Development of Novel Processes for Sulfur-Containing Scaffolds, Natural Product Orbicularisine and Uricosuric Agent Sulfinpyrazone

By

Priyanka Halder
(Registration Number: 10CC18J26007)

A Thesis Submitted to the
Academy of Scientific & Innovative Research

For the Award of the Degree of

DOCTOR OF PHILOSOPHY

In

SCIENCE

Under the Supervision of

Dr. Santosh B. Mhaske

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Sector 19, Kamla Nehru Nagar,
Ghaziabad, U.P. – 201002, India

May, 2023

Certificate

This is to certify that the work incorporated in this Ph.D. thesis entitled, "**Development of Novel Processes for Sulfur-Containing Scaffolds, Natural Product Orbicularisine and Uricosuric Agent Sulfinpyrazone**", submitted by **Priyanka Halder** to the Academy of Scientific and Innovative Research (AcSIR) in fulfillment of the requirements for the award of the Degree of *Doctor of Philosophy in Science*, embodies original research work carried-out by the student. We, further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research material(s) obtained from other source(s) and used in this research work has/have been duly acknowledged in the thesis. Image(s), illustration(s), figure(s), table(s) etc., used in the thesis from other source(s), have also been duly cited and acknowledged.

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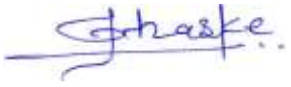

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I, **Priyanka Halder**, a Ph.D. student of the Academy of Scientific and Innovative Research (AcSIR) with Registration No. **10CC18J26007** hereby undertake that, the thesis entitled "**Development of Novel Processes for Sulfur-Containing Scaffolds, Natural Product Orbicularisine and Uricosuric Agent Sulfinpyrazone**" has been prepared by me and that the document reports original work carried out by me and is free of any plagiarism in compliance with the UGC Regulations on *"Promotion of Academic Integrity and Prevention of Plagiarism in Higher Educational Institutions (2018)"* and the CSIR Guidelines for "*Ethics in Research and in Governance (2020)"*.

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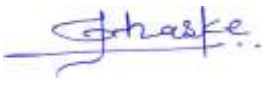

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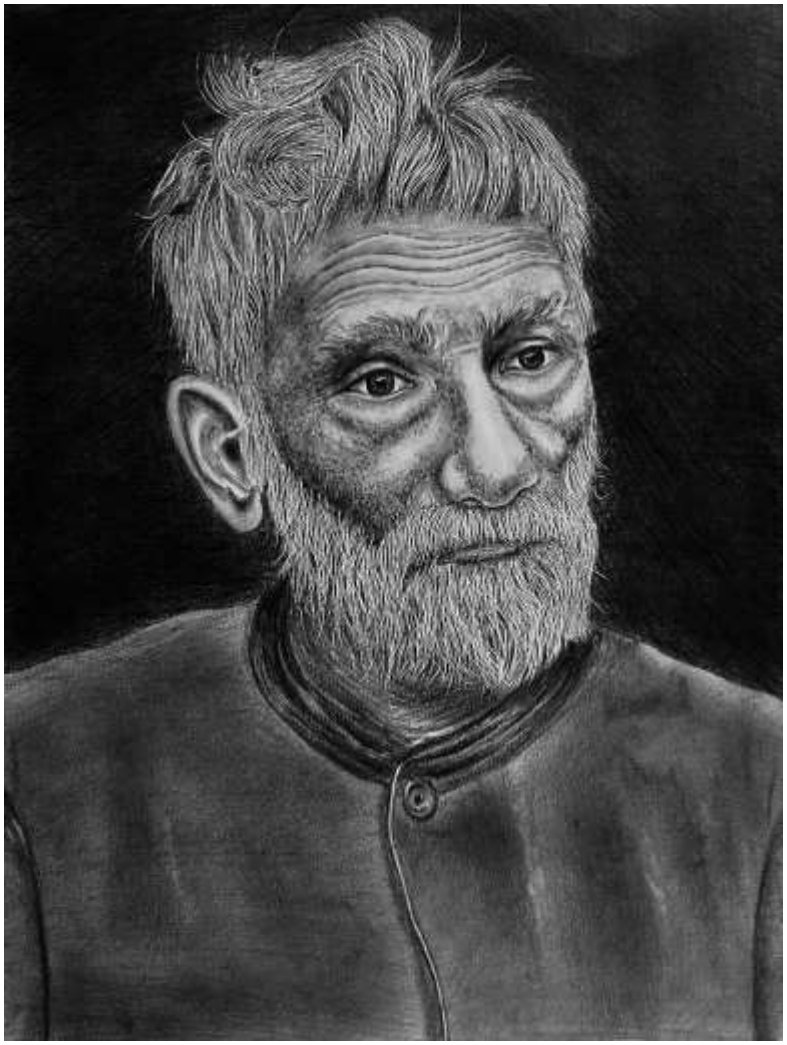

Acharya Prafulla Chandra Ray

Father of Indian Chemistry

"There is no delight like that which springs from a discovery; it is a joy that gladdens the heart."

-The immortal Scheele

TO MY PARENTS

for encouraging me to fly

&

TO MY HUSBAND

for helping me to spread the wings to fly higher

Acknowledgement

The journey of my doctoral research would have been impossible without many individual's kind support, encouragement and cooperation. Herein I take this opportunity to express my heartfelt gratitude to all of them.

Foremost, I want to offer this endeavour to the Almighty God for the wisdom he has bestowed upon me, and the strength, peace of mind and good health he has given me to complete my research successfully. I bow down in front of him for everything that has ever happened to me.

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This Ph. D. would not have been possible without the funding that I have received from CSIR, New Delhi. I would like to acknowledge CSIR-New Delhi for the financial assistance.

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fruitful suggestions and motivation during the crucial period of my PhD journey. I would also like to express my heartfelt thanks to my co-authors, Dr. Vivek, Dr. Milind, Mahesh, Prashant and, Dr. Nilesh for assisting me in my research project. Besides, I would like to extend my deep sense of gratitude to Mahesh, Zeel and Sayali for being there in my time of need as good friends.

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I must take this opportunity to express my very profound gratitude and love to the most special person, my best friend and guide, "Mr. Subhamay Barui" for his unconditional love, moral support, valuable suggestions and constant motivation to achieve what I desire. I must appreciate his patience for tolerating all my frustration and never getting tired of listening to my research-related talk even though that is far from his domain. I would like to extend my reverence to him for always being a ray of sunshine, even on my darkest days, and never allowing me to face any failure alone. I want to thank God for blessing me with his existence in my life and for blessing us to reach the top of the mountain of our desires.

Lastly, I also place on record my sense of gratitude to one and all who, directly or indirectly, have lent their hand in this journey.

Thank you

Priyanka

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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

Chemical Notations	
Ac	Acetyl
AcOH	Acetic Acid
ACN	Acetonitrile
Ar	Aryl
APS	Ammonium persulfate
BRSM	Based on recovered starting material
BHT	Butylated hydroxytoluene
Boc	*t*-Butyloxycarbonyl
Bn	Benzoyl
Bz	Benzyl
$CDCl_3$	Deuterated Chloroform
DCM	Dichloromethane
DCE	Dichloethane
DMF	Dimethyl formamide
DMSO	Dimethyl sulphoxide
Et	Ethyl
EtOH	Ethanol
EtOAc	Ethyl acetate
LHMDS	Lithium bis(trimethylsilyl)amide
LCMS	Liquid chromatography–mass spectrometry

Me	Methyl
MBH	Mortia-Baylis-Hillman
MOM	methoxymethyl
NBS	N-bromo succinimide
NCS	N-chloro succinimide
NIS	N-iodo succinimide
PIDA	(Diacetoxyiodo) benzene
Ph	Phenyl
PMB	*p* -Methylbenzyl
p-TSA	*p*-Toluene sulfonic acid
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
QIK	Quinone Imine Ketal

Other Notations	
calcd	Calculated
δ	Chemical shift
J	Coupling constant in NMR
equiv.	Equivalents
eq.	Equitation
ESI	Electrospray ionization Mass spectrometry
HRMS	High Resolution Mass Spectrometry
m/*z*	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 in a round bottom flask or Schlenk tube equipped with a stirring bar 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). Visualization of the developed TLC plate was performed by irradiation with UV light. Column chromatographic purifications were carried out on flash silica gel (240−400 mesh) using petroleum ether, ethyl acetate, DCM, acetone and methanol as eluents unless otherwise noted. The ^{1}H, ^{13}C NMR spectra were recorded on 200/400/500 MHz, and 50/100/125 MHz NMR spectrometers, respectively in $CDCl_3$/DMSO-d_6/MeOH-d_4/Acetone d^6. Chemical shifts were reported as δ values from standard peaks. The multiplicities of signals are designated by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), quint. (quintet), m (multiplet). Coupling constants (J) are reported in hertz. Melting points recorded are uncorrected. Mass spectra were taken on LC-MS (ESI) or GCMS spectrometer. High-resolution mass spectrometry (HRMS) was performed on a TOF/Q-TOF mass spectrometer.

Synopsis Report

AcSIR	**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 Sciences**
Name of the Candidate	Priyanka Halder
Degree Enrollment No. &Date	Ph. D. in Chemical Sciences (10CC18J26007); January 2018
Laboratory	CSIR-NCL, Pune
Title of the Thesis	Development of Novel Processes for Sulfur-Containing Scaffolds, Natural Product Orbicularisine and Uricosuric Agent Sulfinpyrazone
Research Supervisor	Dr. Santosh B. Mhaske (AcSIR, CSIR-NCL, Pune)

Introduction:

Organosulfur compounds play a crucial role in a wide range of bioactive natural products and pharmaceuticals. To date, nearly 1000 natural products and 150 FDA-approved pharmaceutical drugs containing organosulfur moiety are known.[1] Hence, developing a new methodology or synthetic route for sulfur-containing bioactive natural products and pharmaceuticals has been an enticing topic of research in medicinal and synthetic organic chemistry. The present thesis mainly focuses on our research in the area of organosulfur chemistry, which comprises the synthesis of sulfur-containing novel scaffolds, natural products and pharmaceutical agents through the C–C, C–heteroatom and N–N bond formation. **Chapter 1** presents a brief overview of sulfur-containing natural products and pharmaceuticals. Due to the multiple valance states (S^{2-} to S^{6+}) of sulfur, sulfur-containing natural products are present in numerous forms in nature. Most of them exhibit potent biological activities and pharmacological properties. Therefore, sulfur-containing functional groups have been acknowledged as essential

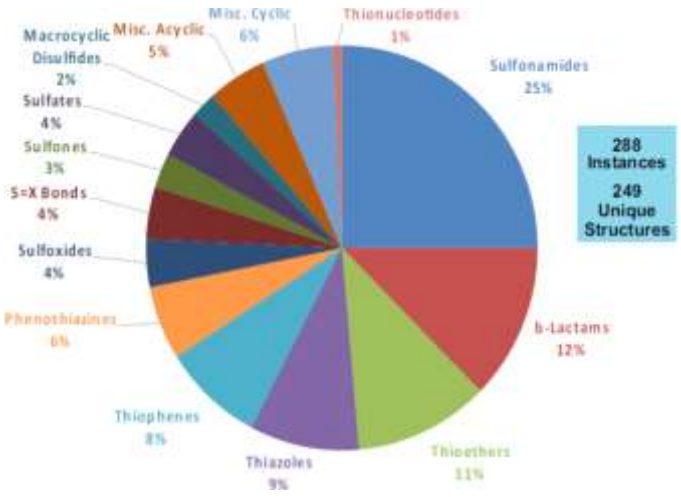

Figure 1: US FDA-Approved Sulfur-Containing Drugs[1b]

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pharmacophores in the medicinal, agrochemical and food industries. This chapter describes some representative examples of sulfur-containing natural products and pharmaceutical compounds in detail. **Chapter 2** is divided into two sections, which discloses two different methodologies for the construction of organosulfur compounds. **Section I** deals with the transition metal-free regioselective C–S bond formation using sodium sulfinate salts to achieve one-pot synthesis of aryl sulfones via *in-situ* formation of quinone imine ketal. **Section II** demonstrates a novel method to construct scaffolds containing SCF_3 moiety, which can enhance the pharmacological properties of organic molecules due to its intrinsic property. Highly functionalized SCF_3-containing building blocks were constructed from simple α-SCF_3 ketones using Morita-Baylis-Hillman (MBH) adducts. **Chapter 3** portrays our studies towards the first total synthesis of the organosulfur natural product Orbicularisine. A practical and efficient synthetic route has been developed for the construction of highly functionalized thiazine moiety. We have successfully built a spiro-oxindolofuranone fused thiazine ring of the Orbicularisine molecule, which can be converted to the natural product by simple transformations. **Chapter 4** reveals a new process for the uricosuric drug Sulfinpyrazone, where the pyrazolidine-3,5-dione core has constructed without using carcinogenic and expensive hydrazine substrates. Intramolecular dehydrogenative N–N bond formation has been achieved to synthesize pyrazolidine-3,5-diones from easily accessible dianilide precursors. This chapter also demonstrates the importance and bioactivity of our novel key intermediates.

Statement of the problem:

Despite the abundance of sulfur-containing compounds in plants, marine and terrestrial organisms, it remains a considerable challenge to supply enough compounds for biomedical studies. Hence, bio and chemical synthetic approaches have been shown to be powerful tools in the production of natural products and related scaffolds. The pharma industry needs to find a reliable, effective solution to galvanise the drug discovery effort, and bring down the costs of the production of drugs. In this context, developing new efficient methods or new synthetic routes for sulfur-containing novel scaffolds, bioactive natural products and pharmaceuticals is an attractive subject of all-time interest to synthetic organic chemists. This has encouraged us to advance our studies in the development of novel methods for sulfur-containing scaffolds, and their application in the synthesis of bioactive natural products and drugs.

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Methodology:

Results:

Chapter 1: Organosulfur Motifs as Privileged Pharmacophores in Bioactive Natural products and Pharmaceuticals

Sulfur is a ubiquitous heteroatom in bioactive natural products and pharmaceutical drugs, which shows a unique medicinal attribute.[2] In the living organism, it is the most essential element and the seventh most abundant mineral in the human body. Sulfur belongs to the 16 group elements of the periodic table just below the oxygen atom, which are called chalcogens. However, its unique characteristics like larger atomic size, low electronegativity and various oxidation state, differentiate it from oxygen and make it capable of bonding with various types of atoms. Therefore, enormous number of sulfur-containing pharmacophores are regularly encountered in various drugs and natural products. Additionally, its applications are widely spread in our daily life as an essential household item as well as in the regular comestibles. Most organosulfur compounds, especially sulfides and thiosulfides have an unpleasant smell, however it has been used for thousands of centuries because of its distinct properties and that has turned up plethora of useful compounds in pharmaceutical, agrochemical, material as well as in the food industry. Until now, almost 1000 organosulfur natural products have been extracted from both marine, and terrestrial organisms worldwide and 41 commercial drugs appeared in the top 200 medicines by retail sales in 2019.[1] Therefore, synthesis of organosulfur compounds via the simple C−S bond formation is of utmost importance.

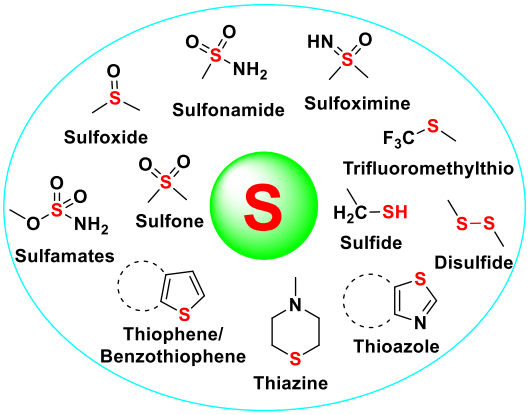

Figure 2: Sulfur Containing Functional Groups

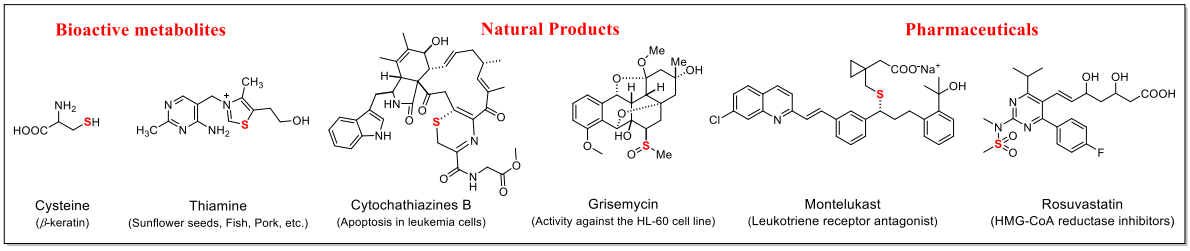

Figure 3: Examples of Bioactive Organosulfur Metabolites, Natural products, and Pharmaceuticals

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Chapter 2: Novel Methods for the Construction of Organosulfur Scaffolds

Organosulfur compounds display a broad range of pharmaceutical applications as well as distinct biological activity, hence C−S bond formation stands at the forefront of investigation in modern synthetic organic chemistry. This chapter is divided into two sections and presents our novel approaches towards the synthesis of organosulfur scaffolds.

Section I: Transition-Metal-Free Regioselective One-Pot Synthesis of Aryl Sulfones from Sodium Sulfinates via Quinone Imine Ketal

This section describes novel method for the synthesis of aryl sulfones via the C−S bond formation. Aryl sulfones are recognized as an important scaffold for their enormous application in agrochemicals, pharmaceuticals, and material chemistry.[3] Additionally, aryl sulfones are also versatile reactive intermediates in organic synthesis and used in well-known organic transformations such as the Ramberg−Bäcklund reaction and the Julia olefination. In the past decades, tremendous efforts have been devoted to the development of novel methodologies for the incorporation of sulfone-containing substituents into organic frameworks. The most common method utilizes the reaction of pre-functionalized aromatic/heteroaromatic halides and sulfinate salts in the presence of a transition-metal catalyst. Herein, we presented a convenient one-pot transition-metal-free protocol for the regioselective synthesis of aryl sulfones via the formation of quinine imine ketal. A broad range of functionality on *p*-anisidine substrates, as well as sulfinate salts was tolerated under mild reaction conditions to provide the corresponding aryl sulfones in good to excellent yields.[4]

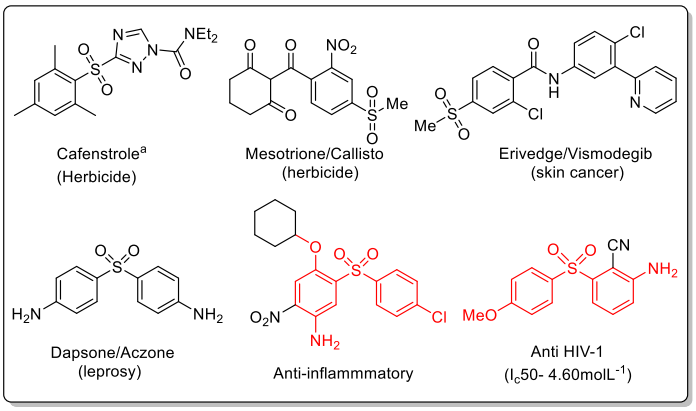
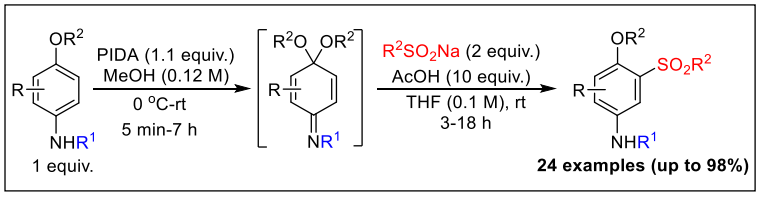


Figure 4: Bioactive Compounds Containing Sulfone



Scheme 1. Synthesis of Aryl Sulfones from Sodium Sulfinates via Quinone Imine Ketal[4]

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Section II: Construction of Unique SCF_3-Containing Building Blocks via Allylic Alkylation of Morita-Baylis-Hillman Adducts

This section presents an efficient process for the construction of highly functionalized SCF_3-containing building blocks. The strong electron-withdrawing trifluoromethylthio (SCF_3) group is one of the most sought after among numerous sulfur-containing moieties. It shows a remarkable effect on API's biological properties, such as high lipophilicity parameter, protein binding affinity, and metabolic stability. These distinctive properties of SCF_3-containing drug candidates enhance their membrane permeability and absorption rate. Therefore, the development of the new methods to incorporate SCF_3 moieties into organic

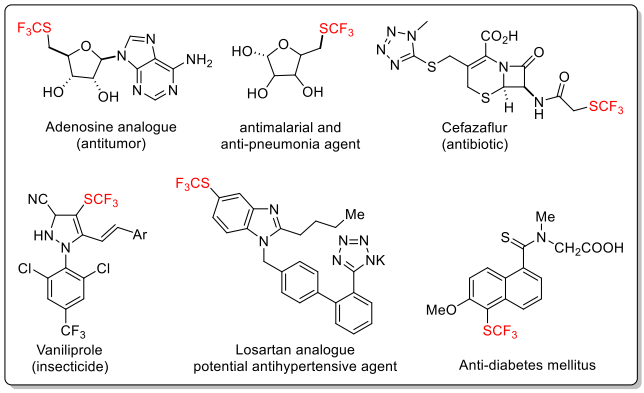
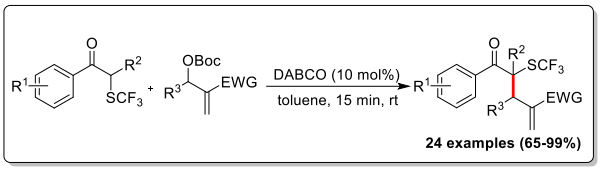
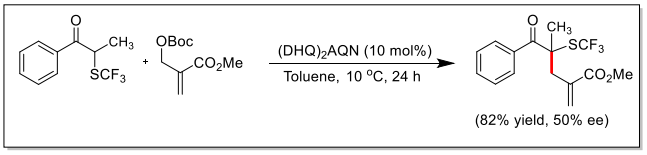


Figure 5: Bioactive Compounds Featuring SCF_3 Moiety

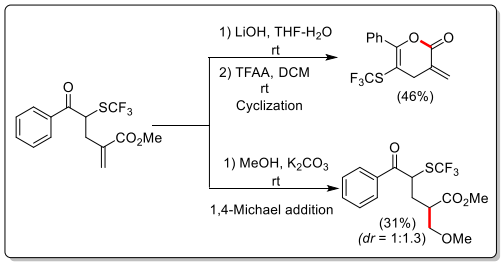


Scheme 2. Reaction of MBH Carbonates with α-SCF_3 Ketones[5]

compounds have been a subject of intensive research. The classical methods include halogen-fluorine exchange reactions in chloro- or bromomethylsulfides and the trifluoromethylation of sulfur-containing compounds. The developed protocol features facile access to organofluorine compounds having SCF_3 moiety on the stereogenic carbon centre via Lewis's base-catalyzed allylic alkylation of MBH adducts with α-SCF_3 ketones. The developed protocol is mild, operationally simple, and high yielding. Furthermore, the importance of this method has been established by converting the trifluoromethylthioalkylated product to



Scheme 3. Preliminary Investigation of Enantioselectivity of the Reaction



Scheme 4. Transformations of Trifluoro-methylthio Alkylated Product

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value-added building blocks using simple transformations. Preliminary screening shows moderate enantioselectivity for a representative substrate using the chiral Lewis base $(DHQ)_2AQN$.[5]

Chapter 3: Studies Towards the Synthesis of Natural Product Orbicularisine

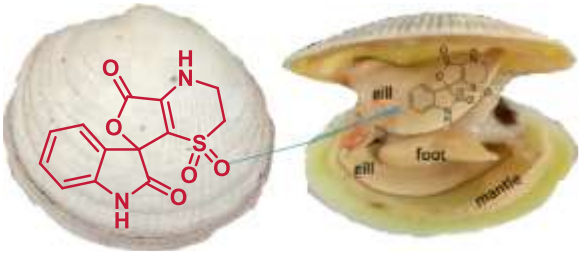
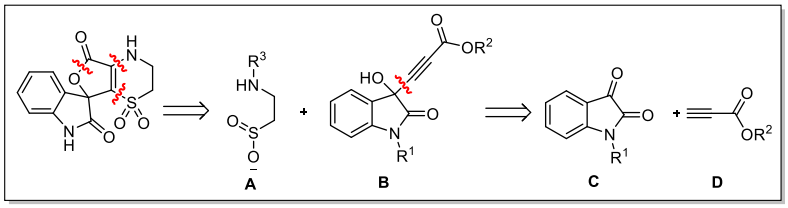
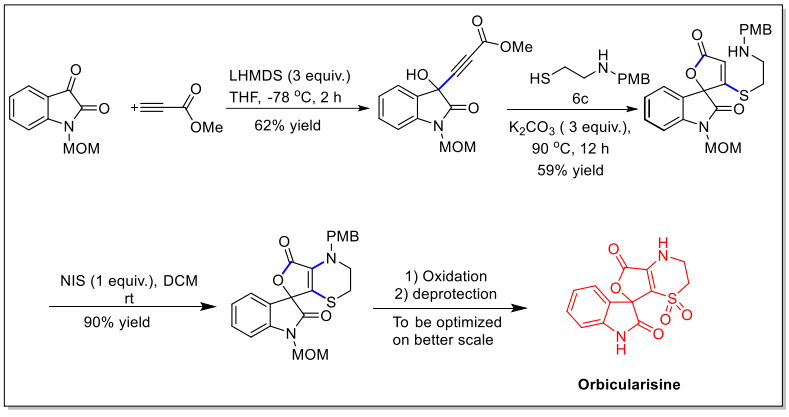


Figure 6. Structure of Orbicularisine

Natural products have played an important role in drug discovery. Among them, sulfur-containing natural products are most sought after and they are mostly isolated from both terrestrial and marine organisms. Since 2004, after the introduction of the first sulfur-containing marine natural product Ziconotide[6] as an analgesic for chronic pain, marine organisms became the most attractive source of novel scaffolds for the drug discovery. In this chapter, we demonstrate our study on the first total synthesis of organosulfur compound Orbicularisine, which was first isolated in a racemic form in 2017 from the gill filament of the bivalve mollusc *Codakia orbicularis*, which belongs to the family of Lucinidae.[7] Structurally Orbicularisine contains one single stereocenter with spiro-oxindolofuranone fused thiazine skeleton. Although the bioassays of original fraction of orbicularisine do not show any bioactivity, the organic molecule with spirooxindole or thiazine scaffolds endows a wide spectrum of bioactivity, including antibiotic, anticancer, anti-HIV, etc.[8] Therefore, this inimitable structural skeleton and various bioactivities made them a privileged building block in the generation of a library of its congeners in search of novel bioactive molecules and challenging targets for its total synthesis. To the best of our knowledge, no synthetic pathway has been reported hitherto, which



Scheme 5. Retrosynthetic Plan for the Synthesis of Orbicularisine



Scheme 6. Synthetic Route for the Synthesis of Spiro-oxindolofuranone Fused Thiazine Skeleton

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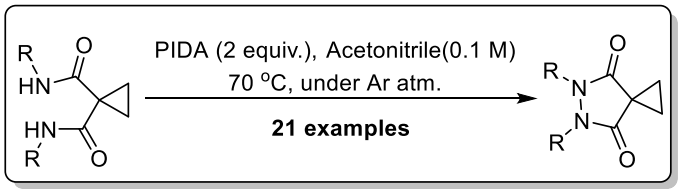
prompted us to explore its synthetic route as well as bioactivity. Herein, we have reported our studies towards the first total synthesis of Orbicularisine molecule through the most straightforward route.

Our retrosynthetic plan, shown in scheme 5, allowed us to recognise C−N, C−O, and C−S bond disconnection for the construction of spiro moiety with the lactone and thiazine ring of the Orbicularisine from the intermediate **B**, which would be possible to synthesize from the commercially available compounds isatin **C** and propiolate derivative **D**. After so many trials and errors, we have developed an efficient synthetic route for the synthesis of Orbicularisine molecule starting from the MOM protected isatin and methyl propiolate. The spiro-oxindolofuranone fused thiazine skeleton of compound was constructed with a good overall yield 33% in 3 steps. Furthermore, transformation to complete the first total synthesis of Orbicularisne molecule via the oxidation of sulfur moiety followed by the deprotection of PMB and MOM group needs to be optimized on a better scale.

Chapter 4: Facile Access to Pyrazolidine-3,5-diones via Metal Free Oxidative Dehydrogenative N−N Bond Formation: Novel Process for Uricosuric Agent Sulfinpyrazone

Chapter 4 deals with the synthesis of functionalized pyrazolidine-3,5-diones based on the metal free oxidative dehydrogenative N–N bond formation of easily accessible dianilide precursors. The applicability of this method has been demonstrated in the synthesis of the uricosuric drug Sulfinpyrazone from an inexpensive starting material aniline. In 1959, Sulfinpyrazone was approved by the US Food and Drug Administration (FDA) and later marketed by Novartis as Anturane brand name.[9] In every instance, pyrazolidine-3,5-diones core of the Sulfinpyrazone drug has been constructed by the traditional condensation reaction between the derivatives of malonic ester and diphenylhydrazine, which is highly carcinogenic and expensive.[10] Therefore, the synthesis of Sulfinpyrazone drug and its congeners exhibits major drawbacks for up-scaling in the industry with environment and health concerns. To overcome this disadvantage, we envisioned a novel synthetic strategy to construct the pyrazolidine-3,5-diones core via N–N bond formation using PIDA as an oxidizing agent. The developed protocol has been generalized by preparing various derivatives of pyrazolidine-3,5-diones with a good yield. Furthermore, this key intermediate has been used to access the Sulfinpyrazone drug by the opening of cyclopropane ring with the nucleophile thiophenol to obtain well-known intermediate **5**. The oxidation of intermediate **5** to furnish the final drug



Scheme 7. Oxidative N–N Bond Formation

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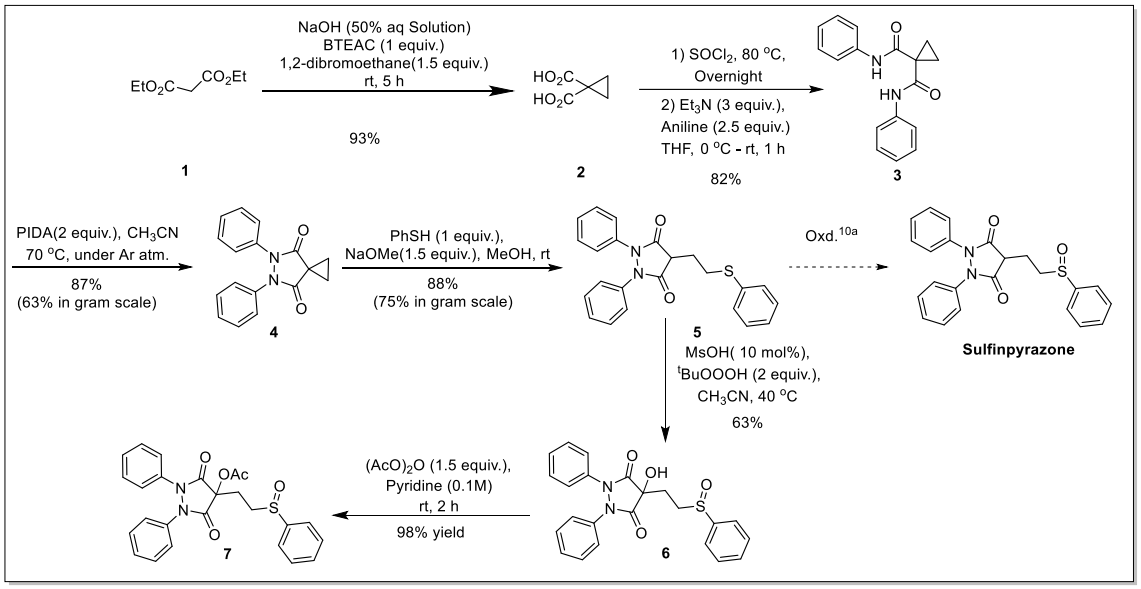
molecule is well reported in literature.[10a] Thus a formal synthesis of the drug Sulfinpyarazone has been achieved in the most efficient manner. However, considering the presence of oxidation prone active methylene in the intermediate **5**, we tried the reported reaction condition for the oxidation of sulfur moiety out of curiosity. Interestingly, we observed the formation of over oxidized compound **6**, where the active methylene group also got oxidized as anticipated. The structure was confirmed by the single-crystal X-ray analysis of it acetylated intermediate **7**.



Scheme 8. Synthetic Route for the Synthesis of Uricosuric Agent Sulfinpyrazone

Conclusions:

In conclusion, we have demonstrated two unique and efficient methodologies for the synthesis of aryl sulfones and highly functionalized SCF_3-containing building blocks. We have also demonstrated our studies towards the first total synthesis of natural product Orbicularisine and reported a novel process for the uricosuric drug Sulfinpyrazone by the preparation of key intermediate pyrazolidine-3,5-dione via N−N bond formation. We believe that the protocols and novel routes developed herein would be useful in drug discovery programmes.

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Publications:

1. **Halder, P**.; Humne, V. T.; Mhaske, S. B. *J. Org. Chem.* **2019**, *84*, 1372.
2. **Halder, P**.; Pol, M. D.; Ahire, M. M.; Mhaske, S. B. *Org. Biomol. Chem.* **2020**, *18*, 2085.
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Chapter 1

Organosulfur Motifs as Privileged Pharmacophores in Bioactive Natural Products and Pharmaceuticals

Organosulfur Motifs as Privileged Pharmacophores in Bioactive Natural Products and Pharmaceuticals

1.1. Abstract:

Organosulfur motif is a privileged pharmacophore present in several bioactive natural products and pharmaceuticals. Over the century, their applications in the synthetic and pharmaceutical field have gradually increased as a significant bioactive organic scaffold. Therefore, a lot of research has been focused on the development of new methods or synthetic routes for the preparation of bioactive organosulfur compounds. This chapter mainly describes a concise summary of the sulfur-containing bioactive natural products and pharmaceuticals along with their synthetic applications and sets the stage for our planned research.

1.2. Introduction:

Sulfur is a ubiquitous heteroatom in bioactive natural products and pharmaceutical drugs, which shows unique medicinal properties.[1] In 1777, Antoine Lavoisier first recognized sulfur as an element. However, from antient times, it has been used as medicine and known to have healing power to the Greeks. Additionally, sulfur element is also of tremendous interest in astrochemistry, agrochemical and material field.[2] Every year, millions of tons of sulfur is used to make batteries, fertilizers, vulcanize rubbers, oil refining, mineral extraction, and many other industrial applications.[3, 2c] Owing to the high abundance of sulfur element (the tenth most rich element in the universe and fifth most on earth),[2b] it has been found in diverse places, including interplanetary space, deep within the oceans, and inside of volcano hot springs.[2b] Sulfur plays a vital role in the natural chemical diversity and redox biological reactions of all living beings depending on their functions.[4] Marine organisms are the most plentiful source of sulfur-containing natural products since the distinct marine environment, like low temperature, high salt concentration, high pressure,

and hypoxia, helps to metabolize most of the inorganic sulfate into structurally diverse, bioactive sulfur-containing natural products.[5] After discovering Tyrian purple in 1909, which was formed from sulfur-containing precursors, marine organisms have become center of attention as a latent source of bioactive natural products which have evolved as new chemical entities for drug discovery.[5] In 1965, Cephalosphorine C was launched as the first marine-derived antibiotic drug after some structural modification.[6] Later, many sulfur containing marine derived compounds such as, Ziconotide (used for chronic pain), Brentuximab (antibody-drug conjugate), Kahalalide F (ES-285) (succeeded in phase I trials as an antitumor agent), Dolastatin 10 (shows anticancer activity, presently in phase II trials), and Trabectedin (anticancer agent) etc. have been discovered for clinical application.[7] Among terrestrial organisms, animals cannot incorporate inorganic sulfur into the organic molecule.[8] However, higher species like a human can produce sulfur-containing secondary metabolite by the consumption of plant tissue.[8] Alliaceous (garlic and onion) and Cruciferous (broccoli, cabbage, radish, cauliflower) vegetables are the primary source of sulfur from plants and contribute almost 42% of total sulfur needs.[9] Other terrestrial organisms can produce sulfur-containing primary metabolite by incorporating sulfur into the organic molecule and the effects of this sulfur metabolite are wide-reaching on human health.[8] It plays a vital role in cellular biochemistry and protects against inflammation, oxidative stress and many chronic diseases.[10] Sulfur is also essential for synthesizing bioactive compounds which maintain the metabolic health of human like, the production of *S*-Adenosylmethionine

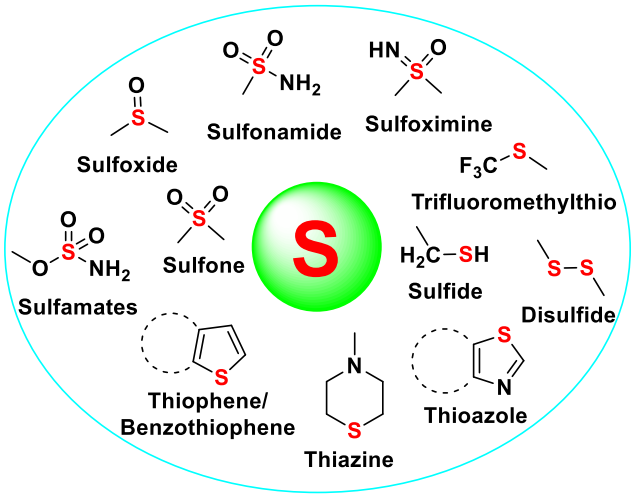


Figure 1. Sulfur containing functional groups

(SAM) which act as a methyl donor for methylation reactions in human cell.[11] Sulfur-containing amino acids (cysteine, methionine, homocysteine, and taurine), vitamins (lipic acid, biotin, thiamine), peptides (glutathione), and bioinorganic ligands of bacterial iron-sulfur proteins play a vital role in redox biochemistry.[11]

Sulfur belongs to the 16 group elements of the periodic table which is called chalcogens; just below the oxygen atom. However, its unique characteristics like larger atomic size, low electronegativity and various oxidation state, differentiate it from oxygen and make it capable of bonding with multiple types of atoms.[4] Sulfur atom has a range of oxidation state from -2 to +6 and exists in numerous forms in nature (Figure. 1).[2b] Therefore, enormous number of sulfur-containing pharmacophores are regularly encountered in synthetic chemistry and paves ways to explore their potential in biological and pharmacological fields.[12]

1.3. Importance of Organosulfur Compounds:

The importance of organosulfur compounds has widely distributed to all over the nature and they exist as a biologically active pharmacophores in diverse natural compounds and pharmaceuticals. Additionally, they have also proved to be of reactive intermediates for the synthesis of new biologically important molecule. Therefore, the below section demonstrated the importance of organosulfur compounds in the area of natural products, pharmaceuticals, reactive intermediates as well as in the food industry.

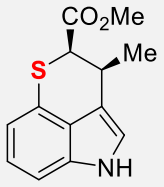
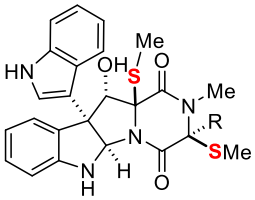
1.3.1. Bioactive Natural Products:

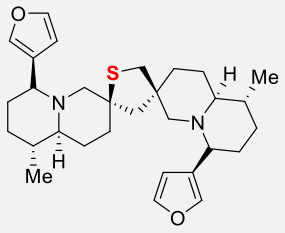
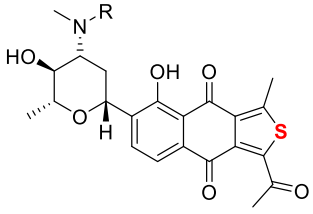
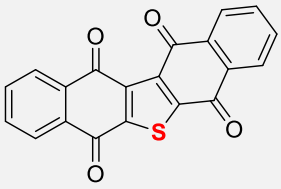
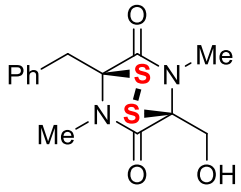
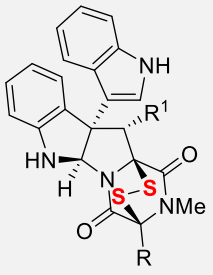
Undoubtedly, sulfur natural products are one of the most excellent sources of new chemical entities in modern drug discovery.[13] The specific characteristics of sulfur natural products and their various structural analogues advance their applicability in the pharmaceutical field and help to explore the structure-activity relationship. For example, some clinical drugs like well-known β-lactam-based

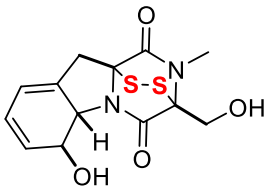
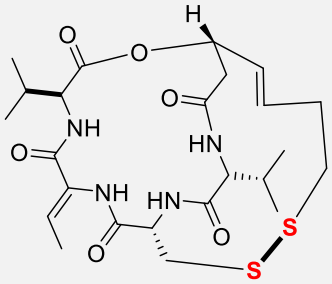
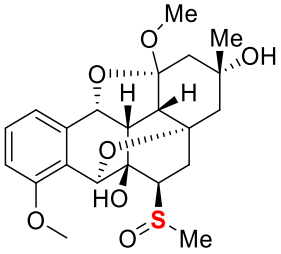
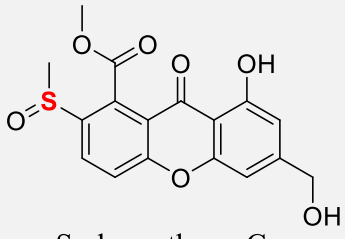
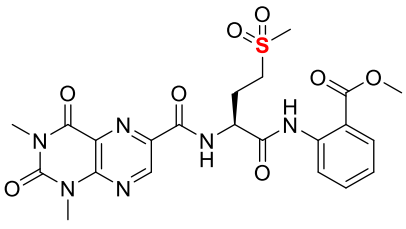
antibiotic Penicillin, Cephalosporin, antitumor drugs Ecteinascidin-743, and Calicheamicin γ1 have been developed from sulfur natural products.[5] Additionally, various sulfur containing new drugs have been derived from natural products by sulfurization (e.g., antibiotic Quinupristin and Dalfopristin both are obtained from Pristinamycin natural products) or modification of sulfur natural products (e.g., semi-synthesis of Ixabepilone from sulfur-containing natural compound Epothilone B).[5, 13a] In addition, some natural products themself exhibit a broad range of biological activities, like Epipolythiodiketopiperazine alkaloids (shows anti-bacterial, antimalarial, cytotoxic properties, etc.), Chuangxinmycin (antibiotic), and Gombamide A (cytotoxic properties).[13a] Till now, almost 1000 sulfur-containing natural products have been extracted from both marine and terrestrial organism.[13a]

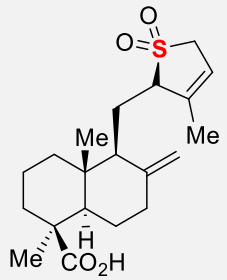
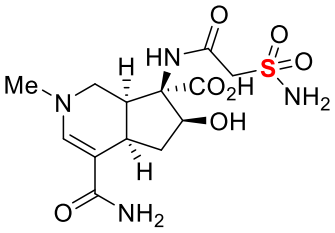
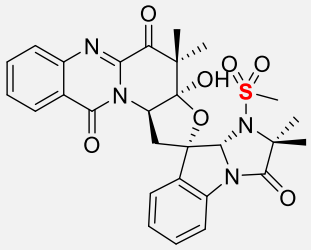
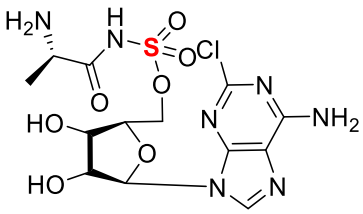
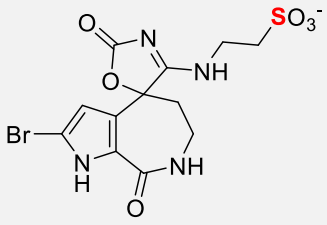
Table 1 shows some examples of sulfur containing natural products with their bioactivity and references related to their synthesis.

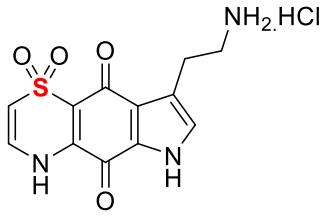
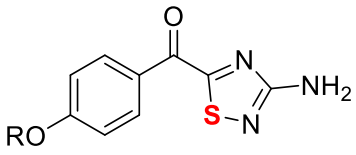
Table 1. Examples of Sulfur-Containing Natural Products

Entry	Organosulfur compound	Source (activity) [Ref]	Synthesis [Ref]
1.	 Chuangxinmycin methyl ester	*Actinoplanes jinanensis* (Antibiotic)[13a]	M. J. Dickens *et. al.*[13a]
2.	 Gliocladin A: R = H T988 B: R = CH_2OH Bionectin C: R = H	*Gliocladium roseum* *Tilachlidium sp.* *Bionectra byssicola* (Cytotoxicity against murine P388 lymphocytic leukemia cells)[13a]	J. E. DeLorbe *et. al.*[13a] S. Sato *et. al.*[13a] A. Coste *et. al.*[13a]

3.	 Neothiobinupharidine	Fresh water plant *Nuphar lutea* (Cytotoxicity on cancer cells)[13a]	D. J. Jansen *et. al.*[13a]
4.	 R = H; Thioquinomycins A R = CH_3; Thioquinomycins B	Marine-derived *Streptomyces sp.* SS17F (Inhibits PKCα and ROCK2 protein kinases)[5]	Not known
5.	 Seriniquinone	Bacterium *Serinicoccus sp.* (Anticancer agent)[5]	L. Trzoss *et. al.*[5]
6.	 (+) Hyalodendrin	Liquid cultures of a species of *Hyalodendron*, *Hyphomycete* (Antimicrobial activity)[13a]	T. Fukuyama *et. at*[13a]
7.	 Gliocladine C: R = Me, R^1 = OH Leptosin D: R = i-Pr, R^1 = OH T988 C: R = CH_2OH, R^1 = OH Bionectin A: R = H, R^1 = OH Gliocclatine: R = Me, R^1 = H	Gliocladine: wheat solid-substrate fermentation of *Gliocladium roseum* (Antinematodal activity) Leptosin D: Mycelium of a strain of *Leptosphaeria sp.* (No activity) T988 C: *Tilachlidium sp.* (Cytotoxicity against cultured P388 leukemia cells.) Bionectin A: Fungus *Bionectra byssicola* F120. (Antibacterial activity)[13a]	J. E. DeLorbe *et. al.*[13a]

8.	 Gliotoxin	Wood fungus *Gliocladium fimbriatum* (Antibacterial and antiviral activity (but it was discarded from clinical practice due to its toxicity))[5]	T. Fukuyama *et. at.*[5]
9.	 Romidepsin	*Chromobacterium violaceum* (Anticancer)[14]	K. W. Li *et. al.*[14]
10.	 Grisemycin	Gene cluster in *Streptomyces griseus* IFO 13350 (Cytotoxic activity against HL-60 cells)[5]	Not known
11.	 Sydoxanthone C	Deep-sea-derived fungus *Aspergillus sp.*[5] (Not known)	Not known
12.	 Penilumamide C	Gorgonian-derived fungus *Aspergillus sp.* XS-20090B15[13a] (No known)	T. Reddy *et. al.*[13a]

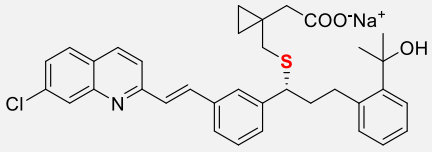
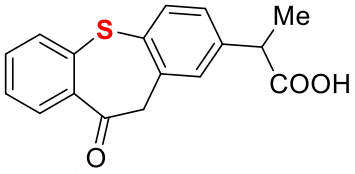
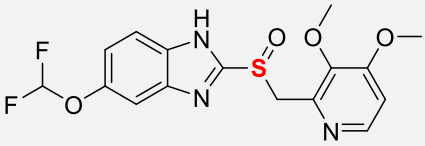
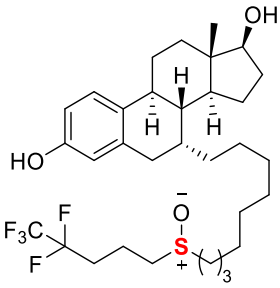
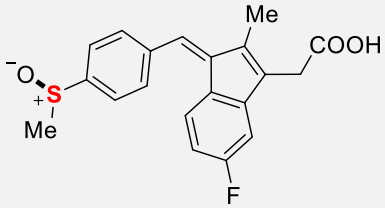
13.	 Dihydrothiophene sulfone diterpenoid	Bulbs of *Fritillaria anhuiensis*[13a] (Not known)	D. J. Mack *et. al.*[13a]
14.	 Altemicidin	Actinomycete strain *Streptomyces sioyaensis.* (Acaricidal and antitumor activities)[13a]	A. S. Kende *et. al*[13a] C. S. H. Magnani *et. al.*[13a]
15.	 Scedapin C	Marine fungus *Scedosporium apiospermum*. (Antiviral activity against the hepatitis C virus)[5]	Not known
16.	 Ascamycin	Fermentation broth of a Streptomyces. (Antibacterial) [15]	M. Ubukata *et. al.*[15]
17.	 Callyspongisine B	Australian marine sponge, *Callyspongia sp.*[13a] (Not known)	Not known

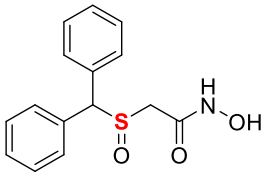
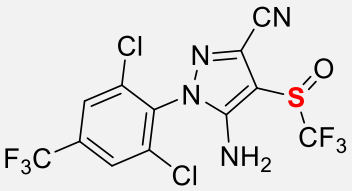
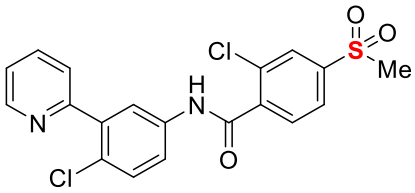
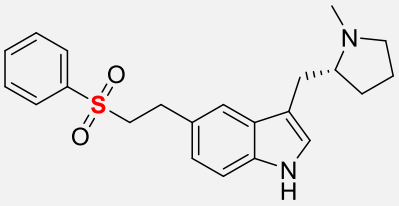
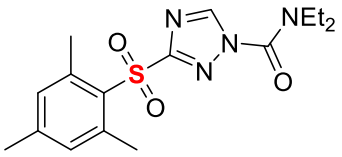
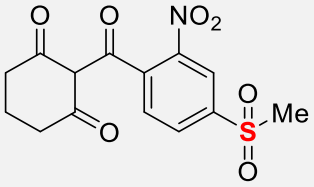
18.	 Thiaplakortone A	Australian marine sponge *Plakortis lita*. (Antimalaria)[16]	R. H. Pouwer *et. al.*[16]
19.	 Peniciline V	*Penicillium mold* (Antibiotic Activity)[17]	J. C. Sheehan *et. al.*[17]
20.	 R = H; Polycarpathiamines A R = Me; Polycarpathiamines B	Ascidian *Polycarpa aurata* (Cytotoxic activity against L5178Y murine lymphoma cells (IC_{50} 0.41 μM))[13a]	E. K. Davison *et. al.*[13a]

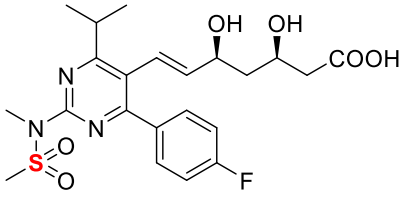
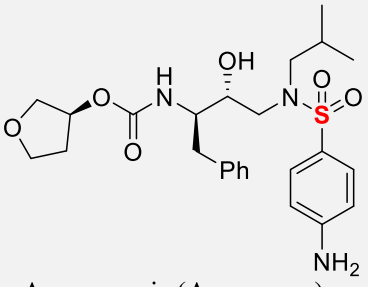
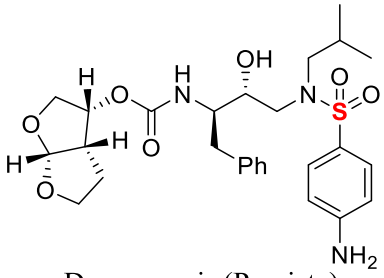
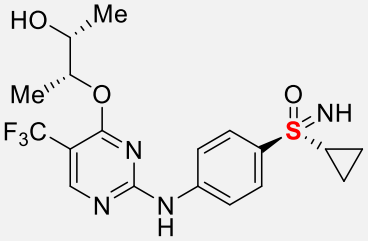
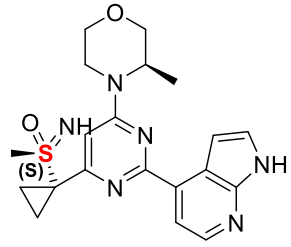
1.3.2. Pharmaceutical Drugs:

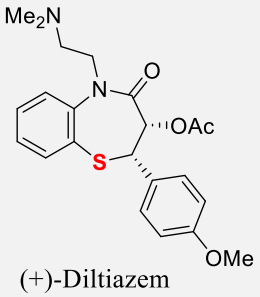
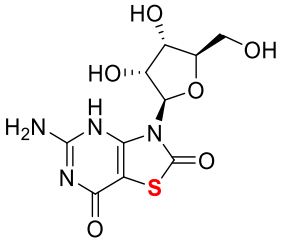
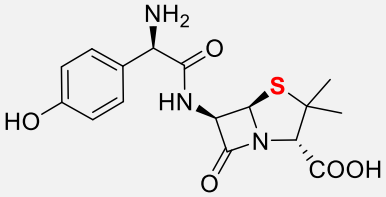
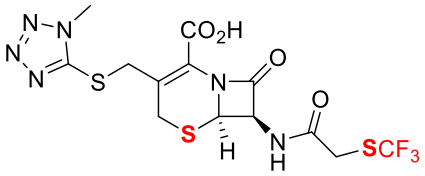
Historically, there is a long-standing relationship of sulfur functionalities with pharmaceutically active compounds.[18] From discovery of sulfonamide drugs as the first antibiotic agent, it paved the way of antibiotic revolution in medicine.[18b] Worldwide, 41 commercial drugs appeared in the top 200 medicines by retail sales in 2019.[5] Among them, some functional moieties exist in higher frequencies. Sulfonamides, sulfones, sulfoxide, sulfides and sulfur heterocycles introduce plentiful blockbuster drugs regularly.[18b] For example, sulfonamide containing Sulfa drug, Penicillin G having lactam moiety, act as a potent antibiotic.[18b] Similarly, Pantoprazole or Fulvestrant both contain sulfoxide moiety are used to treat gastro-oesophageal reflux disease (GORD) and breast cancer.[18] The following table displays some examples of essential pharmaceuticals drugs with their synthesis references.

Table 2. Examples of Sulfur Containing Pharmaceuticals

Entry	Compound	Marketed company (activity)	Synthesis[ref]
1.	 Montelucast Sodium (Singulair)	Merck Frosst, Canada (Anti-asthma, Anti-allergic)[19]	M. L. Belley *et. al.*[19c]
2.	 Zaltoprofen (Soleton)	(Anti-inflammatory)[20]	Wang et. al.[20]
3.	 Pantoprazole Base (Protonix)	Altana (Inhabits gastric acid secretion proton pump inhibitor)[21]	Dr. B. Kohl *et. al.*[21c]
4.	 Fulvestrant (Faslodex)	Astra Zeneca (Breast Cancer) [18d]	D. Caprioglio *et. al.* [18d]
5.	 Sulindac (Clinoril)	Merck (Nonsteroidal Anti-inflammatory) [18d]	T. Y. Shen *et. al.* [18d]

6.	 Adrafinil (Olmifon)	Cephalon, Inc. (Central nervous system stimulant)[12]	N. W. Milgram *et. al.*[12]
7.	 Flipronil (Fiprofit)	Rhône-Poulenc (Insecticide)[12]	K. H. Gharda *et. al.*[12]
8.	 Vismodegib (Erivedge)	Genentech, INC. (South San Francisco, CA) (Skin Cancer, Hedgehog Pathway Inhibitor)[18d]	J. Gunzner *et. al.*[18d]
9.	 Eletriptan (Relpax)	Pfizer, New York (Treatment of the headache phase of migraine attack)[12]	J. E. Macor *et. al.*[12]
10.	 Cafenstrole	Herbicide[12]	Y. Ma *et. al.*[12]
11.	 Mesotrione/Callisto	Syngenta (Herbicide)[12]	G. Mitchell *et. al.*[12]

12.	 Rosuvastin (Crestor)	AstraZeneca (Treat high cholesterol)[18d]	K. Hirai *et. al.*[18d]
13.	 Amprenavir (Agenerase)	Vertex Pharmaceuticals (GlaxoSmithKline) (Treat HIV infection)[18d]	C. T. Baker *et. al.*[18d]
14.	 Darunanavir (Prezista)	Janssen Therapeutics (Inhibiting HIV-1 and HIV-2 viruses)[18]	A. K. Ghosh *et. al.*[18]
15.	 Roniciclib (Kisqali)	Bayer Schering Pharma (CDK inhibitor)[22]	U. Lücking *et. al.*[22]
16.	 Ceralasertib (AZD6378)	AstraZeneca (ATR inhibitor)[18c]	M. A. Graham *et. al.*[18c]

17.	 (+)-Diltiazem (Cardizm)	Tanabe Seiyaku Co., LTD, Japan (Calcium-channel Blocker)[23]	O. Miyata *et. al.*[23d]
18.	 Isatoribine	Anadys Pharmaceuticals (Agonist of TLR7)	K. Nagahara *et. al.*
19.	 Amoxicillin (Amoxil)	Bristol-Myers Company, New York (Antibiotic)[18b]	J. H. Grossman *et. al.* [18b]
20.	 Cefazaflur	Fujisawa Pharmaceutical Co., Ltd. Antibiotic[18b]	K. Kariyone *et. al.* [18b]

1.3.3. **Reactive Intermediate**:

In addition to the medicinal and biological importance, organosulfur compounds are versatile reactive intermediates and perform a prominent role in synthetic organic chemistry through the development of new bond-forming reactions or by the redeployment of traditional functional moieties and their activity.[24] Organic transformations, like Chugaev elimination, Corey–Winter olefin synthesis, Ramberg–Bäcklund reaction, Julia olefination are well known for the olefin

synthesis, where organosulfur scaffolds were utilized for the preparation of reactive intermediate or used as a starting precursor. Barton–McCombie deoxygenation, Pummerer rearrangement, and Johnson–Corey–Chaykovsky reactions are also well-established organic transformations for the synthesis of an important organic molecules using reactive organosulfur intermediates.[24a] Apart from this, organosulfur compounds are also used as an important reagent for some vital organic transformations such as swern oxidation, Corey–Kim oxidation, Mozingo reduction, etc. Sulfur-containing ligands, organocatalysts and metal catalysts have also occupied a vast area of the synthetic field and are used in many asymmetric transformations.[25]

1.3.4. Sulfur Rich Food:

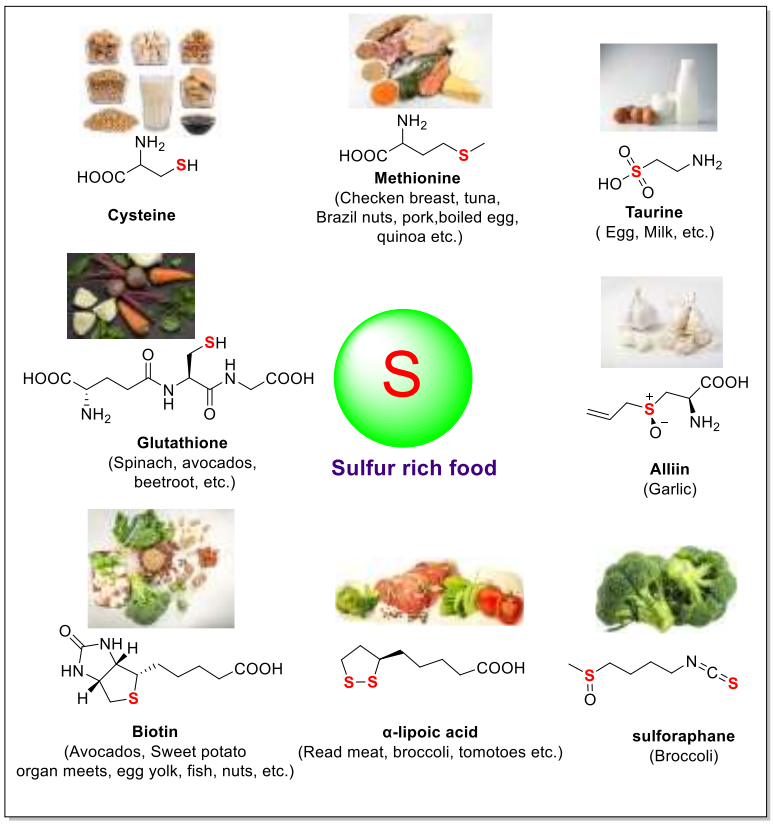


Figure 2. Examples of sulfur rich food

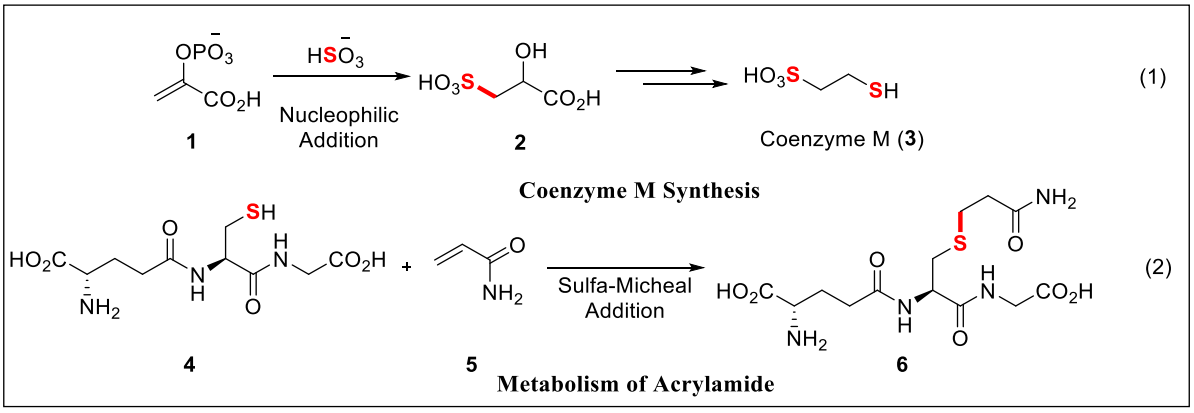
Furthermore, the applications of organosulfur compounds are widely spread in our daily life as an essential household item and in the regular comestibles. Most of the organosulfur compound especially, sulfides and thiosulfides have an unpleasant smell. However, They have been used for thousands of centuries for its distinct properties and turned up into plethora of useful compounds in pharmaceutical, agrochemical, material as well as in the food industry.[2,26] Natural food containing organosulfur compounds may hold the key benefits of health and reduce lots of diseases because of their distinct

properties like, antioxidant, anticarcinogenic and anti-inflammatory.[27] They are mainly found in allium vegetables, cereals, pulses, cooked fish and meat (Figure. 2) . Moreover, organosulfur compounds are extensively used in artificial foods as a flavor to improve the smell and taste.[26] Hence, due to their ubiquity applications, synthesis of organosulfur molecule is inevitably needed in organic synthetic field.

1.4. Biosynthetic Pathway for the Synthesis of Organosulfur Metabolite:

Sulfur is one of the most abundant elements, which is crucial for all living organism and have taken a significant place in maintaining life on the planet.[28] From the evolution of life, it has been closely linked to many biochemical processes in eukaryotic and prokaryotic cells. Therefore, numerous sulfur-containing bioactive metabolites, which are essential for the metabolism or diverse biological functions, are mainly obtained by several enzymatic reactions or chemical mechanisms through the formation of C−S bonds.[29] In the biological process of human body, C–S bond formation has been found to be a very significant type of reaction.

Scheme 1. C−S Bond Formation in Coenzyme M Synthesis and Metabolism of Acrylamide[11]

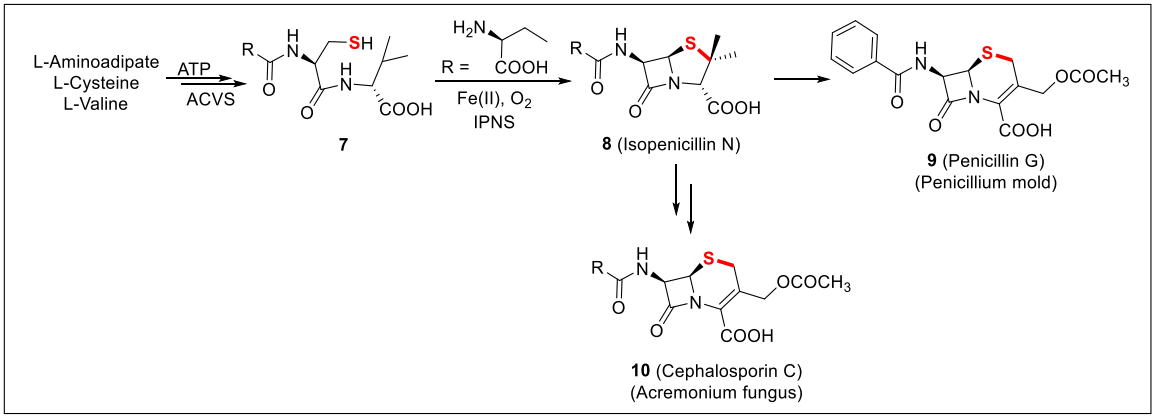


For example, the biosynthesis of Coenzyme M in bacteria is initiated by synthesizing phosphosulfolactate via the nucleophilic addition of bisulfite to phosphoenolpyruvate (PEP) (Scheme 1, equation 1). Acrylamide, a toxic agent formed naturally in food after cooking at high

temperature, is metabolized by the sulfa-Michael addition reaction of glutathione with acrylamide and excreted from our body via urine (Scheme 1, equation 2).[11]

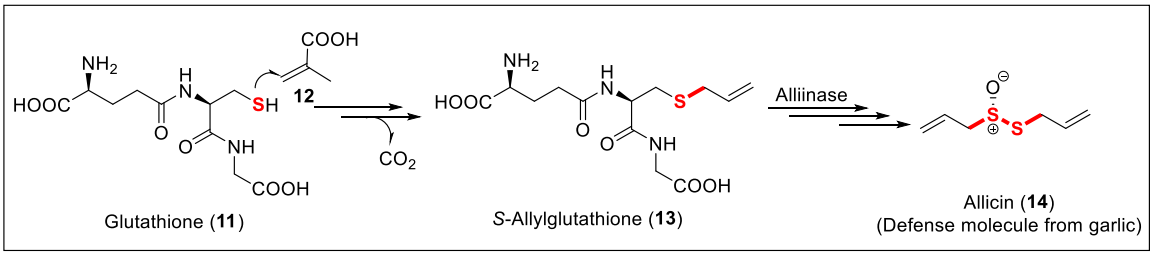
Penicillin and Cephalosporin are two crucial classes of clinically used β-lactam antibiotics, derived from penicillium mold and acremonium fungus, respectively. The enzyme nonheme iron-dependent oxygenase plays a vital role in their biosynthetic pathway. Isopenicillin N synthase catalyze the radical-based C−S bond formation reaction to construct the core structure of Isopenicillin N, which is the common intermediate for the antibiotic Penicillin G and Cephalosporin C (Scheme 2).[29]

Scheme 2. C−S Bond Formation in Biosynthesis of Penicillin G and Cephalosphorin C[29]



Allicin is most abundant pharmacologically active organosulfur molecule, derived from garlic and its biosynthesis is initiated by the formation of S-allylglutathione via sulfa Michael addition reaction of glutathione with acrylic acid (Scheme 3).[29]

Scheme 3. C−S Bond Formation in Biosynthesis of Allicin[29]



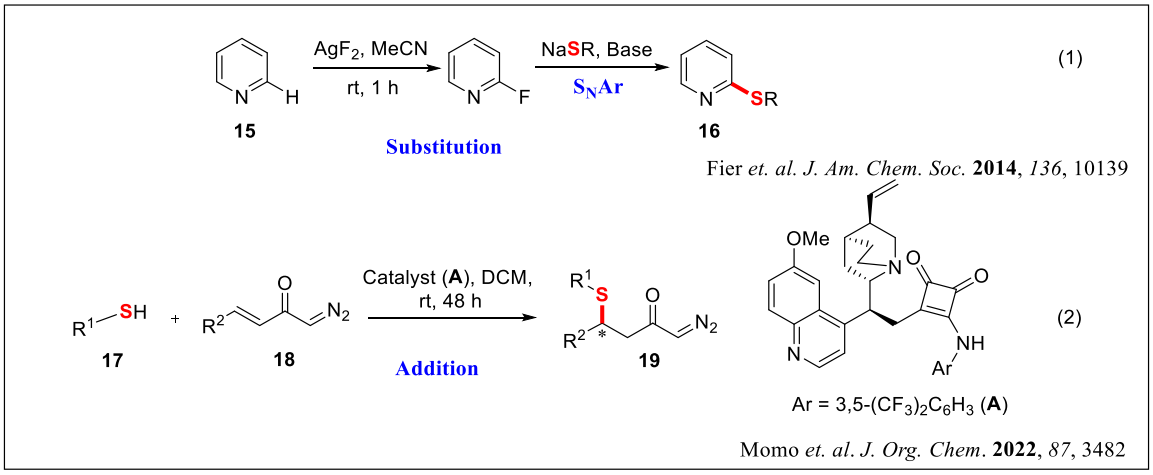
1.5. Importance of C−S Bond Formation in the Synthesis of Organosulfur Molecules:

From the beginning of organic synthesis, the development of new methods or synthetic routes for bioactive organosulfur molecules have magnetized many organic synthetic chemists, and over the past decades, it has been studied broadly to incorporate sulfur atoms into bioactive organic molecules.[24,25,30] Various innate properties of sulfur atom allow it to undergo different reactions and form bonds with carbon or several heteroatoms.[24d,31] Among them, C−S bond formations attribute a special class of reactions in the organic synthesis process. To date, substantial growth has been achieved for the synthesis of organosulfur scaffolds via the selective C−S bond formation using various sulfur-containing functional groups.[11] Thiols and sulfides are widely used in different synthetic transformations like addition, substitution or nucleophilic ring-opening reaction to form C−S bonds.[32] Additionally, sulfides are also used as superlative reagents in different C−H functionalization reactions, mainly in cross-coupling.[32b] However, recently the use of masked sulfide derivatives or surrogates of sulfide compounds has been extended due to their odour and the toxicity to metal catalysts.[33] Various sulfurizing reagents were also developed to incorporate sulfur atoms into the organic molecules.[34] In addition, a lot of research has been devoted to construct chiral organosulfur compounds,[25] and several approaches have already been introduced successfully with excellent optical purity, like, organocatalytic sulfa-Michael addition,[32a,d,f] Diels-Alder reaction,[35] and allylic sulfonylation.[36] The following section describes some examples of synthetic transformations to demonstrate the importance of C−S bond formation in the synthesis of organosulfur scaffolds.

Construction of biologically active sulfur natural products and pharmaceuticals through classical methods like substitution, addition and ring-opening reactions are always useful in sulfur chemistry.[11] In 2014, Hartwig group reported late-stage functionalization of structurally diverse

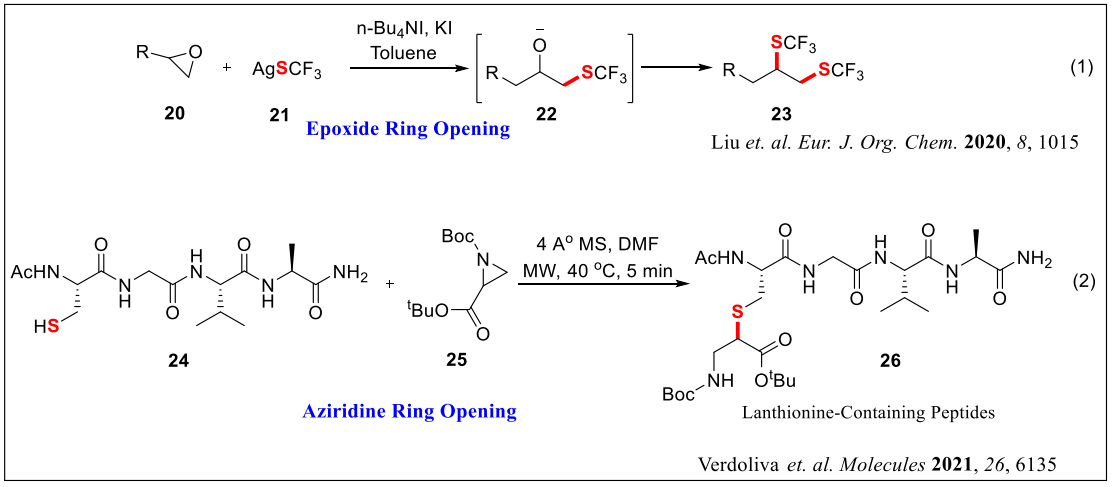
bioactive molecules through aromatic nucleophilic substitution reaction of 2-fluor-heteroarenes by sulfur nucleophiles (Scheme 4, equation 1).[37]

Scheme 4. C−S Bond Formation through Substitution[37] and Addition Reaction[38]



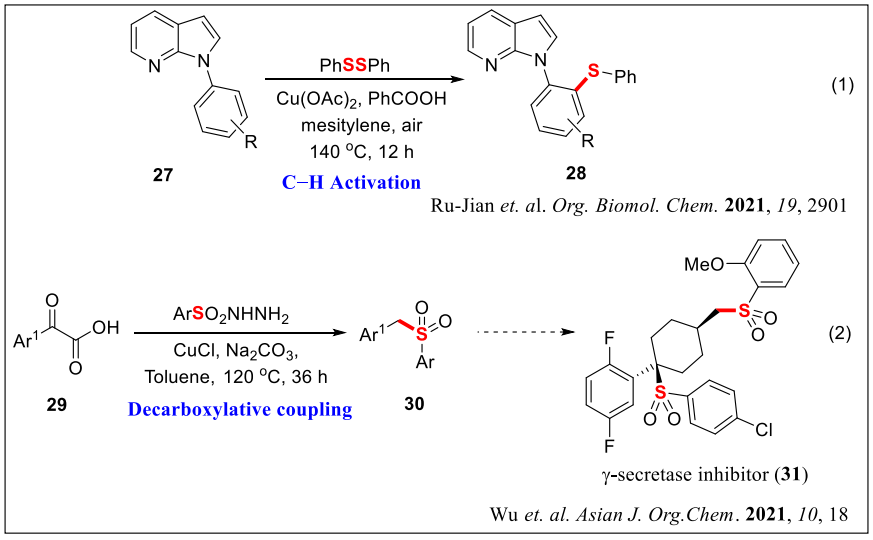
Organocatalytic sulfa-Michael addition reaction is one of the privileged enantioselective transformations to access enantioenriched organosulfur compounds via the nucleophilic addition of sulfur moiety.[32a,d,f] In last year, Burtoloso groups synthesized highly enantioenriched thiol compounds by the quinone-derived squramide mediated sulfa-Michael addition reaction of thiol nucleophiles (Scheme 4, equation 2).[38]

Scheme 5. C−S Bond Formation via Ring Opening of Epoxide[39] and Aziridine[40]



Similarly, ring-opening reactions of epoxides[32d] and aziridines[11] by sulfur nucleophile also represent an appropriate method for making new C−S bonds. Plentiful approaches have been reported for the thiolysis of epoxide rings.[32d] In 2020, Liu *et. al.* reported 1,2-bistrifluorothiolation of epoxide by the tandem nucleophilic ring opening followed by the deoxytrifluoromethylthiolation strategies using $AgSCF_3$ reagent (Scheme 5, equation 1).[39] Later, Luca group also developed a protocol for the synthesis of Lanthionine-Containing Peptides through the aziridine ring opening reaction by sulfur nucleophile (Scheme 5, equation 2). [40]

Scheme 6. C−S Bond Formation through C−H functionalization[42, 44]

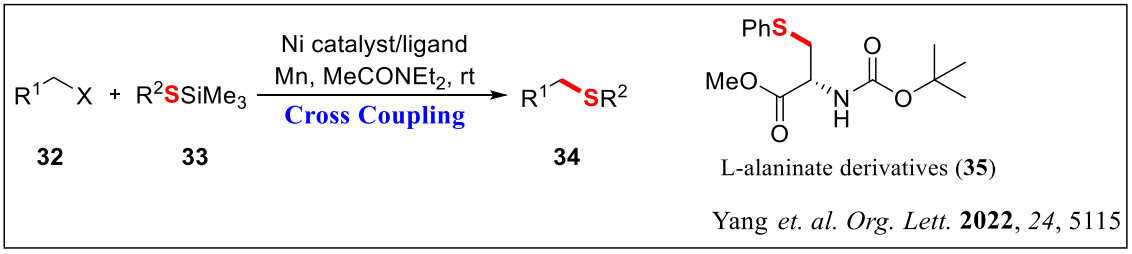


Transition-metal-catalyzed bond forming reactions have reformed the area of traditional synthetic organic chemistry by emerging a wide range of new synthetic methods.[41] Over the past decades, construction of organosulfur compounds via the transition-metal-catalyzed C−S bond formation reactions have been found erratic as compare to other methods because of the poisonous impact on catalysts by the sulfur, particularly by thiol or sulfide scaffolds.[33] In recent years, this problem has been resolved successfully, and various metal-catalyzed novel protocols have been developed for the formation of C−S bonds.[41] In 2021, Jian *et. al.* established a method for Cu-catalyzed ortho-directed C−H sulfenylation of *N*-aryl-7-azaindoles using disulfide as a sulfur

source (Scheme 6, equation 1).[42] Like C−H activation reaction, decarboxylative C−S coupling reactions have also appeared as an attractive protocol to construct several bioactive organosulfur compounds.[43] In this regard, Wu group synthesized a series of aryl sulfones through the decarboxylative reductive sulfonylation process with aryl sulfonyl hydrazide (Scheme 6, equation 2).[44]

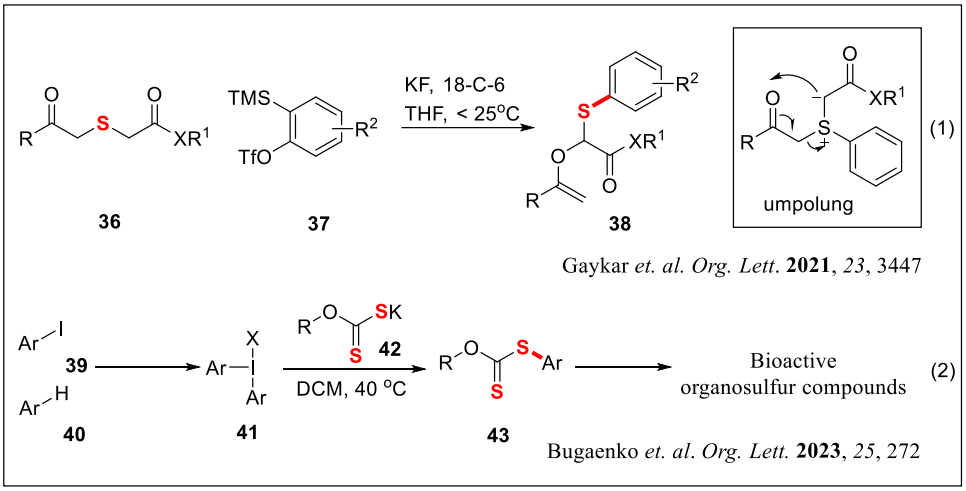
Transitional-metal-catalyzed C−S cross-coupling reactions of organohalides are also very promising reactions in the orthodox C−S bond forming transformations.[41a] In the last year, Ni-catalyzed C−S cross-coupling reaction of alkyl halides was reported by Yang *et. al.* to synthesize thioethers using arylthiosilane as a promising electrophilic thiolation reagent (Scheme 7).[45]

Scheme 7. C−S Bond Formation via Cross Coupling[45]



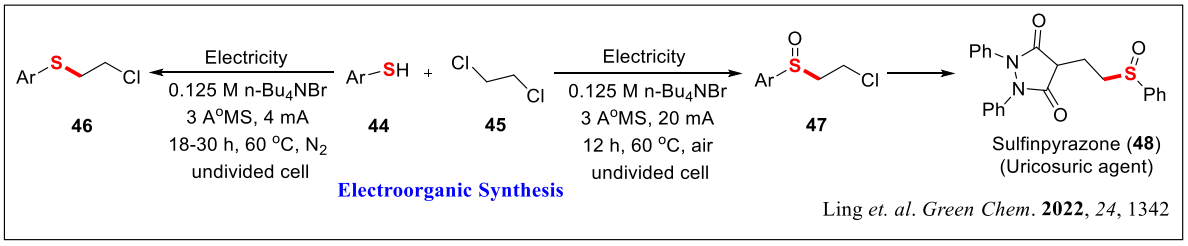
Transition-metal-free C−S bond formation is an alternative robust and sustainable way for the development of novel synthetic routes to bioactive organosulfur compounds.[46] The use of highly reactive aryne intermediates in the transition-metal-free C−S bond formations is of growing interest in the synthetic research area and has achieved a great success for the synthesis of organosulfur compounds.[46] In 2021, Biju group used arynes intermediate for the synthesis of thiosulfide derivatives via the *in-situ* formation of sulfur ylide, which underwent umpolung oxa-[2,3] sigmatropic rearrangement (Scheme 8, equation 1).[47] Recently, Bugaenko and coworkers developed a protocol for the transition-metal-free S-arylation of potassium O-alkyl xanthates and provided organosulfur compounds having O-alkyl xanthates, which are very challenging to achieve under such conditions (Scheme 8, equation 2).[48]

Scheme 8. Transition-Metal-Free C−S Bond Formation[48]



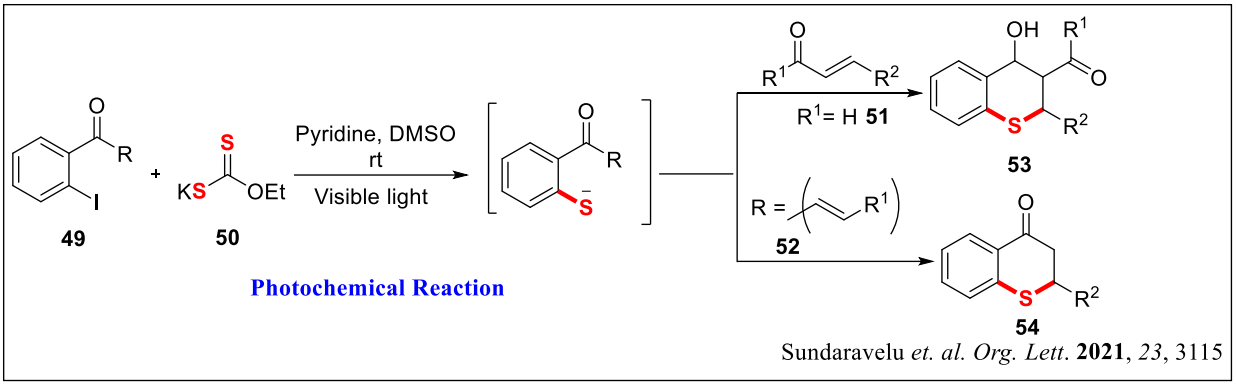
A green, sustainable, and simple synthetic route is always of a great interest in organic synthetic field. Electroorganic synthesis is one of the atom-economic routes for synthesizing organosulfur compounds via C−S or S−X bond formation.[31a] Ling group developed an electrocatalytic approach for the divergent synthesis of sulfide and sulfoxide scaffolds. Further, they extended this method for the total synthesis of uricosuric agent sulfinpyrazone (Scheme 9).[49]

Scheme 9. C−S Bond Formation through Electroorganic synthesis[49]



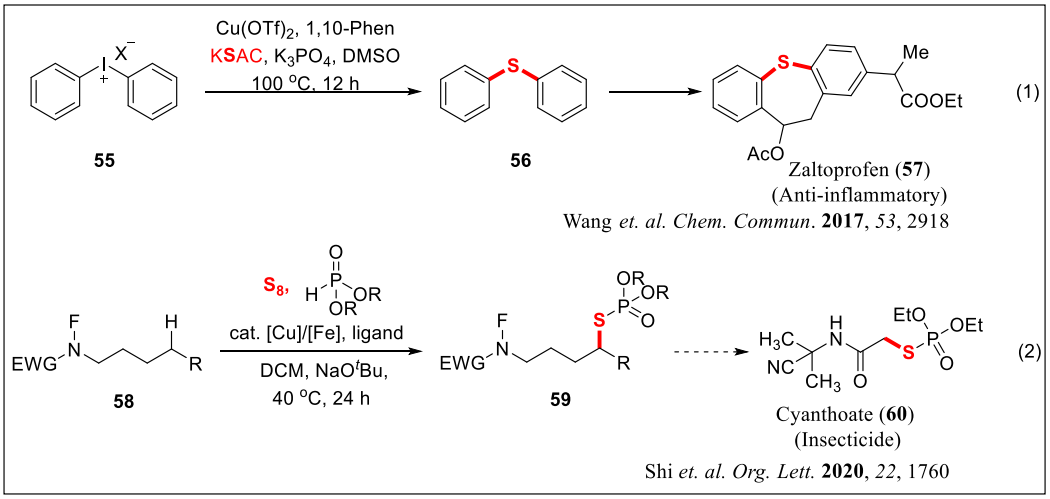
The generation of sulfur radicals especially, thionyl and sulfonyl radical, from photoredox SET oxidation reaction has also been studied extensively.[31b] Over the past decades, several methods have been proposed for the construction of bioactive organosulfur compounds by forming C−S or S−X bonds.[31b] In 2021, Sundaravelu *et. al.* developed visible light-mediated C−S cross-coupling reaction. Various thiochromane derivatives were achieved by the domino reaction through two consecutive C−S bond formations (Scheme 10).[50]

Scheme 10. C−S Bond Formation through Photochemical Reaction[50]



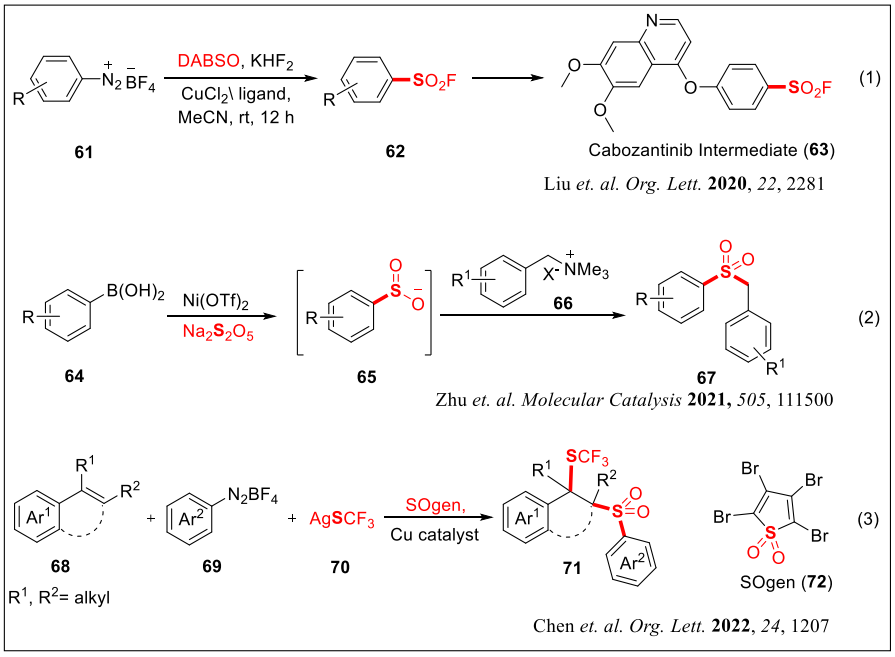
Due to the diverse distinct properties of sulfur atom, synthesis of organosulfur compounds is always a challenging subject in modern synthetic organic chemistry. The main obstacle in sulfur chemistry is the unpleasant odour of organosulfur compounds, especially sulfide/disulfide and the strong coordination of lone pairs of sulfur atom with the metal catalysts.[33] Additionally, the diverse oxidation state of the sulfur atoms also leads to the synthetic challenge in selective oxidation. Furthermore, the disulfide functional group, which is abundant in various bioactive molecules, can undergo reversible bond cleavage under mild reaction conditions.[33] Thus, developing green and sustainable sulfurizing agents or SO_2 surrogates for the synthesis of organosulfur compounds is continuously being followed.[51] Over the past few decades, the use of sulfurizing reagents as a source of sulfur to incorporate into bioactive organic molecules has increased rapidly.[51a,c] In 2017, Jiang groups developed a method for the intra or inter molecular construction of sulfide compounds using sulfur salt (KSAc) as a source of sulfur. Further, they applied this method for the synthesis of anti-inflammatory agent Zaltoprofen (Scheme 11, equation 1).[20] Elemental sulfur is a profusely accessible, odourless and inexpensive element, which is widely used for the incorporation of sulfur atoms into the bioactive molecules.[51a] Shi *et. al*. incorporated $SP(O)(OR)_2$ group into organic molecule for the synthesis of s-alkyl phosphorothioates via copper catalyzed $C(SP^3)$−H functionalization using sulfur source S_8 (Scheme 11, equation 2).[52]

Scheme 11. C−S Bond Formation Using Sulfurizing Reagents[20, 52]



Apart from the sulfurizing agents, SO_2 surrogates (such as DABSO, sulfiting agents etc.) are also very common sulfur source for the synthesis of organosulfone compounds.[51b] In 2020, Lui group synthesized arenesulfonyl fluoride utilizing DABSO as a SO_2 surrogate (Scheme 12, equation 1).[53]

Scheme 12. C−S Bond Formation Using SO_2 Surrogates[53, 54, 55]

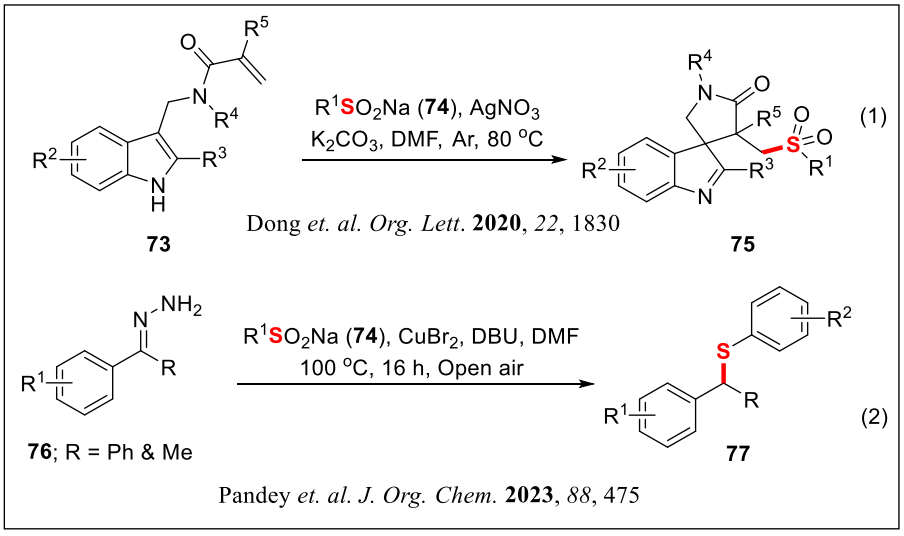


Zhu group also used sulfiting agent $Na_2S_2O_5$ as a source of sulfonyl group for the synthesis of arylsulfones from boronic acid derivatives (Scheme 12, equation 2).[54] Recently, Chen et. al.

used SOgen for the ex-situ generation of SO_2 and $AgSCF_3$ for the thio-sulfonylation of styrene derivatives and constructed a skeleton having both the important active functional groups SCF_3 and sulfone (Scheme 12, equation 3).[55]

Sodium sulfinate salts, as non-hygroscopic, odourless, easy to handle and readily available chemical feedstock have received important attention for their dual and versatile role in organic synthesis.[56] It can act as an indispensable reagent for the sulfonylation and sulfenylation reactions. In 2020, Wang group synthesized sulfonylated heterocycles using sodium sulfinate as a sulfonylating reagent (Scheme 13, equation 1).[57] Recently, Pandey et. al. published a protocol for the thiolation of aryl hydrozones via Cu-catalyzed C−S bond formation (Scheme 13, equation 2).[58]

Scheme 13. C−S Bond Formation using Sodium Sulfinate Salt[57, 58]



1.6. Synthetic Pathway of Sulfur-Containing Bioactive Natural Products and Pharmaceuticals:

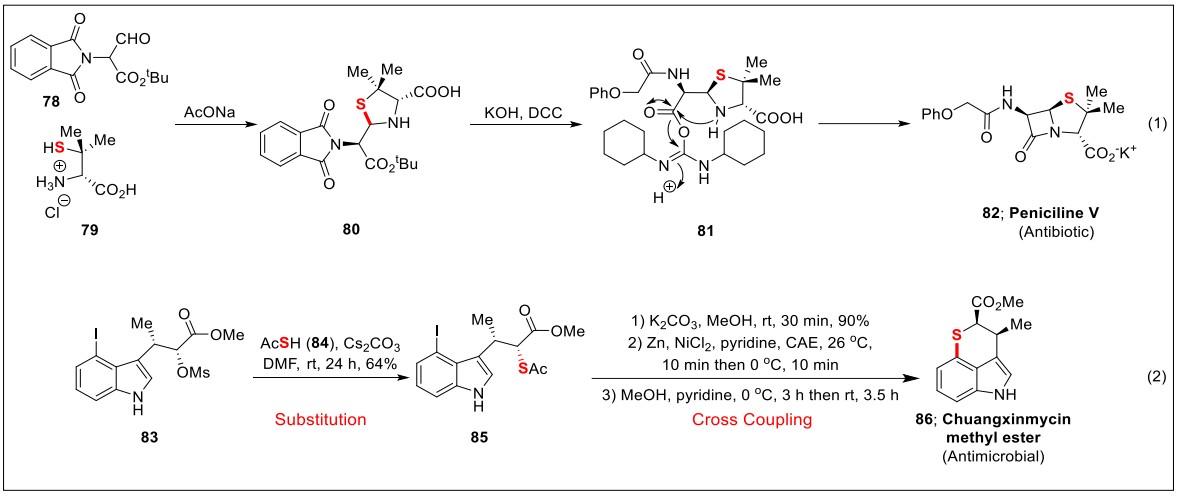
Natural products and pharmaceuticals having sulfur-containing building blocks are interesting chemical entities with a huge structural diversity, and most of them have carbon-sulfur bonds. C−S bond occupies a very prominent position in orthodox synthetic organic chemistry and it is ubiquitous in a broad spectrum of molecules with significant biological and pharmaceuticals

properties. Thus, the synthesis of sulfur-containing bioactive natural products and pharmaceuticals inevitably requires to make carbon-sulfur bonds. In this regard, the following section describes the importance of C−S bond formation in synthesizing some bioactive natural products and pharmaceuticals.

1.6.1. Bioactive Natural Products:

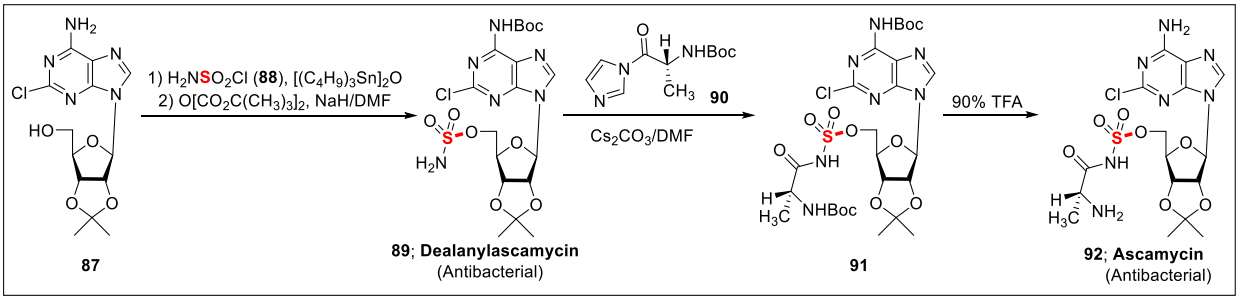
Organosulfur compounds having *β*-lactam moiety is a class of compounds, which have received so much attention for their unique antibacterial activity, and the discovery of this antibiotic was a turning point in modern medicine for the antibiotic revolution. In 1929, Scottish physician Alexander Fleming first discovered the Penicillin antibiotic, isolated from *Penicillium* mold by Chain, Florey and coworkers. In 1957, Sheehan group first developed the efficient synthetic route for the total synthesis of Penicillin V.[17] The synthesis of Penicillin V was initiated by the formation of thiazolium ring, which was obtained by the condensation reaction of D-penicillamine **78** with the derivative of cysteine **79**. Further, the *β*-lactam ring of Penicillin V was obtained using the coupling reagent DCC (Scheme 14, equation 1).[17]Aryl thioether containing Chuangxinmycin natural product was isolated from a soil microorganism *Actinoplanestsinanensis n. sp.* in 1976. It shows potent antibacterial activity and has been used for the prevention of *Escherischia coli* infections in China.[13a] Over the past decades, various synthetic approaches have been reported for synthesizing Chungxinmycin.[59] However, Peng and coworkers recently developed a nickel-catalyzed intramolecular C−S cross-coupling reaction of thiols with aryl iodide **85** and applied as a key step for the synthesis of Chuangxinmycin natural product. The tricyclic thioether building block was constructed from the intermediate **85** by the nickel-catalyzed intramolecular C−S cross-coupling reaction and another C−S bond of the intermediate **85** was obtained by the substitution reaction of intermediate **83** with acylated sulfide **84** (Scheme 14, equation 2).[13a]

Scheme 14. Synthesis of Penicillin V[17] and Chuangxinmycin Methylester[13a]



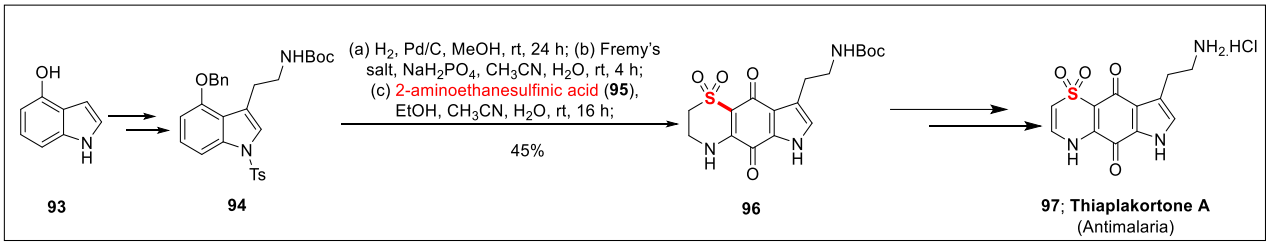
Ascamycin and Dealamylascamycin are two nucleoside antibiotics having 5'-O-sulfonamide ribonucleosides containing organosulfur scaffolds, isolated from the fermentation broth of a *Streptomyces*. Although both the natural products share a common structural skeleton, their bacterial activity is different. Compared to Ascamycin, Dealamylascamycin exhibits a broad spectrum of activity against several gram-positive and gram-negative bacteria. Whereas, Ascamycin shows activity against some bacterial genera, like pathogenic plant species.[60] The synthesis of Ascamycin compound was initiated by the formation of 2-chloroadenosine nucleoside **87**, and then by treating with sulfomyl chloride **88** followed by the Boc protection, Dealamylascamycin **89** was formed. Further, the Ascamycin **92** antibiotic was derived from this Dealamylascamycin antibiotic **89** through the formation of intermediate **91** (Scheme 15).[15]

Scheme 15. Synthesis of Ascamycin and Dealamylascamycin[15]



Thiazine fused quinone containing organosulfur alkaloid Thiaplakortone was isolated in 2013 from the Australian marine sponge *Plakortis lita* and exhibits potent in vitro antimalarial activity.[16a] In the same year, Pouwer *et. al.* first developed a synthetic route for Thiaplakortone alkaloid, and the thiazine fused quinone ring was derived from the intermediate **96** utilizing 2-aminoethanesulfinic acid **95** as a sulfur source. Initially, deprotection of benzyl group followed by the oxidation with Fremy's salt provided quinone derivative, which was further transformed to intermediate **96** by addition/oxidation sequence in the presence of 2-aminoethanesulfinic acid **95** (Scheme 16).[16b]

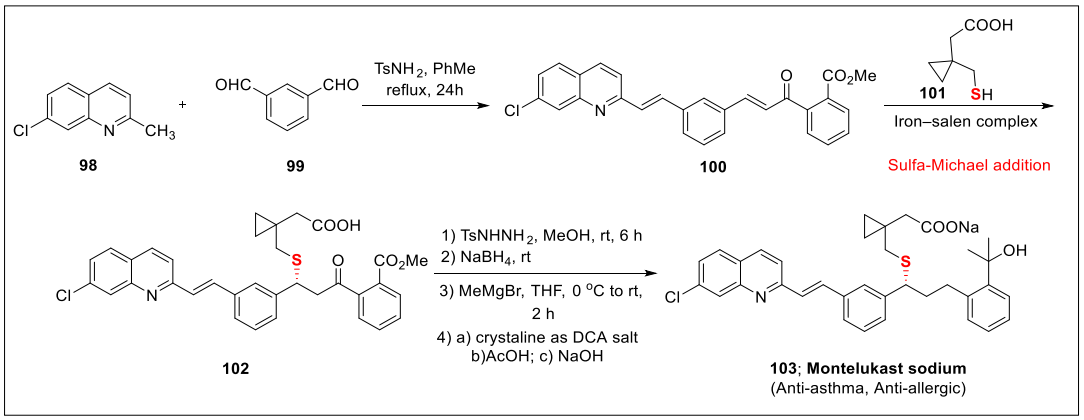
Scheme 16. Synthesis of Thiaplakortone A[16b]



1.6.2. Pharmaceuticals:

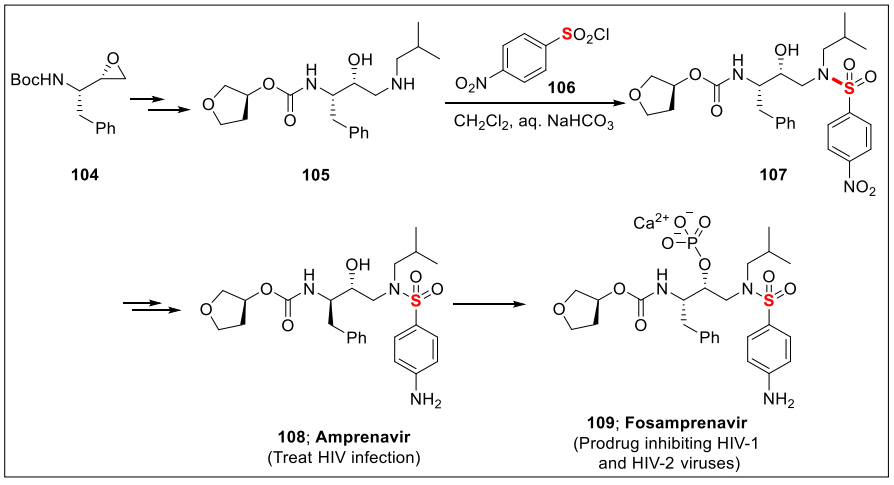
In 1990, Merck Frosst Canada introduced Montelukast sodium as an LTD_4 antagonist. Later, it was approved by FDA in 1998 and commercialized under the marketed name Singulair. It is one of the most prescribed medicines to treat asthma and seasonal allergies. Belley *et. al*. first invented a novel synthetic process for the leukotriene antagonist, Montelukast sodium;[19c] after that, several processes were reported for their synthesis.[19] In 2014, White and co-workers developed a new synthetic strategy for the asymmetric synthesis of Montelukast agent in four steps with 72% overall yield. In this synthetic route, C−S bond formation took place by iron-catalyzed sulfa-Michael addition reaction of thiol intermediate **101** with α, β-unsaturated ketone **100**, which was synthesized from commercially available starting materials **98** and **99** via the one-pot Michael-Aldol condensation reaction (Scheme 17).[19b]

Scheme 17. Synthesis of Montelukast Sodium[19b]



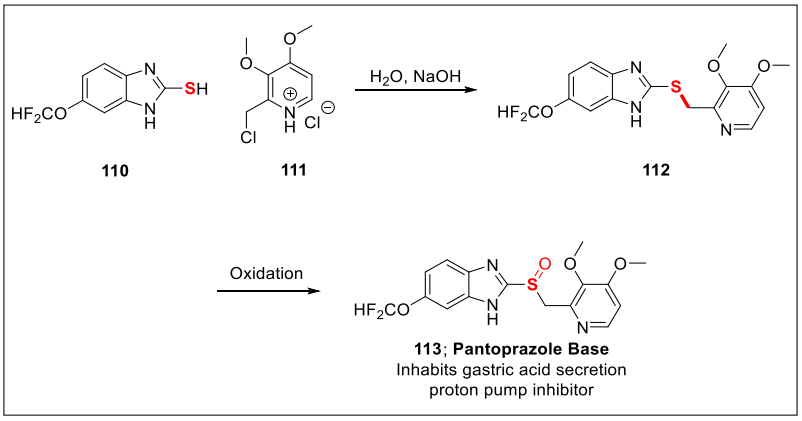
Amprenavir and Fosamprenavir are other organosulfur agents having sulfonamide functionalities, known as an HIV protease inhibitor. Amprenavir was developed by Vertex and GlaxoSmithKline and got FDA approval in 1999. In 2003, Fosamprenavir was also launched by GlaxoSmithKline as a prodrug of Amprenavir with more therapeutic efficiency. Sulfonamide moiety of Amprenavir was constructed from the intermediate **105** using sulfonylchloride **106** as a source of sulfur and the intermediate **107** obtained, which is further converted to Amprenavir drug **108** followed by the Fosemprenavir **109** (Scheme 18).[22] Over the past decades, its synthesis has also been published by several approaches and in most cases, sulfonyl chloride is used as a sulfur source.[61]

Scheme 18. Synthesis of Amprenavir and Fosamprenavir [22]



The sulfoxide-containing organosulfur drug Pantoprazole is a pharmaceutically active agent with an effective anti-ulcer activity. It is a proton pump inhibitor and used to treat gastr-oesophageal reflux disorder. The synthetic process of Pantoprazole was first disclosed in 1985 by Byk Gulden (a subsidiary of Altana). They described the synthesis of Pantoprazole by the substitution reaction of intermediate **111** with 5-difluoromethoxy-2-mercaptobenzimidazole **110** (source of sulfur) followed by the oxidation of thioether **112** (Scheme 19).[21c] After that, plentiful methods have been developed for the selective oxidation of thioether to afford the sulfoxide moiety of Pantoprazole by avoiding the formation of impurities.[21]

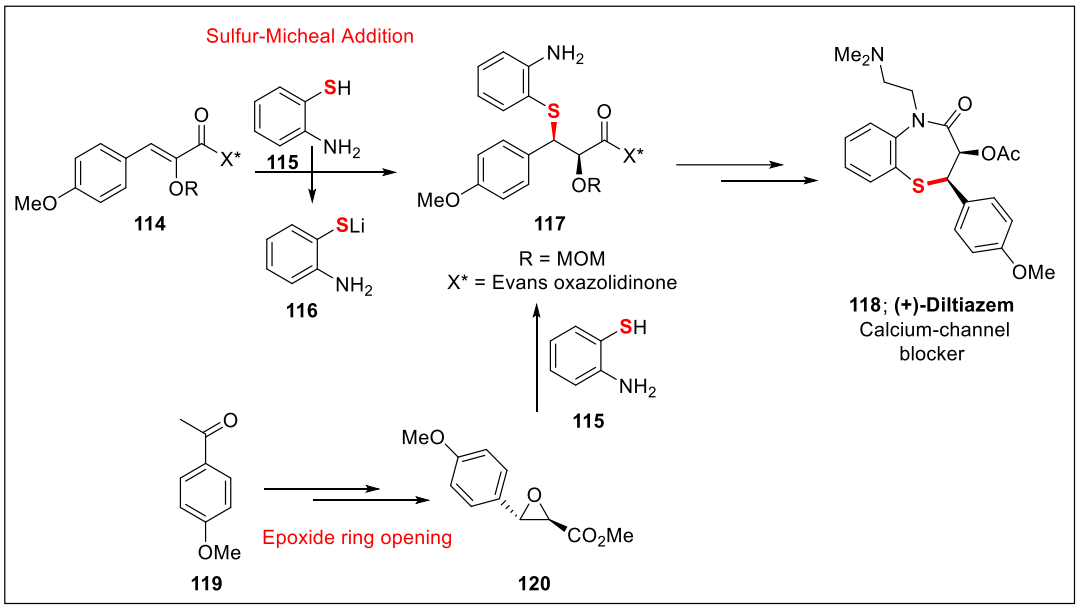
Scheme 19. Synthesis of Pantoprazole Base[21c]



Diltiazem hydrochloride, a derivative of benzothiazepin, is mainly used for the prevention of high blood pressure, coronary vasodilating activity, angina and heart arrhythmias. In 1974, Tanabe Seiyaku Co. Ltd first introduced Diltiazem hydrochloride as a useful calcium channel blocker. It contains two stereogenic centers and among the four diastereomers, only (+) -(2*S*, 3*S*)-isomer shows potent pharmaceutical activity.[23] Therefore, asymmetric synthesis of Diltiazem hydrochloride has always been in a superior position of investigation. Till date, a huge number of synthetic routes have been reported to improve the enantiomeric purity and overall yield.[23] In those synthetic approaches, C−S bond is generally constructed by the asymmetric sulfa Michael addition reaction[23d] or epoxide ring opening reaction[23c] utilizing 2-amino thiophenolate **115** as a sulfur

source. After that, benzothiazepine ring was formed by the intramolecular amide bond formation (Scheme 20).[23]

Scheme 20. Synthesis of (+) Diltiazem[23]



1.7. Conclusion:

The inherent properties and diverse oxidation states of sulfur allow it to play a significant role in a wide range of bioactive natural products and pharmaceuticals. Organosulfur compounds are also distributed all over the natural kingdoms and profusely found in marine organisms, which is one of the prominent source for novel drug discovery. Almost 1000 sulfur natural products have been extracted from both marine and terrestrial organism. Sulfur-containing pharmaceuticals have also opened a new era in the modern medicinal field. Nearly, 150 FDA-approved pharmaceutical drugs containing sulfur moiety are known. Therefore, developing new synthetic routes and methods for sulfur-containing novel scaffolds, bioactive natural products, and pharmaceuticals is an attractive subject of all-time interest to mordern synthetic organic chemists. This has encouraged us to advance our studies in developing novel methods for sulfur-containing scaffolds and their application in the synthesis of bioactive natural products and drugs.

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Chapter 2

Novel Methods for the Construction of Organosulfur Scaffolds

Novel Methods for the Construction of Organosulfur Scaffolds

2.1. Introduction:

Organosulfur compounds display a broad range of pharmaceutical applications and diverse biological activity.[1] For a century, sulfur-containing organic compounds have maintained their status as a new chemical entity in drug discovery[2] and widely-spread in bioactive natural products.[3] To date, nearly 1000 natural products and 150 FDA-approved pharmaceutical drugs containing organosulfur moiety are known.[4] Due to the divers oxidation state of the sulfur elements, a variety of sulfur-containing scaffolds like sulfone, sulfide, sulfonamide, trifluoromethylthio, beta-lactam etc., are well investigated both in the synthetic and application fields.[5] Therefore, developing novel methods for the construction of crucial sulfur-containing building blocks is an attractive topic in medicinal and synthetic organic chemistry. A literature survey reveals that plentiful methods have been discovered to construct sulfur-containing building blocks. The most conventional approaches are the direct bond formation of sulfur atom with other heteroatoms, which is formed either by the classical methods (like addition, substitution, ring opening etc.)[6] or by the C−H functionalization via a traditional cross-coupling or decarboxylation reaction.[7] Different types of thionating reagents or sulfinate salts are also used to incorporate sulfur atom into the bioactive organic molecules.[8] In this regard, we have developed two different methodologies for the construction of organosulfur compounds, which is discussed in detail in this chapter. This chapter is divided into two sections,

Section I: Transition-Metal-Free Regioselective One-Pot Synthesis of Aryl Sulfones from Sodium Sulfinates via Quinone Imine Ketal.

Section II: Construction of Unique SCF_3-Containing Building Blocks via Allylic Alkylation of Morita-Baylis-Hillman Adducts.

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Chapter 2

Section I

Transition-Metal-Free Regioselective One-Pot Synthesis of Aryl Sulfones from Sodium Sulfinates via Quinone Imine Ketal

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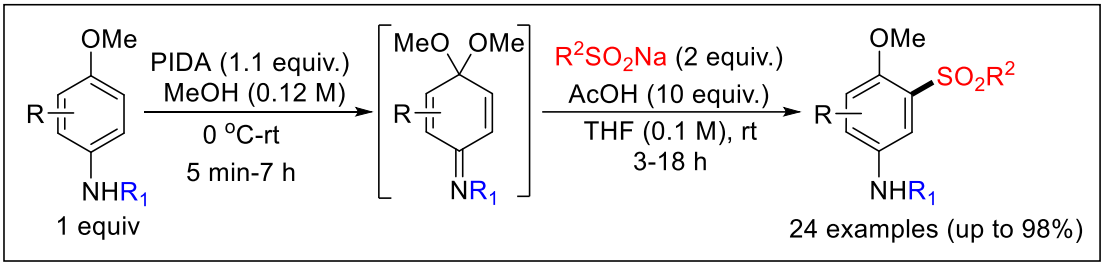
Section I: Transition-Metal-Free Regioselective One-Pot Synthesis of Aryl Sulfones from Sodium Sulfinates via Quinone Imine Ketal

2.1.1. Abstract:

This section deals with the synthesis of organosulfone compounds by the C−S bond formation. A novel, efficient, and regioselective transition-metal-free one-pot synthesis of aryl sulfones via the reactive quinone imine ketal intermediate is demonstrated using easily accessible bench-stable sulfinate salts. A broad range of functionality on *p*-anisidine substrates as well as sulfinate salts was tolerated under mild reaction conditions to provide the corresponding aryl sulfones in good to excellent yields.



2.1.2. Introduction:

Organosulfones are recognized as privileged functional groups having an immense application in agrochemicals,[1] pharmaceuticals[2] and material chemistry.[3] Among them, aryl sulfones are known to be antifungal,[4] antibacterial[5] and anti-tumoral[6] agents as well as the inhibitors of HIV-1 reverse transcriptase.[7] Figure 1 shows selected biologically active molecules featuring aryl sulfone pharmacophore.[1,2,7] In addition to their medicinal importance, aryl sulfones are also versatile reactive intermediates in organic synthesis and used in well-known organic transformations such as the Ramberg−Backlund reaction and the Julia olefination.[8] In the past decades, tremendous efforts have been devoted to the development of novel methodologies for the incorporation of sulfone-containing substituents into organic frameworks.[9] Due to their

compelling synthetic utility[8] and substantial biological[1,2,4-7] as well as material applications,[3] the development of facile methods for aryl sulfones has stimulated considerable interest.

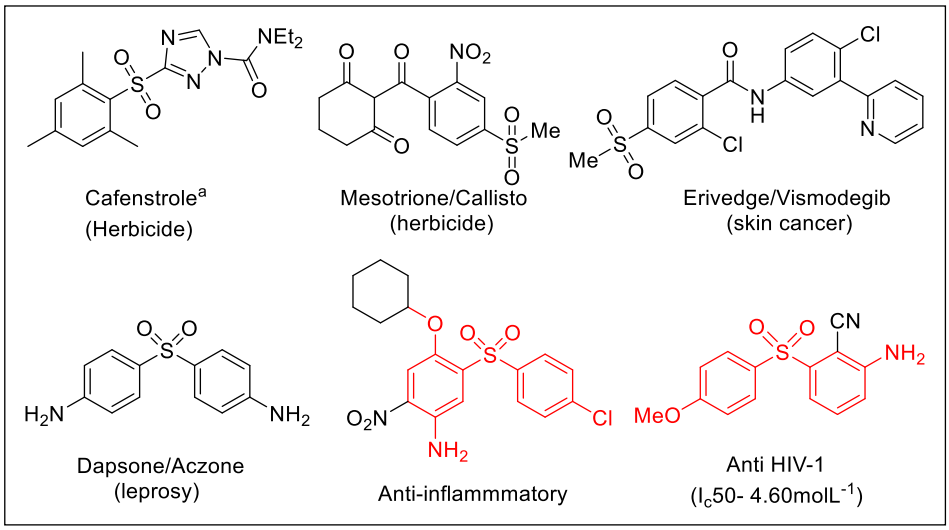


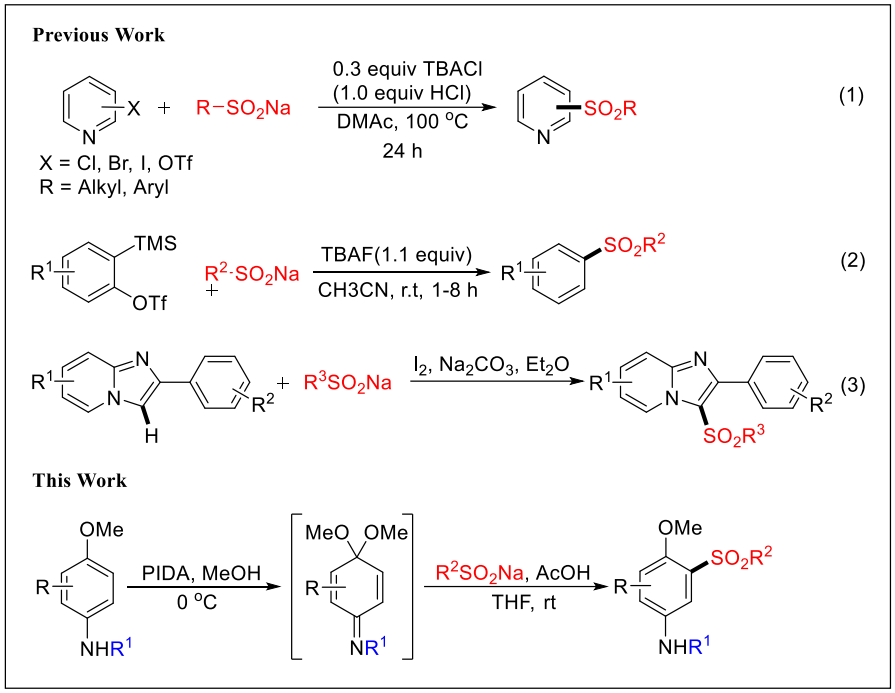
Figure 1. Bioactive compounds containing sulfone

2.1.3. Literature Review:

The most common method utilizes the reaction of pre-functionalized aromatic/heteroaromatic halides and sulfinate salts in the presence of a transition-metal catalyst.[9c,g,i] Recently, Peddinti *et al* reported catalyst-free sulfonylation of 2-methoxyphenols via masked *o*-benzoquinone using sulfonyl hydrazides at 70 °C.[9f] Zeng *et al* developed electrochemical oxidation of aminophenols in the presence of benzenesulfinate.[9j] Previously, Kolesnikov and co-workers reported sulfonylation of *N*-(arylthio)-1,4-benzoquinonimines with benzenesulfininate to obtain various aryl sulfones.[9k] In 2011, Maloney and co-workers developed the transition-metal-free sulfonylation of pyridines using sulfinate salts (Scheme 1, eq. 1).[10] In 2014, we reported the method for the synthesis of aryl sulfones using in situ generated arynes (eq. 2).[11] Very recently, Shao and co-workers reported the difunctionalization of imidazo[1,2-a]-pyridine to access sulfones using sulfinate salts (eq. 3).[12] In addition to these advancements few other transition-

metal free methods using sodium sulfinate salts had been developed for the synthesis of organosulfones,[13] but to the best of our knowledge quinone imine ketal (QIK) has not been utilized for the synthesis of aryl sulfones.

Scheme 1. Selected Transition-Metal-Free approaches to Aryl Sulfones using Sodium Sulfinates



2.1.4. Origin of the Work:

QIK has emerged as the powerful synthetic intermediate for the development of novel methodologies[14] and total synthesis of natural products.[15] Their remarkable electrophilicity addresses a variety of organic transformation such as cycloaddition reaction,[14h] nucleophilic addition reaction,[14a,b,d-g] multicomponent reaction,[14c] among others. We hypothesized that the QIK formed *in situ* in the reaction mixture could be utilized as a latent sulfone functionalized aromatic ring employing acid-mediated activation. This design will ultimately enrich the chemistry of quinone-related compounds. Herein, we report the mild and efficient protocol for the synthesis of aryl sulfones utilizing QIK as a potent intermediate.

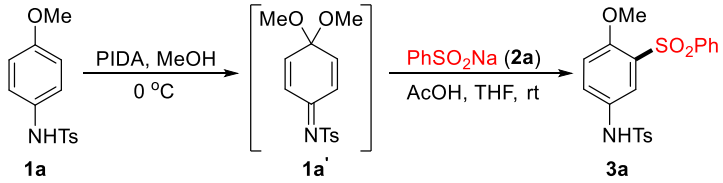
2.1.5. Objective of the Work:

Due to the extensive application of organosulfone compounds, we envisioned that the various types of organosulfone compounds could be possible to synthesize by using easily accessible bench-stable sodium sulfinate salts.[9-13] In the recent years, sulfinate salts have acknowledged as a privileged building block for the construction of various type of sulfur-containing compounds[16] and used to incorporate SO_2 group into the different bioactive organic molecules.[17] Inspired from those methods we have also used several sodium sulfinate salts for the synthesis of various organosulfone compounds via the insitu formation of QIK from commercially available *p*-anisidine substrates.

2.1.6. Result and Discussion:

The optimization of the protocol was achieved by changing various reaction parameters. Initially, *N*-tosyl QIK **1a'** generated *in situ* from *N*-tosyl *p*-anisidine (**1a**) in methanol was treated with sulfinate salt (1.1 equiv) and AcOH (10 equiv) at rt. The expected product **3a** was obtained in 32% yield in 12 h (Table 1, entry 1). To our delight, the yield improved substantially and the reaction time also reduced to 6 h when THF was used as the solvent for the second step (entry 2).

Table 1. Optimization of Reaction Condition[a]



Sr. No.	*solvent*[b]	*AcOH (equiv)*	***2a*** *(equiv)*	*time (h)*	*yield (%)*[c]
1	MeOH	10	1.1	12	32
2	THF	10	1.1	06	83

3	THF	01	1.1	12	52
4	THF	02	1.1	12	55
5	THF	08	1.1	12	60
6	THF	15	1.1	06	50
7	THF	20	1.1	06	48
8	THF	10	2.0	03	84
9[d]	THF	10	1.5	06	90
10[d]	THF	10	2.0	03	97

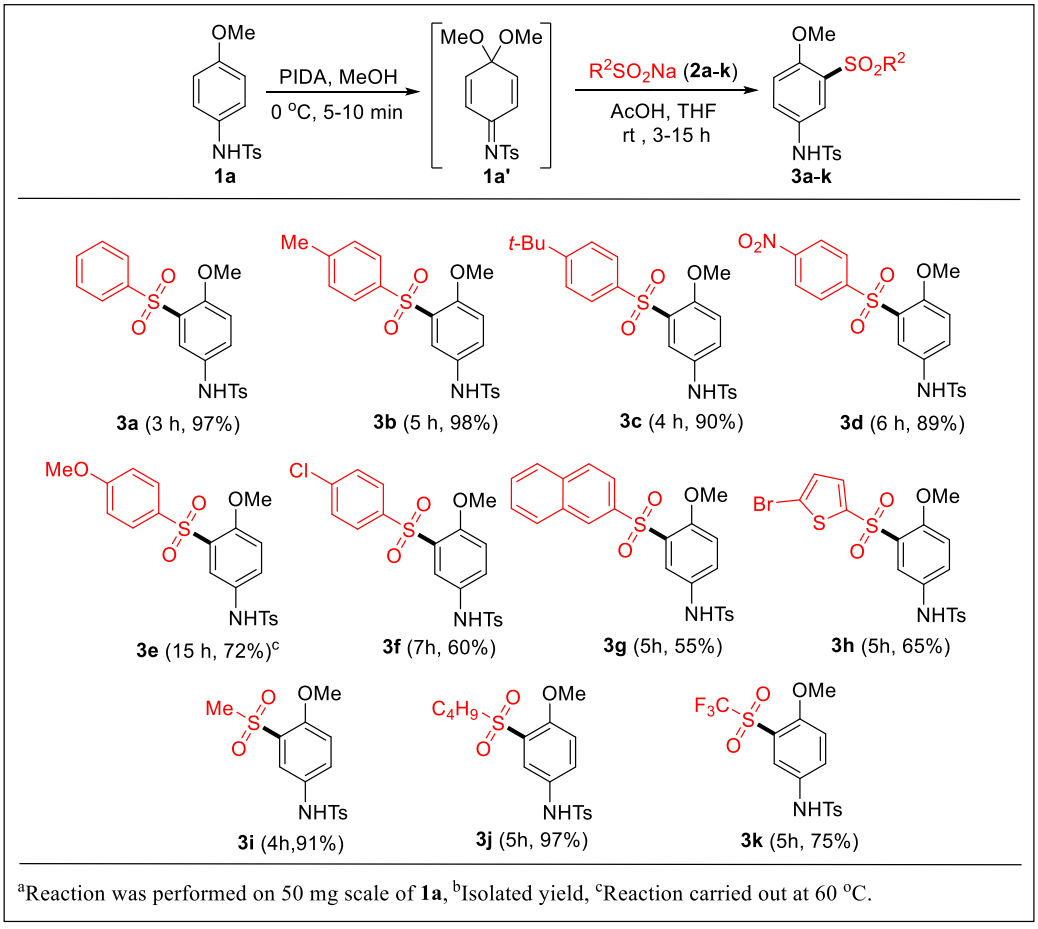
[a]All the reactions were performed on 20 mg scale of **1a**, [b]Solvent for the second step, [c]Isolated yield, [d]Acetic acid was added after 1 h to the reaction mixture containing sulfinate salt.

The addition of less or more equivalents of AcOH resulted into low yields (entries 3-7). For further improvement in the yield, more equivalents of sulfinate salt was used, however, the yield did not improve (entry 8). Hence, the addition sequence of the second step was modified. The solution of QIK **1a'** and sulfinate salt **2a** in THF was stirred for 1 h followed by the addition of acetic acid, which resulted in the enhancement of the yield (entry 9). When 2 equiv of **2a** was used, the desired product **3a** was obtained in excellent yield (entry 10).

With the optimized reaction condition (Table 1, entry 10) in hand, we investigated the substrate scope of this newly developed protocol by reacting different sulfinate salts **2a**-**k** with **1a** (Scheme 2). The optimized condition worked well for a variety of aryl, alkyl and heteroaryl sulfinate salts. Unsubstituted as well as alkyl substituted aryl sulfone moiety-containing compounds **3a**, **3b**, and **3c** were formed in excellent yields. The aryl sulfinate containing an electron withdrawing substituent furnished the corresponding sulfone **3d** in excellent yield under the optimized condition. On the other hand, probably due to the electron releasing effect of the methoxy group, aryl sulfinate **2e** needed little extra time and temperature than anticipated to obtain the product **3e** in better yield. The halo substituted sulfinate salt showed similar effect on

the reaction and the desired product **3f** was formed in moderate yield. The polyaromatic sulfinate salt reacted well and conceded the product **3g** in moderate yield. The sulfinate salt having the heteroaromatic ring also underwent the reaction smoothly to provide the product **3h** in good yield. Overall, the reaction of sulfinate salts having electron rich aromatic ring (**2e-h**) was slower and provided lower yields as compared to the aryl sulfinate salts having electron neutral/deficient aromatic ring (**2a-d**). Pleasingly, aliphatic sulfinate salts also reacted well under the developed protocol and the corresponding sulfones **3i** and **3j** were synthesized in excellent yields. Trifluoromethyl substituted sulfone **3k** was synthesized in very good yield under these conditions.

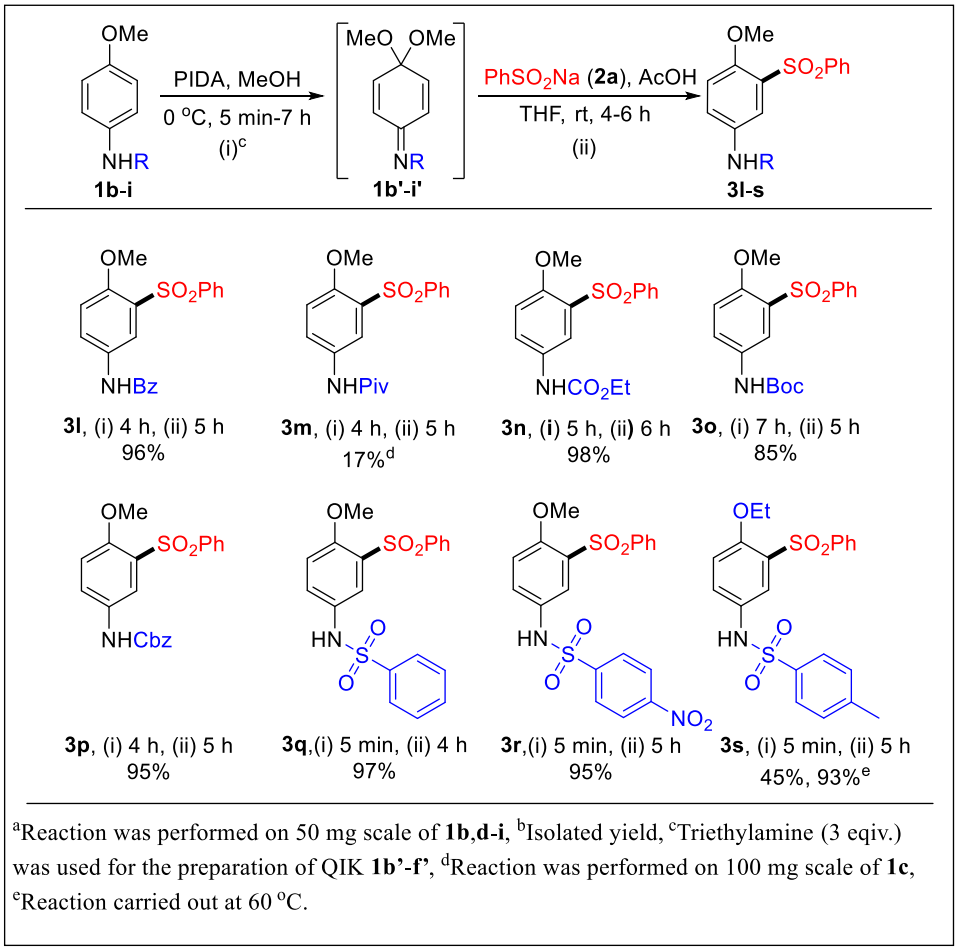
Scheme 2. Synthesis of Sulfones from Various Sodium Sulfinates[a,b]



[a]Reaction was performed on 50 mg scale of **1a**, [b]Isolated yield, [c]Reaction carried out at 60 °C.

After exploring the reactivity pattern of various sulfinate salts, we further planned to explore the scope of the reaction using variously substituted *p*-anisidines (Scheme 3 and 4). Various *N*-substituents, as well as *O*-substituents on *p*-anisidines (**1b-i**) were tested under the developed protocol. The *in situ* formation of QIKs (**1b'-f'**) from the corresponding amide and carbamate containing substrates (**1b-f**) required addition of triethylamine and more time as compared to the sulfonamide containing substrates (**1g-i**).

Scheme 3. Synthesis of Sulfones from Various *N*, *O*-Substituted *p*-Anisidines[a,b]

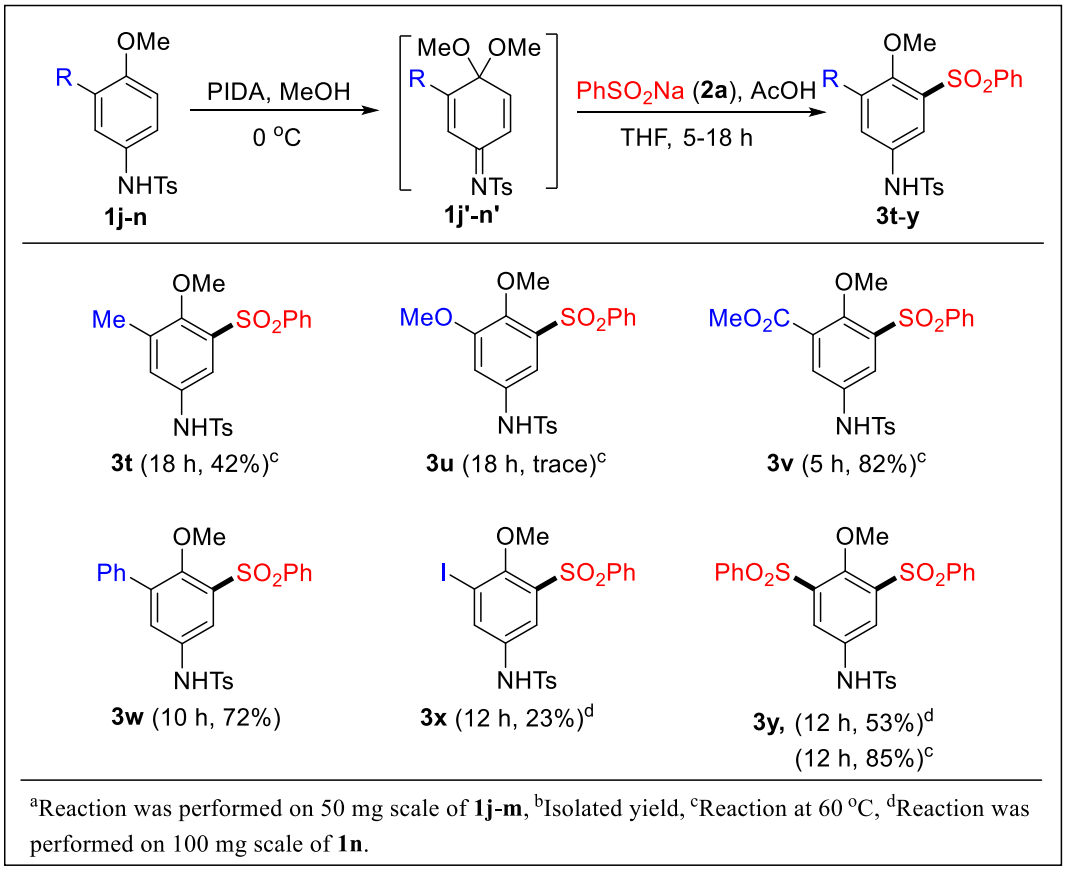


[a]Reaction was performed on 50 mg scale of **1b**,**d-i**, [b]Isolated yield, [c]Triethylamine (3 eqiv.) was used for the preparation of QIK **1b'-f'**, [d]Reaction was performed on 100 mg scale of **1c**, [e]Reaction carried out at 60 °C.

The benzoate protected *p*-anisidine **1b** provided the product **3l** in an excellent yield. Whereas, pivaloyl protected *p*-anisidine **1c** furnished sulfone **3m** in low yield. It can be reasoned that the steric hindrance of the bulkier pivaloyl moiety present in the close proximity of the amide

nitrogen resists the reaction with PIDA. The carbamate group-containing substrates **1d**, **1e**, and **1f** provided the desired products **3n**, **3o,** and **3p** respectively in very good yields. Various sulfonamide containing sulfones **3q** and **3r** were synthesized in excellent yields. The scope of the protocol was also tested using ethoxy substituted sulfonamide substrate **1i** and the expected product **3s** was formed in a moderate yield under the optimized protocol. The steric hindrance of the ethyl group might be inhibiting the nucleophilic attack of the sulfinate salt at rt. However, the yield of **3s** was significantly increased to 93% by elevating the reaction temperature.

Scheme 4. Synthesis of Sulfones using Various Aryl Ring-Substituted *p*-Anisidines[a,b]

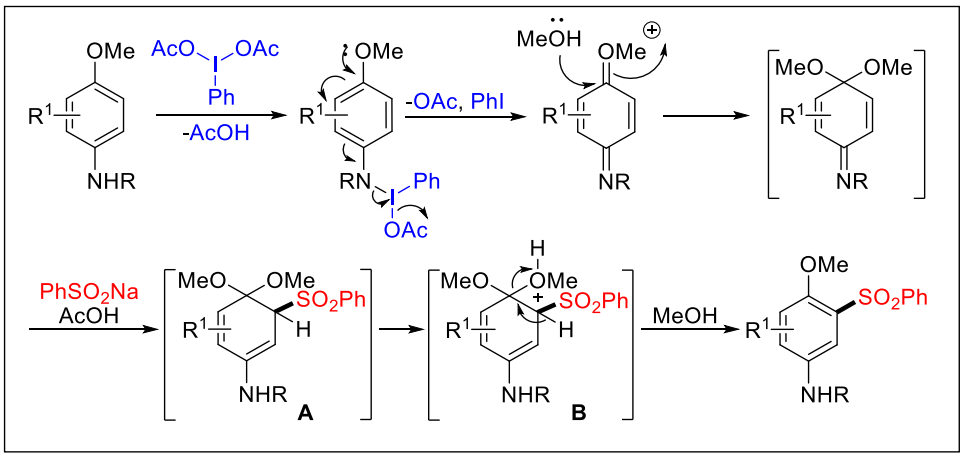


[a]Reaction was performed on 50 mg scale of **1j-m**, [b]Isolated yield, [c]Reaction at 60 °C, [d]Reaction was performed on 100 mg scale of **1n**.

The scope of the reaction using various substituents on the aryl ring of *p*-anisidines was also studied (Scheme 4). It has been observed that higher temperature was necessary for the reaction with methyl substituted *p*-anisidine to obtain the sulfone **3t** in moderate yield.

Unfortunately, electron donating substituents on *p*-anisidine did not afford the sulfone **3u** under the developed protocol. Hence, we isolated the corresponding QIK **1k'** and performed the next reaction, but the product **3u** was formed in only trace amount. We were unable to isolate sufficient quantity of the product **3u** by usual flash column chromatography, but HRMS analysis showed the product formation. Electron withdrawing group on *p*-anisidine moiety was well tolerated and the product **3v** was obtained in very good yield at little higher temperature. The phenyl substituted compound **3w** was formed in a good yield. Interestingly, from the substrate **1n** containing iodine group, two different products **3x** and **3y** were formed under the optimized conditions, but at high temperature exclusively disulfone **3y** was formed in good yield. The product **3y** may be formed by the displacement of iodine group. In general, substituted *p*-anisidines resulted in inferior yields (Scheme 4) than that of the unsubstitued *p*-anisidnes (Scheme 2 and 3) because the reaction leads to more substituted aromatic ring. Furthermore, the presence of electron rich substituents on *p*-anisidines (**1j**, **1k**) provided lower yields (**3t**, **3u**) due to less electrophilic QIK intermediates, whereas *p*-anisidines having electron withdrawing substituents (**1l**, **1m and 1n**) provided better yields (**3v**, **3w** and **3x, y**) because of the more electrophilic QIK intermeidates.

Figure 2. Plausible Reaction Mechanism



The regioselectivity of the interesting protocol was confirmed by the 2D NMR analysis of the substrates **3a**, **3v**, **3x** and **3y**. The scalability of the reaction was also investigated. We performed the reaction of **1a** on 1 mmol scale, and the expected product **3a** was obtained in 88% yield.

A plausible mechanism of the reaction based on the above observations and literature report[18] is depicted in Figure 2. First, the QIK was formed in the presence of PIDA by the usual mechanism.[19] Phenyl sulfinate attacks QIK to form the intermediate **[A]** by Michael addition. The rearomatization occurs by the removal of methanol in the presence of acetic acid to get the desired sulfone product.

2.1.7. Conclusion:

In conclusion, a convenient one-pot transition-metal-free protocol has been developed for the preparation of aryl sulfones regioselectively via the formation of QIKs in good to excellent yields. This developed protocol is operationally simple, high yielding and does not require excess reagent and additives. Various types of sulfones such as diaryl sulfones, aryl-alkyl sulfones, and aryl-heteroaryl sulfones can be prepared easily by following this method. We are in the process of applying this method for the synthesis of bioactive molecules, natural products, drugs, and drug intermediates.

2.1.8. Experimental section:

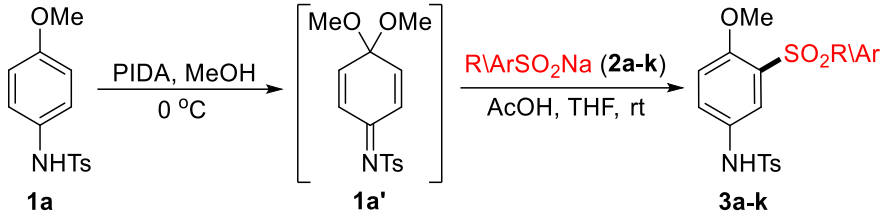
1. Additional Information:

All the *N*-substituted *p*-anisidines were prepared using known literature procedures.[14f, 20] The quinone imine ketals were prepared in situ as per the literature procedures.[14f, 19a] Sodium sulfinates **2a**, **2i** and **2k** were purchased from commercial sources and rest of the sodium sulfinates were prepared using known literature procedures.[13e, 21]

2. Experimental Procedure:

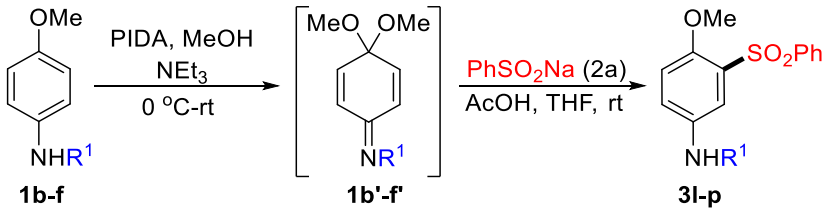
I] General Experimental Procedure for the Synthesis of Sulfones:

A] Synthesis of Sulfones 3a-k:



To a solution of tosylated *p*-anisidine **1a** (50 mg, 1 equiv) in methanol (0.12 M) was added (diacetoxyiodo)benzene (PIDA, 64 mg, 1.1 equiv) at 0 °C. The resulting mixture was stirred at 0 °C and the reaction progress was monitored by TLC (approx. 5 min). After complete consumption of **1a**, MeOH was evaporated on a rotatory evaporator and the residue was dissolved in THF (0.1 M). To this solution was added the corresponding sulfinate salt **2a-k** (2 equiv) and the reaction mixture was stirred for 1 h at room temperature followed by the addition of AcOH (10 equiv). After stirring for 3-15 h at room temperature, THF was evaporated in *vacuo* and the residue was purified by flash silica gel column chromatography using a gradient of ethyl acetate-petroleum ether to afford the corresponding sulfones **3a-k** in good to excellent yields.

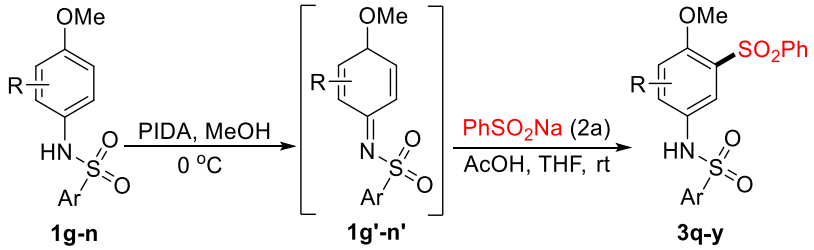
B] Synthesis of Sulfones 3l-p:



To a solution of *N*-substituted *p*-anisidine **1b-f** (50 mg, 1 equiv) and NEt_3 (3 equiv) in MeOH (0.34 M), a solution of PIDA (2 equiv) in MeOH (0.34 M) was added dropwise at 0 °C under an

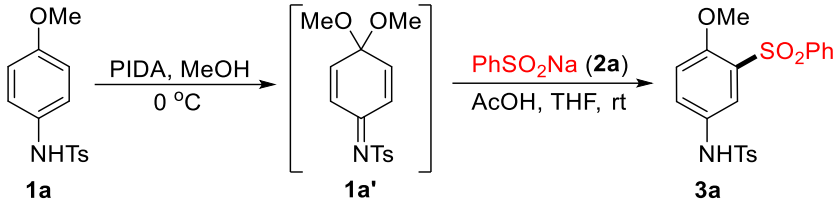
argon atmosphere. The reaction mixture was stirred at 0 °C for 1 h and gradually warmed to rt. After complete consumption of **1b-f**, MeOH was evaporated on a rotatory evaporator and the residue was dissolved in THF (0.1 M). To the resulting solution was added sulfinate salt **2a** (2 equiv) and the reaction mixture was stirred for 1 h at room temperature followed by the addition of AcOH (10 equiv). After being stirred for 4-6 h at room temperature, THF was evaporated on a rotatory evaporator and the residue was purified by flash silica gel column chromatography using a gradient of ethyl acetate-petroleum ether to afford the corresponding sulfones **3l-p** in good to excellent yields.

C] Synthesis of Sulfones 3q-y:



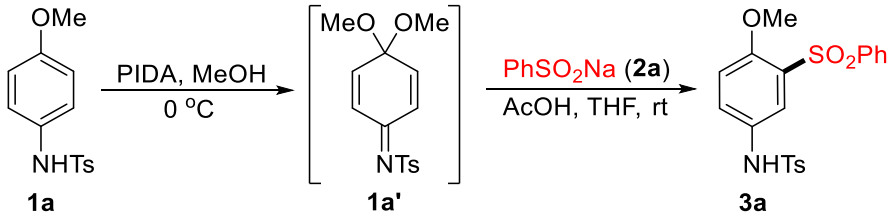
To a solution of *N*-substituted *p*-anisidine **1g-n** (50 mg, 1 equiv) in methanol (0.12 M) was added PIDA (1.1 equiv) at 0 °C. The resulting mixture was stirred at 0 °C and the reaction progress was monitored by TLC (approx. 5 min). After complete consumption of **1g-n**, MeOH was evaporated on a rotatory evaporator and the residue was dissolved in THF (0.1 M). To this solution was added sulfinate salt **2a** (2 equiv) and the reaction mixture was stirred for 1 h at room temperature followed by the addition of AcOH (10 equiv). After stirring for 4-18 h at room temperature, THF was evaporated in *vacuo* and the residue was purified by flash silica gel column chromatography using a gradient of ethyl acetate-petroleum ether to afford the corresponding sulfones **3q-y** in good to excellent yields.

II] Typical Experimental Procedure for the Preparation of 3a on 0.18 mmol Scale:



To a solution of **1a** (50 mg, 1 equiv) in methanol (1.5 mL, 0.12 M) was added PIDA (64 mg, 1.1 equiv) at 0 °C. The resulting mixture was stirred at 0 °C and the reaction progress was monitored by TLC (approx. 5 min). After complete consumption of **1a**, MeOH was evaporated on a rotatory evaporator and the residue was dissolved in THF (1.8 mL, 0.1 M). To this solution was added **2a** (59 mg, 2 equiv) and the reaction mixture was stirred for 1 h at room temperature followed by the addition of AcOH (108 μL, 10 equiv). After stirring for 3 h at room temperature, THF was evaporated in *vacuo* and the residue was purified by flash silica gel column chromatography using a gradient of ethyl acetate-petroleum ether (2:3) to afford the sulfone **3a** in 97% yield (73 mg).

III] Experimental Procedure for the Preparation of 3a on 1 mmol Scale:

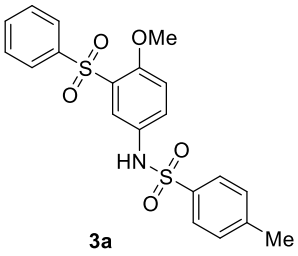


To a solution of **1a** (277 mg, 1 mmol) in methanol (8.3 mL, 0.12 M) was added PIDA (354 mg, 1.1 mmol) at 0 °C. The resulting mixture was stirred at 0 °C and the reaction progress was monitored by TLC (approx. 5 min). After complete consumption of **1a**, MeOH was evaporated on a rotatory evaporator and the residue was dissolved in THF (10 mL, 0.1 M). To this solution was added **2a** (328 mg, 2 mmol) and the reaction mixture was stirred for 1 h at room temperature followed by the addition of AcOH (600 μL, 10 mmol). After stirring for 3 h at room temperature,

THF was evaporated in *vacuo* and the residue was purified by flash silica gel column chromatography using a gradient of ethyl acetate-petroleum ether (2:3) to afford the sulfone **3a** in 88% yield (367 mg).

3. Characterization Data of Compounds:

***N*-(4-Methoxy-3-(phenylsulfonyl)phenyl)-4-methylbenzenesulfonamide (3a)**



3a

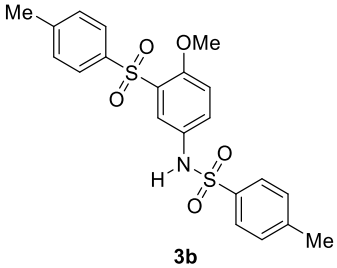
Reaction time: 3 h; R*f*: 0.5 (2:3 EtOAc:Pet. Ether); Off white solid, (73 mg, 97% yield); Mp = 190-192 ^{o}C.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.21 (s, 1H), 7.76-7.66 (m, 4H), 7.59 (d, *J* = 7.9 Hz, 4H), 7.41-7.30 (m, 3H), 7.06 (d, *J* = 9.2 Hz, 1H), 3.64 (s, 3H), 2.37 (s, 3H).

^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 153.6, 143.4, 140.5, 136.0, 133.5, 130.4, 129.7, 129.2, 129.0, 128.2, 127.7, 126.8, 121.9, 114.4, 56.2, 20.9.

HRMS (ESI-TOF) m/z: $[M+Na]^{+}$ calcd for $C_{20}H_{19}NO_5S_2Na$ 440.0597, found 440.0594.

***N*-(4-Methoxy-3-tosylphenyl)-4-methylbenzenesulfonamide (3b)**



3b

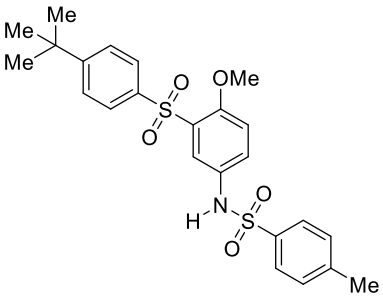
Reaction time: 5 h; R*f*: 0.7 (2:3 EtOAc:Pet. Ether); White solid, (76 mg, 98% yield); Mp = 191-193 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.9 Hz, 2H), 7.63-7.55 (m, 3H), 7.51 (dd, *J* = 8.6 and 2.4 Hz, 1H), 7.31-7.23 (m, 4H), 6.84 (d, *J* = 9.2 Hz, 1H), 6.71 (s, 1H), 3.74 (s, 3H), 2.43 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 144.2 (2C), 137.8, 135.5, 131.0, 129.8, 129.5, 129.2 (2C), 128.5, 127.3, 124.6, 113.4, 56.2, 21.6.

HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{21}H_{21}NO_5S_2Na$ 454.0753, found 454.0751.

***N*-(3-((4-(tert-Butyl)phenyl)sulfonyl)-4-methoxyphenyl)-4-methylbenzenesulfonamide (3c)**



3c

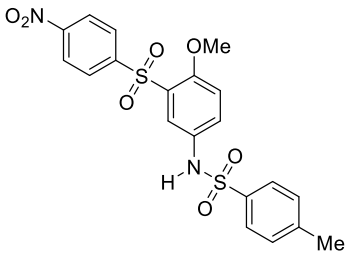
Reaction time: 4 h; R*f*: 0.6 (2:3 EtOAc:Pet. Ether); White solid, (77 mg, 90% yield); Mp = 176-178 ^oC.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.6 Hz, 2H), 7.64-7.57 (m, 3H), 7.53-7.45 (m, 3H), 7.25 (d, *J* = 8.5 Hz, 2H), 6.87 (s, 1H), 6.84 (d, *J* = 9.2 Hz, 1H), 3.76 (s, 3H), 2.42 (s, 3H), 1.33 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 155.0, 144.1, 137.7, 135.5, 130.8, 129.8, 129.4, 129.2, 128.3, 127.3, 125.5, 124.6, 113.4, 56.2, 35.2, 31.0, 21.6.

HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{24}H_{27}NO_5S_2Na$ 496.1223, found 496.1222.

***N*-(4-Methoxy-3-((4-nitrophenyl)sulfonyl)phenyl)-4-methylbenzenesulfonamide (3d)**



3d

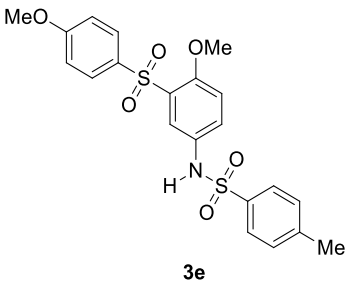
Reaction time: 6 h; R*f*: 0.5 (2:3 EtOAc:Pet. Ether); Pale yellow solid, (74 mg, 89% yield) Mp = 171-173 ^oC.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 6.7 Hz, 2H), 8.05 (d, *J* = 7.3 Hz, 2H), 7.72 (s, 1H), 7.65 (d, *J* = 7.3 Hz, 2H), 7.52 (d, *J* = 8.6 Hz, 1H), 7.28 (d, *J* = 6.1 Hz, 2H), 7.19 (s, 1H), 6.87 (d, *J* = 8.6 Hz, 1H), 3.76 (s, 3H), 2.44 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 150.4, 146.4, 144.4, 135.4, 131.4, 129.8, 129.7 (2C), 127.6, 127.3, 124.4, 123.8, 113.5, 56.3, 21.6.

HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{20}H_{18}N_2O_7S_2Na$ 485.0448, found 485.0445.

***N*-(4-Methoxy-3-((4-methoxyphenyl)sulfonyl)phenyl)-4-methylbenzenesulfonamide (3e)**



3e

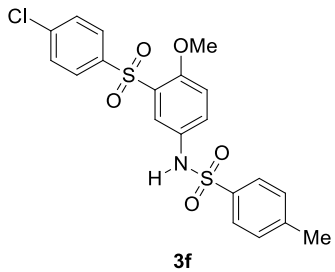
Reaction time: 15 h; R*f*: 0.4 (1:1 EtOAc:Pet. Ether); White solid; (58 mg, 72% yield (at 60 ^oC); Mp = 178-180 ^oC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.5 Hz, 2H), 7.64-7.56 (m, 3H), 7.50 (dd, *J* = 8.5 and 2.4 Hz, 1H), 7.25 (d, *J* = 7.9 Hz, 2H), 6.94 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 1H), 6.75 (s, 1H), 3.87 (s, 3H), 3.76 (s, 3H), 2.43 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.4, 154.9, 144.1, 135.6, 132.3, 130.7 (2C), 129.9, 129.8, 129.2, 127.3, 124.4, 113.7, 113.4, 56.2, 55.6, 21.6.

HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{21}H_{21}NO_6S_2Na$ 470.0702, found 470.0699.

***N*-(3-((4-Chlorophenyl)sulfonyl)-4-methoxyphenyl)-4-methylbenzenesulfonamide (3f)**



3f

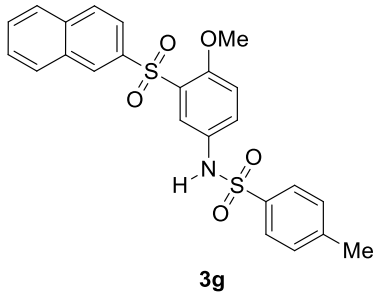
Reaction time: 7 h; R*f*: 0.4 (2:3 EtOAc:Pet. Ether); White solid, (49 mg, 60% yield); Mp = 186-188 ^oC.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.8 Hz, 2H), 7.66-7.61 (m, 3H), 7.54 (dd, *J* = 8.8 and 2.3 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.32-7.25 (m, 2H), 6.90 (s, 1H), 6.87 (d, *J* = 8.8 Hz, 1H), 3.77 (s, 3H), 2.45 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 144.2, 139.9, 139.2, 135.6, 131.1, 129.9, 129.8, 129.4, 128.9, 128.8, 127.3, 124.5, 113.4, 56.2, 21.6.

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{20}H_{19}ClNO_5S_2$ 452.0388, found 452.0383.

***N*-(4-Methoxy-3-(naphthalen-2-ylsulfonyl)phenyl)-4-methylbenzenesulfonamide (3g)**



3g

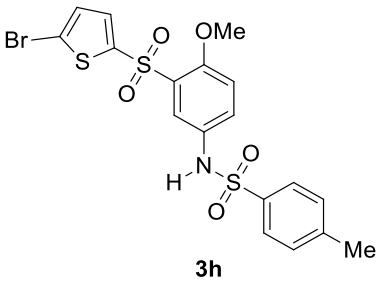
Reaction time: 5 h; R*f*: 0.5 (2:3 EtOAc:Pet. Ether); White solid, (46 mg, 55% yield); Mp = 168-170 ^oC.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 7.99 (d, *J* = 7.9 Hz, 1H), 7.91 (d, *J* = 6.1 Hz, 2H), 7.81-7.74 (m, 2H), 7.71-7.60 (m, 4H), 7.52 (dd, *J* = 9.2 and 3.1 Hz, 1H), 7.27 (t, *J* = 8.2 Hz, 2H), 7.14 (s, 1H), 6.82 (d, *J* = 8.5 Hz, 1H), 3.71 (s, 3H), 2.43 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 144.1, 137.6, 135.5, 135.0, 131.9, 130.8, 130.2, 129.7, 129.4, 129.3, 129.1, 129.0, 128.6, 127.8, 127.4, 127.3, 124.5, 123.2, 113.4, 56.2, 21.6.

HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{24}H_{21}NO_5S_2Na$: 490.0753, found: 490.0751.

***N*-(3-((5-Bromothiophen-2-yl)sulfonyl)-4-methoxyphenyl)-4-methylbenzenesulfonamide (3h)**



3h

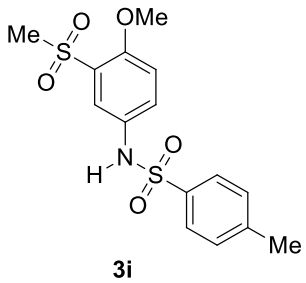
Reaction time: 5 h; R*f*: 0.5 (1:1 EtOAc:Pet. Ether); Off white solid, (59 mg, 65% yield); Mp = 177-179 ^oC.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.51 (m, 4H), 7.46 (s, 1H), 7.26 (d, *J* = 7.9 Hz, 2H), 7.05 (s, 1H), 6.93 (d, *J* = 8.5 Hz, 1H), 6.64 (s, 1H), 3.92 (s, 3H), 2.43 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 144.3, 142.5, 135.4, 134.5, 131.4, 130.2, 129.9, 129.4, 129.1, 127.3, 124.3, 122.0, 113.5, 56.3, 21.6.

HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{18}H_{16}{}^{81}BrNO_5S_3Na$ 525.9246, found 525.9241.

***N*-(4-Methoxy-3-(methylsulfonyl)phenyl)-4-methylbenzenesulfonamide (3i)**



3i

Reaction time: 4 h; R*f*: 0.5 (1:1 EtOAc:Pet. Ether); White solid, (58 mg, 91% yield); Mp = 206-208 ^oC.

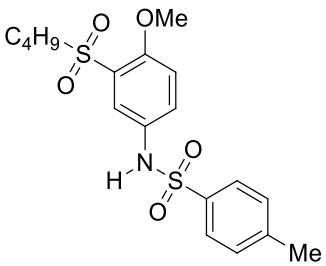
^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.24 (s, 1H), 7.59 (d, *J* = 7.9 Hz, 2H), 7.54 (d, *J* = 2.4 Hz, 1H), 7.37-7.32 (m, 3H), 7.19 (d, *J* = 8.5 Hz, 1H), 3.86 (s, 3H), 3.18 (s, 3H), 2.33 (s, 3H).

^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 153.6, 143.4, 136.2, 130.4, 129.8, 128.5, 128.0, 126.7, 121.3, 114.1, 56.5, 42.5, 21.0.

HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{15}H_{17}NO_5S_2Na$ 378.0440, found 378.0439.

***N*-(3-(Butylsulfonyl)-4-methoxyphenyl)-4-methylbenzenesulfonamide (3j)**

Reaction time: 5 h; R*f*: 0.5 (2:3 EtOAc:Pet. Ether); White solid, (69 mg, 97% yield); Mp = 134-136 ^oC.



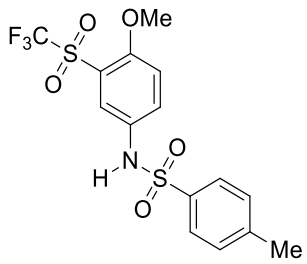
3j

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65-7.57 (m, 3H), 7.43 (d, *J* = 3.1 Hz, 1H), 7.22 (d, *J* = 7.9 Hz, 2H), 7.03 (s, 1H), 6.98 (d, *J* = 8.5 Hz, 1H), 3.94 (s, 3H), 3.29 (t, *J* = 7.9 Hz, 2H), 2.38 (s, 3H), 1.58-1.48 (m, 2H), 1.41-1.33 (m, 2H), 0.88 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 144.1, 135.6, 130.3, 129.8, 129.7, 127.3, 127.0, 124.8, 113.3, 56.6, 53.9, 24.4, 21.5, 21.4, 13.5.

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{18}H_{24}NO_5S_2$ 398.1090, found 398.1085.

***N*-(4-Methoxy-3-((trifluoromethyl)sulfonyl)phenyl)-4-methylbenzenesulfonamide (3k)**



3k

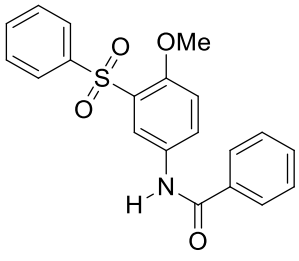
Reaction time: 5 h; R*f*: 0.5 (2:3 EtOAc:Pet. Ether); white solid, (55 mg, 75% yield); Mp = 112-114 ^oC.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 7.87 (d, *J* = 9.8 Hz, 1H), 7.75 (d, *J* = 8.3 Hz, 2H), 7.28 (m, 4H), 3.81 (s, 3H), 2.40 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 144.8, 135.6, 133.1, 129.9, 127.4, 125.6, 122.3, 119.6 (q, *J* = 326.0 Hz, CF_3), 117.4, 115.7, 56.0, 21.6.

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{15}H_{15}F_3NO_5S_2$ 410.0338, found 410.0334.

***N*-(4-Methoxy-3-(phenylsulfonyl)phenyl)benzamide (3l)**



3l

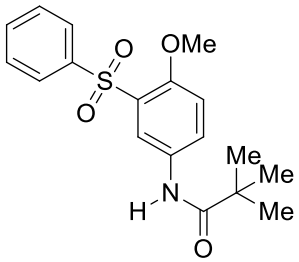
Reaction time: 5 h; R*f*: 0.5 (2:3 EtOAc:Pet. Ether); White solid, (78 mg, 96% yield); Mp = 176-178 ^oC.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 8.37 (dd, *J* = 8.5 and 1.8 Hz, 1H), 8.26 (d, *J* = 2.4 Hz, 1H), 7.94 (d, *J* = 7.9 Hz, 2H), 7.87 (d, *J* = 7.3 Hz, 2H), 7.56 (t, *J* = 7.3 Hz, 1H), 7.50-7.40 (m, 3H), 7.31 (t, *J* = 7.6 Hz, 2H), 6.91 (d, *J* = 9.2 Hz, 1H), 3.72 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (one aromatic carbon overlaps): 166.1, 153.4, 140.9, 134.2, 133.1, 131.8, 131.7, 128.5, 128.5, 128.4, 128.3, 127.2, 121.7, 113.2, 56.2.

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{20}H_{18}NO_4S$ 368.0951, found 368.0946.

N-(4-Methoxy-3-(phenylsulfonyl)phenyl)pivalamide (3m)



3m

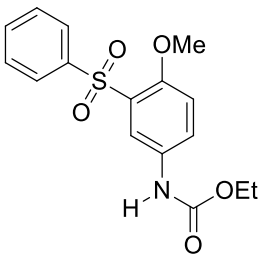
Reaction time: 5 h; R*f*: 0.6 (2:3 EtOAc:Pet. Ether); White solid, (28 mg, 17% yield); Mp = 129-131 ^oC.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (dd, J = 8.3 and 2.3 Hz, 1H), 8.00 (d, J = 2.3 Hz, 1H), 7.96 (d, J = 7.5 Hz, 2H), 7.65 (s, 1H), 7.57 (t, J = 7.5 Hz, 1H), 7.48 (t, J = 7.5 Hz, 2H), 6.87 (d, J = 9.0 Hz, 1H), 3.72 (s, 3H), 1.30 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 153.5, 141.1, 133.1, 131.4, 128.6, 128.5, 128.3, 128.2, 121.7, 113.2, 56.2, 39.5, 27.5.

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{18}H_{22}NO_4S$ 348.1264, found 348.1260.

Ethyl (4-methoxy-3-(phenylsulfonyl)phenyl)carbamate (3n)



3n

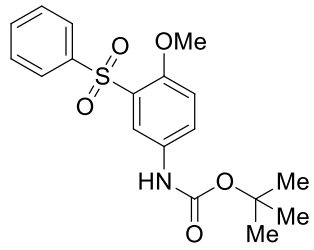
Reaction time: 6 h; R*f*: 0.4 (2:3 EtOAc:Pet. Ether); White solid, (84 mg, 98% yield); Mp = 141-143 ^oC.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98-7.95 (m, 3H), 7.84 (bs, 1H), 7.60-7.55 (m, 1H), 7.51-7.45 (m, 2H), 6.93 (s, 1H), 6.87 (d, J = 9.2 Hz, 1H), 4.22 (q, J = 7.6 Hz, 2H), 3.72 (s, 3H), 1.29 (t, J = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 153.0, 141.1, 133.0, 131.3, 128.9, 128.5, 128.4, 126.4, 120.5, 113.4, 61.4, 56.2, 14.5.

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{16}H_{18}NO_5S$ 336.0900, found 336.0897.

***tert*-Butyl (4-methoxy-3-(phenylsulfonyl)phenyl)carbamate (3o)**



3o

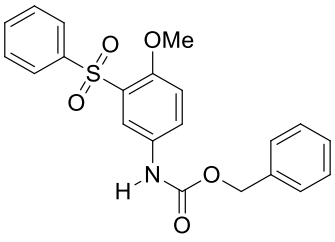
Reaction time: 5 h; R*f*: 0.6 (2:3 EtOAc:Pet. Ether); White solid, (69 mg, 85% yield); Mp = 182-184 ^oC.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 7.3 Hz, 3H), 7.81 (bs, 1H), 7.57 (t, J = 7.3 Hz, 1H), 7.48 (t, J = 7.6 Hz, 2H), 6.85 (d, J = 8.5 Hz, 1H), 6.74 (s, 1H), 3.71 (s, 3H), 1.51 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 152.8, 141.3, 133.0, 131.8, 129.1, 128.5, 128.4, 126.2, 120.5, 113.4, 80.9, 56.2, 28.3.

HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{18}H_{21}NO_5SNa$ 386.1033, found 386.1031.

Benzyl (4-methoxy-3-(phenylsulfonyl)phenyl)carbamate (3p)



3p

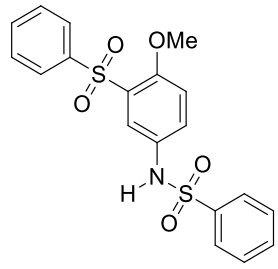
Reaction time: 5 h; R*f*: 0.6 (2:3 EtOAc:Pet. Ether); White solid, (73 mg, 95% yield); Mp = 170-172 ^oC.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00-7.91 (m, 3H), 7.85 (bs, 1H), 7.57 (t, J = 7.3 Hz, 1H), 7.47 (t, J = 8.0 Hz, 2H), 7.41-7.29 (m, 5H), 7.00 (s, 1H), 6.86 (d, 9.2 Hz, 1H), 5.20 (s, 2H), 3.72 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 153.1, 141.0, 135.9, 133.0, 131.1, 129.0, 128.6, 128.5, 128.4, 128.3, 128.2, 126.4, 120.6, 113.4, 67.1, 56.2.

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{21}H_{20}NO_5S$ 398.1057, found 398.1053.

***N*-(4-Methoxy-3-(phenylsulfonyl)phenyl)benzenesulfonamide (3q)**



3q

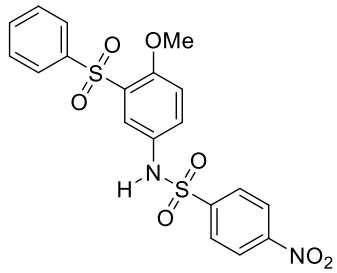
Reaction time: 4 h; R*f*: 0.5 (2:3 EtOAc:Pet. Ether); White solid, (74 mg, 97% yield); Mp = 173-175 ^oC.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.28 (s, 1H), 7.72-7.62 (m, 7H), 7.61-7.52 (m, 4H), 7.35 (dd, *J* = 8.5 and 1.8 Hz, 1H), 7.06 (d, *J* = 9.2 Hz, 1H), 3.64 (s, 3H).

^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 153.8, 140.5, 138.8, 133.6, 133.1, 130.2, 129.6, 129.3, 129.0, 128.3, 127.8, 126.8, 122.3, 114.4, 56.2.

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{19}H_{18}NO_5S_2$ 404.0621, found 404.0616.

***N*-(4-Methoxy-3-(phenylsulfonyl)phenyl)-4-nitrobenzenesulfonamide (3r)**



3r

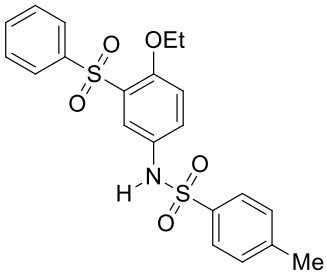
Reaction time: 5 h; R*f*: 0.5 (1:1 EtOAc:Pet. Ether); Pale yellow solid, (69 mg, 95% yield); Mp = 183-185 ^oC.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.64 (s, 1H), 8.41 (d, *J* = 9.2 Hz, 2H), 7.95 (d, *J* = 8.4 Hz, 2H), 7.75 (d, *J* = 6.9 Hz, 2H), 7.72-7.63 (m, 2H), 7.56 (t, *J* = 7.6 Hz, 2H), 7.37 (dd, *J* = 9.2 and 3.1 Hz, 1H), 7.10 (d, *J* = 9.2 Hz, 1H), 3.66 (s, 3H).

^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 154.2, 150.0, 144.2, 140.4, 133.7, 130.0, 129.4, 129.0, 128.5, 128.4, 127.9, 124.7, 122.7, 114.6, 56.3.

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{19}H_{17}N_2O_7S_2$ 449.0472, found 449.0466.

***N*-(4-Ethoxy-3-(phenylsulfonyl)phenyl)-4-methylbenzenesulfonamide (3s)**



3s

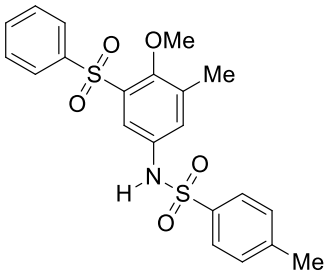
Reaction time: 5 h; R*f*: 0.5 (2:3 EtOAc:Pet. Ether); White solid, [33 mg, 45% yield (at rt); 69 mg, 93% yield (at 60 ^oC)]; Mp = 168-170 ^oC.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.3 Hz, 2H), 7.66-7.56 (m, 4H), 7.53-7.43 (m, 3H), 7.25 (d, *J* = 7.9 Hz, 2H), 6.94 (s, 1H), 6.80 (d, *J* = 9.2 Hz, 1H), 3.94 (q, *J* = 7.3 Hz, 2H), 2.42 (s, 3H), 1.28 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 144.1, 140.8, 135.5, 133.1, 131.1, 129.7, 129.0, 128.8, 128.6, 128.4, 127.3, 124.6, 113.9, 65.0, 21.6, 14.2.

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{21}H_{22}NO_5S_2$ 432.0934, found 432.0928.

***N*-(4-Methoxy-3-methyl-5-(phenylsulfonyl)phenyl)-4-methylbenzenesulfonamide (3t)**



3t

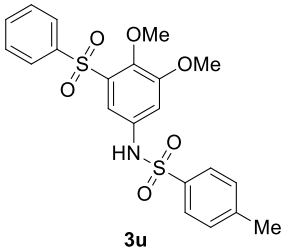
Reaction time: 18 h; R*f*: 0.6 (2:3 EtOAc:Pet. Ether); White solid, [31 mg, 42% yield (at 60 ^oC)]; Mp = 169-171 ^oC.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.6 Hz, 2H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.53 (d, *J* = 3.1 Hz, 1H), 7.47 (t, *J* = 8.1 Hz, 2H), 7.35 (d, *J* = 2.3 Hz, 1H), 7.26 (d, *J* = 8.4 Hz, 3H), 3.78 (s, 3H), 2.42 (s, 3H), 2.20 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 144.2, 141.2, 135.7, 135.1, 134.9, 133.2, 132.5, 130.7, 129.8, 128.7, 127.9, 127.3, 120.2, 61.8, 21.6, 16.2.

HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{21}H_{21}NO_5S_2Na$ 454.0753, found 454.0754.

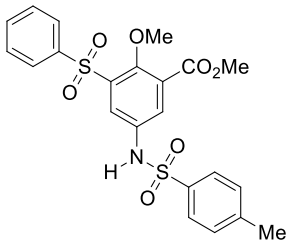
***N*-(3,4-Dimethoxy-5-(phenylsulfonyl)phenyl)-4-methylbenzenesulfonamide (3u)**



3u

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{21}H_{21}NO_6S_2Na$ 470.0702, found 470.0697.

Methyl 2-methoxy-5-(4-methylphenylsulfonamido)-3-(phenylsulfonyl)benzoate (3v)



3v

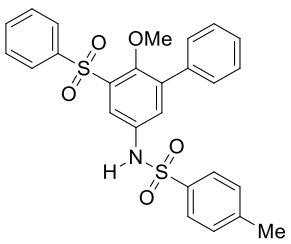
Reaction time: 5 h; R*f*: 0.4 (1:49 Acetone:DCM); White solid, [58 mg, 82% yield (at 60 ^oC)]; Mp = 172-174 ^oC.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 2H), 7.84 (d, J = 7.6 Hz, 2H), 7.70 (d, J = 8.4 Hz, 2H), 7.62-7.55 (m, 2H), 7.48 (t, J = 7.6 Hz, 2H), 7.26 (d, J = 7.6 Hz, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 2.41 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 155.5, 144.5, 140.6, 136.9, 135.4, 133.6, 132.6, 130.1, 129.9, 128.9, 128.1, 127.4, 126.6, 125.9, 64.1, 52.8, 21.6;

HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{22}H_{21}NO_7S_2Na$ 498.0652, found 498.0655.

***N*-(6-Methoxy-5-(phenylsulfonyl)-[1,1'-biphenyl]-3-yl)-4-methylbenzenesulfonamide (3w)**



3w

Reaction time: 10 h; R*f*: 0.4 (2:3 EtOAc:Pet. Ether); White solid, (50 mg, 72% yield); Mp = 128-130 ^oC.

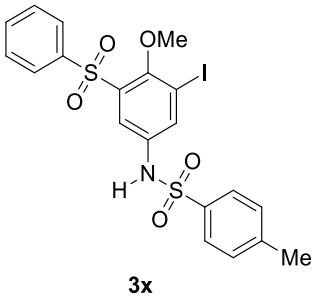
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 7.6 Hz, 2H), 7.64 (d, J = 7.6

Hz, 3H), 7.52 (t, *J* = 7.3 Hz, 1H), 7.44-7.39 (m, 3H), 7.28 (s, 6H), 7.19 (d, *J* = 8.4 Hz, 2H), 3.09 (s, 3H), 2.33 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 144.3, 141.2, 137.4, 136.0, 135.7, 135.6, 133.3, 132.6, 130.3, 129.8, 128.8, 128.6, 128.6, 128.3, 128.1, 127.4, 121.2, 61.2, 21.6.

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{26}H_{24}NO_5S_2$ 494.1090, found 494.1085.

***N*-(3-Iodo-4-methoxy-5-(phenylsulfonyl)phenyl)-4-methylbenzenesulfonamide (3x)**



3x

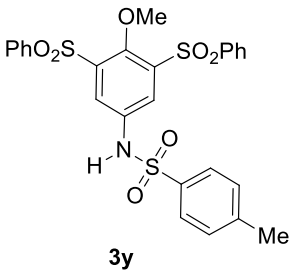
Reaction time: 12 h; R*f*: 0.4 (1:4 EtOAc:Pet. Ether); White solid, (31 mg, 23% yield); Mp = 185-187 ^oC.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 2.7 Hz, 1H), 7.84 (d, *J* = 7.3 Hz, 2H), 7.73-7.68 (m, 3H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.36 (s, 1H), 7.29 (d, *J* = 8.4 Hz, 2H), 3.94 (s, 3H), 2.43 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8, 144.6, 140.5, 137.6, 136.0, 135.5, 134.2, 133.7, 130.0, 128.9, 128.1, 127.4, 122.4, 93.7, 63.1, 21.6.

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{20}H_{19}INO_5S_2$ 543.9744, found 543.9751.

***N*-(4-Methoxy-3,5-bis(phenylsulfonyl)phenyl)-4-methylbenzenesulfonamide (3y)**



3y

Reaction time: 12 h; R*f*: 0.2 (1:4 EtOAc:Pet. Ether); White solid (73 mg, 53% yield (at rt); 59 mg, 85% yield (at 60 ^oC from 50 mg **1n**)); Mp = 223-225 ^oC.

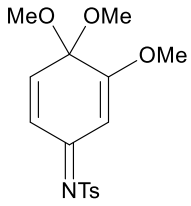
^{1}H NMR (500 MHz, DMSO-*d_6*) δ 10.98 (s, 1H), 7.98 (s, 2H), 7.64 (t, *J*

= 7.6 Hz, 4H), 7.57 (d, *J* = 8.0 Hz, 4H), 7.47 (t, *J* = 7.6 Hz, 4H), 7.40 (d, *J* = 8.0 Hz, 2H), 3.89 (s, 3H), 2.36 (s, 3H).

^{13}C NMR (125 MHz, DMSO-*d*$_6$) δ 151.5, 144.2, 139.8, 137.7, 135.4, 135.0, 134.1, 130.0, 129.2, 127.1, 126.8, 125.4, 66.6, 21.0.

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{26}H_{24}NO_7S_3$ 558.0709, found 558.0707.

4-Methyl-N-(3,4,4-trimethoxycyclohexa-2,5-dien-1-ylidene)benzenesulfonamide (1k')[22]



1k'

Reaction time: 5 min; R*f*: 0.3 (2:3 EtOAc:Pet. Ether); pale yellow solid (54 mg, 98% yield) as a mixture of trans and cis-isomer in 1.8:1 ratio; Mp = 115-117 ^{o}C.

^{1}H NMR (200 MHz, DMSO-*d*$_6$) δ 7.81 (d, *J* = 7.83 Hz, 2H), 7.43 (d, *J* = 8.2 Hz, 2.4H), 6.91 (d, *J* = 10.5 Hz, 0.4H), 6.81 (d, *J* = 10.1 Hz, 0.6H), 6.63 (s, 0.6H), 6.37 (dd, *J* = 8.8 and 1.4 Hz, 0.6 H), 5.78 (s, 0.3H), 3.86 (s, 1.9H), 3.81 (s, 1H), 3.21 (s, 6H), 2.4 (s, 3H).

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{16}H_{20}NO_5S$ 338.1057, found 338.1055.

2.1.9. References:

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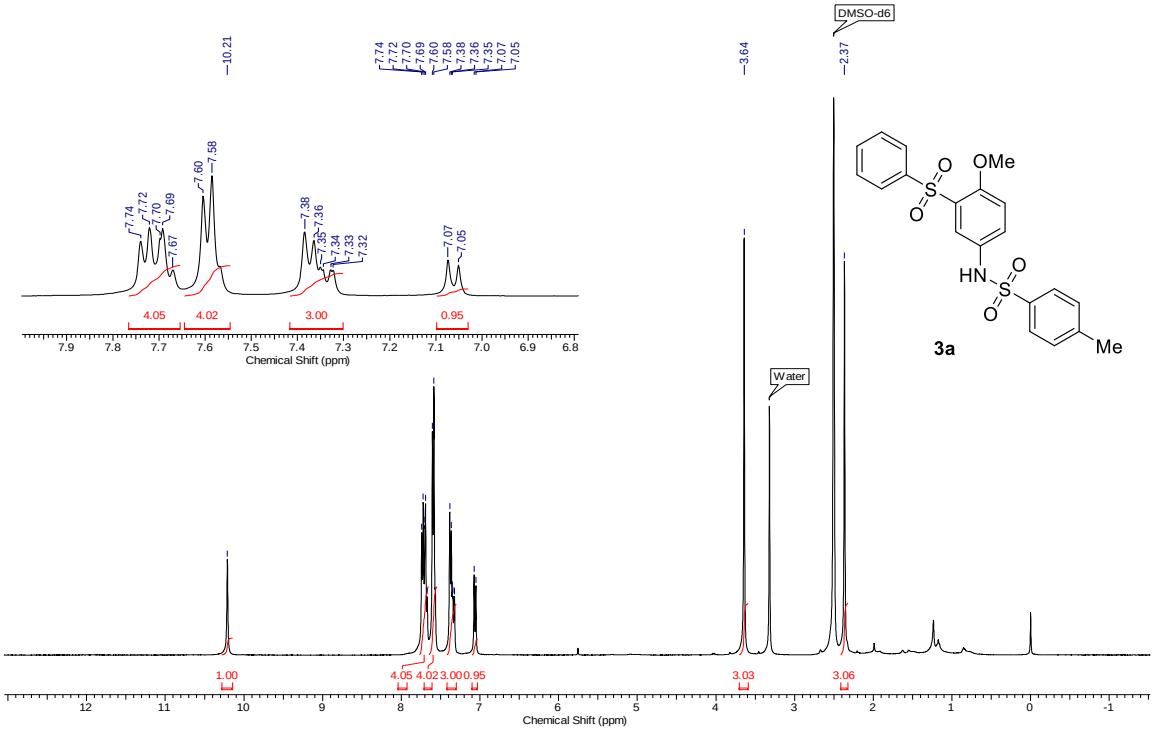
2.1.10. Copies of ^{1}H NMR, ^{13}C NMR, and 2D-NMR

^{1}H NMR, 400 MHz



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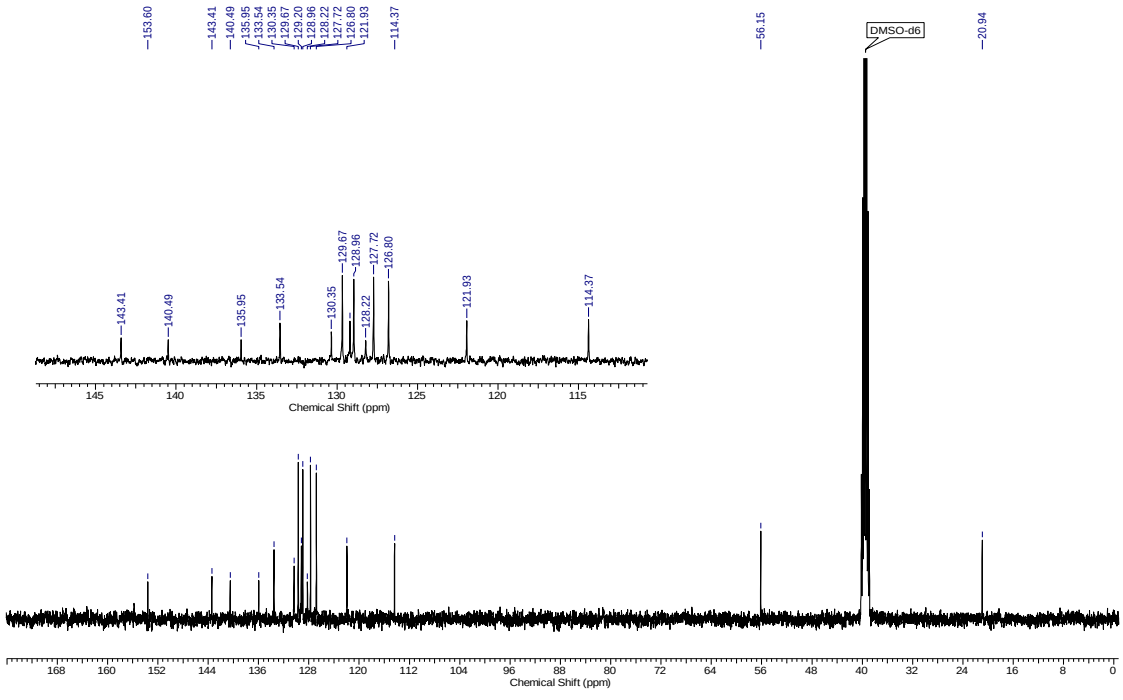
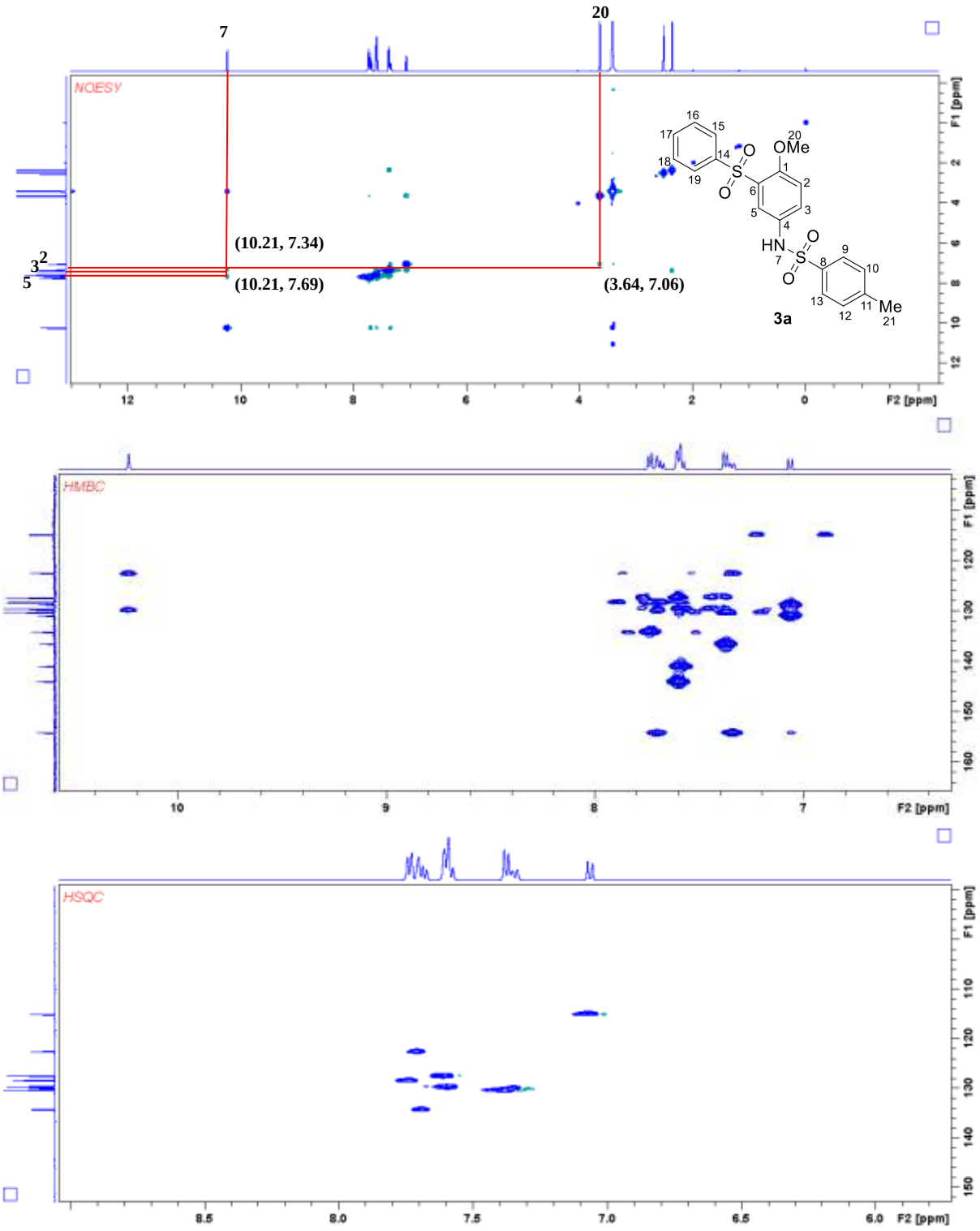


2D NMR (NOESY, HMBC & HSQC)



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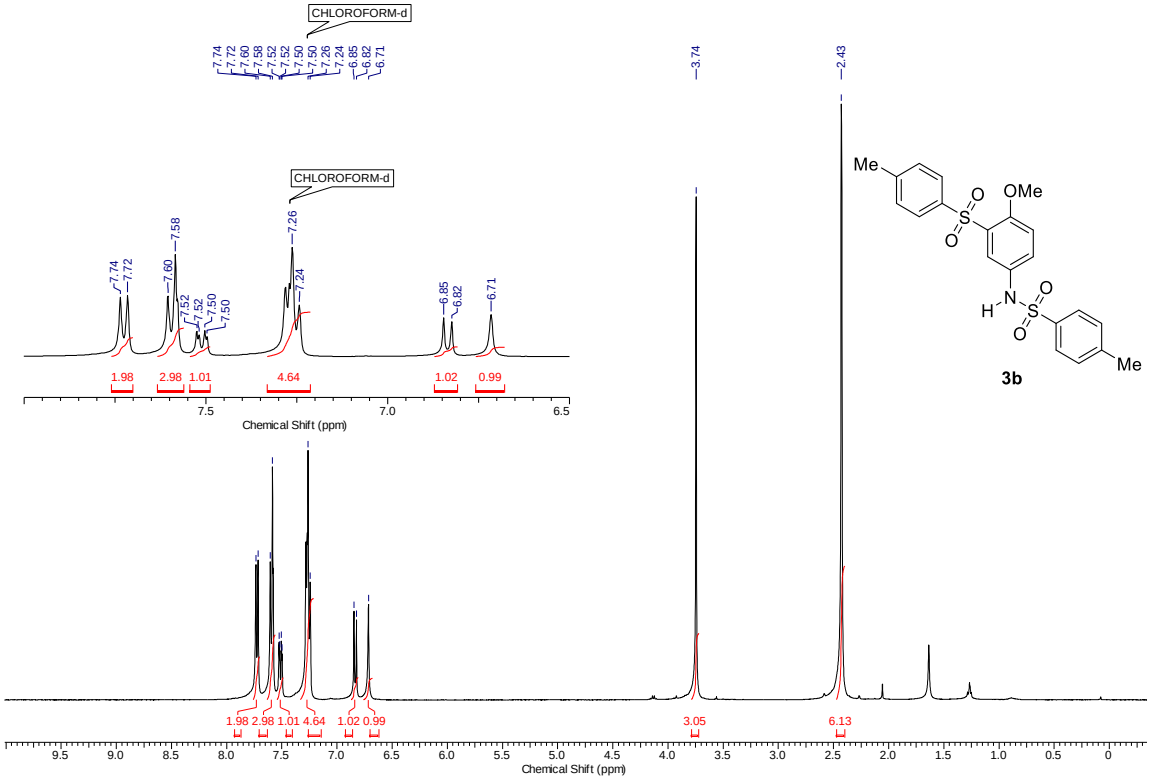

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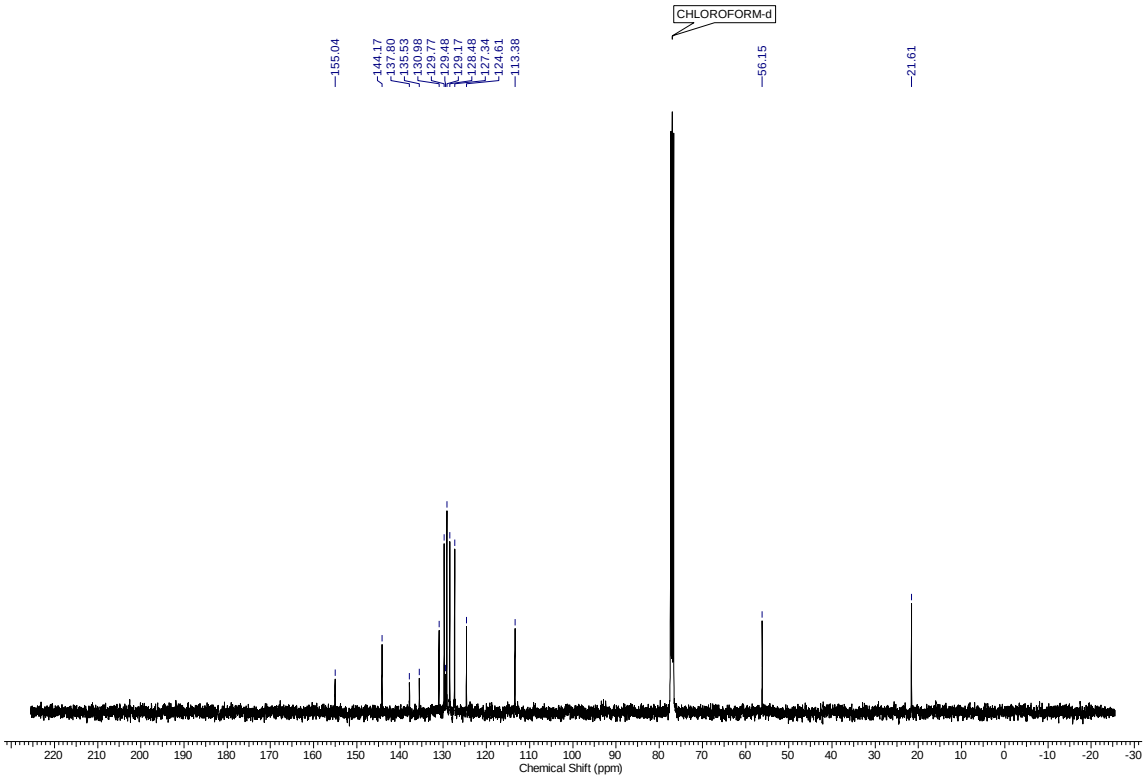

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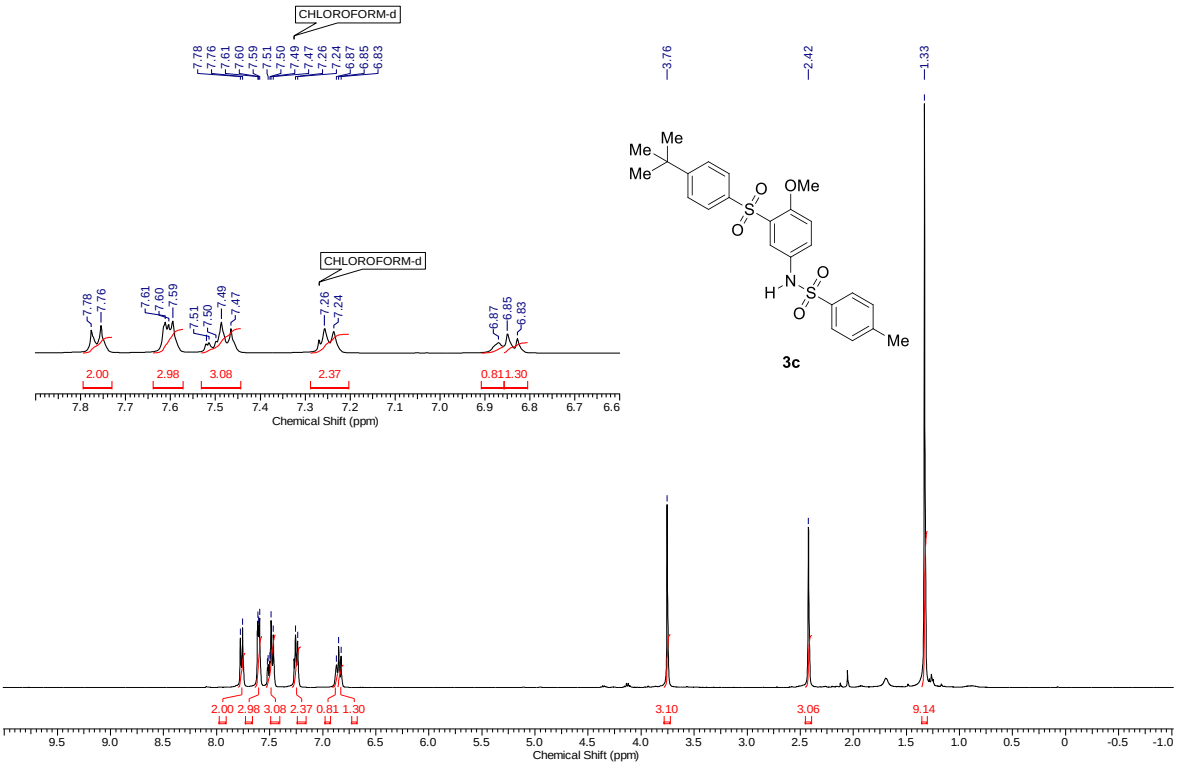

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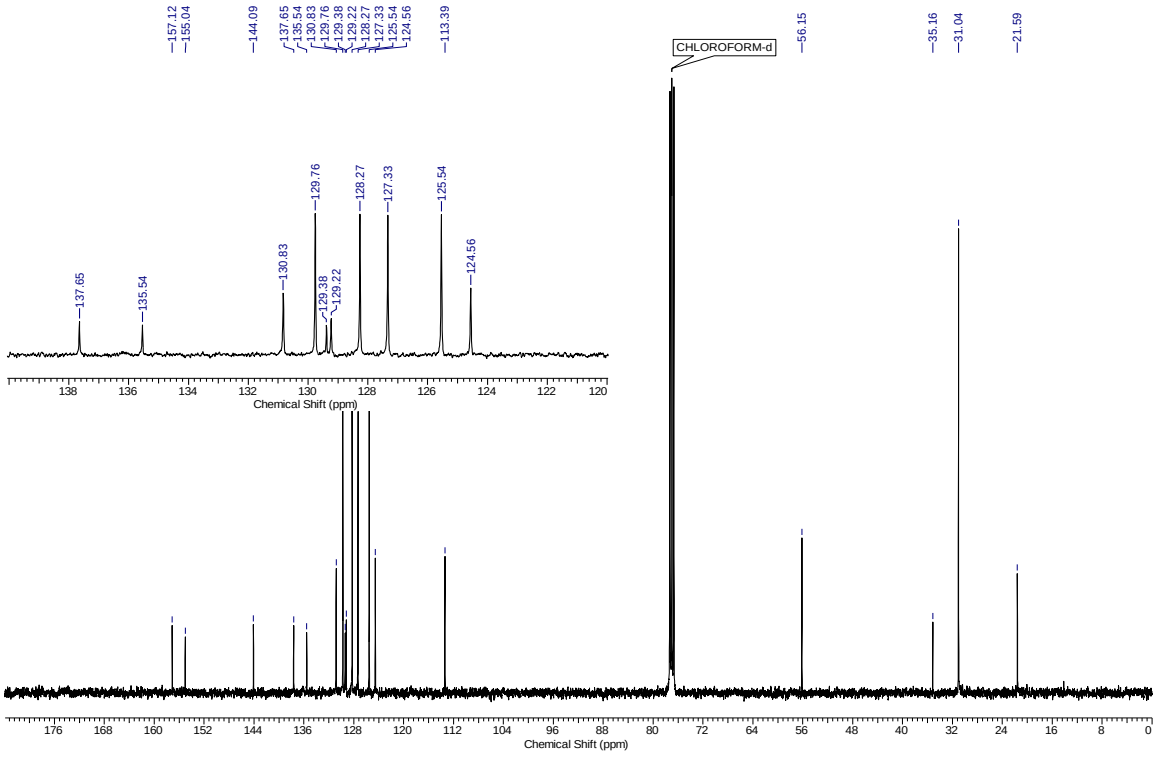

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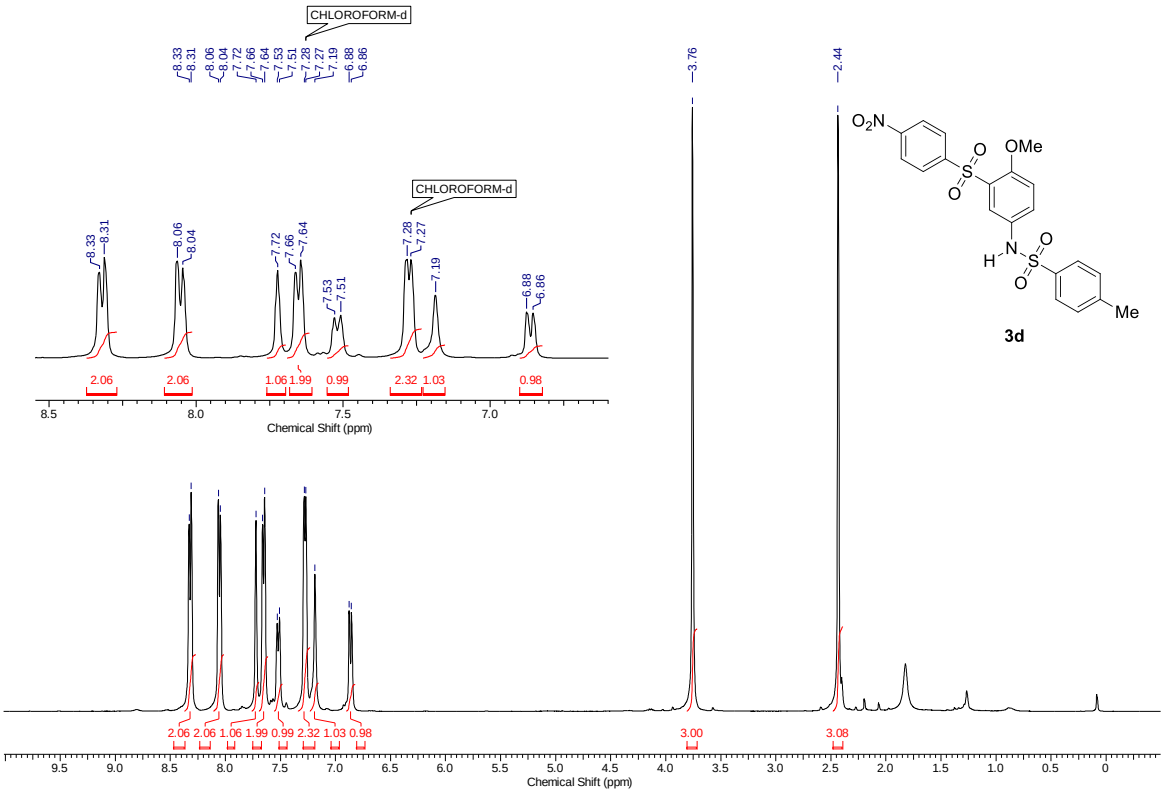

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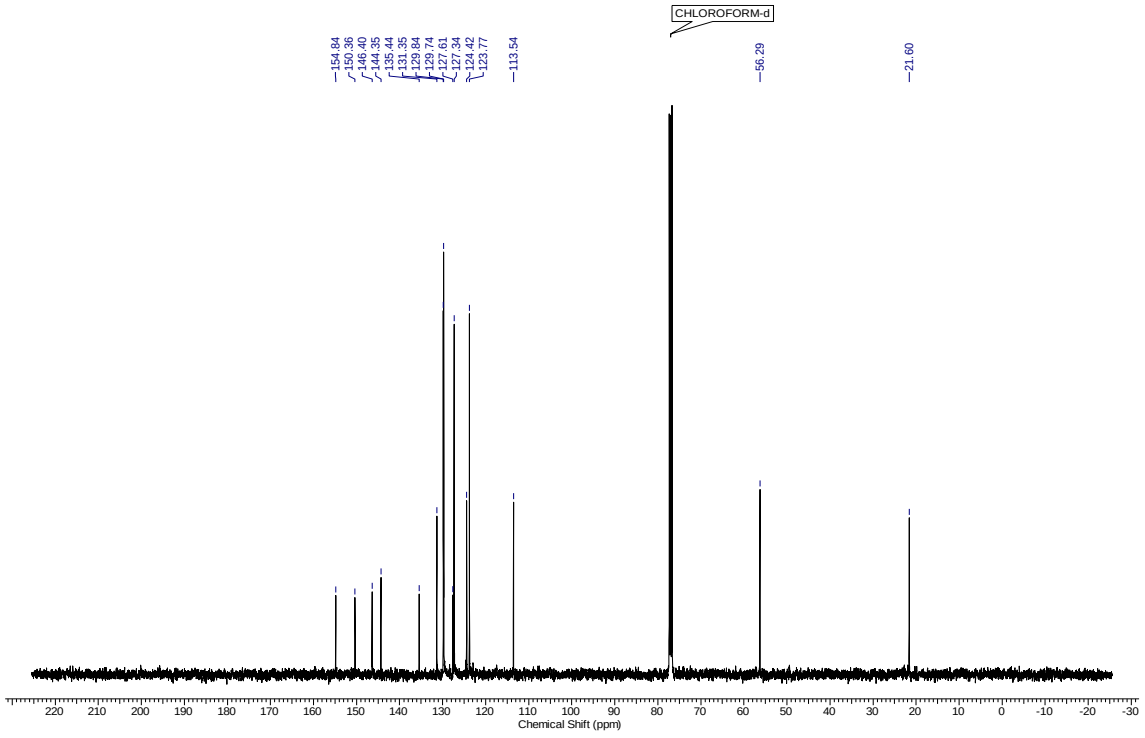

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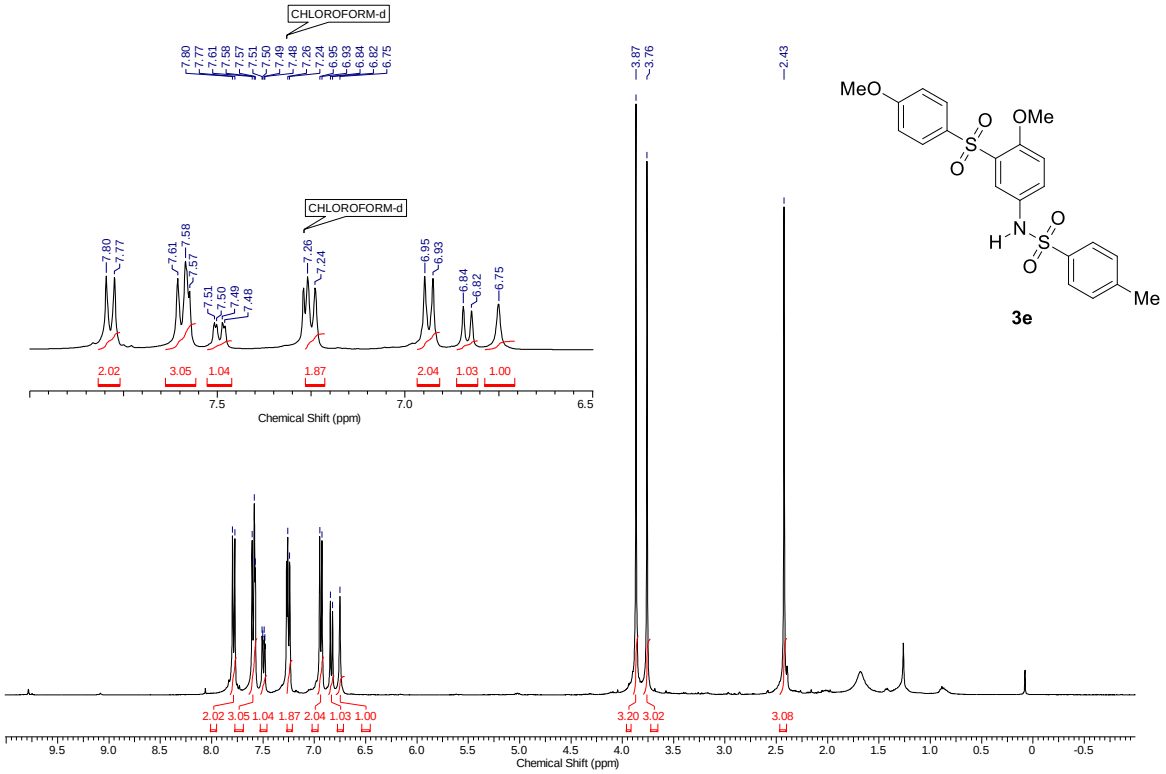

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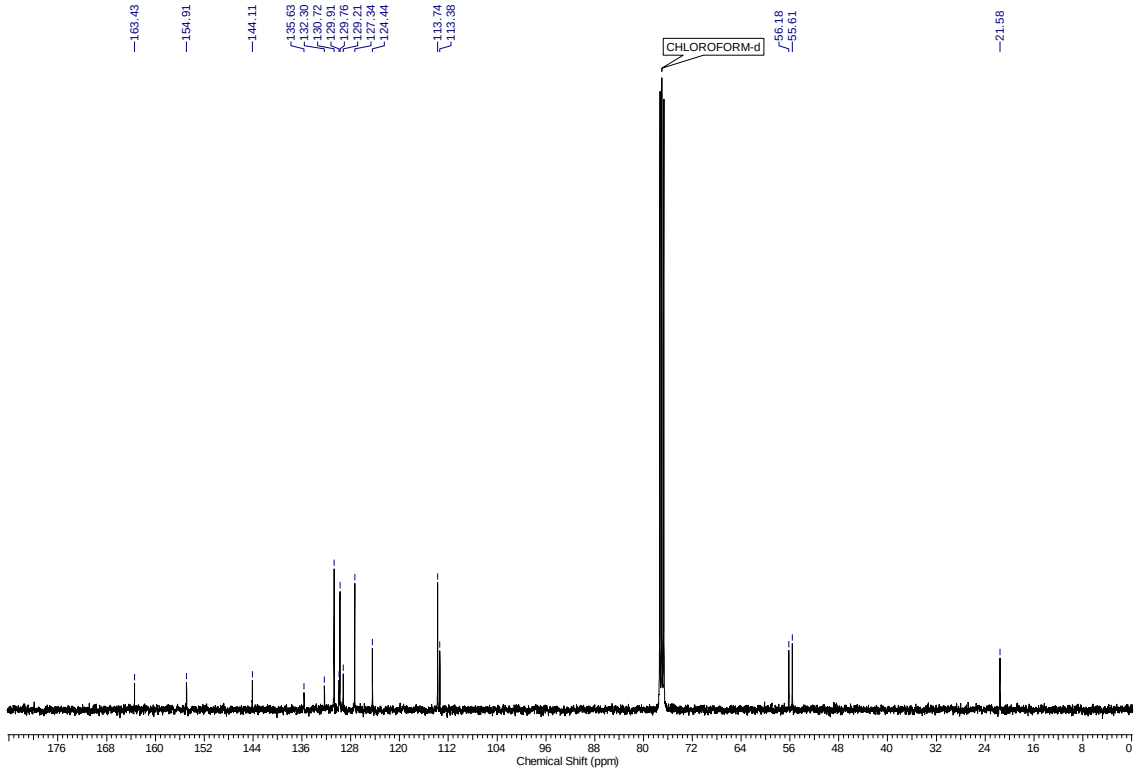

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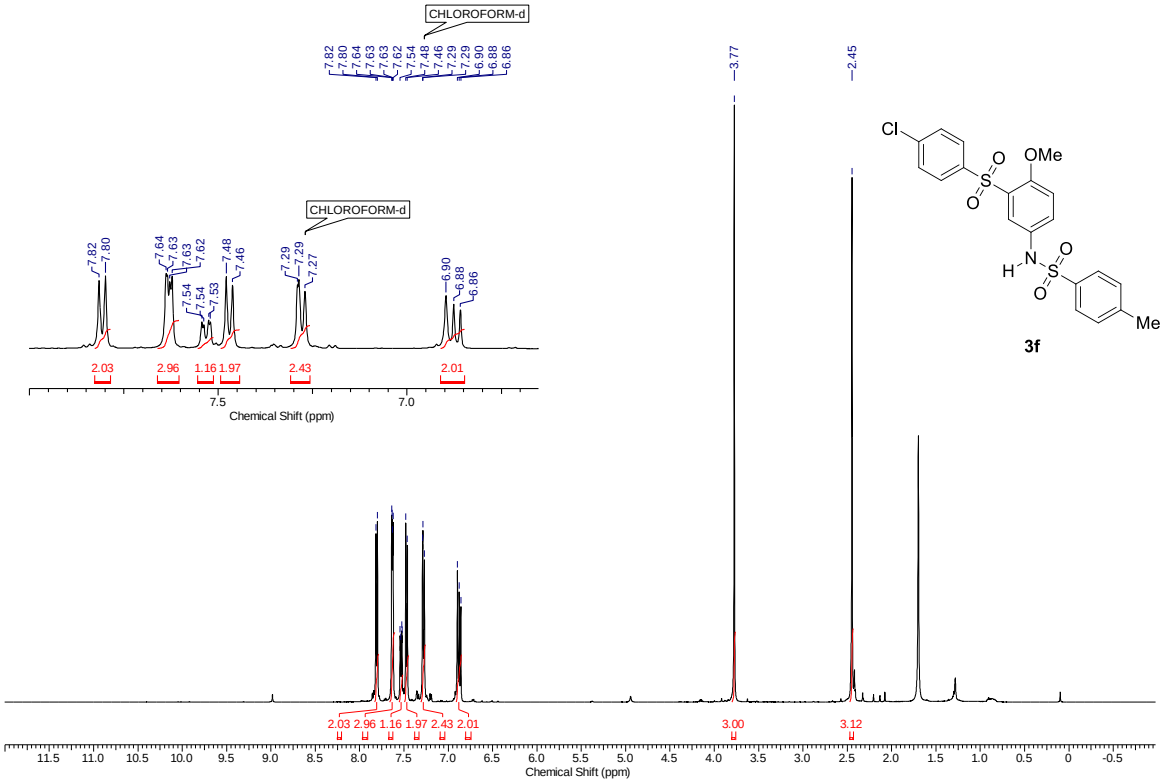

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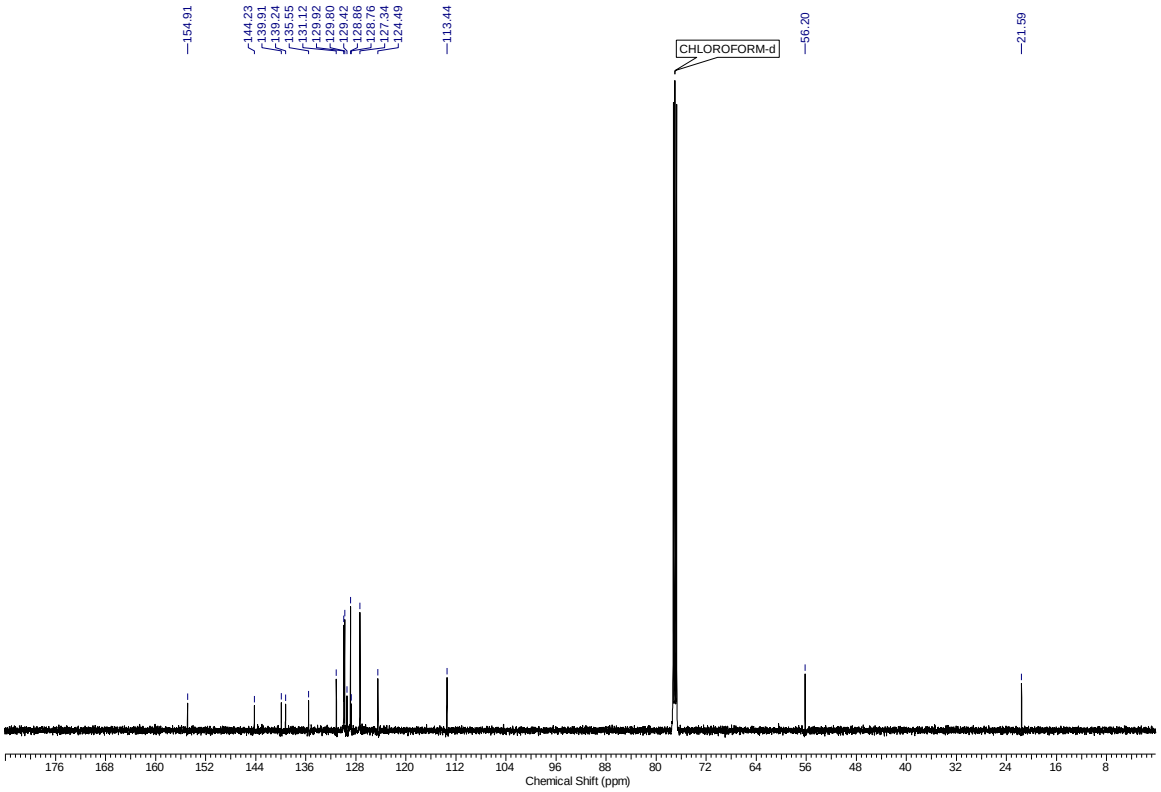

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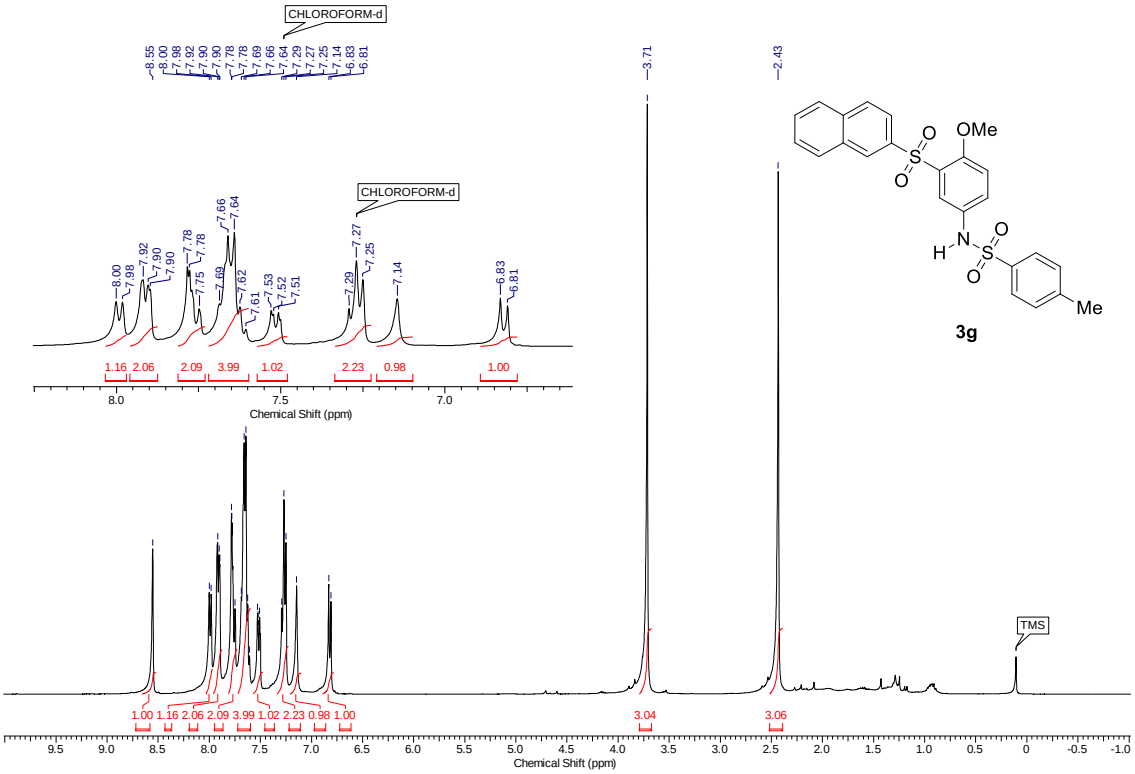

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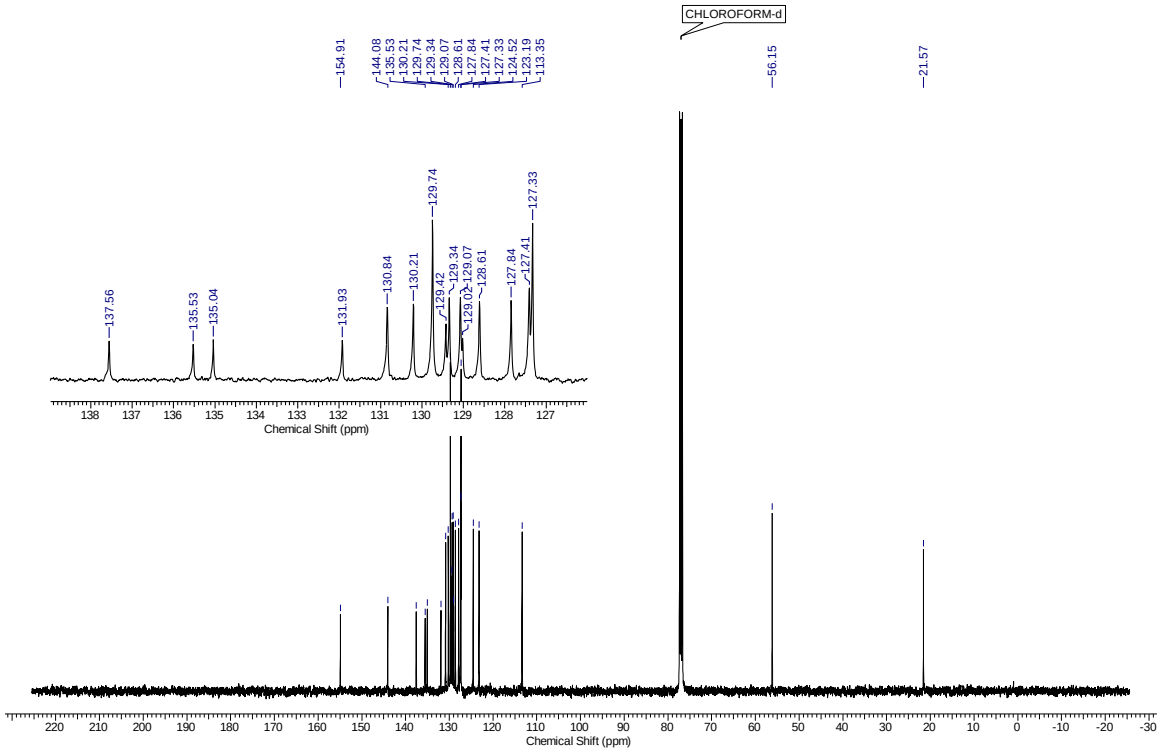

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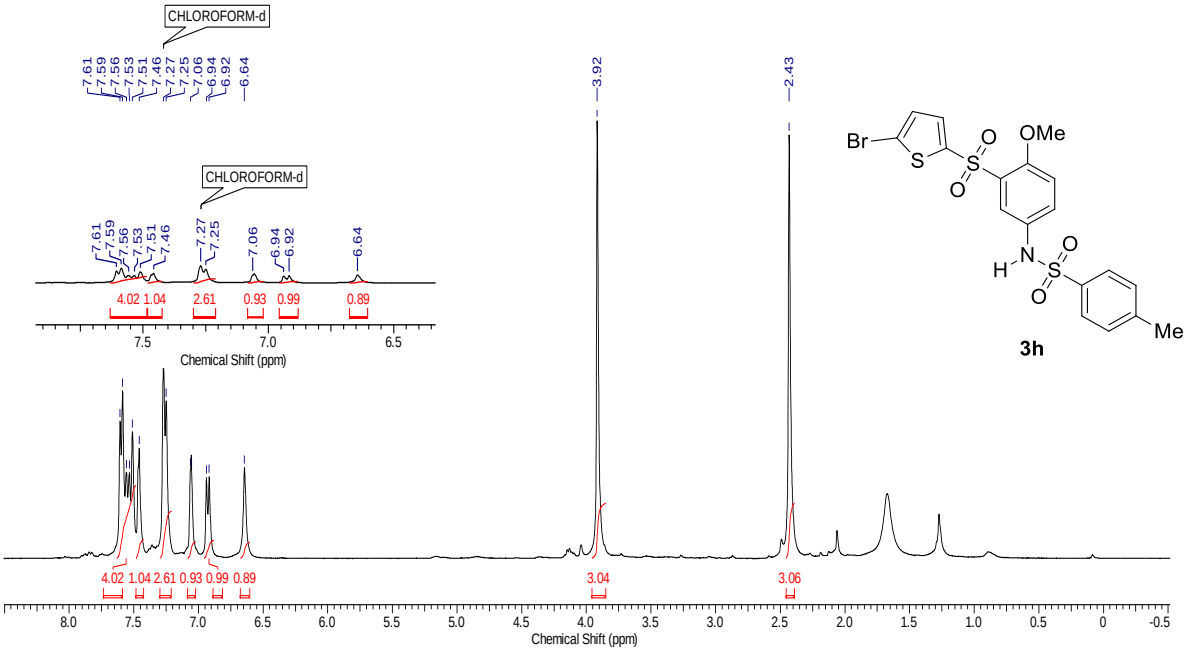

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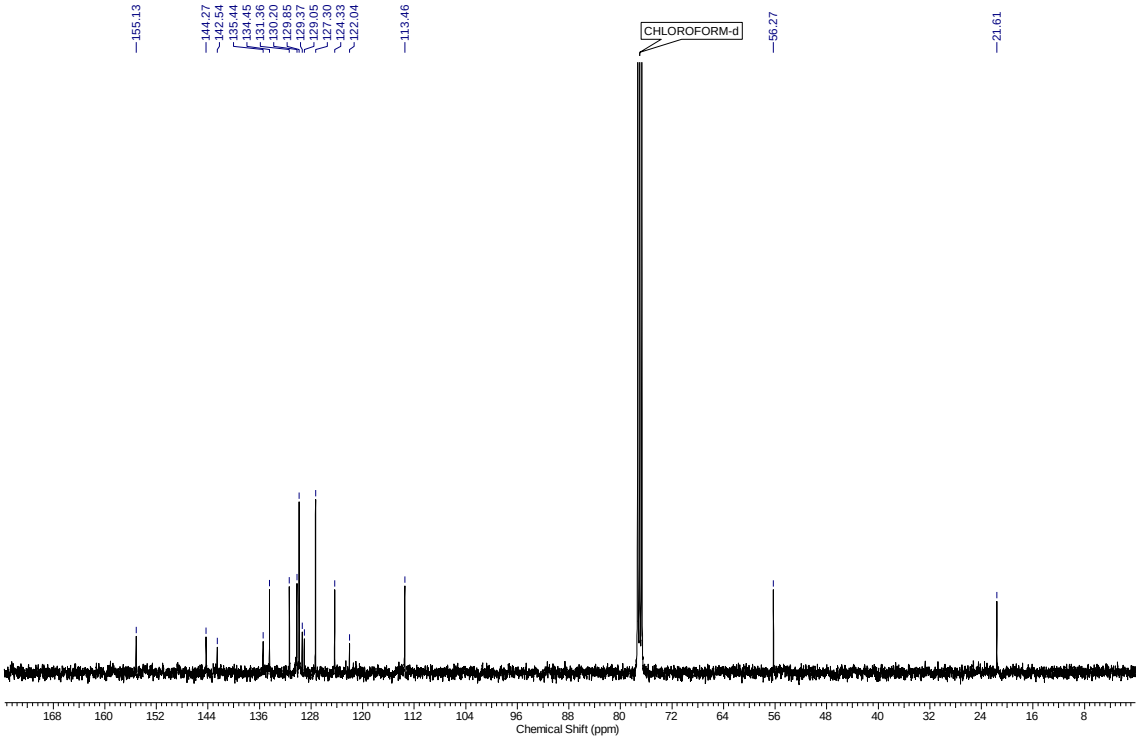

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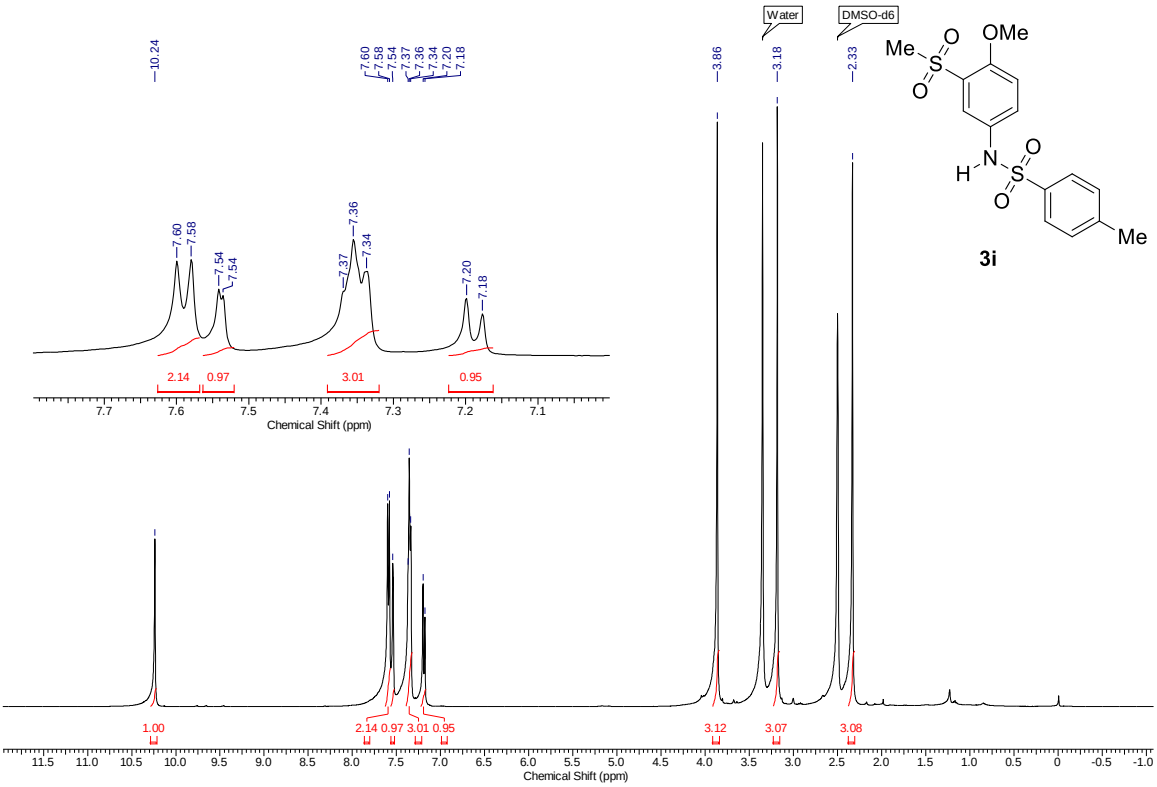

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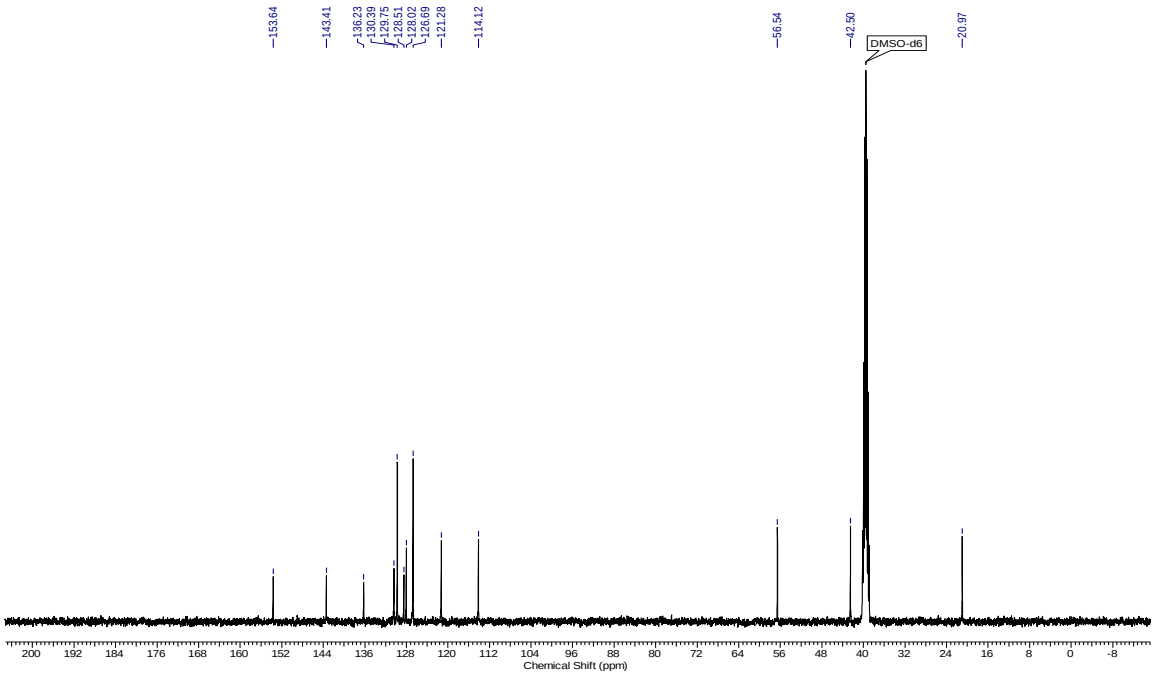

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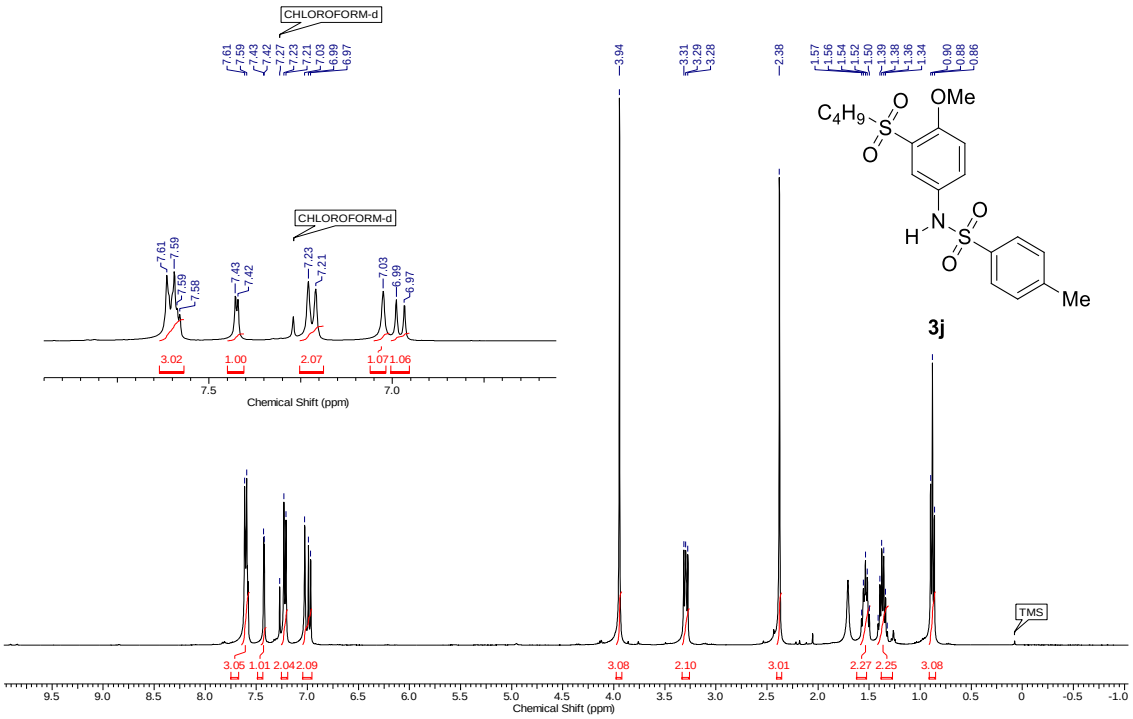

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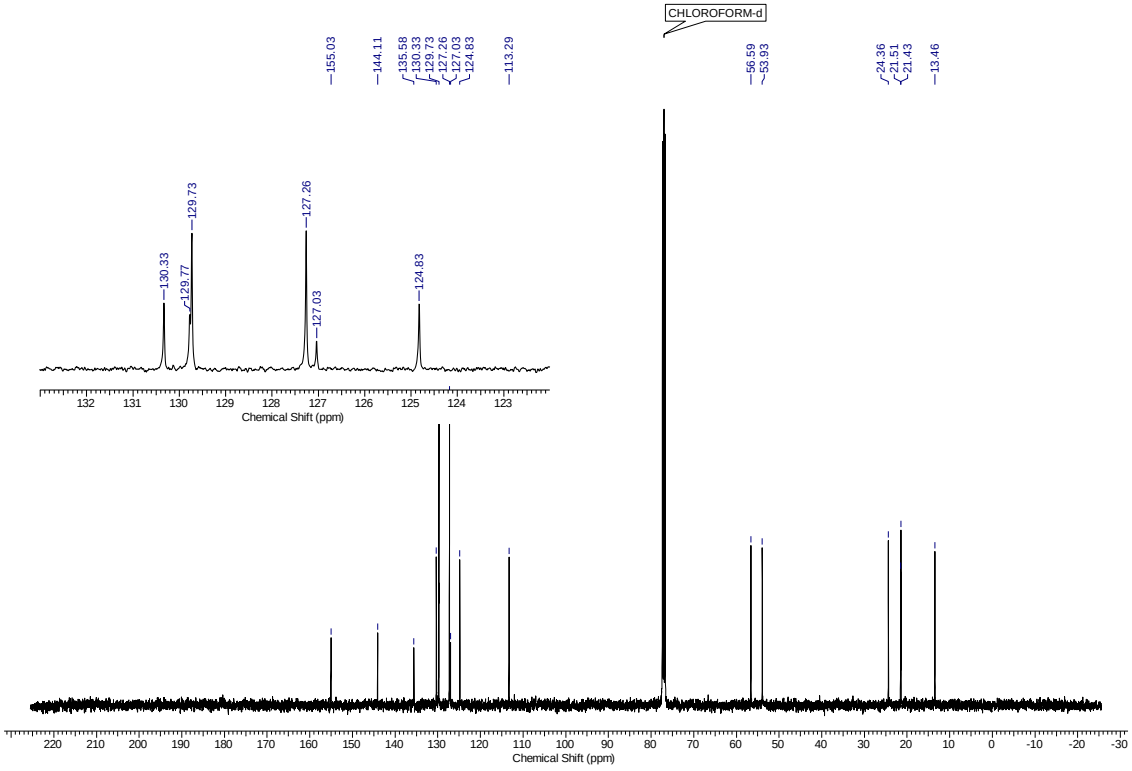

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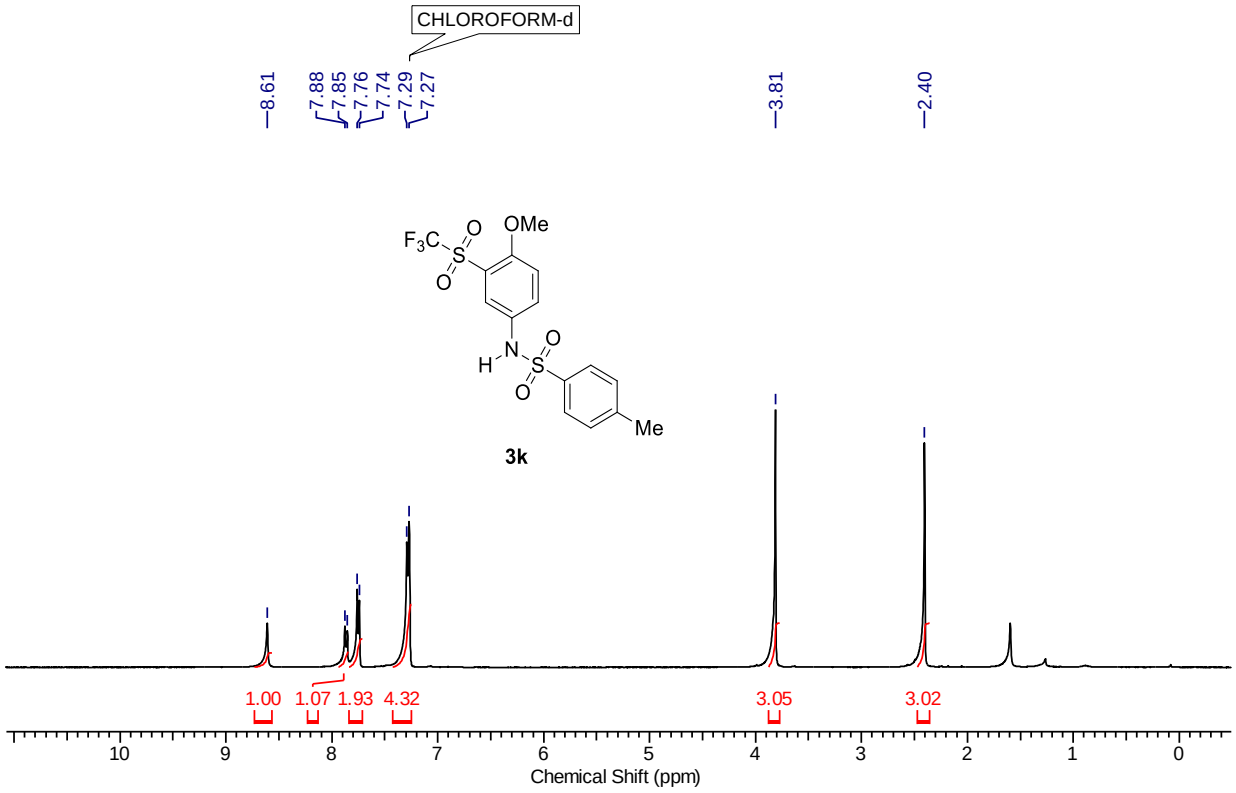

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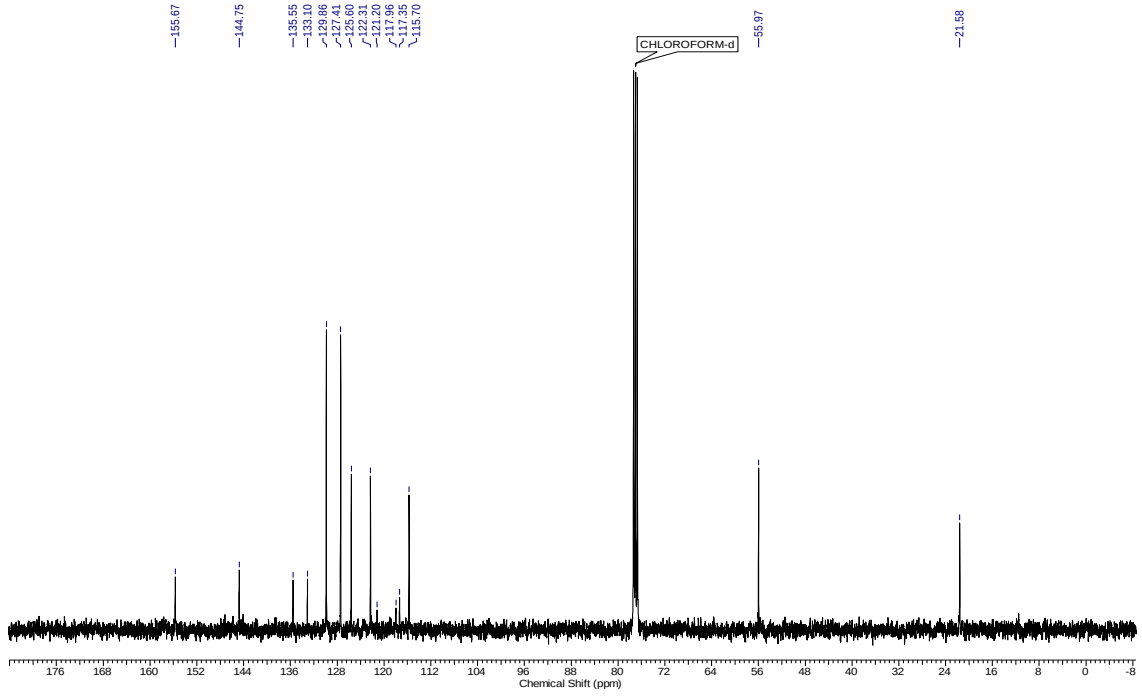

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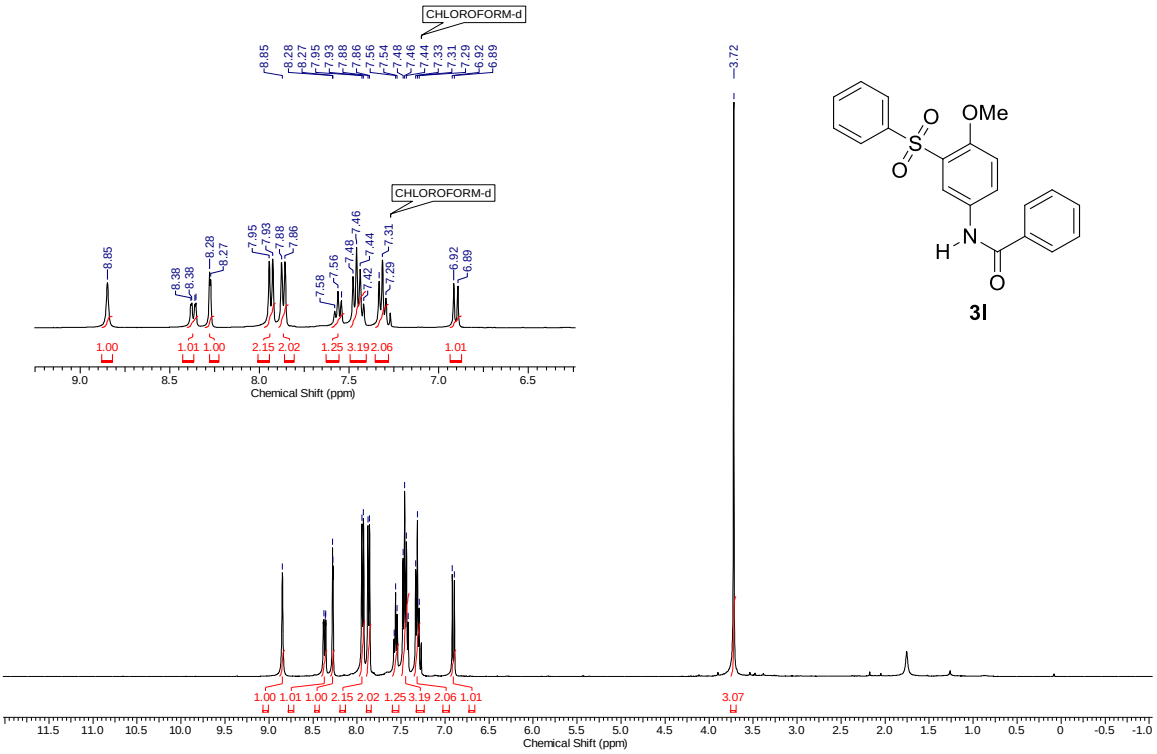

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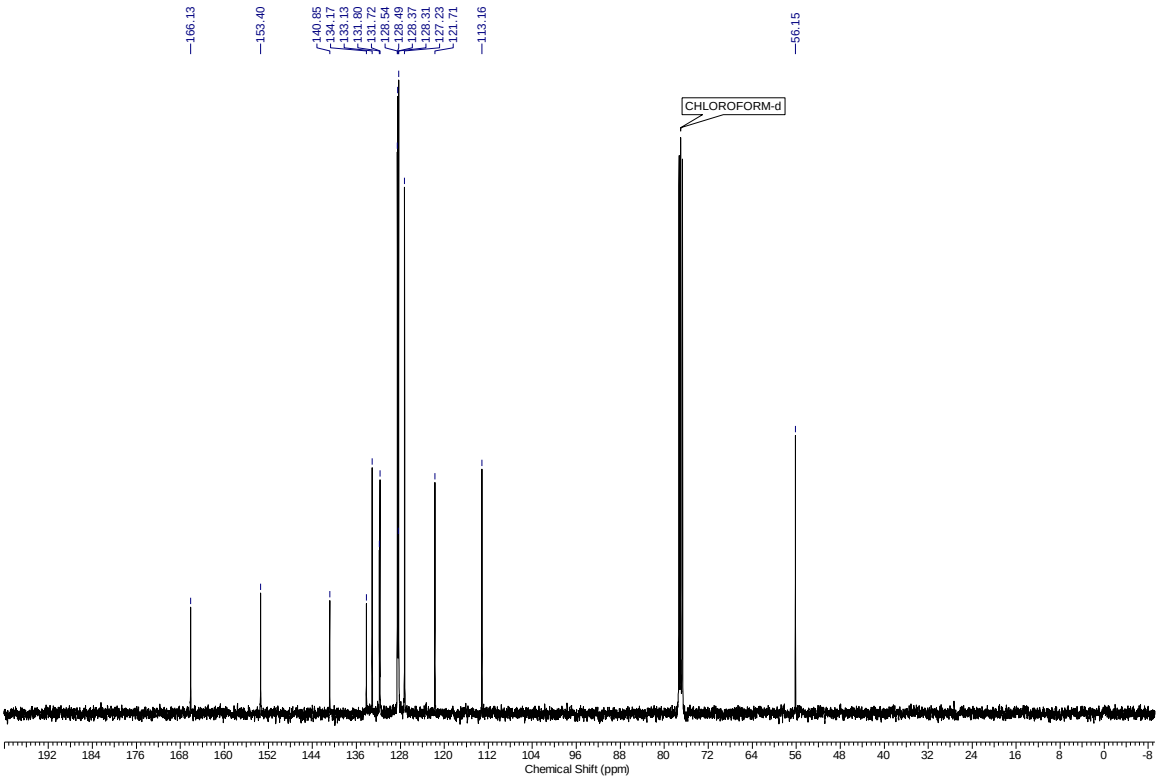

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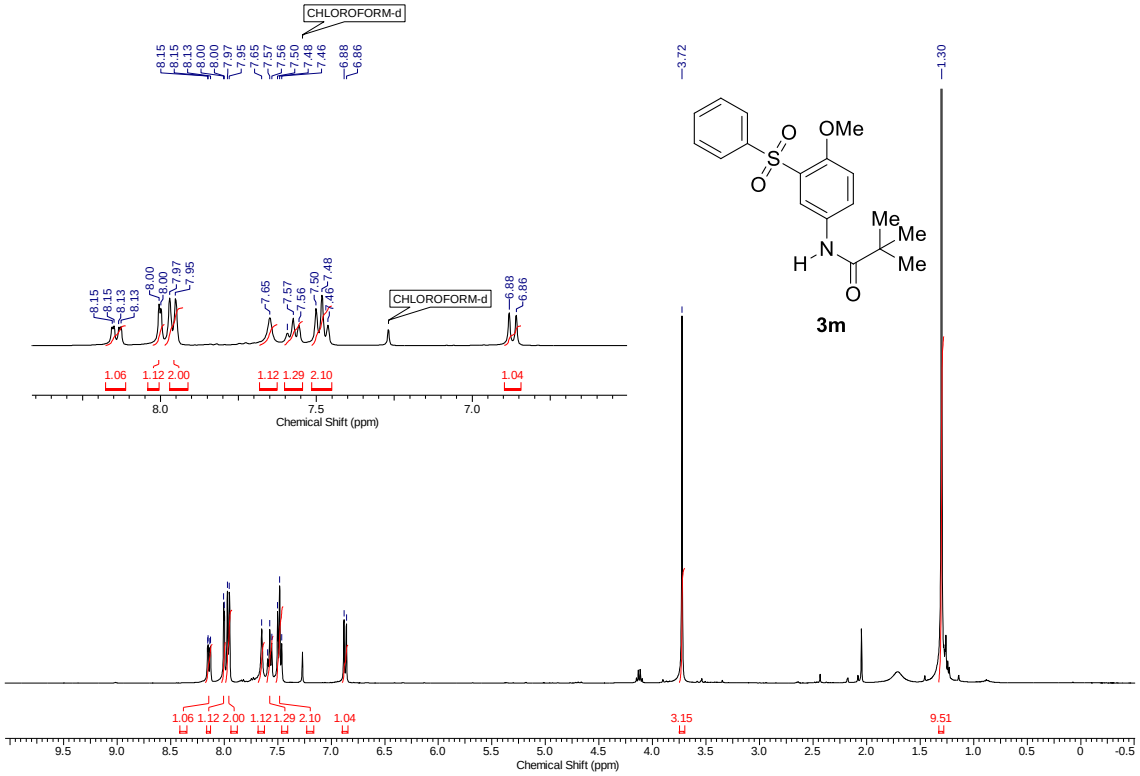

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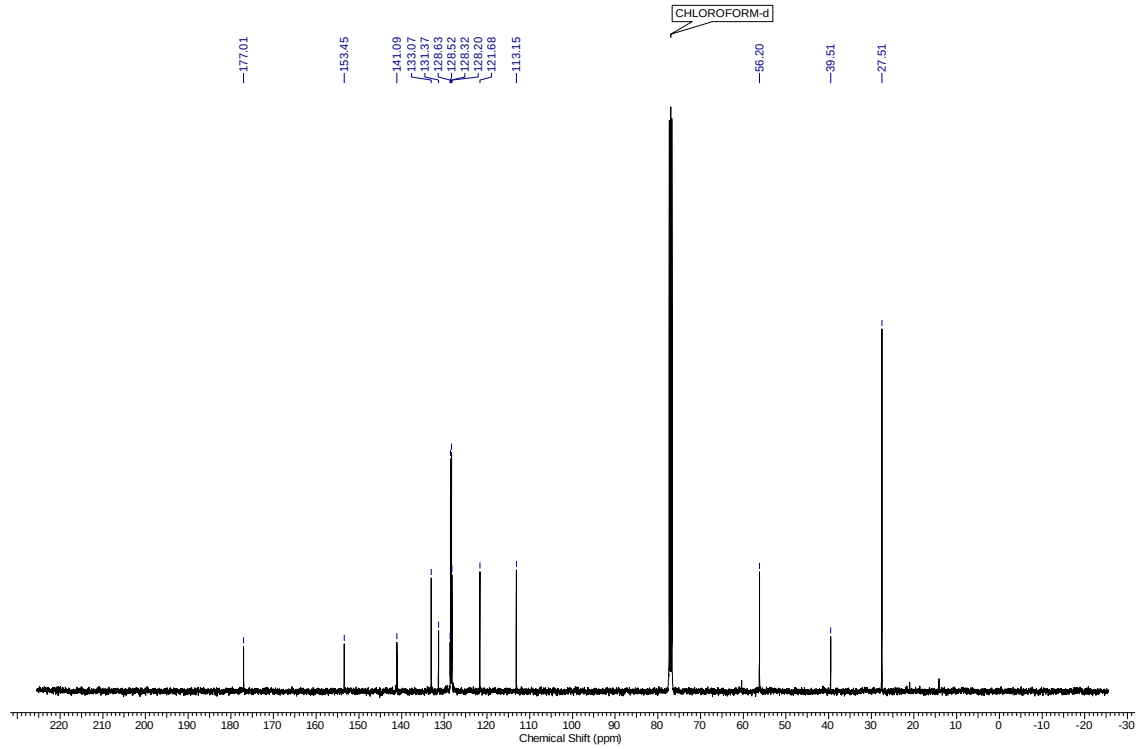

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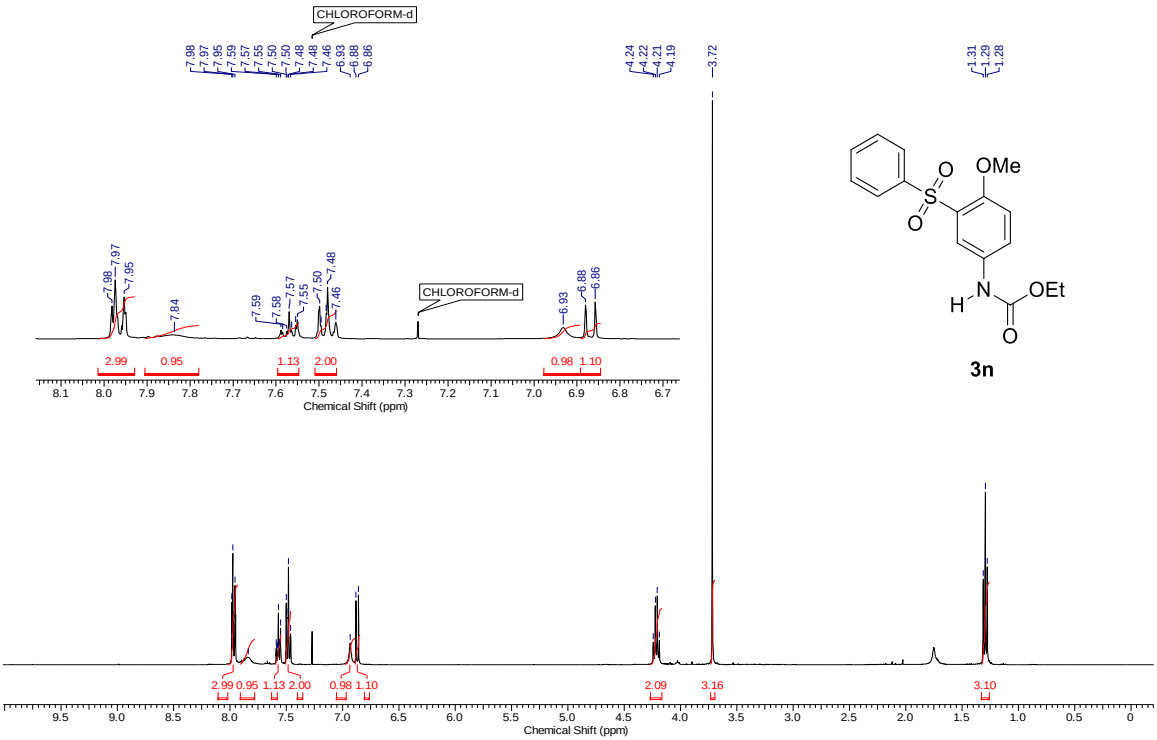

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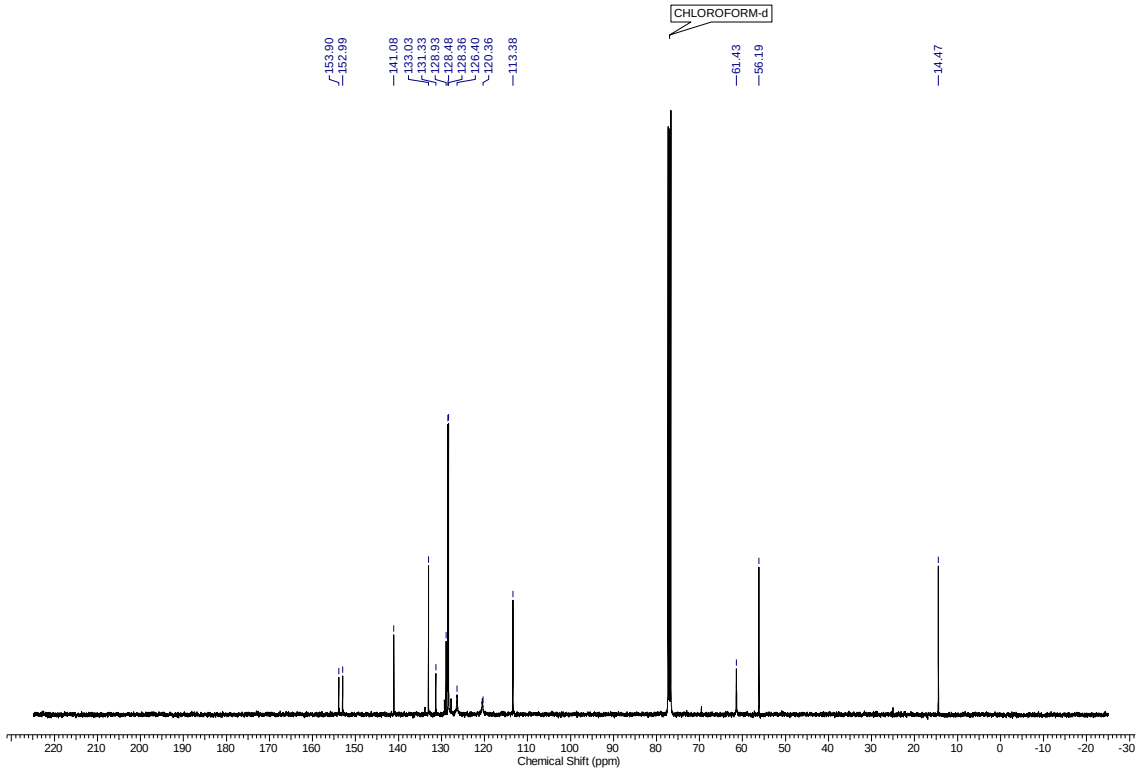

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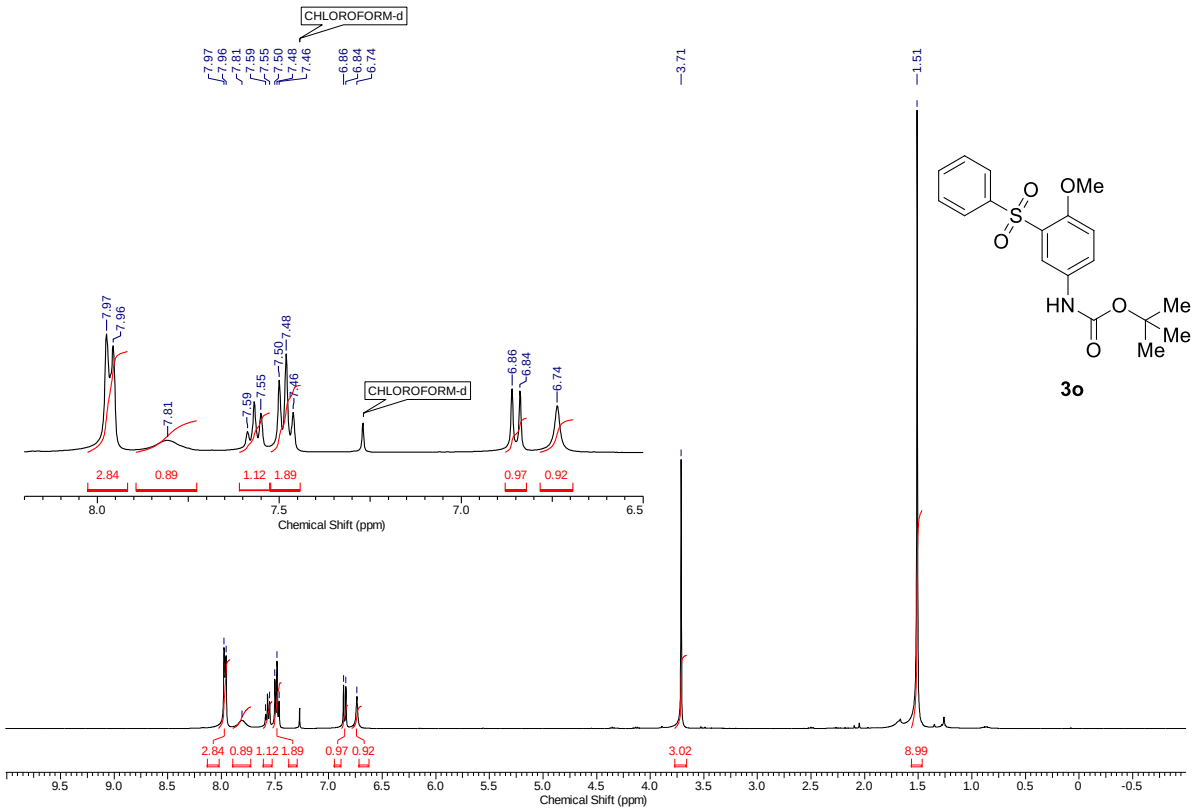

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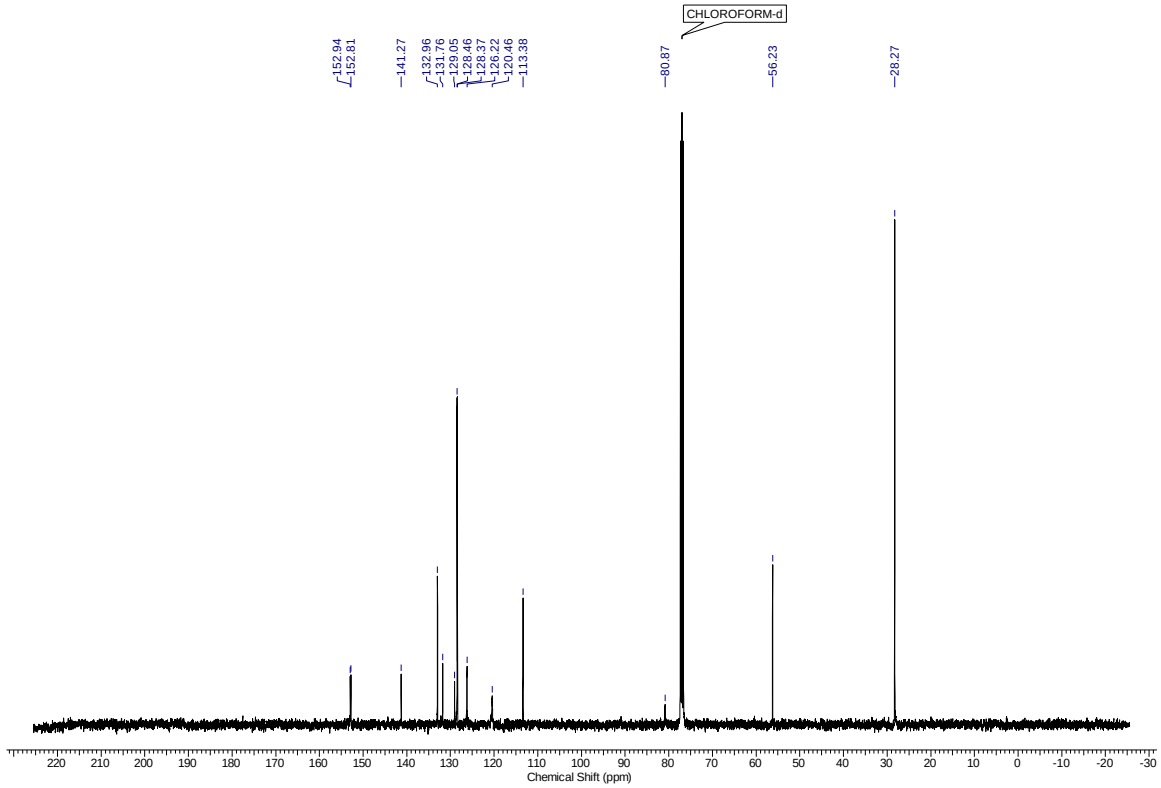

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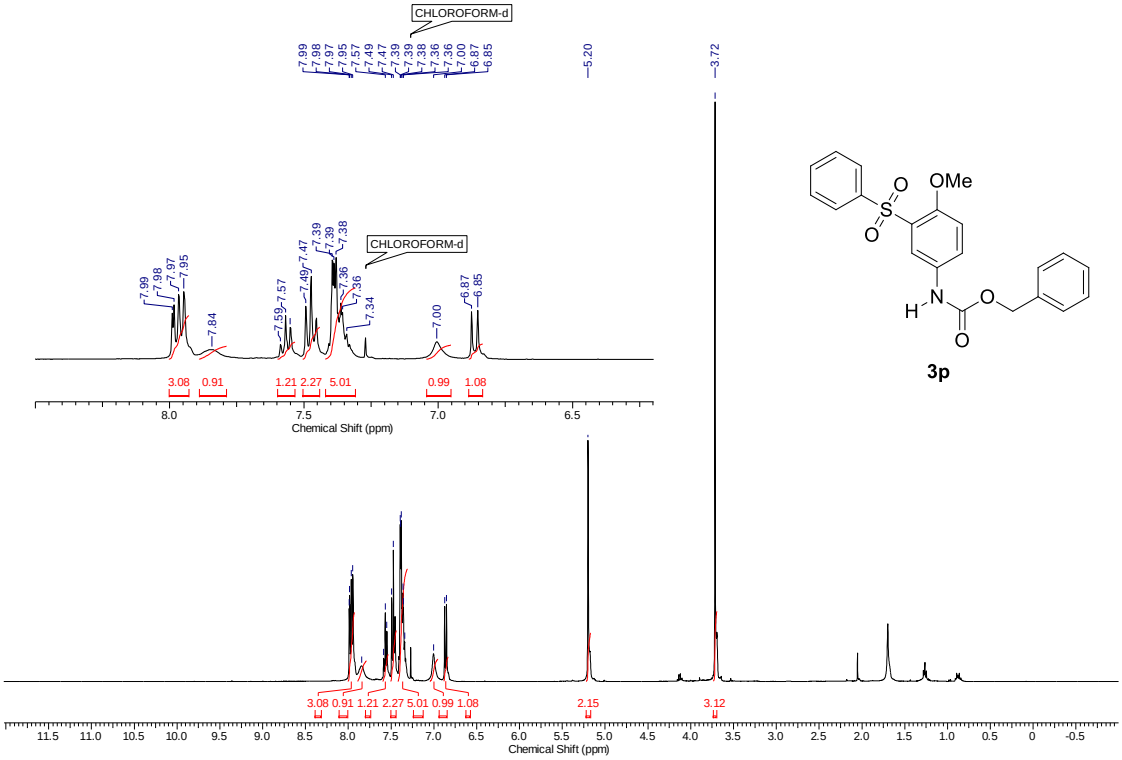

3p

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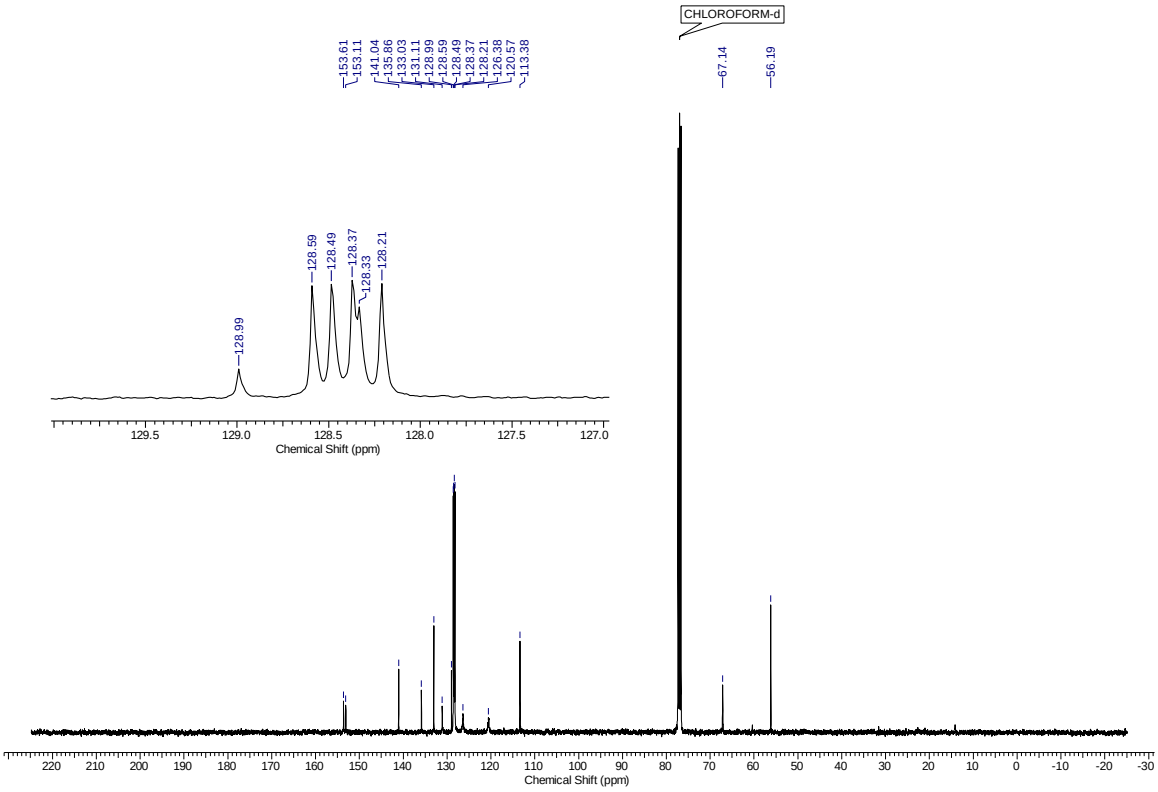

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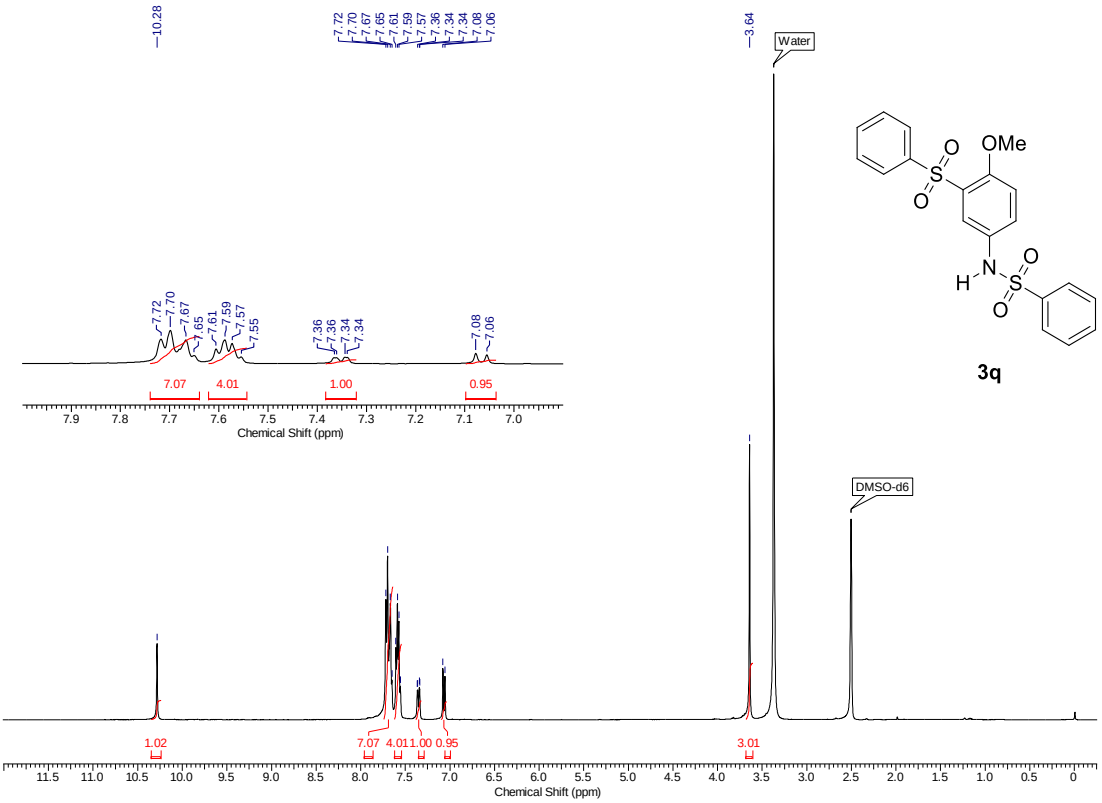

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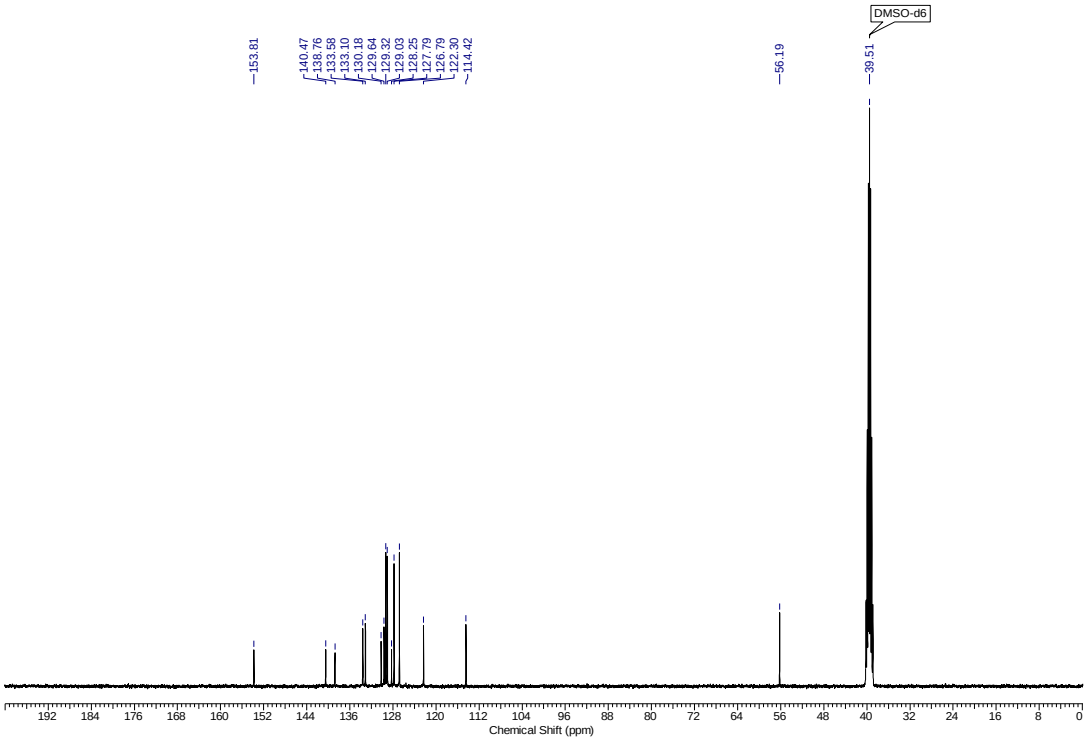

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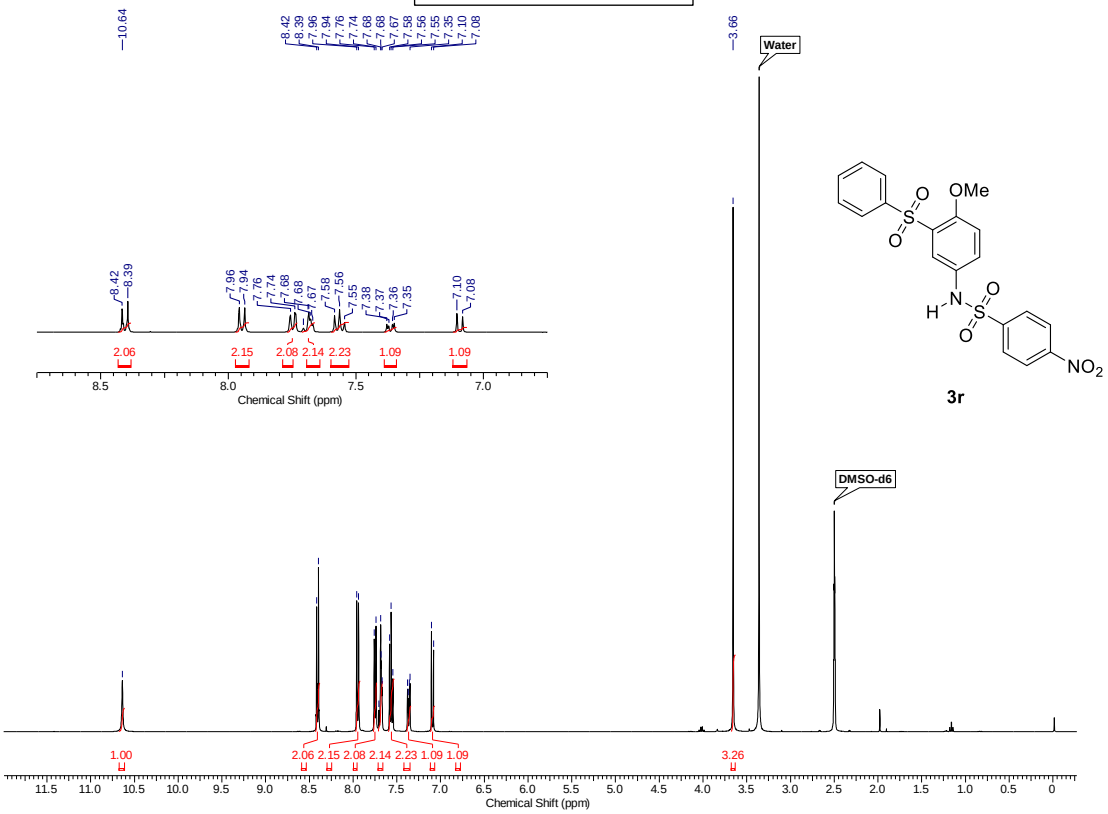

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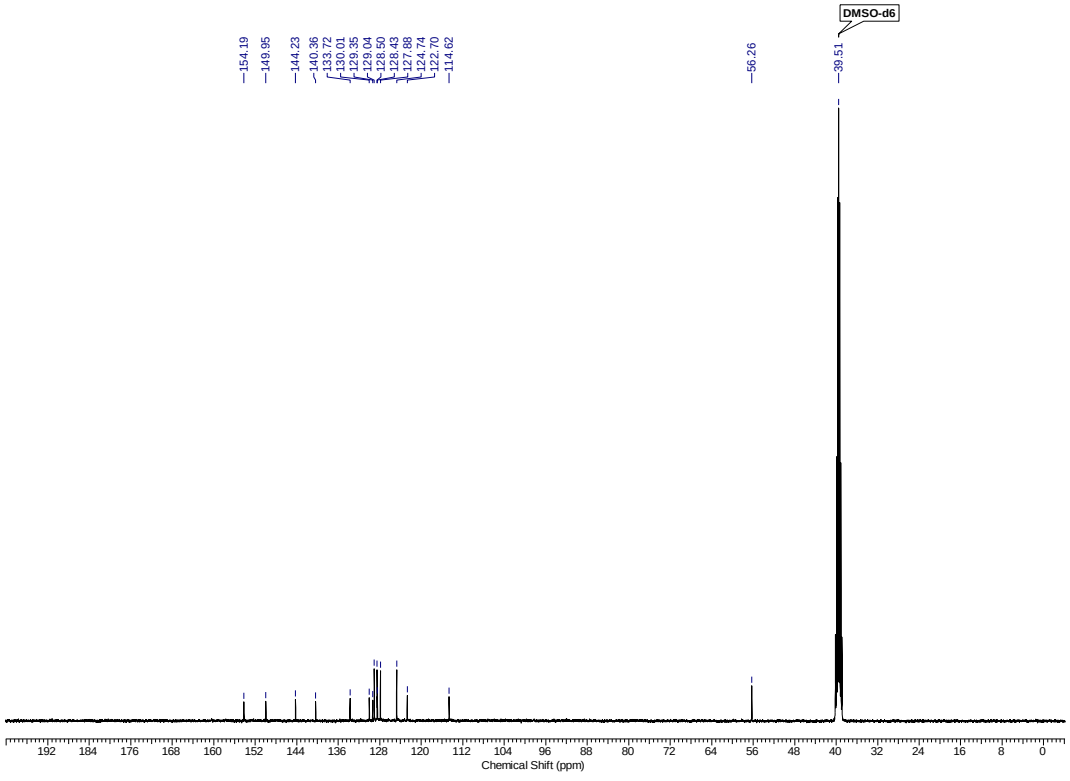

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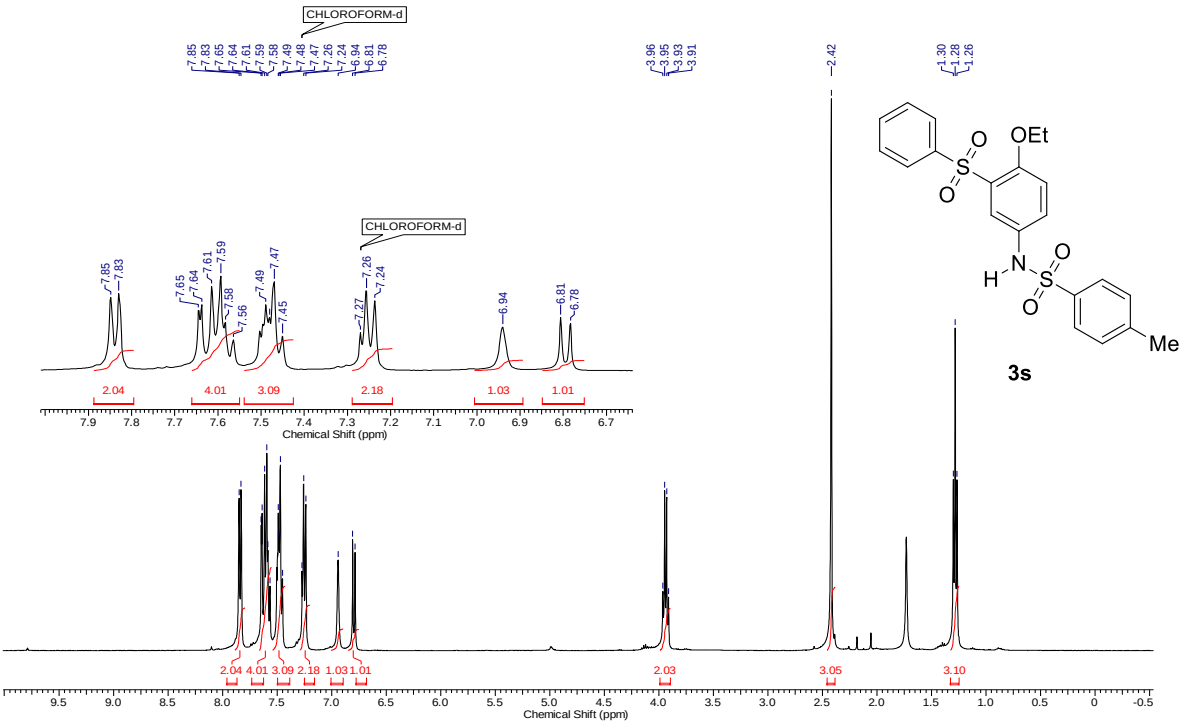

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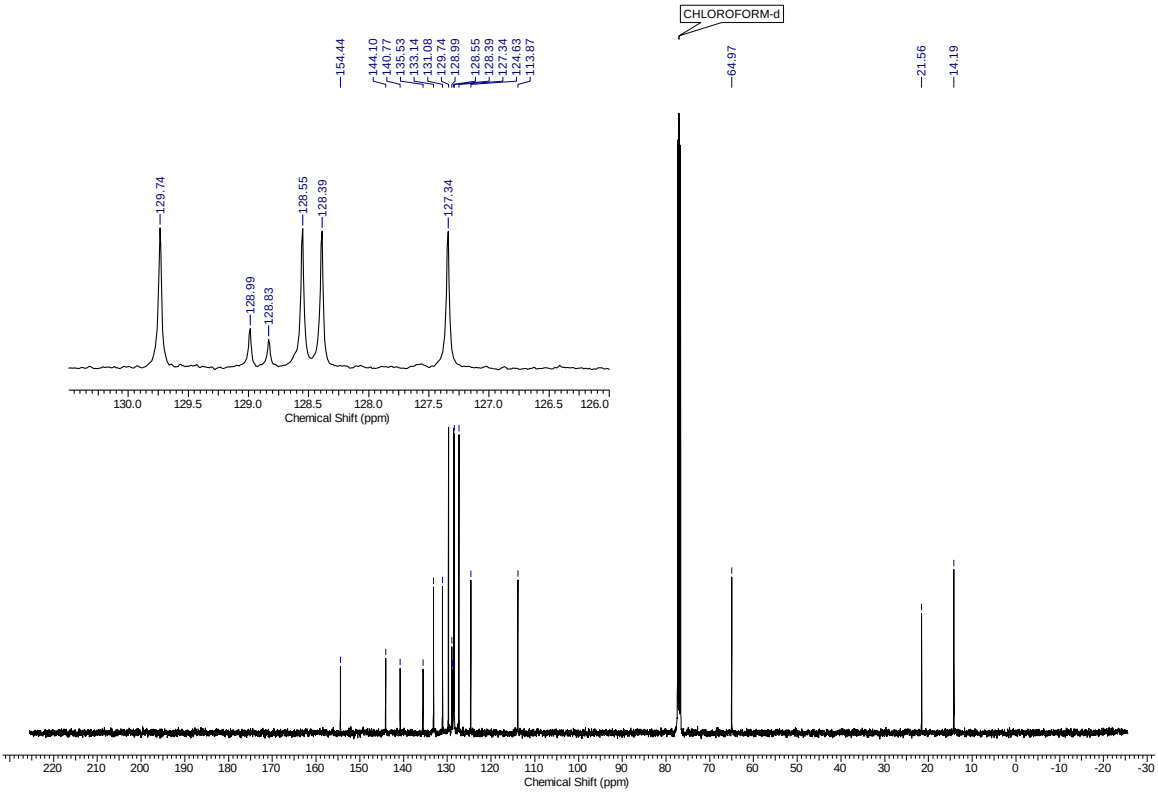

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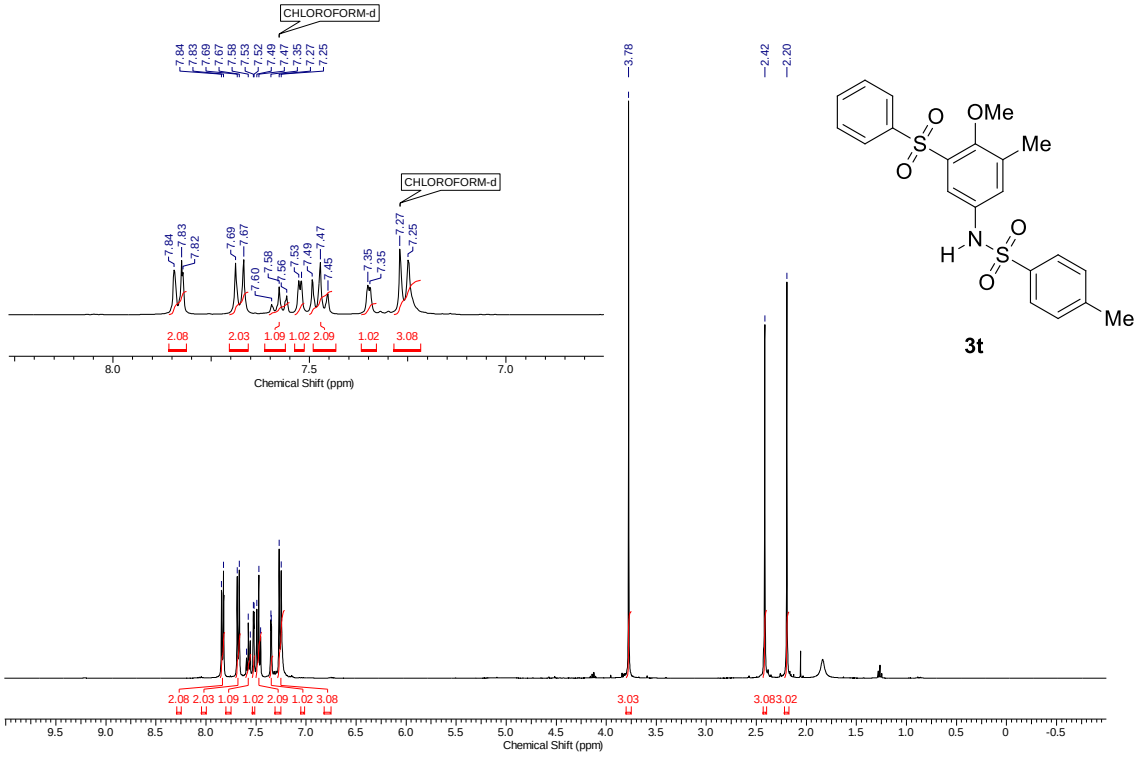

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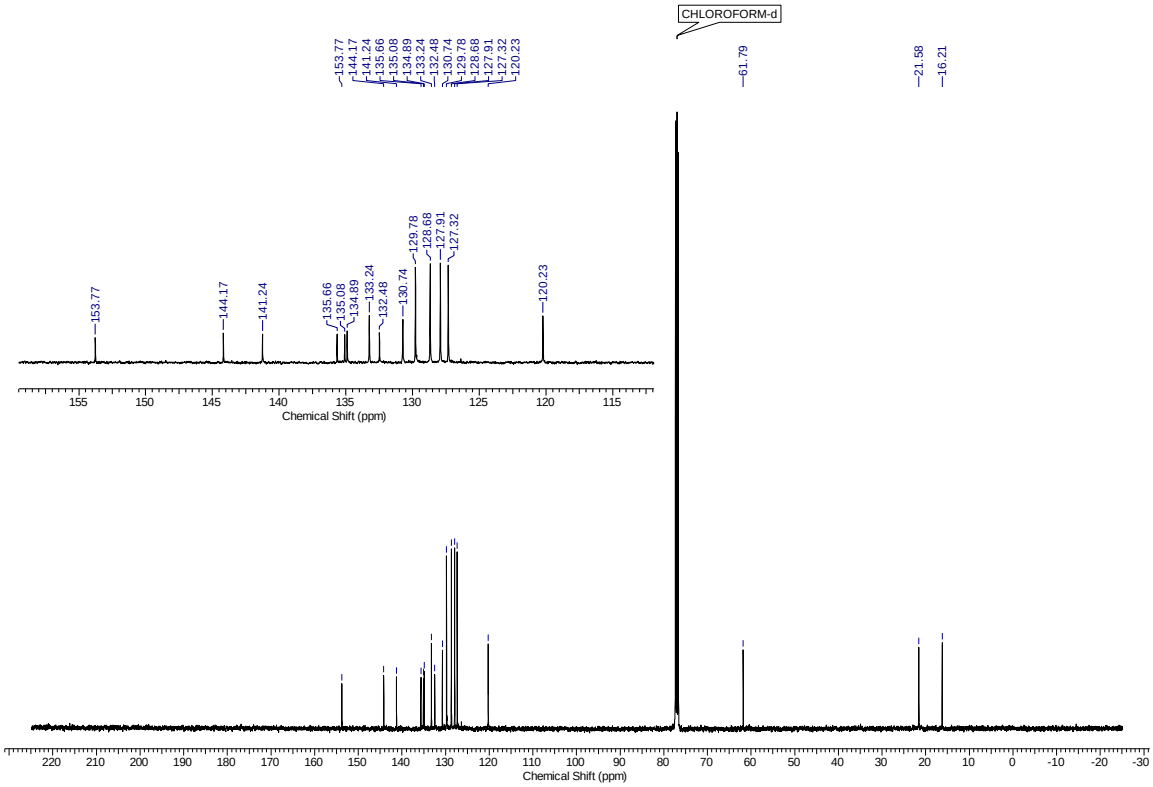

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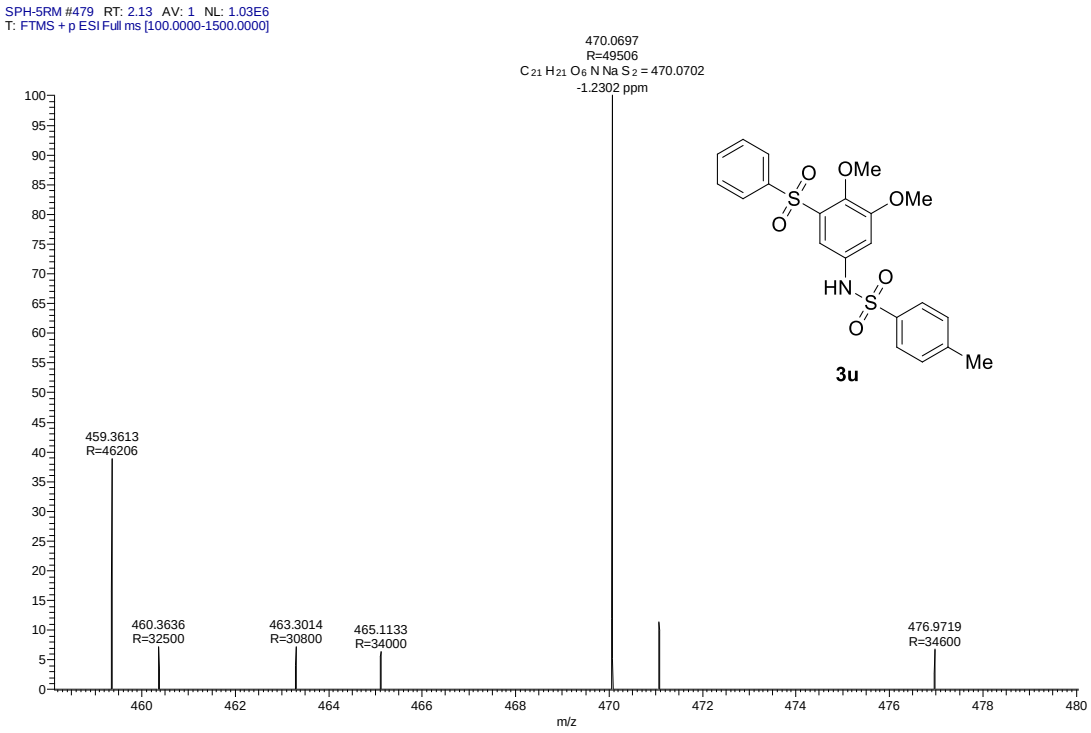

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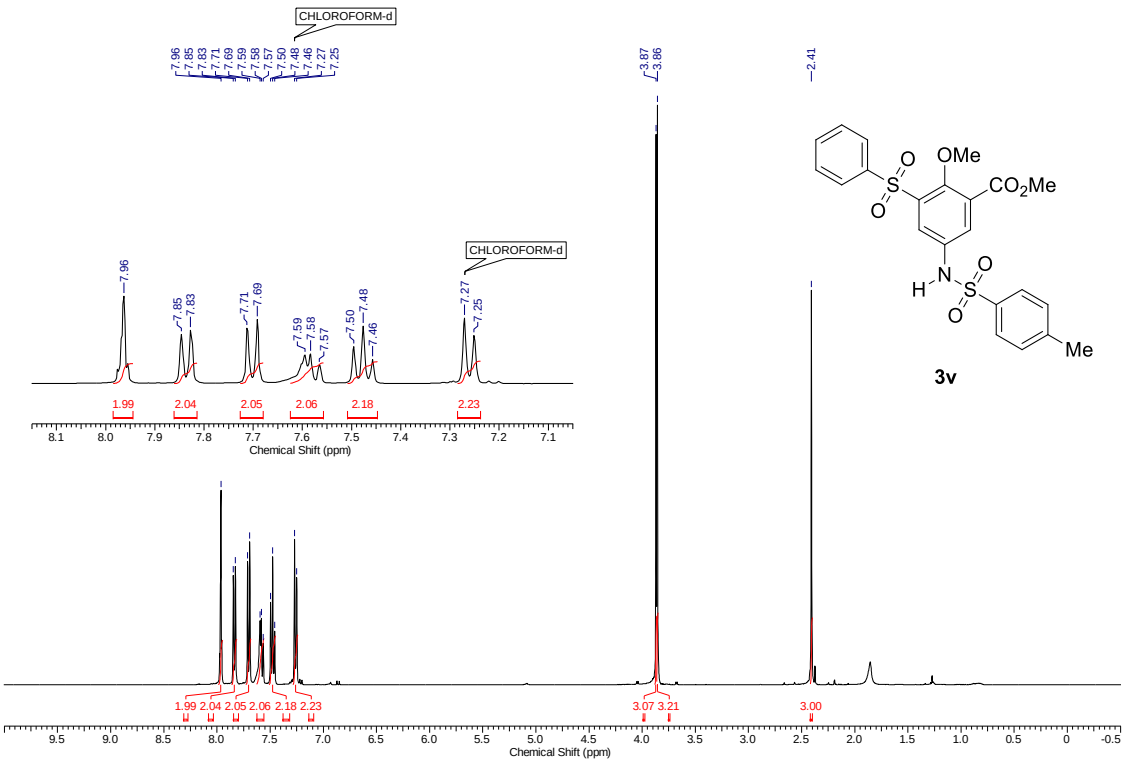

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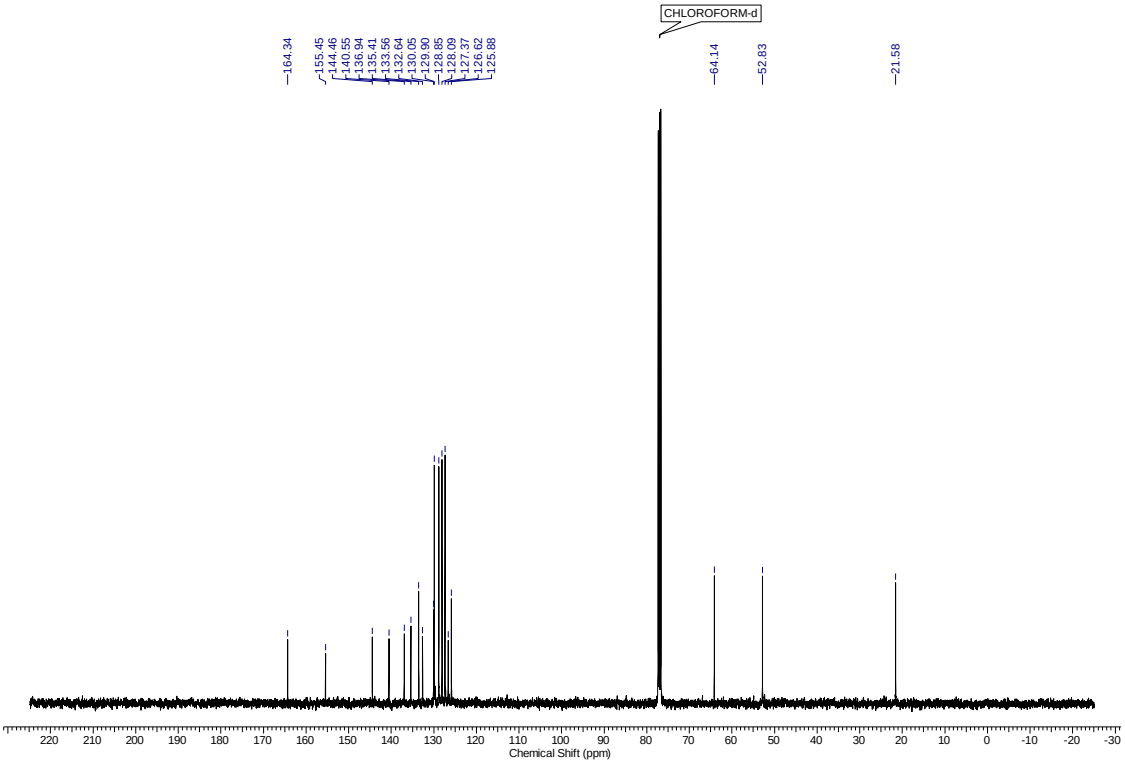

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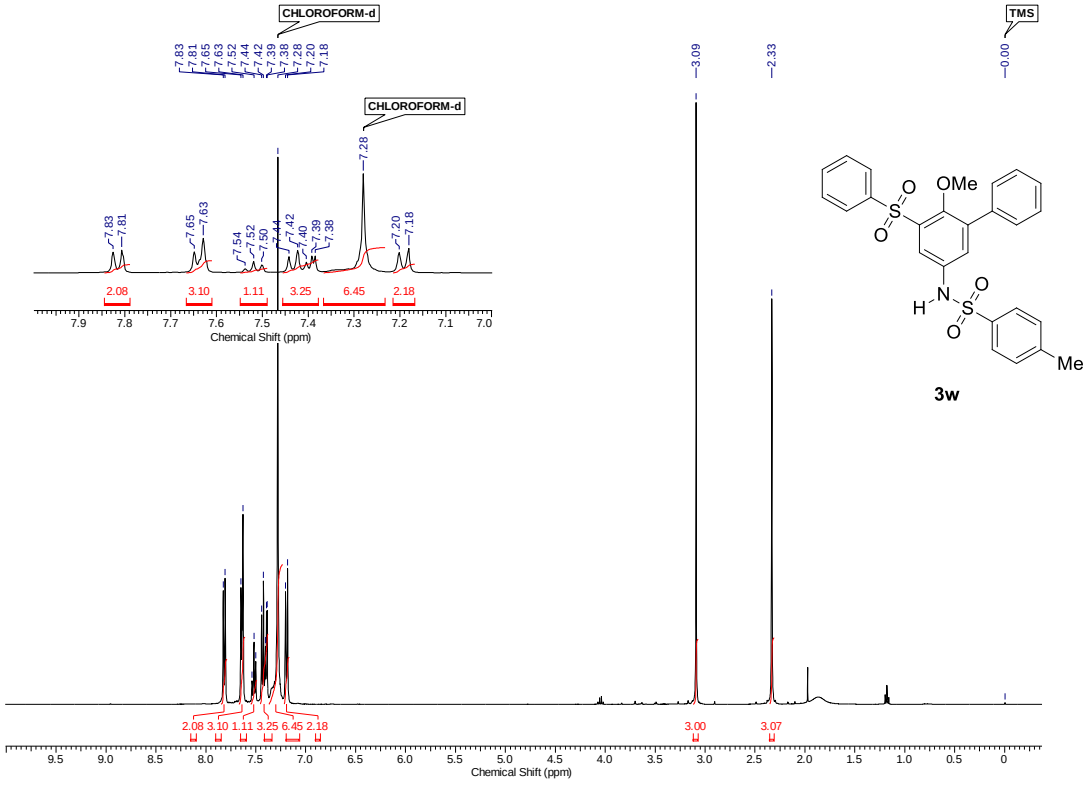

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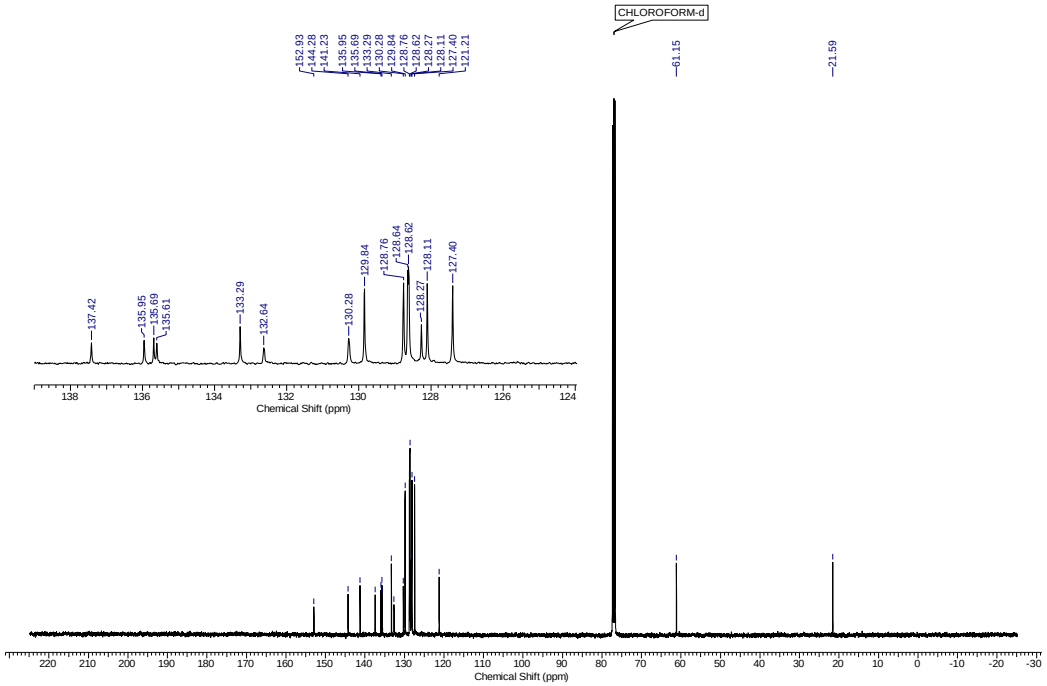
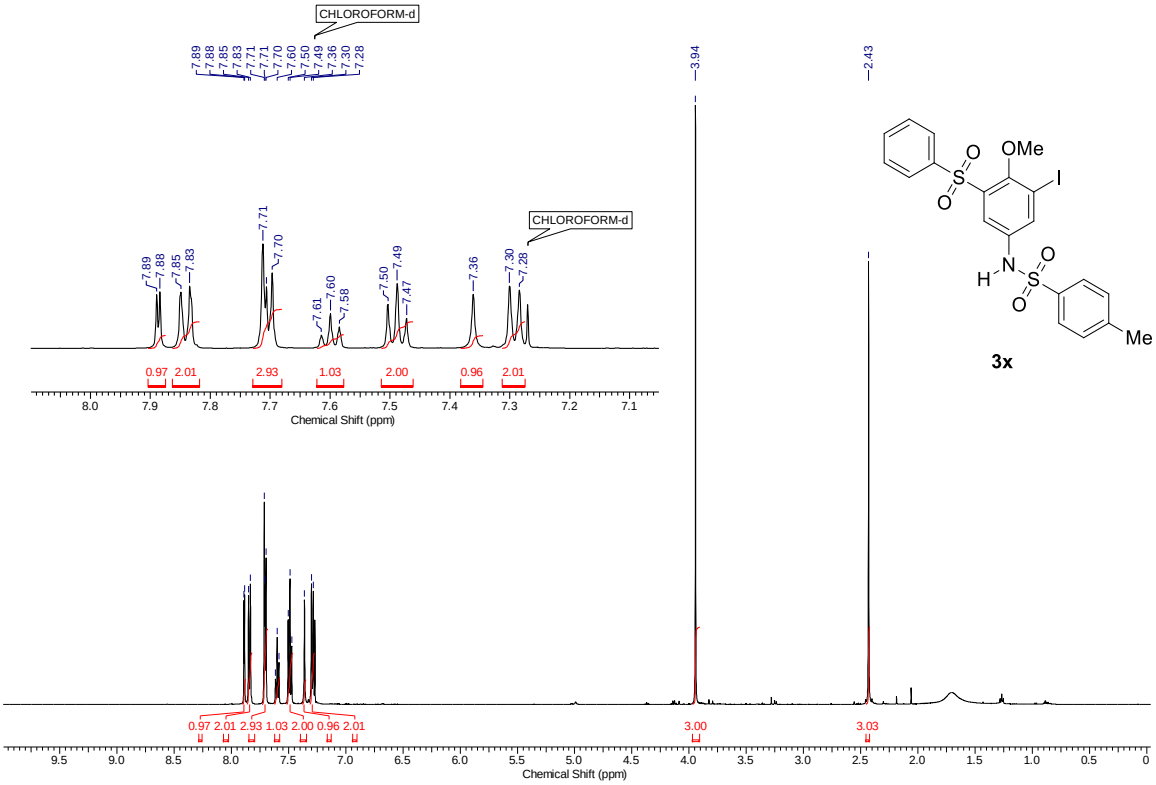
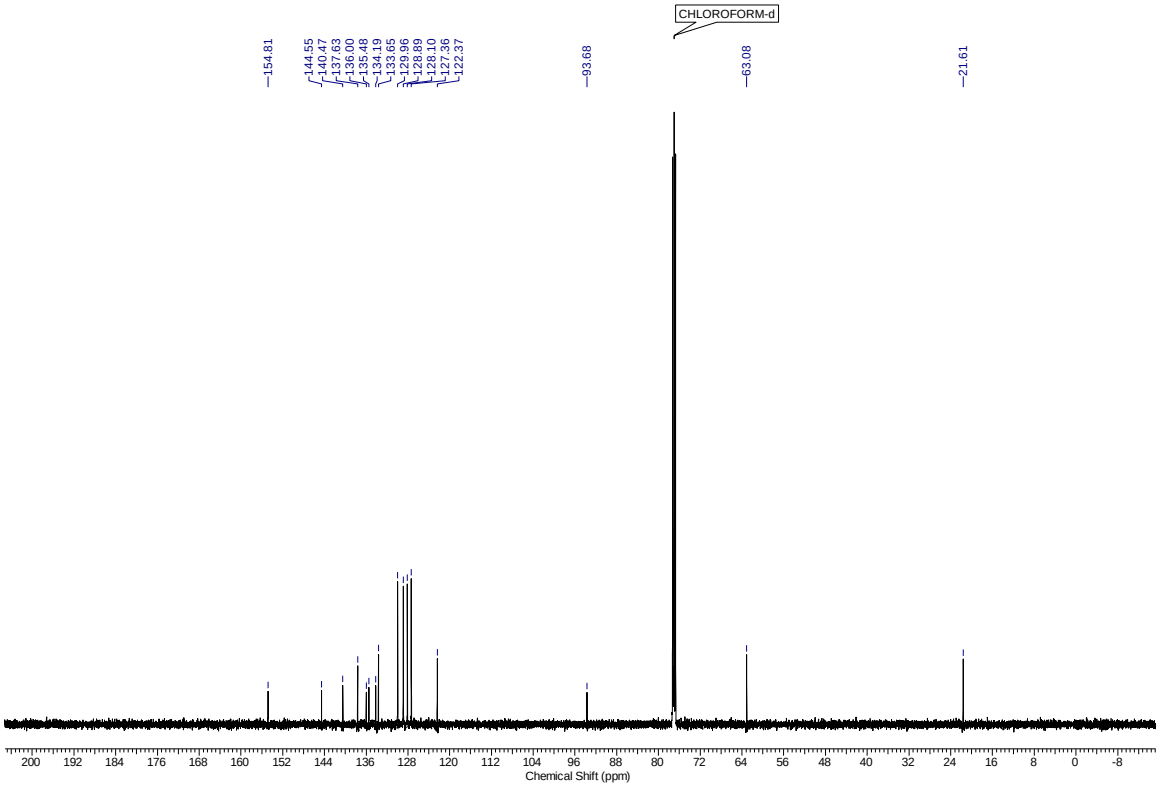


^{1}H NMR, 500 MHz



^{13}C NMR, 125 MHz



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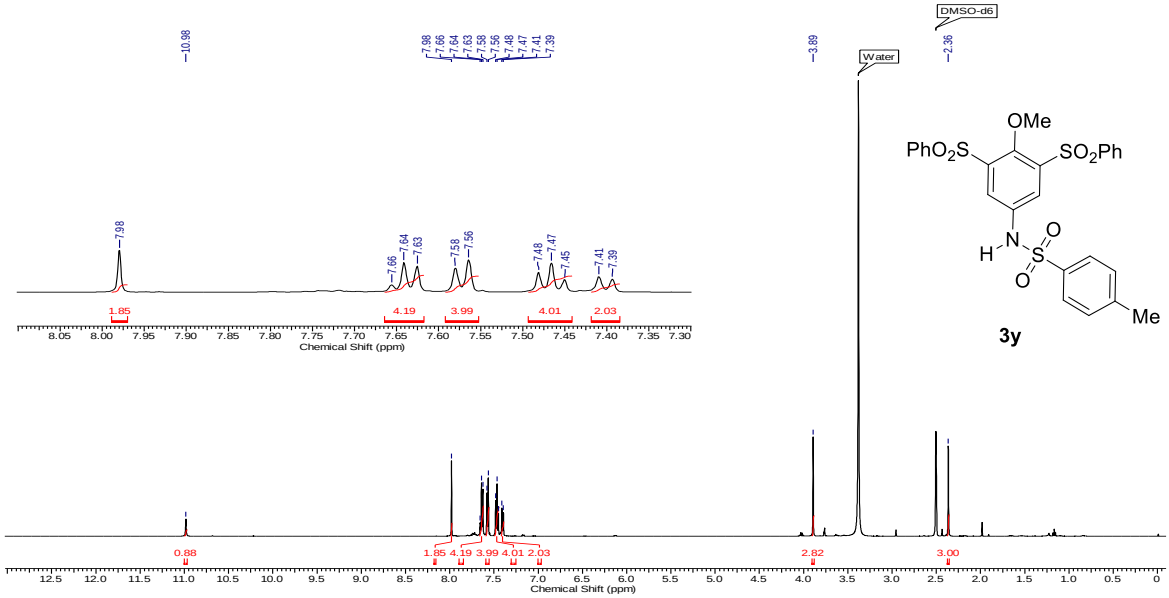

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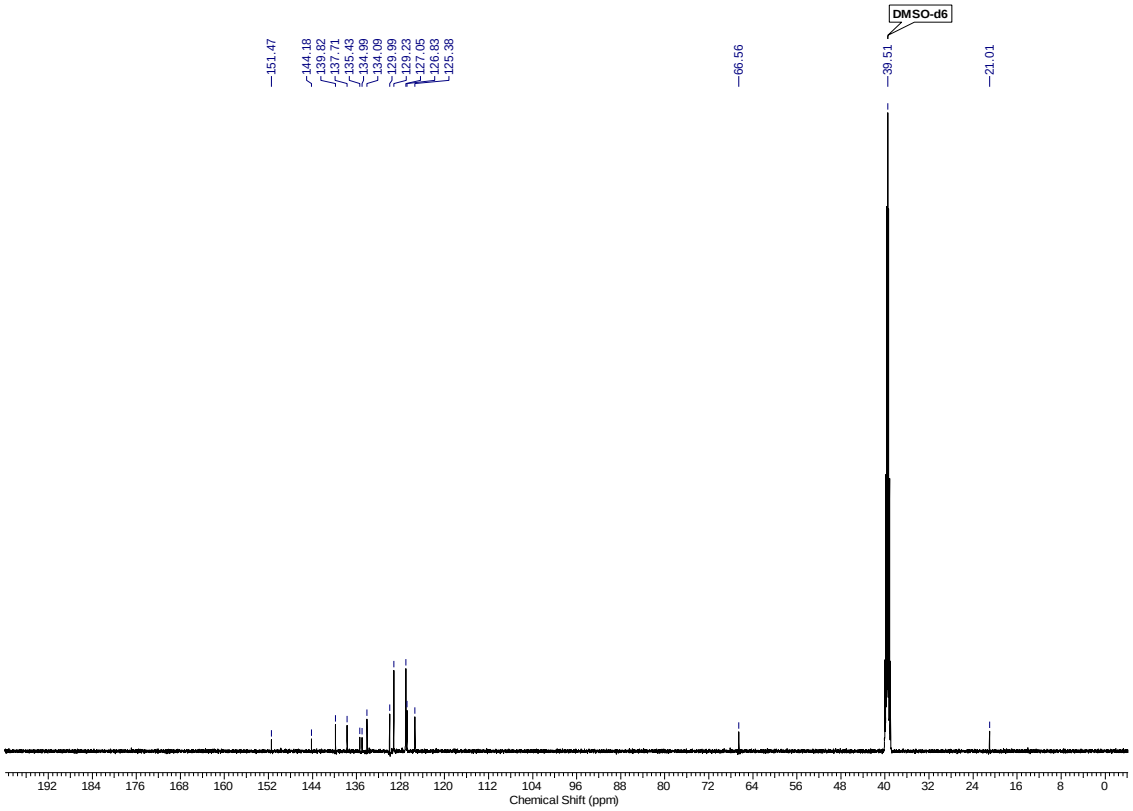

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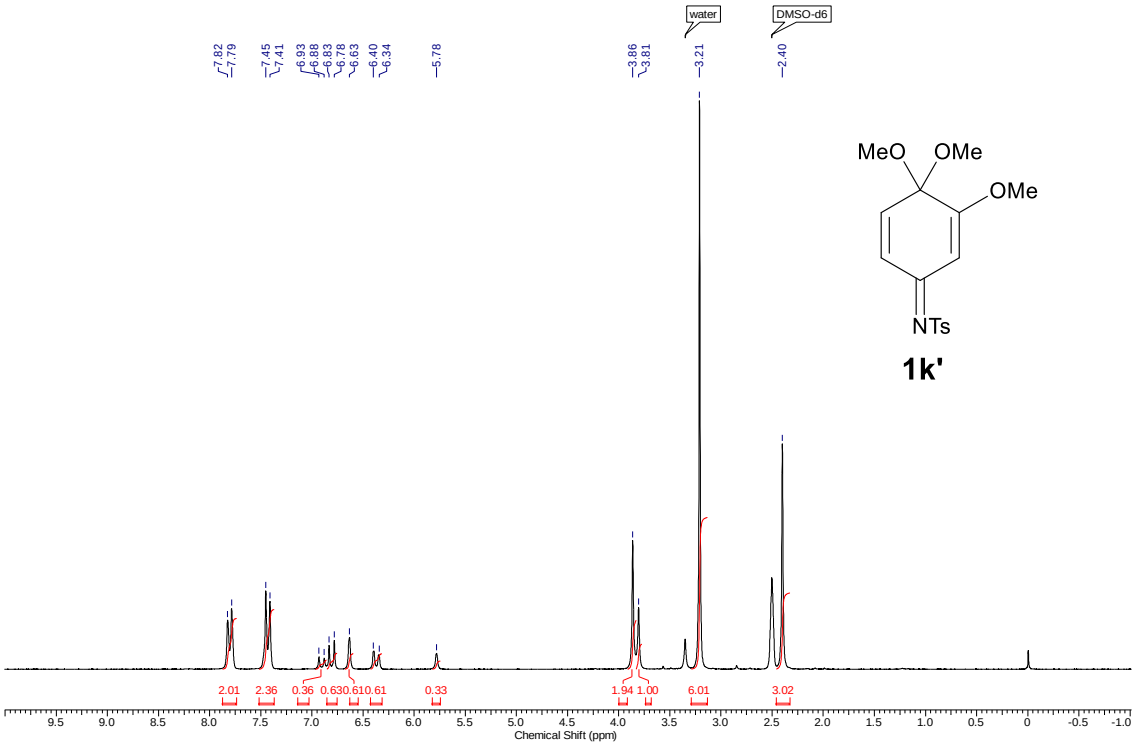
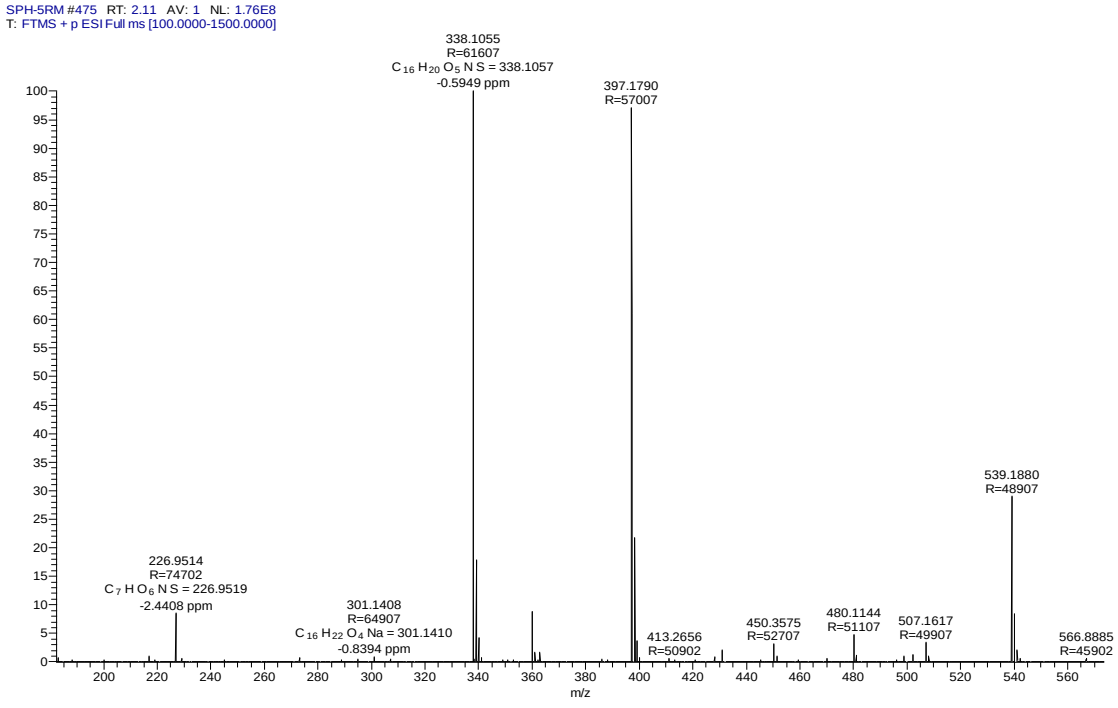


ESI-HRMS Spectra



Chapter 2

Section II

Construction of Unique SCF_3-Containing Building Blocks via Allylic Alkylation of Morita-Baylis-Hillman Adducts

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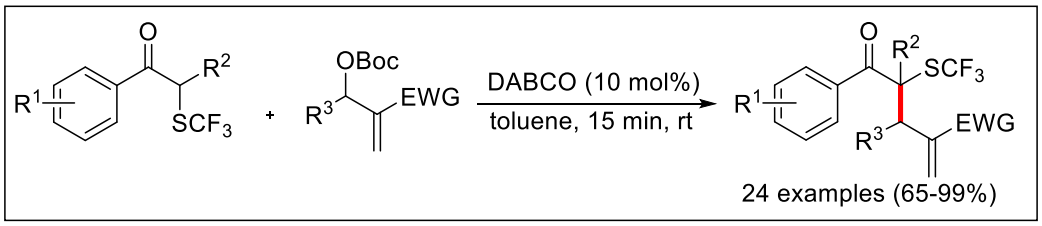
Calcatelli *et. al*. *Synthesis* **2020**, *52*, 2922.

Section II: Construction of Unique SCF_3-Containing Building Blocks via Allylic Alkylation of Morita-Baylis-Hillman Adducts

2.2.1. Abstract:

Section II demonstrates a novel method for the construction of SCF_3-containing building blocks by Lewis base-catalyzed allylic alkylation of Morita-Baylis-Hillman adducts with α-SCF_3 ketones. The developed strategy provides efficient access to a series of highly functionalized scaffolds featuring trifluoromethanesufinyl motif on a stereogenic carbon with an excellent yield and moderate enantioselectivity. Furthermore, the applicability of this method has been enhanced by offering a simple transformation of the trifluoromethylthioalkylated product to value-added building blocks.



2.2.2. Introduction:

Organofluorine compounds find significant applications in pharmaceuticals, agrochemicals, fine chemicals, and advanced materials owing to the inherent properties of the fluorine atom.[1] Substantial changes in the chemical, physical, and biological properties of an organic compound could be achieved by the incorporation of fluorine.[2] Although fluorine is the most abundant halogen in the earth's crust, natural products containing fluorine are incredibly scarce, which limits their usage as building blocks.[3] To fulfill the growing demand for fluorinated building blocks, the development of novel processes to synthesize structurally diverse organofluorine compounds is indispensable.[3,4]

The strong electron-withdrawing trifluoromethylthio (SCF_3) group is one of the most sought after among various fluorine-containing moieties.[5] It shows a remarkable effect on API's biological properties such as high lipophilicity parameter, protein binding affinity, and metabolic stability. These distinctive properties of SCF_3-containing drug candidates enhance their membrane permeability and absorption rate.[5c,6] Many bioactive molecules feature the SCF_3 group as a vital pharmacophore (Figure 1).[7] Therefore, the development of the new methods to incorporate SCF_3 moieties into organic compounds has been a subject of intensive research.[5,6,8]

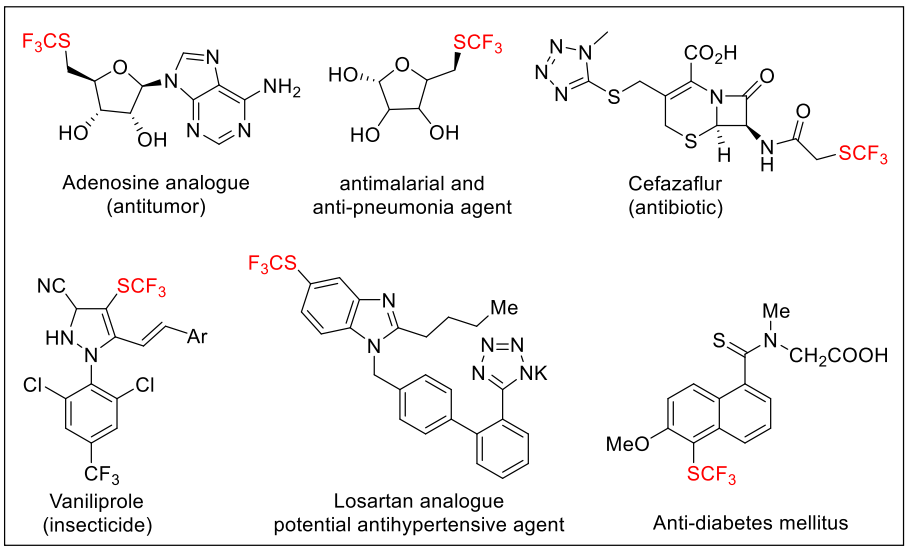


Figure 1. Bioactive compounds featuring SCF_3 moiety

2.2.3. Literature Review:

The classical methods include halogen-fluorine exchange reactions on chloro- or bromomethyl sulfides and the trifluoromethylation of sulfur-containing compounds.[9] In the past few decades, tremendous efforts have been devoted to the development of novel trifluoromethylthiolation reagents. A series of electrophilic, nucleophilic, radical, and oxidative trifluoromethylthiolation reagents have been developed and utilized in the transition-metal-catalyzed cross-coupling or C−H activation reactions.[10] Major pharmaceutical companies prefer outsourcing fluorinated

building blocks instead of in-house preparation to utilize them for the synthesis of more complex fluorinated compounds. Hence, making such processes and high value fluorinated building blocks readily accessible is an area of immense contemporary interest.[4,8f] In this context, recently, we have reported a novel method for the insertion of aryne into prefuntionalized α-SCF_3 ketones to access ortho-difunctionalized arenes having a trifluoromethylthio functional group.[11]

2.2.4. Origin of the Work:

In continuation of our research interest, we were curious to utilize Morita-Baylis-Hillman (MBH) adducts to synthesize highly functionalized SCF_3-containing building blocks from simple α-SCF_3 ketones. A literature survey revealed that trifluoromethyl and monofluoromethyl groups had been incorporated in MBH adducts via allylic alkylation.[12] Interestingly, direct trifluoromethylthiolation of MBH adducts was reported in 2015 by Cahard and co-workers[13] as well as Shi and co-workers[14] successively utilizing Zard's trifluoromethylthiolation reagent. Additionally, Cahard group elegantly utilized a combination of Ruppert-Prakash reagent, S_8, and KF to achieve the same transformation.[13] Shi and co-workers developed difluoromethylthiolation of MBH adducts of isatins using Zard's reagent.[15] Recently, Quing and co-workers reported trifluoromethylthiolation of MBH alcohols using $AgSCF_3$ in high yields and excellent regioselectivities.[16] However, the proposed reaction between α-SCF_3-ketones and MBH adducts to implant the SCF_3-group in an organic molecule has not been reported until now.

2.2.5. Objective of the Work:

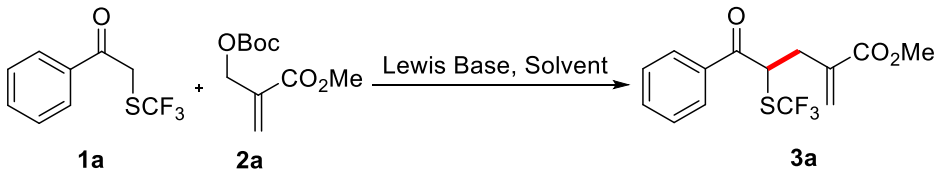
Because of the extensive occurrence of fluorine containing compounds in our every aspect of daily life and the distinctive biological properties of SCF_3-moiety on API, we thought that SCF_3 containing organic molecule could have great interest in the synthesis of pharmaceutically and

agrochemically important molecules. Our objective was to investigate the reactivity of α-SCF_3-ketones with MBH adducts and convert the trifluoromethylthio alkylated product to important fluorinated scaffolds for the synthesis of complex value-added molecules. Therefore, herein we have reported our studies on the allylic alkylation of MBH adducts with α-SCF_3 Ketones in the presence of catalytic Lewis base to afford the corresponding highly functionalized building blocks containing SCF_3 group on the stereogenic carbon center.

2.2.6. Result and discussion:

The optimization of the protocol was initially explored for the allylic alkylation of the MBH carbonate **2a** with α-SCF_3 ketone **1a** using various Lewis base catalysts in DCE at room temperature (Table 1, entries 1-4). DABCO was found to provide a better yield of the desired product **3a** in less time as compared to the other bases (Table 1, entry 4). Gratifyingly, we observed that the expected product **3a** was obtained in quantitative yield within 15 min. at room temperature when toluene was used as the solvent (Table 1, entry 8). It should be noted that the nonpolar solvent has a significant acceleration effect to improve the yield as compared to polar solvents (entries 4-8). Furthermore, the variation of catalyst loading was also examined. The use of less or more equivalents of the catalyst furnished lower yields though the starting material was consumed within 10-15 min. (Table 1, entries 9 & 10).

Table 1. Optimization of Reaction Condition[a,b]



1a **2a** **3a**

Sr. No.	*Solvent*	*Base*	*Base (equiv.)*	*Time*	*Yield (%)* [b]
1.	DCE	Et_3N	10 mol%	3 h	77
2.	DCE	DMAP	10 mol%	3 h	64

3.	DCE	DIPA	10 mol%	2 days	29
4.	DCE	DABCO	10 mol%	15 min	92
5.	dioxane	DABCO	10 mol%	15 min	88
6.	THF	DABCO	10 mol%	15 min	76
7.	ACN	DABCO	10 mol%	15 min	70
8.	toluene	DABCO	10 mol%	15 min	>99
9.	toluene	DABCO	5 mol%	15 min	83
10.	toluene	DABCO	8 mol%	15 min	86

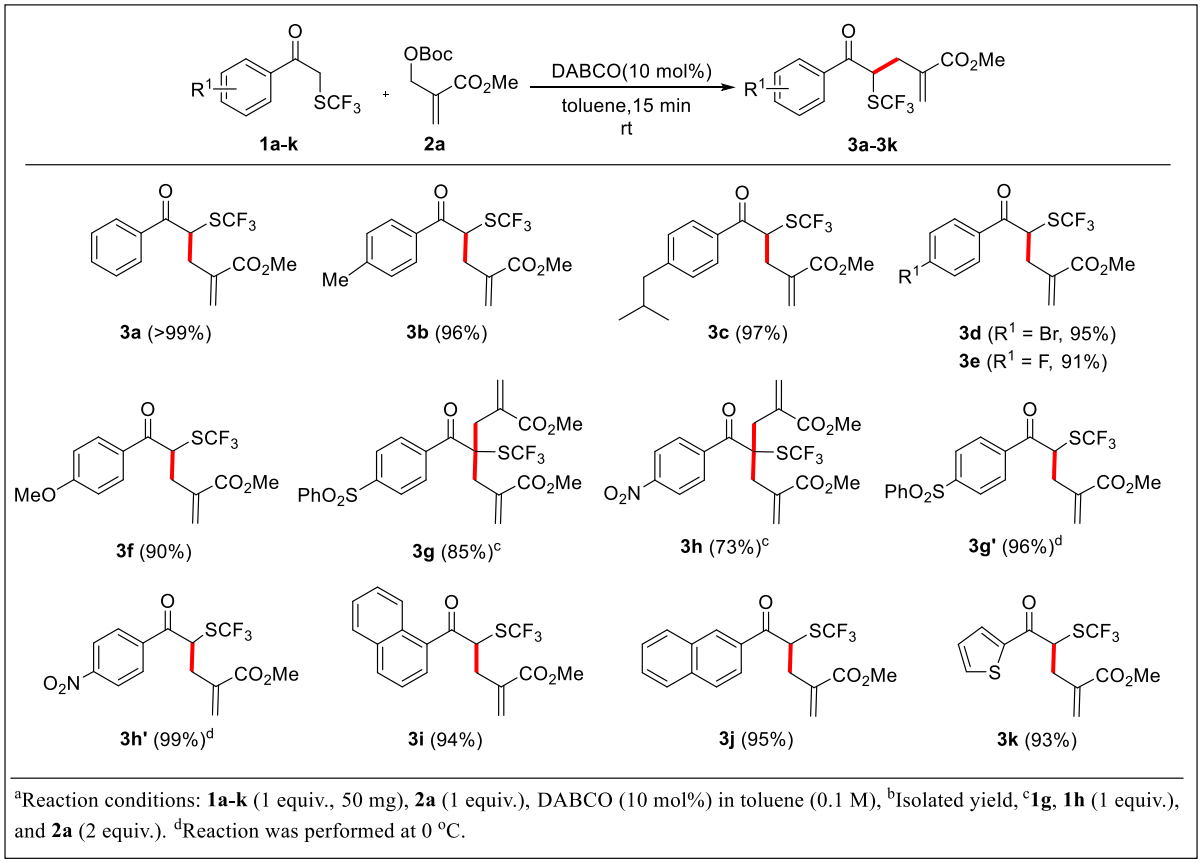
[a]Reaction conditions: **1a** (1 equiv., 20 mg, 0.09 mmol), **2a** (1 equiv., 20 mg, 0.09 mmol), base in solvent (0.1 M, 0.9 mL), [b]Isolated yield.

The reproducibility of the protocol was confirmed by performing the reaction on one millimole scale under the optimized reaction condition (Table 1, entry 8), which provided the trifluoromethylthiolated product **3a** in 99% yield demonstrating its scalability.

After optimizing the reaction condition, we focused on the substrate scope study of the newly developed protocol (Scheme 1). Initially, variation in the substituents (R^1) present on the aromatic ring of α-SCF_3 ketones was investigated. The α-SCF_3 ketone substrates with unsubstituted as well as alkyl-substituted aromatic ring worked well to furnish the desired products **3a**, **3b**, and **3c** in excellent yields. The halo substituted ketones **1d** and **1e** worked equally well to furnish the corresponding products **3d** and **3e** respectively. The optimized reaction condition was compatible with the electron-donating group, and the expected product **3f** was formed in 90% yield. However, electron-withdrawing group substituted ketones **1g** and **1h** directly furnished dialkylated products **3g** and **3h** instead of the desired products **3g'** and **3h'**, hence the reaction was taken to completion by taking two equivalents of MBH carbonates. Monoalkylated products **3g'** and **3h'** could be obtained exclusively in excellent yields by reducing the reaction temperature to 0 ^oC. It was reasoned that the electron-withdrawing group of the aromatic ring enhanced the acidic character of the proton alpha to the carbonyl of monoalkylated product. Hence, it can easily form a carbanion under the standard reaction

condition and react with another molecule of MBH carbonate **2a** to provide dialkylated products. We were pleased to find that the substrate with polyaromatic, as well as heteroaromatic ring also worked very well under the optimized condition and afforded the corresponding products **3i**, **3j**, and **3k** in excellent yields.

Scheme 1. Reaction of MBH Carbonates with Various Aryl Substituted α-SCF_3 Ketones[a, b]

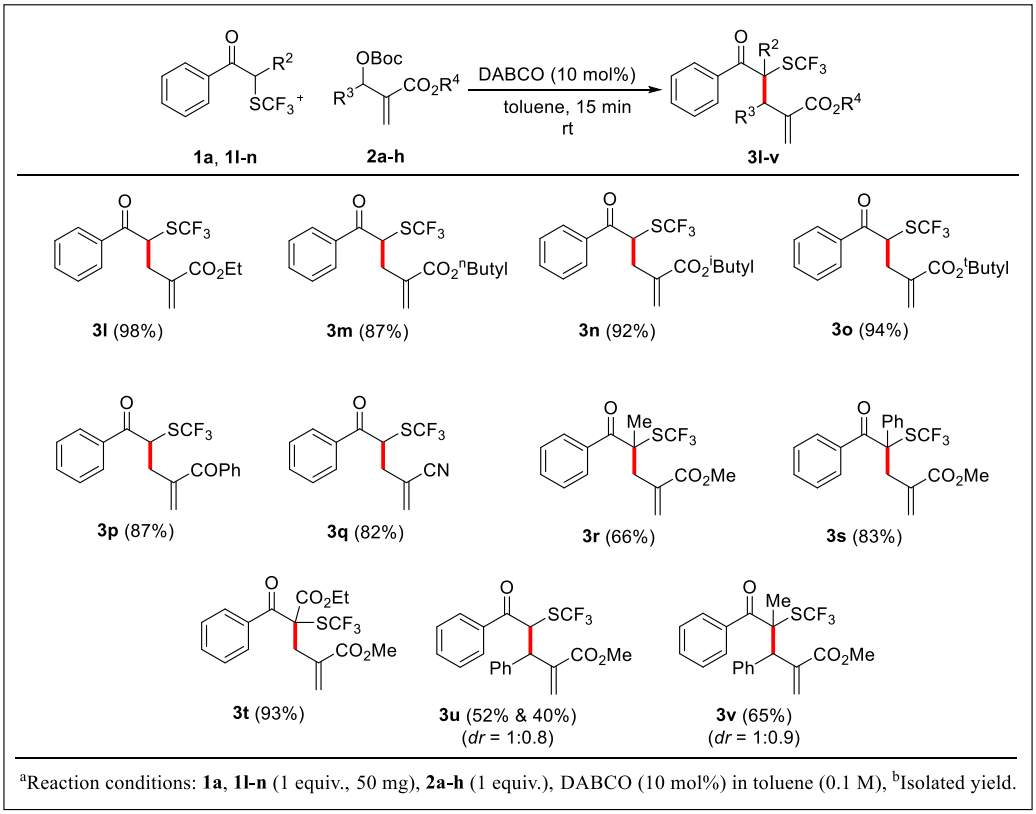


[a]Reaction conditions: **1a-k** (1 equiv., 50 mg), **2a** (1 equiv.), DABCO (10 mol%) in toluene (0.1 M), [b]Isolated yield, [c]**1g**, **1h** (1 equiv.), and **2a** (2 equiv.). [d]Reaction was performed at 0 °C.

We were prompted to explore the substrate scope by varying the substituents on MBH carbonates and α-position of phenyl ketones (Scheme 2). The reaction of substrates with variation in the ester group of MBH carbonate progressed smoothly to obtain the desired products **3l-3o** in excellent yields. The substrates containing phenyl ketone (**2f)** and cyano (**2g**) as an electron-withdrawing group also showed good compatibility and furnished the products **3p** and **3q** in very good yields. Furthermore, the developed protocol was also successfully employed

on α-substituted phenyl ketones and β-substituted MBH carbonates. Comparatively, less product formation was observed for the reaction between alkyl (α-Me) substituted ketone **1l** and MBH carbonate **2a**. However, the substrates **1m** and **1n** having electron-withdrawing phenyl and ethyl ester moieties respectively furnished the relevant products **3s** and **3t** smoothly with excellent yield. Finally, we scrutinized the reaction of the MBH carbonate **2h** having phenyl substituent at the α-position with the unsubstituted α-SCF_3 ketone **1a** and methyl-substituted α-SCF_3 ketones **1l**. Interestingly, this combination of substrates also worked smoothly under the developed conditions. The reaction between the substrates **1a** and **2h** provided the product **3u** as a separable diastereomeric mixture. However, the product **3v** was formed as an inseparable diastereomeric mixture with good yield.

Scheme 2. Substrate Scope for Allylic Alkylation Reaction[a,b]

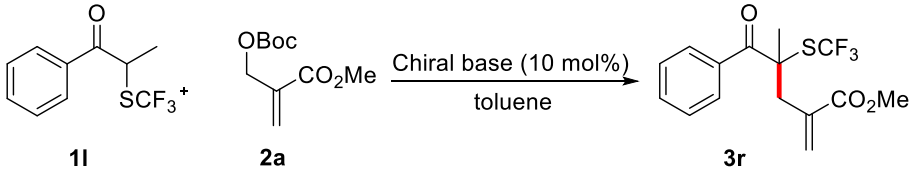


[a]Reaction conditions: **1a**, **1l-n** (1 equiv., 50 mg), **2a-h** (1 equiv.), DABCO (10 mol%) in toluene (0.1 M), [b]Isolated yield.

Overall, the developed process worked well for a wide range of substrates with varyingly substituted α-SCF_3 ketones as well as MBH adducts and provided the expected products with good to excellent yield.

After demonstrating the broad substrate scope successfully, a preliminary investigation of the enantioselectivity of the developed protocol using various chiral Lewis base catalysts was initiated. The reaction between α-SCF_3 ketone **1l** and MBH carbonate **2a** was performed in the presence of few commercially available chiral alkaloids as Lewis base catalysts in toluene (Table 2). Interestingly, $(DHQ)_2AQN$ showed good catalytic activity and provided the product with excellent yield and moderate enantioselectivity (Table 2, entry 3). Encouraged by this initial screening, we are now working on detailed studies by variation in substrates, catalysts, solvents, time, temperature, and additives.

Table 2. Preliminary Investigation of Enantioselectivity of the Reaction[a,b]



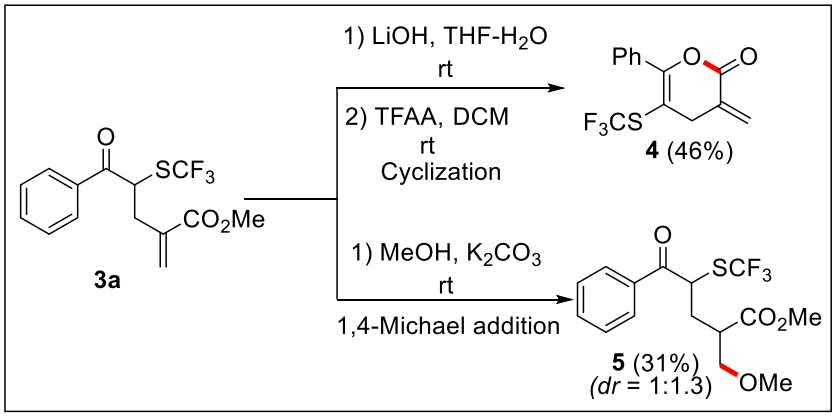
1l **2a** **3r**

Sr. no.	*Base*	*Temp*	*Time (h)*	*Yield (%)[b]*	*ee (%)[c]*
1.	Quinine	rt	24	86	13
2.	Cinchonidine	rt	24	94	8
3.	$(DHQ)_2AQN$	rt	24	93	49
4.	$(DHQ)_2PHAL$	rt	24	61	31
5.	$(DHQD)_2PYR$	rt	24	26	7
6.	$(DHQ)_2AQN$	10 °C	24	82	50
7.	$(DHQ)_2AQN$	0 °C	24	71	47

[a]Reaction conditions: **1l** (1 equiv., 20 mg, 0.085 mmol), **2a** (1 equiv., 19 mg, 0.085 mmol), base in solvent (0.1 M, 0.9 mL), [b]Isolated yield. NR= No Reaction.

The products obtained by the developed protocol may serve as important fluorinated building blocks for the synthesis of complex value-added products. We have demonstrated the synthetic utility of this protocol by cyclization and 1,4-Michael addition reaction of the representative trifluoromethylthio alkylated product **3a** (Scheme 3). Cyclization of the product **3a** was achieved by hydrolysis using LiOH, followed by the treatment with TFAA to obtain pyrone **4** in 46% yield. The product **4** features a pyrone moiety, which is a privileged scaffold in drug discovery. The treatment of compound **3a** with methanol in the presence of a mild base provided product **5** in 31% yield via the 1,4-Michael addition reaction. Similarly, other heteroatom or carbon nucleophiles can be reacted for the diversity-oriented synthesis of bigger libraries of fluorinated compounds for molecular screening in bioactivity studies or material applications.

Scheme 3. Further Transformations of Trifluoromethylthio Alkylated Product



2.2.7. Conclusion:

Fluorine-containing compounds are now an integral part of every aspect of daily life, and our ability to construct them efficiently will have a major impact on their wider applications. In this context, reported herein is a facile process to access highly functionalized SCF_3-containing building blocks via Lewis base-catalyzed allylic alkylation of MBH adducts with α-SCF_3

ketones. The developed protocol is mild and operationally simple. A variety of organofluorine compounds having SCF_3 moiety on the stereogenic carbon centre were smoothly prepared in good to excellent yields. Furthermore, the importance of this method has been established by converting the trifluoromethylthio alkylated product to value-added building blocks using simple transformations. Preliminary screening shows moderate enantioselectivity for a representative substrate using the chiral Lewis base $(DHQ)_2AQN$. Currently, we are focusing on the generalization of the chiral version of the protocol and its application in the synthesis of pharmaceutically and agrochemically important molecules.

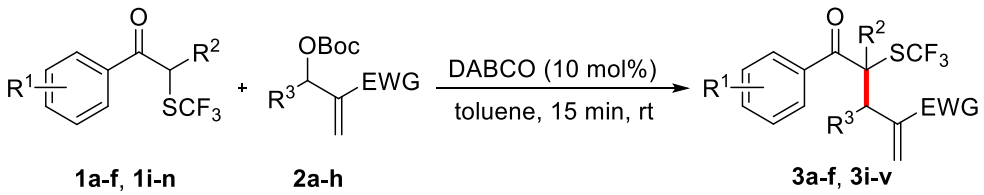
2.2.8. Experimental section

1. Additional Information:

All the α-SCF_3 ketones were prepared from the easily accessible α-bromo phenyl ketones[9c] using know literature procedures.[17] Morita-Baylis-Hillman (MBH) adducts were prepared as per the literature procedures.[18] All the Lewis base catalysts were purchased from the commercial sources.

2. Experimental Procedures:

a) General Experimental Procedure for the Preparation of Compounds 3a-f, 3i-v (Scheme 1 and Scheme 2):

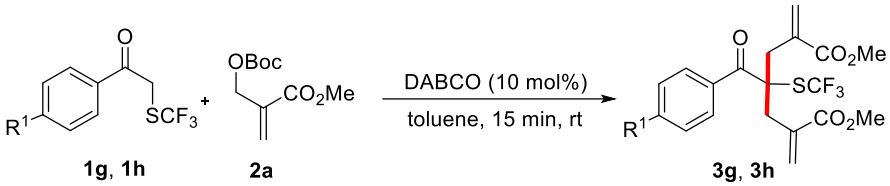


1a-f, 1i-n **2a-h** **3a-f, 3i-v**

To the solution of α-SCF_3 ketones **1a-f**, **1i-n** (1 equiv, 50 mg) in toluene (0.1 M) were added DABCO (10 mole %) and MBH adducts **2a-h** (1 equiv) at room temperature. The resulting

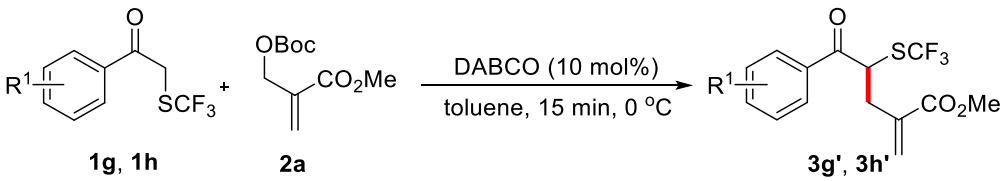
mixture was stirred at room temperature and the reaction progress was monitored by TLC (approx. 15 min). After completion of the reaction, toluene was evaporated in *vacuo* and the residue was purified by flash silica gel column chromatography using a gradient of ethyl acetate-petroleum ether to afford the products **3a-f**, **3i-v** in good to excellent yields (66-99%).

b) General Experimental Procedure for the Preparation of Compounds 3g and 3h (Scheme 1):



To the solution of α-SCF_3 ketones **1g** and **1h** (1 equiv, 50 mg) in toluene (0.1 M) were added DABCO (10 mole %) and MBH-carbonate **2a** (2 equiv) at room temperature. The resulting mixture was stirred at room temperature and the reaction progress was monitored by TLC (approx. 15 min). After completion of the reaction, toluene was evaporated in *vacuo* and the residue was purified by flash silica gel column chromatography using a gradient of ethyl acetate-petroleum ether to afford the products **3g** and **3h** in very good yields (85% and 73% respectively).

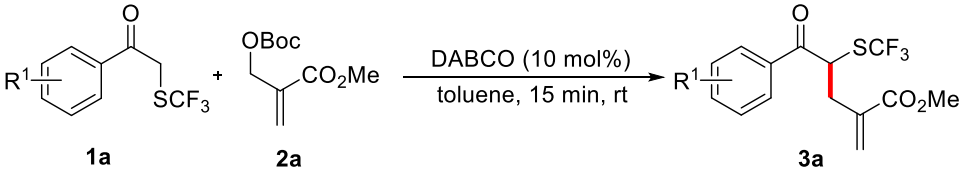
c) General Experimental Procedure for the Preparation of Compounds 3g' and 3h' (Scheme 1):



To the solution of α-SCF_3 ketones **1g** and **1h** (1 equiv, 50 mg) in toluene (0.1 M) were added DABCO (10 mole %) and MBH-carbonate **2a** (1 equiv) at 0 °C. The resulting mixture was

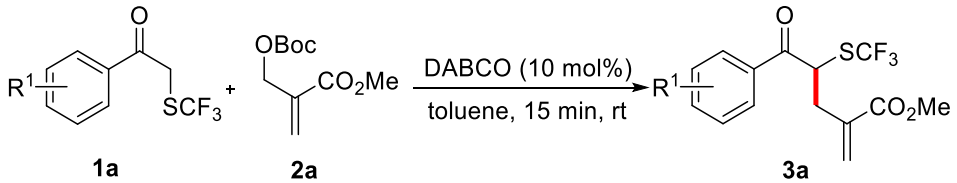
stirred at 0 °C and the reaction progress was monitored by TLC (approx. 15 min). After completion of the reaction, toluene was evaporated in *vacuo* and the residue was purified by flash silica gel column chromatography using a gradient of ethyl acetate-petroleum ether to afford the products **3g'** and **3h'** in excellent yields (96% and 99% respectively).

d) Typical Experimental Procedure for the Preparation of Compound 3a:



To the solution of α-SCF_3 ketone **1a** (1 equiv, 50 mg, 0.23 mmol) in toluene (0.1 M, 2.3 mL) were added DABCO (10 mole %, 2.6 mg, 0.023 mmol) and MBH-carbonate **2a** (1 equiv, 49.1 mg, 0.23 mmol) at room temperature. The resulting mixture was stirred at room temperature and the reaction progress was monitored by TLC (approx. 15 min). After completion of the reaction, toluene was evaporated in *vacuo* and the residue was purified by flash silica gel column chromatography using a gradient of ethyl acetate-petroleum ether (1:49) to afford the product **3a** in >99 % (71.7 mg) yield.

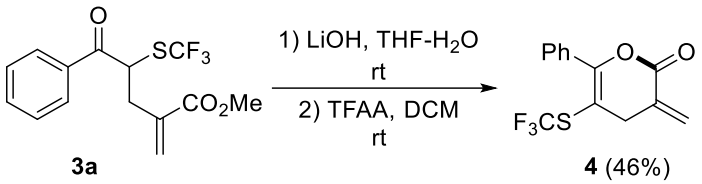
e) Representative Experimental Procedure at 1 mmol Scale for the Synthesis of Compound 3a:



To the solution of α-SCF_3 ketone **1a** (1 equiv, 220 mg, 1 mmol) in toluene (0.1 M, 22 mL) were added DABCO (10 mole %, 11.2 mg) and MBH-carbonate **2a** (1 equiv, 216 mg, 1 mmol) at

room temperature. The resulting mixture was stirred at room temperature and the reaction progress was monitored by TLC (approx. 15 min). After completion of the reaction, toluene was evaporated in *vacuo* and the residue was purified by flash silica gel column chromatography using a gradient of ethyl acetate-petroleum ether (1:49) to afford the product **3a** in 99 % (314.8 mg) yield.

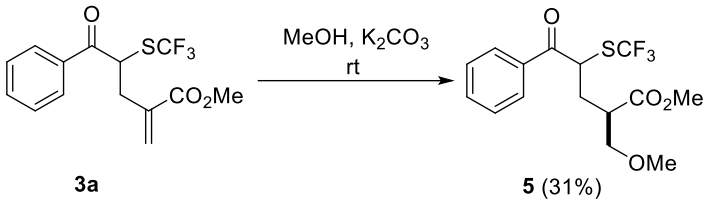
f) Experimental Procedure for the Preparation of Pyrone 4:



3a **4** (46%)

A modified literature procedure was used for the preparation of pyrone **4**.[4] To the solution of compound **3a** (100 mg, 0.314 mmol) in aqueous THF (1:1) was added LiOH (66 mg, 1.57 mmol, 5 equiv.) at room temperature. The resulting mixture was stirred for 2 hrs at room temperature. After complete consumption of **3a**, the reaction mixture was acidified with dilute HCl solution and extracted with DCM (15 mL x 3). The DCM layer was dried over with $MgSO_4$ and evaporated in *vacuo* to obtain a crude acid intermediate as a white solid in 99% (95 mg) yield. To the solution of the crude acid (80 mg, 0.263 mmol) in DCM (4 mL) was added trifluoroacetic anhydride (TFAA, 111 mg, 0.526 mmol, 2 equiv) and the reaction mixture was stirred at room temperature for 2 h. After the usual aqueous extractive workup followed by column chromatographic purification process using a gradient of ethyl acetate-petroleum ether (1:19), pyrone **4** was obtained as a colourless liquid in 46% yield (34.6 mg).

g) Experimental Procedure for the Preparation of Compound 5:



3a **5** (31%)

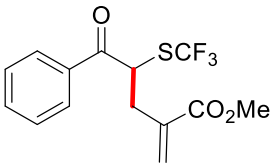
To the solution of the compound **3a** (100 mg, 1 equiv, 0.314 mmol) in MeOH (4 mL) was added K_2CO_3 (87 mg, 2 equiv, 0.629 mmol) and the resulting mixture was stirred overnight at 50 ^oC. After completion of the reaction, MeOH was evaporated by rotatory vacuum and the residue was purified by flash silica gel column chromatography using a gradient of ethyl acetate-petroleum ether (1:12) to afford the product **5** in 31% (34.1 mg) yield.

3. Characterization Data of Compounds:

Methyl 2-methylene-5-oxo-5-phenyl-4-((trifluoromethyl)thio)pentanoate (3a)

Reaction time: 15 min.; R*f*: 0.5 (1:19, EtOAc:Pet. ether); thick oil; 71.7 mg, >99% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.9 Hz, 2H), 7.64 (t, *J* = 7.3 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 2H), 6.30 (s, 1H), 5.75 (s, 1H), 5.25 (t, *J* = 7.6 Hz, 1H), 3.78 (s, 3H), 3.17 (dd, *J* = 14.0 and 6.7 Hz, 1H), 2.85 (dd, *J* = 14.0 and 7.9 Hz, 1H).



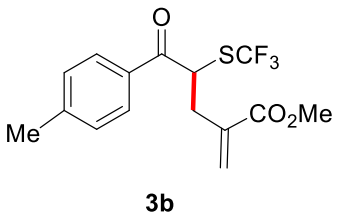
3a

^{13}C NMR (100 MHz, $CDCl_3$) δ 195.9, 166.8, 134.8, 134.7, 134.1, 130.5, 130.3 (q, *J* = 301 Hz, CF_3), 129.0, 128.7, 52.1, 46.2, 36.2.

HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{14}H_{13}F_3O_3SNa$ 341.0430, found 341.0428.

Methyl 2-methylene-5-oxo-5-(p-tolyl)-4-((trifluoromethyl)thio) pentanoate (3b)

Reaction time: 15 min.; R*f*: 0.5 (1:19, EtOAc:Pet. ether); thick oil; 68 mg, 96% yield.



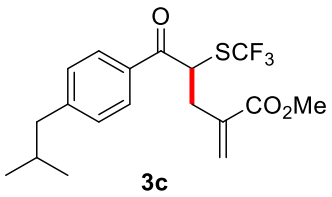
3b

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 8.5 Hz, 2H), 7.31 (d, J = 7.9 Hz, 2H), 6.28 (s, 1H), 5.74 (s, 1H), 5.23 (t, J = 7.3 Hz, 1H), 3.78 (s, 3H), 3.15 (dd, J = 14.0 and 7.3 Hz, 1H), 2.84 (dd, J = 14.0 and 7.3 Hz, 1H), 2.44 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 195.4, 166.8, 145.3, 134.9, 132.2, 130.38 (q, J = 306.7 Hz, CF_3), 130.35, 129.7, 128.9, 52.1, 46.1, 36.3, 21.7.

HRMS (ESI-TOF) m/z: $[M+Na]^+$calcd for $C_{15}H_{15}F_3O_3SNa$ 355.0586, found 355.0583.

Methyl-5-(4-isobutylphenyl)-2-methylene-5-oxo-4((trifluoromethyl)thio)pentanoate (3c)



3c

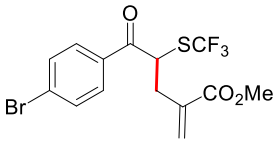
Reaction time: 15 min.; R*f*: 0.5 (1:19, EtOAc:Pet. ether); thick oil; 66 mg, 97% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 7.9 Hz, 2H), 7.20 (d, J = 8.5 Hz, 2H), 6.20 (s, 1H), 5.66 (s, 1H), 5.15 (t, J = 7.3 Hz, 1H), 3.69 (s, 3H), 3.08 (dd. J = 14.0 and 6.7 Hz, 1H), 2.76 (dd, J = 13.4, 7.3 Hz, 1H), 2,47 (d, J = 7.3 Hz, 2H), 1.84 (septet, J = 6.7 Hz, 1H), 0.84 (d, J = 6.7 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 195.4, 166.8, 148.9, 134.9, 132.4, 130.1 (q, J = 307.4 Hz, CF_3), 130.4, 129.7, 128.7, 52.1, 46.2, 45.4, 36.4, 30.1, 22.3.

HRMS (ESI-TOF) m/z: $[M+Na]^+$calcd for $C_{18}H_{21}F_3O_3SNa$ 397.1056, found 397.1057.

Methyl 5-(4-bromophenyl)-2-methylene-5-oxo-4-((trifluoromethyl)thio)pentanoate (3d)



3d

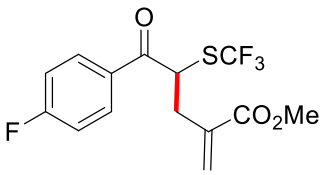
Reaction time: 15 min.; R*f*: 0.5 (1:19, EtOAc:Pet. ether); thick oil; 63 mg, 95% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 8.5 Hz, 2H), 6.22 (s, 1H), 5.67 (s, 1H), 5.10 (t, *J* = 7.6 Hz, 1H), 3.70 (s, 3H), 3.06 (dd, *J* = 14.0 and 6.7 Hz, 1H), 2.74 (dd, *J* = 14.0 and 7.9 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 194.9, 166.8, 134.7, 133.4, 132.3, 130.6, 130.21 (q, *J* = 308.3 Hz, CF_3), 130.19, 129.6, 52.1, 46.1, 36.2.

HRMS (ESI-TOF) m/z: $[M+Na]^+$calcd for $C_{14}H_{12}F_3{}^{81}BrO_3SNa$ 420.9514, found 420.9505.

Methyl 5-(4-fluorophenyl)-2-methylene-5-oxo-4-((trifluoromethyl)thio)pentanoate (3e)



3e

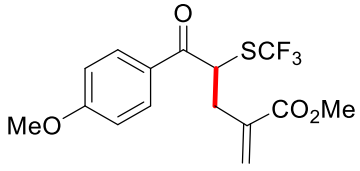
Reaction time: 15 min.; R*f*: 0.5 (1:19, EtOAc:Pet. ether); thick oil; 64 mg, 91% yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 8.08-7.89 (m, 2H), 7.23-7.03 (m, 2H), 6.23 (d, *J* = 0.9 Hz, 1H), 5.68 (d, *J* = 1.0 Hz, 1H), 5.13 (dd, *J* = 7.7 and 6.6 Hz, 1H), 3.71 (s, 3H), 3.07 (dd, *J* = 14.0 and 6.8 Hz, 1H), 2.74 (dd, *J* = 14.0 and 8.1 Hz, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 194.3, 166.8, 166.3 (d, *J* = 256.9 Hz, C-F), 134.7, 131.5 (d, *J* = 9.5 Hz), 131.1 (d, *J* = 2.9 Hz), 130.5, 130.3 (q, *J* = 307.7 Hz, CF_3), 116.2 (d, *J* = 22.0 Hz), 52.1, 46.2, 36.3.

HRMS (ESI-TOF) m/z: $[M+Na]^+$calcd for $C_{14}H_{12}F_4O_3SNa$ 359.0335, found 359.0333.

Methyl-5-(4-methoxyphenyl)-2-methylene-5-oxo-4-((trifluoromethyl)thio)pentanoate (3f)



3f

Reaction time: 15 min.; R*f*: 0.5 (1:9, EtOAc:Pet. ether); thick oil; 63 mg, 90% yield.

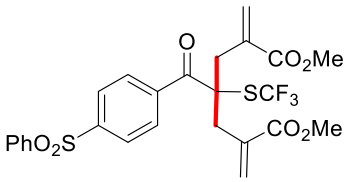
^{1}H NMR (200 MHz, $CDCl_3$) δ 8.01 (d, *J* = 9.0 Hz, 2H), 7.00 (d, *J*

= 9.0 Hz, 2H), 6.28 (s, 1H), 5.74 (s, 1H), 5.21 (t, *J* = 7.5 Hz, 1H), 3.89 (s, 3H), 3.78 (s, 3H), 3.15 (dd, *J* = 13.9 and 7.1 Hz, 1H), 2.83 (dd, *J* = 13.9 and 7.8 Hz, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 194.3, 166.8, 164.4, 134.9, 131.2, 130.5 (q, *J* = 307.3 Hz, CF_3), 130.3, 127.5, 114.2, 55.6, 52.1, 46.0, 36.5.

HRMS (ESI-TOF) m/z: $[M+Na]^+$calcd for $C_{15}H_{15}F_3O_4SNa$ 371.0535, found 371.0532.

Dimethyl 2,6-dimethylene-4-(4-(phenylsulfonyl)benzoyl)-4-(trifluoromethyl)thio)heptanedioate (3g)



3g

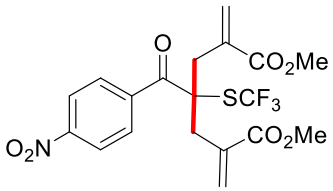
Reaction time: 15 min.; R*f*: 0.5 (1:4, EtOAc:Pet. ether); white solid, 66 mg, 85% yield; Mp = 117-119 ^oC.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.5 Hz, 2H), 7.93-7.86 (m, 4H), 7.53 (t, *J* = 7.3 Hz, 1H), 7.46 (t, *J* = 7.3 Hz, 2H), 6.28 (s, 2H), 5.65 (s, 2H), 3.54 (s, 6H), 3.23-3.07 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 197.7, 167.1, 144.5, 140.7, 140.6, 134.2, 133.7, 130.3, 129.9, 129.5, 129.3(q, *J* = 310.6 Hz, CF_3), 127.9, 127.4, 64.8, 52.2, 37.0.

HRMS (ESI-TOF) m/z: $[M+Na]^+$calcd for $C_{25}H_{23}F_3O_7S_2Na$ 579.0730, found 579.0730.

Dimethyl-2,6-dimethylene-4-(4-nitrobenzoyl)-4-((trifluoromethyl)thio)heptanedioate (3h)



3h

Reaction time: 15 min.; R*f*: 0.5 (3:17, EtOAc:Pet. ether); thick oil; 63 mg, 73% yield.

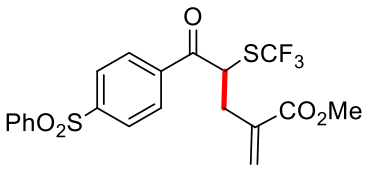
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.5 Hz, 2H), 8.06 (d, *J* =

8.5 Hz, 2H), 6.33 (s, 2H), 5.71 (s, 2H), 3.60 (s, 6H), 3.27-3.12 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 167.1, 149.5, 142.0, 134.2, 130.4, 130.2, 129.7 (q, J = 309.8 Hz, CF_3), 123.3, 64.8, 52.2, 37.1.

HRMS (ESI-TOF) m/z: $[M+Na]^+$calcd for $C_{19}H_{18}F_3O_7NSNa$ 484.0648, found 484.0650.

Methyl 2-methylene-5-oxo-5-(4-(phenylsulfonyl)phenyl)-4-((trifluoromethyl)thio)pentanoate (3g')



3g'

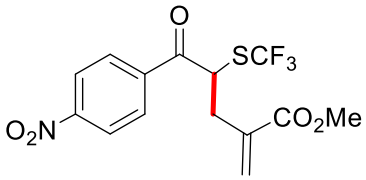
Reaction time: 15 min.; R*f*: 0.2 (1:1, DCM:Pet. ether); White solid; 61 mg, 96% yield at 0^o C; MP = 110-112 ^{o}C.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18-8.04 (m, 4H), 7.98 (d, J = 7.6 Hz, 2H), 7.66- 7.51 (m, 3H), 6.30 (s, 1H), 5.76 (s, 1H), 5.18 (t, J = 7.1 Hz, 1H), 3.76 (s, 3H), 3.14 (dd, J = 14.1 and 6.9 Hz, 1 H), 2.81 (dd, J = 13.7 and 8.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 194.6, 166.8, 146.3, 140.5, 138.1, 134.4, 133.8, 130.8, 129.52, 129.50, 130.0 (q, J = 308.0 Hz, CF_3), 128.2, 128.0, 52.2, 46.5, 35.9.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{20}H_{18}F_3O_5S_2$ 459.0542, found 459.0539.

Methyl 2-methylene-5-(4-nitrophenyl)-5-oxo-4-((trifluoromethyl)thio)pentanoate (3h')



3h'

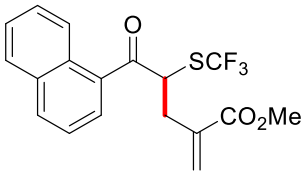
Reaction time: 15 min.; R*f*: 0.2 (1:19, EtOAc:Pet. ether); yellow thick oil; 67.8 mg, 99% yield at 0^o C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, J = 9.2 Hz, 2H), 8.19 (d, J = 9.2 Hz, 2H), 6.34 (s, 1H), 5.80 (s, 1H), 5.22 (t, J = 7.3 Hz, 1H), 3.79 (s, 3H), 3.18 (dd, J = 14.0 and 6.7 Hz, 1H), 2.83 (dd, J = 14.0 and 7.9 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 194.4, 166.8, 150.8, 139.3, 134.4, 130.0 (q, J = 307.5 Hz, CF_3), 130.8, 129.8, 124.1, 52.2, 46.6, 35.9.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{14}H_{13}F_3O_5SN$ 364.0461, found 364.0459.

Methyl 2-methylene-5-(naphthalen-1-yl)-5-oxo-4-((trifluoromethyl)thio)pentanoate (3i)



3i

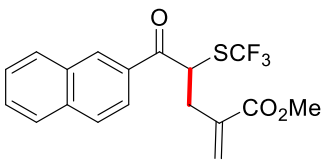
Reaction time: 15 min.; R*f*: 0.3 (1:19, EtOAc:Pet. ether); thick oil; 64 mg, 94% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, J = 7.9 Hz, 1H), 7.97 (d, J = 8.5 Hz, 1H), 7.89 (d, J = 7.3 Hz, 1H), 7.82 (d, J = 7.9 Hz, 1H), 7.60-7.40 (m, 3H), 6.19 (s, 1H), 5.70 (s, 1H), 5.19 (t, J = 7.6 Hz, 1H), 3.67 (s, 3H), 3.17 (dd, J = 14.0 and 7.3 Hz, 1H), 2.86 (dd, J = 14.0 and 7.9 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 198.3, 166.8, 134.9, 134.0 (2C), 133.5, 130.6, 130.34, 130.27 (q, J = 307.5, CF_3), 128.5, 128.4, 128.2, 126.8, 125.5, 124.3, 52.1, 49.3, 36.2.

HRMS (ESI-TOF) m/z: $[M+Na]^+$calcd for $C_{18}H_{15}F_3O_3SNa$ 391.0586, found 391.0587.

Methyl 2-methylene-5-(naphthalen-2-yl)-5-oxo-4-((trifluoromethyl)thio)pentanoate (3j)



3j

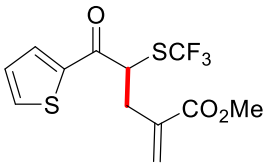
Reaction time: 15 min.; R*f*: 0.5 (1:19, EtOAc:Pet. ether); white solid; 65 mg, 95% yield, Mp = 60-62 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.95 (t, J = 10.4 Hz, 2H), 7.85 (d, J = 8.5 Hz, 1H), 7.81 (d, J = 7.9 Hz, 1H), 7.56 (t, J = 7.0 Hz, 1H), 7.50 (t, J = 7.3 Hz, 1H), 6.20 (s, 1H), 5.68 (s, 1H), 5.34 (t, J = 7.6 Hz 1H), 3.70 (s, 3H), 3.14 (dd, J = 13.4 and 6.7 Hz, 1H), 2.83 (dd, J = 14.0, 7.9 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 195.8, 166.8, 136.0, 134.9, 132.5, 132.0, 130.8, 130.43, 130.41 (q, J = 306.7 Hz, CF_3), 129.9, 129.1, 128.9, 127.8, 127.1, 124.0, 52.1, 46.4, 36.5.

HRMS (ESI-TOF) m/z: $[M+Na]^+$calcd for $C_{18}H_{15}F_3O_3SNa$ 391.0586, found 391.0590.

Methyl 2-methylene-5-oxo-5-(thiophen-2-yl)-4-((trifluoromethyl)thio)pentanoate (3k)



3k

Reaction time: 15 min.; R*f*: 0.2 (1:19, EtOAc:Pet. ether); thick oil; 66 mg, 93% yield.

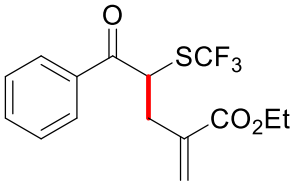
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 3.7 Hz, 1H), 7.69 (d, J = 4.9 Hz, 1H), 7.11 (t, J = 4.4 Hz, 1H), 6.22 (s, 1H), 5.67 (s, 1H), 4.98 (t, J = 7.6 Hz, 1H), 3.71 (s, 3H), 3.06 (dd, J = 14.0 and 7.3 Hz, 1H), 2.77 (dd, J = 14.0 and 7.9 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 188.5, 166.7, 141.7, 136.0, 134.7, 133.5, 130.5, 130.3 (q, J = 307.5 Hz, CF_3), 128.6, 52.1, 47.4, 36.5.

HRMS (ESI-TOF) m/z: $[M+Na]^+$calcd for $C_{12}H_{11}F_3O_3S_2Na$ 346.9994, found 346.9993.

Ethyl 2-methylene-5-oxo-5-phenyl-4-((trifluoromethyl)thio)pentanoate (3l)

Reaction time: 15 min.; R*f*: 0.5 (1:19, EtOAc:Pet. ether); thick oil; 74 mg, 98% yield.



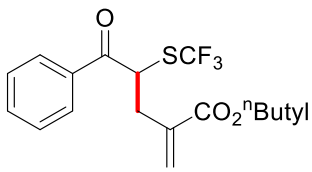
3l

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 7.3 Hz, 2H), 7.63 (t, J = 7.3 Hz, 1H), 7.52 (t, J = 7.6 Hz, 2H), 6.30 (s, 1H), 5.72 (s, 1H), 5.27 (t, J = 7.3 Hz, 1H), 4.30-4.18 (m, 2H), 3.16 (dd, J = 14.0 and 7.3 Hz, 1H), 2.85 (dd, J = 14.0 and 7.3 Hz, 1H), 1.31 (t, J = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 195.9, 166.3, 135.1, 134.7, 134.1, 130.4 (q, J= 307.5 Hz, CF_3), 130.3, 129.0, 128.7, 61.1, 46.2, 36.4, 14.1.

HRMS (ESI-TOF) m/z: $[M+Na]^+$calcd for $C_{15}H_{15}F_3O_3SNa$ 355.0586, found 355.0587.

Butyl 2-methylene-5-oxo-5-phenyl-4-((trifluoromethyl)thio)pentanoate (3m)



3m

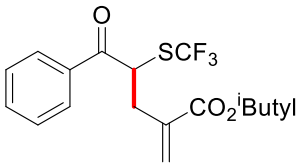
Reaction time: 15 min.; R*f*: 0.5 (1:19, EtOAc:Pet. ether); thick oil; 71 mg, 87% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05-7.97 (m, 2H), 7.67-7.58 (m, 1H), 7.55-7.48 (m, 2H), 6.29 (d, *J* = 0.9 Hz, 1H), 5.73 (d, *J* = 1.4 Hz, 1H), 5.27 (t, *J* = 7.3 Hz, 1H), 4.19 (td, *J* = 6.4 and 1.8 Hz, 2H), 3.16 (dd, *J* = 13.7 and 6.9 Hz, 1H), 2.85 (dd, *J* = 14.2 and 8.2 Hz, 1H), 1.71-1.62 (m, 2H), 1.43-1.33 (m, 2H), 0.95 (t, *J* = 7.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 196.0, 166.4, 135.1, 134.7, 134.1, 130.3, 129.0, 128.8 (q, *J* = 307.7 Hz, CF_3), 128.7, 65.0, 46.2, 36.4, 30.6, 19.1, 13.7.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{17}H_{20}F_3O_3S$ 361.1080, found 361.1076.

***iso*-Butyl 2-methylene-5-oxo-5-phenyl-4-((trifluoromethyl)thio)pentanoate (3n)**



3n

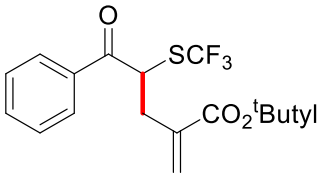
Reaction time: 15 min.; R*f*: 0.5 (1:19, EtOAc:Pet. ether); thick oil; 75 mg, 92% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.3 Hz, 2H), 7.63 (t, *J* = 7.3 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 2H), 6.30 (s, 1H), 5.74 (s, 1H), 5.27 (t, *J* = 7.7 Hz, 1H), 3.97 (dd, *J* = 6.9 and 2.8 Hz, 2H), 3.17 (dd, *J* = 13.7 and 6.9 Hz, 1H), 2.85 (dd, *J* = 14.2 and 6.0 Hz, 1H), 2.06-1.93 (m, 1H), 0.96 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 196.0, 166.4, 135.1, 134.8, 134.1, 130.3 (q, *J* = 308.3 Hz, CF_3), 130.2, 128.9, 128.7, 71.2, 46.2, 36.4, 29.7, 27.7, 19.0.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{17}H_{20}F_3O_3S$ 361.1080, found 361.1076.

Tert-butyl 2-methylene-5-oxo-5-phenyl-4-((trifluoromethyl)thio)pentanoate (3o)



3o

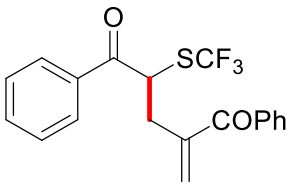
Reaction time: 15 min.; R*f*: 0.5 (1:19, EtOAc:Pet. ether); thick oil; 77 mg, 94% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.2 Hz, 2H), 7.63 (t, *J* = 8.0 Hz, 1H), 7.51 (t, *J* = 7.9 Hz, 2H), 6.19 (s, 1H), 5.63 (s, 1H), 5.29 (t, *J* = 7.8 Hz, 1H), 3.09 (dd, *J* = 13.7 and 7.3 Hz, 1H), 2.83 (dd, *J* = 13.7 and 7.8 Hz, 1H), 1.50 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 196.4, 165.4, 136.4, 134.9, 134.1, 130.4 (q, *J* = 307.8 Hz, CF_3), 129.5, 128.9, 128.7, 81.4, 46.2, 36.6, 28.0.

HRMS (ESI-TOF) m/z: $[M+Na]^+$calcd for $C_{17}H_{19}F_3O_3SNa$ 383.0899, found 383.0900.

2-methylene-1,5-diphenyl-4-((trifluoromethyl)thio)pentane-1,5-dione (3p)



3p

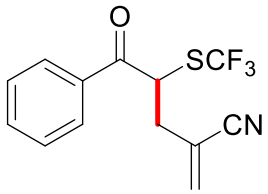
Reaction time: 15 min.; R*f*: 0.5 (1:9, EtOAc:Pet. ether); yellow thick oil; 72 mg, 87% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.4 Hz, 2H), 7.65-7.49 (m, 6H), 7.43 (t, *J* = 7.6 Hz, 2H), 6.09 (s, 1H), 5.86 (s, 1H), 5.32 (t, *J* = 7.3 Hz, 1H), 3.32 (dd, *J* = 13.7 and 6.9 Hz, 1H), 3.01 (dd, *J* = 13.7 and 8.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 197.6, 196.2, 142.3, 137.3, 134.7, 134.1, 133.4 (q, *J* = 307.5 Hz, CF_3), 132.42, 132.36, 129.4, 129.0, 128.8, 128.3, 46.4, 36.2.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{19}H_{16}F_3O_2S$ 365.0818, found 365.0814.

2-methylene-5-oxo-5-phenyl-4-((trifluoromethyl)thio)pentanenitrile (3q)



3q

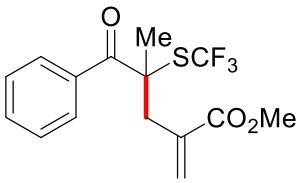
Reaction time: 15 min.; R*f*: 0.4 (1:9, EtOAc:Pet. ether); thick oil; 53 mg, 82% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.6 Hz, 2H), 7.67 (t, *J* = 7.3 Hz, 1H), 7.55 (t, *J* = 8.0 Hz, 2H), 6.00 (s, 1H), 5.90 (s, 1H), 4.99 (dd, *J* = 8.4 and 6.9 Hz, 1H), 3.21 (dd, *J* = 14.5 and 8.4 Hz, 1H), 2.91 (dd, *J* = 14.5 and 6.9 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 193.7, 135.0, 134.5, 134.1, 129.9 (q, *J* = 308.6 Hz, CF_3), 129.1, 128.7, 118.0, 117.5, 44.6, 37.3.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{13}H_{11}ONF_3S$ 286.0508, found 286.0504.

Methyl 4-methyl-2-methylene-5-oxo-5-phenyl-4-((trifluoromethyl)thio)pentanoate (3r)



3r

Reaction time: 15 min.; R*f*: 0.5 (1:19, EtOAc:Pet. ether); thick oil; 47 mg, 66% yield.

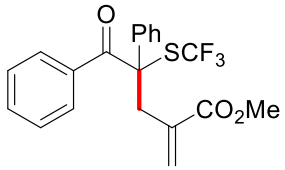
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.3 Hz, 2H), 7.47 (t, *J* = 7.3 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 2H), 6.30 (s, 1H), 5.58 (s, 1H), 3.64 (s, 3H), 3.19-3.06 (m, 2H), 1.60 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1, 167.4, 135.9, 134.5, 132.5 (q, *J* = 306.7 Hz, CF_3), 132.3, 131.1, 129.5, 128.3, 58.8, 52.2, 39.2, 24.0.

HRMS (ESI-TOF) m/z: $[M+Na]^+$calcd for $C_{15}H_{15}F_3O_3SNa$ 355.0586, found 355.0584.

HPLC: Chiralpak IE, n-hexane/IPA = 97:3, 1.0 mL/min, λ = 230 nm, tR (major) = 8.200 min, tR (minor) = 7.350 min (75:25 er).

Methyl 2-methylene-5-oxo-4,5-diphenyl-4-((trifluoromethyl)thio)pentanoate (3s)



3s

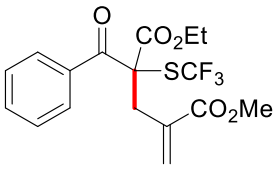
Reaction time: 15 min.; R*f*: 0.4 (1:9, EtOAc:Pet. ether); thick oil; 55 mg, 83% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.6 Hz, 2H), 7.43-7.22 (m, 8H), 6.29 (s, 1H), 5.61 (s, 1H), 3.84 (d, *J* = 14.5 Hz, 1H), 3.52 (d, *J* = 14.5 Hz, 1H), 3.38 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 195.5, 167.4, 137.3, 134.9, 133.9, 132.8, 130.7, 130.6, 129.6 (q, *J* = 309.1 Hz, CF_3), 128.9, 128.7, 128.0, 127.3, 68.6, 51.6, 38.5.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{20}H_{18}F_3O_3S$ 395.0923, found 395.0916.

1-ethyl 5-methyl 2-benzoyl-4-methylene-2-((trifluoromethyl)thio)pentanedioate (3t)



3t

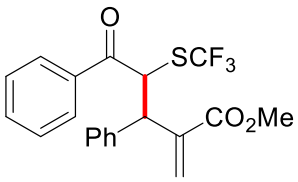
Reaction time: 15 min.; R*f*: 0.4 (1:6, EtOAc:Pet. ether); thick oil; 62 mg, 93% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05-7.95 (m, 2H), 7.57 (t, *J* = 7.3 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 6.46 (s, 1H), 5.84 (s, 1H), 4.20-4.00 (m, 2H), 3.63 (s, 3H), 3.55 (s, 2H), 0.98 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 190.0, 168.1, 167.0, 134.5, 133.9, 133.5, 132.0, 129.3 (q, *J* = 308.6 Hz, CF_3), 129.0, 128.5, 66.8, 63.3, 51.9, 36.7, 13.2.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{17}H_{18}F_3O_5S$ 391.0822, found 391.0821.

Methyl 2-methylene-5-oxo-3,5-diphenyl-4-((trifluoromethyl)thio)pentanoate (3u-diastereomer 1)



3u-diastereomer 1

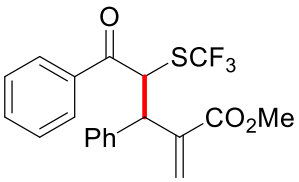
Reaction time: 15 min.; R*f*: 0.3(1:19, EtOAc:Pet. ether); White solid; 47 mg, 52% yield; MP = 90-92 ^{o}C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.84 (d, *J* = 7.9 Hz, 2H), 7.54 (t, *J* = 7.3 Hz, 1H), 7.41 (t, *J* = 7.63 Hz, 2H), 7.32 (d, *J* = 7.3 Hz, 2H), 7.19-7.04 (m, 3H), 6.45 (s, 1H), 6.00 (s, 1H), 5.90 (d, *J* = 11.6 Hz, 1H), 4.54 (d, *J* = 7.6 Hz, 1H), 3.76 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$)δ 195.8, 166.5, 139.2, 138.4, 135.5, 133.6, 130.0 (q, *J* = 30 Hz, CF_3), 128.6, 128.5, 128.4 (3C), 127.4, 52.1, 50.7, 48.1.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{20}H_{18}F_3O_3S$ 395.0923, found 395.0920.

Methyl 2-methylene-5-oxo-3,5-diphenyl-4-((trifluoromethyl)thio)pentanoate (3u-diastereomer 2)



3u-diastereomer 2

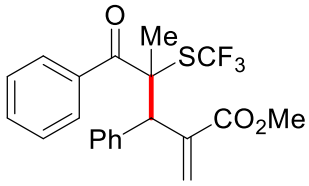
Reaction time: 15 min.; R*f*: 0.2 (1:19, EtOAc:Pet. ether); thick oil; 36 mg, 40% yield.

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.05 (d, *J* = 7.9 Hz, 2H), 7.64 (t, *J* = 7.3 Hz, 1H), 7.53 (t, *J*= 7.6 Hz, 2H), 7.41-7.26 (m, 5H), 6.22 (s, 1H), 5.76 (s, 1H), 5.65 (d, *J* = 10.4 Hz, 1H), 4.62 (d, *J*= 11.0 Hz, 1H), 3.64 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$)δ 195.4, 166.3, 140.2, 137.4, 135.2, 133.9, 129.2, 128.9, 128.8, 128.6, 128.3 (q, *J* = 307.9 Hz, CF_3), 127.8, 127.0, 52.1, 50.1, 49.6.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{20}H_{18}F_3O_3S$ 395.0923, found 395.0919.

Methyl (4R)-4-methyl-2-methylene-5-oxo-3,5-diphenyl-4-((trifluoromethyl)thio)pentanoate (3v)



3v

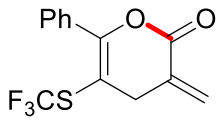
Reaction time: 15 min.; R*f*: 0.4 (1:19, EtOAc:Pet. ether); thick oil; 57 mg, 65% yield as mixture of two diastereomers in 1:0.89 ratio.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.23 (m, 13H), 7.21-7.10 (m, 7H), 6.44 (d, *J* = 3.1 Hz, 2H), 6.27 (s, 0.89H), 6.00 (s, 1H), 5.51 (d, *J* = 17.1 Hz, 1.79H), 3.65 (s, 3H), 3.64 (s, 2.07H), 2.23 (s, 3H), 1.90 (s, 2.65H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 165.5, 161.7, 156.7, 140.3, 140.0, 138.2, 138.0, 133.0, 132.7, 131.46 (q, *J* = 314 Hz, CF_3), 131.43 (q, *J* = 311.3 Hz, CF_3), 130.0, 129.6, 129.3, 129.2, 128.3, 128.3, 128.1, 128.0, 127.9, 127.9, 127.5, 126.4, 126.3, 78.3, 78.2, 51.8, 51.7, 29.72, 29.69, 20.1, 19.6.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{21}H_{20}F_3O_3S$ 409.1080, found 409.1082.

3-methylene-6-phenyl-5-((trifluoromethyl)thio)-3,4-dihydro-2H-pyran-2-one (4)



4

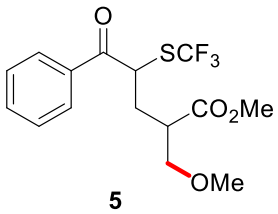
Reaction time: 15 min.; R*f*: 0.3 (1:9, EtOAc:Pet. ether); thick oil; 34.6 mg, 46% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63-7.50 (m, 2H), 7.49-7.39 (m, 3H), 6.52 (s, 1H), 5.85 (s, 1H), 3.69 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 157.9, 131.8, 130.2, 130.0, 129.4 (q, *J* = 311.3 Hz, CF_3), 129.2, 128.1 (2C), 99.7 (d, *J* = 1.5 Hz), 36.0.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{13}H_{10}F_3O_2S$ 287.0348, found 287.0344.

Methyl 2-(methoxymethyl)-5-oxo-5-phenyl-4-((trifluoromethyl)thio)pentanoate (5)



5

Reaction time: 15 min.; R*f*: 0.4 (1:9, EtOAc:Pet. ether); thick oil; 34 mg, 31% yield as mixture of two diastereomers in 1:1.3 ratio.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08-8.03 (m, 2H), 8.00-7.94 (m, 1.57H), 7.67-7.60 (m, 1.73H), 7.56-7.47 (m, 3.53H), 5.10 (dd, *J* = 9. 2 and 6.1 Hz, 1H), 5.01 (dd, *J* = 9.2 and 5.3 Hz, 0.82H), 3.75 (s, 3H), 3.66 (s, 2.49H), 3.65-3.52 (m, 3H), 3.29 (s, 2.32H), 3.22 (s, 3H), 3.06-2.98 (m, 1H), 2.78-2.70 (m, 0.78H), 2.70-2.60 (m, 1H), 2.58-2.47 (m, 0.86H), 2.43-2.33 (m, 0.85H), 2.12-2.03 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 195.5, 195.2, 173.3, 173.2, 134.9, 134.8, 134.4, 134.1, 134.0, 133.39 (q, *J* = 307.7 Hz, CF_3), 133.36 (q, *J* = 307.7 Hz, CF_3), 128.9, 128.8, 128.7, 73.1, 72.8, 58.88, 58.85, 52.1, 52.0, 46.4, 45.2, 43.3, 42.9, 32.1, 31.8.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{15}H_{18}F_3O_4S$ 351.0872, found 351.0867.

2.2.9. References:

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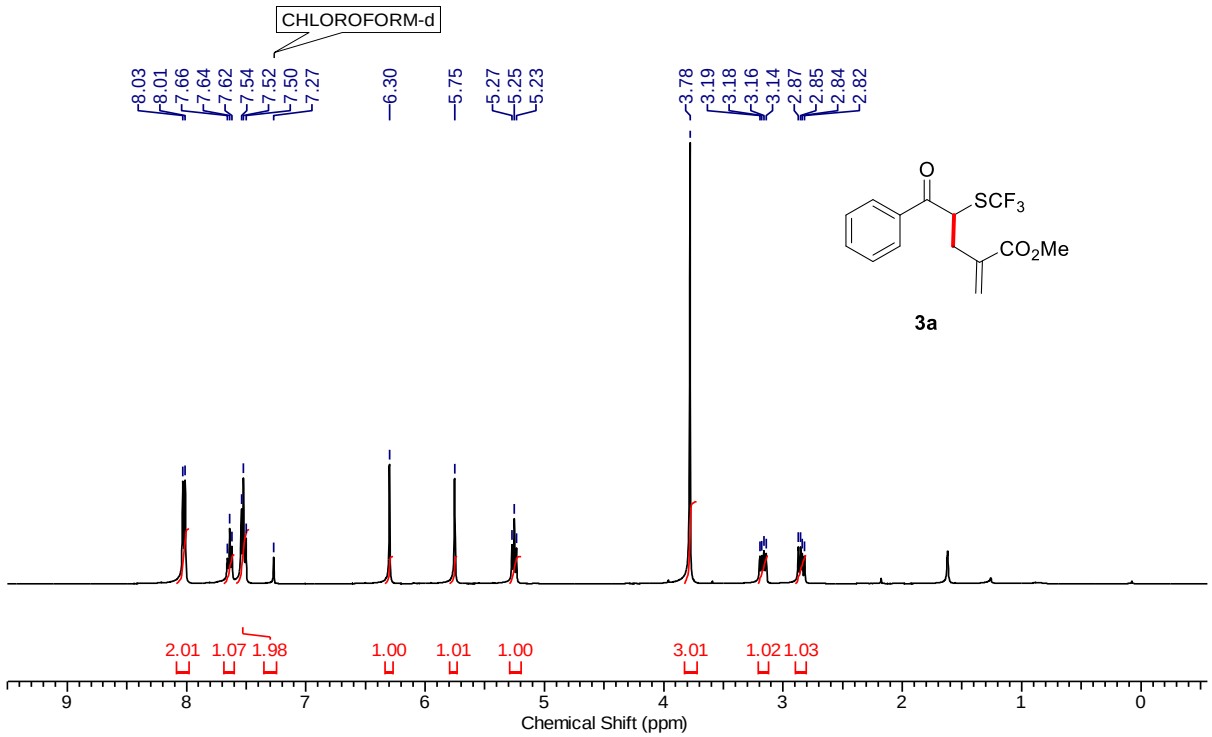
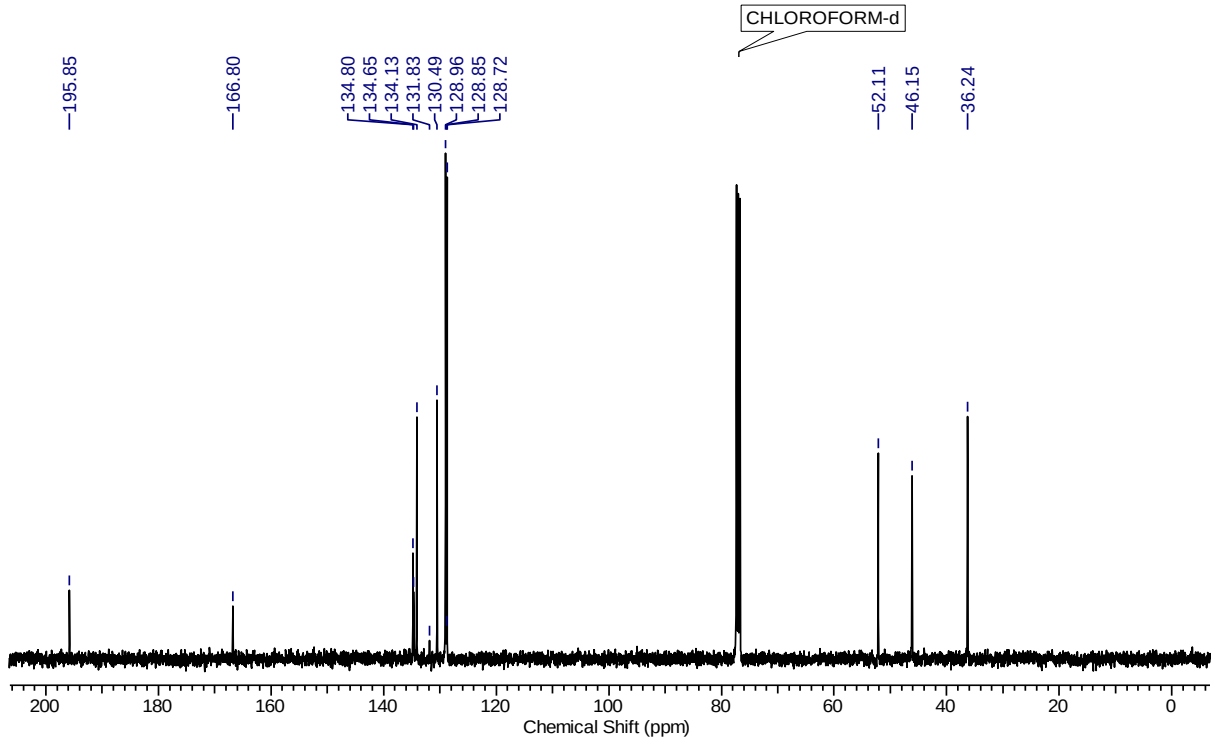
2.2.10 Copies of ^{1}H and ^{13}C NMR spectra:

^{1}H NMR, 400 MHz



^{13}C NMR, 100 MHz



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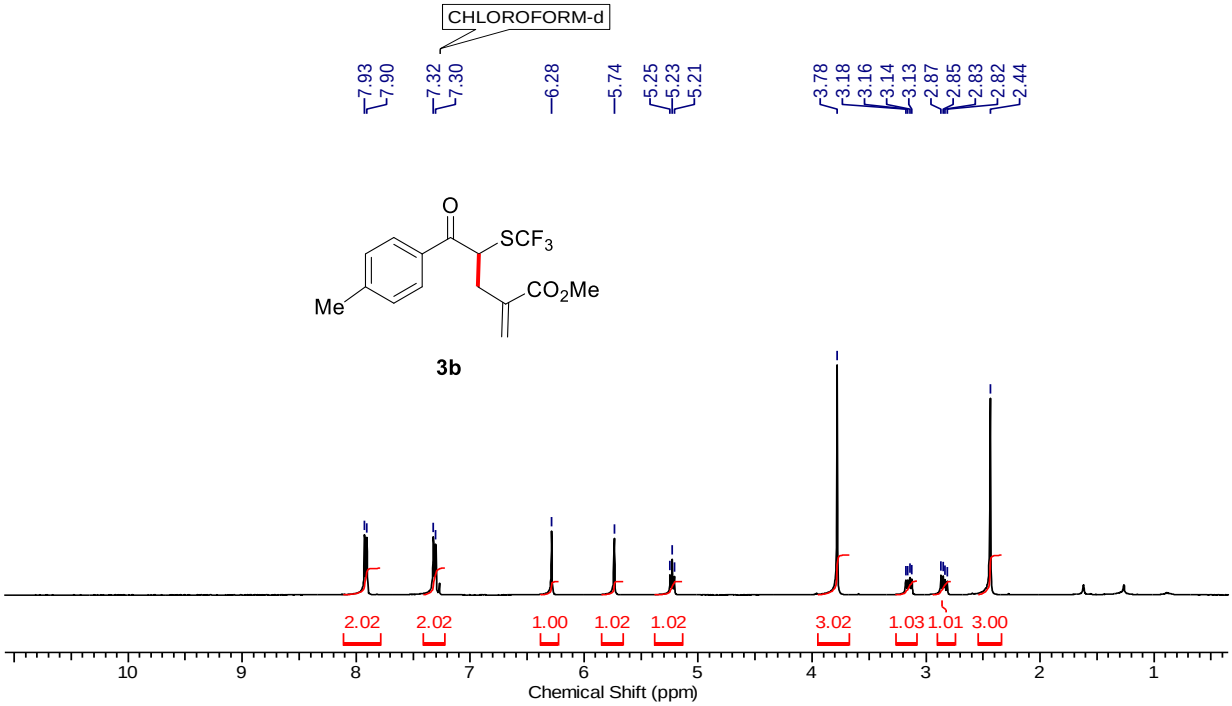
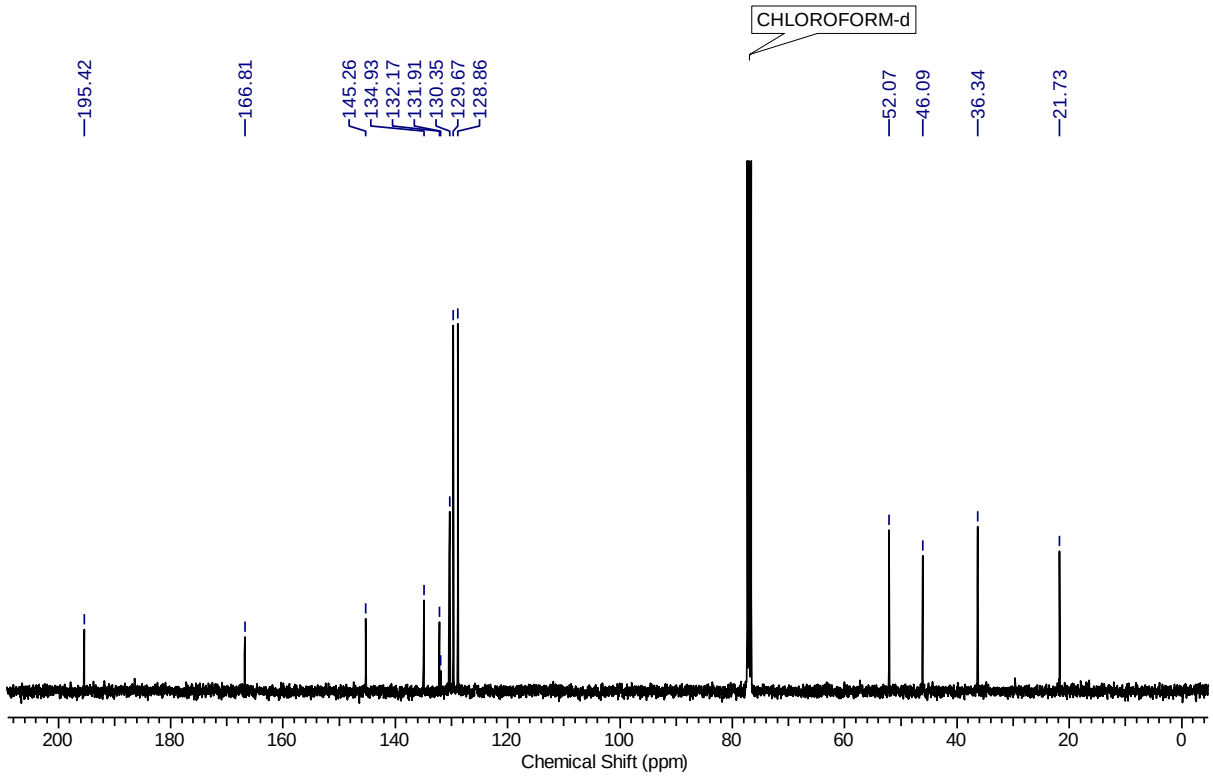


3b

^{13}C NMR, 100 MHz



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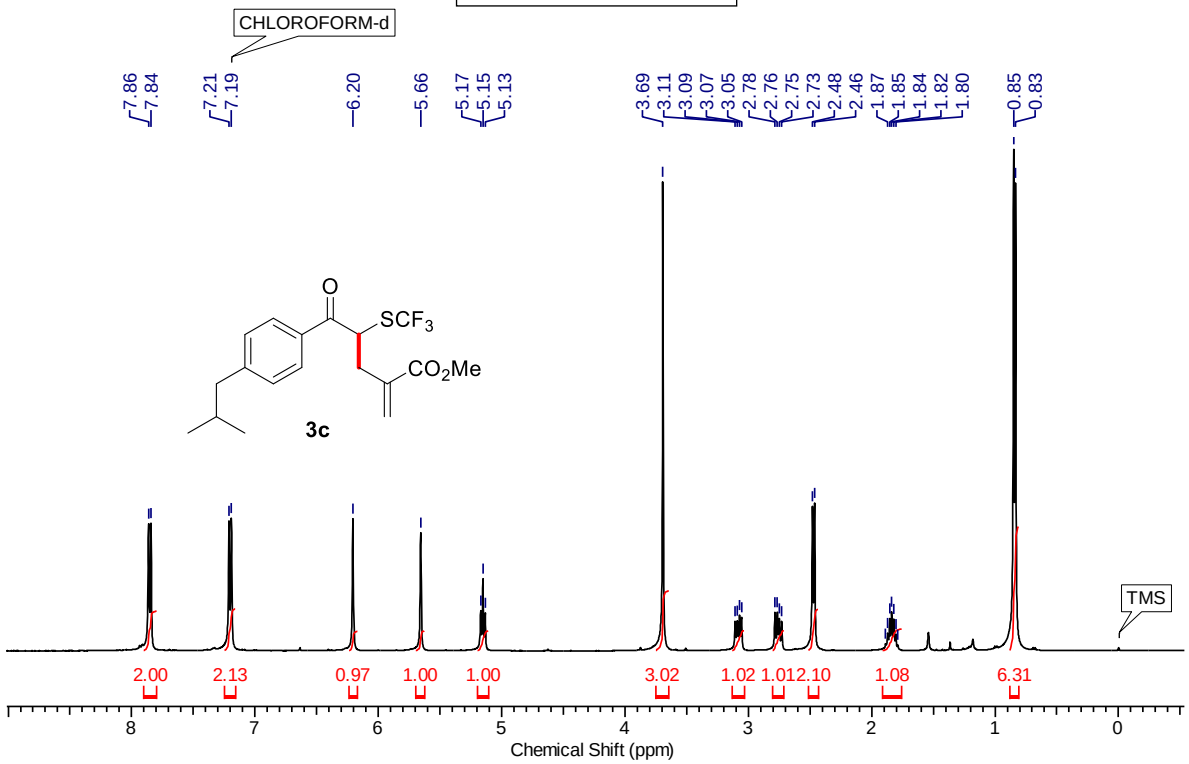

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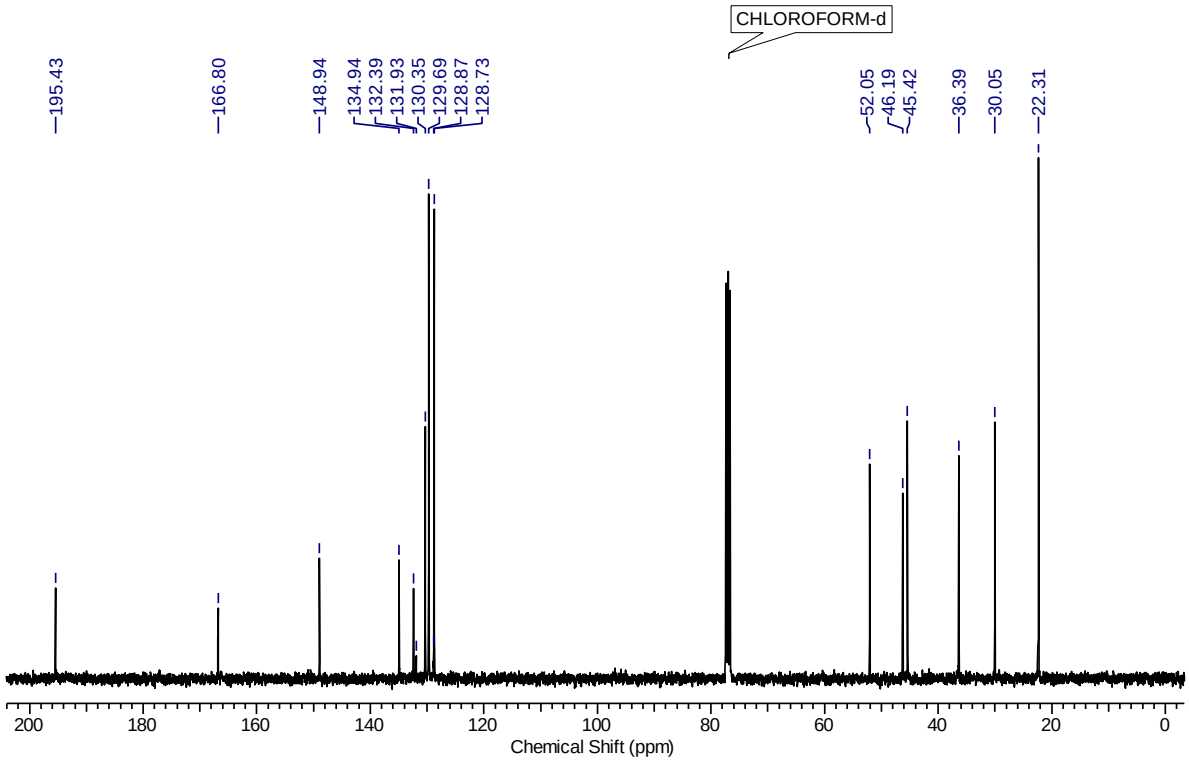

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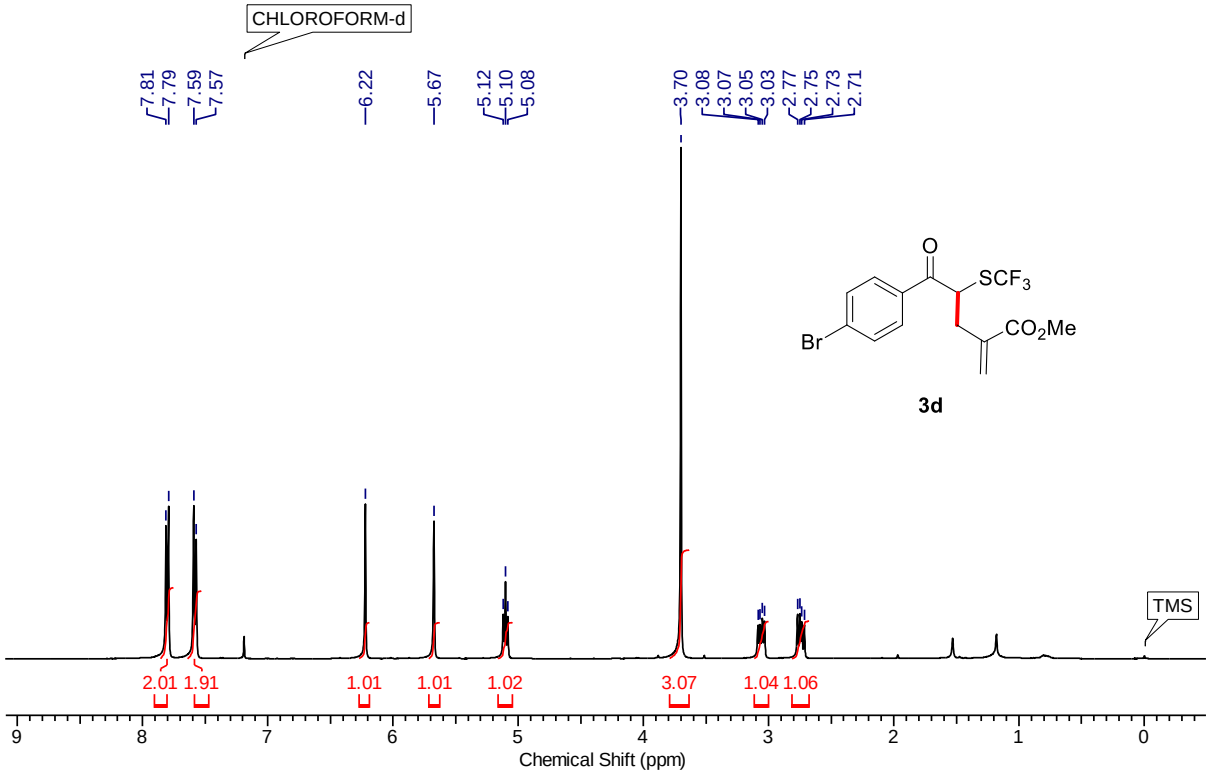

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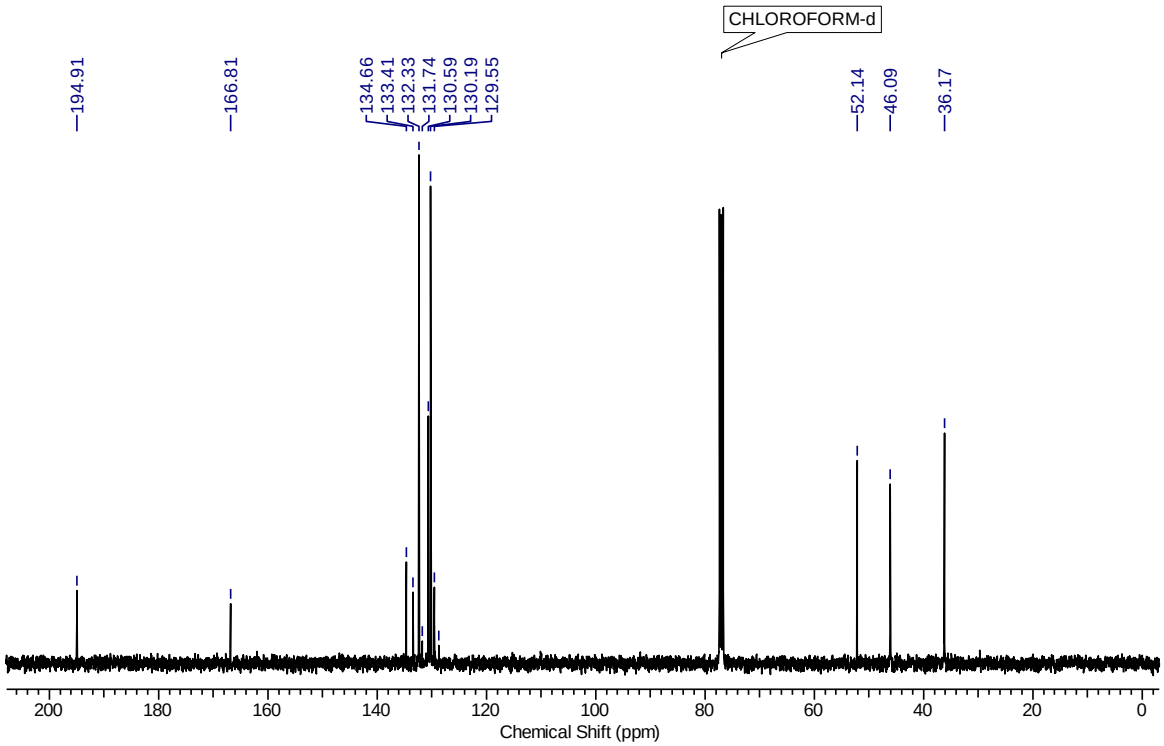

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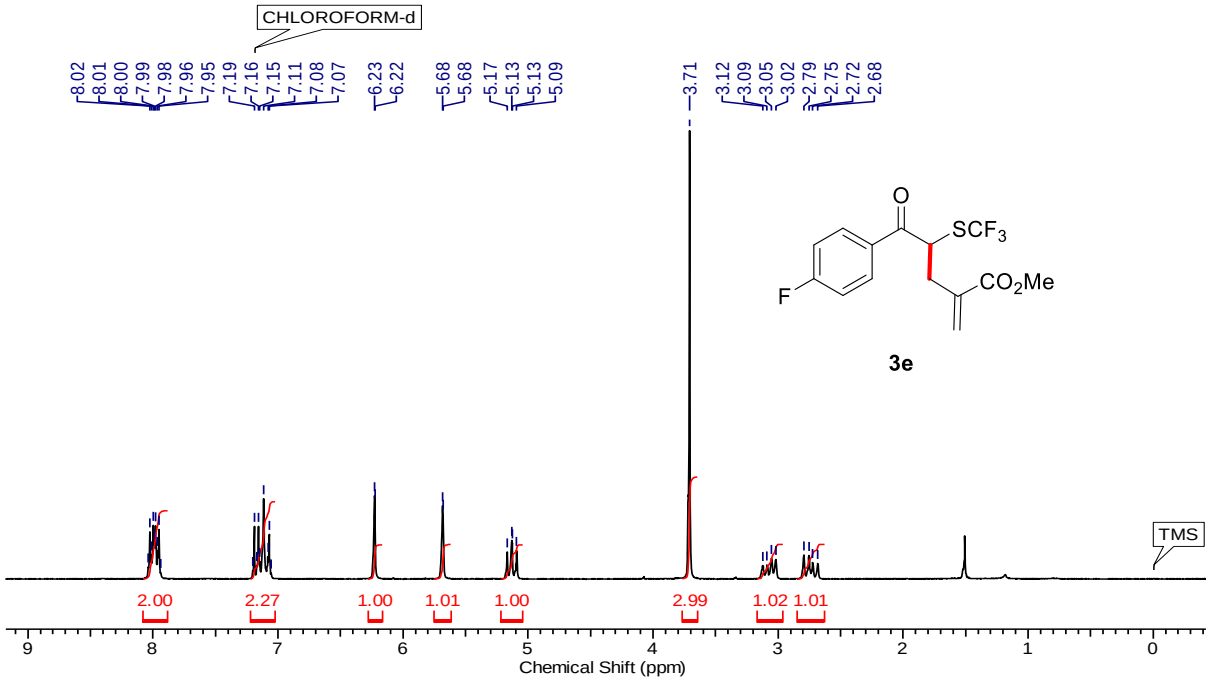

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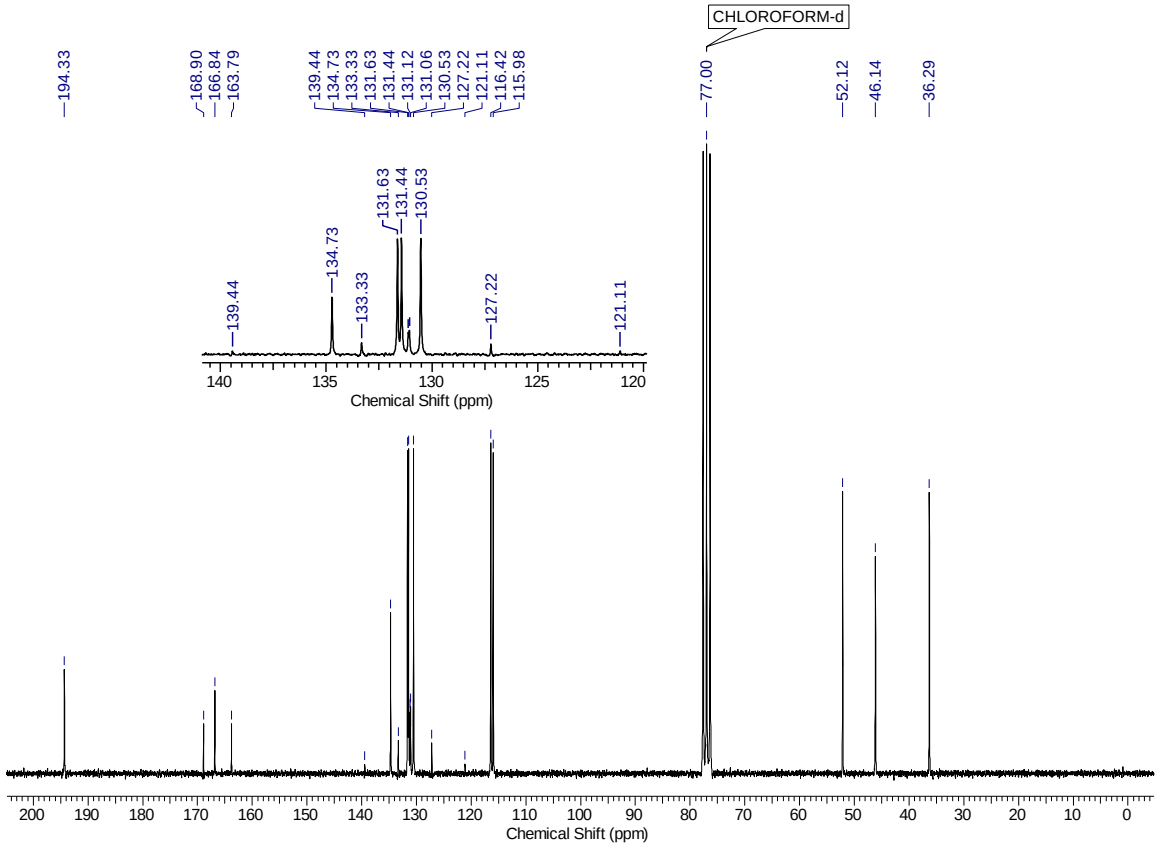

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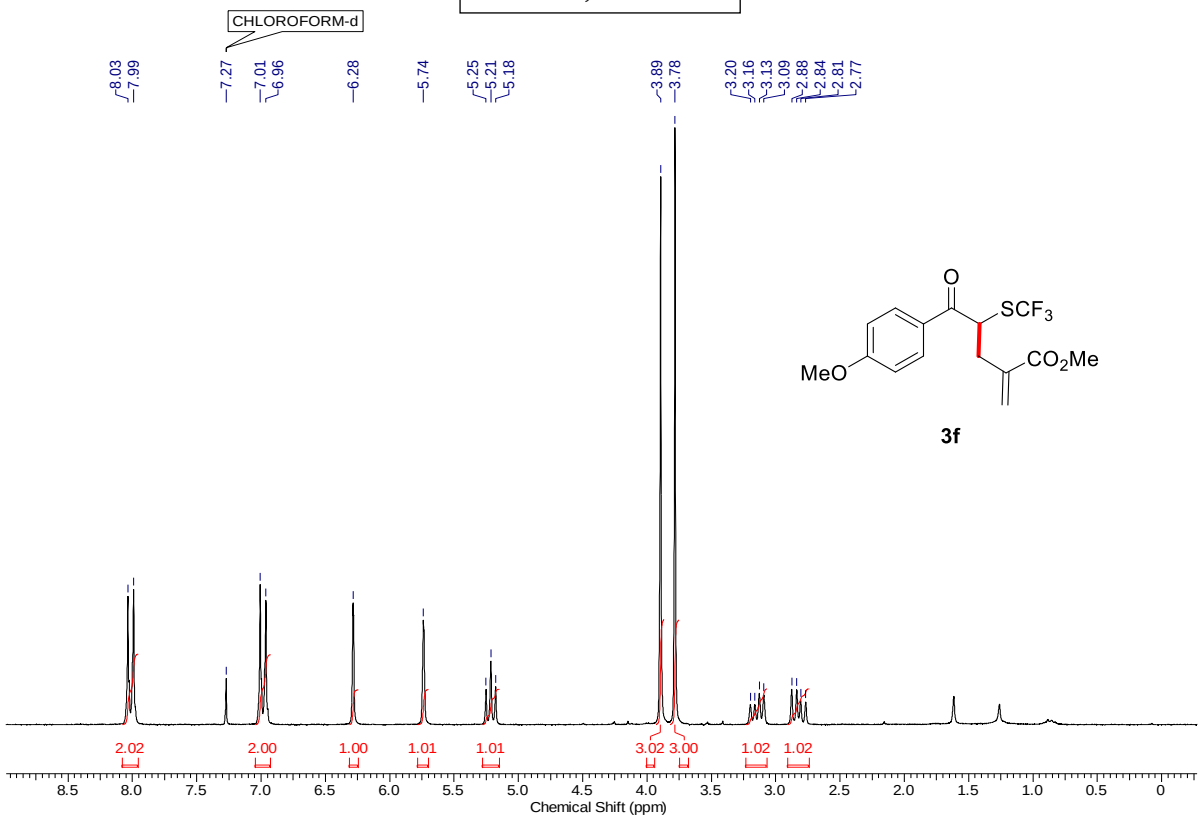

3f

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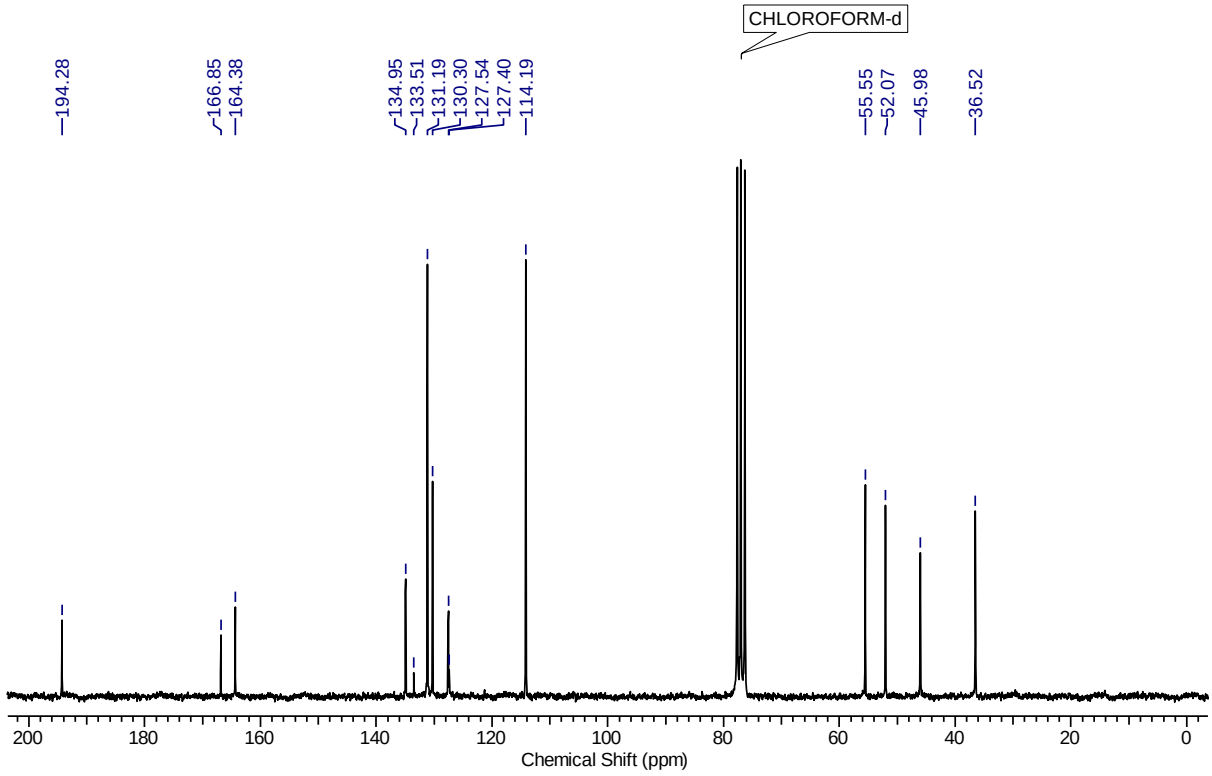

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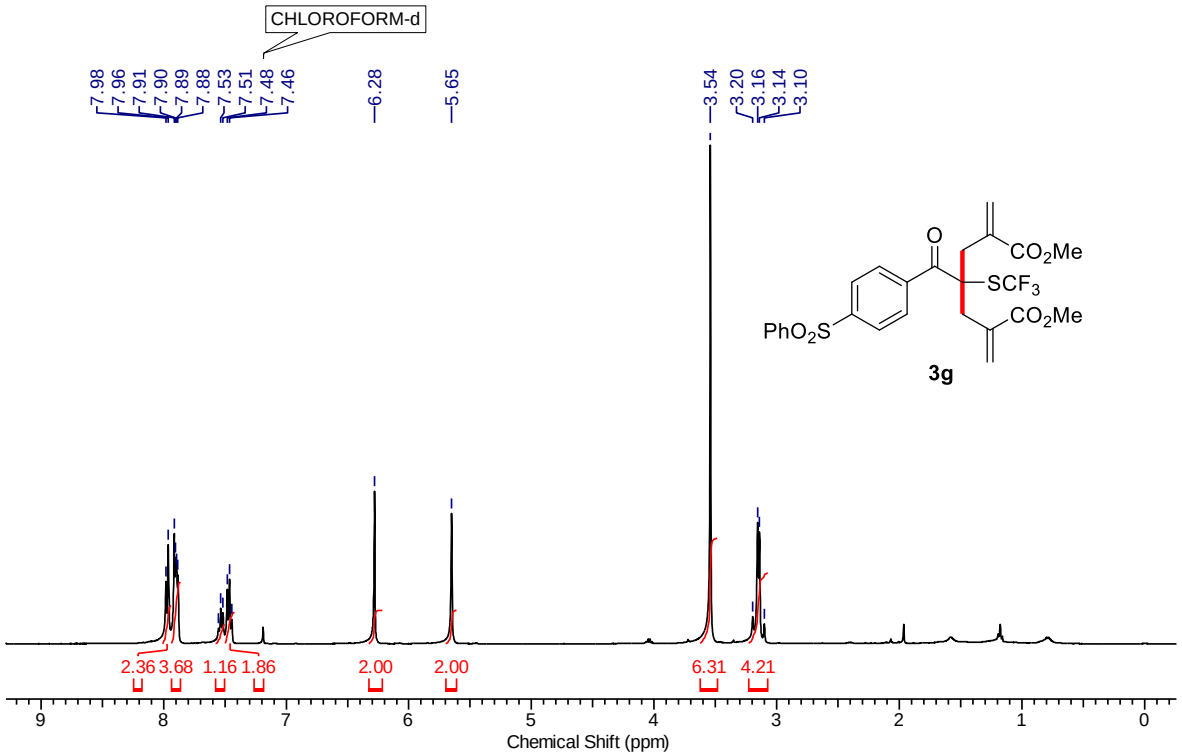

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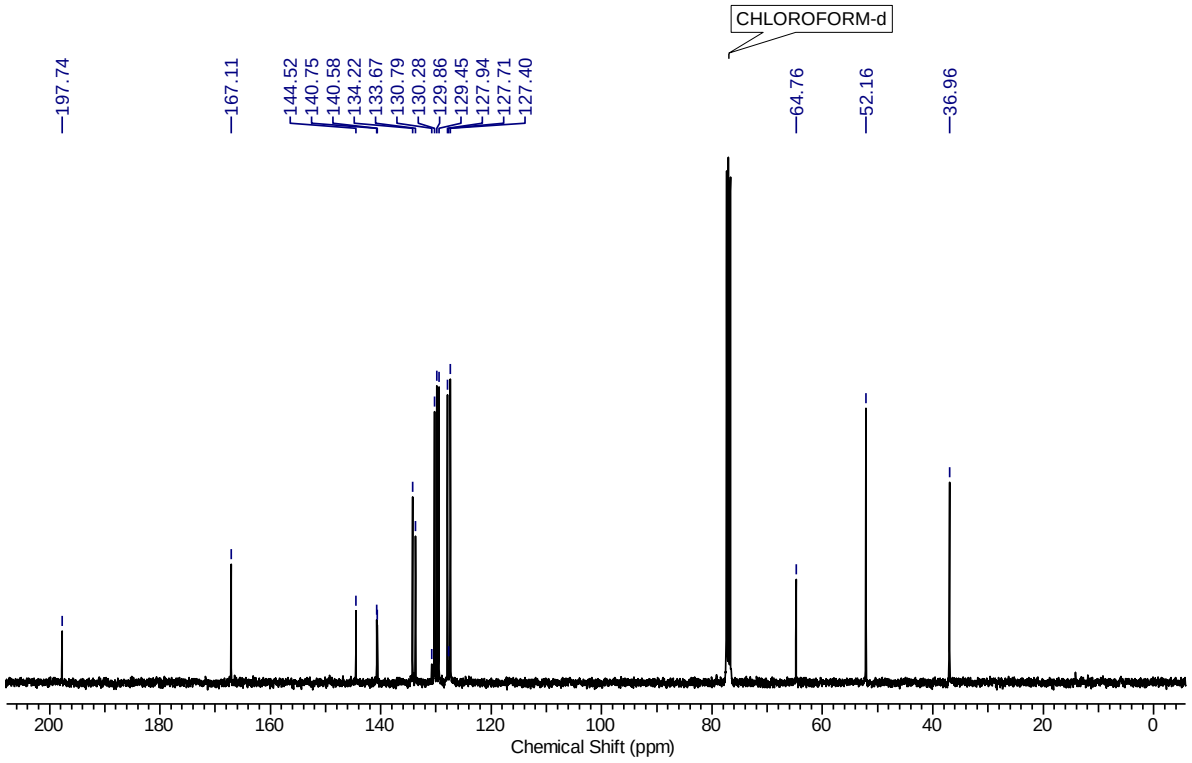

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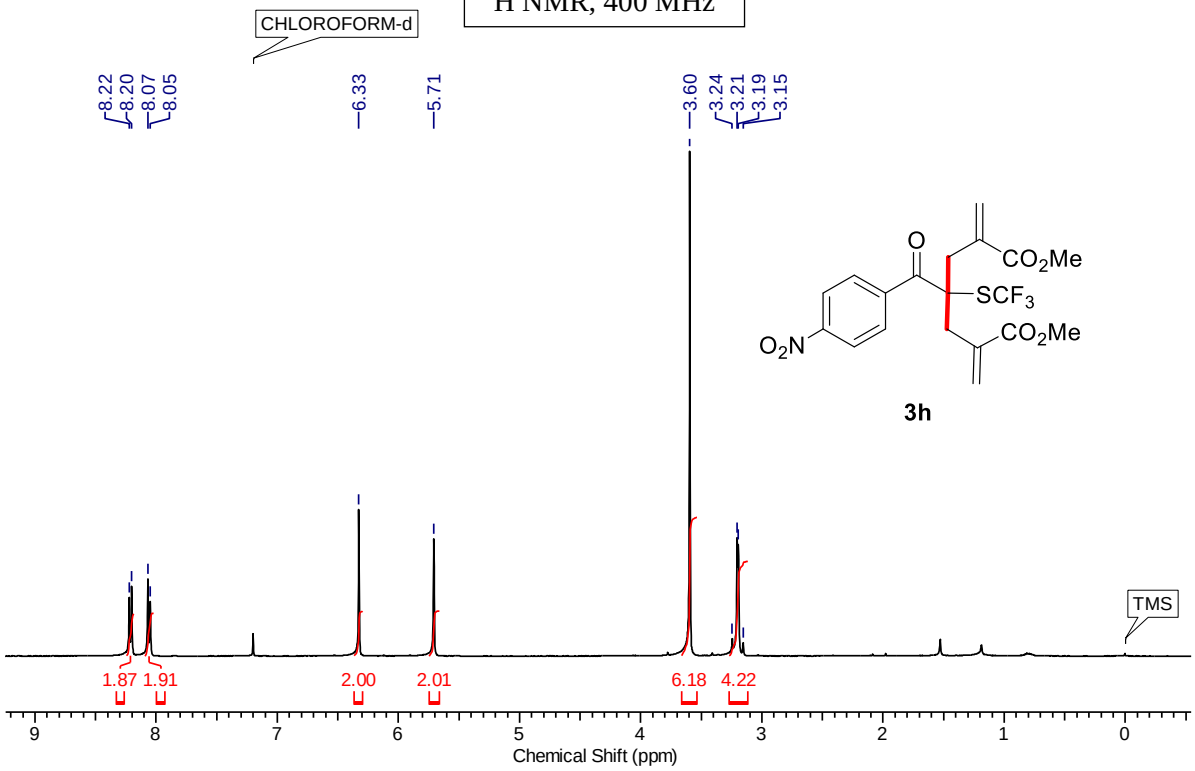

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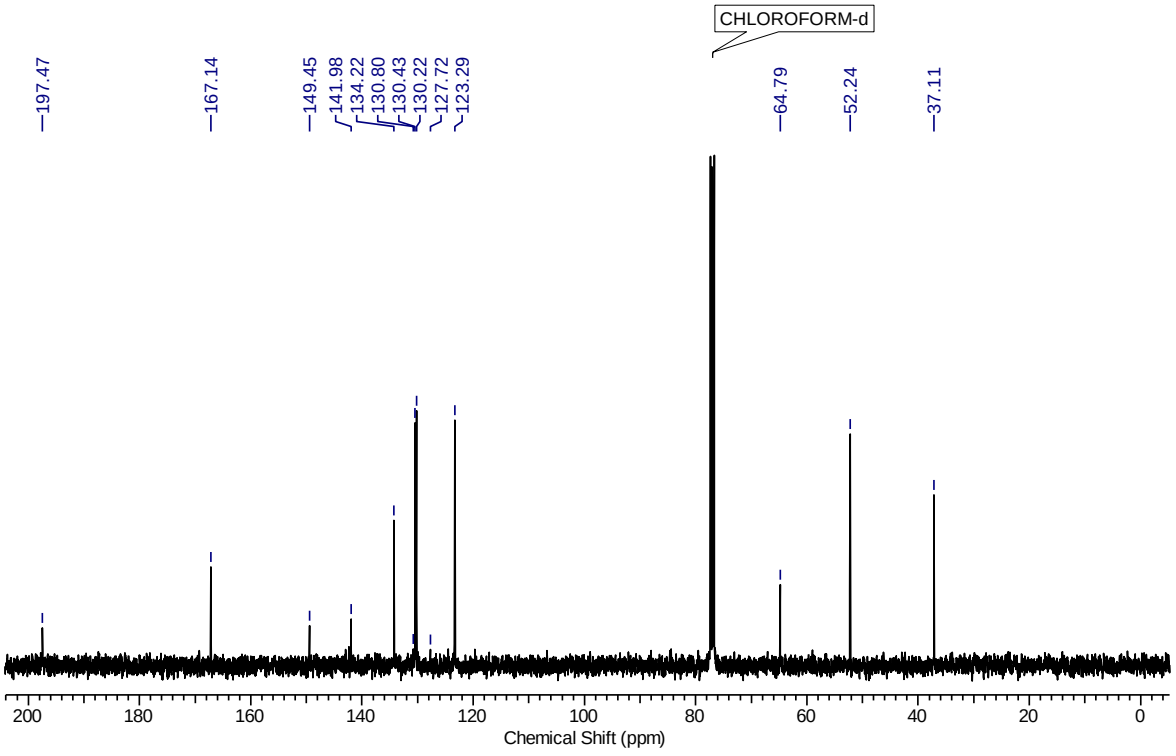

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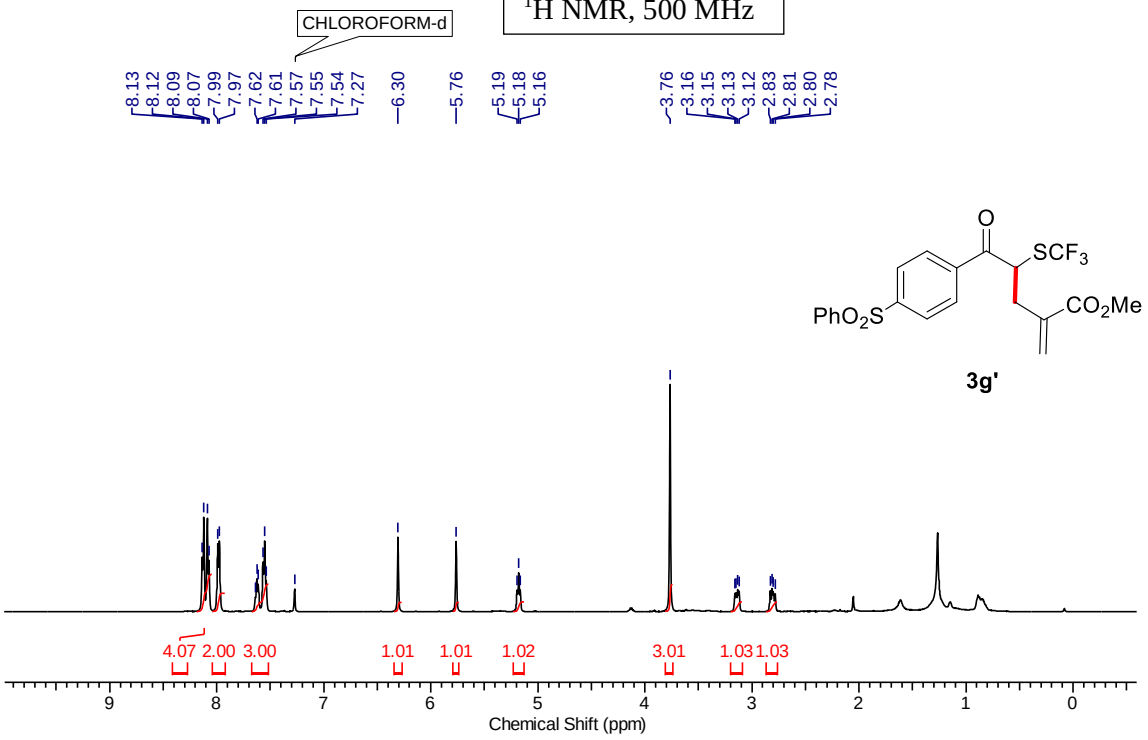

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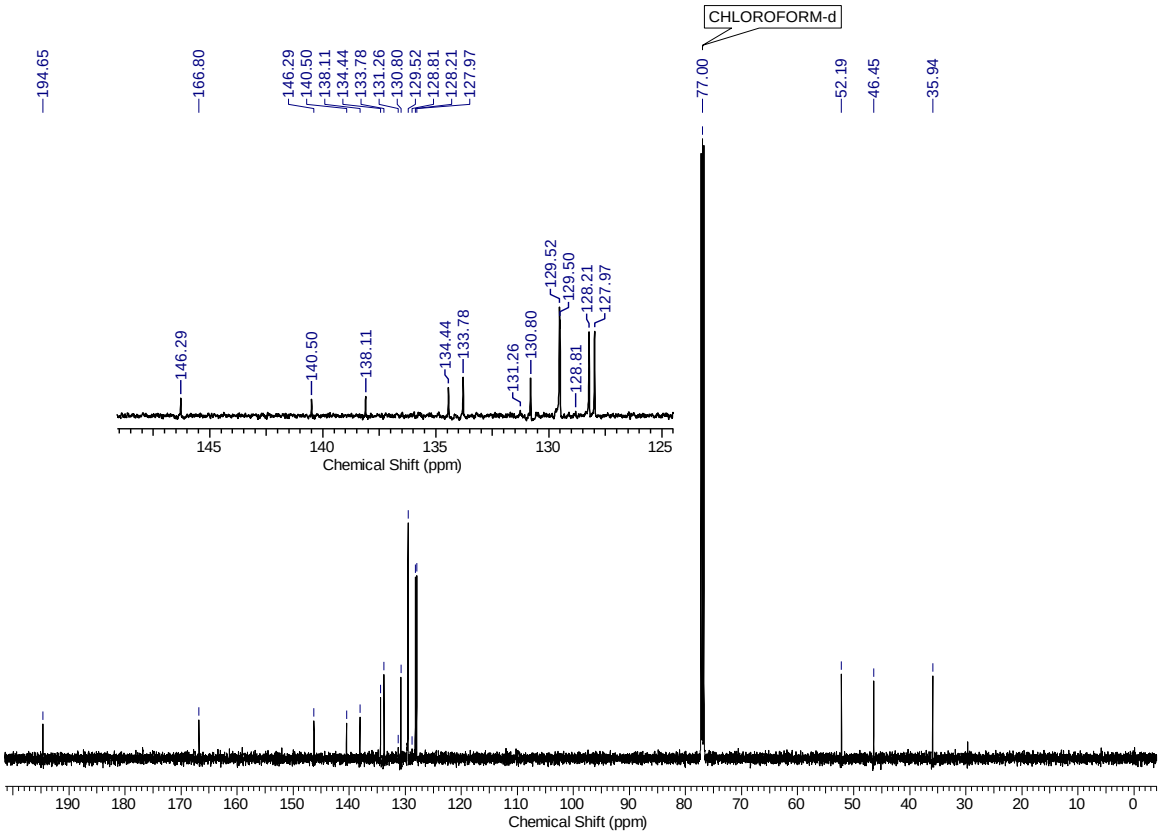

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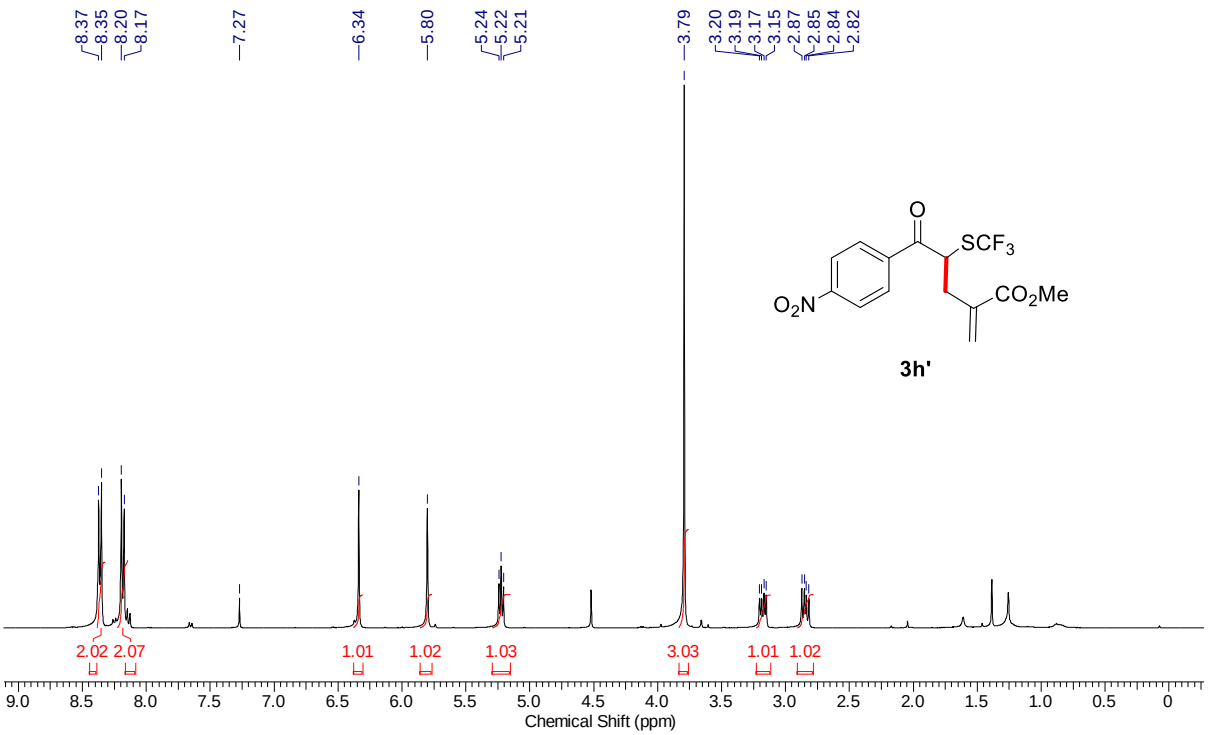

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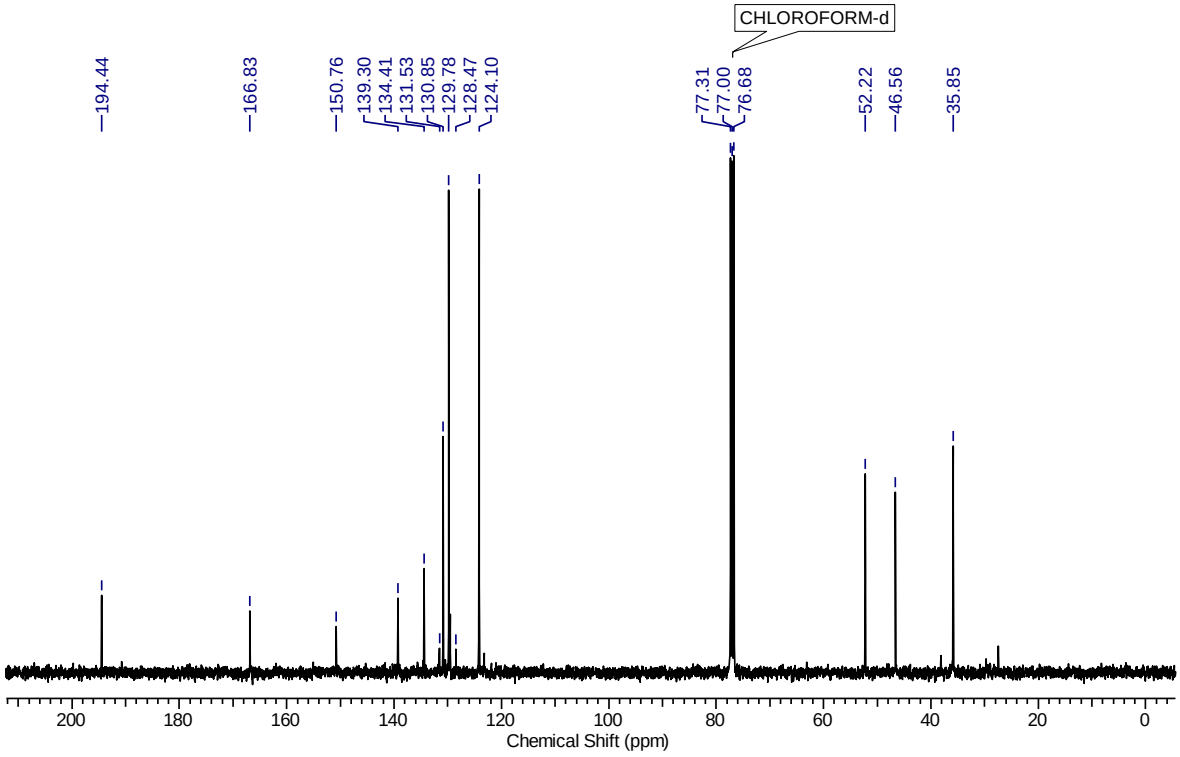

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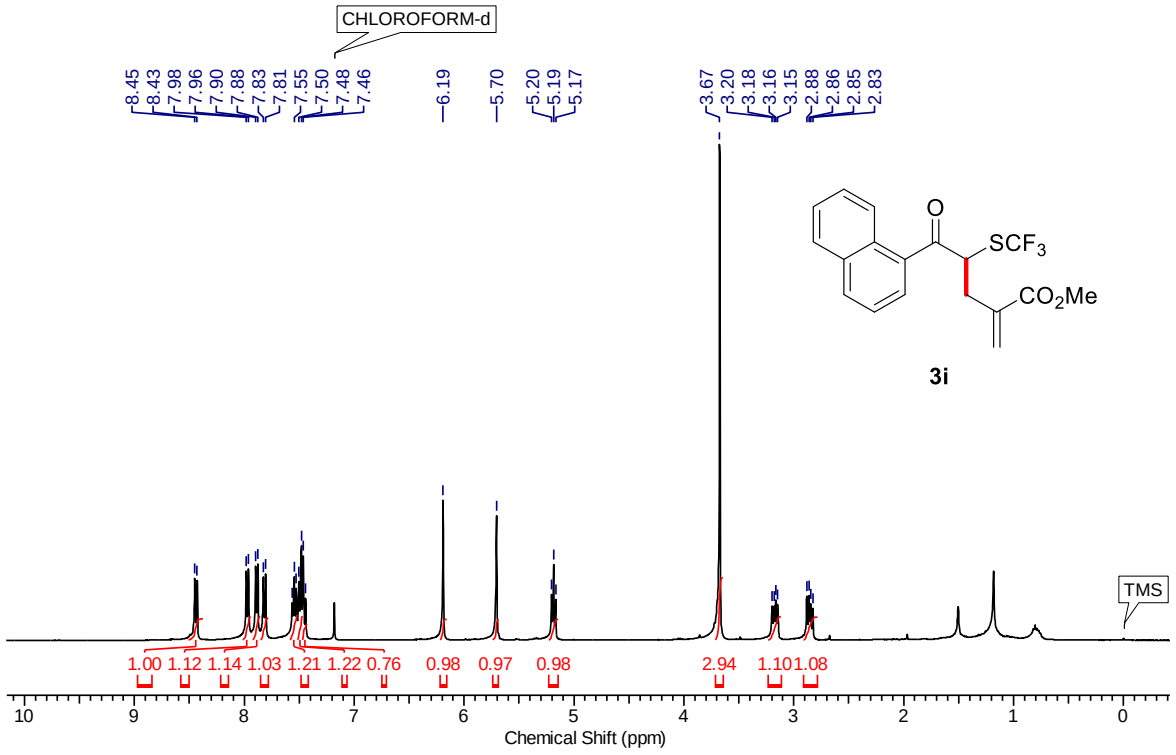

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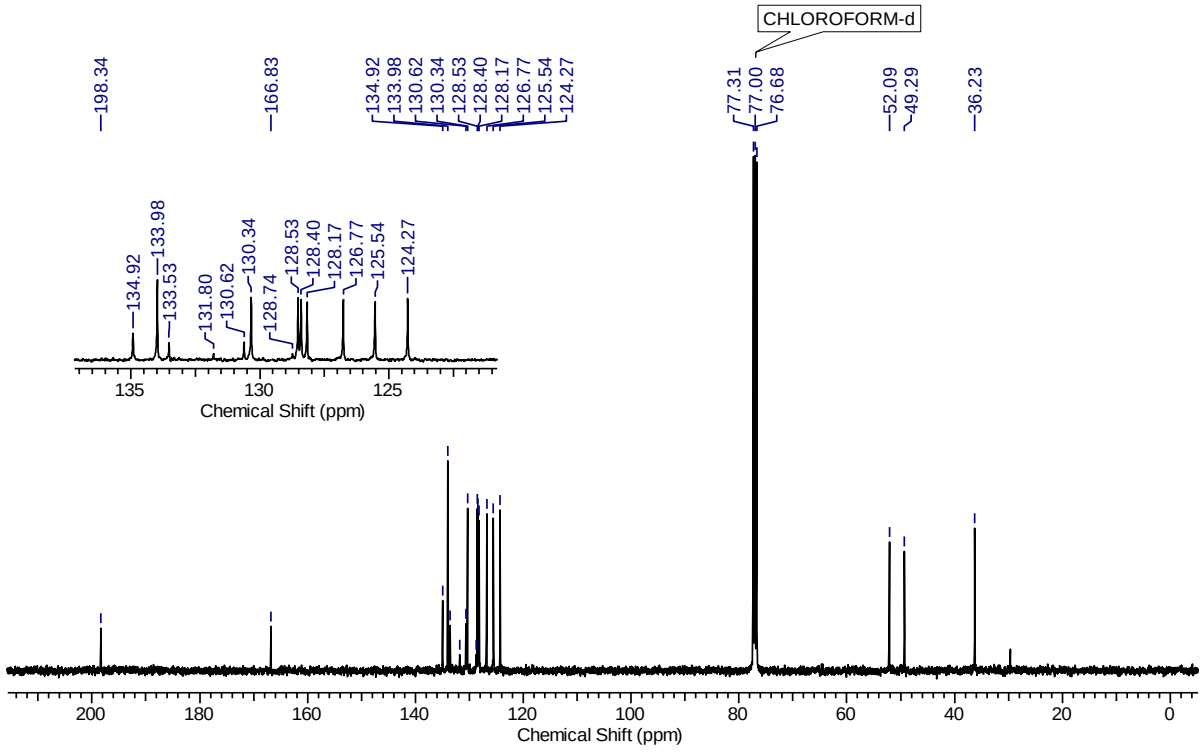
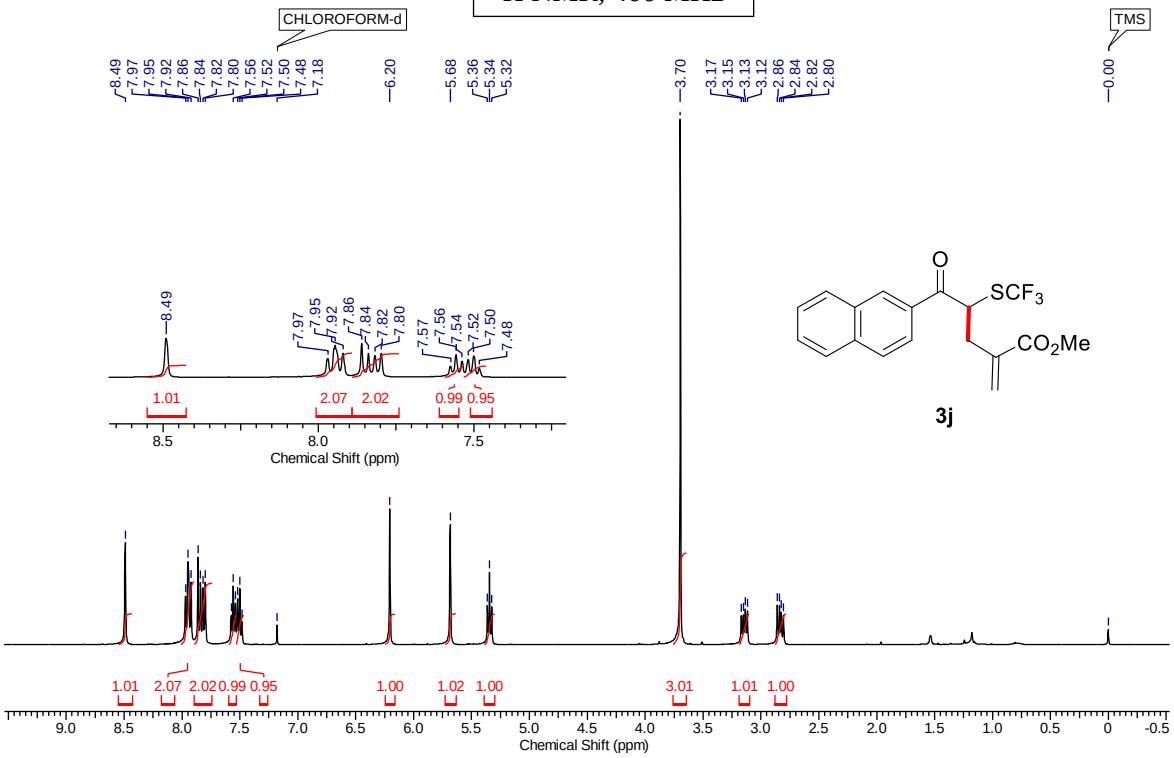
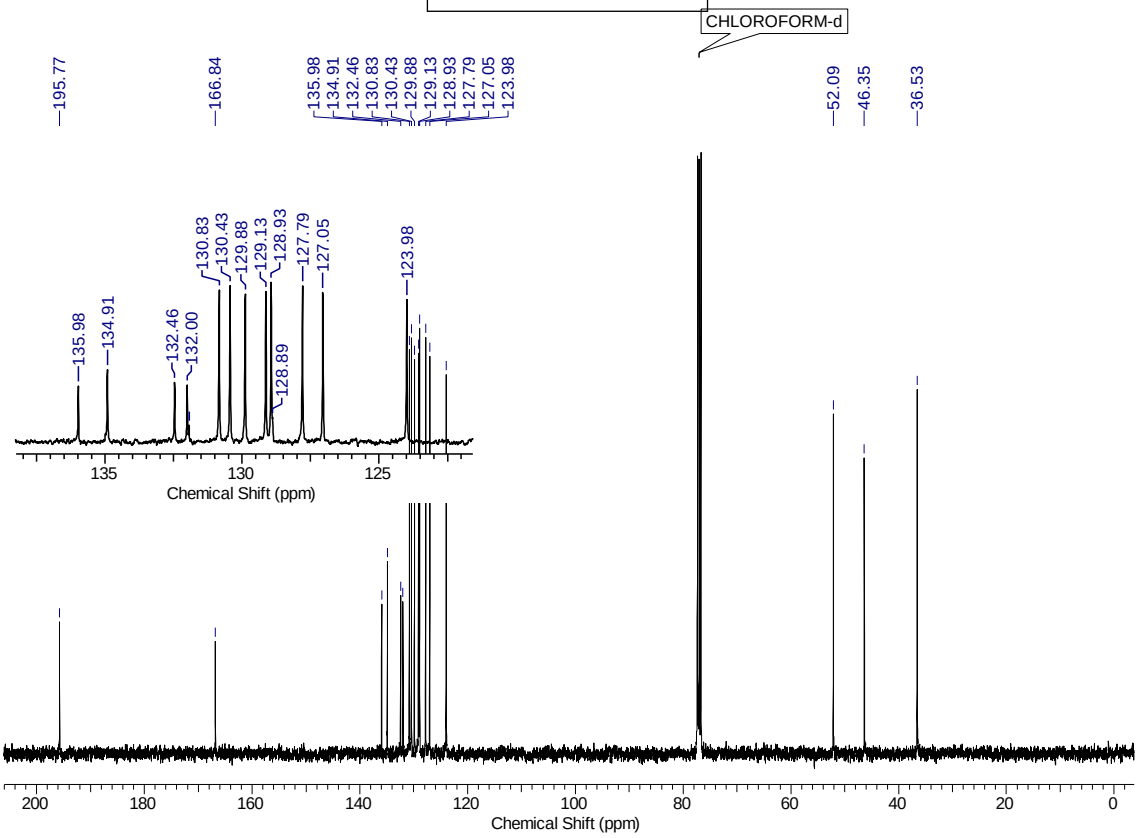


^{1}H NMR, 400 MHz



3j

^{13}C NMR, 100 MHz



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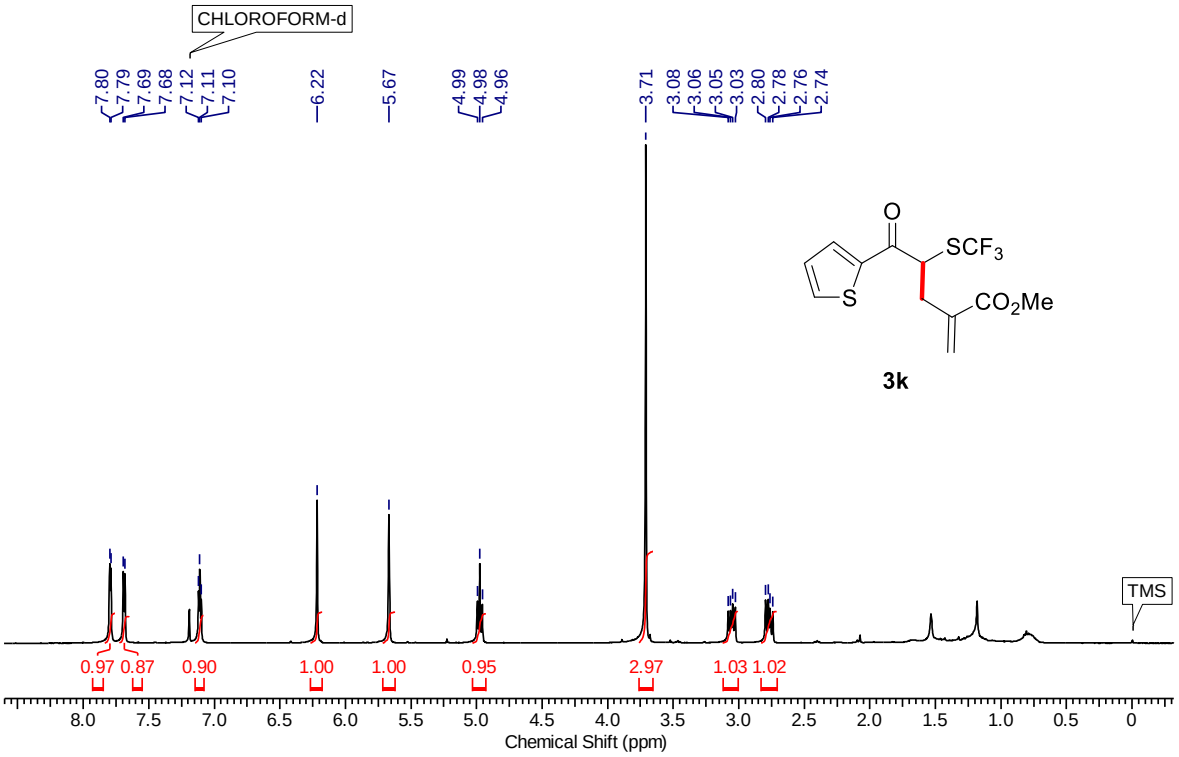

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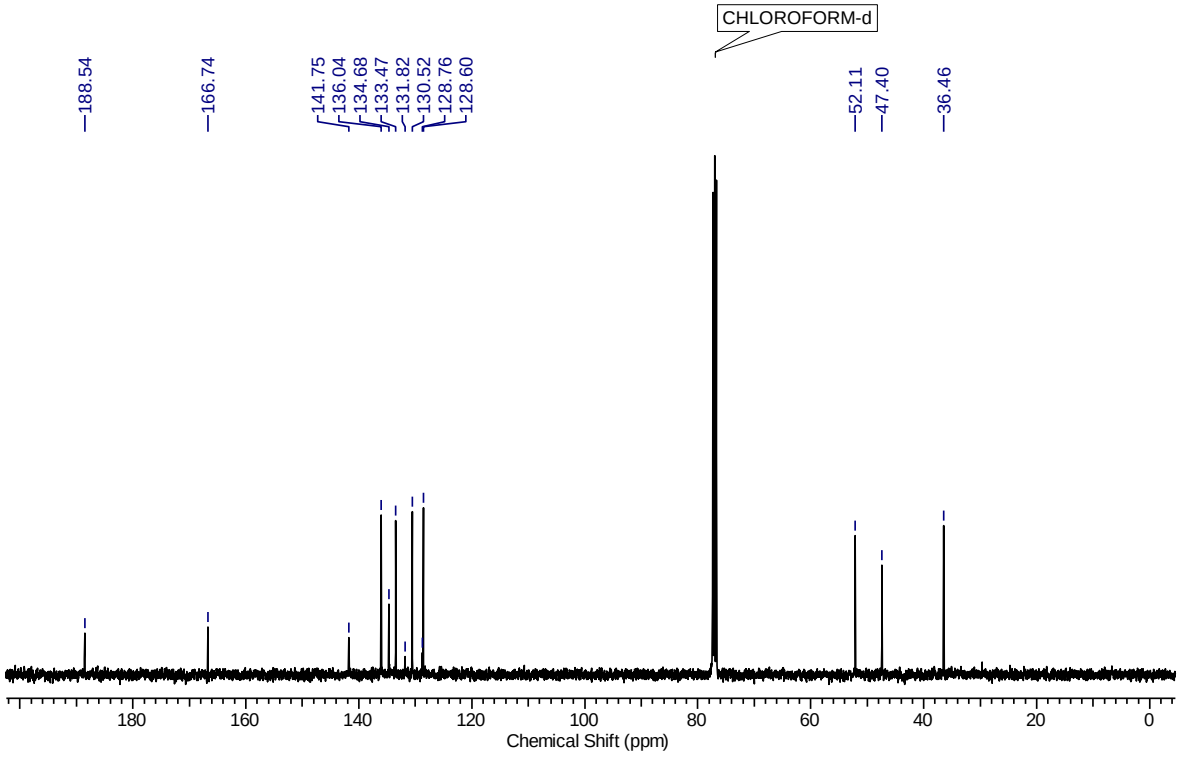

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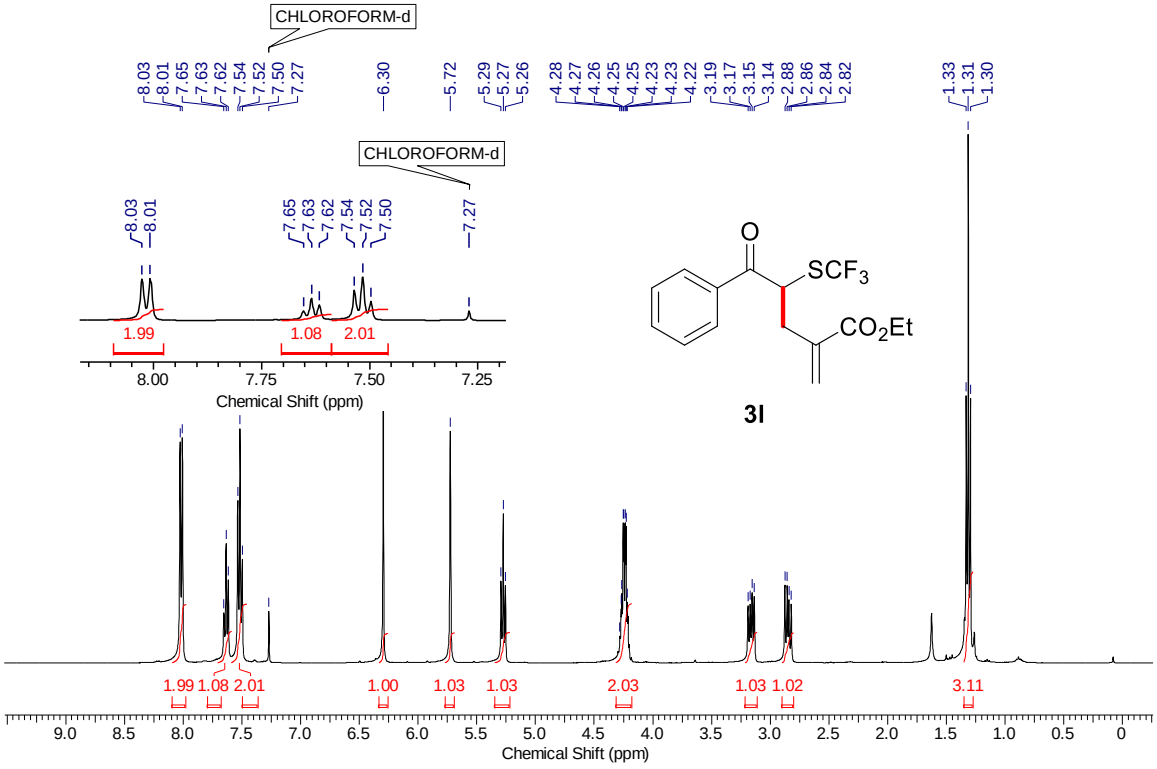

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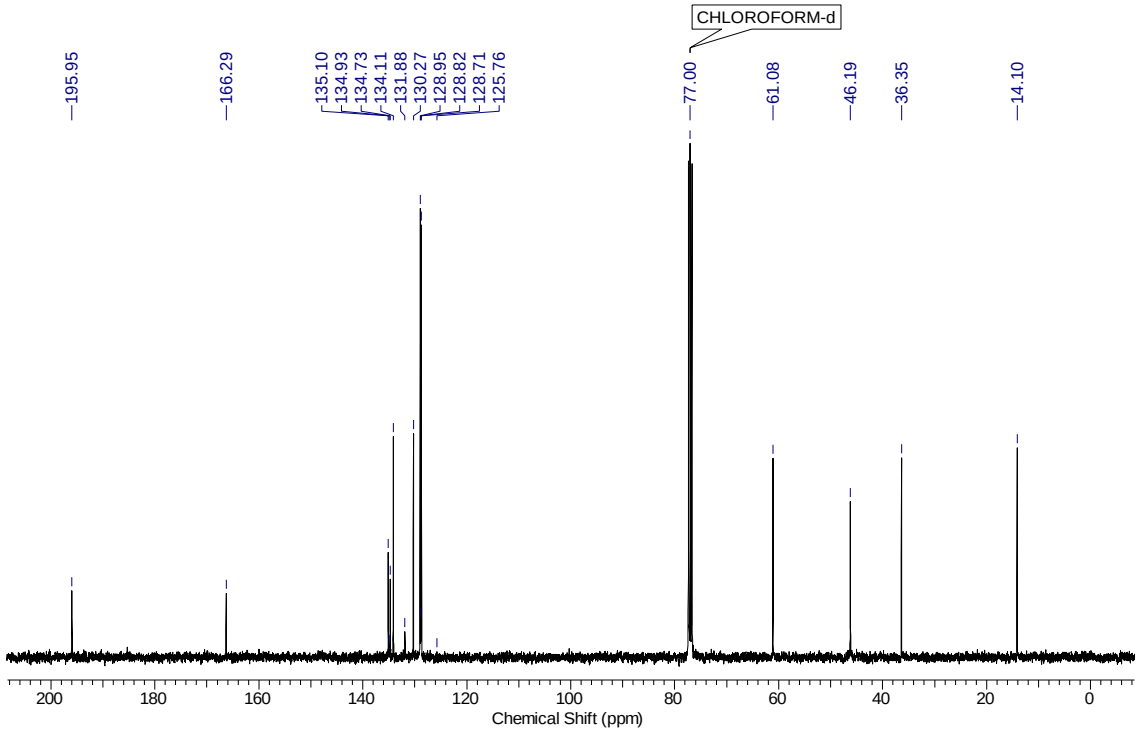

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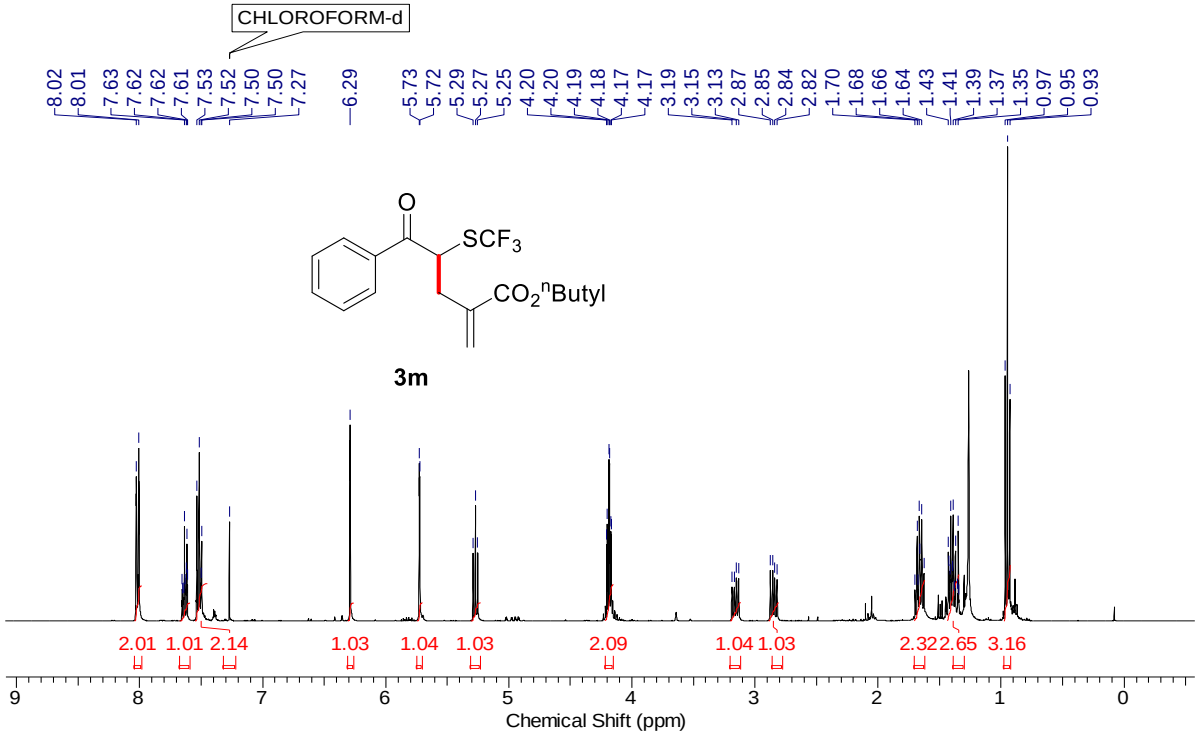

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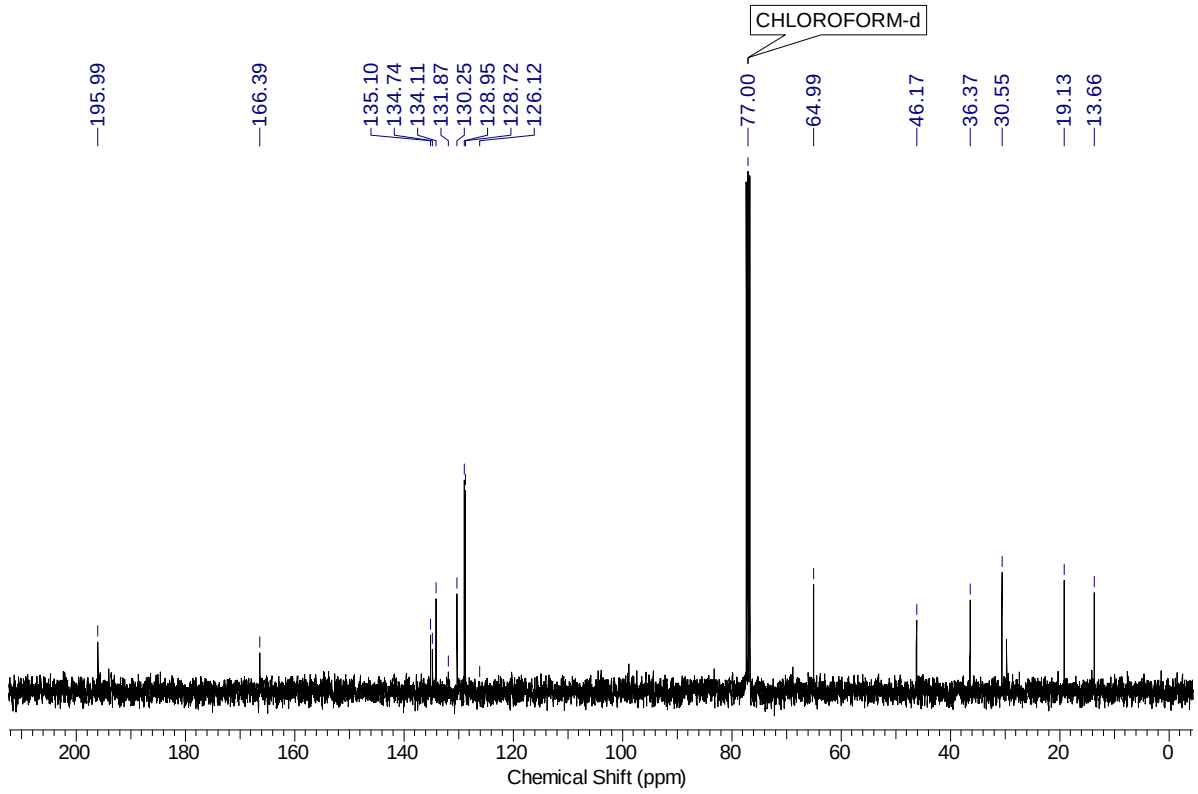

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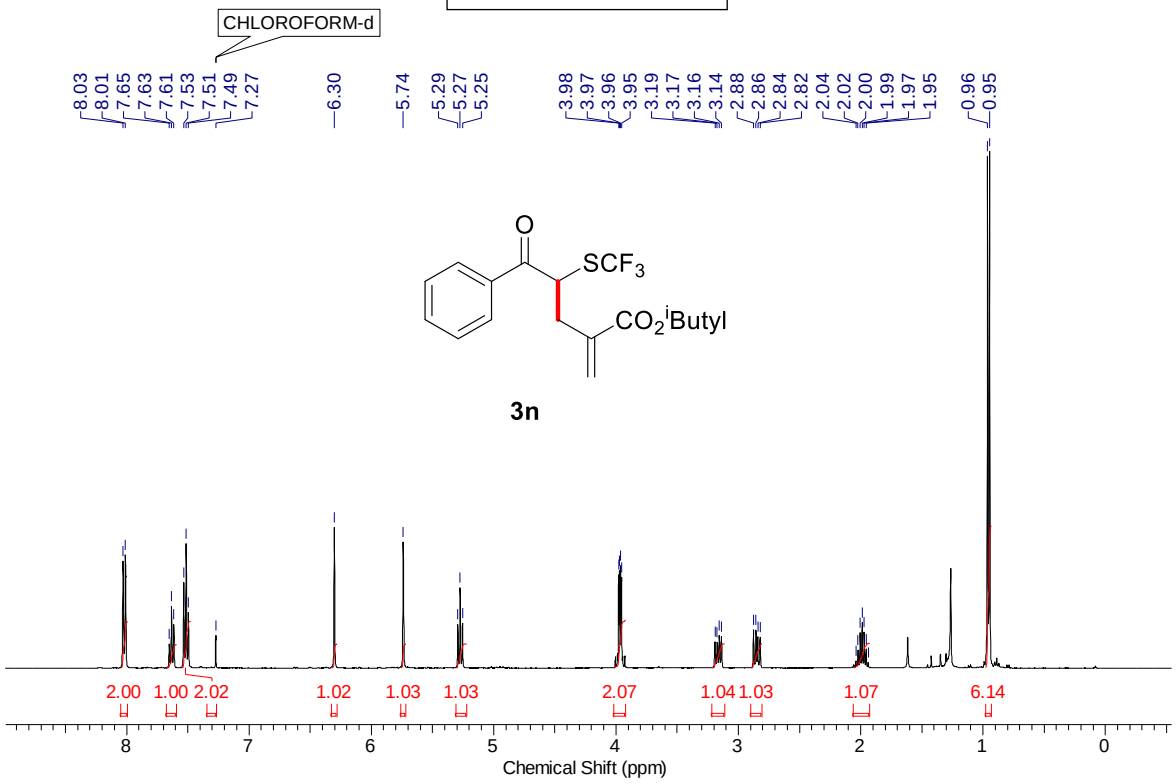

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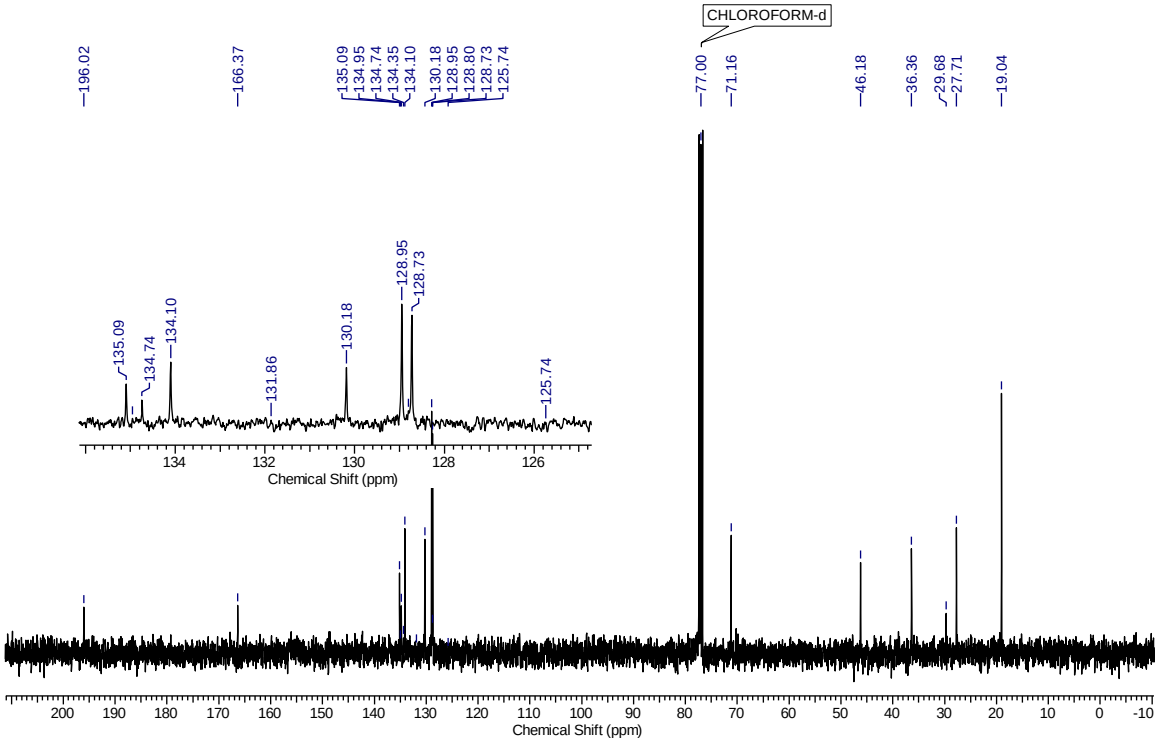

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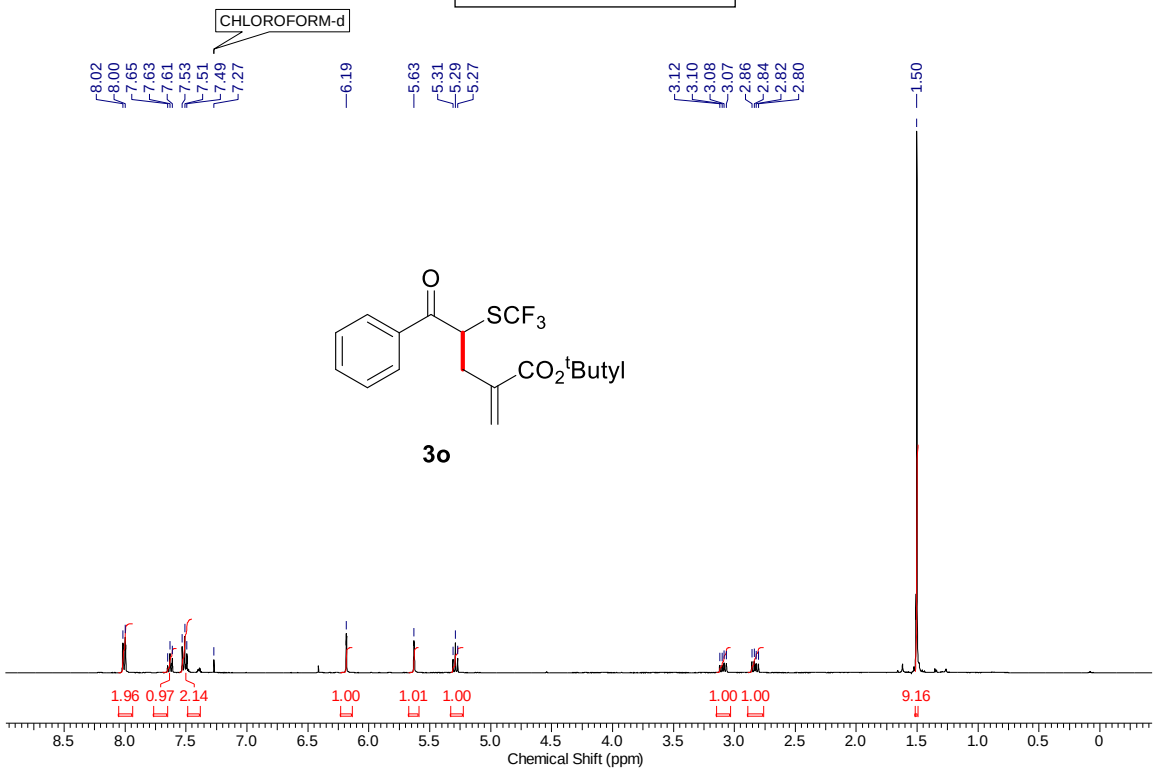

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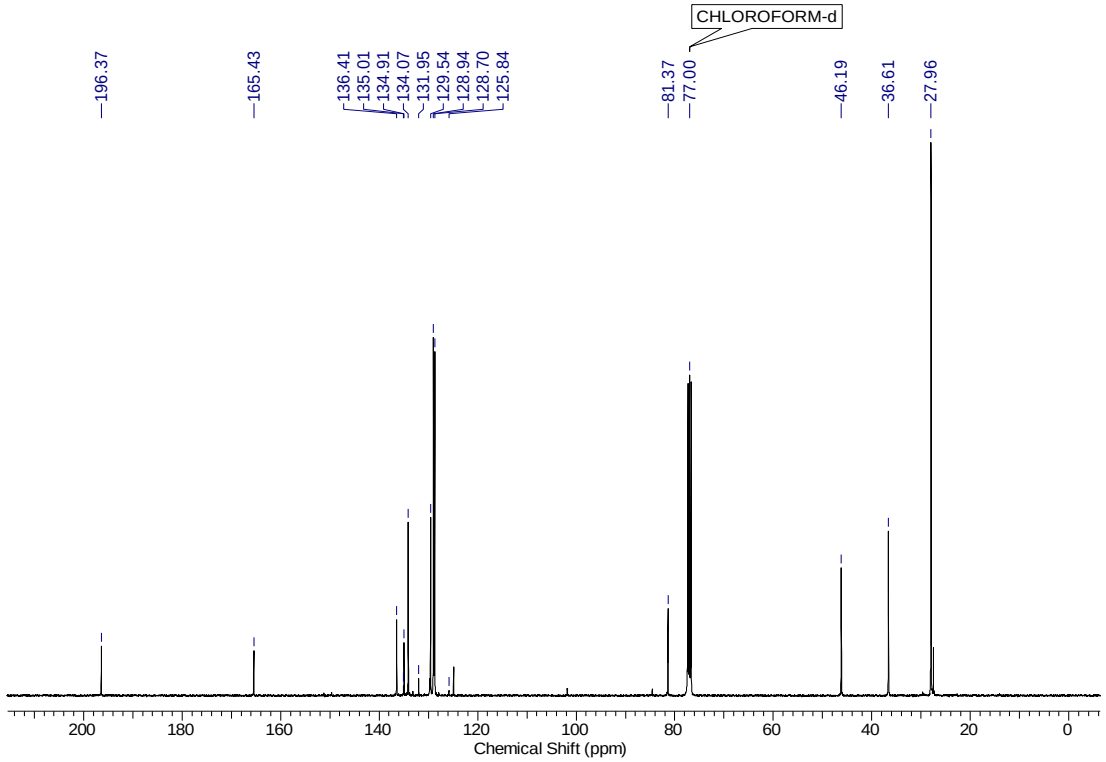

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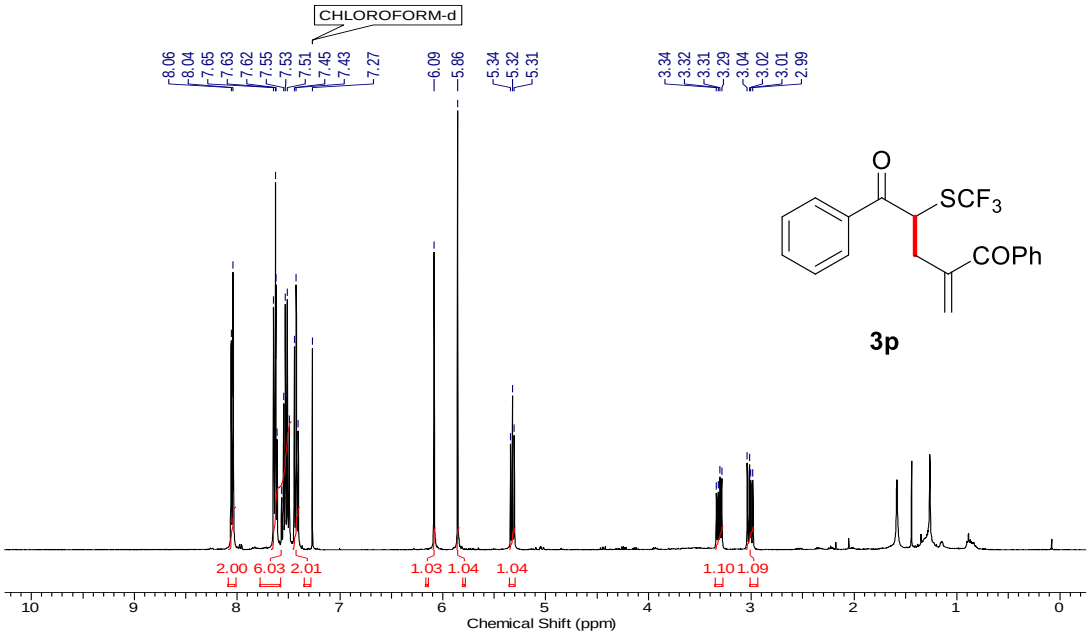

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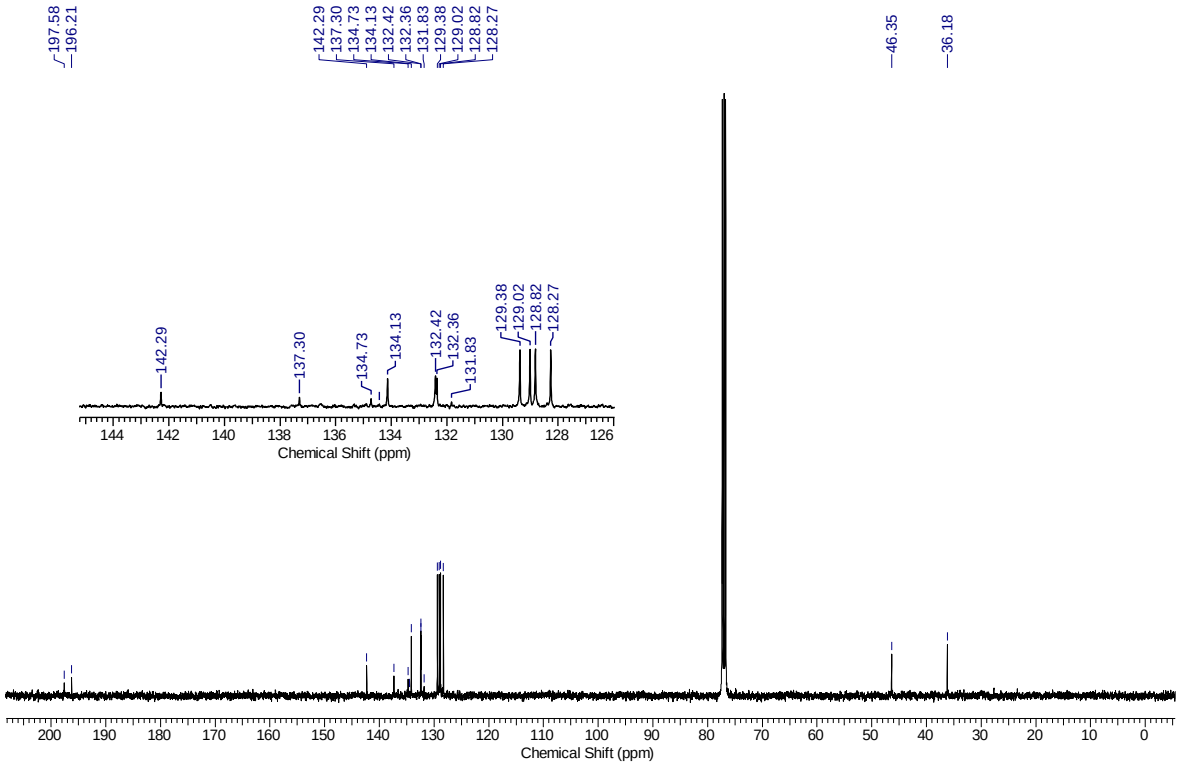

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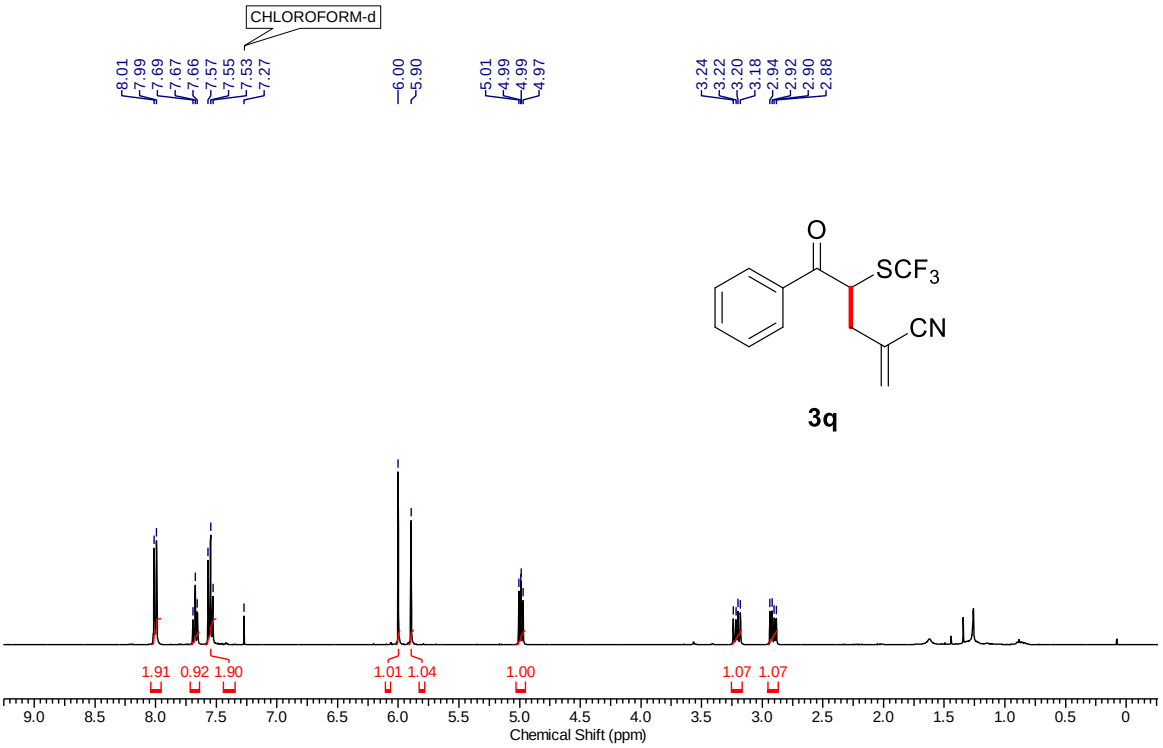

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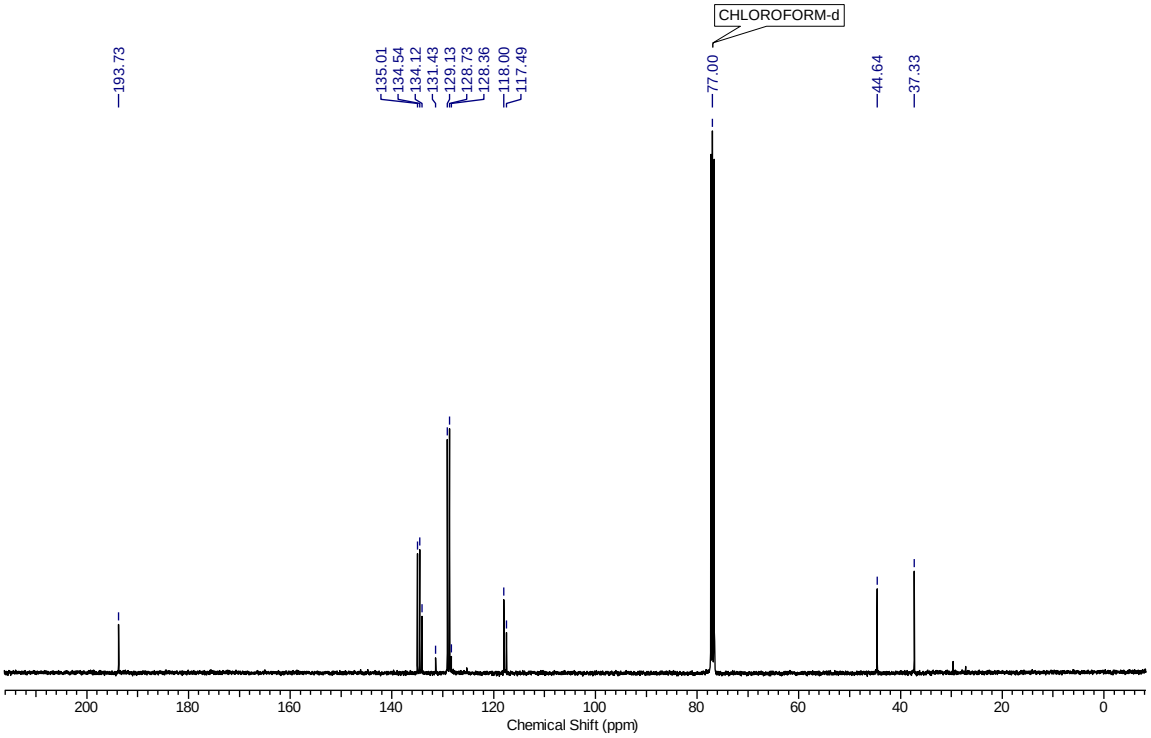

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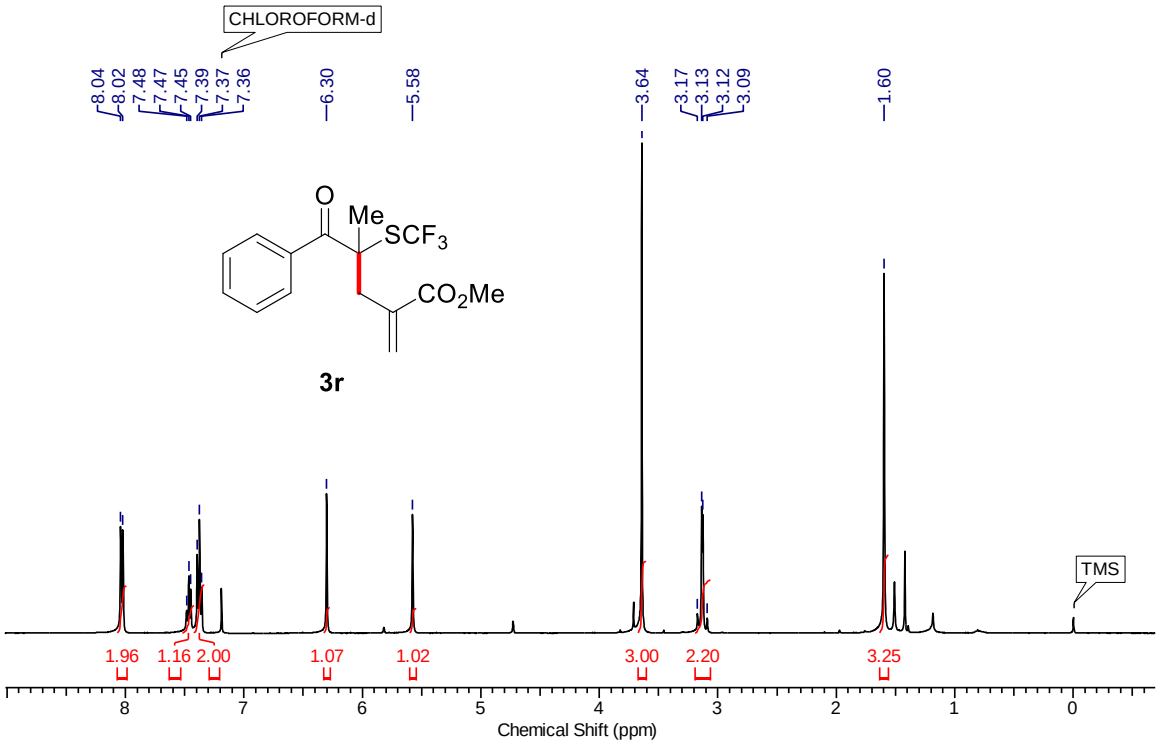

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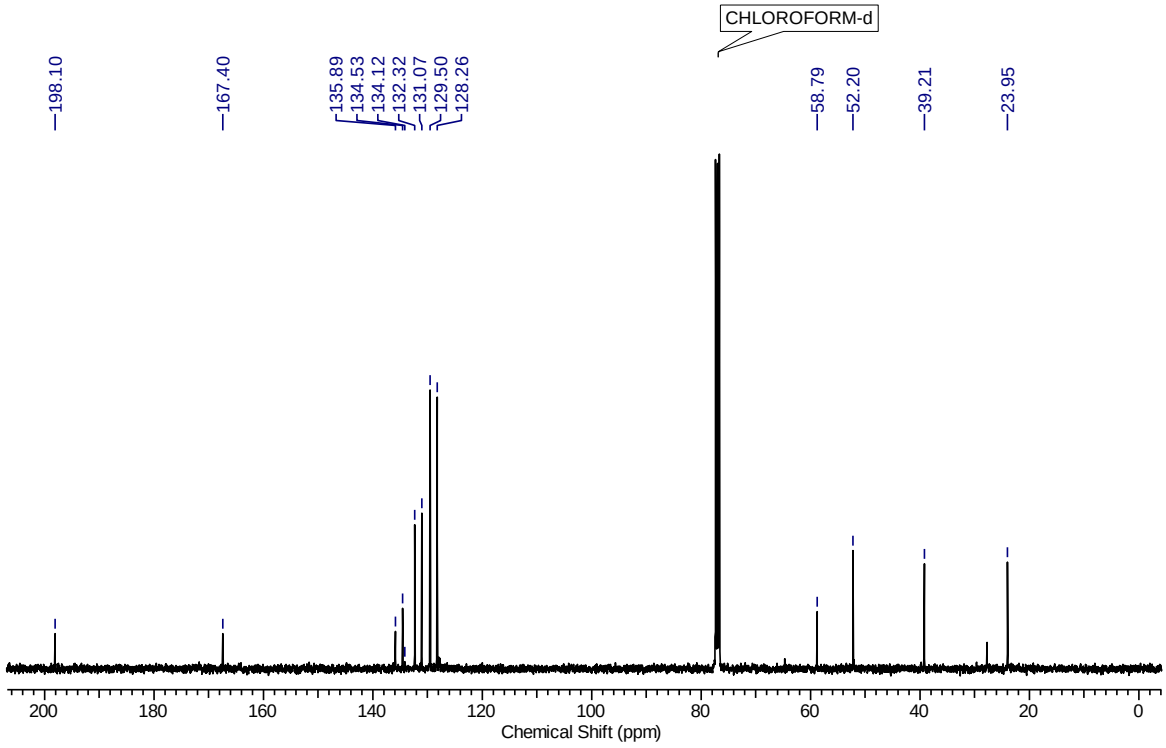

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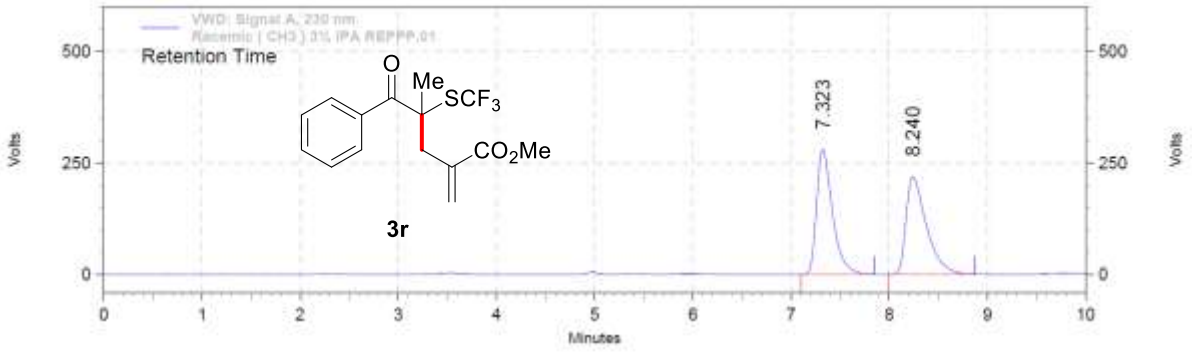

VWD: Signal A, 230 nm Results

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8.240	52770429	50.01	3667304	43.85
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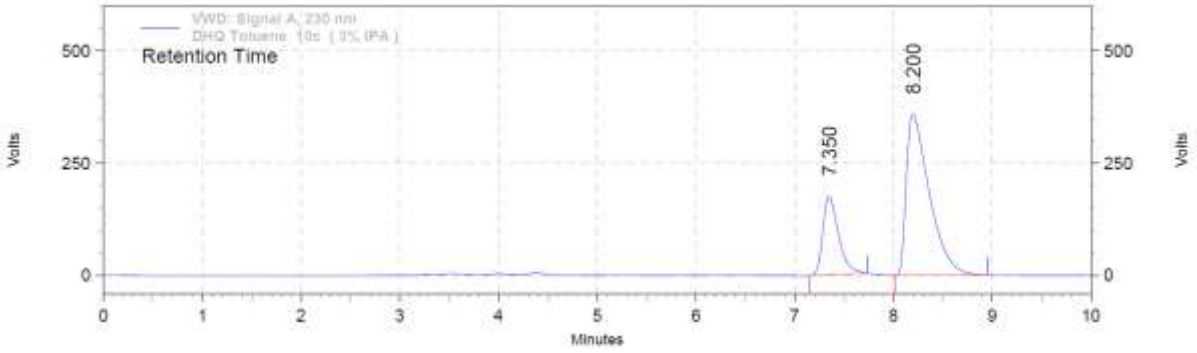

VWD: Signal A, 230 nm Results

Retention Time	Area	Area %	Height	Height %
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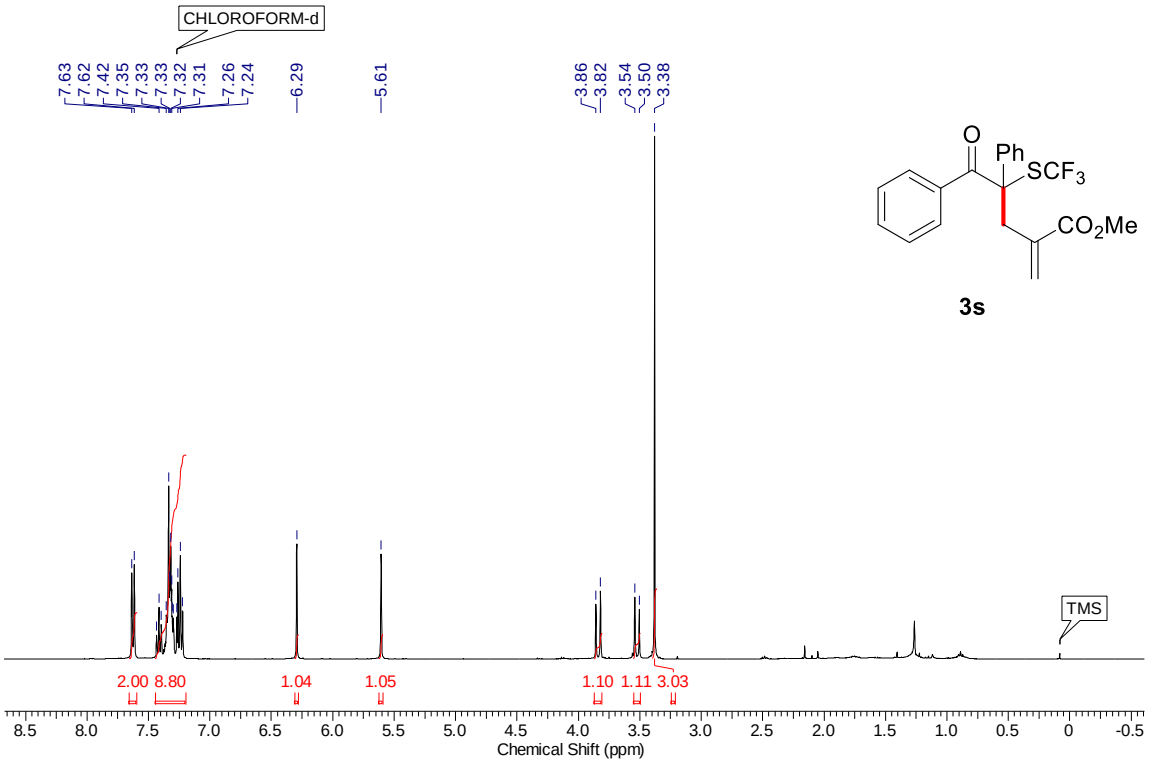
^{1}H NMR, 400 MHz



3s

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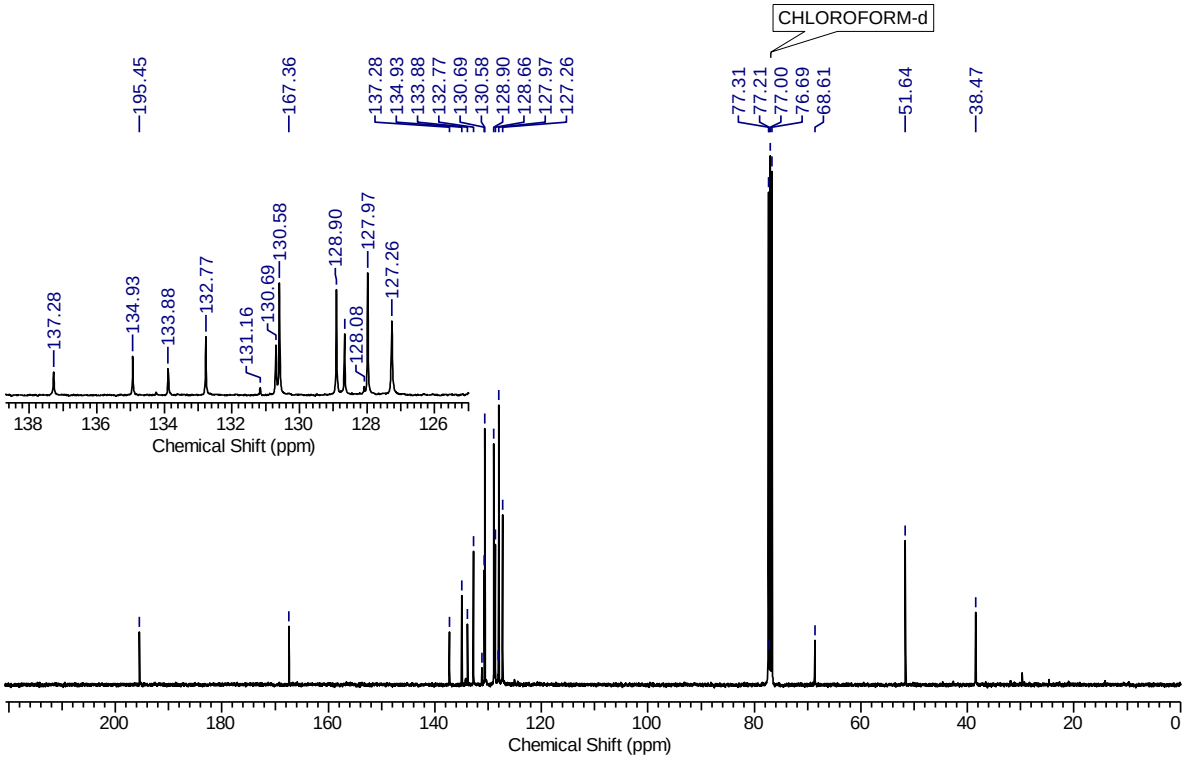
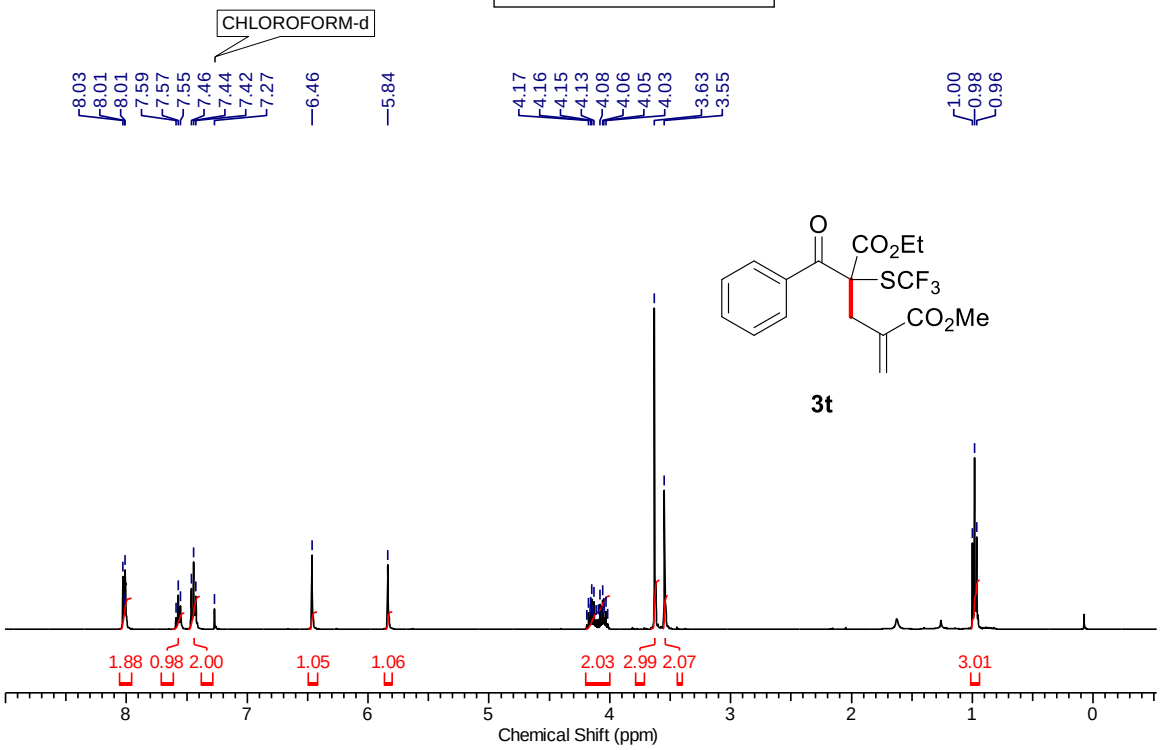


^{1}H NMR, 400 MHz



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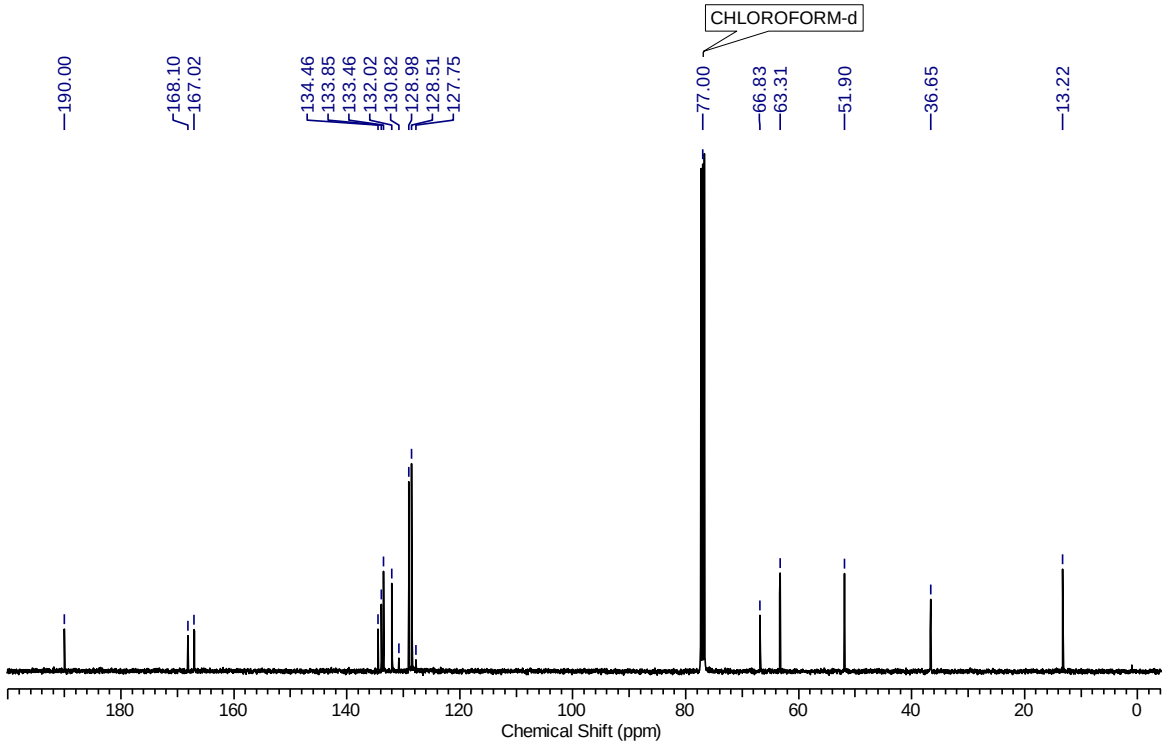
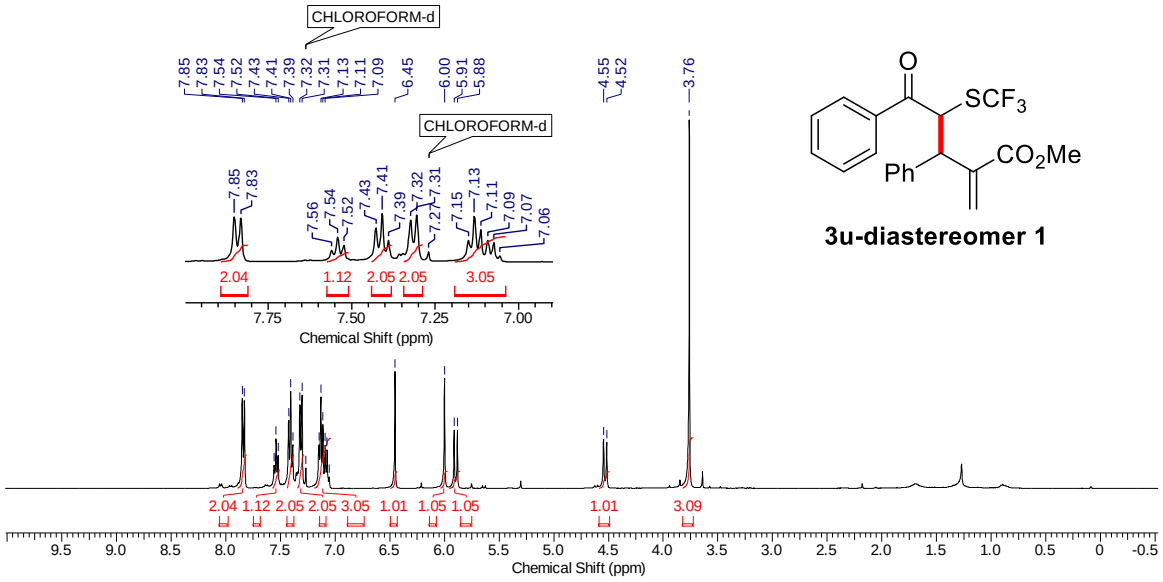


^{1}H NMR, 400 MHz



3u-diastereomer 1

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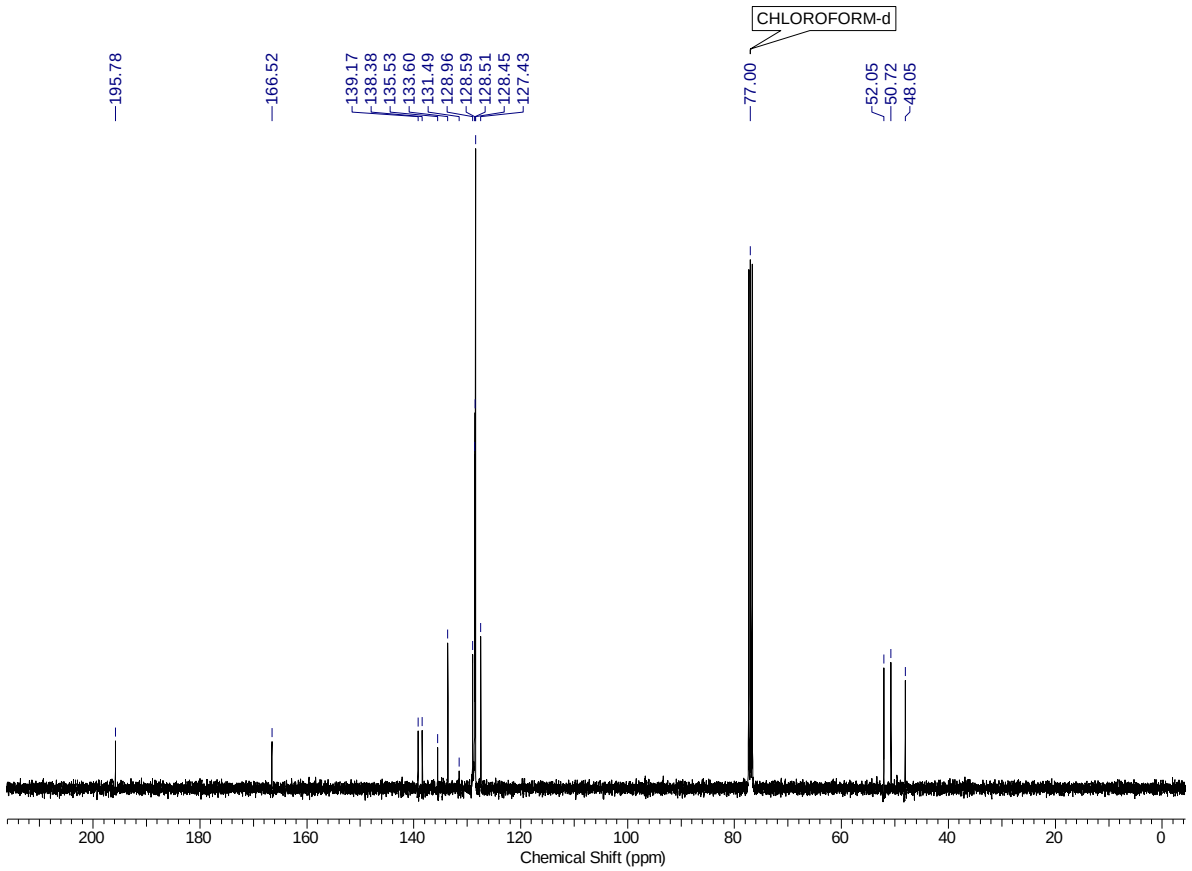

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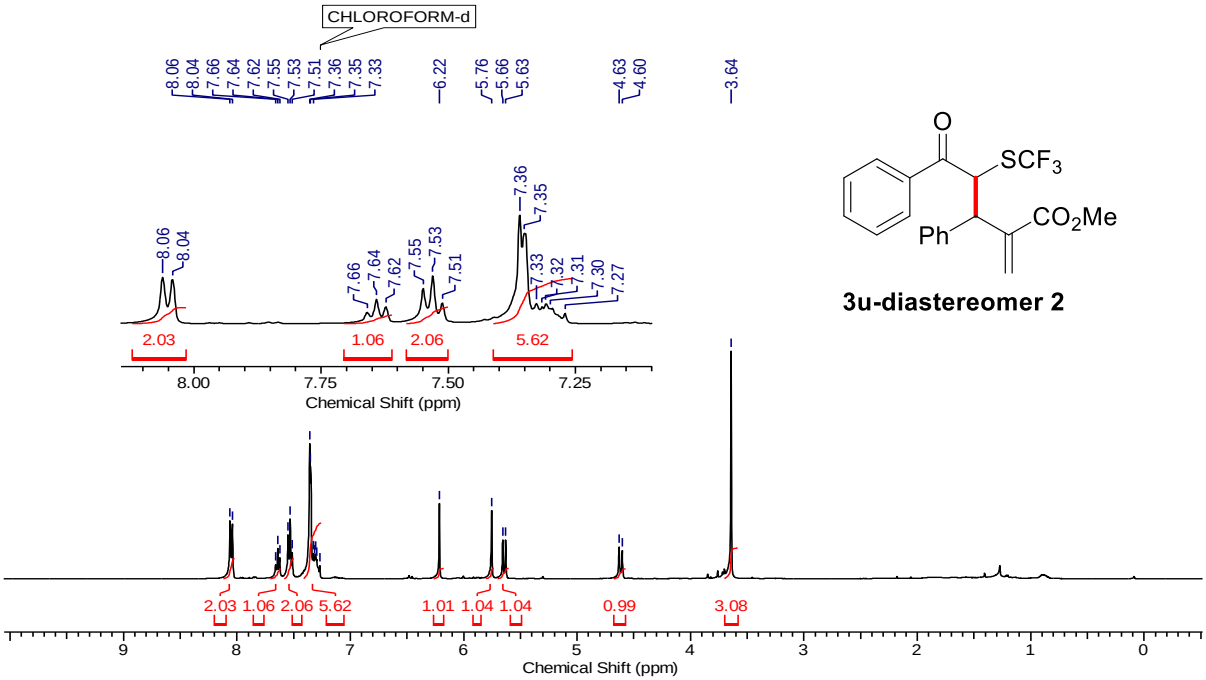

3u-diastereomer 2

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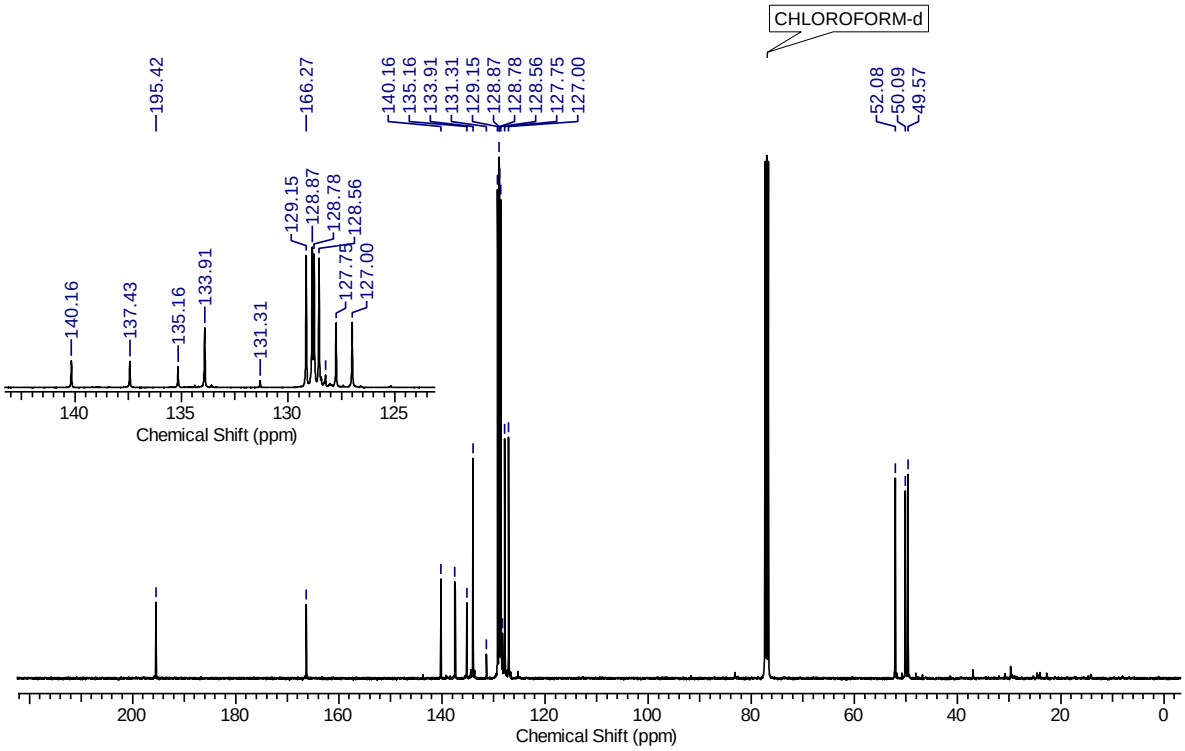
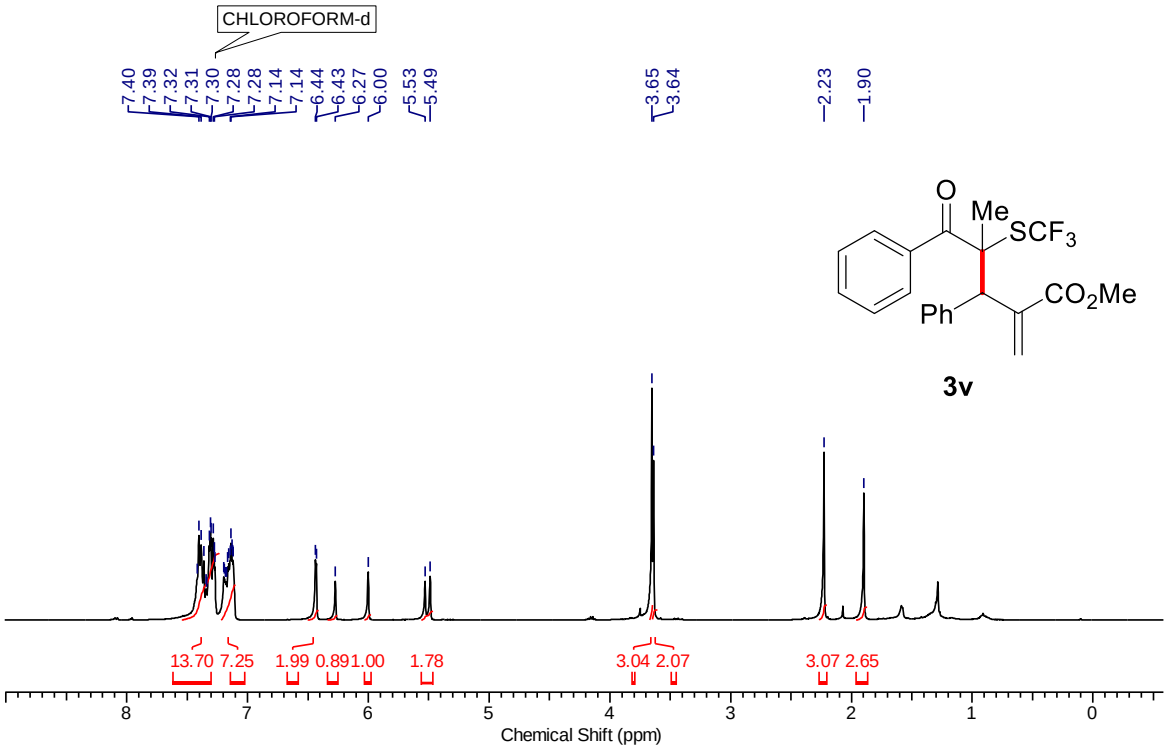


^{1}H NMR, 400 MHz



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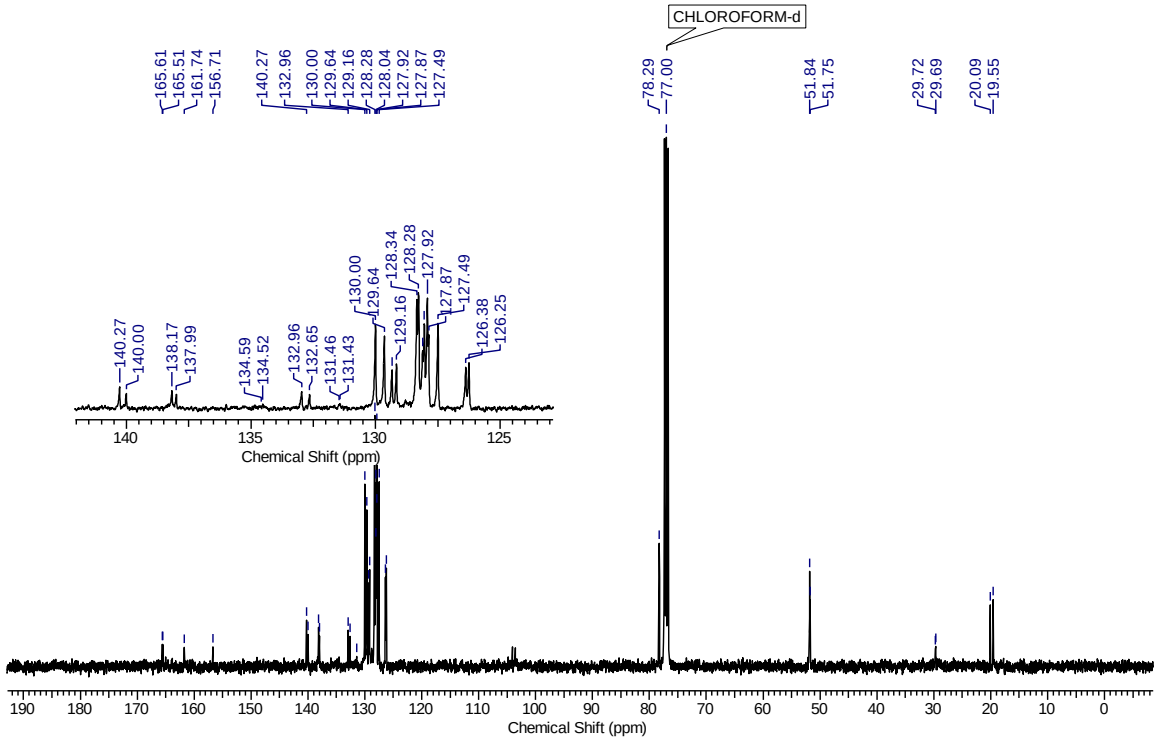

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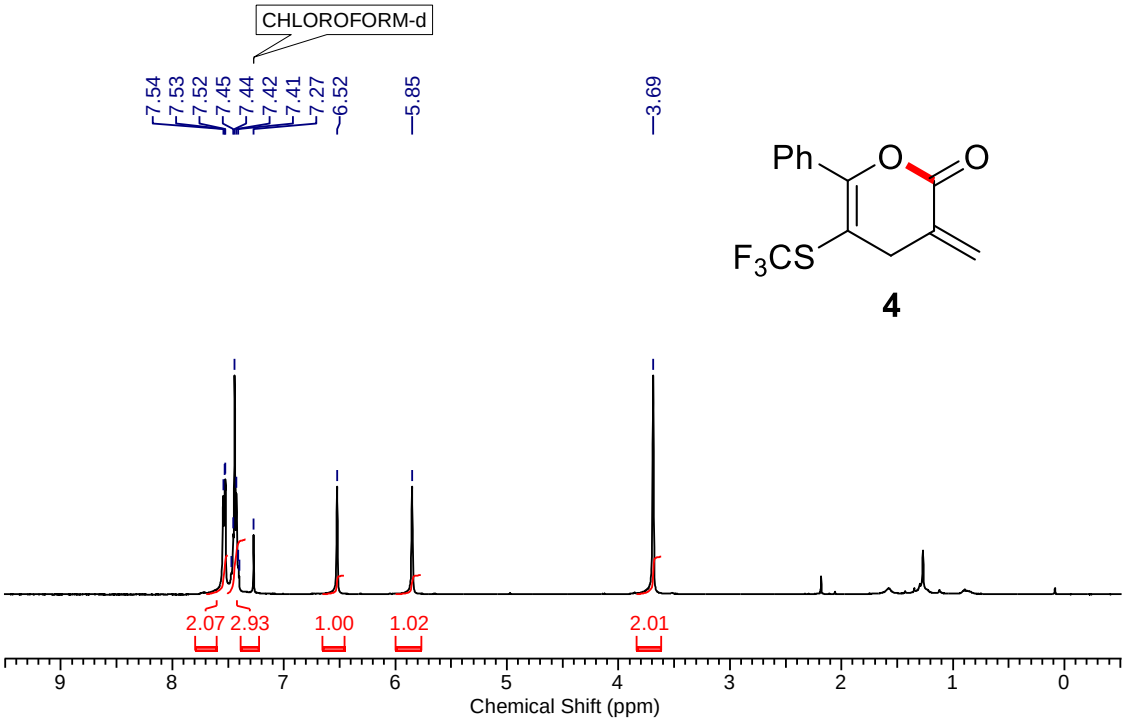
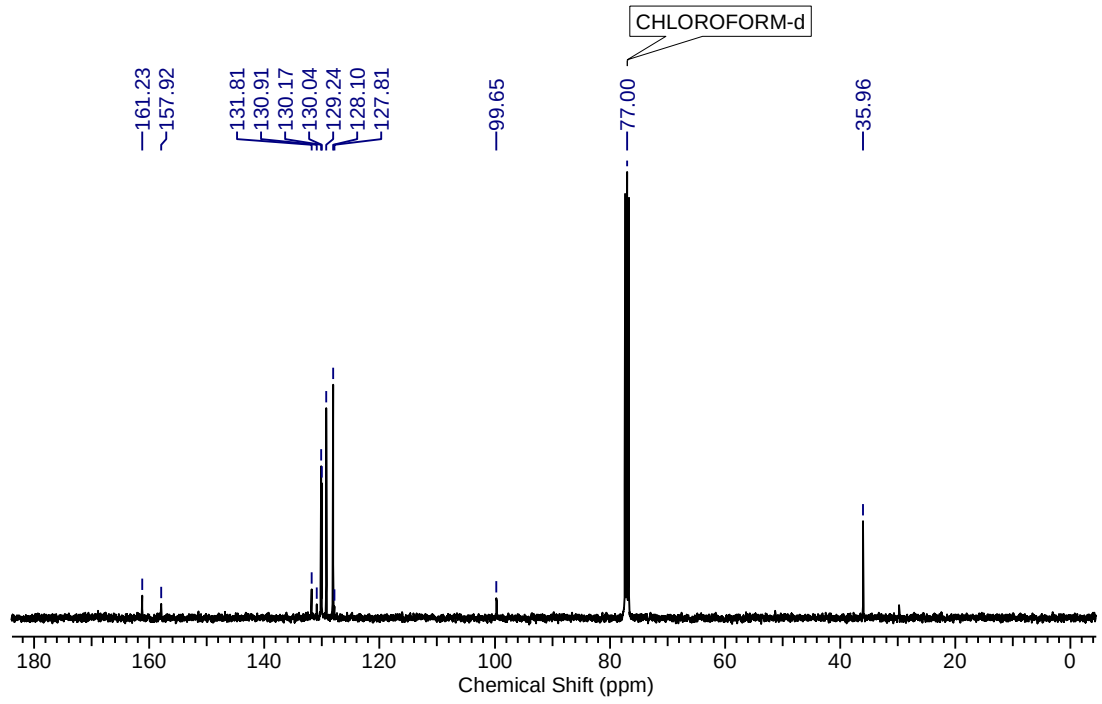
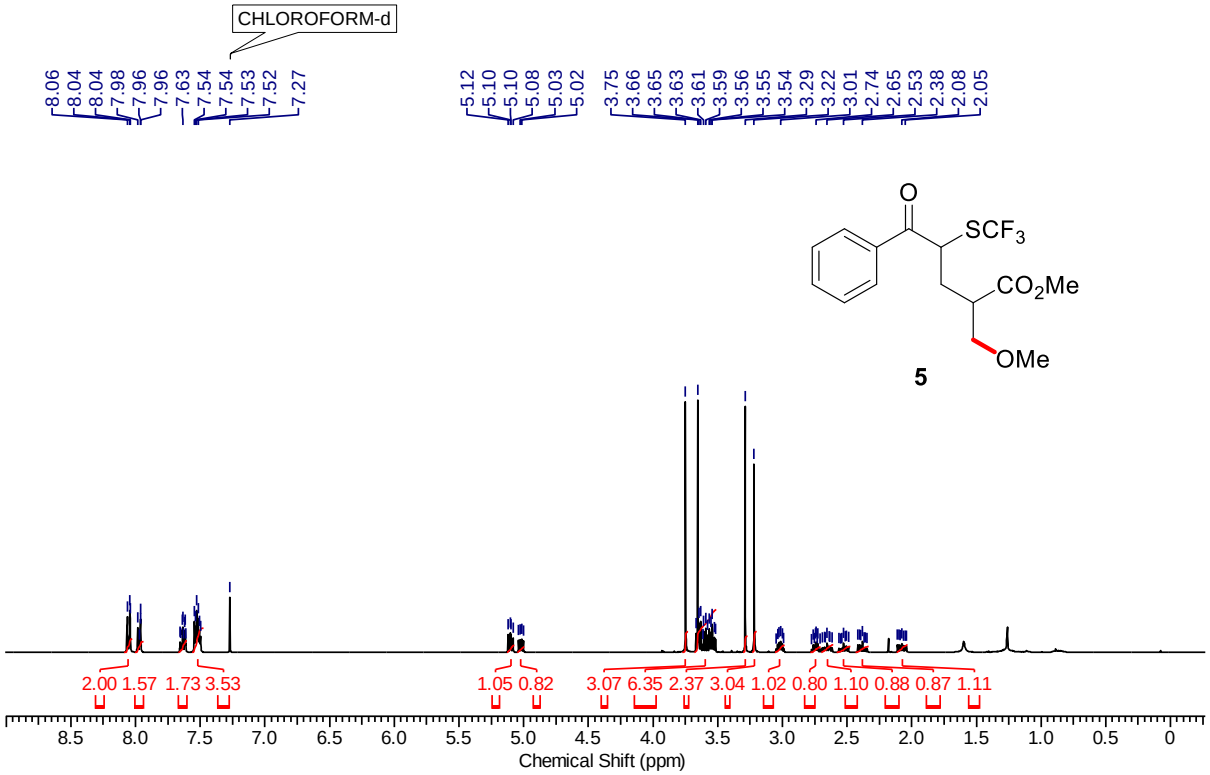


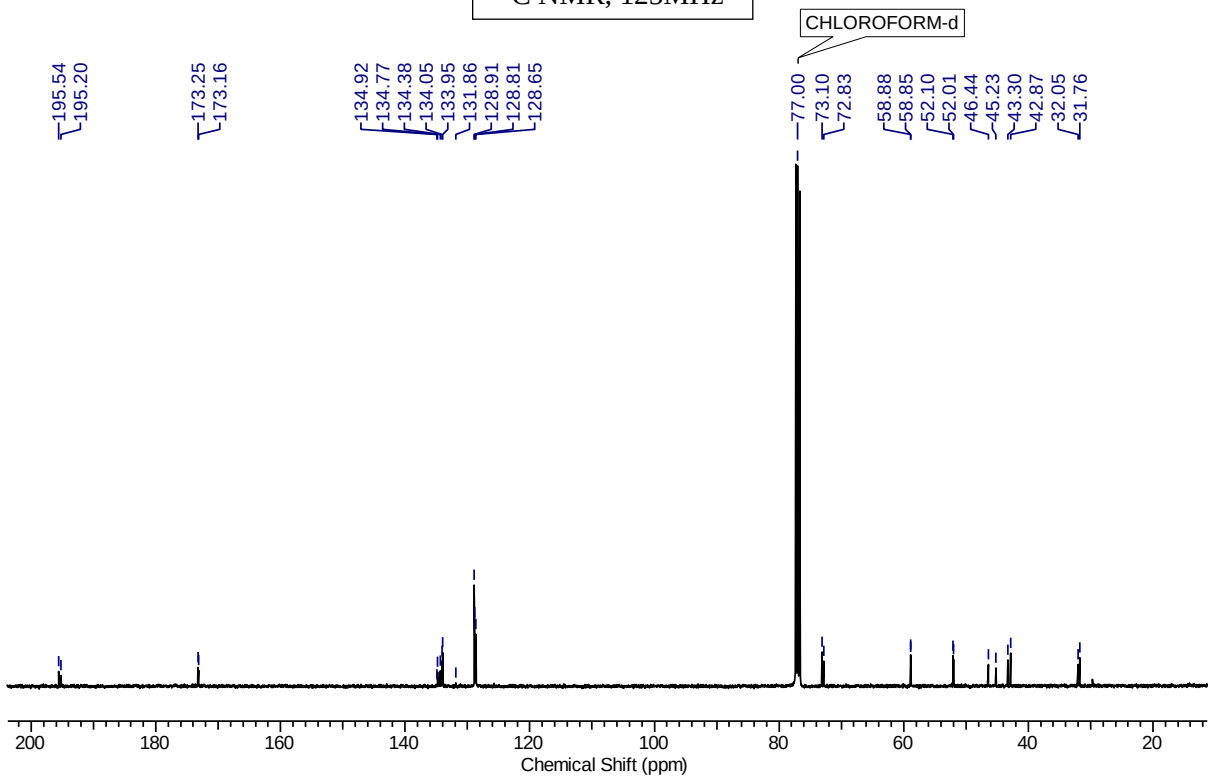
^{13}C NMR, 100 MHz



^{1}H NMR, 500 MHz



^{13}C NMR, 125MHz



Chapter 3

Studies Towards the Synthesis of Natural Product Orbicularisine

Studies Towards the Synthesis of Natural Product Orbicularisine

3.1. Abstract:

Chapter 3 portrays our studies towards the first total synthesis of organosulfur natural product orbicularisine. A practical and efficient synthetic route has been developed to construct a highly functionalized thiazine moiety of orbicularisine molecule. We have successfully built a spiro-oxindolofuranone fused thiazine ring of the orbicularisine molecule, which can be converted to the natural product by simple transformations.

3.2. Introduction:

Natural products are purified organic compounds or substances having a specific pharmacological or biological activity.[1] From ancient times, it has been closely linked to the human body through traditional medicines or natural poisons[2] and has played an essential role in drug discovery.[3] Among them, sulfur-containing natural products are one of the most sought-after and mostly isolated from terrestrial and marine organisms.[4] Figure 1 shows some examples of marine natural products containing sulfur functional groups.[5]

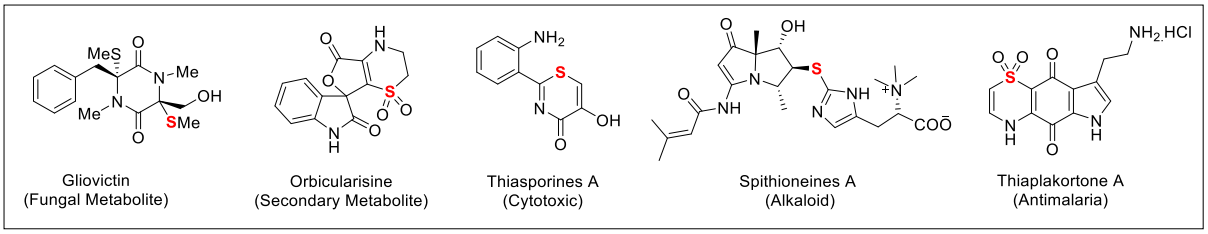


Figure 1. Examples of marine natural product

Sulfur is the fourth abundant element in seawater, hence sulfur-containing metabolites are profusely present in marine organisms and exhibit promising bio-activities, including antibiotic, antitumor, anti-inflammatory and enzyme-inhibitory activities.[6] However, supplying enough compounds from natural sources for biomedical research remains a considerable challenge due to

their inadequacy of resources. Thus, bio and synthetic chemical approaches have been shown to be powerful tools in the production of natural products and related scaffolds. Over the past decades, the total synthesis of sulfur-containing natural products and their associated derivatives/analogues has been the subject of intensive research by synthetic organic chemists.

3.3. Literature Review:

Orbicularisine, a naturally occurring organosulfur compound, was first isolated in a racemic form in 2017 from the gill filament of bivalve mollusc Codakia Orbicularis, which belongs to the family of Lucinidae.[5b] This mollusca mainly populates in the shallow-marine sea-grass beds and capable to produce a variety of secondary metabolites by the sulfur oxidizing endosymbiotic organism.[7] Since 2004, after the introduction of the first sulfur-containing marine mollusca derived natural product Ziconotide[8] as an analgesic for chronic pain, Kahalalide F (ES-285)[9] (succeeded in phase I of clinical trials) and dolastatin 10[10](currently in phase II of clinical trials) as an anticancer, marine mollusca became the most attractive source of novel scaffolds for the drug discovery.[11]

3.4. Origin of the Work:

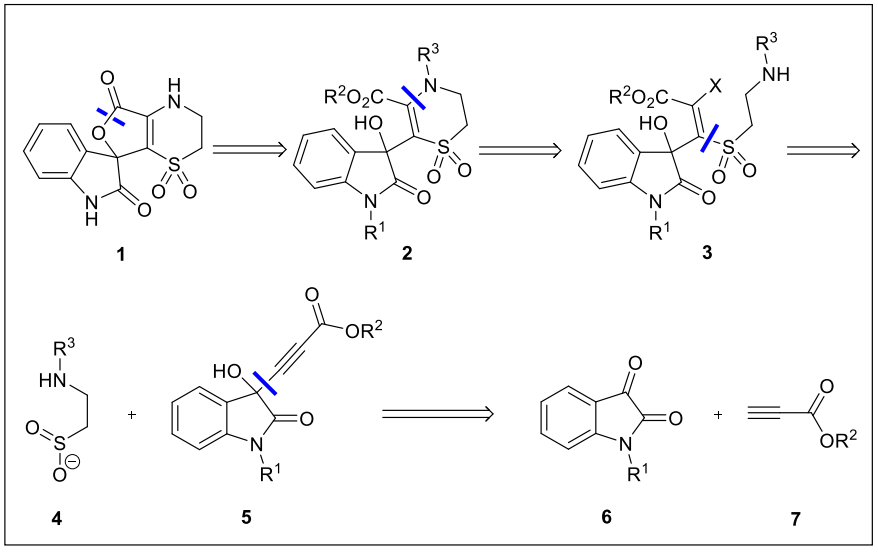
Structurally orbicularisine contains single stereocenter with spiro-oxindolofuranone fused thiazine skeleton and is present in nature as a racemic form. Even though the bioassays of the original fraction of orbicularisine does not show any bioactivity, the organic molecule having spirooxindole[12] or thiazine[13] scaffolds endows a wide spectrum of bioactivity, including antibiotic, anticancer, anti-HIV, etc. It is worth noting that Thiaplakortone A (figure 1.) having similar functional scaffold shows antimalarial activity. Therefore, this inimitable structural skeleton and various bioactivities made them a privileged building block for the generation of a library of its congeners in search of novel bioactive molecules and their total synthesis is a very challenging target. As far as we know, no synthetic pathway for the total synthesis of orbicularisine molecule

has been reported hitherto and which prompted us to explore its synthetic route as well as its bioactivity. Herein, we have reported the first total synthesis of orbicularisine molecules through the simplest route.

3.5. Objective of the Work:

Our retrosynthetic plan, shown in scheme 1, allowed us to recognize C–N and C–O bond disconnection as a key step for the construction of spiro moiety with the lactone and thiazine ring, which could be possible to synthesize by the lactonization of intermediate **2** followed by the cross-coupling C–H amination of the intermediate **3**. After that, C–S bond of the intermediate **3** was disconnected to sulfinate **4** and oxindole precursors **5** inspired by the 1,4 Michael addition reaction. Then, the compound **5** was supposed to be obtained from the commercially available compounds isatin **6** and propiolate derivative **7**.

Scheme 1. Retrosynthetic Plan

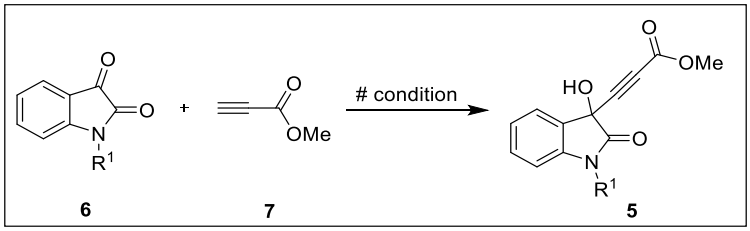


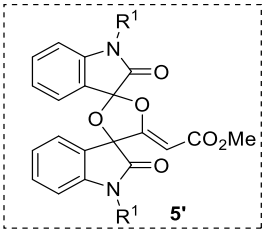
3.6. Result and Discussion:

According to the above-mentioned retrosynthetic plan (scheme 1), we commenced our synthetic route to the target molecule orbicularisine **1** with the commercially available compound isatin **6**,

which reacted with methyl propiolate **7** to deliver the intermediate **5**.[14] To improve the yield of intermediate **5**, we have tried different reaction conditions by changing starting materials, base and the equivalent of reactants.

Table 1. Optimization Studies for the Formation of Intermediate **5**





Entry	*R^1*	*Conditions*	*Yield (%)* [b]
1.	Tr (**5a**)	**6a** (1 equiv.), **7** (1.1 equiv.), $NaNH_2$ (1.5 equiv.)	trace
2.	Tr (**5a**)	**6a** (1 equiv.), **7** (1.1 equiv.), LHMDS (1.5 equiv.), -78 ^oC	11
3.	Bn (**5b**)	**6b** (1 equiv.), **7** (1.1 equiv.), LHMDS (1.5 equiv.), -78 ^oC	14
4.	Bn (**5b**)	**6b** (1 equiv.), **7** (1.1 equiv.), n-BuLi (1.5 equiv.), -78 ^oC	trace
5.	Bn (**5b**)	**6b** (1 equiv.), **7** (1.1 equiv.), LDA (1.5 equiv.), -78 ^oC	Complex reaction mixture
6.	Me (**5c**)	**6c** (1 equiv.), **7** (1.1 equiv.), LHMDS (1.5 equiv.), -78 ^oC	35
7.	MOM (**5d**)	**6d** (1 equiv.), **7** (1.1 equiv.), LHMDS (1.5 equiv.), -78 ^oC	47
8.	H (**5e**)	**6e** (1 equiv.), **7** (1.1 equiv.), LHMDS (1.5 equiv.), -78 ^oC	43
9.	H (**5e**)	**6e** (1 equiv.), **7** (2 equiv.), LHMDS (3 equiv.), -78 ^oC	62

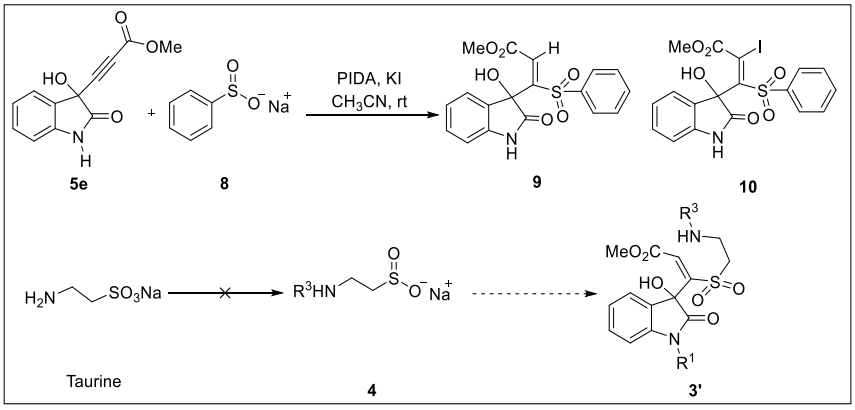
[b]Isolated yield.

Our first attempt using $NaNH_2$ promoted nucleophilic addition of methyl propiolate **7** to trityl isatin **6a** offered our expected product **5a** in trace amount along with the unexpected dimer compound **5'** in major amount, which was formed by the further attack of oxygen ion to another isatin moiety (table 1, entry 1).[15] Hence, we tried to stop the attack by decreasing the temperature, changing base and by the insitu protection of alcohol in the reaction mixture, but our every effort failed to get our expected product **5a**. However, in presence of LHMDS at -78 ^oC, slight improvement in the yield was observed (table 1, entry 2). Changing protecting group to benzyl **6b** did not give better yield of the expected intermediate **5b** (table 1, entry 3). Screening of different

bases like, *n*-BuLi, LDA, NaHMDS etc. also failed to provide our expected product (table 1, entries 4 & 5). Hence, we continued the reaction by keeping LHMDS as a base. Interestingly, methyl protected isatin **6c** showed enhanced yield of intermediate **5c** to 35% in the presence of 1.1 equiv. of LHMDS at -78 ^{o}C (table 1, entry 6); however, MOM protected isatin **6d** offered better yield (table 1, entry 7) under the same reaction condition. Further running the reaction with simple isatin **6e** using the same reaction condition could not improve the yield of the product **5e** (table 1, entry 8). However, it was found that the intermediate **5e** was formed in 62% yield with simple isatin **6e** in presence of 2 equivalents of **7** and 3 equivalents of base LHMDS in THF at -78 ^{o}C after 2 h stirring.

Having the compound **5e** in good quantities from isatin **6e**, we pursued to address the synthesis of compound **3** by using *N*-protected sulfinate salt of hypotaurine **4**. Model study was performed to establish the feasibility of the iodosulfonylation of internal alkynes **5e**. In the presence of PIDA and KI in acetonitrile, the reaction of alkynes **5e** with sodium benzene sulfinate salt **8** provided compound **9** instead of our expected compound **10**. To obtain our expected compound **10**, various reaction conditions were performed. However, all the attempts were found to be failed. Then, we changed our retrosynthetic plan for the construction of thiazine ring to C-H bond activation instead of cross-coupling rection.

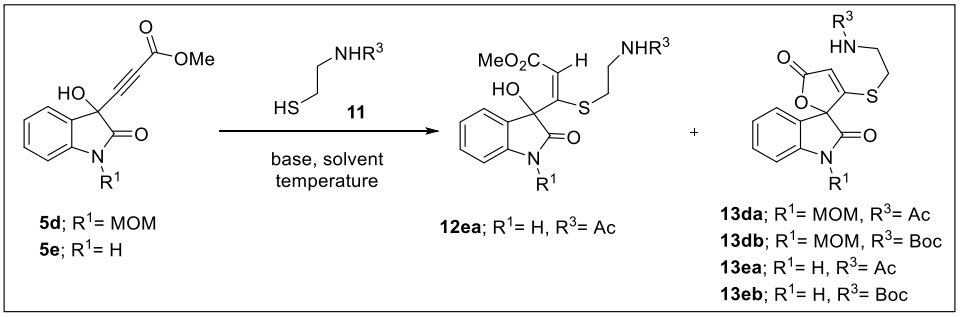
Scheme 2. Model Reaction



Based on the intriguing result from the model study, we focused on the synthesis of compound **3'** using a suitable decorated sulfinate salt. For this purpose, we have tried to utilize modified reaction conditions for synthesizing *N*-protected sulfinate salt from different starting molecules like, hypotaurine, taurine, etc. but all the efforts failed after multiple trials and errors (scheme 2).

Then, we planned a new synthetic route for the synthesis of compound **3'** by the oxidation of compound **12** which could be obtained from compound **5** by the 1,4 Michael addition reaction of nucleophile **11**. In presence of 1 equivalent K_2CO_3 and water at 50 ^oC, compound **12** was formed along with another new compound **13**. Interestingly, the characterization of compound **13** showed that it contains spiro-indolofuranone skeleton which is present in our final natural product orbicularisine **1**. Then, we focused to improve the yield of the intermediate **13ea**. However, under such condition, compound **12ea** was formed as a major product (table 2, entry 1). Therefore, to increase the selectivity for the formation of compound **13ea**, we have screened many different conditions by changing base, solvent, temperature and mole ratio of bases and reactants, which is summarized in table 2.

Table 2. Optimization Studies for the Formation of Intermediate **13**



5d; R^1= MOM
5e; R^1= H

12ea; R^1= H, R^3= Ac

13da; R^1= MOM, R^3= Ac
13db; R^1= MOM, R^3= Boc
13ea; R^1= H, R^3= Ac
13eb; R^1= H, R^3= Boc

Entry	*Conditions*	*R^3*	*Yield (**12:13**)^{a,b}*
1.	K_2CO_3 (1 equiv.), H_2O, 50 ^oC, 1h	Ac	(1:0.05)
2.	K_2CO_3 (1 equiv.), ACN, 50 ^oC, 1h	Ac	(1:0.37)
3.	NaOMe (1 equiv.), MeOH, 50 ^oC, 1h	Ac	(1:0.20)
4.	K_2CO_3 (1 equiv.), ACN, 50 ^oC, 1h	Ac	(1:0.43)

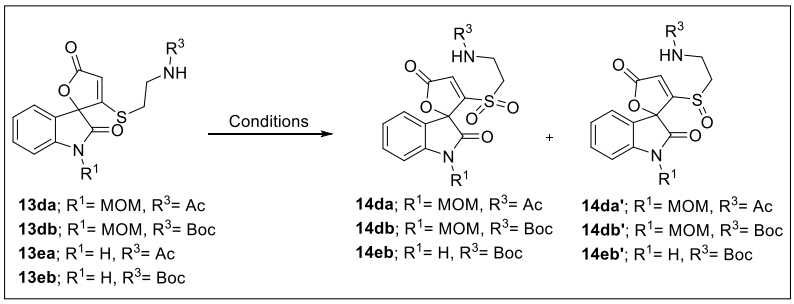
5.	K_2CO_3 (1 equiv.), ACN, reflux, 1h	Ac	(1:0.35)
6.	K_2CO_3 (2.5 equiv.), ACN, 50 ^oC, 1h	Ac	(1:0.89)
7.	K_2CO_3(2.5 equiv.), MeOH, 50 ^oC, 1h	Ac	(1:0.57)
8.	K_2CO_3(2.5 equiv.), Dioxane, 90 ^oC, 1h	Ac	(1:0.46)
9.	K_2CO_3 (2.5 equiv.), ACN, 50 ^oC, 1h	Boc	(1:0.55)
10.	K_2CO_3 (3 equiv.), ACN, reflux, overnight	AC	64% (0:1)[b]
11.	K_2CO_3 (3 equiv.), ACN, reflux, overnight	Boc	41% (0:1) [b]

[a]NMR ratio for entries 1-9, [b]Isolated yield for entries 10 & 11.

After multiple trials and errors, the compound **13ea** was obtained selectively by using K_2CO_3 in acetonitrile with 64% yield (table 2, entry 10). However, the yield was diminished to 41% by changing to Boc-protected cysteamine **11b** under the same reaction condition (table 2, entry 11).

After having compound **13** in good amount, the next step was set for the oxidation of sulfur. Initially, we used *m*CPBA as an oxidant in DCM at room temperature and a trace amount of sulfone compound **14** was obtained. Further studies for getting sulfone compound **14** with a good yield led to offer sulfoxide or the decomposition of starting material (table 3). Finally, by the treatment of compound **13eb** with 3 equiv. *m*CPBA in DCE under refluxing condition furnished the expected sulfone compound **14eb** with an excellent yield (table 3, entry 7).

Table 3. Optimization Studies for the Formation of Intermediate **14**.



Entry	*Conditions*	*Observation*
1.	mCPBA (3 equiv.), DCM, rt	Not able to isolate
2.	30% aq H_2O_2(2.2 equiv.), 70 ^oC	Sulfoxide formed
3.	Oxone (1.5 equiv.), TEA (20 mol%), ACN/H_2O, rt	Sulfoxide formed

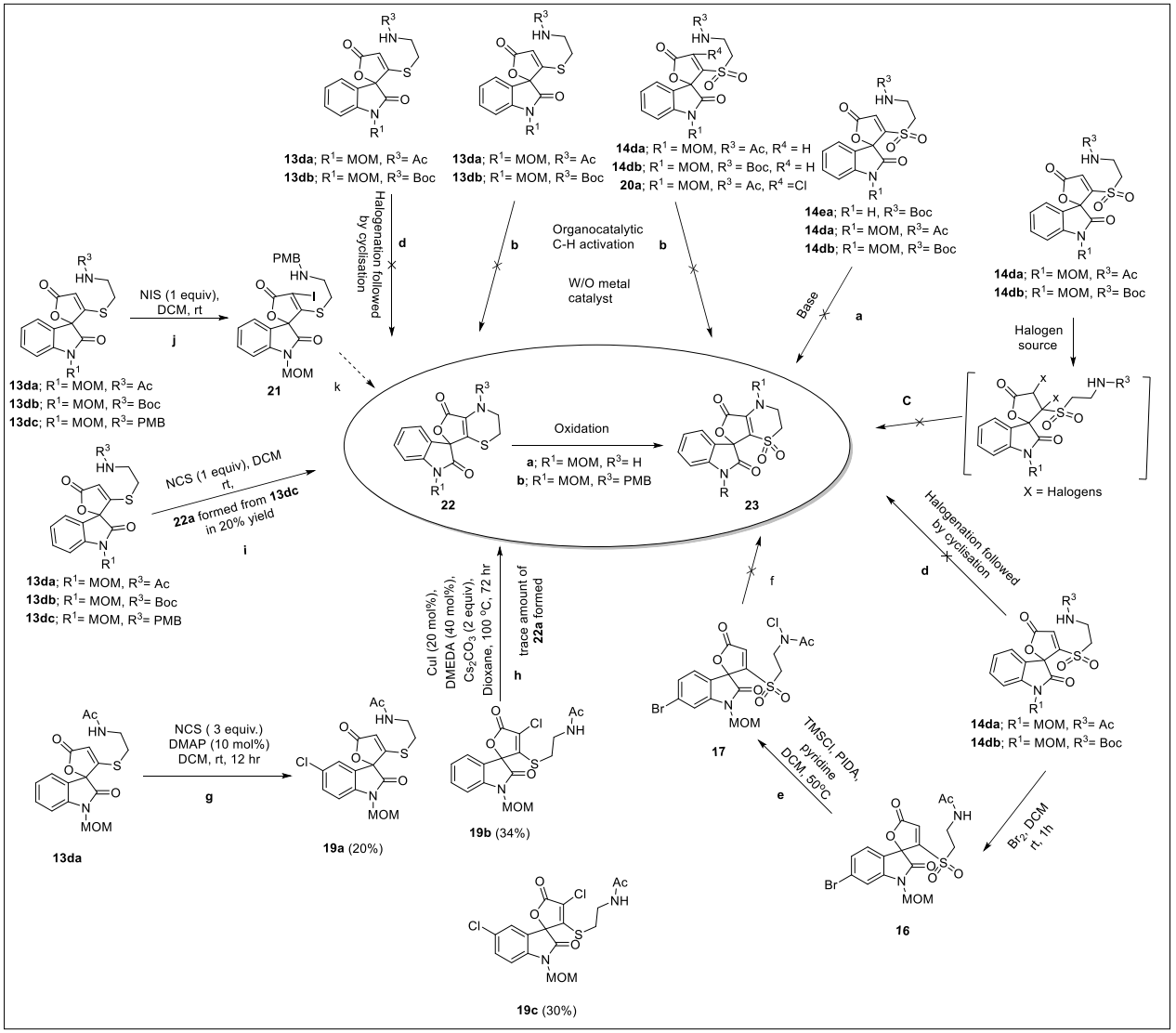
4.	$KHSO_5$(2.5 equiv.) $NaHCO_3$(2.6 equiv.), Acetone, H_2O	Sulfoxide formed
5.	$NaIO_4$(1.1 equiv.), $KMnO_4$(0.6 equiv.), $MgSO_4$(cat.), Acetone/water	Starting material decomposed
6.	H_5IO_6(4 equiv.), CrO_3(0.2 equiv.), CH_3CN	Starting material decomposed
7.	*m*CPBA (3 equiv.), DCE, 90 ^{o}C	Sulfone **14eb** formed with 87 % yield

[b]Isolated yield.

The next step was the construction of thiazine ring of the target molecule orbicularisine by the C–N bond formation, which would be the key step for the synthesis of orbicularisine molecule. Initially, we used the intermediate **14** as a starting precursor for the formation of thiazine moiety by the simple 1,4 Michael addition of α, β-unsaturated sulfonyl compound. However, screening with different organic and inorganic base led to the decomposition of starting material (scheme 3, path a). Organocatalytic intramolecular C–H amination also failed to provide our expected intermediate in various reaction conditions (scheme 3, path b). Then, we changed our strategy to construct the thiazine skeleton via halogenation followed by the cyclization reaction, which is well established in the literature.[16] For the halogenation reaction, first we prepared MOM group protected intermediate **5d** in 65% yield (gram-scale) which was converted to sulfone intermediate containing Boc group protected carbamate moiety **14db** with 34% yield over two steps under the optimized condition (gram scale). Upon treatment with different halogenating agents like Br_2, NBS, NCS, NIS, I_2, $CuBr_2$, NaBr, and also the catalytic condition in different solvent at various temperature resulted the deprotection of Boc group or aromatic halogenation (scheme 3, path c and d). Then, we decided to alter the protecting group of amines with acyl group to afford the compound **14da** in 69% over two steps (gram scale) and treated with various reaction conditions (scheme 3, paths c & d). Yet, all the attempts failed to give our expected product. Whereas, treatment of bromo substituted sulfone compound **16** with TMSCL, PIDA and pyridine in DCM

at 50 ^{o}C furnished *N*-chlorinated sulfone compound **17** with 59% yield (scheme 3, path e). Inspired from the literature survey, we planned to form C–N bond from N-chlorinated compound **17** in presence of various metal or photocatalyst (scheme 3, path f). However, none of them worked well to offer the expected product. To our delight, when we treated the compound **13da** with 3 equivalents of NCS and 10 mol% DMAP in DCM, we have observed the formation of compound **19b** in 39% yield along with other side products **19a** and **19c**.

Scheme 3. Attempts for C-N Bond Formation of the Thiazine Moiety

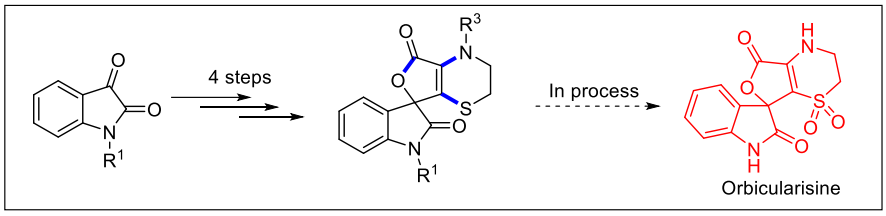


However, further attempts did not improve the yield of the chloro compound **19b** selectively (scheme 3, path g). After successfull formation of chloro compound **19b**, we turned our attention towards our final step to form C–N bond of the thiazine moiety. Surprisingly, final cyclisation happened in presence of CuI, DMEDA, CS_2CO_3 in dioxane at 100 ^oC temperature with the *insitu* deprotection of acyl group; nevertheless, the product **22a** was formed in poor yield to complete the synthesis of orbicularisine molecule (scheme 3, path h). Changing the reaction condition as well as the isolation procedure did not improve the yield of the compound **22a**. However, treatment of PMB protected intermediate **13dc** with 1 equiv. NCS in DCM at rt, the yield of the compound **22a** was increased upto 20% (scheme 3, path i). Interestingly, when we treated intermediate **13dc** with 1 equiv. NIS, instead of the C-N bond formation we have observed that the olefin iodination has taken place and **21** was formed with an excellent yield (scheme 3, path j). Further, we used both the intermediates **13dc** and **21** as a starting precursor for the formation of thiazine moiety via organocatalytic amination reaction via C-H activation or cross coupling reaction. However, our expected compound was not observed under catalytic or non-catalytic conditions (scheme 3, path k). Presently, we are working on the improvement of yield of the expected product **22** and also trying to optimize the further steps to complete the total synthesis of organosulfur natural products orbicularisine molecule **1**.

3.7. Conclusion:

In summary, we have made the efforts towards the first total synthesis of organosulfur natural products orbicularisine. We have successfully constructed spiro-indolofuranone fused thiazine skeleton from easily assessable compounds isatin and methyl propiolate in 4 steps with 0.07% overall yield. The optimization study for improving the yield is still in the process and transformation to complete the first total synthesis of orbicularisne molecule via the oxidation of

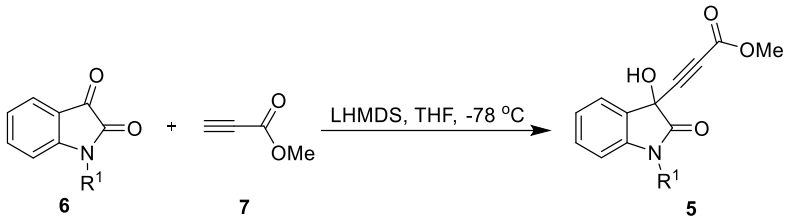
sulfur moiety followed by the deprotection of PMB and MOM group needs to be optimized on a better scale. Moreover, orbicularisine synthesis utilizing our developed protocol will be useful for the generation of a library of its congeners in search of novel antimalarial lead molecules.



3.8. Experimental Section

1. Experimental Procedures and Characterization Data of Compounds:

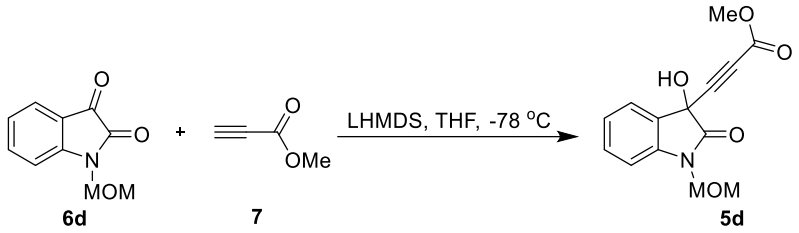
I] General Experimental Procedure for the Synthesis of Intermediate 5d-e (Modified Procedure):[14]



To a solution of methyl propiolate **7** (2 equiv.) in dry THF (50 ml), LHMDS (1 M in THF) (3 equiv) was added dropwise at -78 °C temperature. After stirring for 1 hour, a solution of isatin derivatives **6d-e** (1 equiv., 1 gm) in dry THF (50 ml) was added slowly to the solution of alkynyl lithium reagent at -78 °C and kept stirring for 3 hours. Then, the reaction mixture was quenched by NH_4Cl (30 ml), warmed up to room temperature and extracted with ethyl acetate (3*40 ml). The combine organic part was washed with brine solution and dried over anhydrous Na_2SO_4. Evaporation of the solvent under vacuo to dryness followed by the purification of the crude product using flash silica gel column chromatography with a gradient of pet ether:ethyl acetate (9:1 to 4:1) provided the expected intermediate **5d-e** with good yield.

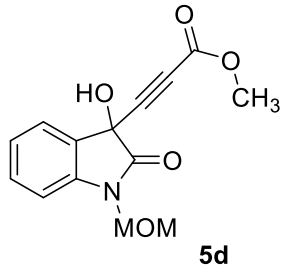
The formation of intermediate **5c** was confirmed by comparing their characteristic data with the reported literature.[14]

II] Typical Experimental Procedure for the Preparation of Representative Intermediate 5d:



To a solution of methyl propiolate **7** (2 equiv., 879.6 mg, 10.5 mmol) in dry THF (50 ml), LHMDS (1 M in THF) (3 equiv., 16 ml, 15.7 mmol) was added dropwise at -78 ^{o}C temperature. After stirring for 1 hour, a solution of isatin derivatives **6d** (1 equiv., 1 gm, 5.24 mmol) in dry THF (50 ml) was added slowly to the solution of alkynyl lithium reagent at -78 ^{o}C and kept stirring for 3 hours. Then, the reaction mixture was quenched by NH_4Cl (30 ml), warmed up to room temperature and extracted with ethyl acetate (3*40 ml). The combine organic part was washed with brine solution and dried over anhydrous Na_2SO_4. Evaporation of the solvent under vacuo to dryness followed by the purification of the crude product using flash silica gel column chromatography with a gradient of pet ether:ethyl acetate (4:1) provided the expected intermediate **5d** as a yellow solid in 65% yield (0.936 gm) .

Methyl 3-(3-hydroxy-1-(methoxymethyl)-2-oxoindolin-3-yl)propiolate (5d)



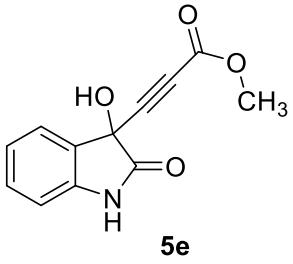
Reaction time: 2h; R*f*: 0.6 (2:3, EtOAc:Pet. ether); Yellow solid; Mp = 93-95 ^{o}C; 0.936 g, 65% yield (1 gram scale).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.5 Hz, 1H), 7.41 (td, *J* = 7.9 & 1.4 Hz, 1H), 7.20 (td, *J* = 7.6 & 1.0 Hz, 1H), 7.08 (d, *J* = 7.9 Hz, 1H), 5.14 (s, 2H), 3.88 (brs, 1H), 3.77 (s, 3H), 3.37 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 153.1, 141.4, 131.3, 126.5, 125.2, 124.5, 110.7, 82.6, 77.2, 72.0, 69.2, 56.6, 53.0.

HRMS (ESI-TOF) m/z: $[M+Na]^+$calcd for $C_{14}H_{13}O_5NNa$ 298.0686, found 298.0677.

Methyl 3-(3-hydroxy-2-oxoindolin-3-yl)propiolate (5e)



5e

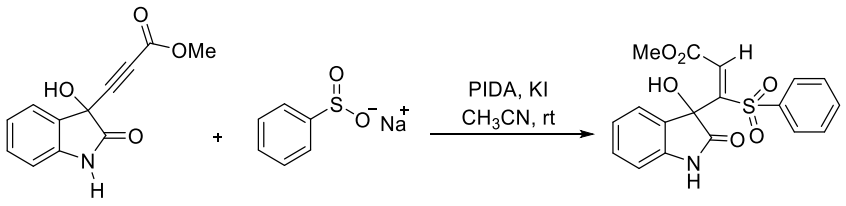
Reaction time: 2h; R*f*: 0.5 (2:3, EtOAc:Pet. ether); White solid; Mp = 158-160 ^oC; 0.974 g, 62% yield (1 gram scale).

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.75 (brs, 1H), 7.44 (s, 1H), 7.42 (d, *J* = 7.5 Hz, 1H), 7.32 (td, *J* = 7.8 & 1.3 Hz, 1H), 7.06 (td, *J* = 7.6 & 1.0 Hz, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 3.71 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d_6) δ 173.1, 152.7, 141.3, 130.7, 129.1, 124.7, 122.7, 110.5, 85.0, 75.3, 68.6, 53.2.

HRMS (ESI-TOF) m/z: $[M+Na]^+$calcd for $C_{12}H_9O_4NNa$ 254.0424, found 254.0418.

III] Experimental Procedure for the Synthesis of Compound 9 (Model Reaction):

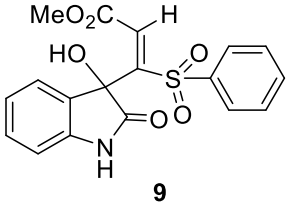


5e **8** **9**

PIDA (104.5 mg, 1.5 equiv., 0.32 mmol) was added to a suspension mixture of alkyne **5e** (1 equiv., 50 mg, 0.22 mmol), sodium benzene sulfinate **8** (142 mg, 4 equiv., 0.86 mmol) and KI (35.9 mg, 1 equiv., 0.22 mmol) in CH_3CN (1 mL), and the reaction mixture was vigorously stirred at room temperature for 1 hour. Upon completion of the reaction, the reaction mixture was quenched by

the addition of sat. aq $Na_2S_2O_3$, basified with sat. aq $NaHCO_3$, and extracted with EtOAc. The combined organic extracts were washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash silica gel column chromatography using a gradient of pet ether:ethyl acetate (1:1) to obtain the expected product in 72% yield (58.1 mg).

Methyl (E)-3-(3-hydroxy-2-oxoindolin-3-yl)-3-(phenylsulfonyl)acrylate (9)



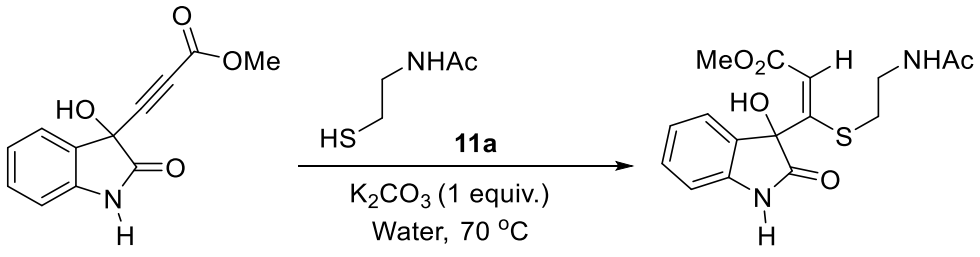
9

Reaction time: 1h; R*f*: 0.6 (3:1, EtOAc:Pet. ether); Sticky liquid; 58 mg, 72% yield.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.58 (s, 1H), 7.60 (tt, *J* = 7.2 & 1.4 Hz, 1H), 7.50 (s, 1H), 7.45-7.32 (m, 4H), 7.14 (td, *J* = 7.8 & 1.3 Hz, 2H), 6.82 (d, *J* = 7.8 Hz, 1H), 6.38 (td, *J* = 7.5 & 0.9 Hz, 1H), 6.26 (d, *J* = 7.0 Hz, 1H), 3.80 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d$_6$) δ 174.7, 165.9, 145.6, 143.1, 139.5, 133.7, 133.6, 130.0, 128.9, 127.7, 127.0, 124.9, 121.4, 109.8, 75.0, 52.4.

IV] Experimental Procedure for the Synthesis of Intermediate 12ea:

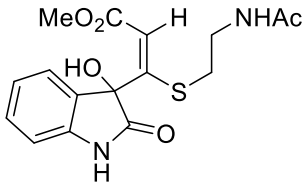


5e **12ea**

To the solution of *N*-acyl cysteamine **11a** (1 equiv., 25.75 mg, 0.22 mmol) in water (2 ml), K_2CO_3 (1 equiv., 29.87 mg, 0.22 mmol) was added in one portion at room temperature and stirred for 5 mins. Then, intermediate **5e** (1 equiv., 50 mg, 0.22 mmol) was added and the resulting mixture was stirred for 1 hour at 70 °C. After completion of reaction (check on TLC), it was concentrated

in *vacuo* and purified by flash silica gel column chromatography using a gradient of MeOH:DCM (1:19) to provide the product **12ea** in 73% yield (55.3 mg).

Methyl (E)-3-((2-acetamidoethyl)thio)-3-(3-hydroxy-2-oxoindolin-3-yl)acrylate (12ea)



12ea

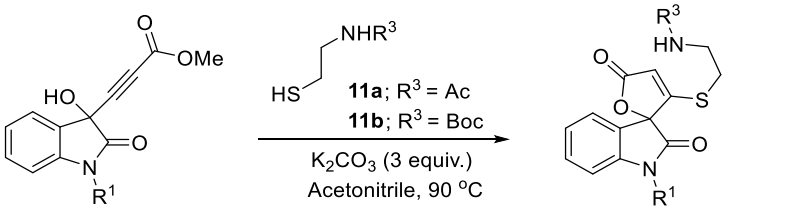
Reaction time: 1h; R*f*: 0.5 (1:10, MeOH:DCM); Sticky liquid; 55.3 mg, 73% yield.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.62 (brs, 1H), 7.73 (t, *J* = 5.5 Hz, 1H), 7.27 (t, *J* = 7.6 Hz, 1H), 7.07 (d, *J* = 7.3 Hz, 1H), 6.99-6.93 (m, 2H), 6.90-6.81 (m, 2H), 3.70 (s, 3H), 2.95-2.85 (m, 2H), 2.77-2.68 (m, 2H), 1.72 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d$_6$) δ 176.0, 169.0, 164.7, 152.5, 143.2, 130.1 (2C), 124.3, 122.0, 120.0, 109.9, 80.1, 51.5, 37.9, 34.1, 22.5.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{16}H_{19}O_5N_2S$ 351.1009, found 351.1003.

V] General Experimental Procedure for the Synthesis of Intermediate 13:



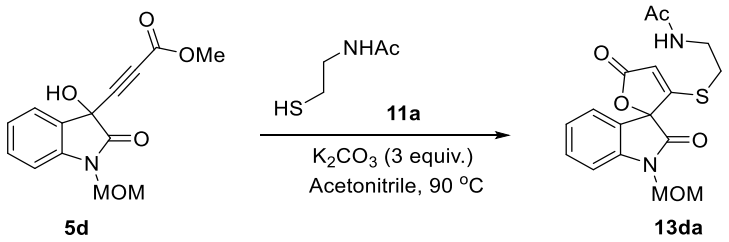
5d; R^1= MOM
5e; R^1= H

13da; R^1= MOM, R^3= Ac
13db; R^1= MOM, R^3= Boc
13ea; R^1= H, R^3= Ac
13eb; R^1= H, R^3= Boc

To the solution of *N*-protected cysteamine **11a-b** (1 equiv.) in Acetronitrile (0.1 M), K_2CO_3 (3 equiv.) was added in one portion at room temperature and stirred for 5 mins. Then, intermediate **5d-e** (1 equiv.) was added and the resulting mixture was stirred for overnight at 90 ^{o}C temperature.

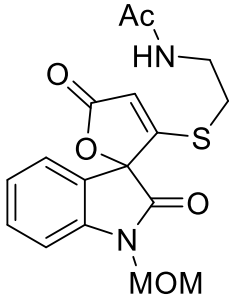
After completion of reaction, it was concentrated in *vacuo* and purified by flash silica gel column chromatography to provide the product **13** in good yield.

VI] Typical Experimental Procedure for the Preparation of Representative Intermediat 13da:



To the solution of *N*-protected cysteamine **11a** (1 equiv., 433 mg, 3.6 mmol) in Acetronitrile (36 ml, 0.1 M), K_2CO_3 (3 equiv., 1.5 gm, 10.9 mmol) was added in one portion at room temperature and stirred for 5 mins. Then, intermediate **5d** (1 equiv., 1 gm, 3.6 mmol) was added and the resulting mixture was stirred for overnight at 90 °C temperature. After completion of reaction (approx. 12 hrs.), it was concentrated in *vacuo* and purified by flash silica gel column chromatography using a gradient of pet ether:acetone (1:1) provided the expected intermediate **13da** as a white solid in 77% yield (1.01 gm).

***N*-(2-((1'-(Methoxymethyl)-2',5-dioxo-5H-spiro[furan-2,3'-indolin]-3-yl)thio)ethyl)acetamide (13da)**



13da

Reaction time: 12h; R*f*: 0.5 (1:1, Acetone:Pet. ether); White solid; Mp = 98-100 °C; 1.01 g, 77% yield (1 gram scale).

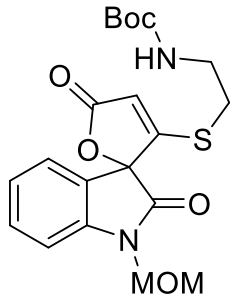
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (td, *J* = 7.9 & 1.6 Hz, 1H), 7.25-7.16 (m, 2H), 7.14 (d, *J* = 8.0 Hz, 1H), 6.32 (brs, 1H), 6.26 (s, 1H), 5.22 (d, *J* = 11.0 Hz, 1H), 5.11 (d, *J* = 11.1 Hz, 1H), 3.63-3.53 (m, 1H), 3.47-3.39 (m, 1H), 3.38 (s, 3H), 3.22-3.13 (m, 1H), 3.12-3.03 (m, 1H), 1.98 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 170.7, 170.1, 166.8, 142.7, 132.3, 125.2, 124.5, 122.0, 112.5, 110.9, 87.0, 72.1, 56.5, 38.1, 32.2, 22.9.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{17}H_{19}O_5N_2S$ 363.1009, found 363.1004.

***tert*-Butyl (2-((1'-(methoxymethyl)-2',5-dioxo-5H-spiro[furan-2,3'-indolin]-3-yl)thio)ethyl)carbamate (13db)**

Reaction time: 12h; R*f*: 0.4 (1:1, EtOAc:Pet. ether); White solid; Mp = 65-67 ^{o}C; 0.886 g, 58% yield (1 gram scale).



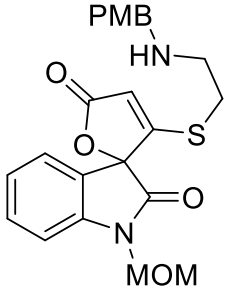
13db

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (td, *J* = 7.8 & 1.5 Hz, 1H), 7.25-7.11 (m, 3H), 6.24 (s, 1H), 5.22 (d, *J* = 11.1 Hz, 1H), 5.11 (d, *J* = 11.0 Hz, 1H), 4.88 (brs, 1H), 3.44-3.22 (m, 5H), 3.19-3.03 (m, 2H), 1.44 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 170.1, 166.8, 155.6, 142.7, 132.1, 125.2, 124.4, 122.3, 112.2, 110.8, 86.9, 80.1, 72.1, 56.6, 38.9, 32.9, 28.3.

HRMS (ESI-TOF) m/z: $[M+Na]^+$calcd for $C_{20}H_{24}O_6N_2NaS$ 443.1247, found 443.1240.

3-((2-((4-Methoxybenzyl)amino)ethyl)thio)-1'-(methoxymethyl)-5H-spiro[furan-2,3'-indoline]-2',5-dione (13dc)



13dc

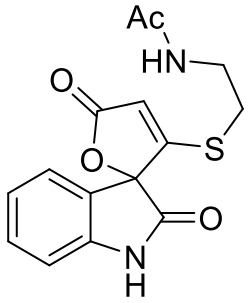
Reaction time: 12h; R*f*: 0.3 (2:3, EtOAc:Pet. ether); Yellow solid; Mp = 135-137 ^{o}C; 1.1 g, 69% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (t, *J* = 7.8 Hz, 1H), 7.31-7.26 (m, 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.13 (t, *J* = 8.4 Hz, 3H), 6.82 (d, *J* = 8.6 Hz, 2H), 5.18 (d, *J* = 10.9 Hz, 1H), 5.10 (d, *J* = 10.9 Hz, 1H), 4.90 (s, 1H), 4.54 (t, *J* = 5.3 Hz, 1H), 3.80 (s, 3H), 3.56 (s, 2H), 3.36 (s, 3H), 3.18-3.10 (m, 2H), 2.58-2.52 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 170.9, 165.2, 158.9, 143.0, 132.1, 129.8, 129.3, 125.3, 124.5, 122.5, 114.1, 110.7, 83.7, 82.8, 72.0, 56.7, 55.3, 43.6, 35.3, 29.5.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{23}H_{25}O_5N_2S$ 441.1479, found 441.1470.

***N*-(2-((2',5-Dioxo-5H-spiro[furan-2,3'-indolin]-3-yl)thio)ethyl)acetamide (13ea)**



13ea

Reaction time: 12h; R*f*: 0.5 (1:10, MeOH:DCM); White solid; Mp = 203-205 ^oC; 0.881 g, 64% yield.

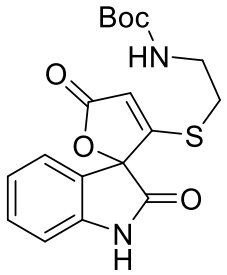
^{1}H NMR (500 MHz, DMSO-d_6) δ 11.11 (brs, 1H), 8.11 (t, *J* = 5.5 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.26 (d, *J* = 7.3 Hz, 1H), 7.08 (t, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.57 (s, 1H), 3.29-3.21 (m, 2H), 3.10-3.02 (m, 2H), 1.78 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6) δ 170.8, 170.4, 169.8, 168.0, 142.8, 132.1, 125.4, 123.2 (2C), 111.1 (2C), 86.6, 37.0, 31.9, 22.5.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{15}H_{15}O_4N_2S$ 319.0747 found 319.0742.

***tert*-Butyl (2-((2',5-dioxo-5H-spiro[furan-2,3'-indolin]-3-yl)thio)ethyl)carbamate (13eb)**

Reaction time: 12h; R*f*: 0.4 (1:1, EtOAc:Pet. ether); Yellow solid; Mp = 213-215 ^oC; 0.667 g, 41% yield.



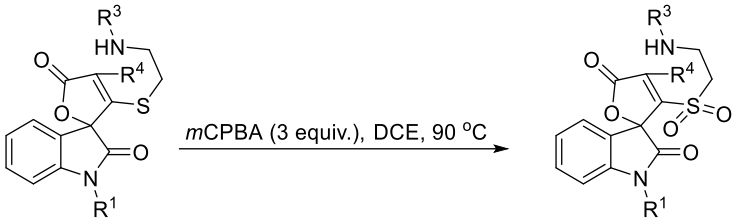
13eb

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.10 (brs, 1H), 7.41 (t, *J* = 7.4 Hz, 1H), 7.25 (d, *J* = 7.4 Hz, 1H), 7.13-7.01 (m, 2H), 6.98 (d, *J* = 7.8 Hz, 1H), 6.51 (s, 1H), 3.19-3.11 (m, 2H), 3.09-3.00 (m, 2H), 1.36 (s, 9H).

^{13}C NMR (100 MHz, DMSO-d_6) δ 170.7, 170.4, 168.1, 155.6, 142.8, 132.0, 125.3, 123.2, 123.1, 111.0, 110.8, 86.6, 78.1, 38.2, 32.2, 28.2.

HRMS (ESI-TOF) m/z: $[M+Na]^+$calcd for $C_{18}H_{20}O_5N_2NaS$ 399.0985, found 399.0976.

VII] General Experimental Procedure for the Synthesis of Intermediate 14:

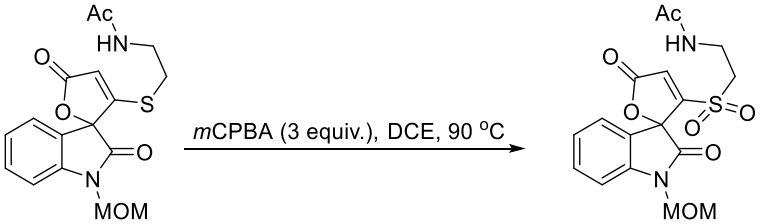


13da; R^1 = MOM, R^3 = Ac, R^4 = H
13db; R^1 = MOM, R^3 = Boc, R^4 = H
13eb; R^1 = H, R^3 = Boc, R^4 = H
19b; R^1 = MOM, R^3 = Ac, R^4 = Cl

14da; R^1= MOM, R^3= Ac, R^4 = H
14db; R^1= MOM, R^3= Boc, R^4 = H
14eb; R^1= H, R^3= Boc, R^4 = H
20b; R^1 = MOM, R^3 = Ac, R^4 = Cl

To the solution of intermediate **13** (1 equiv.) in DCE (0.05 M), *m*CPBA (3 equiv.) was added in one portion and stirred for overnight at 90 °C. After complete consumption of intermediate **13** (check on TLC), the rection mixture was cooled and concentrated on *vacuo* followed by the purification by flash silica gel column chromatography gave the intermediate **14** in excellent to good yield.

VIII] Typical Experimental Procedure for the Preparation of Representative Intermediat 14da:

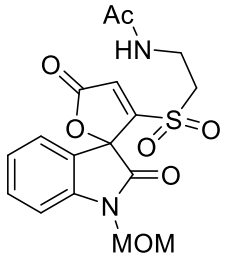


13da **14da**

To the solution of intermediate **13da** (1 equiv., 1 gm, 2.8 mmol) in DCE (0.05 M), *m*CPBA (3 equiv., 1.4 gm, 8.3 mmol) was added in one portion and stirred for overnight at 90 °C. After complete consumption of intermediate **13da** (check on TLC), the rection mixture was cooled and concentrated on *vacuo* followed by the purification by flash silica gel column chromatography

using a gradient of pet ether:acetone (1:1) provided the expected intermediate **14da** as a white solid in 89% yield (0.969 gm).

***N*-(2-((1'-(Methoxymethyl)-2',5-dioxo-5H-spiro[furan-2,3'-indolin]-3-yl)sulfonyl)ethyl)acetamide (14da)**



14da

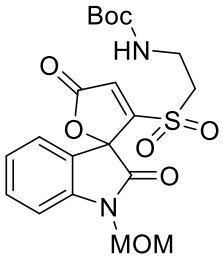
Reaction time: 12h; R*f*: 0.6 (1:1, Acetone:Pet. ether); White solid; Mp = 135-137 ^{o}C; 0.969 g, 89% yield.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.08 (t, *J* = 4.7 Hz, 1H), 7.78 (s, 1H), 7.62 (dd, *J* = 7.5 & 0.8 Hz, 1H), 7.56 (td, *J* = 7.8 & 1.3 Hz, 1H), 7.27 (d, *J* = 7.9 Hz, 1H), 7.22 (td, *J* = 7.6 & 0.8 Hz, 1H), 5.14 (s, 2H), 3.39-3.30 (m, 4H), 3.28 (s, 3H), 1.79 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d$_6$) δ 169.9, 168.7, 168.0, 159.4, 143.4, 132.9, 130.7, 126.2, 124.2, 119.4, 111.4, 85.0, 72.0, 56.2, 54.0, 32.2, 22.4.

HRMS (ESI-TOF) m/z: $[M+H]^{+}$calcd for $C_{17}H_{19}O_7N_2S$ 395.0907, found 395.0902.

***tert*-Butyl(2-((1'-(methoxymethyl)-2',5-dioxo-5H-spiro[furan-2,3'-indolin]-3-yl)sulfonyl)ethyl)carbamate (14db)**



14db

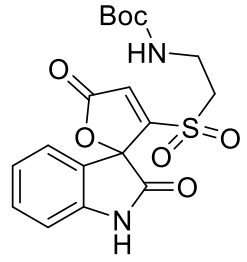
Reaction time: 12h; R*f*: 0.5 (1:3, Acetone:Pet. ether); Yellow solid; Mp = 118-120 ^{o}C; 0.635 g, 59% yield.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.78 (s, 1H), 7.62 (d, *J* = 7.4 Hz, 1H), 7.56 (td, *J* = 7.8 & 1.1 Hz, 1H), 7.27 (d, *J* = 7.9 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.05 (brs, 1H), 5.15 (s, 2H), , 3.37-3.30 (m, 3H), 3.28 (s, 3H), 3.26-3.19 (m, 1H), 1.38 (s, 9H).

^{13}C NMR (125 MHz, DMSO-d$_6$) δ 168.6, 167.9, 159.4, 155.3, 143.4, 132.9, 130.9, 126.1, 124.0, 119.3, 111.3, 84.9, 78.5, 71.9, 56.1, 54.1, 33.6, 28.1.

HRMS (ESI-TOF) m/z: $[M+Na]^+$calcd for $C_{20}H_{24}O_8N_2NaS$ 475.1146, found 475.1138.

***tert*-Butyl (2-((2',5-dioxo-5H-spiro[furan-2,3'-indolin]-3-yl)sulfonyl)ethyl)carbamate (14eb)**



14eb

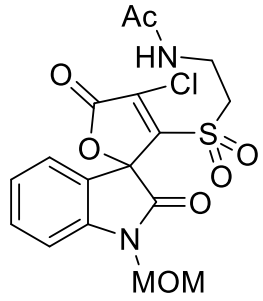
Reaction time: 12h; R*f*: 0.5 (1:1, EtOAc:Pet. ether); Yellow solid; Mp = 160-162 ^{o}C; 472 mg, 87% yield (500 mg).

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 11.31 (brs, 1H), 7.71 (s, 1H), 7.53 (d, *J* = 7.3 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.14-7.03 (m, 2H), 7.01 (d, *J* = 8.0 Hz, 1H), 3.33-3.18 (m, 4H), 1.39 (s, 9H).

^{13}C NMR (125 MHz, DMSO-d$_6$) δ 169.1, 168.2, 159.8, 155.3, 143.5, 132.8, 130.5, 126.2, 122.9, 120.2, 111.4, 85.4, 78.5, 54.1, 33.6, 28.1.

HRMS (ESI-TOF) m/z: $[M+Na]^+$calcd for $C_{18}H_{20}O_7N_2NaS$ 431.0883, found 431.0875.

***N*-(2-((4-Chloro-1'-(methoxymethyl)-2',5-dioxo-5H-spiro[furan-2,3'-indolin]-3-yl)sulfonyl)ethyl)acetamide (20b)**



20b

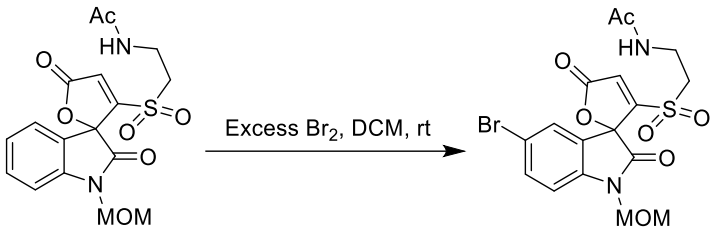
Reaction time: 6h; R*f*: 0.4 (1:1, EtOAc:Pet. ether); Brown solid; Mp = 83-85 ^{o}C; 399.9 mg, 74% yield (500 mg scale).

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.07 (brs, 1H), 7.88 (d, *J* = 7.5 Hz, 1H), 7.57 (t, *J* = 7.8 Hz, 1H), 7.32-7.18 (m, 2H), 5.15 (s, 2H), 3.38-3.30 (m, 4H), 3.29 (s, 3H), 1.78 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d_6) δ 169.7, 168.2, 164.0, 148.8, 143.6, 133.3, 133.1, 126.7, 124.2, 119.2, 111.4, 84.3, 72.0, 56.1, 54.4, 31.6, 22.4.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{17}H_{18}O_7N_2ClS$ 429.0518, found 429.0511.

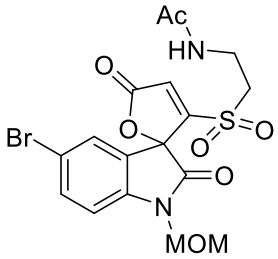
IX] Experimental Procedure for the Synthesis of Intermediate 16:



14da **16**

Excess bromine was added to the solution of intermediate **14da** (50 mg, 0.13 mmol) in DCM (1.5 ml) at rt and stirred for 1 hour. After completion of reaction (check by TLC), it was quenched by the saturated solution of $Na_2S_2O_3$ and extracted by the DCM (5 ml) three times and dried over Na_2SO_4. The organic phase was evaporated to dryness under *vacuo* and purified by flash silica gel column chromatography using a gradient of pet ether:ethyl acetate (1:1) to provide the bromo compound **16** in 94% yield (56.9 mg).

***N*-(2-((5'-Bromo-1'-(methoxymethyl)-2',5-dioxo-5H-spiro[furan-2,3'-indolin]-3-yl)sulfonyl)ethyl)acetamide (16)**



16

Reaction time: 1h; R*f*: 0.6 (1:1, Acetone:Pet. ether); Yellow solid; Mp = 150-152 ^oC; 56.9 mg, 94% yield.

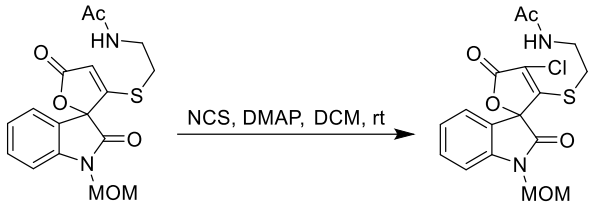
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 8.5 & 2.0 Hz, 1H), 7.44 (d, *J* = 1.9 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 1H), 7.03 (s, 1H), 6.36 (t, *J* = 5.5 Hz,

1H), 5.21 (d, *J* = 11.1 Hz, 1H), 5.13 (d, *J* = 11.1 Hz, 1H), 3.81-3.74 (m, 1H), 3.65-3.50 (m, 2H), 3.41 (s, 3H), 3.20-3.12 (m, 1H), 1.98 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 168.7, 166.5, 161.1, 142.2, 136.0, 128.6, 128.2, 121.5, 117.2, 113.1, 85.1, 72.8, 56.8, 54.5, 33.8, 22.8.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{17}H_{18}O_7N_2{}^{79}BrS$ 473.0013, found 473.0005.

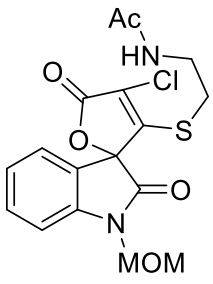
X] Experimental Procedure for the Synthesis of Intermediate 19b:



14da **19b**

To a solution of intermediate **14da** (500 mg, 1.38 mmol, 1.00 equiv) in DCM (10 mL), *N*-chlorosuccinimide (553.2 mg, 3.00 equiv., 4.14 mmol) and 4-dimethylaminopyridine (16.9 mg, 0.10 equiv., 0.138 mmol) was added and the solution was stirred at room temperature for overnight. After completion of reaction, the solution was concentrated under reduced pressure and purified by flash silica gel column chromatography using a gradient of acetone:Pet. ether (3:7) to provide the chloro compound **19b** in 39% yield.

***N*-(2-((4-Chloro-1'-(methoxymethyl)-2',5-dioxo-5H-spiro[furan-2,3'-indolin]-3-yl)thio)ethyl)acetamide (19b)**



19b

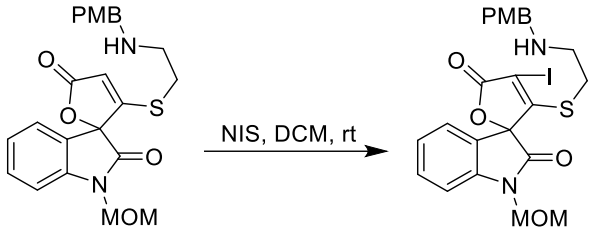
Reaction time: 20h; R*f*: 0.3 (3:7, Acetone:Pet. ether); White solid; Mp = 108-110 ^oC; 213.3 mg, 39% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (t, *J* = 7.6 Hz, 1H), 7.26-7.08 (m, 3H), 6.24 (brs, 1H), 5.27 (d, *J* = 10.9 Hz, 1H), 5.13 (d, *J* = 10.9 Hz, 1H), 3.86-3.76 (m, 1H), 3.55-3.46 (m, 1H), 3.41 (s, 3H), 3.39-3.32 (m, 1H), 2.99-2.89 (m, 1H), 1.96 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 170.6, 165.7, 152.8, 143.0, 132.9, 125.5, 124.9, 121.9, 120.5, 111.1, 86.3, 72.2, 56.7, 39.6, 30.4, 22.9.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{17}H_{18}O_5N_2ClS$ 397.0619, found 397.0613.

XI] Experimental Procedure for the Synthesis of Intermediate 21:



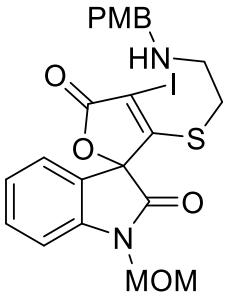
14dc **21**

To an oven dried schlenk tube, intermediate **14dc** (500 mg, 1.14 mmol, 1 equivalent) and NIS (255.7 mg, 1.14 mmol, 1 equivalent) were added followed by the addition of dry DCM (11.4 ml, 0.1 M). After 4 hours stirring at room temperature, the reaction mixture was concentrated on *vacuo* and purified by flash silica gel column chromatography using a gradient of pet ether:ethyl acetate (1:4) to afford the corresponding intermediate **21** as a sticky liquid in 85% yield (546.7 mg).

4-Iodo-3-((2-((4-methoxybenzyl)amino)ethyl)thio)-1'-(methoxymethyl)-5H-spiro[furan-2,3'-indoline]-2',5-dione (21)

Reaction time: 4h; R*f*: 0.3 (2:3, EtOAc:Pet. ether); Brown solid; Mp = 90-92 ^oC; 546.7 mg, 85% yield.

^{1}H NMR (400 MHz, $CDCL_3$) δ 7.49 (td, J = 7.8 & 1.3 Hz, 1H), 7.27 (d, J = 7.3 Hz, 1H), 7.19 (t, J = 7.5 Hz, 1H), 7.12 (t, J = 8.7 Hz, 3H), 6.82 (d, J = 8.6 Hz, 2H), 5.20-5.09 (m, 3H), 3.80 (s, 3H), 3.51 (s, 2H), 3.37 (s, 3H), 3.19-3.07 (m, 1H), 3.05-2.93 (m, 1H), 2.40-2.31 (m, 2H).

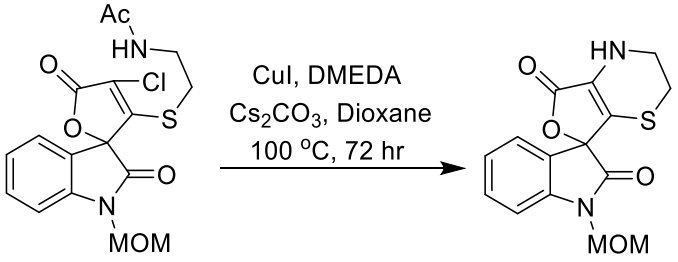


21

^{13}C NMR (100 MHz, $CDCL_3$) δ 169.6, 169.2, 163.7, 158.9, 142.7, 132.5, 129.8, 129.1, 125.4, 124.7, 122.0, 114.1 (2C), 111.1, 83.4, 72.1, 56.8, 55.3, 41.3, 35.1, 31.0.

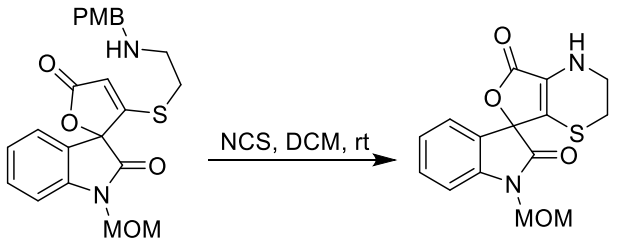
HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{23}H_{24}O_5N_2IS$ 567.0445, found 567.0458.

XII] Experimental Procedure for the Synthesis of Intermediate 22a:



19b **22a**

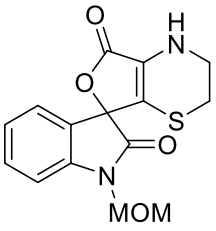
Procedure A: To an oven dried schlenk tube, intermediate **19b** (50 mg, 1 equiv., 0.13 mmol), CuI (4.8 mg, 0.2 equiv., 0.025 mmol) and Cs_2CO_3 (82.3 mg, 2 equiv., 0.25 mmol,) were added followed by the dioxane (1.3 ml) and DMEDA (4.45 mg, 0.4 equiv., 0.050 mmol). After 72 hrs stirring at 100 °C, the reaction mixture was cooled and concentrated on *vacuo*. The crude reaction mixture was purified by flash silica gel column chromatography using a gradient of pet ether:ethyl acetate (2:3) to afford the corresponding intermediate **22a** as a sticky liquid.



14dc **22a**

Procedure B: To an oven dried schlenk tube, intermediate **14dc** (100 mg, 1 equiv., 0.23 mmol) and NCS (30.3 mg, 1 equiv., 0.23 mmol) were added followed by the addition of dry DCM (4 ml). After overnight stirring at room temperature, the reaction mixture was concentrated on *vacuo* and purified by flash silica gel column chromatography using a gradient of pet ether:ethyl acetate (2:3) to afford the corresponding intermediate **22a** as a white solid in 20% yield (14.4 mg).

1'-(Methoxymethyl)-3,4-dihydro-2H,5H-spiro[furo[3,4-b][1,4]thiazine-7,3'-indoline]-2',5-dione (22a)



22a

Reaction time: 5h; R*f*: 0.4 (9:1, EtOAc: Methanol); White solid; Mp = 240-242 ^{o}C; 14.4 mg, 20% yield;

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.75 (brs, 1H), 7.50 (td, *J* = 7.9 & 1.3 Hz, 1H), 7.32 (d, *J* = 6.9 Hz, 1H), 7.24 (d, *J* = 7.9 Hz, 1H), 7.18 (td, *J* = 7.5 & 0.6 Hz, 1H), 5.13 (d, *J* = 11.0 Hz, 1H), 5.07 (d, *J* = 11.0 Hz, 1H), 3.51-3.43 (m, 2H), 3.28 (s, 3H), 2.92-2.78 (m, 2H).

^{13}C NMR (100 MHz, DMSO-d$_6$) δ 170.7, 169.1, 156.5, 143.5, 131.8, 124.9, 123.9, 123.0, 110.9, 82.3, 81.6, 71.6, 56.1, 42.1, 22.6.

HRMS (ESI-TOF) m/z: $[M+H]^{+}$calcd for $C_{15}H_{15}O_4N_2S$ 319.0747, found 319.0743.

3.9. References:

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3.10. Copies of ^{1}H NMR and ^{13}C NMR Spectra:

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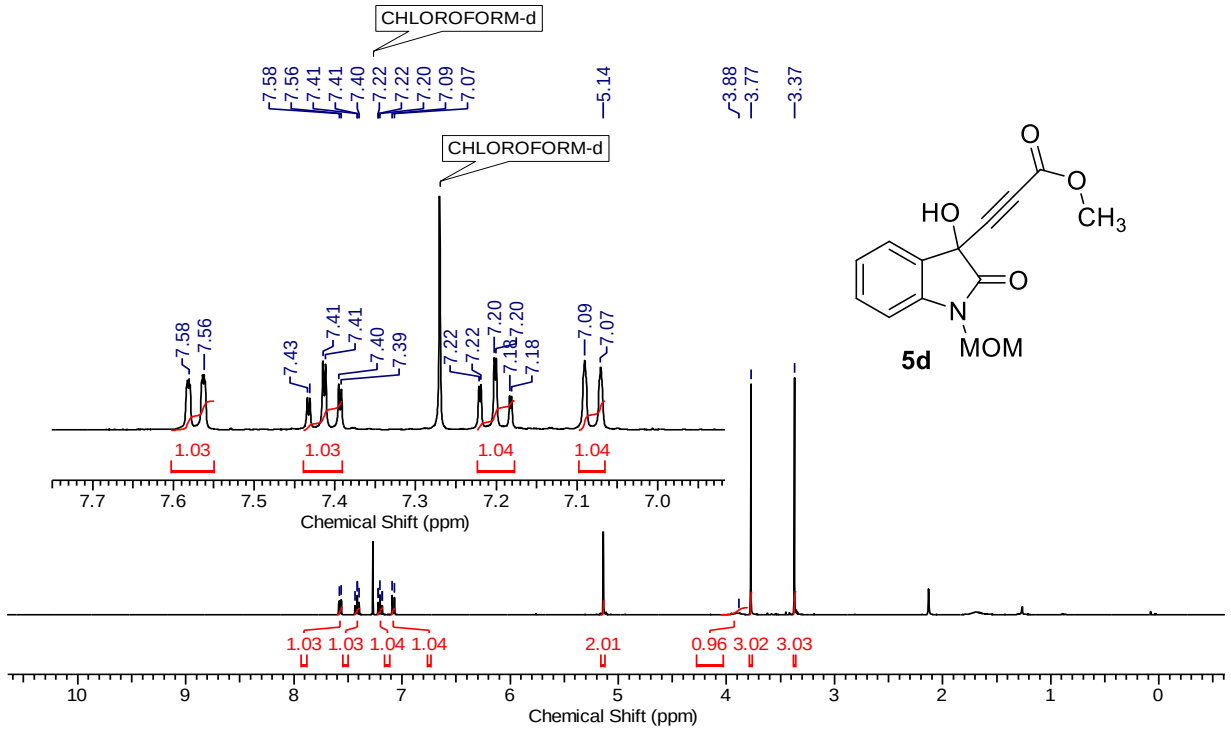
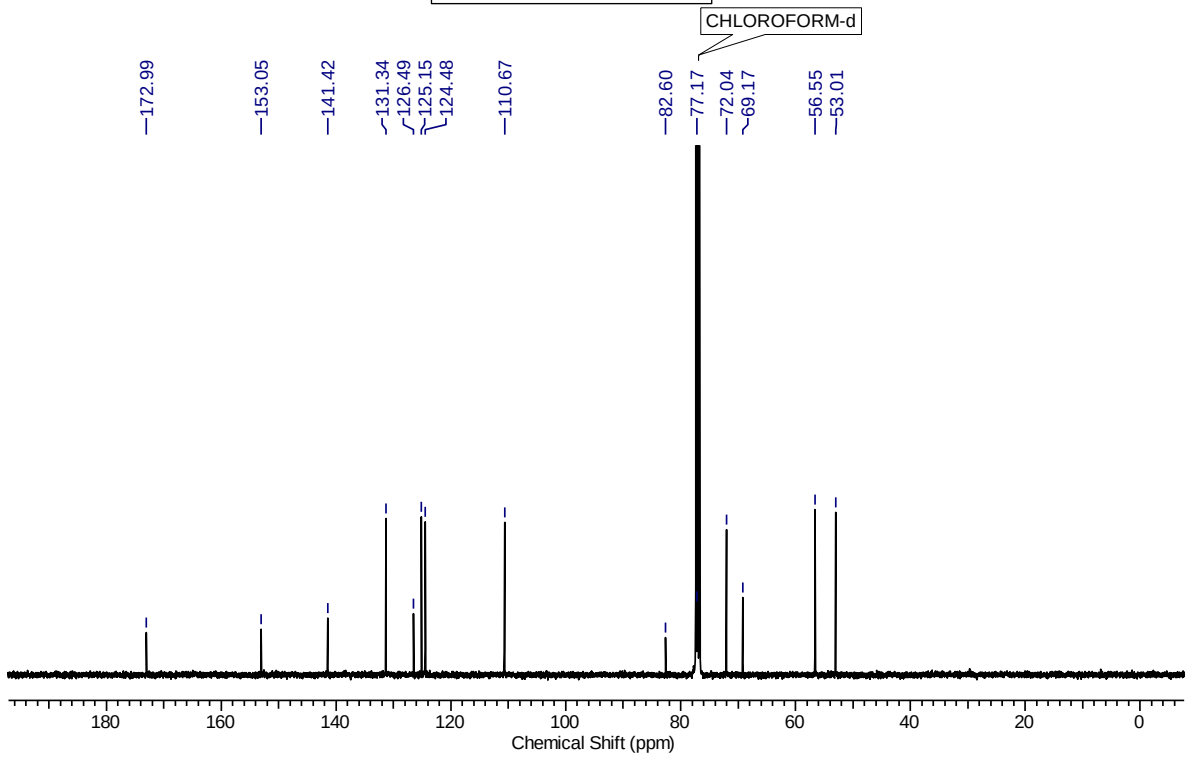


^{13}C NMR, 100 MHz



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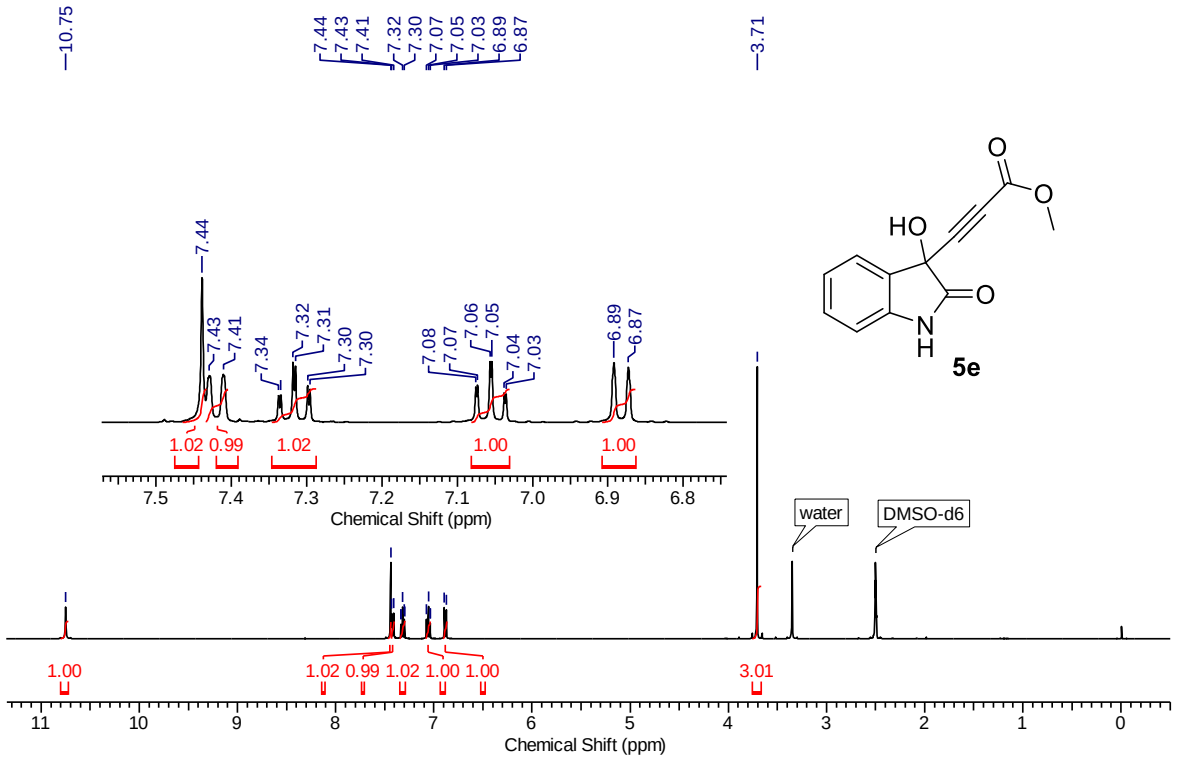

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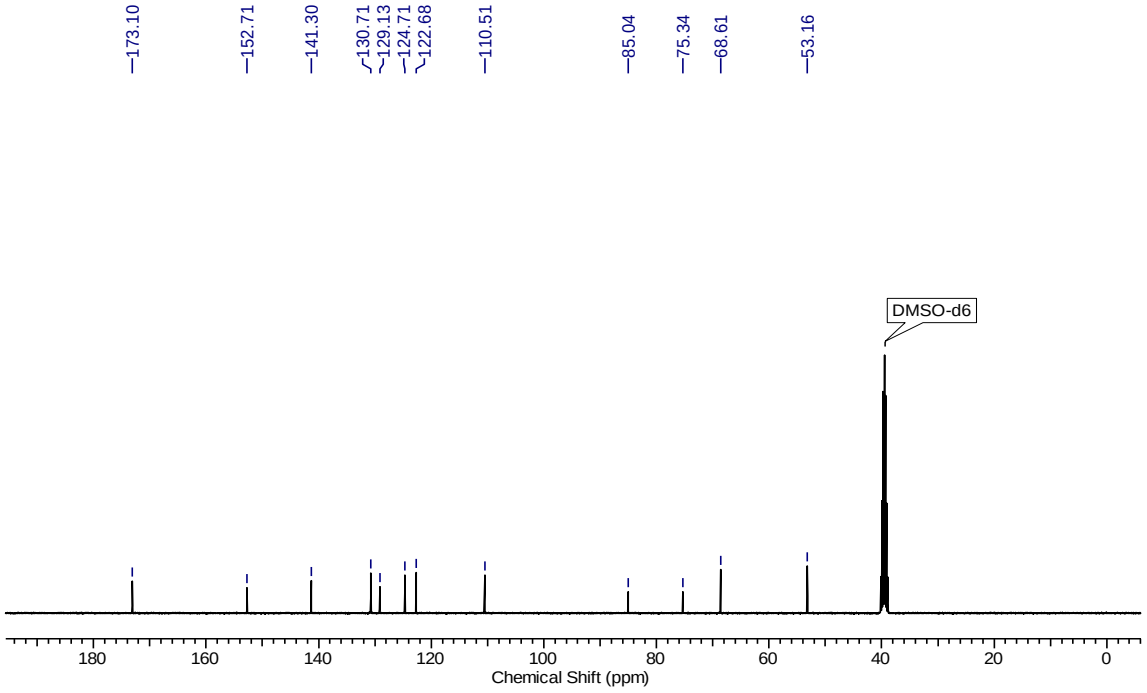

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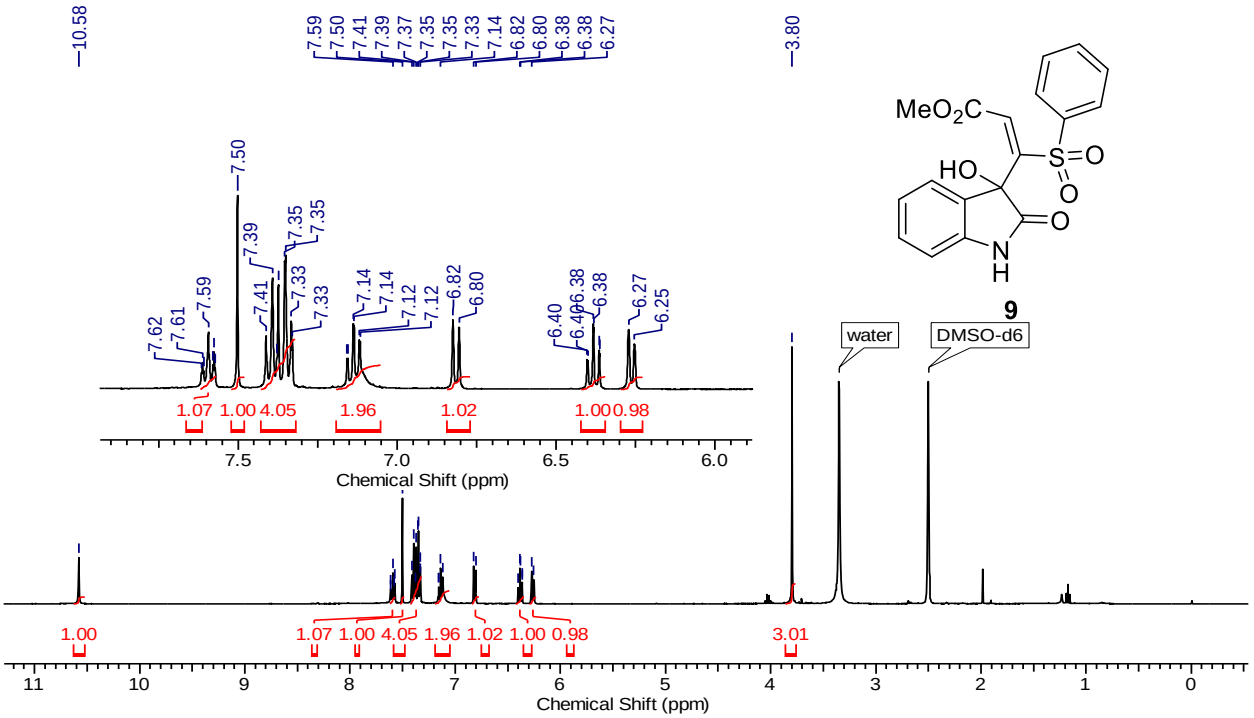

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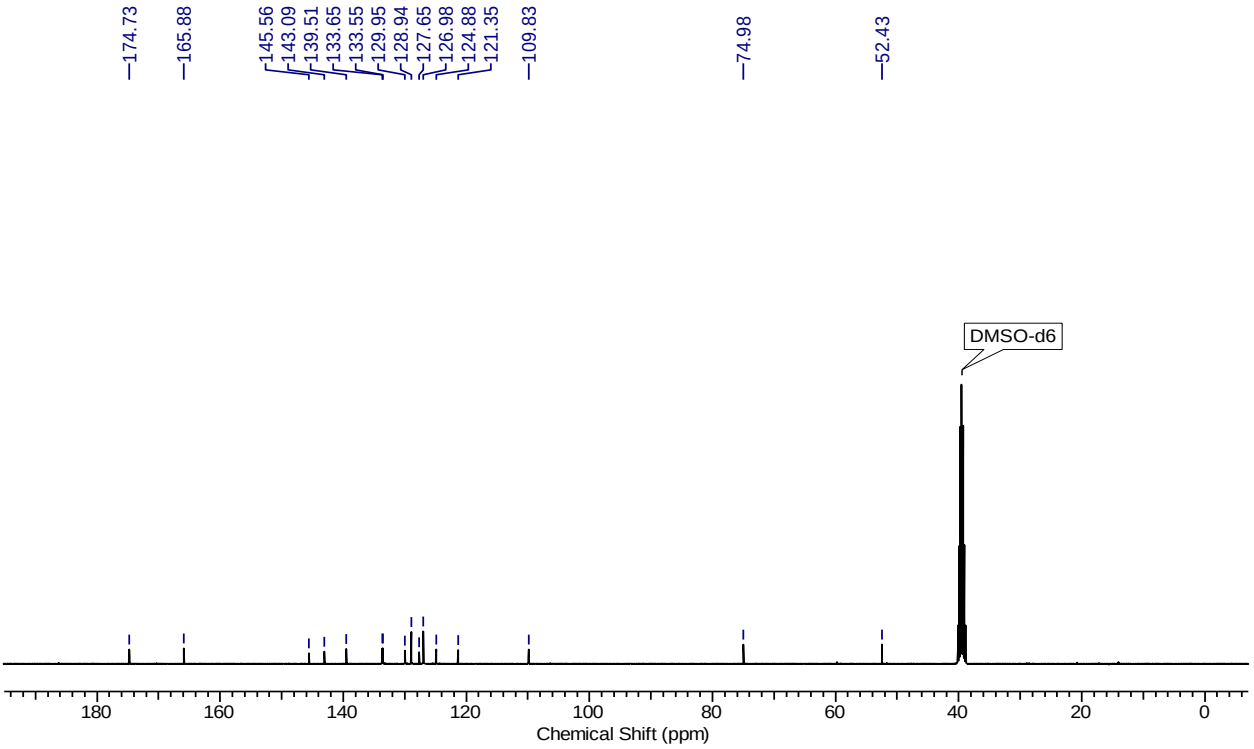

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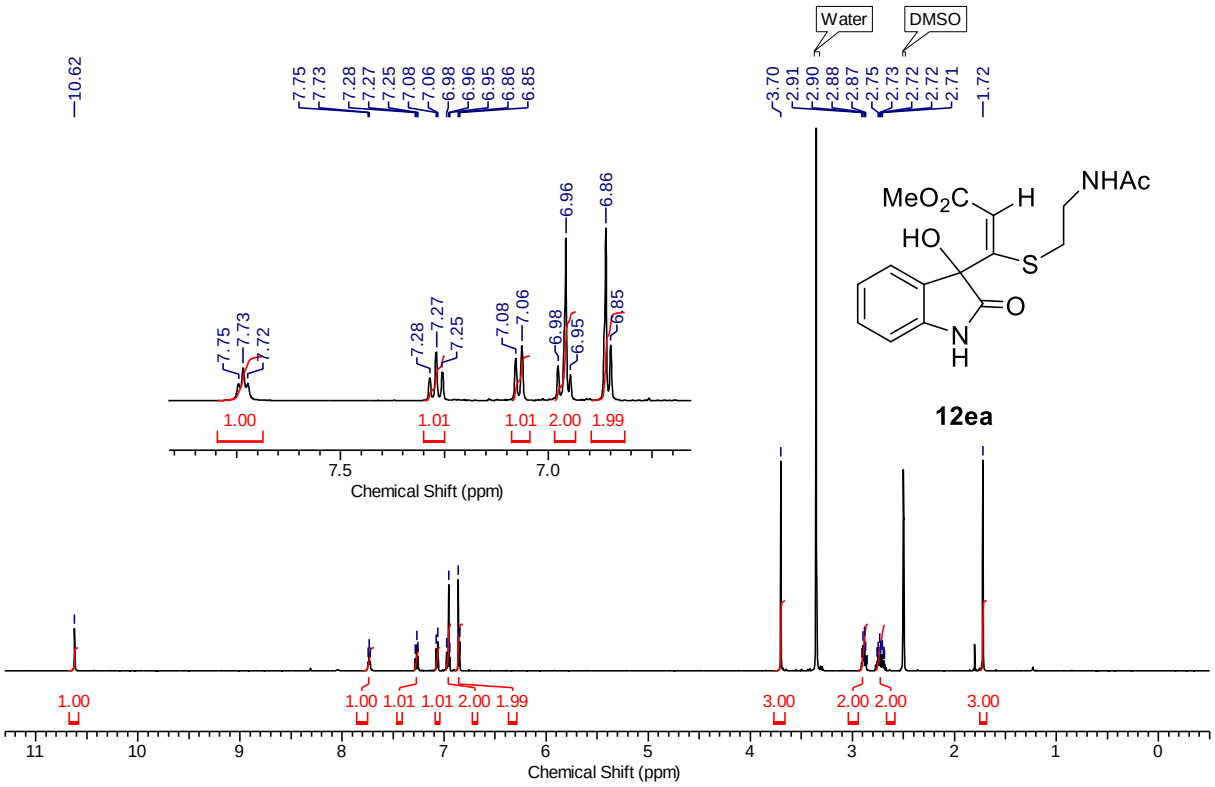

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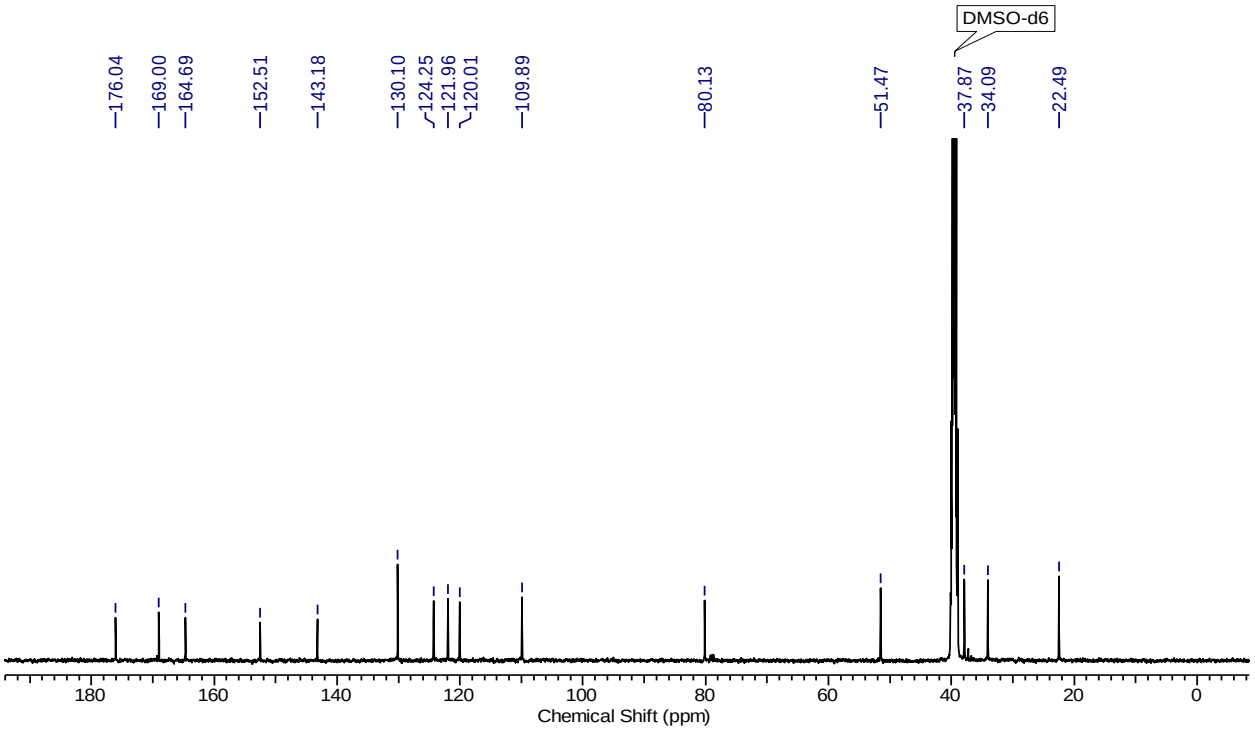

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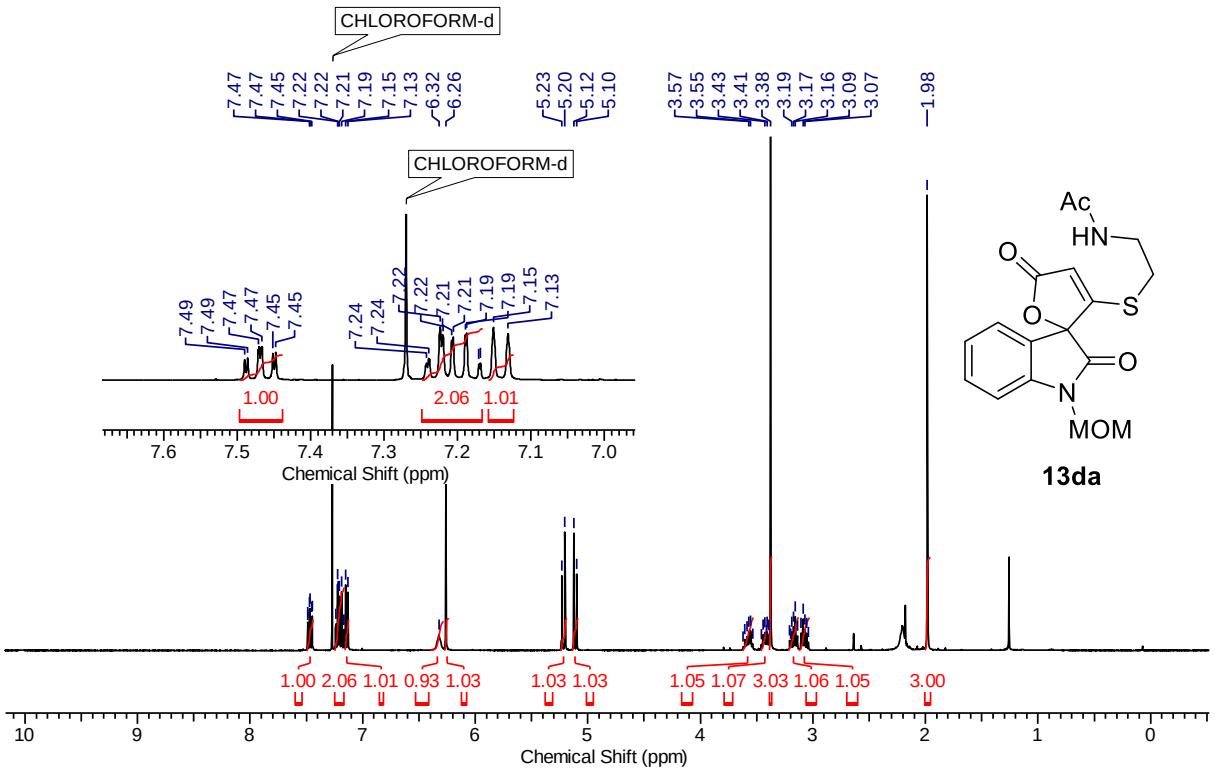

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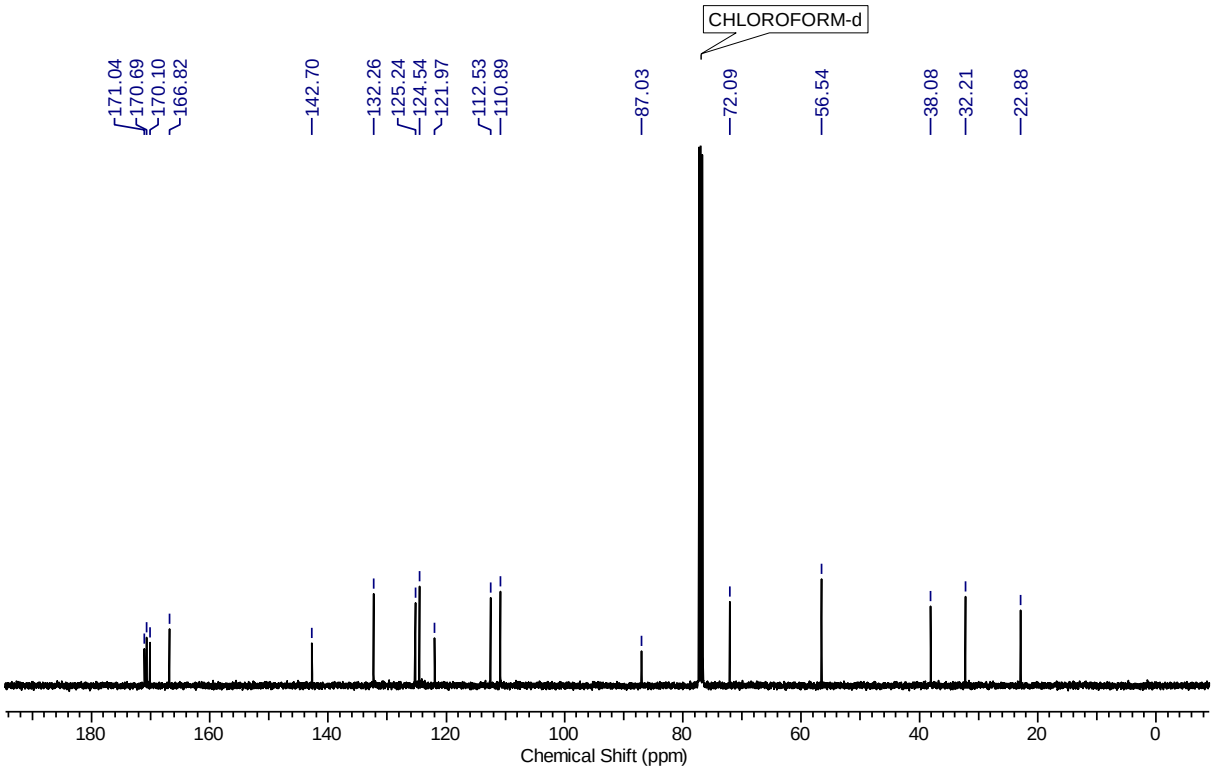

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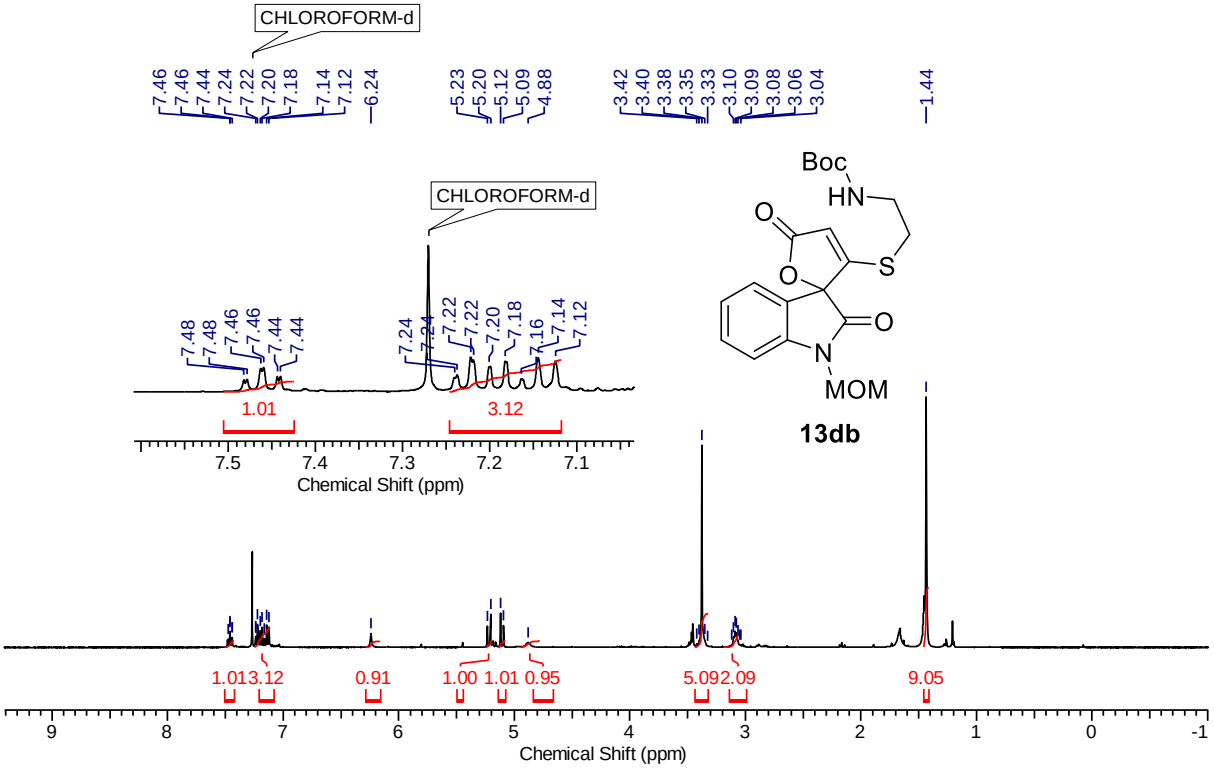

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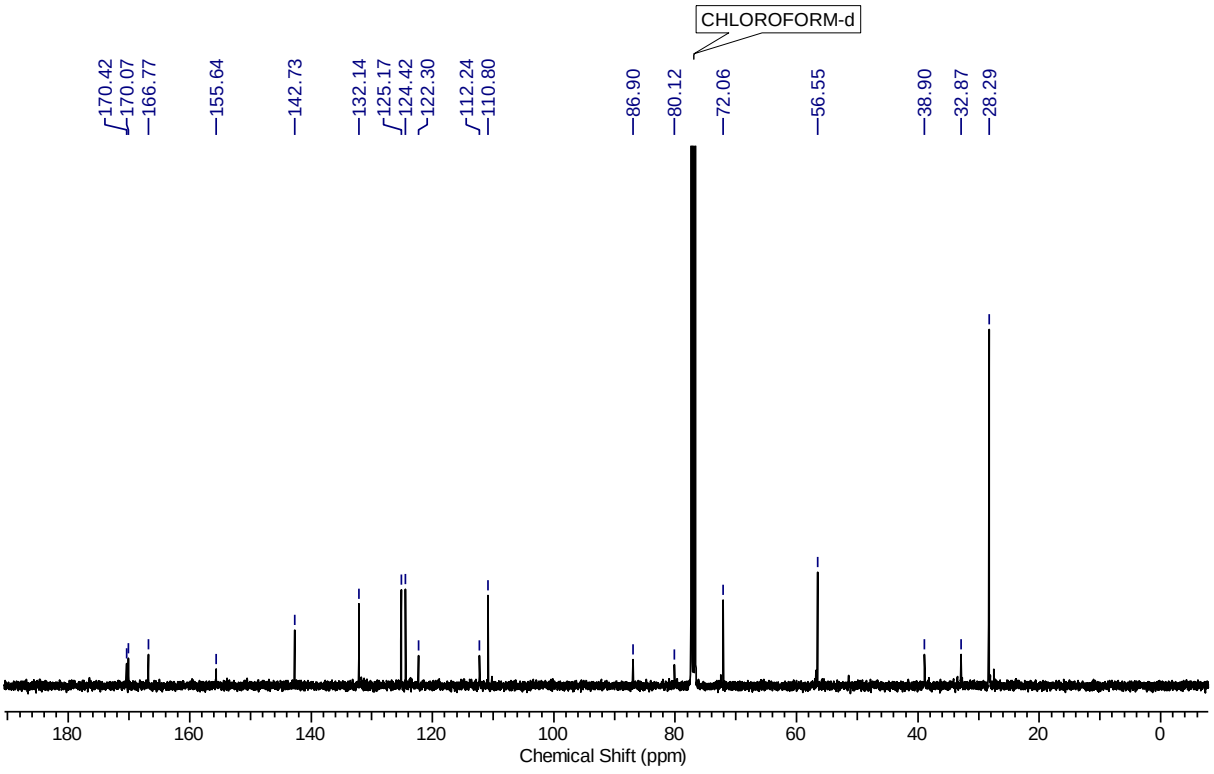

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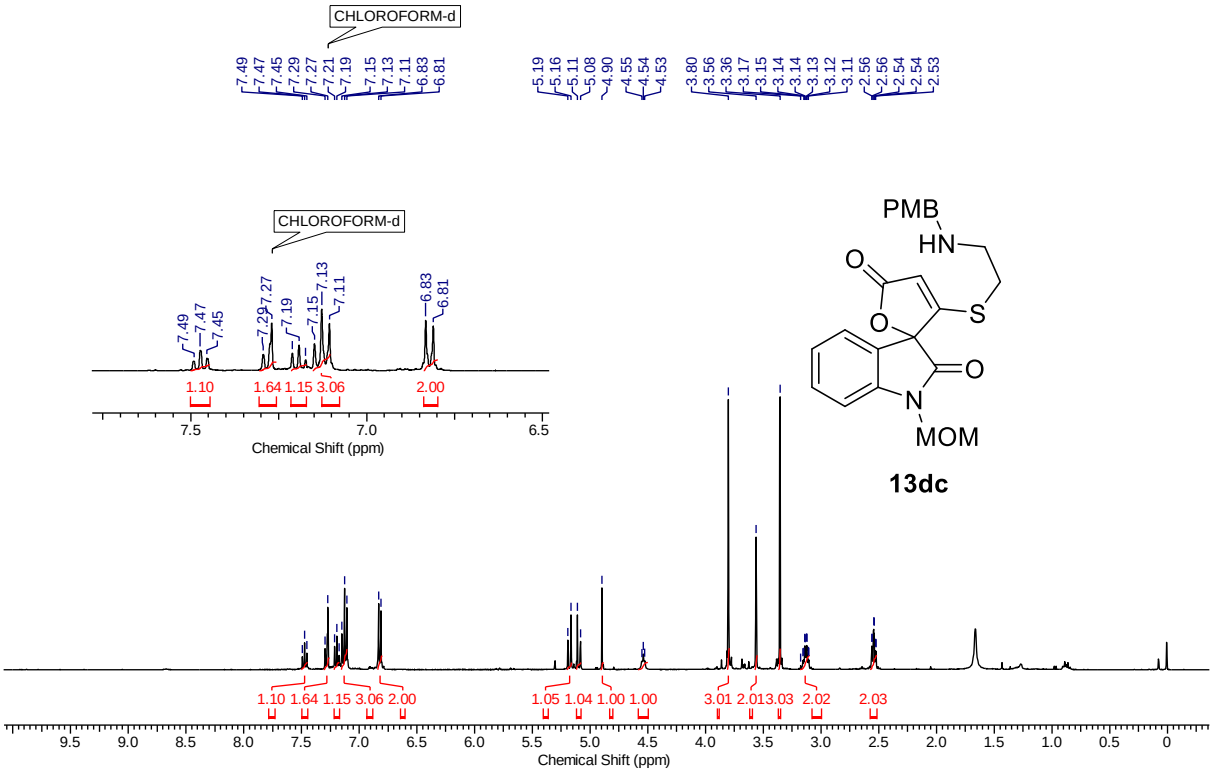

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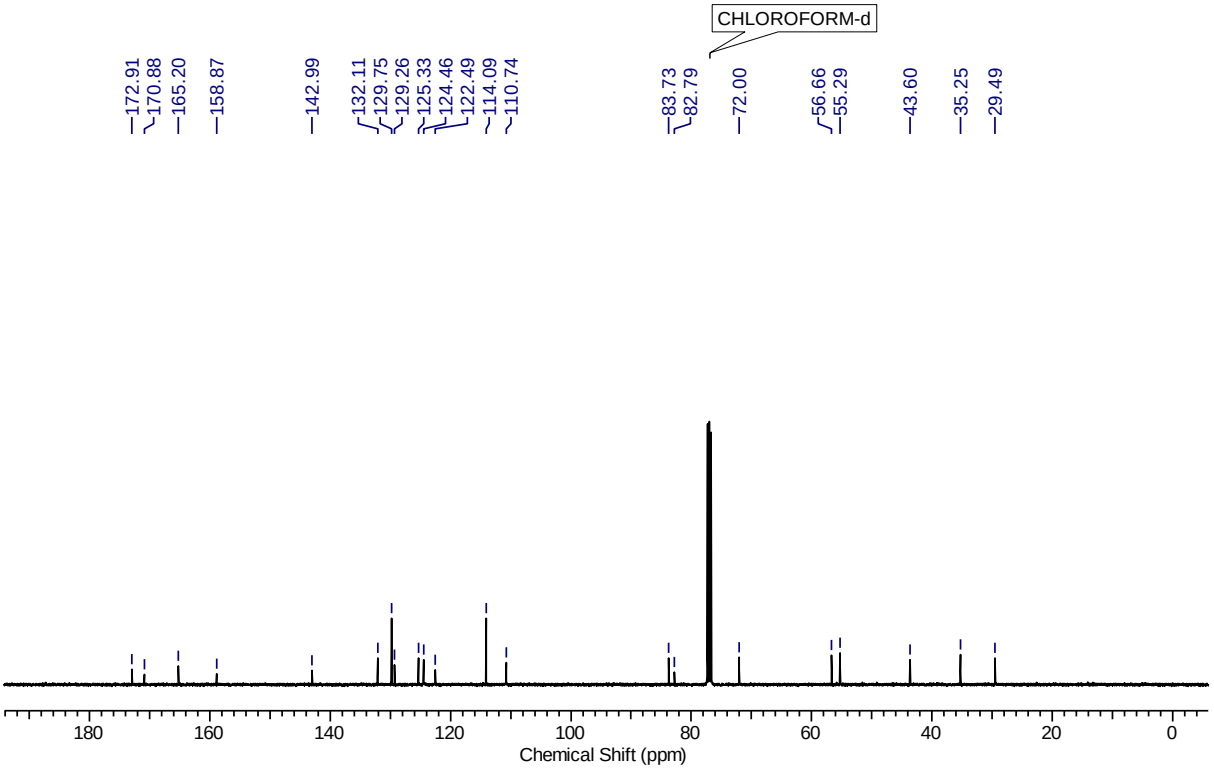

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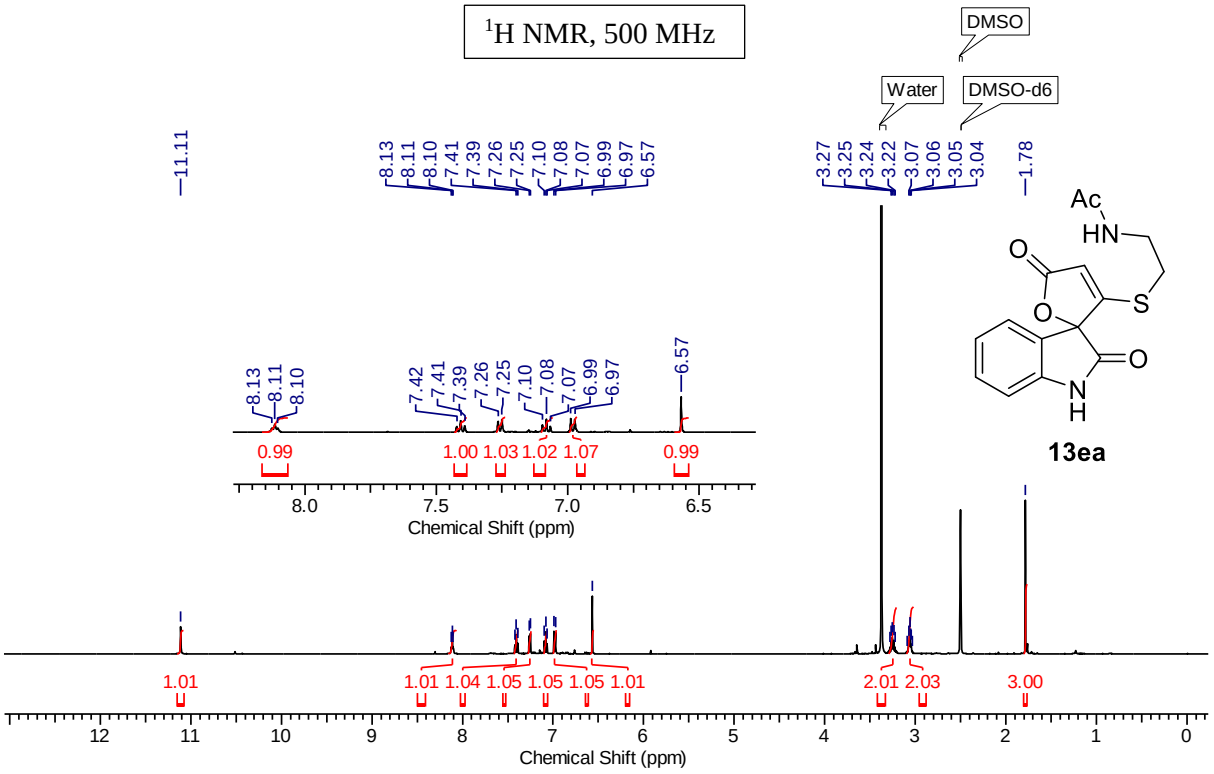

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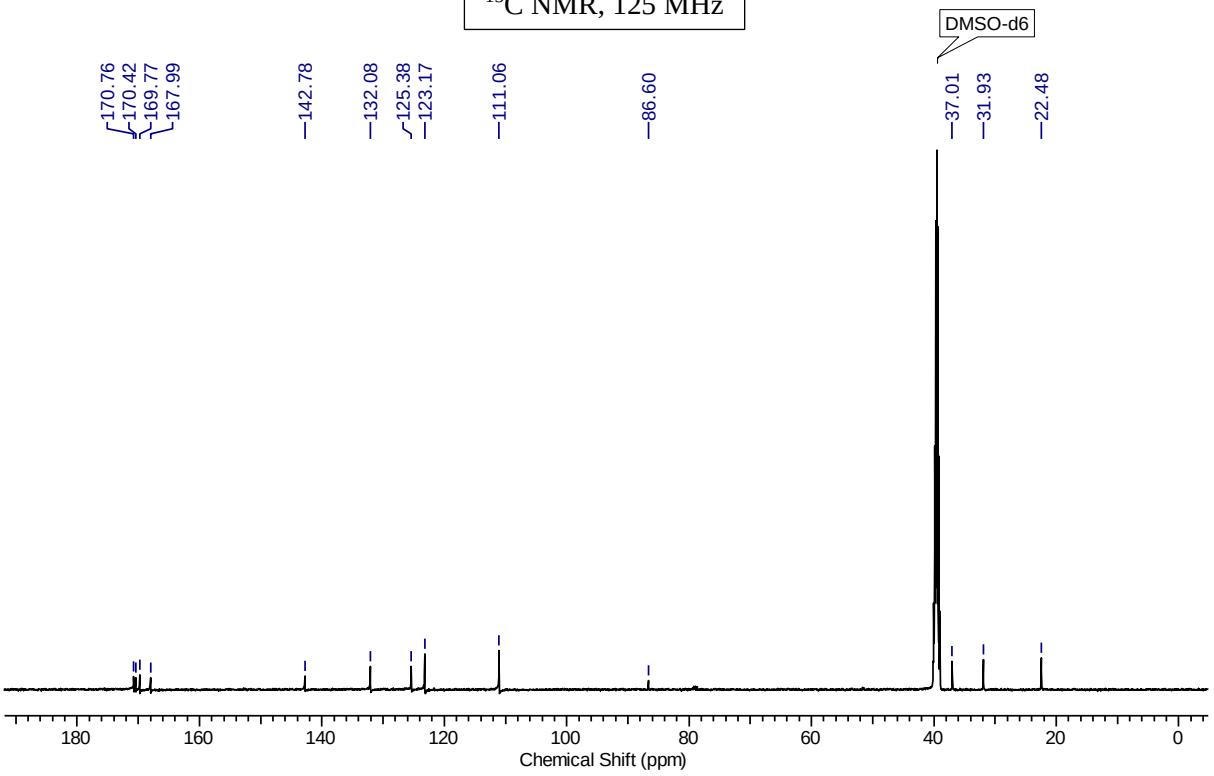

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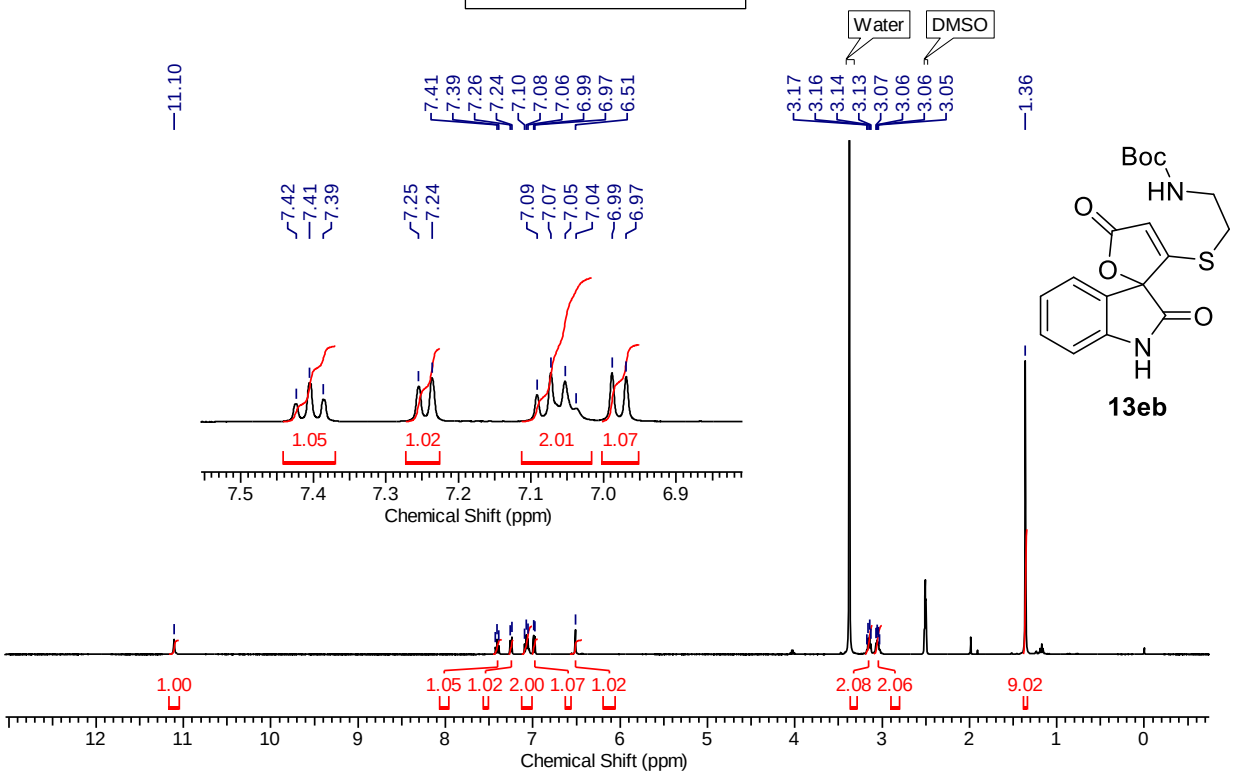

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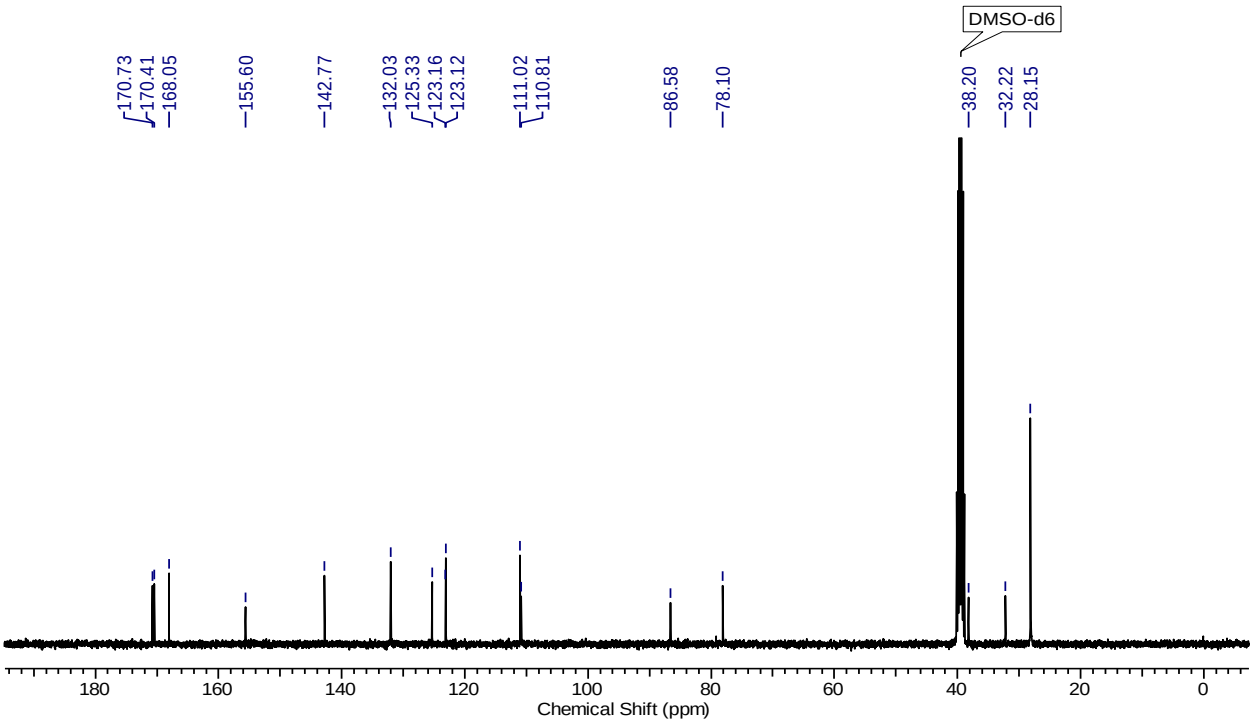

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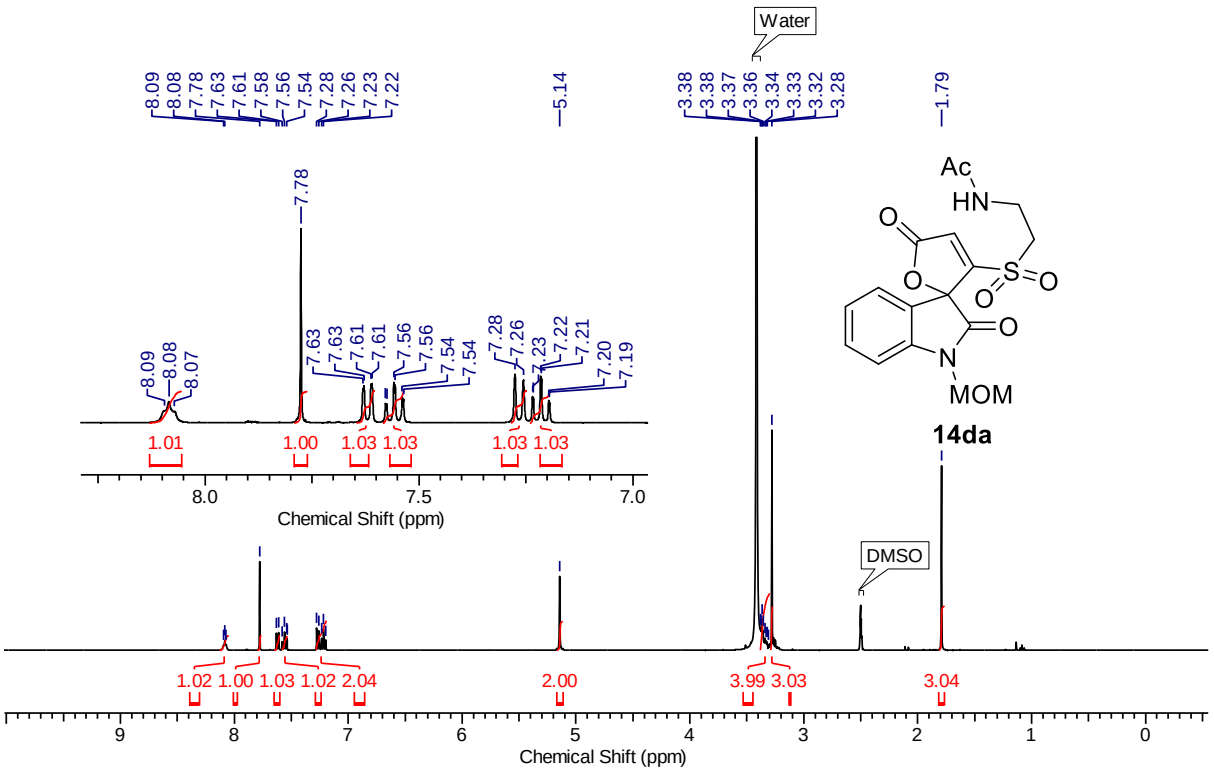

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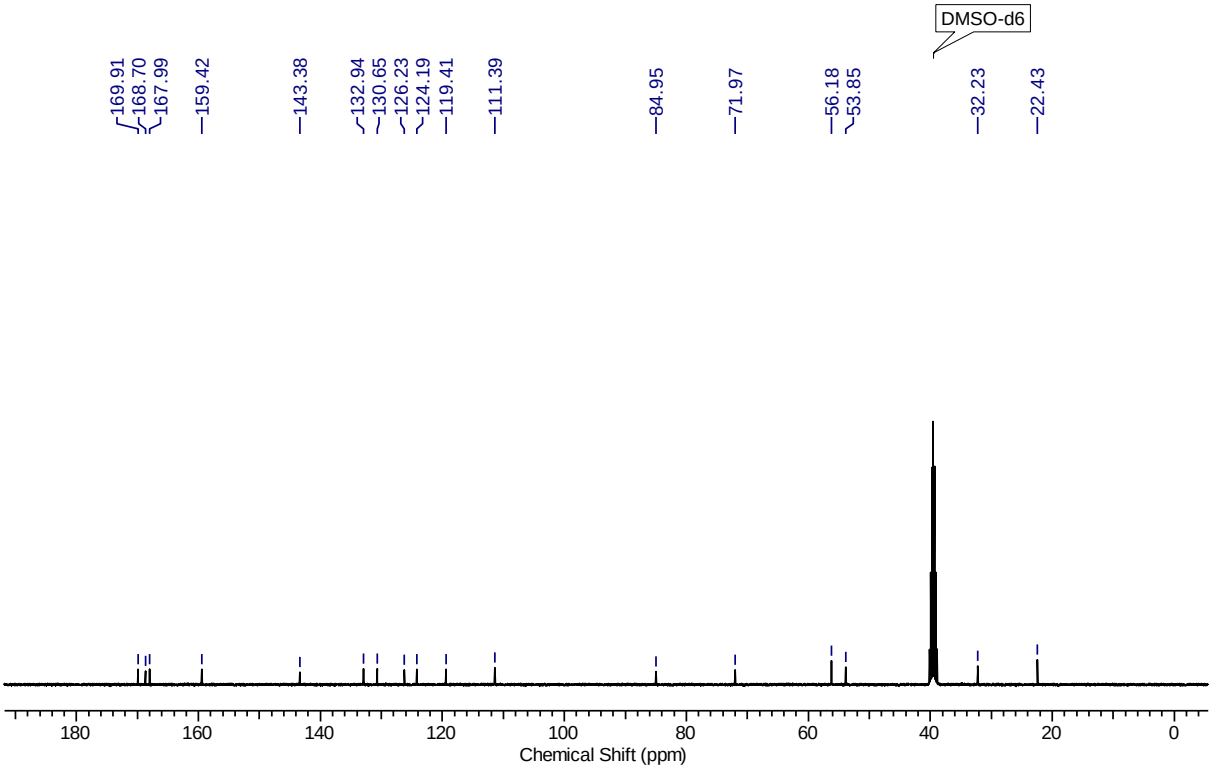

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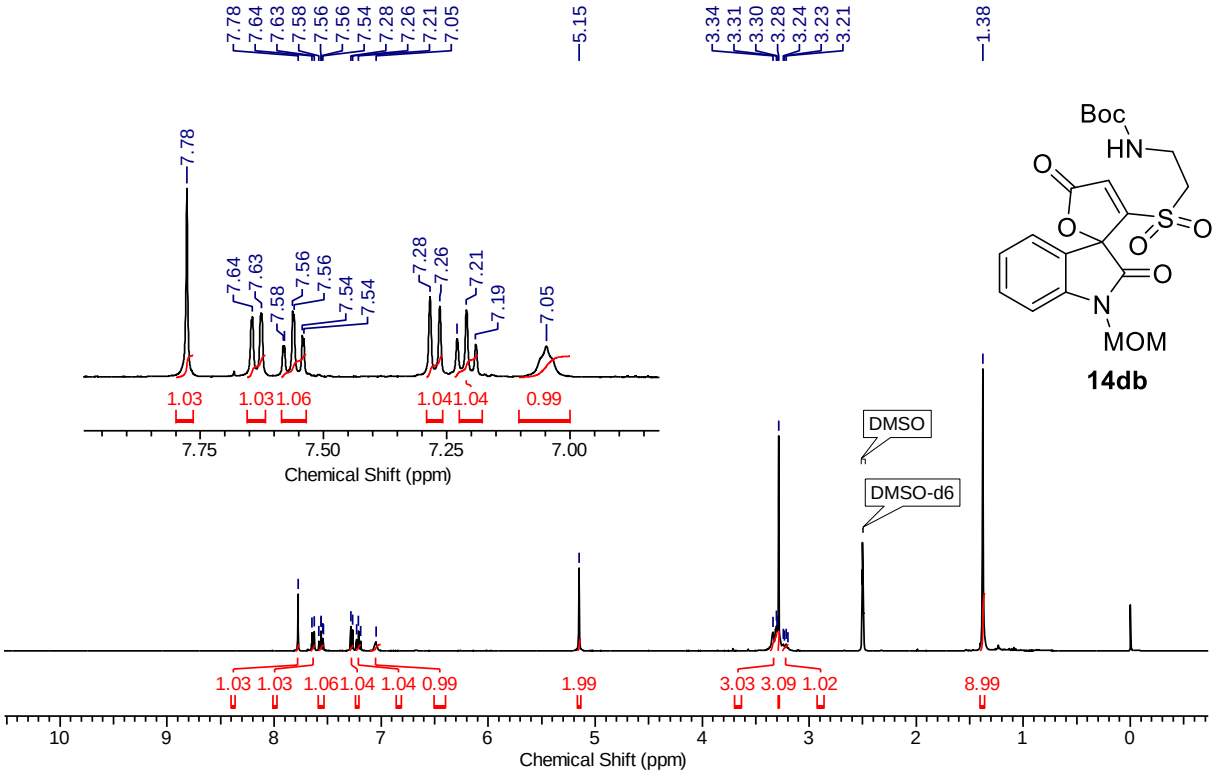

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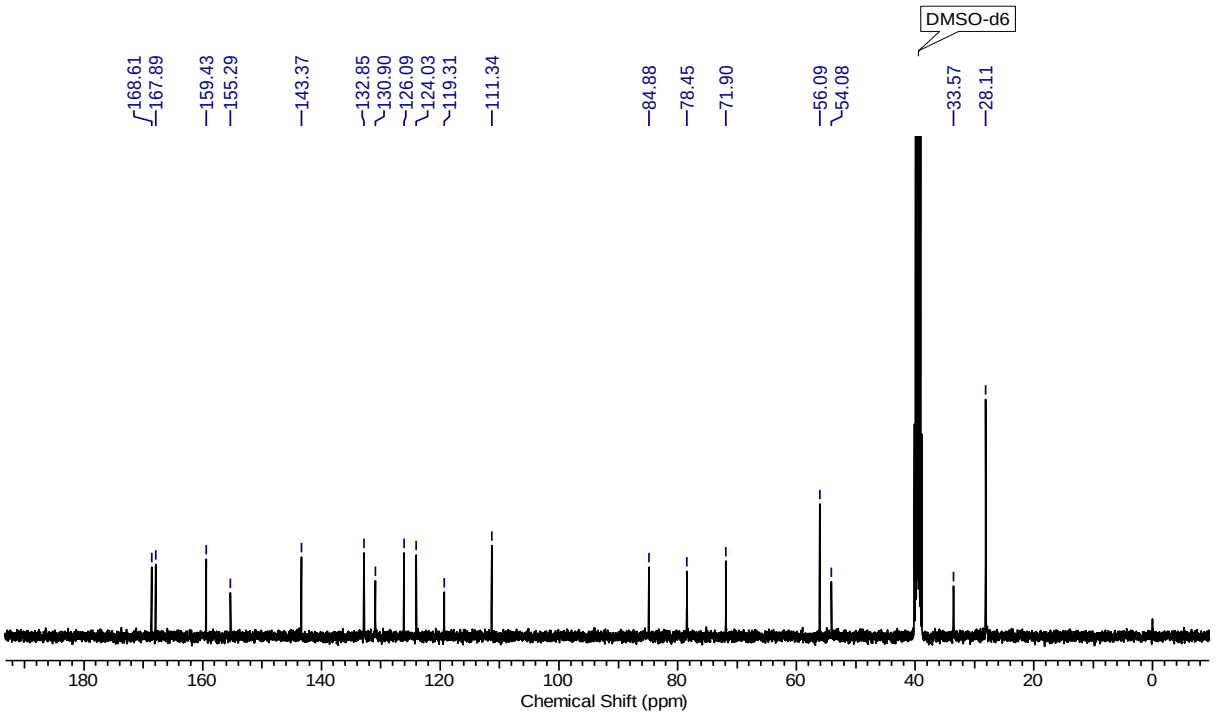

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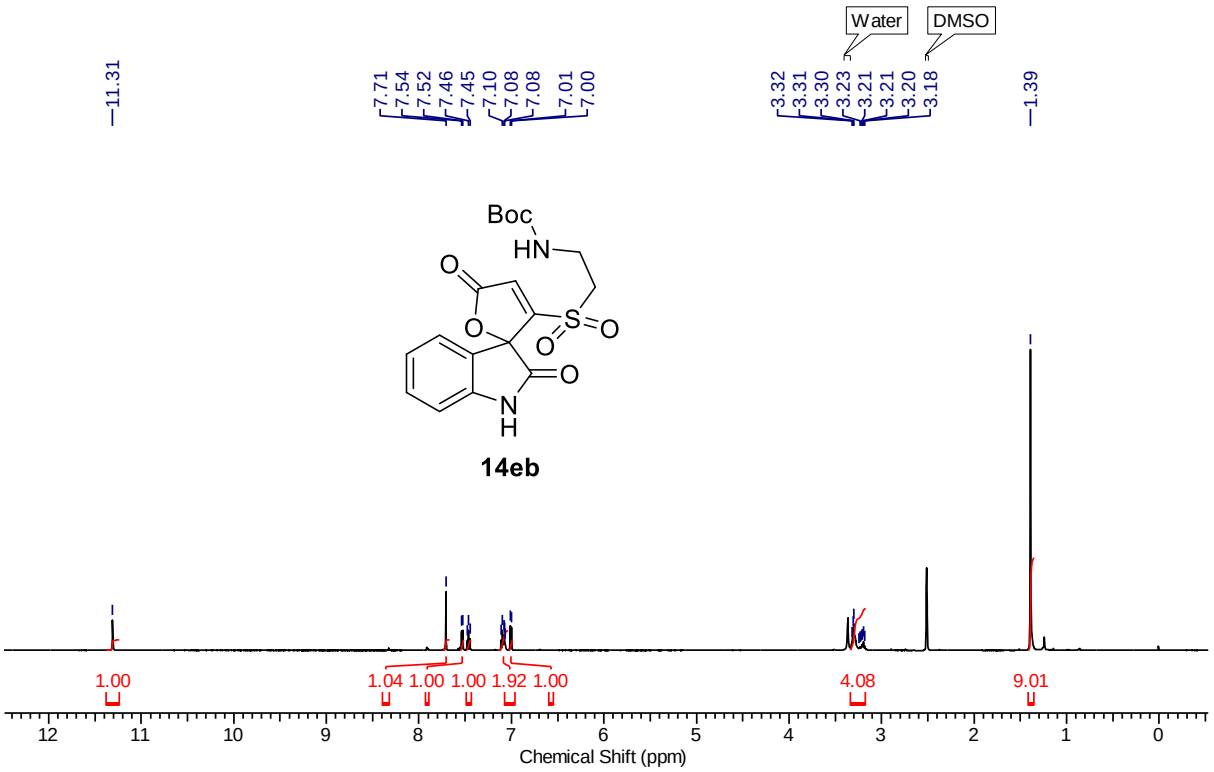

14eb

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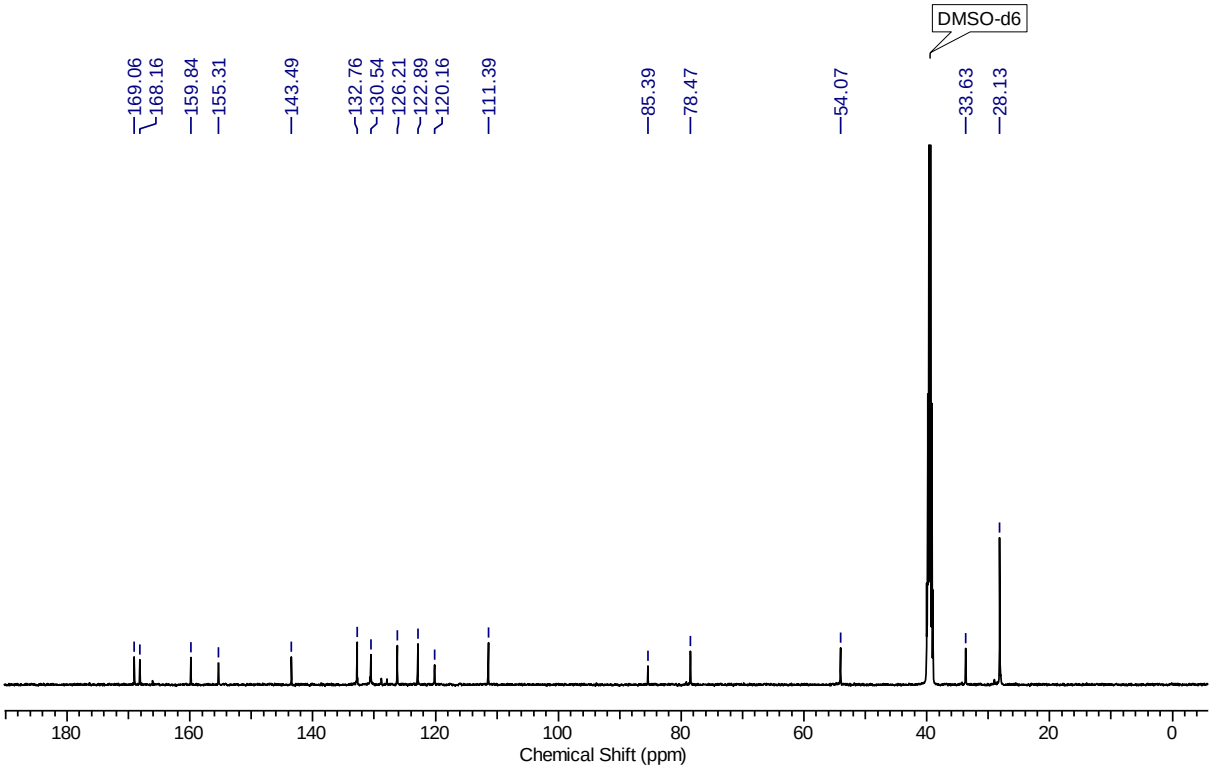

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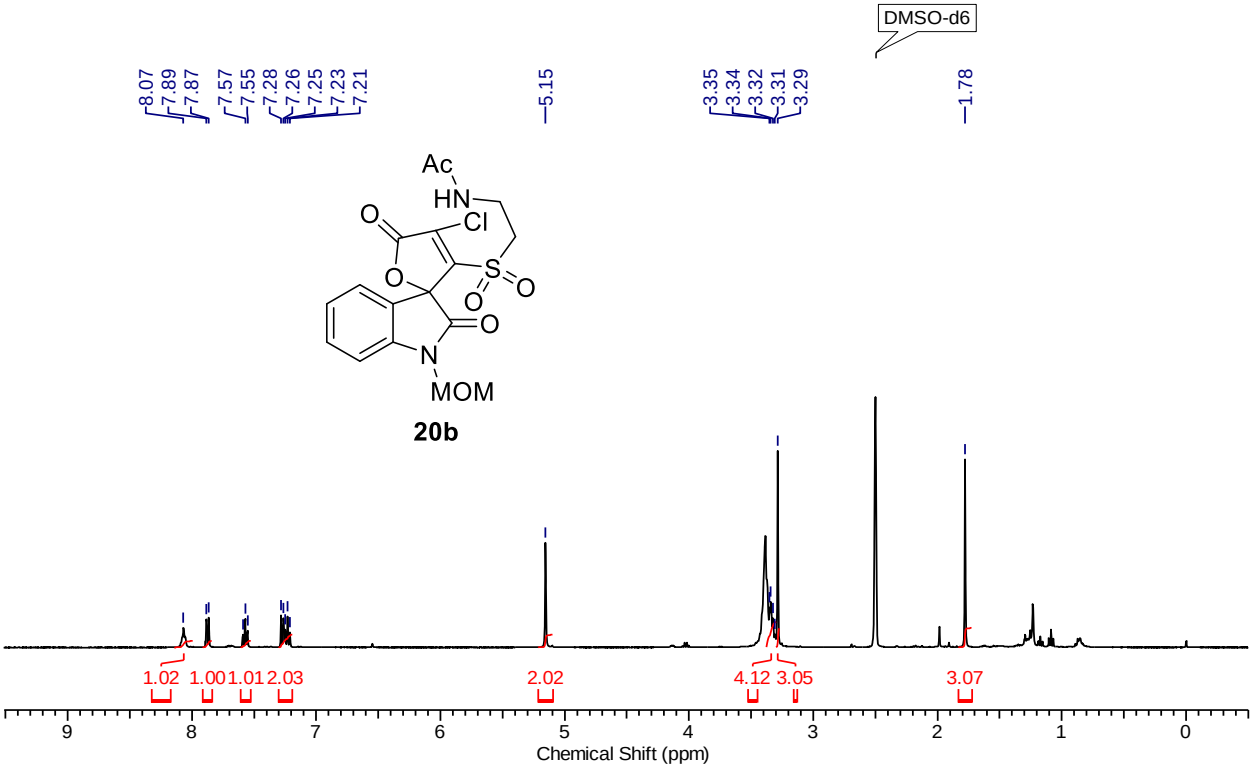

20b

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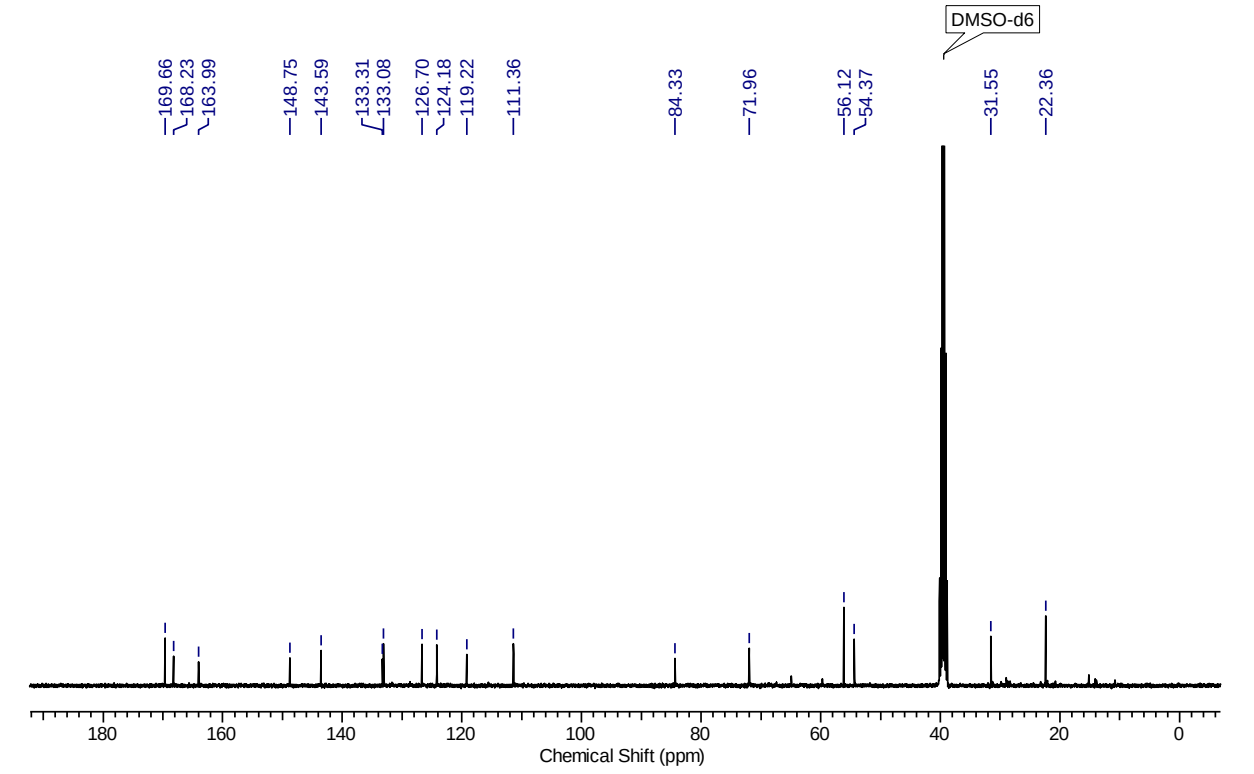

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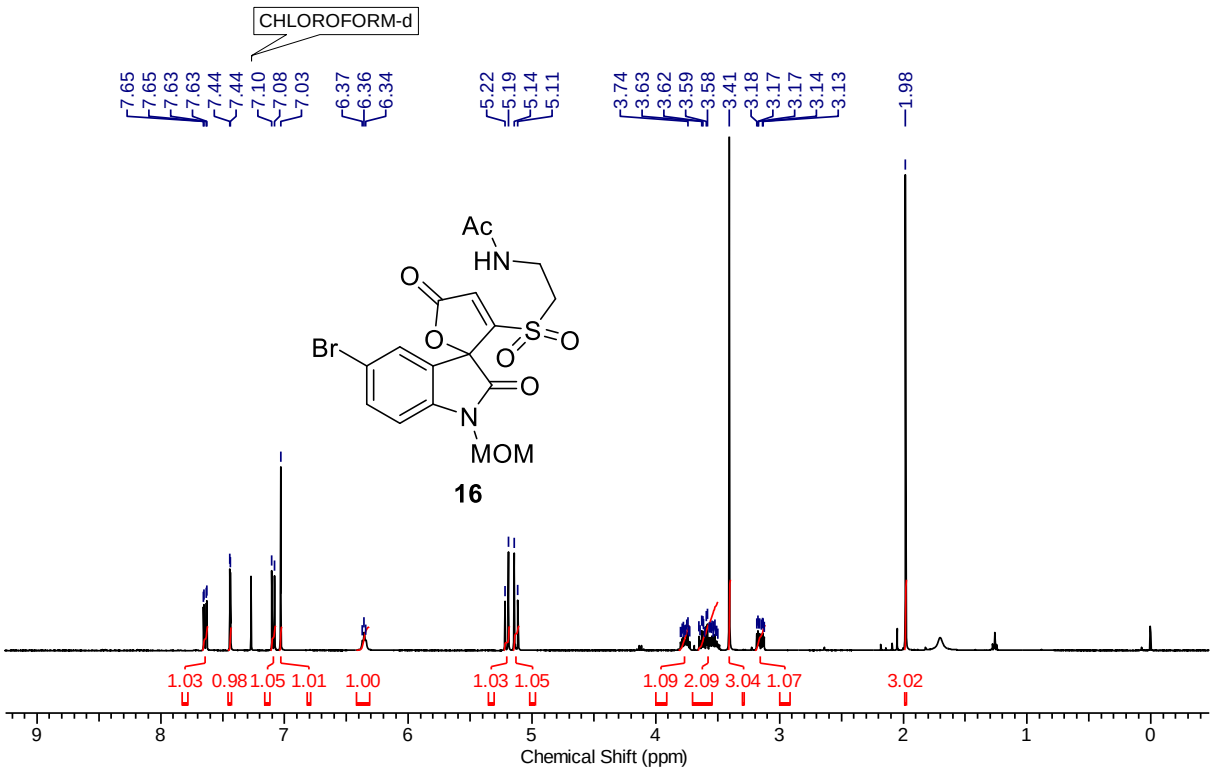
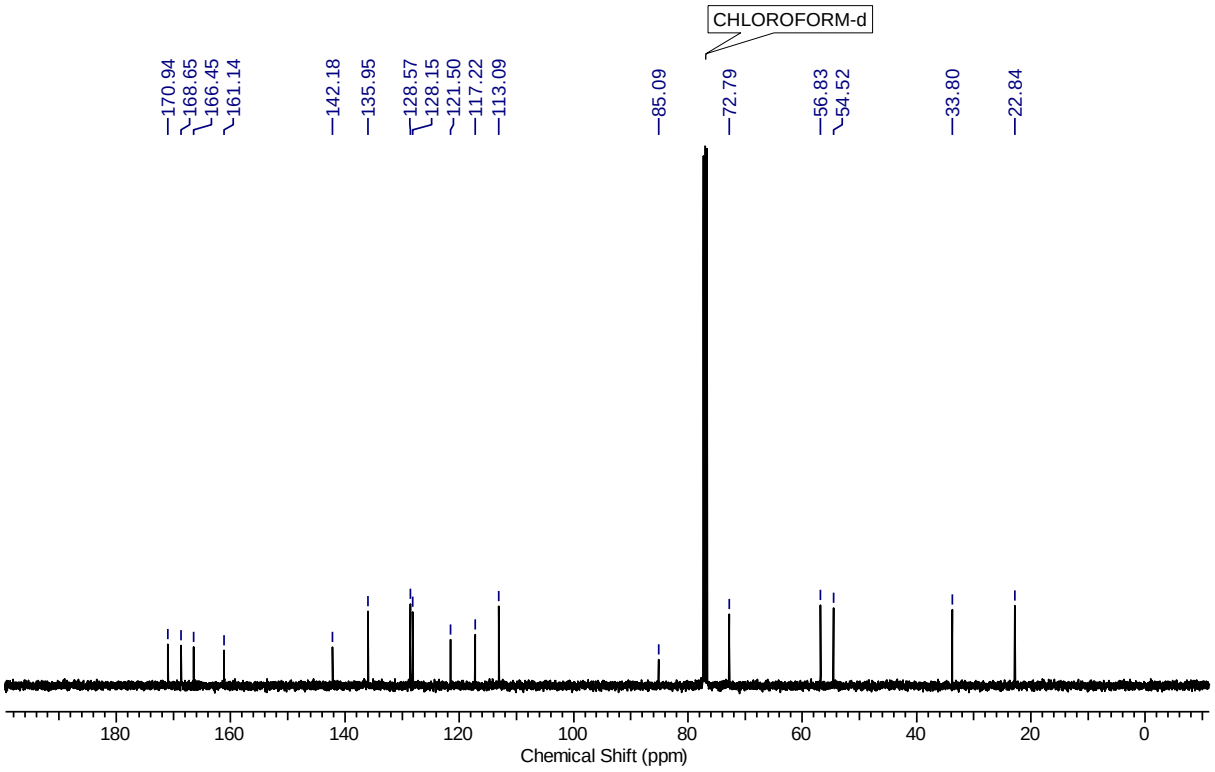


^{13}C NMR, 100 MHz



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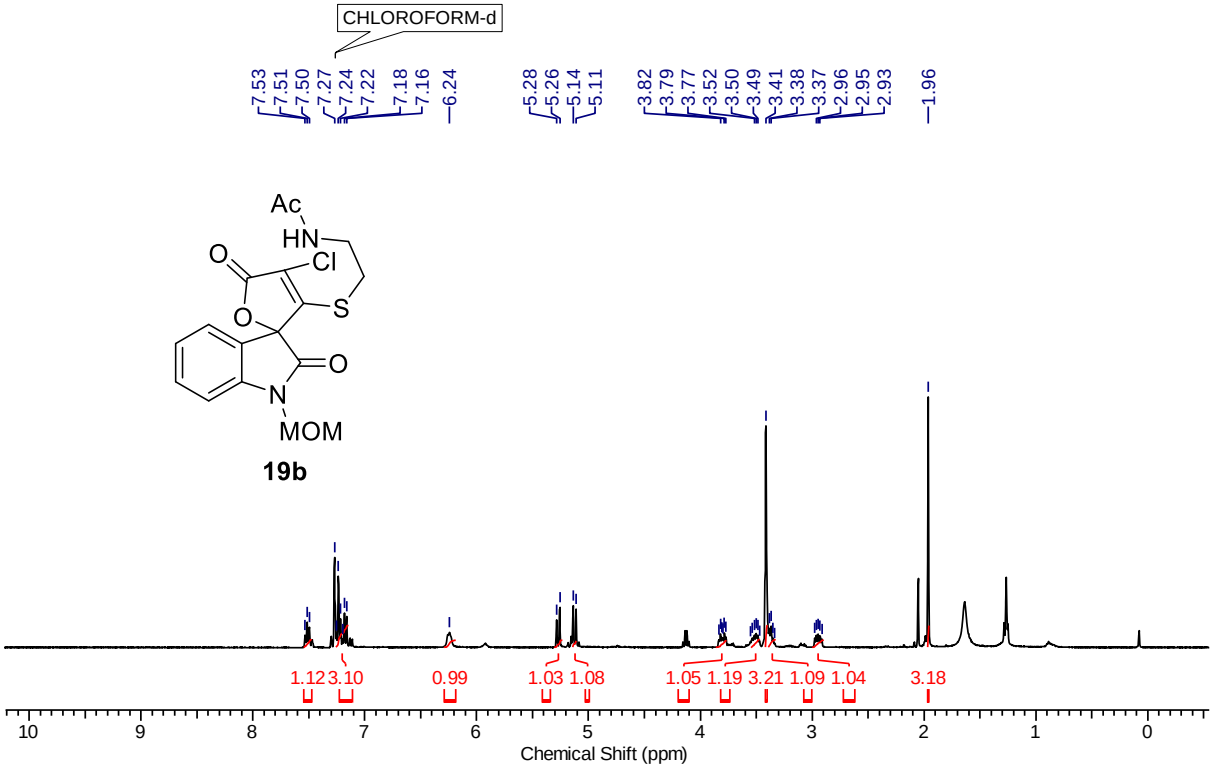

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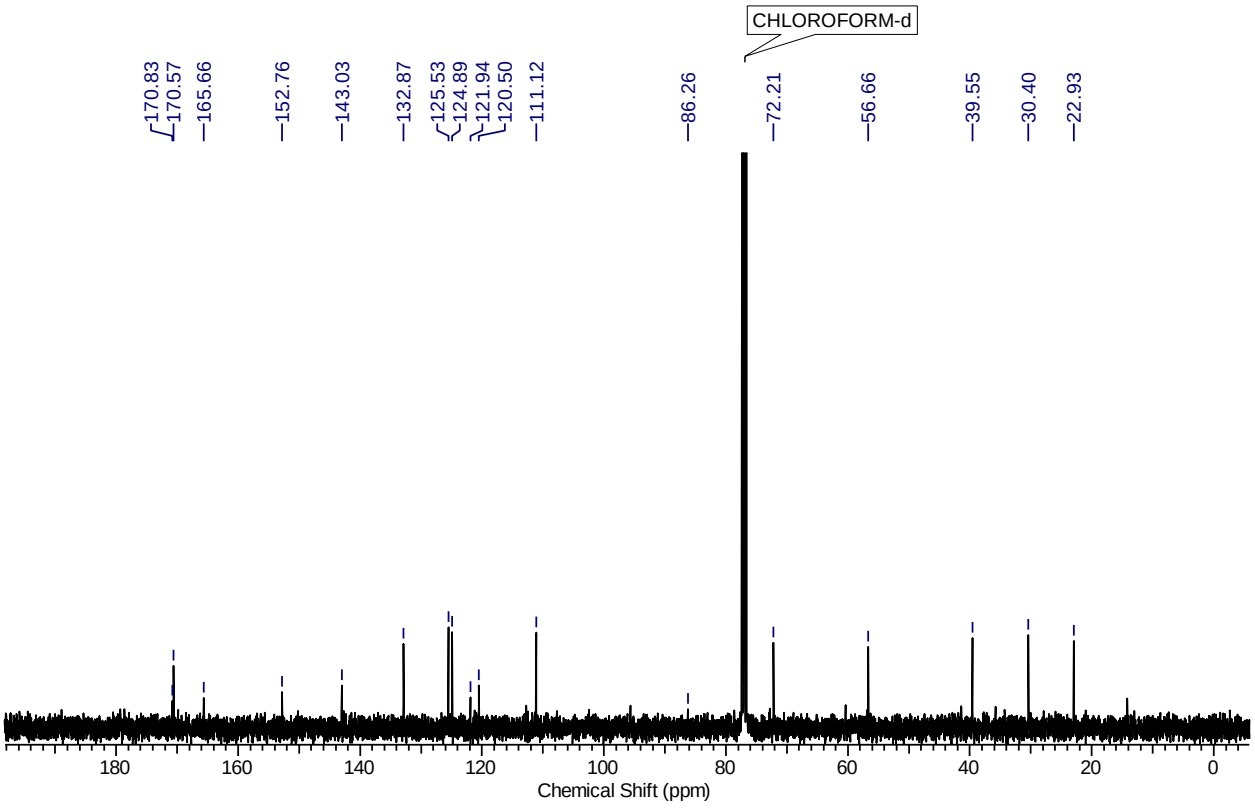
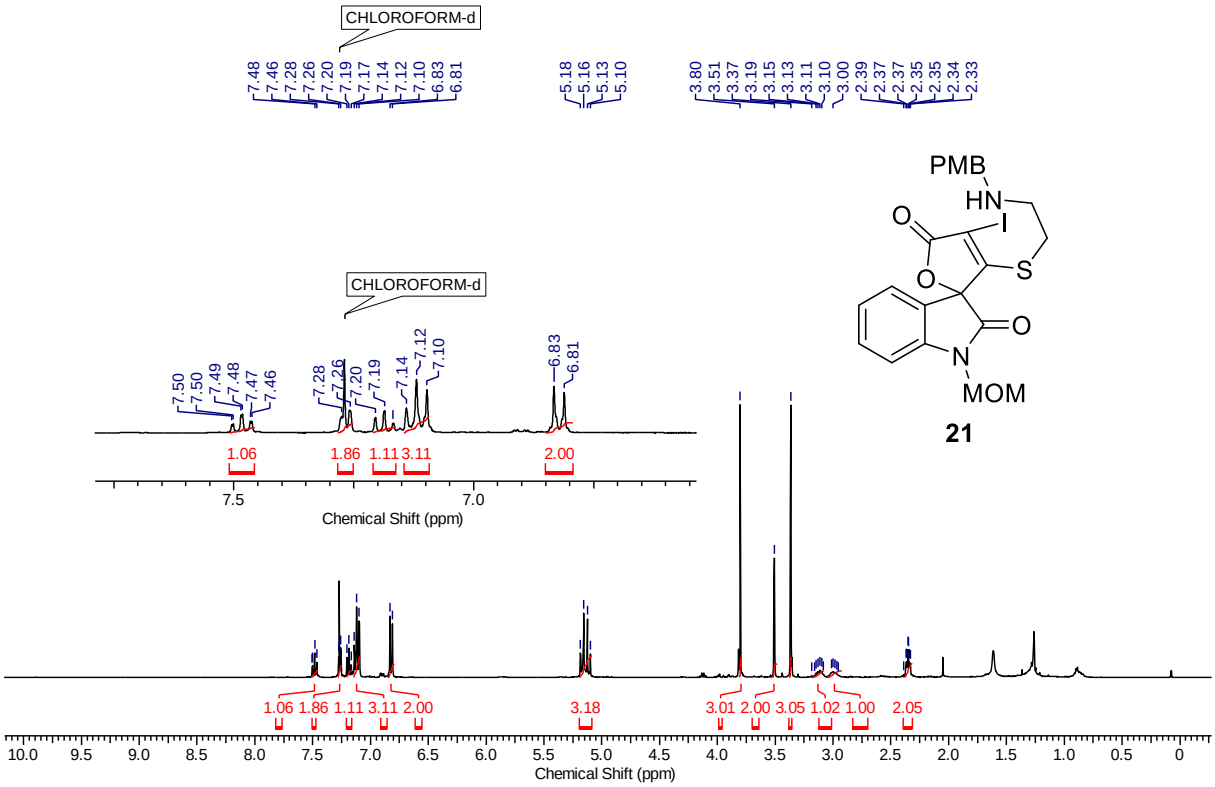
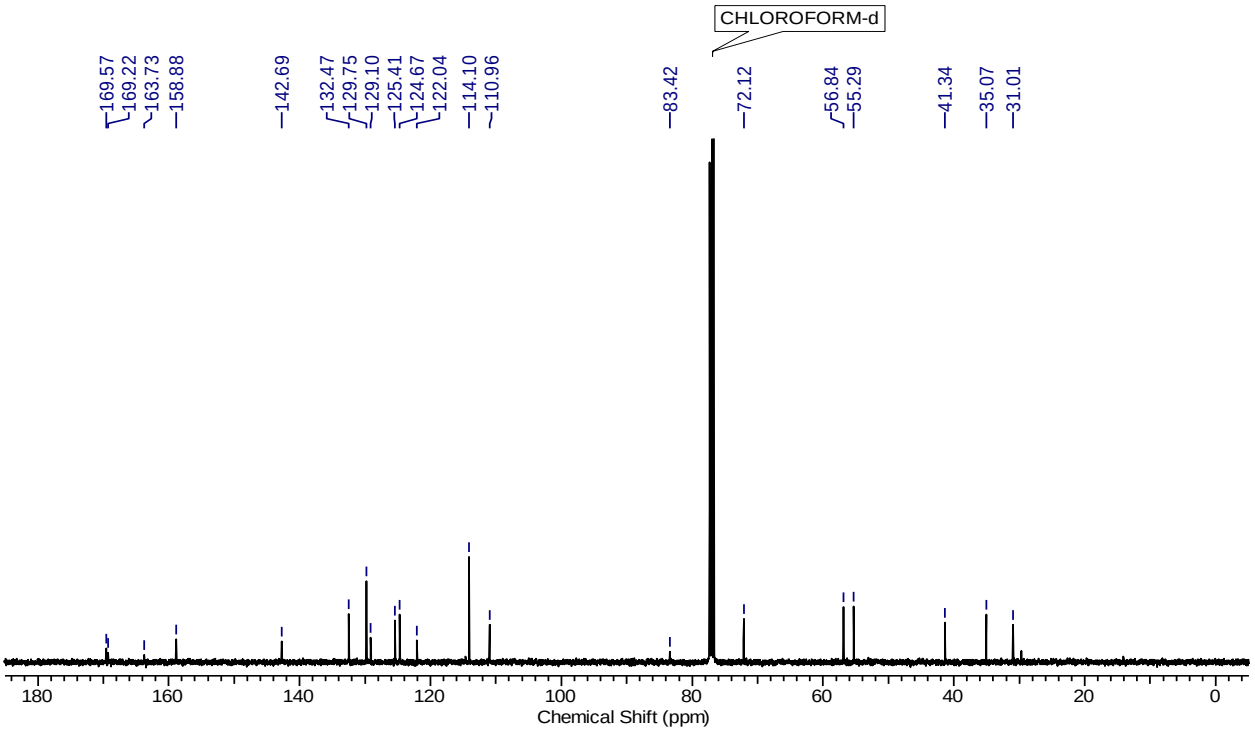


^{1}H NMR, 400 MHz



^{13}C NMR, 100 MHz



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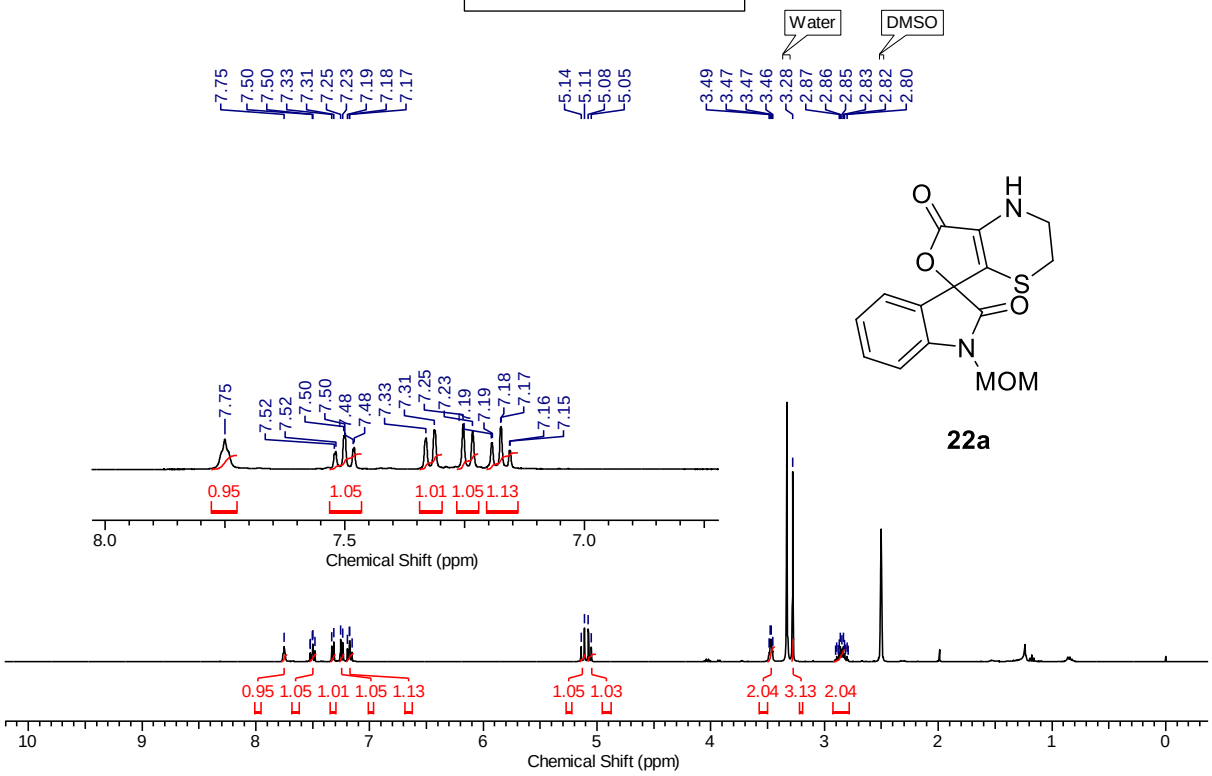
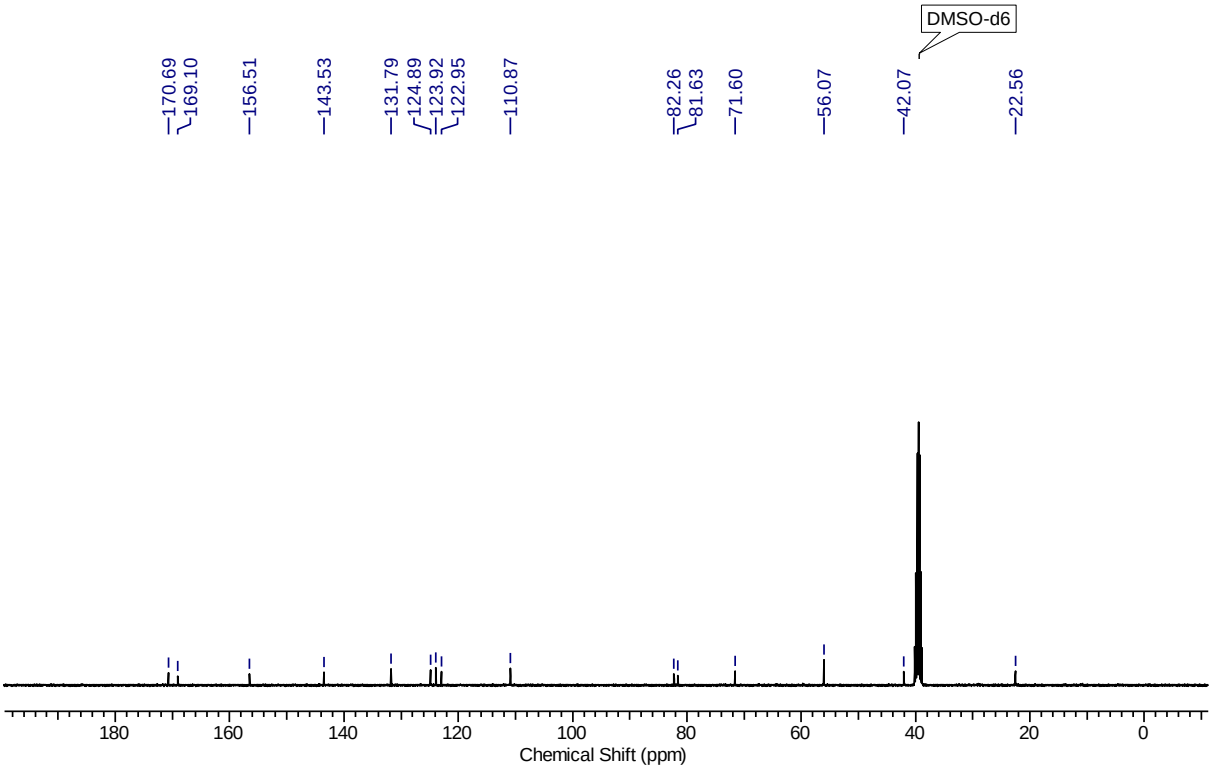


^{13}C NMR, 100 MHz



Chapter 4

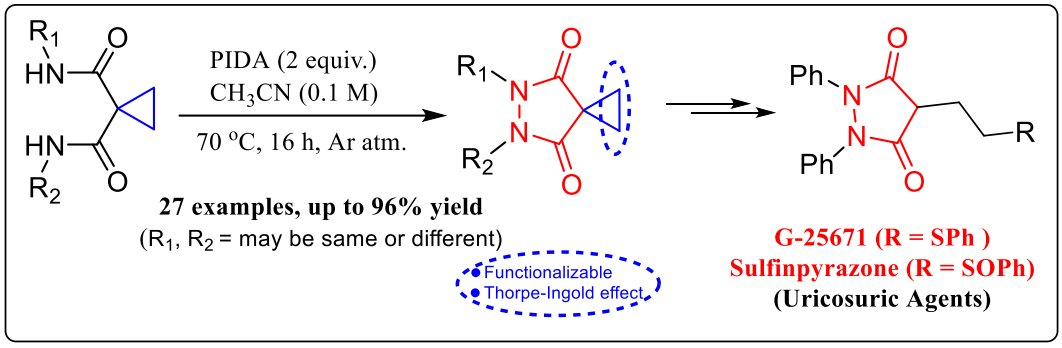
Construction of Pyrazolidine-3,5-diones via Metal-Free Oxidative Dehydrogenative N–N Bond Formation: Novel Process for Uricosuric Agents G-25671 and Sulfinpyrazone

Chapter 4

Construction of Pyrazolidine-3,5-diones via Metal-Free Oxidative Dehydrogenative N–N Bond Formation: Novel Process for Uricosuric Agents G-25671 and Sulfinpyrazone

4.1. Abstract:

Traditionally, toxic and expensive hydrazine building blocks are required to construct pharmaceutically important pyrazolidine-3,5- diones. Herein, we have described a novel method for their synthesis based on the metal-free oxidative dehydrogenative N–N bond formation by PIDA-mediated reaction of easily accessible dianilide precursors. The developed mild reaction protocol features a good functional group tolerance and scalability. The application of this method is demonstrated by offering a unique route for the synthesis of uricosuric agents G-25671 and sulfinpyrazone from inexpensive starting material aniline via smooth functionalization of well-designed diversity oriented cyclopropyl key intermediate.



4.2. Introduction:

Functionalized pyrazolidine-3,5-diones features an interesting class of heterocyclic compounds with a diverse biological activity including, anti-microbial, anti-bacterial, anti-inflammatory, COX-2 inhibition, and anti-analgesics, as well as material applications.[1] For instance, sulfinpyrazone, a derivative of phenylbutazone and its intermediate G-25671 are of specific importance (Figure 1). They exhibit potent anti-uricosuric activity by reducing the concentration of uric acid in the blood.[2] Sulfinpyrazone can also stop platelet aggregation by inhibiting COX and

increasing platelet survival time.[3,2b] It shows weak anti-inflammatory, analgesic effects and prevents gouty arthritis.[4,2b] It was approved by the US Food and Drug Administration (FDA) in 1959, and later marketed by Novartis under Anturane brand name.

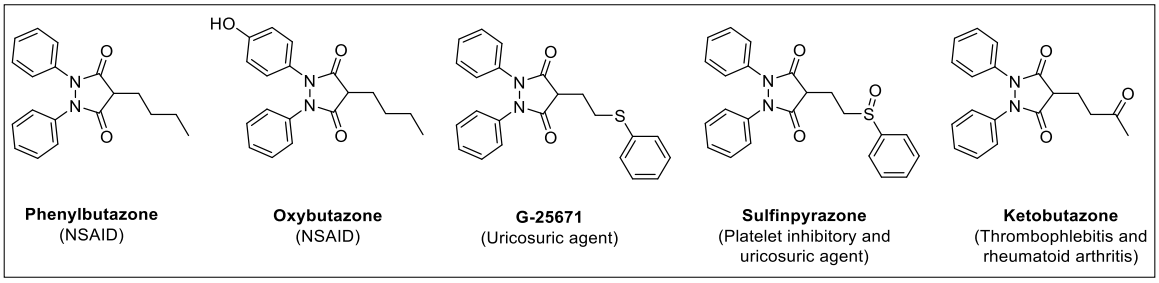


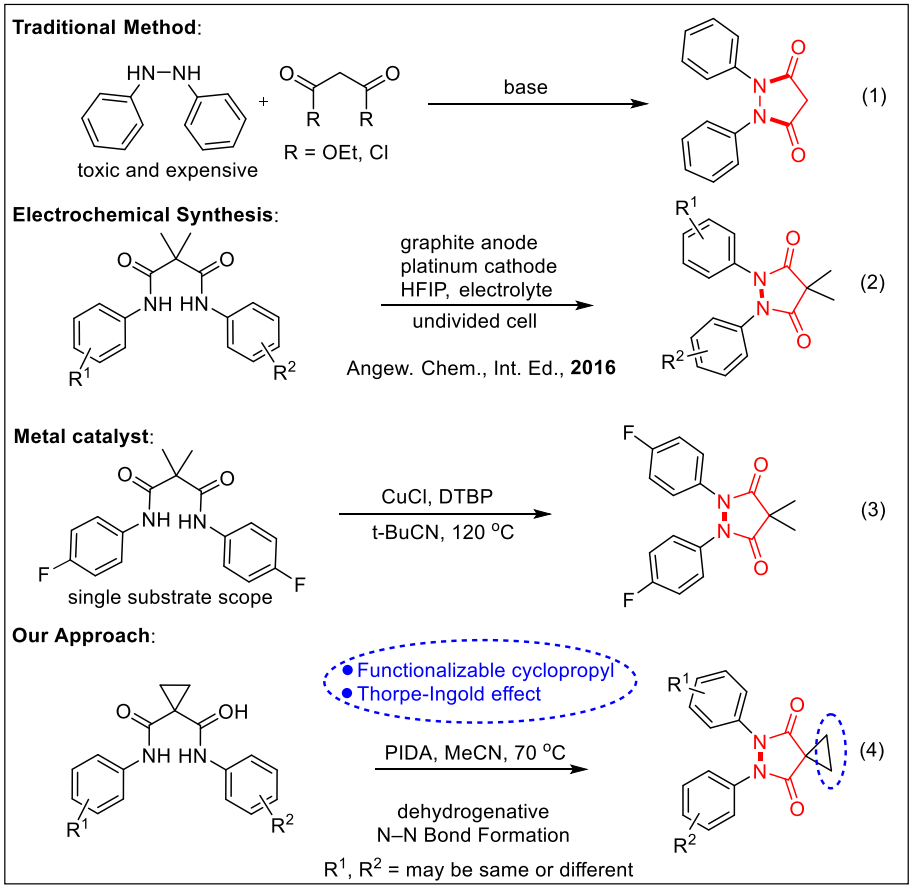
Figure 1. Derivatives of Phenylbutazone

4.3. Literature Review:

The construction of pyrazolidine-3,5-diones has been attracting increased attention because of its immense diversity in the biological as well as pharmaceutical field.[5] In the last few decades, research on the construction of functionalized pyrazolidine-3,5-diones to explore their biological activity shows that, it was commonly prepared by the traditional condensation reaction between the derivatives of malonic ester or malonic acid chloride and diphenylhydrazine (Scheme 1, eq. 1).[6] This method was developed by Emil Fischer in the late 19th century.[7] However, the use of diphenylhydrazine substrate inevitably leads to environment and health concerns, which is a major drawback in the synthesis of sulfinpyrazone class of drugs. [8] The carcinogenic nature of hydrazine building blocks requires extra safety arrangements for its preparation and handling which poses a major challenge for up-scaling in industry. Furthermore, the cost of the diphenylhydrazine is very high (₹44,200/100 gm in TCI) and only the simple unsubstituted hydrazine is commercially available.[8a] Thus, the generation of library of these key drug intermediates relies on the ominous synthetic route with low efficiency. To address this issue, development of economic and environment friendly synthetic route has always been of great interest. Therefore, the

sulfinpyrazone drug and its potent intermediate G-25671 featuring the pyrazolidine-3,5-dione core and possessing uricosuric activity caught our attention. To date, few routes have resulted in the successful process development of this drug and they involve the use of carcinogenic and expensive diphenylhydrazine as a starting material for the formation of pyrazolidine-3,5-diones core.[9] We believe that in situ preparation of diphenylhydrazine via N–N bond formation could be a way to overcome the above challenges.

Scheme 1. Previous Work and Our Approach



4.4. Origin of the Work:

Nitrogen-nitrogen bond, particularly in the cyclic compounds is an omnipresent structural framework in numerous bioactive natural products, drugs, dyes, and organic materials.[10] Complementarily, in last few decades, several remarkable methods have been developed to form

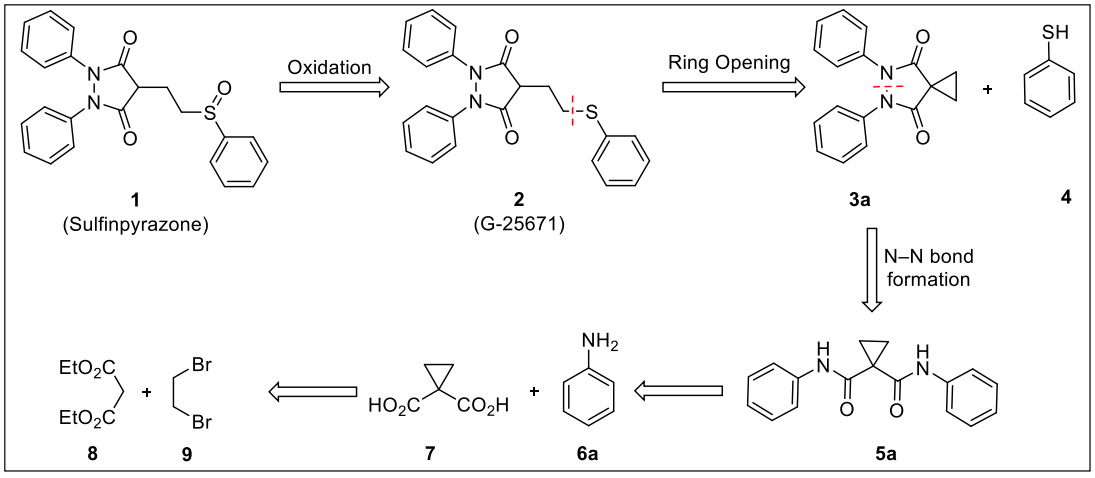
intermolecular as well as intramolecular N–N bond via various pathways and sources.[11] By the reason of high electronegativity of nitrogen atom and the nucleophilic nature of N–H functional group, retrosynthetic disconnection of N–N bond has always been an infrequently targeted ways[11b] and its formation becomes more challenging in dehydrogenative N–N coupling reactions.[11c] Although, the dehydrogenative coupling reactions have reformed the area of orthodox organic transformations by providing an excellent efficiency, step and atom economy;[12] a precisely designed oxidizing system is required to activate the particular N–H bond by avoiding undesired C–C and C–N coupled side products.[11c] To the best of our knowledge, the use of simple and easily accessible dianilide precursors for the construction of pyrazolidine-3,5-diones via intramolecular N–N bond formation was not achieved until a significant work reported by Waldvogel to access pyrazolidine-3,5-diones through electrochemical anodic N–N bond formation using undivided cell (Scheme 1, eq. 2).[8a,13] Undoubtedly, organic electrosynthesis is an environmentally benign process;[14] but it has its own advantages and shortcomings specially at commercial scale.[15] Of late, copper catalyzed intramolecular N–N bond formation to access pyrazolidine-3,5-dione was developed by Bing-Feng Shi; however, this method was limited to single substrate scope (Scheme 1, eq. 3).[16] In the modern economy model, decreasing the production cost for the drug synthesis in large scale with enhanced safety is becoming a major concern. In this context, to provide a general access to pyrazolidine-3,5-diones, we planned a novel metal-free synthetic strategy via N–N bond formation. We envisioned that the presence of functionalizable cyclopropyl moiety would also facilitate the N–N bond formation by exerting ring strain according to Thorpe-Ingold effect. Accordingly, presented herein is an efficient method for metal-free intramolecular dehydrogenative N–N bond formation via hypervalent iodine mediated reaction of dianilide

precursors providing pyrazolidine-3,5-dione core of sulfinpyrazone class of drugs under mild reaction condition (Scheme 1, eq. 4).

4.5. Objective of the Work:

Our retrosynthetic plan is illustrated in Scheme 2, wherein, the synthesis of sulfinpyrazone by the known selective oxidation of sulfide **2** would be possible. The sulfide **2** could be achieved from our key intermediate **3a** by means of a nucleophilic cyclopropane ring opening with thiophenol (**4**) as the nucleophile. The pyrazolidine-3,5-dione core of intermediate **3a** could be constructed by the novel intramolecular dehydrogenative N–N bond formation of dianilide **5a**. The preparation of dianilide **5a** was planned from easily accessible starting material aniline (**6a**) and diacid **7**. The acid **7** could be synthesized from the commercially available precursors diethylmalonate (**8**), and 1,2-dibromoethane (**9**) utilizing reported reaction condition.[17]

Scheme 2. Retrosynthetic Analysis of Sulfinpyrazone and G-25671

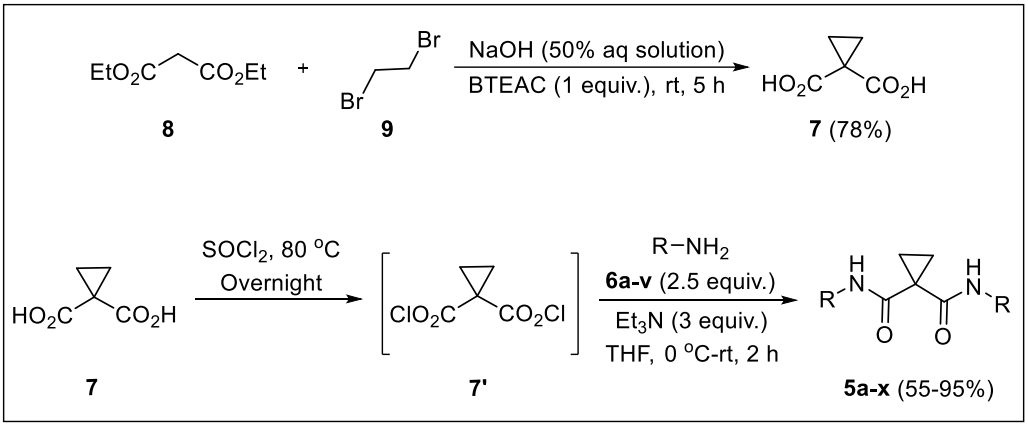


4.6. Result and Discussion:

We began our investigation with the preparation of our key component dianilide **5a** on gram scale. Cyclopropane ring containing malonic acid **7** was achieved starting from diethylmalonate **8**, and 1,2-dibromoethane **9** with an excellent yield using the reported procedure.[17] The treatment of

substrate **7** with thionyl chloride under refluxing condition provided unstable dichloride **7'**, which was further reacted with aniline **6a** in presence of the base triethylamine to deliver dianilide **5a** in very good yield (86% on gram scale) (Scheme 3). Similarly, dianilides **5b-z** were synthesized in good to excellent yields.

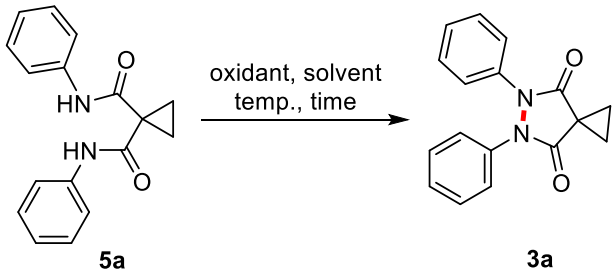
Scheme 3. Synthesis of Dianilides **5a-x**



Once the dianilide **5a** was in hand, we focused on the optimization of our desired intramolecular dehydrogenative N–N bond formation. At the outset of our study, we used $KMnO_4$ as an oxidant in acetone at 60 °C (Table 1, entry 1), but our expected product was not obtained. Catalytic condition like CuBr as well as photocatalyst $[Mes\text{-}acr]^+BF_4^-$ also failed to provide our expected product (Table 1, entries 2 & 3). Considering environmentally benign and distinct properties of hypervalent iodine reagents, we were curious to explore their reactivity for the proposed N–N bond forming transformation. Hypervalent iodine reagents are often used as alternatives to transition metals in the C–C, C–X and for N–N bond forming reactions.[11,18] Interestingly, when we used hypervalent iodine reagent diacetoxyiodobenzene (PIDA) as an oxidant, we observed the formation of our expected product with moderate yield in HFIP at 40 °C temperature (Table 1, entry 4). Furthermore, increasing temperature as well as the equivalent ratio of PIDA did not show any improvement in the yield (Table 1, entries 5-7). However, under such

condition many inseparable UV active spots were seen on TLC with complete consumption of dianilide. The yield did not improve substantially with other hypervalent iodine reagents like PhIO and PIFA under the same reaction condition (Table 1, entries 8 & 9). To optimize the reaction, various solvents were tested in the presence of 2 equivalent of PIDA, but the expected product was not observed due to insolubility of the dianilide **5a** in those solvents (Table 1, entry 10). Surprisingly, shifting solvent to acetonitrile provided the expected product in better yield with the recovery of starting material (Table 1, entry 11). However, changing oxidizing agent to PhIO in acetonitrile did not work well (Table 1, entry 12). To further increase the yield of the product a different reaction condition was examined, where we used 20 mol% iodobenzene and 1.2 equivalent of *m*-CPBA as well as oxone as an oxidant to generate hypervalent iodine reagent in situ in the reaction system (Table 1, entries 13 & 14).

Table 1. Optimization of Reaction Conditions[a]



5a **3a**

Sr. no	*Conditions*	*Solvent*	*Temp. (°C)*	*Time (h)*	*Yield[b] (%)*
1.	$KMnO_4$ (2.5 equiv.)	acetone	60	24	NR
2.	$CuBr_2$ (20 mol%), O_2	DMSO	120	24	NR
3.	$[Mes\text{-}acr]^+ BF_4^-$,(1 mol%)	HFIP	25	24	NR
4.	PIDA (1 equiv.)	HFIP	40	16	30 (43)[c]
5.	PIDA (1equiv.)	HFIP	70	16	24
6.	PIDA (1.5 equiv.)	HFIP	70	16	30
7.	PIDA (2 equiv.)	HFIP	70	16	40
8.	PhIO (2 equiv.)	HFIP	70	16	38

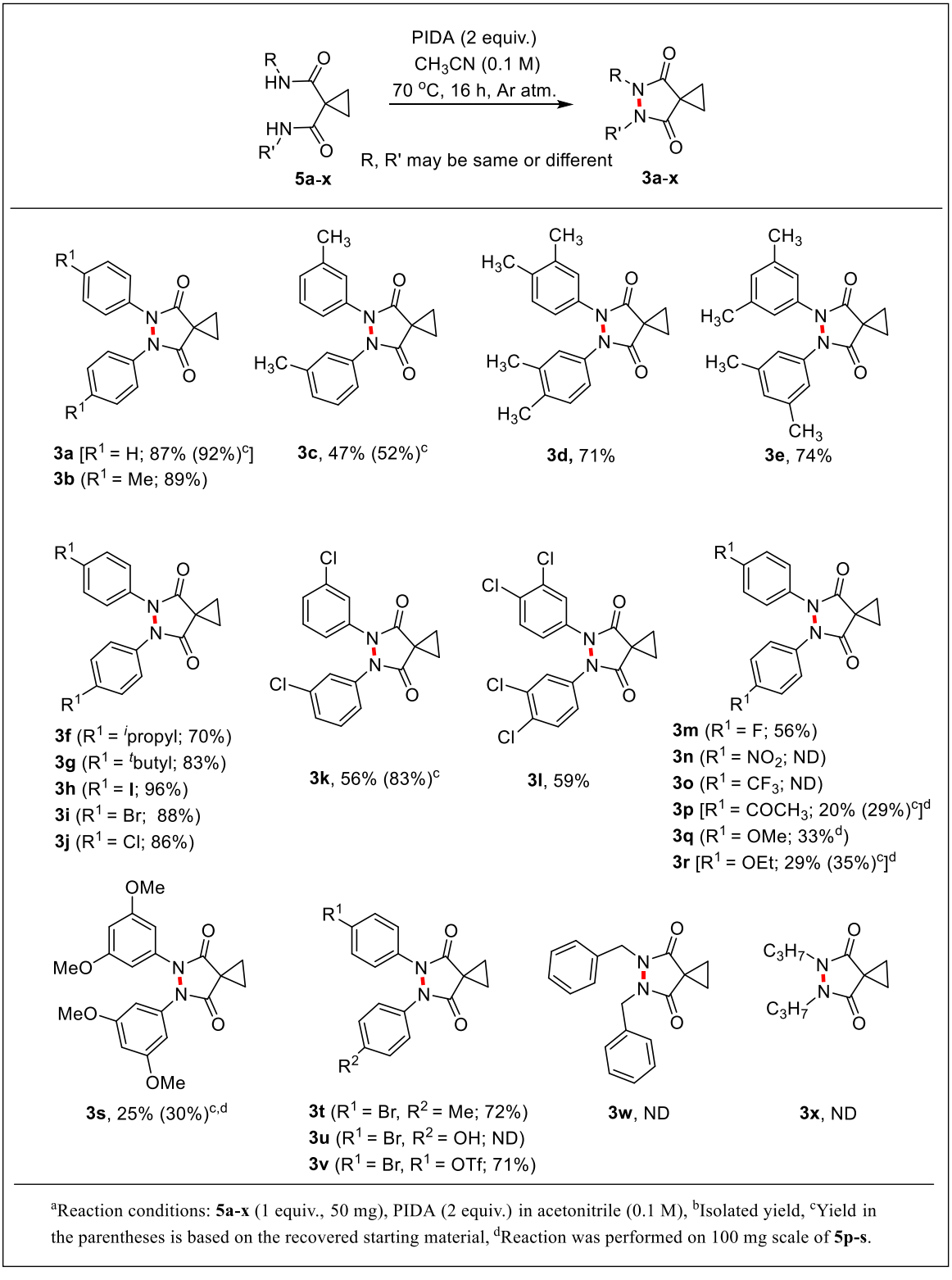
9.	PIFA (2 equiv.)	HFIP	70	16	15
10.	PIDA (2 equiv.)	DMF/EtOH/ THF/IPA/ MeOH/DCE/^{t}BuOH	70	16	NR
11.	PIDA (2 equiv.)	ACN	70	16	56 (74)[c]
12.	PhIO (2 equiv.)	ACN	70	16	41 (64)[c]
13.	PhI (20 mol%), m-CPBA (1.2 equiv.)	ACN	25	12	44
14.	PhI (20 mol%), Oxone (3 equiv.)	HFIP	70	17	NR
15.	PIDA (2 equiv.), HFIP (3 equiv.)	MeOH	70	16	24
16.	PIDA (2 equiv.), HFIP (3 equiv.)	toluene	70	16	34
17.	PIDA (2 equiv.), HFIP (3 equiv.)	ACN	70	16	68 (72)[c]
18.	PIDA (2 equiv.)	HFIP:MeOH (1:1)	70	16	37
19.	PIDA (2 equiv.)	HFIP:toluene (1:1)	70	16	20
20.	PIDA (2equiv.)	HFIP: heptane (1:1)	70	16	38
21.	PIDA (2 equiv.)	HFIP:hexane (1:1)	70	16	30
22.	PIDA (2 equiv.)	HFIP: ACN (1:1)	70	16	61(75)[c]
23.	PIDA (2 equiv.), under argon	Dry ACN	70	16	87 (92)[c]
24.	PIDA (2 equiv.), under argon, 4A^{o}MS	ACN	70	16	61 (74)[c]
25.	PIDA (2equiv.), under argon, 3A^{o}MS	ACN	70	16	63 (71)[c]
26.	PhIO (2 equiv.), under argon	Dry ACN	70	16	23
27.	IBX (2 equiv.), under argon	Dry ACN	70	16	NR
28.	DMP (2 equiv.), under argon	Dry ACN	70	16	NR
29.	PhI (20 mol%), *m*-CPBA (3 equiv)	Dry ACN	70	16	26
30.	PhI (20 mol%), Oxone (3 equiv)	Dry ACN	70	16	NR

[a]Reaction conditions: **5a** (20 mg, 1.0 equiv.), Oxidant in solvent (0.1 M, 0.7 ml). [b]Isolated yield. [c]Yield in the parentheses is based on the recovered starting material.

Still, such condition also failed to give better yield. Due to the radical stabilizing properties of HFIP, we thought that, the combination of HFIP with other solvent could increase the yield. Therefore, the permutation and combination of HFIP with different polar and non-polar solvent was performed, but they ended up in unsatisfactory results (Table 1, entries 15-22). Fortuitously, the substrate **5a** showed enhanced formation of the desired product **3a** in the presence of 2 equivalent of PIDA in dry acetonitrile at 70 ^{o}C temperature under argon atmosphere after 16 h (Table 1, entry 23). Further efforts for the optimization using different additives did not provide significant change in the yield (Table 1, entries 24 & 25). Moreover, for enhancing the yield of the product using catalytic hypervalent iodine reagents[18] (Table 1, entries 26-30) did not show substantial improvement in the yield. Finally, after screening many variations in oxidant, mole ratio of oxidant, solvent, temperature and time, the optimized yield for the pyrazolidine-3,5-dione **3a** was 87% and based on the recovery of the starting material, the yield was 92% (Table 1, entry 23).

To explore the substrate scope of this protocol, various dianilides bearing different substituents were tested (Scheme 4). Initially, we started with the variation of substituents on the aromatic part of dianilide. The *para* methyl substituted substrate **5b** furnished the expected product **3b** with an excellent yield compared to the unsubstituted product **3a**. However, incorporation of methyl substituent to the *meta* position of dianilide diminished the yield to obtain 47% of **3c**. Additionally, this reaction also worked well for 3,4 and 3,5-dimethyl substituted dianilides **5d** and **5e** to afford the corresponding products **3d** and **3e** respectively with better yields. The optimal reaction condition worked smoothly with the dianilide **5f** having *p*-^{i}propyl group to provide the expected product **3f** in 70% yield. Interestingly, the dianilide **5g** having *tert*-butyl group furnished improved yield of the desired product **3g**.

Scheme 4. Substrate Scope of the Oxidative N–N Bond Formation to Achieve Various Pyrazolidine-3,5-diones Derivatives[a,b]

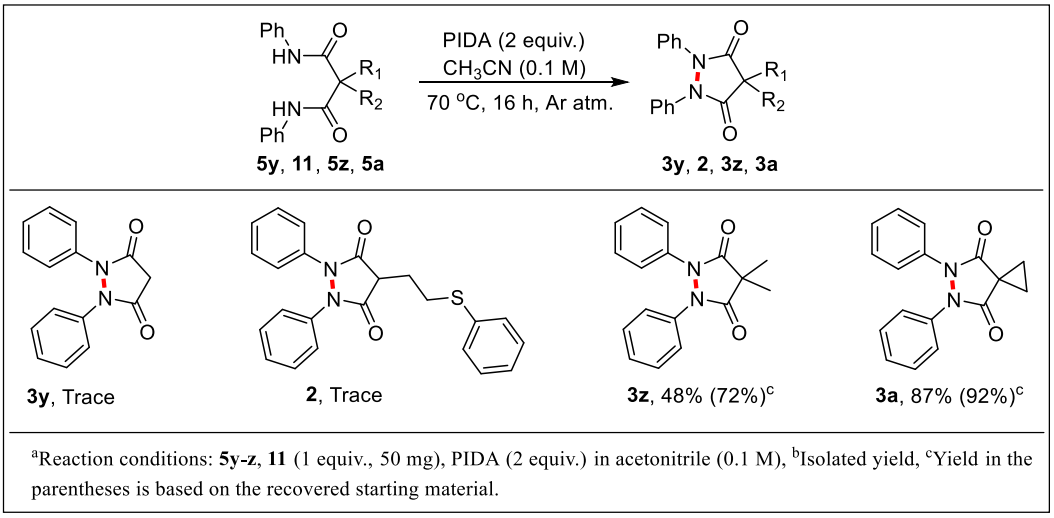


[a]Reaction conditions: **5a-x** (1 equiv., 50 mg), PIDA (2 equiv.) in acetonitrile (0.1 M), [b]Isolated yield, [c]Yield in the parentheses is based on the recovered starting material, [d]Reaction was performed on 100 mg scale of **5p-s**.

The iodo substituent at the *para* position of dianilide resulted into the desired product **3h** in an excellent yield. The other halo-substituted dianilides **5i**, and **5j** worked equally well under this reaction condition to provide the corresponding products **3i**, and **3j** respectively with excellent yields. However, the product **3k** was obtained in diminished yield, just due to the presence of chloro group at *meta* position. Whereas, di-chloro substituted dianilide **5l** provided the desired product **3l** in relatively better yield. Compared to the other halogen group, the high electronegative nature of fluorine atom decreased the yield of the product **3m**. Strong electron withdrawing group like *p*-NO_2 and *p*-CF_3 substituted dianilides **5n** and **5o** failed to give the expected products **3n** and **3o** respectively. However, comparatively less electron withdrawing group *p*-$COCH_3$ containing dianilide **5p** provided the desired product **3p** in 20% yield. This investigation reveals that the electronic nature of the substituent on the aromatic ring plays a significant role in this transformation. To check the electronic nature of this protocol, a series of electron donating group containing dianilides were tested and it showed that dianilides having *p*-MeO, *p*-EtO, and 3,5-dimethoxy group **5q**, **5r** and **5s** worked better compared to electron withdrawing group containing dianilides and provided the expected products **3q**, **3r**, and **3s** respectively in 25-33 % yield. Non-symmetrical pyrazolidine-3,5-diones **3t**, and **3v** were obtained in a very good yield under the optimized reaction condition. Thus, our protocol could be easily applied in the synthesis of non-symmetrical oxybutazone analogue **3v**. Further usual transformations may lead to the synthesis of oxybutzone (Fig. 1). However, as expected dianilide **5u** with hydroxy substituent failed to furnish the desired product. Benzylic as well as aliphatic diamides **5w** and **5x** did not work under the optimized reaction condition. We reasoned that the anticipated intermediate amidyl radical might not be stable on the benzylic as well as aliphatic substrates. Overall, our protocol worked well with dianilides (scheme 4).

We also studied the effect of malonamide substituents on N–N bond forming reaction (Scheme 5). Unsubstituted malonamide, mono-alkyl substituted and di-methyl substituted malomides were prepared and subjected to the standard conditions for comparison with our cyclopropyl substituted malonamide **3a**. Unsubstituted and mono-alkyl substituted malonamide furnished the desired products **3y** and **2** only in trace amounts, but the dimethyl substituted malonamide could provide the cyclized product **3z** in moderate yield. The above trend clearly indicates that our choice of the cyclopropyl substituent is playing dual role. According to the Thorpe-Ingold effect it is exerting the necessary ring strain for facilitating the intramolecular cyclization over the other side reactions and it also serves as a handle for further functionalization.

Scheme 5. Effect of malonamide substituents on pyrazolidine-3,5-dione formation[a,b]

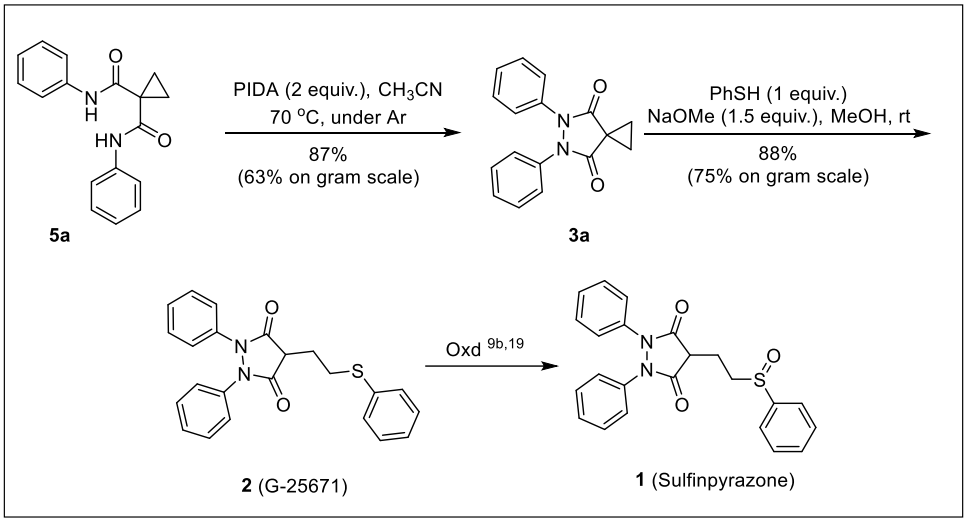


[a]Reaction conditions: **5y-z**, **11** (1 equiv., 50 mg), PIDA (2 equiv.) in acetonitrile (0.1 M), [b]Isolated yield, [c]Yield in the parentheses is based on the recovered starting material.

After complete investigation of the substrate scope of this transformation, we focused on the development of novel process for uricosuric agents G-25671 and sulfinpyrazone utilizing the functionalizable cyclopropyl moiety (Scheme 6). A gram scale reaction was performed using the optimized reaction condition to get the key intermediate **3a** in 63% yield (unoptimized). With this key intermediate **3a**, we proceeded to open the cyclopropane ring using thiophenol **4** as a nucleophile under various reaction conditions. Much to our delight, generation of thiophenolate

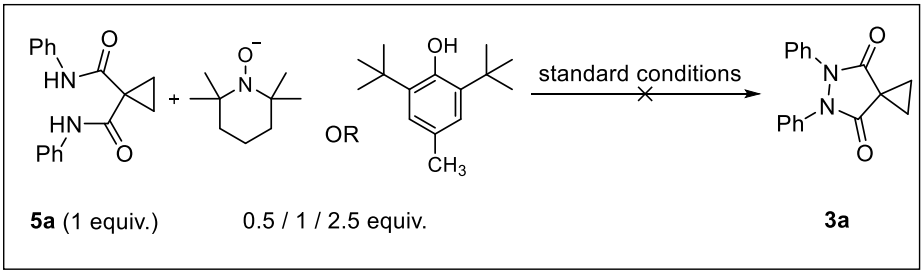
anion followed by the opening of cyclopropane ring using NaOMe in methanol afforded G-25671 (**2**) in 88% yield. The transformation of the G-25671 (**2**) to sulfinpyrazone is well documented in the literature, [9b, 19] thus we have completed a formal synthesis of sulfinpyrazone.

Scheme 6. Application of the Protocol to Sulfinpyrazone Class of Drugs



The mechanism of the developed protocol is not yet clear but probably it goes via either radical[l8,13,16] or nitrenium[11e,f] intermediate. However, based on the reactivity pattern of the electron neutral, electron withdrawing and donating dianilides, and aliphatic diamides, we believe that it follows a radical mechanism. Additionally, a complete inhibition of the reaction in the presence of 0.5-2.5 equiv. of BHT and TEMPO (Scheme 7) also indicates the involvement of highly unstable N-centred amidyl radicals like the reported electrochemical oxidation.[13] However, the involvement of nitrenium intermediate cannot be ruled out. A detailed study of the mechanism is warranted.

Scheme 7. Control Experiments



4.7. Conclusion:

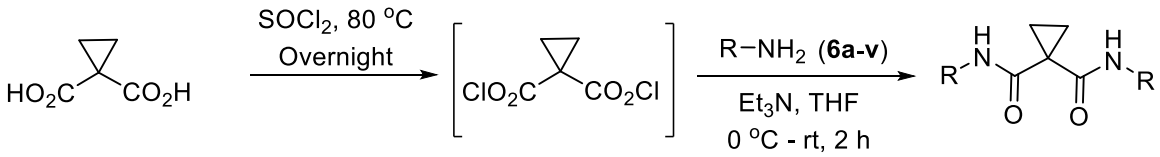
In summary, a new general greener protocol for the synthesis of pyrazolidine-3,5-diones is established by avoiding the use of highly carcinogenic and expensive diphenylhydrazines. The demonstrated method allows an easy access to structurally divers pyrazolidine-3,5-diones using oxidative dehydrogenative intramolecular N–N bond formation of easily accessible dianilides utilizing hypervalent iodine reagent PIDA. This transformation was further applied in the development of a novel process for uricosuric agents G-25671 and sulfinpyrazone in a good yield. The salient feature of this synthetic route to the sulfinpyrazone drug is its simplicity and high efficiency. The product **3a** could be a key intermediate for the synthesis of other phenylbutazone derivatives. The good substrate scope of the developed protocol may pave the way towards the synthesis of other potential congeners to study the structure-activity relationship.

4.8. Experimental Section

1. Experimental Procedures:

The substrate cyclopropane-1,1-dicarboxylic acid **7** was prepared using known literature procedure.[17] The dianildies **5y** and **5z** were prepared as per the literature procedure.[20]

I] General Experimental Procedure for the Synthesis of Dianilides 5a-s, 5w, 5x:



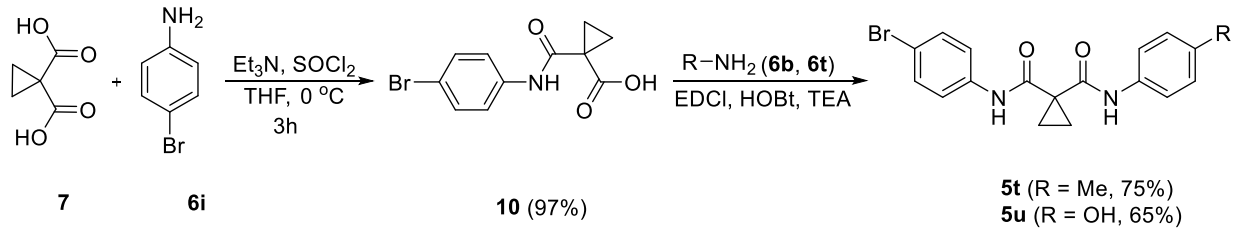
An oven dried two-neck round bottom flask was charged with cyclopropane-1,1-dicarboxylic acid **7** (1.54 mmol, 1 equiv.) and thionyl chloride (5 ml) under argon. After overnight stirring at

refluxing condition (90 °C), the excess of thionyl chloride was removed by distillation, yielding the dichloride **7'** as a yellow oil. The product was used in the next step without further purification.

To the solution of cyclopropane-1,1-dicarbonylchloride **7'** (1.54 mmol, 1 equiv.) in THF (10 ml), the solution of amines **6a-v** (3.85 mmol, 2.5 equiv.) and triethyl amine (4.62 mmol, 3 equiv.) in THF (5 ml) was added dropwise at 0 ^{o}C temperature with vigorous stirring. Combination of these two solutions caused the precipitation of triethylamine hydrochloride as a finely dispersed powder. After two hours stirring at room temperature, the reaction mixture was diluted with water (15 mL) and extracted with EtOAc (3 x 30 mL). The organic layer was separated and washed with brine solution once and dried over anhydrous Na_2SO_4. Evaporation of the solvent under vacuo to dryness followed by the purification of the crude product using column chromatography pet ether: ethyl acetate (4:1 to 1:4) provided the expected dianilides **5a-s, 5w, 5x** in very good yields.

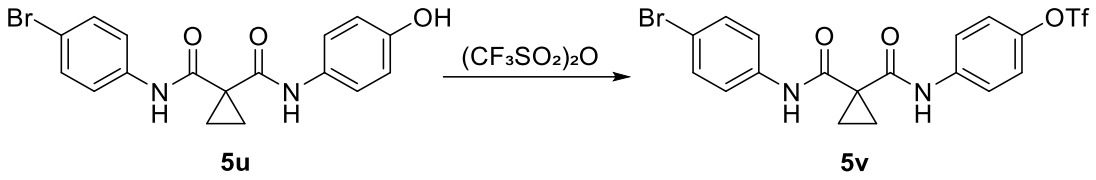
The dianilides **5a-d**, **5g**, **5i-k**, **5m**, **5o**, **5q-r**, **5w** were prepared by the same procedure and their structure was confirmed by comparing their characteristic data with the reported literature.[21]

Synthesis of Dianilides 5t-u:



The intermediate **10** was prepared by following the reported procedure and used for the next step directly.[22] Similarly, dianilides **5t** and **5u** were synthesized following the reported procedure by slightly modifying the coupling reagent.[13]

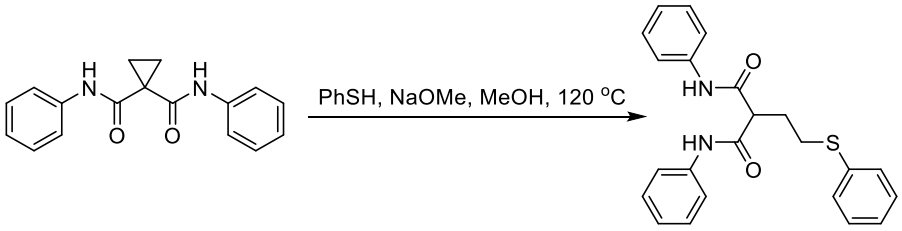
Synthesis of Dianilides 5v:



5u **5v**

Dianilide **5v** was synthesized by treatment of triflic anhydride with the danilide **5u** using known literature procedure.[13]

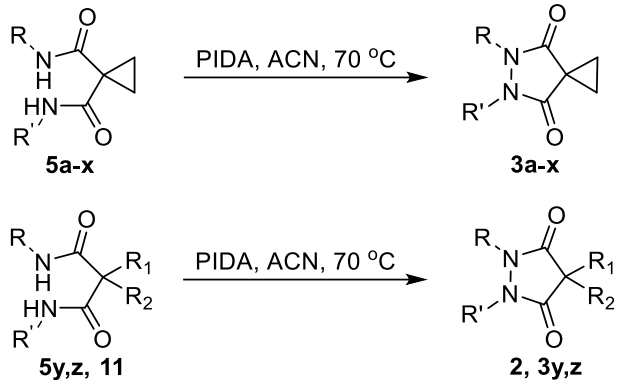
Experimental Procedure for the Synthesis of dianilide 11:



5a **11**

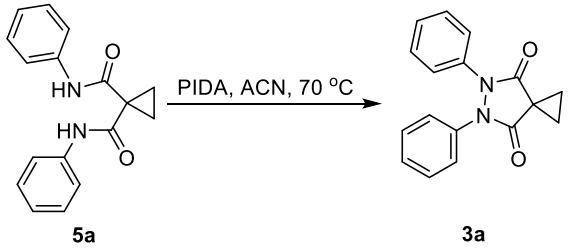
An oven dried pressure tube was charged with sodium methoxide (5.8 mg, 0.11 mmol, 1.5 equiv.) under argon atmosphere. Dry methanol (0.7 ml, 0.1 M) followed by the thiophenol (7.9 mg, 0.07 mmol, 1 equiv.) was added and the reaction mixture was kept for 30 min. at room temperature before adding the dianilide **5a** (20 mg, 0.07 mmol, 1 equiv.). After stirring the reaction mixture at 120 ^{o}C for the completion of the reaction (monitored by TLC, approx. 12h), the solvent was evaporated and the residue was mixed with water (5 ml) and EtOAc (5 ml). The aqueous part was extracted with EtOAc (3 x 5 ml) and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude mixture was purified by flash column chromatography using pet ether: ethyl acetate (4:1) to provide pure sulfide compound **11** in 81% (16.6 mg) yield as a colorless sticky solid.

II] General Experimental Procedure for the Preparation of Pyrazolidine-3,5-dione Derivatives 3a-z:



To an oven dried Schlenk tube containing dianilide **5a-z**, **11** (50 mg, 1 equiv.) and diacetoxyiodobenzene (2 equiv.) under argon was added dry acetonitrile (0.1 M). The reaction mixture was placed in a preheated oil bath at 70 °C and stirred for 16 hours. After completion of the reaction (TLC) it was cooled to room temperature and the solvent was evaporated on a rotatory evaporator. The residue was purified by flash silica gel column chromatography using a gradient of pet ether: ethyl acetate (4:1 to 3:2) to afford the corresponding pyrazolidine-3,5-dione derivatives **2**, **3a-z** in good to excellent yield.

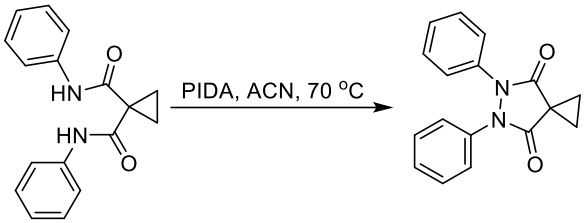
III] Typical Experimental Procedure for the Preparation of Representative Product 3a:



To an oven dried Schlenk tube containing dianilide **5a** (50 mg, 0.18 mmol, 1 equiv.) and diacetoxyiodobenzene (115 mg, 0.36 mmol, 2 equiv.) was added dry acetonitrile (1.8 ml, 0.1 M). The reaction mixture was placed on preheated oil bath at 70 °C and stirred for 16 hours. After completion of the reaction (TLC) it was cooled to room temperature and the solvent was

evaporated on a rotatory evaporator. The residue was purified by flash silica gel column chromatography using a gradient of pet ether: ethyl acetate (6:1) to afford the corresponding pyrazolidine-3,5-dione derivative **3a** as a white solid in 87% yield (43.2 mg) and in based on the recovery of starting material 92% yield.

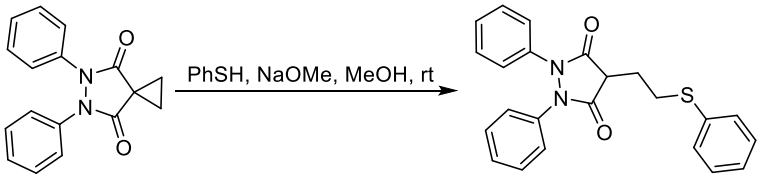
IV] Gram Scale Experimental Procedure for the Preparation of Representative Product 3a:



5a **3a**

To an oven dried Schlenk tube containing dianilide **5a** (1 gm, 3.6 mmol, 1 equiv.) and diacetoxyiodobenzene (2.3 g, 7.14 mmol, 2 equiv.) was added dry acetonitrile (36 ml, 0.1 M). The reaction mixture was placed on preheated oil bath at 70 °C and stirred for 24 hours. After completion of the reaction (TLC) it was cooled to room temperature and the solvent was evaporated on a rotatory evaporator. The residue was purified by flash silica gel column chromatography using a gradient of pet ether: ethyl acetate (6:1) to afford the corresponding pyrazolidine-3,5-dione derivative **3a** as a white solid in 63% yield (0.626 g) and in based on the recovery of starting material 67 % yield.

V] Synthesis of G-25671 (2):



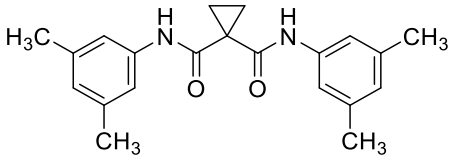
3a **2**

An oven dried two-neck round bottom flask was charged with sodium methoxide (14.6 mg, 0.27 mmol, 1.5 equiv.) under argon atmosphere. Dry methanol (1.8 ml, 0.1 M) followed by the

thiophenol (19.8 mg, 0.18 mmol, 1 equiv.) was added and the reaction mixture was kept for 30 min at room temperature before adding the key intermediate **3a** (50 mg, 0.18 mmol, 1 equiv.). After the completion of the reaction (monitored by TLC, approx. 2h), the solvent was evaporated and the residue was mixed with water (5 ml) and EtOAc (5 ml). The aqueous part was extracted with EtOAc (3 x 5 ml) and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude mixture was purified using flash column chromatography pet ether: ethyl acetate (4:1 to 1:1) to provide pure sulfide compound **2** in 88% (61.4 mg) as a colorless to solid.

2. Characterization Data of Compounds:

N,N'-bis(3,5-Dimethylphenyl)cyclopropane-1,1-dicarboxamide (5e)



5e

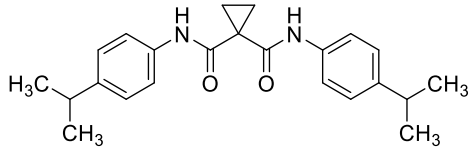
Reaction time: 2h; R*f*: 0.3 (1:4, EtOAc: Pet. ether); White solid; Mp = 185-187 ^oC; 485.9 mg, 94% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (brs, 2H), 7.16 (s, 4H), 6.79 (s, 2H), 2.31 (s, 12H), 1.61 (s, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 138.7, 137.1, 126.5, 118.4, 29.6, 21.3, 17.0.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{21}H_{25}N_2O_2$ 337.1911, found 337.1895.

***N,N'*-bis(4-*iso*Propylphenyl)cyclopropane-1,1-dicarboxamide (5f)**



5f

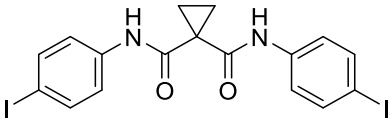
Reaction time: 2h; R*f*: 0.5 (1:4, EtOAc: Pet. ether); White solid; Mp = 130-132 ^oC; 520.8 mg, 93% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (brs, 2H), 7.42 (d, *J* = 8.5 Hz, 4H), 7.20 (d, *J* = 8.4 Hz, 4H), 2.89 (septet, *J* = 6.9 Hz, 2H), 1.61 (s, 4H), 1.25 (s, 6H), 1.23 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 145.6, 134.9, 126.9, 120.8, 33.6, 29.6, 24.0, 17.0.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{23}H_{29}O_2N_2$ 365.2224, found 365.2224.

N,N'-bis(4-Iodophenyl)cyclopropane-1,1-dicarboxamide (5h)



5h

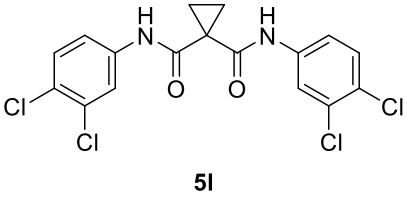
Reaction time: 2h; R*f*: 0.4 (2:3, EtOAc: Pet. ether); Brown solid; Mp = 195-197 ^oC; 703.9 mg, 86% yield.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.09 (brs, 2H), 7.63 (d, *J* = 8.8 Hz, 4H), 7.46 (d, *J* = 8.7 Hz, 4H), 1.43 (s, 4H).

^{13}C NMR (100 MHz, DMSO-d_6) δ 168.1, 138.8, 137.1, 122.5, 87.2, 32.1, 15.4.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{17}H_{15}O_2N_2I_2$ 532.9217, found 532.9210.

N,N'-bis(3,4-Dichlorophenyl)cyclopropane-1,1-dicarboxamide (5l)



5l

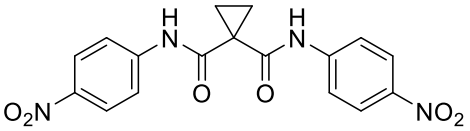
Reaction time: 2h; R*f*: 0.4 (2:3, EtOAc: Pet. ether); Yellowish solid; Mp = 213-215 ^oC; 531.2 mg, 83% yield.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.28 (brs, 2H), 8.11-7.95 (m, 2H), 7.56-7.54 (m, 4H), 1.44 (s, 4H).

^{13}C NMR (100 MHz, DMSO-d_6) δ 168.0, 139.2, 130.7, 130.4, 124.9, 121.5, 120.2, 32.4, 15.4.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{17}H_{13}O_2N_2Cl_4$ 416.9726, found 416.9723.

N,N'-bis(4-Nitrophenyl)cyclopropane-1,1-dicarboxamide (5n)



5n

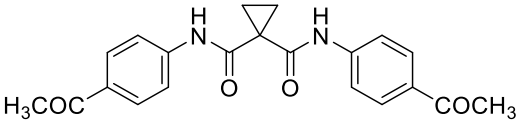
Reaction time: 2h; R*f*: 0.2 (3:2, EtOAc: Methanol); White solid; Mp = 265-267 ^{o}C. 296 mg, 52% yield.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.61 (brs, 2H), 8.27-8.16 (m, 4H), 7.92-7.86 (m, 4H), 1.51 (s, 4H).

^{13}C NMR (100 MHz, DMSO-d$_6$) δ 168.5, 145.4, 142.5, 124.8, 119.9, 33.1, 15.8.

HRMS (ESI-TOF) m/z: $[M-H]^-$calcd for $C_{17}H_{13}O_6N_4$ 369.0830, found 369.0846.

***N,N'*-bis(4-Acetylphenyl)cyclopropane-1,1-dicarboxamide (5p)**



5p

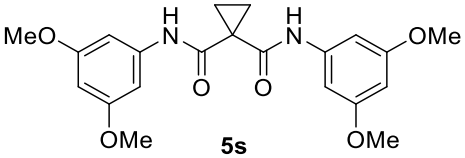
Reaction time: 2h; R*f*: 0.4 (4:1, EtOAc: Pet. ether); Yellow solid; Mp = 213-215 ^{o}C; 336 mg, 60% yield.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.32 (brs, 2H), 7.92 (d, *J* = 8.7 Hz, 4H), 7.78 (d, *J* = 8.8 Hz, 4H), 2.53 (s, 6H), 1.50 (s, 4H).

^{13}C NMR (100 MHz, DMSO-d$_6$) δ 196.6, 168.3, 143.4, 131.9, 129.2, 119.4, 32.5, 26.4, 15.6.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{21}H_{21}O_4N_2$ 365.1496, found 365.1494.

***N,N'*-bis(3,5-Dimethoxyphenyl)cyclopropane-1,1-dicarboxamide (5s)**



5s

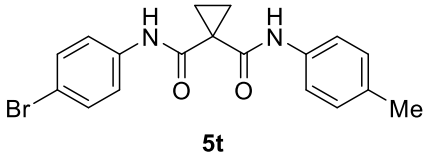
Reaction time: 2h; R*f*: 0.4 (3:7, EtOAc: Pet. ether); White solid; Mp = 195-197 ^{o}C; 480 mg, 78% yield.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.90 (brs, 2H), 6.91 (d, *J* = 2.1 Hz, 4H), 6.22 (t, *J* = 2.3 Hz, 2H), 3.70 (s, 12H), 1.43 (s, 4H).

^{13}C NMR (100 MHz, DMSO-d$_6$) δ 168.2, 160.3, 140.6, 98.6, 95.8, 55.1, 32.0, 15.3.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{21}H_{25}O_6N_2$ 401.1707, found 401.1704.

N-(4-Bromophenyl)-N-(p-tolyl)cyclopropane-1,1-dicarboxamide (5t)



5t

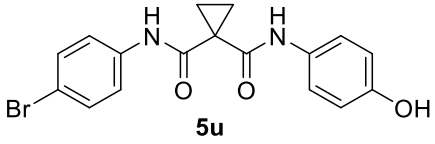
Reaction time: 15h; R*f*: 0.4 (1:4, EtOAc: Pet. ether); White solid; Mp = 220-222 ^oC; 73% yield over two steps from **7**.

^{1}H NMR (400 MHz, DMSO-d^6) δ 10.17 (brs, 1H), 9.88 (brs, 1H), 7.60 (d, *J* = 7.9 Hz, 2H), 7.46 (d. *J* = 7.9 Hz, 4H), 7.10 (d, *J* = 7.9 Hz, 2H), 2.25 (s, 3H), 1.45 (s, 4H).

^{13}C NMR (100 MHz, DMSO-d^6) δ 168.4, 167.9, 138.2, 136.2, 132.6, 131.3, 128.8, 122.3, 120.6, 115.2, 31.5, 20.4, 15.5.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{18}H_{18}BrN_2O_2$ 373.0546, found 373.0553.

N-(4-Bromophenyl)-N-(4-hydroxyphenyl)cyclopropane-1,1-dicarboxamide (5u)



5u

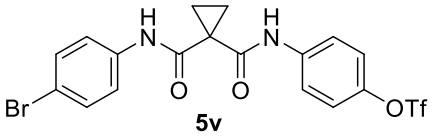
Reaction time: 15h; R*f*: 0.6 (1:19, MeOH: DCM); White solid; Mp = 162-164 ^oC; 63% yield over two steps.

^{1}H NMR (400 MHz, DMSO-d^6) δ 10.27 (brs, 1H), 9.66 (brs, 1H), 9.21 (brs, 1H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 7.9 Hz, 2H), 6.68 (d, *J* = 8.0 Hz, 2H), 1.44 (s, 4H).

^{13}C NMR (100 MHz, DMSO-d^6) δ 168.4, 167.8, 153.8, 138.2, 131.3, 130.1, 122.6, 122.2, 115.1, 114.8, 31.1, 15.5.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{17}H_{16}BrN_2O_3$ 375.0339, found 375.0333.

4-(1-((4-Bromophenyl)carbamoyl)cyclopropane-1-carboxamido)phenyl trifluoromethanesulfonate (**5v**)



5v

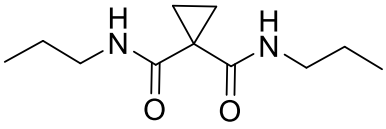
Reaction time: 12h; R*f*: 0.4 (1:4, EtOAc: Pet. ether); White solid; Mp = 135-137 ^{o}C; 60.8 mg, 90% yield.

^{1}H NMR (400 MHz, DMSO-d^{6}) δ 10.28, (brs, 1H), 10.10 (brs, 1H), 7.79 (d, *J* = 8.5 Hz, 2H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.56-7.36 (m, 4H), 1.45 (s, 4H).

^{13}C NMR (100 MHz, DMSO-d^{6}) δ 168.2, 167.9, 144.4, 139.4, 138.3, 131.3, 122.3, 121.8, 121.6, 118.3 (q, *J* = 320.4 Hz, CF_3), 115.2, 32.0, 15.4.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{18}H_{15}BrF_3N_2O_5S$ 506.9832, found 506.9832.

***N,N'*-Dipropylcyclopropane-1,1-dicarboxamide (5x)**



5x

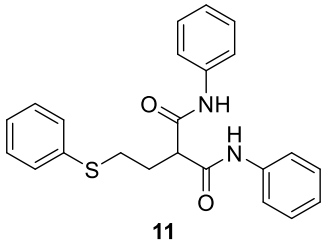
Reaction time: 2h; R*f*: 0.5 (2:3, EtOAc:Pet. ether); White solid; Mp = 48-50 ^{o}C; 254.4 mg, 78% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (brs, 2H), 3.25-3.17 (m, 4H), 1.58-1.48 (m, 4H), 1.35 (s, 4H), 0.92 (t, *J* = 7.4 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 41.5, 28.2, 22.6, 16.1, 11.4.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{11}H_{21}O_2N_2$ 213.1598, found 213.1600.

N^{1},N^{3}-Diphenyl-2-(2-(phenylthio)ethyl)malonamide (11)



11

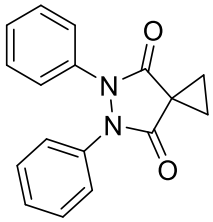
Reaction time: 12h; R*f*: 0.3 (1:4, EtOAc: Pet. ether); colorless sticky solid; 16.6 mg, 81% yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 9.07 (brs, 2H), 7.56 (d, *J* = 7.6 Hz, 4H), 7.36-7.31 (m, 6H), 7.23-7.13 (m, 5H), 3.74 (t, *J* = 7.5 Hz, 1H), 3.06 (t, *J* = 7.0 Hz, 2H), 2.39 (q, *J* = 7.1 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 137.2, 134.8, 129.9, 129.05, 129.01, 126.6, 124.9, 120.3, 54.7, 32.5, 31.7.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{23}H_{23}N_2O_2S$ 391.1475, found 391.1475.

5,6-Diphenyl-5,6-diazaspiro[2.4]heptane-4,7-dione (3a)



3a

Reaction time: 16h; R*f*: 0.5 (1:4, EtOAc: Pet. ether); White solid; Mp = 163-165 ^{o}C; 43.2 mg, 87% yield.

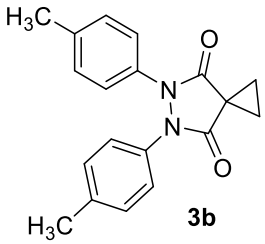
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.30 (m, 8H), 7.22-7.15 (m, 2H), 1.92 (s, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 136.4, 128.9, 126.5, 122.2, 26.9, 21.8.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{17}H_{15}O_2N_2$ 279.1128, found 279.1126.

5,6-Di-*p*-tolyl-5,6-diazaspiro[2.4]heptane-4,7-dione (3b)

Reaction time: 16h; R*f*: 0.6 (1:4, EtOAc: Pet. ether); White solid; Mp = 160-162 ^{o}C; 44.2 mg, 89% yield.



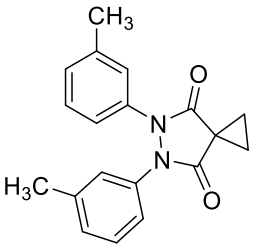
3b

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.4 Hz, 4H), 7.13 (d, *J* = 8.4 Hz, 4H), 2.29 (s, 6H), 1.89 (s, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 136.5, 133.8, 129.5, 122.6, 26.8, 21.5, 21.0.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{19}H_{19}O_2N_2$ 307.1441, found 307.1435.

5,6-di-*m*-Tolyl-5,6-diazaspiro[2.4]heptane-4,7-dione (3c)



3c

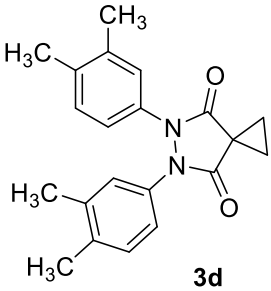
Reaction time: 16h; R*f*: 0.6 (1:4, EtOAc:Pet. ether); Thick oil; 23.3 mg, 47% yield (brsm-52%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (s, 2H), 7.20 (t, *J* = 7.8 Hz, 2H), 7.12 (d, *J* = 8.3 Hz, 2H), 6.99 (d, *J* = 7.5 Hz, 2H), 2.33 (s, 6H), 1.90 (s, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 138.9, 136.4, 128.7, 127.4, 123.3, 119.4, 26.9, 21.7, 21.4.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{19}H_{19}O_2N_2$ 307.1441, found 307.1438.

5,6-bis(3,4-Dimethylphenyl)-5,6-diazaspiro[2.4]heptane-4,7-dione (3d)



3d

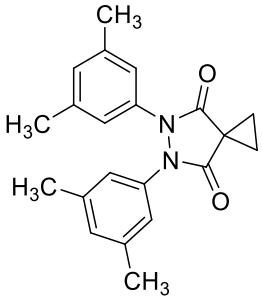
Reaction time: 16h; R*f*: 0.4 (1:4, EtOAc:Pet. ether); White solid; Mp = 127-129 ^{o}C; 35.3 mg, 71% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 1.3 Hz, 2H), 7.09-6.99 (m, 4H), 2.22 (s, 6H), 2.18 (s, 6H), 1.87 (s, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 137.3, 135.4, 134.1, 129.9, 124.3, 120.2, 26.8, 21.4, 19.9, 19.3.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{21}H_{23}O_2N_2$ 335.1754, found 335.1756.

5,6-bis(3,5-Dimethylphenyl)-5,6-diazaspiro[2.4]heptane-4,7-dione (3e)



3e

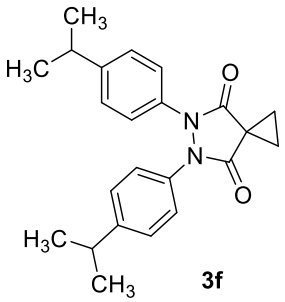
Reaction time: 16h; R*f*: 0.5 (1:4, EtOAc:Pet. ether); White Solid; Mp = 172-174 ^{o}C; 36.8 mg, 74% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (s, 4H), 6.82 (s, 2H), 2.27 (s, 12H), 1.87 (s, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 138.6, 136.4, 128.6, 120.5, 26.8, 21.5, 21.3.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{21}H_{23}O_2N_2$ 335.1754, found 335.1755.

5,6-bis(4-*iso*-Propylphenyl)-5,6-diazaspiro[2.4]heptane-4,7-dione (3f)



3f

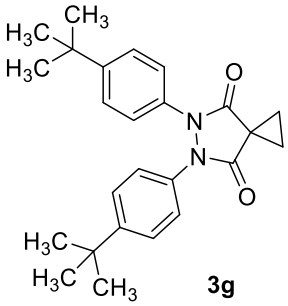
Reaction time: 16h; R*f*: 0.4 (1:4, EtOAc:Pet. ether); White solid; Mp = 80-82 ^oC; 34.8 mg, 70% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.5 Hz, 4H), 7.18 (d, *J* = 8.4 Hz, 4H), 2.86 (septate, *J* = 6.9 Hz, 2H), 1.89 (s, 4H), 1.21 (s, 6H), 1.19 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 147.2, 134.1, 126.9, 122.3, 33.6, 26.9, 23.8, 21.7.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{23}H_{27}O_2N_2$ 363.2067, found 363.2069.

5,6-bis(4-(*tert*-Butyl)phenyl)-5,6-diazaspiro[2.4]heptane-4,7-dione (3g)



3g

Reaction time: 16h; R*f*: 0.6 (1:4, EtOAc:Pet. ether); White solid; Mp = 145-147 ^oC; 41.3 mg, 83% yield.

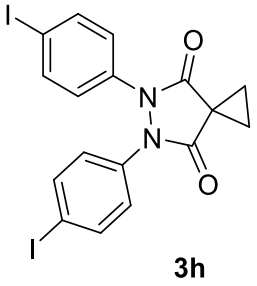
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.2 Hz, 4H), 7.30 (d, *J* = 8.5 Hz, 4H), 1.89 (s, 4H), 1.27 (s, 18H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 149.4, 133.9, 125.8, 121.8, 34.5, 31.2, 26.8, 21.7.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{25}H_{31}O_2N_2$ 391.2380, found 391.2385.

5,6-bis(4-Iodophenyl)-5,6-diazaspiro[2.4]heptane-4,7-dione (3h)

Reaction time: 16h; R*f*: 0.4 (1:4, EtOAc:Pet. ether); White solid; Mp = 207-209 ^oC; 47.8 mg, 96% yield.



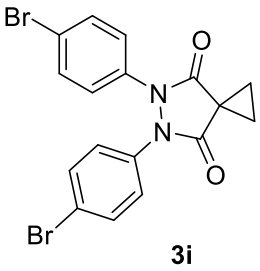
3h

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 8.9 Hz, 4H), 7.10 (d, J = 8.9 Hz, 4H), 1.94 (s, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 138.1, 136.0, 123.6, 91.1, 26.8, 22.4.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{17}H_{13}O_2N_2I_2$ 530.9061, found 530.9064.

5,6-bis(4-Bromophenyl)-5,6-diazaspiro[2.4]heptane-4,7-dione (3i)



3i

Reaction time: 16h; R*f*: 0.4 (1:4, EtOAc:Pet. ether); Brown solid; Mp = 183-185 ^{o}C; 43.8 mg, 88% yield.

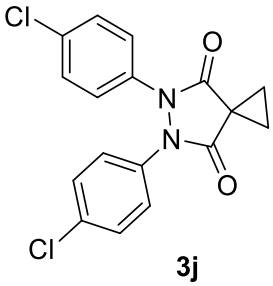
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.42 (m, 4H), 7.26-7.21 (m, 4H), 1.94 (s, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 135.3, 132.2, 123.5, 120.0, 26.8, 22.4.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{17}H_{13}O_2N_2{}^{79}Br_2$ 434.9338, found 434.9333.

5,6-bis(4-Chlorophenyl)-5,6-diazaspiro[2.4]heptane-4,7-dione (3j)

Reaction time: 16h; R*f*: 0.3 (1:4, EtOAc:Pet. ether); Yellow solid; Mp = 162-164 ^{o}C; 42.8 mg, 86% yield.



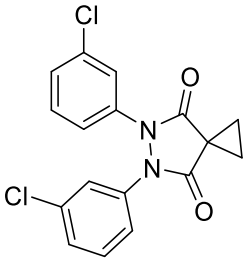
3j

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.19 (m, 8H), 1.94 (s, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 134.7, 132.2, 129.2, 123.2, 26.8, 22.3.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{17}H_{13}O_2N_2Cl_2$ 347.0349, found 347.0346.

5,6-bis(3-Chlorophenyl)-5,6-diazaspiro[2.4]heptane-4,7-dione (3k)



3k

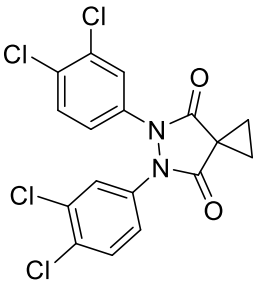
Reaction time: 16h; R*f*: 0.3 (1:4, EtOAc: Pet. ether); Thick oil; 27.8 mg, 56% yield (brsm-83%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (t, *J* = 1.9 Hz, 2H), 7.32-7.26 (m, 2H), 7.25-7.17 (m, 4H), 1.96 (s, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 137.5, 134.9, 130.1, 126.9, 122.1, 119.8, 26.8, 22.5.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{17}H_{13}O_2N_2Cl_2$ 347.0349, found 347.0348.

5,6-bis(3,4-Dichlorophenyl)-5,6-diazaspiro[2.4]heptane-4,7-dione (3l)



3l

Reaction time: 16h; R*f*: 0.3 (1:4, EtOAc:Pet. ether); White solid; Mp = 175-177 ^{o}C; 29.4 mg, 59% yield.

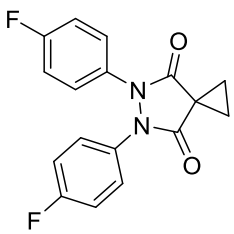
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 2.5 Hz, 2H), 7.43 (d, *J* = 8.6 Hz, 2H), 7.18 (dd, *J* = 8.8 & 2.5 Hz, 2H), 1.98 (s, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 135.5, 133.3, 130.8, 130.7, 123.6, 120.7, 26.7, 22.9.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{17}H_{11}O_2N_2Cl_4$ 414.9569, found 414.9562.

5,6-bis(4-Fluorophenyl)-5,6-diazaspiro[2.4]heptane-4,7-dione (3m)

Reaction time: 16h; R*f*: 0.4 (1:4, EtOAc:Pet. ether); White solid; Mp = 110-112 ^{o}C; 27.8 mg, 56% yield.



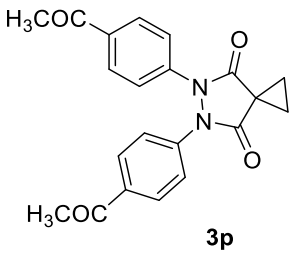
3m

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.29 (m, 4H), 7.09-7.00 (m, 4H), 1.93 (s, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 160.9 (d, J = 247.2 Hz), 132.1 (d, J = 3.1 Hz), 124.4 (d, J = 8.4 Hz), 116.0 (d, J = 22.9 Hz), 26.7, 22.0.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{17}H_{13}O_2N_2F_2$ 315.0940, found 315.0939.

5,6-bis(4-Acetylphenyl)-5,6-diazaspiro[2.4]heptane-4,7-dione (3p)



3p

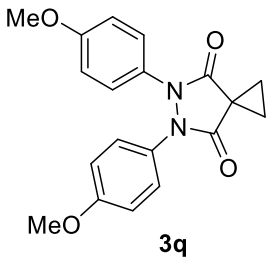
Reaction time: 16h; R*f*: 0.4 (2:3, EtOAc: Pet. ether); Thick oil; 19.9 mg (100 mg scale), 20% yield (brsm-29%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00-7.90 (m, 4H), 7.55-7.39 (m, 4H), 2.56 (s, 6H), 2.0 (s, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 196.6, 170.9, 140.2, 134.8, 129.4, 121.1, 27.0, 26.5, 22.8.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{21}H_{19}O_4N_2$ 363.1339, found 363.1341.

5,6-bis(4-Methoxyphenyl)-5,6-diazaspiro[2.4]heptane-4,7-dione (3q)



3q

Reaction time: 16h; R*f*: 0.4 (1:1, EtOAc: Pet. ether); White solid; Mp = 185-187 ^{o}C; 32.8 mg (100 mg scale), 33% yield.

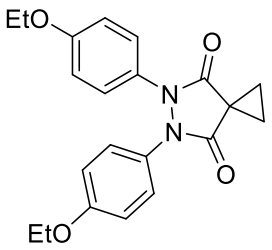
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 9.0 Hz, 4H), 6.84 (d, J = 9.0 Hz, 4H), 3.76 (s, 6H), 1.89 (s, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 158.3, 128.9, 125.2, 114.2, 55.4, 26.8, 21.3.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{19}H_{19}O_4N_2$ 339.1339, found 339.1344.

5,6-Bis(4-Ethoxyphenyl)-5,6-diazaspiro[2.4]heptane-4,7-dione (3r)

Reaction time: 16h; R*f*: 0.3 (1:9, Acetone:Pet. ether); Brown solid; Mp = 158-160 ^{o}C; 28.8 mg (100 mg scale), 29% yield (brsm-35%).



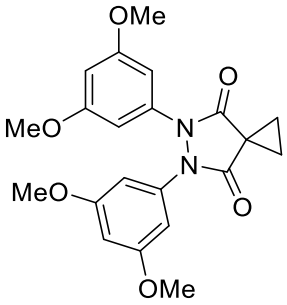
3r

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.20 (m, 4H), 6.85-6.79 (m, 4H), 3.97 (q, *J* = 7.0 Hz, 4H), 1.88 (s, 4H), 1.38 (t, *J* = 6.9 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 157.8, 128.7, 125.3, 114.7, 63.6, 26.8, 21.2, 14.7.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{21}H_{23}O_4N_2$ 367.1652, found 367.1647.

5,6-bis(3,5-Dimethoxyphenyl)-5,6-diazaspiro[2.4]heptane-4,7-dione (3s)



3s

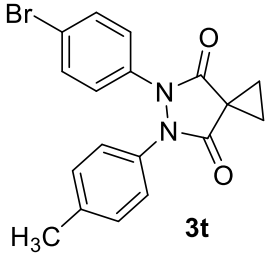
Reaction time: 16h; R*f*: 0.4 (2:3, EtOAc:Pet. ether); White solid; Mp = 173-175 ^{o}C; 24.9 mg (100 mg scale), 25% yield (brsm-30%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.57 (d, *J* = 2.3 Hz, 4H), 6.30 (t, *J* = 2.2 Hz, 2H), 3.73 (s, 12H), 1.90 (s, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 160.9, 138.3, 100.8, 98.8, 55.5, 27.0, 22.0.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{21}H_{23}O_6N_2$ 399.1551, found 399.1555.

5-(4-Bromophenyl)-6-(p-tolyl)-5,6-diazaspiro[2.4]heptane-4,7-dione (**3t**)



3t

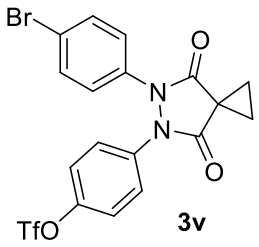
Reaction time: 16h; R*f*: 0.5 (1:4, EtOAc: Pet. ether); White solid; Mp = 140-142 ^{o}C; 35.8 mg, 72% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.5 Hz, 2H), 7.36-7.06 (m, 6H), 2.31 (s, 3H), 1.92 (s, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 171.0, 136.8, 135.3, 133.8, 132.0, 129.7, 123.7, 122.4, 119.7, 26.8, 21.9, 21.0.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{18}H_{16}BrN_2O_2$, 371.0390 found 371.0392.

4-(6-(4-Bromophenyl)-4,7-dioxo-5,6-diazaspiro[2.4]heptan-5-yl)phenyl trifluoromethanesulfonate (**3v**)



3v

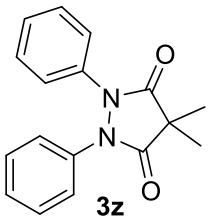
Reaction time: 16h; R*f*: 0.6 (1:4, EtOAc: Pet. ether); Yellowish sticky solid; 35.3 mg, 71% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.41 (m, 4H), 7.35-7.09 (m, 4H), 1.96 (s, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 171.1, 146.9, 136.1, 135.4, 132.3, 123.3, 123.0, 122.1, 120.2, 118.6 (q, J = 321.2 Hz, CF_3), 26.8, 22.7.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{18}H_{13}BrF_3N_2O_5S$ 504.9675, found 504.9693.

4,4-dimethyl-1,2-diphenylpyrazolidine-3,5-dione (3z)[23]



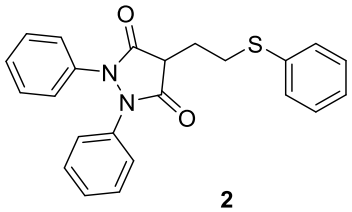
3z

Reaction time: 16h; R*f*: 0.4 (1:4, EtOAc: Pet. ether); colorless sticky solid; 9.5 mg (20 mg scale), 48% yield (brsm-72%).

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.37-7.30 (m, 8H), 7.23-7.16 (m, 2H), 1.52 (s, 6H).

GC-MS m/z: $[M]^+$calcd for $C_{17}H_{16}N_2O_2$ 280.3, found 280.3.

1,2-Diphenyl-4-(2-(phenylthio)ethyl)pyrazolidine-3,5-dione (2)[24]



2

Reaction time: 1h; R*f*: 0.6 (3:7, EtOAc:Pet. ether); White solid; Mp = 100-102 ^{o}C (lit.[20] Mp = 110-113 ^{o}C); 61.4 mg (50 mg scale), 88% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.23 (m, 12H), 7.23-7.11 (m, 3H), 3.64 (t, *J* = 6.3 Hz, 1H), 3.22 (t, *J* = 7.1 Hz, 2H), 2.37 (q, *J* = 6.7 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 135.7, 134.7, 129.9, 129.0, 128.9, 126.8, 126.5, 122.6, 44.4, 30.3, 27.0.

HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{23}H_{21}O_2N_2S$ 389.1318, found 389.1315.

4.9. References:

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4.10. Copies of ^{1}H NMR and ^{13}C NMR Spectra:

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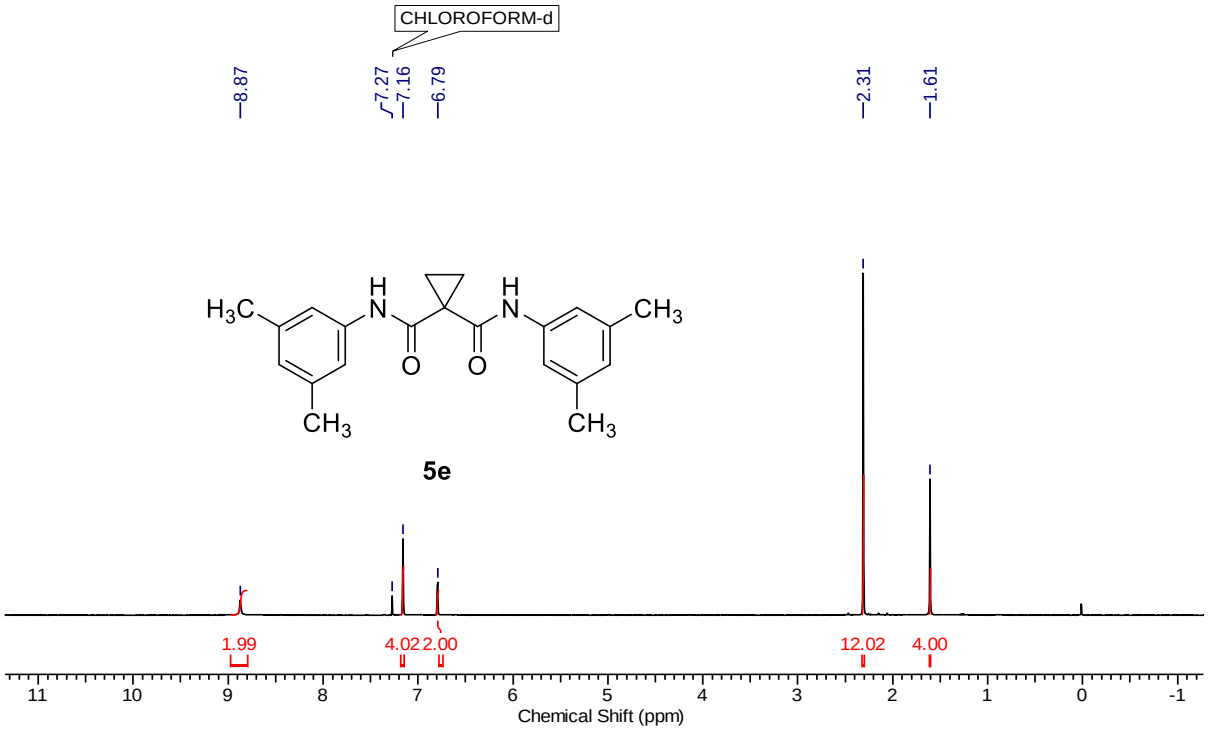

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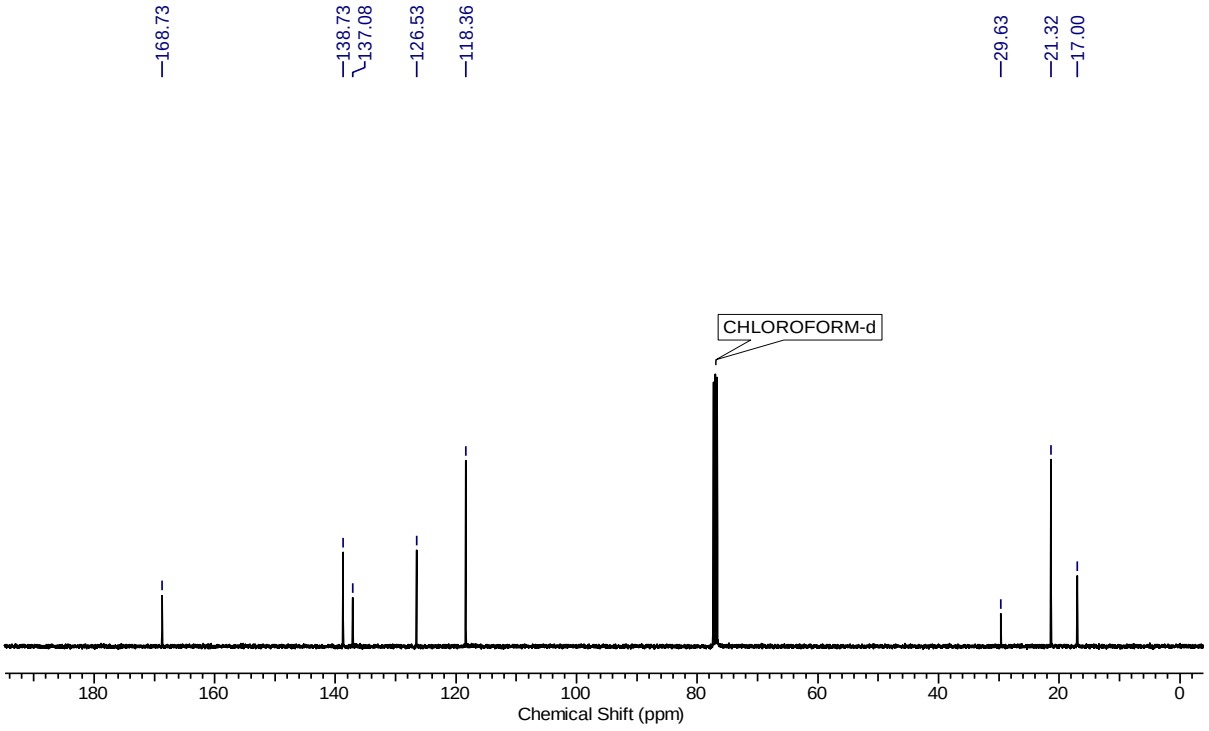

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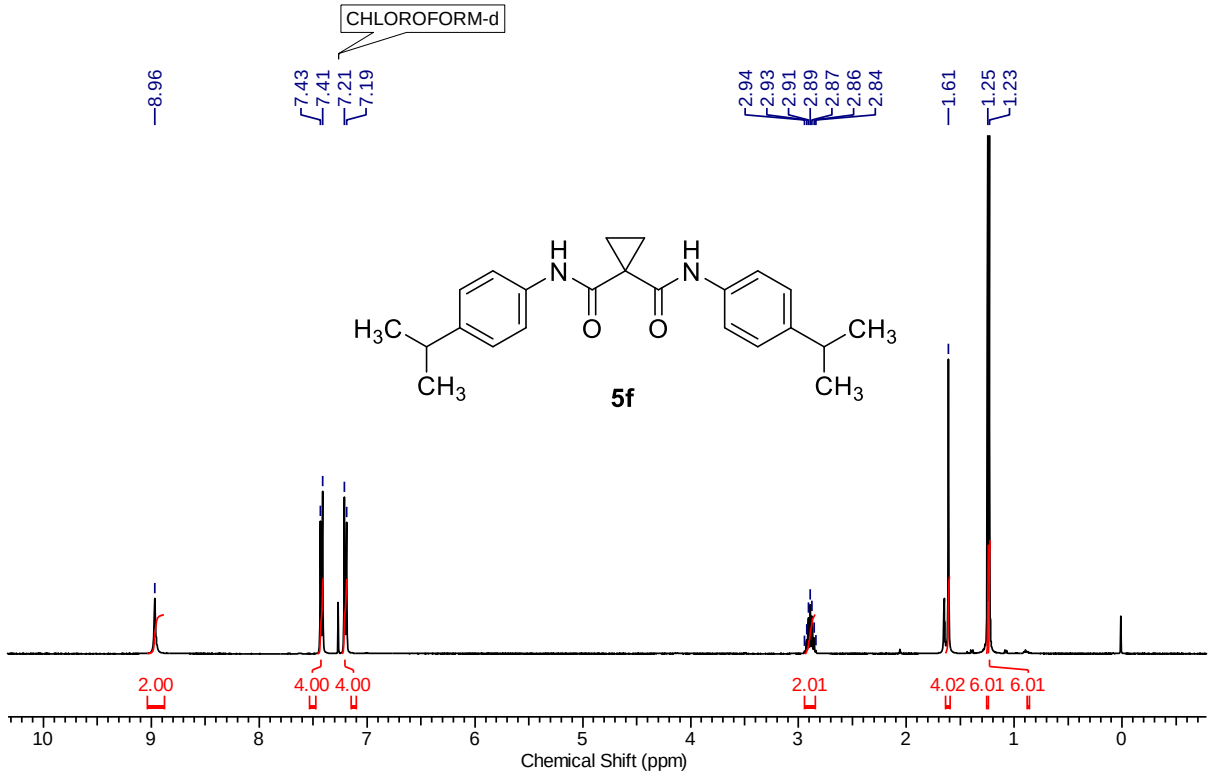

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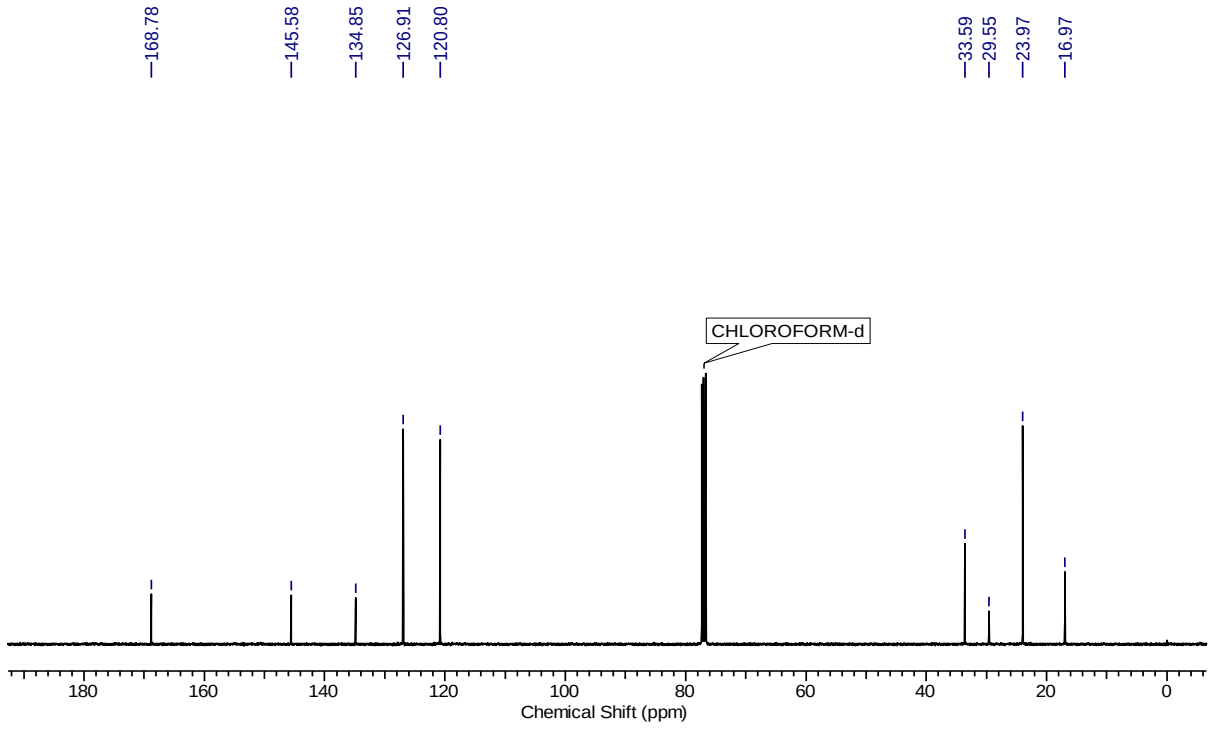

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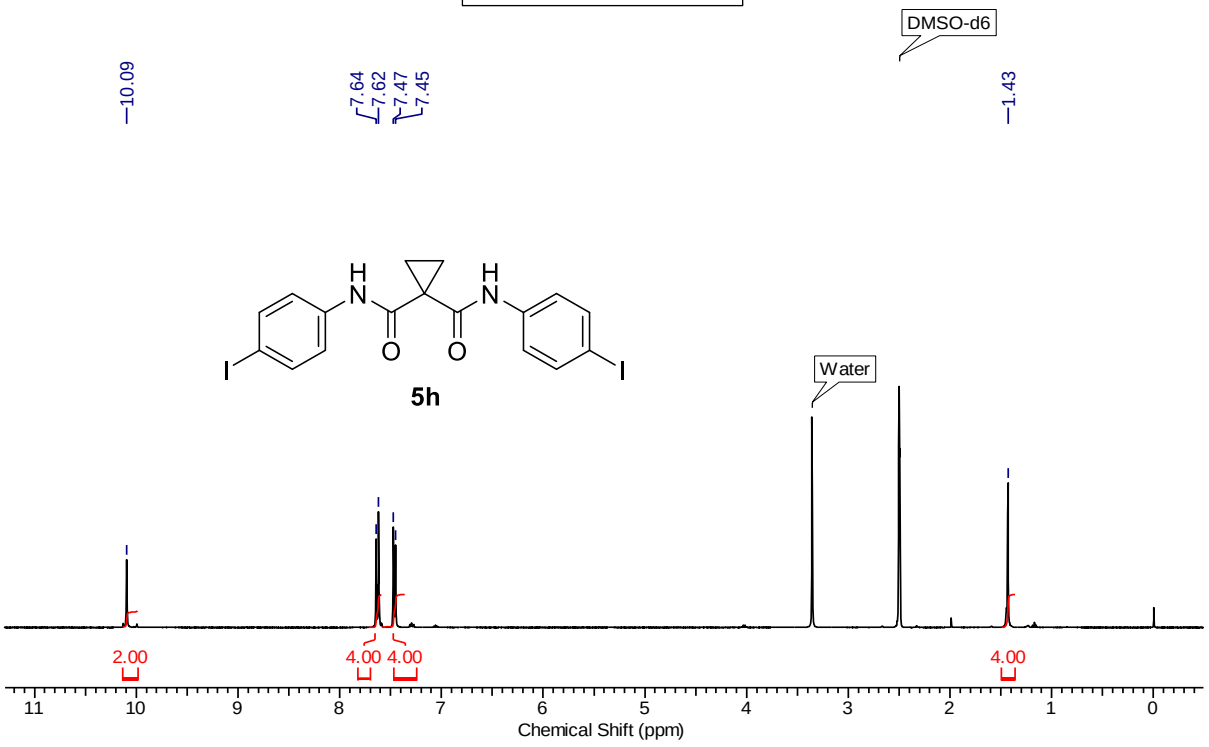

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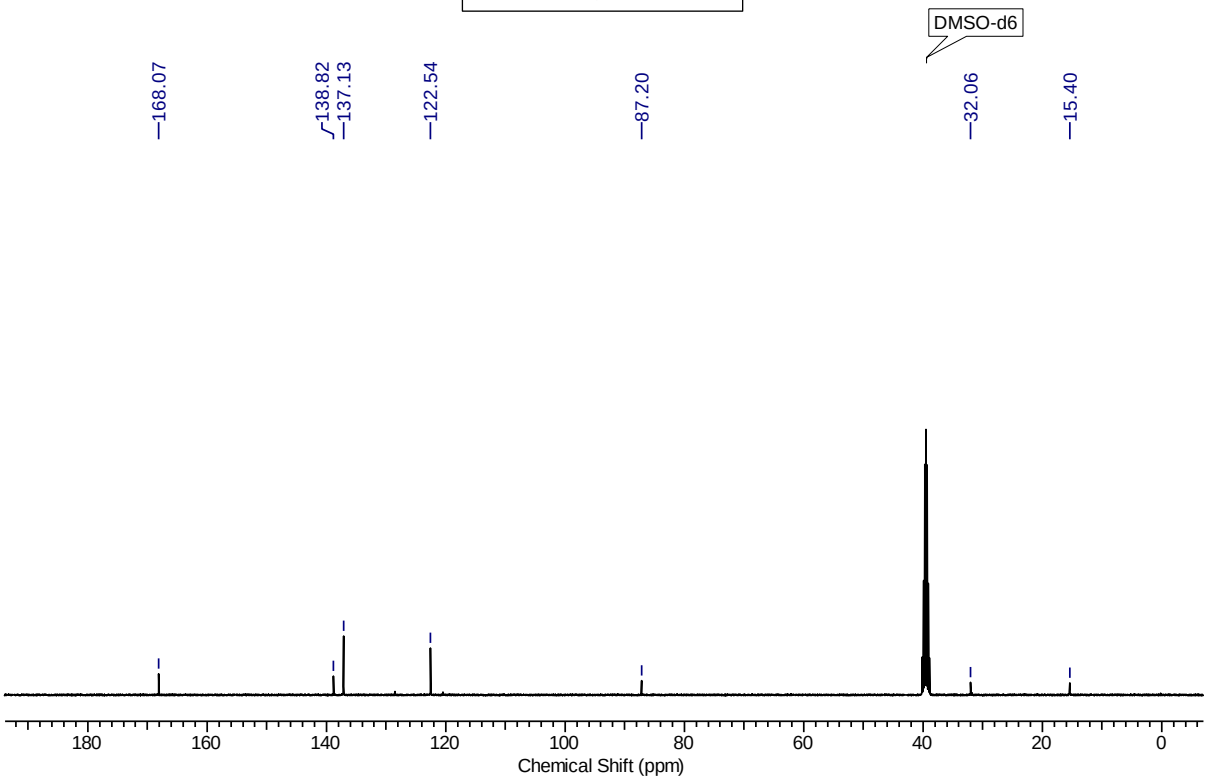

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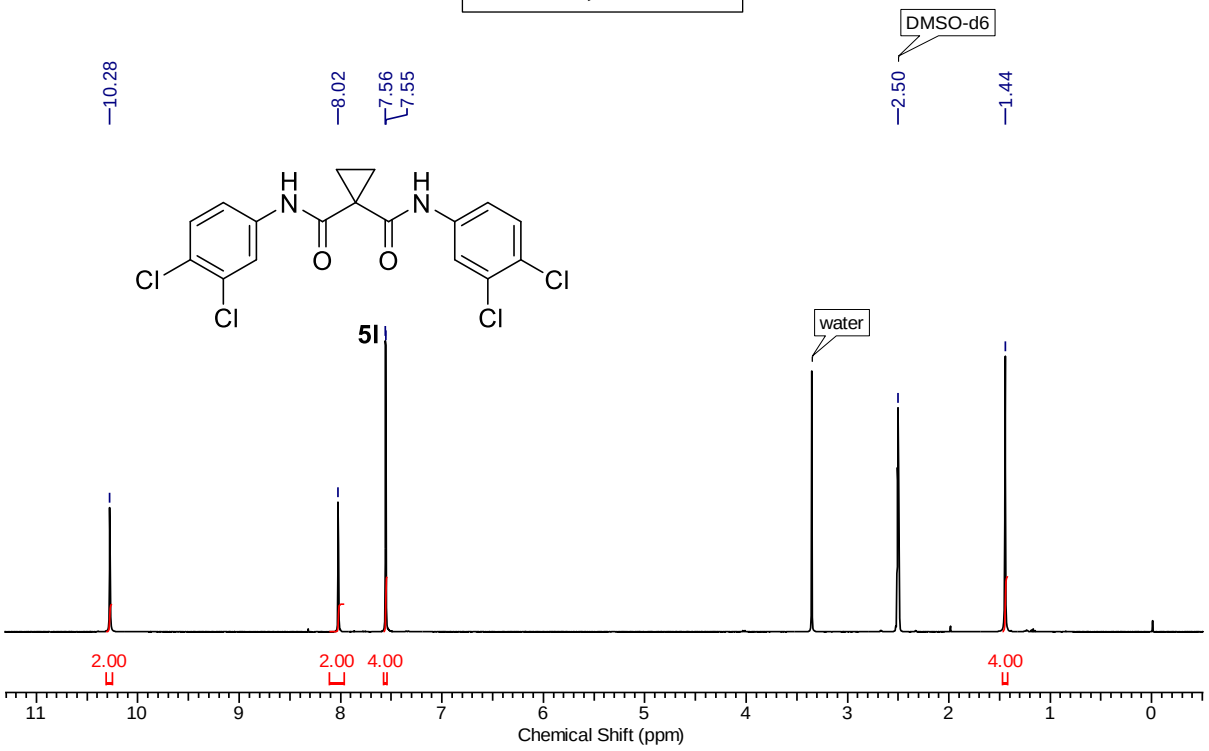

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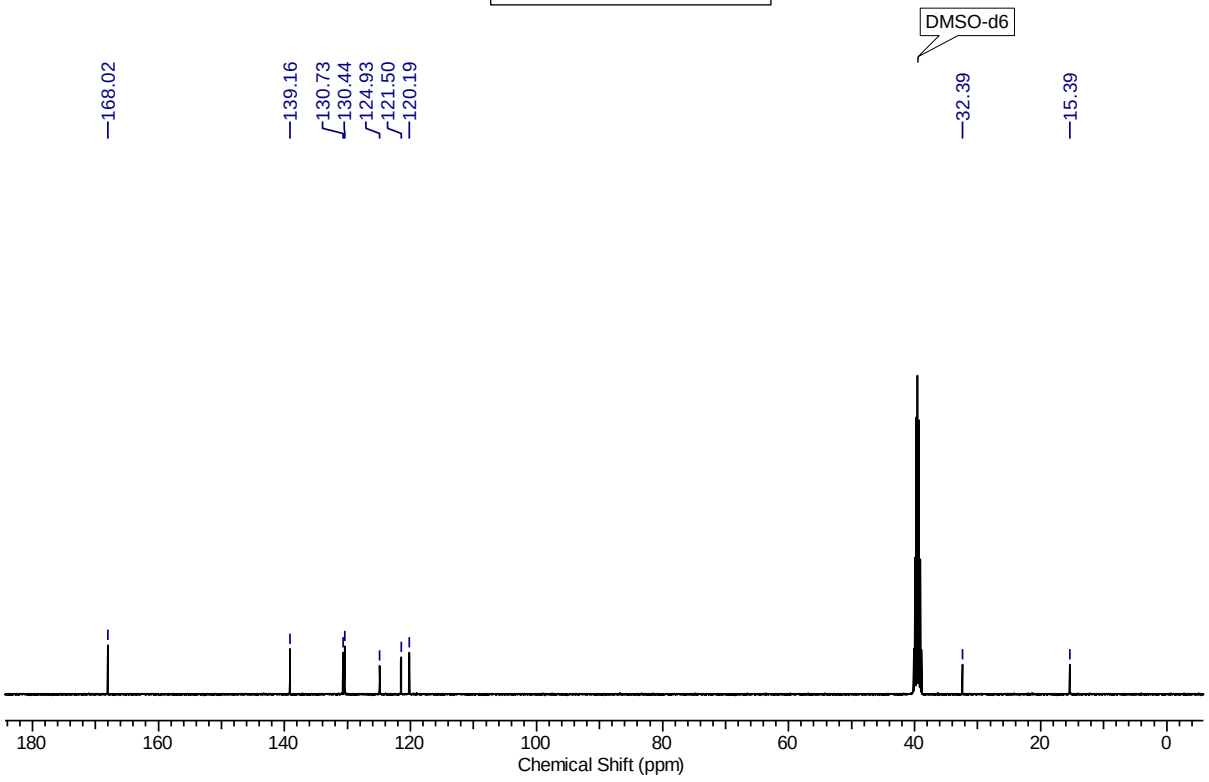

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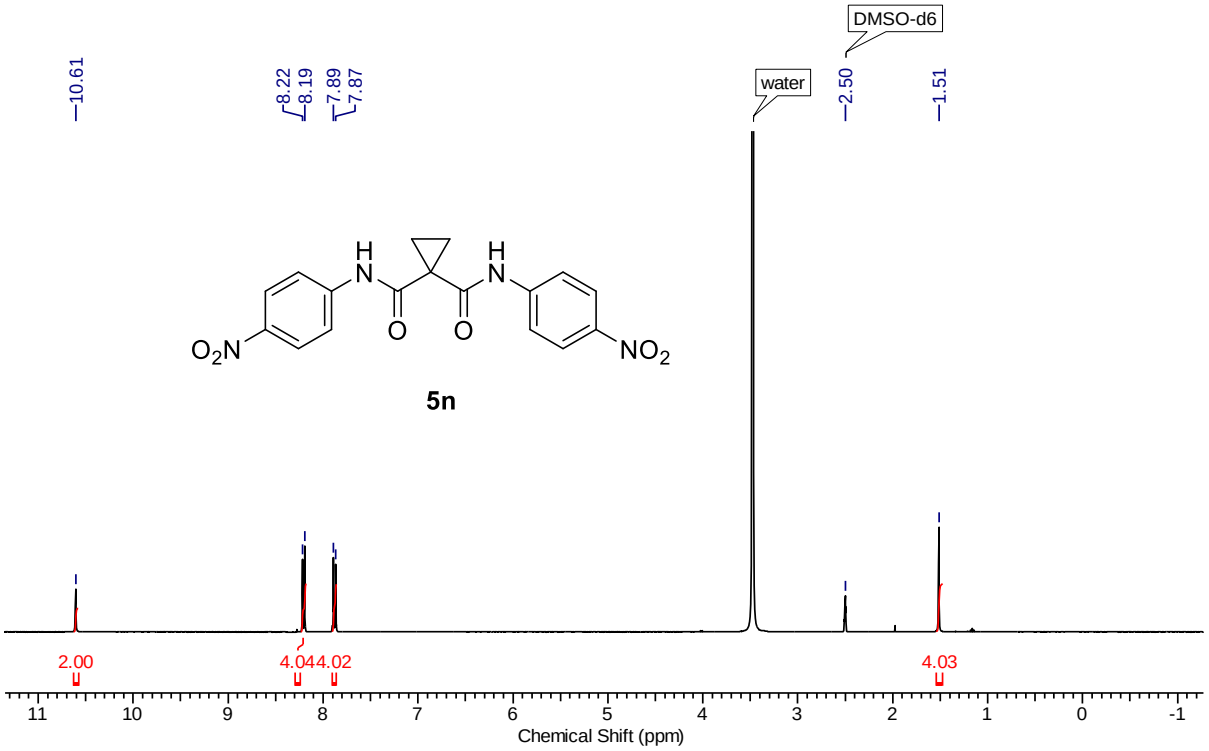

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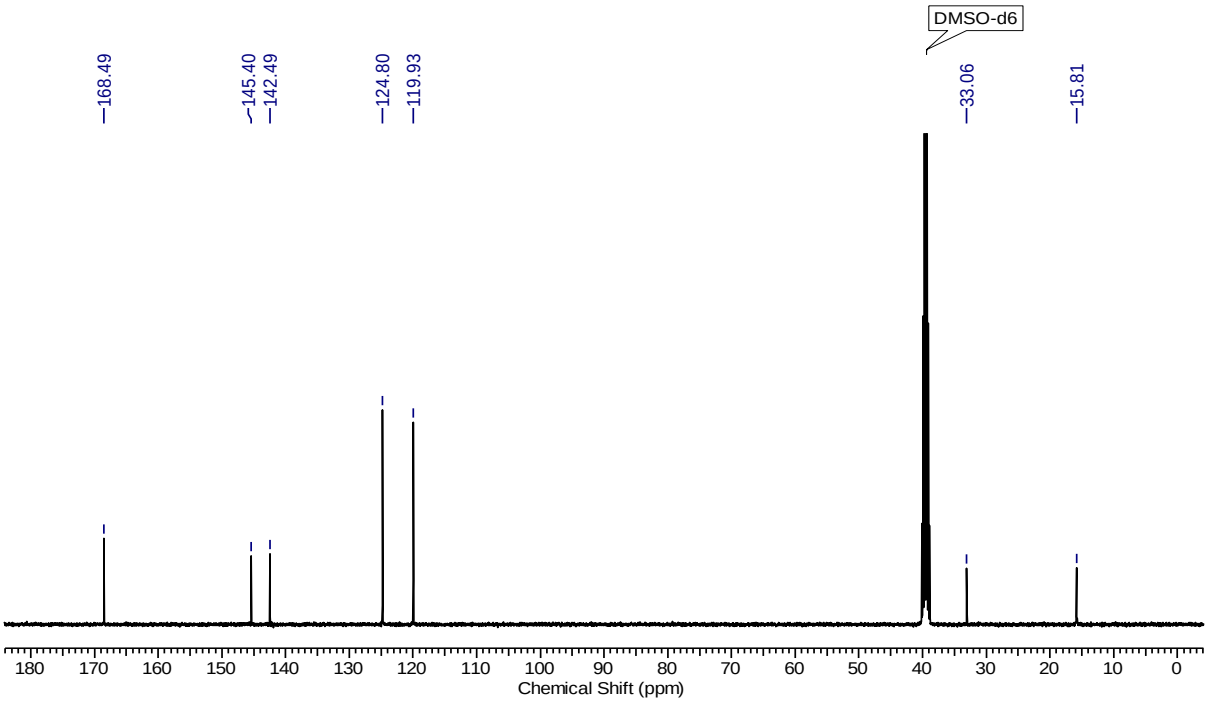

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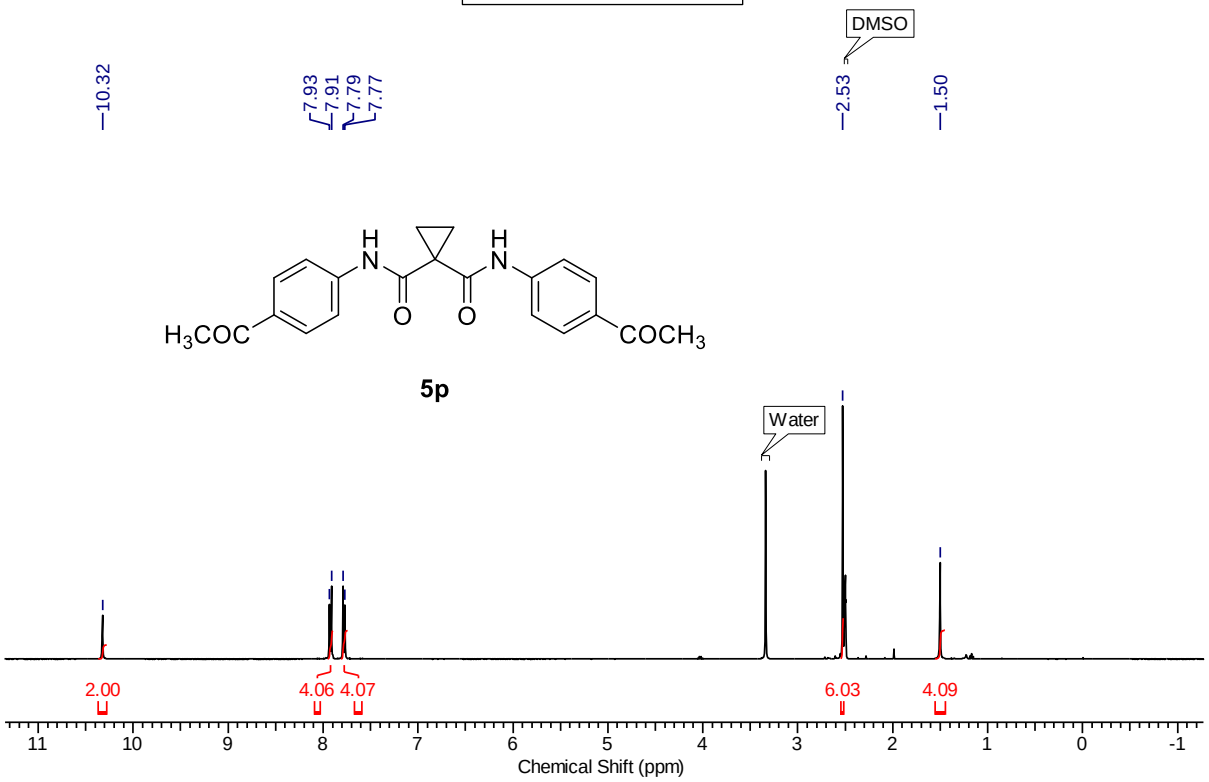

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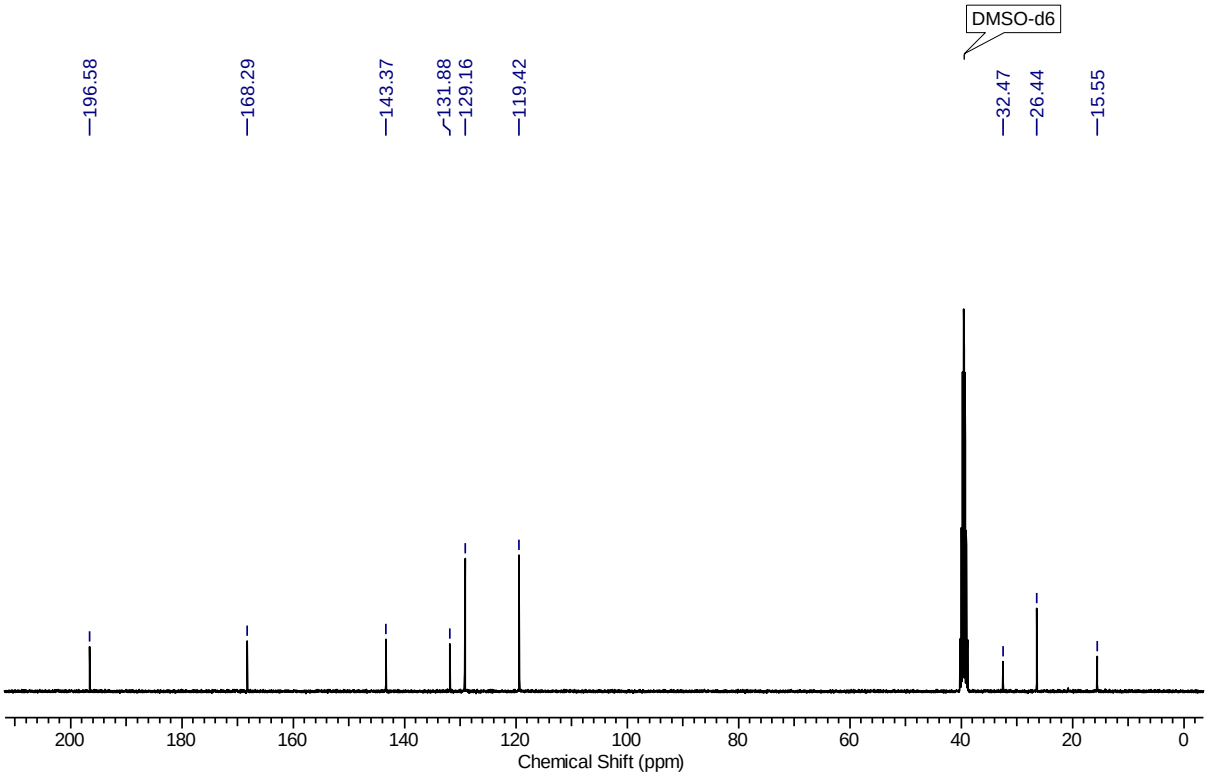

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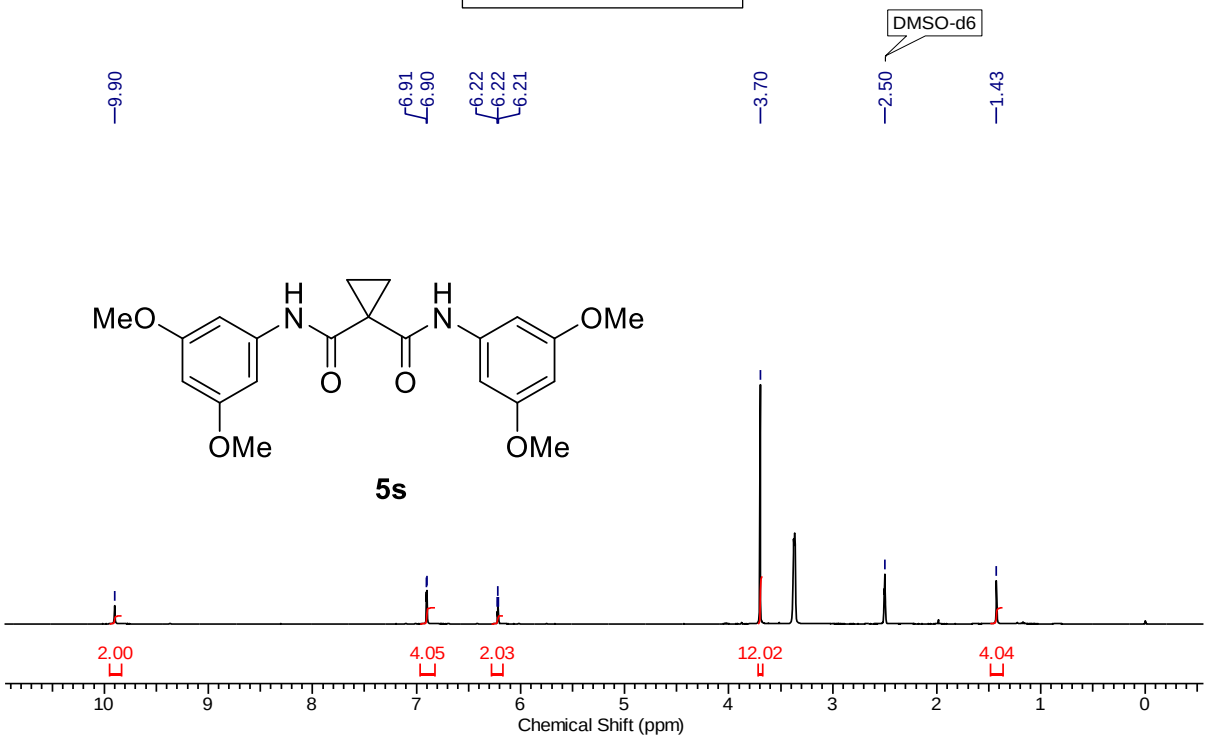

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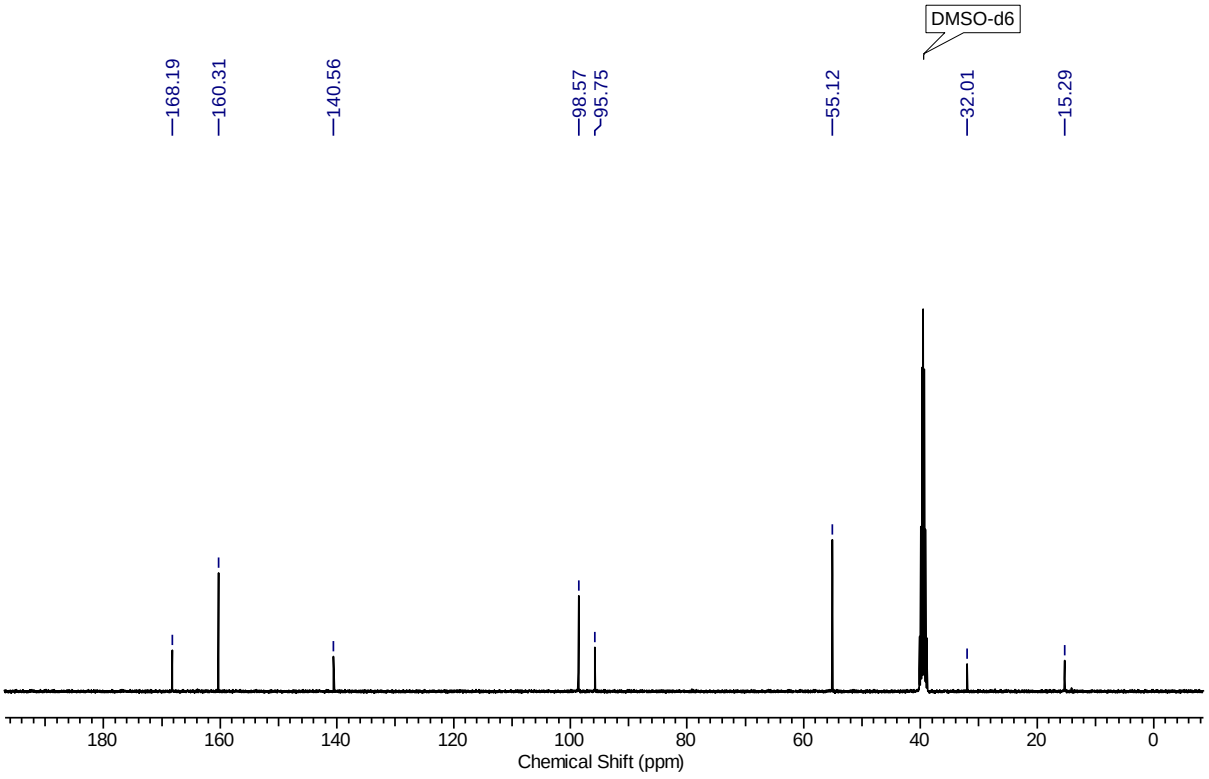

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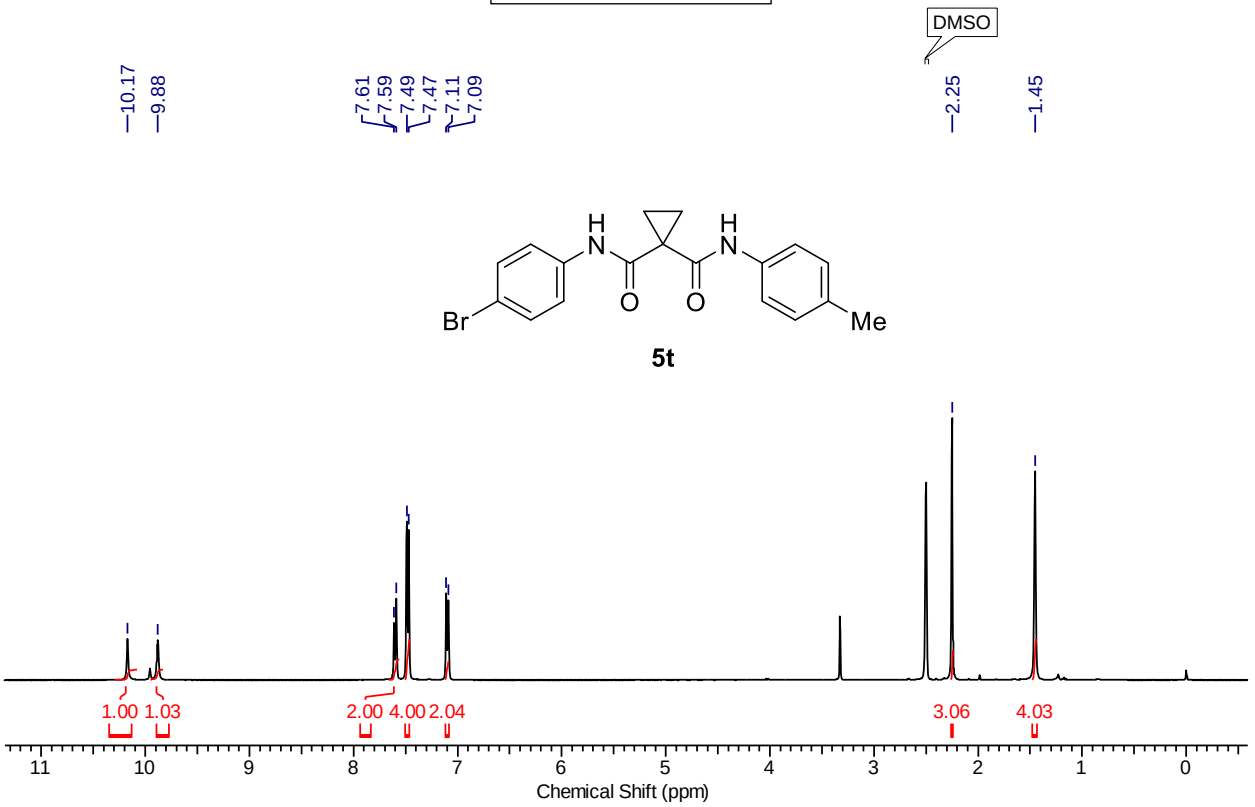

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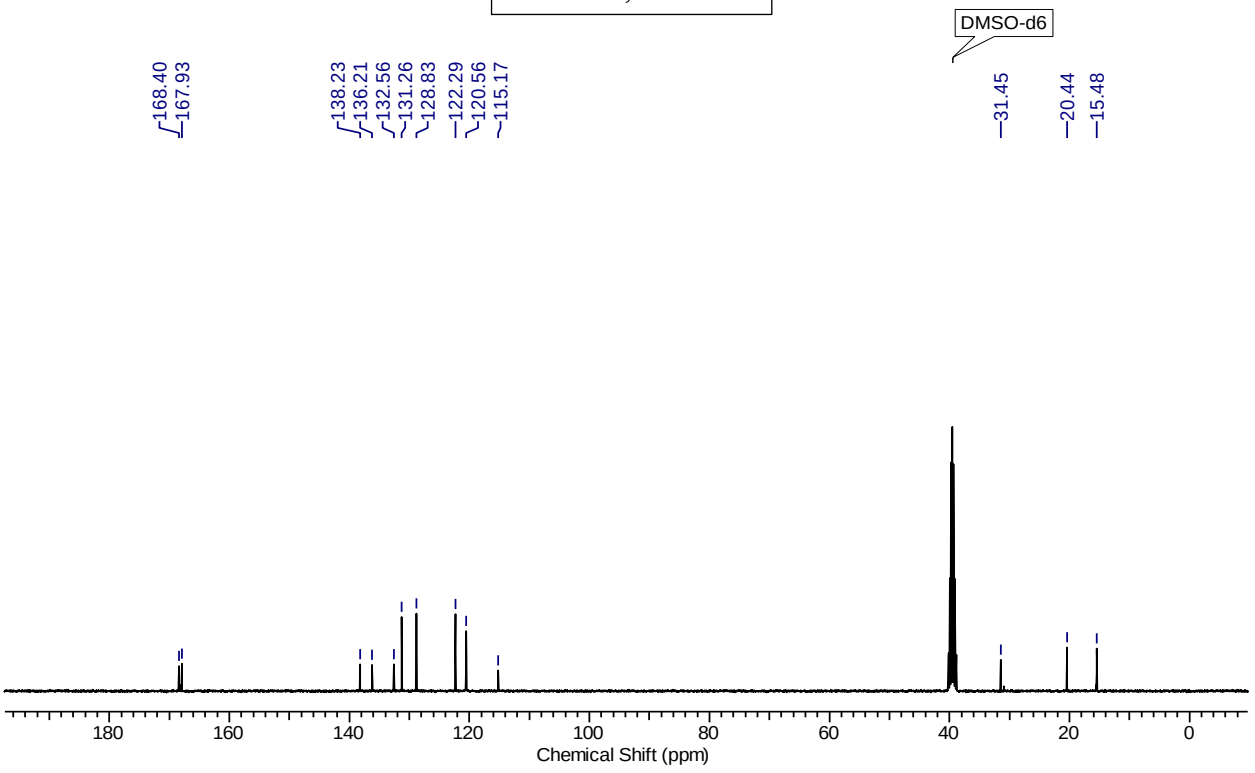

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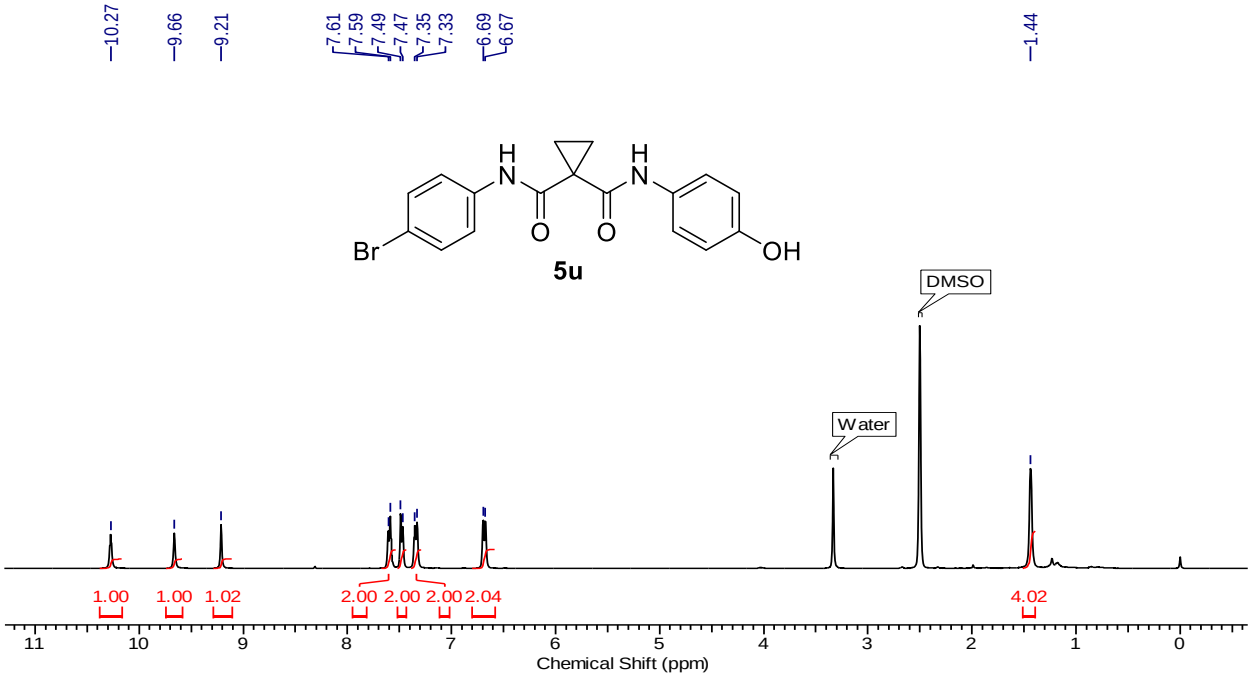

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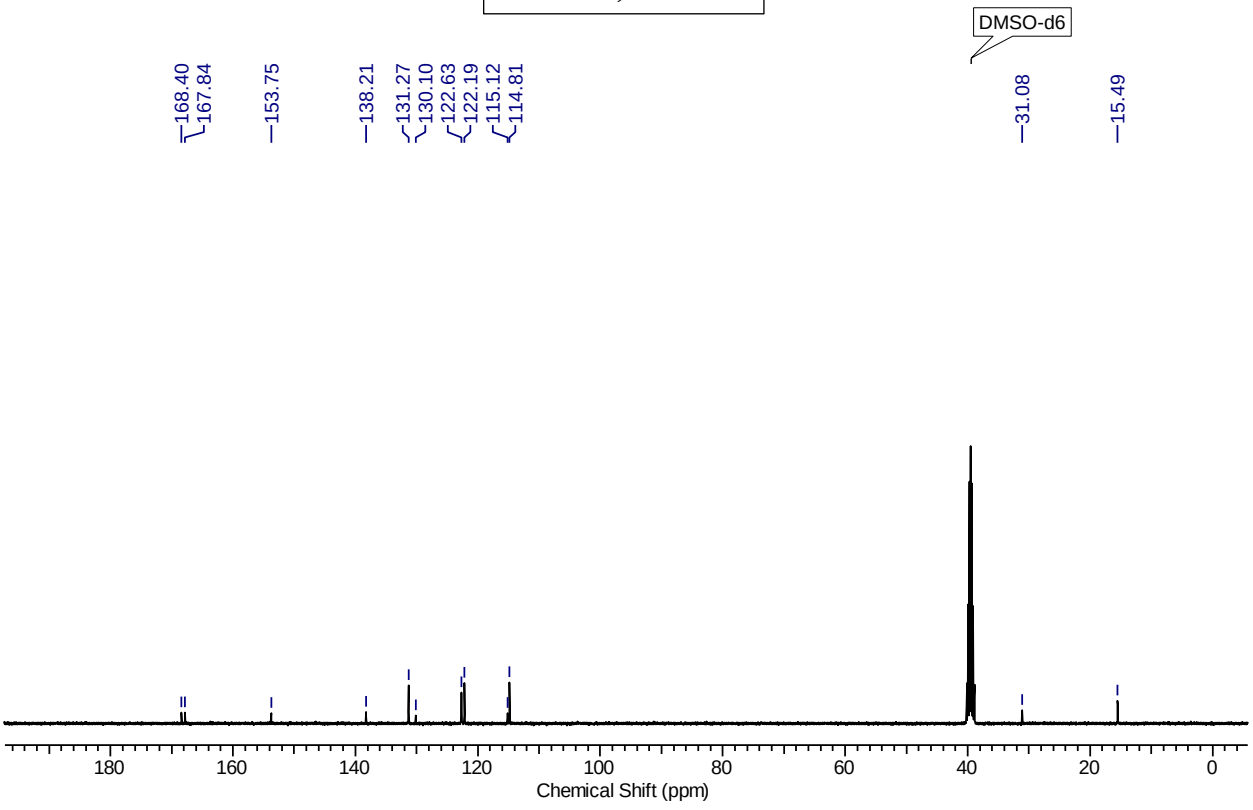

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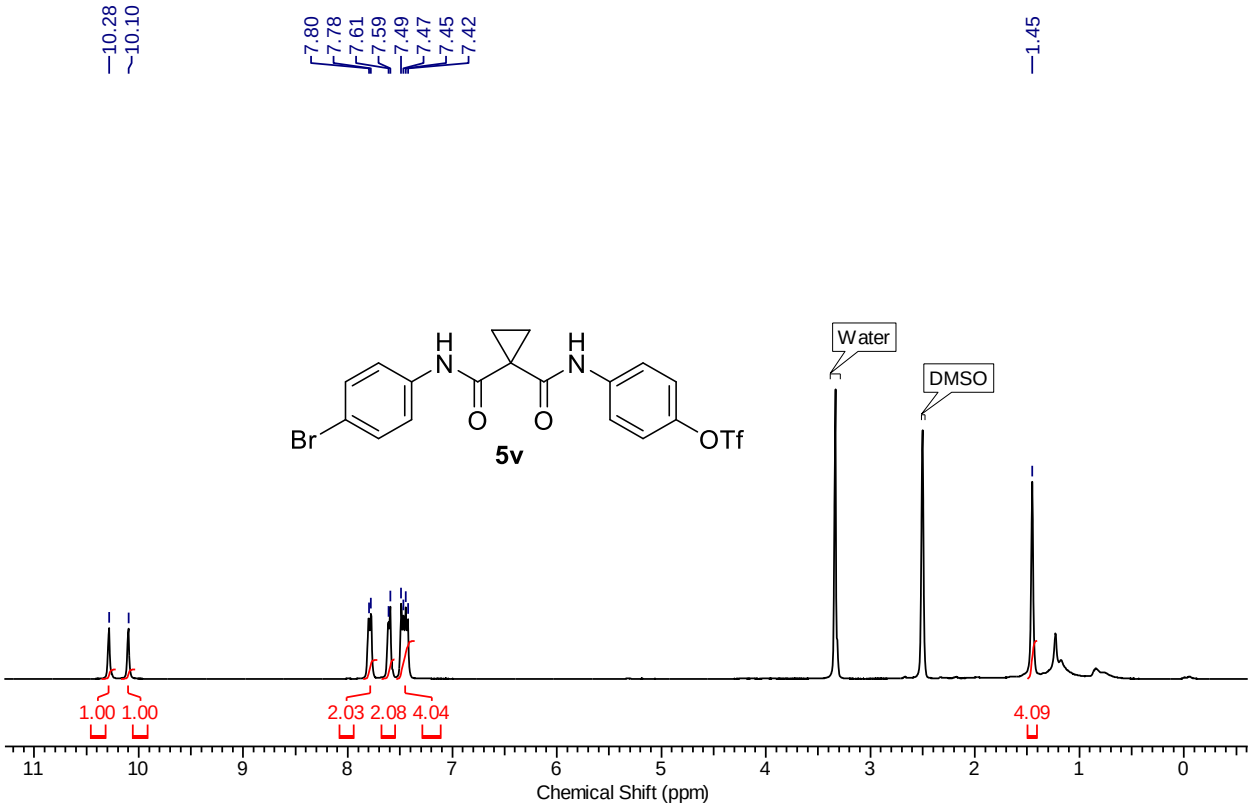

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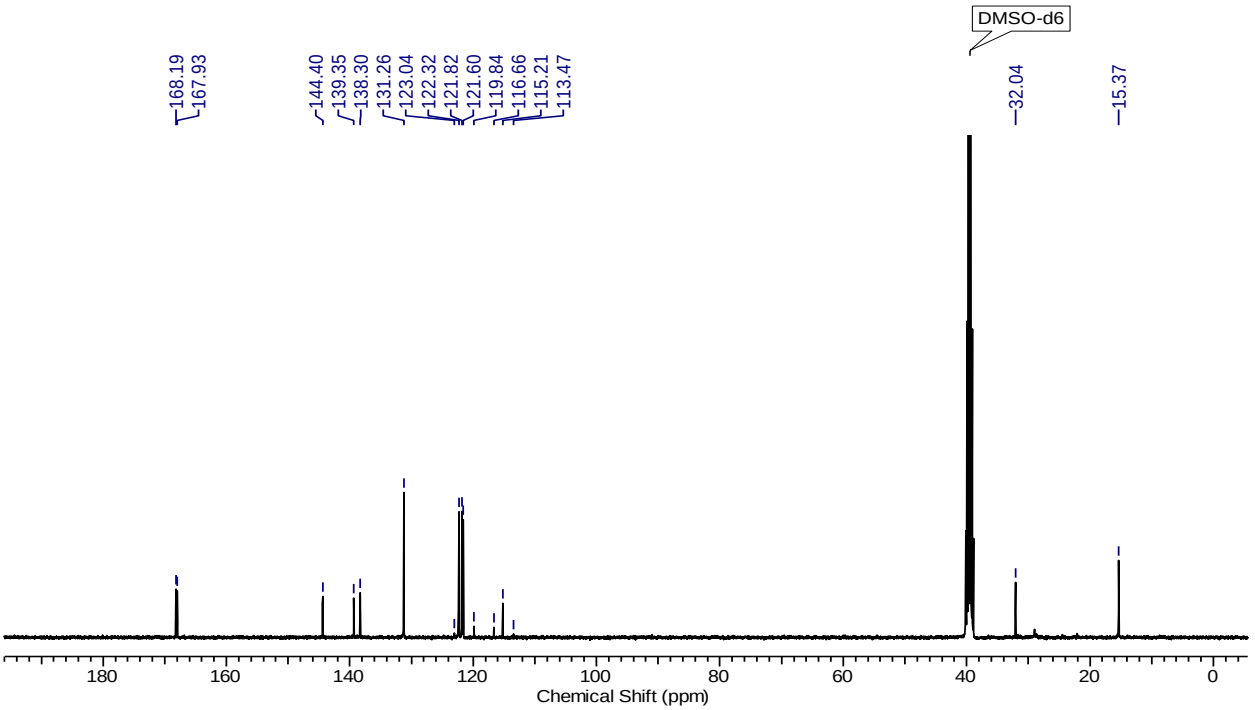
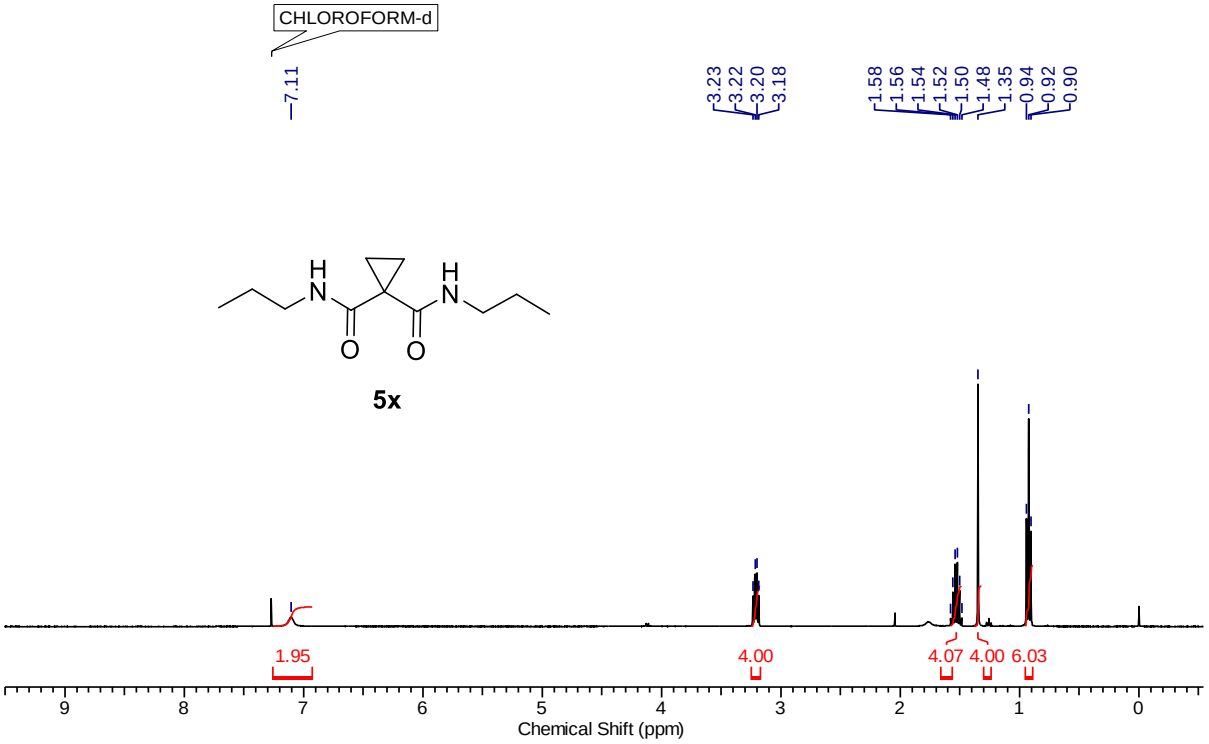
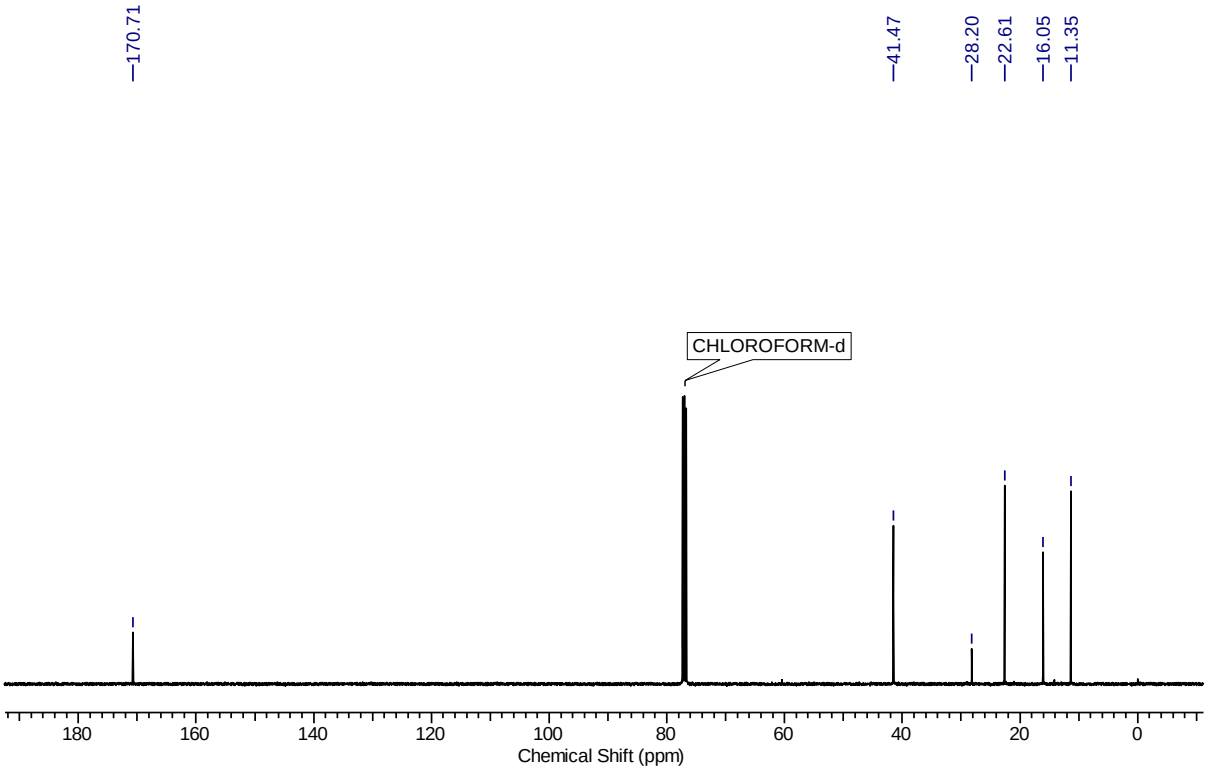


^{1}H NMR, 400 MHz



5x

^{13}C NMR, 100 MHz



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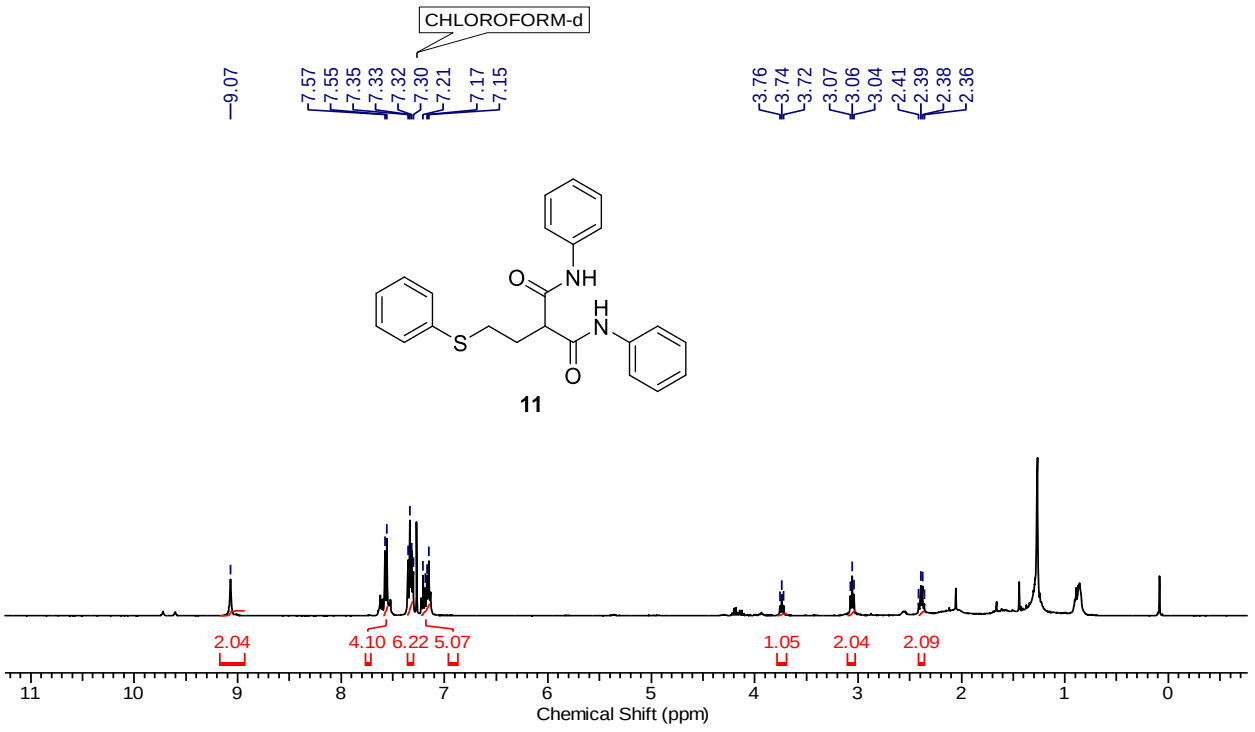

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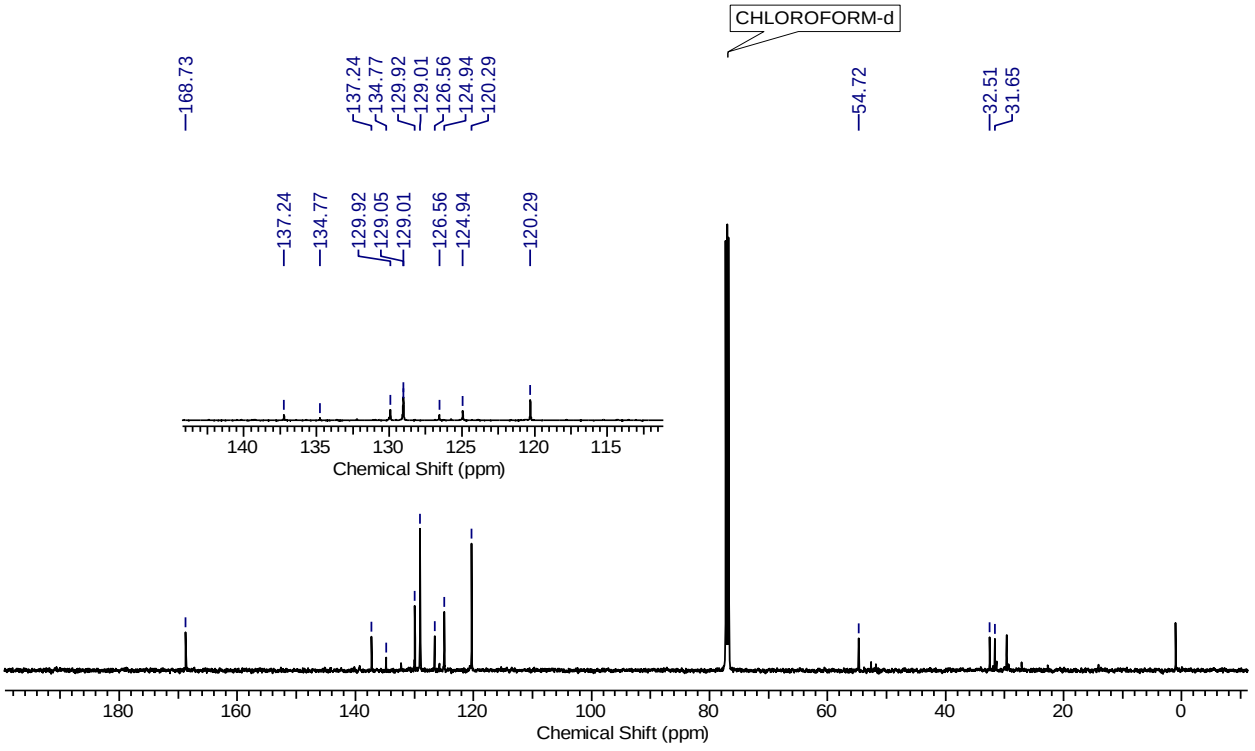

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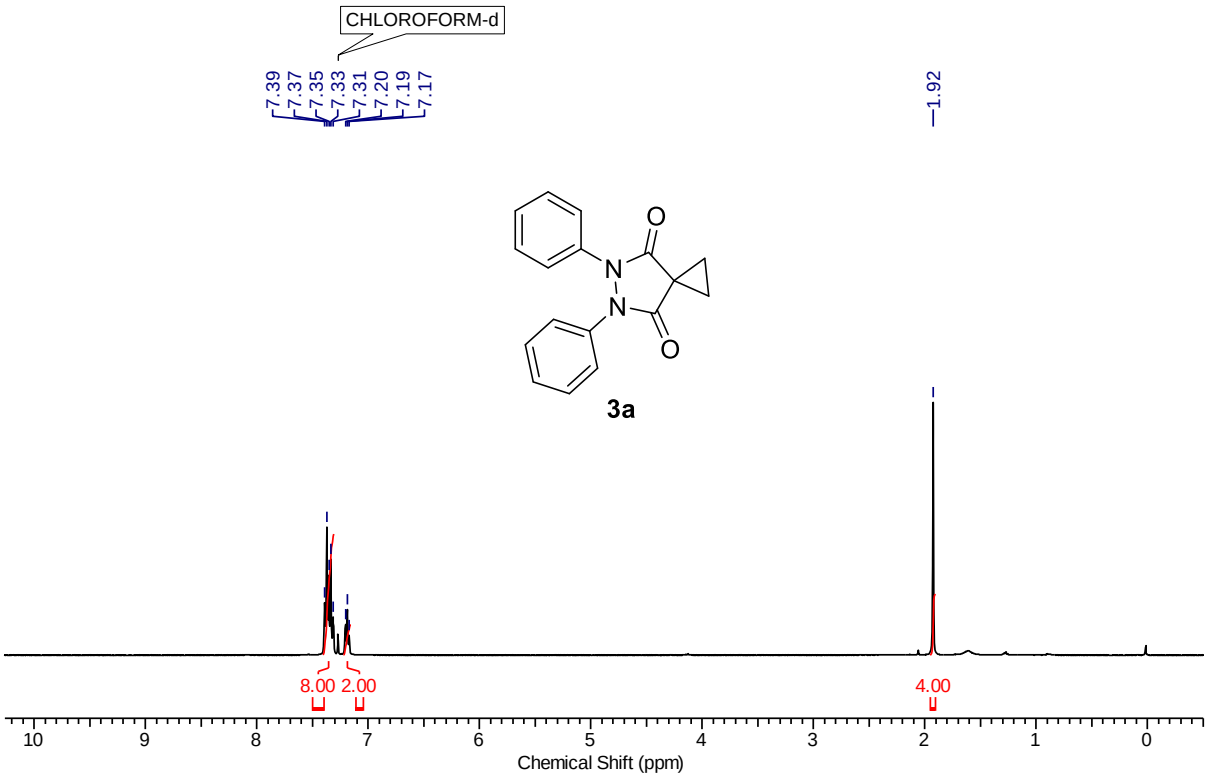
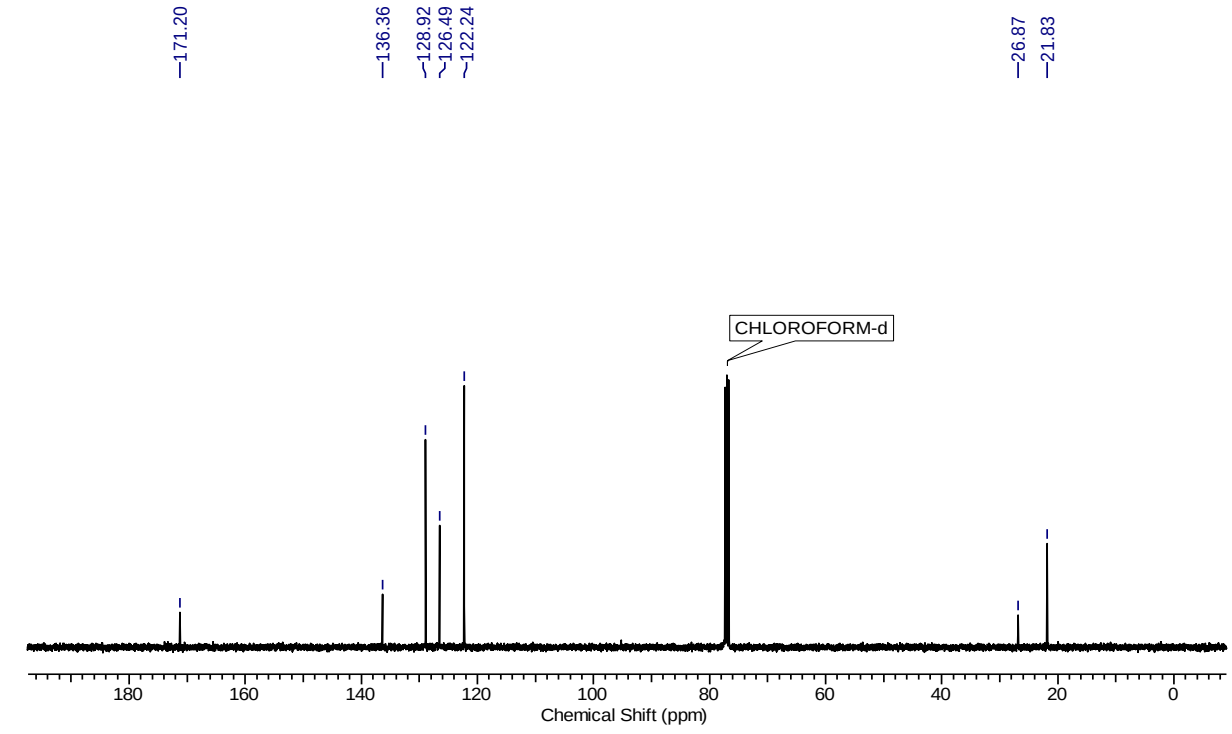
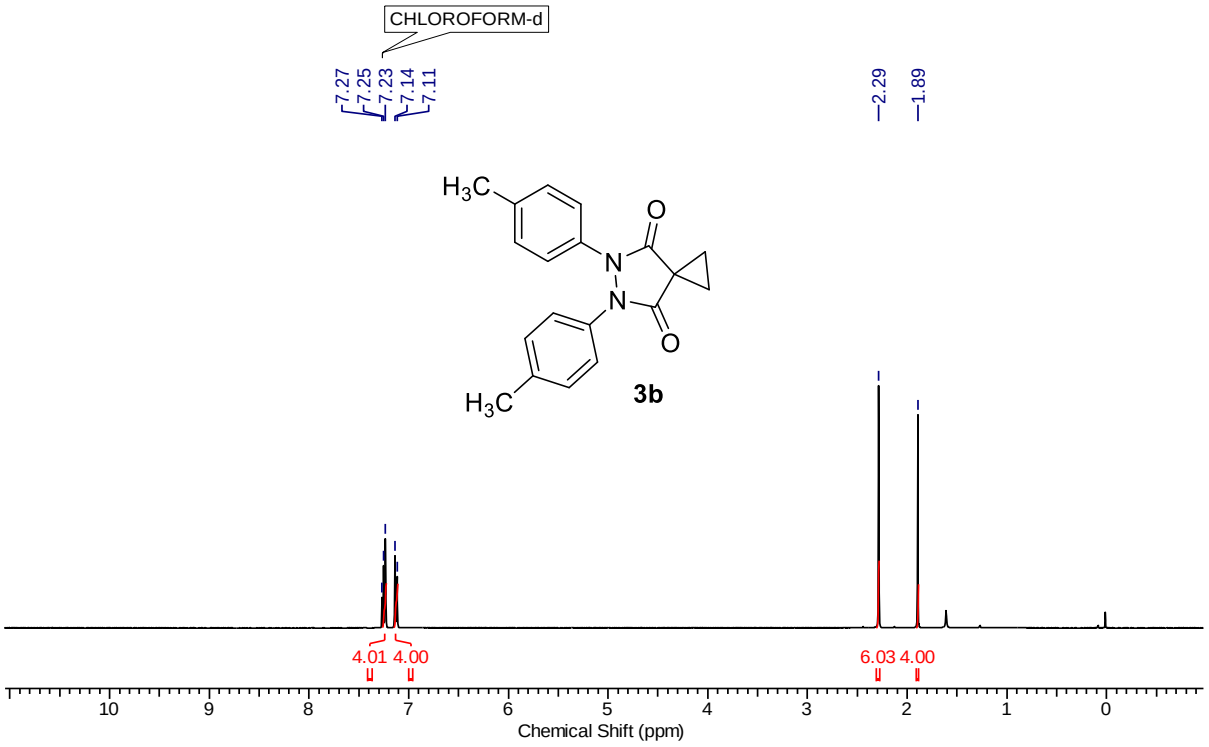


^{13}C NMR, 100 MHz



^{1}H NMR, 400 MHz



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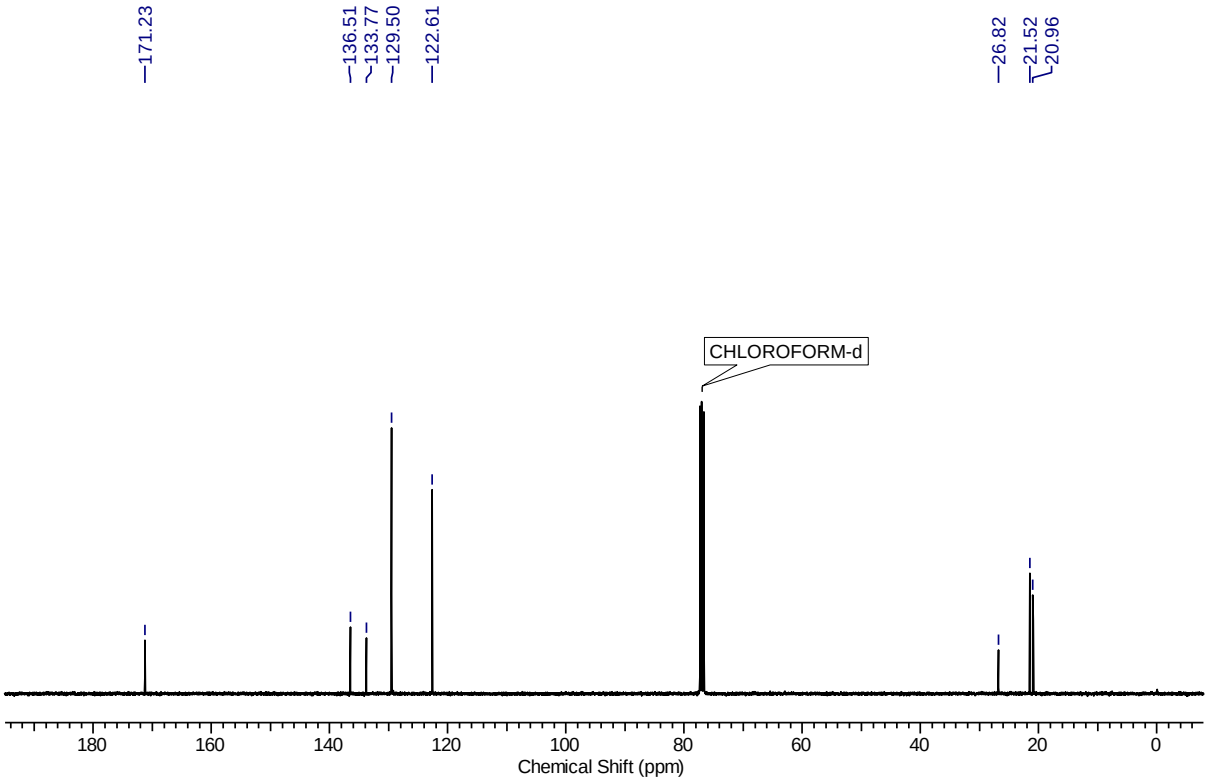

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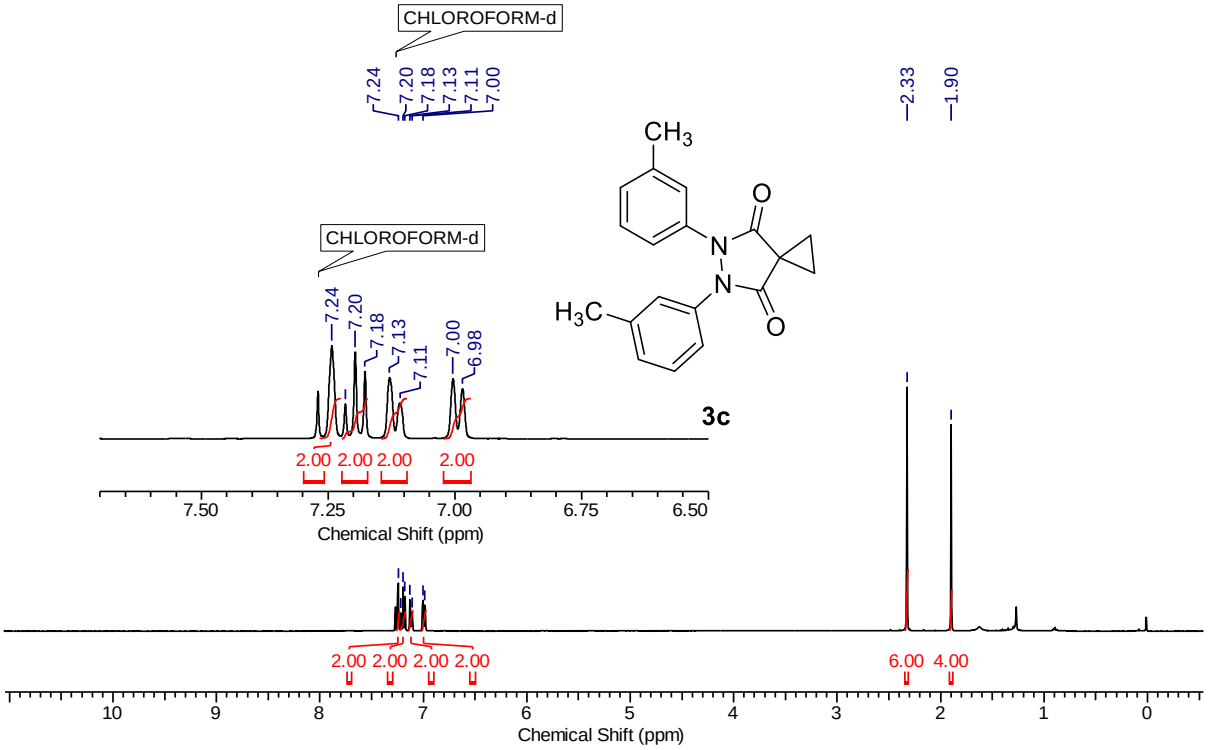

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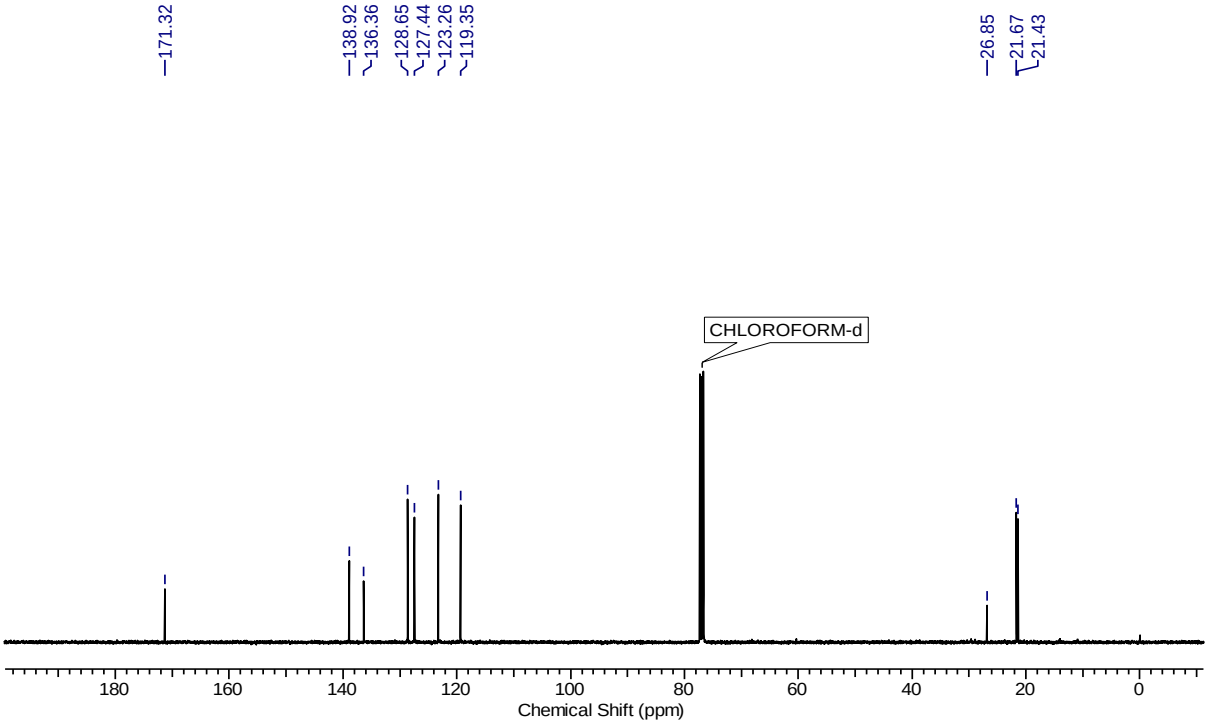

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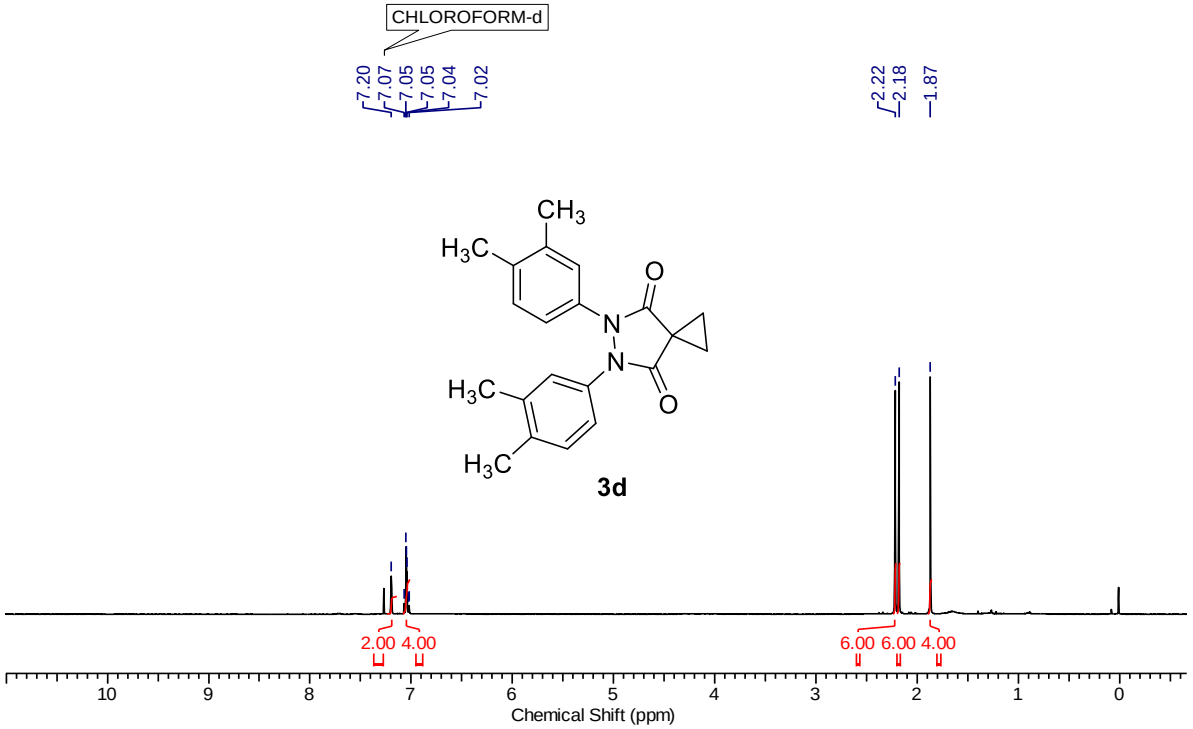

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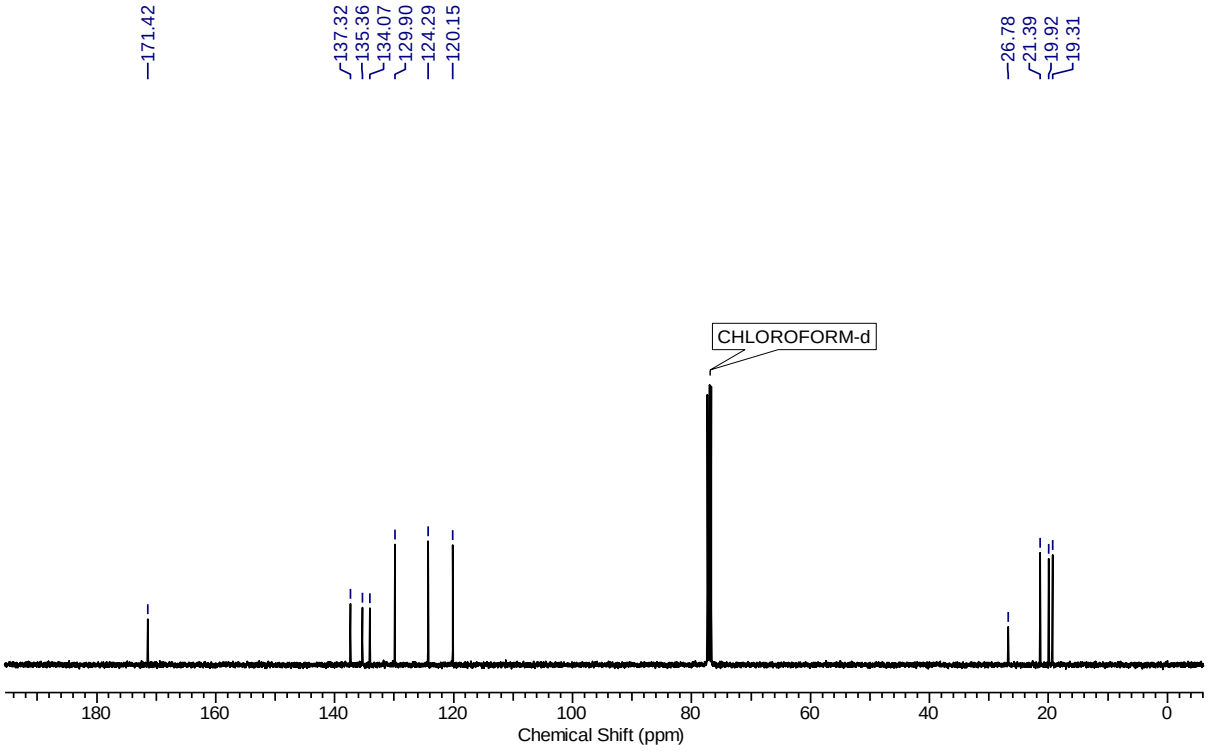
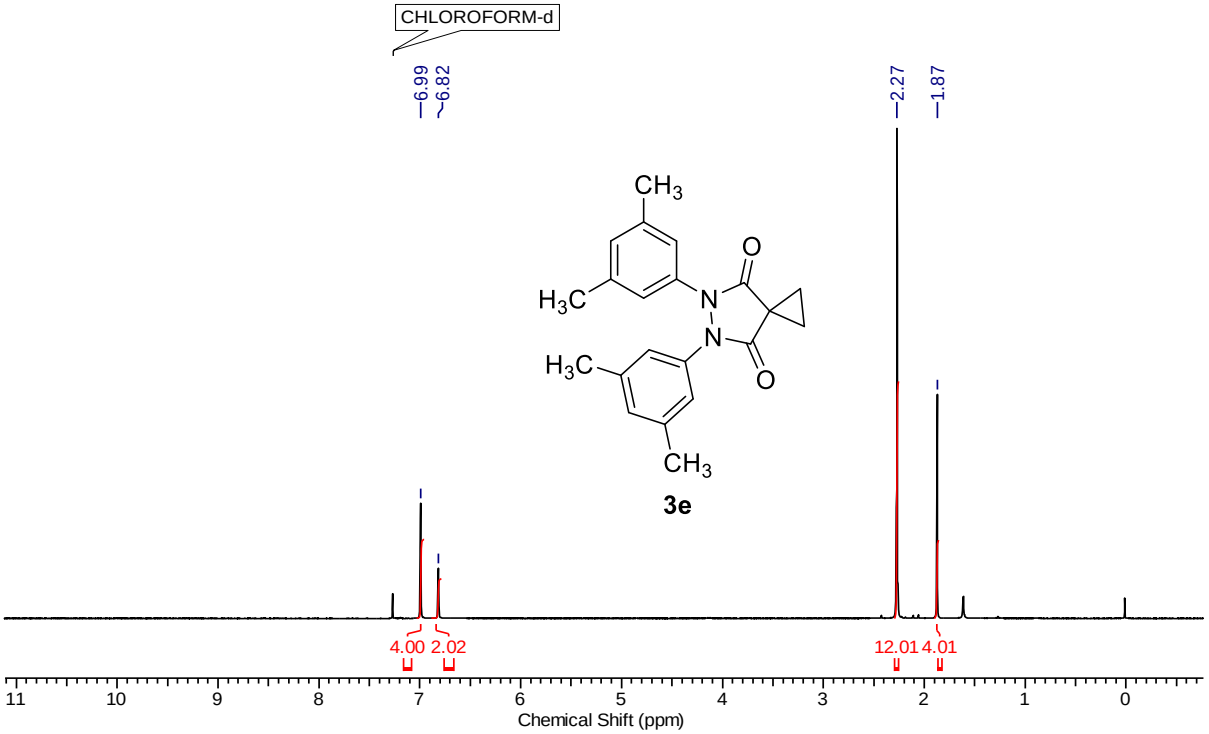


^{1}H NMR, 400 MHz



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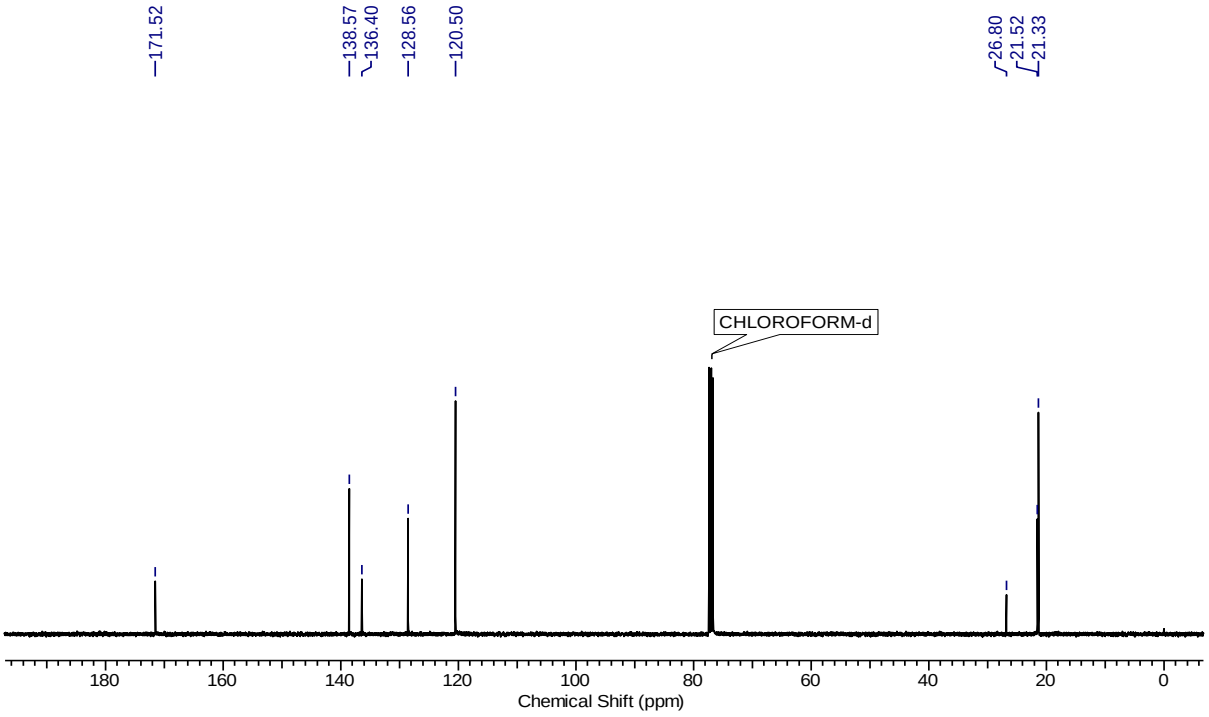

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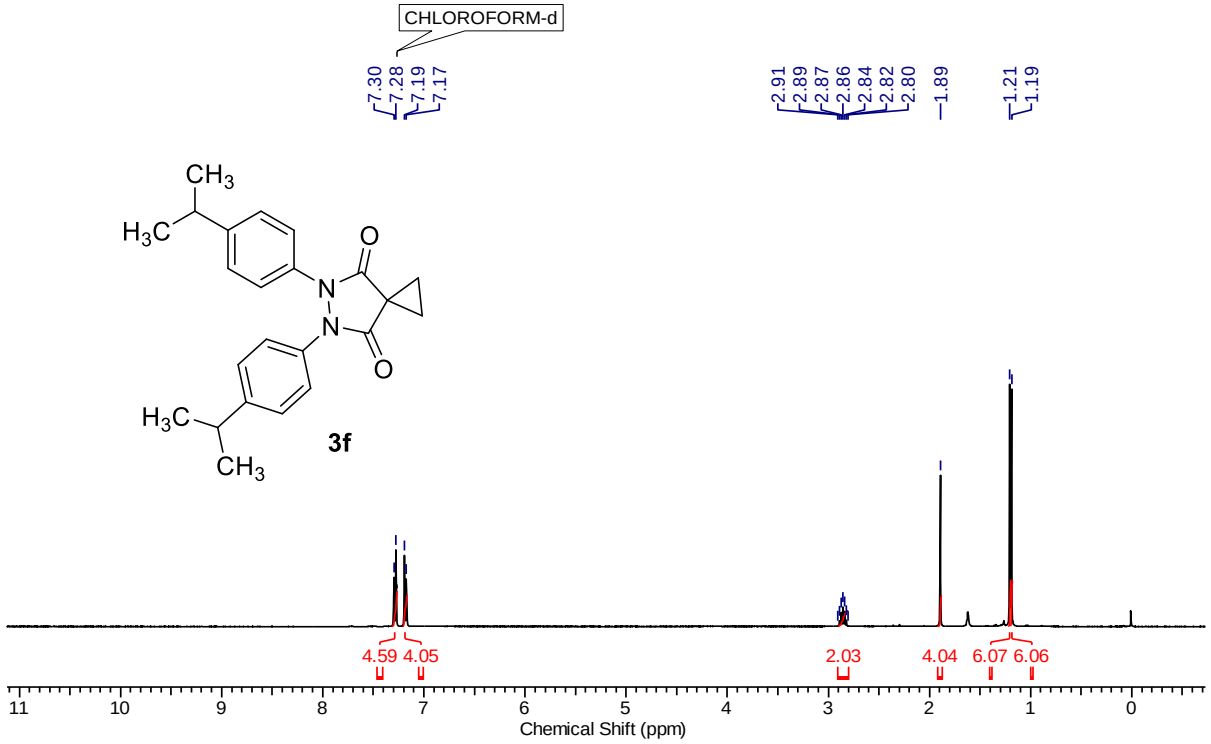
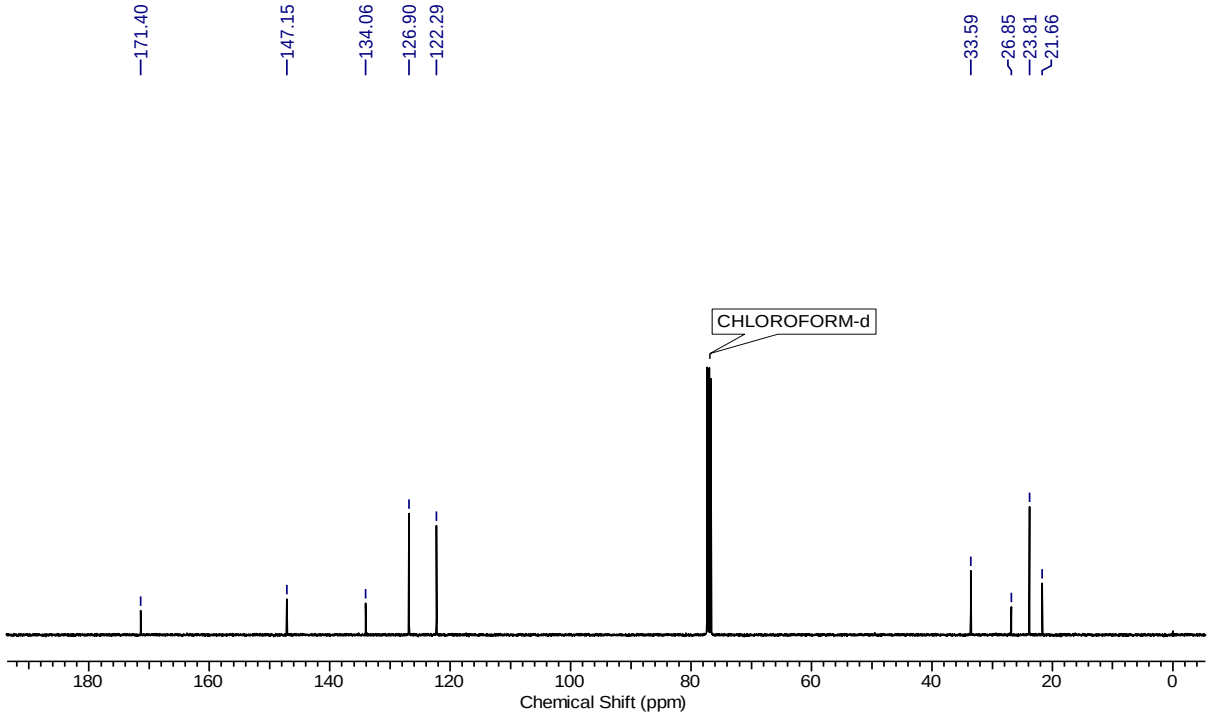


^{13}C NMR, 100 MHz



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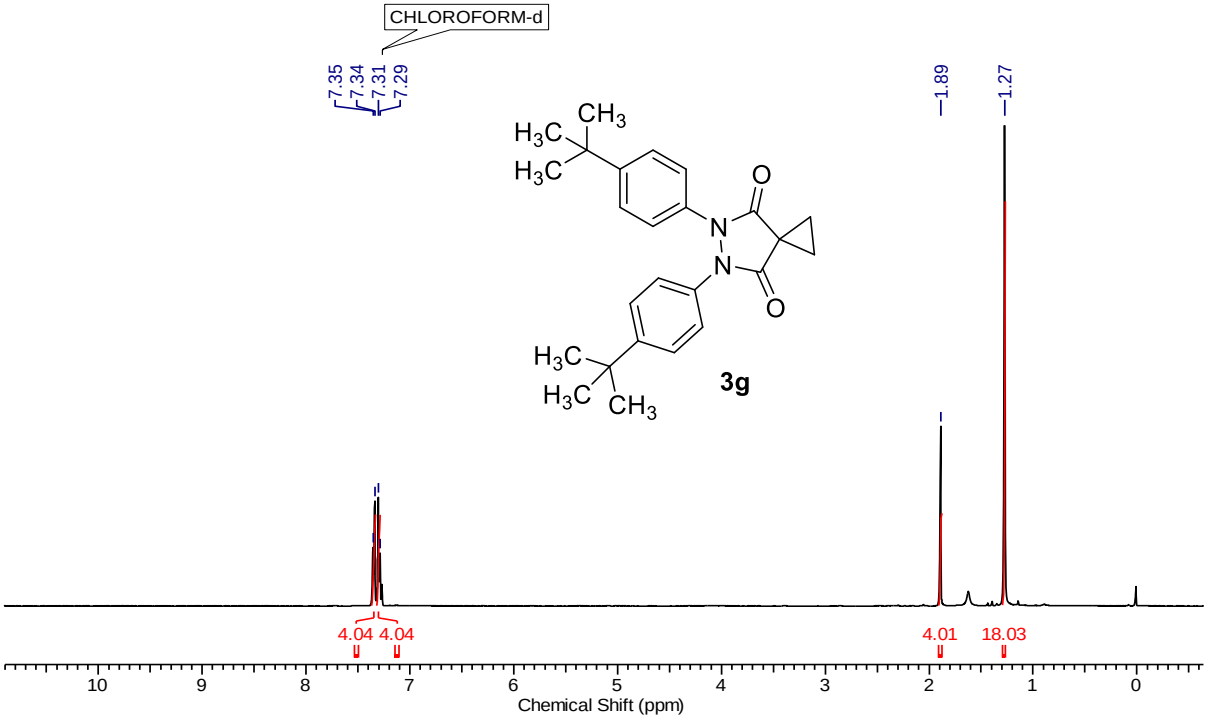
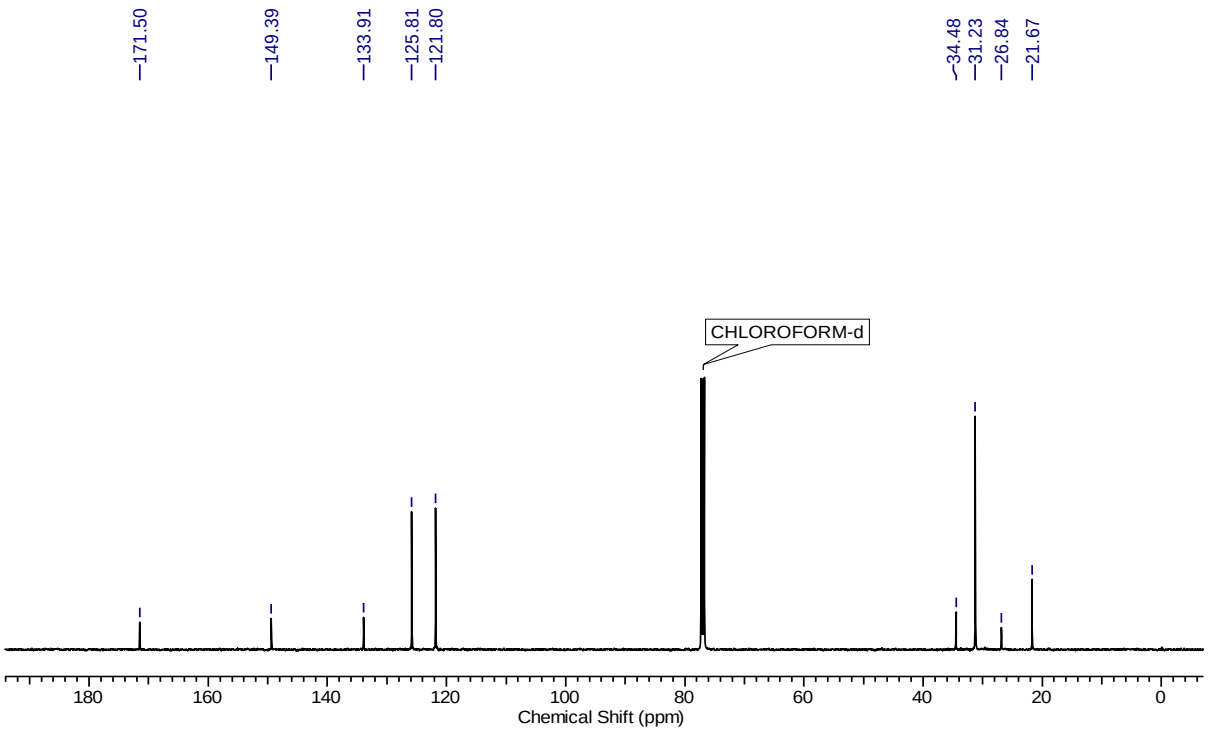
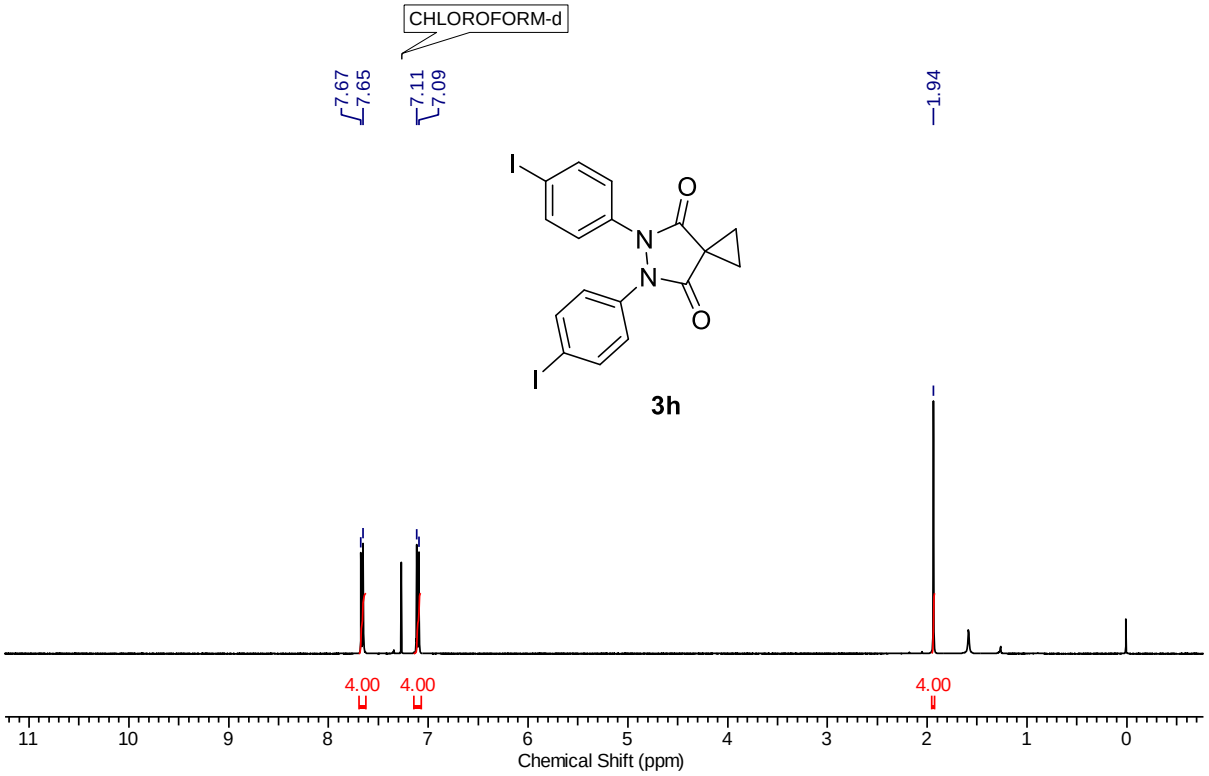


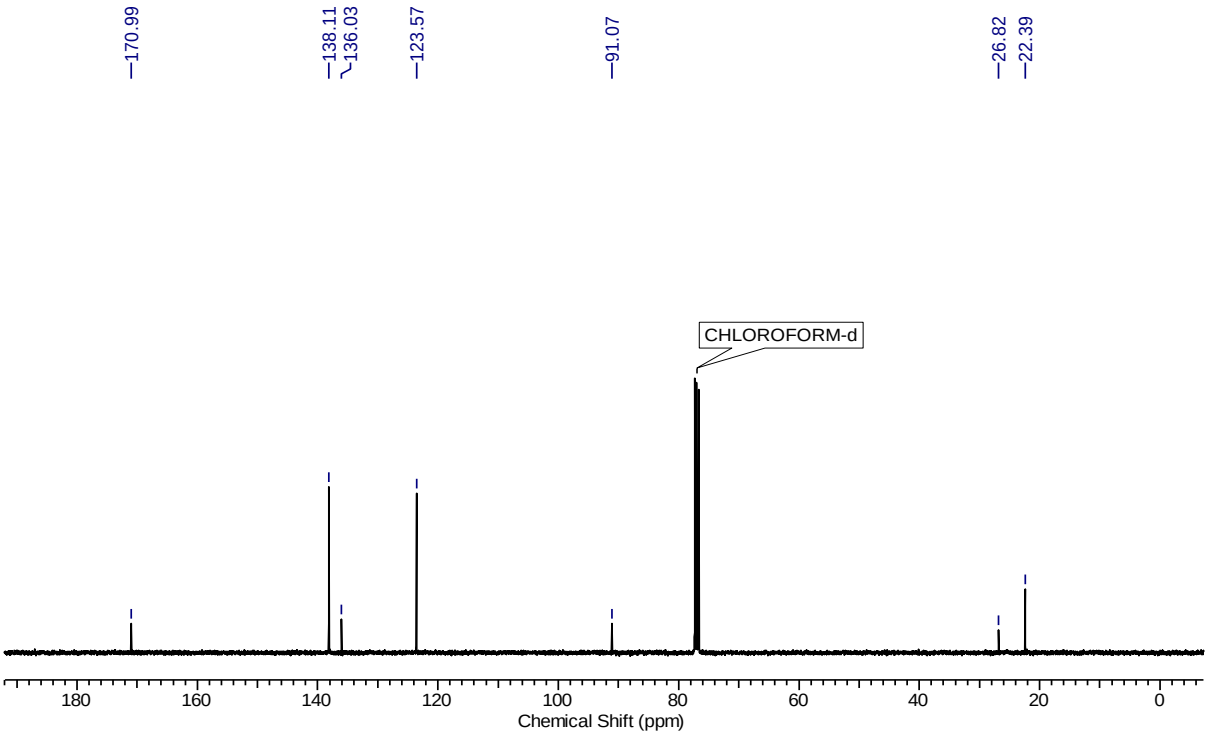
^{13}C NMR, 125 MHz



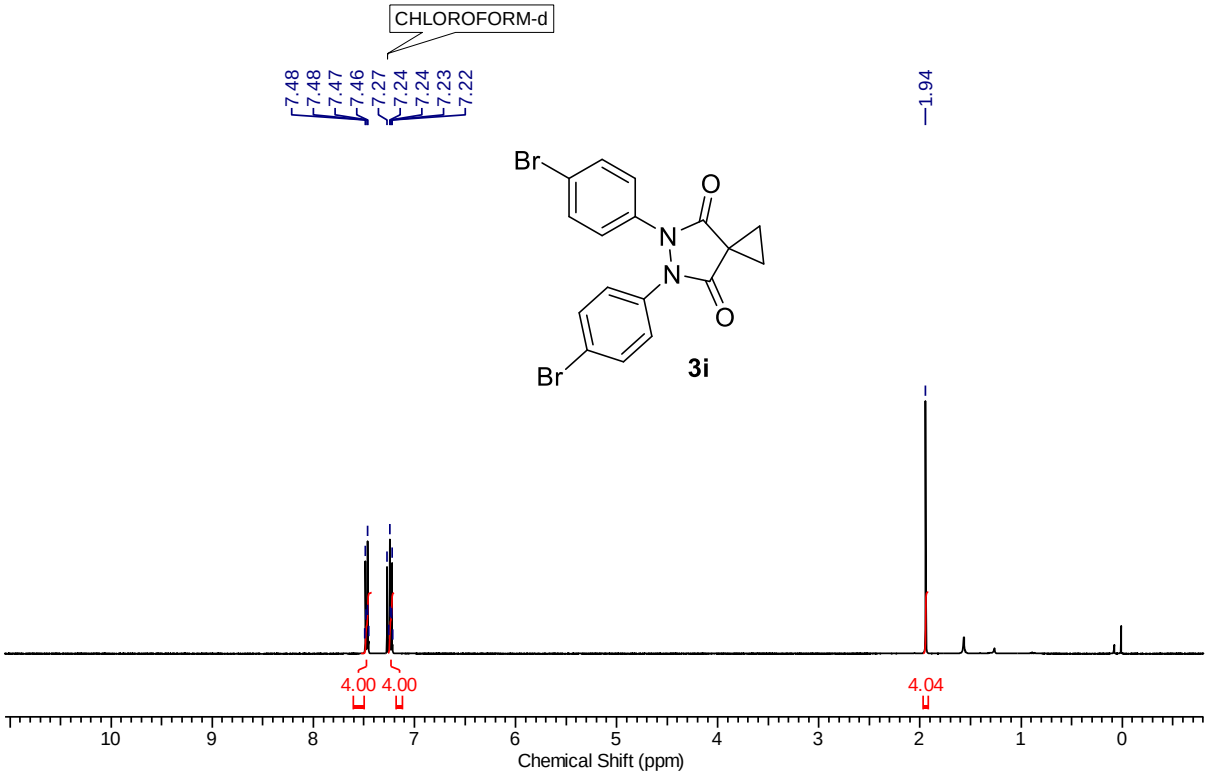
^{1}H NMR, 400 MHz



^{13}C NMR, 100 MHz



^{1}H NMR, 400 MHz



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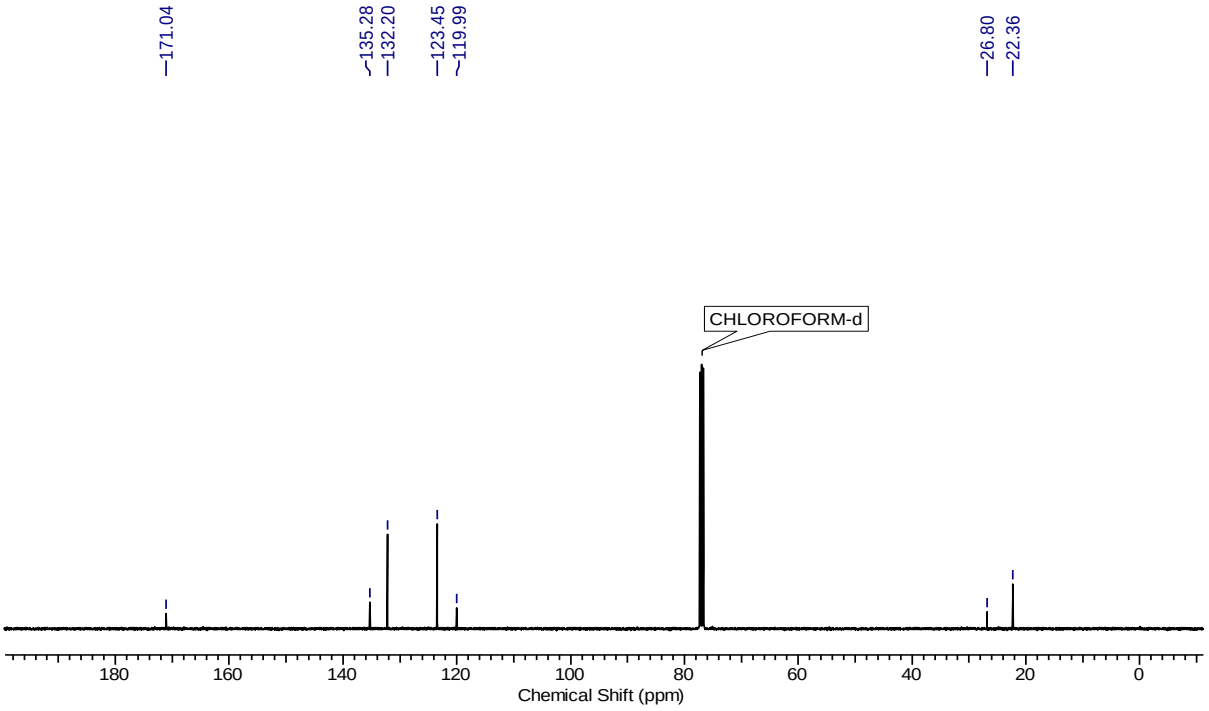
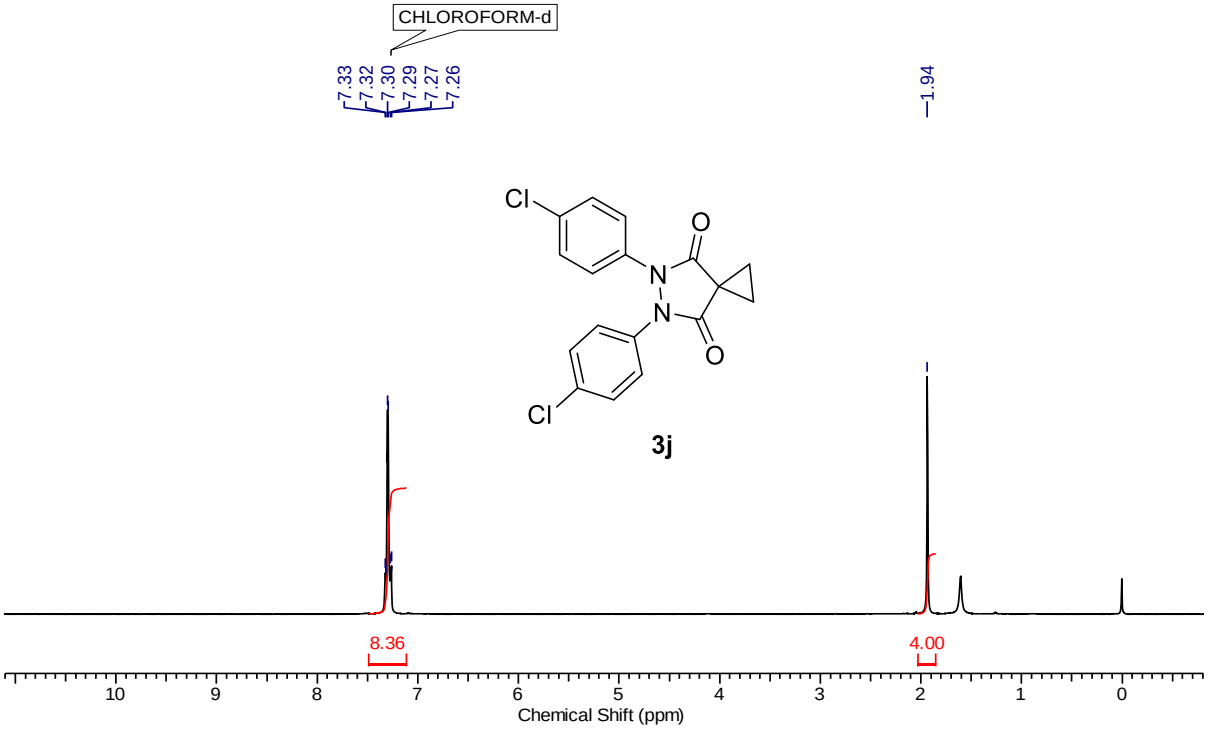
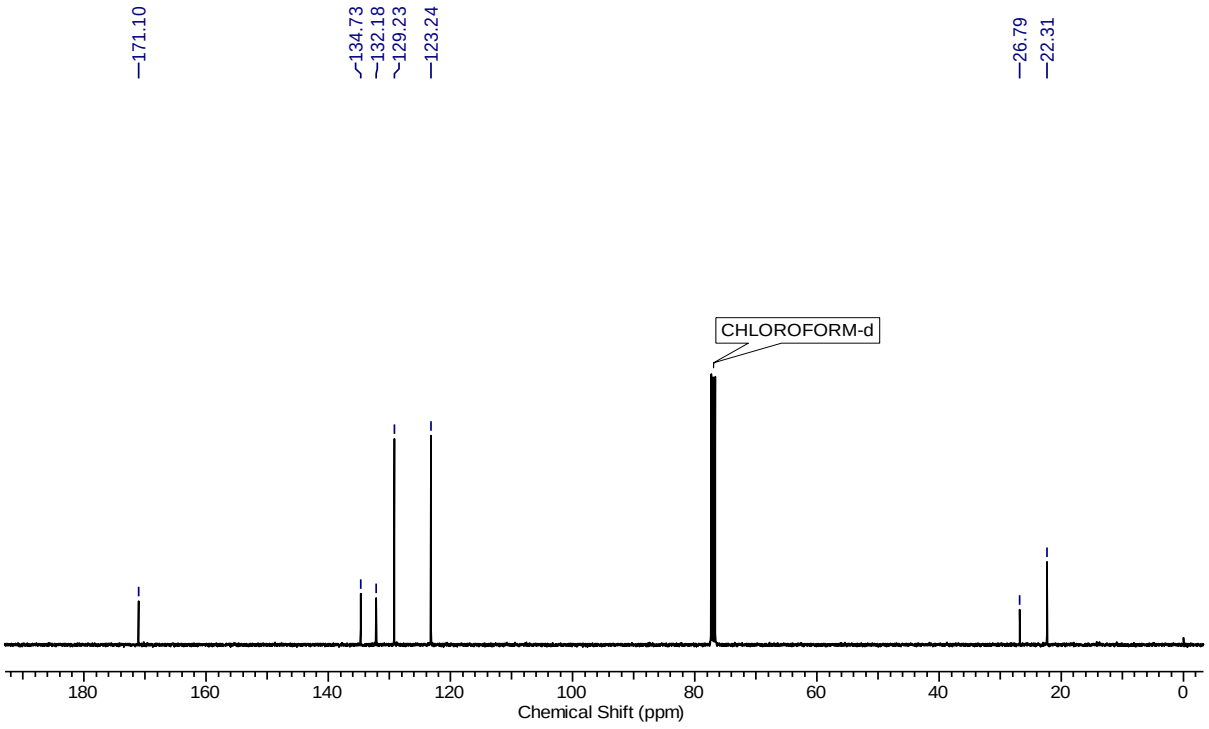


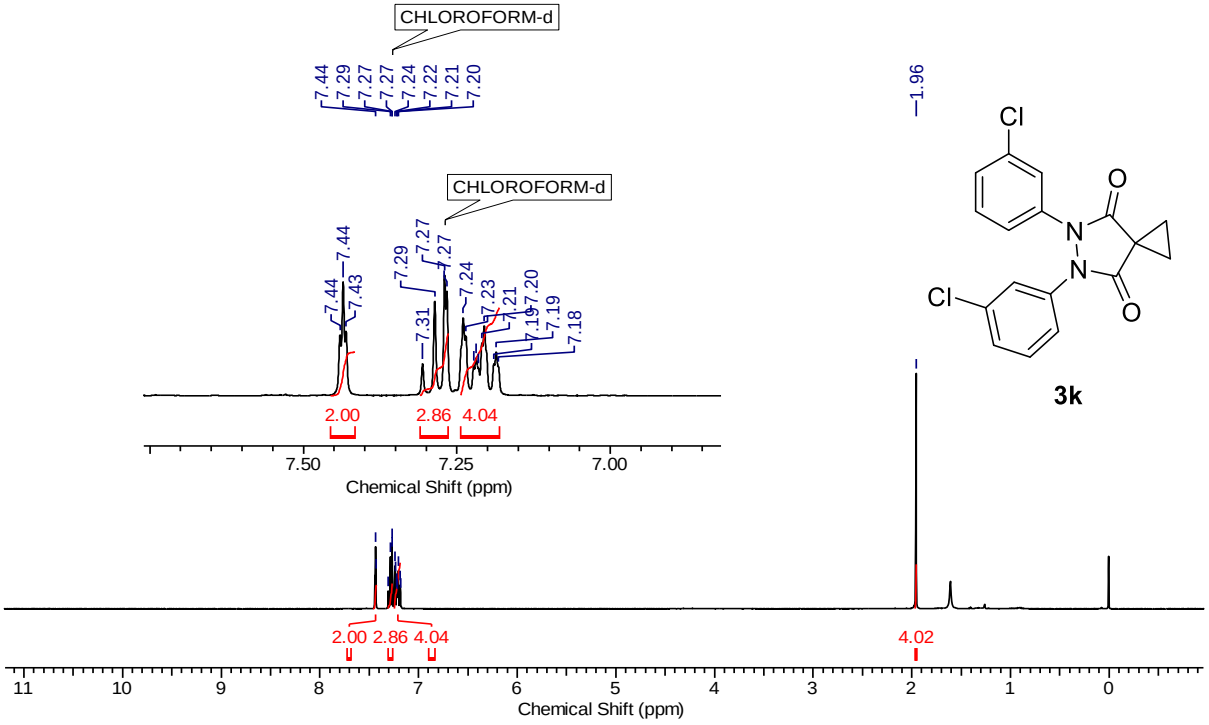
^{1}H NMR, 400 MHz



^{13}C NMR, 100 MHz



^{1}H NMR, 400 MHz



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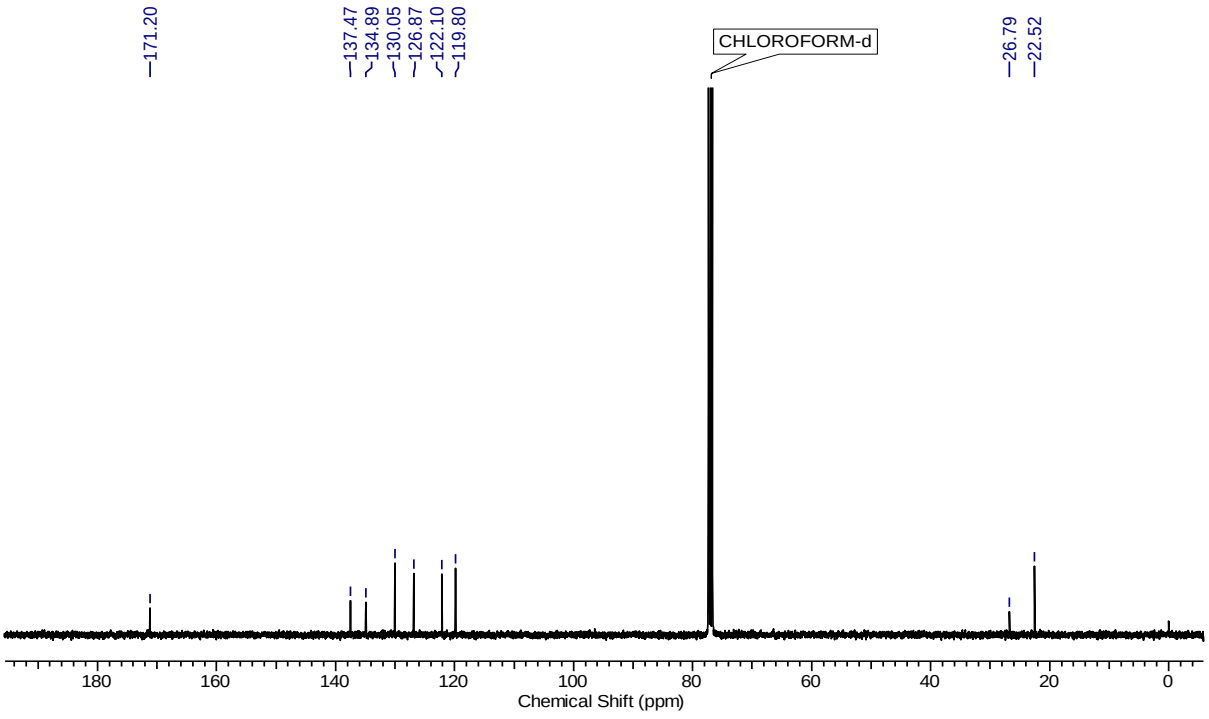
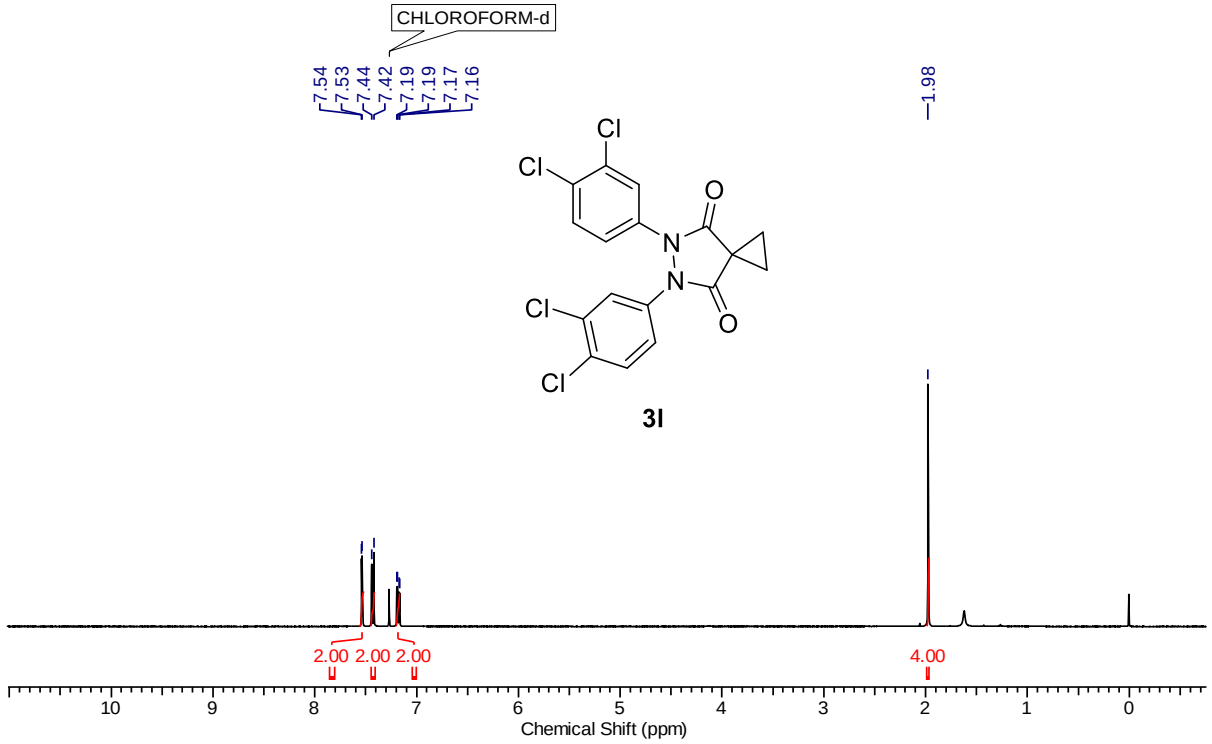
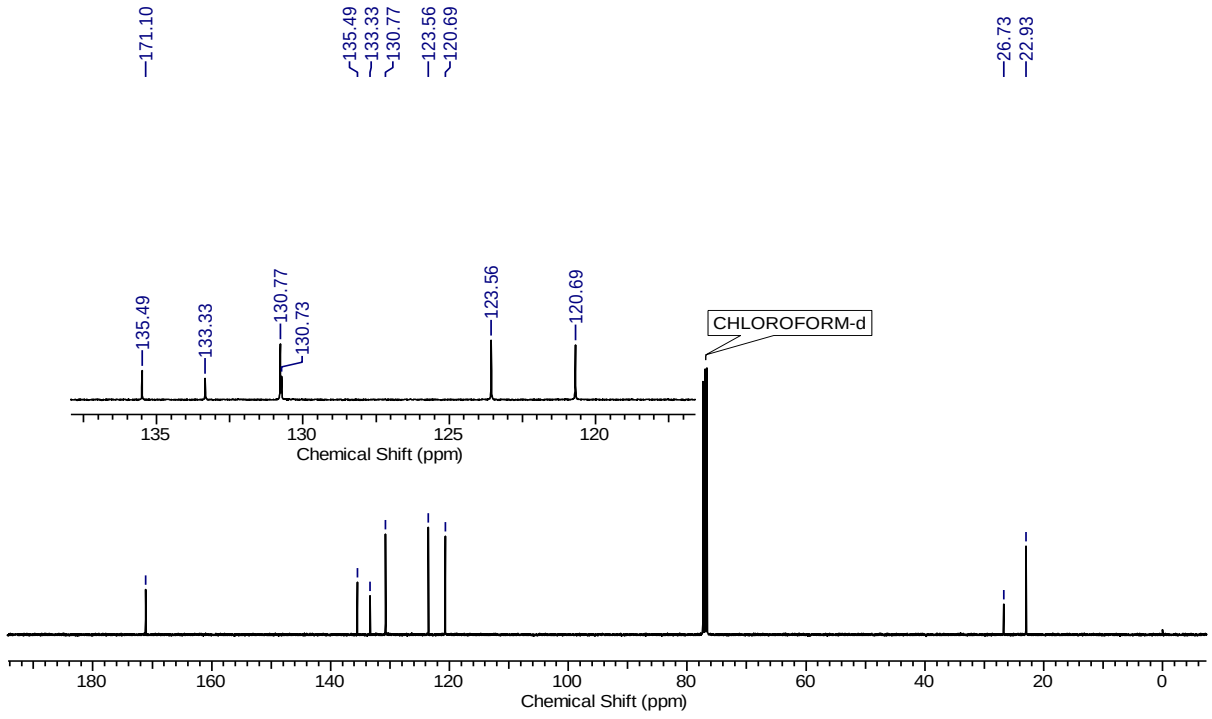


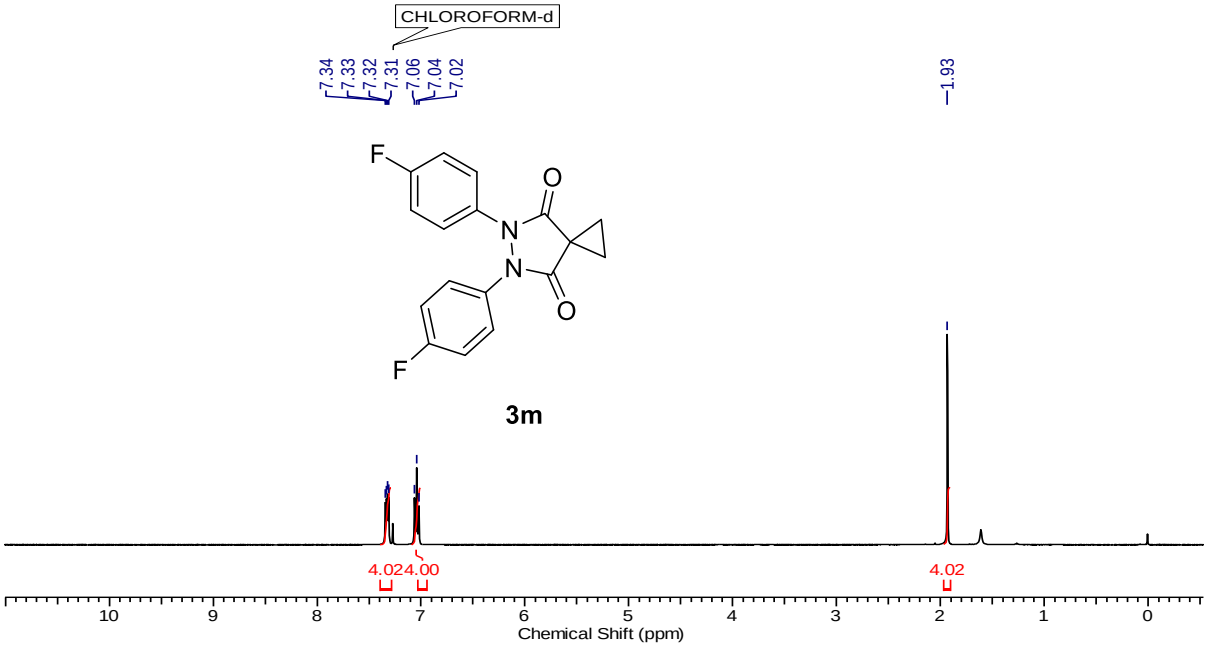
^{1}H NMR, 400 MHz



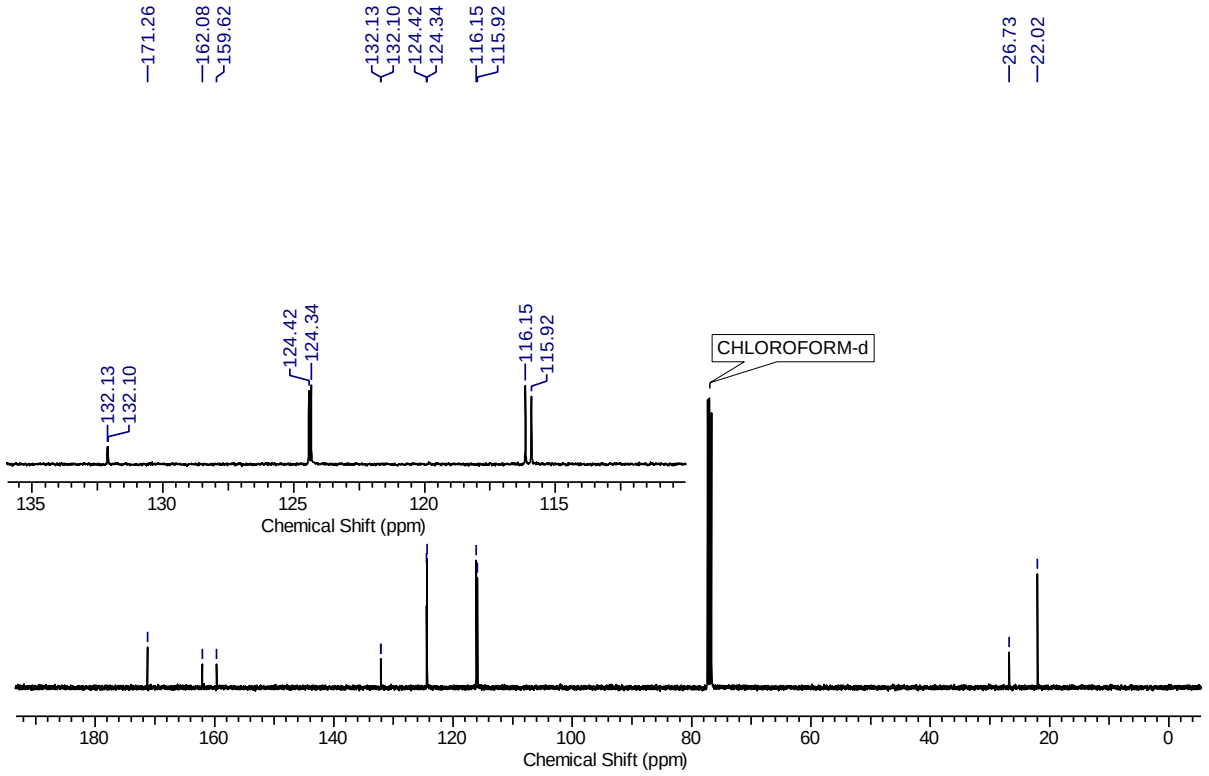
^{13}C NMR, 100 MHz



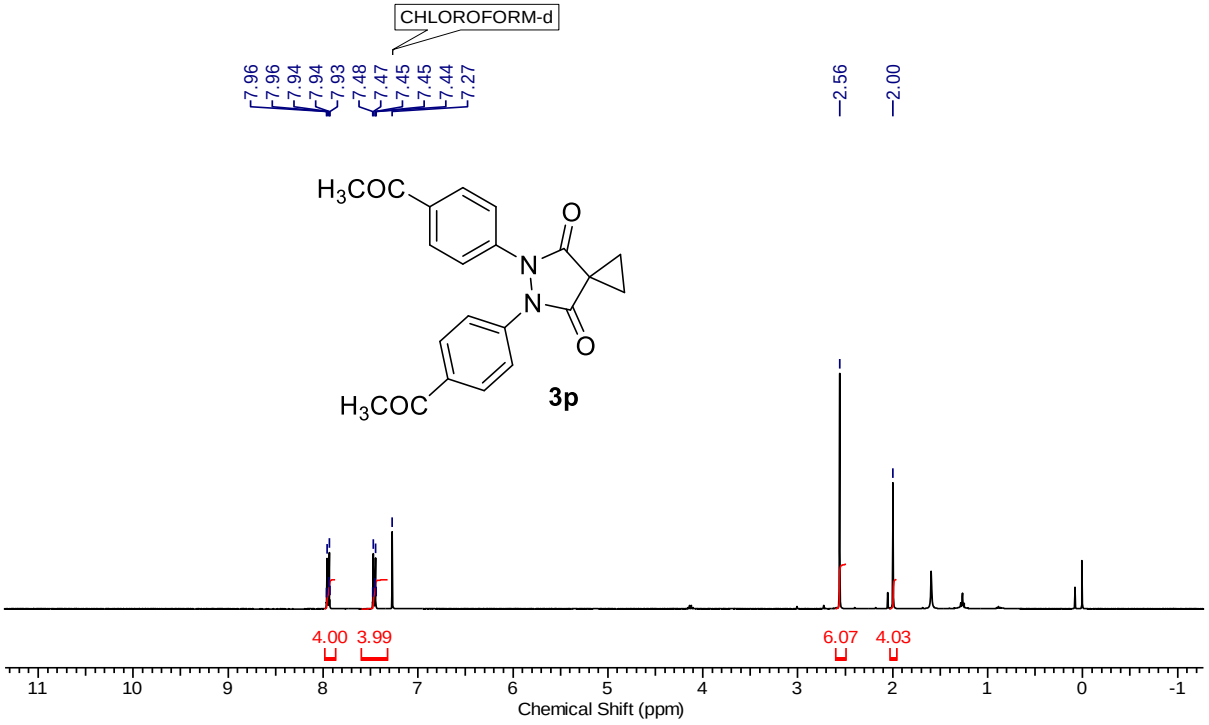
^{1}H NMR, 400 MHz



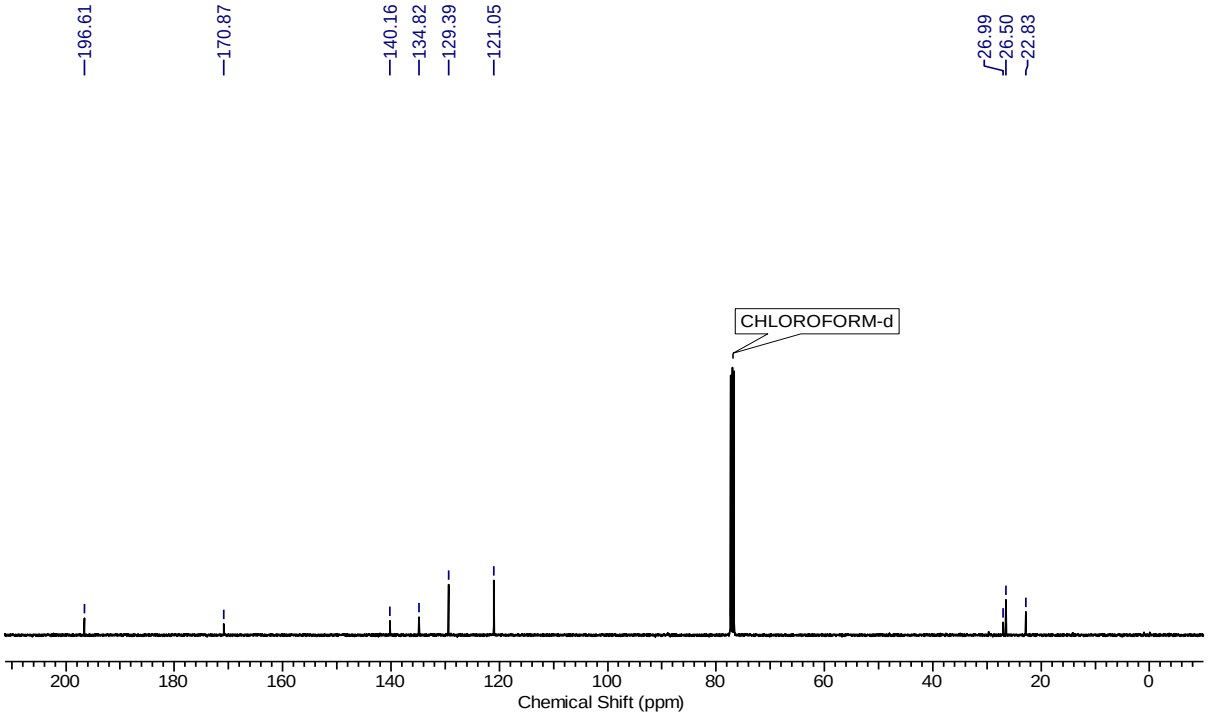
^{13}C NMR, 100 MHz



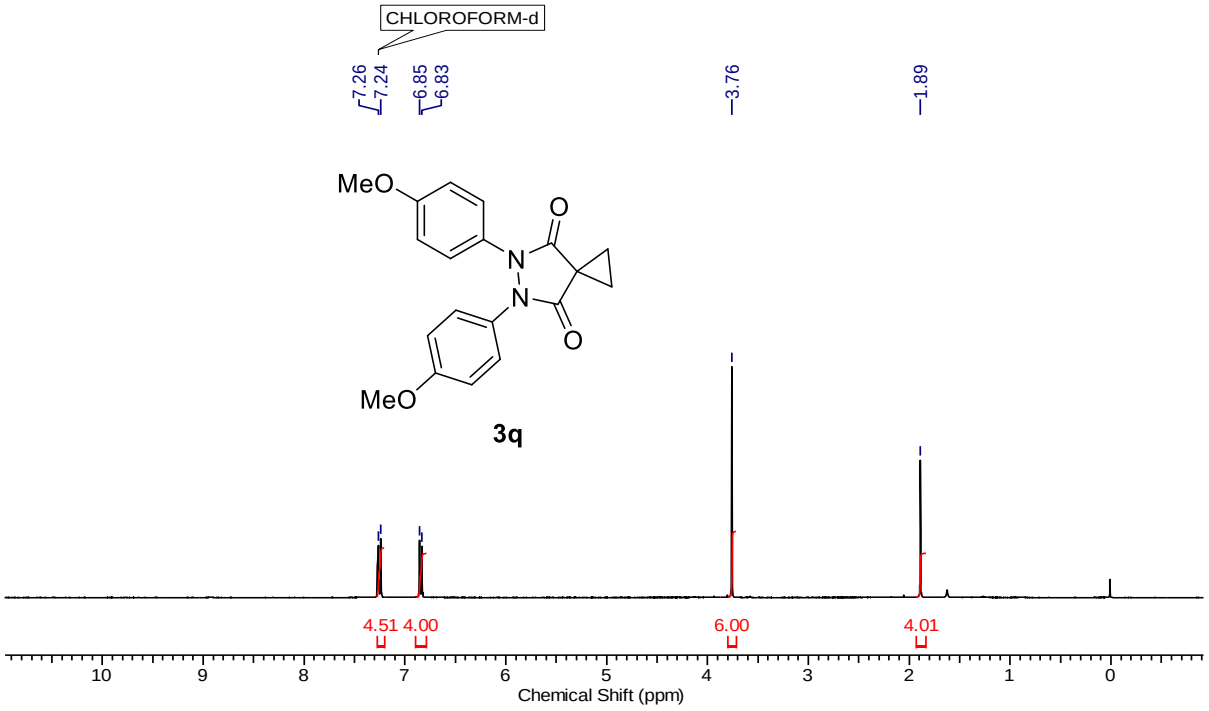
^{1}H NMR, 400 MHz



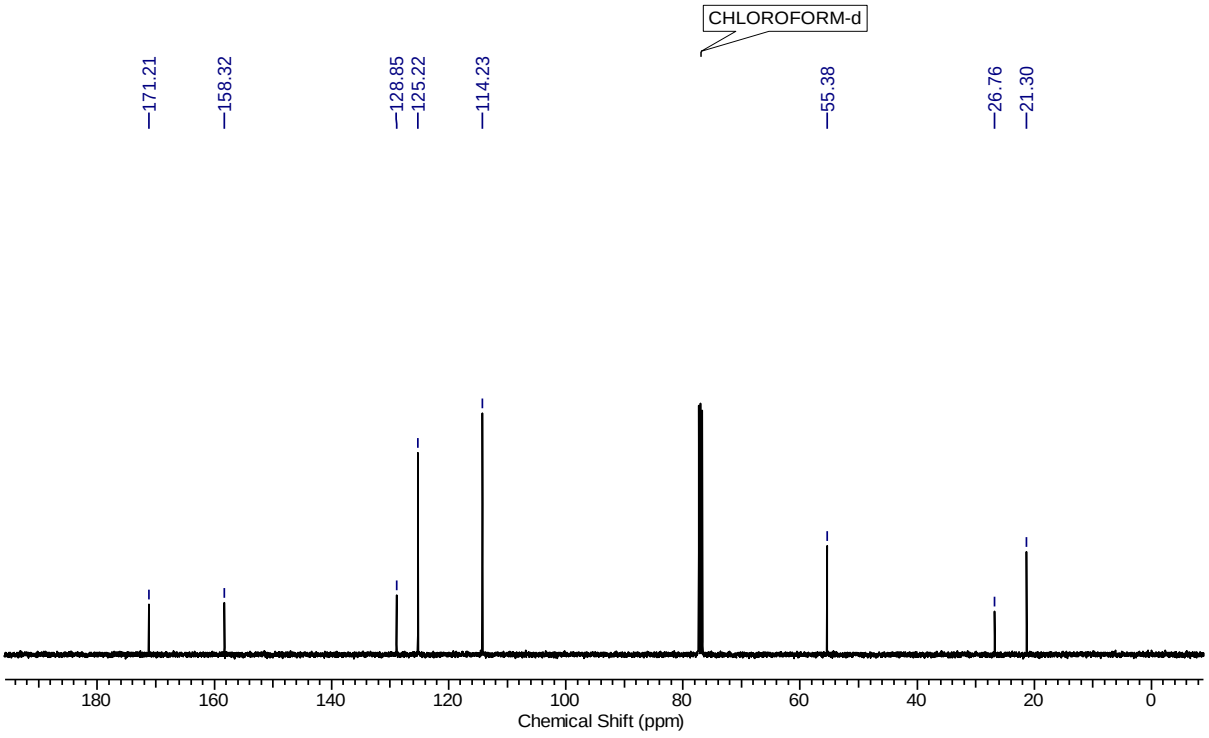
^{13}C NMR, 100 MHz



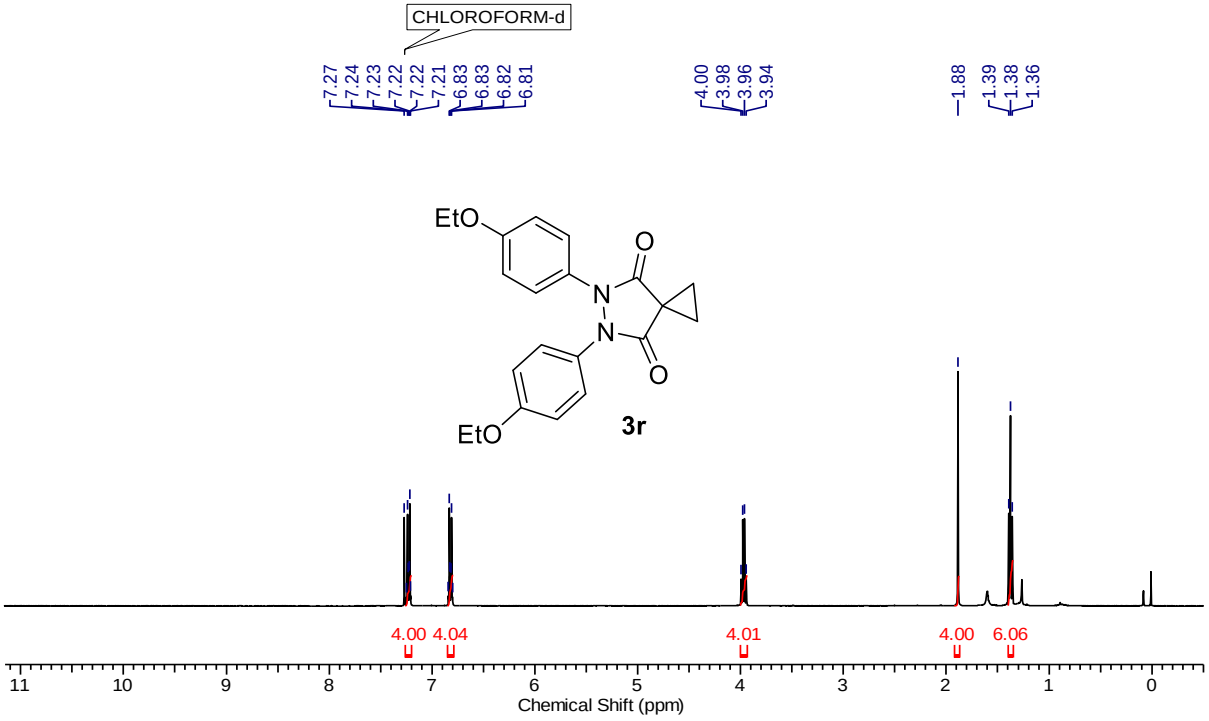
^{1}H NMR, 400 MHz



^{13}C NMR, 100 MHz



^{1}H NMR, 400 MHz



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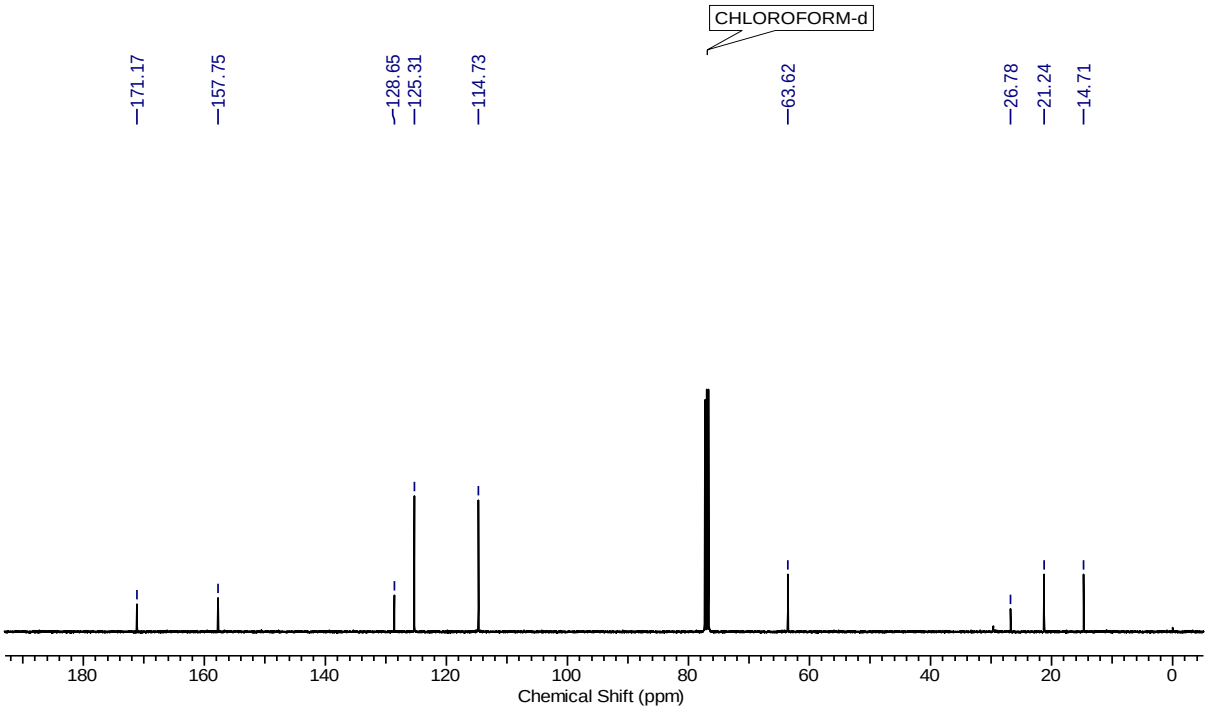

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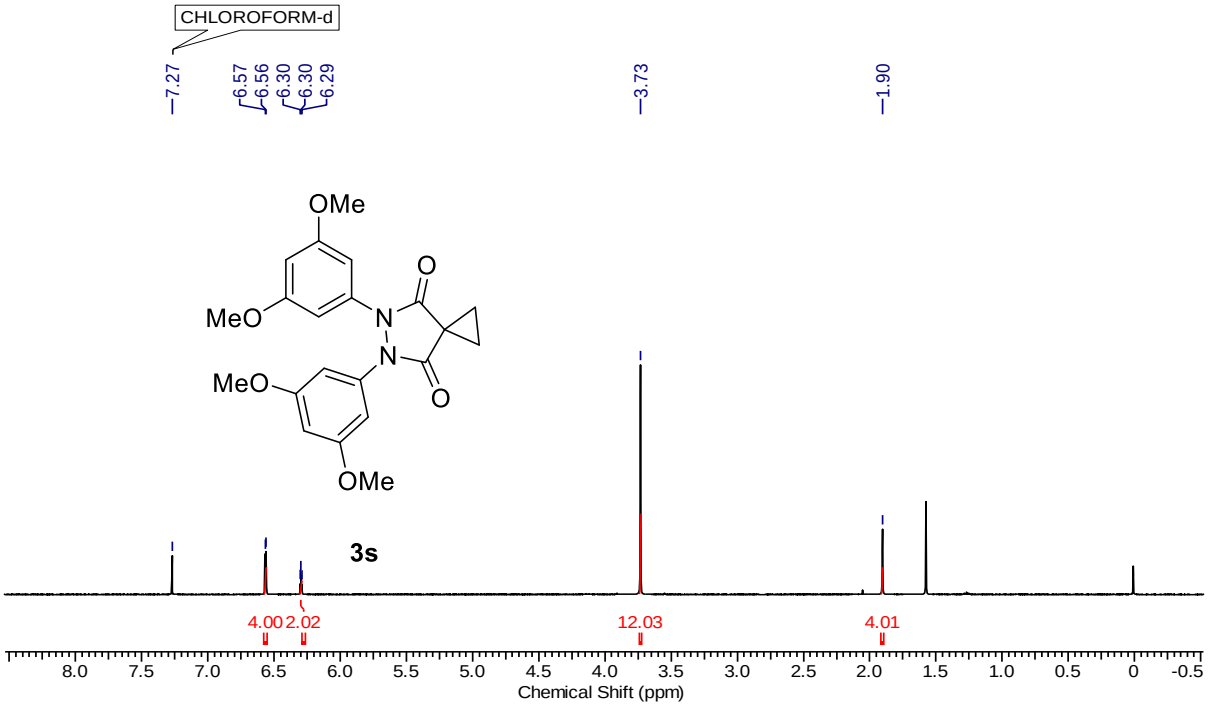

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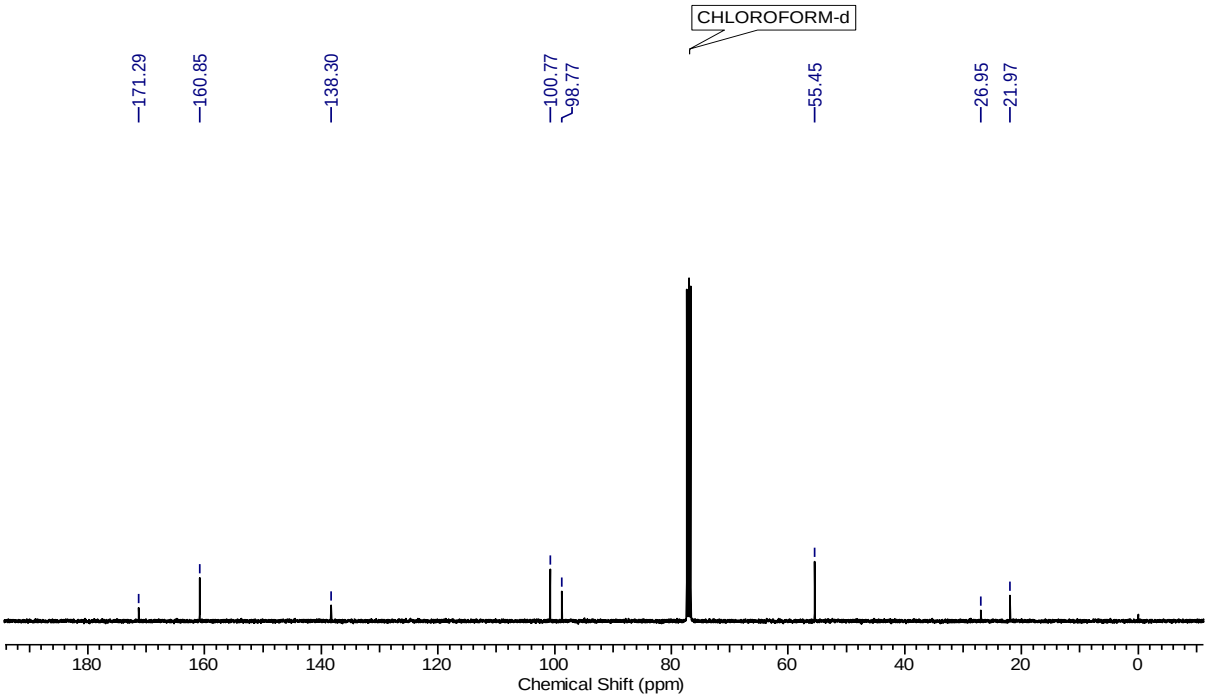
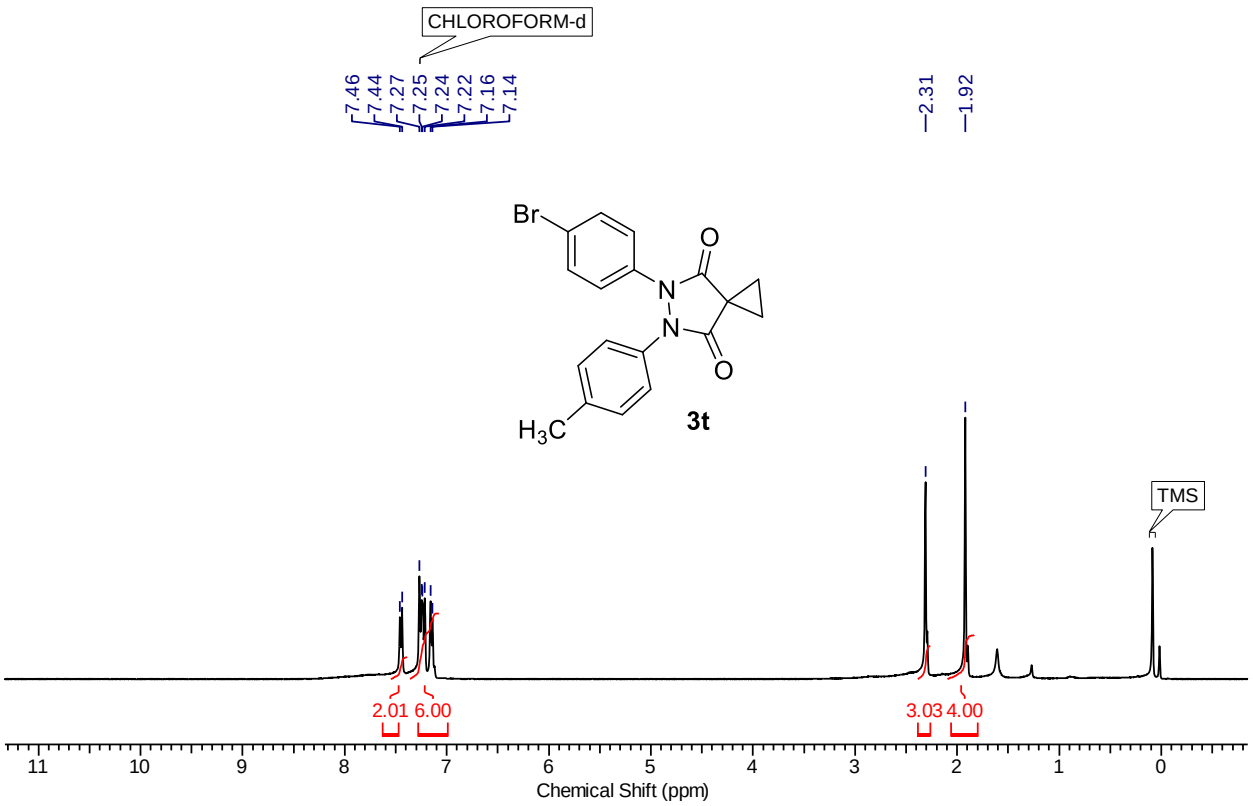
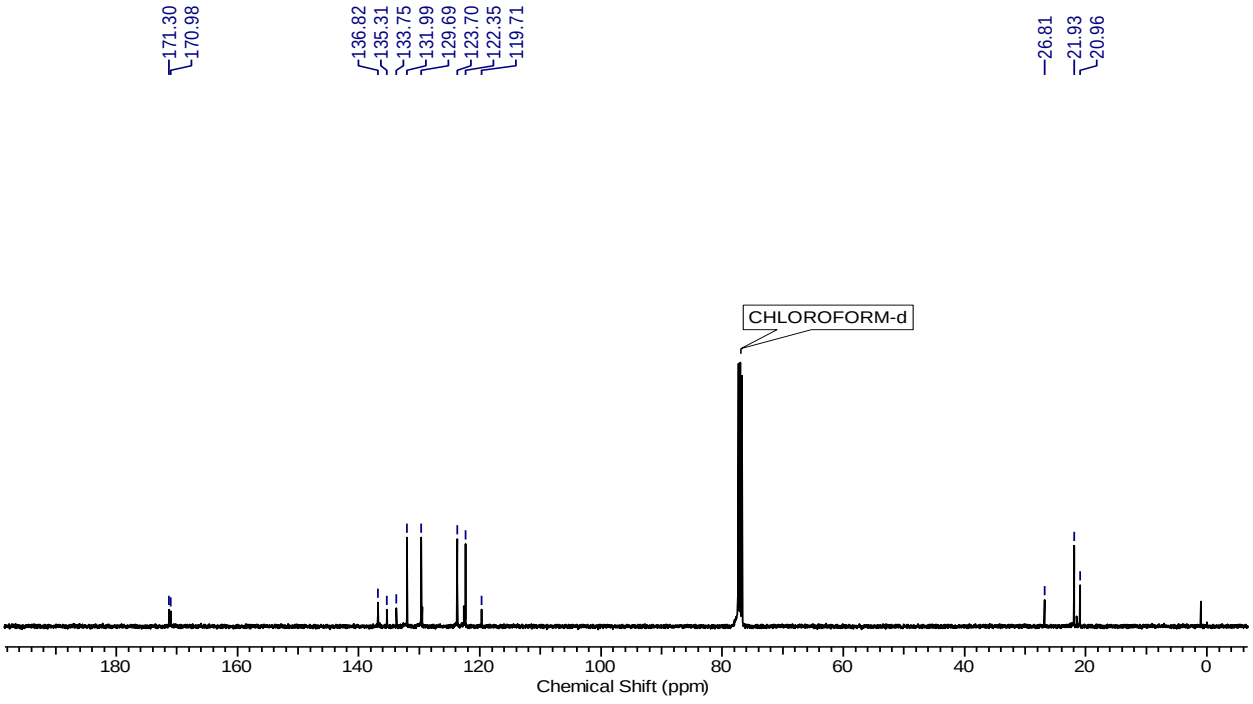


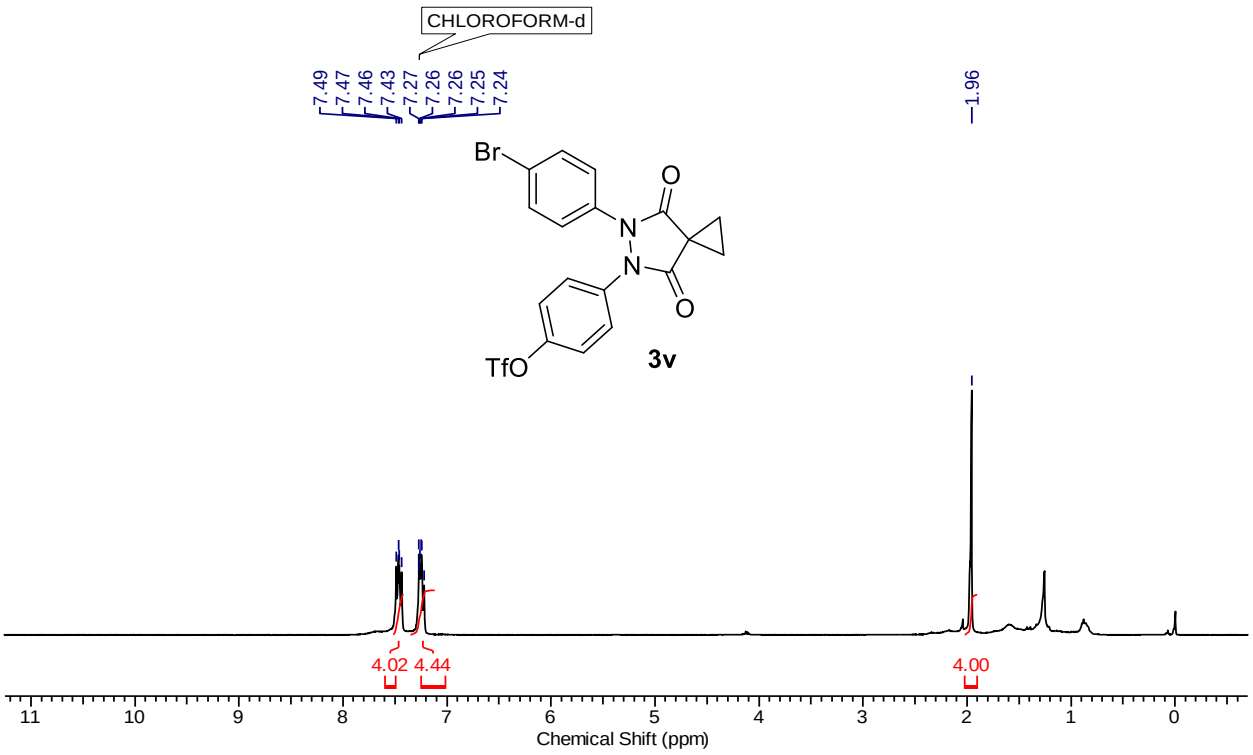
^{1}H NMR, 400 MHz



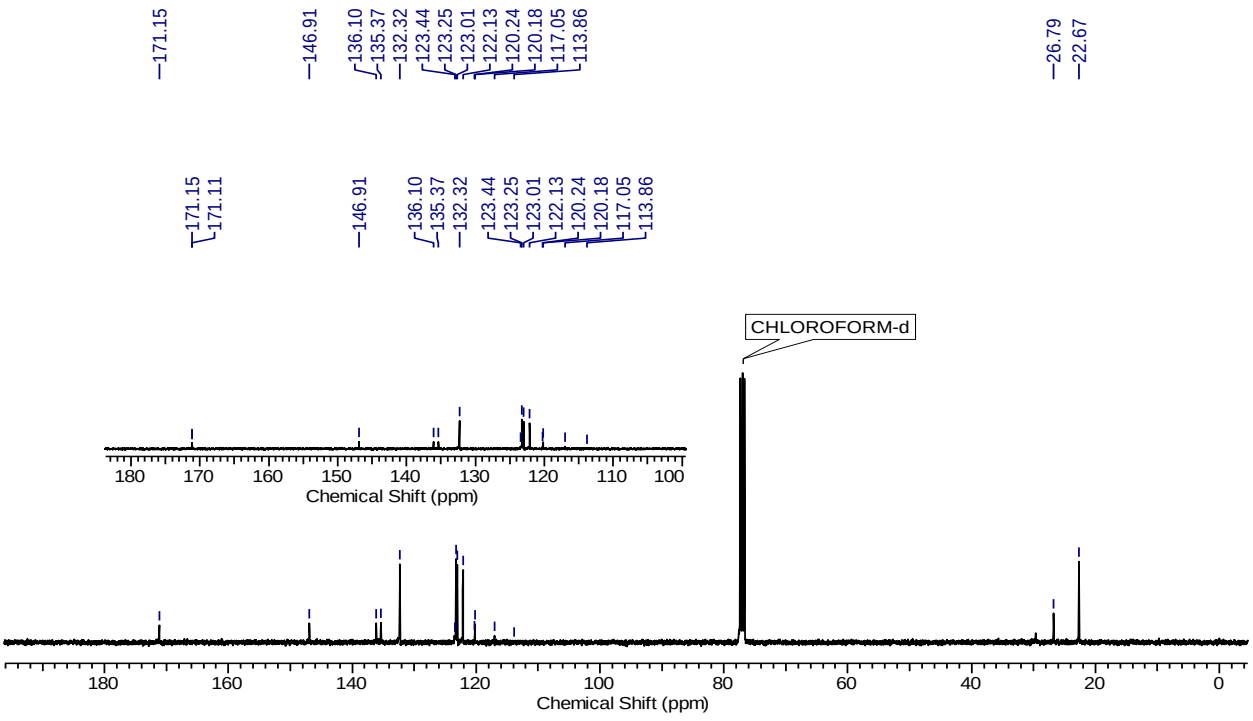
^{13}C NMR, 100 MHz



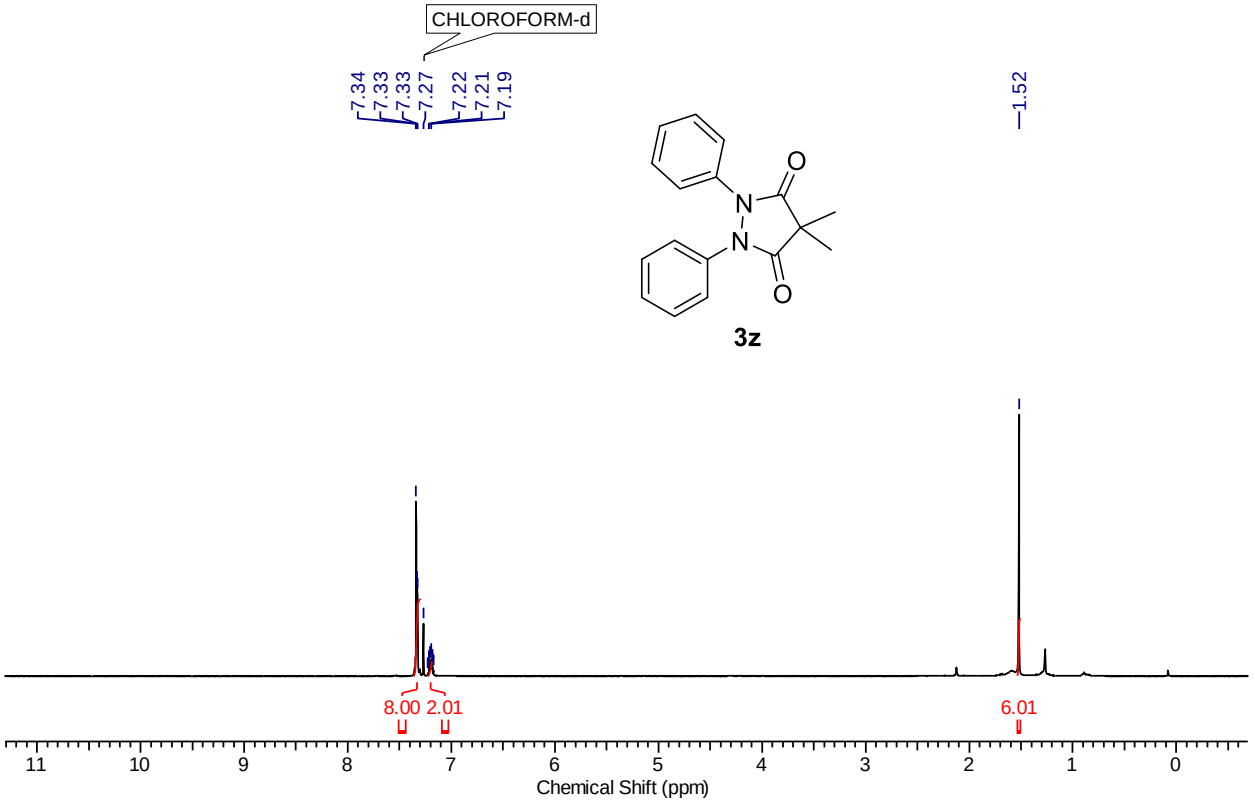
^{1}H NMR, 400 MHz



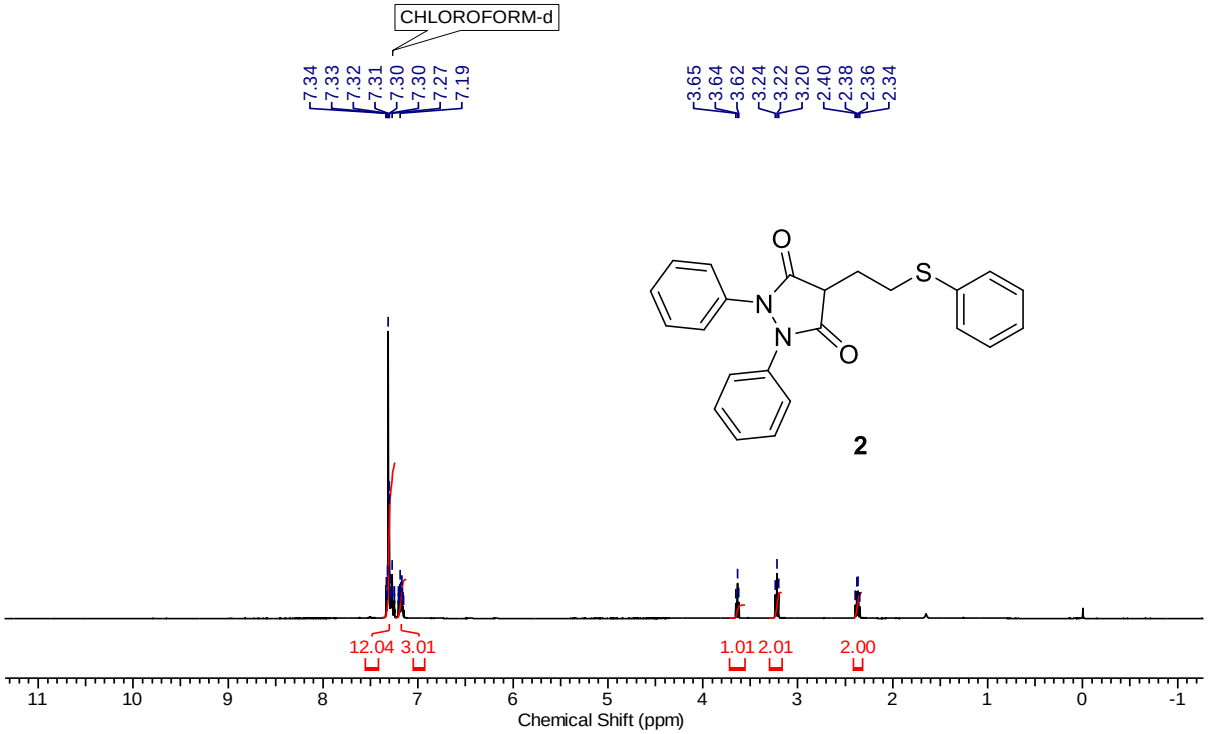
^{13}C NMR, 100 MHz



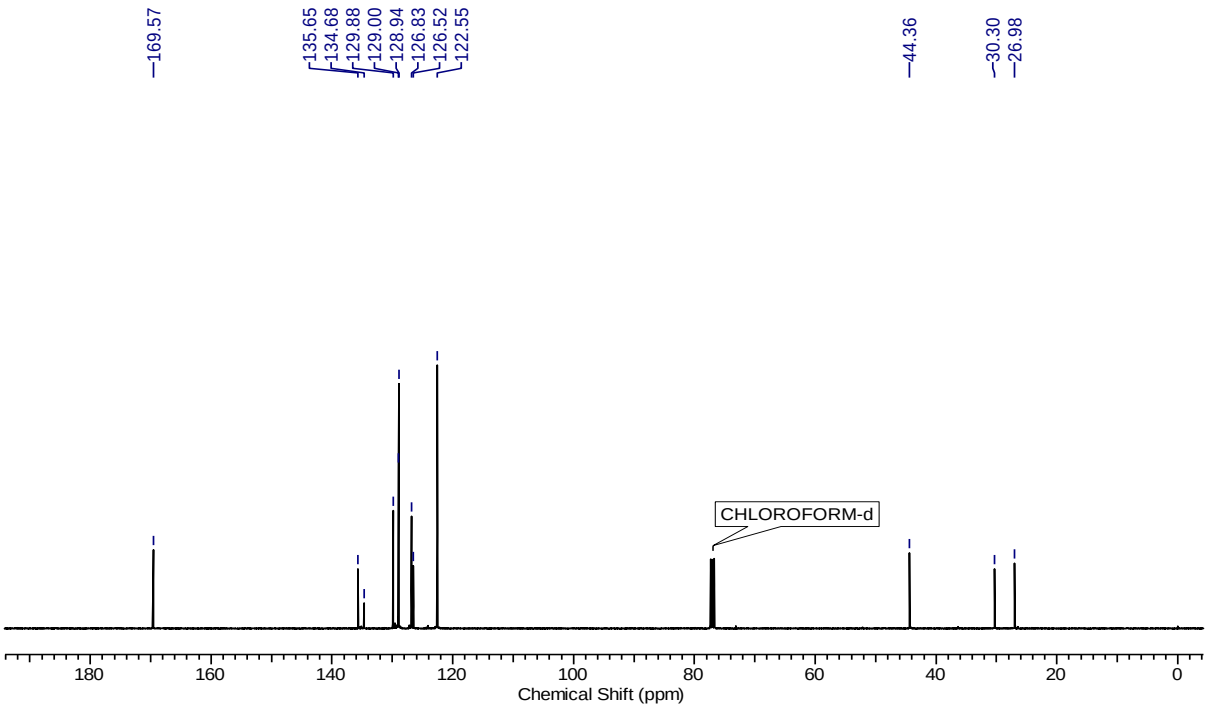
^{1}H NMR, 200 MHz



^{1}H NMR, 400 MHz



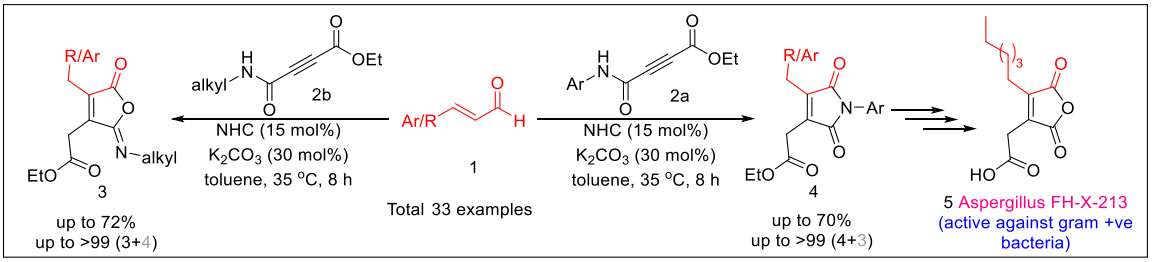
^{13}C NMR, 100 MHz



Completed Project:

Apart from my Ph. D. thesis work, I have also contributed my experience for the development of a novel process to construct highly functionalized maleimides and isomaleimides via NHC-catalyzed [3 + 2] annulation reaction α, β-unsaturated aldehydes with *N*-substituted carbamoylpropiolates and applied this protocol for the preparation of antibacterial natural product Aspergillus FH-X-213.

Scheme 1. NHC-Catalyzed Annulation Reaction and Application to Total Synthesis of Natural Product Aspergillus FH-X-213.



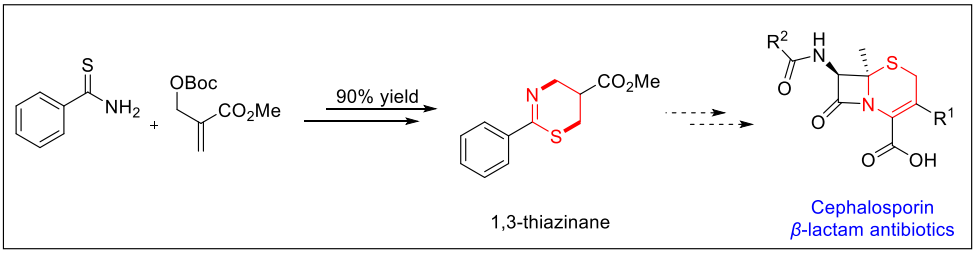
This work has been published in *J. Org. Chem.* **2021**, *86*, 9466.

Undergoing Project:

Project 1:

In this project, we have developed a new method for the construction of dihydro-1,3-thiazine core of of Cephalosporin β-lactam antibiotics. This protocol represents an annulation reaction of thiobenzamide with MBH adduct. Further, we will extend this method for the total synthesis of cephalosporine class molecule and other potential congeners to study the structure-activity relationship.

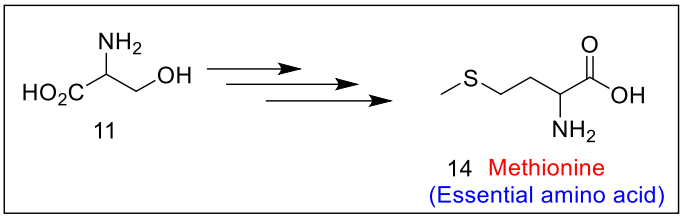
Scheme 2. Synthesis for Dihydrothiazine Core of Cephalosporins



Project 2:

This project involves the synthesis of one of the most essential amino acid methionine. We have planned to synthesis of this amino acid from easily available amino acid L-serine through the economic and environment friendly route.

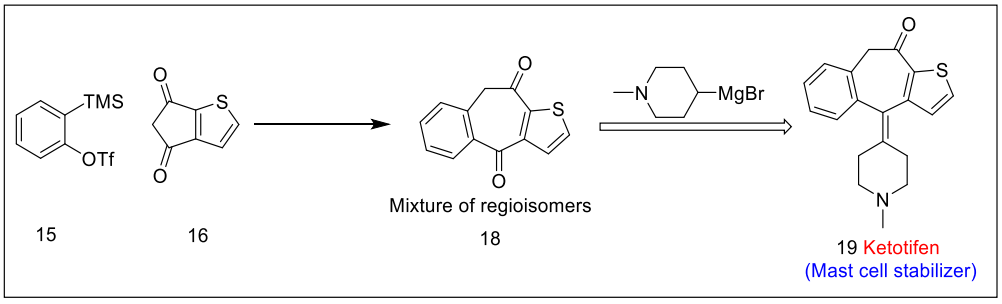
Scheme 3: Synthesis of Methionine Amino Acid



Project 3:

This project demonstrated the synthesis of ketotifen intermediate through the annulation reaction of aryne precursor with thiophene derivative **16**. However, controlling the regioselectivity of this process is challenging. We have tried many trials and error to overcome this challenge and ended up with mixture of regioisomers. We are now in processes to develop a suitable condition for regioselective synthesis of ketotifen intermediate and further convert to target ketotifen molecule.

Scheme 4: Synthesis of Ketotifen Molecule



Abstract

Name of the Student: Priyanka Halder **Registration No**.: 10CC18J26007
Faculty of Study: Chemical Science **Year of Submission**: 2023
AcSIR academic centre/CSIR Lab: NCL, Pune **Name of the Supervisor**: Dr. Santosh B. Mhaske
Title of the Thesis: Development of Novel Processes for Sulfur-Containing Scaffolds, Natural Product Orbicularisine and Uricosuric Agent Sulfinpyrazone.

From ancient times, organosulfur compounds have had a long-lasting relationship with pharmaceutical drugs and bioactive natural products. Due to the inherent properties of the sulfur atom, organosulfur compounds play a significant role in natural chemical diversity. They are widely spread all over bioactive natural products and pharmaceuticals. *Chapter 1* mainly presents a brief overview of the bioactive organosulfur compounds and it focuses on the importance of C−S bond formation for synthesizing sulfur-containing scaffolds, natural products and pharmaceuticals. *Chapter 2* includes two different methodologies for the construction of organosulfur compounds. Which is divided into two sections, *Section I* deals with the synthesis of organosulfone compounds via transition-metal-free regioselective C─S bond formation using sodium sulfinate salts as a sulfur source. Various types of organosulfone compounds were prepared through the in-situ generation of quinone imine ketal from commercially available *p*-anisidine substrates in good to excellent yield. This developed protocol is operationally simple, high yielding and does not require excess reagents and additives. The regioselectivity of this protocol was confirmed by the 2D NMR, and it also tolerates the gram scale preparation. *Section II* involves our study on the construction of highly functionalized SCF_3-containing building blocks via Lewis's base-catalyzed allylic alkylation of MBH adducts with α-SCF_3 ketones. This protocol leads to the monoalkylation of MBH adduct to achieve pharmaceutically important organofluorine compounds having SCF_3 moiety on the stereogenic carbon center with a very excellent yield. The developed protocol tolerates a wide range of substrate scopes on both substrates and shows moderate enantioselectivity for a representative substrate using the chiral Lewis base $(DHQ)_2AQN$ under the optimized reaction condition. Moreover, we have also established the application of this method for synthesizing some value-added building blocks using simple transformation of trifluoromethylthio alkylated product. *Chapter 3* portrays our efforts towards the first total synthesis of the organosulfur compound orbicularisine. Different synthetic routes and intermediates were examined to construct highly functionalized spiro-oxiindolofuranone fused thiazine moiety of orbicularisine molecule, and we have successfully built the complete skeleton of the target molecule. However, the yield of the intermediate is very low for further transformations. We have tried several reaction conditions to improve the yield and planned different synthetic routes for the construction of spiro-oxiindolofuranone fused thiazine moiety of orbicularisine, but all the efforts have been found ineffective. The work is under progress. *Chapter 4* demonstrates a new method for the construction of pyrazolidine-3,5-dione moiety by avoiding the use of toxic and expensive hydrazine building blocks. Easily accessible dianilide precursors were used to achieve structurally diverse pyrazolidine-3,5-diones derivatives via the intramolecular dehydrogenative N–N bond-forming reaction. This transformation was further applied in the development of a novel process of uricosuric agents G-25761 and sulfinpyrazone.

List of publication(s) in SCI Journal(s) emanating from the thesis work:

Publications

1. **Halder, P.**; Humne, V. T.; Mhaske, S. B. "Transition-Metal-Free Regioselective One-Pot Synthesis of Aryl Sulfones from Sodium Sulfinates via Quinone Imine Ketal" *J. Org. Chem.* **2019**, *84*, 1372-1378.

2. **Halder, P.**; Pol, M. D.; Ahire, M. M.; Mhaske, S. B. "Construction of unique SCF_3-containing building blocks via allylic alkylation of Morita–Baylis–Hillman adducts" *Org. Biomol. Chem.*, **2020**, *18*, 2085-2093.

3. 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/Isomaleimides and Synthesis of Aspergillus FH-X-213" *J. Org. Chem*. **2021**, *86*, 9466–9477.

4. **Halder, P**.; Mhaske, S. B. "PIDA-Mediated N–N Bond Formation to Access Pyrazolidine-3,5-diones: Novel Process for Uricosuric Agents G-25671 and Sulfinpyrazone" Manuscript under revision in *Chem Comm* [Received best poster award in "National Science Day Conference 2023"].

5. **Halder, P**.; Yadav, P. A.; Mhaske, S. B. "Total Synthesis of Orbicularisine" Manuscript under preparation.

Patent:

Halder, P.; Mhaske, S. B. "Pyrazolidine-3,5-dione Based Compounds and A Process for Preparation Thereof" NCLI- INV-2022-0064.

List of Papers with Abstract Presented (oral or poster) at National or International Conferences/Seminars:

1. Participated and presented poster in XIV J-NOST Conference for Research Scholars organized at CSIR-Indian Institute of Chemical Technology, Hyderabad during 28th November to 1st December, 2018.
2. Participated and presented poster on National Science Day 2019 held during February 2019, at CSIR-national Chemical Laboratory, Pune India.
3. Participated in oral presentation NCL-RF conference-2022 held during November 2022, at CSIR-national Chemical Laboratory, Pune India.
4. Participated and presented poster in "National Science Day Conference 2023" held during February 2023, at CSIR-National Chemical Laboratory, Pune, India.

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Transition-Metal-Free Regioselective One-Pot Synthesis of Aryl Sulfones from Sodium Sulfinates via Quinone Imine Ketal

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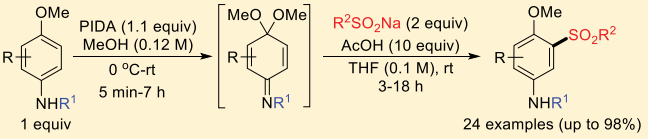
Supporting Information

ABSTRACT: A novel, efficient, and regioselective transition-metal-free one-pot synthesis of aryl sulfones via the reactive quinone imine ketal intermediate is demonstrated using easily accessible bench-stable sulfinate salts. A broad range of functionality on *p*-anisidine substrates as well as sulfinate salts was tolerated under mild reaction conditions to provide the corresponding aryl sulfones in good to excellent yields.



INTRODUCTION

Organosulfones are recognized as privileged functional groups having an immense application in agrochemicals,[1] pharmaceuticals,[2] and material chemistry.[3] Among them, aryl sulfones are known to be antifungal,[4] antibacterial,[5] and antitumoral[6] agents as well as the inhibitors of HIV-1 reverse transcriptase.[7] Figure 1 shows selected biologically active molecules featuring an aryl

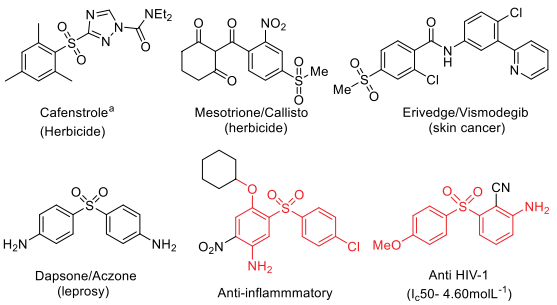
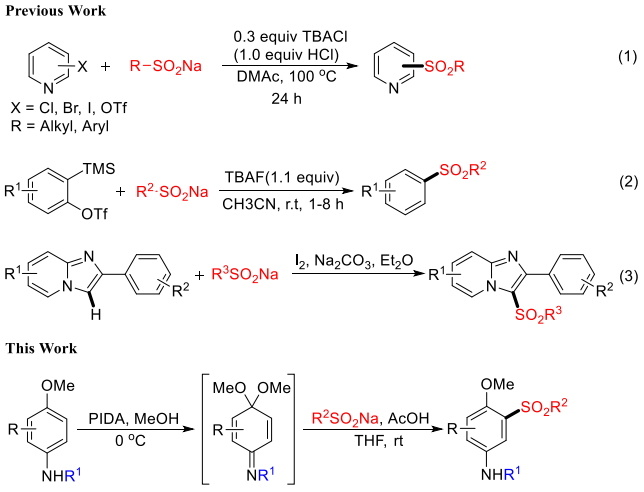


Figure 1. Bioactive compounds containing sulfone.[1,2,7]

sulfone pharmacophore.[1,2,7] In addition to their medicinal importance, aryl sulfones are also versatile reactive intermediates in organic synthesis and used in well-known organic transformations such as the Ramberg−Backlund reaction and the Julia olefination.[8] In the past decades, tremendous efforts have been devoted to the development of novel methodologies for the incorporation of sulfone-containing substituents into organic frameworks.[9] Due to their compelling synthetic utility[8] and substantial biological[1,2,4−7] as well as material applications,[3] the development of facile methods for aryl sulfones has stimulated considerable interest.

The most common method utilizes the reaction of prefunctionalized aromatic/heteroaromatic halides and sulfinate salts in the presence of a transition-metal catalyst.[9c,g,i] Recently, Peddinti et al. reported catalyst-free sulfonylation of 2-methoxyphenols via masked *o*-benzoquinone using sulfonyl hydrazides at 70 °C.[9f] Zeng et al. developed electrochemical oxidation of aminophenols in the presence of benzenesulfinate.[9j] Previously, Kolesnikov and co-workers reported sulfonylation of *N*-(arylthio)-1,4-benzoquinonimines with benzenesulfininate to obtain various aryl sulfones.[9k] In 2011, Maloney and co-workers developed the transition-metal-free sulfonylation of pyridines using sulfinate salts (Scheme 1, eq 1).[10] In 2014, we reported the method for the synthesis of aryl sulfones using in situ generated arynes (Scheme 1, eq 2).[11] Very recently, Shao and co-workers reported the difunctionalization of imidazo[1,2-*a*]-pyridine to access sulfones using sulfinate

Scheme 1. Selected Transition-Metal-Free Approaches to Aryl Sulfones Using Sodium Sulfinates



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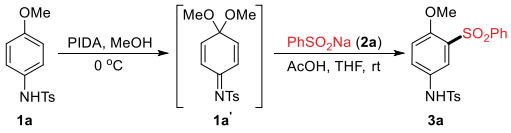
salts (Scheme 1, eq 3).[12] In addition to these advancements a few other transition-metal-free methods using sodium sulfinate salts had been developed for the synthesis of organosulfones,[13] but to the best of our knowledge, quinone imine ketal (QIK) has not been utilized for the synthesis of aryl sulfones.

QIK has emerged as the powerful synthetic intermediate for the development of novel methodologies[14] and total synthesis of natural products.[15] Their remarkable electrophilicity addresses a variety of organic transformation such as cycloaddition reaction,[14h] nucleophilic addition reaction,[14a,b,d−g] multicomponent reaction,[14c] among others. We hypothesized that the QIK formed in situ in the reaction mixture could be utilized as a latent sulfone functionalized aromatic ring employing acid-mediated activation. This design will ultimately enrich the chemistry of quinone-related compounds. Herein, we report the mild and efficient protocol for the synthesis of aryl sulfones utilizing QIK as a potent intermediate.

RESULTS AND DISCUSSION

The optimization of the protocol was achieved by changing various reaction parameters. Initially, *N*-tosyl QIK **1a′** generated in situ from *N*-tosyl *p*-anisidine (**1a**) in methanol was treated with sulfinate salt (1.1 equiv) and AcOH (10 equiv) at rt. The expected product **3a** was obtained in 32% yield in 12 h (Table 1, entry 1). To our delight, the yield

Table 1. Optimization of Reaction Conditions[a]



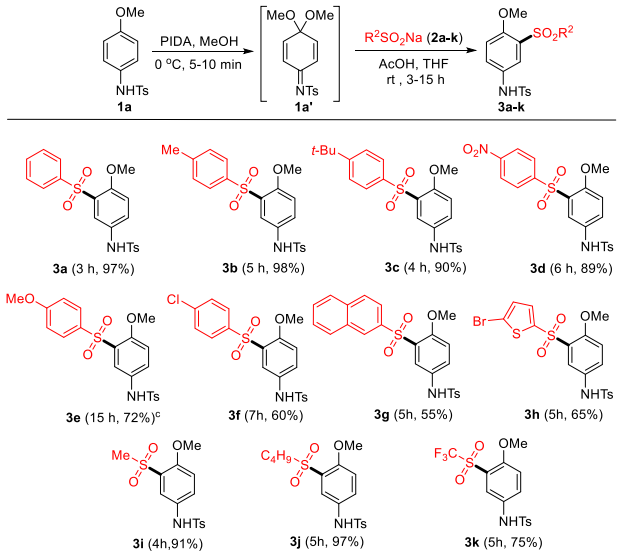
entry	solvent[b]	AcOH (equiv)	**2a** (equiv)	time (h)	yield (%)[c]
1	MeOH	10	1.1	12	32
2	THF	10	1.1	06	83
3	THF	01	1.1	12	52
4	THF	02	1.1	12	55
5	THF	08	1.1	12	60
6	THF	15	1.1	06	50
7	THF	20	1.1	06	48
8	THF	10	2.0	03	84
9[d]	THF	10	1.5	06	90
10[d]	THF	10	2.0	03	97

[a]All of the reactions were performed on a 20 mg scale of **1a**. [b]Solvent for the second step. [c]Isolated yield. [d]Acetic acid was added after 1 h to the reaction mixture containing sulfinate salt.

improved substantially and the reaction time also reduced to 6 h when THF was used as the solvent for the second step (entry 2). The addition of less or more equivalents of AcOH resulted into low yields (entries 3−7). For further improvement in the yield, more equivalents of sulfinate salt were used; however, the yield did not improve (entry 8). Hence, the addition sequence of the second step was modified. The solution of QIK **1a′** and sulfinate salt **2a** in THF was stirred for 1 h followed by the addition of acetic acid, which resulted in the enhancement of the yield (entry 9). When 2 equiv of **2a** was used, the desired product **3a** was obtained in excellent yield (entry 10).

With the optimized reaction condition (Table 1, entry 10) in hand, we investigated the substrate scope of this newly developed protocol by reacting different sulfinate salts **2a−k** with **1a** (Scheme 2). The optimized condition worked well for a variety of aryl, alkyl, and heteroaryl sulfinate salts.

Scheme 2. Synthesis of Sulfones from Various Sodium Sulfinates[a,b]



[a]Reaction was performed on a 50 mg scale of **1a**. [b]Isolated yield. [c]Reaction carried out at 60 °C.

Unsubstituted as well as alkyl-substituted aryl sulfone moiety-containing compounds **3a**, **3b**, and **3c** were formed in excellent yields. The aryl sulfinate containing an electron-withdrawing substituent furnished the corresponding sulfone **3d** in an excellent yield under the optimized condition. On the other hand, probably due to the electron-releasing effect of the methoxy group, aryl sulfinate **2e** needed a little extra time and temperature than anticipated to obtain the product **3e** in a better yield. The halo-substituted sulfinate salt showed a similar effect on the reaction, and the desired product **3f** was formed in a moderate yield. The polyaromatic sulfinate salt reacted well and conceded the product **3g** in a moderate yield. The sulfinate salt having the heteroaromatic ring also underwent the reaction smoothly to provide the product **3h** in a good yield. Overall, the reaction of sulfinate salts having an electron-rich aromatic ring (**2e−h**) was slower and provided lower yields as compared to the aryl sulfinate salts having an electron-neutral/deficient aromatic ring (**2a−d**). Pleasingly, aliphatic sulfinate salts also reacted well under the developed protocol and the corresponding sulfones **3i** and **3j** were synthesized in excellent yields. Trifluoromethyl-substituted sulfone **3k** was synthesized in a very good yield under these conditions.

After exploring the reactivity pattern of various sulfinate salts, we further planned to explore the scope of the reaction using variously substituted *p*-anisidines (Schemes 3 and 4). Various N-substituents, as well as O-substituents on *p*-anisidines (**1b−i**), were tested under the developed protocol. The in situ formation of QIKs (**1b′−f′**) from the corresponding amide- and carbamate-containing substrates (**1b−f**) required addition of triethylamine and more time as compared to the sulfonamide-containing substrates (**1g−i**). The benzoate-protected *p*-anisidine **1b** provided the product **3l** in an excellent yield, whereas pivaloyl-protected *p*-anisidine **1c** furnished sulfone **3m** in a low yield. It can be reasoned that the steric hindrance of the bulkier pivaloyl moiety present in

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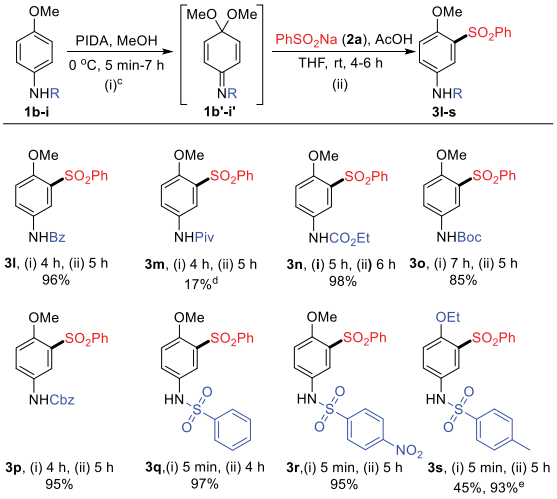
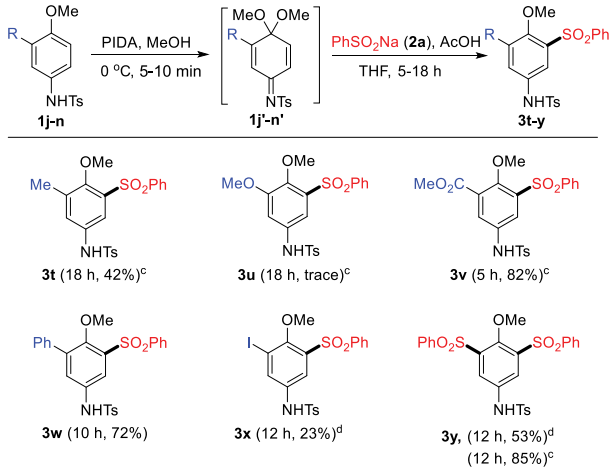
Scheme 3. Synthesis of Sulfones from Various N,O-Substituted *p*-Anisidines[a,b]



[a]Reaction was performed on a 50 mg scale of **1b,d−i**. [b]Isolated yield. [c]Triethylamine (3 equiv) was used for the preparation of QIK **1b′−f′**. [d]Reaction was performed on a 100 mg scale of **1c**. [e]Reaction carried out at 60 °C.

Scheme 4. Synthesis of Sulfones Using Various Aryl Ring-Substituted *p*-Anisidines[a,b]



[a]Reaction was performed on a 50 mg scale of **1j−m**. [b]Isolated yield. [c]Reaction at 60 °C. [d]Reaction was performed on a 100 mg scale of **1n**.

the close proximity of the amide nitrogen resists the reaction with PIDA. The carbamate group-containing substrates **1d**, **1e**, and **1f** provided the desired products **3n**, **3o**, and **3p**, respectively, in very good yields. Various sulfonamide-containing sulfones **3q** and **3r** were synthesized in excellent yields. The scope of the protocol was also tested using ethoxy-substituted sulfonamide substrate **1i**, and the expected product **3s** was formed in a moderate yield under the optimized protocol. The steric hindrance of the ethyl group might be inhibiting the nucleophilic attack of the sulfinate salt at rt. However, the yield of **3s** was significantly increased to 93% by elevating the reaction temperature.

The scope of the reaction using various substituents on the aryl ring of *p*-anisidines was also studied (Scheme 4). It has been observed that a higher temperature was necessary for the reaction with methyl-substituted *p*-anisidine to obtain the sulfone **3t** in a moderate yield. Unfortunately, electron-donating substituents on *p*-anisidine did not afford the sulfone **3u** under the developed protocol. Hence, we isolated the corresponding QIK **1k′** and performed the next reaction, but the product **3u** was formed in only a trace amount. We were unable to isolate sufficient quantity of the product **3u** by usual flash column chromatography, but HRMS analysis showed the product formation. The electron-withdrawing group on the *p*-anisidine moiety was well-tolerated, and the product **3v** was obtained in a very good yield at a little higher temperature. The phenyl-substituted compound **3w** was formed in a good yield. Interestingly, from the substrate **1n** containing an iodine group, two different products, **3x** and **3y**, were formed under the optimized conditions, but at a high temperature, exclusively disulfone **3y** was formed in a good yield. The product **3y** may be formed by the displacement of an iodine group. In general, substituted *p*-anisidines resulted in inferior yields (Scheme 4) than that of the unsubstitued *p*-anisidnes (Schemes 2 and 3) because the reaction leads to a more substituted aromatic ring. Furthermore, the presence of electron-rich substituents on *p*-anisidines (**1j**, **1k**) provided lower yields (**3t**, **3u**) due to less electrophilic QIK intermediates, whereas *p*-anisidines having electron-withdrawing substituents (**1l**, **1m**, and **1n**) provided better yields (**3v**, **3w** and **3x**, **3y**) because of the more electrophilic QIK intermeidates.

The regioselectivity of the interesting protocol was confirmed by the 2D NMR analysis of the substrates **3a**, **3v**, **3x**, and **3y**. The scalability of the reaction was also investigated. We performed the reaction of **1a** on 1 mmol scale, and the expected product **3a** was obtained in 88% yield.

A plausible mechanism of the reaction based on the above observations and literature report[16] is depicted in Figure 2.

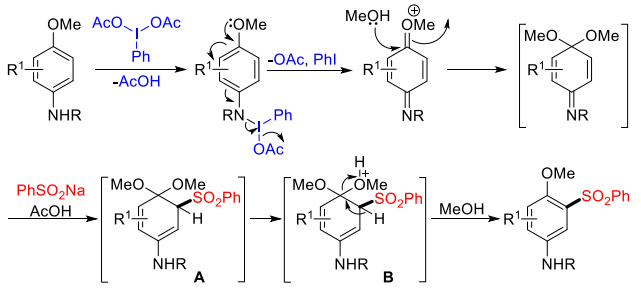


Figure 2. Plausible reaction mechanism.

First, the QIK was formed in the presence of PIDA by the usual mechanism.[17] Phenyl sulfinate attacks QIK to form the intermediate **A** by Michael addition. The rearomatization occurs by the removal of methanol in the presence of acetic acid to get the desired sulfone product.

CONCLUSION

In conclusion, a convenient one-pot transition-metal-free protocol has been developed for the preparation of aryl sulfones regioselectively via the formation of QIKs in good to excellent yields. This developed protocol is operationally simple, high yielding, and does not require excess reagent and additives. Various types of sulfones such as diaryl sulfones, aryl-alkyl sulfones, and aryl-heteroaryl sulfones can be prepared easily by following this method. We are in the process of

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applying this method for the synthesis of bioactive molecules, natural products, drugs, and drug intermediates.

EXPERIMENTAL SECTION

General Considerations. All reagents and solvents were used as received from commercial sources unless and otherwise noted. All experiments were carried out in a round-bottom flask equipped with a stirring bar. Aluminum plates precoated with silica gel 60 PF254, 0.25 mm or 0.5 mm, were utilized for thin-layer chromatography (TLC) to monitor the progress of a reaction. Visualization of the developed TLC plate was performed by irradiation with UV light. Column chromatographic purifications were carried out on flash silica gel (240−400 mesh) using ethyl acetate and petroleum ether as eluents. The ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were recorded on 200/400/500 MHz and 100/125 MHz NMR spectrometers, respectively, in $CDCl_3$ or DMSO-d_6. Chemical shifts were reported as δ values from standard peaks. The melting points were recorded on a Buchi instrument and are uncorrected. High-resolution mass spectrometry (HRMS) was performed on a TOF/Q-TOF mass spectrometer. All of the N-substituted *p*-anisidines were prepared using known literature procedures.[14f,18] The quinone imine ketals were prepared in situ as per the literature procedures.[14f,17a] Sodium sulfinates **2a**, **2i**, and **2k** were purchased from commercial sources, and the rest of the sodium sulfinates were prepared using known literature procedures.[13e,19]

Experimental Procedures. *General Experimental Procedure for the Synthesis of Sulfones. Synthesis of Sulfones **3a**−**k**.* To a solution of tosylated *p*-anisidine **1a** (50 mg, 1 equiv) in methanol (0.12 M) was added (diacetoxyiodo)benzene (PIDA, 64 mg, 1.1 equiv) at 0 °C. The resulting mixture was stirred at 0 °C, and the reaction progress was monitored by TLC (approximately 5 min). After complete consumption of **1a**, MeOH was evaporated on a rotatory evaporator and the residue was dissolved in THF (0.1 M). To this solution was added the corresponding sulfinate salt **2a**−**k** (2 equiv), and the reaction mixture was stirred for 1 h at room temperature followed by the addition of AcOH (10 equiv). After stirring for 3−15 h at room temperature, THF was evaporated in vacuo and the residue was purified by flash silica gel column chromatography using a gradient of ethyl acetate−petroleum ether to afford the corresponding sulfones **3a**−**k** in good to excellent yields.

*Synthesis of Sulfones **3l**−**p**.* To a solution of N-substituted *p*-anisidine **1b**−**f** (50 mg, 1 equiv) and NEt_3 (3 equiv) in MeOH (0.34 M) was added a solution of PIDA (2 equiv) in MeOH (0.34 M) dropwise at 0 °C under an argon atmosphere. The reaction mixture was stirred at 0 °C for 1 h and gradually warmed to rt. After complete consumption of **1b**−**f**, MeOH was evaporated on a rotatory evaporator and the residue was dissolved in THF (0.1 M). To the resulting solution was added sulfinate salt **2a** (2 equiv), and the reaction mixture was stirred for 1 h at room temperature followed by the addition of AcOH (10 equiv). After the mixture was stirred for 4−6 h at room temperature, THF was evaporated on a rotatory evaporator and the residue was purified by flash silica gel column chromatography using a gradient of ethyl acetate−petroleum ether to afford the corresponding sulfones **3l**−**p** in good to excellent yields.

*Synthesis of Sulfones **3q**−**y**.* To a solution of N-substituted *p*-anisidine **1g**−**n** (50 mg, 1 equiv) in methanol (0.12 M) was added PIDA (1.1 equiv) at 0 °C. The resulting mixture was stirred at 0 °C, and the reaction progress was monitored by TLC (approximately 5 min). After complete consumption of **1g**−**n**, MeOH was evaporated on a rotatory evaporator and the residue was dissolved in THF (0.1 M). To this solution was added sulfinate salt **2a** (2 equiv), and the reaction mixture was stirred for 1 h at room temperature followed by the addition of AcOH (10 equiv). After the mixture was stirred for 4−18 h at room temperature, THF was evaporated in vacuo and the residue was purified by flash silica gel column chromatography using a gradient of ethyl acetate−petroleum ether to afford the corresponding sulfones **3q**−**y** in good to excellent yields.

*Typical Experimental Procedure for the Preparation of **3a** on a 0.18 mmol Scale.* To a solution of **1a** (50 mg, 1 equiv) in methanol (1.5 mL, 0.12 M) was added PIDA (64 mg, 1.1 equiv) at 0 °C. The resulting mixture was stirred at 0 °C, and the reaction progress was monitored by TLC (approximately 5 min). After complete consumption of **1a**, MeOH was evaporated on a rotatory evaporator and the residue was dissolved in THF (1.8 mL, 0.1 M). To this solution was added **2a** (59 mg, 2 equiv), and the reaction mixture was stirred for 1 h at room temperature followed by the addition of AcOH (108 μL, 10 equiv). After stirring for 3 h at room temperature, THF was evaporated in vacuo and the residue was purified by flash silica gel column chromatography using a gradient of ethyl acetate−petroleum ether (2:3) to afford the sulfone **3a** in 97% yield (73 mg).

*Experimental Procedure for the Preparation of **3a** on a 1 mmol Scale.* To a solution of **1a** (277 mg, 1 mmol) in methanol (8.3 mL, 0.12 M) was added PIDA (354 mg, 1.1 mmol) at 0 °C. The resulting mixture was stirred at 0 °C, and the reaction progress was monitored by TLC (approximately 5 min). After complete consumption of **1a**, MeOH was evaporated on a rotatory evaporator and the residue was dissolved in THF (10 mL, 0.1 M). To this solution was added **2a** (328 mg, 2 mmol), and the reaction mixture was stirred for 1 h at room temperature followed by the addition of AcOH (600 μL, 10 mmol). After stirring for 3 h at room temperature, THF was evaporated in vacuo and the residue was purified by flash silica gel column chromatography using a gradient of ethyl acetate−petroleum ether (2:3) to afford the sulfone **3a** in 88% yield (367 mg).

*N-(4-Methoxy-3-(phenylsulfonyl)phenyl)-4-methylbenzenesulfonamide (**3a**).* This compound was obtained as an off white solid (73 mg, 97% yield): mp 190−192 °C; reaction time 3 h; R_f 0.5 (2:3 EtOAc−petroleum ether); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.21 (s, 1H), 7.76−7.66 (m, 4H), 7.59 (d, J = 7.9 Hz, 4H), 7.41−7.30 (m, 3H), 7.06 (d, J = 9.2 Hz, 1H), 3.64 (s, 3H), 2.37 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMS-d_6) δ 153.6, 143.4, 140.5, 136.0, 133.5, 130.4, 129.7, 129.2, 129.0, 128.2, 127.7, 126.8, 121.9, 114.4, 56.2, 20.9; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{20}H_{19}NO_5S_2Na$ 440.0597, found 440.0594.

*N-(4-Methoxy-3-tosylphenyl)-4-methylbenzenesulfonamide (**3b**).* This compound was obtained as a white solid (76 mg, 98% yield): mp 191−193 °C; reaction time 5 h; R_f 0.7 (2:3 EtOAc−petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 7.9 Hz, 2H), 7.63−7.55 (m, 3H), 7.51 (dd, J = 8.6 and 2.4 Hz, 1H), 7.31−7.23 (m, 4H), 6.84 (d, J = 9.2 Hz, 1H), 6.71 (s, 1H), 3.74 (s, 3H), 2.43 (s, 6H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 155.0, 144.2 (2C), 137.8, 135.5, 131.0, 129.8, 129.5, 129.2 (2C), 128.5, 127.3, 124.6, 113.4, 56.2, 21.6; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{21}H_{21}NO_5S_2Na$ 454.0753, found 454.0751.

*N-(3-((4-(tert-Butyl)phenyl)sulfonyl)-4-methoxyphenyl)-4-methylbenzenesulfonamide (**3c**).* This compound was obtained as a white solid (77 mg, 90% yield): mp 176−178 °C; reaction time 4 h; R_f 0.6 (2:3 EtOAc−petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.6 Hz, 2H), 7.64−7.57 (m, 3H), 7.53−7.45 (m, 3H), 7.25 (d, J = 8.5 Hz, 2H), 6.87 (s, 1H), 6.84 (d, J = 9.2 Hz, 1H), 3.76 (s, 3H), 2.42 (s, 3H), 1.33 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 157.1, 155.0, 144.1, 137.7, 135.5, 130.8, 129.8, 129.4, 129.2, 128.3, 127.3, 125.5, 124.6, 113.4, 56.2, 35.2, 31.0, 21.6; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{24}H_{27}NO_5S_2Na$ 496.1223, found 496.1222.

*N-(4-Methoxy-3-((4-nitrophenyl)sulfonyl)phenyl)-4-methylbenzenesulfonamide (**3d**).* This compound was obtained as a pale yellow solid (74 mg, 89% yield): mp 171−173 °C; reaction time 6 h; R_f 0.5 (2:3 EtOAc−petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, J = 6.7 Hz, 2H), 8.05 (d, J = 7.3 Hz, 2H), 7.72 (s, 1H), 7.65 (d, J = 7.3 Hz, 2H), 7.52 (d, J = 8.6 Hz, 1H), 7.28 (d, J = 6.1 Hz, 2H), 7.19 (s, 1H), 6.87 (d, J = 8.6 Hz, 1H), 3.76 (s, 3H), 2.44 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 154.8, 150.4, 146.4, 144.4, 135.4, 131.4, 129.8, 129.7 (2C), 127.6, 127.3, 124.4, 123.8, 113.5, 56.3, 21.6; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{20}H_{18}N_2O_7S_2Na$ 485.0448, found 485.0445.

*N-(4-Methoxy-3-((4-methoxyphenyl)sulfonyl)phenyl)-4-methylbenzenesulfonamide (**3e**).* This compound was obtained as a white solid (58 mg, 72% yield (at 60 °C)): mp 178−180 °C; reaction time 15 h; R_f 0.4 (1:1 EtOAc−petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.5 Hz, 2H), 7.64−7.56 (m, 3H), 7.50 (dd, J = 8.5 and 2.4 Hz, 1H), 7.25 (d, J = 7.9 Hz, 2H), 6.94 (d, J = 8.5 Hz, 2H),

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6.83 (d, J = 8.6 Hz, 1H), 6.75 (s, 1H), 3.87 (s, 3H), 3.76 (s, 3H), 2.43 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 163.4, 154.9, 144.1, 135.6, 132.3, 130.7 (2C), 129.9, 129.8, 129.2, 127.3, 124.4, 113.7, 113.4, 56.2, 55.6, 21.6; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{21}H_{21}NO_6S_2Na$ 470.0702, found 470.0699.

*N-(3-((4-Chlorophenyl)sulfonyl)-4-methoxyphenyl)-4-methylbenzenesulfonamide (**3f**).* This compound was obtained as a white solid (49 mg, 60% yield): mp 186−188 °C; reaction time 7 h; R_f 0.4 (2:3 EtOAc−petroleum ether); ^1H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, J = 8.8 Hz, 2H), 7.66−7.61 (m, 3H), 7.54 (dd, J = 8.8 and 2.3 Hz, 1H), 7.47 (d, J = 8.4 Hz, 2H), 7.32−7.25 (m, 2H), 6.90 (s, 1H), 6.87 (d, J = 8.8 Hz, 1H), 3.77 (s, 3H), 2.45 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 154.9, 144.2, 139.9, 139.2, 135.6, 131.1, 129.9, 129.8, 129.4, 128.9, 128.8, 127.3, 124.5, 113.4, 56.2, 21.6; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{20}H_{19}ClNO_5S_2$ 452.0388, found 452.0383.

*N-(4-Methoxy-3-(naphthalen-2-ylsulfonyl)phenyl)-4-methylbenzenesulfonamide (**3g**).* This compound was obtained as a white solid (46 mg, 55% yield): mp 168−170 °C; reaction time 5 h; R_f 0.5 (2:3 EtOAc−petroleum ether); ^1H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 7.99 (d, J = 7.9 Hz, 1H), 7.91 (d, J = 6.1 Hz, 2H), 7.81−7.74 (m, 2H), 7.71−7.60 (m, 4H), 7.52 (dd, J = 9.2 and 3.1 Hz, 1H), 7.27 (t, J = 8.2 Hz, 2H), 7.14 (s, 1H), 6.82 (d, J = 8.5 Hz, 1H), 3.71 (s, 3H), 2.43 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 154.9, 144.1, 137.6, 135.5, 135.0, 131.9, 130.8, 130.2, 129.7, 129.4, 129.3, 129.1, 129.0, 128.6, 127.8, 127.4, 127.3, 124.5, 123.2, 113.4, 56.2, 21.6; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{24}H_{21}NO_5S_2Na$ 490.0753, found 490.0751.

*N-(3-((5-Bromothiophen-2-yl)sulfonyl)-4-methoxyphenyl)-4-methylbenzenesulfonamide (**3h**).* This compound was obtained as an off white solid (59 mg, 65% yield): mp 177−179 °C; reaction time 5 h; R_f 0.5 (1:1 EtOAc−petroleum ether); ^1H NMR (400 MHz, $CDCl_3$) δ 7.61−7.51 (m, 4H), 7.46 (s, 1H), 7.26 (d, J = 7.9 Hz, 2H), 7.05 (s, 1H), 6.93 (d, J = 8.5 Hz, 1H), 6.64 (s, 1H), 3.92 (s, 3H), 2.43 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 155.1, 144.3, 142.5, 135.4, 134.5, 131.4, 130.2, 129.9, 129.4, 129.1, 127.3, 124.3, 122.0, 113.5, 56.3, 21.6; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{18}H_{16}{}^{81}BrNO_5S_3Na$ 525.9246, found 525.9241.

*N-(4-Methoxy-3-(methylsulfonyl)phenyl)-4-methylbenzenesulfonamide (**3i**).* This compound was obtained as a white solid (58 mg, 91% yield): mp 206−208 °C; reaction time 4 h; R_f 0.5 (1:1 EtOAc−petroleum ether); ^1H NMR (400 MHz, DMSO-d_6) δ 10.24 (s, 1H), 7.59 (d, J = 7.9 Hz, 2H), 7.54 (d, J = 2.4 Hz, 1H), 7.37−7.32 (m, 3H), 7.19 (d, J = 8.5 Hz, 1H), 3.86 (s, 3H), 3.18 (s, 3H), 2.33 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 153.6, 143.4, 136.2, 130.4, 129.8, 128.5, 128.0, 126.7, 121.3, 114.1, 56.5, 42.5, 21.0; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{15}H_{17}NO_5S_2Na$ 378.0440, found 378.0439.

*N-(3-(Butylsulfonyl)-4-methoxyphenyl)-4-methylbenzenesulfonamide (**3j**).* This compound was obtained as a white solid (69 mg, 97% yield): mp 134−136 °C; reaction time 5 h; R_f 0.5 (2:3 EtOAc−petroleum ether); ^1H NMR (400 MHz, $CDCl_3$) δ 7.65−7.57 (m, 3H), 7.43 (d, J = 3.1 Hz, 1H), 7.22 (d, J = 7.9 Hz, 2H), 7.03 (s, 1H), 6.98 (d, J = 8.5 Hz, 1H), 3.94 (s, 3H), 3.29 (t, J = 7.9 Hz, 2H), 2.38 (s, 3H), 1.54 (m, 2H), 1.37 (m, 2H), 0.88 (t, J = 7.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 155.0, 144.1, 135.6, 130.3, 129.8, 129.7, 127.3, 127.0, 124.8, 113.3, 56.6, 53.9, 24.4, 21.5, 21.4, 13.5; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{24}NO_5S_2$ 398.1090, found 398.1085.

*N-(4-Methoxy-3-((trifluoromethyl)sulfonyl)phenyl)-4-methylbenzenesulfonamide (**3k**).* This compound was obtained as a white solid (55 mg, 75% yield): mp 112−114 °C; reaction time 5 h; R_f 0.5 (2:3 EtOAc−petroleum ether); ^1H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 7.87 (d, J = 9.8 Hz, 1H), 7.75 (d, J = 8.3 Hz, 2H), 7.28 (m, 4H), 3.81 (s, 3H), 2.40 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 155.7, 144.8, 135.6, 133.1, 129.9, 127.4, 125.6, 122.3, 119.6 (q, J = 326.0 Hz, CF_3), 117.4, 115.7, 56.0, 21.6; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{15}F_3NO_5S_2$ 410.0338, found 410.0334.

*N-(4-Methoxy-3-(phenylsulfonyl)phenyl)benzamide (**3l**).* This compound was obtained as a white solid (78 mg, 96% yield): mp 176−178 °C; reaction time 5 h; R_f 0.5 (2:3 EtOAc−petroleum ether); ^1H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 8.37 (dd, J = 8.5 and 1.8 Hz, 1H), 8.26 (d, J = 2.4 Hz, 1H), 7.94 (d, J = 7.9 Hz, 2H), 7.87 (d, J = 7.3 Hz, 2H), 7.56 (t, J = 7.3 Hz, 1H), 7.50−7.40 (m, 3H), 7.31 (t, J = 7.6 Hz, 2H), 6.91 (d, J = 9.2 Hz, 1H), 3.72 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (one aromatic carbon overlaps) 166.1, 153.4, 140.9, 134.2, 133.1, 131.8, 131.7, 128.5, 128.5, 128.4, 128.3, 127.2, 121.7, 113.2, 56.2; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{20}H_{18}NO_4S$ 368.0951, found 368.0946.

*N-(4-Methoxy-3-(phenylsulfonyl)phenyl)pivalamide (**3m**).* This compound was obtained as a white solid (28 mg, 17% yield): mp 129−131 °C; reaction time 5 h; R_f 0.6 (2:3 EtOAc−petroleum ether); ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (dd, J = 8.3 and 2.3 Hz, 1H), 8.00 (d, J = 2.3 Hz, 1H), 7.96 (d, J = 7.5 Hz, 2H), 7.65 (s, 1H), 7.57 (t, J = 7.5 Hz, 1H), 7.48 (t, J = 7.5 Hz, 2H), 6.87 (d, J = 9.0 Hz, 1H), 3.72 (s, 3H), 1.30 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 177.0, 153.5, 141.1, 133.1, 131.4, 128.6, 128.5, 128.3, 128.2, 121.7, 113.2, 56.2, 39.5, 27.5; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{22}NO_4S$ 348.1264, found 348.1260.

*Ethyl (4-Methoxy-3-(phenylsulfonyl)phenyl)carbamate (**3n**).* This compound was obtained as a white solid (84 mg, 98% yield): mp 141−143 °C; reaction time 6 h; R_f 0.4 (2:3 EtOAc−petroleum ether); ^1H NMR (400 MHz, $CDCl_3$) δ 7.98−7.95 (m, 3H), 7.84 (bs, 1H), 7.60−7.55 (m, 1H), 7.51−7.45 (m, 2H), 6.93 (s, 1H), 6.87 (d, J = 9.2 Hz, 1H), 4.22 (q, J = 7.6 Hz, 2H), 3.72 (s, 3H), 1.29 (t, J = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 153.9, 153.0, 141.1, 133.0, 131.3, 128.9, 128.5, 128.4, 126.4, 120.5, 113.4, 61.4, 56.2, 14.5; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{16}H_{18}NO_5S$ 336.0900, found 336.0897.

*tert-Butyl (4-Methoxy-3-(phenylsulfonyl)phenyl)carbamate (**3o**).* This compound was obtained as a white solid (69 mg, 85% yield): mp 182−184 °C; reaction time 5 h; R_f 0.6 (2:3 EtOAc−petroleum ether); ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 7.3 Hz, 3H), 7.81 (bs, 1H), 7.57 (t, J = 7.3 Hz, 1H), 7.48 (t, J = 7.6 Hz, 2H), 6.85 (d, J = 8.5 Hz, 1H), 6.74 (s, 1H), 3.71 (s, 3H), 1.51 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 152.9, 152.8, 141.3, 133.0, 131.8, 129.1, 128.5, 128.4, 126.2, 120.5, 113.4, 80.9, 56.2, 28.3; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{18}H_{21}NO_5SNa$ 386.1033, found 386.1031.

*Benzyl (4-Methoxy-3-(phenylsulfonyl)phenyl)carbamate (**3p**).* This compound was obtained as a white solid (73 mg, 95% yield): mp 170−172 °C; reaction time 5 h; R_f 0.6 (2:3 EtOAc−petroleum ether); ^1H NMR (400 MHz, $CDCl_3$) δ 8.00−7.91 (m, 3H), 7.85 (bs, 1H), 7.57 (t, J = 7.3 Hz, 1H), 7.47 (t, J = 8.0 Hz, 2H), 7.41−7.29 (m, 5H), 7.00 (s, 1H), 6.86 (d, 9.2 Hz, 1H), 5.20 (s, 2H), 3.72 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 153.6, 153.1, 141.0, 135.9, 133.0, 131.1, 129.0, 128.6, 128.5, 128.4, 128.3, 128.2, 126.4, 120.6, 113.4, 67.1, 56.2; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{21}H_{20}NO_5S$ 398.1057, found 398.1053.

*N-(4-Methoxy-3-(phenylsulfonyl)phenyl)benzenesulfonamide (**3q**).* This compound was obtained as a white solid (74 mg, 97% yield): mp 173−175 °C; reaction time 4 h; R_f 0.5 (2:3 EtOAc−petroleum ether); ^1H NMR (400 MHz, DMSO-d_6) δ 10.28 (s, 1H), 7.72−7.62 (m, 7H), 7.61−7.52 (m, 4H), 7.35 (dd, J = 8.5 and 1.8 Hz, 1H), 7.06 (d, J = 9.2 Hz, 1H), 3.64 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 153.8, 140.5, 138.8, 133.6, 133.1, 130.2, 129.6, 129.3, 129.0, 128.3, 127.8, 126.8, 122.3, 114.4, 56.2; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{19}H_{18}NO_5S_2$ 404.0621, found 404.0616.

*N-(4-Methoxy-3-(phenylsulfonyl)phenyl)-4-nitrobenzenesulfonamide (**3r**).* This compound was obtained as a pale yellow solid (69 mg, 95% yield): mp 183−185 °C; reaction time 5 h; R_f 0.5 (1:1 EtOAc−petroleum ether); ^1H NMR (400 MHz, DMSO-d_6) δ 10.64 (s, 1H), 8.41 (d, J = 9.2 Hz, 2H), 7.95 (d, J = 8.4 Hz, 2H), 7.75 (d, J = 6.9 Hz, 2H), 7.72−7.63 (m, 2H), 7.56 (t, J = 7.6 Hz, 2H), 7.37 (dd, J = 9.2 and 3.1 Hz, 1H), 7.10 (d, J = 9.2 Hz, 1H), 3.66 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 154.2, 150.0, 144.2, 140.4, 133.7, 130.0, 129.4, 129.0, 128.5, 128.4, 127.9, 124.7, 122.7, 114.6, 56.3; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{19}H_{17}N_2O_7S_2$ 449.0472, found 449.0466.

*N-(4-Ethoxy-3-(phenylsulfonyl)phenyl)-4-methylbenzenesulfonamide (**3s**).* This compound was obtained as a white solid [33 mg,

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45% yield (at rt); 69 mg, 93% yield (at 60 °C)]: mp 168−170 °C; reaction time 5 h; R_f 0.5 (2:3 EtOAc−petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 7.3 Hz, 2H), 7.66−7.56 (m, 4H), 7.53−7.43 (m, 3H), 7.25 (d, J = 7.9 Hz, 2H), 6.94 (s, 1H), 6.80 (d, J = 9.2 Hz, 1H), 3.94 (q, J = 7.3 Hz, 2H), 2.42 (s, 3H), 1.28 (t, J = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 154.4, 144.1, 140.8, 135.5, 133.1, 131.1, 129.7, 129.0, 128.8, 128.6, 128.4, 127.3, 124.6, 113.9, 65.0, 21.6, 14.2; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{21}H_{22}NO_5S_2$ 432.0934, found 432.0928.

*N-(4-Methoxy-3-methyl-5-(phenylsulfonyl)phenyl)-4-methylbenzenesulfonamide (**3t**).* This compound was obtained as a white solid [31 mg, 42% yield (at 60 °C)]: mp 169−171 °C; reaction time 18 h; R_f 0.6 (2:3 EtOAc−petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 7.6 Hz, 2H), 7.68 (d, J = 8.4 Hz, 2H), 7.58 (t, J = 7.6 Hz, 1H), 7.53 (d, J = 3.1 Hz, 1H), 7.47 (t, J = 8.1 Hz, 2H), 7.35 (d, J = 2.3 Hz, 1H), 7.26 (d, J = 8.4 Hz, 3H), 3.78 (s, 3H), 2.42 (s, 3H), 2.20 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 153.8, 144.2, 141.2, 135.7, 135.1, 134.9, 133.2, 132.5, 130.7, 129.8, 128.7, 127.9, 127.3, 120.2, 61.8, 21.6, 16.2; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{21}H_{21}NO_5S_2Na$ 454.0753, found 454.0754.

*N-(3,4-Dimethoxy-5-(phenylsulfonyl)phenyl)-4-methylbenzenesulfonamide (**3u**).* HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{21}H_{21}NO_6S_2Na$, 470.0702; found, 470.0697.

*Methyl 2-Methoxy-5-(4-methylphenylsulfonamido)-3-(phenylsulfonyl)benzoate (**3v**).* This compound was obtained as a white solid [58 mg, 82% yield (at 60 °C)]: mp 172−174 °C; reaction time 5 h; R_f 0.4 (1:49 acetone−DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 2H), 7.84 (d, J = 7.6 Hz, 2H), 7.70 (d, J = 8.4 Hz, 2H), 7.62−7.55 (m, 2H), 7.48 (t, J = 7.6 Hz, 2H), 7.26 (d, J = 7.6 Hz, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 2.41 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.3, 155.5, 144.5, 140.6, 136.9, 135.4, 133.6, 132.6, 130.1, 129.9, 128.9, 128.1, 127.4, 126.6, 125.9, 64.1, 52.8, 21.6; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{22}H_{21}NO_7S_2Na$ 498.0652, found 498.0655.

*N-(6-Methoxy-5-(phenylsulfonyl)-[1,1′-biphenyl]-3-yl)-4-methylbenzenesulfonamide (**3w**).* This compound was obtained as a white solid (50 mg, 72% yield): mp 128−130 °C; reaction time 10 h; R_f 0.4 (2:3 EtOAc−petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 7.6 Hz, 2H), 7.64 (d, J = 7.6 Hz, 3H), 7.52 (t, J = 7.3 Hz, 1H), 7.44−7.39 (m, 3H), 7.28 (s, 6H), 7.19 (d, J = 8.4 Hz, 2H), 3.09 (s, 3H), 2.34 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.9, 144.3, 141.2, 137.4, 136.0, 135.7, 135.6, 133.3, 132.6, 130.3, 129.8, 128.8, 128.6, 128.6, 128.3, 128.1, 127.4, 121.2, 61.2, 21.6; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{26}H_{24}NO_5S_2$ 494.1090, found 494.1085.

*N-(3-Iodo-4-methoxy-5-(phenylsulfonyl)phenyl)-4-methylbenzenesulfonamide (**3x**).* This compound was obtained as a white solid (31 mg, 23% yield): mp 185−187 °C; reaction time 12 h; R_f 0.4 (1:4 EtOAc−petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, J = 2.7 Hz, 1H), 7.84 (d, J = 7.3 Hz, 2H), 7.73−7.68 (m, 3H), 7.60 (t, J = 7.6 Hz, 1H), 7.49 (t, J = 7.6 Hz, 2H), 7.36 (s, 1H), 7.29 (d, J = 8.4 Hz, 2H), 3.94 (s, 3H), 2.43 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 154.8, 144.6, 140.5, 137.6, 136.0, 135.5, 134.2, 133.7, 130.0, 128.9, 128.1, 127.4, 122.4, 93.7, 63.1, 21.6; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{20}H_{19}INO_5S_2$ 543.9744, found 543.9751.

*N-(4-Methoxy-3,5-bis(phenylsulfonyl)phenyl)-4-methylbenzenesulfonamide (**3y**).* This compound was obtained as a white solid (73 mg, 53% yield (at rt); 59 mg, 85% yield (at 60 °C from 50 mg **1n**)): mp 223−225 °C; reaction time 12 h; R_f 0.2 (1:4 EtOAc−petroleum ether); ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.98 (s, 1H), 7.98 (s, 2H), 7.64 (t, J = 7.6 Hz, 4H), 7.57 (d, J = 8.0 Hz, 4H), 7.47 (t, J = 7.6 Hz, 4H), 7.40 (d, J = 8.0 Hz, 2H), 3.89 (s, 3H), 2.36 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 151.5, 144.2, 139.8, 137.7, 135.4, 135.0, 134.1, 130.0, 129.2, 127.1, 126.8, 125.4, 66.6, 21.0; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{26}H_{24}NO_7S_3$ 558.0709, found 558.0707.

*4-Methyl-N-(3,4,4-trimethoxycyclohexa-2,5-dien-1-ylidene)-benzenesulfonamide (**1k′**).*[20] This compound was obtained as a pale yellow solid (54 mg, 98% yield) as a mixture of trans and cis isomers in a 1.8:1 ratio: mp 115−117 °C; reaction time 5 min; R_f 0.3 (2:3 EtOAc−petroleum ether); ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.81 (d, J = 7.83 Hz, 2H), 7.43 (d, J = 8.2 Hz, 2.4H), 6.91 (d, J = 10.5 Hz, 0.4H), 6.81 (d, J = 10.1 Hz, 0.6H), 6.63 (s, 0.6H), 6.37 (dd, J = 8.8 and 1.4 Hz, 0.6 H), 5.78 (s, 0.3H), 3.86 (s, 1.9H), 3.81 (s, 1H), 3.21 (s, 6H), 2.4 (s, 3H); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{16}H_{20}NO_5S$ 338.1057, found 338.1055.

■ ASSOCIATED CONTENT

Supporting Information

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NMR spectra and HRMS chromatographs of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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Construction of unique SCF_3-containing building blocks *via* allylic alkylation of Morita–Baylis–Hillman adducts†

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Lewis base-catalyzed allylic alkylation of Morita–Baylis–Hillman adducts with α-SCF_3 ketones has been demonstrated. The developed strategy provides efficient access to a series of highly functionalized scaffolds featuring trifluoromethanesufinyl motif on a stereogenic carbon.

Introduction

Organofluorine compounds find significant applications in pharmaceuticals, agrochemicals, fine chemicals, and advanced materials owing to the inherent properties of the fluorine atom.[1] Substantial changes in the chemical, physical, and biological properties of an organic compound could be achieved by the incorporation of fluorine.[2] Although fluorine is the most abundant halogen in the earth's crust, natural products containing fluorine are incredibly scarce, which limits their usage as building blocks.[3] To fulfill the growing demand for fluorinated building blocks, the development of novel processes to synthesize structurally diverse organofluorine compounds is indispensable.[3,4]

The strong electron-withdrawing trifluoromethylthio (SCF_3) group is one of the most sought after among various fluorine-containing moieties.[5] It shows a remarkable effect on API's biological properties such as high lipophilicity parameter, protein binding affinity, and metabolic stability. These distinctive properties of SCF_3-containing drug candidates enhance their membrane permeability and absorption rate.[5c,6] Many bioactive molecules feature the SCF_3 group as a vital pharmacophore (Fig. 1).[7] Therefore, the development of the new methods to incorporate SCF_3 moieties into organic compounds has been a subject of intensive research.[5,6,8] The classical methods include halogen-fluorine exchange reactions in chloro- or bromomethyl sulfides and the trifluoromethylation of sulfur-containing compounds.[9] In the past few decades, tremendous efforts have been devoted to the development of novel trifluoromethylthiolation reagents. A series of electrophilic, nucleophilic, radical, and oxidative trifluoromethylthiolation reagents have been developed and utilized in the transition-metal-catalyzed cross-coupling or C–H activation reactions.[10] Major pharmaceutical companies prefer outsourcing fluorinated building blocks instead of in-house preparation to utilize them for the synthesis of more complex fluorinated compounds. Hence, making such processes and high value fluorinated building blocks readily accessible is an area of immense contemporary interest.[4,8f] In this context, recently, we have reported a novel method for the insertion of aryne into prefuntionalized α-SCF_3 ketones to access *ortho*-difunctionalized arenes having a trifluoromethylthio functional group.[11]

In continuation of our research interest, we were curious to utilize Morita–Baylis–Hillman (MBH) adducts to synthesize highly functionalized SCF_3-containing building blocks from simple α-SCF_3 ketones. A literature survey revealed that trifluoromethyl and monofluoromethyl groups had been incorporated in MBH adducts *via* allylic alkylation.[12] Interestingly, direct trifluoromethylthiolation of MBH adducts was reported in 2015 by Cahard and co-workers[13] as well as Shi and co-

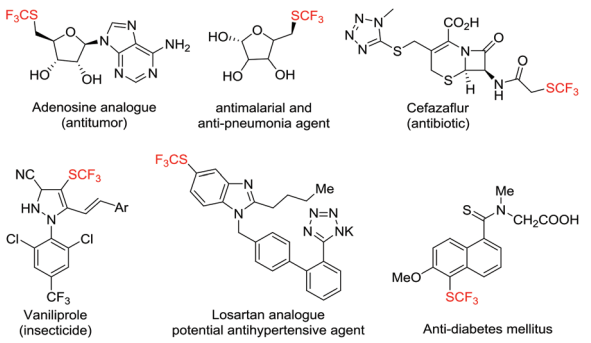

Fig. 1 Bioactive compounds featuring SCF_3 moiety.

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workers[14] successively utilizing Zard's trifluoromethylthiolation reagent. Additionally, Cahard group elegantly utilized a combination of Ruppert–Prakash reagent, S_8, and KF to achieve the same transformation.[13] Shi and co-workers developed difluoromethylthiolation of MBH adducts of isatins using Zard's reagent.[15] Recently, Qing and co-workers reported trifluoromethylthiolation of MBH alcohols using $AgSCF_3$ in high yields and excellent regioselectivities.[16] However, the proposed reaction between α-SCF_3-ketones and MBH adducts to implant the SCF_3-group in an organic molecule has not been reported until now.[17] Herein, we report our studies on the allylic alkylation of MBH adducts with α-SCF_3 Ketones in the presence of catalytic Lewis base to afford the corresponding highly functionalized building blocks containing SCF_3 group on the stereogenic carbon.

Results and discussion

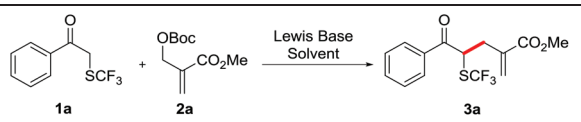
The optimization of the protocol was initially explored for the allylic alkylation of the MBH carbonate **2a** with α-SCF_3 ketone **1a** using various Lewis base catalysts in DCE at room temperature (Table 1, entries 1–4). DABCO was found to provide a better yield of the desired product **3a** in less time as compared to the other bases (entry 4). We also tried the reaction in various solvents using DABCO as the Lewis base. Gratifyingly, we observed that the expected product **3a** was obtained in quantitative yield within 15 min at room temperature when toluene was used as the solvent (entry 8). It should be noted that the nonpolar solvent has a significant acceleration effect to improve the yield as compared to polar solvents (entries 4–8). Furthermore, the variation of catalyst loading was also examined. The use of less or more equivalents of the catalyst furnished lower yields though the starting material was consumed within 10–15 min (entries 9 and 10).

The reproducibility of the protocol was confirmed by performing the reaction on one millimole scale under the optimized reaction condition (entry 8), which provided the trifluoromethylthiolated product **3a** in 99% yield demonstrating its scalability.

After optimizing the reaction condition, we focused on the substrate scope study of the newly developed protocol (Scheme 1). Initially, variation in the substituents (R^1/R^2) present on the aromatic ring of α-SCF_3 ketones was investigated. The α-SCF_3 ketone substrates with unsubstituted as well as alkyl-substituted aromatic ring worked well to furnish the desired products **3a**, **3b**, and **3c** in excellent yields. The halo substituted ketones **1d**, **1d′** and **1e** worked equally well to furnish the corresponding products **3d**, **3d′** and **3e** respectively. The optimized reaction condition was compatible with the electron-donating group, and the expected product **3f** was formed in 90% yield.

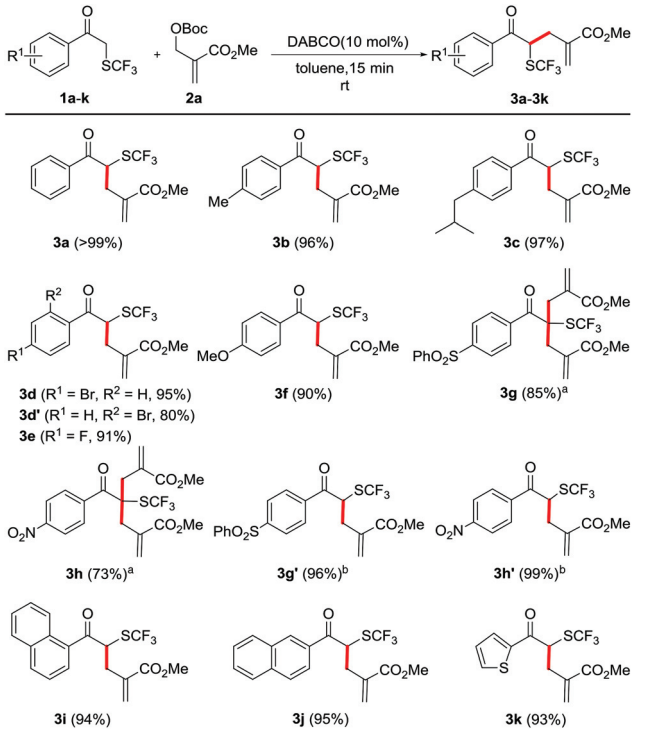
However, electron-withdrawing group substituted ketones **1g** and **1h** directly furnished dialkylated products **3g** and **3h** instead of the desired products **3g′** and **3h′**, hence the reaction was taken to completion by taking two equivalents of MBH carbonates. Monoalkylated products **3g′** and **3h′** could be obtained exclusively in excellent yields by reducing the reaction temperature to 0 °C. It was reasoned that the electron-withdrawing group of the aromatic ring enhanced the acidic character of the proton alpha to the carbonyl of monoalkylated product. Hence, it can easily form a carbanion under the standard reaction condition and react with another molecule of MBH carbonate **2a** to provide dialkylated products. We were

Table 1 Optimization of reaction condition[a,b]



Sr. no.	Solvent	Base	Base (equiv.)	Time	Yield[b] (%)
1.	DCE	Et_3N	10 mol%	3 h	77
2.	DCE	DMAP	10 mol%	3 h	64
3.	DCE	DIPA	10 mol%	2 day	29
4.	DCE	DABCO	10 mol%	15 min	92
5.	Dioxane	DABCO	10 mol%	15 min	88
6.	THF	DABCO	10 mol%	15 min	76
7.	ACN	DABCO	10 mol%	15 min	70
8.	Toluene	DABCO	10 mol%	15 min	>99
9.	Toluene	DABCO	5 mol%	15 min	83
10.	Toluene	DABCO	8 mol%	15 min	86

[a] Reaction conditions: **1a** (1 equiv., 20 mg, 0.09 mmol), **2a** (1 equiv., 20 mg, 0.09 mmol), base in solvent (0.1 M, 0.9 mL). [b] Isolated yield.



Scheme 1 Reaction of MBH carbonates with various aryl substituted α-SCF_3 ketones. Reaction conditions: **1a–k** (1 equiv., 50 mg), **2a** (1 equiv.), DABCO (10 mol%) in toluene (0.1 M), isolated yield, [a] **1g**, **1h** (1 equiv.), and **2a** (2 equiv.). [b] Reaction was performed at 0 °C.

pleased to find that the substrate with polyaromatic, as well as heteroaromatic ring also worked very well under the optimized condition and afforded the corresponding products **3i**, **3j**, and **3k** in excellent yields.

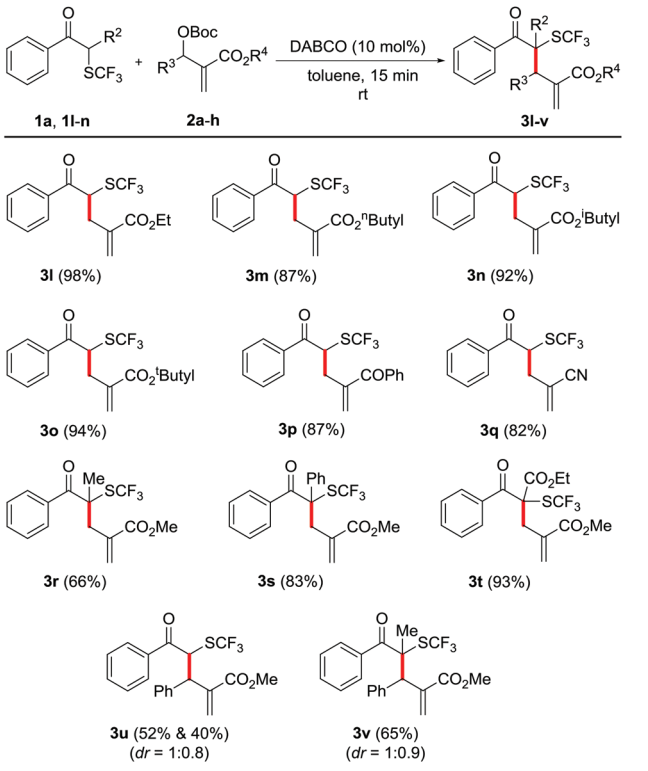
We were prompted to explore the substrate scope by varying the substituents on MBH carbonates and α-position of phenyl ketones (Scheme 2). The reaction of substrates with variation in the ester group of MBH carbonate progressed smoothly to obtain the desired products **3l–3o** in excellent yields. The substrates containing phenyl ketone (**2f**) and cyano (**2g**) as an electron-withdrawing group also showed good compatibility and furnished the products **3p** and **3q** in very good yields. Furthermore, the developed protocol was also successfully employed on α-substituted phenyl ketones and β-substituted MBH carbonates. Comparatively, less product formation was observed for the reaction between alkyl (α-Me) substituted ketone **1l** and MBH carbonate **2a**. However, the substrates **1m** and **1n** having electron-withdrawing phenyl and ethyl ester moieties respectively furnished the relevant products **3s** and **3t** smoothly with excellent yield.

Finally, we scrutinized the reaction of the MBH carbonate **2h** having phenyl substituent at the α-position with the unsubstituted α-SCF_3 ketone **1a** and methyl-substituted α-SCF_3 ketones **1l**. Interestingly, this combination of substrates also worked smoothly under the developed conditions. The reaction between the substrates **1a** and **2h** provided the product **3u** as a separable diastereomeric mixture. However, the product **3v** was formed as an inseparable diastereomeric mixture with good yield.

Overall, the developed process worked well for a wide range of substrates with varyingly substituted α-SCF_3 ketones as well as MBH adducts and provided the expected products with good to excellent yields.

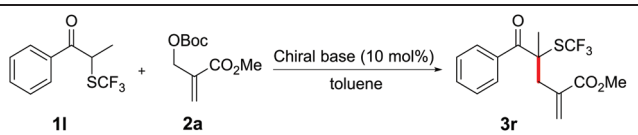
After demonstrating the broad substrate scope successfully, a preliminary investigation of the enantioselectivity of the developed protocol using various chiral Lewis base catalysts (see ESI†) was initiated. The reaction between α-SCF_3 ketone **1l** and MBH carbonate **2a** was performed in the presence of few commercially available chiral alkaloids as Lewis base catalysts in toluene (Table 2). Interestingly, $(DHQ)_2AQN$ showed good catalytic activity and provided the product with excellent yield and moderate enantioselectivity (Table 2, entry 3). Encouraged by this initial screening, we are now working on detailed studies by variation in substrates, catalysts, solvents, time, temperature, and additives.

The products obtained by the developed protocol may serve as important fluorinated building blocks for the synthesis of complex value-added products. We have demonstrated the synthetic utility of this protocol by cyclization and 1,4-Michael



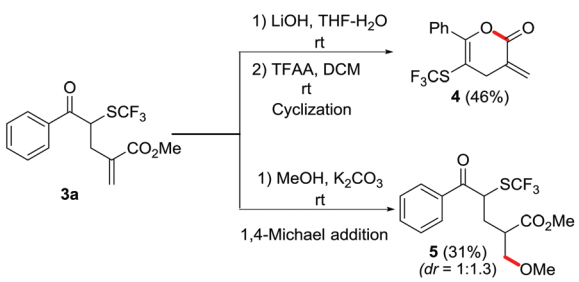
Scheme 2 Substrate scope for allylic alkylation reaction. Reaction conditions: **1a**, **1l–n** (1 equiv., 50 mg), **2a–h** (1 equiv.), DABCO (10 mol%) in toluene (0.1 M), isolated yield.

Table 2 Preliminary investigation of enantioselectivity of the reaction[a,b]



Entry	Base	Temp	Time (h)	Yield[b] (%)	ee (%)
1.	Quinine	rt	24	86	13
2.	Cinchonidine	rt	24	94	8
3.	$(DHQ)_2AQN$	rt	24	93	49
4.	$(DHQ)_2PHAL$	rt	24	61	31
5.	$(DHQD)_2PYR$	rt	24	26	7
6.	$(DHQ)_2AQN$	10 °C	24	82	50
7.	$(DHQ)_2AQN$	0 °C	24	71	47
8.	Thiourea cat. A	rt	24	NR	—
9.	Thiourea cat. B	rt	24	NR	—
10.	β-Isocupreidine	rt	24	64	15

[a] Reaction conditions: **1l** (1 equiv., 20 mg, 0.085 mmol), **2a** (1 equiv., 19 mg, 0.085 mmol), base in solvent (0.1 M, 0.9 mL). [b] Isolated yield. NR = no reaction.



Scheme 3 Further transformations of trifluoromethylthio alkylated product.

addition reaction of the representative trifluoromethylthioalkylated product **3a** (Scheme 3). Cyclization of the product **3a** was achieved by hydrolysis using LiOH, followed by the treatment with TFAA to obtain pyrone **4** in 46% yields. The product **4** features a pyrone moiety, which is a privileged scaffold in drug discovery. The treatment of compound **3a** with methanol in the presence of a mild base provided product **5** in 31% yield *via* the 1,4-Michael addition reaction. The starting material **3a** was not consumed completely and the formation of side products was not observed. Similarly, other heteroatom or carbon nucleophiles can be reacted for the diversity-oriented synthesis of bigger libraries of fluorinated compounds for molecular screening in bioactivity studies or material applications.

Conclusion

Fluorine-containing compounds are now an integral part of every aspect of daily life, and our ability to construct them efficiently will have a major impact on their wider applications. In this context, reported herein is a facile process to access highly functionalized SCF_3-containing building blocks *via* Lewis base-catalyzed allylic alkylation of MBH adducts with α-SCF_3 ketones. The developed protocol is mild and operationally simple. A variety of organofluorine compounds having SCF_3 moiety on the stereogenic carbon centre were smoothly prepared in good to excellent yields. Furthermore, the importance of this method has been established by converting the trifluoromethylthioalkylated product to value-added building blocks using simple transformations. Preliminary screening shows moderate enantioselectivity for a representative substrate using the chiral Lewis base $(DHQ)_2AQN$. Currently, we are focusing on the generalization of the chiral version of the protocol and its application in the synthesis of pharmaceutically and agrochemically important molecules.

Experimental section

General information

All reagents and solvents were used as received from commercial sources unless and otherwise noted. All experiments were carried out in a round bottom flask equipped with a stirring bar. Aluminium plates precoated with silica gel 60 PF254, 0.25 mm or 0.5 mm, were utilized for thin-layer chromatography (TLC) to monitor the progress of a reaction. Visualization of the developed TLC plate was performed by irradiation with UV light. Column chromatographic purifications were carried out on flash silica gel (240–400 mesh) using ethyl acetate and petroleum ether as eluents. The ^1H and ^{13}C NMR spectra were recorded on 200/400/500 MHz and 50/100/125 MHz NMR spectrometers respectively in $CDCl_3$. Chemical shifts were reported as δ values from standard peaks. The multiplicities of signals are designated by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), quint. (quintet), m (multiplet). Coupling constants (J) are reported in hertz. The melting points were recorded on a Buchi instrument, and are uncorrected. High-resolution mass spectrometry (HRMS) was performed on a TOF/Q-TOF mass spectrometer. The enantiomeric ratio of product was determined by chiral HPLC analysis using Agilent technologies 1260 Infinity series. All the α-SCF_3 ketones were prepared from the easily accessible α-bromo phenyl ketones[9c] using know literature procedures.[18] Morita–Baylis–Hillman (MBH) adducts were prepared as per the literature procedures.[19] All the Lewis base catalysts were purchased from the commercial sources.

Experimental procedure

General experimental procedure for the preparation of compounds 3a–f, 3i–v (Schemes 1 and 2)

To the solution of α-SCF_3 ketones **1a–f**, **1i–n** (1 equiv., 50 mg) in toluene (0.1 M) were added DABCO (10 mol%) and MBH adducts **2a–h** (1 equiv.) at room temperature. The resulting mixture was stirred at room temperature and the reaction progress was monitored by TLC (approx. 15 min). After completion of the reaction, toluene was evaporated *in vacuo* and the residue was purified by flash silica gel column chromatography using a gradient of ethyl acetate–petroleum ether to afford the products **3a–f**, **3i–v** in good to excellent yields (66–99%).

General experimental procedure for the preparation of compounds 3g and 3h (Scheme 1)

To the solution of α-SCF_3 ketones **1g** and **1h** (1 equiv., 50 mg) in toluene (0.1 M) were added DABCO (10 mol%) and MBH-carbonate **2a** (2 equiv.) at room temperature. The resulting mixture was stirred at room temperature and the reaction progress was monitored by TLC (approx. 15 min). After completion of the reaction, toluene was evaporated *in vacuo* and the residue was purified by flash silica gel column chromatography using a gradient of ethyl acetate–petroleum ether to afford the products **3g** and **3h** in very good yields (85% and 73% respectively).

General experimental procedure for the preparation of compounds 3g′ and 3h′ (Scheme 1)

To the solution of α-SCF_3 ketones **1g** and **1h** (1 equiv., 50 mg) in toluene (0.1 M) were added DABCO (10 mol%) and MBH-carbonate **2a** (1 equiv.) at 0 °C. The resulting mixture was stirred at 0 °C and the reaction progress was monitored by TLC (approx. 15 min). After completion of the reaction, toluene was evaporated *in vacuo* and the residue was purified by flash silica gel column chromatography using a gradient of ethyl acetate–petroleum ether to afford the products **3g′** and **3h′** in excellent yields (96% and 99% respectively).

Typical experimental procedure for the preparation of compound 3a

To the solution of α-SCF_3 ketone **1a** (1 equiv., 50 mg, 0.23 mmol) in toluene (0.1 M, 2.3 mL) were added DABCO

(10 mol%, 2.6 mg, 0.023 mmol) and MBH-carbonate **2a** (1 equiv., 49.1 mg, 0.23 mmol) at room temperature. The resulting mixture was stirred at room temperature and the reaction progress was monitored by TLC (approx. 15 min). After completion of the reaction, toluene was evaporated *in vacuo* and the residue was purified by flash silica gel column chromatography using a gradient of ethyl acetate–petroleum ether (1 : 49) to afford the product **3a** in >99% (71.7 mg) yield.

Representative experimental procedure at 1 mmol scale for the synthesis of compound 3a

To the solution of α-SCF_3 ketone **1a** (1 equiv., 220 mg, 1 mmol) in toluene (0.1 M, 22 mL) were added DABCO (10 mol%, 11.2 mg) and MBH-carbonate **2a** (1 equiv., 216 mg, 1 mmol) at room temperature. The resulting mixture was stirred at room temperature and the reaction progress was monitored by TLC (approx. 15 min). After completion of the reaction, toluene was evaporated *in vacuo* and the residue was purified by flash silica gel column chromatography using a gradient of ethyl acetate–petroleum ether (1 : 49) to afford the product **3a** in 99% (314.8 mg) yield.

Experimental procedure for the preparation of pyrone 4

A modified literature procedure was used for the preparation of pyrone **4**.[20] To the solution of compound **3a** (100 mg, 0.314 mmol) in aqueous THF (1 : 1) was added LiOH (66 mg, 1.57 mmol, 5 equiv.) at room temperature. The resulting mixture was stirred for 2 h at room temperature. After complete consumption of **3a**, the reaction mixture was acidified with dilute HCl solution and extracted with DCM (15 mL × 3). The DCM layer was dried over with $MgSO_4$ and evaporated *in vacuo* to obtain a crude acid intermediate as a white solid in 99% (95 mg) yield. To the solution of the crude acid (80 mg, 0.263 mmol) in DCM (4 mL) was added trifluoroacetic anhydride (TFAA, 111 mg, 0.526 mmol, 2 equiv.) and the reaction mixture was stirred at room temperature for 2 h. After the usual aqueous extractive workup followed by column chromatographic purification process using a gradient of ethyl acetate–petroleum ether (1 : 19), pyrone **4** was obtained as a colourless liquid in 46% yield (34.6 mg).

Experimental procedure for the preparation of compound 5

To the solution of the compound **3a** (100 mg, 1 equiv., 0.314 mmol) in MeOH (4 mL) was added K_2CO_3 (87 mg, 2 equiv., 0.629 mmol) and the resulting mixture was stirred overnight at 50 °C. After completion of the reaction, MeOH was evaporated by rotatory vacuum and the residue was purified by flash silica gel column chromatography using a gradient of ethyl acetate–petroleum ether (1 : 12) to afford the product **5** in 31% (34.1 mg) yield.

Characterization data of compounds

Methyl-2-methylene-5-oxo-5-phenyl-4-((trifluoromethyl)thio) pentanoate (3a). Reaction time: 15 min; R_f: 0.5 (1 : 19, EtOAc : Pet. ether); thick oil; 71.7 mg, >99% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.02 (d, J = 7.9 Hz, 2H), 7.64 (t, J = 7.3 Hz, 1H), 7.52 (t, J = 7.6 Hz, 2H), 6.30 (s, 1H), 5.75 (s, 1H), 5.25 (t, J = 7.6 Hz, 1H), 3.78 (s, 3H), 3.17 (dd, J = 14.0 and 6.7 Hz, 1H), 2.85 (dd, J = 14.0 and 7.9 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 195.9, 166.8, 134.8, 134.7, 134.1, 130.5, 130.3 (q, J = 301 Hz, CF3), 129.0, 128.7, 52.1, 46.2, 36.2; **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{14}H_{13}F_3O_3SNa$ 341.0430, found 341.0428.

Methyl-2-methylene-5-oxo-5-(*p*-tolyl)-4-((trifluoromethyl)thio) pentanoate (3b). Reaction time: 15 min; R_f: 0.5 (1 : 19, EtOAc : Pet. ether); thick oil; 68 mg, 96% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.92 (d, J = 8.5 Hz, 2H), 7.31 (d, J = 7.9 Hz, 2H), 6.28 (s, 1H), 5.74 (s, 1H), 5.23 (t, J = 7.3 Hz, 1H), 3.78 (s, 3H), 3.15 (dd, J = 14.0 and 7.3 Hz, 1H), 2.84 (dd, J = 14.0 and 7.3 Hz, 1H), 2.44 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 195.4, 166.8, 145.3, 134.9, 132.2, 130.38 (q, J = 306.7 Hz, CF_3), 130.35, 129.7, 128.9, 52.1, 46.1, 36.3, 21.7; **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{15}H_{15}F_3O_3SNa$ 355.0586, found 355.0583.

Methyl-5-(4-isobutylphenyl)-2-methylene-5-oxo-4((trifluoromethyl)thio)pentanoate (3c). Reaction time: 15 min; R_f: 0.5 (1 : 19, EtOAc : Pet. ether); thick oil; 66 mg, 97% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.85 (d, J = 7.9 Hz, 2H), 7.20 (d, J = 8.5 Hz, 2H), 6.20 (s, 1H), 5.66 (s, 1H), 5.15 (t, J = 7.3 Hz, 1H), 3.69 (s, 3H), 3.08 (dd, J = 14.0 and 6.7 Hz, 1H), 2.76 (dd, J = 13.4, 7.3 Hz, 1H), 2.47 (d, J = 7.3 Hz, 2H), 1.84 (septet, J = 6.7 Hz, 1H), 0.84 (d, J = 6.7 Hz, 6H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 195.4, 166.8, 148.9, 134.9, 132.4, 130.1 (q, J = 307.4 Hz, CF_3), 130.4, 129.7, 128.7, 52.1, 46.2, 45.4, 36.4, 30.1, 22.3; **HRMS (ESI-TOF) m/z:** $[M + Na]^+$ calcd for $C_{18}H_{21}F_3O_3SNa$ 397.1056, found 397.1057.

Methyl-5-(4-bromophenyl)-2-methylene-5-oxo-4-((trifluoromethyl)thio)pentanoate (3d). Reaction time: 15 min; R_f: 0.5 (1 : 19, EtOAc : Pet. ether); thick oil; 63 mg, 95% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.80 (d, J = 8.5 Hz, 2H), 7.58 (d, J = 8.5 Hz, 2H), 6.22 (s, 1H), 5.67 (s, 1H), 5.10 (t, J = 7.6 Hz, 1H), 3.70 (s, 3H), 3.06 (dd, J = 14.0 and 6.7 Hz, 1H), 2.74 (dd, J = 14.0 and 7.9 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 194.9, 166.8, 134.7, 133.4, 132.3, 130.6, 130.21 (q, J = 308.3 Hz, CF_3), 130.19, 129.6, 52.1, 46.1, 36.2; **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{14}H_{12}F_3{}^{81}BrO_3SNa$ 420.9514, found 420.9505.

Methyl 5-(2-bromophenyl)-2-methylene-5-oxo-4-((trifluoromethyl)thio)pentanoate (3d′). Reaction time: 15 min; R_f: 0.5 (1 : 19, EtOAc : Pet. ether); thick oil; 53 mg, 80% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.63 (d, J = 7.9 Hz, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.41 (t, J = 7.5 Hz, 1H), 7.35 (d, J = 7.6 Hz, 1H), 6.37 (s, 1H), 5.82 (s, 1H), 5.06 (t, J = 7.6 Hz, 1H), 3.77 (s, 3H), 3.23 (dd, J = 14.1 and 6.8 Hz, 1H), 2.89 (dd, J = 14.3 and 8.4 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 197.9, 166.8, 138.9, 134.9, 133.8, 132.4, 130.7, 130.1, 129.9 (q, J = 307.4 Hz, CF_3), 127.4, 119.3, 52.1, 49.6, 34.5; **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{13}O_3{}^{79}BrF_3S$ 396.9715, found 396.9719.

Methyl-5-(4-fluorophenyl)-2-methylene-5-oxo-4-((trifluoromethyl)thio)pentanoate (3e). Reaction time: 15 min; R_f: 0.5 (1 : 19, EtOAc : Pet. ether); thick oil; 64 mg, 91% yield; **^{1}H NMR (200 MHz, $CDCl_3$)** δ 8.08–7.89 (m, 2H), 7.23–7.03 (m, 2H), 6.23 (d, J = 0.9 Hz, 1H), 5.68 (d, J = 1.0 Hz, 1H), 5.13 (dd, J = 7.7 and 6.6 Hz, 1H), 3.71 (s, 3H), 3.07 (dd, J = 14.0 and 6.8 Hz, 1H), 2.74 (dd, J = 14.0 and 8.1 Hz, 1H); **^{13}C NMR (50 MHz, $CDCl_3$)**

δ 194.3, 166.8, 166.3 (d, J = 256.9 Hz, C–F), 134.7, 131.5 (d, J = 9.5 Hz), 131.1 (d, J = 2.9 Hz), 130.5, 130.3 (q, J = 307.7 Hz, CF_3), 116.2 (d, J = 22.0 Hz), 52.1, 46.2, 36.3; **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{14}H_{12}F_4O_3SNa$ 359.0335, found 359.0333.

Methyl-5-(4-methoxyphenyl)-2-methylene-5-oxo-4-((trifluoromethyl)thio)pentanoate (3f). Reaction time: 15 min; R_f: 0.5 (1 : 9, EtOAc : Pet. ether); thick oil; 63 mg, 90% yield; **^{1}H NMR (200 MHz, $CDCl_3$)** δ 8.01 (d, J = 9.0 Hz, 2H), 7.00 (d, J = 9.0 Hz, 2H), 6.28 (s, 1H), 5.74 (s, 1H), 5.21 (t, J = 7.5 Hz, 1H), 3.89 (s, 3H), 3.78 (s, 3H), 3.15 (dd, J = 13.9 and 7.1 Hz, 1H), 2.83 (dd, J = 13.9 and 7.8 Hz, 1H); **^{13}C NMR (50 MHz, $CDCl_3$)** δ 194.3, 166.8, 164.4, 134.9, 131.2, 130.5 (q, J = 307.3 Hz, CF_3), 130.3, 127.5, 114.2, 55.6, 52.1, 46.0, 36.5; **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{15}H_{15}F_3O_4SNa$ 371.0535, found 371.0532.

Dimethyl2,6-dimethylene-4-(4-(phenylsulfonyl)benzoyl)-4-((trifluoromethyl)thio)heptanedioate (3g). Reaction time: 15 min; R_f: 0.5 (1 : 4, EtOAc : Pet. ether); white solid, 66 mg, 85% yield; Mp = 117–119 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.97 (d, J = 8.5 Hz, 2H), 7.93–7.86 (m, 4H), 7.53 (t, J = 7.3 Hz, 1H), 7.46 (t, J = 7.3 Hz, 2H), 6.28 (s, 2H), 5.65 (s, 2H), 3.54 (s, 6H), 3.23–3.07 (m, 4H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 197.7, 167.1, 144.5, 140.7, 140.6, 134.2, 133.7, 130.3, 129.9, 129.5, 129.3(q, J = 310.6 Hz, CF_3), 127.9, 127.4, 64.8, 52.2, 37.0; **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{25}H_{23}F_3O_7S_2Na$ 579.0730, found 579.0730.

Dimethyl-2,6-dimethylene-4-(4-nitrobenzoyl)-4-((trifluoromethyl)thio)heptanedioate (3h). Reaction time: 15 min; R_f: 0.5 (3 : 17, EtOAc : Pet. ether); thick oil; 63 mg, 73% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.21 (d, J = 8.5 Hz, 2H), 8.06 (d, J = 8.5 Hz, 2H), 6.33 (s, 2H), 5.71 (s, 2H), 3.60 (s, 6H), 3.27–3.12 (m, 4H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 197.5, 167.1, 149.5, 142.0, 134.2, 130.4, 130.2, 129.7 (q, J = 309.8 Hz, CF_3), 123.3, 64.8, 52.2, 37.1; **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{19}H_{18}F_3O_7NSNa$ 484.0648, found 484.0650.

Methyl 2-methylene-5-oxo-5-(4-(phenylsulfonyl)phenyl)-4-((trifluoromethyl)thio)pentanoate (3g′). Reaction time: 15 min; R_f: 0.2 (1 : 1, DCM : Pet. ether); white solid; 61 mg, 96% yield at 0° C; Mp = 110–112 °C; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.18–8.04 (m, 4H), 7.98 (d, J = 7.6 Hz, 2H), 7.66–7.51 (m, 3H), 6.30 (s, 1H), 5.76 (s, 1H), 5.18 (t, J = 7.1 Hz, 1H), 3.76 (s, 3H), 3.14 (dd, J = 14.1 and 6.9 Hz, 1 H), 2.81 (dd, J = 13.7 and 8.0 Hz, 1 H); **^{13}C NMR (125 MHz, $CDCl_3$)** δ 194.6, 166.8, 146.3, 140.5, 138.1, 134.4, 133.8, 130.8, 129.52, 129.50, 130.0 (q, J = 308.0 Hz, CF_3), 128.2, 128.0, 52.2, 46.5, 35.9; **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{18}F_3O_5S_2$ 459.0542, found 459.0539.

Methyl 2-methylene-5-(4-nitrophenyl)-5-oxo-4-((trifluoromethyl)thio)pentanoate (3h′). Reaction time: 15 min; R_f: 0.2 (1 : 19, EtOAc : Pet. ether); yellow thick oil; 67.8 mg, 99% yield at 0° C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.36 (d, J = 9.2 Hz, 2H), 8.19 (d, J = 9.2 Hz, 2H), 6.34 (s, 1H), 5.80 (s, 1H), 5.22 (t, J = 7.3 Hz, 1H), 3.79 (s, 3H), 3.18 (dd, J = 14.0 and 6.7 Hz, 1H), 2.83 (dd, J = 14.0 and 7.9 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 194.4, 166.8, 150.8, 139.3, 134.4, 130.0 (q, J = 307.5 Hz, CF_3), 130.8, 129.8, 124.1, 52.2, 46.6, 35.9; **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{13}F_3O_5SN$ 364.0461, found 364.0459.

Methyl 2-methylene-5-(naphthalen-1-yl)-5-oxo-4-((trifluoromethyl)thio)pentanoate (3i). Reaction time: 15 min; R_f: 0.3 (1 : 19, EtOAc : Pet. ether); thick oil; 64 mg, 94% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.44 (d, J = 7.9 Hz, 1H), 7.97 (d, J = 8.5 Hz, 1H), 7.89 (d, J = 7.3 Hz, 1H), 7.82 (d, J = 7.9 Hz, 1H), 7.60–7.40 (m, 3H), 6.19 (s, 1H), 5.70 (s, 1H), 5.19 (t, J = 7.6 Hz, 1H), 3.67 (s, 3H), 3.17 (dd, J = 14.0 and 7.3 Hz, 1H), 2.86 (dd, J = 14.0 and 7.9 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 198.3, 166.8, 134.9, 134.0 (2C), 133.5, 130.6, 130.34, 130.27 (q, J = 307.5, CF_3), 128.5, 128.4, 128.2, 126.8, 125.5, 124.3, 52.1, 49.3, 36.2; **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{18}H_{15}F_3O_3SNa$ 391.0586, found 391.0587.

Methyl 2-methylene-5-(naphthalen-2-yl)-5-oxo-4-((trifluoromethyl)thio)pentanoate (3j). Reaction time: 15 min; R_f: 0.5 (1 : 19, EtOAc : Pet. ether); white solid; 65 mg, 95% yield, Mp = 60–62 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.49 (s, 1H), 7.95 (t, J = 10.4 Hz, 2H), 7.85 (d, J = 8.5 Hz, 1H), 7.81 (d, J = 7.9 Hz, 1H), 7.56 (t, J = 7.0 Hz, 1H), 7.50 (t, J = 7.3 Hz, 1H), 6.20 (s, 1H), 5.68 (s, 1H), 5.34 (t, J = 7.6 Hz 1H), 3.70 (s, 3H), 3.14 (dd, J = 13.4 and 6.7 Hz, 1H), 2.83 (dd, J = 14.0, 7.9 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 195.8, 166.8, 136.0, 134.9, 132.5, 132.0, 130.8, 130.43, 130.41 (q, J = 306.7 Hz, CF_3), 129.9, 129.1, 128.9, 127.8, 127.1, 124.0, 52.1, 46.4, 36.5; **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{18}H_{15}F_3O_3SNa$ 391.0586, found 391.0590.

Methyl 2-methylene-5-oxo-5-(thiophen-2-yl)-4-((trifluoromethyl)thio)pentanoate (3k). Reaction time: 15 min; R_f: 0.2 (1 : 19, EtOAc : Pet. ether); thick oil; 66 mg, 93% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.80 (d, J = 3.7 Hz, 1H), 7.69 (d, J = 4.9 Hz, 1H), 7.11 (t, J = 4.4 Hz, 1H), 6.22 (s, 1H), 5.67 (s, 1H), 4.98 (t, J = 7.6 Hz, 1H), 3.71 (s, 3H), 3.06 (dd, J = 14.0 and 7.3 Hz, 1H), 2.77 (dd, J = 14.0 and 7.9 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 188.5, 166.7, 141.7, 136.0, 134.7, 133.5, 130.5, 130.3 (q, J = 307.5 Hz, CF_3), 128.6, 52.1, 47.4, 36.5; **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{12}H_{11}F_3O_3S_2Na$ 346.9994, found 346.9993.

Ethyl 2-methylene-5-oxo-5-phenyl-4-((trifluoromethyl)thio) pentanoate (3l). Reaction time: 15 min; R_f: 0.5 (1 : 19, EtOAc : Pet. ether); thick oil; 74 mg, 98% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.02 (d, J = 7.3 Hz, 2H), 7.63 (t, J = 7.3 Hz, 1H), 7.52 (t, J = 7.6 Hz, 2H), 6.30 (s, 1H), 5.72 (s, 1H), 5.27 (t, J = 7.3 Hz, 1H), 4.30–4.18 (m, 2H), 3.16 (dd, J = 14.0 and 7.3 Hz, 1H), 2.85 (dd, J = 14.0 and 7.3 Hz, 1H), 1.31 (t, J = 7.3 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 195.9, 166.3, 135.1, 134.7, 134.1, 130.4 (q, J = 307.5 Hz, CF_3), 130.3, 129.0, 128.7, 61.1, 46.2, 36.4, 14.1; **HRMS** (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{15}H_{15}F_3O_3SNa$ 355.0586, found 355.0587.

Butyl 2-methylene-5-oxo-5-phenyl-4-((trifluoromethyl)thio) pentanoate (3m). Reaction time: 15 min; R_f: 0.5 (1 : 19, EtOAc : Pet. ether); thick oil; 71 mg, 87% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.05–7.97 (m, 2H), 7.67–7.58 (m, 1H), 7.55–7.48 (m, 2H), 6.29 (d, J = 0.9 Hz, 1H), 5.73 (d, J = 1.4 Hz, 1H), 5.27 (t, J = 7.3 Hz, 1H), 4.19 (td, J = 6.4 and 1.8 Hz, 2H), 3.16 (dd, J = 13.7 and 6.9 Hz, 1H), 2.85 (dd, J = 14.2 and 8.2 Hz, 1H), 1.71–1.62 (m, 2H), 1.43–1.33 (m, 2H), 0.95 (t, J = 7.8 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 196.0, 166.4, 135.1, 134.7, 134.1, 130.3, 129.0, 128.8 (q, J = 307.7 Hz, CF_3), 128.7, 65.0,

46.2, 36.4, 30.6, 19.1, 13.7; **HRMS** (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{17}H_{20}F_3O_3S$ 361.1080, found 361.1076.

Isobutyl 2-methylene-5-oxo-5-phenyl-4-((trifluoromethyl)thio)pentanoate (3n). Reaction time: 15 min; R_f: 0.5 (1 : 19, EtOAc : Pet. ether); thick oil; 75 mg, 92% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.02 (d, J = 7.3 Hz, 2H), 7.63 (t, J = 7.3 Hz, 1H), 7.51 (t, J = 7.8 Hz, 2H), 6.30 (s, 1H), 5.74 (s, 1H), 5.27 (t, J = 7.7 Hz, 1H), 3.97 (dd, J = 6.9 and 2.8 Hz, 2H), 3.17 (dd, J = 13.7 and 6.9 Hz, 1H), 2.85 (dd, J = 14.2 and 6.0 Hz, 1H), 2.06–1.93 (m, 1H), 0.96 (d, J = 6.9 Hz, 6H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 196.0, 166.4, 135.1, 134.8, 134.1, 130.3 (q, J = 308.3 Hz, CF_3), 130.2, 128.9, 128.7, 71.2, 46.2, 36.4, 29.7, 27.7, 19.0; **HRMS** (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{17}H_{20}F_3O_3S$ 361.1080, found 361.1076.

***tert*-Butyl 2-methylene-5-oxo-5-phenyl-4-((trifluoromethyl)thio)pentanoate (3o).** Reaction time: 15 min; R_f: 0.5 (1 : 19, EtOAc : Pet. ether); thick oil; 77 mg, 94% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.01 (d, J = 8.2 Hz, 2H), 7.63 (t, J = 8.0 Hz, 1H), 7.51 (t, J = 7.9 Hz, 2H), 6.19 (s, 1H), 5.63 (s, 1H), 5.29 (t, J = 7.8 Hz, 1H), 3.09 (dd, J = 13.7 and 7.3 Hz, 1H), 2.83 (dd, J = 13.7 and 7.8 Hz, 1H), 1.50 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 196.4, 165.4, 136.4, 134.9, 134.1, 130.4 (q, J = 307.8 Hz, CF_3), 129.5, 128.9, 128.7, 81.4, 46.2, 36.6, 28.0; **HRMS** (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{17}H_{19}F_3O_3SNa$ 383.0899, found 383.0900.

2-Methylene-1,5-diphenyl-4-((trifluoromethyl)thio)pentane-1,5-dione (3p). Reaction time: 15 min; R_f: 0.5 (1 : 9, EtOAc : Pet. ether); yellow thick oil; 72 mg, 87% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.05 (d, J = 8.4 Hz, 2H), 7.65–7.49 (m, 6H), 7.43 (t, J = 7.6 Hz, 2H), 6.09 (s, 1H), 5.86 (s, 1H), 5.32 (t, J = 7.3 Hz, 1H), 3.32 (dd, J = 13.7 and 6.9 Hz, 1H), 3.01 (dd, J = 13.7 and 8.4 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 197.6, 196.2, 142.3, 137.3, 134.7, 134.1, 133.4 (q, J = 307.5 Hz, CF_3), 132.42, 132.36, 129.4, 129.0, 128.8, 128.3, 46.4, 36.2; **HRMS** (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{16}F_3O_2S$ 365.0818, found 365.0814.

2-Methylene-5-oxo-5-phenyl-4-((trifluoromethyl)thio)pentanenitrile (3q). Reaction time: 15 min; R_f: 0.4 (1 : 9, EtOAc : Pet. ether); thick oil; 53 mg, 82% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.00 (d, J = 7.6 Hz, 2H), 7.67 (t, J = 7.3 Hz, 1H), 7.55 (t, J = 8.0 Hz, 2H), 6.00 (s, 1H), 5.90 (s, 1H), 4.99 (dd, J = 8.4 and 6.9 Hz, 1H), 3.21 (dd, J = 14.5 and 8.4 Hz, 1H), 2.91 (dd, J = 14.5 and 6.9 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 193.7, 135.0, 134.5, 134.1, 129.9 (q, J = 308.6 Hz, CF_3), 129.1, 128.7, 118.0, 117.5, 44.6, 37.3; **HRMS** (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{13}H_{11}ONF_3S$ 286.0508, found 286.0504.

Methyl 4-methyl-2-methylene-5-oxo-5-phenyl-4-((trifluoromethyl)thio)pentanoate (3r). Reaction time: 15 min; R_f: 0.5 (1 : 19, EtOAc : Pet. ether); thick oil; 47 mg, 66% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.03 (d, J = 7.3 Hz, 2H), 7.47 (t, J = 7.3 Hz, 1H), 7.37 (t, J = 7.6 Hz, 2H), 6.30 (s, 1H), 5.58 (s, 1H), 3.64 (s, 3H), 3.19–3.06 (m, 2H), 1.60 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 198.1, 167.4, 135.9, 134.5, 132.5 (q, J = 306.7 Hz, CF_3), 132.3, 131.1, 129.5, 128.3, 58.8, 52.2, 39.2, 24.0; **HRMS** (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{15}H_{15}F_3O_3SNa$ 355.0586, found 355.0584; **HPLC**: Chiralpak IE, *n*-hexane/IPA = 97 : 3, 1.0 mL min^{-1}, λ = 230 nm, tR (major) = 8.200 min, tR (minor) = 7.350 min (75 : 25 er).

Methyl 2-methylene-5-oxo-4,5-diphenyl-4-((trifluoromethyl)thio)pentanoate (3s). Reaction time: 15 min; R_f: 0.4 (1 : 9, EtOAc : Pet. ether); thick oil; 55 mg, 83% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.63 (d, J = 7.6 Hz, 2H), 7.43–7.22 (m, 8H), 6.29 (s, 1H), 5.61 (s, 1H), 3.84 (d, J = 14.5 Hz, 1H), 3.52 (d, J = 14.5 Hz, 1H), 3.38 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 195.5, 167.4, 137.3, 134.9, 133.9, 132.8, 130.7, 130.6, 129.6 (q, J = 309.1 Hz, CF_3), 128.9, 128.7, 128.0, 127.3, 68.6, 51.6, 38.5; **HRMS** (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{20}H_{18}F_3O_3S$ 395.0923, found 395.0916.

1-Ethyl 5-methyl 2-benzoyl-4-methylene-2-((trifluoromethyl)thio)pentanedioate (3t). Reaction time: 15 min; R_f: 0.4 (1 : 6, EtOAc : Pet. ether); thick oil; 62 mg, 93% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.05–7.95 (m, 2H), 7.57 (t, J = 7.3 Hz, 1H), 7.44 (t, J = 7.6 Hz, 2H), 6.46 (s, 1H), 5.84 (s, 1H), 4.20–4.00 (m, 2H), 3.63 (s, 3H), 3.55 (s, 2H), 0.98 (t, J = 7.3 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 190.0, 168.1, 167.0, 134.5, 133.9, 133.5, 132.0, 129.3 (q, J = 308.6 Hz, CF_3), 129.0, 128.5, 66.8, 63.3, 51.9, 36.7, 13.2. **HRMS** (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{17}H_{18}F_3O_5S$ 391.0822, found 391.0821.

Methyl 2-methylene-5-oxo-3,5-diphenyl-4-((trifluoromethyl)thio)pentanoate (3u-diastereomer 1). Reaction time: 15 min; R_f: 0.3(1 : 19, EtOAc : Pet. ether); white solid; 47 mg, 52% yield; Mp = 90–92 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.84 (d, J = 7.9 Hz, 2H), 7.54 (t, J = 7.3 Hz, 1H), 7.41 (t, J = 7.63 Hz, 2H), 7.32 (d, J = 7.3 Hz, 2H), 7.19–7.04 (m, 3H), 6.45 (s, 1H), 6.00 (s, 1H), 5.90 (d, J = 11.6 Hz, 1H), 4.54 (d, J = 7.6 Hz, 1H), 3.76 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 195.8, 166.5, 139.2, 138.4, 135.5, 133.6, 130.0 (q, J = 30 Hz, CF_3), 128.6, 128.5, 128.4 (3C), 127.4, 52.1, 50.7, 48.1; **HRMS** (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{20}H_{18}F_3O_3S$ 395.0923, found 395.0920.

Methyl 2-methylene-5-oxo-3,5-diphenyl-4-((trifluoromethyl)thio)pentanoate (3u-diastereomer 2). Reaction time: 15 min; R_f: 0.2 (1 : 19, EtOAc : Pet. ether); thick oil; 36 mg, 40% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.05 (d, J = 7.9 Hz, 2H), 7.64 (t, J = 7.3 Hz, 1H), 7.53 (t, J = 7.6 Hz, 2H), 7.41–7.26 (m, 5H), 6.22 (s, 1H), 5.76 (s, 1H), 5.65 (d, J = 10.4 Hz, 1H), 4.62 (d, J = 11.0 Hz, 1H), 3.64 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 195.4, 166.3, 140.2, 137.4, 135.2, 133.9, 129.2, 128.9, 128.8, 128.6, 128.3 (q, J = 307.9 Hz, CF_3), 127.8, 127.0, 52.1, 50.1, 49.6; **HRMS** (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{20}H_{18}F_3O_3S$ 395.0923, found 395.0919.

Methyl (4R)-4-methyl-2-methylene-5-oxo-3,5-diphenyl-4-((trifluoromethyl)thio)pentanoate (3v). Reaction time: 15 min; R_f: 0.4 (1 : 19, EtOAc : Pet. ether); thick oil; 57 mg, 65% yield as mixture of two diastereomers in 1 : 0.89 ratio; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.54–7.23 (m, 13H), 7.21–7.10 (m, 7H), 6.44 (d, J = 3.1 Hz, 2H), 6.27 (s, 0.89H), 6.00 (s, 1H), 5.51 (d, J = 17.1 Hz, 1.79H), 3.65 (s, 3H), 3.64 (s, 2.07H), 2.23 (s, 3H), 1.90 (s, 2.65H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 165.6, 165.5, 161.7, 156.7, 140.3, 140.0, 138.2, 138.0, 133.0, 132.7, 131.46 (q, J = 314 Hz, CF_3), 131.43 (q, J = 311.3 Hz, CF_3), 130.0, 129.6, 129.3, 129.2, 128.3, 128.3, 128.1, 128.0, 127.9, 127.9, 127.5, 126.4, 126.3, 78.3, 78.2, 51.8, 51.7, 29.72, 29.69, 20.1, 19.6; **HRMS** (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{21}H_{20}F_3O_3S$ 409.1080, found 409.1082.

3-Methylene-6-phenyl-5-((trifluoromethyl)thio)-3,4-dihydro-2*H*-pyran-2-one (4). Reaction time: 15 min; R_f: 0.3 (1 : 9, EtOAc : Pet. ether); thick oil; 34.6 mg, 46% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.63–7.50 (m, 2H), 7.49–7.39 (m, 3H), 6.52 (s, 1H), 5.85 (s, 1H), 3.69 (s, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 161.2, 157.9, 131.8, 130.2, 130.0, 129.4 (q, J = 311.3 Hz, CF_3), 129.2, 128.1 (2C), 99.7 (d, J = 1.5 Hz), 36.0; **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{13}H_{10}F_3O_2S$ 287.0348, found 287.0344.

Methyl 2-(methoxymethyl)-5-oxo-5-phenyl-4-((trifluoromethyl)thio)pentanoate (5). Reaction time: 15 min; R_f: 0.4 (1 : 9, EtOAc : Pet. ether); thick oil; 34 mg, 31% yield as mixture of two diastereomers in 1 : 1.3 ratio; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.08–8.03 (m, 2H), 8.00–7.94 (m, 1.57H), 7.67–7.60 (m, 1.73H), 7.56–7.47 (m, 3.53H), 5.10 (dd, J = 9.2 and 6.1 Hz, 1H), 5.01 (dd, J = 9.2 and 5.3 Hz, 0.82H), 3.75 (s, 3H), 3.66 (s, 2.49H), 3.65–3.52 (m, 3H), 3.29 (s, 2.32H), 3.22 (s, 3H), 3.06–2.98 (m, 1H), 2.78–2.70 (m, 0.78H), 2.70–2.60 (m, 1H), 2.58–2.47 (m, 0.86H), 2.43–2.33 (m, 0.85H), 2.12–2.03 (m, 1H); **^{13}C NMR (125 MHz, $CDCl_3$)** δ 195.5, 195.2, 173.3, 173.2, 134.9, 134.8, 134.4, 134.1, 134.0, 133.39 (q, J = 307.7 Hz, CF_3), 133.36 (q, J = 307.7 Hz, CF_3), 128.9, 128.8, 128.7, 73.1, 72.8, 58.88, 58.85, 52.1, 52.0, 46.4, 45.2, 43.3, 42.9, 32.1, 31.8; **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{18}F_3O_4S$ 351.0872, found 351.0867.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

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Annulation of Enals with Carbamoylpropiolates via NHC-Catalyzed Enolate Pathway: Access to Functionalized Maleimides/Isomaleimides and Synthesis of Aspergillus FH-X-213

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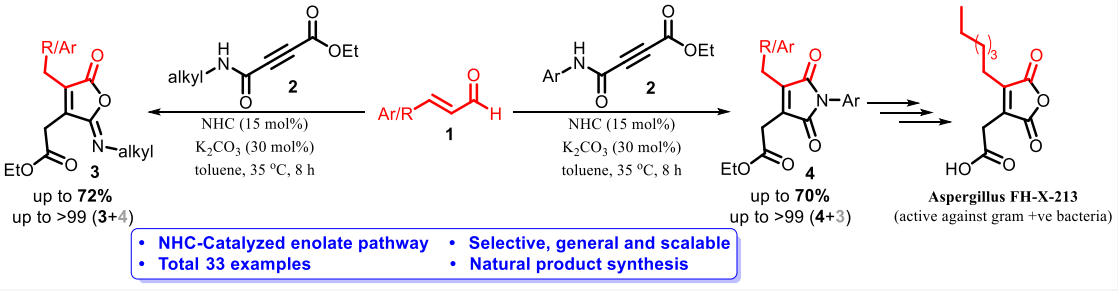


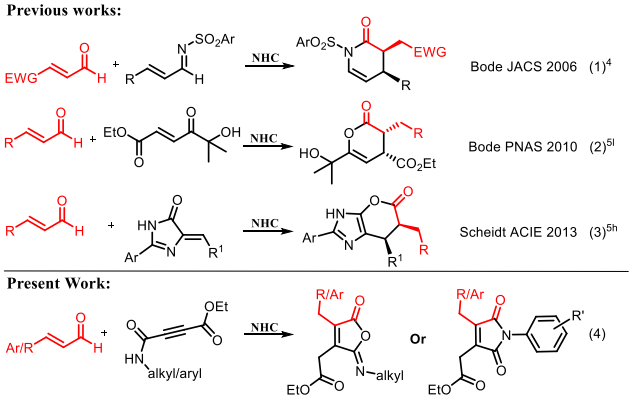
ABSTRACT: Herein we report the *N*-heterocyclic carbene (NHC)-catalyzed [3 + 2] annulation of α,β-unsaturated aldehydes with carbamoylpropiolates via an unusual enolate pathway leading to the construction of highly functionalized maleimides or isomaleimides. The electronic effect imposed by the alkyl/aryl group present on the amide nitrogen of carbamoylpropiolates plays a crucial role in the selective formation of these important five-membered heterocyclic building blocks. The developed protocol is mild and tolerates a wide range of substituents on both substrates. The application of this protocol in the synthesis of the antibacterial natural product Aspergillus FH-X-213 has also been demonstrated.

INTRODUCTION

Organocatalysis by *N*-heterocyclic carbenes (NHCs) is an important synthesis tool of contemporary interest. It has had remarkable growth in the past two decades due to its effectiveness in constructing several scaffolds useful in pharmaceutical and material applications under milder and environmentally friendly reaction conditions from simple and readily available starting materials.[1] The two most common modes of NHC reactivity, wherein the reaction follows either acyl anion or homoenolate pathway, are well-studied and documented in the literature; however, the enolate pathway is relatively less explored.[1,2]

The NHC-catalyzed enolate pathway was indirectly employed by intramolecularly using substrates such as ketenes, α-haloaldehydes, alkylacetic esters, or with well-designed enals.[3] However, the use of simple commercially available or easily accessible enals in the intermolecular reactions was not achieved until the pioneering work reported by Bode.[4] This investigation was followed by the utilization of α,β-unsaturated ketones, esters, imines, and activated chalcones as electrophilic coupling partners for annulation or hetero-Diels−Alder reaction by Nair, Glorious, Chi, Scheidt, and others (Scheme 1).[5] Interestingly, the alkyne-based electrophilic reacting partners have never been utilized. Chi reported an important observation that the presence of an electron-withdrawing

Scheme 1. NHC-Catalyzed Annulation Reactions via Enolate Pathway and This Work



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group on the electrophilic partner moderates the reactivity mode of the NHC-activated enals leading to the selective formation of enolate pathway products.[5k] Continuing our interest in the development of novel methodologies using NHC catalysis and their application in the synthesis of natural product,[6] we were curious to explore such mode of NHC's reactivity in the development of novel processes to access industrially important heterocyclic scaffolds. Heterocycles are common structural motifs in bioactive natural products and marketed drugs.[7]

Nitrogen heterocycles, in particular maleimides (MIs) and isomaleimides (IMIs), are one type of those privileged heterocyclic scaffolds abundant in many bioactive molecules, natural products, drugs, or advanced materials.[8] They can be easily transformed to the corresponding maleic acid/anhydride, which is also one of the common cores in several natural products (Figure 1).[9] Moreover, MIs/IMIs are

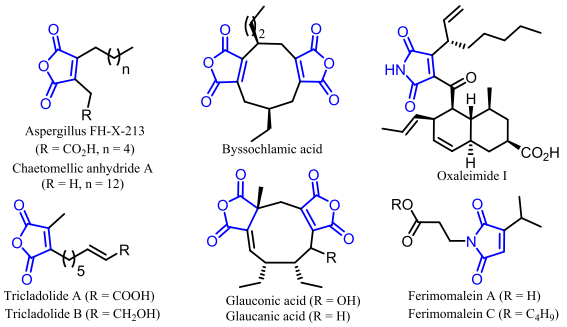


Figure 1. Selected anhydride and maleimide bioactive natural products

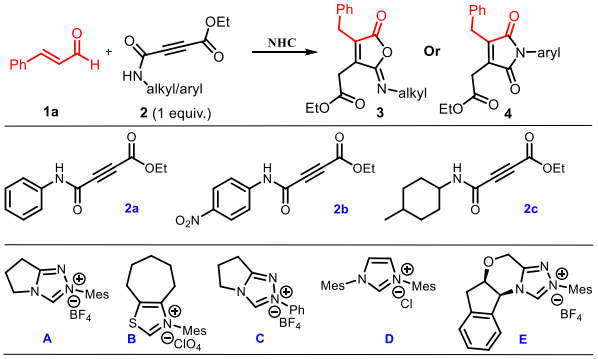
important building blocks of industrial interest and they are most sought after targets subsequent to their initial synthesis.[10] Since then, several methods for their preparation have been disclosed in the literature; however, novel facile methods are always desired.[11]

Considering the literature background, the scope to employ the relatively less exploited NHC reactivity, and the significance of MI/IMI scaffolds, we endeavored to develop a novel protocol for the construction of MIs/IMIs utilizing the rarely explored intermolecular reaction of the NHC-bound enolates from α,β-unsaturated aldehydes with carbamoylpropiolate (CAP) as the activated electrophilic coupling partner.

RESULT AND DISCUSSION

We commenced our investigation by performing the reaction of cinnamaldehyde (**1a**) with CAP **2a** in the presence of NHC precursors **A**−**E** and a few others (see the Supporting Information). To our delight, the first attempt using NHC-**A** (20 mol %), K_2CO_3 (40 mol %), and 1 equiv each of substrates **1a** and **2a** in THF at room temperature furnished the desired products though in less than 5% yield (Table 1, entry 1). Several permutations and combinations (Table 1, entries 2−18) using NHC precursors, polar and nonpolar solvents, organic and inorganic bases, reaction time, additives, temperature, variation in equivalents of all components, and so on provided an optimal reaction condition to obtain IMI **3u** and MI **4u** in 65% combined yield and 1:5.7 ratio (Table 1, entry 16) in 8 h. To understand the electronic effect of the substituents on the formation of the products, the developed protocol was applied on two different types of CAP substrates,

Table 1. Optimization of the Reaction Condition[a]



sr no.	1a (equiv)	temp (°C)	solvent	NHC (mol %)	% yield (3/4)[b]
1	1.0	rt	THF	**A**, 20	<5
2	1.0	rt	THF	**B**, 20	
3	1.0	rt	THF	**C**, 20	
4	1.0	rt	THF	**D**, 20	<9
5	1.0	rt	THF	**E**, 20	<17
6	1.0	rt	dioxane	**E**, 20	29 (38:62)
7	1.0	rt	MeCN	**E**, 20	
8	1.0	rt	benzene	**E**, 20	34 (31:69)
9	1.0	rt	toluene	**E**, 20	40 (24:76)
10	1.0	rt	xylene	**E**, 20	25 (28:72)
11	1.0	35	toluene	**E**, 20	49 (22:78)
12	1.0	50	toluene	**E**, 20	35 (15:85)
13	1.2	35	toluene	**E**, 20	57 (19:81)
14	1.5	35	toluene	**E**, 20	64 (19:81)
15	2.0	35	toluene	**E**, 20	63 (20:80)
16	**1.5**	**35**	**toluene**	**E, 15**	**65**(15:85)
17[c]	1.5	35	toluene	**E**, 15	41 (19:81)
18[d]	1.5	35	toluene	**E**, 15	
19[e]	**1.5**	**35**	**toluene**	**E, 15**	**68**(11:89)
20[f]	**1.5**	**35**	**toluene**	**E, 15**	**66**(95:05)

[a]Reaction conditions: **2a**−**c** (0.1 mmol), **1a**, K_2CO_3 (entries 1−15 = 40 mol %; entries 16, 19, and 20 = 30 mol %), NHC, solvent (1 mL) in Schlenk tube with side arm, reaction time: 24 h for entries 1−10 and 8 h for entries 11−20. [b]Isolated yield. [c]Using Cs_2CO_3 as base. [d]Using NEt_3 as base. [e]Using substrate **2b**. [f]Using substrate **2c**.

2b and **2c**, containing a nitrogen substituted with electron-deficient and -rich group, respectively. Interestingly, substrate **2b** shows enhanced formation of MI **4ab** (Table 1, entry 19), whereas **2c** shows selective formation of IMI **3a** (Table 1, entry 20) in good yields. On the basis of these intriguing results (Table 1, entries 16, 19, and 20), we planned to explore the substrate scope of the NHC-enolate-driven [3 + 2] annulation protocol for the selective formation of IMIs and MIs.

First, we tested the substrate scope for IMI synthesis by utilizing alkyl-substituted CAP **2c** (Scheme 2). The reaction with substrates such as cinnamaldehyde and 3-methyl cinnamaldehyde leads to the formation of IMI products **3a** and **3b**, respectively, in good yield and selectivity as expected. The aldehydes substituted with strong electron-donating groups and halides were also found to be compatible, leading to related products **3c**−**g** in good selectivity. The cinnamaldehyde substrates with strong electron-withdrawing and polyaromatic substituents worked well to obtain IMIs **3h**−**k** in good to moderate yields and high selectivity. The protocol also tolerated heterocyclic enal to provide IMI **3l** in moderate yield. The enal substrates with aliphatic β-substituents worked even

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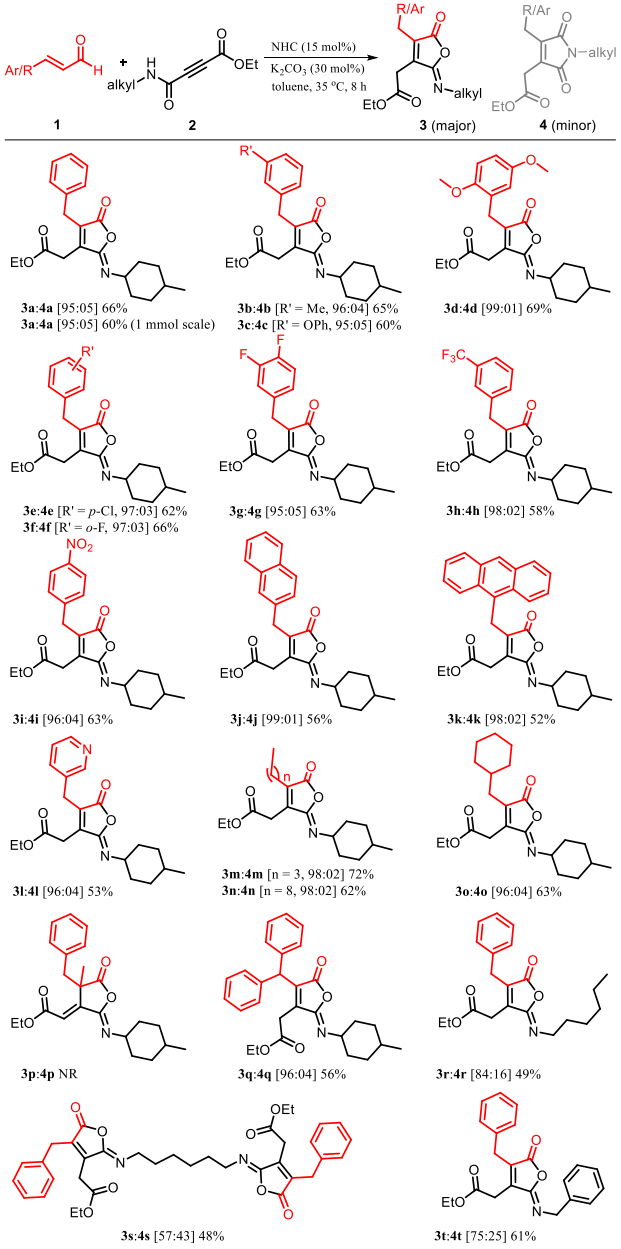
Scheme 2. Annulation of Enals with *N*-Alkyl-Substituted Carbamoylpropiolate[a]

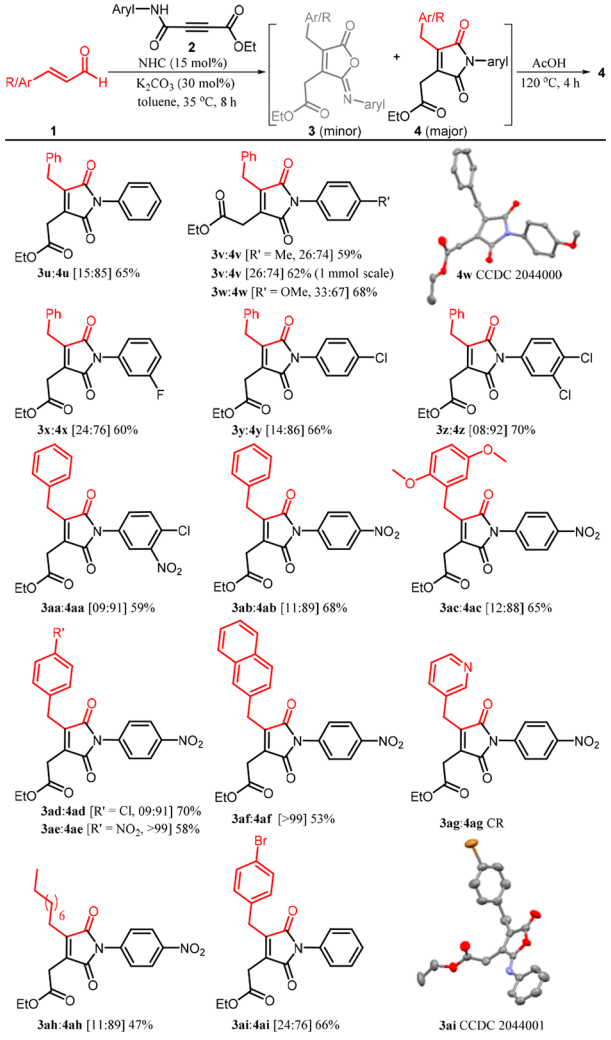


[a]Reaction conditions: **1** (0.15 mmol), **2** (0.1 mmol), NHC-**E** (15 mol %), K_2CO_3 (30 mol %), toluene (1 mL), in Schleck tube with side arm for 8 h. Isolated yields are given as percentages. NR = no reaction.

better with excellent selectivity to furnish IMIs **3m**−**o** in very good yields. The α-methyl-substituted cinnamaldehyde failed to give product **3p**, probably because of the steric hindrance at the α-position as the reaction follows the enolate pathway. However, β-phenyl-substituted cinnamaldehyde worked well to provide product **3q** in moderate yield. The variation in the aliphatic substituents on CAP nitrogen was also studied. Long-chain primary alkyl- and benzyl-substituted CAPs worked well, similar to its cyclic substituted analogues leading to the formation of IMIs **3r**−**t**; however, the selectivity dropped down.

We next aimed to explore the substrate scope of *N*-aryl-substituted CAPs with cinnamaldehyde derivatives to achieve

Scheme 3. Annulation of Enals with *N*-Aryl-Substituted Carbamoylpropiolate[a]



[a]Reaction condition: **1** (0.15 mmol), **2** (0.1 mmol), NHC-**E** (15 mol %), K_2CO_3 (30 mol %), toluene (1 mL), in Schleck tube with side arm for 8 h. Isolated yield given as a percentage is for product **4**. CR = complex reaction mixture.

the selective formation of MIs (Scheme 3). To simplify the process, after completion of the reaction, the ratio of IMI versus MI was determined by ^{1}H NMR of the reaction mixture before converting it completely to MI by heating in acetic acid. First, we varied the substituents on the aromatic ring of CAP. The CAP substrates with phenyl, *p*-tolyl, an electron-donating group, and halo-substituent worked well to obtain corresponding MIs **4u**−**z**. Substrates containing a strong electron-withdrawing nitro group interestingly furnished MI products **4aa** and **4ab** with comparatively high selectivity, probably due to higher thermodynamic stability of the MI product. On the basis of this observation, we planned to vary enal substituents keeping *para*-nitro-substituted CAP **2b** as the common electrophilic partner. Various cinnamaldehydes with electron-donating/withdrawing, halide, and polyaromatic substituents underwent a smooth transformation to furnish excellent selectivity (**4ac**−**af**). Gratifyingly, a complete selectivity to obtain MIs **4ae** and **4af** was observed when both the reacting partners with electron-withdrawing groups were used; hence, further heating in acetic acid was not carried out in these two

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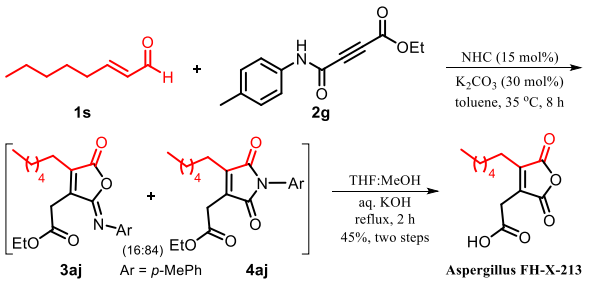
cases. However, heterocyclic-substituted MI **4ag** could not be synthesized using our standard protocol. Aliphatic enal with a long alkyl chain also reacted well with CAP **2b** to furnish MI **4ah**; however, the yield was lower compared to that of the aromatic enals. Additional support for the structure of the formed products was obtained by single-crystal X-ray analysis (see the Supporting Information) of MI **4w** and bromo-substituted IMI **3ai**.

The scalability of the developed protocol was demonstrated by performing the reaction of the CAP **2c** on a 1 mmol scale to obtain IMI **3a** in good yield (Scheme 2). Similarly, the reaction of CAP **2g** followed by heating the reaction mixture in acetic acid worked equally well on a 1 mmol scale to obtain MI **4v** in good yield (Scheme 3).

The successful demonstration of the broad substrate scope studies of our NHC-catalyzed protocol prompted us to explore its potential application in the concise synthesis of natural product Aspergillus FH-X-213 (Scheme 4). It was first isolated

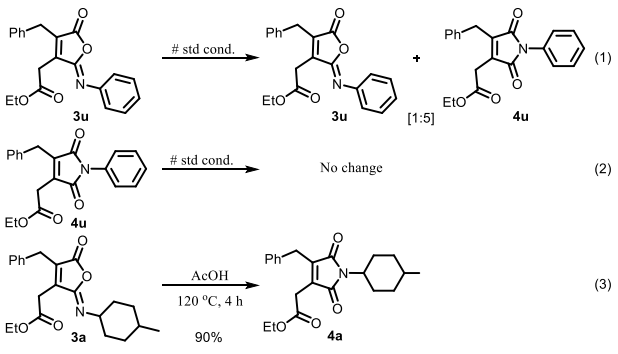
Scheme 4. Total Synthesis of Natural Product Aspergillus FH-X-213



in 1972 and displays activity against Gram-positive bacteria.[12] To date, four total syntheses of Aspergillus FH-X-213 have been reported in the literature.[13] We subjected *trans*-2-octenal (**1s**) and CAP **2g** to our standard reaction conditions. The resultant reaction mixture containing desired products MI **4aj** and IMI **3aj** was then evaporated in vacuo to remove toluene. The residue was refluxed in THF/methanol (1:2) and aqueous KOH.[13b] The usual workup and purification furnished the natural product Aspergillus FH-X-213 in 45% yield over two steps (Scheme 4). It should also be possible to extend this protocol to the total synthesis of chaetomellic anhydride A, byssochlamic acid, and related natural products (Figure 1).[9]

We carried out a few control experiments to understand the reaction pathway. Pure IMI **3u** was subjected to the standard reaction condition, and we observed the mixture of **3u** and **4u** in a 1:5 proportion (Scheme 5, eq 1). However, pure MI **4u**

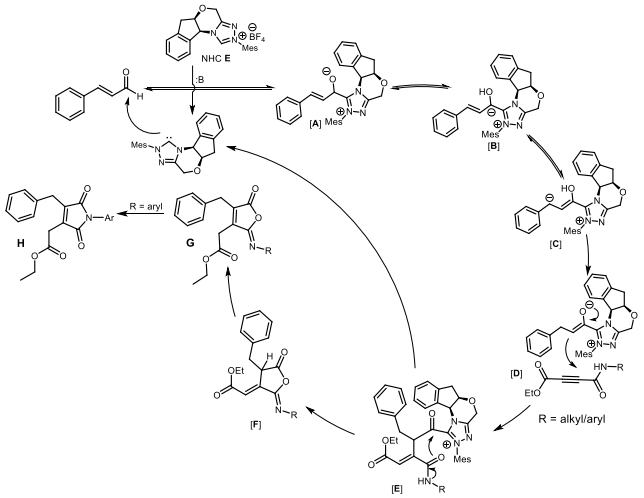
Scheme 5. Control Experiments



did not show any change under the standard reaction condition (Scheme 5, eq 2). Similar to the conversion of *N*-aryl IMIs to MIs (Scheme 3), *N*-alkyl IMI **3a** could be converted smoothly to MI **4a** in excellent yield (Scheme 5, eq 3). These experiments indicate that IMI could be the actual intermediate during the course of the reaction. These observations also corroborate with the studies indicating the preferred formation of IMIs as products of kinetic control and the formation of the thermodynamically stable MIs via the rearrangement of IMIs depending on the nature of the substituent present on the nitrogen.[14]

On the basis of the experimental observations and literature precedence,[5] a plausible reaction mechanism has been proposed as depicted in Scheme 6. The Breslow intermediate

Scheme 6. Plausible Reaction Mechanism



[**B**], formed from NHC-**E** and cinnamaldehyde, converts to the homoenolate equivalent [**C**] upon the migration of the negative charge. It then leads to the formation of the enolate equivalent [**D**] after proton abstraction. The regioselective attack of the active intermediate enolate [**D**] on CAP leads to the generation of intermediate **E**, which upon the internal attack of oxygen on carbonyl expels NHC for the further catalytic cycle and forms IMI product **G** after proton migration. However, the substrates with an aromatic substituent on the nitrogen transforms to the stable MI product **H**. The more electron-deficient nature of the CAP might favor the enolate pathway;[5k] hence, we did not observe the formation of the corresponding six-membered N-substituted glutarimide products via a typical homoenolate pathway.

In summary, we have demonstrated a general and scalable NHC-catalyzed highly selective enolate-driven intermolecular annulation of α,β-unsaturated aldehydes with CAPs leading to synthetically valuable products MIs and IMIs. The choice of CAPs as an optimal electron-deficient reacting partner was critical to the success of the enolate-pathway-based protocol. To the best of our knowledge, this report is the first example of alkynes as the electrophilic-reacting substrates in NHC-catalyzed reactions. The protocol has also been extended for the synthesis of natural product Aspergillus FH-X-213. However, it would be necessary to develop a simple, achiral catalyst based on this work for practical application of the process. We are now working on the development of this

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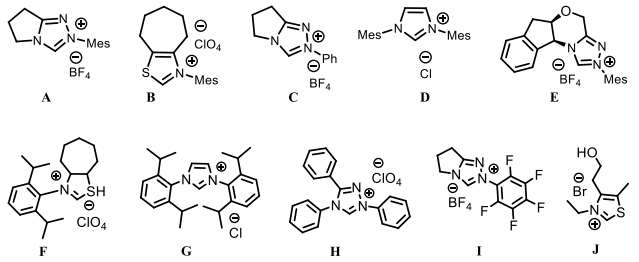
protocol for the asymmetric synthesis of functionalized succinimides utilizing enal enolates and their application in the construction of related natural products and drugs.

EXPERIMENTAL SECTION

General Information. All reagents and solvents were used as received from commercial sources unless otherwise noted. All experiments were carried out in a Schlenk tube with a side arm. Aluminum metal plates precoated with silica gel 60 PF254 (0.25 or 0.5 mm) were utilized for thin-layer chromatography (TLC). Visualization of the developed TLC plate was carried out by irradiation with UV light. Column chromatographic purifications were carried out on flash silica gel (240−400 mesh) using ethyl acetate and petroleum ether as eluents. The ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were recorded on 200/400/500 and 100/125 MHz NMR spectrometers, respectively, in $CDCl_3$. Chemical shifts were reported as δ values from standard peaks. The $^{13}C\{^{1}H\}$ NMR spectra of compounds **3o**, **4x**, **4aa**, and **4ac** show one less carbon because of overlapping peaks. The melting points are uncorrected. High-resolution mass spectrometry (HRMS) was carried out on a ESI-TOF/Q-TOF mass spectrometer. All carbamoylpropiolate starting materials were prepared according to the literature procedure starting from the corresponding isocyanate and ethyl propiolate. All the aldehydes were purchased from a commercial source and used without further purification. The following NHC precursors were screened during the optimization of the protocol. They were prepared according to the literature procedures.[15]



Experimental Procedures. *General Procedure I for the Synthesis of Carbamoylpropiolates.* All the carbamoylpropiolates were prepared according to the reported procedure.[16] Ethyl propiolate (1.0 equiv) was dissolved in THF (5 mL), and the solution was cooled to −78 °C, followed by the slow addition of *n*-BuLi (1.2 equiv, 1.5 M in hexane). The mixture was stirred for 30 min, and a solution of the corresponding isocyanate (500 mg, 1.0 equiv) in THF (5 mL) was added dropwise. The reaction mixture was then stirred for 3−5 h at same temperature, and acetic acid (1 mL) was added to quench the reaction after completion. The reaction mixture was allowed to warm to room temperature, water was added and the aqueous layer was extracted with ethyl acetate (20 mL × 3). The combined organic extract was dried over anhydrous Na_2SO_4, filtered, and concentrated using a rotary evaporator under vacuum. The obtained residue was subjected to flash column chromatography on silica-gel using ethyl acetate and petroleum ether (1:4) to afford the corresponding compounds.

*General Procedure II for the Selective Synthesis of Isomaleimides **3a−t** Using N-Alkyl-Substituted Carbamoylpropiolates.* An oven-dried Schlenk tube equipped with a magnetic stirring bar was charged with carbamoylpropiolate (0.1 mmol, 1 equiv), aldehyde (0.15 mmol, 1.5 equiv), NHC-**E** (6.3 mg, 0.015 mmol, 15 mol %), and K_2CO_3 (4.1 mg, 0.030 mmol, 30 mol %) under an argon atmosphere. To this mixture, toluene (1.0 mL) was added, and the Schlenk tube was backfilled with argon and heated at 35 °C in a preheated oil bath. The progress of the reaction was monitored using TLC analysis. The reaction was stopped after 8 h, and the solvent was evaporated under reduced pressure. The crude reaction mixture was purified by flash column chromatography using ethyl acetate and petroleum ether as eluents to obtain isomaleimides **3a−t** in good to moderate yields.

*General Procedure III for the Selective Synthesis of Maleimides **4u−ai** Using N-Aryl-Substituted Carbamoylpropiolates.* An oven-dried Schlenk tube equipped with a magnetic stirring bar was charged with carbamoylpropiolate (0.1 mmol, 1 equiv), aldehyde (0.15 mmol, 1.5 equiv), NHC-**E** (6.3 mg, 0.015 mmol, 15 mol %), and K_2CO_3 (4.1 mg, 0.030 mmol, 30 mol %) under an argon atmosphere. To this mixture, toluene (1.0 mL) was added, and the Schlenk tube was backfilled with argon and heated at 35 °C in a preheated oil bath. The progress of the reaction was monitored using TLC analysis. The reaction was stopped after 8 h, and the solvent was evaporated under reduced pressure. Acetic acid (1 mL) was added to the crude reaction mixture, and the reaction was heated to 120 °C for 4 h. The acetic acid was then evaporated, and the residue was dissolved in EtOAc and washed with water, aqueous saturated $NaHCO_3$ (10 mL × 2), and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated using a rotary evaporator under vacuum. The obtained crude residue was purified by flash column chromatography using ethyl acetate and petroleum ether as eluents.

*Typical Experimental Procedure **IV** for the Preparation of Representative Isomaleimide Product **3a**.* An oven-dried Schlenk tube equipped with a magnetic stirring bar was charged with ethyl 4-((4-methylcyclohexyl)amino)-4-oxobut-2-ynoate (**2c**, 23.7 mg, 0.1 mmol, 1 equiv), cinnamaldehyde (**1a**, 20 mg, 0.15 mmol, 1.5 equiv), NHC-**E** (6.3 mg, 0.015 mmol, 15 mol %), and K_2CO_3 (4.1 mg, 0.030 mmol, 30 mol %) under an argon atmosphere. To this mixture, toluene (1.0 mL) was added, and the Schlenk tube was backfilled with argon and heated at 35 °C in a preheated oil bath. The progress of the reaction was monitored using TLC analysis. The reaction was stopped after 8 h, and the solvent was evaporated under reduced pressure. The crude reaction mixture was purified by flash column chromatography using ethyl acetate and petroleum ether (1:9) to afford isomaleimide product **3a** (**3a**/**4a** = 95:05) in 66% (24.3 mg) yield.

*Typical Experimental Procedure **V** for the Preparation of Representative Maleimide Product **4u**.* An oven-dried Schlenk tube equipped with a magnetic stirring bar was charged with ethyl 4-oxo-4-(phenylamino)but-2-ynoate (**2a**, 21.7 mg, 0.1 mmol, 1 equiv), cinnamaldehyde (**1a**, 20 mg, 0.15 mmol, 1.5 equiv), NHC-**E** (6.3 mg, 0.015 mmol, 15 mol %), and K_2CO_3 (4.1 mg, 0.030 mmol, 30 mol %) under an argon atmosphere. To this mixture, toluene (1.0 mL) was added, and the Schlenk tube was backfilled with argon and heated at 35 °C in a preheated oil bath. The progress of the reaction was monitored using TLC analysis. The reaction was stopped after 8 h, and solvent was evaporated under reduced pressure (the ^{1}H NMR analysis shows **3u**/**4u** = 17:83). Acetic acid (1 mL) was added to the crude reaction mixture, and the reaction was heated to 120 °C for 4 h. The acetic acid was then evaporated, and the residue was dissolved in EtOAc and washed with water, aqueous saturated $NaHCO_3$ (10 mL × 2), and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated using a rotary evaporator under vacuum. The obtained crude residue was purified by flash column chromatography using ethyl acetate and petroleum ether (1:6) to afford pure maleimide product **4u** in 65% (22.6 mg) yield.

*Procedure **VI** for **1** mmol Scale Experiments. Procedure **VI-A** for the Synthesis of **3a**.* An oven-dried Schlenk tube equipped with a magnetic stirring bar was charged with carbamoylpropiolate **2c** (237 mg, 1 mmol, 1 equiv), cinnamaldehyde (198 mg, 1.5 mmol, 1.5 equiv), NHC-**E** (63 mg, 0.15 mmol, 15 mol %), and K_2CO_3 (41 mg, 0.30 mmol, 30 mol %) under an argon atmosphere. To this mixture, toluene (10 mL) was added, and the Schlenk tube was backfilled with argon and heated at 35 °C in a preheated oil bath. The progress of the reaction was monitored using TLC analysis. The reaction was stopped after 8 h, and the solvent was evaporated under reduced pressure. The crude reaction mixture was purified by flash column chromatography using ethyl acetate and petroleum ether (1:9) to afford isomaleimide product **3a** (**3a**/**4a** = 95:05) in 60% (221 mg) yield.

*Procedure **VI-B** for the Synthesis of **4v**.* An oven-dried Schlenk tube equipped with a magnetic stirring bar was charged with carbamoylpropiolate **2g** (230 mg, 1 mmol, 1 equiv), cinnamaldehyde (198 mg, 1.5 mmol, 1.5 equiv), NHC-**E** (63 mg, 0.15 mmol, 15 mol %), and K_2CO_3 (41 mg, 0.30 mmol, 30 mol %) under an argon

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atmosphere. To this mixture, toluene (10 mL) was added, and the Schlenk tube was backfilled with argon and heated at 35 °C in a preheated oil bath. The progress of the reaction was monitored using TLC analysis. The reaction was stopped after 8 h, and solvent was evaporated under reduced pressure (the ^{1}H NMR analysis shows **3v**/**4v** = 26:74). Acetic acid (10 mL) was added to the crude reaction mixture, and the reaction was heated to 120 °C for 4 h. The acetic acid was then evaporated, and the residue was dissolved in EtOAc and washed with water, aqueous saturated $NaHCO_3$ (50 mL × 2), and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated using a rotary evaporator under vacuum. The obtained crude residue was purified by flash column chromatography using ethyl acetate and petroleum ether (1:6) to afford pure maleimide product **4v** in 62% (224 mg) yield.

*Control Experiments (Procedures **VII**). Experimental Procedure **VII-A** for the Reaction of Isomaleimide **3u** under Standard Conditions.* An oven-dried Schlenk tube equipped with a magnetic stirring bar was charged with isomaleimide **3u** (17.5 mg, 0.05 mmol, 1 equiv), NHC-**E** (3 mg, 0. 0075 mmol, 15 mol %), and K_2CO_3 (2 mg, 0. 015 mmol, 30 mol %) under an argon atmosphere. To this mixture, toluene (0.5 mL) was added, and the Schlenk tube was backfilled with argon and heated at 35 °C in a preheated oil bath. The reaction was stopped after 8 h, and the solvent was evaporated under reduced pressure. The crude product was purified by the flash column chromatography using ethyl acetate and petroleum ether (1:9) to obtain **3u** and **4u** (1:5) in 92% (16 mg) yield.

*Experimental Procedure **VII-B** for the Reaction of Maleimide **4u** under Standard Conditions.* An oven-dried Schlenk tube equipped with a magnetic stirring bar was charged with maleimide **4u** (17.5 mg, 0.05 mmol, 1 equiv) NHC-**E** (3 mg, 0. 0075 mmol, 15 mol %), and K_2CO_3 (2 mg, 0. 015 mmol, 30 mol %) under an argon atmosphere. To this mixture, toluene (0.5 mL) was added, and the Schlenk tube was backfilled with argon and heated at 35 °C in a preheated oil bath. The reaction was stopped after 8 h, and it was found that all the starting material remained unchanged.

*Procedure **VII-C** for Synthesis of Maleimide **4a** from Corresponding Isomaleimide **3a**.* A known protocol[17] for the conversion of isomaleimide to maleimides was applied for the preparation of **4a** from **3a**. A solution of isomaleimide **3a** (20 mg) in glacial acetic acid (1 mL) was heated at 120 °C for 4 h. The acetic acid was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate. The organic layer was washed with water, aqueous $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated using a rotary evaporator under vacuum. The obtained crude residue was purified by flash column chromatography using ethyl acetate and petroleum ether (1:6) to afford pure maleimide product **4a** in 90% (18 mg) yield.

*Procedure **VIII** for the Synthesis of Natural Product Aspergillus FH-X-213. Procedure **VIII-A** (Step 1).* An oven-dried Schlenk tube equipped with a magnetic stirring bar was charged with carbamoylpropiolate **2g** (46 mg, 0.2 mmol, 1 equiv), *trans*-2-octenal (38 mg, 0.3 mmol, 1.5 equiv), NHC-**E** (12.5 mg, 0.03 mmol, 15 mol %), and K_2CO_3 (8.2 mg, 0.06 mmol, 30 mol %) under an argon atmosphere. To this mixture, toluene (2.0 mL) was added, and the Schlenk tube was backfilled with argon and heated at 35 °C in a preheated oil bath. The progress of the reaction was monitored using TLC analysis. The reaction was stopped after 8 h, and the solvent was evaporated under reduced pressure. The crude product was passed through the flash column using ethyl acetate and petroleum ether (1:6), and the obtained mixture of compounds **3aj** and **4aj** (43 mg, **3aj**/**4aj** = 16:84) was utilized for the next step.

*Procedure **VIII-B** (Step 2).* The reported protocol[13b] for the conversion of maleimide to maleic anhydride was applied on the above obtained mixture of products. To a stirred solution of isomaleimides **3aj** and maleimide **4aj** (43 mg) in a THF/methanol mixture (1:2, 2 mL) was added 20% aqueous KOH solution (1.5 mL), and the reaction mixture was refluxed for 2 h with stirring. The reaction mixture was concentrated to remove THF/MeOH, and the aqueous layer was acidified with 2 N HCl followed by extraction with diethyl ether (3 × 20 mL). The combined organic layer was washed with water and brine, dried over Na_2SO_4, and filtered. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue with petroleum ether and ethyl acetate furnished 22 mg of natural product Aspergillus FH-X-213 in 45% yield over two steps.

Characterization Data of Compounds. *Ethyl 4-((4-Nitrophenyl)amino)-4-oxobut-2-ynoate (**2b**).* Title compound **2b** was prepared according to general procedure **I** as a yellow solid in 42% yield (335 mg). R_f 0.5 (ethyl acetate/petroleum ether, 1:3); mp: 128−130 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.28−8.26 (m, 1H), 8.26 (d, J = 9.1 Hz, 2H), 7.74 (d, J = 9.1 Hz, 2H), 4.34 (q, J = 7.1 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm) 152.0, 148.4, 144.4, 142.1, 125.2, 119.7, 76.2, 75.5, 63.4, 13.9. HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{12}H_{11}N_2O_5$, 263.0667. Found, 263.0674.

*Ethyl 4-(Hexylamino)-4-oxobut-2-ynoate (**2d**).* Title compound **2d** was prepared according to general procedure **I** as colorless liquid in 62% yield (549 mg). R_f 0.6 (ethyl acetate/petroleum ether, 1:3). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.00 (brs, 1H), 4.29 (q, J = 7.1 Hz, 2H), 3.36−3.28 (m, 2H), 1.57−1.50 (m, 2H), 1.38−1.29 (m, 9H), 0.92−0.87 (m, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm) 152.3, 150.7, 76.7, 73.7, 62.9, 40.1, 31.3, 29.1, 26.4, 22.5, 13.96, 13.90. HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{12}H_{20}NO_3$, 226.1442. Found, 226.1445.

*Diethyl 4,4′-(Hexane-1,6-diylbis(azanediyl))bis(4-oxobut-2-ynoate) (**2e**).* Title compound **2e** was prepared according to general procedure **I** as a white solid in 60% yield (649 mg). R_f 0.5 (ethyl acetate/petroleum ether, 1:2); mp: 91−93 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.38 (br, 2H), 4.28 (q, J = 7.1 Hz, 4H), 3.32 (q, J = 6.4 Hz, 4H), 1.59−1.52 (m, 4H), 1.37−1.30 (m, 10H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm) 152.3, 150.9, 76.7, 73.9, 62.9, 39.7, 28.9, 26.0, 13.9. HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{18}H_{25}N_2O_6$, 365.1712. Found, 365.1711.

*Ethyl 4-((4-Methoxyphenyl)amino)-4-oxobut-2-ynoate (**2h**).* Title compound **2h** was prepared according to general procedure **I** as a white solid in 57% yield (472 mg). R_f 0.5 (ethyl acetate/petroleum ether, 1:3); mp: 77−79 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.80 (brs, 1H), 7.41−7.52 (m, 2H), 6.85−6.92 (m, 2H), 4.31 (q, J = 6.9 Hz, 2H), 3.80 (s, 3H), 1.35 (t, J = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm) 157.2, 152.3, 148.1, 129.6, 121.8, 114.3, 76.7, 74.4, 63.0, 55.5, 13.9. HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{13}H_{14}NO_4$, 248.0922. Found, 248.0928.

*Ethyl 4-((3-Fluorophenyl)amino)-4-oxobut-2-ynoate (**2i**).* Title compound **2i** was prepared according to general procedure **I** as a yellow liquid in 52% yield (446 mg). R_f 0.5 (ethyl acetate/petroleum ether, 1:3). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.91 (brs, 1H), 7.45−7.52 (m, 1H), 7.35−7.28 (m, 1H), 7.20−7.12 (m, 1H), 6.92−6.85 (m, 1H), 4.33 (q, J = 7.1 Hz, 2H), 1.36 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm) 162.9 (CF, J = 246.3 Hz), 152.2, 148.2, 138.0 (CF, J = 10.9 Hz), 130.4 (CF, J = 9.5 Hz), 115.2 (CF, J = 2.9 Hz), 112.4 (CF, J = 21.8 Hz), 107.7 (CF, J = 26.9 Hz), 76.7, 74.8, 63.2, 13.9. HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{12}H_{11}FNO_3$, 236.0722. Found, 236.0727.

*Ethyl 4-((3,4-Dichlorophenyl)amino)-4-oxobut-2-ynoate (**2k**).* Title compound **2k** was prepared according to general procedure **I** as a white solid in 51% yield (387 mg). R_f 0.5 (ethyl acetate/petroleum ether, 1:3); mp: 69−71 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.95 (brs, 1H), 7.77 (d, J = 2.5 Hz, 1H), 7.42 (d, J = 8.6 Hz, 1H), 7.36 (dd, J = 8.8, 2.5 Hz, 1H), 4.33 (q, J = 7.3 Hz, 2H), 1.36 (t, J = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm) 152.1, 148.2, 135.9, 133.2, 130.8, 129.1, 121.8, 119.2, 76.5, 75.1, 63.3, 13.9. HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{12}H_{10}{}^{35}Cl_2NO_3$, 285.9190. Found, 285.9188.

*Ethyl 4-((4-Chloro-3-nitrophenyl)amino)-4-oxobut-2-ynoate (**2l**).* Title compound **2l** was prepared according to general procedure **I** as a white solid in 44% yield (329 mg). R_f 0.5 (ethyl acetate/petroleum ether, 1:3); mp: 99−101 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.53 (brs, 1H), 8.18 (d, J = 2.5 Hz, 1H), 7.77 (dd, J = 8.8, 2.6 Hz, 1H), 7.54 (d, J = 8.9 Hz, 1H), 4.34 (q, J = 7.1 Hz, 2H), 1.36 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm) 152.2, 148.5,

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147.9, 136.2, 132.5, 124.1, 123.0, 116.8, 76.2, 75.5, 63.6, 13.9. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{12}H_{10}{}^{35}ClN_2O_5$, 297.0278. Found, 297.0280.

*Ethyl (Z)-2-(4-Benzyl-2-((4-methylcyclohexyl)imino)-5-oxo-2,5-dihydrofuran-3-yl)acetate (**3a**).* Title compound **3a** was prepared according to the procedure **IV** as sticky solid in 66% yield (24.3 mg, **3a**/**4a** = 95:05). Reaction time 8 h/35 °C. R_f 0.7 (ethyl acetate/petroleum ether, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.35−7.18 (m, 5H), 4.11 (q, J = 6.9 Hz, 2H), 3.77 (s, 2H), 3.70−3.76 (m, 1H), 3.44 (s, 2H), 1.76−1.68 (m, 4H), 1.49−1.35 (m, 3H), 1.22 (t, J = 6.9 Hz, 3H), 1.08−0.99 (m, 2H), 0.90 (d, J = 6.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 168.03, 167.96, 149.8, 142.4, 136.8, 136.0, 128.82, 128.78, 127.1, 61.5, 57.9, 33.4, 33.3, 31.8, 30.3, 30.1, 22.3, 14.0. HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{28}NO_4$, 370.2013. Found, 370.2017.

*Ethyl (Z)-2-(4-(3-Methylbenzyl)-2-((4-methylcyclohexyl) imino)-5-oxo-2,5-dihydrofuran-3-yl)acetate (**3b**).* Title compound **3b** was prepared according to general procedure **II** as sticky solid in 65% yield (25 mg, **3b**/**4b** = 96:04): Reaction time 8 h/35 °C. R_f 0.7 (ethyl acetate/petroleum ether, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.19 (t, J = 7.4 Hz, 1H), 7.08−6.98 (m, 3H), 4.11 (q, J = 7.2 Hz, 2H), 3.81−3.70 (m, 3H), 3.43 (s, 2H), 2.32 (s, 3H), 1.76 (m, 4H), 1.49−1.35 (m, 3H), 1.22 (t, J = 7.1 Hz, 3H), 1.08−0.98 (m, 2H), 0.90 (d, J = 6.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 168.04, 168.0, 149.9, 142.3, 138.5, 136.9, 135.9, 129.5, 128.7, 127.8, 125.8, 61.4, 57.9, 33.4, 33.3, 31.8, 30.2, 30.1, 22.3, 21.3, 14.0. HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{23}H_{30}NO_4$, 384.2169. Found, 384.2175.

*Ethyl (Z)-2-(2-((4-Methylcyclohexyl)imino)-5-oxo-4-(3-phenoxybenzyl)-2,5-dihydrofuran-3-yl)acetate (**3c**).* Title compound **3c** was prepared according to general procedure **III** as sticky solid in 60% yield (28 mg, **3c**/**4c** = 95:05). Reaction time 8 h/35 °C. R_f 0.5 (ethyl acetate/petroleum ether, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.38−7.32 (m, 2H), 7.27−7.22 (m, 1H), 7.15−7.08 (m, 1H), 7.02−6.94 (m, 3H), 6.93−6.88 (m, 1H), 6.88−6.84 (m, 1H), 4.11 (q, J = 6.9 Hz, 2H), 3.83−3.68 (m, 3H), 3.45 (s, 2H), 1.77−1.67 (m. 4H), 1.51−1.36 (m, 3H), 1.22 (t, J = 6.9 Hz, 3H), 1.08−1.0 (m, 2H), 0.91 (d, J = 6.9 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 167.9, 167.8, 157.6, 156.8, 149.9, 142.6, 137.9, 136.4, 130.0, 129.8, 123.5, 123.4, 119.2, 118.9, 117.2, 61.5, 58.0, 33.4, 33.2, 31.7, 30.2, 30.1, 22.3, 14.0. HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{28}H_{32}NO_5$, 462.2275. Found, 462.2281.

*Ethyl (Z)-2-(4-(2,5-Dimethoxybenzyl)-2-((4-methylcyclo hexyl)-imino)-5-oxo-2,5-dihydrofuran-3-yl)acetate (**3d**).* Title compound **3d** was prepared according to general procedure **II** as sticky solid in 69% yield (30 mg, **3d**/**4d** = 99:01). Reaction time 8 h/35 °C. R_f 0.5 (ethyl acetate/petroleum ether, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.88 (d, J = 1.5 Hz, 1H), 6.76 (d, J = 2.3 Hz, 2H), 4.10 (q, J = 7.3 Hz, 2H), 3.76 (s, 3H), 3.76 (s, 3H), 3.73−3.69 (m, 3H), 3.51 (s, 2H), 1.74−1.8 (m, 4H), 1.46−1.37 (m, 3H), 1.22 (t, J = 7.3 Hz, 3H), 1.06−0.99 (m, 2H), 0.9 (m, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 168.3, 168.1, 153.5, 151.2, 150.0, 142.0, 136.5, 125.2, 117.0, 112.7, 111.1, 61.3, 57.8, 55.7, 33.4, 33.3, 31.8, 30.0, 29.7, 25.0, 22.4, 14.0. HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{24}H_{32}NO_6$, 430.2224. Found, 430.2230.

*Ethyl (Z)-2-(4-(4-Chlorobenzyl)-2-((4-methylcyclohexyl) imino)-5-oxo-2,5-dihydrofuran-3-yl)acetate (**3e**).* Title compound **3e** was prepared according to general procedure **II** as sticky solid in 62% yield (25 mg, **3e**/**4e** = 97:03). Reaction time 8 h/35 °C. R_f 0.6 (ethyl acetate/petroleum ether, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.27 (d, J = 8.3 Hz, 2H), 7.18 (d, J = 8.3 Hz, 2H), 4.12 (q, J = 7.1 Hz, 2H), 3.80−3.70 (m, 3H), 3.46 (s, 2H), 1.77−1.68 (m, 4H), 1.50−1.35 (m, 3H), 1.23 (t, J = 7.1 Hz, 3H), 1.07−1.0 (m, 2H), 0.9 (d, J = 6.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 167.9, 167.8, 149.6, 142.6, 136.3, 134.4, 133.0, 130.1, 128.9, 61.6, 58.0, 33.4, 33.2, 31.8, 30.2, 29.6, 22.3, 14.0. HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{27}NO_4Cl$, 404.1623. Found, 404.1627.

*Ethyl (Z)-2-(4-(2-Fluorobenzyl)-2-((4-methylcyclohexyl) imino)-5-oxo-2,5-dihydrofuran-3-yl)acetate (**3f**).* Title compound **3f** was prepared according to general procedure **II** as sticky solid in 66% yield (25.5 mg, **3f**/**4f** = 97:03). Reaction time 8 h/35 °C. R_f 0.5 (ethyl acetate/petroleum ether, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.37−7.32 (m, 1H), 7.27−7.22 (m, 1H), 7.12−7.07 (m, 1H), 7.06−7.00 (m, 1H), 4.12 (q, J = 7.1 Hz, 2H), 3.79 (s, 2H), 3.77−3.68 (m, 1H), 3.52 (s, 2H), 1.77−1.63 (m, 4H), 1.50−1.34 (m, 3H), 1.23 (t, J = 7.1 Hz, 3H), 1.07−0.97 (m, 2H), 0.9 (d, J = 6.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 168.0, 167.7, 160.79 (d, J = 245.6 Hz), 149.7, 142.7, 135.6, 131.32 (d, J = 3.6 Hz), 129.01 (d, J = 8.0 Hz), 124.41 (d, J = 3.6 Hz), 122.9 (d, J = 15.3 Hz), 115.4 (d, J = 21.8 Hz), 61.4, 57.9, 33.4, 33.3, 31.8, 30.0, 23.6, 22.3, 14.0. HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{27}NO_4F$, 388.1919. Found, 388.1921.

*Ethyl (Z)-2-(4-(3,4-Difluorobenzyl)-2-((4-methylcyclo hexyl)-imino)-5-oxo-2,5-dihydrofuran-3-yl)acetate (**3g**).* Title compound **3g** was prepared according to general procedure **II** as sticky solid in 63% yield (25.5 mg, **3g**/**4g** = 95:05). Reaction time 8 h/35 °C. R_f 0.6 (ethyl acetate/petroleum ether, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.15−7.02 (m, 2H), 7.0−6.94 (m, 1H), 4.14 (q, J = 7.3 Hz, 2H), 3.80−3.73 (m, 1H), 3.72 (s, 2H), 3.49 (s, 2H), 1.75−1.68 (m, 4H), 1.50−1.36 (m, 3H), 3.87 (t, J = 7.3 Hz, 3H), 1.08−0.97 (m, 2H), 0.9 (d, J = 6.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 167.9, 167.6, 150.25 (dd, J = 249.2, 12.5 Hz), 149.5, 149.48 (dd, J = 248.2, 12.5 Hz), 142.8, 135.9, 132.8 (dd, J = 8.6, 3.8 Hz), 124.82 (dd, J = 5.8, 3.8 Hz), 117.77 (d, J = 18.2 Hz), 117.5 (d, J = 17.3 Hz), 61.7, 58.1, 33.4, 33.2, 31.7, 30.2, 29.4, 22.3, 14.0. HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{26}NO_4F_2$, 406.1824. Found, 406.1829.

*Ethyl (Z)-2-(2-((4-Methylcyclohexyl)imino)-5-oxo-4-(3-(trifluoromethyl)benzyl)-2,5-dihydrofuran-3-yl)acetate (**3h**).* Title compound **3h** was prepared according to general procedure **II** as sticky solid in 58% yield (25.3 mg, **3h**/**4h** = 98:02). Reaction time 8 h/35 °C. R_f 0.5 (ethyl acetate/petroleum ether, 1:4). ^{1}H NMR (400 MHz, CDC_{l3}) δ (ppm) 7.52 (d, J = 6.9 Hz, 1H), 7.49 (s, 1H), 7.48−7.40 (m, 2H), 4.12 (q, J = 7.1 Hz, 2H), 3.83 (s, 2H), 3.79−3.71 (m, 1H), 3.487 (s, 2H), 1.76−1.69 (m, 4H), 1.50−1.34 (m, 3H), 1.22 (t, J = 7.1 Hz, 3H), 1.09−0.98 (m, 2H), 0.90 (d, J = 6.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 167.8, 167.7, 149.5, 142.9, 136.9, 135.8, 132.26, 132.25, 131.3, 129.3, 125.5 (q, J = 8.0 Hz), 124.01 (q, J = 7.3 Hz), 61.6, 58.1, 33.4, 33.2, 31.8, 30.2, 30.1, 22.3, 14.0. HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{23}H_{27}F_3NO_4$, 438.1887. Found, 438.1892.

*Ethyl (Z)-2-(2-((4-Methylcyclohexyl)imino)-4-(4-nitrobenzyl)-5-oxo-2,5-dihydrofuran-3-yl)acetate (**3i**).* Title compound **3i** was prepared according to general procedure **II** as sticky solid in 63% yield (26 mg, **3i**/**4i** = 96:04). Reaction time 8 h/35 °C. R_f 0.5 (ethyl acetate/petroleum ether, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.18 (d, J = 8.6 Hz, 2H), 7.44 (d, J = 8.6 Hz, 2H), 4.14 (q, J = 7.1 Hz, 2H), 3.87 (s, 2H), 3.80−3.70 (m, 1H), 3.53 (s, 2H), 1.78−1.67 (m, 4H), 1.47−1.35 (m, 3H), 1.24 (t, J = 7.1 Hz, 3H), 1.09−0.99 (m, 2H), 0.9 (d, J = 6.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 167.9, 167.5, 149.3, 147.1, 143.4, 143.3, 135.3, 129.7, 124.0, 61.8, 58.2, 33.4, 33.2, 31.8, 30.2, 30.1, 22.3, 14.1. HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{27}N_2O_6$, 415.1864. Found, 415.1867.

*Ethyl (Z)-2-(2-((4-Methylcyclohexyl)imino)-4-(naphthalen-2-yl-methyl)-5-oxo-2,5-dihydrofuran-3-yl)acetate (**3j**).* Title compound **3j** was prepared according to general procedure **II** as sticky solid in 56% yield (23.4 mg, **3j**/**4j** = 99:01). Reaction time 8 h/35 °C. R_f 0.6 (ethyl acetate/petroleum ether, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.83−7.75 (m, 3H), 7.68 (s, 1H), 7.51−7.43 (m, 2H), 7.35 (d, J = 8.4 Hz, 1H), 4.04 (q, J = 7.1 Hz, 2H), 3.94 (s, 2H), 3.80−3.72 (m, 1H), 3.47 (s, 2H), 1.78−1.68 (m, 4H), 1.50−1.36 (m, 3H), 1.15 (t, J = 7.1 Hz, 3H), 1.08−0.98 (m, 2H), 0.9 (d, J = 6.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 168.02, 168.01, 149.8, 142.6, 136.7, 133.5, 133.4, 132.4, 128.6, 127.64, 127.55, 127.4, 126.9, 126.3, 125.9, 61.4, 58.0, 33.4, 33.3, 31.8, 30.4, 30.2, 22.3, 14.0. HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{26}H_{30}NO_4$, 420.2169. Found, 420.2177.

*Ethyl (Z)-2-(4-(Anthracen-9-ylmethyl)-2-((4-methylcyclohexyl)-imino)-5-oxo-2,5-dihydrofuran-3-yl)acetate (**3k**).* Title compound **3k** was prepared according to general procedure **II** as sticky solid in

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52% yield (24.3 mg, **3k**/**4k** = 98:02). Reaction time 8 h/35 °C. R_f 0.6 (ethyl acetate/petroleum ether, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.48 (s, 1H), 8.11−8.01 (m, 4H), 7.56−7.45 (m, 4H), 4.78 (s, 2H), 3.80−3.70 (m, 1H), 3.44 (q, J = 7.3 Hz, 2H), 2.43 (s, 2H), 1.71−1.63 (m, 4H), 136−1.28 (m, 4H), 1.06−0.99 (m, 2H), 0.89−0.86 (m, 5H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm) 168.6, 167.2, 150.0, 142.5, 136.1, 131.4, 130.2, 129.4, 127.8, 127.0, 126.6, 125.2, 123.9, 60.7, 57.9, 33.4, 33.3, 31.7, 28.9, 24.0, 22.3, 13.6. HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{30}H_{32}NO_4$, 470.2326. Found, 470.2330.

*Ethyl (Z)-2-(2-((4-Methylcyclohexyl)imino)-5-oxo-4-(pyridin-3-ylmethyl)-2,5-dihydrofuran-3-yl)acetate (**3l**).* Title compound **3l** was prepared according to general procedure **II** as sticky solid in 53% yield (20 mg, **3l**/**4l** = 96:04). Reaction time 8 h/35 °C. R_f 0.4 (ethyl acetate/petroleum ether, 1:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.57 (m, 2H), 7.64−7.55 (m, 1H), 7.26−7.22 (m, 1H), 4.13 (q, J = 7.1 Hz, 2H), 3.77 (s, 2H), 7.76−3.70 (m, 1H), 3.51 (s, 2H), 1.75−1.67 (m, 4H), 1.49−1.34 (m, 3H), 1.23 (t, J = 7.3 Hz, 3H), 1.08−0.97 (m, 2H), 0.90 (d, J = 6.6 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm) 167.8, 167.6, 149.9, 149.5, 148.5, 142.9, 136.4, 135.7, 131.8, 123.6, 61.7, 58.1, 33.4, 33.2, 31.8, 30.20, 27.6, 22.3, 14. HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{21}H_{27}N_2O_4$ 371.1970. Found, 371.1966.

*Ethyl (Z)-2-(4-Butyl-2-((4-methylcyclohexyl)imino)-5-oxo-2,5-dihydrofuran-3-yl)acetate (**3m**).* Title compound **3m** was prepared according to general procedure **II** as sticky solid in 72% yield (26 mg, **3m**/**4m** = 98:02). Reaction time 8 h/35 °C. R_f 0.6 (ethyl acetate/petroleum ether, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 4.16 (q, J = 7.1 Hz, 2H), 3.8−3.7 (m, 1H), 3.51 (s, 2H), 2.39 (t, J = 7.7 Hz, 2H), 1.77−166 (m, 4H), 1.58−1.50 (m, 2H), 1.46−1.32 (m. 5H), 1.26 (t, J = 7.1 Hz, 3H), 1.10−0.98 (m, 2H), 0.95−0.87 (m, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm) 168.3, 168.1, 149.9, 141.6, 138.6, 61.4, 57.8, 33.5, 33.3, 31.8, 30.1, 29.7, 24.1, 22.6, 22.3, 14.1, 13.7. HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{19}H_{30}NO_4$, 336.2169. Found, 336.2174.

*Ethyl (Z)-2-(2-((4-Methylcyclohexyl)imino)-4-nonyl-5-oxo-2,5-dihydrofuran-3-yl)acetate (**3n**).* Title compound **3n** was prepared according to general procedure **II** as sticky solid in 62% yield (25 mg, **3n**/**4n** = 98:02). Reaction time 8 h/35 °C. R_f 0.7 (ethyl acetate/petroleum ether, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 4.16 (q, J = 7.1 Hz, 2H), 3.39−3.67 (m, 1H), 3.51 (s, 2H), 2.39 (t, J = 7.8 Hz, 2H), 1.78−1.69 (m, 4H), 1.60−1.52 (m, 2H), 1.48−1.40 (m, 2H), 1.33−1.22 (m, 18H), 1.09−0.98 (m, 2H), 0.9−0.88 (m, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm) 168.3, 168.1, 149.9, 141.5, 138.6, 61.4, 57.8, 33.5, 33.3, 31.81, 31.79, 30.1, 29.5, 29.4, 29.24, 29.23, 27.6, 24.4, 22.62, 22.4, 14.08, 14.06. HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{24}H_{40}NO_4$, 406.2952. Found, 406.2954.

*Ethyl (Z)-2-(4-(Cyclohexylmethyl)-2-((4-methylcyclohexyl)-imino)-5-oxo-2,5-dihydrofuran-3-yl)acetate (**3o**).* Title compound **3o** was prepared according to general procedure **II** as sticky solid in 63% yield (24 mg, **3o**/**4o** = 96:04). Reaction time 8 h/35 °C. R_f 0.7 (ethyl acetate/petroleum ether, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 4.16 (q, J = 6.9 Hz, 2H), 3.79−3.67 (m, 1H), 3.50 (s, 2H), 2.29 (d, J = 6.9 Hz, 2H), 1.81−1.57 (m, 12H), 1.50−1.35 (m, 3H), 1.26−1.23 (m, 4H), 1.21−1.15 (m, 2H), 1.05−0.97 (m. 2H), 0.91 (d. J = 6.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm) 168.3, 149.8, 142.4, 137.5, 61.4, 57.8, 36.8, 33.5, 33.3, 33.2, 31.9, 31.8, 30.4, 26.1, 26.0, 22.4, 14.1. HRMS (ESI−TOF) m/z [M + H]+ calcd for $C_{22}H_{34}NO_4$, 376.2482. Found, 376.2487.

*Ethyl (Z)-2-(4-Benzhydryl-2-((4-methylcyclohexyl) imino)-5-oxo-2,5-dihydrofuran-3-yl)acetate (**3q**).* Title compound **3q** was prepared according to general procedure **II** as sticky solid in 56% yield (25 mg, **3q**/**4q** = 96:04). Reaction time 8 h/35 °C. R_f 0.5 (ethyl acetate/petroleum ether, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.35−7.28 (m, 6H), 7.20 (d, J = 7.3 Hz, 4H), 5.48 (s, 1H), 4.03 (q, J = 7.3 Hz, 2H), 3.80−3.70 (m, 1H), 3.09 (s, 2H), 1.77−1.67 (m, 4H), 1.47−1.37 (m, 3H), 1.20 (t, J = 7.3 Hz, 3H), 1.08−0.98 (m, 2H), 0.9 (d, J = 6.5 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm) 168.1, 167.5, 149.9, 143.1, 139.0, 138.7, 128.9, 128.8, 127.4, 61.23, 57.9, 47.7, 33.4, 33.3, 31.8, 30.0, 22.3, 14.0. HRMS (ESI−TOF) m/z [M + H]+ calcd for $C_{28}H_{32}NO_4$, 446.2331. Found, 446.2329.

*Ethyl (Z)-2-(4-Benzyl-2-(hexylimino)-5-oxo-2,5-dihydrofuran-3-yl)acetate (**3r**).* Title compound **3r** was prepared according to general procedure **II** as sticky solid in 49% yield (17.4 mg, **3r**/**4r** = 84:16). Reaction time 8 h/35 °C. R_f 0.5 (ethyl acetate/petroleum ether, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.37−7.27 (m, 2H), 7.27−7.17 (m, 3H), 4.12 (q, J = 7.6, 2H), 3.78 (s, 2H). 3.57 (J = 7.6 Hz, 2H), 3.44 (s, 2H), 1.65−1.52 (m, 2H), 1.32−1.27 (m, 6H), 1.22 (t, J = 6.9 Hz, 3H), 0.88 (t, J = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm) 168.0, 167.8, 151.0, 142.1, 137.0, 135.9, 128.82, 128.75, 127.1, 61.5, 49.3, 31.5, 30.31, 30.27, 30.1, 29.7, 27.0, 22.6, 14.0. HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{21}H_{28}NO_4$, 358.2018. Found, 358.2023.

*Ethyl (Z)-2-(4-Benzyl-2-((4-methoxyphenyl)imino)-5-oxo-2,5-dihydrofuran-3-yl)acetate (**3w**).* Title compound **3w** was prepared according to general procedure **II**. The obtained mixture of products (**3w**/**4w** = 33:67, 68% yield) was purified to isolate **3w** as a white solid in 23% yield (8.7 mg). Reaction time 8 h/35 °C. R_f 0.6 (ethyl acetate/petroleum ether, 1:4); mp: 116−118 °C. ^{1}H NMR (400 MHz, $CDCl_3$) of pure isomaleimide **3w** δ (ppm) 7.47 (dd, J = 9.1, 2.3 Hz, 2H), 7.34−7.28 (m, 2H), 7.27−7.22 (m, 3H), 6.88 (dd, J = 9.1, 2.3 Hz, 2H), 4.14 (q, J = 7.1 Hz, 2H), 3.82 (s, 5H), 3.56 (2H), 1.23 (t, J = 7.1, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm) 168.2, 168.1, 158.9, 148.0, 143.4, 136.5, 136.0, 135.9, 128.9, 128.8, 127.9, 127.1, 114.1, 61.6, 55.4, 30.4, 30.3, 14.1. HRMS (ESI−TOF) m/z: [M + H]$^+$ calcd for $C_{22}H_{22}NO_5$, 380.1497. Found, 380.1490.

*Ethyl (Z)-2-(4-(4-Bromobenzyl)-5-oxo-2-(phenylimino)-2,5-dihydrofuran-3-yl)acetate (**3ai**).* Title compound **3ai** was prepared according to general procedure **II**. The obtained mixture of products (**3ai**/**4ai** = 24:76, 66% yield) was purified to isolate **3ai**as a white solid in 17% yield (8 mg). Reaction time 8 h/35 °C. R_f 0.6 (ethyl acetate/petroleum ether, 1:4); mp: 80−82 °C. ^{1}H NMR (400 MHz, $CDCl_3$) of pure isomaleimide **3ai** δ (ppm) 7.47 (m, 2H), 7.41−7.33 (m, 4H), 7.25−7.21 (1H), 7.17−7.13 (m, 2H), 4.17 (q, J = 7.1 Hz, 2H), 3.79 (s, 2H), 3.61 (s, 2H), 1.26 (J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm) 167.9, 167.7, 149.5, 143.4, 143.3, 136.4, 134.7, 132.0, 130.6, 128.9, 127.0, 124.9, 121.2, 61.8, 30.2, 29.9, 14.1. HRMS (ESI−TOF) m/z: [M + H]+ calcd for $C_{21}H_{19}BrNO_4$, 428.0497. Found, 428.0493.

*Ethyl 2-(4-Benzyl-1-(4-methylcyclohexyl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)acetate (**4a**).* Title compound **4a** was prepared according to experimental procedure **VII-C** as sticky solid in 90% yield (18 mg). Reaction time 4 h/120 °C. R_f 0.6 (ethyl acetate/petroleum ether, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.34−7.27 (m, 2H), 7.27−7.17 (m, 3H), 4.11 (q, J = 6.9 Hz, 2H), 3.92−3.82 (m, 1H), 3.76 (s, 2H), 3.28 (s, 2H), 2.15−2.03 (m, 2H), 1.76 (m, 2H), 1.64−1.62 (m, 2H), 1.46−1.37 (m, 1H), 1.22 (t, J = 6.9 Hz, 3H), 1.07−0.95 (m, 2H), 0.9 (d, J = 6.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm) 171.3, 171.1, 168.5, 141.4, 136.25, 133.3, 128.9, 128.8, 126.9, 61.5, 50.9, 34.4, 31.5, 30.0, 29.6, 28.8, 22.2, 14.0. HRMS (ESI−TOF) m/z: [M + H]+ calcd for $C_{22}H_{28}NO_4$, 370.2018. Found, 370.2010.

*Diethyl 2,2′-(Hexane-1,6-diylbis(4-benzyl-2,5-dioxo-2,5-dihydro-1H-pyrrole-1,3-diyl))diacetate (**4s**).* General procedure **II** provided inseparable mixture of **3s** and **4s** (**3s**/**4s** = 57:43); hence, for characterization purposes, the mixture was refluxed in acetic acid to obtain pure maleimide **4s** as a sticky solid in 48% yield (30 mg). Reaction time 8 h/35 °C (toluene), followed by 4 h/120 °C (AcOH). R_f 0.3 (ethyl acetate/petroleum ether, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.33−7.27 (m, 4H), 7.26−7.18 (m, 6H), 4.11 (q, J = 6.75 Hz, 4H), 3.78 (s, 4H), 3.48 (t, J = 7.0 Hz, 4H), 3.31 (s, 4H), 1.60−1.53 (m, 4H), 1.32−1.27 (m, 4H), 1.24 (t, J = 6.8 Hz, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm) 171.3, 171.1, 168.4, 141.7, 136.2, 133.6, 128.9, 128.8, 127.0, 61.5, 38.1, 30.0, 28.9, 28.4, 26.2, 14.0. HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{36}H_{41}N_2O_8$, 629.2862. Found, 629.2863.

*Ethyl 2-(1,4-Dibenzyl-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)-acetate (**4t**).* General procedure **II** provided inseparable mixture of **3t** and **4t** (**3t**/**4t** = 75:25); hence, for characterization purposes, the

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mixture was refluxed in acetic acid to obtain pure maleimide **4t** as a sticky solid in 61% yield (22 mg). Reaction time 8 h/35 °C (toluene), followed by 4 h/120 °C (AcOH). R_f 0.4 (ethyl acetate/petroleum ether, 1:4). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.36−7.27 (m, 6H), 7.26−7.28 (m, 4H), 4.66 (s, 2H), 4.09 (q, J = 7.3 Hz, 2H), 3.78 (s, 2H), 3.30 (s, 2H), 1.20 (t, J = 7.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ (ppm) 171.0, 170.8, 168.3, 142.0, 136.3 136.0, 133.9, 128.9, 128.8, 128.6, 128.4, 127.8, 127.0, 61.5, 41.8, 30.1, 28.9, 14.0. HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{22}NO_4$, 364.1548. Found, 364.1542.

*Ethyl 2-(4-Benzyl-2,5-dioxo-1-phenyl-2,5-dihydro-1H-pyrrol-3-yl)acetate (**4u**).* Title compound **4u** was prepared according to procedure **V** as a white solid in 65% yield (22.6 mg). Reaction time 8 h/35 °C (toluene), followed by 4 h/120 °C (AcOH). R_f 0.5 (ethyl acetate/petroleum ether, 1:4); mp: 78−80 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.46−7.39 (m, 2H), 7.39−7.28 (m, 5H), 7.28−7.21 (m, 3H), 4.13 (q, J = 7.3 Hz, 2H), 3.86 (s, 2H), 3.40 (s, 2H), 1.23 (t, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 170.0, 169.8, 168.2, 142.0, 135.9, 133.8, 131.6, 128.93, 128.92, 128.8, 127.5, 127.1, 125.6, 61.6, 30.1, 29.0, 14.0. HRMS (ESI−TOF) m/z: [M + H]+ calcd for $C_{21}H_{20}NO_4$, 350.1392. Found, 350.1397.

*Ethyl 2-(4-Benzyl-2,5-dioxo-1-(p-tolyl)-2,5-dihydro-1H-pyrrol-3-yl)acetate (**4v**).* Title compound **4v** was prepared according to general procedure **III** as a white solid in 59% yield (21 mg). Reaction time 8 h/35 °C (toluene), followed by 4 h/120 °C (AcOH). R_f 0.5 (ethyl acetate/petroleum ether, 1:4); mp: 85−87 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.5−7.1 (m, 9H), 4.15 (q, J = 7.3 Hz, 2H), 3.88 (s, 2H), 3.41 (s, 2H), 2.38 (s, 3H), 1.25 (t, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 170.2, 170.0, 168.3, 142.0, 137.6, 136.0, 133.8, 129.6, 129.0, 128.9, 127.1, 125.6, 61.6, 30.2, 29.0, 21.1, 14.0. HRMS (ESI−TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{22}NO_4$, 364.1549. Found, 364.1549.

*Ethyl 2-(4-Benzyl-1-(4-methoxyphenyl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)acetate (**4w**).* Title compound **4w** was prepared according to general procedure **III** as a white solid in 68% yield (25.7 mg). Reaction time 8 h/35 °C. R_f 0.4 (ethyl acetate/petroleum ether, 1:4); mp: 129−131 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.36−7.30 (m, 2H), 7.30−7.22 (m, 5H), 6.97 (d, J = 7.0 Hz, 2H), 4.15 (q, J = 7.3 Hz, 2H), 3.87 (s, 2H), 3.83 (s, 3H), 3.41 (s, 2H), 1.25 (t, J = 7.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 170.3, 170.1, 168.3, 158.4, 142.0, 135.9, 133.7, 129.0, 128.9, 127.2, 127.1, 124.2, 114.3, 61.6, 55.4, 30.1, 29.0, 14.0. HRMS (ESI−TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{22}NO_5$, 380.1497. Found, 380.1497.

*Ethyl 2-(4-Benzyl-1-(3-fluorophenyl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)acetate (**4x**).* Title compound **4x** was prepared according to general procedure **III** as a white solid in 60% yield (22 mg). Reaction time 8 h/35 °C (toluene), followed by 4 h/120 °C (AcOH). R_f 0.4 (ethyl acetate/petroleum ether, 1:4); mp: 75−77 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.44−7.37 (m, 1H), 7.35−7.30 (m, 2H), 7.30−7.22 (m, 4H), 7.22−7.17 (m, 1H), 7.07−7.02 (m, 1H), 4.15 (q, J = 7.2 Hz, 2H), 3.88 (s, 2H), 3.42 (s, 2H), 1.25 (t, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 169.6, 169.4, 168.1, 152.6 (d, J = 246.3), 142.2, 135.7, 134.0, 133.03 (d, J = 10.2 Hz), 130.07 (d, J = 9.4 Hz), 128.97, 128.95, 120.87 (d, J = 3.6 Hz), 114.41 (d, J = 21.1 Hz), 112.85 (d, J = 24.7 Hz), 61.7, 30.2, 29.0, 14.0. HRMS (ESI−TOF) m/z: [M + H]+ calcd for $C_{21}H_{19}FNO_4$, 368.1298. Found, 368.1306.

*Ethyl 2-(4-Benzyl-1-(4-chlorophenyl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)acetate (**4y**).* Title compound **4y** was prepared according to general procedure **III** as pale yellow solid in 66% yield (25 mg). Reaction time 8 h/35 °C (toluene), followed by 4 h/120 °C (AcOH). R_f 0.4 (ethyl acetate/petroleum ether, 1:4); mp: 72−74 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.45−7.39 (m, 2H), 7.37−7.34 (m, 2H), 7.34−7.23 (m, 5H), 4.16 (q, J = 7.3 Hz, 2H), 3.88 (s, 2H), 3.42 (s, 2H), 1.25 (t, J = 7.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 169.7, 169.5, 168.2, 142.2, 135.7, 134.0, 133.2, 130.2, 129.2, 129.0, 128.9, 127.2, 126.7, 61.7, 30.2, 29.0, 14.0. HRMS (ESI−TOF) m/z: [M + H]+ calcd for $C_{21}H_{19}ClNO_4$, 384.1002. Found, 384.0998.

*Ethyl 2-(4-Benzyl-1-(3,4-dichlorophenyl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)acetate (**4z**).* Title compound **4z** was prepared according to general procedure **III** as sticky solid in 70% yield (29 mg). Reaction time 8 h/35 °C (toluene), followed by 4 h/120 °C (AcOH). R_f 0.5 (ethyl acetate/petroleum ether, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.59 (d, J = 2.4 Hz, 1H), 7.52 (d, J = 8.6 Hz, 1H), 7.35−7.30 (m, 3H), 7.30−7.24 (m, 3H), 4.16 (q, J = 7.1 Hz, 2H), 3.87 (s, 2H), 3.42 (s, 2H), 1.26 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 169.4, 169.2, 168.1, 142.4, 135.6, 134.2, 132.9, 131.5, 131.1, 130.6, 129.0, 128.9, 127.3, 127.0, 124.4, 61.8, 30.2, 29.0, 14.1. HRMS (ESI−TOF) m/z: [M + H]+ calcd for $C_{21}H_{18}Cl_2NO_4$, 418.0612. Found, 418.0620.

*Ethyl 2-(4-Benzyl-1-(4-chloro-3-nitrophenyl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)acetate (**4aa**).* Title compound **4aa** was prepared according to general procedure **III** as pale yellow solid in 59% yield (25 mg). Reaction time 8 h/35 °C (toluene), followed by 4 h/120 °C (AcOH). R_f 0.4 (ethyl acetate/petroleum ether, 1:4); mp: 79−81 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.12 (d, J = 2.4 Hz, 1H), 7.72 (dd, J = 2.4, 8.76 Hz, 1H), 7.62 (d, J = 8.8 Hz, 1H), 7.37−7.31 (m, 2H), 7.321−7.24 (m, 3H), 4.17 (q, J = 7.1 Hz, 2H), 3.89 (s, 2H), 3.44 (s, 2H), 1.27 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 169.0, 168.8, 167.9, 142.7, 135.4, 134.5, 132.2, 131.3, 129.0, 129.0, 128.9, 127.4, 125.3, 121.7, 61.9, 30.3, 29.1, 14.1. HRMS (ESI−TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{18}ClN_2O_6$, 429.0853. Found, 429.0857.

*Ethyl 2-(4-Benzyl-1-(4-nitrophenyl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)acetate (**4ab**).* Title compound **4ab** was prepared according to general procedure **III** as a pale yellow solid in 68% yield (27 mg). Reaction time 8 h/35 °C (toluene), followed by 4 h/120 °C (AcOH). R_f 0.4 (ethyl acetate/petroleum ether, 1:4); mp: 95−97 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.31 (dd, J = 9.2, 2.1 Hz, 2H), 7.72 (dd, J = 9.2, 2.1 Hz, 2H), 7.37−7.31 (m, 2H), 7.30−7.23 (m, 3H), 4.17 (q, J = 7.1 Hz, 2H), 3.90 (s, 2H), 3.45 (s, 2H), 1.27 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 169.2, 169.0, 168.0, 145.9, 142.7, 137.5, 135.4, 134.5, 129.0, 129.0, 127.3, 124.9, 124.4, 61.8, 30.2, 29.1, 14.1. HRMS (ESI−TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{19}N_2O_6$, 395.1243. Found, 395.1235.

*Ethyl 2-(4-(2,5-Dimethoxybenzyl)-1-(4-nitrophenyl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)acetate (**4ac**).* Title compound **4ac** was prepared according to general procedure **III** as a pale yellow solid in 65% yield (29.5 mg). Reaction time 8 h/35 °C (toluene), followed by 4 h/120 °C (AcOH). R_f 0.3 (ethyl acetate/petroleum ether, 1:4); mp: 93−95 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.31 (d, J = 9.3 Hz, 2H), 7.72 (d, J = 9.3 Hz, 2H), 6.94−6.90 (m, 1H), 6.80−6.77 (m, 2H), 4.17 (q, J = 7.3 Hz, 2H), 3.83 (s, 2H), 3.79 (s, 3H), 3.77 (s, 3H), 3.53 (s, 2H), 1.27 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 169.2, 168.3, 153.6, 151.4, 145.8, 142.4, 137.7, 134.2, 124.9, 124.5, 124.4, 117.4, 112.9, 111.3, 61.6, 55.76, 55.70, 29.0, 25.1, 14.1. HRMS (ESI−TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{23}N_2O_8$, 455.1454. Found, 455.1444.

*Ethyl 2-(4-(4-Chlorobenzyl)-1-(4-nitrophenyl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)acetate (**4ad**).* Title compound **4ad** was prepared according to general procedure **III** as a sticky solid in 70% yield (30 mg). Reaction time 8 h/35 °C (toluene), followed by 4 h/120 °C (AcOH). R_f 0.5 (ethyl acetate/petroleum ether, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.32 (dd, J = 7.2, 2.2 Hz, 2H), 7.71 (dd, J = 7.2, 2.2 Hz, 2H), 7.35−7.27 (m, 2H), 7.26−7.18 (, 2H), 4.18 (q, J = 7.2 Hz, 2H), 3.87 (s, 2H), 3.48 (s, 2H), 1.28 (t, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 169.0, 168.8, 167.9, 145.9, 142.2, 137.4, 134.7, 133.9, 133.3, 130.3, 129.1, 125.0, 124.4, 61.9, 29.6, 29.1, 14.0. HRMS (ESI−TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{18}ClN_2O_6$, 429.0853. Found, 429.0873.

*Ethyl 2-(4-(4-Nitrobenzyl)-1-(4-nitrophenyl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)acetate (**4ae**).* Title compound **4ae** was prepared according to general procedure **II** as a yellow solid in 58% yield (25.5 mg, **3ae**/**4ae** = **4ae** >99). Reaction time 8 h/35 °C (toluene), followed by 4 h/120 °C (AcOH). R_f 0.4 (ethyl acetate/petroleum ether, 1:4); mp: 104−106 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.31 (d, J = 9.2 Hz, 2H), 8.19 (d, J = 8.4 Hz, 2H), 7.70 (d, J = 9.2 Hz, 2H), 7.49 (d, J = 8.4 Hz, 2H), 4.20 (d, J = 7.3 Hz, 2H), 4.0 (s, 2H), 3.55 (s, 2H), 1.28 (t, J = 7.6 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 168.7, 168.5, 167.8, 147.2, 146.0, 142.9, 141.1,

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137.2, 135.5, 129.9, 125.0, 124.4, 124.1, 62.1, 30.0, 29.2, 14.1. HRMS (ESI−TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{18}N_3O_8$, 440.1093. Found, 440.1097.

*Ethyl 2-(4-(Naphthalen-2-ylmethyl)-1-(4-nitrophenyl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)acetate (**4af**).* Title compound **4af** was prepared according to general procedure **II** as pale yellow solid in 53% yield (23.5 mg, **3af**/**4af** = **4af** > 99). Reaction time 8 h/35 °C (toluene), followed by 4 h/120 °C (AcOH). R_f 0.4 (ethyl acetate/petroleum ether, 1:4); mp: 112−114 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.31 (dd, J = 9.3, 2.1 Hz, 2H), 7.85−7.77 (m, 3H), 7.76−7.70 (m, 3H), 7.52−7.46 (m, 2H), 7.40−7.35 (m, 1H), 4.10 (q, J = 7.1 Hz, 2H), 4.07 (s, 2H), 3.47 (s, 2H), 1.18 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 169.2, 169.0, 168.0, 145.9, 142.7, 137.5, 134.7, 133.5, 132.8, 132.4, 128.9, 127.72, 127.70, 127.5, 126.9, 126.5, 126.1, 125.0, 124.4, 61.8, 30.4, 29.1, 14.0. HRMS (ESI−TOF) m/z: $[M]^+$ calcd for $C_{25}H_{20}N_2O_6$, 444.1321. Found, 444.1320.

*Ethyl 2-(1-(4-Nitrophenyl)-4-nonyl-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)acetate (**4ah**).* Title compound **4ah** was prepared according to general procedure **III** as a sticky solid in 47% yield (20 mg). Reaction time 8 h/35 °C (toluene), followed by 4 h/120 °C (AcOH). R_f 0.5 (ethyl acetate/petroleum ether, 1:4). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.32 (d, J = 9.2 Hz, 2H), 7.74 (d, J = 9.2 Hz, 2H), 4.23 (q, J = 6.9 Hz, 2H), 3.55 (s, 2H), 2.52 (t, J = 7.6 Hz, 2H), 1.65−1.58 (m, 2H), 1.33−1.27 (m, 12H), 0.89 (t, J = 6.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ (ppm) 169.3, 169.0, 168.2, 145.9, 145.0, 137.7, 133.9, 125.0, 124.4, 61.8, 31.8, 29.6, 29.4, 29.2, 29.2, 28.1, 24.4, 22.6, 14.11, 14.07. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{23}H_{31}N_2O_6$, 431.2182. Found, 431.2173.

*Ethyl 2-(4-(4-Bromobenzyl)-2,5-dioxo-1-phenyl-2,5-dihydro-1H-pyrrol-3-yl)acetate (**4ai**).* Title compound **4ai** was prepared according to general procedure **III** as a white solid in 66% yield (31 mg). Reaction time 8 h/35 °C. R_f 0.5 (ethyl acetate/petroleum ether, 1:4); mp: 98−100 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.50−7.41 (m, 4H), 7.40−7.32 (m, 3H), 7.20−7.17 (m, 2H), 4.16 (q, J = 7.1 Hz, 2H), 3.83 (s, 2H), 3.45 (s, 2H), 1.27 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 169.9, 169.6, 168.2, 141.4, 134.9, 134.1, 132.0, 131.5, 130.7, 129.0, 127.7, 125.7, 121.1, 61.8, 29.6, 29.1, 14.1. HRMS (ESI−TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{19}BrNO_4$, 428.0497. Found, 428.0498.

*Ethyl 2-(4-Hexyl-2,5-dioxo-1-(p-tolyl)-2,5-dihydro-1H-pyrrol-3-yl)acetate (**4aj**).* General procedure **VIII-A** provided a mixture of **3aj**/**4aj** (16:84, 43 mg). Reaction time 8 h/35 °C. This mixture was used as such for the next reaction. However, for characterization purposes, pure maleimide **4aj** (yellow oil) was prepared using procedure **III**. Reaction time 8 h/35 °C (toluene), followed by 4 h/120 °C (AcOH). R_f 0.7 (ethyl acetate/petroleum ether, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.27−7.20 (m, 4H), 4.21 (q, J = 7.1 Hz, 2H), 3.52 (s, 3H), 2.49 (t, J = 7.9 Hz, 2H), 2.38 (s, 3H), 1.62−1.57 (m, 2H), 1.37−1.26 (m, 9H), 0.90 (t, J = 7.0 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 170.3, 170.0, 168.6, 144.2, 137.5, 133.0, 129.6, 129.1, 125.7, 61.6, 31.4, 29.3, 29.1, 28.1, 24.3, 22.5, 21.1, 14.1, 14.0. ESI-MS $(M + H)^+$ 358.1. Known compound.[13b]

2-(4-Hexyl-2,5-dioxo-2,5-dihydrofuran-3-yl)acetic Acid (Aspergillus FH-X-213). Title compound was prepared according to general procedure **VIII-B** as thick oil starting from the mixture of compounds obtained from procedure **VIII-A** in 45% yield (over two steps, 22 mg). R_f 0.4 (ethyl acetate/petroleum ether, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.57 (s, 2H), 2.50 (t, J = 7.9 Hz, 2H), 1.61 (quintet, J = 7.8 Hz, 2H), 1.36−1.28 (m, 6H), 0.89 (t, J = 6.9 Hz, 3). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 172.0, 165.1 (2 carbons), 148.0, 135.5, 31.3, 29.13, 23.05, 27.5, 24.9, 22.4, 14.0. HRMS (ESI−TOF) m/z: $[M + H]^+$ calcd for $C_{12}H_{17}O_5$, 241.1075. Found, 241.1088. Known compound.[13b]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00782.

Detailed experimental procedures, characterization data, and spectra for all compounds. Crystallographic information for **4w** and **3ai**. (PDF)

FAIR data, including the primary NMR FID files, for compounds **2b**, **2d**, **2e**, **2h**−**2l**, **3a**−**3t**, **3w**, **3ai**, **4u**−**4z**, and **4aa**−**4aj** (ZIP)

Accession Codes

CCDC 2044000 and 2044001 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare the following competing financial interest(s): A patent application based on this chemistry has been submitted.

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Erratum

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