredox catalysis, enabling the efficient functionalization of heteroaromatic compounds through a decarboxylative process, which uses carboxylic acids as alkyl radical precursors.

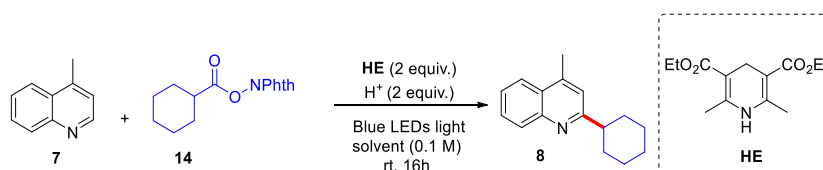
This transformation proceeds without the use of any external oxidant and requires only 0.3 equivalents of base, making the reaction highly efficient.



Scheme 1.7 Decarboxylative alkylation of heteroarenes^[27]

The process benefits from the elimination of hydrogen gas (H₂) and carbon dioxide (CO₂) as by-products, which is nontoxic by-product. This elimination of H₂ and CO₂ simplifies the reaction workup and increases the atom economy of the transformation, further enhancing its sustainability.

In 2022, Chan and co-workers reported a decarboxylative heteroarene alkylation using *N*-(Acyloxy) phthalimide, facilitated by Hantzsch ester in presence of blue LED light irradiation (Scheme 1.8).^[28] This method provides an efficient and mild approach for introducing alkyl groups into *N*-heteroaromatic compounds, utilizing visible light photoredox catalysis. The metal-free protocol demonstrated broad synthetic utility by enabling the alkylation of variously substituted *N*-hydroxyphthalimide (NHPI) esters, to provide alkylated *N*-heterocyclic products. The reaction conditions are mild, demonstrate excellent functional group tolerance, and do not require the additional carboxylic acid.

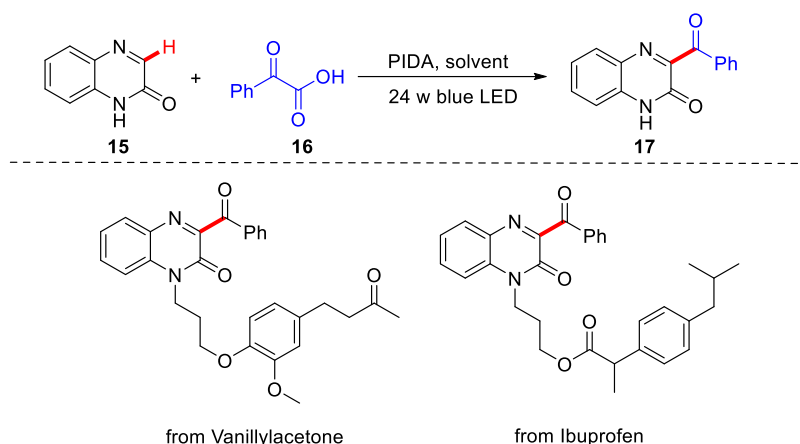


Scheme 1.8 Organophotoredox catalyzed decarboxylative alkylation of heteroarene^[28]

Consequently, this approach is suitable for drug motif and compounds with delicate functional groups, facilitating late-stage functionalization that is particularly valuable in medicinal chemistry.

Xuan and colleagues reported a decarboxylative acetylation reaction that involved C₃-H acylation of quinoxalin-2(1*H*)-ones promoted by the visible light in an aqueous environment.

Notably, this reaction proceeded without the need for a photoredox catalyst (Scheme 1.9).^[29]



Scheme 1.9 Visible-light mediated decarboxylative acylation reaction^[29]

This approach offered moderate reaction conditions, including the use of water as the solvent, no need for a photoredox catalyst, and visible light irradiation. It also demonstrated good functional group endurance and enabled late-stage modification pharmaceuticals.

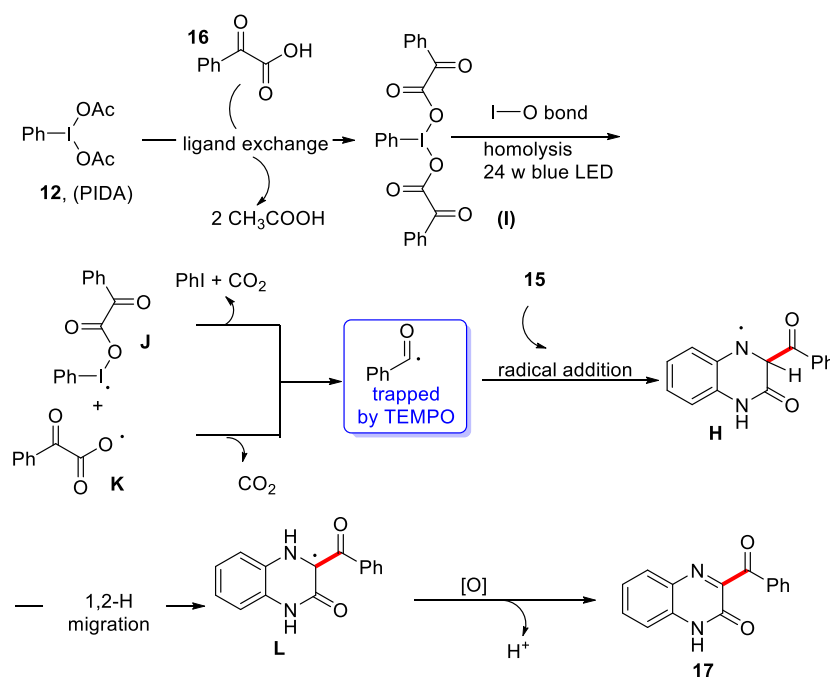
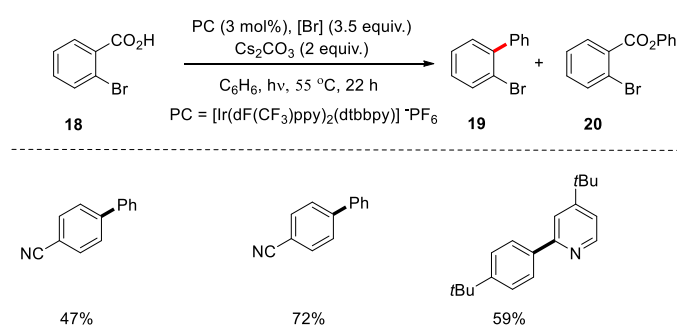


Figure 1.5. Proposed mechanism for decarboxylative acetylation^[29]

A plausible reaction mechanism was proposed in Figure 1.5. The process initiates with hypervalent iodine(III) (I) formation through a ligand interchange between 2-oxo-2-phenylacetic acid **16** and PIDA **12**. Upon exposure to visible light, (I) undergoes I–O bond

homolysis, generating the iodine-centered radical **J** and the oxygen-centered radical **K**. Fragmentation of either **J** or **K** generate the acyl radical as verified through radical trapping experiment. The acyl radical then adds to the quinoxalin-2(1H)-one **15**, resulting in nitrogen-centered radical species **H**. This intermediate undergoes a 1,2-H migration to produce the carbon-centered radical **L**. Finally, oxidative deprotonation of **L** yields the desired 3-acylquinoxalin-2(1H)-one product **17**.

In 2017, Glorius and co-worker introduced a decarboxylative arylation reaction that utilizes carboxylic acids. This innovative method facilitates the conversion of carboxylic acids directly into arylated products by effectively removing carbon dioxide (Scheme 1.10).^[30]



Scheme 1.10 Decarboxylative arylation of carboxylic acid by using Ir-photocatalysis^[30]

Significantly, they presented the first instance of generating aryl radicals via visible light-driven decarboxylation of aryl carboxylic acids, employing photoredox catalysis. The suggested mechanism entails the generation of an acyl hypobromite (**O**) in-situ, which inhibits non-productive hydrogen atom abstraction and stabilizes the intermediate aryloxy radical. This stabilization supports the decarboxylation reaction, allowing it to proceed under mild conditions.

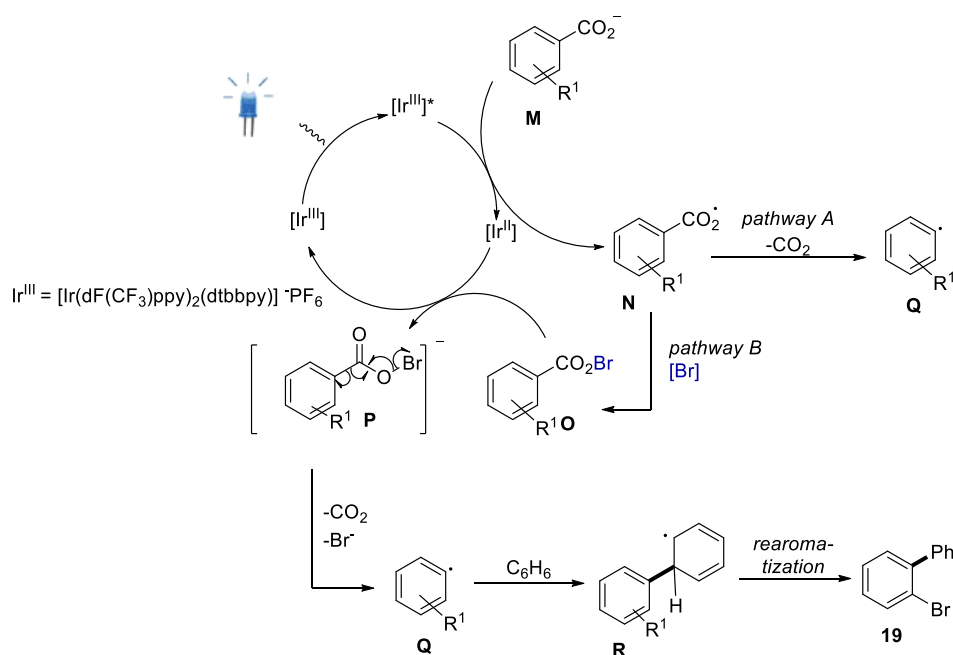


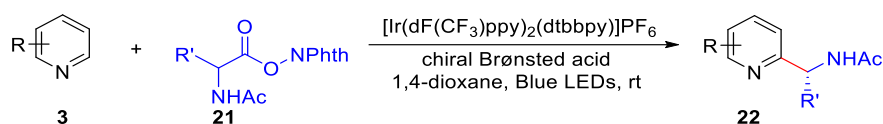
Figure 1.6. Proposed mechanism for decarboxylative arylation^[30]

To gain a better understanding of the reaction mechanism (Figure 1.6), the kinetics of the excited photocatalyst (PC) were investigated using Stern–Volmer luminescence quenching. The results suggest that the excited PC (Ir(III)* / Ir(II)) undergoes reductive quenching by the benzoate anion (**M**), leading to the formation of the aroyloxy radical **N** (Scheme 1.6). Two possible pathways for the decarboxylation of **N** to generate the aryl radical have been proposed. Pathway A suggests direct decarboxylation of **N**, which is thermodynamically favorable but unlikely under the given experimental conditions. Pathway B, on the other hand, proposes that **N** undergoes bromination to form the hypobromite intermediate **O**, which helps to prevent unproductive interactions of **N** with the solvent. Based on stoichiometric studies with compound **O**, it is hypothesized that Ir(II), with its sufficiently negative reduction potential ($E_{1/2}^{\text{III/II}} = 1.37 \text{ V vs. SCE}$), reduces **O** to generate the radical anion **P**. This anion then undergoes decarboxylation to form the aryl radical (**Q**). Theoretical studies suggest that the reduction of **P** to the radical anion leads to a concerted bond dissociation, where both the C–C and O–Br bonds break simultaneously, releasing CO₂, a bromide ion, and the phenyl radical. The resulting aryl radical (**Q**), generated through either pathway, then

reacts with a (hetero)arene, forming the cyclohexadienyl radical **R**. This intermediate is oxidized to the aryl cation and subsequently undergoes deprotonation, yielding the final biaryl product **19**.

1.1.5 Enantioselective Minisci-type reaction

In 2018, Phipps and co-workers described an asymmetric form of the Minisci-type reaction, utilizing a chiral Brønsted acid in combination with iridium photocatalysis (Scheme 1.11).^[13] This unorthodox work allowed for the enantioselective functionalization of heteroarenes through the classic Minisci radical addition pathway. The use of a chiral Brønsted acid was key to inducing asymmetry, while iridium photocatalysis enabled the emergence of reactive radical intermediates under mild conditions.



Scheme 1.11 Enantioselective Minisci type C–H functionalization of heteroarenes^[13]

This development expanded the scope of Minisci reactions, making it possible to form C–C bonds with high enantioselectivity, which is highly valuable for the synthesis of complex, chiral bioactive molecules (Scheme 1.11). In the same year (2018),^[31] Jiang and co-workers also developed an alternative approach to achieving an enantioselective Minisci-type reaction. Their protocol utilized a dicyanopyrazine-derived chromophore (DPZ) photosensitizer along with a chiral phosphoric acid (CPA) as the enantioselective reagent. Under visible light irradiation, this system enabled the selective functionalization of heteroarenes with high enantioselectivity, marking a significant advancement in photocatalytic asymmetric radical reactions.

In the mechanism proposed by Phipps and his team, they hypothesized that hydrogen bonding between chiral phosphates, the nucleophilic radical [T], and the pyridinium

counterion facilitate the formation of species [U]. The radical then adds to [U], generating the aminium ion intermediate [V], which deprotonates to form the neutral radical [W]. This radical [W] is later oxidized via a single-electron transfer, resulting in the formation of the desired product **22** (Figure 1.7).^[13]

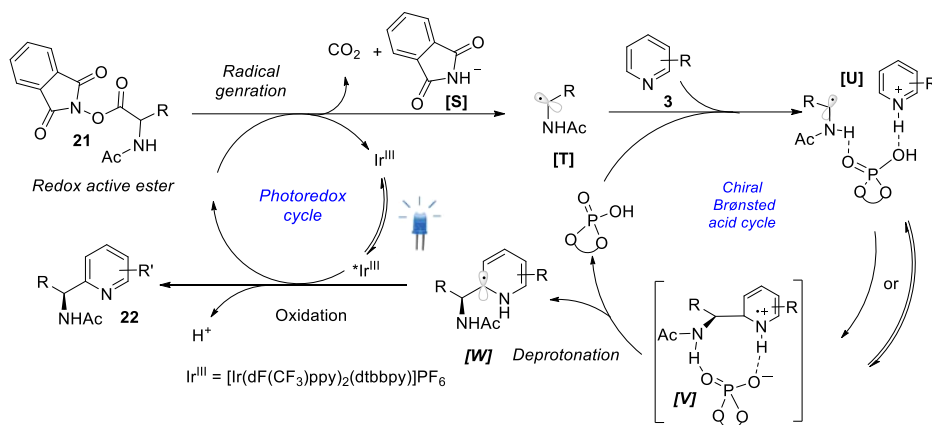
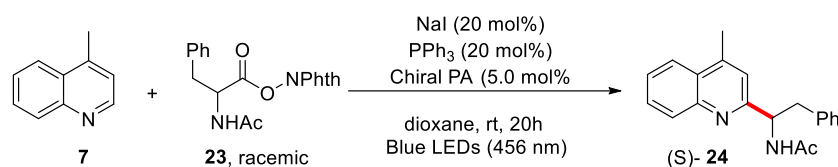


Figure 1.7. Proposed mechanism for decarboxylative enantioselective alkylation

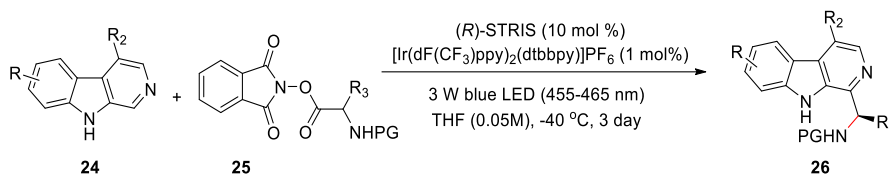
In 2019, Fu group presented a sophisticated method for conducting an enantioselective Minisci-type reaction under mild conditions, enabling the introduction of alkyl functionality into a quinolone structure (Scheme 1.12).^[32] This breakthrough expanded the toolbox for enantioselective radical chemistry and provided a valuable method for functionalizing quinolone derivatives with high stereocontrol.



Scheme 1.12 Decarboxylative alkylation mediated by triphenylphosphine and sodium iodide^[32]

The combination of sodium iodide and triphenylphosphine, activated by 456nm blue light-emitting diodes, effectively catalyzed the alkylation of 4-methylquinoline via decarboxylative coupling with redox-active esters, eliminating the requirement for transition metals.

In 2023, Wang and his team published a study on the enantioselective C–H functionalization of β -carboline, employing a Minisci-type radical mechanism. This process was facilitated under a cooperative catalytic system that combined chiral phosphoric acid and photo-redox catalysis (Scheme 1.13).^[33]



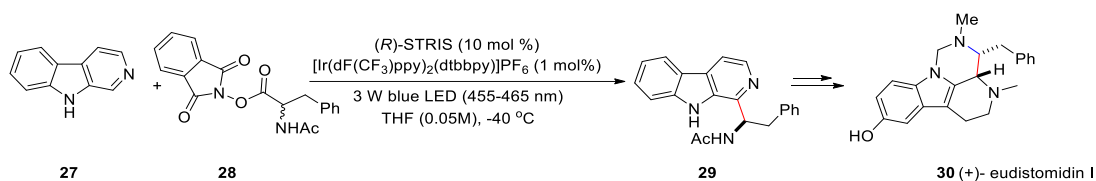
Scheme 1.13 Enantioselective Minisci reaction of β -carboline.^[33]

The aminoalkylated β -carboline has been successfully synthesized with excellent enantioselectivity, using readily available alanine-derived redox-active esters and β -carboline as starting materials. This approach provides a straightforward and efficient means of producing enantioenriched β -carboline, which are essential building blocks in many natural products and bioactive compounds. Furthermore, the method has shown outstanding efficiency in the asymmetric total synthesis of marine alkaloids, underscoring its practical value in synthetic chemistry.

1.1.6 Decarboxylative C–H functionalization of nitrogen-containing heteroarenes in natural product and drug synthesis

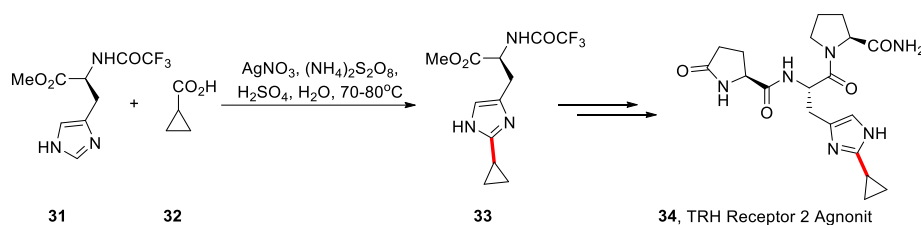
In the past decades, functionalization of C–H bond has materialized as a highly investigated area in organic chemistry. Numerous studies have been published in scientific journals focusing on methodological advancements that employ both transition metal and photoredox catalysis. Additionally, in recent years, this C–H functionalization approach has been effectively applied in the construction of bioactive natural products and pharmaceutical. In 2023, Wang and colleagues presented a sophisticated method to synthesize (+)-eudistomiin I by employing an Ir-photocatalyzed system along with a chiral phosphoric acid cooperative

catalytic approach. In this approach, decarboxylative C–H functionalization of β -carboline is a key step (Scheme 1.14).^[33]



Scheme 1.14. Application decarboxylative C–H functionalization in natural product^[33]

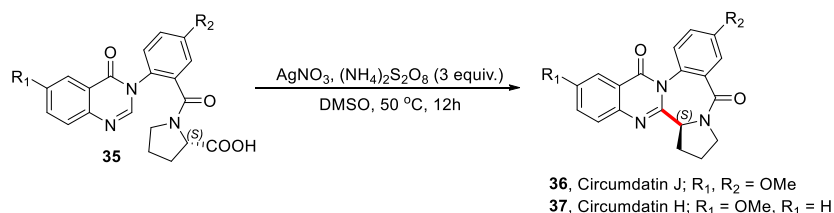
Jain and co-workers in 2008 reported silver catalysed decarboxylative C–H functionalization of heteroarene in the total synthesis of TRH Receptor 2 Agnonit (Scheme 1.15).^[34]



Scheme 1.15. Decarboxylative C–H functionalization in the synthesis of Thyrotropin-Releasing Hormone (TRH)^[34]

In 2018, Our group reported silver catalyzed intramolecular decarboxylative cyclization to access circumdatin class of natural products (Scheme 1.16).^[35]

Furthermore, existing literature on the construction of natural products and pharmaceuticals through decarboxylative C–H bond functionalization highlights the significance of this methodology.



Scheme 1.16. Decarboxylative Intramolecular Asymmetric Radical Cyclization^[35]

We believe that advancing new methodologies with photoredox catalysis for decarboxylative Carbon–Carbon bond formation and applying them in the total synthesis of natural products and drug molecules would greatly interest organic and medicinal chemists.

Section 1.2 Decarboxylative C–heteroatom bond forming reactions

Decarboxylative C–heteroatom bond formation is a crucial reaction in synthetic organic chemistry, playing an important role in the creation of bioactive compounds and the development of pharmaceutical agents. The decarboxylative C–heteroatom bond formation using promptly available carboxylic acids are highly interesting approaches for construction of C–C and C–heteroatom bond formation. The organic compounds containing C–O/C–N/C–S bond formation have several applications in pharmaceutical, agrochemical and material science.^[36] In this reaction, the C–heteroatom bond is established as the carboxylate group is eliminated as gaseous carbon dioxide (CO₂) during the decarboxylation step. This approach offers significant advantages, mostly because carboxylic acids are abundant, inexpensive, and widely available as feedstock chemicals. These acids are often synthesized through pathways orthogonal to traditional starting materials like organic halides, making them highly versatile intermediates in organic synthesis. Additionally, carboxylic acids are typically stable, easy to handle, and can be sourced from both renewable and non-renewable resources, adding to the sustainability and practicality of these methods. The decarboxylation strategy allows for the selective formation of C–heteroatom bonds under mild conditions, making it attractive for use in the synthesis of pharmaceuticals, natural products, and other complex molecules. This transformation can often be carried out without the need for transition metals, further enhancing its appeal in green chemistry applications. Decarboxylative couplings for the formation of C–C or C–heteroatom bonds have been a well-established approach for many years. Recently, advancements in this reaction type have expanded its utility in organic synthesis. The conventional mechanisms by which carboxylic acids and their derivatives enable decarboxylative C–heteroatom bond formation are illustrated in Figure 1.8.

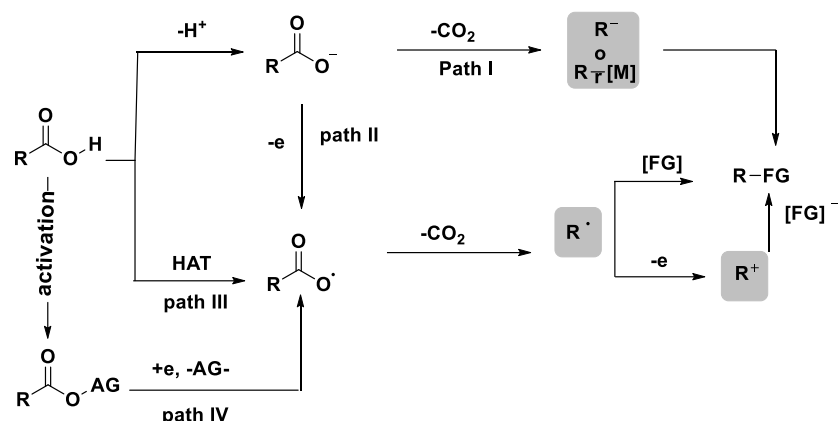


Figure 1.8 Mechanistic pathway for decarboxylative C–heteroatom bond formation^[36]

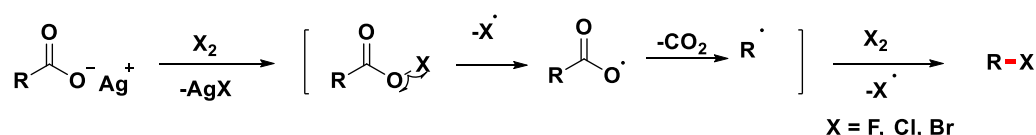
In Path I, the carboxylic acid undergoes decarboxylation, generating a carbanion. This carbanion is stabilized due to coordination with a metal center, which aids in facilitating the subsequent reaction steps (Path I). These intermediates are capable of reacting with several electrophiles containing heteroatoms or with nucleophiles featuring heteroatoms, often in the presence of an oxidizing agent.

Alternatively, the carboxylic acid may undergo homolytic cleavage via single-electron oxidation (Path II) or through HAT mechanism (Path III). This results in the rapid release of carbon dioxide (CO_2) from the carboxylate, generating a carbon-centered radical intermediate. This carbon-centered radical intermediate subsequently reacts with electrophiles containing heteroatoms or with nucleophiles that include heteroatoms, providing C–heteroatom products. The carboxylate radical can be generated through photochemical cleavage or decarboxylative single-electron reduction of carboxylic acid derivatives, like Barton esters (Path IV). The carbon radicals produced from these three different pathways can interact directly with heteroatom reagents, potentially initiating radical chain reactions. Alternatively, these radicals may be oxidized to form carbocations, which can subsequently react with heteroatom nucleophiles.

1.2.1 Classical decarboxylative C–heteroatom (O, N, S) bond-forming reactions

Organic compounds containing carbon-heteroatom bonds play a crucial role in various fields, including natural product synthesis, late-stage functionalization, pharmaceuticals, agrochemicals, and material science.^[15]

The history of decarboxylative C–heteroatom bond formation dates back to 1861,^[37] when Alexander Borodin first invented this transformation. In this reaction, silver acetate is treated with bromine in chloroform as solvent. Following this work, Cläre Hunsdiecker in the 1930s, and Heinz Hunsdiecker developed widely appropriate decarboxylative halogenation methods (scheme 1.17).^[38]



Scheme 1.17 The classical Hunsdiecker-Borodin reaction^[38]

Over the subsequent decades, this area of chemistry evolved significantly, with various methods being developed to achieve decarboxylative C–heteroatom bond formation. Early approaches involved harsh conditions, but advancements in catalysis, especially transition metal catalysis and photoredox catalysis, have enabled decarboxylation under much milder and more controlled conditions. The Kochi modification of the Hunsdiecker-Borodin reaction for aliphatic carboxylic acids involves reacting iodine and lithium chloride or bromide with Pb(IV) acetate.^[39] This version, which likely proceeds via alkyl radical intermediates formed by the single-electron oxidation of the carboxylate anion by Pb(IV), is especially efficient for chlorination and works well with secondary and tertiary carboxylic acids. The Hunsdiecker-Borodin-type decarboxylation forms the foundational concept for most modern C–I, C–Br, and C–Cl bond-forming reactions.^[40] This method can be improved for other C–heteroatom

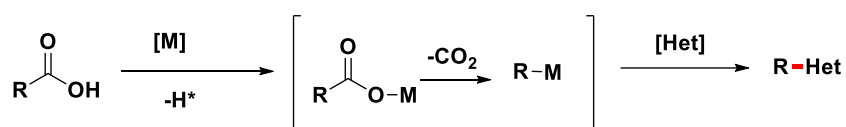


In addition to these traditional concepts of decarboxylative C–heteroatom bond formation in recent years, the development of metal-free and photocatalytic decarboxylation has further expanded the scope of this reaction, allowing for efficient and selective formation of C–heteroatom bonds in complex organic molecules. This reaction has become particularly important in the synthesis of pharmaceuticals, natural products, and fine chemicals, thanks to its versatility and the broad availability of carboxylic acid starting materials.

The Barton decarboxylation is a classical reaction involving radical decarboxylation, where a carboxylic acid is transformed into a thiohydroximate ester, commonly known as a Barton ester. It was first established in 1983.^[41] The thiohydroximate ester undergoes homolytic bond cleavage of the N–O linkage when exposed to photochemical or thermal conditions. The carboxyl radical expels carbon dioxide (CO₂) rapidly with formation of carbon centred radical. The carbon-centered radical can be trapped by polyhalomethanes, disulfides, or diselenides, forming of a new C–heteroatom bond (Scheme 1.19).



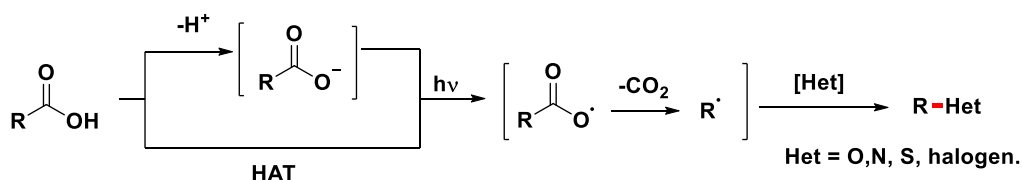
Nilsson and colleagues^[42] showed that copper 2-nitrobenzene carboxylate on pyrolysis generates an aryl-Cu species, which was verified by its reaction with a carbon electrophile. Building on this work, Gooßen et al.^[43] exploited decarboxylation processes within the coordination environment of Cu or Ag catalysts to develop a new strategy for redox-neutral, decarboxylative C–C bond formation, using bimetallic Cu (or Ag)/Pd catalytic systems. Similarly, Myers and colleagues^[44] utilized Pd/Ag catalyst systems for couplings of electron-rich benzoic acids in Heck-type olefination reactions via oxidative decarboxylation.



Scheme 1.20 Heterofunctionalization based on metal-mediated ionic decarboxylation^[44]

Recently, various C–heteroatom bond-formation reactions have been developed that leverage metal-mediated decarboxylation processes. In these reactions, the intermediate aryl metal species reacts with either heteroatom nucleophiles or electrophiles that are within the transition metal's coordination sphere. (Scheme 1.20).

Davidson^[45] and Libman^[46] in the early 1970s, found that carboxyl radicals could be generated from carboxylic acids directly when exposed to a photosensitizer, such as benzophenone, quinones, or 1-cyanonaphthalene, eliminating the need to first convert the acids into activated derivatives (Scheme 1.21).



Scheme 1.21 Photodecarboxylative heterofunctionalization of carboxylic acids^[45]

This process might be proceeding through either a single-electron oxidation or hydrogen atom transfer (HAT) mechanism, resulting in the formation of alkane products via

decarboxylative reduction. Early techniques used ultraviolet light and photosensitizer in stoichiometric amount, but these shortcomings have been addressed by utilizing visible light, such as blue light along with more efficient photosensitizers, which were developed originally for decarboxylative C–heteroatom bond formation. Suitable heteroatom reagents, including O, N, S and halogens, enabled the successful creation of C–heteroatom bonds.

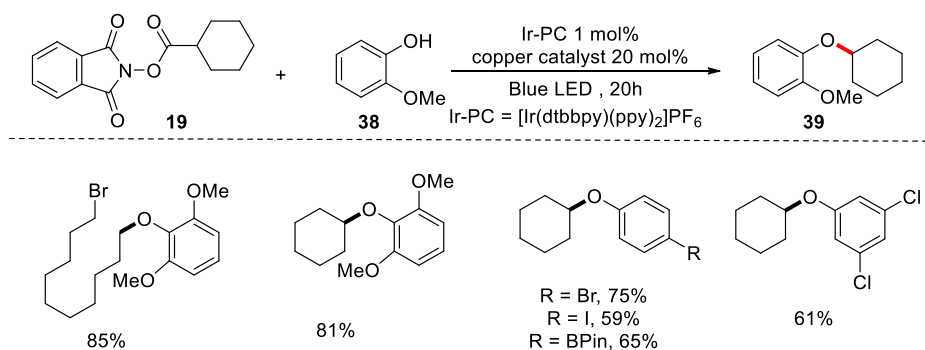
Researchers are actively striving to improve the sustainability of these processes by developing cost-effective photocatalysts that avoid the precious metals (Ir, Ru, and Rh), while also fine-tuning reaction conditions. Moreover, the creation of new, more efficient photocatalysts has the potential to broaden the scope of photochemical decarboxylation in both academic research and industrial applications.

1.2.2 Photodecarboxylative C–heteroatom (O, N, S) bond forming reactions

The C–heteroatom bond formation is a crucial reaction type in organic transformation. This process is typically accomplished through the nucleophilic attack of the heteroatom on the leaving group. An important alternative to this process is the decarboxylative coupling reaction, wherein the C–C bond of the carboxylic group is cleaved, leading to a C–heteroatom bond in its place.

In 2018, Hu and co-workers reported a novel decarboxylative C(sp³)–O bond forming reaction using tandem photoredox and copper catalysis using blue LED light source (Scheme 1.22).^[47] The reaction is effective with a wide variety of aliphatic NHPI compounds but is restricted to only aromatic alcohols. The process is initiated under visible light irradiation by a photoredox catalyst, which triggers the single-electron transfer (SET) from the catalyst to the redox-active ester, leading to the loss of carbon dioxide and the formation of the corresponding alkyl radical.

This approach enables efficient formation of C(sp³)–O bonds through cross-coupling via a copper-catalyzed reaction with oxygen-based nucleophiles.



Scheme 1.22 Decarboxylative sp^3C -O cross coupling^[47]

It excludes the necessity for pre-functionalized substrates, expands the scope of alkylation reactions, and offers broad substrate tolerance, making it valuable for synthesizing diverse oxygen-containing molecules.

This decarboxylative approach presents a more sustainable alternative to traditional cross-coupling methods and demonstrates the potential of tandem catalytic processes in modern organic synthesis. First the excited $^*Ir^{III}$ complex ($E_{1/2} [^*Ir^{III}/Ir^{II}] = +0.66$ vs. SCE in MeCN) interacts with the CuI complex **X**, leading to the formation of the copper(II) species **Z** (see Figure 1.9). A key role in this process is played by Et_3N , which acts as a base. The NHPI ester, with a reduction potential ($E_{1/2}$) lower than -1.28 vs. SCE in MeCN, is reduced by the newly generated Ir^{II} species ($E_{1/2} [Ir^{II}/Ir^{III}] = -1.51$ vs. SCE in MeCN). This reduction regenerates the ground-state photocatalyst and produces a carboxyl radical, which then fragments to form an alkyl radical. The alkyl radical is subsequently captured by the Cu^{II} species **Z**, coordinated with an aryloxy from the phenolic substrate, forming a Cu^{III} alkyl aryloxy intermediate **Y**. Finally, C–O reductive elimination occurs, producing the coupling product alkyl aryl ether and regenerating the Cu^I catalyst **X** (Figure 9).

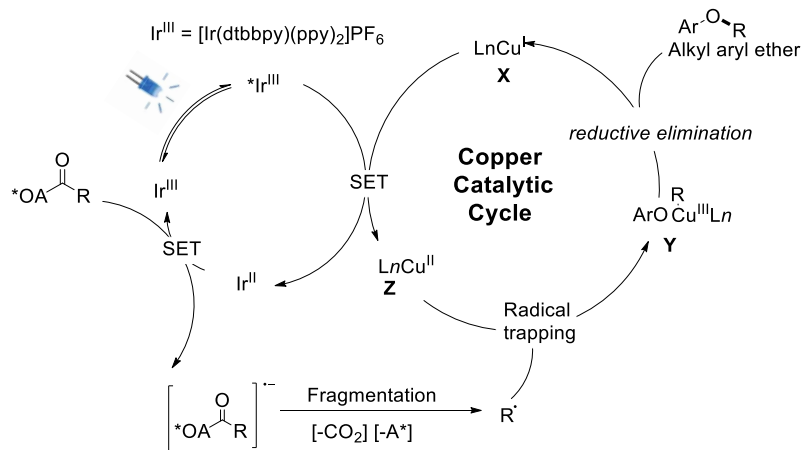
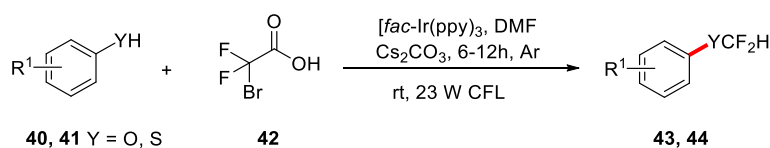


Figure 1.9 Proposed catalytic cycle for decarboxylative C(sp^3)–O coupling^[47]

In 2017, Fu and colleagues reported a decarboxylative difluoromethylation of thiophenols and phenols using difluorobromoacetic acid under visible-light-mediated photoredox conditions (Scheme 1.23).^[48] In this approach, difluorobromoacetic acid acts as a source of the difluoromethyl radical, which is generated via a photoredox-catalyzed single-electron transfer (SET) process. Following decarboxylation, the difluoromethyl radical reacts with phenols or thiophenols, to provide difluoromethylated products. The reaction proceeds under visible-light photocatalysis to generate difluorocarbene, which is subsequently trapped by various phenols and thiophenols. This method achieved the synthesis of target products in good yields, showcasing compatibility with a wide range of reactive functional groups.



Scheme 1.23 Difluoromethylation of phenols and thiophenols with difluorobromoacetic acid^[48]

The mechanism of visible-light photoredox difluoromethylation of phenols (**40**) and thiophenols (**41**) involves the reductive dehalogenation of $\text{BrCF}_2\text{COOCs}$, which has a reduction potential of $E_{1/2 \text{ red}} = -1.29 \text{ V vs SCE}$. This allows fac-Ir(ppy)_3 to act as an electron donor, capable of reducing **AA** from its excited state ($E_{1/2 \text{ IV/III}} = -1.73 \text{ V vs SCE}$). The

proposed mechanism, illustrated in Figure 1.10, begins with the treatment of compound **42** with Cs_2CO_3 , leading to the formation of carboxylate **AA** and CsHCO_3 . Similarly, when **40** or **41** reacts with Cs_2CO_3 , it generates products **40'** or **41'** along with CsHCO_3 . The photocatalyst Ir(III) is excited to its excited state [Ir(III)] upon visible light irradiation. A single electron transfer (SET) from the excited [Ir(III)] to **AA** generates Ir(IV) and a carbon-centered radical (**AB**), while releasing Br^- . A subsequent SET from the carboxylate anion in (**AB**) to Ir(IV) regenerates the photocatalyst Ir(III), releasing difluorocarbene (**AC**), CO_2 , and Cs^+ (Figure 1.10). The reaction of difluorocarbene (**AC**) with **40'** or **41'** forms products **43'** or **44'**. Finally, treating **43'** or **44'** with CsHCO_3 yields the expected difluoromethylation products **43** or **44**.

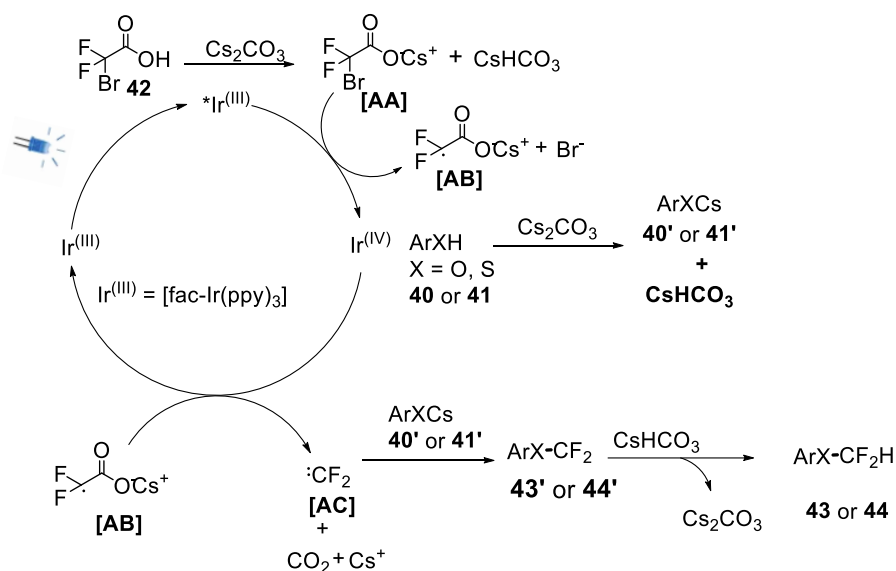
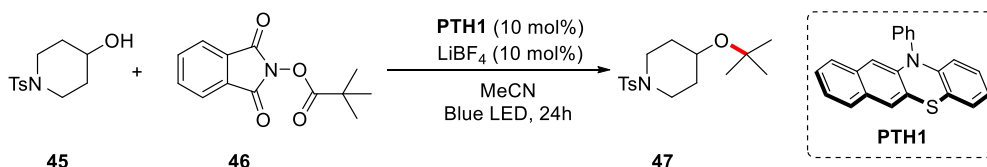


Figure 1.10. Plausible Mechanism on the Visible-Light Photoredox Difluoromethylation^[48]

In 2020, Ohmiya and co-workers reported a decarboxylative $\text{C}(\text{sp}^3)\text{--O}$ bond formation using visible light-mediated organosulfide catalysis (Scheme 1.24).^[49] This method involves the generation of alkyl radicals from carboxylic acid derivatives via decarboxylation, facilitated by an organosulfide catalyst under visible light irradiation. The alkyl radicals formed in this process subsequently undergo cross-coupling with oxygen-based nucleophiles, resulting in

the formation of C(sp³)–O bonds. The decarboxylative coupling of simple aliphatic alcohols, amides, or thiols with secondary or tertiary alkyl carboxylic acid based redox-active esters allows the formation of C(sp³)–X–C(sp³) fragments.



Scheme 1.24 Organophotoredox-Catalyzed Decarboxylative C(sp³)–O Bond Formation^[49]

This innovative approach offers a mild and efficient alternative to traditional methods, avoiding the use of transition metals or harsh reaction conditions. The visible-light activation and organosulfide catalysis provide a sustainable and selective strategy for constructing alkyl-oxygen linkages, expanding the toolbox for radical-mediated bond formations in synthetic organic chemistry.

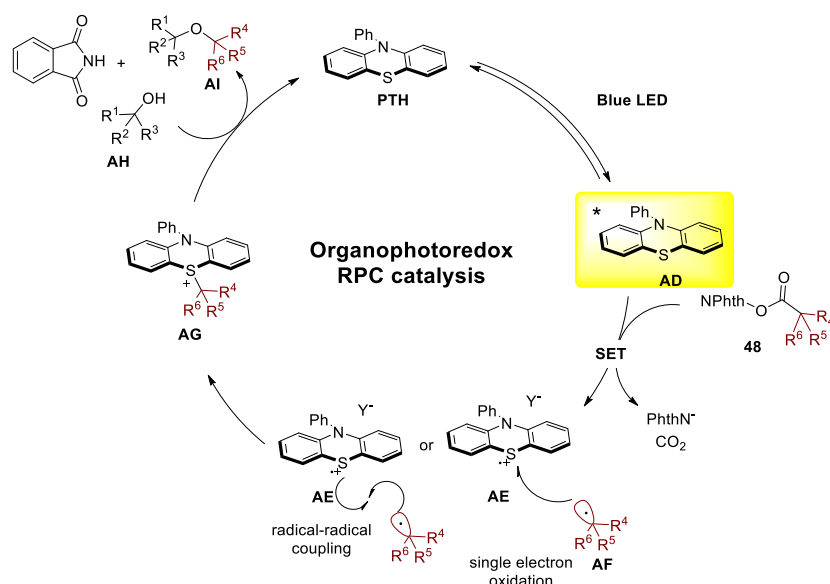
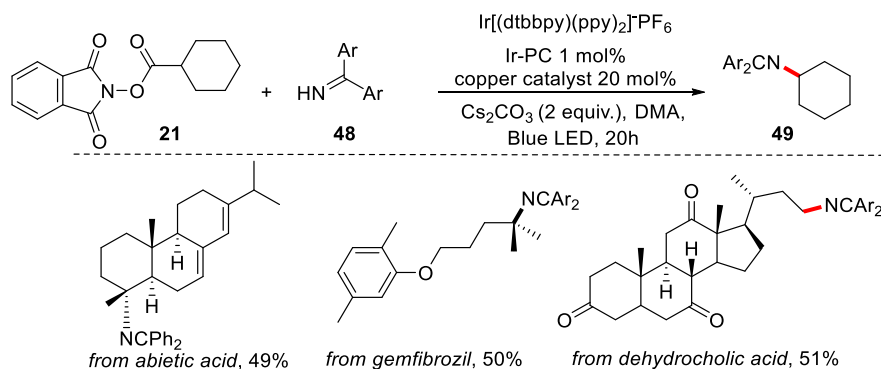


Figure 1.11. Proposed catalytic cycle^[49]

This method successfully produced a various bulky dialkyl ethers in good to moderate yields. Nevertheless, the system demonstrated some limitations in terms of the scope of carboxylates, as only certain stabilized secondary and tertiary NHPI esters were efficiently

converted. Remarkably, the addition of lithium tetrafluoroborate (LiBF_4) in catalytic amount was found to be crucial for the reaction. The catalytic cycle starts with the excitation of phenothiazine upon LED light irradiation, leading to the formation of the highly reducing excited state (**AD**). The excited catalyst (**AD**) then undergoes a SET to the redox-active ester **48**, producing the radical cation form of the catalyst (**AE**) and an alkyl radical (**AF**). The interaction between (**AE**) and (**AF**) can occur through single electron oxidation of (**AF**) by (**AE**) (right bottom) or via radical–radical coupling (left bottom), resulting in the formation of an alkylsulfonium intermediate (**AG**). Finally, the reaction of the carbocation released from (**AG**) with an alcohol nucleophile (**AH**) furnish the product (**AI**), followed by deprotonation and regeneration of the organosulfide catalyst (Figure 1.11).

In 2018, Hu and co-workers reported a sequential photoredox and copper-catalyzed strategy to achieve coupling reactions of alkyl redox-active esters (Scheme 1.25).^[50] This approach enables the generation of alkyl radicals via photoredox catalysis, followed by copper-mediated cross-coupling with nucleophiles, providing an efficient method for constructing $\text{C}(\text{sp}^3)$ -heteroatom bonds. The dual-catalyst system offers a mild and versatile platform for the decarboxylative functionalization of redox-active esters, significantly expanding the scope of alkylation reactions in synthetic chemistry. This method allows the transfer of primary, secondary, and tertiary alkyl groups, and tolerates a variety of functional groups.



Scheme 1.25 Intramolecular C–N coupling of alkyl NHPI esters^[50]

It provides an efficient approach for the functionalization of natural products and drug molecules, streamlining the synthesis of pharmaceuticals.

The process begins with the coordination of low-valent copper (**AJ**) catalyst to benzophenone imines, to generate the copper(I) amido species (**AK**) via deprotonation (Figure 1.12). Simultaneously, the photocatalyst (PC) is excited, generating the complex (PC*), which reduces the NHPI ester through a SET, leading to alkyl radical formation upon fragmentation. This alkyl radical is then captured by (**AK**), resulting in the intermediate (**AL**). The formation of high-valent metal alkyl amido complex (**AM**) and regeneration of the photocatalyst takes place via oxidation of (**AL**) by the oxidized photocatalyst (PC⁺). The amido complex (**AM**) undergoes reductive elimination, yielding the desired coupling product and regenerating the photocatalyst, thus completing catalytic cycle of the copper. In this mechanism, photoredox catalyst plays two essential roles: generating an alkyl radical from its NHPI ester and enabling the one-electron oxidation of the copper alkyl amido complex (transforming **AL** to **AM** via SET). The first step is crucial, as the activation of alkyl NHPI esters under thermal conditions using metal amido species have not been reported, while the second step helps overcome the challenge of C(sp³)–N reductive elimination.

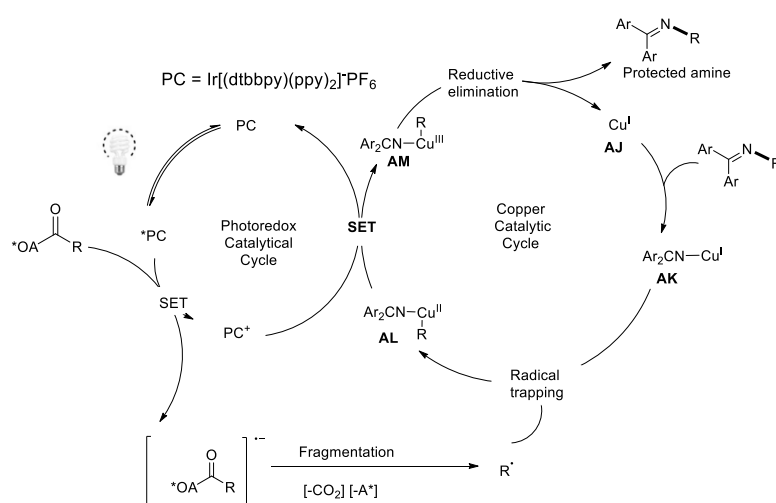
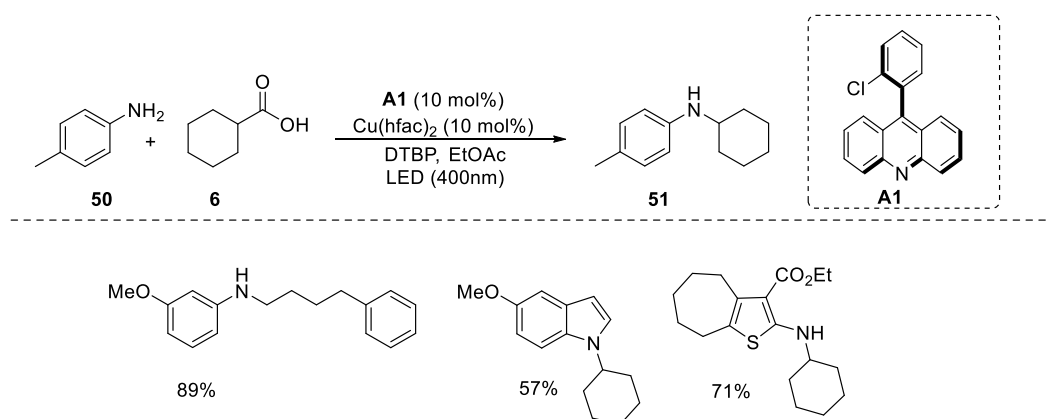


Figure 1.12 proposed catalytic cycle^[50]

In 2020, Larionov and co-worker reported selective C–N bond forming reaction from alkyl carboxylic acid and aromatic amine (Scheme 1.26).^[51] This reaction, facilitated by visible-light-driven acridine catalysis in a decarboxylation process, enables the synthesis of N-alkylated anilines, and nitrogen heterocycles.

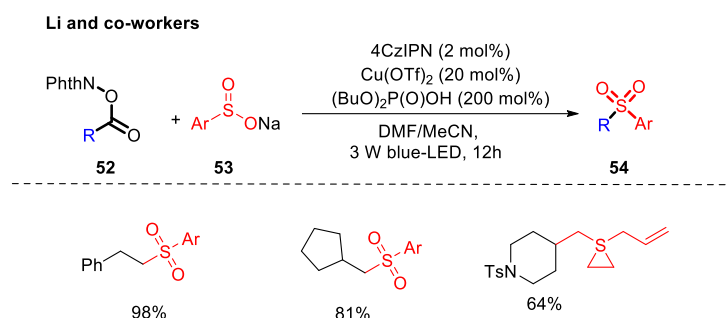


Scheme 1.26 Acridine photocatalyzed decarboxylative N-alkylation^[51]

Further illustrations, such as double alkylation, tandem ring formation, incorporation of metabolically stable deuterated methyl groups etc. highlight the versatility of the direct decarboxylative alkylation (DDA) reaction.

Li and colleagues introduced a decarboxylative sulfonation reaction utilizing organophotoredox and copper catalysis (Scheme 1.27^[52]). This redox-neutral approach demonstrates a wide substrate scope and excellent functional group tolerance, making it suitable for late-stage modifications of bioactive natural products and pharmaceuticals. The proposed mechanism suggests that sulfonyl groups are transferred from the Cu(II)–SO₂R complex to alkyl radicals.

Decarboxylative C-heteroatom bond-forming reactions are valuable in natural product and drug synthesis due to their ability to efficiently introduce diverse heteroatoms (such as oxygen, nitrogen, and sulfur) into complex molecules. These reactions offer simplified synthetic routes, reducing the synthetic steps with better overall yields.

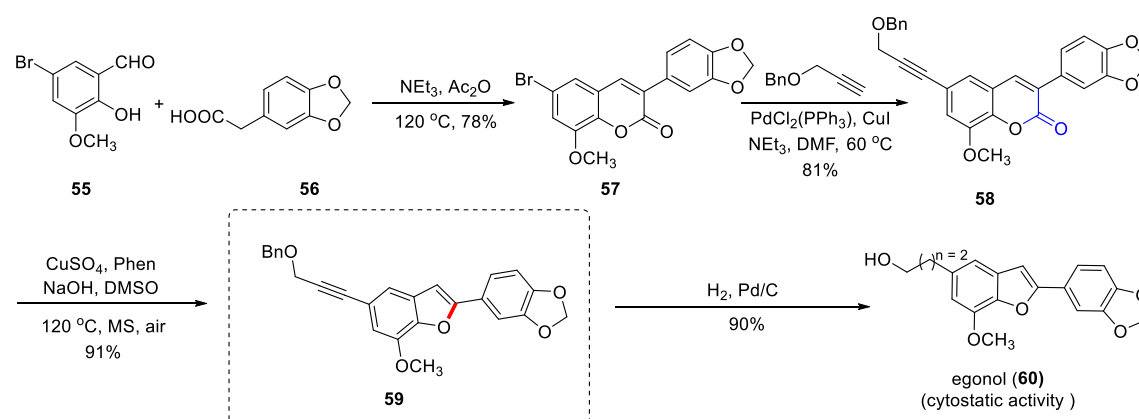


Scheme 1.27 Decarboxylative radical sulfonylation^[52]

1.2.3 Decarboxylative C-hetroatom bond forming reactions in natural product and drug synthesis

They also provide excellent regioselectivity and functional group tolerance, making them compatible with sensitive molecules. Additionally, decarboxylative methods enable the construction of bioactive scaffolds often found in natural products and pharmaceuticals. With their redox-neutral nature, these reactions are environmentally friendly and economically viable, enhancing their utility in pharmaceutical synthesis.

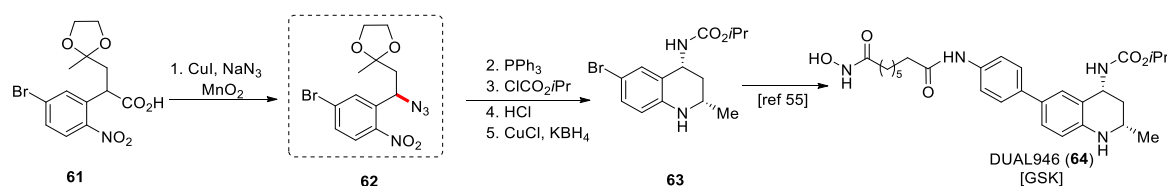
Wang and co-workers in 2024 have reported the synthesis of Egonol natural product. It is started from 5-bromo-3-methoxysalicylaldehyde (55) and 2-(benzo[d][1,3] dioxol-5-yl)acetic acid, 3-arylcoumarinderivative 56 was obtained via Perkin reaction with 78% yield (Scheme 1.28).^[53]



Scheme 1.28 Synthesis of egonol based on copper-catalyzed decarboxylative intramolecular C–O coupling^[53]

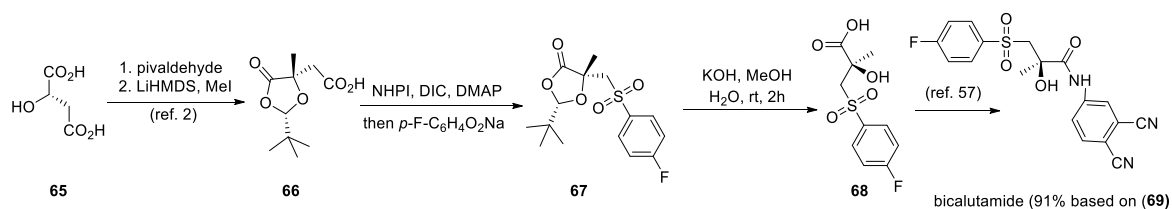
By using Sonogashira coupling, 3-arylcoumarin (**57**) coupled with benzyl-protected prop-2-yn-1-ol to afford 6-alkyl substituted 3-arylcoumarin (**58**) with 81% yield. Benzyl group was able to tolerate the reaction system of copper-catalyzed decarboxylative intramolecular C–O coupling. Next, compound (**58**) converted into corresponding 2-arylbenzo[*b*]furan (**59**) using CuSO₄/Phen system. Finally, hydroxyl deprotection and alkyne reduction were simultaneously accomplished in the presence of Pd/C and hydrogen. The overall yield of egonol (**60**) was 51.7%, which is a significant improvement than previous synthetic routes.

In 2020, Lundgren and colleagues demonstrated the potential of catalytic decarboxylative amination reactions for the synthesis of complex molecules, such as the DUAL946 compound. They successfully applied a decarboxylative azidation strategy, utilizing oxidative copper catalysis, to achieve the formal synthesis of a series of histone deacetylase/bromodomain/extra-terminal protein (HDAC/BET) inhibitors (Scheme 1.29).^[54]



Scheme 1.29 Decarboxylative azidation and synthesis of the DUAL946 intermediate

Li and co-worker in 2020 reported organophotocatalyzed decarboxylative sulfonylation reaction in total synthesis of drug bicalutamide (Scheme 1.30).^[56]



Scheme 1.30 Application in the synthesis of Bicalutamide ^[56]

We believe that the development of new methodologies utilizing organophotocatalysis, particularly in the context of natural products and drug molecules synthesis would be highly valuable to both organic and medicinal chemists.

1.2.4 Conclusion

The decarboxylative formation of C–C and C–heteroatom bonds has evolved as a highly useful synthetic tool in modern organic chemistry. Over recent decades, substantial advances have been made in decarboxylative C–H functionalization processes, driven by transition-metal catalysis and novel photochemical decarboxylation platforms. These methodologies have proven invaluable in constructing complex molecular architectures that would otherwise be challenging to construct from simple building blocks. Despite these advancements, there are relatively few reports where C–H functionalization has been effectively applied in the total synthesis of natural products and bioactive molecules, or pharmaceutical agents. The efficiency and versatility of C–H functionalization protocols have sparked growing interest in developing new synthetic methodologies that exploit this chemistry, particularly for the efficient construction of natural products and drug molecules.

The C–heteroatom bond formation has become a central focus within organocatalysis, attracting significant attention due to its broad utility and the diverse reactivity modes it enables. The ability to efficiently form these bonds has opened new pathways in catalysis, making organocatalytic methods indispensable tools for modern organic synthesis. By combining C–H functionalization strategies with C–heteroatom bond formation, chemists can develop novel, highly efficient synthetic routes to complex molecules, advancing both the methodology and application in the synthesis of natural product and drug discovery.

The background on C–H functionalization of heteroarenes and C–heteroatom bond formation highlighted their significance, motivating us to pursue further research in these areas. Our findings and contributions to this work are detailed in this thesis under the working chapters 2-4.

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Chapter 2

Enantioselective Intramolecular Decarboxylative C–H Bond Functionalization of Quinazolinone with Amino Acids by Visible Light Photoredox Catalysis

S. R. Sonavane, S. B. Mhaske, *Chem. Asian J.* **2023**, *18*, e202300235

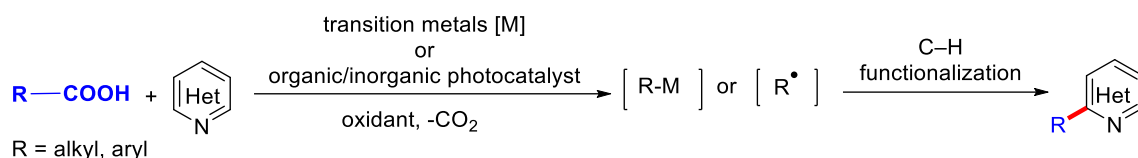
2.1 Abstract

The present chapter describes the development of a novel visible light-mediated intramolecular decarboxylative C–H functionalization of Csp^2 –H bond adjacent to the nitrogen of a heteroarene, which has been achieved by iridium-photocatalyzed decarboxylative radical cyclization. This method offers rapid entry to the synthesis of quinazolinone scaffolds from easily accessible starting materials. The newly developed protocol is mild, operationally simple, oxidant free and general. The utility of this unique Csp^3 – Csp^2 bond forming reaction has been demonstrated in the syntheses of Circumdatin, Sclerotigenine and Benzomalvin A class of quinazolinone natural products and their congeners. The present work represents an interesting example of the memory of chirality in decarboxylative C–C bond forming enantioselective photoredox reaction.

2.2 Introduction

2.2.1 Photodecarboxylative C–H bond Functionalization of nitrogen-containing heteroarenes.

Over the last decade, visible-light photoredox catalysis has emerged as a versatile and powerful strategy in synthetic organic chemistry for constructing novel C–C and C-heteroatom bonds.^[1] It is a mild and operationally simple process for laboratory and industrial applications. Particularly, the visible light-mediated C–H functionalization of electron-deficient heteroarenes has been one of the most prevalent research areas.^[2] The nucleophilic carbon-centered radical generated adjacent to the nitrogen of α -amino acid by decarboxylative processes can be readily functionalized and transformed into pharmacologically active molecules.^[3] The generation and utilization of such carbon centered radical is an appealing approach for the construction of medicinally relevant pharmacophore.^[4]



Scheme 1. Typical decarboxylative C–H functionalization process

The C–H bond functionalization of nitrogen-containing heteroarenes using alkyl and aryl carboxylic acids is a compelling field of research in synthetic organic chemistry. These processes typically involve metal catalysts that facilitate the cleavage of the carboxylic acid, resulting in the extrusion of carbon dioxide and the formation of either C–metal or carbon centred radical species. Organic/inorganic photocatalyst as well as transition-metals such as palladium, silver, rhodium, gold, and copper are commonly employed as catalysts for these transformations.^[5] Decarboxylation of the carboxylic acid yields a functionalized product through two potential intermediates: radicals and C–metal species (Scheme 1).

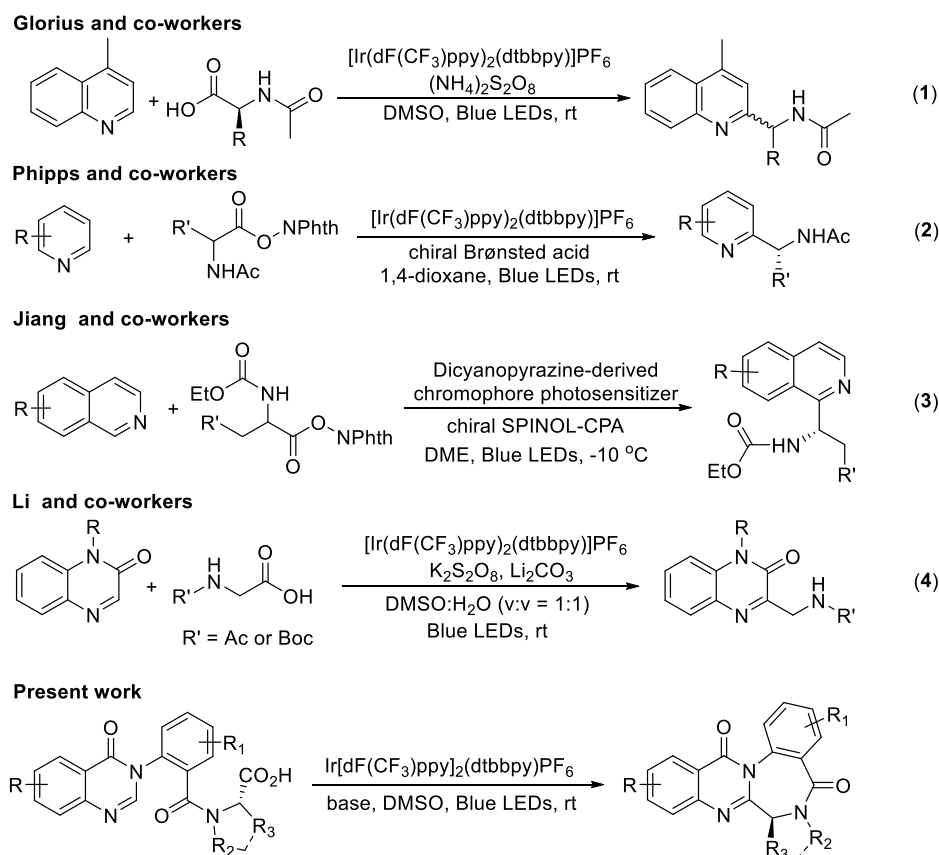
2.2.2 History of decarboxylative C–H bond functionalization of nitrogen containing heteroarens

The C–H bond functionalization of nitrogen-containing heteroarenes is a topic of significant interest in modern synthetic chemistry. This reaction involves the activation and functionalization of carbon-hydrogen bonds selectively, often in aromatic systems, in the presence of nitrogen-containing heteroarenes. Nitrogen-containing heteroarenes, such as pyridines, pyrroles, indoles, quinolines, and imidazoles, are commonly encountered in pharmaceutical and materials chemistry due to their unique electronic properties and biological activity.

The classical Minisci reaction,^[6] invented in 1971, has witnessed a tremendous improvement over the period and several Minisci-type alkylation reactions by utilizing novel catalytic systems and a wide range of prefunctionalized alkylating agents instead of carboxylic acids

have been documented.^[7] Recently, Minisci-type direct alkylation of heteroarenes with alkyl bromides via photoredox catalysis has been also reported.^[8] Glorius and co-workers disclosed the first visible light-mediated direct alkylation of heteroarenes with carboxylic acids without prefunctionalization [Scheme 1, eq 1].^[9]

This important breakthrough using easily available carboxylic acids as alkylating agents in combination with a mild photoredox catalysis for alkylation of heteroarenes is notable. In the same year, Fu and co-workers independently reported photoredox/Brønsted acid catalyzed direct alkylation of heteroarenes with α -amino acid-derived redox-active esters (RAEs) *N*-acyloxyphthalimides.^[10] Phipps and co-workers as well as Jiang and co-workers reported photoredox reaction of *N*-acyloxyphthalimides to achieve enantioselective Minisci-type addition to heteroarenes with high enantiomeric excess using chiral Brønsted acid catalysis [Scheme 1, eq 2 and 3].^[11,12]



Scheme 2. History of decarboxylative C–H bond Functionalization of heteroarenes.

Recently, Li and co-workers disclosed a direct decarboxylative arylation of alkyl carboxylic acids with quinoxaline-2(1*H*)-ones via visible light-mediated photoredox catalysis in aqueous solution.^[13] There are few other reports on photoredox catalyzed decarboxylative C–H bond functionalization of heteroarenes, however examples of asymmetric version are rare.^[1f,14] In this context, our interest in developing novel methodologies and their application in the natural product synthesis prompted us to revisit our own methodology developed for the enantioselective synthesis of quinazolinone alkaloids using AgNO₃-mediated decarboxylative intramolecular cyclization strategy.^[15] However, the yields were moderate, the substrate scope was limited and a large excess of oxidant was necessary. We envisioned that such transformation would be facile by using newly emerged photoredox catalysis platform under milder reaction condition.

Interestingly, until now, decarboxylative intramolecular C–H functionalization of heteroarene with amino acids has not been explored in the literature by using photoredox catalysis. Additionally, there are rare examples of memory of chirality (MOC) utilizing photodecarboxylative C–C bond forming reactions of amino acids.

We envisioned the possibility of chiral pool-based asymmetric synthesis approach via transfer of chirality through conformational (atropisomeric) memory of an unsterilized secondary radical intermediate on quinazolinone substrates by photoredox catalysis. We planned to develop a photo-redox catalyzed protocol and demonstrate its application in Circumdatin, Scleritogenine, Benzomalvin etc. class of natural quinazolinone alkaloids, which are known for their excellent biological activities (Figure 1).^[17] Presented herein is intramolecular enantioselective decarboxylative C–H functionalization of proline-containing quinazolinones by visible-light photoredox catalysis to obtain bioactive quinazolinone natural products and their analogues without the need of chiral auxiliary.

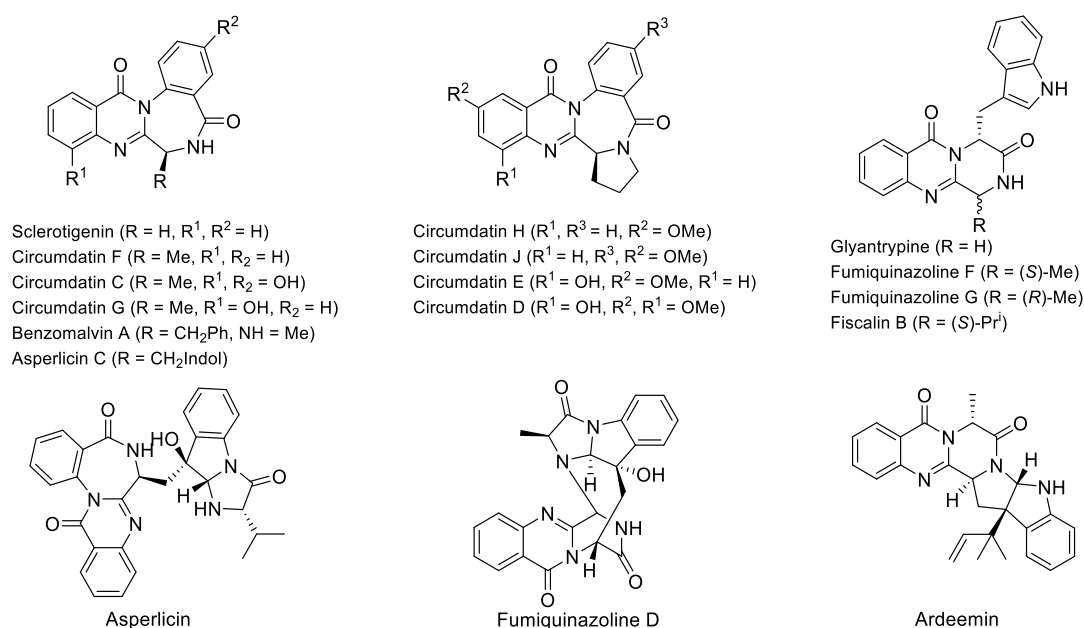
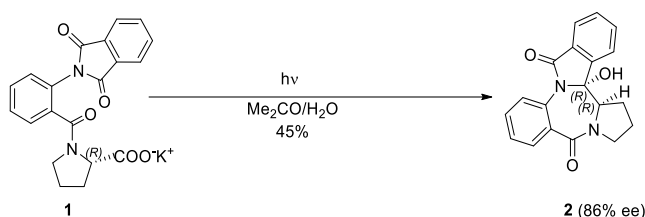


Figure 1. Quinazolinone-based bioactive natural products

2.3 Memory of chirality (MOC)

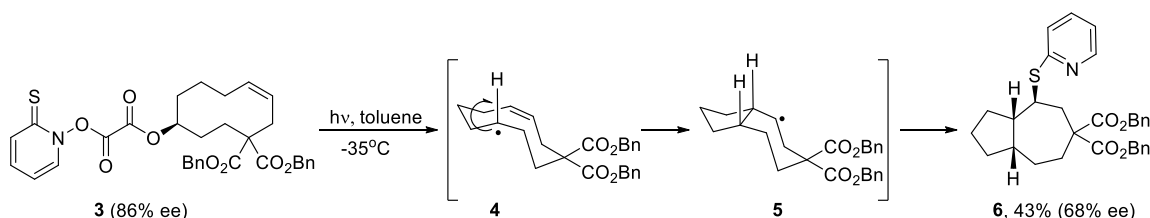
The concept memory of chirality refers to a phenomenon wherein the chirality of a starting compound with a chiral sp^3 carbon can be retained in the final product, though the reaction occurs at the chiral center through various reactive intermediates like carbanions, singlet monoradicals, biradicals, or carbenium ions. The concept "memory of chirality" was reported by Fuji and Kawabata as a valuable principle in asymmetric synthesis.^[16b] It involves the planarization of a stereogenic centre during a series of reactions, resulting in the creation of a chiral product that is non-racemic. This process highlights how changes in molecular geometry can influence the stereochemical outcome in subsequent steps. The transformation does not involve asymmetric induction from chiral auxiliaries; instead, it is driven entirely by the chiral memory present in the intermediates. This means that the inherent chirality of the intermediates plays a crucial role in defining the final outcome. The duration of these intermediates and their conformational flexibility are critical factors influencing the level of stereoselectivity. In addition to the reactions involving carbanions,^[16b] carbenium ions,^[19] or

monoradicals,^[18] the combination reactions of diradicals are particularly promising because they typically have very low, or even negligible, activation barriers. The method was recently reported by Griesbeck and colleagues via 1, 5-diradical intermediates with singlet multiplicity, which were generated photochemically leading to the cyclization (Scheme 3).^[16b] These intermediates have very short lifetimes, resulting in nearly complete “memory of chirality”. These triplet diradicals were anticipated to show significantly lower memory effects because of their longer lifetimes. To investigate this, researchers examined the photocatalyzed decarboxylative cyclization of phthaloylanthranilic acid analogues and discovered unexpectedly high ee in the combination of radical involving a triplet 1,7-diradical.



Scheme 3. Intramolecular photocyclization via memory of chirality

The intramolecular photodecarboxylative cyclization of this substrate yields the cyclized product **2** with inversion of configuration. The memory of chirality observed in the formation of product **2** is attributed to the non-diaryl atropisomeric 1,7-diradical intermediate, along with the atropisomeric effect of the system. This configuration restricts rotation around the central C–N single bond in the arylamide and the amide moiety.



Scheme 4. Intramolecular radical trans annulative coupling via MOC developed by Rychnovsky

Rychnovsky demonstrated decarboxylative intramolecular radical transannulative carbon-carbon bond formation via MOC. *N*-Oxypyridine-2-thione (**3**) upon photodecarboxylation furnished bicyclo[5.3.0]decane (**6**) in moderate yield and 68% enantiopurity (Scheme 4). The attack of the chiral intermediate **4** on the alkene forms five-membered ring system and the generated new radical reacts with sulfur radical to form cyclized product **6** via radical-radical coupling interaction.

The memory of chirality (MOC) remains less studied as compared to the rest of the areas of synthetic organic chemistry.^[20] Instances of MOC through intermolecular decarboxylative radical interaction are scarce, with only two documented cases of MOC. The first example, presented by Rychnovsky, involved transannular radical cyclization through photodecarboxylative coupling (Scheme 4),^[21] while the second example was reported by Griesbeck (Scheme 3).^[16b]

2.4 Origin of the work

Literature reports highlight that quinazolinone alkaloids, particularly those in the circumdatin class, exhibit intriguing biological activities. These natural products have garnered significant interest due to their potential therapeutic effects, including notable anticancer, antimicrobial, and anti-inflammatory properties. Their unique chemical structures and biological profiles make them promising candidates for further research and drug development.

Literature shows that intermolecular photodecarboxylative C–H functionalization processes have been explored, but there has been limited investigation into intramolecular photodecarboxylation cyclization processes. In this context, the quinazolinone structure features an electron-deficient carbon site, which allows for further functionalization through coupling with amino acids. The intramolecular photodecarboxylative cyclization approach can be utilized to generate bioactive quinazolinone alkaloids. The intramolecular

photodecarboxylative cyclization protocol can offer quinazolinone bioactive alkaloids.^[17] In this work, we present a protocol for iridium-photocatalyzed intramolecular decarboxylative cyclization of quinazolinones using amino acids, leveraging the memory of chirality.

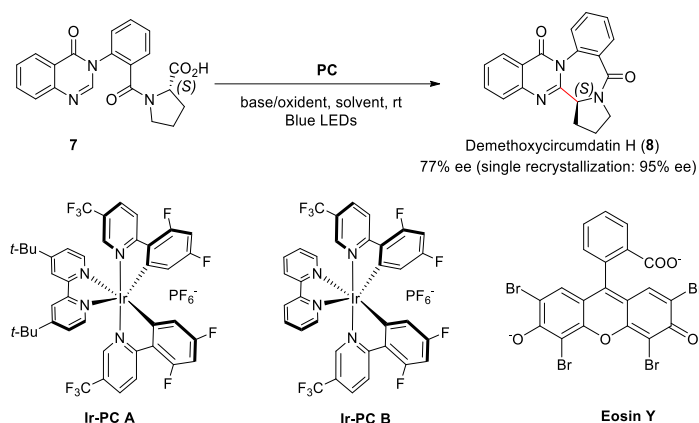
2.5 Results and discussion

We began our investigation using acid **7** (1 equiv.) as a model substrate, which was prepared as shown in Scheme 5 following our reported protocol with little modification.^[15] In the initial attempt, reaction was performed using 1 mol% of Ir-PC **A** along with oxidant ammonium persulfate (2 equiv.) in DMSO solvent, under irradiation of 30 W blue LEDs at ambient temperature.

To our pleasure the formation of expected product demethoxycircumdatin **H** (**8**) was observed in 38% yield (Table 1, entry 1). We were encouraged by the favourable result, hence screened several rational permutations and selected entries are provided in Table 1. First, we tried DBU as a base, which helped moderately to enhance the yield (Table 1, entry 2). Many other organic bases such as DABCO (Table 1, entry 3), triethylamine, tributylamine, N, N-diisopropylethylamine, tetramethyl ethylenediamine etc. were tested, however we did not observe much improvement in the yield.

Hence, we moved towards inorganic bases. Photo-catalyzed decarboxylative C–C bond forming reactions are known to work well with cesium carbonate as the base.^[22]

Interestingly, cesium carbonate worked well on our substrate and we observed substantial improvement in the yield (Table 1, entry 4). We screened other catalysts including Ir-PC **B** and Eosin **Y**, but Ir-PC **A** was found to be more efficient (Table 1, entry 5-6). Next, the reaction was performed without the oxidant and we were pleased to find that the reaction was still working well with better yield (Table 1, entry 7).

Table 1. Optimization of the Decarboxylative Cyclization Protocol.

entry	photocatalyst (mol%)	oxidant 2 equiv.	solvent	base (equiv.)	yield (%) ^b	ee (%)
1	Ir-PC A (1.0)	(NH ₄) ₂ S ₂ O ₈	DMSO	-	38%	ND
2	Ir-PC A (1.0)	(NH ₄) ₂ S ₂ O ₈	DMSO	DBU (2.0)	55%	ND
3	Ir-PC A (1.0)	(NH ₄) ₂ S ₂ O ₈	DMSO	DABCO (2.0)	27%	ND
4	Ir-PC A (1.0)	(NH ₄) ₂ S ₂ O ₈	DMSO	Cs ₂ CO ₃ (2.0)	74%	ND
5	Ir-PC B (1.0)	(NH ₄) ₂ S ₂ O ₈	DMSO	Cs ₂ CO ₃ (2.0)	65%	ND
6	Eosin Y (1.0)	(NH ₄) ₂ S ₂ O ₈	DMSO	Cs ₂ CO ₃ (2.0)	trace	ND
7	Ir-PC A (1.0)	-	DMSO	Cs ₂ CO ₃ (2.0)	81%	ND
8	Ir-PC A (1.0)	-	DMSO	Cs₂CO₃ (1.1)	86%	77
9	Ir-PC A (1.0)	-	DMSO	K ₂ CO ₃ (1.1)	57%	ND
10	Ir-PC A (1.0)	-	DMF	Cs ₂ CO ₃ (1.1)	46%	ND
11	Ir-PC A (1.0)	-	ACN	Cs ₂ CO ₃ (1.1)	62%	ND
12	Ir-PC A (2.0)	-	DMSO	Cs ₂ CO ₃ (1.1)	69%	ND
13	Ir-PC A (0.5)	-	DMSO	Cs ₂ CO ₃ (1.1)	61%	ND
14	Ir-PC A (0.25)	-	DMSO	Cs ₂ CO ₃ (1.1)	43%	ND
^c 15	Ir-PC A (1.0)	-	DMSO	Cs ₂ CO ₃ (1.1)	trace	ND
16	-	-	DMSO	Cs ₂ CO ₃ (1.1)	N.D.	ND

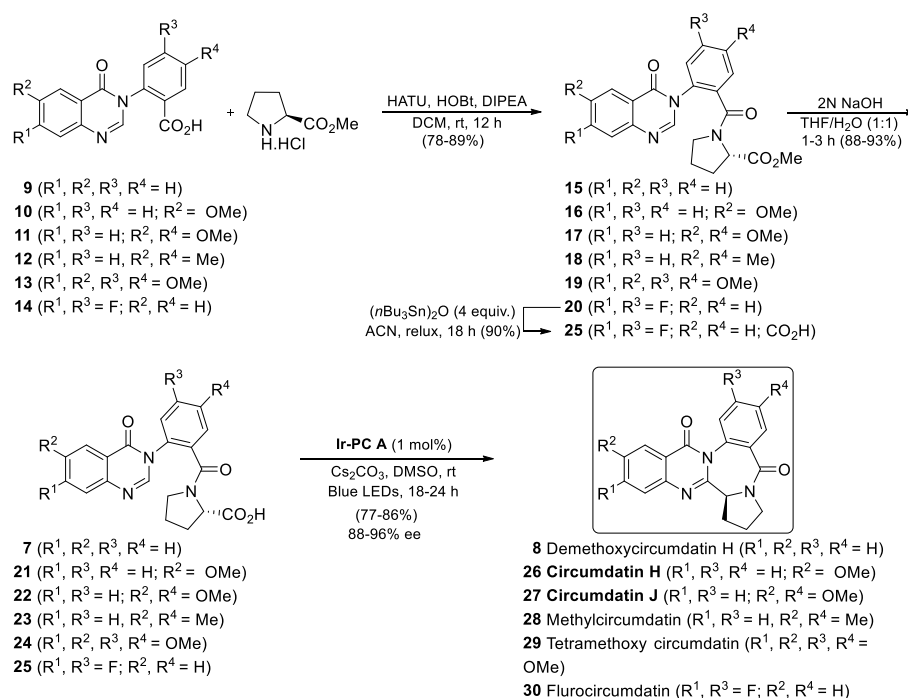
[a] Reactions were performed on a 0.082 mmol scale of acid 1 under irradiation of 30 W blue LEDs for 18 h under argon. [b] Yields reported are isolated yields. [c] Reaction was performed in the absence of blue LEDs. ND = Not determined

Further studies revealed that only 1.1 equiv. of cesium carbonate was sufficient for this transformation to furnish 86% yield of product **8** (Table 1, entry 8). Further, we tested other inorganic bases, solvents (Table 1, entries 9-11) and effect of catalyst loading (Table 1, entries 12-14), however, we did not observe notable improvement in the yield. Control experiments shows that no reaction was observed in the absence of either blue LED

irradiation or photocatalyst (Table 1, entry 15 and 16 respectively). Our elaborate studies finally provided us optimized reaction condition, wherein 1 mol% Ir-PC **A** and 1.1 equiv. cesium carbonate as the base in DMSO solvent provided 86% yield with 77% ee (single recrystallization: 95% ee) (Table 1, entry 8).

The acids **10-14** were prepared and coupled with *L*-proline methyl ester using HATU coupling agent to obtain esters **16-20** in very good yields (Scheme 2). The esters **16-19** were hydrolyzed with NaOH in THF:Water (1:1) to furnish acids **21-24** in excellent yields. The hydrolysis of ester **20** under the same condition however did not furnish the desired acid **25**, instead we observed displacement of fluorine with hydroxyl group. Hence, we used bis(tributyltin)oxide condition on **20**, which worked well to provide acid **25** in quantitative yield. The acids **21-25** were then subjected to our standard photo redox reaction condition. The optimized protocol worked well on substrate **21** to furnish the desired natural product Circumdatin H (**26**) in 81% yield with 76% ee (single recrystallization: 87% ee) (Scheme 5). Our protocol also worked on dimethoxy substrate **22** to provide Circumdatin J (**27**) natural product in 85% yield and 71% ee (single recrystallization: 96% ee) (Scheme 5). After successfully synthesizing two pyrrolidine based natural products, we moved towards exploring use of the protocol for synthesizing different derivatives. The acids **23** and **24** could be smoothly transformed to the corresponding methyl and methoxy substituted circumdatin analogues **28** & **29** in 79% yield with 82% ee (single recrystallization: 93% ee) and 80% yield with 72% ee (single recrystallization: 93% ee) respectively using our protocol (Scheme 5). Similarly, fluorine containing quinazolinone substrate **25** furnished the desired product **30** in 77% yield and 70% ee (single recrystallization: 95% ee) (Scheme 5), which shows that fluorine substituted quinazolinone substrate is compatible under our reaction conditions. After successfully demonstrating the application of our protocol on proline-containing

substrates to provide circumdatin natural products and their analogues, we were curious to see whether it could be applied to substrate containing acyclic amino acid.

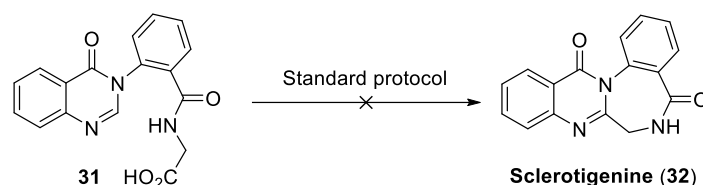


Scheme 5. Synthesis of proline-containing circumdatin class of natural products and their analogues

Accordingly, the acid **31** was prepared starting from compound **9** following our reported procedure.^[16] However, the acid **31** remained unchanged under the standard protocol and we didn't observe the natural product Sclerotigenine (**32**, Scheme 6). Hence, we planned to use substrates with protecting group or apply the protocol in the synthesis of N-substituted natural products, so that unprotected NH group would not interfere with the photo-catalyzed radical formation.

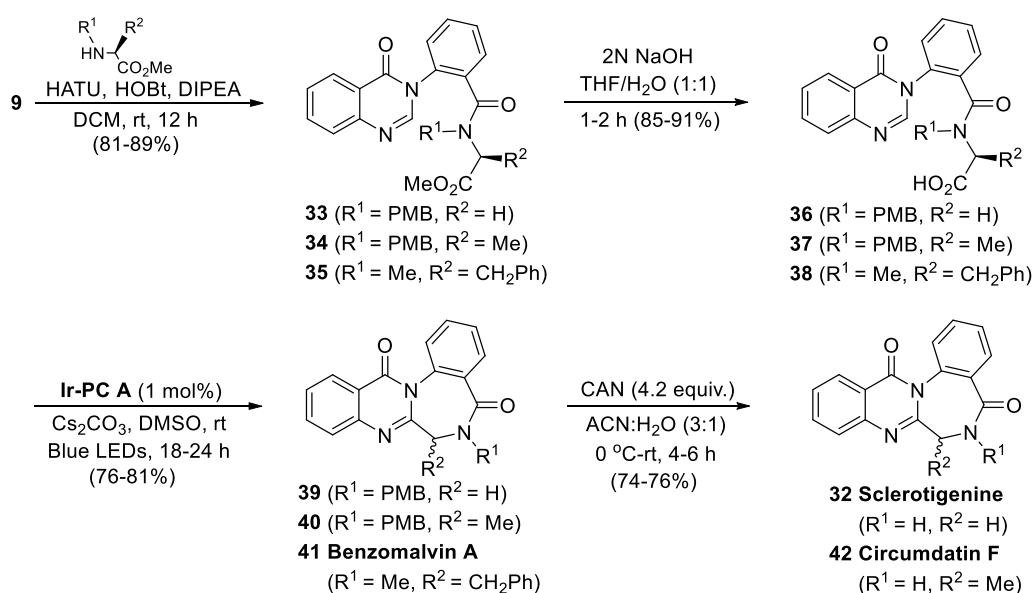
In this context, we prepared the esters **33–35** in good yields from the acid **9**, wherein we used either PMB protected or *N*-methylated amino acids. Hydrolysis of the esters **33–35** provided corresponding acids **36–38** respectively in very good yields (Scheme 7).

These acids were subjected to our standard photoredox protocol and all of them efficiently furnished the corresponding cyclized alkaloids **39–41**. The product **41** is the quinazolinone natural product ($\pm$)-Benzolmalvin A which was obtained in 76% yield (Scheme 7).



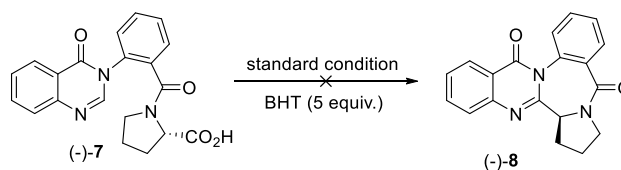
Scheme 6. Attempted Synthesis of Sclerotigenine with Unprotected Glycine.

The PMB protected precursor **39** upon deprotection using CAN furnished Sclerotigenine (**32**) natural product in 74% yield. Similarly, deprotection of precursor **40** provided the natural product ($\pm$)-Circumdatin F (**42**) in 76% yield. We observed the loss of enantioselectivity in the formation of natural product Benzomalvin A (**41**) and Circumdatin F (**42**) Scheme (7). We hypothesized that the radical generated on open-chain amino acids might be converting to planar configuration, whereas it might be less planar in the case of proline.

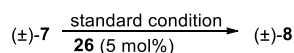


Scheme 7. Application of the protocol on acyclic *N*-PMB protected/*N*-Me substituted amino acid substrate

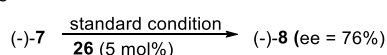
Additionally, the substrates containing bulkier proline ring might be atropisomerically locked across C–N bond between quinazolinone nitrogen and aniline carbon, whereas the substrates containing acyclic amino acid chain may move relatively more freely leading to racemic products. It might be possible to achieve enantioselectivity on such substrates utilizing chiral auxiliaries, however that is not the main purpose of current study.

Radical Trapping Experiments:**Autocatalysis experiments:**

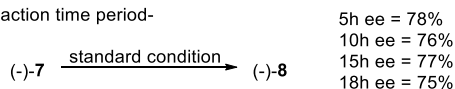
a) Racemic starting material-



b) Enantiopure starting material-



c) Product ee over reaction time period-

**Scheme 8. Mechanistic studies**

Overall, though there are other synthetic routes reported in the literature for the synthesis^[15,17,24–29] of Circumdatin H & J, Benzomalvin A, Sclerotigenine and Circumdatin F natural products, we have demonstrated a novel and unique approach utilizing a mild and oxidant-free photo-redox catalysis protocol.

A preliminary mechanistic study using BHT as the radical scavenger indicates that the developed protocol follows a radical pathway (Scheme 8). Our initial observations such as enantiopure acid substrate **7** provides enantio-enriched product **8**, whereas racemic acid substrate **7** provides racemic product **8** indicates that the stereoinduction is not happening by autocatalysis mechanism but plausibly via memory of chirality.

The autocatalysis mechanism was completely ruled out by performing additional mechanistic studies (Scheme 8), wherein we studied the effect of addition of enantiopure product **26** on the ee of the product **8** and also observed the changes in the ee over a time period under our standard reaction conditions. The addition of enantiopure product **26** did not show any effect on the ee of product **8** and at various time intervals it remained approximately constant.

2.6 Conclusion

In summary, we have disclosed the first oxidant and chiral ligand free C–H bond functionalization of quinazolinone heteroarenes by Iridium-catalyzed intramolecular photo-decarboxylative cyclization method and its application. This straightforward approach provides a facile access to biologically active quinazolinone natural products and their analogues using commercially available α -amino acids as coupling partners. Our work represents the first example of photo induced intramolecular C(sp³)- C(sp²) bond forming decarboxylative enantioselective cyclization reaction to access proline-containing quinazolinone alkaloids via memory of chirality. Currently, we are working on improvement of enantioselectivity by enhancing the lifetime of the radical intermediate by controlling the conformational (atropisomeric) flexibility and its application in other heteroarenes and natural products.

2.7 Experimental Section

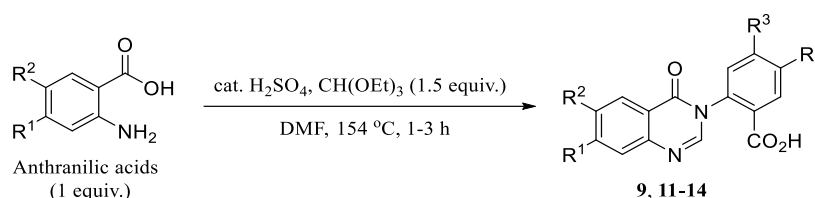
Note 1: For intermediate esters and acids a complex mixture of atropisomers and amide rotamers resulted into multiple peaks and broad signals, hence not all signals are distinguishable/visible.

Note 2: Racemic compounds for HPLC were prepared using general procedures II-IV.

Note 3: We prepared a 50:50 mixture of proline enantiomers manually by weight for the synthesis of the corresponding racemic compounds. Hence, the integration ratio of the peaks in the HPLC chromatograms are not exactly 50:50 for those racemic compounds.

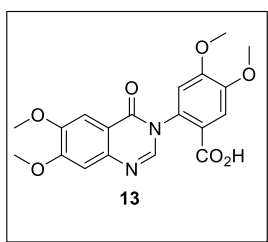
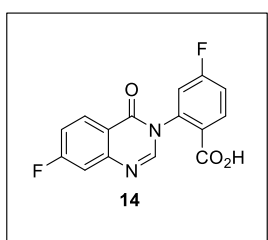
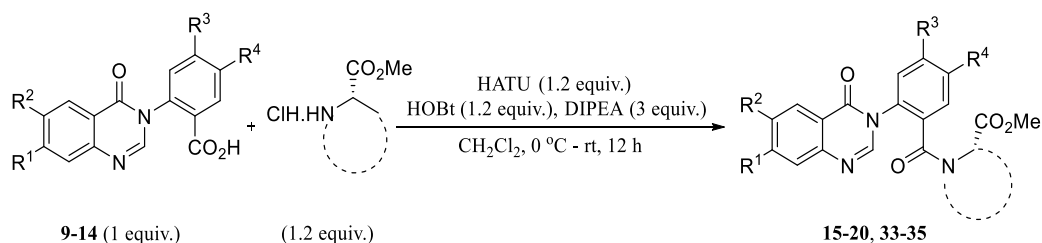
2.7.1 Experimental procedures and data:

[A] General procedure-I: Synthesis of **9**, **11-14**:



The known compounds **9**, **11**, **12** were prepared as per the literature procedure.^[15,24] The new compounds **13** and **14** were prepared following the reported procedure.^[15] To a stirred solution of anthranilic acid (1 equiv.), triethylorthoformate (1.5 equiv.) and DMF (5 mL for 1 g of anthranilic acid) was added concentrated H₂SO₄ (cat., 2 drops) at room temperature and the reaction mixture was heated gradually. The low-boiling substances formed during the reaction at 80-100 °C were removed by distillation. After the temperature rose to 154 °C the heating was continued for another 1-3 h at the same temperature. The reaction mixture was then cooled to room temperature and poured into ice-water with continuous stirring. The precipitated solid was collected by filtration and recrystallized using DMF/H₂O (1:1) to obtain the corresponding pure acids **9**, **11-14** after drying.

The analytical and spectral data of the known acids **9**, **11** and **12** is in agreement with the reported data.^[15]

2-(6, 7-Dimethoxy-4-oxoquinazolin-3(4H)-yl)-4,5-dimethoxybenzoic acid (13):**13:** Off-white solid; mp: 306-308 °C**¹H NMR** (400 MHz, DMSO-*d*₆): δ 12.58 (bs, 1H), 8.13 (s, 1H), 7.55 (s, 1H), 7.45 (s, 1H), 7.20 (s, 1H), 7.18 (s, 1H), 3.94 (s, 3H), 3.89 (s, 3H), 3.87 (s, 3H), 3.83 (s, 3H).**¹³C NMR** (101 MHz, DMSO-*d*₆): δ 171.3, 165.5, 159.8, 154.6, 152.1, 148.7, 148.4, 146.1, 144.1, 131.7, 120.8, 115.1, 113.2, 108.1, 105.4, 56.2, 56.0, 55.8, 55.7.**HRMS-ESI** (m/z) calcd for (C₁₉H₁₈N₂O₇+H)⁺: 387.1187, found: 387.1174.**4-Fluoro-2-(7-fluoro-4-oxoquinazolin-3(4H)-yl) benzoic acid (14):****14:** White solid; mp: 274-276 °C.**¹H NMR** (DMSO-*d*₆, 400 MHz): δ 13.21 (bs, 1H), 8.40 (s, 1H), 8.24 (dd, *J* = 8.9, 6.3 Hz, 1H), 8.16 (dd, *J* = 8.9, 6.3 Hz, 1H), 7.67 (dd, *J* = 9.3, 2.6 Hz, 1H), 7.58-7.50 (m, 2H), 7.50-7.35 (m, 1H).**¹³C NMR** (101 MHz, DMSO-*d*₆): δ 166.0 (d, *J*_{C-F} = 251.8 Hz), 165.1, 164.2 (d, *J*_{C-F} = 252.5 Hz), 159.7, 150.2 (d, *J*_{C-F} = 12.9 Hz), 148.4, 139.2 (d, *J*_{C-F} = 11.4 Hz), 133.9 (d, *J*_{C-F} = 9.9 Hz), 129.8 (d, *J*_{C-F} = 10.7 Hz), 125.9 (d, *J*_{C-F} = 3.1 Hz), 119.0 (d, *J*_{C-F} = 1.5 Hz), 117.8 (d, *J*_{C-F} = 24.4 Hz), 116.9 (d, *J*_{C-F} = 20.6 Hz), 116.0 (d, *J*_{C-F} = 22.8 Hz), 112.8 (d, *J*_{C-F} = 22.1 Hz).**HRMS-ESI** (m/z) calcd for (C₁₅H₈F₂N₂O₃+H)⁺: 303.0576, found: 303.0565.**[B] General procedure-II: Synthesis of compounds 15-20, 33-35:**

To a solution of acid **9-14** (1 equiv.) in DCM (10 mL for 1 g of acid) was added, HATU (1.2 equiv.) and HOBT (1.2 equiv.) followed by DIPEA (3 equiv.) at 0 °C with continuous stirring for 10 minutes. Later, a solution of amino acid methyl ester hydrochloride/*N*-methyl phenyl alanine methyl ester hydrochloride/PMB-protected glycine methyl ester hydrochloride/PMB-protected alanine methyl ester hydrochloride (1.2 equiv.) in DCM (2 mL) was added drop

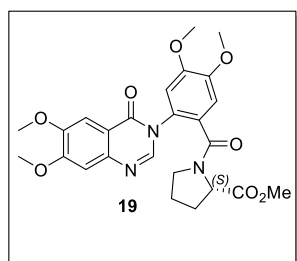
wise at 0 °C to the reaction mixture in five minutes with continuous stirring. The reaction mixture was allowed to warm to room temperature and stirred overnight. After completion of reaction (checked by TLC), it was quenched with saturated aqueous NH_4Cl (10 mL), and extracted with DCM (3×15 mL). The combined organic layers were washed with saturated aqueous NaHCO_3 solution (3×20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The crude products were purified by silica gel column chromatography using ethyl acetate and petroleum ether as eluents to obtain corresponding products **15-20**, and **33-35** in good yields.

The analytical and spectral data of the known esters **15-18** and **35** is in agreement with the reported data.^[15]

[C] Typical experimental procedure for the synthesis of representative compound 19:

To the solution of acid **7** (500 mg, 1.29 mmol, 1 equiv.) in DCM (5 mL) was added HATU (590 mg, 1.55 mmol, 1.2 equiv.) and HOBT (210 mg, 1.55 mmol, 1.2 equiv.), followed by DIPEA (501 mg, 675 μL , 3.88 mmol, 3 equiv.) at 0 °C with continuous stirring for 10 minutes. Then a solution of proline methyl ester hydrochloride (256 mg, 1.55 mmol, 1.2 equiv.) in DCM (2 mL) was added drop wise at 0 °C to the reaction mixture in five minutes with continuous stirring. The reaction mixture was allowed to warm to room temperature and stirred overnight. After completion of reaction (checked by TLC), it was quenched with saturated aqueous NH_4Cl (10 mL) solution, and extracted with DCM (3×10 mL). The combined organic layers were washed with saturated aqueous NaHCO_3 solution (3×10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The crude product was purified by silica gel column chromatography using ethyl acetate and petroleum ether (6:4) as eluents to obtain corresponding product **19** in 82 % yield as a white solid (554 mg).

Methyl (2-(6,7-dimethoxy-4-oxoquinazolin-3(4H)-yl)-4,5-dimethoxybenzoyl)-L-prolinate (19**):**



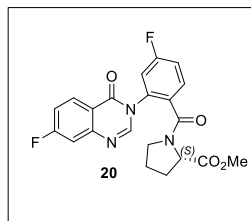
19: 82% white solid; mp: 125-127 °C; R_f : 0.3 (8:2, ethyl acetate:petroleum ether); $[\alpha]^{24}_D -52$ (c 0.8, CHCl_3).

^1H NMR (400 MHz, CDCl_3 , mixture of atropisomers and rotamers): δ 8.02 (s, 1H), 7.65-7.53 (m, 1H), 7.15 (s, 1H), 7.04-6.82 (m, 2H), 4.63-4.37 (m, 1H), 4.01-3.86 (m, 12H), 3.71-3.19 (m, 5H), 2.22-2.15 (m, 1H), 1.93-1.77 (m, 3H).

^{13}C NMR (101 MHz, CDCl_3): δ 173.4, 172.6, 166.8, 160.5, 155.1, 155.0, 149.9, 149.4, 149.3, 149.1, 146.1, 145.8, 144.3, 128.8, 127.9, 127.6, 127.1, 115.4, 111.4, 109.9, 109.4, 108.3, 105.6, 105.4, 61.2, 58.7, 58.4, 56.3, 56.2, 56.1, 52.2, 49.5, 45.7, 30.9, 29.6, 29.5, 25.3, 24.7, 22.5.

HRMS-ESI (m/z) calcd for $(\text{C}_{25}\text{H}_{27}\text{N}_3\text{O}_8+\text{H})^+$: 498.1871, found: 498.1862.

Methyl (4-fluoro-2-(7-fluoro-4-oxoquinazolin-3(4*H*)-yl)benzoyl)-*L*-prolinate (20):



20: 78% white solid; mp: 114-116 °C; R_f : 0.4 (4:6, ethyl acetate:petroleum ether); $[\alpha]_D^{24}$ -64 (c 1.2, CHCl_3).

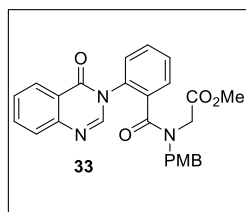
^1H NMR (400 MHz, CDCl_3 , mixture of atropisomers and rotamers): δ 8.30-8.25 (m, 1H), 8.10 (s, 1H), 7.67-7.39 (m, 2H), 7.33-7.24 (m, 3H), 4.59-4.42 (m, 1H), 3.75-3.22 (m, 5H), 2.29-2.14 (m, 1H), 1.98-1.86

(m, 3H). **^{13}C NMR** (101 MHz, CDCl_3): δ 173.1, 172.3, 167.8, 166.2, 165.3, 164.2, 161.7, 160.0, 150.2, 150.1, 147.1, 136.0, 131.9, 129.6, 129.4, 129.3, 117.1, 116.5, 116.2, 116.1, 113.6, 113.3, 113.2, 61.4, 58.5, 52.4, 52.2, 49.8, 49.1, 45.9, 30.9, 29.6, 29.4, 25.4, 24.6, 22.5.

^{19}F NMR (377 MHz, CDCl_3) δ -102.0 (s), -102.3 (s), -102.8 (s), -107.5 (s), -107.8 (s), -108.2 (s).

HRMS-ESI (m/z) calcd for $(\text{C}_{21}\text{H}_{17}\text{F}_2\text{N}_3\text{O}_4+\text{H})^+$: 414.1260, found: 414.1251.

Methyl *N*-(4-methoxybenzyl)-*N*-(2-(4-oxoquinazolin-3(4*H*)-yl) benzoyl)glycinate (33):

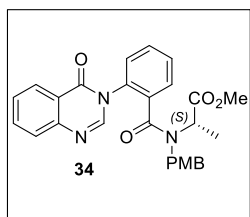


33: 89% white solid; mp: 65-67 °C; R_f : 0.4 (6:4, ethyl acetate:petroleum ether).

^1H NMR (400 MHz, CDCl_3 , mixture of atropisomers and rotamers): δ 8.35 (d, J = 7.8 Hz, 0.4H), 8.18-8.11 (m, 1.6H), 7.85-7.77 (m, 2H), 7.60-7.40 (m, 4H), 7.43 (d, J = 7.8 Hz, 0.4H), 7.38 (d, J = 7.8 Hz, 0.6H), 7.08 (d, J = 7.6 Hz, 0.7H), 6.82 (d, J = 7.6 Hz, 0.7H), 6.74 (d, J = 7.5 Hz, 1.3H), 6.29 (d, J = 7.5 Hz, 1.2H), 5.36 (d, J = 14.5 Hz, 0.5H), 4.65 (d, J = 15.6 Hz, 0.2H), 4.34 (d, J = 15.8 Hz, 0.3H), 4.22-4.06 (m, 1H), 3.81-3.61 (m, 7H), 3.31 (s, 1H).

^{13}C NMR (101 MHz, CDCl_3): δ 170.1, 168.9, 168.7, 168.4, 161.0, 159.2, 158.8, 147.8, 146.9, 146.6, 135.6, 134.9, 134.70, 134.65, 134.4, 130.73, 130.69, 129.8, 129.7, 129.4, 128.9, 128.7, 127.8, 127.6, 127.4, 127.25, 127.22, 127.05, 127.02, 126.8, 122.0, 114.2, 113.7, 55.2, 55.0, 53.1, 52.2, 51.8, 49.0, 47.9, 45.5.

HRMS-ESI (m/z) calcd for $(\text{C}_{26}\text{H}_{23}\text{N}_3\text{O}_5+\text{H})^+$: 458.1715, found: 458.1714.

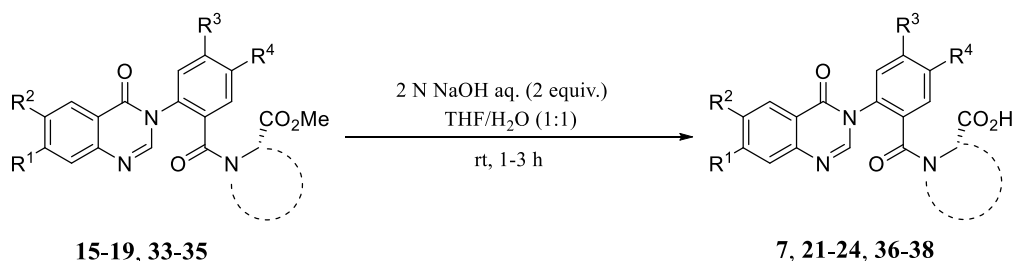
Methyl *N*-(4-methoxybenzyl)-*N*-(2-(4-oxoquinazolin-3(4*H*)-yl) benzoyl) alaninate (34**):**

34: 81% white solid; mp: 68-70 °C; R_f : 0.4 (5:5, ethyl acetate:petroleum ether); $[\alpha]^{24}_D -64.89$ (c 0.8, CHCl_3).

^1H NMR (500 MHz, CDCl_3 , mixture of atropisomers and rotamers): δ 8.34-8.24 (m, 1H), 8.17-8.09 (m, 1H), 7.87-7.79 (m, 2H), 7.60-7.41 (m, 6H), 7.22-7.06 (m, 1H), 6.91 (d, $J = 7.8$ Hz, 0.7H), 6.84 (d, $J = 6.9$ Hz, 0.3), 6.72-6.64 (m, 0.6H), 6.16 (d, $J = 8.2$ Hz, 0.4), 5.13 (d, $J = 15.8$ Hz, 0.3H), 4.83 (d, $J = 17.0$ Hz, 0.3H), 4.67-4.65 (m, 0.5H), 4.33 (d, $J = 16.7$ Hz, 0.5H), 3.94-3.70 (m, 3.6H), 3.59-3.54 (m, 1.4H), 3.41-2.98 (m, 2H), 2.74 (s, 0.5H), 1.35-1.18 (m, 3H).

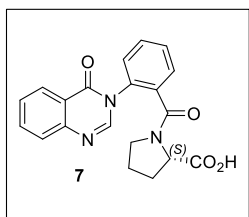
^{13}C NMR (126 MHz, CDCl_3): δ 172.5, 171.1, 170.5, 168.8, 168.5, 161.2, 161.1, 160.9, 159.0, 158.1, 148.2, 148.1, 146.9, 146.7, 146.4, 136.1, 135.4, 135.2, 134.8, 134.6, 134.4, 130.7, 130.5, 130.4, 130.1, 129.7, 129.5, 129.2, 128.9, 128.7, 128.5, 128.4, 128.3, 128.0, 127.8, 127.5, 127.2, 126.9, 126.7, 126.6, 122.2, 114.1, 113.5, 113.2, 58.1, 55.2, 55.0, 54.5, 53.8, 52.5, 52.3, 52.1, 51.9, 51.6, 46.5, 46.0, 34.1, 33.7, 29.6, 16.6, 16.2, 14.3, 12.6.

HRMS-ESI (m/z) calcd for ($\text{C}_{27}\text{H}_{25}\text{N}_3\text{O}_5 + \text{H}$) $^+$: 472.1867, found: 472.1866

[D] General procedure-III: Synthesis of **7, **21-24**, **36-38**:**

To the solution of ester **15-19**, **33-35** (1 equiv.) in THF/water (1:1) [10 mL for 1 g of ester] was added aqueous 2 N NaOH (2 equiv.) drop wise at room temperature with continuous stirring and the reaction mixture was stirred until complete consumption of the starting material (checked by TLC). THF was then removed in *vacuo* followed by dilution with water (5 mL for 1 g scale) and addition of ethyl acetate (10 mL for 1 g scale). The organic layer was separated and the aqueous layer was acidified with citric acid up to pH 2 and extracted with ethyl acetate (15 mL X 3 for 1 g). The ethyl acetate layer was separated, dried over anhydrous Na_2SO_4 and concentrated in *vacuo* to obtain the corresponding amino acids **7**, **21-24**, **36-38** in quantitative yields.

The analytical and spectral data of the known acids **7**, **21-23** and **38** is in agreement with the reported data.^[15]

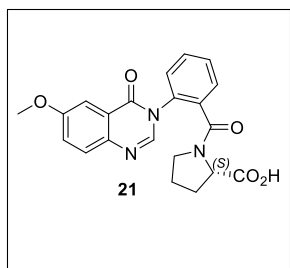
(2-(4-Oxoquinazolin-3(4H)-yl) benzoyl)-L-proline (7):^[15]

7: 92% white solid; mp: 184-186 °C; R_f : 0.3 (9:1, Dichloromethane:methanol+one drop acetic acid); $[\alpha]^{24}_D -86$ (c 1.8, CHCl_3).

^1H NMR (400 MHz, CDCl_3 , mixture of atropisomers and rotamers): δ 8.27-8.19 (m, 2H), 7.80-7.30 (m, 7H), 5.88 (bs., 1H acid proton),

4.60-4.35 (m, 1H), 3.80-3.30 (m, 2H), 2.25-1.85 (m, 4H).

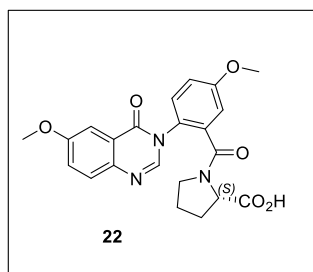
ESIMS $[\text{M}+\text{H}]^+$ (m/z): 364.

(2-(6-Methoxy-4-oxoquinazolin-3(4H)-yl) benzoyl)-L-proline (21):^[15]

21: 93% white solid; mp: 116-118 °C; R_f : 0.3 (9:1, Dichloromethane:methanol+one drop acetic acid); $[\alpha]^{24}_D -93.2$ (c 0.5, CHCl_3).

^1H NMR (400 MHz, CDCl_3 , mixture of atropisomers and rotamers): δ 8.05 (s, 1H), 7.70-7.24 (m, 7H), 4.55-4.40 (m, 1H), 3.91 (s, 3H), 3.86-3.50 (m, 2H), 2.20-2.10 (m, 2H), 2.10-1.90 (m, 2H).

ESIMS $[\text{M}+\text{H}]^+$ (m/z): 394.

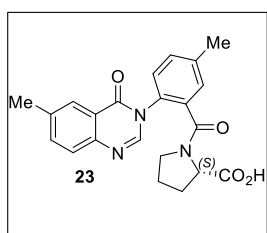
(5-Methoxy-2-(6-methoxy-4-oxoquinazolin-3(4H)-yl)benzoyl)-L-proline (22):^[15]

22: 88% white solid; mp: 125-127 °C; R_f : 0.3 (9:1, Dichloromethane: methanol+ one drop acetic acid); $[\alpha]^{24}_D -76.1$ (c 0.4, CHCl_3).

^1H NMR (400 MHz, CDCl_3 , mixture of atropisomers and rotamers): δ 8.10-7.99 (m, 1H), 7.70-7.30 (m, 3H), 7.24-7.00 (m, 3H), 6.45 (bs., 1H acid proton), 4.65-4.35 (m, 1H), 3.91-3.70 (m,

6H), 3.65-3.30 (m, 2H), 2.25-1.80 (m, 4H).

ESIMS $[\text{M}+\text{H}]^+$ (m/z): 424.

(5-Methyl-2-(6-methyl-4-oxoquinazolin-3(4H)-yl)benzoyl)-L-proline (23):^[15]

23: 90% white solid; mp: 129-131 °C; R_f : 0.3 (9:1, Dichloromethane:methanol+one drop acetic acid); $[\alpha]^{24}_D -83$ (c 0.5, CHCl_3).

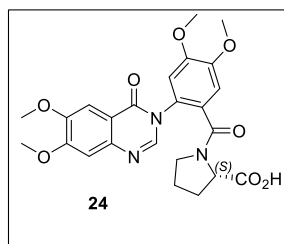
^1H NMR (400 MHz, CDCl_3 , mixture of atropisomers and rotamers): δ 8.10-8.00 (m, 2H), 7.65-7.30 (m, 4H), 7.30-7.20 (m, 1H), 5.70 (bs., 1H acid proton), 4.60-4.30 (m, 1H), 3.70-3.20 (m, 2H), 2.50-2.25 (m, 6H), 2.20-1.80 (m, 4H).

ESIMS[$\text{M}+\text{H}$] $^+$ (m/z): 392.

(E) Typical experimental procedure for the synthesis of representative compound 24:

To the solution of ester **19** (500 mg, 1.06 mmol, 1 equiv.) in THF/water (1:1, 5 mL) was added aqueous NaOH (80 mg, 1 mL 2 N, 2 mmol, 2 equiv.) drop wise at room temperature with continuous stirring and the reaction mixture was stirred until complete consumption of the starting material (checked by TLC). THF was then removed in vacuo followed by dilution with water (5 mL) and addition of ethyl acetate (5 mL). The organic layer was separated and the aqueous layer was acidified with citric acid up to pH 2 and extracted with ethyl acetate (5 mL X 3). The ethyl acetate layer was separated, dried over anhydrous Na_2SO_4 and concentrated in vacuo to obtain the corresponding amino acid **24** in 91% yield as a white solid (438 mg).

2-(6,7-Dimethoxy-4-oxoquinazolin-3(4H)-yl)-4,5-dimethoxybenzoic acid (24):

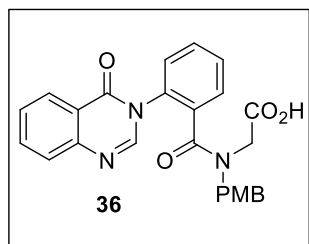


24: 91% white solid; mp: 110-112 $^{\circ}\text{C}$; R_f : 0.3 (9:1, Dichloromethane:methanol+one drop acetic acid); $[\alpha]^{24}_{\text{D}} -15.83$ (c 0.9, CHCl_3).

^1H NMR (400 MHz, CDCl_3 , mixture of atropisomers and rotamers): δ 8.10-7.90 (m, 1H), 7.60-7.45 (m, 1H), 7.01-6.80 (m, 3H), 4.50-4.43 (m, 1H), 4.02-3.85 (m, 12H), 3.60-3.30 (m, 2H), 2.25-2.10 (m, 1H), 2.10-1.70 (m, 3H).
 ^{13}C NMR (101 MHz, CDCl_3): δ 173.8, 166.8, 160.3, 155.1, 150.5, 150.1, 149.64, 149.55, 149.3, 146.0, 145.5, 142.7, 128.0, 127.5, 127.0, 126.6, 115.0, 114.9, 112.1, 111.9, 110.1, 109.0, 107.2, 105.5, 59.6, 59.2, 56.5, 56.43, 56.40, 56.35, 56.3, 56.2, 50.2, 49.3, 29.6, 29.2, 29.1, 25.1, 24.8, 22.6, 19.4.

HRMS-ESI (m/z) calcd for $(\text{C}_{24}\text{H}_{25}\text{N}_3\text{O}_8+\text{H})^+$: 484.1714, found: 484.1701.

***N*-(4-Methoxybenzyl)-*N*-(2-(4-oxoquinazolin-3(4H)-yl)benzoyl) glycine (36):**



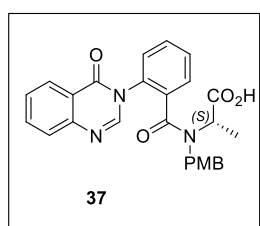
36: 85% white solid; mp: 180-182 $^{\circ}\text{C}$; R_f : 0.3 (9:1, Dichloromethane:methanol+one drop acetic acid).
 ^1H NMR (400 MHz, CDCl_3 , mixture of atropisomers and rotamers): δ 8.34-8.23 (m, 1H), 8.11-8.09 (m, 1H), 7.82-7.77 (m, 2H), 7.57-7.51 (m, 2H), 7.41-7.29 (m, 3H), 7.22-7.00 (m, 3.6H), 6.67 (d, $J = 7.1\text{Hz}$,

0.4H), 5.68 (d, $J = 7.5$ Hz, 0.2H), 5.52 (bs., 0.4H), 4.71 (bs., 0.2H), 4.46-4.40 (m, 0.2H), 3.45-3.30 (m, 2H), 3.19 (s, 1H), 2.98 (s, 1H), 2.74 (s, 2H).

^{13}C NMR (126 MHz, CDCl_3): δ 172.3, 171.4, 169.1, 168.5, 161.1, 159.3, 158.8, 147.6, 147.1, 146.9, 134.9, 134.6, 134.4, 130.9, 130.8, 130.0, 129.8, 129.4, 128.9, 128.7, 127.8, 127.6, 127.3, 127.2, 127.0, 126.9, 122.1, 121.8, 114.3, 113.8, 55.3, 55.1, 53.2, 49.0, 47.9, 45.7.

HRMS-ESI (m/z) calcd for $(\text{C}_{25}\text{H}_{21}\text{N}_3\text{O}_5+\text{H})^+$: 444.1554, found: 444.1532.

***N*-(4-Methoxybenzyl)-*N*-(2-(4-oxoquinazolin-3(4*H*)-yl) benzoyl) alanine (37):**



37: 89% white solid; mp: 182-184 °C; R_f : 0.3 (9:1, Dichloromethane: methanol+ one drop acetic acid); $[\alpha]_D^{24}$ -47.3 (c 0.8, CHCl_3).

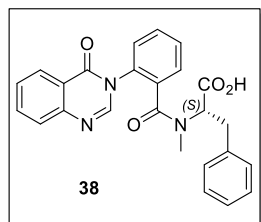
^1H NMR (400 MHz, CDCl_3 , mixture of atropisomers and rotamers): δ 8.35-8.10 (m, 2H), 7.90-7.35 (m, 7.5H), 7.16 (d, $J = 7.4$ Hz, 0.5H), 7.08(d, $J = 7.6$ Hz, 0.3H), 6.93 (d, $J = 8.1$ Hz, 0.7H), 6.83 (d, $J = 7.1$

Hz, 0.5H), 6.70 (d, $J = 8.5$ Hz, 0.7H), 6.56 (d, $J = 7.6$ Hz, 0.3H), 6.11 (d, $J = 8.5$ Hz, 0.5H), 5.21 (d, $J = 15.8$ Hz, 0.3H), 4.85 (d, $J = 17.0$ Hz, 0.4H), 4.71-4.55 (m, 0.7H), 4.40-4.20 (m, 0.6H), 3.90-3.50 (m, 4H), 1.35-1.10 (m, 3H).

^{13}C NMR (101 MHz, CDCl_3): δ 175.9, 168.9, 161.2, 161.0, 158.0, 147.9, 147.0, 146.7, 136.0, 134.8, 134.7, 134.3, 131.0, 130.6, 130.2, 130.0, 129.2, 129.1, 128.3, 127.72, 127.65, 127.6, 127.0, 126.9, 126.7, 122.2, 122.0, 114.3, 113.5, 113.2, 58.2, 55.3, 55.0, 46.8, 16.7, 12.5.

HRMS-ESI (m/z) calcd for $(\text{C}_{26}\text{H}_{23}\text{O}_5\text{N}_3+\text{H})^+$: 458.1710, found: 458.1696.

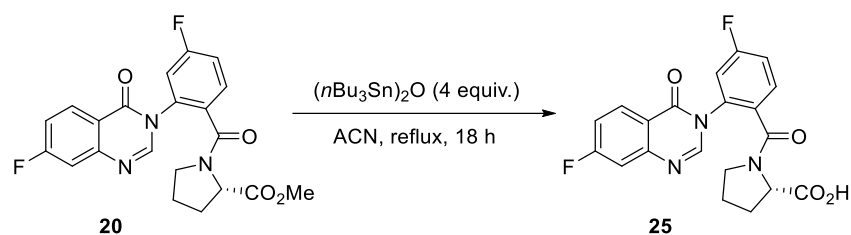
***N*-Methyl-*N*-(2-(4-oxoquinazolin-3(4*H*)-yl)benzoyl)phenylalanine (38):^[15]**



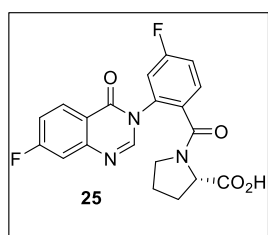
38: 91% white solid; mp: 158-160 °C; R_f : 0.3 (9:1, Dichloromethane:methanol+one drop acetic acid); $[\alpha]_D^{24}$ -32.9 (c 3, CHCl_3).

^1H NMR (400 MHz, CDCl_3 , mixture of atropisomers and rotamers): δ 8.25 (d, $J = 7.9$ Hz, 0.9H), 8.14 (s, 1.1H), 7.70-7.28 (m, 7.5H), 7.25-7.00 (m, 4H), 6.74 (s, 0.5H), 5.48 (s, 0.5H), 4.97 (bs., 1H acid proton), 4.50 (s, 0.5H), 3.55-3.30 (m, 1H), 3.21-2.70 (m, 4H).

ESIMS $[\text{M}+\text{H}]^+$ (m/z): 428.

[F] Procedure for the synthesis of compound 25:

A reported hydrolysis procedure was applied on compound **20**.^[23] The reaction mixture containing ester **20** (500 mg, 1.21 mmol, 1 equiv.) and $(n\text{Bu}_3\text{Sn})_2\text{O}$ (2.89 g, 2.47 mL, 4.84 mmol, 4 equiv.) in ACN (15 mL) was heated under reflux condition for 18 h. After completion of reaction (checked by TLC) solvent was evaporated in *vacuo*. The crude product was purified by silica gel flash chromatography using dichloromethane and methanol (9:1) as eluents to afford the product **25** in 90% yield as a white solid (437 mg).

(4-Fluoro-2-(7-fluoro-4-oxoquinazolin-3(4*H*)-yl) benzoyl)-*L*-proline (25):

25: 90% white solid; mp: 134-136 °C; R_f : 0.3 (9:1, Dichloromethane:methanol+one drop acetic acid); $[\alpha]^{24}_D -40.42$ (c 1, CHCl_3).

^1H NMR (500 MHz, CDCl_3 , mixture of atropisomers and rotamers): δ 8.30-8.10 (m, 2H), 7.65-7.29 (m, 2H), 7.23-7.00 (m, 3H), 4.55-4.30 (m, 1H), 3.70-3.20 (m, 2H), 2.30-2.10 (m, 1H), 2.05-1.75 (m, 3H).

^{13}C NMR (126 MHz, CDCl_3): δ 175.7, 174.5, 173.9, 167.7, 166.8, 166.5, 166.0, 165.7, 164.0, 163.2, 162.2, 162.0, 160.0, 149.7, 149.2, 147.6, 147.4, 136.2, 135.9, 135.8, 135.5, 132.2, 131.7, 131.4, 129.6, 128.9, 118.6, 118.4, 117.0, 116.9, 116.5, 116.3, 113.2, 113.0, 61.5, 58.9, 50.1, 49.4, 46.0, 36.8, 30.9, 29.6, 26.8, 26.2, 25.3, 24.7, 22.4, 13.4.

^{19}F NMR (377 MHz, CDCl_3) δ -102.3 (s), -108.4 (s).

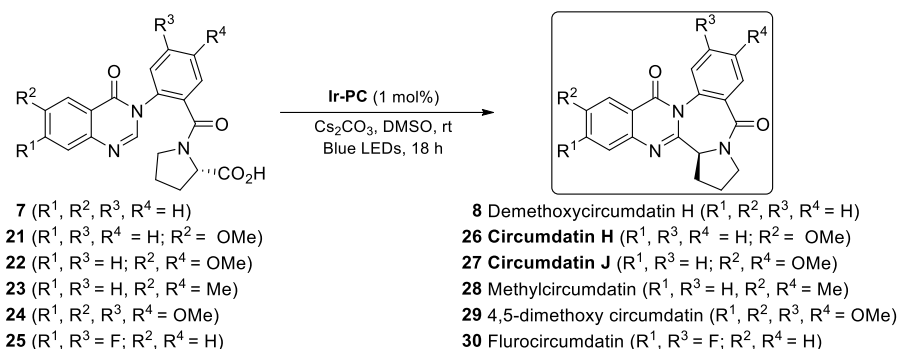
HRMS-ESI (m/z) calcd for $(\text{C}_{20}\text{H}_{15}\text{F}_2\text{N}_3\text{O}_4+\text{H})^+$: 400.1103, found: 400.1088.

[G] General procedure-V: Visible-Light Mediated Functionalization of quinazolinone alkaloids to obtain products 8, 26-30, 39-41: An oven dried schlenk tube containing a stirring bar, $[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$ (1 mol%), cesium carbonate (1.1 equiv.) and quinazolinone acid (**7**, **21-25**, **36-38**, 1 equiv.) was evacuated well, flushed and refilled with argon. Anhydrous DMSO was added via syringe and the reaction mixture was stirred under irradiation of 30 W blue LEDs (approximately 5 cm away from the light source) over 18-24 h at room temperature. After completion of reaction, the mixture was diluted with ethyl acetate

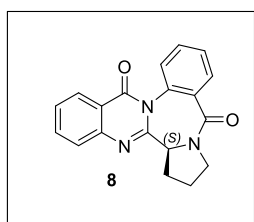
and washed with saturated aqueous NaHCO_3 solution. The aqueous phase was extracted with ethyl acetate three times and the combined organic phase was washed with brine. The united organic phases were dried over anhydrous Na_2SO_4 . The solvent was evaporated under reduced pressure and the crude product was purified by silica gel column chromatography using ethyl acetate and petroleum ether as eluents to obtain alkaloids **8**, **26-30**, **39-41** in good yields.

Note: Improved enantiomeric excess was obtained by recrystallization, wherein most of the undesired isomer crystallized out from the solution of isopropanol for all the final products.

Demethoxycircumdatin H (8), Circumdatin H (26) Circumdatin J (27), Methylcircumdatin (28), 4, 5-dimethoxycircumdatin (29), and Florocircumdatin (30):



(S)-5b,6,7,8-Tetrahydro-10H,16H-benzo[6,7]pyrrolo[2',1':3,4][1,4]diazepino[2,1-b]



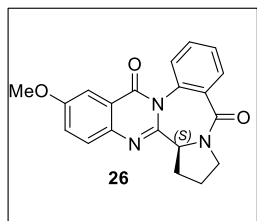
quinazoline -10,16-dione [Demethoxycircumdatin H 8]:^[15,25]

8: 86% (22.5 mg from 30 mg of 7) white solid; mp: 214-216 °C; R_f : 0.5 (7:3, ethyl acetate: petroleum ether); $[\alpha]_D^{24} -62.3.3$ (c 1.1, CHCl_3) ee = 77%, after recrystallization, $[\alpha]_D^{24} -42.3$ (c 0.5, CHCl_3) ee = 95%. {Lit. $[\alpha]_D^{20} -124.60$ (c 0.5, MeOH)}.^[25]

^1H NMR (400 MHz, CDCl_3): δ 8.31 (d, $J = 7.3$ Hz, 1H), 8.00 (d, $J = 7.5$ Hz, 1H), 7.80 (t, $J = 7.0$ Hz, 1H), 7.73 (d, $J = 7.5$ Hz, 1H), 7.60-7.56 (m, 2H), 7.55-7.50 (m, 2H), 4.56 (d, $J = 7.3$ Hz, 1H), 3.83-3.75 (m, 1H), 3.65-3.60 (m, 1H), 3.25-3.15 (m, 1H), 2.35-2.28 (m, 1H), 2.20-2.00 (m, 2H).

^{13}C NMR (101 MHz, CDCl_3): δ 164.5, 161.7, 153.6, 146.0, 134.8, 133.2, 132.3, 130.8, 129.9, 128.7, 128.3, 127.56, 127.55, 127.4, 121.5, 58.9, 46.5, 27.0, 23.7.

ESIMS[M+H]⁺ (m/z): 318.

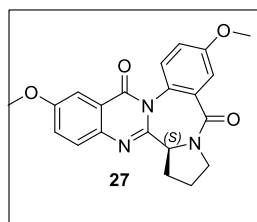
Circumdatin H (26):^[14,29]

26: 81% (22.4 mg from 30 mg of **21**) white solid; mp: 198-200 °C; R_f : 0.5 (5:5, ethyl acetate: petroleum ether); $[\alpha]^{24}_D -45.1$ (c 0.8, CHCl_3) ee = 76%, after recrystallization, $[\alpha]^{24}_D -51.3$ (c 0.8, CHCl_3) ee = 87%. {Lit. $[\alpha]^{25}_D -57.2$ (c 0.36 CHCl_3)} ee = 99%.^[29]

^1H NMR (400 MHz, CDCl_3): δ 8.00 (d, J = 7.5 Hz, 1H), 7.70-7.63 (m, 2H), 7.60-7.50 (m, 3H), 7.38 (dd, J = 8.9, 3.0 Hz, 1H), 4.55 (d, J = 7.5 Hz, 1H), 3.93 (s, 3H), 3.85-3.75 (m, 1H), 3.65-3.60 (m, 1H), 3.20-3.10 (m, 1H), 2.35-2.25 (m, 1H), 2.18-2.00 (m, 2H).

^{13}C NMR (101 MHz, CDCl_3): δ 164.5, 161.7, 159.0, 151.5, 140.6, 133.4, 132.5, 130.7, 129.9, 129.2, 128.6, 128.4, 124.9, 122.3, 106.9, 58.8, 55.9, 46.5, 27.0, 23.7.

ESIMS $[\text{M}+\text{H}]^+$ (m/z): 348, $[\text{M}+\text{Na}]^+$: 370.

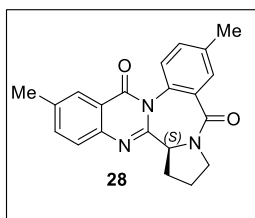
Circumdatin J (27):^[15,29]

27: 85% (22.7 mg from 30 mg of **21**) white solid; mp: 180-182 °C; R_f : 0.4 (5:5, ethyl acetate: petroleum ether); $[\alpha]^{24}_D -54.8$ (c 0.5, CHCl_3) ee = 71%, after recrystallization, $[\alpha]^{24}_D -63.3$ (c 0.6, CHCl_3) ee = 96%. {Lit. $[\alpha]^{25}_D -50.0$ (c 0.80 CHCl_3)} ee = 97%.^[29]

^1H NMR (400 MHz, CDCl_3): δ 7.70-7.60 (m, 2H), 7.50-7.45 (m, 2H), 7.37 (dd, J = 8.9, 3.0 Hz, 1H), 7.11 (dd, J = 8.9, 3.1 Hz, 1H), 4.57 (dd, J = 8.0, 1.5 Hz, 1H), 3.93 (s, 3H), 3.91 (s, 3H), 3.85-3.75 (m, 1H), 3.65-3.57 (m, 1H), 3.19-3.10 (m, 1H), 2.34-2.27 (m, 1H), 2.19-2.04 (m, 2H).

^{13}C NMR (101 MHz, CDCl_3): δ 164.4, 161.8, 159.2, 158.9, 151.7, 140.6, 133.5, 129.7, 129.1, 126.2, 124.8, 122.3, 117.9, 112.8, 106.8, 58.8, 55.9, 55.8, 46.6, 27.0, 23.7.

ESIMS $[\text{M}+\text{H}]^+$ (m/z): 378

[Methylylcircumdatin 28]:^[15]

28: 79% (21 mg from 30 mg of **17**) white solid; mp: 199-202 °C; R_f : 0.5 (6:4, ethyl acetate: petroleum ether); $[\alpha]^{24}_D -83.4$ (c 0.5, CHCl_3) ee = 82%, after recrystallization, $[\alpha]^{23}_D -71.2$ (c 0.6, CHCl_3) ee = 93% ee. {Lit. $[\alpha]^{27}_D -88.0$ (c 0.5, CHCl_3)} ee = 77%.^[15]

^1H NMR (400 MHz, CDCl_3): δ 8.10 (s, 1H), 7.80 (d, J = 2.0 Hz, 1H), 7.60 (s, 2H), 7.44 (d, J = 8.3 Hz, 1H), 7.40-7.36 (m, 1H), 4.54 (dd, J = 7.9, 1.4 Hz, 1H), 3.80-3.75 (m, 1H), 3.64-

3.57 (m, 1H), 3.19-3.14 (m, 1H), 2.50 (s, 3H), 2.46 (s, 3H), 2.34-2.30 (m, 1H), 2.16-2.03 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 164.7, 161.8, 152.9, 144.1, 138.8, 137.8, 136.1, 132.0, 131.6, 130.8, 130.0, 128.1, 127.4, 126.9, 121.2, 58.9, 46.5, 27.0, 23.7, 21.3, 21.0.

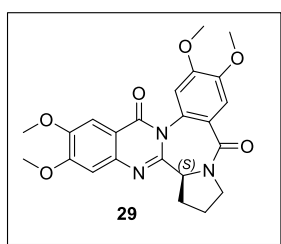
ESIMS[M+H] $^+$ (m/z): 346

(H) Typical experimental procedure for the synthesis of representative compound 29:

An oven dried schlenk tube containing a stirring bar, $[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$ (0.67 mg, 0.060 μmol 1 mol%), cesium carbonate (21.64 mg, 0.066 mmol, 1.1 equiv.) and quinazolinone acid (30 mg, 0.060 mmol, 1 equiv.) was evacuated well, flushed and refilled with argon. Anhydrous DMSO (1 ml) was added via syringe and the reaction mixture was stirred under irradiation of 30 W blue LEDs (approximately 5 cm away from the light source) over 18 h at room temperature. After completion of reaction (checked by TLC), the mixture was diluted with ethyl acetate and washed with saturated aqueous NaHCO_3 solution. The aqueous phase was extracted with ethyl acetate (5 mL X 3) three times and the combined organic extracts were washed with brine. The united organic phases were dried over anhydrous Na_2SO_4 . The solvent was evaporated under reduced pressure and the crude product was purified by silica gel column chromatography using ethyl acetate and petroleum ether (5:5) as eluents to obtain Circumdatin alkaloid **29** in 80% yield (22.3 mg).

(S)-2,3,12,13-tetramethoxy-5b,6,7,8-tetrahydro-10H,16H-

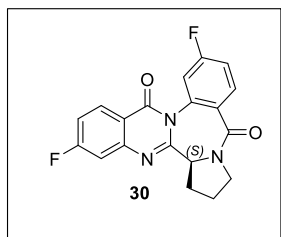
benzo[6,7]pyrrolo[2',1':3,4][1,4]diazepino[2,1-b]quinazoline-10,16-dione (**29**)



29: 80% (22.3 mg from 30 mg of **24**) white solid; mp: 241-243 $^{\circ}\text{C}$; R_f : 0.4 (7:3, ethyl acetate: petroleum ether); $[\alpha]^{24}_{\text{D}} -16.08$ (c 3, CHCl_3) ee = 72%, after recrystallization, $[\alpha]^{24}_{\text{D}} -13.8$ (c 0.8, CHCl_3) ee = 93%.

^1H NMR (400 MHz, CDCl_3): δ 7.64 (s, 1H), 7.43 (s, 1H), 7.11 (s, 1H), 7.03 (s, 1H), 4.56 (d, $J = 7.6$ Hz, 1H), 4.05 (s, 3H), 4.01 (s, 3H), 4.00 (s, 3H), 3.93 (s, 3H), 3.78-3.70 (m, 1H), 3.66-3.59 (m, 1H), 3.20-3.10 (m, 1H), 2.35-2.28 (m, 1H), 2.20-2.04 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3): δ 164.6, 161.1, 155.2, 152.8, 150.2, 149.5, 148.8, 142.4, 127.2, 125.1, 114.7, 111.1, 111.0, 108.0, 106.3, 58.9, 56.38, 56.37, 56.3, 56.2, 46.5, 27.0, 23.8.

HRMS-ESI (m/z) calcd for $(\text{C}_{23}\text{H}_{23}\text{N}_3\text{O}_6+\text{H})^+$: 438.1660, found: 438.1649.

(S)-3,13-difluoro-5b,6,7,8-tetrahydro-10H,16H-**benzo[6,7]pyrrolo[2',1':3,4][1,4]diazepino[2,1-b]quinazoline-10,16-dion (30)**

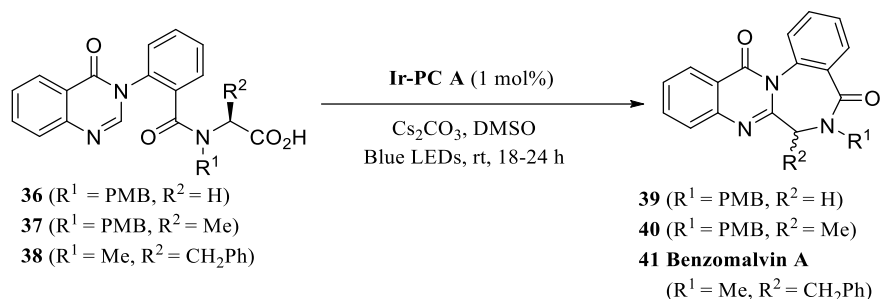
30: 77% (20.5 mg from 30 mg of **25**) white solid; mp: 210-212 °C; R_f : 0.4 (4:6, ethyl acetate: petroleum ether); $[\alpha]^{24}_D -43.9$ (c 1.4, CHCl_3) ee = 70%, after recrystallization, $[\alpha]^{20}_D -17.9$ (c 0.4, CHCl_3) ee = 95%.

^1H NMR (400 MHz, CDCl_3) δ 8.33 (dd, J = 8.8, 6.0 Hz, 1H), 8.01 (dd, J = 8.8, 6.1 Hz, 1H), 7.38 (dd, J = 9.3, 2.4 Hz, 1H), 7.32 (dd, J = 9.6, 2.4 Hz, 1H), 7.28-7.20 (m, 2H), 4.54 (dd, J = 7.8, 1.5 Hz, 1H), 3.82-3.76 (m, 1H), 3.65-3.57 (m, 1H), 3.18-3.13 (m, 1H), 2.32-2.29 (m, 1H), 2.22-2.05 (m, 2H).

^{13}C NMR (101 MHz, CDCl_3): δ 167 (d, $J_{\text{C-F}}$ = 255.6 Hz), 163.61, 163.0 (d, $J_{\text{C-F}}$ = 252.5 Hz), 160.6, 154.5, 148.2 (d, $J_{\text{C-F}}$ = 12.9 Hz), 134.5 (d, $J_{\text{C-F}}$ = 10.7 Hz), 132.1 (d, $J_{\text{C-F}}$ = 9.1 Hz), 130.4 (d, $J_{\text{C-F}}$ = 10.8 Hz), 128.7, 118.0, 116.6 (d, $J_{\text{C-F}}$ = 3.8 Hz), 116.4, 116.0 (d, $J_{\text{C-F}}$ = 25.9 Hz), 113.2 (d, $J_{\text{C-F}}$ = 21.3 Hz), 58.9, 46.6, 27.0, 23.7.

^{19}F NMR (377 MHz, CDCl_3) δ -102. (s), -107 (s).

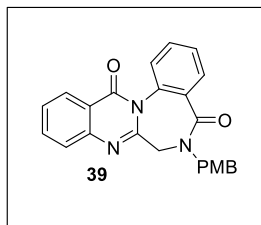
HRMS-ESI (m/z) calcd for $(\text{C}_{19}\text{H}_{13}\text{F}_2\text{N}_3\text{O}_2+\text{H})^+$: 354.1049, found: 354.1033.

Alkaloids 39, 40 and Benzomalvin A (41):**(I) Typical experimental procedure for the synthesis of representative compound 39:**

An oven dried schlenk tube containing a stirring bar, $[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$ (0.76 mg, 0.067 μmol , 1 mol%), cesium carbonate (24 mg, 0.074 mmol, 1.1 equiv.) and quinazolinone acid (30 mg, 1 equiv.) was evacuated well, flushed and refilled with argon. Anhydrous DMSO was added via syringe and the reaction mixture was stirred under irradiation of 30 W blue LEDs (approximately 5 cm away from the light source) over 18h at room temperature. After completion of reaction (checked by TLC), the mixture was diluted with ethyl acetate and washed with saturated aqueous NaHCO_3 solution. The aqueous phase was extracted with ethyl acetate (5 mL X 3) and the combined organic phase was washed

with brine. The united organic phases were dried over anhydrous Na_2SO_4 . The solvent was evaporated under reduced pressure and the crude product was purified by silica gel column chromatography using ethyl acetate and petroleum ether (4:6) as eluents to obtain alkaloid **39** in 80% yield (21.5 mg).

6-(4-Methoxybenzyl)-6,7-dihydrobenzo[6,7][1,4]diazepino[2,1-b]quinazoline-5,13-dione



(39):

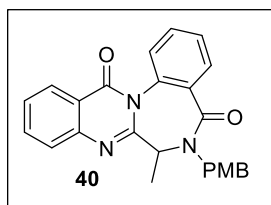
39: 80% (21.5 mg from 30 mg of **36**) light yellow solid; mp: 122-124 °C; R_f : 0.4 (5:5, ethyl acetate: petroleum ether).

^1H NMR (400 MHz, CDCl_3) δ 8.33 (dd, J = 8.00, 1.3 Hz, 1H), 8.04-8.00 (m, 1H), 7.85-7.70 (m, 1H), 7.68-7.50 (m, 5H), 7.32-7.25 (m, 2H), 6.84-6.80 (m, 2H), 5.23 (d, J = 14.6 Hz, 1H), 4.40-4.25 (m, 2H), 4.18-4.10 (m, 1H), 3.75 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3): δ 166.3, 161.1, 159.3, 152.3, 146.2, 134.8, 133.5, 131.1, 130.9, 130.5, 129.8, 128.8, 128.3, 127.65, 127.59, 127.5, 127.4, 121.5, 114.1, 55.2, 51.7, 49.8.

HRMS-ESI (m/z) calcd for $(\text{C}_{24}\text{H}_{19}\text{N}_3\text{O}_3+\text{H})^+$: 398.1504, found: 398.1503.

6-(4-Methoxybenzyl)-7-methyl-6,7-dihydrobenzo[6,7][1,4]diazepino[2,1-b]quinazoline-5,13-dione (40)



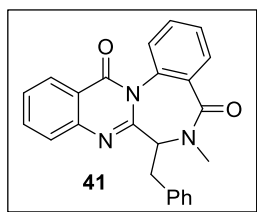
40: 81% yield as mixture of two diastereomers in 1:0.3 ratio. (22 mg from 30 mg of **37**) off white solid; mp: 164-166 °C; R_f : 0.5 (6:4, ethyl acetate: petroleum ether); $[\alpha]^{24}_D$ 0.8 (c 0.9, CHCl_3).

^1H NMR (400 MHz, CDCl_3) δ 8.33-8.28 (m, 1.3H), 8.03-7.99 (m, 1.3H), 7.79-7.71 (m, 1.3H), 7.61-7.49 (m, 6.6H), 7.30 (d, J = 8.6 Hz, 0.6H), 7.14 (d, J = 8.5 Hz, 2H), 6.80 (d, J = 8.6 Hz, 0.6H), 6.60 (d, J = 8.5 Hz, 2H), 5.25 (d, J = 14.4 Hz, 0.3H), 4.96 (d, J = 15.3 Hz, 1H), 4.78 (q, J = 6.9 Hz, 1H), 4.72 (q, J = 7.6 Hz, 0.3H), 4.63-4.59 (d, J = 15.3 Hz, 1H), 4.41-4.37 (d, J = 14.5 Hz, 0.3H), 3.74 (s, 0.9H), 3.58 (s, 3H), 1.70 (d, J = 6.9 Hz, 3H), 0.88 (d, J = 7.6 Hz, 0.9H).

^{13}C NMR (101 MHz, CDCl_3): δ 167.7, 165.5, 161.6, 161.3, 159.2, 158.4, 154.7, 153.6, 146.3, 145.9, 134.9, 134.4, 133.3, 133.0, 132.0, 131.6, 131.0, 130.9, 130.8, 130.1, 130.0, 129.9, 128.8, 128.5, 128.5 (2C), 127.9, 127.6, 127.6, 127.6, 127.4, 127.3, 127.3, 127.2, 121.4, 121.3, 114.0, 113.6, 60.8, 55.2, 55.0, 53.8, 51.9, 44.5, 16.6, 13.9.

HRMS-ESI (m/z) calcd for $(\text{C}_{25}\text{H}_{21}\text{N}_3\text{O}_3+\text{H})^+$: 412.1656, found: 412.1662.

Benzomalvin A (41):^[27] The analytical and spectral data of the known natural product



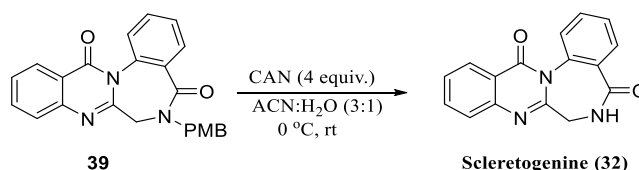
benzomalvin A (**41**) is in agreement with the reported data except for the optical rotation.^[27]

41: 76% yield as mixture of two diastereomers in 1:0.17 ratio. (20.3 mg from 30 mg of **38**) white solid; mp: 106-108 °C; R_f: 0.5 (6:4, ethyl acetate: petroleum ether); [α]²⁴_D 0.04 (c 0.8, CHCl₃) {Lit. [α]²¹

_D -109 (c 1.0, MeOH)}^[27] **¹H NMR** (400MHz, CDCl₃) δ 8.37-8.33 (m, 1.2H), 8.09-8.04 (m, 0.2H), 7.98-7.96 (m, 1H), 7.86-7.81 (m, 2.3H), 7.70-7.55 (m, 5.1H), 7.30-7.22 (m, 6.2H), 7.04-7.01 (m, 0.4H), 4.95-4.85 (m, 1H), 4.83-4.79 (m, 0.2H), 3.90-3.78 (m, 1.2H), 3.50-3.40 (m, 1.2H), 3.15 (s, 3H), 2.95 (s, 0.5H).

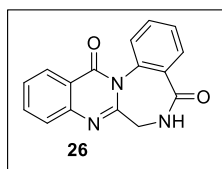
¹³C NMR (101 MHz, CDCl₃): δ 167.3, 161.2, 153.7, 151.8, 145.9, 136.6, 135.9, 135.0, 134.8, 132.9, 131.4, 131.1, 130.9, 130.7, 129.9, 129.1, 129.0, 128.9, 128.8, 128.7, 128.1, 127.8, 127.7, 127.7, 127.5, 127.4, 127.3, 126.9, 121.7, 121.4, 70.3, 58.3, 38.3, 33.1, 27.9, 24.7. **HRMS-ESI** (m/z) calcd for (C₂₄H₁₉N₃O₂+H)⁺: 382.1555, found: 382.1552.

[J] 6,7-Dihydrobenzo[6,7][1,4]diazepino[2,1-*b*]quinazoline-5,13-dione [Scleretogenine (30)]:



PMB group was deprotected using literature known procedure.^[23] To the solution of PMB protected substrate **39** (30 mg, 0.075 mmol, 1 equiv.) in acetonitrile and water (3:1 v/v, 2 mL) at 0 °C was added solid CAN (165.64 mg, 4 equiv.) in one portion and the resulting orange solution was stirred at 0 °C for 4 h. After completion of reaction (monitored by TLC), it was diluted with EtOAc and saturated NaHCO₃. The resulting suspension was stirred for 30 minutes at rt, and it was vacuum filtered through a pad of celite. After the two layers were separated, the organic layer was washed once with brine. The combined aqueous layers were saturated with solid NaCl and extracted with EtOAc. The organic layers were combined and dried over Na₂SO₄. After filtration, the solvent was evaporated under reduced pressure and the crude residue was purified by silica gel chromatography using ethyl acetate and petroleum ether (7:3) to furnish scleretogenine (**32**) natural product in 74% yield (15.2 mg).

The analytical and spectral data of the natural product scleretogenine (**32**) is in agreement with the reported data.^[24]

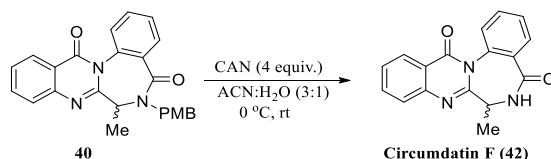


32: 74% (15.2 mg from 30 mg of **39**) white solid; mp: 297-299 °C; R_f : 0.3 (8:2, ethyl acetate: petroleum ether).

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.35-8.30 (m, 1H), 8.03-7.99 (m, 1H), 7.85-7.78 (m, 1H), 7.72-7.70 (m, 1H), 7.67-7.62 (m, 2H), 7.60-7.52 (m, 2H), 7.07 (t, J = 6.1 Hz, 1H), 4.40-4.20 (m, 2H); $^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 168.2, 161.4, 153.6, 146.2, 135.1, 133.7, 131.5, 130.4, 129.8, 129.1, 128.1, 127.8, 127.6, 127.3, 121.5, 47.1.

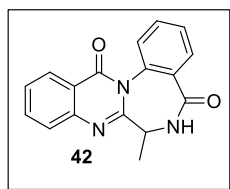
HRMS-ESI (m/z) calcd for $(\text{C}_{16}\text{H}_{11}\text{N}_3\text{O}_2+\text{H})^+$: 278.0929, found: 278.0934.

[K] 7-Methyl-6,7-dihydrobenzo [6,7] [1,4]diazepino[2,1-*b*]quinazoline-5,13-dione [Circumdatin F (42**)]:**



PMB group was deprotected using literature known procedure.^[28] To the solution of PMB protected substrate **40** (30 mg, 0.072 mmol, 1 equiv) in acetonitrile and water (3:1 v/v, 2 mL) at 0 °C was added solid CAN (159 mg, 0.29 mmol, 4 equiv.) in one portion and the resulting orange solution was stirred at 0 °C for 6 h. After completion of reaction (monitored by TLC), it was diluted with EtOAc and saturated aqueous NaHCO_3 . The resulting suspension was stirred for 30 min at rt, and it was vacuum filtered through a pad of celite. After the two layers were separated, the organic layer was washed once with brine. The combined aqueous layers were saturated with solid NaCl and extracted with EtOAc. The organic layers were combined and dried over Na_2SO_4 . After filtration, the solvent was evaporated under reduced pressure and the crude residue was purified by silica gel chromatography using ethyl acetate and petroleum ether (6:4) to furnish Circumdatin F (**42**) natural product 76% yield (15.5 mg).

The analytical and spectral data of circumdatin F (**42**) is in agreement with the reported data.^[29]



42: 76% (15.5 mg from 30 mg of **39**) white solid; mp: 251-254 °C; R_f : 0.3 (8:2, ethyl acetate: petroleum ether); $[\alpha]^{24}_{\text{D}} -1.19$ (c 0.5, CHCl_3). {Lit. $[\alpha]^{29}_{\text{D}} -152.4$ (c 0.4, CHCl_3)}^[29a] $^1\text{H NMR}$ (CDCl_3 , 400MHz): δ 8.33 (dd, J = 8.0, 1.5 Hz, 1H), 7.99-7.96 (m, 1H), 7.83-7.73 (m, 2H),

7.65-7.52 (m, 4H), 6.28 (d, J = 6.1 Hz, 1H), 4.45-4.36 (m, 1H), 1.72 (d, J = 6.6 Hz, 3H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 167.5, 161.6, 154.9, 146.2, 134.9, 133.5, 131.4, 130.5, 129.9, 129.0, 128.4, 127.71, 127.66, 127.5, 121.5, 49.9, 15.5.

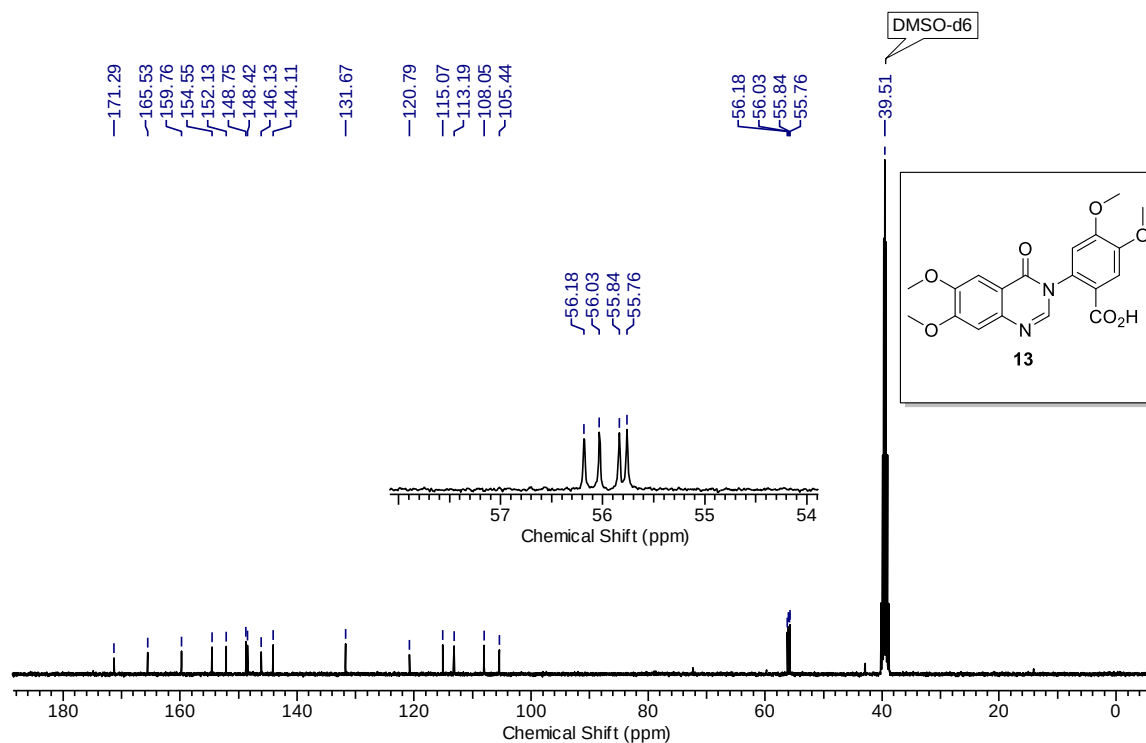
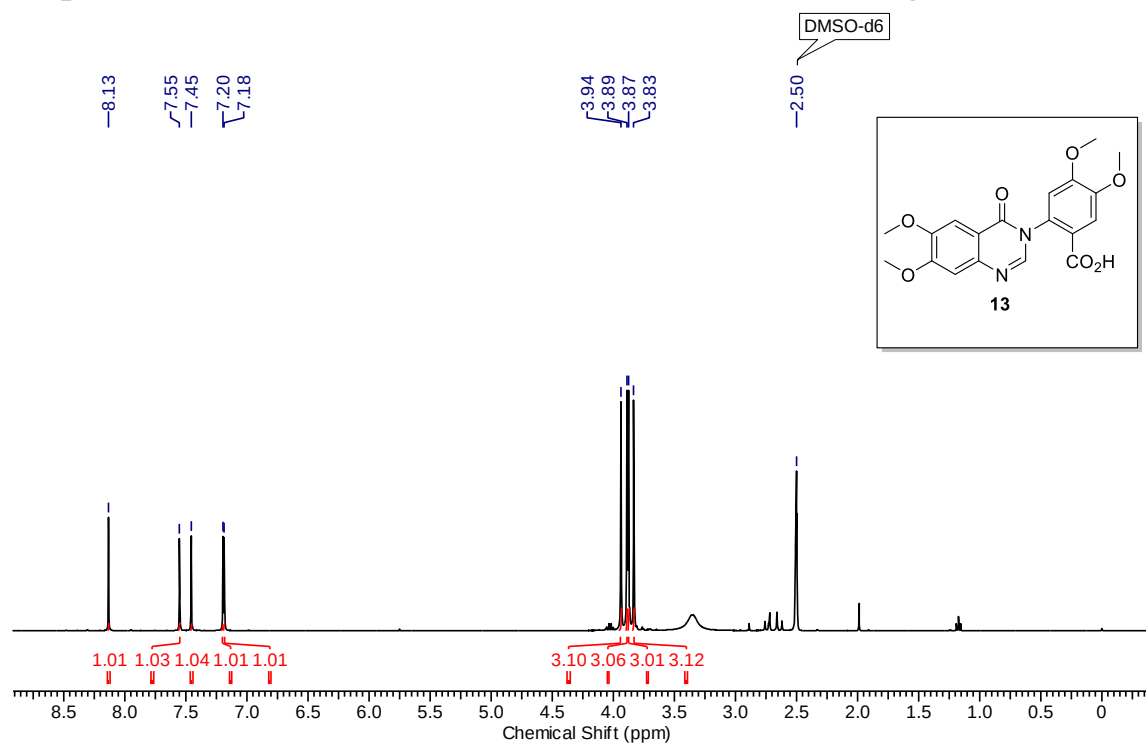
HRMS-ESI (m/z) calcd for $(\text{C}_{17}\text{H}_{13}\text{N}_3\text{O}_2+\text{H})^+$: 292.1085, found: 292.1078.

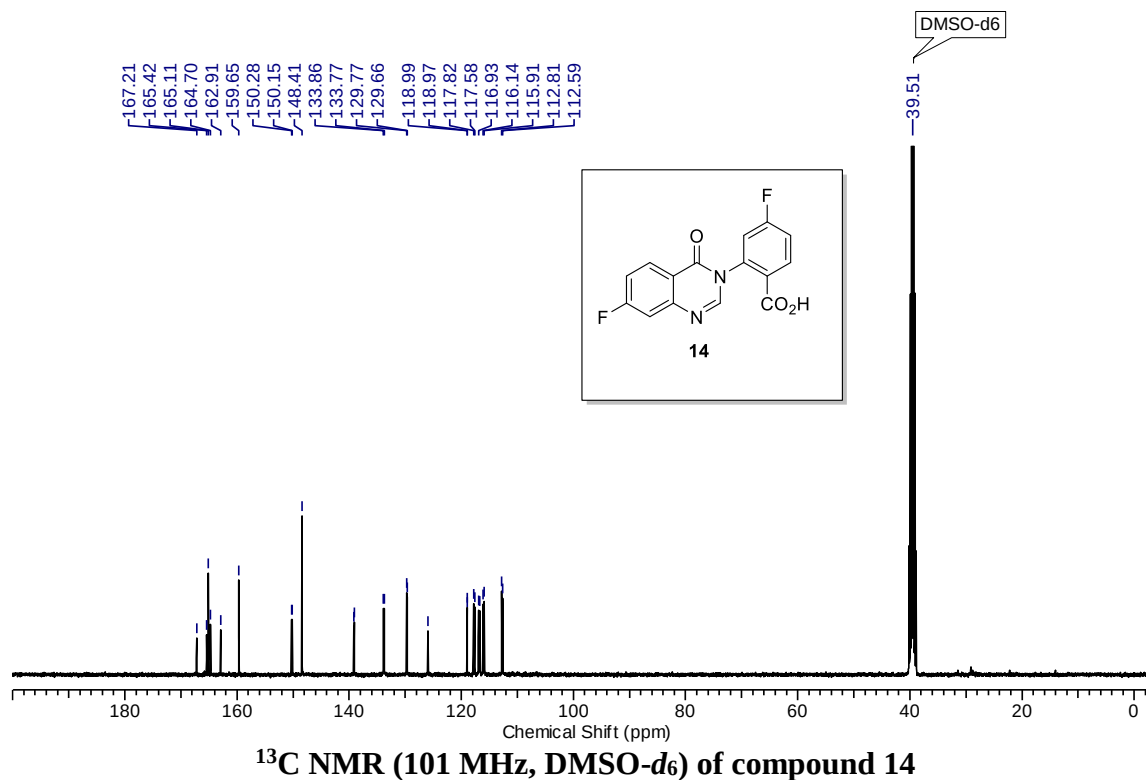
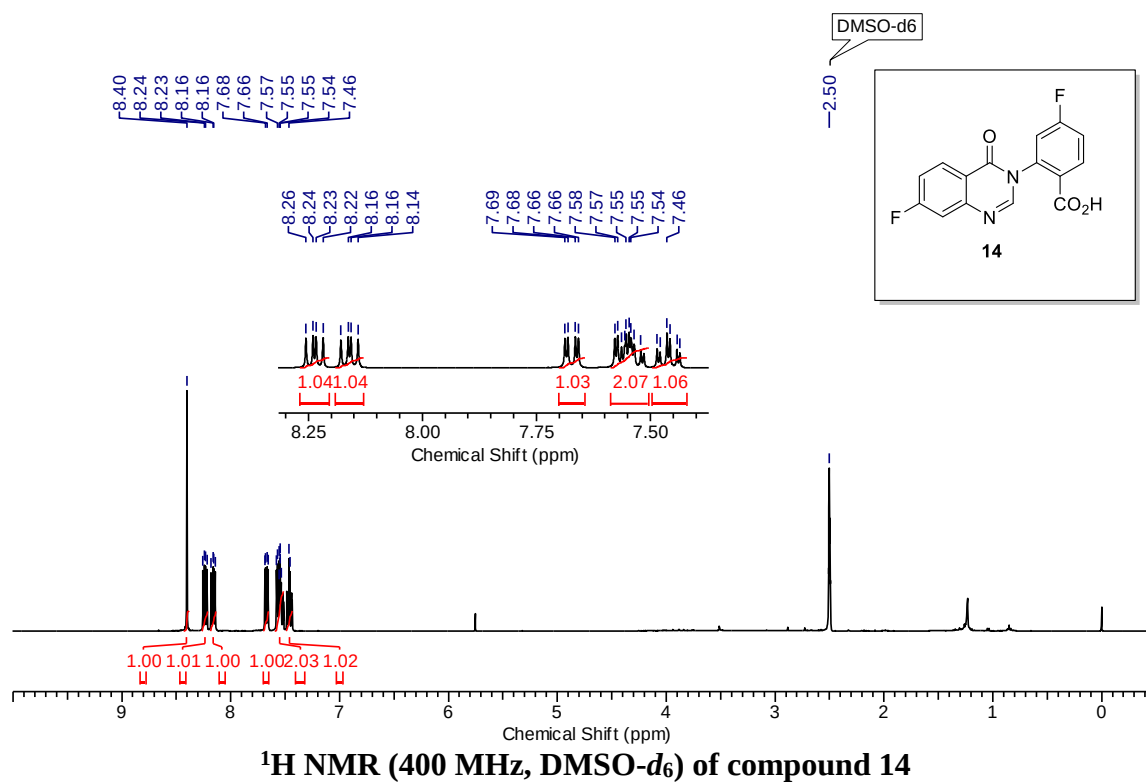
2.8 References:

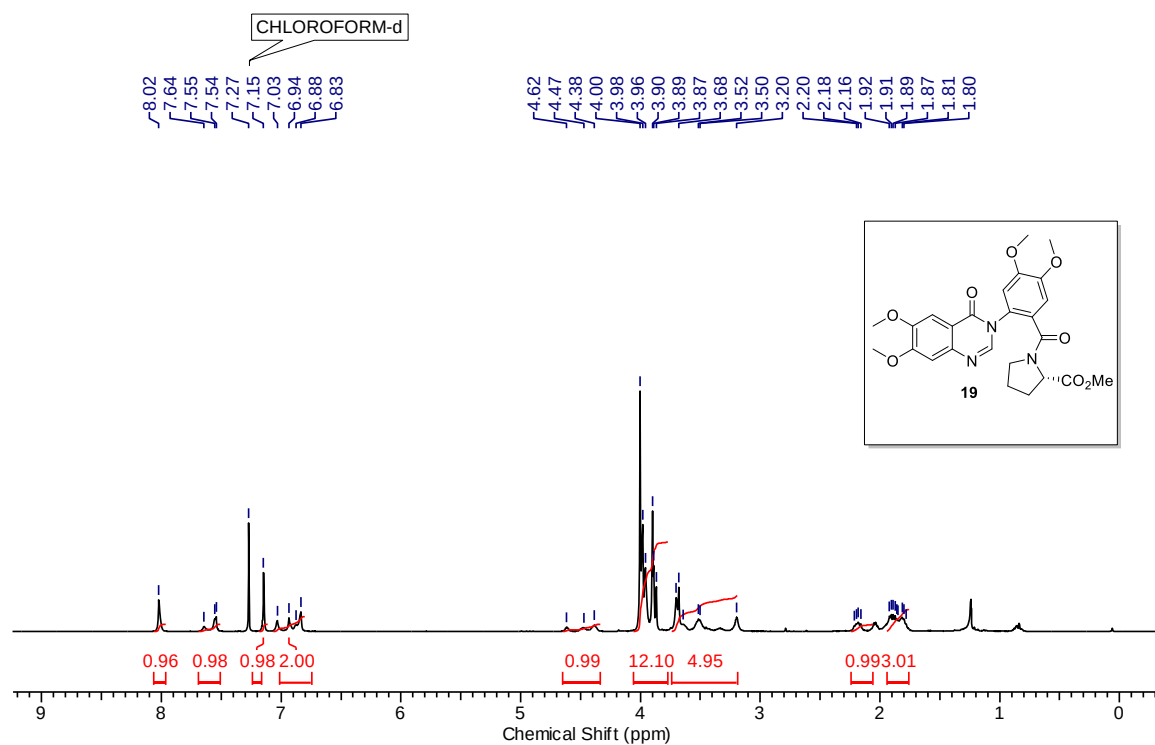
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- [2] For selected example of visible light-mediated C–H bond functionalization of electron-deficient heteroarenes: a) X. Shao, X. Wu, S. Wu, C. Zhu, *Org. Lett.* **2020**, *22*, 7450–7454; b) Z. Wang, Q. Liu, X. Ji, G. J. Deng, H. Huang, *ACS Catal.* **2020**, *10*, 154–159; c) X. A. Liang, L. Niu, S. Wang, J. Liu, A. Lei, *Org. Lett.* **2019**, *21*, 2441–2444; d) X. L. Lyu, S. S. Huang, H. J. Song, Y. Liu, Q. M. Wang, *Org. Lett.* **2019**, *21*, 5728–5732; e) Z. Wang, X. Ji, J. Zhao, H. Huang, *Green Chem.* **2019**, *21*, 5512–5516; f) J. Genovino, Y. Lian, Y. Zhang, T. O. Hope, A. Juneau, Y. Gagné, G. Ingle, M. Frenette, *Org. Lett.* **2018**, *20*, 3229–3232; g) N. B. Bissonnette, M. J. Boyd, G. D. May, S. Giroux, P. Nuhant, *J. Org. Chem.* **2018**, *83*, 10933–10940; h) G. X. Li, X. Hu, G. He, G. Chen, *ACS Catal.* **2018**, *8*, 11847–11853; i) X. Wu, H. Zhang, N. Tang, Z. Wu, D. Wang, M. Ji, Y. Xu, M. Wang, C. Zhu, *Nat. Commun.* **2018**, *9*, 3343; j) J. Jin, D. W. C. MacMillan, *Angew. Chem. Int. Ed.* **2015**, *54*, 1565–1569.
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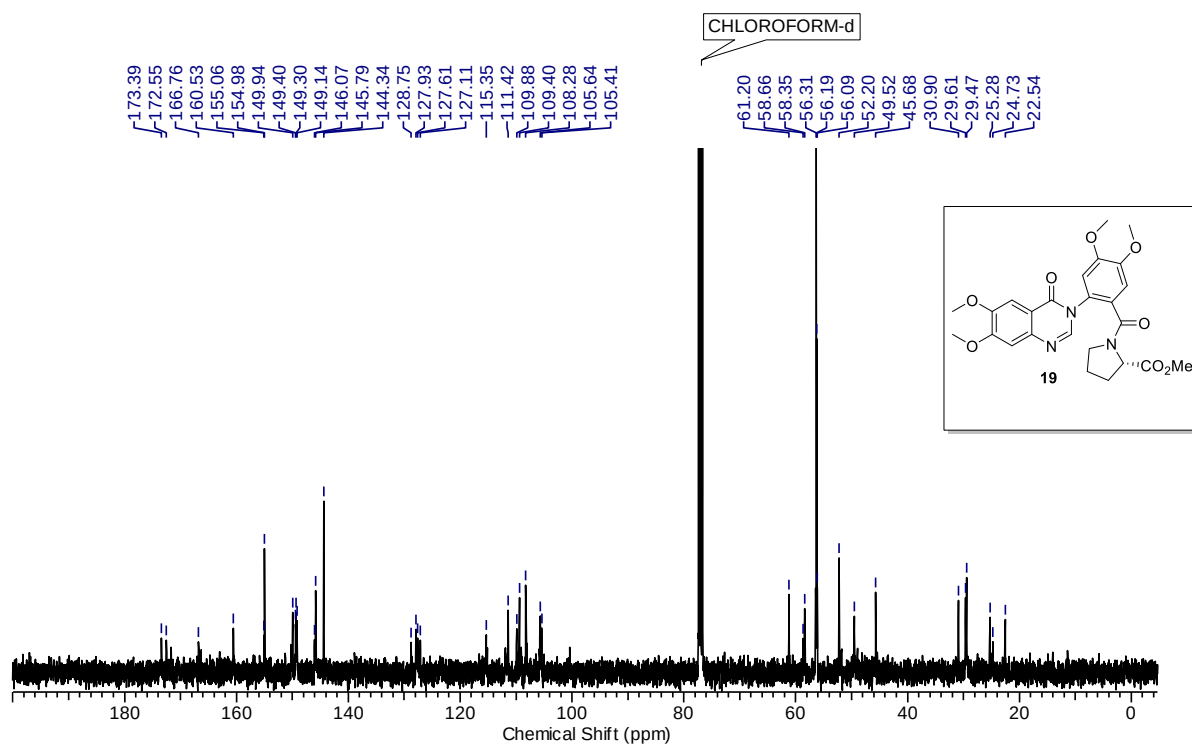
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2.9 Spectra of ^1H , ^{13}C , DEPT NMR and HRMS Chromatogram.

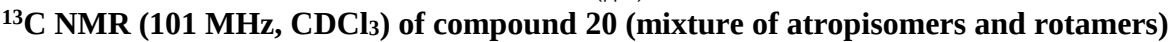


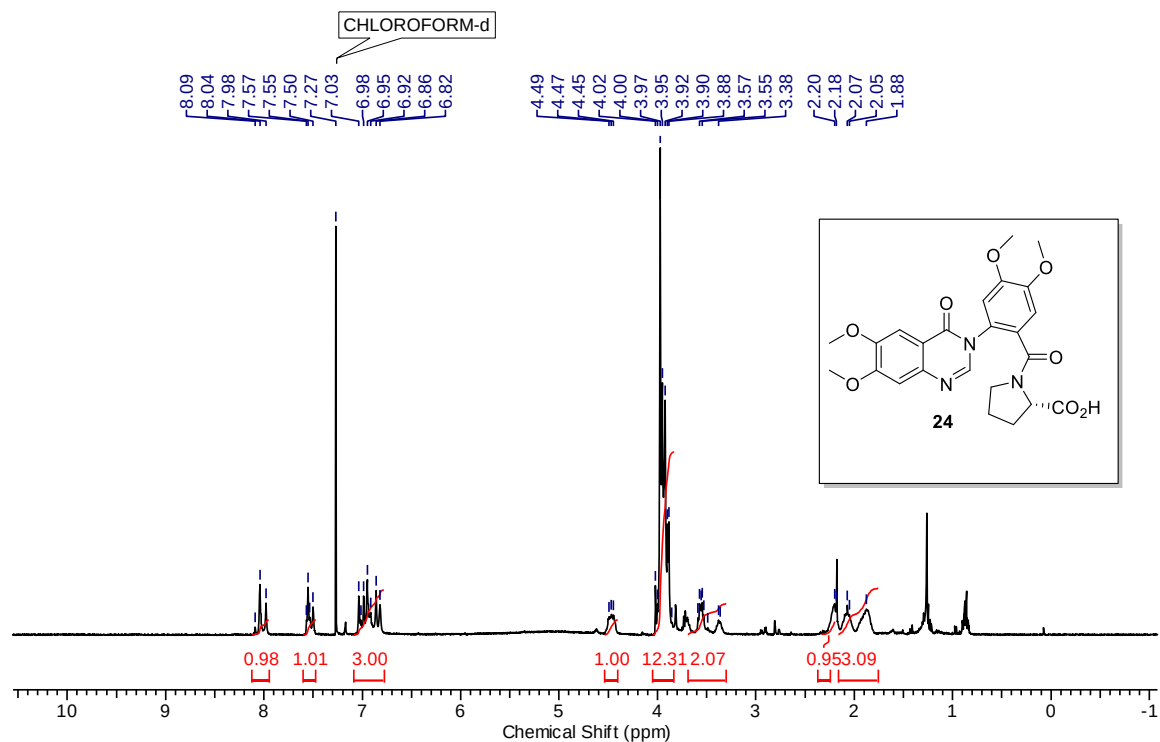


¹H NMR (400 MHz, CDCl₃) of compound 19 (mixture of atropisomer and rotamer)

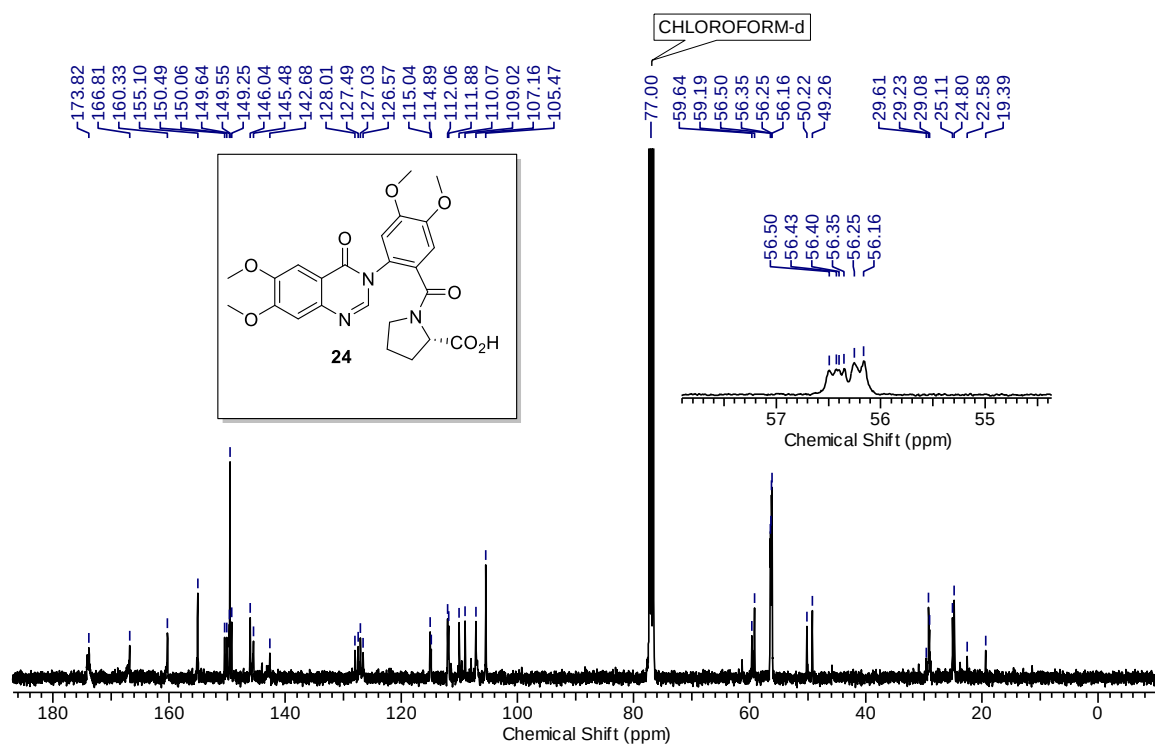


¹³C NMR (101 MHz, CDCl₃) of compound 19 (mixture of atropisomer and rotamer)

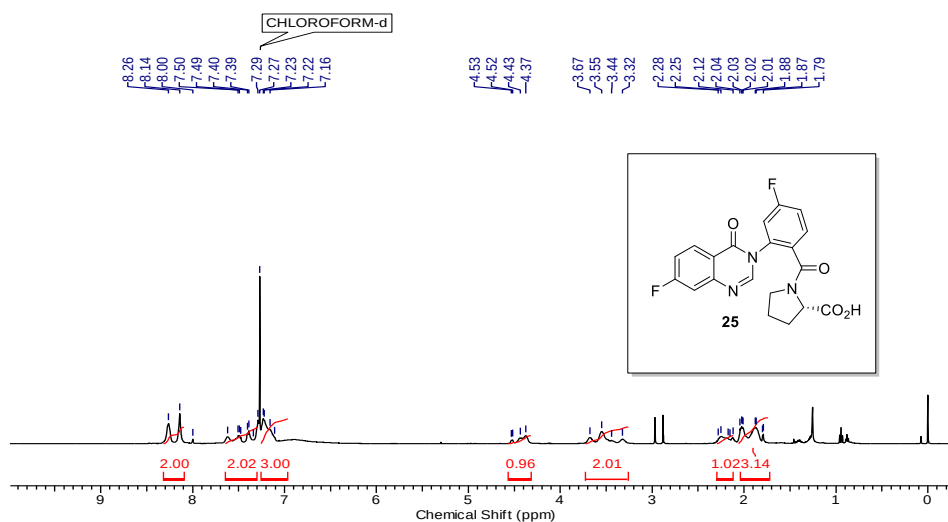




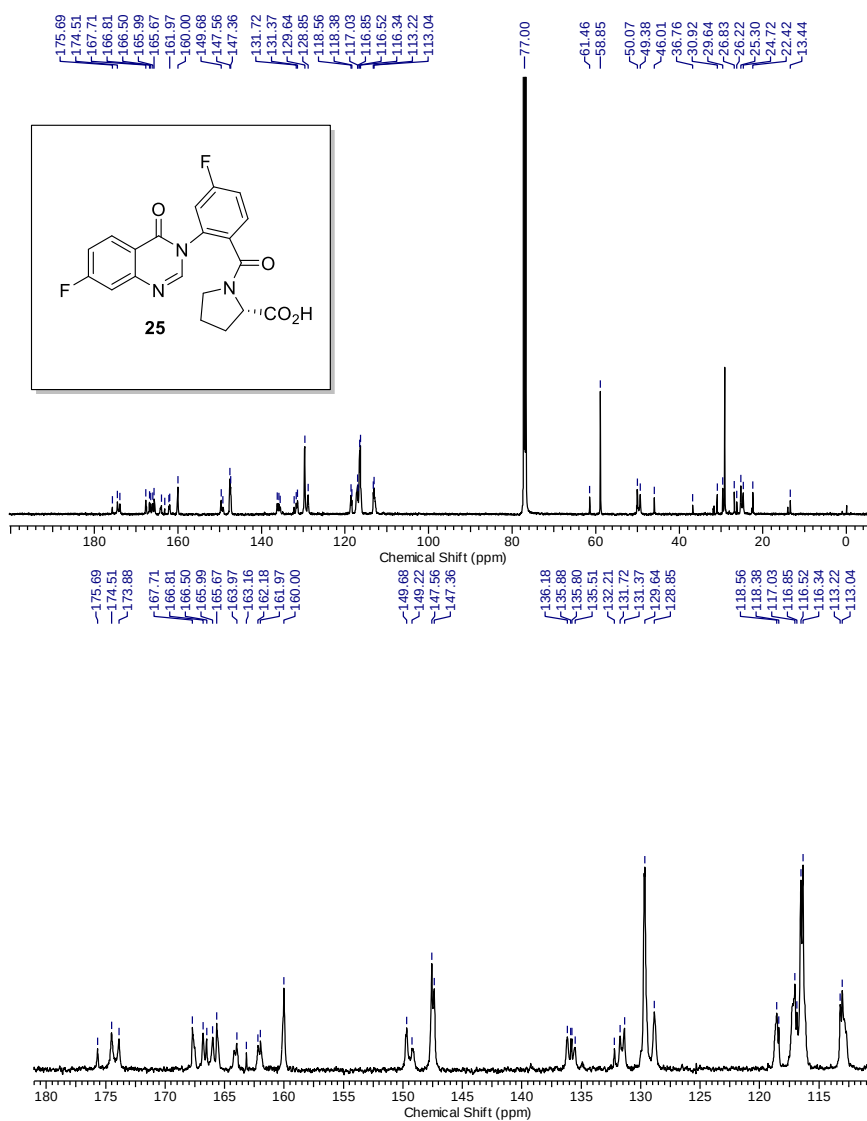
¹H NMR (400 MHz, CDCl₃) of compound 24 (mixture of atropisomers and rotamers)



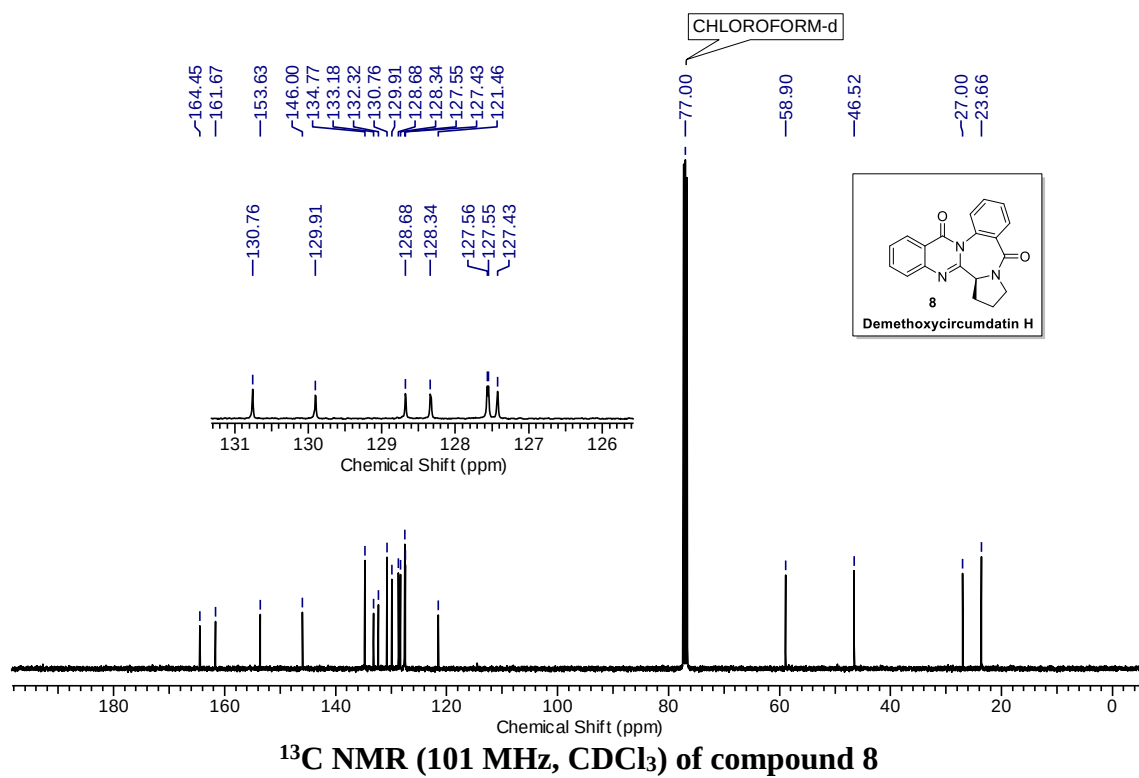
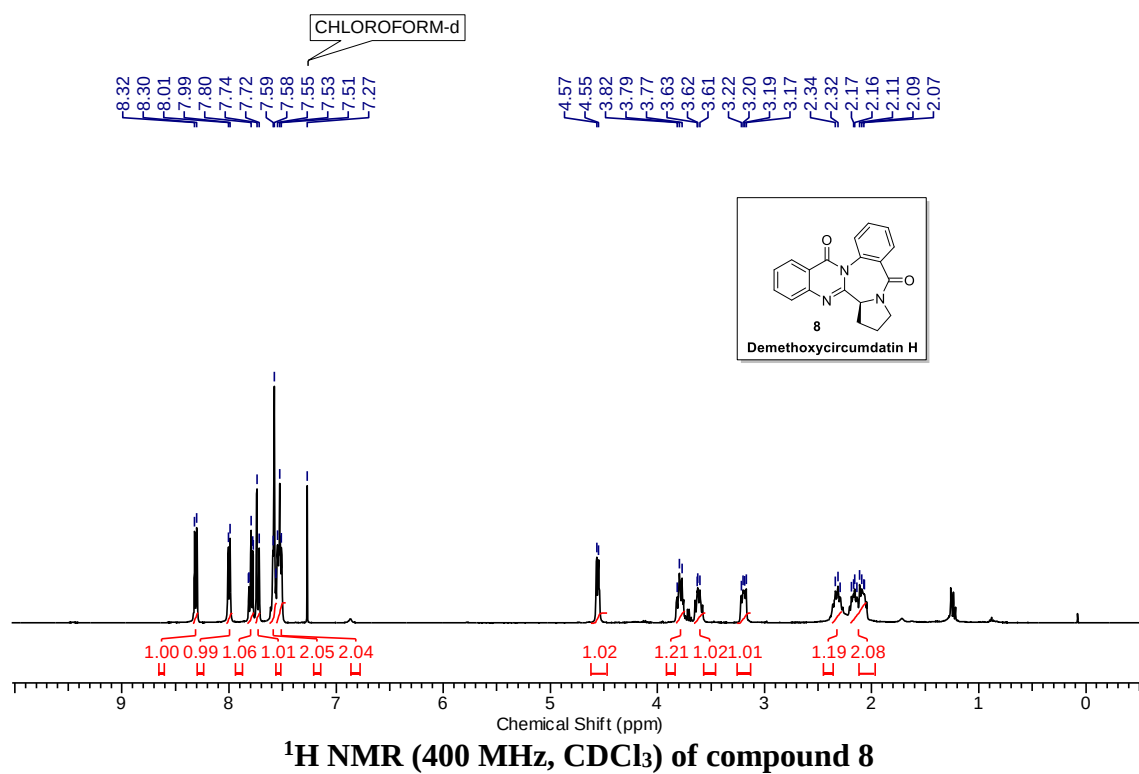
¹³C NMR (101 MHz, CDCl₃) of compound 24 (mixture of atropisomers and rotamers)

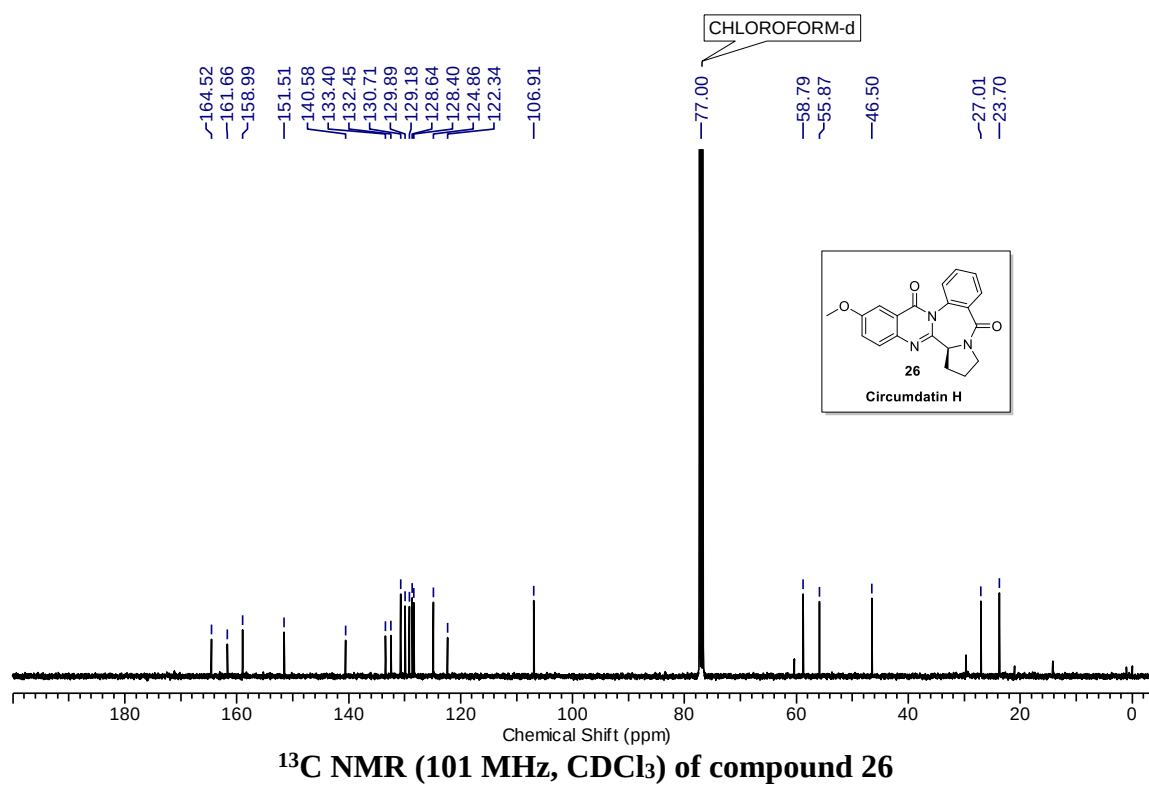
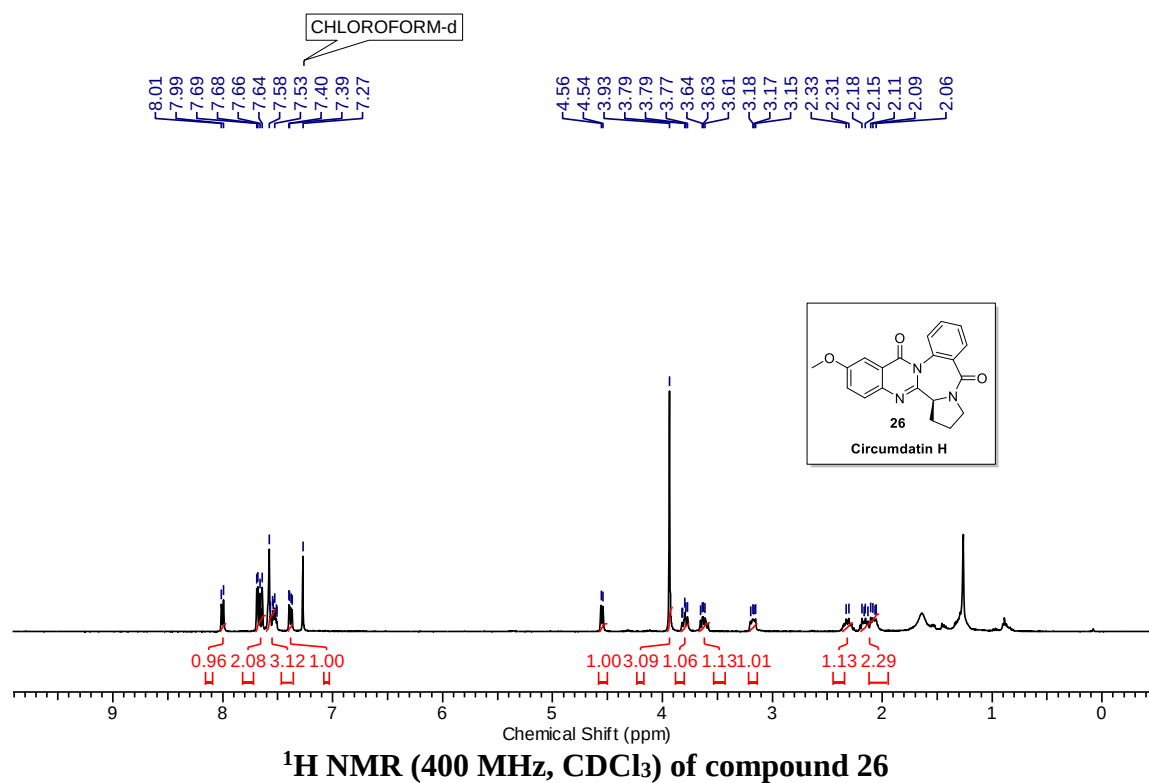


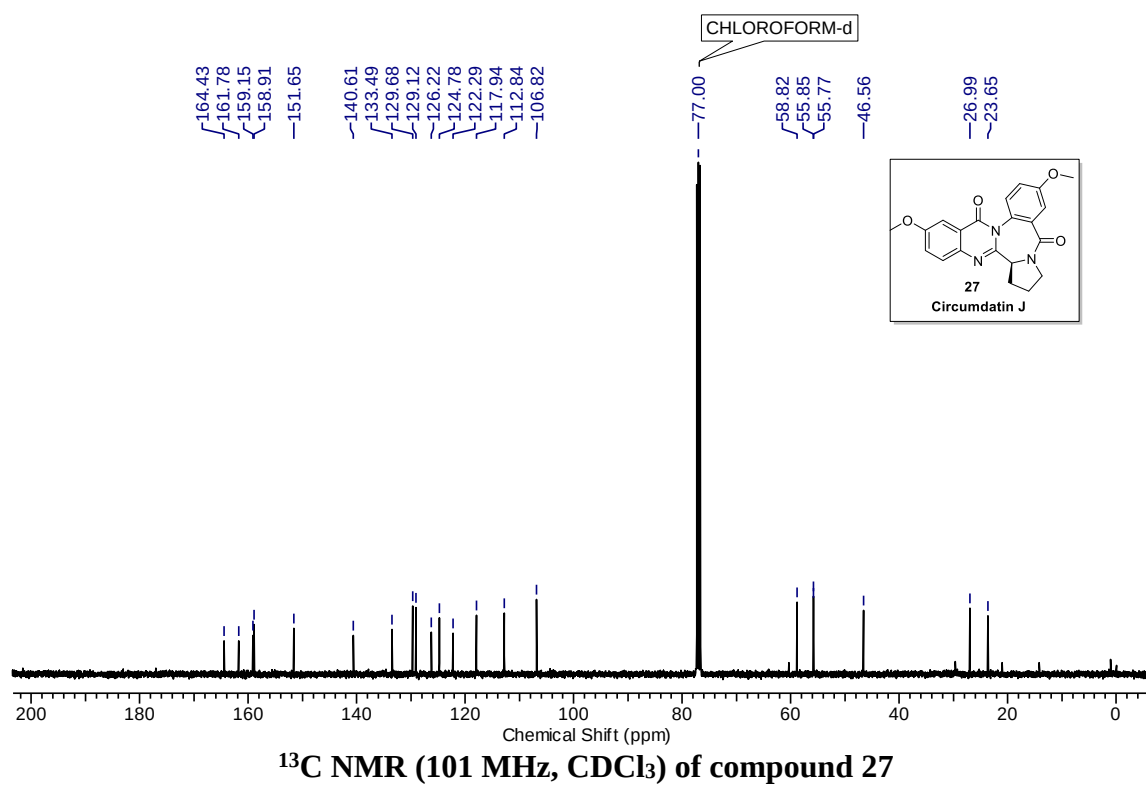
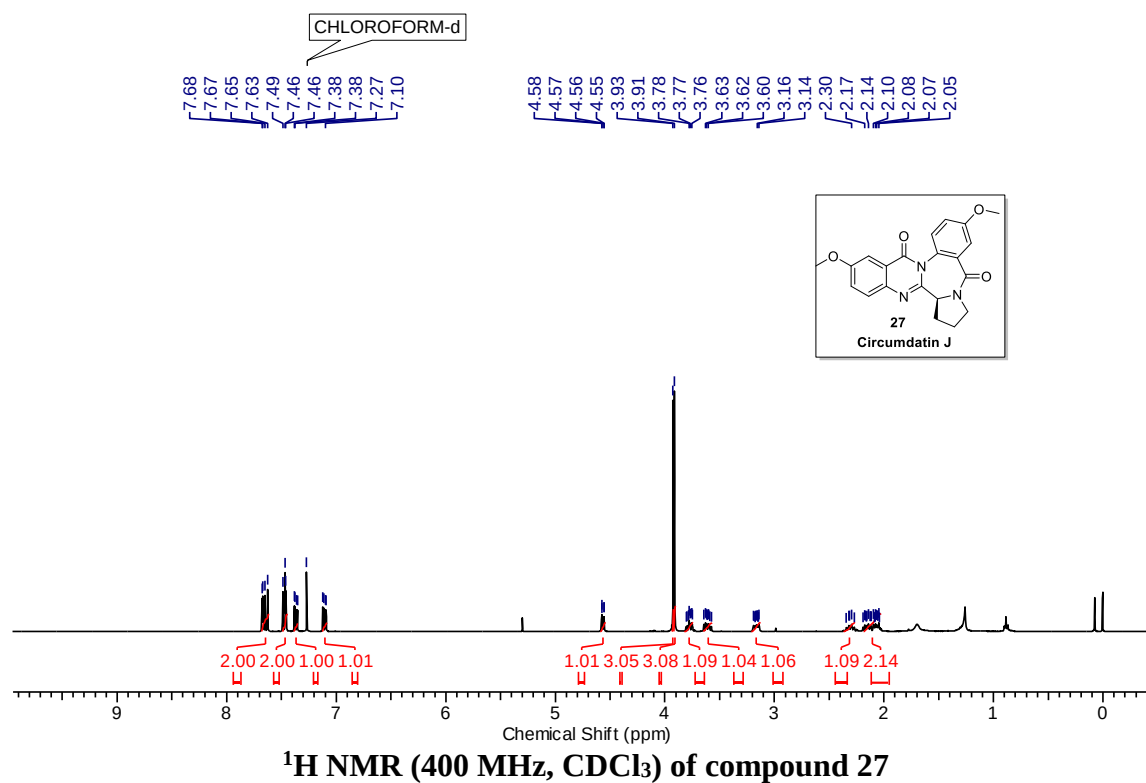
^1H NMR (400 MHz, CDCl_3) of compound 25 (mixture of atropisomers and rotamers)

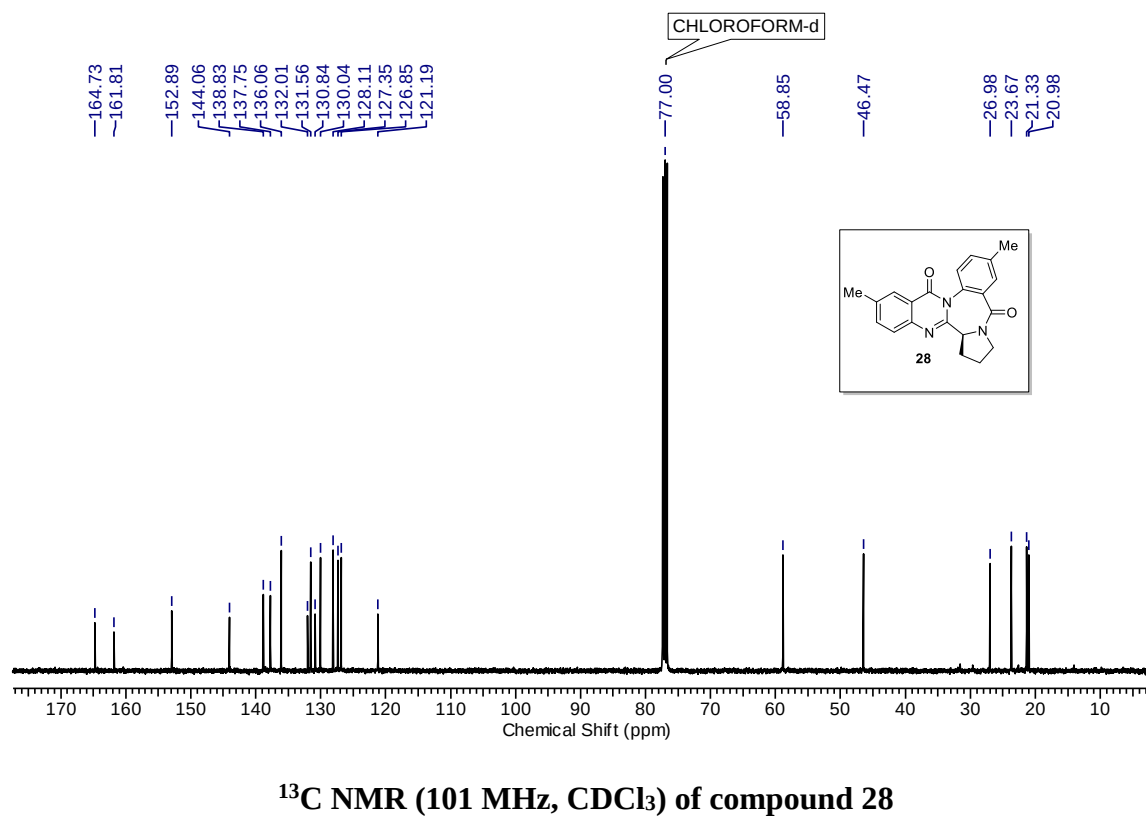
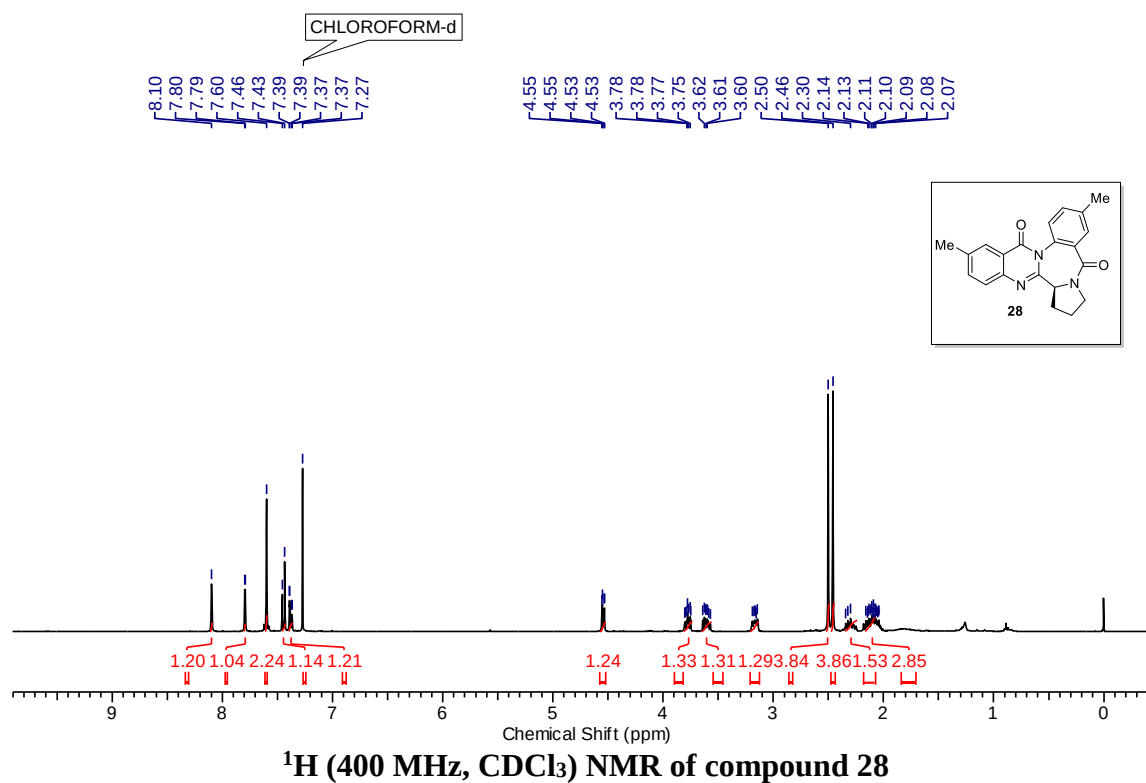


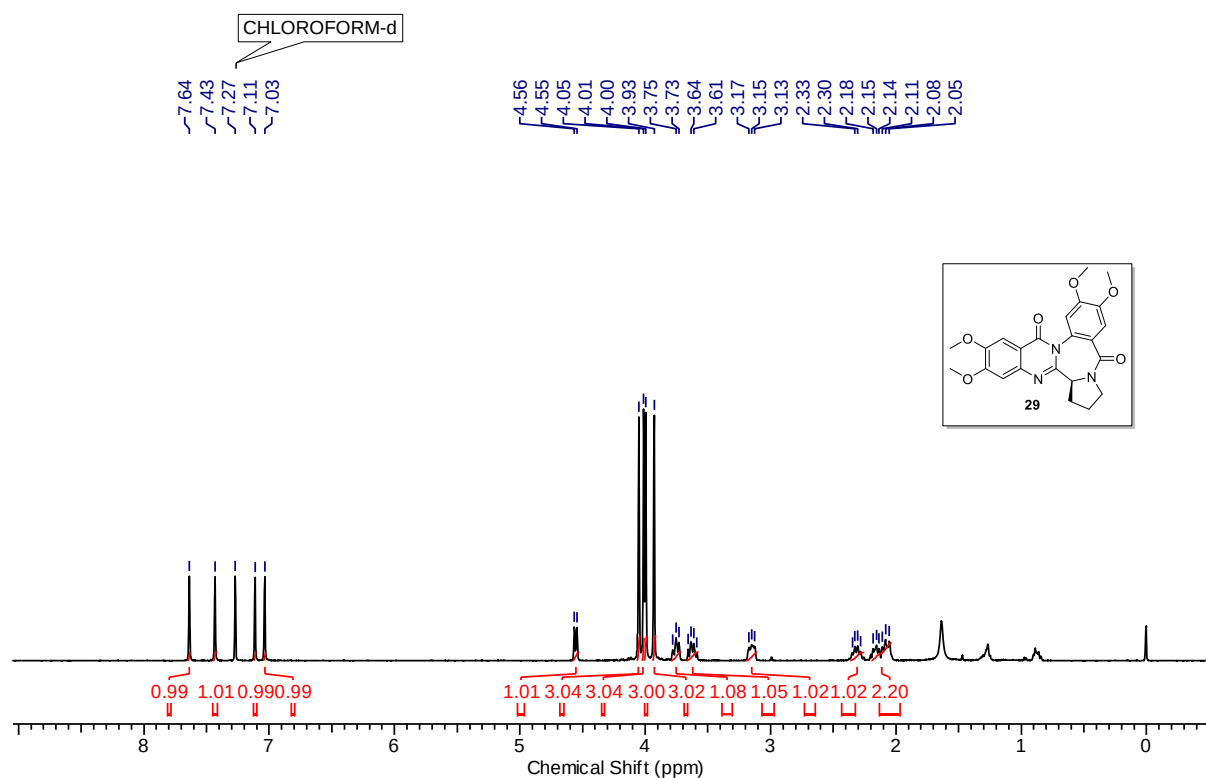
^{13}C NMR (101 MHz, CDCl_3) of compound 25 (mixture of atropisomers and rotamers)



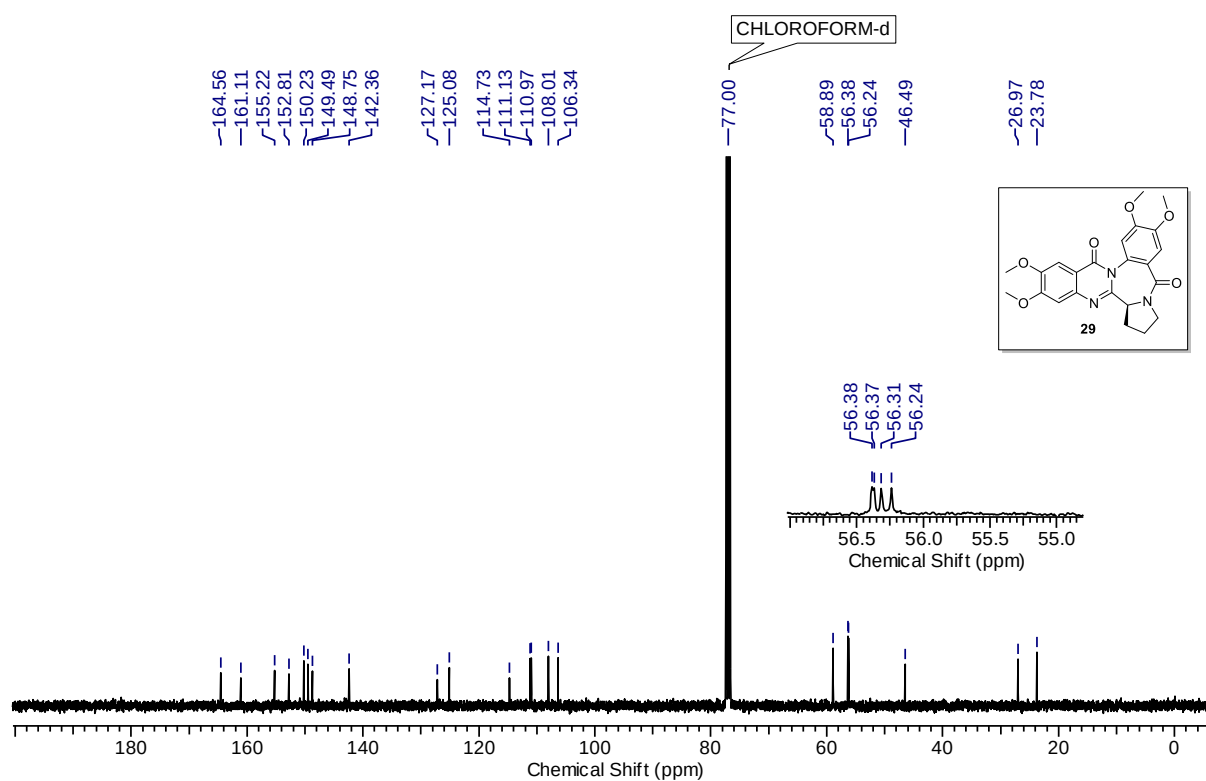




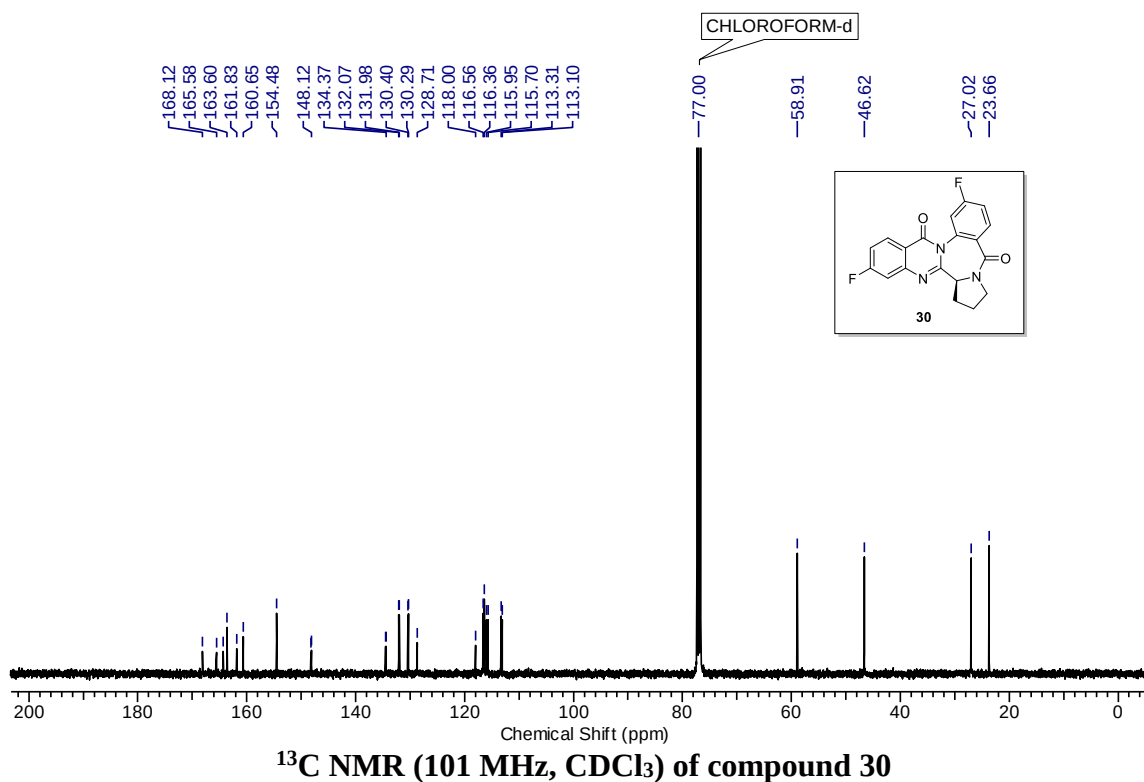
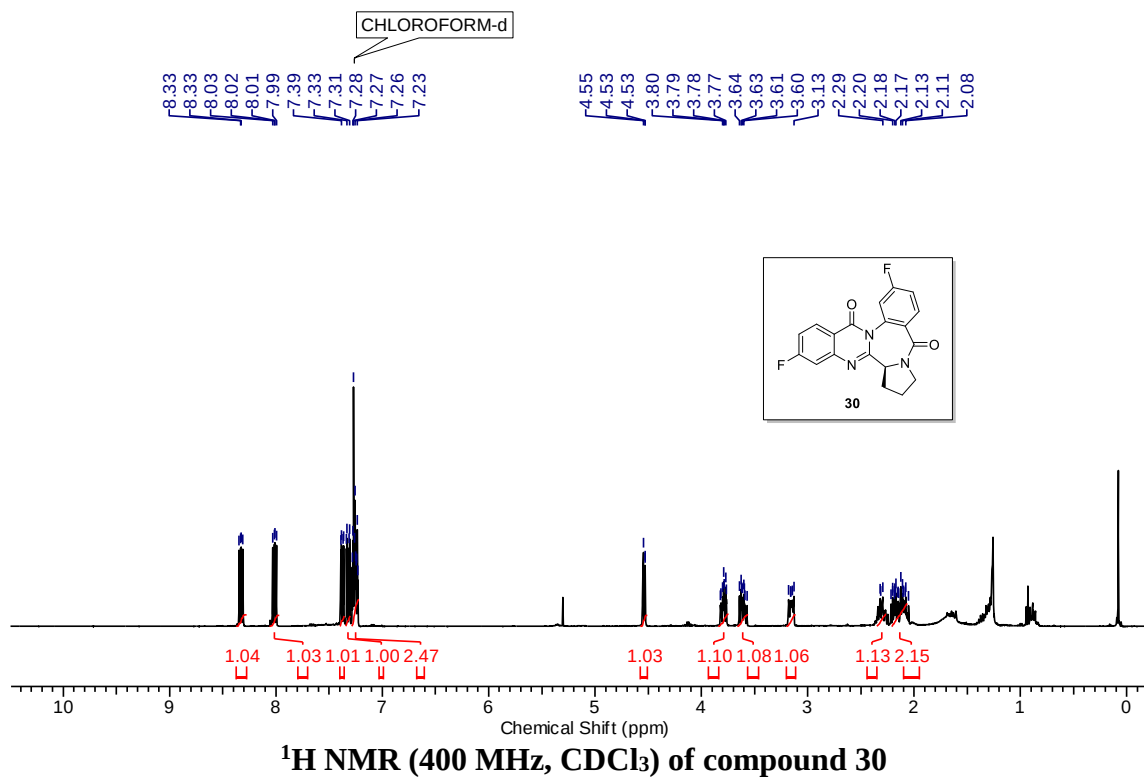


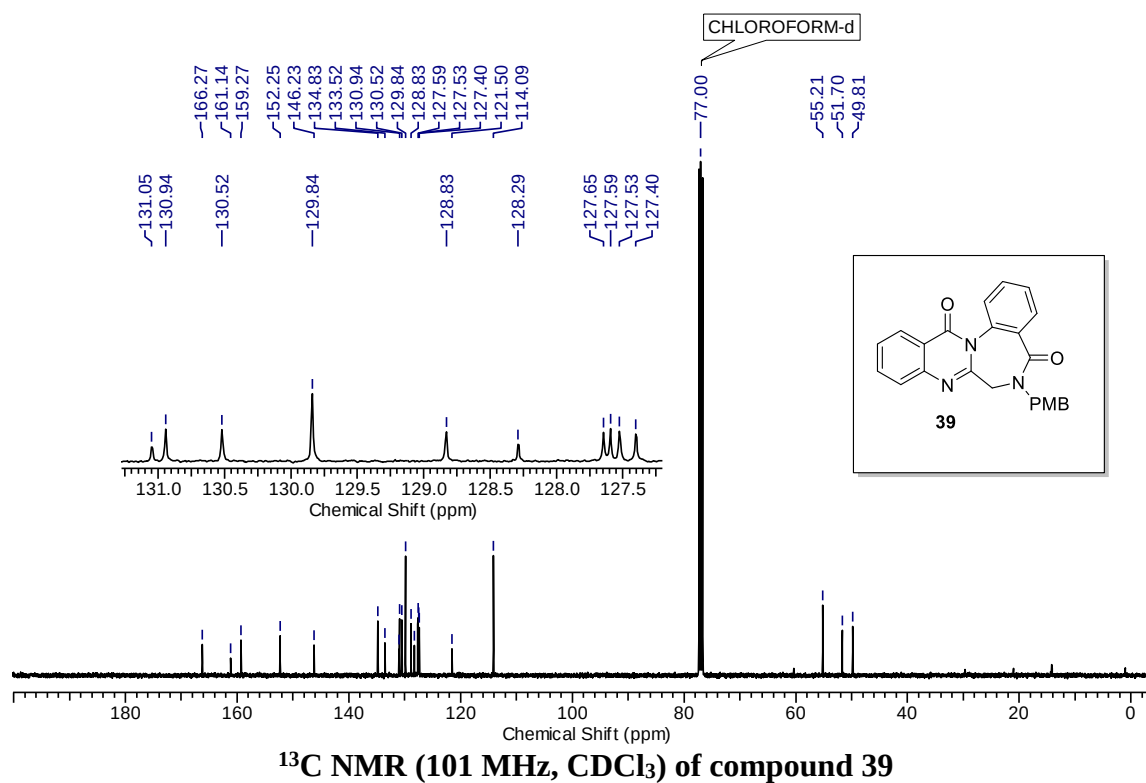
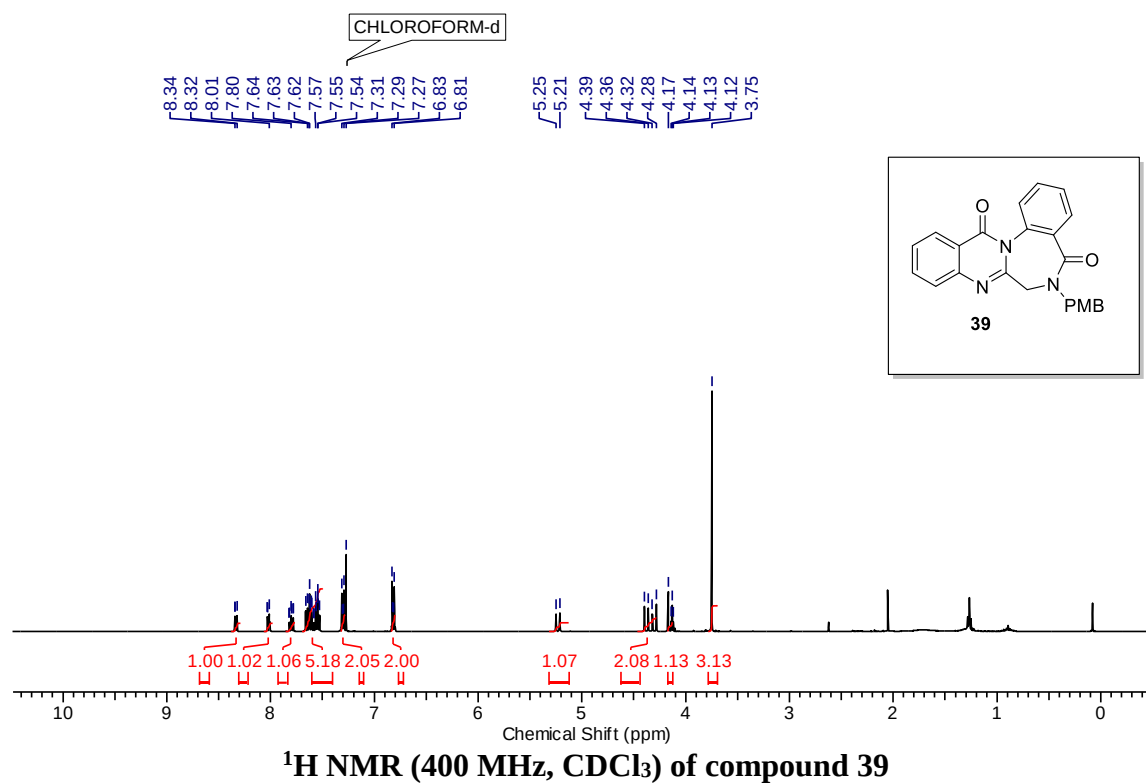


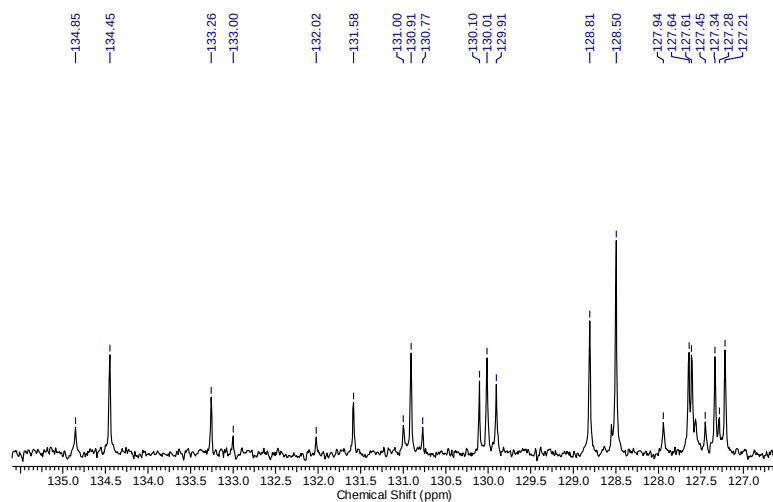
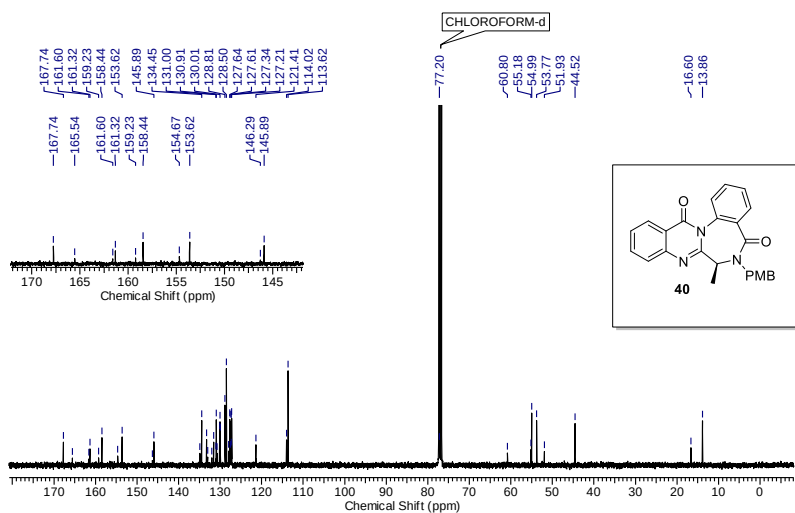
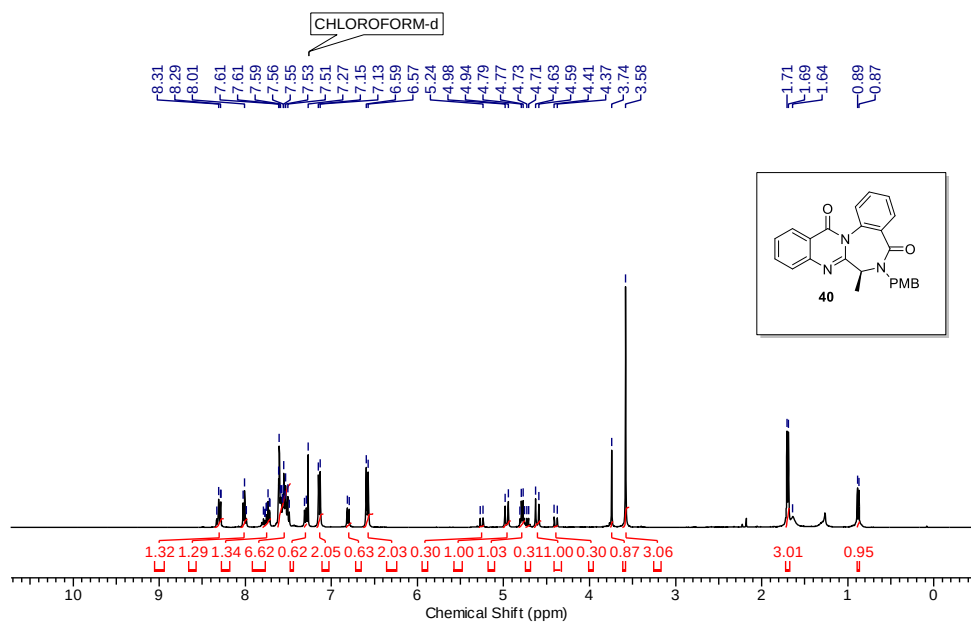
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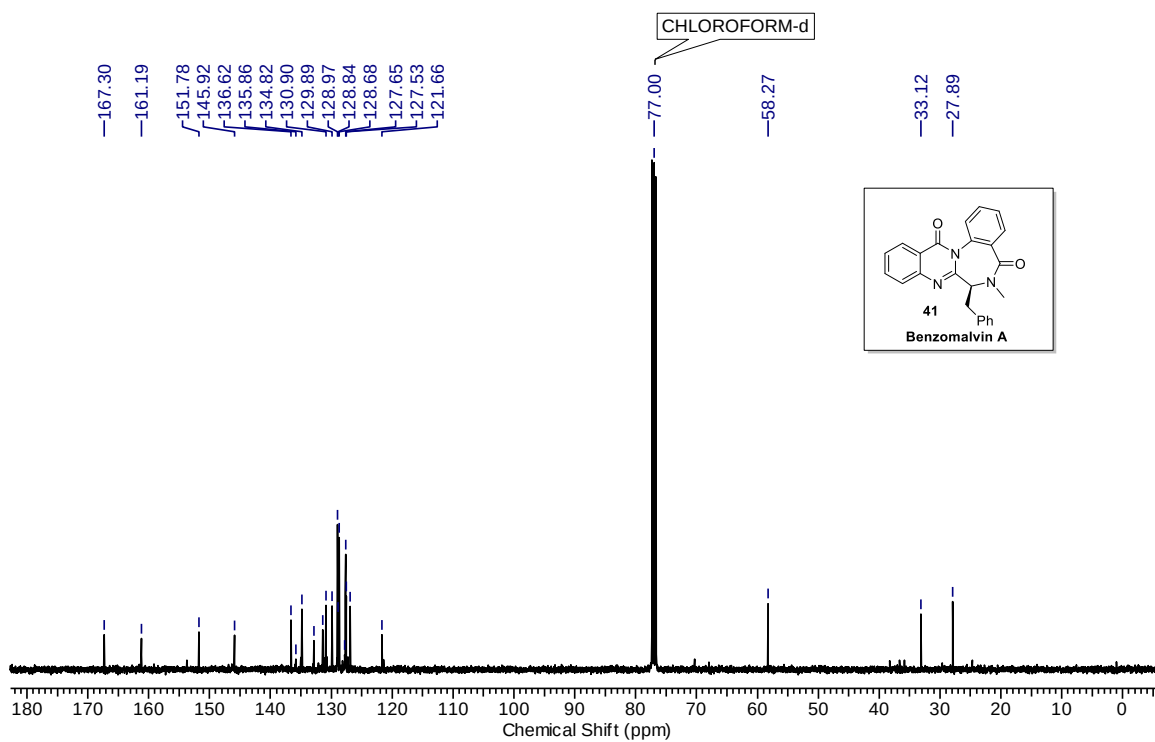
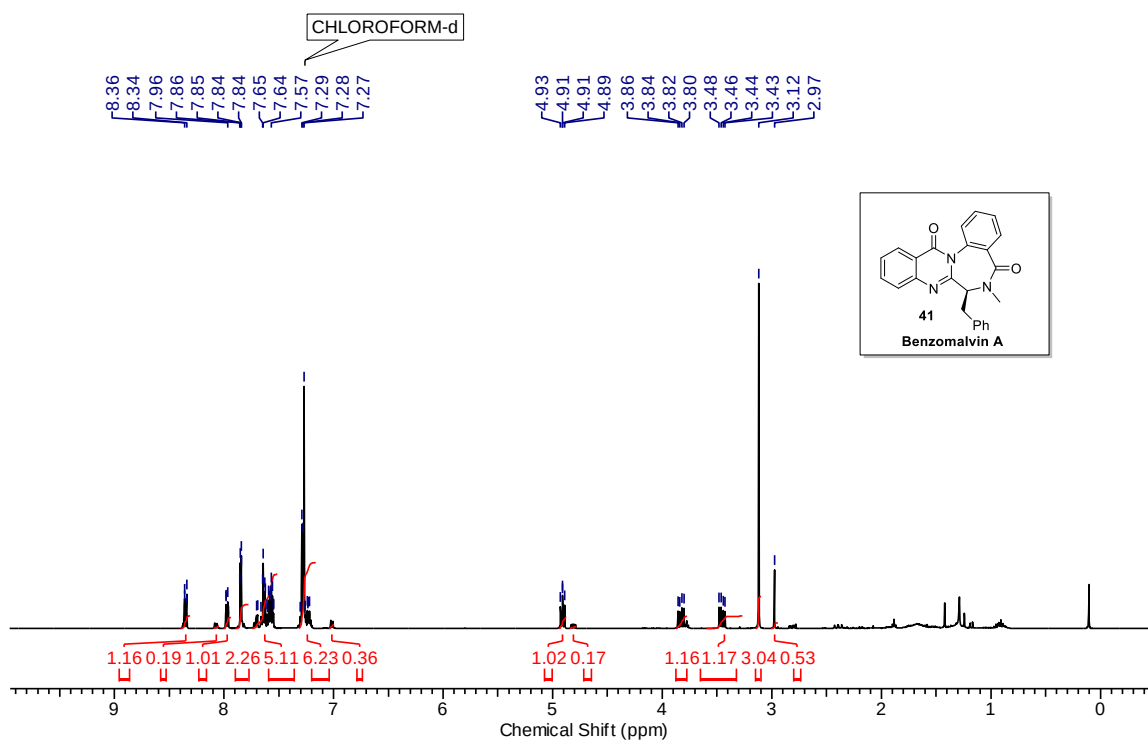
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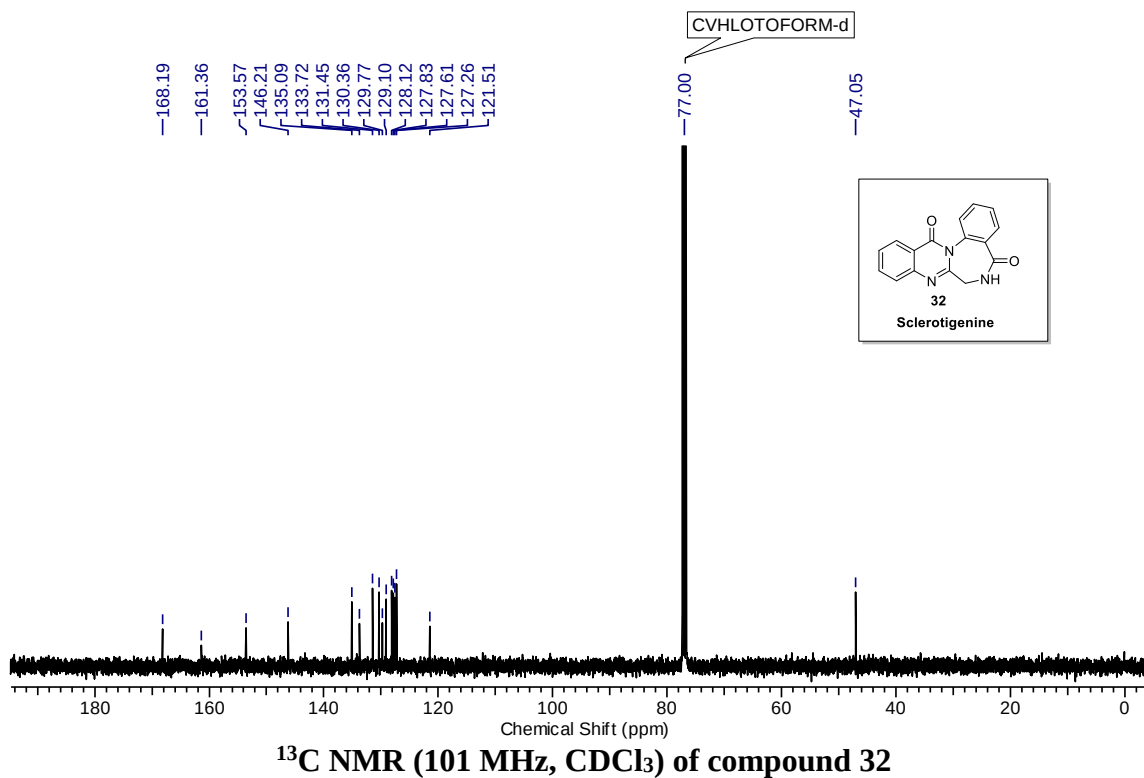
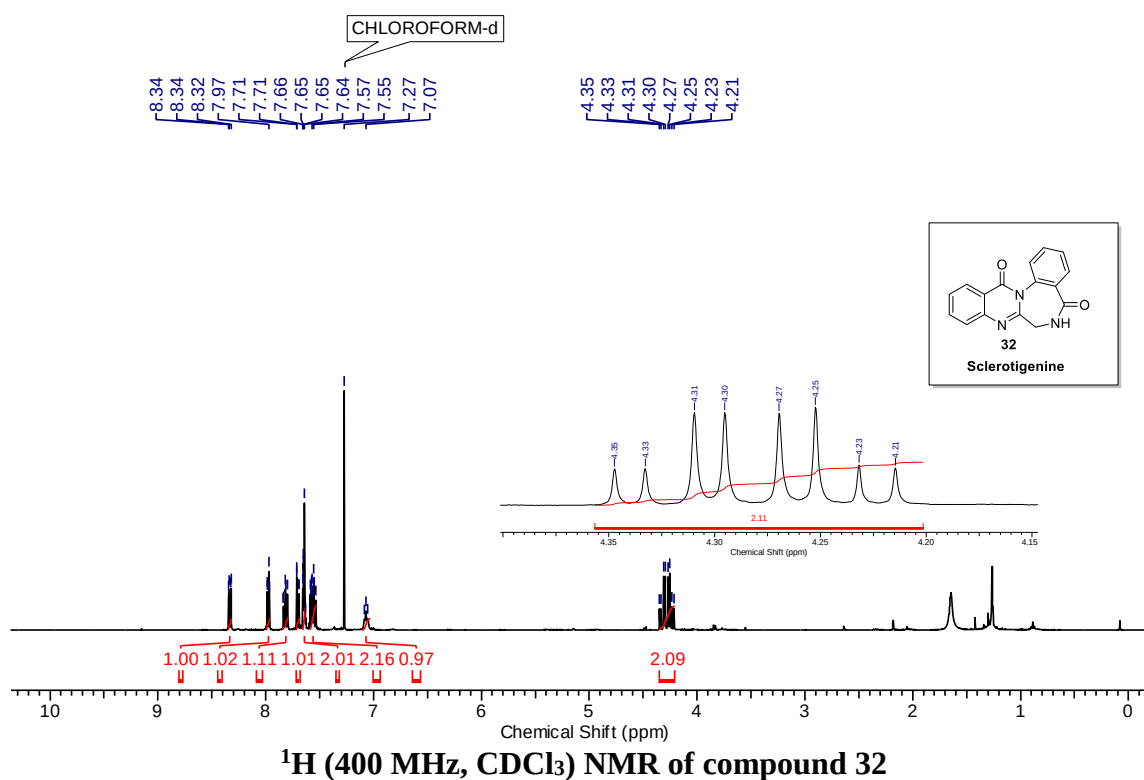


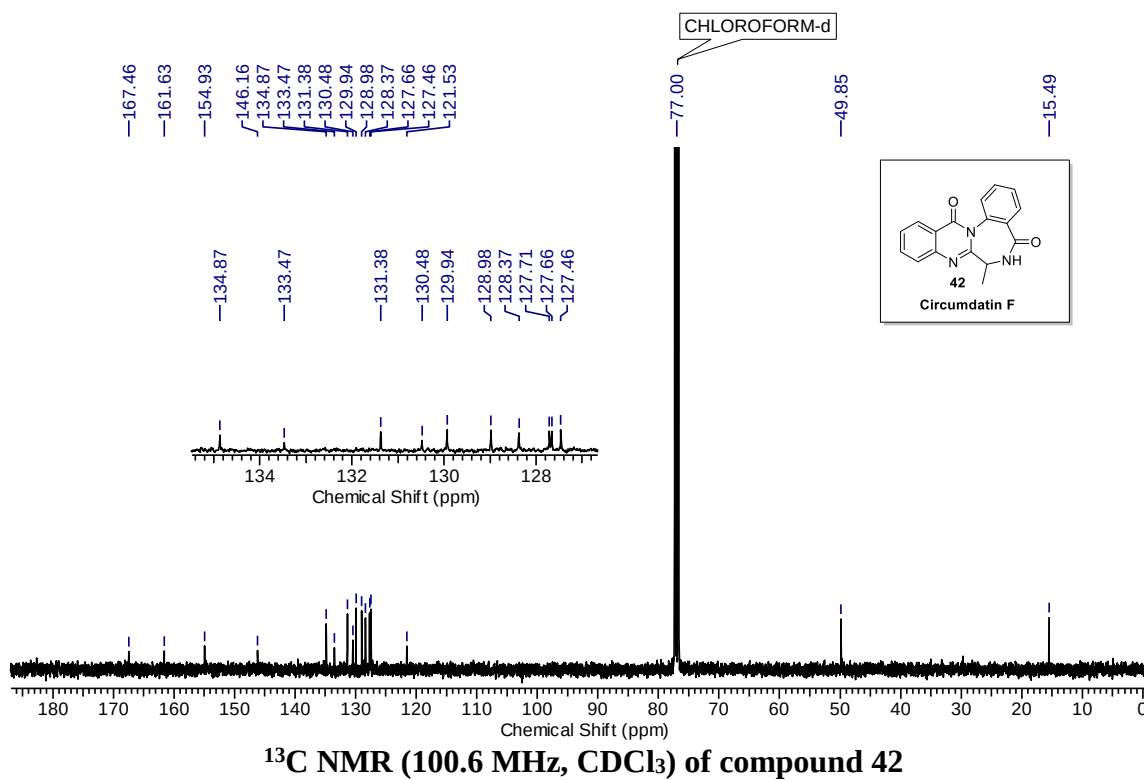
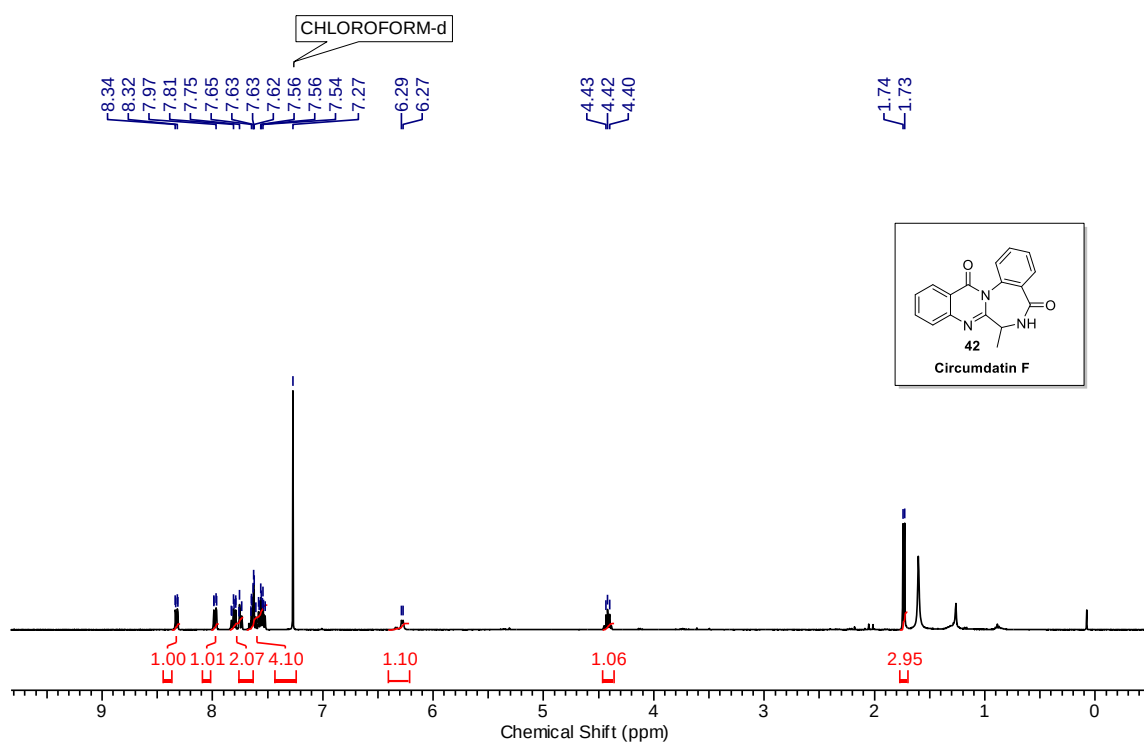




¹³C NMR (101 MHz, CDCl₃) of compound 40

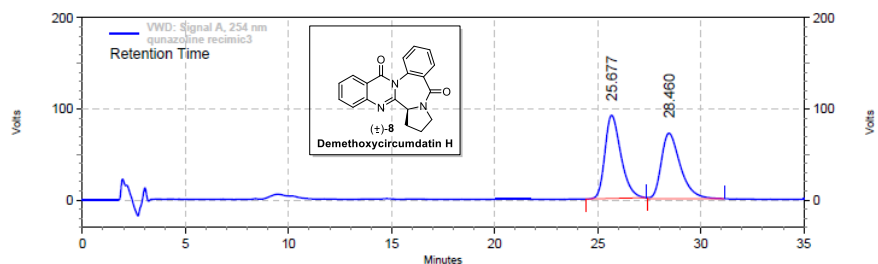






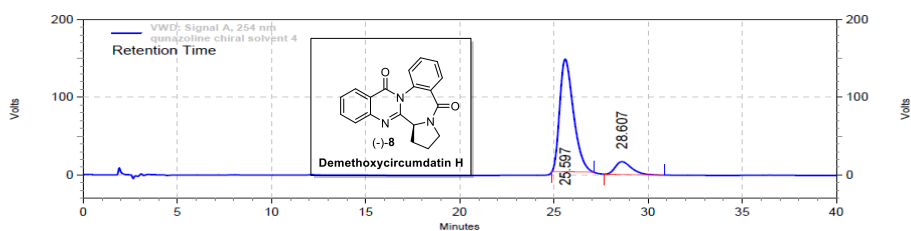
2.10 Copies of HPLC chromatograms:

Column: Chiralpak AD-H (250 mm x 4.6mm); **Mobile Ph:** IPA:PE:DEA (30:70:0.25); **Wavelength:** 254nm; **Flow:** 1.0 ml/min.; **Inject vol:** 5µL



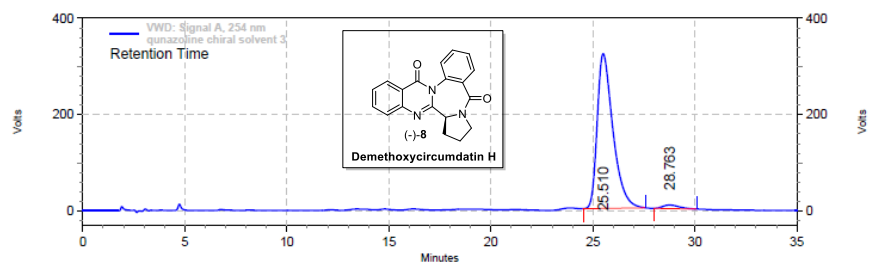
VWD: Signal A,
254 nm Results

Retention Time	Area	Area %	Height	Height %
25.677	82727248	51.46	1531265	55.89
28.460	78023469	48.54	1208324	44.11
Totals	160750717	100.00	2739589	100.00



VWD: Signal A,
254 nm Results

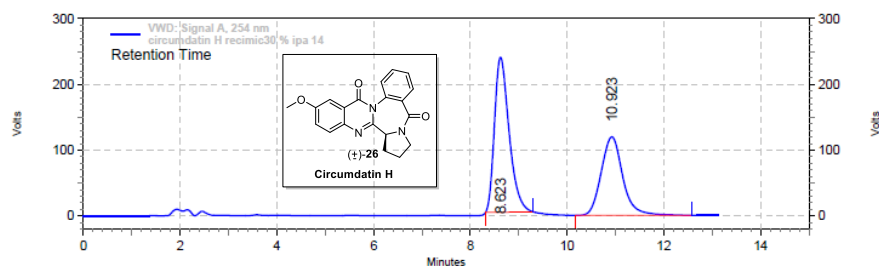
Retention Time	Area	Area %	Height	Height %
25.597	123693839	88.25	2433438	89.84
28.607	16462612	11.75	275188	10.16
Totals	140156451	100.00	2708626	100.00



VWD: Signal A,
254 nm Results

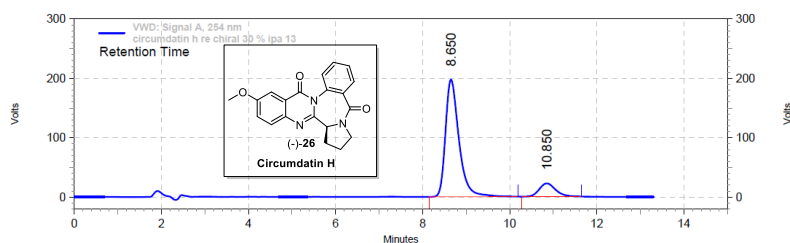
Retention Time	Area	Area %	Height	Height %
25.510	287880986	97.65	5382929	97.74
28.763	6935920	2.35	124482	2.26
Totals	294816906	100.00	5507411	100.00

Column: Chiralpak AD-H (250 mm x 4.6mm); **Mobile Ph:** IPA:PE:DEA (30:70:0.25);
Wavelength: 254nm; **Flow:** 1.0 ml/min.; **Inject vol:** 5µL



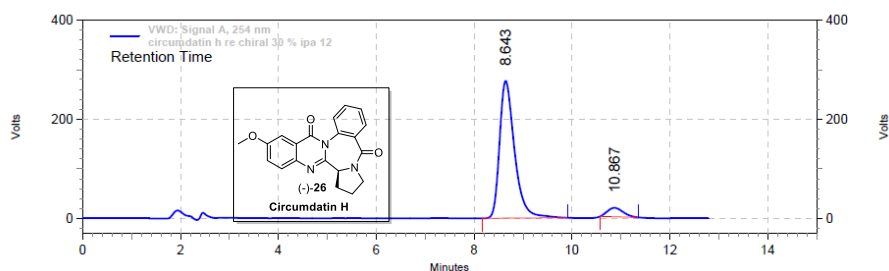
VWD: Signal A,
254 nm Results

Retention Time	Area	Area %	Height	Height %
8.623	83031360	57.41	3949420	66.40
10.923	61592626	42.59	1998056	33.60
Totals	144623986	100.00	5947476	100.00



VWD: Signal A,
254 nm Results

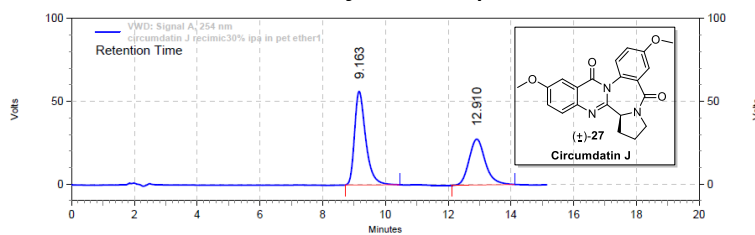
Retention Time	Area	Area %	Height	Height %
8.650	71199333	87.99	3311438	89.86
10.850	9719414	12.01	373649	10.14
Totals	80918747	100.00	3685087	100.00



VWD: Signal A,
254 nm Results

Retention Time	Area	Area %	Height	Height %
8.643	98968142	93.63	4638107	93.91
10.867	6729765	6.37	300877	6.09
Totals	105697907	100.00	4938984	100.00

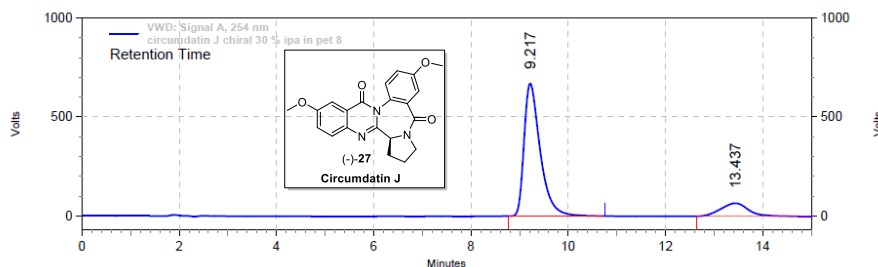
Column: Chiralpak AD-H (250 mm x 4.6mm); **Mobile Ph:** IPA:PE:DEA (30:70:0.25);
Wavelength: 254nm; **Flow:** 1.0 ml/min.; **Inject vol:** 5µL



VWD: Signal A,

254 nm Results

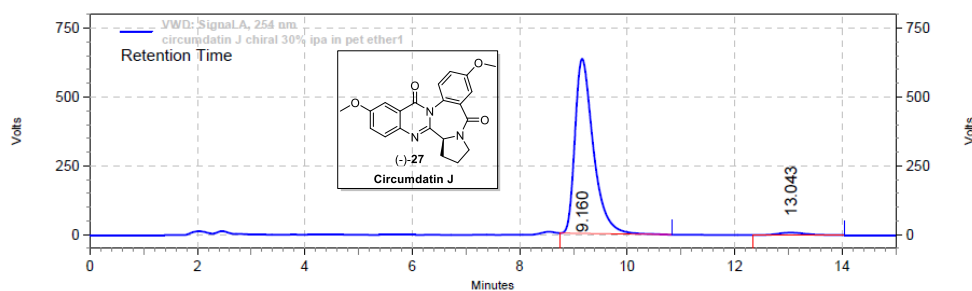
Retention Time	Area	Area %	Height	Height %
9.163	23454475	58.42	946755	67.11
12.910	16693374	41.58	464051	32.89
Totals	40147849	100.00	1410806	100.00



VWD: Signal A,

254 nm Results

Retention Time	Area	Area %	Height	Height %
9.217	258991574	85.46	11219627	91.02
13.437	44070779	14.54	1106773	8.98
Totals	303062353	100.00	12326400	100.00



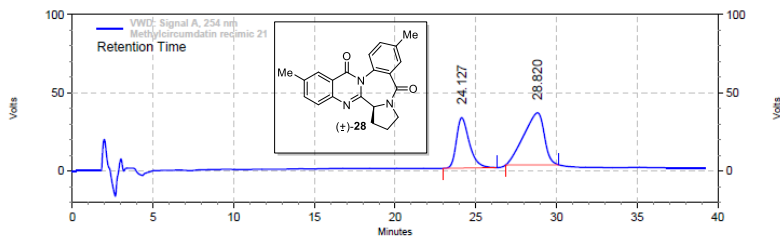
VWD: Signal A,

254 nm Results

Retention Time	Area	Area %	Height	Height %
9.160	252110084	97.97	10636093	98.59
13.043	5212430	2.03	152082	1.41
Totals	257322514	100.00	10788175	100.00

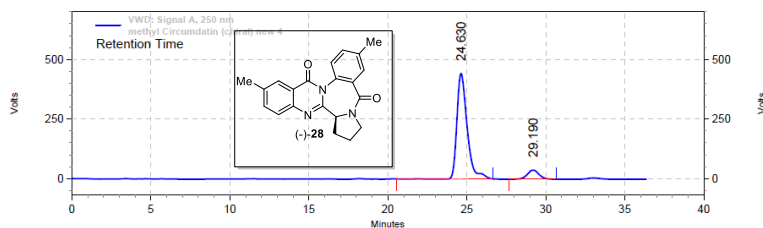
Column: Chiralpak AD-H (250 mm x 4.6mm); **Mobile Ph:** IPA:PE:DEA (30:70:0.25);

Wavelength: 254nm; **Flow:** 1.0 ml/min.; **Inject vol:** 5µL



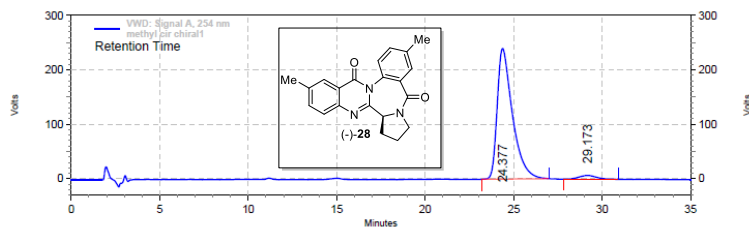
VWD: Signal A,
254 nm Results

Retention Time	Area	Area %	Height	Height %
24.127	29899784	37.59	539551	49.12
28.820	49647391	62.41	558893	50.88
Totals	79547175	100.00	1098444	100.00



VWD: Signal A,
250 nm Results

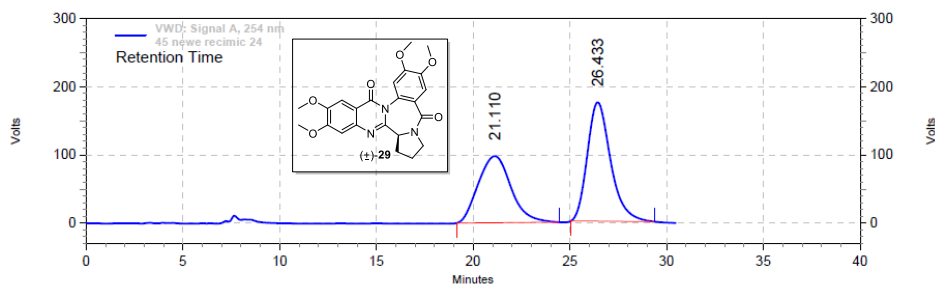
Retention Time	Area	Area %	Height	Height %
24.630	332632257	90.98	7419228	92.01
29.190	32976288	9.02	644315	7.99
Totals	365608545	100.00	8063543	100.00



VWD: Signal A,
254 nm Results

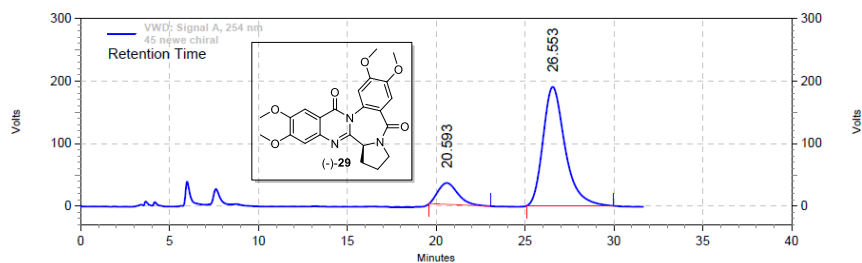
Retention Time	Area	Area %	Height	Height %
24.377	240838733	96.65	4024193	97.15
29.173	8359655	3.35	118254	2.85
Totals	249198388	100.00	4142447	100.00

Column: Chiralpak AD-H (250 mm x 4.6mm); **Mobile Ph:** EtOH:PE:DEA (50:50:0.25);
Wavelength: 254nm; **Flow:** 1.0 ml/min.; **Inject vol:** 5µL



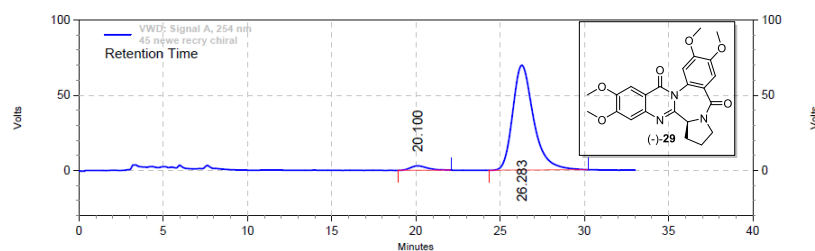
VWD: Signal A,
254 nm Results

Retention Time	Area	Area %	Height	Height %
21.110	192466672	44.04	1637811	35.93
26.433	244563413	55.96	2920285	64.07
Totals	437030085	100.00	4558096	100.00



VWD: Signal A,
254 nm Results

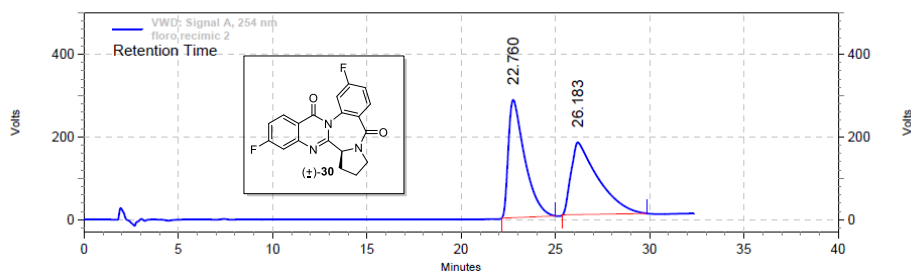
Retention Time	Area	Area %	Height	Height %
20.593	44042848	13.80	570821	15.19
26.553	275063303	86.20	3187097	84.81
Totals	319106151	100.00	3757918	100.00



VWD: Signal A,
254 nm Results

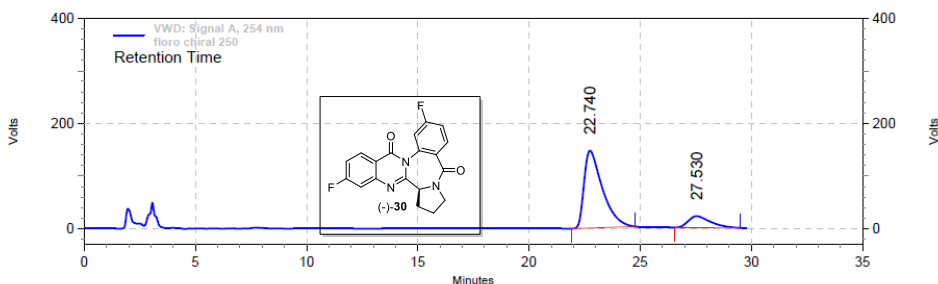
Retention Time	Area	Area %	Height	Height %
20.100	3442732	3.30	48668	4.00
26.283	100757488	96.70	1168100	96.00
Totals	104200220	100.00	1216768	100.00

Column: Chiralpak AD-H (250 mm x 4.6mm); **Mobile Ph:** IPA:PE: DEA (30:70:0.25);
Wavelength: 254nm; **Flow:** 1.0 ml/min.; **Inject vol:** 5µL



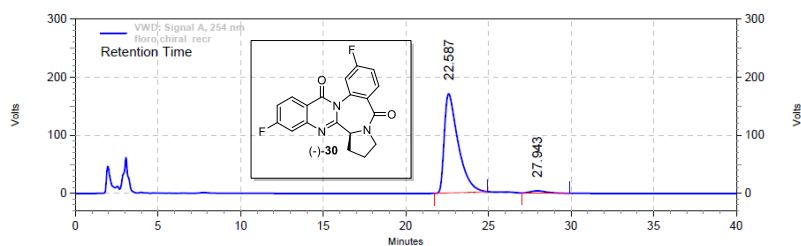
**VWD: Signal A,
254 nm Results**

Retention Time	Area	Area %	Height	Height %
22.760	288553514	49.85	4773356	62.01
26.183	290241668	50.15	2924536	37.99
Totals	578795182	100.00	7697892	100.00



**VWD: Signal A,
254 nm Results**

Retention Time	Area	Area %	Height	Height %
22.740	141679802	84.80	2469441	87.06
27.530	25392023	15.20	366924	12.94
Totals	167071825	100.00	2836365	100.00

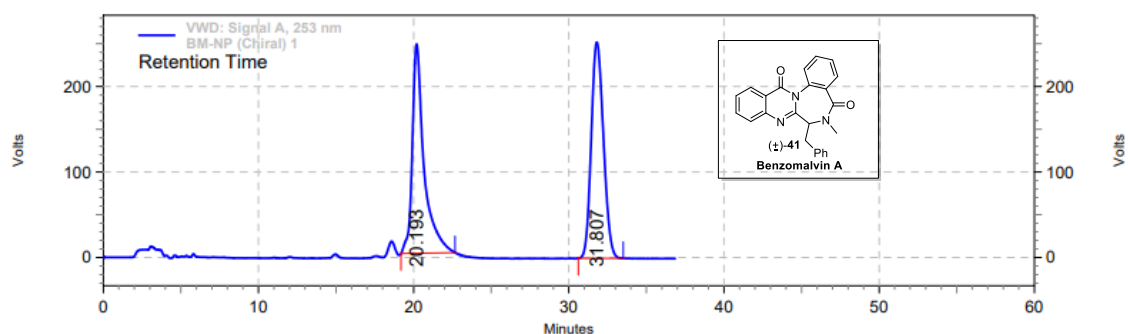


**VWD: Signal A,
254 nm Results**

Retention Time	Area	Area %	Height	Height %
22.587	166699372	97.63	2858809	97.84
27.943	4054807	2.37	63071	2.16
Totals	170754179	100.00	2921880	100.00

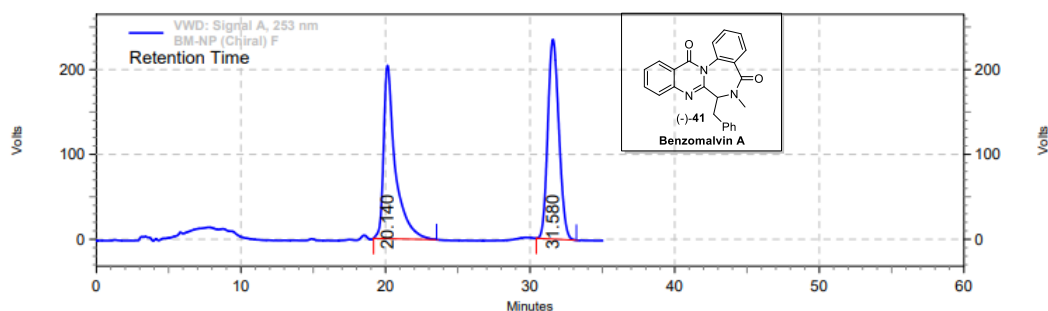
Column: Chiralpak AD-H (250 mm x 4.6mm); Mobile Ph: IPA:PE: DEA (15:85);

Wavelength: 254nm; Flow: 1.0 ml/min.; Inject vol: 5µL



**VWD: Signal A,
253 nm Results**

Retention Time	Area	Area %	Height	Height %
20.193	215806670	48.19	4103653	49.18
31.807	232027994	51.81	4240751	50.82
Totals	447834664	100.00	8344404	100.00

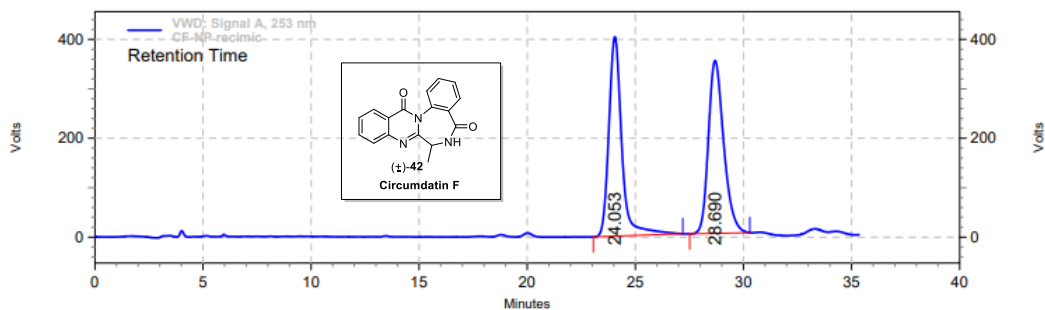


**VWD: Signal A,
253 nm Results**

Retention Time	Area	Area %	Height	Height %
20.140	191927730	47.66	3424331	46.46
31.580	210753552	52.34	3946673	53.54
Totals	402681282	100.00	7371004	100.00

Column: Chiralpak AD-H (250 mm x 4.6mm); Mobile Ph: IPA:PE: DEA (15:85);

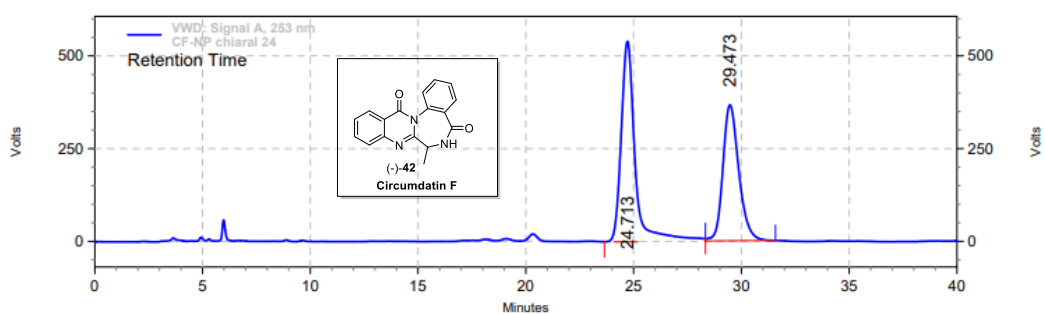
Wavelength: 254nm; Flow: 1.0 ml/min.; Inject vol: 5µL



**VWD: Signal A,
253 nm Results**

Retention Time	Area	Area %	Height	Height %
24.053	281386389	49.41	6768076	53.58
28.690	288138453	50.59	5863904	46.42

Totals	569524842	100.00	12631980	100.00
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**VWD: Signal A,
253 nm Results**

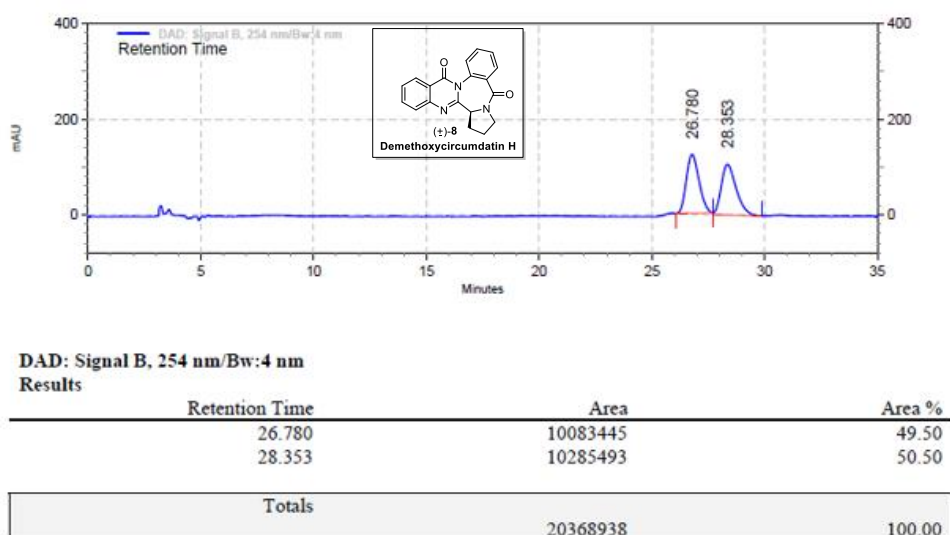
Retention Time	Area	Area %	Height	Height %
24.713	412523147	56.64	9076298	59.60
29.473	315833885	43.36	6151270	40.40

Totals	728357032	100.00	15227568	100.00
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Study on autocatalysis: Standard reaction was performed separately on racemic and enantiopure acid substrate **7** in the presence of 5 mol% of enantiopure compound **20**.

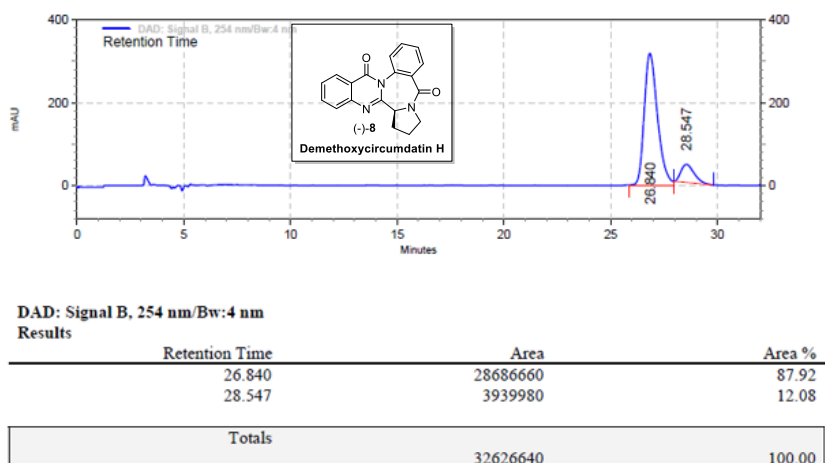
Column: Chiralpak AD-H (250 mm x 4.6mm); Mobile Ph: IPA:PE: DEA (30:70:0.25);

Wavelength: 254nm; **Flow:** 1.0 ml/min.; **Inject vol:** 5 μ L (Racemic starting material **7**)



Column: Chiralpak AD-H (250 mm x 4.6mm); **Mobile Ph:** IPA:PE:DEA (30:70:0.25);

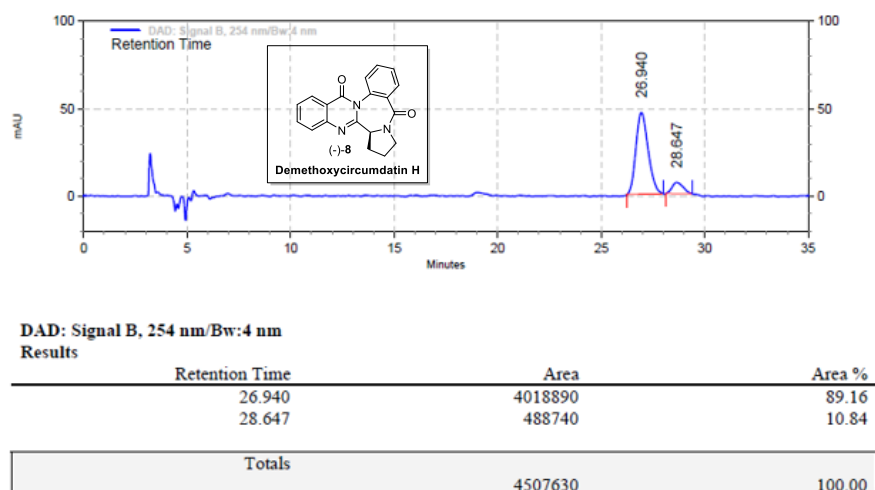
Wavelength: 254nm; **Flow:** 1.0 ml/min.; **Inject vol:** 5 μ L (Enantiopure starting material **7**)



Study on autocatalysis: Standard reaction was performed on enantiopure acid substrate 7 and the ee was determined every 5 hours.

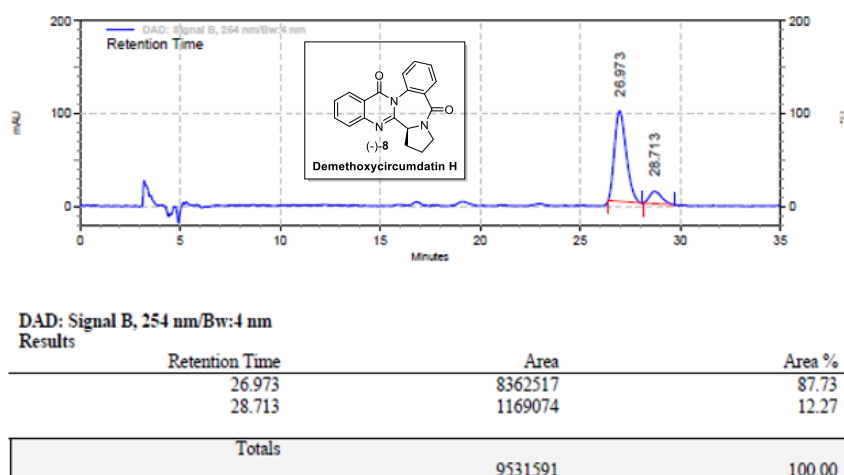
Column: Chiralpak AD-H (250 mm x 4.6mm); **Mobile Ph:** IPA:PE:DEA (30:70:0.25);

Wavelength: 254nm; **Flow:** 1.0 ml/min.; **Inject vol:** 5 μ L (Sample 1 – 5 h)

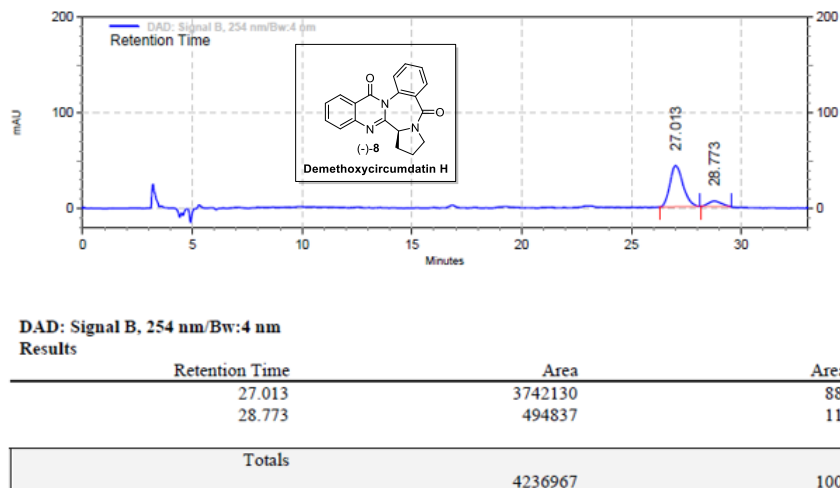


Column: Chiralpak AD-H (250 mm x 4.6mm); **Mobile Ph:** IPA:PE:DEA (30:70:0.25);

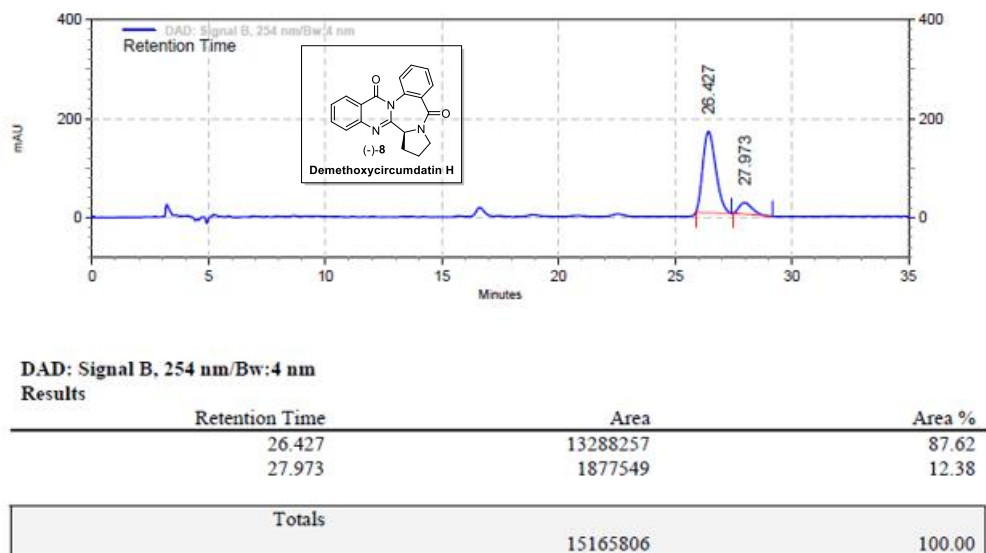
Wavelength: 254nm; **Flow:** 1.0 ml/min.; **Inject vol:** 5 μ L (Sample 2 - 10 h)



Column: Chiralpak AD-H (250 mm x 4.6mm); **Mobile Ph:** IPA:PE:DEA (30:70:0.25);
Wavelength: 254nm; **Flow:** 1.0 ml/min.; **Inject vol:** 5µL (Sample 3 – 15 h)



Column: Chiralpak AD-H (250 mm x 4.6mm); **Mobile Ph:** IPA:PE:DEA (30:70:0.25);
Wavelength: 254nm; **Flow:** 1.0 ml/min.; **Inject vol:** 5µL (Sample 4 – 18 h)



Chapter 3

Studies Towards the Asymmetric Synthesis of Dextromethorphan Key Intermediate by Decarboxylative C–C Bond Forming Reaction

Studies Towards the Asymmetric Synthesis of Dextromethorphan Key Intermediate by Decarboxylative C–C Bond Forming Reaction

3.1 Abstract

This chapter provide details of our endeavours in developing decarboxylative C–C bond formation strategies, Focusing on their application in the synthesis of key intermediates for dextromethorphan API. We investigated the use of metal-catalyzed as well as photocatalyzed decarboxylative C–H functionalization of olefins along with electrophilic substitution reactions involving ketones. The synthesis of the necessary precursor for the pivotal step was successfully accomplished, which was followed by attempts to achieve decarboxylative cyclization. Despite of various reaction conditions, the outcome was either the formation of undesired products or no reaction at all. These results underscore the necessity for an optimized catalyst system to facilitate the intended transformation.

3.2 Introduction

Dextromethorphan (DXM) is an important active pharmaceutical ingredient (API) being used over 50 years as an over-the-counter cough suppressant. Another isomer Levomethorphan is the L-isomer of 3-methoxy-N-methylmorphinan. In contrast to DXM, it exhibits strong narcotic analgesic properties.^[1] DXM belongs to the morphine class of medications with sedative, dissociative, and stimulant properties. It has largely supplanted codeine as a cough suppressant. In comparison to codeine, it causes less respiratory depression, fewer gastrointestinal issues, and a lower risk of dependence or misuse. Addiction is uncommon, even when taken in large doses over extended periods. It is used in many cold and cough

formulations and is classified as an antitussive drug.^[2] Dextromethorphan (DXM) was launched in 1958 as the first cough suppressant that is not derived from opioids.^[3]

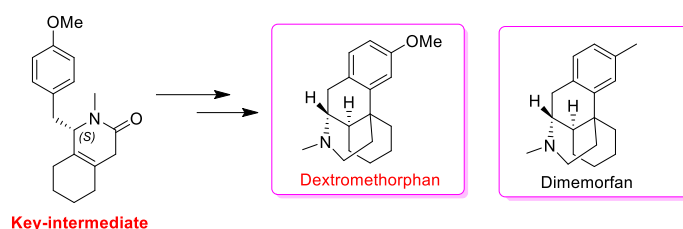
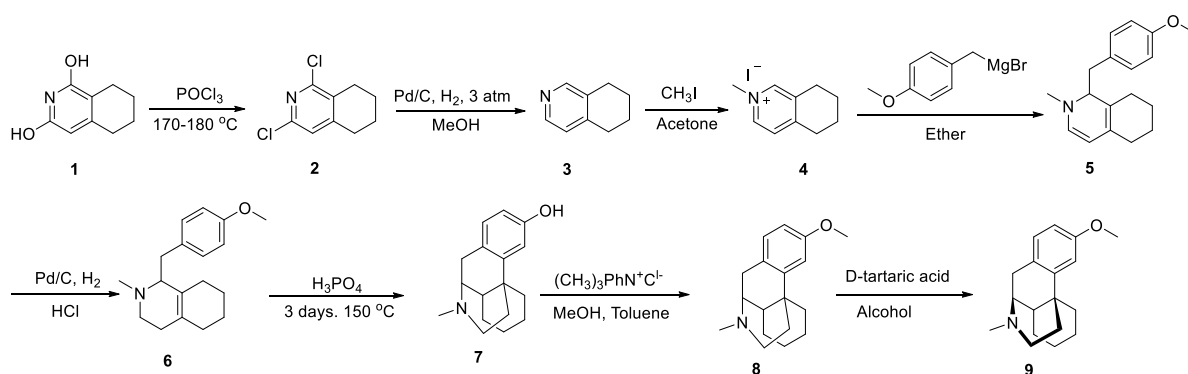


Figure 1. Dextromethorphan key intermediate

It was derived from morphine, but it does not have the analgesic or addictive properties of opioids. DXM, either on its own or in combination with additional medications, has been explored as a treatment for conditions such as depression,^[4] pain,^[5] and pseudo bulbar effect.^[6] In the synthesis of dextromethorphan, (S)-1-(4-methoxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline [(S)-1-(4-methoxybenzyl)-OHIQ], serves as the key synthetic intermediate in its industrial production (Figure 1). DXM was approved by the U.S. food and drug administration (FDA) as a cough suppressant and has been marketed under various brand names, Mucinex DM, Robitussin, Nyquil, Theraflu, Delsym, Coricidin, and Nuedexta, with Robitussin being one of the most recognizable.^[7] By the 1960s and 1970s, DXM had gained popularity as an over-the-counter medication for cough relief and, praised for its efficacy and safety compared to codeine.



Scheme 1. Chemical synthesis of dextromethorphan (DXM)^[20]

Several methods for synthesizing dextromethorphan intermediate have been previously reported, but original synthesis ^[8,9] and resolution ^[10] are shown in Scheme 1. The synthesis of DXM, as described in earlier literature, follows a multi-step process. ^[20] The procedure begins with 5,6,7,8-tetrahydroisoquinoline-1,3-diol (**1**), which on treatment with phosphorus oxychloride yielded dichlorotetrahydroisoquinoline **2**. Next, hydrogenation of **2** with palladium on carbon results in tetrahydroisoquinoline **3**, which was methylated using iodomethane to form a compound **4**. When **4** reacts with 4-methoxybenzylmagnesium bromide, N-methyl tetrahydroisoquinoline **5** was formed, which was then hydrogenated into tetrahydroisoquinoline **6**. The cyclization of **6** using phosphoric acid at 150 °C formed hydroxy-N-methylmorphinan **7**. Methylation of **7** resulted in racemic mixture of methoxy-N-methylmorphinan **8**, which was subsequently separated into its enantiomers using D-tartaric acid, giving pure DXM **9**.

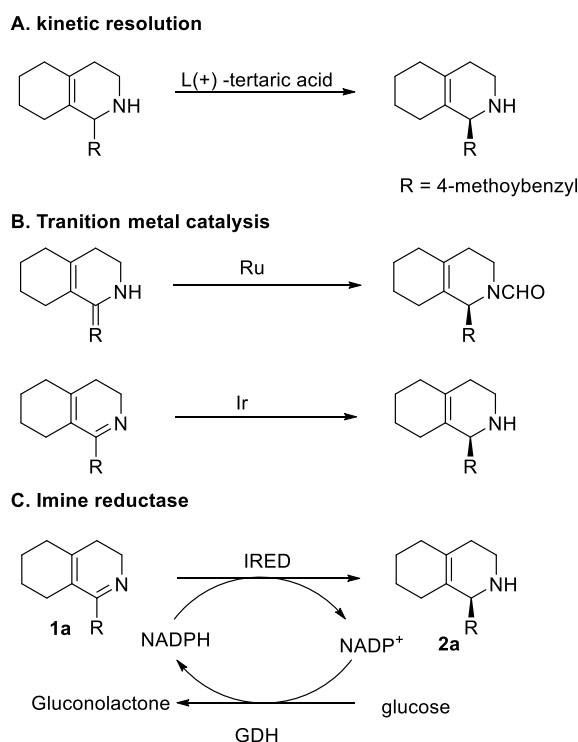
One approach involves the kinetic resolution of racemic amines to obtain their optically pure forms. ^[15] However, this method is considered economically and environmentally unattractive, as it yields a maximum of only 50% yield. Additionally, the process requires the use of NaBH₄, Pa-catalyst, high pressure, corrosive reagents such as sulfuric acid, KOH, and sodium methoxide, along with extended reaction times. The objective of our work is to enhance existing techniques by reducing the amounts of acids and bases used and recovering reagents whenever feasible, thereby minimizing pollutants and lowering operating costs.

Over the past three decades, the C–H functionalization reaction has been advanced for the activation of unreactive olefins. Significant advancements have been achieved in the decarboxylative formation of C–C and C–heteroatom bonds in alkenes through cross-coupling and C–H functionalization techniques. ^[11] The development of C–H functionalization reactions, including both metal-catalyzed and photocatalyzed processes for

unactivated alkenes, in a single operational step is highly appealing. These strategies are considered powerful and practical.

3.3 Literature Review

Since discovery of DXM in 1953, It has attracted significant attention from organic chemists due to its use as a non-opioid cough suppressant, making it one of the most widely utilized antitussives.^[2] It has been synthesized through various methods since its discovery, either in racemic or enantiomeric forms.^[12] It was first synthesized in 1949 by researcher at the University of Rochester. It is the dextrorotatory form of the racemic methorphan, which was patented by Hoffmann-La Roche in 1954.^[13] The first asymmetric synthesis was developed by O. Häfliger and co-workers in 1956.^[14] It was developed as a derivative of morphine, specifically to provide a non-narcotic alternative for treating coughs.



Scheme 2. Selected methods for the synthesis of key DXM intermediate

The synthesis of dextromethorphan involves two key steps: the *N*-formylation of (–)-octabase and the subsequent cyclization of the *N*-formylated product. This process leads to the formation of (+)-3-methoxy-*N*-methylnorphinan, which serves as a crucial intermediate for the industrial production of dextromethorphan (DXM).

Several strategies have been developed for the synthesis of key dextromethorphan intermediate with high enantiomeric purity (scheme 2).

A) Kinetic Resolution with L(+)-Tartaric Acid

Kinetic resolution is a widely used technique for separating enantiomers from a racemic mixture. In the case of dextromethorphan, this process involves the use of L(+)-tartaric acid to preferentially crystallize one enantiomer. The steps are as follows:

1. **Formation of Diastereomeric Salts:** The racemic mixture of dextromethorphan is treated with L(+)-tartaric acid, leading to the formation of diastereomeric salts.^[15]
2. **Selective Crystallization:** The differing solubility and physical properties, diastereomers can be separated via crystallization. This process enables the isolation of the desired enantiomer from the mixture. While this method is efficient and straightforward, it may require additional purification to achieve high purity of the target enantiomer.^[16]

B) Transition Metal-Catalyzed Asymmetric Hydrogenation

Asymmetric hydrogenation is an effective method for selectively synthesizing one enantiomer of dextromethorphan using chiral catalysts.

Chiral Catalysts: The use of transition metals based catalyst, particularly **iridium**^[17] or **rhodium**^[18], are used in combination with chiral ligands to facilitate the hydrogenation of prochiral intermediates.

1. **High Enantioselectivity:** The choice of metal and ligand plays an important role in defining the selectivity of the reaction, allowing the preferential formation of one enantiomer over the other.
2. **Streamlined Synthesis:** This method minimizes the need for subsequent purification steps, as the asymmetric hydrogenation reaction directly produces the desired enantiomer. Iridium catalysts are noted for their high activity and selectivity, while rhodium catalysts also provide excellent enantioselectivity depending on the ligand configuration.

C) Biocatalysis/Enzyme Catalysis^[19]

Biocatalysis, which uses enzymes to catalyze reactions, offers an eco-friendly and efficient method for the synthesis of enantiopure dextromethorphan. Key benefits of biocatalysts include:

1. **Mild Reaction Conditions:** Enzyme-catalyzed reactions typically occur under mild conditions, such as ambient temperature and pressure, and in aqueous media, reducing the environmental impact compared to traditional chemical processes.
2. **Stereoselectivity:** Enzymes are highly selective and can catalyze reactions that favour the formation of a specific enantiomer, leading to high optical purity in the product.
3. **Minimal Purification:** Due to the high specificity of enzymes, side reactions are minimized, which reduces the need for extensive purification steps and makes the process more efficient.
4. **Green Chemistry:** Biocatalysis aligns with the principles of green chemistry by reducing the need for toxic solvents and offering a sustainable alternative for pharmaceutical production.

The methods of **kinetic resolution**, **transition metal-catalyzed asymmetric hydrogenation**, and **biocatalysis** each present valuable approaches for synthesizing enantiopure dextromethorphan. These methods provide complementary advantages in terms of efficiency, selectivity, and environmental sustainability.

3.4 Origin of the work

From the literature reports it has been observed that, various efforts have been made towards the synthesis of Dextromethorphan in the racemic as well as enantiomeric form after its discovery as nonopioid cough suppressant.^[2] The cost-effective asymmetric synthesis of DXM key intermediate is an important challenge of industrial scale production.^[20] In this context, herein we have described our efforts towards the asymmetric synthesis of DXM key intermediate.

3.5 Objective of the work

Forming C–C or C–X (where X = N, S, O, or halogen) bonds through selective C–H functionalization of unactivated olefins presents a significant challenge. This selective C–H bond functionalization is known to be both step- and atom-efficient, making it valuable for constructing complex molecules from simple, readily available starting materials. The aim of this work is to develop an efficient approach for the asymmetric synthesis of the DXM key intermediate, employing both metal-catalyzed and photocatalyzed intramolecular decarboxylative cyclization.

The reaction scheme illustrates the synthesis of compounds 18, 19, 20, and 21 from cyclohexanone (10). The process involves several steps:

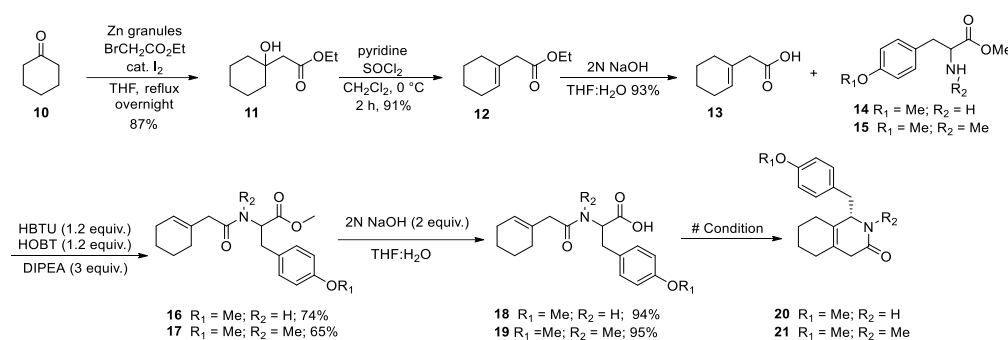
- 10** (Cyclohexanone) is converted to **13** (a cyclohexene derivative with a carboxylic acid group).
- 13** is converted to an intermediate (a cyclohexene derivative with a carboxylic acid group and a side chain).
- The intermediate is converted to **18** (where $R_1 = \text{Me}$, $R_2 = \text{H}$) or **19** (where $R_1 = \text{Me}$, $R_2 = \text{Me}$).
- The intermediate is converted to **20** (where $R_1 = \text{Me}$, $R_2 = \text{H}$) or **21** (where $R_1 = \text{Me}$, $R_2 = \text{Me}$).

The structures of **18**, **19**, **20**, and **21** are shown as cyclohexene derivatives with a carboxylic acid group and a side chain. The side chain is defined by the substituents R_1 and R_2 .

The synthesis of acid **13** should be possible by utilizing the Reformatsky reaction protocol on commercially available cyclohexanone **10**, followed by dehydroxylation with thionyl chloride in the presence of pyridine (Scheme 3).

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carboxylic acid **13** quantitatively. Next, we coupled this olefinic acid **13** with tyrosine esters **14/15** using HBTU as the coupling reagent, resulting in the formation of compounds **16** and **17** in good isolated yields (74%, 65%). Further, we hydrolysed **16** and **17** using 2N NaOH to obtain our key acid intermediates **18** and **19** in quantitative yields. This approach highlights the efficiency of our synthetic route, paving the way for the subsequent steps in the synthesis of Dextromethorphan and its analogues.

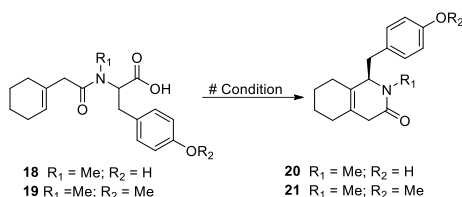


Scheme 4. Synthetic route A for the key dextromethorphan intermediate

After getting key acids in hand, we tried several reaction conditions containing metal catalysts, bases and solvents to achieve the decarboxylative cyclized product. Initially we attempted the reaction using palladium and copper-based catalysts under various conditions, but we observed undesired product formation in trace amount or, in some cases, starting material as such unreacted. (Scheme 4).

Route B:

After several attempts with route A, we decided to explore an alternative approach by moving towards route B. In this context, we have envisioned a retrosynthetic plan for the key intermediate of dextromethorphan **29**, **30**, considering the use of a ketonic substrate. The plan focuses on the electrophilic reactivity of the substrate, which promotes intramolecular nucleophilic cyclization, leading to the the desired product **29** or **30** (Scheme 5)

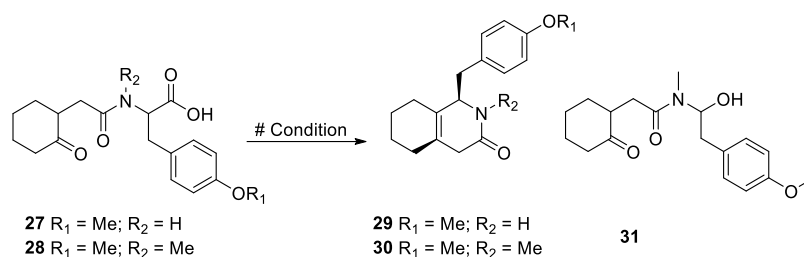
Table 1. Optimization of reaction condition

Sr. No.	catalyst	additive (equiv.)	base (equiv.)	oxidant (equiv.)	solvent	time (h)	temp. (°C)	observation
1	Pd(OAc) ₂ (10 mol%)	1, 10 phen. (10 mol%)	Cs ₂ CO ₃ (1.1)	APS (1.5)	DMSO	18	100	NR
2	Pd(OAc) ₂ (10 mol%)	-	Cs ₂ CO ₃ (1.1)	APS (1.5)	DMSO	18	100	NR
3	Pd(TFA) ₂ (10 mol%)	-	Cs ₂ CO ₃ (1.1)	APS (1.5)	DMSO	18	100	NR
4	Pd(TFA) ₂ (10 mol%)	-	Cs ₂ CO ₃ (1.1)	APS (1.5)	DMSO	18	100	NR
5	Pd(TFA) ₂ (10 mol%)	-	Cs ₂ CO ₃ (1.1)	-	1,4 dioxan	18	100	NR
6	Pd(TFA) ₂ (15 mol%)	-	Cs ₂ CO ₃ (1.1)	-	1,4 dioxan	18	100	NR
7	Pd(OAc) ₂ (10 mol%)	1, 10 phen. (10 mol%)	Cs ₂ CO ₃ (1.1)	APS (1.5)	DMAc	18	100	NR
8	AgNO ₃ (20 mol%)	-	Cs ₂ CO ₃ (3)	APS (3)	DMSO	12	80	NR
9	Pd (OAc) ₂ (5 mol%)+Cu (OAc) ₂ (20 mol%)	1,10 phen. (10 mol%)	Cs ₂ CO ₃ (1.1)	-	Toluene	18	120	NR
10	Ir-PC-1 (1 mol%) + Pd(TFA) ₂ (5 mol%)	-	K ₂ HPO ₄ (1.5)	-	ACN	14	60	NR
11	Ir-PC-2 (1 mol%) + Pd(TFA) ₂ (5 mol%)	-	K ₂ HPO ₄ (1.5)	-	ACN	14	60	NR
12	Ir-PC-1 (1 mol%)	-	Cs ₂ CO ₃ (1.1)	APS (1.5)	ACN	19	RT	NR
13	Ir-PC-2 (1 mol%)	-	Cs ₂ CO ₃ (1.1)	APS (1.5)	ACN	19	RT	NR
14	RFTA (5 mol%)	-	Cs ₂ CO ₃ (1.1)	APS (1.5)	DMSO	12	RT	NR

The key dextromethorphan intermediate **29**, **30** could be obtained from **27** and **28** by decarboxylative electrophilic substitution reaction. The key intermediate acids **27** and **28** can

After getting the key precursor **27** and **28** in hand, we tried several conditions, but we could not observe cyclized product formation. Instead of cyclized product formation, we observed undesired oxidized product **31** (entry 9, Table. 2). Our next goal is to discover a suitable condition to achieve the required synthetic transformation. We believe that Route B might work well and provide cyclized product.

Table 2. Optimization of reaction condition



Sr. No.	Catalyst	Additive (equiv.)	Base (equiv.)	Oxidant (equiv.)	Solvent	Time (h)	Temp. (°C)	Observation
1	AgNO ₃ (20 mol%)	ZnCl ₂ (2)	-	APS (2)	DMF	10 h	60 °C	NR
2	Ir-PC(1 mol%)	TFA (2)	-	1.5 (APS)	DMAc	12 h	60 °C	NR
3	Ir-PC(1 mol%)	ZnCl ₂ (2)	Cs ₂ CO ₃ (2)	1 (APS)	DMSO	14 h	RT	NR
4	-	Sc(OTf) ₂ (0.1)	Cs ₂ CO ₃ (2)	-	DMSO	12 h	60 °C	
5	-	BF ₃ ·(OEt) ₂ (0.5)	Cs ₂ CO ₃ (2)	-	DMSO	12 h	60 °C	
6	RFTA (5 mol%)	-	Cs ₂ CO ₃ (2)	-	DMSO	18 h	RT	NR
7	Ir-PC(1 mol%)	Sc(OTf) ₂ (0.1)	Cs ₂ CO ₃ (2)	-	DMF	14 h	RT	
8	Ir-PC(1 mol%)	Bi(OTf) ₂ (0.1)	Cs ₂ CO ₃ (2)	-	DMF	14 h	RT	
9	Ir-PC(1 mol%)	Cu(OTf) ₂ (0.1)	Cs ₂ CO ₃ (2)	-	DMF	14 h	RT	Product 31 formed
10	RFTA (5 mol%)	Cu(OTf) ₂ (0.1)	Cs ₂ CO ₃ (1.1)		DMSO	15 h	RT	Product 32 formed

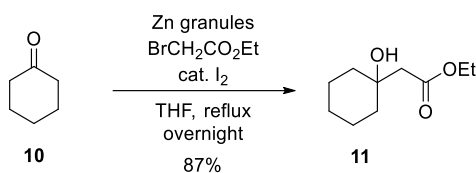
3.7 Conclusion

In summary, our focus was on synthesizing precursors for metal-catalyzed and photodecarboxylative cyclization reactions to generate Dextromethorphan key intermediate. Our synthesis started with commercially available cyclohexanone. We tested two routes and various combinations of reagents and conditions but encountered challenges, either forming undesired products or leaving the starting material unreacted. These results highlight the necessity for thorough optimization of the reaction conditions. Our next goal is to identify the appropriate conditions for successful transformation, which will enable the synthesis of morphine-class compounds and related natural products with similar pharmacological properties. This chapter lays the groundwork for developing a synthetic strategy to produce these bioactive molecules.

3.8 Experimental Section

Note: Intermediate compounds **17**, **19**, **27**, **28**, and **29** have complex mixture of amide rotamers, which resulted into multiple peaks and broad signals, hence not all signals are distinguishable/visible.

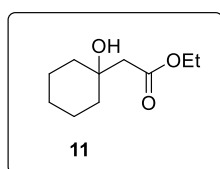
[A] Synthesis of ethyl 2-(1-hydroxy cyclohexyl) acetate (**11**):



The compound **11** was synthesized by literature known procedure.^[22]

In a 100 mL three-necked round-bottom flask equipped with a reflux condenser, zinc granules (4.25 g, 65 mmol), a single crystal of iodine, cyclohexanone (5.18 mL, 50 mmol), and anhydrous tetrahydrofuran (THF, 50 mL) were mixed under a nitrogen atmosphere. Ethyl 2-bromoacetate (6.68 mL, 60 mmol) was then added dropwise to the mixture via a dropping funnel at room temperature. The reaction mixture was stirred at 50 °C for 30 minutes, then refluxed at 65 °C overnight. After cooling to room temperature, the reaction was quenched with 1 M aq. HCl solution. The aqueous phase was extracted three times with diethyl ether (Et₂O), and the combined organic extracts were washed once with brine, dried over anhydrous sodium sulfate (Na₂SO₄), and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel using a hexane: ethyl acetate mixture (9:1) as the eluent, to provide ethyl 2-(1-hydroxycyclohexyl) acetate (**11**) 8.3 g, 87% yield.

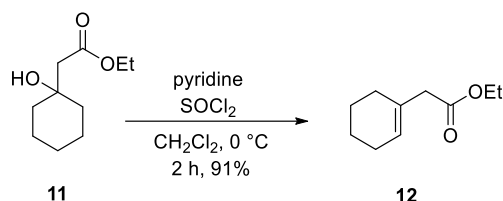
Ethyl 2-(1-hydroxycyclohexyl) acetate (**11**):^[22]



: 87% light yellow oil, R_f: 0.3 (9:1, hexane: EtOAc);

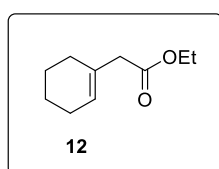
¹H NMR (400 MHz, CDCl₃): δ 4.17 (q, *J* = 7.1 Hz, 2 H), 3.42 (s, 1 H), 2.47 (s, 2 H), 1.74 - 1.60 (m, 4 H), 1.58 - 1.49 (m, 1 H), 1.49 - 1.37 (m, 4 H), 1.34 - 1.22 (m, 4 H).

ESIMS[M+H]⁺ (*m/z*): 186.

[B] Synthesis of ethyl 2-(cyclohex-1-en-1-yl)acetate (12):

Compound **11** was synthesized by following the literature known procedure.^[22]

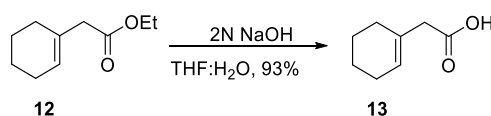
To an ice-cold solution of Ethyl 2-(1-hydroxycyclohexyl)acetate (5 g, 26.84 mmol) and pyridine (2.54 mL, 32 mmol) in anhydrous dichloromethane (CH_2Cl_2 , 50 mL), thionyl chloride (2.413 mL, 20 mmol) was added dropwise at 0 °C over 20 minutes under a nitrogen atmosphere. The reaction mixture was then stirred at 0 °C for 2 hours. Afterward, the reaction was quenched with water, and the organic phase was extracted three times with CH_2Cl_2 . The combined organic extracts were washed twice with saturated aqueous sodium bicarbonate (NaHCO_3) and once with brine. The extracts were dried over anhydrous sodium sulfate (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography on silica gel, using a hexane: ethyl acetate (EtOAc) mixture (9:1) as the eluent, yielding ethyl 2-(cyclohex-1-en-1-yl) acetate (**12**) (4.1 g, 24.4 mmol) in 91% yield.

Ethyl 2-(1-hydroxycyclohexyl) acetate (12):^[22]

: 91% light yellow oil, R_f 0.4 (9:1, hexane: EtOAc)

$^1\text{H NMR}$ (200 MHz, CDCl_3): δ 5.67 - 4.42 (m, 1 H), 4.24 - 4.04 (m, 2 H), 3.03 - 2.81 (m, 2 H), 2.09 - 1.94 (m, 3 H), 1.71 - 1.50 (m, 5 H), 1.32 - 1.22 (m, 3 H).

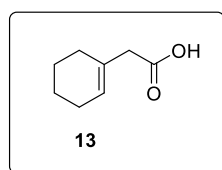
ESIMS[$\text{M}+\text{H}$]⁺ (m/z): 168.

[C] Synthesis of 2-(cyclohex-1-en-1-yl)acetic acid (13):

To the solution of ester **12** (3 g, 17.23 mmol, 1 equiv.) in THF/water (1:1, 30 mL) was added aqueous NaOH (1.426 g, 17.8 mL 2N, 35.71 mmol, 2 equiv.) drop wise at room temperature

with continuous stirring and the reaction mixture was stirred until complete consumption of the starting material (checked by TLC). THF was then removed in a *vacuo* followed by dilution with water (40 mL) and the addition of ethyl acetate (30 mL). The organic layer was separated and the aqueous layer was acidified with citric acid up to pH 2 and extracted with ethyl acetate (15 mL X 3). The ethyl acetate layer was separated, dried over anhydrous Na₂SO₄, and concentrated in *vacuo* to obtain the corresponding acid **13** in 93% yield as a light yellow oil (2.3g).

Ethyl 2-(1-hydroxycyclohexyl) acetate **13:**^[23]

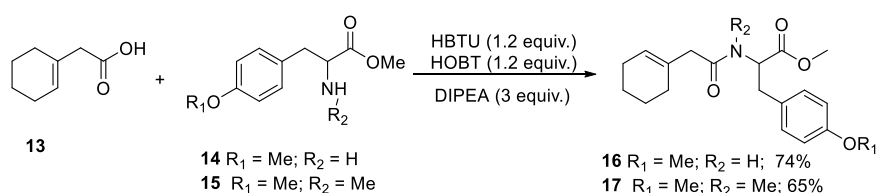


: 93% light yellow oil, *R*_f: 0.3 (4:6, hexane: EtOAc)

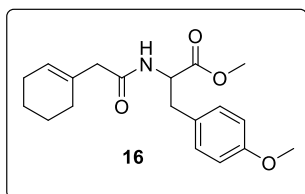
¹H NMR (400 MHz, CDCl₃): δ 5.60 (br. s., 1 H), 2.98 (s, 2 H), 2.02 (br. s., 4 H), 1.78 - 1.41 (m, 4 H).

ESIMS[M+H]⁺ (*m/z*): 140

[D] Synthesis of compounds **16, **17**:**



To a solution of acid **13** (1 equiv.) in DMF (15 mL for 1 g of acid) was added, HBTU (1.5 equiv.) and HOBT (1.5 equiv.) followed by DIPEA (3 equiv.) at 0 °C with continuous stirring for 10 minutes. Later, a solution of amino acid methyl ester **14/15** (1.2 equiv.) in DMF (10 mL) was added dropwise at 0 °C to the reaction mixture in ten minutes with continuous stirring. After completion of addition, reaction mixture was allowed to warm to room temperature and then stirred overnight. After completion of the reaction (checked by TLC), the DMF solvent was removed in *vacuo*, and then the residue was quenched with saturated aqueous NH₄Cl (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with saturated aqueous NaHCO₃ solution (3 × 20 mL) and brine (20 mL), dried over anhydrous Na₂SO₄, and concentrated in *vacuo*. The resulting crude product was purified by flash column chromatography on silica gel using hexane: ethyl acetate mixture (4:6) as the eluent, yielded **16/17** in 74 and 65%.



Methyl 2-(2-(cyclohex-1-en-1-yl)acetamido)-3-(4-methoxyphenyl)propanoate (16):

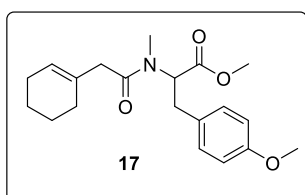
: 74%, colourless sticky liquid; R_f : 0.3 (3:7, ethyl acetate: petroleum ether).

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.02 - 6.97 (m, 2 H), 6.85 - 6.79 (m, 2 H), 6.15 (d, J = 7.8 Hz, 1 H), 5.58 (br. s., 1 H), 4.87 - 4.79 (m, 1 H), 3.79 (s, 3 H), 3.73 (s, 3 H), 3.11 - 2.99 (m, 2 H), 2.86 (s, 2 H), 2.01 (br. s., 2 H), 1.95 - 1.80 (m, 2 H), 1.59 - 1.47 (m, 4 H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 172.1, 170.7, 158.7, 132.5, 130.2, 127.7, 127.3, 114.0, 55.2, 52.8, 52.2, 46.1, 36.9, 28.3, 25.3, 22.6, 21.8.

HRMS-ESI (m/z) calcd for $(\text{C}_{19}\text{H}_{25}\text{NO}_4+\text{H})^+$: 332.1856, found: 332.1850.

Methyl 2-(2-(cyclohex-1-en-1-yl)-N-methylacetamido)-3-(4-methoxyphenyl)propanoate (17):



: 65%, colourless sticky liquid; R_f : 0.4 (3:7, ethyl acetate: petroleum ether).

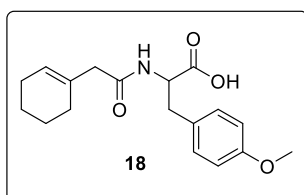
$^1\text{H NMR}$ (400 MHz, CDCl_3 , mixture of rotamer): δ 7.12 - 7.00 (m, 2 H), 6.77 (d, J = 8.6 Hz, 2 H), 5.41 - 5.28 (m, 1 H), 5.14 - 5.08 (m, 1 H), 3.74 - 3.72 (m, 3 H), 3.70 - 3.67 (m, 3 H), 3.34 - 3.24 (m, 1 H), 2.94 - 2.76 (m, 5 H), 2.00 - 1.62 (m, 4 H), 1.56 - 1.37 (m, 5 H)

$^{13}\text{C NMR}$ (101 MHz, CDCl_3 , mixture of rotamer): δ 171.6, 171.3, 170.6, 158.4, 158.2, 131.0, 130.0, 129.7, 129.6, 129.6, 128.7, 124.5, 123.9, 114.0, 113.6, 62.3, 61.7, 57.5, 57.2, 55.0, 55.0, 54.9, 52.2, 51.9, 45.8, 43.3, 36.5, 34.6, 33.6, 32.7, 29.2, 28.0, 27.9, 25.1, 25.0, 22.5, 22.4, 21.8, 21.8

HRMS-ESI (m/z) calcd for $(\text{C}_{20}\text{H}_{27}\text{NO}_4+\text{H})^+$: 346.2013, found: 346.2008.

The hydrolysis of compounds **16** and **17** was carried out following the procedure C.

2-(2-(cyclohex-1-en-1-yl)acetamido)-3-(4-methoxyphenyl)propanoic acid (18):



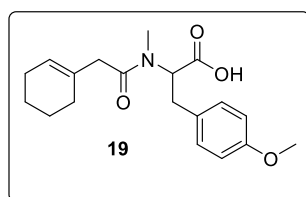
: 94%, colourless sticky gum; R_f : 0.3 (3:7, ethyl acetate: petroleum ether).

^1H NMR (400 MHz, CDCl_3): δ 7.11 - 7.00 (m, 2 H), 6.89 - 6.75 (m, 2 H), 6.25 (d, J = 7.6 Hz, 2 H), 5.56 (br. s., 1 H), 4.81 (q, J = 7.4 Hz, 1 H), 3.79 (s, 3 H), 3.22 - 3.03 (m, 2 H), 2.87 (s, 2 H), 1.99 (br. s., 2 H), 1.83 (d, J = 16.8 Hz, 2 H), 1.58 - 1.44 (m, 4 H).

^{13}C NMR (101 MHz, CDCl_3): δ 174.4, 172.1, 158.8, 132.1, 130.3, 127.7, 127.4, 114.1, 55.2, 53.0, 45.8, 36.2, 28.2, 25.3, 22.6, 21.8.

HRMS-ESI (m/z) calcd for $(\text{C}_{18}\text{H}_{23}\text{NO}_4 + \text{H})^+$: 318.1700, found: 318.1694.

2-(2-(cyclohex-1-en-1-yl)-N-methylacetamido)-3-(4-methoxyphenyl)propanoic acid 19:



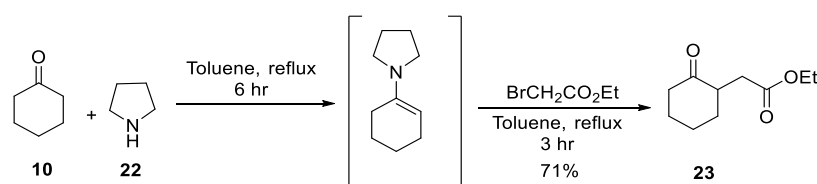
: 95%, colourless sticky gum; R_f : 0.3 (3:7, ethyl acetate: petroleum ether).

^1H NMR (400 MHz, mixture of rotamer): δ 7.15 - 7.07 (m, 2 H), 6.89 - 6.74 (m, 2 H), 5.36 (br. s., 0.20 H), 5.28 (dd, J = 5.0, 11.4 Hz, 0.8 H), 5.20 (br. s., 0.8 H), 4.67 (dd, J = 4.7, 10.0 Hz, 0.20 H), 3.84 - 3.66 (m, 3 H), 3.39 - 3.25 (m, 1 H), 3.09 - 2.88 (m, 3 H), 2.83 (s, 2 H), 1.91 (br. s., 2 H), 1.81 - 1.64 (m, 2 H), 1.60 - 1.42 (m, 4 H), 1.40 - 1.27 (m, 1 H).

^{13}C NMR (101 MHz, 101 MHz, CDCl_3 , mixture of rotamer): δ 174.4, 173.9, 173.1, 172.4, 158.6, 158.4, 131.7, 130.8, 129.9, 129.8, 128.7, 125.0, 124.5, 114.2, 113.9, 61.9, 59.1, 55.2, 55.2, 43.5, 34.6, 33.7, 33.5, 29.7, 28.2, 28.0, 25.2, 22.6, 22.5, 21.9, 21.9.

HRMS-ESI (m/z) calcd for $(\text{C}_{19}\text{H}_{25}\text{NO}_4 + \text{H})^+$: 332.1856, found: 332.1852.

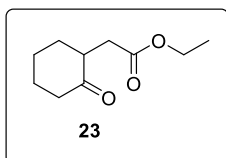
[E] Synthesis of ethyl 2-(2-oxocyclohexyl)acetate (24):



Ethyl 2-(2-oxocyclohexyl) acetate (23): Cyclohexanone (**10**, 5 g, 51.02 mmol), pyrrolidine (**23**, 7.2 g, 102.04 mmol), and $\text{PhB}(\text{OH})_2$ (311 mg, 2.55 mmol) were heated at reflux in toluene (20 mL) for 6 h with azeotropic removal of water. After completion of 6 h, the solvent was evaporated under reduced pressure and fresh dry toluene (20 mL) was added to the residue, and followed by addition of ethyl bromoacetate solution (10 g, 61.2 mmol) in toluene (10 mL) was added under nitrogen. The reaction mixture was heated at reflux for 3.0 h. Then, H_2O (20 mL) was added, and the mixture was stirred at room temperature for 1.0 h.

The mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with H₂O (30 mL) and brine (30 mL), dried with anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane/EtOAc, 90:10) to give **23** (6.7 g, 71 %) as a yellowish oil. The spectroscopic data for **23** is identical to the reported in the literature.^[24]

Ethyl 2-(1-hydroxycyclohexyl) acetate (23):^[24]



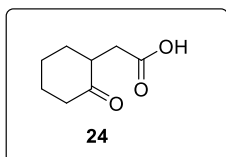
: 71% light yellow oil, R_f: 0.3 (9:1, hexane:EtOAc).

¹H NMR (400 MHz, CDCl₃): δ 4.26 - 4.04 (m, 2 H), 3.01 - 2.64 (m, 2 H), 2.53 - 2.32 (m, 2 H), 2.26 - 2.05 (m, 3 H), 1.92 - 1.63 (m, 3 H), 1.51 - 1.35 (m, 1 H), 1.34 - 1.21 (m, 3 H).

ESIMS[M+H]⁺ (m/z): 185.

The hydrolysis of compound **23** was done by flowing procedure C

2-(2-oxocyclohexyl)acetic acid 24:^[24]



: 91% colourless sticky solid; R_f: 0.22 (3:7, ethyl acetate: petroleum ether).

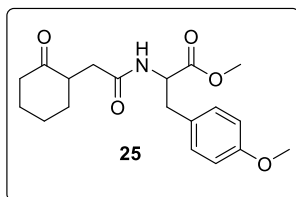
¹H NMR (400 MHz, CDCl₃): δ 2.89 - 2.72 (m, 2 H), 2.47 - 2.30 (m, 2 H), 2.25 - 2.08 (m, 3 H), 1.93 - 1.83 (m, 1 H), 1.78 - 1.55 (m, 2 H), 1.51 - 1.33 (m, 1 H).

ESIMS[M+H]⁺ (m/z): 157.

The spectroscopic data for **23** and **24** are identical to those reported in the literature.^[24]

Amidation of acid compound 24 to obtain esters 25 and 26 by following procedure D

Methyl N-methyl-N-(2-(2-oxocyclohexyl)acetyl)tyrosinate (25):



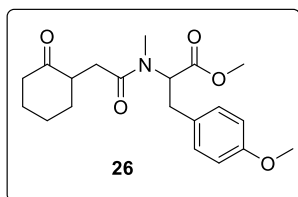
: 86%, colourless sticky solid; R_f: 0.34 (4:6, ethyl acetate: petroleum ether).

¹H NMR (CDCl₃, 400 MHz): δ 7.13 - 7.04 (m, 2 H), 6.87 - 6.80 (m, 2 H), 6.19 (d, J = 7.8 Hz, 1 H), 4.87 - 4.77 (m, 1 H), 3.79 (s, 3 H), 3.71 (s, 3 H), 3.12 - 2.96 (m, 2 H), 2.91 - 2.80 (m, 1 H), 2.67 - 2.58 (m, 1 H), 2.45 - 2.28 (m, 2 H), 2.18 - 2.02 (m, 3 H), 1.91 - 1.83 (m, 1 H), 1.77 - 1.57 (m, 3 H).

¹³C NMR (101 MHz, CDCl₃): δ 212.1, 172.1, 171.2, 158.6, 130.3, 127.8, 113.9, 55.2, 53.1, 52.2, 47.6, 42.0, 37.0, 36.5, 34.3, 27.9, 25.2.

HRMS-ESI (m/z) calcd for (C₁₉H₂₅NO₅+H)⁺: 348.1805, found: 348.1797.

Methyl 2-(2-(cyclohex-1-en-1-yl)-N-methylacetamido)-3-(4-methoxyphenyl)propanoate (26):



: 63%, colourless sticky solid; R_f : 0.4 (3:7, ethyl acetate: petroleum ether).

$^1\text{H NMR}$ (400 MHz, CDCl_3 , mixture of rotamer): δ 7.16 - 7.00 (m, 2 H), 6.87 - 6.75 (m, 2 H), 5.23 - 4.97 (m, 1 H), 3.80 - 3.62

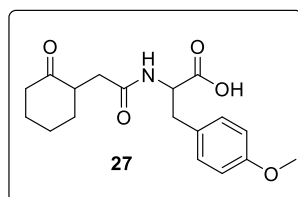
(m, 6 H), 3.33 - 3.18 (m, 1 H), 3.01 - 2.95 (m, 1 H), 2.88 - 2.75 (m, 4 H), 2.42 - 2.27 (m, 2 H), 2.20 - 2.00 (m, 2 H), 1.94 - 1.86 (m, 1 H), 1.85 - 1.75 (m, 1 H), 1.73 - 1.58 (m, 2 H), 1.37 - 1.07 (m, 2 H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3 , mixture of rotamer): δ 212.0, 211.7, 172.1, 172.0, 171.5, 171.3, 158.3, 130.0, 129.9, 129.7, 129.7, 129.5, 129.2, 129.0, 114.3, 114.2, 114.1, 113.8, 113.8, 61.4, 59.5, 58.6, 55.1, 52.2, 52.1, 47.2, 47.0, 41.9, 41.9, 34.4, 34.1, 33.8, 33.8, 33.7, 33.0, 33.0, 32.9, 28.1, 28.0, 25.2, 25.1.

HRMS-ESI (m/z) calcd for $(\text{C}_{20}\text{H}_{28}\text{NO}_5+\text{H})^+$: 362.1962, found: 362.1947

Hydrolysis of compound **25** and **26** was done by following procedure C

Methyl N-methyl-N-(2-(2-oxocyclohexyl)acetyl)tyrosinate (27):



: 97%, colourless sticky solid; R_f : 0.22 (3:7, ethyl acetate: petroleum ether).

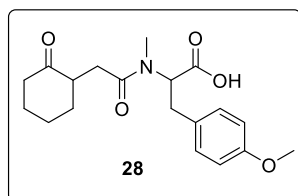
$^1\text{H NMR}$ (400 MHz, CDCl_3 , mixture of rotamer): δ 7.71 (br. s., 1 H), 7.19 - 6.98 (m, 2 H), 6.82 (br. s., 2 H), 4.88 - 4.36 (m, 1 H),

3.77 (br. s., 3 H), 3.50 - 2.26 (m, 5 H), 2.23 - 1.01 (m, 8 H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3 , mixture of rotamer): δ 212.7, 212.5, 176.3, 174.3, 172.6, 172.5, 172.3, 164.3, 158.9, 158.6, 158.5, 131.1, 130.5, 130.3, 130.1, 129.9, 128.0, 127.8, 127.5, 117.7, 117.6, 114.1, 114.0, 113.9, 113.8, 113.6, 98.9, 63.6, 57.7, 55.3, 55.2, 53.6, 53.3, 47.6, 43.7, 41.9, 41.9, 36.5, 36.4, 36.4, 36.3, 34.5, 34.4, 34.2, 34.1, 34.0, 32.6, 32.1, 29.7, 28.4, 28.3, 27.9, 27.8, 26.8, 26.7, 25.2, 25.1, 24.3, 23.2, 22.8, 22.6, 22.2, 20.3, 19.0.

HRMS-ESI (m/z) calcd for $(\text{C}_{18}\text{H}_{23}\text{NO}_5+\text{H})^+$: 334.1649, found: 334.1645.

Methyl 2-(2-(cyclohex-1-en-1-yl)-N-methylacetamido)-3-(4-methoxyphenyl)propanoate 28:



: 92%, colourless sticky solid; R_f : 0.22 (3:7, ethyl acetate: petroleum ether).

¹H NMR (400 MHz, CDCl₃, mixture of rotamer): δ 7.16 - 7.02 (m, 2 H), 6.84 - 6.76 (m, 2 H), 4.62 - 5.21 (m, 1 H), 3.76 (s, 3 H), 3.35 - 3.20 (m, 1 H), 3.06 - 2.94 (m, 1 H), 2.87 - 2.77 (m, 3 H), 2.42 - 2.26 (m, 2 H), 2.18 - 1.46 (m, 6 H) 1.36 - 1.10 (m, 2 H), 0.91 - 0.77 (m, 1 H).
¹³C NMR (101 MHz, CDCl₃, mixture of rotamer): δ 212.4, 212.0, 173.1, 172.9, 158.6, 158.3, 130.0, 129.9, 129.8, 129.2, 128.9, 128.8, 114.2, 114.2, 113.9, 113.9, 55.2, 55.2, 47.2, 47.2, 41.9, 41.9, 34.6, 34.5, 34.3, 34.1, 33.8, 33.6, 33.5, 33.1, 33.0, 31.5, 28.1, 28.0, 27.9, 25.2, 25.2, 25.1, 22.6, 22.6, 14.1.

HRMS-ESI (m/z) calcd for (C₁₉H₂₅NO₅+H)⁺: 348.1805, found: 348.1800.

[F] General photochemical reaction condition tried for cyclization

An oven dried schlenk tube containing a stirring bar, [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆, Ir-PC (1 mol%), cesium carbonate (1.1 equiv.) and acid (**18/19/27/28**, 1 equiv.) was evacuated well, flushed and refilled with argon. Anhydrous solvent was added via syringe and the reaction mixture was stirred under irradiation of 30 W blue LEDs (approximately 5 cm away from the light source) over 12-19 h at room temperature. The reaction mixture was diluted with ethyl acetate and washed with saturated aqueous NaHCO₃ solution. The aqueous phase was extracted with ethyl acetate three times and the combined organic phase was washed with brine. The united organic phases were dried over anhydrous Na₂SO₄. The solvent was evaporated under reduced pressure and the crude product (undesired) was purified by silica gel column chromatography using ethyl acetate and petroleum ether as eluents.

[G] Experimental procedure for the synthesis of compound 21 using Pd-catalysis:

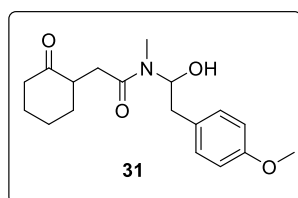
An oven dried schlenk tube containing a stirring bar, Pd(OAc)₂ (2.03 mg, 5 mol%) and Cu(OAc)₂ (20 mol%), (6.5 mg, 0.036 mmol), 1,10 phen. (3.26 mg, 0.018 mmol, 10 mol%), cesium carbonate (21.64 mg, 0.066 mmol, 1.1 equiv.) and acid **19** (60 mg, 0.18 mmol, 1 equiv.) were evacuated well, flushed, and refilled with argon. Anhydrous toluene (2 ml) was added via syringe and the reaction mixture was stirred over 18 h at 120 °C temperature. The reaction mixture was diluted with ethyl acetate and washed with saturated aqueous NaHCO₃ solution. The aqueous phase was extracted with ethyl acetate (5 mL X 3) three times and the combined organic extracts were washed with brine. The united organic phases were dried over anhydrous Na₂SO₄. The solvent was evaporated under reduced pressure and the crude

product was purified by silica gel column chromatography using ethyl acetate and petroleum ether (5:5) as eluents to obtain undesired product instead of product **21**.

[H] Experimental procedure for the synthesis of compound 30: An oven dried schlenk tube containing a stirring bar, $[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$, Ir-PC (1.97 mg, 0.0017 mmol, 1 mol%), and $\text{Cu}(\text{OAc})_2$ (10 mol%), (3.12 mg, 0.018 mmol), cesium carbonate (112.73 mg, 0.34 mmol, 2 equiv.) and acid **29** (60 mg, 0.17 mmol, 1 equiv.) were evacuated well, flushed, and refilled with argon. Anhydrous DMF (2 mL) added via syringe and the reaction mixture was stirred under irradiation of 30 W blue LEDs (approximately 5 cm away from the light source) over 14 h at room temperature. The reaction mixture was diluted with ethyl acetate and washed with saturated aqueous NaHCO_3 solution. The aqueous phase was extracted with ethyl acetate (5 mL X 3) three times and the combined organic extracts were washed with brine. The united organic phases were dried over anhydrous Na_2SO_4 . The solvent was evaporated under reduced pressure and the crude product was purified by silica gel column chromatography using ethyl acetate and petroleum ether (5:5) as eluents to obtain undesired product. **31** in 12% yield (7.3 mg) instead of product **30**.

N-(1-hydroxy-2-(4-methoxyphenyl)ethyl)-N-methyl-2-(2-oxocyclohexyl)acetamide:

: 28%, yellowish oil; R_f : 0.37 (4:6, ethyl acetate: petroleum ether). (Tentative structure)



^1H NMR (400 MHz, CDCl_3 , mixture of rotamer): δ 7.18 - 7.13 (m, 2 H), 6.87 - 6.81 (m, 2 H), 6.07 - 5.95 (m, 1 H), 5.37 - 5.30 (m, 1), 3.79 - 3.72 (m, 3 H), 3.35 - 3.30 (m, 3 H), 2.90 - 2.82 (m, 2 H), 2.68 - 2.51 (m, 1 H), 2.45 - 2.32 (m, 2 H), 2.21 - 2.11 (m, 2 H), 2.08

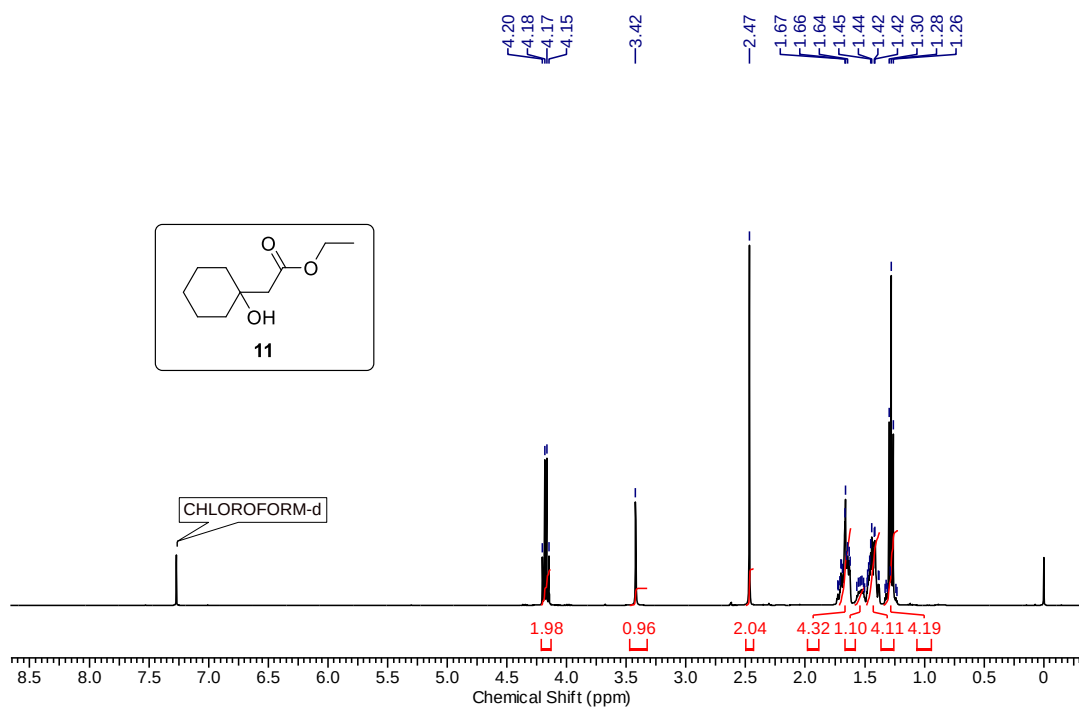
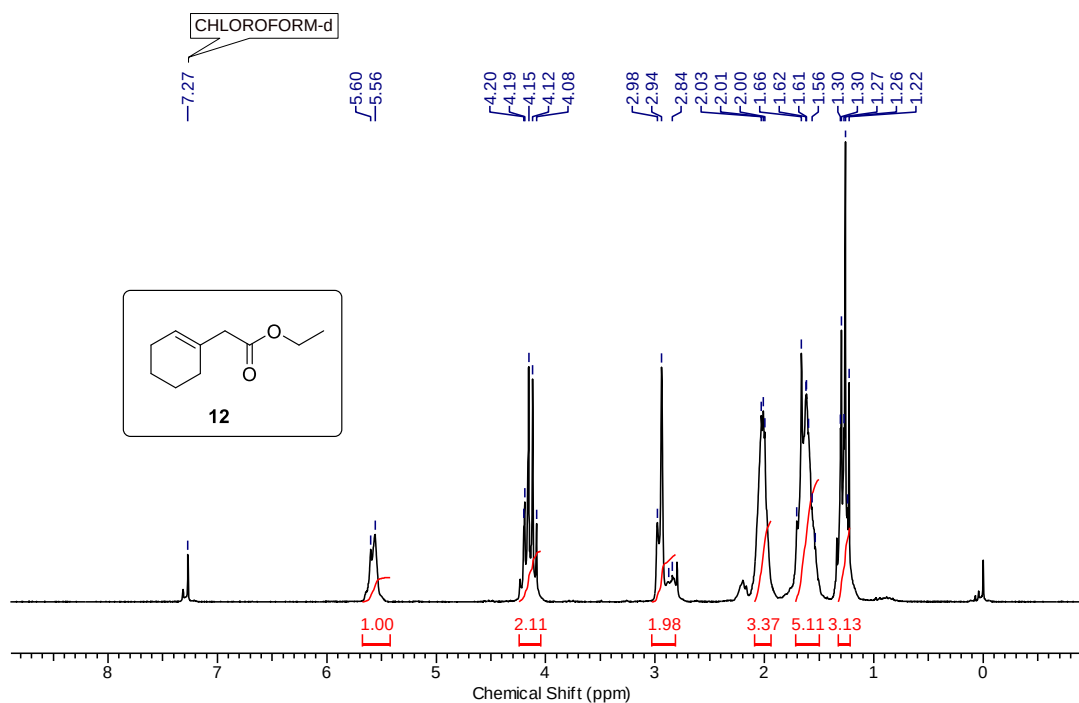
- 1.98 (m, 2 H), 1.95 - 1.82 (m, 2 H), 1.78 - 1.52 (m, 3 H).

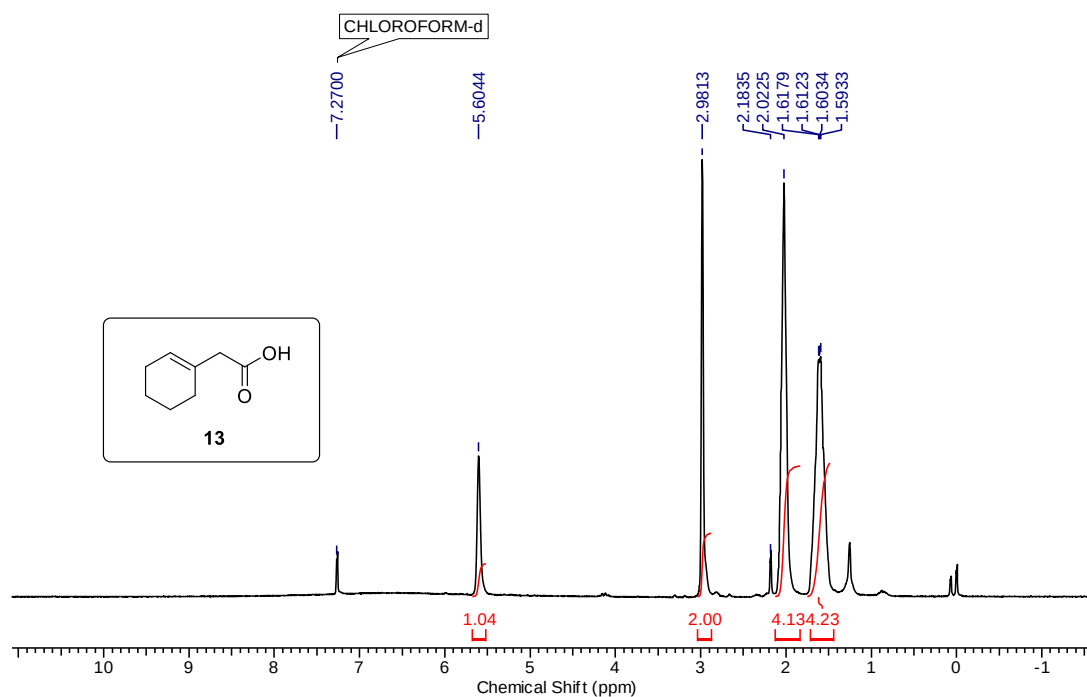
^{13}C NMR (101 MHz, CDCl_3 , mixture of rotamer): δ 212.3, 172.1, 158.4, 130.8, 130.6, 128.1, 127.9, 113.8, 80.96, 80.89, 55.9, 55.8, 55.2, 47.7, 47.5, 42.0, 41.9, 40.6, 40.4, 36.9, 34.0, 27.89, 25.2.

3.9 Reference:

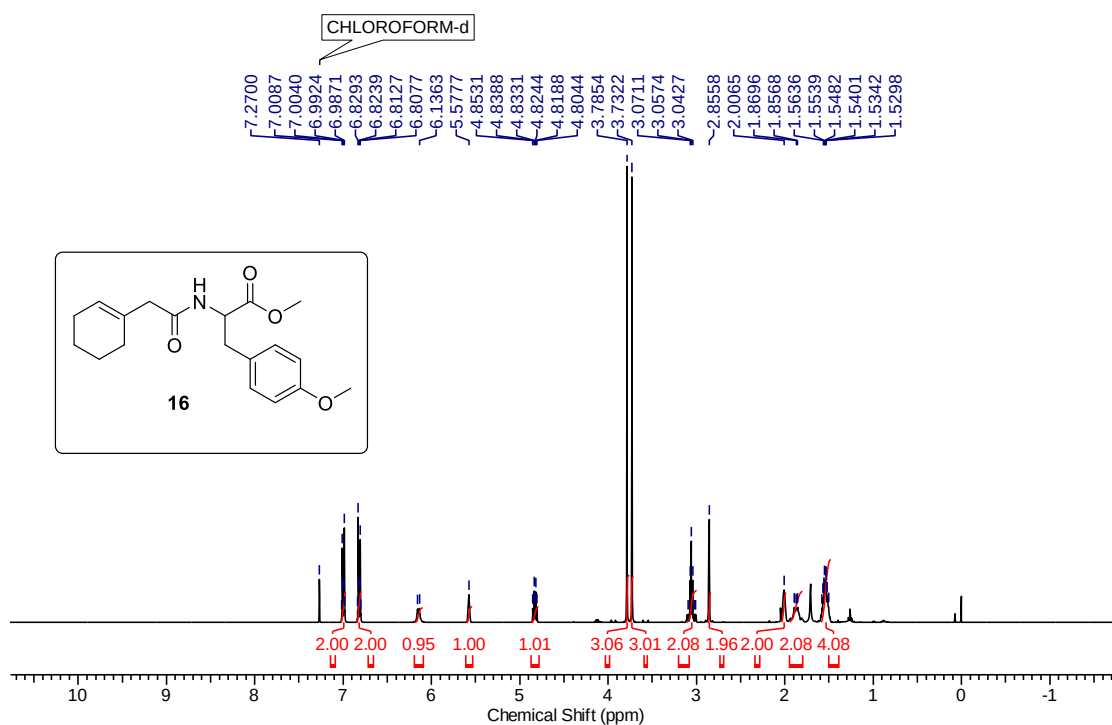
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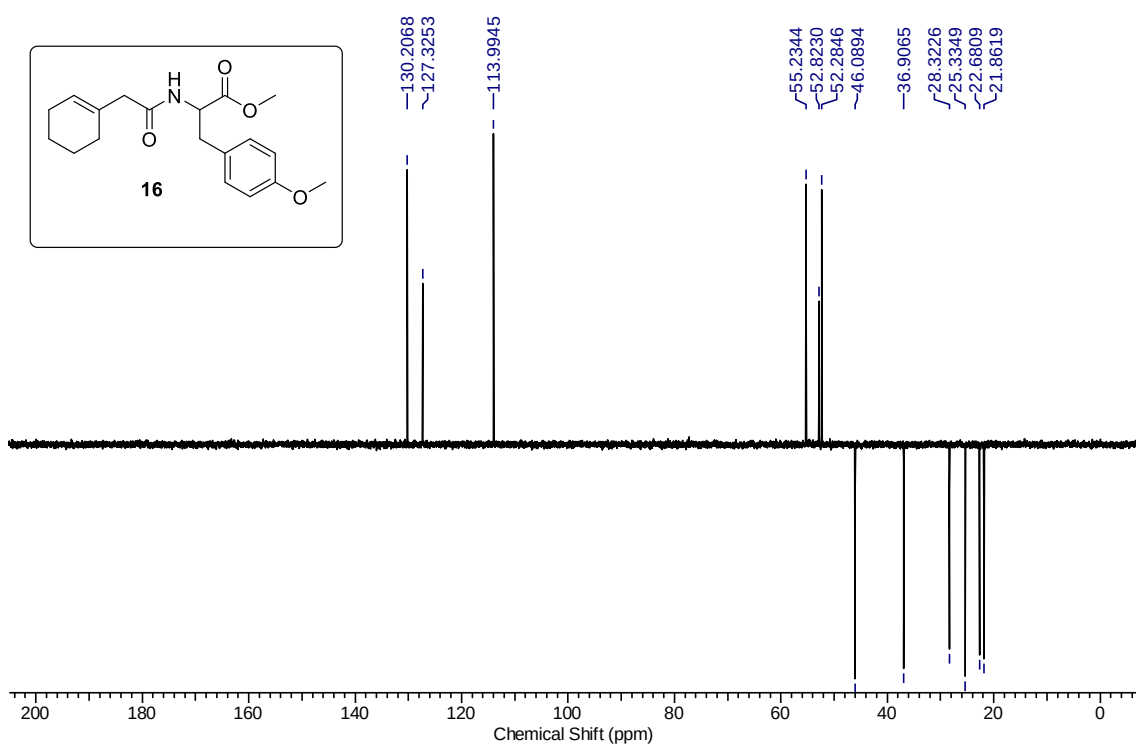
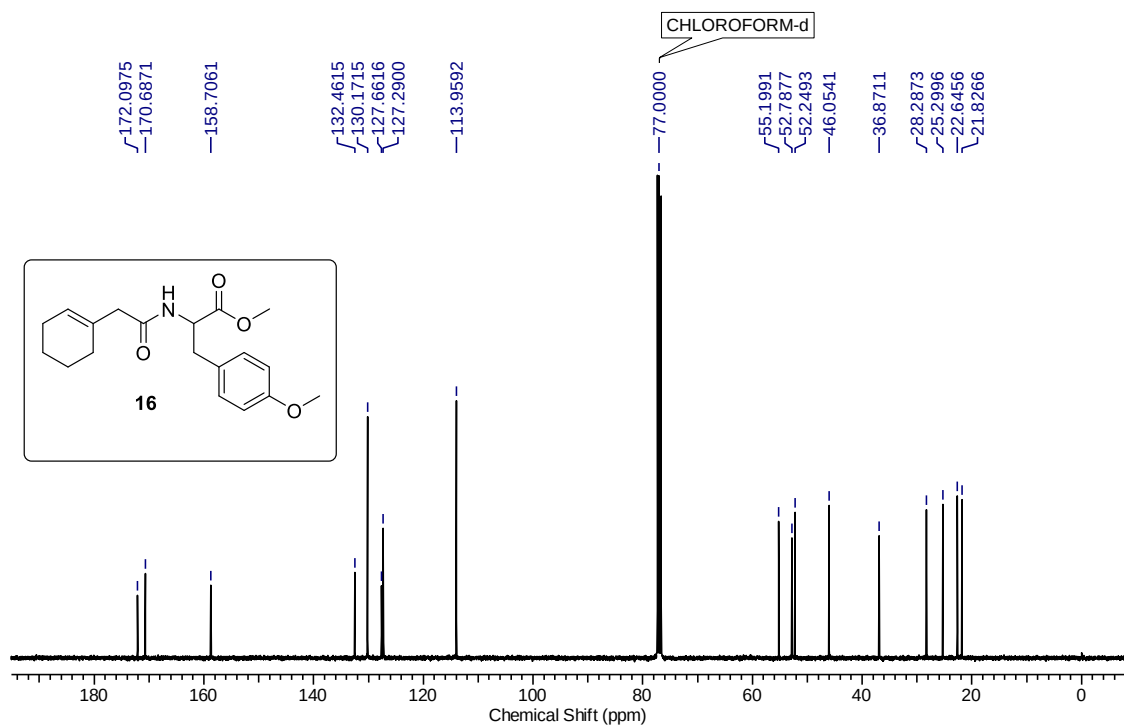
3.10 Spectra of ^1H , ^{13}C , DEPT NMR Chromatogram. ^1H (400 MHz, CDCl_3) NMR of compound 11 ^1H (200 MHz, CDCl_3) NMR of compound 12

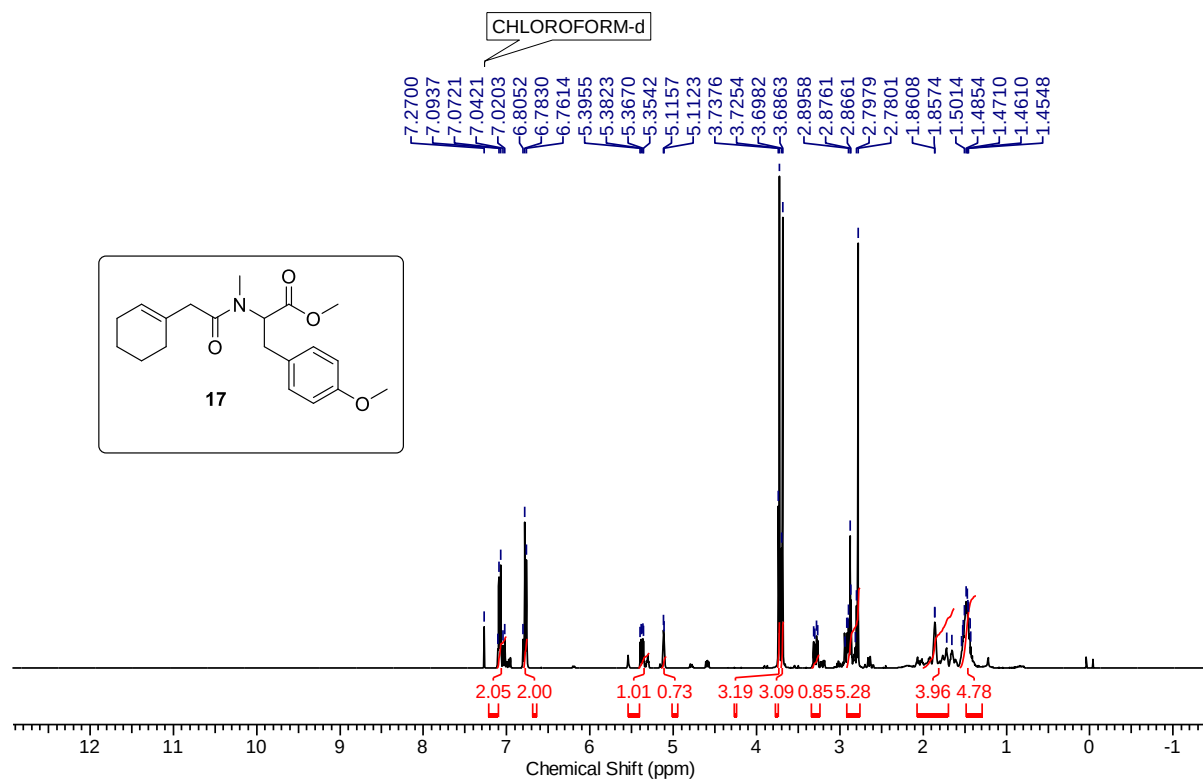


^1H (200 MHz, CDCl_3) NMR of compound 13

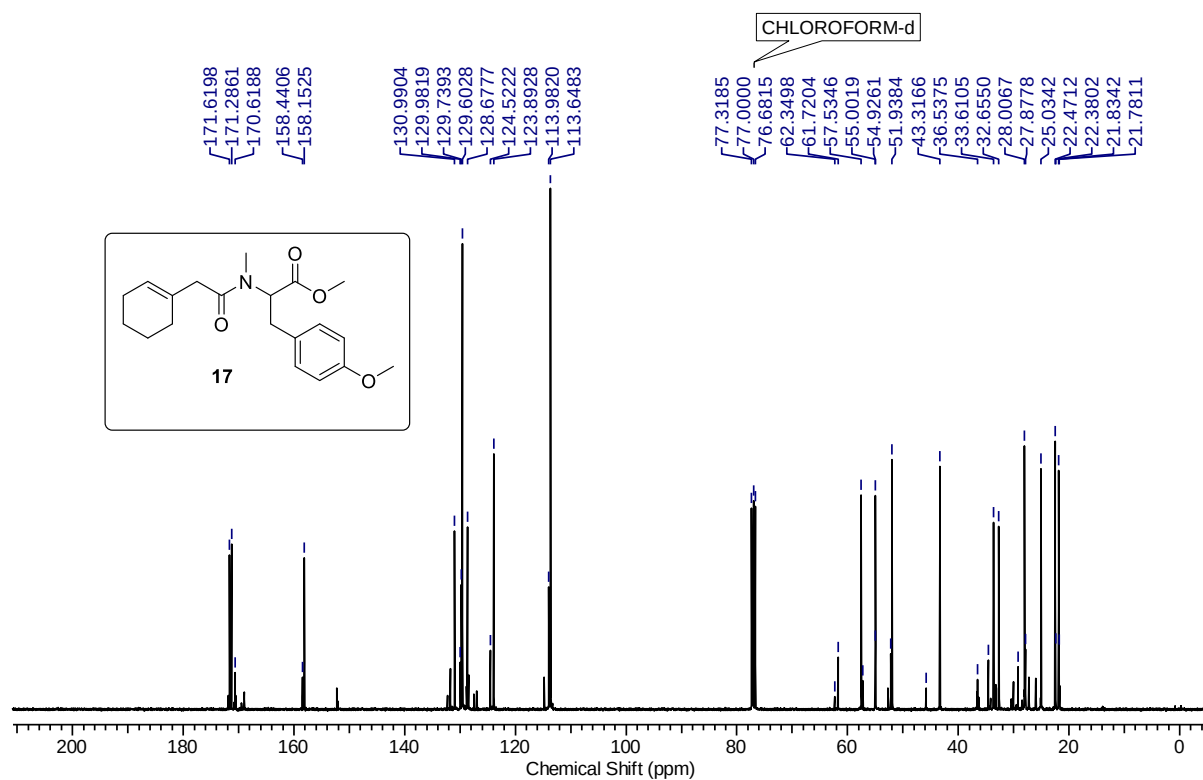


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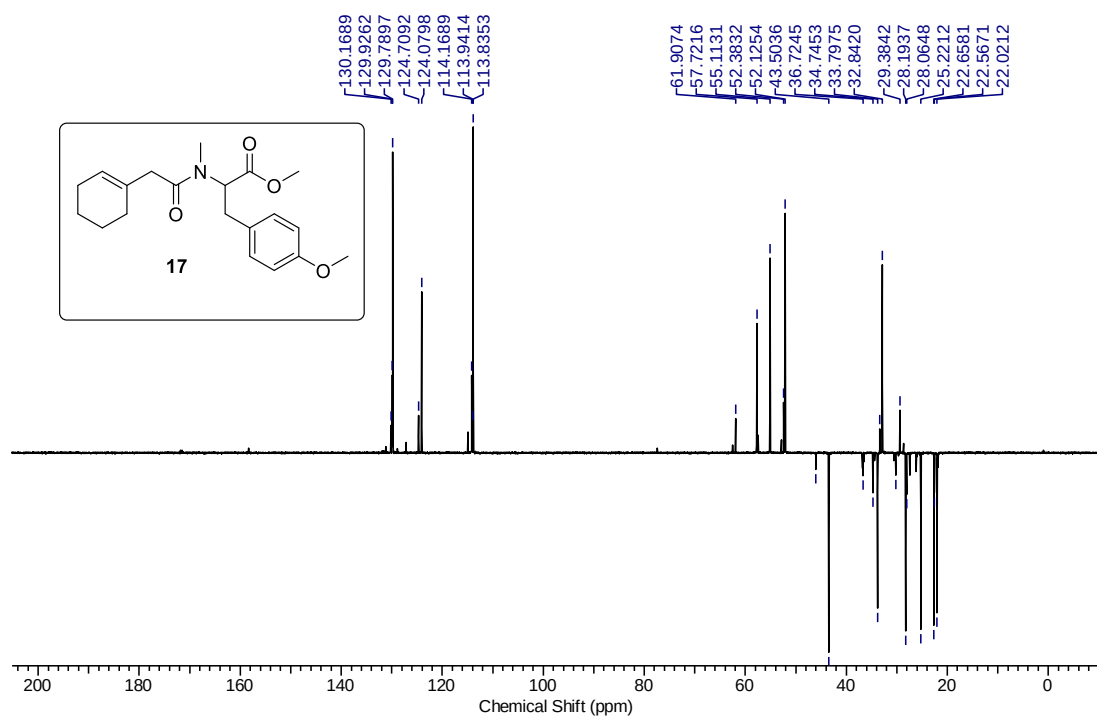
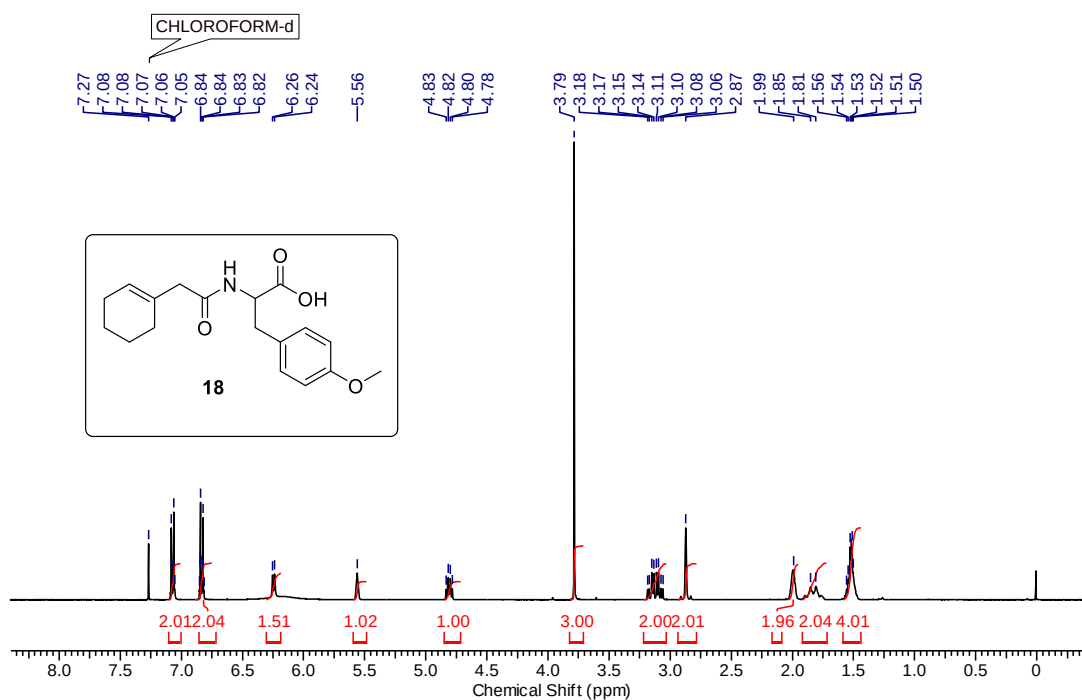


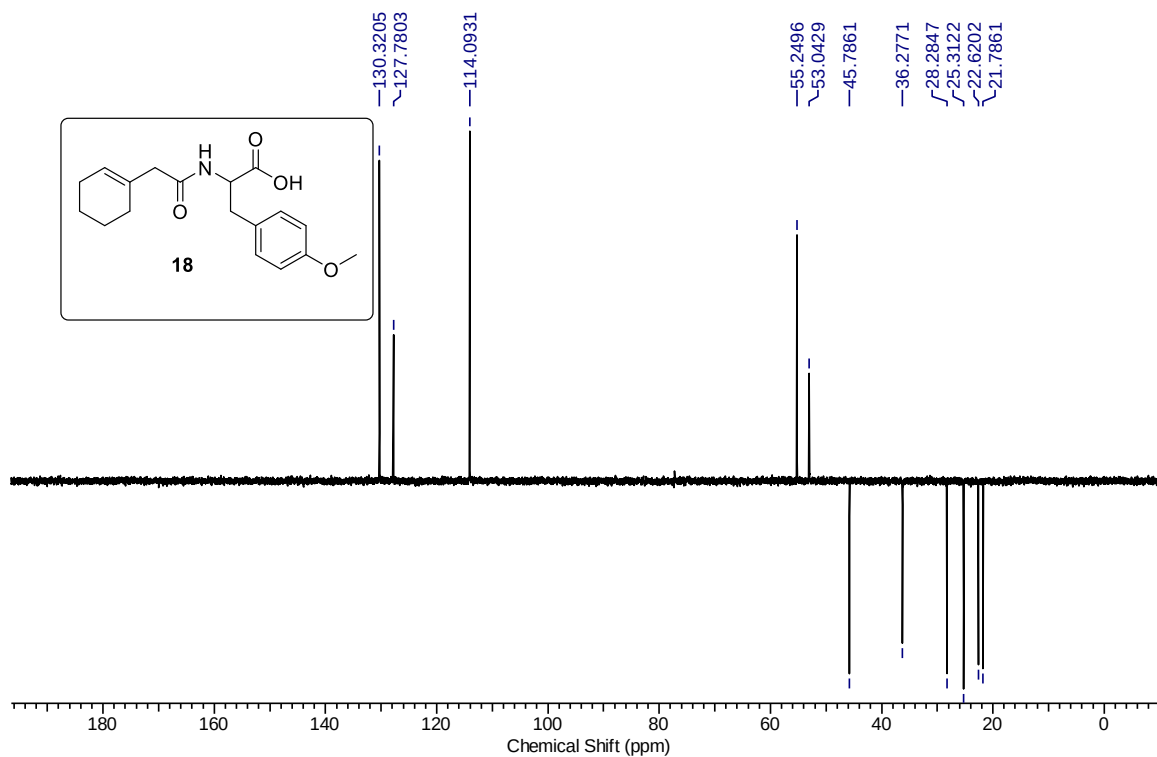
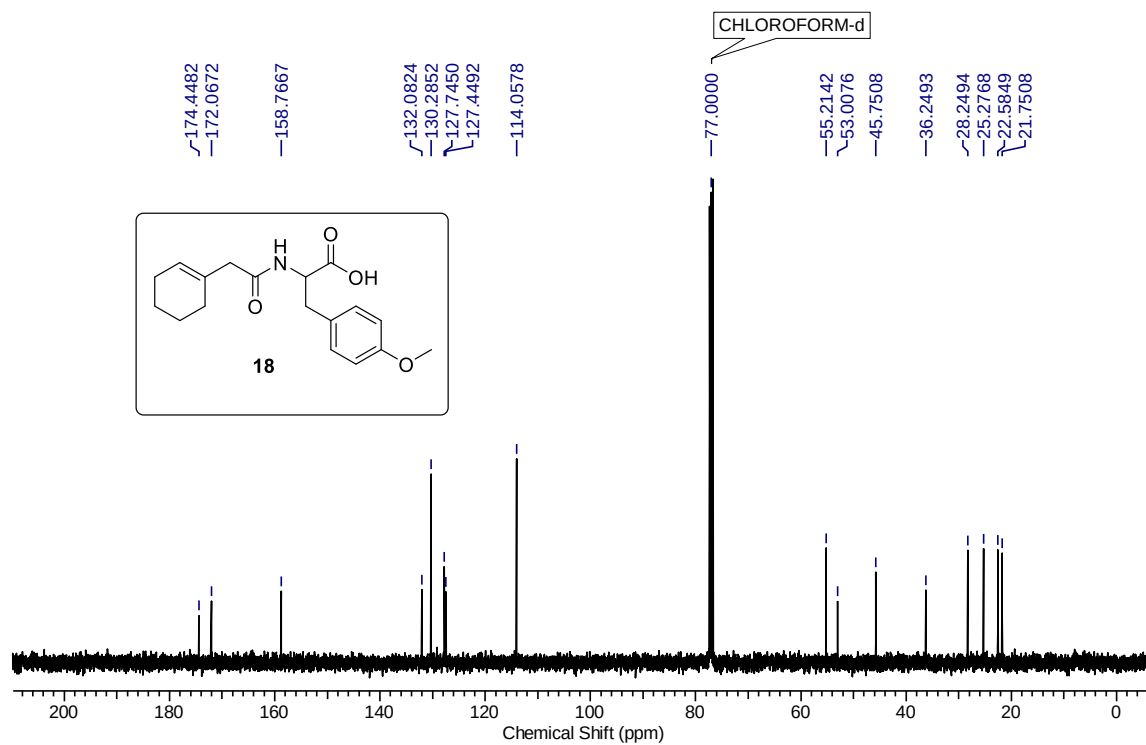


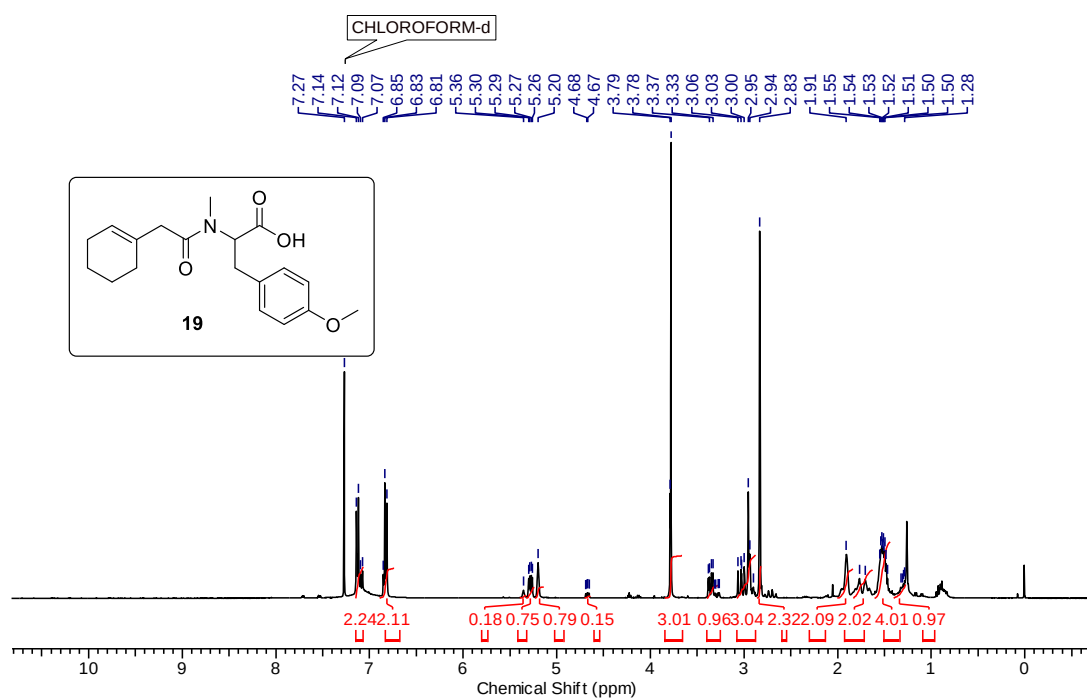
^1H (400 MHz, CDCl_3 , mixture of rotamer) NMR of compound 17



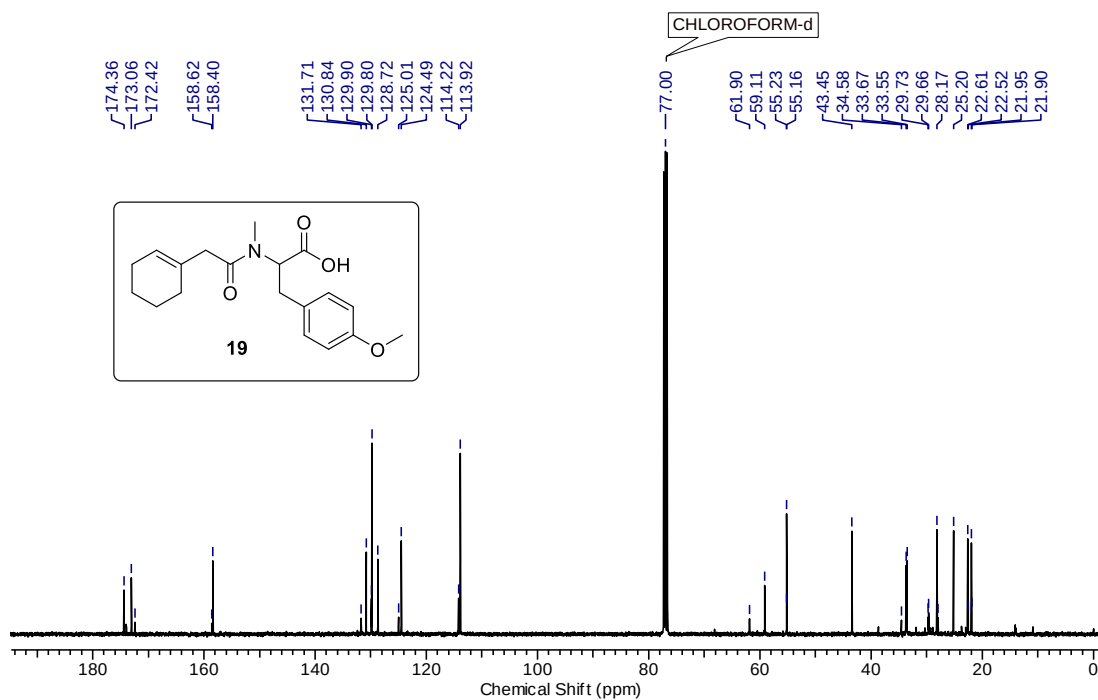
^{13}C (101 MHz, CDCl_3 , mixture of rotamer) NMR of compound 17

DEPT (101 MHz, CDCl₃, mixture of rotamer) NMR of compound 17¹H (400 MHz, CDCl₃) NMR of compound 18

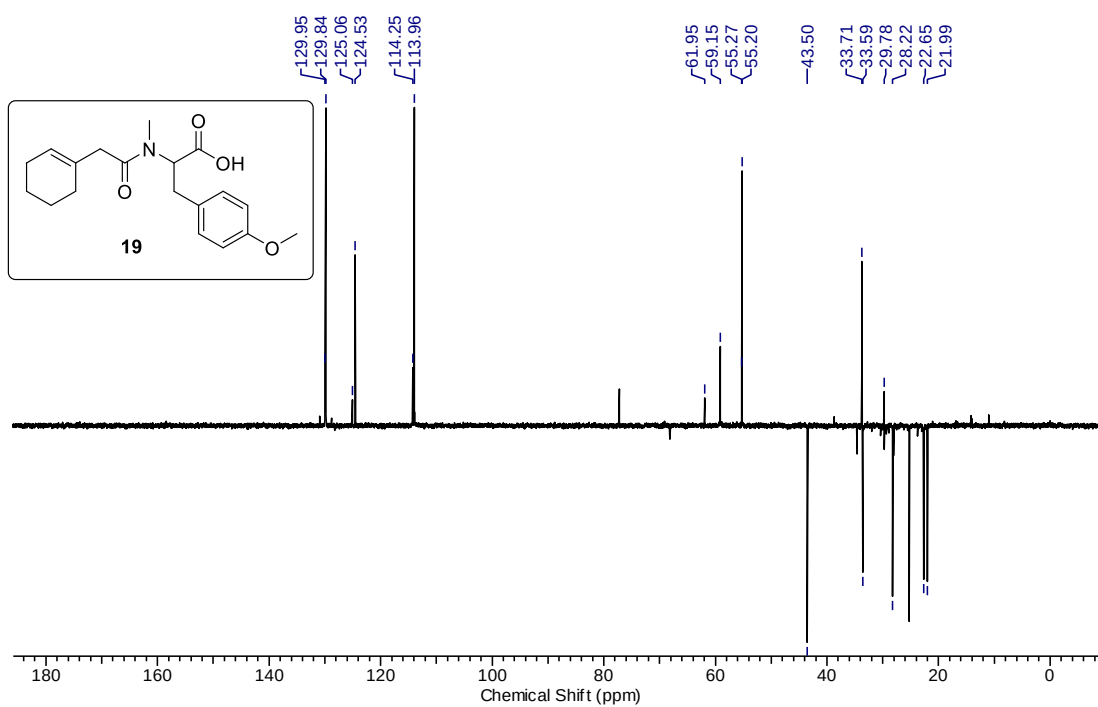
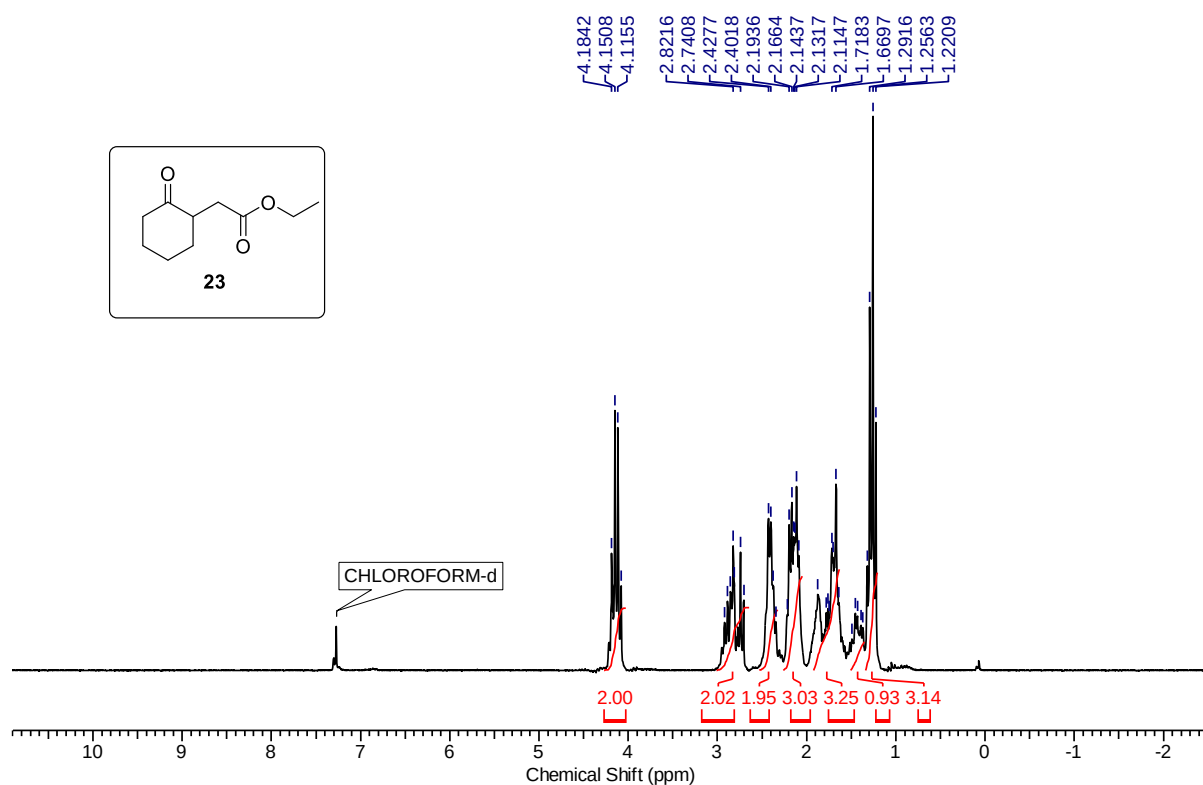


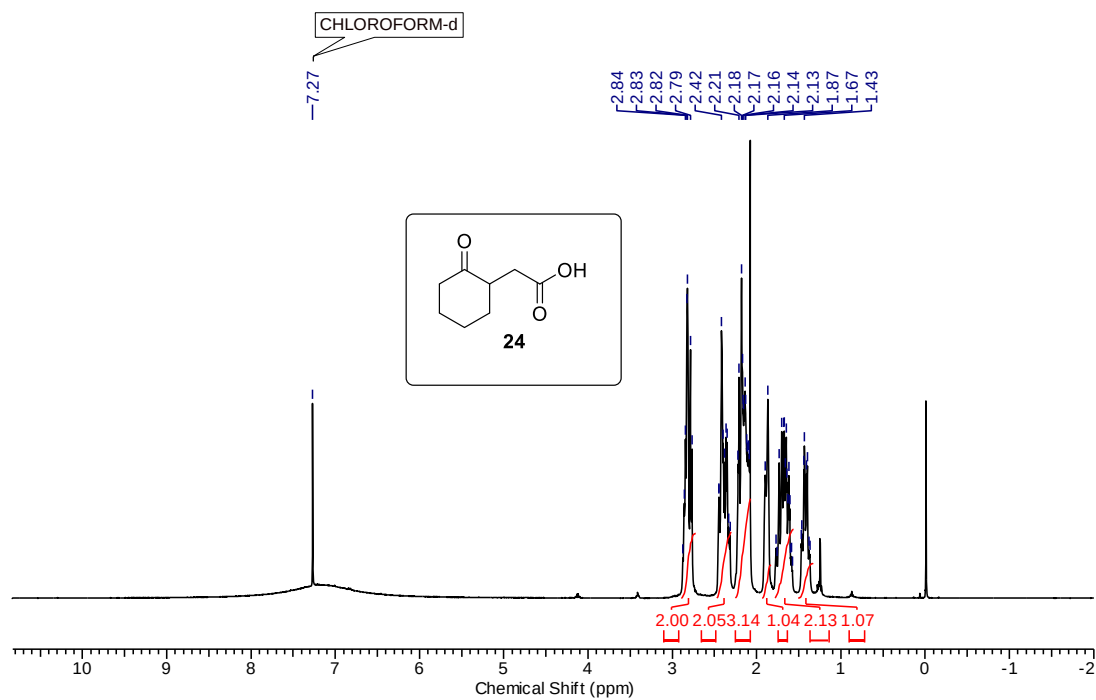


^1H (400 MHz, CDCl_3 , mixture of rotamer) NMR of compound 19

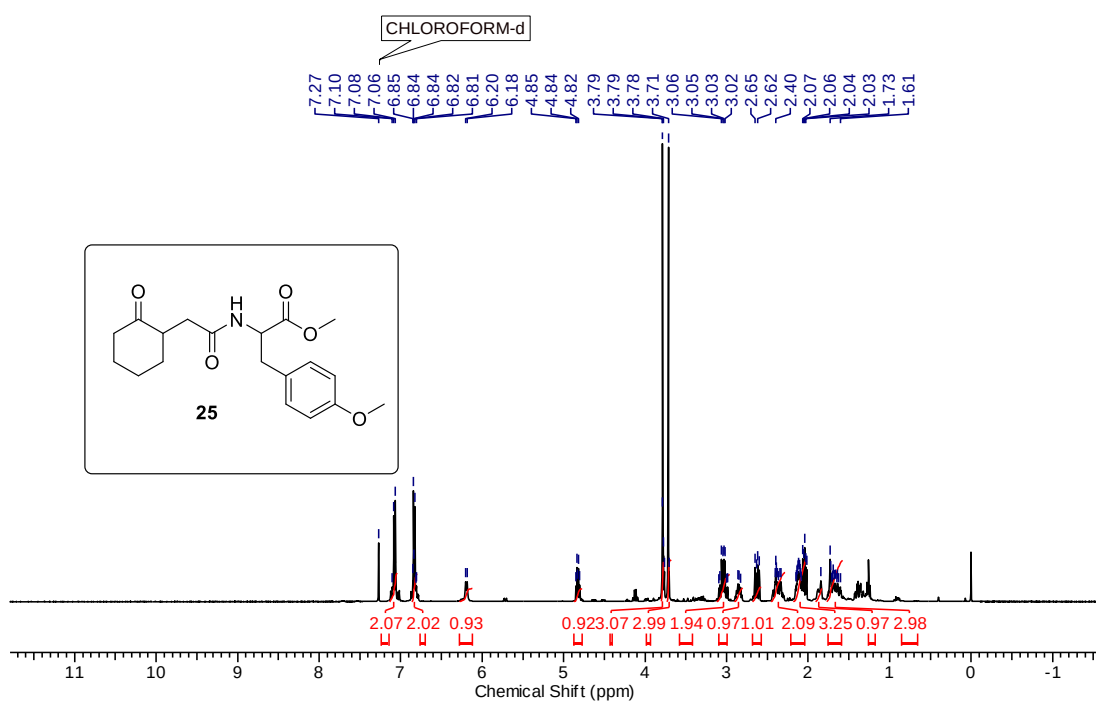


^{13}C (101 MHz, CDCl_3 , mixture of rotamer) NMR of compound 19

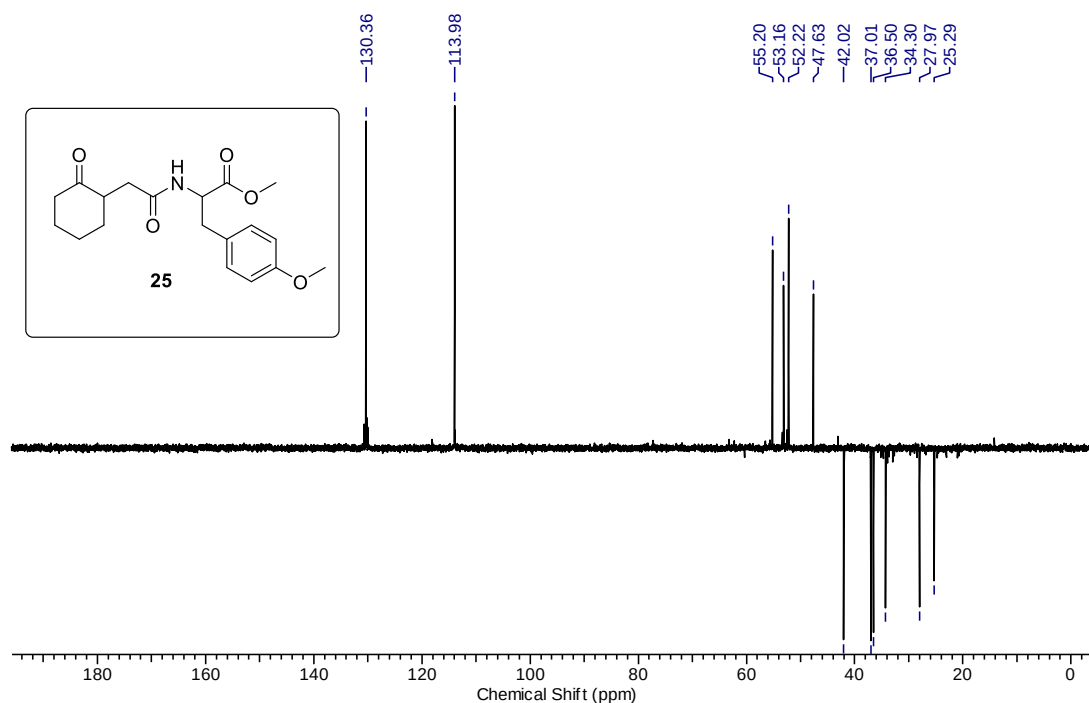
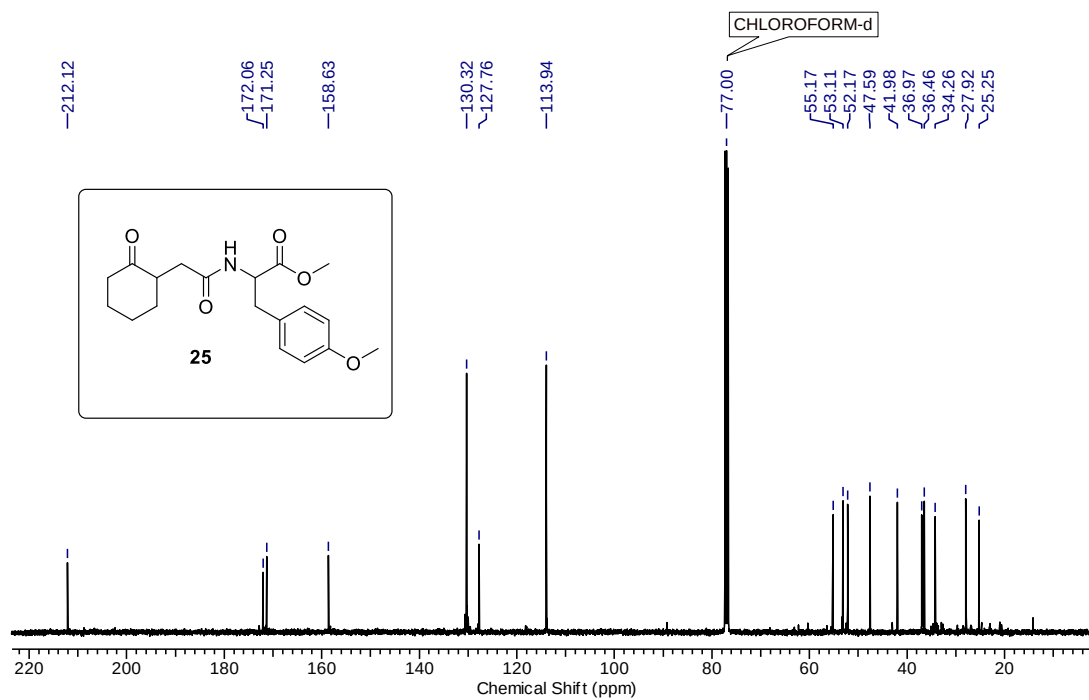
DEPT (101 MHz, CDCl_3 , mixture of rotamer) NMR of compound 19 ^1H (400 MHz, CDCl_3) NMR of compound 23

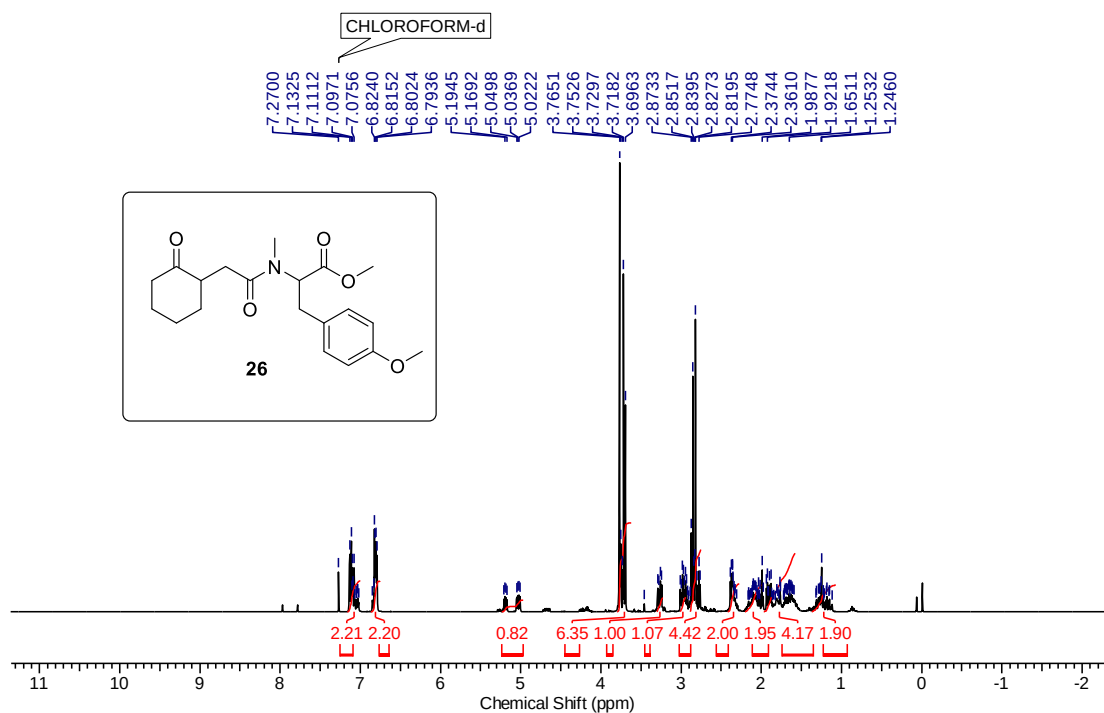


¹H (400 MHz, CDCl₃) NMR of compound 24

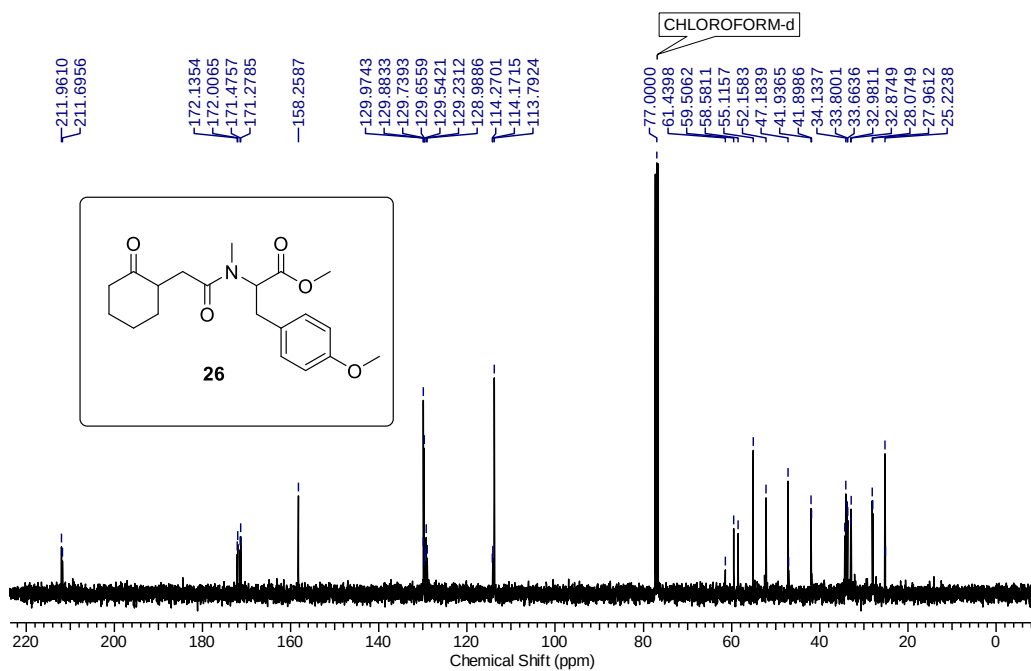


¹H (400 MHz, CDCl₃) NMR of compound 25

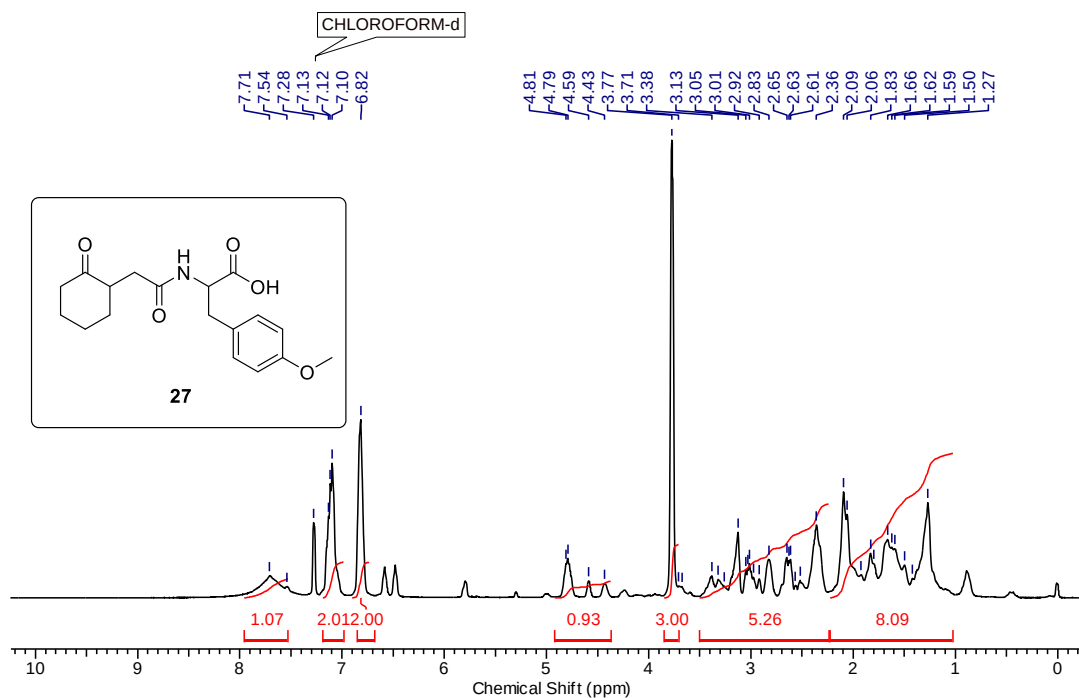
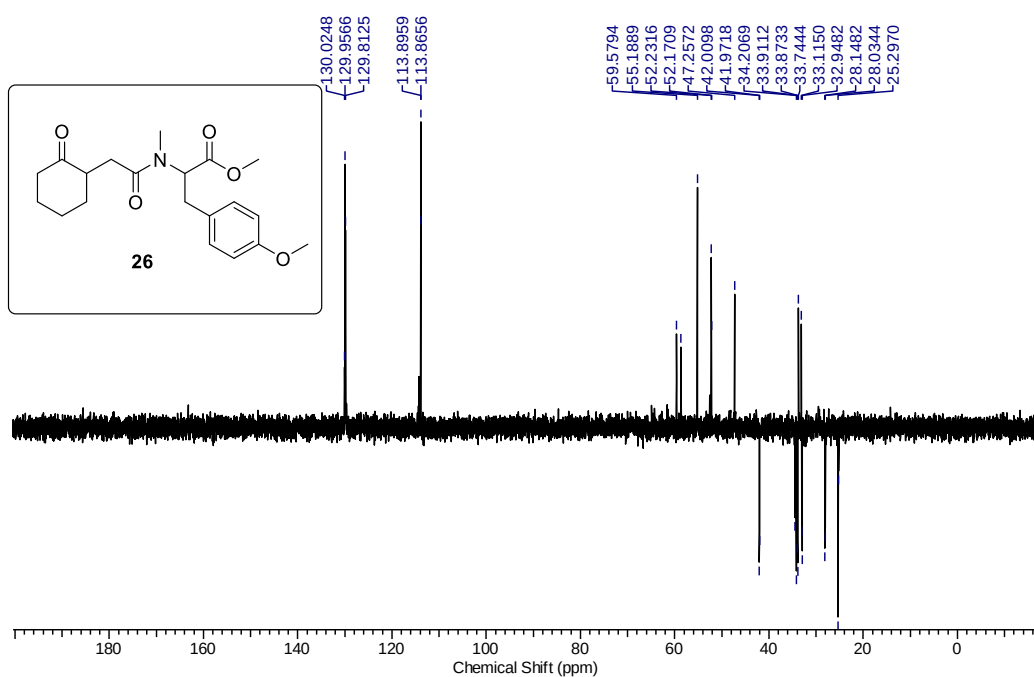


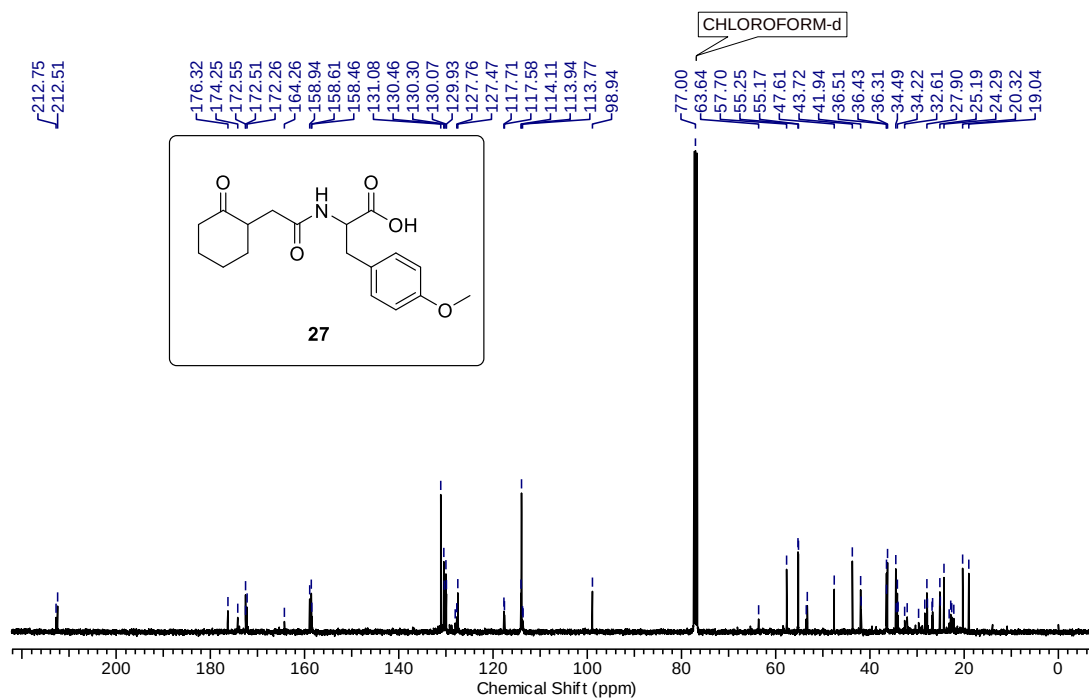


¹H (400 MHz, CDCl₃, mixture of rotamer) NMR of compound 26

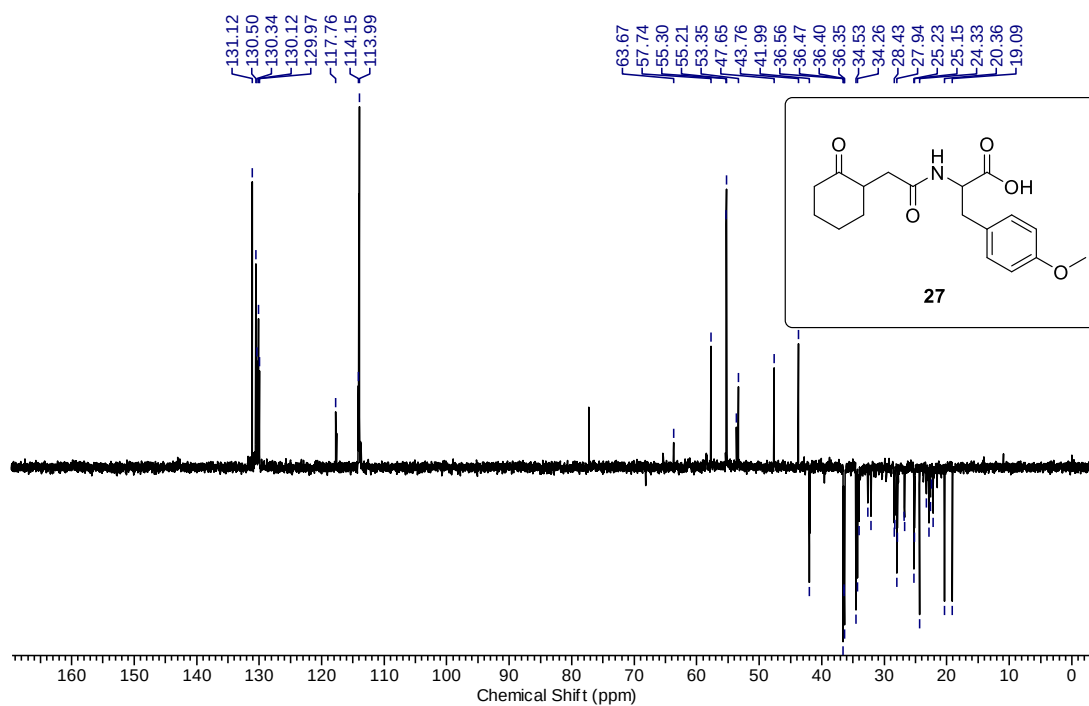


¹³C NMR (101 MHz, CDCl₃, mixture of rotamer) of compound 26

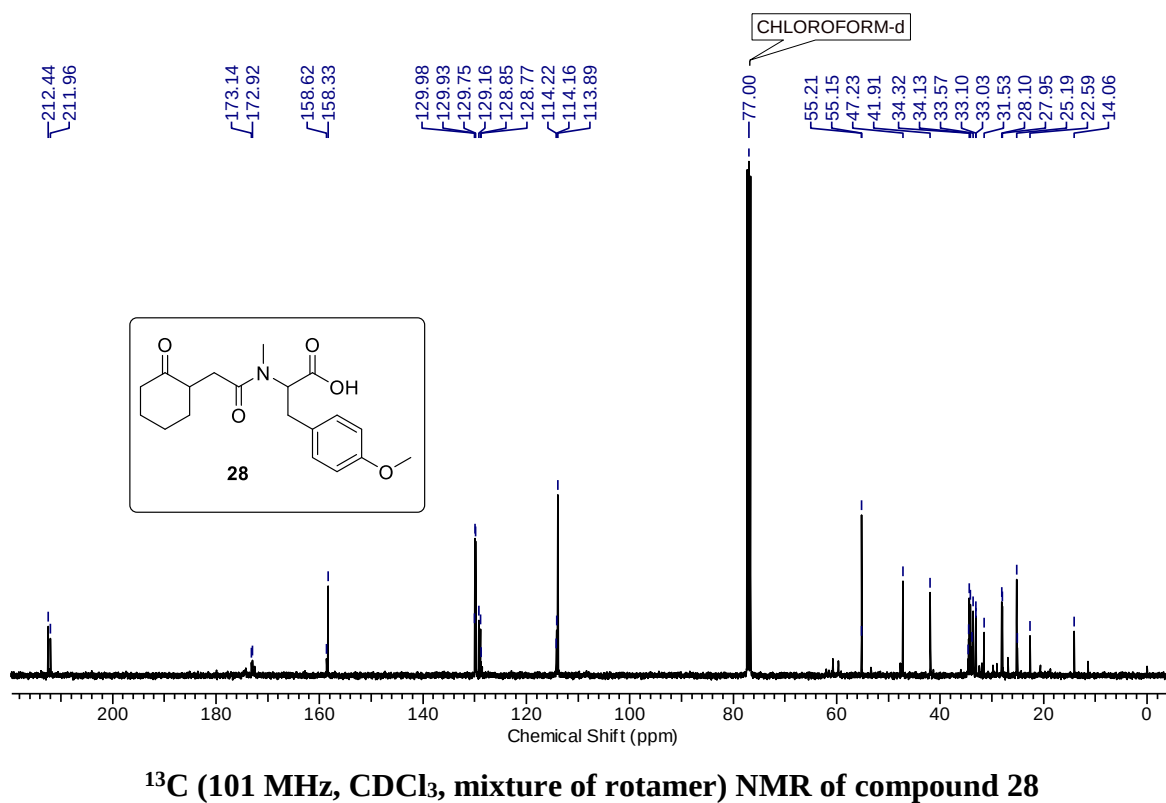
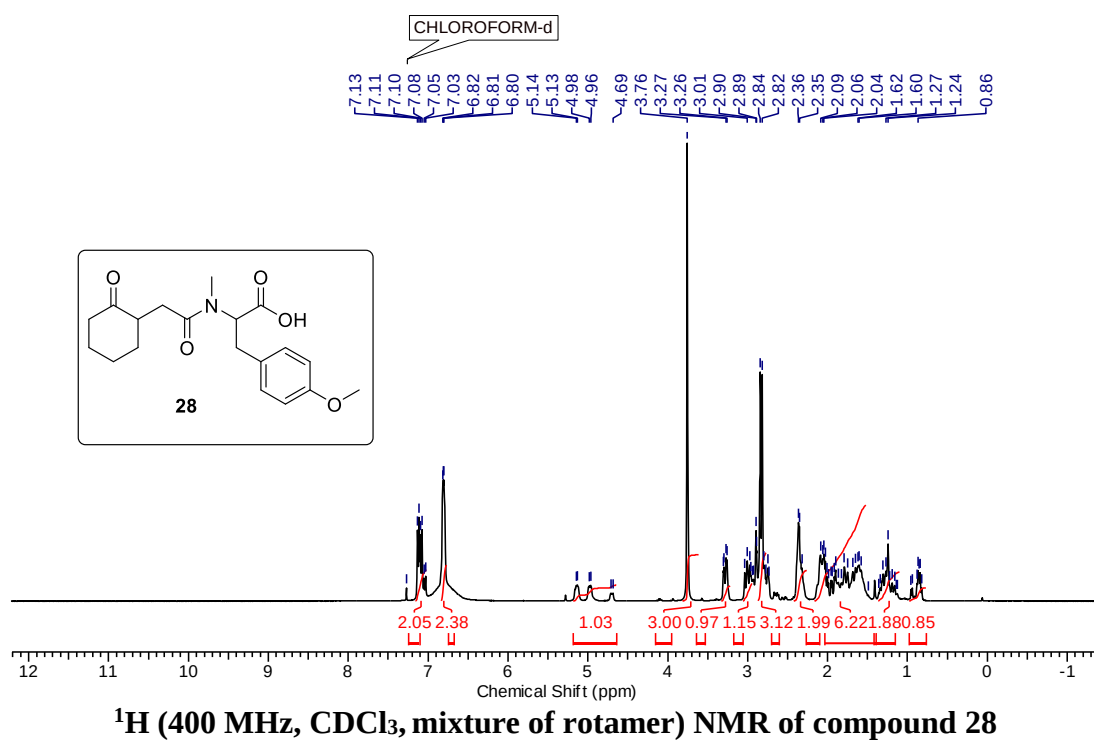


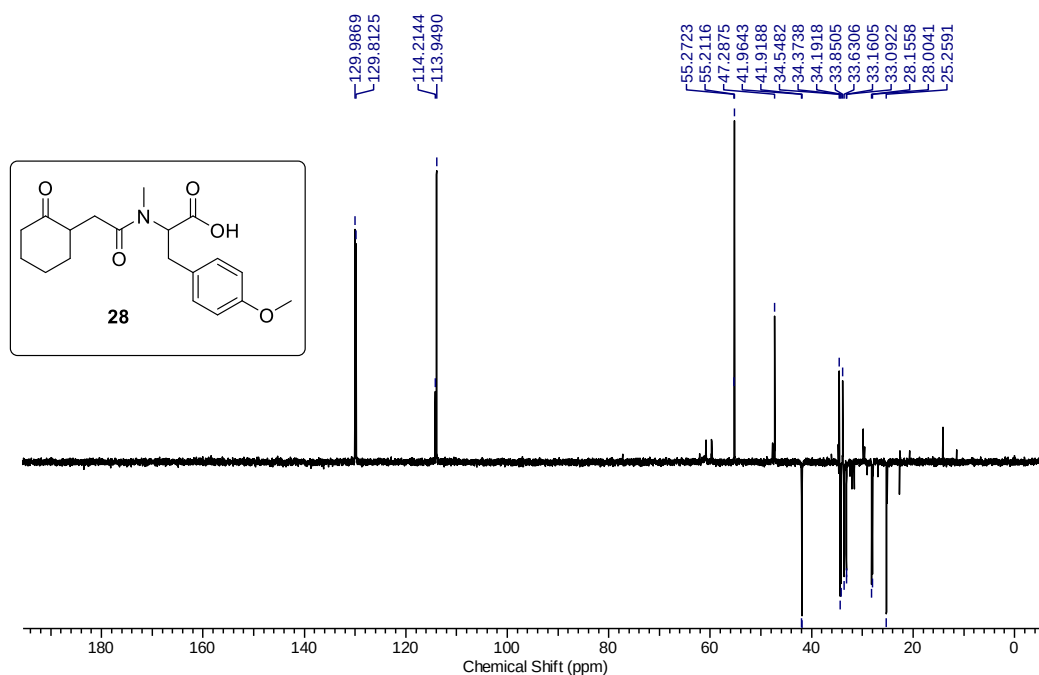


¹H (400 MHz, CDCl₃, mixture of rotamer) NMR of compound 27

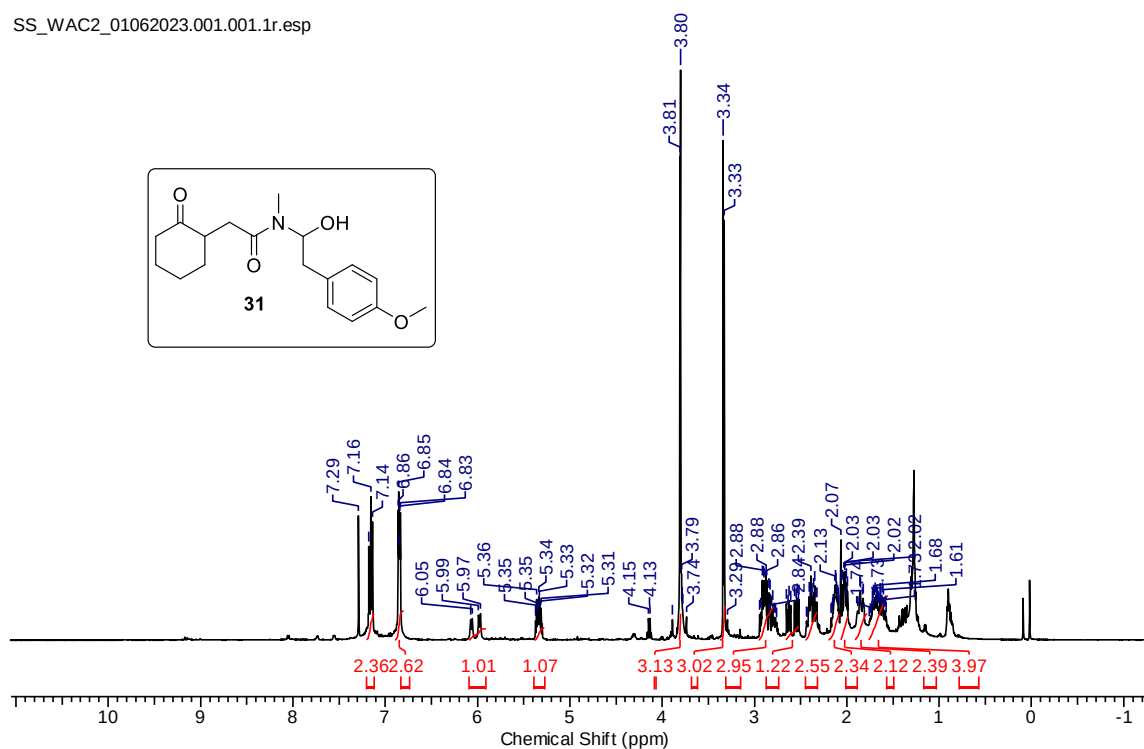


DEPT (101 MHz, CDCl₃, mixture of rotamer) of compound 27

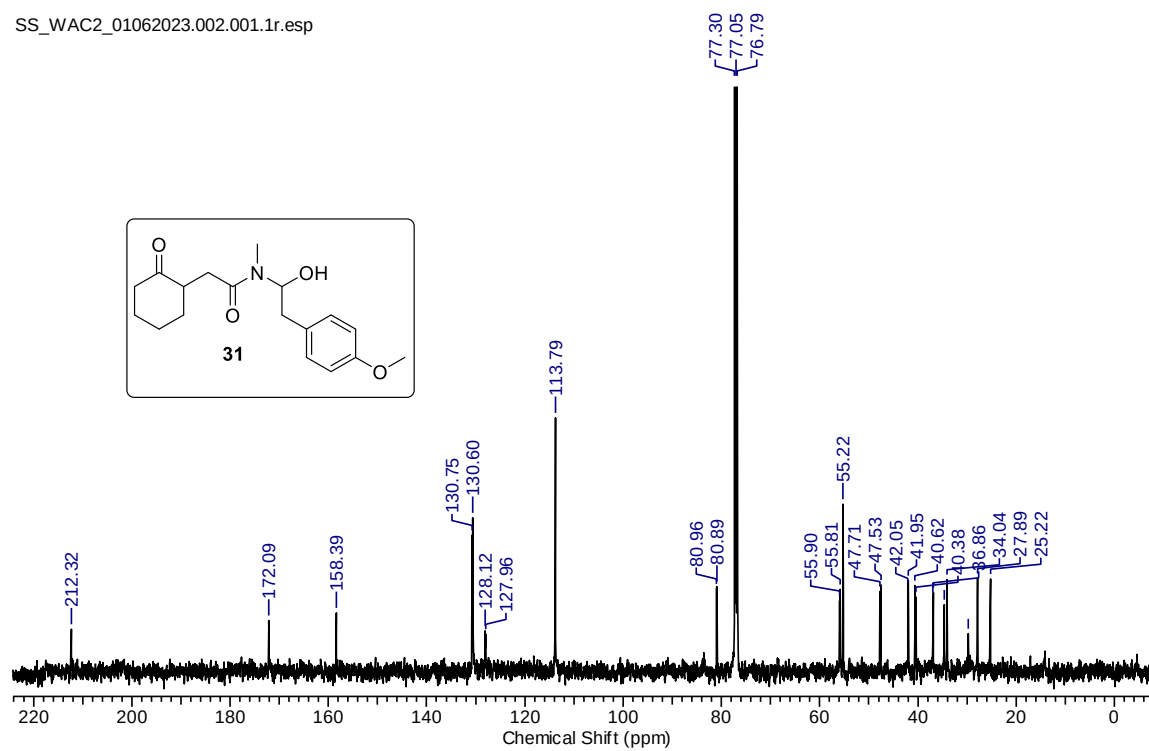


DEPT (101 MHz, CDCl₃, mixture of rotamer) NMR of compound 28

SS_WAC2_01062023.001.001.1r.esp

¹H (400 MHz, CDCl₃, mixture of rotamer) NMR of compound 31

SS_WAC2_01062023.002.001.1r.esp



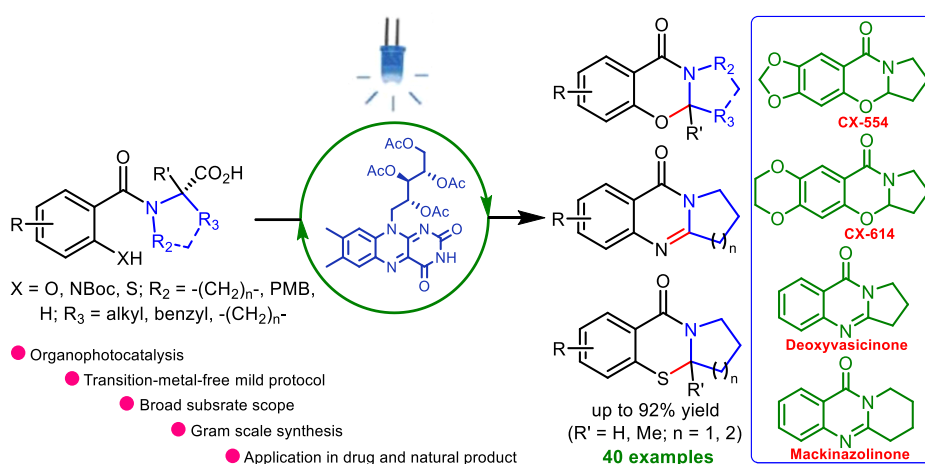
Chapter 4

Organophotoredox-Catalyzed Decarboxylative C–X Bond Formation: Synthesis of Ampikin APIs and Quinazolinone Alkaloids

S. R. Sonavane, T. B. Kale, G. J. Bhatt, S. B. Mhaske *ChemRxiv* DOI 10.26434/chemrxiv-2024-6lql3, **2024**. (*Manuscript communicated to SCI journal.*)

4.1 Abstract

This chapter describes a novel and general protocol for metal-free intramolecular decarboxylative construction of carbon-heteroatom (oxygen, nitrogen, and sulfur) bond, enabling direct access to the bioactive ampakine and quinazolinone class of molecules. The cross-coupling of natural or unnatural amino acid based electrophiles with phenols, amides, and thiophenols via organophotoredox catalysis represents an innovative approach towards the synthesis of bioactive heterocycles. The present approach utilizes photochemical decarboxylative single electron oxidation to generate carbon-centered radical intermediate directly from amino acids under mild conditions, eliminating the need for preactivation. The designated protocol offers a convenient method to synthesize ampakine drug molecules CX-614 and CX-554, which have promising potential for treating Alzheimer's and Parkinson's diseases. Interestingly, with nitrogen nucleophile, quinazolinone class of natural products deoxyvasicinone and mackinazolinone could be synthesized, whereas sulfur nucleophile furnished thiazinone scaffolds. The reported protocol exhibits high functional group tolerance and scalability. A plausible mechanism has been proposed based on fluorescence quenching experiments and cyclic voltammetry analysis.



4.2 Introduction

4.2.1 Photodecarboxylative C–heteroatom bond formation

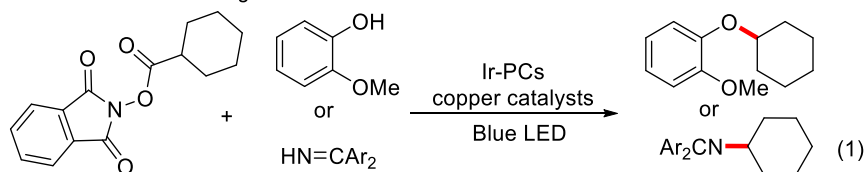
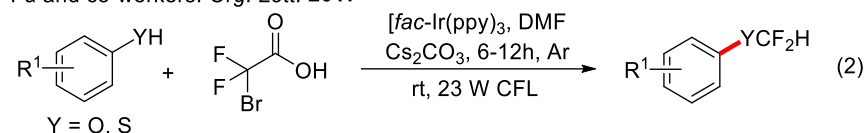
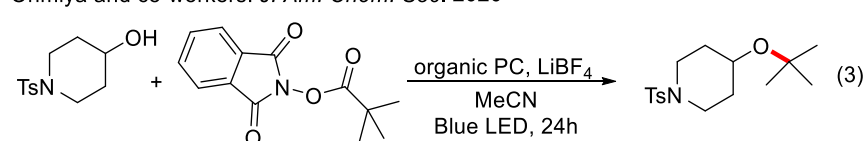
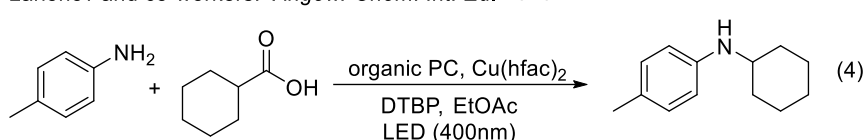
Over the past decade, visible light-mediated reactions forming C–C and C-heteroatom bonds have shown a significant development in synthetic organic chemistry. These reactions enable the synthesis of complex molecules by facilitating single-electron transfer events with organic substrates.^[1] Many groups have extensively explored several important methods for constructing photo-induced decarboxylative C–C bond-forming reactions without prefunctionalization, which represent significant advancements in synthetic organic chemistry field.^{[1],[2]}

Despite the advances in C–C bond-forming reactions, there has been comparatively less exploration in forging C–O/N/S bonds in a general manner through decarboxylative coupling reactions.^[2f, 3] These reactions are notably difficult to achieve by the conventional two-electron pathways and require harsh conditions. The traditional organic chemistry methods encounter significant challenges concerning the compatibility of functional groups under strongly basic conditions necessary for S_N2 reactions, as well as their inability to accommodate sterically hindered substrates and the *p*K_a requirements of the nucleophile.^[4] The S_N1 reaction involving alkenes or alkyl halides provides an alternative to S_N2, but it requires highly acidic conditions. This limitation restricts its compatibility with many functional groups, often leading to side reactions and degradation.^[5] The transition-metal-catalyzed (*sp*³)C-heteroatom bond forming reaction between alkyl electrophiles and alkyl/aryl heteroatom nucleophiles are challenging because of the sluggish oxidative addition of the alkyl electrophile and the susceptibility of the in-situ generated alkyl metal complex to β -hydride elimination.^[6] Hence, novel catalytic systems are needed to facilitate efficient and selective formation of (*sp*³)C-heteroatom bonds. In the realm of electrochemistry, Baran and colleagues introduced a practical and an elegant electrochemical approach for synthesizing sterically hindered (*sp*³)C–O–C(*sp*³) scaffolds. The

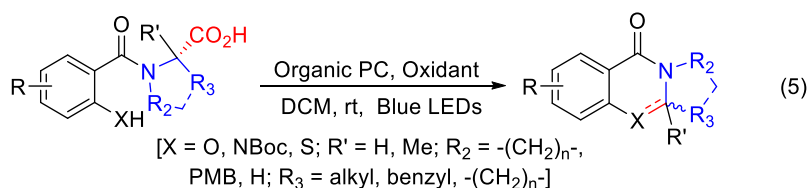
electrochemical method efficiently generates these structures from aliphatic alcohols and alkyl carboxylic acids, offering a versatile and less cumbersome alternative for such transformations.^{[3c],[3j]} Remarkably, the protocol constructing (sp^3)C–X–C(sp^2) (X = O, N, and S) motifs are highly coveted in the synthesis of a wide array of natural products and pharmaceuticals.^[7] Among the various methods for obtaining (sp^3)C–X–C(sp^2) scaffold via decarboxylation process, the direct formation of (sp^3)C-heteroatom bonds by using nucleophiles such as phenols, amides/amines, thiophenols, with electrophiles like alkyl carboxylic acids stands out as a privileged and popular approach.^[3a,3b,3d,3e,8] However, a general strategy utilizing organophotoredox catalysis for intramolecular decarboxylative (sp^3)C–heteroatom bond formation under mild conditions remains elusive, and there are currently no documented examples involving phenols, thiophenols or amides as nucleophile and natural/unnatural amino acids without any pre-activation as electrophiles. We were interested in developing photodecarboxylative cyclization reaction as a facile approach via catalytic generation of iminium ion^[9] for (sp^3)C–O/N/S bond formation in S_N1 manner.

4.3 Literature review

Previous research highlights the effectiveness of intramolecular dehydrogenative coupling reactions for synthesizing oxazine structures. Typically, these reactions demand harsh conditions and often involve metal catalysts.^[10] Therefore, we hypothesized whether decarboxylative photoredox-catalyzed generation of iminium ions, followed by in situ nucleophilic addition of heteroatoms can be achieved within a photocatalytic cycle. Literature survey revealed that Hu and colleagues demonstrated a decarboxylative (sp^3)C–O^[8b] and (sp^3)C–N^[3b] cross-coupling reaction using tandem photoredox and copper catalysis (Figure 1, eq. 1).

Previous work: (sp^3)C–X bond formation reactionHu and co-workers: *Angew. Chem. Int. Ed.* **2018**^[3b,8b]Fu and co-workers: *Org. Lett.* **2017**^[8a]Ohmiya and co-workers: *J. Am. Chem. Soc.* **2020**^[3f]Larionov and co-workers: *Angew. Chem. Int. Ed.* **2020**^[3e]

This work: Intramolecular decarboxylative C–X bond formation

**Figure 1.** Previous and Present work on photocatalyzed (sp^3)C–X bond forming reactions

Similarly, Fu and co-workers demonstrated a photoredox-catalyzed difluoromethylation of phenols and thiophenols (Figure 1, eq. 2).^[8a] However, these strategies require transition metal-based photocatalysts, and Hu's approach requires prefunctionalization of the acid substrates. Moreover, Ohmiya and colleagues reported organophotoredox-catalyzed decarboxylative reaction that combines aliphatic alcohol nucleophiles with redox-active esters of secondary or tertiary alkyl carboxylic acids (Figure 1, eq. 3).^[3f] Larionov and colleagues reported a visible-light and copper mediated direct intermolecular decarboxylative N-alkylation reaction using organophotocatalysis (Figure 1, eq. 4).^[3e] Inspired by the above interesting reports, we planned

to develop a protocol for intramolecular organophotoredox catalyzed decarboxylative cyclization of heteroatom-containing nucleophiles with amino acids. Herein, we report catalytic in situ generation of iminium ions directly from natural/unnatural amino acid substrates by decarboxylative single electron oxidation, that were leveraged to provide a wide array of C–X (X = O, N, S) bonds by trapping with heteroatom nucleophiles (Figure 1, eq. 5).

4.4 Results and Discussion

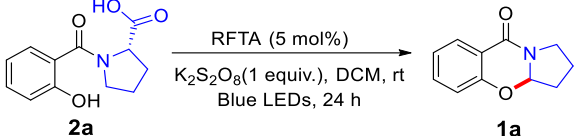
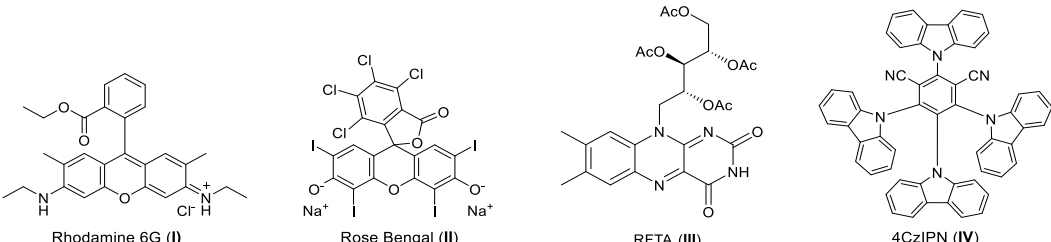
We commenced our work by first investigating the photocatalytic decarboxylative cyclization of salicylic acid derivative **2a** (Table 1), which was prepared by amidation of salicylic acid with proline ester to form methyl (2-hydroxybenzoyl)prolinate (**2'a**) followed by its hydrolysis. The inexpensive organophotocatalyst riboflavin tetraacetate (RFTA, **III**) was found to be the best photocatalyst, among several metal and organic catalyst studies i.e Ir-PC A, Ir-PC B, R6G, Rosebengal, Methylene blue, 4CzIPN, and Mes-Acr-Me•ClO₄ in our extensive screening (see experimental section). The optimal reaction system comprised 5 mol% of RFTA **III** as the photocatalyst, 1 equiv. of K₂S₂O₈ as an oxidant under irradiation of 450 nm (30 W) blue LEDs. Under these conditions, the desired oxazinone product **1a** was obtained in 90% yield. Control experiments show that no product was observed without either blue LED irradiation (Table 1, entry 5) or photocatalyst **III** (Table 1, entry 6).

The optimized reaction condition described above was used to explore the substrate scope (Table 2). To achieve this, we synthesized the salicylic acid derivatives **2a-2q** in good to excellent yields. These acids were subjected to our standard protocol to furnish ampakine derivatives. Ampakines are class of drugs useful in the treatment of Alzheimer and Parkinson's diseases.^[11]

The protocol demonstrated good tolerance for halo-substituted salicylic acid derivatives to provide the products **1b-1f** in good to excellent yields. The compounds **1b-1f** have valuable

handles for further functionalization through conventional cross-coupling reactions. The methyl and *tert*-butyl substituted acids were found to be favourable under this catalytic system, but furnished the corresponding products **1g** and **1h** in moderate yields, probably due to the instability of the generated iminium ion or bulkiness of the substituted group.

Table 1. Optimization of the decarboxylative C–O bond formation protocol^[a, b]

		
		
entry	Change from standard conditions ^a	yield (%) ^b
1	None	90%
2	I , MeCN, (NH ₄) ₂ S ₂ O ₈	ND
3	II , MeCN, (NH ₄) ₂ S ₂ O ₈	ND
4	IV , MeCN, (NH ₄) ₂ S ₂ O ₈	7%
5	no light (dark)	NR
6	no III	NR
7	no K ₂ S ₂ O ₈	16%
8	in Air	52%
9	420 nm instead of 450 nm LED	34%

[a] **2a** (0.25 mmol), K₂S₂O₈ (1 equiv.), RFTA (5 mol%) in DCM (2 mL), Blue LEDs (450 nm, 30 W), 24 h, rt.

[b] Isolated yields. NR = No reaction, ND = Not detected.

The electron-donating, polyaromatic and electron-withdrawing groups were accommodated well producing the desired products **1i-1n** in moderate to good yields. Notably, phenyl-

substituted salicylic acids and diflunisal (analgesic and anti-inflammatory drug)^[12] derivatives were also compatible giving good yields of the desired products **1o** and **1p** respectively. Furthermore, heterocyclic acid was effectively processed under this catalytic system, yielding the corresponding product **1q** in very good yield (Table 2).

Table 2. Decarboxylative (sp^3)C–O bond formation of salicylic acid derivatives^[a]

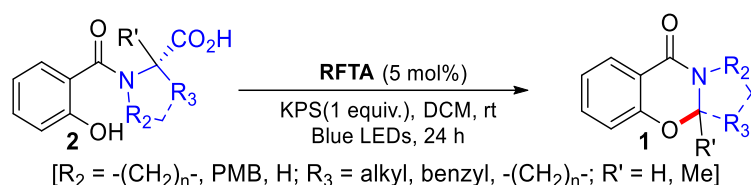
Substrate scope of salicylic acid derivatives			
 1a , 90% (Gram scale 78%)	 1b , 74%	 1c , 58%	 1d , 76%
 1e , 63%	 1f , 85%	 1g , 54%	 1h , 45%
 1i , 75%	 1j , 52%	 1k , 52%	 1l , 33%
 R = NO ₂ , 1m , 62% R = CF ₃ , 1n , 68%	 1o , 81%	 from Diflunisal, 1p , 72%	 1q , 74%

[a] **2** (0.25 mmol), K₂S₂O₈ (1 equiv.), RFTA (5 mol%) in DCM (2 mL), Blue LEDs (450 nm, 30 W), 24 h, rt. [b] reaction time 36h.

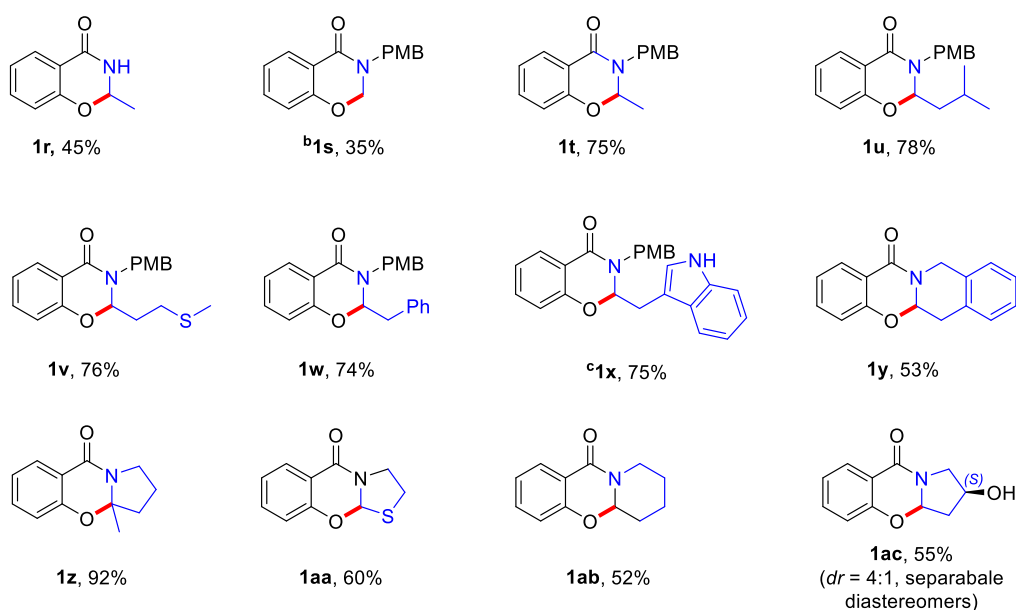
After successfully applying the optimized protocol to salicylic acid derivatives containing proline moiety to generate a library of oxazinone analogues (Table 2), we sought to test its efficacy with the substrate containing cyclic/acyclic amino acid motifs (Table 3). Interestingly, the alanine substrate yielded the expected cyclized product **1r** in 45% yield, however, the unprotected glycine substrate did not react under our standard conditions, likely due to the

instability of the iminium ion intermediate or it's difficult to generate. To enhance the yield, we opted to protect the free amide –NH group with PMB. This modification was effective yielding the cyclized products **1s** and **1t** in moderate and very good yield respectively. Given the accomplishment of the protected substrates, we decided to proceed with additional entries using the PMB-protection.

Table 3. Decarboxylative (sp^3)C–O bond formation with amino acids^[a]



Substrate scope of natural/unnatural amino acids



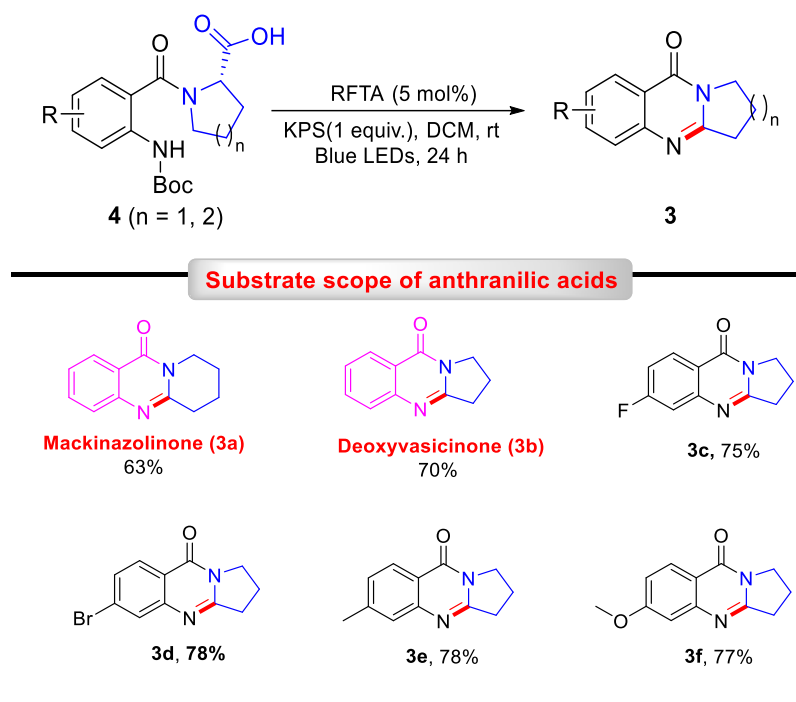
[a] **2** (0.25 mmol), K₂S₂O₈ (1 equiv.), RFTA (5 mol%) in DCM (2 mL), Blue LEDs (450 nm, 30 W), 24 h, rt. [b] additive Cs₂CO₃, [c] reaction time 36h.

In this context, we prepared the salicylic acid derivatives **2u-2x** with the various PMB-protected natural amino acids in good to excellent yields. These acids were subjected to our standard photoredox protocol, and all of them efficiently furnished the corresponding cyclized products **1u-1x**.

Furthermore, various unnatural amino acids demonstrated favourable performance under optimized conditions yielding cyclized products **1y-1ab** with moderate to excellent yields (Table 3). Interestingly, the protocol worked well with the substrate containing (2*S*,4*R*)-4-hydroxyproline to furnish the corresponding cyclized product **1ac** in moderate yield, although the alcohol group was not protected. Moreover, hydroxyl group controlled chirality induction was observed to obtain the product as a separable mixture of diastereomers (4:1).

The study of C–N bond formation began with the synthesis of Boc-protected derivatives of anthranilic acid **4a-4f** containing proline, in excellent yields. These acids were subjected to our standard photoredox protocol and all of them serendipitously furnished the corresponding Boc-eliminated cyclized quinazolinone products **3a-3f** in very good yields (Table 4).

Table 4. Decarboxylative (*sp*³)C–N bond formation in anthranilic acid derivatives^[a]



[a] **4** (0.25 mmol), K₂S₂O₈ (1 equiv.), RFTA (5 mol%) in DCM (2 mL), Blue LEDs (450 nm, 30 W), 24 h, rt.

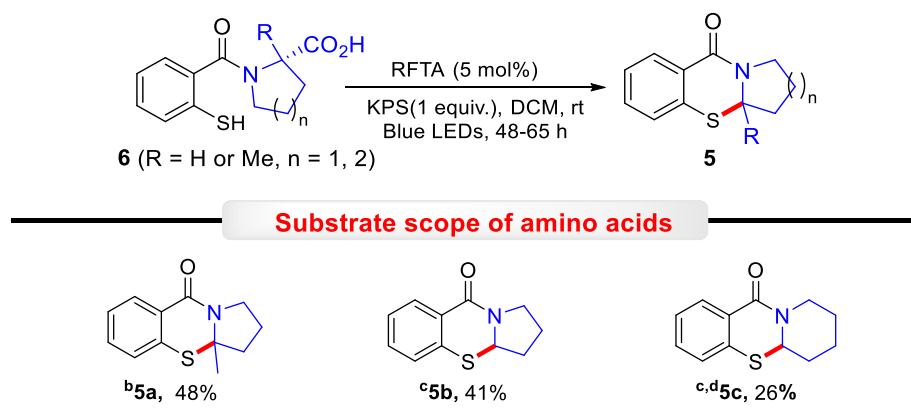
The *L*-pipecolic acid and proline based Boc-protected anthranilic acid derivatives **4a** and **4b** could be smoothly transformed into the corresponding quinazolinone natural product mackinazolinone (**3a**) and deoxyvasicinone (**3b**) respectively with good yields.^[13] The halo,

methyl and methoxy substituted derivatives of anthranilic acid also worked well to deliver deoxyvasicinone congeners **3c-3f** in good yields (Table 4).

We also tested the efficacy of this interesting photocatalyzed quinazolinone forming protocol with other protecting groups such as N-acyl, N-methyl, N-phenyl etc. The protocol worked fine with N-acyl substrate but not as good as N-Boc protected substrate. N-methyl substrate could not be prepared and N-phenyl substrate formed undesired product.

Notably, the extension to C–S bond formation could provide an access to valuable (sp^3)C–S–C(sp^2) fragments (Table 5). Thiosalicylic acid derivatives **6a-6c** were prepared and subjected to our standard protocol. The acids **6a-6c** delivered cyclized products **5a-5c** in moderate yields. The yield of thio substrates were overall less, indicating the need of screening different light sources or use of pre-activated substrates for better yields.^[3h, 3k]

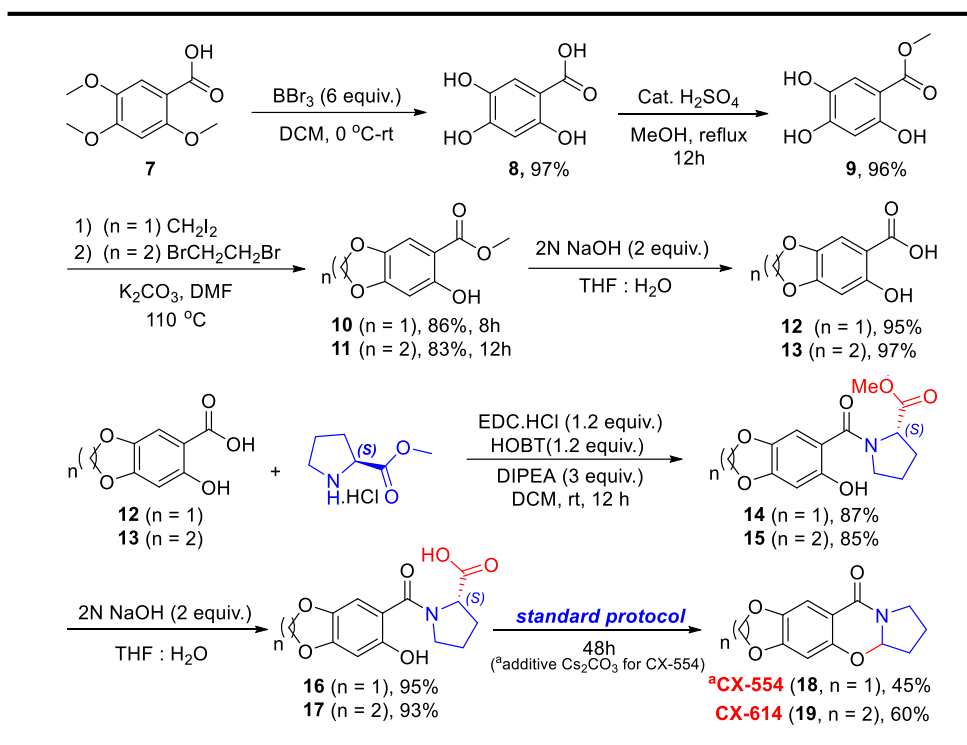
Table 5. Decarboxylative (sp^3)C–S bond formation of thiosalicylic acid derivatives^[a]



[a] **6** (0.25 mmol), $K_2S_2O_8$ (1 equiv.), RFTA (5 mol%) in DCM (2 mL), Blue LEDs (450 nm, 30 W), rt. [b] reaction time 65 h. [c] reaction time 48 h. [d] additive CS_2CO_3 .

After successfully generalizing the protocol (Table 2-5), we tested the scalability of the reaction on a gram scale. The gram-scale reaction on the substrate **2a** afforded 78% isolated yield of the cyclized product **1a**.

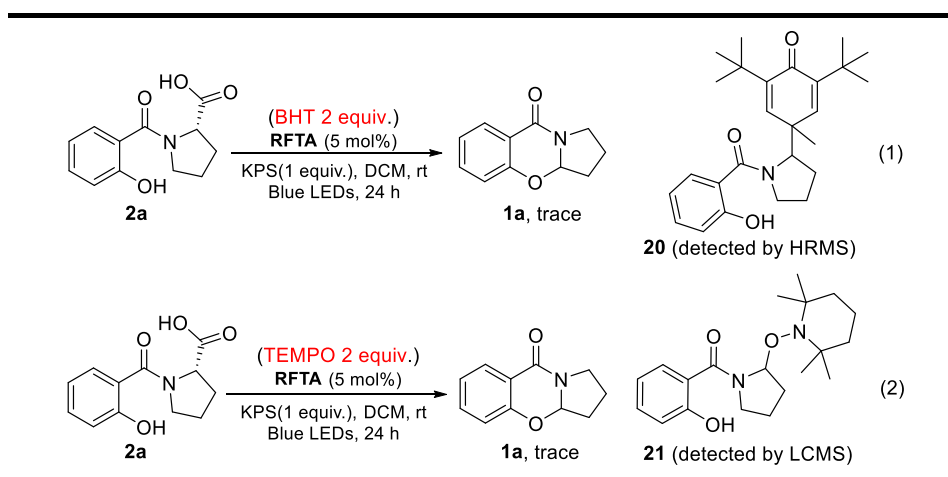
We also wanted to demonstrate the application of our protocol in the synthesis of **CX-614** and **CX-554**, which are investigational new drugs developed by Cortex Pharmaceuticals, along with its derivatives.^[11]



Scheme 1. Total synthesis of **CX-614** and **CX-554**

They have garnered significant interest due to their effects on AMPA receptors and their capacity to enhance brain-derived neurotrophic factor (BDNF) synthesis.^[14] We have devised seven-step synthetic route (Scheme 1), which has yielded **CX-614** with an overall yield of 36% and its analog **CX-554** with an overall yield of 28%.

To enhance our understanding of the developed process, we conducted a series of spectroscopic analyses and control experiments. The radical trapping experiments with known radical scavengers BHT and TEMPO indicated that the reaction probably follows a radical pathway as the reaction was inhibited substantially (Scheme 2).

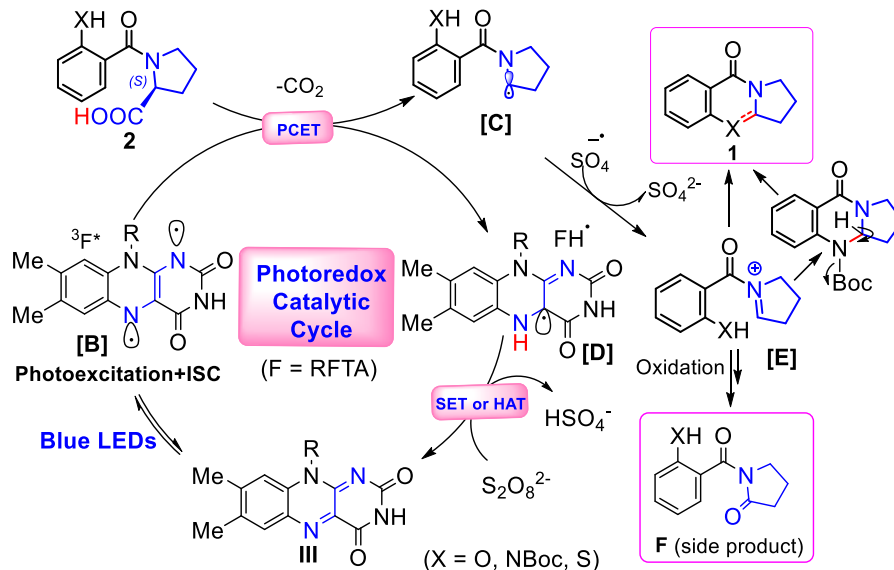


Scheme 2. Control Experiments

Furthermore, corresponding adduct masses were identified by HRMS/LCMS. Fluorescence quenching studies provided direct evidence of the nucleophilic radical initiation process. We observed diminished emission intensity of RFTA* in the presence of carboxylic acid **2a**. This dynamic quenching of RFTA* by carboxylic acid **2a** supports the proton-coupled electron transfer (PCET) to afford the related acyloxy radical [**C**] as a key-step. In addition, CV analysis of the substrate **2a** indicates single-electron transfer or PCET in this photo-oxidative coupling reaction.

We have depicted a plausible reaction mechanism based on the above control experiments and literature studies^[15-17] (Scheme 3). Under visible light irradiation, the flavin photocatalyst **III**, after intersystem crossing, was predicted to convert into a triplet-excited state [**B**]. This highly oxidizing species [**B**] ($E_{\text{red}} = +1.50 \text{ V vs SCE}$)^[15] then interacts with amino acid **2** ($E_{\text{oxi}} \approx 0.73 \text{ V vs Ag/AgCl}$), initiating single-electron transfer. The acidic proton of the carboxylic acid can be abstracted by the excited Flavin [**B**], due to its basicity, which facilitates either a direct deprotonation or a proton-coupled electron transfer (PCET) pathway.^[16] The resulting carboxyl radical rapidly undergoes decarboxylation,^[17] generating a radical intermediate [**C**]. This intermediate reacts with the sulfate radical anion derived from $\text{K}_2\text{S}_2\text{O}_8$ ^[18] forming a transient iminium ion [**E**] via radical-polar crossover.^[11] The iminium intermediate is subsequently

intercepted by oxygen-, nitrogen-, or sulfur-based nucleophiles, yielding the final cyclized products.



Scheme 3. Plausible Reaction Mechanism

Subsequently, the hydroflavin radical **[D]**, generated during the reaction, reduces persulfate^[18] to regenerate the sulfate radical anion. This reduced species abstract a hydrogen atom (HAT) from $\text{FH}^\bullet$ [$E_{\text{red}}(\text{RF}/\text{RFH}^\bullet) = -0.60 \text{ V vs SCE}$]^[19] and restores the active flavin photocatalyst, ensuring a redox-neutral catalytic cycle.

4.5 Conclusion

In summary, we have developed an unprecedented organophotoredox catalyzed, transition-metal-free general approach for the intramolecular decarboxylative C-heteroatom bond formation, a feat traditionally reserved for precious metal catalysts like Ir and Rh with specific ligands. This scalable method uses an inexpensive organocatalyst and it is applicable in the synthesis of a broad range of C–O/C–N/C–S bond containing scaffolds. We have established the usefulness of the protocol in the efficient synthesis of medicinally relevant oxazinone, thiazinone and quinazolinone derivatives. A series of control experiments, fluorescence

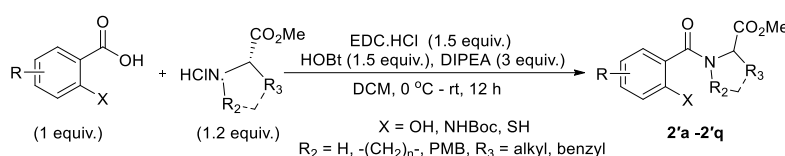
quenching, and cyclic voltammetry studies indicates that the transformation is driven via an oxidative quenching mechanistic cycle. To the best of our knowledge, our work signifies the use of this catalytic pathway, which might be the first general example of the organophotoredox-catalyzed intramolecular C–O/C–N/C–S bond forming protocol employing the reaction of simple non-activated amino acid fragments with phenol/aromatic amide and thiophenol. The developed method has the potential to enable cross-decarboxylative inter/intramolecular C–heteroatom bond formation as an efficient tool to produce complex heterocyclic bioactive agents and natural products.

4.6 Experimental Section:

Riboflavin tetra acetate (RFTA) was prepared from commercial (-)-Riboflavin according to a reported procedure.^[20]

Note: Intermediate acids **2b-2d**, **2f-2h**, **2l-2n**, **2s**, **2y**, **2aa**, **2ab**, **4b**, **4c**, **4g**, **6'a**, **6'c**, **6b**, **6c** have complex mixture of amide rotamers, which resulted into multiple peaks and broad signals, hence not all signals are distinguishable/visible.

[A] General procedure-I: Synthesis of compounds **2'a-2'q**:



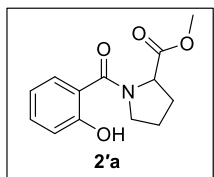
To a solution of salicylic acid derivatives (1 equiv.) in DCM (10 mL for 1 g of acid) was added, EDC.HCl (1.5 equiv.) and HOBt (1.5 equiv.) followed by DIPEA (3 equiv.) at 0 °C with continuous stirring for 10 minutes. Later, a solution of amino acid methyl ester hydrochloride (1.2 equiv.) in DCM (10 mL) was added dropwise at 0 °C to the reaction mixture for 10 minutes with continuous stirring. The reaction mixture was allowed to warm to room temperature and stirred overnight. After completion of the reaction (checked by TLC), it was quenched with saturated aqueous NH_4Cl solution (10 mL), and extracted with ethyl acetate (3×15 mL). The combined organic layers were washed with saturated aqueous NaHCO_3 solution (3×20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4 , and concentrated in *vacuo*. The crude products were purified by silica gel column chromatography using ethyl acetate and petroleum ether as eluents to obtain corresponding products **2'b-2'q** in good yields.

[B] Typical experimental procedure for the synthesis of representative compound **2'a**:

To the solution of salicylic acid (1.0 g, 7.24 mmol, 1 equiv.) in DCM (10 mL) was added EDC.HCl (2.074 g, 10.86 mmol, 1.5 equiv.) and HOBt (1.467 g, 10.86 mmol, 1.5 equiv.), followed by DIPEA (2.8 g, 3.77 mL, 21.7 mmol, 3 equiv.) at 0 °C with continuous stirring for 10 minutes. Then a solution of proline methyl ester hydrochloride (1.43 g, 8.68 mmol, 1.2 equiv.) in DCM (5 mL) was added drop wise at 0 °C to the reaction mixture in 10 minutes with continuous stirring. The reaction mixture was allowed to warm to room temperature and stirred overnight. After completion of reaction (checked by TLC), it was quenched with saturated

aqueous NH_4Cl solution (20 mL), and extracted with ethyl acetate (3×15 mL). The combined organic layers were washed with saturated aqueous NaHCO_3 solution (3×15 mL) and brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The crude product was purified by silica gel column chromatography using ethyl acetate and petroleum ether (6:4) as eluents to obtain corresponding product **2'a** in 81 % yield as a thick oil (1.47g).

Methyl (2-hydroxybenzoyl)prolinate (2'a):



: 81% thick oil; R_f : 0.4 (6:4, ethyl acetate: petroleum ether).

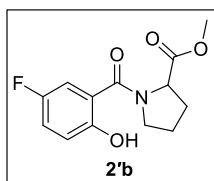
^1H NMR (400 MHz, CDCl_3): δ 10.73 (s, 1 H), 7.51 (s, 1 H), 7.38 - 7.30 (m, 1 H), 6.96 (d, $J = 8.25$ Hz, 1 H), 6.84 (t, $J = 7.50$ Hz, 1 H), 4.67 (t, $J = 7.75$ Hz, 1 H), 3.94 - 3.82 (m, 2 H), 3.76 (s, 3 H), 2.39 - 2.28 (m, 1 H), 2.12

- 1.90 (m, 3 H).

^{13}C NMR (101 MHz, CDCl_3): δ 172.4, 170.4, 160.0, 133.1, 128.2, 118.2, 117.7, 116.6, 60.1, 52.3, 50.9, 28.9, 25.8.

HRMS-ESI (m/z) calcd for $(\text{C}_{13}\text{H}_{15}\text{NO}_4 + \text{H})^+$: 250.1074, found: 250.1069.

Methyl (5-fluoro-2-hydroxybenzoyl)prolinate (2'b):



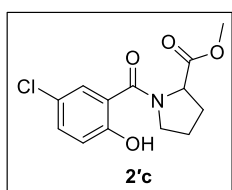
: 86% white solid; mp: 98-99°C; R_f : 0.4 (6:4, ethyl acetate: petroleum ether).

^1H NMR (400 MHz, CDCl_3): δ 10.45 (s, 1 H), 7.25 - 7.19 (m, 1 H), 7.13 - 7.05 (m, 1 H), 6.94 (dd, $J = 9.1, 4.8$ Hz, 1 H), 4.68 (dd, $J = 7.9, 6.3$ Hz, 1 H), 3.92 - 3.81 (m, 2 H), 3.78 (s, 3 H), 2.41 - 2.31 (m, 1 H), 2.17 - 1.94 (m, 3 H).

^{13}C NMR (101 MHz, CDCl_3): δ 172.3, 169.3, 156.2, 154 (d, $J_{\text{C-F}} = 238.04$ Hz), 120.4 (d, $J_{\text{C-F}} = 22.9$ Hz), 119.0 (d, $J_{\text{C-F}} = 7.06$ Hz), 116.7, 114.1 (d, $J_{\text{C-F}} = 25.2$ Hz), 60.2, 52.5, 50.8, 28.9, 25.9.

HRMS-ESI (m/z) calcd for $(\text{C}_{13}\text{H}_{14}\text{FNO}_4 + \text{H})^+$: 268.0980, found: 268.0975.

Methyl (5-chloro-2-hydroxybenzoyl)prolinate (2'c):



: 69% white solid; mp: 112°C; R_f : 0.3 (3:7, ethyl acetate: petroleum ether).

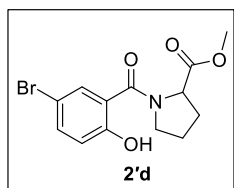
^1H NMR (400 MHz, CDCl_3): δ 10.66 (br. s., 1 H), 7.50 (br. s., 1 H), 7.30 (dd, $J = 2.5, 8.9$ Hz, 1 H), 6.93 (d, $J = 8.9$ Hz, 1 H), 4.68 (t, $J = 7.5$, 1 H),

3.94 - 3.81 (m, 2 H), 3.78 (s, 3 H), 2.41 - 2.32 (m, 1 H), 2.17 - 2.08 (m, 1 H), 2.08 - 1.90 (m, 2 H).

^{13}C NMR (101 MHz, CDCl_3): δ 172.2, 169.2, 158.6, 133.0, 127.6, 123.0, 119.3, 117.7, 60.3, 52.5, 50.9, 28.9, 25.8.

HRMS-ESI (m/z) calcd for $(\text{C}_{13}\text{H}_{14}\text{ClNO}_4+\text{H})^+$: 284.0684, found: 284.0685.

Methyl (5-bromo-2-hydroxybenzoyl) proline (2'd):



: 68% white solid; mp: 96-97°C; R_f : 0.4 (4:6, ethyl acetate: petroleum ether).

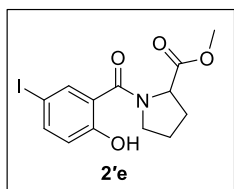
^1H NMR (400 MHz, CDCl_3): δ 10.68 (s, 1 H), 7.63 (s, 1 H), 7.43 (dd, J = 8.9, 2.4 Hz, 1 H), 6.91 - 6.85 (m, 1 H), 4.72 - 4.62 (m, 1 H), 3.91 - 3.81

(m, 2 H), 3.81 - 3.75 (m, 3 H), 2.40 - 2.30 (m, 1 H), 2.15 - 1.92 (m, 3 H).

^{13}C NMR (101 MHz, CDCl_3): δ 172.2, 169.0, 159.1, 135.9, 130.5, 119.8, 118.4, 109.9, 60.2, 52.5, 50.9, 28.9, 25.8.

HRMS-ESI (m/z) calcd for $(\text{C}_{13}\text{H}_{14}\text{BrNO}_4+\text{H})^+$: 328.0179, found: 328.0174.

Methyl (2-hydroxy-5-iodobenzoyl)proline (2'e):



: 56% brown gum; R_f : 0.3 (3:7, ethyl acetate: petroleum ether).

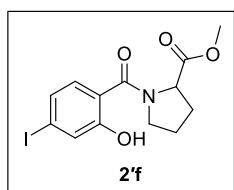
^1H NMR (400 MHz, CDCl_3): δ 10.69 (br. s., 1 H), 7.80 (br. s., 1 H), 7.60 (d, J = 8.8 Hz, 1 H), 6.77 (d, J = 8.8 Hz, 1 H), 4.67 (t, J = 7.1 Hz, 1 H), 3.90 - 3.79 (m, 2 H), 3.78 (s, 3 H), 2.39 - 2.29 (m, 1 H), 2.15 - 2.09 (m, 1

H), 2.06 - 1.93 (m, 2 H).

^{13}C NMR (101 MHz, CDCl_3): δ 172.2, 168.9, 159.8, 141.6, 136.5, 120.3, 119.1, 79.2, 60.3, 52.6, 51.0, 28.9, 25.9.

HRMS-ESI (m/z) calcd for $(\text{C}_{13}\text{H}_{14}\text{INO}_4+\text{H})^+$: 376.0040, found: 376.0039.

Methyl (2-hydroxy-4-iodobenzoyl) proline (2'f):



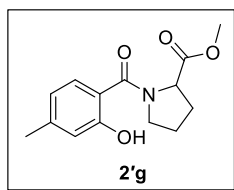
: 74% light yellow thick oil; R_f : 0.4 (3:7, ethyl acetate: petroleum ether).

^1H NMR (400 MHz, CDCl_3): δ 10.93 (s, 1 H), 7.38 (s, 1 H), 7.21 (s, 2 H), 4.69 - 4.63 (m, 1 H), 3.89 - 3.79 (m, 2 H), 3.77 (s, 3 H), 2.40 - 2.28 (m, 1 H), 2.15 - 1.92 (m, 3 H).

^{13}C NMR (101 MHz, CDCl_3): δ 172.2, 169.9, 160.5, 129.0, 127.4, 127.1, 116.1, 99.4, 60.2, 52.5, 50.9, 28.9, 25.8.

HRMS-ESI (m/z) calcd for (C₁₃H₁₄INO₄+H)⁺: 376.0040, found: 376.0039.

Methyl (2-hydroxy-4-methylbenzoyl)prolinate (2'g):



: 81% brown viscous oil; R_f: 0.35 (3:7, ethyl acetate: petroleum ether).

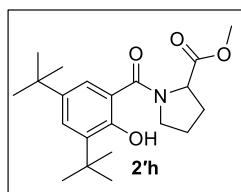
¹H NMR (400 MHz, CDCl₃): δ 10.93 (br. s., 1 H), 7.41 (br. s., 1 H), 6.79 (s, 1 H), 6.66 (d, *J* = 8.0 Hz, 1 H), 4.68 (t, *J* = 7.1 Hz, 1 H), 3.95 - 3.81 (m, 2 H), 3.77 (s, 3 H), 2.39 - 2.33 (m, 1 H), 2.32 (s, 3 H), 2.14 - 2.07 (m,

1 H), 2.06 - 1.87 (m, 2 H).

¹³C NMR (101 MHz, CDCl₃): δ 172.5, 170.6, 160.5, 144.2, 128.1, 119.2, 118.1, 113.8, 60.2, 52.4, 51.0, 29.0, 25.8, 21.5.

HRMS-ESI (m/z) calcd for (C₁₄H₁₇NO₄+H)⁺: 264.1230, found: 264.1229.

Methyl (3,5-di-tert-butyl-2-hydroxybenzoyl)prolinate (2'h):



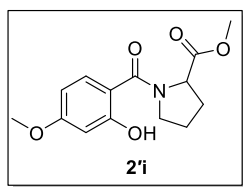
: 90% white solid; mp: 60-61°C; R_f: 0.55 (2:8, ethyl acetate: petroleum ether).

¹H NMR (400 MHz, CDCl₃): δ 10.76 (br. s., 1 H), 7.40 (d, *J* = 2.0 Hz, 1 H), 7.35 (br. s., 1 H), 4.69 (t, *J* = 7.2 Hz, 1 H), 3.92 - 3.83 (m, 2 H), 3.78 (s, 3 H), 2.41 - 2.30 (m, 1 H), 2.15 - 2.01 (m, 2 H), 1.96 - 1.88 (m, 1 H), 1.42 (s, 9 H), 1.30 (s, 9 H).

¹³C NMR (101 MHz, CDCl₃): δ 172.6, 171.8, 156.5, 139.4, 137.2, 127.4, 122.5, 116.0, 60.0, 52.4, 51.1, 35.1, 34.3, 31.4, 29.4, 29.1, 26.0.

HRMS-ESI (m/z) calcd for (C₂₁H₃₁NO₄+H)⁺: 362.2326, found: 362.2324.

Methyl (2-hydroxy-4-methoxybenzoyl)prolinate (2'i):

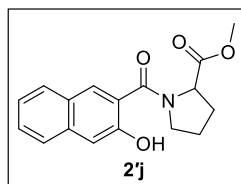


: 79% thick oil; R_f: 0.5 (4:6, ethyl acetate: petroleum ether).

¹H NMR (400 MHz, CDCl₃): δ 11.57 (s, 1 H), 7.46 (d, *J* = 8.6 Hz, 1 H), 6.46 (d, *J* = 2.5 Hz, 1 H), 6.39 (dd, *J* = 8.9, 2.6 Hz, 1 H), 4.65 (t, *J* = 7.2 Hz, 1 H), 3.92 - 3.83 (m, 2 H), 3.79 (s, 3 H), 3.75 (s, 3 H), 2.36 - 2.25 (m, 1 H), 2.15 - 2.05 (m, 1 H), 2.03 - 1.89 (m, 2 H).

¹³C NMR (101 MHz, CDCl₃): δ 172.6, 170.5, 163.5, 163.2, 129.6, 109.0, 105.7, 101.4, 60.3, 55.3, 52.3, 50.8, 28.9, 25.8.

HRMS-ESI (m/z) calcd for (C₁₄H₁₇NO₅+H)⁺: 280.1179, found: 280.1175.

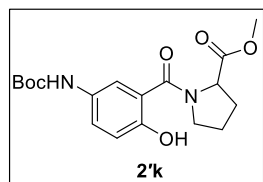
Methyl (3-hydroxy-2-naphthoyl)prolinate (2'j):

: 62% white solid; mp: 118-120°C; R_f : 0.21 (3:7, ethyl acetate: petroleum ether).

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 10.00 (br. s., 1 H), 8.04 (br. s., 1 H), 7.75 (d, $J = 7.9$ Hz, 1 H), 7.69 (d, $J = 8.3$ Hz, 1 H), 7.48 (t, $J = 7.6$ Hz, 1 H), 7.37 - 7.29 (m, 2 H), 4.76 (t, $J = 7.1$ Hz, 1 H), 4.05 - 3.95 (m, 1 H), 3.95 - 3.87 (m, 1 H), 3.81 (s, 3 H), 2.49 - 2.34 (m, 1 H), 2.20 - 2.05 (m, 2 H), 2.03 - 1.90 (m, 1 H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 172.4, 170.0, 155.0, 136.2, 129.4, 128.5, 128.3, 126.7, 126.3, 124.0, 119.7, 111.9, 60.1, 52.5, 51.2, 29.1, 25.8.

HRMS-ESI (m/z) calcd for $(\text{C}_{17}\text{H}_{17}\text{NO}_4 + \text{H})^+$: 300.1230, found: 300.1228.

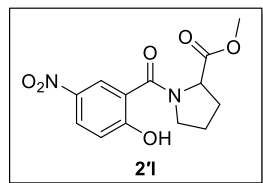
Methyl (5-((tert-butoxycarbonyl)amino)-2-hydroxybenzoyl)prolinate (2'k):

: 61% brown solid; mp: 64-65°C; R_f : 0.47 (4:6, ethyl acetate: petroleum ether).

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 10.49 (br. s., 1 H), 7.87 (br. s., 1 H), 7.08 (d, $J = 7.3$ Hz, 1 H), 6.89 (d, $J = 8.8$ Hz, 1 H), 6.47 (br. s., 1 H), 4.66 (t, $J = 6.8$ Hz, 1 H), 4.02 - 3.86 (m, 2 H), 3.77 (s, 3 H), 2.38 - 2.29 (m, 1 H), 2.17 - 2.08 (m, 1 H), 2.06 - 1.90 (m, 2 H), 1.51 (s, 9 H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 172.4, 170.1, 156.0, 153.0, 129.2, 124.4, 119.1, 117.9, 116.4, 80.3, 60.3, 52.4, 51.0, 28.9, 28.3, 25.9.

HRMS-ESI (m/z) calcd for $(\text{C}_{18}\text{H}_{24}\text{N}_2\text{O}_6 + \text{H})^+$: 365.1707, found: 365.1702.

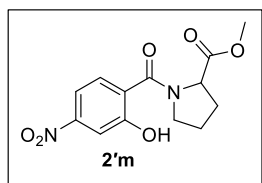
Methyl (2-hydroxy-5-nitrobenzoyl)prolinate (2'l):

: 56% yellow solid; mp: 128-130°C; R_f : 0.24 (3:7, ethyl acetate: petroleum ether).

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 12.09 (br. s., 1 H), 8.59 (br. s., 1 H), 8.26 (dd, $J = 8.8$ Hz, 2.6 Hz, 1 H), 7.07 (d, $J = 9.1$ Hz, 1 H), 4.71 (t, $J = 6.5$ Hz, 1 H), 4.11 - 3.98 (m, 1 H), 3.98 - 3.91 (m, 1 H), 3.80 (s, 3 H), 2.44 - 2.31 (m, 1 H), 2.22 - 2.18 (m, 1 H), 2.13 - 1.99 (m, 2 H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 171.8, 168.6, 166.3, 139.0, 128.6, 124.9, 118.7, 115.6, 60.7, 52.6, 51.0, 28.7, 25.9.

HRMS-ESI (m/z) calcd for $(\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_6 + \text{H})^+$: 295.0925, found: 295.0925.

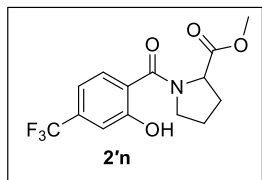
Methyl (2-hydroxy-4-nitrobenzoyl)prolinate (2'm):

: 71% thick oil; R_f : 0.3 (4:6, ethyl acetate: petroleum ether).

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 10.71 (br. s, 1 H), 7.81 - 7.77 (m, 1 H), 7.73 - 7.61 (m, 2 H), 4.71 (t, J = 6.9 Hz, 1 H), 3.93 - 3.74 (m, 5 H), 2.45 - 2.33 (m, 1 H), 2.19 - 1.96 (m, 3 H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 172.1, 168.4, 160.3, 150.3, 128.9, 122.4, 113.0 (2C), 60.2, 52.6, 50.7, 28.8, 25.7.

HRMS-ESI (m/z) calcd for $(\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_6+\text{H})^+$: 295.0925, found: 295.0927.

Methyl (2-hydroxy-4-(trifluoromethyl)benzoyl)prolinate (2'n):

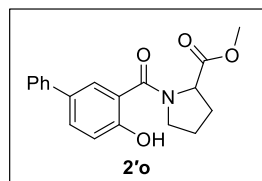
: 78% thick oil; R_f : 0.4 (4:6, ethyl acetate: petroleum ether).

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 10.77 (s, 1 H), 7.64 (d, J = 7.0 Hz, 1 H), 7.24 (s, 1 H), 7.11 (d, J = 8.2 Hz, 1 H), 4.70 (t, J = 7.2 Hz, 1 H),

3.93 - 3.71 (m, 5 H), 2.43 - 2.32 (m, 1 H), 2.09 - 1.91 (m, 3 H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 172.2, 169.1, 159.8, 134.5 (q, $J_{\text{C,F}}$ = 32.8 Hz), 128.7, 123 (q, $J_{\text{C,F}}$ = 273.1 Hz), 119.9, 115.0, 114.9, 60.1, 52.5, 50.8, 28.8, 25.7.

HRMS-ESI (m/z) calcd for $(\text{C}_{14}\text{H}_{14}\text{F}_3\text{NO}_4+\text{H})^+$: 318.0948, found: 318.0945.

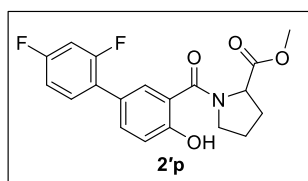
Methyl (4-hydroxy-[1,1'-biphenyl]-3-carbonyl)prolinate (2'o):

: 81% thick oil; R_f : 0.5 (3:7, ethyl acetate: petroleum ether).

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 10.71 (s, 1 H), 7.72 - 7.38 (m, 6 H), 7.38 - 7.30 (m, 1 H), 7.09 - 6.80 (m, 1 H), 4.78 - 4.63 (m, 1 H), 4.02 - 3.84 (m, 2 H), 3.77 (s, 3 H), 2.43 - 2.26 (m, 1 H), 2.14 - 1.91 (m, 3 H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 172.4, 172.2, 170.3, 160.0, 159.4, 140.2, 132.1, 132.0, 132.0, 131.9, 131.9, 131.6, 128.8, 128.5, 128.4, 128.2, 126.9, 126.7, 126.7, 126.6, 119.7, 118.2, 117.8, 116.9, 60.2, 52.5, 52.4, 52.4, 51.0, 28.9, 25.9

HRMS-ESI (m/z) calcd for $(\text{C}_{19}\text{H}_{19}\text{NO}_4+\text{H})^+$: 326.1387, found: 326.1381.

Methyl (2',4'-difluoro-4-hydroxy-[1,1'-biphenyl]-3-carbonyl) proline (2'p):

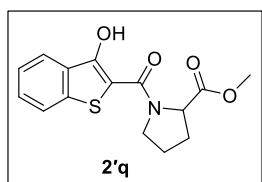
: 77% thick oil; R_f : 0.3 (4:6, ethyl acetate: petroleum ether).

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 10.84 (s, 1 H), 7.71 (s, 1 H), 7.50 - 7.44 (m, 1 H), 7.40 - 7.32 (m, 1 H), 7.06 (d, $J = 8.6$ Hz, 1 H), 6.98 - 6.87 (m, 2 H), 4.71 (t, $J = 7.2$ Hz, 1 H), 4.03 - 3.87 (m, 2 H),

3.82 (s, 3 H), 2.40 - 2.11 (m, 1 H), 2.20 - 1.92 (m, 3 H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 172.4, 170.2, 162.1 (dd, $J_{\text{C-F}} = 246.4, 11.4$ Hz), 159.8, 159.3 (dd, $J_{\text{C-F}} = 238.4, 6.8$ Hz), 133.5, 131.0 (dd, $J_{\text{C-F}} = 9.1, 4.6$ Hz), 128.8, 124.9, 124.3 (dd, $J_{\text{C-F}} = 9.2, 3.8$ Hz), 118.1, 116.6, 111.8 (dd, $J_{\text{C-F}} = 16.8, 3.8$ Hz), 104.6 (dd, $J_{\text{C-F}} = 25.1, 1.5$ Hz), 60.2, 52.4, 51.0, 28.9, 25.9.

HRMS-ESI (m/z) calcd for $(\text{C}_{19}\text{H}_{17}\text{F}_2\text{NO}_4 + \text{H})^+$: 362.1198, found: 362.1189.

Methyl (3-hydroxybenzo[*b*]thiophene-2-carbonyl)proline (2'q):

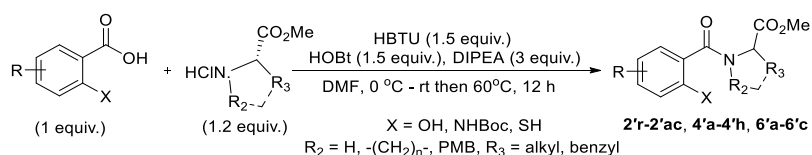
: 82% light yellow oil; R_f : 0.4 (4:6, ethyl acetate: petroleum ether).

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 12.98 (s, 1 H), 7.98 (d, $J = 7.9$ Hz, 1 H), 7.72 (d, $J = 8.1$ Hz, 1 H), 7.51 - 7.45 (m, 1 H), 7.43 - 7.36 (m, 1 H), 4.75 (s, 1 H), 4.17 - 4.04 (m, 1 H), 4.02 - 3.88 (m, 1 H), 3.79 (s, 3

H), 2.36 - 2.02 (m, 4 H)

$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 172.4, 166.9, 161.5, 138.0, 130.6, 128.4, 124.4, 122.9, 122.4, 101.1, 60.1, 52.5, 47.4, 28.7, 25.2.

HRMS-ESI (m/z) calcd for $(\text{C}_{15}\text{H}_{15}\text{NO}_4\text{S} + \text{H})^+$: 306.0795, found: 306.0792.

[C] General procedure-II: Synthesis of compounds 2'r-2'ac, 4'a-4'h, 6'a-6'c

To a solution of salicylic/*N*-Boc anthranilic/thiosalicylic acid (1 equiv.) in DMF (15 mL for 1 g of acid) was added, HBTU (1.5 equiv.) and HOBT (1.5 equiv.) followed by DIPEA (3 equiv.) at 0 °C with continuous stirring for 10 minutes. Later, a solution of amino acid methyl ester (1.2 equiv.) in DMF (10 mL) was added dropwise at 0 °C to the reaction mixture in five minutes with continuous stirring. The reaction mixture was allowed to warm to room temperature and then stirred 60 °C overnight. After completion of the reaction (checked by TLC), the DMF

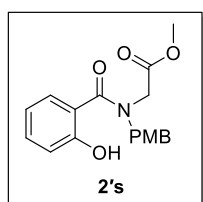
solvent was removed in *vacuo* and then residue was quenched with saturated aqueous NH_4Cl solution (10 mL), and extracted with EtOAc (3×15 mL). The combined organic layers were washed with saturated aqueous NaHCO_3 solution (3×20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4 , and concentrated in *vacuo*. The crude product was purified by silica gel column chromatography using ethyl acetate and petroleum ether as eluents to obtain corresponding products **2'r-2'ac**, **4'a-4'h**, **6'a-6'c** in good yields.

The analytical and spectral data of the known esters **2'r**,^[21] **4'b**,^[22] are in agreement with the reported data.

[D] Typical experimental procedure for the synthesis of representative compound **2's**:

To the solution of salicylic acid (1.0 g, 7.24 mmol, 1 equiv.) in DMF (15 mL) was added HBTU (4.13 g, 10.86 mmol, 1.5 equiv.) and HOBT (1.467g, 10.86 mmol, 1.5 equiv.), followed by DIPEA (2.8 g, 3.77 mL, 21.7 mmol, 3 equiv.) at 0 °C with continuous stirring for 10 minutes. Then a solution of PMB protected glycine methyl ester (1.81 g, 8.68 mmol, 1.2 equiv.) in DMF (10 mL) was added drop wise at 0 °C to the reaction mixture in fifteen minutes with continuous stirring. The reaction mixture was allowed to warm to room temperature and then stirred at 60 °C overnight. After completion of reaction (checked by TLC), solvent was removed under reduced pressure, then residue was quenched with saturated aqueous NH_4Cl (20 mL) solution, and extracted with EtOAc (3×15 mL). The combined organic layers were washed with saturated aqueous NaHCO_3 solution (3×15 mL) and brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The crude product was purified by silica gel column chromatography using ethyl acetate and petroleum ether (6:4) as eluents to obtain corresponding product **2's** in 47 % yield as a thick oil (1.11 g).

Methyl *N*-(2-hydroxybenzoyl)-*N*-(4-methoxybenzyl)glycinate (**2's**):

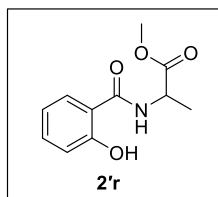


: 47% thick oil; R_f : 0.3 (6:4, ethyl acetate: petroleum ether).

^1H NMR (400 MHz, CDCl_3): δ 9.28 (s, 1 H), 7.35 - 7.29 (m, 2 H), 7.22 - 7.15 (m, 2 H), 7.01 (d, $J = 7.9$ Hz, 1 H), 6.94 - 6.89 (m, 2 H), 6.83 - 6.77 (m, 1 H), 4.74 (s, 2 H), 4.10 (s, 2 H), 3.81 (s, 3 H), 3.77 (s, 3 H).

^{13}C NMR (101 MHz, CDCl_3): δ 172.4, 169.7, 159.3, 157.9, 132.8, 128.5, 127.5, 127.3, 119.0, 117.9, 117.5, 114.4, 55.2, 53.5, 52.4, 47.5

HRMS-ESI (m/z) calcd for $(\text{C}_{18}\text{H}_{19}\text{NO}_5 + \text{H})^+$: 330.1336, found: 330.1329.

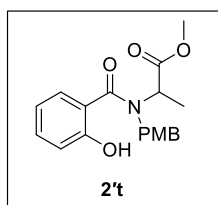
Methyl (2-hydroxybenzoyl)alaninate (2'r)^[21]:

: 74% white solid; mp: 80-81°C; *R*_f: 0.4 (5:5, ethyl acetate: petroleum ether).

¹H NMR (400 MHz, CDCl₃): δ 12.09 (s, 1 H), 7.73 - 7.38 (m, 2 H), 7.02 - 6.95 (m, 2 H), 6.89 - 6.85 (m, 1 H), 4.81 - 4.74 (m, 1 H), 3.82 (s, 3 H), 1.54 (d, *J* = 7.1 Hz, 3 H).

¹³C NMR (101 MHz, CDCl₃): δ 173.4, 169.4, 161.6, 134.5, 125.7, 118.7, 118.6, 113.7, 52.8, 48.2, 18.4.

HRMS-ESI (*m/z*) calcd for (C₁₁H₁₃NO₄+H)⁺: 224.0917, found: 224.0918.

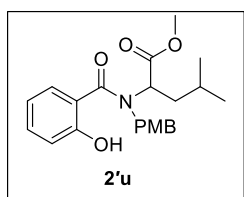
Methyl *N*-(2-hydroxybenzoyl)-*N*-(4-methoxybenzyl) alaninate (2't):

: 51% thick oil; *R*_f: 0.5 (4:6, ethyl acetate: petroleum ether).

¹H NMR (400 MHz, CDCl₃): δ 9.56 (s, 1 H), 7.38 - 7.29 (m, 4 H), 7.00 (d, *J* = 7.5 Hz, 1 H), 6.95 (d, *J* = 8.6 Hz, 2 H), 6.75 (t, *J* = 6.8 Hz, 1 H), 4.81 (d, *J* = 16.6 Hz, 1 H), 4.66 (d, *J* = 16.6 Hz, 1 H), 4.18 (s, 1 H), 3.83 (s, 3 H), 3.76 (s, 3 H), 1.56 (d, *J* = 7.1 Hz, 3 H).

¹³C NMR (101 MHz, CDCl₃): δ 172.7, 171.8, 159.2, 158.6, 132.9, 128.3, 128.1, 127.2, 118.9, 118.1, 117.4, 114.3, 56.5, 55.3, 53.0, 52.5, 29.7, 14.7.

HRMS-ESI (*m/z*) calcd for (C₁₉H₂₁NO₅+H)⁺: 344.1492, found: 344.1484.

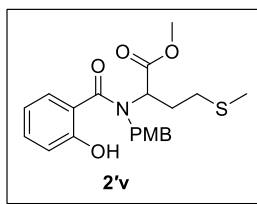
Methyl *N*-(2-hydroxybenzoyl)-*N*-(4-methoxybenzyl)leucinate (2'u):

: 53% thick oil; *R*_f: 0.4 (4:6, ethyl acetate: petroleum ether).

¹H NMR (400 MHz, CDCl₃): δ 8.98 (br. s, 1 H), 7.41 (d, *J* = 7.8 Hz, 1 H), 7.34 - 7.27 (m, 3 H), 7.01 - 6.96 (m, 1 H), 6.89 (d, *J* = 8.6 Hz, 2 H), 6.86 - 6.79 (m, 1 H), 4.75 - 4.59 (m, 2 H), 4.53 - 4.24 (m, 1 H), 3.80 (s, 3 H), 3.67 (s, 3 H), 1.73 - 1.63 (m, 1 H), 1.62 - 1.49 (m, 1 H), 1.32 - 1.21 (m, 1 H), 0.83 - 0.70 (m, 6 H).

¹³C NMR (101 MHz, CDCl₃): δ 172.7, 171.6, 159.0, 157.8, 132.5, 128.9, 127.4, 119.0, 118.3, 117.9, 113.9, 113.8, 64.8, 58.9, 55.2, 52.3, 38.7, 25.1, 22.3, 22.0.

HRMS-ESI (*m/z*) calcd for (C₂₂H₂₇NO₅+H)⁺: 386.1962, found: 386.1958.

Methyl N-(2-hydroxybenzoyl)-N-(4-methoxybenzyl)methioninate (2'v):

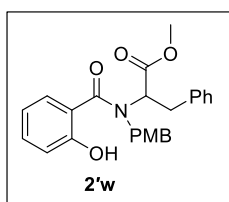
: 43% thick oil; R_f : 0.4 (4:6, ethyl acetate: petroleum ether).

^1H NMR (400 MHz, CDCl_3): δ 9.22 (s, 1 H), 7.44 - 7.37 (m, 1 H), 7.37 - 7.29 (m, 3 H), 7.01 (d, $J = 8.3$ Hz, 1 H), 6.92 (d, $J = 8.5$ Hz, 2 H), 6.87 - 6.78 (m, 1 H), 4.81 - 4.62 (m, 2 H), 4.28 (br. s., 1 H), 3.79

(s, 3 H), 3.71 (s, 3 H), 2.71 - 2.46 (m, 3 H), 2.15 - 2.05 (m, 1 H), 2.00 (s, 3 H).

^{13}C NMR (101 MHz, CDCl_3): δ 172.5, 171.1, 159.2, 157.6, 132.5, 129.1, 127.8, 127.4, 119.1, 118.2, 117.8, 114.1, 59.0, 56.8, 55.2, 52.4, 31.2, 28.9, 15.1.

HRMS-ESI (m/z) calcd for $(\text{C}_{21}\text{H}_{25}\text{NO}_5\text{S}+\text{H})^+$: 404.1526, found: 404.1522.

Methyl N-(2-hydroxybenzoyl)-N-(4-methoxybenzyl)phenylalaninate (2'w):

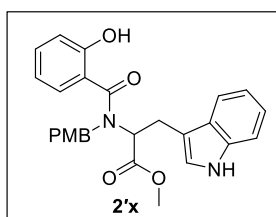
: 40% thick oil; R_f : 0.4 (4:6, ethyl acetate: petroleum ether).

^1H NMR (400 MHz, CDCl_3): δ 9.28 (br. s., 1 H), 7.36 - 7.27 (m, 4 H), 7.24 - 7.19 (m, 1 H), 7.17 - 7.09 (m, 2 H), 7.08 - 6.98 (m, 3 H), 6.82 (d, $J = 8.6$ Hz, 2 H), 6.77 (t, $J = 7.5$ Hz, 1 H), 4.63 (d, $J = 15.9$ Hz, 1 H),

4.21 - 3.94 (m, 2 H), 3.84 - 3.77 (m, 3 H), 3.73 (s, 3 H), 3.53 - 3.37 (m, 2 H).

^{13}C NMR (101 MHz, CDCl_3): δ 172.6, 170.6, 159.2, 158.6, 137.8, 132.8, 129.4, 129.3, 129.1, 128.7, 127.4, 126.9, 118.8, 118.1, 117.5, 114.0, 61.7, 55.3, 52.4, 37.8, 35.2.

HRMS-ESI (m/z) calcd for $(\text{C}_{25}\text{H}_{25}\text{NO}_5+\text{H})^+$: 420.1805, found: 420.1799.

(2-(2-hydroxy-N-(4-methoxybenzyl)benzamido)-3-methoxy-3-oxopropyl)-11-indigane (2'x):

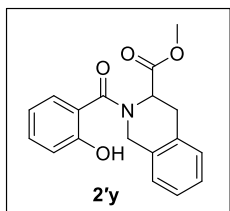
: 48% white solid; mp: 97-98°C; R_f : 0.4 (4:6, ethyl acetate: petroleum ether).

^1H NMR (400 MHz, CDCl_3): δ 9.30 (br. s., 1 H), 8.15 (s, 1 H), 7.42 - 7.26 (m, 3 H), 7.22 - 7.14 (m, 2 H), 7.10 - 6.87 (m, 5 H), 6.80 - 6.61 (m, 3 H), 4.58 (d, $J = 15.8$ Hz, 1 H), 4.47 - 4.30 (m, 1 H), 4.20 - 3.86

(m, 1 H), 3.78 (s, 3 H), 3.74 (s, 3 H), 3.62 (s, 2 H).

^{13}C NMR (101 MHz, CDCl_3): δ 172.4, 171.0, 159.0, 157.8, 136.2, 132.7, 132.4, 129.1, 127.4, 127.2, 123.5, 122.0, 119.5, 118.9, 118.3, 118.2, 117.8, 113.8, 113.5, 111.3, 60.4, 58.1, 55.2, 52.3, 24.9.

HRMS-ESI (m/z) calcd for $(\text{C}_{27}\text{H}_{26}\text{N}_2\text{O}_5+\text{H})^+$: 459.1914, found: 459.1910.

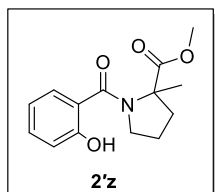
Methyl 2-(2-hydroxybenzoate)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (2'y):

: 19%, white solid; mp: 60-61°C, R_f : 0.3 (3:7, ethyl acetate: petroleum ether).

^1H NMR (400 MHz, CDCl_3): δ 9.14 (br. s., 1 H), 7.56 - 7.31 (m, 2 H), 7.26 - 7.18 (m, 3 H), 7.08 (br. s., 1 H), 7.04 (d, J = 8.1 Hz, 1 H), 6.95 (t, J = 7.5 Hz, 1 H), 5.31 (s, 1 H), 5.12 - 4.87 (m, 1 H), 4.87 - 4.65 (m, 1 H), 3.71 (s, 3 H), 3.31 (d, J = 5.4 Hz, 2 H).

^{13}C NMR (101 MHz, CDCl_3): δ 171.7, 171.3, 158.2, 132.9, 132.3, 131.8, 128.3, 128.1, 127.4, 127.1, 126.1, 119.0, 118.0, 117.7, 53.4, 52.7, 48.4, 30.7.

HRMS-ESI (m/z) calcd for $(\text{C}_{18}\text{H}_{17}\text{NO}_4+\text{H})^+$: 312.1230, found: 312.1227.

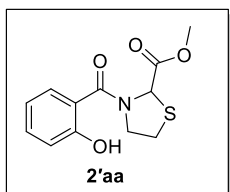
Methyl 1-(2-hydroxybenzoyl)-2-methylpyrrolidine-2-carboxylate (2'z):

: 45%, white solid; mp: 95-96°C, R_f : 0.38 (3:7, ethyl acetate: petroleum ether).

^1H NMR (400 MHz, CDCl_3): δ 10.55 (br. s., 1 H), 7.45 (dd, J = 1.4, 7.9 Hz, 1 H), 7.38 - 7.30 (m, 1 H), 6.97 (d, J = 8.3 Hz, 1 H), 6.84 (t, J = 7.6 Hz, 1 H), 3.98 - 3.91 (m, 1 H), 3.88 - 3.80 (m, 1 H), 3.74 (s, 3 H), 2.28 - 2.19 (m, 1 H), 2.17 - 2.06 (m, 1 H), 2.02 - 1.91 (m, 2 H), 1.71 (s, 3 H).

^{13}C NMR (101 MHz, CDCl_3): δ 174.2, 169.9, 159.9, 133.0, 128.0, 118.1, 117.8, 117.4, 66.9, 52.4, 51.8, 38.5, 24.7, 22.2.

HRMS-ESI (m/z) calcd for $(\text{C}_{14}\text{H}_{17}\text{NO}_4+\text{H})^+$: 264.1230, found: 264.1236.

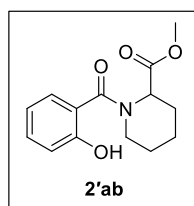
Methyl 3-(2-hydroxybenzoyl) thiazolidine-2-carboxylate (2'aa):

: 65% thick oil; R_f : 0.4 (4:6, ethyl acetate: petroleum ether).

^1H NMR (400 MHz, CDCl_3): δ 9.86 (br. s., 1 H), 7.46 - 7.33 (m, 2 H), 7.01 (d, J = 8.1 Hz, 1 H), 6.92 - 6.84 (m, 1 H), 5.66 (s, 1 H), 4.35 - 4.09 (m, 2 H), 3.82 (s, 3 H), 3.34 - 3.26 (m, 1 H), 3.12 - 3.04 (m, 1 H).

^{13}C NMR (101 MHz, CDCl_3): δ 170.3, 165.0, 159.4, 133.6, 127.9, 118.7, 118.0, 117.0, 61.2, 53.0, 52.6, 31.0

HRMS-ESI (m/z) calcd for $(\text{C}_{12}\text{H}_{13}\text{NO}_4\text{S}+\text{H})^+$: 268.0638, found: 268.0640.

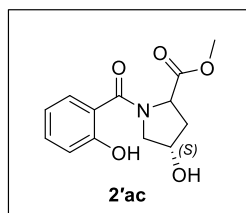
Methyl 1-(2-hydroxybenzoyl)piperidine-2-carboxylate (2'ab):

: 36% white solid; mp: 123-125°C; R_f : 0.37 (3:7, ethyl acetate: petroleum ether).

^1H NMR (400 MHz, CDCl_3): δ 8.94 (s, 1 H), 7.36 - 7.27 (m, 2 H), 7.02 - 6.98 (m, 1 H), 6.91 - 6.85 (m, 1 H), 5.35 (s, 1 H), 4.20 - 3.97 (m, 1 H), 3.81 (s, 3 H), 3.27 (s, 1 H), 2.39 - 2.34 (m, 1 H), 1.85 - 1.77 (m, 2 H), 1.77 - 1.63 (m, 1 H), 1.58 - 1.42 (m, 2 H).

^{13}C NMR (101 MHz, CDCl_3): δ 171.6, 162.0, 157.7, 132.4, 128.0, 119.0, 118.1, 117.8, 53.8, 52.6, 45.2, 26.7, 25.2, 21.1.

HRMS-ESI (m/z) calcd for $(\text{C}_{14}\text{H}_{17}\text{NO}_4+\text{H})^+$: 264.1230, found: 264.1226.

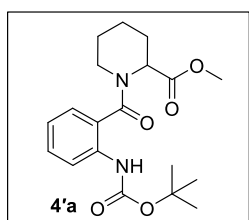
Methyl (4S)-4-hydroxy-1-(2-hydroxybenzoyl) pyrrolidine-2-carboxylate (2'ac):

: 63% thick oil; R_f : 0.3 (6:4, ethyl acetate: petroleum ether).

^1H NMR (400 MHz, CDCl_3): δ 10.66 (s, 1 H), 7.46 (d, J = 7.6 Hz, 1 H), 7.39 - 7.33 (m, 1 H), 6.98 (d, J = 8.4 Hz, 1 H), 6.86 (t, J = 7.6 Hz, 1 H), 4.91 (t, J = 8.4 Hz, 1 H), 4.58 (s, 1 H), 4.04 (d, J = 10.8 Hz, 1 H), 3.89 - 3.68 (m, 4 H), 2.42 - 2.30 (m, 1 H), 2.18 - 1.98 (m, 1 H).

^{13}C NMR (101 MHz, CDCl_3): δ 172.7, 171.0, 159.5, 133.2, 128.3, 118.5, 117.7, 116.7, 70.2, 60.4, 58.6, 52.5, 37.0.

HRMS-ESI (m/z) calcd for $(\text{C}_{13}\text{H}_{15}\text{NO}_5+\text{H})^+$: 266.1023, found: 266.1024.

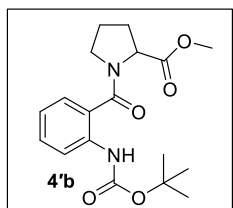
Methyl 1-(2-((tert-butoxycarbonyl)amino)benzoyl)piperidine-2-carboxylate (4'a):

: 68% colourless liq.; R_f : 0.6 (3:7, ethyl acetate: petroleum ether).

^1H NMR (400 MHz, CDCl_3): δ 8.13 (d, J = 7.8 Hz, 1 H), 7.65 (s, 1 H), 7.35 (t, J = 7.8 Hz, 1 H), 7.22 (d, J = 6.8 Hz, 1 H), 7.02 (t, J = 7.3 Hz, 1 H), 5.53 (s, 1 H), 3.80 (s, 3 H), 3.59 (d, J = 13.0 Hz, 1 H), 3.22 - 3.07 (m, 1 H), 2.38 (d, J = 12.5 Hz, 1 H), 1.76 (d, J = 11.3 Hz, 3 H), 1.50 (s, 9 H), 1.45 - 1.34 (m, 2 H).

^{13}C NMR (101 MHz, CDCl_3): δ 171.4, 170.0, 152.9, 136.3, 130.4, 126.8, 124.0, 122.2, 120.2, 80.4, 52.5, 52.2, 45.4, 28.2, 26.2, 25.2, 21.1.

HRMS-ESI (m/z) calcd for $(\text{C}_{19}\text{H}_{26}\text{N}_2\text{O}_5+\text{H})^+$: 363.1914, found: 363.1906.

Methyl (2-((tert-butoxycarbonyl)amino)benzoyl)prolinate (4'b)^[22]:

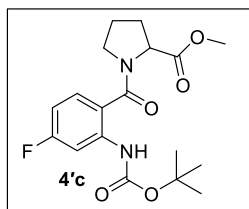
: 78% white solid mp: 90-91°C; *R_f*: 0.4 (4:6, ethyl acetate: petroleum ether).

¹H NMR (400 MHz, CDCl₃): δ 8.32 (s, 1 H), 8.16 (d, *J* = 8.4 Hz, 1 H), 7.39 - 7.30 (m, 2 H), 7.00 (t, *J* = 7.4 Hz, 1 H), 4.72 - 4.62 (m, 1 H), 3.77 (s, 3 H), 3.63 - 3.55 (m, 1 H), 3.52 - 3.46 (m, 1 H), 2.36 - 2.20 (m, 1 H),

2.09 - 1.94 (m, 2 H), 1.91 - 1.81 (m, 1 H), 1.49 (s, 9 H).

¹³C NMR (101 MHz, CDCl₃): δ 172.4, 168.7, 152.9, 137.2, 130.9, 127.1, 123.4, 121.6, 120.1, 80.2, 59.0, 52.3, 49.9, 29.3, 28.2, 25.2.

HRMS-ESI (*m/z*) calcd for (C₁₈H₂₄N₂O₅+H)⁺: 349.1758, found: 349.1753.

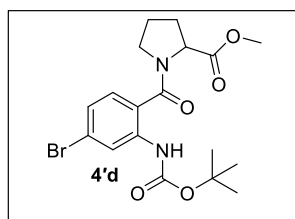
Methyl (2-((tert-butoxycarbonyl)amino)-4-fluorobenzoyl)prolinate (4'c):

: 96% colourless liq.; *R_f*: 0.3 (3:7, ethyl acetate: petroleum ether).

¹H NMR (400 MHz, CDCl₃): δ 8.62 (s, 1 H), 8.04 (d, *J* = 11.6 Hz, 1 H), 7.35 (t, *J* = 7.3 Hz, 1 H), 6.75 - 6.66 (m, 1 H), 4.74 - 4.59 (m, 1 H), 3.79 (s, 3 H), 3.64 - 3.48 (m, 2 H), 2.43 - 2.29 (m, 1 H), 2.08 - 1.99 (m, 2 H), 2.00 - 1.88 (m, 1 H), 1.50 (s, 9 H).

¹³C NMR (101 MHz, CDCl₃): δ 172.5, 168.3, 164.1 (d, *J_{C-F}* = 247.9 Hz), 152.7, 140.0 (d, *J_{C-F}* = 12.21 Hz), 129.1 (d, *J_{C-F}* = 9.9 Hz), 118.7 (d, *J_{C-F}* = 2.2 Hz), 108.5 (d, *J_{C-F}* = 22.1 Hz), 107.3 (d, *J_{C-F}* = 27.5 Hz), 80.8, 59.2, 52.4, 50.2, 29.3, 28.2, 25.4.

HRMS-ESI (*m/z*) calcd for (C₁₈H₂₃FN₂O₅Na)⁺: 389.1483, found: 389.1473.

Methyl (4-bromo-2-((tert-butoxycarbonyl)amino)benzoyl)prolinate (4'd):

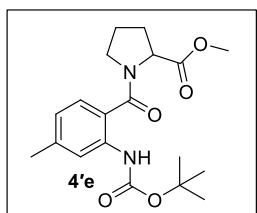
77% white solid; mp: 115°C; *R_f*: 0.3 (3:7, ethyl acetate: petroleum ether).

¹H NMR (400 MHz, CDCl₃): δ 8.46 (s, 1 H), 8.43 (s, 1 H), 7.21 (d, *J* = 8.1 Hz, 1 H), 7.16 - 7.10 (m, 1 H), 4.72 - 4.62 (m, 1 H), 3.78 (s, 3 H), 3.60 - 3.54 (m, 1 H), 3.51 - 3.45 (m, 1 H), 2.40 - 2.31 (m, 1

H), 2.06 - 1.98 (m, 2 H), 1.93 - 1.84 (m, 1 H), 1.49 (s, 9 H).

¹³C NMR (101 MHz, CDCl₃): δ 172.3, 168.0, 152.6, 138.7, 128.4, 125.3, 124.5, 122.7, 121.6, 80.8, 59.1, 52.4, 50.0, 29.2, 28.2, 25.3.

HRMS-ESI (*m/z*) calcd for (C₁₈H₂₃BrN₂O₅Na)⁺: 449.0683, found: 449.0674.

Methyl (2-((tert-butoxycarbonyl)amino)-4-methylbenzoyl)prolinate (4'e):

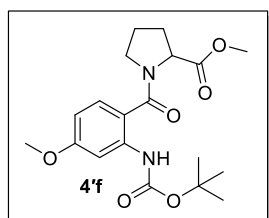
: 75% white solid; mp: 81-82°C; R_f : 0.4 (4:6, ethyl acetate: petroleum ether).

^1H NMR (400 MHz, CDCl_3): δ 8.46 (s, 1 H), 8.02 (s, 1 H), 7.25 (d, J = 7.8 Hz, 1 H), 6.80 (d, J = 7.6 Hz, 1 H), 4.72 - 4.63 (m, 1 H), 3.76 (s, 3 H), 3.65 - 3.48 (m, 2 H), 2.35 - 2.28 (m, 4 H), 2.05 - 1.93 (m, 2 H), 1.91

- 1.80 (m, 1 H), 1.48 (s, 9 H).

^{13}C NMR (101 MHz, CDCl_3): δ 172.5, 169.0, 153.0, 141.6, 137.5, 127.3, 122.3, 120.4 (2C), 80.1, 59.1, 52.3, 50.1, 29.3, 28.2, 25.3, 21.7.

HRMS-ESI (m/z) calcd for ($\text{C}_{19}\text{H}_{26}\text{N}_2\text{O}_5 + \text{H}$) $^+$: 363.1914, found: 363.1903.

Methyl (2-((tert-butoxycarbonyl)amino)benzoyl)prolinate (4'f):

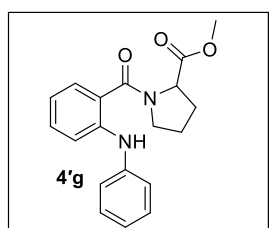
: 81% white solid; mp: 96-97°C; R_f : 0.4 (4:6, ethyl acetate: petroleum ether).

^1H NMR (400 MHz, CDCl_3): δ 8.84 (s, 1 H), 7.87 (s, 1 H), 7.32 (d, J = 7.1 Hz, 1 H), 6.54 (d, J = 8.5 Hz, 1 H), 4.68 (s, 1 H), 3.85 (s, 3 H), 3.78 (s, 3 H), 3.72 - 3.50 (m, 2 H), 2.41 - 2.30 (m, 1 H), 2.05 - 1.96

(m, 2 H), 1.94 - 1.82 (m, 1 H), 1.50 (s, 9 H).

^{13}C NMR (101 MHz, CDCl_3): δ 172.7, 169.3, 161.9, 152.9, 140.1, 129.1, 114.8, 108.1, 104.3, 80.3, 59.3, 55.4, 52.3, 50.5, 29.3, 28.3, 25.6.

HRMS-ESI (m/z) calcd for ($\text{C}_{19}\text{H}_{26}\text{N}_2\text{O}_5 + \text{H}$) $^+$: 379.1864, found: 379.1858.

Methyl (2-(phenylamino)benzoyl)prolinate (4'g):

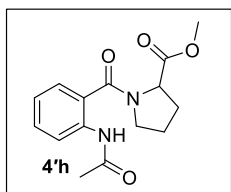
: 84% colourless liq.; R_f : 0.34 (4:6, ethyl acetate: petroleum ether).

^1H NMR (400 MHz, CDCl_3): δ 7.62 (s, 1 H), 7.38 (t, J = 7.7 Hz, 2 H), 7.32 - 7.21 (m, 3 H), 7.18 (d, J = 7.8 Hz, 2 H), 6.97 (t, J = 7.3 Hz, 1 H), 6.85 (t, J = 7.4 Hz, 1 H), 4.71 (t, J = 6.8 Hz, 1 H), 3.79 (s, 3 H), 3.73 - 3.62 (m, 1 H), 3.61 - 3.50 (m, 1 H), 2.44 - 2.27 (m, 1 H), 2.08 -

1.83 (m, 3 H).

^{13}C NMR (101 MHz, CDCl_3): δ 172.9, 169.4, 142.1, 142.0, 130.7, 129.2, 128.1, 122.8, 121.6, 119.2, 118.8, 115.6, 58.8, 52.5, 49.6, 29.4, 25.3.

HRMS-ESI (m/z) calcd for ($\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_3 + \text{H}$) $^+$: 325.1547, found: 325.1542.

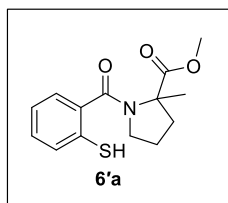
Methyl (2-acetamidobenzoyl) proline (4'h):

: 38% colourless liq.; R_f : 0.4 (4:6, ethyl acetate: petroleum ether).

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.99 (s, 1 H), 8.39 (d, $J = 8.4$ Hz, 1 H), 7.45 - 7.31 (m, 2 H), 7.10 (t, $J = 7.5$ Hz, 1 H), 4.72 (dd, $J = 5.3, 8.6$ Hz, 1 H), 3.82 (s, 3 H), 3.57 - 3.42 (m, 2 H), 2.42 - 2.32 (m, 1 H), 2.20 (s, 3 H), 2.09 - 1.90 (m, 3 H)

$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 172.9, 169.1, 168.6, 136.1, 130.8, 126.6, 124.8, 123.1, 121.6, 58.8, 52.6, 49.6, 29.3, 25.1, 24.7.

HRMS-ESI (m/z) calcd for $(\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_4 + \text{H})^+$: 291.1339, found: 291.1336.

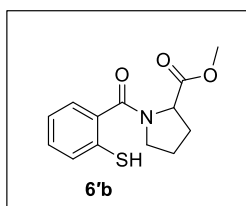
Methyl 1-(2-mercaptobenzoyl)-2-methylpyrrolidine-2-carboxylate (6'a):

: 29% yellow liquid; R_f : 0.32 (5:5, ethyl acetate: petroleum ether).

$^1\text{H NMR}$ (400 MHz, CDCl_3 , mix. of rotamers): δ 7.70 (d, $J = 7.6$ Hz, 1 H), 7.35 - 7.29 (m, 1 H), 7.28 - 7.23 (m, 2 H), 3.79 (s, 3 H), 3.46 - 3.34 (m, 2 H), 2.31 - 2.19 (m, 1 H), 2.03 - 1.90 (m, 3 H), 1.76 (d, $J = 3.1$ Hz, 3 H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3 , mixture of rotamers): δ 174.1, 174.1, 166.9, 166.9, 136.8, 136.7, 134.1, 133.9, 129.9, 129.9, 128.1, 128.1, 127.1, 127.0, 126.6, 126.5, 65.9, 52.4, 50.1, 50.1, 39.0, 24.1, 21.6, 21.5.

HRMS-ESI (m/z) calcd for $(\text{C}_{14}\text{H}_{17}\text{NO}_3\text{S} + \text{H})^+$: 278.0845, found: 278.0854.

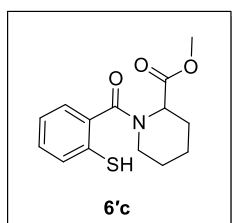
Methyl (2-mercaptobenzoyl)proline (6'b):

: 38% thick oil; R_f : 0.4 (4:6, ethyl acetate: petroleum ether).

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.76 - 7.65 (m, 1 H), 7.38 - 7.30 (m, 2 H), 7.26 - 7.16 (m, 1 H), 4.75 - 4.62 (m, 0.8 H), 4.20 - 4.15 (m, 0.2 H), 3.79 (s, 3 H), 3.55 (s, 1 H), 3.49 - 3.39 (m, 1 H), 3.36 - 3.28 (m, 1 H), 2.41 - 2.24 (m, 1 H), 2.07 - 1.96 (m, 2 H), 1.94 - 1.81 (m, 1 H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 172.4, 167.7, 136.6, 134.4, 130.1, 128.6, 127.1, 127.0, 58.7, 52.2, 49.0, 29.5, 24.9.

HRMS-ESI (m/z) calcd for $(\text{C}_{13}\text{H}_{15}\text{NO}_3\text{S} + \text{H})^+$: 264.0689, found: 264.0701.

Methyl 1-(2-mercaptobenzoyl)piperidine-2-carboxylate (6'c):

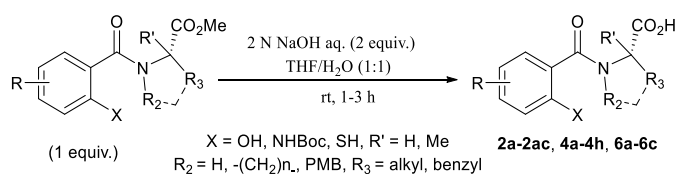
: 34% yellow liq.; R_f : 0.48 (7:3, ethyl acetate: petroleum ether).

$^1\text{H NMR}$ (400 MHz, CDCl_3 , mix. of rotamers): δ 7.76 - 7.62 (m, 1 H), 7.39 - 7.18 (m, 3 H), 5.57 (br. s, 0.8 H), 4.70 (d, J = 12.8 Hz, 0.2 H), 4.25 (br. s, 0.2 H), 3.76 (s, 3 H), 3.41 (d, J = 13.1 Hz, 0.8 H), 3.21 (t, J = 12.8 Hz, 0.8 H), 2.87 (t, J = 12.8 Hz, 0.2 H), 2.36 (d, J = 13.5 Hz, 0.8 H), 2.16

(d, J = 13.5 Hz, 0.2 H), 1.76 (d, J = 11.3 Hz, 3 H), 1.60 - 1.31 (m, 3 H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3 , mix. of rotamers): δ 171.2, 171.0, 168.9, 135.7, 134.0, 130.0, 129.8, 128.1, 127.7, 127.3, 127.1, 126.6, 126.5, 126.4, 58.1, 52.4, 52.3, 51.9, 45.4, 39.7, 27.5, 26.6, 25.4, 24.5, 21.1, 21.0.

HRMS-ESI (m/z) calcd for $(\text{C}_{14}\text{H}_{17}\text{NO}_3\text{S-H})^-$: 278.0845, found: 278.0832.

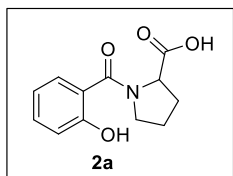
[E] General procedure-III: Synthesis of 2a-2ac, 4a-4h, 6a-6c.

To the solution of esters **2'a-2'ac**, **4'a-4'h**, **6'a-6'c** (1 equiv.) in THF/water (1:1) [10 mL for 1 g of ester] was added aqueous 2N NaOH solution (2 equiv.) drop wise at room temperature with continuous stirring and the reaction mixture was stirred until complete consumption of the starting material (checked by TLC). THF was then removed in *vacuo* followed by dilution with water (5 mL for 1 g scale) and addition of ethyl acetate (10 mL for 1 g scale). The organic layer was separated and the aqueous layer was acidified with citric acid up to pH 2 and extracted with ethyl acetate (15 mL X 3 for 1 g). The ethyl acetate layer was separated, dried over anhydrous Na_2SO_4 and concentrated in *vacuo* to obtain the corresponding acids **2a-2ac**, **4a-4h**, **6a-6c** in quantitative yields.

(F) Typical experimental procedure for the synthesis of representative compound 2a: To the solution of ester **2'a** (1 g, 4.01 mmol, 1 equiv.) in THF/water (1:1, 10 mL) was added aqueous NaOH solution (321 mg, 4 mL 2 N, 2 mmol, 2 equiv.) drop wise at room temperature with continuous stirring and the reaction mixture was stirred until complete consumption of the starting material (checked by TLC). THF was then removed in a *vacuo* followed by dilution with water (15 mL) and the addition of ethyl acetate (5 mL). The organic layer was separated

and the aqueous layer was acidified with citric acid up to pH 2 and extracted with ethyl acetate (15 mL X 3). The ethyl acetate layer was separated, dried over anhydrous Na_2SO_4 , and concentrated in *vacuo* to obtain the corresponding acids **2a** in 94% yield as a white solid (889 mg).

(2-hydroxybenzoyl)proline (2a):



: 94% white solid; mp: 128°C; R_f : 0.3 (1:9, MeOH: DCM).

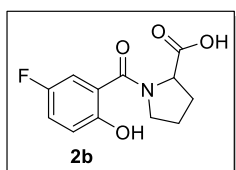
^1H NMR (400 MHz, CDCl_3): δ 7.55 - 7.45 (m, 1 H), 7.36 (t, J = 7.8 Hz, 1 H), 6.99 (d, J = 8.3 Hz, 1 H), 6.86 (t, J = 7.6 Hz, 1 H), 4.78 - 4.67 (m, 1 H), 3.86 (t, J = 5.7 Hz, 2 H), 2.45 - 2.30 (m, 1 H), 2.21 - 2.03 (m, 2 H),

2.02 - 1.90 (m, 1 H).

^{13}C NMR (101 MHz, CDCl_3): δ 176.3, 170.7, 159.7, 133.3, 128.2, 118.4, 117.9, 116.8, 60.1, 51.1, 28.7, 25.8.

HRMS-ESI (m/z) calcd for $(\text{C}_{12}\text{H}_{13}\text{NO}_4 + \text{H})^+$: 236.0917, found: 236.0917.

(5-fluoro-2-hydroxybenzoyl)proline (2b):



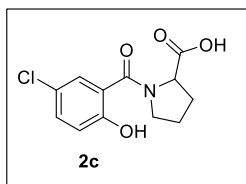
: 96% white solid; mp: 182°C; R_f : 0.3 (1:9, MeOH: DCM).

^1H NMR (400 MHz, $\text{DMSO}-d_6$, mixture of rotamers): δ 12.5 (br. s, 1 H), 9.91 (br. s, 1 H), 7.16 - 7.00 (m, 1 H), 6.97 - 6.75 (m, 2 H), 4.45 - 4.18 (m, 1 H), 3.66 - 3.26 (m, 2 H), 2.34 - 2.15 (m, 1 H), 2.05 - 1.75 (m, 3 H).

^{13}C NMR (101 MHz, $\text{DMSO}-d_6$, mixture of rotamers): δ 173.5 ($J_{\text{C-F}}$ = 35.2 Hz), 166.1 ($J_{\text{C-F}}$ = 10.3 Hz), 154.9 ($J_{\text{C-F}}$ = 235.5 Hz), 150.2 ($J_{\text{C-F}}$ = 110.04 Hz), 125.6, 124.9, 117.4, 117.3, 116.9, 116.7, 114.8, 114.5, 114.1, 113.9, 59.2, 58.6, 47.7, 46.0, 40.1, 39.9, 39.7, 39.3, 39.1, 38.9, 30.7, 29.1, 24.4, 22.5.

HRMS-ESI (m/z) calcd for $(\text{C}_{12}\text{H}_{12}\text{FNO}_4 + \text{H})^+$: 254.0824, found: 254.0816.

(5-chloro-2-hydroxybenzoyl)proline (2c):



: 92% White solid; mp: 162-163°C; R_f : 0.19 (1:9, MeOH: DCM).

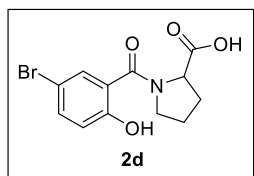
^1H NMR (400 MHz, $\text{DMSO}-d_6$, mixture of rotamers): δ 12.56 (br. s., 1 H), 10.21 (br. s., 1 H), 7.31 - 7.21 (m, 1 H), 7.09- 6.99 (d, J = 2.6 Hz, 1 H), 6.92 - 6.85 (d, J = 8.7 Hz, 1 H), 4.40 - 4.17 (m, 1 H), 3.56 - 3.31 (m,

2 H), 2.28 - 2.17 (m, 1 H), 1.97 - 1.78 (m, 3 H).

^{13}C NMR (101 MHz, DMSO- d_6 , mixture of rotamers): δ 173.5, 173.1, 165.9, 165.7, 152.6, 151.7, 130.2, 129.9, 128.0, 127.3, 126.4, 126.0, 122.4, 122.3, 117.9, 117.7, 59.2, 58.5, 47.6, 46.0, 30.7, 29.1, 24.3, 22.4.

HRMS-ESI (m/z) calcd for ($\text{C}_{12}\text{H}_{12}\text{NClO}_4 + \text{H}$) $^+$: 270.0528, found: 270.0528.

(5-bromo-2-hydroxybenzoyl)proline (2d):



: 93% white solid; mp: 152-153°C; R_f : 0.3 (1:9, MeOH: DCM).

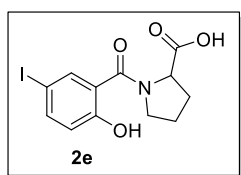
^1H NMR (400 MHz, DMSO- d_6 , mixture of rotamers): δ 12.38 (br. s, 1 H), 10.33 (br. s, 1 H), 7.45 - 7.32 (m, 1 H), 7.21 (d, J = 2.5 Hz, 1 H), 6.90 - 6.80 (m, 1 H), 4.36 - 4.30 (dd, J = 4.1, 8.6 Hz, 1 H), 3.61 - 3.26

(m, 2 H), 2.31 - 2.16 (m, 1 H), 2.03 - 1.75 (m, 3 H).

^{13}C NMR (101 MHz, DMSO- d_6 , mixture of rotamers): δ 173.7, 173.5, 166.3, 166.0, 153.2, 152.4, 133.4, 133.1, 131.1, 130.3, 127.0, 126.8, 118.6, 118.4, 110.1, 59.5, 58.8, 24.6, 22.7.

HRMS-ESI (m/z) calcd for ($\text{C}_{13}\text{H}_{12}\text{BrNO}_4 + \text{H}$) $^+$: 314.0022, found: 314.0026.

(2-hydroxy-5-iodobenzoyl)proline (2e):



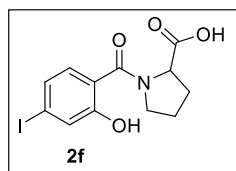
: 99% White solid; mp: 140-142°C; R_f : 0.25 (1:9, MeOH: DCM).

^1H NMR (400 MHz, CDCl_3): δ 7.77 (br. s., 1 H), 7.61 (d, J = 8.6 Hz, 1 H), 6.78 (d, J = 8.8 Hz, 1 H), 4.70 (t, J = 6.7 Hz, 1 H), 3.94 - 3.77 (m, 2 H), 2.46 - 2.30 (m, 1 H), 2.21 - 2.09 (m, 2 H), 2.04 - 1.92 (m, 1 H).

^{13}C NMR (101 MHz, CDCl_3): δ 176.3, 169.1, 159.3, 141.7, 136.4, 120.3, 119.6, 79.4, 60.1, 50.9, 28.8, 25.7.

HRMS-ESI (m/z) calcd for ($\text{C}_{12}\text{H}_{12}\text{INO}_4 + \text{H}$) $^+$: 361.9884, found: 361.9881.

(2-hydroxy-4-iodobenzoyl)proline (2f):

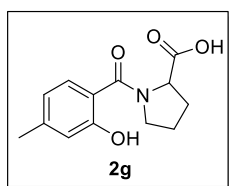


: 95% white solid; mp: 180-181°C; R_f : 0.4 (1:9, MeOH: DCM).

^1H NMR (400 MHz, DMSO- d_6 , mixture of rotamers): δ 12.46 (br. s, 1 H), 10.31 (br. s, 1 H), 7.32 - 7.10 (m, 2 H), 6.99 - 6.77 (m, 1 H), 4.42 - 4.16 (m, 1 H), 3.62 - 3.26 (m, 2 H), 2.34 - 2.12 (m, 1 H), 1.98 - 1.78 (m, 3 H).

^{13}C NMR (101 MHz, DMSO- d_6 , mixture of rotamers): δ 173.4, 173.2, 172.0, 166.7, 166.6, 154.8, 153.7, 130.4, 129.7, 127.8, 127.7, 124.6, 124.3, 123.9, 96.2, 95.8, 59.2, 58.6, 47.8, 46.0, 30.7, 29.1, 24.4, 22.4, 21.1.

HRMS-ESI (m/z) calcd for ($\text{C}_{12}\text{H}_{12}\text{INO}_4 + \text{H}$) $^+$: 361.9884, found: 361.9874.

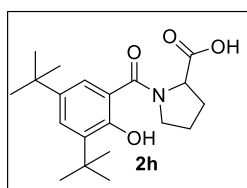
(2-hydroxy-4-methylbenzoyl)proline (2g):

: 99% white solid; mp: 156-157°C; R_f : 0.16 (1:9, MeOH: DCM).

$^1\text{H NMR}$ (400 MHz, $\text{CDCl}_3 + \text{DMSO-d}_6$): δ 7.36 - 7.28 (m, 1 H), 6.67 (s, 1 H), 6.57 (d, $J = 7.9$ Hz, 1 H), 4.55 (t, $J = 6.7$ Hz, 1 H), 3.86 - 3.64 (m, 2 H), 2.23 (s, 4 H), 2.05 - 1.92 (m, 2 H), 1.90 - 1.80 (m, 1 H).

$^{13}\text{C NMR}$ (101 MHz, $\text{CDCl}_3 + \text{DMSO-d}_6$): δ 173.0, 169.0, 158.2, 142.4, 127.3, 118.6, 116.7, 114.5, 59.3, 49.6, 28.1, 24.8, 20.6.

HRMS-ESI (m/z) calcd for $(\text{C}_{13}\text{H}_{15}\text{NO}_4 + \text{H})^+$: 250.1074, found: 250.1072.

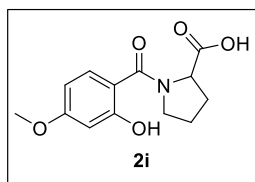
(3,5-di-tert-butyl-2-hydroxybenzoyl)proline (2h):

: 79% white solid; mp: 70-73°C; R_f : 0.44 (1:9, MeOH: DCM).

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 10.56 (br. s., 1 H), 7.41 (d, $J = 2.4$ Hz, 1 H), 7.32 (br. s., 1 H), 6.71 (br. s., 1 H), 4.73 (t, $J = 7.0$ Hz, 1 H), 3.89 - 3.77 (m, 2 H), 2.46 - 2.30 (m, 1 H), 2.22 - 2.05 (m, 2 H), 1.97 - 1.87 (m, 1 H), 1.42 (s, 9 H), 1.30 (s, 9 H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 176.5, 172.2, 156.3, 139.7, 137.3, 127.7, 122.5, 115.9, 60.0, 51.4, 35.2, 34.3, 31.4, 29.4, 28.7, 25.9.

HRMS-ESI (m/z) calcd for $(\text{C}_{20}\text{H}_{29}\text{NO}_4 + \text{H})^+$: 348.2169, found: 348.2168.

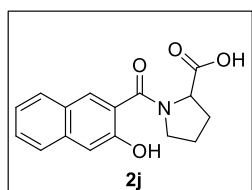
(2-hydroxy-4-methoxybenzoyl)proline (2i):

: 96% white solid; mp: 117-118°C; R_f : 0.4 (1:9, MeOH: DCM).

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.94 (br. s., 1 H), 7.44 (d, $J = 8.6$ Hz, 1 H), 6.46 (d, $J = 2.3$ Hz, 1 H), 6.39 (dd, $J = 2.2, 8.8$ Hz, 1 H), 4.67 (t, $J = 6.5$ Hz, 1 H), 3.83 (d, $J = 6.1$ Hz, 2 H), 3.79 (s, 3 H), 2.40 - 2.26 (m, 1 H), 2.17 - 2.03 (m, 2 H), 1.99 - 1.84 (m, 1 H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 176.7, 170.7, 163.6, 162.7, 129.6, 109.1, 105.9, 101.5, 60.3, 55.3, 51.0, 28.6, 25.8.

HRMS-ESI (m/z) calcd for $(\text{C}_{13}\text{H}_{15}\text{NO}_5 + \text{H})^+$: 266.1023, found: 266.1017.

(3-hydroxy-2-naphthoyl)proline (2j):

: 87% brown solid; mp: 165-166°C; R_f : 0.27 (1:9, MeOH: DCM).

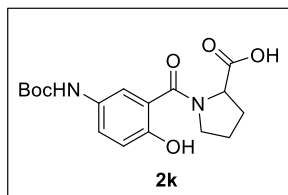
$^1\text{H NMR}$ (400 MHz, $\text{CDCl}_3 + \text{DMSO-d}_6$): δ 9.97 (br. s., 1 H), 7.99 (s, 1 H), 7.76 - 7.59 (m, 2 H), 7.44 (t, $J = 7.3$ Hz, 1 H), 7.34 - 7.24 (m, 2 H),

4.72 (t, $J = 6.8$ Hz, 1 H), 3.96 - 3.74 (m, 2 H), 2.46 - 2.27 (m, 1 H), 2.17 - 2.04 (m, 2 H), 2.03 - 1.85 (m, 1 H).

^{13}C NMR (101 MHz, $\text{CDCl}_3 + \text{DMSO-d}_6$): δ 173.7, 169.2, 154.0, 135.6, 128.7, 128.1, 127.7, 126.7, 125.9, 123.5, 121.1, 111.1, 59.9, 50.3, 29.0, 25.3.

HRMS-ESI (m/z) calcd for $(\text{C}_{16}\text{H}_{15}\text{NO}_4 + \text{H})^+$: 286.1074, found: 286.1072.

(5-((tert-butoxycarbonyl)amino)-2-hydroxybenzoyl)proline (2k):



: 71% White solid; mp: 72-75°C; R_f : 0.1 (1:9, MeOH: DCM).

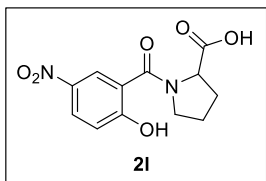
^1H NMR (400 MHz, CDCl_3): δ 7.84 (br. s., 1 H), 7.20 - 7.00 (m, 1 H), 6.91 (d, $J = 8.8$ Hz, 1 H), 6.44 (br. s., 1 H), 4.72 (t, $J = 6.6$ Hz, 1 H), 3.99 - 3.84 (m, 2 H), 2.44 - 2.25 (m, 1 H), 2.21 - 2.10 (m, 2 H),

2.00 - 1.90 (m, 1 H), 1.51 (s, 9 H).

^{13}C NMR (101 MHz, CDCl_3): δ 175.9, 170.2, 155.2, 129.4, 124.4, 119.0, 117.9, 117.0, 80.5, 60.1, 51.0, 28.7, 28.3, 28.2, 25.7, 20.7.

HRMS-ESI (m/z) calcd for $(\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_6 + \text{H})^+$: 351.1551, found: 351.1556.

(2-hydroxy-5-nitrobenzoyl)proline (2l):



: 79% white solid; mp: 208-210°C, R_f : 0.1 (1:9, MeOH: DCM).

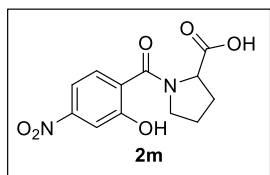
^1H NMR (400 MHz, DMSO- d_6 , mixture of rotamers): δ 12.15 (br. s., 1 H), 8.23 - 8.10 (m, 1 H), 8.02 - 7.83 (m, 1H), 7.09 - 7.00 (m, 1H), 4.46 - 4.36 (m, 0.7 H), 4.22 - 4.12 (m, 0.3 H), 3.62 - 3.50 (m, 0.6 H),

3.42 - 3.28 (m, 1.4), 2.32 - 2.17 (m, 1 H), 2.02 - 1.75 (m, 3 H).

^{13}C NMR (101 MHz, DMSO- d_6 , mixture of rotamers): δ 173.5, 173.1, 165.2, 165.0, 160.1, 159.6, 139.2, 139.1, 126.6, 126.4, 125.4, 125.2, 125.0, 124.3, 116.8, 116.7, 59.4, 58.6, 47.6, 46.2, 30.7, 29.1, 24.3, 22.5.

HRMS-ESI (m/z) calcd for $(\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_6 + \text{H})^+$: 281.0768, found: 281.0768.

(2-hydroxy-4-nitrobenzoyl)proline (2m):



: 91% white solid; mp: 137-138°C; R_f : 0.3 (0.5:9.5, MeOH: DCM).

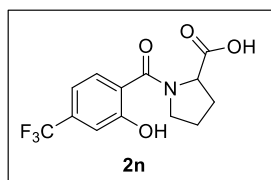
^1H NMR (400 MHz, DMSO- d_6 , mixture of rotamers): δ 12.61 (s, 1 H), 10.94 (s, 1 H), 7.82 - 7.60 (m, 2 H), 7.34 - 7.25 (m, 1 H), 4.47 - 4.11 (m, 1 H), 3.64 - 3.23 (m, 2 H), 2.35 - 2.18 (m, 1 H), 2.05 - 1.75

(m, 3 H).

^{13}C NMR (101 MHz, DMSO- d_6 , mixture of rotamers): δ 173.2, 173.0, 165.6, 165.3, 154.2, 153.7, 148.5, 148.3, 131.2, 131.2, 129.9, 129.1, 114.1, 113.9, 110.5, 110.4, 59.2, 58.4, 47.5, 46.1, 30.7, 29.1, 24.3, 22.4.

HRMS-ESI (m/z) calcd for ($\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_6+\text{H}$) $^+$: 281.0768, found: 281.0777.

(2-hydroxy-4-(trifluoromethyl)benzoyl)proline (2n):



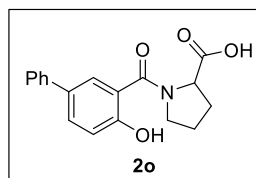
: 93% white solid; mp: 114-115°C; R_f : 0.3 (0.5:9.5, MeOH: DCM).

^1H NMR (400 MHz, DMSO- d_6 , mixture of rotamers): δ 12.5 (br. s, 1 H), 10.7 (br. s, 1 H), 7.46 - 7.01 (m, 3 H), 4.48 - 4.14 (m, 1 H), 3.51 - 3.64 (m, 0.5 H), 3.47 - 3.20 (m, 1.5 H), 2.38 - 2.14 (m, 1 H), 2.07 - 1.77 (m, 3 H).

^{13}C NMR (101 MHz, DMSO- d_6 , mixture of rotamers): δ 173.3, 173.1, 166.1, 165.9, 154.0, 153.3, 131.1, 130.8, 130.6, 130.5, 130.3, 130.2, 129.9, 129.1, 128.8, 128.6, 127.8, 125.1, 122.4, 119.7, 115.7, 115.6, 115.5, 115.5, 112.5, 112.4, 112.3, 112.2, 59.2, 58.5, 47.6, 46.0, 30.7, 29.1, 24.3, 22.4.

HRMS-ESI (m/z) calcd for ($\text{C}_{13}\text{H}_{12}\text{F}_3\text{NO}_4+\text{H}$) $^+$: 304.0791, found: 304.0785.

(4-hydroxy-[1,1'-biphenyl]-3-carbonyl)proline (2o):



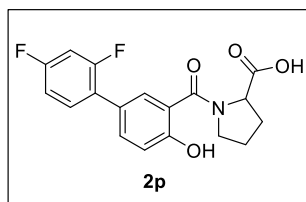
: 91% white solid; mp: 81-82°C; R_f : 0.3 (1:9, MeOH: DCM).

^1H NMR (400 MHz, CDCl_3): δ 9.36 (br. s., 1 H), 7.77 - 7.22 (m, 7 H), 7.11 - 6.78 (m, 1 H), 4.80 - 4.59 (m, 1 H), 3.99 - 3.62 (m, 2 H), 2.45 - 2.27 (m, 1 H), 2.20 - 2.00 (m, 2 H), 1.99 - 1.83 (m, 1 H).

^{13}C NMR (101 MHz, CDCl_3): δ 176.2, 170.4, 158.7, 140.1, 132.3, 132.2, 132.1, 131.8, 131.6, 130.5, 128.8, 128.6, 128.5, 126.9, 126.5, 119.7, 118.2, 117.8, 117.4, 60.0, 51.0, 28.7, 25.7

HRMS-ESI (m/z) calcd for ($\text{C}_{18}\text{H}_{17}\text{NO}_4+\text{H}$) $^+$: 312.1230, found: 312.1221.

(2',4'-difluoro-4-hydroxy-[1,1'-biphenyl]-3-carbonyl)proline (2p):



: 96% white solid; mp: 181-182°C; R_f : 0.3 (0.5:9.5, MeOH: DCM).

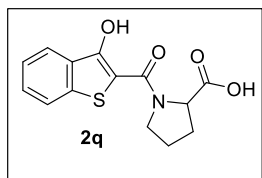
^1H NMR (400 MHz, CDCl_3): δ 10.52 (br. s., 1 H), 7.68 (s, 1 H), 7.48 (d, J = 8.5 Hz, 1 H), 7.39 - 7.30 (m, 1 H), 7.07 (d, J = 8.5 Hz, 1 H), 6.99 - 6.85 (m, 2 H), 6.30 (br. s., 1 H), 4.74 (t, J = 6.7 Hz, 1 H), 4.01 - 3.80 (m, 2 H), 2.46 - 2.31 (m, 1 H), 2.25 - 2.07 (m, 2 H),

2.04 - 1.90 (m, 1 H)

^{13}C NMR (101 MHz, CDCl_3): δ 176.3, 170.4, 163.3, 160.9, 160.8, 159.5, 158.3, 133.6, 131.0, 130.9, 130.9, 128.8, 125.1, 124.3, 118.2, 111.8, 111.6, 104.7, 104.4, 104.2, 60.1, 51.1, 28.7, 25.8.

HRMS-ESI (m/z) calcd for $(\text{C}_{18}\text{H}_{15}\text{F}_2\text{NO}_4+\text{H})^+$: 348.1042, found: 348.1032.

(3-hydroxybenzo[*b*]thiophene-2-carbonyl)proline (2q):



: 90% white solid; mp: 185°C; R_f : 0.4 (0.5:9.5, MeOH: DCM).

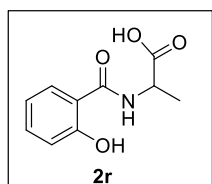
^1H NMR (400 MHz, CDCl_3): δ 12.70 (br. s., 1 H), 8.00 (d, J = 8.0 Hz, 1 H), 7.73 (d, J = 8.1 Hz, 1 H), 7.51 (t, J = 7.4 Hz, 1 H), 7.42 (t, J = 7.5 Hz, 1 H), 6.08 (br. s., 1 H), 4.81 (s, 1 H), 4.19 - 3.85 (m, 2 H),

2.47 - 2.04 (m, 4 H).

^{13}C NMR (101 MHz, CDCl_3): δ 174.0, 167.9, 161.9, 138.4, 130.6, 128.8, 124.6, 123.2, 122.4, 100.8, 60.6, 47.8, 27.9, 25.2.

HRMS-ESI (m/z) calcd for $(\text{C}_{14}\text{H}_{14}\text{NO}_4\text{S}+\text{H})^+$: 292.0638, found: 292.0642.

(2-hydroxybenzoyl) alanine (2r):



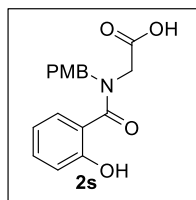
: 93% white solid; mp: 135-136°C; R_f : 0.3 (0.5:9.5, MeOH: DCM).

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 8.98 (d, J = 6.9 Hz, 1 H), 7.94 (dd, J = 1.3, 7.9 Hz, 1 H), 7.43 - 7.35 (m, 1 H), 6.95 - 6.86 (m, 2 H), 4.47 (quint., J = 7.1 Hz, 1 H), 1.42 (d, J = 7.3 Hz, 3 H).

^{13}C NMR (101 MHz, $\text{DMSO}-d_6$): δ 174.0, 168.1, 159.6, 133.8, 128.6, 118.8, 117.4, 115.6, 48.2, 17.2.

HRMS-ESI (m/z) calcd for $(\text{C}_{10}\text{H}_{11}\text{NO}_4+\text{H})^+$: 210.0761, found: 210.0785.

***N*-(2-hydroxybenzoyl)-*N*-(4-methoxybenzyl)glycine (2s):**

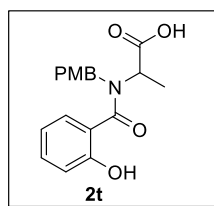


: 89% white solid mp: 172-173°C; R_f : 0.3 (0.5:9.5, MeOH: DCM).

^1H NMR (400 MHz, $\text{DMSO}-d_6$, mixture of rotamers): δ 7.37 - 6.99 (m, 4 H), 6.97 - 6.73 (m, 4 H), 4.66 (s, 1 H), 4.34 (s, 1 H), 3.89 (s, 1 H), 3.81 - 3.57 (m, 4 H).

^{13}C NMR (101 MHz, $\text{DMSO}-d_6$, mixture of rotamers): δ 170.5, 170.1, 169.5, 169.4, 158.7, 158.5, 153.4, 152.8, 130.3, 129.2, 129.0, 128.9, 128.1, 127.9, 123.8, 123.7, 119.1, 115.9, 115.6, 113.9, 55.1, 54.9, 52.0, 48.8, 47.6, 45.3.

HRMS-ESI (m/z) calcd for $(\text{C}_{17}\text{H}_{17}\text{NO}_5+\text{H})^+$: 316.1179, found: 316.1180.

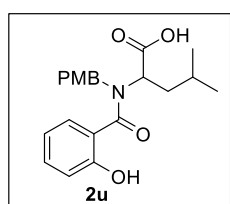
***N*-(2-hydroxybenzoyl)-*N*-(4-methoxybenzyl)alanine (2t):**

: 88% white solid; mp: 125-126°C; R_f : 0.2 (0.5:9.5, MeOH: DCM).

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.38 - 7.28 (m, 4 H), 7.00 (d, J = 8.3 Hz, 1 H), 6.95 (d, J = 8.1 Hz, 2 H), 6.77 (t, J = 7.4 Hz, 1 H), 4.87 - 4.77 (m, 1 H), 4.19 - 4.08 (m, 1 H), 4.66 (s, 1 H), 3.83 (s, 3 H), 1.56 (d, J = 6.8 Hz, 3 H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 176.2, 172.8, 159.2, 157.8, 136.3, 132.8, 130.9, 128.2, 127.3, 119.1, 118.0, 114.4, 56.4, 55.3, 53.6, 14.5.

HRMS-ESI (m/z) calcd for $(\text{C}_{18}\text{H}_{19}\text{NO}_5 + \text{H})^+$: 330.1336, found: 330.1331.

***N*-(2-hydroxybenzoyl)-*N*-(4-methoxybenzyl)leucine (2u):**

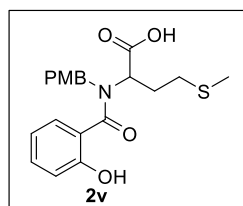
: 93% white solid; mp: 67-68°C; R_f : 0.2 (0.5:9.5, MeOH: DCM).

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 9.57 (s, 1 H), 7.43 - 7.37 (m, 1 H), 7.35 - 7.28 (m, 3 H), 6.99 (d, J = 8.3 Hz, 1 H), 6.90 (d, J = 8.5 Hz, 2 H), 6.84 (t, J = 7.4 Hz, 1 H), 4.79 (d, J = 15.8 Hz, 1 H), 4.57 (d, J = 15.8 Hz, 1 H),

4.31 - 4.04 (m, 1 H), 3.80 (s, 3 H), 2.32 - 1.96 (m, 1 H), 1.75 - 1.53 (m, 2 H), 0.89 - 0.65 (m, 6 H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 176.1, 173.1, 159.2, 157.5, 132.7, 129.0, 127.6, 119.3, 118.4, 118.0, 114.2, 68.2, 59.2, 55.3, 38.6, 25.2, 22.2.

HRMS-ESI (m/z) calcd for $(\text{C}_{21}\text{H}_{25}\text{NO}_5 + \text{H})^+$: 372.1805, found: 372.1807.

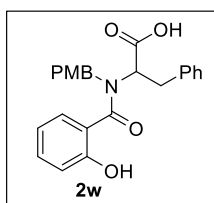
***N*-(2-hydroxybenzoyl)-*N*-(4-methoxybenzyl)methionine (2v):**

: 91% white solid; mp: 60-61°C; R_f : 0.3 (0.5:9.5, MeOH: DCM).

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.13 (br. s., 1 H), 7.41 - 7.20 (m, 4 H), 7.00 - 6.72 (m, 4 H), 4.84 - 4.43 (m, 2 H), 4.35 - 4.00 (m, 1 H), 3.89 (m, 3 H), 2.46 (br. s, 2 H), 2.10 (d, J = 6.3 Hz, 1 H), 2.18 - 1.84 (m, 3 H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 175.1, 173.0, 159.4, 157.4, 132.8, 129.2, 127.6, 119.4, 118.3, 118.1, 118.0, 114.3, 59.2, 55.3, 31.4, 29.7, 28.9, 15.1.

HRMS-ESI (m/z) calcd for $(\text{C}_{20}\text{H}_{23}\text{NO}_5\text{S} + \text{H})^+$: 390.1370, found: 390.1369.

***N*-(2-hydroxybenzoyl)-*N*-(4-methoxybenzyl)phenylalanine (2w):**

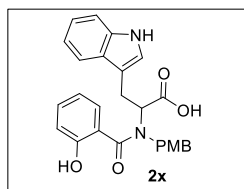
: 95% white solid; mp: 60-61°C; R_f : 0.4 (0.5:9.5, MeOH: DCM).

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.31 (br. s, 1 H), 7.35 - 7.29 (m, 4 H), 7.15 (d, J = 7.4 Hz, 3 H), 7.06 - 6.96 (m, 3 H), 6.86 - 6.76 (m, 3 H), 4.63 (d, J = 15.8 Hz, 1 H), 4.07 (br. s., 1 H), 3.89 - 3.72 (m, 4 H), 3.57 - 3.33 (m, 2 H).

^{13}C NMR (101 MHz, CDCl_3): δ 174.7, 172.8, 159.3, 158.0, 137.6, 136.6, 132.8, 129.4, 129.4, 128.8, 127.6, 127.0, 119.1, 118.3, 118.3, 114.2, 61.6, 55.3, 34.8, 22.3.

HRMS-ESI (m/z) calcd for $(\text{C}_{24}\text{H}_{23}\text{NO}_5+\text{H})^+$: 406.1649, found: 406.1656.

N^α -(2-hydroxybenzoyl)- N^α -(4-methoxybenzyl)tryptophan (2x):



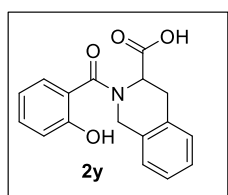
: 93% white solid; mp: 114-115°C; R_f : 0.3 (0.5:9.5, MeOH: DCM).

^1H NMR (400 MHz, CDCl_3): δ 8.20 (s, 1 H), 7.44 - 7.33 (m, 2 H), 7.27 - 7.16 (m, 1 H), 7.12 - 6.82 (m, 6 H), 6.71 (d, J = 8.1 Hz, 3 H), 4.56 (d, J = 15.5 Hz, 1 H), 4.27 (s, 1 H), 3.87 - 3.77 (m, 1 H), 3.95 - 3.78 (m, 1 H), 3.74 (s, 3 H), 3.73 - 3.55 (m, 2 H).

^{13}C NMR (101 MHz, CDCl_3): δ 174.5, 172.5, 172.5, 159.0, 156.2, 136.2, 132.2, 130.8, 129.4, 127.4, 127.1, 123.9, 122.0, 119.4, 118.3, 117.6, 113.8, 111.4, 111.0, 110.9, 60.4, 55.1, 34.1, 24.8.

HRMS-ESI (m/z) calcd for $(\text{C}_{26}\text{H}_{24}\text{N}_2\text{O}_5+\text{H})^+$: 445.1758, found: 445.1753.

2-(2-hydroxybenzoyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (2y):



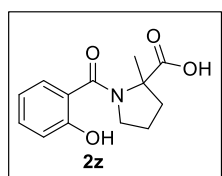
: 99%, white solid; mp: 185-186°C, R_f : 0.25 (5:5, MeOH: DCM).

^1H NMR (400 MHz, CDCl_3 +DMSO- d_6 , mixture of rotamers): δ = 7.25 - 7.08 (m, 6 H), 6.96 - 6.75 (m, 2 H), 5.37 - 5.0 (m, 1 H), 4.58 - 4.38 (m, 2 H), 3.28 - 3.09 (m, 2 H).

^{13}C NMR (101 MHz, CDCl_3 +DMSO- d_6 , mixture of rotamers): δ 170.7, 170.5, 167.5, 167.4, 152.0, 151.8, 131.5, 131.0, 130.6, 130.1, 128.8, 128.7, 126.7, 126.7, 126.5, 126.2, 125.0, 124.8, 124.7, 124.6, 124.1, 121.9, 117.6, 117.5, 114.4, 114.3, 54.0, 49.8, 44.6, 41.1, 29.8, 28.9.

HRMS-ESI (m/z) calcd for $(\text{C}_{17}\text{H}_{15}\text{NO}_4+\text{H})^+$: 298.1074, found: 298.1071.

1-(2-hydroxybenzoyl)-2-methylpyrrolidine-2-carboxylic acid (2z):

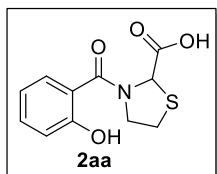


: 94%, white solid; mp: 157-158°C; R_f : 0.37 (1:9, MeOH: DCM);

^1H NMR (400 MHz, DMSO- d_6): δ 7.26 - 7.17 (m, 1 H), 7.14 - 7.07 (m, 1 H), 6.90 - 6.79 (m, 2 H), 3.52 - 3.43 (m, 1 H), 3.36 - 3.27 (m, 1 H), 2.15 - 2.05 (m, 1 H), 1.93 - 1.78 (m, 3 H), 1.53 (s, 3 H).

^{13}C NMR (101 MHz, DMSO- d_6): δ 175.0, 166.8, 153.8, 130.4, 127.7, 124.6, 118.9, 116.0, 65.0, 48.9, 38.6, 23.6, 21.5.

HRMS-ESI (m/z) calcd for $(\text{C}_{13}\text{H}_{15}\text{NO}_4+\text{H})^+$: 250.1074, found: 250.1077.

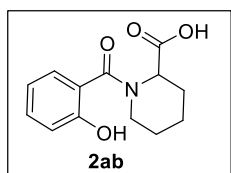
3-(2-hydroxybenzoyl)thiazolidine-2-carboxylic acid (2aa):

: 93% white solid; mp: 114-115°C; R_f : 0.3 (0.5:9.5, MeOH: DCM).

$^1\text{H NMR}$ (400 MHz, DMSO- d_6 , mixture of rotamers): δ 10.06 (br. s., 1 H), 7.39 - 6.70 (m, 4 H), 5.58 - 4.92 (m, 1 H), 4.34 - 3.51 (m, 2 H), 3.29 - 2.93 (m, 2 H)

$^{13}\text{C NMR}$ (101 MHz, DMSO- d_6 , mixture of rotamers): δ 171.1, 167.1, 161.2, 153.5, 135.6, 131.0, 130.3, 128.2, 124.0, 119.2, 117.1, 116.0, 60.0, 59.8, 59.2, 54.9, 50.7, 48.5, 30.5, 29.3

HRMS-ESI (m/z) calcd for ($\text{C}_{11}\text{H}_{11}\text{NO}_4 + \text{H}$) $^+$: 254.0482, found: 254.0479.

1-(2-hydroxybenzoyl)piperidine-2-carboxylic acid (2ab):

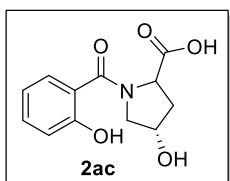
: 95% white solid; mp: 172-173°C; R_f : 0.58 (2.5:7.5, MeOH: DCM).

$^1\text{H NMR}$ (400 MHz, DMSO- d_6 , mixture of rotamer): δ 12.75 (br. s, 1 H), 9.79 (br. s, 1 H), 7.21 (t, $J = 7.4$ Hz, 1 H), 7.05 (t, $J = 7.3$ Hz, 1 H), 6.92 - 6.76 (m, 2 H), 5.21 (s, 0.6 H), 4.45 (s, 0.4 H), 4.14 (s, 0.3 H), 3.33

(d, $J = 12.8$ Hz, 0.7 H), 3.09 (t, $J = 12.2$ Hz, 0.6 H), 2.82 (t, $J = 12.1$ Hz, 0.4 H), 2.25 - 1.98 (m, 1 H), 1.76 - 1.46 (m, 3 H), 1.47 - 1.18 (m, 2 H).

$^{13}\text{C NMR}$ (101 MHz, DMSO- d_6 , mixture of rotamer): δ 172.4, 172.3, 168.3, 153.3, 153.0, 130.1, 128.0, 127.9, 124.0, 119.1, 115.7, 57.0, 51.3, 44.5, 38.6, 27.3, 26.5, 25.0, 24.4, 20.9

HRMS-ESI (m/z) calcd for ($\text{C}_{13}\text{H}_{15}\text{NO}_4 + \text{H}$) $^+$: 250.1074, found: 250.1070.

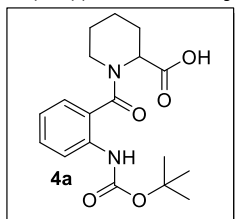
(4S)-4-hydroxy-1-(2-hydroxybenzoyl)pyrrolidine-2-carboxylic acid (2ac):

: 93% white solid; mp: 114-115°C; R_f : 0.3 (0.5:9.5, MeOH: DCM).

$^1\text{H NMR}$ (400 MHz, DMSO- d_6): δ 7.32 - 7.11 (m, 2 H), 6.96 - 6.77 (m, 2 H), 4.46 (t, $J = 7.8$ Hz, 1 H), 4.37 - 4.14 (m, 2 H), 3.67 - 3.54 (m, 1 H), 3.23 - 3.13 (m, 1 H), 2.22 - 2.07 (m, 1 H), 2.06 - 1.92 (m, 1 H).

$^{13}\text{C NMR}$ (101 MHz, DMSO- d_6): δ 174.5, 168.1, 155.1, 131.1, 128.0, 123.1, 118.7, 116.4, 68.7, 56.4, 48.7, 37.6.

HRMS-ESI (m/z) calcd for ($\text{C}_{12}\text{H}_{13}\text{NO}_5 + \text{H}$) $^+$: 252.0866, found: 252.0865.

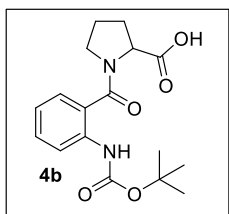
1-(2-((tert-butoxycarbonyl)amino)benzoyl)piperidine-2-carboxylic acid (4a):

: 97% white solid; mp: 76-77°C; R_f : 0.67 (0.5:9.5, MeOH: DCM).

^1H NMR (400 MHz, CDCl_3): δ 9.67 (br. s., 1 H), 8.10 - 8.01 (m, 1 H), 7.57 (s, 1 H), 7.38 - 7.34 (m, 1 H), 7.29 - 7.20 (m, 1 H), 7.05 (t, J = 7.2 Hz, 1 H), 5.56 (s, 1 H), 3.60 (d, J = 12.8 Hz, 1 H), 3.27 - 3.09 (m, 1 H), 2.40 (d, J = 12.5 Hz, 1 H), 1.86 - 1.55 (m, 3 H), 1.49 (s, 9 H), 1.41 - 1.37 (m, 2 H).

^{13}C NMR (101 MHz, CDCl_3): δ 172.4, 172.3, 168.3, 153.3, 153.0, 130.1, 128.0, 127.9, 124.0, 119.1, 115.7, 57.0, 51.3, 25.0, 24.4, 20.9.

HRMS-ESI (m/z) calcd for ($\text{C}_{18}\text{H}_{24}\text{N}_2\text{O}_5 + \text{H}$) $^+$: 349.1758, found: 349.1751.

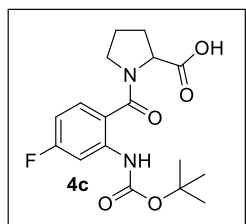
(2-((tert-butoxycarbonyl)amino)benzoyl)proline (4b):

: 94% white solid; mp: 137-138°C; R_f : 0.3 (0.5:9.5, MeOH: DCM).

^1H NMR (400 MHz, $\text{DMSO}-d_6$, mixture of rotamers): δ 8.71 (s, 1 H), 7.81 (d, J = 8.3 Hz, 0.7 H), 7.63 (d, J = 8.3 Hz, 0.3 H), 7.43 - 7.23 (m, 2 H), 7.15 - 7.03 (m, 1 H), 4.44 - 4.35 (m, 1 H), 3.65 - 3.48 (m, 1 H), 3.58 - 3.34 (m, 2 H), 2.34 - 2.21 (m, 1 H), 2.00 - 1.77 (m, 3 H), 1.44 (s, 9 H).

^{13}C NMR (101 MHz, $\text{DMSO}-d_6$, mixture of rotamers): δ 173.9, 173.4, 168.5, 167.5, 152.7, 152.6, 136.1, 135.8, 130.2, 130.0, 128.1, 127.4, 126.8, 126.1, 122.9, 122.5, 122.0, 120.7, 79.6, 79.5, 61.0, 58.7, 49.4, 46.2, 30.8, 29.1, 28.0, 24.9, 22.4.

LC-MS (m/z) calcd for ($\text{C}_{17}\text{H}_{22}\text{F}_3\text{N}_2\text{O}_5 + \text{H}$) $^+$: 335.

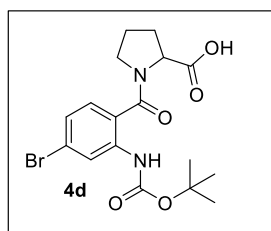
(2-((tert-butoxycarbonyl)amino)-4-fluorobenzoyl)proline (4c):

: 93% white solid; mp: 77-78°C; R_f : 0.37 (0.5:9.5, MeOH: DCM).

^1H NMR (400 MHz, CDCl_3 , mixture of rotamers): δ 8.51 (s, 1 H), 8.00 (d, J = 11.4 Hz, 1 H), 7.33 (t, J = 7.3 Hz, 1 H), 6.89 (br. s., 1 H), 6.75 - 6.68 (m, 1 H), 4.71 (t, J = 7.3 Hz, 1 H), 3.63 - 3.45 (m, 2 H), 2.46 - 2.33 (m, 1 H), 2.21 - 2.09 (m, 1 H), 2.07 - 1.98 (m, 1 H), 1.97 - 1.84 (m, 1 H), 1.49 (s, 9 H).

^{13}C NMR (101 MHz, CDCl_3 , mixture of rotamers): δ 176.2, 168.7, 164.1 (d, $J_{\text{C-F}}$ = 248.7 Hz), 152.7, 139.7, 129.1 (d, $J_{\text{C-F}}$ = 10.7 Hz), 118.7, 108.8 (d, $J_{\text{C-F}}$ = 22.1 Hz), 107.6 (d, $J_{\text{C-F}}$ = 28.3 Hz), 81.0, 59.2, 50.3, 31.6, 29.1, 28.2, 25.4, 22.6, 14.1.

HRMS-ESI (m/z) calcd for ($\text{C}_{17}\text{H}_{21}\text{FN}_2\text{O}_5\text{Na}$) $^+$: 375.1327, found: 375.1315.

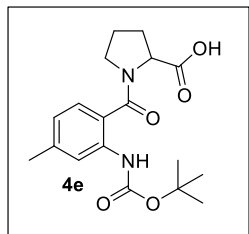
(4-bromo-2-((tert-butoxycarbonyl)amino)benzoyl)proline (4d):

: 85% white solid; mp: 102°C; R_f : 0.58 (0.5:9.5, MeOH: DCM)

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.42 (s, 1 H), 8.33 (s, 1 H), 7.23 - 7.14 (m, 2 H), 4.71 (dd, J = 6.6, 8.1 Hz, 1 H), 3.62 - 3.42 (m, 2 H), 2.46 - 2.32 (m, 1 H), 2.21 - 2.09 (m, 1 H), 2.08 - 1.98 (m, 1 H), 1.95 - 1.84 (m, 1 H), 1.49 (s, 9 H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 176.0, 168.6, 152.7, 138.5, 128.4, 127.8, 125.5, 124.9, 123.1, 81.1, 59.2, 50.2, 29.1, 28.2, 25.3.

HRMS-ESI (m/z) calcd for $(\text{C}_{17}\text{H}_{21}\text{BrN}_2\text{O}_5\text{Na})^+$: 435.0526, found: 435.0515.

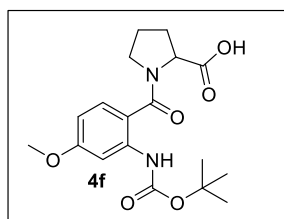
(2-((tert-butoxycarbonyl)amino)-4-methylbenzoyl)proline (4e):

: 83% white solid; mp: 78-79°C; R_f : 0.3 (0.5:9.5, MeOH: DCM).

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 9.44 (s, 1 H), 8.31 (s, 1 H), 7.96 (s, 1 H), 7.22 (d, J = 7.8 Hz, 1 H), 6.82 (d, J = 7.8 Hz, 1 H), 4.69 (t, J = 7.2 Hz, 1 H), 3.63 - 3.43 (m, 2 H), 2.34 (s, 4 H), 2.16 - 2.05 (m, 1 H), 2.03 - 1.93 (m, 1 H), 1.91 - 1.80 (m, 1 H), 1.47 (s, 9 H)

$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 176.3, 169.5, 153.1, 141.7, 137.1, 127.3, 122.6, 120.8, 120.6, 80.3, 59.1, 50.1, 29.1, 28.2, 25.2, 21.7

HRMS-ESI (m/z) calcd for $(\text{C}_{18}\text{H}_{24}\text{N}_2\text{O}_5+\text{H})^+$: 349.1758, found: 349.1758.

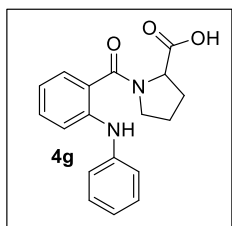
(2-((tert-butoxycarbonyl)amino)-4-methoxybenzoyl)proline (4f):

: 89% white solid; mp: 94-95°C; R_f : 0.3 (0.5:9.5, MeOH: DCM).

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.70 (s, 1 H), 7.80 (s, 1 H), 6.52 (dd, J = 2.0, 8.5 Hz, 1 H), 4.68 (t, J = 6.8 Hz, 1 H), 3.83 (s, 3 H), 3.68 - 3.42 (m, 2 H), 2.34 (s, 1 H), 2.19 - 2.09 (m, 1 H), 2.05 - 1.93 (m, 1 H), 1.91 - 1.80 (m, 1 H), 1.49 (s, 9 H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 176.3, 169.7, 161.9, 153.1, 139.7, 129.1, 115.1, 108.3, 104.6, 80.6, 59.7, 55.4, 50.6, 29.1, 28.3, 25.5.

HRMS-ESI (m/z) calcd for $(\text{C}_{18}\text{H}_{24}\text{N}_2\text{O}_6+\text{H})^+$: 365.1707, found: 365.1696.

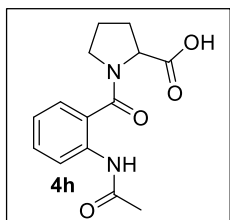
(2-(phenylamino)benzoyl)proline (4g):

: 93% white solid; mp: 77-78°C; R_f : 0.37 (0.5:9.5, MeOH: DCM)

$^1\text{H NMR}$ (400 MHz, CDCl_3 , mixture of rotamer): δ 7.43 - 7.30 (m, 3 H), 7.26 - 7.17 (m, 3 H), 7.17 - 7.07 (m, 2 H), 6.96 - 6.81 (m, 2 H), 4.74 (t, J = 6.6 Hz, 1 H), 3.70 - 3.48 (m, 2 H), 2.38 - 2.26 (m, 1 H), 2.19 - 2.03 (m, 1 H), 2.03 - 1.79 (m, 2 H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3 , mixture of rotamer): δ 174.9, 170.3, 168.6, 165.4, 142.0, 141.7, 141.1, 140.3, 131.9, 130.8, 130.2, 130.1, 129.3, 129.2, 128.2, 128.1, 127.5, 125.7, 125.2, 123.1, 121.5, 119.2, 119.0, 116.1, 59.1, 57.6, 49.7, 46.9, 29.0, 26.7, 25.0, 23.7.

HRMS-ESI (m/z) calcd for ($\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_3+\text{H}$) $^+$: 311.1390, found: 311.1386.

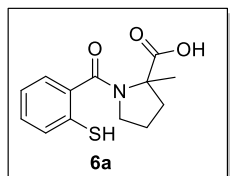
(2-acetamidobenzoyl)proline (4h):

: 90% white solid; mp: 114-115°C; R_f : 0.3 (0.5:9.5, MeOH: DCM).

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.94 (s, 1 H), 8.20 (d, J = 8.4 Hz, 1 H), 7.41 (t, J = 7.8 Hz, 1 H), 7.32 (d, J = 7.4 Hz, 1 H), 7.14 (t, J = 7.5 Hz, 1 H), 5.46 (br. s, 1 H), 4.70 (dd, J = 5.3, 8.5 Hz, 1 H), 3.56 - 3.34 (m, 2 H), 2.42 - 2.30 (m, 1 H), 2.17 - 2.13 (m, 3 H), 2.01 - 1.89 (m, 2 H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 174.6, 170.0, 169.3, 135.4, 130.9, 126.5, 125.8, 123.8, 122.5, 59.1, 49.7, 29.3, 25.0, 24.3.

HRMS-ESI (m/z) calcd for ($\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_4+\text{H}$) $^+$: 277.1183, found: 277.1178.

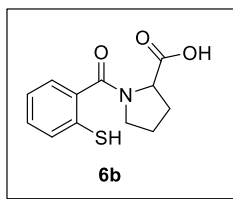
1-(2-mercaptobenzoyl)-2-methylpyrrolidine-2-carboxylic acid (6a):

: 34% yellow liq.; R_f : 0.48 (7:3, ethyl : petroleum ether).

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.37 - 7.32 (m, 1 H), 7.31 - 7.26 (m, 2 H), 7.26 - 7.19 (m, 1 H), 5.18 (br. s., 1 H), 3.49 - 3.24 (m, 2 H), 2.60 - 2.46 (m, 1 H), 2.03 - 1.89 (m, 3 H), 1.81 (s, 3 H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 176.0, 169.5, 136.3, 130.6, 129.7, 128.3, 126.7, 126.0, 67.0, 50.4, 38.7, 23.8, 21.6.

HRMS-ESI (m/z) calcd for ($\text{C}_{13}\text{H}_{15}\text{NO}_3\text{S}-\text{H}$) $^-$: 266.0845, found: 266.0842.

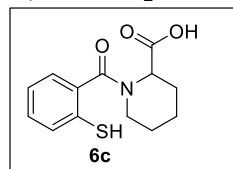
(2-mercaptobenzoyl)proline (6b):

: 93% white solid; mp: 114-115°C; R_f : 0.3 (0.5:9.5, MeOH:DCM).

$^1\text{H NMR}$ (400 MHz, CDCl_3 , mixture of rotamers): δ 8.10 - 7.95 (m, 1 H), 7.34 - 7.22 (m, 3 H), 4.82 - 4.68 (m, 1 H), 3.80 (d, J = 5.9 Hz, 1 H), 3.54 - 3.39 (m, 1 H), 3.39 - 3.18 (m, 1 H), 2.36 - 2.19 (m, 2 H), 2.01 - 1.87 (m, 2 H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3 , mixture of rotamers): δ 174.3, 169.7, 167.0, 137.2, 136.7, 135.6, 131.5, 131.2, 130.3, 130.2, 129.7, 129.2, 129.0, 127.9, 126.9, 125.6, 63.6, 58.9, 48.9, 47.2, 29.1, 26.4, 24.7, 22.7.

HRMS-ESI (m/z) calcd for $(\text{C}_{12}\text{H}_{13}\text{NO}_3\text{S}+\text{H})^+$: 266.0885, found: 266.0891.

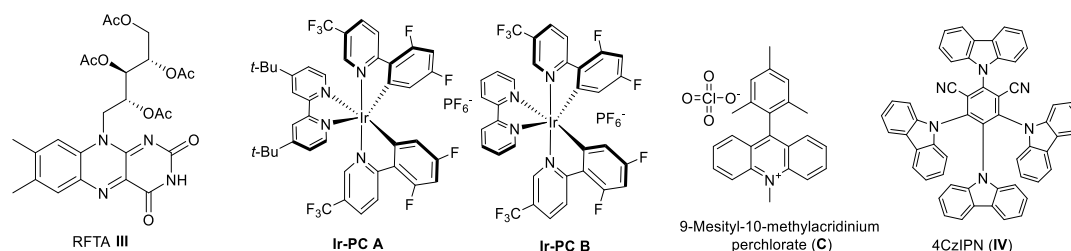
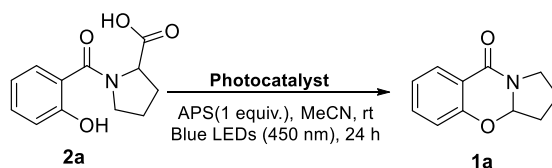
1-(2-mercaptobenzoyl)piperidine-2-carboxylic acid (6c):

59% yellow semi solid; R_f : 0.36 (0.5:9.5, MeOH:DCM).

$^1\text{H NMR}$ (400 MHz, CDCl_3 , mixture of rotamer): δ 7.35 - 7.18 (m, 4 H), 5.57 (s, 1 H), 4.70 (d, J = 12.5 Hz, 0.35 H), 4.22 (br. s., 0.5 H), 3.86 - 3.69 (m, 0.25 H), 3.53 - 2.78 (m, 2 H), 2.49 - 2.13 (m, 1 H), 1.95 - 1.30 (m, 5 H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3 , mixture of rotamer): δ 175.0, 170.5, 169.6, 130.8, 130.1, 130.0, 129.5, 129.4, 127.5, 126.9, 126.7, 126.2, 125.6, 125.6, 124.6, 58.0, 52.0, 45.5, 39.7, 27.6, 26.4, 25.2, 24.5, 21.0, 20.9.

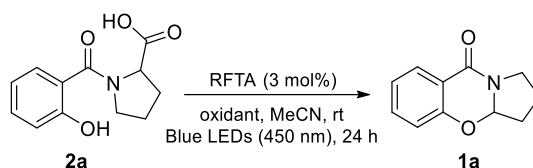
HRMS-ESI (m/z) calcd for $(\text{C}_{13}\text{H}_{15}\text{NO}_3\text{S}-\text{H})^-$: 264.0685, found: 264.0673.

4.6.1 Optimization of reaction conditions**Table 6. Photocatalyst optimization^a****Figure 2. The chemical structure of the photocatalysts used in this work.**

Sr.no.	Photocatalysts	Yield (%) ^b
1	Rhodamine 6G	ND
2	Rosebengal	ND
3	Methylene blue	ND
4	4CzIPN	7
5	Mes-Acr-Me•ClO ₄	19
6	RFTA	65
7	Ir-PC A	ND
8	Ir-PC B	ND

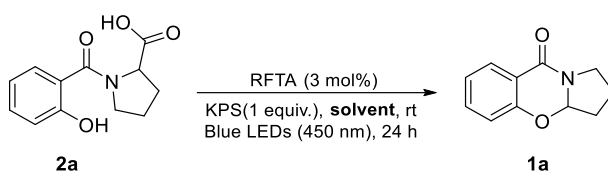
^a**Reaction conditions:** **2a** (0.25 mmol), (NH₄)₂S₂O₈ (1 equiv.), Photocatalyst (3 mol% in MeCN(2 mL), Blue LEDs (30 W, 450 nm) for 24 h at room temperature (rt). ^bisolated yield. ND = Not detected

Table 7. Oxidant optimization^a



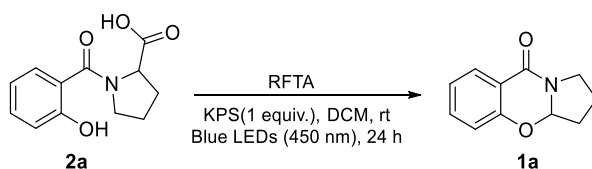
Sr.no.	Photocatalysts	Yield (%) ^b
1	NaClO ₂	trace
2	NaIO ₄	trace
3	(NH ₄) ₂ S ₂ O ₈	65
4	Na ₂ S ₂ O ₈	70
5	K₂S₂O₈	72
6	DTBP	23
7	Chloranil	46
8	PhI(OAc) ₂	48
9	Benzoyl peroxide (BzO) ₂ .	-
10	BQ	-
11	DDQ	-

^a**Reaction conditions:** **2a** (0.25 mmol), **Oxidant**, RFTA (3 mol%) in MeCN (2 mL), Blue LEDs (30 W, 450 nm) for 24 h at room temperature (rt). ^bisolated yield.

Table 8. Optimization of Solvents^a

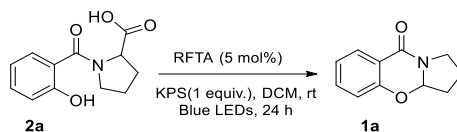
Sr.no.	Solvents	Yield (%) ^b
1	1,4-Dioxane	49
2	DMSO	11
3	DMF	6
4	MeCN	72
5	H ₂ O	ND
6	MeOH	44
7	DCM	79
8	DCE	67
9	Toluene	11
10	Acetone	54

^a**Reaction conditions:** 2a (0.25 mmol), K₂S₂O₈ (1 equiv.), RFTA (3 mol%), **solvent**, Blue LEDs (30 W, 450 nm) for 24 h at room temperature (rt). ^bisolated yield. ND = Not detected

Table 9. Optimization of Mole percent of PC ^a

Sr.no.	PC mol %	Yield (%) ^b
1	0.25	27
2	0.5	37
3	1	53
4	2	27
5	3	79
6	5	90
7	10	59

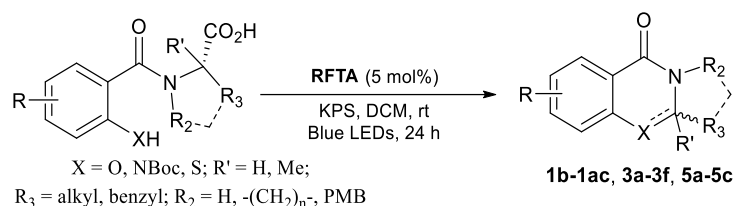
^a**Reaction conditions:** 2a (0.25 mmol), K₂S₂O₈ (1 equiv.), RFTA in DCM (2 mL), Blue LEDs (30 W, 450 nm) for 24 h at room temperature (rt). ^bisolated yield.

Table 10. Light source optimization^a

Sr.no.	Light source	Yield (%) ^b
1	420 nm	34
2	450 nm	90
3	50 W blue LED	67
4	25 W CFL	27
5	30 W green LED	trace

^a**Reaction conditions:** 2a (0.25 mmol), K₂S₂O₈ (1 equiv.), RFTA (5 mol%) in DCM (2 mL), Light source, for 24 h at room temperature (rt). ^bisolated yield

[G] General procedure-IV: Synthesis of 1a-1ac, 3a-3f, 5a-5c



An oven dried schlenk tube containing a stirring bar, RFTA (5 mol%), K₂S₂O₈ (1 equiv.) and salicylic acid derivatives **2a-2ac**, **4a-4f**, **6a-6c** (1 equiv.) was evacuated well, flushed and refilled with argon. Anhydrous DCM was added via syringe and the reaction mixture was stirred under irradiation of 30 W blue LEDs (approximately 5 cm away from the light source) over 24-65 h at room temperature. After completion of reaction, the mixture was diluted with ethyl acetate and washed with saturated aqueous NaHCO₃ solution. The aqueous phase was extracted with ethyl acetate three times and the combined organic phase was washed with brine. The united

organic phases were dried over anhydrous Na₂SO₄. The solvent was evaporated under reduced

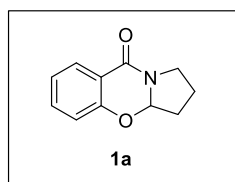
pressure and the crude product was purified by silica gel column chromatography using ethyl acetate and petroleum ether as eluents to obtain the products **1a-1ac**, **3a-3f**, and **5a-5c** in moderate to excellent yields.

The analytical and spectral data of the known compounds **1a-1c**, **1g**, **1i**, **1o**, **1r**, **1t**, **3a-3f**, **5c** are in agreement with the reported data.^[11, 13, 23-27]

(H) Typical experimental procedure for the synthesis of representative compound 1a:

An oven dried schlenk tube containing a stirring bar, RFTA (6.94 mg, 0.0127 μmol 5 mol%), $\text{K}_2\text{S}_2\text{O}_8$ (68.93 mg, 0.25 mmol, 1 equiv.) and salicylic acid (**2a**, 60 mg, 0.25 mmol, 1 equiv.) was evacuated well, flushed and refilled with argon. Anhydrous DCM was added via syringe and the reaction mixture was stirred under irradiation of 30 W blue LEDs (approximately 5 cm away from the light source) over 24 h at room temperature. After completion of reaction, the mixture was diluted with ethyl acetate and washed with saturated aqueous NaHCO_3 solution. The aqueous phase was extracted with ethyl acetate (5 mL x 3) three times and the combined organic phase was washed with brine. The united organic phases were dried over anhydrous Na_2SO_4 . The solvent was evaporated under reduced pressure and the crude product was purified by silica gel column chromatography using ethyl acetate and petroleum ether as eluents to obtain compound **1a** in 90% yield (43.4 mg).

1,2,3,3a-tetrahydro-9H-benzo[e]pyrrolo[2,1-b][1,3]oxazin-9-one (1a**)^[11]:**



: 90% (43.4 mg from 60 mg of **2a**) thick oil; R_f : 0.3 (2:8, ethyl acetate: petroleum ether).

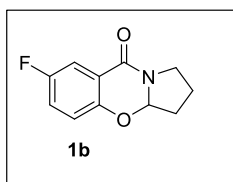
^1H NMR (400 MHz, CDCl_3): δ 7.92 (dd, $J = 1.6, 7.8$ Hz, 1 H), 7.44 - 7.36 (m, 1 H), 7.13 - 7.05 (m, 1 H), 6.95 (d, $J = 8.1$ Hz, 1 H), 5.48 (t, $J = 5.8$ Hz, 1 H), 3.90 - 3.78 (m, 1 H), 3.63 - 3.58 (m, 1 H), 2.47 - 2.37 (m, 1 H), 2.28 - 2.18 (m, 1 H), 2.13 - 2.06 (m, 1 H), 1.99 - 1.87 (m, 1 H).

^{13}C NMR (101 MHz, CDCl_3): δ 160.8, 157.2, 133.6, 127.8, 122.5, 119.6, 116.3, 88.3, 44.2, 31.8, 21.2.

HRMS-ESI (m/z) calcd for $(\text{C}_{11}\text{H}_{11}\text{NO}_2 + \text{H})^+$: 190.0863, found: 190.0861.

7-fluoro-1,2,3,3a-tetrahydro-9H-benzo[e]pyrrolo[2,1-b][1,3]oxazin-9-one (1b)^[11]:

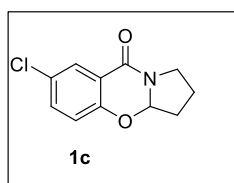
: 74% (36 mg from 60 mg of **2b**) thick oil; *R_f*: 0.4 (6:4, ethyl acetate: petroleum ether).



¹H NMR (400 MHz, CDCl₃): δ 7.61 (dd, *J* = 3.1, 8.1 Hz, 1 H), 7.17 - 7.08 (m, 1 H), 6.94 (dd, *J* = 4.3, 8.9 Hz, 1 H), 5.48 (t, *J* = 5.8 Hz, 1 H), 3.91 - 3.80 (m, 1 H), 3.66 - 3.58 (m, 1 H), 2.49 - 2.40 (m, 1 H), 2.30 - 2.20 (m, 1 H), 2.18 - 2.07 (m, 1 H), 2.01 - 1.90 (m, 1 H).

¹³C NMR (101 MHz, CDCl₃): δ 160.0, 158.2 (d, *J_{C-F}* = 241.85 Hz), 153.3, 120.8 (d, *J_{C-F}* = 24.14 Hz), 117.9 (d, *J_{C-F}* = 7.63 Hz), 113.8 (d, *J_{C-F}* = 24.41 Hz), 88.8, 44.4, 31.8, 21.3.

HRMS-ESI (*m/z*) calcd for (C₁₁H₁₀FNO₂+H)⁺: 208.0768, found: 208.0768.

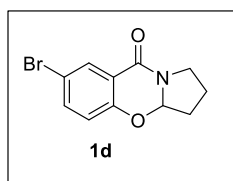
7-chloro-1,2,3,3a-tetrahydro-9H-benzo[e]pyrrolo[2,1-b][1,3]oxazin-9-one (1c)^[11]:

: 58% (27.5 mg from 60 mg of **2c**) white solid; mp: 70- 80°C, *R_f*: 0.3 (3:7, ethyl acetate: petroleum ether).

¹H NMR (400 MHz, CDCl₃): δ 7.90 (d, *J* = 2.6 Hz, 1 H), 7.37 (dd, *J* = 2.6, 8.8 Hz, 1 H), 6.92 (d, *J* = 8.6 Hz, 1 H), 5.49 (t, *J* = 5.8 Hz, 1 H), 3.89 - 3.81 (m, 1 H), 3.67 - 3.58 (m, 1 H), 2.51 - 2.40 (m, 1 H), 2.32 - 2.21 (m, 1 H), 2.19 - 2.07 (m, 1 H), 2.02 - 1.89 (m, 1 H).

¹³C NMR (101 MHz, CDCl₃): δ 159.8, 155.8, 133.6, 128.0, 127.6, 121.0, 118.0, 88.8, 44.4, 31.8, 21.3.

HRMS-ESI (*m/z*) calcd for (C₁₁H₁₀NClO₂+H)⁺: 224.0473, found: 224.0475.

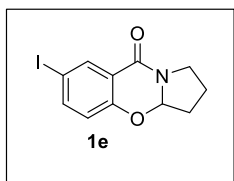
7-bromo-1,2,3,3a-tetrahydro-9H-benzo[e]pyrrolo[2,1-b][1,3]oxazin-9-one (1d):

: 76% (39 mg from 60 mg of **2d**) white solid; mp: 80-81°C; *R_f*: 0.3 (2:8, ethyl acetate: petroleum ether).

¹H NMR (400 MHz, CDCl₃): δ 8.04 (d, *J* = 2.5 Hz, 1 H), 7.51 (dd, *J* = 2.5, 8.6 Hz, 1 H), 6.86 (d, *J* = 8.6 Hz, 1 H), 5.48 (t, *J* = 5.9 Hz, 1 H), 3.90 - 3.80 (m, 1 H), 3.66 - 3.57 (m, 1 H), 2.48 - 2.39 (m, 1 H), 2.30 - 2.20 (m, 1 H), 2.17 - 2.06 (m, 1 H), 1.99 - 1.90 (m, 1 H).

¹³C NMR (101 MHz, CDCl₃): δ 159.7, 156.3, 136.5, 130.6, 121.3, 118.4, 115.2, 88.7, 44.4, 31.8, 21.3.

HRMS-ESI (*m/z*) calcd for (C₁₁H₁₀⁸¹BrNO₂+H)⁺: 269.9947, found: 269.9945.

7-iodo-1,2,3,3a-tetrahydro-9H-benzo[e]pyrrolo[2,1-b][1,3]oxazin-9-one (1e):

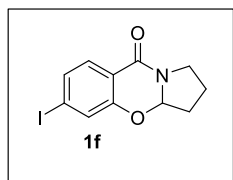
: 63% (32 mg from 60 mg of **2e**) white solid; mp: 102-103°C,

R_f: 0.3 (3:7, ethyl acetate: petroleum ether).

¹H NMR (400 MHz, CDCl₃): δ 8.21 (d, *J* = 2.3 Hz, 1 H), 7.69 (dd, *J* = 2.3, 8.6 Hz, 1 H), 6.74 (d, *J* = 8.5 Hz, 1 H), 5.47 (t, *J* = 5.8 Hz, 1 H), 3.87 - 3.79 (m, 1 H), 3.65 - 3.57 (m, 1 H), 2.49 - 2.39 (m, 1 H), 2.30 - 2.19 (m, 1 H), 2.17 - 2.06 (m, 1 H), 2.00 - 1.89 (m, 1 H).

¹³C NMR (101 MHz, CDCl₃): δ 159.5, 157.0, 142.3, 136.6, 121.7, 118.8, 88.7, 85.1, 44.5, 31.9, 21.3.

HRMS-ESI (m/z) calcd for (C₁₁H₁₀NIO₂+H)⁺: 315.9829, found: 315.9825.

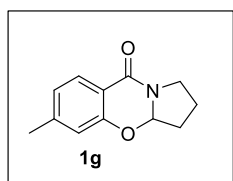
6-iodo-1,2,3,3a-tetrahydro-9H-benzo[e]pyrrolo[2,1-b][1,3]oxazin-9-one (1f):

: 85% (44.6 mg from 60 mg of **2f**) white solid; mp: 110-111°C; R_f: 0.3 (3:7, ethyl acetate: petroleum ether).

¹H NMR (400 MHz, CDCl₃): δ 7.62 (d, *J* = 7.9 Hz, 1 H), 7.47 (d, *J* = 8.2 Hz, 1 H), 7.37 (s, 1 H), 5.49 (t, *J* = 5.8 Hz, 1 H), 3.88 - 3.77 (m, 1 H), 3.66 - 3.55 (m, 1 H), 2.48 - 2.37 (m, 1 H), 2.30 - 2.21 (m, 1 H), 2.18 - 2.06 (m, 1 H), 2.02 - 1.89 (m, 1 H).

¹³C NMR (101 MHz, CDCl₃): δ 160.4, 157.4, 132.0, 129.1, 125.8, 119.3, 99.7, 88.7, 44.4, 31.8, 21.2.

HRMS-ESI (m/z) calcd for (C₁₁H₁₀INO₂+H)⁺: 315.9829, found: 315.9818.

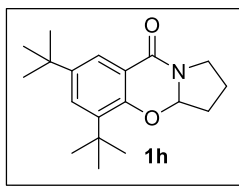
6-methyl-1,2,3,3a-tetrahydro-9H-benzo[e]pyrrolo[2,1-b][1,3]oxazin-9-one (1g)^[11]:

: 54% (26.3 mg from 60 mg of **2g**) white solid; mp: 72-73°C; R_f: 0.25 (3:7, ethyl acetate: petroleum ether).

¹H NMR (400 MHz, CDCl₃): δ .80 (d, *J* = 7.9 Hz, 1 H), 6.94 - 6.89 (m, 1 H), 6.76 (s, 1 H), 5.46 (t, *J* = 5.8 Hz, 1 H), 3.83 (td, *J* = 7.3, 11.5 Hz, 1 H), 3.65 - 3.57 (m, 1 H), 2.47 - 2.37 (m, 1 H), 2.36 (s, 3 H), 2.29 - 2.18 (m, 1 H), 2.16 - 2.05 (m, 1 H), 1.99 - 1.87 (m, 1 H).

¹³C NMR (101 MHz, CDCl₃): δ 161.1, 157.3, 144.9, 127.7, 123.6, 117.1, 116.6, 88.4, 44.2, 31.9, 21.7, 21.3.

HRMS-ESI (m/z) calcd for (C₁₂H₁₃NO₂+H)⁺: 204.1019, found: 204.1019.

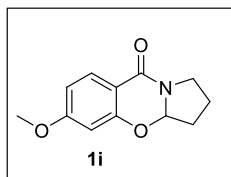
5,7-di-tert-butyl-1,2,3,3a-tetrahydro-9H-benzo[e]pyrrolo[2,1-b][1,3]oxazin-9-one (1h):

: 45% (23.6 mg from 60 mg of **2h**) white solid; mp: 120-122°C; R_f : 0.45 (3:7, ethyl acetate: petroleum ether).

^1H NMR (400 MHz, CDCl_3): δ 7.82 (d, J = 2.5 Hz, 1 H), 7.46 (d, J = 2.5 Hz, 1 H), 5.41 (t, J = 5.8 Hz, 1 H), 3.91 - 3.82 (m, 1 H), 3.66 - 3.58 (m, 1 H), 2.50 - 2.40 (m, 1 H), 2.34 - 2.24 (m, 1 H), 2.19 - 2.08 (m, 1 H), 2.01 - 1.89 (m, 1 H), 1.38 (s, 9 H), 1.33 (s, 9 H).

^{13}C NMR (101 MHz, CDCl_3): δ 161.8, 153.7, 144.7, 137.3, 128.1, 122.2, 120.0, 87.7, 44.3, 34.8, 34.6, 32.0, 31.4, 29.7, 21.5.

HRMS-ESI (m/z) calcd for $(\text{C}_{19}\text{H}_{27}\text{NO}_2+\text{H})^+$: 302.2115, found: 302.2111.

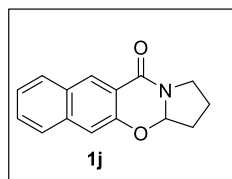
6-methoxy-1,2,3,3a-tetrahydro-9H-benzo[e]pyrrolo[2,1-b][1,3]oxazin-9-one (1i)^[11]:

: 75% (36.3 mg from 60 mg of **2i**) white solid; mp: 117-118°C; R_f : 0.4 (4:6, ethyl acetate: petroleum ether).

^1H NMR (400 MHz, CDCl_3): δ 7.84 (d, J = 8.6 Hz, 1 H), 6.65 (dd, J = 2.4, 8.6 Hz, 1 H), 6.45 (d, J = 2.4 Hz, 1 H), 5.48 (t, J = 5.8 Hz, 1 H), 3.85 - 3.74 (m, 4 H), 3.64 - 3.56 (m, 1 H), 2.47 - 2.37 (m, 1 H), 2.29 - 2.17 (m, 1 H), 2.17 - 2.05 (m, 1 H), 1.98 - 1.87 (m, 1 H).

^{13}C NMR (101 MHz, CDCl_3): δ 164.2, 161.0, 159.0, 129.3, 112.7, 109.5, 100.8, 88.7, 55.5, 44.2, 31.9, 21.3.

HRMS-ESI (m/z) calcd for $(\text{C}_{12}\text{H}_{13}\text{NO}_3+\text{H})^+$: 220.0968, found: 220.0968.

1,2,3,3a-tetrahydro-11H-naphtho[2,3-e]pyrrolo[2,1-b][1,3]oxazin-11-one (1j)^[11]:

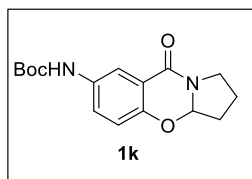
: 52% (26 mg from 60 mg of **2j**) yellow solid: 114-115 °; R_f : 0.22 (3:7, ethyl acetate: petroleum ether).

^1H NMR (400 MHz, CDCl_3): δ 8.53 (s, 1 H), 7.92 (d, J = 8.3 Hz, 1 H), 7.75 (d, J = 8.3 Hz, 1 H), 7.53 (t, J = 7.5 Hz, 1 H), 7.42 (t, J = 7.5 Hz, 1 H), 7.35 (s, 1 H), 5.55 (t, J = 6.0 Hz, 1 H), 3.96 - 3.89 (m, 1 H), 3.74 - 3.67 (m, 1 H), 2.54 - 2.46 (m, 1 H), 2.35 - 2.26 (m, 1 H), 2.21 - 2.13 (m, 1 H), 2.03 - 1.94 (m, 1 H)

^{13}C NMR (101 MHz, CDCl_3): δ 161.0, 153.5, 136.3, 129.39, 129.37, 129.35, 128.4, 126.9, 125.0, 120.0, 112.0, 88.5, 44.5, 32.1, 21.1.

HRMS-ESI (m/z) calcd for (C₁₅H₁₃NO₂+H)⁺: 240.1019, found: 240.1017.

tert-butyl(9-oxo-1,2,3,3a-tetrahydro-9H-benzo[e]pyrrolo[2,1-b][1,3]oxazin-7-yl)carbamate (1k):



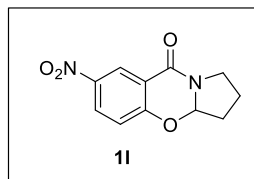
: 52% (27 mg from 60 mg of **2k**) white solid; mp: 210-212°C; R_f: 0.22 (4:6, ethyl acetate: petroleum ether).

¹H NMR (400 MHz, CDCl₃): δ 7.76 (br. s., 1 H), 7.70 (br. s., 1 H), 6.92 (d, *J* = 8.8 Hz, 1 H), 6.79 (br. s., 1 H), 5.46 (t, *J* = 5.8 Hz, 1 H), 3.85 (td, *J* = 7.3, 11.7 Hz, 1 H), 3.67 - 3.56 (m, 1 H), 2.48 - 2.37 (m, 1 H), 2.24 (dt, *J* = 8.3, 13.6 Hz, 1 H), 2.16 - 2.08 (m, 1 H), 1.99 - 1.88 (m, 1 H), 1.52 (s, 9 H).

¹³C NMR (101 MHz, CDCl₃): δ 160.7, 153.0, 152.9, 133.6, 125.0, 119.8, 117.9, 116.9, 88.5, 80.6, 44.3, 31.9, 28.3, 21.3.

HRMS-ESI (m/z) calcd for (C₁₆H₂₀N₂O₄+H)⁺: 305.1496, found: 305.1500.

7-nitro-1,2,3,3a-tetrahydro-9H-benzo[e]pyrrolo[2,1-b][1,3]oxazin-9-one (1l):



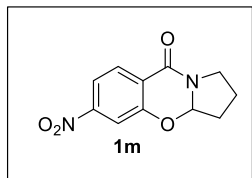
: Reaction time 36 h. 33% (16.3 mg from 60 mg of **2l**) yellow solid; mp: 108-110°C; R_f: 0.16 (3:7, ethyl acetate: petroleum ether).

¹H NMR (400 MHz, CDCl₃): δ 8.83 (d, *J* = 2.9 Hz, 1 H), 8.31 (dd, *J* = 2.8, 9.0 Hz, 1 H), 7.10 (d, *J* = 9.0 Hz, 1 H), 5.59 (t, *J* = 5.8 Hz, 1 H), 3.93 - 3.85 (m, 1 H), 3.70 - 3.62 (m, 1 H), 2.57 - 2.47 (m, 1 H), 2.39 - 2.28 (m, 1 H), 2.22 - 2.10 (m, 1 H), 2.07 - 1.96 (m, 1 H).

¹³C NMR (101 MHz, CDCl₃): δ 161.7, 158.8, 143.1, 128.8, 124.4, 120.0, 117.7, 89.3, 44.7, 31.8, 21.2.

HRMS-ESI (m/z) calcd for (C₁₁H₁₀N₂O₄+H)⁺: 235.0713, found: 235.0713.

6-nitro-1,2,3,3a-tetrahydro-9H-benzo[e]pyrrolo[2,1-b][1,3]oxazin-9-one (1m):



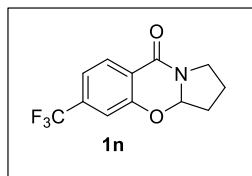
: Reaction time 36 h. 62% (31 mg from 60 mg of **2m**) white solid; mp: 125-126°C; R_f: 0.4 (3:7, ethyl acetate: petroleum ether).

¹H NMR (400 MHz, CDCl₃): δ 8.11 (d, *J* = 8.4 Hz, 1 H), 7.95 (dd, *J* = 2.1, 8.4 Hz, 1 H), 7.83 (d, *J* = 2.0 Hz, 1 H), 5.59 (t, *J* = 5.8 Hz, 1 H), 3.97 - 3.83 (m, 1 H), 3.70 - 3.62 (m, 1 H), 2.56 - 2.47 (m, 1 H), 2.38 - 2.29 (m, 1 H), 2.22 - 2.12 (m, 1 H), 2.04 - 1.94 (m, 1 H).

^{13}C NMR (101 MHz, CDCl_3): δ 159.0, 157.6, 151.0, 129.2, 124.6, 117.3, 112.4, 89.3, 44.6, 31.8, 21.2.

HRMS-ESI (m/z) calcd for $(\text{C}_{11}\text{H}_{10}\text{N}_2\text{O}_4+\text{H})^+$: 235.0713, found: 235.0713.

6-(trifluoromethyl)-1,2,3,3a-tetrahydro-9H-benzo[e]pyrrolo[2,1-b][1,3]oxazin-9-one



(1n):

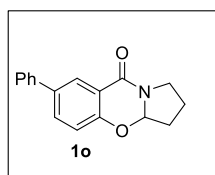
: 68% (34.6 mg from 60 mg of **2n**) thick oil; R_f : 0.4 (5:5, ethyl acetate: petroleum ether).

^1H NMR (400 MHz, CDCl_3): δ 8.05 (d, J = 8.1 Hz, 1 H), 7.36 (d, J = 8.1 Hz, 1 H), 7.24 (s, 1 H), 5.54 (t, J = 5.9 Hz, 1 H), 3.93 - 3.80 (m, 1 H), 3.71 - 3.55 (m, 1 H), 2.54 - 2.42 (m, 1 H), 2.37 - 2.22 (m, 1 H), 2.20 - 2.10 (m, 1 H), 2.04 - 1.93 (m, 1 H).

^{13}C NMR (101 MHz, CDCl_3): δ 159.7, 157.3, 135.5 (q, J = 32.8 Hz), 128.8, 124.6, 122.5, 119.2 (q, J = 3.8 Hz), 114.1 (q, J = 3.8 Hz), 88.9, 44.5, 31.8, 21.2.

HRMS-ESI (m/z) calcd for $(\text{C}_{12}\text{H}_{10}\text{F}_3\text{NO}_2+\text{H})^+$: 258.0736, found: 258.0739.

7-phenyl-1,2,3,3a-tetrahydro-9H-benzo[e]pyrrolo[2,1-b][1,3]oxazin-9-one (1o**)^[11]:**



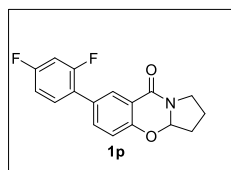
: 81% (41.3 mg from 60 mg of **2o**) thick oil; R_f : 0.4 (4:6, ethyl acetate: petroleum ether).

^1H NMR (400 MHz, CDCl_3): δ 8.18 (d, J = 2.1 Hz, 1 H), 7.68 (dd, J = 2.3, 8.5 Hz, 1 H), 7.60 (d, J = 7.4 Hz, 2 H), 7.44 (t, J = 7.6 Hz, 2 H), 7.39 - 7.31 (m, 1 H), 7.05 (d, J = 8.5 Hz, 1 H), 5.55 (t, J = 5.8 Hz, 1 H), 3.89 (td, J = 7.3, 11.5 Hz, 1 H), 3.71 - 3.61 (m, 1 H), 2.47 (td, J = 6.4, 12.7 Hz, 1 H), 2.36 - 2.24 (m, 1 H), 2.20 - 2.10 (m, 1 H), 2.04 - 1.92 (m, 1 H).

^{13}C NMR (101 MHz, CDCl_3): δ 160.9, 156.7, 139.7, 135.9, 132.4, 128.8, 127.3, 126.8, 126.3, 119.9, 116.9, 88.6, 44.4, 32.0, 21.3.

HRMS-ESI (m/z) calcd for $(\text{C}_{17}\text{H}_{15}\text{NO}_2+\text{H})^+$: 266.1176, found: 266.1173.

7-(2,4-difluorophenyl)-1,2,3,3a-tetrahydro-9H-benzo[e]pyrrolo[2,1-b][1,3]oxazin-9-one



(1p):

: 72% (38 mg from 60 mg of **2p**) white solid; mp: 154-155 °C; R_f : 0.4 (4:6, ethyl acetate: petroleum ether).

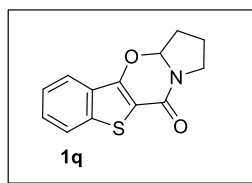
^1H NMR (400 MHz, CDCl_3): δ 8.05 (s, 1 H), 7.62 - 7.54 (m, 1 H), 7.47 - 7.37 (m, 1 H), 7.04 (d, J = 8.6 Hz, 1 H), 7.00 - 6.87 (m, 2 H), 5.55 (t, J = 5.8 Hz, 1 H), 3.92 -

3.83 (m, 1 H), 3.69 - 3.60 (m, 1 H), 2.51 - 2.42 (m, 1 H), 2.35 - 2.23 (m, 1 H), 2.18 - 2.08 (m, 1 H), 2.03 - 1.90 (m, 1 H).

^{13}C NMR (101 MHz, CDCl_3): δ 162.3 (dd, $J_{\text{C-F}} = 249.4, 11.7$ Hz), 160.7, 159.8 (dd, $J_{\text{C-F}} = 250.9, 12.7$ Hz), 15.8, 134 (d, $J_{\text{C-F}} = 3.7$ Hz), 131.2 (dd, $J_{\text{C-F}} = 9.5, 5.1$ Hz), 129, 128.1 (d, $J_{\text{C-F}} = 2.2$ Hz), 124.0 (dd, $J_{\text{C-F}} = 9.5, 3.7$ Hz), 119, 116, 111.6 (dd, $J_{\text{C-F}} = 17.6, 3.6$ Hz), 104 (dd, $J_{\text{C-F}} = 24.9, 1.5$ Hz), 88.6, 44.4, 31.9, 21.3.

HRMS-ESI (m/z) calcd for $(\text{C}_{17}\text{H}_{13}\text{F}_2\text{NO}_2 + \text{H})^+$: 302.0987, found: 302.978.

1,2,3,11a-tetrahydro-5H-benzo[4,5]thieno[2,3-e]pyrrolo[2,1-b][1,3]oxazin-5-one (1q):



: 74% (37.5 mg from 60 mg of **2q**) white solid; mp: 135°C; R_f : 0.3 (3:7 ethyl acetate: petroleum ether).

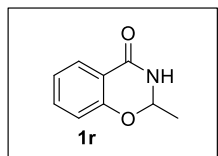
^1H NMR (400 MHz, CDCl_3): δ 7.80 (dd, $J = 3.9, 7.9$ Hz, 2 H), 7.55 - 7.32 (m, 2 H), 5.77 (t, $J = 5.3$ Hz, 1 H), 3.93 - 3.82 (m, 1 H), 3.68 - 3.57

(m, 1 H), 2.57 - 2.38 (m, 2 H), 2.25 - 2.11 (m, 1 H), 2.10 - 1.95 (m, 1 H).

^{13}C NMR (101 MHz, CDCl_3): δ 158.9, 155.3, 140.3, 128.9, 127.9, 124.6, 123.6, 122.1, 113.1, 91.4, 44.6, 31.5, 22.2.

HRMS-ESI (m/z) calcd for $(\text{C}_{13}\text{H}_{11}\text{NO}_2\text{S} + \text{H})^+$: 246.0583, found: 246.0584.

2-methyl-2,3-dihydro-4H-benzo[e][1,3]oxazin-4-one (1r)^[23]:



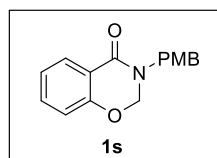
: 45% (21 mg from 60 mg of **2r**) white solid; mp: 85 - 86°C; R_f : 0.3 (4:6, ethyl acetate: petroleum ether).

^1H NMR (400 MHz, CDCl_3): δ 7.95 (dd, $J = 1.6, 7.8$ Hz, 1 H), 7.52 - 7.42 (m, 1 H), 7.11 (t, $J = 7.2$ Hz, 1 H), 6.98 (d, $J = 8.3$ Hz, 1 H), 6.84 (s, 1 H), 5.45 (t, $J = 5.6$ Hz, 1 H), 1.67 (d, $J = 5.6$ Hz, 3 H).

^{13}C NMR (101 MHz, CDCl_3): δ 163.9, 157.9, 134.6, 128.2, 122.4, 118.0, 116.6, 80.9, 20.3.

ESIMS [M+H]⁺ (m/z): 164.

3-(4-methoxybenzyl)-2,3-dihydro-4H-benzo[e][1,3]oxazin-4-one (1s):



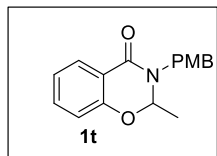
: Additive Cs_2CO_3 (1 equiv., 0.19 mmol, 62 mg), 35% (18 mg from 60 mg of **2s**) thick oil; R_f : 0.4 (5:5, ethyl acetate: petroleum ether).

^1H NMR (400 MHz, CDCl_3): δ 8.03 (dd, $J = 1.6, 7.8$ Hz, 1 H), 7.48 - 7.41 (m, 1 H), 7.29 (s, 2 H), 7.17 - 7.11 (m, 1 H), 6.95 (d, $J = 8.3$ Hz, 1 H), 6.92 - 6.85 (m, 2 H), 5.11 (s, 2 H), 4.72 (s, 2 H), 3.81 (s, 3 H).

^{13}C NMR (101 MHz, CDCl_3): δ 162.1, 159.3, 157.8, 134.0, 129.3, 128.6, 128.3, 122.6, 118.9, 116.3, 114.3, 77.4, 55.3, 47.0.

HRMS-ESI (m/z) calcd for $(\text{C}_{16}\text{H}_{15}\text{NO}_3 + \text{H})^+$: 270.1125, found: 270.1122.

3-(4-methoxybenzyl)-2-methyl-2,3-dihydro-4H-benzo[e][1,3]oxazin-4-one (1t)^[23]:



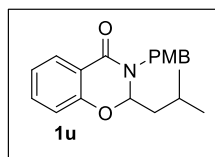
: 75% (39 mg from 60 mg of **2t**) thick oil; R_f : 0.4 (5:5, ethyl acetate: petroleum ether).

^1H NMR (400 MHz, CDCl_3): δ 8.02 (dd, $J = 1.5, 7.8$ Hz, 1 H), 7.49 - 7.42 (m, 1 H), 7.31 - 7.27 (m, 2 H), 7.15 - 7.09 (m, 1 H), 6.95 - 6.87 (m, 3 H), 5.44 (q, $J = 5.9$ Hz, 1 H), 5.14 (d, $J = 15.3$ Hz, 1 H), 4.31 (d, $J = 15.3$ Hz, 1 H), 3.82 (s, 3 H), 1.47 (d, $J = 6.0$ Hz, 3 H).

^{13}C NMR (101 MHz, CDCl_3): δ 161.3, 159.1, 155.5, 134.1, 129.1, 128.8, 128.3, 122.2, 118.1, 116.8, 114.2, 84.1, 55.3, 45.9, 18.7.

HRMS-ESI (m/z) calcd for $(\text{C}_{17}\text{H}_{17}\text{NO}_3 + \text{H})^+$: 284.1281, found: 284.1281.

2-isobutyl-3-(4-methoxybenzyl)-2,3-dihydro-4H-benzo[e][1,3]oxazin-4-one (1u):



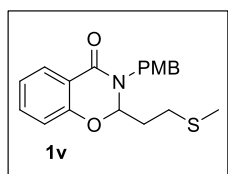
: 78% (40.3 mg from 60 mg of **2u**) thick oil; R_f : 0.5 (3:7, ethyl acetate: petroleum ether).

^1H NMR (400 MHz, CDCl_3): δ 7.99 (dd, $J = 1.6, 7.8$ Hz, 1 H), 7.47 - 7.39 (m, 1 H), 7.27 (d, $J = 8.5$ Hz, 2 H), 7.10 (t, $J = 7.6$ Hz, 1 H), 6.89 (d, $J = 8.8$ Hz, 3 H), 5.27 (dd, $J = 2.9, 10.4$ Hz, 1 H), 5.23 (d, $J = 15.1$ Hz, 1 H), 4.11 (d, $J = 15.1$ Hz, 1 H), 3.81 (s, 3 H), 2.0 - 1.91 (m, 1 H), 1.80 - 1.72 (m, 1 H), 1.35 - 1.29 (m, 1 H), 0.89 (d, $J = 6.5$ Hz, 3 H), 0.85 (d, $J = 6.8$ Hz, 3 H).

^{13}C NMR (101 MHz, CDCl_3): δ 160.8, 159.2, 155.0, 134.1, 129.4, 128.6, 128.1, 122.2, 118.5, 117.0, 114.2, 85.8, 55.3, 46.3, 40.5, 24.4, 23.1, 21.5.

HRMS-ESI (m/z) calcd for $(\text{C}_{20}\text{H}_{23}\text{NO}_3 + \text{H})^+$: 326.1751, found: 326.1752.

3-(4-methoxybenzyl)-2-(2-(methylthio)ethyl)-2,3-dihydro-4H-benzo[e][1,3]oxazin-4-one (1v):



: 76% (40.3 mg from 60 mg of **2v**) thick oil; R_f : 0.5 (3:7, ethyl acetate: petroleum ether).

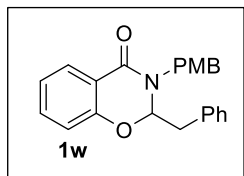
^1H NMR (400 MHz, CDCl_3): δ 7.99 (dd, $J = 1.5, 7.8$ Hz, 1 H), 7.51 - 7.39 (m, 1 H), 7.30 (d, $J = 8.5$ Hz, 2 H), 7.15 - 7.04 (m, 1 H), 6.96 - 6.82 (m, 3

H), 5.46 (dd, $J = 3.1, 9.8$ Hz, 1 H), 5.08 (d, $J = 15.0$ Hz, 1 H), 4.33 (d, $J = 15.0$ Hz, 1 H), 3.80 (s, 3 H), 2.56 - 2.44 (m, 2 H), 2.28 - 2.14 (m, 1 H), 1.99 (s, 3 H), 1.83 - 1.69 (m, 1 H).

^{13}C NMR (101 MHz, CDCl_3): δ 160.7, 159.2, 154.7, 134.2, 129.4, 128.6, 128.2, 122.4, 118.4, 116.9, 114.2, 85.7, 55.2, 46.7, 31.4, 29.3, 15.5.

HRMS-ESI (m/z) calcd for ($\text{C}_{19}\text{H}_{21}\text{NO}_3 + \text{H}$) $^+$: 344.1315, found: 344.1308.

2-benzyl-3-(4-methoxybenzyl)-2,3-dihydro-4H-benzo[e][1,3]oxazin-4-one (1w):



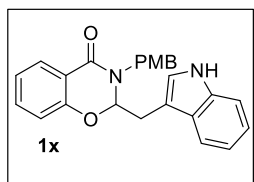
: 74% (39 mg from 60 mg of **2w**) thick oil; R_f : 0.4 (3:7, ethyl acetate: petroleum ether).

^1H NMR (400 MHz, CDCl_3): δ 8.05 (dd, $J = 1.6, 7.8$ Hz, 1 H), 7.52 - 7.45 (m, 1 H), 7.35 - 7.28 (m, 3 H), 7.22 (d, $J = 8.6$ Hz, 2 H), 7.14 (t, $J = 7.6$ Hz, 1 H), 7.08 (d, $J = 6.6$ Hz, 2 H), 6.93 - 6.90 (m, 1 H), 6.88 (d, $J = 8.6$ Hz, 2 H), 5.37 (dd, $J = 4.9, 8.3$ Hz, 1 H), 5.16 (d, $J = 15.1$ Hz, 1 H), 3.89 (d, $J = 15.1$ Hz, 1 H), 3.80 (s, 3 H), 3.17 (dd, $J = 8.4, 14.0$ Hz, 1 H), 2.88 (dd, $J = 4.9, 14.0$ Hz, 1 H).

^{13}C NMR (101 MHz, CDCl_3): δ 160.5, 159.3, 154.9, 135.4, 134.3, 129.5, 129.4, 128.7, 128.4, 128.2, 127.1, 122.3, 118.5, 117.2, 114.3, 87.7, 55.3, 47.1, 39.0.

HRMS-ESI (m/z) calcd for ($\text{C}_{23}\text{H}_{21}\text{NO}_3 + \text{H}$) $^+$: 360.1594, found: 360.1595.

2-((1H-indol-3-yl)methyl)-3-(4-methoxybenzyl)-2,3-dihydro-4H-benzo[e][1,3]oxazin-4-one (1x):

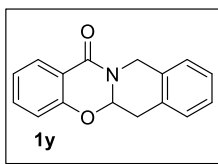


: Reaction time 36 h. 75% (40.5 mg from 60 mg of **2x**) thick oil; R_f : 0.3 (4:6, ethyl acetate: petroleum ether).

^1H NMR (400 MHz, CDCl_3): δ 8.15 (s, 1 H), 8.06 (dd, $J = 1.6, 7.7$ Hz, 1 H), 7.49 - 7.42 (m, 1 H), 7.41 - 7.34 (m, $J = 8.5$ Hz, 2 H), 7.22 (t, $J = 7.9$ Hz, 1 H), 7.17 - 7.08 (m, 4 H), 7.02 (d, $J = 2.3$ Hz, 1 H), 6.91 (d, $J = 7.9$ Hz, 1 H), 6.87 - 6.81 (m, $J = 8.6$ Hz, 2 H), 5.51 (dd, $J = 5.4, 7.8$ Hz, 1 H), 5.17 (d, $J = 15.0$ Hz, 1 H), 3.86 (d, $J = 15.0$ Hz, 1 H), 3.79 (s, 3 H), 3.32 (dd, $J = 7.8, 15.0$ Hz, 1 H), 3.20 - 3.07 (m, 1 H).

^{13}C NMR (101 MHz, CDCl_3): δ 160.7, 159.2, 155.0, 136.0, 134.2, 129.5, 128.5, 128.2, 127.1, 123.2, 122.3, 122.2, 119.7, 118.5, 118.3, 117.1, 114.2, 111.3, 109.7, 86.7, 55.3, 47.2, 28.8.

HRMS-ESI (m/z) calcd for ($\text{C}_{25}\text{H}_{22}\text{N}_2\text{O}_3 + \text{H}$) $^+$: 399.1703, found: 399.1701.

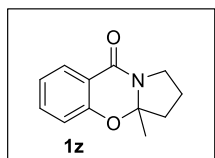
5a,6-dihydro-11H,13H-benzo[5,6][1,3]oxazino[3,2-b]isoquinolin-13-one (1y):

: 53%, (27 mg from 60 mg of **2y**) White solid; mp: 130-130°C; R_f : 0.55 (3:7, ethyl acetate: petroleum ether).

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.99 (dd, $J = 1.5, 7.8$ Hz, 1 H), 7.48 - 7.42 (m, 1 H), 7.32 - 7.27 (m, 4 H), 7.16 - 7.10 (m, 1 H), 6.99 (d, $J = 8.1$ Hz, 1 H), 5.52 (t, $J = 6.4$ Hz, 1 H), 5.05 (d, $J = 16.1$ Hz, 1 H), 4.73 (d, $J = 16.1$ Hz, 1 H), 3.36 (d, $J = 6.4$ Hz, 2 H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 162.0, 157.0, 134.0, 133.8, 131.5, 128.4, 128.1, 127.7, 127.5, 126.2, 122.6, 119.2, 116.2, 84.0, 42.9, 34.8.

HRMS-ESI (m/z) calcd for $(\text{C}_{16}\text{H}_{13}\text{NO}_2+\text{H})^+$: 252.1019, found: 252.1017.

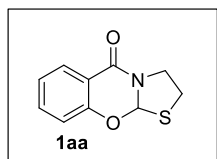
3a-methyl-1,2,3,3a-tetrahydro-9H-benzo[e]pyrrolo[2,1-b][1,3]oxazin-9-one (1z):

: 92%, (45 mg from 60 mg of **2z**) colourless thick oil; R_f : 0.3 (3:7, ethyl acetate: petroleum ether)

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.91 (dd, $J = 1.5, 7.8$ Hz, 1 H), 7.48 - 7.36 (m, 1 H), 7.12 - 7.00 (m, 1 H), 6.95 - 6.84 (m, 1 H), 3.86 (td, $J = 8.1, 11.9$ Hz, 1 H), 3.68 - 3.58 (m, 1 H), 2.42 - 2.34 (m, 1 H), 2.32 - 2.23 (m, 1 H), 2.13 - 2.02 (m, 1 H), 1.97 - 1.90 (m, 1 H), 1.51 (s, 3 H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 160.0, 155.4, 133.9, 127.7, 122.1, 118.4, 116.9, 94.7, 44.3, 39.1, 23.8, 20.6.

HRMS-ESI (m/z) calcd for $(\text{C}_{12}\text{H}_{13}\text{NO}_2+\text{H})^+$: 204.1019, found: 204.1024.

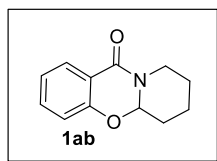
2,3-dihydro-5H,10aH-benzo[e]thiazolo[2,3-b][1,3]oxazin-5-one (1aa):

: 60% (29.5 mg from 60 mg of **2aa**) thick oil; R_f : 0.4 (3:7, ethyl acetate: petroleum ether)

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.93 (dd, $J = 1.5, 7.8$ Hz, 1 H), 7.51 - 7.43 (m, 1 H), 7.20 - 7.12 (m, 1 H), 7.02 (d, $J = 8.3$ Hz, 1 H), 6.52 (s, 1 H), 4.71 (dd, $J = 5.4, 11.6$ Hz, 1 H), 3.65 - 3.55 (m, 1 H), 3.39 - 3.27 (m, 1 H), 3.02 - 2.90 (m, 1 H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 160.2, 156.4, 134.4, 128.2, 123.2, 118.8, 116.8, 93.3, 49.0, 29.0.

HRMS-ESI (m/z) calcd for $(\text{C}_{10}\text{H}_9\text{NO}_2\text{S}+\text{H})^+$: 208.0427, found: 208.0429.

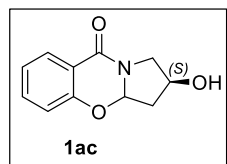
5a,6,8,9-tetrahydro-7H,11H-benzo[e]pyrido[2,1-b][1,3]oxazin-11-one (1ab):

: 52% (25.6 mg from 60 mg of **2ab**) light yellow solid; mp: 55-56°C; R_f : 0.49 (3:7, ethyl acetate: petroleum ether).

^1H NMR (400 MHz, CDCl_3): δ 7.95 (dd, $J = 1.6, 7.8$ Hz, 1 H), 7.47 - 7.39 (m, 1 H), 7.11 - 7.04 (m, 1 H), 6.91 (d, $J = 8.3$ Hz, 1 H), 5.22 (dd, $J = 4.2, 9.8$ Hz, 1 H), 4.55 - 4.43 (m, 1 H), 2.83 - 2.74 (m, 1 H), 2.29 - 2.19 (m, 1 H), 1.99 - 1.91 (m, 1 H), 1.87 - 1.78 (m, 2 H), 1.61 - 1.45 (m, 2 H).

^{13}C NMR (101 MHz, CDCl_3): δ 163.5, 156.6, 134.0, 128.1, 122.2, 117.5, 116.0, 85.9, 41.3, 31.4, 23.5, 21.2.

HRMS-ESI (m/z) calcd for $(\text{C}_{12}\text{H}_{13}\text{NO}_2 + \text{H})^+$: 204.1019, found: 204.1017.

3-hydroxy-1,2,3,3a-tetrahydro-9H-benzo[e]pyrrolo[2,1-b][1,3]oxazin-9-one (1ac):

: 55% (mixture of separable isomers), (27 mg from 60 mg of **2ac**) thick oil; R_f : 0.4 (5:5, ethyl acetate: petroleum ether); **diastereomer 1 (1ac)**: $[\alpha]^{24}_{\text{D}} -49.6$ (c 1.1, CHCl_3); **diastereomer 2 (1ac)**: $[\alpha]^{24}_{\text{D}} +19.6$ (c 0.4, CHCl_3).

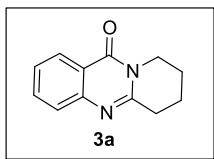
^1H NMR (400 MHz, CDCl_3): **diastereomer 1 (1ac)**: δ 7.93 (dd, $J = 1.5, 7.8$ Hz, 1 H), 7.48 - 7.39 (m, 1 H), 7.12 (t, $J = 7.2$ Hz, 1 H), 6.98 (d, $J = 8.1$ Hz, 1 H), 5.75 (dd, $J = 5.8, 7.4$ Hz, 1 H), 4.67 (t, $J = 4.7$ Hz, 1 H), 3.99 (dd, $J = 4.6, 12.8$ Hz, 1 H), 3.72 (d, $J = 12.8$ Hz, 1 H), 2.57 (dd, $J = 5.6, 13.5$ Hz, 1 H), 2.40 - 2.30 (m, 1 H).

^{13}C NMR (101 MHz, CDCl_3): δ 161.3, 157.2, 134.0, 128.1, 122.8, 119.6, 116.7, 87.6, 68.6, 53.6, 40.7.

Diastereomer 2 (1ac): δ 7.93 (dd, $J = 1.5, 7.8$ Hz, 1 H), 7.48 - 7.39 (m, 1 H), 7.12 (t, $J = 7.2$ Hz, 1 H), 6.98 (d, $J = 8.1$ Hz, 1 H), 5.75 (dd, $J = 5.8, 7.4$ Hz, 1 H), 4.67 (t, $J = 4.7$ Hz, 1 H), 3.99 (dd, $J = 4.6, 12.8$ Hz, 1 H), 3.72 (d, $J = 12.8$ Hz, 1 H), 2.57 (dd, $J = 5.6, 13.5$ Hz, 1 H), 2.40 - 2.33 (m, 1 H).

^{13}C NMR (101 MHz, CDCl_3): δ 161.3, 157.3, 134.0, 127.9, 122.8, 119.5, 116.5, 87.6, 67.9, 52.9, 40.7

HRMS-ESI (m/z) calcd for $(\text{C}_{11}\text{H}_{11}\text{NO}_3 + \text{H})^+$: 206.812, found: 206.813.

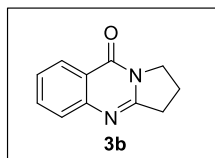
Mackinazolinone (3a)^[13]:

: 63% (21.4 mg from 60 mg of **4a**) light yellow solid; mp: 94-95°C {lit: m.p. 98.5 - 99.5 °C}⁶; R_f: 0.31 (4:6, ethyl acetate: petroleum ether).

¹H NMR (400 MHz, CDCl₃): δ 8.27 (d, *J* = 7.9 Hz, 1 H), 7.76 - 7.69 (m, 1 H), 7.62 (d, *J* = 8.1 Hz, 1 H), 7.48 - 7.37 (m, 1 H), 4.09 (t, *J* = 6.1 Hz, 2 H), 3.02 (t, *J* = 6.6 Hz, 2 H), 2.09 - 1.92 (m, 4 H).

¹³C NMR (101 MHz, CDCl₃): δ 162.2, 154.9, 147.3, 134.2, 126.7, 126.3, 126.1, 120.4, 42.3, 31.9, 22.1, 19.3.

HRMS-ESI (*m/z*) calcd for (C₁₂H₁₂N₂O+H)⁺: 201.1022, found: 201.1021.

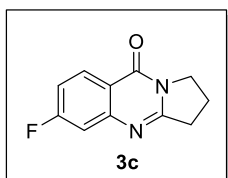
Deoxyvasicinone (3b)^[13]:

: 70% (23 mg from 60 mg of **4b**) white solid; mp: 97- 98°C {lit:⁶ m.p. 106-108°C}; R_f: 0.3 (7:3, ethyl acetate: petroleum ether).

¹H NMR (400 MHz, CDCl₃): δ 8.26 (d, *J* = 7.6 Hz, 1 H), 7.81 - 7.55 (m, 2 H), 7.43 (t, *J* = 7.1 Hz, 1 H), 4.19 (t, *J* = 6.9 Hz, 2 H), 3.16 (t, *J* = 7.6 Hz, 2 H), 2.38 - 2.18 (m, 2 H).

¹³C NMR (101 MHz, CDCl₃): δ 160.9, 159.4, 149.0, 134.1, 126.7, 126.3, 126.2, 120.4, 46.4, 32.5, 19.5.

ESIMS [M+H]⁺ (*m/z*): 187.

6-fluoro-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (3c)^[13]:

: 75% (26 mg from 60 mg of **4c**) off white solid; mp: 198°C; R_f: 0.2 (7:3, ethyl acetate: petroleum ether).

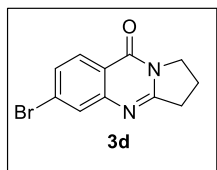
¹H NMR (400 MHz, CDCl₃): δ 8.27 (dd, *J* = 6.2, 8.8 Hz, 1 H), 7.28 (dd, *J* = 2.5, 9.8 Hz, 1 H), 7.15 (dt, *J* = 2.4, 8.5 Hz, 1 H), 4.20 (t, *J* = 7.2 Hz, 2 H), 3.18 (t, *J* = 8.0 Hz, 2 H), 2.34 - 2.24 (m, 2 H).

¹³C NMR (101 MHz, CDCl₃): δ 166.34 (d, *J*_{C-F} = 254.06 Hz), 160.8, 160.2, 151.3 (d, *J*_{C-F} = 12.97 Hz), 129.0, (d, *J*_{C-F} = 10.68 Hz), 117.2, (d, *J*_{C-F} = 2.29 Hz), 115.0, (d, *J*_{C-F} = 23.65 Hz), 112.2, (d, *J*_{C-F} = 22.12 Hz), 46.5, 32.6, 19.4.

HRMS-ESI (*m/z*) calcd for (C₁₁H₉FN₂O+H)⁺: 205.0772, found: 205.0772.

6-bromo-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (3d)^[24]:

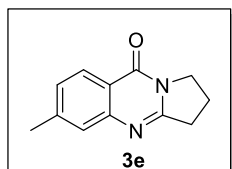
: 78% (27 mg from 60 mg of **4d**) white solid; mp: 197°C; R_f: 0.26 (7:3, ethyl acetate: petroleum ether).



¹H NMR (400 MHz, CDCl₃): δ 8.10 (d, *J* = 8.5 Hz, 1 H), 7.80 (s, 1 H), 7.58 - 7.45 (m, 1 H), 4.19 (t, *J* = 7.3 Hz, 2 H), 3.17 (t, *J* = 7.9 Hz, 2 H), 2.37 - 2.23 (m, 2 H).

¹³C NMR (101 MHz, CDCl₃): δ 160.7, 160.4, 150.2, 129.5 (2C), 128.7, 127.8, 119.3, 46.6, 32.6, 19.4.

HRMS-ESI (*m/z*) calcd for (C₁₁H₉BrN₂O+H)⁺: 264.9971, found: 264.9970.

6-methyl-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (3e)^[25]:

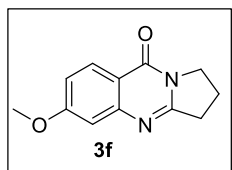
: 78% (26.8 mg from 60 mg of **4e**) white solid; mp: 97- 98°C; R_f: 0.3 (4:6, ethyl acetate: petroleum ether).

¹H NMR (400 MHz, CDCl₃): δ 8.16 (d, *J* = 8.1 Hz, 1 H), 7.43 (s, 1 H), 7.28 - 7.24 (m, 1 H), 4.19 (t, *J* = 7.2 Hz, 1 H), 3.16 (t, *J* = 7.9 Hz, 2 H),

2.49 (s, 3 H), 2.33 – 2.23 (m, 2 H).

¹³C NMR (101 MHz, CDCl₃): δ 160.9, 159.4, 149.2, 145.0, 127.8, 126.5, 126.1, 118.0, 46.4, 32.5, 21.8, 19.5.

HRMS-ESI (*m/z*) calcd for (C₁₂H₁₂N₂O +H)⁺: 201.1022, found: 201.1031.

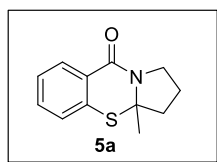
6-methoxy-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (3f)^[26]:

: 77% (27.3 mg from 60 mg of **4f**) white solid; mp: 138-139°C; R_f: 0.3 (4:6, ethyl acetate: petroleum ether).

¹H NMR (400 MHz, CDCl₃): δ 8.15 (d, *J* = 8.5 Hz, 1 H), 7.09 - 6.91 (m, 2 H), 4.17 (t, *J* = 7.1 Hz, 2 H), 3.89 (s, 3 H), 3.14 (t, *J* = 7.9 Hz, 2 H), 2.35 - 2.21 (m, 2 H).

¹³C NMR (101 MHz, CDCl₃): δ 164.4, 160.5, 160.1, 151.4, 127.8, 116.1, 114.0, 107.6, 55.5, 46.4, 32.5, 19.4.

HRMS-ESI (*m/z*) calcd for (C₁₂H₁₂N₂O₂+H)⁺: 317.0972, found: 317.0968.

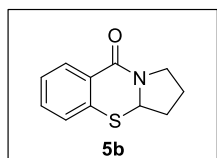
3a-methyl-1,2,3,3a-tetrahydro-9H-benzo[e]pyrrolo[2,1-b][1,3]thiazin-9-one (5a):

Reaction time 65 h. 48% (24 mg from 60 mg of **6a**) yellow liq.; R_f : 0.40 (5:5, ethyl acetate: petroleum ether).

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.14 - 8.04 (m, 1 H), 7.41 - 7.35 (m, 1 H), 7.28 (s, 1 H), 7.27 - 7.24 (m, 1 H), 3.82 (dd, J = 6.0, 8.3 Hz, 2 H), 2.46 - 2.37 (m, 1 H), 2.36 - 2.24 (m, 1 H), 2.18 - 2.00 (m, 2 H), 1.61 (s, 3 H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 162.2, 134.7, 131.8, 129.9, 129.0, 127.7, 126.0, 67.2, 46.3, 40.7, 28.4, 21.7.

HRMS-ESI (m/z) calcd for ($\text{C}_{12}\text{H}_{13}\text{NOS-H}$): 220.0791, found: 220.0791.

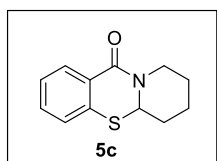
1,2,3,3a-tetrahydro-9H-benzo[e]pyrrolo[2,1-b][1,3]thiazin-9-one (5b):

: Reaction time 48 h. 41% (20 mg from 60 mg of **6b**) thick oil; R_f : 0.4 (5:5, ethyl acetate: petroleum ether).

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.09 (dd, J = 1.2, 7.7 Hz, 1 H), 7.39 - 7.33 (m, 1 H), 7.31 - 7.26 (m, 2 H), 5.15 (t, J = 7.1 Hz, 1 H), 3.89 - 3.73 (m, 2 H), 2.54 - 2.44 (m, 1 H), 2.20 - 2.10 (m, 2 H), 2.00 - 1.90 (m, 1 H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 162.8, 135.8, 131.7, 130.1, 130.0, 127.3, 126.2, 59.6, 46.0, 32.5, 23.0.

HRMS-ESI (m/z) calcd for ($\text{C}_{11}\text{H}_{11}\text{NO}_3+\text{H}$) $^+$: 206.0634, found: 206.0634.

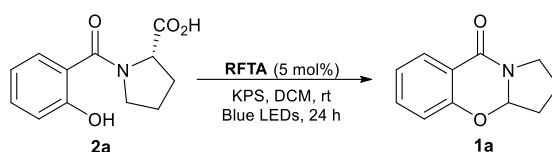
5a,6,8,9-tetrahydro-7H,11H-benzo[e]pyrido[2,1-b][1,3]thiazin-11-one (5c)^[27]:

: Reaction time 48 h. Additive Cs_2CO_3 (1 equiv., 0.22 mmol, 73.5 mg), 26% (13 mg from 60 mg of **6c**) yellow liq.; R_f : 0.7 (4:6, ethyl acetate: petroleum ether)

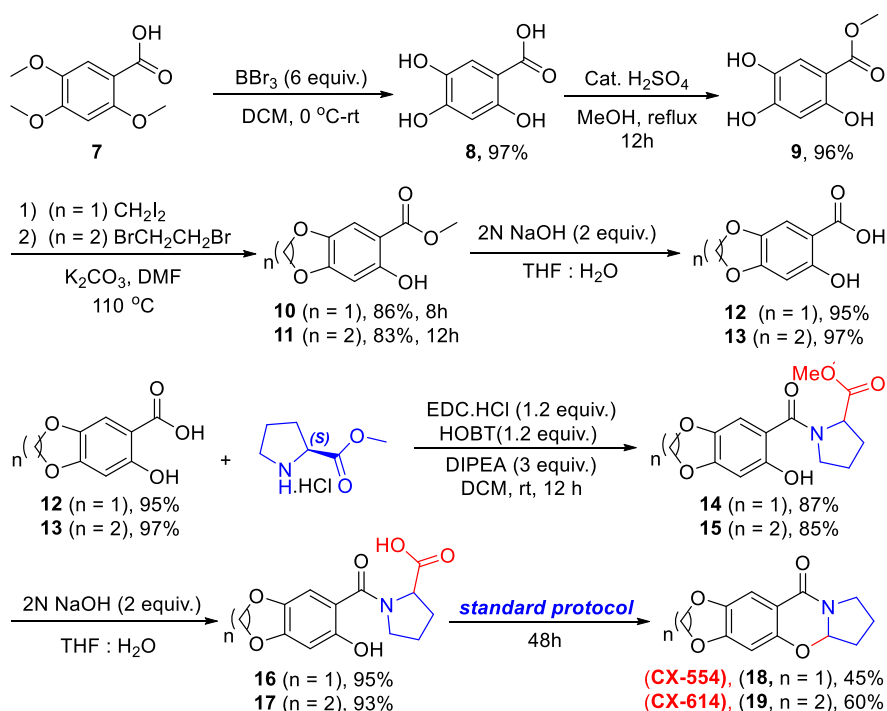
$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.17 (d, J = 7.1 Hz, 1 H), 7.41 - 7.31 (m, 1 H), 7.26 - 7.16 (m, 2 H), 4.84 (dd, J = 3.9, 10.8 Hz, 1 H), 4.55 (d, J = 13.5 Hz, 1 H), 3.08 - 2.95 (m, 1 H), 2.12 - 1.89 (m, 3 H), 1.87 - 1.79 (m, 1 H), 1.73 - 1.53 (m, 4 H)

$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 164.8, 134.9, 131.9, 130.7, 127.7, 126.5, 125.8, 59.1, 44.5, 31.9, 23.7, 23.1

HRMS-ESI (m/z) calcd for ($\text{C}_{12}\text{H}_{13}\text{NOS}+\text{H}$) $^+$: 220.0791, found: 220.0790.

(I) Procedure for gram scale reactionGram scale reaction setup for **1a**Isolated product **1a**

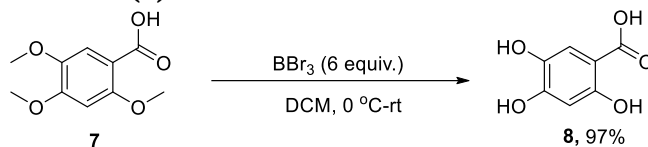
To an oven-dried 50 ml round bottom flask equipped with a stirring bar was added salicylic acid derivative **2a** (1 g, 0.42 equiv.), $K_2S_2O_8$ (1 equiv.), RFTA (5 mol%), and DCM (5 mL). The reaction mixture was irradiated with 450 nm Blue LED from ~5 cm distance under argon atmosphere and stirred at room temperature (under the continuous flow of fan to maintain the temperature at 25-30 °C) for 48 h (monitored by TLC).

(J) Synthesis of target molecule CX-614 and CX-554:

After completion of the reaction, the solvent was removed under reduced pressure and the crude residue was purified by column chromatography over silica gel (100-200 mesh size)

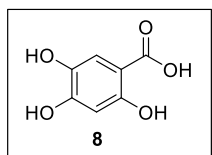
using mixture of petroleum ether/EtOAc (7:3) as an eluent to afford the corresponding desired 1,2,3,3a-tetrahydro-9H-benzo[e]pyrrolo[2,1-b][1,3]oxazin-9-one (**1a**) in 78% (630 mg) isolated yield.

2,4,5-trihydroxybenzoic acid (**8**):



The compound **8** was synthesized according to previously reported method in the literature.^[28] The solution of 2,4,5-trimethoxybenzoic acid **7** (3.0 g, 14.15 mmol) in 56 mL DCM (4mL/mmol) was allowed to stir at 0 °C under nitrogen atmosphere for 15 minutes. Then 2.0 molar BBr₃ in DCM (42 mL, 84 mmol) was added drop wise to the reaction mixture and stir it overnight. After completion of the reaction, carefully quench the mixture by pouring it into ice-cold water. Exercise caution as strong acidic fumes may evolve during this process. A white precipitate formed was filtered and washed with cold water to remove any residual reagents. The solid was dried to obtain the desired product **8** in 97% yield (2.34 g).

2,4,5-trihydroxybenzoic acid (8**):** 97% white solid; mp: 187-188°C; R_f: 0.3 (0.5:9.5, MeOH:DCM).

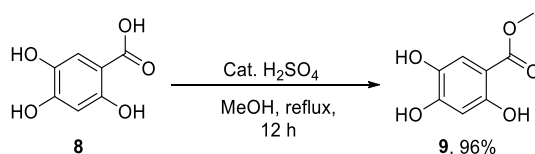


¹H NMR (400 MHz, DMSO-d₆): δ 7.12 (s, 1 H), 6.30 (s, 1 H).

¹³C NMR (101 MHz, DMSO-d₆): δ 172.1, 156.6, 153.5, 138.4, 114.9, 103.1, 102.7.

HRMS-ESI (m/z) calcd for (C₇H₆O₅+H)⁺: 171.0288, found: 171.0287.

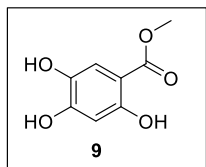
Methyl 2,4,5-trihydroxybenzoate (**9**):



The compound **9** was prepared by modification of the literature reported procedure.^[28] Trihydroxybenzoic acid (2.0 g, 11.76 mmol, 1.0 equiv) was dissolved in MeOH (30 mL), and 98% sulfuric acid (1 mL, 10 mmol, 1.0 equiv) was added. The mixture was heated to reflux for 24 h. After that time the reaction solution was cooled to room temperature and concentrated in *vacuo*. The resulting crude residue was dissolved in a sat. NaHCO₃ solution and extracted with

CH₂Cl₂. The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated and dried under vacuum to afford methyl benzoate in 96% yield (2.076 g) as a white solid.

Methyl 2,4,5-trihydroxybenzoate (**9**):



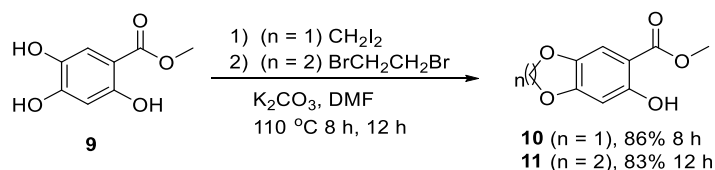
: 96% white solid; mp: 73-73°C; R_f: 0.4 (4:6, ethyl acetate:petroleum ether).

¹H NMR (400 MHz, DMSO-d₆): δ 10.28 (s, 1 H), 10.09 (br. s., 1 H), 8.87 (br. s., 1 H), 7.12 (s, 1 H), 6.32 (s, 1 H), 3.81 (s, 3 H).

¹³C NMR (101 MHz, DMSO-d₆): δ 169.7, 156.0, 153.7, 138.7, 114.2, 103.2, 102.2, 52.0.

HRMS-ESI (m/z) calcd for (C₈H₈O₅+H)⁺:185.0444, found: 185.0448.

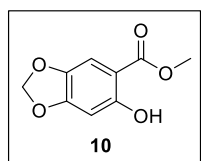
Synthesis of products **10** & **11**:



The compounds **10** and **11** were synthesized according to previously reported methods in the literature.^[10]

The solution of methyl 2,4,5-trihydroxybenzoate (**9**, 1 g, 5.43 mmol) and anhydrous K₂CO₃ (2.5 g/6 mmol, 2.2g) in 10 mL dry DMF (10 mL/5.4 mmol) was allowed to stir at room temperature under nitrogen atmosphere for 10 minutes. Diiodomethane (860 μL, 6.5 mmol) or 1,2-dibromoethane (516 μL, 6.5 mmol) was added drop wise to the reaction mixture. After 10 minutes, it was heated to 110 °C and continued for 12 h. Then water was added to the reaction mixture and it was extracted with ethyl acetate (3 X 20 mL). The combined organic layer was dried over anhydrous Na₂SO₄. The crude product was purified by column chromatography using ethyl acetate:pet. ether (2:3). The desired products **10** & **11** were obtained in 86% (879 mg) and 83% (948 mg) yield respectively.

Methyl 6-hydroxybenzo[d][1,3]dioxole-5-carboxylate (**10**)^[29]:



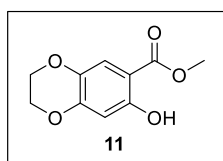
: 86% white solid; mp: 74-75°C; R_f: 0.4 (4:6, ethyl acetate:petroleum ether)

^1H NMR (400 MHz, CDCl_3): δ 11.05 (s, 1 H), 7.17 (s, 1 H), 6.45 (s, 1 H), 5.96 (s, 2 H), 3.90 (s, 3 H).

^{13}C NMR (101 MHz, CDCl_3): δ 170.4, 160.1, 153.8, 140.5, 106.7, 103.9, 101.7, 98.2, 52.1

HRMS-ESI (m/z) calcd for $(\text{C}_9\text{H}_8\text{O}_5+\text{H})^+$: 197.0444, found: 197.0453.

Methyl 7-hydroxy-2,3-dihydrobenzo[b][1,4]dioxine-6-carboxylate (11):



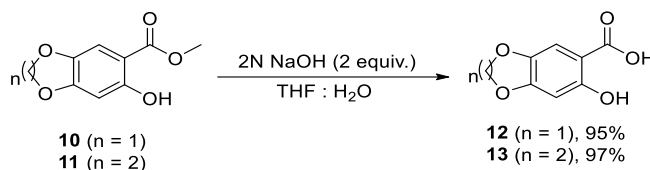
: 83% white solid; mp: 65-66°C; R_f : 0.3 (4:6, ethyl acetate:petroleum ether).

^1H NMR (400 MHz, CDCl_3): δ 10.47 (s, 1 H), 7.31 (s, 1 H), 6.45 (s, 1 H), 4.30 - 4.26 (m, 2 H), 4.21 - 4.17 (m, 2 H), 3.90 (s, 3 H).

^{13}C NMR (101 MHz, CDCl_3): δ 170.1, 157.1, 150.2, 136.5, 117.1, 105.4, 104.7, 64.9, 63.8, 52.0.

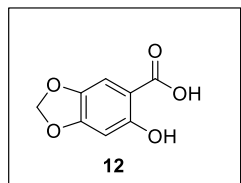
HRMS-ESI (m/z) calcd for $(\text{C}_{10}\text{H}_{10}\text{O}_5+\text{H})^+$: 211.0601, found: 211.0599.

Hydrolysis of products 10 and 11 to obtain acids 12 and 13:



Hydrolysis was done following the general procedure E.

6-hydroxybenzo[d][1,3]dioxole-5-carboxylic acid (12)^[30]:



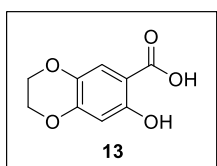
: 95% white solid; mp: 197-198°C; R_f : 0.3 (0.5:9.5, MeOH:DCM).

^1H NMR (400 MHz, DMSO- d_6): δ 7.14 (s, 1 H), 6.57 (s, 1 H), 6.04 (s, 2 H)

^{13}C NMR (101 MHz, DMSO- d_6): δ 172.0, 159.6, 153.5, 140.2, 106.8, 103.9, 101.9, 97.9.

HRMS-ESI (m/z) calcd for $(\text{C}_8\text{H}_6\text{O}_5+\text{H})^+$: 183.0288, found: 184.0285.

7-hydroxy-2,3-dihydrobenzo[b][1,4]dioxine-6-carboxylic acid (13):



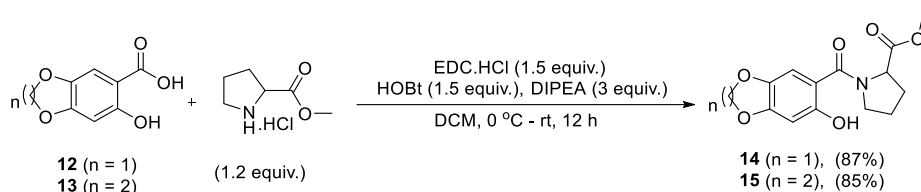
: 97% white solid; mp: 185-186°C; R_f : 0.3 (0.5:9.5, MeOH:DCM).

^1H NMR (400 MHz, DMSO- d_6): δ 7.19 (s, 1 H), 6.40 (s, 1 H), 4.28 (s, 2 H), 4.20 (s, 2 H).

^{13}C NMR (101 MHz, DMSO- d_6): δ 171.4, 156.5, 149.9, 136.2, 117.0, 105.5, 104.1, 64.8, 63.6

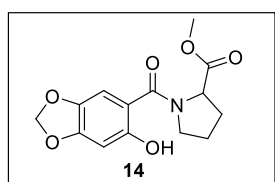
HRMS-ESI (m/z) calcd for (C₉H₈O₅+H)⁺: 197.0444, found: 197.0444.

Amidation of products 12 and 13 to obtain esters 14 and 15:



Amidation was done following the general procedure A.

Methyl (6-hydroxybenzo[d][1,3]dioxole-5-carbonyl)prolinate (14):



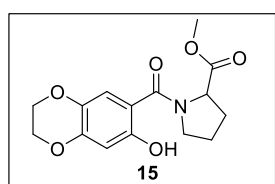
: 87% white solid; mp: 81-82°C; R_f: 0.4 (4:6, ethyl acetate:petroleum ether).

¹H NMR (400 MHz, CDCl₃): δ 11.35 (br. s., 1 H), 6.97 (s, 1 H), 6.48 (s, 1 H), 5.94 (s, 2 H), 4.66 (t, *J* = 7.3 Hz, 1 H), 3.92 - 3.80 (m, 2 H), 3.76 (s, 3 H), 2.33 (td, *J* = 5.9, 7.8 Hz, 1 H), 2.12 (td, *J* = 5.7, 11.3 Hz, 1 H), 2.03 - 1.86 (m, 2 H).

¹³C NMR (101 MHz, CDCl₃): δ 172.5, 170.6, 158.7, 151.5, 139.6, 107.3, 106.3, 101.5, 99.1, 60.4, 52.4, 50.9, 29.0, 25.8.

HRMS-ESI (m/z) calcd for (C₁₄H₁₅NO₆+H)⁺: 294.0972, found: 294.0984.

Methyl (7-hydroxy-2,3-dihydrobenzo[b][1,4]dioxine-6-carbonyl)prolinate (15):



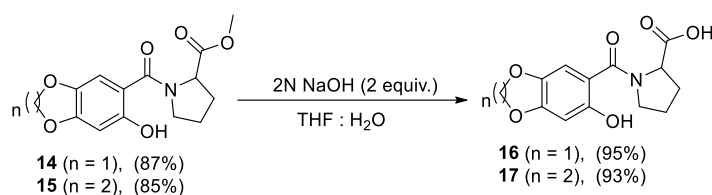
: 85% thick oil; R_f: 0.4 (4:6, ethyl acetate:petroleum ether)

¹H NMR (400 MHz, CDCl₃): δ 10.83 (br. s., 1 H), 7.07 (s, 1 H), 6.48 (s, 1 H), 4.66 (t, *J* = 7.1 Hz, 1 H), 4.32 - 4.26 (m, 2 H), 4.21 (d, *J* = 4.1 Hz, 2 H), 3.92 - 3.83 (m, 2 H), 3.77 (s, 3 H), 2.33 (dd, *J* = 6.3, 13.1 Hz, 1 H), 2.11 (td, *J* = 5.7, 11.4 Hz, 1 H), 2.05 - 1.91 (m, 2 H).

¹³C NMR (101 MHz, CDCl₃): δ 172.6, 170.1, 156.1, 147.8, 135.4, 116.3, 109.3, 105.3, 64.9, 64.0, 60.4, 52.4, 50.9, 29.0, 25.8.

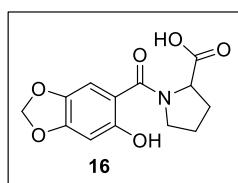
HRMS-ESI (m/z) calcd for (C₁₅H₁₇NO₆+H)⁺: 308.1129, found: 308.1132.

Hydrolysis of products 14 and 15 to obtain acids 16 and 17:



Hydrolysis was done following the general procedure E.

(6-hydroxybenzo[d][1,3]dioxole-5-carbonyl)proline (16):



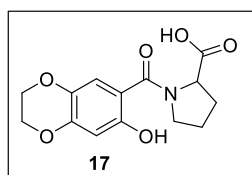
: 95% white solid; mp: 141-142°C; R_f : 0.2 (0.5:9.5, MeOH:DCM).

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 6.95 (s, 1 H), 6.49 (s, 1 H), 5.95 (s, 2 H), 4.68 (t, J = 7.6 Hz, 1 H), 3.84 (t, J = 6.4 Hz, 2 H), 2.41 - 2.27 (m, 1 H), 2.20 - 2.06 (m, 2 H), 2.02 - 1.87 (m, 1 H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 176.6, 170.9, 158.4, 151.6, 139.8, 107.3, 106.3, 101.6, 99.2, 60.4, 51.1, 28.7, 25.8

HRMS-ESI (m/z) calcd for $(\text{C}_{13}\text{H}_{13}\text{NO}_6 + \text{H})^+$: 280.0816, found: 280.827.

(7-hydroxy-2,3-dihydrobenzo[b][1,4]dioxine-6-carbonyl)proline (17):



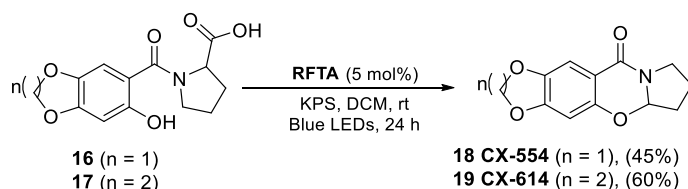
: 93% white solid; mp: 114-115°C; R_f : 0.3 (0.5:9.5, MeOH:DCM).

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.04 (s, 1 H), 6.48 (s, 1 H), 4.68 (dd, J = 5.9, 8.0 Hz, 1 H), 4.32 - 4.24 (m, 2 H), 4.24 - 4.14 (m, 2 H), 3.86 (t, J = 6.4 Hz, 2 H), 2.33 (dd, J = 6.7, 7.9 Hz, 1 H), 2.17 - 2.08 (m, 2 H), 2.0 - 1.87 (m, 1 H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 176.4, 170.4, 155.9, 147.9, 135.5, 116.2, 109.2, 105.4, 64.9, 64.0, 60.3, 51.0, 28.6, 25.8.

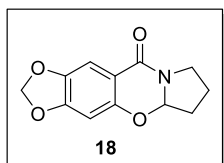
HRMS-ESI (m/z) calcd for $(\text{C}_{14}\text{H}_{15}\text{NO}_6 + \text{H})^+$: 294.0972, found: 294.0983.

Synthesis of CX-554 (18) & CX-614 (19) End game:



The reaction was performed following the general procedure G with **16** & **17** (0.25 mmol, 60 mg). White solid of CX-614 and CX-554 was obtained after 60-120 mesh silica gel column purification using pet ether: ethyl acetate (6:4) mixture as eluent.

5a,6,7,8-tetrahydro-10H-[1,3]dioxolo[4',5':4,5]benzo[1,2-e]pyrrolo[2,1-b][1,3]oxazin-10-one (18):^[11]



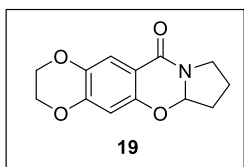
: Reaction time 48 h. Additive Cs₂CO₃ (1 equiv., 0.21 mmol, 70 mg), 45% (22.6 mg from 60 mg of **16**) white solid; mp: 111 -112°C; R_f: 0.3 (4:6, ethyl acetate: petroleum ether).

¹H NMR (400 MHz, CDCl₃): δ 7.31 (s, 1 H), 6.45 (s, 1 H), 5.99 (s, 2 H), 5.44 (t, *J* = 5.7 Hz, 1 H), 3.88 - 3.77 (m, 1 H), 3.64 - 3.52 (m, 1 H), 2.46 - 2.34 (m, 1 H), 2.26 - 2.16 (m, 1 H), 2.14 - 2.03 (m, 1 H), 2.00 - 1.84 (m, 1 H).

¹³C NMR (101 MHz, CDCl₃): δ 160.8, 154.1, 152.0, 143.4, 112.7, 106.1, 101.9, 97.8, 88.7, 44.3, 31.8, 21.5.

ESIMS [M+H]⁺ (m/z): 234.

2,3,6a,7,8,9-hexahydro-11H-[1,4]dioxino[2',3':4,5]benzo[1,2-e]pyrrolo[2,1-b][1,3]oxazin-11-one (19):^[10, 11]



: Reaction time 48 h. 60% (30.2 mg from 60 mg of **17**) white solid; mp: 154-155°C; R_f: 0.3 (4:6, ethyl acetate: petroleum ether).

¹H NMR (400 MHz, CDCl₃): δ 7.41 (s, 1 H), 6.45 (s, 1 H), 5.42 (t, *J* = 5.7 Hz, 1 H), 4.32 - 4.25 (m, 2 H), 4.25 - 4.18 (m, 2 H), 3.87 - 3.73 (m, 1 H), 3.65 - 3.50 (m, 1 H), 2.46 - 2.32 (m, 1 H), 2.25 - 2.14 (m, 1 H), 2.13 - 2.01 (m, 1 H), 2.00 - 1.85 (m, 1 H).

¹³C NMR (101 MHz, CDCl₃): δ 160.7, 152.1, 148.1, 139.3, 115.8, 113.2, 104.5, 88.6, 64.8, 63.8, 44.2, 31.9, 21.3.

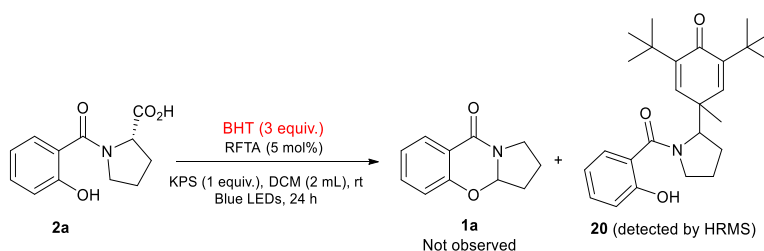
ESIMS [M+H]⁺ (m/z): 248.

The analytical and spectral data of the known drug molecules CX- 514 (**18**) and CX-614 (**19**) are in agreement with the reported data.^[10, 11]

4.7 Mechanistic studies

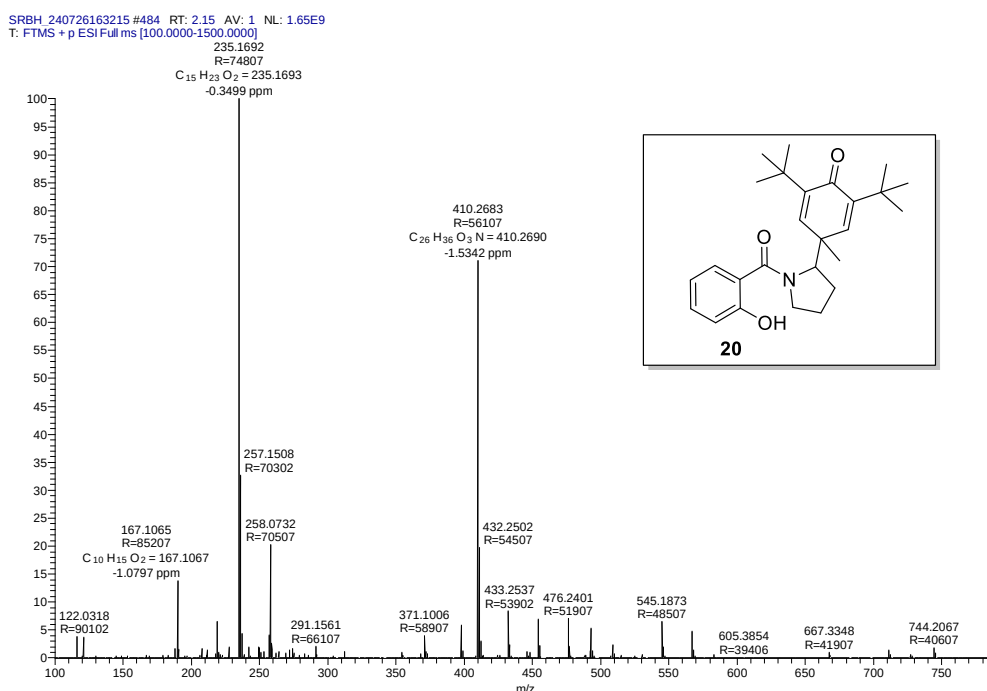
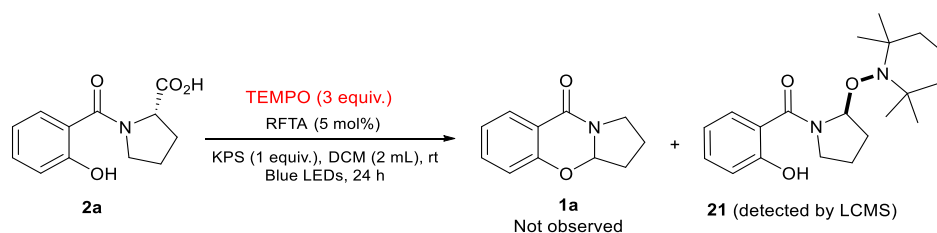
4.7.1 Control experiments

Procedure for radical trapping experiment with BHT



Scheme 4. Radical trapping reaction with BHT

The reaction under the optimized reaction conditions was conducted in the presence of 3.0 equivalents of BHT (Butylated Hydroxytoluene) as a radical scavenger. Under this conditions, the corresponding product **1a** was not observed. This experiment suggests a radical pathway. Moreover, the corresponding BHT adduct formed by the trapping of the photogenerated carbon-centered radical by BHT was detected by **HRMS-ESI** (m/z) calcd for $(C_{26}H_{21}NO_3+H)^+$: 410.2690, found: 410.2683.

**Figure 3.** HRMS data of BHT trapped radical intermediate.**Procedure for radical trapping experiment with TEMPO****Scheme 5.** Radical trapping reaction with TEMPO

The reaction under the optimized reaction conditions was conducted in the presence of 3.0 equivalents of TEMPO (2,2,6,6-Tetramethylpiperidine 1-oxyl, 2,2,6,6-Tetramethyl-1-piperidinyloxy) as a radical scavenger. Under such conditions, the corresponding product **1a** was not observed. This experiment suggests that reaction proceeds via radical pathway. Moreover, the corresponding TEMPO adduct formed by the trapping of the photo generated carbon-centered radical by TEMPO was detected by **LC-MS** (m/z) calcd for $(C_{26}H_{21}NO_3+H)^+$: 347

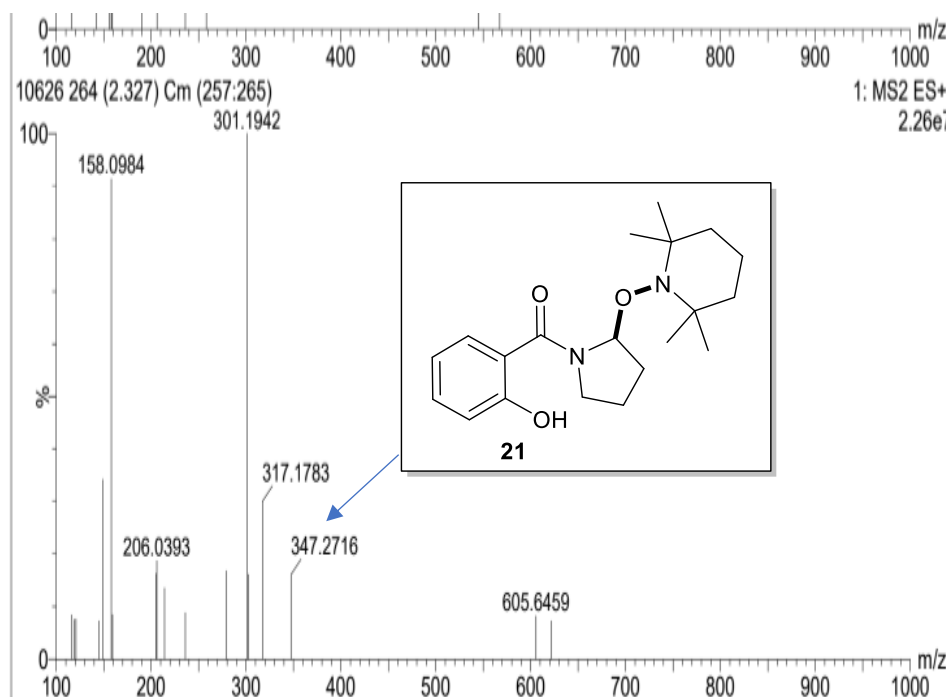


Figure 4. LC-MS data of TEMPO trapped radical intermediate.

4.7.2 Fluorescence Quenching Experiments

Fluorescence spectra were collected on FS5 Spectro fluorophotometer. The solutions were exposed to irradiation at 450 nm, and the resulting luminescence was recorded at 530 nm. For the fluorescence quenching experiments, stock solutions of Riboflavin Tetraacetate (RFTA) with a concentration of 1.36×10^{-4} M and a salicylic acid derivative **2a** with a concentration of 1.4×10^{-2} M were prepared. In a gas-tight 10 mm quartz cuvette, samples were prepared by mixing a fixed volume of the RFTA stock solution with varying amounts (see figure 4) of potential quenchers. Before measurement, the samples were purged with N_2 for 10 minutes. Following this, the samples were irradiated at 450 nm, and their emission spectra were recorded around 530 nm. As depicted in the accompanying figure, significant fluorescence quenching was observed, with the extent of quenching depending on the concentration of the quenchers.

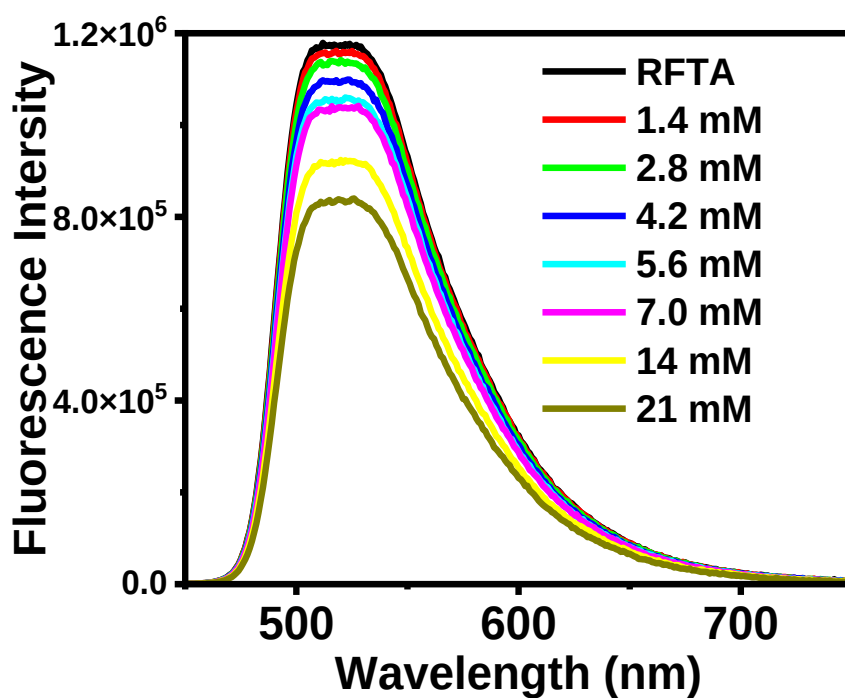


Figure 5. Fluorescence quenching of RFTA with carboxylic acid **2a**.

These experiments clearly show that carboxylic acid **2a** is an effective quencher of the fluorescence of RFTA*.

4.7.3 Stern-Volmer plot

I_0/I versus the quencher concentration was mapped, where I_0 is the emission intensity of RFTA at 530 nm in the absence of a quencher and I is the observed intensity, as a function of the quencher **2a** concentration was measured and the subsequent Stern-Volmer plot was calculated for comparison from the linear fit.

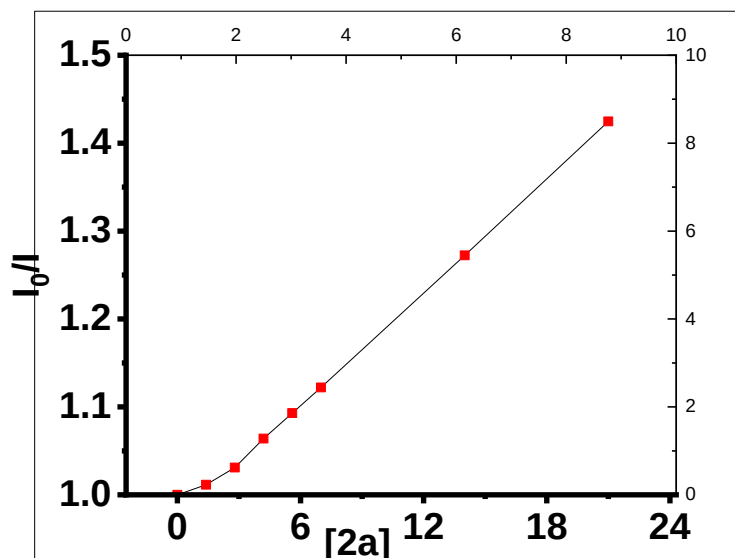


Figure 6. Steady-state Stern–Volmer quenching plot of RFTA with **2a**.

The Stern-Volmer plot proved that the compound **2a** is a potential fluorescence quencher of the excited state of RFTA* (Figure 6).

4.7.4 Cyclic Voltammetry experiment

A glassy-carbon electrode (3 mm diameter, disc-electrode) was used as the working electrode, a Pt-wire as auxiliary electrode and an Ag–AgCl as reference electrode.

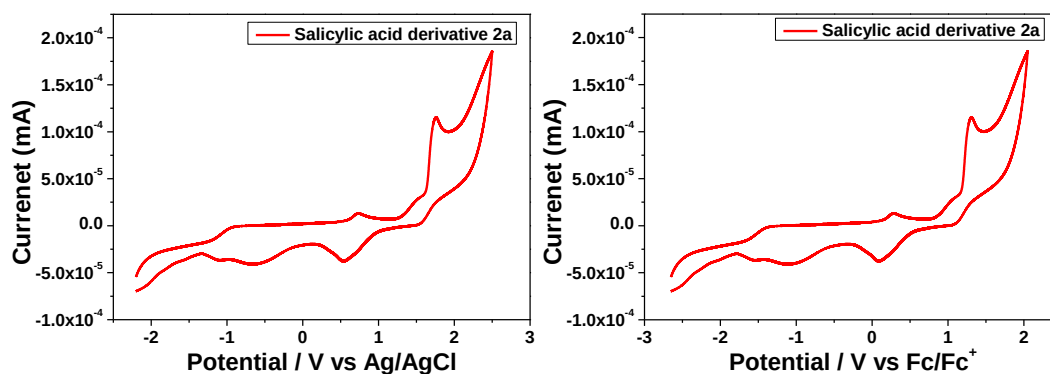


Figure 7. Cyclic voltammetry of **2a** was performed in CH_2Cl_2 using $n\text{-Bu}_4\text{NPF}_6$ (0.1 M) at 100 mV/s scan rate vs Ag/AgCl.

In the positive scan, we observe three oxidation peaks at 0.73 V, 1.1 V and 1.9 V. The first two peaks (0.73 V and 1.1 V) are reversible, while the last peak (1.9 V) is irreversible. In the negative scan, we observe two reduction peaks at (1.5 V) and (0.6 V), with the second reduction peak exhibiting reversible behaviour.

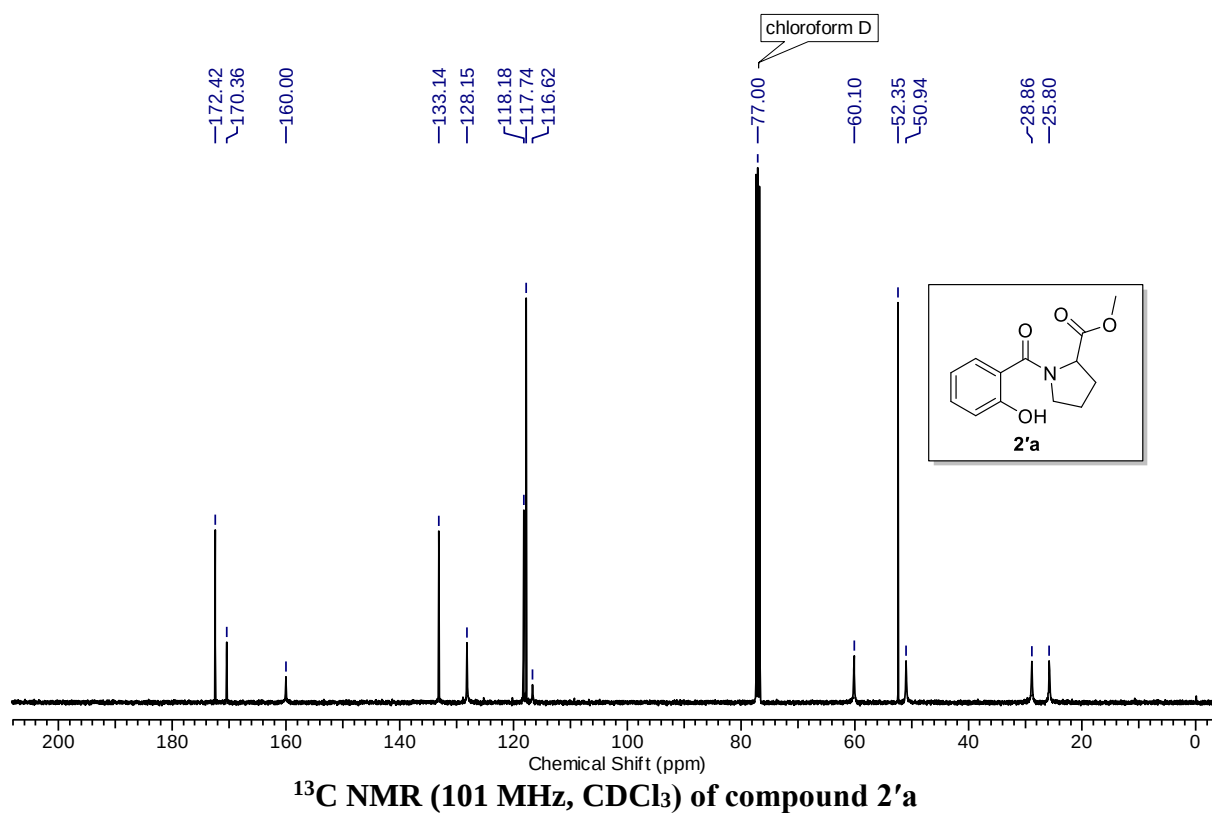
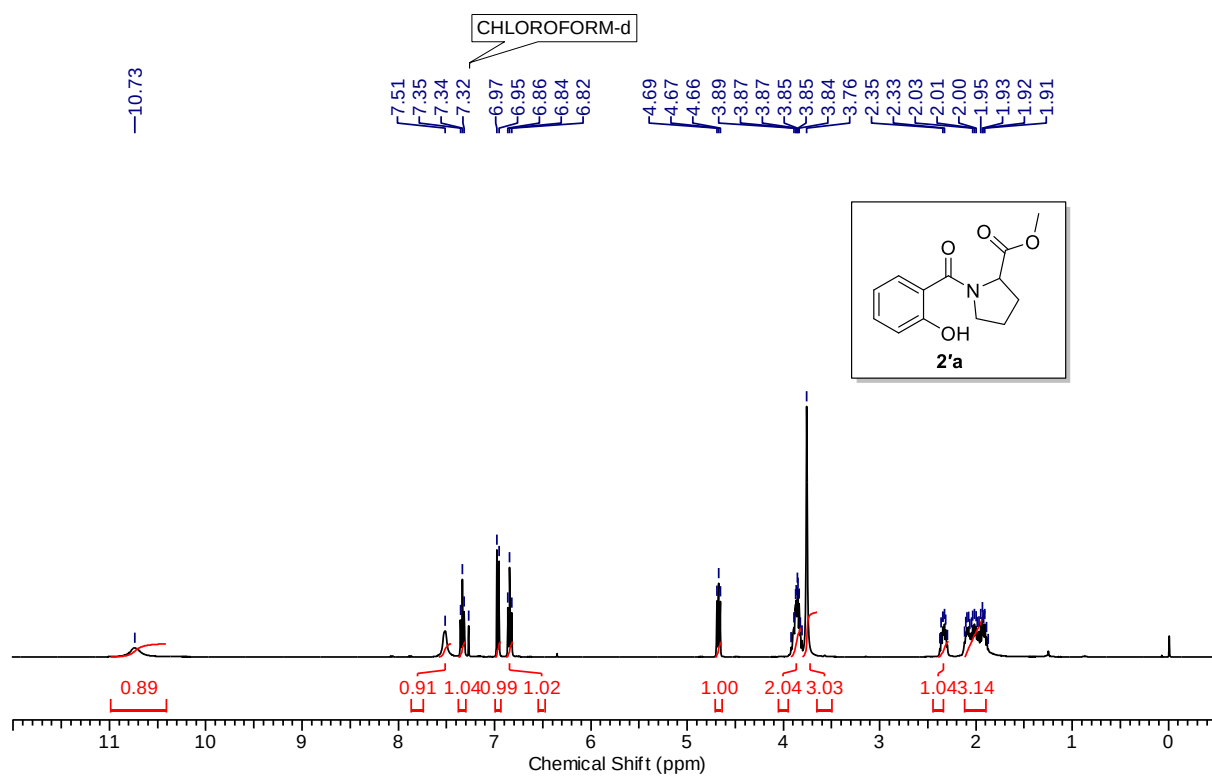
The cyclic voltammetry studies indicates that the transformation is driven via an oxidative quenching mechanistic cycle.

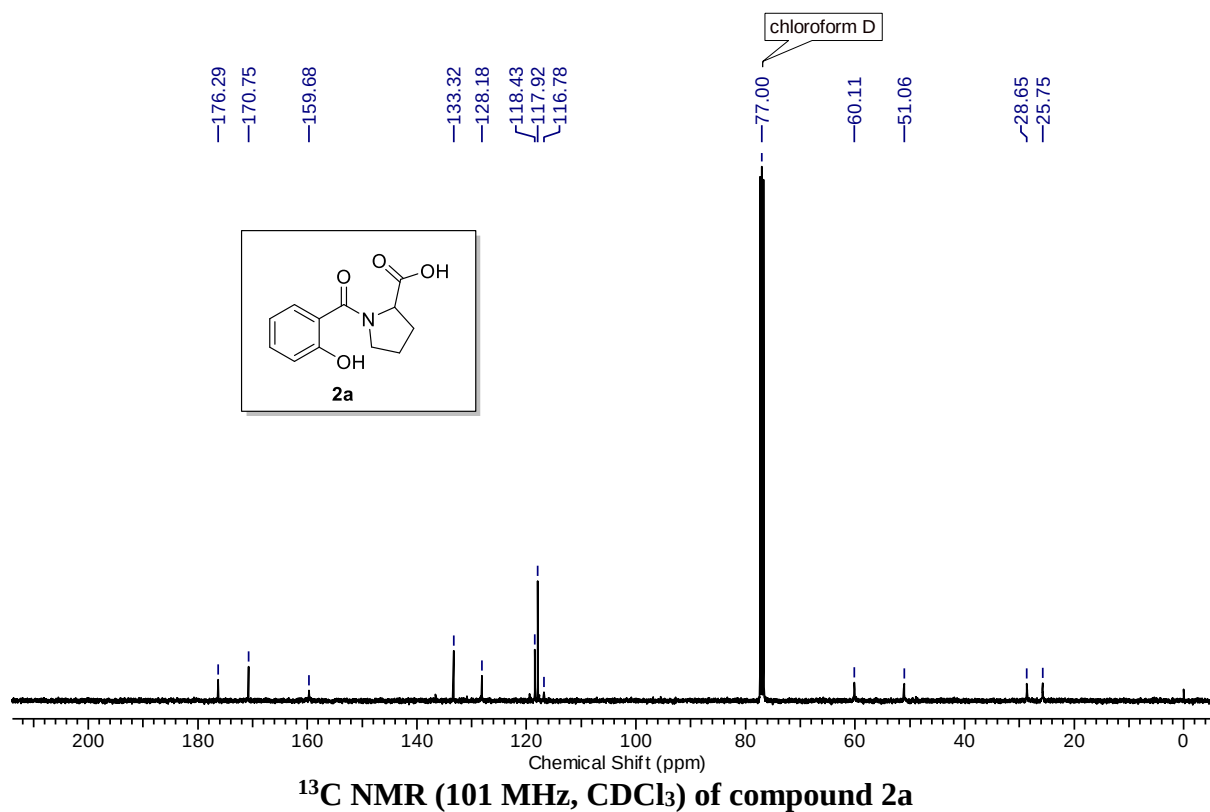
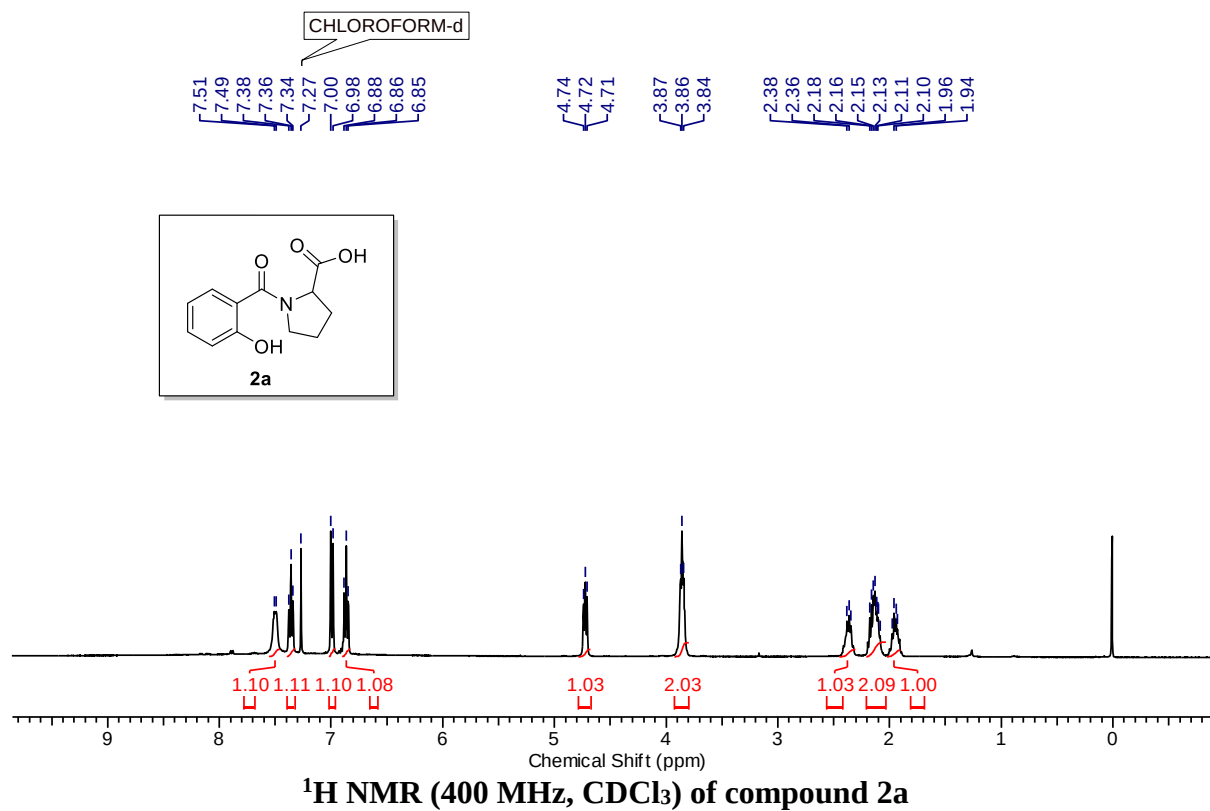
4.8 References:

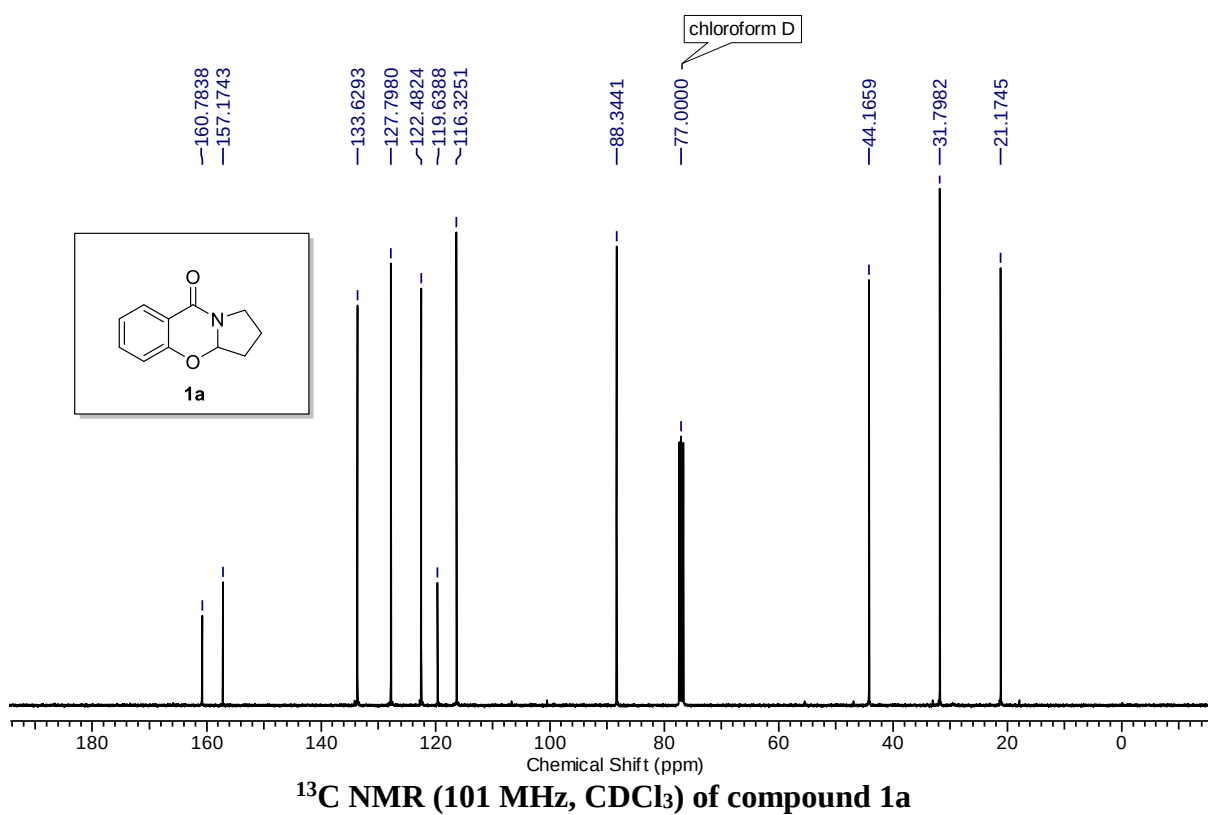
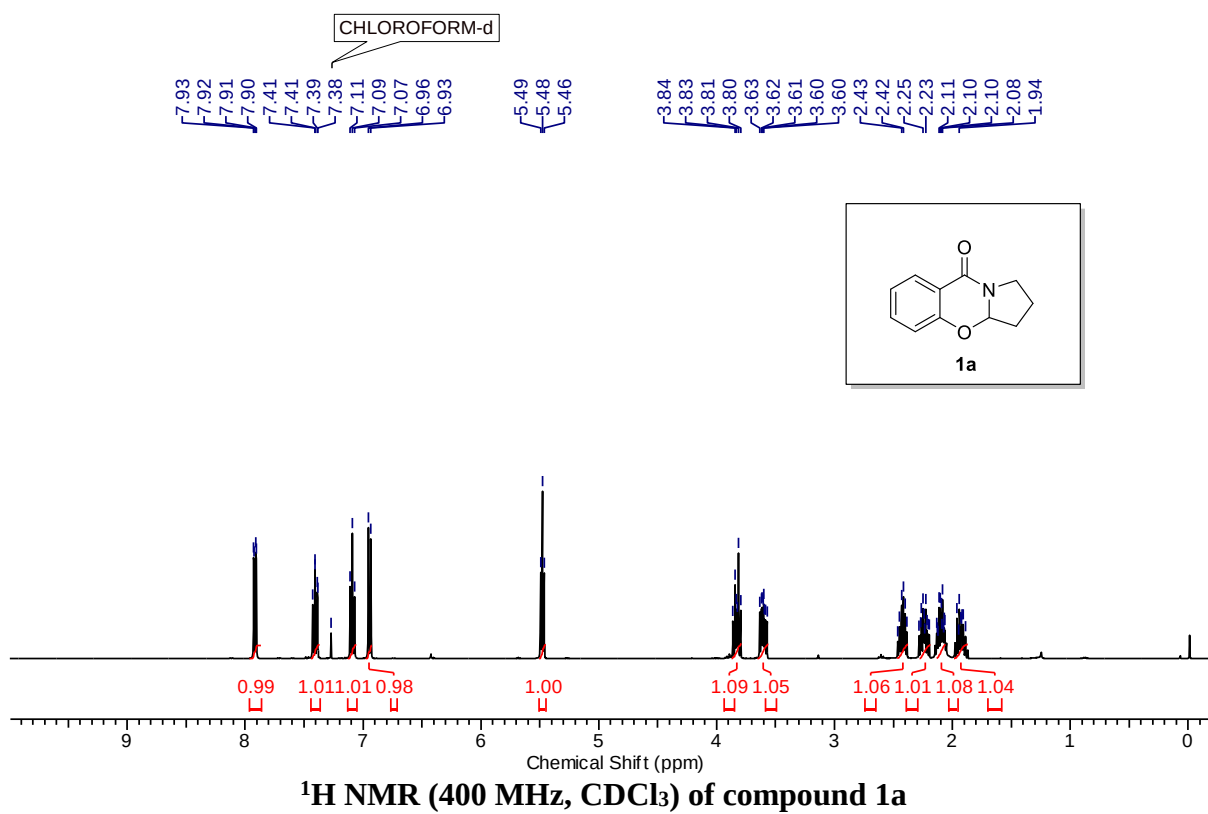
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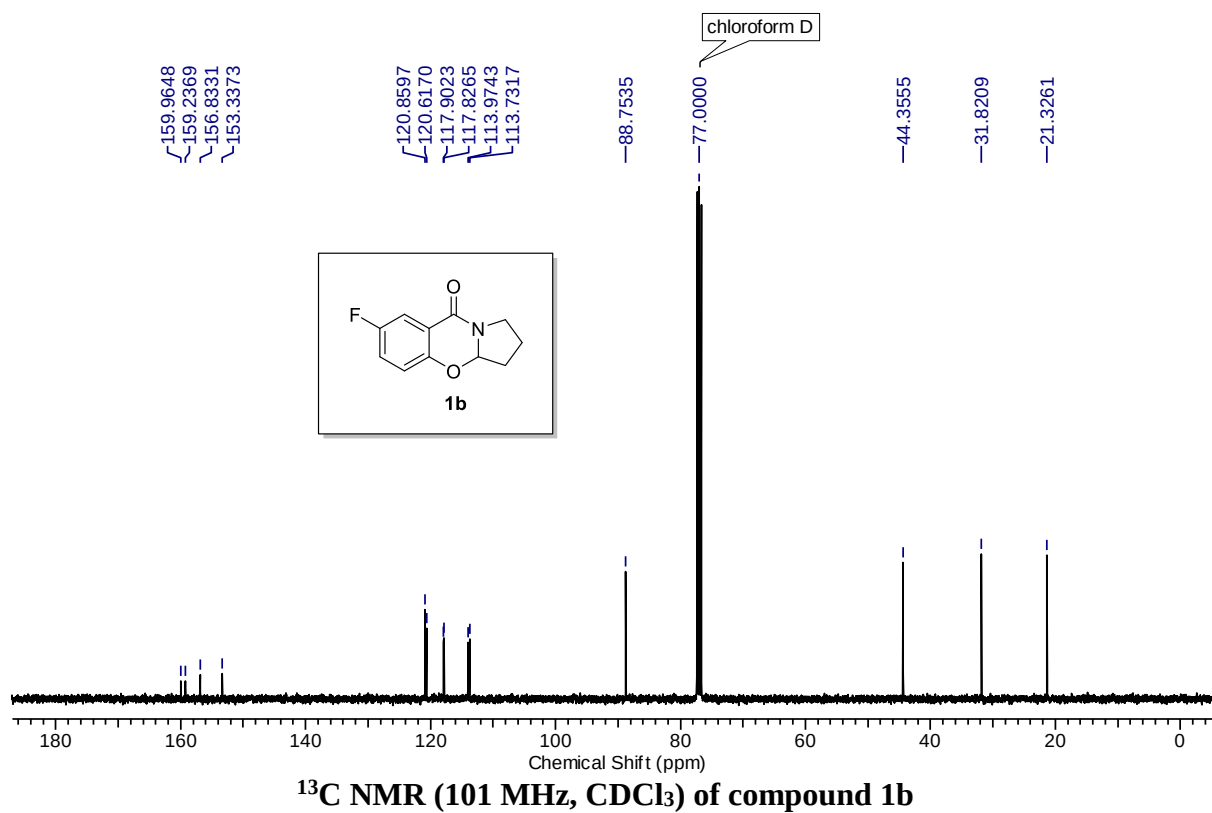
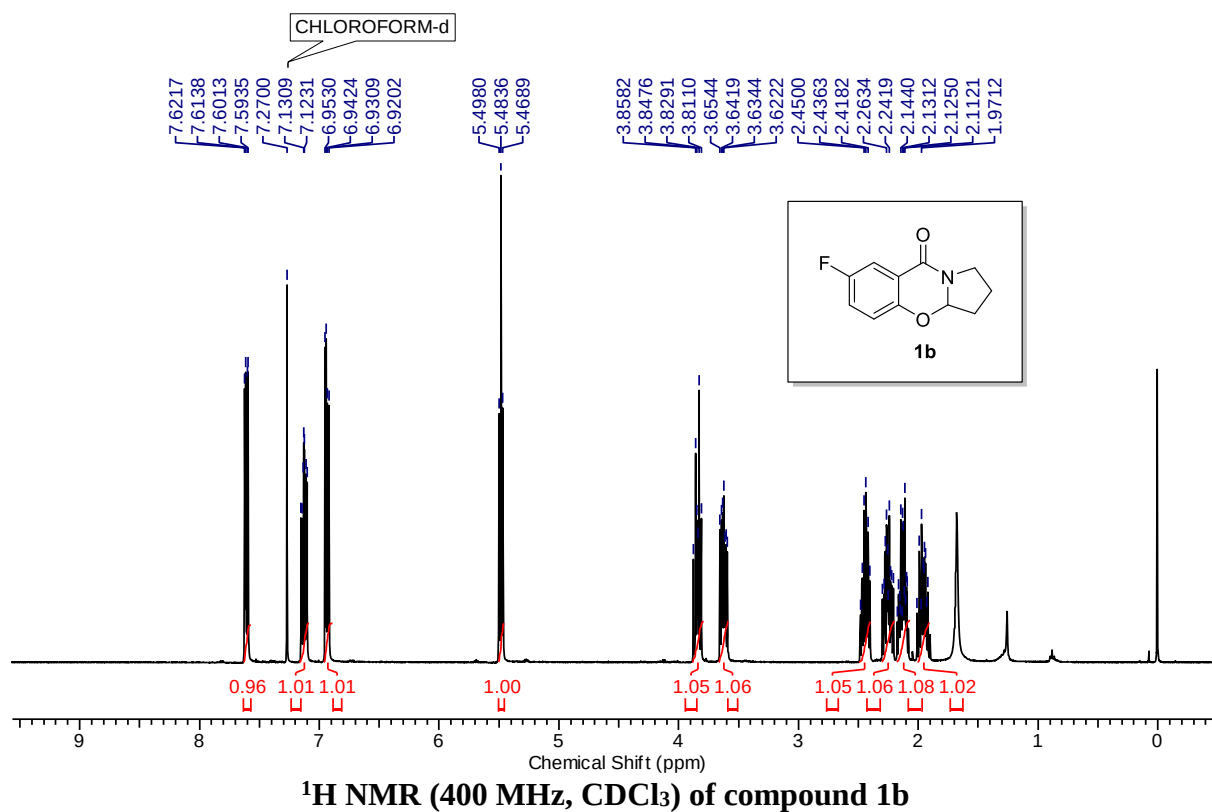
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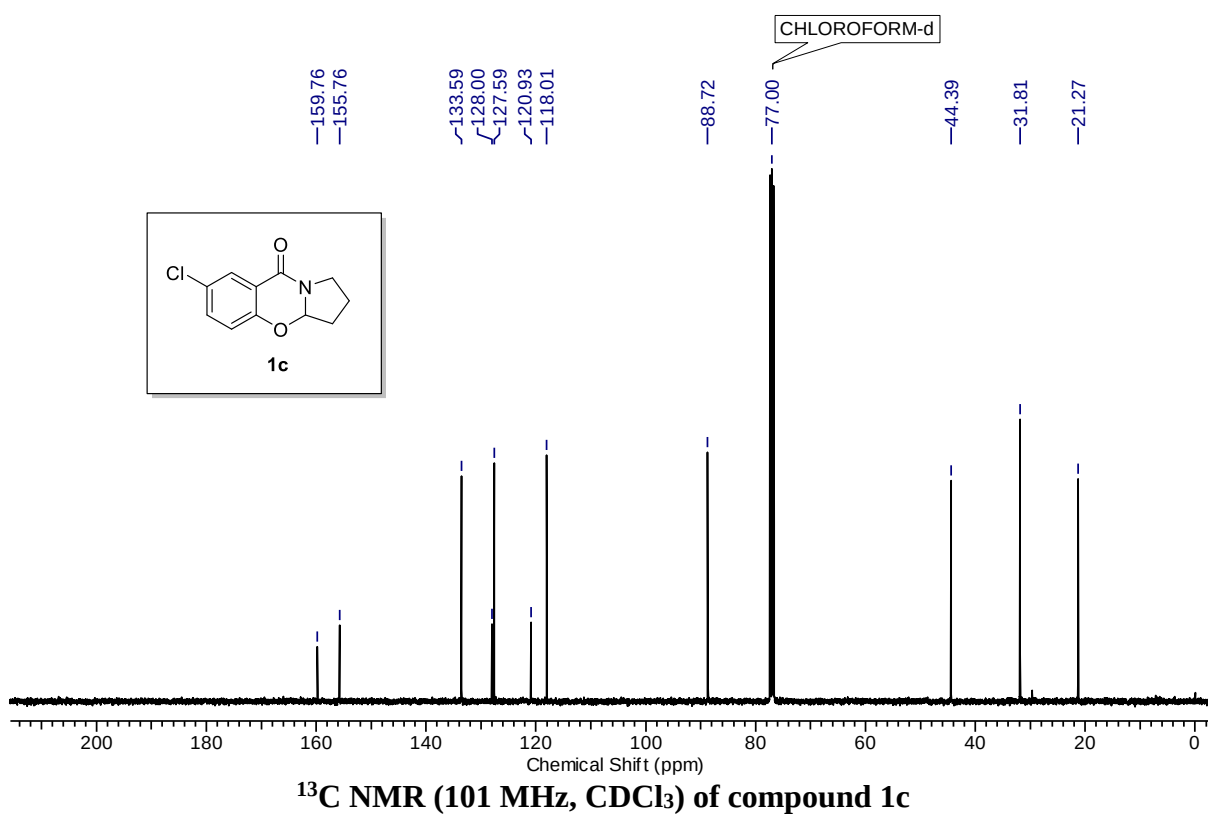
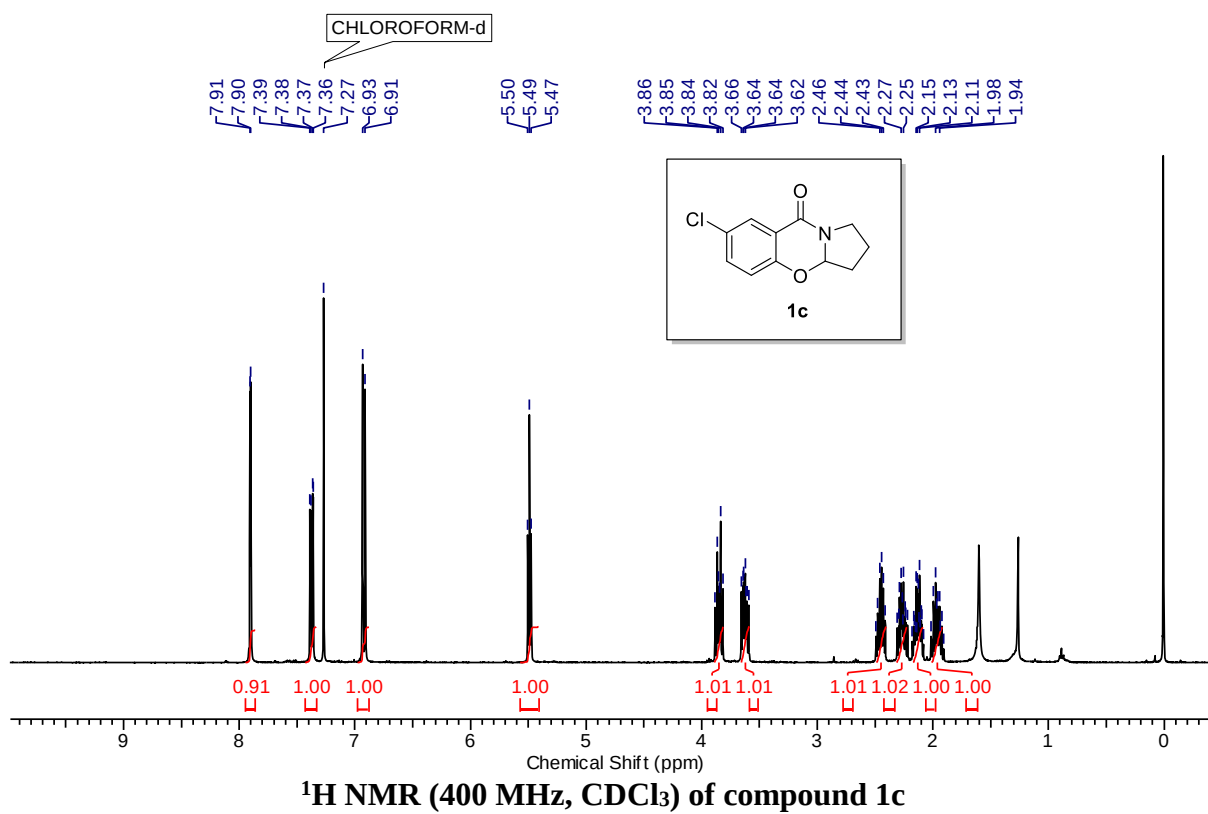
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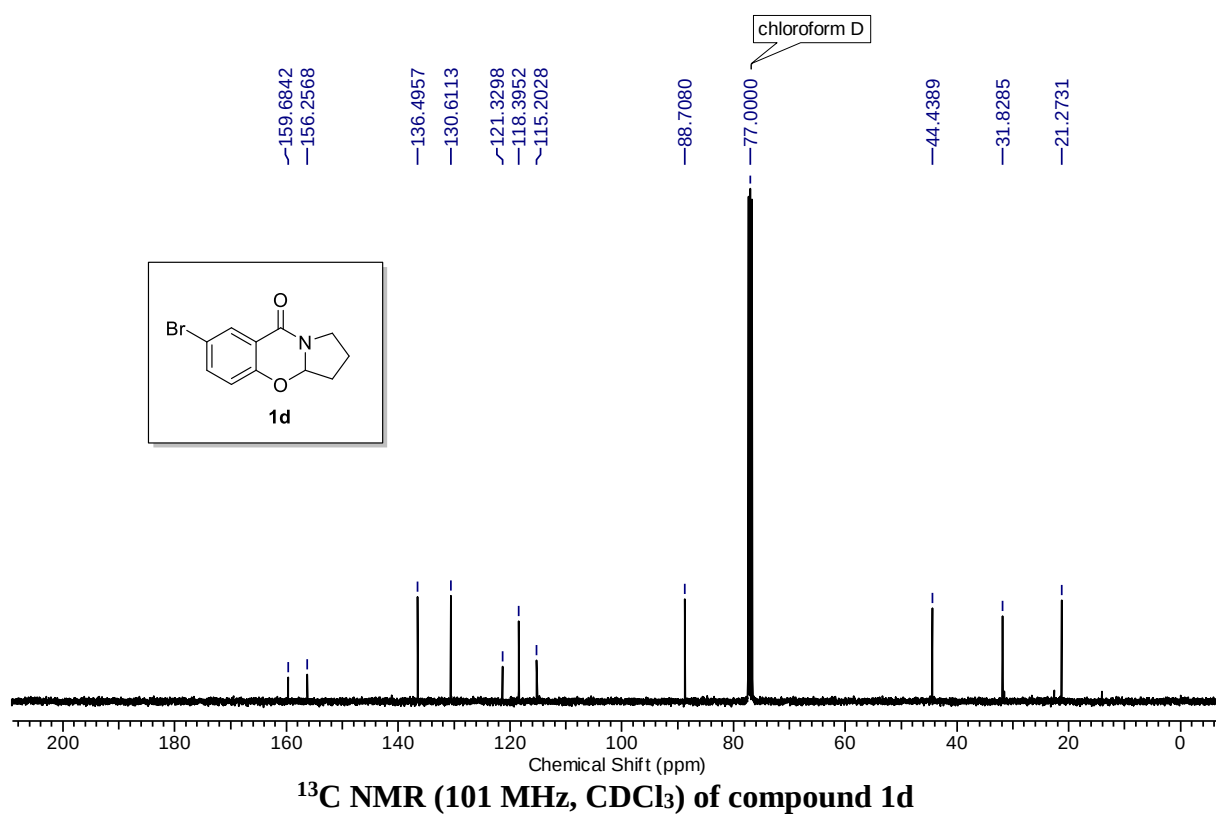
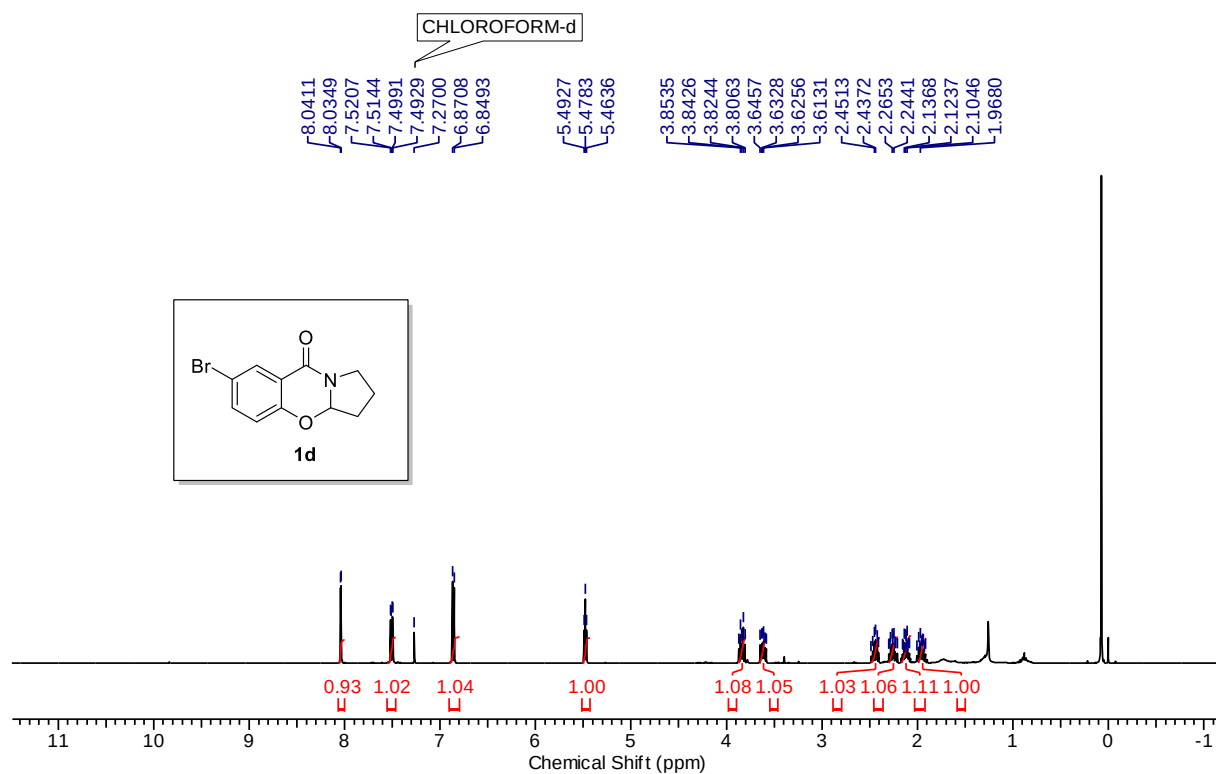
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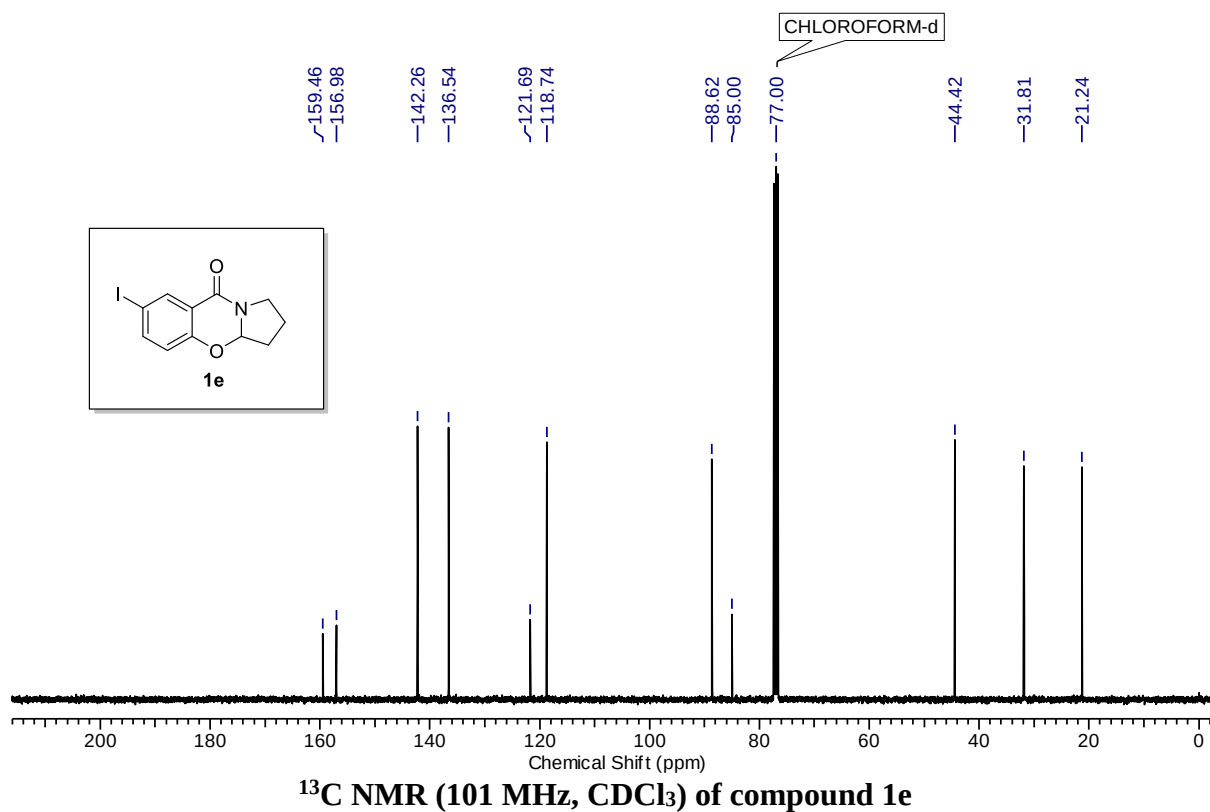
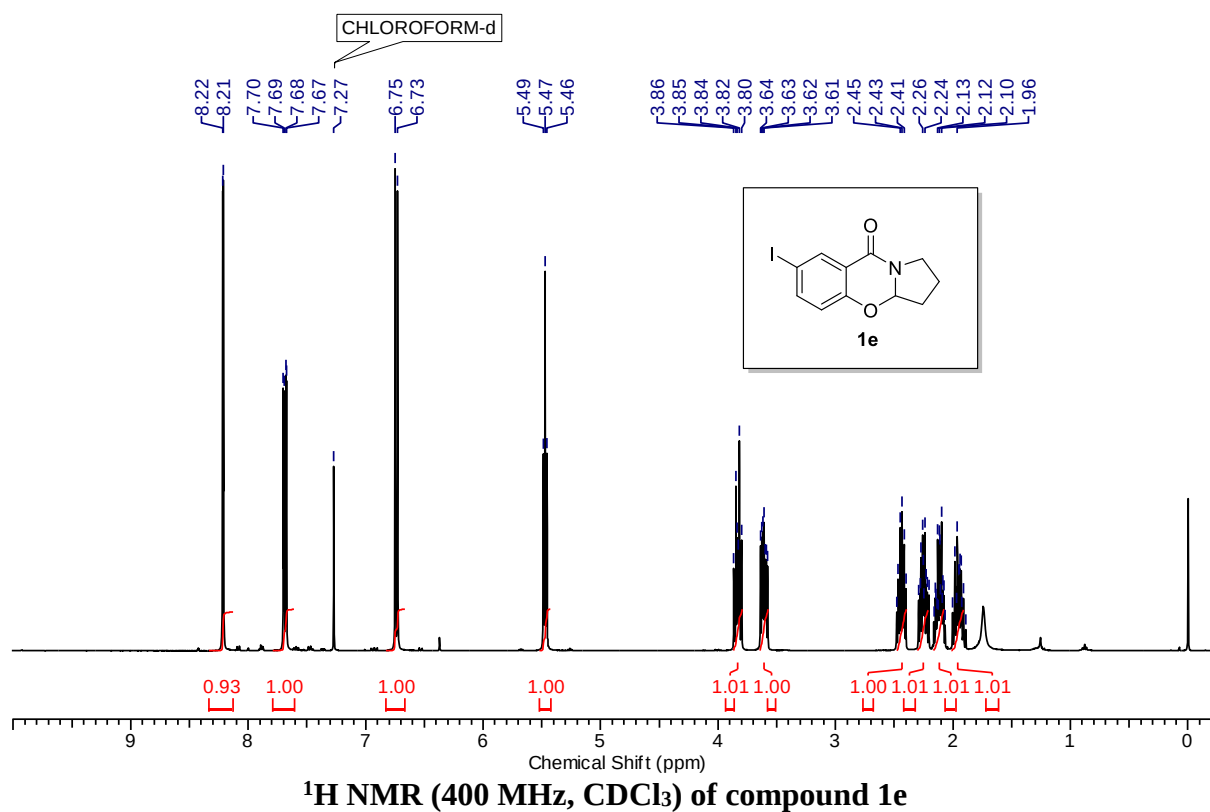


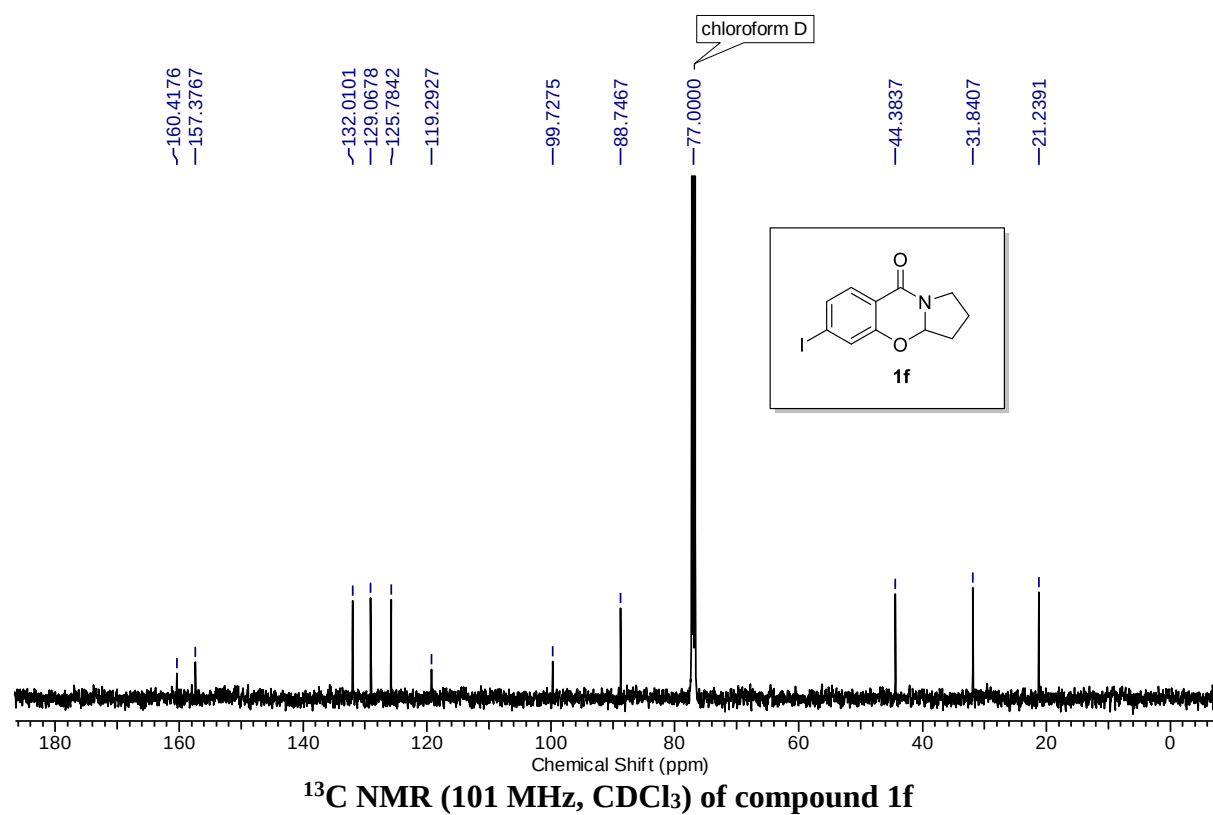
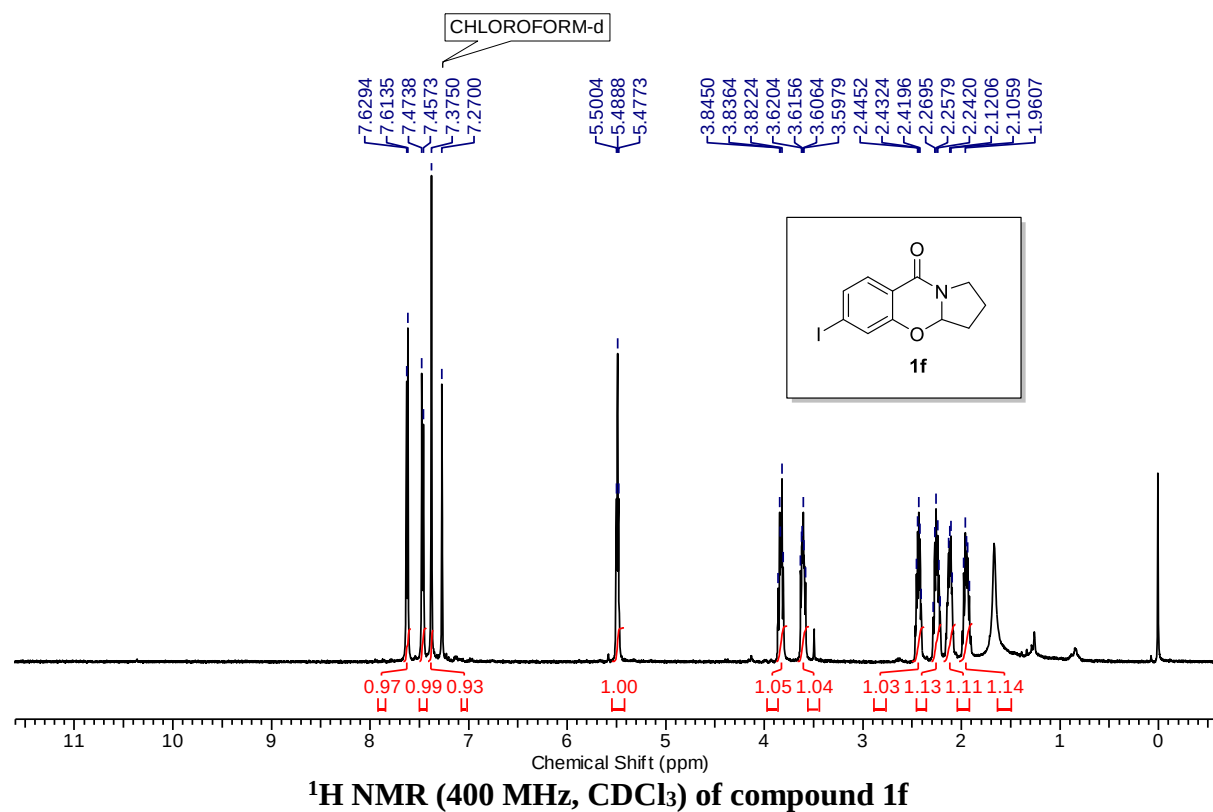


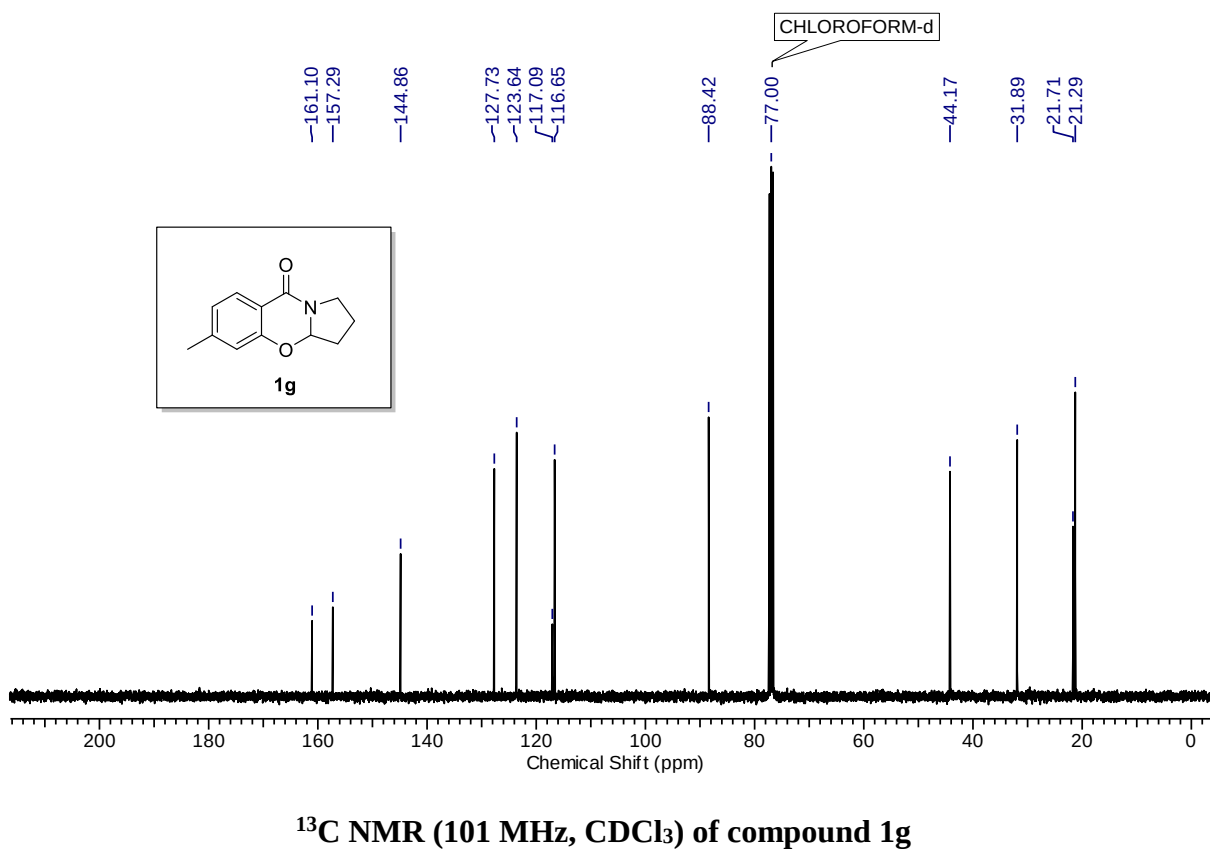
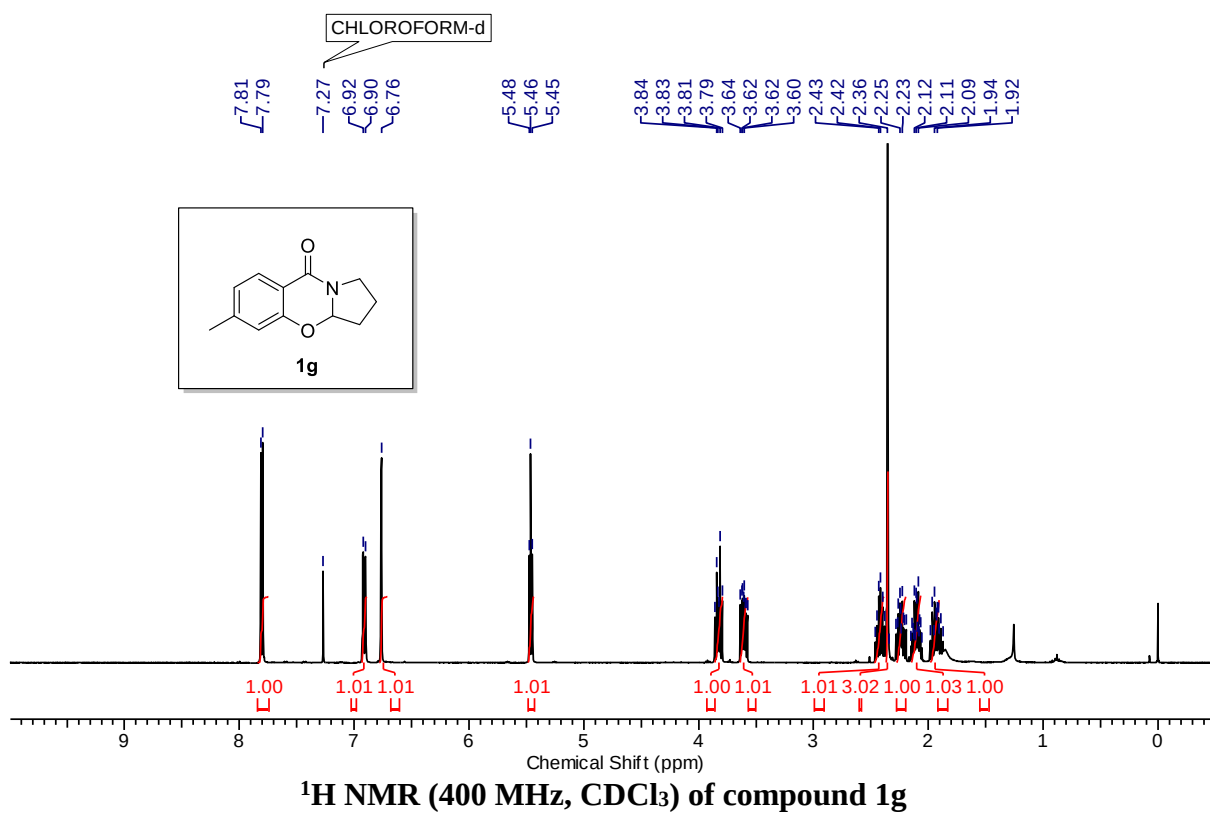


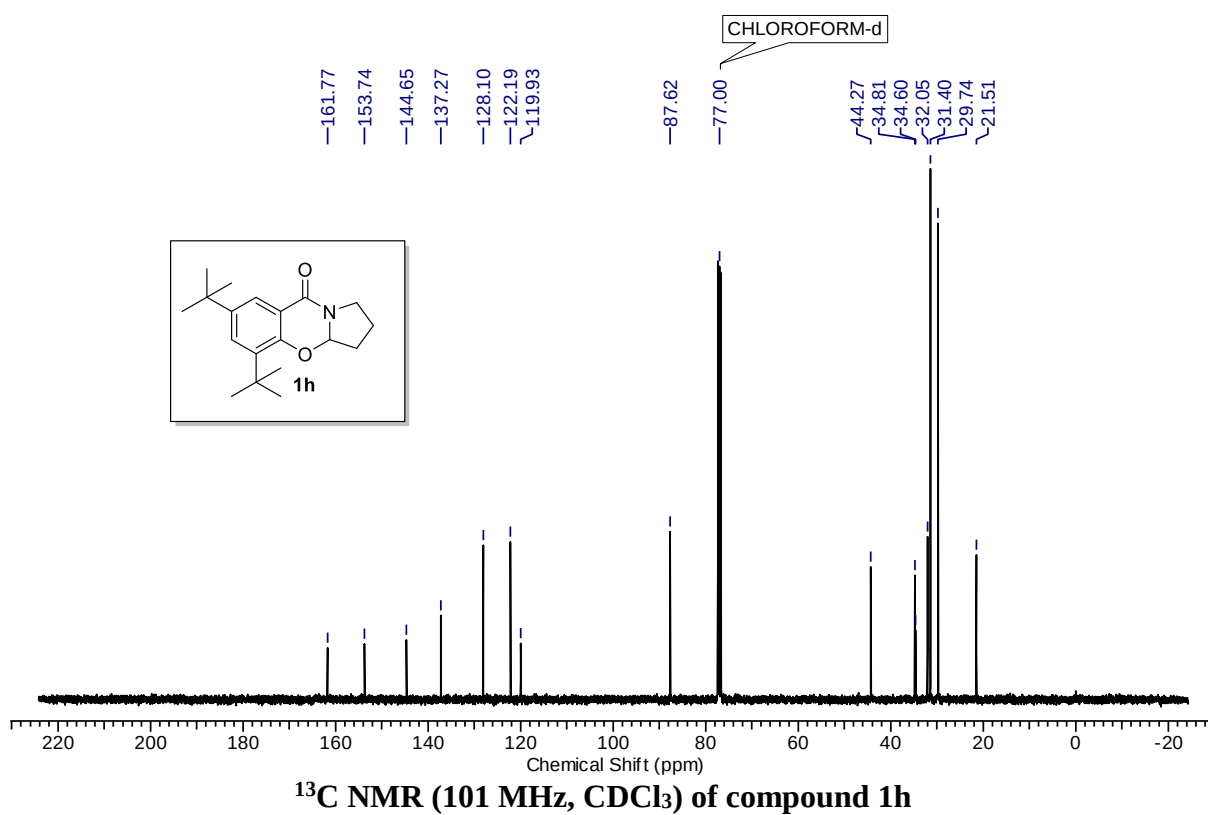
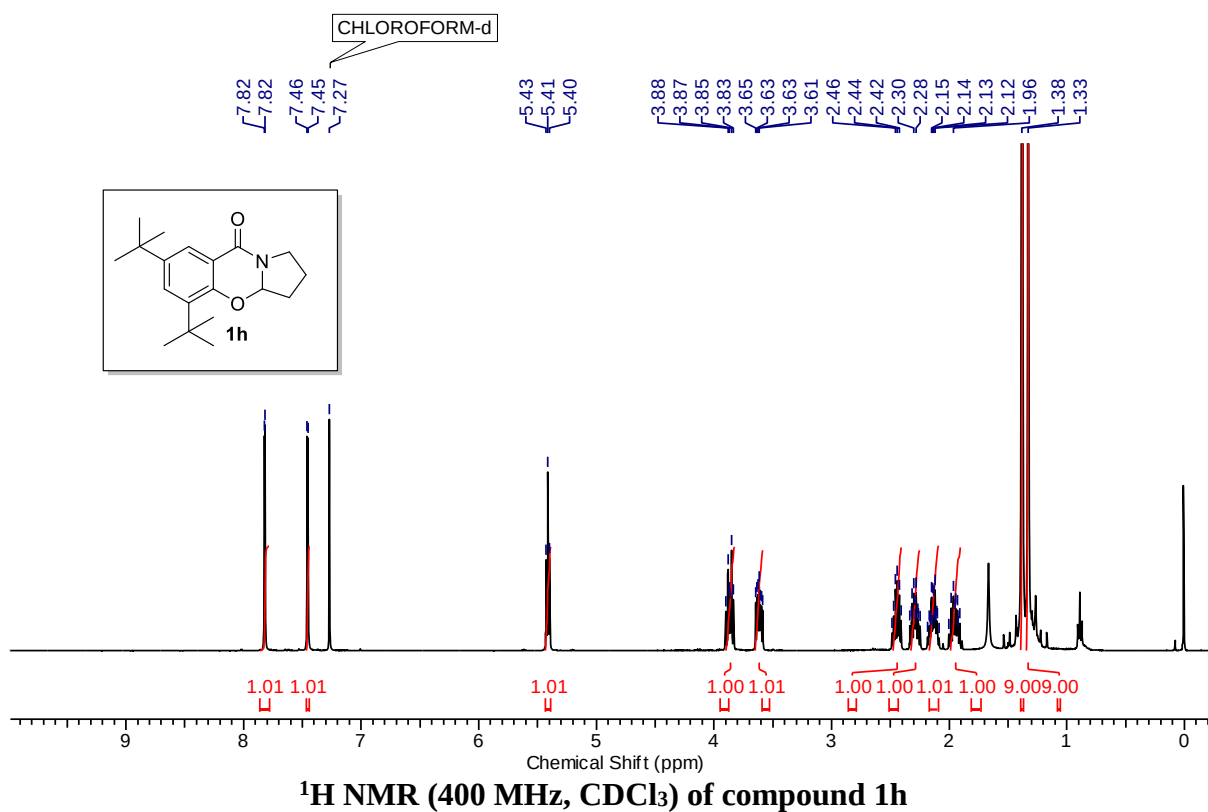


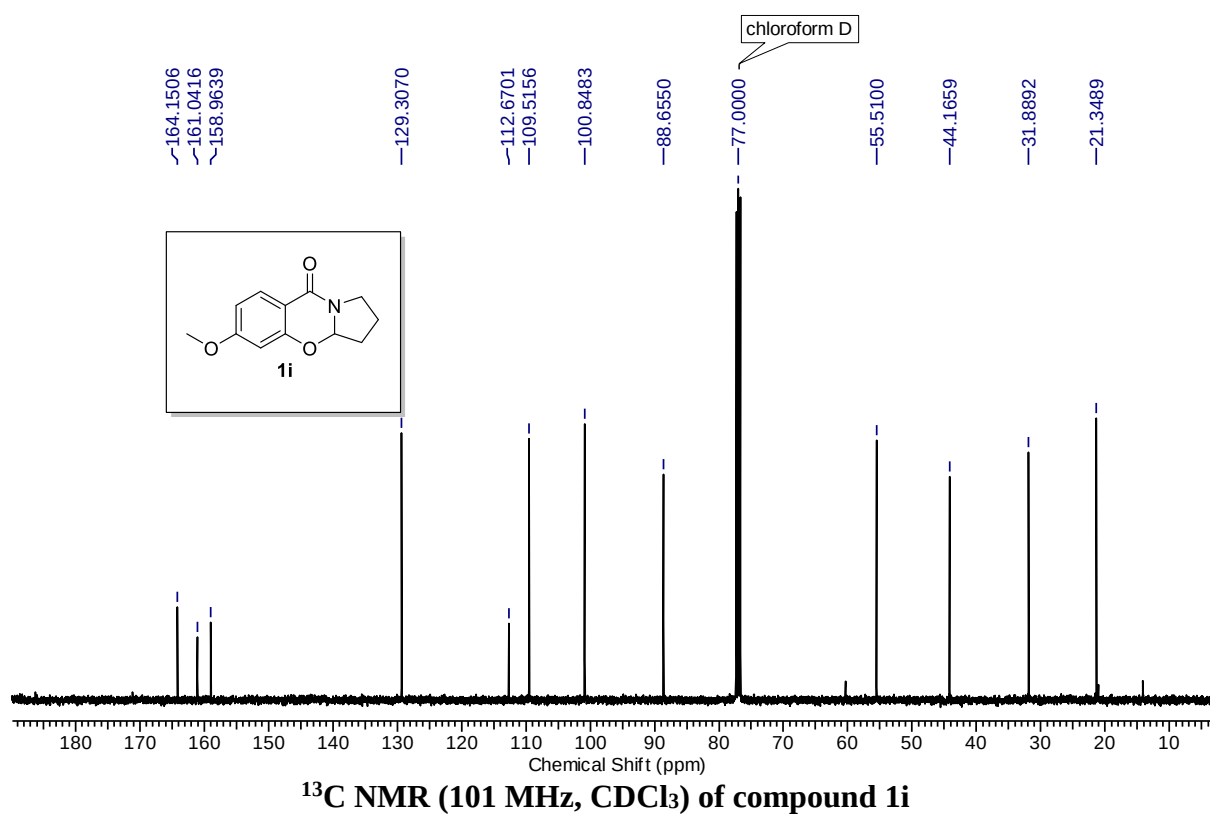
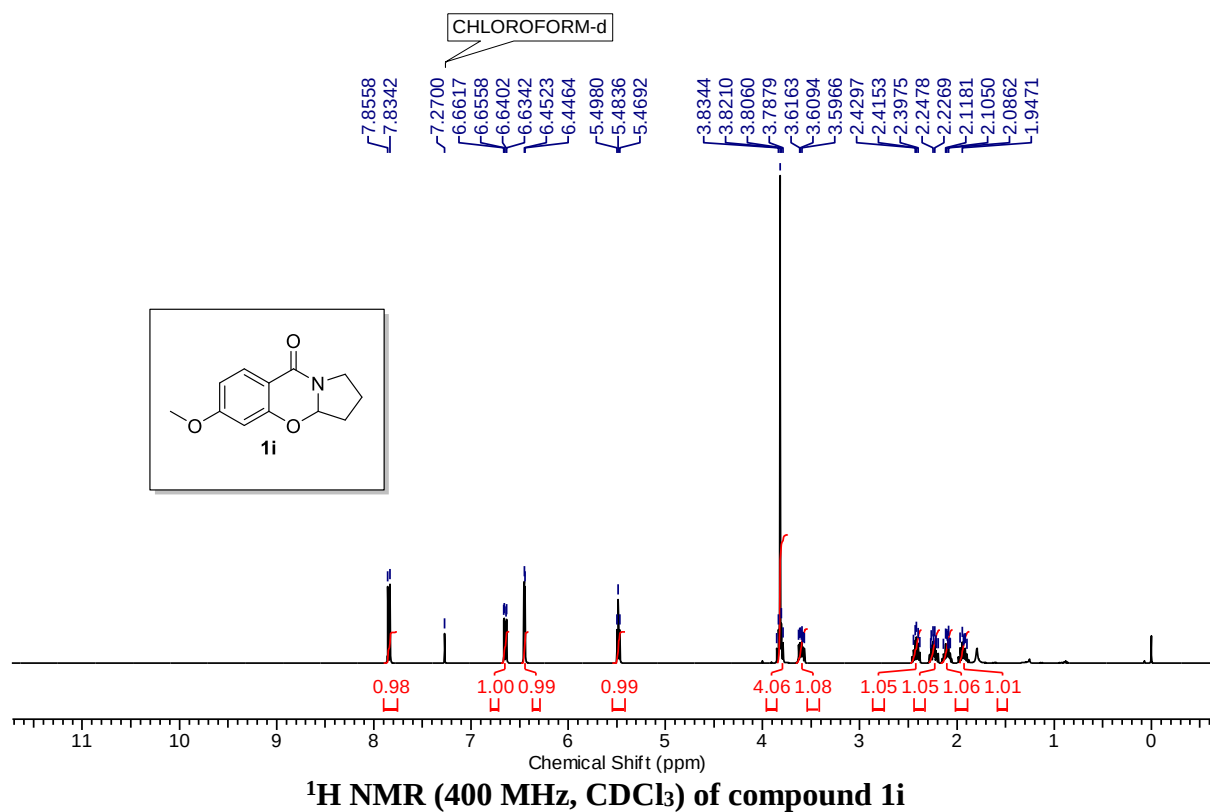


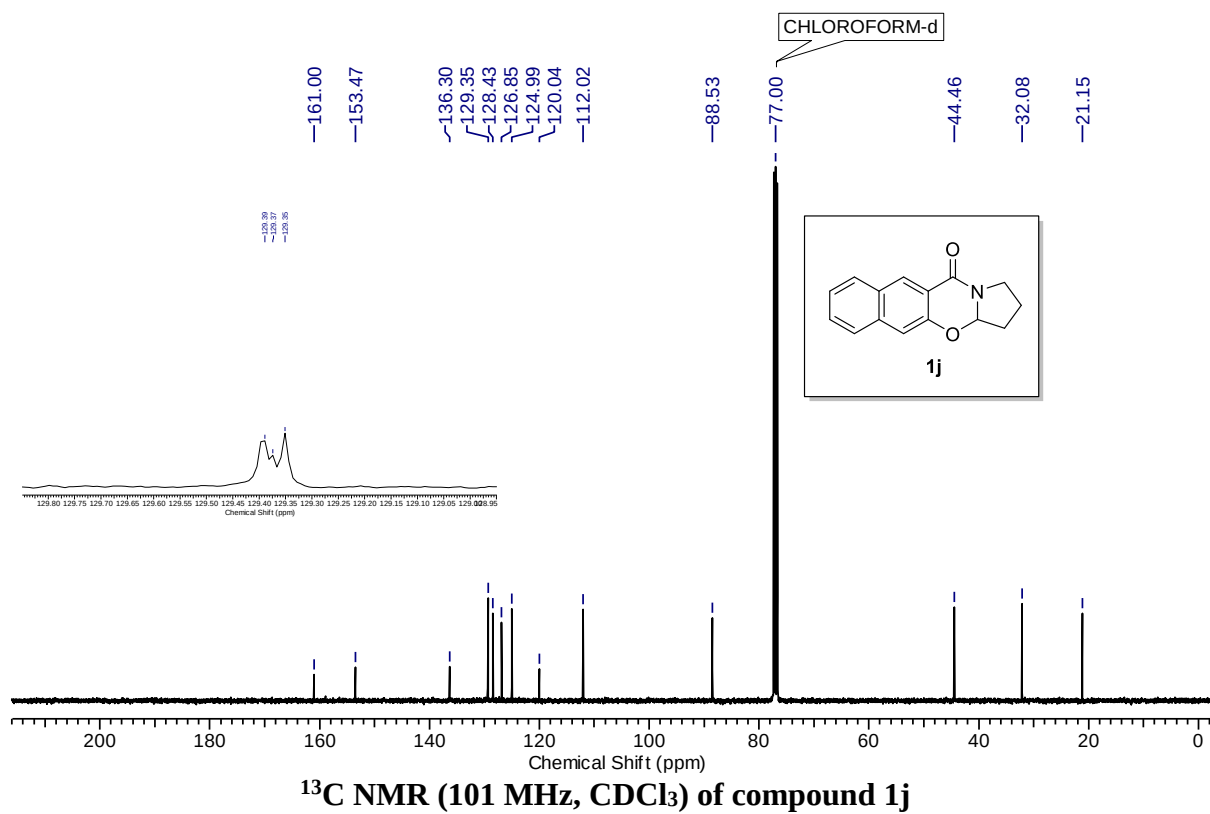
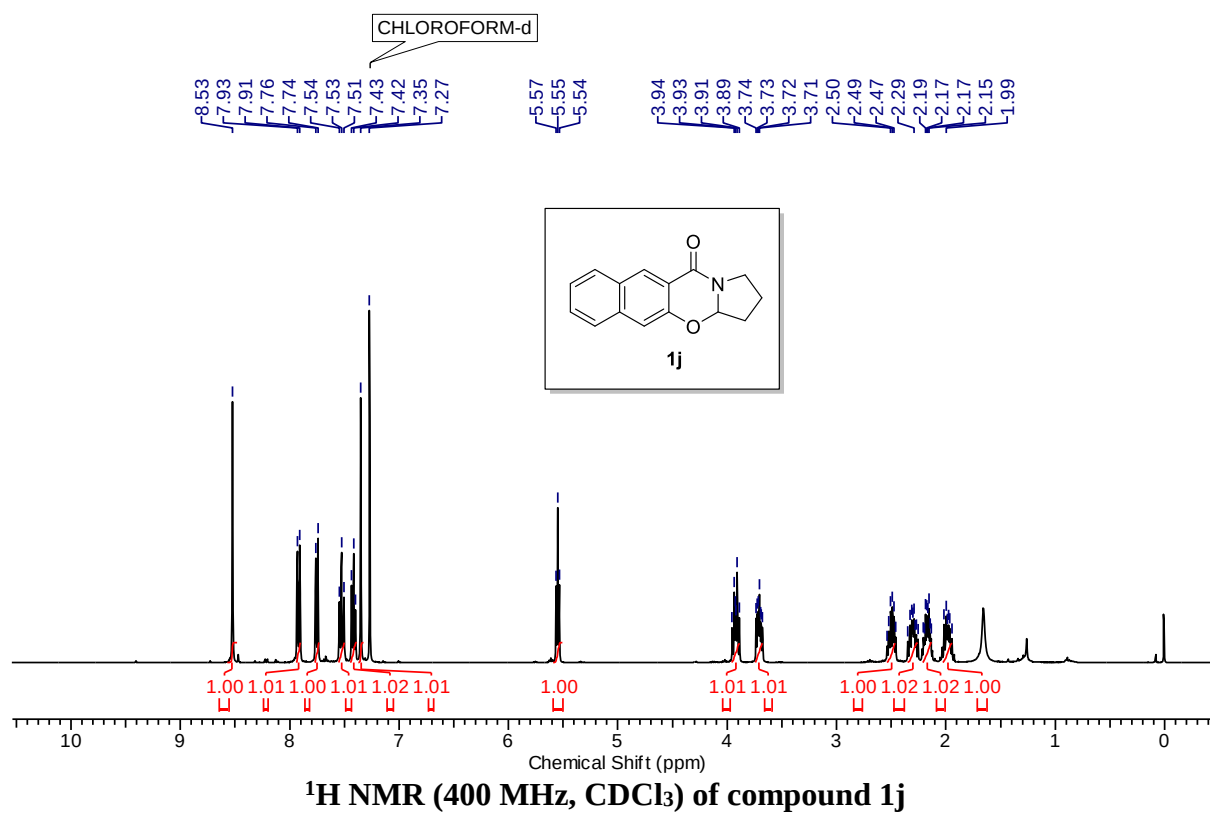


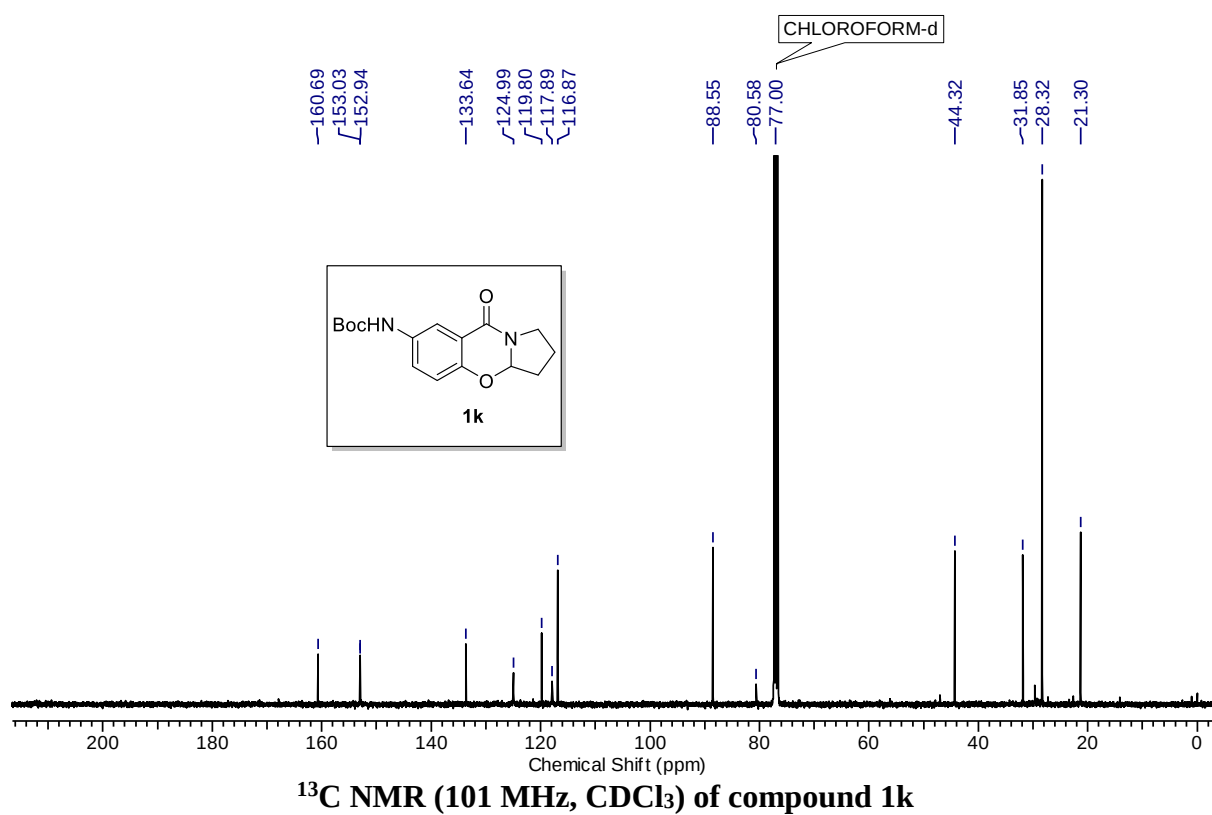
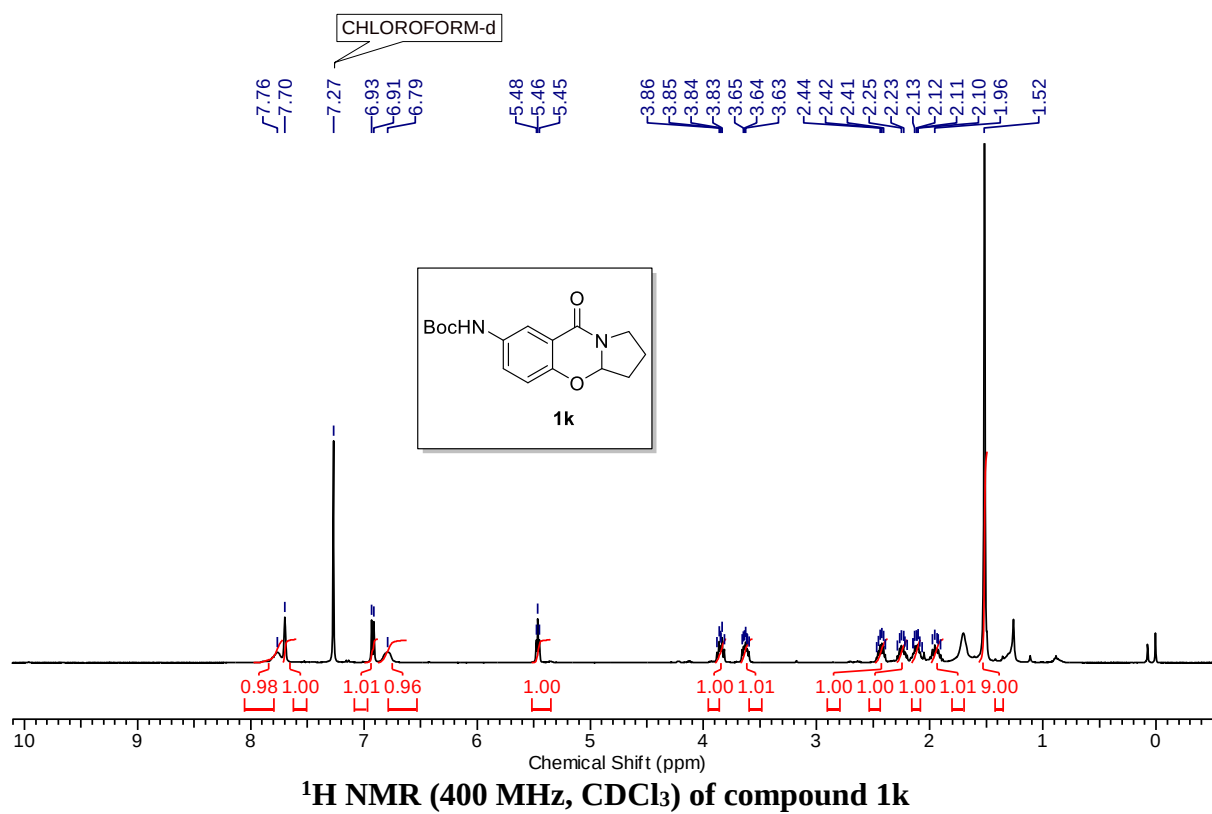


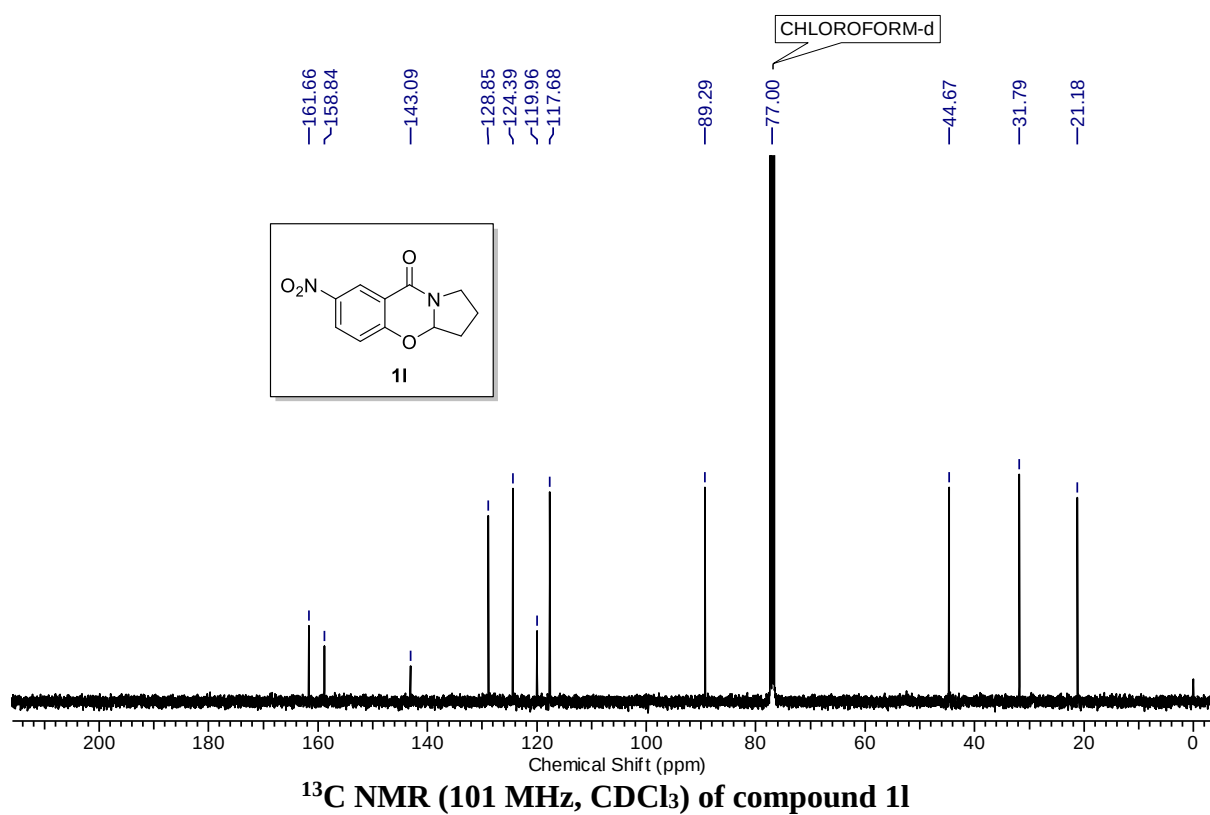
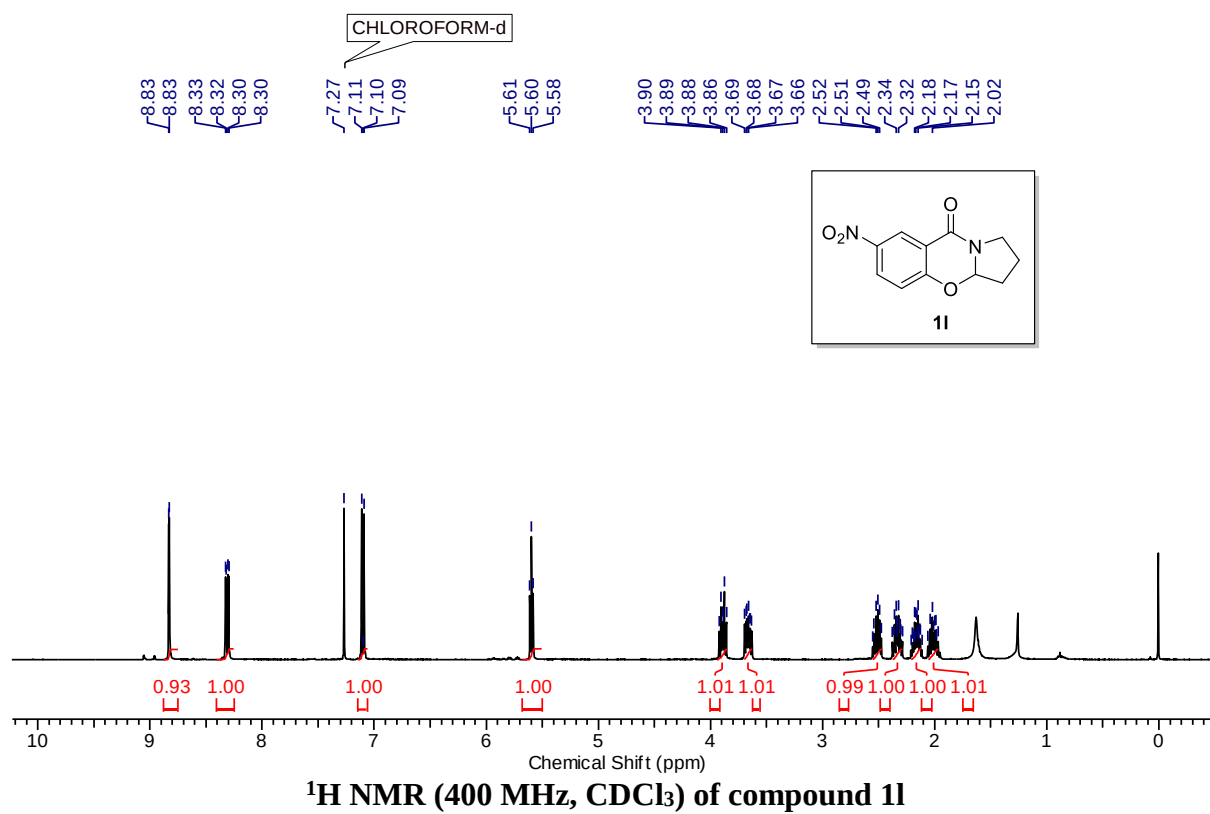


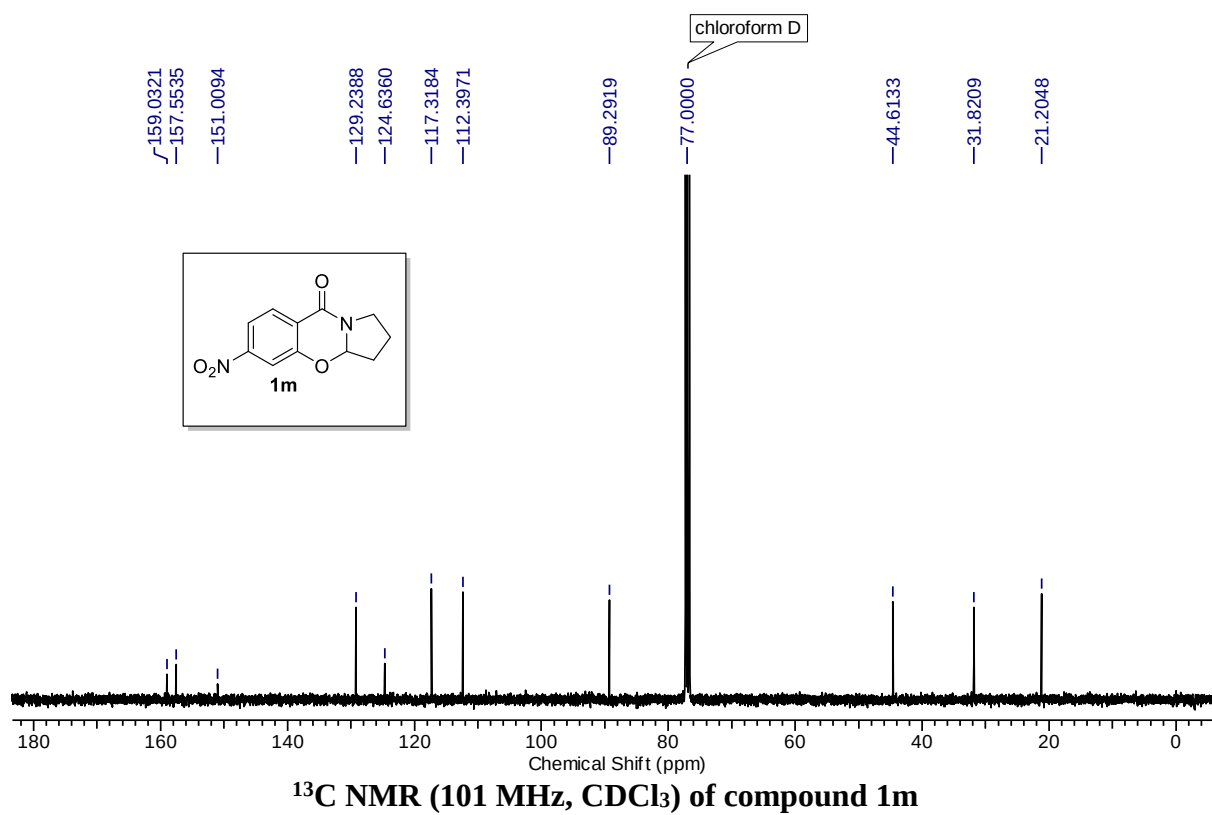
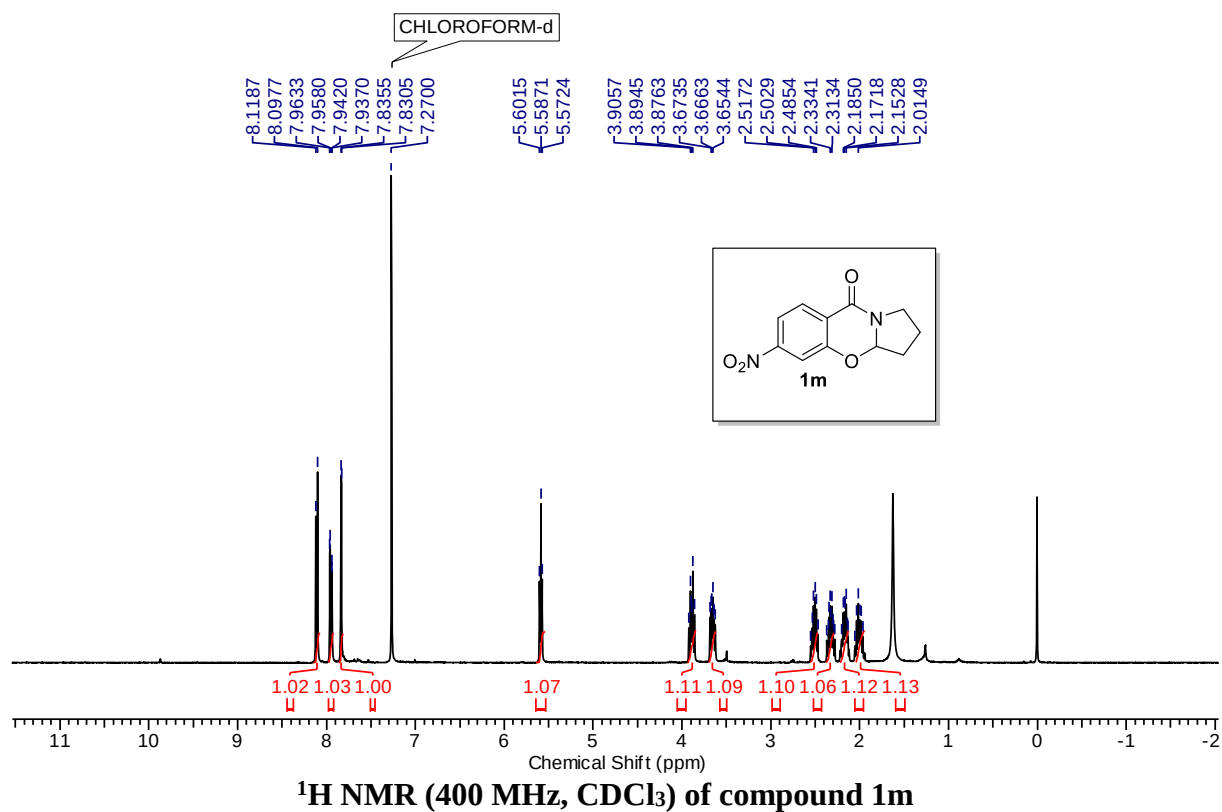


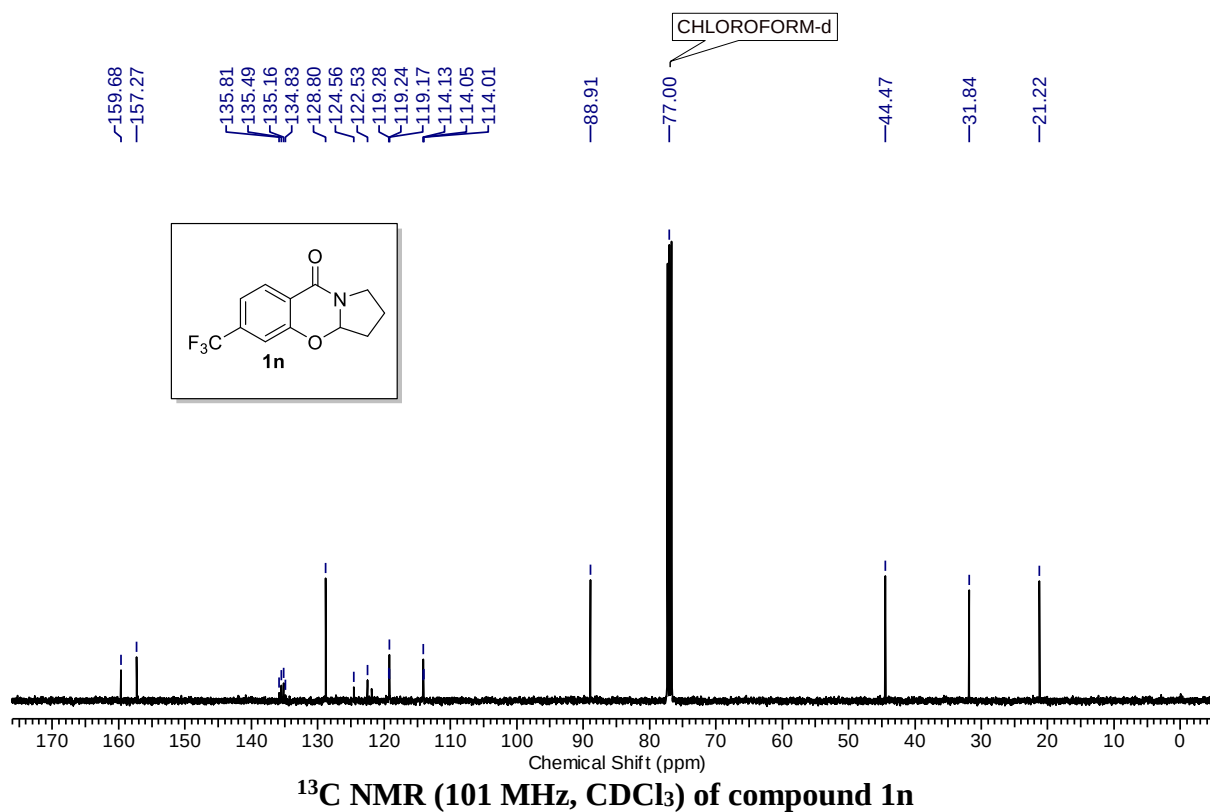
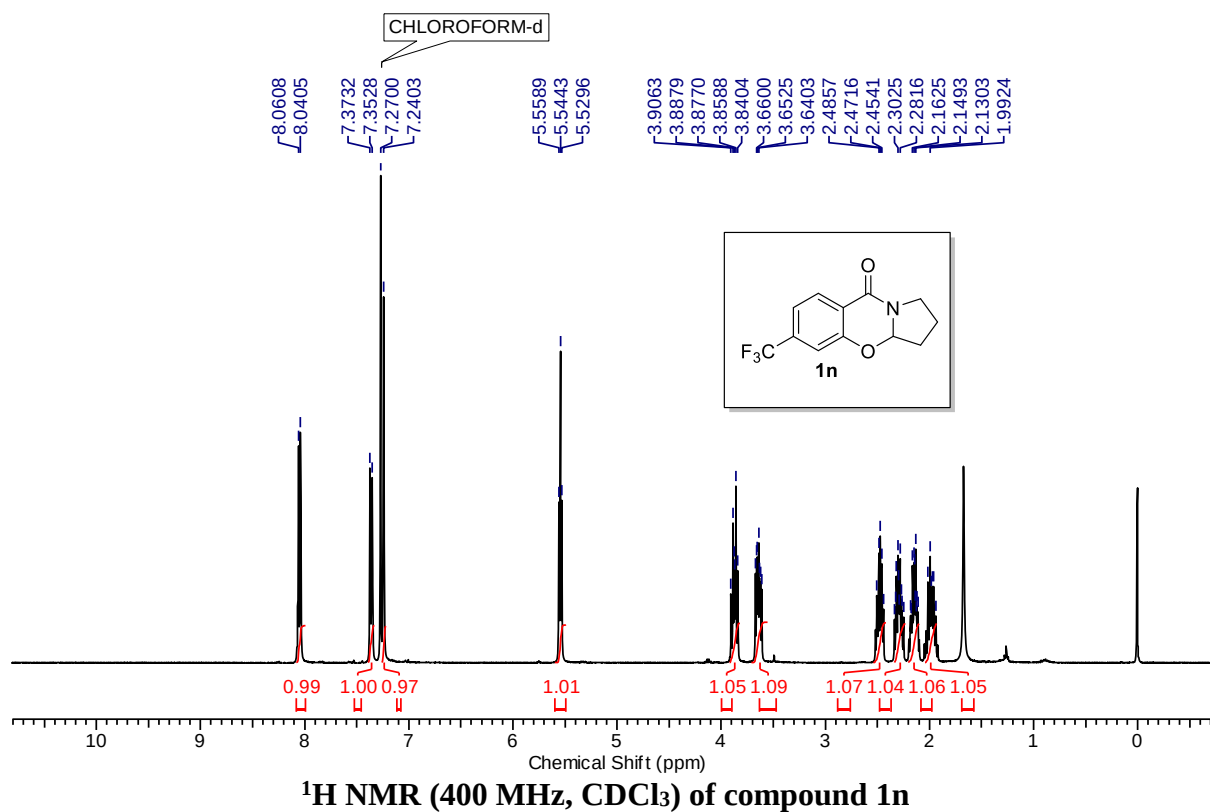


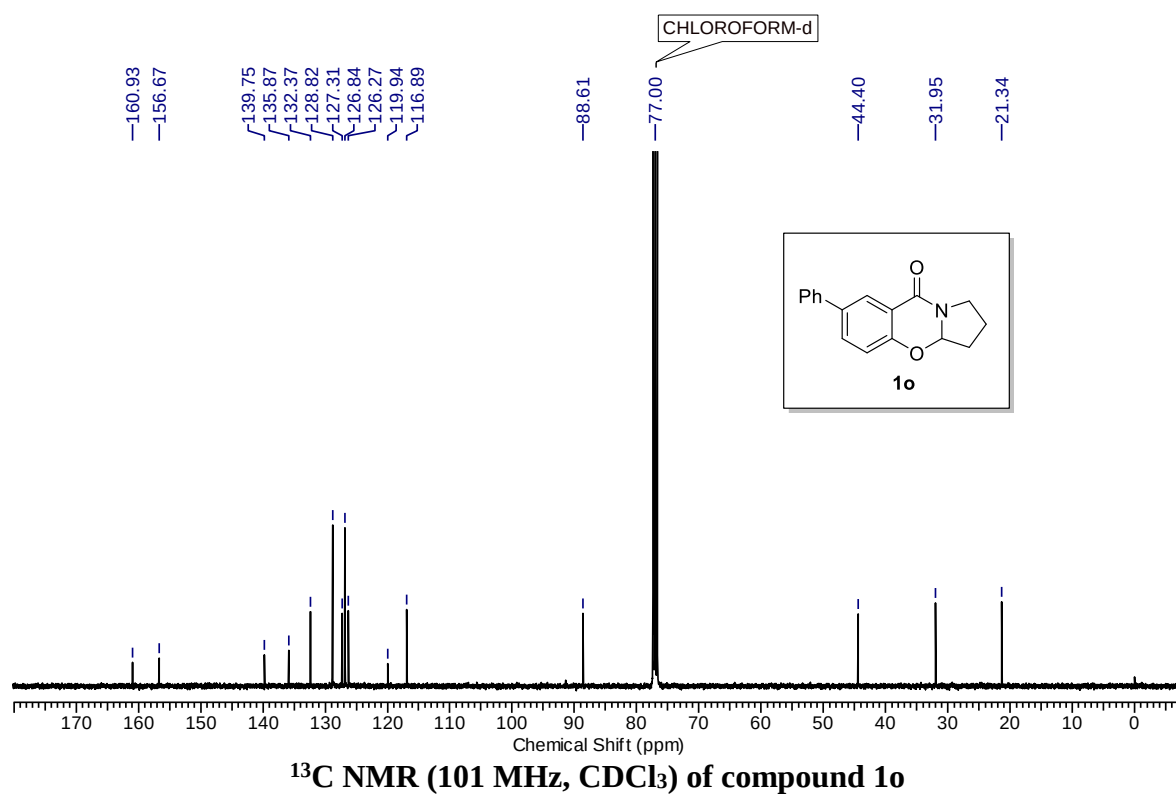
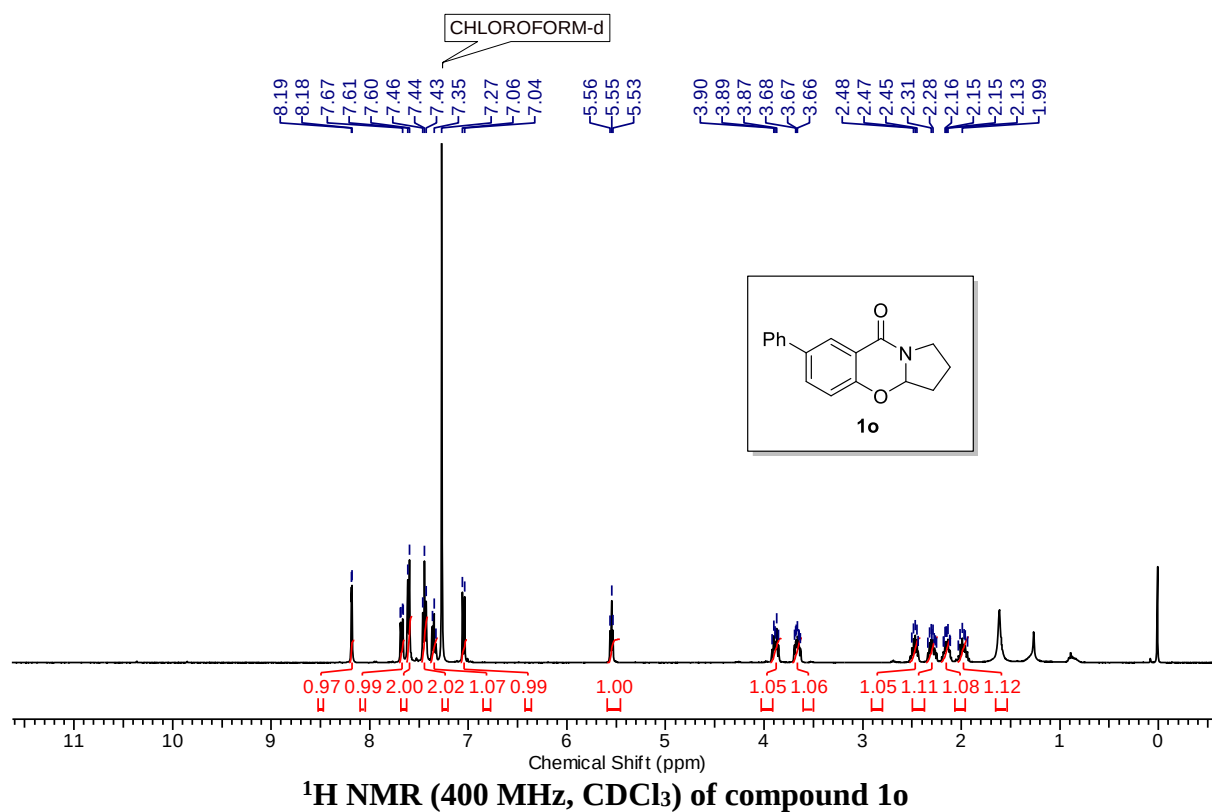


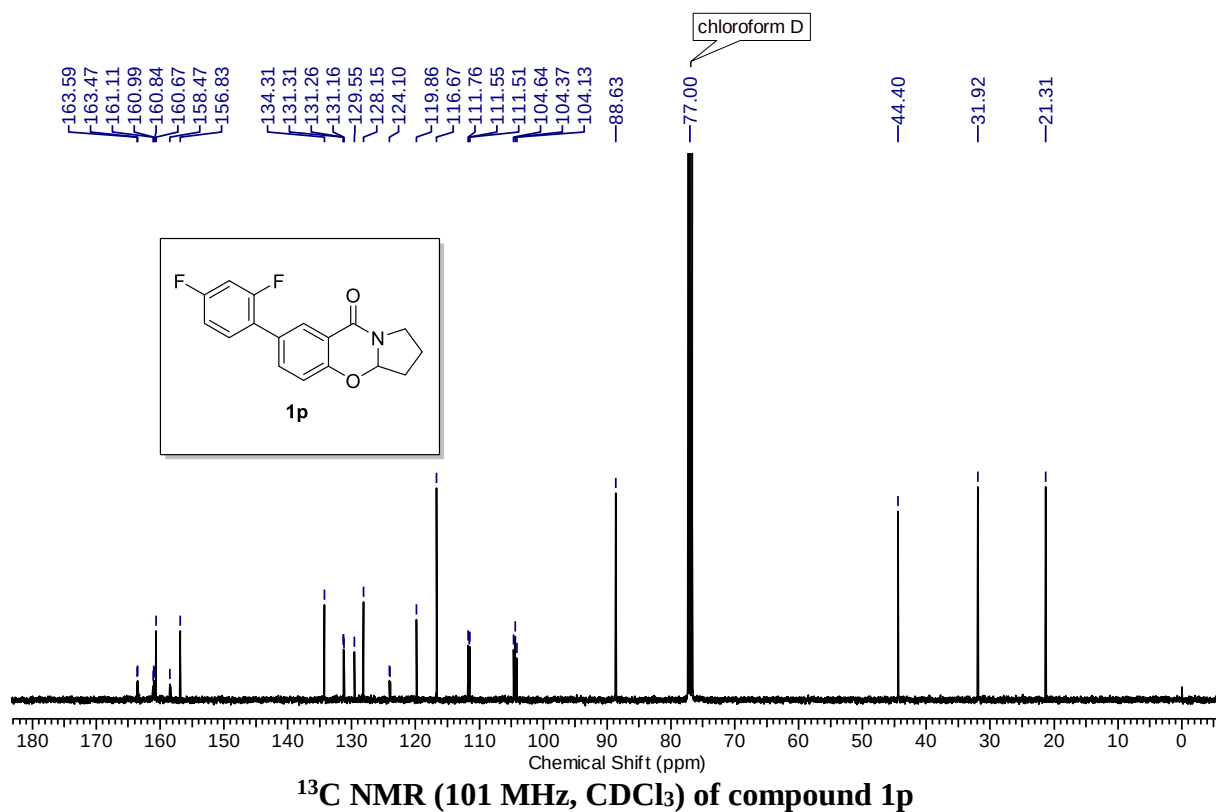
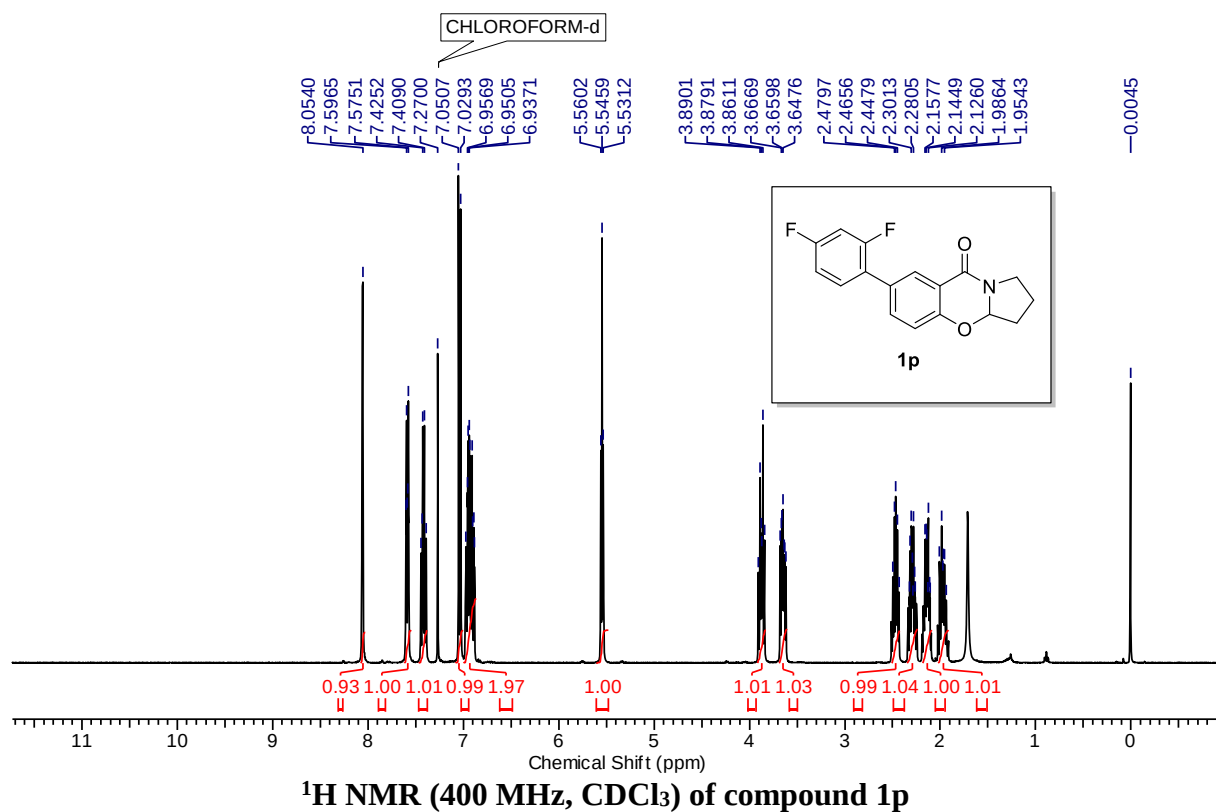


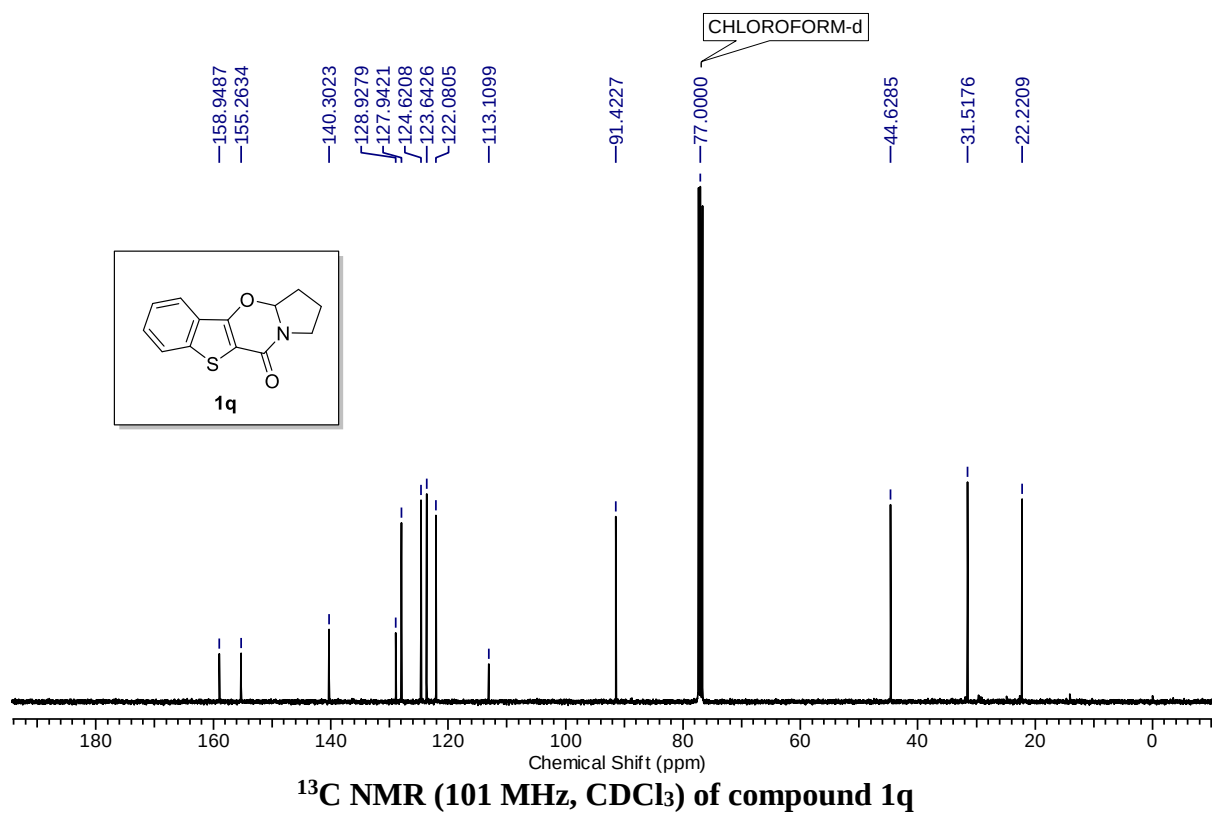
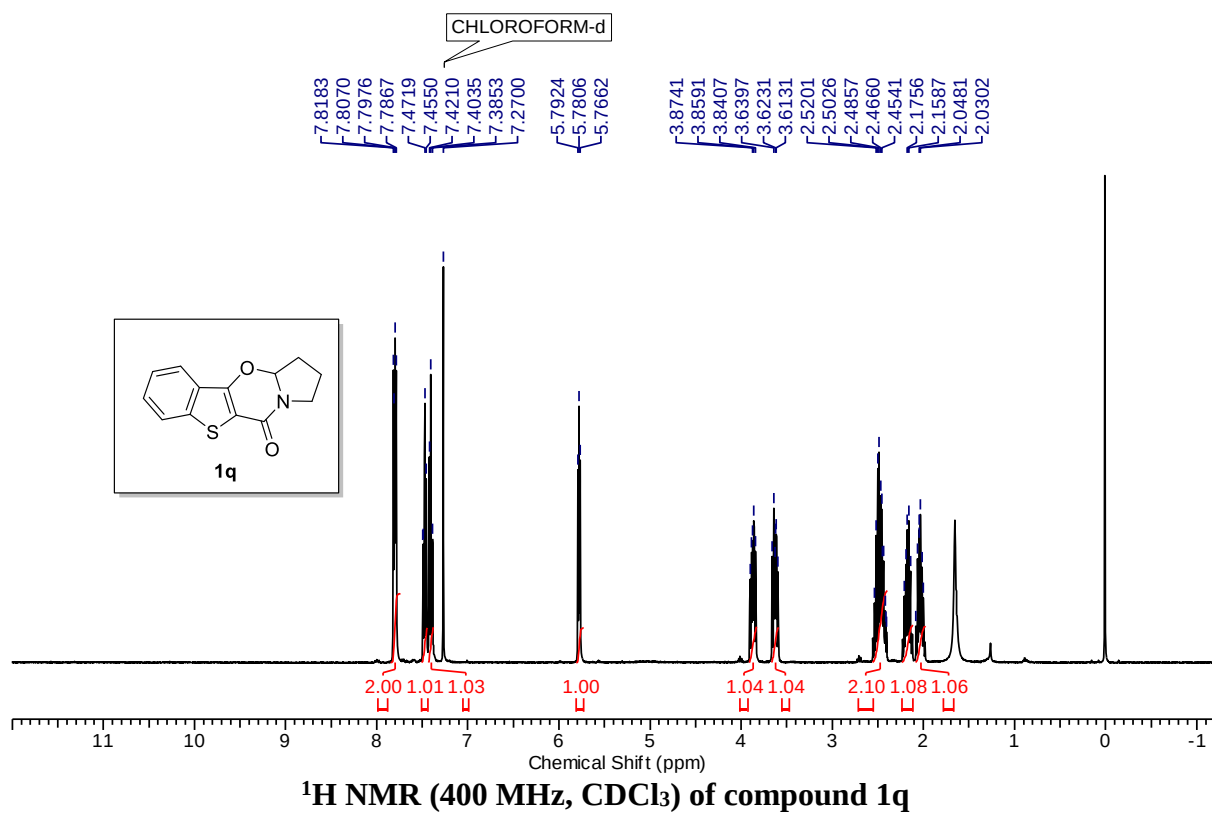


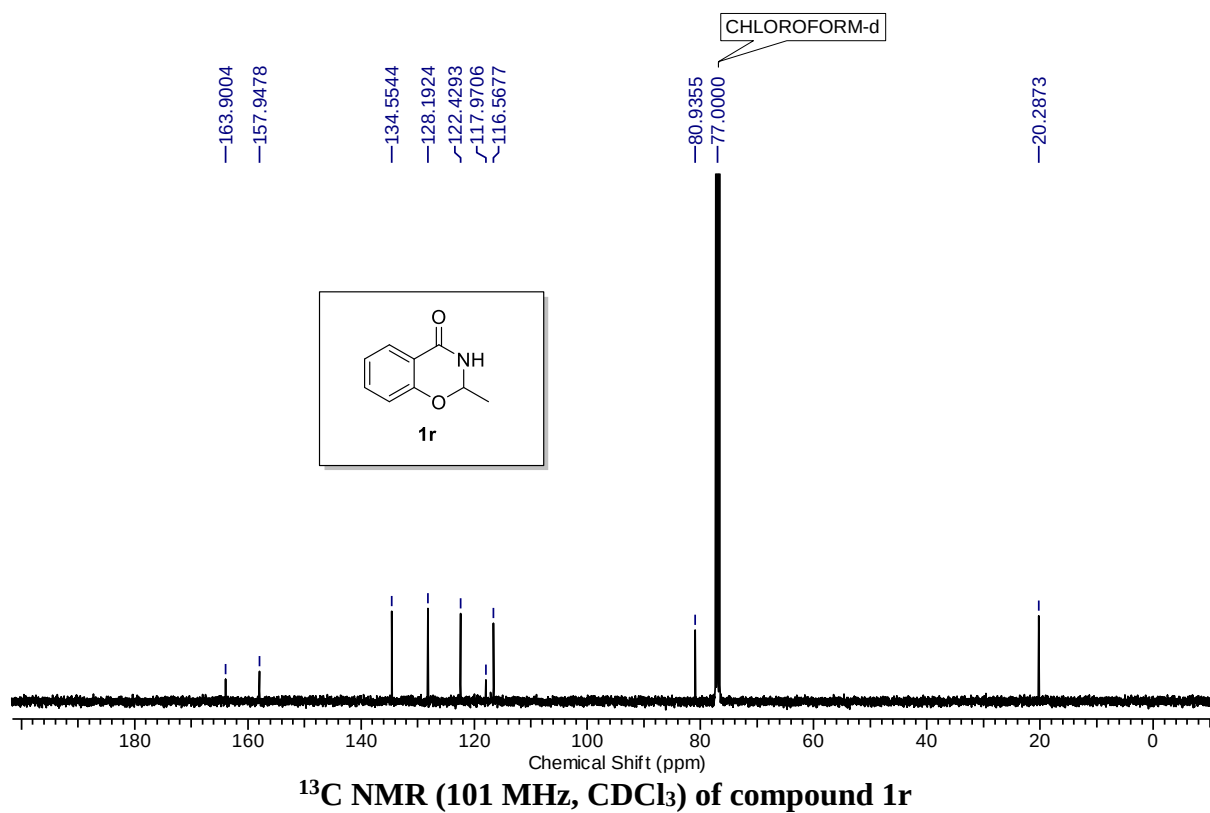
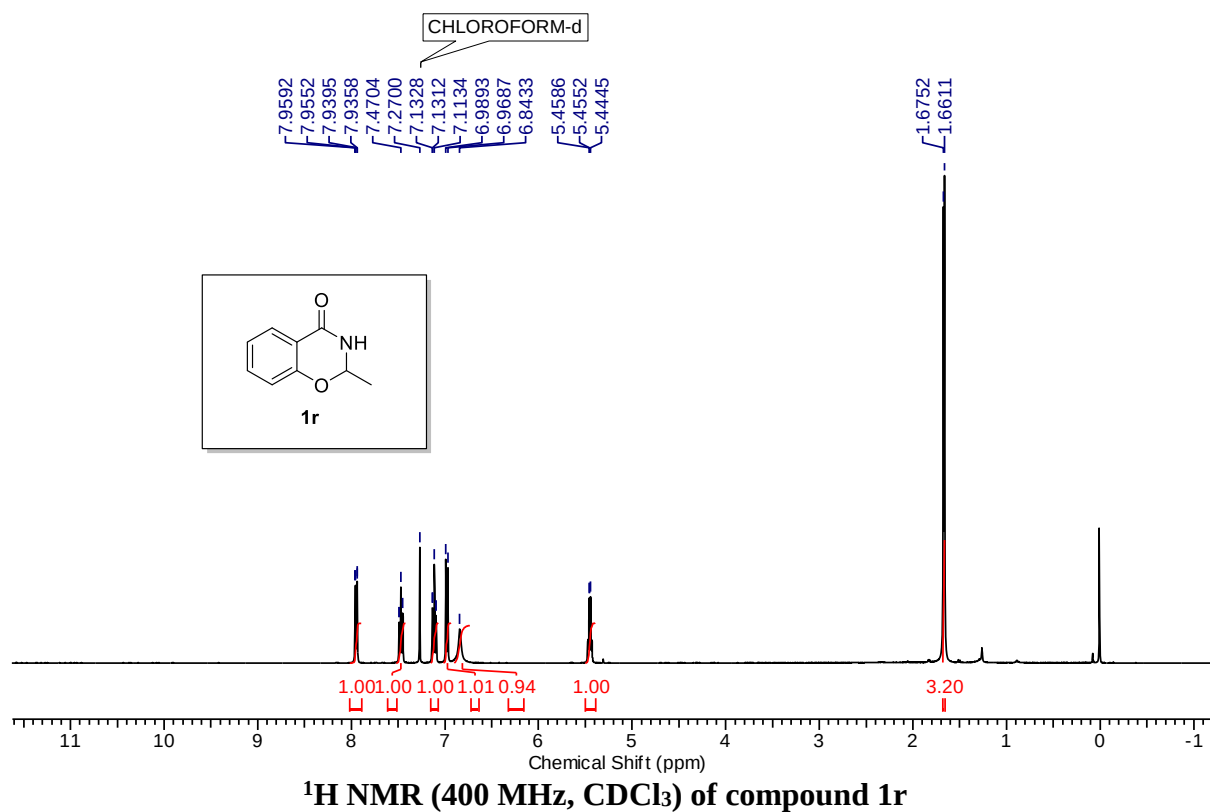


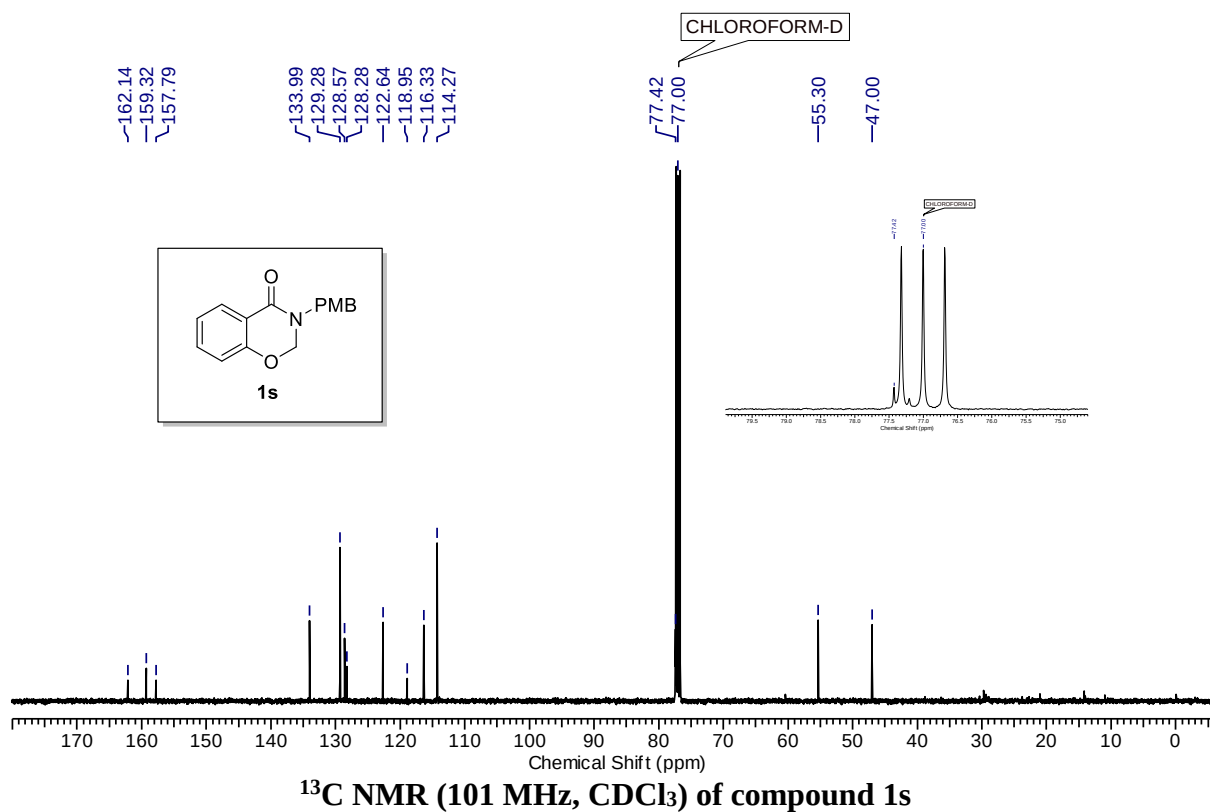
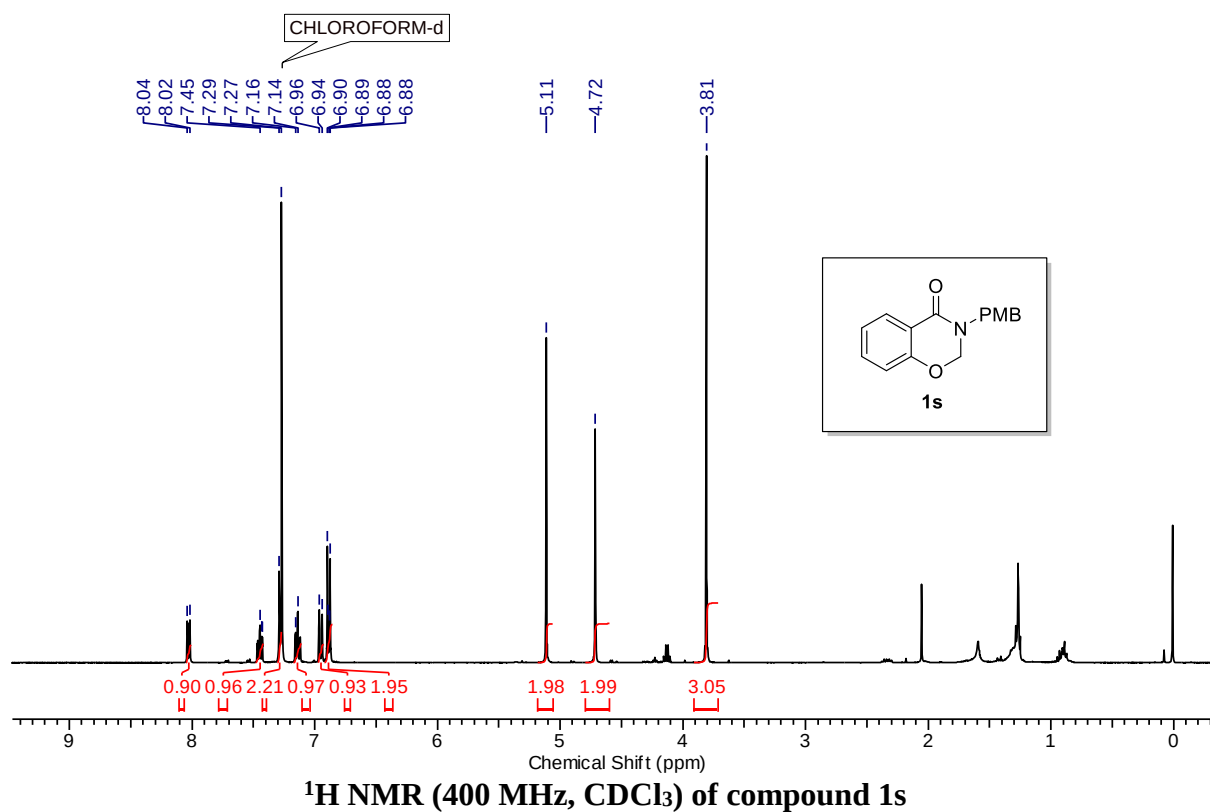


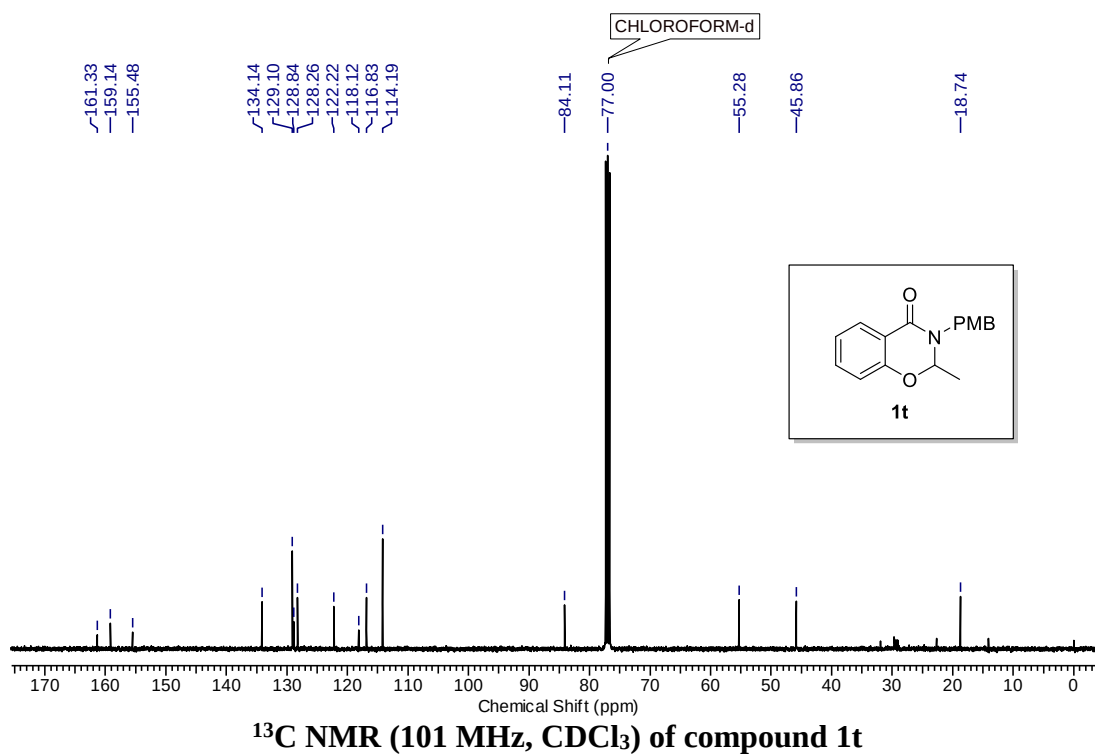
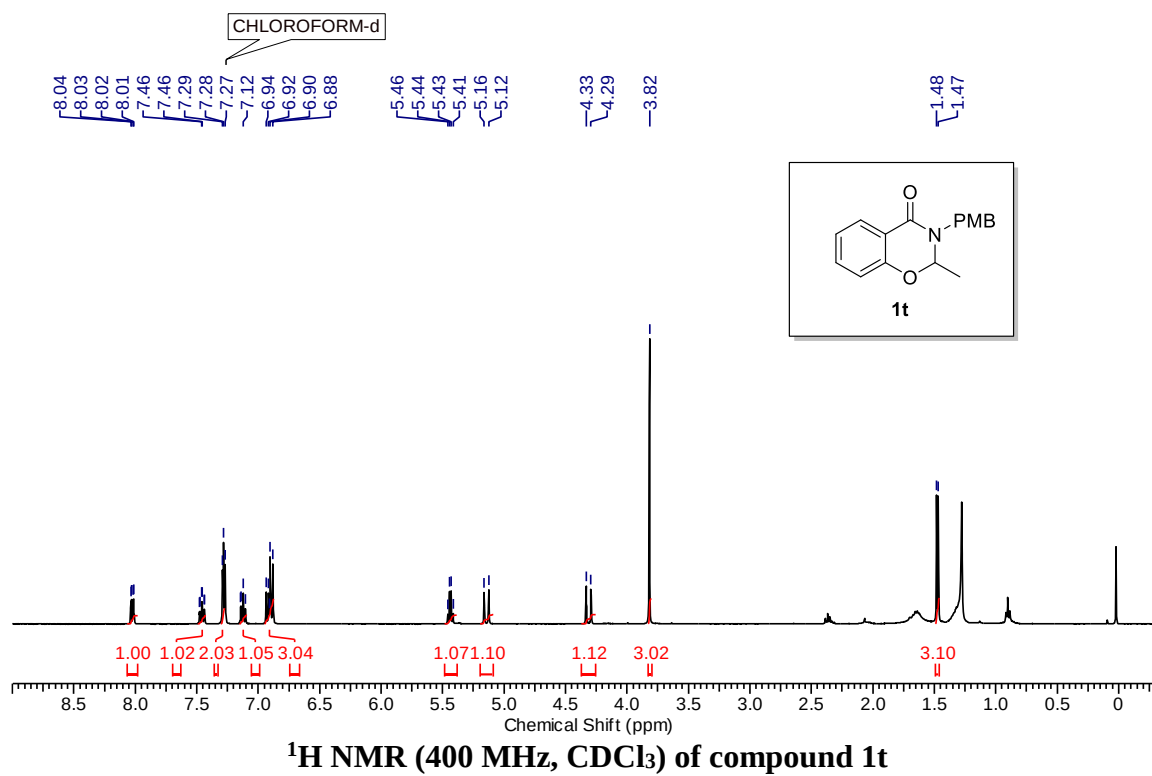


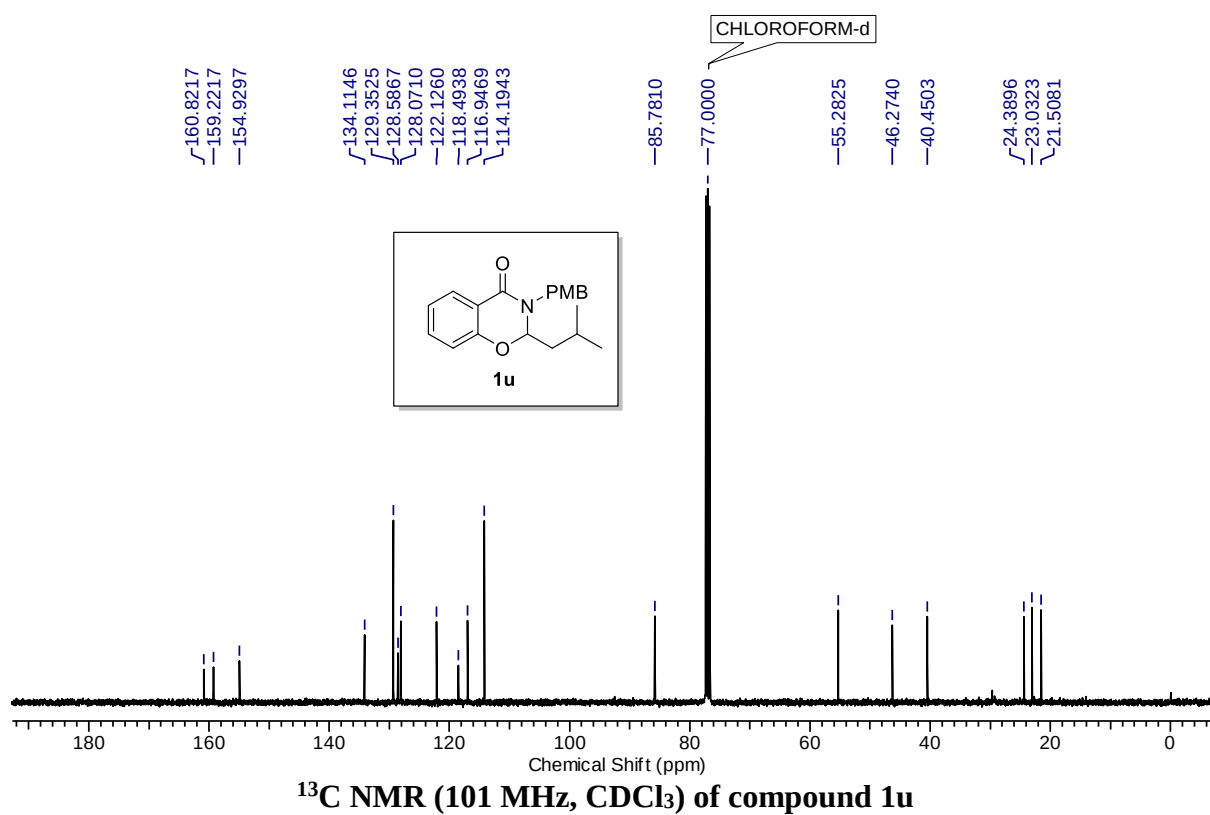
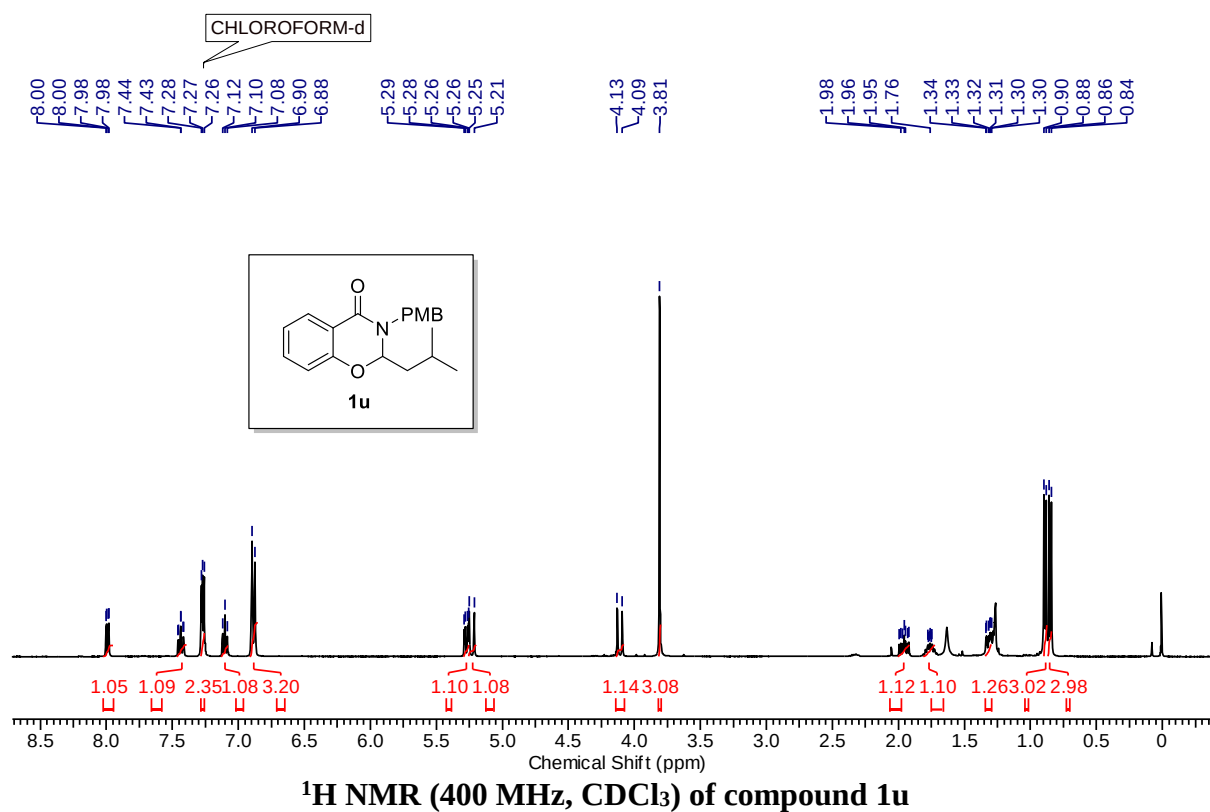


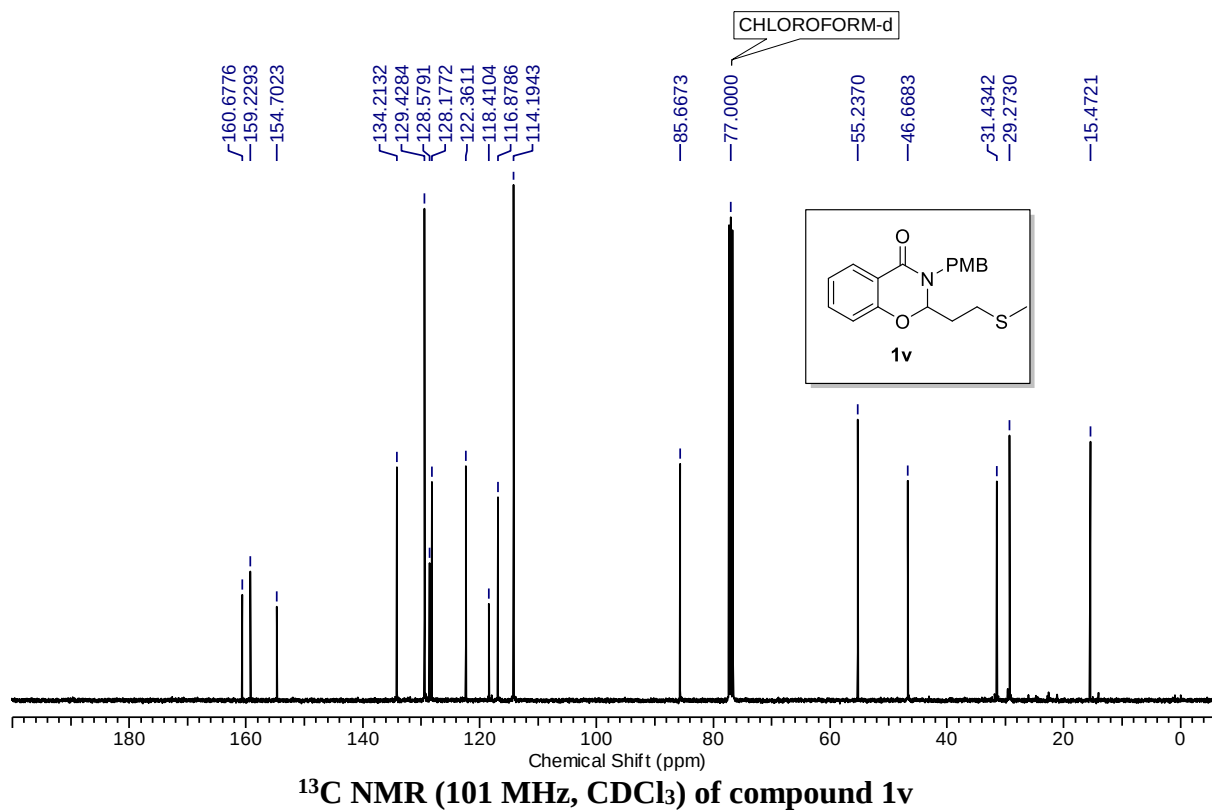
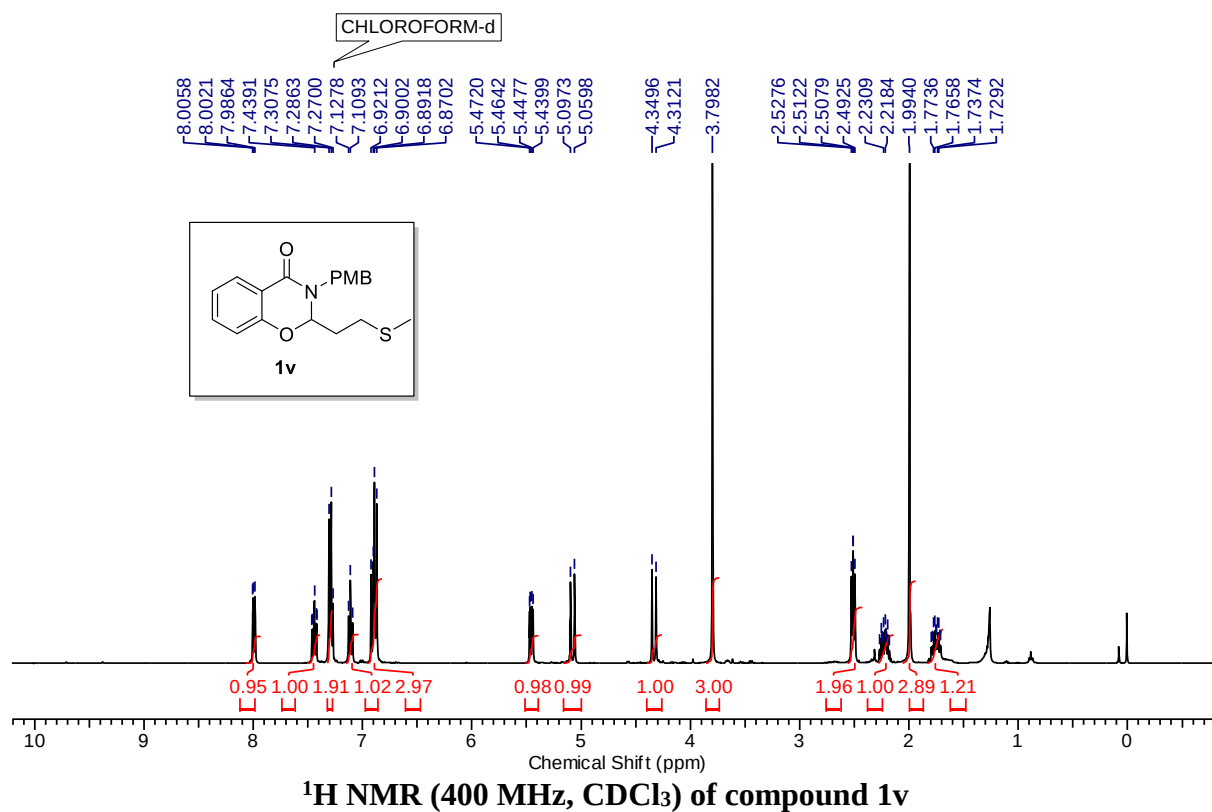


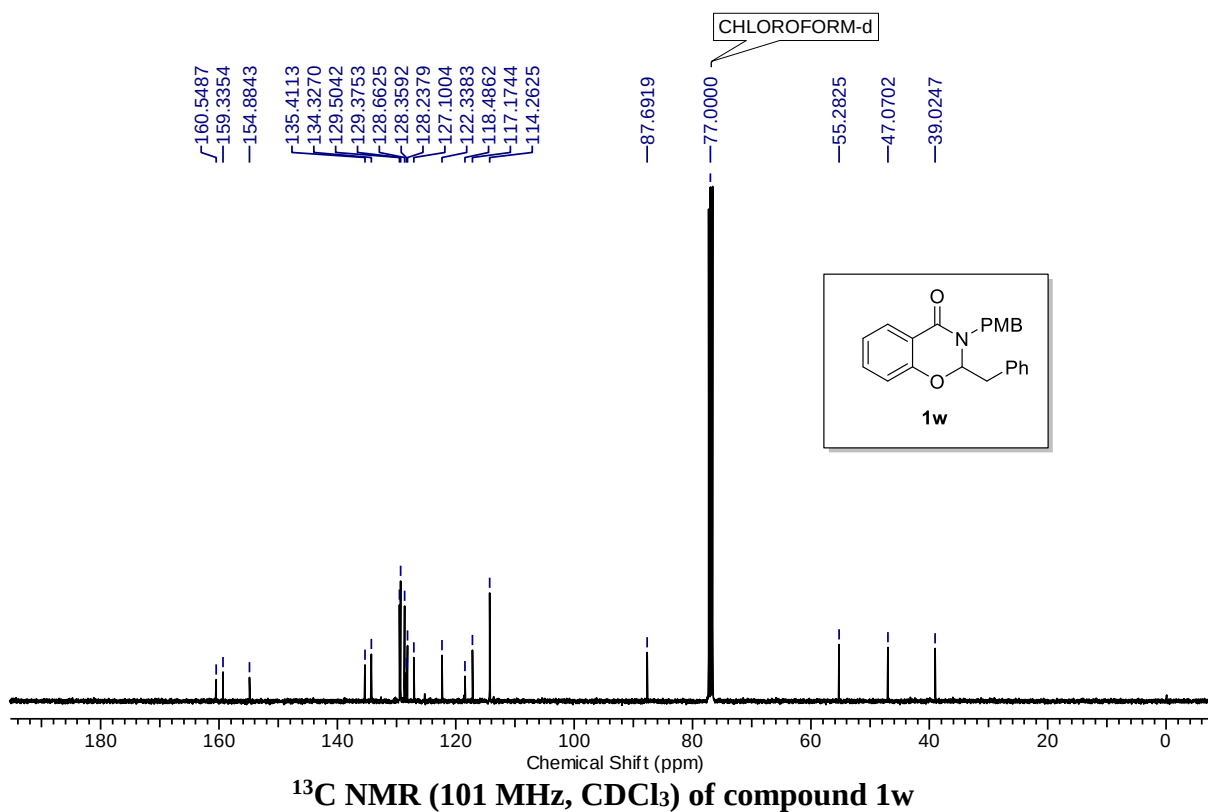
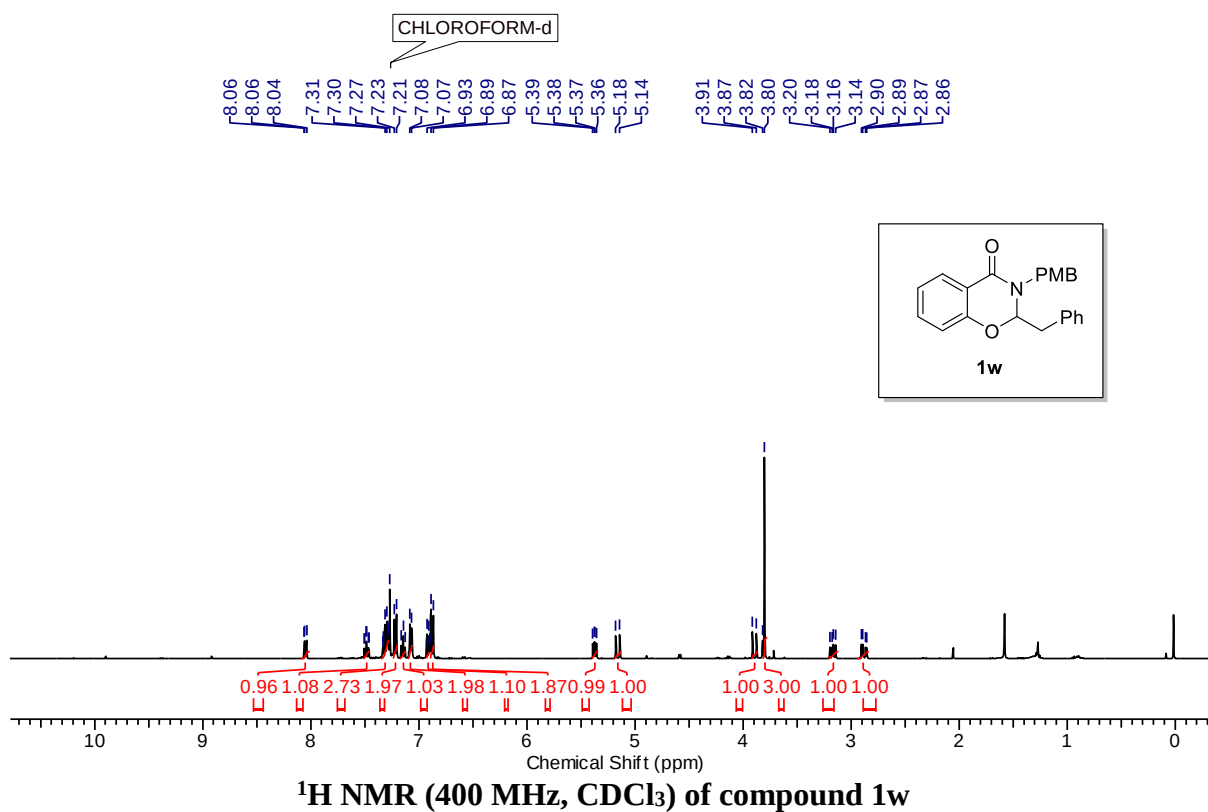


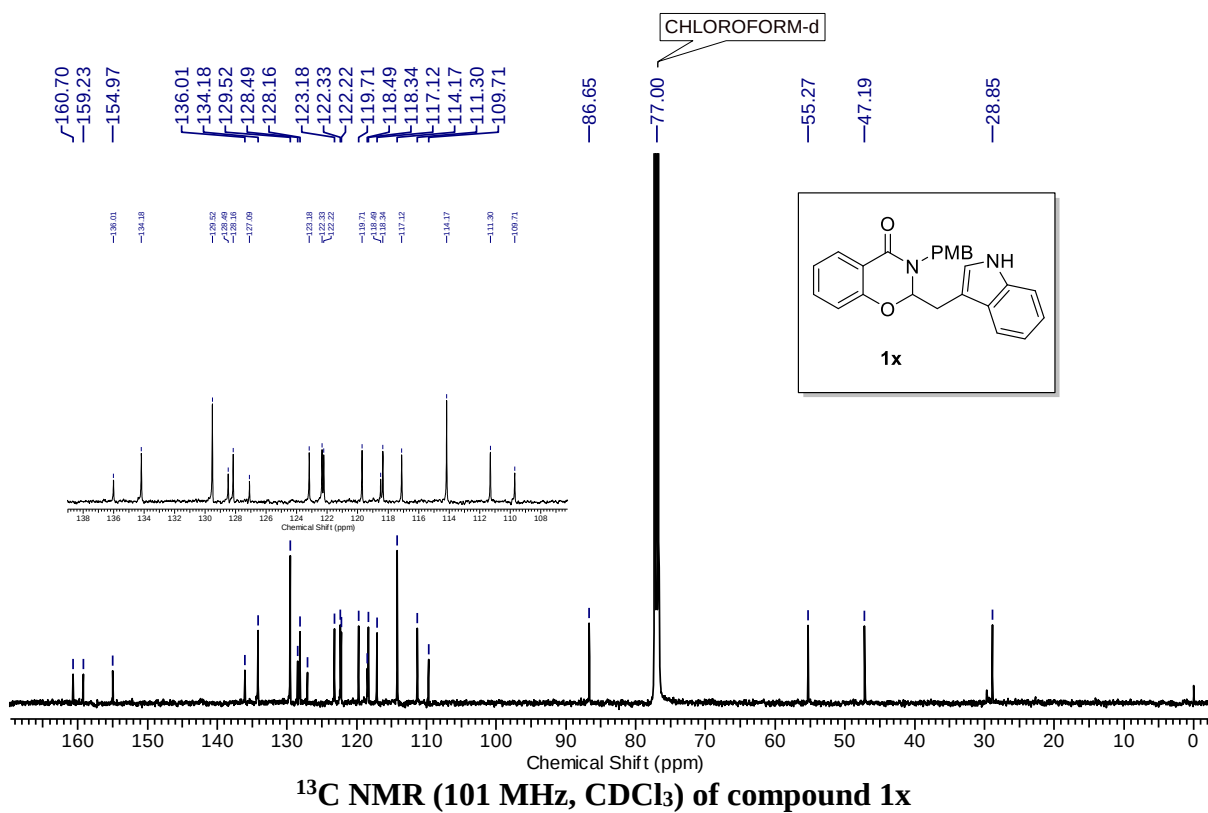
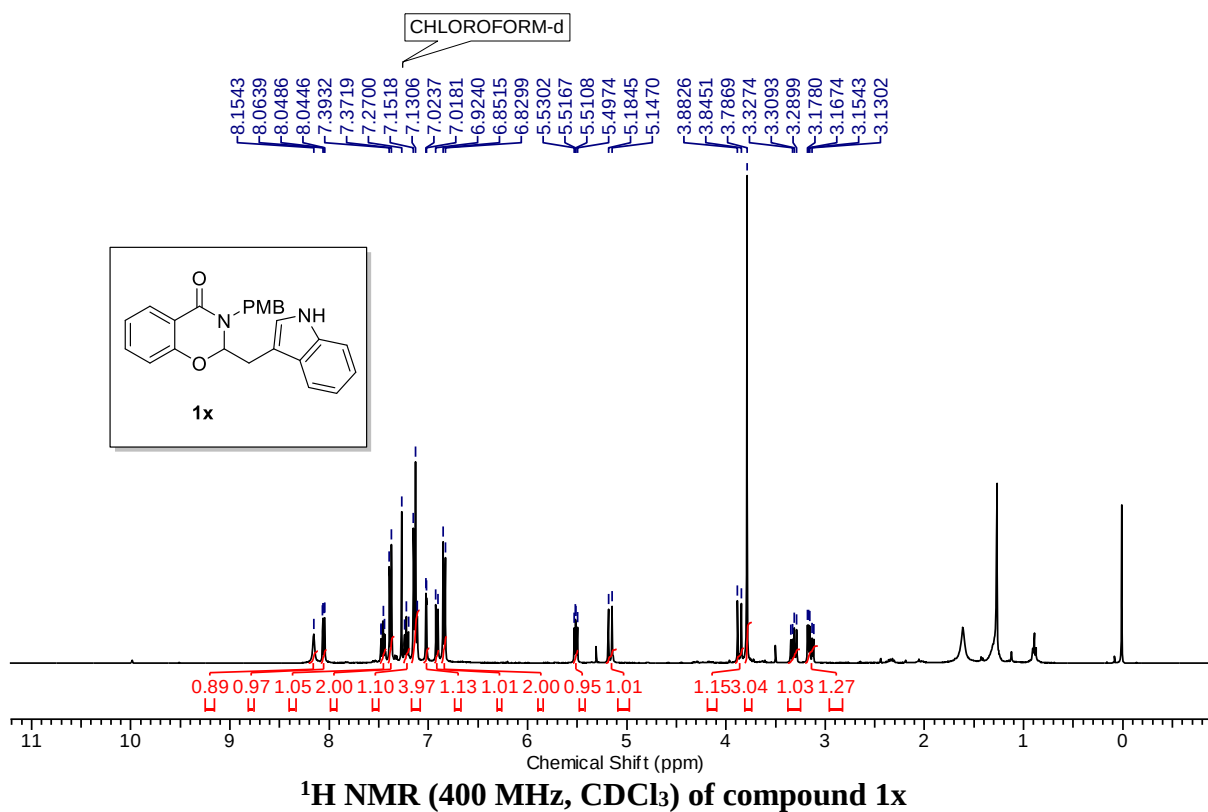


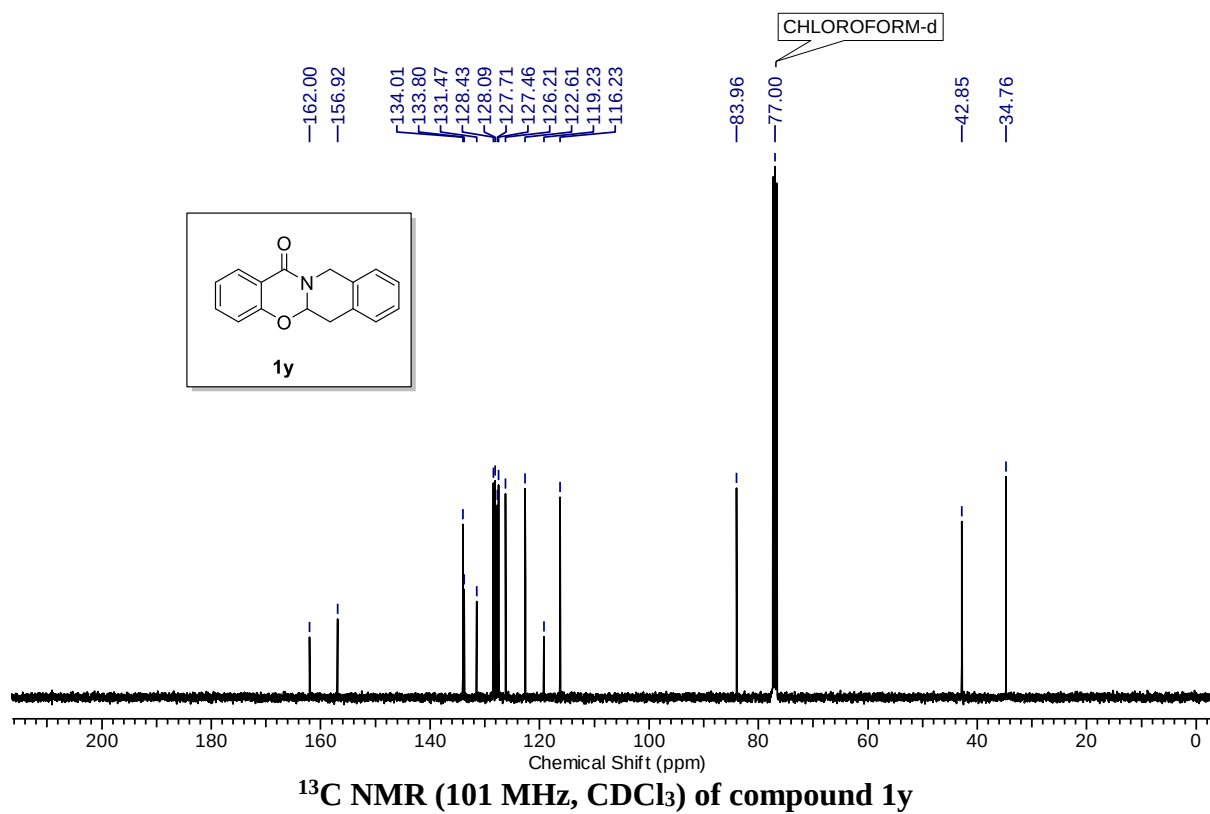
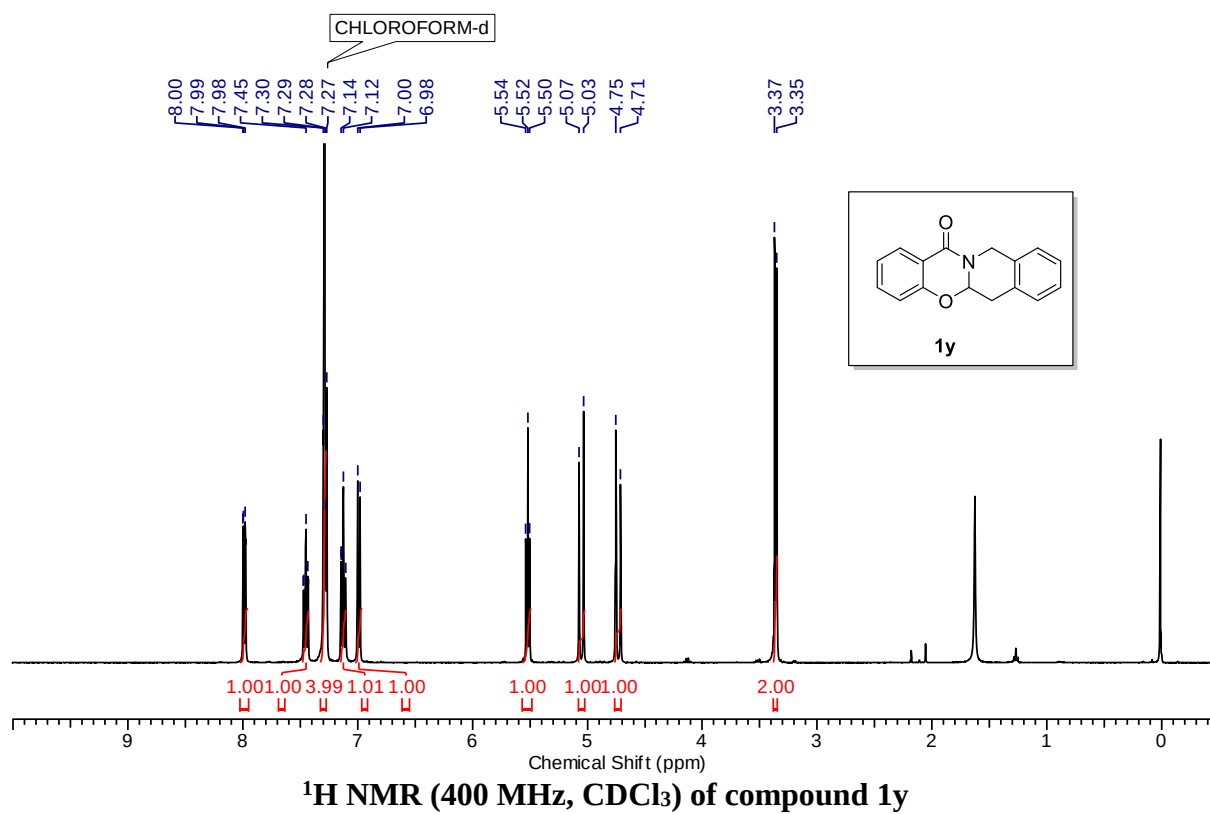


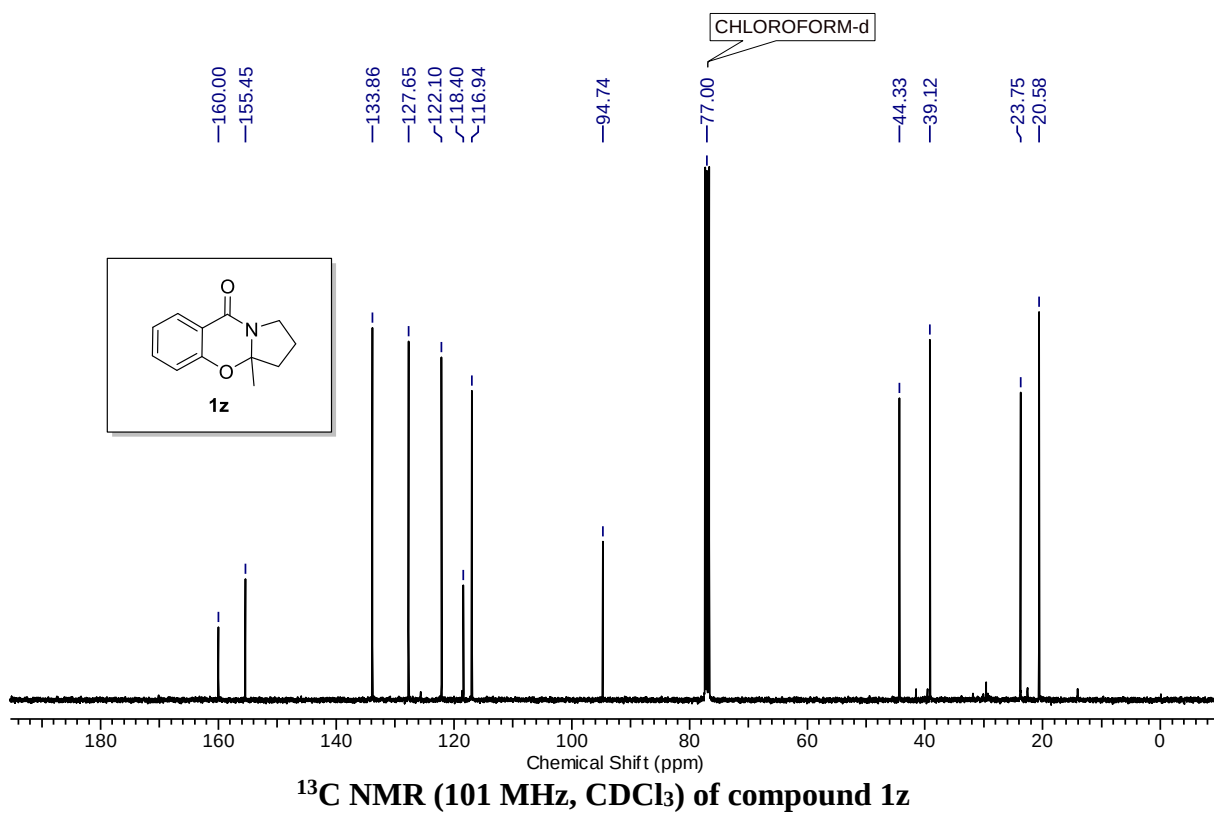
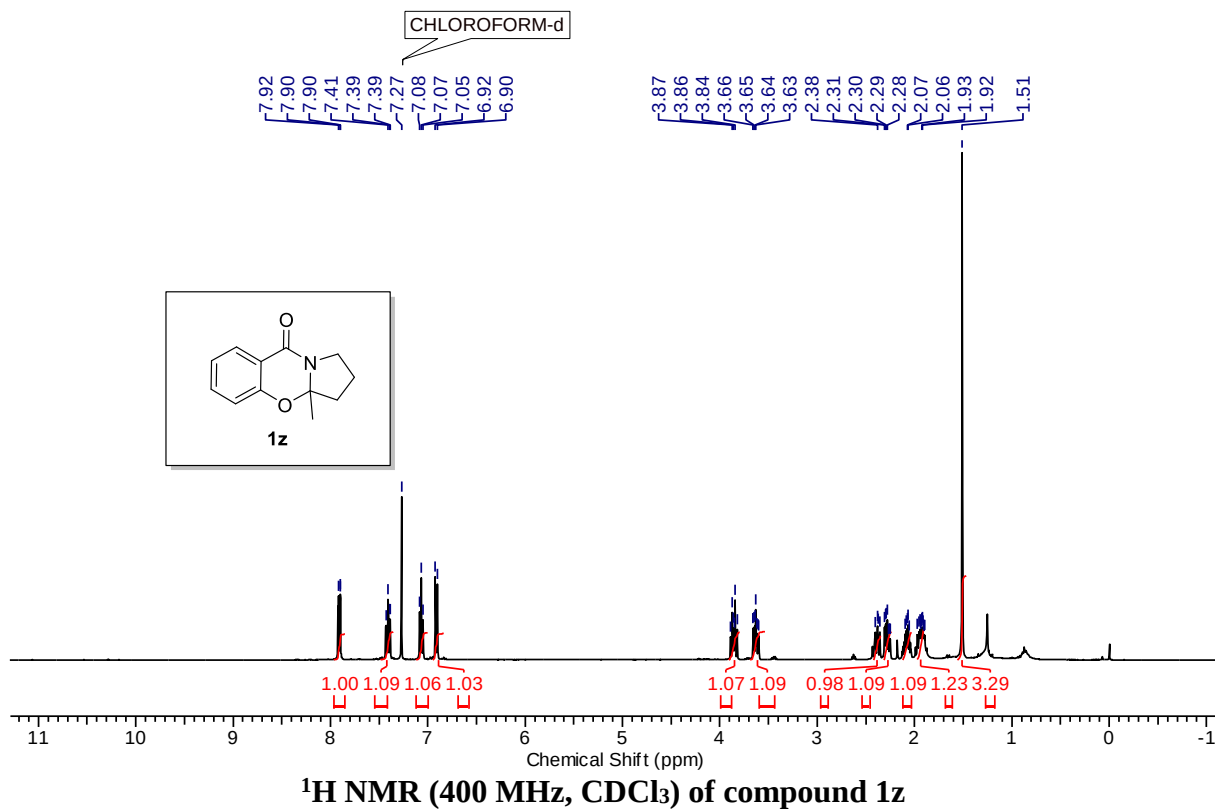


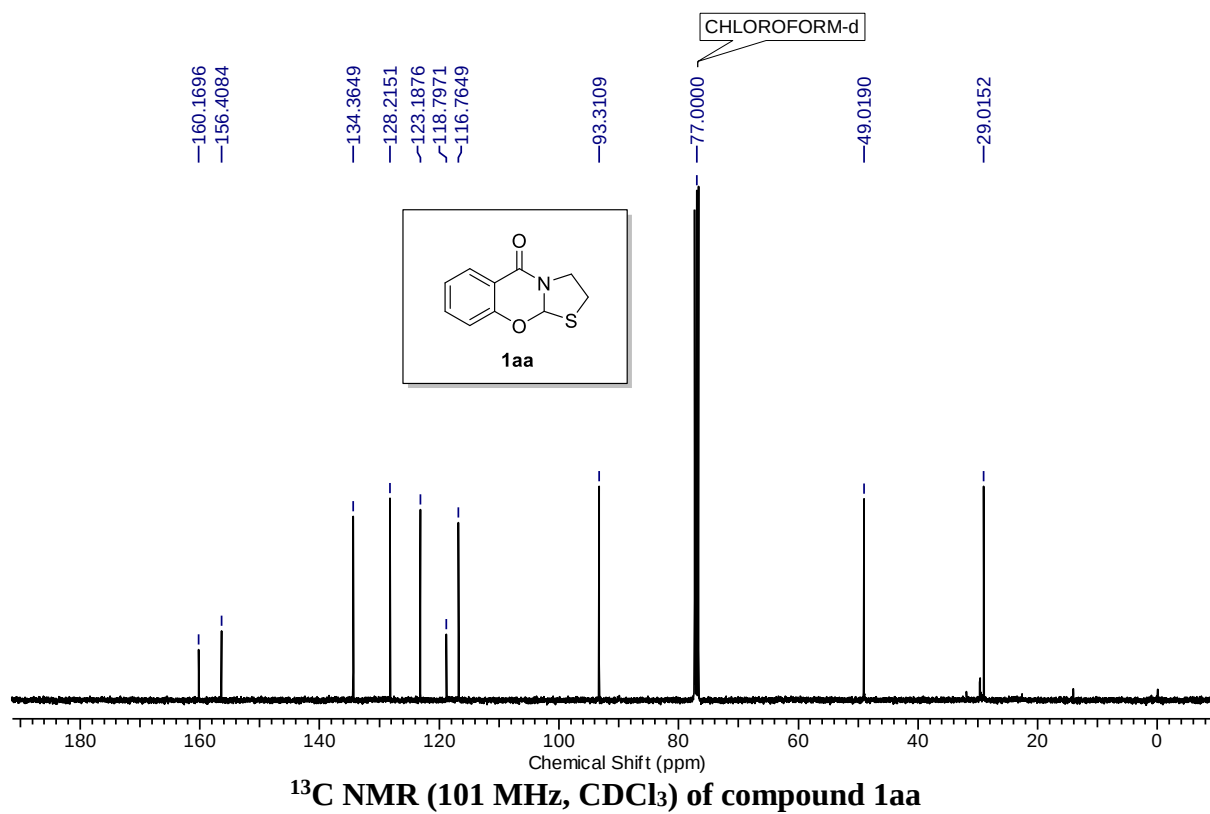
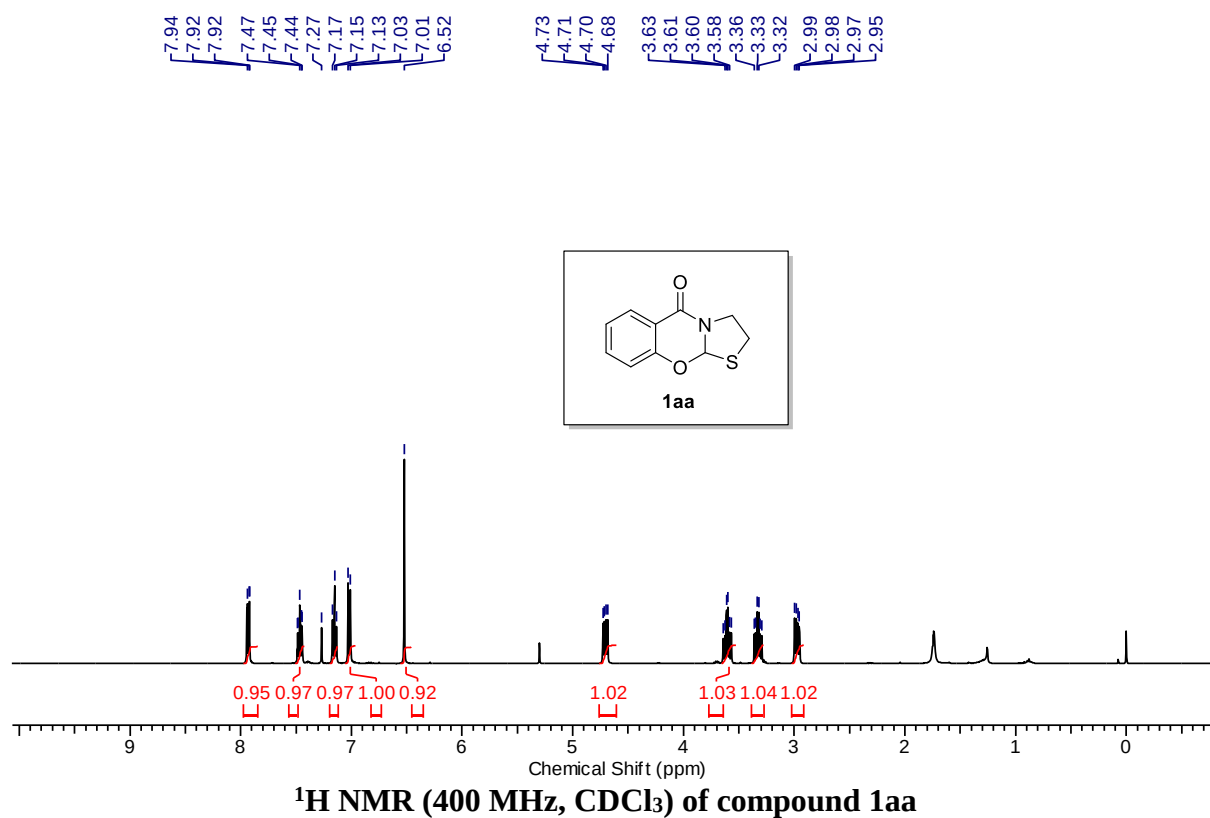


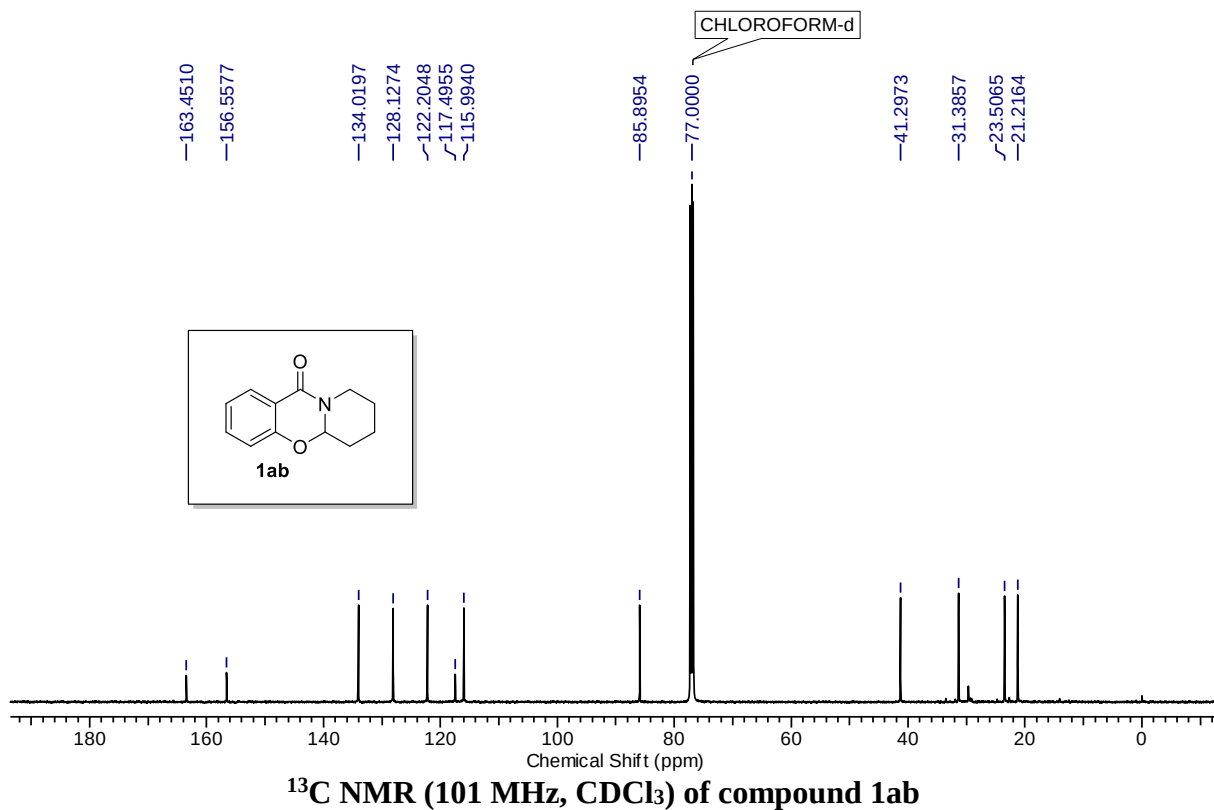
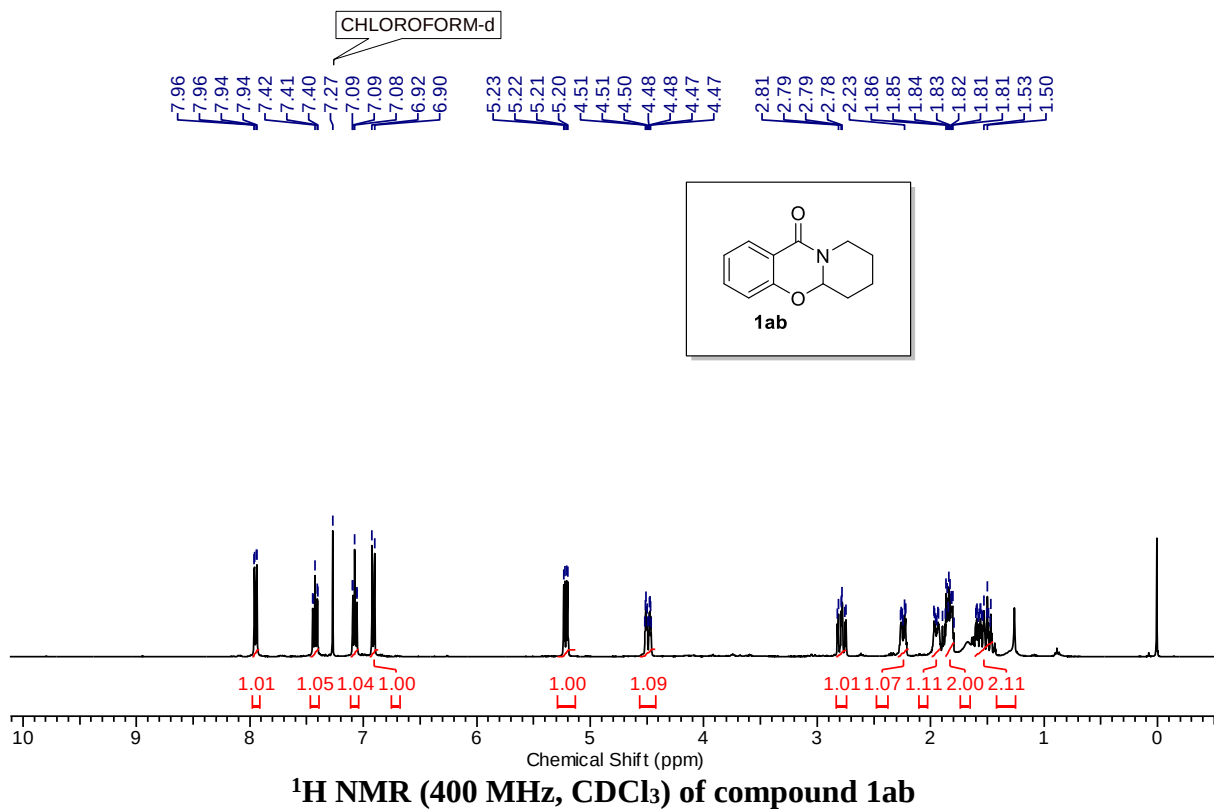


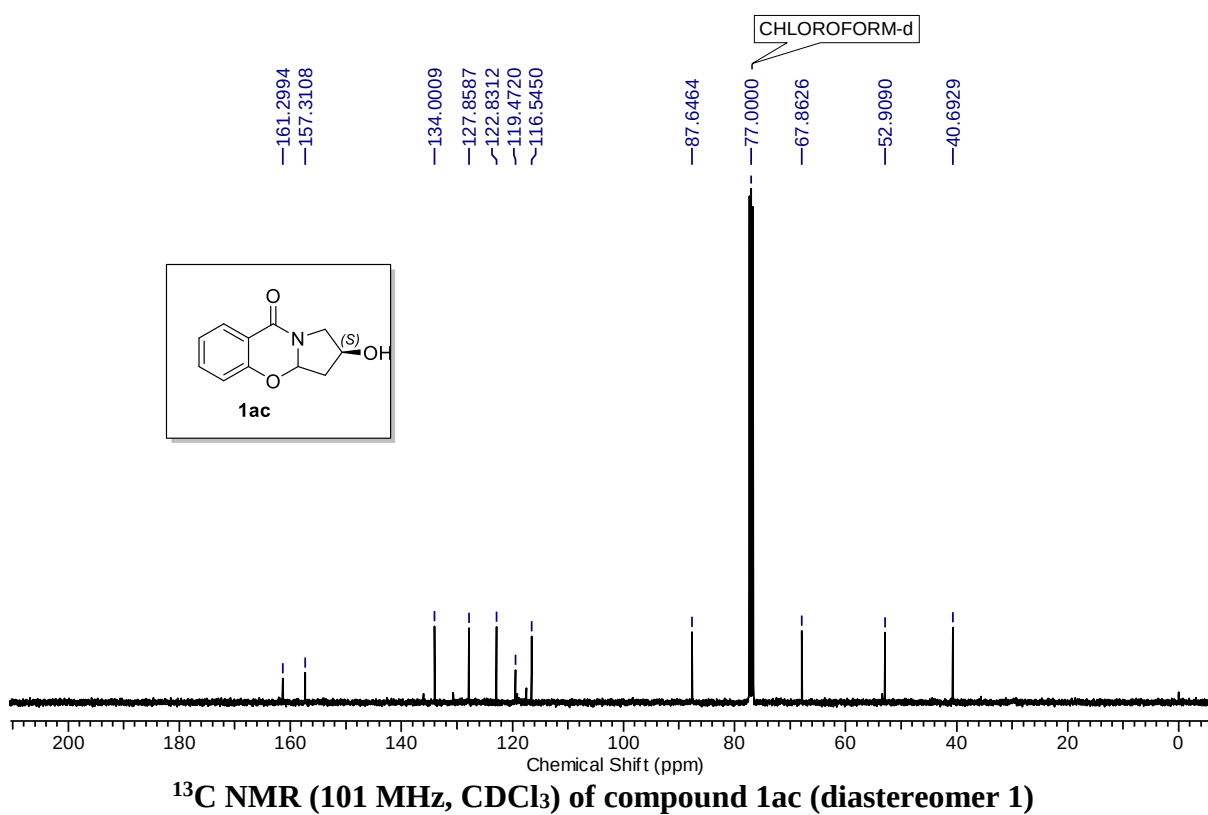
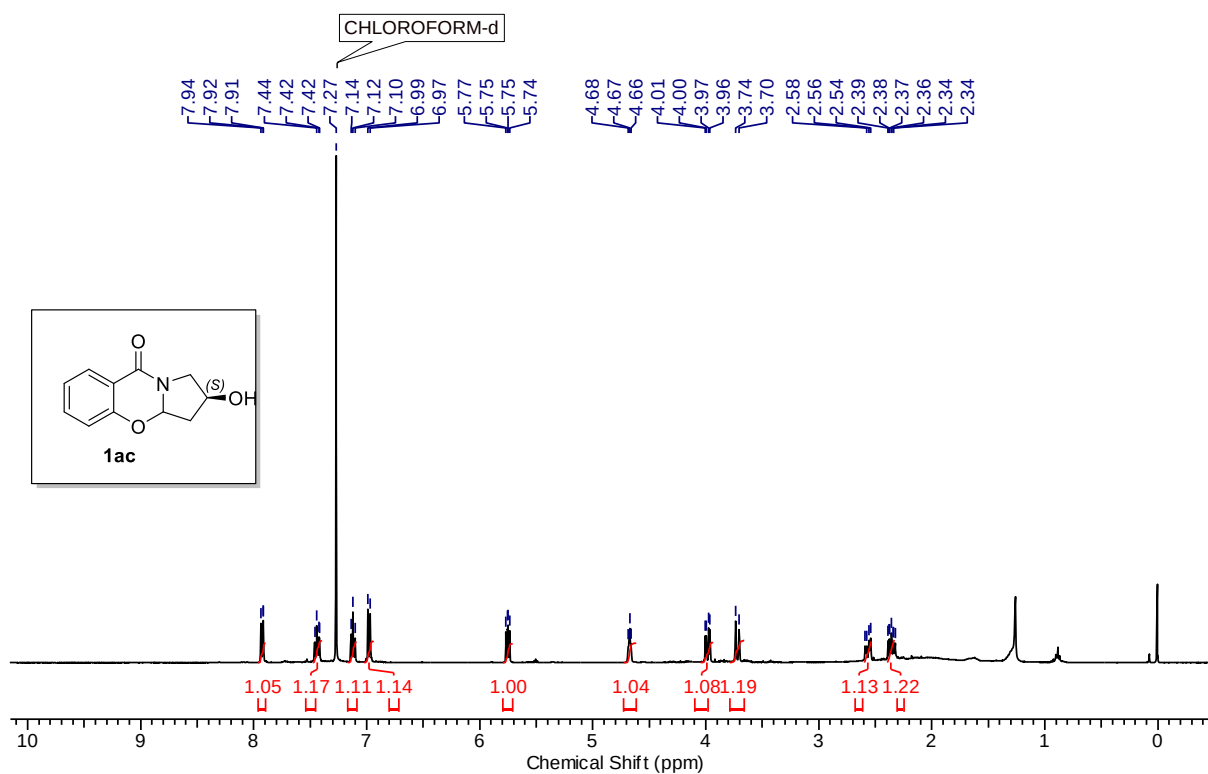


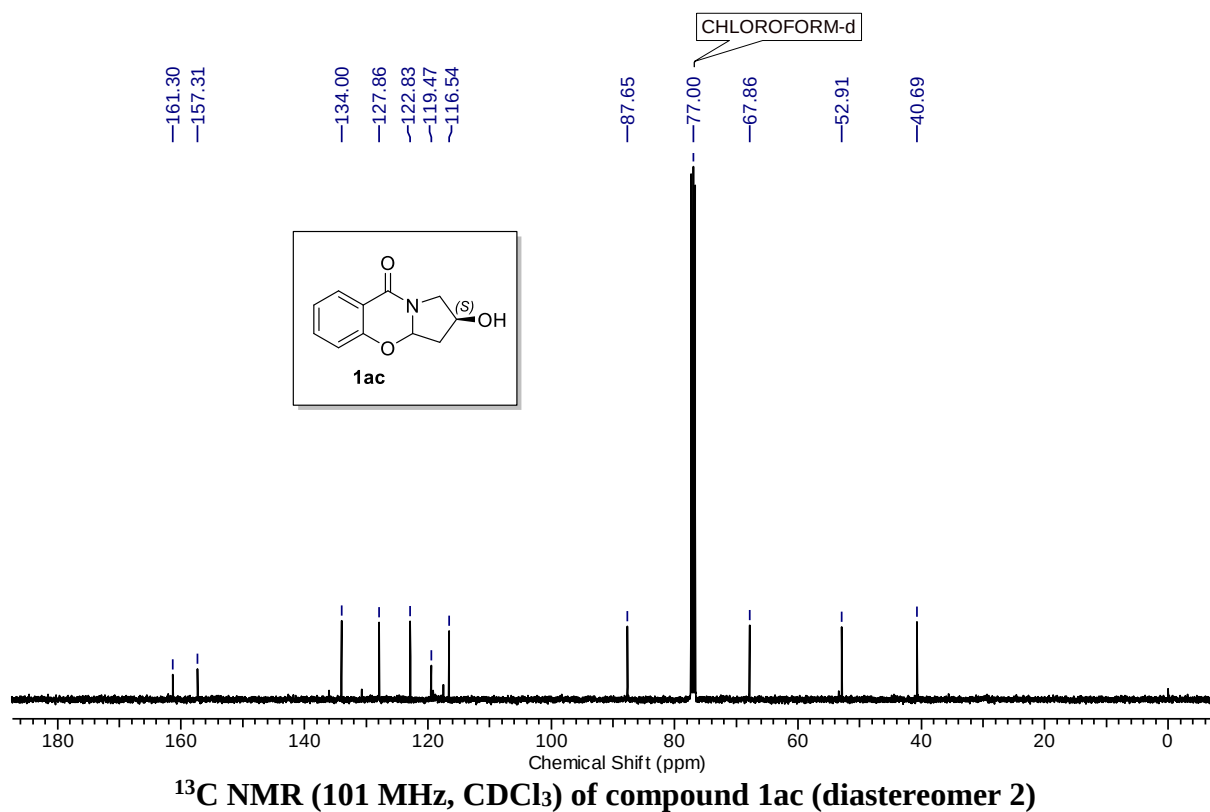
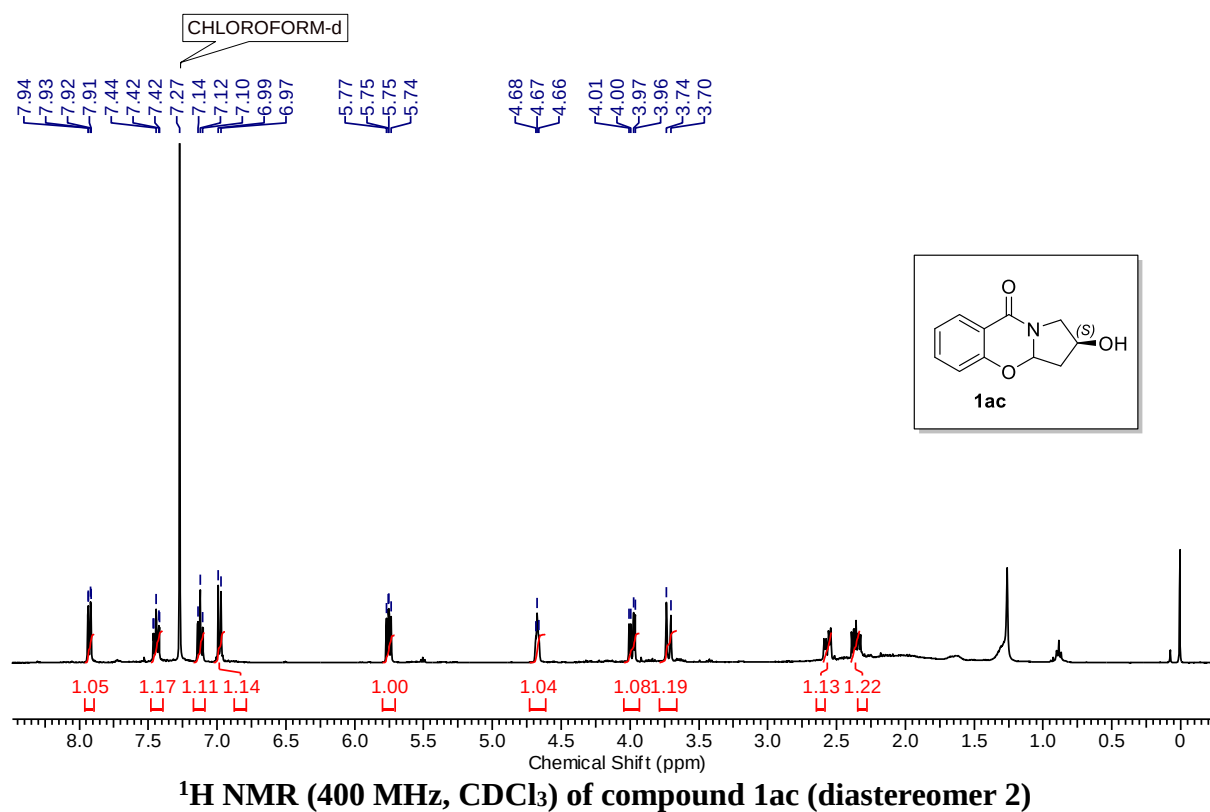


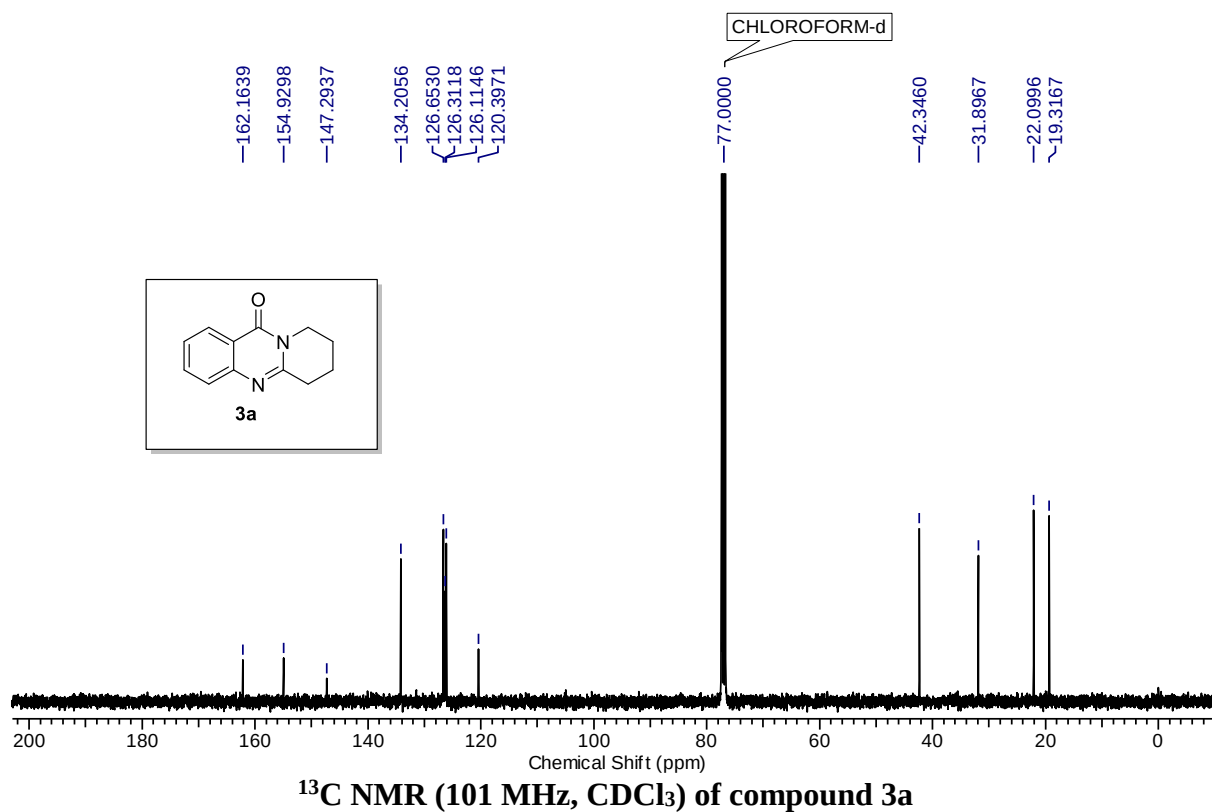
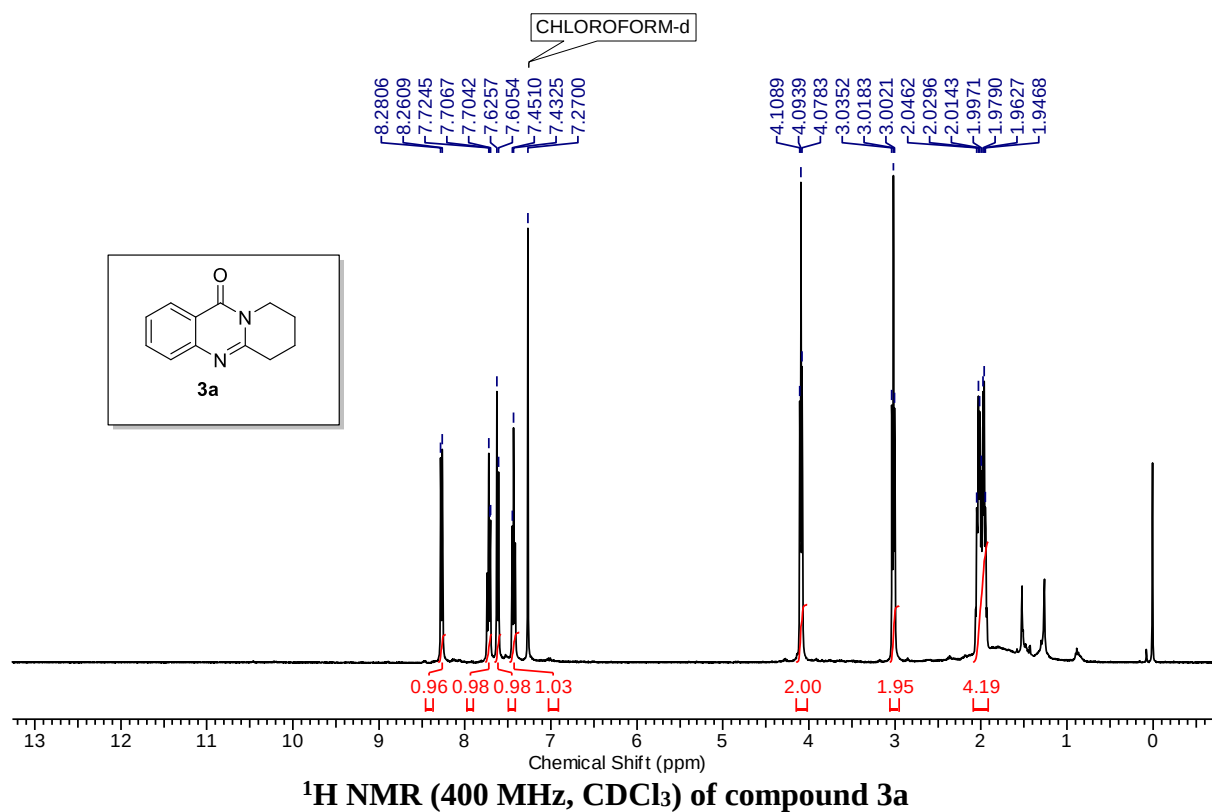


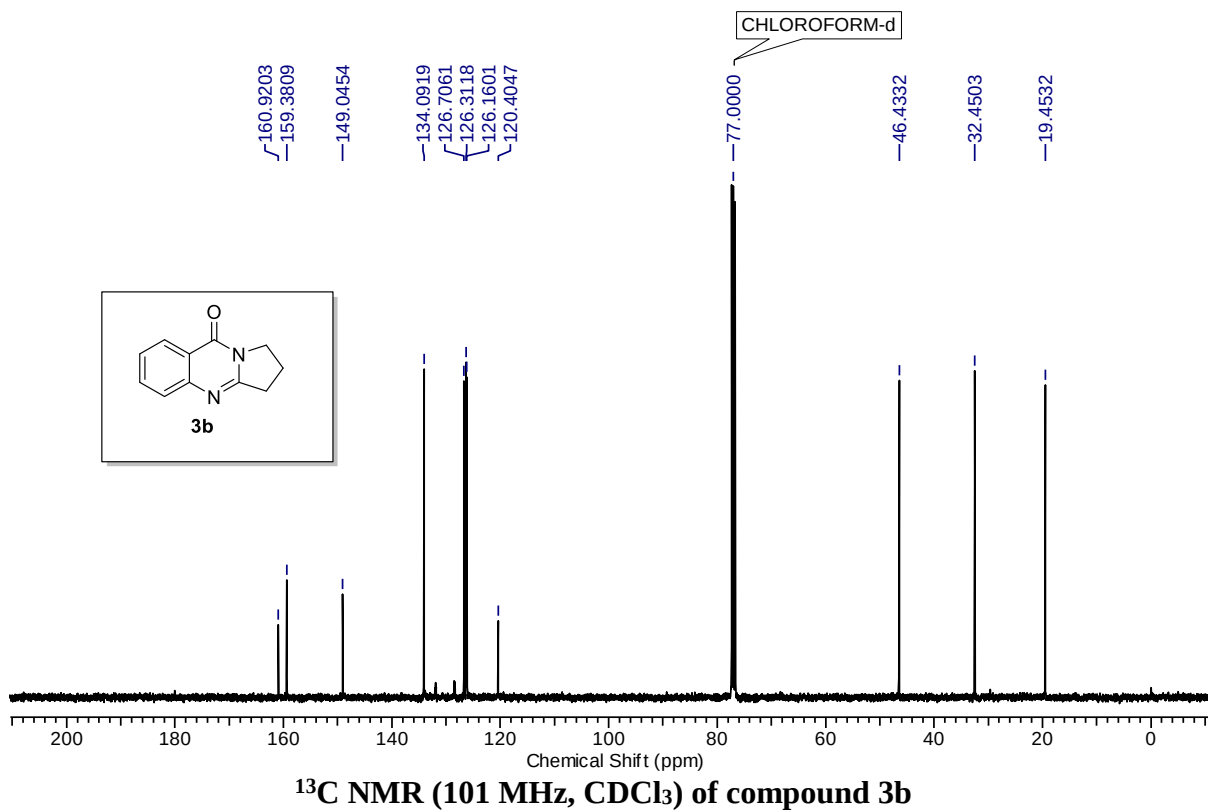
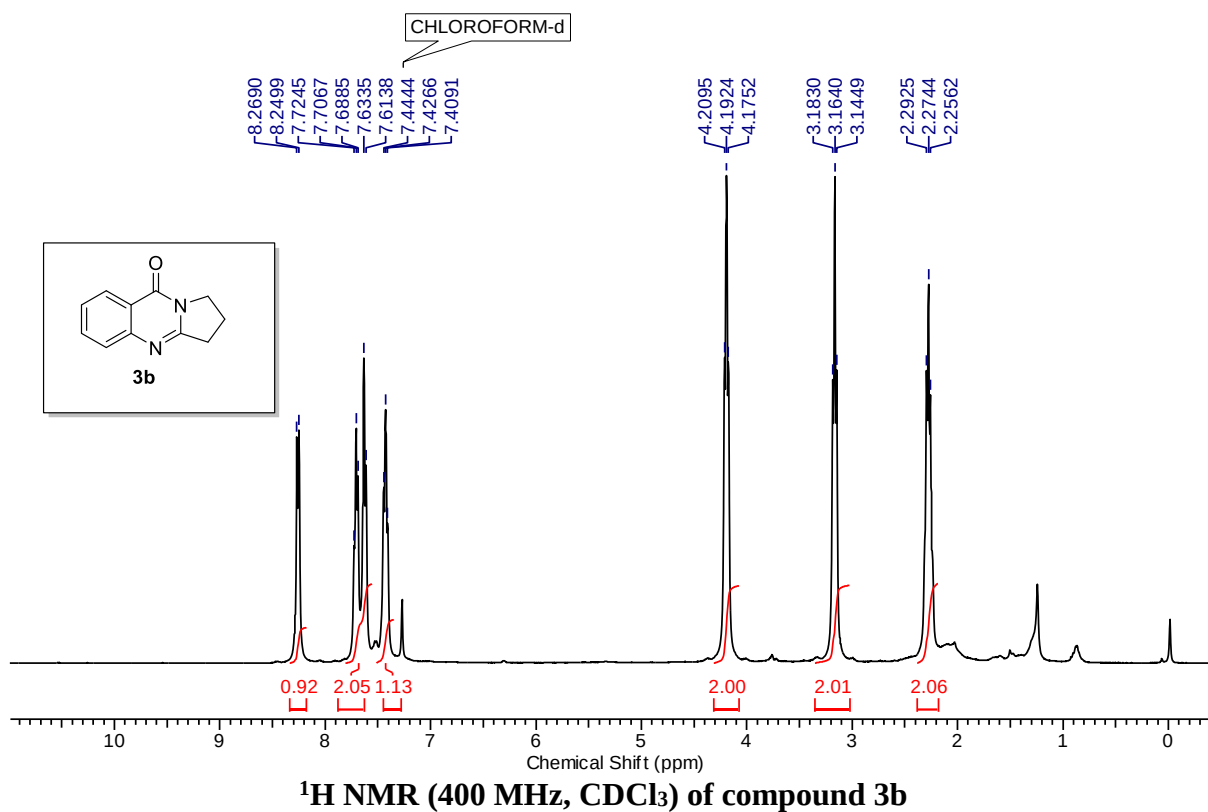


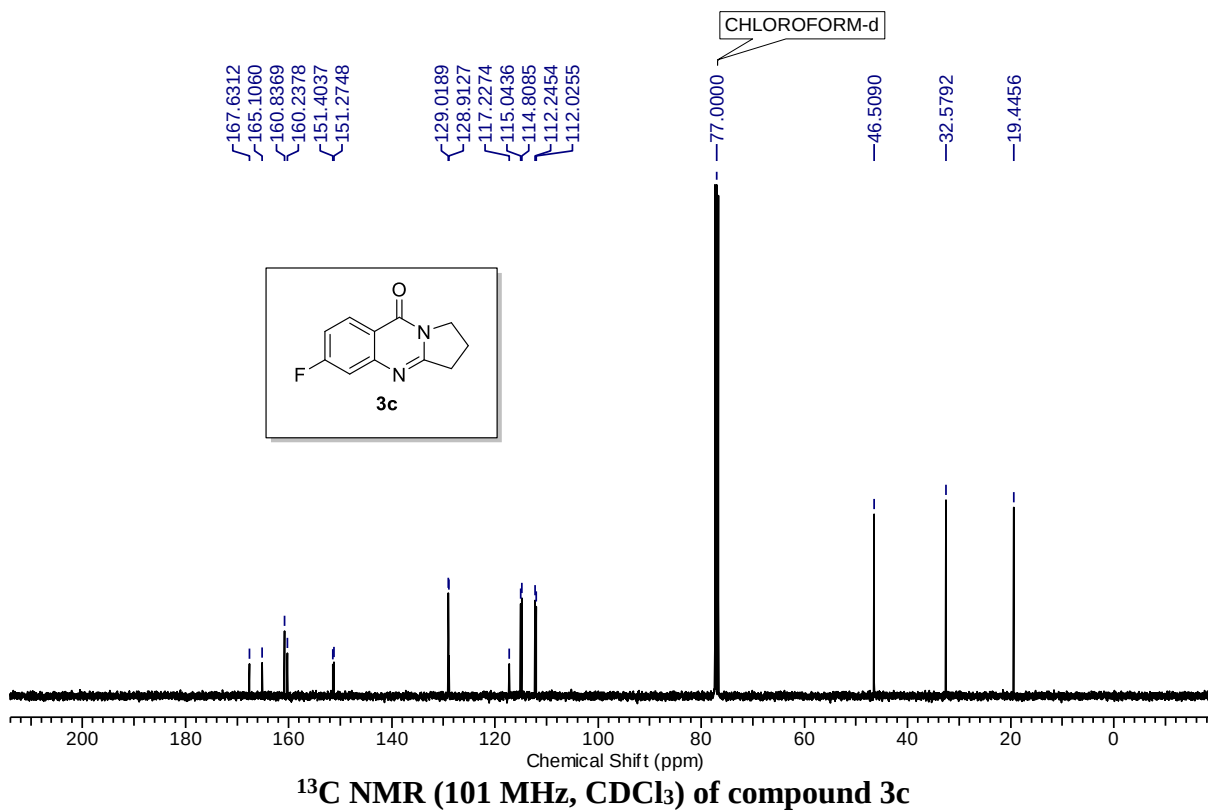
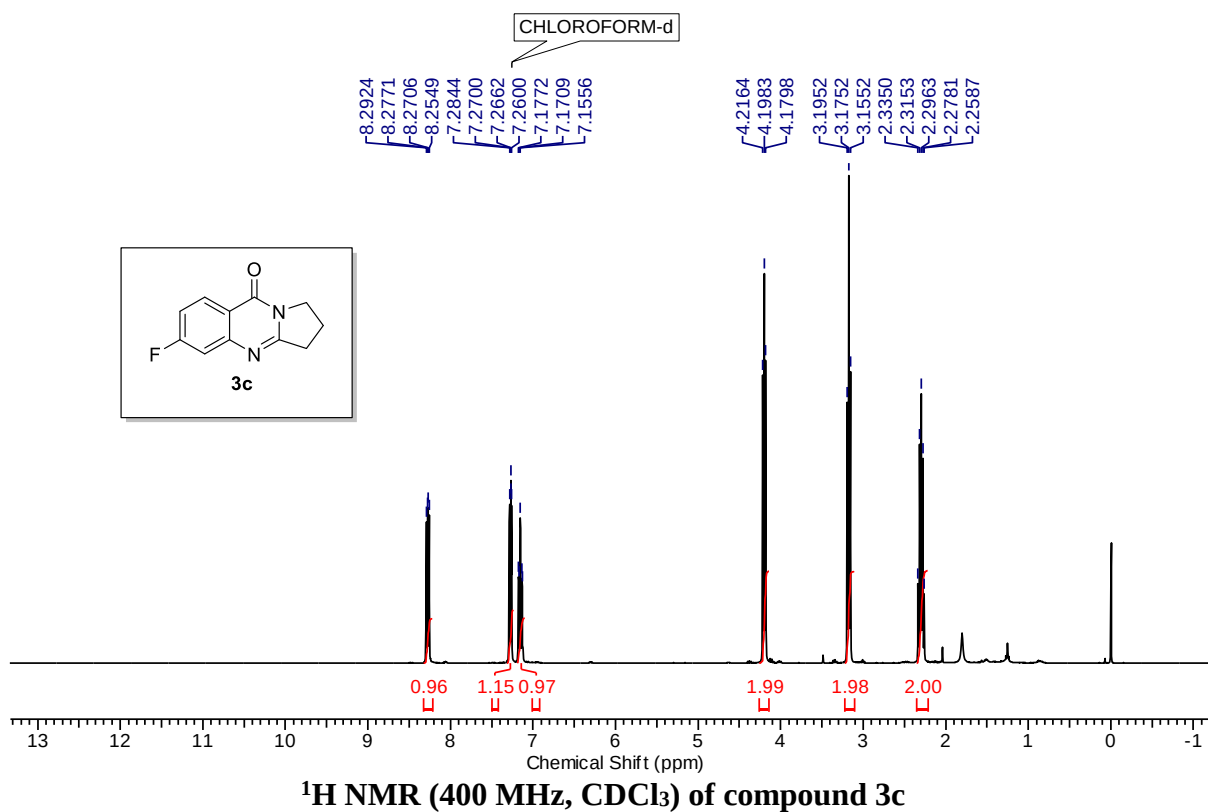


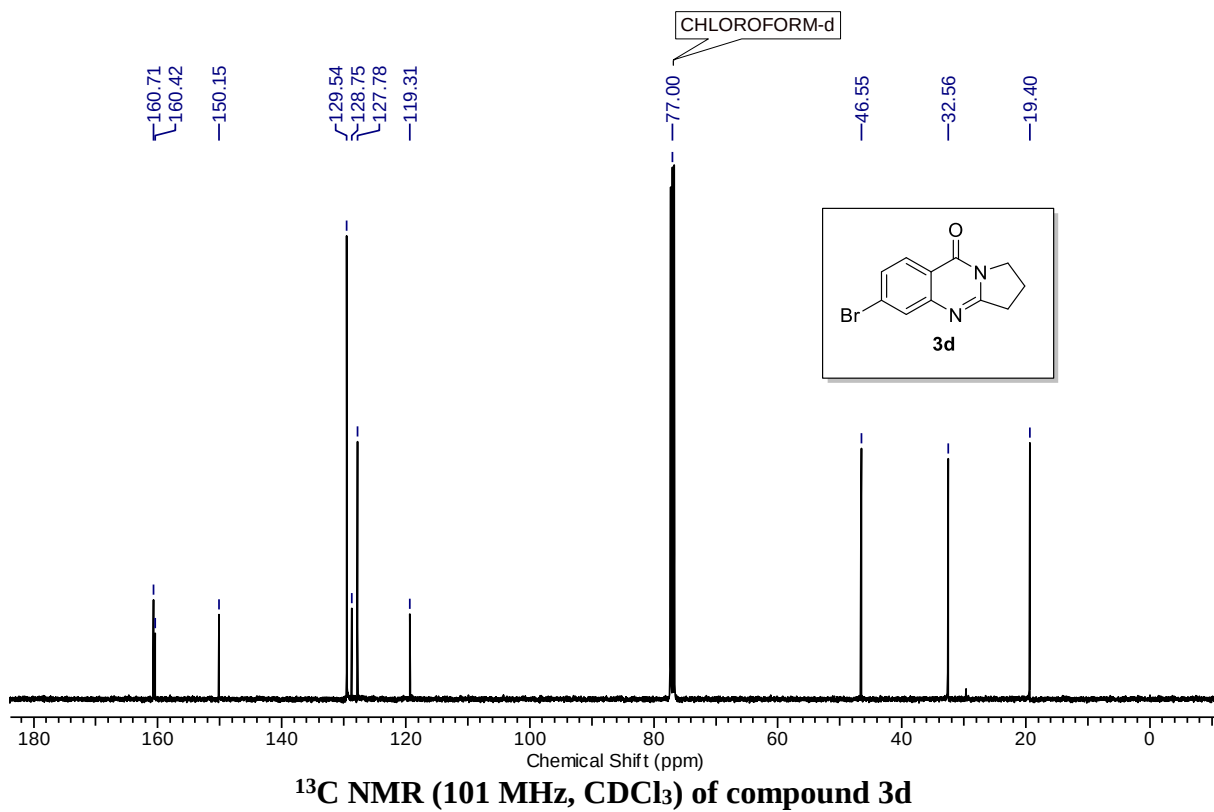
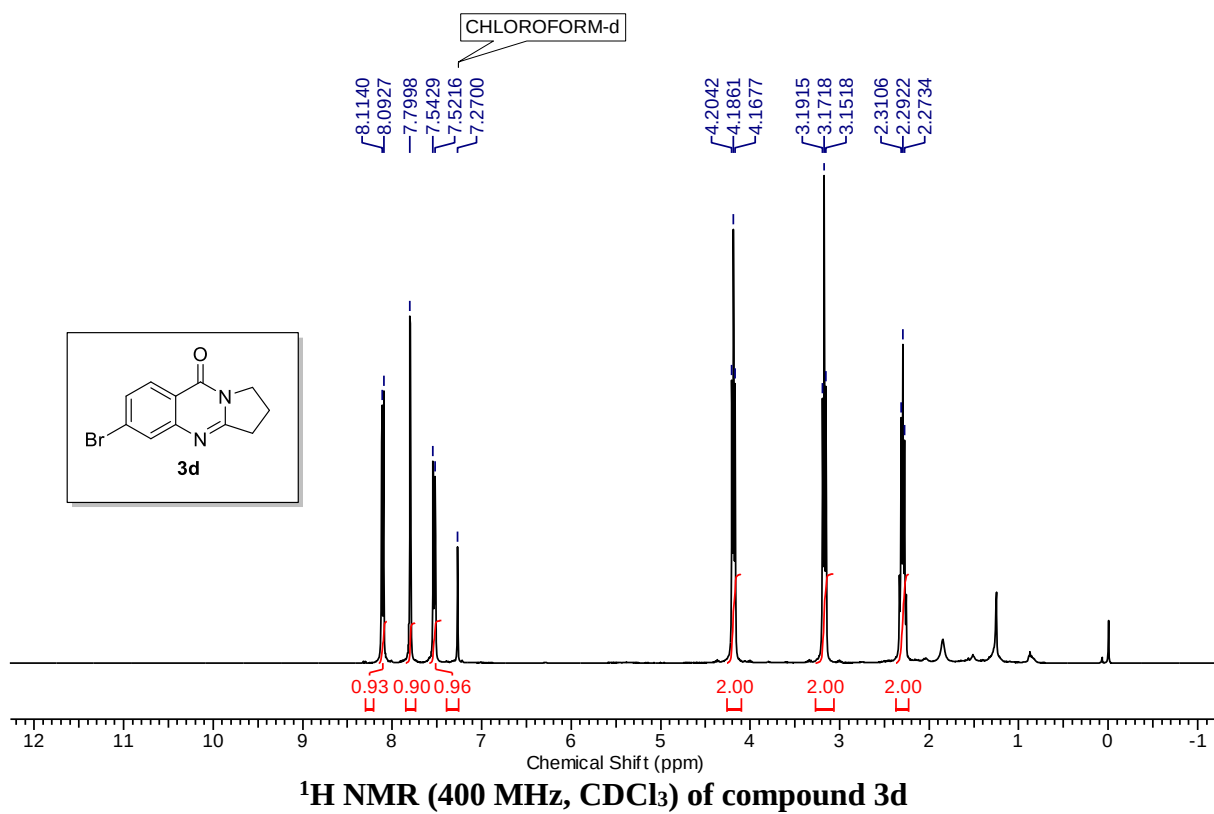


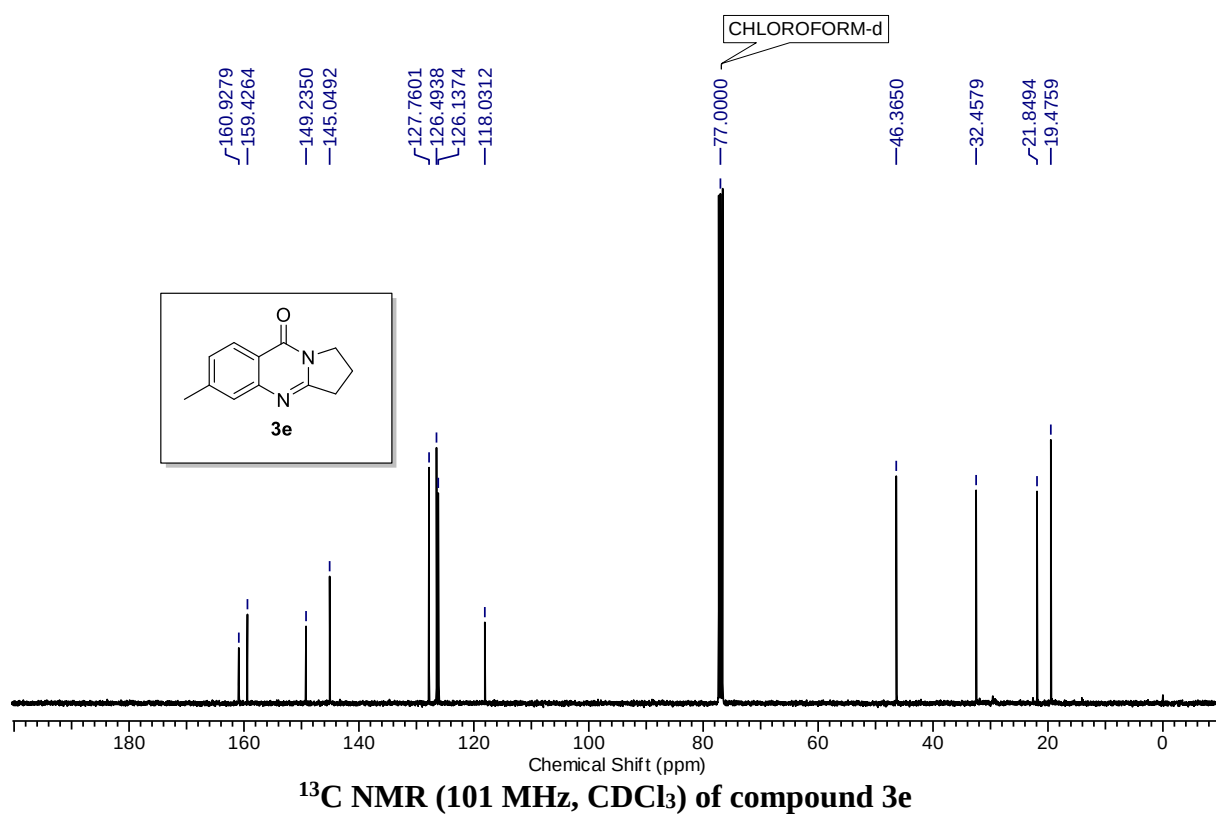
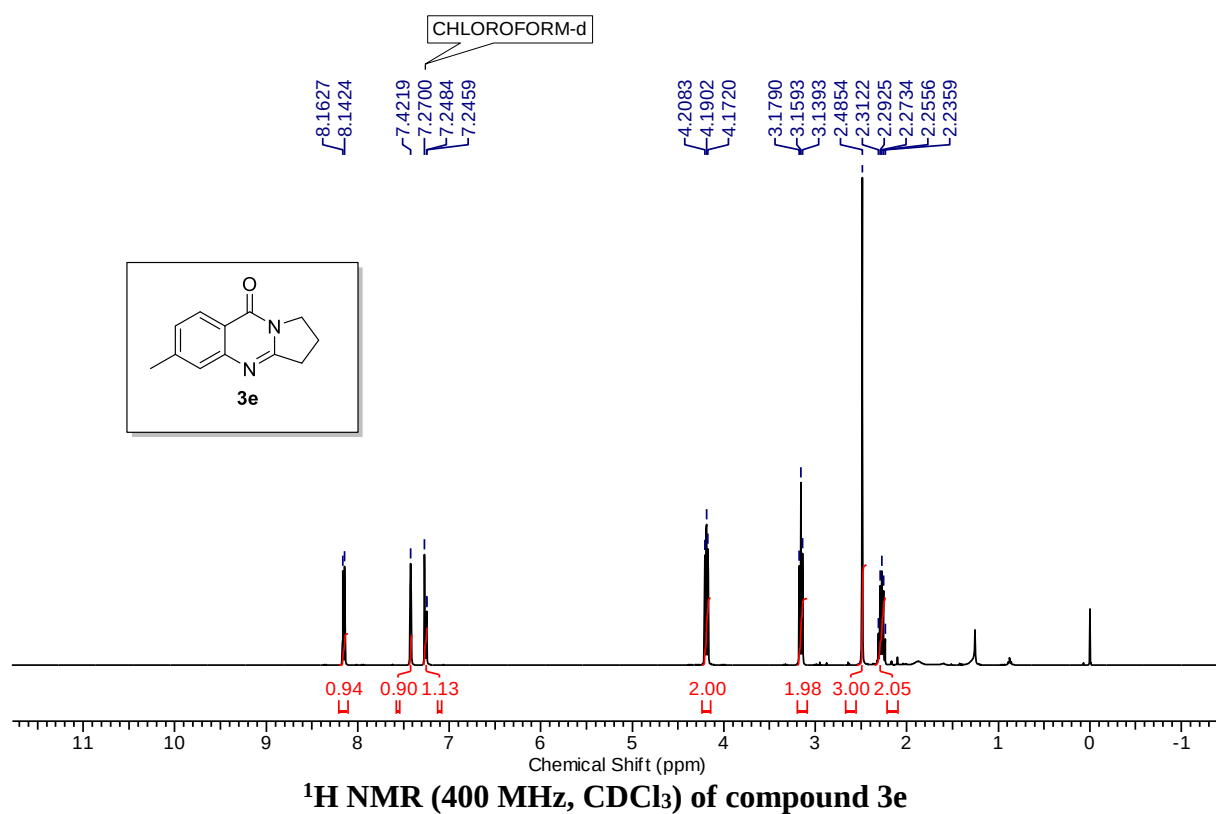


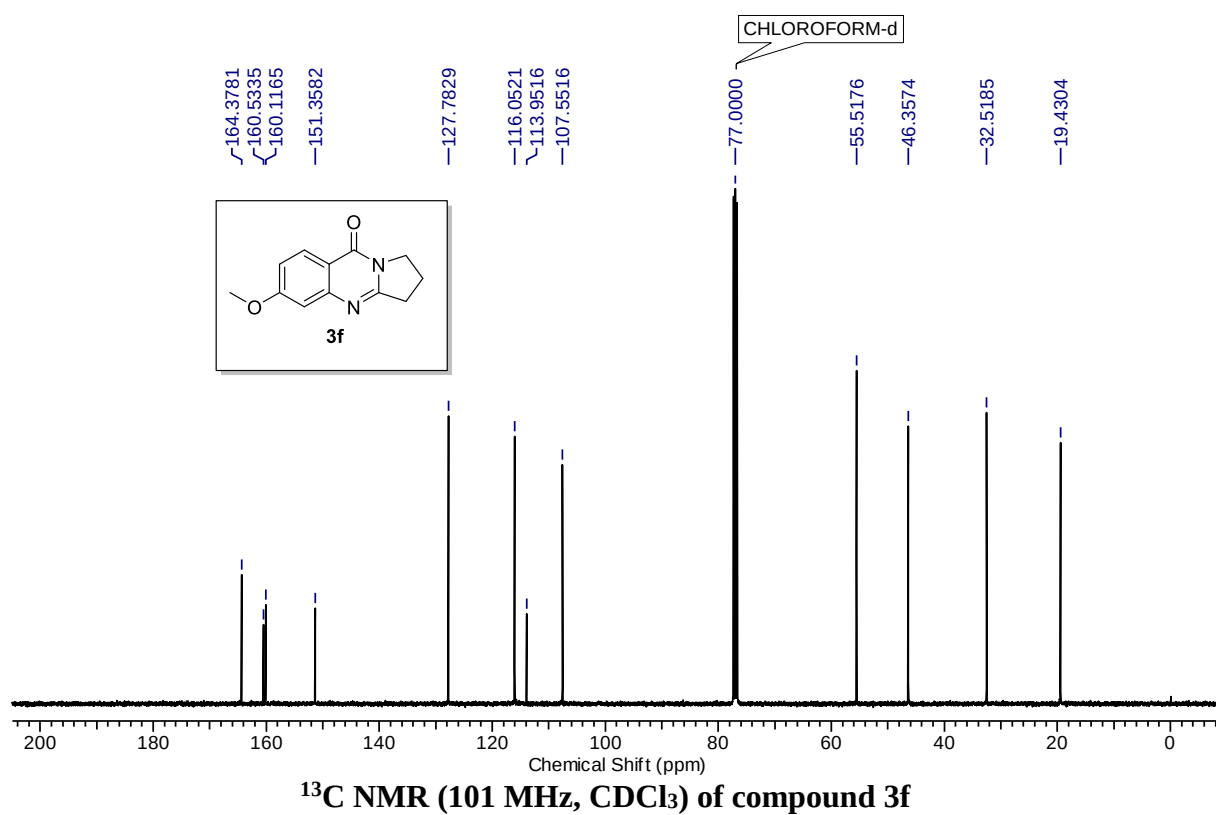
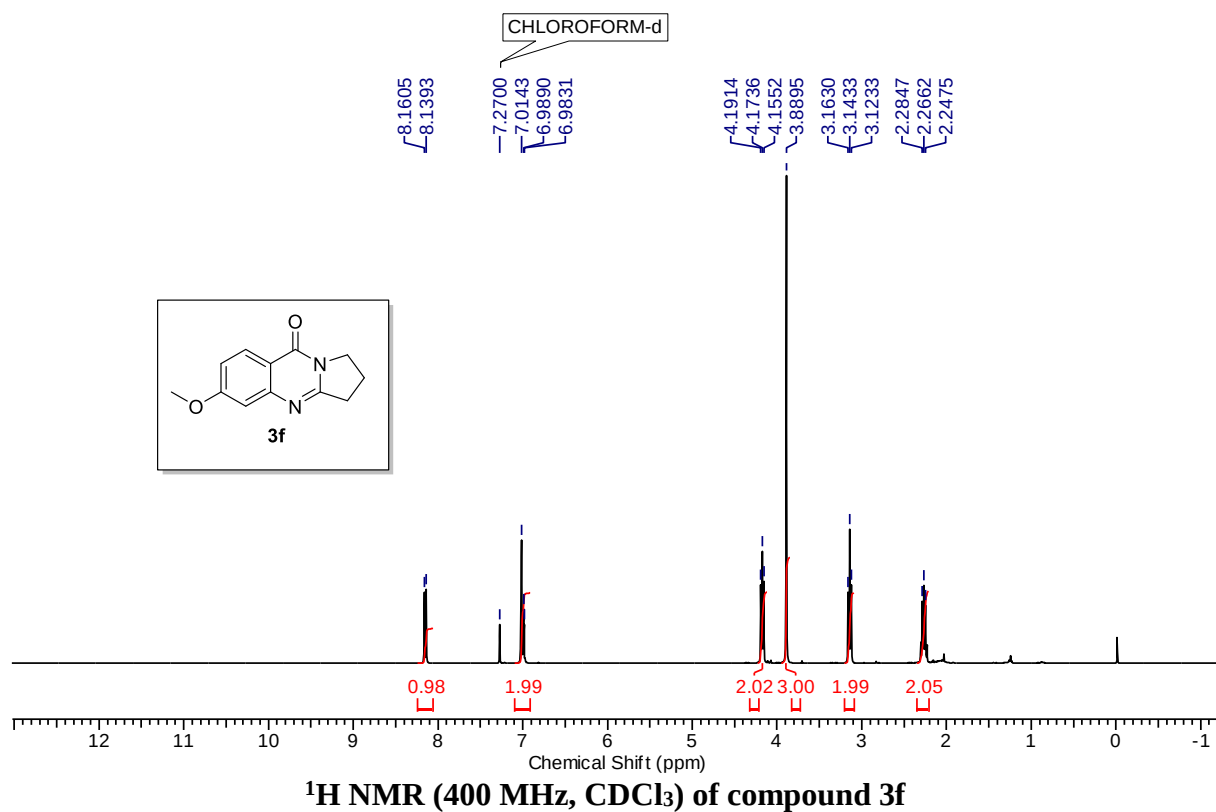


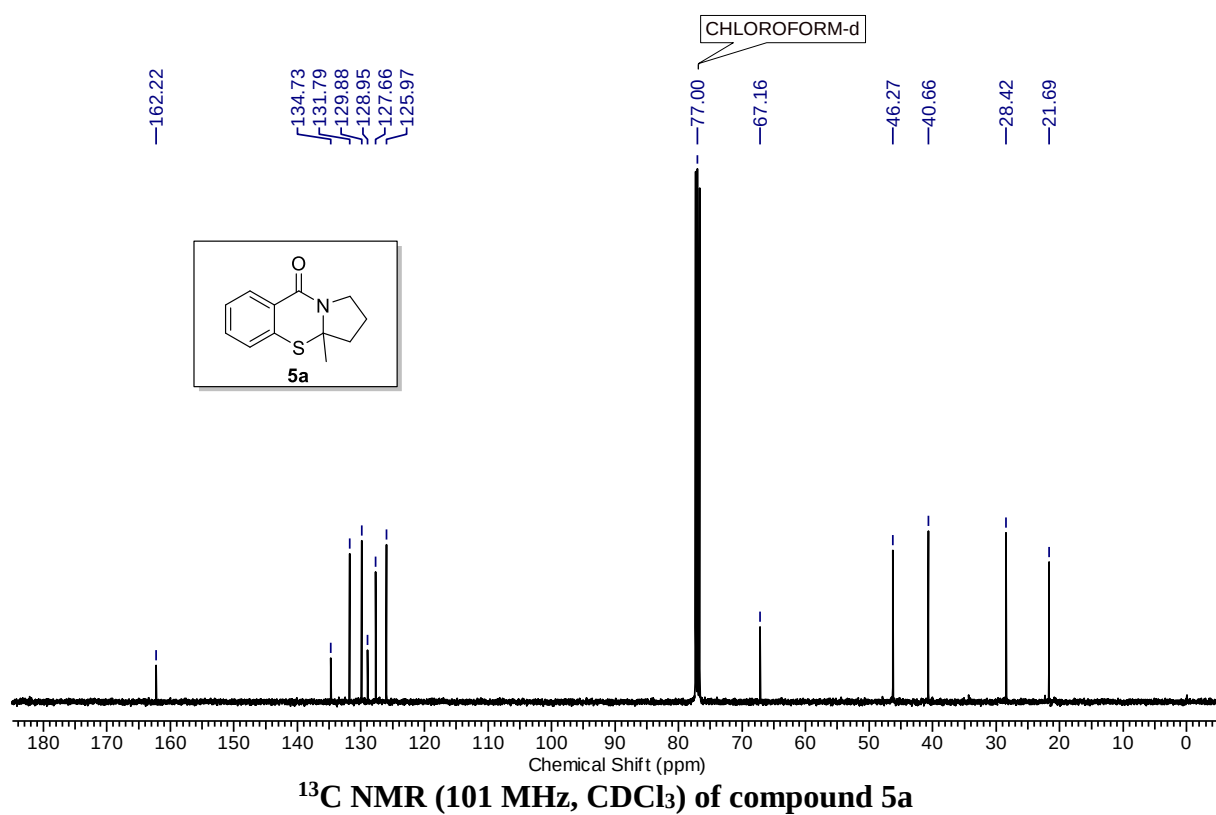
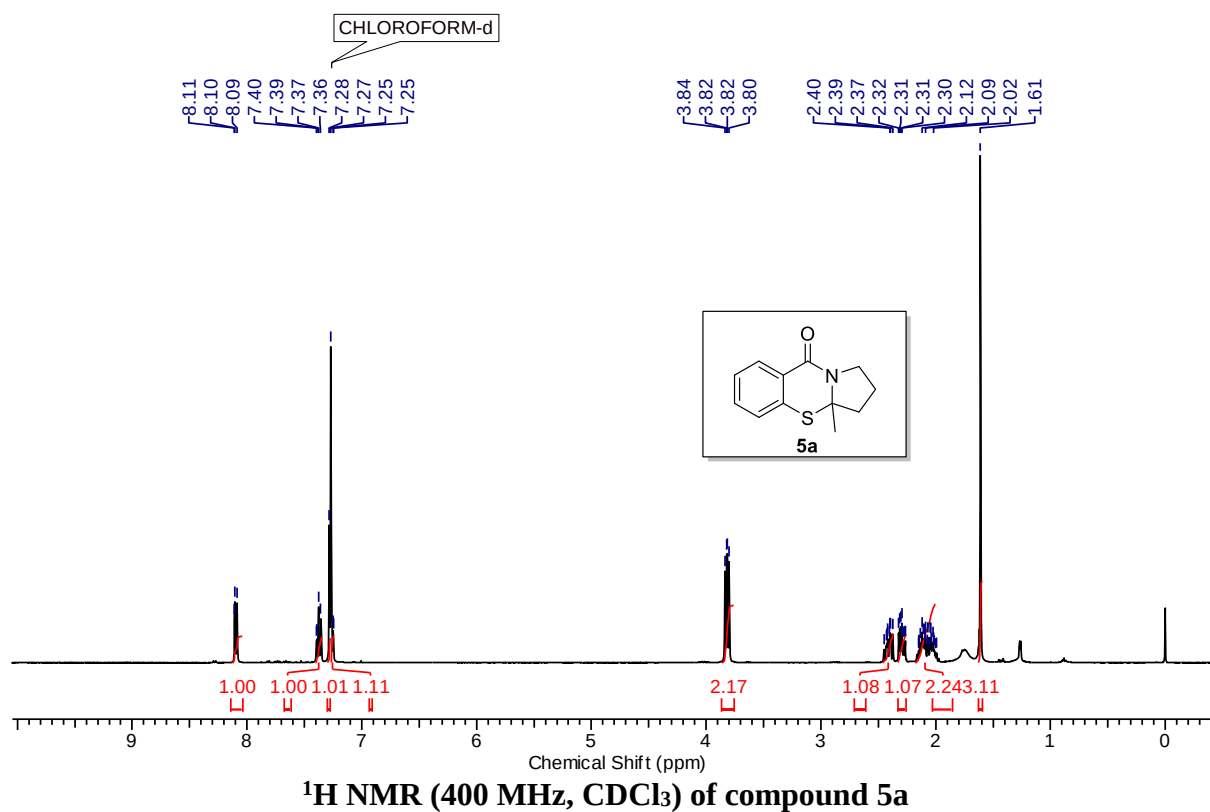


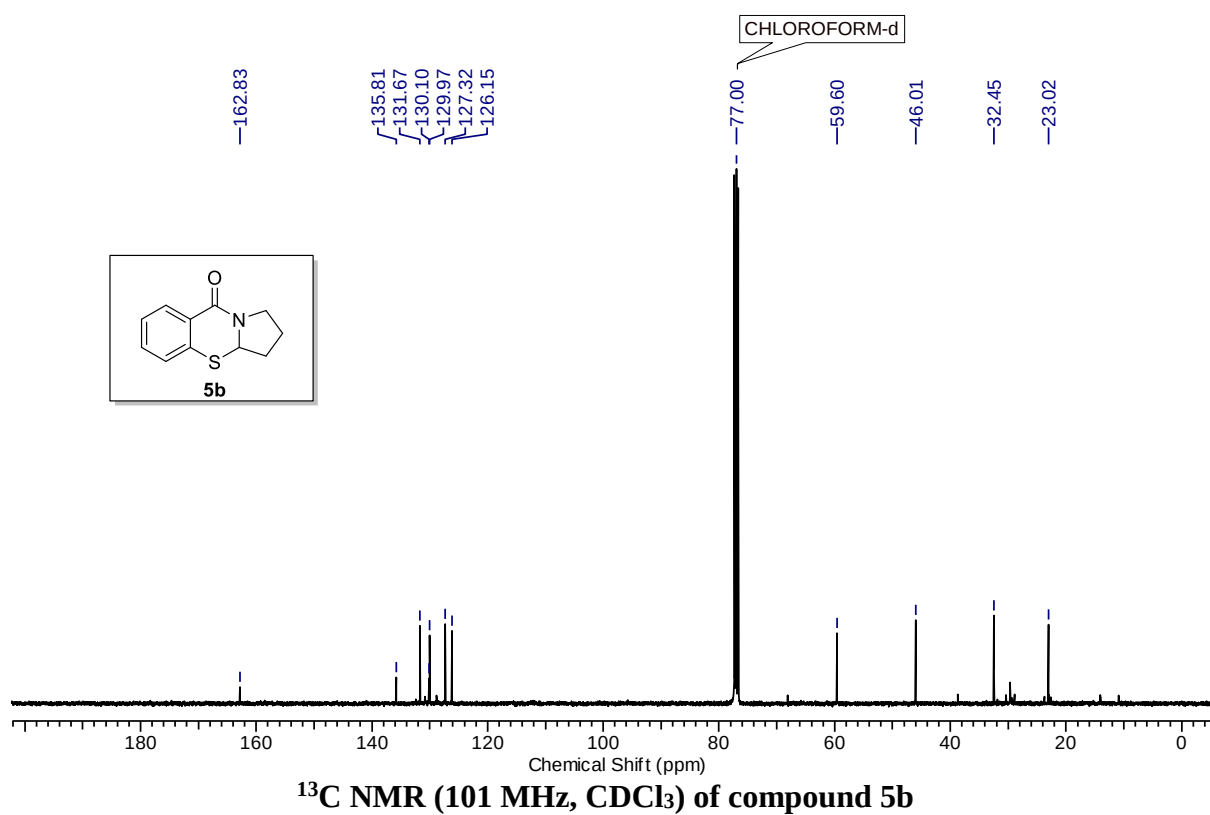
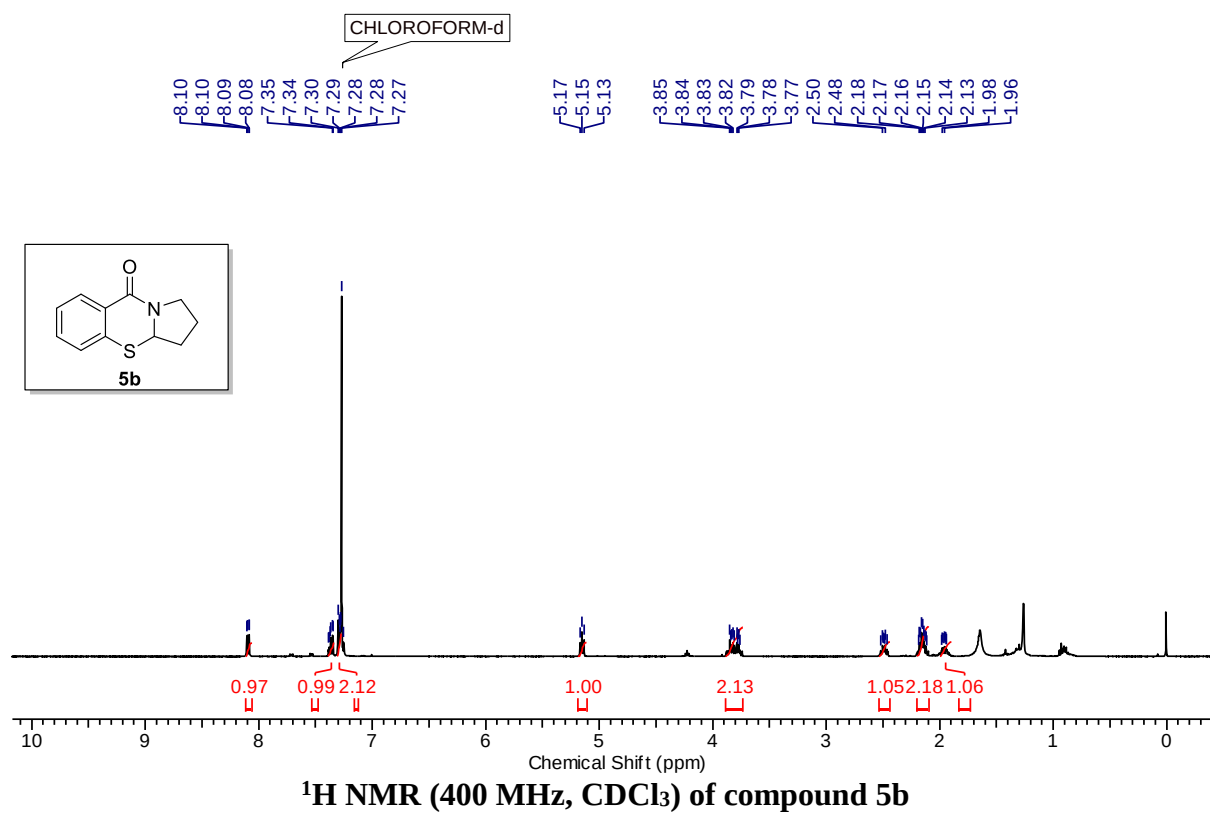


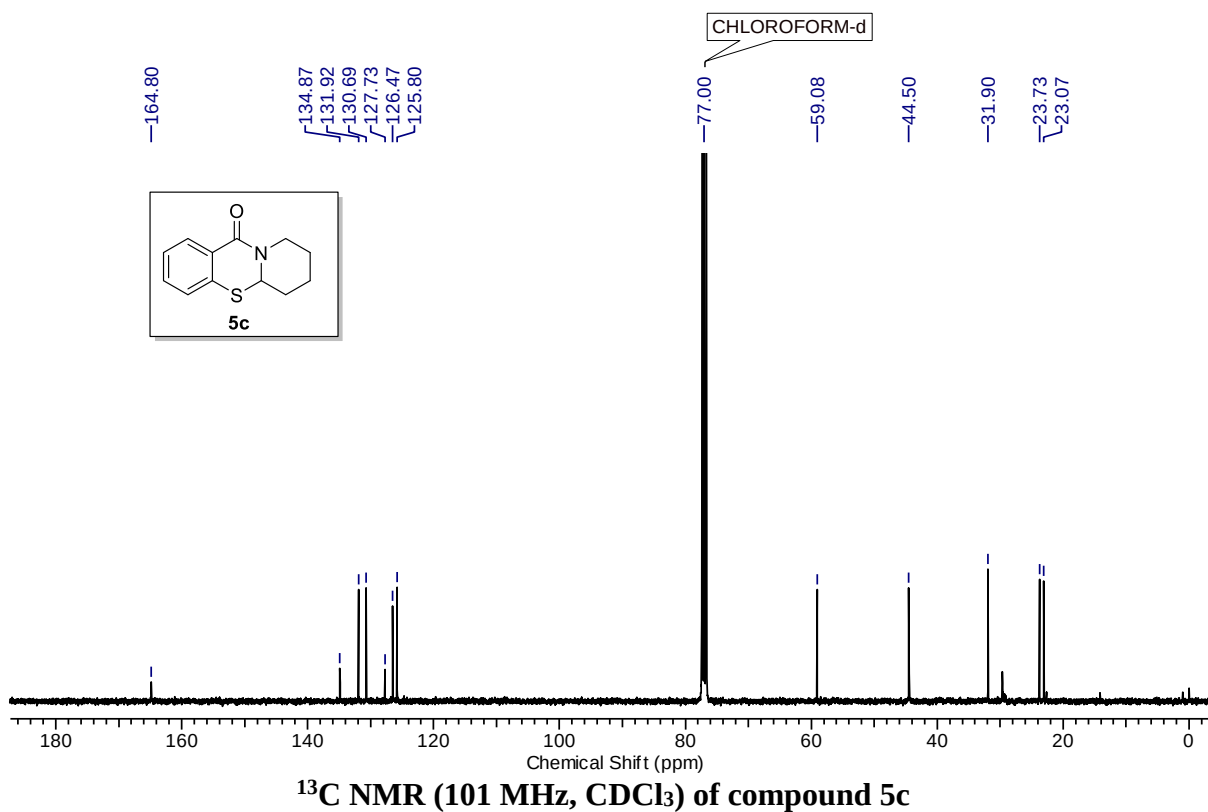
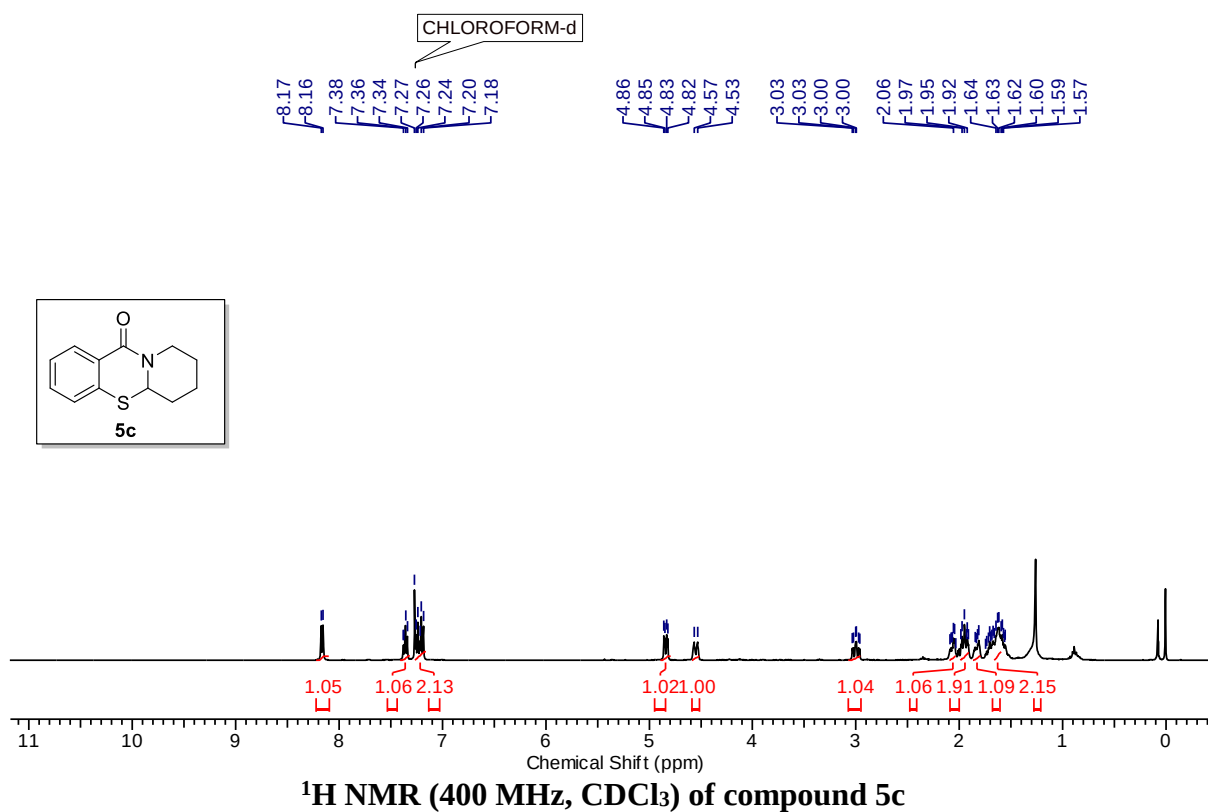


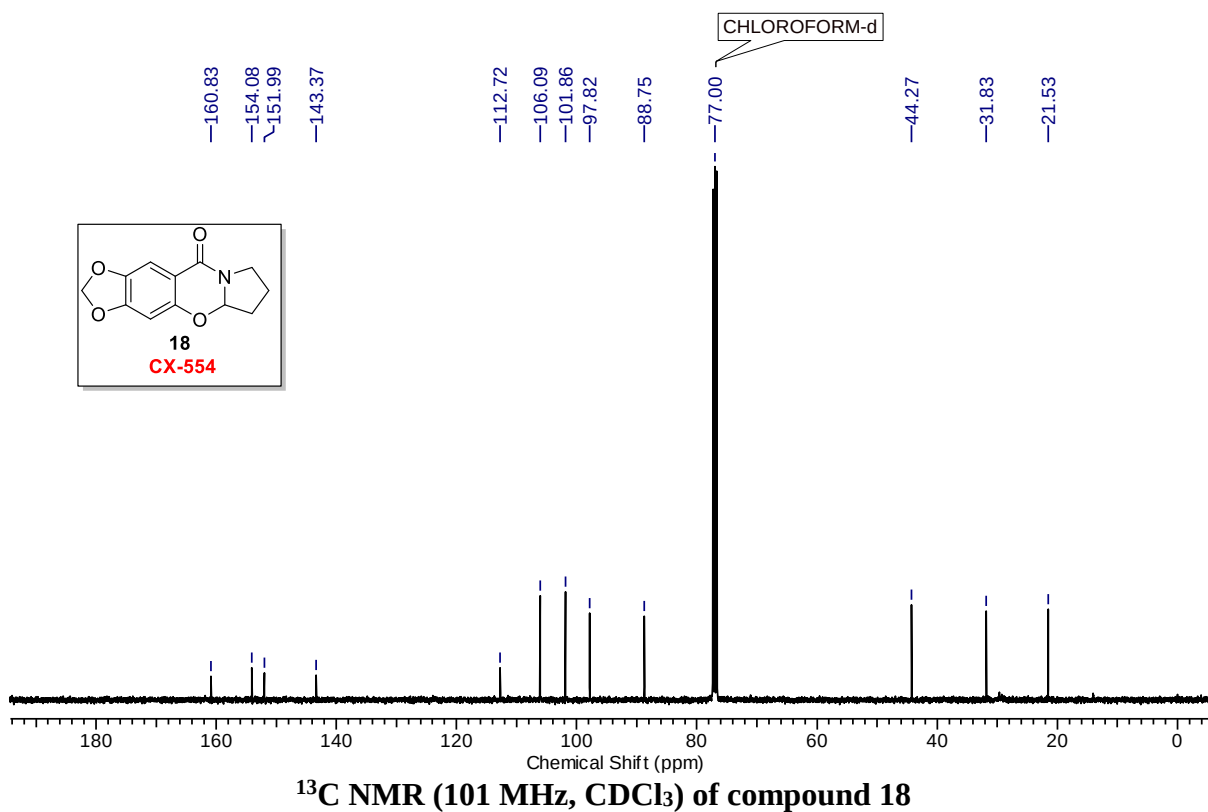
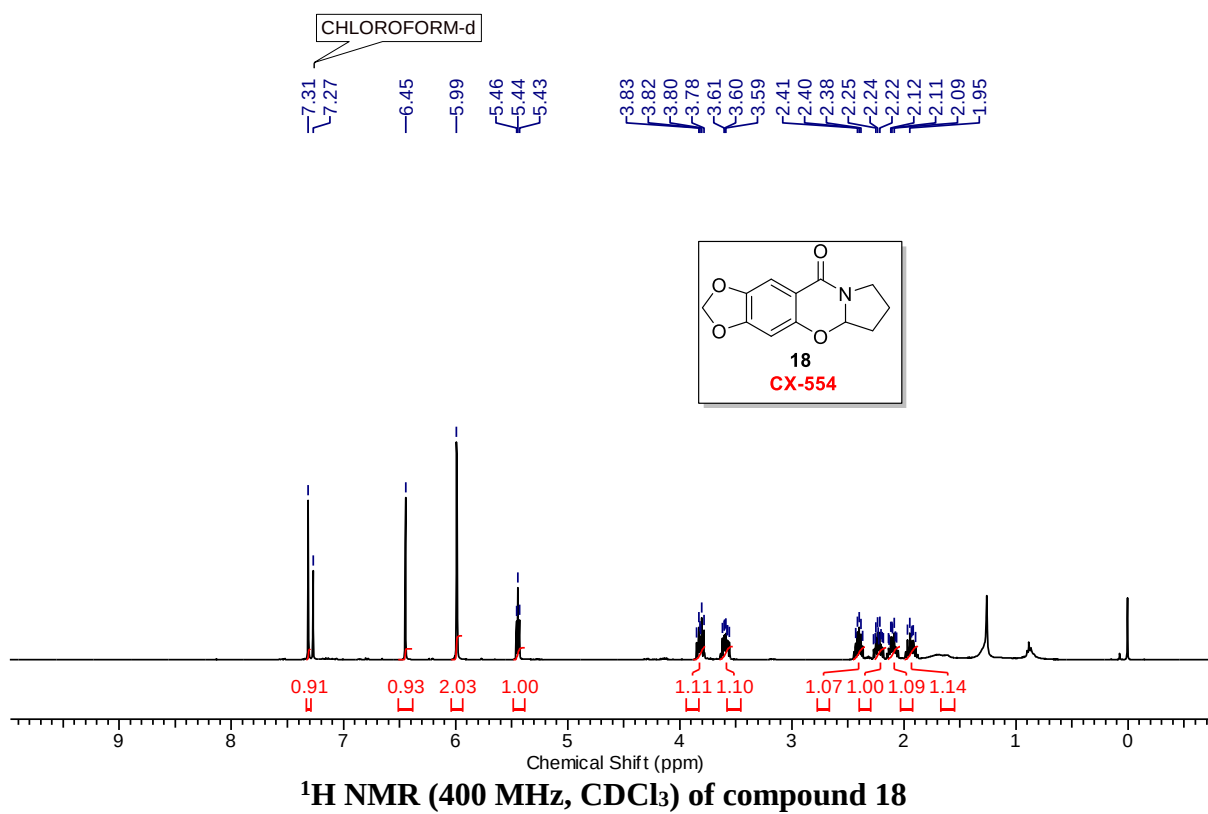


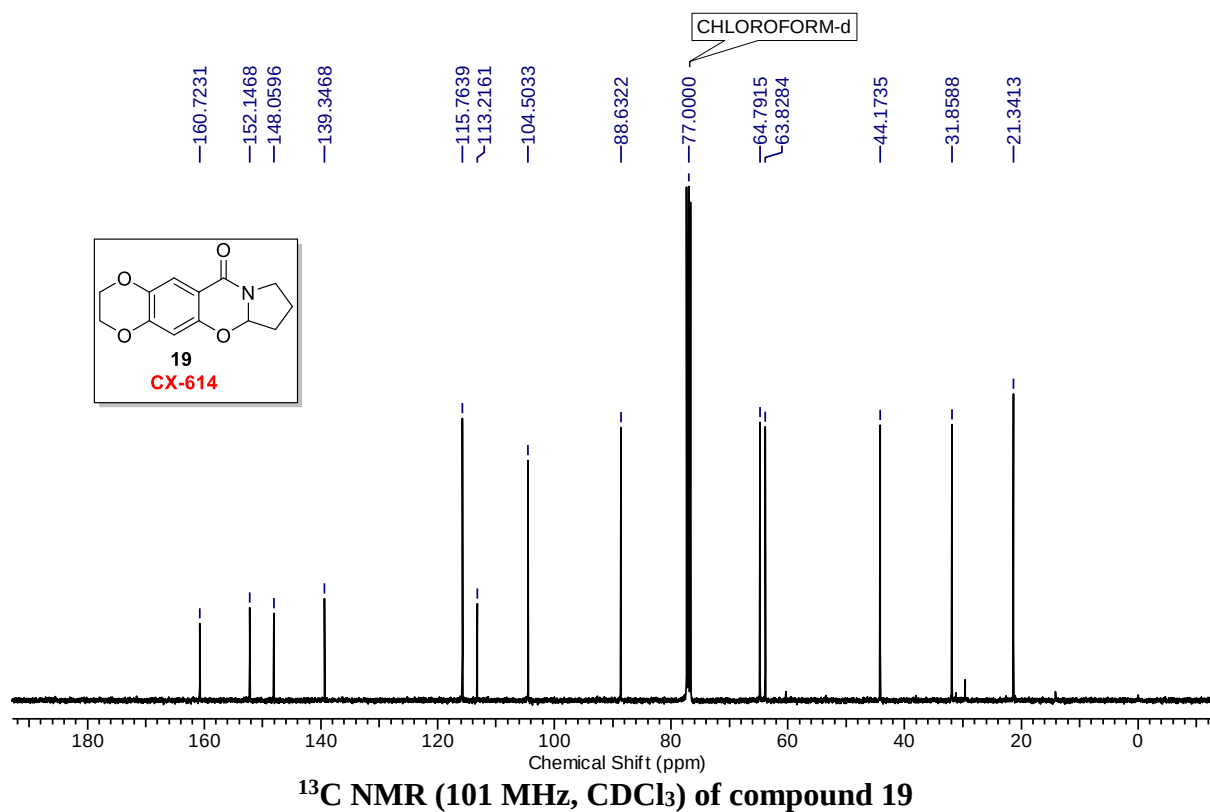
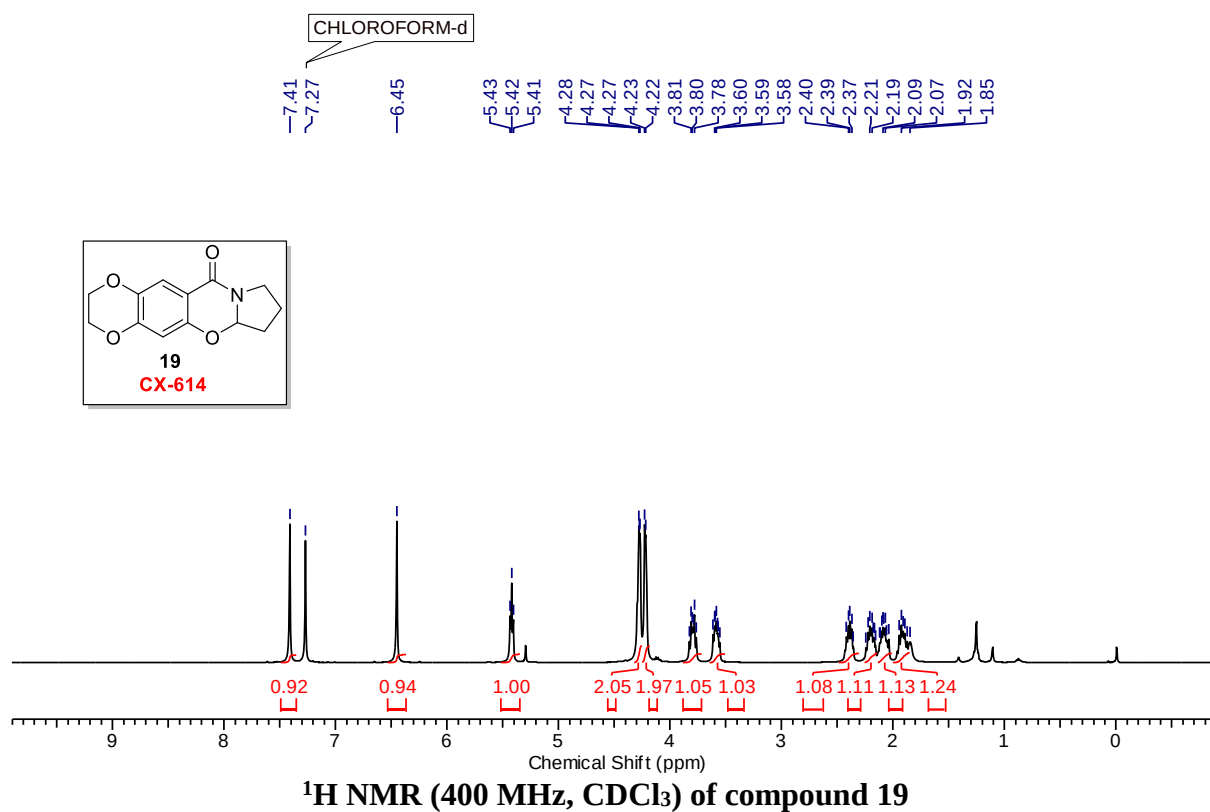








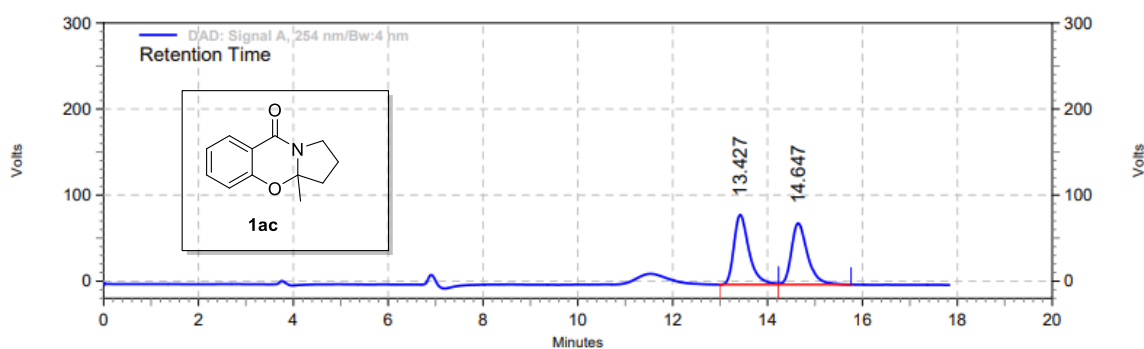




4.10 Copies of HPLC chromatograms: HPLC chromatogram for racemic methyl proline

Column: Chiralpak AD-H (250 mm x 4.6mm); Mobile Ph: IPA: Hexane (10:90);

Wavelength: 254nm; Flow: 1.0 ml/min.; Inject vol: 5µl

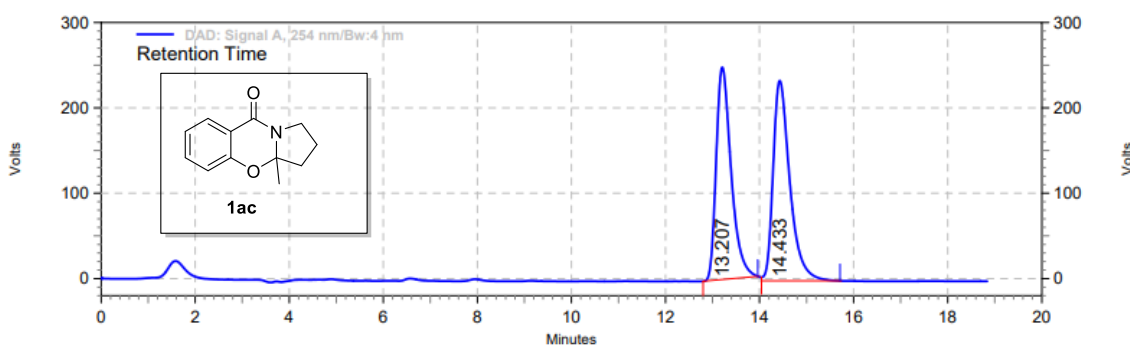


DAD: Signal A, 254 nm/Bw:4 nm

Results

Retention Time	Area	Area %
13.427	3753605	51.53
14.647	3530527	48.47
Totals	7284132	100.00

HPLC chromatogram for enantiopure methyl proline



DAD: Signal A, 254 nm/Bw:4 nm

Results

Retention Time	Area	Area %
13.207	11502383	48.63
14.433	12151939	51.37
Totals	23654322	100.00

ABSTRACT

Name of the Student: Sonavane Sameer Raghunath

Registration No. : 10CC19J26016

Faculty of Study: Chemical Sciences

Year of Submission: 2024

AcSIR academic centre/CSIR Lab:

Name of the Supervisor(s): Dr. Santosh B. Mhaske

CSIR-National Chemical Laboratory, Pune

Title of the thesis: Decarboxylative C–C and C–Heteroatom Bond Forming Reactions: New Methods and Their Application in Total Synthesis

Over the past two decades, Decarboxylative C–C and C–Heteroatom Bond Forming Reactions have garnered significant attention due to their application in the synthesis of molecules with wide-ranging biological, pharmaceutical, and agrochemical properties. Herein, we report some methodologies and their application in the synthesis of biologically active natural products and drug molecules.

The present thesis describes the development of novel decarboxylative C–C and C–heteroatom bond-forming reactions and their application in the synthesis of natural products, biologically active molecules, and Active Pharmaceutical Ingredients (APIs). The thesis is categorized into four chapters. The first chapter provide a general introduction to decarboxylative C–C and C–heteroatom bond-forming reactions. Particularly, it describe decarboxylative C–H bond functionalization of nitrogen-containing heteroarenes and their applications. The second chapter encompasses the development of new protocol for decarboxylative C–H bond functionalization of quinazolinones with amino acids by visible light photoredox catalysis. We also present the application of the protocol in the total synthesis of circumdatin class of quinazolinone natural products and their congeners. The third chapter demonstrates our studies toward the asymmetric synthesis of the key intermediate of dextromethorphan API *via* the decarboxylative C–C bond-forming reaction. Dextromethorphan is commonly used as a cough suppressant. The fourth chapter deals with the organophotoredox-catalyzed decarboxylative C–heteroatom bond formation for the synthesis of biologically important Ampakine APIs and quinazolinone based natural products such as deoxyvasicinone, and mackinazolinone. The developed protocol was applied in the synthesis of the drug molecules CX-614, and CX-554, which are used in the treatment of neurodegenerative diseases such as Alzheimer's and Parkinson's. Overall, this thesis summarises new scalable approaches on decarboxylative C–C and C-heteroatom bond formation reactions for synthesizing various structurally complex and bioactive scaffolds of pharmaceutical importance.

List of publication(s) in SCI Journal(s) (Thesis Related)

1. **S. R. Sonavane**, S. B. Mhaske, Enantioselective Intramolecular Decarboxylative C–H Bond Functionalization of Quinazolinones with Amino Acids by Visible Light Photoredox Catalysis. *Chem. Asian J.* **2023**, *18*, e202300235
2. S. B. Mhaske, **S. R. Sonavane**, *Indian patent*, **2024**-NF-0101.
3. **S. R. Sonavane**, T. B. Kale, G. J. Bhatt, S. B. Mhaske, Organophotoredox-Catalyzed Decarboxylative C(sp³)–X Bond Formation: Facile Access to Ampikine APIs and Quinazolinone Alkaloids. *ChemRxiv DOI* 10.26434/chemrxiv-2024-6lql3, **2024**.
4. **S. R. Sonavane**, T. B. Kale, G. J. Bhatt, S. B. Mhaske, Organophotoredox-Catalyzed Decarboxylative C(sp³)–X Bond Formation: Facile Access to Ampikine APIs and Quinazolinone Alkaloids. *Manuscript communicated to SCI journal*.
5. S. B. Mhaske, **S. R. Sonavane**, *Filed patent no.* **2023**-NF-0177.

List of publication(s) in SCI Journal(s) (not related to thesis)

6. A. B. Viveki, M. D. Pol, P. Halder, **S. R. Sonavane**, S. B. Mhaske, *J. Org. Chem.* **2021**, *86*, 9466.

Erratum

Erratum

Enantioselective Intramolecular Decarboxylative C–H Bond Functionalization of Quinazolinones with Amino Acids by Visible Light Photoredox Catalysis

 Sameer R. Sonavane^[a, b] and Santosh B. Mhaske^{*[a, b]}

Abstract: The direct visible light-mediated intramolecular decarboxylative C–H functionalization of Csp^2 –H bond adjacent to the nitrogen of a heteroarene has been achieved by iridium-catalyzed photodecarboxylative radical cyclization. This method offers rapid entry to the synthesis of quinazolinone scaffolds from easily accessible starting materials. The newly developed protocol is mild, operationally simple,

oxidant free and general. The utility of this unique Csp^3 – Csp^2 bond forming reaction has been demonstrated in the syntheses of Circumdatin, Sclerotigenine and Benzomalvin A class of quinazolinone natural products and their congeners. The present work represents an interesting example of use of memory of chirality in decarboxylative C–C bond forming enantioselective photoredox reaction.

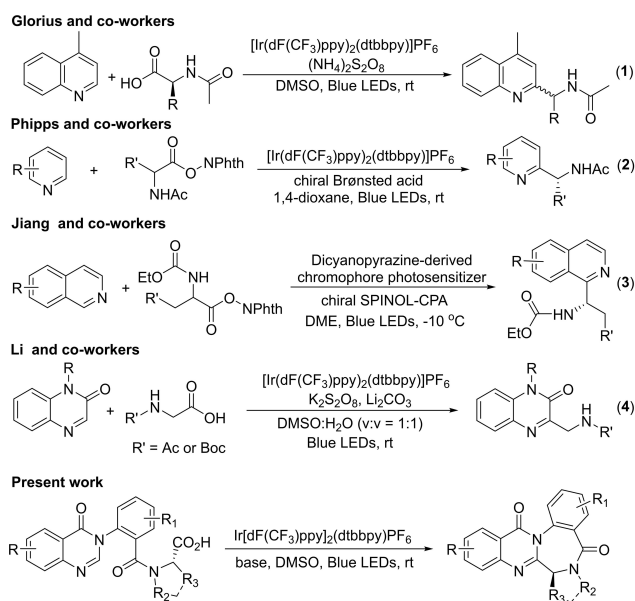
Introduction

Over the past decade, visible light photoredox catalysis has emerged as a versatile and powerful strategy in synthetic organic chemistry for the construction of novel C–C and C–heteroatom bonds.^[1] It is mild and operationally simple process for laboratory and industrial applications. Particularly, the visible light-mediated C–H bond functionalization of electron-deficient heteroarenes has been one of the most prevalent research area.^[2] The nucleophilic carbon centered radical generated adjacent to the nitrogen of α -amino acid by decarboxylative processes can be readily functionalized and simply transformed to pharmacologically active molecules.^[3] The generation and utilization of such carbon centered radical is an appealing approach for the construction of medically relevant pharmacophores.^[4]

The classical Minisci reaction,^[5] invented in 1971, has witnessed a tremendous improvement over the period and several Minisci-type alkylation reactions by utilizing novel catalytic systems and a broad range of prefunctionalized alkylating agents instead of carboxylic acids have been documented.^[6] Recently, Minisci-type direct alkylation of heteroarenes with alkyl bromides via photoredox catalysis has been also reported.^[7] Glorius and co-workers disclosed the first visible light-mediated direct alkylation of heteroarenes with carboxylic acids without any prefunctionalization [Scheme 1, eq 1].^[8] This important breakthrough on the use of easily available carboxylic acids as alkylating agents in combination with mild photo-

redox catalysis for alkylation of heteroarenes is notable. In the same year, Fu and co-workers independently reported photoredox/Bronsted acid catalyzed direct alkylation of heteroarenes with α -amino acid-derived redox-active esters (RAEs) *N*-acyloxyphthalimides.^[9]

Phipps and co-workers as well as Jiang and co-workers reported photoredox reaction of *N*-acyloxyphthalimides to achieve enantioselective Minisci-type addition to heteroarenes with high enantiomeric excess using chiral Bronsted acid catalysis [Scheme 1, eq 2 and 3].^[10,11] Recently, Li and co-workers disclosed a direct decarboxylative heteroarylation of aliphatic carboxylic acids with quinoxaline-2(1*H*)-ones via visible light-mediated photoredox catalysis in aqueous solution.^[12] There are few other reports on photoredox catalyzed decarboxylative C–H functionalization of heteroarenes, however examples of



Scheme 1. Known Photo-catalyzed Decarboxylative C–H Functionalization of Heteroarenes with Amino Acids and Present Work.

[a] S. R. Sonavane, Dr. S. B. Mhaske
 Division of Organic Chemistry, CSIR-National Chemical Laboratory (CSIR-NCL), Pune-411008 (India)
 E-mail: sb.mhaske@ncl.res.in

[b] S. R. Sonavane, Dr. S. B. Mhaske
 Academy of Scientific and Innovative Research (AcSIR), Ghaziabad – 201002 (India)

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This manuscript is part of a joint special collection highlighting the chemistry research from CSIR Institutes in India

asymmetric version are rare.^[16,13] In this context, our interest in developing novel methodologies and their application in the natural product synthesis prompted us to revisit our own methodology developed for the enantioselective synthesis of quinazolinone alkaloids using AgNO₃-mediated decarboxylative intramolecular cyclization strategy.^[14] However, the yields were moderate, the substrate scope was limited and a large excess of oxidant was necessary.

We envisioned that such transformation would be facile by using newly emerged photoredox catalysis platform under milder reaction conditions. Interestingly, until now, intramolecular decarboxylative C–H bond functionalization of heteroarene with amino acids is not explored in the literature by using photoredox catalysis. Additionally, there are rare examples of memory of chirality (MOC) utilizing photo-decarboxylative C–C bond forming reactions of amino acids.^[15] We envisioned the possibility of chiral pool-based asymmetric synthesis approach via chirality transfer through conformational (atropisomeric) memory of an unstabilized secondary radical intermediate on quinazolinone substrates by photoredox catalysis. We planned to develop a photo-redox catalyzed protocol and demonstrate its application in Circumdatin, Sclerotigenine, and Benzomalvin etc. class of natural quinazolinone alkaloids, which are known for their excellent biological activities (Figure 1).^[16] Presented herein is enantioselective intramolecular decarboxylative C–H bond functionalization of proline-containing quinazolinones by visible light photoredox catalysis to obtain bioactive quinazolinone natural products and their analogues without the need of chiral auxiliary.

Results and Discussion

We began our investigation using acid **1** (1 equiv.) as a model substrate, which was prepared as shown in Scheme 2 following our reported protocol with little modification.^[14] In the initial attempt, reaction was performed using 1 mol% of Ir-PC **A** along with oxidant ammonium persulfate (2 equiv.) in DMSO solvent, under irradiation of 30 W blue LEDs at room temperature. To our delight we observed the formation of expected product demethoxycircumdatin **H** (**2**) in 38% yield (Table 1, entry 1). Encouraged by this favourable result, we screened several rational permutations and selected entries are provided in Table 1. First, we tried DBU as a base, which helped moderately to enhance the yield (Table 1, entry 2). Many other organic bases such as DABCO (Table 1, entry 3), triethylamine, tributylamine, *N,N*-diisopropylethylamine, tetramethylethylenediamine etc. were tested, however we did not observe much improvement in the yield. Hence, we moved towards inorganic bases. Photo-catalyzed decarboxylative C–C bond forming reactions are known to work well with cesium carbonate as the base.^[17] Interestingly, cesium carbonate worked well on our substrate and we observed substantial improvement in the yield (Table 1, entry 4). We screened other catalysts including Ir-PC **B** and Eosin **Y**, but Ir-PC **A** was found to be more efficient (Table 1, entry 5–6). Next, we performed the reaction in the absence of

oxidant and were pleased to find that the reaction was still working well with better yield (Table 1, entry 7).

Further studies revealed that only 1.1 equiv. of cesium carbonate was sufficient for this transformation to furnish 86% yield of product **2** (Table 1, entry 8). Further, we tested other inorganic bases, solvents (Table 1, entries 9–11) and effect of catalyst loading (Table 1, entries 12–14), however, we did not observe notable improvement in the yield. Control experiments show that no reaction was observed in the absence of either blue LED irradiation (Table 1, entry 15) or photocatalyst (Table 1, entry 16). Our elaborate studies finally provided us optimized reaction conditions, wherein 1 mol% Ir-PC **A** and 1.1 equiv. cesium carbonate as the base in DMSO solvent provided 86% yield with 77% ee (single recrystallization: 95% ee) (Table 1, entry 8).

With the optimized conditions in hand, we commenced substrate scope studies and its application in the natural product synthesis. The acids **4–8** were prepared and coupled with *L*-proline methyl ester using HATU coupling agent to obtain esters **10–14**, respectively in very good yields

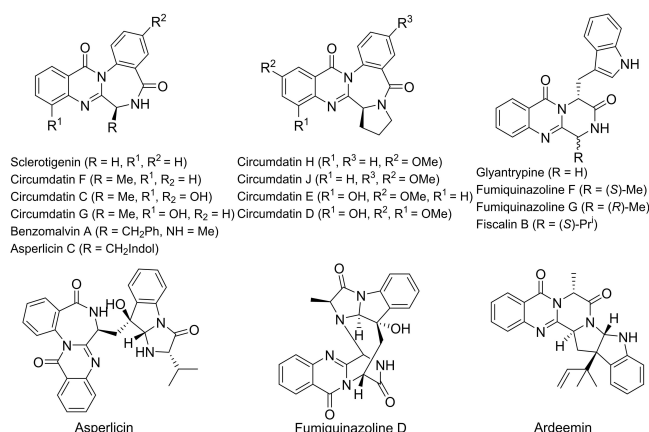
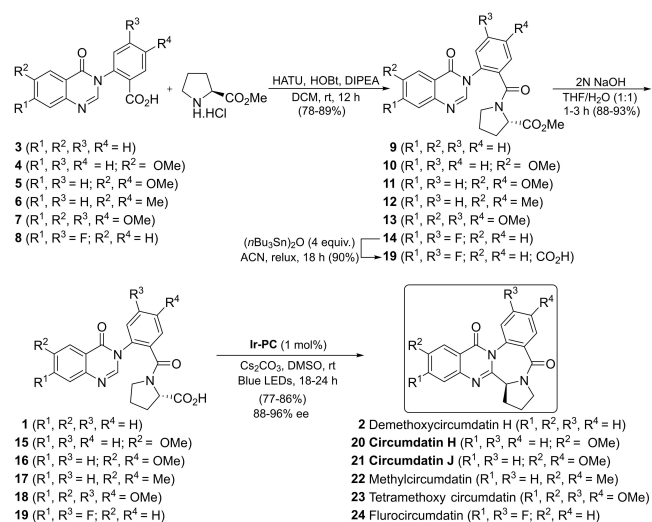


Figure 1. Quinazolinone based bioactive natural products.



Scheme 2. Synthesis of Proline-containing Circumdatin Class of Natural Products and Their Analogues.

Table 1. Optimization of the Decarboxylative Cyclization Protocol.

entry	photocatalyst (mol%)	oxidant 2 equiv.	solvent	base (equiv.)	yield (%) ^b
1	Ir-PC A (1.0)	APS	DMSO	–	38%
2	Ir-PC A (1.0)	APS	DMSO	DBU (2.0)	55%
3	Ir-PC A (1.0)	APS	DMSO	DABCO (2.0)	27%
4	Ir-PC A (1.0)	APS	DMSO	Cs ₂ CO ₃ (2.0)	74%
5	Ir-PC B (1.0)	APS	DMSO	Cs ₂ CO ₃ (2.0)	65%
6	Eosin Y (1.0)	APS	DMSO	Cs ₂ CO ₃ (2.0)	trace
7	Ir-PC A (1.0)	–	DMSO	Cs ₂ CO ₃ (2.0)	81%
8	Ir-PC A (1.0)	–	DMSO	Cs ₂ CO ₃ (1.1)	86%
9	Ir-PC A (1.0)	–	DMSO	K ₂ CO ₃ (1.1)	57%
10	Ir-PC A (1.0)	–	DMF	Cs ₂ CO ₃ (1.1)	46%
11	Ir-PC A (1.0)	–	ACN	Cs ₂ CO ₃ (1.1)	62%
12	Ir-PC A (2.0)	–	DMSO	Cs ₂ CO ₃ (1.1)	69%
13	Ir-PC A (0.5)	–	DMSO	Cs ₂ CO ₃ (1.1)	61%
14	Ir-PC A (0.25)	–	DMSO	Cs ₂ CO ₃ (1.1)	43%
15	Ir-PC A (1.0)	–	DMSO	Cs ₂ CO ₃ (1.1)	trace
16	–	–	DMSO	Cs ₂ CO ₃ (1.1)	N.D.

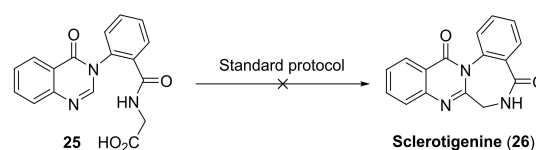
[a] Reactions were performed on a 0.082 mmol scale of acid 1 under irradiation of 30 W blue LEDs for 18 h under argon. [b] Yields reported are isolated yields. [c] Reaction was performed in the absence of blue LEDs. APS-ammonium persulfate.

(Scheme 2). The esters **10–13** were hydrolyzed with NaOH in THF:Water (1:1) to furnish acids **15–18** in excellent yields. The hydrolysis of ester **14** under the same conditions however did not furnish the desired acid **19**, instead we observed displacement of fluorine with hydroxyl group (see SI). Hence, we used bis(tributyltin)oxide condition,^[18] which worked well to provide acid **19** in quantitative yield. The acids **15–19** were then subjected to our standard photo redox reaction conditions. The optimized protocol worked well on substrate **15** to furnish the desired natural product Circumdatin H (**20**) in 81% yield with 76% ee (single recrystallization: 87% ee) (Scheme 2). Our protocol also worked well on dimethoxy substituted precursor **16** to provide natural product Circumdatin J (**21**) in 85% yield with 71% ee (single recrystallization: 96% ee) (Scheme 2).

After successfully synthesizing two pyrrolidine based natural products, we moved towards exploring application of the protocol in the synthesis of different derivatives. The acids **17** and **18** could be smoothly transformed to the corresponding methyl and methoxy substituted circumdatin analogues **22** & **23** in 79% yield with 82% ee (single recrystallization: 93% ee) and 80% yield with 72% ee (single recrystallization: 93% ee) respectively using our protocol (Scheme 2). Similarly, fluorine containing quinazolinone substrate **19** furnished the desired product **24** in 77% yield with 70% ee (single recrystallization: 95% ee) (Scheme 2), which shows that fluorine substituted

quinazolinone substrate is compatible under our reaction conditions. After successfully demonstrating the application of our protocol on proline-containing substrates to provide circumdatin natural products and their analogues, we were curious to see whether it could be applied on substrate containing acyclic amino acid.

Accordingly, the acid **25** was prepared starting from compound **3** following our reported procedure.^[14] However, the acid **25** remained unchanged under the standard protocol and we did not observe the formation of the natural product Sclerotigenine (**26**, Scheme 3). Hence, we planned to use substrates with protecting group or apply the protocol in the synthesis of N-substituted natural products, so that unprotected NH group would not interfere with the photo-catalyzed radical formation. In this context, we prepared the esters **27–29** in good yields from the acid **3**, wherein we used either PMB protected or N-methylated amino acids. Hydrolysis of the esters



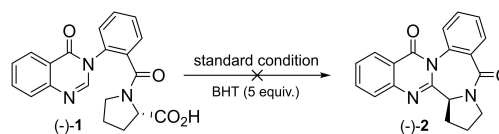
Scheme 3. Attempted Synthesis of Sclerotigenine with Unprotected Glycine.

27–29 provided corresponding acids 30–32 respectively in very good yields. These acids were subjected to our standard photo-redox protocol and all of them efficiently furnished the corresponding cyclized alkaloids 33–35. The product 35 is the quinazolinone natural product (±)-Benzomalvin A which was obtained in 76% yield. The PMB protected precursor 33 upon deprotection using CAN furnished Sclerotigenine (26) natural product in 74% yield. Similarly, deprotection of precursor 34 provided the natural product (±)-Circumdatin F (36) in 76% yield. We observed the loss of enantioselectivity in the formation of natural product Benzomalvin A (35) and Circumdatin F (36). We hypothesized that the radical generated on open-chain amino acids might be converting to planar configuration, whereas it might be less planar in the case of proline. Additionally, the substrates containing bulkier proline ring might be atropisomerically locked across C–N bond between quinazolinone nitrogen and aniline carbon, whereas the substrates containing acyclic amino acid chain may move relatively more freely leading to racemic products. It might be possible to achieve enantioselectivity on such substrates utilizing chiral auxiliaries, however that is not the main purpose of current study (Scheme 4).

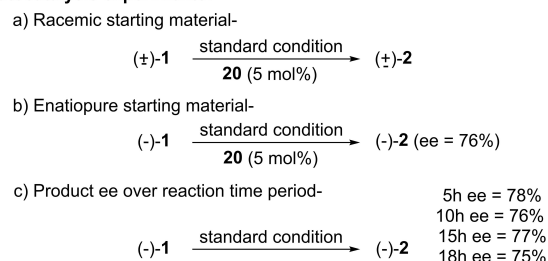
Overall, though there are other synthetic routes reported in the literature for the synthesis^[14,16,19–25] of Circumdatin H & J, Benzomalvin A, Sclerotigenine and Circumdatin F natural products, we have demonstrated a novel and unique approach utilizing a mild and oxidant-free photo-redox catalysis protocol.

A preliminary mechanistic study using BHT as the radical scavenger indicates that the developed protocol follows a radical pathway (Scheme 5). Our initial observations such as enantiopure acid substrate 1 provides enantio-enriched product 2, whereas racemic acid substrate 1 provides racemic product 2 indicates that the stereoinduction is not happening by autocatalysis mechanism but plausibly via memory of chirality. The autocatalysis mechanism was completely ruled out by performing additional mechanistic studies (Scheme 5a–c), wherein we studied the effect of addition of enantiopure product 20 on the ee of the product 2 and also observed the changes in the ee over a time period under our standard reaction conditions. The addition of enantiopure product 20 did

Radical Trapping Experiment:



Autocatalysis experiments:



Scheme 5. Mechanistic studies.

not show any effect on the ee of product 2 and at various time intervals it remained approximately constant.

Conclusion

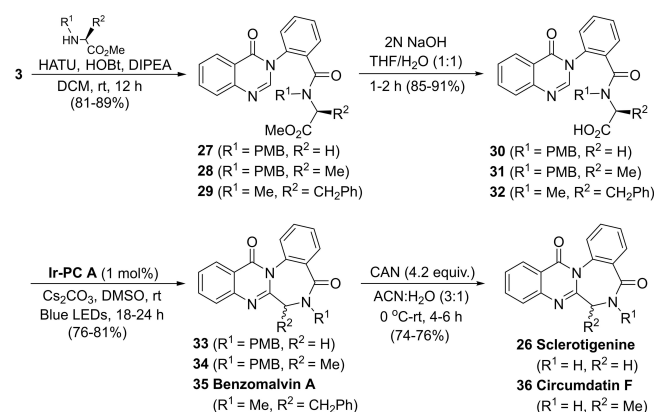
In summary, we have disclosed first oxidant and chiral ligand free C–H bond functionalization of quinazolinone heteroarenes by Iridium-catalyzed intramolecular photodecarboxylative cyclization method and its application. This straightforward approach provides a facile access to biologically active quinazolinone natural products and their analogues using commercially available α -amino acids as coupling partners. Our work represents the first example of photo induced intramolecular Csp³–Csp² bond forming decarboxylative enantioselective cyclization reaction to access proline-containing quinazolinone alkaloids via memory of chirality. Currently, we are working on improvement of enantioselectivity by enhancing the lifetime of the radical intermediate by controlling the conformational (atropisomeric) flexibility and its application in other heteroarenes and natural products.

Experimental Section

Essential Experimental Procedures/Data and all other characterization data, original spectra, etc., has been provided in the Supporting Information.

Supporting Information

Additional references cited within the Supporting Information.^[26–33]



Scheme 4. Application of the Protocol on Acyclic N-PMB Protected/N-Me Substituted Amino Acid Substrates.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: C–H functionalization · Minisci reaction · memory of chirality · photoredox catalysis · photodecarboxylative cyclization · quinazolinone alkaloid · radical

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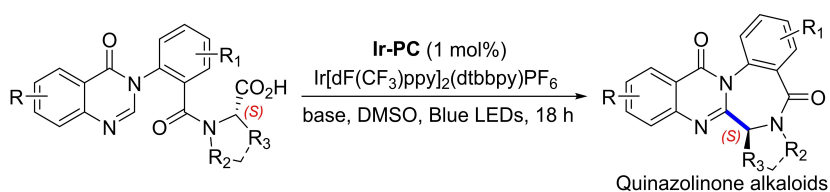
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RESEARCH ARTICLE



- Rare photo-induced intramolecular decarboxylative cyclization
- Example of memory of chirality using photoredox catalysis
- A general, operationally simple and mild protocol
- Oxidant and chiral ligand free
- Applicable to complex molecule synthesis

A highly efficient Ir(III)-catalyzed photodecarboxylative cyclization of quinazolinone heteroarenes is reported. The reaction proceeded under opera-

tionally simple conditions and furnishes circumdatin class of quinazolinone bioactive Natural products.

S. R. Sonavane, Dr. S. B. Mhaske*

1 – 6

Enantioselective Intramolecular Decarboxylative C–H Bond Functionalization of Quinazolinones with Amino Acids by Visible Light Photoredox Catalysis



Organophotoredox-Catalyzed Heteroatom Bond Formation: Access to Ampakine APIs and Quinazolinone Alkaloids

Sameer R. Sonavane,^[b] Tushar B. Kale,^[b] Gaurang J. Bhatt,^[b] and Santosh B. Mhaske^{*[a]}

[a] Dr. Santosh B. Mhaske
Division of Organic Chemistry
CSIR-National Chemical Laboratory, Pune-411008, India
Academy of Scientific and Innovative Research
Ghaziabad-201002, India
E-mail: sb.mhaske@ncl.res.in

[b] S. R. Sonavane, T. B. Kale, G. J. Bhatt
Division of Organic Chemistry
CSIR-National Chemical Laboratory, Pune-411008, India
Academy of Scientific and Innovative Research
Ghaziabad-201002, India

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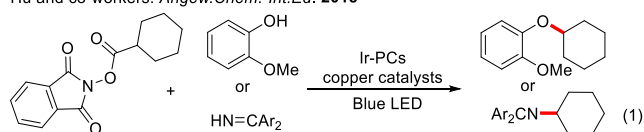
Abstract: The study describes a novel and general protocol for metal-free intramolecular decarboxylative construction of carbon-heteroatom (oxygen, nitrogen, and sulfur) bond, enabling direct access to the bioactive ampakine and quinazolinone class of molecules. The cross-coupling of natural or unnatural amino acid based electrophiles with phenols, amides, and thiophenols via organophotoredox catalysis represents an innovative approach towards the synthesis of bioactive heterocycles. The present approach utilizes photochemical decarboxylative single electron oxidation to generate carbon-centered radical intermediate directly from amino acids under mild conditions, eliminating the need for preactivation. The designated protocol offers a convenient method to synthesize ampakine drug molecules CX-614 and CX-554, which have promising potential for treating Alzheimer's and Parkinson's diseases. Interestingly, with nitrogen nucleophile, quinazolinone class of natural products deoxyvasicinone and mackinazolinone could be synthesized, whereas sulfur nucleophile furnished dihydro-thiazenone scaffolds. The reported protocol exhibits high functional group tolerance and scalability. A plausible mechanism has been proposed based on fluorescence quenching experiments and cyclic voltammetry analysis.

Introduction

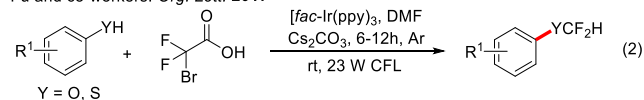
Over the past decade, visible light-mediated reactions forming C–C and C–heteroatom bonds have shown a significant development in synthetic organic chemistry. These reactions enable the synthesis of complex molecules by facilitating single-electron transfer events with organic substrates.^[1] Many groups have extensively explored several important methods for constructing photo-induced decarboxylative C–C bond-forming reactions without prefunctionalization, which represent significant advancements in the field of synthetic organic chemistry.^{[1],[2]}

Previous work: (sp^3)C–X bond formation reaction

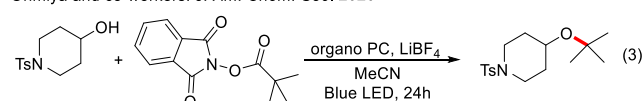
Hu and co-workers: *Angew. Chem. Int. Ed.* **2018**^[3b,8b]



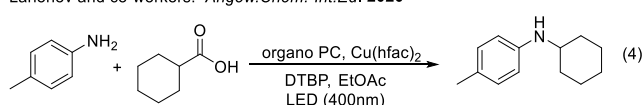
Fu and co-workers: *Org. Lett.* **2017**^[8a]



Ohmiya and co-workers: *J. Am. Chem. Soc.* **2020**^[3f]



Larionov and co-workers: *Angew. Chem. Int. Ed.* **2020**^[3e]



This work: Intramolecular decarboxylative C–X bond formation

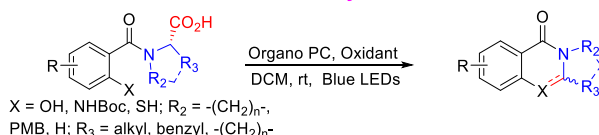


Figure 1. Previous and Present work on photocatalyzed (sp^3)C–X bond forming reactions

Despite the advances in C–C bond-forming reactions, there has been comparatively less exploration in forging C–O/N/S bonds in a general manner through decarboxylative coupling reactions.^[2f] These reactions are notably difficult to achieve by the conventional two-electron pathways and require harsh conditions.

The traditional organic chemistry methods encounter significant challenges concerning the compatibility of functional groups under strongly basic conditions necessary for S_N2 reactions, as well as their inability to accommodate sterically hindered substrates and the pK_a requirements of the nucleophile.^[4] The S_N1 reaction involving alkyl halides or alkenes provides an alternative to S_N2 , but it requires highly acidic conditions. This limitation restricts its compatibility with many functional groups, often leading to side reactions and degradation.^[5] The transition-metal catalyzed (sp^3)C-heteroatom bond forming reaction between alkyl/aryl heteroatom nucleophiles and alkyl electrophiles are challenging due to the sluggish oxidative addition of the alkyl electrophile and the susceptibility of the in-situ generated alkyl metal complex to β -hydride elimination.^[6] Hence, novel catalytic systems are needed to facilitate efficient and selective formation of (sp^3)C-heteroatom bonds. In the realm of electrochemistry, Baran and colleagues introduced an elegant and practical electrochemical approach for synthesizing sterically hindered (sp^3)C–O–C(sp^3) fragments. Their method efficiently generates these structures from aliphatic alcohols and alkyl carboxylic acids, offering a versatile and less cumbersome alternative for such transformations.^[3c] Remarkably, the protocol constructing (sp^3)C–X–C(sp^2) (X = oxygen, nitrogen, and sulfur) motifs are highly coveted in the synthesis of a wide range of natural products and pharmaceuticals.^[7] Among the various methods for obtaining (sp^3)C–X–C(sp^2) scaffold via decarboxylation process, the direct formation of (sp^3)C-heteroatom bonds using nucleophiles such as phenols, amides/amines, thiophenols, with electrophiles like alkyl carboxylic acids stands out as a privileged and popular approach.^[3a, 3b, 3d, 3e, 8] However, a general strategy utilizing organophotoredox catalysis for intramolecular decarboxylative (sp^3)C–heteroatom bond formation under mild conditions remains elusive, and there are currently no documented examples involving phenols, thiophenols or amides as nucleophile and natural/unnatural amino acids as electrophiles. We were interested in developing photodecarboxylative cyclization reaction as a facile approach via catalytic generation of iminium ion^[9] for (sp^3)C–O/N/S bond formation in S_N1 manner.

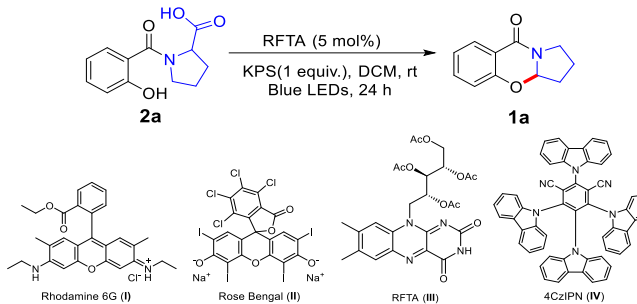
Previous research highlights the effectiveness of intramolecular dehydrogenative coupling reactions for synthesizing dihydro-oxazine structures. Typically, these reactions demand harsh conditions and often involve metal catalysts.^[10] Therefore, we hypothesized whether decarboxylative photoredox-catalyzed generation of iminium ions, followed by in situ nucleophilic addition of heteroatoms can be achieved within a photocatalytic cycle. Literature survey revealed that Hu and colleagues demonstrated a decarboxylative (sp^3)C–O^[8b] and (sp^3)C–N^[3b] cross-coupling reaction using tandem photoredox and copper catalysis. (Figure 1, eq. 1). Similarly, Fu and co-workers reported a photoredox-catalyzed difluoromethylation of phenols and thiophenols (Figure 1, eq. 2).^[8a] However, these strategies require transition metal-based photocatalysts, and Hu's approach requires prefunctionalization of the acid substrates. Moreover, Ohmiya and colleagues reported organophotoredox catalyzed decarboxylative coupling that combines simple aliphatic alcohol nucleophiles with redox-active esters derived from tertiary or

secondary alkyl carboxylic acids (Figure 1, eq. 3).^[3f] Larionov and colleagues reported a visible-light and copper mediated direct intermolecular decarboxylative N-alkylation reaction using organophotocatalysis.^[3e] Inspired by the above interesting reports, we planned to develop a protocol for organophotoredox catalyzed decarboxylative cyclization of heteroatom-containing nucleophiles with amino acids. Herein, we report catalytic in situ generation of iminium ions from natural/unnatural amino acids by decarboxylative single electron oxidation, that were leveraged to provide a wide array of C–X (X = O, N, S) bonds by trapping with heteroatom nucleophiles (Figure 1).

Results and Discussion

We commenced our work by first investigating the photocatalytic decarboxylative cyclization of salicylic acid derivative **2a** (Table 1), which was prepared by amidation of salicylic acid with proline ester to form methyl (2-hydroxybenzoyl)prolinate **2'a** followed by its hydrolysis (see SI).

Table 1. Optimization of the decarboxylative C–O bond formation protocol^[a, b]



entry	Change from standard conditions ^a	yield (%) ^b
1	None	90%
2	I	ND
3	II	ND
4	IV	7%
5	no light (dark)	NR
6	no III	NR
7	no KPS	16%
8	in Air	52%
9	420 nm instead of 450 nm LED	34%

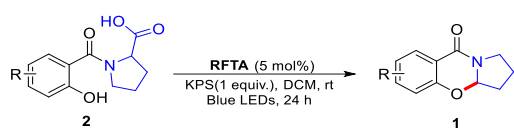
[a] **2a** (0.25 mmol), $K_2S_2O_8$ (1 equiv.), RFTA (5 mol%) in DCM (2 mL), Blue LEDs (450 nm, 30 W), 24 h, rt. [b] Isolated yields. NR = No reaction, ND = Not detected.

The inexpensive organophotocatalyst riboflavin tetraacetate (RFTA, **III**) was found to be the best photocatalyst in our extensive screening (see SI). The optimal reaction system comprised 5 mol% of RFTA **III** as the photocatalyst, 1 equiv. of KPS as an oxidant under irradiation of 450 nm (30 W) blue LEDs. Under

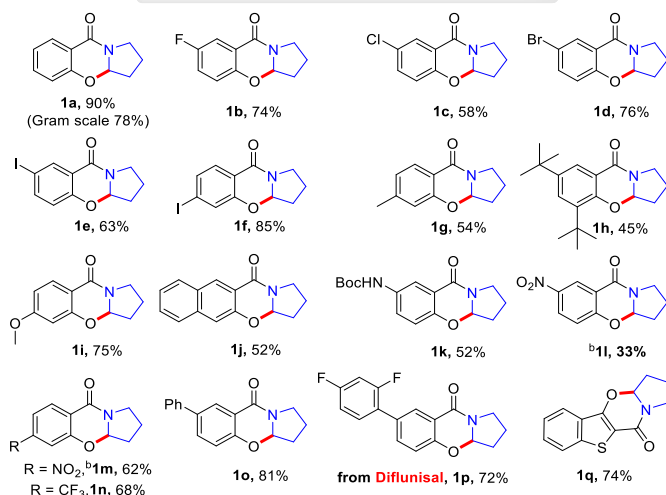
these conditions, the desired dihydro-oxazinone product **1a** was obtained in **90%** yield. Control experiments show that no product was observed without either blue LED irradiation (Table 1, entry 5) or photocatalyst (Table 1, entry 6).

The optimized reaction condition described above was used to explore the substrate scope (Table 2). To achieve this, we synthesized the salicylic acid derivatives **2a-2q** in good to moderate yields (see SI). These acids were subjected to our standard protocol to furnish ampakine derivatives. Ampakines are class of drugs useful in the treatment of Alzheimer and Parkinson's diseases.^[11]

Table 2. Decarboxylative (sp^3)C–O bond formation of salicylic acid derivatives^[a]



Substrate scope of salicylic acid derivatives

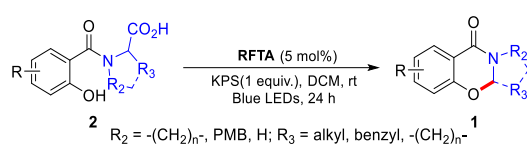


[a] **2** (0.25 mmol), K₂S₂O₈ (1 equiv.), RFTA (5 mol%) in DCM (2 mL), Blue LEDs (450 nm, 30 W), 24 h, rt. [b] reaction time 36 h.

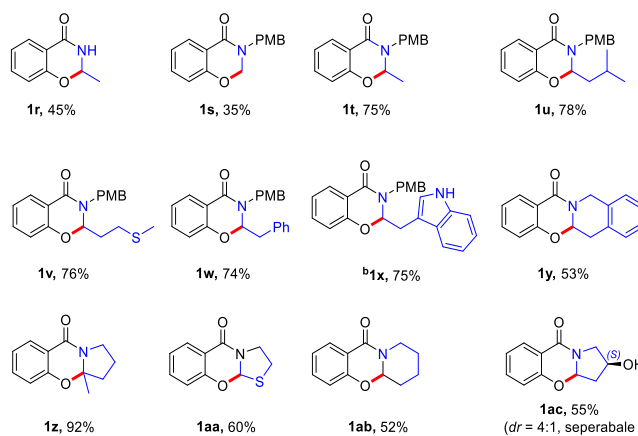
The protocol demonstrated good tolerance for halo-substituted salicylic acid derivatives to provide the products **1b-1f** in good to excellent yields. These products have valuable handles for further transformations through conventional cross-coupling reactions. The methyl and *tert*-butyl substituted acids were found to be favorable under this catalytic system but furnished the corresponding products **1g** and **1h** in moderate yields probably due to the instability of the generated iminium ion or bulkiness of the substituted group. The electron-donating, polyaromatics and electron-withdrawing groups were accommodated well producing the desired products **1i-1n** in moderate to good yields. Notably, phenyl-substituted salicylic acids and diflunisal (analgesic and anti-inflammatory drugs)^[12] derivatives were also compatible giving good yields of the desired products **1o** and **1p** respectively. Furthermore, heterocyclic acid was effectively processed under this catalytic system, yielding the corresponding product **1q** in very good yield (Table 2).

After successfully applying the optimized protocol to salicylic acid derivatives containing proline moiety to generate a library of oxazinone analogues (Table 2), we sought to test its efficacy with the substrate containing cyclic/acyclic amino acid motifs (Table 3). Interestingly, the alanine substrate yielded the expected cyclized product **1r** in 45% yield, however, the unprotected glycine substrate did not react under the standard conditions likely due to the instability of the iminium ion intermediate or it's difficult to generate. To enhance the yield, we opted to protect the free amide –NH group with a PMB. This modification was effective yielding the cyclized products **1s** and **1t** in moderate and very

Table 3. Decarboxylative (sp^3)C–O bond formation with amino acids^[a]



Substrate scope of natural/unnatural amino acids

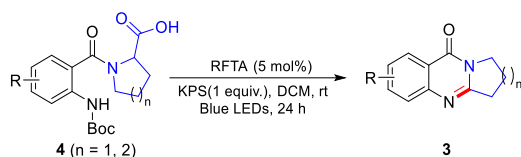


[a] **2** (0.25 mmol), K₂S₂O₈ (1 equiv.), RFTA (5 mol%) in DCM (2 mL), Blue LEDs (450 nm, 30 W), 24 h, rt. [b] reaction time 36 h.

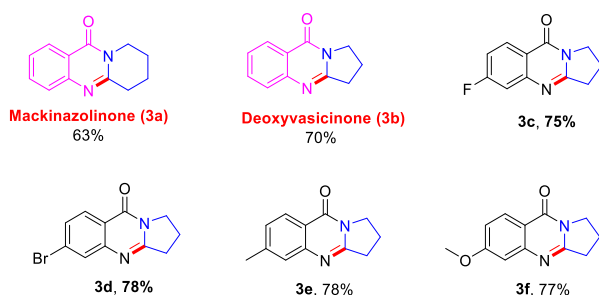
good yield respectively. Given the accomplishment of the protected substrates, we decided to proceed with additional entries using the PMB-protection. In this context, we prepared the salicylic acid derivatives **2s-2x** with the various PMB-protected natural amino acids in moderate to good yields. These acids were subjected to our standard photoredox protocol, and all of them efficiently furnished the corresponding cyclized products **1u-1x**. Furthermore, various unnatural amino acids demonstrated favourable performance under optimized conditions yielding cyclized products **1y-1ab** with moderate to good yields. (Table 3). Interestingly, the protocol worked well with the substrate containing (2*S*,4*R*)-4-hydroxyproline to furnish the corresponding cyclized product **1ac** in moderate yield, although the alcohol group was not protected. Moreover, hydroxyl group controlled chirality induction was observed to obtain the product as a separable mixture of diastereomers (4:1).

The study of C–N bond formation began with the synthesis of Boc-protected derivatives of anthranilic acid containing proline **4a–4f** in excellent yields (see SI). These acids were subjected to our standard photoredox protocol and all of them serendipitously furnished the corresponding Boc-eliminated cyclized products **3a–3f** in very good yields (Table 4).

Table 4. Decarboxylative (sp^3)C–N bond formation in anthranilic acid derivatives^[a]



Substrate scope of anthranilic acids



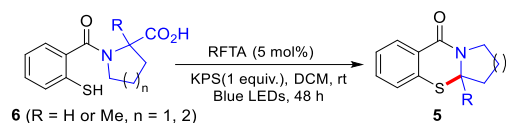
[a] **4** (0.25 mmol), $K_2S_2O_8$ (1 equiv.), RFTA (5 mol%) in DCM (2 mL), Blue LEDs (450 nm, 30 W), 24 h, rt.

The *L*-pipecolic acid and proline based Boc-protected anthranilic acid derivatives **4a** and **4b** could be smoothly transformed into the corresponding quinazolinone natural product mackinazolinone (**3a**) and deoxyvasicinone (**3b**) respectively with good yields.^[13] The halo, methyl and methoxy substituted derivatives of anthranilic acid also worked well to deliver deoxyvasicinone congeners **3c–3f** in good yields (Table 4).

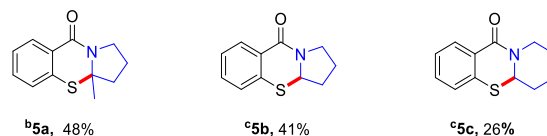
We also tested the efficacy of this interesting photocatalyzed quinazolinone forming protocol with other protecting groups such as *N*-acyl, *N*-methyl, *N*-phenyl etc (see SI). The protocol worked fine with *N*-acyl substrate but not as good as *N*-Boc protected substrate. *N*-methyl substrate could not be prepared and *N*-phenyl substrate formed undesired product **3g** without decarboxylation (see SI).

Notably, the extension to C–S bond formation could provide an access to valuable (sp^3)C–S–C(sp^2) fragments (Table 5). Thiosalicylic acid derivatives **6a–6c** were prepared and subjected to our standard protocol. The acids **6a–6c** delivered cyclized products **5a–5c** in moderate yields. The yield of thio substrates were less probably because sulphur is less nucleophilic as compare to oxygen/nitrogen.

Table 5. Decarboxylative (sp^3)C–S bond formation of thiosalicylic acid derivatives^[a]



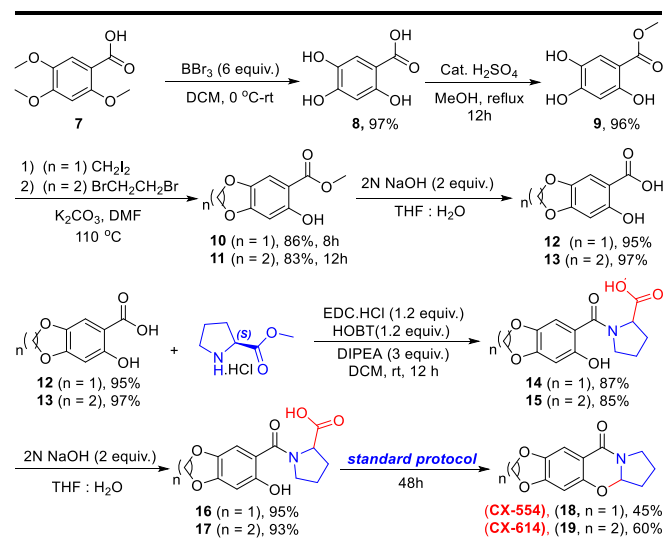
Substrate scope of anthranilic acids



[a] **6** (0.25 mmol), $K_2S_2O_8$ (1 equiv.), RFTA (5 mol%) in DCM (2 mL), Blue LEDs (450 nm, 30 W), 24 h, rt. [b] reaction time 65h. [c] reaction time 48h.

After successfully generalizing the protocol (Table 2–5), we tested the scalability of the reaction on a gram scale. The gram-scale reaction on the substrate **2a** afforded 78% isolated yield of the cyclized product **1a** (see SI).

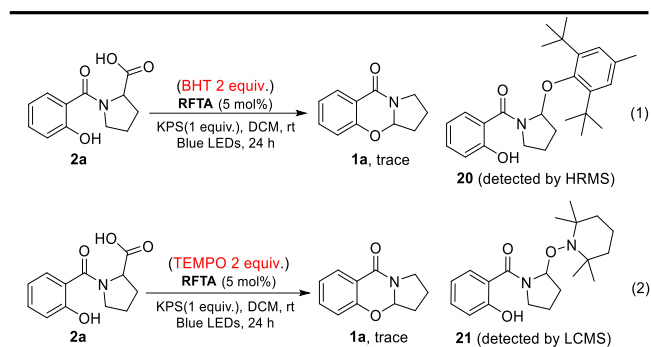
We also wanted to demonstrate the application of our protocol in the synthesis of **CX-614** and **CX-554**, which are investigational new drugs developed by Cortex Pharmaceuticals, along with its derivatives.^[11] They have garnered significant interest due to their effects on AMPA receptors and their capacity to enhance brain-derived neurotrophic factor (BDNF) synthesis.^[14] We have devised seven-step synthetic route (Scheme 1), which has yielded **CX-614** with an overall yield of 36% and its analog **CX-554** with an overall yield of 28%.



Scheme 1. Total synthesis of **CX-614** and **CX-554**

To enhance understanding of the developed process, we conducted a series of spectroscopic analyses and control experiments. The radical trapping experiments with known radical scavengers BHT and TEMPO indicated that the reaction probably

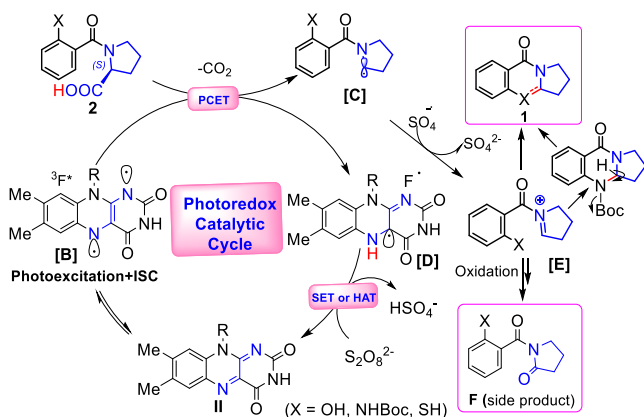
follows a radical pathway as the reaction was inhibited substantially (Scheme 2).



Scheme 2. Control Experiments

Furthermore, corresponding adduct masses were identified by HRMS/LCMS. Fluorescence quenching studies provided direct evidence of the nucleophilic radical initiation process (see SI). We observed diminished emission intensity of RFTA* in the presence of carboxylic acid **2a**. This dynamic quenching of RFTA* by carboxylic acid **2a** supports the proton-coupled electron transfer (PCET) to afford the corresponding acyloxy radical [**C**] as a key-step of the proposed mechanism. In addition, CV analysis of the substrate **2a** indicates single-electron transfer or PCET in this photo-oxidative coupling reaction.

We have depicted a plausible reaction mechanism based on the above control experiments and literature studies^{[15],[16],[17]} (Scheme 3).



Scheme 3. Plausible Reaction Mechanism

Mechanistically, we anticipated that, upon irradiation with visible light ($\lambda_{\text{max}} \approx 450 \text{ nm}$) and after rapid inter-system crossing, the long-lived triplet-excited state of flavin would be oxidant enough ($E_{\text{red}} = +1.50 \text{ V vs SCE}$)^[15] to undergo single-electron oxidation of amino acid carboxylates [E_{oxi} from $0.73 \text{ V vs Ag/AgCl}$]. Importantly, the excited state flavin moiety can also act as a base (pK_a of $\text{RFH}^{\bullet} = 8.3$), favouring the deprotonation of carboxylic acid before its single electron oxidation,^[16] or in a proton-coupled electron transfer (PCET). After rapid decarboxylation of the acid **2** ($k \approx 10^9 \text{ s}^{-1}$),^[17] the generated radical [**C**] is intercepted by the sulfate radical anion generated from KPS ($E_{1/2} = 1.75 \text{ V vs SCE}$),^[18] affording the iminium ion [**E**], which subsequently get trapped by

a nucleophile (O, N, S) to deliver the respective cyclized products. The sulfate radical dianion could be reduced by the hydroflavin radical [**D**] [$E_{\text{red}} (\text{KPS}^{\bullet}/\text{KPS}^-) = 2.01 \text{ vs SCE}$; $E_{\text{red}} (\text{RF}/\text{RFH}^{\bullet}) = -0.60 \text{ V vs SCE}$] regenerating the photocatalyst and producing sulphate radical anion after protonation in a redox-neutral process.

Conclusion

In summary, we have developed an unprecedented organophoto catalyzed, transition-metal-free general approach for the decarboxylative C-heteroatom bond formation, a feat traditionally reserved for precious metal catalysts like Ir and Rh with specific ligands. This scalable method uses an inexpensive organocatalyst and it is applicable in the synthesis of a broad range of C–O/C–N/C–S bond containing scaffolds. We have demonstrated the application of the protocol in the synthesis of medically relevant dihydro-oxazinone/thiazinone and quinazolinone derivatives. A series of control experiments, fluorescence quenching, and cyclic voltammetry studies indicates that the transformation is driven via an oxidative quenching mechanistic cycle. To the best of our knowledge, our work represents the use of this new catalysis pathway in the first general example of the organophotoredox-catalyzed C–O/C–N/C–S coupling reaction employing simple phenol/aromatic amide and thiophenol. The developed method has the potential to enable cross-decarboxylative inter/intramolecular C–heteroatom bond formation as a tool to synthesize complex heterocyclic bioactive agents and natural products.

Supporting Information

The authors have cited additional references within the Supporting Information.

Acknowledgements

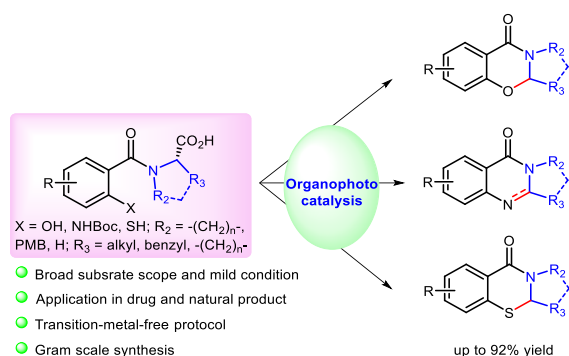
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Keywords: Organophotoredox catalysis • Ampakines • Decarboxylation • Quinazolinone • Heterocyclic

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We present photoredox-catalyzed decarboxylative intramolecular carbon-heteroatom bond formation reaction that offers a versatile method for synthesizing ampakine, quinazolinone, and dihydro-thiazene scaffolds from readily available natural and unnatural amino acids. This novel protocol is general, metal-free, and employs cost-effective and environment friendly organophotocatalyst.