Development of Nitrogen Directed C-H Activation Protocols for the Synthesis of Natural Products, Drugs and New Scaffolds

Thesis Submitted to AcSIR

For the Award of the Degree of

DOCTOR OF PHILOSOPHY

In

CHEMICAL SCIENCES

By

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Under the guidance of

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November 2018

...dedicated to my beloved mother

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Thesis Certificate

This is to certify that the work incorporated in this Ph.D. thesis entitled **Development of Nitrogen Directed C-H Activation Protocols for the Synthesis of Natural Products, Drugs and New Scaffolds** submitted by **Mr. Dnyaneshwar N. Garad** to Academy of Scientific and Innovative Research (AcSIR) in fulfilment of the requirements for the award of the Degree of Doctor of Philosophy, embodies original research work under my supervision. I 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 obtained from other sources has been duly acknowledged in the thesis. Any text, illustration, table etc. used in the thesis from other sources, have been duly cited and acknowledged.

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30/11/2018
(Research Supervisor)

Declaration by the Candidate

I hereby declare that the original research work embodied in this thesis entitled "**Development of Nitrogen Directed C-H Activation Protocols for the Synthesis of Natural Products, Drugs and New Scaffolds**" submitted to Academy of Scientific and Innovative Research for the award of degree of Doctor of Philosophy (Ph.D.) is the outcome of experimental investigations carried out by me under the supervision of **Dr. Santosh B. Mhaske**, Senior Scientist, Division of Organic Chemistry, CSIR-National Chemical Laboratory, Pune. I affirm that the work incorporated is original and has not been submitted to any other academy, university or institute for the award of any degree or diploma.

November 2018
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I am highly thankful to my chemistry teachers and mentors through my graduation and post-graduation, who have been tremendous source of inspiration. The people who helped me to achieve my goals and shape my career: **Prof. M. S. Wadia**, **Prof. D. D. Dhavale, and Prof. R. S. Kusurkar** are the best chemistry teachers I have ever had.

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Last but not the least; I would like to thank my family for their patience, support and faith in me throughout my Ph.D. journey.

Dnyaneshwar N. Garad

Contents

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Abbreviations

Units

°C	Degree centigrade
mg	Milligram
hr	Hour
min	Minutes
mL	Millilitre
µg	Microgram
Hz	Hertz
MHz	Megahertz
mmol	Millimole
ppm	Parts per million

Chemical Notations

Ac	Acetyl
AcOH	Acetic Acid
Ar	Aryl
brsm	Based on recovered starting material
DMAc	Dimethyl acetate
DMAP	*N*,*N*-Dimethyl-4-aminopyridine
DMF	Dimethyl formamide
DMSO	Dimethyl sulphoxide
Et	Ethyl
EtOH	Ethanol
EDCI	1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride
EtOAc	Ethyl acetate
HMDS	Bis(trimethylsilyl)amine
MeCN	Acetonitrile
m-CPBA	*m*-Chloroperbenzoic Acid
NMP	N-Methyl-2-pyrrolidone
n-BuLi	*n*-Butyl Lithium
Ph	Phenyl
PivOH	Pivalic acid
p-TSA	*p*-Toluene sulfonic acid
TMS	Trimethylsilyl

TFA	Trifluoroacetic acid
THF	Tetrahydrofuran

Other Notations

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

General information

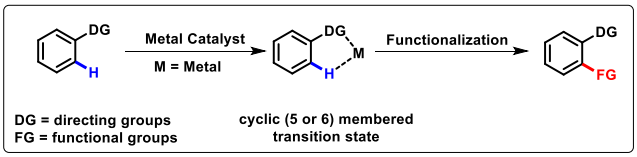
All reagents and solvents were used as received from commercial sources. All experiments were carried out under argon atmosphere unless otherwise noted. Pre-coated plates (silica gel 60 PF254, 0.25 mm or 0.5 mm) were utilized for thin layer chromatography (TLC). Column chromatographic purifications were carried out on flash silica-gel (240–400 mesh) using petroleum ether and ethyl acetate as eluents unless otherwise noted. The ^{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/acetone-d_6. Chemical shifts were reported as δ values from standard peaks. 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 of the Thesis to be Submitted to the Academy of Scientific and Innovative Research for Award of the Degree of Doctor of Philosophy in Chemistry

Name of the Candidate	Mr. Dnyaneshwar Nilkanth Garad
Degree Enrolment no. and Date	Ph. D. in Chemical Sciences (10CC12A26048); August 2012
Title of the Thesis	Development of Nitrogen Directed C–H Activation Protocols for the Synthesis of Natural Products, Drugs and New Scaffolds
Research Supervisor	Dr. Santosh B. Mhaske (AcSIR, CSIR-NCL, Pune)

Abstract: The thesis is mainly based on the development and application of nitrogen directed C–H activation methodologies in the synthesis of natural products, new scaffolds, and drugs. We have successfully developed Pd–catalyzed "olefin amidation/C–H activation" protocol for the synthesis of (±)-8-oxocanadine and (±)-8-oxostylopine protoberberine alkaloids and formal synthesis of the drug tetrahydropalmatine. Quinazolinone directed C(sp^2)–arylation and C(sp^3)–acetoxylation protocols have also been developed for the synthesis of new quinazolinones using Pd-catalysis. Novel Ru–catalyzed regioselective cascade annulation of acrylamides with 2-alkynoates via aza-Michael/C–H activation sequence for the synthesis of various 6-oxo nicotinic acid esters has been developed. The regioselectivity is confirmed by silver mediated protodecarboxylation of the corresponding 6-oxo nicotinic acid to furnish 2-pyridone. The detection of ruthenacycle intermediate (HRMS) in the reaction mixture and the nonreactivity of the phenyl and *t*-butyl substituted 2-alkynoates under the developed protocol suggests a plausible mechanism and involvement of allene intermediates.

Introduction: Recently, C–H bond functionalization has become a powerful tool for the synthesis of various scaffolds, natural products, and pharmaceuticals. The concept of C–H functionalization has gained significant attention from the synthetic community as an ideal method for the formation of carbon–carbon and carbon–heteroatom bonds in the synthesis of complex scaffolds.



Scheme 1. Directed C–H Bond Activation

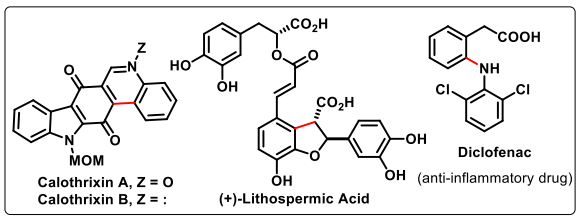


Figure 1. Synthesis Known using C–H Bond Activation

It provides direct access and delivers more atom-economical paths in the synthesis of complex structures as compared to the traditional organic synthesis. Until now, several C–H activation reactions in organic compounds have been developed using various directing groups. The directing group plays a crucial role in selective C–H bond activation process since organic molecule contains many hydrogen atoms (Scheme 1).

A directing group chelates with a metal so that proximal hydrogen could be activated to gain the selectivity. Directing groups are either mono-dentate or bi-dentate chelating groups. Installation and removal of such directing groups require two extra steps. Very few examples of inherent or intrinsic directing groups are known where substrate itself acts as a directing group. Undeniably, numerous publications on the C–H activation topic have been reported in the literature and the development of new catalytic processes continues to evolve at a rapid pace, but their successful applications to the synthesis of complex natural products or pharmaceuticals are still rare. This brief introduction demonstrates history and development of C–H activation and few examples of the natural product and drug synthesis, where C–H activation step is used as a key-step for constructing the core of natural products or drugs (Figure 1). We believe that developing newer C–H activation methods for total synthesis of molecules would lead to the development of useful reactions for organic chemists.

Chapter 1. Pd(II)-Catalyzed Tandem "Olefin Amidation/C–H Activation" Protocol for the Synthesis of Protoberberine Class of Natural Products and Drug

In the first chapter, we describe a unique intramolecular Pd-catalyzed tandem oxidative olefin amidation/C–H activation (carboamidation) protocol for the synthesis of a protoberberine class of natural products. They are a subdivision of natural products containing isoquinoline skeleton. Protoberberines are secondary metabolites having significant biological activities because of their ability to bind or insert in DNA. Isolated from a wide range of plants, all members of the protoberberine class feature a 5,8,13,13a-tetrahydro-6H-isoquinolino[3,2-a]-isoquinoline moiety, typically functionalized with hydroxy, methoxy, or methylenedioxy substituents (Figure 2). Canadine, stylopine, etc are some of the important protoberberine natural products and tetrahydropalmatine is an anxiolytic and sedative drug found in the Chinese herb *Yan Hu Suo*.

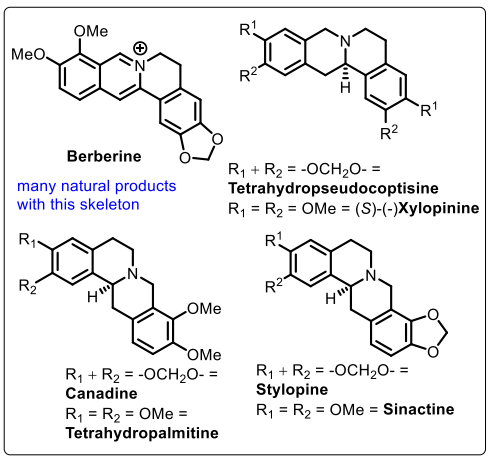
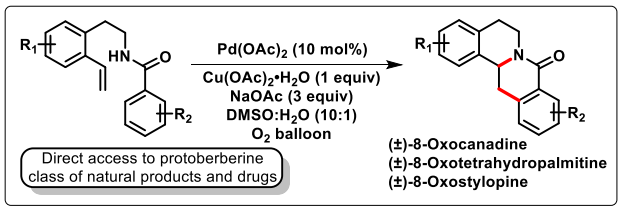


Figure 2. Selected Natural Products and Drugs Containing Protoberberine Core



Scheme 2. Synthesis of Protoberberine Alkaloids using Carboamidation Protocol

Protoberberine alkaloids exhibit antifungal, antibacterial, anti-inflammatory, antimalarial, antidiabetic, and anticancer activities. A novel Pd(II)-catalyzed approach for the synthesis of a protoberberine core is developed and successfully applied for the synthesis of natural products and drug (Scheme 2). Short and efficient syntheses of (±)-8-oxocanadine, (±)-8-oxotetrahydropalmatine, and (±)-8-oxostylopine were achieved by implementing this novel protocol as a key step. A formal synthesis of the drug 'tetrahydropalmatine' has been also achieved. It is also a first report on the synthesis of the tetracyclic core from intramolecular annulation of amide and styrene. Two new bonds, C–N and C–C, have been formed in a single step by an intramolecular tandem "amidation/C–H activation" sequence.

Chapter 2. Quinazolinone Directed C–H Bond Activation

Quinazolinones are one of the important nitrogen-containing heterocyclic motifs found in more than 200 natural products as well as in several drugs (Figure 3). Quinazolinone derivatives possess a wide range of pharmacological activities such as antimalarial, anticancer, antimicrobial, antidiabetic, anti-inflammatory, antihypertensive, anticonvulsant, diuretic, among others. Given their importance, we have developed C–H bond activation protocols for quinazolinones using substrate itself as a directing group. The study projected in chapter 2 is divided into two sections. Section 1 describes the study about a concept of quinazolinone as an intrinsic directing group for Pd-catalyzed C(sp^2)–H bond activation and its successful use in the regioselective monoarylations of several quinazolinones to get medicinally important novel quinazolinones (Scheme 3).

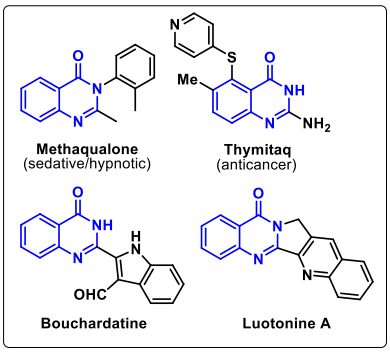
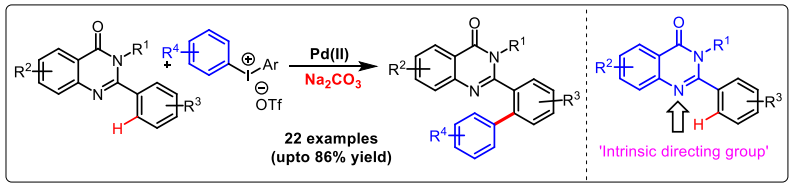


Figure 3. Selected Natural Products and Pharmaceuticals Featuring Quinazolinone Core



Scheme 3. Quinazolinones Directed C(sp^2)–Arylations

The use of diaryliodonium triflates as arylation reagents for quinazolinone directed C–H activation is a first report of arylation for diversification of quinazolinones. The protocol provided 22 new arylated quinazolinones. This novel protocol would be useful in the late-stage derivatization of bioactive quinazolinones and natural products for SAR studies.

Section 2 shows the use of quinazolinone as an intrinsic directing group first time for the C(sp^3)–H bond activation to obtain several C(sp^3)–acetoxylated quinazolinones. Quinazolinone scaffold has been successfully used as an intrinsic directing group for Pd-catalyzed C(sp^3)–H functionalization (Scheme 4).

Many of the quinazolinone natural products having good therapeutic assets commonly encompass β or γ sp^3-oxidized carbons (Figure 4), which could be accessed potentially by selective oxidation using a metal-catalyzed directed C–H activation process. Here we have developed the protocol for acetoxylations of benzylic positions as well as mono acetoxylations of γ–methyl groups. In this process, we have observed that the use of base was found to be crucial for the monoselective acetoxylations. Overall, we have synthesized 18 novel acetoxylated quinazolinones compounds. The application of the catalytic process for *in situ* generation of the oxidant diacetoxy iodobenzene (PIDA) from iodobenzene and oxone in acetic acid has also been demonstrated in this section.

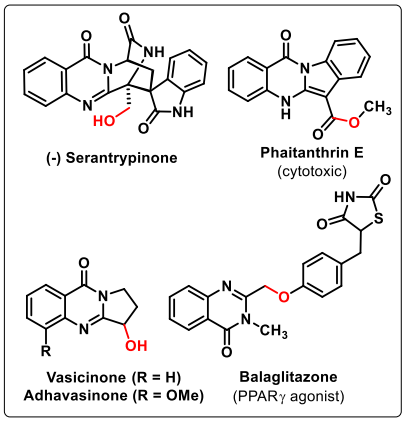
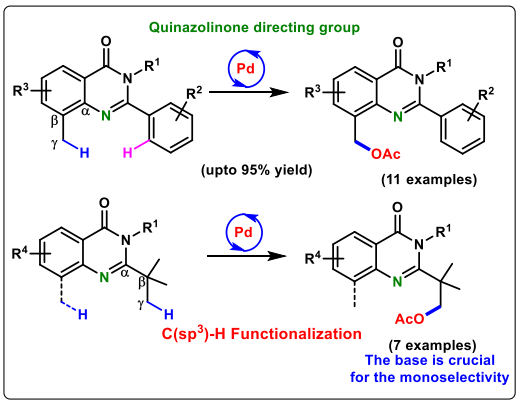


Figure 4. Selected Quinazolinone Natural Products Containing β or γ sp^3–Oxidized Carbons



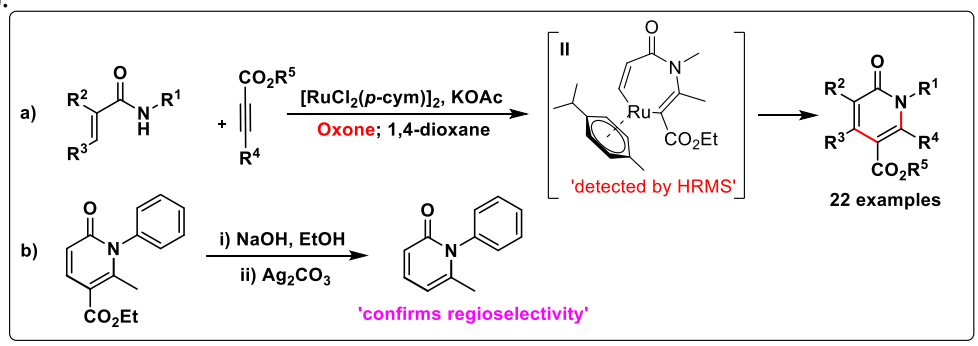
Scheme 4. Quinazolinone Directed C(sp^3) –Acetoxylations

The developed acetoxylation protocol would be useful in the synthesis of natural products and derivatization of bioactive quinazolinones for SAR studies. A base-controlled monoselective acetoxylation demonstrated herein may find important applications in the area of C–H activation.

Chapter 3: Ru–Catalyzed Cascade Annulation of Acrylamides with 2-Alkynoates by aza-Michael/C–H Activation Sequence for the Synthesis of Various 6-Oxo Nicotinic Acid Esters

Chapter 3 deals with Ruthenium-catalyzed inverse regioselective cascade annulation of acrylamides with 2-alkynoates to synthesize various 6-oxo nicotinic acid esters (Scheme 5a). The corresponding hydroxypyridinecarboxylic acids are the biologically important class of compounds. In particular, they have been used for metal chelation therapy because they have good binding capacity towards aluminum(III) and iron(III). Flavipucine, ciclopirox, pirfenidone are some of the natural products and drugs featuring pyridone core. As a result, several classical methods for their preparations are reported in the literature. C–H Bond activation has emerged as a cost and step-economical tool for the synthesis of these types of heterocycles. Herein, we have developed a protocol for annulation of acrylamides with 2-alkynoates for the synthesis of various 6-oxo nicotinic acid esters using ruthenium catalysis. The reaction follows aza-Michael/C–H activation sequence to accomplish complete reverse regioselectivity on the contrary to the other known ruthenium catalyzed protocols. Previous annulation protocols of dialkyl or

diaryl substituted alkynes with benzamides or acrylamides follow C–C followed by C–N bond formation cascade. Whereas, in the present protocol, since we have 2-alkynoates as an alkyne partner with acrylamide, the regioselectivity gets reversed. The regioselectivity of this protocol was confirmed by synthesizing 6-methyl-1-phenylpyridin-2(1H)-one by silver mediated protodecarboxylation process (Scheme 5b).



Scheme 5. a) Ru-Catalysed Reverse Regioselective Cascade Annulation of Acrylamides with Alkynes, b) Regioselectivity Confirmation by Silver Mediated Decarboxylation

The protocol has been generalized to access varyingly substituted 6-oxo nicotinic acid esters. It has been observed that the reaction works only when $\mathbf{R^4}$ of 2-alkynoates is primary or secondary alkyl. It suggests the involvement of allene intermediates in the reaction. Moreover, oxone is used as an oxidant for ruthenium catalyst, which is inexpensive and ecologically benign. We have also developed a redox-neutral annulation protocol at room temperature wherein N–OMe substituted acrylamide was used as the substrate. Few control experiments and the detection of ruthenacycle intermediate (HRMS) in the reaction mixture sheds some light on the probable reaction mechanism.

In summary, we have successfully developed novel synthetic methodologies involving nitrogen directed C–H activation protocols for the synthesis of protoberberine natural products, drug tetrahydropalmatine, novel quinazolinones alkaloids and various 6-oxo nicotinic acid esters with reverse regioselectivity. Our developed protocols herein would be useful in organic and medicinal chemistry and may find important applications in the area of C–H activation guided drug discovery.

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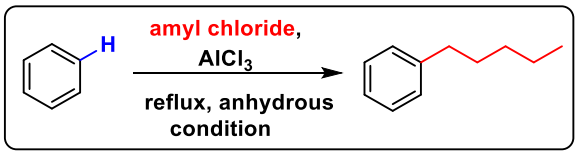
1. Garad, D. N.; Mhaske, S. B. *Org. Lett.* **2016**, *18*, 3862.
2. Garad, D. N.; Viveki, A. B.; Mhaske, S. B. *J. Org. Chem.* **2017**, *82*, 6366.
3. Garad, D. N.; Mhaske, S. B. *J. Org. Chem.* **2017**, *82*, 10470.
4. Garad, D. N.; Mhaske, S. B. *Manuscript submitted*. **2018**.
5. Garad, D. N.; Tanpure, S. D.; Mhaske, S. B. *Beilstein J. Org. Chem.* **2015,** *11*, 1008.

Introduction

Direct functionalization of C–H bond has emerged as an important tool for the synthesis of several scaffolds from simple building blocks without or less prefunctionalization. In the last two decades the area of C–H activation has been evolving in rapid pace and several reports in this area is the evidence of its importance. However, the use of C–H bond activation in the total synthesis of natural products, drugs and bioactive molecules is still underdeveloped, which prompted us to explore these processes.

0.1. Introduction of C–H Bond Activation:

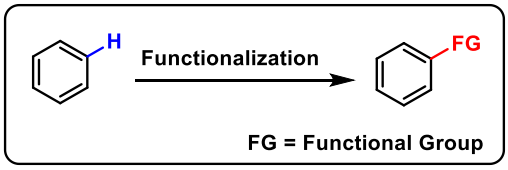
Synthetic chemists are always interested in the development of cheapest and cleanest routes for the synthesis of organic molecules. Over the last few decades, the formation of C–C bonds by the most economic ways has become an area of increasing importance among both industrial and academic research. The sustainable nature of reaction depends upon atom economy of reaction, which in turn depends upon the minimal number of reactants. Another way to achieve clean and atom economical processes is to directly use readily available starting materials as substrates without prefunctionalization to minimize the total number of steps. Such processes should be also achievable under acceptable thermodynamic conditions i.e. optimum temperature and pressure.[1]



Scheme 1. Friedel-Crafts reaction

The first example of C–H bond functionalization kind of reaction known in the literature is the Friedel-Crafts alkylation (FC alkylation), which was named after its inventors. In 1877, Charles Friedel and James Crafts reported amyl benzene formation after the treatment of amyl chloride with $AlCl_3$ in benzene (Scheme 1).[2] Mechanistically, it is not actual C–H bond activation

reaction since it follows the electrophilic aromatic substitution reaction pathway, but overall it is transformation of C–H bond into C–C bond. The concept of C–H activation follows a different mechanism than the electrophilic aromatic substitution has gained significant attention from the synthetic community as an ideal method for the formation of carbon-carbon and carbon-heteroatom bonds (Scheme 2).

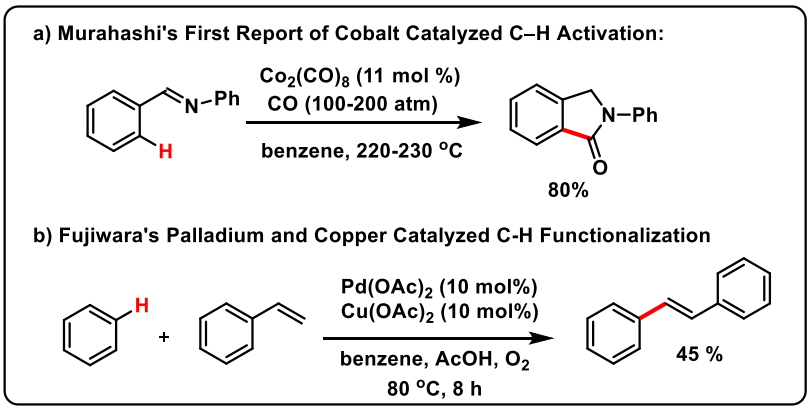


Scheme 2. C-H bond functionalization

Recently, C–H bond functionalization has become a powerful tool for the synthesis of various scaffolds, natural products, and pharmaceuticals.[3] It provides direct access and delivers more atom-economical paths in the synthesis of complex structures as compared to the traditional organic synthesis.

0.2. History of C-H activation:

Some of the pioneering C–H bond activation protocols in the literature are shown in scheme 3. In 1955, Shunsuke Murahashi reported cobalt-catalyzed annulation reaction of imine and carbon

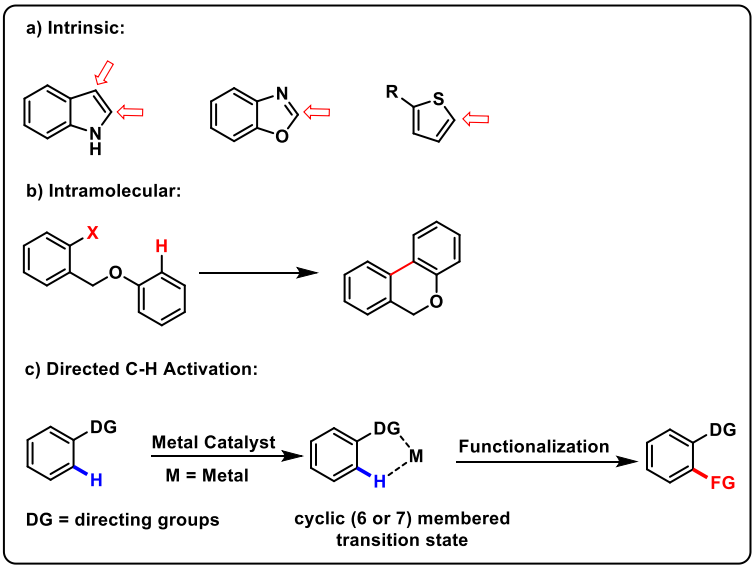


Scheme 3. History of C-H activation

monoxide (CO) by C–H bond activation reaction for the synthesis of *N*-phenyl isoindolinone (Scheme 3a).[4] Later in 1969, Fujiwara group reported Heck-type reaction using palladium/copper catalytic system for C–H functionalization (Scheme 3b).[5] Followed by these selected examples, recent years have witnessed an upsurge in the area of C–H bond functionalization. Few selected aspects of these transformations are summarized below.

0.3. Control of Regioselectivity:

The regioselective C–H bond activation is a challenging task since organic compounds possess ubiquitous C–H bonds. The regioselectivity in C–H bond activation could be achieved by three different ways such as intrinsic, intramolecular and directed C–H activation. Intrinsically, regioselectivity is being achieved by electronic nature or acidity difference in C–H bond of the



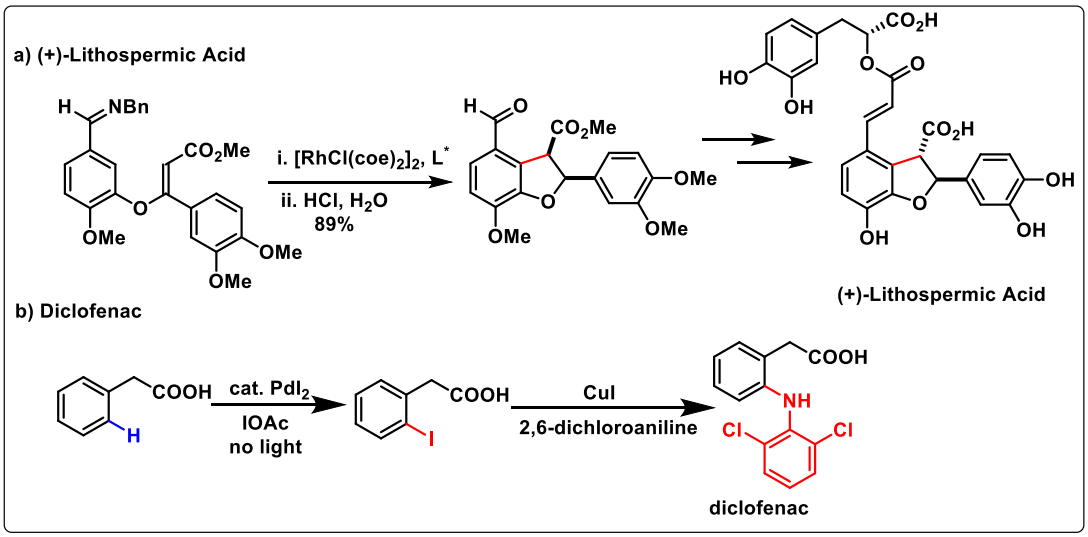
Scheme 4. Control of regioselectivity

substrates. For instance, substrates such as indole, benzoxazole and thiophene possess heteroatoms in their scaffold which makes adjacent C–H bonds electronically different than others thus controls the regioselectivity of C–H activation process (Scheme 4a). Intramolecular reactions also control regioselectivity in C–H bond activation process by the formation of five or

six-membered ring size (Scheme 4b). The use of directing groups has been established as a successful strategy among other methods to enhance the reactivity and to control the selectivity in C–H functionalization reactions. The directing group plays a crucial role in selective C–H bond activation since organic molecule contains many hydrogen atoms. A directing group chelates with a metal so that proximal hydrogen (by the formation of 6 or 7 membered transition states) could be activated to gain the selectivity (Scheme 4c).[6] Until now, several C–H activation reactions in organic compounds have been reported using various directing groups. Directing groups are either mono-dentate or bi-dentate chelating groups.

0.4. C–H Activation in Natural Product and Drug Synthesis:

Undeniably, numerous publications on the C–H activation topic have been reported in the literature and the development of new catalytic processes continues to evolve at a rapid pace, but their successful applications to the synthesis of complex natural products or pharmaceuticals are still rare.[3] Ellman and co-workers in 2005 have shown an elegant synthesis of (+)-lithospermic acid using rhodium catalyzed C–H bond activation by asymmetric intramolecular alkylation as

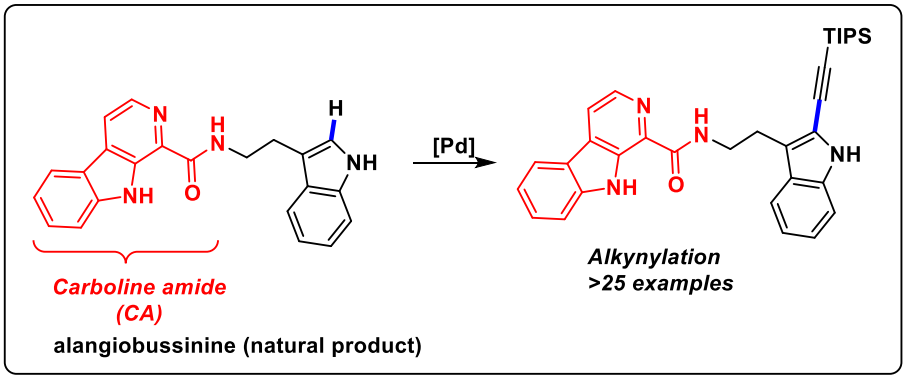


Scheme 5. Selected examples of C-H activation in the total synthesis of drug and natural product

the critical step (Scheme 5a).[7] Whereas Yu group in 2010 reported palladium catalyzed *ortho*-C–H iodination in expedient synthesis of the drug diclofenac (Scheme 5b).[8] Additionally some other known literature reports on natural products and drugs synthesis using C–H bond activation shows importance of this technique in the atom and step economy of reaction.[3] We believe that developing newer C–H activation methods for total synthesis of molecules would lead to the development of useful reactions for organic chemists. In this regard, in chapter 1 of this thesis, we have developed carboamidation protocol for the synthesis of protoberberine class of natural products and drug via C–H bond activation.

0.5. C–H Activation by Intrinsic Directing Group:

Installation and removal of directing groups require two extra steps. Very few examples of inherent or intrinsic directing groups are known where substrate itself acts as a directing group.[9]

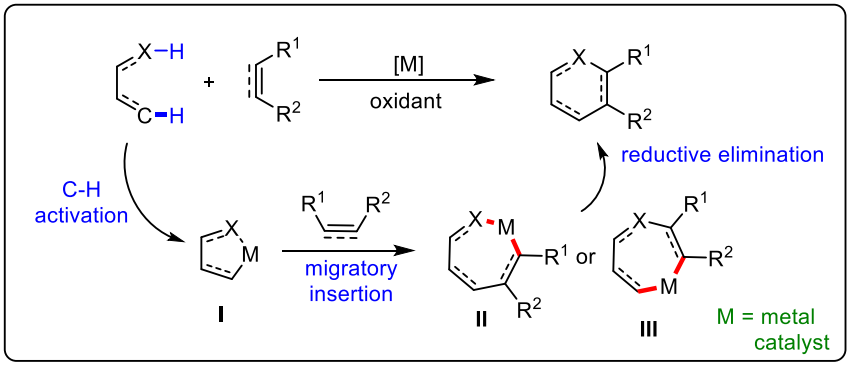


Scheme 6. Selected example of C-H activation by intrinsic directing group

Sarpong and coworkers reported C(sp^2)−H functionalization using *β*-carboline amide as an intrinsic directing group. Various substrates and the natural products such as alangiobussinine and the core of marinacarboline were functionalized using carboline-directed *δ*-C(sp^2)−H alkynylations (Scheme 6).[10] In Chapter 2 of this thesis, we have successfully applied quinazolinone scaffold as an intrinsic directing group for C(sp^2)-arylation and C(sp^3)-acetoxylations reactions to obtain novel quinazolinones of biological interest.

0.6. C–H Activation in Annulation Reactions:

Mostly C–H bond activation protocols have been used for simple functionalizations or additions but recent years have witnessed substantial improvement in related transformations that can be used in the formally known as cycloaddition reactions or annulation reactions.[11] These transformations are synthetically more important because it converts readily available substrates into highly valuable cyclic products in a rapid and sustainable manner. The general mechanism



Scheme 7. General mechanism for the metal catalyzed annulation involving C–H bond activation

of these transformations is depicted in Scheme 7. First, the metal catalyst co-ordinates with the heteroatom present in the substrates and activates proximal C–H bond to form metallacyclic intermediate **I**. The migratory insertion of metallacycle **I** into alkyne/alkene generates two possible intermediates **II** or **III** depending upon electronic/steric nature of substituents of used alkyne/alkene. The reactions involving intermediate **II** (C–C bond formation followed by C–X bond formation) are most studied as compared with the intermediate **III** (C–X bond formation followed by C–C bond formation). In this context, in chapter 3 of this thesis, we have developed annulation protocol using electronically biased alkyne (alkynontes) for the inverse regioselective synthesis of pyridones. The synthesized pyridones are biologically important 6-oxo nicotinic acid esters.

0.7. Conclusion:

The C–H bond activation protocol has emerged as a powerful tool for C–C and C–heteroatom bond construction. Tremendous catalytic C–H activation processes have been reported in the last two decades. However, there are very few reports known in literature where it has been successfully applied for the total synthesis of natural products and pharmaceuticals. The fascinating efficient transformations possible using C–H activation protocol enhanced our interest in the application of C–H bond activation chemistry for the synthesis of important scaffolds**.** This thesis is the outcome of our venture in this area.

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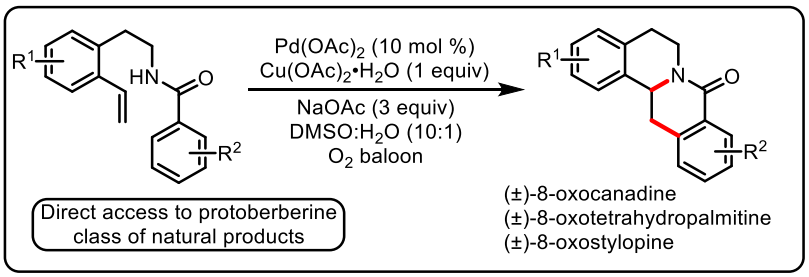
Chapter 1

Pd(II)-Catalyzed Tandem “Olefin Amidation/C–H Activation" Protocol for the Synthesis of Protoberberine Class of Natural Products and Drug

1.1. Abstract:

Chapter 1 describes Pd(II)-catalyzed intramolecular tandem olefin amidation-C–H activation protocol (carboamidation) for the synthesis of 8-oxoprotoberberine core. The tandem process of C–N and C–C bond formation was successfully applied for the syntheses of natural product precursors (±)-8-oxocanadine, (±)-8-oxotetrahydropalmitine and (±)-8-oxostylopine, which can be easily, converted to the respective protoberberine natural products and drug. The synthetic route established herein comprises amide-coupling, regioselective iodination, Stille coupling and carboamidation protocols. The short synthetic route demonstrated would be useful for the synthesis of a large number of natural products and their analogues featuring protoberberine scaffold.



This work has been published in *Org. Lett*. **2016**, *18*, 3862.

1.2. Introduction:

An alkaloid can be simply defined as a cyclic/acyclic compound containing nitrogen atom in a negative oxidation state which is widely distributed in living organisms.[1] The protoberberine alkaloids are subdivision of natural products containing isoquinoline skeleton. They are secondary metabolites having significant biological activities because of their ability to bind or insert in DNA.[1] Isolated from a wide range of plants, all members of protoberberine class feature

a 5,8,13,13a-tetrahydro-6*H*- isoquinolino[3,2-a]isoquinoline moiety, typically functionalized with hydroxy, methoxy or methylenedioxy substituents (Figure 1).[1,2] Canadine, stylopine, among others are some of the important protoberberine natural products and tetrahydropalmatine is an anxiolytic and sedative drug found in the Chinese herb *Yan Hu Suo*. Biologically, protoberberines have been synthesized from their very efficient bio-precursor tyrosine, which forms their A and D ring and part of C and D ring.[1b] The parent compound, berberine is the most widely studied alkaloid, which exhibits anti-fungal, anti-bacterial, anti-inflammatory, anti-malarial, anti-diabetic, and anti-cancer activities.[3]

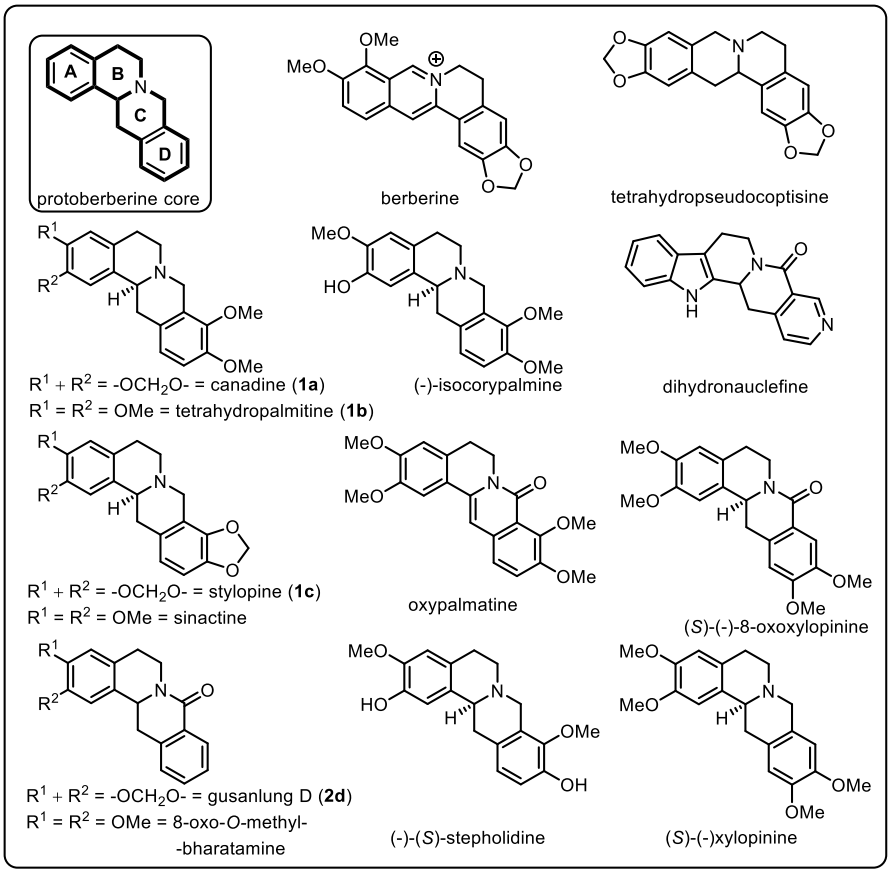


Figure 1. Selected natural products containing protoberberine core[1-3]

1.3. Literature Review:

Protoberberine class of natural products have acquired immense attention of the scientific community for their synthesis by various approaches, including few transition-metal-catalyzed methods for their construction.[1-3] Phosphane-free Pd(0)-catalyzed intramolecular aromatic amination and Pd-catalyzed direct aromatic carbonylation using carbon monoxide (CO) as the carbon source in the synthesis of 8-oxoberberines have been developed by Orito and co-workers.[2e,f,i] The intramolecular aromatic amination protocol developed by Orito group uses Pd(0) catalytic system based on $Pd(OAc)_2$ and $Cu(OAc)_2$ in the presence of K_2CO_3, whereas Pd(II)-catalyzed direct aromatic carbonylation has been carried out in a $Pd(OAc)_2$-$Cu(OAc)_2$ catalytic system. The other Pd-catalyzed method such as enolate arylation[1a] was developed by Donohoe group and utilized in the concise synthesis of the berberine alkaloids as well as in the construction of isoquinoline core. The intramolecular Heck type reaction[2g] have been utilized by Argade group for the synthesis of protoberberine gusanlung D.

Difunctionalization of olefins is a powerful strategy in organic synthesis for the construction of complex alkaloid natural products.[4b] We envisioned that an intramolecular tandem C–N/C–C bond formation (carboamidation) of internal olefins by C–H activation could be an interesting method to construct isoquinoline core for the synthesis of protoberberine alkaloids. In this context, the literature survey revealed that aminoarylation reactions of olefins/alkynes known in the literature requires aryl halides as a coupling partner.[4] The tandem Pd-catalyzed intramolecular amidation of alkenes followed by intermolecular C–H activation of arenes has been reported by Michael et al. in 2009 (Figure 2, eq. 1).[5] Here, arenes were used as solvent as well as reactants and Pd(II) catalyst was used for reaction in the presence of strong oxidant *N*-fluorobenzenesulfonimide (NFBS). They have also proposed the reaction mechanism involving

Pd(II)/Pd(IV) intermediates. Several other examples of intermolecular tandem C–C/C–N bond formation using various amines, alkenes and aryl sources as well as aminoarylation reactions between aryl halides and alkenes bearing pendant nitrogen nucleophiles also have been reported.[4,6,7] Directing group (*N*–OPiv amide) specific, rhodium-catalyzed intramolecular amidoarylation of olefins has been reported by Rovis et al (Figure 2, eq. 2).[8] *N*–OPiv amide also acts as a stoichiometric oxidant, which makes the catalytic ring closure a redox neutral process. This process is external oxidant free process where substrate itself acts as a terminal oxidant. There are few examples known in the literature wherein difunctionalization of internal alkynes by rhodium catalyst has been achieved by tandem amidation-C–H activation sequence (Figure 2, eq. 3).[9] The rhodium catalyzed process using external oxidant and its redox neutral version where substrate itself work as a oxidant were independently reported by Gulias group and Park group respectively.

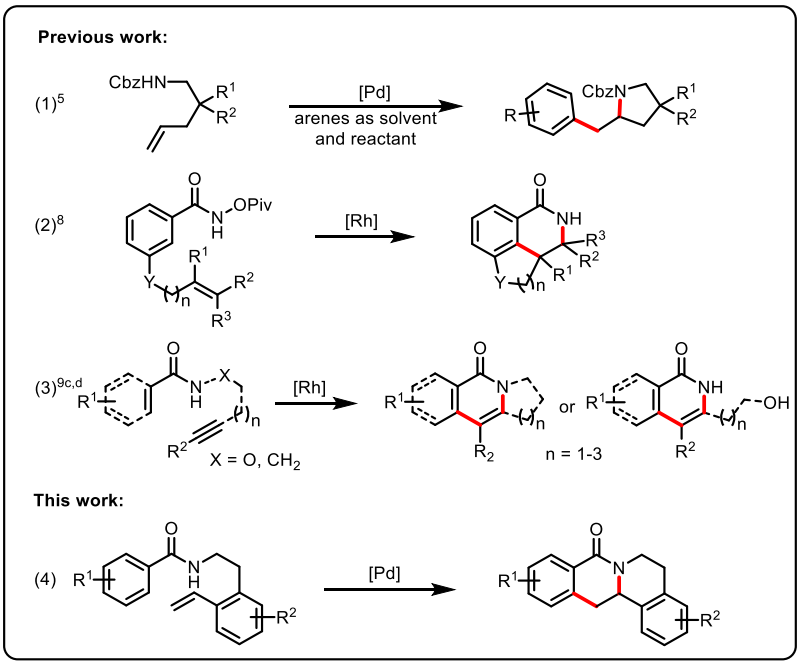


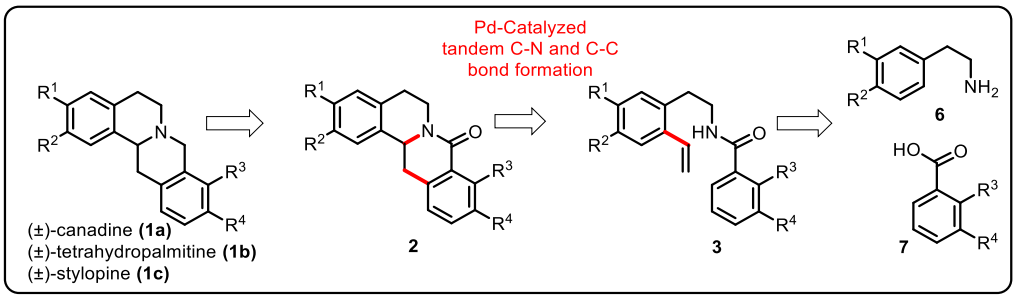
Figure 2. Difunctionalization of olefins and alkynes

1.4. Origin of the work:

In literature the difunctionalization of internal olefins to access isoquinolinone core of protoberberine alkaloids was not known until this report (Figure 2, eq. 4). In this report, we have described a unique intramolecular Pd-catalyzed tandem oxidative olefin amidation and C–H activation protocol for the synthesis of protoberberine class of natural products.

1.5. Objective of the work:

The retrosynthetic plan for this work is shown in Scheme 1. The protoberberine natural products and drug **1a-c** can be easily accessed by the reduction of its corresponding 8-oxoberberine derivative **2**, which would be obtained from vinyl amide **3** using the proposed Pd-catalyzed tandem olefin amidation-C–H activation protocol. Vinyl amide **3** could be generated from the corresponding aryl ethyl amine **6** and carboxylic acid **7** in three simple steps namely amide coupling, regioselective iodination and Stille coupling.

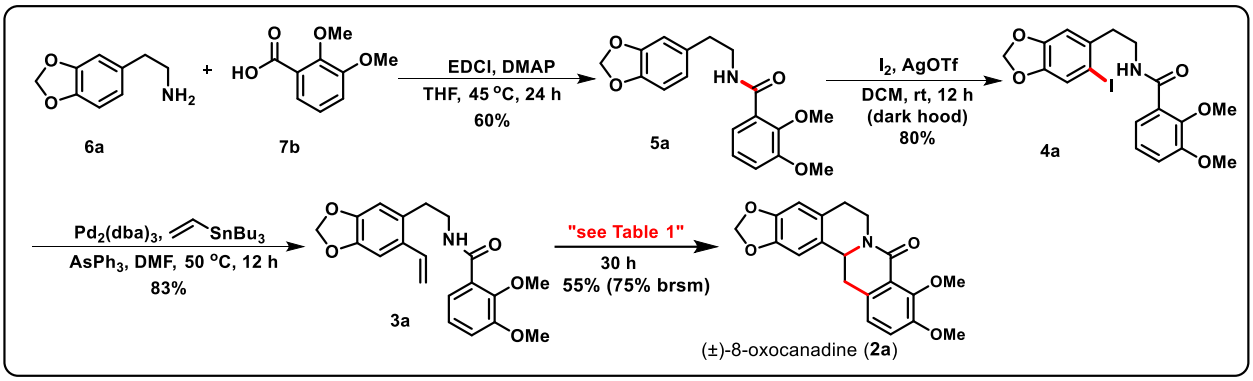


Scheme 1. Retrosynthetic analysis of protoberberines

1.6. Result and Discussion:

The synthesis of (±) 8-oxocanadine (**2a**) began with the coupling of the corresponding aryl ethyl amine **6a** and carboxylic acid **7b** using EDC·HCl[10] to obtain amide **5a** in good yield (scheme 2). The amide **5a** was then treated with iodine and silver triflate[11] in dark atmosphere to furnish iodo-amide **4a** in very good yield and excellent regioselectivity. The iodo-amide **4a** was further

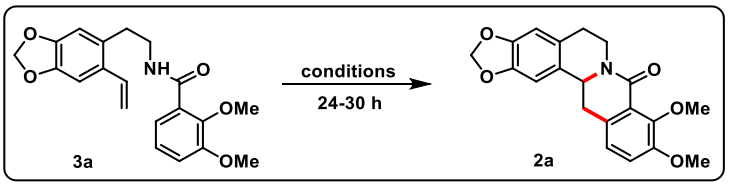
treated with tributyl(vinyl)stannane under Stille coupling conditions[10] catalyzed by $Pd_2(dba)_3$ and triphenylarsane as a ligand to get vinyl-amide **3a** in very good yield, which was used as a precursor for carboamidation protocol.



Scheme 2. Synthesis of (±)-8-oxocanadine (**2a**)

Various catalysts, oxidants and reaction conditions were screened on vinyl-amide **3a** for the expected tandem amidation-C–H activation reaction to get optimized protocol (Table 1).

Table 1. Optimization of the carboamidation protocol[a]



entry	catalyst (mol %)	oxidant (equiv)	additive (equiv)	solvent/temp	yield (%)[a]
1	$Pd(OAc)_2$ (10)	$Cu(OAc)_2$ (0.2)	AgOAc (2)	DMF/110 °C	15
2	$Pd(OAc)_2$ (10)	$Cu(OAc)_2$ (0.2)	NaOAc (2)	DMF/110 °C	25
3	$Pd(OAc)_2$ (10)	$Cu(OAc)_2 \cdot H_2O$ (2)	NaOAc (2)	*t*-Amyl alcohol/115 °C	-
4	$[RhCp^*Cl_2]_2$ (2.5)	$Cu(OAc)_2$ (0.2)	AgOAc (1.5)	CH_3CN/110 °C	-
5	$[RuCl_2(p\text{-cy})]_2$(5)	$Cu(OAc)_2 \cdot H_2O$ (2)	$AgSbF_6$ (0.2)	1,4-dioxane/ 100 °C	-
6	$Pd(OAc)_2$ (10)	$Cu(OAc)_2$ (0.2)	NaOAc (2)	DMSO/100 °C	30
7	$Pd(OAc)_2$ (10)	$Cu(OAc)_2$ (2), O_2	NaOAc (2)	DMSO/100 °C	35
8	$Pd(OAc)_2$ (10)	$Cu(OAc)_2 \cdot H_2O$ (2), O_2	KOAc (2)	DMSO/100 °C	25

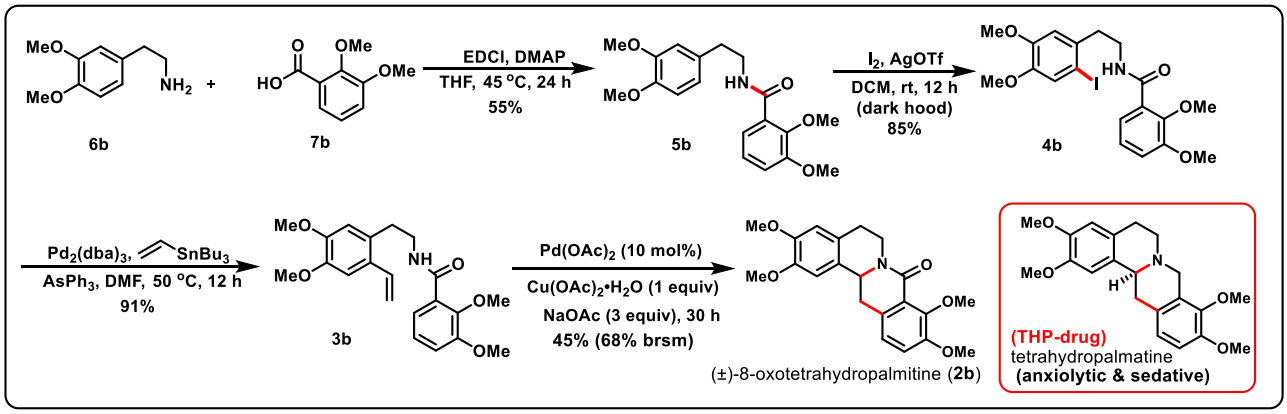
9	$Pd(OAc)_2$ (10)	$Cu(OAc)_2 \cdot H_2O$ (2), O_2	NaOAc (2), PivOH (0.4)	DMSO/100 °C	40
10	$Pd(OAc)_2$ (10)	O_2	NaOAc (2), PivOH (0.4)	DMSO/100 °C	-
11	$Pd(OAc)_2$ (10)	$Cu(OAc)_2 \cdot H_2O$ (2), O_2	NaOAc (2), PivOH (0.4)	DMSO:H_2O (9:1)/100 °C	45
12[b]	**$Pd(OAc)_2$ (10)**	**$Cu(OAc)_2 \cdot H_2O$ (1), O_2**	**NaOAc (3)**	**DMSO:H_2O (10:1)/100 °C**	**55 (75% brsm)**
13	$[RhCp^*Cl_2]_2$ (2.5)	$Cu(OAc)_2 \cdot H_2O$ (1), O_2	NaOAc (3)	DMSO:H_2O (10:1)/100 °C	-
14	$Pd(TFA)_2$ (10)	$Cu(OAc)_2 \cdot H_2O$ (1), O_2	NaOAc (3)	DMSO:H_2O (10:1)/100 °C	42
15	$PdCl_2$ (10)	$CuCl_2 \cdot 2H_2O$ (1)	NaOAc (3)	DMSO:H_2O (10:1)/100 °C	20
16	$Pd(OAc)_2$ (10)	$Cu(OAc)_2 \cdot H_2O$ (1), O_2	NaOAc (3)	DMAc:H_2O (9:1)/100 °C	33
17	$Pd(OAc)_2$ (10)	$Cu(OAc)_2 \cdot H_2O$ (1), O_2	NaOAc (3)	DMAc:DMSO (9:1)/100 °C	35

a) All reactions were performed on 18 mg (0.05 mmol) scale of vinyl-amide **3a**. b) Solvent used DMSO: H_2O (0.3: 0.03) mL.

The first reaction towards this aim was by using catalytic $Pd(OAc)_2$ and $Cu(OAc)_2$ in the presence of base/additive AgOAc at 110 °C in DMF, which gave the expected product **2a**, though in low yield (entry 1). The base/additive AgOAc was replaced by NaOAc, which enhanced the yield by 10% (entry 2). Variation in metal catalysts or solvents did not show the formation of the expected product (entries 3-5). Interestingly, the change in solvent from DMF to DMSO and performing the reaction under oxygen atmosphere showed improvement in yield to 35% along with 30% starting material recovery (entries 6 & 7). After variations in additives (entries 8-11) we could find an optimized reaction condition (entry 12), wherein the highest possible yield of product (±) 8-oxocanadine (**2a**, 55%, 75% brsm) could be obtained. However, further modifications (entries 13-17) or variation in catalyst loading did not show improvement in the yield.

After having optimal conditions in hands, we turned our attention to develop a general scope of the protocol. The synthesis of various 8-oxoprotoberberines was carried out by following the same sequence used for the synthesis of (±) 8-oxocanadine (**2a**). Initially, the amide coupling of

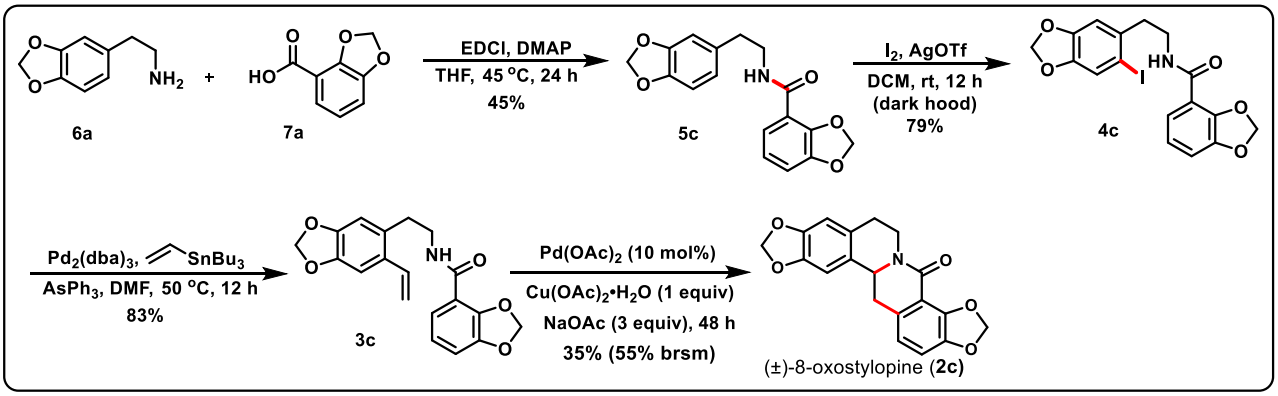
the corresponding aryl ethyl amine **6b** and carboxylic acid **7b** using EDC·HCl and catalytic DMAP[10] was carried out to obtain amide **5b** in moderate yield (scheme 3). The amide **5b** was then subjected for regioselective iodination using iodine and silver triflate[11] in dark to furnish iodo-amide **4b** in excellent yield.



Scheme 3. Synthesis of (±)-8-oxotetrahydropalmitine (**2b**)

The iodo-amide **4b** was further treated with tributyl(vinyl)stannane under Stille coupling conditions[10] to get vinyl-amide **3b** in excellent yield. After having vinyl-amide **3b** in hand, we applied the developed carboamidation protocol on vinyl-amides **3b**, which provided the cyclized product (±) 8-oxotetrahydropalmitine (**2b**) in 45% (68% brsm) yield.

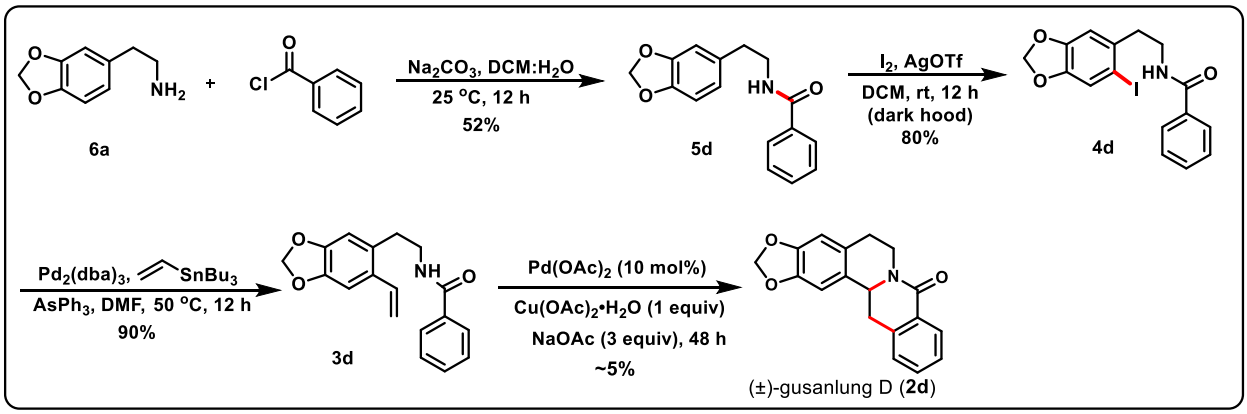
Subsequently, synthesis of (±)-8-oxostylopine (**2c**) was commenced by following similar reactions sequence which was used for synthesis of **2a** and **2b**. The amide coupling of the



Scheme 4. Synthesis of (±)-8-oxostylopine (**2c**)

corresponding aryl ethyl amine **6a** and carboxylic acid **7a** by using EDCI[10] was carried out to obtain amide **5c** in adequate yield (scheme 4).The amide **5c** was then subjected for regioselective iodination[11] in dark atmosphere and furnished iodo-amide **4c** in good yield. The iodo-amide **4c** was further treated with tributyl(vinyl)stannane under Stille coupling conditions[10] to get vinyl-amide **3c** in very good yield. After having vinyl-amide **3c** in hand, we applied the developed carboamidation protocol on vinyl-amides **3c**, which provided the cyclized product (±) 8-oxostylopine (**2c**) in 35% (55% brsm) yield.

Successful synthesis of electron rich 8-oxoprotoberberines **2a-c** (Scheme 2-4) prompted us to test the developed protocol for the synthesis of natural products having electron deficient scaffolds. The structure of gusanlung D (**2d**) shows 'D-ring' of its core is electron deficient than 8-oxoprotoberberines **2a-c** (Figure 1). The synthetic route of gusanlung D (**2d**) is depicted in scheme 5. The amide **5d** was synthesized by coupling of the corresponding aryl ethyl amine **6a** and benzoyl chloride in the presence of Na_2CO_3 in biphasic solvent system DCM:H_2O in moderate yield.



Scheme 5. Attempt for synthesis of (±)-gusanlung (**2d**)

The amide **5d** was then subjected under iodination condition with iodine and silver triflate[11] in dark hood to furnish iodo-amide **4d** in very good yield and regioselectivity. The iodo-amide **4d**

was further reacted with tributyl(vinyl)stannane under Stille coupling conditions[10] catalyzed by Pd(0) and triphenylarsane as a ligand to get vinyl-amide **3d** in excellent yield. After having vinyl-amide **3d** in hand, we applied the developed carboamidation protocol on vinyl-amides **3d** but unfortunately cyclized product **2d** was observed in less than 5% by TLC and most of the starting material remained unreacted. Its formation was confirmed by LC-MS and HRMS analysis. We were unable to isolate enough compound for NMR analysis.

Overall, we have successfully synthesized 8-oxoberberines **2a-c** in moderate isolated yields and based on recovered starting materials moderate to good yields (Scheme 2-4). Unfortunately, vinyl-amide **3d** when subjected to our developed protocol showed formation of only a trace amount of natural product gusanlung D (**2d**). When the reaction temperature was raised to 120-140 °C, decomposition of vinyl-amide **3d** was observed. It shows that the developed protocol fails to deliver the cyclized product in case of electronically deficient vinyl amide substrates (Scheme 5). The analytical and spectral data of 8-oxoberberines **2a-c** is consistent with the reported data.[2e] Their transformation to the corresponding natural products and drug (±)-canadine (**1a**), (±)-tetrahydropalmitine (**1b**) and (±)-stylopine (**1c**) has been well-documented in the literature.[2j,k,m,n]

A proposed mechanism for the intramolecular carboamidation protocol developed herein has been depicted in Figure 3. The active catalyst might be formed by the coordination of DMSO with Pd(II), which catalyzes further transformations.[12] First, Pd(II) coordinates with nitrogen and olefin of **3a** to form intermediate **I** followed by amino-palladation gave intermediated **II.** The proximal C-H bond activation of intermediate **II** results into palladacycle **III**. The reductive elimination of Pd(II) from palladacycle **III** furnish the expected cyclized product **2a** and $Pd(0)L_n$. The intrinsically unstable form of the catalyst "$Pd(0)L_n$" generated in the reaction mixture

reoxidizes (Figure 3, i) by the oxidant to complete the catalytic cycle; however, a competing reaction, which deactivates Pd(0) to catalytically inactive palladium black,[13] might be the reason behind the incomplete conversion (Figure 3, ii).

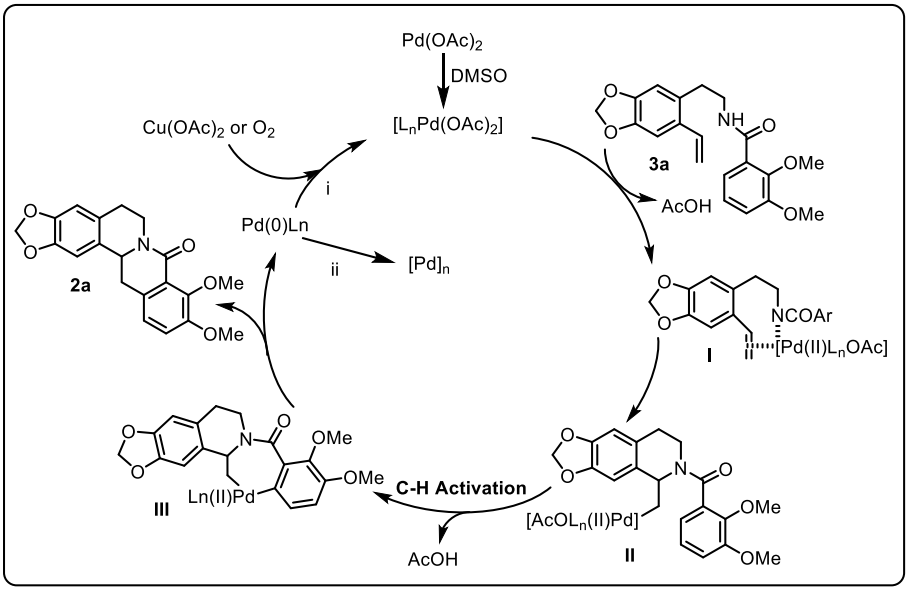


Figure 3. Proposed mechanism for the intramolecular carboamidation

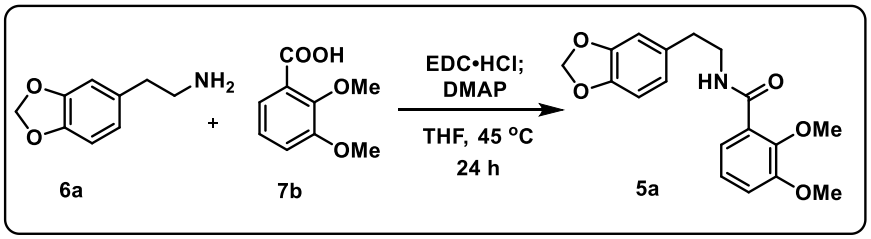
1.7. Conclusion:

In summary, a novel Pd(II)-catalyzed approach for the synthesis of protoberberine core has been developed. The two new bonds, C–N and C–C have been formed in a single step by intramolecular tandem 'amidation-C–H activation' sequence. A short and efficient syntheses of (±)-8-oxocanadine, (±)-8-oxotetrahydropalmitine and (±)-8-oxostylopine have been achieved by implementing this novel protocol as a key step. A formal synthesis of the drug 'tetrahydropalmatine' has been also achieved. It is also a first report on the synthesis of the tetracyclic core from intramolecular annulation of amide and styrene. Currently, we are working on the total synthesis of other natural alkaloids in this class using the developed protocol.

1.8. Experimental Procedures and Characterization Data of Compounds:

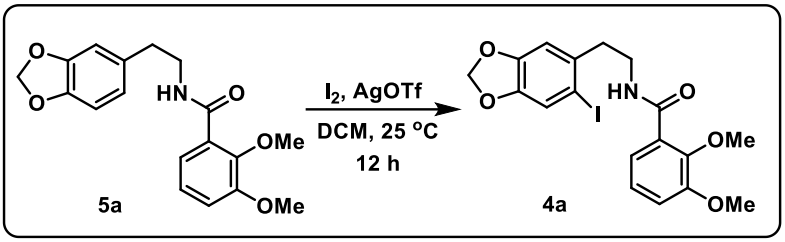
I) Experimental Procedures for the Synthesis of (±) 8-Oxocanadine (2a):

i) Synthesis of Amide 5a:[10]



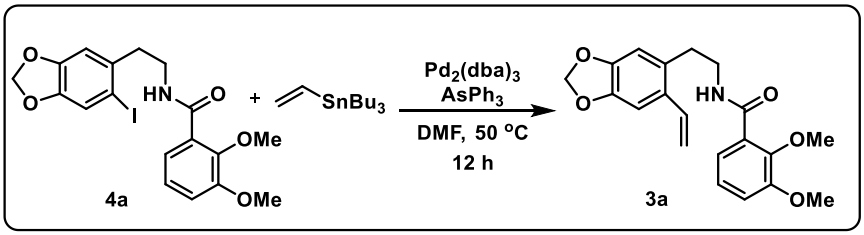
The amide **5a** was prepared by modifying the known procedure.[10] To a solution of amine **6a** (0.9 g; 5.44 mmol) in THF (20 mL) was added acid **7b** (1.29 g; 7.08 mmol) and DMAP (33.23 mg; 0.27 mmol). The resulting mixture was stirred for 5 min. at room temperature. EDC·HCl (2.08 g; 10.88 mmol) was added portion wise over 5 min. and the reaction mixture was stirred for 24 h at 45 °C. The reaction mixture was diluted by adding 60 mL of ethyl acetate and the organic layer was washed with brine, saturated solution of aqueous $NaHCO_3$ and water. The organic layer was dried over anhydrous Na_2SO_4, evaporated under *vacuo* and the residue was purified by column chromatography to afford amide **5a** (1.07 g; 60% yield) as a thick oil. R*f*: 0.4 (3:7 EtOAc:Pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.79 (t, J = 6.8 Hz, 2H), 3.61 (s, 3H), 3.64 (q, J = 6.8 Hz, 2H), 3.80 (s, 3H), 5.85 (s, 2H), 6.64 (dd, J = 8.1, 1.5 Hz, 1H), 6.66-6.71 (m, 2H), 6.95 (dd, J = 8.1, 1.5 Hz, 1H), 7.06 (t, J = 8.1 Hz, 1H), 7.63 (dd, J = 8.1, 1.5 Hz, 1H), 7.95 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.1, 40.9, 56.0, 61.0, 100.8, 108.3, 109.0, 115.2, 121.6, 122.8, 124.3, 126.6, 132.9, 146.1, 147.5, 147.8, 152.5, 165.1; HRMS-ESI (m/z) calcd $(C_{18}H_{19}NO_5 + H)^+$: 330.1336, found: 330.1339.

ii) Synthesis of Iodo-Amide 4a:



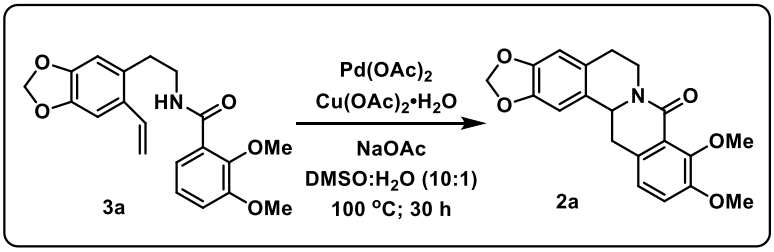
The Iodo compound **4a** was prepared by modifying known procedure.[11] To a solution of amide **5a** (0.8 g; 2.43 mmol) in DCM (15 mL) was added AgOTf (0.624 g; 2.43 mmol) and stirred at 25 °C for 2 min. The solution of iodine (0.616 g; 2.43 mmol) in DCM (15 mL) was added to the above solution drop-wise over 5 min. and the resulting mixture was stirred for 12 h at 25 °C in dark hood. The reaction mixture was filtered through a short pad of celite with DCM as an eluent. The combined organic layers were washed with aqueous NH_3, aqueous Na_2SO_3 and water. The DCM layer was dried over anhydrous Na_2SO_4, evaporated under *vacuo* and purified by column chromatography to afford iodo compound **4a** (0.884 g; 80% yield) as a colorless solid. R*f*: 0.5 (2:3 EtOAc:Pet. ether); mp 101-103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.93 (t, J = 7.1 Hz, 2H), 3.60 (q, J = 7.1 Hz, 2H), 3.73 (s, 3H), 3.82 (s, 3H), 5.87 (s, 2H), 6.74 (s, 1H), 6.96 (dd, J = 8.1, 1.5 Hz, 1H), 7.08 (t, J = 8.1 Hz, 1H), 7.18 (s, 1H), 7.64 (dd, J = 8.1, 1.5 Hz, 1H), 7.97 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.8, 40.1, 56.0, 61.2, 88.0, 101.6, 109.7, 115.3, 118.7, 122.8, 124.4, 126.6, 134.9, 147.1, 147.5, 148.5, 152.5, 165.3; HRMS-ESI (m/z) calcd $(C_{18}H_{18}NIO_5 + H)^+$: 456.0302, found: 456.0309.

iii) Synthesis of Vinyl-Amide 3a:[10]



The vinyl-amide **3a** was prepared by using known procedure.[10] To a solution of compound **4a** (0.455 g, 1 mmol) in 20 mL of DMF, tributyl(vinyl)tin (0.44 mL, 1.5 mmol), $Pd_2(dba)_3$ (92 mg, 0.1 mmol) and $AsPh_3$ (0.244 g, 0.8 mmol) were added. The solution was stirred for 12 h at 50 °C under an argon atmosphere. After cooling to ambient temperature the reaction mixture was quenched with saturated NH_4Cl solution and extracted with ethyl acetate (20 mL x 3). The organic layer was washed with water (10 mL x 3), dried over Na_2SO_4, and concentrated after filtration. The crude product was purified by column chromatography to afford a vinyl-amide **3a** (0.295 g; 83% yield) as a colorless solid. R*f*: 0.6 (1:1 EtOAc:Pet. ether); mp 75-77 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.88 (t, J = 7.1 Hz, 2H), 3.56 (q, J = 7.1 Hz, 2H), 3.68 (s, 3H), 3.81 (s, 3H), 5.15 (d, J = 11.0 Hz, 1H), 5.45 (d, J = 17.1 Hz, 1H), 5.85 (s, 2H), 6.63 (s, 1H), 6.86-6.98 (m, 3H), 7.07 (t, J = 8.1 Hz, 1H), 7.63 (dd, J = 8.1, 1.5 Hz, 1H), 7.96 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.7, 40.7, 56.0, 61.1, 100.9, 105.6, 109.8, 114.3, 115.3, 122.8, 124.3, 126.6, 130.4, 130.5, 133.6, 146.7, 147.3, 147.5, 152.5, 165.3; HRMS-ESI (m/z) calcd $(C_{20}H_{21}NO_5 + H)^+$: 356.1492, found: 356.1493.

iv) Synthesis of (±) 8-Oxocanadine (2a):

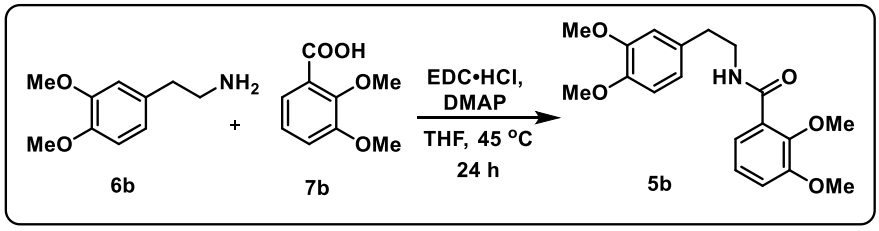


Vinyl-amide **3a** (18 mg, 0.05 mmol), $Pd(OAc)_2$ (1.12 mg, 0.005 mmol), $Cu(OAc)_2 \cdot H_2O$ (10 mg, 0.05 mmol) and NaOAc (12.3 mg, 0.15 mmol) were dissolved in DMSO (0.3 mL) and H_2O (30 µl) in a Schlenk tube. The reaction mixture was evacuated and filled back with oxygen three times. The reaction mixture was stirred at 100 °C in preheated oil bath for 30 h under oxygen. It

was allowed to cool to room temperature and diluted with ethyl acetate (25 mL) and washed with warm water (10 mL x 4). Organic layer was dried over anhydrous Na_2SO_4, evaporated under *vacuo* and purified by column chromatography to afford title compound **2a** (9.7 mg; 55% yield) as a colorless solid. 5 mg of starting material **3a** was also recovered, hence based on recovered starting material the yield of **2a** is 75%. R*f*: 0.4 (1:1 EtOAc:Pet. ether); mp 198-202 °C (lit.[14] mp 198–200 °C; lit.[2i] mp 198–202 °C; lit.[2e] mp 209–211 °C; lit.[15] mp 217–218 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.63-2.97 (m, 5H), 3.82 (s, 3H), 3.94 (s, 3H), 4.62 (dd, J = 12.9, 2.7 Hz, 1H), 4.87-4.95 (m, 1H), 5.88 (s, 2H), 6.59 (s, 1H), 6.60 (s, 1H), 6.86 (d, J = 8.3 Hz, 1H), 6.93 (d, J = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.9, 38.2, 39.2, 55.3, 56.2, 61.6, 101.1, 106.1, 108.6, 115.2, 122.0, 123.5, 128.8, 128.9, 130.8, 146.5, 146.7, 150.1, 153.1, 162.6; HRMS-ESI (m/z) calcd ($C_{20}H_{19}NO_5$ + H)$^+$: 354.1336, found: 354.1338.

II) Experimental Procedures for the Synthesis of (±) 8-Oxotetrahydropalmatine (2b):

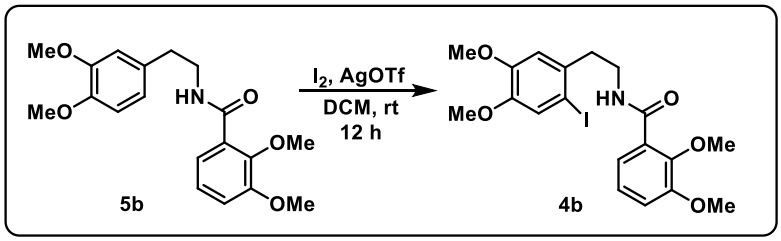
i) Synthesis of Amide 5b:



The amide **5b** was prepared from amine **6b** (0.5 g, 2.75 mmol) and 2, 3 dimethoxy benzoic acid **7b** (0.551 g, 3 mmol) following the same procedure as used in synthesis of amide **5a** to afford the title compound **5b** (0.524 g, 55% yield) as a colorless solid. R*f*: 0.4 (1:1 EtOAc:Pet. ether); mp 93-94 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.83 (t, J = 7.1 Hz, 2H), 3.56 (s, 3H), 3.68 (q, J = 7.1 Hz, 2H), 3.79 (s, 6H), 3.80 (s, 3H), 6.70-6.78 (m, 3H), 6.95 (dd, J = 8.1, 1.5 Hz, 1H), 7.07 (t, J = 8.1 Hz, 1H), 7.64 (dd, J = 8.1, 1.5 Hz, 1H), 7.98 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

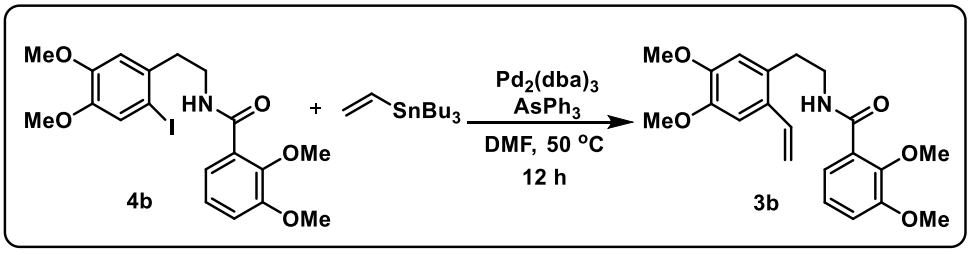
35.0, 40.9, 55.8, 55.9, 56.0, 61.0, 111.4, 111.8, 115.2, 120.6, 122.8, 124.3, 126.6, 131.6, 147.5, 147.7, 149.1, 152.5, 165.1; HRMS-ESI (m/z) calcd ($C_{19}H_{23}NO_5$ + H)$^+$: 346.1649, found: 346.1650.

ii) Synthesis of Iodo-Amide 4b:



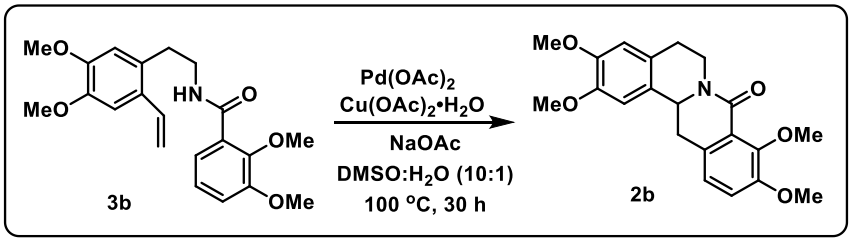
The iodo-amide **4b** was prepared from amide **5b** (0.520 g, 1.5 mmol) according to the same procedure as used in the synthesis of iodo-amide **4a**. The title compound **4b** (0.601 g, 85% yield) was obtained as a thick oil. R*f*: 0.5 (1:1 EtOAc:Pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.95 (t, *J* = 7.0 Hz, 2H), 3.63 (q, *J* = 7.0 Hz, 2H), 3.68 (s, 3H), 3.72 (s, 3H), 3.78 (s, 3H), 3.81 (s, 3H), 6.73 (s, 1H), 6.97 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.08 (t, *J* = 8.1 Hz, 1H), 7.16 (s, 1H), 7.64 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.99 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.8, 55.9, 56.0, 56.2, 61.1, 88.1, 112.7, 115.4, 121.7, 122.7, 124.4, 126.6, 134.1, 147.5, 148.2, 149.4, 152.6, 165.3; HRMS-ESI (m/z) calcd ($C_{19}H_{22}NIO_5$ + H)$^+$: 472.0615, found: 472.0620.

iii) Synthesis of vinyl-amide 3b:



The vinyl-amide **3b** was prepared from iodo-amide **4b** (0.472 g, 1.0 mmol) according to same procedure as used in the synthesis of vinyl-amide **3a** to obtain the title compound **3b** (0.338 g, 91% yield) as thick oil. R*f*: 0.5 (1:1 EtOAc:Pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.91 (t, J = 7.1 Hz, 2H), 3.59 (q, J = 7.1 Hz, 2H), 3.64 (s, 3H), 3.77 (s, 3H), 3.80 (s, 3H), 3.83 (s, 3H), 5.17 (d, J = 11.0 Hz, 1H), 5.50 (d, J = 17.1 Hz, 1H), 6.64 (s, 1H), 6.89-6.99 (m, 3H), 7.07 (t, J = 8.1 Hz, 1H), 7.64 (dd, J = 8.1, 1.5 Hz, 1H), 7.98 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.3, 40.7, 55.9, 56.0, 61.0, 108.6, 112.8, 113.9, 115.3, 122.7, 124.3, 126.6, 129.1, 133.7, 147.5, 147.8, 148.8, 152.5, 165.3; HRMS-ESI (m/z) calcd $(C_{21}H_{25}NO_5 + H)^+$: 372.1805, found: 372.1808.

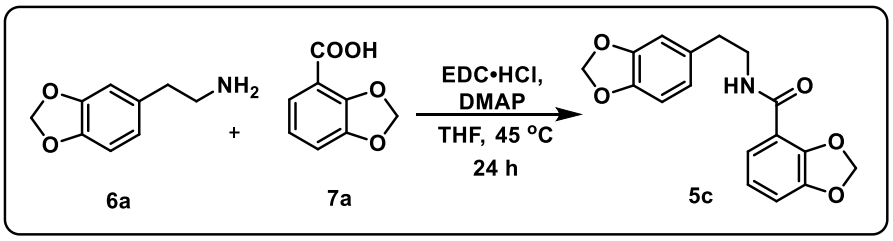
iv) Synthesis of (±) 8-Oxotetrahydropalmatine (2b):



The cyclic-amide **2b** was prepared from vinyl-amide **3b** (18.6 mg, 0.05 mmol) according to the same procedure as used in the synthesis of cyclic-amide **2a** to furnish the title compound **2b** (8.3 mg; 45% yield) as a colorless solid. 6.4 mg of starting material **3b** was also recovered, hence based on recovered starting material the yield of **2b** is 68%. R*f*: 0.3 (1:1 EtOAc:Pet. ether); mp 166-168 °C (lit.[15] mp 167–168 °C; lit.[2j] mp 169–170 °C; lit.[2e,i] mp 171–172 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.64-2.90 (m, 4H), 2.96 (dd, J = 15.2, 2.9 Hz, 1H), 3.82 (s, 9H), 3.95 (s, 3H), 4.66 (dd, J = 12.7, 2.9 Hz, 1H), 4.93-5.03 (m, 1H), 6.61 (s, 1H), 6.62 (s, 1H), 6.88 (d, J = 8.3 Hz, 1H), 6.94 (d, J = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.4, 38.2, 39.2, 55.0, 55.9, 56.1, 56.2, 61.6, 109.1, 111.4, 115.2, 122.0, 123.6, 127.5, 127.7, 130.9, 147.9, 148.0, 150.1, 153.1, 162.7; HRMS-ESI (m/z) calcd $(C_{21}H_{23}NO_5 + Na)^+$: 392.1468, found: 392.1460.

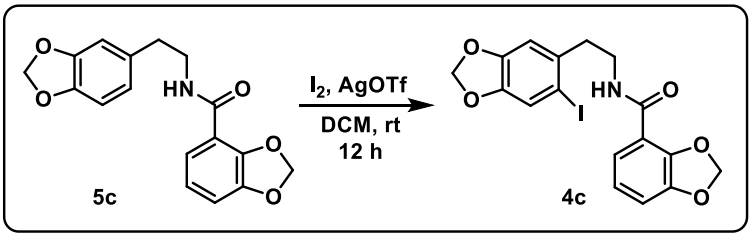
III) Experimental Procedures for the Synthesis of (±) 8-Oxostylopine (2c):

i) Synthesis of Amide 5c:



The amide **5c** was prepared from amine **6a** (0.173 g, 1.05 mmol) and benzo[d][1,3]dioxole-4-carboxylic acid **7a** (0.174 g, 1.05 mmol) according to same procedure as used in the synthesis of amide **5a** to afford the title compound **5c** (0.148 g, 45% yield) as a colorless solid. R*f*: 0.4 (3:7 EtOAc:Pet. ether); mp 89-91 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.76 (t, J = 6.8 Hz, 2H), 3.60 (q, J = 6.8 Hz, 2H), 5.87 (s, 2H), 5.95 (s, 2H), 6.59-6.72 (m, 3H), 6.82-6.89 (m, 2H), 6.95 (bs, 1H), 7.46-7.54 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 35.5, 41.3, 100.9, 101.3, 108.3, 109.3, 111.5, 115.9, 121.8, 122.0, 122.4, 132.8, 145.0, 146.2, 147.5, 147.8, 163.3; HRMS-ESI (m/z) calcd $(C_{17}H_{15}NO_5 + Na)^+$: 336.0842, found: 336.0836.

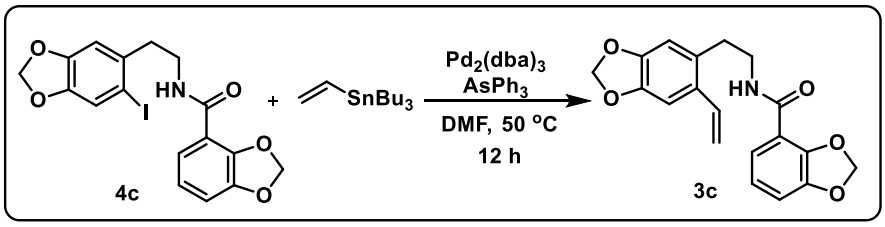
ii) Synthesis of iodo-amide 4c:



The iodo-amide **4c** was prepared from amide **5c** (0.1 g, 0.32 mmol) according to the same procedure as used in the synthesis of iodo-amide **4a** to yield title compound **4c** (0.11 g, 79% yield) as a colorless solid. R*f*: 0.45 (3:7 EtOAc:Pet. ether); mp 121-123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.92 (t, J = 6.8 Hz, 2H), 3.59 (q, J = 6.8 Hz, 2H), 5.89 (s, 2H), 5.98 (s, 2H), 6.74 (s, 1H), 6.83-6.91 (m, 2H), 6.95 (bs, 1H), 7.18 (s, 1H), 7.46-7.54 (m, 1H); ^{13}C NMR (100 MHz,

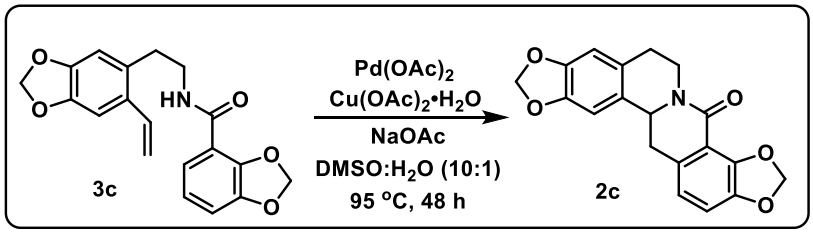
$CDCl_3$) δ 39.9, 40.1, 88.0, 101.3, 101.6, 110.0, 111.6, 115.9, 118.7, 122.0, 122.4, 134.9, 145.0, 147.2, 147.5, 148.6, 163.5; HRMS-ESI (m/z) calcd $(C_{17}H_{14}NIO_5 + Na)^+$: 461.9809, found: 461.9807.

iii) Synthesis of vinyl-amide 3c:



The vinyl-amide **3c** was prepared from iodo-amide **4c** (0.11 g, 0.25 mmol) according to the same procedure as used in the synthesis of vinyl-amide **3a** to give the title compound **3c** (0.07 g, 83% yield) as colorless solid. R*f*: 0.45 (3:7 EtOAc:Pet. ether) mp 111-113 °C;; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.86 (t, *J* = 7.3 Hz, 2H), 3.54 (q, *J* = 6.7 Hz, 2H), 5.14 (d, *J* = 10.9 Hz, 1H), 5.45 (d, *J* = 17.1 Hz, 1H), 5.87 (s, 2H), 5.95 (s, 2H), 6.62 (s, 1H), 6.83-6.99 (m, 5H), 7.45-7.54 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.8, 40.8, 101.0, 101.3, 105.5, 110.0, 111.5, 114.2, 115.9, 122.0, 122.4, 130.3, 130.5, 133.6, 145.0, 146.8, 147.3, 147.4, 163.4; HRMS-ESI (m/z) calcd $(C_{19}H_{17}NO_5 + Na)^+$: 362.0999, found: 362.0996.

iv) Synthesis of (±) 8-Oxostylopine (2c):

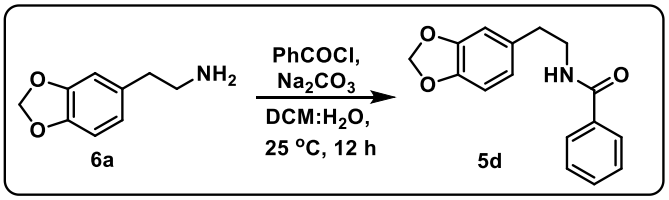


The cyclic-amide **2c** was prepared according to the procedure as used in the synthesis of cyclic-amide **2a** after little modifications. Vinyl-amide **3c** (17 mg, 0.05 mmol), $Pd(OAc)_2$ (0.56 mg, 0.0025 mmol), $Cu(OAc)_2 \cdot H_2O$ (10 mg, 0.05 mmol) and NaOAc (12.3 mg, 0.15 mmol) were

dissolved in DMSO (0.5 mL) and H_2O (50 µl) in a Schlenk tube. The reaction mixture was evacuated and filled back with oxygen three times. The reaction mixture was stirred at 95 °C in preheated oil bath for 24 h under oxygen. $Pd(OAc)_2$ (0.56 mg, 0.0025 mmol) was added and the reaction mixture was further heated for another 24 h. It was allowed to cool to room temperature and diluted with ethyl acetate (25 mL) and washed with warm water (10 mL x 4). Organic layer was dried over anhydrous Na_2SO_4, evaporated under *vacuo* and purified by column chromatography to afford title compound **2c** (6 mg; 35% yield) as a colorless solid. 6 mg of starting material **3c** was also recovered, hence based on recovered starting material the yield of **2c** is 55%. R*f*: 0.35 (1:1 EtOAc:Pet. ether); mp 251-253 °C (lit.[14] mp 250–252 °C; lit.[2k] mp 267–270 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.60-2.72 (m, 1H), 2.74-2.93 (m, 3H), 3.03 (dd, J = 15.2, 3.4 Hz, 1H), 4.65-4.73 (m, 1H), 4.81-4.93 (m, 1H), 5.89 (s, 2H), 6.01 (bs, 1H), 6.10 (bs, 1H), 6.56-6.65 (m, 3H), 6.77-6.82 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.6, 38.2, 38.3, 55.6, 101.1, 102.3, 105.9, 108.7, 110.8, 112.7, 119.2, 128.6, 128.7, 130.5, 146.6, 146.7, 147.9, 148.0, 162.4; HRMS-ESI (m/z) calcd $(C_{19}H_{15}NO_5 + Na)^+$: 360.0842, found: 360.0844.

IV) Experimental Procedures for the Attempted Synthesis of (±)-Gusanlung D:

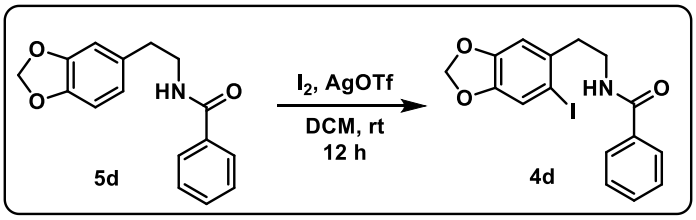
i) Synthesis of amide 5d:



The solution of amine **6a** (0.5 g; 3.03 mmol) and Na_2CO_3 (0.963 g; 9.09 mmol) in DCM (10 mL) and water (10 mL) was stirred for 5 min at room temperature followed by the addition of benzoyl chloride (0.352 mL; 3.03 mmol). The reaction mixture was stirred for 12 h at room temperature

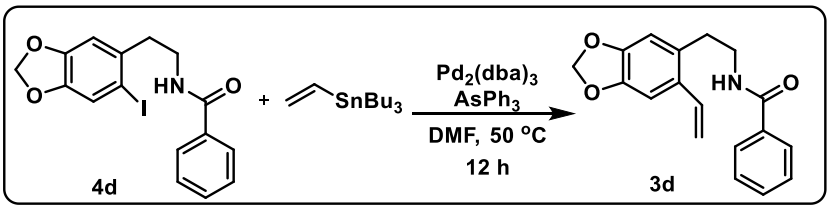
and diluted with DCM (50 mL). The DCM layer was washed with aqueous solution of sodium carbonate and brine. It was then dried over anhydrous Na_2SO_4, evaporated under *vacuo* and the crude product was purified by column chromatography to afford an amide **5d** (0.424 g; 52% yield) as a colorless solid. R*f*: 0.5 (1:2 EtOAc:Pet. ether); mp 113-116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.78 (t, J = 6.8 Hz, 2H), 3.59 (q, J = 6.8 Hz, 2H), 5.87 (s, 2H), 6.11 (bs, 1H), 6.60 (dd, J = 7.8, 1.5 Hz, 1H), 6.67 (d, J = 1.2 Hz, 1H), 6.69 (d, J = 7.8 Hz, 1H), 7.29-7.37 (m, 2H), 7.38-7.44 (m, 1H), 7.59-7.65 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.4, 41.2, 100.9, 108.4, 109.1, 121.7, 126.8, 128.6, 131.4, 132.6, 134.6, 146.2, 147.9, 167.5; HRMS-ESI (m/z) calcd $(C_{16}H_{15}NO_3 + H)^+$: 270.1125, found: 270.1102.

ii) Synthesis of iodo-amide 4d:



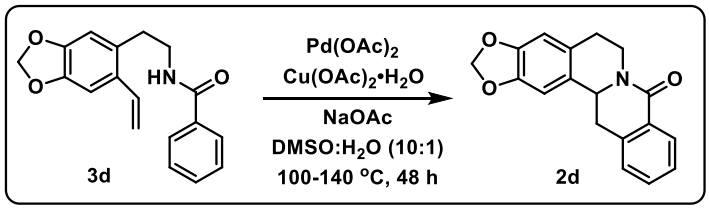
The iodo-amide **4d** was prepared from amide **5d** (0.404 g, 1.5 mmol) according to same procedure as used in the synthesis of iodo-amide **4a** to furnish the title compound **4d** (0.474 g, 80% yield) as a colorless solid. R*f*: 0.5 (3:7 EtOAc:Pet. ether); mp 128-132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.93 (t, J = 6.8 Hz, 2H), 3.59 (q, J = 6.8 Hz, 2H), 5.88 (s, 2H), 6.22 (bs, 1H), 6.72 (s, 1H), 7.17 (s, 1H), 7.31-7.39 (m, 2H), 7.40-7.46 (m, 1H), 7.65-7.72 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.0, 40.3, 87.9, 101.6, 109.8, 118.7, 126.9, 128.6, 131.5, 134.5, 134.8, 147.3, 148.7, 167.6; HRMS-ESI (m/z) calcd $(C_{16}H_{14}NIO_3 + H)^+$: 396.0091, found: 396.0058.

iii) Synthesis of vinyl-amide 3d:



The vinyl-amide **3d** was prepared from iodo-amide **4d** (0.395 g, 1 mmol) according to the same procedure as used in the synthesis of vinyl-amide **3a** to obtain the title compound **3d** (0.266 g, 90% yield) as colorless solid. R*f*: 0.5 (3:7 EtOAc:Pet. ether) mp 124-126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.87 (t, J = 6.8 Hz, 2H), 3.54 (q, J = 6.8 Hz, 2H), 5.14 (d, J = 11 Hz, 1H), 5.46 (d, J = 17.4 Hz, 1H), 5.87 (s, 2H), 6.15 (bs, 1H), 6.60 (s, 1H), 6.90 (dd, J = 11, 17.4 Hz 1H), 6.95 (s, 1H), 7.30-7.37 (m, 2H), 7.38-7.44 (m, 1H), 7.60-7.67 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.7, 41.1, 101.0, 105.6, 109.8, 114.5, 126.8, 128.5, 130.3, 130.5, 131.4, 133.6, 134.5, 146.8, 147.5, 167.6; HRMS-ESI (m/z) calcd $(C_{18}H_{17}NO_3 + H)^+$: 296.1281, found: 296.1259.

iv) Attempted Synthesis of (±)-Gusanlung D (2d):



For the synthesis of (±)-Gusanlung D (**2d**), the vinyl-amide **3d** (15 mg, 0.05 mmol) was subjected to a standard procedure used in the synthesis of cyclic-amide **2a**, but only a trace amount of compound was formed [HRMS-ESI (m/z) calcd $(C_{18}H_{15}NO_3 + H)^+$: 294.1125, found: 294.1123] even after heating at 100 °C for 48 h. Most of the starting material **3d** was recovered from reaction mixture (12 mg; 80%). However, heating the reaction mixture at higher temperature (140 °C) resulted in the decomposition of the starting material.

1.9. References:

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1.10. Spectra:

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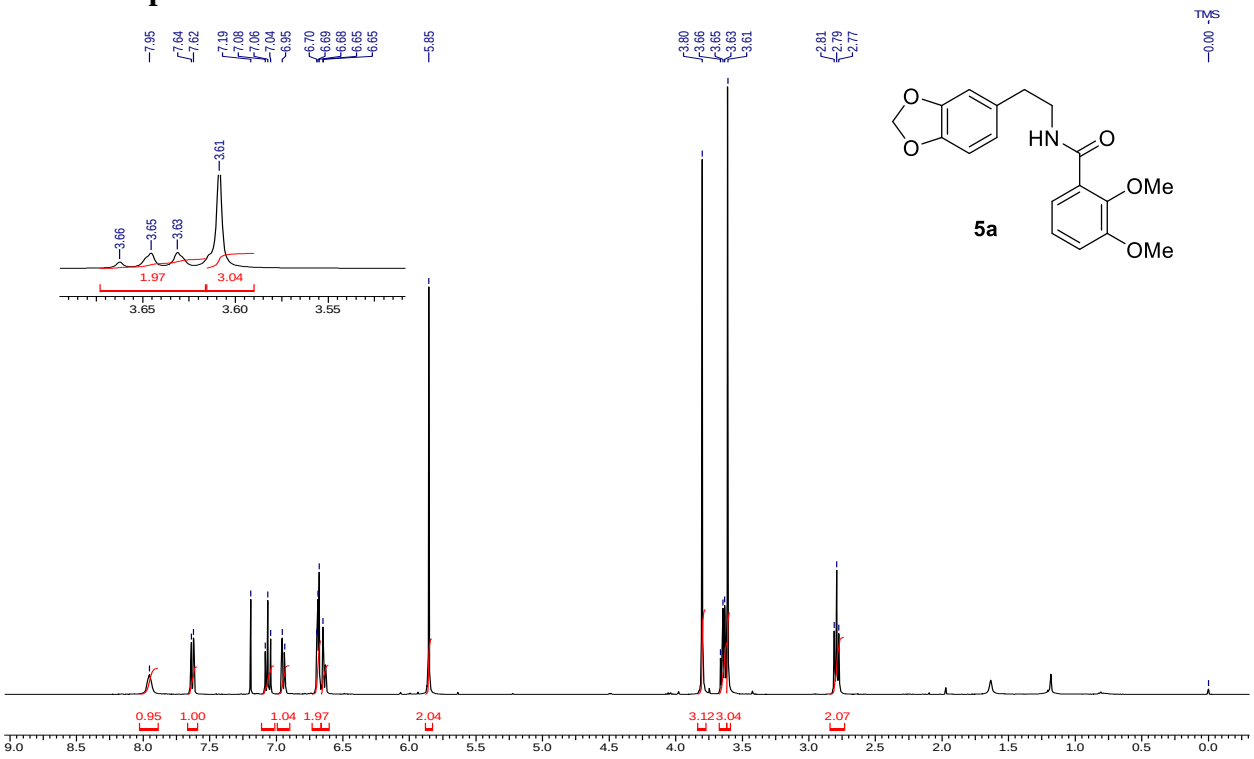

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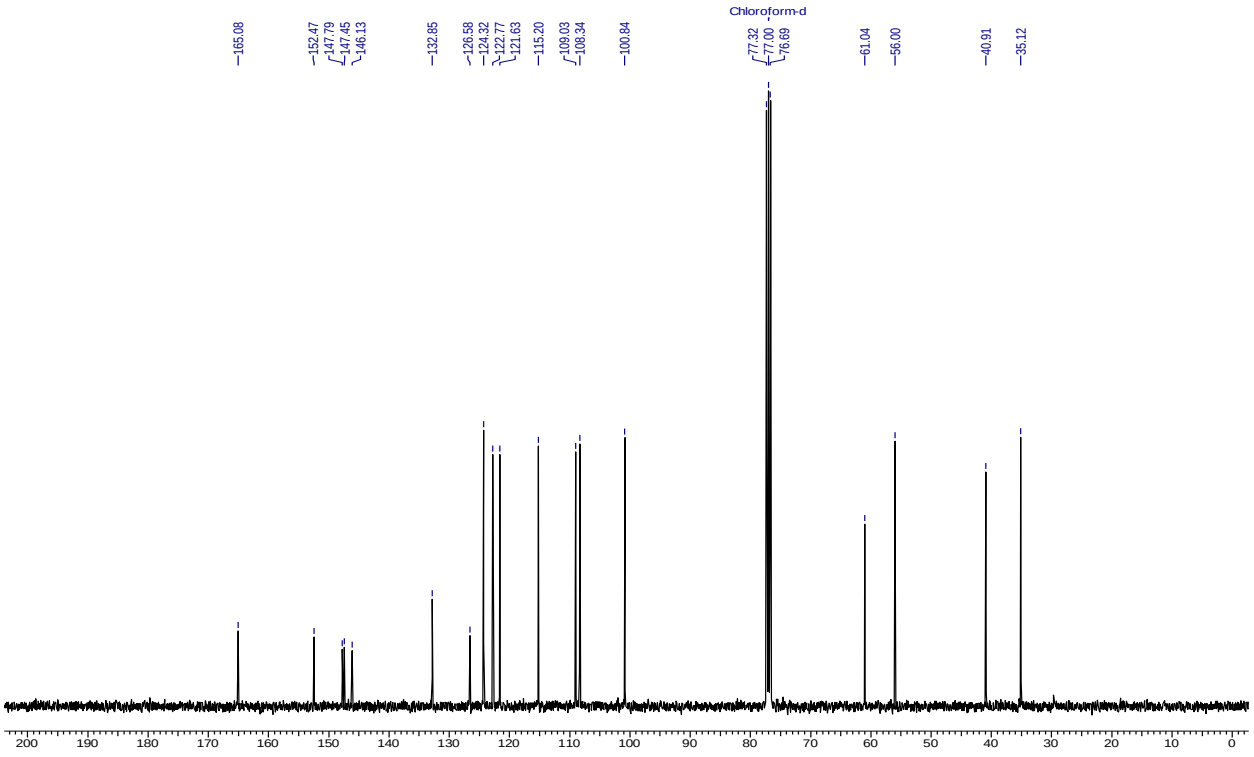

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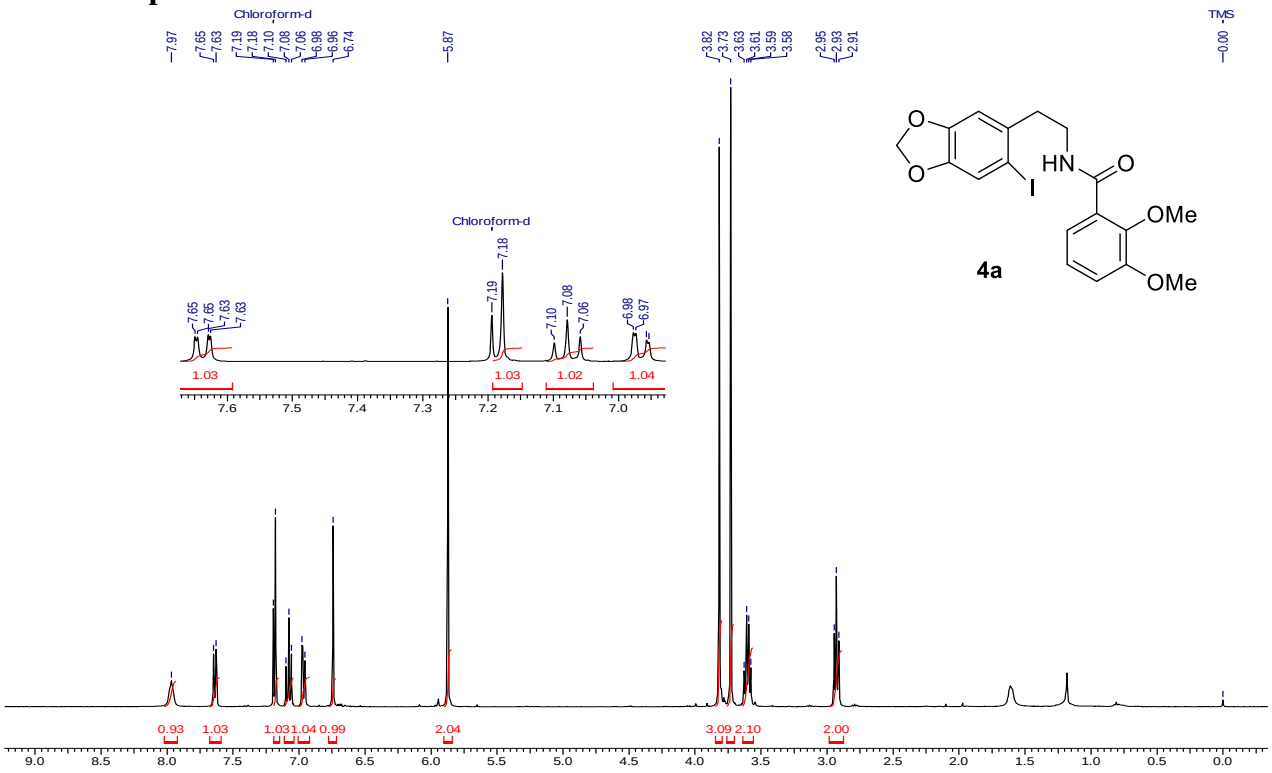

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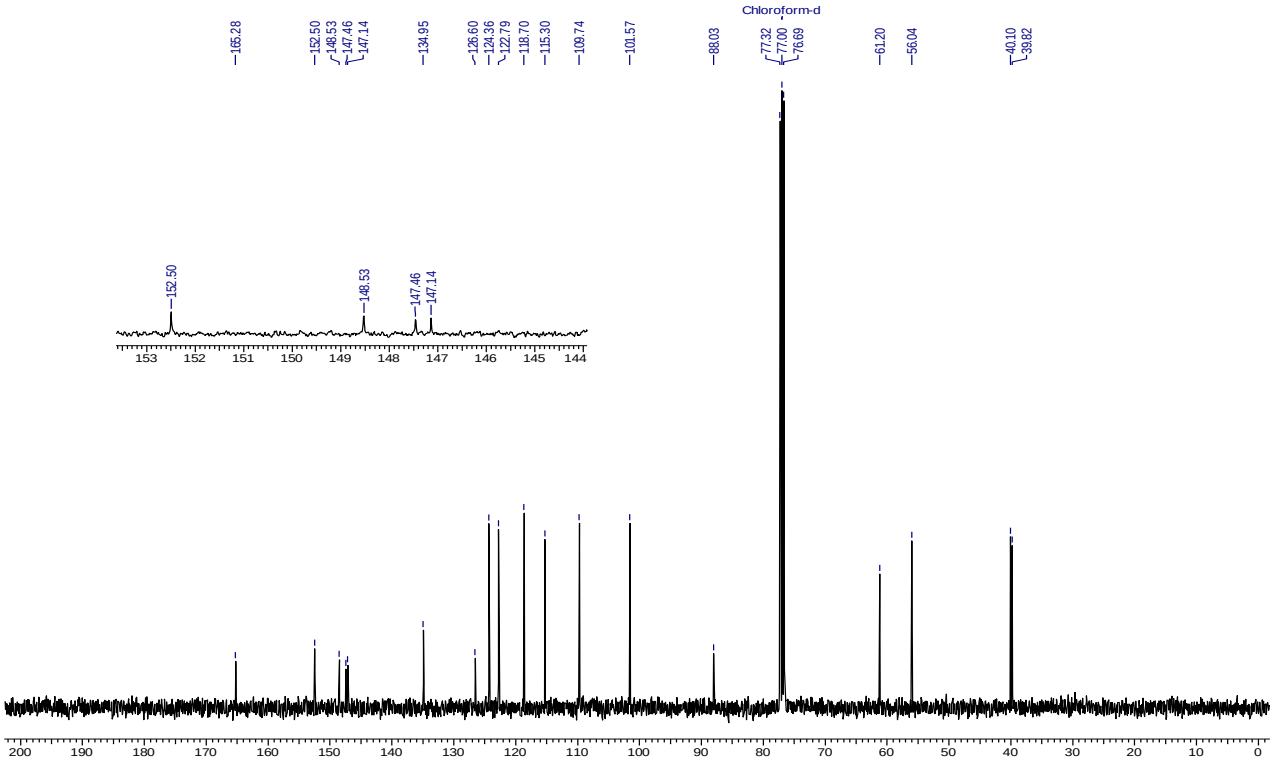

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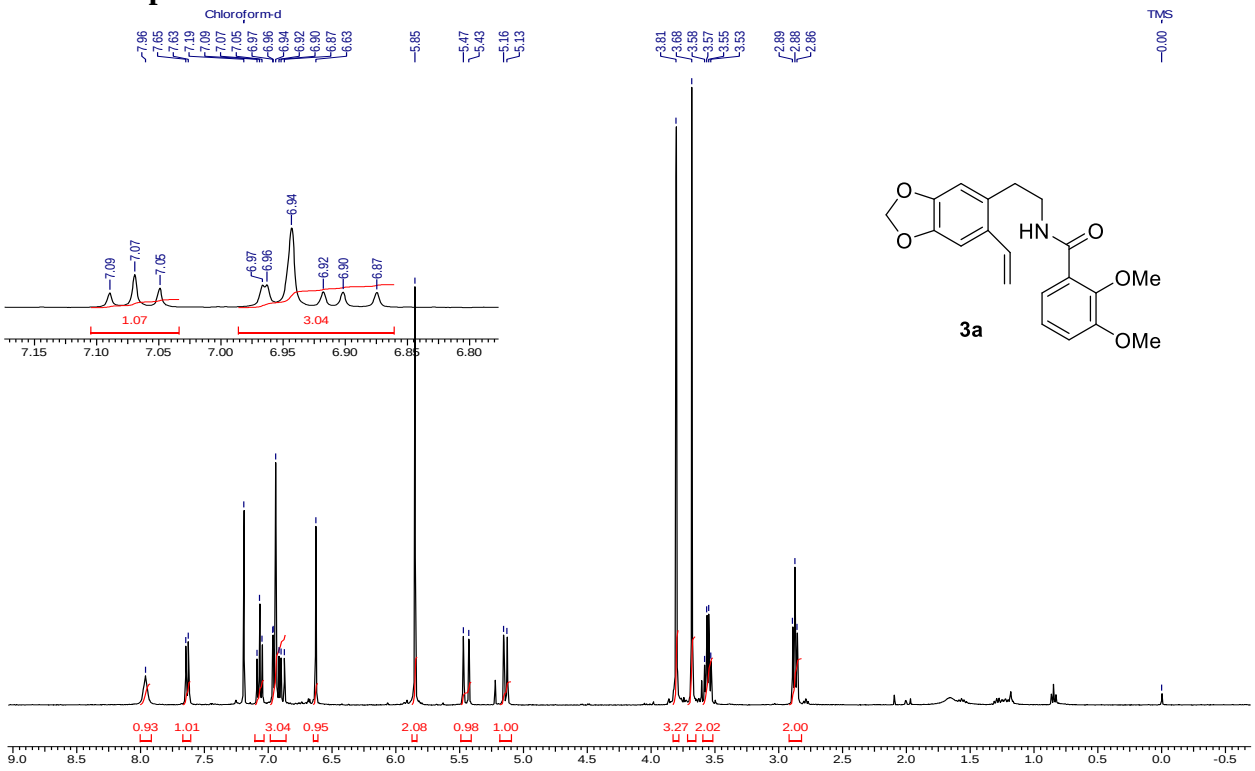

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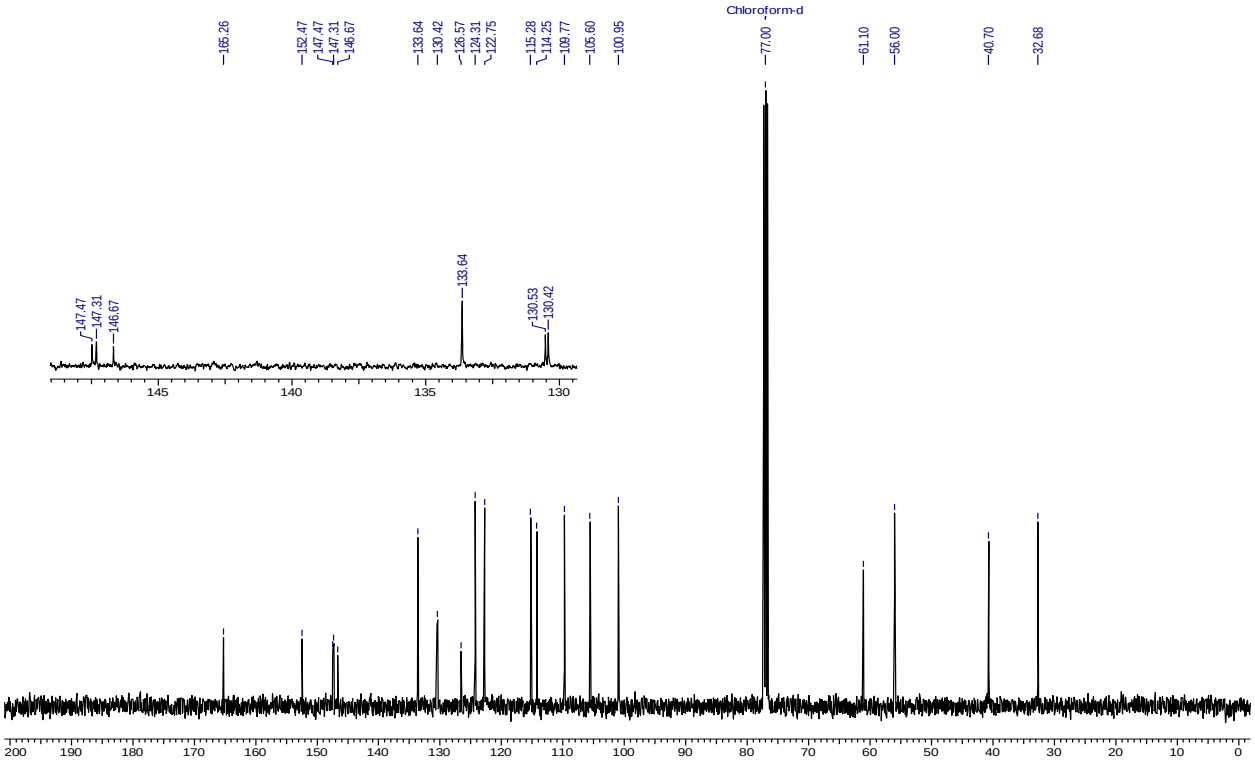

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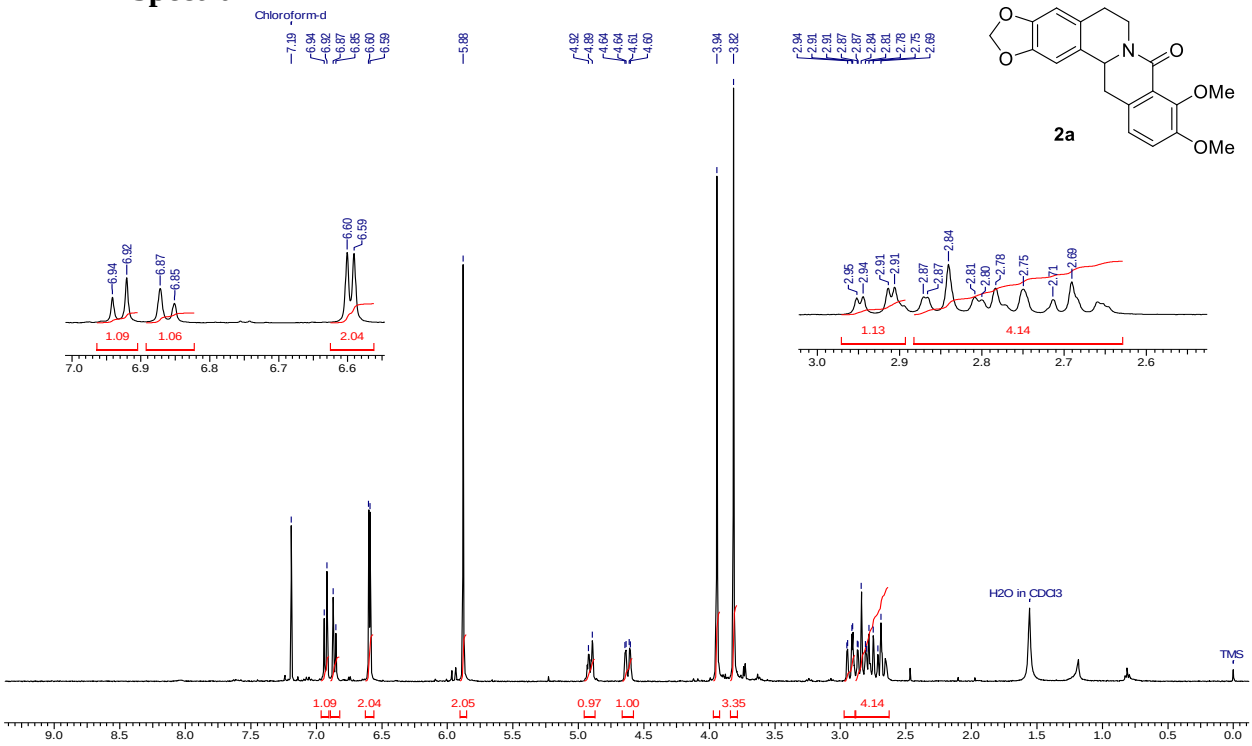

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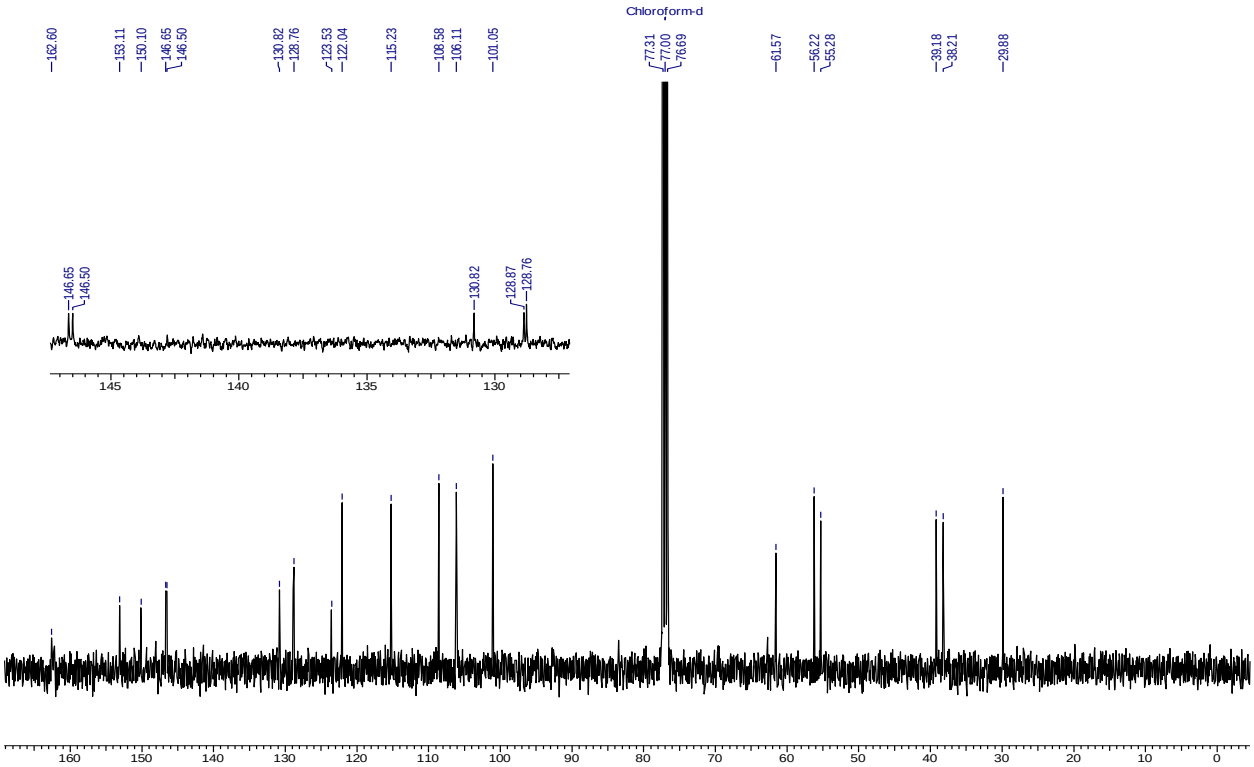

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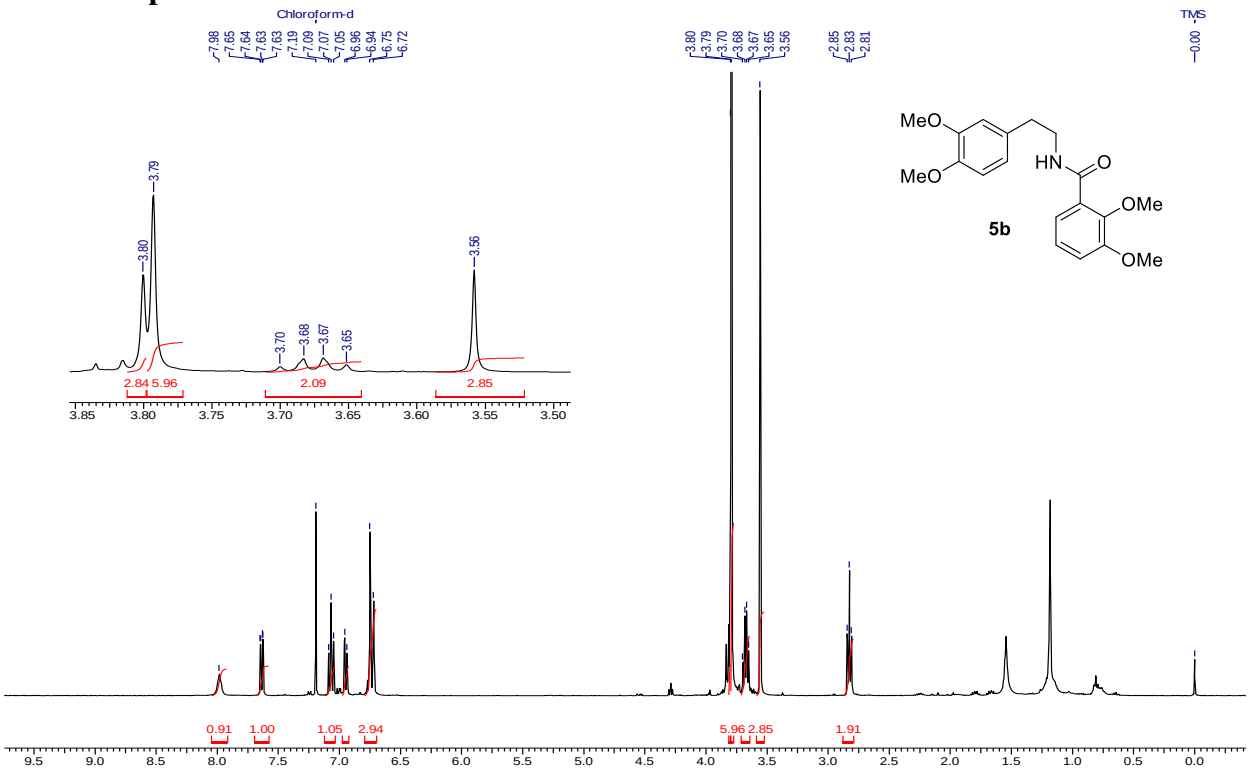

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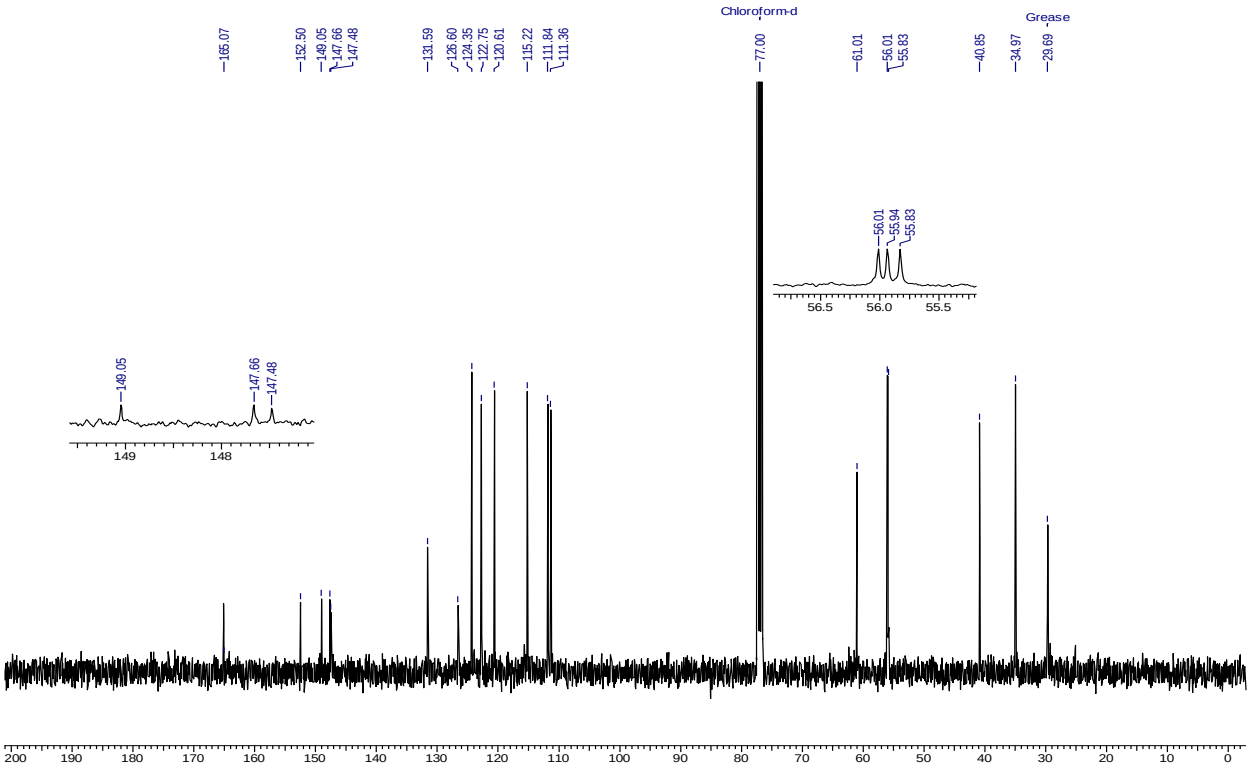

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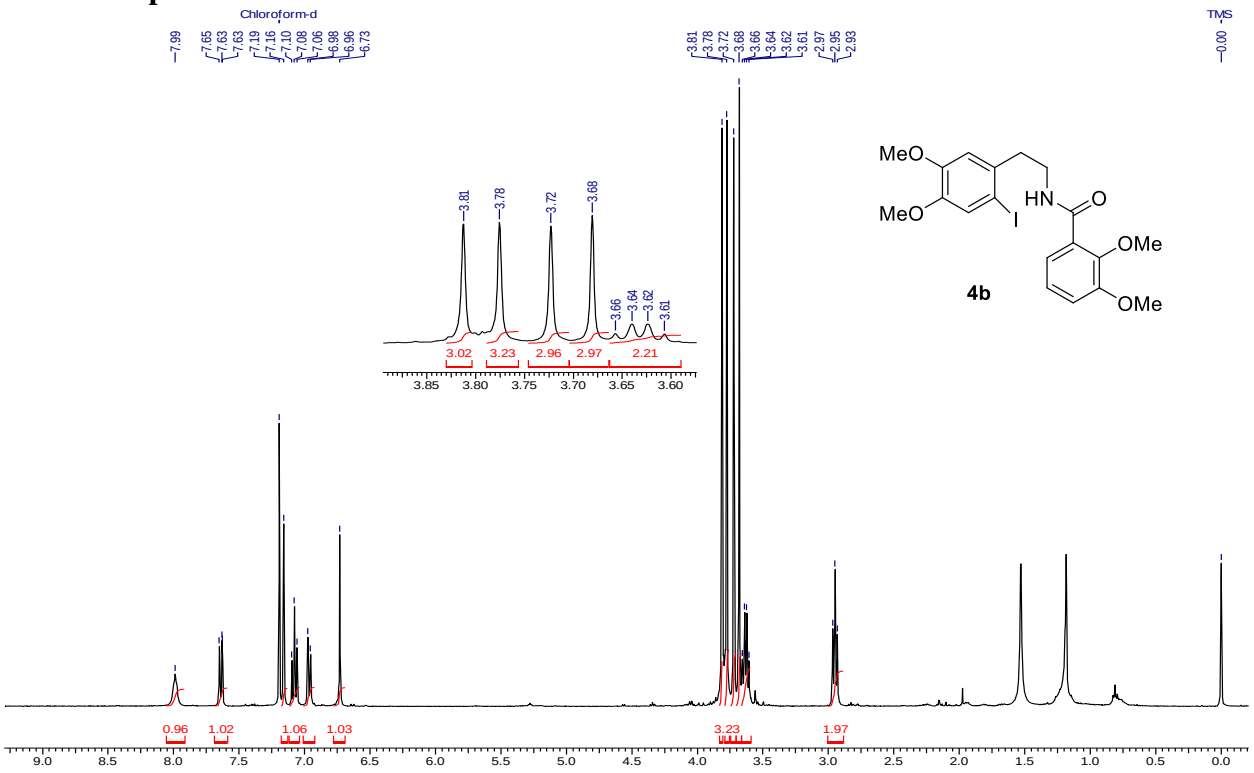

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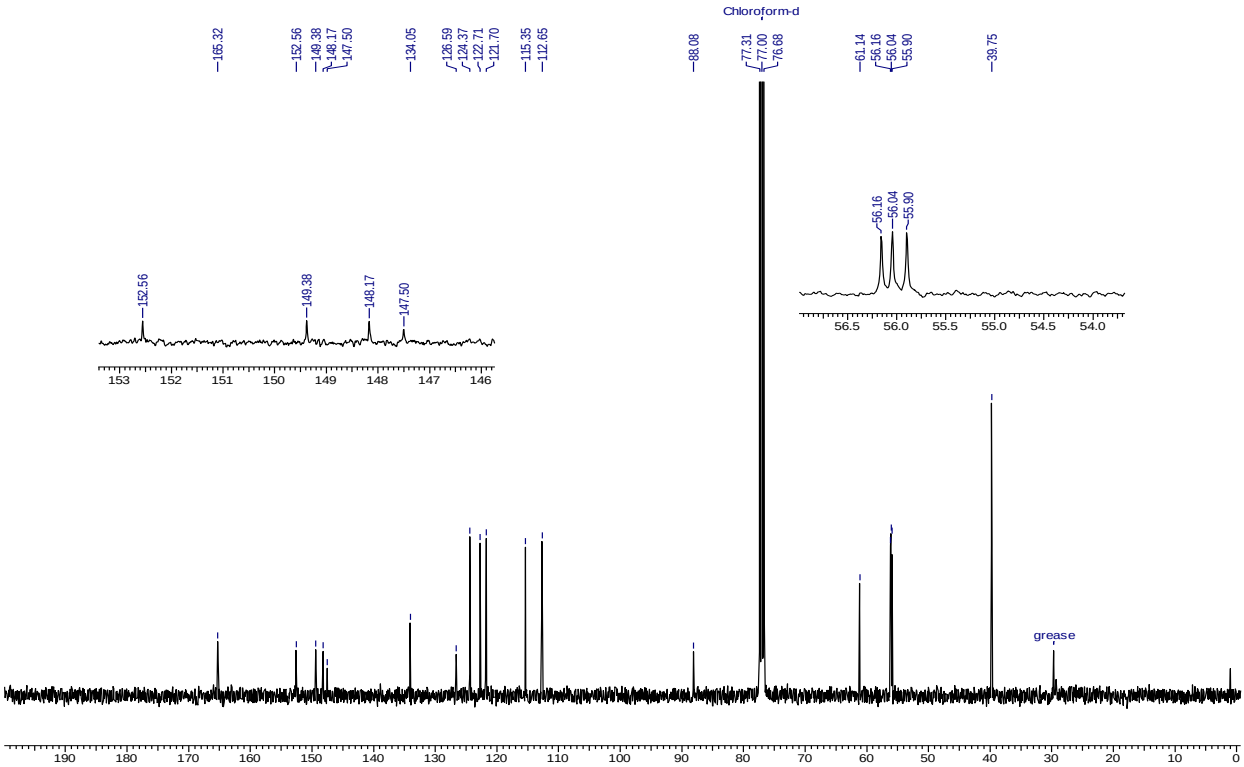

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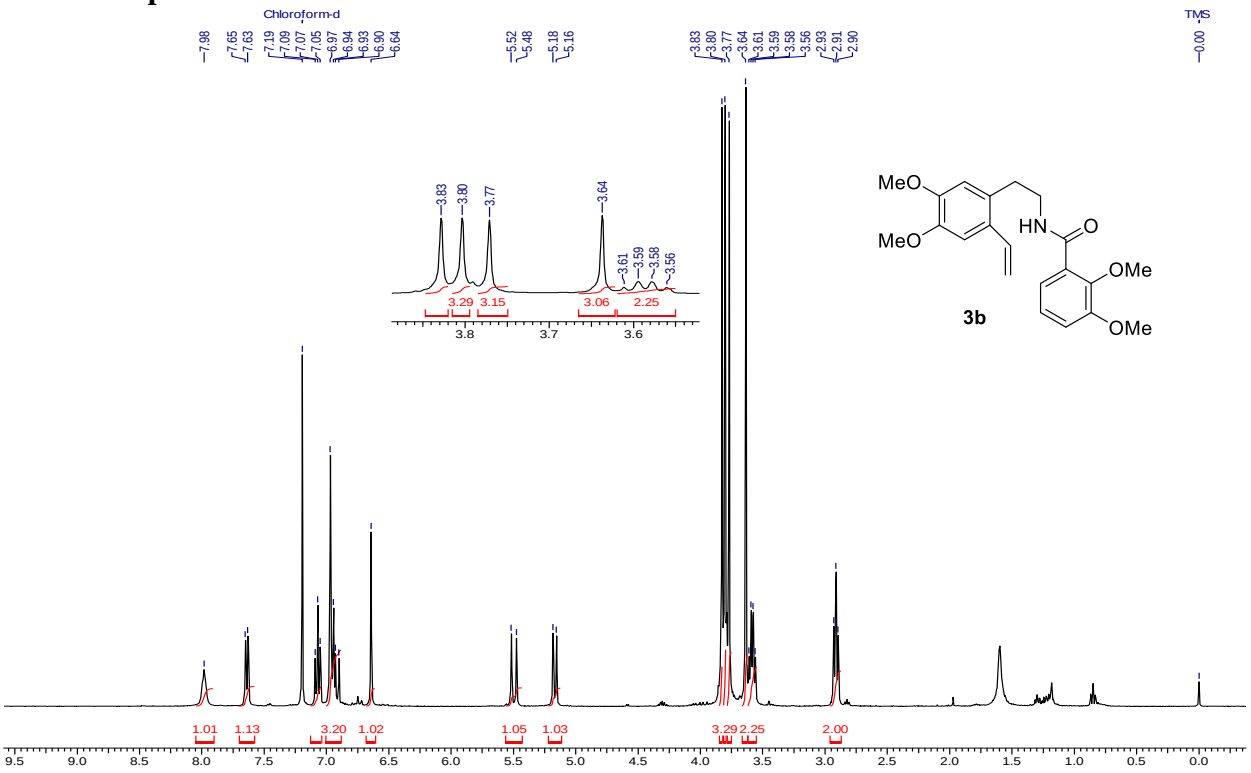

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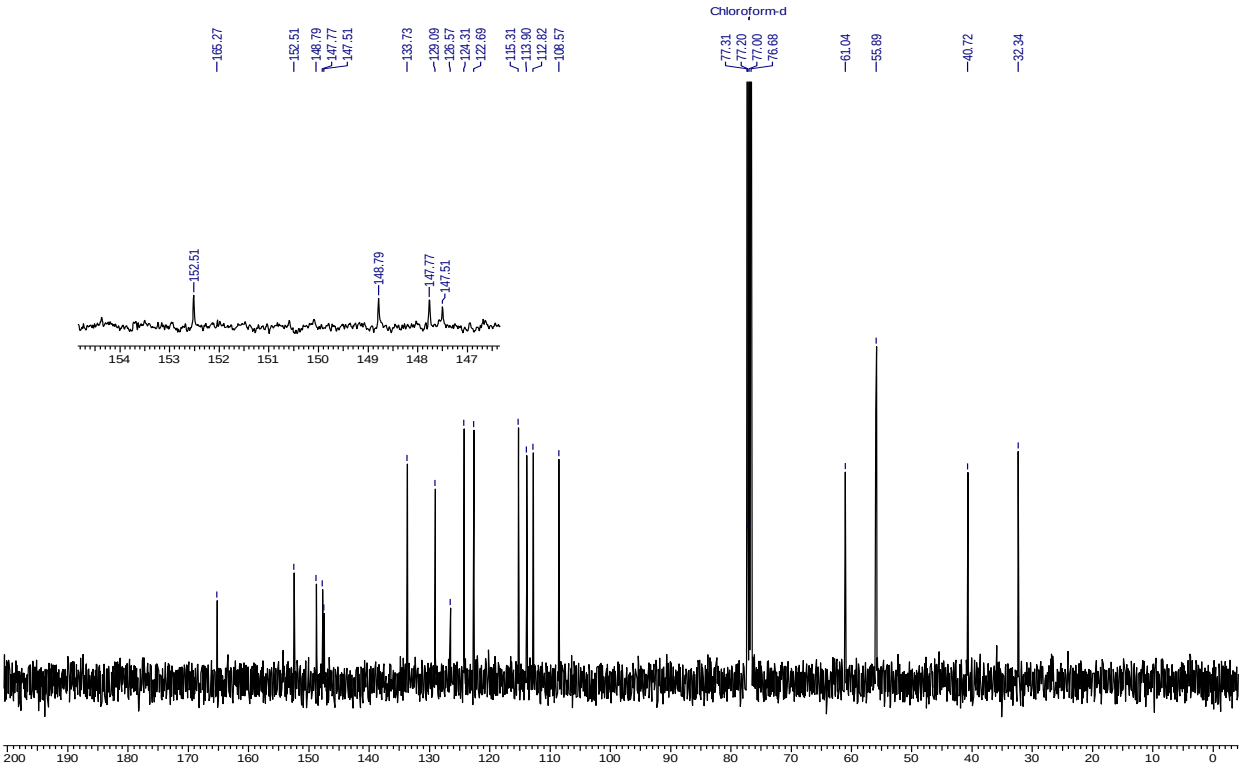

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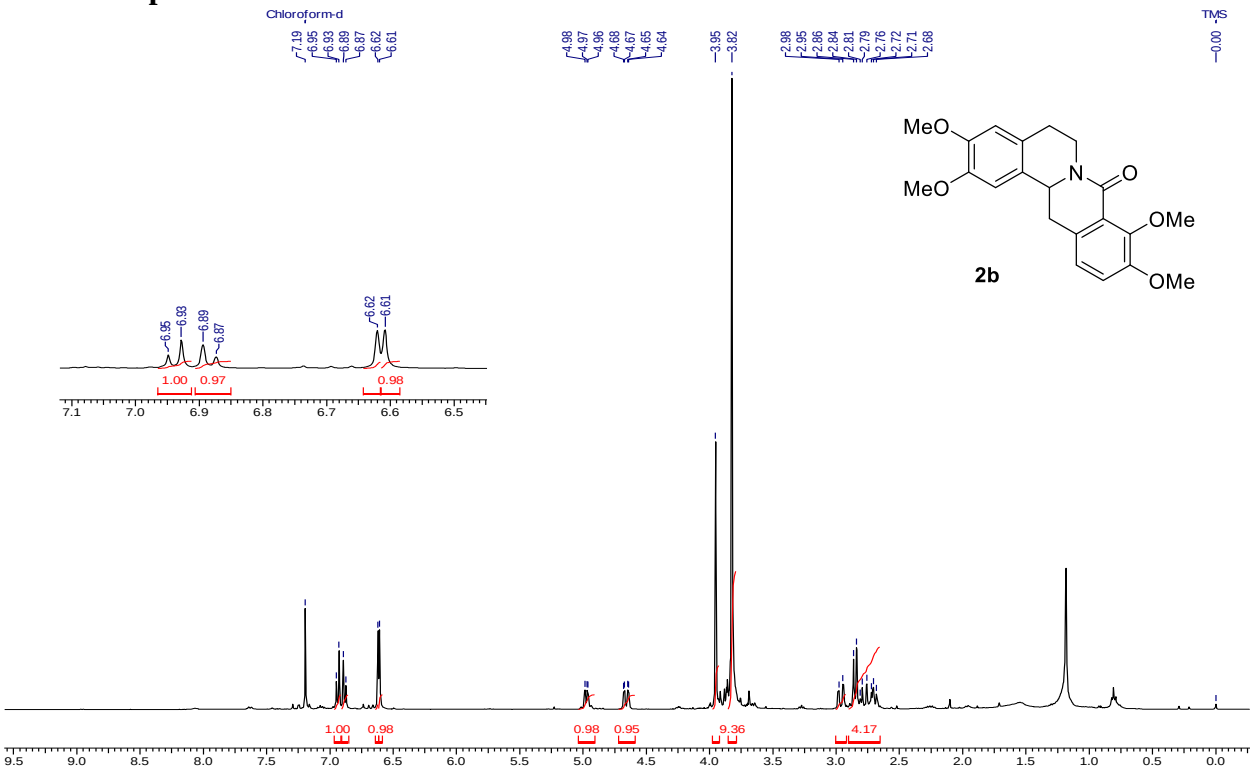

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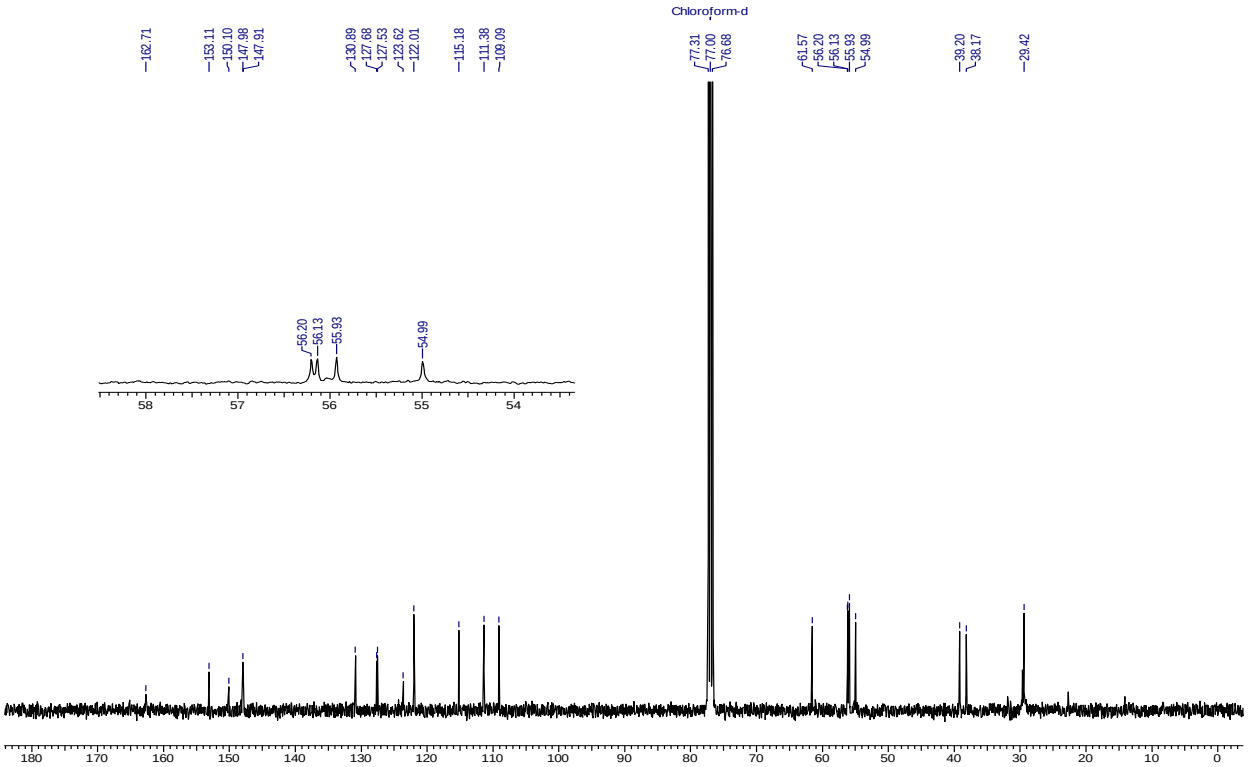

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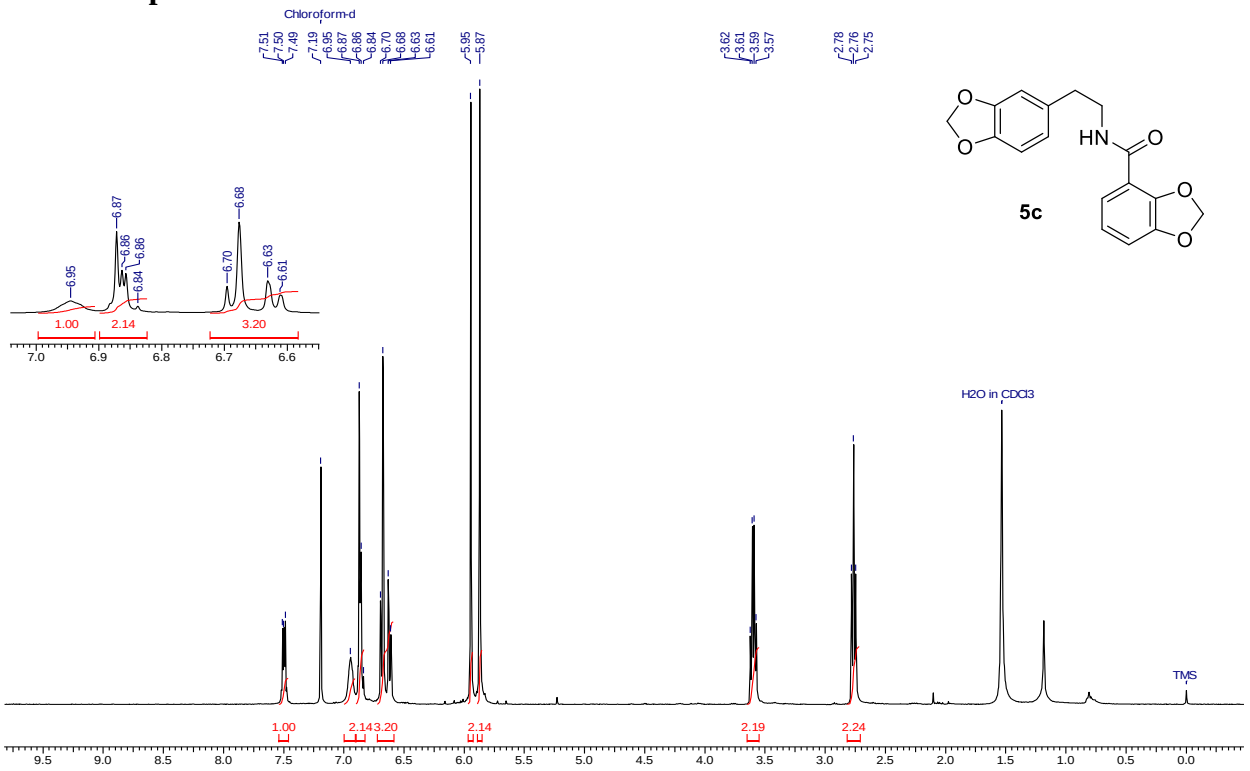

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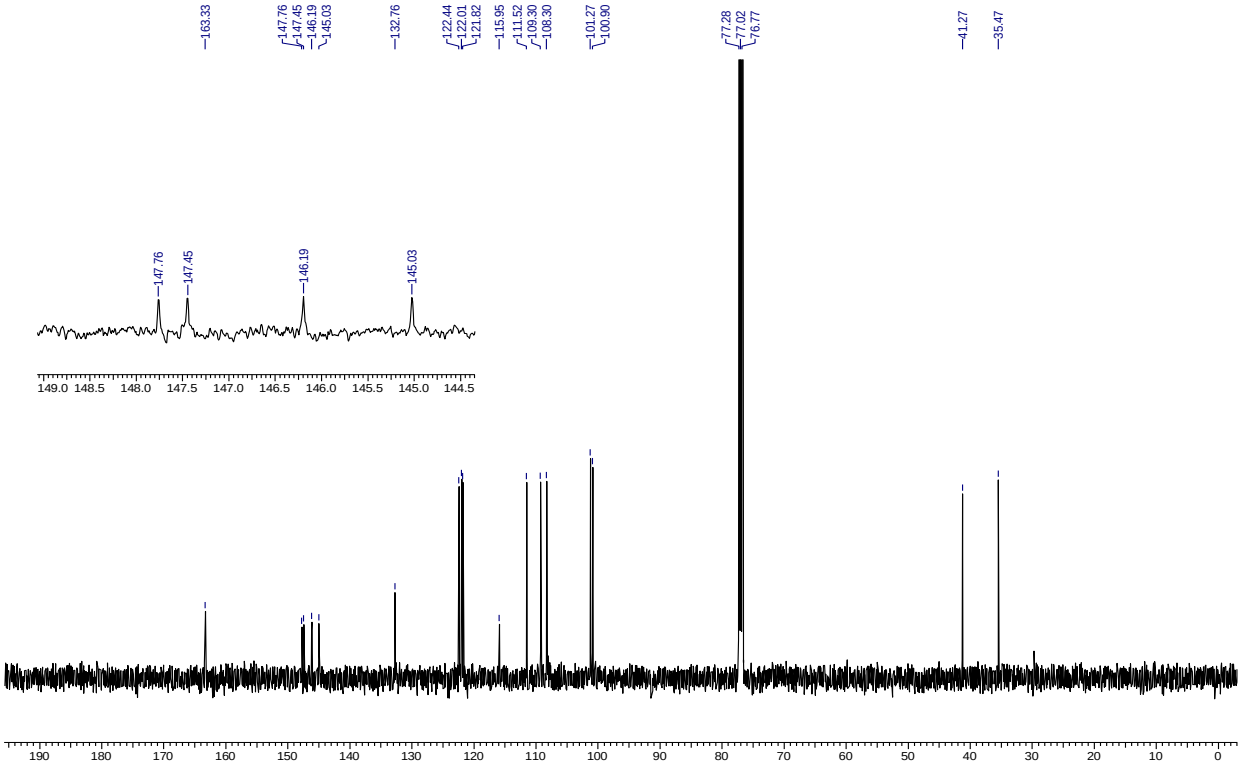

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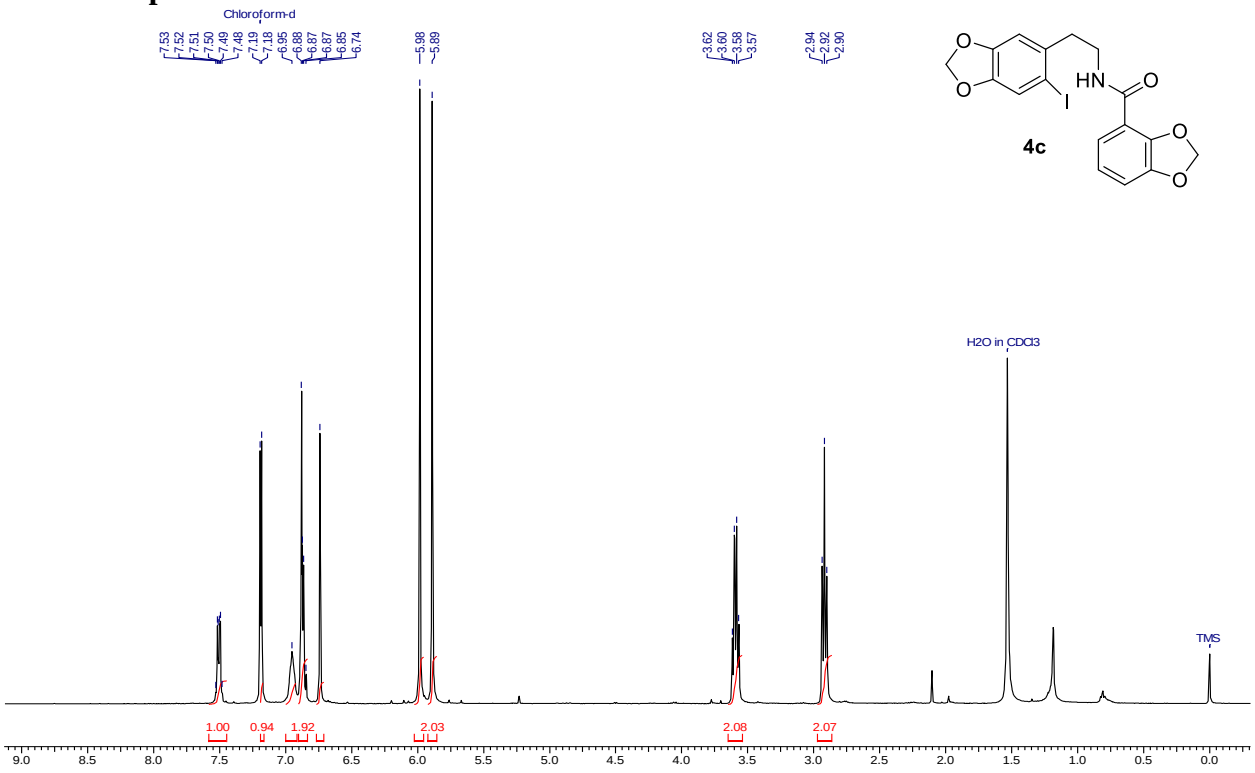

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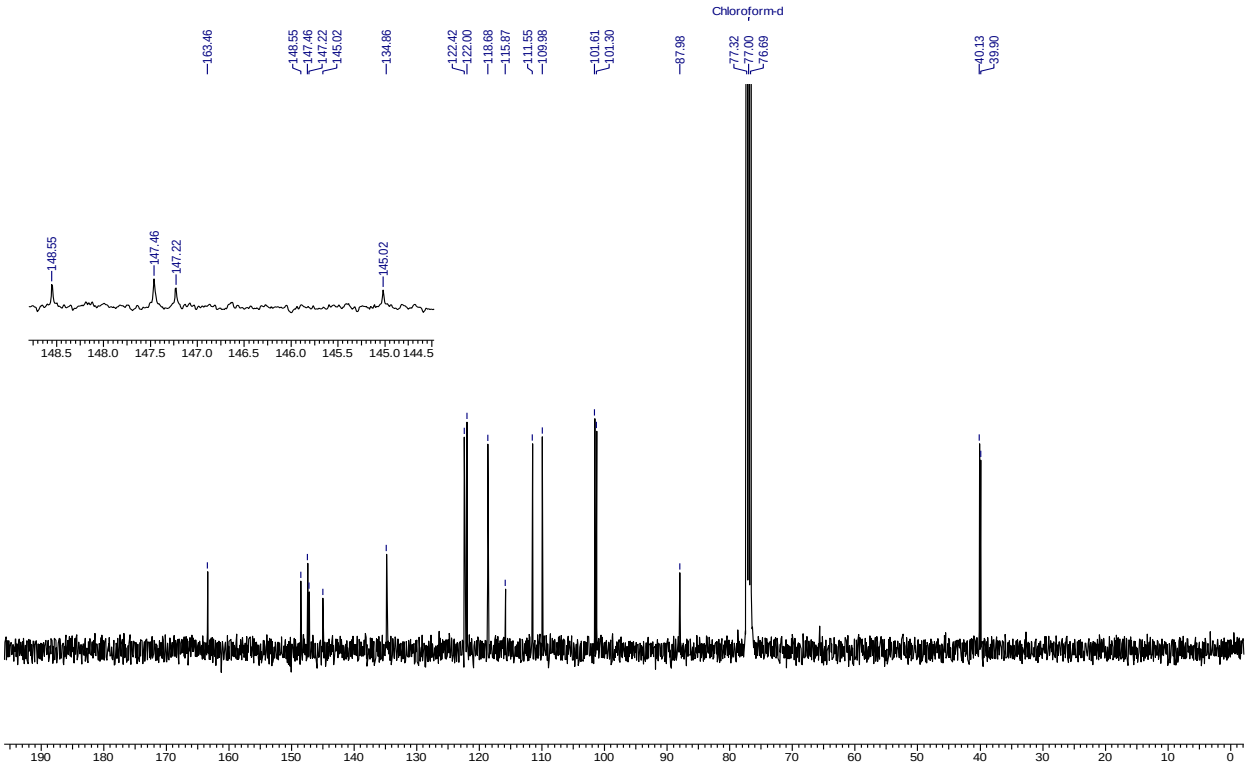

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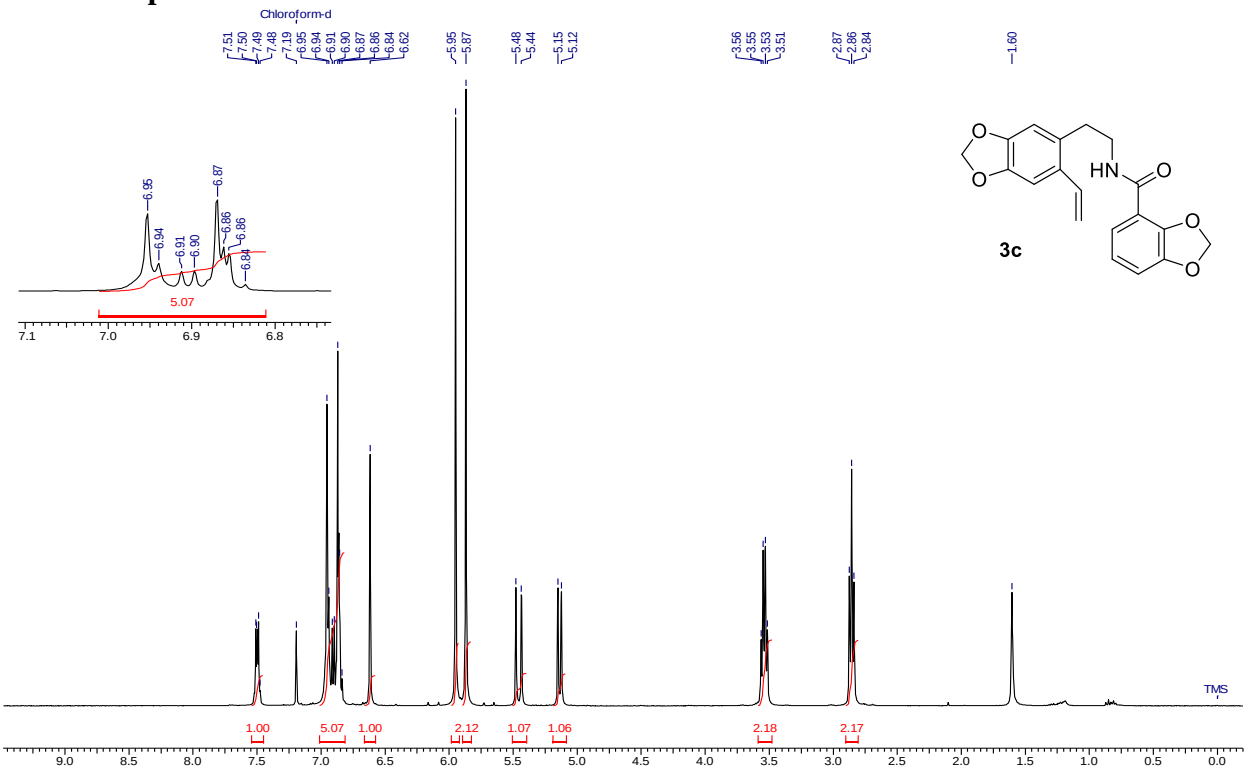

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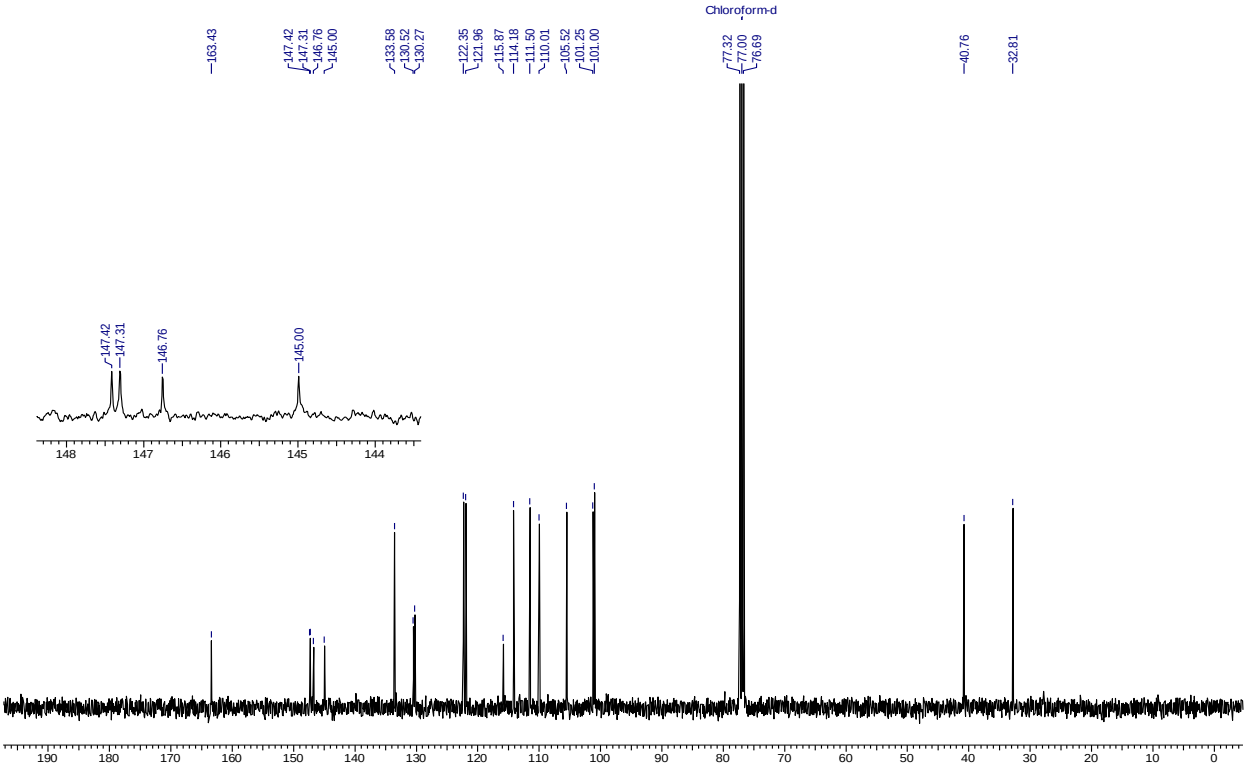

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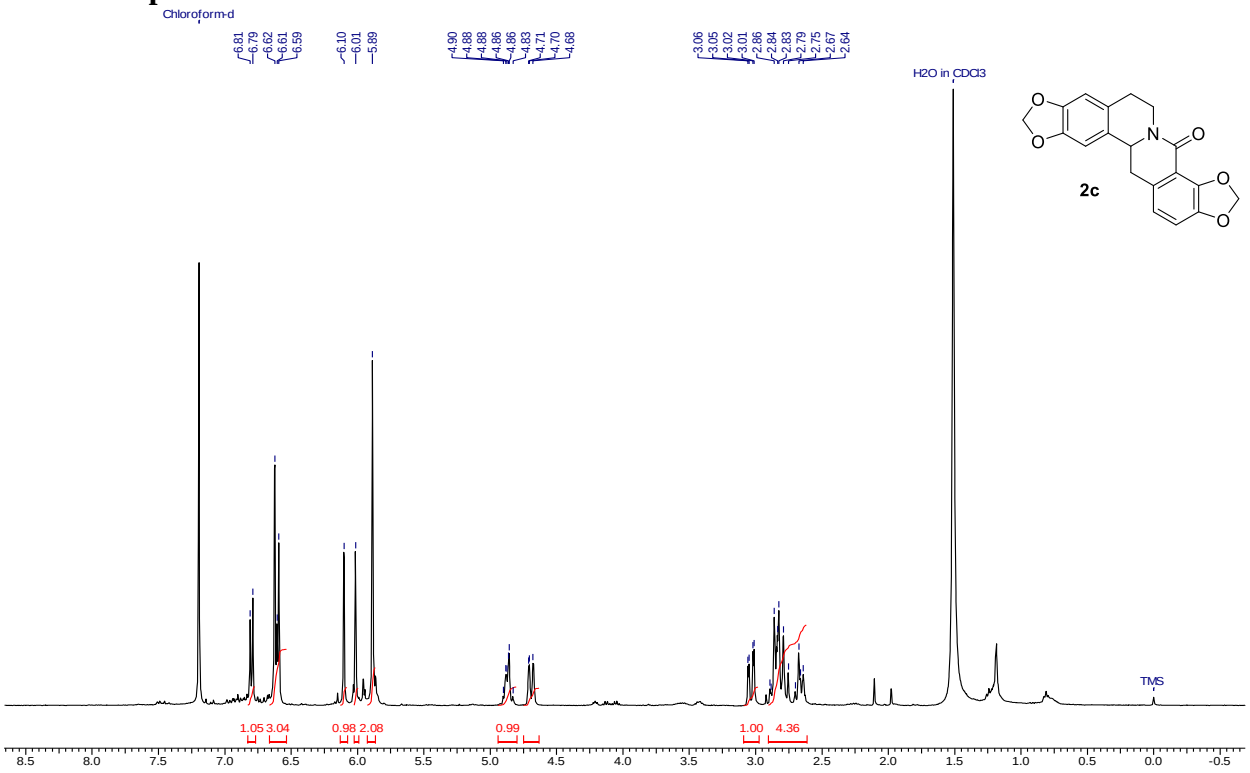

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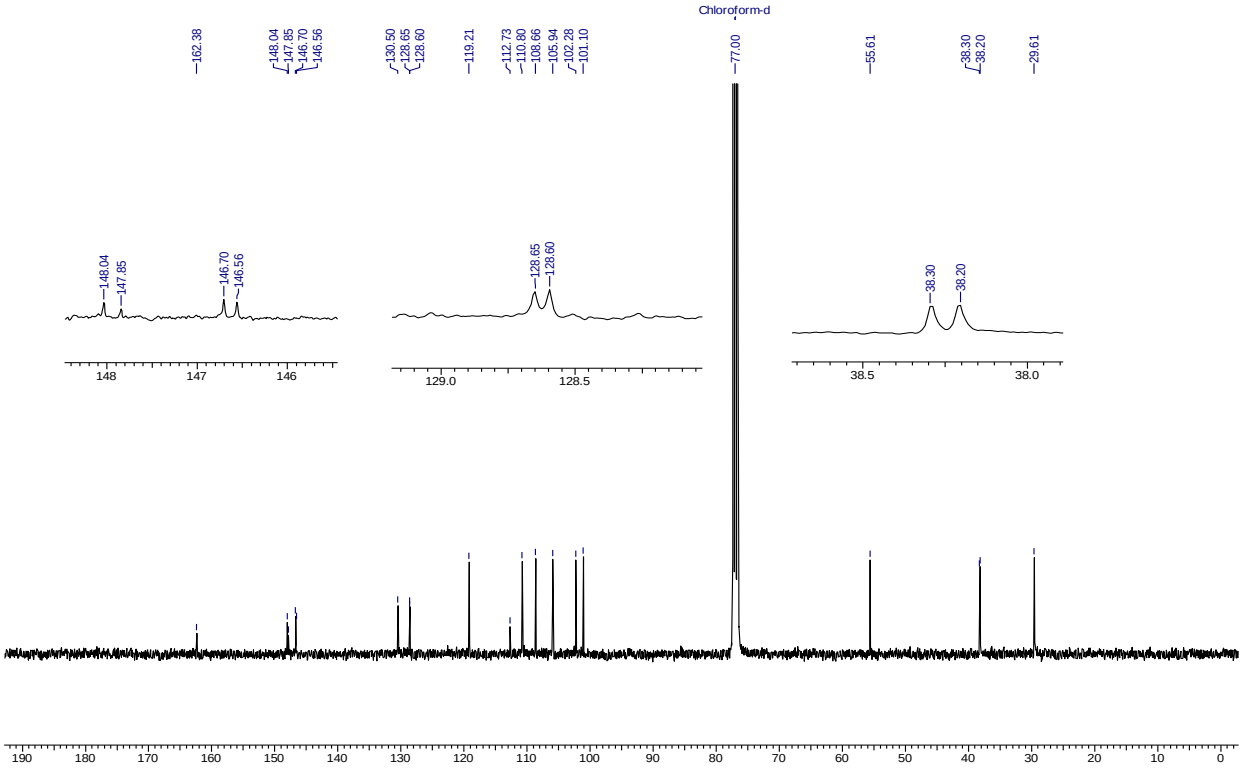

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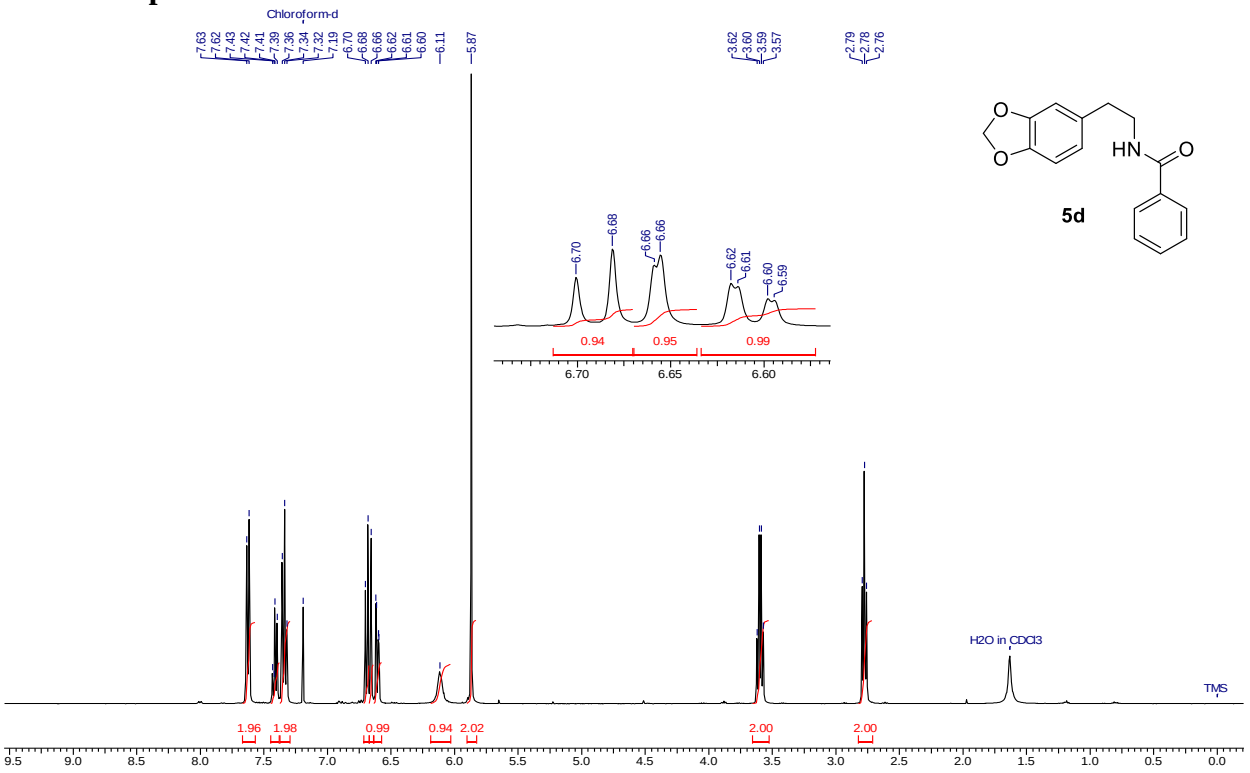

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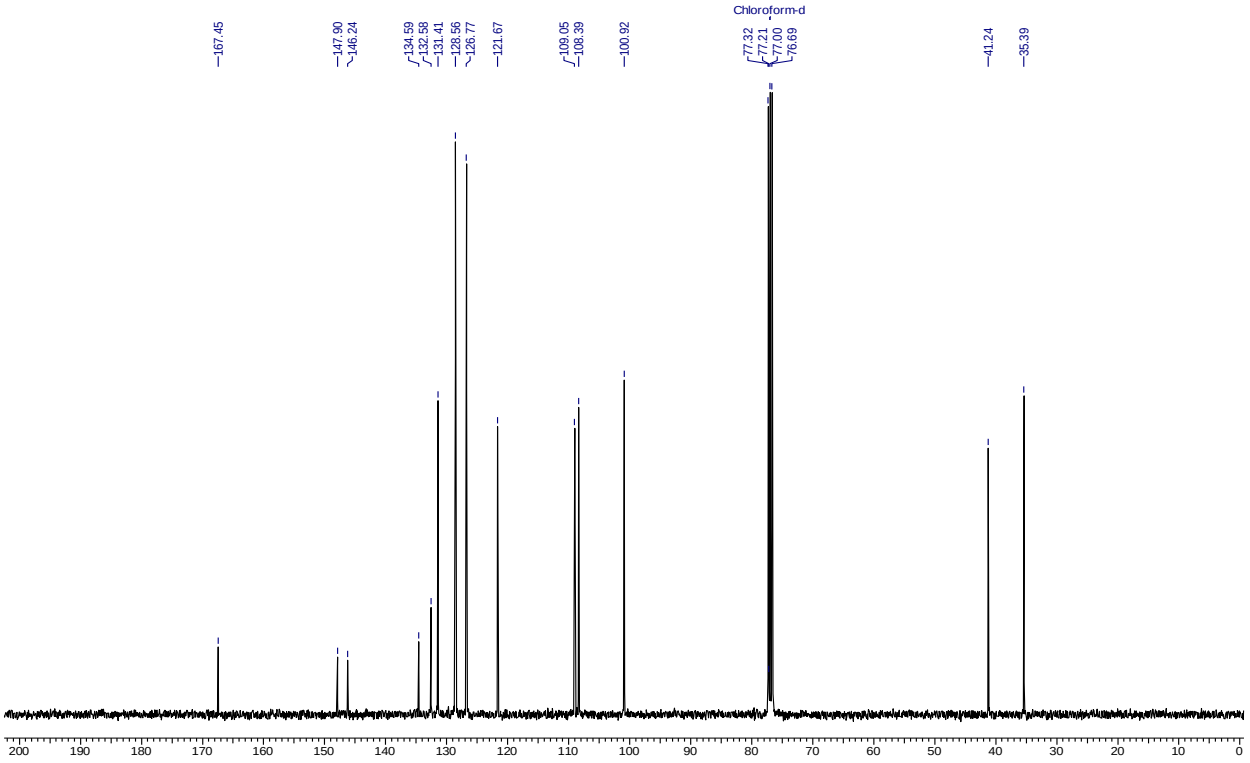

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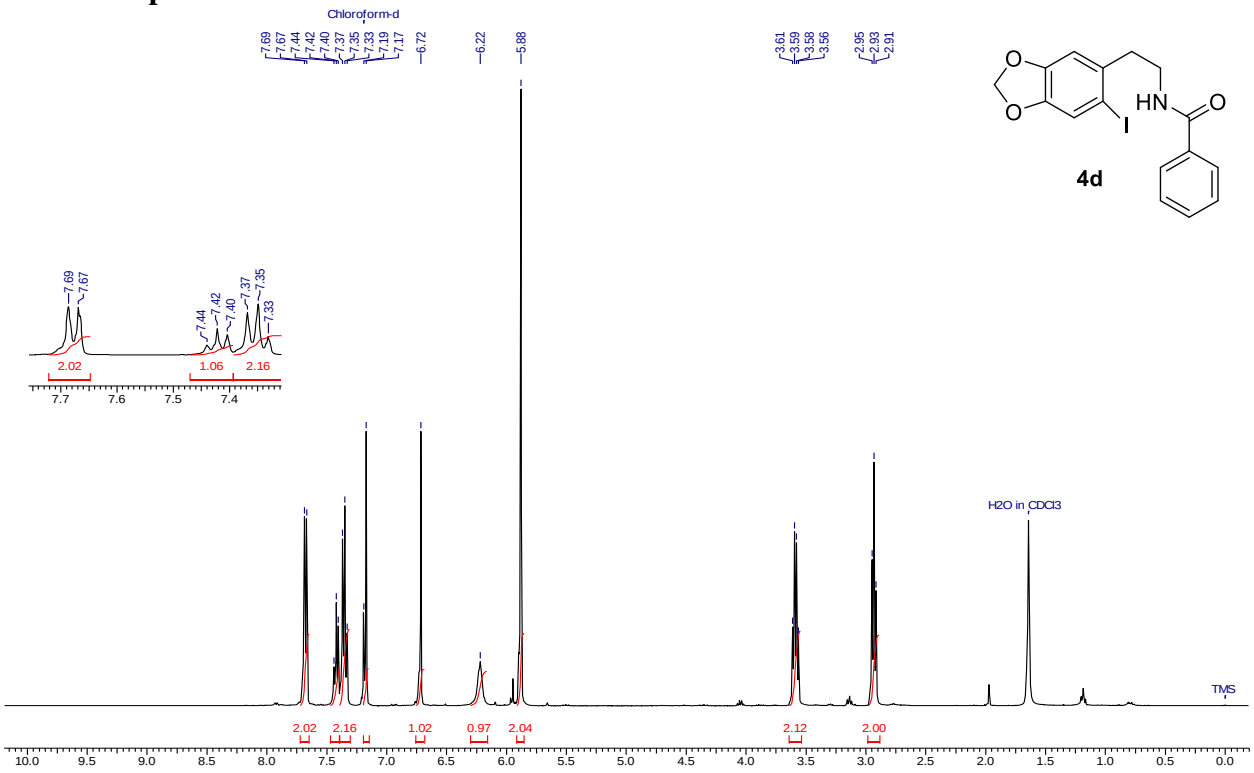

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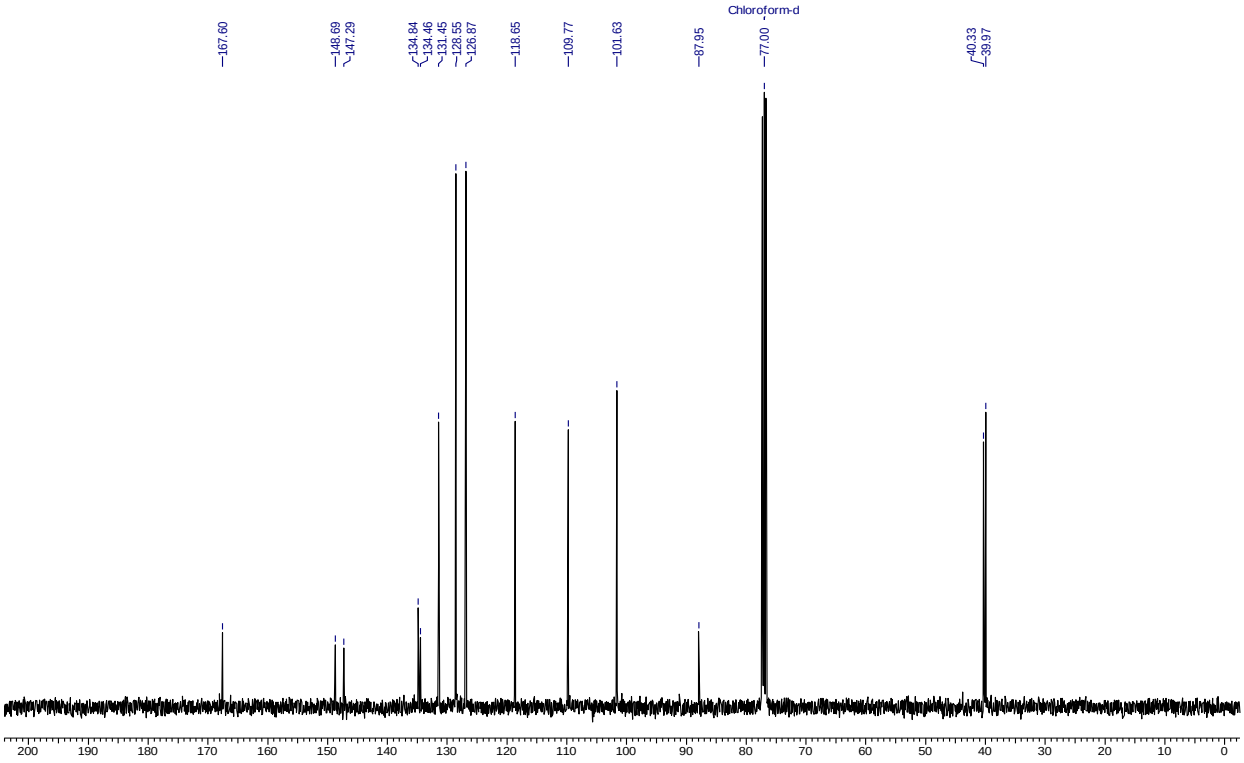

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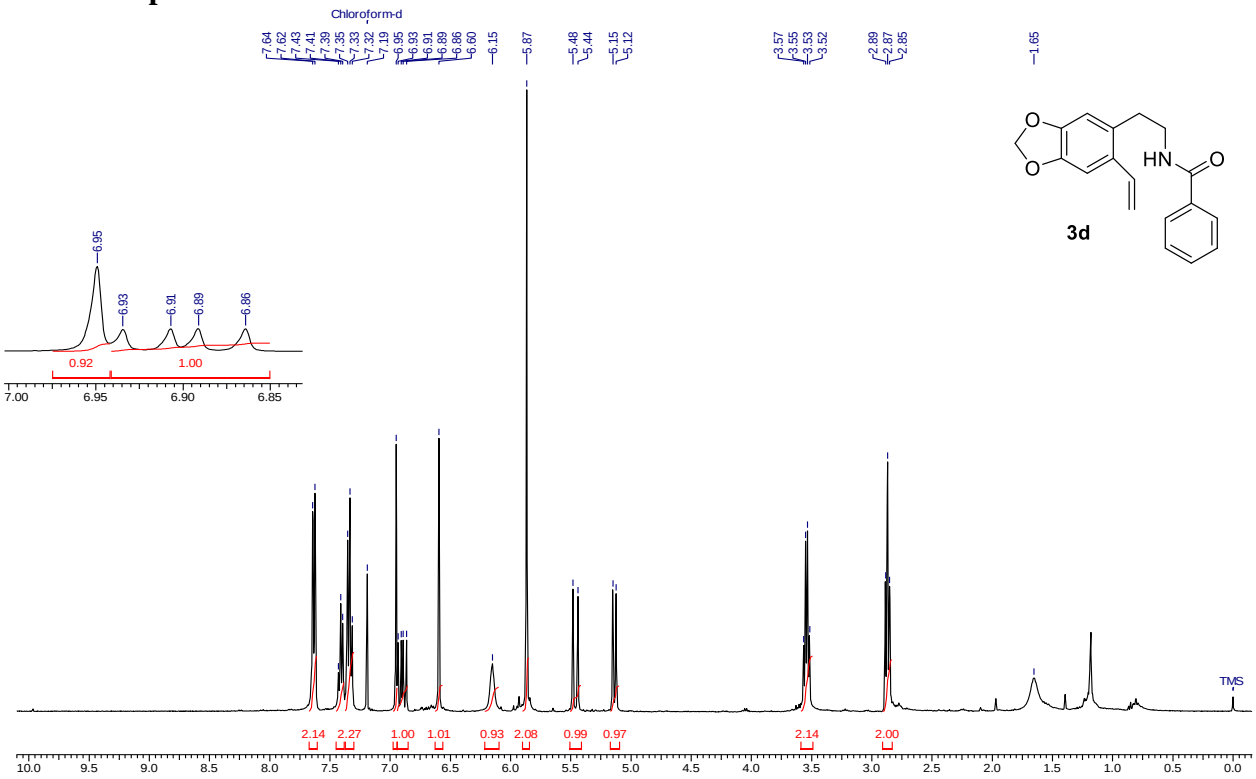

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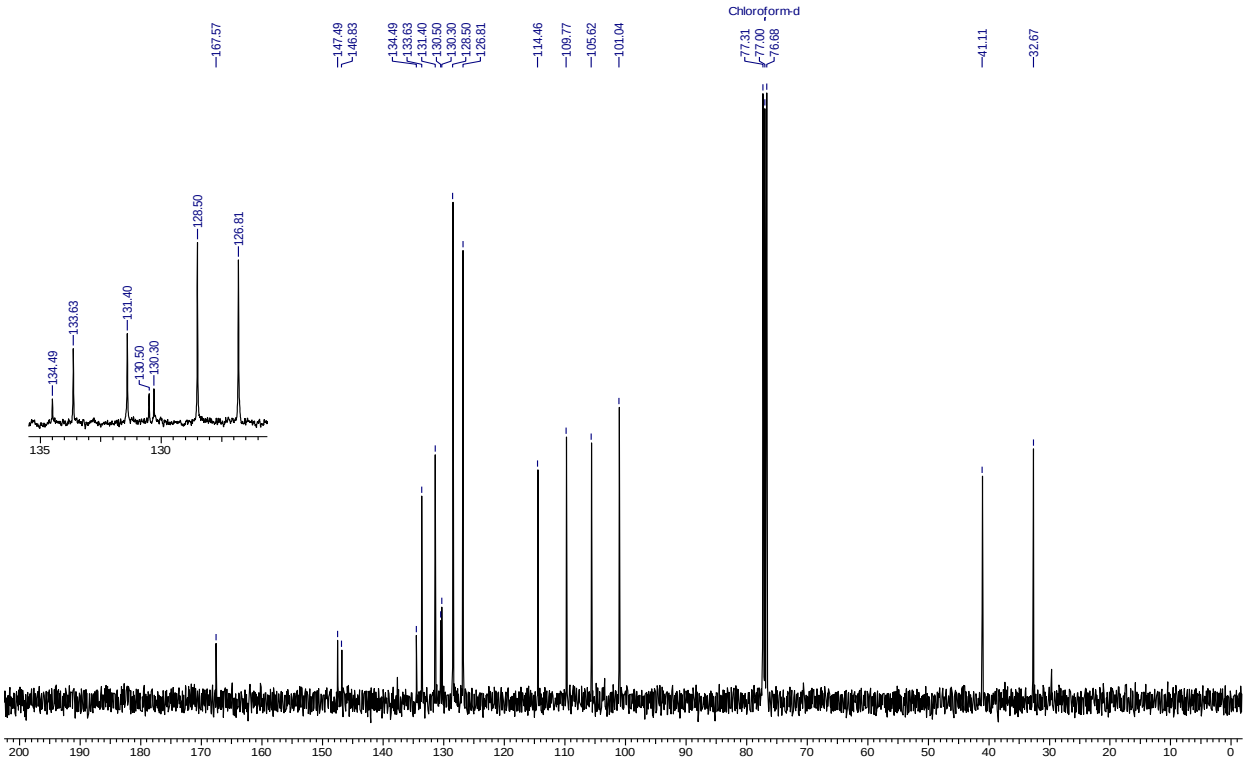

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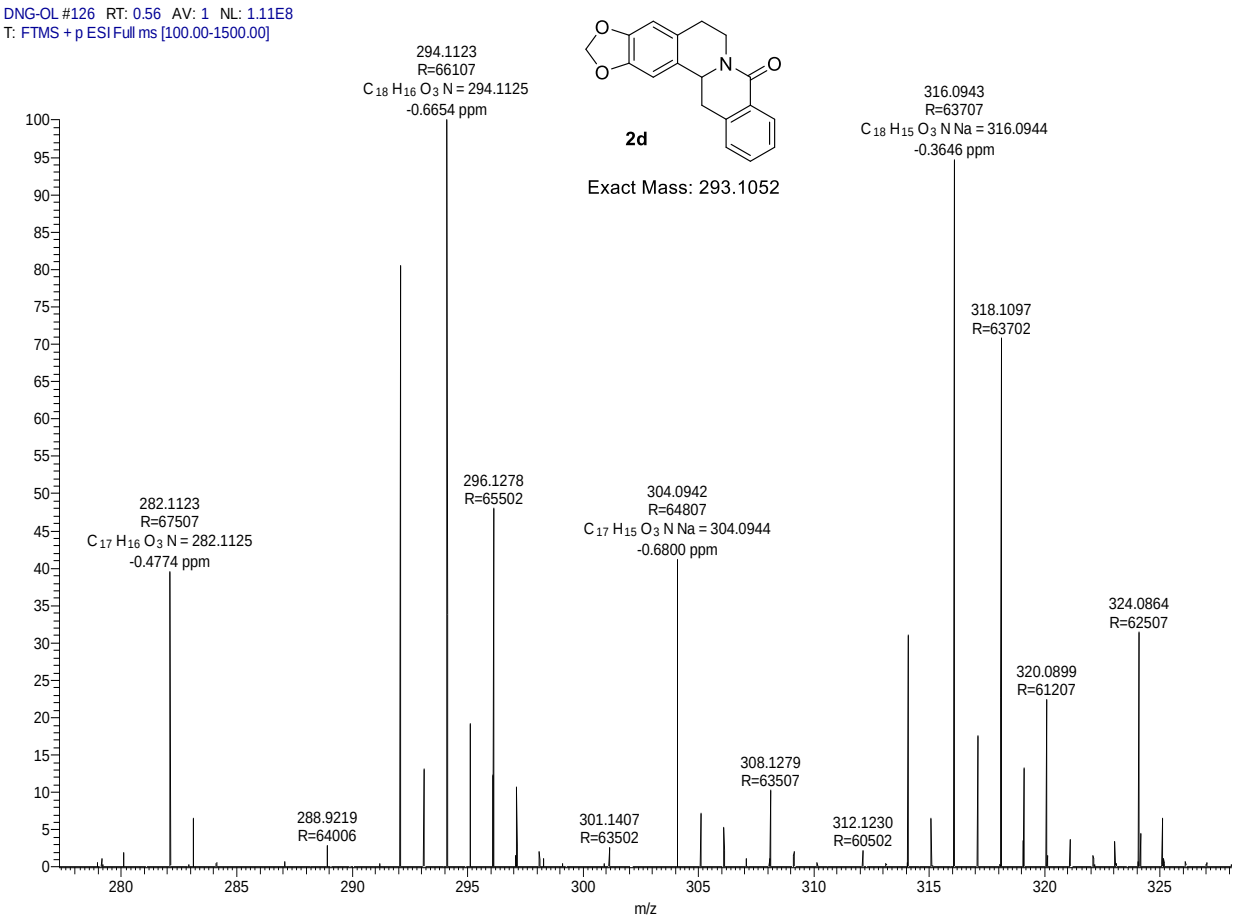


Chapter 2

Quinazolinone Directed C–H Bond Activation

Quinazolinone Directed C–H Bond Activation

2.1. Abstract:

The existence of *N*-heterocycles is an essential structural feature in several biologically active compounds, which encourage organic chemists to develop novel strategies for their synthesis. Among the various *N*-heterocyclic scaffolds, quinazolinones are one of the important classes of compounds found in many natural products and drugs. Quinazolinone derivatives possess a wide range of medicinal and pharmacological activities. The need to synthesize a library of various quinazolinone compounds and derivatization of quinazolinone natural products for SAR studies has stimulated the development of step and atom economical processes such as C–H bond activation. Given their importance, we have developed C–H bond activation protocols for quinazolinones using substrate itself as a directing group.

2.2. Background:

Several classical synthetic routes for the construction of quinazolinone core are known in the literature which uses cyclization reaction of 2-aminobenzoic acids and aldehydes or their derivatives.[1] Albeit some advanced synthetic strategies for constructing quinazolinone core are reported, but very few strategies are known where quinazolinone compounds itself were functionalized by metal catalysis.[2] Quinazolinone scaffold contains two nitrogen atoms within their structure which prompted us to use it as an intrinsic directing group for metal catalyst for proximal C–H bond functionalization. Accordingly it was successfully applied for C(sp^2)-arylation and C(sp^2)-acetoxylation. Based on these transformations, this chapter is divided into two sections as follows.

Section 1: Pd-Catalyzed Regioselective Mono-Arylation: Quinazolinone as the Inherent Directing Group for C(sp^2)–H Activation

Section 2: Diversification of Quinazolinones by Pd-Catalyzed C(sp^3)-Acetoxylation

2.3. References

1. (a) Kshirsagar, U. A. *Org. Biomol. Chem.* **2015**, *13*, 9336. (b) Mhaske, S. B.; Argade, N. P. *Tetrahedron* **2006**, *62*, 9787.
2. Rohokale, R. S.; Kshirsagar, U. A. *Synthesis* **2016**, *48*, 1253.

Chapter 2

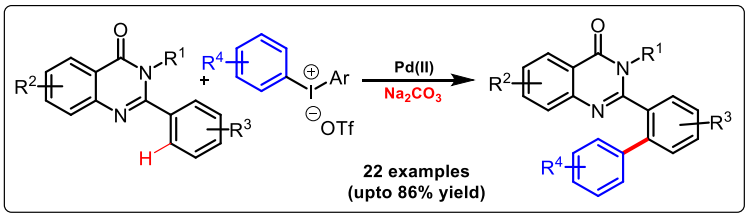
Section 1

Pd-Catalyzed Regioselective Mono-Arylation: Quinazolinone as the Inherent Directing Group for C(sp^2)–H Activation

Section 1: Pd-Catalyzed Regioselective Mono-Arylation: Quinazolinone as the Inherent Directing Group for C(sp^2)–H Activation

2.1.1. Abstract:

The Pd-catalyzed quinazolinone-directed regioselective mono-arylation of aromatic rings by C–H bond activation has been developed. The developed protocol uses diaryliodonium triflates as an aryl source which also ultimately serves as an oxidant for Pd-catalyst. A broad substrate scope is demonstrated for both quinazolinones as well as diaryliodonium triflates. Use of base was found to be crucial for this transformation, unlike the known nitrogen-directed arylations. All the novel quinazolinones of biological interest were synthesized using operationally simple Pd-catalyzed arylation reaction. The Pd(II)/Pd(IV) mechanism has been proposed for the developed protocol.



This work has been published in *J. Org. Chem*. **2017**, *82*, 6366.

2.1.2. Introduction:

More than 70% of the top branded drugs contain at least one heterocyclic nucleus as a part of its overall skeleton. In particular, many synthetic drugs, bioactive natural products, and agrochemicals encompassing nitrogen-heterocyclic scaffolds are most common.[1] Quinazoline is a nitrogen-containing fused bicyclic framework which is also known as benzo-1,3-diazine or 1,3-diazanaphthalene. It is naturally occurred in Chinese plant aseru and first isolated from the same plant.[1a] The properties of quinazolines varies with substituent attached to them at various

positions. Several derivatives of quinazolines such as ketone substituent attached to it known as ketoquinazoline or quinazolinone are reported in the literature. Quinazolinones are one of the important nitrogen-containing heterocyclic motifs found in more than 200 natural products as well as in several drugs (Figure 1).[1b,2] The quinazolinone derivatives possess wide range of pharmacological properties such as antimalarial, anticancer, antimicrobial, anti-diabetic, anti-inflammatory, antihypertensive, anticonvulsant, diuretic among others.[1-3] The synthesis of various natural, and synthetic derivatives of quinazolinones has acquired immense attention by the scientific community because of their wide range of biological properties.[1-3]

The application of C–H bond functionalization to form new carbon-carbon (C–C) and C–heteroatom (C–X) bonds in the synthesis of structurally complex natural or unnatural compounds has emerged as a powerful tool, and it is an area of contemporary interest.[4] It provides direct access and delivers more atom economical paths in the synthesis of complex structures as compared to the traditional organic synthesis. Until now several C–H activation reactions in the organic compounds have been developed with or without directing groups.[4]

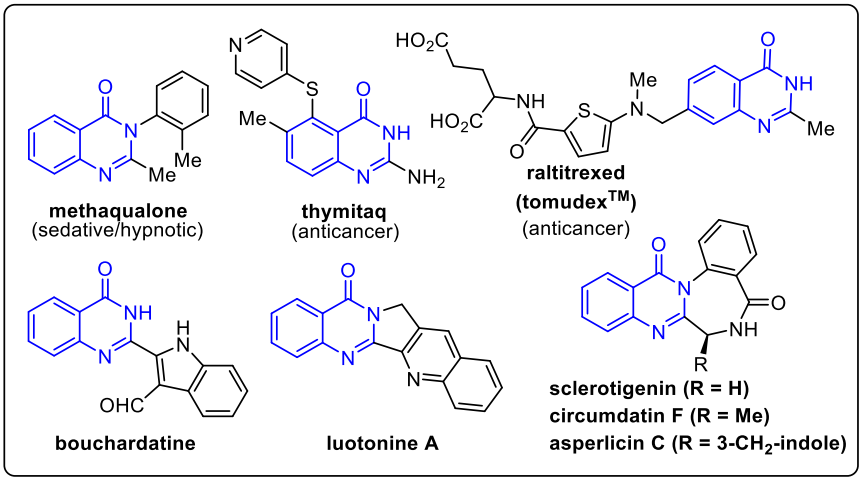
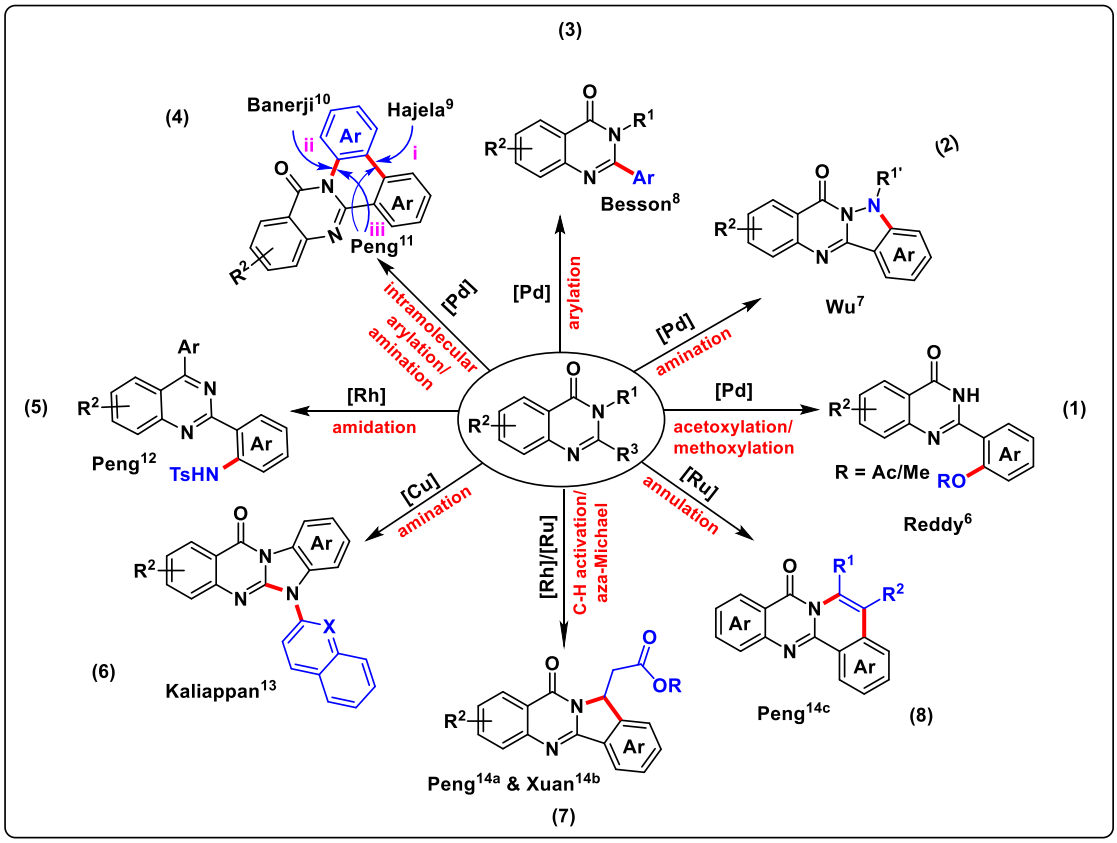


Figure 1. Selected quinazolinone drugs, and natural products.[1,2]

The metal-catalyzed inter- or intramolecular aromatic C–arylation is one of the widely used key-step in the total synthesis of several natural products,[4h] and the late-stage derivatization of bioactive molecules.[4g]

2.1.3. Literature Review:

The literature survey revealed that, although there are several classical methods available for the synthesis of novel quinazolinone derivatives,[2,5] there are only few reports in the literature where quinazolinone compounds itself were functionalized by metal catalysis. Pd-catalyzed methods such as acetoxylaton/methoxylation were reported by Reddy et al. (Scheme 1, eq 1).[6]



Scheme 1. Known transition-metal catalyzed functionalization of quinazolinone compounds

Intramolecular aerobic oxidative C–H amination of quinazolinones and their potential utility has been demonstrated for fluorescent materials by Wu and co-workers (Scheme 1, eq 2).[7] Besson

and co-workers reported Cu/Pd catalyzed microwave-enhanced regioselective arylation of (2H)-quinazolin-4-ones with aryl iodides (Scheme 1, eq 3).[8] Pd-catalyzed syntheses of phenanthridine/benzoxazine fused quinazolinones were reported using three different approaches. Intramolecular biaryl cross-coupling on two distinct skeletons by C–H bond activation with bromoarenes was reported by Hajela group (Scheme 1, eq 4i),[9] Banerji et al. developed regioselective intramolecular oxidative C–H amination from cyclic strained amides of quinazolinones with only linear fusion of two heterocyclic cores (Scheme 1, eq 4ii),[10] and cascade C–H/N–H arylation for modular synthesis of quinazolinone fused phenanthridinones was reported by Peng group (Scheme 1, eq 4iii).[11] Few other metal catalysts such as Ru, Cu and Rh were utilized in the quinazolinone/quinazoline functionalization. Rhodium-catalyzed regioselective direct C–H amidation by sulfonyl azides as the amine source to provide a variety of amide-functionalized 2,4-diarylquinazolines in high efficiency was reported by Peng et al. (Scheme 1, eq 5),[12] Cu-catalyzed C−H functionalization/two-fold C−N bond formation protocol for the syntheses of N-aryl benzimidazoquinazolinones was developed by Kaliappan (Scheme 1, eq 6),[13] and Rh/Ru-catalyzed cascade C−H activation/aza-Michael reactions with olefins was developed by Peng and Xuan group independently (Scheme 1, eq 7).[14a,b] Additionally, the annulation reaction with alkynes was reported by Peng and co-workers (Scheme 1, eq 8).[14c]

2.1.4. Origin of the Work:

In literature, few reports on quinazolinone functionalization with transition metal catalyst were known but to the best of our knowledge quinazolinone scaffold has not been used as an inherent directing group for metal-catalyzed C−H activation process until this report. In this account, we have planned to use quinazolinone scaffold as an inherent-directing group for the metal catalyst

for intermolecular arylation of quinazolinone compounds using diaryliodonium triflates as aryl source.

2.1.5. Objective of the work:

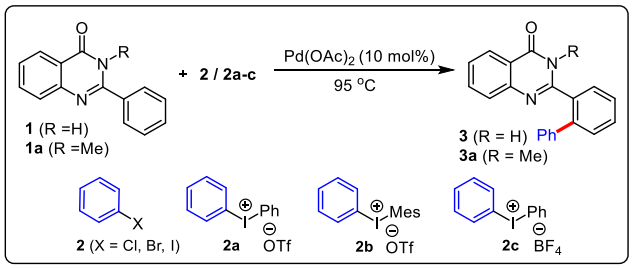
Due to the extensive occurrence of quinazolinone nucleus in bioactive organic compounds, we envisioned that the quinazolinone core could be exploited as the inherent directing group for the metal-catalyzed regioselective arylation, which would afford novel quinazolinones for structure-activity-relationship (SAR) studies. Herein, we report a protocol for the arylation of various quinazolinones.

2.1.6. Result and Discussion:

The optimization of the protocol was carried out by screening various reaction parameters. Initial attempts on N−H free quinazolinone **1** as the substrate with various aryl sources **2/2a-c** failed to produce coupling product **3**. Hence, we planned to study the protocol on various *N*-substituted quinazolinones. The *N*-methyl substituted quinazolinone substrate **1a** on treatment with halo-benzenes **2**, Pd-catalyst, and other additives did not furnish the expected product **3a** under various reaction conditions (Table 1). These observations suggest that more activated arylation reagent was necessary for this transformation. Diaryliodonium salts are well-known compounds as an arylation reagent due to their easy accessibility, and high reactivity.[15] Because of their highly electron-deficient nature, and good leaving group aptitude, they serve as versatile arylation agents with various metal catalysts.[16] Hence, we changed the phenyl source from halo-benzenes to diphenyliodonium triflate **2a**, and to our delight the expected product **3a** was formed in 35% yield (entry 2). The variation in solvents did not show the formation of expected product (entries 3, 4). Also the use of unsymmetrical iodonium salt **2b** or iodonium salt **2c** having

different counterion gave lower yields (entries 5, 6). We did not observe the expected product **3a** in the absence of a base (entry 7), and the substrate **1a** was recovered unchanged, which suggests that the use of base is crucial for this reaction. This observation is in contrast to the reported Pd-

Table 1. Optimization Studies



entry[a, b]	**2/2a-c** (equiv)	additive (equiv)	solvent	yield (%)[c]
1	**2** (2)	AgOAc (2)	AcOH	N.R.
2	**2a** (1)	K_2CO_3 (1)	AcOH	35
3	**2a** (1)	K_2CO_3 (1)	toulene	N.R.
4	**2a** (1)	K_2CO_3 (1)	1,4-dioxane	N.R.
5	**2b** (1)	K_2CO_3 (1)	AcOH	30
6	**2c** (1)	K_2CO_3 (1)	AcOH	25
7	**2a** (1)	-	AcOH	N.R.
8	**2a** (2)	Na_2CO_3 (2)	AcOH	55
9	**2a (3)**	**Na_2CO_3 (2)**	**AcOH**	**71**
10	**2a** (3)	NaOAc (2)	AcOH	35
11	**2a** (3)	Na_2CO_3 (2)	PivOH	Trace
12	**2a** (3)	Na_2CO_3 (2)	AcOH:PivOH	48

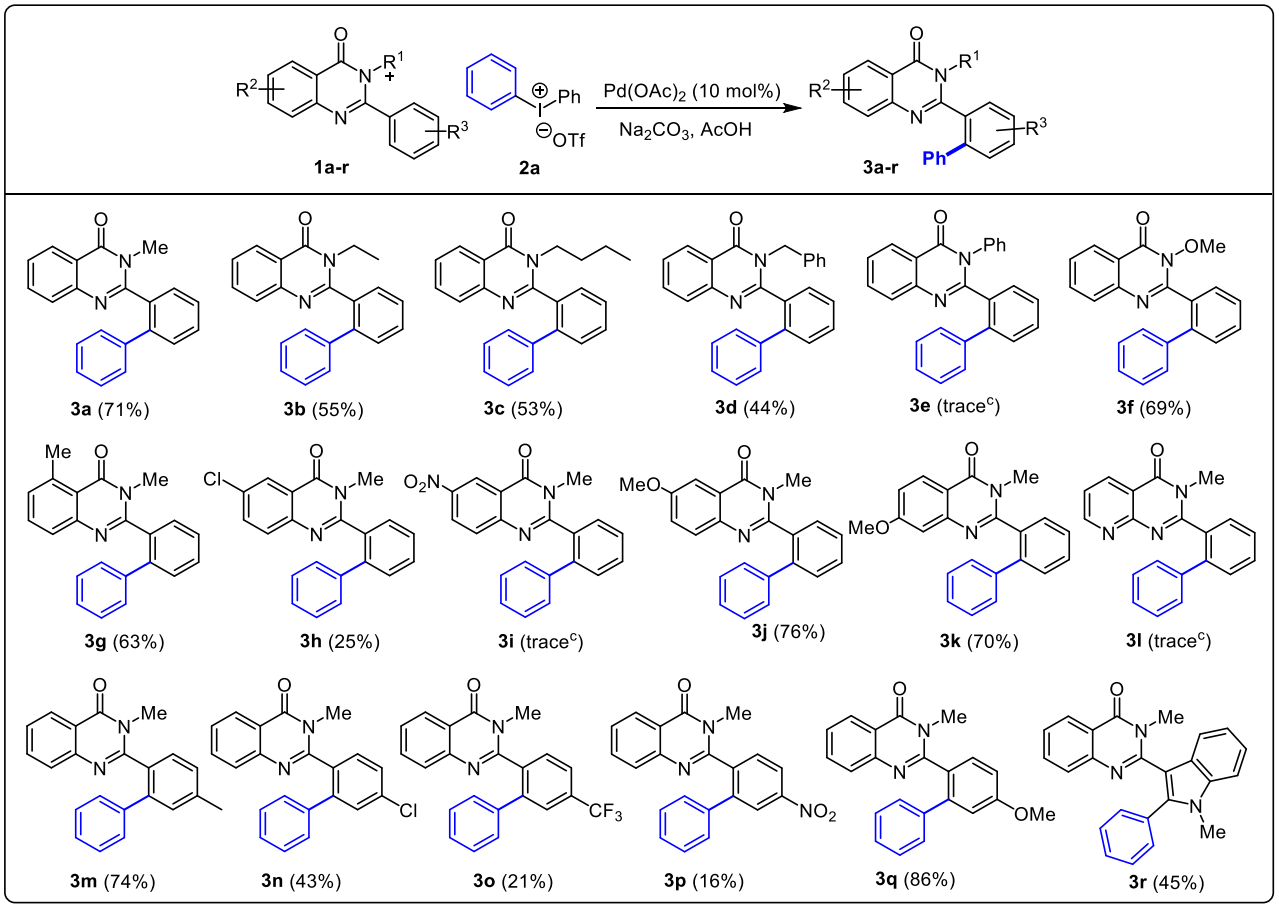
[a]Selected entries, [b]Reaction conditions: **1a**(0.2 mmol), AcOH (1 mL) in sealed tube for 36 h. [c]Isolated yield. N.R. = No reaction.

catalyzed nitrogen-directed arylation by C−H activation using diaryliodonium salts.[4j,k] When two equivalents of the iodonium salt **2a** was used in combination with Na_2CO_3, we observed an improvement in the yield to 55% (entry 8). The highest possible yield of the product **3a** was 71% wherein three equivalent of salt **2a** was used (entry 9). Further, variation in the optimized conditions like a change in the base NaOAc (entry 10), solvent PivOH (entry 11), solvent

combinations of AcOH : PivOH (entry 12), and temperature, among others resulted in either low or trace amount of product formation.

With the optimized conditions in hand, we next turned our attention to develop a general scope of the protocol. We planned to study the effect of substituent variation in the quinazolinone core on the arylation reaction (Table 2). Initially, the effect of *N*-substitution was studied. *N*-Primary alkyl substituted quinazolinones furnished the expected products **3a-c** with moderate to good yields.

Table 2. Pd-Catalyzed Arylation of Various Quinazolinones[a,b]

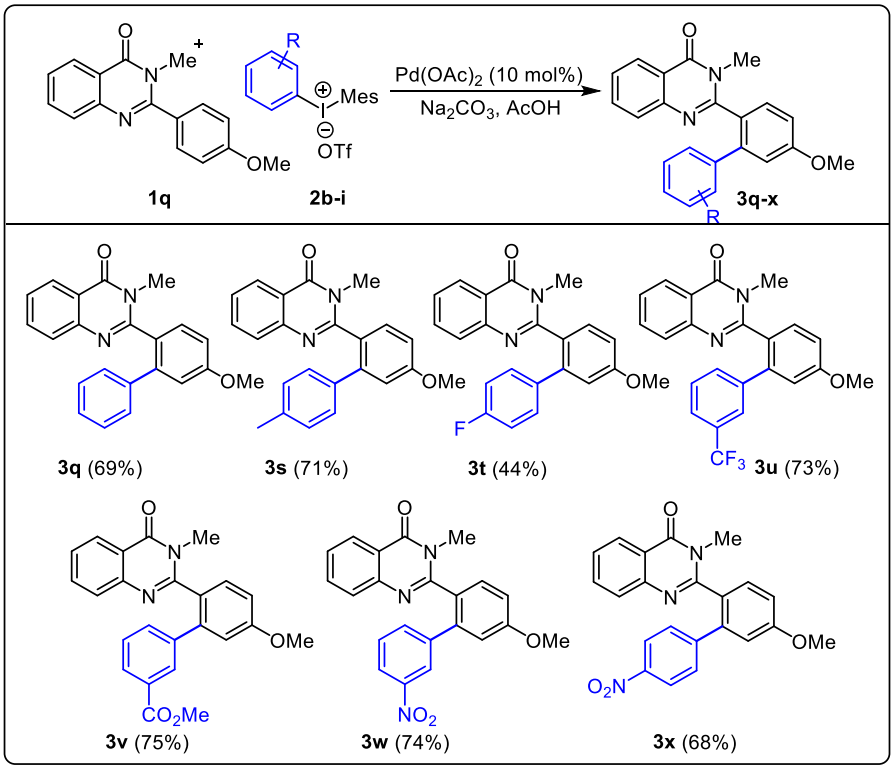


[a]Reaction conditions: **1a-r** (0.2 mmol), **2a** (0.6 mmol), $Pd(OAc)_2$ (10 mol%), Na_2CO_3 (0.4 mmol), AcOH (1 mL), 30-36 h, 90-120 °C. [b]Isolated yield. [c]Trace product formation was confirmed by TLC, and HRMS.

We observed that with the increase in the chain length the yield of the respective product decreases. The quinazolinone substrate with *N*-benzyl substituent resulted in the moderate yield of **3d**. The *N*-phenyl substituted quinazolinone provided only trace amount of product **3e**. The reason behind this observation might be the steric hindrance caused by the *N*-phenyl ring, which enforces the other phenyl ring out of the plane, thus inhibiting the formation of palladacycle. The quinazolinone substrate with *N*-methoxy substituent furnished **3f** in good yield. The *N*-methyl substituted quinazolinone provided better yield than the substrates with other *N*-substituents, hence keeping the *N*-methyl substitution constant, the further scope of the arylation reaction with varyingly substituted quinazolinone core was explored. 5-Methyl-substituted quinazolinone gave the corresponding arylated product **3g** in good yield; however, 6-chloro, and 6-nitro-substituted quinazolinones resulted in low, and trace yield of products **3h**, and **3i** respectively. Most probably, the electron withdrawing substituents weakens the coordinating ability of these substrates with the metal catalyst, which resulted in lower yields. Electron-rich substituents provided the arylated products **3j** and **3k** in very good yields. The heterocyclic substrate could only afford trace amount of product **3l** due to electron withdrawing effect of the pyridine ring. Furthermore, we began to explore the substrate scope of the aromatic ring attached to the quinazolinone core. The quinazolinone substrate with alkyl substituted aromatic ring resulted in the decent yield of product **3m**, however, as anticipated chloro, and other electron withdrawing substituents resulted in moderate to a low yield of products **3n-p**. Electron-rich substituent enhanced the C−H activation process, and the product **3q** was obtained in excellent yield. Pleasingly, the heterocyclic indole substrate could be arylated at the 2-position of indole to afford the product **3r**.

We also investigated the application of various diaryliodonium triflates in the developed arylation protocol (Table 3). The substrate **1q** was chosen for this purpose. It is well known that the sterically less hindered aryl group of diaryliodonium triflate undergoes metal-catalyzed coupling,[16d] hence we kept sterically hindered mesitylene as one of the substituents in the arylation reagent, and varied other aryl substituents. Various substituents on the arylation reagent

Table 3. Pd-Catalyzed Arylation with Various Diaryliodonium Triflates[a,b]



[a]Reaction conditions: **1q** (0.2 mmol), **2b-i** (0.6 mmol), $Pd(OAc)_2$ (10 mol%), Na_2CO_3 (0.4 mmol), AcOH (1 mL), 30-36 h, 90-95 ^oC. [b]Isolated yield.

were tolerated under the developed protocol. The arylated products such as unsubstituted **3q** and methyl substituted **3s** could be obtained in very good yields. The *para*-fluoro compound **3t** was obtained in moderate yield. The arylation reagents with electron withdrawing groups underwent smooth reactions under the developed protocol. The trifluoromethyl and ester groups at *meta*-position of arylation reagent were well tolerated, and expected products **3u** and **3v** have been

synthesized in decent yields respectively. Nitro groups at *meta*- and *para*-positions of arylating reagents provided good yields of products **3w**, and **3x** respectively. Overall, it was observed that electron withdrawing groups on arylation reagents facilitates the reaction. It can be reasoned that the palladium insertion takes place promptly on more electron deficient coupling partner. As evident from the substrate scope study (Tables 2, and 3), the developed protocol is very general, and it will be suitable for the generation of a library of quinazolinone compounds.

A plausible mechanism for the developed arylation protocol is depicted in Figure 2, based on the literature precedence.[4j,7,17] We believe that in the first step Pd(II) coordinates with the imine nitrogen of quinazolinone **1a**, and activates the proximal proton to form a five-membered palladacycle **A**.

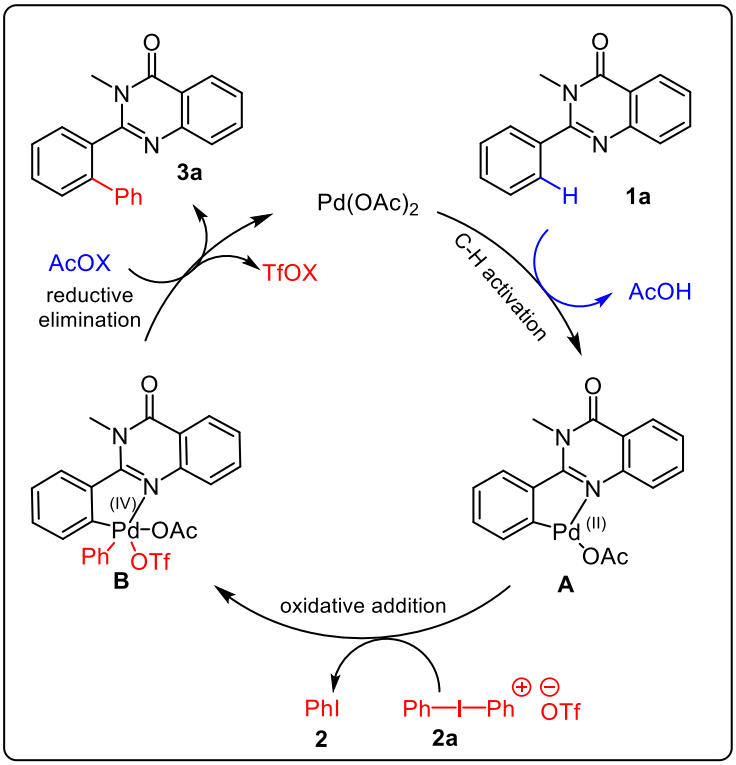


Figure 2. Proposed mechanism.

Diphenyliodonium triflate **2a** oxidatively adds to the palladacycle **A** [Pd(II)] to form the palladacycle **B** [Pd(IV)]. Subsequently, base promoted reductive elimination affords product **3a**, and Pd(II) regenerates for the next catalytic cycles.

2.1.7. Conclusion:

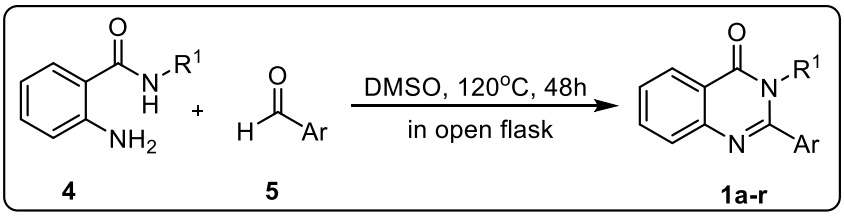
In summary, quinazolinone scaffold has been demonstrated as the inherent directing group in Pd-catalyzed intermolecular regioselective mono-arylation reaction. Diaryliodonium triflates have been used as arylation reagents in the C−H activation process, which provided a wide range of new quinazolinones. This novel protocol could be used for late-stage derivatization of bioactive quinazolinones, and natural products for SAR studies. This newly developed directing group could be used for other C−H activation processes such as in the natural product synthesis or in the development of novel methodologies. The novel derivatives synthesized here could be screened for anticancer and antimalarial activities.

2.1.8. Experimental Procedures and Characterization Data of Compounds:

All diaryliodonium triflates[15c-d,18] and quinazolinone starting materials[19,20] were prepared according to well-known literature procedures.

I) Experimental Procedures for the Synthesis of Starting Materials:

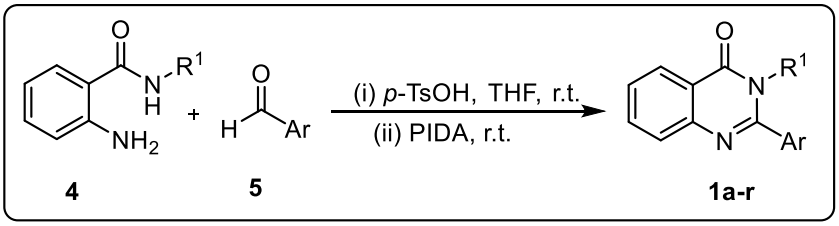
Method A:



The literature known procedure was followed.[19] *N*-Substituted anthranilamides (1.0 mmol; 1.0 equiv.), and aromatic aldehydes (1.2 mmol; 1.2 equiv.) were dissolved in DMSO (5 mL). Then,

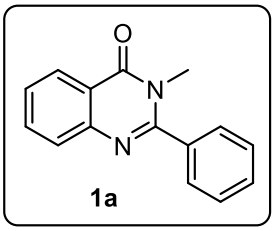
the reaction mixture was stirred at 120 ^{o}C in an open flask, and the progress was monitored by TLC. After complete consumption (48 h) of the starting materials, the reaction mixture was poured onto water and extracted with DCM. The organic layer was combined, dried over anhydrous sodium sulfate, and concentrated in *vacuo*. The crude mixture was purified by silica gel column chromatography using Pet. ether / EtOAc (5:1) as an eluent to afford 2,3-disubstituted-4(3H)-quinazolinones **1a-r**.

Method B:



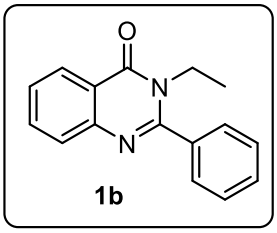
The literature known procedure was followed.[20] To the solution of *N*-substituted anthranilamides **4** (1 mmol) and *p*-TsOH (0.05 mmol) in THF (10 mL) was added aldehyde **5** (1.1 mmol) and the reaction mixture was then stirred at room temperature (RT) for 10 min., followed by portion wise addition of PIDA (1.5 mmol) over 5 min. After stirring for 1 h, the reaction mixture was diluted with EtOAc (20 mL), quenched with the saturated aqueous $NaHCO_3$ solution (20 mL), and then extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine (3 × 30 mL), dried over sodium sulfate and concentrated in *vacuo*. The crude mixture was purified by silica gel column chromatography using Pet. ether / EtOAc (5:1) as an eluent to afford 2,3-disubstituted-4(3H)-quinazolinones **1a-r**.

3-methyl-2-phenylquinazolin-4(3H)-one (1a):[19]



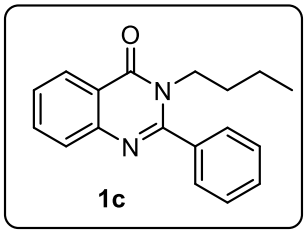
Following the **Method A** procedure, **1a** was obtained as white solid (178 mg; 75% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 8.35 (dt, J = 7.9, 1.1 Hz, 1H), 7.80-7.73 (m, 2H), 7.63-7.43 (m, 6H), 3.51 (s, 3H).

3-ethyl-2-phenylquinazolin-4(3H)-one (1b):[21]



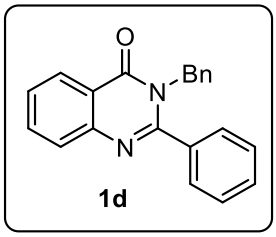
Following the **Method A** procedure, **1b** was obtained as white solid (167 mg; 67% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 8.35 (dt, J = 7.9, 1.0 Hz, 1H), 7.80-7.72 (m, 2H), 7.59-7.47 (m, 6H), 4.05 (q, J = 7.1 Hz, 2H), 1.23 (t, J = 7.1 Hz, 3H).

3-butyl-2-phenylquinazolin-4(3H)-one (1c):[5b]



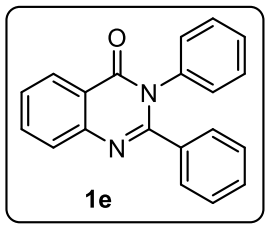
Following the **Method A** procedure **1c** was obtained as white solid (122 mg; 44% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 8.34 (m, 1H), 7.79-7.70 (m, 2H), 7.56-7.46 (m, 6H), 4.05-3.92 (m, 2H), 1.65-1.50 (m, 2H), 1.28-1.08 (m, 2H), 0.78 (t, J = 7.1 Hz, 3H).

3-benzyl-2-phenylquinazolin-4(3H)-one (1d):[19]



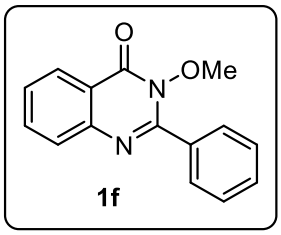
Following the **Method A** procedure, **1d** was obtained as white solid (119 mg; 38% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 8.43-8.34 (m, 1H), 7.83-7.73 (m, 2H), 7.59-7.50 (m, 1H), 7.50-7.31 (m, 5H), 7.26-7.15 (m, 3H), 6.99-6.87 (m, 2H), 5.29 (s, 2H).

2,3-diphenylquinazolin-4(3H)-one (1e):[19]



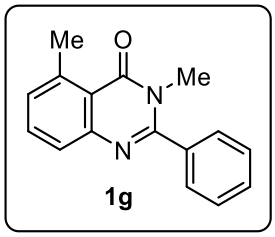
Following the **Method A** procedure **1e** was obtained as white solid (203 mg; 68% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 8.37 (dt, J = 7.9, 1.0 Hz, 1H), 7.87-7.80 (m, 2H), 7.60-7.50 (m, 1H), 7.39-7.27 (m, 5H), 7.26-7.13 (m, 5H).

3-methoxy-2-phenylquinazolin-4(3H)-one (1f):[20]



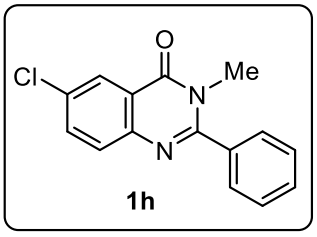
Following the **Method B** procedure, **1f** was obtained as white solid (163 mg; 65% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 8.36 (dt, J = 7.9, 1 Hz, 1H), 7.96-7.86 (m, 2H), 7.82-7.76 (m, 2H), 7.61-7.46 (m, 4H), 3.78 (s, 3H).

3,5-dimethyl-2-phenylquinazolin-4(3H)-one (1g):



Following the **Method A** procedure, **1g** was obtained as white solid (113 mg; 45% yield). R*f*: 0.4 (1:4 EtOAc: Pet. ether); mp 105-107 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.63-7.48 (m, 7H), 7.30-7.22 (m, 1H), 3.46 (s, 3H), 2.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 163.2, 155.8, 148.9, 140.9, 135.5, 133.4, 129.9, 129.5, 128.8, 127.9, 125.7, 119.1, 34.1, 23.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{15}N_2O$, 251.1179; found, 251.1181.

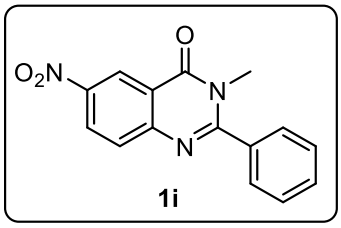
6-chloro-3-methyl-2-phenylquinazolin-4(3H)-one (1h):



Following the **Method B** procedure, **1h** was obtained as white solid (192 mg; 67% yield). R*f*: 0.35 (1:4 EtOAc: Pet. ether); mp 126-128 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.30 (s, 1H), 7.78-7.64 (m,

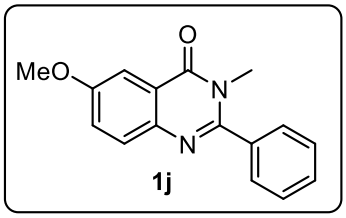
2H), 7.62-7.45 (m, 5H), 3.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 161.7, 156.4, 145.8, 135.1, 134.7, 132.7, 130.2, 129.2, 128.9, 127.9, 126.0, 121.5, 34.4; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{12}N_2OCl$, 271.0633; found, 271.0636.

3-methyl-6-nitro-2-phenylquinazolin-4(3H)-one (1i):[22]



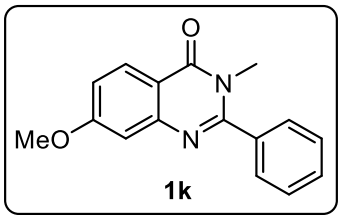
Following the **Method A** procedure, **1i** was obtained as yellow solid (90 mg; 32% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 9.21 (d, J = 2.5 Hz, 1H), 8.55 (dd, J = 9.0, 2.5 Hz, 1H), 7.85 (d, J = 9.0 Hz, 1H), 7.64-7.57 (m, 5H), 3.57 (s, 3H).

6-methoxy-3-methyl-2-phenylquinazolin-4(3H)-one (1j):[23]



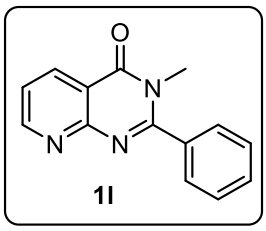
Following the **Method A** procedure, **1j** was obtained as white solid (102 mg; 38% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 7.78-7.65 (m, 2H), 7.63-7.48 (m, 5H), 7.37 (dd, J = 9.0, 3 Hz, 1H), 3.95 (s, 3H), 3.52 (s, 3H).

7-methoxy-3-methyl-2-phenylquinazolin-4(3H)-one (1k):[23]



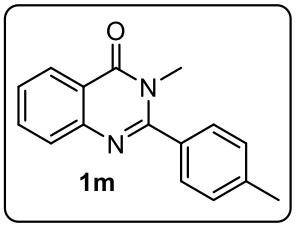
Following the **Method A** procedure, **1k** was obtained as white solid (120 mg; 45% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 8.24 (d, J = 8.8 Hz, 1H), 7.61-7.48 (m, 5H), 7.14 (d, J = 2.4 Hz, 1H), 7.09 (dd, J = 8.8, 2.4 Hz, 1H), 3.91 (s, 3H), 3.49 (s, 3H).

3-methyl-2-phenylpyrido[2,3-d]pyrimidin-4(3H)-one (1l):[24]



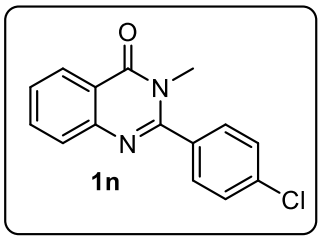
Following the **Method A** procedure **1l** was obtained as white solid (87 mg; 37% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 9.01 (dd, J = 4.6, 2 Hz, 1H), 8.66 (dd, J = 7.9, 2 Hz, 1H), 7.71-7.60 (m, 2H), 7.58-7.41 (m, 4H), 3.56 (s, 3H).

3-methyl-2-(p-tolyl)quinazolin-4(3H)-one (1m):[25]



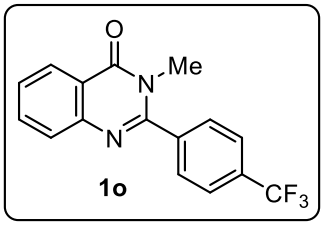
Following the **Method A** procedure, **1m** was obtained as white solid (160 mg; 64% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 8.34 (d, J = 7.8 Hz, 1H), 7.70-7.69 (m, 2H), 7.56-7.41 (m, 3H), 7.33 (d, J = 8 Hz, 2H), 3.52 (s, 3H), 2.45 (s, 3H).

2-(4-chlorophenyl)-3-methylquinazolin-4(3H)-one (1n):[21]



Following the **Method A** procedure, **1n** was obtained as white solid (152 mg; 56% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 8.32 (d, J = 7.5 Hz, 1H), 7.83-7.67 (m, 2H), 7.60-7.45 (m, 5H), 3.50 (s, 3H).

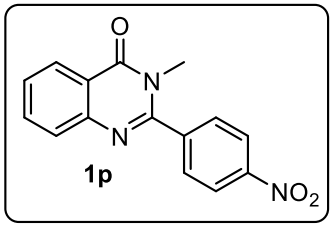
3-methyl-2-(4-(trifluoromethyl)phenyl)quinazolin-4(3H)-one (1o):



Following the **Method B** procedure, **1o** was obtained as white solid (131 mg; 43% yield). R*f*: 0.35 (1:4 EtOAc: Pet. ether); mp 119-121 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.35 (d, J = 7.9 Hz, 1H), 7.88-7.69 (m, 6H), 7.54 (t, J = 7.3 Hz, 1H), 3.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.4, 154.7, 147, 138.7, 134.5, 132.1 (q, J = 33.1 Hz), 128.6, 127.5,

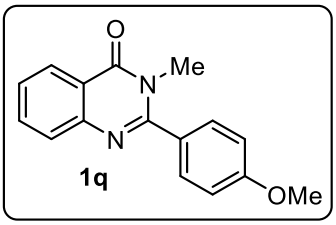
127.4, 126.8, 125.9 (q, *J* = 3.8 Hz), 123.6 (q, *J* = 272 Hz), 120.6, 34.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{12}N_2OF_3$, 305.0896; found, 305.0893.

3-methyl-2-(4-nitrophenyl)quinazolin-4(3H)-one (1p):[25]



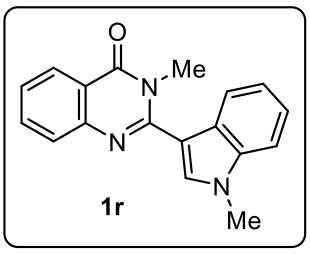
Following the **Method B** procedure, **1p** was obtained as yellow solid (129 mg; 46% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 8.43 (d, *J* = 8.8 Hz, 2H), 8.37 (d, *J* = 8.7 Hz, 1H), 7.87-7.74 (m, 4H), 7.63-7.51 (m, 1H), 3.51 (s, 3H).

2-(4-methoxyphenyl)-3-methylquinazolin-4(3H)-one (1q):[21]



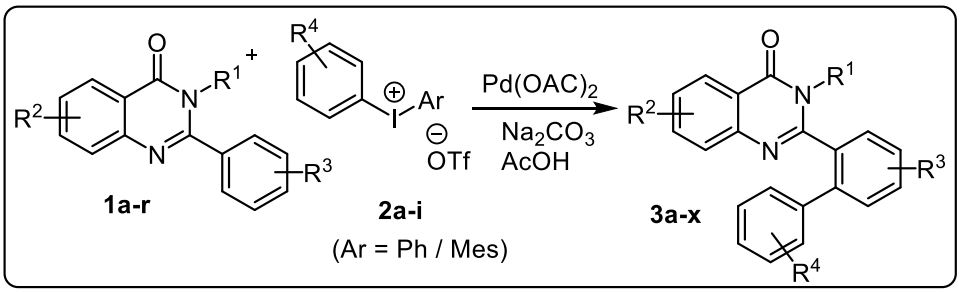
Following the **Method A** procedure, **1q** was obtained as white solid (181 mg; 68% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 8.32 (d, *J* = 7.7 Hz, 1H), 7.78-7.68 (m, 2H), 7.59-7.44 (m, 3H), 7.08-6.98 (m, 2H), 3.88 (s, 3H), 3.54 (s, 3H).

3-methyl-2-(1-methyl-1H-indol-3-yl)quinazolin-4(3H)-one (1r):



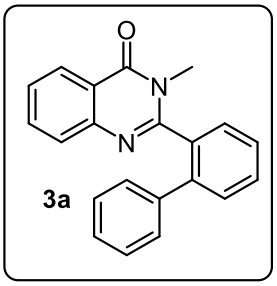
Following the **Method A** procedure, **1r** was obtained as white solid (130 mg; 45% yield). R*f*: 0.4 (1:1 EtOAc: Pet. ether); mp 194-196 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.35 (d, *J* = 7.3 Hz, 1H), 7.80-7.70 (m, 3H), 7.55 (s, 1H), 7.51-7.45 (m, 1H), 7.42 (d, *J* = 7.9 Hz, 1H), 7.34 (t, *J* = 7.9 Hz, 1H), 7.27 (t, *J* = 7.9 Hz, 1H), 3.91 (s, 3H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 163.3, 152.1, 147.9, 136.8, 134.1, 130.6, 127.2, 126.6, 126.4, 126.2, 122.9, 121.2, 120.7, 120.1, 110.5, 109.9, 34.1, 33.2; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{16}N_3O$, 290.1288; found, 290.1293.

II) General Experimental Procedure for Arylations by C-H Activation:



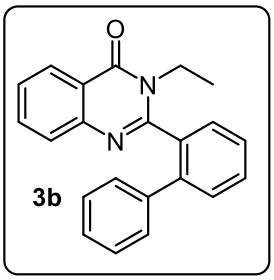
A sealed tube was charged with quinazolinone **1a-r** (0.2 mmol), diaryl iodonium triflate **2a-i** (0.6 mmol), sodium carbonate (42 mg; 0.4 mmol) and $Pd(OAc)_2$ (4.5 mg; 10 mol%). To the above mixture AcOH (1 ml; 0.2M) was added and flushed twice with argon gas. The tube was packed with screw cap and placed in preheated oil bath at 90 ^{o}C-120 ^{o}C. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to RT after 30-36 h, diluted with ethyl acetate and evaporated under *vacuo* to dryness. After aqueous workup the residue was purified by column chromatography to afford pure quinazolinone **3a-x**.

2-([1,1'-biphenyl]-2-yl)-3-methylquinazolin-4(3H)-one (3a):



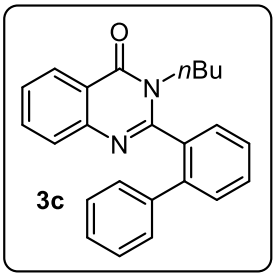
Following the general experimental procedure, **3a** was obtained as a colorless solid (44 mg; 71% yield); Reaction Time: 36 h at 95 ^{o}C. R*f*: 0.4 (1:4 EtOAc:Pet. ether); mp 125-127 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.27 (d, J = 7.9 Hz, 1H), 7.84-7.76 (m, 2H), 7.67-7.57 (m, 2H), 7.56-7.47 (m, 3H), 7.37-7.30 (m, 2H), 7.27-7.22 (m, 3H), 3.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.1, 156.4, 147.1, 140.2, 139.4, 134.2, 134.1, 130.4, 130.2, 129.2, 128.7, 128.5, 128.1, 128, 127.5, 126.9, 126.7, 120.4, 32.6; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{17}N_2O$, 313.1335; found, 313.1337.

2-([1,1'-biphenyl]-2-yl)-3-ethylquinazolin-4(3H)-one (3b):



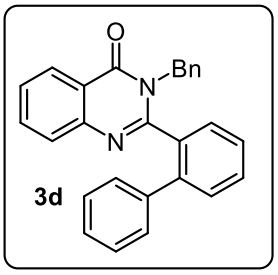
Following the general experimental procedure, **3b** was obtained as a colorless solid (36 mg, 55% yield); Reaction time: 36 h at 100 ^{o}C; R_f: 0.4 (1:4 EtOAc:Pet. ether); mp 137-139 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.27 (d, J = 7.93, 1H), 7.88-7.75 (m, 2H), 7.65-7.55 (m, 2H), 7.54-7.49 (m, 3H), 7.40-7.32 (m, 2H), 7.26-7.16 (m, 3H), 4.0-3.90 (m, 1H), 3.37-3.27 (m, 1H), 0.96 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 161.5, 156.1, 146.6, 140.0, 139.3, 134.3, 133.7, 130.4, 130.1, 129.2, 128.7, 128.6, 127.9, 127.8, 127.2, 127, 126.7, 120.8, 40.5, 13.5; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{19}N_2O$, 327.1492; found, 327.1495.

2-([1,1'-biphenyl]-2-yl)-3-butylquinazolin-4(3H)-one (3c):



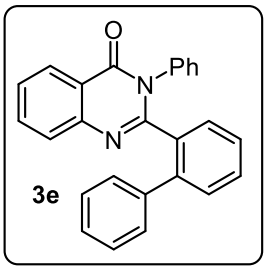
Following the general experimental procedure, **3c** was obtained as a colorless solid (37 mg, 53% yield); Reaction time: 30 h at 90 ^{o}C; R_f: 0.4 (1:4 EtOAc:Pet. ether); mp 108-110 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.26 (d, J = 7.94, 1H), 7.83-7.76 (m, 2H), 7.63-7.56 (m, 2H), 7.55-7.48 (m, 3H), 7.37-7.32 (m, 2H), 7.26-7.21 (m, 3H), 3.87-3.77 (m, 1H), 3.27-3.17 (m, 1H), 1.45-1.32(m, 2H), 1.11-1.0(m, 2H), 0.66 (t, J = 7.32, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 161.8, 156.2, 147, 140, 139.4, 134.2, 134.1, 130.3, 130, 129.5, 128.6, 127.9, 127.8, 127.4, 126.8, 126.7, 120.9, 45, 30.1, 19.8, 13.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{23}N_2O$, 355.1805; found, 355.1806.

2-([1,1'-biphenyl]-2-yl)-3-benzylquinazolin-4(3H)-one (3d):



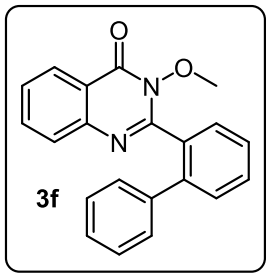
Following the general experimental procedure, **3d** was obtained as a colorless solid (34 mg, 44% yield); Reaction time: 36 h at 120 ^{o}C; R_f: 0.4 (1:4 EtOAc:Pet. ether); mp 84-85 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.29 (d, J = 7.94, 1H), 7.82 (d, J = 6.72 Hz, 2H), 7.59-7.50 (m, 3H), 7.40-7.28 (m, 5H), 7.27-7.20 (m, 2H), 7.16-7.09 (m, 3H), 6.77 (d, J = 7.32, 2H), 5.27 (d, J = 15 Hz, 1H), 4.30 (d, J = 15 Hz, 1H),^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162, 156.3, 146.8, 139.9, 139.4, 136.2, 134.5, 133.7, 130.4, 130, 129.9, 128.8, 128.7, 128.3, 128, 127.7, 127., 127.3, 127.1, 120.8, 47.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{21}N_2O$, 389.1648; found, 389.1648.

2-([1,1'-biphenyl]-2-yl)-3-phenylquinazolin-4(3H)-one (3e):



Following the general experimental procedure, **3e** was formed in trace amount by TLC analysis and also confirmed by LC-HRMS; Reaction time: 36 h at 120 ^{o}C; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{19}N_2O$, 375.1492; found, 375.1500.

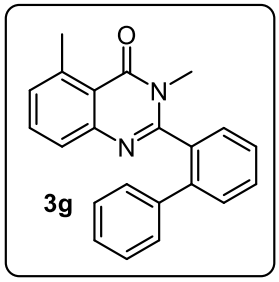
2-([1,1'-biphenyl]-2-yl)-3-methoxyquinazolin-4(3H)-one (3f):



Following the general experimental procedure, **3f** was obtained as a colorless solid (45 mg; 69% yield); Reaction Time: 36 h at 90 ^{o}C. R*f*: 0.4 (1:3 EtOAc:Pet. ether); mp 101-103 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.28 (d, J = 7.9 Hz, 1H), 7.82-7.76 (m, 2H), 7.65 (d, J = 7.3 Hz, 1H), 7.61 (d, J = 7.3 Hz, 1H), 7.55-7.48 (m, 3H), 7.37-7.31 (m, 2H), 7.26-7.20 (m, 3H), 3.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 157.6, 156.5, 146.3, 141.6, 140.1, 134.4, 131.4,

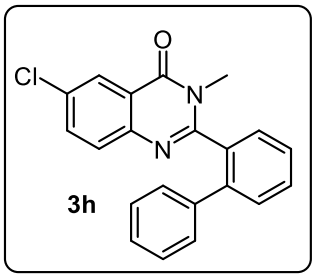
130.5, 130, 129.1, 128.5, 128.4, 127.9, 127.5, 127.2, 127, 126.7, 122.7, 64; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{17}N_2O_2$, 329.1285; found, 329.1286.

2-([1,1'-biphenyl]-2-yl)-3,5-dimethylquinazolin-4(3H)-one (3g):



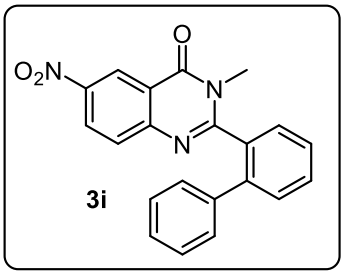
Following the general experimental procedure, **3g** was obtained as a colorless solid (41 mg; 63% yield); Reaction Time: 36 h at 95 ^oC. R*f*: 0.4 (1:4 EtOAc:Pet. ether); mp 124-126 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.66-7.49 (m, 6H), 7.39-7.32 (m, 2H), 7.29-7.23 (m, 4H), 2.95 (s, 3H), 2.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.7, 156.1, 148.8, 140.9, 140.2, 139.6, 134.2, 133.3, 130.3, 130.2, 129.5, 129.2, 128.7, 128.6, 128.1, 127.9, 125.7, 119, 32.5, 23.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{19}N_2O$, 327.1492; found, 327.1494.

2-([1,1'-biphenyl]-2-yl)-6-chloro-3-methylquinazolin-4(3H)-one (3h):



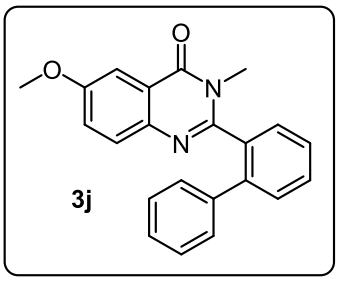
Following general experimental procedure **3h** was obtained as a colorless solid (17 mg; 25% yield); Reaction Time: 36 h at 120 ^oC. R*f*: 0.35 (1:3 EtOAc:Pet. ether); mp 129-131 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.22 (s, 1H), 7.76-7.69 (m, 2H), 7.66-7.60 (m, 1H), 7.59-7.51 (m, 3H), 7.34-7.29 (m, 2H), 7.27-7.21 (m, 3H), 3.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 161.1, 156.7, 145.6, 140.3, 139.3, 134.8, 133.8, 132.7, 130.6, 130.2, 129.2, 129.1, 128.8, 128.5, 128.1, 127.06, 126, 121.4, 32.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{16}N_2OCl$, 347.0946; found, 347.0951.

2-([1,1'-biphenyl]-2-yl)-3-methyl-6-nitroquinazolin-4(3H)-one (3i):



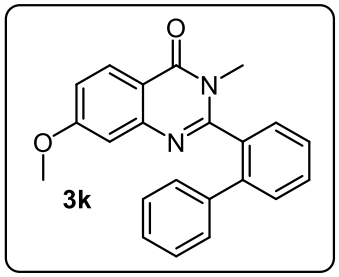
Following the general experimental procedure, **3i** was formed in trace amount by TLC analysis and also confirmed by LC-HRMS; Reaction time: 36 h at 120 ^{o}C; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{16}N_3O_3$, 358.1186; found, 358.1188.

2-([1,1'-biphenyl]-2-yl)-6-methoxy-3-methylquinazolin-4(3H)-one (3j):



Following the general experimental procedure, **3j** was obtained as a colorless solid (52 mg; 76% yield); Reaction Time: 36 h at 95 ^{o}C. R*f*: 0.35 (1:2 EtOAc:Pet. ether); mp 177-179 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.74 (d, *J* = 8.5 Hz, 1H), 7.65-7.48 (m, 5H), 7.39 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.35-7.29 (m, 2H), 7.28-7.20 (m, 3H), 3.93 (s, 3H), 3.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162, 158.5, 154.2, 141.8, 140.3, 139.5, 134.1, 130.4, 130.1, 129.3, 129.1, 128.7, 128.5, 128.1, 127.9, 124.7, 121.2, 105.9, 55.8, 32.6; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{19}N_2O_2$, 343.1441; found, 343.1441.

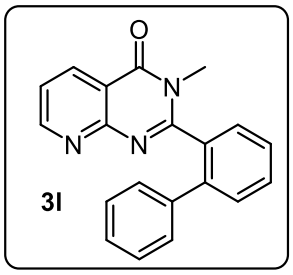
2-([1,1'-biphenyl]-2-yl)-7-methoxy-3-methylquinazolin-4(3H)-one (3k):



Following general experimental procedure **3k** was obtained as a colorless solid (48 mg; 70% yield); Reaction Time: 36 h at 95 ^{o}C. R*f*: 0.35 (1:2 EtOAc:Pet. ether); mp 197-199 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.15 (d, *J* = 8.6 Hz, 1H), 7.65-7.48 (m, 4H), 7.37-7.30 (m, 2H), 7.28-7.22 (m, 3H), 7.19 (d, *J* = 1.8 Hz, 1H), 7.08 (dd, *J* = 8.5, 1.8 Hz, 1H), 3.94 (s, 3H), 2.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 164.5, 161.7, 157.2, 149.3,

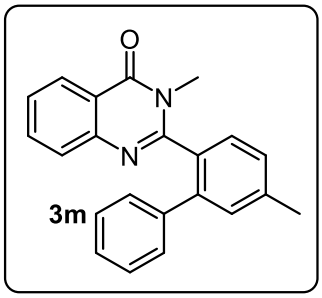
140.1, 139.4, 134.2, 130.4, 130.1, 129.1, 128.7, 128.5, 128.2, 128.03, 128, 117.2, 114, 107.8, 55.6, 32.4; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{19}N_2O_2$, 343.1441; found, 343.1432.

2-([1,1'-biphenyl]-2-yl)-3-methylpyrido[2,3-d]pyrimidin-4(3H)-one (3l):



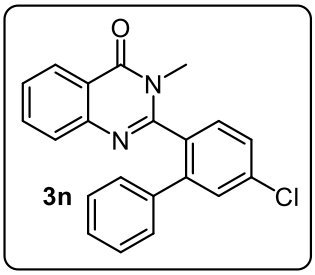
Following the general experimental procedure, **3l** was formed in trace amount by TLC analysis and also confirmed by LC-HRMS; Reaction time: 36 h at 120 ^oC; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{16}N_3O$, 314.1288; found, 314.1286.

3-methyl-2-(5-methyl-[1,1'-biphenyl]-2-yl)quinazolin-4(3H)-one (3m):



Following the general experimental procedure, **3m** was obtained as a colorless solid (48 mg; 74% yield); Reaction Time: 36 h at 95 ^oC. R*f*: 0.4 (1:4 EtOAc:Pet. ether); mp 151-153 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.26 (d, J = 7.9 Hz, 1H), 7.82-7.74 (m, 2H), 7.55-7.44 (m, 2H), 7.38-7.29 (m, 4H), 7.26-7.17 (m, 3H), 3.00 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.2, 156.6, 147.2, 140.5, 140.1, 139.6, 134.2, 131.4, 130.8, 129.1, 128.68, 128.66, 128.5, 127.8, 127.4, 126.8, 126.6, 120.4, 32.6, 21.4; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{19}N_2O$, 327.1492; found, 327.1494.

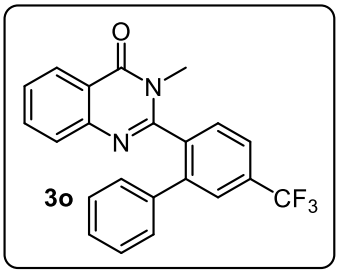
2-(5-chloro-[1,1'-biphenyl]-2-yl)-3-methylquinazolin-4(3H)-one (3n):



Following the general experimental procedure, **3n** was obtained as a colorless solid (30 mg, 43% yield); Reaction time: 30 h at 90 ^oC; R_f: 0.5 (1:2 EtOAc:Pet. ether); mp 148-150 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.26 (d, J = 7.9 Hz, 1H), 7.83-7.75 (m, 2H), 7.58-

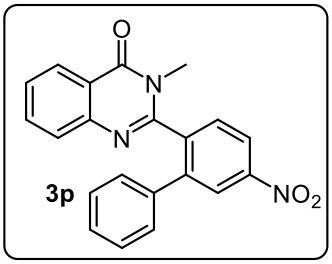
7.48 (m, 4H), 7.34-7.29 (m, 2H), 7.29-7.21 (m, 3H), 2.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162, 155.4, 147, 142, 138.2, 136.4, 134.4, 132.6, 130.7, 130.1, 128.9, 128.5, 128.4, 128.1, 127.5, 127.1, 126.7, 120.5, 32.5; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{16}N_2OCl$, 347.0946; found, 347.0941.

3-methyl-2-(5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)quinazolin-4(3H)-one (3o):



Following the general experimental procedure, **3o** was obtained as a colorless solid (16 mg; 21% yield); Reaction Time: 36 h at 120 ^{o}C. R*f*: 0.35 (1:2 EtOAc:Pet. ether); mp 140-142 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.28 (d, J = 7.9 Hz, 1H), 7.85-7.70 (m, 5H), 7.54 (t, J = 7.3 Hz, 1H), 7.39-7.32 (m, 2H), 7.32-7.27 (m, 3H), 3.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 161.9, 155, 146.9, 141.2, 138, 137.3, 134.5, 132.6 (q, J = 33.1 Hz), 130, 129, 128.7, 128.4, 127.5, 127.3, 127.1 (q, J = 3.9 Hz), 126.8, 124.9 (q, J = 3.9 Hz), 123.6 (q, J = 272 Hz), 120.5, 32.6; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{16}N_2OF_3$, 381.1209; found, 381.1209.

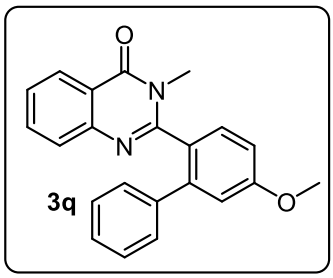
3-methyl-2-(5-nitro-[1,1'-biphenyl]-2-yl)quinazolin-4(3H)-one (3p):



Following the general experimental procedure, **3p** was obtained as a colorless solid (11 mg; 16% yield); Reaction Time: 36 h at 120 ^{o}C. R*f*: 0.3 (1:2 EtOAc:Pet. ether); mp 215-217 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.43 (s, 1H), 8.39 (d, J = 8.6 Hz, 1H), 8.28 (d, J = 7.9 Hz, 1H), 7.87-7.75 (m, 3H), 7.56 (t, J = 7.3 Hz, 1H), 7.41-7.29 (m, 5H), 2.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 161.7, 154.3, 148.9, 146.8, 142.1, 139.7, 137.2, 134.6,

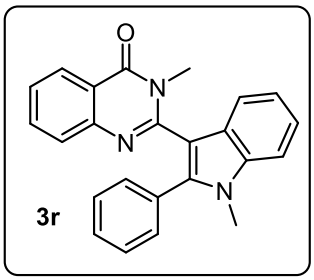
130.8, 129.2, 128.4, 127.56, 127.55, 126.8, 125.1, 122.8, 120.5, 32.4; HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{21}H_{16}N_3O_3$, 358.1186; found, 358.1185.

2-(5-methoxy-[1,1'-biphenyl]-2-yl)-3-methylquinazolin-4(3H)-one (3q):



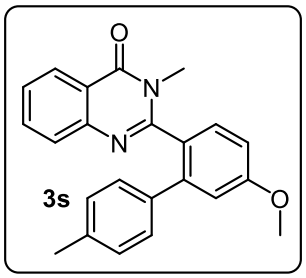
Following the general experimental procedure, **3q** was obtained as a colorless solid (59 mg, 86% yield); Reaction time: 30 h at 90 ^{o}C; R_f: 0.5 (1:1 EtOAc:Pet. ether); mp 192-194 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.25 (d, J = 7.94, 1H), 7.81-7.75 (m, 2H), 7.55-7.46 (m, 2H), 7.36-7.32 (m, 2H), 7.26-7.22 (m, 3H), 7.07-7.07 (m, 2H), 3.92 (s, 3H), 3.0 (s, 3H); ;^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.3, 161, 156.5, 147.2, 141.9, 139.5, 134.2, 130.8, 128.7, 128.4, 128.1, 127.4, 126.9, 126.8, 126.6, 120.4, 115.5, 113.4, 55.6, 32.7; HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{22}H_{19}N_2O_2$, 343.1441; found, 343.1443.

3-methyl-2-(1-methyl-2-phenyl-1H-indol-3-yl)quinazolin-4(3H)-one (3r):



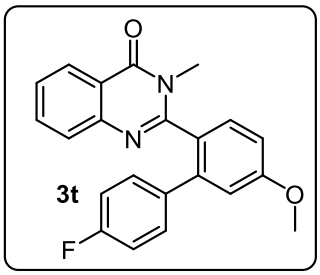
Following the general experimental procedure, **3r** was obtained as a colorless solid (33 mg; 45% yield); Reaction Time: 36 h at 100 ^{o}C. R*f*: 0.5 (1:4 EtOAc:Pet. ether); mp 198-200 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.31 (d, J = 7.9 Hz, 1H), 7.79-7.72 (m, 2H), 7.64 (d, J = 7.9 Hz, 1H), 7.51-7.33 (m, 8H), 7.28-7.23 (m, 1H), 3.80 (s, 3H), 3.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 163, 152.2, 147.8, 140, 137.5, 134, 130.6, 129.9, 129.02, 128.95, 127.5, 126.8, 126.6, 126.5, 123.1, 121.5, 120.4, 119.6, 110, 109.5, 32.9, 31.4; HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{24}H_{20}N_3O$, 366.1601; found, 366.1606.

2-(5-methoxy-4'-methyl-[1,1'-biphenyl]-2-yl)-3-methylquinazolin-4(3H)-one (3s):



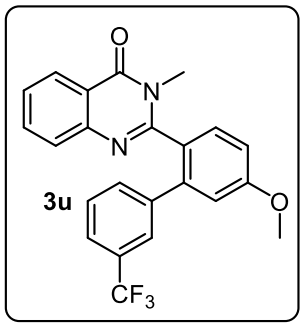
Following the general experimental procedure, **3s** was obtained as a colorless solid (51 mg, 71% yield); Reaction time: 36 h at 95 ^{o}C; R_f: 0.5 (1:1 EtOAc:Pet. ether); mp 130-132 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.26 (d, J = 7.93, 1H), 7.84-7.76 (m, 2H), 7.54-7.44 (m, 2H), 7.22 (m, J = 7.32, 2H), 7.08-7.00 (m, 4H), 3.91 (s, 3H), 2.99 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.3, 160.9, 156.7, 147.3, 141.9, 138, 136.6, 134.2, 130.8, 129.5, 128.2, 127.4, 126.8, 126.7, 126.6, 120.4, 115.4, 113.1, 55.5, 32.60 21.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{21}N_2O_2$, 357.1598; found, 357.1600.

2-(4'-fluoro-5-methoxy-[1,1'-biphenyl]-2-yl)-3-methylquinazolin-4(3H)-one (3t):



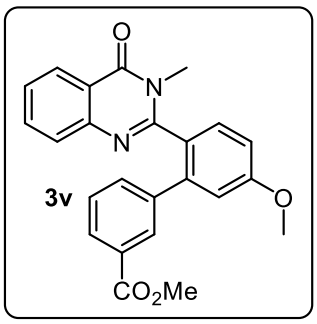
Following the general experimental procedure, **3t** was obtained as a colorless solid (32 mg, 44% yield); Reaction time: 36 h at 90 ^{o}C; R_f: 0.5 (1:1 EtOAc:Pet. ether); mp 155-157 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.26 (d, J = 7.62, 1H), 7.82-7.7.76 (m, 2H), 7.53-7.48 (m, 2H), 7.34-7.29 (m, 2H), 7.05 (dd, J = 2.7, 8.6 Hz, 1H), 7.01 (d, J = 2.7, 1H), 6.95 (t, J = 8.6 Hz 2H), 3.92 (s, 3H), 3.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 162.5 (d, J = 248 Hz), 162.2, 161, 156.2, 147.2, 140.8, 135.5 (d, J = 2.86 Hz), 134.3, 130.8, 130.1 (d, J = 7.63 Hz), 127.4, 126.9, 126.9, 126.7, 120.4, 115.8 (d, J = 21 Hz), 115.6, 113.4, 55.56, 32.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{18}N_2O_2F$, 361.1347; found, 361.1347.

2-(5-methoxy-3'-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)-3-methylquinazolin-4(3H)-one (3u):



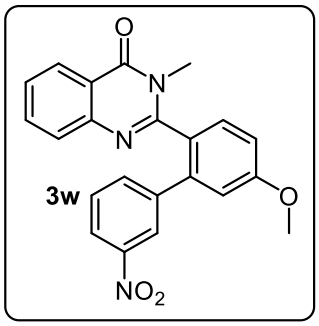
Following the general experimental procedure, **3u** was obtained as a colorless solid (60 mg; 73% yield); Reaction Time: 36 h at 95 ^{o}C. R*f*: 0.3 (1:2 EtOAc:Pet. ether); mp 142-144 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.25 (d, J = 7.3 Hz, 1H), 7.83-7.72 (m, 2H), 7.68 (s, 1H), 7.57-7.45 (m, 4H), 7.35 (t, J = 7.3 Hz, 1H), 7.13-7.07 (m, 1H), 7.05 (d, J = 1.8 Hz, 1H), 3.94 (s, 3H), 3.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.2, 161, 155.6, 146.9, 140.21, 140.17, 134.3, 131.6, 131.1 (q, J = 32.4 Hz), 130.7, 129.2, 127.3, 127, 126.9, 126.6, 125.5 (q, J = 3.9 Hz), 124.7 (q, J = 3.9 Hz), 123.6 (q, J = 272.8 Hz), 120.3, 115.6, 113.9, 55.7, 32.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{18}N_2O_2F_3$, 411.1315; found, 411.1324.

Methyl 5'-methoxy-2'-(3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)-[1,1'-biphenyl]-3-carboxylate (3v):



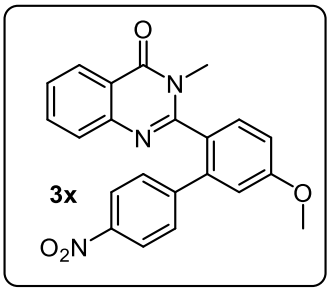
Following the general experimental procedure, **3v** was obtained as a colorless solid (60 mg, 75% yield); Reaction time: 30 h at 90 ^{o}C.R_f: 0.4 (1:2 EtOAc:Pet. ether); mp 118-120 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.25 (d, J = 7.94, 1H), 8.09 (s, 1H), 7.92 (d, J = 3.66, 1H), 7.78 (d, J = 3.66, 2H), 7.56-7.47 (m, 3H), 7.30 (d, J = 7.94, 1H), 7.11-7.06 (m, 2H), 3.93 (s, 3H), 3.72 (s, 3H), 3.0 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.4, 162.2, 161, 156, 147.1, 140.6, 139.56, 134.2, 132.6, 130.7, 129.6, 129.1, 128.8, 127.4, 126.9, 126.6, 120.4, 115.5, 113.8, 55.6, 52, 32.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{21}N_2O_4$, 401.1496; found, 401.1505.

2-(5-methoxy-3'-nitro-[1,1'-biphenyl]-2-yl)-3-methylquinazolin-4(3H)-one (3w):



Following the general experimental procedure, **3w** was obtained as a colorless solid (57 mg, 74% yield); Reaction time: 30 h at 90 ^{o}C; R_f: 0.5 (1:1 EtOAc:Pet. ether); mp 158-160 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.33 (s, 1H), 8.24 (d, J = 7.9 Hz, 1H), 8.12 (d, J = 7.9 Hz, 1H), 7.82-7.74 (m, 2H), 7.63 (d, J = 7.3, 1H), 7.55 (d, J = 8.5, 1H), 7.51 (t, J = 7.32, 1H), 7.39 (t, J = 7.93. 1H), 7.13 (d, J = 8.5, 1H), 7.07 (s, 1H), 3.95 (s, 3H), 3.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.2, 161.1, 155.2, 148.3, 146.9, 141.1, 139.2, 134.5, 134.3, 130.8, 129.7, 127.4, 127.2, 126.6, 126.7, 123.6, 122.9, 120.3, 115.8, 114.3, 55.7, 32.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{18}N_3O_4$, 388.1292; found, 388.1292.

2-(5-methoxy-4'-nitro-[1,1'-biphenyl]-2-yl)-3-methylquinazolin-4(3H)-one (3x):



Following general experimental procedure **3x** was obtained as a colorless solid (53 mg, 68% yield); Reaction time: 36 h at 90 ^{o}C; R_f: 0.5 (1:1 EtOAc:Pet. eher); mp 205-207 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.26 (d, J = 7.94, 1H), 8.12 (d, J = 8.54, 2H), 7.82-7.72 , 2H), 7.58-7.49 (m, 4H), 7.13 (dd, J = 8.54, 1.83, 1H), 7.05 (s, 1H), 3.94 (s, 3H), 3.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.1, 161, 155.3, 147.3, 146.9, 146.1, 139.5, 134.5, 130.9, 129.4, 127.4, 127.3, 126.8, 126.7, 123.9, 120.3, 115.8, 114.4, 55.7, 32.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{18}N_3O_4$, 388.1292; found, 388.1298.

2.1.9. References:

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2.1.10. Selected Spectra:

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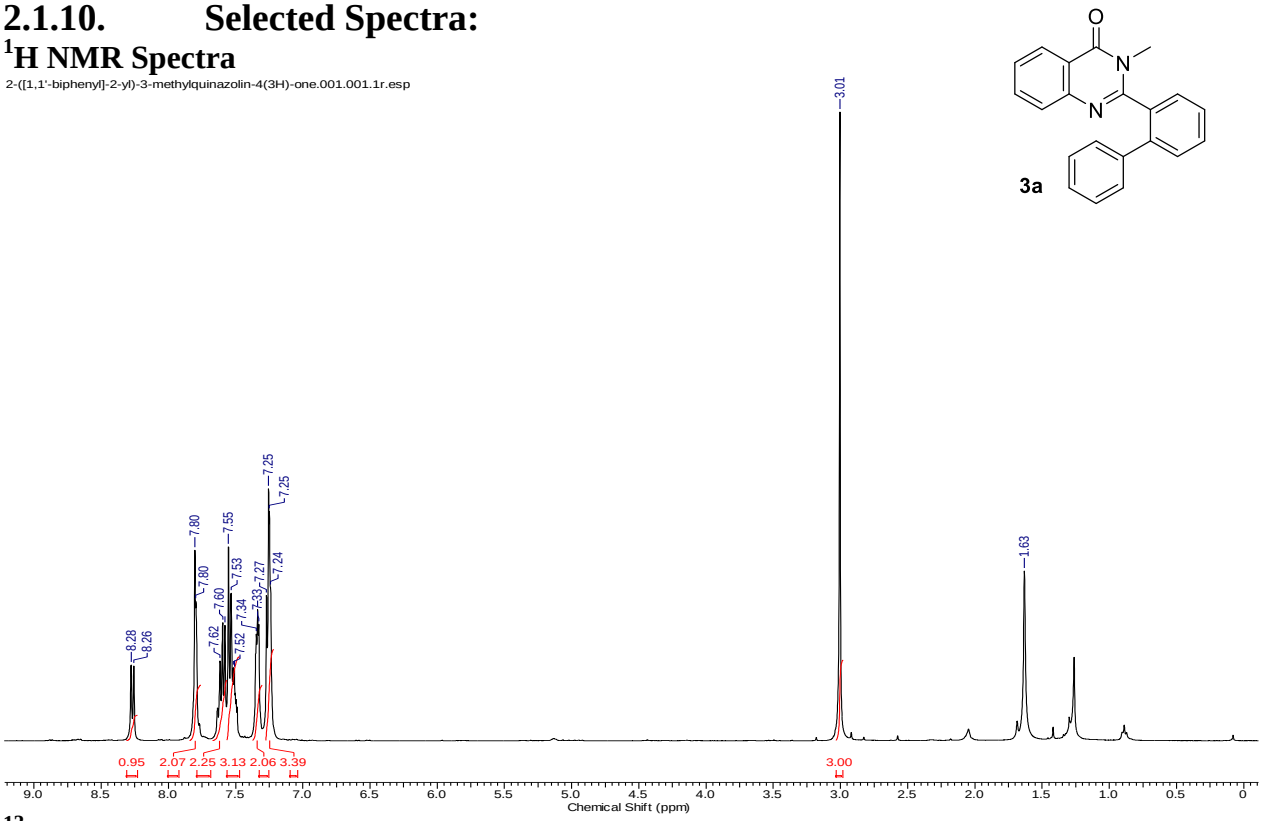

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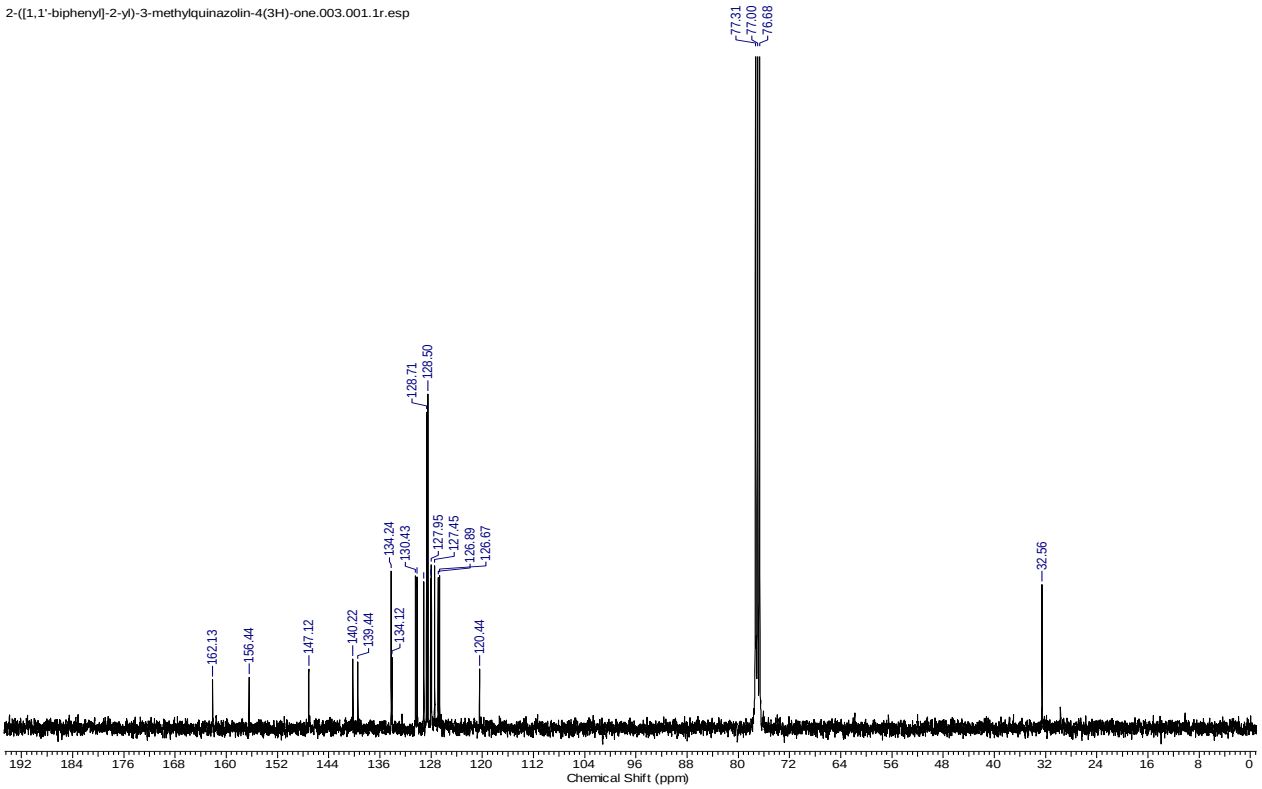

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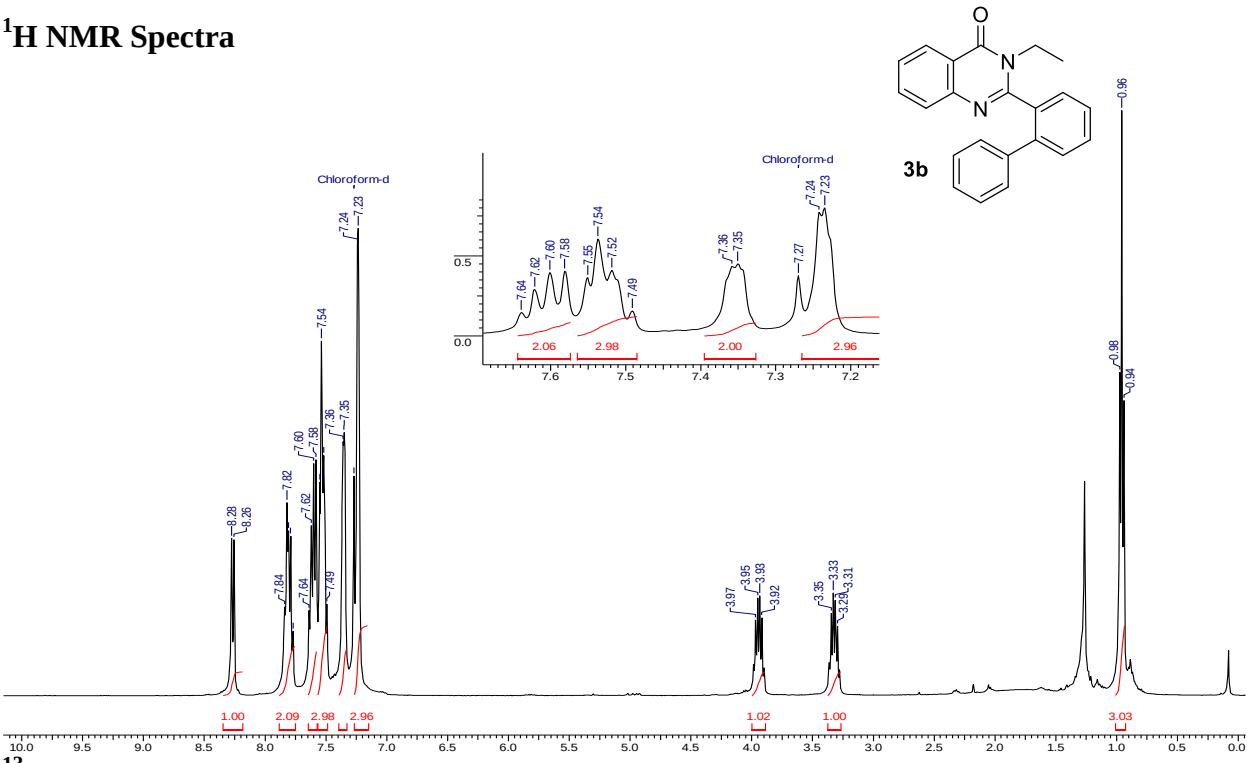

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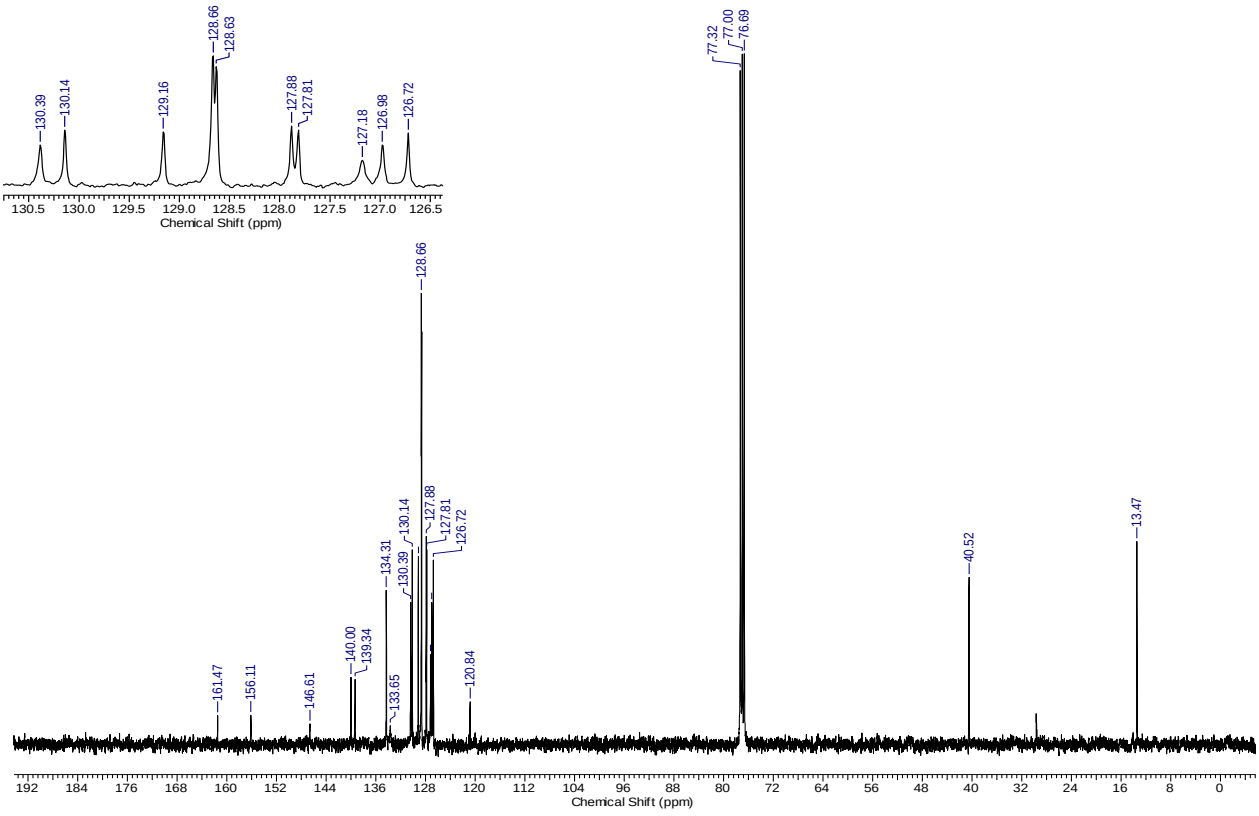

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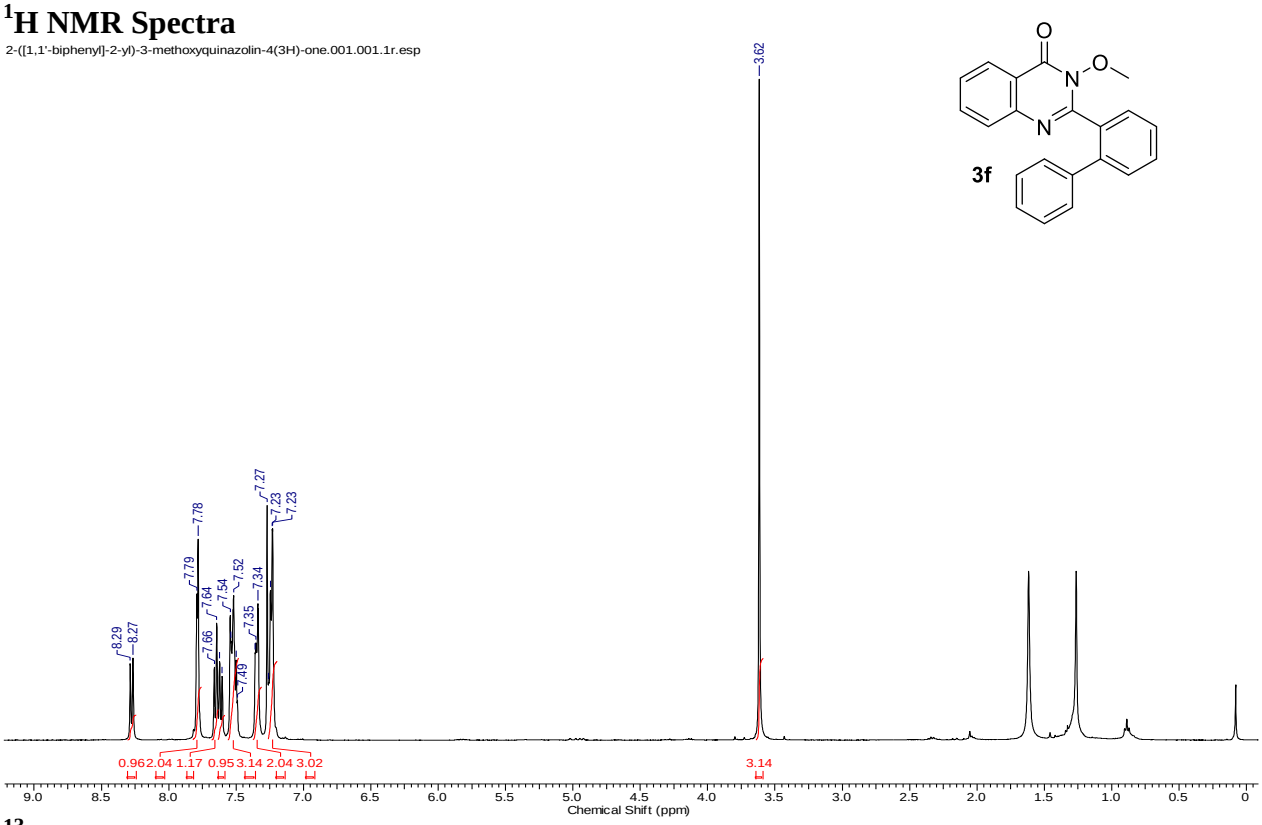

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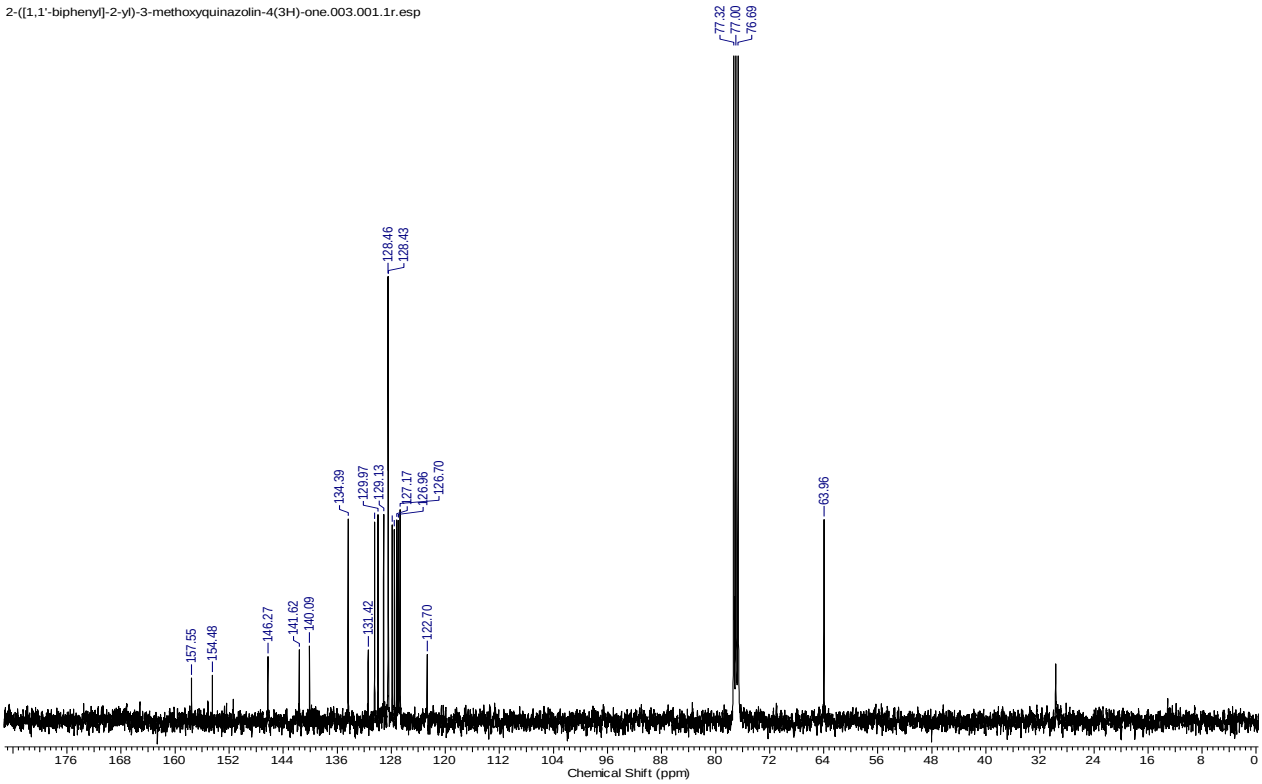

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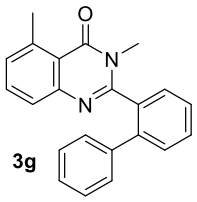

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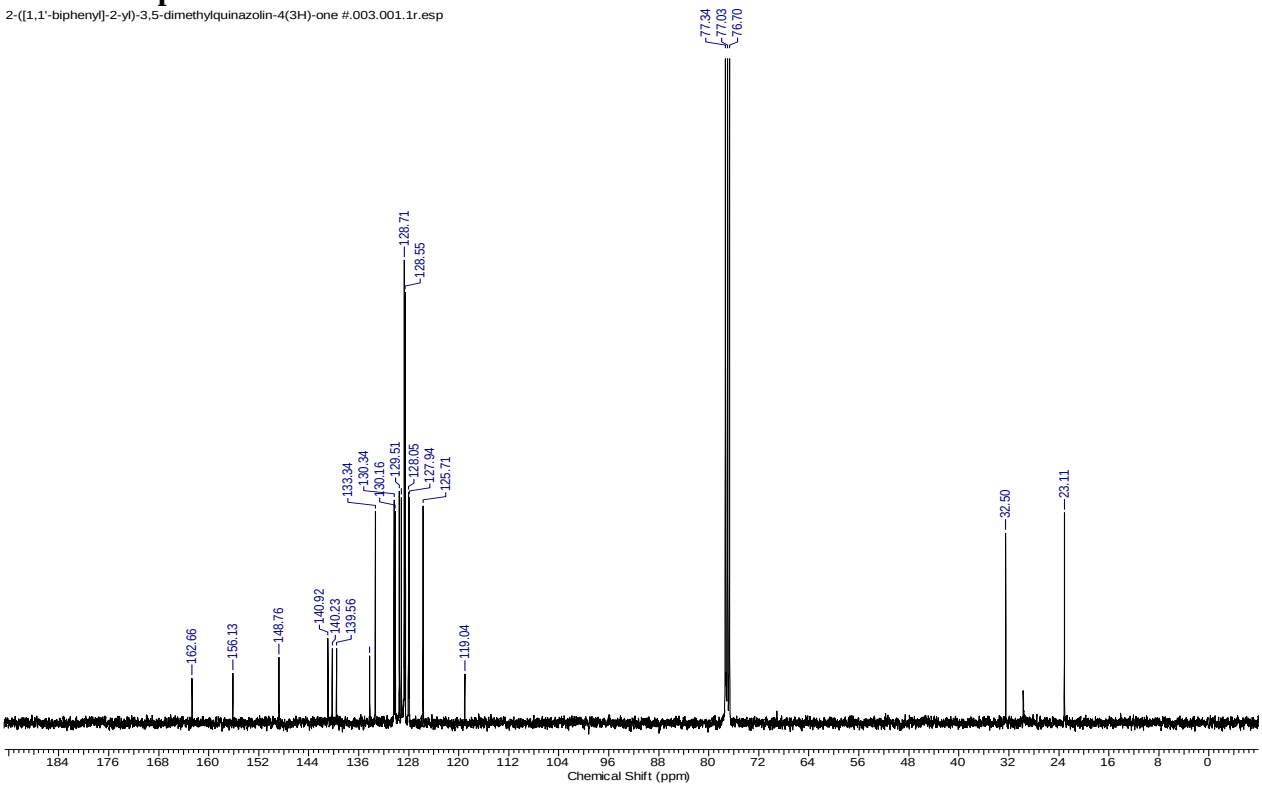

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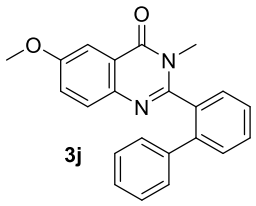

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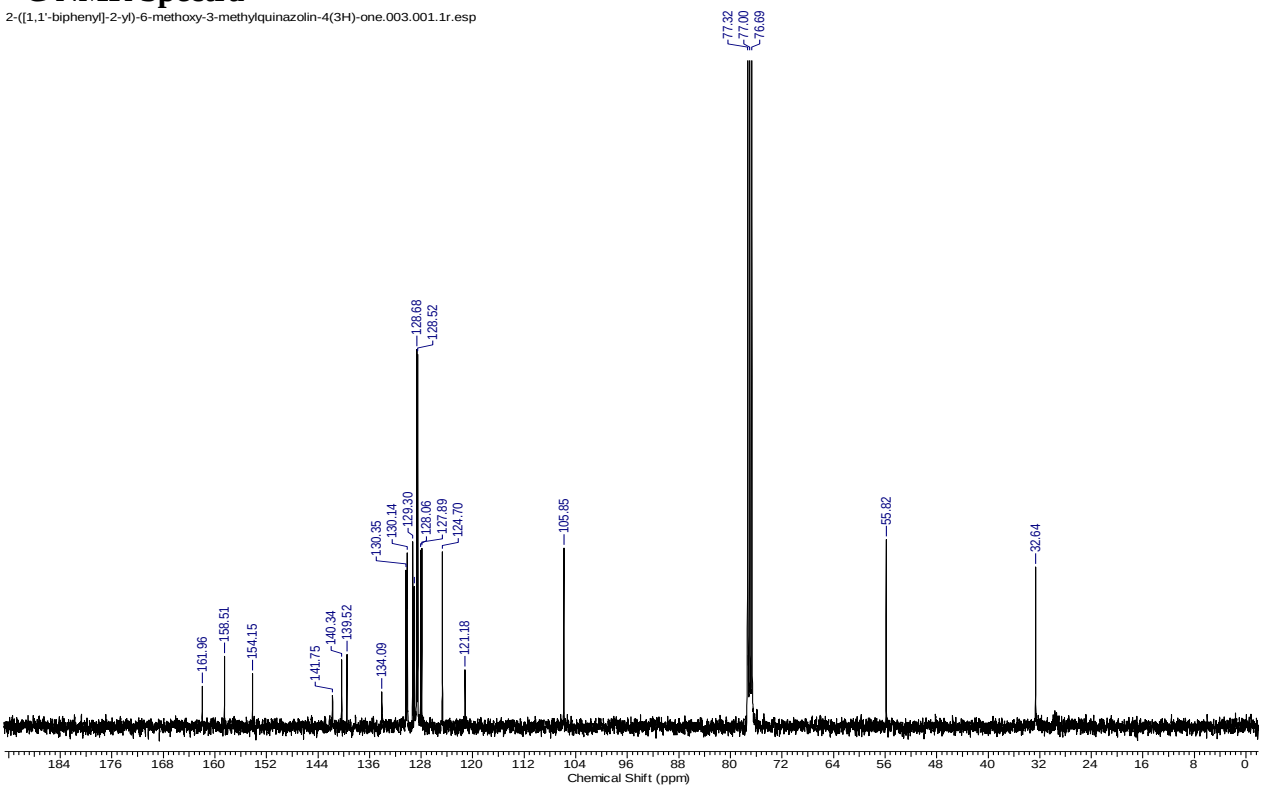

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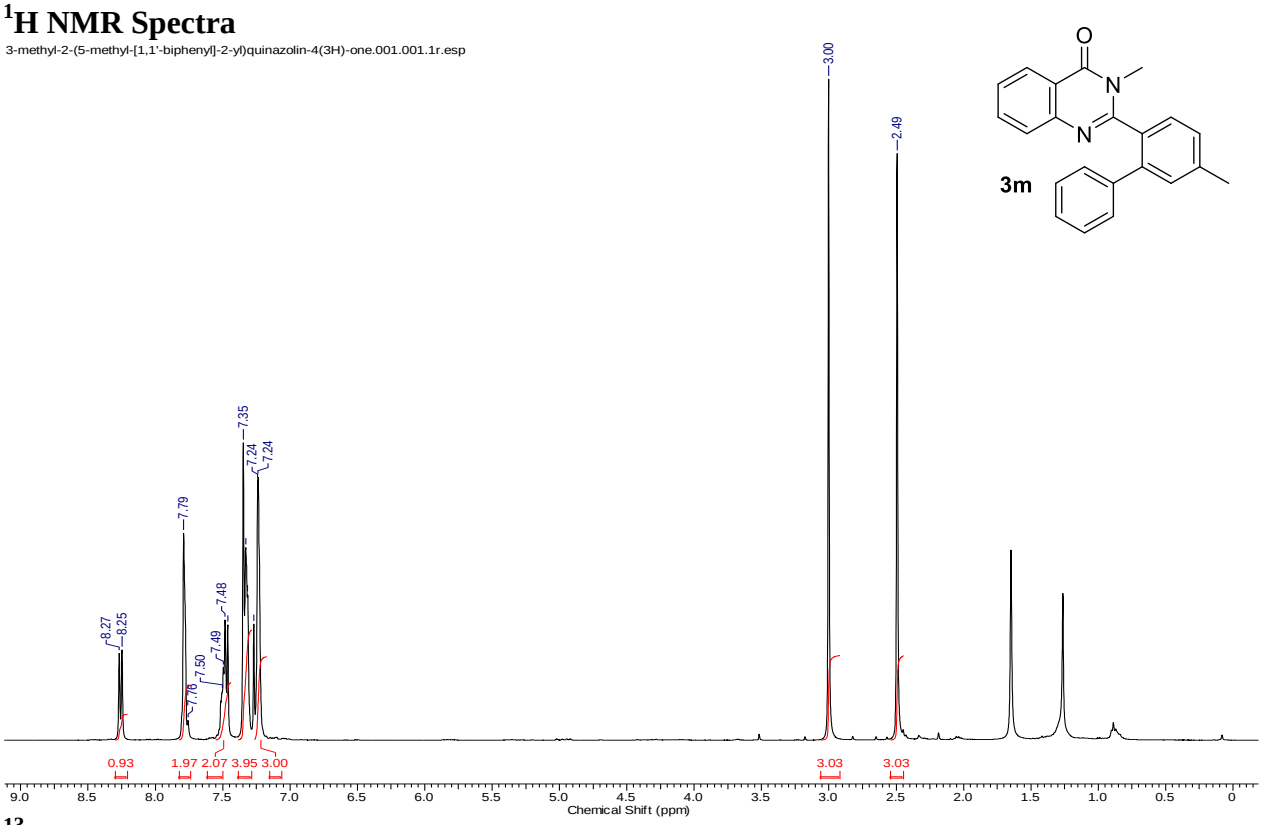

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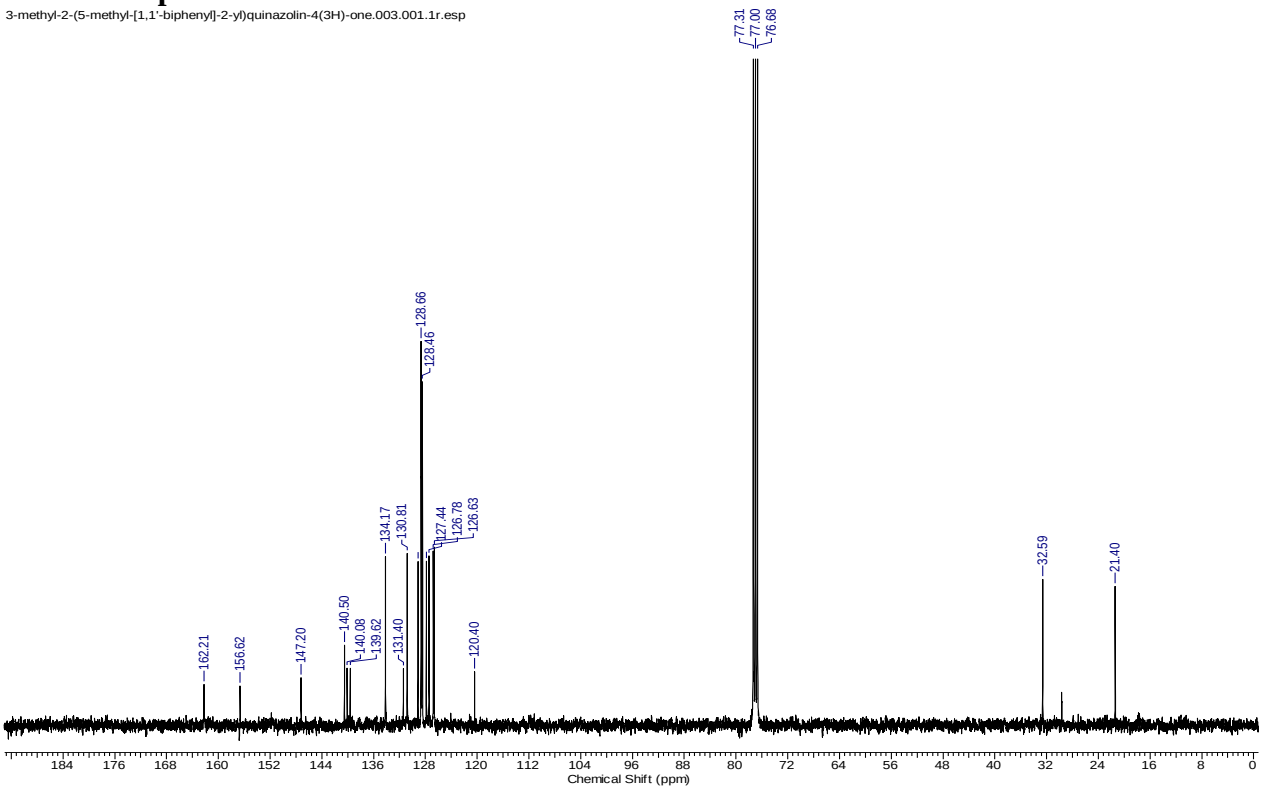

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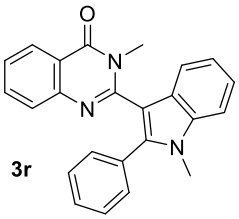

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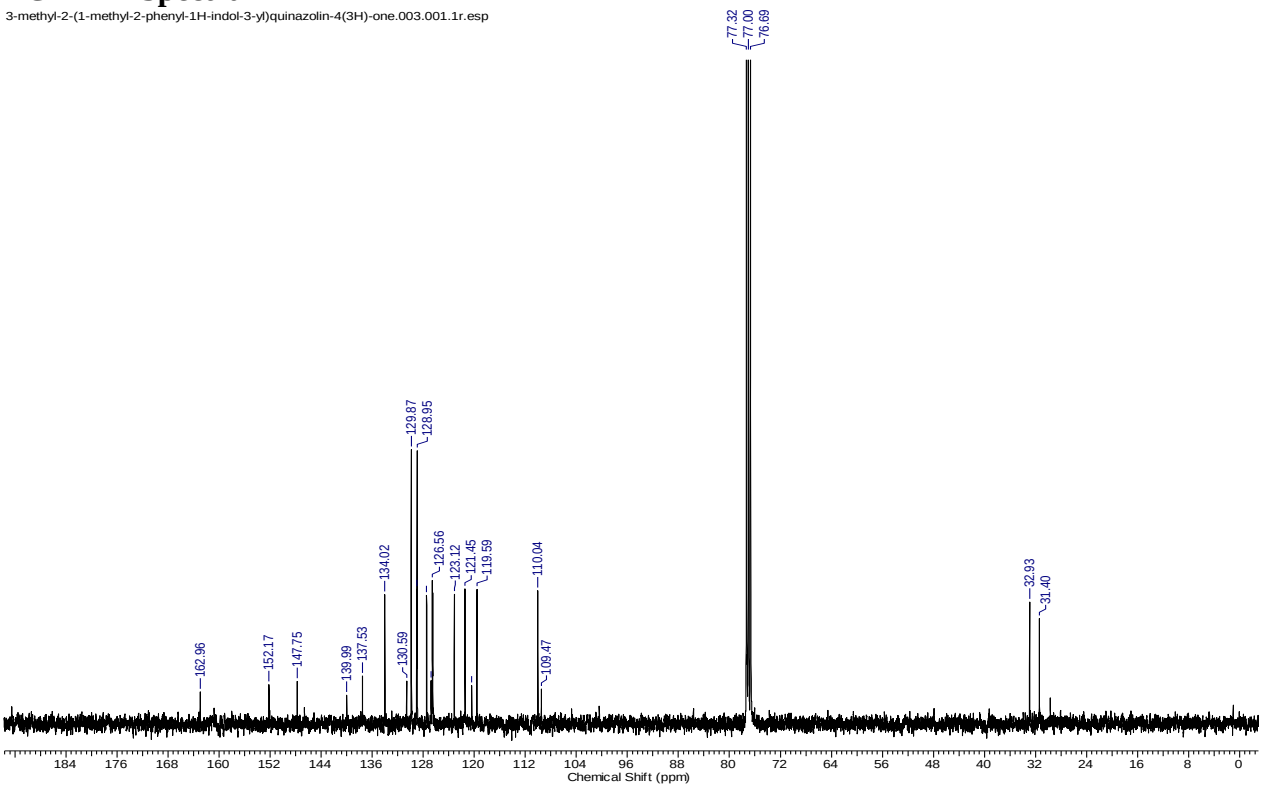

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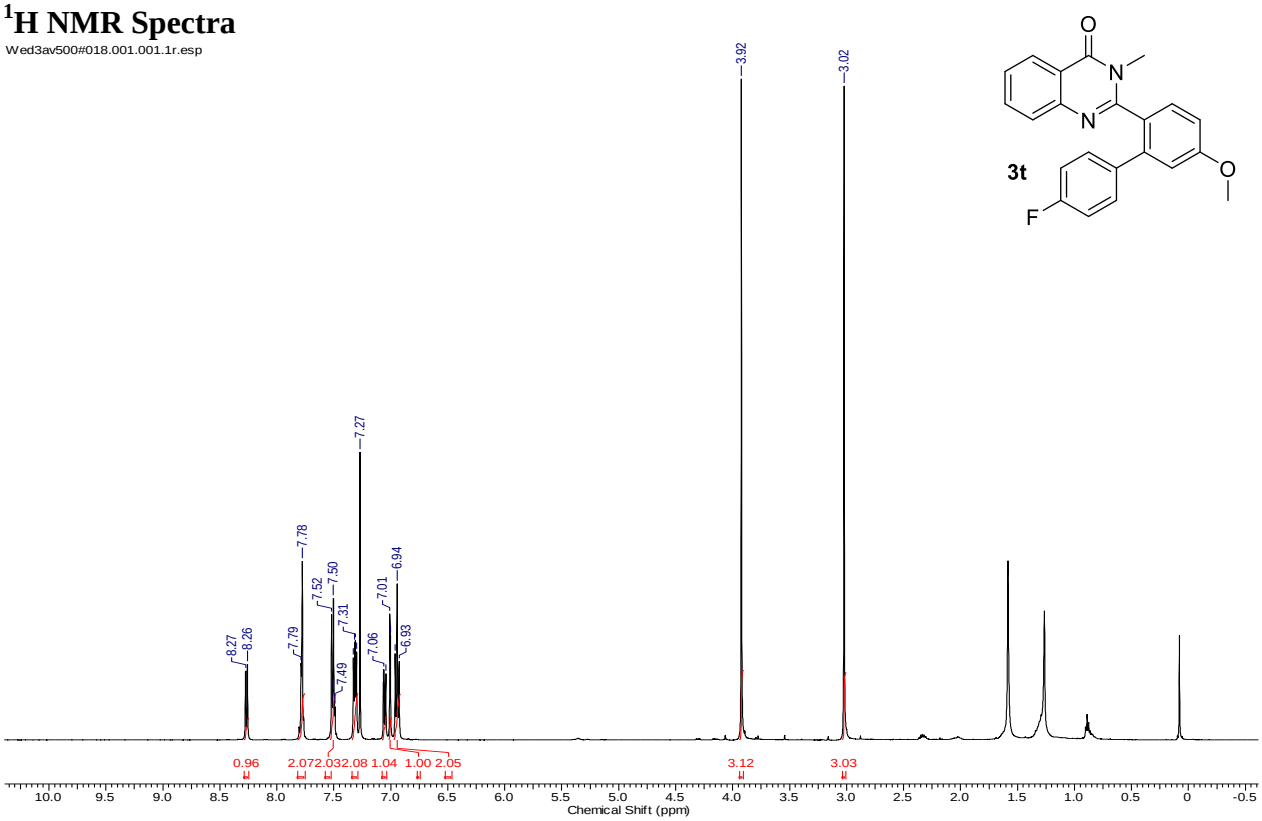

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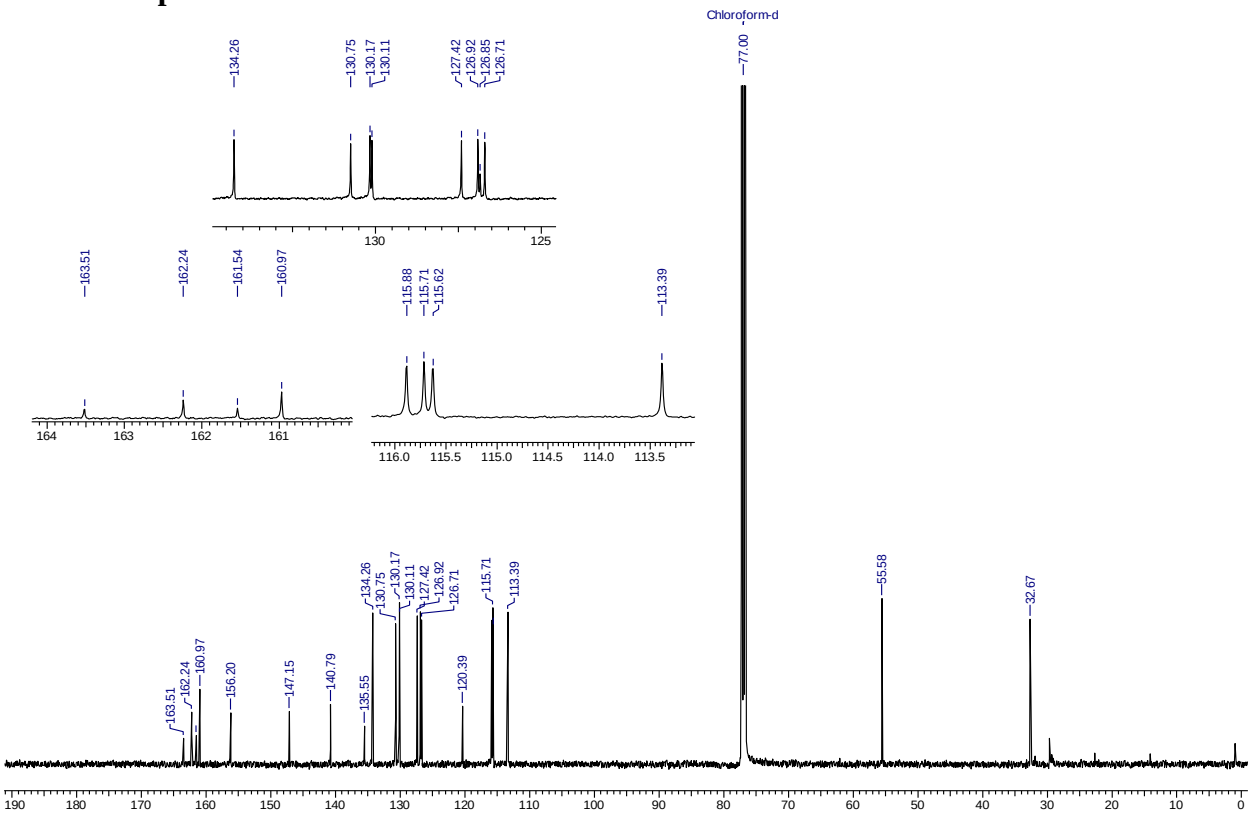

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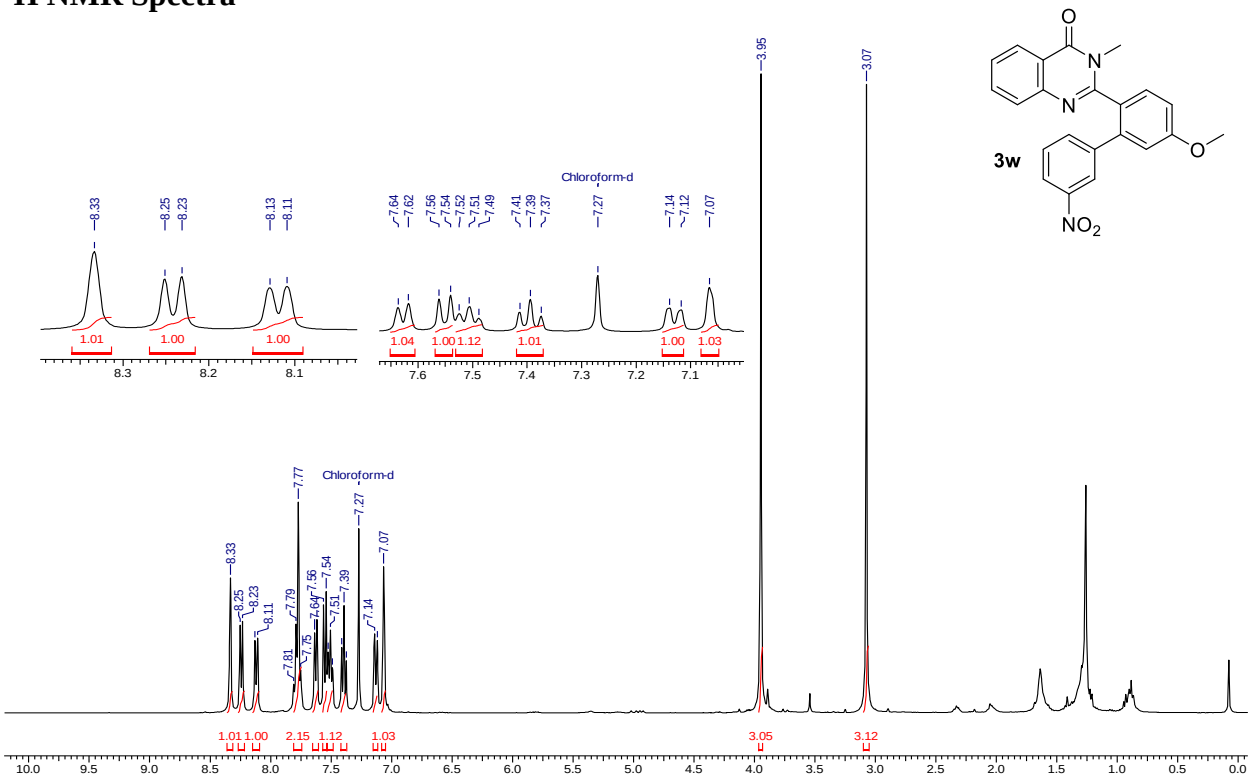

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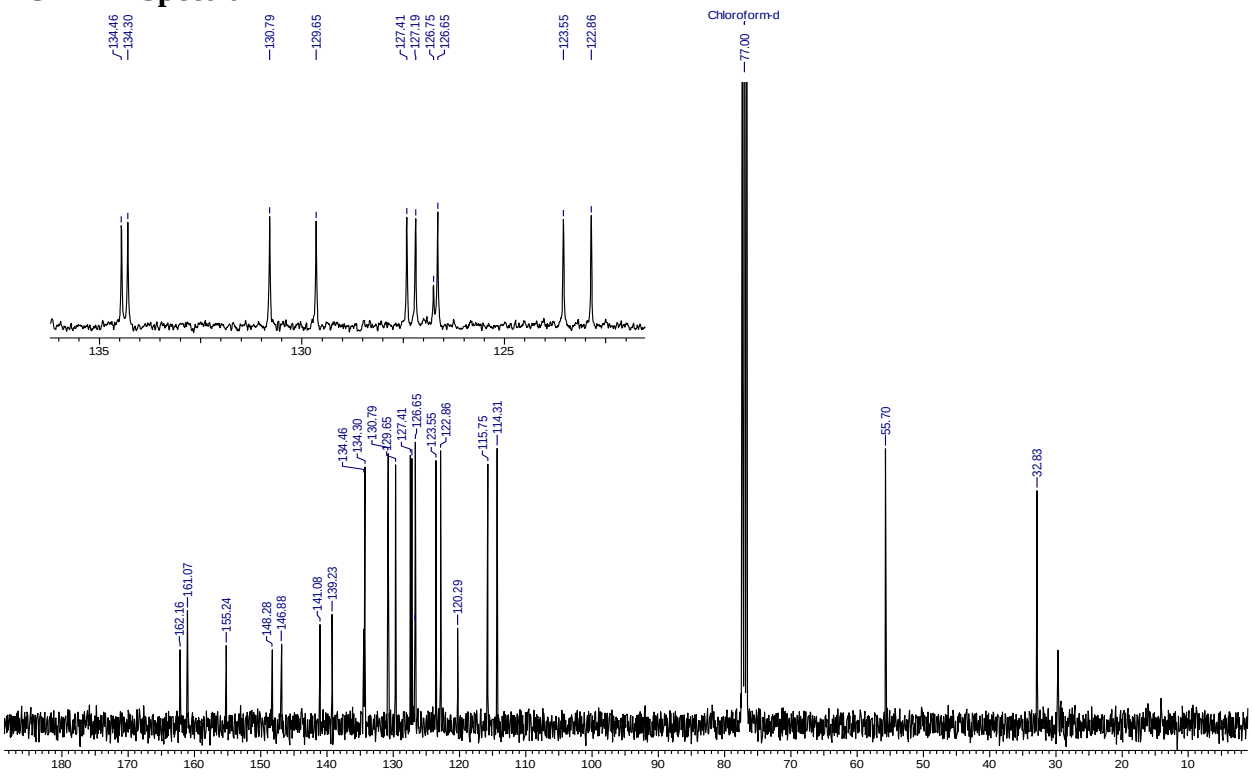


Chapter 2

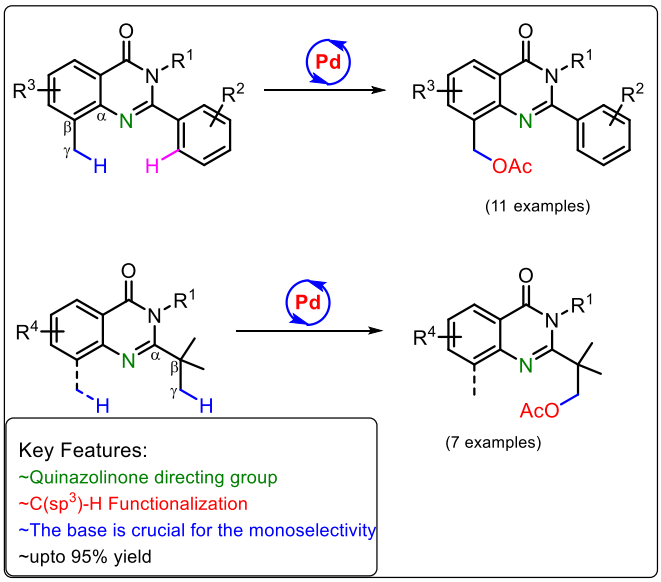
Section 2

Diversification of Quinazolinones by Pd-Catalyzed C(sp^3)-Acetoxylation

Section 2: Diversification of Quinazolinones by Pd-Catalyzed C(sp^3)-Acetoxylation

2.2.1. Abstract:

The quinazolinone ring has been employed as a directing group for C(sp^3)–H functionalization for the first time. The proximal C-γ(sp^3)–H bonds have been oxidized by palladium-catalyzed acetoxylation reaction. Various functional groups on the quinazolinone scaffold were tolerated to provide novel quinazolinone derivatives. The use of base was found to be crucial for the monoselective acetoxylations. The activation of C(sp^3)–H bond was favored over C(sp^2)–H bond, as well as activation of C-γ(sp^3)–H bond was preferred over benzylic C(sp^3)–H bond.



This work has been published in *J. Org. Chem*. **2017**, *82*, 10470.

2.2.2. Introduction:

Quinazolinones is one of the significant classes of heterocyclic compounds, which are commonly found in many natural products and pharmaceuticals.[1] Several biological activities such as antimalarial, antidiabetic, antihypertensive, anticonvulsant, diuretic, anticancer, hypnotic,

antitussive, anti-inflammatory, among others possessed by the quinazolinone alkaloids have gained considerable attention in synthetic as well as medicinal chemistry. Many of the quinazolinone natural products like phaitanthrin E, (–) serantrypinone, vasicinone, adhavasinone balaglitazone, tryptanthrin, among others having good therapeutic assets commonly encompass β or γ sp^3-oxidized carbons (Figure 1).[1c,e] We envisioned that they could be potentially accessed by selective oxidation using metal catalyzed directed C–H activation process.

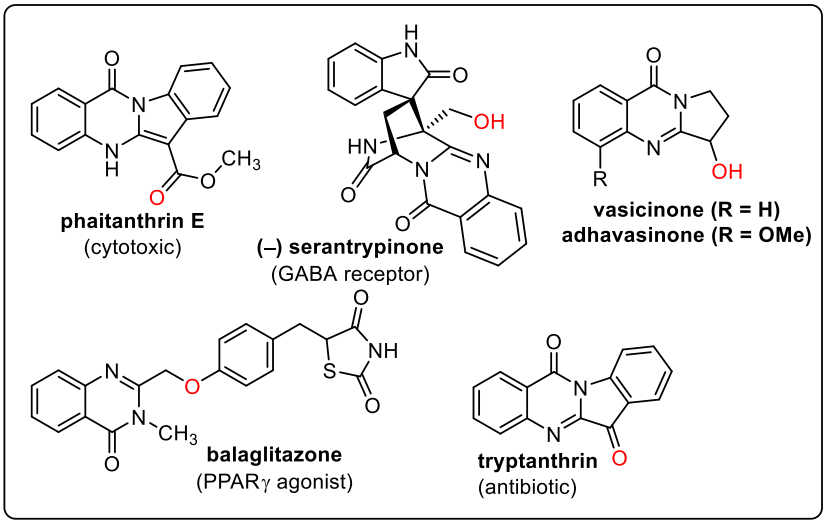


Figure 1. Selected Quinazolinone Natural Products Containing β or γ sp^3-oxidized Carbons

Such C–H bond activation process would assist to eliminate the number of steps and also avoid pre-functionalization of starting materials. The major challenge associated with C–H bond activation is regio-selectivity because organic compounds contain a wide variety of C–H bonds. One of the best ways to overcome the regio-selectivity issue is to use a directing-group, which can bring a metal catalyst into close proximity of precise C–H bond by chelation with a metal catalyst. The major development in the area of C–H bond activation mainly focuses on the C(sp^2)–H bond functionalization. The C(sp^2)–H bonds are comparatively easy to activate because of arene's/olefin's π-stabilizing interaction with a metal catalyst to form strong olefin/aryl-metal bond. In contrast, activation of C(sp^3)–H bonds is underdeveloped and

challenging because of the absence of π-stabilizing interaction with metal center similar to arenes/olefins.[2]

2.2.3. Literature Review:

Directed C–H bond activation has emerged as a powerful tool for the transformation of a C–H bond into C–C and C–X bond (X = O, N, F, Cl, Br, I, Si). Formation of cyclopalladated complexes using monodentate/bidentate chelating group coordination is well known in the literature.[2] Some pioneering examples of Pd(II) palladacycles resulting from a directed C(sp^3)–H bond activation were reported in the literature (Figure 2).[3]

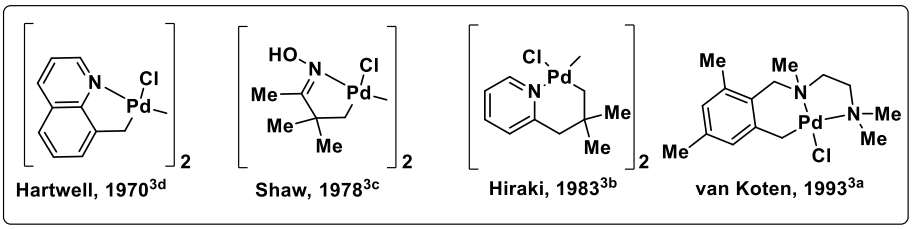
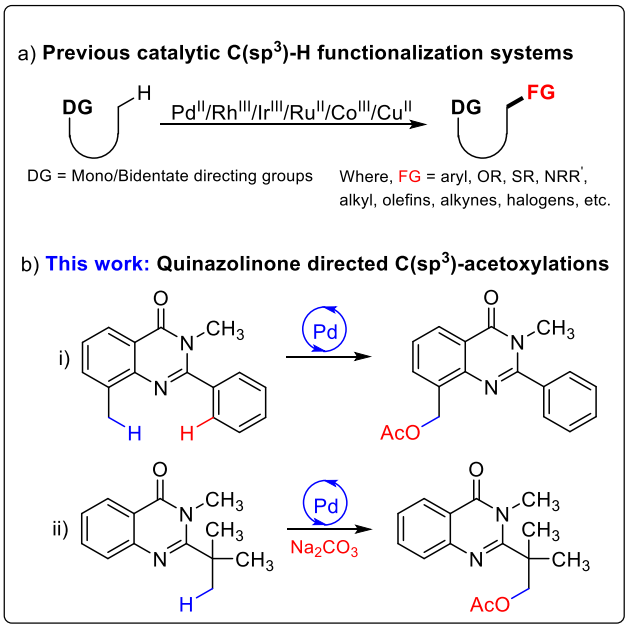


Figure 2. Known pioneering examples of Pd(II) palladacycles resulted from directed C(sp^3)–H bond activation

Notable development has been done in the area of C(sp^3)–H bond activation where various directing groups (including mono as well as bidentate) have been exploited in the C(sp^3)–H bond functionalization.[2-4] Several metal catalysts like Pd, Rh, Ir, Ru, Co, Cu, and Fe have been used for introducing various functional groups on the sp^3 carbons. Arylation, alkylation, olefination, alkynylation, alkoxylation, acetoxylation, hydroxylation, amination, and halogenation are some of the functionalizations, which are often used for C(sp^3)–H diversification by transition metal catalysis (Scheme 1a).[2-7] Though the quinazolinone scaffolds have been synthesized by several advanced strategies[1b] and few metal-catalyzed C(sp^2)–H activation approaches,[8] nevertheless, to

the best of our knowledge, quinazolinone-directed C(sp^3)-H functionalization was not known until this report.



Scheme 1. Transition metal-catalyzed C(sp3)−H functionalizations

2.2.4. Origin of the Work:

Site-selective C−H bond functionalization now could be considered as a reliable strategy for derivatization of complex synthetic intermediates, but its use for late-stage diversification of bioactive molecules is limited, particularly at unactivated sp^3-hybridized C–H bonds of bioactive compounds. Recently, our laboratory has introduced a new protocol for regioselective C(sp^2)-arylations of quinazolinone, directed by intrinsic quinazolinone scaffold.[9] In continuation of our interest in the functionalization of quinazolinone alkaloids by C–H bond activation, we anticipated that quinazolinone scaffold could be used as an intrinsic directing group for the C(sp^3)–H functionalizations. The C(sp^3)-acetoxylation is widely studied process by using various directing groups. In this context, herein we planned to develop quinazolinone directed diverse C(sp^3)-acetoxylations (Scheme 1b).

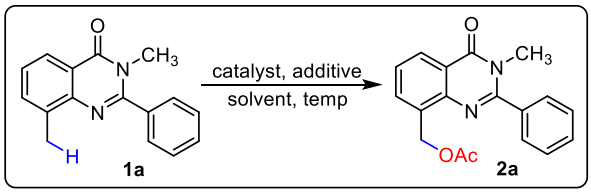
2.2.5. Objective of the work:

Due to the extensive occurrence of quinazolinone scaffold in bioactive natural products and pharmaceuticals, derivatization of quinazolinones would provide novel quinazolinones for the screening of various biological activities. We envisioned that the quinazolinone core could be exploited as the intrinsic directing group for the metal-catalyzed C(sp^3)–H bond activation, which would afford novel quinazolinones for structure-activity-relationship (SAR) studies and developed protocol could be used for the synthesis of natural products and diversification of bioactive molecules.

2.2.6. Result and Discussion:

The optimization of the desired protocol was carried out on the substrate **1a** (Table 1). We first attempted the commonly used C(sp^3)-acetoxylation reaction condition using Pd-catalyst and diacetoxy iodobenzene (PIDA) in acetic acid, but we observed the expected product **2a** formation in moderate yields (entries 1, 2). Interestingly, we did not observe any C(sp^2)-acetoxylated product for this substrate.[8f] Increase in the oxidant mole ratio showed a little improvement in the yield (entry 3). To our delight, when the catalyst loading was doubled, the expected product **2a** was obtained in very good yield (entry 4). Further increase in the oxidant did not improve the yield substantially (entry 5). Many other deviations from the standard condition (entry 4) including solvent, additive, without metal, other metal-catalyst and oxidants resulted in either no reaction or inferior yields (entries 6-11). It is interesting to note that the optimized reaction condition (entry 4) could furnish acetoxylated product **2a** in good yield without using acetic anhydride as a co-solvent, which is generally used for such acetoxylation reactions.

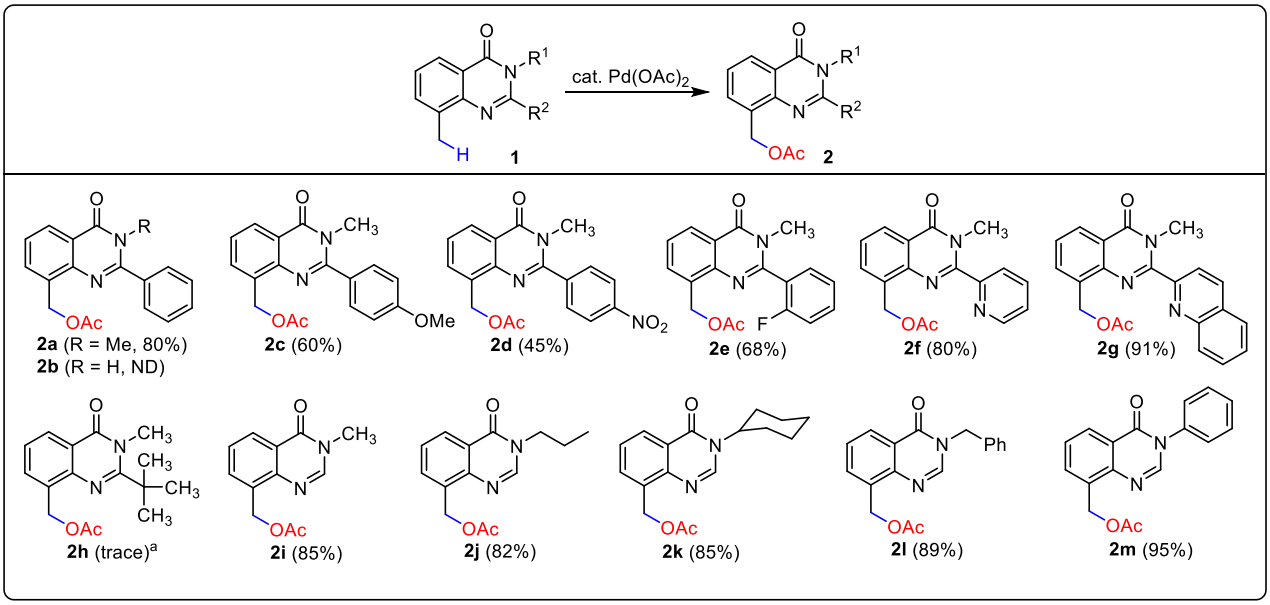
Table 1. Optimization Studies



entry[a]	catalyst (x mol%)	oxidant (equiv)	solvent/temp °C	yield (%)[b]
1	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (1)	AcOH/100	52
2	$Pd(OAc)_2$ (5)	$PhI(OAc)_2$ (1.1)	AcOH/120	58
3	$Pd(OAc)_2$ (5)	$PhI(OAc)_2$ (1.5)	AcOH/120	63
4	**$Pd(OAc)_2$ (10)**	**$PhI(OAc)_2$ (1.5)**	**AcOH/120**	**80**
5	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (2)	AcOH/120	81
6	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (1.5)	toluene/120	N.R.
7[c]	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (1.5)	AcOH/120	62
8	--	$PhI(OAc)_2$ (1.5)	AcOH/120	N.R.
9	$Cu(OAc)_2$ (10)	$PhI(OAc)_2$ (1.5)	AcOH/120	N.R.
10	$Pd(OAc)_2$ (10)	$K_2S_2O_8$ (1.5)	AcOH/120	13
11	$Pd(OAc)_2$ (10)	oxone (1.5)	AcOH/120	25

[a]Reaction conditions: **1a** (0.2 mmol), AcOH (1 mL) in glass tube with screw cap for 24 h. [b]Isolated yield. N.R. = No reaction. [c]Additive: 1.5 equiv Na_2CO_3

After having the identified optimal condition, we next evaluated the scope of the reaction with respect to the substituent variation at various positions of quinazolinones (Scheme 2). The N-H free quinazolinone, when subjected under the developed protocol, ended up in the complex reaction mixture, and no expected product **2b** was detected. Hence, initially *N*-Me substitution was kept constant and the effect of variation at the second position of quinazolinone ring was studied. As mentioned above, quinazolinone with the phenyl ring substituent at the second position provided product **2a** in very good yield, however with electron-donating/withdrawing and halo-substituents on the phenyl ring the expected products **2c-e** were observed in moderate to good yields. The steric hindrance of the aromatic ring at the second position might be affecting the metal coordination and thus resulting in the moderate yields. Pleasingly, the quinazolinones with heterocyclic substituents at the second position produced expected products



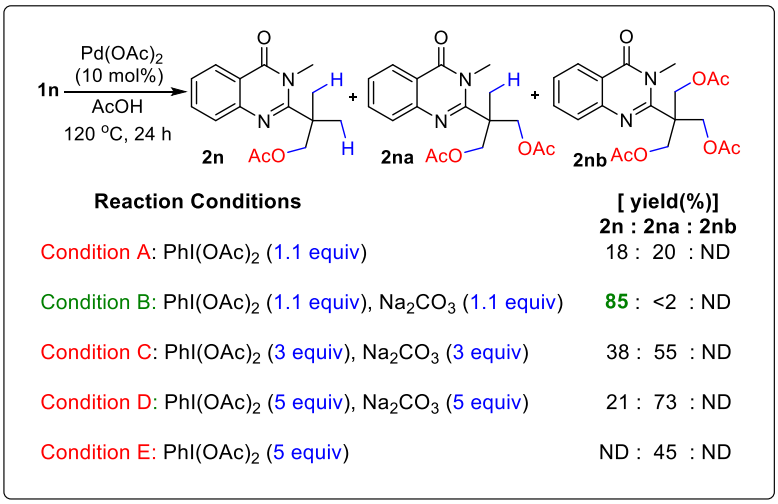
[a]Instead other isomer (scheme 4, **2p**) formed as a major product. ND = not detected.

Scheme 2. Palladium catalyzed benzylic-acetoxylations of various quinazolinones

2f and **2g** in good to excellent yields. Probably the heteroatoms of these substituents coordinate with the metal catalyst more effectively, and substrates behave like a bidentate directing group and hence enhance the reaction. Surprisingly, when alkyl substituted quinazolinone was subjected under the developed protocol, the expected product **2h** was formed in a trace amount along with the formation of other C(sp^3)-acetoxylation product. The quinazolinone without substitution at the second position provided product **2i** in very good yield. Furthermore, the scope of the reaction with respect to *N*-substituent variation was studied. Various *N*-substitutions were well tolerated and furnished the corresponding products such as primary alkyl **2j**, cyclohexyl **2k**, benzyl **2l** and phenyl **2m** in very good to excellent yields.

The result obtained in the scheme 2 with substrate **1h**, prompted us to investigate the scope of the C(sp^3)-acetoxylation reaction on 2-*tert*-butyl substituted quinazolinones. We prepared substrate **1n** for this study (Scheme 3). Application of our standard condition on **1n** provided the monoacetoxylated product **2n** and diacetoxylated product **2na** in almost equivalent ratio

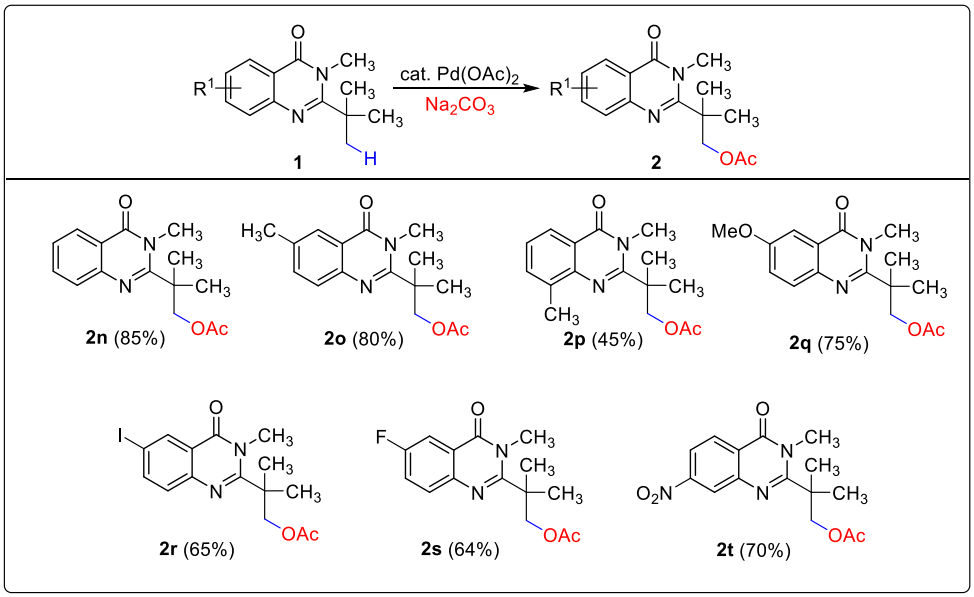
(Condition A). To improve the selectivity, we tried few additives, and gratifyingly addition of sodium carbonate furnished selectively the monoacetoxylated product **2n** in very good yield (Condition B). The crucial effect of a base on the outcome of a reaction was previously observed for C(sp^2)/C(sp^3)-arylation.[9,10] Further increase in the oxidant and additive showed enhancement in the diacetoxylated product **2na** along with substantial amount of monoacetoxylated product **2n** (Condition C, D). However, in the absence of the base, we observed the exclusive formation of diacetoxylated product **2na** in moderate yield (Condition E). We did not observe the formation of the corresponding triacetoxylated product **2nb** in any of these reactions.



Reaction Conditions	[yield(%)] 2n : 2na : 2nb
Condition A: $PhI(OAc)_2$ (1.1 equiv)	18 : 20 : ND
Condition B: $PhI(OAc)_2$ (1.1 equiv), Na_2CO_3 (1.1 equiv)	**85** : <2 : ND
Condition C: $PhI(OAc)_2$ (3 equiv), Na_2CO_3 (3 equiv)	38 : 55 : ND
Condition D: $PhI(OAc)_2$ (5 equiv), Na_2CO_3 (5 equiv)	21 : 73 : ND
Condition E: $PhI(OAc)_2$ (5 equiv)	ND : 45 : ND

Scheme 3. The effect of a base on Palladium catalyzed C(sp^3)-acetoxylations

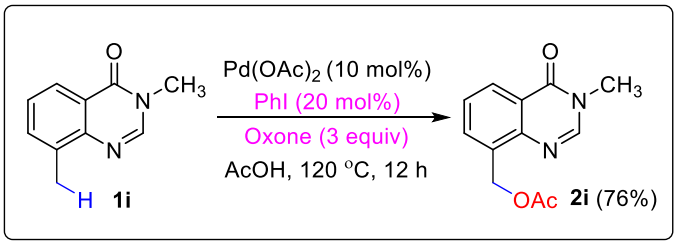
With the optimized condition (scheme 3) for selective monoacetoxylation of 2-*tert*-butyl quinazolinones in hand, we planned to study the scope of the reaction (Scheme 4). The quinazolinone substrate without any substitution at aromatic ring afforded the product **2n** in good yield. The methyl substituted quinazolinones **2o** and **2p** were obtained in good and moderate yields respectively. The 6-methoxy substituted quinazolinone under the developed protocol conceded product **2q** formation in good yield. The reaction scope could be further extended to



Trace amount of diacetoxylated products were observed in all the cases.

Scheme 4. Palladium-catalyzed C(sp^3)-acetoxylations of various quinazolinones

obtain iodo **2r** and fluoro **2s** quinazolinones. The electron deficient quinazolinone with a nitro substituent was also tolerated and furnished the product **2t** in very good yield.



Scheme 5. Reaction with catalytic Iodobenzene and Oxone

Having developed a wide substrate scope of the reaction, we decided to study a catalytic version of our protocol, which may be useful for practical applications. The reagent PIDA could be regenerated *in situ* in the reaction from iodobenzene (20 mol%) and oxone in the acetic acid, which would eventually act as an oxidant for the metal catalyst (Scheme 5). The product **2i** was synthesized in good yield using this catalytic process.

A plausible mechanism for the developed C(sp^3)-H activation protocol is depicted in figure 3. According to the literature analogy,[6i] we believe that in the first step, Pd(II) chelates with the imine nitrogen of quinazolinone **1** and activates the C(sp^3)-H bond to form a five-membered palladacycle **A**. PIDA oxidatively adds to the palladacycle **A** to form the palladacycle **B** [Pd(IV)]. The final step involves C-O bond forming reductive elimination to afford the product **2**. It may proceed either by an intramolecular elimination from the metal center or S_N2 attack by an external acetate ion.[6i]

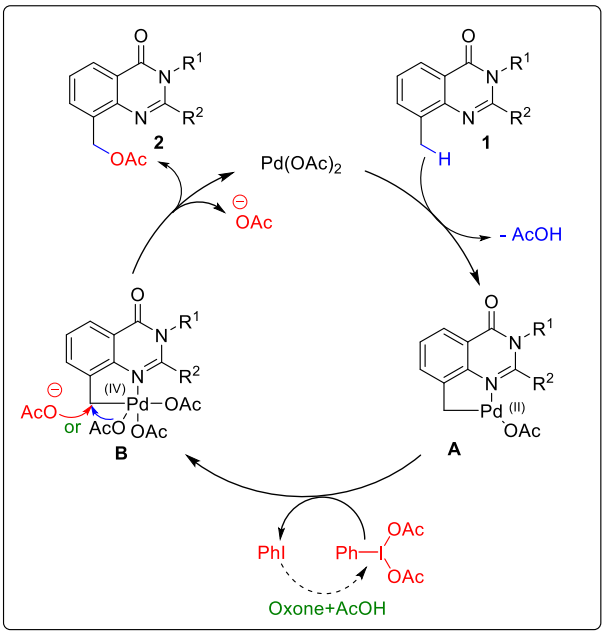


Figure 3. Plausible mechanism

2.2.7. Conclusion:

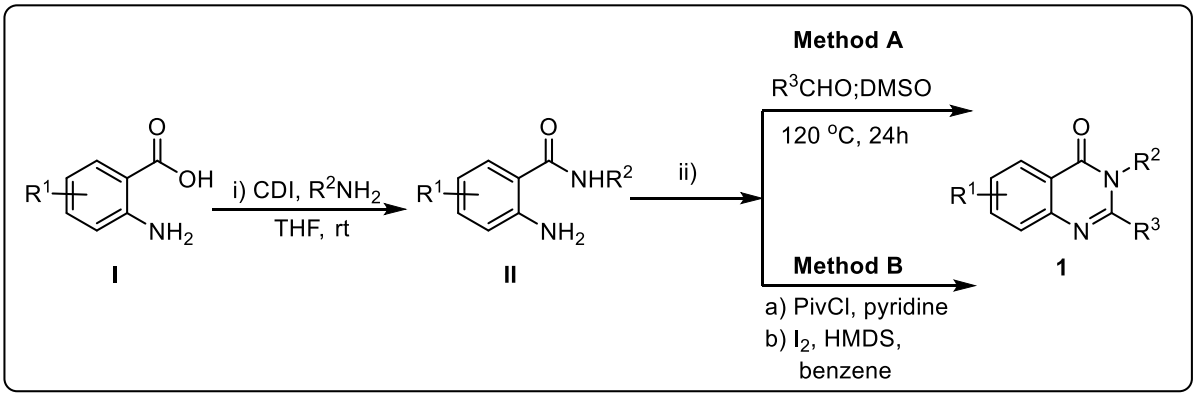
In summary, quinazolinone scaffold has been successfully used as an inherent directing group for Pd-catalyzed C(sp^3)-H functionalization. Diverse novel quinazolinone derivatives have been synthesized. The developed acetoxylation protocol could be used for the synthesis of natural products and derivatization of bioactive quinazolinones for SAR studies. A base controlled monoselective acetoxylation demonstrated herein may find important applications in the area of

C-H activation. Currently, the work towards the development of quinazolinone directed asymmetric C-H activation processes for the synthesis of bioactive natural products and their congeners is underway in our laboratory.

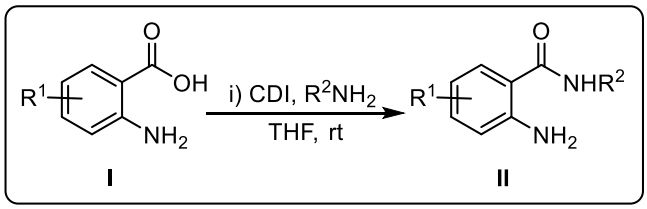
2.2.8. Experimental Procedures and Characterization Data of Compounds:

I) Experimental Procedures for the Synthesis of Starting Materials:

All quinazolinone starting materials were prepared according to modified literature procedures.[11,12]



Step i: General Procedure for the Synthesis of Anthranilamides:

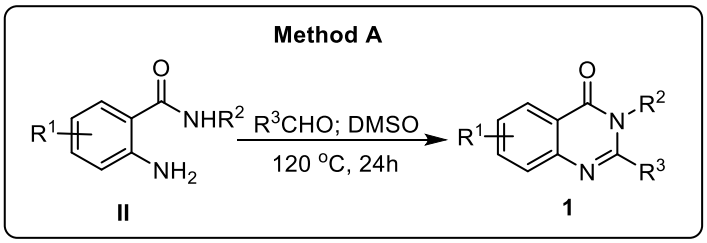


To a solution of substituted anthranilic acid **I** (1 mmol) in THF (5 mL) was added 1,1'-carbonyldiimidazole (CDI) (1 mmol) under argon atmosphere and the resulting reaction mixture was stirred at room temperature (RT) for 12 h. The corresponding amine (1.1 mmol) [or 40% aqueous solution in case of methyl amine (5 mmol)] was added to the above reaction mixture at

RT and stirred for another 4 h. It was diluted with ethyl acetate (50 mL), and the organic layer was washed with water and brine followed by drying over anhydrous sodium sulfate and concentration in *vacuo*. The crude anthranilamide **II** was used further without purification.

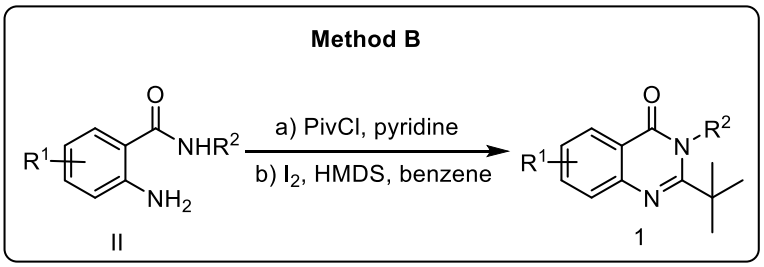
Step ii: General Procedures for the Synthesis of Quinazolinones from Anthranilamides:

Method A:



The *N*-substituted anthranilamides **II** from step (i) (1.0 mmol; 1.0 equiv) and the corresponding aldehydes (1.1 mmol; 1.1 equiv) [or 40% aqueous solution in the case of formaldehyde (1.5 mmol; 1.5 equiv)] were dissolved in DMSO (5 mL). The reaction mixture was stirred at 120 ^{o}C in an open flask and the progress was monitored by TLC. After complete consumption (24 h) of the starting materials, the reaction mixture was poured onto water and extracted with DCM. The organic layer was combined, dried over anhydrous sodium sulfate, and concentrated in *vacuo*. The crude mixture was purified by silica gel column chromatography using petroleum ether / EtOAc (5-10:1) as eluents to afford quinazolinone **1**.

Method B:

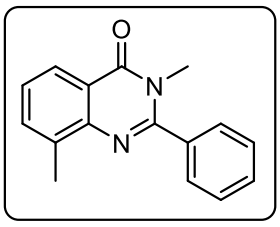


(a) To the solution of *N*-substituted anthranilamides **II** from step (i) (1.0 mmol; 1.0 equiv) in DCM (10 mL) was added pyridine (3 mmol; 3 equiv). After 5 minutes pivaloyl chloride (1.1 mmol; 1.1 equiv) was added slowly at RT and the resulting mixture was stirred for another 6 h.

The reaction mixture was then diluted with DCM (50 mL) and washed with HCl (aqueous, 1M), saturated aqueous $NaHCO_3$ and brine. The organic phase was dried over sodium sulfate and concentrated in *vacuo.* The crude product was used further without purification.

(b) Iodine (4 mmol; 4 equiv) was added to the solution of crude product from step (a) (1.0 mmol; 1.0 equiv) in benzene (10 mL). Subsequently HMDS (5 mmol; 5 equiv) was added slowly and the reaction mixture was heated to 80 ^oC for 12 h. It was allowed to cool to RT and diluted with DCM (50 mL). The organic layer was washed with aqueous Na_2SO_3, brine and water. The organic layer was dried over anhydrous sodium sulfate and concentrated in *vacuo.* The crude product was purified by silica gel column chromatography using petroleum ether / EtOAc (5-10:1) as eluents to afford quinazolinone **1**.

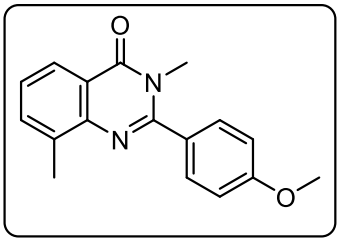
3,8-Dimethyl-2-phenylquinazolin-4(3*H*)-one (1a)



Following the **Method A** procedure, **1a** was obtained as a colorless solid (153 mg; 61% yield). R*f*: 0.5 (1:4 EtOAc: Pet. ether); mp 121-124 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.19 (d, J = 7.9 Hz, 1H), 7.65-7.58 (m, 3H), 7.56-7.50 (m, 3H), 7.39 (t, J = 7.9 Hz, 1H), 3.52 (s, 3H), 2.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 163.3, 154.6, 146, 136.1, 135.8, 134.8, 129.9, 128.6, 128.4, 126.5, 124.3, 120.4, 34.4, 17.3; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{16}H_{15}ON_2$ 251.1179, found 251.1177.

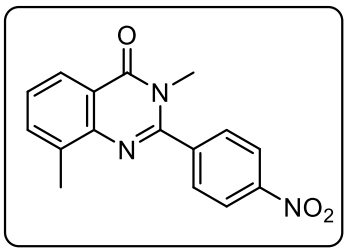
2-(4-Methoxyphenyl)-3,8-dimethylquinazolin-4(3*H*)-one (1c)

Following the **Method A** procedure, **1c** was obtained as a colorless solid (118 mg; 42% yield). R*f*: 0.4 (1:4 EtOAc: Pet. ether); mp 161-163 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.17 (d, J = 7.9 Hz, 1H), 7.64-7.52 (m, 3H), 7.37 (t, J = 7.9 Hz, 1H), 7.04 (d, J = 8.5 Hz, 2H), 3.90 (s, 3H),



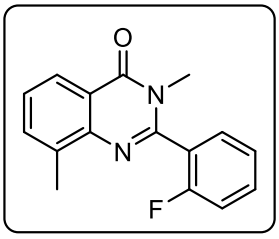
3.56 (s, 3H), 2.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 163.5, 160.9, 154.5, 146.1, 135.9, 134.7, 130.2, 128.2, 126.2, 124.3, 120.3, 114, 55.4, 34.6, 17.3; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{17}H_{17}O_2N_2$ 281.1285, found 281.1284.

3,8-Dimethyl-2-(4-nitrophenyl)quinazolin-4(3*H*)-one (1d)



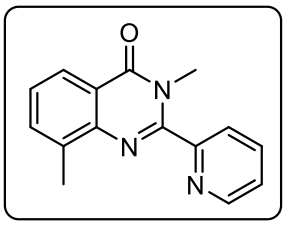
Following the **Method A** procedure, **1d** was obtained as a pale yellow solid (148 mg; 50% yield). R*f*: 0.5 (1:3 EtOAc: Pet. ether); mp 221-223 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.41 (d, *J* = 8.5 Hz, 2H), 7.19 (d, *J* = 7.9 Hz, 1H), 7.83 (d, *J* = 8.5 Hz, 2H), 7.64 (d, *J* = 6.7 Hz, 1H), 7.43 (d, *J* = 7.4 Hz, 1H), 3.52 (s, 3H), 2.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.8, 152.3, 148.5, 145.6, 141.5, 136.3, 135.1, 129.7, 127.3, 124.4, 124, 120.6, 34.2, 17.2; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{16}H_{14}O_3N_3$ 296.1030, found 296.1030.

2-(2-Fluorophenyl)-3,8-dimethylquinazolin-4(3*H*)-one (1e)



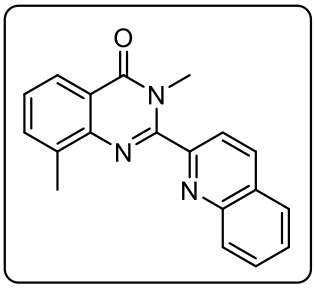
Following the **Method A** procedure, **1e** was obtained as a colorless solid (161 mg; 60% yield). R*f*: 0.5 (1:4 EtOAc: Pet. ether); mp 129-131 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.20 (d, *J* = 7.9 Hz, 1H), 7.66-7.49 (m, 3H), 7.41 (t, *J* = 7.9 Hz, 1H), 7.34 (t, *J* = 7.9 Hz, 1H), 7.22 (t, *J* = 9.2 Hz, 1H), 3.48 (s, 3H), 2.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.7, 159.4 (d, *J* = 248.9 Hz), 150.4, 146, 136.2, 134.8, 132 (d, *J* = 8.5 Hz), 130.7 (d, *J* = 3.1 Hz), 126.8, 124.9 (d, *J* = 3.1 Hz), 124.3, 124 (d, *J* = 15.4 Hz), 120.7, 115 (d, *J* = 20.8 Hz), 32.8 (d, *J* = 3.9 Hz), 17.3; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{16}H_{14}ON_2F$ 269.1085, found 269.1084.

3,8-Dimethyl-2-(pyridin-2-yl)quinazolin-4(3*H*)-one (1f)



Following the **Method A** procedure, **1f** was obtained as a colorless solid (138 mg; 55% yield). R*f*: 0.5 (1:2.3 EtOAc: Pet. ether); mp 165-167 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.72 (d, J = 4.3 Hz, 1H), 8.20 (d, J = 7.9 Hz, 1H), 7.96-7.88 (m, 2H), 7.61 (d, J = 7.3 Hz, 1H), 7.48-7.37 (m, 2H), 3.65 (s, 3H), 2.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 163.1, 154.1, 152.3, 148.5, 145.8, 137.2, 136.1, 134.7, 126.8, 124.9, 124.5, 124.4, 120.9, 33.6, 17.2; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{15}H_{14}ON_3$ 252.1131, found 252.1129.

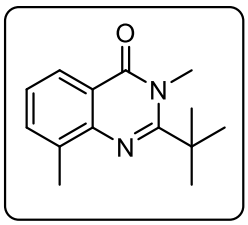
3,8-Dimethyl-2-(quinolin-2-yl)quinazolin-4(3*H*)-one (1g)



Following the **Method A** procedure, **1g** was obtained as a colorless solid (157 mg; 52% yield). R*f*: 0.5 (1:4 EtOAc: Pet. ether); mp 198-200 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.38 (d, J = 8.5 Hz, 1H), 8.23 (d, J = 7.9 Hz, 1H), 8.16 (d, J = 8.5 Hz, 1H), 8.05 (d, J = 7.9 Hz, 1H), 7.93 (d, J = 7.9 Hz, 1H), 7.81 (t, J = 7.9 Hz, 1H), 7.66 (t, J = 7.9 Hz, 1H), 7.62 (d, J = 7.3 Hz, 1H), 7.42 (t, J = 7.9 Hz, 1H), 3.78 (s, 3H), 2.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 163.2, 153.6, 152.4, 146.7, 145.8, 137.3, 136.2, 134.7, 130.2, 129.7, 128, 127.8, 127.6, 127, 124.5, 121.9, 121, 33.7, 17.3; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{19}H_{16}ON_3$ 302.1288, found 302.1284.

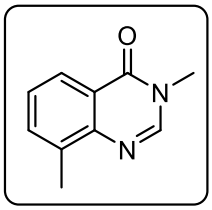
2-(*tert*-Butyl)-3,8-dimethylquinazolin-4(3*H*)-one (1h)

Following the **Method B** procedure, **1h** was obtained as a beige solid (124 mg; 54% yield). R*f*: 0.5 (1:6 EtOAc: Pet. ether); mp 56-58 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.09 (d, J = 7.9 Hz, 1H), 7.55 (d, J = 7.3 Hz, 1H), 7.32 (t, J = 7.9 Hz, 1H), 3.76 (s, 3H), 2.60 (s, 3H), 1.57 (s,



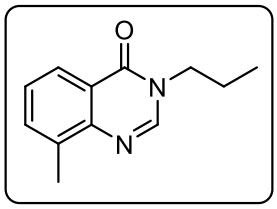
9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 164.4, 159.9, 145.1, 136.1, 134.3, 126, 123.9, 119.7, 39.6, 33.4, 29.6, 17; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{14}H_{19}ON_2$ 231.1492, found 231.1491.

3,8-Dimethylquinazolin-4(3*H*)-one (1i)



Following the **Method A** procedure, **1i** was obtained as a colorless solid (139 mg; 80% yield). R*f*: 0.5 (1:2 EtOAc: Pet. ether); mp 81-84 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.16 (d, J = 7.9 Hz, 1H), 8.06 (s, 1H), 7.59 (d, J = 7.3 Hz, 1H), 7.38 (t, J = 7.9 Hz, 1H), 3.59 (s, 3H), 2.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 161.9, 146.9, 145.5, 135.8, 134.8, 126.8, 124.2, 121.9, 34, 17.4; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{10}H_{11}ON_2$ 175.0866, found 175.0865.

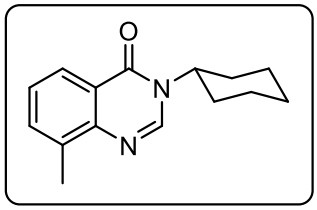
8-Methyl-3-propylquinazolin-4(3*H*)-one (1j)



Following the **Method A** procedure, **1j** was obtained as a colorless solid (136 mg; 67% yield). R*f*: 0.4 (1:4 EtOAc: Pet. ether); mp 100-102 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.17 (d, J = 7.9 Hz, 1H), 8.05 (s, 1H), 7.59 (d, J = 7.3 Hz, 1H), 7.38 (t, J = 7.9 Hz, 1H), 3.97 (t, J = 6.7 Hz, 2H), 2.61 (s, 3H), 1.89-1.80 (m, 2H), 1.00 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 161.4, 146.7, 145.4, 135.7, 134.7, 126.7, 124.4, 122.2, 48.5, 22.6, 17.4, 11.1; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{12}H_{15}ON_2$ 203.1179, found 203.1176.

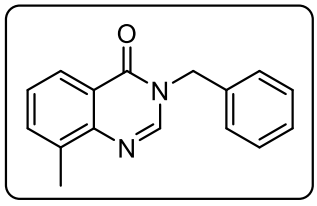
3-Cyclohexyl-8-methylquinazolin-4(3*H*)-one (1k)

Following the **Method A** procedure, **1k** was obtained as a colorless solid (109 mg; 45% yield). R*f*: 0.5 (1:6 EtOAc: Pet. ether); mp 162-164 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.17 (d, J



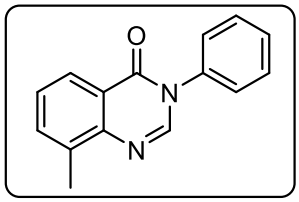
= 7.6 Hz, 1H), 8.16 (s, 1H), 7.59 (d, *J* = 6.9 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 4.86-4.76 (m, 1H), 2.61 (s, 3H), 2.01 (d, *J* = 11.4 Hz, 2H), 1.94 (d, *J* = 13.3 Hz, 2H), 1.79 (d, *J* = 13.7 Hz, 1H), 1.69-1.58 (m, 2H), 1.58-1.46 (m, 2H), 1.32-1.20 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 161, 146.1, 142.7, 135.5, 134.7, 126.7, 124.6, 121.9, 53.2, 32.6, 25.9, 25.3, 17.3; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{15}H_{19}ON_2$ 243.1492, found 243.1490.

3-Benzyl-8-methylquinazolin-4(3*H*)-one (1l)



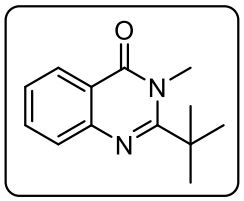
Following the **Method A** procedure, **1l** was obtained as a colorless solid (163 mg; 65% yield). R*f*: 0.5 (1:4 EtOAc: Pet. ether); mp 143-144 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.19 (d, *J* = 7.9 Hz, 1H), 8.14 (s, 1H), 7.61 (d, *J* = 7.3 Hz, 1H), 7.44-7.28 (m, 6H), 5.21 (s, 2H), 2.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 161.4, 146.6, 145.1, 135.9, 135.8, 134.9, 129, 128.3, 128, 126.9, 124.6, 122.2, 49.5, 17.4; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{16}H_{15}ON_2$ 251.1179, found 251.1175.

8-Methyl-3-phenylquinazolin-4(3*H*)-one (1m)



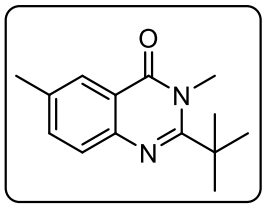
Following the **Method A** procedure, **1m** was obtained as a colorless solid (85 mg; 36% yield). R*f*: 0.4 (1:9 EtOAc: Pet. ether); mp 117-119 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.23 (d, *J* = 7.9 Hz, 1H), 8.16 (s, 1H), 7.66 (d, *J* = 7.3 Hz, 1H), 7.56 (t, *J* = 7.3 Hz, 2H), 7.50 (t, *J* = 7.3 Hz, 1H), 7.47-7.41 (m, 3H), 2.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 161.1, 146.4, 144.8, 137.6, 136, 135.2, 129.6, 129, 127.2, 127, 124.9, 122.4, 17.4; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{15}H_{13}ON_2$ 237.1022, found 237.1019.

2-(*tert*-Butyl)-3-methylquinazolin-4(3*H*)-one (1n)



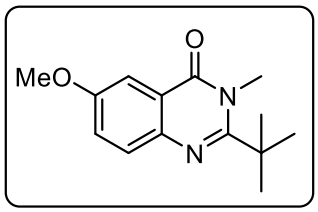
Following the **Method B** procedure, **1n** was obtained as a colorless solid (119 mg; 55% yield). R*f*: 0.5 (1:6 EtOAc: Pet. ether); mp 63-65 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.25 (d, J = 7.9 Hz, 1H), 7.70 (t, J = 7.3 Hz, 1H), 7.64 (d, J = 7.9 Hz, 1H), 7.43 (t, J = 7.3 Hz, 1H), 3.76 (s, 3H), 1.55 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 164, 161.3, 146.7, 133.8, 127.4, 126.4, 126.3, 119.8, 39.2, 33.6, 29.6; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{13}H_{17}ON_2$ 217.1335, found 217.1335.

2-(*tert*-Butyl)-3,6-dimethylquinazolin-4(3*H*)-one (1o)



Following the **Method B** procedure, **1o** was obtained as a colorless solid (104 mg; 45% yield). R*f*: 0.5 (1:9 EtOAc: Pet. ether); mp 104-106 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.04 (s, 1H), 7.53 (t, J = 9.2 Hz, 2H), 3.75 (s, 3H), 2.48 (s, 3H), 1.55 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 164.1, 160.4, 144.8, 136.5, 135.4, 127.3, 125.7, 119.6, 39.1, 33.6, 29.7, 21.3; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{14}H_{19}ON_2$ 231.1492, found 231.1490.

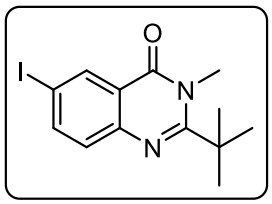
2-(*tert*-Butyl)-6-methoxy-3-methylquinazolin-4(3*H*)-one (1q)



Following the **Method B** procedure, **1q** was obtained as a thick oil (99 mg; 40% yield). R*f*: 0.5 (1:4 EtOAc: Pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.61 (d, J = 2.4 Hz, 1H), 7.57 (d, J = 8.6 Hz, 1H), 7.31 (dd, J = 8.6, 2.4 Hz, 1H), 3.92 (s, 3H), 3.77 (s, 3H), 1.55 (s,

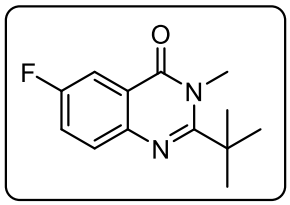
9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 163.9, 159.1, 158.1, 141.5, 129.1, 124.4, 120.5, 105.4, 55.8, 39, 33.7, 29.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{14}H_{19}O_2N_2$ 247.1441, found 247.1439.

2-(*tert*-Butyl)-6-iodo-3-methylquinazolin-4(3*H*)-one (1r)



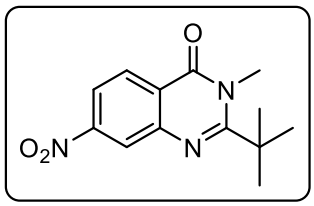
Following the **Method B** procedure, **1r** was obtained as a colorless solid (120 mg; 35% yield). R*f*: 0.5 (1:9 EtOAc: Pet. ether); mp 109-111 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.58 (d, J = 1.8 Hz, 1H), 7.95 (dd, J = 8.6, 1.8 Hz, 1H), 7.37 (d, J = 8.6 Hz, 1H), 3.74 (s, 3H), 1.54 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.6, 162.1, 146, 142.6, 135.2, 129.4, 121.5, 90.6, 39.4, 33.8, 29.6; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{13}H_{16}ON_2I$ 343.0302, found 343.0299.

2-(*tert*-Butyl)-6-fluoro-3-methylquinazolin-4(3*H*)-one (1s)



Following the **Method B** procedure, **1s** was obtained as a colorless solid (112 mg; 48% yield). R*f*: 0.5 (1:9 EtOAc: Pet. ether); mp 69-71 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.87 (dd, J = 8.6, 2.4 Hz, 1H), 7.65 (dd, J = 9.2, 4.9 Hz, 1H), 7.42 (dt, J = 8.6, 2.4 Hz, 1H), 3.76 (s, 3H), 1.55 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 163.4 (d, J = 3.1 Hz), 160.7 (d, J = 247.4 Hz), 160.6 (d, J = 1.5 Hz), 143.4, 129.9 (d, J = 8.5 Hz), 122.5 (d, J = 23.9 Hz), 120.9 (d, J = 8.5 Hz), 110.9 (d, J = 23.9 Hz), 39.2, 33.7, 29.6; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{13}H_{16}ON_2F$ 235.1241, found 235.1240.

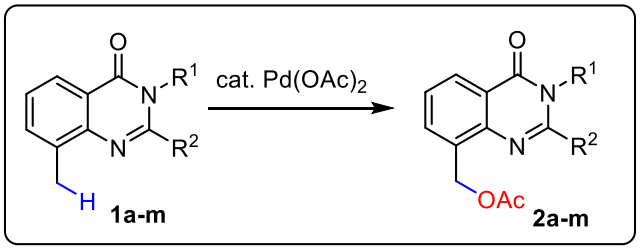
2-(*tert*-Butyl)-3-methyl-7-nitroquinazolin-4(3*H*)-one (1t)



Following the **Method B** procedure, **1t** was obtained as a pale yellow solid (86 mg; 33% yield). R*f*: 0.5 (1:4 EtOAc: Pet. ether); mp 152-154 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.49 (d, J = 1.8 Hz, 1H), 8.39 (d, J = 8.6 Hz, 1H), 8.18 (dd, J = 8.6, 1.8 Hz, 1H), 3.79 (s, 3H), 1.57 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 163.9, 162.8, 151.4, 147.2, 128.3, 123.8, 123.2, 120, 39.6, 33.9, 29.5; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{13}H_{16}O_3N_3$ 262.1186, found 262.1185.

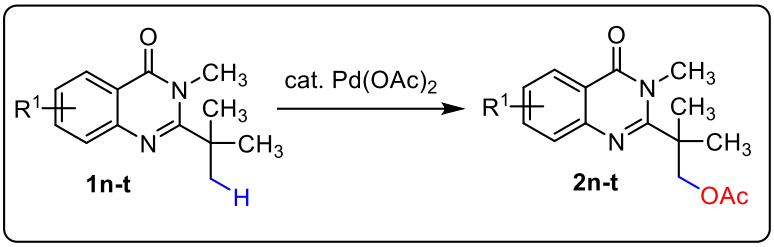
II) Experimental Procedures for Pd-Catalyzed C(sp^3)-Acetoxylation:

General Procedure- 1:



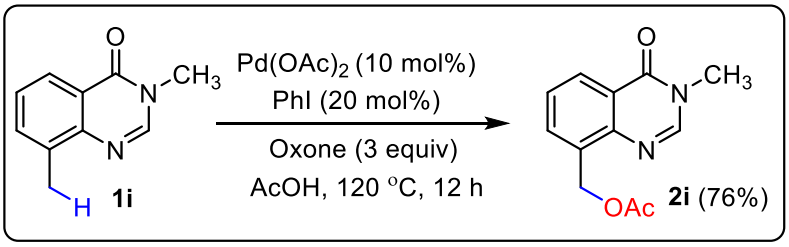
A glass tube with screw cap was charged with quinazolinone **1a-m** (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol) and diacetoxy iodobenzene (PIDA) (0.3 mmol). To this mixture, AcOH (1 mL; 0.2M) was added and the tube was flushed twice with argon gas. It was sealed with a Teflon screw cap and placed in a preheated oil bath at 120 °C. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to RT after 8-24 h, diluted with ethyl acetate, and evaporated under *vacuo* to dryness. The residue was purified by column chromatography to afford pure quinazolinone **2a-m**.

General Procedure-2:



A glass tube with screw cap was charged with quinazolinone **1n-t** (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol), diacetoxy iodobenzene (PIDA) (0.22 mmol) and sodium carbonate (0.22 mmol). To this mixture, AcOH (1 mL; 0.2M) was added and the tube was flushed twice with argon gas. It was sealed with a teflon screw cap and placed in a preheated oil bath at 120 °C. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to RT after 24 h, diluted with ethyl acetate, and evaporated under *vacuo* to dryness. The residue was purified by column chromatography to afford pure quinazolinone **2n-t**.

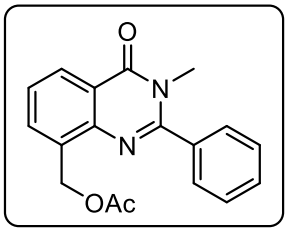
III) Experimental Procedure-3 (Catalytic PIDA):



A glass tube with screw cap was charged with quinazolinone **1i** (35 mg; 0.2 mmol), $Pd(OAc)_2$ (4.5 mg; 0.02 mmol), iodobenzene (5 µL; 0.04 mmol) and oxone (185 mg; 0.6 mmol). To this mixture, AcOH (1 mL; 0.2M) was added and the tube was flushed twice with argon gas. It was sealed with a teflon screw cap and placed in a preheated oil bath at 120 °C. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to RT after 12 h, diluted with

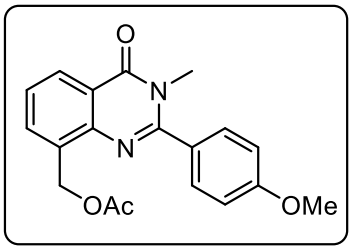
ethyl acetate, and evaporated under *vacuo* to dryness. The residue was purified by column chromatography to afford pure quinazolinone **2i** (35 mg; 76%).

(3-Methyl-4-oxo-2-phenyl-3,4-dihydroquinazolin-8-yl)methyl acetate (2a)



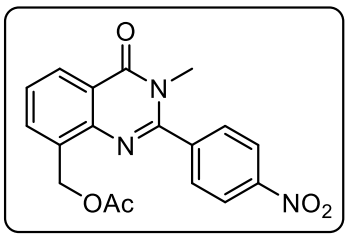
According to the **general procedure-1**, the title compound **2a** was obtained as a colorless solid (49 mg; 80% yield); reaction time: 24 h; R*f*: 0.4 (1:4 EtOAc: Pet. ether); mp 137-139 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.31 (d, J = 7.9 Hz, 1H), 7.80 (d, J = 7.3 Hz, 1H), 7.65-7.58 (m, 2H), 7.57-7.46 (m, 4H), 5.62 (s, 2H), 3.54 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.9, 162.9, 155.5, 145.2, 135.4, 133.2, 133, 130.1, 128.6, 128.4, 126.6, 126.5, 120.5, 62, 34.5, 21; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{18}H_{17}O_3N_2$ 309.1234, found 309.1230.

(2-(4-Methoxyphenyl)-3-methyl-4-oxo-3,4-dihydroquinazolin-8-yl)methyl acetate (2c)



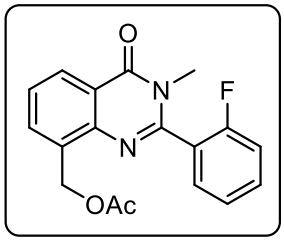
According to the **general procedure-1**, the title compound **2c** was obtained as a colorless solid (41 mg; 60% yield); reaction time: 24 h; R*f*: 0.5 (1:3 EtOAc: Pet. ether); mp 117-119 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.29 (d, J = 7.9 Hz, 1H), 7.79 (d, J = 7.3 Hz, 1H), 7.58 (d, J = 8.5 Hz, 2H), 7.47 (d, J = 7.3 Hz, 1H), 7.04 (d, J = 8.5 Hz, 2H), 5.62 (s, 2H), 3.90 (s, 3H), 3.57 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.9, 163.1, 161.1, 155.3, 145.3, 133, 130.2, 127.7, 126.5, 126.3, 120.3, 113.9, 62, 55.5, 34.7, 21.1; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{19}H_{19}O_4N_2$ 339.1339, found 339.1335.

(3-Methyl-2-(4-nitrophenyl)-4-oxo-3,4-dihydroquinazolin-8-yl)methyl acetate (2d)



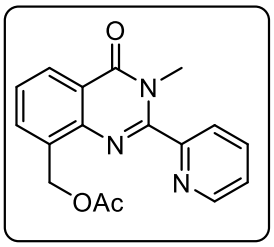
According to the **general procedure-1**, the title compound **2d** was obtained as a pale yellow solid (32 mg; 45% yield); reaction time: 24 h; R*f*: 0.4 (1:3 EtOAc: Pet. ether); mp 201-203 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.41 (d, J = 8.5 Hz, 2H), 8.32 (d, J = 7.9 Hz, 1H), 7.88-7.77 (m, 3H), 7.55 (t, J = 7.9 Hz, 1H), 5.58 (s, 2H), 3.53 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.8, 162.4, 153.3, 148.6, 144.8, 141, 133.4, 129.7, 127.4, 126.6, 124, 120.6, 61.7, 34.3, 21; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{18}H_{16}O_5N_3$ 354.1084, found 354.1077.

(2-(2-Fluorophenyl)-3-methyl-4-oxo-3,4-dihydroquinazolin-8-yl)methyl acetate (2e)



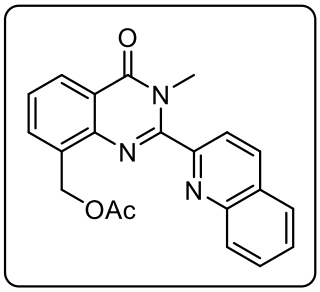
According to the **general procedure-1**, the title compound **2e** was obtained as a colorless solid (44 mg; 68% yield); reaction time: 24 h; R*f*: 0.4 (1:3 EtOAc: Pet. ether); mp 89-91 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.32 (d, J = 8 Hz, 1H), 7.82 (d, J = 7.3 Hz, 1H), 7.60-7.49 (m, 3H), 7.34 (t, J = 7.6 Hz, 1H), 7.23 (t, J = 8.8 Hz, 1H), 5.60 (s, 2H), 3.50 (d, J = 1.5 Hz, 3H), 2.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 170.9, 162.3, 159.3 (d, J = 248.9 Hz), 151.4, 145.2, 133.3, 133, 132.2 (d, J = 8.6 Hz), 130.7 (d, J = 1.9 Hz), 126.9, 126.6, 124.9 (d, J = 2.9 Hz), 123.7 (d, J = 15.3 Hz), 120.8, 115.9 (d, J = 21 Hz), 61.9, 32.9, (d, J = 3.8 Hz), 21; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{18}H_{16}O_3N_2F$ 327.1139, found 327.1135.

(3-Methyl-4-oxo-2-(pyridin-2-yl)-3,4-dihydroquinazolin-8-yl)methyl acetate (2f)



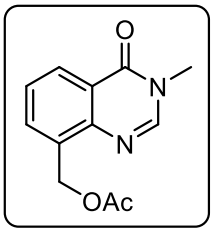
According to the **general procedure-1**, the title compound **2f** was obtained as a colorless solid (50 mg; 80% yield); reaction time: 12 h; R*f*: 0.4 (1:2 EtOAc: Pet. ether); mp 164-166 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.72 (d, *J* = 4.3 Hz, 1H), 8.33 (d, *J* = 7.9 Hz, 1H), 7.92 (d, *J* = 3.7 Hz, 2H), 7.81 (d, *J* = 7.3 Hz, 1H), 7.52 (t, *J* = 7.3 Hz, 1H), 7.46 (m, 1H), 5.63 (s, 2H), 3.68 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.9, 162.7, 153.8, 153.2, 148.4, 145, 137.3, 133.2, 133.1, 126.9, 126.7, 125.1, 124.7, 121, 61.9, 33.7, 21; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{17}H_{16}O_3N_3$ 310.1186, found 310.1181.

(3-Methyl-4-oxo-2-(quinolin-2-yl)-3,4-dihydroquinazolin-8-yl)methyl acetate (2g)



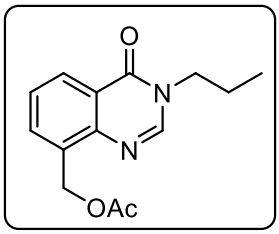
According to the **general procedure-1**, the title compound **2g** was obtained as a colorless solid (65 mg; 91% yield); reaction time: 12 h; R*f*: 0.5 (1:3 EtOAc: Pet. ether); mp 175-177 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.41-8.32 (m, 2H), 8.15 (d, *J* = 8.6 Hz, 1H), 8.04 (d, *J* = 8.6 Hz, 1H), 7.94 (d, *J* = 7.9 Hz, 1H), 7.86-7.77 (m, 2H), 7.67 (t, *J* = 7.3 Hz, 1H), 7.54 (t, *J* = 7.3 Hz, 1H), 5.65 (s, 2H), 3.81 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.9, 162.8, 153.2, 146.6, 144.9, 137.3, 133.2, 133.1, 130.3, 129.7, 128, 127.97, 127.7, 127, 126.8, 121.9, 121, 61.9, 33.8, 21; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{21}H_{18}O_3N_3$ 360.1343, found 360.1338.

(3-Methyl-4-oxo-3,4-dihydroquinazolin-8-yl)methyl acetate (2i)



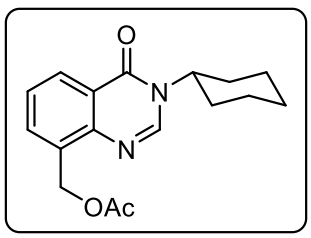
According to the **general procedure-1**, the title compound **2i** was obtained as a colorless solid (39 mg; 85% yield); reaction time: 12 h; R*f*: 0.4 (1:2 EtOAc: Pet. ether); mp 128-130 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.30 (d, J = 7.9 Hz, 1H), 8.08 (s, 1H), 7.81 (d, J = 7.3 Hz, 1H), 7.50 (t, J = 7.9 Hz, 1H), 5.58 (s, 2H), 3.60 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.8, 161.5, 146.4, 146.37, 133.8, 133, 126.9, 126.7, 122.1, 61.9, 34.1, 21; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{12}H_{13}O_3N_2$ 233.0921, found 233.0918.

(4-Oxo-3-propyl-3,4-dihydroquinazolin-8-yl)methyl acetate (2j)



According to the **general procedure-1**, the title compound **2j** was obtained as a colorless solid (43 mg; 82% yield); reaction time: 18 h; R*f*: 0.3 (1:4 EtOAc: Pet. ether); mp 97-100 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.29 (d, J = 7.9 Hz, 1H), 8.06 (s, 1H), 7.80 (d, J = 7.3 Hz, 1H), 7.48 (t, J = 7.9 Hz, 1H), 5.58 (s, 2H), 3.97 (t, J = 7.3 Hz, 2H), 2.13 (s, 3H), 1.89-1.77 (m, 2H), 1.00 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.8, 160.9, 146.3, 146.2, 133.8, 132.9, 126.8, 122.2, 61.9, 48.5, 22.6, 21, 11.1; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{14}H_{17}O_3N_2$ 261.1234, found 261.1231.

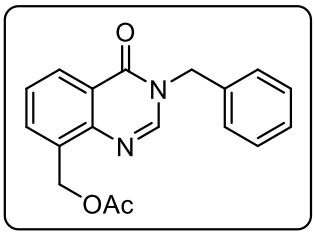
(3-Cyclohexyl-4-oxo-3,4-dihydroquinazolin-8-yl)methyl acetate (2k)



According to the **general procedure-1**, the title compound **2k** was obtained as a colorless solid (51 mg; 85% yield); reaction time: 11 h; R*f*: 0.4 (1:6 EtOAc: Pet. ether); mp 115-117 ^{o}C; ^{1}H NMR (400 MHz,

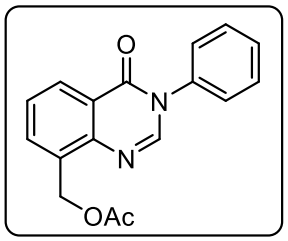
$CDCl_3$) δ (ppm) 8.30 (d, J = 7.9 Hz, 1H), 8.18 (s, 1H), 7.80 (d, J = 7.3 Hz, 1H), 7.48 (t, J = 7.9 Hz, 1H), 5.58 (s, 2H), 4.81 (t, J = 11 Hz, 1H), 2.14 (s, 3H), 2.05-1.89 (m, 4H), 1.80 (d, J = 12.8 Hz, 1H), 1.70-1.45 (m, 4H), 1.35-1.17 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.9, 160.6, 145.6, 143.7, 133.9, 132.7, 127.2, 126.7, 122, 61.9, 53.4, 32.6, 25.9, 25.2, 21; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{17}H_{21}O_3N_2$ 301.1547, found 301.1543.

(3-Benzyl-4-oxo-3,4-dihydroquinazolin-8-yl)methyl acetate (2l)



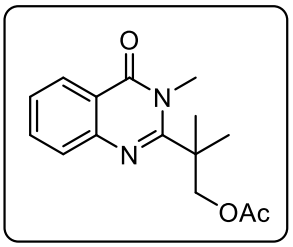
According to the **general procedure-1**, the title compound **2l** was obtained as a colorless solid (55 mg; 89% yield); reaction time: 8 h; R*f*: 0.4 (1:4 EtOAc: Pet. ether); mp 124-126 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.32 (d, J = 7.9 Hz, 1H), 8.15 (s, 1H), 7.82 (d, J = 7.3 Hz, 1H), 7.50 (t, J = 7.9 Hz, 1H), 7.41-7.29 (m, 5H), 5.58 (s, 2H), 5.21 (s, 2H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.8, 161, 146.1, 146, 135.6, 134, 133.1, 129, 128.4, 128.1, 127, 122.3, 61.8, 49.6, 21; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{18}H_{17}O_3N_2$ 309.1234, found 309.1230.

(4-Oxo-3-phenyl-3,4-dihydroquinazolin-8-yl)methyl acetate (2m)



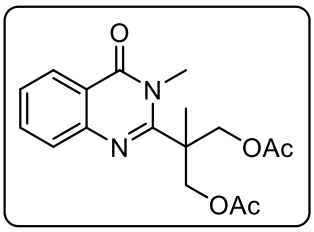
According to the **general procedure-1**, the title compound **2m** was obtained as a colorless solid (56 mg; 95% yield); reaction time: 12 h; R*f*: 0.3 (1:6 EtOAc: Pet. ether); mp 141-143 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.36 (d, J = 7.9 Hz, 1H), 8.17 (s, 1H), 7.86 (d, J = 7.3 Hz, 1H), 7.61-7.47 (m, 4H), 7.45-7.39 (m, 2H), 5.63 (s, 2H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.8, 160.6, 146, 145.7, 137.4, 134.3, 133.2, 129.6, 129.1, 127.3, 126.9, 122.5, 61.9, 21; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{17}H_{15}O_3N_2$ 295.1077, found 295.1074.

2-Methyl-2-(3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)propyl acetate (2n)



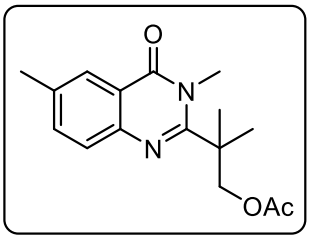
According to the **general procedure-2**, the title compound **2n** was obtained as a beige solid (47 mg; 85% yield); reaction time: 24 h; R*f*: 0.5 (1:3 EtOAc: Pet. ether); mp 75-77 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.25 (d, *J* = 7.9 Hz, 1H), 7.71 (t, *J* = 7.9 Hz, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.45 (t, *J* = 7.9 Hz, 1H), 4.52 (s, 2H), 3.75 (s, 3H), 2.06 (s, 3H), 1.56 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 171.1, 163.8, 158.2, 146.4, 134, 127.5, 126.8, 126.4, 119.9, 72.1, 42.4, 33, 23.6, 21; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{15}H_{19}O_3N_2$ 275.1390, found 275.1385.

2-Methyl-2-(3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)propane-1,3-diyl diacetate (2na)



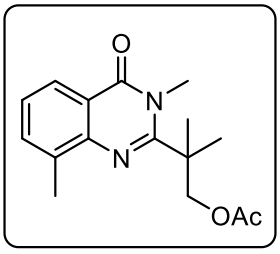
According to the **general procedure-2** with PIDA (3 equiv or 5 equiv) and Na_2CO_3 (3 equiv or 5 equiv), the title compound **2na** was obtained as a beige solid (37 mg; 55% yield or 49 mg; 73% yield respectively); with 5 equiv of PIDA without base (30 mg; 45% yield), reaction time: 24 h; R*f*: 0.3 (1:3 EtOAc: Pet. ether); mp 114-116 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.26 (d, *J* = 7.9 Hz, 1H), 7.73 (t, *J* = 7.3 Hz, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.47 (t, *J* = 7.3 Hz, 1H), 4.67 (d, *J* = 11.6 Hz, 2H), 4.57 (d, *J* = 11.6 Hz, 2H), 3.75 (s, 3H), 2.03 (s, 6H), 1.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.7, 163.5, 155, 146.1, 134.1, 127.6, 127.1, 126.5, 120, 66.4, 46, 32.1, 20.8, 18.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{17}H_{21}O_5N_2$ 333.1445, found 333.1440.

2-(3,6-Dimethyl-4-oxo-3,4-dihydroquinazolin-2-yl)-2-methylpropyl acetate (2o)



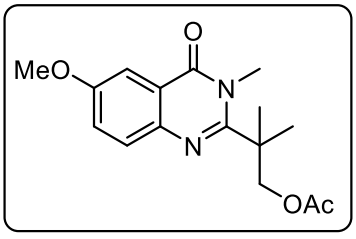
According to the **general procedure-2**, the title compound **2o** was obtained as a colorless solid (46 mg; 80% yield); reaction time: 24 h; R*f*: 0.3 (1:6 EtOAc: Pet. ether); mp 100-102 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.04 (s, 1H), 7.52 (apparent s, 2H), 4.51 (s, 2H), 3.74 (s, 3H), 2.48 (s, 3H), 2.05 (s, 3H), 1.55 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 171.1, 163.8, 157.3, 144.5, 136.9, 135.5, 127.3, 125.7, 119.7, 72.1, 42.3, 32.9, 23.7, 21.3, 21; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{16}H_{21}O_3N_2$ 289.1547, found 289.1545.

2-(3,8-Dimethyl-4-oxo-3,4-dihydroquinazolin-2-yl)-2-methylpropyl acetate (2p)



According to the **general procedure-2**, the title compound **2p** was obtained as a beige solid (26 mg; 45% yield); reaction time: 24 h; R*f*: 0.5 (1:4 EtOAc: Pet. ether); mp 81-82 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.10 (d, J = 7.9 Hz, 1H), 7.57 (d, J = 7.3 Hz, 1H), 7.34 (t, J = 7.9 Hz, 1H), 4.54 (s, 2H), 3.75 (s, 3H), 2.56 (s, 3H), 2.07 (s, 3H), 1.57 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 171.1, 164.2, 156.9, 144.9, 136.1, 134.5, 126.4, 124.1, 119.9, 72.2, 42.7, 32.9, 23.7, 21.3, 21; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{16}H_{21}O_3N_2$ 289.1547, found 289.1541.

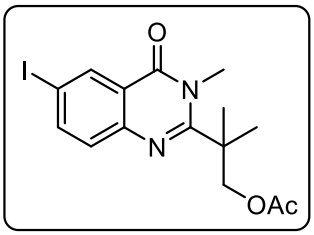
2-(6-Methoxy-3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)-2-methylpropyl acetate (2q)



According to the **general procedure-2**, the title compound **2q** was obtained as a colorless solid (46 mg; 75% yield); reaction time: 24 h; R*f*: 0.3 (1:4 EtOAc: Pet. ether); mp 118-120 ^{o}C; ^{1}H

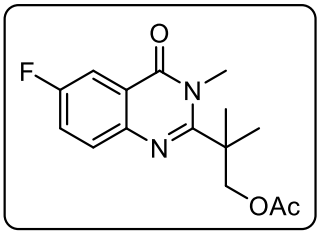
NMR (400 MHz, $CDCl_3$) δ (ppm) 7.60 (d, J = 2.4 Hz, 1H), 7.55 (d, J = 9 Hz, 1H), 7.30 (dd, J = 9, 2.4 Hz, 1H), 4.50 (s, 2H), 3.91 (s, 3H), 3.75 (s, 3H), 2.05 (s, 3H), 1.54 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 171.1, 163.7, 158.4, 155.9, 141.2, 129.1, 124.5, 120.6, 105.5, 72.1, 55.8, 42.2, 33, 23.7, 21; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{16}H_{21}O_4N_2$ 305.1496, found 305.1493.

2-(6-Iodo-3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)-2-methylpropyl acetate (2r)



According to the **general procedure-2**, the title compound **2r** was obtained as a colorless solid (52 mg; 65% yield); reaction time: 24 h; R*f*: 0.3 (1:6 EtOAc: Pet. ether); mp 131-133 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.58 (s, 1H), 7.96 (dd, J = 8.5, 1.8 Hz, 1H), 7.35 (d, J = 8.5 Hz, 1H), 4.49 (s, 2H), 3.74 (s, 3H), 2.05 (s, 3H), 1.55 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 171, 162.4, 159, 145.7, 142.8, 135.2, 129.4, 121.6, 91, 71.9, 42.6, 33.1, 23.6, 21; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{15}H_{18}O_3N_2I$ 401.0357, found 401.0363.

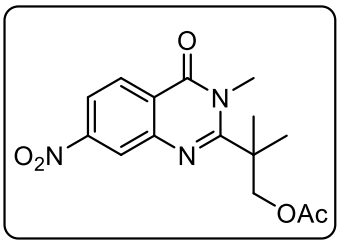
2-(6-Fluoro-3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)-2-methylpropyl acetate (2s)



According to the **general procedure-2**, the title compound **2s** was obtained as a colorless solid (37 mg; 64% yield); reaction time: 24 h; R*f*: 0.3 (1:6 EtOAc: Pet. ether); mp 106-108 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.87 (dd, J = 7.9, 2.4 Hz, 1H), 7.63 (dd, J = 9.2, 4.9 Hz, 1H), 7.43 (dt, J = 8.5, 2.4 Hz, 1H), 4.50 (s, 2H), 3.75 (s, 3H), 2.06 (s, 3H), 1.55 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 171, 163.1 (d, J = 3.1 Hz), 160.9 (d, J = 247.4 Hz), 157.5 (d, J = 1.5 Hz), 143.1, 130 (d, J = 8.5 Hz), 122.7 (d, J = 23.9 Hz), 121.1 (d, J = 9.3 Hz), 111.1 (d, J =

23.1 Hz), 72, 42.4, 33.1, 23.7, 21; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{15}H_{18}O_3N_2F$ 293.1296, found 293.1293.

2-Methyl-2-(3-methyl-7-nitro-4-oxo-3,4-dihydroquinazolin-2-yl)propyl acetate (2t)



According to the **general procedure-2**, the title compound **2t** was obtained as a colorless solid (45 mg; 70% yield); reaction time: 24 h; R*f*: 0.3 (1:4 EtOAc: Pet. ether); mp 117-119 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.47 (d, J = 1.8 Hz, 1H), 8.41 (d, J = 9.2 Hz, 1H), 8.20 (dd, J = 8.6, 1.8 Hz, 1H), 4.52 (s, 2H), 3.78 (s, 3H), 2.06 (s, 3H), 1.58 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.9, 162.6, 160.9, 151.5, 146.8, 128.4, 123.9, 123.2, 120.4, 71.6, 42.9, 33.4, 23.8, 20.9; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{15}H_{18}O_5N_3$ 320.1241, found 320.1239.

2.2.9. References:

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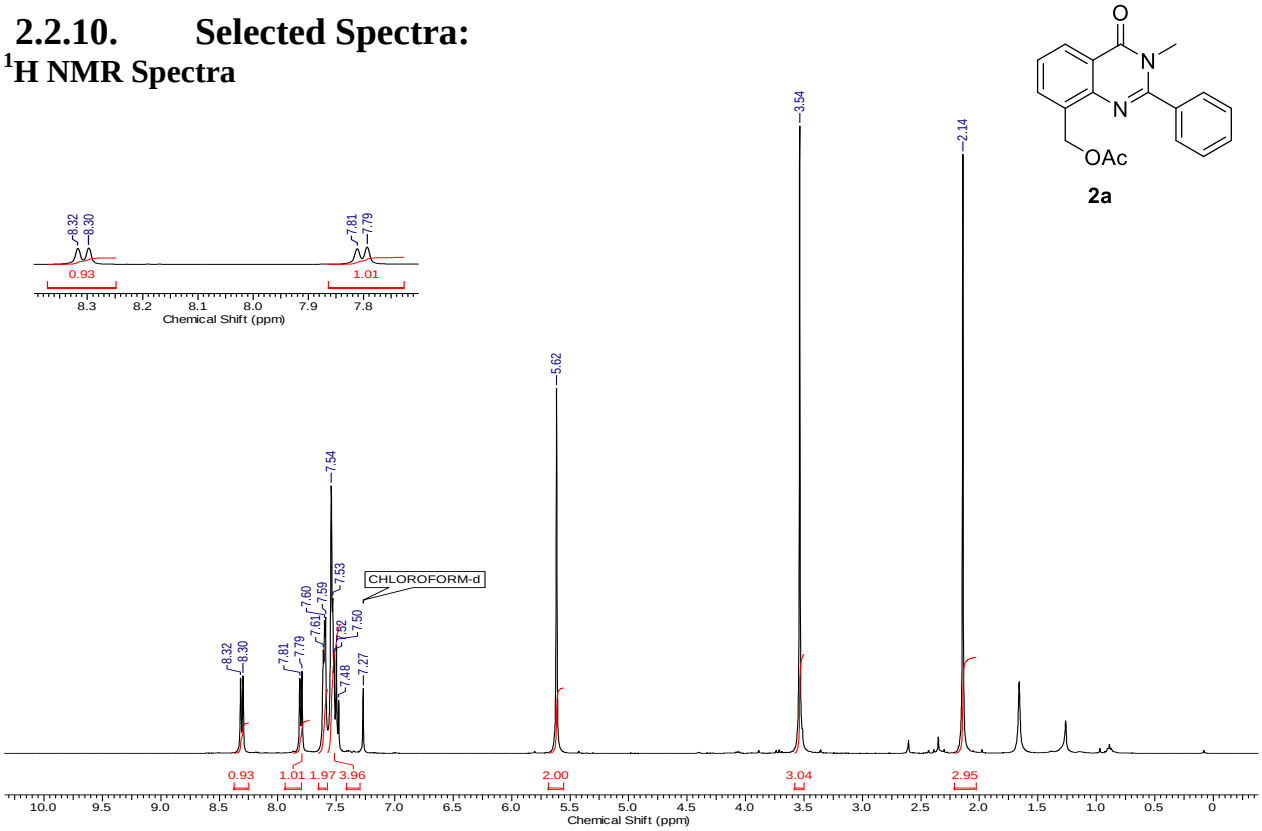
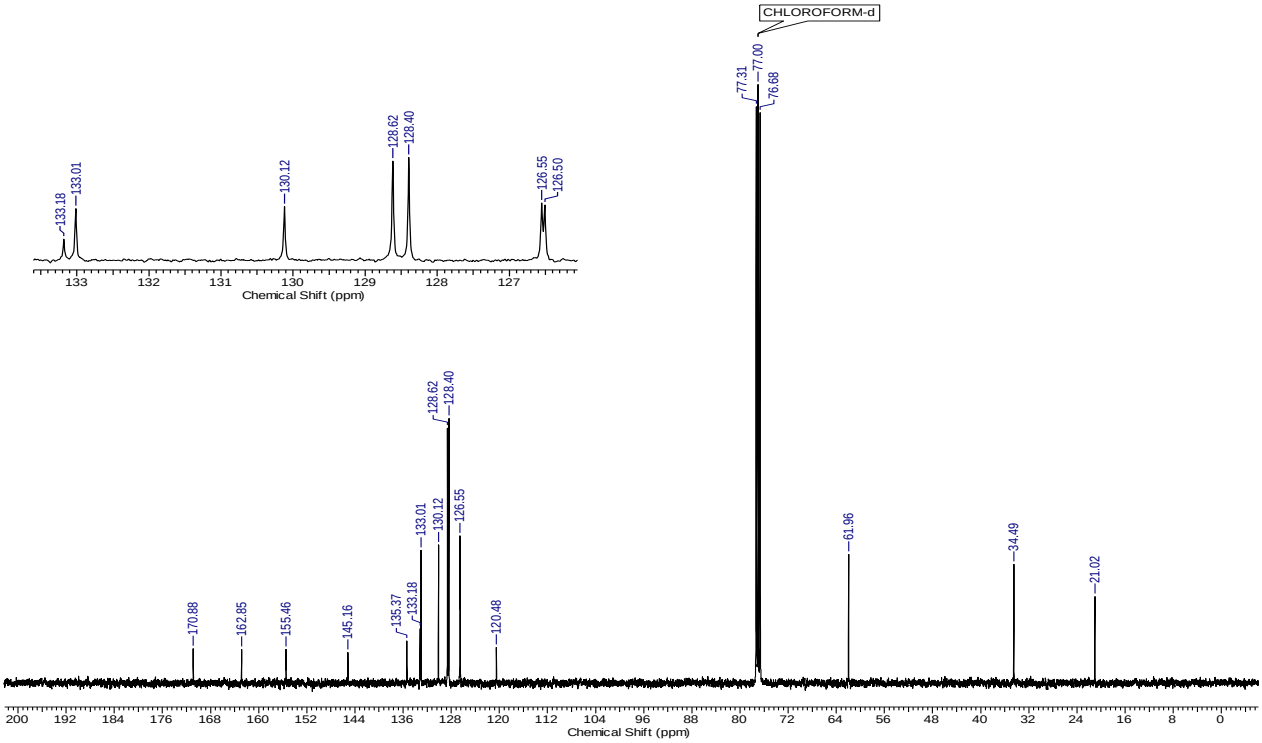
2.2.10. Selected Spectra:

^{1}H NMR Spectra



^{13}C NMR Spectra



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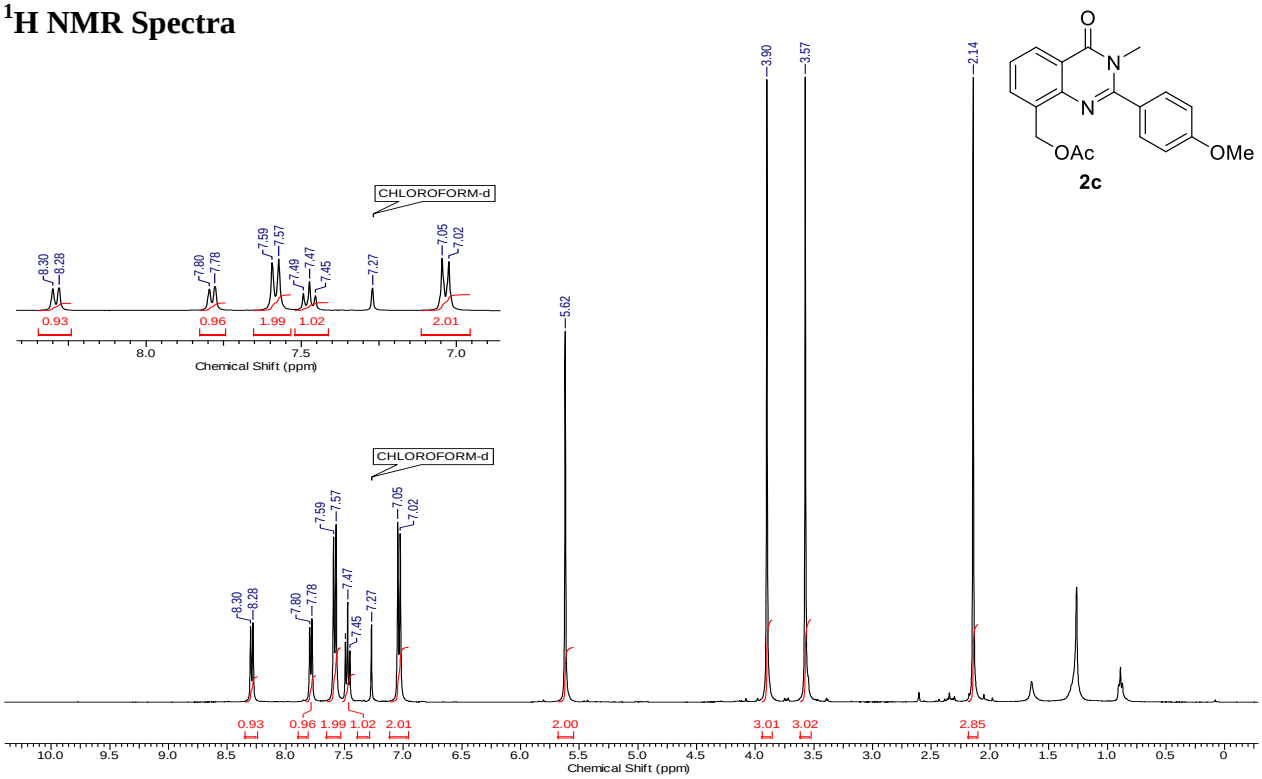

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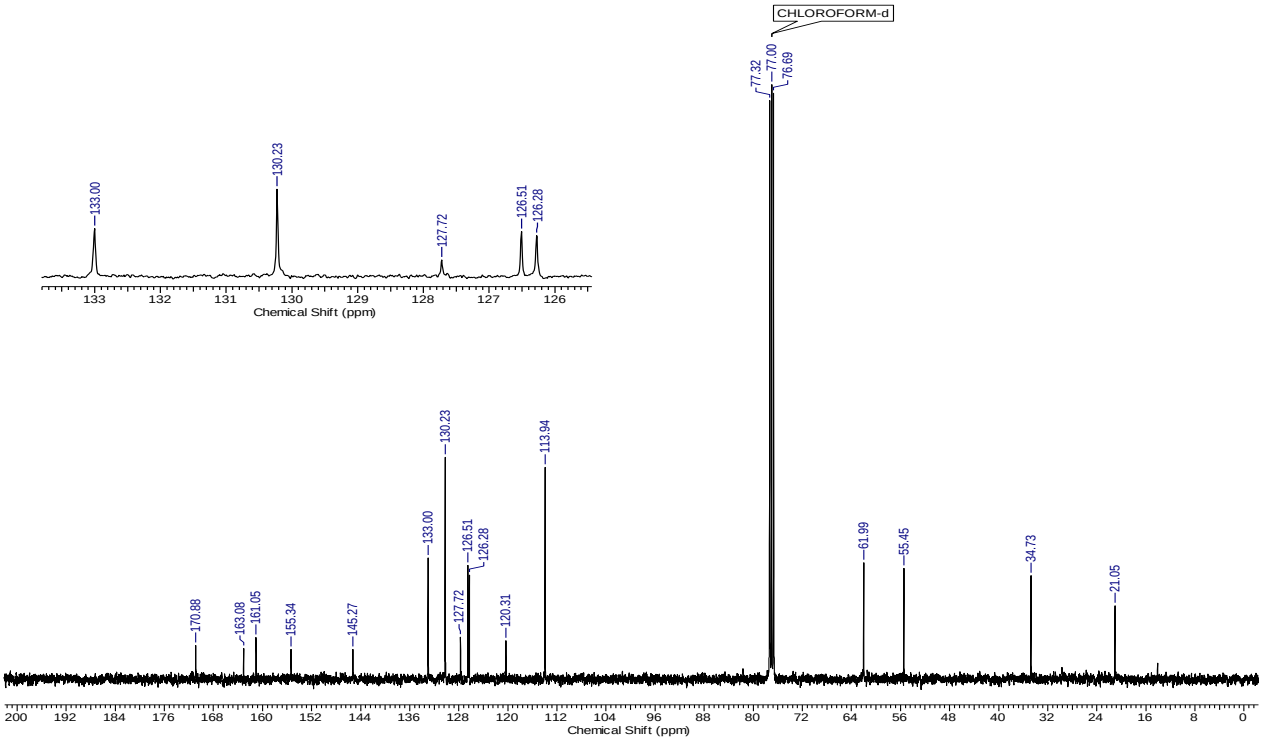

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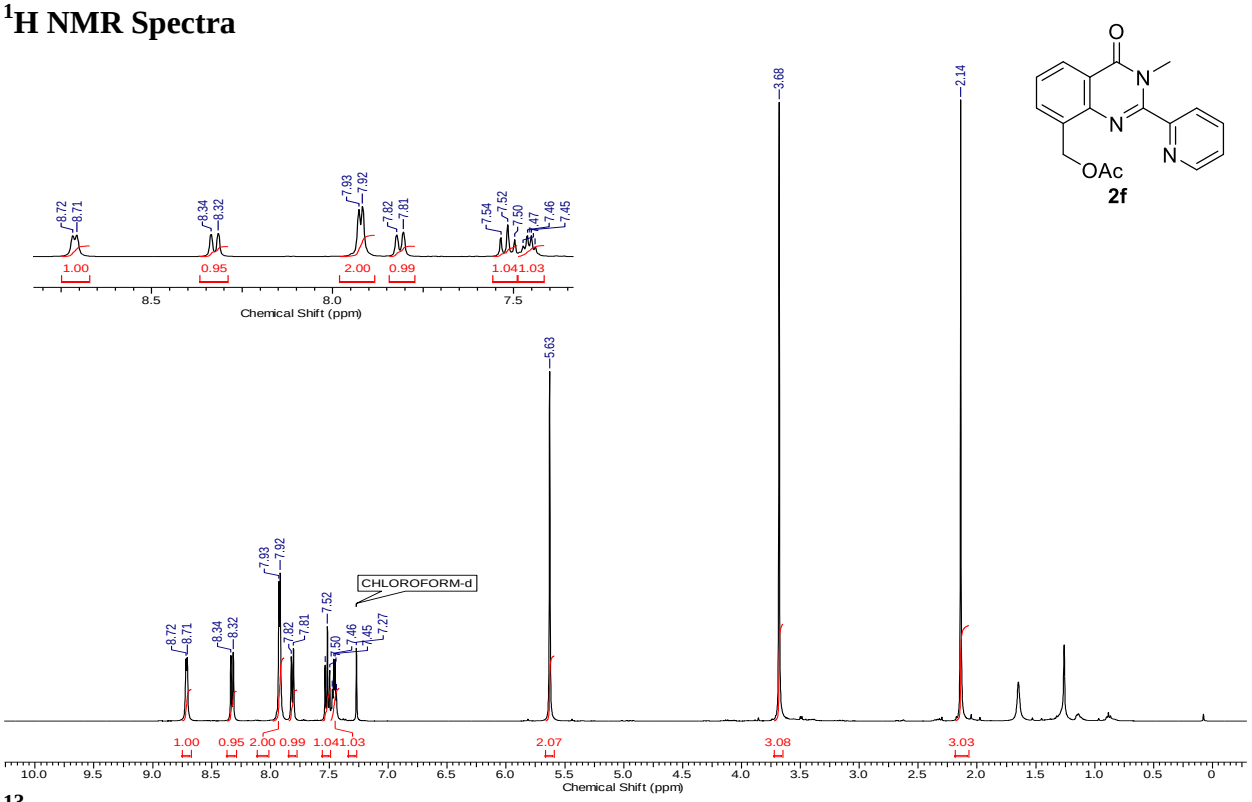

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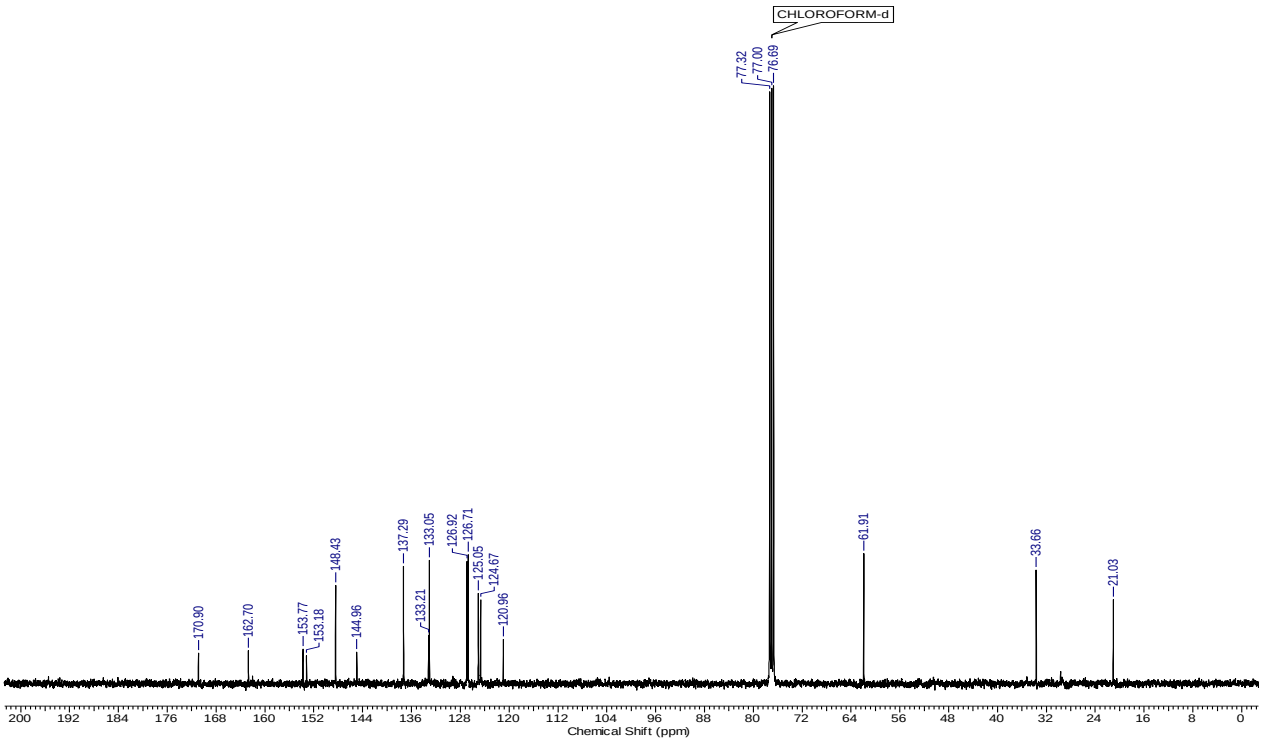

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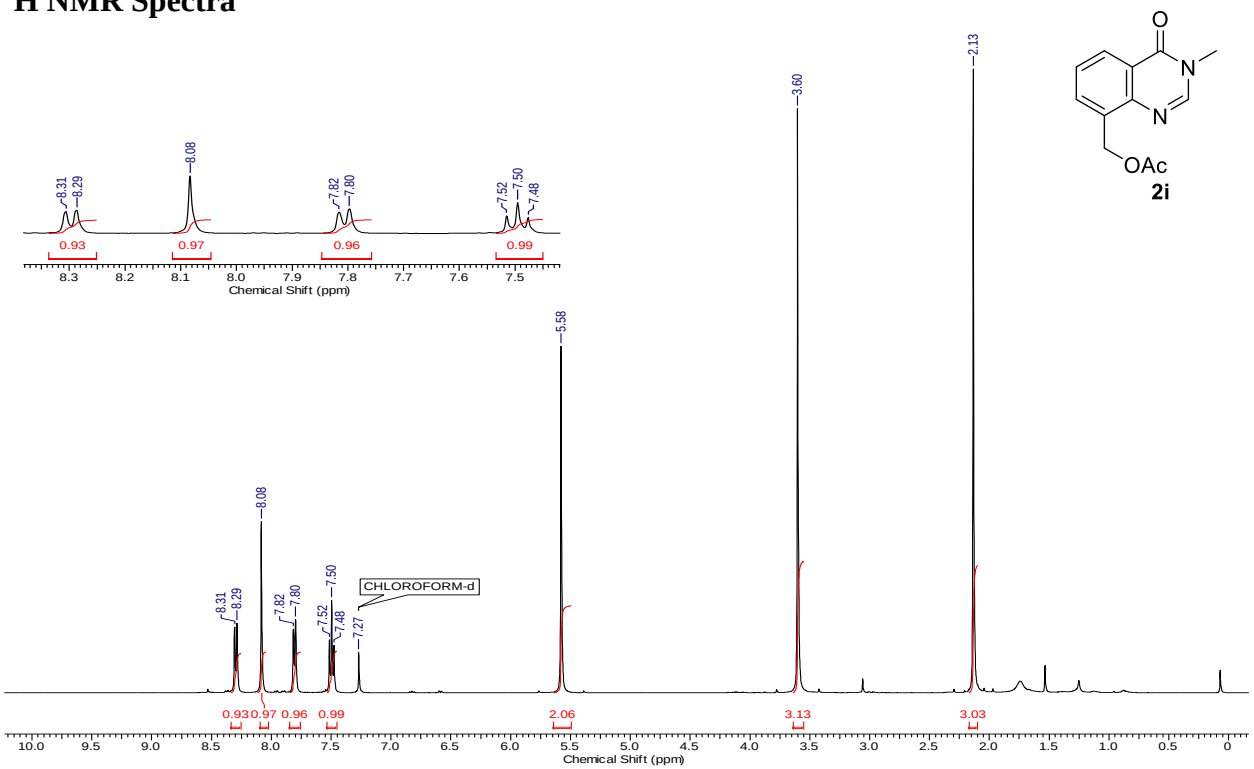

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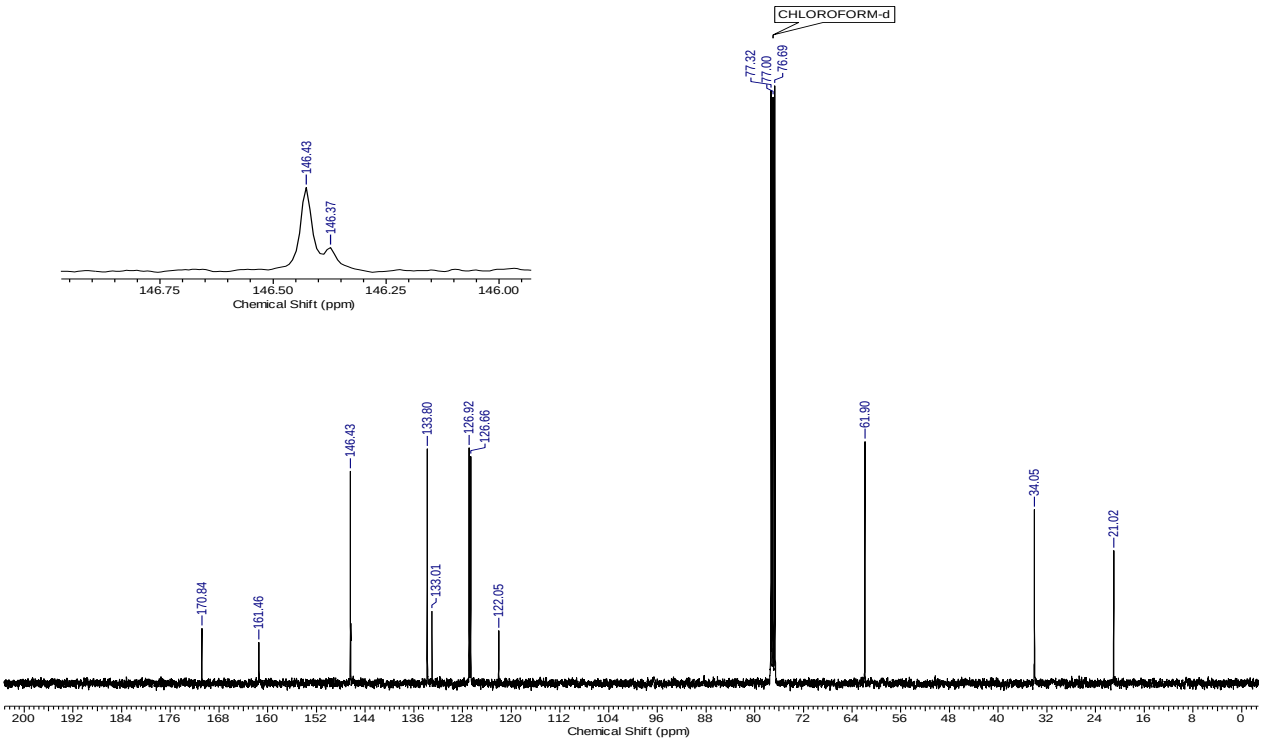

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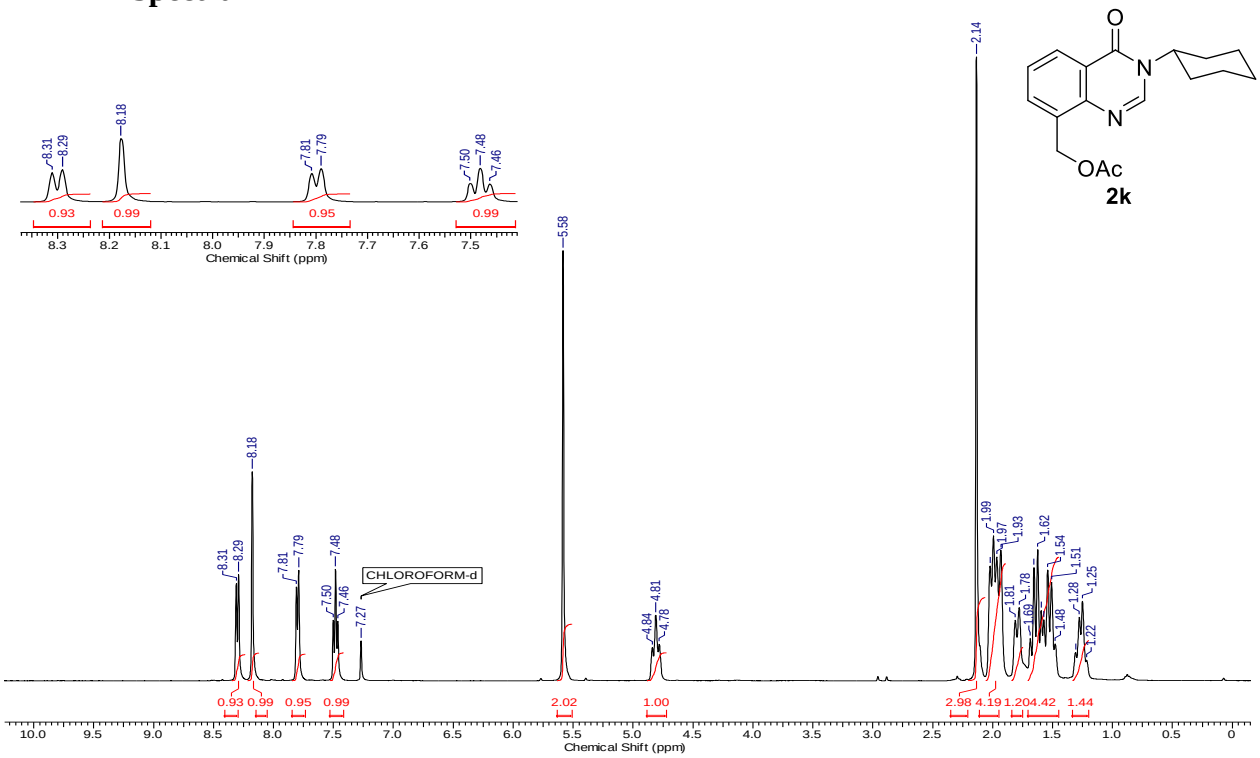

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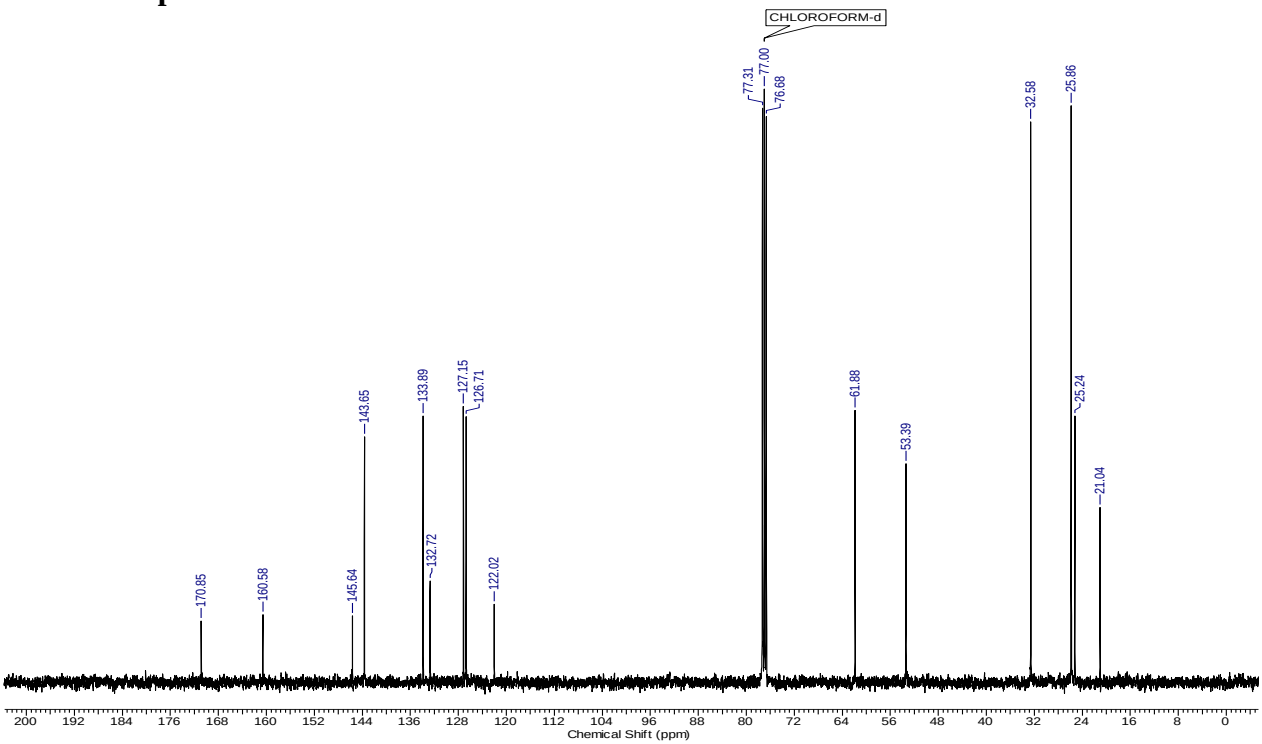

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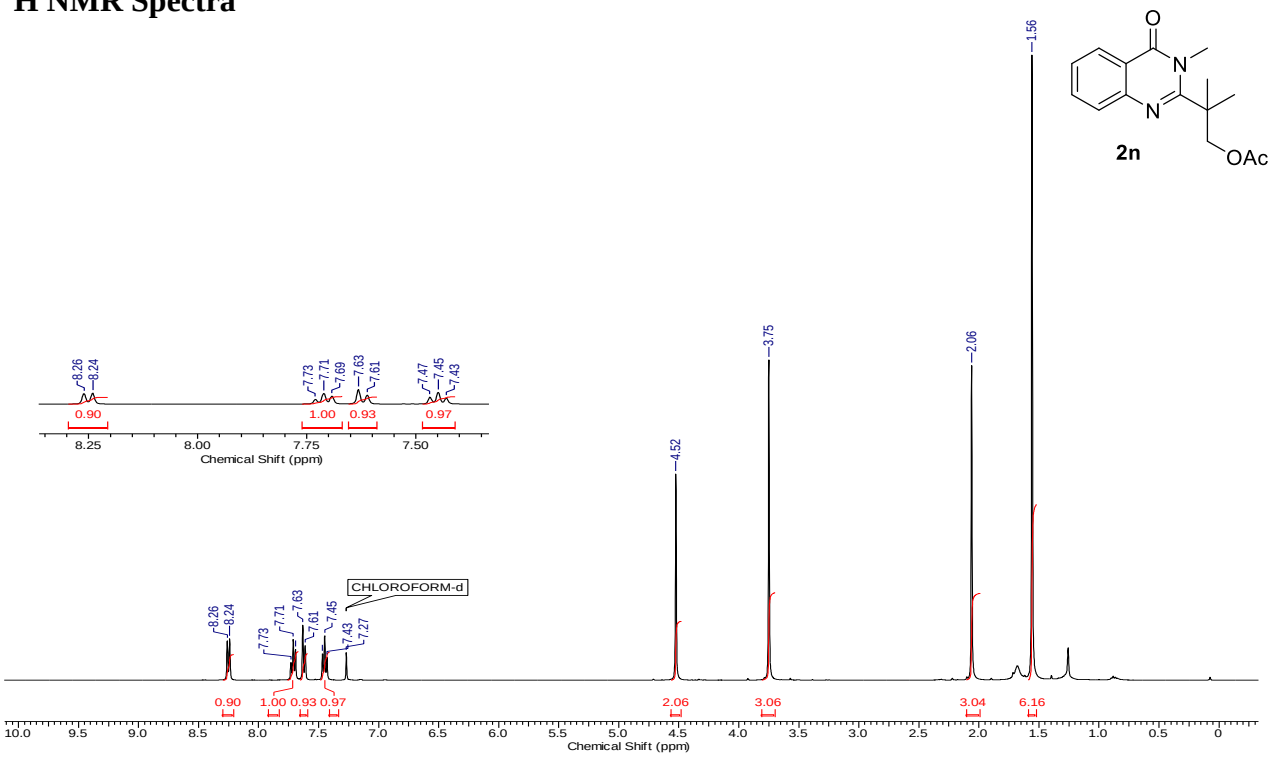

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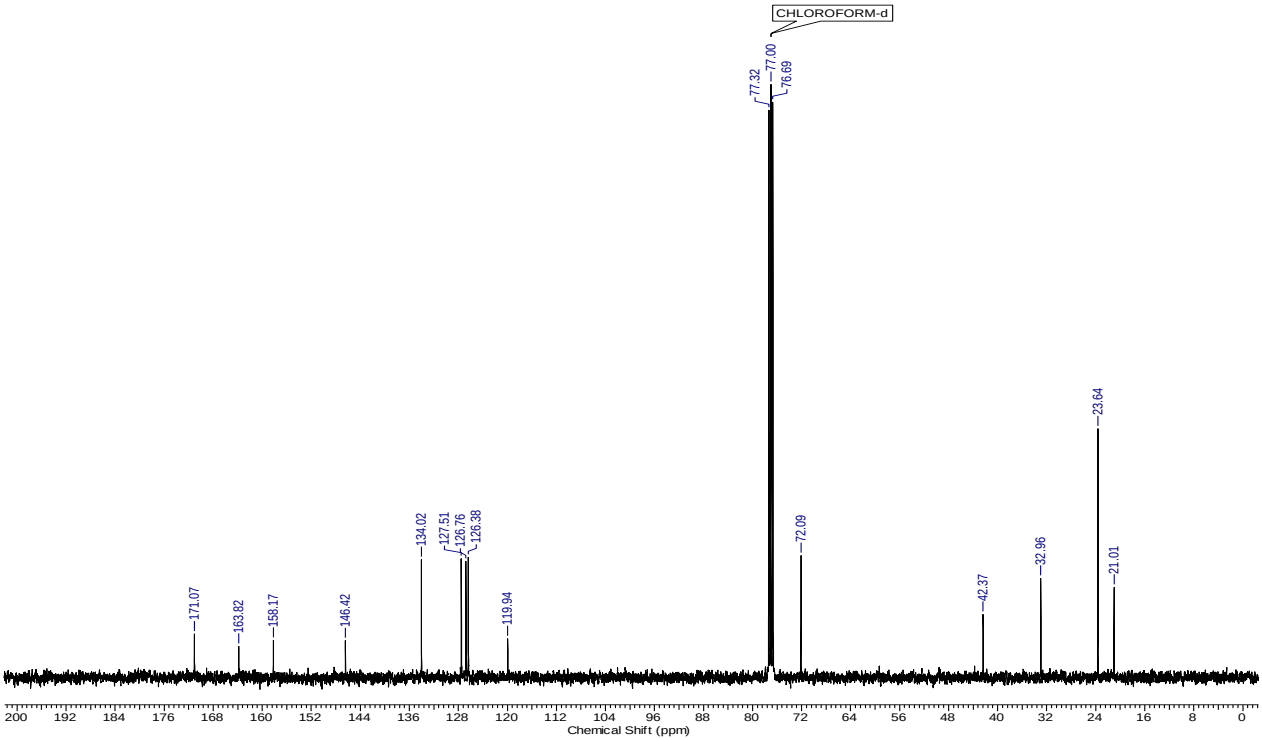

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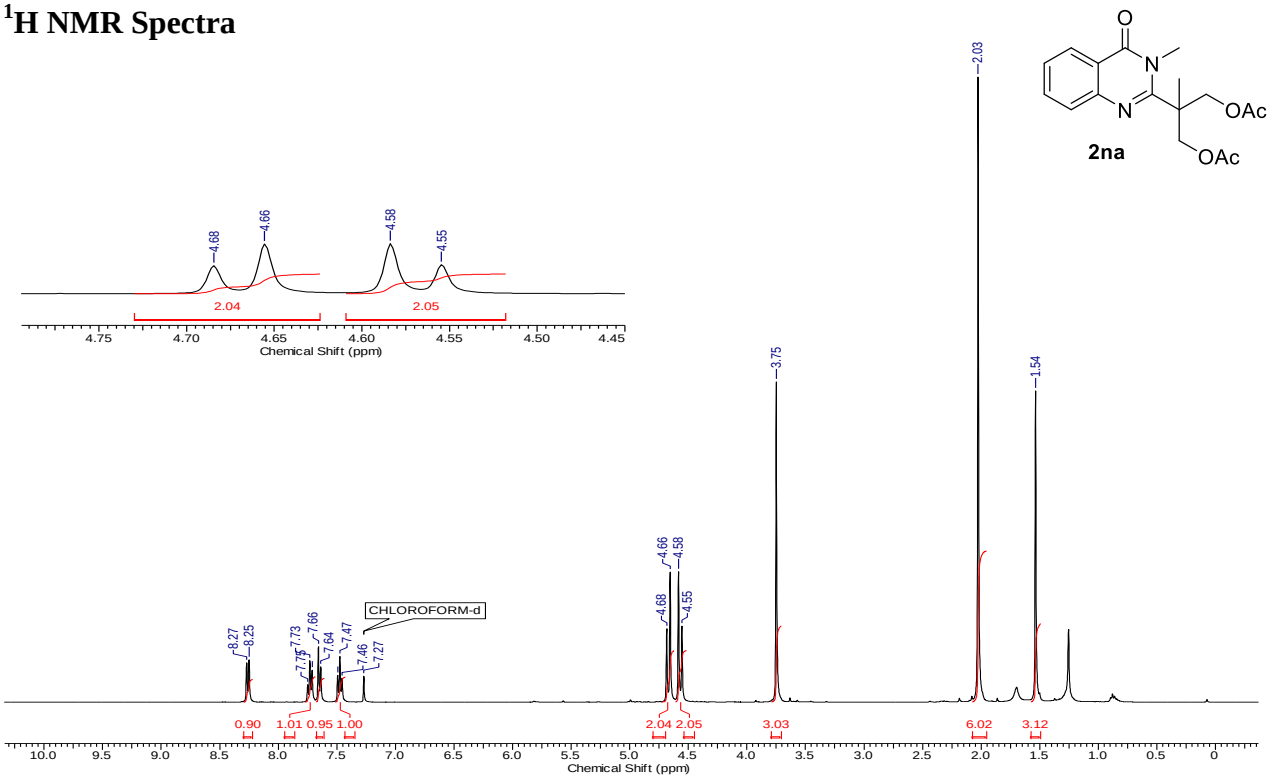

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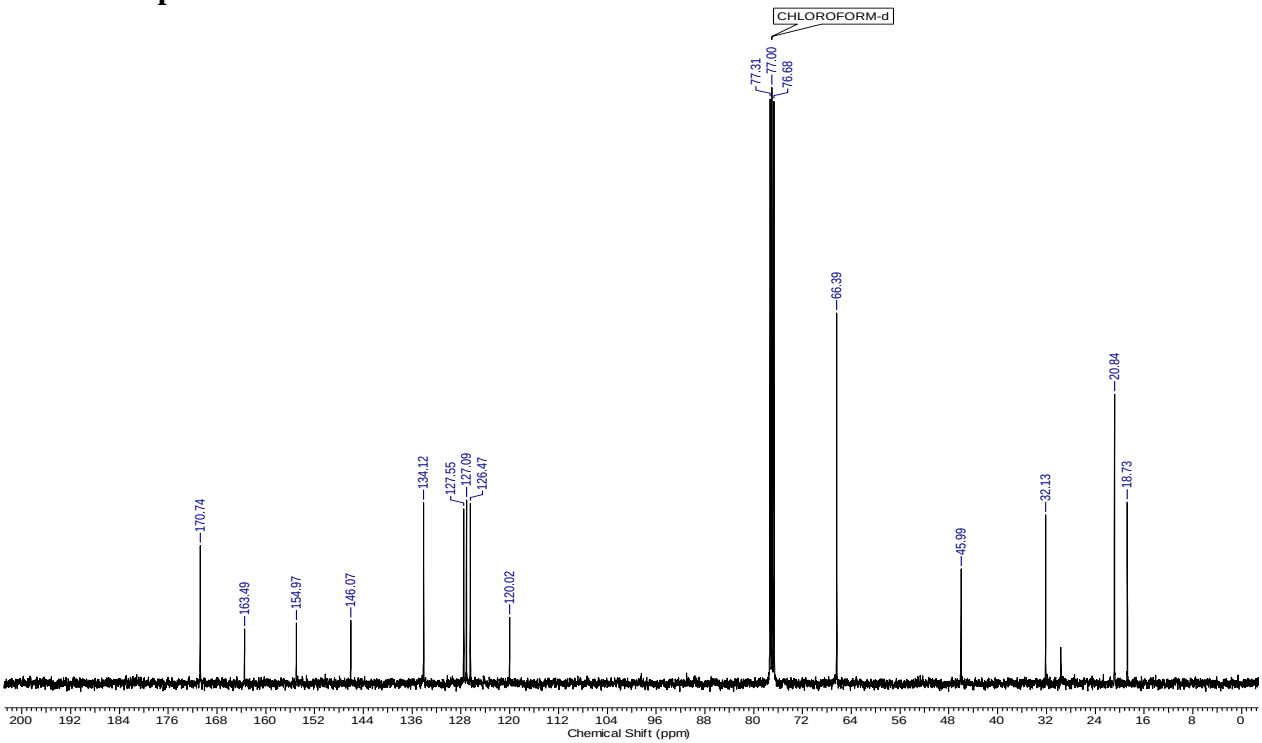

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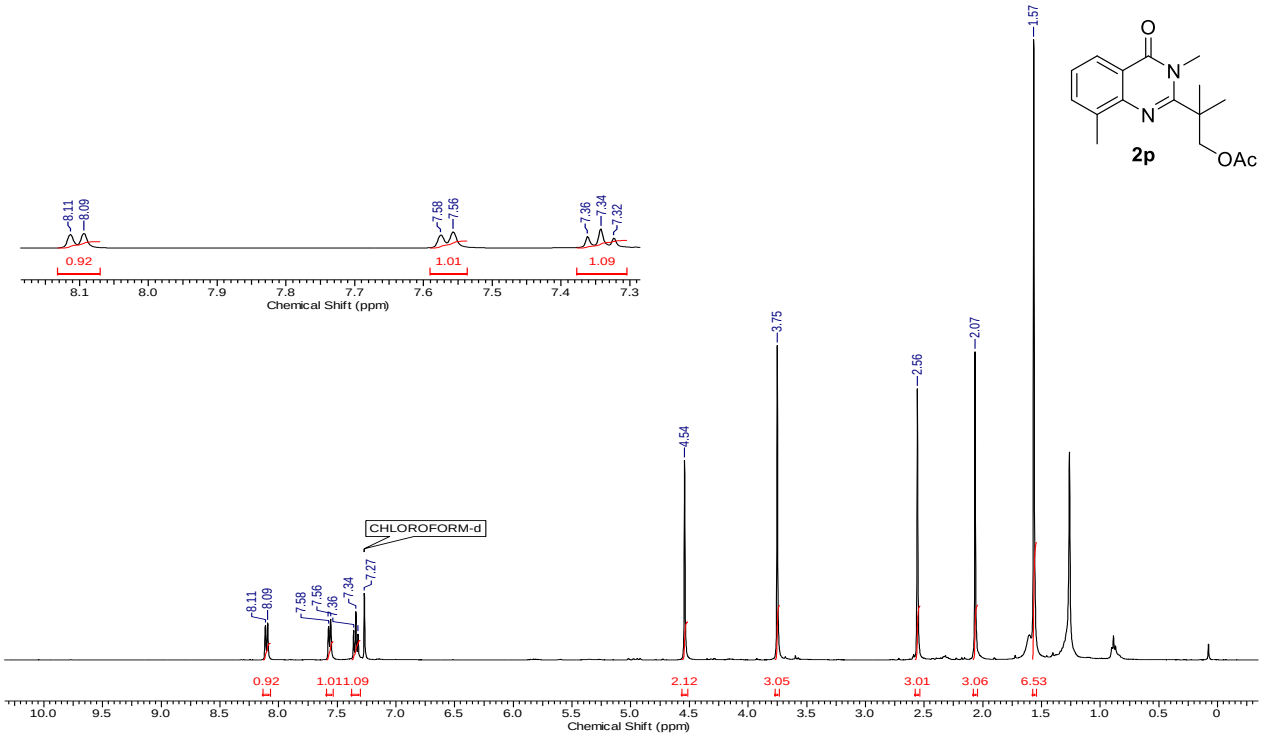

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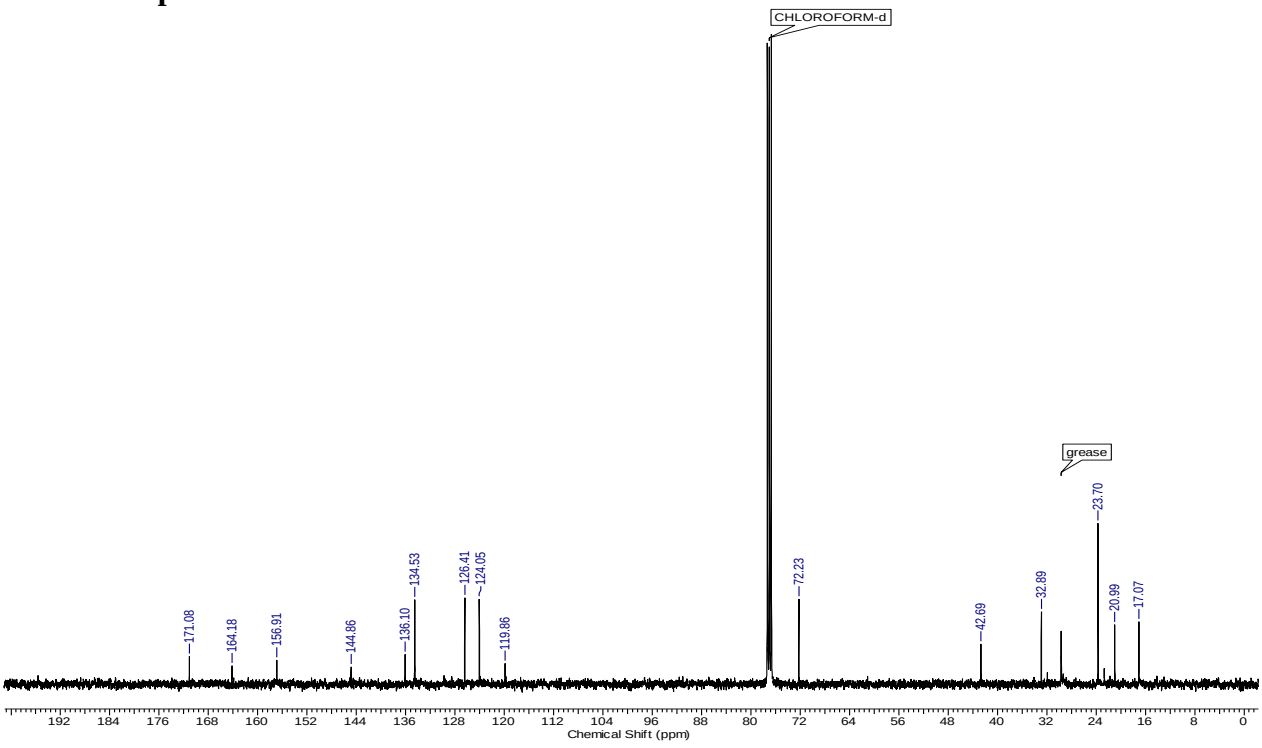

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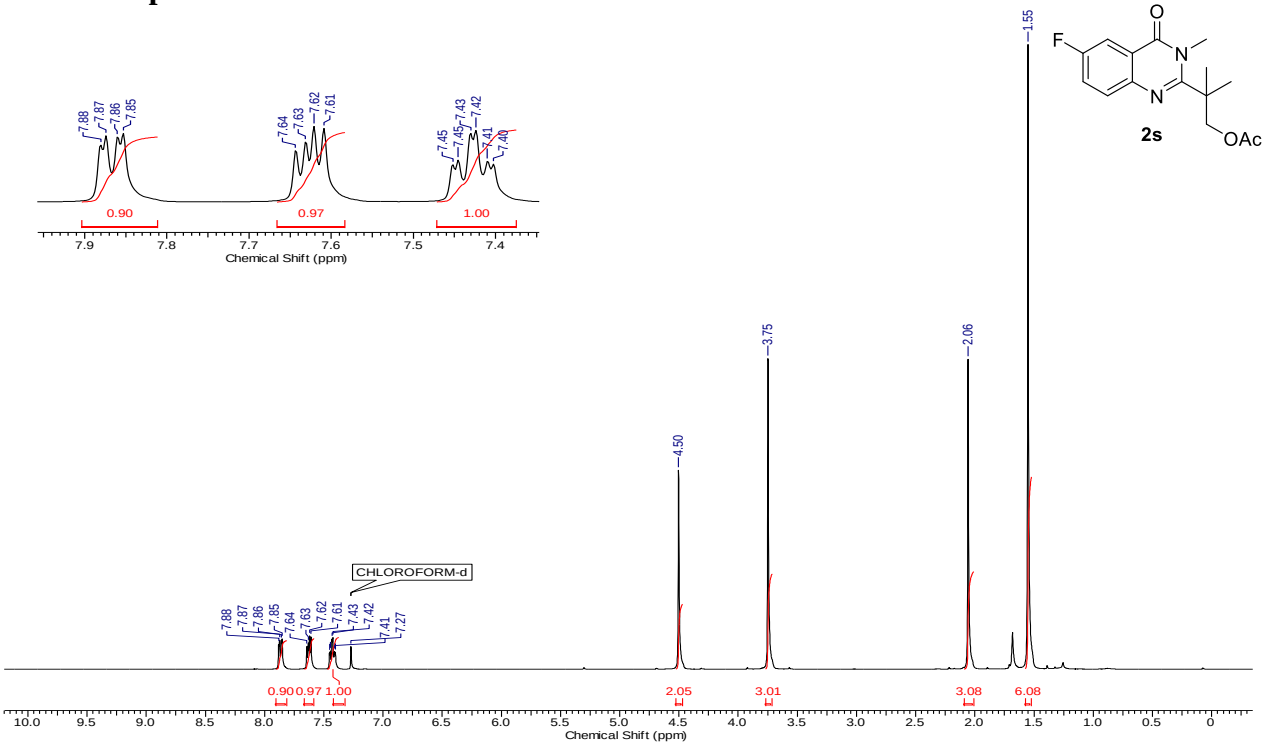

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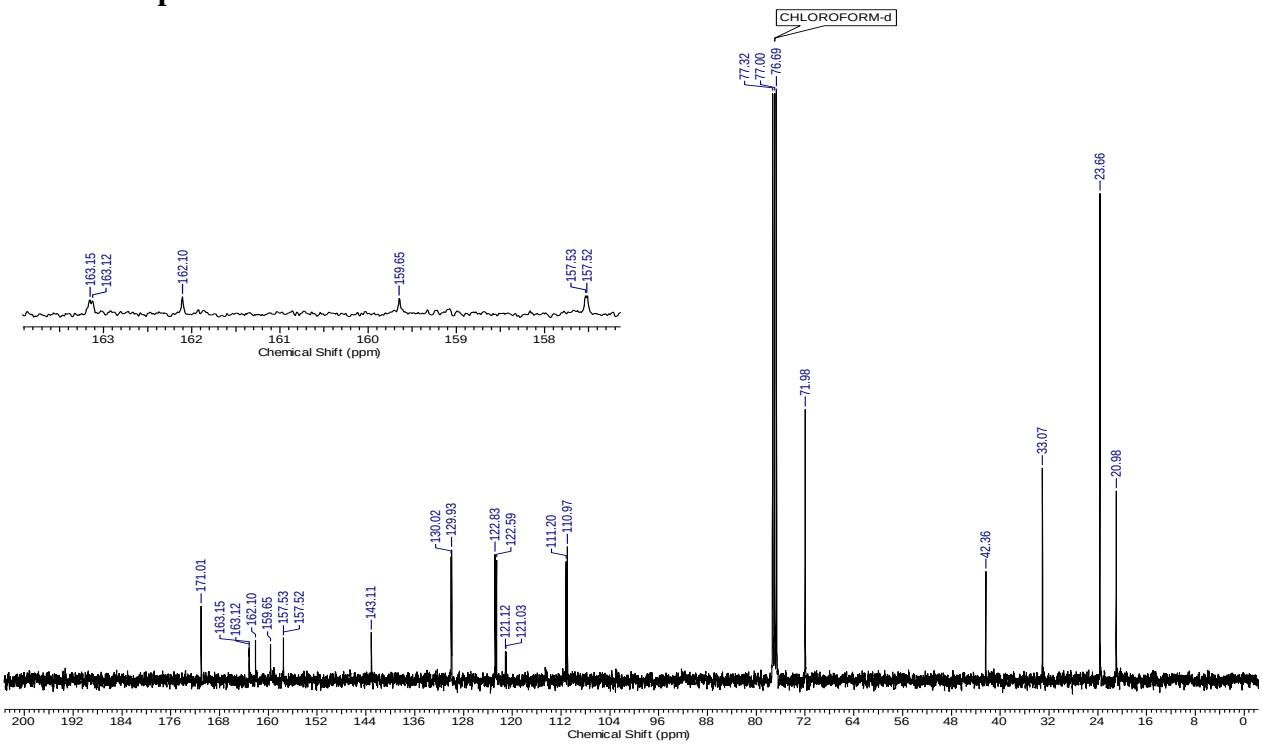
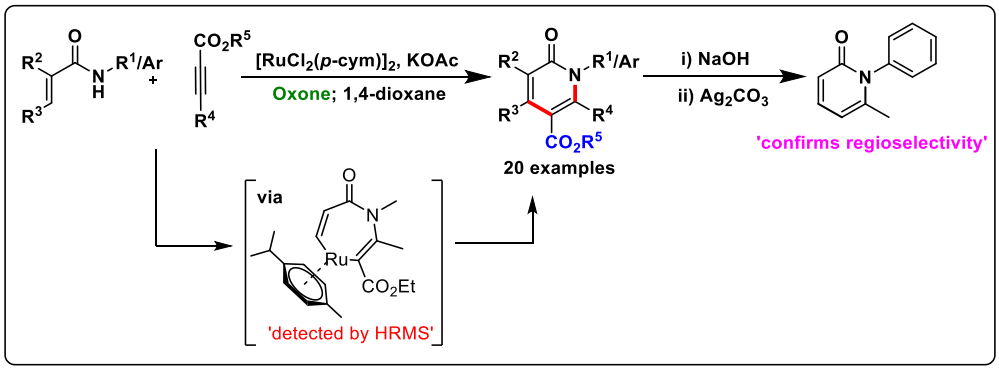


Chapter 3

Ru–Catalyzed Cascade Annulation of Acrylamides with 2-Alkynoates by aza-Michael/C–H Activation Sequence for the Synthesis of Various 6-Oxo Nicotinic Acid Esters

3.1. Abstract:

Chapter 3 deals with Ru–catalyzed regioselective cascade annulation of acrylamides with 2-alkynoates via aza-Michael/C–H activation sequence for the synthesis of various 6-oxo nicotinic acid esters. The regioselectivity of the protocol has been confirmed by performing silver mediated protodecarboxylation of the corresponding 6-oxo nicotinic acid to furnish 2-pyridone. The developed protocol is copper or silver salt-free and uses inexpensive, safe, and environmentally benign peroxide-based 'Oxone' as the sole oxidant. Redox-neutral version of the protocol is also demonstrated. The control reactions were undertaken to detect reaction intermediates for the understanding of the reaction mechanism.



3.2. Introduction:

Pyridone is one of the privileged heteroaromatic rings, which widely occurr in biologically active molecules, natural products, and pharmaceutical agents.[1] In particular, 6-oxo nicotinic acid esters and hydroxypyridinecarboxylic acids constitute the biologically important class of compounds.[2] They are used for metal chelation therapy because of their good binding capacity towards aluminum(III) and iron(III). Milrinone, ciclopirox, pirfenidone, cytisine, flavipucine,

camptothecin (CPT) and perampanel are some of the important natural products and pharmaceuticals featuring pyridone core (Fig. 1).[1-3] As a result, several methods for the selective preparation of these heterocycles and their derivatives are reported in the literature.[1a,b,2a,4] Among these methods C–H bond activation has emerged as a cost and step economical tool for the synthesis of the pyridone class of *N*-heterocycles because it avoids the pre-activation steps of starting materials, such as halogenation and stoichiometric metalation, which are most commonly required in traditional cross-coupling reactions.[5] Transition-metal-catalyzed oxidative

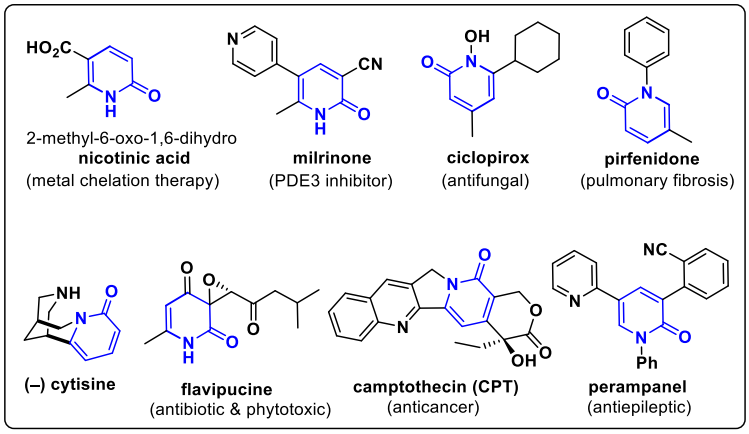


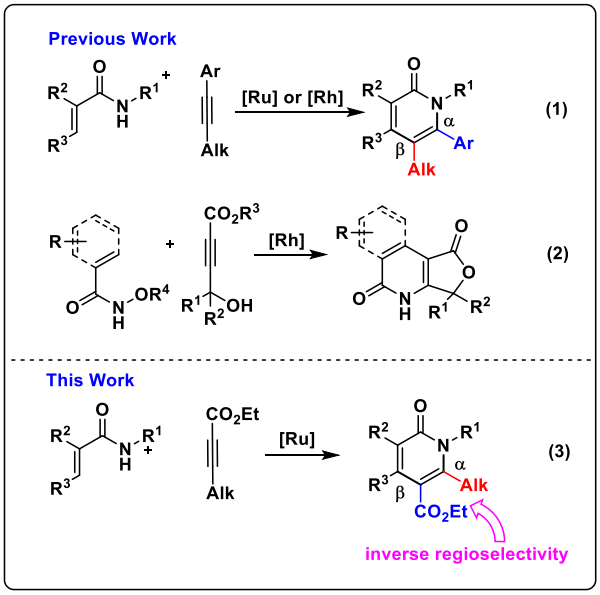
Figure 1. Selected Pyridone Containing Natural Products and Drugs[1-3]

annulation of amides with alkynes by C-H bond activation is one of the most commonly used methods for the synthesis of pyridones[6] and isoquinolones.[7] Transition metal-catalyzed annulations from acrylamides/acryloyl-hydroxamates and alkynes, proceeding with C-H bond activation and leading to pyridones, are known. However, it should be noted that the latter annulation reactions have been much less investigated than related processes involving benzamides or benzhydroxamates as a route to isoquinolones.

3.3. Literature Review:

Previously, ruthenium and rhodium catalytic systems with stoichiometric copper salts as an oxidant have been employed on acrylamides and unsymmetrical alkynes for the regioselective

synthesis of *β*-alkyl pyridones (Scheme 1, eq 1).[6e,f] Recently, Fan and co-workers reported Rh-catalyzed redox neutral annulation protocol for the annulation of benzoyl and acryloyl hydroxamates with ynoates possessing a tertiary propargyl alcohol for the regioselective synthesis of *γ*-lactone ring-fused pyridones (Scheme 1, eq 2).[8] The regioselectivity of this protocol was accomplished by the chelation of metal catalyst with hydroxyl group present in the ynoates. The literature known strategies[5-8] mostly follow C-H activation/alkyne insertion sequence to form C–C bond followed by C–N bond formation via reductive elimination to get 3-alkyl substituted pyridones.



Scheme 1. Annulation of Acrylamides with unsymmetrical Alkynes/2-Alkynoates

3.4. Origin of the Work:

We envisioned that $RuCl_2$(*p*-cymene) catalyzed reaction might follow aza-Michael/C–H activation sequence with 2-alkynoates due to the high electron withdrawing nature of the ester moiety to accomplish complete reverse regioselectivity on the contrary to the known ruthenium or rhodium catalyzed protocols with other unsymmetrical alkynes.

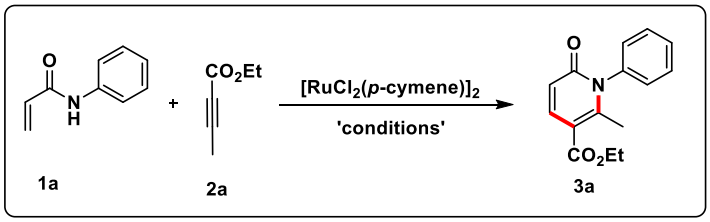
3.5. Objective of the work:

In the context of getting revere regioselectivity, we have developed a protocol for inverse regioselective oxidative annulation of acrylamides with 2-alkynoates for the synthesis of various 6-oxo nicotinic acid esters (*α*-alkyl pyridones) using ruthenium catalysis (Scheme 1, eq 3). The developed protocol is copper or silver salt-free and uses inexpensive, safe, and environmentally benign peroxide-based 'Oxone' as the sole oxidant. We have also investigated redox-neutral version of the protocol by employing acryloyl-hydroxamates as a substrate. We further describe a few control reactions, which shed some light on the regioselectivity and mechanism of this transformation.

3.6. Result and Discussion:

We began to optimize the oxidative coupling by employing *N*-phenyl acrylamide (**1a**) and ethyl 2-butynoate (**2a**, Table 1). First, we attempted the literature known oxidative annulation conditions[6f] with $[RuCl_2(p\text{-cymene})]_2$ catalyst and copper acetate in *t*-amyl alcohol but ended up in the complex reaction mixture, and the expected product **3a** was not observed (entry 1). Interestingly, the change in the solvent from *t*-amyl alcohol to DCE resulted in the expected

Table 1. Optimization Studies



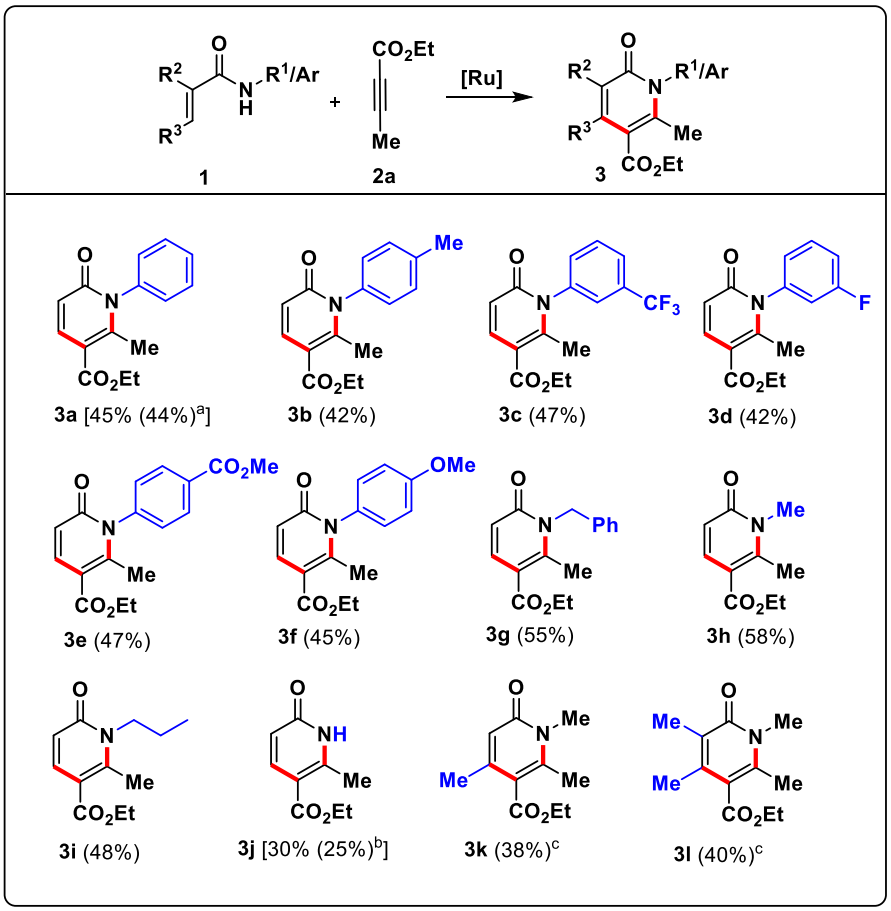
entry	catalyst (mol%)	additive (equiv)	oxidant (equiv)	solvent/temp (^oC)	result[a,b]
1	5	-	$Cu(OAc)_2$ (2)	TAA/120	--
2	5	-	$Cu(OAc)_2$ (2)	DCE/100	18%
3	5	-	$Cu(OAc)_2$ (2)	1,4-dioxane/110	22%
4	5	KOAc (0.1)	$K_2S_2O_8$ (2)	1,4-dioxane/110	35%

5	5	KOAc (0.1)	Oxone (2)	1,4-dioxane/110	45%
6	5	KOAc (0.1)	Oxone (2)	1,4-dioxane/100	35%
7	5	KOAc (0.1)	Oxone (2)	1,4-dioxane/120	40%
8	2	KOAc (0.1)	Oxone (2)	1,4-dioxane/110	30%
9	10	KOAc (0.1)	Oxone (2)	1,4-dioxane/110	46%
10	20	KOAc (0.1)	Oxone (2)	1,4-dioxane/110	44%

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), $[RuCl_2(p\text{-cym})]_2$ (5 mol%), KOAc (10 mol%), oxidant (0.6 mmol), 1,4 dioxane (3 mL) in glass tube for 30 h at 110 ^oC. [b]Isolated yield. TAA = *t*-amyl alcohol.

product formation though in low yield (entry 2). Remarkably, single regioisomer formation was observed in the reaction. When the reaction was performed in 1,4-dioxane at 110 ^oC, little improvement in the yield was observed (entry 3). To our delight, when 10 mol% KOAc additive and nonmetallic oxidant $K_2S_2O_8$ was used with Ru-catalyst $[RuCl_2(p\text{-cymene})]_2$, a substantial increment in the yield was observed (entry 4). Pleasingly, a clean reaction was observed (entry 5) when catalytic $[RuCl_2(p\text{-cymene})]_2$ and KOAc along with Oxone was used as the oxidant. The known annulation protocols usually require stoichiometric amounts of mostly metallic oxidants, which compromises the overall sustainable nature of C−H bond activation process.[5,6] The use of inexpensive and non-metallic oxidants in such protocols is still rare.[9] Herein, we have demonstrated its use in the regioselective annulation protocol using ruthenium catalysis. Further deviation in the reaction temperature (entries 6, 7) or variation in the catalyst loading (entries 8-10) did not show considerable improvement in the yield. The probable reason for the low yield of this transformation is the instability of the starting materials at a higher temperature under the present conditions. To check the stability of alkynoates we subjected **2a** to our reaction condition in the absence of **1a** and observed decomposition of **2a**. Only 45% of **2a** could be recovered after 24 h. Thus, the optimum condition for this transformation is as follows: $[RuCl_2(p\text{-cym})]_2$ (5 mol%), KOAc (10 mol%), Oxone (2 equiv) in 1,4-dioxane at 110 ^oC.

After having optimal conditions in hand, we turned our attention to the evaluation of the scope of the reaction (Scheme 2). The protocol has been generalized to access varyingly substituted 6-oxo nicotinic acid esters. Initially, *N*-aryl substituted pyridones were synthesized using various *N*-aryl substituted acrylamides and ethyl 2-butynoate (**2a**). As mentioned in the optimization studies, the *N*-phenyl substituted acrylamide furnished pyridone **3a** in 45% yield. We also performed the reaction of **1a** with **2a** at the 10 mmol scale and observed consistency in the yield (44%) of **3a**. The *N*-(*p*-tolyl) substituted acrylamide delivered pyridone **3b** in moderate yield



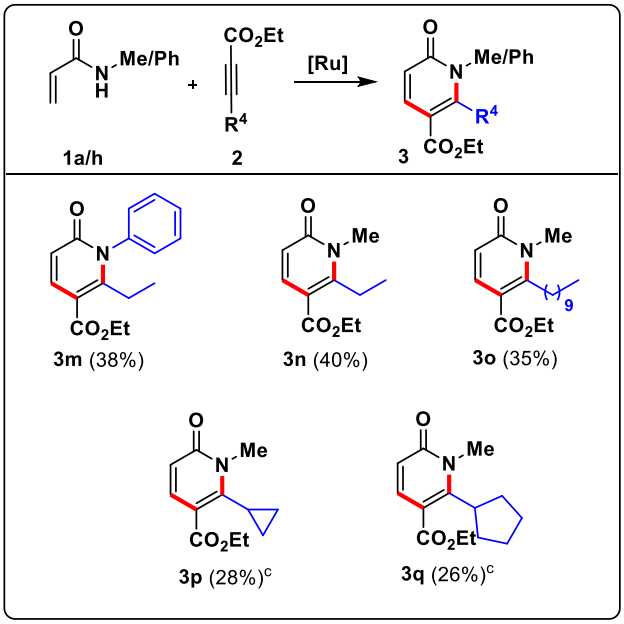
[a]10 mmol scale reaction, [b]Reaction with *N*-Acetyl acrylamide, [c]Reaction was carried out at 120 °C in the sealed tube

Scheme 2. Ru-Catalyzed Annulation of Various Acrylamides with ethyl 2-butynoate

under the developed protocol. *N*-(3-(Trifluoromethyl) phenyl)acrylamide and *N*-(3-fluorophenyl)acrylamide smoothly underwent oxidative annulation with **2a** and furnished the

corresponding pyridones **3c** and **3d** respectively in acceptable yields. Electron withdrawing ester group and electron releasing methoxy group at the para position of phenyl ring attached to the nitrogen of acrylamide did not affect much on annulation reaction and analogous pyridones **3e** and **3f** were obtained in modest yields. Various *N*-alkyl substituted acrylamides have also been used for the oxidative annulation with **2a** and resulted into formation of *N*-benzyl **3g**, *N*-Methyl **3h**, and *N*-propyl **3i** pyridones in better yields as compared to the *N*-aryl acrylamides. Whereas, annulation of acrylamide and alkynoate **2a** produced pyridone **3j** in 30% yield. The formation of pyridone **3j** was also observed when *N*-acetyl acrylamide was used as the substrate. Acetyl group deprotection was observed under these conditions and **3j** was isolated in 25% yield. The data of **3j** is in agreement with the literature report,[10] which confirms the regioselectivity of our protocol. The effect of substituents on the various position of *N*-methyl acrylamide was also studied and varyingly methyl substituted pyridones **3k** and **3l** were synthesized with reasonable yields. It should be noted that for the synthesis of pyridones **3k** and **3l**, a higher reaction temperature and longer reaction time were required and these reactions were performed in a sealed tube. The higher temperature required for these substrates may be due to the steric effect of methyl substituents at the β-position of acrylamides.

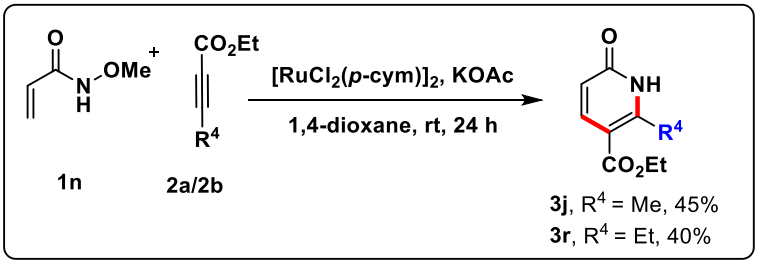
After having studied the substrate scope with respect to various *N*-substituted acrylamides, we decided to study the substrate scope with various 2-alkynoates (Scheme 3). The reaction of *N*-phenyl acrylamide and ethyl 2-pentynoate conceded pyridone **3m** in moderate yield. As observed above in the substrate scope studies (Scheme 2) *N*-methyl acrylamide furnished the highest yield of pyridone **3h**, hence for further studies *N*-methyl acrylamide was chosen as a fixed substrate and reacted with various alkynoates. The pyridones with various substituents at the second position such as ethyl **3n**, decyl **3o**, cyclopropyl **3p**, and cyclopentyl **3q** were synthesized in low



Scheme 3. Ru-Catalyzed Annulation of *N*-Me/Ph Acrylamides with 2-Alkynoates

to moderate yields from the corresponding alkynoates. For the synthesis of pyridones **3p** and **3q** also higher temperature and more time were required, and these reactions were performed in a sealed tube. Probably, steric hindrance of cyclopropyl and cyclopentyl rings of 2-alkynoate affects the rate of annulation.

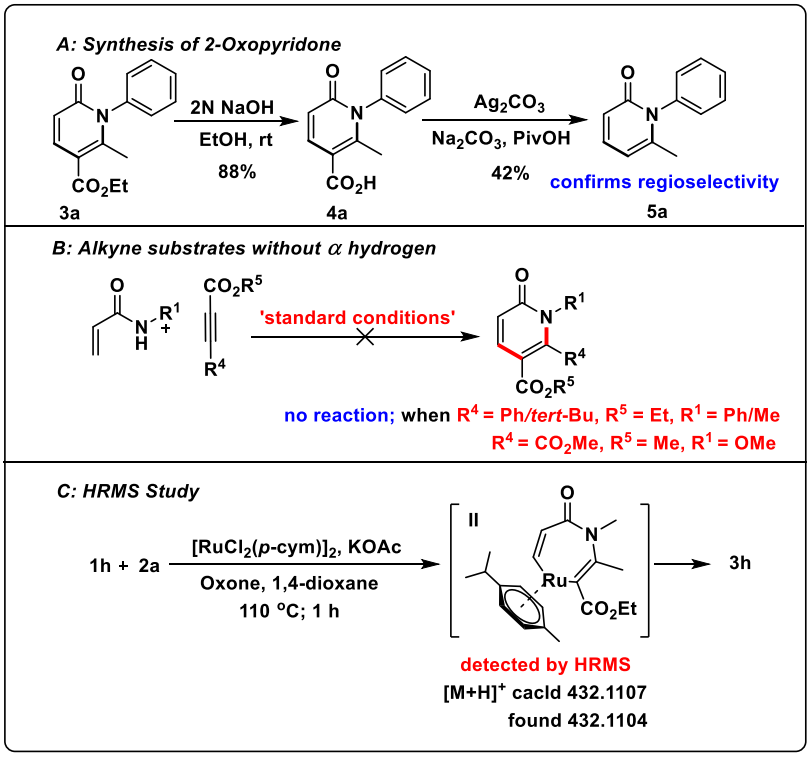
After having studied the substrate scope of oxidative annulation protocol with the external oxidant, we decided to study oxidant-free annulation reaction of acrylamides and 2-alkynoates (Scheme 4). One solution to overcome the use of an external oxidizing reagent involves the development of redox-neutral version with hydroxamates.[7f,g] When *N*-methoxy acrylamide **1n** was reacted with ethyl 2-butynoate (**2a**) at room temperature without external oxidant, the



Scheme 4. Ru-Catalyzed Redox-Neutral Annulation of *N*-Methoxy Acrylamide with 2-Alkynoates

corresponding N-H free pyridone **3j** was obtained in 45% yield. Comparison of the NMR spectral data of **3j** with those described in the literature[10] for this compound confirms the structure of this latter compound and the regioselectivity of the ruthenium-catalyzed annulation. The N-H free pyridone **3r** was also synthesized by employing redox neutral strategy using *N*-methoxy acrylamide **1n** and ethyl 2-pentynoate as substrates. Here, the substrate itself acts as an oxidant and no external oxidant is required for these reactions.

The regioselectivity of our protocol was also confirmed by synthesizing 6-methyl-1-phenylpyridin-2(1H)-one (Scheme 5A). Initially, ester hydrolysis of pyridone **3a** was carried out

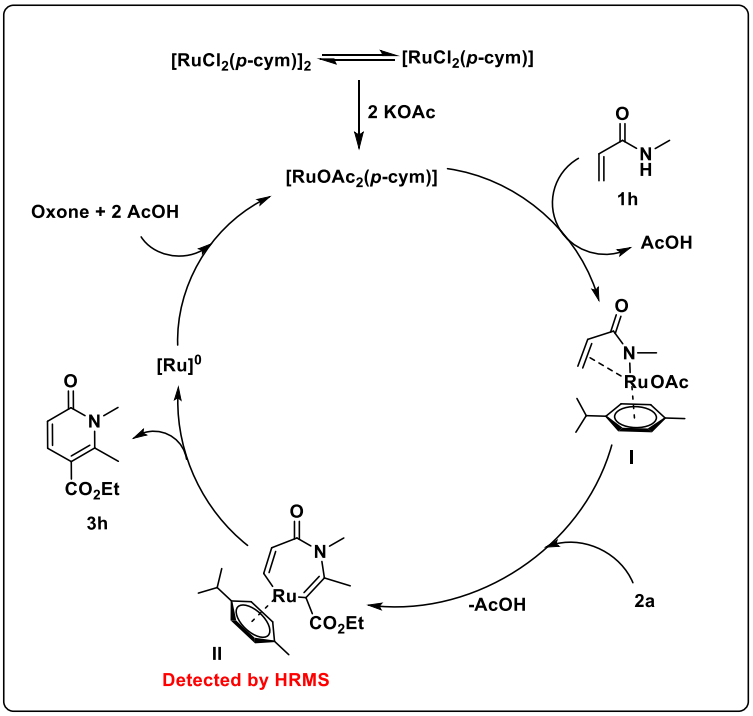


Scheme 5. Control Reactions

using aqueous NaOH in ethanol to obtain acid **4a** in excellent yield. The acid **4a** was then subjected under various protodecarboxylation conditions. Under the silver carbonate mediated condition in *N*,*N*-dimethylacetamide it furnished the pyridone **5a** in 42% yield. The NMR

spectral data of compound **5a** were consistent with those described in the literature.[11] This reconfirms our hypothesis and regioselectivity of this protocol. Additionally, it shows the utility of our method for the synthesis of 2-pyridones. During the substrate scope study, we utilized 2-alkynoates having α-hydrogens. We were curious to know the outcome of the protocol in the absence of α-hydrogen. Interestingly, when $\mathbf{R^4}$ of 2-alkynoates is phenyl/tertiary butyl/ester (Scheme 5B), the expected products were not observed, which could be mostly due to steric/electronic factors. However, the protocol works well when $\mathbf{R^4}$ is the primary or secondary alkyl group, which suggests that the possible involvement of allene intermediates in the reaction cannot be ruled out. The HRMS study of the reaction mixture was also carried out to detect the possible intermediates of the reaction (Scheme 5C), and interestingly M+H peak of ruthenacycle **II** was detected by HRMS analysis.

A plausible reaction mechanism is proposed based on the above experimental outcome (Scheme 6) and literature reports.[7d,e] Initially, ligand exchange of ruthenium catalyst with potassium acetate to form diacetate ruthenium *p*-cymene as an active catalyst. The acrylamide **1h** reacts with the active catalyst formed to get intermediate **I** with the loss of one molecule of acetic acid. The intermediate **I** then reacts with alkynoate **2a** first through Michael addition then followed by with C-H bond activation to furnish the ruthenacycle intermediate **II** (detected by HRMS). Product **3h** could be formed after reductive elimination of metal from ruthenacycle **II**. The oxidation of Ru(0) to Ru(II) by Oxone makes the active catalyst available for further catalytic cycles.



Scheme 6. Proposed Mechanism

3.7. Conclusion:

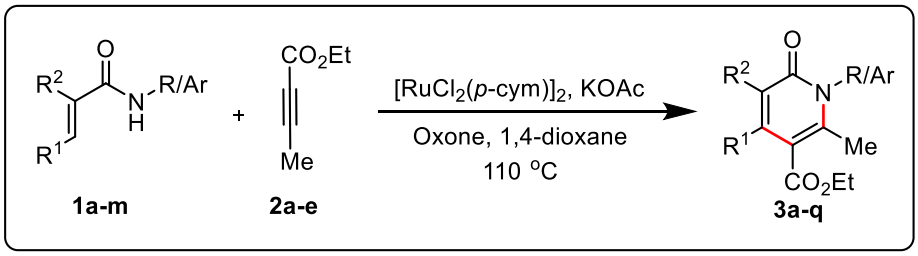
In summary, Ruthenium catalyzed inverse regioselective annulation of acrylamides with alkynes has been developed. The reverse regioselectivity and tentative mechanism is supported by controlled experiments. The annulation protocol is further extended as the redox neutral process, where the substrate acts as an oxidant for the metal catalyst. Diverse novel 6-oxo nicotinic acid esters have been synthesized using the developed protocol. The developed protocol uses non-metallic, inexpensive, safe, and environmentally benign oxidant. Further improvement in the protocol to access various 6-oxo nicotinic acid esters in higher yields and its application in the synthesis of natural products and bioactive molecules is under progress in our laboratory.

3.8. Experimental Procedures and Characterization Data of Compounds:

N-alkyl and *N*-alkoxy substituted acrylamides,[12] *N*-aryl substituted acrylamides[13] and commercially unavailable 2-alkynoate[14] starting materials were prepared according to literature procedures.

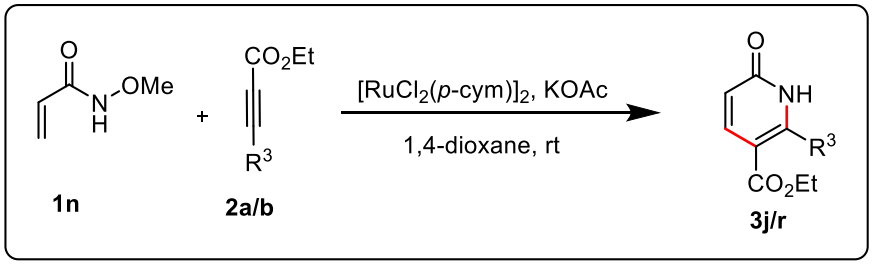
I) Experimental Procedures for Ru–Catalyzed Annulation:

General Procedure-1:



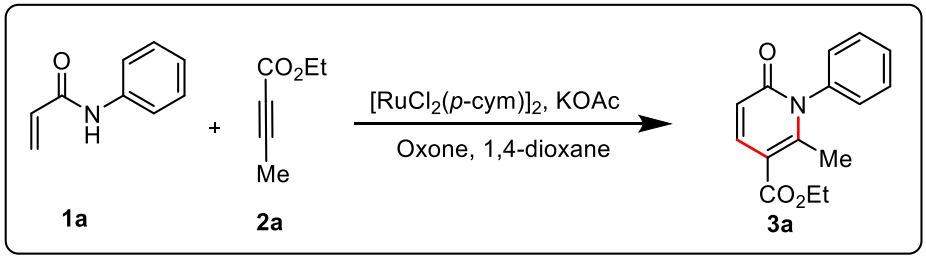
To a mixture of $[RuCl_2(p\text{-cymene})]_2$ (0.015 mmol; 9.2 mg) and KOAc (0.03 mmol; 3 mg) in a glass tube with side arm was added 1,4-dioxane (3 mL; 0.1M) under argon atmosphere and the reaction mixture was stirred for 1 h at room temperature (rt). Acrylamide **1a-m** (0.3 mmol), 2-alkynoate **2a-e** (0.6 mmol) and Oxone (0.6 mmol; 185 mg) were added to the above mixture and the glass tube was placed in a preheated oil bath at 110 ^{o}C for the stipulated time. The progress of the reaction was monitored by TLC. After complete consumption of acrylamide **1a-m** (30-40 h), the reaction mixture was cooled to rt, diluted with ethyl acetate, filtered through a short pad of celite, and the filtrate was evaporated under *vacuo* to dryness. The resulting residue was purified by column chromatography to afford pure pyridones **3a-q**.

General Procedure-2:



To a mixture of $[RuCl_2(p\text{-cymene})]_2$ (0.015 mmol; 9.2 mg) and KOAc (0.03 mmol; 3 mg) in glass tube with side arm was added 1,4-dioxane (3 mL; 0.1M) under argon atmosphere and the reaction mixture was stirred for 1 h at rt. Acrylamide **1n** (0.3 mmol) and 2-alkynoate **2a/b** (0.6 mmol) were added to the above mixture and it was stirred at rt. The progress of the reaction was monitored by TLC. After complete consumption of acrylamide **1n** (24 h), the reaction mixture was diluted with ethyl acetate, filtered through a short pad of celite, and the filtrate was evaporated under *vacuo* to dryness. The resulting residue was purified by column chromatography to afford pure pyridones **3j/r.**

II) Procedure for the Preparation of Pyridone 3a on 10 mmol Scale:

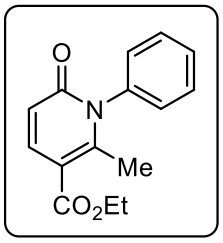


To a mixture of $[RuCl_2(p\text{-cymene})]_2$ (0.5 mmol; 306 mg) and KOAc (1 mmol; 98 mg) in a glass tube with side arm was added 1,4-dioxane (100 mL; 0.1M) under argon atmosphere and the reaction mixture was stirred for 1 h at rt. *N*-Phenyl arylamide (**1a**, 10 mmol; 1.47 gm), ethyl 2-butynoate (**2a**, 20 mmol; 2.24 mL) and Oxone (20 mmol; 6.15 gm) were added to the above

mixture and the glass tube was placed in preheated oil bath at 110 ^{o}C for 30 h. The progress of the reaction was monitored by TLC. After complete consumption of acrylamide **1a** (30 h) the reaction mixture was cooled to rt, diluted with ethyl acetate, filtered through short pad of celite, and the filtrate was evaporated under *vacuo* to dryness. The resulting residue was purified by column chromatography to afford pure pyridone **3a** (1.13 g; 44%).

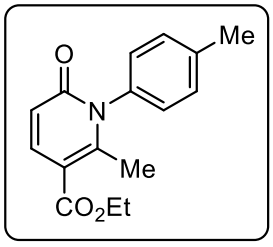
III) Characterization Data of Pyridones (3a-s):

Ethyl 2-methyl-6-oxo-1-phenyl-1,6-dihydropyridine-3-carboxylate (3a)



According to the **general procedure-1**, the title compound **3a** was obtained as a thick oil (35 mg; 45% yield); reaction time: 30 h; R*f*: 0.5 (2:3 EtOAc: Pet. ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.98 (d, J = 9.8 Hz, 1H), 7.55 (t, J = 7.3 Hz, 2H), 7.48 (t, J = 7.3 Hz, 1H), 7.16 (d, J = 7.3 Hz, 2H), 6.53 (d, J = 9.8 Hz, 1H), 4.32 (q, J = 6.7 Hz, 2H), 2.37 (s, 3H), 1.37 (t, J = 6.7 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 165.5, 163.3, 153.9, 140.4, 138.4, 130, 129.1, 127.7, 117.3, 109.2, 60.9, 19.7, 14.3; **HRMS** (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{15}H_{15}O_3NNa$ 280.0944, found 280.0943.

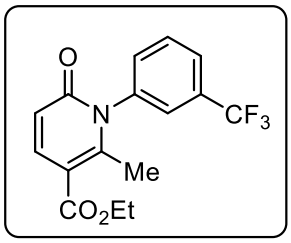
Ethyl 2-methyl-6-oxo-1-(p-tolyl)-1,6-dihydropyridine-3-carboxylate (3b)



According to the **general procedure-1**, the title compound **3b** was obtained as a thick oil (34 mg; 42% yield); reaction time: 30 h; R*f*: 0.5 (2:3 EtOAc: Pet. ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.97 (d, J = 9.6 Hz, 1H), 7.34 (d, J = 8.7 Hz, 2H), 7.04 (d, J = 8.3 Hz, 2H), 6.53 (d, J = 9.2 Hz, 1H), 4.31 (q, J = 7.3 Hz, 2H), 2.43 (s, 3H), 2.38 (s, 3H), 1.37 (t, J = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 165.6, 163.4, 154.2, 140.3, 139.1, 135.7, 130.7, 127.4, 117.2,

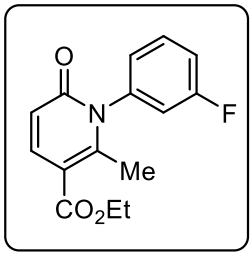
109.2, 60.9, 21.2, 19.7, 14.3; **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{16}H_{18}O_3N$ 272.1281, found 272.1280.

Ethyl 2-methyl-6-oxo-1-(3-(trifluoromethyl)phenyl)-1,6-dihydropyridine-3-carboxylate (3c)



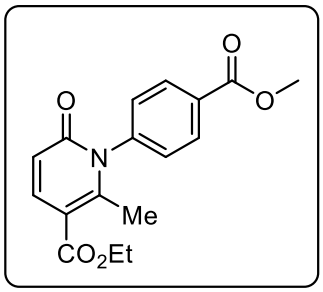
According to the **general procedure-1**, the title compound **3c** was obtained as a thick oil (46 mg; 47% yield); reaction time: 30 h; R*f*: 0.5 (2:3 EtOAc: Pet. ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 8.01 (d, *J* = 9.8 Hz, 1H), 7.77 (d, *J* = 7.9 Hz, 1H), 7.70 (t, *J* = 7.9 Hz, 1H), 7.47 (s, 1H), 7.40 (d, *J* = 7.9 Hz, 1H), 6.55 (d, *J* = 9.8 Hz, 1H), 4.33 (q, *J* = 7.3 Hz, 2H), 2.37 (s, 3H), 1.38 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 165.3, 163, 153.2, 140.8, 138.9, 132.6 (q, *J* = 33.9 Hz), 131.6, 130.7, 126.1 (q, *J* = 3.9 Hz), 125.1 (q, *J* = 3.9 Hz), 123.3 (q, *J* = 272.8 Hz), 117.5, 109.7, 61.1, 19.8, 14.3; **HRMS** (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{16}H_{14}O_3NF_3Na$ 348.0818, found 348.0815.

Ethyl 1-(3-fluorophenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (3d)



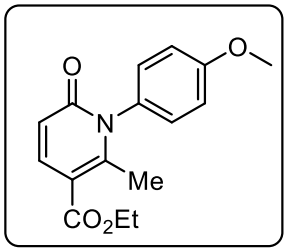
According to the **general procedure-1**, the title compound **3d** was obtained as a thick oil (35 mg; 42% yield); reaction time: 30 h; R*f*: 0.5 (2:3 EtOAc: Pet. ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.99 (d, *J* = 10.1 Hz, 1H), 7.57-7.48 (m, 1H), 7.21 (td, *J* = 8.2, 2.8 Hz, 1H), 6.98 (dt, *J* = 7.8, 1 Hz, 1H), 6.94 (dt, *J* = 8.7, 2.3 Hz, 1H), 6.53 (d, *J* = 9.6 Hz, 1H), 4.33 (q, *J* = 6.9 Hz, 2H), 2.40 (s, 3H), 1.38 (t, *J* = 6.9 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 165.4, 163.3 (d, *J* = 249.2 Hz), 163, 153.5, 140.7, 139.7 (d, *J* = 10.5 Hz), 131.3 (d, *J* = 8.6 Hz), 123.8 (d, *J* = 2.9 Hz), 117.4, 116.4 (d, *J* = 20.1 Hz), 115.7 (d, *J* = 23 Hz), 109.5, 61.1, 19.6, 14.3; **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{15}H_{15}O_3NF$ 276.1030, found 276.1028.

Ethyl 1-(4-(methoxycarbonyl) phenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (3e)



According to the **general procedure-1**, the title compound **3e** was obtained as a thick oil (44 mg; 47% yield); reaction time: 30 h; R*f*: 0.5 (2:3 EtOAc: Pet. ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 8.23 (d, *J* = 8.7 Hz, 2H), 7.99 (d, *J* = 10.1 Hz, 1H), 7.27 (d, *J* = 8.7 Hz, 2H), 6.54 (d, *J* = 9.6 Hz, 1H), 4.32 (q, *J* = 7.3 Hz, 2H), 3.96 (s, 3H), 2.37 (s, 3H), 1.38 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 165.96, 165.4, 162.98, 153.2, 142.4, 140.7, 131.4, 130.96, 128.1, 117.4, 109.5, 61.1, 52.4, 19.7, 14.3; **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{17}H_{18}O_5N$ 316.1179, found 316.1178.

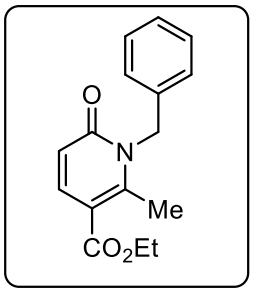
Ethyl 1-(4-methoxyphenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (3f)



According to the **general procedure-1**, the title compound **3f** was obtained as a thick oil (39 mg; 45% yield); reaction time: 30 h; R*f*: 0.5 (2:3 EtOAc: Pet. ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.97 (d, *J* = 9.6 Hz, 1H), 7.09-7.03 (m, 4H), 6.54 (d, *J* = 9.6 Hz, 1H), 4.32 (q, *J* = 6.9 Hz, 2H), 3.86 (s, 3H), 2.40 (s, 3H), 1.38 (t, *J* = 6.9 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 165.6, 163.6, 159.8, 154.4, 140.4, 130.9, 128.7, 117.2, 115.2, 109.3, 60.9, 55.5, 19.7, 14.3; **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{16}H_{18}O_4N$ 288.1230, found 288.1227.

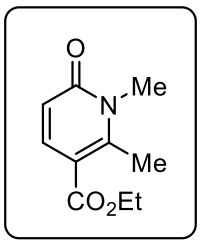
Ethyl 1-benzyl-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (3g)

According to the **general procedure-1**, the title compound **3g** was obtained as a thick oil (45 mg; 55% yield); reaction time: 30 h; R*f*: 0.5 (2:3 EtOAc: Pet. ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.94 (d, *J* = 9.6 Hz, 1H), 7.35-7.25 (m, 3H), 7.13 (d, *J* = 7.3 Hz, 2H), 6.56 (d, *J*



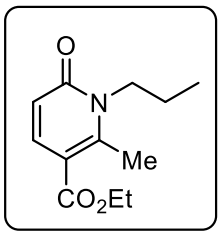
= 9.6 Hz, 1H), 5.45 (s, 2H), 4.29 (q, *J* = 6.9 Hz, 2H), 2.72 (s, 3H), 1.36 (t, *J* = 6.9 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 165.7, 163.2, 153.9, 140.1, 135.7, 128.9, 127.5, 126.3, 116.6, 109.9, 60.96, 47.5, 17.7, 14.3; **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{16}H_{18}O_3N$ 272.1281, found 272.1279.

Ethyl 1,2-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxylate (3h)



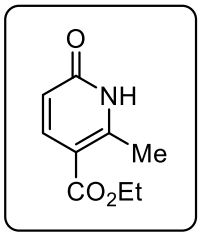
According to the **general procedure-1**, the title compound **3h** was obtained as a thick oil (34 mg; 58% yield); reaction time: 30 h; R*f*: 0.5 (1:1 EtOAc: Pet. ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.87 (d, *J* = 9.8 Hz, 1H), 6.45 (d, *J* = 9.8 Hz, 1H), 4.29 (q, *J* = 7.3 Hz, 2H), 3.60 (s, 3H), 2.78 (s, 3H), 1.35 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 165.7, 163.2, 153.6, 139.6, 116, 109.6, 60.9, 31.6, 17.9, 14.2; **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{10}H_{14}O_3N$ 196.0968, found 196.0967.

Ethyl 2-methyl-6-oxo-1-propyl-1,6-dihydropyridine-3-carboxylate (3i)



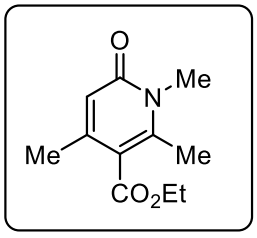
According to the **general procedure-1**, the title compound **3i** was obtained as a thick oil (32 mg; 48% yield); reaction time: 30 h; R*f*: 0.5 (1:1 EtOAc: Pet. ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.84 (d, *J* = 9.8 Hz, 1H), 6.42 (d, *J* = 9.8 Hz, 1H), 4.28 (q, *J* = 7.3 Hz, 2H), 4.06 (t, *J* = 7.3 Hz, 2H), 2.80 (s, 3H), 1.77-1.64 (m, 2H), 1.35 (t, *J* = 7.3 Hz, 3H), 1.01 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 165.8, 162.9, 153, 139.6, 116.5, 109.5, 60.9, 46.2, 21.6, 17.2, 14.3, 11.3; **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{12}H_{18}O_3N$ 224.1281, found 224.1280.

Ethyl 2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (3j)[10]



According to the **general procedure-1** and by using acrylamide and *N*-acetyl acrylamide, the title compound **3j** was obtained as a thick oil (16 mg; 30% yield) and (14 mg; 25% yield) respectively; reaction time: 30 h; whereas by using **general procedure-2** and *N*-methoxy acrylamide, the title compound **3j** was obtained as a thick oil (25 mg; 45% yield); reaction time: 24 h; R*f*: 0.4 (2:1 EtOAc: Pet. ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 12.92 (bs, 1H), 8.06 (d, J = 9.8 Hz, 1H), 6.43 (d, J = 9.8 Hz, 1H), 4.31 (q, J = 7.3 Hz, 2H), 2.74 (s, 3H), 1.37 (t, J =7.6 Hz, 3H), **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 165.3, 164.8, 152.9, 143, 116, 109.4, 60.8, 19.7, 14.3; **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_9H_{12}O_3N$ 182.0812, found 182.0811.

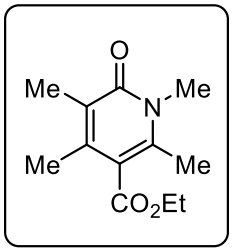
Ethyl 1,2,4-trimethyl-6-oxo-1,6-dihydropyridine-3-carboxylate (3k)



According to the **general procedure-1** at 120 ^{o}C in the glass tube with screw cap, the title compound **3k** was obtained as a thick oil (24 mg; 38% yield); reaction time: 40 h; R*f*: 0.5 (1:1 EtOAc: Pet. ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 6.32 (s, 1H), 4.34 (q, J = 7.3 Hz, 2H), 3.52 (s, 3H), 2.39 (s, 3H), 2.17 (s, 3H), 1.37 (t, J = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 167.8, 162.6, 147.4, 145.7, 117.1, 114.8, 61.4, 31.1, 20.4, 18.5, 14.2; **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{11}H_{16}O_3N$ 210.1125, found 210.1123.

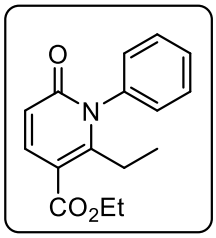
Ethyl 1,2,4,5-tetramethyl-6-oxo-1,6-dihydropyridine-3-carboxylate (3l)

According to the **general procedure-1** at 120 ^{o}C in the glass tube with screw cap, the title compound **3l** was obtained as a thick oil (27 mg; 40% yield); reaction time: 40 h; R*f*: 0.5 (1:1 EtOAc: Pet. ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 4.35 (q, J = 7.3 Hz, 2H), 3.55 (s, 3H),



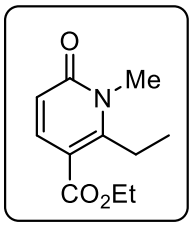
2.34 (s, 3H), 2.12 (s, 6H), 1.38 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 168.6, 162.9, 141.7, 140.7, 123.8, 115.5, 61.4, 31.7, 18.2, 17.3, 14.2, 13; **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{12}H_{18}O_3N$ 224.1281, found 224.1279.

Ethyl 2-ethyl-6-oxo-1-phenyl-1,6-dihydropyridine-3-carboxylate (3m)



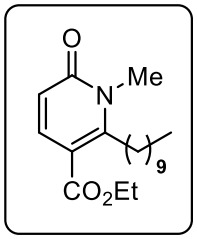
According to the **general procedure-1**, the title compound **3m** was obtained as a thick oil (31 mg; 38% yield); reaction time: 30 h; R*f*: 0.5 (2:3 EtOAc: Pet. ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 8.01 (d, *J* = 9.8 Hz, 1H), 7.59-7.47 (m, 3H), 7.20 (d, *J* = 6.8 Hz, 2H), 6.52 (d, *J* = 9.8 Hz, 1H), 4.32 (q, *J* = 6.8 Hz, 2H), 2.84 (q, *J* = 6.8 Hz, 2H), 1.38 (t, *J* = 7.5 Hz, 3H), 1.04 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 165, 163.5, 159.4, 140.9, 137.9, 129.7, 129.1, 128.2, 117.3, 108.2, 60.9, 24.8, 14.3, 13.7; **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{16}H_{18}O_3N$ 272.1281, found 272.1279.

Ethyl 2-ethyl-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (3n)



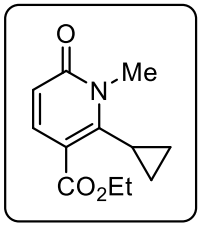
According to the **general procedure-1**, the title compound **3n** was obtained as a thick oil (25 mg; 40% yield); reaction time: 30 h; R*f*: 0.5 (1:1 EtOAc: Pet. ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.89 (d, *J* = 9.8 Hz, 1H), 6.45 (d, *J* = 9.2 Hz, 1H), 4.29 (q, *J* = 6.7 Hz, 2H), 3.64 (s, 3H), 3.22 (q, *J* = 7.3 Hz, 2H), 1.36 (t, *J* = 6.7 Hz, 3H), 1.30 (t, *J* =7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 165.3, 163.4, 158.2, 139.9, 116.2, 108.7, 60.8, 30.96, 24, 14.2, 12.5; **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{11}H_{16}O_3N$ 210.1125, found 210.1123.

Ethyl 2-decyl-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (3o)



According to the **general procedure-1**, the title compound **3o** was obtained as a thick oil (34 mg; 35% yield); reaction time: 30 h; R*f*: 0.5 (1:1 EtOAc: Pet. ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.89 (d, J = 9.8 Hz, 1H), 6.44 (d, J = 9.8 Hz, 1H), 4.29 (q, J = 6.7 Hz, 2H), 3.63 (s, 3H), 3.16 (t, J =7.3 Hz, 2H), 1.66-1.57 (m, 2H), 1.51-1.43 (m, 2H), 1.36 (t, J = 7.3 Hz, 3H), 1.31-1.22 (m, 12H), 0.89 (t, J = 6.7 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 165.4, 163.5, 157.6, 139.9, 116.1, 108.8, 60.8, 31.9, 31.1, 30.7, 29.8, 29.5, 29.3, 29.2, 28.4, 22.7, 14.3, 14.1; **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{19}H_{32}O_3N$ 322.2377, found 322.2374.

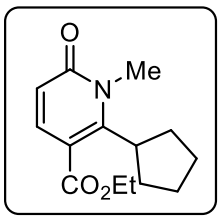
Ethyl 2-cyclopropyl-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (3p)



According to the **general procedure-1** at 120 ^{o}C in the glass tube with screw cap, the title compound **3p** was obtained as a thick oil (18 mg; 28% yield); reaction time: 40 h; R*f*: 0.5 (1:1 EtOAc: Pet. ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.63 (d, J = 9.8 Hz, 1H), 6.49 (d, J = 9.8 Hz, 1H), 4.32 (q, J = 7.3 Hz, 2H), 3.74 (s, 3H), 2.05-1.95 (m, 1H), 1.37 (t, J = 7.3 Hz, 3H), 1.23 (apparent q, J = 6.1 Hz, 2H), 0.63 (apparent q, J = 6.1 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 166.4, 163.3, 154.7, 139.1, 117.3, 113.3, 61.2, 32.7, 14.3, 14.25, 9.9; **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{12}H_{16}O_3N$ 222.1125, found 222.1124.

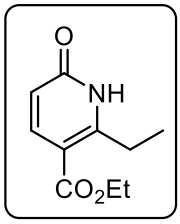
Ethyl 2-cyclopentyl-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (3q)

According to the **general procedure-1** at 120 ^{o}C in the glass tube with screw cap, the title compound **3q** was obtained as a thick oil (19 mg; 26% yield); reaction time: 40 h; R*f*: 0.5 (1:1 EtOAc: Pet. ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.76 (d, J = 9.9 Hz, 1H), 6.51 (d, J =



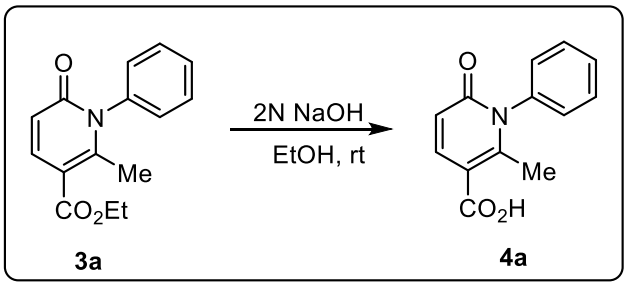
9.9 Hz, 1H), 4.40-4.25 (m, 3H), 3.57 (s, 3H), 2.11-1.98 (m, 4H), 1.97-1.86 (m, 4H), 1.36 (t, *J* = 6.9 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 166.7, 163.97, 158, 140, 116, 111.9, 61.2, 40.1, 34.2, 30.7, 27, 14.2; **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{14}H_{20}O_3N$ 250.1438, found 250.1436.

Ethyl 2-ethyl-6-oxo-1,6-dihydropyridine-3-carboxylate (3r)



According to the **general procedure-2**, the title compound **3r** was obtained as a thick oil (23 mg; 40% yield); reaction time: 24 h; R*f*: 0.4 (2:1 EtOAc: Pet. ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 12.68 (bs, 1H), 8.03 (d, *J* = 9.9 Hz, 1H), 6.42 (d, *J* = 9.2 Hz, 1H), 4.32 (q, *J* = 7.6 Hz, 2H), 3.11 (q, *J* = 7.6 Hz, 2H), 1.37 (t, *J* = 7.6 Hz, 3H), 1.34 (t, *J* = 7.6 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 165.5, 164.7, 158.2, 143.1, 116.4, 108.2, 60.8, 26.1, 14.2, 13.9; **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{10}H_{14}O_3N$ 196.0968, found 196.0968.

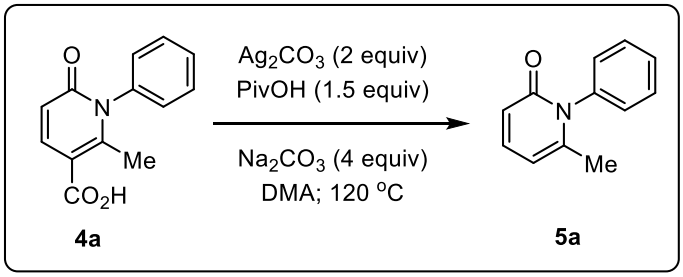
2-Methyl-6-oxo-1-phenyl-1,6-dihydropyridine-3-carboxylic acid (4a)



To a round bottom flask containing the solution of ester **3a** (1 mmol, 257 mg) in EtOH (20 mL) was added 2N aqueous NaOH (10 mL) at rt. The resulting mixture was stirred at rt until completion of the reaction (2h). The reaction mixture was then diluted with water and transferred to a separating funnel and washed with ethyl acetate (2 x 5 mL). The aqueous layer was acidified

to pH 2 with dil. HCl and extracted with EtOAc (3 x 20 mL). The organic layer was dried over Na_2SO_4 and evaporated under *vacuo* to dryness to afford pure acid **4a** (202 mg; 88% yield), which was used in the next step without further purification. **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm) 12.77 (bs, 1H), 7.94 (d, J = 9.8 Hz, 1H), 7.55 (t, J = 7.3 Hz, 2H), 7.48 (t, J = 7.3 Hz, 1H), 7.28 (d, J = 7.3 Hz, 2H), 6.40 (d, J = 9.8 Hz, 1H), 2.28 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ (ppm) 166.8, 162.2, 153.9, 140.9, 138.6, 129.6, 128.7, 128.2, 116.4, 108.7, 19.4; **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{13}H_{12}O_3N$ 230.0812, found 230.0810.

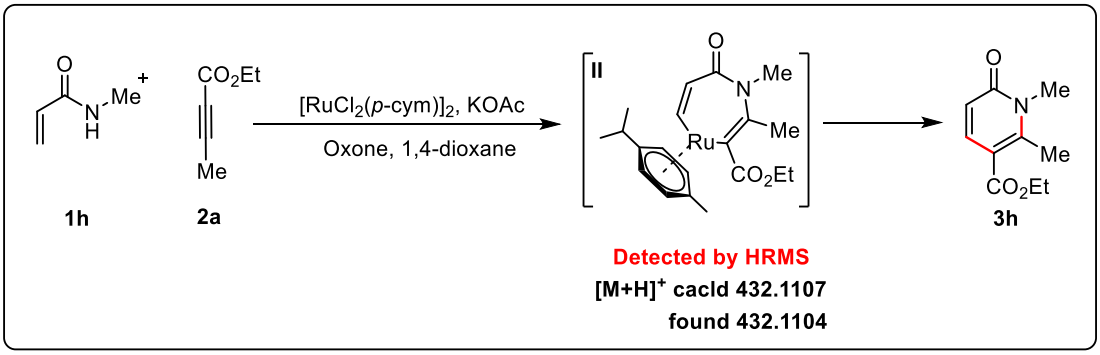
6-Methyl-1-phenylpyridin-2(1H)-one (5a)[11]



A glass tube with side arm was charged with acid **4a** (0.1 mmol, 23 mg), Ag_2CO_3 (0.2 mmol, 55 mg), PivOH (0.15 mmol, 15 µL), Na_2CO_3 (0.4 mmol, 43 mg) and DMA (1 mL). The glass tube was placed in preheated oil bath at 120 ^{o}C for 24 h. After 24 h, the reaction was cooled to rt, diluted with ethyl acetate and filtered through a short pad of celite. The filtrate was washed two times with water, dried over Na_2SO_4 and evaporated under *vacuo* to dryness. The resulting residue was purified by column chromatography to afford pure pyridone **5a** (8 mg; 42%); R*f*: 0.3 (1:1 EtOAc: Pet. ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.56-7.50 (m, 2H), 7.48-7.43 (m, 1H), 7.31 (dd, J = 9.2, 6.9 Hz, 1H), 7.23-7.18 (m, 2H), 6.55 (d, J = 9.2 Hz, 1H), 6.11 (d, J = 6.9 Hz, 1H), 1.96 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 164, 146.4, 139.6, 138.8, 129.8,

128.8, 127.8, 118.5, 106.1, 21.6; **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{12}H_{12}ON$ 186.0913, found 186.0914.

IV)HRMS Study of Ruthenacycle:



A glass tube with side arm was charged with $[RuCl_2(p\text{-cymene})]$ (0.02 mmol; 12 mg) and KOAc (0.04 mmol; 4 mg) under argon atmosphere. To this reaction mixture, 1,4-dioxane (4 mL; 0.1M) was added and stirred for 1 h at rt. *N*-Methyl acrylamide **1h** (0.2 mmol), ethyl 2-butynoate **2a** (0.4 mmol) and Oxone (0.4 mmol) were added to the mixture and it was stirred at 110 ^oC for 1 h. The reaction mixture was immediately subjected to mass analysis. **HRMS of Ruthenacycle(III)** (ESI-TOF) m/z**:** $[M+H]^+$ calcd for $C_{20}H_{28}O_3NRu$ 432.1107, found 432.1104.

3.9. References:

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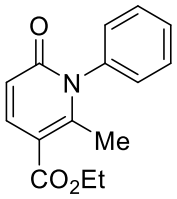
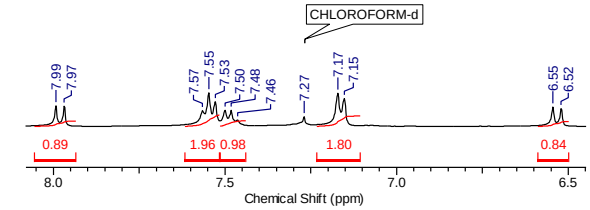
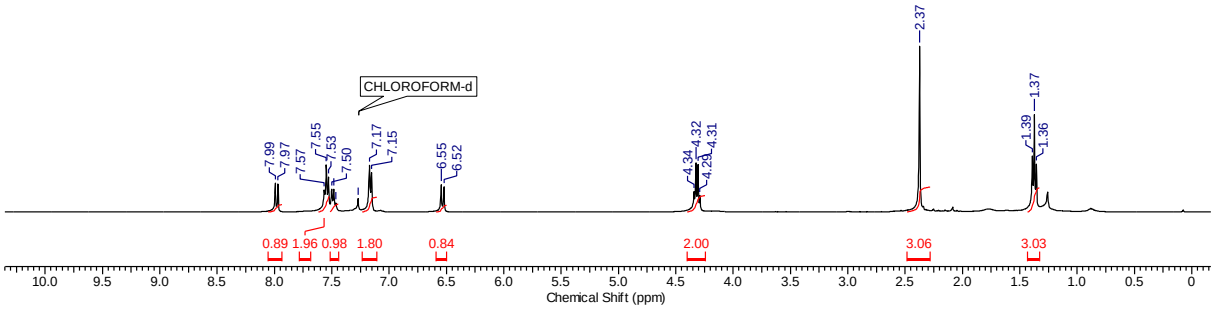
3.10. Spectra:



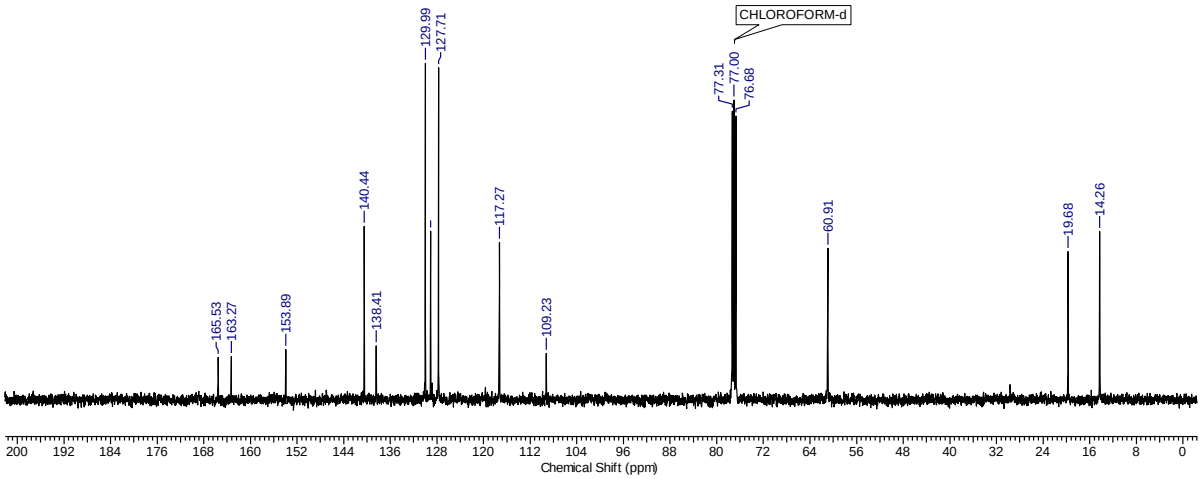
3a

^{1}H NMR, 400 MHz





^{13}C NMR, 100 MHz



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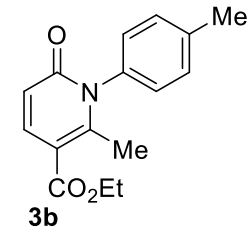
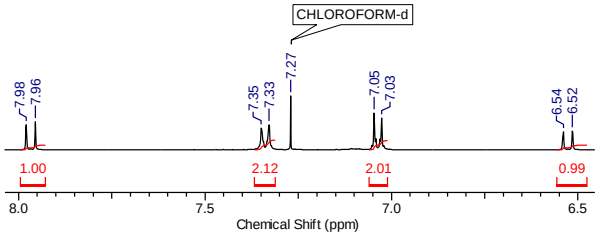
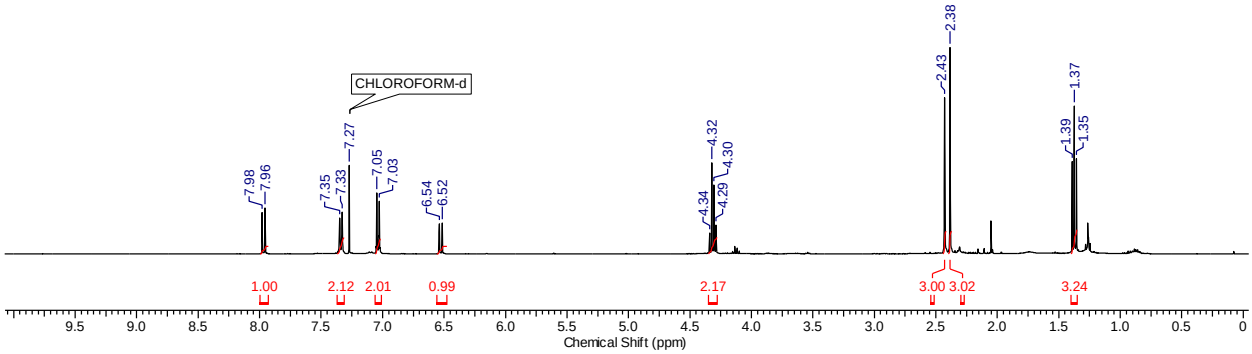


3b





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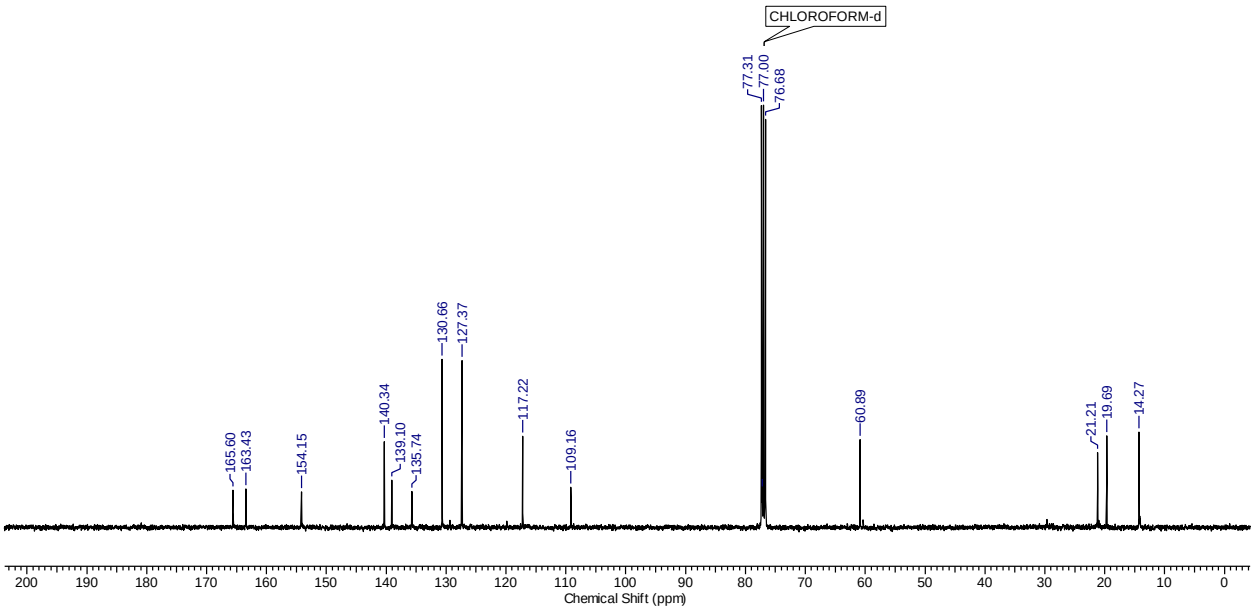

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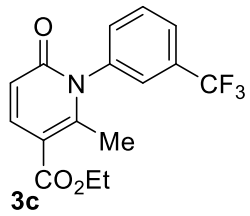

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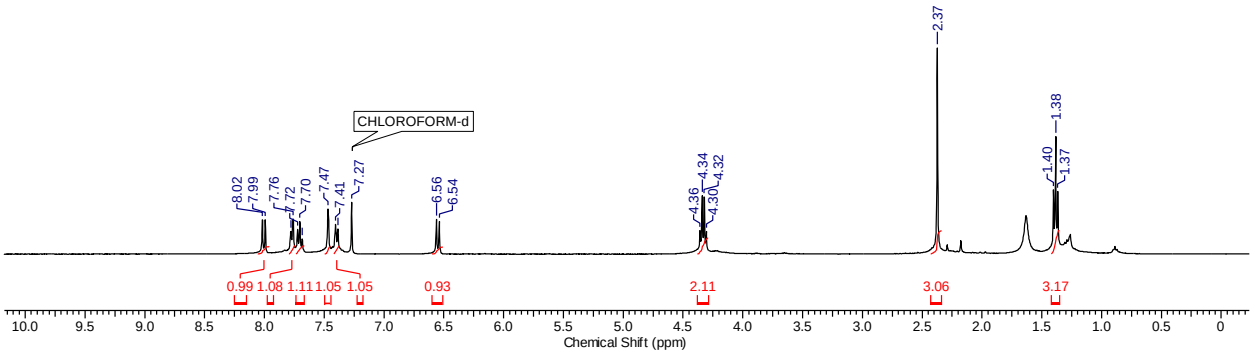

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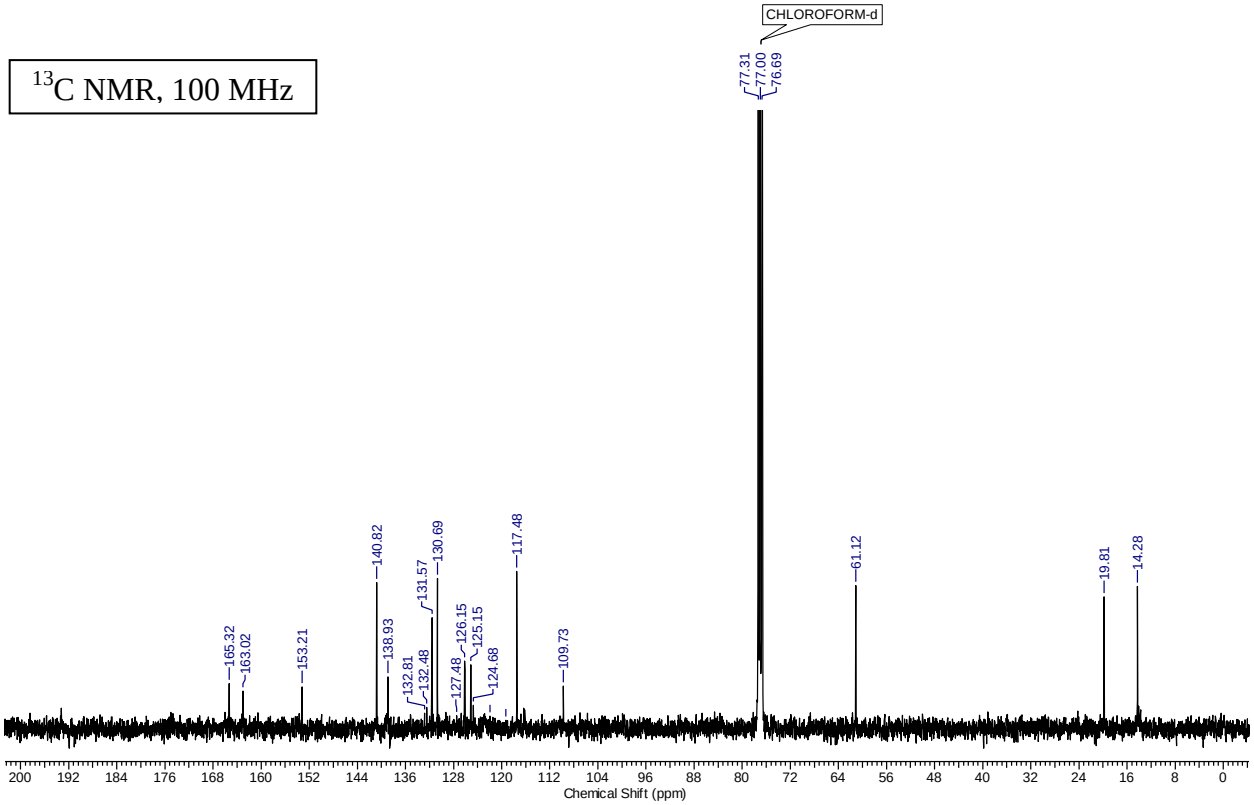

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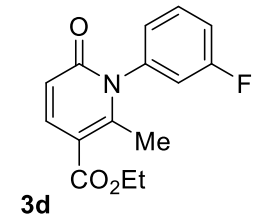

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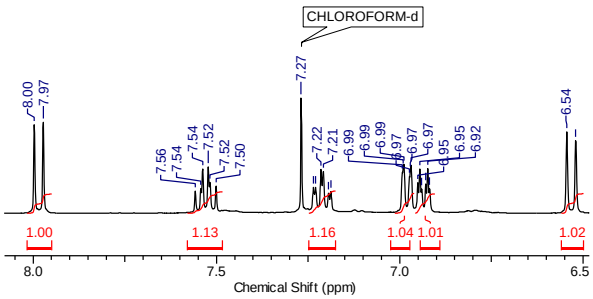

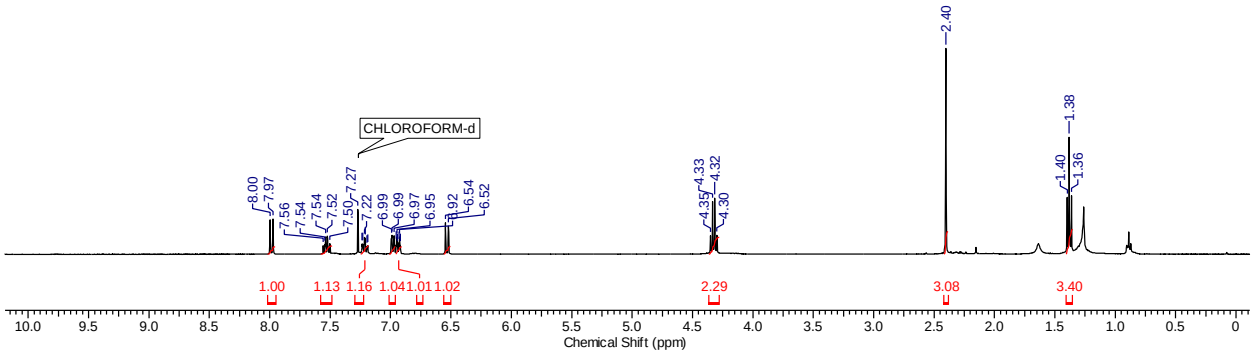

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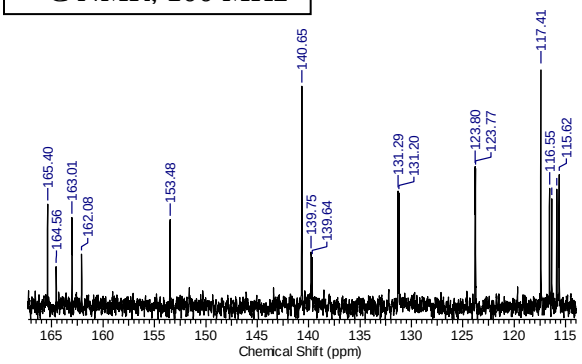

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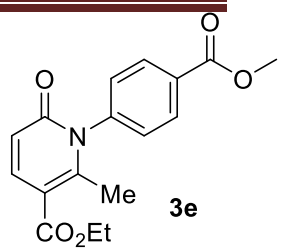

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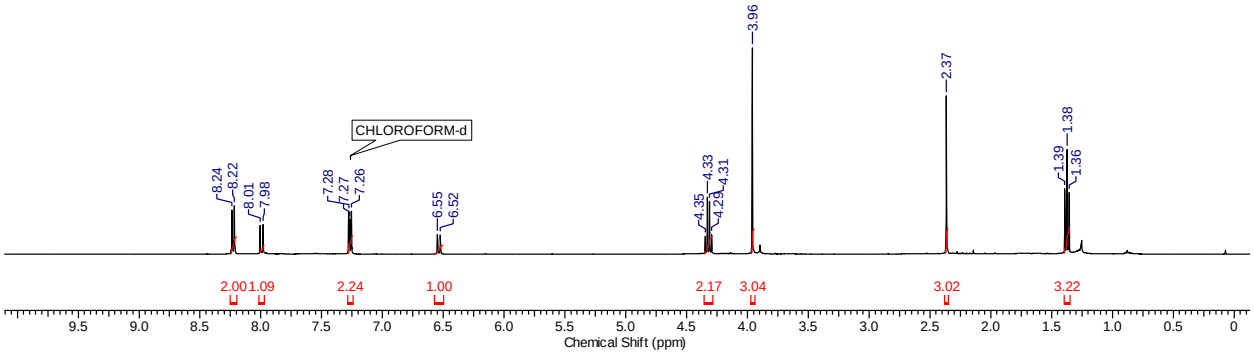

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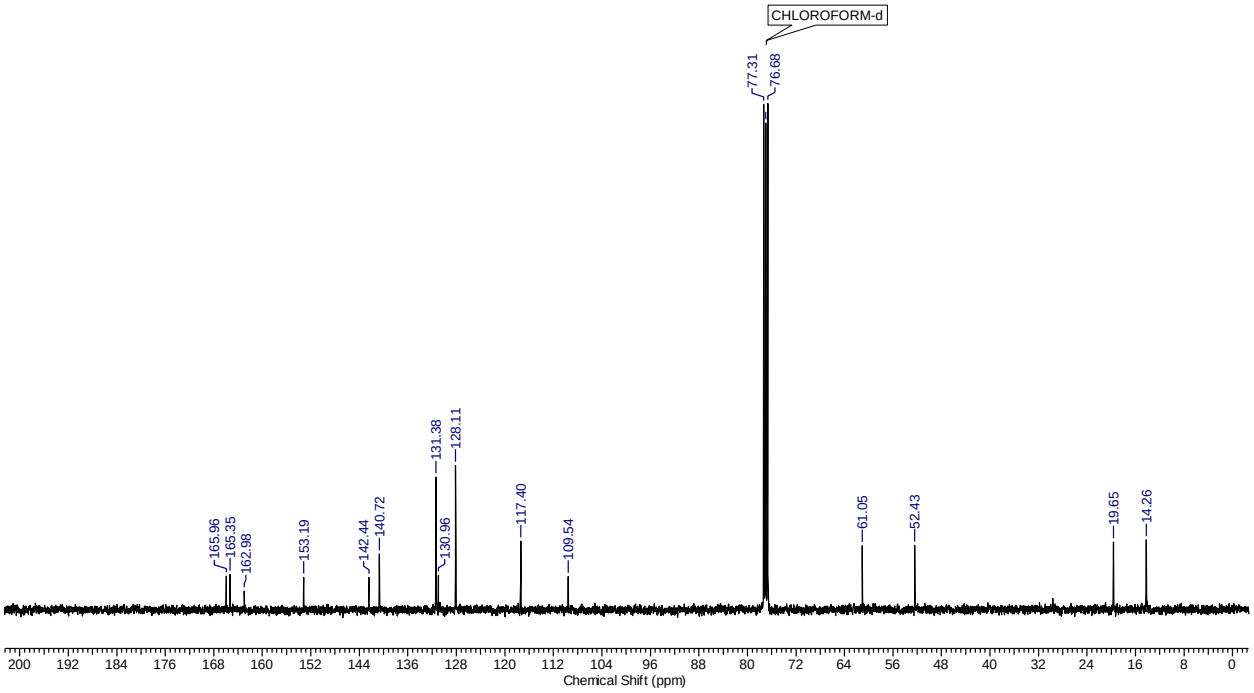

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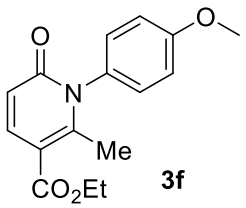

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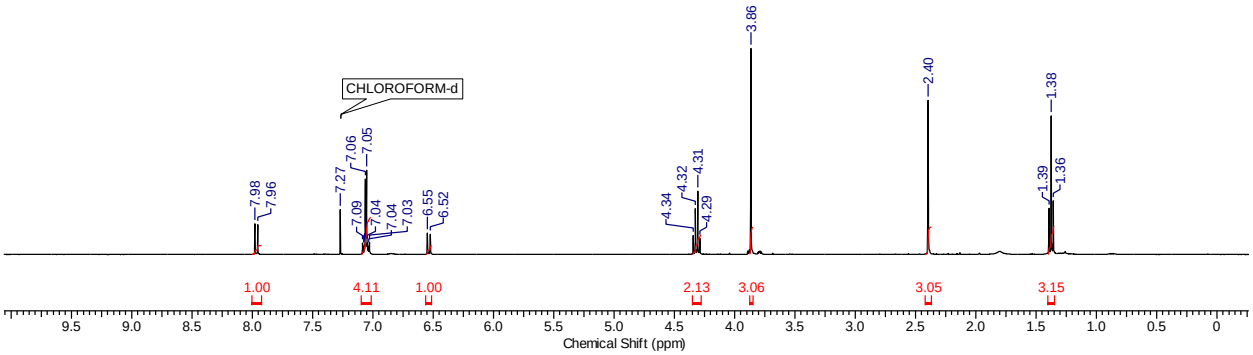

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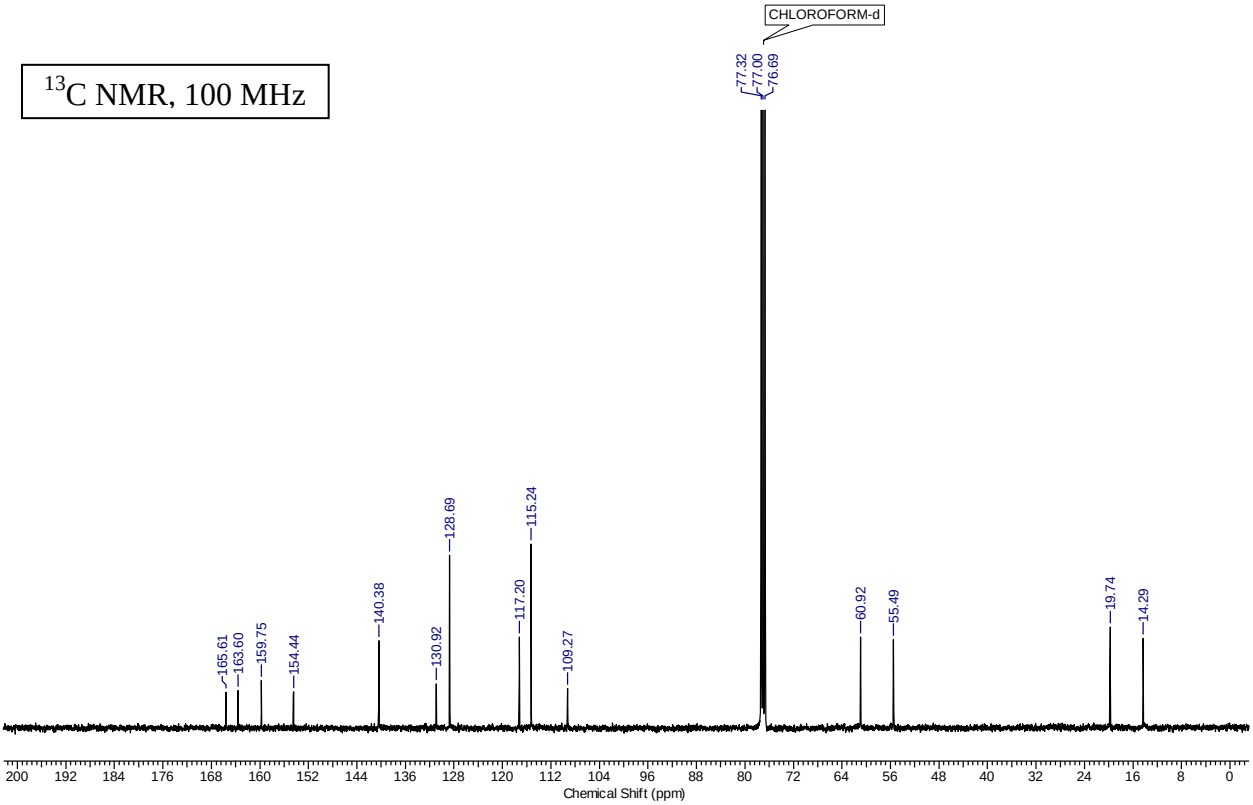

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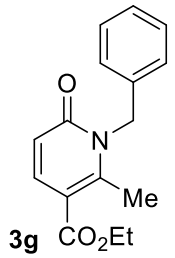

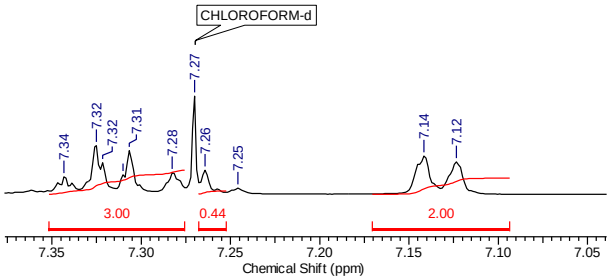

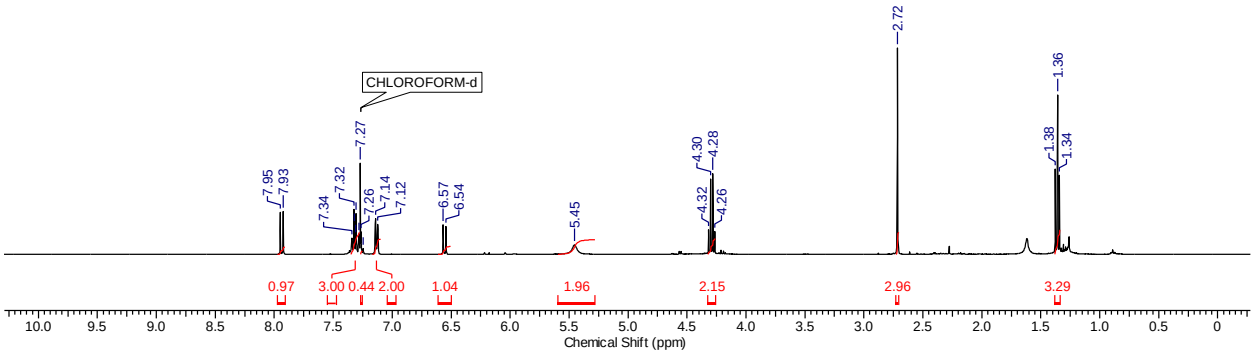

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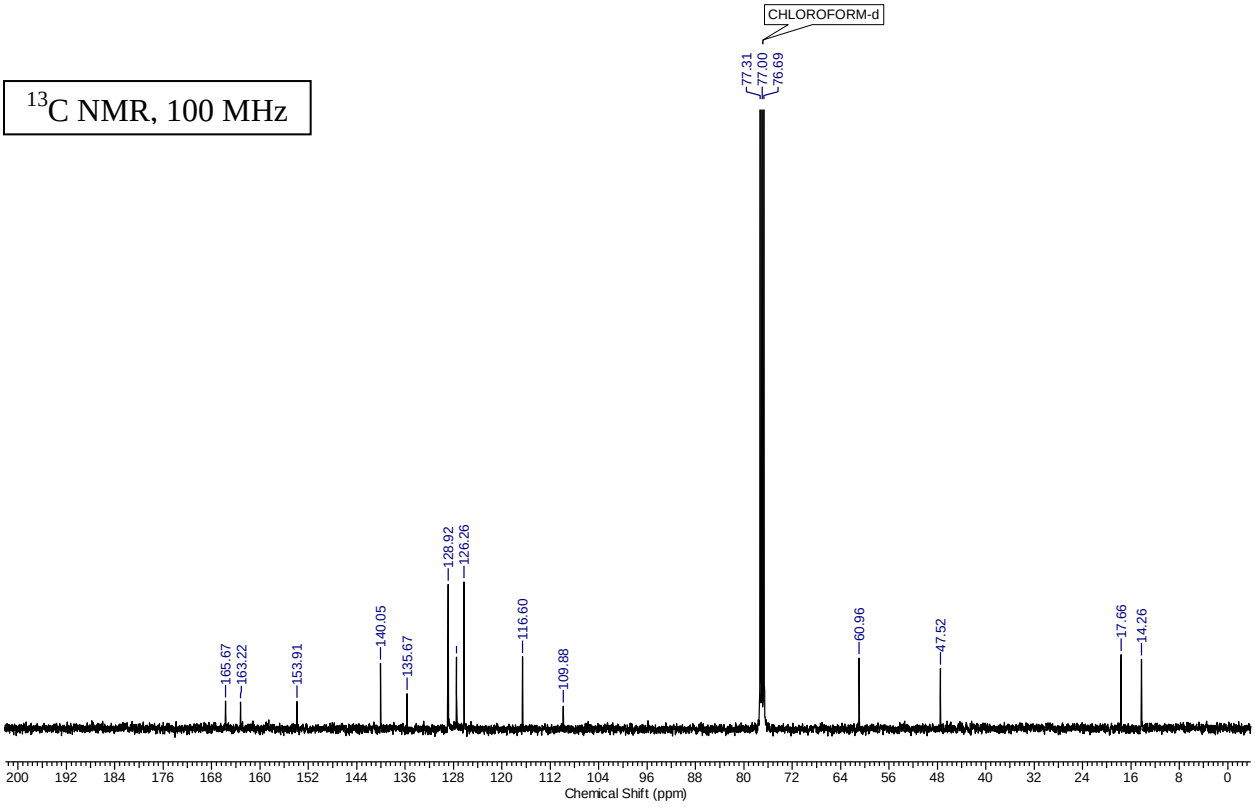

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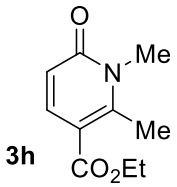
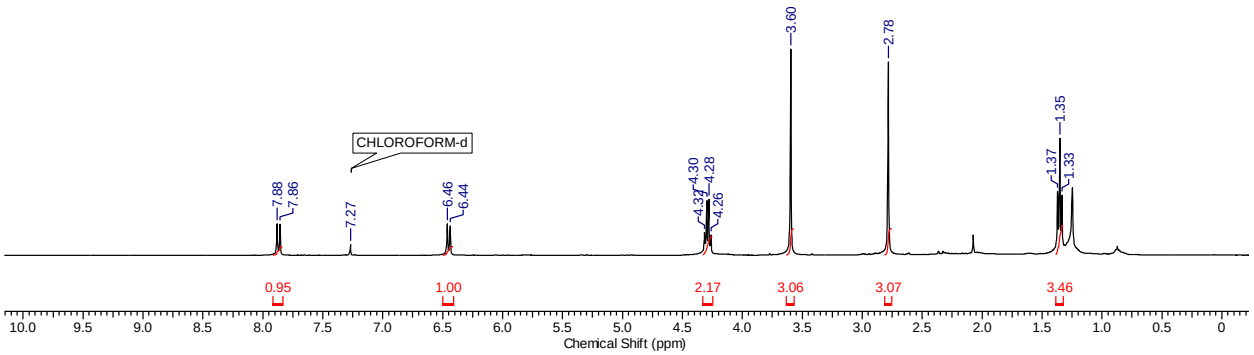
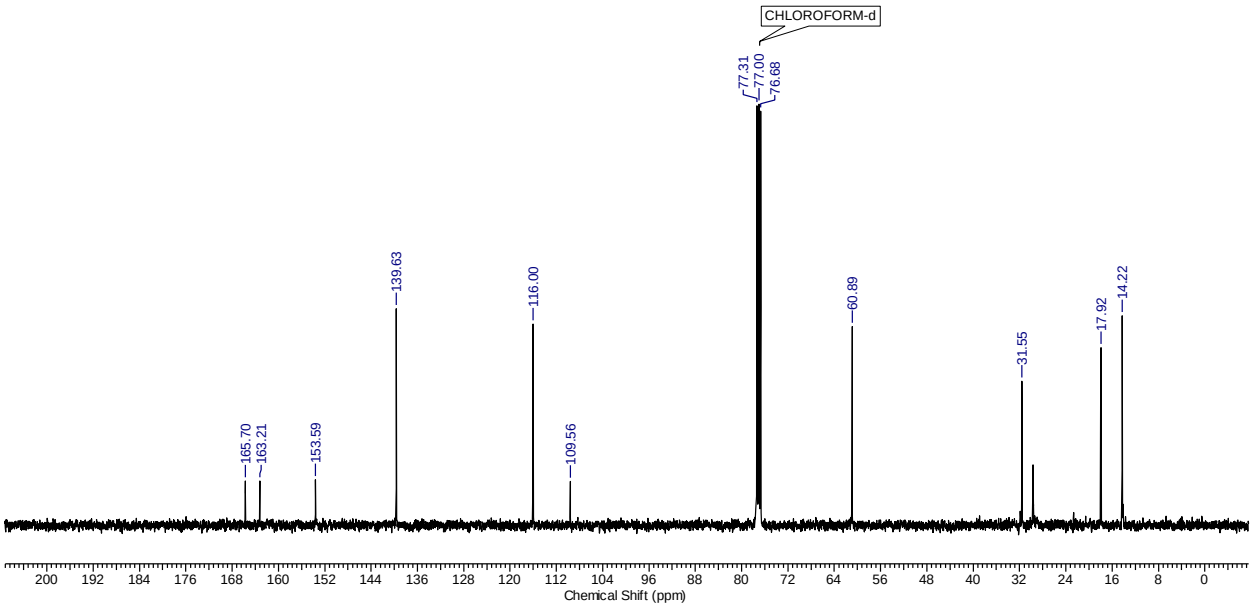


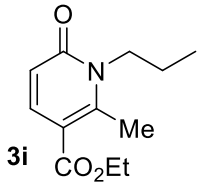
3h



^{13}C NMR, 100 MHz



^{1}H NMR, 400 MHz



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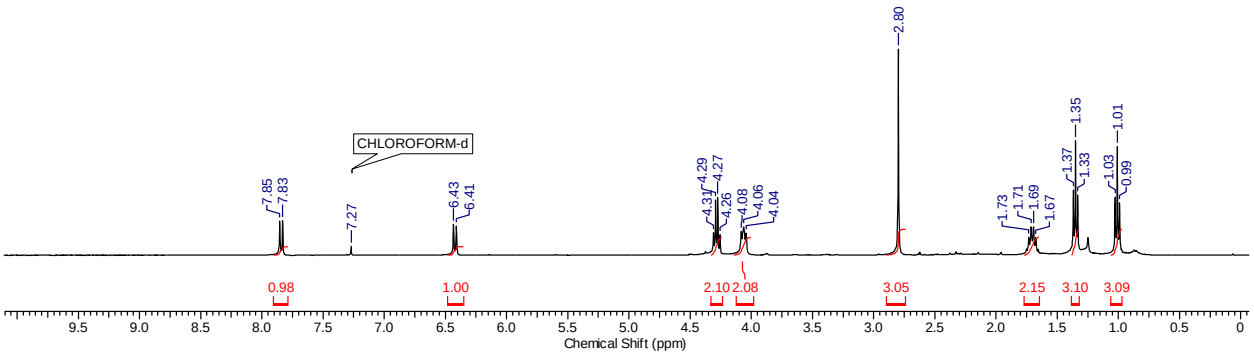

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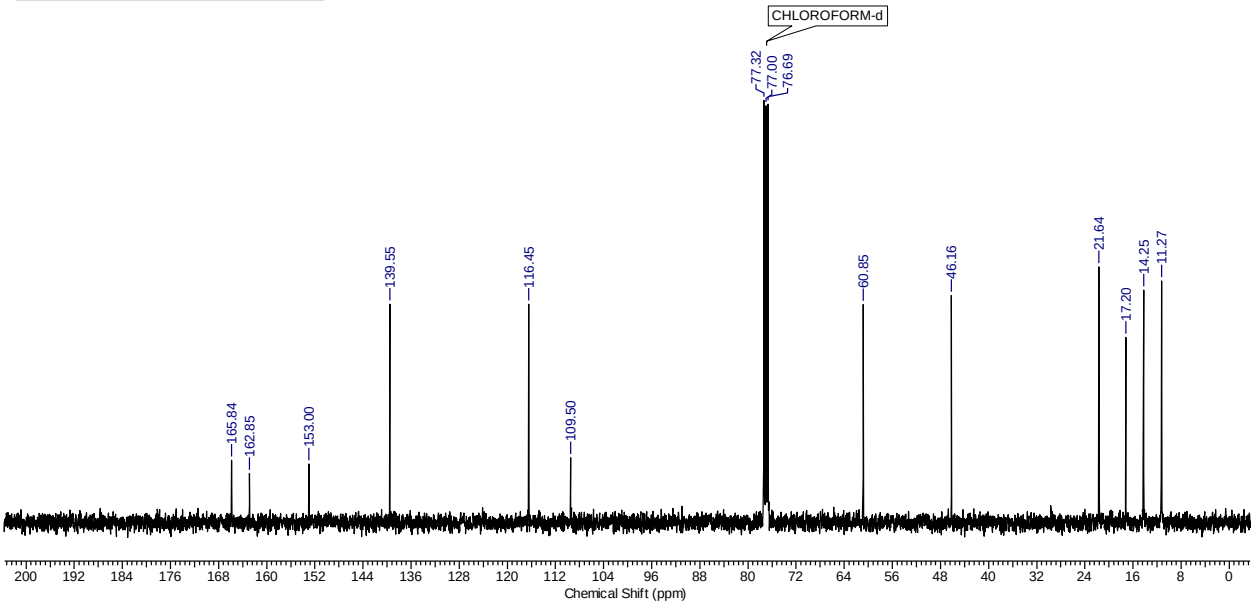

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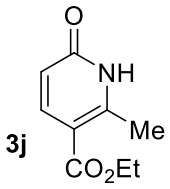

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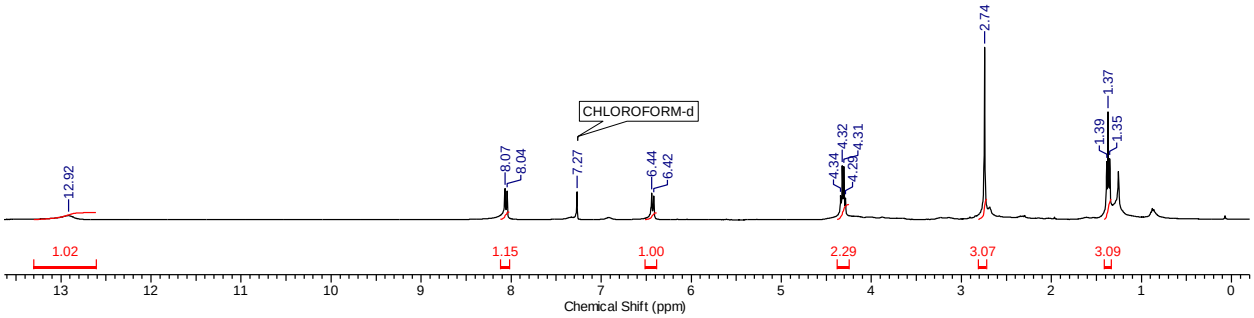

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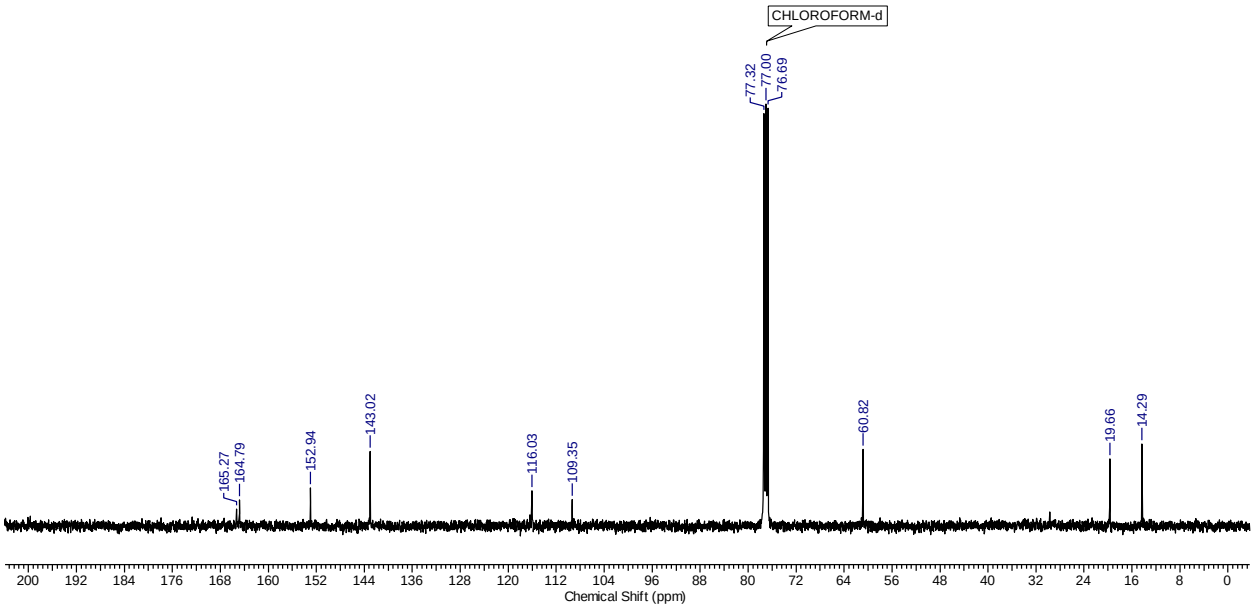

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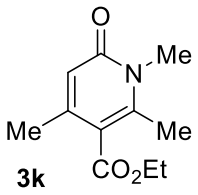

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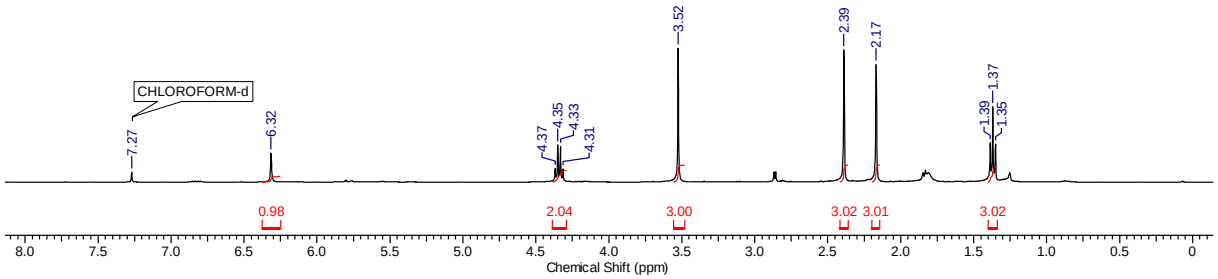

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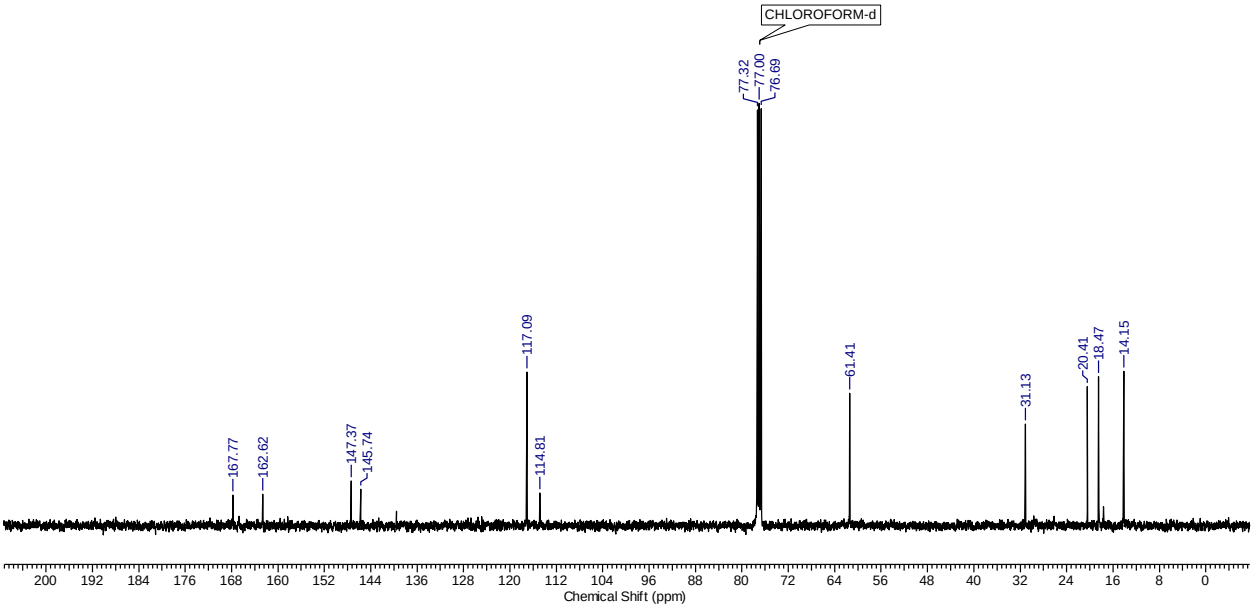

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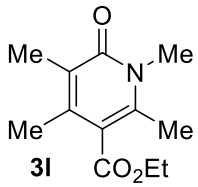

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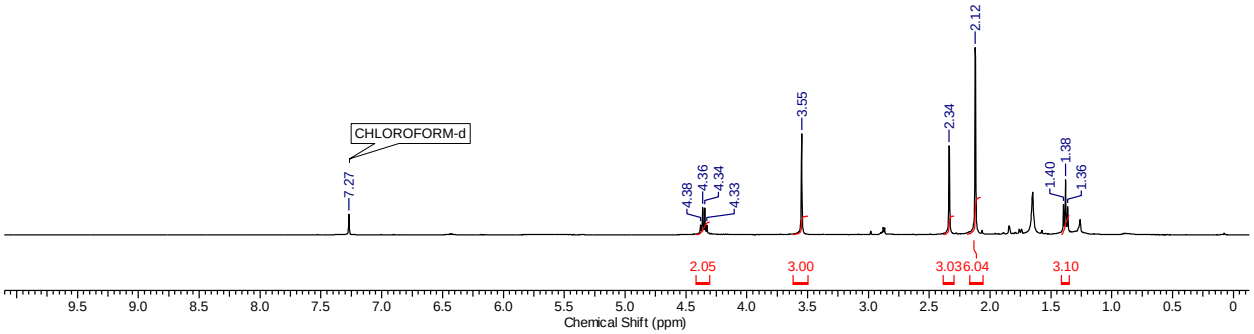

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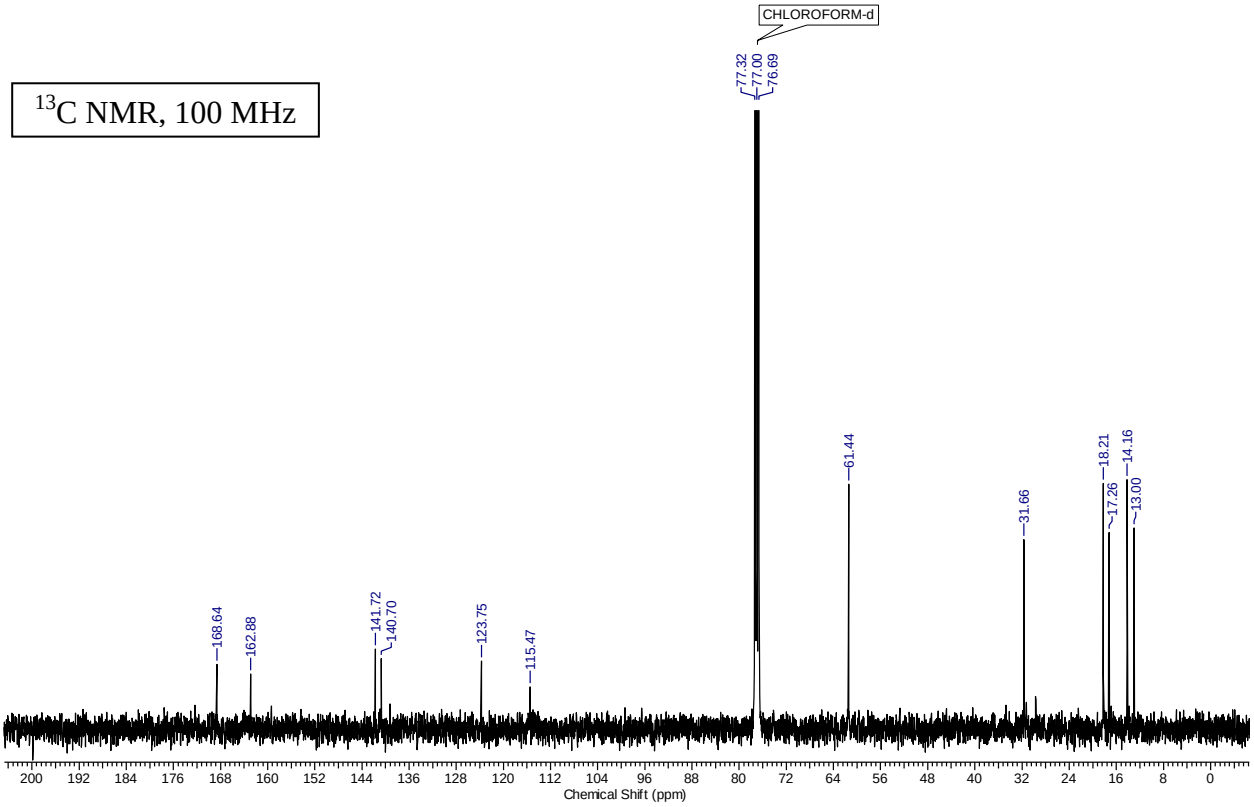

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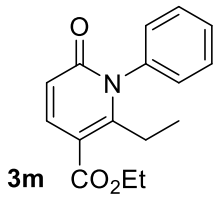

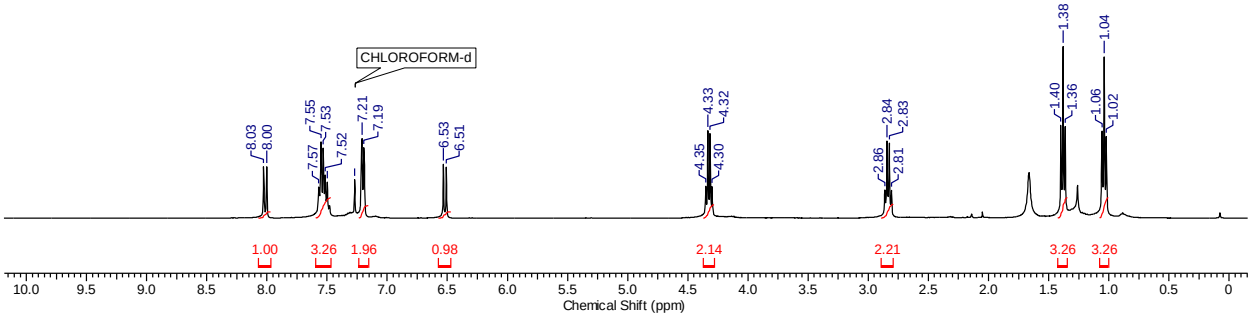

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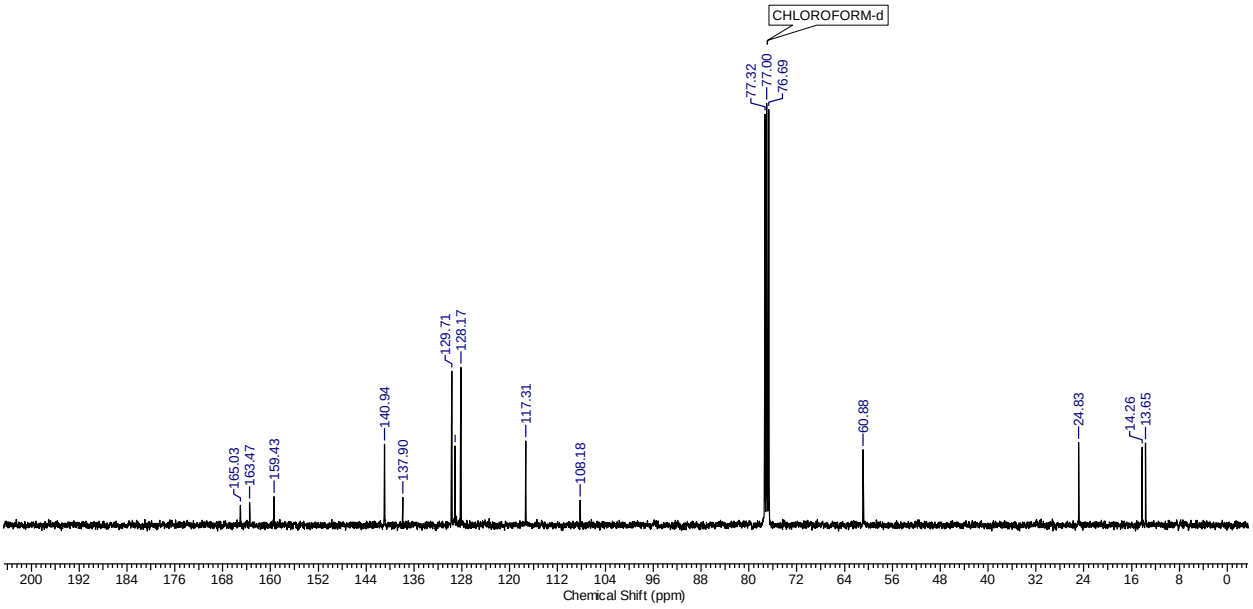
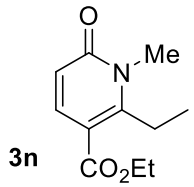


^{1}H NMR, 400 MHz



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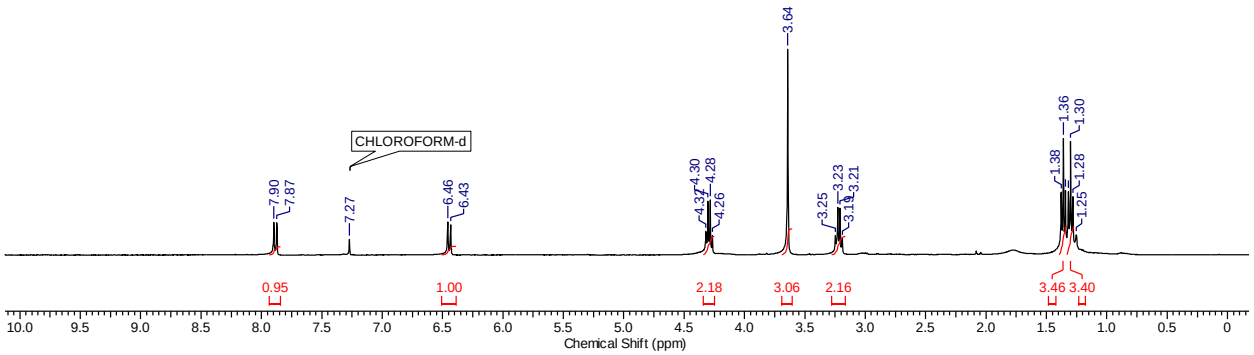

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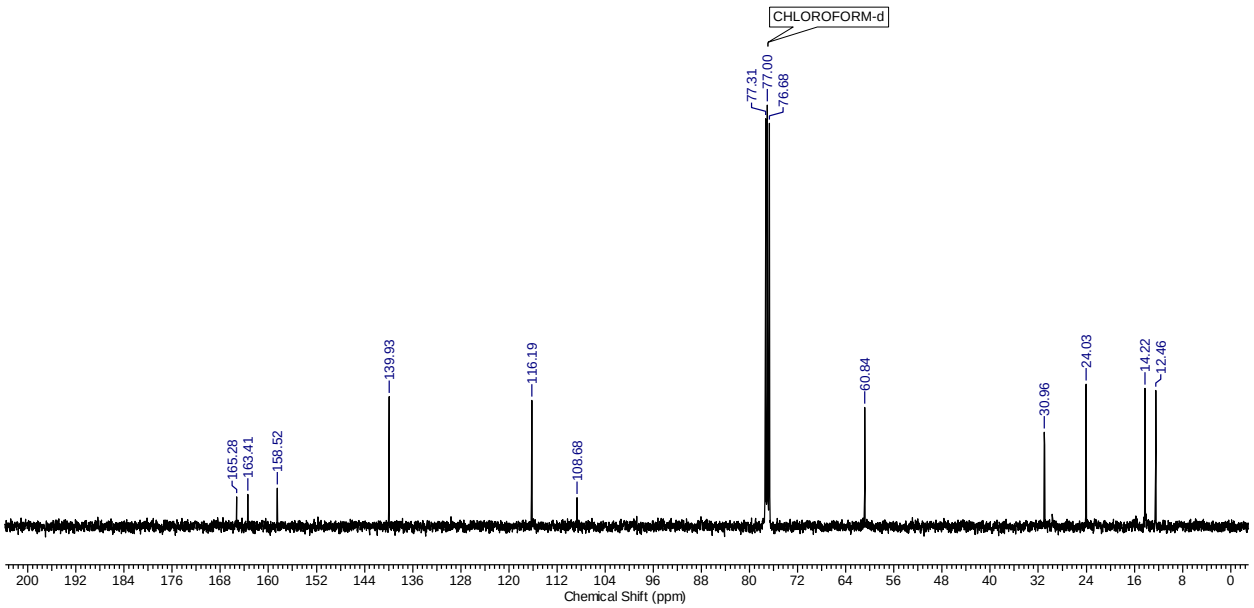

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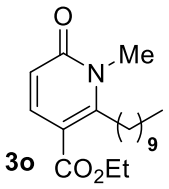

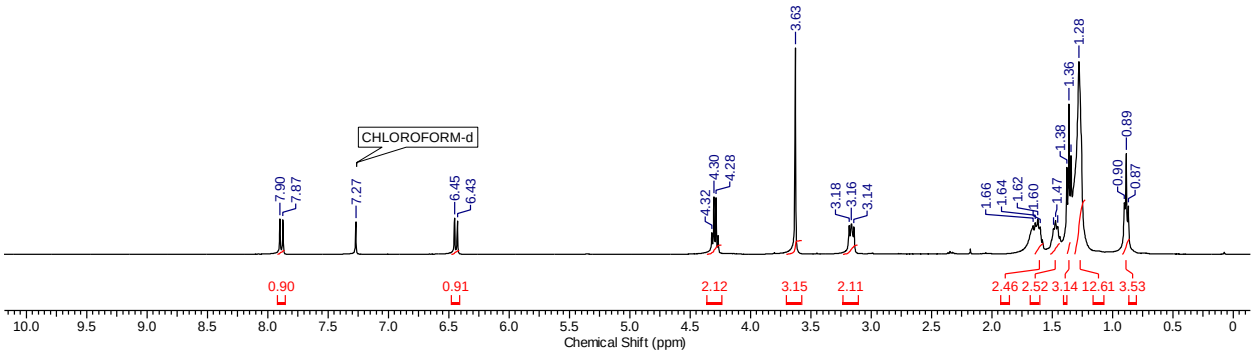

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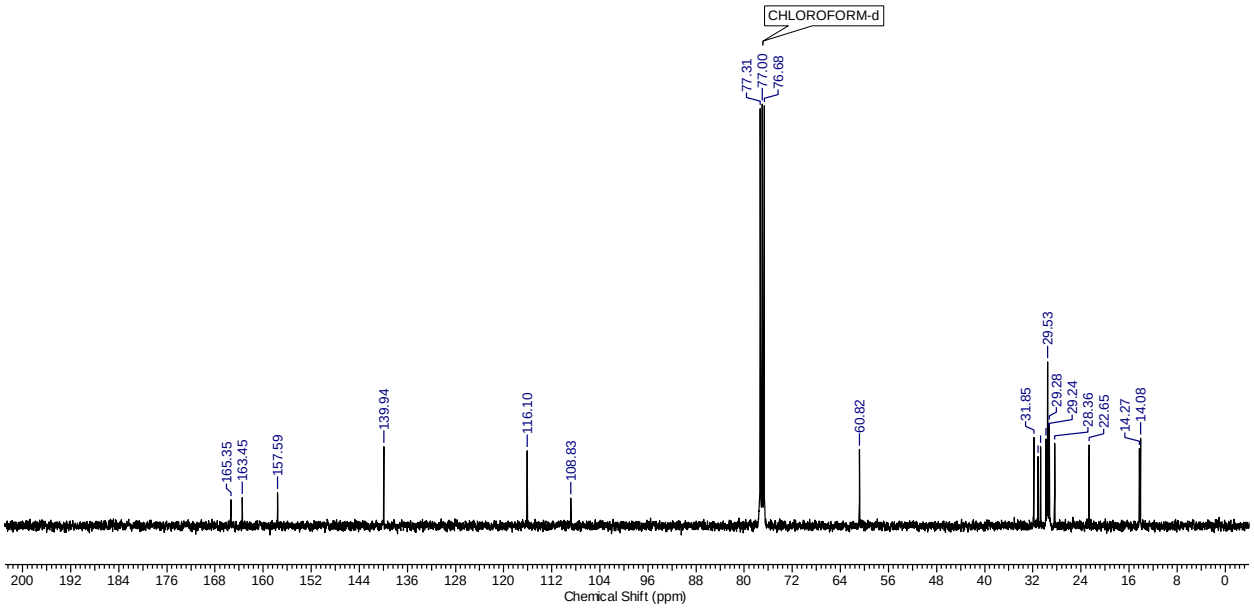

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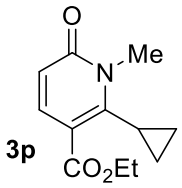
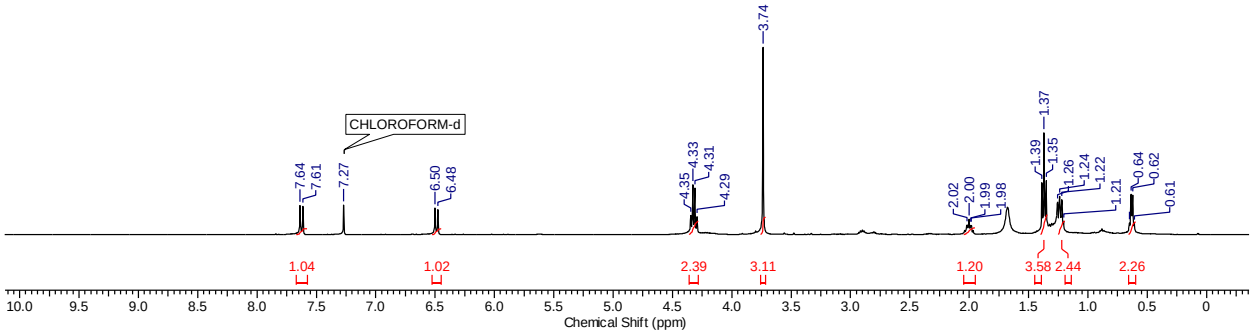
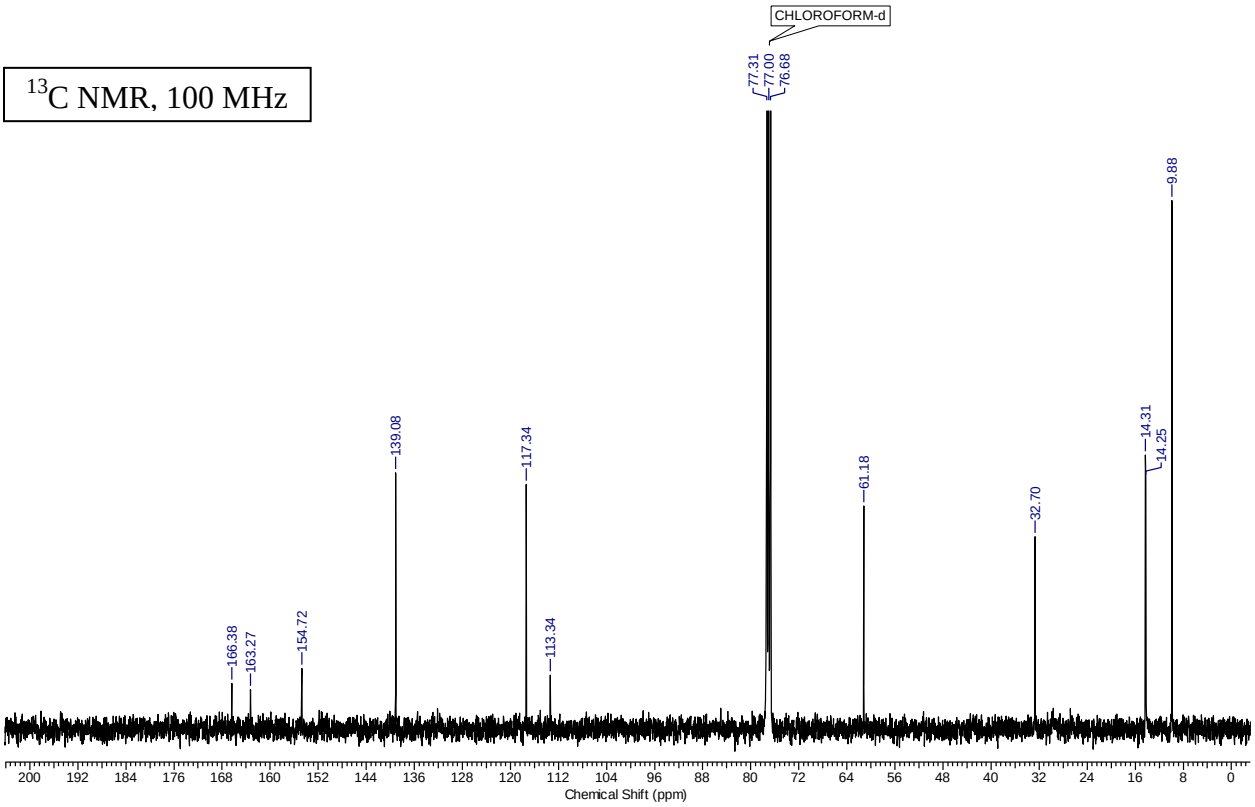




^{13}C NMR, 100 MHz



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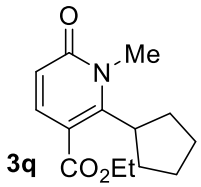

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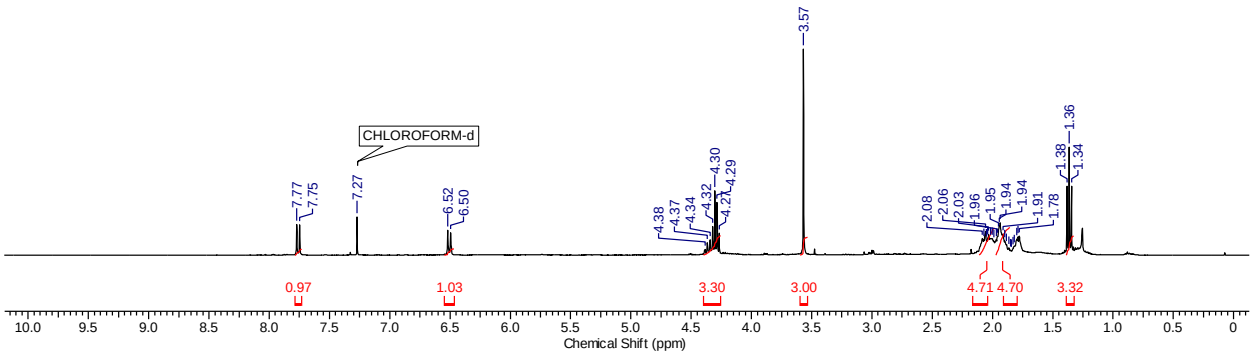

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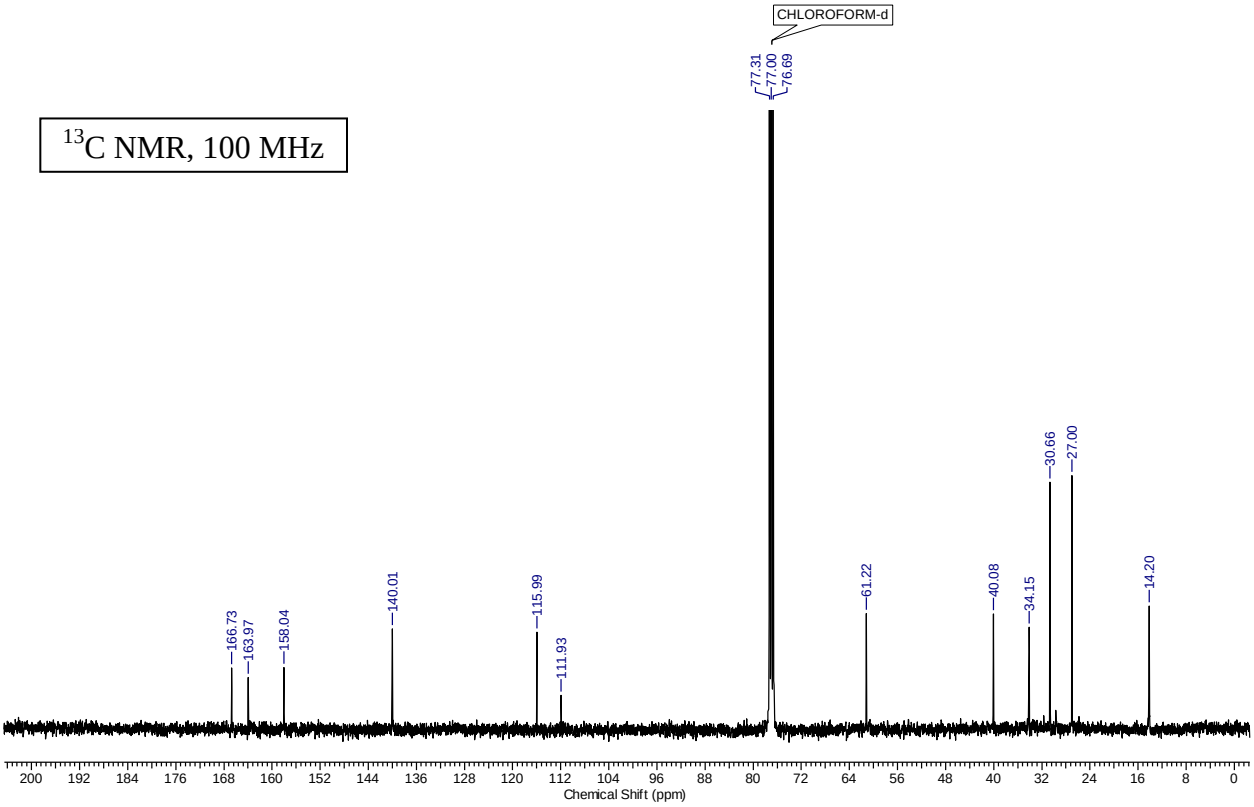

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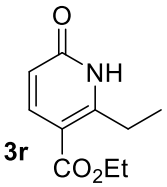

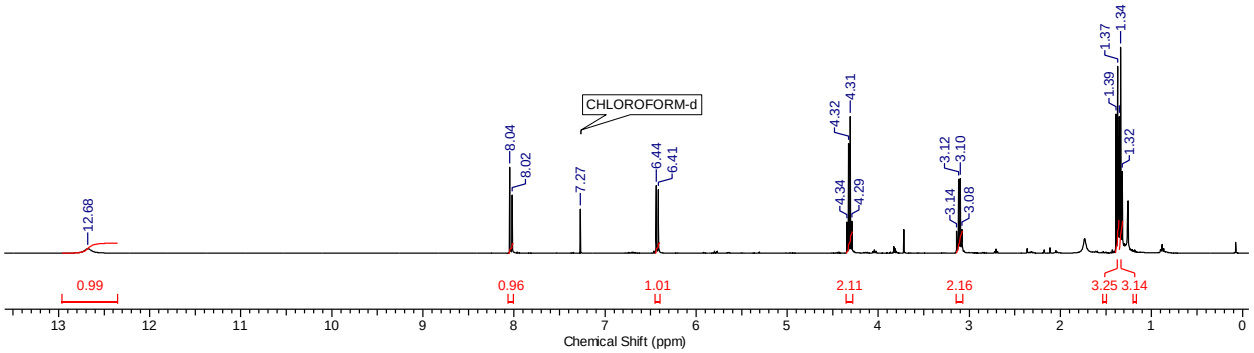

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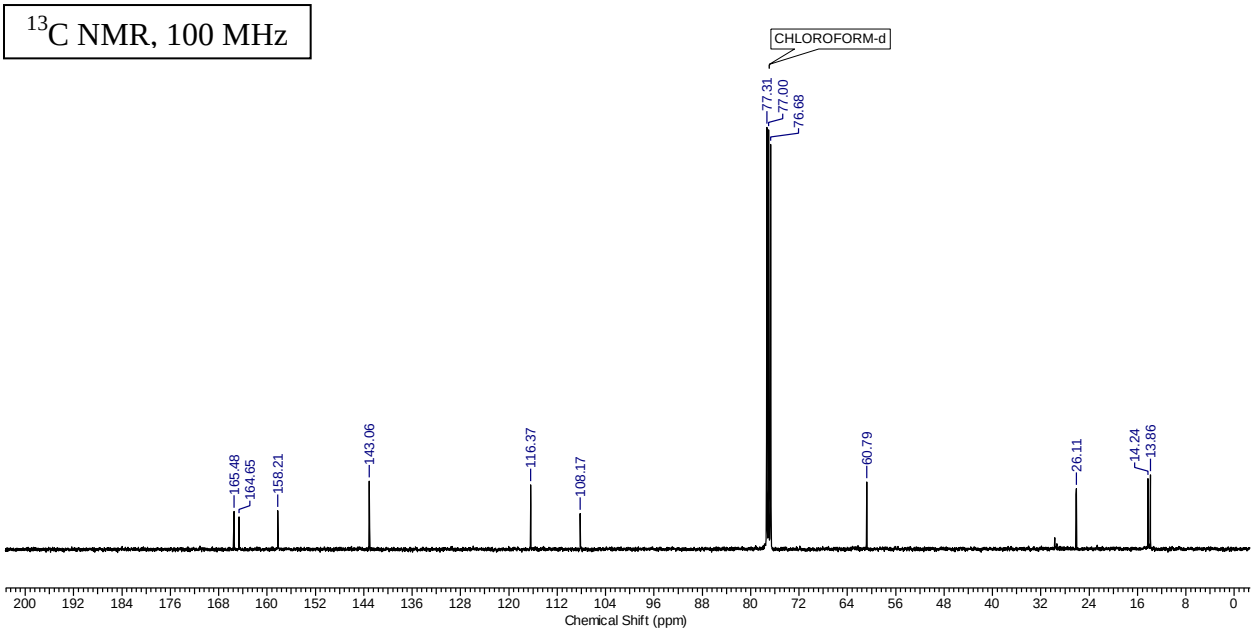

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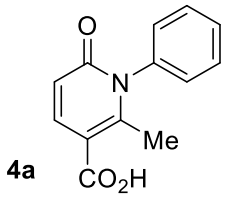
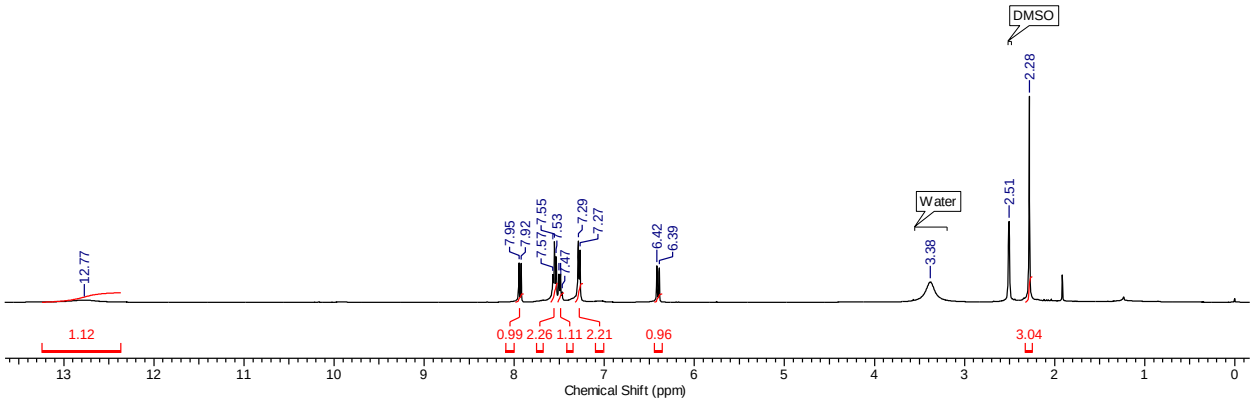
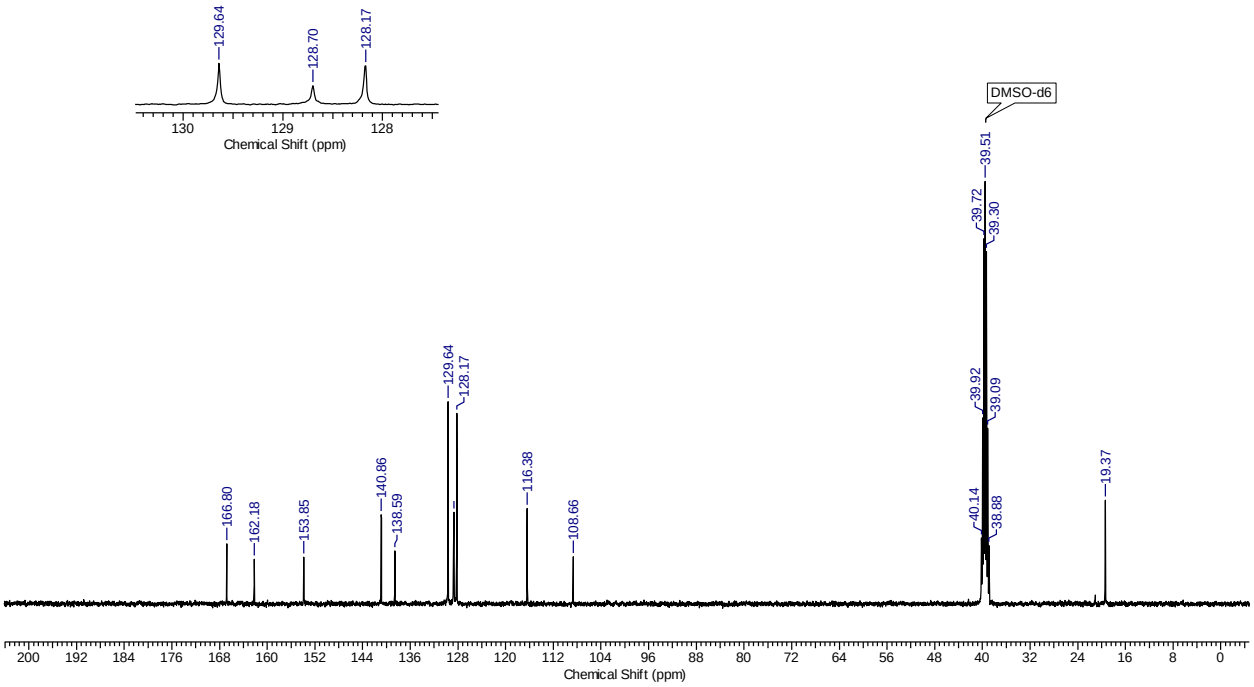


4a



^{13}C NMR, 100 MHz



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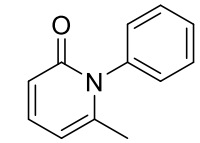
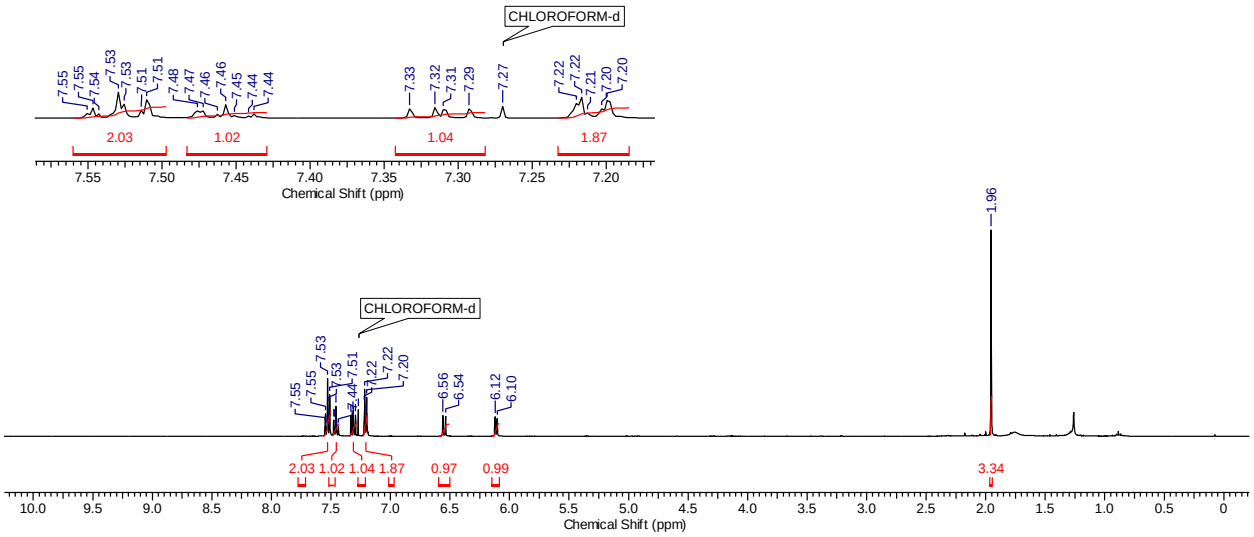
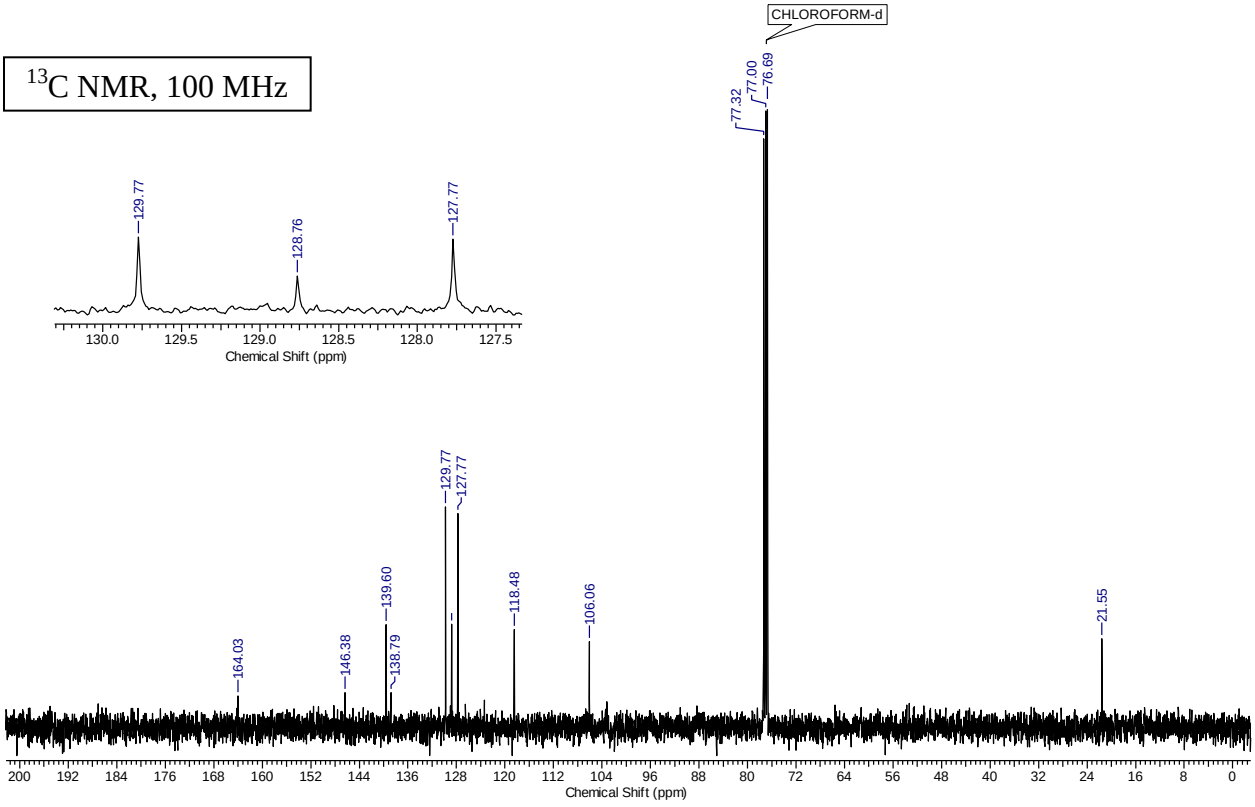


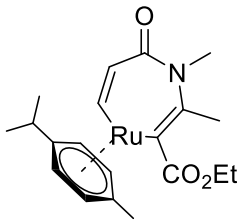
5a

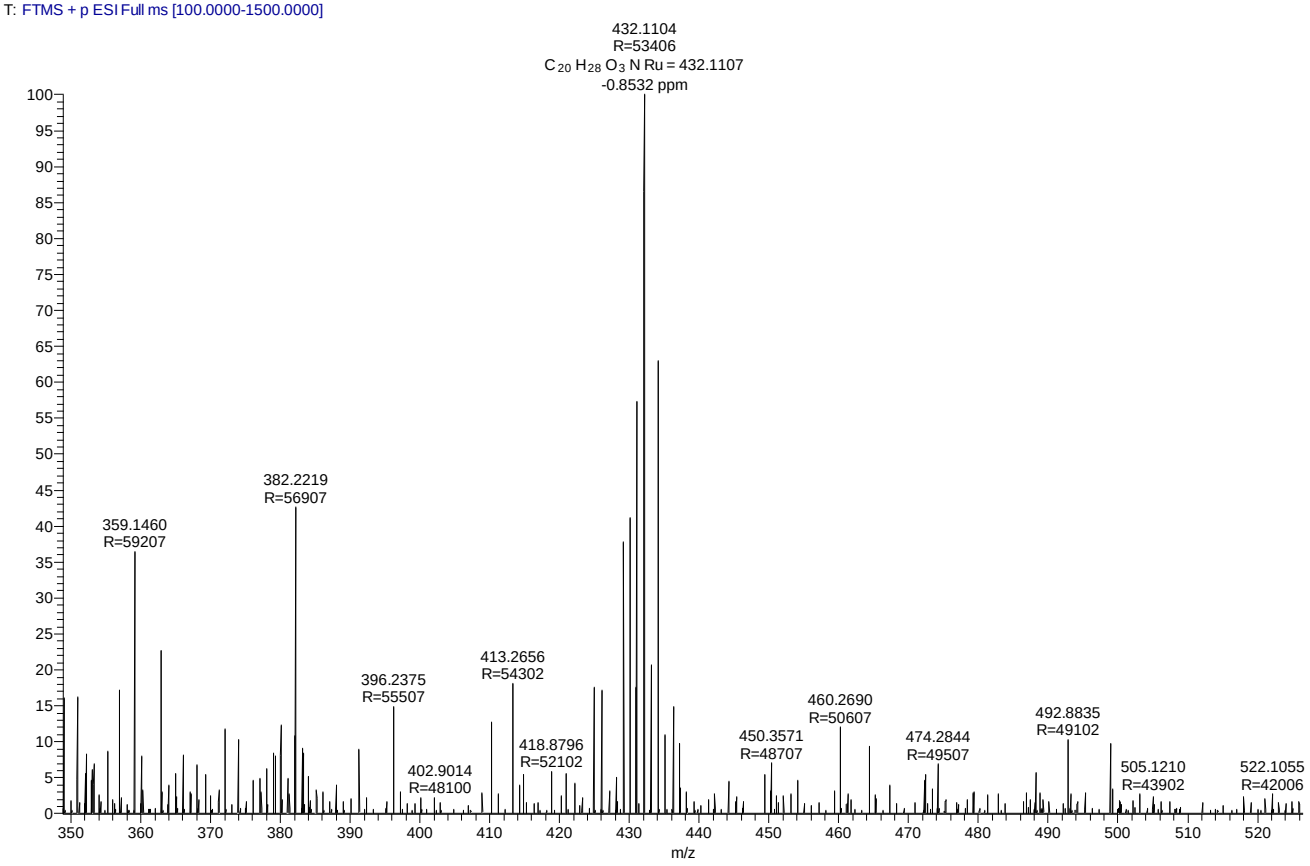


^{13}C NMR, 100 MHz



HRMS Spectra of Ruthenacycle

 III	$[M+H]^+$ calculated for $C_{20}H_{28}O_3NRu$ 432.1107, found 432.1104.

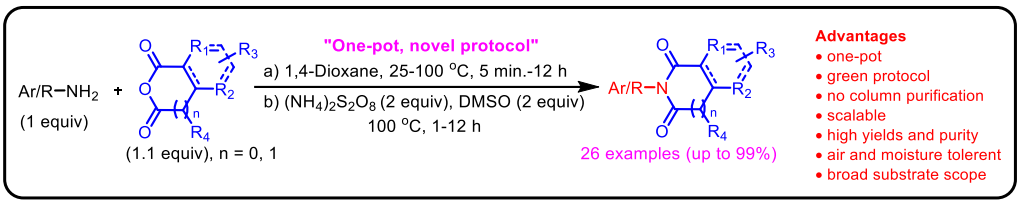


Publications and Patents

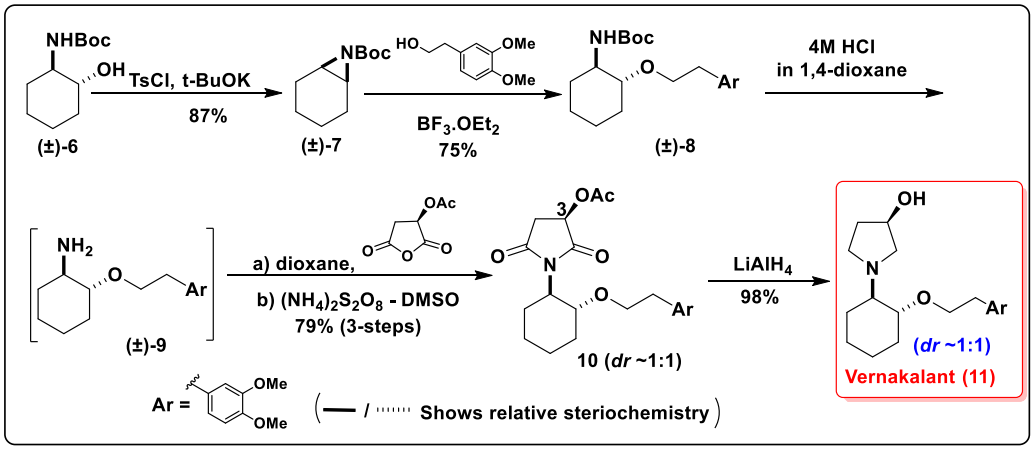
1. **Garad, D. N.**; Mhaske, S. B. "Diversification of Quinazolinones by Pd-Catalyzed C(sp^3)-Acetoxylation" *J. Org. Chem.* **2017**, *82*, 10470−10478.
2. **Garad, D. N.**; Viveki, A. B.; Mhaske, S. B. "Pd-Catalyzed Regioselective Mono-Arylation: Quinazolinone as the Inherent Directing Group for C(sp^2)−H Activation" *J. Org. Chem.* **2017**, *82*, 6366−6372.
3. **Garad, D. N.**; Mhaske, S. B. "Pd(II)-Catalyzed Intramolecular Tandem Olefin Amidation/C−H Activation Protocol for the Syntheses of the Protoberberine Class of Natural Products" *Org. Lett.* **2016**, *18*, 3862-3865.
4. **Garad, D. N.**; Mhaske, S. B. "Ru–Catalysed Reverse Regioselective Cascade Annulation of Acrylamides with Alkynes by aza-Michael/C–H Activation Sequence" *Manuscript communicated.* **2018**.
5. **Garad, D. N.**; Tanpure, S. D.; Mhaske, S. B. "Radical-Mediated Dehydrative Preparation of Cyclic Imides Using $(NH4)_2S_2O_8$-DMSO: Application to the Synthesis of Vernakalant" *Beilstein J. Org. Chem.* **2015,** *11*, 1008–1016.
6. Rao, V. U. B.; Jadhav, A. P.; **Garad, D.**; Singh. R. P. "Asymmetric Vinylogous Mannich Reaction of Silyloxy Furans with Ntert-Butanesulfinyl Ketimines" *Org. Lett.* **2014**, *16*, 648−651.

Patents

7. Mhaske, S. B.; **Garad, D. N.** "Process for synthesis of imides and Vernakalant" IN2014DE02999 A 20160831 **2016**
8. Mhaske, S. B.; **Garad, D. N.** "Novel quinazolinone alkaliod, process for preparation and use thereof" IN201711008388 A 20180914 **2018**



Scheme 1. Radical-mediated dehydrative preparation of cyclic imides



Scheme 2. Practical synthesis of the drug vernakalant

This work has been published in "*Beilstein J. Org. Chem.* **2015**, *11*, 1008."

Erratum

Erratum